Palladium-catalyzed ring opening of fused bicyclic vinylcyclopropanes

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Nikolai Wurzer

aus *Etzenricht*

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Prüfungsausschuss:	Vorsitz	:	Prof. Dr. Patrick Nürnberger
	1. Gutachter	:	Prof. Dr. Oliver Reiser
	2. Gutachter	:	Prof. Dr. Alexander Breder
	3. Prüfer	:	Prof. Dr. Manfred Scheer

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Für meine Großeltern

[redacted] *und* [redacted]

„Die Wissenschaft fängt eigentlich erst
da an, interessant zu werden,
wo sie aufhört“ (Justus von Liebig)

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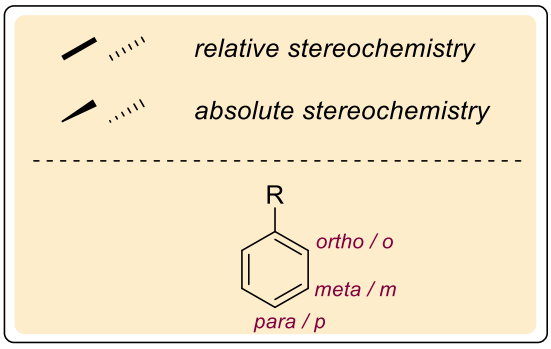
Abbreviations

°C	degree Celcius
Ac	acetyl
Ad	adamantly
aq.	aqueous
Ar	aryl
Atm	atmosphere
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
brsm	based on recovered starting material
c	concentration
calc.	calculated
CCDC	Cambridge crystallgraphic data centre
COSY	correlated spectroscopy
Cy	cyclohexyl
crm	complex reaction mixture
δ	chemical shift
dba	dibenzylideneacetone
dppp	1,3-Bis(diphnyl-phosphino)propane
DBU	1,8-Diazabicyclo(5.4.0) undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
E	electrophile
EI	electron ionization
equiv	equivalents
ESI	electro spray ionization
eV	electronvolt
EWG	electron withdrawing group
e.r.	enantiomeric ratio
gem	geminal
hex	hexyl
HMBC	hetero multiple bond correlation
HSQC	heteronuclear single quantum coherence
*i*Pr	*iso*-propyl
J	coupling constant
LA	Lewis acid
λ	wavelength
M	molar (mol/L)
m-CPBA	3-chlorobenzene-1-carbo-peroxoic acid
Mes	mesitylene
Ms	mesyl
MV	microwave
NBS	*N*-bromosuccinimid
NIS	*N*-iodosuccinimid
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
naphth	naphthyl

oct	octyl	*t*Bu	*tert*-butyl
ox	oxidant	Tf	trifluoromethanesulfonyl
Ph	phenyl	TFA	trifluoroacetic acid
PivOH	pivalic acid	tfc	3-(trifluormethyl-hydroxymethylen)-*d*-camphorato
PMB	para-methoxybenzyl		
py	pyridine		
r.t.	room temperature	TMS	trimethylsilyl
SEM	2-(trimethylsilyl)-ethoxymethyl	Tol	tolyl
		Ts	tosyl
TBA	tetrabutylammonium	wt%	weight percent
TBAHS	tetrabutylammonium hydrogensulfate		



A. Introduction

1. Cyclopropanes – an important motive in pharmaceuticals

Cyclopropanes – three-membered cyclic hydrocarbons – play an important role in the pharmaceutical industry. Despite their high ring strain of approximately 28 kcal/mol,[1] the cyclopropane moiety can be found in various pharmaceutically relevant compounds. After its first incorporation into drug candidates back in 1960,[2] this structural motive gained considerable attention in recent years (Figure **1**). For instance, among the 200 highest grossing pharmaceutical drugs in the year 2020, nine contain this three-membered cyclic structure.[3]

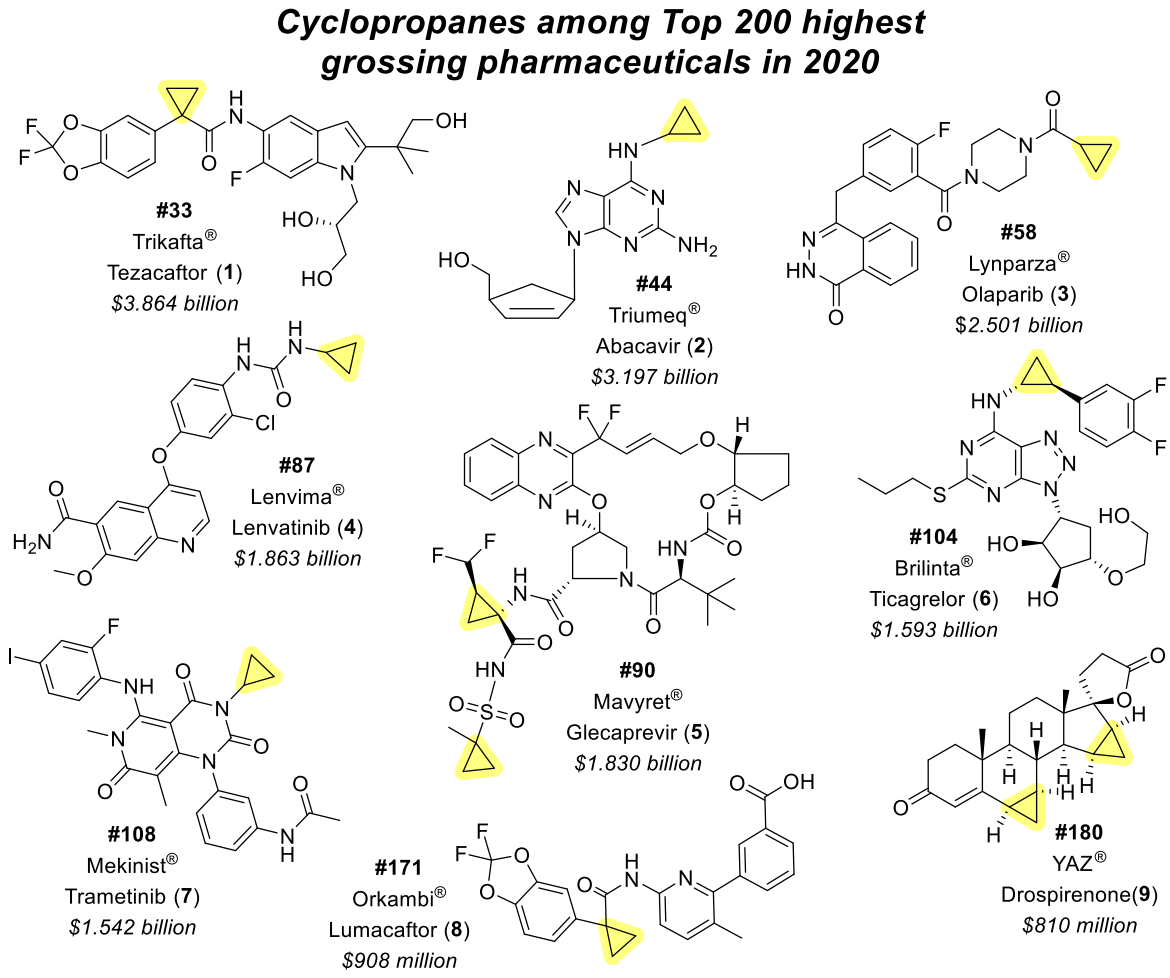
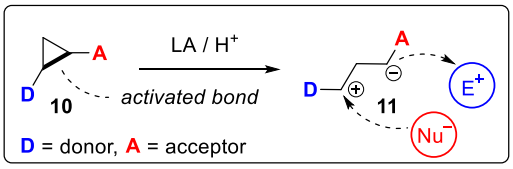


Figure 1. Top 200 grossing pharmaceuticals in 2020.[3]

Ranking in place #33 is Tezacaftor (**1**) which is sold under its trade-name Trikafta® as a fixed-dose combination with Elexacaftor and Ivacaftor for the treatment of cystic fibrosis[4,5] generated a revenue of $3.864 billion dollars. On rank #44 is Abacavir (**2**) which is better known as Triumeq® being one of the most promising therapeutic agents against HIV/AIDS. This combination drug additionally consisting of Dolutegravir and Lamivudine achieved a

revenue $3.197 billion US dollars.[6] Next, on position #58 is Olaparib (**3**) which is commercially available under its brand name Lynparza®. This $2.501 billion dollar-selling cyclopropyl ketone finds it application in chemotherapy for the treatment of e.g. ovarian cancer.[7] On rank #87 is cyclopropyl amide Lenvatinib (**4**) (Lenvima®) which is likewise used as anti-cancer drug for the treatment of thyroid cancer and managed to achieve retail sales of $1.863 billion dollars.[8] Closely following on rank #90 is hepatitis C medication Glecaprevir (**5**) (Mavyret®) which managed to achieve gross profit on sales in the amount of $1.839 billion US dollars.[9] Ranking in place #104 is disubstituted cyclopropyl amine Ticagrelor (**6**). This drug known under its trade name Brilinta® is a potent P2Y antagonist and is used to treat patients suffering from cardiovascular diseases. Manufactured by AstraZeneca, this compound likewise achieved billions dollar revenues.[10,11] Anti-cancer drug Trametinib (Mekinist®) having generated a revenue of $1.542 billion dollar can be found on place #108. In combination with Dabrafenib it is specifically used for the treatment of metastatic melanoma.[12] Lastly Lumacaftor (**8**) (Orkambi®) and Drospirenone (**9**) (YAZ®) scoring in ranks #171 and #180 find their application in the treatment of patients with cystic fibrosis[13] and as contraceptive,[14] respectively. Similarly, both drugs achieved a total retail sale of over one billion US dollars.

In summary, cyclopropanes have a substantial impact for the design and synthesis of novel and potent pharmaceuticals. However, not only the cyclopropyl group itself is a desirable target structure, but cyclopropanes have also proven to be versatile and powerful building blocks during drug syntheses. This is mostly achieved by cleaving one of the highly strained bonds through which the synthesis of more complex scaffolds and molecules is feasible. More often than not the inherent reactivity of donor-acceptor substituted cyclopropanes **10** is frequently utilized in synthetic strategies. Upon treatment with either Lewis or Brønsted acid, it is possible to cleave the activated bond between donor and acceptor group giving rise to a zwitterionic species **11** that can react with either nucleophiles, electrophiles or undergo cycloadditions if nucleophile and electrophile are linked (Scheme **1**). This strategy has been used in a plethora of different reactions and natural product syntheses and granted facile access to more sophisticated molecules.[15–26]



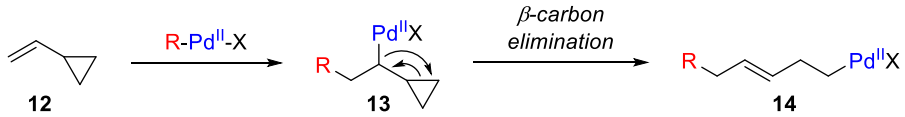
Scheme 1. Reactivity of donor-acceptor substituted cyclopropanes.

2. Palladium-catalyzed ring opening of cyclopropanes

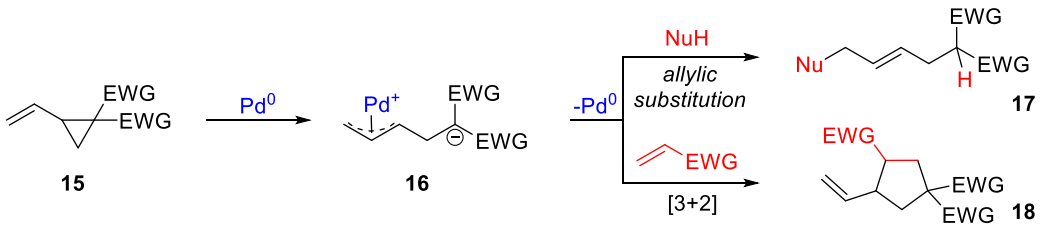
2.1 Overview

Besides the aforementioned ring-opening reactivity of donor-acceptor cyclopropanes which is traditionally triggered by the use of Lewis or Brønsted acids, transition metal-catalyzed bond cleavage of cyclopropanes has gained considerable interest in the synthetic community in recent years. Their popularity arose as this method also allows for the selective bond cleavage of non-activated cyclopropanes. Typically, transition metals like iridium, rhodium, ruthenium, zirconium, nickel, iron, or palladium find their application in a broad variety of different transformations.[27–32] The following review, however, will focus specifically on palladium-catalyzed transformations as this transition metal is not unique in its reactivity, but offers a broad variety of different synthetic strategies for the catalytic ring opening of cyclopropanes (Scheme **2**).

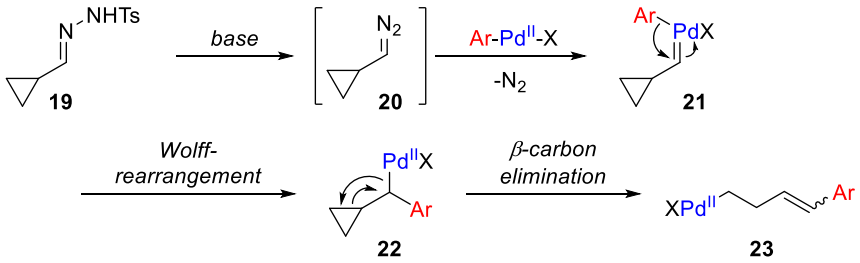
a) Carbo/hydropalladation of vinylcyclopropanes



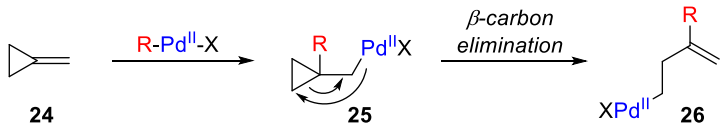
b) Vinyl cyclopropyl-di(EWG) as synthons for (η^3-allyl)-Pd-complexes



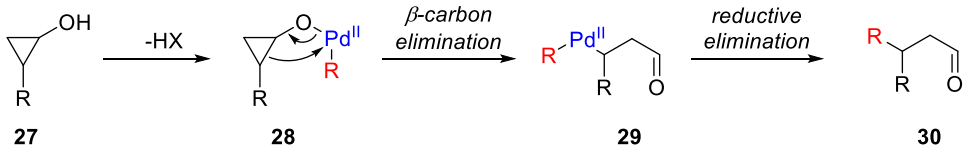
c) Cyclopropyl hydrazones cross couplings

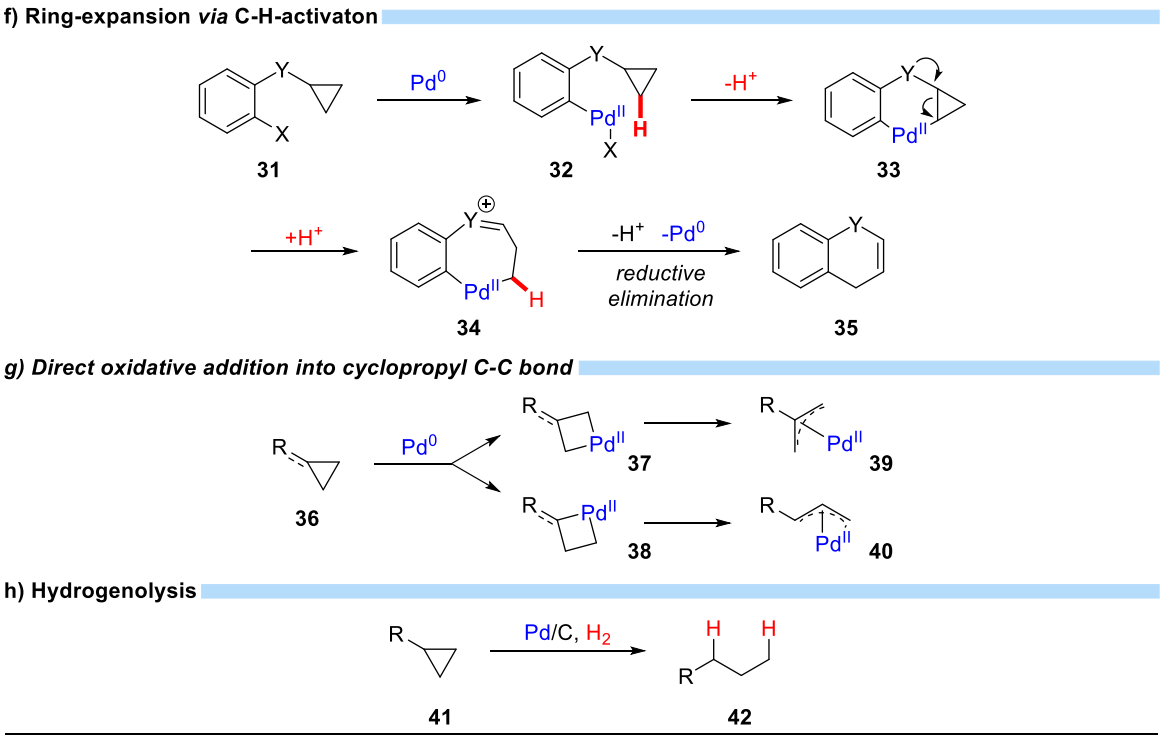


d) Element-palladation of alkyliden cyclopropanes



e) Cyclopropanols as synthons for homo enolates





Scheme 2. Various synthetic strategies for the Pd-catalyzed ring opening of cyclopropanes.

The first strategies we will focus on encompass the use of vinyl-substituted cyclopropanes **12** as they allow for - depending on the substitution pattern of the cyclopropane ring - different synthetic routes. A plain carbo-/hydropalladation gives rise to an organopalladium species **13** where the Pd is situated on the α-cyclopropyl position (Scheme **2a**). From here, a β-carbon elimination of the cyclopropyl C-C bond will open the strained ring to give open-chained intermediate **14** that can undergo further transformations.[33–37] Likewise, if the vinylcyclopropane bears electron withdrawing groups (EWG), the substrate acts as a allyl synthon that upon treatment with Pd(0) opens up to generate η^3-allyl-Pd-complex **16** that can either undergo allylic substitution reactions[38,39] or may be employed in [3+2]-cycloadditions (Scheme **2b**).[40–64]

However, the previously mentioned α-cyclopropyl Pd-species which is capable of ring-cleavage *via* β-carbon elimination can also be generated by different approaches. One possibility is the use of cyclopropyl tosylhydrazones **19** which can be deprotonated under basic conditions to give carbene intermediate **20** that can react with aryl-Pd(II)-complexes (Scheme **2c**). The resulting carbenoid **21** is prone to Wolff-rearrangement to generate species **22** where the Pd is now sitting on the α-cyclopropyl position from which the β-carbon elimination is initiated.[65–67] Another possibility to generate an α-cyclopropyl Pd-species is by direct *element*-palladation of alkylidene cyclopropanes (given that this step features the appropriate regioselectivity) to give **25** from where β-carbon elimination can take place

(Scheme **2d**).[68–75] Interestingly, this process additionally allows ring-opening polymerizations of aryl methylenecyclopropanes.[76,77]

Furthermore, cyclopropanols **27** also offer the possibility for Pd-catalyzed ring openings as these substrates act as synthons for homo-enolates under appropriates reaction conditions. The oxygen can coordinate to Pd(II) which formally gives rise to an α-cyclopropyl Pd-species **28** that is likewise capable of triggering the β-carbon elimination (Scheme **2e**).[78–85]

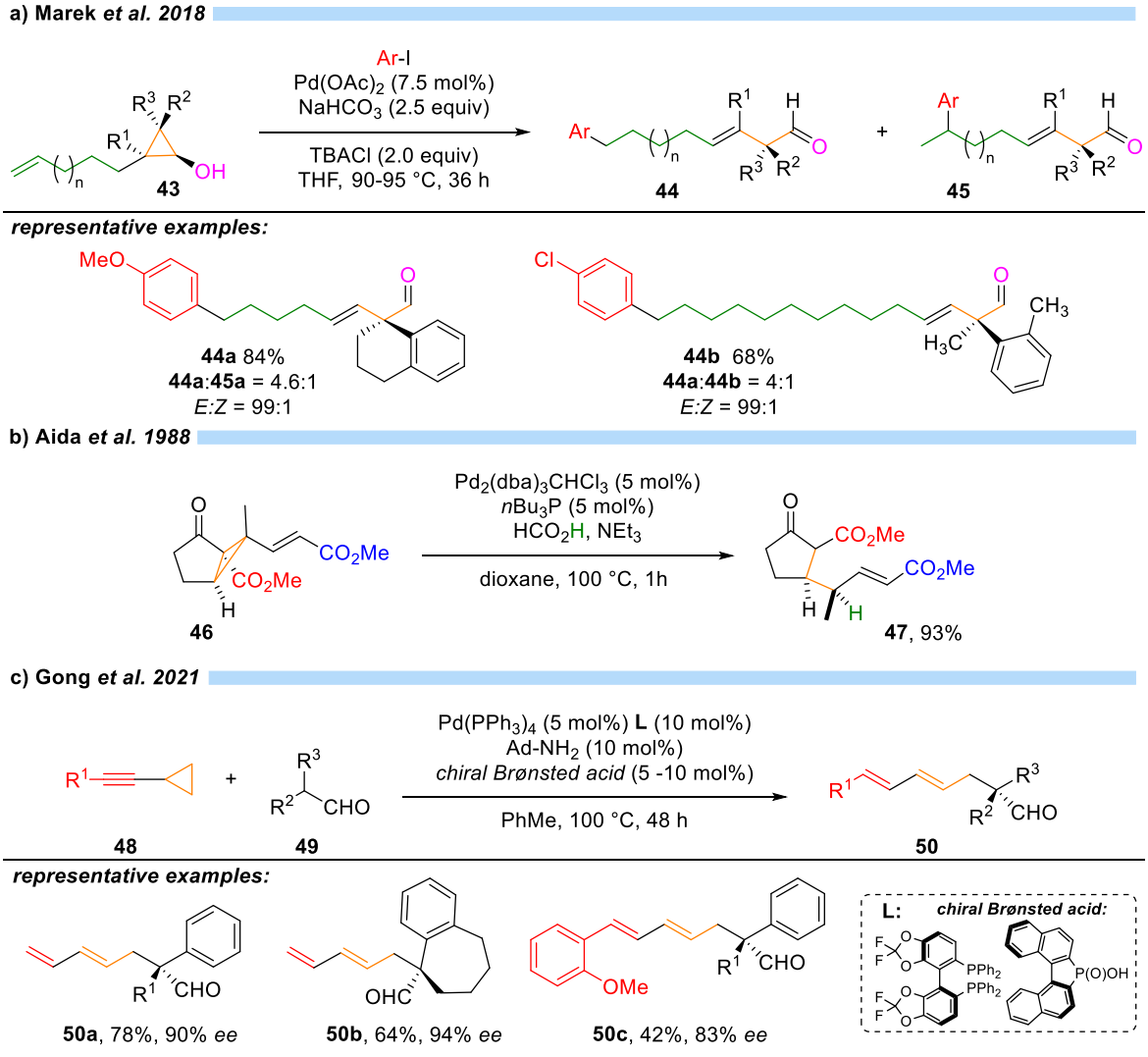
Another noteworthy approach makes use of Pd-catalyzed C-H insertion/activation into the cyclopropyl C-H bond. Generally, substrates with core-structure **31** are most suitable for this strategy. After the initial oxidative addition of Pd(0) into the aryl-X bond, the resulting intermediate **32** possesses a suitable geometry for the insertion in to the cyclopropyl C-H bond to form **33**. With the aid of the electron pushing nature of the heteroatom Y, the endocyclic bond of the generated bicycle is then cleaved and the catalytic cycle is closed by reductive elimination to give product **35** (Scheme **2f**).[86–90]

Further strategies approach the ring opening *via* a direct oxidative addition of Pd(0) into the cyclopropyl C-C bond generating intermediates **37** or **38**, respectively. Depending on the selectivity of this step, these intermediates then rearrange to form η^3-allyl-Pd-complexes **39** or **40** which can further undergo various transformations (Scheme **2g**).[91–103]

Lastly, certain substrates also offer bond cleavage by direct hydrogenolysis using palladium on charcoal (Scheme **2h**).[104–113]

2.2 Carbo/hydropalladation of vinyl cyclopropanes

One way to cleave the cyclopropyl bond is, as already discussed above, the placement of palladium at the α-cyclopropyl position which will trigger the β-carbon elimination. Marek and co-workers demonstrated this concept impressively in 2018, where they could show that by subjecting cyclopropane **43** bearing a terminal olefin to Heck-arylation conditions they were able to trigger the ring opening to obtain arylation products **44** and **45**, respectively (Scheme **3a**). The reaction was then terminated by oxidizing the alcohol moiety to its corresponding aldehyde by β-hydride elimination.[114] Noteworthy, this strategy does not strictly require the use of vinylcyclopropanes as the Pd will undergo chain-walking along the alkyl tail to eventually reach the α-cyclopropyl position.[33] In the same year, the group also published a similar approach using oxidative Heck conditions for the stereoselective synthesis of unsaturated acyclic molecules bearing up to four stereocenters.[35]



Scheme 3. Carbo/hydropalladation of vinylcyclopropanes - literature examples.

Furthermore, is was shown that it is also feasible to increase the distance between cyclopropyl group and alcohol as the Pd will undergo further chain-walking after the β-carbon elimination.[34]

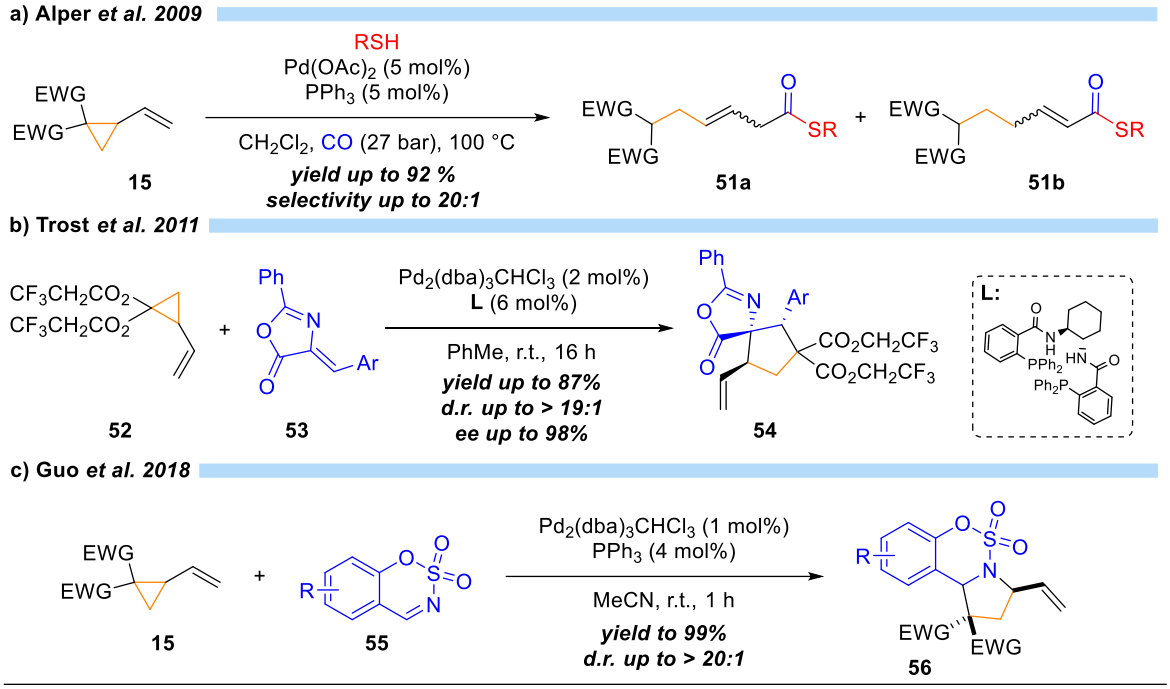
The same concept is also applicable when using hydropalladations instead of carbopalladations. Early reports date back to 1988 when Aida and co-workers demonstrated cyclopropyl bond cleavage by reacting vinylcyclopropane **46** with *in situ* generated Pd-H species which adds to the Michael system and triggers the cleavage of the exocyclic bond (Scheme **3b**).[37] Recently, Gong *et al.* showcased this method by combining transition metal catalysis, enamine catalysis and chiral Brønsted acid catalysis at once. The initial step for this triple-catalysis is the addition of a palladium hydride complex to alkynyl cyclopropane **48** which shows similar reactivity to vinylcyclopropanes by undergoing a β-carbon elimination. The resulting organopalladium intermediate then reacts further with the *in situ* generated enamine while the stereochemistry is controlled by both a chiral phosphine ligand on the Pd as well as the chiral Brønsted acid to give **50** in good yields and enantiomeric excess (Scheme **3c**).[36]

2.3 Vinyl cyclopropyl-di(EWG) as synthons for (η^3-allyl)-Pd-complexes

Compared to regular vinylcyclopropanes, vinyl cyclopropanes bearing two electron withdrawing groups on the same carbon open up new catalytic possibilities. Upon Pd-catalysis these substrates act as synthons for the formation of (η^3-allyl)-Pd-complexes which, depending on the reaction partner, offer various types of reactions. For instance, Alper and co-workers demonstrated in 2009 that in the presence of a thiol and carbon monoxide the resulting (η^3-allyl)-Pd-complex can undergo thiocarbonylations to give thioesters **51** in excellent yields and with strong selectivities (Scheme **4a**).[39]

In 2011, the group of Barry Trost showed that these highly reactive intermediates can also undergo [3+2] cycloadditions when appropriate olefins are offered in the reactions. In their report, alkylidene azalactones **53** underwent the cycloaddition to construct highly complex spiro products **54** with overall good diastereoselectivity. Additionally, employing a chiral phosphine ligand in the reaction rendered this process enantioselective yielding the desired products in excellent enantiomeric excess (Scheme **4b**).[55] Likewise, applying this principle to the [3+2] hetero-cycloaddition between vinylcyclopropanes **15** and sulfamate-derived cyclic imines **55** allowed for the facile constructions of poly-substituted pyrrolidines. (Scheme **4c**).[40] In 2008, Johnson also showcased that upon reacting **15** with carbonyl containing substrates it is also possible to access highly substituted spiro-tetrahydrofurans.[44] Later in

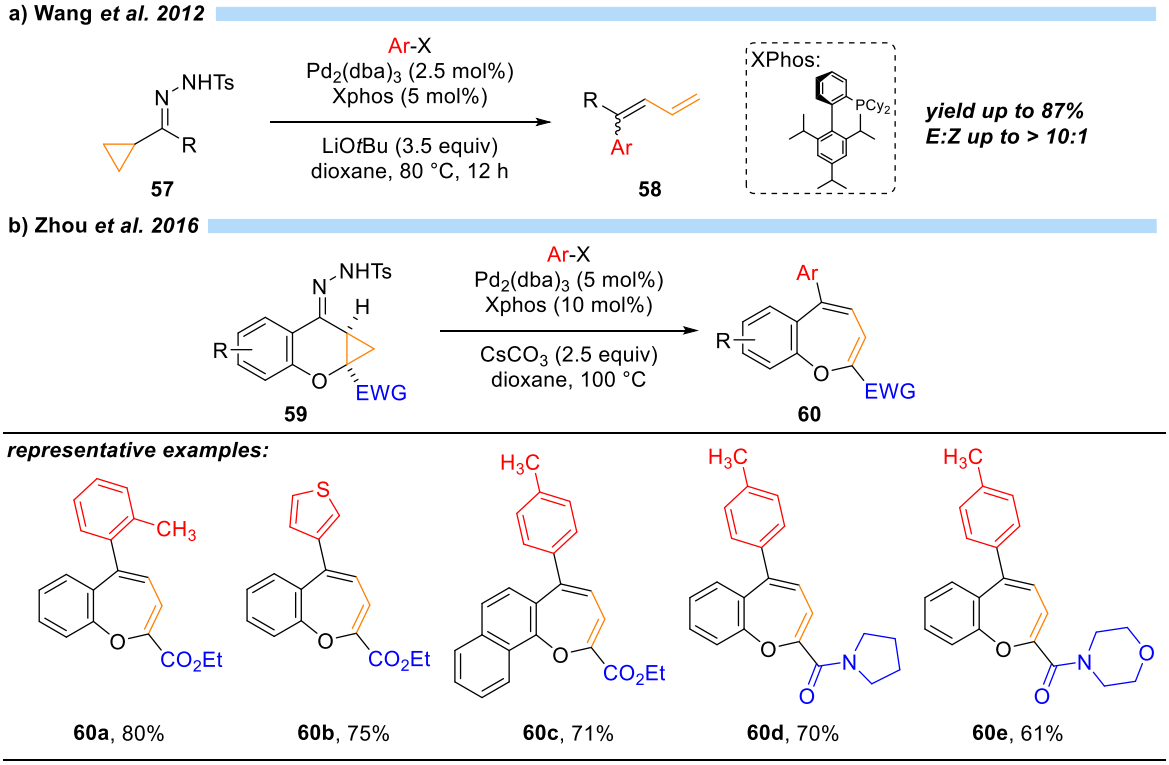
2013, Shi rendered this process enantioselective by employing chiral imidazole phosphine ligands.[45]



Scheme 4. Vinyl cyclopropyl-di(EWG) as synthons for (η3-allyl)-Pd-complexes - literature examples.

2.4 Cyclopropyl hydrazones cross-couplings

Tosylhydrazones have been widely established in palladium-catalyzed cross-coupling reactions.[67] Upon deprotonation with strong bases, these compounds tend to form carbene intermediates which can react with preformed aryl-palladium species. After Wolff-rearrangement, the palladium sits in its designated α-cyclopropyl position from which it can trigger the β-carbon elimination. The first report of a Pd-catalyzed ring opening of cyclopropanes using tosylhydrazones was published by Wang *et al.* in 2012 where the reaction between **57** and aryl halides afforded diaryl butadienes in good yields. However, the reaction suffered from poor *E*:*Z* selectivity (Scheme **5a**).[65] In 2016, Zhou and co-workers circumvent these selectivity issues by employing **59** being obtained from the corresponding cyclopropanated chromanones in cross-couplings. Interestingly, these substrates tend to undergo an endocyclic cyclopropane cleavage granting regiospecifically access to the ring-expanded benzoxepines **59**.[66] Further literature examples for this particular approach for the ring opening of cyclopropanes remain to be seen (Scheme **5b**).

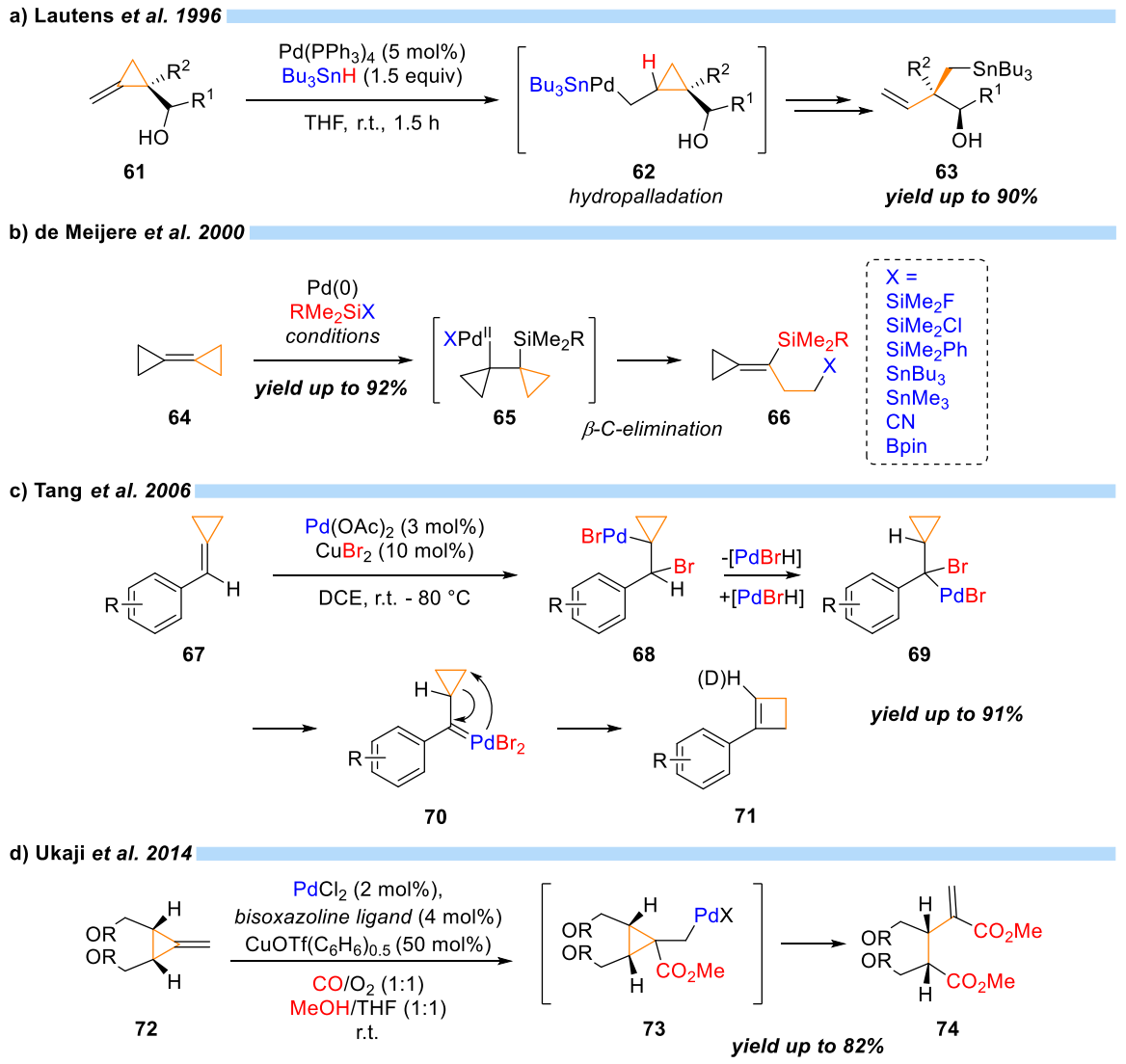


Scheme 5. Cyclopropyl hydrazones cross-couplings - literature examples.

2.5 Element-palladation of alkylidene cyclopropanes

Another possibility to induce ring-cleavage *via* β-carbon elimination is the use alkylidene cyclopropanes. Similarly to vinylcyclopropanes, the palladium can be placed at the α-cyclopropyl position upon carbopalladation or in general elementpalladation, respectively. An early report of Lautens *et al.* in 1996 describes the hydrostannation of methylenecyclopropanes. After the transmetallation between tributyltin hydride and Pd(0), a palladium hydride species is generated which undergoes hydropalladation onto the substrate **61** (Scheme **6a**). The resulting intermediate **62** having the Pd-$SnBu_3$ complex at the α-cyclopropyl position triggers the β-carbon elimination and terminates the reaction *via* reductive elimination to furnish **63**. Applying threefold excess of tributyltin hydride in the reaction promotes an additional hydrostannation of the generated product.[73]

In the year 2000, de Meijere and co-workers reported an intriguing approach using symmetric bicyclopropylidenes **64** in palladium-catalyzed additions of disilanes, silylstannanes, silylboranes and silylcyanides (Scheme **6b**). Upon addition, one of the cyclopropyl rings was cleaved and the reaction was terminated by a reductive elimination to afford functionally substituted methylenecyclopropanes **66**.[69]

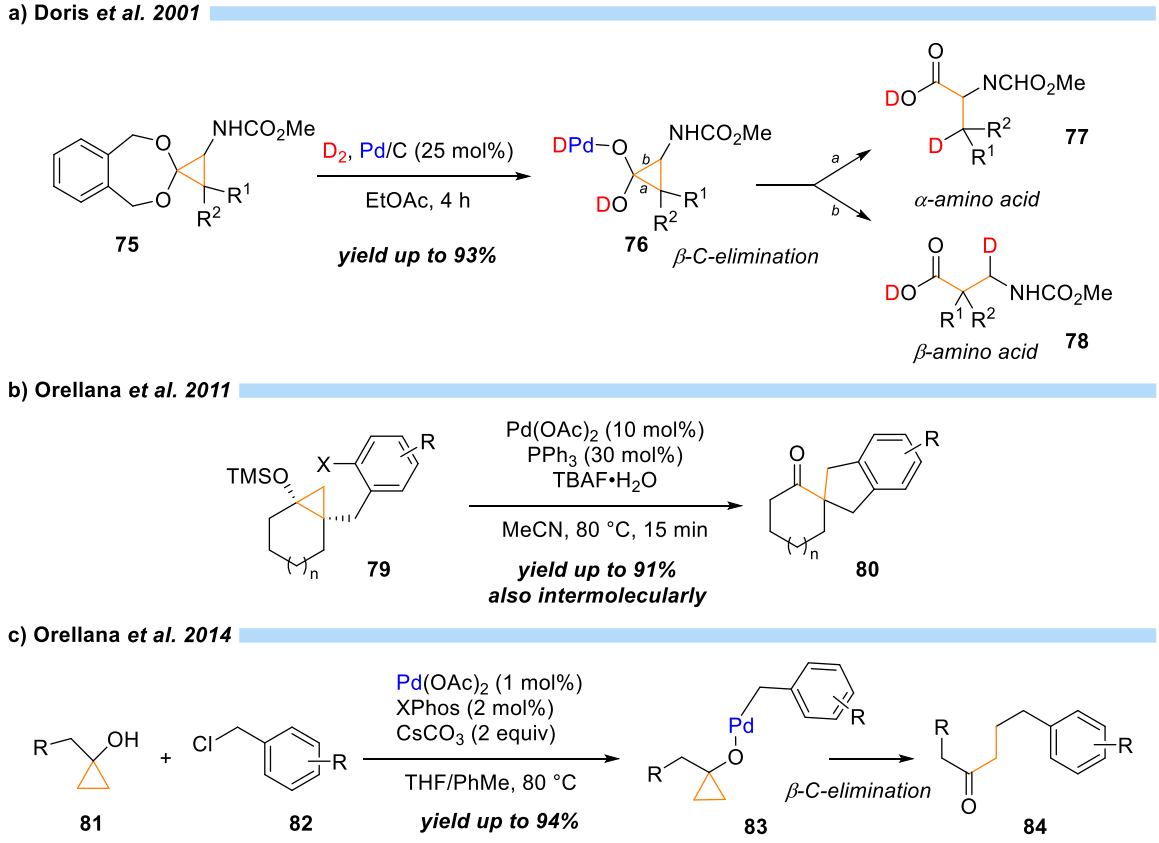


Scheme 6. Elementpalladation of alkylidene cyclopropanes – literature examples.

In 2006, Tang published a protocol for the selective ring enlargement of aryl-substituted methylenecyclopropanes **67** (Scheme **6c**). Here, the *in situ* generated $PdBr_2$ initially adds to the double bond with "wrong" regioselectivity". After β-hydride elimination and subsequent re-addition, intermediate **69** rearranges to give carbenoid intermediate **70** which triggers the β-carbon elimination to eventually yield cyclobutene **71**. This proposed mechanism was also supported by labelled deuterium experiments.[72] Lastly, Ukaji *et al.* showcased this approach by desymmetrization of meso-methylenecyclopropane **72** under copper co-catalysis. In this attempt, the ring opening was achieved by bisalkoxycarbonylation to yield diester **74**. However, enantioselectivity remained poor regardless of the employed bisoxazoline ligands (Scheme **6d**).[68]

2.6 Palladium-catalyzed ring opening of cyclopropanols

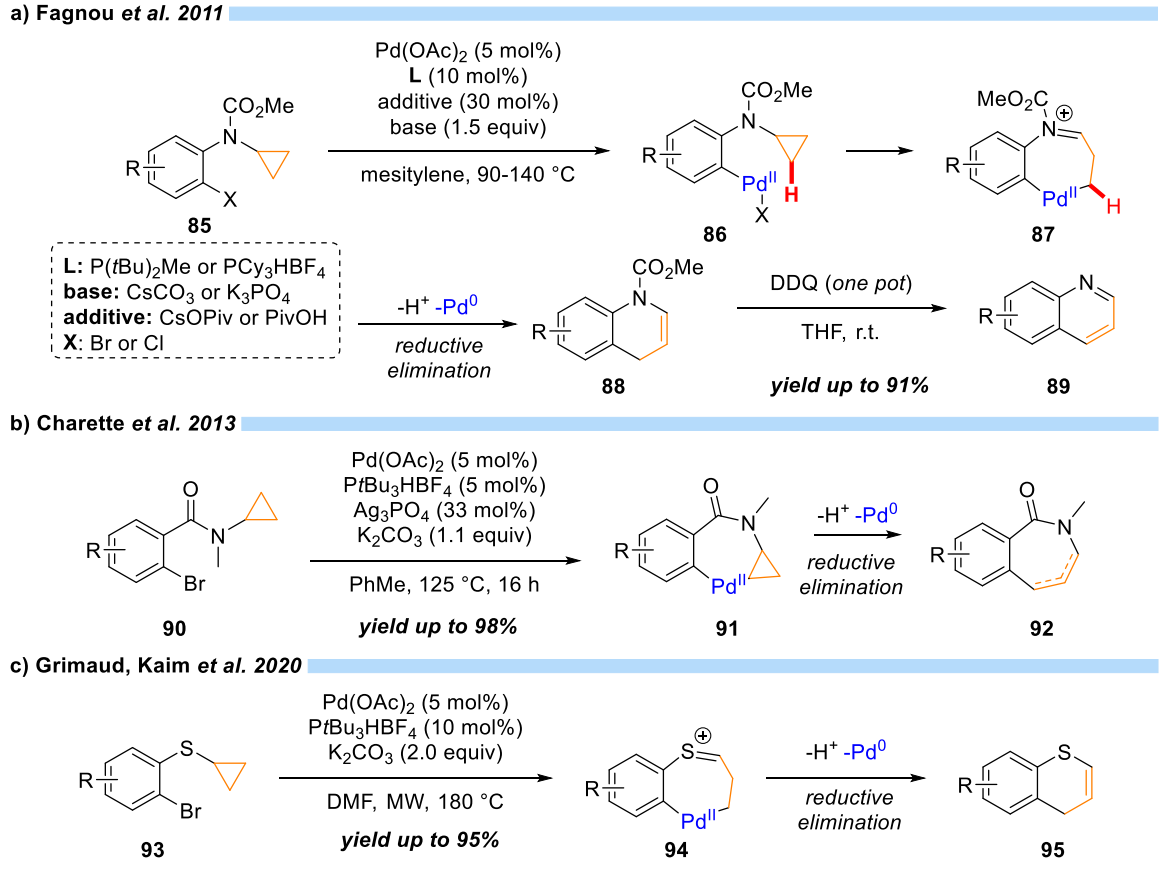
The principle of cyclopropyl ring cleavage in general follows the previous discussed approaches. Upon coordination of palladium to the alcohol moiety, the resulting intermediate bears the palladium likewise on the α-cyclopropyl position from which the β-carbon elimination can occur. Additionally, the electron pushing nature of the oxygen atom supports the ring-opening process. Thus, cyclopropanols can also be regarded as synthons for homoenolates.[78] This principle was applied for the synthesis of deutero-labelled amino acids by ring cleavage of cyclopropandiols **75**. Upon deuteriogenolysis, both alcohols become deprotected to generate intermediate **76** from which β-carbon elimination is triggered. Depending on the selectivity of the ring cleavage, both α- and β-amino acids **77**/**78** are generated with this protocol (Scheme **7a**).[83] In 2011, Orellana and co-workers reported an intramolecular method for facile access to α-spiro ketones **80** from silyl protected cyclopropanols **79** in excellent yields (Scheme **7b**). When applied to intermolecular couplings, the this procedure grants access to α-benzyl cyclic ketones.[85] In 2014, the same group demonstrated that the palladium-catalyzed ring opening of cyclopropanols is also feasible with benzylation, not only arylation (Scheme **7c**).[84]



Scheme 7. Palladium-catalyzed ring opening of cyclopropanols - literature examples.

2.7 Ring expansion *via* C-H activation

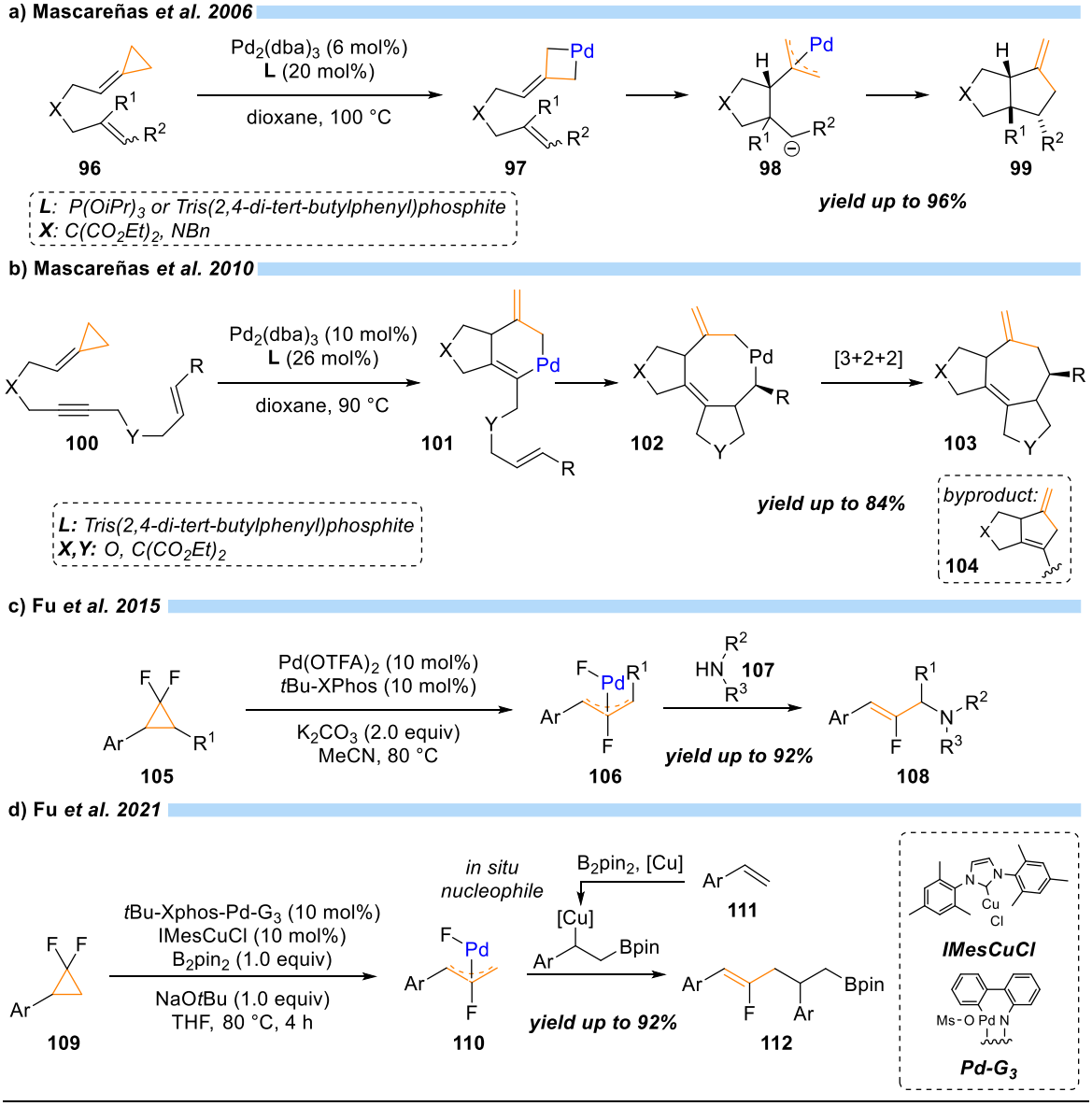
The ring cleavage of cyclopropanes can furthermore be indirectly achieved by C-H activation in certain cases. Fagnou and co-workers first demonstrated this idea in 2011 by reacting substrate **85** with an appropriate catalytic palladium system (Scheme **8a**). Initially, Pd is introduced into the substrate *via* oxidative addition into the C-X bond which locates the Pd closely to the cyclopropyl ring. Intermediate **86** then undergoes an intramolecular C(sp^3)-H insertion upon which the electron donating character of the heteroatoms enables an endocyclic ring opening to give intermediate **87**. Lastly the reaction is terminated by reductive elimination to afford dihydroquinoline **88** which can be oxidized to their corresponding quinolines **89** or alternatively reduced to tetrahydroquinolines.[88] In 2013, Charette showcased that this concept can also be utilized to synthesize larger ring systems like benzo[c]azepines **92** when the *N*-(cyclopropyl) moiety is not directly attached to the aryl ring but part of a benzoic amide (Scheme **8b**).[90] Recently, Grimaud and Kaim also extended this protocol for the synthesis of 4*H*-thiochromenes **95** (Scheme **8c**).[86]



Scheme 8. Ring expansion *via* C-H activation - literature examples.

2.8 Direct oxidative addition in cyclopropyl C-C bond

Under certain reaction conditions, it is also possible to achieve a direct oxidative addition into the cyclopropyl C-C bond which then triggers the ring fragmentation to generate highly reactive intermediates which can react further. An early report, where this concept was applied in a synthetically useful manner was describes by Mascareñas in 2006 where alk-5-enylidencyclopropanes **96** were reacted with a palladium catalyst coordinated to a suitable ligand (Scheme **9a**). After direct oxidative addition into the cyclopropyl C-C bond to **97**, the cyclopropyl ring fragmented upon formation of an (η^3-allyl)-Pd-complexes and annulation towards a five-membered cyclic intermediate **98**, which further cyclized with the generated carbanion in an allylic substitution reaction. Product **99** can also be described as the outcome of a formal intramolecular [3+2]-cycloaddition.[92]



Scheme 9. Direct oxidative addition in cyclopropyl C-C bond - literature examples.

In 2010, the group described the same reaction principle but extended the annulation cascade to a [3+2+2]-cycloaddition by offering a further C-C-π-bond which furnished fused 5-7-5 membered tricyclic ring systems **103** alongside small quantities of [3+2]-byproduct **104** in which the cascade sequence aborted after the first annulation in a reductive elimination of intermediate **101** (Scheme **9b**).[91]

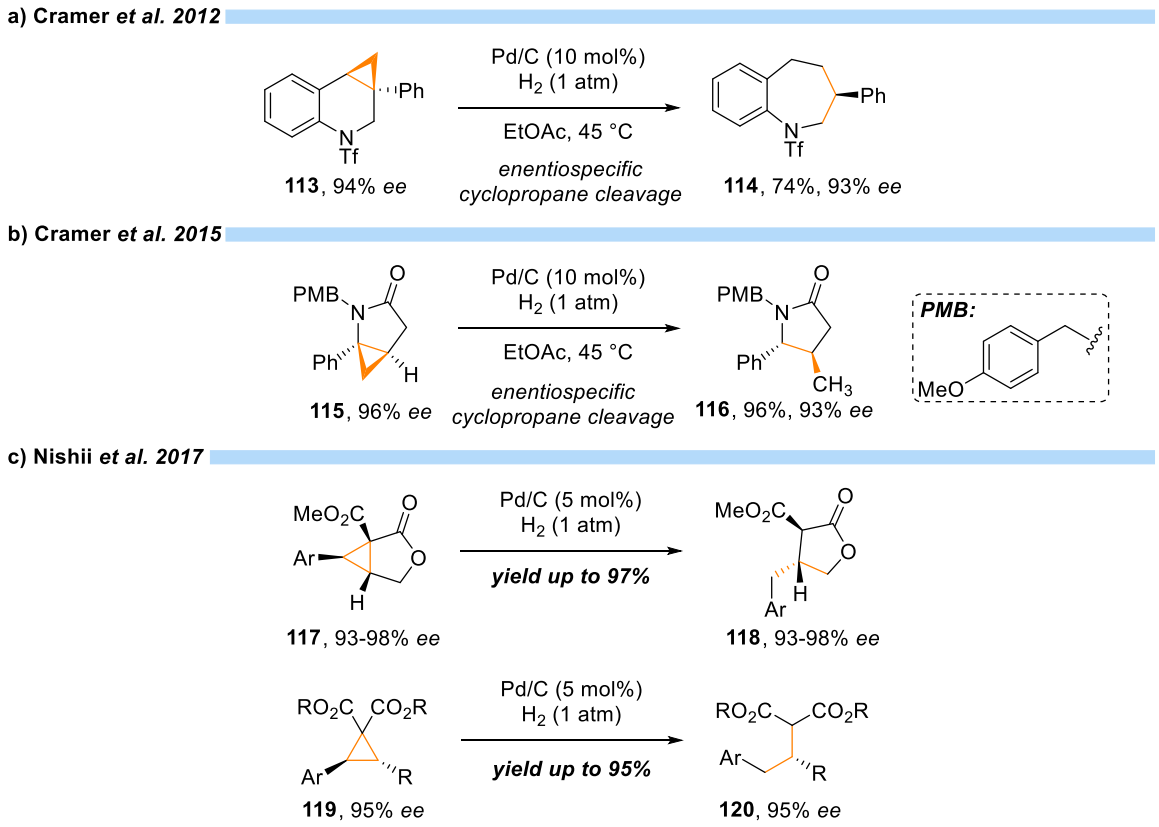
A different approach for the direct oxidative addition of palladium into the cyclopropyl C-C bond is the use of *gem*-difluorinated cyclopropanes **105** (Scheme **9c**). After the discovery of the chemoselective Pd-catalyzed C-F bond activation of allylic *gem*-difluorides,[115,116] the same reactivity was discovered for *gem*-difluorinated cyclopropanes by Yao Fu and co-workers in 2015. A direct oxidative addition into the C-C bond of **105** causes the ring-fragmentation and the formation of an (η^3-allyl)-Pd-F-complex that can be trapped by amines **107** in an allylic substitution to furnish allyl amines **108**.[100]

One example how this reactivity can be further applied was published by the same group in 2021 where they described a three-component reaction between *gem*-difluorinated cyclopropanes **109**, alkenes **111** and borane B_2pin_2. After activation of substrate **109**, the highly reactive organo-palladium intermediate **110** reacts with an *in situ* generated nucleophile under copper co-catalysis to give monofluoroalkenes **112** (Scheme **9d**).[103]

2.9 Hydrogenolysis of cyclopropanes

The simplest method to achieve the ring opening of cyclopropanes is by hydrogenation with palladium on charcoal since, according to the Walsh model,[117] σ-bonds in cyclopropanes can be viewed as π-bonds due to their low bonding angle of only 60° and the therefore resulting orbital geometry. However, this so-called *hydrogenolysis* is only feasible under some circumstances and selectivities cannot be generalized.

For instance, Nicolai Cramer and co-workers showcased a hydrogenolysis of cyclopropanes in 2012 as synthetic transformation for tetrahydroquinolines **113** which were obtained by C-H activation chemistry. Upon hydrogenation with Pd/C, they observed the cleavage of the endocyclic bond resulting in ring-enlargement to hexahydrobenzo[b]azocine **114** in 74% with nearly perfect preservation of the enantiomeric excess (Scheme **10a**).[109] In 2015, they showcased another synthetic application for cyclopropanated pyrrolidone **115** which was likewise synthesized *via* C-H activation. However, this time the enantiospecific cleavage of the exocyclic bond was observed to give lactam **116** (Scheme **10b**).[106]



Scheme 10. Hydrogenolysis of cyclopropanes - literature examples.

Furthermore, the hydrogenolysis of cyclopropanes was also impressively demonstrated by Nishii *et al.* in 2017 where the ring cleavage of donor-acceptor substituted cyclopropanes **117** and **119** was described (Scheme **10c**). In their report, the group was able to access β-benzyl-γ-butyrolactones **118** from cyclopropanated enantioenriched lactones **117** without epimerization of the stereocenters in excellent yields. Additionally, hydrogenolysis of cyclopropanated styrenes **119** gave γ-aryl-α,α-diester **120** in comparable yields. Likewise, the reactions did not suffer from epimerization of the stereocenters. In both reactions the activated bond between donor and acceptor was selectively cleaved.[105]

2.10 Conclusion

In this brief literature overview it has been shown that cyclopropanes are not only highly valuable structures in pharmaceuticals and bioactive compounds, but that this structural motive also offers a plethora of different synthetic transformations under transition metal catalysis. Especially palladium has proven itself to be a versatile player being capable of a broad range of various catalytic processes for the cleavage of highly strained cyclopropanes. In most cases, the reactivity of these substrates under transition metal catalysis can be attributed to the highly distorted orbital geometry causing the hybridization of the C-H/C-substituent bonds to rather show sp^2-character than sp^3-character.[117] In other words, the C-H/ C-substituent bonds contain higher s-proportion. In turn, the highly strained ring-C-C bonds have more p-character and thus behave like π-bonds.[1,118] The model of Förster[119] which was later refined by Coulson and Moffitt[120] even describe the bonding situation as an overlap of two sp^5-hybrid orbitals causing the C-C bonds to be highly bent outside of the C-C bond direction. Therefore, the reactivity the C-C bonds in cyclopropanes often resembles the reactivity of C=C bonds in olefins.[1]

3. References (Introduction)

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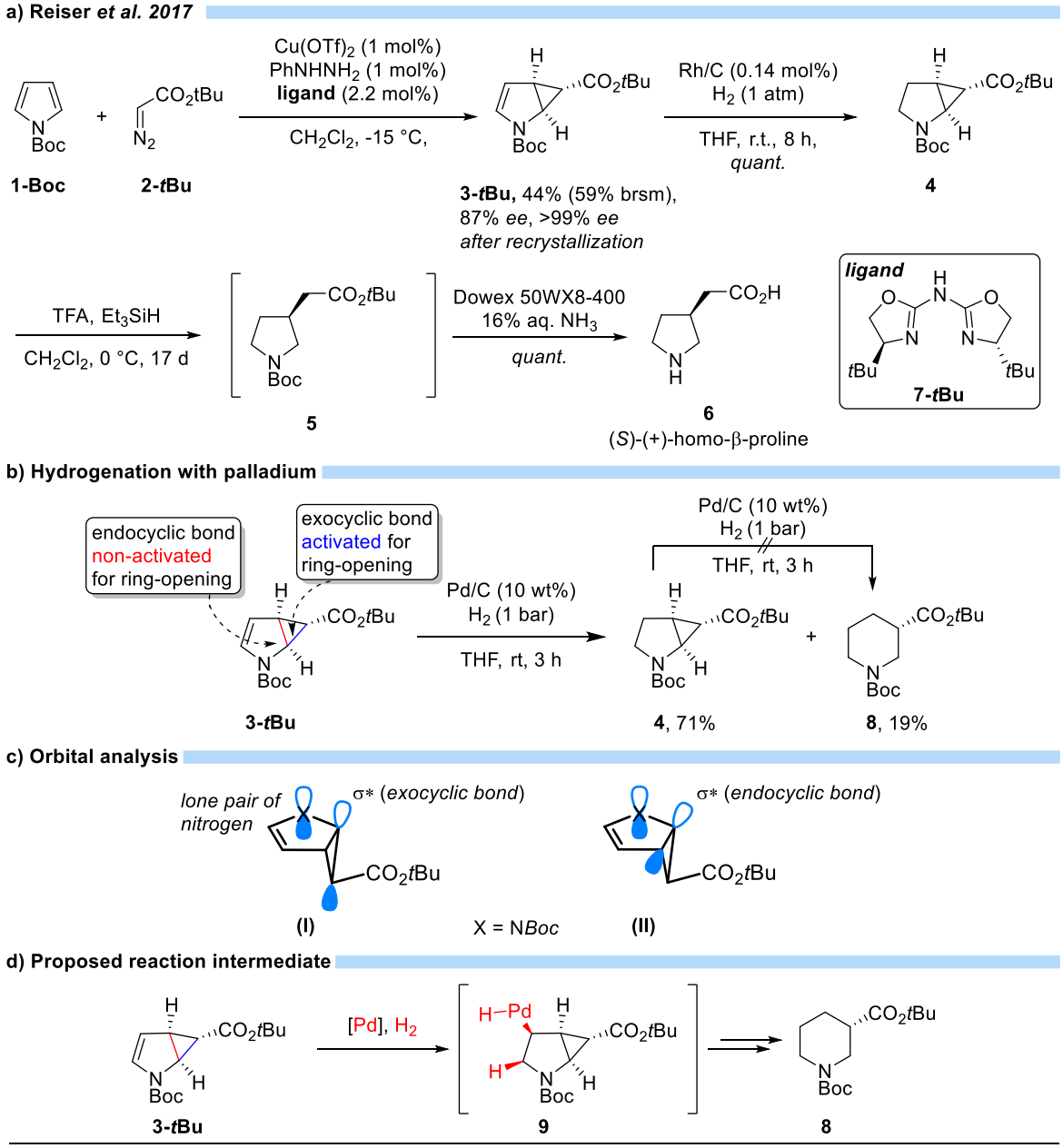
B. Main Part

1. Palladium-catalyzed ring opening of cyclopropanated furans

1.1 Introduction

1.1.1 Previous work on Pd-catalyzed ring openings of cyclopropanated heterocycles

In 2017, Reiser and co-workers reported the enantioselective synthesis of (*S*)-(+)-β-homo proline (**6**) from pyrrole **1**. The desymmetrizing enantio- and diastereoselective cyclopropanation was carried out using diazoacetate **2-*t*Bu** and a chiral Cu(I)-aza(bis)oxazoline (**7-*t*Bu**) catalyst which was generated *in situ* by reduction of Cu(II) to Cu(I) with phenyl hydrazine,

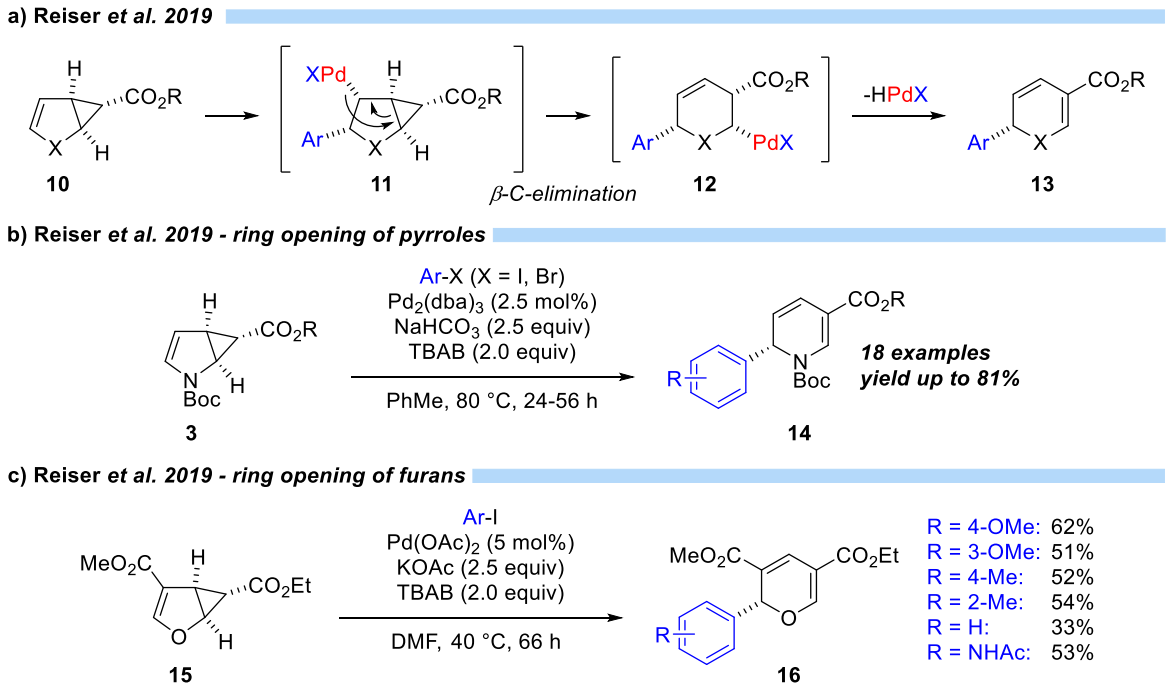


Scheme 11. Previous work: Synthesis of (*S*)-(+)-β-homo proline (**6**) by Reiser *et al.* (2017).

giving cyclopropanated pyrrole **3** in 44% yield (59% based on recovered starting material, brsm) and 87% *ee* (Scheme **11a**). After recrystallization to enantiopurity, **3** was hydrogenated to **4** to using 0.14 mol% of rhodium on charcoal and subsequently subjected to TFA/Et_3SiH to cleave the activated bond of the donor-acceptor cyclopropane. Finally, after treatment with an acidic ion-exchanger, **5** was fully deprotected and saponified to obtain (*S*)-(+)-β-homo proline (**6**) in an overall yield of 44% (59% brsm).[1]

Interestingly, when rhodium was replaced by pallium during the hydrogenation step, the unexpected generation of six-membered piperidine **8** as a by-product was additionally observed in 19% yield (Scheme **11b**).[2] However, resubjecting fully hydrogenated pyrrolidine **4** to reaction conditions resulted in no conversion, indicating that **8** was formed directly from **3**.

This unexpected ring-enlargement was surprising as a closer orbital analysis of **3** shows that the lone-pair of the heteroatom is actually in alignment with the σ*-orbital of the exocyclic bond, hence activating this bond (**I**, Scheme **11c**). This particular reactivity was taken advantage of for the transformation of **4** to **5**, where treatment with a Brønsted acid allowed the selective cleavage of the exocyclic bond. However, the endocyclic bond is not activated as the nitrogen lone-pair lies perpendicularly to the σ*-orbital of the C-C cyclopropane bond (**II**, Scheme **11c**). Thus, the endocyclic ring opening should not be allowed and the formation of **8** cannot take place from **4**.

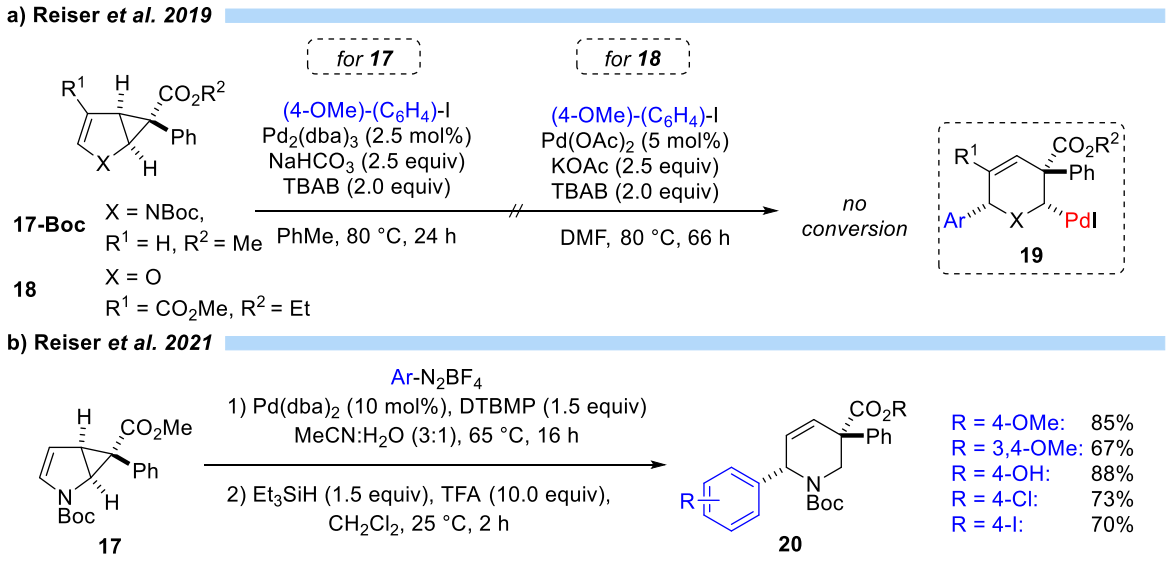


Scheme 12. Previous work: Palladium-catalyzed ring opening of cyclopropanated heterocycles by Reiser *et al.* (2019).

Therefore, a hydropalladium-intermediate **10** where the Pd sits on the α-cyclopropyl position was proposed that is responsible for the ring opening *via* β-carbon elimination (Scheme **11d**). Inspired by this experimental finding, Reiser then hypothesized that an organopalladium intermediate of type **9** being able to undergo ring opening by β-carbon-elimination could also be accessed by subjecting the cyclopropanated bicycle to Heck-arylation conditions (Scheme **12a**). After carbopalladation, the palladium would be placed at the α-cyclopropyl position which triggers a 1,3-migration upon ring expansion to give the analogous six-membered products. This concept was previously demonstrated by Marek and co-workers for acyclic substrates.[3–5]

Subjecting pyrrole **3** to Heck-arylation conditions allowed the facile access to arylated dihydropyridines **14** in good chemical yield. Noteworthy, when enantiopure starting material was employed in the reaction, a complete transfer of chirality was observed into the product, as the carbopalladation occurs preferably from the convex face of the bicyclic system (Scheme **12b**).

Analogously, cyclopropanated furan derivative **15** showed a similar reactivity, giving the corresponding arylated 2*H*-pyrans. Unfortunately, the substrate scope for this particular transformation turned out to be limited to electron donating substrates and yields did not exceed 62% (Scheme **12c**).[2]



Scheme 13. Previous work: Palladium-catalyzed ring opening of *gem*-disubstituted cyclopropanated heterocycles by Reiser *et al.*

Further limitations of this process became apparent when *gem*-disubstituted cyclopropanes, i.e. cyclopropanes with two substituents on the same carbon, of type **17** or **18** were employed in the ring-opening chemistry as these substrates showed no conversion. According to our

mechanistic proposal, this is due to the generation of intermediate **19** which usually terminates the reaction in a *trans*-β-hydride elimination. However, using *gem*-disubstituted cyclopropanes, no β-hydrogen is available for elimination, hence, disrupting the catalytic cycle (Scheme **13a**).[2]

In the case of pyrroles, this issue was later overcome by the use of aryl diazonium salts instead of aryl halides in combination with an aqueous solvent (Scheme **13b**). The palladium in intermediate **19** gets displaced by water to give rise to hemiaminals which were then reduced to the corresponding tetrahydropyridines **20** in a one pot reaction using Et_3SiH/TFA in excellent yields.[6]

1.1.2 Pyrans – a privileged class of heterocycles

Heterocycles represent one of the most abundant class of compounds which occur naturally. Additionally, many of these substances exhibit tremendous biological activity and are thus used as pharmaceuticals or precursors for drug design and development.[7–9] However, among various kinds of heterocyclic compounds, pyrans gained extraordinary interest for researchers since their subunit is ubiquitous in nature. These six-membered, oxygen-containing cyclic compounds can be found in several molecular scaffolds like benzopyrans, flavones, coumarins, xanthones and carbohydrates whatsoever. Moreover, these substance classes are of considerable importance as they represent the core structures in a variety of natural products like catechin (**21**) and anticancer medications with considerably high biological activity.[10]

Noteworthy exponents are for instance Epicalyxin F (**22**), an anti-tumor drug which exhibits vast antiproliferative activity against HT-1080 fibrosarcoma and colon 26-L5 carcinoma,[11] as well as GDC-0927 (**23**, Figure **2**).

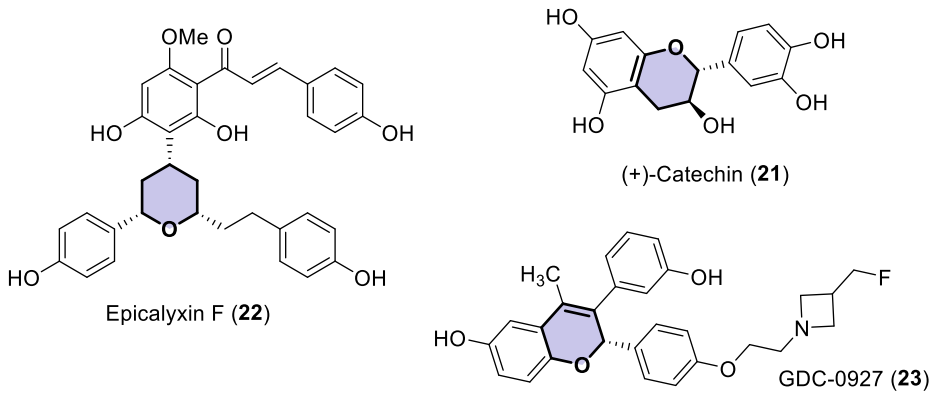


Figure 2. Biologically active pyrans.

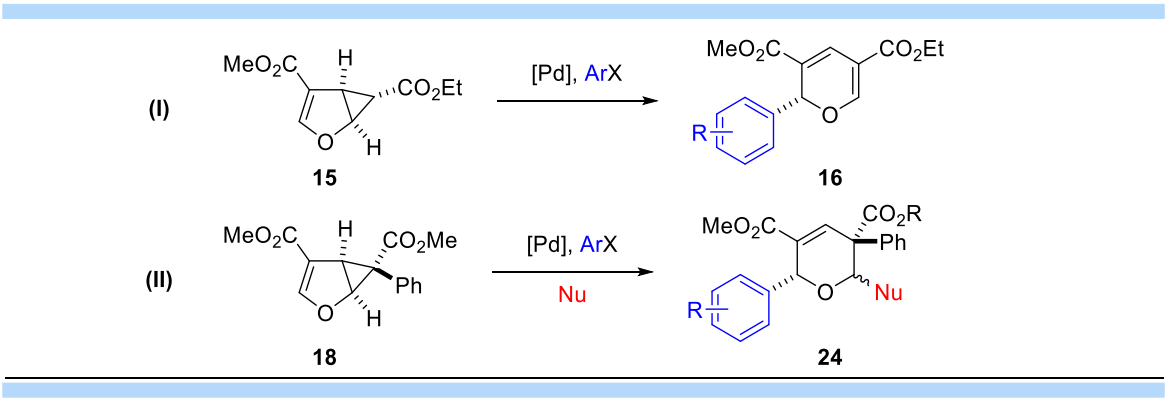
Latter one is a potent, selective estrogen receptor degrader and full antagonist which is currently in clinical trials for the treatment of breast cancer.[12] Since pyran based pharmaceuticals are a

very promising remedy for cancer being nowadays a primary cause of death in our society,[13] the development of novel synthetic pathways for a facile access to these desired heterocyclic structures is essential. The most common approaches for the synthesis of pyrans are hetero Diels-Alder reactions[14–16], electrocyclic reactions[17] and intermolecular as well as intramolecular condensations.[18–23] However, those reactions often lack stereocontrol which is urgently required for the synthesis of pharmacologically active substances.

1.1.3 Aim of this chapter

The aim of this chapter will be divided into two main objectives. First of all, the existing protocol for the synthesis of 2*H*-pyrans **16** from monocyclopropanated furans **15** should be improved towards higher yields, greater reaction efficiency and broader substrate scope that is not limited to electron donating substituents (eq. I, Scheme **14**).

Next, a protocol for the successful activation of *gem*-disubstituted cyclopropanated furans should be established. Therefor, suitable nucleophiles should be employed to displace the palladium in the former unreactive intermediate to close the catalytic cycle and to grant access to a library of differently substituted dihydro-2*H*-pyrans (eq. II, Scheme **14**).

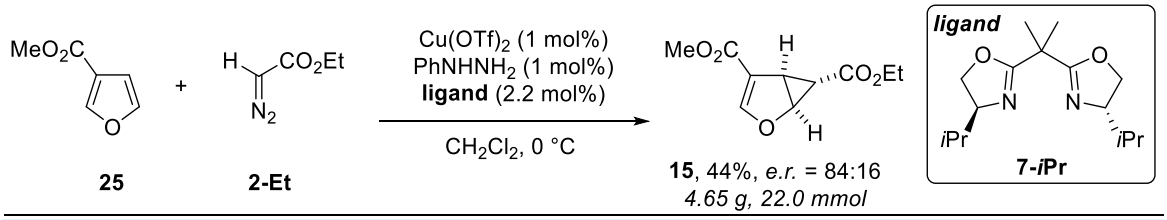


Scheme 14. Aim of this chapter.

1.2 Heck-Matsuda coupling conditions

1.2.1 Heck-Matsuda cross-coupling of monocyclopropanated furans

The Heck-Matsuda reaction is a well-established reaction in organic synthesis. The usage of highly reactive yet bench stable aryl diazonium salts as coupling partner offers an efficient alternative to the previously discovered Heck-Mizoroki-reaction which typically uses aryl halides. Further advantages for the use of tetrafluoro borate or hexafluoro phosphate aryl diazonium salts besides generally higher yields are the strongly decreased reaction times as well as the possibility to carry out reaction at room temperature. In many cases, degassing of the reaction mixture is not also necessary. Additionally, under certain circumstances, the cross-coupling reactions can be performed even base and ligand free.[24–26]

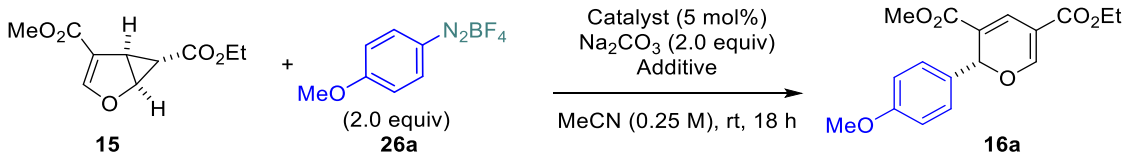


Scheme 15. Starting material synthesis.

For the starting material synthesis, furan 3-ester **25** was reacted with ethyl diazoacetate **2-Et** and an *in situ* generated Cu(I)-aza(bis)oxazoline (**7-*i*Pr**) catalyst by reduction of Cu(II) to Cu(I) with phenyl hydrazine, giving cyclopropanated furan **15** as a single diastereomer in 44% yield and an enantiomeric ratio of 84:16 (Scheme **15**).[27]

Having **15** in hand, a number of Pd-catalyzed screening reactions with 4-methoxybenzenediazonium tetrafluoroborate (**26a**) were then carried out in order to determine ideal reaction parameters for the synthesis of arylated 2*H*-pyrans **16** (Table **1**). First, various solvents were used in the reaction with both $Pd_2(dba)_3$ (dba = dibenzylideneacetone) as a Pd(0) precursor and $Pd(OAc)_2$ as a Pd(II) precursor. While methanol, dimethylformamide (DMF) and tetrahydrofuran (THF) turned out to be unsuitable for the desired transformation, acetonitrile (MeCN) gave with both catalysts yields in the range of 21-28% (entries 1-8, Table **1**). Having identified MeCN as an appropriate solvent, other palladium catalyst precursors were studied in the aforementioned reaction. Among the investigated palladium sources $PdCl_2$, palladium(II) acetylacetonate $Pd(C_5H_7O_2)_2$, $[Pd(MeCN)_2]Cl_2$ and palladium(II) trifluoroacetate $Pd(CF_3CO_2)_2$ showed the latter the highest performance giving the desired product in 38% yield (entries 9-12, Table **1**).

Table 1. Screening of reaction parameters for the Pd-catalyzed Heck-Matsuda coupling of **15**.



#	Catalyst	Comment	NMR Yield
1	$Pd_2(dba)_3$	MeOH as solvent	-
2	$Pd_2(dba)_3$	-	21%
3	$Pd_2(dba)_3$	DMF as solvent, no conversion	-
4	$Pd_2(dba)_3$	THF as solvent	traces
5	$Pd(OAc)_2$	MeOH as solvent, no conversion	-
6	$Pd(OAc)_2$	-	28%
7	$Pd(OAc)_2$	DMF as solvent	traces
8	$Pd(OAc)_2$	THF as solvent	4%
9	$PdCl_2$	-	28%
10	$Pd(C_5H_7O_2)_2$	-	30%
11	$[Pd(MeCN)_2]Cl_2$	-	25%
12	$Pd(CF_3CO_2)_2$	-	37%
13	$Pd(CF_3CO_2)_2$	TBAHS (2 equiv)	29%
14	$Pd(CF_3CO_2)_2$	NaOAc as base	32%
15	$Pd(CF_3CO_2)_2$	NaOAc as base + TBAHS (2 equiv)	28%
16	$Pd(CF_3CO_2)_2$	KOAc as base, no conversion	-
17	$Pd(CF_3CO_2)_2$	T = 45 °C	22%
18	$Pd(CF_3CO_2)_2$	MeCN/H_2O (5/1) as solvent, no conversion	-
19	$Pd(CF_3CO_2)_2$	stepwise addition of **26a** (1 equiv + 1 equiv after 30min)	43%
20	$Pd(CF_3CO_2)_2$	stepwise addition of **26a** (3 x 1 equiv after 30min each)	37%
21	$Pd(CF_3CO_2)_2$	10 mol% catalyst, stepwise addition of **26a** (1 equiv + 1 equiv after 30min)	50%
22	$Pd(CF_3CO_2)_2$	10 mol% catalyst, stepwise addition of **26a** (3 x 1 equiv after 30min each)	47%
23	$Pd(CF_3CO_2)_2$	1.5 equiv **15**, 1.0 equiv **26a**	50%
24	$Pd(CF_3CO_2)_2$	2.0 equiv **15**, 1.0 equiv **26a**	45%
25	$Pd(CF_3CO_2)_2$	1.5 equiv **15**, 1.0 equiv **26a**, 10 mol% catalyst	58%

26	$Pd(CF_3CO_2)_2$	2.0 equiv **15**, 1.0 equiv **26a**,10 mol% catalyst	60%
27	$Pd(CF_3CO_2)_2$	5 equiv. **26a**, 5 mol% catalyst	38%
28	$Pd(CF_3CO_2)_2$	5 equiv **26a**, 10 mol% catalyst	44%
29	$Pd(CF_3CO_2)_2$	5 equiv. **26a**, 5 mol% catalyst , stepwise addition of **26a** (first 3 equiv of **26a** and 2.5 mol% catalyst, then rest after 30 min)	35%
30	$Pd(CF_3CO_2)_2$	5 equiv **26a**, 10 mol% catalyst, stepwise addition of **26a** (first 3 equiv of **26a** and 5 mol% catalyst, then rest after 30 min)	43%
31	**$Pd(CF_3CO_2)_2$**	1,5 equiv **15,** 10 mol% catalyst, stepwise addition of **26a** (3 x 0.33 equiv after 10 min each)	**63%**
32	$Pd(CF_3CO_2)_2$	2 equiv **15,** 10 mol% catalyst, stepwise addition of **26a** (3 x 0.33 equiv 10 min each)	62%
33	$Pd(CF_3CO_2)_2$	4 equiv of base 2.0 equiv **15**, 10 mol% catalyst	61%

All reactions were performed under N_2-atmosphere using degassed and dried solvents on a 0.3 mmol scale with respect to the limiting substrate. Yields were determined by crude ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard.

Next, different bases were screened. While default Na_2CO_3 with the addition of tetrabutylammonium hydrogen sulfate (TBAHS) led to a slight decrease in yield, similar performances were observed with sodium acetate and sodium acetate in combination with TBAHS. When KOAc was used as base, no conversion of **15** could be observed (entries 13-16, Table **1**). An increase in temperature to 45 °C led to decreased 22% yield indicating that higher temperatures most likely cause a more rapid decomposition of **26a** (entry 17, Table **1**). Noteworthy, the reaction does also not tolerate the addition of water which was indicated by a black palladium precipitate during the reaction (entry 18, Table **1**).

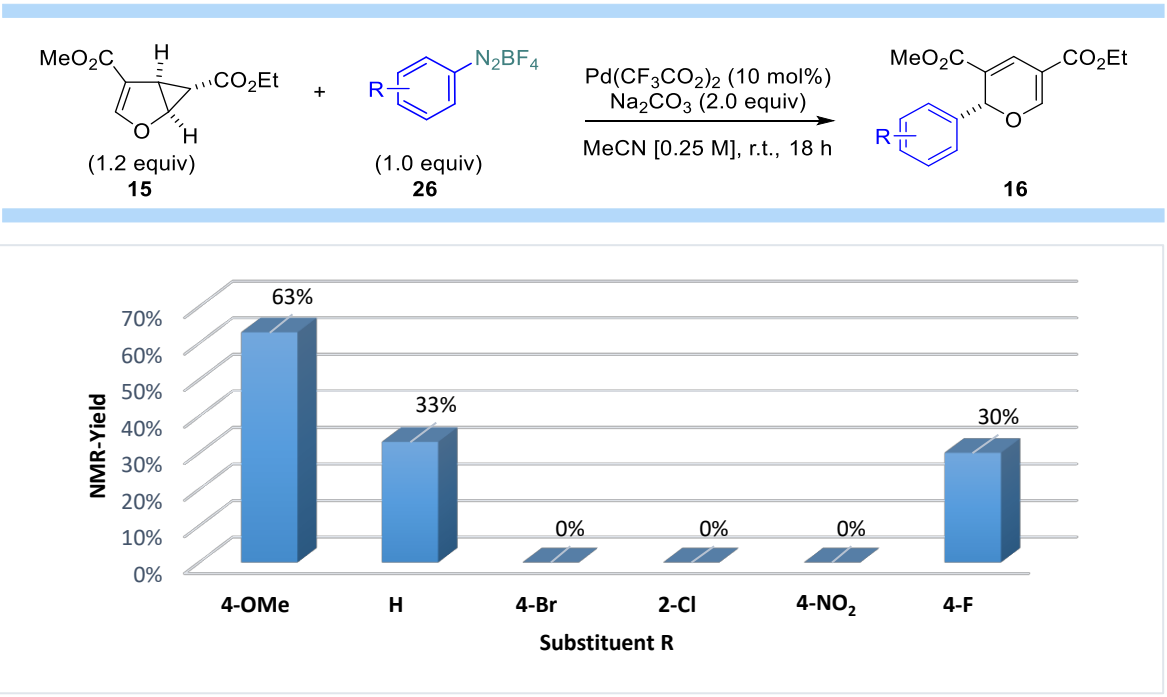
Since catalyst, base and solvent screening revealed $Pd(CF_3CO_2)_2$ in combination with Na_2CO_3 in acetonitrile as the most promising reagents for the desired transformation, an elaborate screening of several stoichiometric variations was then conducted.

A first success was achieved by adding **26a** in two 1-equivalent-portions as opposed to adding all at once giving **16a** in 43% yield. Increasing the amount of **26a** to three 1-equivalent-portions led to a slight decrease in yield (entries 19-20, Table **1**). However, repeating the same experiments with double catalyst loading of 10 mol%-Pd increased the yield further to 50% and 47%, respectively (entries 21-22, Table **1**).

Flipping the stoichiometry by offering excess **15** under regular addition of **26a** also allowed to increase the yield up to 50% (entries 23-24, Table **1**). When at the same time the catalyst

loading was increased to 10% mol%-Pd the yield could be boosted to 60% (entries 25-26, Table **1**). However, employing vast excess (5.0 equiv) of aryldiazonium salt **26a** caused a significant decrease in yield under various stoichiometric combinations (entries 27-30, Table **1**).

At this point, it was clear that the best results were achieved when furan **15** was used in excess for the cross-coupling reaction. When at the same time **26a** was again added stepwise in three 0.33-equivalent-portions the yield could be further increased to 63% (entries 31-32, Table **1**). Lastly, it was shown that doubling the amount of base used in the reaction had no significant influence on the product formation.



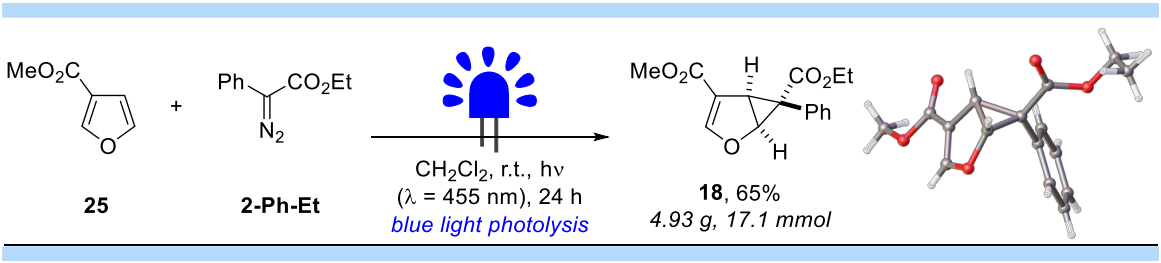
Scheme 16. Substrate scope for the synthesis of 2*H*-pyrans **16** under Heck-Matsuda reaction conditions. All reactions were performed on a 0.3 mmol scale using 1.2 equivalents of furan **15** for economical reasons. For R = 4-OMe 1.5 equivalents of **15** were used. Yields were determined by crude ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard.

Having found suitable reaction parameters, various aryl diazonium salts were then subjected to reaction conditions in order to test the robustness of the protocol (Scheme **16**). Switching from strongly electron donating *para*-methoxy substituent giving 63% yield to electronically neutral phenyl diazonium salt (R = H) led to a significant decrease in yield to 33%. Unfortunately, *para*-bromo (R = 4-Br), *ortho*-chloro (R = 2-Cl) and *para*-nitro (R = 4-NO_2) substituents caused the reaction to completely shut down giving no indication for any product formation. Lasty, electron withdrawing *para*-fluoro substituent (R = 4-F) furnished 30% yield of product.

Overall, it was shown that the Heck-Matsuda variant of the classic Heck reaction offers no improvement over the previously[2] established reaction conditions for the synthesis of 2*H*-pyrans **16** from monocyclopropanated furan **15**, as the substrate scope appeared to be even more limited.

1.2.2 Heck-Matsuda cross-coupling of *gem*-disubstituted cyclopropanated furans

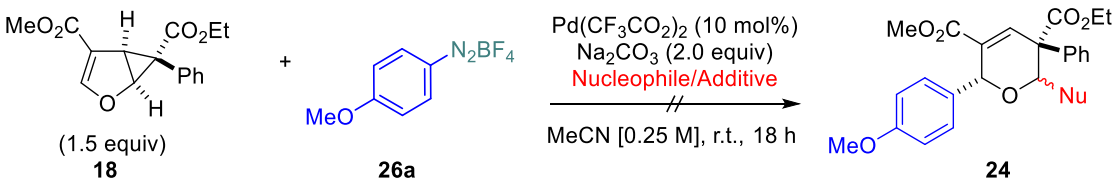
Even though the Heck-Matsuda conditions using aryl diazonium salts instead of aryl halides for the cross-coupling reaction of furans to their corresponding six-membered analogous did not provide any improvement over classic reaction conditions, the question remained whether this protocol allowed for the successful activation of *gem*-disubstituted cyclopropanated furans **18**.



Scheme 17. Starting material synthesis for *gem*-disubstituted cyclopropanated furan **18** and X-ray structure of **18**.

The starting material synthesis for this study was a straightforward cyclopropanation of furan 3-ester **25** with aryl diazoacetate **2-Ph-Et** under blue light irradiation. This protocol, developed by Huw M. L. Davies and co-workers in 2018,[28] enables the diastereoselective cyclopropanation of the heterocyclic substrate without the use of expensive and toxic transition metal catalysts *via* photolysis of the diazoester. Besides being catalyst-free, this protocol also tolerates the use of non-dried solvents and can be run open to air. As demonstrated for the synthesis of **18**, the cyclopropanation can also be carried out in large scale providing 4.93 g (17.1 mmol, 65%) of product (Scheme **17**). The relative stereochemistry was additionally confirmed by X-ray crystallography.

Table 2. Test reactions for the activation of *gem*-disubstituted cyclopropanated furan **18**.



Entry	Deviation from standard conditions	Additive (equiv)	Nu	NMR Yield
1	-	-	-	-
2	45 °C	-	-	-
3	-	HCO_2Na (1.5)	H	-
4	45 °C	HCO_2Na (1.5)	H	-
5	65 °C	HCO_2Na (1.5)	H	-
6	reflux	HCO_2Na (1.5)	H	-
7	-	H_2O (20)	OH	-
8	65 °C	H_2O (20)	OH	-
9	65 °C	HCO_2H (1.5)	H	-
10	65 °C no base,	HCO_2Na (1.5)	H	-
11	65 °C	$TBABF_4$ (2 equiv) HCO_2Na (1.5 equiv)	H	-
12	65 °C MeCN/DMF (1/1)	$TBABF_4$ (2 equiv) HCO_2Na (1.5 equiv)	H	-
13	65 °C DTBMP as base	$TBABF_4$ (2 equiv) HCO_2Na (1.5 equiv)	H	-
14	65 °C MeCN/DMF (1/1) DTBMP as base	$TBABF_4$ (2 equiv) HCO_2Na (1.5 equiv)	H	-

All reactions were carried out on a 0.3 mmol scale with respect to **26a**.

Having the necessary starting material in hand, we commenced our studies for the activation of substrate **18** under Heck-Matsuda conditions. In order to displace the Pd in the resulting organopalladium intermediate with an appropriate nucleophile, a reductive approach using formates was chosen. This strategy has been applied in literature numerous times whenever reactions are not able to terminate *via* the usual β-hydride elimination.[29–39]

Initially, no additives were added to the reaction to confirm that the default Heck-Matsuda protocol leads to no conversion of the starting material **18** at room temperature or elevated

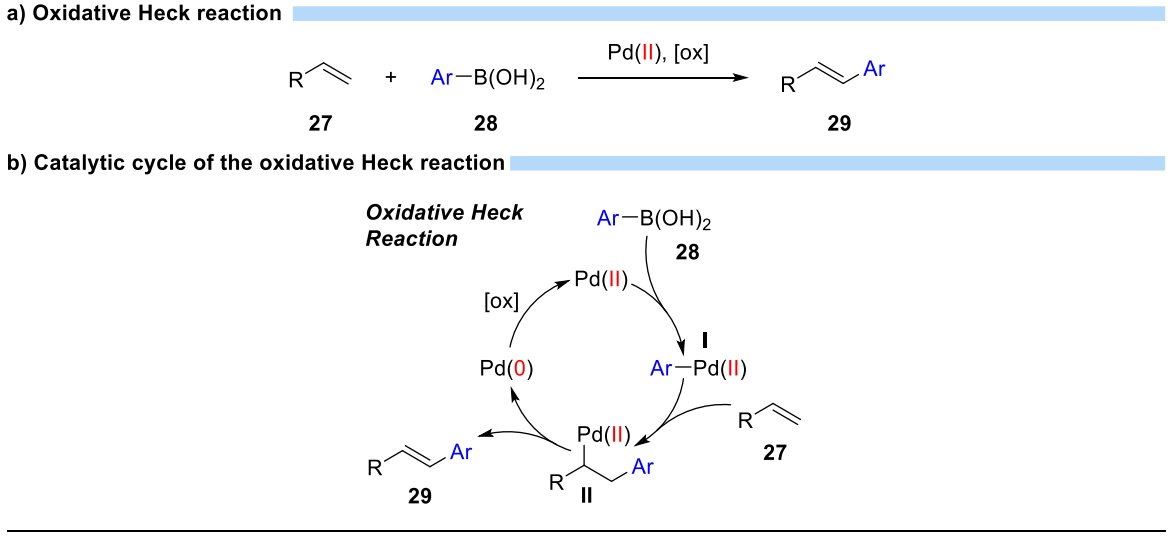
temperatures (entries 1-2, Table **2**). Unfortunately, the addition of 1.5 equivalents sodium formate to the reaction was also not able to deliver the desired product (entries 3-6, Table **2**). When instead of formates, water was offered as nucleophile, likewise no conversion was observed (entries 7-8, Table **2**). Also formic acid instead of sodium formate did not provide the desired transformation (entries 9-10, Table **2**). Lastly, in an attempt to avoid solubility issues, tetrabutylammonium tetrafluoroborate was added in combination with a more polar solvent mixture (MeCN/DMF, 1/1). Additionally, DTBMP (2,6-di-*tert*-butyl-4-methylpyridine) was used as a base. However, none of these conditions was able to provide the desired product.

As the Heck-Matsuda variant of the Heck-arylation was not able to improve the existing protocol[2] for the synthesis of 2*H*-pyrans **16** from monocyclopropanated furan **15** and was not able to activate *gem*-disubstituted furans **18** it was decided to cease further investigations even though aryl diazonium salts turned out to be potent coupling partners for the closely related cyclopropanated pyrroles.[6]

1.3 Oxidative Heck coupling conditions

1.3.1 Literature background

The oxidative Heck reaction, or often also referred to as the "boron-Heck reaction" is like the Heck-Matsuda arylation an alternative to the classic Mizoroki-Heck reaction. Instead of aryl halides, this reaction uses aryl boronic acids **28** as cross-coupling reagents (Scheme **18a**). Compared to the general catalytic Heck cycle, the oxidative Heck reaction starts with a transmetallation between a Pd(II)-precursor and the aryl boronic acid **28**. From here, it follows the usual catalytic pathway that is known for these types of reactions. After carbopalladation onto the olefin **27** to intermediate **II**, the palladium undergoes a *syn*-β-hydride elimination to furnish the desired arylated product **29** and Pd(0) which is then re-oxidized to Pd(II) with the help of an external oxidant to close the catalytic cycle (Scheme **18b**).[3,40–50]



Scheme 18. The oxidative Heck reaction - an overview. [ox] = oxidant.

The oxidative Heck reaction offers many advantages over the regular Heck reaction. While not requiring high temperatures as no oxidative addition into a carbon-halide bond takes place, this strategy gained lots of attention since also no bases are required in some cases as no acidic hydrogen halides are generated. Furthermore, besides being mild and efficient, this variant has also shown great functional group tolerance and is less sensitive to air or moisture.[40]

Another advantage of this halide-free protocol is the fact that no Pd-halide species are formed as intermediates during the catalytic cycle. Hence, is it more likely for this reaction to proceed *via* a cationic pathway rather than a neutral route. This feature makes this reaction highly attractive for enantioselective catalysis.[40,45]

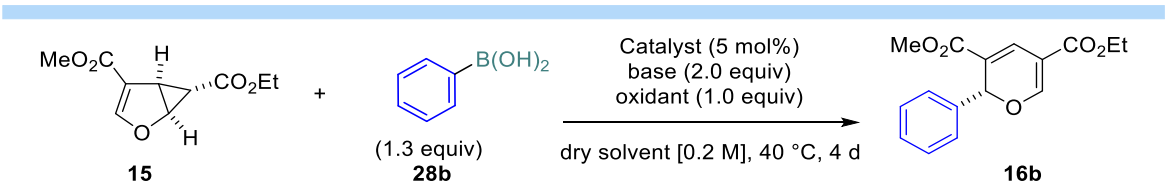
1.3.2 Oxidative Heck cross-coupling of monocyclopropanated furans

Having already synthesized the necessary starting material **15**, we started subjecting the substrate to reaction conditions using phenyl boronic acid **28b** as the model substrate in combination with $Pd(OAc)_2$ as the Pd(II) source and Na_2CO_3 as base. After many failed attempts with $Cu(OAc)_2$ as oxidant we decided to exchange it with $CuCl_2$ under N_2-atmosphere.

First, various solvents were examined (entries 1-9, Table **3**). Among different polar and non-polar solvents, the reaction performed best in THF giving **16b** in 21% NMR yield (entry 3, Table **3**).

After having identified the most suitable solvent for this transformation, several Pd(II)-sources were examined. Besides Pd(II)-acetylacetonate $Pd(C_5H_7O_2)_2$ which resulted in no conversion of furan **15**, all palladium catalysts showed similar reactivities (entries 10-15, Table **3**). Nonetheless, $[Pd(MeCN)_2]Cl_2$ marginally outperformed the other catalysts delivering 24% of product.

Table 3. Reaction optimization studies for the oxidative Heck reaction on **15**.



Entry	Catalyst (5 mol%)	Solvent	Oxidant	Base	Comment	Atm.	NMR Yield
1	$Pd(OAc)_2$	DMF	$CuCl_2$	Na_2CO_3	-	N_2	6%
2	$Pd(OAc)_2$	DMA	$CuCl_2$	Na_2CO_3	-	N_2	3%
3	$Pd(OAc)_2$	THF	$CuCl_2$	Na_2CO_3	-	N_2	21%
4	$Pd(OAc)_2$	PhMe	$CuCl_2$	Na_2CO_3	-	N_2	7%
5	$Pd(OAc)_2$	MeCN	$CuCl_2$	Na_2CO_3	-	N_2	4%
6	$Pd(OAc)_2$	Dioxane	$CuCl_2$	Na_2CO_3	-	N_2	12%
7	$Pd(OAc)_2$	Acetone	$CuCl_2$	Na_2CO_3	-	N_2	8%
8	$Pd(OAc)_2$	NMP	$CuCl_2$	Na_2CO_3	-	N_2	3%
9	$Pd(OAc)_2$	DMSO	$CuCl_2$	Na_2CO_3	-	N_2	-
10	$Pd(CF_3CO_2)_2$	THF	$CuCl_2$	Na_2CO_3	-	N_2	21%
11	$[Pd(PPh_3)_2]Cl_2$	THF	$CuCl_2$	Na_2CO_3	-	N_2	-
12	$[Pd(MeCN)_2]Cl_2$	THF	$CuCl_2$	Na_2CO_3	-	N_2	24%
13	$[Pd(PhCN)_2]Cl_2$	THF	$CuCl_2$	Na_2CO_3	-	N_2	23%

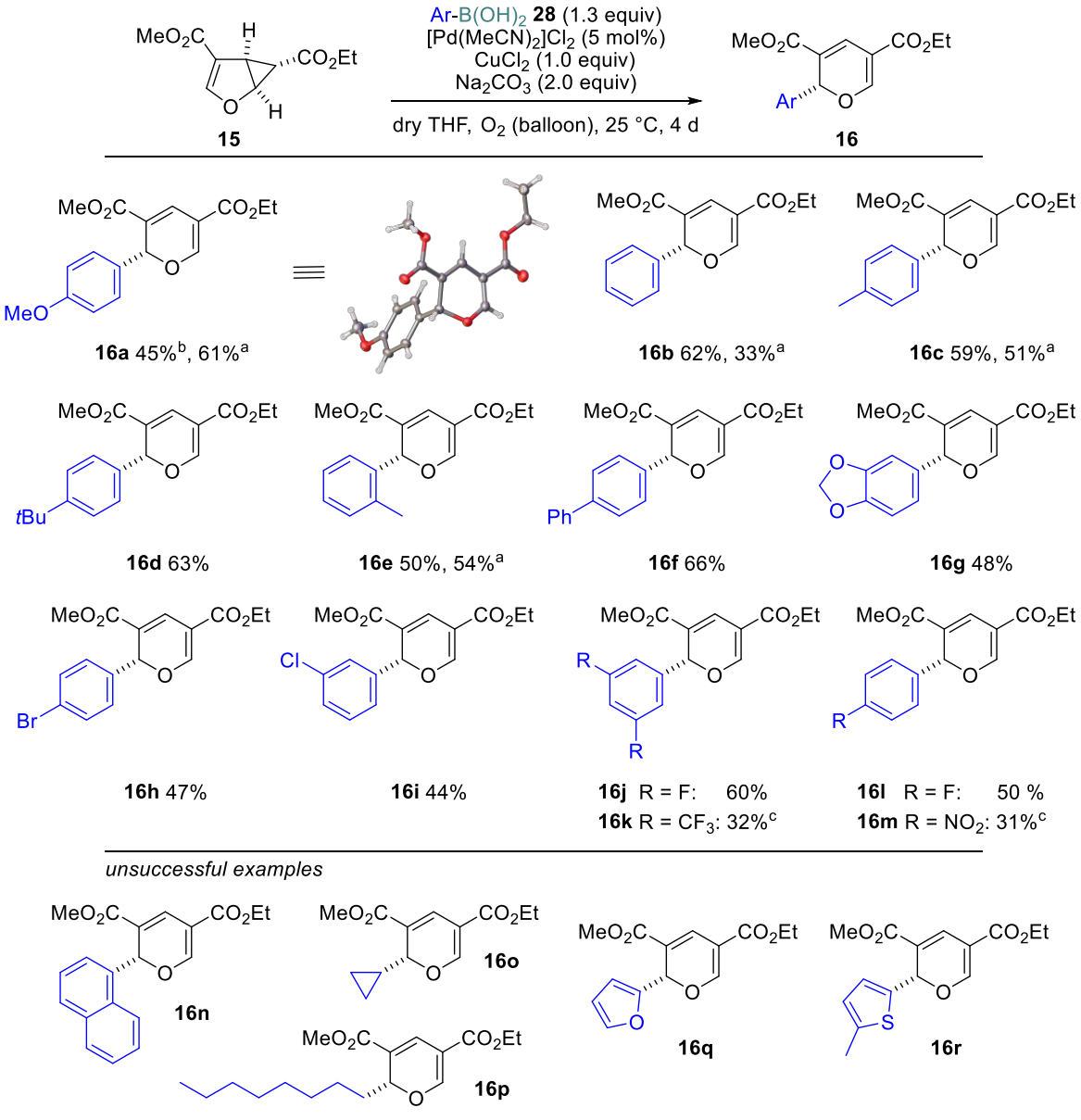
14	$Pd(C_5H_7O_2)_2$	THF	$CuCl_2$	Na_2CO_3	-	N_2	-
15	$PdCl_2$	THF	$CuCl_2$	Na_2CO_3	-	N_2	20%
16	$[Pd(MeCN)_2]Cl_2$	THF	$CuCl_2$	Na_2CO_3	-	O_2	44%
17	$[Pd(MeCN)_2]Cl_2$	THF	Ag_2CO_3	Na_2CO_3	-	N_2	-
18	$[Pd(MeCN)_2]Cl_2$	THF	$CuCl_2$	Na_2CO_3	TBAB (2 equiv)	O_2	-
19	$[Pd(MeCN)_2]Cl_2$	THF	$CuCl_2$	KOAc	-	O_2	-
20	$[Pd(MeCN)_2]Cl_2$	THF	$CuCl_2$	KOAc	TBAB (2 equiv)	O_2	-
21	$[Pd(MeCN)_2]Cl_2$	THF	$CuCl_2$	$NaHCO_3$	-	O_2	39%
22	$[Pd(MeCN)_2]Cl_2$	THF	$CuCl_2$	K_2CO_3	-	O_2	-
23	$[Pd(MeCN)_2]Cl_2$	THF	$CuCl_2$	K_2HPO_4	-	O_2	-
24	$[Pd(MeCN)_2]Cl_2$	THF	$CuCl_2$	-	-	O_2	-
25	$[Pd(MeCN)_2]Cl_2$	THF	$CuCl_2$	Na_2CO_3	c = 0.5 M	O_2	46%
26	$[Pd(MeCN)_2]Cl_2$	THF	$CuCl_2$	Na_2CO_3	c = 0.5 M 50 °C	O_2	39%
27	**$[Pd(MeCN)_2]Cl_2$**	**THF**	**$CuCl_2$**	**Na_2CO_3**	**c = 0.5 M r.t.**	**O_2**	**62% (isolated)**
28	$[Pd(MeCN)_2]Cl_2$	THF	$CuCl_2$	Na_2CO_3	H_2O (0.3 mL)	O_2	traces

Reactions performed on a 0.3 mmol scale with respect to **15**, Yields were determined by crude ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. Atm. = atmosphere.

When the reaction was performed in pure oxygen atmosphere (balloon, 1 atm.) instead of inert gas atmosphere, the yield could be almost doubled to 44% (entry 16, Table **3**). In return, Ag_2CO_3 failed to close the catalytic cycle resulting in no conversion (entry 17, Table **3**).

Next, a thorough screening of different bases was carried out. Curiously, none of the employed bases like KOAc, K_2CO_3, K_2HPO_3 or no base at all managed to generate any traces of the desired product. Also the combination of Na_2CO_3 with TBAB resulted in no conversion. Strangely, only Na_2CO_3 and $NaHCO_3$ furnished the desired product whereby the latter performed slightly worse (entries 18-24, Table **3**).

Lastly, it was discovered that an increase of the concentration from 0.2 to 0.5 mol/L and lowering the temperature from 40 °C to room temperature resulted in 62% product formation (entries 25-27, Table **3**). However, the addition of water to the reaction mixture was not tolerated resulting only in trace amounts of **16b**.



Scheme 19. Substrate scope for the synthesis of 2*H*-pyrans **16** from monocyclopropanated furan **15**. Reactions were carried out on a 0.5 mmol scale using 1 mL of solvent [0.5 M], all yields are isolated yields, [a]isolated yield under standard Heck conditions,[2] i.e. Aryl **iodide** (1.3 equiv), $Pd(OAc)_2$ (5 mol%), KOAc (2.5 equiv), TBAB (2.0 equiv), DMF, 40 °C, 66 h, [b]Reaction was stirred for 7 d, [c]isolated yields using 3.0 equiv of boronic acid in 3 mL of solvent.

Having found suitable reaction conditions for the synthesis of 2*H*-pyrans **16** from cyclopropanated furan **15** we then examined the behavior of variously substituted aryl boronic acids **28** in the catalytic process to synthesize a library of differently substituted 2-aryl-2*H*-pyrans **16** (Scheme **19**). Additionally, whenever possible the yields were compared with our previously obtained results.[2]

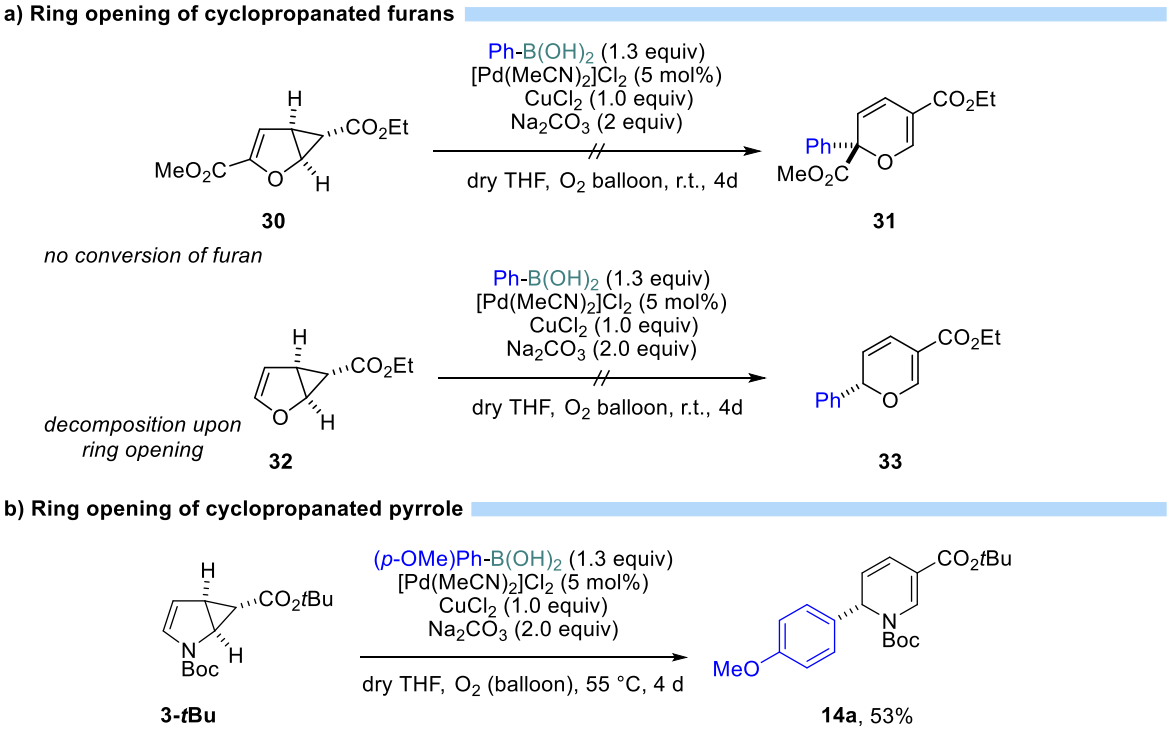
Starting off with electron donating *p*-methoxy phenylboronic acid **28a** we were able to detect 45% after a prolonged reaction time of seven days to ensure full conversion of the starting material. This result, however, is lower than the previously investigated 2*H*-pyran synthesis using aryl iodides providing 61% yield. Nonetheless, the structure of the product could be confirmed by X-ray crystallography. In turn, unsubstituted phenylboronic acid **28b** gave almost twice as much yield as the old protocol. For *p*-methyl phenylboronic acid **28c**, the new protocol offered only a slight improvement giving 59% isolated yield showing a similar performance as *p*-*tert*-butyl phenyl boronic acid **28** which provided the product in 63% yield.
When *ortho*-methyl substituted phenyl boronic acid was employed in the cross-coupling process, a similar reactivity to the old protocol was observed giving 50% yield.
Para-phenyl substituent delivering 66% of product **16f** showed the best performance among all tested aryl boronic acids while benzo[d]-[1,3]dioxole substituent gave similar results to *para*-methoxy phenylboronic acid **28a**. Switching to halide substituted aryl boronic acids, products **16h** and **16i** were obtained in 47% for *para*-bromo and 44% for *ortho*-chloro substitution, respectively.
Moving to electron withdrawing substituents, surprising 60% yield were observed with 3,5-difluoro substituents while increasing the electron withdrawing force to CF_3-groups with the same substitution pattern decreased the yield to 32%. A similar reactivity was observed with *para*-fluoro phenylboronic acid giving 50% yield of product **16l** while even stronger electron withdrawing *para*-nitro groups lowered the yield to 31%.
Lastly, in order test the limitations of this protocol, we started with extremely sterically demanding 2-naphthyl boronic acid which resulted in no conversion. Likewise, the reaction conditions were not able to activate alkyl boronic acids as well as heterocyclic boronic acids.

Overall, the newly developed oxidative Heck protocol offers an advantage over the previously established Heck protocol using aryl halides giving better yields, providing broader substrate variety as well as much cleaner reaction mixtures as the cross-couplings were carried out under extremely mild conditions. Additionally, inert gas atmosphere is no longer required as all reactions were performed under pure oxygen atmosphere.

To further test the versatility of this protocol we decided to subject other cyclopropanated furans to reaction conditions. Therefore, cyclopropanes **30** having the ester group at the 2-position[51] and furan **32** bearing no ester group[52] were prepared in a similar approach to cyclopropanated furan **15** (*cf.* Scheme **15**). Unfortunately, neither of the two furan derivatives yielded the desired pyran product **31** or **33**, respectively (Scheme **20a**). For furan **30**, the unreactivity may be attributed to an ambiguously polarized double bond. Compared to furan **15** having a strictly polarized double bond as part a Michael-system, moving the ester group to the 2-position may render this substrate unreactive under Heck-conditions. Likewise, steric repulsion between the ester and the phenyl group may be responsible for the observed inertia as they would be placed on the same carbon atom.

In the case of unsubstituted furan **32**, decomposition of the starting material was observed to give a mixture of various open-chained aldehydes. This reactivity has first been described by Ernest Wenkert and co-workers in 1990 who discovered that the presence of an ester group drastically enhances the stability of this substrate.[53]

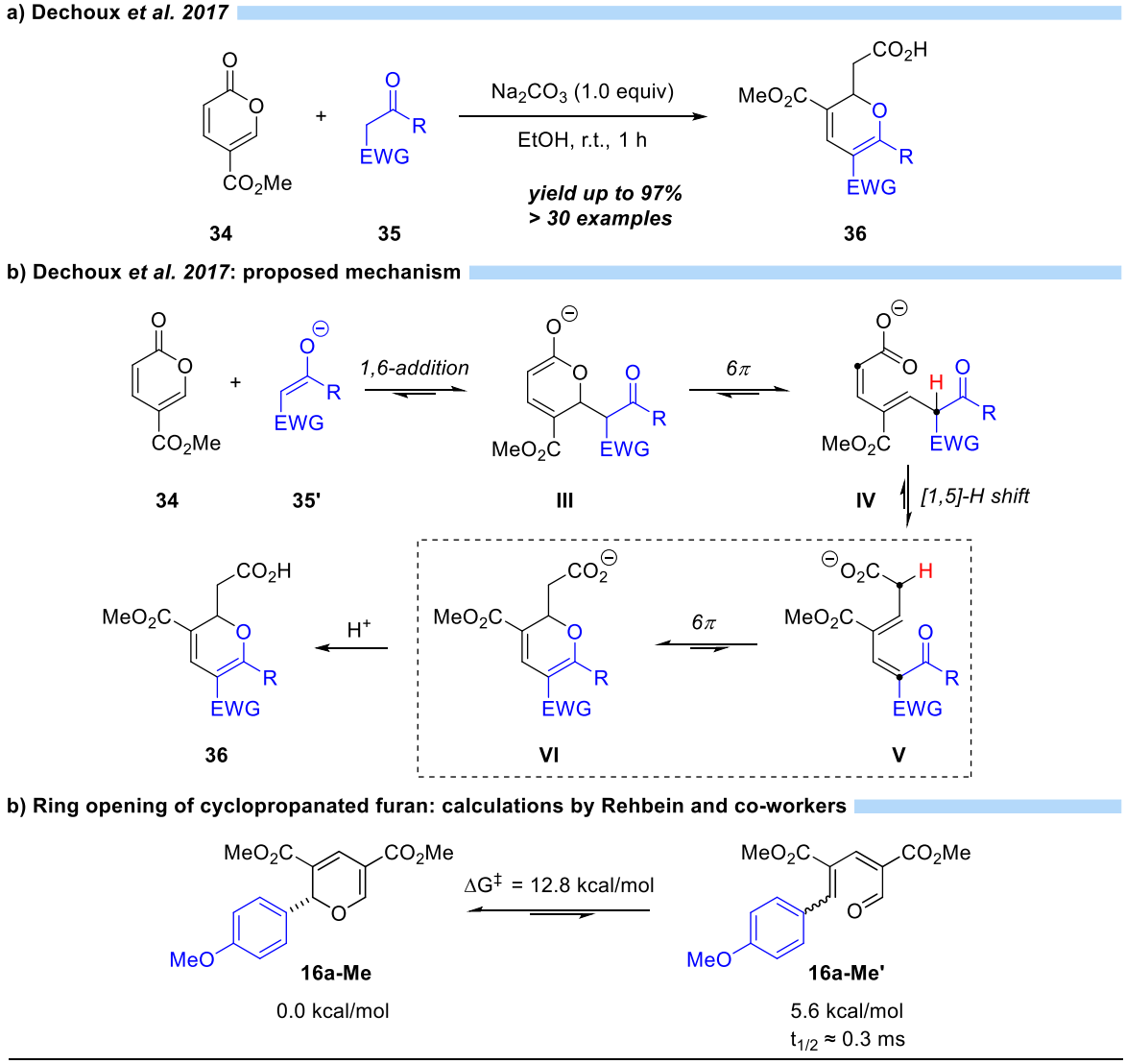
Cyclopropanated pyrrole **3-*t*Bu**, however, underwent the desired transformation to dihydropyridine **14a** in 53% yield under increased reaction temperature to ensure a better conversion of the staring material (Scheme **20b**).



Scheme 20. Ring-opening reactions of cyclopropanated furans and pyrrole.

Finally, the last issue that has yet to be investigated on was whether the formation of 2*H*-pyrans **16** from cyclopropanated furan **15** follows a transfer of chirality. As proven for the case of pyrroles by Reiser in 2019,[2] the reaction featured a clean transfer of chirality as the carbopalladation occurs preferably from the convex face of the strained bicyclic system (*cf.* Scheme **12b**).

As furan **15** was obtained in enantiomerically enriched form (e.r. = 86:14), we measured optical rotation for the obtained 2*H*-pyrans. Surprisingly, all substrates showed an optical rotation of $[\alpha]_D^{20} = 0\ °$, i.e. underwent complete racemization. A possible explanation for this observation might be given by the experimental findings of Dechoux *et al.* in 2017 (Scheme **21a**). In their report, they presented the synthesis of 2*H*-pyrans **36** from pyranones **34** and ketones **35**.



Scheme 21. Rational for the racemization of 2*H*-pyrans **16** based on literature by Dechoux *et at.* (2017).

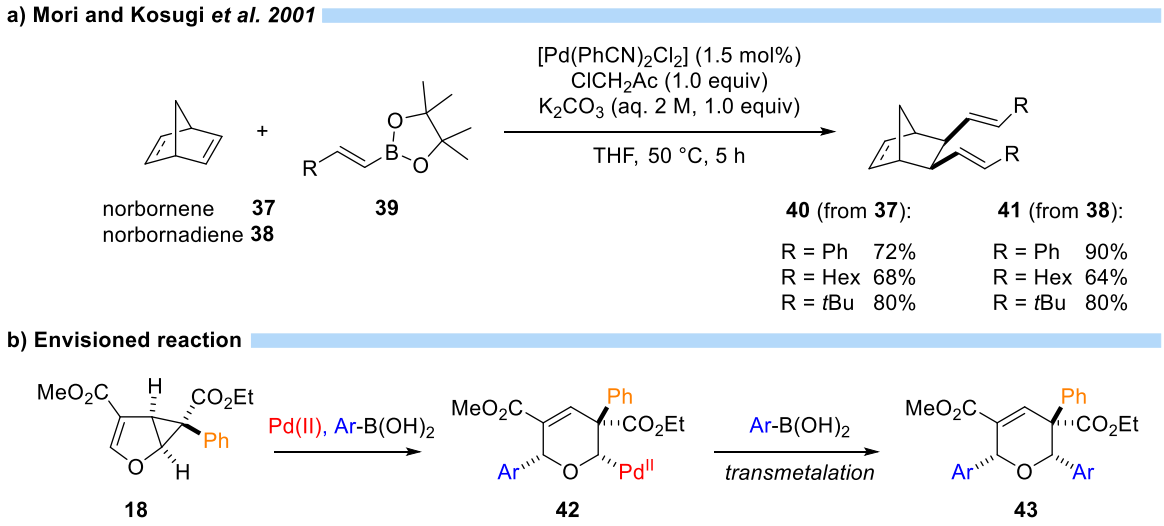
According to their mechanistic proposal (Scheme **21b**) the reaction is initiated by a 1,6-addition of enolate **35** to **34** giving intermediate **III** which then instantly undergoes a 6π-electrocyclic ring opening to open-chained intermediate **IV**. After a [1,5]-hydride shift to intermediate **V**, the compound recyclizes in a further 6π-electrocyclic reaction to pyran **VI**. Even though being equilibria reactions, the equilibrium of the entire mechanistic sequence lies strongly on the product side providing **36** in excellent yields.[54]

Due to the extremely close resemblance of **36** and **16** we were prompted to carry out theoretical investigations on the racemization of **16**. In collaboration with the research group of Prof. Dr. Julia Rehbein (University of Regensburg) DFT calculations[1] for model substrate **16a-Me** were conducted (Scheme **21c,** for details see Appendix Scheme **S 2**). Data suggests that if the reaction would indeed undergo said racemization *via* 6π-electrocyclic ring opening to **16a-Me'**, a remarkably low-lying energy barrier of only 12.8 kcal/mol would be required to drive this rapid process whereby the equilibrium strongly lies on the side of **16a-Me**. Hence, **16a-Me** can be considered the thermodynamic product which becomes apparent as both NMR and X-ray data only detect the cyclic form of **16a-Me** as open-chained **16a-Me'** is too short-lived.

[1] Calculations were conducted by Dominik Kreutzer, Aryaman Pattanaik and Ricardo A. Angnes.

1.3.3 Oxidative Heck cross-coupling of *gem*-disubstituted cyclopropanated furans

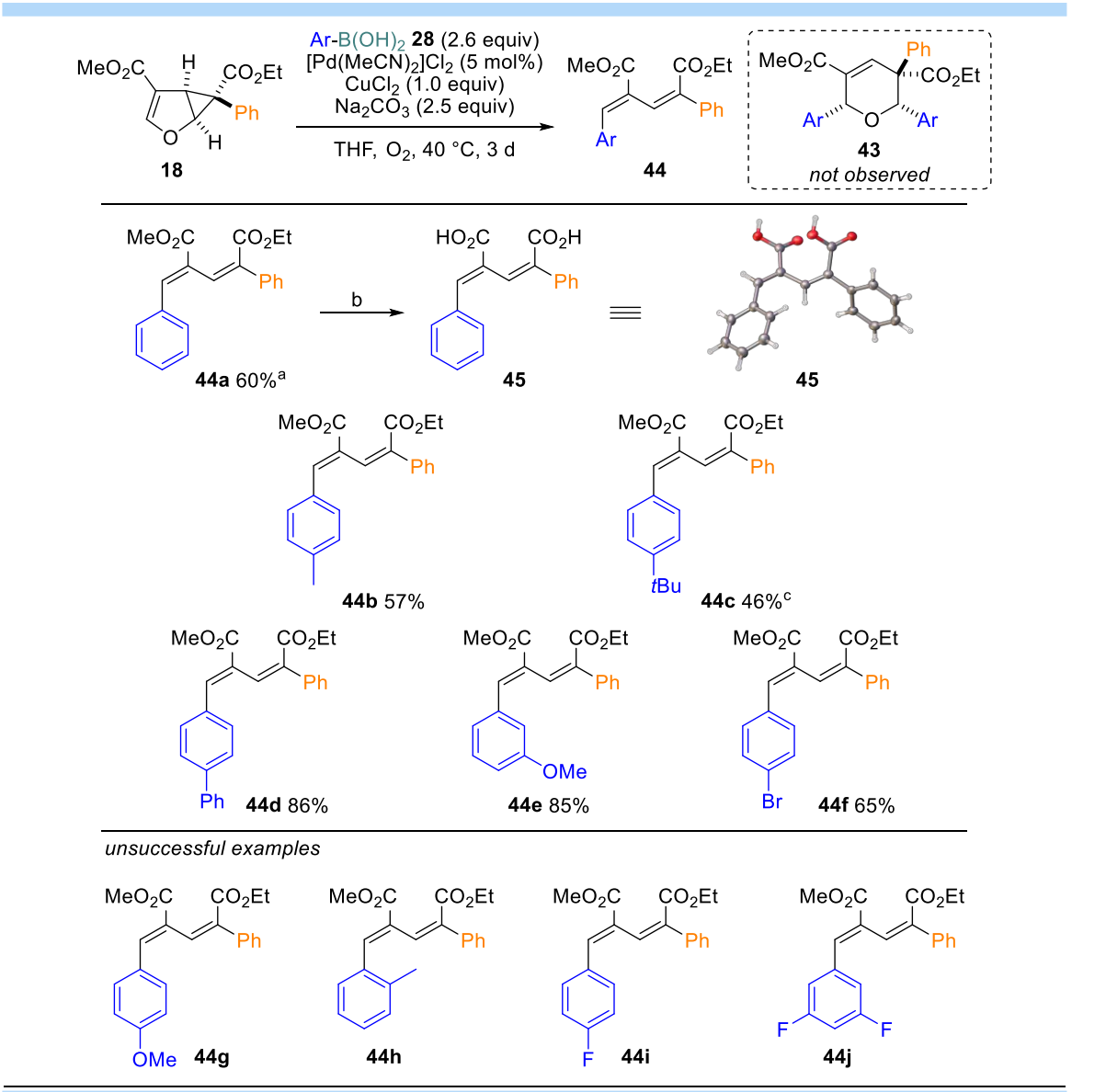
Having thoroughly evaluated the ring opening of monocyclopropanated furan **15** under oxidative Heck-conditions, we wanted to test if the new protocol also allows for a successful activation of *gem*-disubstituted cyclopropanated furans. However, instead of adding a nucleophile to the reaction to replace the palladium in the formerly unreactive organopalladium intermediate, we envisioned an approach similar to Mori and Kosugi *et al.* in 2001 (Scheme **22a**). In their report,[43] the group published an oxidative double vinylation on systems like norbornene **37** and norbornadiene **38**, that is ring systems were the palladium has no possibility for a β-hydride elimination after carbopalladation. Thus, they solved this issue by adding a second equivalent of aryl boronic acid to the reaction in order to trap this unreactive intermediate by a transmetallation. Hereby, they were able to synthesize various 2,3-divinyl norbornenes **40** and norbornadienes **41** in good to excellent yields from vinyl pinacol ester **39**.



Scheme 22. Double arylation - literature evidence and envisioned transformation.

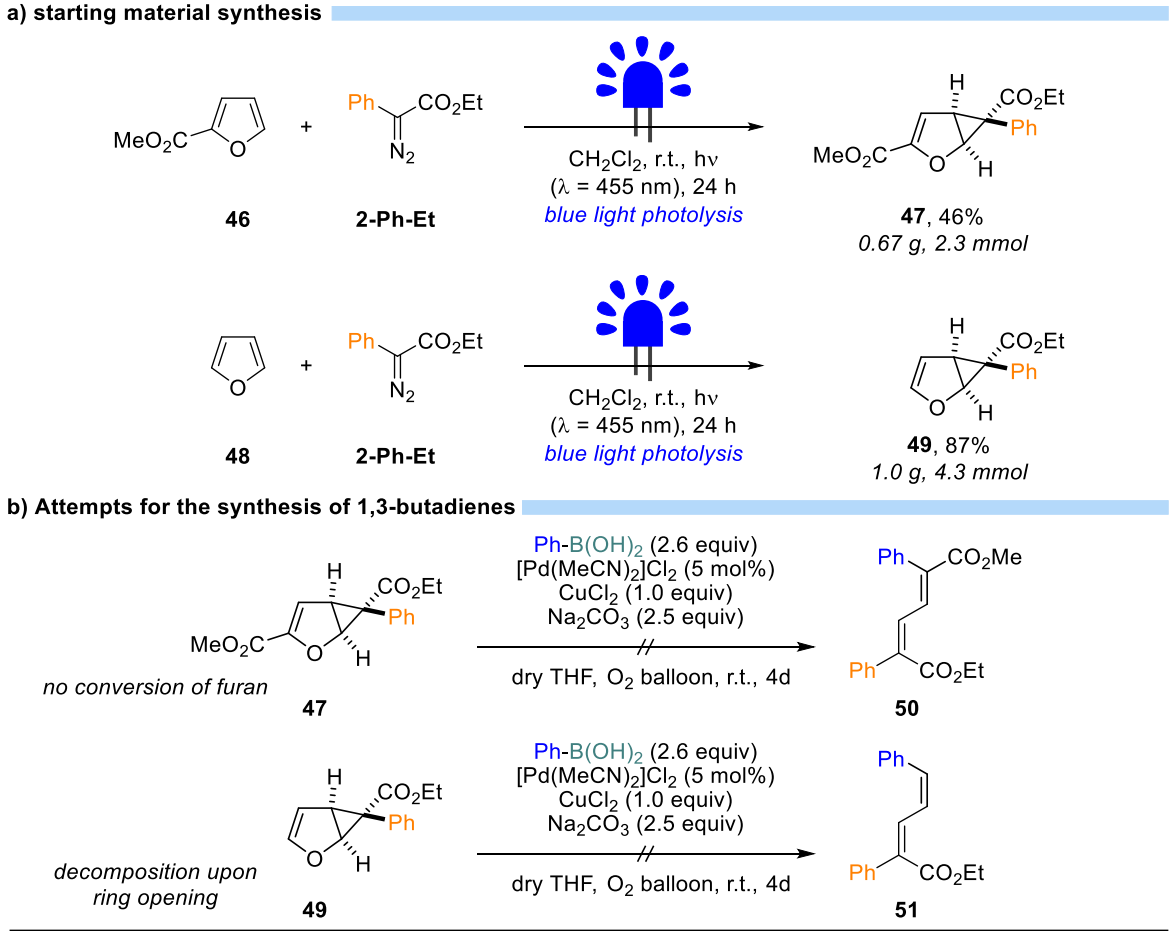
Taking this concept and applying it to our problem set, it should be possible to trap intermediate **42** being generated from **18** by adding a second equivalent of aryl boronic acid to give rise to doubly arylated dihydro-2*H*-pyran **43**. Surprisingly, when **18** was subjected to oxidative Heck coupling conditions, **43** was not observed and instead highly asymmetrically substituted 1,3-butadienes **44** were obtained as a single diastereomers (Scheme **23**). When plain phenyl boronic acid was used, butadiene **44a** was isolated in 60% yield. Stereochemistry was determined 2D-NMR experiments (for details see Appendix). Additional proof of the stereochemistry was gained *via* X-ray crystallography after saponification of **44a** to its respective dicarboxylic acid **45** using LiOH in THF/water giving the product in 97% yield.

While *para*-methyl showed a similar reactivity to the unsubstituted boronic acid, the *para-tert*-butyl substituent reacted sluggishly. Therefore, the reaction temperature needed to be increased to 55 °C to ensure full conversion of **18** as starting material and product could not be separated otherwise. The highest yields were observed for *para*-phenyl and *meta*-methoxy substituted boronic acids giving their corresponding 1,3-butadienes **44d** and **44e** in 86% and 85% yield, respectively.



Scheme 23. Substrate scope for the synthesis of asymmetric 1,3 butadienes **44** from cyclopropanated furan **18**. Reactions were carried out on a 0.5 mmol scale with respect to **18**. [a]Reaction was performed on a 1.0 mmol scale. [b]LiOH (40 equiv), THF/H_2O (1/1), reflux, 18 h, 97%. [c]Reaction performed at 55 °C. At 40 °C only around 80% conversion was observed, and product could not be separated from the starting material.

Lastly, *para*-bromo substituted 1,3-butadiene **44f** was isolated in 65% yield. Unfortunately, various aryl boronic acids did not show the desired reactivity. For instance, *para*-methoxy resulted only in homocoupling of the boronic acid. For *ortho*-methyl, *para*-fluoro and 3,5-difluoro boronic acids we observed no conversion.

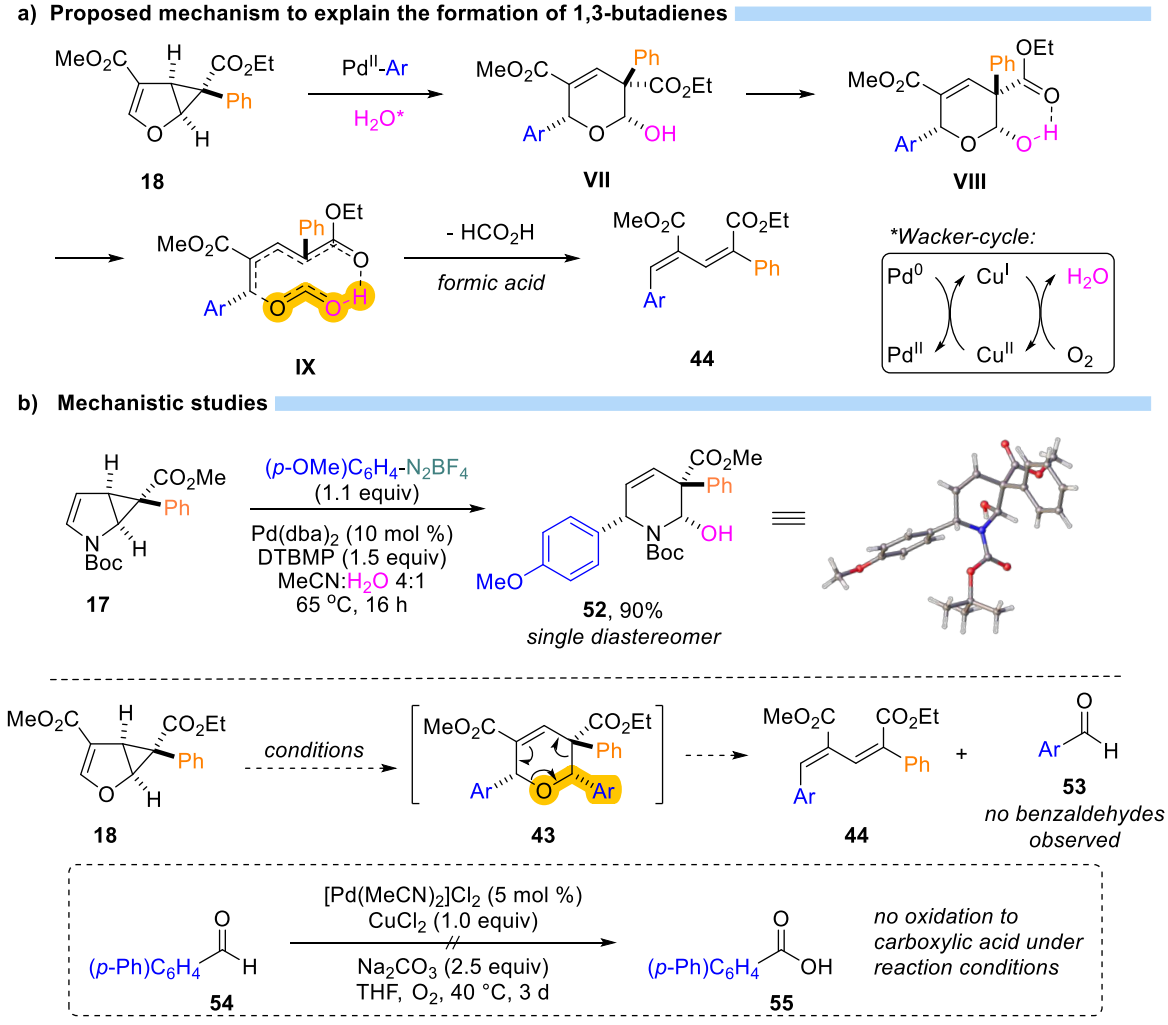


Scheme 24. Starting material synthesis and cross-coupling attempts of other cyclopropanated *gem*-disubstituted furans.

In order to test the boundaries of this novel reactivity, other cyclopropanated *gem*-disubstituted furans needed to be prepared (Scheme **24a**). For the starting material synthesis, the same approach as for the synthesis of **18** was chosen (*cf.* Scheme **17**).[28,55] While furan **46** having the ester group at the 2-position delivered product **47** in 46% (0.67 g, 2.3 mmol), unsubstituted furan (**48**) delivered the corresponding cyclopropane **49** in satisfying 87% yield (1.0 g, 4.3 mmol).

Having these substrates in hand, we immediately commenced our studies for the synthesis of further highly substituted, asymmetric 1,3-butadienes (Scheme **24b**). Unfortunately, both

substrates showed the exact same behavior under oxidative Heck conditions as their mono-cyclopropanated relatives (*cf.* Scheme **20a**), i.e. 2-ester **47** resulted in no conversion while furan **49** suffered from decomposition under the employed reaction conditions.



Scheme 25. Proposed mechanism and mechanistic studies for the formation of 1,3-butadienes.

Even though the clean synthesis of highly asymmetric 1,3-butadienes **44** from **18** is attractive from a synthetic point of view, the mechanism for this particular transformation does not appear to be straight forward. However, the clean diastereoselectivity as well as the nature of the products suggest that the reaction might involve a formal retro Diels-Alder fragmentation pathway (Scheme **25a**). Similarly to the findings of Reiser in 2021 in the case of pyrroles,[6] the organopalladium intermediate can be trapped by water which is being generated in stoichiometric amounts during the ongoing Pd^{II}-Cu^{I}-O_2 Wacker-cycle[56] to give hemiac-

etal **VII**. The resulting intermediate could then form a six-membered H-bonding intermediate **VIII** that undergoes defragmentation upon elimination of formic acid to give 1,3-butadiene **44**.

The presence of hemiacetal **VII** can be supported by the aforementioned generation of hemiaminal **52** as a single diastereomer under aqueous conditions from cyclopropanated pyrrole **17** (Scheme **25b**).[6] Additionally, it can be ruled out that **44** is formed from initially hypothesized doubly arylated **43** as this would imply that benzaldehydes **53** are eliminated.

However, no benzaldehydes could be observed in the reactions and with compound **54** it was representatively demonstrated that is not possible to oxidize benzaldehydes under reaction conditions to their corresponding carboxylic acids as they may easily be lost during an aqueous, basic work-up.

Detailed theoretical investigations on the mechanism are currently underway by the research group of Prof. Dr. Julia Rehbein.

1.4 Summary

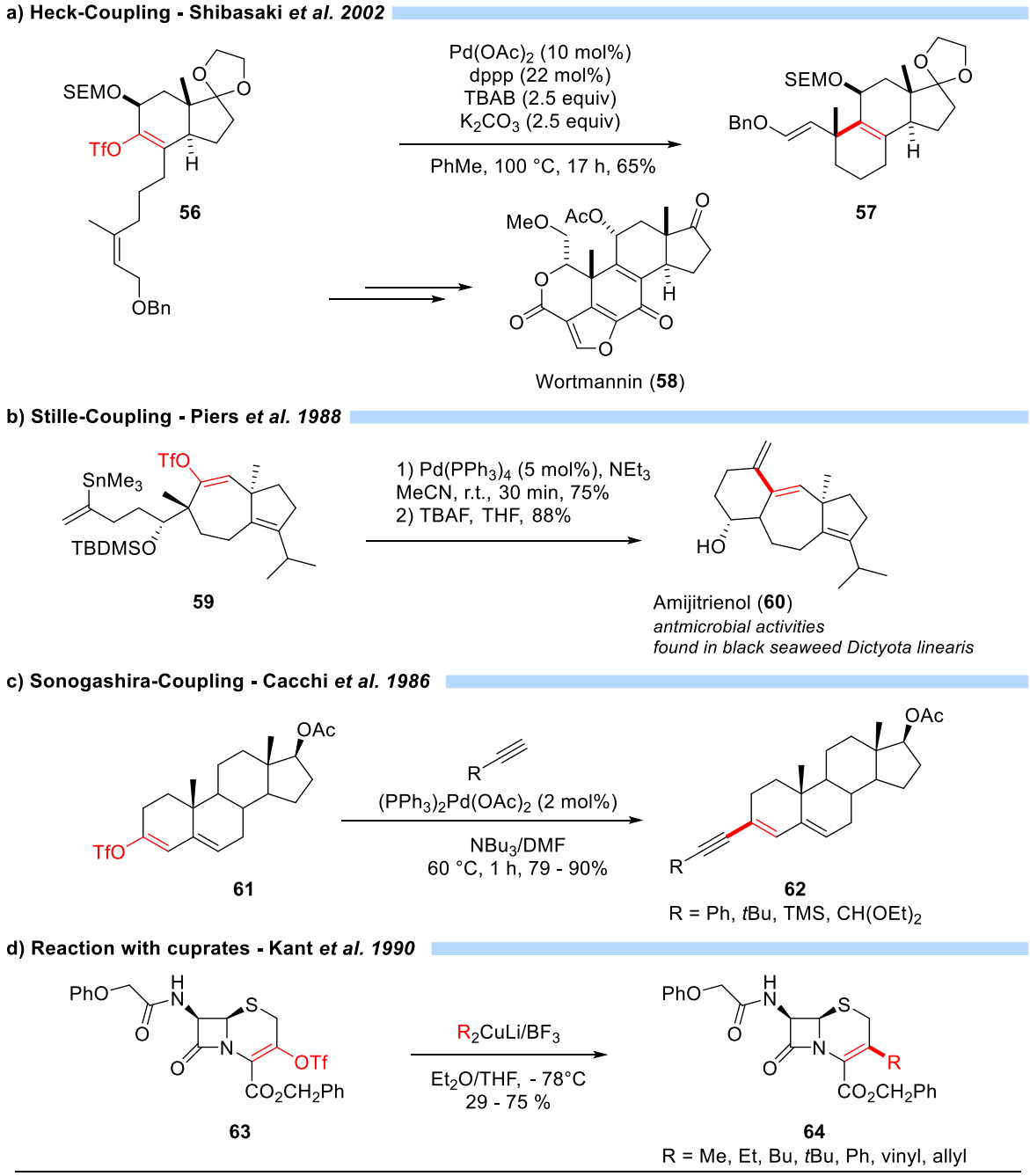
In Summary, a novel protocol for the generation of 2*H*-pyrans from monocyclopropanated furans has been developed. After preliminary attempts using Heck-Matsuda reactions have failed to improve upon the previously developed protocol from Reiser *et. al.* in 2019[2] in terms of substrate diversity and the successful activation of *gem*-disubstituted cyclopropanated furans, an oxidative approach was chosen. Employing this new protocol, a comprehensive library of variously substituted 2*H*-pyrans was prepared. Furthermore, utilizing the boron Heck reaction it was possible to activate *gem*-disubstituted cyclopropanated furans for the first time. Surprisingly, instead of the predicted diaryl-2*H*-pyrans, an unexpected reactivity was discovered giving highly substituted, asymmetric 1,3-butadienes in a diastereoselective manner. Data suggests that a formal retro-Diels-Alder type fragmentation process might be responsible for the observed reactivity.

2. Synthesis of 2-vinyl-dihydropyridines

2.1 Introduction

2.1.1 Vinyl triflates in literature

Aryl and vinyl triflates (trifluoromethanesulfonates, $CF_3SO_3^-$) are well established reagents in natural product synthesis and for the construction of complex molecular scaffolds.[57–66] Especially transition metal catalyzed cross-coupling reactions with vinyl triflates are an attractive tool for the coupling of $C(sp^2)$-$C(sp^2)$ fragments.



Scheme 26. Selected examples of cross-coupling reactions with vinyl triflates.

For instance, Shibasaki *et al.* capitalized on these reagents for the total synthesis of wortmannin (**58**) in 2002 (Scheme **26a**).[65]

In their approach, vinyl triflate **56** was subjected to Heck cross-coupling conditions for the synthesis of annulated ring system **57** which was later converted to **58** in a 26-step total synthesis.

However, besides Heck reactions, vinyl triflates are also versatile coupling reagents for other classic palladium-catalyzed reactions like Stille couplings. One example is the synthesis of amijitrienol (**60**) by Piers and co-workers in 1988.[67] For their synthesis, analogously to Shibasaki, one of the key steps was an intramolecular cyclization using Stille conditions for the construction of a 6-7-5-membered ring system to furnish the natural product after deprotection (Scheme **26b**).

Earlier in 1986,[68] the group of Chacci showcased that vinyl triflates are also suitable reagents for the synthesis of a comprehensive library of different C3-substituted steroids **62**. In their report, they reacted vinyl triflate derivatives of steroids **61** with various terminal alkynes under Sonogashira conditions (Scheme **26c**).

Lastly, the group of Kant demonstrated in 1990 that vinyl triflates offer an efficient strategy for the synthesis of various cephalosporins **64**.[69] In their protocol, vinyl triflates were reacted with organo cuprates to access these β-lactam antibiotic analogues (Scheme **26d**).[70]

Besides being extremely versatile reagents, vinyl triflates are also popular due their simple and quick accessibility. Mostly, these reagents which are often also referred to as enol triflates are prepared from their corresponding ketones or aldehydes.[71–81] Upon treatment with base, the resulting enolates are converted to enol triflates either by the use of either triflic anhydride Tf_2O or Comin's reagent.[82] Alternatively, they can also be prepared from terminal alkynes using triflic acid TfOH.[73,83]

Furthermore, vinyl triflates also shine in cross-coupling reactions due to their high reactivity. For comparison, Hartwig and Jutand conducted thorough kinetic investigations concerning the oxidative addition of palladium being the rate determining step in most reactions.

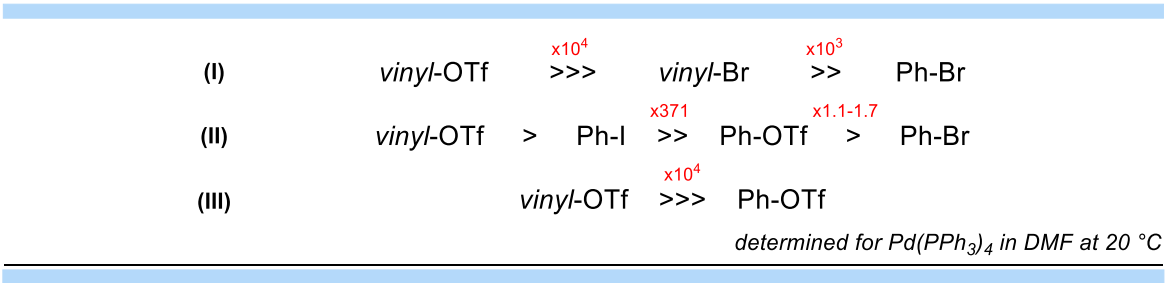
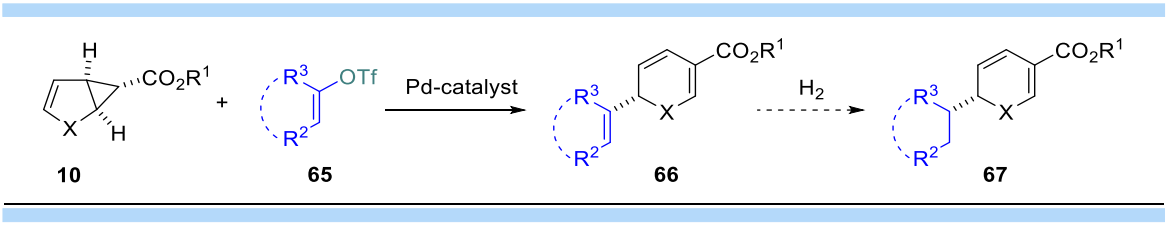


Figure 3. Relative reaction rates of oxidative addition for commonly used substrates.

While the reactivity of generally employed vinyl triflates exceeds the reactivity of vinyl bromides by factor of 10^4 and bromobenzene by factor of 10^7 (eq. I, Figure **3**), their reactivity even outperforms iodobenzene (eq. II, Figure **3**). Notably, even though vinyl triflates possess an extraordinary reactivity, their related aryl triflates are significantly less potent showing reaction rates in between iodo- and bromobenzene (eq. III, Figure **3**).[84–86]

2.1.2 Aim of this chapter

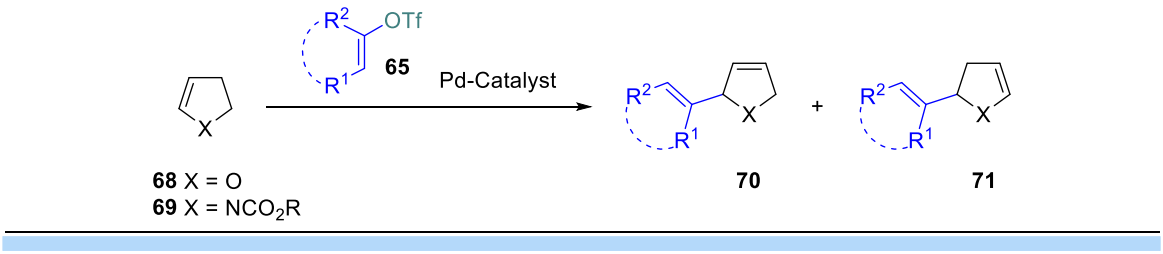
The aim this chapter is the development of a vinylation protocol for the synthesis of 2-vinyl-dihydropoyridines/2*H*-pyrans from cyclopropanated pyrroles and furans **10**. After determining ideal reaction conditions, a comprehensive library of variously substituted vinyl residues should be coupled to the desired target structures. Furthermore, the obtained products should be hydrogenated to give rise to the corresponding 2-alkyl dihydropyridines/2*H*-pyrans which can be considered as the formal outcome of an alkyl-cross-coupling (Scheme **28**).



Scheme 27. Aim of this chapter.

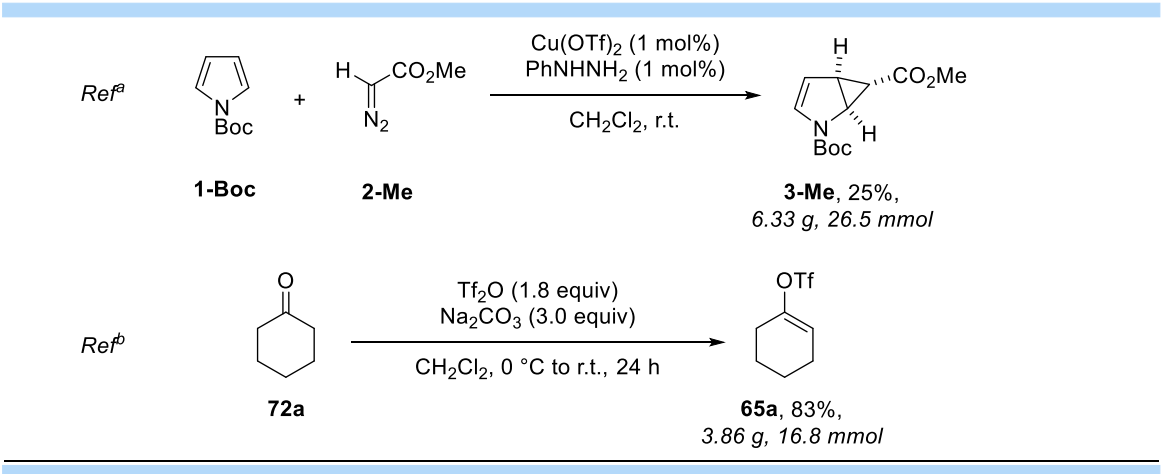
2.2 Vinylation of cyclopropanated pyrroles

Among many examined substrates, the vinylation of 2,3-dihydrofurans and 2,3-dihydropyrroles has been studies extremely thoroughly in the literature as these compounds are popular model substrates for the development of novel ligands for cross-coupling reactions or asymmetric catalysis (Scheme **28**).[87–94]



Scheme 28. Heck-type vinylation of 2,3-dihydrofurans and 2,3-dihydropyrroles.

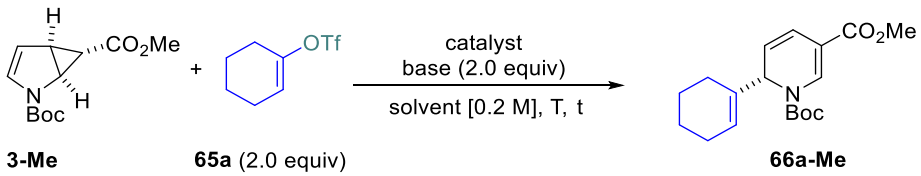
Inspired by these results, we were prompted to commence our studies towards the endocyclic ring opening of cyclopropanated heterocycles upon palladium-catalyzed Heck-type vinylation. Therefor, the necessary starting materials first needed to be synthesized (Scheme **29**). Cyclopropanated N*Boc*-pyrrole **3-Me** which was synthesized following the general Cu(I)-catalyzed cyclopropanation protocol[1] was chosen as the model olefin. Even though the yield for this process was as low as 25%, the reaction could be readily upscaled to obtain 6.33 g (26.5 mmol) of the product. Furthermore, model triflate cyclohexenyl triflate **65a** was synthesized from cyclohexanone following a literature procedure using sodium carbonate as base and triflic anhydride.[71]



Scheme 29. Synthesis of model substrates. Ref[a]:[1], Ref[b]:[71]

Having the necessary starting materials in hand we commenced our optimization studies for the synthesis of 2-vinyl-dihydropyridines (Table **4**). Initially, we started our investigations using similar parameters to Hartwig and Jutand in their kinetic studies (Figure **3**).[84–86] Using 1 mol% of $Pd(PPh_3)_4$ as palladium precursor and sodium carbonate as base, solvents like DMF, DMA and acetonitrile showed only poor conversion and low yields. 59% isolated yield at 75% conversion was overserved in DMSO (entries 1-4, Table **4**). Interestingly, strongly increasing the catalyst loading to 10 mol% only marginally increased the reaction efficiency in DMF and DMA (entries 5-6, Table **4**). In DMSO however, the yield drastically decreased to 25% and additionally byproduct **73** (Figure **4**) was isolated in 18% yield (entry 7, Table **4**). When the reaction was performed in acetonitrile, an increase in catalyst loading did also boost the yield from 11% to 45% (entry 8, Table **4**). Reactions of the highest yielding entries 3 and 8 were then repeated at elevated temperatures which lead to the identification that 1 mol% of catalyst in DMSO giving 69% yield outperforms previous experiments (entries 9-10, Table **4**).

Table 4. Reaction optimization for the synthesis of 2-vinyl-dihydropyridines.



3-Me **65a** (2.0 equiv) **66a-Me**

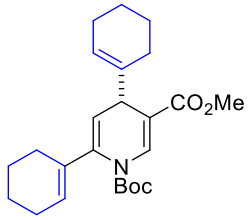
#	Catalyst (mol%)	Base	Solvent (1.5 mL)	T /t	Comment	Conv.[a] of 3	NMR Yield[a]
1	$Pd(PPh_3)_4$ (1)	Na_2CO_3	DMF	60 °C/64 h	-	28%	8%
2	$Pd(PPh_3)_4$ (1)	Na_2CO_3	DMA	60 °C/64 h	-	36%	10%
3	$Pd(PPh_3)_4$ (1)	Na_2CO_3	DMSO	60 °C/40 h	-	75%	59%[b]
4	$Pd(PPh_3)_4$ (1)	Na_2CO_3	MeCN	60 °C/64 h	-	24%	11%
5	$Pd(PPh_3)_4$ (10)	Na_2CO_3	DMF	60 °C/40 h	-	53%	19%
6	$Pd(PPh_3)_4$ (10)	Na_2CO_3	DMA	60 °C/40 h	-	62%	28%
7	$Pd(PPh_3)_4$ (10)	Na_2CO_3	DMSO	60 °C/40 h	-	>95%	25% + 18%[b] **73**
8	$Pd(PPh_3)_4$ (10)	Na_2CO_3	MeCN	60 °C/40 h	-	75%	45%
9	$Pd(PPh_3)_4$ (10)	Na_2CO_3	MeCN	80 °C/64 h	-	60%	36%
10	$Pd(PPh_3)_4$ (1)	Na_2CO_3	DMSO	80 °C/18 h	-	>99%	69%
11	$Pd(PPh_3)_4$ (2)	Na_2CO_3	DMSO	80 °C/18 h	-	>99%	40%

12	**$Pd(PPh_3)_4$ (1)**	**Na_2CO_3**	**DMSO**	**80 °C/18 h**	**1.3 equiv 65a**	**>99%**	**75%**
13	$Pd_2(dba)_3$ (1)	Na_2CO_3	DMSO	80 °C/40 h	1.3 equiv **65a**	69%	50%
14	$Pd(OAc)_2$ (1)	Na_2CO_3	DMSO	80 °C/40 h	1.3 equiv **65a**	73%	37%
15	$Pd(PPh_3)_2Cl_2$ (1)	Na_2CO_3	DMSO	80 °C/40 h	1.3 equiv **65a**	39%	19%
16	$Pd(MeCN)_2Cl_2$ (1)	Na_2CO_3	DMSO	80 °C/40 h	1.3 equiv **65a**	59%	46%
17	$Pd(PPh_3)_4$ (1)	Na_2CO_3	DMSO	80 °C/40 h	TBACl (2 equiv); 1.3 equiv **65a**	92%	70%
18	$Pd(PPh_3)_4$ (1)	Cs_2CO_3	DMSO	80 °C/40 h	1.3 equiv **65a**	<5%	-
19	$Pd(PPh_3)_4$ (1)	$NaHCO_3$	DMSO	80 °C/40 h	1.3 equiv **65a**	65%	45%
20	$Pd(PPh_3)_4$ (1)	KOAc	DMSO	80 °C/40 h	1.3 equiv **65a**	78%	37% + 7% **73**

Reactions performed on a 0.3 mmol scale using 1.5 mL of solvent. [a]determined by crude ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [b]isolated yield. Conv. = conversion.

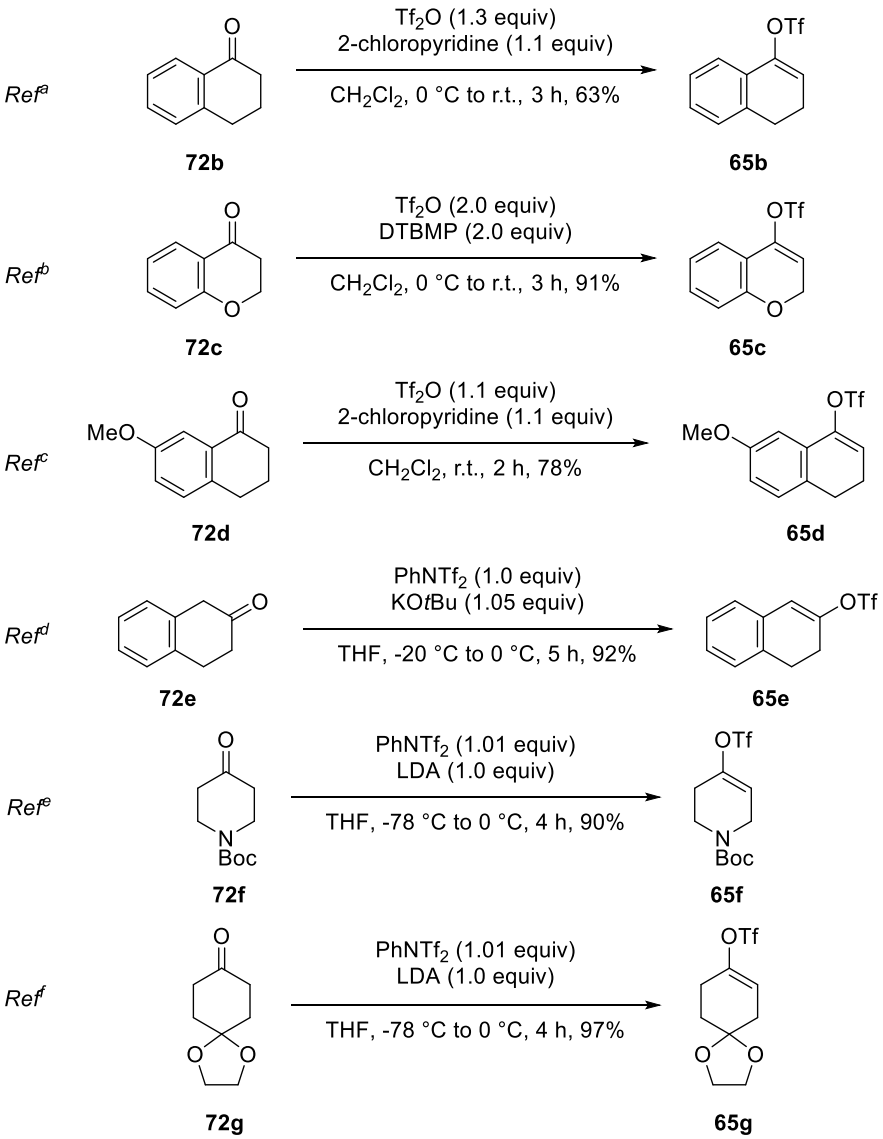
While a slight increase in catalyst loading to 2 mol% caused a decrease in yield, lowering the amount of vinyl triflate **65a** from 2.0 to 1.3 equivalents led to 75% yield at full conversion (entries 11-12, Table **4**). Having found the ideal solvent, reaction temperature and catalyst loading we then continued our optimization studies by varying the palladium source. However, none of the employed catalysts $Pd_2(dba)_3$, $Pd(OAc)_2$ $Pd(PPh_3)_2Cl_2$ or $Pd(MeCN)_2Cl_2$ were able to improve the reaction efficiency (entries 13-16, Table **4**).

Lastly, we conducted a short screening of different bases. While the addition of tetrabutylammonium chloride had almost no impact on product formation, the reaction shut down completely when cesium carbonate was used resulting in no conversion of **3-Me** (entries 17-18, Table **4**). Ultimately, switching from Na_2CO_3 to $NaHCO_3$ resulted in 35% less product formation and sodium acetate as base performed similarly and additionally also promoted to generation of byproduct **73** in 7%.

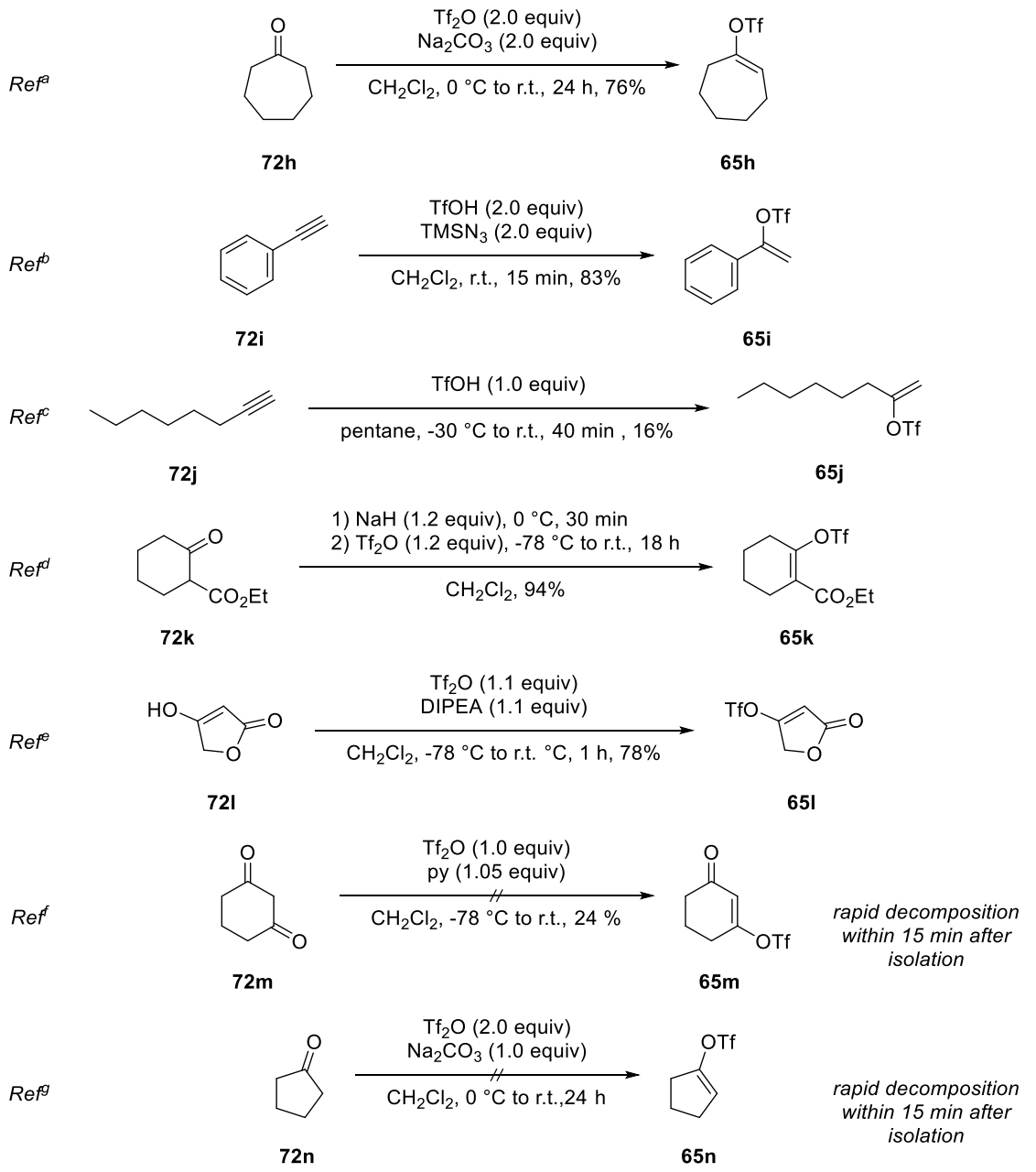


73

Figure 4. Isolated byproduct **73**.



Scheme 30. Synthesis of vinyl triflates I, Ref[a]:[72], Ref[b]:[74], Ref[c]:[75], Ref[d]:[77], Ref[e]:[78], Ref[f]:[78].



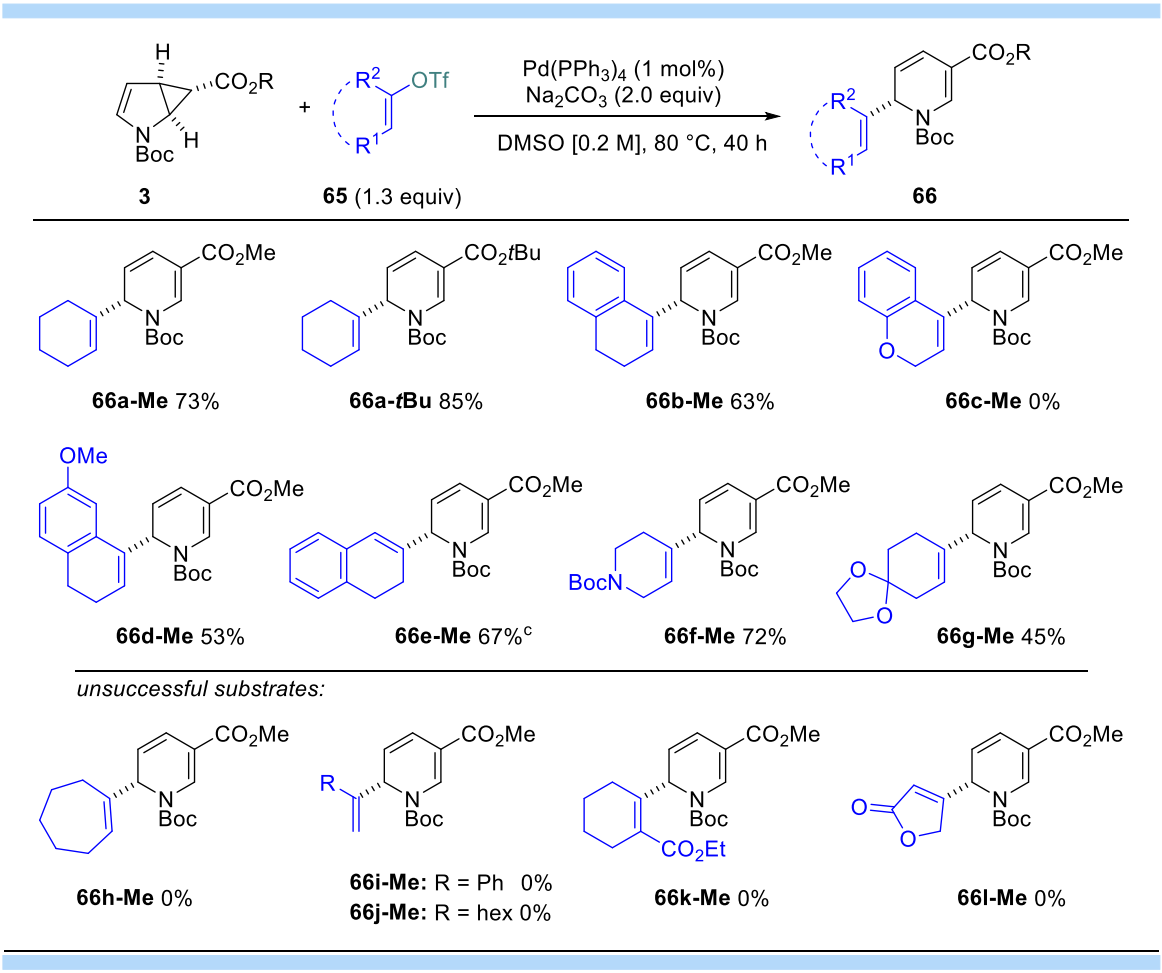
Scheme 31. Synthesis of vinyl triflates II, Ref[a:][79], Ref[b:][83], Ref[c:][73], Ref[d:][80], Ref[e:][81], Ref[f:][95], Ref[g:][79].

Overall, the optimal reaction parameters turned out to be $Pd(PPh_3)_4$ (1 mol%) and Na_2CO_3 as base in DMSO at 80 °C. However, before these conditions were put to test for the synthesis of a library of variously substituted 2-vinyl-dihydropyridines, the necessary vinyl triflates were prepared (Scheme **30** & Scheme **31**).

Generally, most vinyl triflates were prepared from commercially available ketones following known literature procedures that mostly involved treatment with base and trapping of the resulting enolate with triflic anhydride or bis(fluoromethanesulfonyl)aniline $PhNTf_2$ when

strong bases like potassium *tert*-butoxide KO*t*Bu or lithium diisopropyl amide LDA were used as $PhNTf_2$ is less prone to hydrolysis and generally milder compared to triflic anhydride.[82] Notably, for vinyl triflates **65i** and **65j** a different approach was chosen since these compounds were prepared from their corresponding terminal alkynes upon treatment with triflic acid TfOH.[73,83]

Unfortunately, vinyl triflates **65m**[95] and **65n**[79] which were prepared following previously described literature procedures decomposed rapidly only few minutes after isolation and could not be used for the substrate scope preparation.



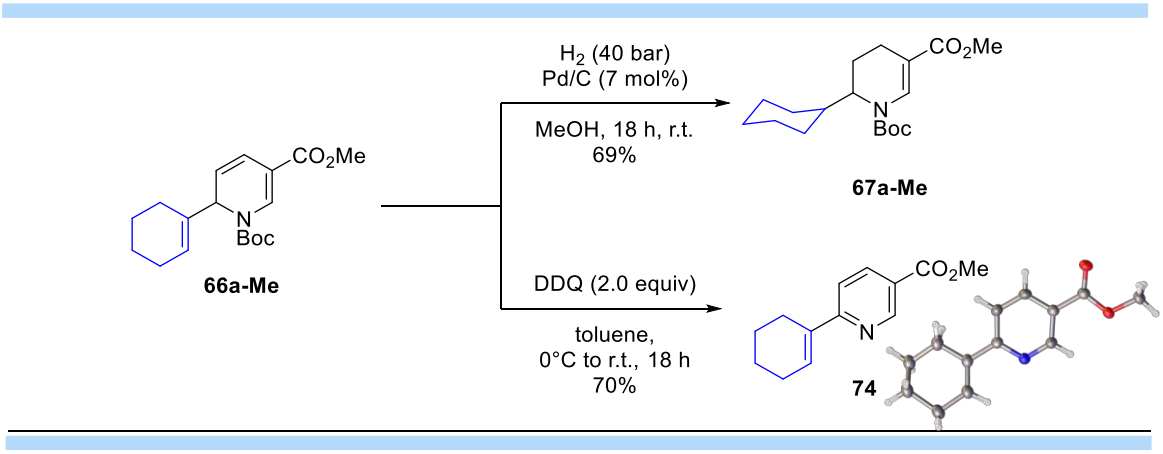
Scheme 32. Substrate scope for the preparation of 2-vinyl-dihydropyridines. All reactions were performed on a 0.5 mmol scale using 2.5 mL of solvent.

For the substrate scope we started with our model substrate **65a** giving the corresponding product in 73% isolated yield (Scheme **32**). Surprisingly, switching from methyl ester **3-Me** to *tert*-butyl ester **3-*t*Bu** on the cyclopropane increased the yield to 85%. However, the isolation of product **66a-*t*Bu** appeared to be much more challenging hence we decided to use **3-Me** for the remaining substrate scope. Vinyl triflate **65b** which was prepared from α-teralone gave the corresponding product **66b-Me** in 63%. Unfortunately, switching to closely

related oxygen containing vinyl triflate **65c** caused a complete shutdown of the reaction which might be explained by a conformational change of the bicyclic starting material induced by the heteroatom. Methoxy substituted vinyl triflate **65d** which was similarly prepared from 7-methoxy-α-teralone on the other hand gave the corresponding product in 53% yield. When we switched from α-teralone derived vinyl triflate **65b** to β-teralone derived triflate **65e** a slight increase in yield could be observed which may be due to less steric repulsion.

When N*Boc*-4-piperidinone derived vinyl triflate **65f** was used, the product was isolated in satisfying 72% yield while acetal **65g** only gave 45% yield.

Interestingly, increasing the ring size from six (**65a**) to seven membered vinyl triflate (**65h**) also caused a shutdown of the reaction which further indicates that the reaction is sensitive to conformational changes. Further limitations of this protocol became apparent when we switched from cyclic to acyclic vinyl triflates which resulted in no conversion of cyclopropane **3-Me**. Also, strongly electron deficient vinyl triflates **65k** and **65l** likewise resulted in no conversion of **3-Me**.



Scheme 33. Synthetic transformation of **66a-Me**.

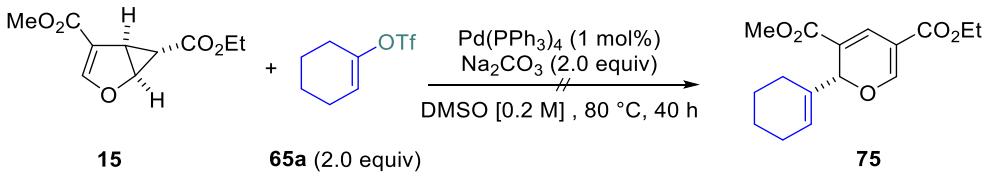
Having explored the substrate scope for this particular transformation we then focused our attention on minor synthetic applications (Scheme **33**). Therefore, model substrate **66a-Me** was subjected to hydrogenation conditions. Notably, hydrogenation with palladium on charcoal at ambient pressure (1 atm) resulted in a mixture of mono and doubly hydrogenated product, hence we increased the hydrogen pressure to 40 bar to ensure full conversion which furnished cyclohexyl substituted dihydropyridine **67a-Me** in 69% yield. This product may also be considered as the outcome of a formal alkylation.

Furthermore, as these dihydropyridines are generally sensitive towards autoxidation we also subjected our model substrate to oxidative conditions using DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) as oxidant which afforded pyridine **74** in 70% yield.

2.3 Studies towards the vinylation of cyclopropanated furans

Having established a protocol for the successful synthesis of 2-vinyl-dihydropyridines *via* endocyclic ring opening of cyclopropanated pyrroles triggered by a Heck-type vinylation we were prompted to expand the substrate scope also towards cyclopropanated furans. Therefor, we subjected previously synthesized cyclopropanated furan ester **15** to standard reaction conditions using vinyl triflate **65a** as the model substrate. However, both preliminary test reactions at 40 °C and at 80 °C resulted in no conversion of either substrate (entries 1-2,Table **5**). When $Pd(PPh_3)_4$ was replaced with $Pd_2(dba)_3$ likewise no conversion was observed (entry 3,Table **5**). Only when $Pd(OAc)_2$ was used as palladium precursor, full conversion of the triflate was observed but only trace amounts of products were detectable upon crude ^{1}H-NMR analysis (entry 4,Table **5**). Also other solvents like DMF, toluene and acetonitrile turned out to be unreactive (entries 5-10, Table **5**) and the desired product could not be synthesized.

Table 5. Studies towards the synthesis of 2-vinyl-2*H*-pyrans.



15 **65a** (2.0 equiv) **75**

Entry	Deviations from standard conditions	Observation
1	40 °C	no conv.
2	none	no conv.
3	$Pd_2(dba)_3$ (5 mol%)	no conv.
4	$Pd(OAc)_2$ (5 mol%)	traces (< 5%) full conversion of triflate
5	$Pd(OAc)_2$ (5 mol%), DMF	no conv.
6	$Pd_2(dba)_3$ (5 mol%), DMF	no conv.
7	$Pd(OAc)_2$ (5 mol%), PhMe	no conv.

8	$Pd_2(dba)_3$ (5 mol%), PhMe	no conv.
9	$Pd(OAc)_2$ (5 mol%), MeCN	no conv.
10	$Pd_2(dba)_3$ (5 mol%), MeCN	no conv.

All reactions were carried out on a 0.3 mmol scale.

2.4 Summary

In summary, we have established a new protocol for the synthesis of 2-vinyl-dihydropyridines from monocyclopropanated pyrroles *via* Heck-type vinylation triggered endocyclic ring opening of the cyclopropane. For our approach, vinyl triflates were chosen as the vinyl transfer reagents due to their easy accessibility as well as high reactivity compared to vinyl halides. After a thorough screening of reaction conditions, the best reaction parameters were identified, and the robustness of this methodology was tested by subjecting a range of variously substituted vinyl triflates to reaction conditions in order to synthesize a small library of differently substituted 2-vinyl-dihydropyridines. While most vinyl triflates delivered the desired products in good yields, some limitation of this process could be identified. It was found that acyclic vinyl triflates as well as electronically strongly deficient vinyl triflates showed no conversion of the cyclopropane. Additionally, it was observed that the reaction is sensitive to the conformation of the employed vinyl triflates as for instance an increase in ring size by one CH_2 unit or the replacement of an CH_2 group by an oxygen atom can shut down the reaction.

After having explored the substrate scope for this transformation, minor synthetic transformations were conducted. Hydrogenation of the obtained products gave rise to the corresponding alkyl-substituted dihydropyridine which may be considered the outcome of a formal alky cross-coupling. In return, when the product was subjected to an oxidative environment, the dihydropyridine was quantitatively oxidized to the corresponding pyridines.

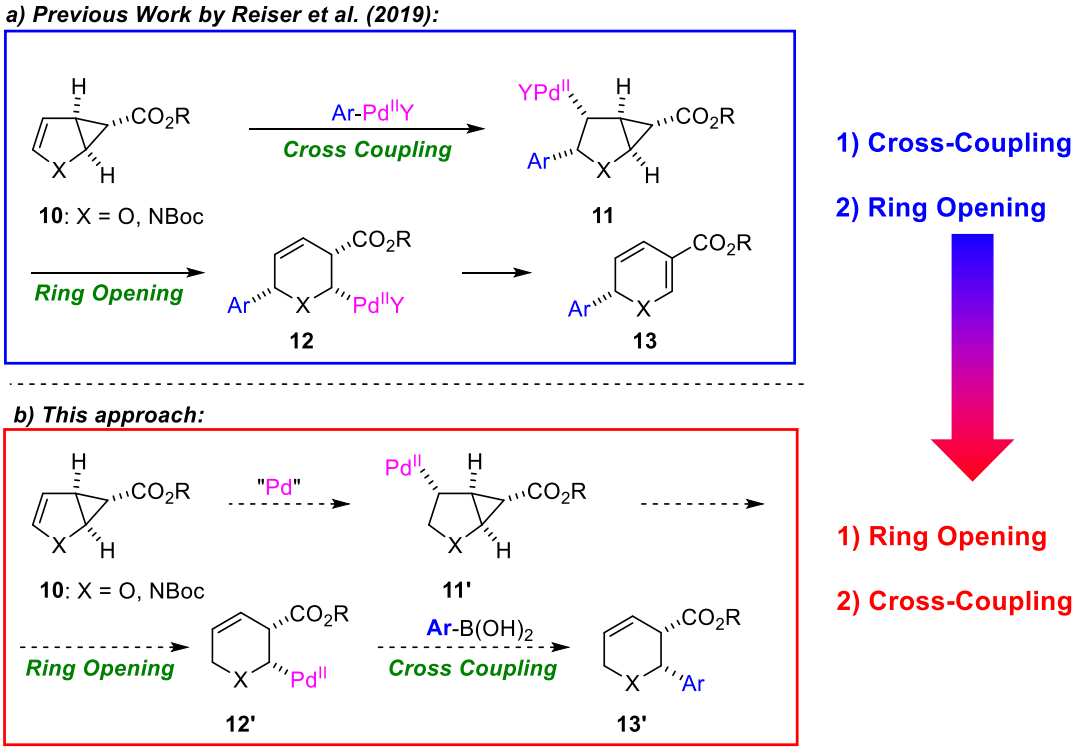
Unfortunately, applying this protocol to a cyclopropanated furan derivative did not give the desired 2-vinyl-2*H*-pyrans but resulted in no conversion under various reaction parameters.

3. Inverse approach – Activation of α-bromo cyclopropanes

3.1 Introduction and Aim of this chapter

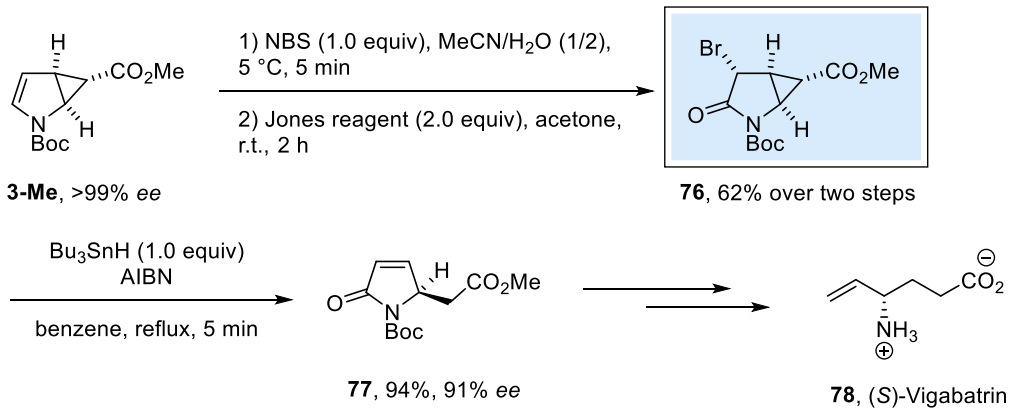
So far, we have thoroughly investigated the endocyclic ring opening of monocyclopropanated heterocycles triggered by Heck-type cross-couplings which is based on the initial report of Reiser and co-workers in 2019.[2] In this approach, the mechanistic proposal always follows the same pattern. After the carbopalladation on cyclopropanated pyrrole or furan **10** the palladium in intermediate **11** is located at the α-cyclopropyl position from which it triggers the endocyclic ring opening by β-carbon elimination with concomitant [1,3]-palladium migration (Scheme **34a**). After intermediate **12** has formed, the reaction is then terminated by a *trans*-β-hydride elimination.

However, the question arose whether the mechanistic step order could be inverted given that an appropriate substrate is used for this approach. In other words, we wondered if it was possible to first somehow introduce palladium into the α-cyclopropyl position of the molecule without the additional introduction of an aryl/vinyl moiety. From here it would trigger the usual ring opening *via* β-carbon elimination and ultimately the reaction would be terminated by a cross-coupling step with e.g. aryl boronic acids.



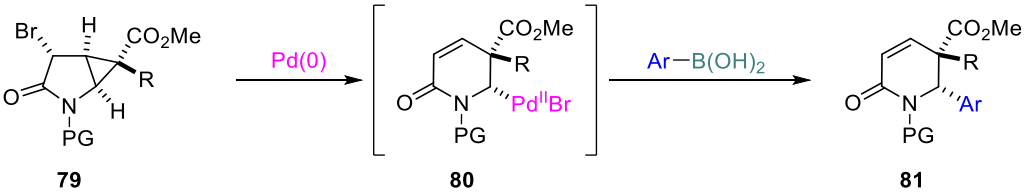
Scheme 34. Previous work vs. new approach for the endocyclic ring opening of cyclopropanated heterocycles.

One attractive starting material for this *inverse approach* was first prepared by Reiser *et al.* in 2006. For their synthesis of enantiopure (*S*)-Vigabatrin which is an irreversible inhibitor of 4-aminobutyrate transaminase (GABA-T) they started from enantiopure cyclopropanated pyrrole **3-Me** which was obtained by preparative chiral HPLC separation. In a two-step procedure consisting of a halohydrin reaction and subsequent oxidation of the alcohol to its corresponding ketone with Jones reagent, α-bromo lactam **76** was obtained in 62%. Next, the product was subjected to a radical initiator and stoichiometric amounts of tributyltin hydride Bu_3SnH generating a radical on the α-cyclopropyl position which then triggered the opening of the exocyclic bond to obtain intermediate **77** under slight erosion of the stereocenter. Finally, (*S*)-Vigabatrin was then prepared from **77** in an 8-step sequence.[96]



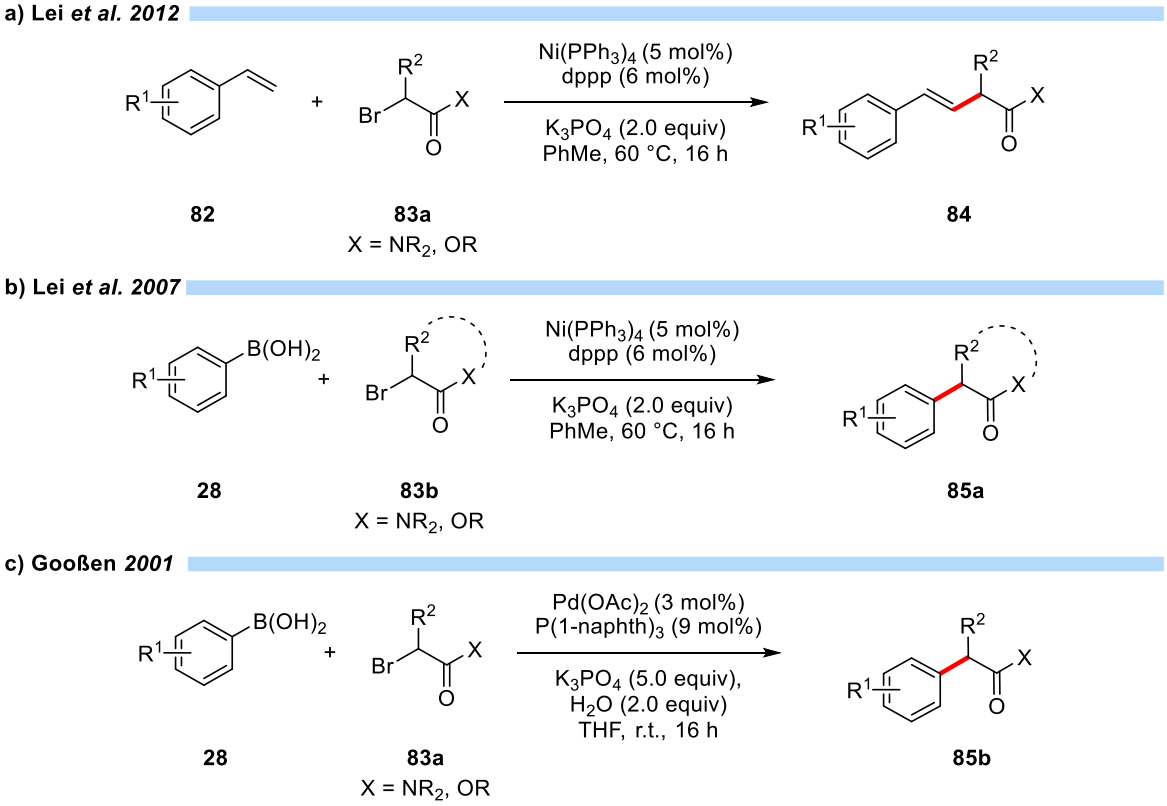
Scheme 35. Synthesis of (*S*)-Vigabatrin by Reiser *et al.* in 2006.[96]

Compound **76** of the total synthesis of (*S*)-Vigabatrin was of particular interest for our envisioned inverse approach. We hypothesized that by reacting compound **79** with a palladium(0) catalyst it would be possible to insert palladium into the carbon-bromine bond which then instantly triggers the opening of the endocyclic bond *via* β-carbon elimination to generate intermediate **80** (Scheme **36**). From here, the reaction is then terminated by a Suzuki-type coupling using boronic acids which would then afford 2-aryl-dihydropyridinones **81**.



Scheme 36. Proposed catalytic transformation.

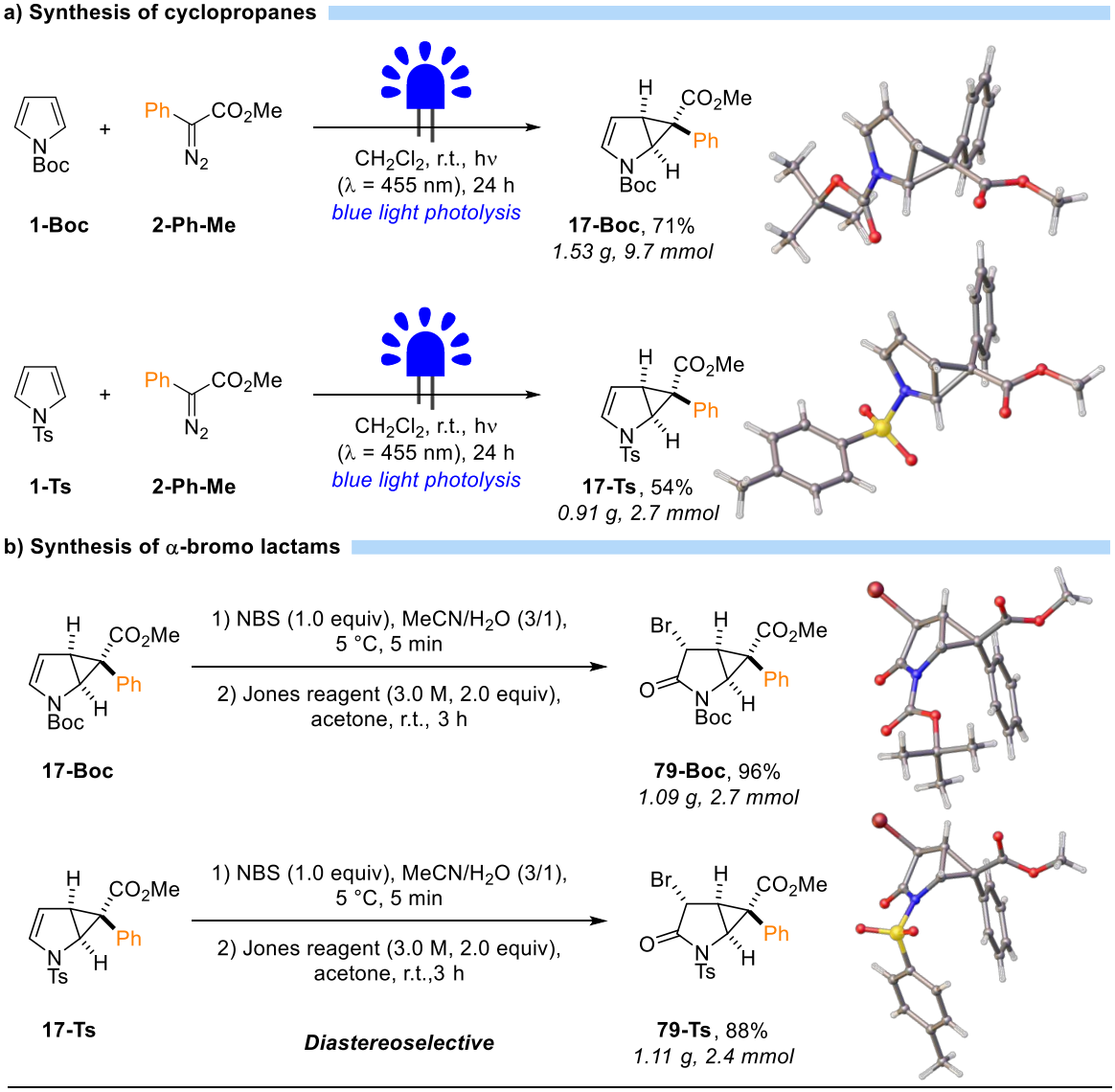
In order to assess the feasibility of this proposal we ran a thorough literature research about transition metal catalyzed activations of α-halo ketones, amides and esters. In general, nickel, cobalt and palladium-based transition metal catalysts are among the most used catalysts for these types of transformations. While some approaches utilize classic cross-coupling approaches like Hiyama coupling using silanes,[97,98] Kumada coupling using Grignard reagents,[99] or Stille type couplings using organotin reagents,[100–103] the majority of literature reports employ boronic acids as cross-coupling reagents in a Suzuki-type fashion.[104–118] Alternatively, it has also been demonstrated that olefins are viable reaction partners.[119,120] Selected examples are shown in Scheme **37**.



Scheme 37. Selected examples for the activation of α-bromo amides and esters.

3.2 Suzuki-type coupling of α-bromo lactams

Based on the literature reports of Reiser[2] and the general cross-coupling reports of α-halo ketones, esters and amides with boronic acids[104–118] we were prompted to start our investigations. For our envisioned approach the necessary starting materials first needed to be synthesized. Following the general procedure of Davies *et al.* we conducted photochemical cyclopropanations of *N*Boc-pyrrole (**1-Boc**) and *N*-tosylpyrrole (**1-Ts**) using aryl diazoacetate **2-Ph-Me** to obtain the corresponding cyclopropanes **17-Boc** and **17-Ts** in 71% and 54% yield, respectively (Scheme **38a**).[28,55] Similar to previously conducted cyclopropanations, this process is diastereoselective whereby the ester group always points to the convex face of the strained bicycle which has also been shown by X-ray crystallography for both substrates.

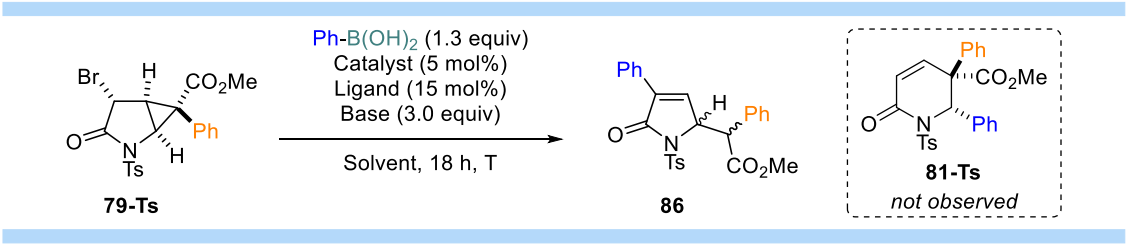


Scheme 38. Starting material synthesis. Photochemical cyclopropanation and synthesis of α-bromo lactams.

In analogy to the synthesis of (*S*)-Vigabatrin,[96] both substrates were then converted to their corresponding α-bromo lactams in a two-step procedure using *N*-bromosuccinimid (NBS) in aqueous acetonitrile to generate a halohydrin intermediate which was then immediately oxidized to its corresponding carbonyl analogue using Jones reagent (Scheme **38b**). The desired compounds **79-Boc** and **79-Ts** were obtained as single diastereomers in excellent yields of 96% and 88%, respectively. Notably, it has been shown by X-ray crystallography that the bromine atom is also pointing to the exocyclic face of the bicycle, i.e. it is placed *trans* to the cyclopropyl moiety.

Having the necessary staring materials in hand we then commenced our optimization studies. After initial attempts inspired by Lei and co-workers using nickel catalysis showed no promising results,[120] we switched to a palladium-based approach. However, as several preliminary experiments with *N*-Boc-protected lactam **79-Boc** only resulted in decomposition and complex reaction mixtures, further parameter screening studies were carried out using the more stable *N*-tosyl protected lactam **79-Ts** (Table **6**).

Table 6. Optimization studies for the activation of α-bromo lactam **79-Ts**.



#	Catalyst	Ligand	Solvent	Base	Com-ment	T (°C)	NMR Yield[a]
1	$Pd(OAc)_2$	P(*o*-Tol)$_3$	PhMe	K_3PO_4	-	r.t.	crm
2	$Pd(OAc)_2$	P(*o*-Tol)$_3$	PhMe	K_3PO_4	-	40	5% *d.r.* 1:1.4
3	$Pd(OAc)_2$	P(*o*-Tol)$_3$	PhMe	K_3PO_4	-	60	31%
4	**$Pd(OAc)_2$**	**P(*o*-Tol)$_3$**	**PhMe**	**K_3PO_4**	**-**	**80**	**43%**
5	$Pd(OAc)_2$	P(*o*-Tol)$_3$	PhMe	K_3PO_4	-	110	20%
6	$Pd(CO_2CF_3)_2$	P(*o*-Tol)$_3$	PhMe	K_3PO_4	-	80	44% *d.r.* 1.75:1
7	**$Pd_2(dba)_3$**	**P(*o*-Tol)$_3$**	**PhMe**	**K_3PO_4**	**-**	**80**	**60%**
8	$Pd(dba)_2$	P(*o*-Tol)$_3$	PhMe	K_3PO_4	-	80	38%
9	$Pd(MeCN)_2Cl_2$	P(*o*-Tol)$_3$	PhMe	K_3PO_4	-	80	52%

10	$Pd(PhCN)_2Cl_2$	P(*o*-Tol)$_3$	PhMe	K_3PO_4	-	80	45%
11	$Pd(PPh_3)_2Cl_2$	P(*o*-Tol)$_3$	PhMe	K_3PO_4	-	80	51%
12	$Pd_2(dba)_3$	P(*o*-Tol)$_3$	Dioxane	K_3PO_4	-	80	58% *d.r.* 1.52:1
13	$Pd_2(dba)_3$	P(*o*-Tol)$_3$	DMF	K_3PO_4	-	80	4%
14	$Pd_2(dba)_3$	P(*o*-Tol)$_3$	THF	K_3PO_4	-	80	34%
15	$Pd_2(dba)_3$	P(*o*-Tol)$_3$	EtOH	K_3PO_4	-	80	crm
16	$Pd_2(dba)_3$	P(*o*-Tol)$_3$	PhMe/H_2O (9/1)	K_3PO_4	-	80	30%
17	**$Pd_2(dba)_3$**	**P(*o*-Tol)$_3$**	**Dioxane/H_2O (9/1)**	**K_3PO_4**	**-**	**80**	**61%**
18	$Pd_2(dba)_3$	P(*o*-Tol)$_3$	THF/H_2O (9/1)	K_3PO_4	-	80	42%
19	$Pd_2(dba)_3$	P(*o*-Tol)$_3$	Dioxane/H_2O (9/1)	K_2CO_3	-	80	41%
20	$Pd_2(dba)_3$	P(*o*-Tol)$_3$	Dioxane/H_2O (9/1)	Cs_2CO_3	-	80	44%
21	$Pd_2(dba)_3$	P(*o*-Tol)$_3$	Dioxane/H_2O (9/1)	KF	-	80	crm
22	$Pd_2(dba)_3$	P(*o*-Tol)$_3$	Dioxane/H_2O (9/1)	CsF	-	80	18% *d.r.* 1:1
23	$Pd_2(dba)_3$	$P(Mes)_3$	Dioxane/H_2O (9/1)	K_3PO_4	-	80	9%
24	$Pd_2(dba)_3$	dppp (7.5 mol%)	Dioxane/H_2O (9/1)	K_3PO_4	-	80	27%
25	$Pd_2(dba)_3$	P(Naphth)$_3$	Dioxane/H_2O (9/1)	K_3PO_4	t-	80	24%
26	$Pd_2(dba)_3$	PCy_3HBF_4	Dioxane/H_2O (9/1)	K_3PO_4	-	80	20%
27	**$Pd_2(dba)_3$**	**P(*o*-Tol)$_3$**	**Dioxane/H_2O (9/1)**	**K_3PO_4**	**2.0 equiv 28b**	**80**	**67%**
28	$Pd_2(dba)_3$	P(*o*-Tol)$_3$	Dioxane/H_2O (9/1)	K_3PO_4	3.0 equiv **28b**	80	56%
29[b]	**$Pd_2(dba)_3$**	**P(*o*-Tol)$_3$**	**Dioxane/H_2O (9/1)**	**K_3PO_4**	**2.0 equiv 28b**	**80**	**71%[c]**

All reactions were performed on a 0.2 mmol scale using 1 mL of solvent. crm = complex reaction mixture. Unless otherwise noted, the product was obtained in a *d.r.* of 2:1.[a]determined by crude ^{1}H-NMR analysis using 1,1,2,2-tetrachloroethane as internal standard. [b]2.5 mol% of $Pd_2(dba)_3$ and 7.5 mol% of P(*o*-Tol)$_3$ were used. [c]isolated yield.

Our starting reaction parameters were chosen inspired by the report of Moberg an co-workers[115] using $Pd(OAc)_2$ as catalyst, P(*o*-tolyl)$_3$ as ligand and K_3PO_4 as base. While the reaction at room temperature resulted in a complex reaction mixture, the unexpected formation of product **86** was observed at elevated temperatures whereby the best result of 43% yield was observed at 80 °C leaving no evidence for the formation of predicted **81-Ts**. Product **86** was obtained as a mixture of two diastereomers in a ratio of 2:1 (entries 1-5, Table **6**). The

structure of the minor diastereomer was confirmed by X-ray crystallography (Figure **5**). The outcome of reaction may be explained by a base promoted enolization of the starting material which caused the opening of the exocyclic bond by interaction with the σ*-orbital of the exocyclic bond similarly to Reiser's observation when the α-bromo lactam **76** was subjected to radical conditions (*cf.* Scheme **35**).[96] The resulting pyrrolidone would then undergo a Suzuki coupling between the C(sp^2)-Br and the phenyl boronic acid to generate **86**. Surprised by this unexpected exocyclic ring cleavage we were nevertheless encouraged to optimize this catalytic transformation as pyrrolidones are synthetically useful compounds and play an important role in medicinal chemistry.[96,121–128]

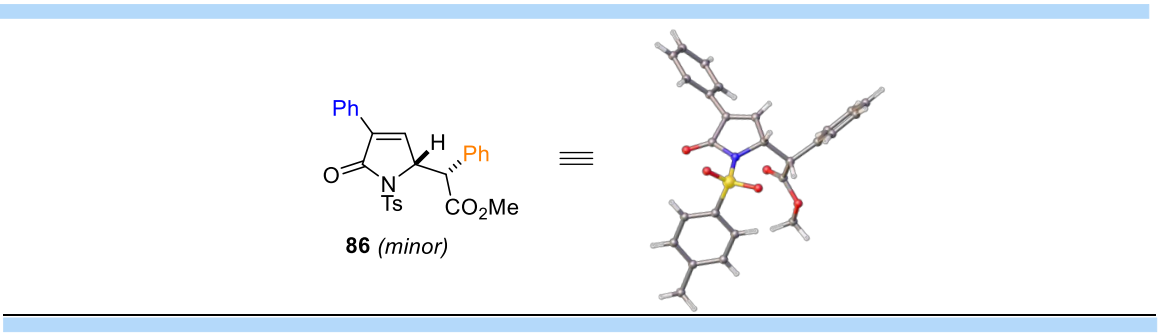
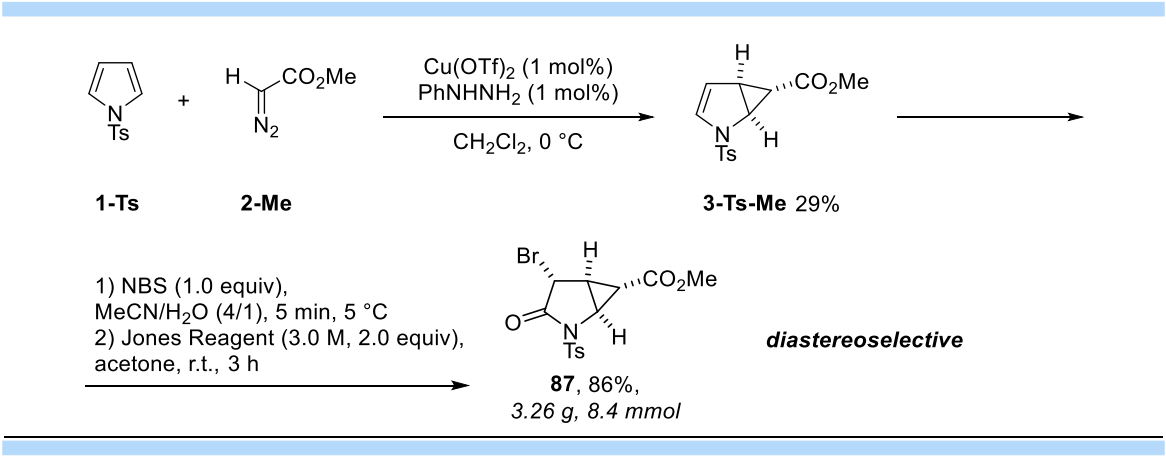


Figure 5. X-ray crystallography of **86** (minor diastereomer).

After having found the ideal reaction temperature for this process, various commonly used and commercially available palladium catalysts were screened. Among all tested Pd-precursors $Pd(CO_2CF_3)_2$, $Pd(dba)_2$, $Pd_2(dba)_3$, $Pd(MeCN)_2Cl_2$, $Pd(PhCN)_2Cl_2$ and $Pd(PPh_3)_2Cl_2$, the best result giving 60% yield was achieved with $Pd_2(dba)_3$ (entries 6-11, Table **6**). Next, upon a comprehensive row of optimizations concerning the ideal solvent (entries 12-18, Table **6**) and base (entries 19-22, Table **6**), no improvements in yield could be achieved. However, when was 9:1 mixture of dioxane and water was used as solvent, all reactants were homogenously dissolved compared to previously used toluene in which an insoluble suspension was observed. Also, screening of different phosphine ligands having various Tolman angles[129] did not deliver any improvements in yield (entries 22-26, Table **6**). Lastly, we discovered that by raising the amounts of phenyl boronic acid from 1.3 equivalents to 2.0 equivalents while at the same time lowering the catalyst loading from 5 mol% to 2.5 mol% we were able to boost the yield to 71% isolated yield (entries 27-29, Table **6**).

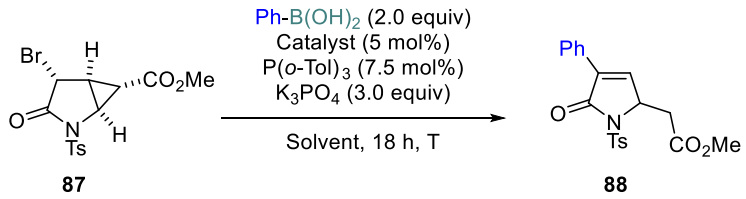


Scheme 39. Starting material synthesis of **87** from *N*-tosylpyrrole.

However, during our investigations we always observed the formation of product **86** in a diastereomeric mixture of 2:1 regardless of the employed reaction conditions. In order to avoid the formation of diastereomers we designed a new starting material for the desired transformation where no phenyl group is attached to the cyclopropyl moiety (Scheme **39**). This way, the two diastereomers can be converted into a single product. For the synthesis we conducted the cyclopropanation using tosyl-protected pyrrole (**1-Ts**) and methyl diazoester **2-Me** to give cyclopropane **3-Ts-Me** which was then immediately subjected to the usual reaction sequence to obtain substrate **87** in 86% (3.26 g, 84 mmol).

Having altered a substantial part of the starting material which might cause differences in reactivity and solubility, we decided to conduct a short re-optimization of reaction parameters using substrate **87** (Table **7**). First, we tested several palladium catalysts for this transformation in toluene where we discovered that $Pd_2(dba)_3$ proved itself to still be the most ideal catalyst for this transformation giving 75% yield (entries 1-4, Table **7**). Next, we tested various solvents which gave the best results for previous substrate **79-Ts**. Interestingly, neither dioxane, dioxane/water (9/1), THF, nor THF/water (9/1) giving yields between 53% and 69% were able to outperform toluene (entries 5-8, Table **7**). Lastly, while increasing the catalyst loading to 5 mol% or decreasing the concentration led to slightly decreased yields (entries 9-10, Table **7**), we observed that the addition of water to the reaction had no influence on the reaction's efficiency providing **88** likewise in 75% yield (entry 11, Table **7**).

Table 7. Re-optimization of reaction parameters for substrate **87**.

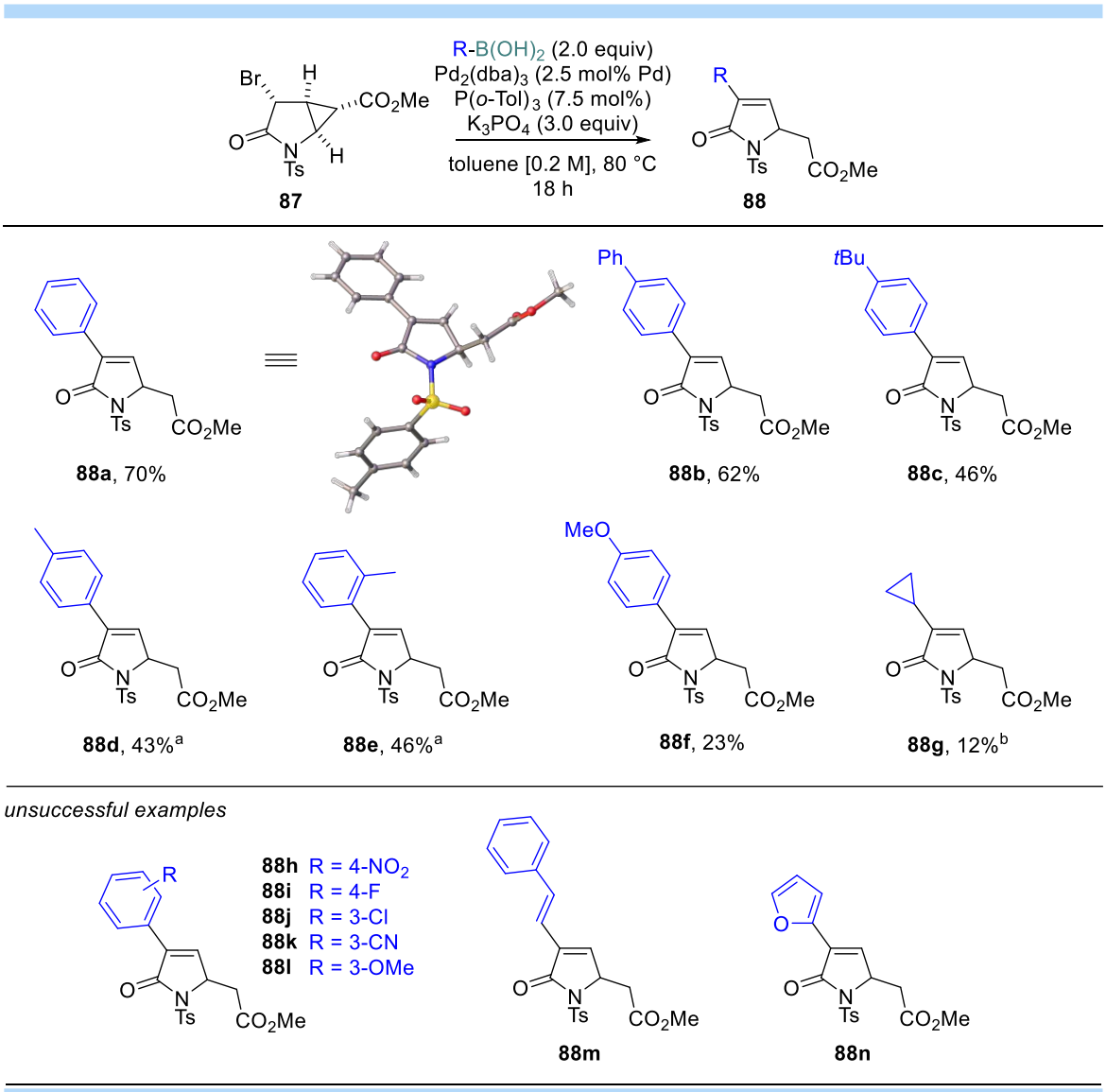


87 **88**

Entry	Catalyst	Solvent	NMR Yield[a]
1	$Pd(OAc)_2$	PhMe	70%
2	**$Pd_2(dba)_3$**	**PhMe**	**75%**
3	$Pd(PPh_3)_4$	PhMe	19%
4	$[PdCl_2(MeCN)_2]$	PhMe	71%
5	$Pd_2(dba)_3$	Dioxane	69%
6	$Pd_2(dba)_3$	Dioxane/H_2O (9/1)	68%
7	$Pd_2(dba)_3$	THF	57%
8	$Pd_2(dba)_3$	THF/H_2O (9/1)	53%
9[b]	$Pd_2(dba)_3$ (5 mol%)	PhMe	65%
10	$Pd_2(dba)_3$	PhMe [0.1 M]	71%
11	**$Pd_2(dba)_3$**	**PhMe/H_2O (9/1)**	**75%**

All reactions were performed on a 0.2 mmol scale using 1 mL of solvent. [a]determined by crude ^{1}H-NMR analysis using 1,1,2,2-tetrachloroethane as internal standard. [b]5 mol% of catalyst were used in combination with 15 mol% P(*o*-Tol)$_3$.

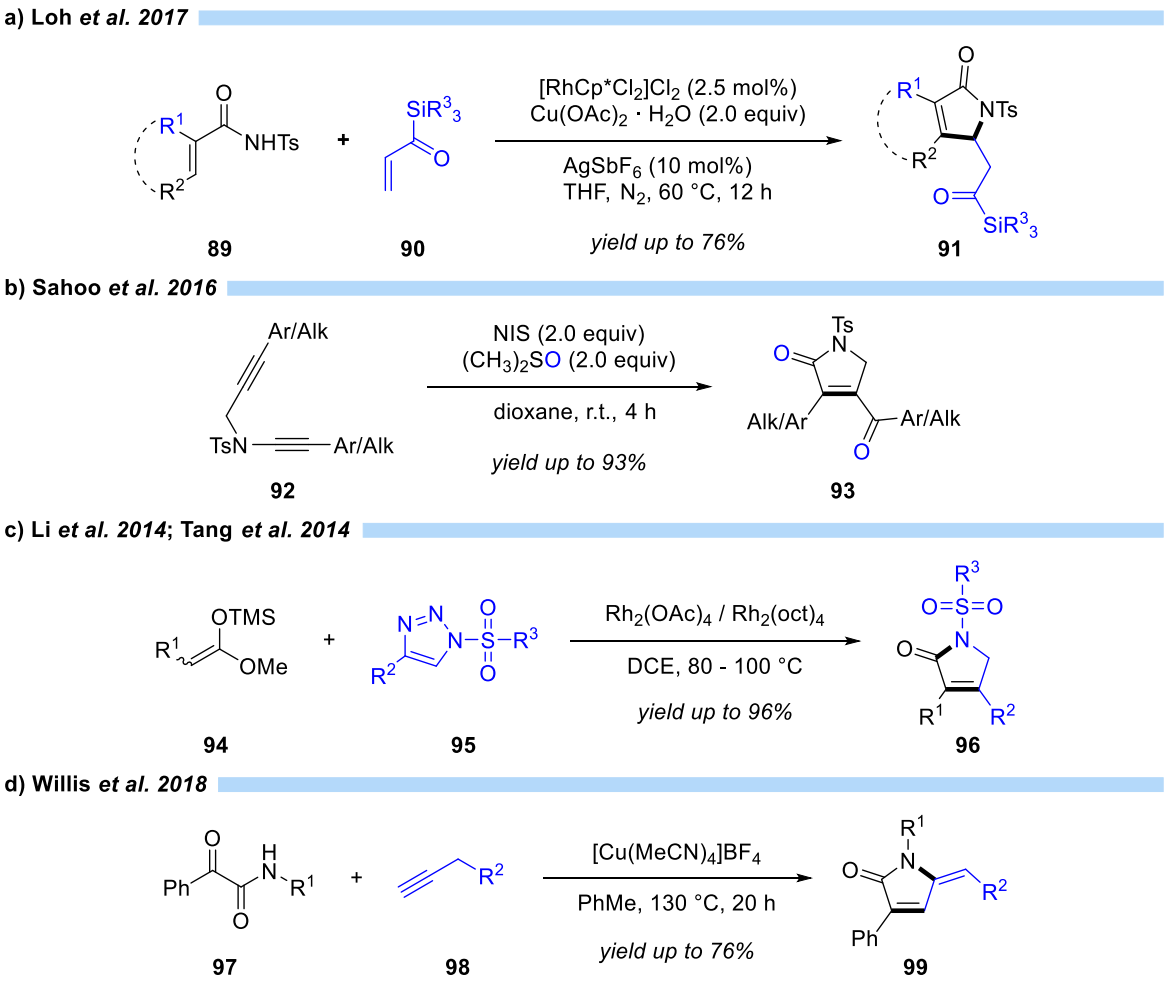
Having re-optimized reaction parameters we continued to explore the substrate scope for this transformation (Scheme **40**). Performing the reaction with model substrate phenyl boronic acid gave **88a** in 70% isolated yield and structure of the product was confirmed by X-ray crystallography. Comparable yields were obtained with biphenyl boronic acid. However, when alkyl substituted phenyl boronic acids were used in the reaction, the corresponding pyrrolidones were isolated in decreased yields between 43% to 46%. Notably, the reactions involving *para*- and *ortho*-substituted phenyl boronic acids were carried out in dioxane as toluene resulted in very low yields. When *para*-methoxy phenyl boronic acid was employed in the catalytic transformation, only 23% of product was isolated as the boronic acid had a strong tendency to dimerize and give the corresponding 1,1'-biphenyl as byproduct. Lastly, cyclopropyl boronic acid gave **88g** in only 12% yield.



Scheme 40. Substrate scope for the synthesis of pyrrolidones **88**. All reactions were carried out on a 0.3 mmol scale using toluene as solvent. [a]1,4-dioxane was used as solvent, [b]using 5 mol% catalyst loading resulted in 10% NMR-yield.

Unfortunately, as we continued our studies on synthesis of 3-substituted pyrrolidones, we also encountered a row of unsuccessful examples. In general, electron withdrawing substituents on the phenyl boronic acid appeared to be unreactive. Furthermore, alkenyl boronic acids and heterocyclic boronic acid also did not provide the desired target molecules.

As the substrate scope for the described transformation appeared to be limited to selected aryl boronic acids, we conducted a literature research about other methodologies to synthesize 3-substituted pyrrolidones for comparison (Scheme **41**). One of the structurally most related approaches was published by Loh and co-workers in 2017. In their approach, a rhodium catalyzed transformation involving C-H-activation and annulation between amide **89** and silyl ketone **90** was described.



Scheme 41. Literature synthesis of 3-substituted pyrrolidones - selected examples.

Even though the starting material synthesis of **89** involved a four-step procedure, the substrate versatility of this approach was impressively showcased with numerous examples. Notably, when the reaction was carried out with an ethyl ester group instead of a silyl keto moiety, the yields did not exceed 16% (Scheme **41a**).[130]

A different approach was reported by Sahoo *et al.* in 2016 who described a metal-free 5-*exo*-*dig* cyclization of yne-tethered ynamides **92** under oxidative conditions promoted by dimethyl sulfoxide as oxygen source and *N*-iodosuccinimid (NIS) to access variously 3,4-substituted pyrrolidones (Scheme **41b**).[131]

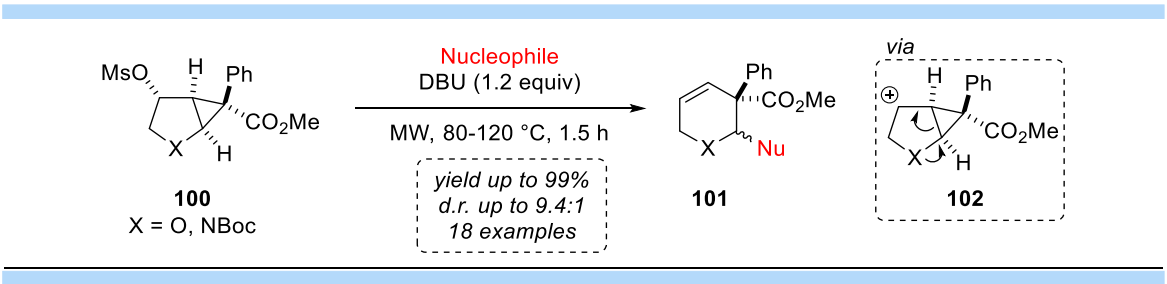
Another strategy was independently described both by Tang and Li in 2014. In their reports, a rhodium-catalyzed transannulation of sulfonyl-1,2,3-triazoles **95** with silyl enol ethers **94** was used to construct pyrrolidones **96**. One of the strong points of this strategy is that different residues on the nitrogen atom can be installed by the use of variously substituted sulfonyl-triazoles **95** (Scheme **41c**).[132,133]

Lastly, Willis and co-workers published a stereoselective copper-catalyzed synthesis of pyrrolidones **99** from α-keto amides **97** and alkynes **98** (Scheme **41d**). Likewise, depending on the employed α-keto amide **97** different substituents on the nitrogen can be attached (Scheme **41d**).[134]

Overall, our reported method for the synthesis of 3-substitued pyrrolidones starting from cyclopropanated pyrrole is an attractive strategy, however, it cannot compete with previously published approaches in literature as the substrate scope for this transformation appeared to be too limited to a few selected examples.

3.3 Studies towards the microwave-assisted ring expansion of α-bromo lactams

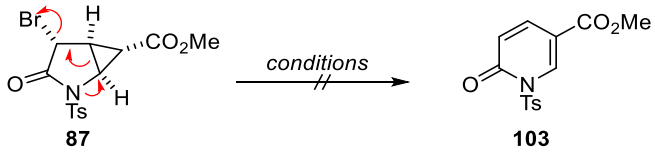
After having observed an unusual reactivity of α-bromo lactams under palladium-catalyzed coupling conditions involving the cleavage of the exocyclic bond instead of the endocyclic bond, we were prompted to investigate for other means of endocyclic ring-cleavages with concomitant ring expansion. One intriguing method for the ring expansion of cyclopropanated furans and pyrroles was demonstrated by Reiser and co-workers in 2021 (Scheme **42**).[135] In this report, the group showcased that under microwave irradiation the *O*-mesyl group in protected cyclopropyl alcohol **100** is eliminated in an E1 type fashion to generate carbocationic intermediate **102** which then triggers the endocyclic ring opening with the aid of the electron donating nature of the heteroatom. The resulting oxonium or iminium ion is then trapped by an appropriate nucleophile.



Scheme 42. Microwave-assisted ring expansion of *O*-mesylated cyclopropanated heterocycles **100** by Reiser (2021).

Given the structural similarity of **100** and **87**, we decided to subject α-bromo lactam **87** directly to microwave conditions in order to eliminate the bromine atom to generate pyridinone **103** after formal elimination of HBr (Table **8**). Unfortunately, initial attempts running the reaction at 150 °C for 30 min in toluene resulted in no conversion (entry 1,Table **8**).

Table 8. Studies towards the microwave-assisted ring opening of **87**.

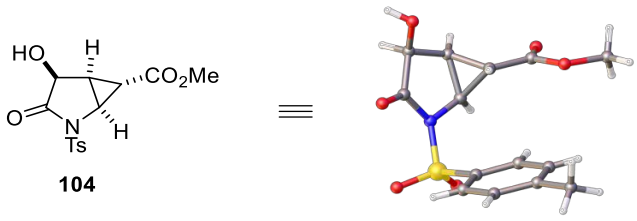


87 **103**

Entry	Conditions (microwave)	Yield
1	toluene, 150 °C, 30 min	no conversion
2	DMSO, 150 °C, 30 min	complex reaction mixture
3	DMSO, 100 °C, 6 h	75 %, unexpected product **104**

Reactions were performed on a 0.2 mmol scale using 1 mL of solvent.

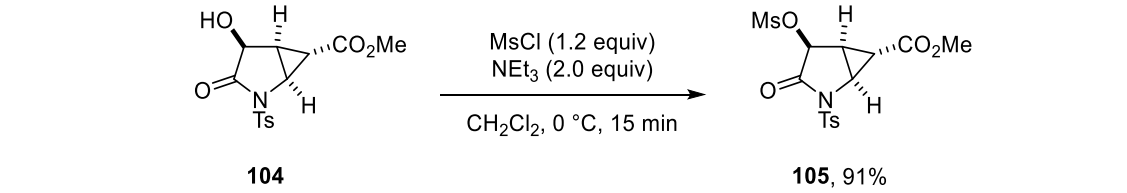
However, when we switched to DMSO as solvent under the same reaction parameters, we observed a complex reaction mixture with various decomposition products (entry 2,Table **8**). Hence, we lowered the temperature to 100 °C and let the reaction stir for 6 hours until **87** showed full conversion. Surprisingly, instead of expected pyridinone **103** we observed the clean formation of α-hydroxy lactam **104** in 75% yield. Notably, X-ray crystallography revealed that the hydroxy group is pointing to the concave face of the bicycle indicating that the process featured a clean S_N2-type substitution of bromine by trace amounts of water in the solvent (Figure **6**).



104

Figure 6. X-ray crystallography of **104**.

Having unexpectedly obtained **104** we then decided to convert the product into its *O*-mesyl derivative using mesyl chloride and triethylamine which gave rise to **105** in 91% (Scheme **43**). As we now had a direct derivative of **100** (*cf.* Scheme **42**) in hand we continued our attempts towards the microwave-assisted ring expansion of **105**.

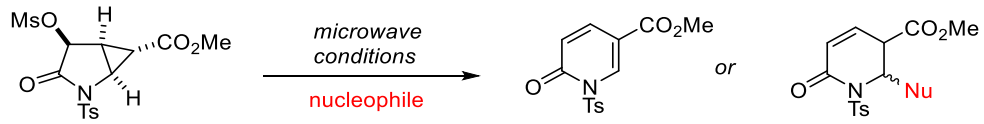


104 **105**, 91%

Scheme 43. Synthesis of **105**.

Our preliminary attempts for the synthesis of pyridinone **103** or **106**, respectively, were carried out in acetonitrile at 100 °C and 130 °C. However, no conversion was observed in both reactions (entries 1-2,Table **9**). Also, the addition of Et_3SiH as nucleophile likewise resulted in no conversion (entry 3, Table **9Table 8**). When we then switched to polar protic solvent methanol, we did not observe a change of outcome at both 100 °C and 115 °C[2], respectively (entries 4-5, Table **9Table 8**). When on the other hand DBU was added as base to the reaction a complex reaction mixture under decomposition of the starting material was observed (entry 6, Table **9**).

Table 9. Studies towards the microwave-assisted ring opening of **105**.



105 **103** **106**

Entry	Conditions	Nucleophile	Yield
1	100 °C, MeCN, 60 min	-	no conversion
2	130 °C, MeCN, 60 min	-	no conversion
3	130 °C, MeCN, Et_3SiH (3.0 equiv), 60 min	H	no conversion
4	100 °C, MeOH, 60 min	OMe	no conversion
5	115 °C, MeOH, 60 min	OMe	no conversion
6	100 °C, MeOH, DBU (1.2 equiv), 60 min	OMe	decomposition

This brought us to the conclusion that both **87** and **100** are unsuitable for the desired endocyclic ring opening *via* E1 type elimination of the respective leaving group Br (for **87**) or

[2] Note that 115 °C is the maximum operating temperature for methanol under microwave conditions.

OMs (for **100**). The cause for this unreactivity may be attributed the carbonyl moiety which strongly destabilized a potentially generated positive charge at the α-position as Reiser and co-worker demonstrated that the reaction works efficiently without carbonyl moiety.[135]

3.4 Summary

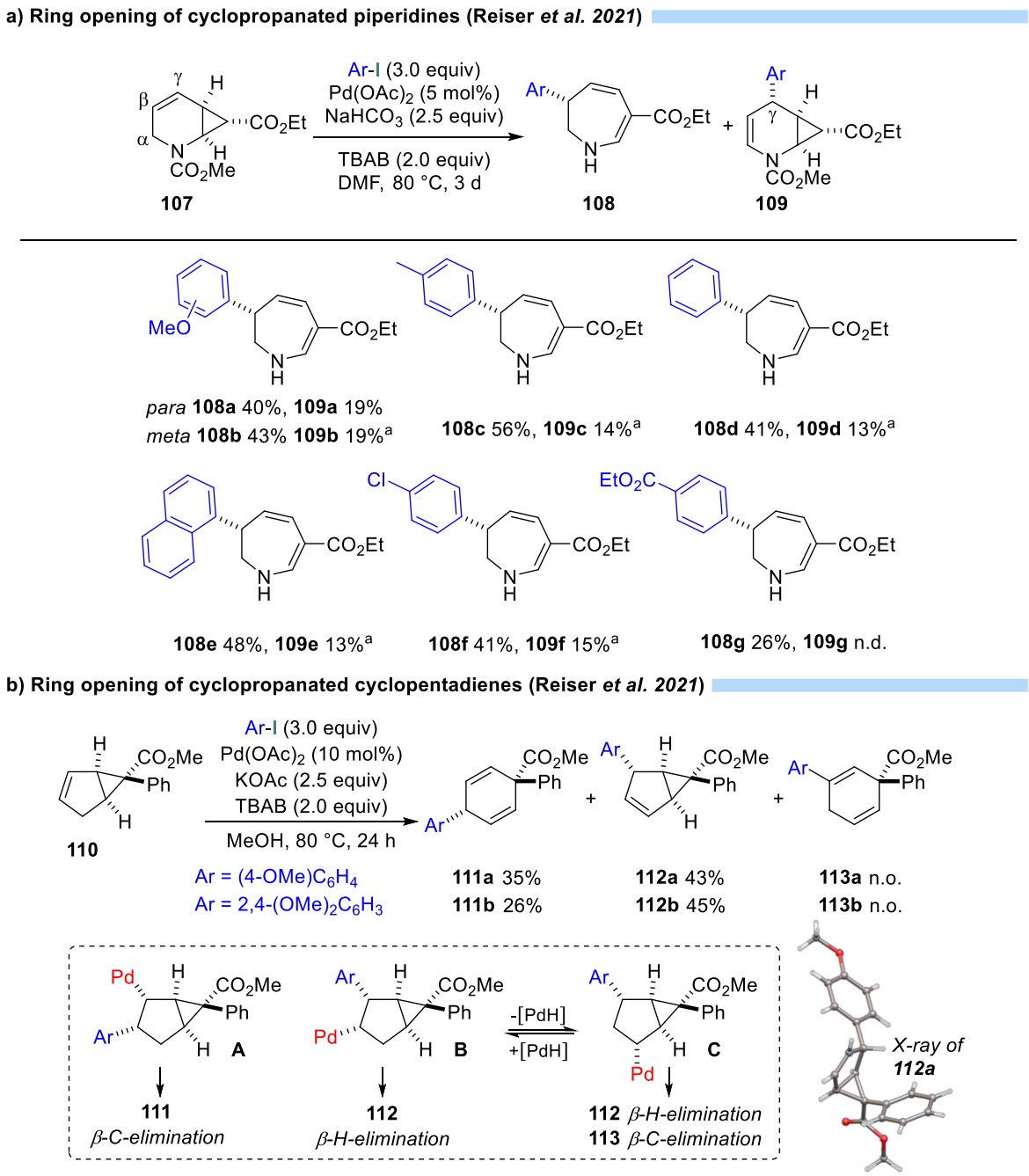
In summary we have shown in this chapter that α-bromo lactams of cyclopropanated pyrroles did not undergo the desired endocyclic ring opening towards substituted pyridinones under palladium-catalyzed cross-coupling conditions with boronic acids. Instead, we observed an exocyclic ring opening to give 3-substituted pyrrolidones. Despite some substrates giving the corresponding products in decent chemical yields, the overall substrate variety appeared to be rather limited to selected boronic acids and, thus, may not compete with other strategies reported in literature.

Likewise, other attempts for the endocyclic ring opening under microwave irradiation inspired by Reiser *et. al.*[135] did not furnish the desired six-membered products.

4. Ring opening of various cyclopropanated bicycles

4.1 Introduction

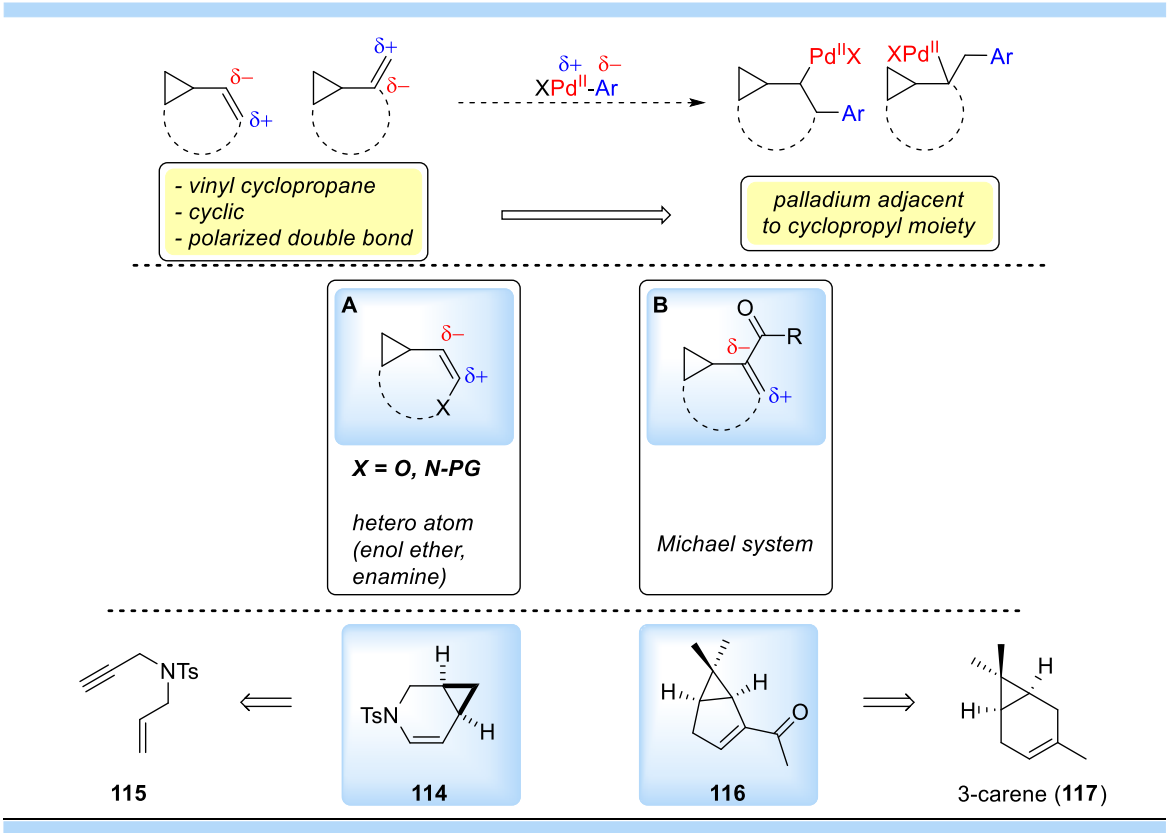
After the ring expansion chemistry *via* endocyclic ring opening triggered by Heck-coupling of cyclopropanated furans and pyrroles has been thoroughly investigated, Reiser *et al.* carried out additional investigations on this particular transformation. In an attempt to further increase the substrate variety, different cyclopropanated hetero- and carbocycles were subjected to reaction conditions (Scheme **44**).[6]



Scheme 44. Previous studies on ring opening of cyclopropanated piperidines and cyclopentadienes.[6] [a]yield of **109** determined by crude ^{1}H-NMR.

Initially, the ring expansion of cyclopropanated six-membered piperidin **107** to its seven-membered azepine analogue was envisioned (Scheme **44a**). Surprisingly, even though the formation of the desired products **108** was observed as the major product, arylated piperidin **109** still having its cyclopropyl moiety was found as a byproduct in nearly all reactions. The generation of byproduct **109** was explained as an initial Heck reaction with "wrong" regioselectivity, i.e. the palladium is not placed adjacent to the cyclopropyl moiety which resulted in a plain Heck-arylation on the γ-position without any ring opening whatsoever. The different reactivity of previously investigated pyrroles and furans compared to cyclopropanated piperidine **107** can be elucidated by the absence of an electronically directing effect. While the double bond in cyclopropanated furans or pyrroles is part of an enamine or enol ether system, respectively, causing the reactions to proceed with clean regioselectivity, the double bond in cyclopropanated piperidin **107** appears to be isolated having no directing effect.

A similar phenomenon can be observed with cyclopropanated cyclopentadiene **110** when subjected to Heck conditions (Scheme **44b**). An interesting feature of this carbocyclic substrate is the fact that also "wrong" adduct **B** may theoretically undergo opening of the endocyclic cyclopropane bond after palladium migration to **C**.[136–139]



Scheme 45. Design of new potential starting materials for the endocyclic ring opening of cyclopropanated bicycles.

However, regardless of the employed reaction conditions, arylation of substrate **110** provided unopened product **112** as the major product, while the ring-opened product **111** could only be isolated in moderate yields as the minor product. Unfortunately, the formation of isomer **113** was not observed This may indicate that in this case, the β-H-elimination outcompetes the palladium migration.

Having these results in mind we started our contemplations for the design of new potential starting materials for the Heck-triggered ring opening of cyclopropanated hetero- or carbocycles (Scheme **45**). Besides the obvious requirements of having a cyclic vinylcyclopropane, it was furthermore necessary for the double bond to have a strict polarization in order to guarantee a clean regioselectivity. Having the negatively polarized carbon adjacent to the cyclopropane would cause - upon carbopalladation - the electrophilic palladium atom to be located at the desired position to initiate the β-carbon elimination. In principle, this concept would also be applicable to exocyclic double bonds as long as the aforementioned prerequisites are fulfilled.

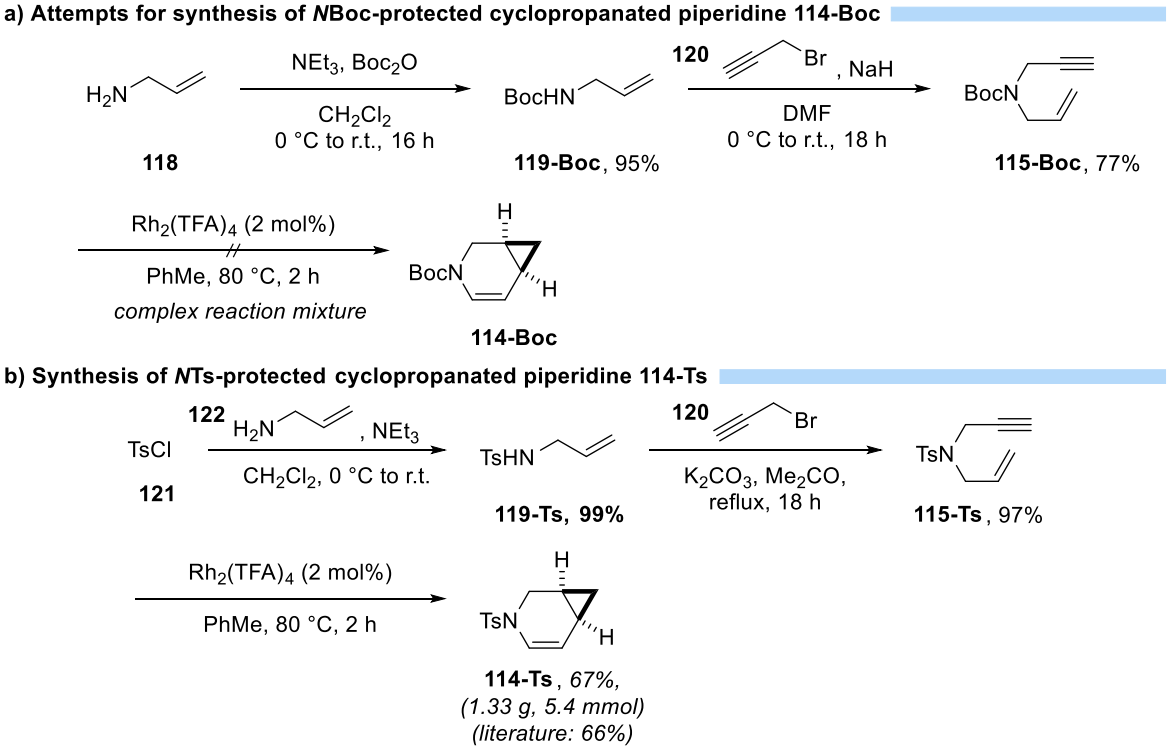
Therefor, two general molecular structures were proposed. While the first structure **A** where the double bond is part of an enamine or enol ether system has already been applied when using cyclopropanated pyrroles and furans, this concept is also applicable to larger ring systems. For instance, substrate **114** which can be readily obtained from enyne-tether **115** would be a suitable starting material for the synthesis of arylated, seven-membered azepines.[140–147] Furthermore, the polarization of the double bond could also be accomplished by incorporating the vinylcyclopropane into a Michael system **B**. One suitable representative for this substrate class is cyclopropanated cyclopentadiene **116** which can be obtained from natural product 3-carene (**117**) in two steps.[148,149]

The aim chapter will be the investigation towards the ring expansion chemistry of the two proposed starting materials **114** and **116** in order to synthesize their corresponding higher ring analogues.

4.2 Ring opening of cyclopropanated piperidines

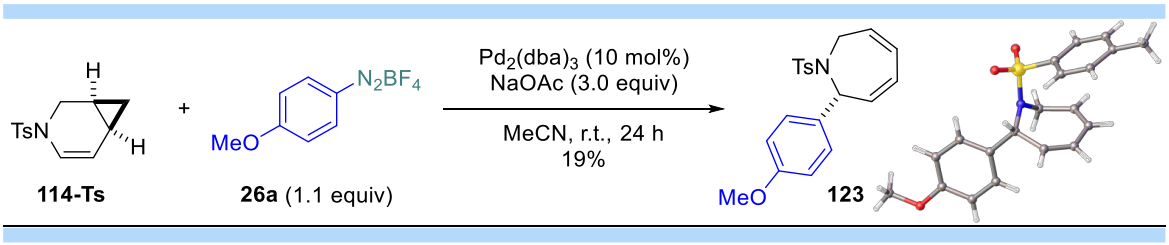
4.2.1 Palladium-catalyzed ring opening

For the ring opening of cyclopropanated piperidines towards their seven-membered analogues the necessary starting materials needed to be synthesized. As opposed to previously synthesized cyclopropyl bicycles which could be accessed by a direct cyclopropanation of the respective heterocycle with a diazo ester, the synthesis of cyclopropanated piperidines **121** followed a different strategy. It has been shown in literature that enyne-tethers can undergo a skeletal reorganization towards cyclopropanated pyrans or piperidines under Pt(II),[144] Au(I),[140] Ir(III),[142,145,147] or Rh(II)[141,143] catalysis. Since the available literature does not describe the aforementioned cyclization with *N*Boc-protected enyne-tethers having the superior protecting group,[150] we synthesized **115-Boc** in a two-step protocol[151,152] and subjected it to reaction conditions under $Rh_2(TFA)_4$ catalysis (Scheme **46a**). Unfortunately, we could only observe the generation of a complex reaction mixture, whereas the synthesis of *N*Tosyl-protected **114-Ts** gave the desired product in 67% yield on a 5.4 mmol scale (1.33 g, Scheme **46b**).[141]



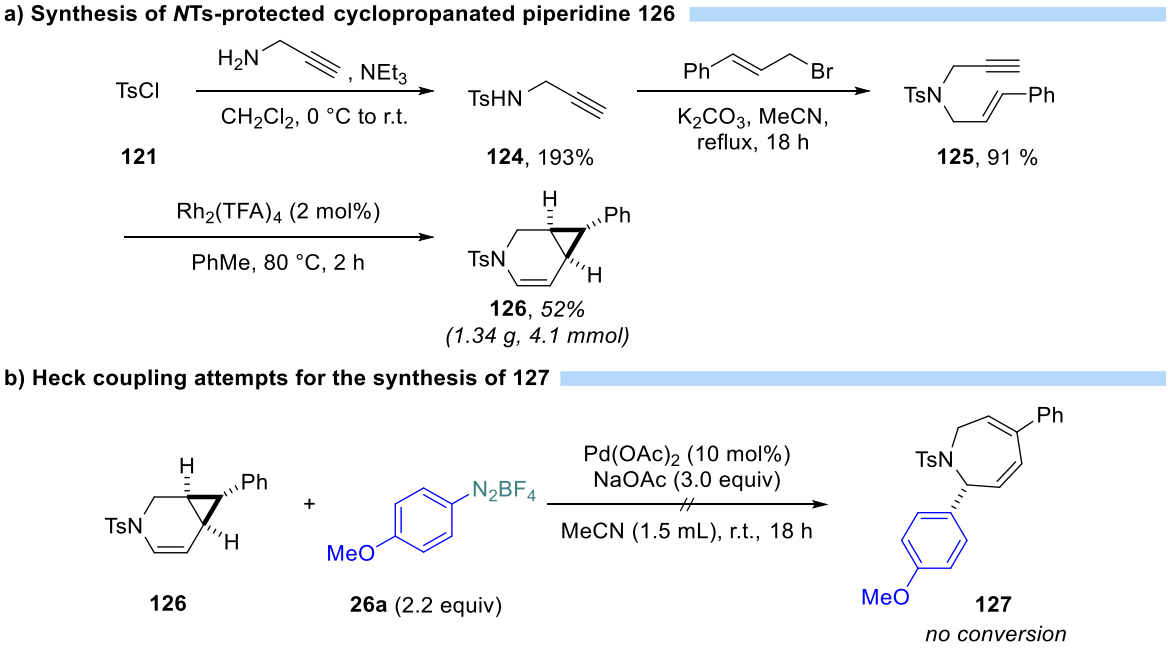
Scheme 46. Starting material synthesis of cyclopropanated piperidines.

Having the desired starting material in hand we then began our investigations towards the palladium-catalyzed ring opening of **114-Ts** to its arylated seven-membered analogue. However, while we were able to isolate the desired product **123** and confirm its structure by X-ray crystallography, the yield was only 19% using aryl diazonium salt **26a** as coupling partner (Scheme **47**). Unfortunately, we were not able to improve the reaction's efficiency by screening various reaction conditions as were either fighting with low conversion of **114-Ts** or the reaction resulted in a complex reaction mixture (for details, see experimental section Table **S 1**; Table **S 2**).



Scheme 47. Synthesis of **123**.

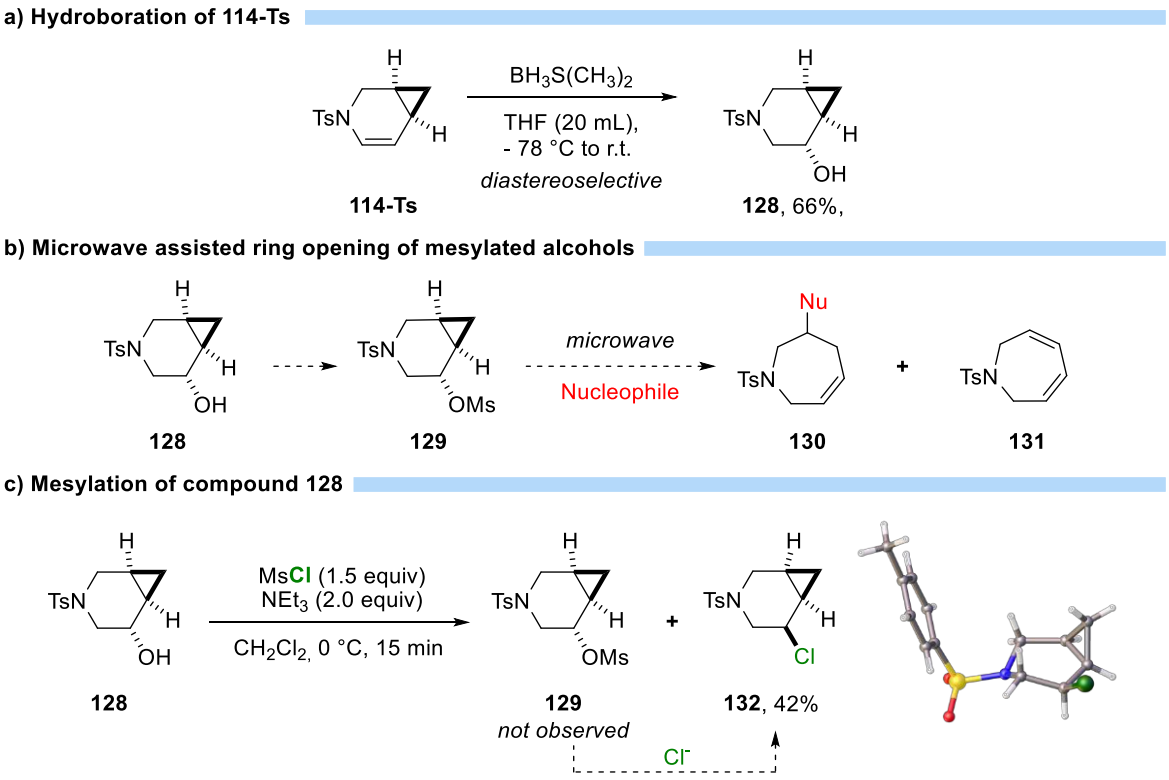
As we have never investigated the palladium-catalyzed ring opening chemistry on unsubstituted cyclopropyl moieties so far, we decided to synthesize phenyl substituted derivative **126** following known literature procedures[141,145] to examine the effect of substitution on the cyclopropyl group (Scheme **48a**). Unfortunately, when we subjected derivative **126** to reaction conditions, no conversion was observed (Scheme **48b**) which might be attributed to steric influence. In general, the poor reactivity of both substrates **123** and **126** may be explained by the presence of the tosyl protecting group as *N*Ts has more sp^3-character and hence tetrahedral geometry than fully planar, sp^2-hybridized *N*Boc group.[153,154] Therefore, further investigations on the palladium-catalyzed ring opening of cyclopropanated piperidines were discontinued.



Scheme 48. Starting material synthesis and coupling attempts of piperidine **126**.

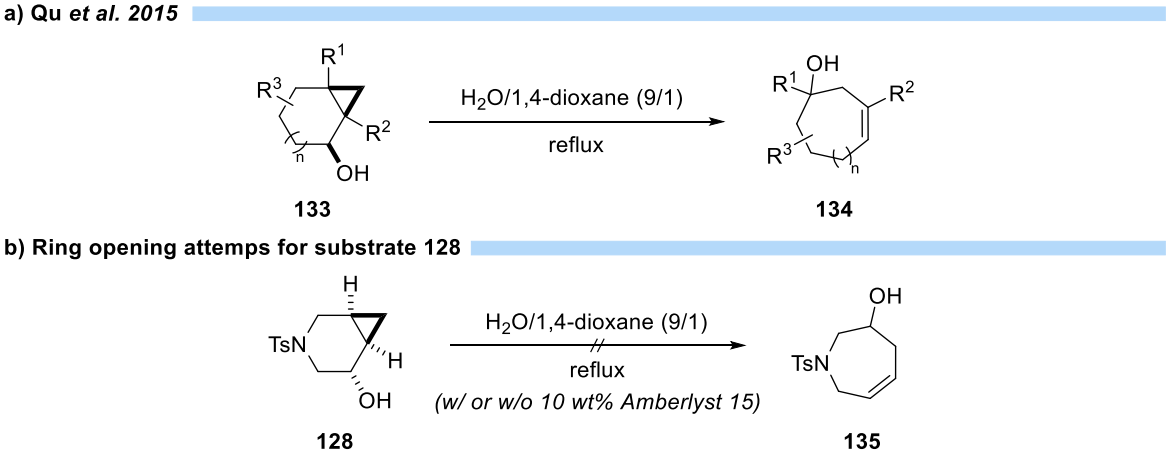
4.2.2 Ring opening *via* cyclopropyl alcohol

After previous attempts on the palladium-catalyzed ring opening of cyclopropanated piperidines have not delivered the desired outcome, other means of ring openings were investigated. As already elucidated in chapter 3.3, the microwave mediated ring opening of mesylated cyclopropyl alcohol developed by Reiser and co-workers[135] is an attractive strategy for the ring expansion of such strained bicycles. Therefor, substrate **114-Ts** was subjected to hydroboration conditions following a literature report to generate the corresponding alcohol **128** diastereoselectivity in 66% yield (Scheme **49a**).[141] Having alcohol **128** in hand we then planned to convert it into its mesyl protected analogue **129** which should be subjected to microwave conditions. After elimination of the OMs group the resulting carbocation can then either be trapped by a nucleophile to give **130** or it can undergo elimination to give conjugated product **131** (Scheme **49b**). Surprisingly, subjecting **128** to mesylation conditions did not provide the desired product but compound **132** was diastereoselectivity isolated in 42% and its structure was confirmed by X-ray crystallography. Presumably, **129** was indeed formed during the reaction but underwent nucleophilic substitution with chloride as OMs is known to be a potent leaving group.[155] As the chlorine atom is pointing to the concave face of the bicycle, it is believed that the substitution followed a clean S_N2-type mechanism (Scheme **49c**).



Scheme 49. Studies towards the microwave mediated ring opening of cyclopropanated piperidine.

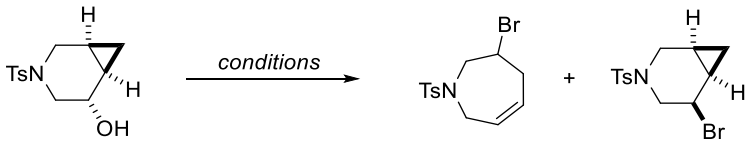
After failed mesylation attempts we then turned our attention towards the ring opening of cyclopropyl alcohols. Inspired by the literature report of Qu and co-workers in 2015 in which the ring opening of various cyclic cyclopropyl alcohols upon simple reflux in water/dioxane is described (Scheme **50a**),[156] we subjected alcohol **128** to the same reaction conditions. Surprisingly, we observed no conversion after 24 hours of reflux. Also, the addition of acidic ion exchanger Amberlyst® 15 did not change the outcome of the reaction (Scheme **50b**).



Scheme 50. Studies towards the hot water promoted ring opening of cyclopropyl alcohol **128**.

After failed attempts, we then decided to increase the acid strength and react substrate **128** directly with aqueous hydrobromic acid as there have been various literature reports on acid-catalyzed ring openings of cyclopropyl alcohols.[157–160] After preliminary attempts in neat HBr at 100 °C resulted in complete decomposition of the starting material (entry1, Table **10**), we decided to lower the reaction temperature to 0 °C and observed the formation of desired seven-membered product **136** alongside unopened product **137**[3] which similarly to **132** underwent a substitution reaction. The two products were formed in a ratio of **136**:**137** = 3:1 whereby **136** was isolated in 49% yield (entry 2, Table **10**). By adding THF as solvent we only observed a reaction between THF and HBr to 4-bromo butanol as byproduct when 5.0 equivalents of HBr were used (entry 3, Table **10**). Increasing the amount of HBr to 30 equivalents delivered **136** in 23% NMR yield and only traces of **137** but large amounts of 4-bromo butanol could still be observed (entry 4, Table **10**). Therefore, a switch of solvent to water-miscible acetonitrile was necessary which gave rise to 49% isolated yield of the desired product with only trace amounts of unopened product **137** detectable (entry 5, Table **10**). In order to test if the yield did not exceed 50% yield due to product decomposition during the reaction, we tried to both lower the amount of HBr or decrease the reaction time to six hours. Unfortunately, both attempts did not give any improvements (entry 6-7, Table **10**). Lastly, Lewis acid conditions using $ZnBr_2$ in combination with TMSBr inverted to selectivity in favor of undesired product **137**.[161]

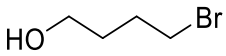
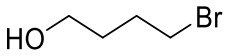
Table 10. Studies towards the HBr induced ring opening of cyclopropyl alcohol **128**.



128 **136** **137**

Entry	Conditions	Observation
1	HBr (47% aq., 30.0 equiv), *neat*, 100 °C, 1 h	*decomposition*
2	HBr (47% aq., 30.0 equiv), *neat*, 0 °C to r.t., 18 h	**136** 49% *(isolated)* **136** : **137** = 3 : 1

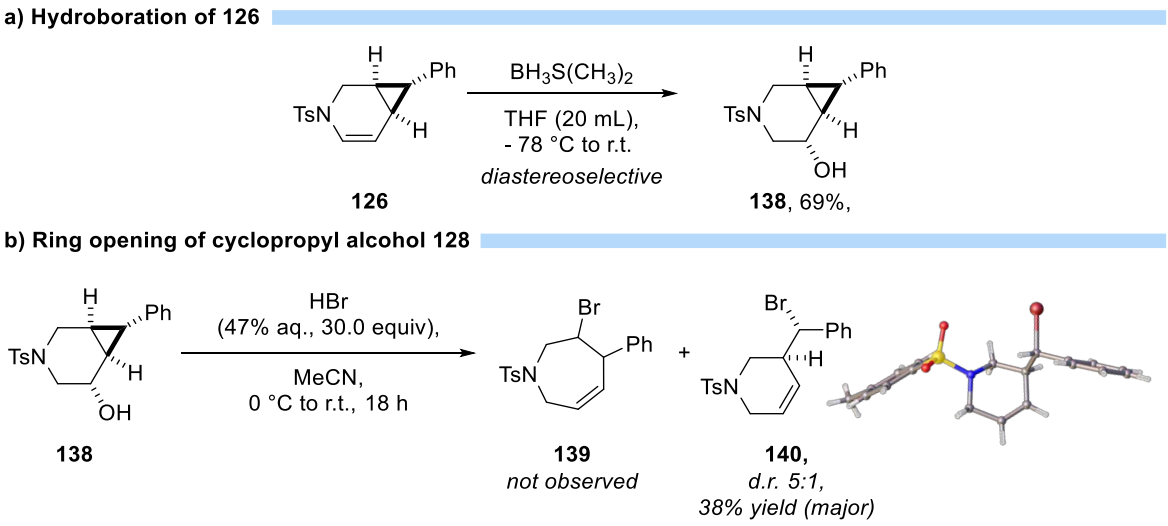
[3] The stereochemistry of **137** was assigned in analogy to **132** due to close resemblance of ^{1}H-NMRs. **137** was not isolated.

3	HBr (47% aq., 5.0 equiv), **THF**, 0 °C to r.t., 18 h	*no conversion* byproduct: 
4	HBr (47% aq., 30.0 equiv), **THF**, 0 °C to r.t., 18 h	*63% conversion* **136** *23% (NMR yield)* **136** : **137** > 20 : 1 byproduct: 
5	HBr (47% aq., 30.0 equiv), **MeCN**, 0 °C to r.t., 18 h	*50% (NMR yield)* *49% (isolated)* **136** : **137** > 20 : 1
6	HBr (47% aq., 10.0 equiv), **MeCN**, 0 °C to r.t., 6 h	**136** *12% (NMR yield)* **137** *16% (NMR yield)* **136** : **137** = 1 : 1.3
7	HBr (47% aq., 30.0 equiv), **MeCN**, 0 °C, 6 h	**136** *42% (NMR yield)* **136** : **137** > 20 : 1
8	$ZnBr_2$, (20 mol%), TMSBr (2.0 equiv), CH_2Cl_2, - 20 °C to 0 °C	**136** : **137** = 1 : 2.8

Reactions were performed on a 0.2 mmol scale. Yields were determined by crude ^{1}H-NMR analysis using 1,3,5-trimethoxy-benzene as internal standard.

Next, we were curious if the phenyl group on the cyclopropyl moiety could give additional stability during the ring opening step as the proposed mechanistic model would follow a carbocation intermediate. Therefore, phenyl substituted cyclopropane **126** was subjected to hydroboration conditions to give the corresponding alcohol **138** in 69% (Scheme **51a**). We then immediately subjected **138** to reaction conditions and were surprised to see that not expected seven-membered azepine **139** but piperidine **140** was formed in 38% yield. The structure which was confirmed by X-ray crystallography showed a cleavage of the exocyclic bond which indicates that the generation of a benzylic carbocation outcompetes the endocyclic ring opening which would generate a secondary carbocation (Scheme **51b**).

As the several ring-opening attempts both under palladium and acidic conditions failed to give the desired products in satisfying yields, further investigations on the endocyclic ring opening of cyclopropanated piperidines were discontinued.

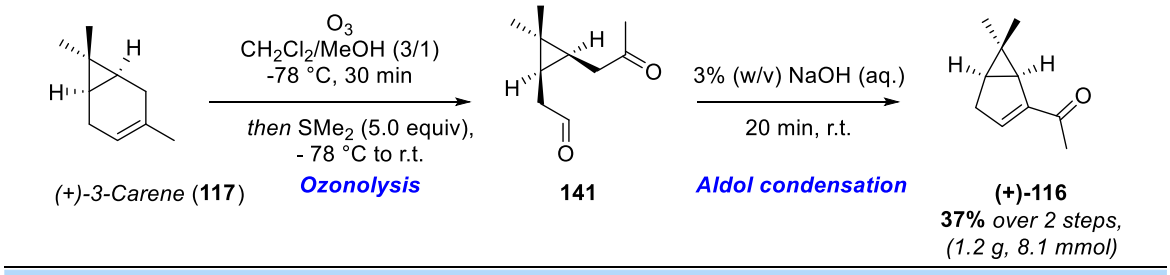


Scheme 51. Hydroboration of **126** and ring opening of **138**.

4.3 Ring opening of cyclopropanated carbocycles

4.3.1 Ring opening of cyclopropanated cyclopentadienes

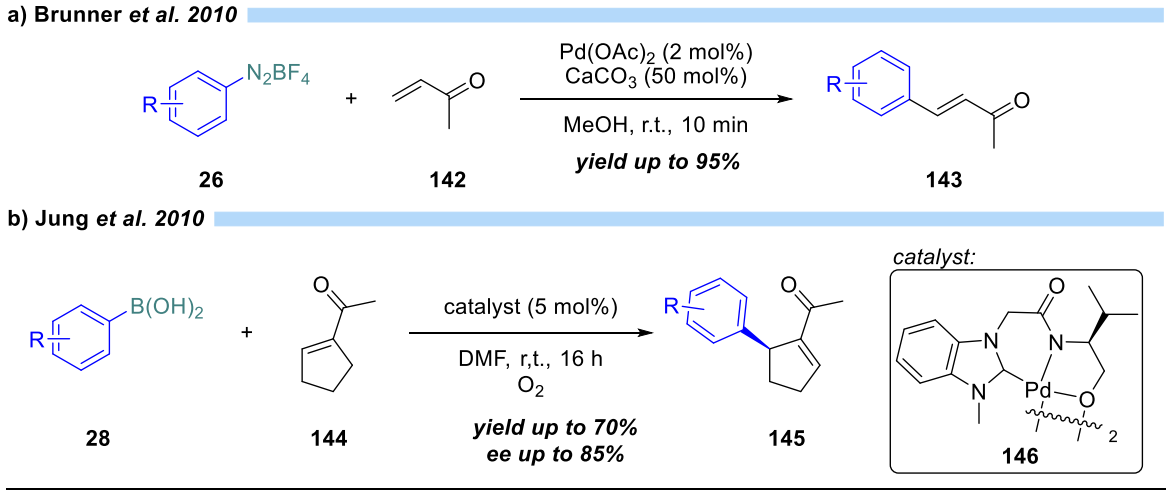
The next bicyclic cyclopropane we intended to investigate upon was purely carbon-based bicycle **(+)-116** which was readily available from natural product (+)-3-carene (**117**). (+)-Carene (**117**) is a popular starting material for the enantioselective total synthesis of natural products or biologically active compounds as it constitutes an inexpensive and commercially available chiral building block.[162–167] For the synthesis of **(+)-116**, **117** was subjected to ozonolysis conditions to cleave the double bond to obtain keto aldehyde **141** which was directly subjected to an aldol condensation under alkaline conditions to furnish **(+)-116** as a pure enantiomer in 37% over both steps (1.2 g, 8.1 mmol, Scheme **52**).[148,149]



Scheme 52. Starting material synthesis of **(+)-116** from (+)-3-carene (**117**).

Interestingly, a literature study revealed that Heck-reactions on enone systems are far less explored than their corresponding higher oxidized acrylate derivatives. Especially asymmetric catalysis still appears to be a major challenge. So far, the most popular approaches for

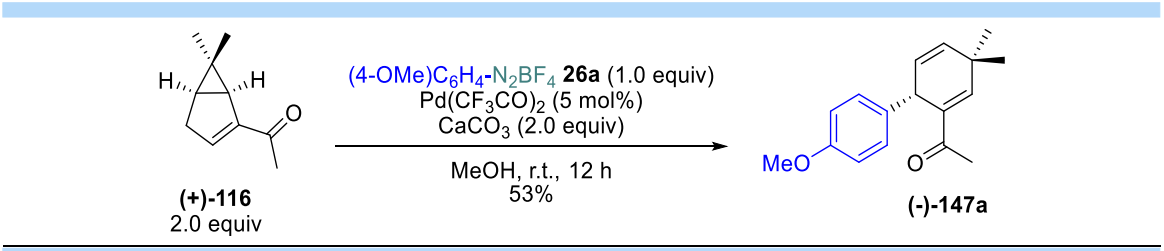
the (asymmetric) Heck-reactions on enone systems are carried out under oxidative conditions as these reactions generally require less harsh reaction conditions.[45,48–50,168–172]



Scheme 53. Heck reactions on enone systems - literature examples.

One literature example we would like to highlight was presented by the group of Heiko Brunner who reported the synthesis of benzalacetones **143** from simple butenone (**142**) and aryl diazonium salts **26** under Mizoroki Heck conditions in great yields (Scheme **53a**).[171] Likewise, Jung and co-workers showcased an oxidative Heck reaction on cyclopentene ketone **144** which shows close resemblance to substrate **(+)-116**. In their approach, aryl boronic acids were chosen as coupling partners using chiral catalyst **146** to asymmetrically generate **145** in moderate yields but good enantioselectivities.[168]

Having the necessary starting material **(+)-116** in hand we commenced our optimization studies towards the synthesis of arylated six-membered carbocycles **147** *via* palladium-catalyzed Heck-reactions. Initially, we opted for a Mizoroki-Heck protocol using aryl diazonium salt **26a** similar to the conditions reported by Brunner *et al.* (Scheme **54**). Unfortunately, regardless of the employed reaction parameters, the yield did not exceed 53% (for detailed screening of reaction parameters, see experimental section Table **S 3**).

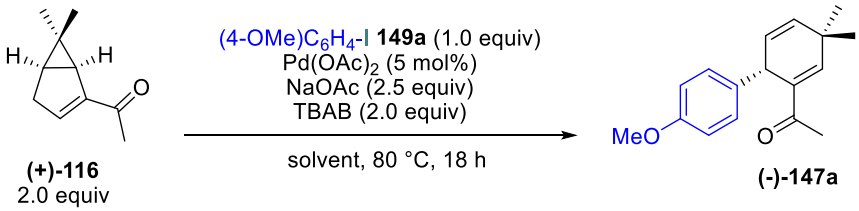


Scheme 54. Synthesis of **(-)-147a** under Mizoroki Heck conditions.

Thus a switch of coupling protocol was necessary. Inspired by the first report of Reiser *et al.* on endocyclic ring openings of cyclopropanated heterocycles (*cf.* Scheme **44b**)[2] we opted for standard Heck conditions using aryl iodides, palladium acetate as catalyst, sodium acetate as base and tetrabutylammonium bromide as additive. Surprisingly, when preliminary test reactions in various solvents were carried out, almost quantitative yields were observed in DMF, toluene and 1,4-dioxane (entries 1,3 and 4, Table **11**) whereas methanol as solvent led to a reduced yield of 78% (entry 2, Table **11**).

As three different solvents afforded **(-)-147a** cleanly in 99% yield, we decided to choose toluene as the solvent of choice for future studies as it is inexpensive and environmentally less harmful than dioxane or DMF.

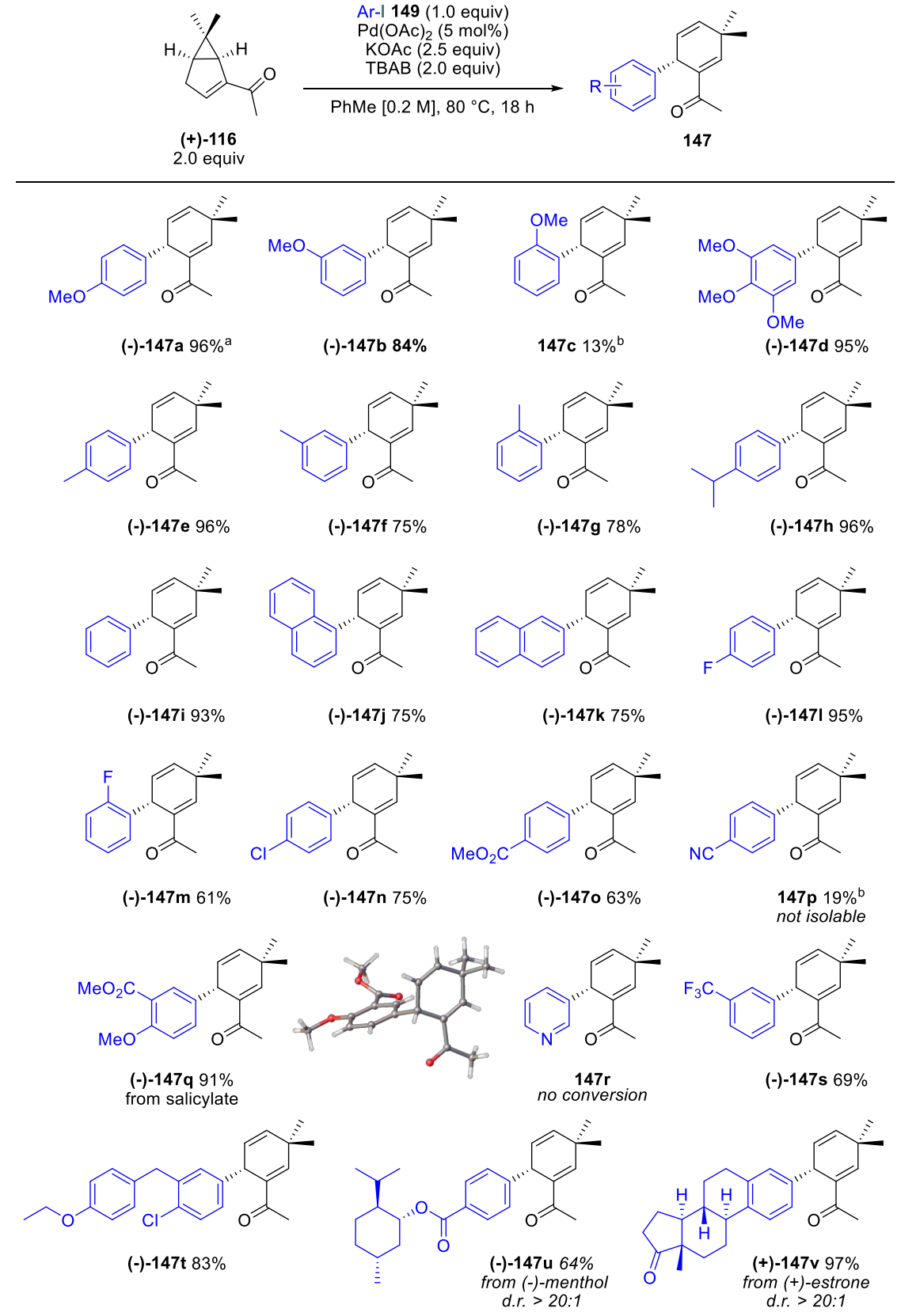
Table 11. Optimization studies for the synthesis of **(-)-147a** under standard Heck conditions.



Entry	Solvent (1.5 mL)	NMR-Yield[a]
1	DMF	**99%**
2	MeOH	78%
3	PhMe	**99%**
4	1,4-dioxane	**99%**

All reactions were carried out on a 0.3 mmol scale. [a]determined by crude ^{1}H-NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

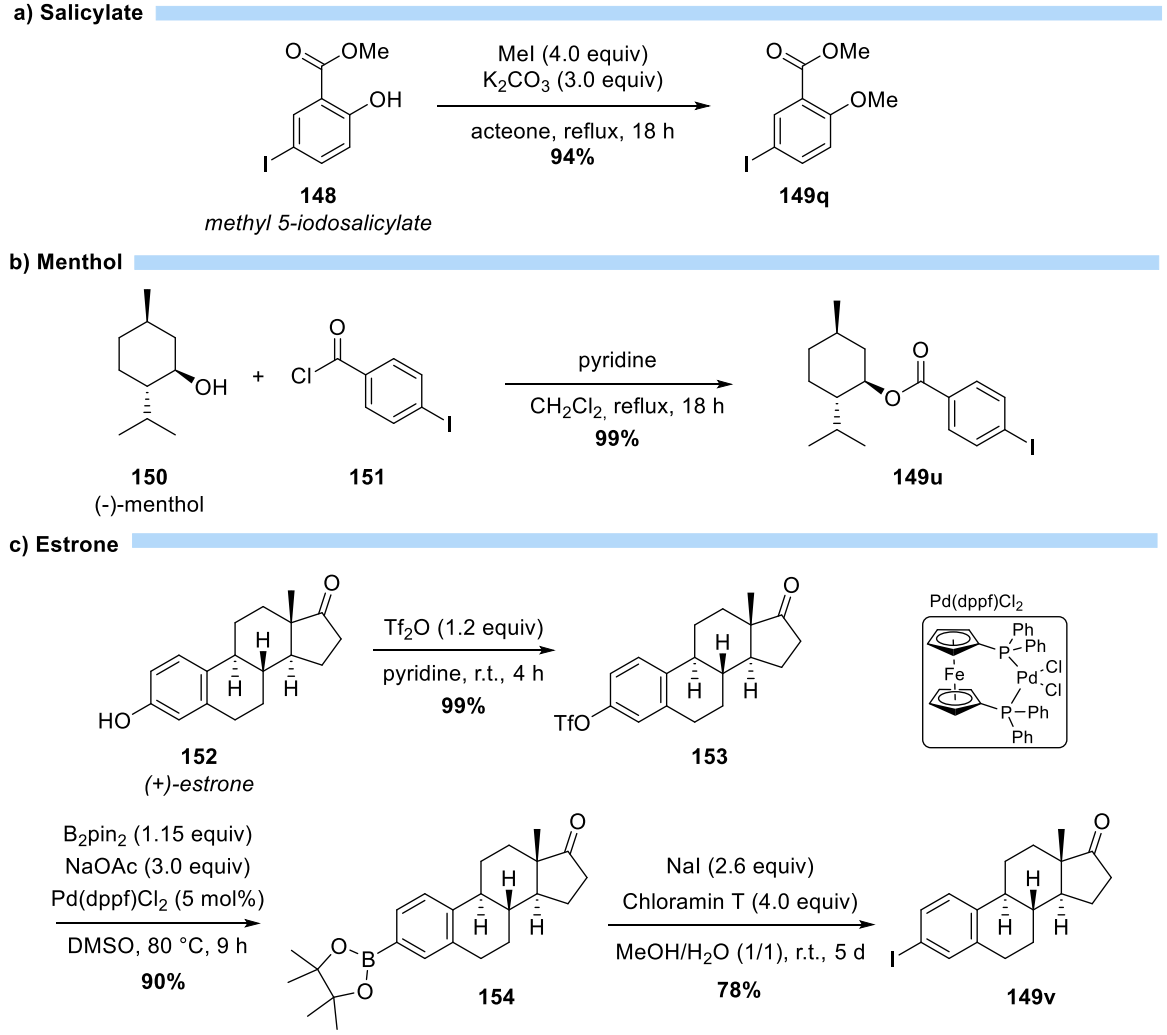
Having found ideal reaction conditions for the synthesis of cyclohexadienes **(-)-147** we began exploring the substrate scope for this transformation using variously substituted aryl iodides (Scheme **55**). Model substrate having a *para*-methoxy group resulted in 96% isolated yield while only 50% yield were observed when 4-bromo anisole instead of 4-iodo anisole was used. Moving the substitution pattern to the *meta* position, the yield only decreased slightly to 86% whereas *ortho*-methoxy substituted product **147c** resulted in a complex reaction mixture and could not be isolated (13% NMR-yield). On the other hand, 3,4,5-trimethoxysubstituted cyclohexadiene **(-)-147d** was isolated in 95% yield. Moving on to less electron donating alkyl substituted substrates we were able to isolate the corresponding



Scheme 55. Substrate scope for the synthesis of enantiopure cyclohexadienes **147.** All reactions were carried out on a 0.5 mmol scale using 2.5 mL of solvent. [a]50% yield when 4-bromoanisole was used instead of 4-iodoanisole, [b]complex reaction mixture, not isolable. Crude ^{1}H-NMR yield using 1,3,5-trimethoxybenzene as internal standard.

products in satisfying 75% to 96% yields. Also, unsubstituted iodobenzene **149i** furnished the corresponding product in 93%. Interestingly, increasing the steric demand to 1-iodo or 2-iodonaphthyl derivatives both resulted in 75% isolated yield.

When we switched from electronically rich or neutral aryl iodides to electronically deficient substrates, we still observed 95% with *para*-fluoro iodobenzene, whereas ortho-fluoro iodobenzene caused a decrease in yield (61%). While electron deficient substituents *para*-chloro and *para*-methyl carboxylate gave the corresponding products **(-)-147n** and **(-)-147o** in good to moderate 75% and 63% yield, respectively, *para*-cyano resulted in a complex reaction mixture. Product **147p** could not be isolated and yields were determined by crude ^{1}H-NMR analysis.

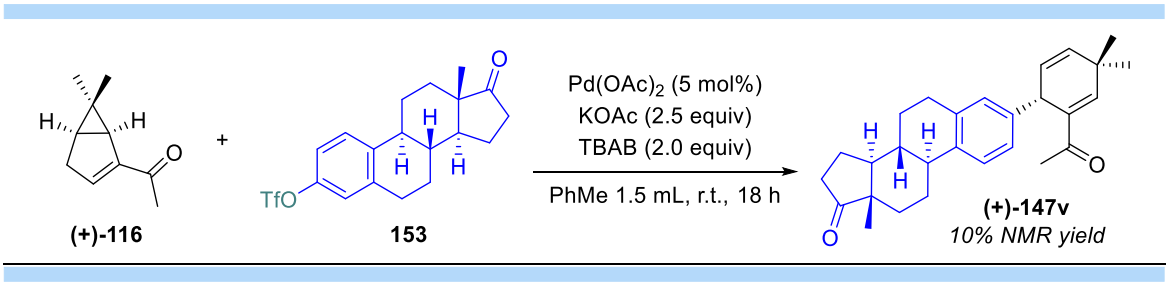


Scheme 56. Synthesis of aryl iodides from bioactive compounds.

Subjecting methyl salicylate **149q** which was synthesized according to a literature procedure (Scheme **56a**)[173] to reaction conditions afforded the corresponding product in 91% yield. Furthermore, the absolute stereochemistry of the products **147** was determined by X-ray

crystallography of **(-)-147q** showing that the carbopalladation occurred from the convex face of the bicycle. The stereochemistry of all other substrates was assigned analogously. Unfortunately, no conversion was observed with heterocyclic 3-iodo pyridine and *meta*-CF_3 substituted iodobenzene resulted in decreased 69% yield whereas satisfying 83% yield were in turn observed with 1-Chloro-2-(4-ethoxybenzyl)-4-iodobenzene (**149t**). Lasty, we wanted to subject enantiopure chiral aryl iodides in order to see if the reaction follows a clean transfer of chirality from enantiopure starting material **(+)-116**. Therefor, substrate **149u** which is derived from enantiopure (-)-menthol (Scheme **56b**)[174] and **149v** which is derived from enantiopure (+)-estrone **152** (Scheme **56c**)[175] were prepared following known literature procedures. Having synthesized both chiral iodobenzenes, we subjected them to reaction conditions and were pleased to find that both substrates gave the desired products **(-)-147u** and **(+)-147v** as a single diastereomer (d.r. >> 20:1 by crude ^{1}H-NMR analysis) in 64% and 97% yields, respectively.

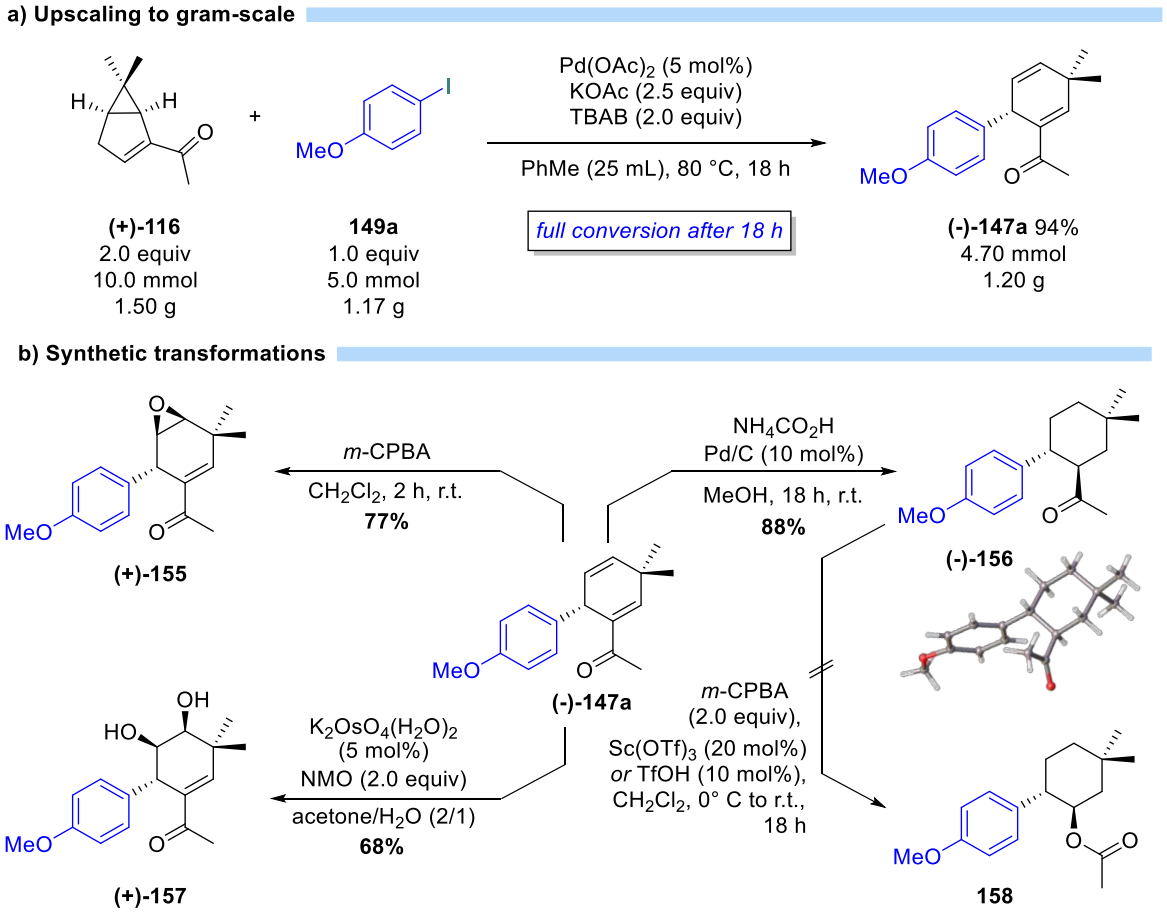
Notably, during the course of the synthesis of estrone iodide **149v**, triflate **153** was obtained as an intermediate (Scheme **56c**). As we have seen in chapter 2 of the present work that aryl triflates are also suitable coupling partners in Heck reactions, we subjected **153** to reaction conditions. However, the corresponding products **(+)-147v** was only detected in 10% NMR yield highlighting that aryl iodides are much more potent reaction partners than aryl triflates (Scheme **57**).



Scheme 57. Synthesis of **(+)-147v** directly from triflate **153**. Yield determined by crude ^{1}H-NMR analysis using 1,3,5-trimethoxybenezene as internal standard.

So far, we have only shown that the reaction features a clean transfer of chirality by having the necessary optical rotation of all products, as well as by obtaining products **(-)-147u** and **(+)-147v** as a single diastereomers from enantiopure starting materials. Unfortunately, determination of the enantiomeric excess of selected examples by chiral HPLC analysis was not possible as no racemic (±)-3-carene was available as reference compound. Therefore, we opted for a chiral lanthanide shift experiment[176] with model substrate **(-)-147a** (for details,

see experimental part Scheme **S 1**). Using tris-[3-(trifluormethyl-hydroxymethylen)-*d*-camphorato]-europium(III) Eu(tfc)$_3$ as chiral shift reagent in super stoichiometric amounts, we were not able to detect a second set of signals while observing significant chemical shifts induced by Eu(tfc)$_3$ which indicates that the presence of a second enantiomer is unlikely.



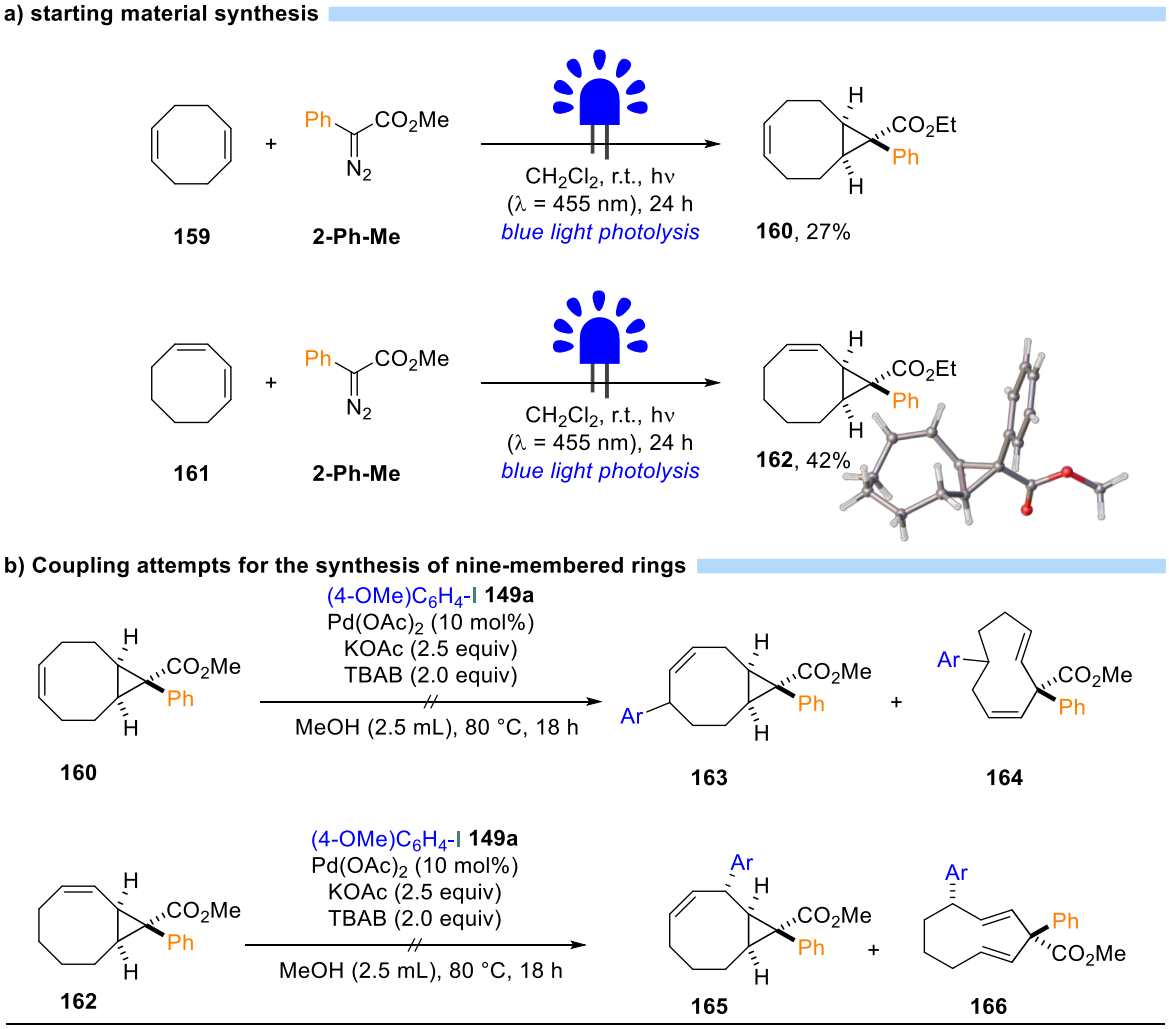
Scheme 58. Upscaling and synthetic transformations. Stereochemistry of compounds **(+)-155** and **(+)-157** could not be determined. *Trans*-selectivity was tentatively assigned in analogy to literature.[177–180]

Lastly, in order to demonstrate the robustness of this process we conducted an upscaling experiment using 5.0 mmol of 4-iodoanisole (**149a**) and 10.0 mmol of **(+)-116** to obtain the corresponding product **(-)-147a** in 94% (1.20 g, 4.7 mmol). Notably, no prolongation of the reaction time was necessary (Scheme **58a**). Having synthetically useful amounts of product in hand we conducted several synthetic transformations to showcase the utility of the obtained compounds (Scheme **58b**). Reacting **(-)-147a** with 3-chlorobenzene-1-carboperoxoic acid *m*-CPBA gave epoxide **(+)-155** in 77% yield. Hydrogenation using ammonium formate in combination with palladium on charcoal gave fully hydrogenated product **(-)-156** in 88% yield. Interestingly, X-ray analysis of the product revealed a *trans*-geometry of aryl and keto moiety indicating that the hydrogenation of the enone system most likely followed a 1,4-

addition. Furthermore, dihydroxylation using catalytic amounts of OsO_4 gave dialcohol **(+)-157** in 68%. Unfortunately, the stereochemistry of compounds **(+)-155** and **(+)-157** could not be determined. Hence, *trans*-selectivity was tentatively assigned in analogy to literature for similar substrates.[177–180] And lastly, attempts to oxidize **(-)-156** to ester **158** in a Bayer-Villiger type oxidation failed under both $Sc(OTf)_3$ and TfOH catalysis.[181]

4.3.2 Ring opening of large bicycles

Having successfully investigated the ring opening of cyclopropanated cyclopentadiene derivative **(+)-116** towards six-membered cyclohexadienes **(-)-147** we intended to further examine the ring opening with concomitant ring enlargement of cyclopropanated carbocycles towards larger ring analogues.



Scheme 59. Starting material synthesis of cyclopropanated cyclooctadienes and Heck coupling attempts.

Reiser and co-workers have previously shown, that a ring-enlargement from six membered piperidines to seven-membered azepines is in principle feasible.[6] Therefore, two suitable

starting materials were synthesized (Scheme **59a**). Following a literature report,[182] 1,5-cyclooctadiene (**159**) and 1,3-cyclooctadiene (**161**) were subjected to blue-light photolysis of diazoester **2-Ph-Me** which gave the desired products **160** and **162** diastereoselectively in 27% and 42% yield, respectively.

Having the necessary starting materials in hand we subjected both substrates to reaction conditions that gave the best results for Reiser *et. al.* in the case of cyclopropanated cyclopentadienes.[6] Theoretically, both substrates can either undergo a plain Heck arylation of the starting material if the carbopalladation proceeds with mismatched regioselectivity, or β-carbon elimination with concomitant ring opening when the palladium is placed adjacent to the cyclopropyl moiety. In the case of substrate **160** the palladium would first have to undergo chain-walking along the hydrocarbon chain to reach the α-cyclopropyl position. Such palladium chain-walking reactivity has already been impressively described by Marek and co-workers for acyclic substrates.[3–5,183,184] Unfortunately, while substrate **160** resulted in a complex reaction mixture, compound **162** showed no conversion which might be attributed to conformational reasons as such [8.1.0]-scaffolds prefer relatively twisted conformations compared to smaller ring-size analogues.

4.4 Summary

In summary, we have shown in this chapter that the ring-opening chemistry triggered by Heck arylations can be successfully expanded towards cyclopropanated piperidines and cyclohexadienes. It was shown that a careful design of the starting materials in terms of electronic properties of the vinyl cyclopropane moiety allows the synthesis of their arylated higher ring analogues in a regioselective fashion. While cyclopropanated piperidines overall reacted poorly yet regioselectively under the employed reaction condition, we could demonstrate that the ring-expansion chemistry with cyclopropanated cyclopentadiene derivatives works in good yields. Having obtained the starting material in an enantioselective manner from natural resources, we could also show that the reaction features a clean transfer of chirality as the products do not appear to suffer from epimerization. Having synthesized a variety of differently substituted, arylated 1,4-cyclohexadienes we could also showcase that the protocol can be upscaled to a 5 mmol scale and that the products offer room for several synthetic transformations.

Unfortunately, the ring expansion of cyclopropanated cyclooctadienes was not successful.

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[183] Cohen, Y.; Cohen, A.; Marek, I. *Chem. Rev.* **2021**, *121*, 140–161.

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C. Summary

The present PhD thesis demonstrates the further development of the endocyclic ring opening of cyclopropanated bicycles/fused bicycles which has first been described in 2019 by Reiser and co-workers who demonstrated that this strategy allows for a facile access to highly substituted, arylated dihydropyridines and 2*H*-pyrans. In particular, this thesis improved upon the overall efficiency of the process as well as increased the substrate diversity both for cyclopropanes as well as coupling reagents.

Initially, a brief introduction about different strategies for the ring opening of cyclopropanes was presented. Especially, the multifaceted role of palladium in cyclopropane chemistry was highlighted. In general, the chapter tried to work out the concept, that placing a palladium atom by means of e.g. carbopalladation or C-H-activation etc. on the α-cyclopropyl position may eventually trigger the desired β-carbon elimination upon [1,3]-migration of the palladium.

In chapter 1 we could show that the synthesis of 2*H*-pyrans could be improved by switching from traditional Heck coupling conditions using aryl halides to oxidative Heck conditions using aryl boronic acids. While the overall yields could only be slightly improved, we were able to access a much greater variety of differently substituted 2*H*-pyrans. Interestingly, when geminal disubstituted cyclopropanated furans were employed in the reaction, the unexpected formation of highly, asymmetrically substituted 1,3-butatienes was observed. Presumably, the underlying mechanism follows a retro Diels-Alder type reaction.

In chapter 2 we demonstrated that the palladium-catalyzed ring opening of cyclopropanated pyrroles towards arylated dihydropyridines is not only limited to arylation processes but may also be conducted upon vinylation of the starting materials. Thereby, vinyl triflates have proven to be powerful coupling reagents that allowed the synthesis of a small library of 2-vinyl dihydropyridines.

In chapter 3 we envisioned an “inverse approach” were we tried to switch the order of the cross-coupling step and the ring-opening/migration step. Therefor, cyclopropanated α-bromo lactams were chosen as substrates as palladium may be introduced into the molecule by means of oxidative addition into the C-Br bond and the reaction would be terminated *via*

transmetallation using aryl boronic acids. Surprisingly, instead of the desired six-membered target structures, we observed the unexpected formation of five-membered pyrrolidones which are the result of an exocyclic ring opening.

Lastly, in chapter 4 it was demonstrated that the ring-opening chemistry can also be extended to cyclopropanated piperidines or cyclopropanated cyclopentadienes to access their corresponding seven-membered azepines or cyclohexenes, respectively. While the former gave the desired product in only unsatisfactory yields, cyclopropanated cyclopentadiene gave the desired ring-expanded compounds in excellent yields with various aryl iodides. Having obtained the starting material as a pure enantiomer from natural resources we could also demonstrate that the process features a clean transfer of chirality.

D. Zusammenfassung

Die vorliegende Dissertation behandelt die Weiterentwicklung der endozyklischen Ringöffnung cyclopropanierter Bizyklen/anellierter gespannter Ringsysteme. Die erstmals im Jahr 2019 von Reiser und Mitarbeitern beschrieben Strategie, welche einfachen Zugang zu hochsubstituierten, arylierten Dihydropyridinen und 2*H*-Pyranen ermöglicht, wurde hinsichtlich ihrer Effizienz, sowie ihrer Substratvielfalt sowohl für Cyclopropane als auch für Kupplungsreagenzien verbessert.

Zunächst wurden in der Einleitung verschiedene Strategien zur Ringöffnung von Cyclopropanen diskutiert. Insbesondere wurde die vielseitige Rolle von Palladium in der Cyclopropanchemie hervorgehoben. Generell wurde in dem Kapitel versucht, das Konzept auszuarbeiten, dass das Platzieren eines Palladiumatoms z.B. mittels Carbopalladierung oder C-H-Aktivierung usw. an der α-cyclopropyl-Position schließlich die gewünschte β-Kohlenstoff-Eliminierung mit einhergehender [1,3]-Migration des Palladiums auslösen kann.

In Kapitel 1 konnten wir zeigen, dass die Synthese von 2*H*-Pyranen durch den Wechsel von traditionellen Heck-Kupplungsbedingungen mit Arylhalogeniden zu oxidativen Heck-Bedingungen mit Arylboronsäuren verbessert werden kann. Während die durchschnittlichen Ausbeuten nur geringfügig verbessert werden konnten, konnten wir dennoch auf eine viel größere Diversität unterschiedlich substituierter 2*H*-Pyrane auf diese Weise darstellen. Interessanterweise wurde beim Einsatz von geminal disubstituierten, cyclopropanierten Furanen in der Reaktion die unerwartete Bildung von asymmetrischen, hochsubstituierten 1,3-Butatienen beobachtet. Vermutlich folgt der zugrundeliegende Mechanismus einer retro Diels-Alder-Reaktion.

In Kapitel 2 haben wir gezeigt, dass die Palladium-katalysierte Ringöffnung von cyclopropanierten Pyrrolen zu arylierten Dihydropyridinen nicht nur auf Arylierungen beschränkt ist, sondern auch durch Vinylierung des Pyrroles durchgeführt werden kann. Dabei haben sich Vinyltriflate als leistungsstarke Kupplungsreagenzien erwiesen, welche die Synthese mehrerer 2-Vinyldihydropyridine ermöglichten.

In Kapitel 3 haben wir uns mit einer „inversen Herangehensweise“ auseinandergesetzt, bei dem die Reihenfolge des Kreuzkupplungsschritts und des Ringöffnungs-/Migrationsschrittes vertauscht werden sollten. Dabei wurden cyclopropanierte α-Bromolactame als Substrate gewählt, da Palladium durch eine oxidative Addition in die C-Br-Bindung in das Molekül eingeführt werden kann und die Reaktion schließlich mittels Transmetallierung mit Arylboronsäuren terminiert werden würde. Überraschenderweise beobachteten wir anstelle der gewünschten sechsgliedrigen Zielstrukturen die unerwartete Bildung von fünfgliedrigen Pyrrolidonen, welche das Resultat einer exocyclischen Ringöffnung sind.

Zuletzt wurde in Kapitel 4 gezeigt, dass die Ringöffnungschemie auch auf cyclopropanierte Piperidine oder cyclopropanierte Cyclopentadiene ausgeweitet werden kann, um die entsprechenden siebengliedrigen Azepine bzw. Cyclohexene zu erhalten. Während erstere das gewünschte Produkt nur in unbefriedigenden Ausbeuten lieferte, reagierte ein cyclopropaniertes Cyclopentadienderviat mit verschiedenen Aryliodiden zu den gewünschten Verbindungen in exzellenten Ausbeuten. Nachdem das Ausgangsmaterial als reines Enantiomer aus natürlichen Ressourcen erhalten wurde, konnte auch gezeigt werden, dass der Prozess einen Chiralitätstransfer ermöglichte.

E. Experimental Part

1. General Information

Commercially available chemicals were purchased in high quality and were used without further purification. All reactions were carried out in flame dried glassware under atmospheric conditions unless otherwise stated. Reactions with moisture or oxygen sensitive reagents were carried out in flame dried glassware under an atmosphere of predried nitrogen. Anhydrous solvents were prepared by established laboratory procedures.[4] CH_2Cl_2, EtOAc and hexanes (40-60 °C) for chromatography were distilled prior to use. All palladium coupling reactions were carried out in flame dried glassware applying three consecutive freeze-pump-thaw cycles. The reported yields are referred to the isolated compounds unless otherwise stated.

Chromatography

Thin layer chromatography was performed with TLC precoated aluminum sheets (Merck) Silica gel 60 F254, 0.2 mm layer thickness. Visualization was done with UV light (λ = 254 nm) and staining with vanillin (6 g vanillin, 100 mL ethanol (95%), 1 mL conc. sulfuric acid), ninhydrin (300 mg ninhydrin, 3 mL conc. acetic acid, 100 mL ethanol) or potassium permanganate (1.0 g KMnO4, 2.0 g Na2CO3, 100 mL water) followed by heating. Column chromatography was performed with silica gel (Merck, 0.063-0.200 mm particle size) and flash silica gel 60 (Merck, 0.040-0.063 mm particle size).

NMR-Spectroscopy

^{1}H NMR spectra were recorded on FT-NMR-spectrometer of the type Bruker Avance 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C, 282 MHz for ^{19}F) or BRUKER Avance III 400 "Nanobay" (400 MHz for ^{1}H, 100 MHz for ^{13}C, 386 MHz for ^{19}F). Chemical shifts for ^{1}H NMR were reported as δ, parts per million (ppm), relative to the signal of $CHCl_3$ at 7.26 ppm, H_2O at 4.79 ppm, relative to the center line signal of the CH_3CN quintet at 1.94 ppm and relative to the center line signal of the DMSO quintet at 2.50 ppm. Spectra were evaluated in 1st order and coupling constants J were reported in Hertz (Hz). The following notations indicate the multiplicity of the signals: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, p = quintet, sex = sextet, hept = septet, and m = multiplet, and combinations thereof. Chemical shifts for ^{13}C NMR were reported as δ, parts per million (ppm), relative to the center line signal of the $CDCl_3$ triplet at 77.16 ppm. NMR yields were determined using diphenoxymethane, 1,1,2,2-tetrachloroethane, 1,3,5-trimethoxybenzene as internal standards.

[4] a) Armarego, W. L. F.; Chai, C. L. L., *Purification of Laboratory Chemicals.* 6 ed.; Butterworth-Heinemann Oxford, 2009.
b) Hünig, S.; Felderhoff, M.; Kemmerer, M.; Kreitmeier, P.; Märkl, G.; Sauer, J.; Seifert, M.; Sustmann, R.; Troll, *Integriertes Organisch-Chemisches Praktikum (I.O.C.-Praktikum);* 1. ed.; Lehmanns, 2007.

IR-Spectroscopy

FTIR spectroscopy was carried out on a Cary 630 FTIR Spectrometer. Solid and liquid compounds were measured neatly, and the wave numbers are reported as cm^{-1} .

Mass Spectrometry

Mass spectra were recorded by the Central Analytical Laboratory (University of Regensburg) using Jeol AccuTOF GCX and Agilent Q-TOF 6540 UHD. High-resolution mass spectra were measured using atmospheric pressure chemical ionization (APCI), electron ionization (EI), electrospray ionization (ESI) with a quadrupole time-of-flight (Q-TOF) detector. Polarimetry Determination of optical rotation was carried out on a MCP 500 Modular Circular Polarimeter by Anton Paar using 589 nm (Na-D-line) as measurement wavelength.

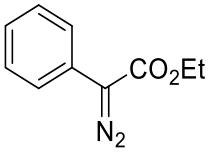
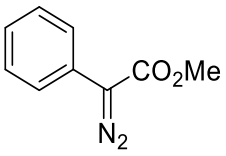
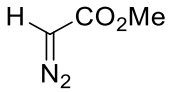
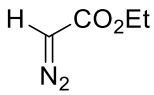
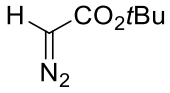
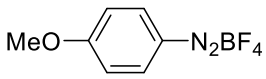
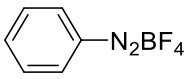
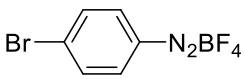
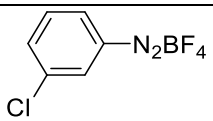
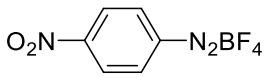
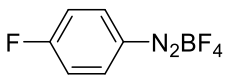
Melting Point Apparatus

The measurement of melting point was carried out on a MPA100 - Automated melting point system by OptiMelt using a ramp rate of 1K/min.

Microwave

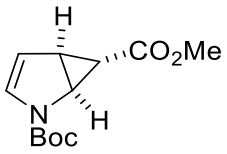
Experiments under microwave irradiation were carried out using an Anton Paar Monowave 300 reactor.

2. Literature known compounds

Chemical structure	Chemical name	Synthesis according to reference
	tert-butyl 1*H*-pyrrole-1-carboxylate (**1-Boc)** 1-tosyl pyrrole (**1-Ts**)	Grehn, L.; Ragnarsson, U. *Angew. Chem. Int. Ed.* **1984**, *23*, 296-297. C. Zonta, F. Fabris. O. De Lucchi, *Org. Lett.* **2005**, *7*, 1003-1006
	ethyl 2-diazo-2-phenylacetate (**2-Ph-Et)**	M. Hu, C. Ni, J. Hu, *J. Am Chem. Soc.* **2012**, 134, 15257-15260.
	methyl 2-diazo-2-phenylacetate (**2-Ph-Me)**	Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063–3070.
	methyl 2-diazoacetate (**2-Me)**	N. E. Searle, *Org. Synth.* **1956**, *36*, 25.
	ethyl 2-diazoacetate (**2-Et)**	
	tert-butyl 2-diazoacetate (**2-*t*Bu)**	D. A. Nicewicz, G. Breteche, J. Johnson, C. Bryan, *Org. Synth.* **2008**, *85*, 278.
aryldiazonium tetrafluoroborates (26)		
	4-methoxybenzenediazonium tetrafluoroborate	1) Hanson, P.; Jones, J. R.; Taylor, A. B.; Walton, P. H.; Timms, A. W., *J. Chem. Soc., Perkin Trans. 2* **2002**, *2*, 1135 - 1150. 2) Roe, A., *Org. React.* **1949**, *5*, 193 – 216.
	benzene diazonium tetrafluoroborate	
	4-bromobenzenediazonium tetrafluoroborate	
	3-chlorobenzenediazonium tetrafluoroborate	
	4-nitrobenzenediazonium tetrafluoroborate	
	4-fluorobenzenediazonium tetrafluoroborate	

3. Experimental Procedures

2-(tert-butyl) 6-methyl-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (3-Me)

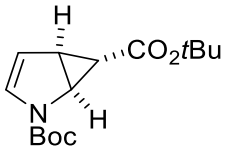


Compound **3-Me** was synthesized according to a literature procedure.[5] A flame dried 250 mL Schlenk flask was purged with nitrogen and charged with $Cu(OTf)_2$ (730 mg, 2.1 mmol, 2 mol%), *N*Boc-pyrrole (**1-Boc**) (17.7 g, 105 mmol, 1.0 equiv.) and CH_2Cl_2 (anhydrous, 45 mL). Phenylhydrazine (207 µL, 228 mg, 2.1 mmol, 2 mol%) was added, causing the solution to turn dark red-brown and methyl 2-diazoacetate (**2-Me**) (15.8 g, 158.0 mmol, 1.5 equiv, 152 g solution of 10.4 wt%) was subsequently added dropwise with the aid of a syringe pump (one drop every 10 seconds) at room temperature. After complete addition the solution was filtered through basic Al_2O_3, which was then washed with CH_2Cl_2 (500 mL). Concentration under reduced pressure afforded a yellow solid which was purified by column chromatography on silica (hexanes/ ethyl acetate = 10/1) and subsequently multiple times recrystallized in pentane (freezer) to obtain **3-Me** as a colorless solid (6.33 g, 26.5 mmol, 25%). Spectroscopic data are in agreement with those reported in literature.

^{1}H-NMR (400 MHz, CDCl3) δ = 6.69 – 6.35 (m, 1H), 5.50 – 5.25 (m, 1H), 4.51 – 4.21 (m, 1H), 3.74 – 3.61 (m, 3H), 2.82 (s, 1H), 1.51 (s, 9H), 0.97 (s, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) *rotamer 1 (rotamer 2)* δ = (173.6), 173.3, (151.3), 151.0, (129.9), 129.7, 109.9, 81.8l, 51.9, (44.3), 44.2, (32.3), 31.1, 28.3, 22.9, (22.8).

di-tert-butyl-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (3-*t*Bu)



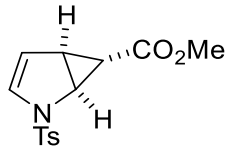
Compound **3-*t*Bu** was synthesized according to a literature procedure.[6] A flame dried 250 mL Schlenk flask was purged with nitrogen and charged with $Cu(OTf)_2$ (217 mg, 0.6 mmol, 1 mol%), *N*Boc-pyrrole (**1-Boc**) (10.0 g, 60 mmol, 1.0 equiv.) and CH_2Cl_2 (anhydrous, 30 mL). Phenylhydrazine (59 µL, 65 mg, 0.6 mmol, 1 mol%) was added, causing the solution to turn dark red-brown and *tert*-butyl 2-diazoacetate (**2-*t*Bu**) (12.79 g, 90.0 mmol, 1.5 equiv, 84.1 g solution of 15.2 wt%) was subsequently added dropwise with the aid of a syringe pump (one drop every 10 seconds) at room temperature. After complete addition the solution was filtered through basic Al_2O_3, which was then washed with CH_2Cl_2 (500 mL). Concentration under reduced pressure afforded a yellow solid which was purified by column chromatography on silica (hexanes/ ethyl acetate = 50/1) and subsequently recrystallized in refluxing pentane to obtain **3-*t*Bu** as a colorless solid (4.05 g, 14.4 mmol, 24%). Spectroscopic data are in agreement with those reported in literature.

^{1}H-NMR (300 MHz, CDCl3) δ = 6.54 – 6.29 (m, 1H), 5.34 – 5.21, (m, 1H), 4.34 – 4.06 (m, 1H), 2.71 – 2.57 (m, 1H), 1.42 (s, 9H), 1.37 (s, 9H), 0.85 – 0.74 (m, 1H).

[5] L. K. A. Pilsl, T. Ertl, O. Reiser, *Org. Lett.* **2017**, *19*, 2754–2757.
[6] L. K. A. Pilsl, T. Ertl, O. Reiser, *Org. Lett.* **2017**, *19*, 2754–2757.

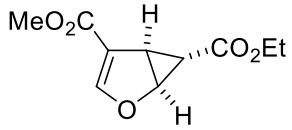
^{13}C-NMR (101 MHz, $CDCl_3$, rotamers1 (rotamer 2) δ= (172.6), 172.62, (151.6), 151.2, 129.6, 110.2, 81.7, 80.9, (44.2), 43.9, (31.9), 30.8, 28.4, 28.3, 24. 2

methyl-2-tosyl-2-azabicyclo[3.1.0]hex-3-ene-6-carboxylate (3-Ts-Me)



A flame dried 100 mL Schlenk flask was purged with nitrogen and charged with $Cu(OTf)_2$ (109 mg, 0.3 mmol, 1 mol%), *N*Tosyl-pyrrole (**1-Ts**) (6.64 g, 30 mmol, 1.0 equiv.) and CH_2Cl_2 (anhydrous, 30 mL). Phenylhydrazine (30 µL, 32 mg, 0.3 mmol, 1 mol%) was added, causing the solution to turn dark red-brown and methyl 2-diazoacetate (**2-Me**) (4.5 g, 45.0 mmol, 1.5 equiv, 34.1 g solution of 13.2 wt%) was subsequently added dropwise with the aid of a syringe pump (one drop every 10 seconds) at room temperature. After complete addition the solution was filtered through basic Al_2O_3, which was then washed with CH_2Cl_2 (500 mL). Concentration under reduced pressure afforded a yellow oil which was purified by column chromatography on silica (hexanes/ ethyl acetate = 5/1) giving a yellow solid. After recrystallization in refluxing pentane **3-Ts-Me** was obtained as a colorless solid (2.51 g, 8.7 mmol, 29%).
R_f (hexanes/ethyl acetate = 3/1) = 0.35; **mp.** = 130 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 7.74 – 7.62 (m, 2H), 7.45 – 7.30 (m, 2H), 6.34 (dd, *J* = 4.0, 1.2 Hz, 1H), 5.46 (dd, *J* = 4.0, 2.6 Hz, 1H), 4.16 (dt, *J* = 6.6, 1.6 Hz, 1H), 3.66 (s, 3H), 2.71 (dt, *J* = 6.6, 2.7 Hz, 1H), 2.44 (s, 3H), 0.52 (dd, *J* = 2.9, 1.8 Hz, 1H).; **^{13}C-NMR** (75 MHz, $CDCl_3$) δ = 172.6, 144.6, 133.7, 130.6, 130.1, 127.5, 113.7, 52.2, 45.6, 31.7, 21.8, 21.0.; **IR** (neat): 3116, 2956, 1722, 1592, 1495, 1439, 1383, 1342, 1293, 1163, 1040, 850, 723, 816, 667 cm^{-1}.; **HRMS** (+ESI, 120 V): calcd. for $C_{14}H_{16}NO_4S$ $[M+H]^+$ 294.0795 found 294.0800.

6-ethyl 4-methyl-2-oxabicyclo[3.1.0]hex-3-ene-4,6-dicarboxylate (15)



Compound **15** was synthesized according to a literature procedure.[7] A flame dried 25 mL Schlenk flask was purged with nitrogen and charged with $Cu(OTf)_2$ (180.8 mg, 500 µmol, 1 mol%), CH_2Cl_2 (anhydrous, 13.5 mL) and (S,S)-*i*Pr-bis(oxazoline)-ligand (**7-*i*Pr**) (293,0 mg, 1.1 mmol, 2.2 mol%) resulting in a deep blue solution. After stirring for 30 min the copper complex solution was transferred into a flame dried 100 mL Schlenk flask under nitrogen atmosphere, equipped with a gas bubbler and containing a solution of 3-furoic acid methyl ester (**25**) (6.31 g, 50.0 mmol, 1.0 equiv) in CH_2Cl_2 (anhydrous, 25 mL) at 0 °C, using a syringe filter. Phenylhydrazine (49 µL, 54.1 mg, 0.5 mmol, 1 mol%) was added, causing the solution to turn into dark red-brown and subsequently, ethyl 2-diazoacetate (8.56 g, 75.0 mmol, 1.5 equiv, 72.5 g solution of 11.8 wt%) was added dropwise with the aid of a syringe pump (one drop every 10 seconds). The reaction mixture was allowed to warm to room temperature after complete addition. Afterwards, the solution was filtered through basic Al_2O_3, which was then washed with CH_2Cl_2 (500 mL). Concentration under reduced pressure afforded a yellow oil which was purified by column chromatography on

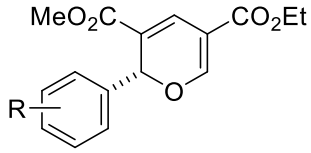
[7] K. Harrar, O. Reiser, *Chem. Commun.* **2012**, *48*, 3457–3459.

silica (hexanes/ ethyl acetate = 19/1) to obtain **15** as a colorless oil (4.65 g, 22.0 mmol, 44%, e.r. = 84:16). Spectroscopic data are in agreement with those reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.20 (d, *J* = 0.8 Hz, 1H), 5.02 (dt, *J* = 5.7, 1.0 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 3.09 (dd, *J* = 5.6, 2.9 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 4H), 1.14 (dd, *J* = 2.8, 0.9 Hz, 1H).

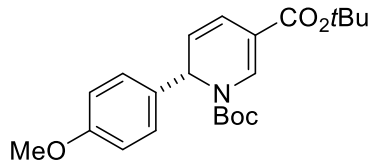
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 171.6, 164.0, 156.4, 115.8, 69.0, 61.1, 51.6, 29.5, 21.6, 14.2.

General procedure (GP-I) for the synthesis of 5-ethyl 3-methyl 2-aryl-2*H*-pyrans-3,5-dicarboxylates



A flame dried 5 mL vial with gas inlet equipped with a magnetic stir bar was charged with furan **15** (106 mg, 0.50 mmol, 1.0 equiv), aryl boronic acid (0.65 mmol, 1.3 equiv), sodium carbonate (106 mg, 1.00 mmol, 2.0 equiv), copper(II)-chloride (anhydrous, 67 mg, 0.50 mmol, 1.0 equiv), bis(acetonitrile)dichloropalladium(II) (6.5 mg, 25 µmol, 0.05 equiv) and THF (anhydrous, 1 mL). After an oxygen balloon was attached to the gas inlet and the flask was flushed thoroughly, the reaction was stirred at room temperature for four days, giving a green suspension. The reaction mixture was then diluted with chloroform and transferred to a round bottomed flask. After removal of the solvent *in vacuo* the residue was dissolved in ethyl acetate and filtered through a short plug of basic aluminum oxide (Brockmann I). After the solvent had been removed under reduced pressure, the pure product was isolated by flash column chromatography on silica gel (hexanes/ ethyl acetate).

di-tert-butyl 6-(4-methoxyphenyl)pyridine-1,3(6H)-dicarboxylate (14a)

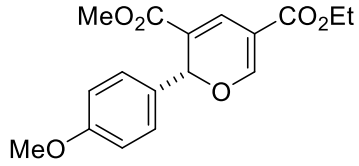


Following the general procedure GP-I (reaction temperature 55 °C) using monocyclopropanated *N*Boc pyrrole (**3-*t*Bu**) (141 mg, 0.5 mmol, 1.0 equiv) and (4-methoxyphenyl)boronic acid (99 mg, 0.65 mmol, 1.3 equiv) gave the title compound as a colorless oil (102 mg, 0.27 mmol, 53%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 15/1). The spectral data are in good accordance with those reported in the literature.[8]

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.89 (bs, 1H), 7.34 – 7.21 (m, 2H), 6.92 – 6.74 (m, 2H), 6.44 (s, 1H), 5.70 (bs, 1H), 5.55 (dd, *J* = 9.8, 5.4 Hz, 1H), 3.79 (s, 3H), 1.51 (s, 9H), 1.43 (s, 9H) (Signal broadening due to rotamers). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 165.2, 159.4, 152.1, 134.8, 128.3, 121.5, 118.8, 113.9, 108.8, 83.1, 80.3, 56.4, 55.3, 28.4, 28.1.

[8] J. Yedoyan, N. Wurzer, U. Klimczak, T. Ertl, O. Reiser, *Angew. Chem. Int. Ed.* **2019**, *58*, 3594–3598.

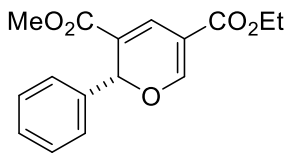
5-ethyl 3-methyl 2-(4-methoxyphenyl)-2H-pyran-3,5-dicarboxylate (16a)



Following the general procedure GP-I with reaction time of 7 days using (4-methoxyphenyl)boronic acid (99 mg, 0.65 mmol, 1.3 equiv) gave the title compound as a colorless solid (71 mg, 0.23 mmol, 45%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 20/1). X-ray grade crystals were obtained by slow evaporation from MeOH. The spectral data are in good accordance with those reported in the literature.[9]

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 1.2 Hz, 1H), 7.60 (d, *J* = 1.2 Hz, 1H), 7.42 – 7.29 (m, 2H), 6.90 – 6.84 (m, 2H), 6.28 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.72 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 165.1, 164.8, 160.6, 158.7, 130.1, 129.8, 129.3, 116.9, 114.2, 107.4, 77.0, 60.7, 55.4, 52.0, 14.5.

5-ethyl 3-methyl 2-phenyl-2*H*-pyran-3,5-dicarboxylate (16b)

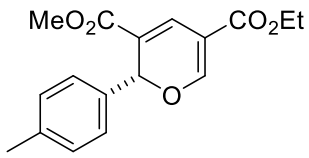


Following the general procedure GP-I using phenyl boronic acid (79 mg, 0.65 mmol, 1.3 equiv) the title compound as a colorless oil (62 mg, 0.31 mmol, 62%) which solidified upon storing for several days at room temperature after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 15/1).

R_f (hexanes/ ethyl acetate = 3/1) = 0.53;**mp.** = 54 – 57 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 1.2 Hz, 1H), 7.63 (d, *J* = 1.2 Hz, 1H), 7.48 – 7.31 (m, 5H), 6.34 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ = 165.0, 164.6, 158.6, 137.8, 129.8, 129.4, 128.7, 127.5, 116.8, 107.5, 77.0, 60.6, 51.9, 14.3; **IR** (neat): 3068, 2982, 2956, 1707, 1640, 1569, 1439, 1405, 1327, 1297, 1238, 1193, 1115, 1074, 988, 746, 701 cm^{-1}; **HRMS** (+APCI): calcd. for $C_{16}H_{17}O_5$ $(M+H)^+$ 289.1071 found 289.1076.

The spectral data are in good accordance with those reported in the literature.[10]

5-ethyl 3-methyl 2-(*p*-tolyl)-2*H*-pyran-3,5-dicarboxylate (16c)



Following the general procedure GP-I using (4-methyl)phenyl boronic acid (88 mg, 0.65 mmol, 1.3 equiv) gave the title compound as a yellow oil (89 mg, 0.30 mmol, 59%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 15/1).

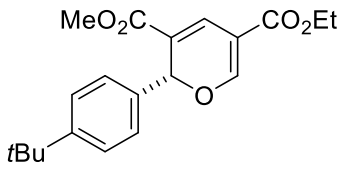
R_f (hexanes/ ethyl acetate = 3/1) = 0.53; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 1.2 Hz, 1H), 7.61 (d, *J* = 1.2 Hz, 1H), 7.36 – 7.28 (m, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 6.30 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 3H), 2.34 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 165.1, 164.7, 158.7, 139.5, 135.0, 129.8, 129.5, 127.7, 116.9, 107.5, 77.1, 60.6, 52.0, 21.4, 14.4; **IR** (neat): 2952,

[9] J. Yedoyan, N. Wurzer, U. Klimczak, T. Ertl, O. Reiser, *Angew. Chem. Int. Ed.* **2019**, *58*, 3594–3598.
[10] J. Yedoyan, N. Wurzer, U. Klimczak, T. Ertl, O. Reiser, *Angew. Chem. Int. Ed.* **2019**, *58*, 3594–3598.

2981, 1703, 1640, 1566, 1439, 1405, 1372, 1293, 1230, 1182, 1111, 1074, 1021, 988, 917, 861, 805, 770 cm^{-1}; **HRMS** (+APCI): calcd. for $C_{17}H_{19}O_5$ $(M+H)^+$ 303.1227 found 303.1232.

The spectral data are in good accordance with those reported in the literature.[11]

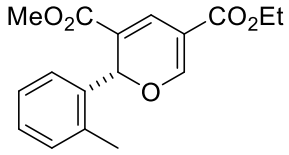
5-ethyl 3-methyl 2-(4-(tert-butyl)phenyl)-2*H*-pyran-3,5-dicarboxylate (16d)



Following the general procedure GP-I using (4-*tert*-butyl)phenyl boronic acid (116 mg, 0.65 mmol, 1.3 equiv) gave the title compound as a white solid (109 mg, 0.32 mmol, 63%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 15/1).

R_f (hexanes/ ethyl acetate = 3/1) = 0.65; **mp.** = 118 – 121 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 1.2 Hz, 1H), 7.62 (d, *J* = 1.2 Hz, 1H), 7.41 – 7.32 (m, 4H), 6.32 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 1.30 (m, 12H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 165.1, 164.6, 158.7, 152.4, 134.8, 129.7, 127.3, 125.7, 116.8, 107.4, 76.9, 60.5, 51.9, 34.7, 31.3, 14.3; **IR** (neat): 3075, 2963, 2870, 1692, 1558, 1446, 1401, 1297, 1241, 1189, 1103, 1018, 917, 857, 757 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{20}H_{25}O_5$ $(M+H)^+$ 345.1697 found 345.1703.

5-ethyl 3-methyl 2-(o-tolyl)-2H-pyran-3,5-dicarboxylate (16e)

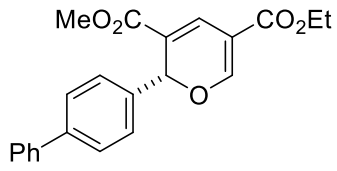


Following the general procedure GP-I using 2-tolyl boronic acid (88 mg, 0.65 mmol, 1.3 equiv) gave the title compound as a yellowish solid (75 mg, 0.38 mmol, 50%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 15/1). The spectral data are in good accordance with those reported in the literature.[12]

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.78 (d, *J* = 1.2 Hz, 1H), 7.54 (d, *J* = 1.2 Hz, 1H), 7.33 – 7.22 (m, 3H), 7.20 – 7.12 (m, 1H), 6.61 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 3H), 2.57 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 165.0, 164.8, 158.7, 137.5, 135.0, 131.2, 130.5, 129.6, 127.7, 126.3, 116.4, 107.2, 73.9, 60.6, 52.0, 19.2, 14.4.

[11] J. Yedoyan, N. Wurzer, U. Klimczak, T. Ertl, O. Reiser, *Angew. Chem. Int. Ed.* **2019**, *58*, 3594–3598.
[12] J. Yedoyan, N. Wurzer, U. Klimczak, T. Ertl, O. Reiser, *Angew. Chem. Int. Ed.* **2019**, *58*, 3594–3598.

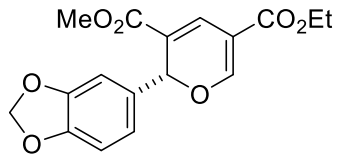
5-ethyl 3-methyl 2-([1,1'-biphenyl]-4-yl)-2H-pyran-3,5-dicarboxylate (16f)



Following the general procedure GP-I using (1,1`-biphenyl)boronic acid (129 mg, 0.65 mmol, 1.3 equiv) gave the title compound as a yellow solid (121 mg, 0.33 mmol, 66%) after purification by column chromatography on silica gel (MeOH/CH_2Cl_2 = 0.5/99.5 to 1/99).

R_f (hexanes/ ethyl acetate = 3/1) = 0.58; **mp.** = 96 – 100 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 7.74 (d, *J* = 1.1 Hz, 1H), 7.66 (d, *J* = 1.2 Hz, 1H), 7.61 – 7.54 (m, 4H), 7.52 – 7.47 (m, 2H), 7.47 – 7.40 (m, 2H), 7.39 – 7.32 (m, 1H), 6.39 (s, 1H), 3.75 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ = 165.1, 164.7, 158.7, 142.4, 140.5, 136.8, 130.0, 128.9, 128.1, 127.7, 127.6, 127.3, 116.8, 107.6, 76.9, 60.7, 52.1, 14.4.; **IR** (neat): 3064, 3034, 2978, 1700, 1640, 1569, 1487, 1439, 1368, 1327, 1234, 1107, 1006, 850, 753, 697 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{22}H_{21}O_5$ $[M+H]^+$ 365.1384 found 365.1388.

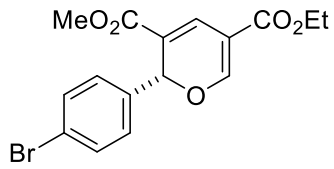
5-ethyl 3-methyl 2-(benzo[d][1,3]dioxol-5-yl)-2H-pyran-3,5-dicarboxylate (16g)



Following the general procedure GP-I using benzo[d][1,3]dioxol-5-ylboronic acid (108 mg, 0.65 mmol, 1.3 equiv) gave the title compound as a yellow oil (80 mg, 0.24 mmol, 48%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 20/1).

R_f (hexanes/ ethyl acetate = 3/1) = 0.48; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 1.2 Hz, 1H), 7.60 (d, *J* = 1.2 Hz, 1H), 6.90 (dq, *J* = 3.4, 1.8 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.23 (s, 1H), 5.96 (s, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 165.0, 164.7, 158.6, 148.7, 148.2, 131.8, 129.9, 121.9, 116.9, 108.5, 108.2, 107.4, 101.5, 77.1, 60.7, 52.0, 14.4; **IR** (neat): 3071, 2982, 2956, 2904, 1700, 1640, 1566, 1487, 1439, 1230, 1189, 1096, 1074, 992, 928, 853, 809, 749 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{17}H_{17}O_7$ $[M+H]^+$ 333.0969 found 333.0969.

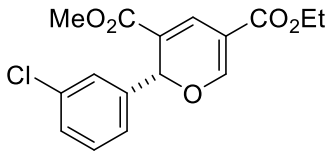
5-ethyl 3-methyl 2-(4-bromophenyl)-2H-pyran-3,5-dicarboxylate (16h)



Following the general procedure GP-I using (4-bromophenyl)boronic acid (131 mg, 0.65 mmol, 1.3 equiv) gave the title compound as a yellow oil (86 mg, 0.24 mmol, 47%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 15/1).

R_f (hexanes/ ethyl acetate = 3/1) = 0.60; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 1.2 Hz, 1H), 7.61 (d, *J* = 1.2 Hz, 1H), 7.51 – 7.47 (m, 2H), 7.31 – 7.27 (m, 2H), 6.28 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 164.9, 164.5, 158.5, 136.9, 132.0, 130.1, 129.3, 123.7, 116.6, 107.7, 76.3, 60.8, 52.1, 14.4; **IR** (neat): 2982, 2952, 1700, 1640, 1566, 1405, 1439, 1368, 1234, 1189, 1111, 1070, 1010, 919, 854, 753 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{16}H_{16}BrO_5$ $[M+H]^+$ 367.0176 found 367.0174.

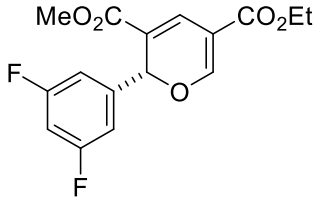
5-ethyl 3-methyl 2-(3-chlorophenyl)-2H-pyran-3,5-dicarboxylate (16i)



Following the general procedure GP-I using (3-chlorophenyl)boronic acid (102 mg, 0.65 mmol, 1.3 equiv) gave the title compound as a colorless oil (71 mg, 0.22 mmol, 44%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 15/1).

R_f (hexanes/ ethyl acetate = 3/1) = 0.60; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 1.2 Hz, 1H), 7.63 (d, *J* = 1.2 Hz, 1H), 7.38 (m, 1H), 7.35 – 7.28 (m, 3H), 6.30 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 164.9, 164.5, 158.5, 139.9, 134.8, 130.3, 130.1, 129.6, 127.8, 125.8, 116.5, 107.8, 76.2, 60.8, 52.1, 14.4; **IR** (neat): 3071,2981, 2952, 1700, 1640, 1566, 1478, 1438, 1405, 1372, 1230, 1185, 1074, 1018, 988, 921, 787, 753, 705 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{16}H_{16}ClO_5$ $[M+H]^+$ 323.0681 found 323.0683.

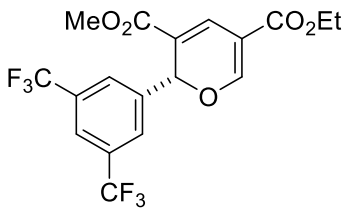
5-ethyl 3-methyl 2-(3,5-difluorophenyl)-2*H*-pyran-3,5-dicarboxylate (16j)



Following the general procedure GP-I using (3,5-difluorophenyl)boronic acid (103 mg, 0.65 mmol, 1.3 equiv) gave the title compound as a white solid (97 mg, 0.30 mmol, 60%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 15/1).

R_f (hexanes/ ethyl acetate = 3/1) = 0.65; **mp.** = 79 – 81 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 1.2 Hz, 1H), 7.64 (d, *J* = 1.2 Hz, 1H), 7.00 – 6.88 (m, 2H), 6.79 (tt, *J* = 8.7, 2.3 Hz, 1H), 6.29 (s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 164.8, 164.3, 163.2 (dd, *J* = 249.9, 12.3 Hz), 158.3, 141.8 (t, $J_{C\text{-}F}$ = 7.8 Hz), 130.5, 116.3, 110.5 (dd, $J_{C\text{-}F}$ = 26.0, 11.7 Hz), 108.1, 104.8 (t, $J_{C\text{-}F}$ = 25.3 Hz), 75.5 (t, $J_{C\text{-}F}$ = 2.2 Hz), 60.9, 52.2, 14.4; **^{19}F-NMR** (282 MHz, $CDCl_3$) δ = -109.1; **IR** (neat): 3079, 2989, 2956, 1696, 1621, 1558, 1446, 1387, 1297, 1238, 1193, 1115, 951, 854, 760 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{16}H_{15}F2O_5$ $(M+H)^+$ 325.0882 found 325.0888.

5-ethyl 3-methyl 2-(3,5-bis(trifluoromethyl)phenyl)-2H-pyran-3,5-dicarboxylate (16k)

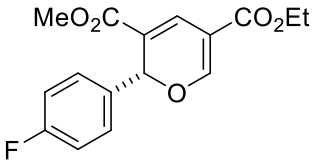


Following the general procedure GP-I using (3,5-ditrifluoromethyl phenyl)boronic acid (387 mg, 1.50 mmol, 3.0 equiv) gave the title compound as a white solid (68 mg, 0.16 mmol, 32%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 15/1).

mp. = 78 – 81 °C; **R_f** (hexanes/ ethyl acetate = 3/1) = 0.65; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.88 (s, 1H), 7.83 (s, 2H), 7.77 (d, *J* = 1.1 Hz, 1H), 7.66 (d, *J* = 1.1 Hz, 1H), 6.43 (s, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 164.7, 164.1, 158.1, 140.7, 132.3 (q, $J_{C\text{-}F}$ = 33.5 Hz), 131.0, 127.7 (d, $J_{C\text{-}F}$ = 4.0 Hz), 123.4 (p, $J_{C\text{-}F}$ = 3.7 Hz), 123.0 (q, $J_{C\text{-}F}$ = 273.0 Hz), 115.9, 108.2, 75.4, 61.1, 52.4, 14.4; **^{19}F-NMR** (377 MHz, $CDCl_3$) δ = -63.3; **IR** (neat): 3064, 2867, 2963, 1696, 1636, 1566, 1439, 1372, 1338, 1279,1238, 1163, 1126,

917, 857, 760, 682 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{18}H_{15}F_6O_5$ 425.0818 $(M+H)^+$ found 425.0825.

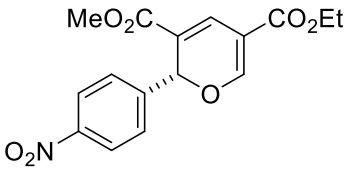
5-ethyl 3-methyl 2-(4-fluorophenyl)-2H-pyran-3,5-dicarboxylate (16l)



Following the general procedure GP-I using (4-fluoro)boronic acid (91 mg, 0.65 mmol, 1.3 equiv) gave the title compound as a colorless oil (76 mg, 0.25 mmol, 50%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 15/1).

R_f (hexanes/ ethyl acetate = 3/1) = 0.65; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 1.2 Hz, 1H), 7.61 (d, *J* = 1.2 Hz, 1H), 7.40 (dd, *J* = 8.4, 5.3 Hz, 2H), 7.04 (t, *J* = 8.6 Hz, 2H), 6.30 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 165.0, 164.6, 163.4 (d, J_{C-F} = 248.5 Hz), 158.5, 133.8 (d, J_{C-F} = 3.3 Hz), 130.0, 129.7 (d, J_{C-F} = 8.6 Hz) 116.8, 115.8 (d, J_{C-F} = 21.7 Hz), 107.6, 76.4, 60.8, 52.1, 14.4; **^{19}F-NMR** (377 MHz, $CDCl_3$) δ = -112.4; **IR** (neat): 3075, 2982, 2956, 1700, 1640, 1603, 1439, 1566, 1510, 1405, 1372, 1320, 1297, 1226, 1185, 1111, 1074, 1014, 861, 828, 746 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{16}H_{16}FO_5$ $[M+H]^+$ 307.0976 found 307.0980.

5-ethyl 3-methyl 2-(4-nitrophenyl)-2H-pyran-3,5-dicarboxylate (16m)



Following the general procedure GP-I using (4-nitrophenyl)boronic acid (250 mg, 1.50 mmol, 3.0 equiv) gave the title compound as a colorless solid (52 mg, 0.16 mmol, 31%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 30/1 to 5/1).

R_f (hexanes/ ethyl acetate = 3/1) = 0.43; **mp.** = 117-119 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 8.24 – 8.19 (m, 2H), 7.71 (d, *J* = 1.2 Hz, 1H), 7.66 (d, *J* = 1.2 Hz, 1H), 7.63 – 7.57 (m, 2H), 6.41 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 164.8, 164.2, 158.3, 148.5, 144.8, 130.5, 128.4, 124.1, 116.5, 108.2, 75.7, 61.0, 52.3, 14.4; **IR** (neat): 3070, 2989, 2960, 2859, 1692, 1644, 1569, 1521, 1446, 1327, 1245, 1193, 1126, 1021, 977, 921, 867 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{16}H_{16}NO_7$ $[M+H^+]$ calc. 334.0921 found 334.0922.

General reaction setup for photochemical cyclopropanation on approx. 5.0 mmol scale:

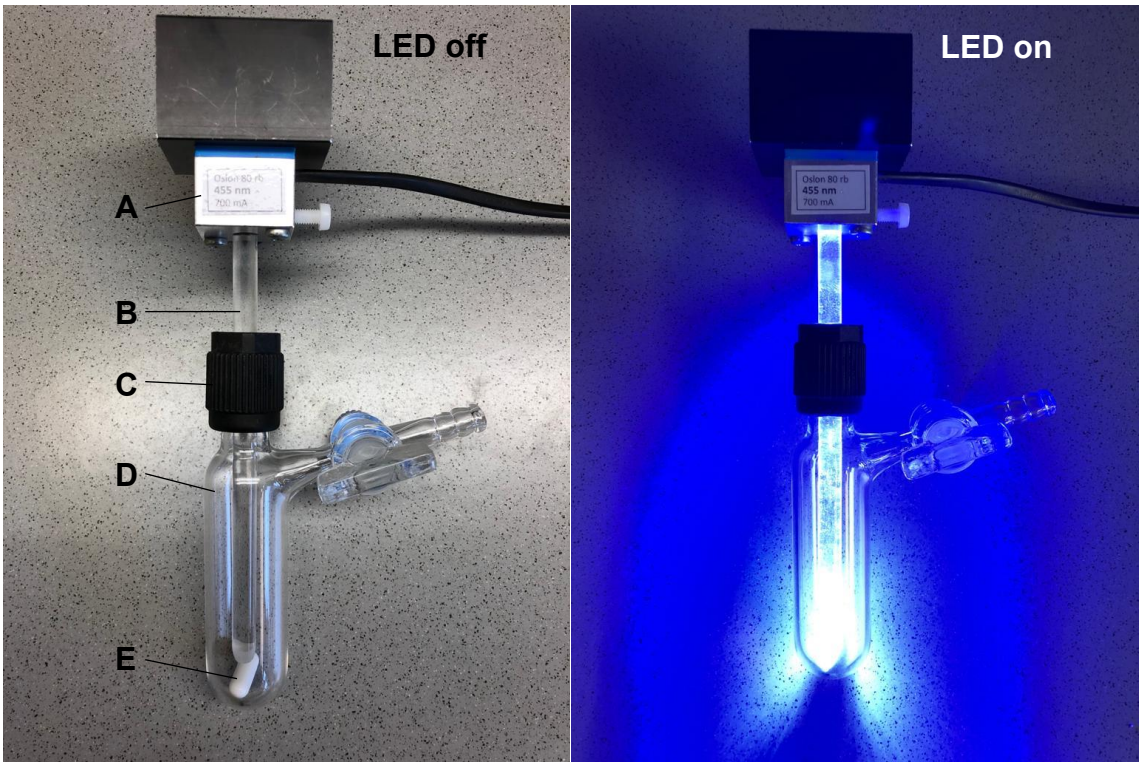
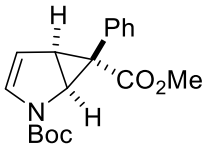


Figure S 1. Setup for photochemical cyclopropanation: **A)** 455 nm LED. **B)** Glass rod as optical fiber with roughened bottom for light dispersion. **C)** sealed Teflon screw cap. **D)** 30 mL Schlenk tube. **E)** Magnetic stir bar.

2-(tert-butyl) 6-methyl-6-phenyl-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (17-Boc)



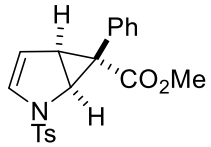
Compound **17-Boc** was synthesized according to a literature procedure.[13] A flame dried 30 mL Schleck tube equipped with a magnetic stir bar was charged with *N*Boc-pyrrole (8.36 g, 50.0 mmol, 7.3 equiv), methyl 2-diazo-2-phenylacetate (1.21 g, 6.8 mmol, 1.0 equiv) and CH_2Cl_2 (anhydrous, 25 mL). The deeply orange-colored reaction mixture was stirred and irradiated with blue light (LED, $\lambda = 455$ nm) for 24 h giving a red-colored solution. After complete consumption of the diazo ester (monitoring by TLC) the solvent was removed *in vacuo* and the excess *N*Boc-pyrrole was removed by vacuum distillation (60 °C, 5 mbar). The product was then purified by flash column chromatography (hexanes/ ethyl acetate = 9/1 to 4/1) affording **17-Boc** (1.53 g, 9.7 mmol, 71%) diastereoselectively as a colorless compound. Spectroscopic data are in agreement with those reported in literature. X-ray grade crystals were obtained by slow evaporation from methanol.

^{1}H-NMR (300 MHz, $CDCl_3$, 60:40 mixture of 2 rotamers) $\delta = 7.31 - 7.17$ (m, 2H), 7.16 – 7.06 (m, 3H), 6.13 (d, $J = 4.0$, 0.4H), 5.97 (d, $J = 4.0$, 0.6H), 5.19 (dd, $J = 4.0$, 2.6 Hz, 0.4H), 5.12 (dd, $J = 4.0$, 2.7 Hz, 0.6H), 4.70 (dd, $J = 6.8$, 1.2 Hz, 0.6H), 4.60 (dd, $J = 6.8$, 1.2 Hz, 0.4H), 3.63 (s, 1.2H), 3.60 (s, 1.8H), 3.32 (dt, $J = 6.8$, 2.4 Hz, 1H), 1f.59 (s, 3.6H), 1.45 (s, 5.4H).

[13] I. D. Jurberg, H. M. L. Davies, *Chem. Sci.* **2018**, *9*, 5112–5118.

^{13}C-NMR (75 MHz, $CDCl_3$, 2 rotamers) δ = 174.2, 173.9, 151.4, 151.3, 132.7, 132.4, 131.2, 131.0, 130.8, 130.5, 127.9, 127.8, 127.4, 127.3, 107.3, 81.9, 81.6, 52.6, 52.6, 49.4, 49.3, 39.6, 38.3, 29.7, 29.3, 28.4, 28.2.

methyl-6-phenyl-2-tosyl-2-azabicyclo[3.1.0]hex-3-ene-6-carboxylate (17-Ts)



Compound **17-Ts** was synthesized according to a literature procedure.[14] A flame dried 30 mL Schleck tube equipped with a magnetic stir bar was charged with *N*Tosyl-pyrrole (5.53 g, 25.0 mmol, 5.0 equiv), methyl 2-diazo-2-phenylacetate (0.88 g, 5.0 mmol, 1.0 equiv) and CH_2Cl_2 (anhydrous, 25 mL). The deeply orange-colored reaction mixture was stirred and irradiated with blue light (LED, λ = 455 nm) for 24 h giving a red-colored solution. After complete consumption of the diazo ester (monitoring by TLC) the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (hexanes/ ethyl acetate = 10/1 to 3/1) to give a yellow solid which was subsequently recrystallized in refluxing methanol to obtain **17-Ts** (0.91 g, 2.7 mmol, 54%) diastereoselectively as a colorless compound. Spectroscopic data are in agreement with those reported in literature.[15] X-ray grade crystals were obtained by slow evaporation from methanol.

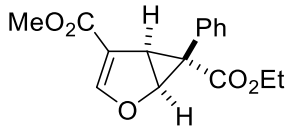
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.72 (d, *J* = 8.3 Hz, 2H), 7.37 – 7.32 (m, 2H), 7.27 (dd, *J* = 3.9, 1.5 Hz, 3H), 7.20 (dd, *J* = 7.0, 2.8 Hz, 2H), 5.96 (dd, *J* = 3.9, 1.5 Hz, 1H), 5.29 (dd, *J* = 3.9, 2.5 Hz, 1H), 4.54 (dd, *J* = 6.5, 1.4 Hz, 1H), 3.62 (s, 3H), 3.15 (dd, *J* = 6.5, 2.5 Hz, 1H), 2.46 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 173.7, 144.5, 135.0, 132.6, 131.0, 130.5, 130.1, 127.9, 127.5, 127.3, 111.5, 52.9, 52.3, 38.8, 28.1, 21.8.

[14] I. D. Jurberg, H. M. L. Davies, *Chem. Sci.* **2018**, *9*, 5112–5118.

[15] J, Fu, N. Wurzer, V. Lehner, O. Reiser, H, M. L. Davies, *Org. Lett.* **2019**, *21*, 6102-6106.

6-ethyl 4-methyl 6-phenyl-2-oxabicyclo[3.1.0]hex-3-ene-4,6-dicarboxylate (18)



Compound **18** was synthesized according to a literature procedure.[16] An oven dried 190 mL custom-built circulating-immersion-well photo reactor was charged with methyl 3-furoate (16.58 g, 131.4 mmol, 5.0 equiv), ethyl 2-diazo-2-phenylacetate (**2-Ph-Et**) (5.0 g, 26.3 mmol, 1.0 equiv) and CH_2Cl_2 (anhydrous, 130 mL). The deeply orange-colored reaction mixture was stirred and irradiated with blue light (LED, λ = 455 nm) for 24 h giving a lightly yellow-colored solution. After complete consumption of the diazo ester (monitoring by TLC) the solvent was removed *in vacuo* and the residual methyl 3-furoate was recovered by vacuum distillation (T_{vap} = 60 °C at 15 mbar) and the product was isolated by flash column chromatography on SiO_2 (hexanes/ acetone = 3/1) and recrystallized in MeOH affording **18** (4.93 g, 17.1 mmol, 65%) diastereoselectively as a colorless compound. X-ray grade crystals were obtained by slow evaporation from methanol.

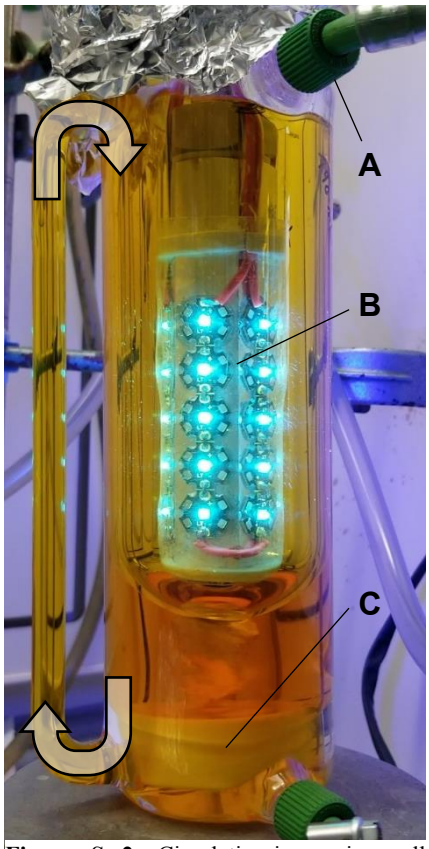
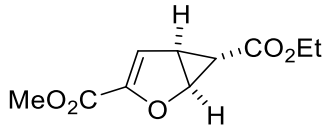


Figure S 2. Circulating-immersion-well photo reactor. **A**) Water-connection for the reactor's cooling-coat. **B**). 455 nm LED finger with built-in water cooling. **C**) Magnetic stir disc providing vertical circulation of the solution *via* hydrostatic pressure difference indicated by arrows.

mp. = 83 – 84 °C; $\mathbf{R_f}$ (hexanes/ ethyl acetate = 3/1) = 0.55; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.32 – 7.21 (m, 3H), 7.20 – 7.10 (m, 2H), 6.69 (d, *J* = 0.8 Hz, 1H), 5.29 (dd, *J* = 5.7, 0.9 Hz, 1H), 4.10 (qd, *J* = 7.1, 2.3 Hz, 2H), 3.71 (s, 3H), 3.54 (d, *J* = 5.6 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 172.4, 164.3, 156.4, 132.3, 129.9, 128.2, 127.8, 113.9, 72.5, 61.7, 51.6, 36.7, 28.5, 14.3; **IR** (neat): 3112, 2997, 2956, 1692, 1607, 1446, 1379, 1290, 1234, 1144, 1100, 1018, 982, 891, 850 cm^{-1}; **HRMS** (+APCI): calcd. for $C_{16}H_{16}O_5$ $[M+H]^+$ 289.1071 found 289.1073.

6-ethyl 3-methyl-2-oxabicyclo[3.1.0]hex-3-ene-3,6-dicarboxylate (30)



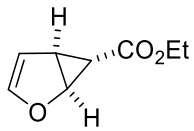
Compound **30** was synthesized according to a literature procedure.[17] A flame dried 50 mL Schlenk flask was purged with nitrogen and charged with $Cu(OTf)_2$ (36.2 mg, 100 µmol, 1 mol%), 2-furoic acid methyl ester (1.26 g, 10 mmol, 1.0 equiv.) and CH_2Cl_2 (anhydrous, 7.7 mL). Phenylhydrazine (10 µL, 10.8 mg, 0.1 mmol, 1 mol%) was added, causing the solution to turn dark red-brown and ethyl 2-diazoacetate (**2-Et**) (1.71 g, 15.0 mmol, 1.5 equiv, 9.69 g solution of 17.7 wt%) was subsequently added dropwise with the

[16] I. D. Jurberg, H. M. L. Davies, *Chem. Sci.* **2018**, *9*, 5112–5118.
[17] R. B. Chhor, B. Nosse, S. Sörgel, C. Böhm, M. Seitz, O. Reiser, *Chem. Eur. J.* **2003**, *9*, 260–270.

aid of a syringe pump (one drop every 10 seconds) at 0 °C. The reaction mixture was allowed to warm to room temperature after complete addition. Afterwards, the solution was filtered through basic Al_2O_3, which was then washed with CH_2Cl_2 (100 mL). Concentration under reduced pressure afforded a yellow oil which was purified by column chromatography on silica (hexanes/ ethyl acetate = 20/1 to 15/1) to obtain **30** as a colorless oil (445 mg, 2.1 mmol, 21%). Spectroscopic data are in agreement with those reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.38 (d, *J* = 2.8 Hz, 1H), 4.96 (dd, *J* = 5.3, 1.1 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 2.85 (dt, *J* = 5.5, 2.8 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.15 (dd, *J* = 2.8, 1.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 171.8, 159.6, 149.2, 116.2, 67.6, 61.1, 52.3, 32.0, 21.5, 14.2.

ethyl-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (32)

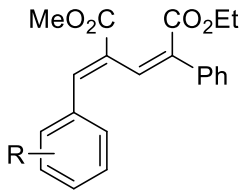


Compound **32** was synthesized according to a literature procedure.[18] A flame dried 100 mL Schlenk flask equipped with a magnetic stir bar and a gas bubbler was purged with nitrogen and charged with $Rh_2(OAc)_4$ (65.5 mg, 148.2 µmol, 0.15 mol%) and furan (28.5 mL). Then, a solution of ethyl 2-diazoacetate (**2-Et**) (10.83 g, 95.0 mmol, 1.0 equiv) in furan (28.5 mL) was added dropwise over a period of 3 hours with the aid of a syringe pump at 10 °C. After complete addition a solution of sodium bicarbonate (22.8 g, 272 mmol) in water (45 mL) was added the mixture was stirred for another 2 hours at 10 °C. The reaction mixture was then extracted with Et_2O (3 x 25 mL) and the combined organic phases were washed with water (25 mL) and brine (25 mL) and dried over Na_2SO_4. The pure product was obtained as a slightly yellow oil (3.88 g, 25 mmol, 26%) after distillation (30 °C, 2.7 mbar). Spectroscopic data are in agreement with those reported in the literature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 6.38 (dt, *J* = 2.6, 0.7 Hz, 1H), 5.48 (t, *J* = 2.6 Hz, 1H), 4.86 (dt, *J* = 5.6, 0.9 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.78 (dt, *J* = 5.5, 2.7 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 4H), 0.95 (ddd, *J* = 2.7, 1.1, 0.6 Hz, 1H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 172.9, 147.2, 106.4, 67.1, 60.7, 31.6, 22.2, 14.3.

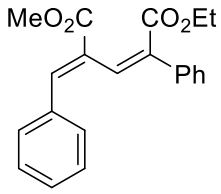
[18] J. A. Monn, M. J. Valli, S. M. Massey, M. M. Hansen, T. J. Kress, J. P. Wepsiec, A. R. Harkness, J. L. Grutsch, R. A. Wright, B. G. Johnson, *J. Med. Chem.* **1999**, *42*, 1027–1040.

General procedure (GP-II) for the synthesis 1-ethyl 5-methyl (E)-4-((Z)-aryl)-2-phenylpent-2-enedioate



A flame dried 5 mL vial with gas inlet equipped with a magnetic stir bar was charged with furan **18** (144 mg, 0.50 mmol, 1.0 equiv), aryl boronic acid (1.30 mmol, 2.6 equiv), sodium carbonate (133 mg, 1.25 mmol, 2.5 equiv), copper(II)-chloride (anhydrous, 67 mg, 0.50 mmol, 1.0 equiv), bis(acetonitrile)dichloropalladium(II) (6.5 mg, 25 µmol, 0.05 equiv) and THF (anhydrous, 2 mL). After an oxygen balloon was attached to the gas inlet and the flask was flushed thoroughly, the reaction was stirred at 40 °C for four days. The reaction mixture was then diluted with chloroform and transferred to a round bottomed flask. After removal of the solvent *in vacuo* the residue was dissolved in ethyl acetate and filtered through a short plug of basic aluminum oxide (Brockmann I). After the solvent had been removed under reduced pressure, the pure product was isolated by flash column chromatography on silica gel.

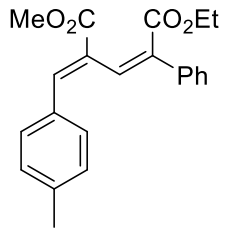
1-ethyl 5-methyl (E)-4-((Z)-benzylidene)-2-phenylpent-2-enedioate (44a)



This reaction was carried out on a 1.0 mmol scale: A flame dried 5 mL vial with gas inlet equipped with a magnetic stir bar was charged with furan **18** (288 mg, 1.00 mmol, 1.0 equiv), aryl boronic acid (2.60 mmol, 2.6 equiv), sodium carbonate (265 mg, 2.50 mmol, 2.5 equiv), copper(II)-chloride (anhydrous, 135 mg, 1.00 mmol, 1.0 equiv), bis(acetonitrile)dichloropalladium(II) (13 mg, 50 µmol, 0.05 equiv) and THF (anhydrous, 2 mL). After an oxygen balloon was attached to the gas inlet and the flask was flushed thoroughly, the reaction was stirred at 40 °C for four days. The reaction mixture was then diluted with chloroform and transferred to a round bottomed flask. After removal of the solvent *in vacuo* the residue was dissolved in ethyl acetate and filtered through a short plug of basic aluminum oxide (Brockmann I). After the solvent had been removed under reduced pressure, the title compound (200 mg, 0.60 mmol, 60 %) was isolated as a yellowish oil by flash column chromatography on silica gel (hexanes/ ethyl acetate = 20/1).

R_f (hexanes/ ethyl acetate = 3/1) = 0.50; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.74 (d, *J* = 1.8 Hz, 1H), 7.49 – 7.41 (m, 4H), 7.40 – 7.28 (m, 6H), 6.82 (d, *J* = 1.8 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 167.6, 167.5, 141.1, 138.3, 137.6, 135.1, 131.3, 130.7, 129.6, 129.1, 128.7, 128.4, 128.4, 128.1, 61.2, 52.3, 14.1; **IR** (neat): 3056, 3029, 2982, 2952, 1715, 1495, 1435, 1372, 1342, 1271, 1241, 1189, 1122, 1025, 760, 693 cm^{-1}; **HRMS** (EI+, 70 eV): calcd. for $C_{21}H_{20}O_4$ [M^{+}] 336.1356 found 336.1350.

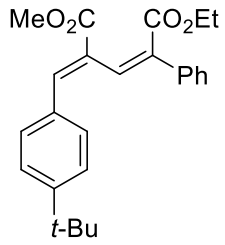
1-ethyl 5-methyl (E)-4-((Z)-4-methylbenzylidene)-2-phenylpent-2-enedioate (44b)



Following the general procedure GP-II using (4-methyl)boronic acid (129 mg, 1.30 mmol, 2.6 equiv) and 1.5 mL of THF gave the title compound as a colorless oil (99 mg, 0.29 mmol, 57%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 15/1).

R_f (hexanes/ ethyl acetate = 3/1) = 0.50; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 1.7 Hz, 1H), 7.39 – 7.33 (m, 2H), 7.30 – 7.24 (m, 5H), 7.10 – 7.06 (m, 2H), 6.73 (d, *J* = 1.8 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 3H), 2.26 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 166.6, 166.5, 140.1, 138.9, 136.8, 136.6, 131.2, 130.4, 129.6, 128.3, 127.3, 127.1, 127.1, 127.0, 60.0, 51.0, 20.4, 13.0; **IR** (neat): 2952, 2882, 1715, 1607, 1510, 1435, 1372, 1342, 1316, 1271, 1241, 1185, 1122, 1025, 907, 813, 734, 697 cm^{-1}; **HRMS** (EI+, 70 eV): calcd. for $C_{22}H_{22}O_4$ [M^{+}] calc. 350.1513 found 350.1510

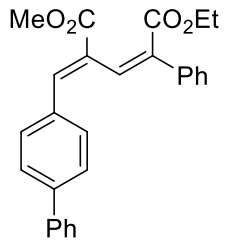
1-ethyl 5-methyl (E)-4-((Z)-4-(tert-butyl)benzylidene)-2-phenylpent-2-enedioate (44c)



Following the general procedure GP-II using (4-tert-butylphenyl)boronic acid (232 mg, 1.30 mmol, 2.6 equiv) and 4 mL of THF (anhydrous) gave the title compound as a colorless oil (90 mg, 0.23 mmol, 46%) after purification by column chromatography on silica gel (hexanes/ diethyl ether = 4/1).

R_f (hexanes/ diethyl ether = 3/2) = 0.50; **mp.** = 66 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.72 (d, *J* = 1.8 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.44 – 7.35 (m, 7H), 6.87 (d, *J* = 1.8 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 1.31 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 167.6, 167.5, 153.0, 140.9, 138.0, 137.7, 132.2, 131.5, 130.6, 128.3, 128.2, 128.1, 125.6, 61.0, 52.1, 34.9, 31.1, 14.0; **IR** (neat): 2948, 2904, 2870, 1707, 1602, 1510, 1439, 1368, 1271, 1241, 1178, 1126, 1025, 995, 831, 697 cm^{-1}; **HRMS** (+APCI, 120 V): calcd. for $C_{25}H_{29}O_4$ $[M+H]^+$ 393.2060 found 393.2060.

1-ethyl 5-methyl (2E,4Z)-4-([1,1'-biphenyl]-4-ylmethylene)-2-phenylpent-2-enedioate (44d)

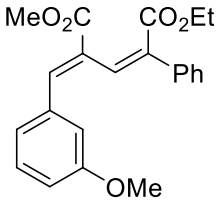


Following the general procedure GP-II using (1,1`-biphenyl)boronic acid (257 mg, 1.30 mmol, 2.6 equiv) gave the title compound as a yellow oil (177 mg, 0.43 mmol, 86%) after purification by column chromatography on silica gel (hexanes/ diethyl ether = 2/1).

R_f (hexanes/ diethyl ether = 3/2) = 0.38; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 1.7 Hz, 1H), 7.63 – 7.55 (m, 6H), 7.51 – 7.35 (m, 8H), 6.90 (d, *J* = 1.8 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 167.7, 167.5, 142.3, 140.6, 140.2, 138.4, 137.7, 134.1, 131.3, 131.3, 129.0, 128.5, 128.4, 128.1, 128.0, 127.3, 127.2, 127.1, 61.2, 52.3, 14.2; **IR** (neat): 3030, 3056, 2982, 2952, 1715, 1603, 1487, 1435, 1372, 1271,

1241, 1185, 1122, 1025, 910, 842, 764, 693 cm^{-1}; **HRMS** (+APCI, 120 V): calcd. for $C_{27}H_{28}NO_4$ $[M+NH_4]^+$ calc. 430.2013 found 430.2015.

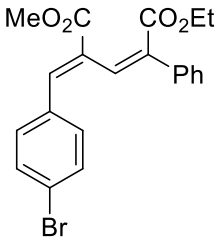
1-ethyl 5-methyl (E)-4-((Z)-3-methoxybenzylidene)-2-phenylpent-2-enedioate (44e)



Following the general procedure GP-II using (3-methoxyphenyl)boronic acid (198 mg, 1.30 mmol, 2.6 equiv) gave the title compound as a colorless oil (160 mg, 0.43 mmol, 85%) after purification by column chromatography on silica gel (hexanes/ diethyl ether = 4/1).

R_f (hexanes/ diethyl ether = 3/2) = 0.33; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 1.8 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.41 – 7.32 (m, 3H), 7.27 (t, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 1fH), 7.01 (t, *J* = 2.1 Hz, 1H), 6.88 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.84 (d, *J* = 1.8 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 3.70 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 167.5, 167.4, 159.5, 140.8, 138.2, 137.6, 136.3, 131.5, 129.6, 129.3, 128.4, 128.3, 128.0, 123.3, 115.8, 115.4, 61.1, 55.2, 52.2, 14.1; **IR** (neat): 2982, 2952, 2837, 1715, 1491, 1595, 1431, 1372, 1342, 1230, 1193, 1118, 1025, 999, 924, 775, 693 cm^{-1}; **HRMS** (+APCI, 120 V): calcd. for $C_{22}H_{23}O_5$ $[M+H]^+$ 367.1540 found 367.1543.

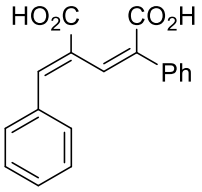
1-ethyl 5-methyl (E)-4-((Z)-4-bromobenzylidene)-2-phenylpent-2-enedioate (44f)



Following the general procedure GP-II using (4-bromophenyl)boronic acid (232 mg, 1.30 mmol, 2.6 equiv) gave the title compound as a colorless oil (135 mg, 0.33 mmol, 65%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 10/1).

R_f (hexanes/ ethyl acetate = 3/1) = 0.50; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 1.7 Hz, 1H), 7.51 – 7.46 (m, 2H), 7.46 – 7.42 (m, 2H), 7.41 – 7.35 (m, 3H), 7.34 – 7.30 (m, 2H), 6.74 (d, *J* = 1.8 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 167.5, 167.2, 139.5, 138.8, 137.4, 133.9, 132.0, 131.9, 130.6, 129.8, 128.5, 128.5, 128.0, 124.0, 61.2, 52.3, 14.1; **IR** (neat): 2982, 2952, 1715, 1588, 1621, 1487, 1435, 1398, 1342, 1305, 1271, 1238, 1122, 1185, 1074, 1008, 902, 842, 760, 693 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{21}H_{20}BrO_4$ $[M+H]^+$ 415.0539 found 415.0535.

(Z)-4-((E)-benzylidene)-2-phenylpent-2-enedioic acid (45)

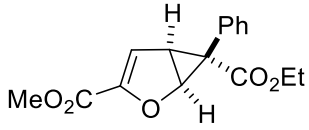


A 5 mL vial with screw cap equipped with a magnetic stir bar was charged with butadiene **44a** (130 mg, 0.39 mmol, 1.0 equiv), lithium hydroxide (370 mg, 15.5 mmol, 40 equiv) and mixture of tetrahydrofuran and water (4 mL, 1:1) and the resulting suspension was subsequently refluxed for 18 hours. After complete hydrolysis of the starting material (monitoring by TLC), the reaction mixture was quenched and acidified with hydrochloric acid solution (10 mL, 1M, acidic reaction to litmus pH indicator). After extraction

with CH_2Cl_2 (3 x 10 mL) the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound as yellow solid (110 mg, 0.37 mmol, 97%). X-ray grade crystals were obtained by vapor diffusion technique using $CHCl_3$ and hexanes.

R_f (hexanes/ diethyl ether = 1/1) = 0.08; **mp.** = 137 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.91 (d, *J* = 1.6 Hz, 1H), 7.60 – 7.35 (m, 10H), 6.90 (d, *J* = 1.7 Hz, 1H; **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 174.1, 172.8, 144.5, 137.5, 137.4, 134.7, 132.0, 131.1, 130.3, 128.8, 128.7, 128.5, 128.5, 128.2; **IR (neat):** 3029 (broad), 2635, 2363, 1692, 1618, 1498, 1448, 1420, 1279, 1252, 1211, 1144, 910, 757, 697 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{18}H_{15}O_4$ $[M+H]^+$ 295.0965 found 295.0963.

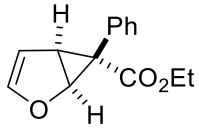
6-ethyl 3-methyl 6-phenyl-2-oxabicyclo[3.1.0]hex-3-ene-4,6-dicarboxylate (47)



Compound **47** was synthesized according to a literature procedure.[19] A flame dried 30 mL Schleck tube equipped with a magnetic stir bar was charged with methyl 2-furoate (3.15 g, 25.0 mmol, 5.0 equiv), ethyl 2-diazo-2-phenylacetate (**2-Ph-Et**) (0.95 g, 5.0 mmol, 1.0 equiv) and CH_2Cl_2 (anhydrous, 25 mL). The deeply orange-colored reaction mixture was stirred and irradiated with blue light (LED, λ = 455 nm) for 24 h giving a yellow-colored solution. After complete consumption of the diazo ester (monitoring by TLC) the solvent was removed *in vacuo* and the product was isolated by flash column chromatography (hexanes/ ethyl acetate = 10/1 to 3/1) affording **47** (0,67 g, 2.3 mmol, 46%) diastereoselectively as a colorless compound.

R_f (hexanes/ethyl acetate = 3/1) = 0.45; **mp.** = 72 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 7.33 – 7.08 (m, 5H), 6.11 (d, *J* = 3.0 Hz, 1H), 5.23 (d, *J* = 5.4 Hz, 1H), 4.10 (qd, *J* = 7.1, 2.1 Hz, 2H), 3.60 (s, 3H), 3.36 (dd, *J* = 5.4, 3.0 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ = 172.7, 159.0, 148.9, 132.4, 129.8, 128.1, 127.7, 114.3, 71.1, 61.7, 52.2, 39.4, 28.8, 14.3; **IR** (neat): 3027, 2960, 2989, 1737, 1692, 1614, 1495, 1443, 1394, 1372, 1305, 1249, 1148, 1114, 954, 883, 842, 790 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{16}H_{17}O_5$ $[M+H]^+$ 289.1071 found 289.1069.

6-ethyl 6-phenyl-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (49)

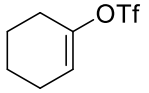


Compound **49** was synthesized according to a literature procedure.[20] A flame dried 30 mL Schleck tube equipped with a magnetic stir bar was charged with furan (3.40 g, 50.0 mmol, 10.0 equiv), ethyl 2-diazo-2-phenylacetate (**2-Ph-Et**) (0.95 g, 5.0 mmol, 1.0 equiv) and CH_2Cl_2 (anhydrous, 25 mL). The deeply orange-colored reaction mixture was stirred and irradiated with blue light (LED, λ = 455 nm) for 24 h giving a yellow-colored solution. After complete consumption of the diazo ester (monitoring by TLC) the solvent was removed *in vacuo* and the product was isolated by flash column chromatography (hexanes/ ethyl acetate = 4/1 + 1.5% NEt_3) affording **49** (1.0 g, 4.3 mmol, 87%) diastereoselectively as a colorless compound.

[19] I. D. Jurberg, H. M. L. Davies, *Chem. Sci.* **2018**, *9*, 5112–5118.
[20] I. D. Jurberg, H. M. L. Davies, *Chem. Sci.* **2018**, *9*, 5112–5118.

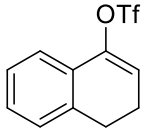
R_f (hexanes/ethyl acetate = 3/1) = 0.73; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.31 – 7.24 (m, 3H), 7.22 – 7.16 (m, 2H), 5.91 (dd, *J* = 2.6, 0.8 Hz, 1H), 5.22 (t, *J* = 2.6 Hz, 1H), 5.14 (dd, *J* = 5.7, 0.8 Hz, 1H), 4.09 (qd, *J* = 7.1, 2.0 Hz, 2H), 3.29 (dd, *J* = 5.6, 2.7 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 173.4, 147.4, 132.8, 131.0, 127.8, 127.2, 104.1, 77.5, 77.2, 76.8, 70.7, 61.3, 39.1, 28.1, 14.3; **IR (neat):** 3060, 3030, 2982, 2121, 1700, 1592, 1498, 1368, 1305, 1245, 1148, 1025, 977, 848, 723, 697 cm^{-1}; **HRMS** (+ESI, 120V): calcd. for $C_{14}H_{18}NO_3$ $[M+NH_4]^+$ 248.1281 found 248.1282.

Cyclohex-1-en-1-yl trifluoromethanesulfonate (65a)



The title compound was prepared following a literature procedure.[21] A flame dried 100 mL Schlenk flask with rubber septum and magnetic stir bar was charged with cyclohexanone (2.07 mL, 20.0 mmol, 1.0 equiv), powdered Na_2CO_3 (anhydrous 6.36 g, 60.0 mmol, 3.0 equiv) and CH_2Cl_2 (anhydrous, 30 mL) under N_2-atmosphere. After cooling the suspension to 0 °C, a solution of trifluoromethanesulfonic anhydride (6.06 mL, 36.0 mmol, 1.8 equiv) in CH_2Cl_2 (anhydrous, 25 mL) was then added dropwise. After complete addition the resulting mixture was allowed to warm to room temperature and stirred for 24 hours. The reaction mixture was then transferred to a separation funnel and washed with sat. $NaHCO_3$ solution (50 mL) and water (50 mL). After drying over Na_2SO_4 and filtration the solvent was removed under reduced pressure and the product was coarsely purified by column chromatography on silica gel (pure pentane). In order to remove last impurities, the product was then distilled by Kugelrohr distillation (65 °C, 2.0 mbar) to obtain the pure title compound as a colorless liquid (3,86 g, 16.8 mmol, 83%). Spectroscopic data are in agreement with those reported in literature. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 5.76 (tt, *J* = 4.1, 1.5 Hz, 1H), 2.31 (tdd, *J* = 6.3, 3.2, 1.5 Hz, 2H), 2.18 (tdd, *J* = 6.0, 4.1, 2.9 Hz, 2H), 1.88 – 1.70 (m, 2H), 1.65 – 1.57 (m, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ = 149.5, 118.6 , 118.3 (q, J_{C-F} = 320.4 Hz), 27.7, 24.0, 22.8, 21.1. **^{19}F-NMR** (377 MHz, $CDCl_3$) δ = -74.7.

3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (65b)



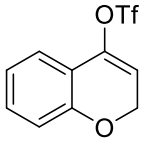
The title compound was prepared following a literature procedure.[22] A flame dried 50 mL Schlenk flask with rubber septum and magnetic stir bar was charged with 1-teralone (1.33 mL, 10.0 mmol, 1.0 equiv), 2-chloropyridine (1.03 mL, 11.0 mmol, 1.1 equiv) and CH_2Cl_2 (anhydrous ,20 mL) under N_2-atmosphere. After cooling the suspension to 0 °C, a solution of trifluoromethanesulfonic anhydride (2.19 mL, 13.0 mmol, 1.3 equiv) in CH_2Cl_2 (anhydrous, 10 mL) was then added dropwise. After complete addition the resulting mixture was allowed to warm to room

[21] A. G. Martínez, A. Herrera, R. Martínez, E. Teso, A. García, J. Osío, L. Pargada, R. Unanue, L. R. Subramanian, M. Hanack, *J. Heterocyclic Chem.* **1988**, *25*, 1237 – 1241.

[22] K. Nogi, T. Fujihara, J. Terao, Y. Tsuji , *J. Org. Chem.* **2015**, *80*, 11618 – 11623.

temperature and stirred for 3 hours. The reaction was quenched by adding water (20 mL). The organic layer was washed with sat. $NaHCO_3$ solution (50 mL) and brine (50 mL) and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (hexanes/ ethyl acetate = 99/1) to obtain the title compound as a yellowish liquid (1.76 g, 6.3 mmol, 63%). Spectroscopic data are in agreement with those reported in literature.[23]
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.37 – 7.32 (m, 1H), 7.29 – 7.22 (m, 2H), 7.19 – 7.14 (m, 1H), 6.01 (t, *J* = 4.8 Hz, 1H), 2.87 (t, *J* = 8.2 Hz, 2H), 2.51 (td, *J* = 8.1, 4.8 Hz, 2H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 146.5, 136.4, 129.3, 128.8, 127.9, 127.1, 121.4, 119.0 (q, $J_{C\text{-}F}$ = 320.4 Hz), 117.9, 27.0, 22.5. **^{19}F-NMR** (377 MHz, $CDCl_3$) δ = -74.2.

2*H*-chromen-4-yl trifluoromethanesulfonate (65c)

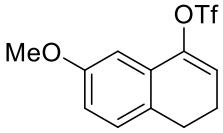


The title compound was prepared following a literature procedure.[24] A 100 mL oven-dried Schlenk flask equipped with a magnetic stir bar and rubber septum was charged with 4-chromanone (500 mg, 3.37 mmol, 1.0 equiv) and CH_2Cl_2 (anhydrous, 20 mL). At 0 °C, 2,6-di-*tert*-butyl-4-methylpyridine (1.39 g, 6.75 mmol, 2.0 equiv) and trifluoromethanesulfonic anhydride (1.11 mL, 6.75 mmol, 2.0 equiv) were subsequently added and the mixture was stirred for 1 hour. The ice bath was removed and stirring was continued for 2 hours. After full consumption of the ketone (monitoring by TLC) the reaction was quenched by the addition of water (50 mL). The phases were separated, and the organic phase was washed with sat. $NaHCO_3$ solution (50 mL) and HCl (0.5 M, 4 x 50 mL) to remove excess pyridine base. The organic phases were dried over Na_2SO_4 and volatiles were removed under reduced pressure to give the title compound as a yellowish oil which was used without further purification (861 mg, 3.07 mmol, 91%). Spectroscopic data are in agreement with those reported in literature.
^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.30 – 7.18 (m, 2H), 6.98 (td, *J* = 7.5, 1.1 Hz, 1H), 6.85 (dd, *J* = 8.5, 1.1 Hz, 1H), 5.76 (t, *J* = 3.9 Hz, 1H), 4.99 (d, *J* = 3.9 Hz, 2H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 155.1, 143.3, 131.7, 122.0, 121.8, 119.9 (q, $J_{C\text{-}F}$ = 320.5 Hz), 117.5, 116.4, 110.2, 65.2. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ = -74.0.

[23] H. Senboku, Y. Fujimura, H. Kamekawa, M. Tokuda, *Electrochim. Acta*. **2000**, *45*, 2995 – 3003.

[24] T. Si, B. Li, W. Xiong, B. Xu, W. Tang, *Org. Biomol. Chem.*, **2017**, *15*, 9903 – 9909.

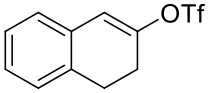
7-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (65d)



The title compound was prepared following a literature procedure.[25] Under N_2 atmosphere, a flame dried 100 mL Schlenk flask with rubber septum and magnetic stir bar was charged with 7-methoxy-3,4-dihydronaphthalene-1(2*H*)-one (1.76 g, 10.0 mmol, 1.0 equiv) and CH_2Cl_2 (anhydrous, 50 mL). To the solution was added 2-chloropyridine (1.03 mL, 11.0 mmol, 1.1 equiv) and trifluoromethanesulfonic anhydride (1.85 mL, 11.0 mmol, 1.1 equiv) and the reaction was stirred for 2 hours at room temperature. The reaction was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (diethyl ether/ pentane = 1/9) to afford the title compound as a colorless oil (2.4 g, 7.8 mmol, 78%). Spectroscopic data are in agreement with those reported in literature.[26]

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.09 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.92 (d, *J* = 2.6 Hz, 1H), 6.81 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.04 (t, *J* = 4.8 Hz, 1H), 3.81 (s, 3H), 2.86 – 2.72 (m, 2H), 2.49 (td, *J* = 8.1, 4.8 Hz, 2H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 158.7, 146.2, 129.6, 128.7, 128.2, 118.6 (q, $J_{C\text{-}F}$ = 320.2 Hz), 118.4, 114.5, 107.2, 55.4, 26.0, 22.7. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ = -74.2.

3,4-dihydronaphthalen-2-yl trifluoromethanesulfonate (65e)



The title compound was prepared following a literature procedure.[27] Under N_2 atmosphere, a flame dried 100 mL Schlenk flask with rubber septum and magnetic stir bar was charged with a solution of 2-teralone (1.39 mL, 10.50 mmol, 1.05 equiv) in THF (anhydrous, 40 mL) and cooled to -20 °C. A solution of potassium *tert*-butoxide (1,18 g, 10.5 mmol, 1.05 equiv) in THF (anhydrous, 10 mL) was then slowly added to the reaction mixture. After complete addition the yellow mixture was allowed to warm to 0 °C and stirred for 1 hour. The reaction mixture was then again cooled down to -20 °C and 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (3.57 g, 10.0 mmol, 1.0 equiv) was portion wise added. After complete addition the solution was allowed to warm to 0 °C and stirred for another 4 hours. After full consumption of the starting materials (monitoring by TLC) the reaction mixture was concentrate to roughly ¼ of its volume under reduced pressure before being diluted with ethyl acetate (50 mL) and water (50 mL). The phases were separated, and the aqueous layer was additionally extracted with ethyl acetate (2 x 50 mL). The combined organic layers were then washed with brine (50 mL) and dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexanes/ ethyl acetate = 9/1) to afford the title compound as a yellowish oil (2.55 g, 9.2 mmol, 92%). Spectroscopic data are in agreement with those reported in literature.

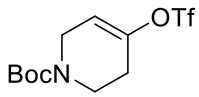
[25] A. B. Dürr, G. Yin, I. Kalvet, F. Napoly, F. Schoenebeck, *Chem. Sci.*, **2016**, *7*, 1076 – 1081.

[26] B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3943 – 3949.

[27] H. Konishi, T. Ueda, and K. Manabe, *Org. Synth.* **2014**, *91*, 39 – 51.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.24 – 7.18 (m, 2H), 7.17 – 7.13 (m, 1H), 7.12 – 7.05 (m, 1H), 6.48 (d, *J* = 1.5 Hz, 1H), 3.07 (t, *J* = 8.4 Hz, 2H), 2.70 (td, *J* = 8.4, 1.3 Hz, 2H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 150.0, 132.9, 131.1, 128.5, 127.5, 127.3, 127.0, 118.7 (q, $J_{C\text{-}F}$ = 320.6 Hz), 118.6, 28.6, 26.6. **^{19}F-NMR** (377 MHz, $CDCl_3$) δ = -74.1.

tert-butyl 4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (65f)



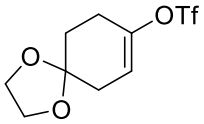
The title compound was prepared following a literature procedure.[28] Under N_2 atmosphere, a flame dried 50 mL Schlenk flask with rubber septum and magnetic stir bar was charged with diisopropylamine (0.7 mL, 4.96 mmol, 1.0 equiv) and THF (anhydrous, 10 mL). After cooling down to -78 °C, *n*-butyllithium (3.13 mL, 1.60 M in hexane, 4.96 mmol, 1,0 equiv) was slowly added and then stirred for 20 min. To the freshly prepared LDA solution was then slowly added a solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (1.0 g, 5.0 mmol, 1.01 equiv) in THF (anhydrous, 10 mL). After stirring for 20 min, 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (1.79 g, 5.0 mmol, 1.01 equiv) was added as a solution in THF (anhydrous, 10 mL). The resulting mixture was allowed to warm to 0 °C and stirred for 4 hours before being quenched with saturated NH_4Cl solution (50 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were additionally washed with sodium hydroxide solution (2M, 3 x 50 mL) in order to remove remaining aniline residues. After drying over Na_2SO_4 and filtration, the solvent was then removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel (hexanes/ ethyl acetate = 10/1) to obtain the title compound as colorless oil (1.48 g, 4.46 mmol, 90%). Spectroscopic data are in agreement with those reported in literature.[29]

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.76 (bs, 1H), 4.04 (m, 2H), 3.63 (t, *J* = 5.7 Hz, 2H), 2.44 (m, 2H), 1.47 (s, 9H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 154.5, 147.0, 129.5, 123.8, 118.8 (q, $J_{C\text{-}F}$ = 320.3 Hz), 115.8, 80.8, 41.8, 28.5 (28.2). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ = -74.3.

[28] G. Li, A. W. Stamford, Y. Huang, K.-C. Cheng, J. Cook, C. Farley, J. Gao, L. Ghibaudi, W. J. Greenlee, M. G. Margaret van Heek, J. J. Hwa, J. Kelly, D. Mullins, E. M. Parker, S. Wainhaus, X. Zhang, *Bioorg. Med. Chem. Lett.* **2008,** *18*, 1146 – 1150.

[29] B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3943 – 3949.

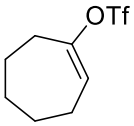
1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (65g)



The title compound was prepared in according to a literature procedure.[30] Under N_2 atmosphere, a flame dried 50 mL Schlenk flask with rubber septum and magnetic stir bar was charged with diisopropylamine (0.7 mL, 5.0 mmol, 1.0 equiv) and THF (anhydrous, 10 mL). After cooling down to -78 °C, *n*-butyllithium (3.13 mL, 1.60 M in hexane, 5.0 mmol, 1,0 equiv) was slowly added and then stirred for 20 min. To the freshly prepared LDA solution was then slowly added a solution of 1,4-dioxaspiro[4.5]decan-8-one (785 mg, 5.02 mmol, 1.01 equiv) in THF (anhydrous, 10 mL). After stirring for 20 min, 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (1.80 g, 5.0 mmol, 1.01 equiv) was added as a solution in THF (anhydrous, 10 mL). The resulting mixture was allowed to warm to 0 °C and stirred for 4 hours before being quenched with saturated NH_4Cl solution (50 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were additionally washed with sodium hydroxide solution (2M, 3 x 50 mL) in order to remove remaining aniline residues. After drying over Na_2SO_4 and filtration, the solvent was then removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel (hexanes/ ethyl acetate = 10/1) to obtain the title compound as colorless oil (1.40 g, 4.86 mmol, 97%). Spectroscopic data are in agreement with those reported in literature.[31]

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.66 (tt, *J* = 4.0, 1.4 Hz, 1H), 3.98 (dd, *J* = 3.3, 1.8 Hz, 4H), 2.53 (dtd, *J* = 6.6, 3.4, 2.6, 1.4 Hz, 2H), 2.41 (dd, *J* = 4.2, 2.4 Hz, 2H), 1.90 (t, *J* = 6.6 Hz, 2H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 148.3, 118.8 (q, J_{C-F} = 320.2 Hz), 116.0, 106.3, 64.8, 34.3, 31.1, 26.5. **^{19}F-NMR** (377 MHz, $CDCl_3$) δ = -74.4.

cyclohept-1-en-1-yl trifluoromethanesulfonate (65h)



The title compound was prepared following a literature procedure.[32] A flame dried 50 mL Schlenk flask with rubber septum and magnetic stir bar was charged with cycloheptanone (1.18 mL, 10.0 mmol, 1.0 equiv), powdered Na_2CO_3 (anhydrous 2.12 g, 20.0 mmol, 2.0 equiv) and CH_2Cl_2 (anhydrous ,15 mL) under N_2-atmosphere. After cooling the suspension to 0 °C, a solution of trifluoromethanesulfonic anhydride (3.36 mL, 20.0 mmol, 2.0 equiv) in CH_2Cl_2 (anhydrous, 15 mL) was then added dropwise. After complete addition the resulting mixture was allowed to warm to room temperature and stirred for 24 hours. The reaction mixture was then transferred to a

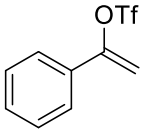
[30] G. Li, A. W.Stamford, Y. Huang, K.-C. Cheng, J. Cook, C. Farley, J. Gao, L. Ghibaudi, W. J. Greenlee, M. G. Margaret van Heek, J. J. Hwa, J. Kelly, D. Mullins, E. M. Parker, S. Wainhaus, X. Zhang, *Bioorg. Med. Chem. Lett.* **2008,** *18*, 1146 – 1150.

[31] B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3943 – 3949.

[32] A. M. Olivares, D. J. Weix, *J. Am. Chem. Soc.* **2018**, *140*, 2446 – 2449.

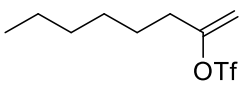
separation funnel and washed with sat. $NaHCO_3$ solution (50 mL) and water (50 mL). After drying over Na_2SO_4 and filtration the solvent was removed under reduced pressure and the product was purified by column chromatography on silica gel (pure pentane) to obtain the pure title compound as a yellowish liquid (1.85 g, 7.6 mmol, 76%). Spectroscopic data are in agreement with those reported in literature.[33]
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.88 (t, *J* = 6.4 Hz, 1H), 2.56 – 2.48 (m, 2H), 2.25 – 2.10 (m, 2H), 1.81 – 1.58 (m, 6H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 153.1, 123.1, 119.1 (q, J_{C-F} = 320.2 Hz), 33.2, 29.9, 26.3, 24.77, 24.7. **^{19}F-NMR** (377 MHz, $CDCl_3$) δ = -74.5.

1-phenylvinyl trifluoromethanesulfonate (65i)



The title compound was prepared following a literature procedure.[34] Under N_2 atmosphere, a flame dried 25 mL Schlenk flask with rubber septum and magnetic stir bar was charged with phenylacetylene (204 mg, 2.0 mmol, 1.0 equiv) and CH_2Cl_2 (anhydrous, 4 mL). To the solution was then added trimethylsilyl azide (530 µL, 4.0 mmol, 2.0 equiv) followed by a dropwise addition of trifluoromethanesulfonic acid (350 µL, 4.0 mmol, 2.0 equiv) the resulting solution was then stirred at room temperature for 15 min. The mixture was then diluted with hexanes (10 mL) and filtered through a short plug of silica gel (3-4 cm) using hexanes. The filtrate was then concentrated under reduced pressure to give the title compound as a colorless oil (420 mg, 1.67 mmol, 83%). Spectroscopic data are in agreement with those reported in literature.[35]
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.61 – 7.51 (m, 2H), 7.48 – 7.39 (m, 3H), 5.61 (d, *J* = 4.0 Hz, 1H), 5.39 (d, *J* = 4.0 Hz, 1H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 153.6, 132.1, 130.4, 129.0, 125.5, 118.5 (q, J_{C-F} = 320.3 Hz), 104.3. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ = -74.3.

oct-1-en-2-yl trifluoromethanesulfonate (65j)



The title compound was prepared following a literature procedure.[36] Under N_2 atmosphere, a solution of 1-octyne (2.26 mL, 15.0 mL, 1.5 equiv) in pentane (5 mL) was cooled down to -30 °C and trifluoromethanesulfonic acid (896 mL, 10.0 mL, 1.0 equiv) was slowly added. After stirring for 10 min, the mixture was allowed to warm to room temperature and stirred for another 30 min before quenching with sat. $NaHCO_3$ solution (20 mL). The layers were separated, and the organic phase was washed with sat. $NaHCO_3$ solution (2 x 20 mL) and dried over K_2CO_3.

[33] H. Senboku, Y. Fujimura, H. Kamekawa, M. Tokuda, *Electrochim. Acta.* **2000**, *45*, 2995 – 3003.

[34] J. Tummatorn, K. Punjajom, W. Rodphon, S. Ruengsangtongkul, N. Chaisan, K. Lumyong, C. Thongsornkleeb, P. Nimnual, S. Ruchirawat, *Org. Lett.* **2019**, *21*, 4694 – 4697.

[35] H. Senboku, Y. Fujimura, H. Kamekawa, M. Tokuda, *Electrochim. Acta.* **2000**, *45*, 2995 – 3003.

[36] H. Senboku, Y. Fujimura, H. Kamekawa, M. Tokuda, *Electrochim. Acta* **2000**, *45,* 2995 – 3003.

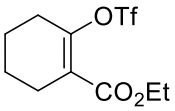
After filtration, volatiles were removed under reduced pressure and the residue was purified by Kugelrohr distillation (70°C, 1 mbar) to give the title compound as colorless oil (427mg, 1.6 mmol, 16%). Spectroscopic data are in agreement with those reported in literature.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.08 (d, *J* = 3.5 Hz, 1H), 4.92 (dt, *J* = 3.5, 1.1 Hz, 1H), 2.37 – 2.30 (m, 2H), 1.59 – 1.49 (m, 2H), 1.39 – 1.26 (m, 6H), 0.93 – 0.86 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 157.3, 118.7 (q, J_{C-F} = 319.9 Hz), 104.1, 34.0, 31.5, 28.4, 26.1, 22.6, 14.1.

^{19}F-NMR (377 MHz, $CDCl_3$) δ = -74.7.

ethyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate (65k)

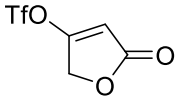


The title compound was prepared following a literature procedure.[37] Under N_2 atmosphere, a flame dried 100 mL Schlenk flask with rubber septum and magnetic stir bar was charged with sodium hydride (60 wt% suspension in mineral oil, 480 mg, 12.0 mmol, 1.2 equiv) and CH_2Cl_2 (anhydrous, 40 mL). Ethyl 2-oxocyclohexane-1-carboxylate (1.67 mL, 10.0 mmol, 1.0 equiv) was added to the suspension at 0 °C and stirred for 30 min while allowing to warm to room temperature. The resulting mixture was then again cooled to -78 °C and trifluoromethanesulfonic anhydride (2.02 mL, 12.0 mmol, 1.2 equiv) was slowly added . The reaction was allowed to warm to room temperature and stirred for 18 hours. After full consumption of the starting material (monitoring by TLC) the reaction was quenched with water (50 mL) and the layers were separated. The organic phase was washed with brine (2 x 50 mL) and dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexanes/ ethyl acetate = 9/1 to 4/1) to afford the title compound as a colorless oil (2.86 g, 9.4 mmol, 94%). Spectroscopic data are in agreement with those reported in literature.[38]

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 4.27 (q, *J* = 7.2 Hz, 1H), 2.47 (tt, *J* = 5.8, 2.7 Hz, 1H), 2.39 (tt, *J* = 6.0, 2.6 Hz, 1H), 1.87 – 1.72 (m, 1H), 1.66 (ttd, *J* = 5.8, 3.8, 1.4 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 2H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 164.9, 151.4, 123.4, 118.4 (q, J_{C-F} = 319.8 Hz), 61.7, 28.6, 26.3, 22.4, 21.1, 14.1.

^{19}F-NMR (282 MHz, $CDCl_3$) δ = -75.3.

5-oxo-2,5-dihydrofuran-3-yl trifluoromethanesulfonate (65l)



The title compound was prepared following a literature procedure.[39] Under N_2 atmosphere, a flame dried 100 mL Schlenk flask with rubber septum and magnetic stir bar was charged with tetronic acid (1.00 g, 10.0 mmol, 1.0 equiv) and CH_2Cl_2 (anhydrous, 30 mL). The solution was cooled down to -78 °C and ethyl diisopropylamine (1.92 mL, 11.0 mmol,

[37] Y. Zou, L. Qin, X. Ren, Y. Lu, Y. Li , J. Zhou, *Chem. Eur. J.* **2013**, *19*, 3504 – 3511.

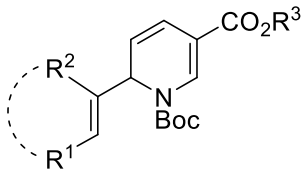
[38] B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3943 – 3949.

[39] R. Grigg, P. Kennewell, V. Savic, *Tetrahedron* **1994**, *50*, 5489 – 5494.

1.1 equiv) was added to the reaction, followed by trifluoromethanesulfonic anhydride (1.85 mL, 11.0 mmol, 1.1 equiv). After stirring for 1 hour the mixture was warmed to room temperature then extracted with water (100 mL) and brine (100 mL). The organic phase was then dried over Na_2SO_4 and after filtration the solvent was removed under reduced pressure. The residue was then purified by Kugelrohr distillation (110 °C, 2 mbar) to afford the title compound as a colorless oil (1,81 g, 7.8 mmol, 78%). Spectroscopic data are in agreement with those reported in literature.[40]

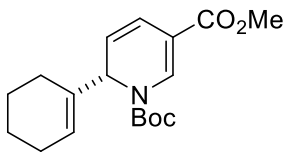
^{1}H-NMR (300 MHz, $CDCl_3$) δ = 6.04 (t, *J* = 1.8 Hz, 1H), 4.88 (d, *J* = 1.8 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ = 169.0, 167.0, 118.7 (q, $J_{C\text{-}F}$ = 321.5 Hz), 104.5, 67.6. **^{19}F-NMR** (282 MHz, $CDCl_3$) δ = -73.0.

General procedure (GP-III) for the synthesis of 1-(tert-butyl) 3-alkyl 6-vinylpyridine-1,3(6H)-dicarboxylates



In an argon filled glove box, a 5 mL flame dried Schlenk tube was charged with $Pd(PPh_3)_4$ (5.8 mg, 5.0 µmol, 0.01 equiv). After removal from the glovebox, the tube was backfilled with nitrogen and charged with monocyclopropanated *N*Boc-pyrrole **3-Me** or **3-*t*Bu** (0.5 mmol, 1.0 equiv) and sodium carbonate (anhydrous, 106 mg, 1.0 mmol, 2.0 equiv). After adding a solution of vinyl triflate (0.65 mmol, 1.3 equiv) in DMSO (anhydrous, 2.5 mL), the mixture was then degassed by three consecutive cycles of freeze-pump-thaw before being stirred at 80 °C for 2 days. After cooling to room temperate, the reaction was diluted with ethyl acetate (15 mL) and water (15 mL) and phases were separated. The organic phase was washed with water (15 mL) and the combined aqueous phases were then additionally re-extracted with ethyl acetate (15 mL). The organic phases were then combined and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexanes/ ethyl acetate) to obtain the pure product.

1-(tert-butyl) 3-methyl 6-(cyclohex-1-en-1-yl)pyridine-1,3(6H)-dicarboxylate (66a-Me)



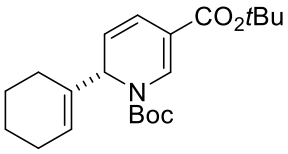
Following the general procedure GP-III using monocyclopropanated pyrrole **3-Me** (120 mg, 0.5 mmol, 1.0 equiv) and cyclohex-1-en-1-yl trifluoromethanesulfonate (150 mg, 0.65 mmol, 1.3 equiv), the title compound was obtained as a colorless oil (117 mg, 0.37 mmol, 73%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 20/1 to 10/1).

R_f (hexanes/ethyl acetate = 5/1) = 0.53; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.95 (s, 1H), 6.35 (dt, *J* = 9.9, 1.3 Hz, 1H), 5.58 – 5.50 (m, 1H), 5.45 – 5.33 (m, 1H), 5.06 (d, *J* = 5.2 Hz, 1H), 3.72 (s, 3H), 2.06 – 1.88 (m, 4H), 1.66 – 1.50 (m, 4H), 1.48 (s, 9H).; **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 166.4, 152.4, 137.4, 136.3, 122.8, 120.6, 119.3, 107.1, 82.9, 59.7, 51.5, 28.1, 25.1, 23.6, 22.6, 22.4; **HRMS** (+ESI, 120 V):

[40] B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3943 – 3949.

calcd. for $C_{18}H_{26}NO_4$ $[M+H]^+$ 320.1856 found 320.1860; **IR** (neat): 2978, 2933, 1707, 1640, 1595, 1439, 1368, 1327, 1245, 1148, 1081, 1044, 973, 921, 878, 772, 738 cm^{-1}.

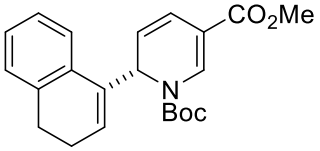
di-tert-butyl 6-(cyclohex-1-en-1-yl)pyridine-1,3(6H)-dicarboxylate (66a-*t*Bu)



Following the general procedure GP-III using monocyclopropanated pyrrole **3-*t*Bu** (141 mg, 0.5 mmol, 1.0 equiv) and cyclohex-1-en-1-yl trifluoromethanesulfonate (150 mg, 0.65 mmol, 1.3 equiv) gave the title compound as a colorless oil (154 mg, 0.43 mmol, 85%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 99/1 to 9/1).

$\mathbf{R_f}$ (hexanes/ethyl acetate = 5/1) = 0.73; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.81 (s, 1H), 6.25 (dt, *J* = 9.9, 1.3 Hz, 1H), 5.58 – 5.44 (m, 1H), 5.32 (ddd, *J* = 9.9, 5.2, 0.9 Hz, 1H), 4.98 (dd, *J* = 6.2, 3.1 Hz, 1H), 1.92 (pt, *J* = 7.6, 4.0 Hz, 4H), 1.55 – 1.44 (m, 4H), 1.42 (s, 18H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 165.2, 152.4, 137.6, 135.3, 122.4, 120.3, 119.4, 108.5, 82.5, 79.9, 59.7, 28.3, 28.0, 25.0, 23.6, 22.6, 22.3; **HRMS** (+ESI, 120 V): calcd. for $C_{21}H_{32}NO_4$ $[M+H]^+$ 362.2326 found 362.2329; **IR** (neat): 2978, 2930, 2840, 1722, 1700, 1640, 1595, 1476, 1368, 1334, 1267, 1126, 1077, 977, 902, 850, 772 cm^{-1}.

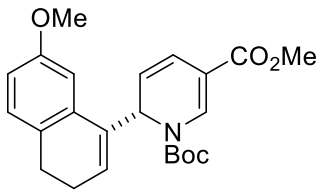
1-(tert-butyl) 3-methyl 6-(3,4-dihydronaphthalen-1-yl)pyridine-1,3(6H)-dicarboxylate (66b-Me)



Following the general procedure GP-III using monocyclopropanated pyrrole **3-Me** (120 mg, 0.5 mmol, 1.0 equiv) and 3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (181 mg, 0.65 mmol, 1.3 equiv) gave the title compound as a colorless oil (116 mg, 0.32 mmol, 63%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 99/1 to 9/1).

$\mathbf{R_f}$ (hexanes/ethyl acetate = 5/1) = 0.50; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 8.13 (s, 1H), 7.30 (d, *J* = 7.4 Hz, 1H), 7.24 – 7.14 (m, 3H), 6.31 (dt, *J* = 10.0, 1.4 Hz, 1H), 5.96 (t, *J* = 4.8 Hz, 1H), 5.84 (d, *J* = 4.9 Hz, 1H), 5.65 (dd, *J* = 10.0, 5.1 Hz, 1H), 3.76 (s, 3H), 2.85 – 2.56 (m, 2H), 2.32 – 2.16 (m, 2H), 1.38 (s, 9H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 166.4, 152.1, 139.1, 136.9, 135.9, 132.3, 128.1, 127.2, 126.6, 123.9, 121.7, 121.4, 118.2, 106.4, 83.2, 54.3, 51.5, 28.2, 28.0, 22.8; **HRMS** (+ESI, 120 V): calcd. for $C_{22}H_{26}NO_4$ $[M+H]^+$ 368.1856 found 368.1860; **IR** (neat): 2982, 2937, 2833, 1707, 1640, 1595, 1439, 1476, 1402, 1368, 1331, 1238, 1148, 1085, 1036, 958, 906, 850, 801, 768, 731 cm^{-1}.

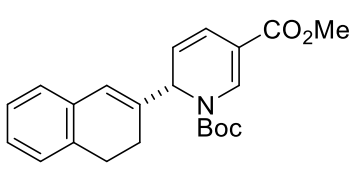
1-(tert-butyl) 3-methyl 6-(7-methoxy-3,4-dihydronaphthalen-1-yl)pyridine-1,3(6H)-dicarboxylate (66d-Me)



Following the general procedure GP-III using monocyclopropanated pyrrole **3-Me** (120 mg, 0.5 mmol, 1.0 equiv) and 7-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (202 mg, 0.65 mmol, 1.3 equiv) gave the title compound as a yellowish oil (106 mg, 0.27 mmol, 53%) after purification by column chromatography on silica gel (pure hexane to hexanes/ ethyl acetate = 9/1).

R_f (hexanes/ethyl acetate = 5/1) = 0.53; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 8.11 (s, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 2.5 Hz, 1H), 6.70 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.31 (dt, *J* = 10.0, 1.4 Hz, 1H), 5.97 (t, *J* = 4.8 Hz, 1H), 5.78 (d, *J* = 5.1 Hz, 1H), 5.65 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 2.71 – 2.55 (m, 2H), 2.29 – 2.14 (m, 2H), 1.38 (s, 9H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 166.3, 158.4, 152.1, 138.8, 135.9, 133.3, 129.0, 128.6, 124.8, 121.4, 118.2, 111.4, 108.8, 106.4, 83.2, 55.4, 54.5, 51.5, 28.0, 27.3, 23.2; **HRMS** (+ESI, 120 V): calcd. for $C_{23}H_{28}NO_5$ $[M+H]^+$ 398.1962 found 398.1973; **IR** (neat): 3101, 2978, 2937, 2833, 1703, 1603, 1640, 1491, 1438, 1398, 1368, 1338, 1241, 1144, 1044, 1084, 962, 850, 805, 772, 727 cm^{-1}.

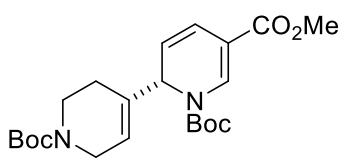
1-(tert-butyl) 3-methyl 6-(3,4-dihydronaphthalen-2-yl)pyridine-1,3(6H)-dicarboxylate (66e-Me)



Following the general procedure GP-III using monocyclopropanated pyrrole **3-Me** (120 mg, 0.5 mmol, 1.0 equiv) and 3,4-dihydronaphthalen-2-yl trifluoromethanesulfonate (181 mg, 0.65 mmol, 1.3 equiv) gave the title compound as a yellow oil (123 mg, 0.33 mmol, 67%) after 18 hours reaction time. Purification was achieved by column chromatography on silica gel (first column: pure hexanes to hexanes/ ethyl acetate = 19/1, second column: CH_2Cl_2/ hexanes = 1/1 to pure CH_2Cl_2). The second column was necessary to remove the oxidation product (pyridine).

R_f (hexanes/ethyl acetate = 5/1) = 0.65; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 8.05 (s, 1H), 7.18 – 7.07 (m, 3H), 7.05 – 7.01 (m, 1H), 6.46 (dt, *J* = 9.9, 1.3 Hz, 1H), 6.30 (s, 1H), 5.51 (dd, *J* = 9.9, 5.3 Hz, 1H), 5.36 (d, *J* = 5.3 Hz, 1H), 3.77 (s, 3H), 2.80 (td, *J* = 8.2, 2.8 Hz, 2H), 2.43 – 2.24 (m, 2H), 1.49 (s, 9H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 166.2, 152.2, 139.5, 136.1, 135.0, 133.9, 127.3, 127.2, 126.6, 126.5, 123.1, 120.1, 119.6, 107.2, 83.3, 58.7, 51.5, 28.1, 28.1, 23.0; **HRMS** (+ESI, 120 V): calcd. for $C_{22}H_{26}NO_4$ $[M+H]^+$ 368.1856 found 368.1860; **IR** (neat): 2978, 2937, 2833, 1703, 1640, 1592, 1476, 1439, 1372, 1338, 1241, 1144, 1081, 1006, 986, 854, 723 cm^{-1}.

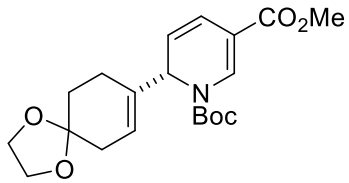
1,1'-di-tert-butyl 5-methyl 3',6'-dihydro-[2,4'-bipyridine]-1,1',5(2H,2'H)-tricarboxylate (66f-Me)



Following the general procedure GP-III using monocyclopropanated pyrrole **3-Me** (120 mg, 0.5 mmol, 1.0 equiv) and tert-butyl 4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (215 mg, 0.65 mmol, 1.3 equiv) gave the title compound as a colorless oil (151 mg, 0.36 mmol, 72%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 19/1).

R_f (hexanes/ethyl acetate = 5/1) = 0.33; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.88 (s, 1H), 6.36 (dt, *J* = 9.9, 1.2 Hz, 1H), 5.47 (s, 1H), 5.37 (dd, *J* = 9.9, 5.4 Hz, 1H), 5.13 (d, *J* = 5.4 Hz, 1H), 3.96 – 3.73 (m, 2H), 3.69 (s, 3H), 3.51 – 3.31 (m, 2H), 2.02 (m, 2H), 1.44 (s, 9H), 1.39 (s, 9H); **^{13}C-NMR** (101 MHz, $CDCl_3$) *rotamer 1* (*rotamer 2*) δ = 166.0, 154.7, 151.9, 135.9 (2 carbons overlapped), 120.1, 119.6, 119.4, 107.4, 83.2, 79.6, 58.2, 51.4, 43.2 (42.8), 40.7 (39.6), 28.4, 28.0, 24.1; **HRMS** (+ESI, 120 V): calcd. for $C_{22}H_{33}N_2O_6$ $[M+H]^+$ 421.2333 found 421.2340; **IR** (neat): 2978, 2933, 1696, 1644, 1592, 1416, 1334, 1238, 1144, 1008, 982, 921, 850, 798, 760, 664 cm^{-1}.

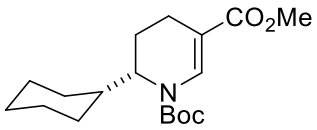
1-(tert-butyl) 3-methyl 6-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)pyridine-1,3(6H)-dicarboxylate (66g)



Following the general procedure GP-III using monocyclopropanated pyrrole **3-Me** (120 mg, 0.5 mmol, 1.0 equiv) and 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (187 mg, 0.65 mmol, 1.3 equiv) gave the title compound as a colorless oil (84 mg, 0.27 mmol, 53%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 3/1).

R_f (hexanes/ethyl acetate = 5/1) = 0.28; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.89 (s, 1H), 6.31 (dt, *J* = 9.9, 1.3 Hz, 1H), 5.41 (t, *J* = 3.5 Hz, 1H), 5.36 (dd, *J* = 10.0, 5.3 Hz, 1H), 5.08 (d, *J* = 5.3 Hz, 1H), 3.87 (s, 4H), 3.66 (s, 3H), 2.26 – 2.05 (m, 4H), 1.65 (t, *J* = 6.5 Hz, 2H), 1.43 (s, 9H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 166.2, 152.2, 137.0, 136.0, 120.3, 120.1, 119.6, 107.7, 107.1, 83.1, 64.4, 64.4, 58.9, 51.4, 35.5, 30.9, 28.0, 23.1; **IR** (neat): 2978, 1703, 1640, 1596, 1439, 1476, 1372, 1342, 1241, 1144, 947, 919, 809, 772, 731 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{20}H_{28}NO_6$ $[M+H]^+$ 378.1911 found 378.1914.

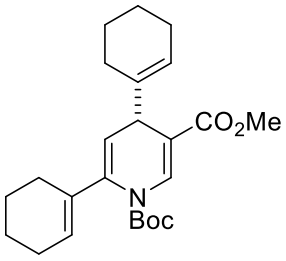
1-(tert-butyl) 3-methyl 6-cyclohexyl-5,6-dihydropyridine-1,3(4H)-dicarboxylate (67a-Me)



And autoclavable vial was charged with dihydropyridine **66a-Me** (112 mg, 351 µmol, 1.0 equiv), Pd on activated charcoal (26 mg, 10 wt%, 25 µmol, 7 mol%) and methanol (anhydrous, 5 mL). The mixture was then intensively stirred under H_2 (40 bar, autoclave) for 18 hours. The suspension was filtered through a short plug of silica gel using ethyl acetate and volatiles were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/ ethyl acetate = 19/1 to 9/1) affording the title compound as a colorless oil (78 mg, 241 µmol, 69%).

R_f (hexanes/ethyl acetate = 5/1) = 0.50; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.98 (bs, 1H), 4.02 (bs, 1H), 3.72 (s, 3H), 2.44 – 2.28 (m, 1H), 2.20 – 1.99 (m, 2H), 1.82 – 1.54 (m, 5H), 1.50 (s, 9H), 1.41 – 0.82 (m, 7H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 168.3, 152.4, 135.4, 107.6, 82.2, 54.4, 51.4, 38.1, 29.6, 28.3, 26.4, 26.3, 21.9, 17.7; **IR** (neat): 2930, 2855, 1700, 1633, 1446, 1342, 1245, 1199, 1152, 1088, 1058, 973, 854, 805, 768 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{18}H_{30}NO_4$ $[M+H]^+$ 324.2169 found 324.2172.

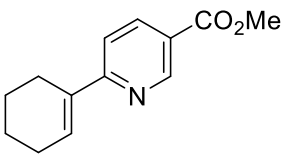
1-(tert-butyl) 3-methyl 4,6-di(cyclohex-1-en-1-yl)pyridine-1,3(4H)-dicarboxylate (73)



Following the general procedure GP-III (optimization Table **4** entry 7) using monocyclopropanated pyrrole **3-Me** (120 mg, 0.5 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (34 mg, 30 µmol, 0.1 equiv), Na_2CO_3 (64mg, 0.6 mmol, 2.0 equiv) and cyclohex-1-en-1-yl trifluoromethanesulfonate (138 mg, 0.6 mmol, 2.0 equiv) in DMSO (anhydrous, 1.5 mL) gave the title compound as byproduct (21 mg, 0.05 mmol, 18%) after stirring for 24 hours at 60 °C. The colorless oil was obtained after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 20/1 to 10/1).

R_f (hexanes/ethyl acetate = 5/1) = 0.65; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.92 (s, 1H), 6.27 (dt, *J* = 10.0, 1.4 Hz, 1H), 5.58 (d, *J* = 5.2 Hz, 1H), 5.43 – 5.40 (m, 1H), 5.28 (ddd, *J* = 10.0, 5.2, 0.9 Hz, 1H), 3.74 (s, 3H), 2.27 – 1.86 (m, 8H), 1.82 – 1.53 (m, 8H), 1.50 (s, 9H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 166.6, 151.8, 139.7, 137.1, 135.9, 130.2, 123.5, 121.9, 118.1, 106.3, 82.8, 56.4, 51.5, 29.9, 28.3, 27.5, 25.3, 23.4, 23.1, 23.0, 22.9, 22.3; **HRMS** (+ESI, 120 V): calcd. for $C_{24}H_{34}NO_4$ $[M+H]^+$ 400.2482 found 400.2484; **IR** (neat): 2978, 2859, 2930, 1707, 1640, 1592, 1439, 1338, 1230, 1148, 1077, 1006, 921, 854, 805 cm^{-1}

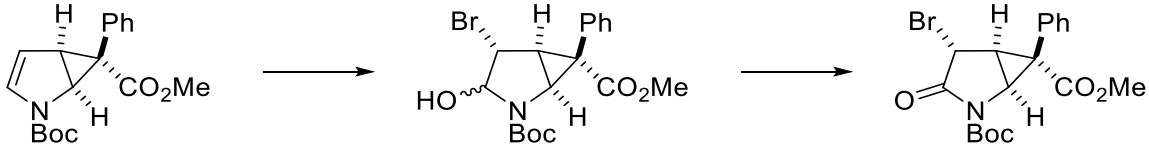
methyl 6-(cyclohex-1-en-1-yl)nicotinate (74)



A 5 mL vial with magnetic stir bar was charged with dihydropyridine **66a-Me** (115 mg, 360 µmol, 1.0 equiv) and toluene (2 mL). The mixture was cooled to 0 °C and 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 164 mg, 720 µmol, 2.0 equiv) was added resulting in a deep red color. After allowing the reaction to warm to room temperature and stirring for 18 hours, the mixture was transferred to a separation funnel and washed with saturated $NaHCO_3$ (30 mL) and brine (30 mL). The combined aqueous phases were additionally extracted with CH_2Cl_2 (2 x 30 mL) and the combined organic phases were then dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexanes/ ethyl acetate = 20/1 to 6/1) to obtain the product as a colorless, crystalline solid (55 mg, 252 µmol, 70%). X-ray grade crystals were obtained by slow evaporation from methanol.

R_f (hexanes/ethyl acetate = 5/1) = 0.54; **mp.** = 80 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 9.09 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.16 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.46 – 7.33 (m, 1H), 6.85 (tt, *J* = 4.0, 1.8 Hz, 1H), 3.89 (s, 3H), 2.53 – 2.44 (m, 2H), 2.30 – 2.21 (m, 2H), 1.81 – 1.72 (m, 2H), 1.70 – 1.59 (m, 2H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 166.0, 162.4, 150.2, 137.4, 136.1, 131.8, 123.4, 118.2, 52.2, 26.2, 25.9, 22.7, 22.0; **HRMS** (EI, 70 eV): calcd. for $C_{13}H_{15}NO_2$ [$M^{\cdot+}$] 217.1097 found 217.1100; **IR** (neat): 2930, 2893, 1718, 1592, 1480, 1435, 1379, 1293, 1197, 1118, 951, 884, 880, 842, 775 cm^{-1}.

2-(tert-butyl) 6-methyl-4-bromo-3-oxo-6-phenyl-2-azabicyclo[3.1.0]hexane-2,6-dicarboxylate (79-Boc)



17-Boc **79-Boc**

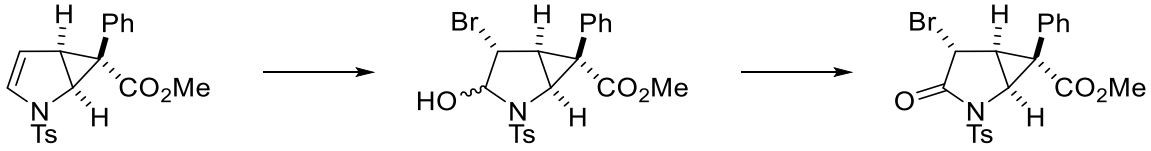
The title compound was prepared following a literature procedure.[41] A 250 mL round bottomed flask with magnetic stir bar was charged with monocyclopropanated pyrrole **17-Boc** (0.87 g, 2.8 mmol, 1.0 equiv). After dissolving the starting material in acetonitrile (30 mL), the mixture was cooled down to 5 °C and water (10 mL) was slowly added (the starting material must not precipitate at this step). Then, *N*-bromosuccinimide (0.54 g, 3.0 mmol, 1.05 equiv) was added in portions and the mixture was stirred for 10 min. The generated bromine (Br_2) indicated by an intense yellow color of the reaction was quenched with small amounts of $Na_2S_2O_3$ resulting in a colorless solution. After full conversion of the starting material (monitoring by TLC), the reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the crude product was transferred into a 100 mL round bottomed flask, dissolved in acetone (50 mL) and cooled to 0 °C. Jones reagent (1.84 mL, 3.0 M, 5.5 mmol, 2.0 equiv) was then

[41] A. Gheorghe, M. Schulte, O. Reiser, *J. Org. Chem.* **2006**, *71*, 2173-2176.

added dropwise to the solution and the reaction was stirred for 3 hours at room temperature. The reaction was carefully quenched with saturated $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were then washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexanes/ ethyl acetate = 4/1) to give the product as white solid (1.09 g, 2.7 mmol, 96%). X-ray grade crystals were obtained by vapor diffusion technique using ethyl acetate and pentane.

R_f (hexanes/ ethyl acetate = 3/1) = 0.54; **mp.** = 125 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.38 – 7.33 (m, 3H), 7.22 – 7.18 (m, 2H), 4.51 (dd, *J* = 7.4, 0.9 Hz, 1H), 4.28 (d, *J* = 0.9 Hz, 1H), 3.65 (s, 3H), 2.93 (d, *J* = 7.4 Hz, 1H), 1.57 (s, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ = 169.9, 167.1, 149.9, 131.6, 129.2, 129.0, 127.9, 84.5, 53.0, 45.4, 41.3, 40.7, 27.9, 27.7; **IR** (neat): 3071, 2993, 1789, 1707, 1435, 1371, 1329, 1249, 1148, 1018, 954, 831, 757, 701, 667 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{18}H_{20}BrNO_5$ $[M+H]^+$410.0598 found 410.0593.

methyl-4-bromo-3-oxo-6-phenyl-2-tosyl-2-azabicyclo[3.1.0]hexane-6-carboxylate (79-Ts)



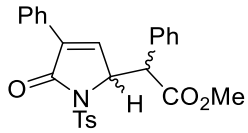
17-Ts **79-Ts**

The title compound was prepared following a literature procedure.[42] A 250 mL round bottomed flask with magnetic stir bar was charged with monocyclopropanated pyrrole **17-Ts** (1.26 g, 2.7 mmol, 1.0 equiv). After dissolving the starting material in acetonitrile (30 mL), the mixture was cooled down to 5 °C and water (10 mL) was slowly added (the starting material must not precipitate at this step). Then, *N*-bromosuccinimide (0.53 g, 3.0 mmol, 1.1 equiv) was added in portions and the mixture was stirred for 10 min. The generated bromine (Br_2) indicated by an intense yellow color of the reaction was quenched with small amounts of $Na_2S_2O_3$ resulting in a colorless solution. After full conversion of the starting material (monitoring by TLC), the reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the crude product was transferred into a 50 mL round bottomed flask, dissolved in acetone (20 mL) and cooled to 0 °C. Jones reagent (1.81 mL, 3.0 M, 5.4 mmol, 2.0 equiv) was then added dropwise to the solution and the reaction was stirred for 3 hours at room temperature. The reaction was carefully quenched with saturated $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were then washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexanes/ ethyl acetate = 3/1) to give the product as white solid (1.11 g, 2.4 mmol, 88%). X-ray grade crystals were obtained by vapor diffusion technique using CH_2Cl_2 and pentane.

[42] A. Gheorghe, M. Schulte, O. Reiser, *J. Org. Chem.* **2006**, *71*, 2173-2176.

mp. = 177 °C; $\mathbf{R_f}$ (hexanes/ ethyl acetate = 3/2) = 0.63; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.95 – 7.88 (m, 2H), 7.38 – 7.28 (m, 7H), 4.67 (dd, *J* = 7.7, 0.9 Hz, 1H), 4.28 (s, 1H), 3.67 (s, 3H), 2.94 (d, *J* = 7.7 Hz, 1H), 2.46 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 170.0, 167.4, 146.1, 134.6, 132.5, 130.0, 129.3, 129.3, 128.3, 127.2, 53.4, 46.9, 41.3, 40.7, 28.3, 21.9; **HRMS** (+ESI, 120 V): calcd. for $C_{20}H_{22}BrN_2O_5S$ $[M+NH_4]^+$ 481.0427 found 481.0430; **IR** (neat): 3094, 1752, 1715, 1595, 1495, 1402, 1368, 1249, 1208, 1159, 1080, 1025, 959, 812, 708 cm^{-}1.

methyl-2-(5-oxo-4-phenyl-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)-2-phenylacetate (86)



A flame dried 5 mL vial with screw cap and magnetic stir bar was charged with bromo ketone **79-Ts** (93 mg, 0.2 mmol, 1.0 equiv), Pd_2dba_3 (2.3 mg, 2.5 µmol, 1.25 mol%, 2.5 mol% Pd), K_3PO_4 (anhydrous, 127 mg, 0.6 mmol, 3.0 equiv), phenyl boronic acid (49 mg, 0.4 mmol, 2.0 equiv) and tri(*o*-tolyl)phosphine (4.6 mg, 15 µmol, 7.5 mol%). After adding dioxane/water (1 mL, 9/1) the mixture was degassed by 3 consecutive cycles of freeze-pump-thaw before being stirred for 18 hours at 80 °C. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through a short plug of silica gel. After removing the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 6/1).

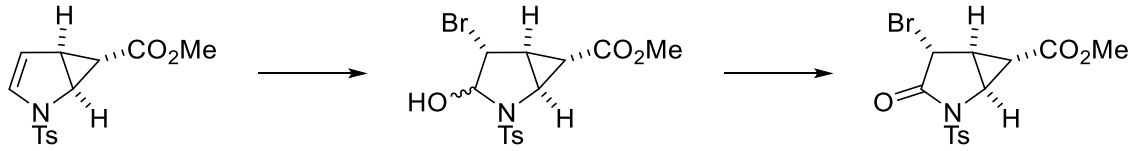
Major diastereomer: white solid (44 mg, 95 µmol, 47%)

$\mathbf{R_f}$ (hexanes/ ethyl acetate = 3/1) = 0.31; **mp.** = 76 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 8.02 – 7.96 (m, 2H), 7.62 (d, *J* = 2.4 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.37 – 7.31 (m, 2H), 7.30 – 7.25 (m, 4H), 7.23 – 7.17 (m, 3H), 7.11 – 7.04 (m, 2H), 5.33 (dd, *J* = 3.8, 2.4 Hz, 1H), 4.98 (d, *J* = 3.8 Hz, 1H), 3.80 (s, 3H), 2.42 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 172.5, 167.8, 145.4, 142.9, 136.1, 135.3, 131.6, 129.8, 129.6, 129.4, 129.2, 128.4, 128.4, 128.3, 128.2, 127.0, 62.1, 53.2, 52.6, 21.7; **IR** (neat): 3064, 2925, 1722, 1595, 1495, 1435, 1367, 1297, 1215, 1167, 1118, 1006, 936, 861, 749, 705 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{26}H_{24}NO_5$ $[M+H]^+$ 462.1370 found 462.1377.

Minor diastereomer: white solid (22 mg, 48 µmol, 24%). X-ray grade crystals were obtained by vapor diffusion technique using CH_2Cl_2 and pentane.

$\mathbf{R_f}$ (hexanes/ ethyl acetate = 3/1) = 0.35; **mp.** = 190 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 8.12 – 8.00 (m, 2H), 7.75 – 7.64 (m, 2H), 7.49 – 7.31 (m, 10H), 7.26 (s, 1H), 5.08 (d, *J* = 4.5 Hz, 1H), 5.00 (dd, *J* = 4.5, 2.3 Hz, 1H), 3.46 (s, 3H), 2.43 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 169.7, 168.4, 145.1, 141.7, 135.7, 135.7, 133.9, 130.0, 129.5, 129.3, 129.2, 128.6, 128.5, 128.5, 128.4, 127.2, 63.9, 52.5, 52.0, 21.7.; **IR** (neat): 3058, 2952 2904, 1715, 1595, 1379, 1495, 1464, 1349, 1163, 1088, 992, 958, 839, 693 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{26}H_{24}NO_5$ $[M+H]^+$ 462.1370 found 462.1374.

methyl-4-bromo-3-oxo-2-tosyl-2-azabicyclo[3.1.0]hexane-6-carboxylate (87)



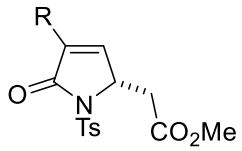
3-Ts-Me **87**

The title compound was prepared following a literature procedure.[43] A 250 mL round bottomed flask with magnetic stir bar was charged with monocyclopropanated pyrrole **3-Ts-Me** (2.86 g, 9.9 mmol, 1.0 equiv). After dissolving the starting material in acetonitrile (80 mL), the mixture was cooled down to 5 °C and water (20 mL) was slowly added (the starting material must not precipitate at this step). Then, *N*-bromosuccinimide (1.75 g, 9.9 mmol, 1.01 equiv) was added in portions and the mixture was stirred for 10 min. The generated bromine (Br_2) indicated by an intense yellow color of the reaction was quenched with small amounts of $Na_2S_2O_3$ resulting in a colorless solution. After full conversion of the starting material (monitoring by TLC), the reaction mixture was extracted with CH_2CL_2 (3 x 50 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the crude product was transferred into a 100 mL round bottomed flask, dissolved in acetone (50 mL) and cooled to 0 °C. Jones reagent (6.49 mL, 3.0 M, 19.5 mmol, 2.0 equiv) was then added dropwise to the solution and the reaction was stirred for 3 hours at room temperature. The reaction was carefully quenched with saturated $NaHCO_3$ solution (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were then washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexanes/ ethyl acetate = 3/1 to 1/1 to 1/3) to give the product as white solid (3.26 g, 8.4 mmol, 87%).

R_f (hexanes/ ethyl acetate = 3/1) = 0.19; **mp.** = 170 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.96 – 7.86 (m, 2H), 7.42 – 7.35 (m, 2H), 4.34 (ddd, *J* = 7.3, 1.6, 1.0 Hz, 1H), 4.27 (d, *J* = 1.0 Hz, 1H), 3.74 (s, 3H), 2.60 (dd, *J* = 7.3, 4.3 Hz, 1H), 2.47 (s, 3H), 1.51 (dd, *J* = 4.3, 1.6 Hz, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 167.9, 167.5, 146.4, 134.0, 130.1, 128.6, 52.8, 41.3, 40.3, 30.9, 23.7, 21.9; **IR** (neat): 2963, 1744, 1711, 1595, 1446, 1405, 1368, 1327, 1301, 1208, 1167, 1141, 1188, 1051, 1010, 903, 880, 808, 731, 664 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{14}H_{15}BrNO_5S$ $[M+H]^+$ 387.9849 found 387.9848.

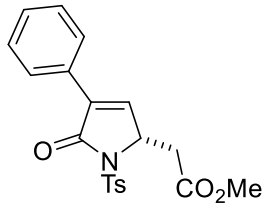
[43] A. Gheorghe, M. Schulte, O. Reiser, *J. Org. Chem.* **2006**, *71*, 2173-2176.

General procedure GP-IV for the synthesis of methyl-2-(5-oxo-4-aryl/alykl-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)acetates (88)



A flame dried 5 mL vial with screw cap and magnetic stir bar was purged with nitrogen and charged with bromo ketone **87** (117 mg, 0.3 mmol, 1.0 equiv), Pd_2dba_3 (3.4 mg, 3.8 µmol, 1.25 mol%, 2.5 mol% of Pd), K_3PO_4 (anhydrous, 191 mg, 0.9 mmol, 3.0 equiv), corresponding boronic acid (0.6 mmol, 2.0 equiv) and tri(*o*-tolyl)phosphine (6.9 mg, 23 µmol, 7.5 mol%). After adding toluene (anhydrous, 1.5 mL) the mixture was degassed by 3 consecutive cycles of freeze-pump-thaw before being stirred for 18 hours at 80 °C. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through a short plug of silica gel. After removing the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexanes/ ethyl acetate).

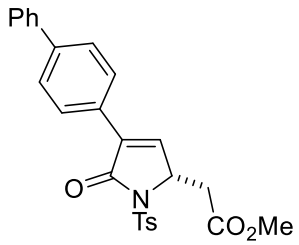
methyl-2-(5-oxo-4-phenyl-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (88a)



Following the general procedure GP-IV using phenyl boronic acid (73 mg, 0.60 mmol, 2.0 equiv) afforded the title compound as yellowish solid (82 mg, 0.21 mmol, 70%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 3/1 to 2/1).

R_f (hexanes/ ethyl acetate = 3/1) = 0.24; **mp.** = 127 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 8.05 – 7.93 (m, 2H), 7.77 – 7.65 (m, 2H), 7.49 (d, *J* = 2.3 Hz, 1H), 7.39 – 7.30 (m, 5H), 5.11 (ddd, *J* = 10.1, 4.1, 2.4 Hz, 1H), 3.74 (s, 3H), 3.67 (dd, *J* = 16.6, 4.2 Hz, 1H), 2.62 (dd, *J* = 16.6, 10.1 Hz, 1H), 2.42 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 170.4, 167.7, 145.5, 143.6, 135.5, 135.5, 129.9, 129.7, 129.6, 128.7, 128.5, 127.2, 57.7, 52.3, 37.7, 21.8; **IR** (neat): 2952, 1715, 1595, 1491, 1442, 1353, 1300, 1211, 1167, 1126, 988, 936, 850, 749, 693 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{20}H_{20}NO_5S$ $[M+H]^+$ 386.1057 found 386.1061.

methyl-2-(4-([1,1'-biphenyl]-4-yl)-5-oxo-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (88b)

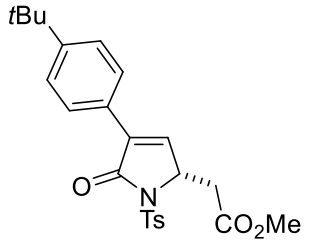


Following the general procedure GP-IV using [1,1'-biphenyl]-4-ylboronic acid (119 mg, 0.60 mmol, 2.0 equiv) afforded the title compound as colorless solid (86 mg, 0.19 mmol, 62%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 3/1 to 2/1).

R_f (hexanes/ ethyl acetate = 3/1) = 0.24; **mp.** = 208 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 8.01 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.63 – 7.54 (m, 4H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.48 – 7.40 (m, 2H), 7.39 – 7.32 (m, 3H), 5.13 (ddd, *J* = 10.1, 4.1, 2.3 Hz, 1H), 3.75 (s, 3H), 3.69 (dd, *J* = 16.6, 4.1 Hz, 1H), 2.64 (dd, *J* = 16.6, 10.1 Hz, 1H), 2.43 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 170.3, 167.7, 145.4, 143.2, 142.2, 140.3, 135.4, 135.0, 129.8, 128.9, 128.5, 128.4, 127.7, 127.5, 127.3, 127.1, 57.7, 52.2, 37.6, 21.7; **IR** (neat): 2956, 1722, 1595, 1487, 1446, 1357, 1308, 1249, 1156,

1115, 999, 842, 760, 693, 664 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{26}H_{24}NO_5S$ $[M+H]^+$ 462.1370 found 462.1376.

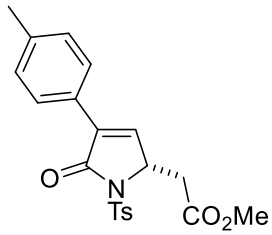
methyl-2-(4-(4-(tert-butyl)phenyl)-5-oxo-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (88c)



Following the general procedure GP-IV using (4-(tert-butyl)phenyl)boronic acid (107 mg, 0.60 mmol, 2.0 equiv) afforded the title compound as yellowish solid (56 mg, 0.13 mmol, 43%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 3/1 to 2/1).

R$_f$ (hexanes/ ethyl acetate = 3/1) = 0.40; **mp.** = 66 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 8.04 – 7.95 (m, 2H), 7.68 – 7.61 (m, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.41 – 7.30 (m, 4H), 5.09 (ddd, *J* = 10.1, 4.2, 2.4 Hz, 1H), 3.73 (s, 3H), 3.66 (dd, *J* = 16.5, 4.1 Hz, 1H), 2.61 (dd, *J* = 16.6, 10.1 Hz, 1H), 2.42 (s, 3H), 1.29 (s, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ = 170.5, 167.9, 152.9, 145.4, 142.8, 135.5, 135.4, 129.8, 128.4, 127.0, 126.8, 125.7, 57.8, 52.3, 37.8, 34.9, 31.3, 21.8; **IR** (neat): 3071, 2960, 2870, 1722, 1655, 1595, 1510, 1439, 1357, 1297, 1167, 1111, 999, 835, 734, 667 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{24}H_{28}NO_5S$ $[M+H]^+$ 442.1683 found 442.1686.

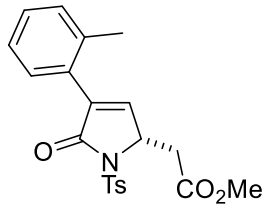
methyl-2-(5-oxo-4-(p-tolyl)-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (88d)



Following the general procedure GP-IV using *p*-tolylboronic acid (82 mg, 0.60 mmol, 2.0 equiv) and 1,4-dioxane (anhydrous, 1.5 mL) as solvent afforded the title compound as colorless solid (50 mg, 0.13 mmol, 42%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 3/1 to 2/1).

R$_f$ (hexanes/ ethyl acetate = 3/1) = 0.33; **mp.** = 133 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 5.05 (ddd, *J* = 10.2, 4.1, 2.4 Hz, 1H), 3.69 (s, 3H), 3.61 (dd, *J* = 16.6, 4.1 Hz, 1H), 2.56 (dd, *J* = 16.5, 10.1 Hz, 1H), 2.38 (s, 3H), 2.29 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 170.3, 167.8, 145.3, 142.5, 139.6, 135.5, 135.2, 129.7, 129.3, 128.3, 127.0, 126.7, 57.6, 52.1, 37.6, 21.7, 21.4; **IR** (neat): 3042, 2926, 2855, 1718, 1513, 1364, 1305, 1208, 1170, 1118, 1081, 1036, 820, 708 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{21}H_{22}NO_5S$ $[M+H]^+$ 400.1213 found 400.1221.

methyl-2-(5-oxo-4-(o-tolyl)-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (88e)

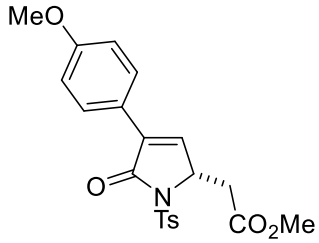


Following the general procedure GP-IV using *o*-tolylboronic acid (82 mg, 0.60 mmol, 2.0 equiv) and 1,4-dioxane (anhydrous, 1.5 mL) as solvent afforded the title compound as yellowish solid (55 mg, 0.13 mmol, 46%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 3/1 to 2/1).

R$_f$ (hexanes/ ethyl acetate = 3/1) = 0.33; **mp.** = 115 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 8.02 – 7.94 (m, 2H), 7.36 – 7.31 (m, 2H), 7.29 – 7.10 (m, 5H), 5.15 (ddd, *J* = 9.6, 4.1, 2.2 Hz, 1H), 3.70 (s, 3H),

3.61 (dd, *J* = 16.4, 4.1 Hz, 1H), 2.72 (dd, *J* = 16.4, 9.6 Hz, 1H), 2.42 (s, 3H), 2.22 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 170.1, 167.7, 146.7, 145.3, 137.5, 136.6, 135.4, 130.5, 129.7, 129.6, 129.3, 129.1, 128.3, 125.7, 58.1, 52.1, 37.6, 21.7, 20.3; **IR** (neat): 3068, 3023, 2952, 2926, 1722, 1595, 1491, 1439, 1357, 1293, 1167, 1111, 995, 910, 865, 813, 787, 760, 731, 664 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{21}H_{22}NO_5S$ $[M+H]^+$ 400.1213 found 400.1218.

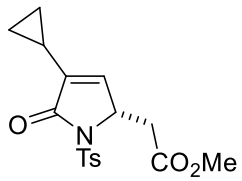
methyl-2-(4-(4-methoxyphenyl)-5-oxo-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)acetate(88f)



Following the general procedure GP-IV using (4-methoxyphenyl)boronic acid (91 mg, 0.60 mmol, 2.0 equiv) afforded the title compound as yellowish solid (28 mg, 0.07 mmol, 23%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 3/1 to 2/1).

R_f (hexanes/ ethyl acetate = 3/1) = 0.20; **mp.** = 117 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 8.03 – 7.94 (m, 2H), 7.74 – 7.64 (m, 2H), 7.39 – 7.30 (m, 3H), 6.90 – 6.82 (m, 2H), 5.08 (ddd, *J* = 10.1, 4.1, 2.4 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.66 (dd, *J* = 16.6, 4.1 Hz, 1H), 2.60 (dd, *J* = 16.6, 10.1 Hz, 1H), 2.42 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ = 170.4, 167.9, 160.5, 145.3, 141.3, 135.4, 134.7, 129.7, 128.5, 128.3, 122.1, 114.0, 57.5, 55.3, 52.1, 37.7, 21.7; **IR** (neat): 3094, 2952, 2848, 1715, 1607, 1513, 1439, 1364, 1293, 1260, 1152, 1111, 1088, 1029, 995, 932, 820, 708, 664 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{21}H_{22}NO_6S$ $[M+H]^+$ 416.1162 found 416.1170.

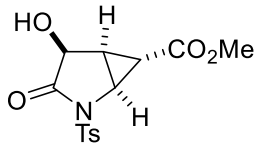
methyl-2-(4-cyclopropyl-5-oxo-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (88g)



Following the general procedure GP-IV using cyclopropylboronic acid (52 mg, 0.60 mmol, 2.0 equiv) afforded the title compound as colorless solid (13 mg, 0.04 mmol, 12%) after purification by column chromatography on silica gel (hexanes/ ethyl acetate = 3/1 to 2/1).

R_f (hexanes/ ethyl acetate = 3/1) = 0.25; **mp.** = 203 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 8.06 – 7.83 (m, 2H), 7.40 – 7.30 (m, 2H), 6.67 (dd, *J* = 2.3, 0.8 Hz, 1H), 4.92 (dddd, *J* = 10.0, 4.0, 2.3, 0.7 Hz, 1H), 3.70 (s, 3H), 3.53 (dd, *J* = 16.5, 4.0 Hz, 1H), 2.54 – 2.38 (m, 4H), 1.61 – 1.49 (m, 1H), 0.89 – 0.80 (m, 2H), 0.71 – 0.62 (m, 2H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 170.4, 168.7, 145.3, 140.8, 139.3, 135.7, 129.8, 128.3, 58.0, 52.1, 37.7, 21.8, 8.2, 8.1, 7.1; **IR** (neat): 3086, 3012, 2952, 2922, 2855, 1722, 1651, 1595, 1439, 1491, 1359, 1308, 1308, 1208, 1163, 1103, 1059, 980, 939, 906, 861, 809, 708 667 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{17}H_{20}NO_5S$ $[M+H]^+$ 350.1057 found 350.1063.

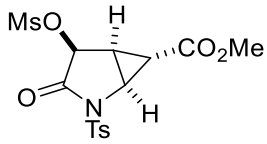
methy-4-hydroxy-3-oxo-2-tosyl-2-azabicyclo[3.1.0]hexane-6-carboxylate (104)



A 5 mL microwave tube was charged with **87** (78 mg, 0.2 mmol, 1.0 equiv) and DMSO (1 mL). The tube was placed in the microwave and heated to 100 °C for 6 h. After cooling to room temperature, the mixture was diluted with ethyl acetate and washed with water (3 x 20 mL) and dried over Na_2SO_4. After volatiles were removed under reduced pressure, the title compound was obtained as a white crystalline solid (49 mg, 0.15 mmol, 75%). X-ray grade crystals were obtained by dissolving in Et_2O and placing in the fridge for several weeks.

R_f (hexanes/ ethyl acetate = 1/1) = 0.28; **mp.** = 162 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.99 – 7.84 (m, 2H), 7.43 – 7.33 (m, 2H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.24 (dd, *J* = 7.5, 1.7 Hz, 1H), 3.72 (s, 3H), 2.66 (bs, 1H), 2.52 (ddd, *J* = 7.5, 6.8, 4.2 Hz, 1H), 2.47 (s, 3H), 1.58 – 1.55 (m, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 170.9, 169.0, 146.4, 134.0, 130.1, 128.5, 70.3, 52.6, 39.9, 25.8, 21.9, 20.4; **HRMS** (+ESI, 120 V): calcd. for $C_{14}H_{16}NO_6S$ $[M+H]^+$ 326.0698 found 326.0693; **IR** (neat): 3370, 2952, 1722, 1595, 1439, 1413, 1379, 1271, 1234, 1148, 1044, 962, 910, 820, 764, 664 cm^{-1}.

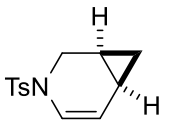
methyl-4-((methylsulfonyl)oxy)-3-oxo-2-tosyl-2-azabicyclo[3.1.0]hexane-6-carboxylate (105)



Under nitrogen, a 5 mL Schlenk flask was charged with **104** (49 mg, 0.15 mmol, 1.0 equiv) and CH_2Cl_2 (anhydrous, 3 mol). The solution was cooled to 0 °C and triethylamine (42 µL, 0.3 mmol, 2.0 equiv) and mesyl chloride (14 µL, 0.18 mmol, 1.2 equiv) were added after which the reaction was stirred for 18 h and allowed to warm to room temperature. The mixture was then washed with 1 M HCl (20 mL), 2 M (20 mL) and brine (20 mL) and then dried over Na_2SO_4. After volatiles were removed under reduced pressure, the title compound was obtained as a white solid (56 mg, 0.14 mmol, 91%) which was used without any further purification.

R_f (hexanes/ ethyl acetate = 1/1) = 0.50; **mp.** = 176 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.94 – 7.87 (m, 2H), 7.43 – 7.36 (m, 2H), 5.56 (d, *J* = 7.0 Hz, 1H), 4.30 (dd, *J* = 7.4, 1.9 Hz, 1H), 3.74 (s, 4H), 3.16 (s, 4H), 2.64 (td, *J* = 7.2, 4.1 Hz, 1H), 2.49 (s, 3H), 1.77 (dd, *J* = 4.2, 1.8 Hz, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 168.1, 165.2, 146.8, 133.7, 130.3, 128.5, 76.6, 52.8, 40.5, 39.9, 27.3, 22.0, 19.0; **HRMS** (+ESI, 120 V): calcd. for $C_{15}H_{18}NO_8S_2$ $[M+H]^+$ 404.0468 found 404.0477; **IR** (neat): 3094, 3042, 2967, 1722, 1595, 1491, 1443, 1410, 1357, 1305, 1252, 1170, 1144, 1085, 1043, 1006, 965, 887, 816, 779, 742 cm^{-1}.

3-Tosyl-3-azabicyclo[4.1.0]hept-4-ene (114-Ts)

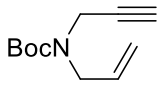


Following a literature procedure,[44] a N_2 purged 100 mL two-necked flask equipped with reflux condenser and magnetic stir bar was charged with *N*-allyl-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**125**) (2.0 g, 8.0 mmol, 1.0 equiv) and toluene (anhydrous, 27 mL). Rhodium(II) trifluoroacetate dimer $Rh_2(CO_2CF_3)_4$ (105 mg, 160 µmol, 2 mol%) was added and the reaction was placed in a preheated oil bath and stirred for 3.5 h at 80 °C. After cooling down to room temperature, the solvent was removed on the rotary evaporator and the residue was purified by column chromatography on silica gel (hexanes/ ethyl acetate 30/1 to 10/1) to afford the pure product as beige solid (1.33 g, 5.4 mmol, 67%). Spectroscopic data are in agreement with those reported in the literature.[45]

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.67 – 7.61 (m, 2H), 7.34 – 7.28 (m, 2H), 6.33 (dt, *J* = 8.1, 0.9 Hz, 1H), 5.40 (dd, *J* = 8.1, 5.4 Hz, 1H), 3.87 (dt, *J* = 11.6, 1.2 Hz, 1H), 3.05 (dd, *J* = 11.6, 3.0 Hz, 1H), 2.42 (s, 4H), 1.62 – 1.43 (m, 1H), 1.12 (tt, *J* = 8.7, 4.9 Hz, 1H), 0.78 (tdd, *J* = 8.3, 4.5, 0.9 Hz, 1H), 0.34 (dt, *J* = 5.7, 4.5 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 143.6, 134.9, 129.7, 127.0, 121.1, 112.1, 40.9, 21.5, 18.5, 13.4, 7.1.

tert-butyl allyl(prop-2-yn-1-yl)carbamate (115-Boc)



Following a literature procedure,[46] a flame dried 100 mL two-necked flask equipped with magnetic stir bar and reflux condenser was charged with *tert*-butyl allylcarbamate (**119-Boc**) (3.14 g, 20.0 mmol, 1.0 equiv) and DMF (anhydrous, 20 mL). At 0 °C, NaH (60 wt% suspension in mineral oil, 0.96 g, 24 mmol, 1.2 equiv,) was added in portions and the mixture was stirred for 1 hour. Then, a solution of propargyl bromide (80 wt% in toluene, 2.86 g, 24.0 mmol, 1.2 equiv) in DMF (anhydrous, 10 mL) was added dropwise over 5 min. After full addition, the ice bad was removed and the reaction was stirred for 5 h at 80 °C. The mixture was subsequently diluted with water (200 mL) and diethyl ether (200 mL) and the phases were separated. The organic phase was additionally washed with water (2 x 200 mL) and then dried over Na_2SO_4. After concentration on the rotary evaporator the residue was purified by column chromatography on silica gel (hexanes/ ethyl acetate = 10/1) to give the title compound as a yellow oil (3.00 g, 15.4 mmol, 77%). Spectroscopic data are in agreement with those reported in the literature.[47]

[44] Y. Lu, H. Yuan, S. Zhou, T. Luo, *Org. Lett.* **2017**, *19*, 620−623.

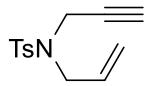
[45] A. Fürstner, F. Stelzer, H. Szillat**,** *J. Am. Chem. Soc.* **2001,** *123,* 11863-11869.

[46] F. Yan, H. Liang, J. Song, J. Cui, Q. Liu, S. Liu, P. Wang, Y. Dong, H. Liu, *Org. Lett.* **2017**, *19*, 86 - 89.

[47] D. P. Becker, D. L. Flynn, *Tetrahedron* **1993**, *49*, 5054 - 5054.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.74 (ddt, *J* = 17.1, 10.2, 5.9 Hz, 1H), 5.18 – 5.04 (m, 2H), 4.05 – 3.83 (m, 4H), 2.16 (t, *J* = 2.5 Hz, 1H), 1.44 (s, 9H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 154.8, 133.3, 117.0, 80.3, 79.6, 71.2, 48.5, 35.4, 28.3.

_N_-allyl-4-methyl-_N_-(prop-2-yn-1-yl)benzenesulfonamide (115-Ts)

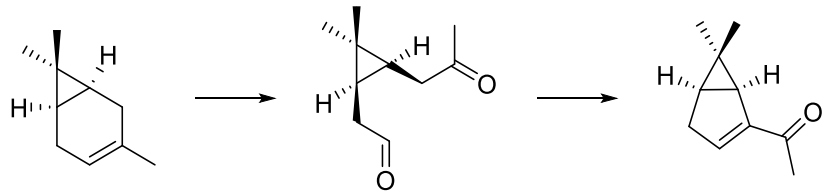


Following a literature procedure,[48] *N*-allyl-4-methylbenzenesulfonamide **(119-Ts)** (5.22 g, 24.7 mmol, 1.0 equiv) and K_2CO_3 (4,10 g, 29.7 mmol, 1.2 equiv) were dissolved in acetone (50 mL). A solution of propargyl bromide (80 wt% in toluene, 3.3 mL, 29.7 mmol, 1.2 equiv) was added and the resulting mixture was refluxed for 18 h. After full conversion of the starting material (monitoring by TLC), the mixture was diluted with water (150 mL) and CH_2Cl_2 (150 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 150 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and concentration under reduced pressure, the residue was purified by filtration through a short plug of silica gel using chloroform to give the title compound as a white crystalline compound (5.97 g, 23.9 mmol, 97%). Spectroscopic data are in agreement with those reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.76 – 7.71 (m, 2H), 7.30 – 7.27 (m, 2H), 5.73 (ddt, *J* = 16.7, 10.0, 6.5 Hz, 1H), 5.36 – 5.20 (m, 2H), 4.09 (d, *J* = 2.5 Hz, 2H), 3.82 (dt, *J* = 6.5, 1.3 Hz, 2H), 2.42 (s, 3H), 2.00 (t, *J* = 2.5 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 143.7, 136.1, 132.0, 129.6, 127.9, 120.1, 76.6, 73.8, 49.1, 35.9, 21.7.

1-(6,6-dimethylbicyclo[3.1.0]hex-2-en-2-yl)ethan-1-one ((+)-116)



(+)-117 **141** **(+)-116**

Following modified literature procedures,[49] a 100 mL Schlenk flask equipped with a magnetic stir bar was charged with (+)-3-Carene **(+)-117** (90 wt%, 5.17 mL, 29.4 mmol, 1.0 equiv), CH_2Cl_2 (anhydrous, 22.5 mL) and methanol (anhydrous, 7.5 mL). After cooling to -78 °C, ozone gas was slowly induced to the solution until ozone saturation indicated by a blue color change was visible (ca. 30 min). The ozone generator was switched off and the reaction mixture was purged with oxygen for additional 5 min until

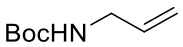
[48] J. Cui, J. Hao, O. A. Ulanovskaya, J. Dundas, J. Liang, S. Kozmin, *A. Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 6763-6768.

[49] a) L. Shi, Y. He, J. Gong, Z. Yang, *Chem. Commun.*, **2020**, *56*, 531-534. b) A. V. Malkov, D. Pernazza, M. Bell, M. Bella, A. Massa, F. Teply, P. Meghani, P. Kočovsky, *J. Org. Chem.* **2003**, *68*, 4727-4742.

a decoloring of the solution was observed. Dimethyl sulfide (10.9 mL, 146.8 mmol, 5.0 equiv) was added and the reaction was allowed to warm to room temperature overnight. The mixture was washed with water (100 mL) and brine (100 mL) and then dried over Na_2SO_4. After concentration under reduced pressure, a solution of sodium hydroxide (3 w/v%, 55 mL) was poured onto the oily residue and the reaction was vigorously stirred for 20 min (it is critical at this stage that the concentration of sodium hydroxide has to be kept under 4 w/v% in order to avoid side reactions. Also, the reaction time is crucial). The suspension was extracted with diethyl ether (3 x 100 mL) and the combined organic phases were washed with water (100 mL) and brine (100 mL) and then dried over Na_2SO_4. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel (hexanes/ diethyl ether = 4/1) to obtain the product as a colorless liquid (1.21 mg, 8.1 mmol, 37%). (Note that the product is somewhat volatile, so high vacuum should be avoided).

R_f (hexanes/ethyl acetate = 5/1) = 0.63; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 6.48 (dt, *J* = 2.4, 1.5 Hz, 1H), 2.66 (ddd, *J* = 20.7, 7.9, 2.7 Hz, 1H), 2.39 – 2.26 (m, 4H), 2.07 (dd, *J* = 6.5, 3.1 Hz, 1H), 1.37 (ddq, *J* = 7.7, 6.4, 1.2 Hz, 1H), 1.09 (s, 3H), 0.75 (s, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 196.4, 146.1, 143.0, 35.3, 33.6, 28.5, 26.9, 26.2, 19.1, 12.9; **HRMS** (EI+, 70 eV): calcd. for $C_{10}H_{14}O$ [$M^{\cdot+}$] 150.1039 found 150.1036; **IR** (neat): 2948, 2896, 1666, 1595, 1424, 1375, 1297, 1256, 995, 798 cm^{-1}.

***tert*-butyl allylcarbamate (119-Boc)**



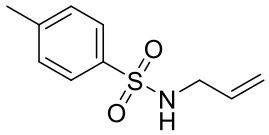
According to a literature procedure,[50] allylamine (2.28 g, 40.0 mmol, 1.0 equiv) and triethylamine (12.3 mL, 88.0 mmol, 2.2 equiv) were dissolved in CH_2Cl_2 (40 mL). At 0 °C, Boc_2O (9.6 g, 44.0 mmol, 1.1 equiv) was added as a solution in CH_2Cl_2 (10 mL) and the resulting mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was then washed with 1M HCl and saturated $NaHCO_3$ solution. The organic phase was dried over Na_2SO_4 and volatiles were removed under reduced pressure to afford a colorless oil that slowly crystallized at room temperature (6.00 g, 38.2 mmol, 95 %). Spectroscopic data are in agreement with those reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.82 (ddt, *J* = 17.1, 10.6, 5.5 Hz, 1H), 5.16 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.09 (dq, *J* = 10.3, 1.5 Hz, 1H), 4.60 (bs, 1H), 3.73 (d, *J* = 5.4 Hz, 2H), 1.44 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 155.9, 135.1, 115.8, 79.5, 43.2, 28.5.

[50] O. Pavlyuk, H. Teller, M. C. McMills *Tetrahedron Lett.* **2009**, *50*, 2716–2718.

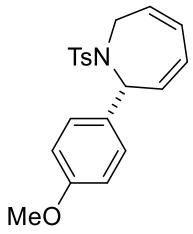
_N_-allyl-4-methylbenzenesulfonamide (119-Ts)



Following a literature procedure,[51] allylamine (2.1 mL, 1.57 g, 27.5 mmol, 1.1 equiv) and triethylamine (3.8 mL, 27.5 mmol, 1.1 equiv) were dissolved in anhydrous CH_2Cl_2 (125 mL). The solution was cooled to 0 °C and tosyl chloride (4.77 g, 25 mmol, 1.0 equiv) was added in portions. Reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The reaction was monitored by TLC. Afterwards, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted three times with CH_2Cl_2, filtered, and concentrated in vacuo to afford the title compound as beige solid (5.2 g, 24.7 mmol, 99%) as a beige solid. Spectroscopic data are in agreement with those reported in the literature.[52]

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.82 – 7.70 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.72 (ddt, *J* = 17.0, 10.2, 5.8 Hz, 1H), 5.20 – 5.04 (m, 2H), 4.62 (t, *J* = 6.5 Hz, 1H), 3.58 (tt, *J* = 6.0, 1.5 Hz, 2H), 2.43 (s, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 143.6, 137.1, 133.1, 129.9, 127.3, 117.8, 45.9, 21.7.

2-(4-methoxyphenyl)-1-tosyl-2,7-dihydro-1H-azepine (123)



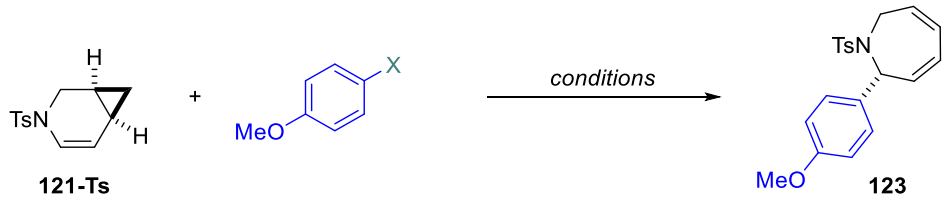
A flame dried 5 mL Schlenk flask with screw cap was charged with 3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (**114-Ts**) (74.8 mg, 0.3 mmol, 1.0 equiv), 4-methoxybenzenediazonium tetrafluoroborate (73.2 mg, 0.33 mmol, 1.1 equiv), sodium acetate (73.8 mg, 0.9 mmol, 3.0 equiv), and $Pd(dba)_2$ (17.3 mg, 30.0 µmol, 10 mol%). Under nitrogen, acetonitrile (degassed, anhydrous, 1.0 mL) was added, and the vial was tightly closed, and the reaction was stirred at room temperature for 24 hours. The mixture was diluted with ethyl acetate and filtered through a plug of silica gel. After volatiles were removed under reduced pressure, the residue was purified by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate 9/1) to obtain the pure product as a colorless solid (20 mg, 0.06 mmol, 19%). X-ray grade crystals were obtained by slow evaporation from hexanes/ ethyl acetate. **R_f** (hexanes/ethyl acetate = 5/1) = 0.44; **mp.** = 133 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.72 – 7.62 (m, 2H), 7.22 – 7.13 (m, 4H), 6.88 – 6.82 (m, 2H), 5.91 – 5.63 (m, 5H), 4.21 (ddd, *J* = 18.9, 6.0, 2.5 Hz, 1H), 3.79 (s, 3H), 3.33 (dt, *J* = 18.9, 2.6 Hz, 1H), 2.40 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 159.5, 143.1, 138.2, 132.2, 132.1, 131.8, 130.6, 129.0, 127.8, 126.3, 126.1, 114.1, 61.0, 55.4, 43.6, 21.7; **HRMS** (+ESI, 120 V): calcd. for

[51] : S. Govaerts, L. Angelini, C. Hampton, L. Malet-Sanz, A. Ruffoni, D. Leonori, *Angew. Chem. Int. Ed.* **2020**, *59*, 15021 – 15028.

[52] S. E. Gibson, K. A. C. Kaufmann, P. R. Haycock,A. J. P. White, D. J. Hardick, M. J. Tozer, *Organometallics* **2007,** *26,* 1578 - 1580.

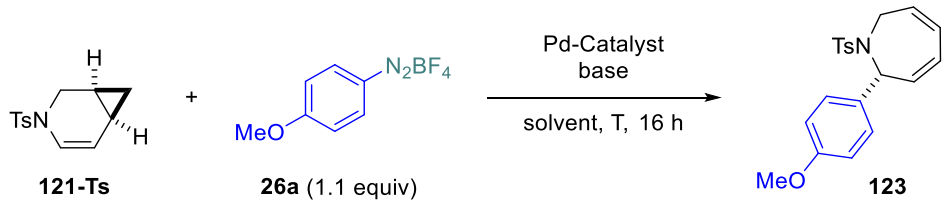
$C_{20}H_{22}NO_3S$ $[M+H]^+$ 356.1315 found 356.1316; **IR (neat):** 3045, 2978, 2922, 2847, 1610, 1510, 1454, 1372, 1320, 1245, 1148, 1088, 1062, 1029, 924, 865, 808, 678 cm^{-1}.

Table S 1. Attempts for the synthesis of **123**.



Entry	X	Conditions	Yield
1	I	$Pd_2(dba)_3$ (6 mol%), *p*-OMe-C_6H_4-I (1.3 equiv), $NaHCO_3$ (2.5 equiv), TBAB (2.0 equiv), Toluene, 80 °C, 24 h	no conversion
2	I	$Pd(OAc)_2$, *p*-OMe-C_6H_4-I (1.3 equiv), KOAc (2.5 equiv), TBAB (2.0 equiv), DMF, 40 °C, 3 d	no conversion
3	N_2BF_4	$Pd(dba)_2$ (10 mol%), *p*-OMe-C_6H_4-N_2BF_4 (1.1 equiv), NaOAc (3.0 equiv), MeCN, 25 °C, 24 h	19% (isolated)

Table S 2. Optimization studies for the synthesis of **123**.

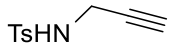


#	Catalyst (mol%)	Base (equiv)	Additive (equiv)	Solvent (1.5 mL)	t (h) / T (°C)	Comment	NMR-Yield
1	$Pd_2(dba)_3$ (5)	NaOAc (3)	--	MeCN	16 / r.t.	-	13%
2	$Pd(OAc)_2$ (5)	NaOAc (3)	--	MeCN	16 / r.t.	-	17%
3	$Pd_2(dba)_3$ (5)	NaOAc (3)	--	MeCN	16 / r.t.	3.0 equiv **26a**	20%
4	$Pd_2(dba)_3$ (5)	--	--	MeCN	16 / r.t.	-	no conv.

5	$Pd_2(dba)_3$ (5)	--	--	MeCN	16 / 50 °C	-	de-comp.
6	$Pd_2(dba)_3$ (5)	DTBMP (2)	--	MeCN	16 / r.t.	-	no conv.
7	$Pd_2(dba)_3$ (5)	DTBMP (2)	TBAHS (2)	MeCN	16 / r.t.	-	no conv.
8	$Pd_2(dba)_3$ (5)	Na_2CO_3 (2)	--	MeCN	16 / r.t.	-	no conv.
9	$Pd_2(dba)_3$ (5)	Na_2CO_3 (2)	TBAHS (2)	MeCN	16 / r.t.	-	no conv.
10	$Pd_2(dba)_3$ (10)	NaOAc (3)	--	MeCN	16 / r.t.	stepwise addition of **26a** (1 equiv + 1.1 equiv after 60 min)	22%
11	**$Pd(OAc)_2$ (10)**	**NaOAc (3)**	**--**	**MeCN**	**16 / r.t.**	stepwise addition of **26a** (1 equiv + 1.1 equiv after 60 min)	**24%**
12	$Pd_2(dba)_3$ (10)	NaOAc (3)	--	MeCN	16 / r.t.	Addition of 2.2 equiv of **26a** over 2 h (syringe pump)	24%
13	$Pd(OAc)_2$ (10)	NaOAc (3)	--	MeCN	16 / r.t.	stepwise addition of **26a** (1 equiv + 1.1 equiv after 60 min)	24%
14	$Pd_2(dba)_3$ (10)	NaOAc (3)	--	MeOH	16 / r.t.	stepwise addition of **26a** (1 equiv + 1.1 equiv after 60 min)	traces
15	$Pd_2(dba)_3$ (10)	NaOAc (3)	--	THF	16 / r.t.	stepwise addition of **26a** (1 equiv + 1.1 equiv after 60 min)	traces

All reactions were performed on a 0.3 mmol scale. Yields were determined by crude ^{1}H-NMR using ethylene carbonate as internal standard.

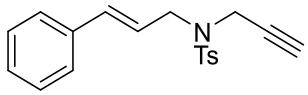
4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (124)



Following a literature procedure,[53] tosylchloride (7.24 g, 38.0 mmol, 1.0 equiv) and triethylamine (9.61 g, 95.0 mmol, 2.5 equiv) were added to a stirred solution of propargylamine (2.20 g, 39.9 mmol, 1.05 equiv) in CH_2Cl_2 (100 mL) at 0 °C. The resulting solution was allowed to warm to room temperature. After stirring for 3 days, diethyl ether (300 mL) was added and the mixture was washed with 1M HCl (100 mL), sat. NH_4Cl solution (100 mL) and brine (150 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound as a white solid (7.36 g, 35.2 mmol, 93%). Spectroscopic data are in agreement with those reported in the literature.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.80 – 7.74 (m, 2H), 7.33 – 7.28 (m, 2H), 4.81 (t, *J* = 6.2 Hz, 1H), 3.82 (dd, *J* = 6.0, 2.5 Hz, 2H), 2.43 (s, 3H), 2.10 (t, *J* = 2.5 Hz, 1H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 144.0, 136.6, 129.8, 127.5, 78.1, 73.1, 33.0, 21.7.

***N*-cinnamyl-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (125)**



Following a literature procedure,[54] 4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (**124**) (6.28 g, 30.0 mmol, 1.0 equiv) and potassium carbonate (16.58 g, 120 mmol, 4.0 equiv) were dissolved in acetonitrile (200 mL). A solution of cinnamyl bromide (11.82 g, 60.0 equiv, 2.0 equiv) in acetonitrile (100 mL) was slowly added and the resulting suspension was stirred at reflux for 18 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue was dissolved dichloromethane (200 mL) and saturated $NaHCO_3$ solution (300 mL). The layers were separated, and the aqueous phase was additionally extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel (hexanes/ ethyl acetate 30/1 to 5/1) and subsequently recrystallized from refluxing hexanes to afford the title compound as a colorless solid (8.87g, 27.3 mmol, 91%). Spectroscopic data are in agreement with those reported in the literature.

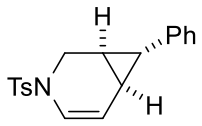
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.80 – 7.72 (m, 2H), 7.37 – 7.23 (m, 7H), 6.58 (dt, *J* = 15.7, 1.3 Hz, 1H), 6.08 (dt, *J* = 15.8, 6.9 Hz, 1H), 4.14 (d, *J* = 2.5 Hz, 2H), 4.00 (dd, *J* = 6.8, 1.3 Hz, 2H), 2.44 (s, 3H), 2.05 (t, *J* = 2.5 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 143.7, 136.2, 136.2, 135.0, 129.7, 128.8, 128.2, 127.9, 126.7, 123.0, 76.8, 74.0, 48.7, 36.0, 21.7.

[53] J. Teske, B. Plietker, *ACS Catal.* **2016**, *6*, 7148−7151.

[54] J. Teske, B. Plietker, *ACS Catal.* **2016**, *6*, 7148−7151.

7-phenyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (126)

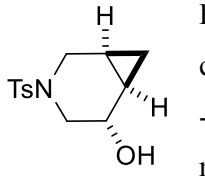


Following a literature procedure,[55] a N_2 purged 100 mL two-necked flask equipped with reflux condenser and magnetic stir bar was charged with *N*-cinnamyl-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**125**) (2.6 g, 8.0 mmol, 1.0 equiv) and toluene (anhydrous, 27 mL). Rhodium(II) trifluoroacetate dimer $Rh_2(CO_2CF_3)_4$ (105 mg, 160 µmol, 2 mol%) was added and the reaction was placed in a preheated oil bath and stirred for 3.5 h at 80 °C. After cooling down to room temperature, the solvent was removed on the rotary evaporator and the residue was purified by column chromatography on silica gel (hexanes/ ethyl acetate 20/1 to 3/1) to afford the pure product as white solid (1.34 g, 4.1 mmol, 52%). Spectroscopic data are in agreement with those reported in the literature.[56]

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.67 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.21 (dd, *J* = 8.2, 6.7 Hz, 2H), 7.17 – 7.10 (m, 1H), 6.84 – 6.73 (m, 2H), 6.43 (d, *J* = 8.0 Hz, 1H), 5.51 (dd, *J* = 8.0, 5.4 Hz, 1H), 4.03 (dt, *J* = 12.1, 1.2 Hz, 1H), 3.16 (dd, *J* = 12.0, 2.9 Hz, 1H), 2.47 (s, 3H), 1.90 (ddt, *J* = 8.4, 4.9, 2.2 Hz, 1H), 1.63 (dd, *J* = 5.1, 3.8 Hz, 1H), 1.46 (ddd, *J* = 9.0, 5.4, 3.8 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 143.9, 140.6, 134.9, 130.0, 128.5, 127.3, 126.0, 125.4, 121.6, 111.3, 40.3, 31.3, 29.1, 21.7, 19.5.

3-tosyl-3-azabicyclo[4.1.0]heptan-5-ol (128)



Following a literature procedure,[57] a flame dried 50 mL Schlenk flask was charged with cyclopropane **114-Ts** (499 mg, 2.0 mmol, 1.0 equiv) and THF (anhydrous, 20 mL). At -78 °C, $BH_3{\cdot}SMe_2$ (10 M, 3.7 mL, 39 mmol, 19.5 equiv) was added dropwise and the mixture was stirred for one hour before allowing to warm to room temperature and continuing stirring overnight. The next day, more $BH_3{\cdot}SMe_2$ (10 M, 1.5 mL, 19 mmol, 10.5 equiv) was added at room temperature and the reaction was stirred for 1.5 hours before carefully adding aqueous NaOH (3M, 3 mL) and H_2O_2 (30%, 3 mL) at 0 °C (**CAUTION!** Vigorous gas evolution!). After the mixture was allowed to slowly warm to room temperature, water (50 mL) and CH_2Cl_2 (50 mL) were added, and the phases were separated. The aqueous phase was additionally extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The brown residue was purified by column chromatography on silica gel (hexanes/ ethyl acetate 1/1) to afford the title compound as a sticky colorless oil (353 mg, 1.3 mmol, 66%).

R_f (hexanes/ethyl acetate = 1/1) = 0.23; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ = 7.66 – 7.58 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.09 (ddd, *J* = 5.2, 3.6, 1.3 Hz, 1H), 3.55 (ddd, *J* = 11.7, 6.7, 1.3 Hz, 1H), 3.06 (dd, *J* = 11.8, 1.8 Hz, 1H), 2.97 (dd, *J* = 12.4, 5.3 Hz, 1H), 2.79 (dd, *J* = 12.4, 3.7 Hz, 1H), 2.43 (s, 3H),

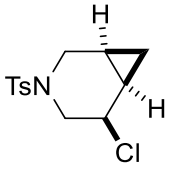
[55] Y. Lu, H. Yuan, S. Zhou, T. Luo, *Org. Lett.* **2017**, *19*, 620−623.

[56] M. Dieckmann, J. Yun-Suk, N. Cramer, *Antgew. Chem. Int. Ed*. **2015**, *54*, 12149−12152.

[57] Y. Lu, H. Yuan, S. Zhou, T. Luo, *Org. Lett.* **2017**, *19*, 620−623.

1.32 – 1.19 (m, 1H), 1.14 (td, *J* = 8.8, 5.5 Hz, 1H), 0.79 – 0.69 (m, 1H), 0.18 (q, *J* = 5.5 Hz, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ = 143.8, 133.5, 129.9, 127.7, 64.9, 48.7, 45.2, 21.7, 16.8, 9.5, 9.1; **HRMS** (+ESI, 120 V): calcd. for $C_{13}H_{18}NO_3S$ $[M+H]^+$ 268.1002 found 268.1003; **IR** (neat): 3489, 3027, 2922, 2851, 1599, 1498, 1457, 1402, 1334, 1230, 1163, 1163, 1088, 1033, 980, 810, 746, 693 cm^{-1}.

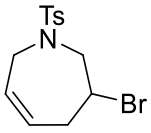
5-chloro-3-tosyl-3-azabicyclo[4.1.0]heptane (132)



An oven-dried 10 mL round bottom flask equipped with a magnetic stir bar was charged with 3-tosyl-3-azabicyclo[4.1.0]heptan-5-ol (**128)** (80.2 mg, 0.3 mmol, 1.0 equiv) and CH_2Cl_2 (anhydrous, 3 mL). At 0 °C, triethylamine (83 µL, 0.6 mmol, 2.0 equiv) was added causing the reaction to turn yellow, followed by the slow addition of mesyl chloride causing the reaction to turn brown. The mixture was stirred for 18 hours. After full conversion of the starting materials (TLC) the reaction was diluted with CH_2Cl_2 (20 mL) and extracted with 1M HCl (30 mL), 2M NaOH (30 mL) and brine (30 mL) and then dried over Na_2SO_4. Volatiles were removed under reduced pressure and the residue was purified by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 5/1) to obtain the pure product as a colorless solid (36 mg, 0.13 mmol, 42%). X-ray grade crystals were obtained by slow evaporation from chloroform.

R_f (hexanes/ethyl acetate = 1/1) = 0.70; **mp.** = 143 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 7.66 – 7.60 (m, 2H), 7.37 – 7.30 (m, 2H), 4.59 (dt, *J* = 8.8, 5.7 Hz, 1H), 3.68 (ddd, *J* = 12.1, 7.1, 1.5 Hz, 1H), 3.56 (ddd, *J* = 12.8, 5.7, 1.6 Hz, 1H), 2.87 (dd, *J* = 12.6, 1.8 Hz, 1H), 2.50 (dd, *J* = 12.8, 8.7 Hz, 1H), 2.44 (s, 3H), 1.60 – 1.48 (m, 2H), 0.84 (td, *J* = 8.7, 5.7 Hz, 1H), 0.55 (q, *J* = 5.7 Hz, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ = 144.0, 133.8, 129.9, 127.6, 54.8, 48.4, 44.5, 21.7, 16.7, 15.3, 9.7; **IR (neat):** 3034, 2922, 2870, 1595, 1479, 1342, 1226, 1156,1092, 1040, 895, 850, 809, 723 cm^{-1}; **HRMS** (+ESI, 120 V): calcd. for $C_{13}H_{17}ClNO_2S$ $[M+H]^+$ 286.0663 found 286.0667.

3-bromo-1-tosyl-2,3,4,7-tetrahydro-1H-azepine (136)



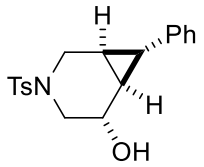
A 5 mL flask was charged with cyclopropyl alcohol **128** (54 mg, 0.2 mmol, 1.0 equiv) and acetonitrile (1 mL). After the solution was cooled to 0 °C, hydrobromic acid (47 wt%, aqueous, 0.7 mL, 6.0 mmol, 30 equiv) was added and the reaction was allowed to warm to room temperature and stirred for 18 h. The reaction was then quenched by pouring onto sat. $NaHCO_3$ solution. After the layers were separated, the aqueous phase was additionally extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic phases were dried over Na_2SO_4. After volatiles were removed under reduced pressure, the residue was purified by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 5/1) to give the title compound as a colorless oil (32 mg, 0.1 mmol, 49%).

R_f (hexanes/ethyl acetate = 5/1) = 0.43; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.75 – 7.62 (m, 2H), 7.38 – 7.30 (m, 2H), 5.89 – 5.59 (m, 2H), 3.64 (dq, *J* = 16.9, 2.4 Hz, 1H), 3.48 (dq, *J* = 16.8, 2.4 Hz, 1H), 3.37 (d, *J* = 6.7 Hz, 2H), 3.31 (dd, *J* = 11.8, 5.1 Hz, 1H), 3.14 (dd, *J* = 11.8, 4.3 Hz, 1H), 2.73 – 2.61 (m, 1H),

2.43 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 143.9, 133.4, 129.9, 127.8, 126.6, 125.3, 46.0, 45.2, 38.1, 33.8, 21.7; **HRMS** (+ESI, 120 V): calcd. for $C_{13}H_{17}NO_2S$ $[M+H]^+$ 330.0158 found 330.0161; **IR** (neat): 3038, 2960, 2922, 2855, 2363, 1599, 1495, 1457, 1349, 1238, 1215, 1167, 1021, 977, 947, 910, 816, 731 cm^{-1}.

.

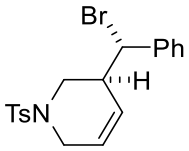
7-phenyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (138)



Following a literature procedure,[58] a flame dried 50 mL Schlenk flask was charged with cyclopropane **126** (488 mg, 1.5 mmol, 1.0 equiv) and THF (anhydrous, 15 mL). At -78 °C, $BH_3{\cdot}SMe_2$ (10 M, 42.7 mL, 28.5 mmol, 19.0 equiv) was added dropwise and the mixture was stirred for one hour before allowing to warm to room temperature and continuing stirring overnight. The next day, more $BH_3{\cdot}SMe_2$ (10 M, 1.4 mL, 15 mmol, 10.0 equiv) was added at room temperature and the reaction was stirred for 1.5 hours before carefully adding aqueous NaOH (3M, 3 mL) and H_2O_2 (30%, 3 mL) at 0 °C (**CAUTION!** Vigorous gas evolution!). After the mixture was allowed to slowly warm to room temperature, water (50 mL) and CH_2Cl_2 (50 mL) were added, and the phases were separated. The aqueous phase was additionally extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The brown residue was purified by column chromatography on silica gel (hexanes/ethyl acetate = 3/1 to 1/1) to afford the title compound as a colorless solid (353 mg, 1.0 mmol, 69%).
R_f (hexanes/ethyl acetate = 1/1) = 0.55; **mp.** = 49 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.69 – 7.62 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.29 – 7.21 (m, 2H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.03 – 6.93 (m, 2H), 4.23 (d, *J* = 5.4 Hz, 1H), 3.51 (dd, *J* = 11.9, 5.9 Hz, 1H), 3.33 (d, *J* = 12.0 Hz, 1H), 3.08 (dd, *J* = 12.3, 4.2 Hz, 1H), 2.89 (dd, *J* = 12.3, 6.0 Hz, 1H), 2.45 (s, 3H), 2.32 (d, *J* = 7.3 Hz, 1H), 1.74 (t, *J* = 5.0 Hz, 1H), 1.63 – 1.48 (m, 2H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 144.0, 141.1, 133.5, 130.0, 128.6, 127.7, 126.1, 125.6, 64.6, 49.2, 45.0, 27.9, 26.6, 21.7, 21.2; **HRMS** (+ESI, 120 V): calcd. for $C_{19}H_{22}NO_3S$ $[M+H]^+$ 344.1315 found 344.1318; **IR** (neat): 3489, 3027, 2922, 2851, 1599, 1498, 1457, 1402, 1334, 1230, 1163, 1088, 1033, 980, 810, 779, 693 cm^{-1}.

[58] Y. Lu, H. Yuan, S. Zhou, T. Luo, *Org. Lett.* **2017**, *19*, 620−623.

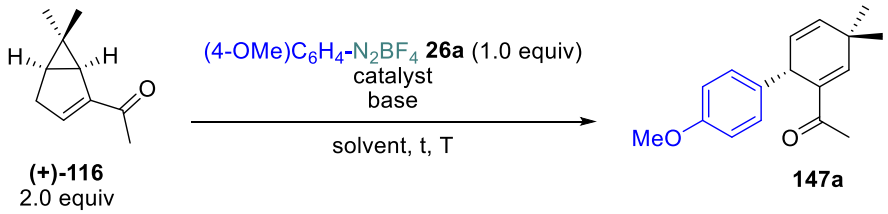
3-(bromo(phenyl)methyl)-1-tosyl-1,2,3,6-tetrahydropyridine (140)



A 5 mL flask was charged with cyclopropyl alcohol **138** (69 mg, 0.2 mmol, 1.0 equiv) and acetonitrile (1 mL). After the solution was cooled to 0 °C, hydrobromic acid (47 wt%, aqueous, 0.7 mL, 6.0 mmol, 30 equiv) was added and the reaction was allowed to warm to room temperature and stirred for 18 h. The reaction was then quenched by pouring onto sat. $NaHCO_3$ solution. After the layers were separated, the aqueous phase was additionally extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic phases were dried over Na_2SO_4. After volatiles were removed under reduced pressure, the residue was purified by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 5/1) to give the title compound as a colorless, crystalline solid (31 mg, 0.76 µmol, 38%). X-ray grade crystals were obtained after slow evaporation from chloroform.

R_f (hexanes/ethyl acetate = 1/1) = 0.38; **mp.** = 134 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.73 – 7.65 (m, 2H), 7.38 – 7.19 (m, 7H), 5.63 – 5.53 (m, 1H), 5.18 (ddt, *J* = 9.8, 4.6, 2.3 Hz, 1H), 4.84 (d, *J* = 10.5 Hz, 1H), 3.74 (dd, *J* = 11.9, 4.2 Hz, 1H), 3.68 (ddt, *J* = 16.8, 3.9, 2.2 Hz, 1H), 2.40 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.9, 140.2, 133.3, 129.9, 128.9, 128.6, 127.9, 127.9, 125.7, 125.2, 56.1, 47.1, 45.5, 43.4, 21.7; **HRMS** (+ESI, 120 V): calcd. for $C_{19}H_{21}BrNO_2S$ $[M+H]^+$ 406.0475 found 406.0475; **IR** (neat): 3034, 2922, 2855, 2363, 1595, 1495, 1349, 1282, 1163, 973, 932, 697 cm^{-1}.

Table S 3. Optimization attempts for the synthesis of **147a** using aryl diazonium salts

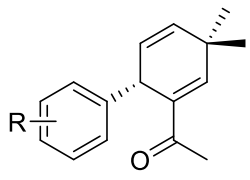


Entry	Pd-catalyst (5 mol%)	Base (equiv)	Solvent (1.5 mL)	T (°C) / t (h)	NMR-Yield
1	$Pd(OAc)_2$	$CaCO_3$ (0.5)	MeOH	r.t. / 1	11%
2	$Pd(OAc)_2$	-	MeOH	r.t. / 1	11%
3	$Pd(OAc)_2$	$CaCO_3$ (0.5)	MeCN	r.t. / 1	no reaction
4	$Pd(OAc)_2$	-	MeCN	r.t. / 1	no reaction
5	$Pd(OAc)_2$	$CaCO_3$ (0.5)	MeOH	r.t. / 12	23%
6	Pd_2dba_3	$CaCO_3$ (0.5)	MeOH	r.t. / 12	27%
7	$[Pd(MeCN)_2]Cl_2$	$CaCO_3$ (0.5)	MeOH	r.t. / 12	27%

8	**$Pd(CF_3CO_2)_2$**	**$CaCO_3$ (0.5)**	**MeOH**	**r.t. / 12**	**32%**
9	$Pd(CF_3CO_2)_2$	Na_2CO_3 (0.5)	MeOH	r.t. / 12	12%
10	$Pd(CF_3CO_2)_2$	DTBMP (0.5)	MeOH	r.t. / 12	30%
11	$Pd(CF_3CO_2)_2$	NaOAc (0.5)	MeOH	r.t. / 12	22%
12	$Pd(CF_3CO_2)_2$	-	MeOH	r.t. / 12	28%
13	$Pd(CF_3CO_2)_2$	$CaCO_3$ (0.5)	MeOH	60 °C / 3 h	30%
14	$Pd(CF_3CO_2)_2$	-	MeOH	60 °C / 3 h	30%
15	**$Pd(CF_3CO_2)_2$ (10 mol%)**	**$CaCO_3$ (0.5)**	**MeOH**	**r.t. / 12**	**53%**
16	$Pd(CF_3CO_2)_2$ (2 mol%)	$CaCO_3$ (0.5)	MeOH	r.t. / 12	14%
17	**$Pd(CF_3CO_2)_2$**	**$CaCO_3$ (2.0)**	**MeOH**	**r.t. / 12**	**53%**
18	**$Pd(CF_3CO_2)_2$ (10 mol%)**	**$CaCO_3$ (2.0)**	**MeOH**	**r.t. / 12**	**46%**
19	$Pd(CF_3CO_2)_2$	$CaCO_3$ (0.5)	MeOH	r.t. / 12 **(+)-116 : 26a = 1 : 2**	**29%**
20	$Pd(CF_3CO_2)_2$ (10 mol%)	$CaCO_3$ (0.5)	MeOH	r.t. / 12 **(+)-116 : 26a = 1 : 2**	**39%**
21	$Pd(CF_3CO_2)_2$	$CaCO_3$ (2.0)	MeOH	r.t. / 12 **(+)-116 : 26a = 1 : 2**	**27%**
22	$Pd(CF_3CO_2)_2$ (10 mol%)	$CaCO_3$ (2.0)	MeOH	r.t. / 12 **(+)-116 : 26a = 1 : 2**	**39%**

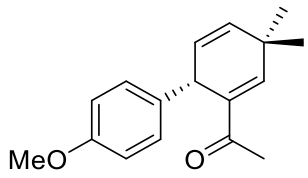
All reactions were carried out on a 0.3 mmol scale.

General procedure (GP-V) for the synthesis 1-(4,4-dimethyl-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-ones (147)



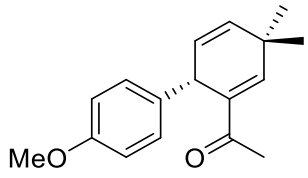
An oven-dried 5 mL Schlenk flask with screw cap equipped with an efficient stir bar was charged with aryl iodide (0.5 mmol, 1.0 equiv), tetrabutylammonium bromide (322 mg, 1.0 mmol, 2.0 equiv), potassium acetate (123 mg, 1.25 mmol, 2.5 equiv) and $Pd(OAc)_2$ (5.6 mg, 25.0 µmol, 5 mol%). Then a solution of 1-(6,6-dimethylbicyclo[3.1.0]hex-2-en-2-yl)ethan-1-one (**(+)-116**) (150 mg, 1.0 mmol, 2.0 equiv) in toluene (2.5 mL) was added and the mixture was degassed by three consecutive cycles of freeze-pump-thaw. After degassing, the mixture was stirred at 80 °C for 18 h before being diluted with ethyl acetate and filtered through a short plug of silica gel. Volatiles were removed under reduced pressure and the residue was purified by column chromatography on silica gel (hexanes/ ethyl acetate). Residual starting material **(+)-116** may be removed by azeotropic distillation using *p*-xylene (60 °C, 5 mbar, rotary evaporator).

(S)-1-(4'-methoxy-4,4-dimethyl-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-one (147a)



Following the general procedure GP-V using 4-iodoanisole (117 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a yellow oil (123 mg, 0.48 mmol, 96%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 9/1).

Procedure for the gram-scale preparation of (S)-1-(4'-methoxy-4,4-dimethyl-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-one ((-)-147a)

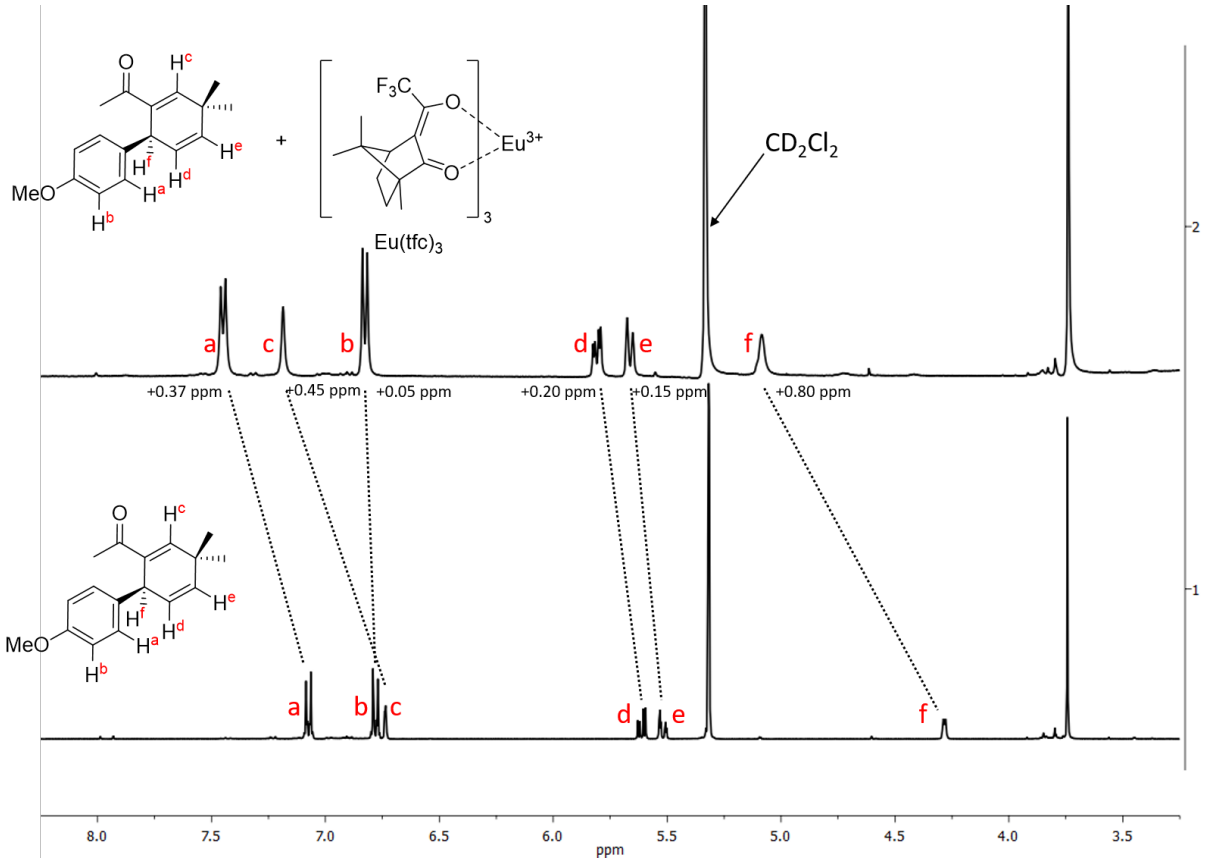


An oven-dried 50 mL Schlenk flask with screw cap equipped with an efficient stir bar was charged with 4-iodoanisole (1.17 g, 5.0 mmol, 1.0 equiv), tetrabutylammonium bromide (3.22 g, 10.0 mmol, 2.0 equiv), potassium acetate (1.23 g, 12.5 mmol, 2.5 equiv) and $Pd(OAc)_2$ (56 mg, 250.0 µmol, 5 mol%). Then a solution of 1-(6,6-dimethylbicyclo[3.1.0]hex-2-en-2-yl)ethan-1-one (**(+)-116**) (1.50 g, 10.0 mmol, 2.0 equiv) in toluene (25 mL) was added and the mixture was degassed by three consecutive cycles of freeze-pump-thaw. After degassing, the mixture was stirred at 80 °C for 18 h before being diluted with ethyl acetate and filtered through a short plug of silica gel. Volatiles were removed under reduced pressure and the residue was purified by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 9/1) to afford the title compound as a yellow oil (1.20 g, 4.7 mmol, 94%).

$\mathbf{R_f}$(hexanes/ethyl acetate = 5/1) = 0.50; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -71.6 ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.17 – 7.08 (m, 2H), 6.86 – 6.75 (m, 2H), 6.69 (dd, *J* = 2.0, 1.1 Hz, 1H), 5.64 (dd, *J* = 9.9, 3.9 Hz, 1H), 5.52 (dt, *J* = 9.9, 1.8 Hz, 1H), 4.34 (dt, *J* = 4.0, 1.3 Hz, 1H), 3.76 (s, 3H), 2.21 (s, 3H), 1.31 (s, 3H), 1.19 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 199.0, 158.2, 146.2, 137.9, 135.6, 131.5, 129.3, 127.2, 113.9, 55.3, 40.3, 34.7, 30.3 (2 carbons overlapped), 26.1; **HRMS** (EI+, 70 eV): calcd. for $C_{17}H_{20}O_2$

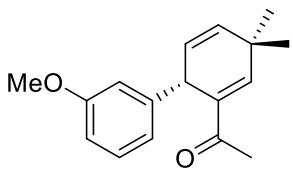
[$M^{\cdot+}$] 256.1458 found 256.1458; **IR** (neat): 3019, 2960, 2837, 1674, 1610, 1510, 1465, 1372, 1249, 1178, 1036, 828 cm^{-1}.

In order to proof that the stereocenter is not epimerizing during the course of the reaction, a chiral lanthanide-induced shift experiment was representatively conducted with product **(-)-147a**. For the sample preparation, an NMR tube was charged with **(-)-147a** (6.4 mg, 25 µmol, 1.0 equiv), tris-[3-(trifluormethyl-hydroxymethylen)-d-camphorato]-europium(III) $Eu(tfc)_3$ (33.5 mg, 37.5 µmol, 1.5 equiv), TMS standard and CD_2Cl_2 (0.6 mL) that was distilled over CaH_2 prior to use. The solution was allowed to sit for 10 min before the ^{1}H-NMR spectrum (400 MHz, 16 scans) was recorded. We were able to detect downfield shifts of various signals (especially proton H^f being located directly at the stereocenter) compared to the reference spectrum (bottom). As only a single set of signals was observed, a significant population of the other enantiomer can be ruled out. This finding was supported by the by the synthesis of substrate **(-)-147u** and **(-)-147v** from enantiopure menthol **149u** and estrone **149v**, respectively, both having a d.r. of > 20:1 (*vide infra*).



Scheme S 1. Chiral lanthanide shift experiment.

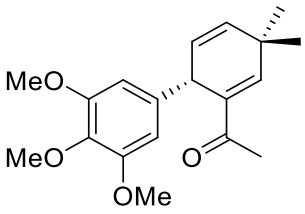
(S)-1-(3'-methoxy-4,4-dimethyl-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-one ((-)-147b)



Following the general procedure GP-V using 3-iodoanisole (117 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a yellowish oil (107 mg, 0.42 mmol, 84%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 9/1).

R_f (hexanes/ethyl acetate = 5/1) = 0.53; $[\alpha]_D^{20}$ = -65.4 ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.21 – 7.15 (m, 1H), 6.80 (dt, *J* = 7.6, 1.3 Hz, 1H), 6.74 – 6.72 (m, 2H), 6.70 (ddd, *J* = 8.1, 2.6, 1.0 Hz, 1H), 5.66 (dd, *J* = 9.9, 3.9 Hz, 1H), 5.53 (dt, *J* = 9.9, 1.8 Hz, 1H), 4.36 (dt, *J* = 4.0, 1.3 Hz, 1H), 3.77 (s, 3H), 2.22 (s, 3H), 1.31 (s, 3H), 1.20 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 198.8, 159.8, 146.6, 145.2, 137.5, 131.7, 129.5, 126.9, 120.7, 114.1, 111.6, 55.2, 41.2, 34.8, 30.3 (2 carbons overlapped), 26.1; **HRMS** (EI+, 70 eV): calcd. for $C_{17}H_{20}O_2$ [$M^{\cdot+}$] 256.1458 found 256.1457; **IR** (neat): 3020, 2960, 2866, 2837, 1674, 1599, 1484, 1435, 1372, 1312, 1249, 1144, 1092, 1047, 984, 872, 779, 701 cm^{-1}.

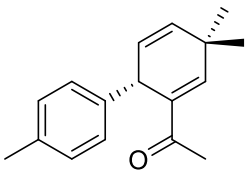
(S)-1-(3',4',5'-trimethoxy-4,4-dimethyl-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-one ((-)-147d)



Following the general procedure GP-V using 5-iodo-1,2,3-trimethoxybenzene (147 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a yellow oil (151 mg, 0.48 mmol, 95%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 9/1).

R_f (hexanes/ethyl acetate = 5/1) = 0.23; $[\alpha]_D^{20}$ = -50.2 ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 6.72 (dd, *J* = 2.0, 1.0 Hz, 1H), 6.42 (s, 2H), 5.67 (dd, *J* = 9.9, 4.0 Hz, 1H), 5.55 (dt, *J* = 9.9, 1.8 Hz, 1H), 4.33 (dt, *J* = 4.1, 1.2 Hz, 1H), 3.81 (s, 6H), 3.79 (s, 3H), 2.24 (s, 3H), 1.32 (s, 3H), 1.20 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 198.9, 153.2, 146.4, 139.1, 137.8, 136.4, 131.9, 126.9, 105.3, 60.9, 56.1, 41.3, 34.8, 30.3, 30.2, 26.1; **HRMS** (EI+, 70 eV): calcd. for $C_{19}H_{24}O_4$ 316.1669 [$M^{\cdot+}$] found 316.1665; **IR** (neat): 2960, 2833, 1674,1625, 1588, 1506, 1454, 1372, 1323, 1245, 1182, 1122, 1006, 924, 898, 831, 716 cm^{-1}.

(S)-1-(4'-methyl-4,4-dimethyl-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-one ((-)-147e)

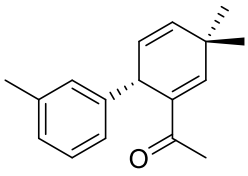


Following the general procedure GP-V using 4-iodotoluene (109 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a yellowish oil (115 mg, 0.48 mmol, 96%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 9/1).

R_f (hexanes/ethyl acetate = 5/1) = 0.71; $[\alpha]_D^{20}$ = -82.5 ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.16 – 6.98 (m, 4H), 6.72 (dd, *J* = 1.9, 1.1, 1H), 5.64 (dd, *J* = 9.9, 3.9, 1H), 5.52 (dt, *J* = 9.9, 1.8, 1H), 4.35 (dt, *J* = 3.9, 1.3, 1H), 2.28 (s, 3H), 2.21 (s, 3H), 1.31 (s, 3H), 1.20 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 198.9, 146.4, 140.5, 137.8, 135.9, 131.5, 129.3, 128.1, 127.1, 40.8, 34.7, 30.3, 30.3,

26.1, 21.2; **HRMS** (EI+, 70 eV): calcd. for $C_{17}H_{20}O$ 240.1509 [M^{+}] found 240.1508; **IR** (neat): 3019, 2960, 2922, 2866, 1674, 1625, 1510, 1469, 1372, 1245, 1178, 1129, 977, 887, 850, 816, 787, 738 cm^{-1}.

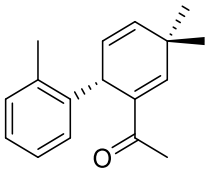
(S)-1-(3',4,4-trimethyl-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-one ((-)-147f)



Following the general procedure GP-V using 3-iodotoluene (109 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a colorless oil (90 mg, 0.38 mmol, 75%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 9/1).

R_f(hexanes/ethyl acetate = 5/1) = 0.65; $[\alpha]_D^{20}$ = -46.0 ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.14 (t, *J* = 7.5 Hz, 1H), 7.06 – 6.92 (m, 3H), 6.73 (dd, *J* = 2.0, 1.1 Hz, 1H), 5.65 (dd, *J* = 9.9, 3.9 Hz, 1H), 5.52 (dt, *J* = 9.9, 1.8 Hz, 1H), 4.35 (dt, *J* = 4.0, 1.3 Hz, 1H), 2.31 (d, *J* = 0.7 Hz, 3H), 2.22 (s, 3H), 1.32 (s, 3H), 1.20 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 198.9, 146.4, 143.4, 138.0, 137.7, 131.5, 129.1, 128.4, 127.2, 127.1, 125.2, 41.2, 34.7, 30.3, 30.3, 26.2, 21.6; **HRMS** (EI+, 70 eV): calcd. for $C_{17}H_{20}O$ 240.1509 [M^{+}] found 240.1506; **IR** (neat): 3019, 2963, 2922, 1771,1722, 1674, 1465, 1249, 1182, 1133, 1096, 1059, 999, 779, 701 cm^{-1}.

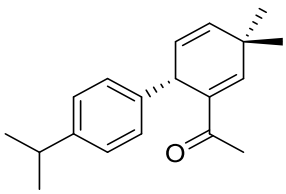
(S)-1-(2',4,4-trimethyl-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-one ((-)-147g)



Following the general procedure GP-V using 2-iodotoluene (109 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a yellow oil (94 mg, 0.39 mmol, 78%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 9/1).

R_f(hexanes/ethyl acetate = 5/1) = 0.70; $[\alpha]_D^{20}$ = -72.2 ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.17 – 7.11 (m, 1H), 7.09 – 7.00 (m, 2H), 6.93 – 6.85 (m, 1H), 6.79 (t, *J* = 1.6 Hz, 1H), 5.60 (dd, *J* = 9.9, 3.7 Hz, 1H), 5.49 (dt, *J* = 9.9, 1.9 Hz, 1H), 4.58 (dt, *J* = 3.4, 1.5 Hz, 1H), 2.53 (s, 3H), 2.21 (s, 3H), 1.32 (s, 3H), 1.21 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 198.8, 146.7, 142.0, 138.0, 135.7, 131.3, 130.5, 126.9, 126.3, 126.2, 125.9, 37.1, 34.7, 30.4, 30.1, 26.0, 19.7; **HRMS** (EI+, 70 eV): calcd. for $C_{17}H_{20}O$ 240.1509 [M^{+}] found 240.1503; **IR** (neat): 3019, 2960, 2922, 2863, 1674, 1625, 1487, 1372, 1282, 1249, 1182, 1129, 1051, 1010, 977, 887, 842, 794, 664 cm^{-1}.

(S)-1-(4'-isopropyl-4,4-dimethyl-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-one ((-)-147h)

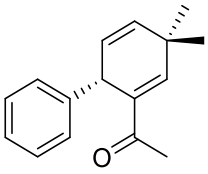


Following the general procedure GP-V using 1-iodo-4-isopropylbenzene (123 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a colorless oil (129 mg, 0.48 mmol, 96%) after purification by column chromatography on silica gel (pure hexane to hexanes/ ethyl acetate = 9/1).

R_f(hexanes/ethyl acetate = 5/1) = 0.73; $[\alpha]_D^{20}$ = -76.9 ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 7.11 (s, 4H), 6.72 (dd, *J* = 2.0, 1.1 Hz, 1H), 5.66 (dd, *J* = 9.9, 3.9 Hz, 1H), 5.52 (dt, *J* = 9.9, 1.9 Hz, 1H), 4.37 (ddd, *J* = 3.9, 1.6, 1.0 Hz, 1H), 2.84 (hept, *J* = 6.9 Hz, 1H), 2.22 (s, 3H), 1.31 (s, 3H), 1.22 (s,

3H), 1.20 (s, 6H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 199.0, 146.8, 146.3, 140.7, 137.8, 131.5, 128.1, 127.2, 126.6, 40.8, 34.7, 33.8, 30.3, 30.3, 26.2, 24.1; **HRMS** (EI+, 70 eV): calcd. for $C_{19}H_{24}O$ 268.1822 [M^{+}] found 268.1818; **IR** (neat): 3019, 2960, 2870, 1674, 1625, 1510, 1420, 1361, 1282, 1245, 1182, 1133, 1055, 1018, 977, 828, 723 cm^{-1}.

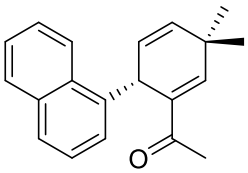
(S)-1-(4,4-dimethyl-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-one ((-)-147i)



Following the general procedure GP-V using 4-iodobenzene (102 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a yellow oil (105 mg, 0.46 mmol, 93%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 9/1).

R_f (hexanes/ethyl acetate = 5/1) = 0.58; $[\alpha]_D^{20}$ = -83.1 ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.48 – 7.42 (m, 2H), 7.40 – 7.32 (m, 3H), 6.92 (dd, *J* = 2.0, 1.1 Hz, 1H), 5.85 (dd, *J* = 9.9, 3.9 Hz, 1H), 5.73 (dt, *J* = 9.9, 1.8 Hz, 1H), 4.58 (dt, *J* = 4.0, 1.3 Hz, 1H), 2.41 (s, 3H), 1.51 (s, 3H), 1.40 (s, 3H).; **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 198.8, 146.5, 143.5, 137.7, 131.6, 128.5, 128.3, 127.0, 126.4, 41.3, 34.7, 30.3, 30.3, 26.1; **HRMS** (EI+, 70 eV): calcd. for $C_{16}H_{18}O$ 226.1352 [M^{+}] found 226.1347; **IR** (neat): 3023, 2960, 2926, 2866, 1674, 1625, 1491, 1453, 1402, 1282, 1245, 1182, 1129, 1074, 1029, 805, 697 cm^{-1}.

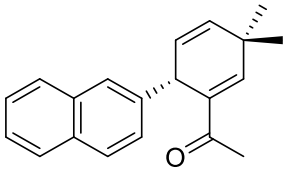
(S)-1-(3,3-dimethyl-6-(naphthalen-1-yl)cyclohexa-1,4-dien-1-yl)ethan-1-one ((-)-147j)



Following the general procedure GP-V using 1-iodonaphthalene (127 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a colorless solid (103 mg, 0.37 mmol, 75%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 9/1).

R_f (hexanes/ethyl acetate = 5/1) = 0.60; $[\alpha]_D^{20}$ = -127.0 ° ($CHCl_3$, c = 1 g/L); **mp.** = 97 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 8.34 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.92 – 7.78 (m, 1H), 7.69 (dt, *J* = 8.3, 1.1 Hz, 1H), 7.58 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H), 7.49 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.35 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.10 (dd, *J* = 7.2, 1.3 Hz, 1H), 6.93 (dd, *J* = 2.0, 1.2 Hz, 1H), 5.82 (dd, *J* = 9.9, 3.8 Hz, 1H), 5.50 (dt, *J* = 9.9, 1.9 Hz, 1H), 5.24 (dt, *J* = 3.3, 1.5 Hz, 1H), 2.22 (s, 3H), 1.33 (s, 3H), 1.26 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 198.9, 147.0, 140.2, 137.6, 134.2, 131.6, 131.3, 129.0, 127.0, 126.3, 126.1, 125.8, 125.7, 124.3, 123.4, 36.4, 34.8, 30.3, 29.9, 26.2; **HRMS** (EI+, 70 eV): calcd. for $C_{20}H_{20}O$ 276.1509 [M^{+}] found 276.1501; **IR** (neat): 3053, 3019, 2960, 2922, 1674, 1625, 1506, 1469, 1357, 1245, 1182, 1126, 1058, 1014, 984, 921, 857, 813, 746 cm^{-1}.

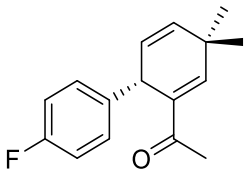
(S)-1-(3,3-dimethyl-6-(naphthalen-2-yl)cyclohexa-1,4-dien-1-yl)ethan-1-one ((-)-147k)



Following the general procedure GP-V using 2-iodonaphthalene (127 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a colorless oil (104 mg, 0.38 mmol, 75%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 9/1).

R_f (hexanes/ethyl acetate = 5/1) = 0.55; $[\alpha]_D^{20}$ = -42.6 ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.81 – 7.70 (m, 3H), 7.64 (d, *J* = 1.7 Hz, 1H), 7.46 – 7.36 (m, 2H), 7.33 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.78 (dd, *J* = 2.0, 1.1 Hz, 1H), 5.71 (dd, *J* = 9.9, 3.9 Hz, 1H), 5.58 (dt, *J* = 9.9, 1.8 Hz, 1H), 4.56 (dd, *J* = 3.5, 1.8 Hz, 1H), 2.21 (s, 3H), 1.38 (s, 3H), 1.24 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 198.8, 146.6, 140.9, 137.7, 133.7, 132.4, 131.9, 128.2, 127.8, 127.7, 126.9, 126.8, 126.7, 126.0, 125.5, 41.4, 34.8, 30.3 (2 carbons overlapped), 26.1; **HRMS** (EI+, 70 eV): calcd. $C_{20}H_{20}O$ 276.1509 [$M^{\cdot+}$] found 276.1501; **IR** (neat): 3019, 2960, 2866, 1670, 1625, 1506, 1469, 1357, 1245, 1182, 1126, 1054, 1014, 984, 887, 857, 813, 746 cm^{-1}.

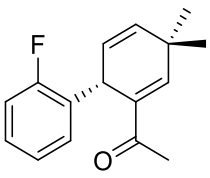
(S)-1-(4'-fluoro-4,4-dimethyl-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-one ((-)-147l)



Following the general procedure GP-V using 1-fluoro-4-iodobenzene (111 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a yellow oil (116 mg, 0.48 mmol, 95%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 9/1).

R_f (hexanes/ethyl acetate = 5/1) = 0.63; $[\alpha]_D^{20}$ = -69.7 ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.19 – 7.12 (m, 2H), 6.96 – 6.89 (m, 2H), 6.72 (dd, *J* = 1.9, 1.1 Hz, 1H), 5.62 (dd, *J* = 9.9, 3.8 Hz, 1H), 5.55 (dt, *J* = 9.9, 1.8 Hz, 1H), 4.37 (dt, *J* = 3.8, 1.3 Hz, 1H), 2.22 (s, 3H), 1.31 (s, 3H), 1.20 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 198.7, 161.5 (d, $J_{C\text{-}F}$ = 244.1 Hz), 146.8, 139.2 (d, $J_{C\text{-}F}$ = 3.1 Hz), 137.7, 131.9, 129.8 (d, $J_{C\text{-}F}$ = 8.0 Hz), 126.8, 115.2 (d, $J_{C\text{-}F}$ = 21.3 Hz), 40.4, 34.8, 30.3, 26.0; **^{19}F-NMR** (377 MHz, $CDCl_3$) δ = -117.6; **HRMS** (EI+, 70 eV): calcd. for $C_{16}H_{17}OF$ 244.1252 [$M^{\cdot+}$] found 244.1258; **IR** (neat): 3023, 2963, 2926, 2866, 1674, 1625, 1506, 1372, 1282, 1245, 1223, 1182, 1133, 1096, 1059, 1014, 977, 835, 738 cm^{-1}.

(S)-1-(2'-fluoro-4,4-dimethyl-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-one ((-)-147m)

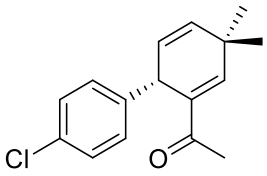


Following the general procedure GP-V using 1-fluoro-2-iodobenzene (111 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a yellow oil (74 mg, 0.30 mmol, 61%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 9/1).

R_f (hexanes/ethyl acetate = 5/1) = 0.63; $[\alpha]_D^{20}$ = -97.9 ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.17 – 7.09 (m, 1H), 7.04 – 6.97 (m, 2H), 6.97 – 6.91 (m, 1H), 6.84 (dd, *J* = 2.0, 1.2 Hz, 1H), 5.66 (dd, *J* = 9.9, 3.8 Hz, 1H), 5.53 (dt, *J* = 9.9, 1.9 Hz, 1H), 4.70 (dt, *J* = 3.4, 1.5 Hz, 1H), 2.24 (s, 3H), 1.28 (s, 3H), 1.21 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 198.3, 160.6 (d, $J_{C\text{-}F}$ = 246.2 Hz), 147.9, 136.4,

132.0, 130.6 (d, $J_{C\text{-}F}$ = 14.7 Hz), 128.9 (d, $J_{C\text{-}F}$ = 4.3 Hz), 127.9 (d, $J_{C\text{-}F}$ = 8.1 Hz), 125.4, 124.3 (d, $J_{C\text{-}F}$ = 3.6 Hz), 115.6 (d, $J_{C\text{-}F}$ = 22.5 Hz), 34.7, 34.1 (d, J = 3.0 Hz), 30.2, 29.8, 25.9; **^{19}F-NMR** (376 MHz, $CDCl_3$) δ = -119.9; **HRMS** (EI+, 70 eV): calcd. for $C_{16}H_{17}OF$ 244.1258 [M^{+}] found 244.1258; **IR** (neat): 3023, 2963, 2926, 2866, 1670, 1629, 1584, 1487, 1372, 1282, 1245, 1182, 1092, 1062, 1014, 864, 813, 753 cm^{-1}.

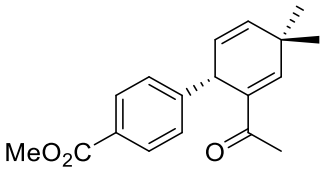
(S)-1-(4'-fluoro-4,4-dimethyl-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-one ((-)-147n)



Following the general procedure GP-V using 1-chloro-4-iodobenzene (119 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a colorless oil (98 mg, 0.38 mmol, 75%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 9/1, then second column using pure hexanes to hexanes/ diethyl ether = 1:1).

R_f (hexanes/ethyl acetate = 5/1) = 0.63; $[\alpha]_D^{20}$ = -33.3 ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.23 – 7.19 (m, 2H), 7.15 – 7.10 (m, 2H), 6.74 – 6.72 (m, 1H), 5.61 (dd, J = 9.9, 3.6 Hz, 1H), 5.56 (dt, J = 9.9, 1.7 Hz, 1H), 4.35 (dt, J = 3.7, 1.2 Hz, 1H), 2.22 (s, 3H), 1.31 (s, 3H), 1.20 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 198.5, 146.9, 142.0, 137.3, 131.9, 129.6, 128.5, 126.3, 40.4, 34.7, 30.1, 30.1, 25.8. (One carbon signal missing in aromatic region due to signal overlap. All expected signals found in aliphatic region.); **^{13}C-NMR** (101 MHz, Acetone) δ = 197.4, 146.9, 142.9, 136.8, 132.1, 131.2, 129.8, 128.2, 126.3, 40.2, 34.4, 24.9. (All signals in aromatic region found, however, aliphatic region shows signal overlap with solvent signals.); **HRMS** (EI+, 70 eV): calcd. for $C_{16}H_{17}OCl$ 260.0957 [M^{+}] found 260.0962; **IR** (neat): 2963, 2926, 2870, 1812, 1771, 1673, 1491, 1405, 1372, 1182, 1092, 1014, 980, 891, 828, 753, 708 cm^{-1}.

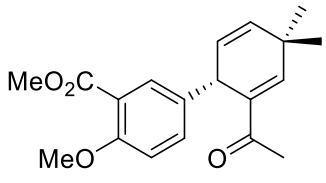
Methyl (S)-2'-acetyl-4',4'-dimethyl-1',4'-dihydro-[1,1'-biphenyl]-4-carboxylate ((-)-147o)



Following the general procedure GP-V using methyl 4-iodobenzoate (131 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a yellow solid (89 mg, 0.31 mmol, 63%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 9/1).

R_f (hexanes/ethyl acetate = 5/1) = 0.55; **mp.** = 89 °C; $[\alpha]_D^{20}$ = -62.9 ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.97 – 7.89 (m, 2H), 7.28 – 7.21 (m, 2H), 6.77 (dd, J = 1.8, 1.1 Hz, 1H), 5.62 (dd, J = 9.9, 3.5 Hz, 1H), 5.57 (dt, J = 9.9, 1.6 Hz, 1H), 4.43 (dt, J = 3.6, 1.2 Hz, 1H), 3.88 (s, 3H), 2.22 (s, 3H), 1.32 (s, 3H), 1.21 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 198.3, 167.0, 148.8, 147.2, 137.0, 132.2, 129.8, 128.2, 128.2, 126.0, 52.0, 41.1, 34.7, 30.1, 30.1, 25.8; **HRMS** (EI+, 70 eV): calcd. for $C_{18}H_{20}O_3$ 284.1407 [M^{+}] found 284.1403; **IR** (neat): 2960, 1722, 1674, 1610, 1435, 1371, 1279, 1249, 1178, 1103, 1021, 977, 924, 857, 772, 708 cm^{-1}.

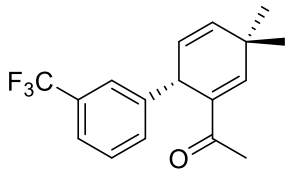
methyl (S)-2'-acetyl-4-methoxy-4',4'-dimethyl-1',4'-dihydro-[1,1'-biphenyl]-3-carboxylate ((-)-147q)



Following the general procedure GP-V using methyl 5-iodo-2-methoxybenzoate (**149q**) (146 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a yellow solid (143 mg, 0.46 mmol, 91%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 2/1). X-ray grade crystals were obtained by slow evaporation from $CHCl_3$.

R_f (hexanes/ethyl acetate = 5/1) = 0.16; $[\alpha]_D^{20} = 35.0$ ° ($CHCl_3$, c = 1 g/L); **mp.** = 133 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.62 (d, J = 2.4 Hz, 1H), 7.33 (dd, J = 8.6, 2.4 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 6.71 (dd, J = 1.9, 1.1 Hz, 1H), 5.62 (dd, J = 9.9, 3.6 Hz, 1H), 5.56 (dt, J = 9.7, 1.6 Hz, 1H), 4.34 (dt, J = 3.8, 1.2 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.21 (s, 3H), 1.33 (s, 3H), 1.20 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 198.7, 166.8, 157.9, 146.8, 137.6, 135.3, 133.7, 132.0, 131.7, 126.6, 119.8, 112.2, 56.2, 52.1, 40.0, 34.8, 30.3, 30.3, 26.0; **HRMS** (EI+, 70 eV): calcd. for $C_{19}H_{22}O_4$ 314.1513 [M^{+}] found 314.1504; **IR** (neat): 2960, 2866, 1730, 1670, 1610, 1498, 1461, 1435, 1301, 1252, 1182, 1081, 1029, 924, 898, 790, 678 cm^{-1}.

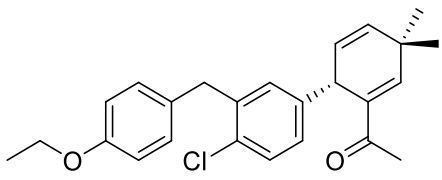
(S)-1-(4,4-dimethyl-3'-(trifluoromethyl)-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-one ((-)-147s)



Following the general procedure GP-V using 3-iodobenzotrifluoride (136 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a yellowish oil (101 mg, 0.34 mmol, 69%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 9/1).

R_f (hexanes/ethyl acetate = 5/1) = 0.63; $[\alpha]_D^{20} = 58.2$ ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.45 – 7.30 (m, 4H), 6.78 (t, *J* = 1.4 Hz, 1H), 5.68 – 5.56 (m, 2H), 4.44 (dt, *J* = 3.2, 1.0 Hz, 1H), 2.24 (s, 3H), 1.33 (s, 3H), 1.22 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 198.4, 147.6, 144.6, 137.2, 132.4, 131.9, 130.7 (q, $J_{C\text{-}F}$ = 31.8 Hz), 128.9, 126.2, 125.0 (q, $J_{C\text{-}F}$ = 3.9 Hz), 124.0 (q, $J_{C\text{-}F}$ = 272.2 Hz), 123.3 (q, $J_{C\text{-}F}$ = 3.7 Hz), 40.9, 34.9, 30.2, 30.2, 25.8; **^{19}F-NMR** (377 MHz, $CDCl_3$) δ = -63.0; **HRMS** (EI+, 70 eV): calcd. for $C_{17}H_{17}OF_3$ 294.1226 [M^{+}] found 294.1224; **IR** (neat): 2967, 2830, 1674, 1629, 1446, 1372, 1327, 1249, 1163, 1122, 1014, 984, 895, 798, 738, 700 cm^{-1}.

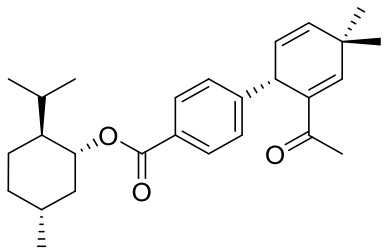
(S)-1-(4'-chloro-3'-(4-ethoxybenzyl)-4,4-dimethyl-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-one ((-)-147t)



Following the general procedure GP-V using 1-chloro-2-(4-ethoxybenzyl)-4-iodobenzene (186 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a yellowish oil (163 mg, 0.41 mmol, 83%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 9/1).

$\mathbf{R_f}$ (hexanes/ethyl acetate = 5/1) = 0.60; $[\alpha]_D^{20}$ = - 46.4 ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 7.23 (d, *J* = 8.1 Hz, 1H), 7.09 – 7.03 (m, 2H), 6.99 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.90 (d, *J* = 2.2 Hz, 1H), 6.85 – 6.78 (m, 2H), 6.67 (dd, *J* = 1.9, 1.1 Hz, 1H), 5.57 (dd, *J* = 9.9, 3.8 Hz, 1H), 5.48 (dt, *J* = 9.9, 1.7 Hz, 1H), 4.30 (dt, *J* = 3.7, 1.2 Hz, 1H), 4.09 – 3.93 (m, 4H), 2.19 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H), 1.17 (s, 3H), 1.16 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 198.6, 157.5, 146.9, 142.3, 139.1, 137.4, 132.0, 131.9, 131.5, 130.6, 130.1, 129.4, 127.5, 126.5, 114.6, 63.5, 40.5, 38.5, 34.7, 30.2, 30.0, 26.0, 15.0; **HRMS** (EI+, 70 eV): calcd. for $C_{25}H_{27}O_2Cl$ 379.1459 [M^{+}] found 379.1456; **IR** (neat): 3019, 2967, 2926, 1771, 1674, 1614, 1513, 1476, 1301, 1245, 1178, 1115, 1044, 988, 958, 746, 664 cm^{-1}.

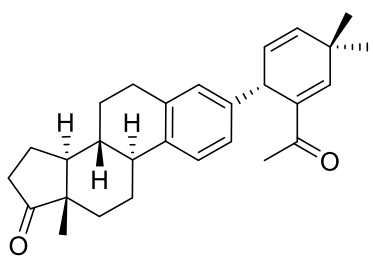
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (S)-2'-acetyl-4',4'-dimethyl-1',4'-dihydro-[1,1'-biphenyl]-4-carboxylate ((-)-147u)



Following the general procedure GP-V using (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 4-iodobenzoate (**149u**) (193 mg, 0.5 mmol, 1.0 equiv) gave the title compound as a colorless oil (127 mg, 0.31 mmol, 62%) after purification by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 9/1).

$\mathbf{R_f}$ (hexanes/ethyl acetate = 3/1) = 0.65; $[\alpha]_D^{20}$ = -121.6 ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 8.05 – 7.86 (m, 2H), 7.31 – 7.21 (m, 2H), 6.80 – 6.76 (m, 1H), 5.62 (dd, *J* = 9.9, 3.3 Hz, 1H), 5.56 (ddd, *J* = 9.9, 1.8, 1.2 Hz, 1H), 4.89 (td, *J* = 10.8, 4.4 Hz, 1H), 4.48 – 4.37 (m, 1H), 2.23 (s, 3H), 2.14 – 2.04 (m, 1H), 1.95 (pd, *J* = 6.9, 2.7 Hz, 1H), 1.77 – 1.65 (m, 2H), 1.52 (ddt, *J* = 12.2, 10.7, 3.1 Hz, 2H), 1.32 (s, 3H), 1.21 (s, 3H), 1.16 – 1.02 (m, 2H), 0.95 – 0.86 (m, 7H), 0.76 (d, *J* = 6.9 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 198.5, 166.1, 148.7, 147.4, 137.2, 132.2, 129.9, 129.0, 128.2, 126.2, 74.7, 47.4, 41.2, 41.1, 34.8, 34.5, 31.6, 30.2, 26.5, 25.9, 23.7, 22.2, 20.9, 16.6; **HRMS** (EI+, 70 eV): calcd. for $C_{27}H_{36}O_3$ 408.2659 [M^{+}] found 408.2657; **IR** (neat): 2955, 2926, 2870, 1711, 1677, 1610, 1457, 1372, 1267, 1012, 1178, 1100, 980, 921, 887, 834, 772, 708 cm^{-1}.

(8R,9S,13S,14S)-3-((S)-2-acetyl-4,4-dimethylcyclohexa-2,5-dien-1-yl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one ((+)-147v)



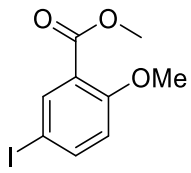
The following reaction was carried out on a 0.4 mmol scale:

An oven-dried 5 mL Schlenk flask with screw cap equipped with an efficient stir bar was charged with (8R,9S,13S,14S)-3-iodo-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (**149v**) (152 mg, 0.4 mmol, 1.0 equiv), tetrabutylammonium bromide (258 mg, 0.8 mmol, 2.0 equiv), potassium acetate (98 mg, 1.0 mmol, 2.5 equiv) and $Pd(OAc)_2$ (4.5 mg, 20.0 µmol, 5 mol%). Then a solution of 1-(6,6-dimethylbicyclo[3.1.0]hex-2-en-2-yl)ethan-1-one (**(+)-116**) (120 mg, 0.8 mmol, 2.0 equiv) in toluene (2.0 mL) was added and the mixture was degassed by three consecutive cycles of freeze-pump-thaw.

After degassing, the mixture was stirred at 80 °C for 18 h before being diluted with ethyl acetate and filtered through a short plug of silica gel. Volatiles were removed under reduced pressure and the residue was purified by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 4/1) to obtain the title compound as a white solid (157 mg, 0.39 mmol, 98%).

R_f (hexanes/ethyl acetate = 5/1) = 0.30; $[\alpha]_D^{20} = +46.5$ ° ($CHCl_3$, c = 1 g/L); **mp.** = 72 °C**; ^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.17 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.95 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.92 – 6.90 (m, 1H), 6.73 (dd, *J* = 2.0, 1.0 Hz, 1H), 5.65 (dd, *J* = 9.8, 3.9 Hz, 1H), 5.51 (dt, *J* = 9.9, 1.8 Hz, 1H), 4.33 (dt, *J* = 4.1, 1.3 Hz, 1H), 2.96 – 2.78 (m, 2H), 2.57 – 2.43 (m, 1H), 2.43 – 2.32 (m, 1H), 2.30 – 1.88 (m, 7H), 1.69 – 1.33 (m, 6H), 1.31 (s, 3H), 1.20 (s, 3H), 0.89 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 221.1, 198.9, 146.7, 140.9, 137.8, 137.7, 136.5, 131.5, 128.8, 127.2, 125.6, 125.5, 50.7, 48.1, 44.5, 40.7, 38.2, 36.0, 34.8, 31.8, 30.3, 30.3, 29.5, 26.7, 26.1, 25.8, 21.7, 14.0; **HRMS** (EI+, 70 eV): calcd. for $C_{28}H_{34}O_2$ 402.2553 [$M^{\cdot+}$] found 402.2557; **IR** (neat): 3015, 2959, 2930, 2866, 1737, 1700, 1625, 1488, 1372, 1289, 1249, 1182, 1133, 1085, 1055, 1010, 891, 824, 753, 667 cm^{-1}.

Methyl 5-iodo-2-methoxybenzoate (149q)



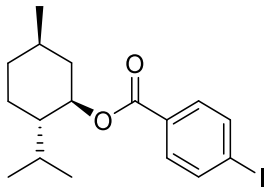
Following a modified literature procedure, [59] a 25 mL round bottomed flask equipped with a magnet stir bar was charged with methyl 5-iodosalicylate (556 mg, 2.0 mmol, 1.0 equiv), potassium carbonate (829 mg, 6,0 mmol, 3.0 equiv) and acetone (10 mL). Iodomethane (1,14 g, 8.0 mmol, 4.0 equiv) was added and the mixture was refluxed for 18 hours. After cooling to room temperature, volatiles were removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL) and then washed with water (2 x 50 mL). After the organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure, the pure product was obtained as a white solid (584 mg, 1.88 mmol, 94%). Spectroscopic data are in agreement with those reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.06 (d, *J* = 2.4 Hz, 1H), 7.72 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 3.88 (s, 3H), 3.88 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 165.3, 159.1, 142.1, 140.1, 122.3, 114.5, 81.8, 56.3, 52.4.

[59] Y. P. Xu, M. Yang, D. H. Pan, *Appl. Radiat. Isot.* **2009**, *67*, 594-597.

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 4-iodobenzoate (149u)

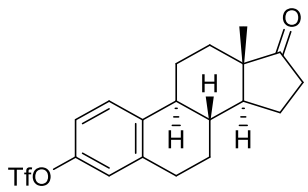


Following a literature procedure,[60] a 50 mL flask was charged with (-)-L-menthol (391 mg, 2.50 mmol, 1.0 equiv) and CH_2Cl_2 (anhydrous, 25 mL). Then, pyridine (0.60 mL, 7.50 mmol, 3.0 equiv) and 4 -iodobenzoyl chloride (733 mg, 2.75 mmol, 1.1 equiv) were added and the solution was stirred for 18 hours at reflux. After full conversion of the starting material (monitoring by TLC), volatiles were removed *in vacuo*, and the residue was dissolved in ethyl acetate (50 mL) and consecutively washed with sat. $NaHCO_3$ solution (50 mL) and water (2 x 50 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The title compound was obtained as a colorless oil (960 mg, 2.49 mmol, 99%) after column chromatography on silica gel (hexanes/ ethyl acetate = 9/1). Spectroscopic data are in agreement with those reported in the literature.[61]

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.82 – 7.77 (m, 2H), 7.76 – 7.69 (m, 2H), 4.92 (td, *J* = 10.9, 4.4 Hz, 1H), 2.11 (dtd, *J* = 12.0, 4.0, 1.7 Hz, 1H), 1.92 (pd, *J* = 7.0, 2.7 Hz, 1H), 1.78 – 1.67 (m, 2H), 1.62 – 1.47 (m, 2H), 1.18 – 1.03 (m, 2H), 0.92 (m, 7H), 0.78 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 165.7, 137.8, 131.2, 130.4, 100.6, 75.3, 47.3, 41.0, 34.4, 31.6, 26.7, 23.8, 22.2, 20.9, 16.7.

(8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl trifluoromethanesulfonate (153)



Following a literature procedure,[62] a 50 mL Schlenk flask was charged with estrone (811 mg, 3.0 mmol, 1.0 equiv). The flask was back-filled with nitrogen and equipped with a rubber septum. Pyridine (10 mL) was added, and the reaction was cooled to 0 °C before trifilic anhydride (1.02 g, 3.6 mmol, 1.2 equiv) was dropwise added causing the solution to turn orange (fume generation was observed). The reaction was allowed to warm to room temperature and stirred for 4 hours. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with water (20 mL) and brine (20 mL). The aqueous layers were then extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic phases were dried over Na_2SO_4. After volatiles were removed under reduced pressure, the oily residue was purified by column

[60] Q. Yan, W. Cui, X. Song, G. Xu, M. Jiang, K. Sun, J. Lv, D. Yang, *Org. Lett.* **2021**, *23*, 3663–3668.

[61] F. Yuan, Z.-L. Hou, P. K. Pramanick, Bo Yao, *Org. Lett.* **2019**, *21*, 9381−9385.

[62] T. Akiyama, Y. Wada, M. Yamada, Y. Shio, T. Honma, S. Shimoda, K. Tsuruta, Y. Tamenori, H. Haneoka, T. Suzuki, K. Harada, H. Tsurugi, K. Mashima, J. Hasegawa, Y. Sato, M. Arisawa, *Org. Lett.* **2020**, *22*, 7244 - 7249.

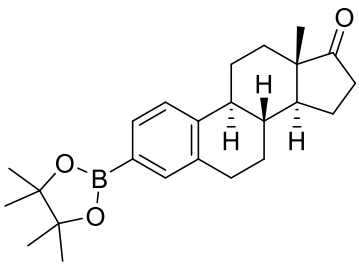
chromatography on silica gel (hexanes/ ethyl acetate = 4/1) to obtain the product as a colorless crystalline solid (1.20 g, 2.97 mmol, 99%). Spectroscopic data are in agreement with those reported in the literature.[63]

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.34 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.04 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.99 (d, *J* = 2.7 Hz, 1H), 2.94 (dd, *J* = 9.1, 4.4 Hz, 2H), 2.73 – 2.47 (m, 1H), 2.45 – 2.36 (m, 1H), 2.30 (td, *J* = 10.7, 4.3 Hz, 1H), 2.22 – 1.96 (m, 4H), 1.72 – 1.43 (m, 6H), 0.92 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 220.5, 147.7, 140.4, 139.4, 127.3, 121.4, 118.9 (q, $J_{C\text{-}F}$ = 320.6 Hz), 118.4, 50.5, 48.0, 44.2, 37.9, 35.9, 31.6, 29.5, 26.2, 25.8, 21.7, 13.9.

^{19}F-NMR (376 MHz, $CDCl_3$) δ = -73.5.

(8R,9S,13S,14S)-13-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (154)



Following a literature report,[64] an oven-dried 25 mL Schlenk flask was charged with estrone **153** (885 mg, 2.20 mmol, 1.0 equiv), B_2pin_2 (643 mg, 2.53 mmol, 1.15 equiv), $PdCl_2$(dppf) (81 mg, 0.11 mmol, 0.05 equiv) and sodium acetate (541 mg, 6.60 mmol, 3.0 equiv). DSMO (anhydrous, degassed, 10 mL) was added, and the mixture was stirred for 16 h at 80 °C. After cooling to room temperature, the reaction was diluted with ethyl acetate (50 mL) and washed with brine (2 x 50 mL). The combined aqueous layers were extracted with ethyl acetate (2 x 50 mL) and the combined organic layers were dried over Na_2SO_4. After volatiles were removed under reduced pressure, the residue was purified by column chromatography on silica gel (hexanes/ ethyl acetate = 20/1 to 10/1 to 4/1) to afford the title compound as a white crystalline solid (749 mg, 2.00 mmol, 90%). Spectroscopic data are in agreement with those reported in the literature.[65]

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.60 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.57 (s, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 2.99 – 2.87 (m, 2H), 2.57 – 2.41 (m, 2H), 2.33 (td, *J* = 10.9, 4.2 Hz, 1H), 2.20 – 1.93 (m, 4H), 1.70 – 1.44 (m, 6H), 1.34 (s, 12H), 0.91 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 220.9, 143.3, 135.9, 135.7, 132.3, 124.9, 83.8, 50.7, 48.1, 44.8, 38.2, 36.0, 31.7, 29.3, 26.6, 25.7, 25.0, 24.9, 21.7, 14.0.

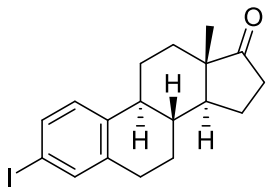
^{11}B-NMR (128 MHz, $CDCl_3$) δ = 30.2.

[63] T. Furuya, A. E. Strom, T. Ritter, *J. Am. Chem. Soc.* **2009**, *131*, 1662 – 1663.

[64] T. Akiyama, Y. Wada, M. Yamada, Y. Shio, T. Honma, S. Shimoda, K. Tsuruta, Y. Tamenori, H. Haneoka, T. Suzuki, K. Harada, H. Tsurugi, K. Mashima, J. Hasegawa, Y. Sato, M. Arisawa, *Org. Lett.* **2020**, *22*, 7244 - 7249.

[65] V. Ahmed, Y. Liu, C. Silvestro, S. D. Taylor, *Bioorg. Med. Chem.* **2006**, *14*, 8564 – 8573.

(8R,9S,13S,14S)-3-iodo-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (149v)

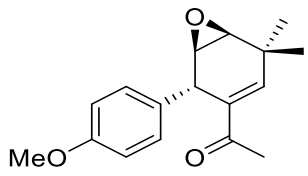


Following a literature report,[66] a 25 mL flask equipped with magnetic stirrer was charged with **154** (494 mg, 1.3 mmol, 1.0 equiv) and a 50:50 mixture of MeOH and H_2O (10 mL). Sodium iodide (253 mg, 1.7 mmol, 1.3 equiv) and a solution of chloramine T (732 mg, 2.6 mmol, 2.0 equiv) in a 50:50 mixture of MeOH and H_2O (4 mL) were subsequently added, causing the reaction to turn intensely yellow. After stirring for three days at room temperature, more sodium iodide (253 mg, 1.7 mmol, 1.3 equiv) and a solution of chloramine T (732 mg, 2.6 mmol, 2.0 equiv) in a 50:50 mixture of MeOH and H_2O (4 mL) were added and the reaction was stirred further for 24 hours. The mixture was then diluted with water (50 mL) and washed with CH_2Cl_2 (3 x 50 mL). The combined organic layers were then washed with brine (100 mL) and dried over Na_2SO_4. After volatiles were removed under reduced pressure, the residue was purified by column chromatography on silica gel (hexanes/ ethyl acetate = 4/1) to obtain the title compound as a colorless crystalline solid (383 mg, 1.0 mmol, 78%). Spectroscopic data are in agreement with those reported in the literature.[67]

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.43 (m, 2H), 7.02 (d, *J* = 9.1 Hz, 1H), 2.87 (dd, *J* = 9.0, 4.1 Hz, 2H), 2.51 (dd, *J* = 18.5, 8.3 Hz, 1H), 2.45 – 2.32 (m, 1H), 2.32 – 2.20 (m, 1H), 2.20 – 1.93 (m, 3H), 1.69 – 1.36 (m, 6H), 0.91 (s, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 220.7, 139.6, 139.3, 137.9, 134.8, 127.6, 91.3, 50.6, 48.1, 44.3, 38.0, 36.0, 31.6, 29.1, 26.4, 25.7, 21.7, 14.0

1-((1R,2S,6S)-2-(4-methoxyphenyl)-5,5-dimethyl-7-oxabicyclo[4.1.0]hept-3-en-3-yl)ethan-1-one ((+)-155)



In a 5 mL round bottomed flask, (S)-1-(4'-methoxy-4,4-dimethyl-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-one (**(-)-147a**) (77 mg, 0.3 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2 mL). *m*-Chloroperoxybenzoic acid (104 mg, 0.6 mmol, 2.0 equiv) was added and the solution was stirred for 2 hours at room temperature. After full conversion of the starting material (monitoring by TLC), the reaction was quenched by the addition sat. sodium thiosulfate solution (25 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were then washed with sat. $NaHCO_3$

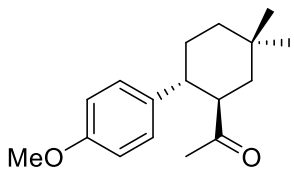
[66] T. Akiyama, Y. Wada, M. Yamada, Y. Shio, T. Honma, S. Shimoda, K. Tsuruta, Y. Tamenori, H. Haneoka, T. Suzuki, K. Harada, H. Tsurugi, K. Mashima, J. Hasegawa, Y. Sato, M. Arisawa, *Org. Lett.* **2020**, *22*, 7244 - 7249.

[67] J. Sheng, H.-Q. Ni, H.-R. Zhang, K.-F. Zhang, Y.-N. Wang, X.-S. Wang, *Angew. Chem. Int. Ed.* **2018**, *57*, 7634 –7639.

solution (20 mL), water (20 mL) and then dried over Na_2SO_4. After volatiles were removed under reduced pressure, the residue was purified by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 4/1) to afford the title compound as a color less oil (63 mg, 0.23 mmol, 77%).

R_f (hexanes/ethyl acetate = 5/1) = 0.33; $[\alpha]_D^{20} =$ + 131.0 ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 7.23 – 7.05 (m, 2H), 6.91 – 6.76 (m, 2H), 6.52 (dd, *J* = 2.2, 1.0 Hz, 1H), 4.39 (s, 1H), 3.77 (s, 3H), 3.36 (dd, *J* = 3.9, 1.6 Hz, 1H), 3.00 (ddd, *J* = 4.0, 2.1, 0.8 Hz, 1H), 2.22 (s, 3H), 1.32 (s, 6H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ = 198.3, 158.7, 144.8, 135.1, 131.5, 129.3, 114.3, 59.4, 57.9, 55.4, 39.2, 34.1, 26.6, 25.9, 25.9; **HRMS** (EI+, 70 eV): calcd. for $C_{17}H_{20}O_3$ 272.1407 [M^{+}] found 272.1407; **IR** (neat): 2967, 2870, 1700, 1610, 1513, 1469, 1305, 1249, 1178, 1111, 978, 947, 891, 842 cm^{-1}.

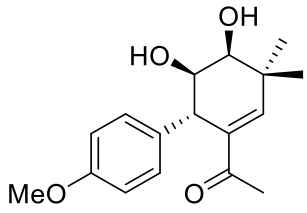
1-((1S,2R)-2-(4-methoxyphenyl)-5,5-dimethylcyclohexyl)ethan-1-one ((-)-156)



In a 5 mL round bottomed flask, (S)-1-(4'-methoxy-4,4-dimethyl-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-one (**(-)-147a**) (77 mg, 0.3 mmol, 1.0 equiv) and ammonium formate (758 mg, 12.0 mmol, 40 equiv) were dissolved in MeOH (5 mL) and Pd/C (32 mg, 10 w%, 0.03 mmol, 0.1 equiv) was added and the reaction was stirred for 18 hours at room temperature. The reaction was then filtered through a plug of silica gel using ethyl acetate and after removal of volatiles under reduced pressure, the title compound was obtained as a colorless solid (69 mg, 0.27 mmol, 88%). X-ray grade crystals were obtained after slow evaporation from PE/EA = 1/1.

R_f (hexanes/ethyl acetate = 5/1) = 0.75; **mp.** = 65 °C; $[\alpha]_D^{20} =$ - 35.0 ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 7.14 – 7.06 (m, 2H), 6.85 – 6.76 (m, 2H), 3.77 (s, 3H), 2.92 (td, *J* = 12.0, 3.5 Hz, 1H), 2.70 – 2.52 (m, 1H), 1.80 (s, 3H), 1.72 – 1.62 (m, 2H), 1.56 – 1.45 (m, 2H), 1.44 – 1.32 (m, 2H), 1.04 (s, 3H), 0.99 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ = 212.7, 158.1, 136.8, 128.3, 114.0, 55.3, 53.7, 45.8, 42.2, 39.1, 33.0, 30.7, 30.4, 30.1, 24.6; **HRMS** (EI+, 70 eV): calcd. for $C_{17}H_{24}O_2$ 260.1771 [M^{+}] found 260.1773; **IR** (neat): 2997, 2926, 2863, 2363, 1711, 1610, 1513, 1461, 1357, 1301, 1178, 1107, 1036, 977, 928, 828, 731 cm^{-1}.

1-((1S,5S,6R)-5,6-dihydroxy-4'-methoxy-4,4-dimethyl-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)ethan-1-one ((+)-157)

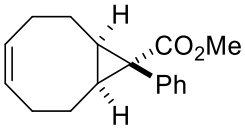


In a 5 mL round bottomed flask, (S)-1-(4'-methoxy-4,4-dimethyl-1,4-dihydro-[1,1'-biphenyl]-2-yl)ethan-1-one (**(-)-147a**) (77 mg, 0.3 mmol, 1.0 equiv) was dissolved in acetone/water (2:1, 3 mL). *N*-Methylmorpholine-*N*-Oxide (70 mg, 0.6 mmol, 2.0 equiv) and $K_2OsO_4 \cdot 2H_2O$ (5,5 mg, 0.015 mmol, 5 mol%) were added and the solution was stirred for 48 hours at room temperature. After full conversion of the starting material (monitoring by TLC), the reaction was diluted with CH_2Cl_2 (20 mL) and water (20 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were then dried over Na_2SO_4. After volatiles were removed under reduced pressure, the residue was purified

by column chromatography on silica gel (pure hexanes to hexanes/ ethyl acetate = 1/1 to pure ethyl acetate) to afford the title compound as a color less oil (59 mg, 0.20 mmol, 68%).

R_f (hexanes/ethyl acetate = 5/1) = 0.15; $[\alpha]_D^{20} = +141.3$ ° ($CHCl_3$, c = 1 g/L); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 7.09 – 6.99 (m, 2H), 6.86 – 6.77 (m, 2H), 6.58 (dd, *J* = 1.5, 0.7 Hz, 1H), 3.92 (dd, *J* = 6.6, 2.3 Hz, 1H), 3.84 (dd, *J* = 6.6, 1.5 Hz, 1H), 3.76 (s, 3H), 3.61 (dd, *J* = 2.3, 0.8 Hz, 1H), 2.26 (s, 2H), 2.14 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ = 199.3, 158.5, 146.4, 137.1, 133.7, 129.0, 114.3, 75.5, 74.6, 55.4, 46.1, 38.0, 28.2, 26.8, 24.4; **HRMS** (EI+, 70 eV): calcd. for $C_{17}H_{22}O_4$ 290.1513 [M^{+}] found 290.1511; **IR** (neat): 3422, 3007, 2960, 2926, 2840, 2363, 1670, 1610, 1513, 1465, 1356, 1301, 1249, 1178, 1111, 1036, 910, 867, 831, 753 cm^{-1}.

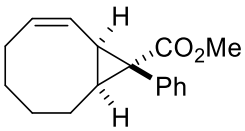
methyl Z-9-phenylbicyclo[6.1.0]non-4-ene-9-carboxylate (160)



Compound **160** was synthesized according to a literature procedure.[1] A flame dried 30 mL Schleck tube equipped with a magnetic stir bar was charged with 1,5-cyclooctadiene (2.45 mL, 20.0 mmol, 10 equiv), methyl 2-diazo-2-phenylacetate **2-Ph-Me** (352 mg, 2.0 mmol, 1.0 equiv) and CH_2Cl_2 (anhydrous, 20 mL). The deeply orange-colored reaction mixture was stirred and irradiated with blue light (LED, λ = 455 nm) for 24 h. After complete consumption of the diazo ester (monitoring by TLC, colorless solution) the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (pure hexanes to hexanes/ diethyl ether = 19/1) affording **37** (140 mg, g, 0.55 mmol, 27%) as colorless crystals. Spectroscopic data are in agreement with those reported in literature.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.22 (m, 3H), 7.22 – 7.13 (m, 2H), 5.64 – 5.54 (m, 2H), 3.56 (s, 3H), 2.30 – 1.97 (m, 8H), 1.22 – 1.03 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 175.6, 134.7, 132.5, 130.1, 128.1, 127.0, 52.4, 36.2, 32.4, 26.8, 26.5.

methyl 9-phenylbicyclo[6.1.0]non-2-ene-9-carboxylate (162)



Compound was synthesized according to a literature procedure.[68] A flame dried 60 mL Schleck tube equipped with a magnetic stir bar was charged with 1,3-cyclooctadiene (5.0 mL, 40.0 mmol, 10 equiv), methyl 2-diazo-2-phenylacetate **2-Ph-Me** (704 mg, 4.0 mmol, 1.0 equiv) and CH_2Cl_2 (anhydrous, 40 mL). The deeply orange-colored reaction mixture was stirred and irradiated with blue light (LED, λ = 455 nm) for 24 h. After complete consumption of the diazo ester (monitoring by TLC, colorless solution) the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (pure hexanes to hexanes/ diethyl ether = 19/1) affording **162** (426 mg, 1.66 mmol, 42%) as colorless crystals. Spectroscopic data are in agreement with those reported in literature. X-ray grade crystals were obtained by slow evaporation from methanol.

[68] Y. Guo, C. Empel, C. Pei, I. Atodiresei, T. Fallon, R. M. Koenigs, Org. Lett. **2020**, *22*, 5126–5130.

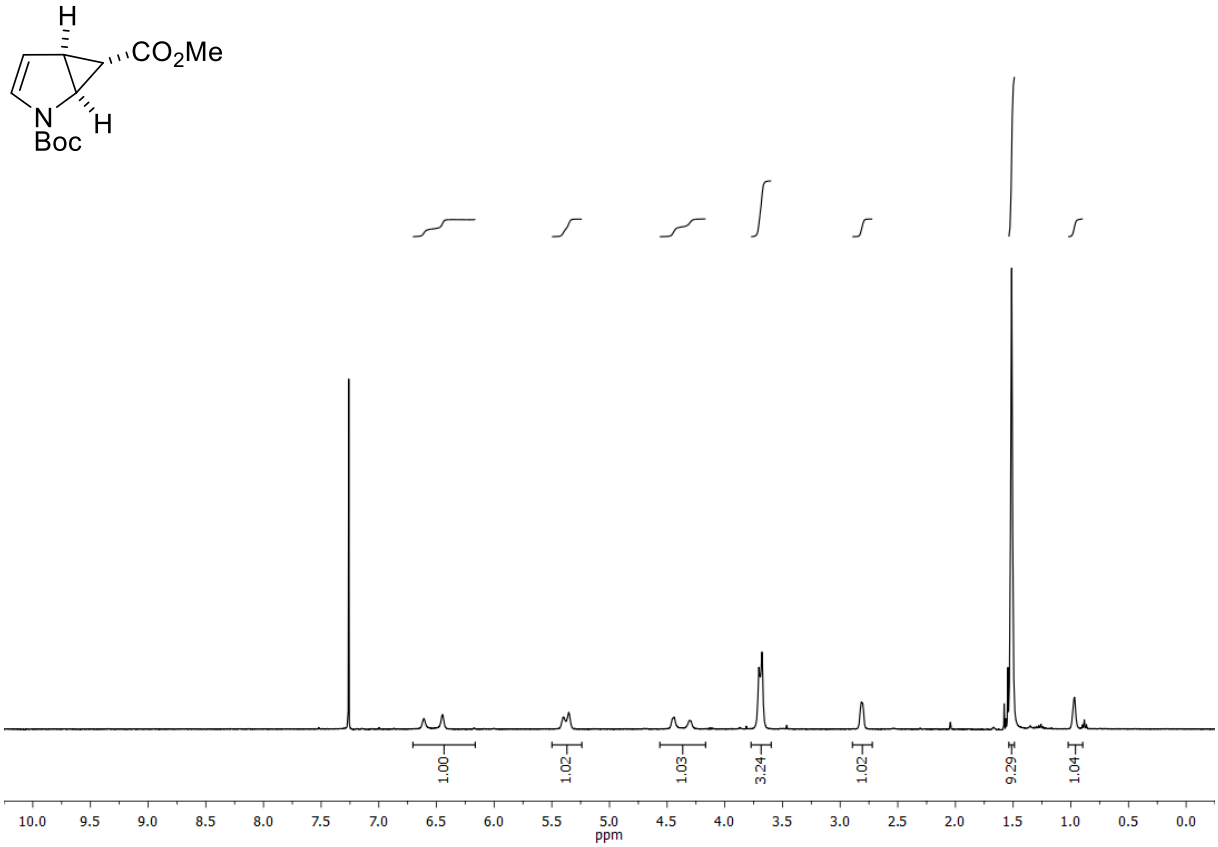
^{1}H-NMR (300 MHz, $CDCl_z$) δ 7.36 – 7.27 (m, 3H), 7.25 – 7.20 (m, 2H), 5.59 (dddd, *J* = 11.6, 7.0, 4.9, 2.5 Hz, 1H), 5.44 (m, f1H), 3.58 (s, 3H), 2.64 – 2.54 (m, 1H), 2.44 – 2.30 (m, 1H), 2.13 – 1.93 (m, 3H), 1.93 – 1.79 (m, 1H), 1.77 – 1.61 (m, 2H), 1.44 – 1.29 (m, 1H), 0.93 – 0.75 (m, 1H).; **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 175.6, 135.8, 134.1, 132.6, 127.9, 127.1, 121.7, 52.6, 34.8, 33.9, 30.4, 30.3, 29.8, 25.5, 24.7.

F. Appendix

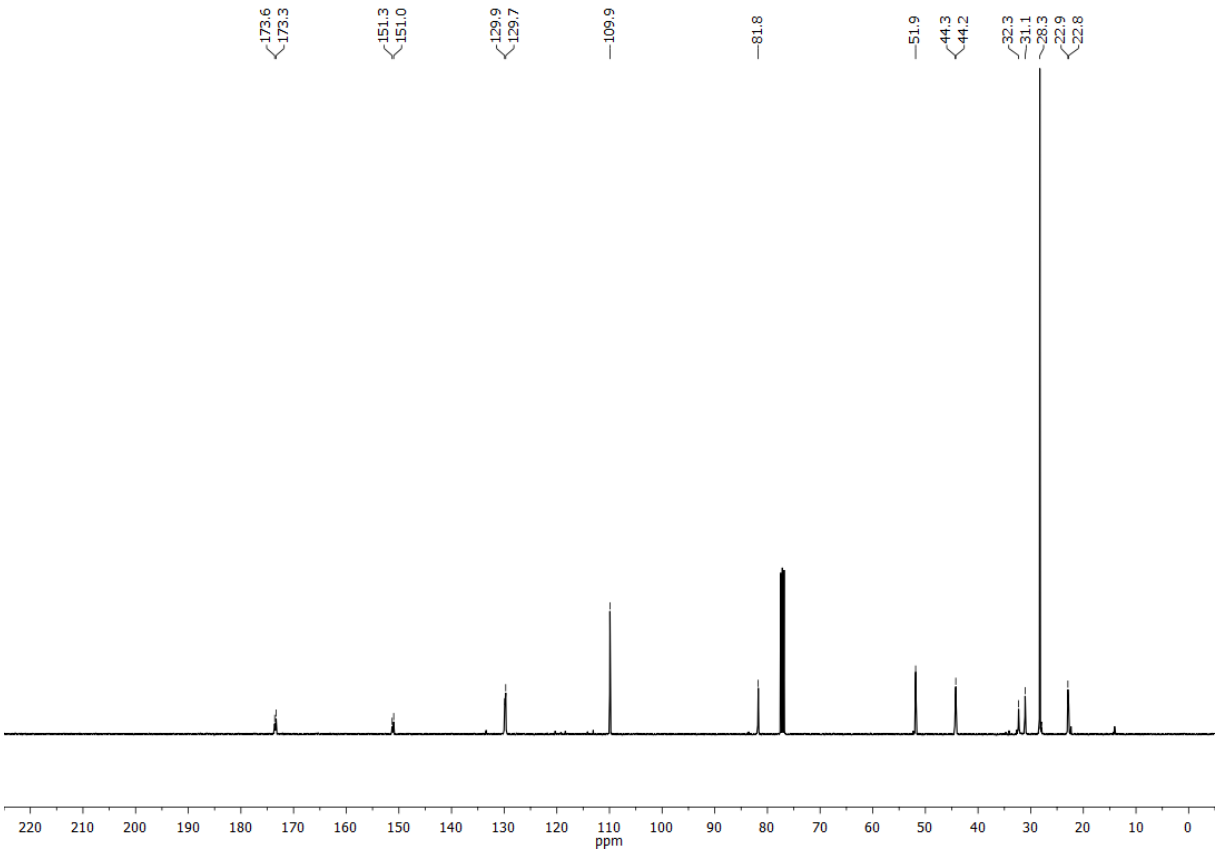
1. NMR-spectra

^{1}H-NMR	first image
^{13}C-NMR	second image
^{19}F-NMR/^{11}B-NMR	third image (next page)

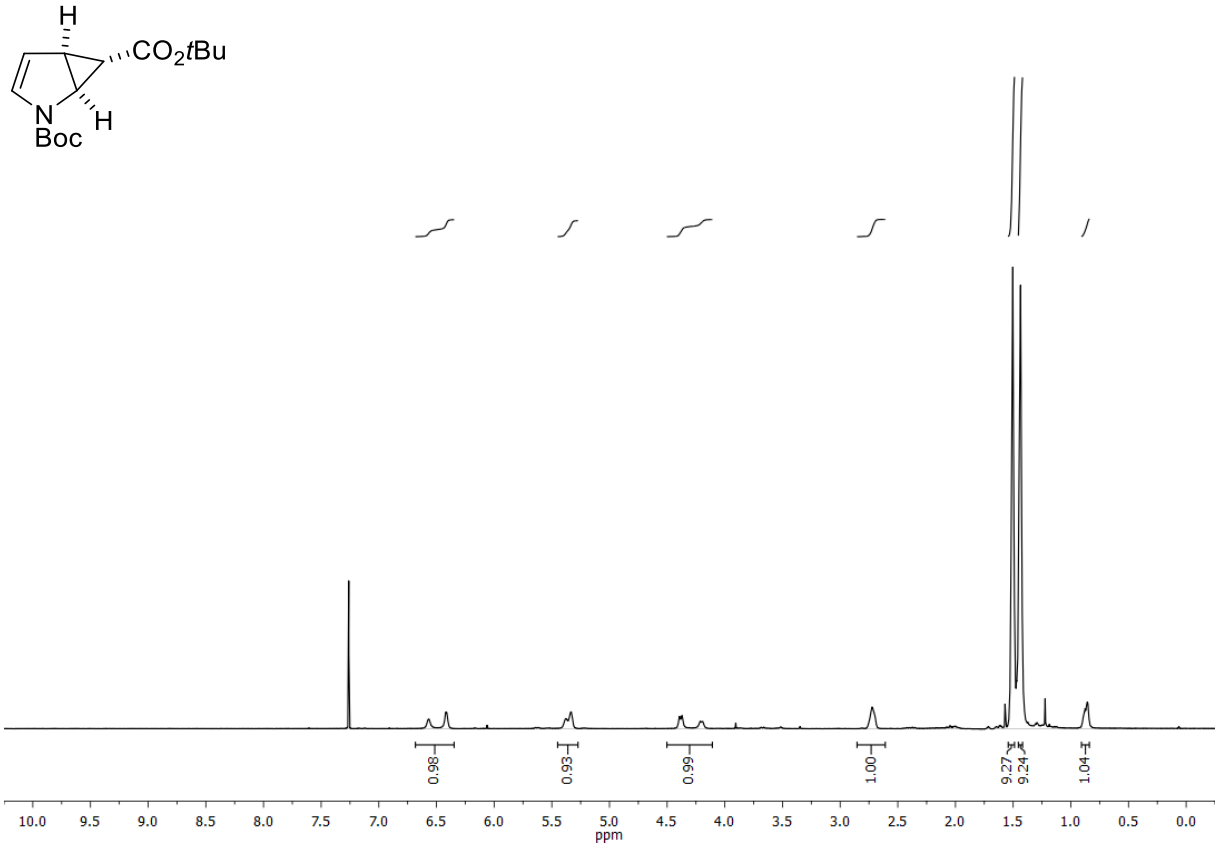
Compound **3-Me** ^{1}**H-NMR** ($CDCl_3$)



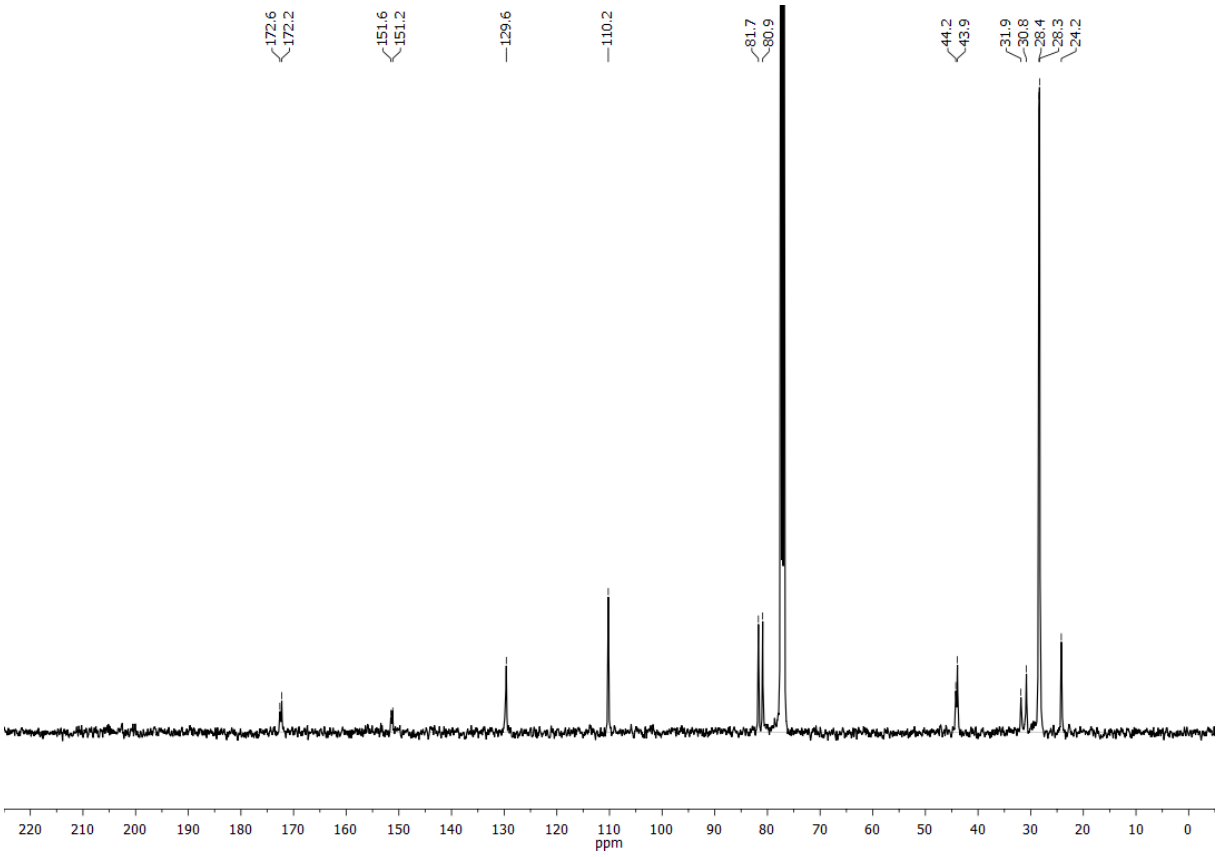
Compound **3-Me** ^{13}**C-NMR** ($CDCl_3$)



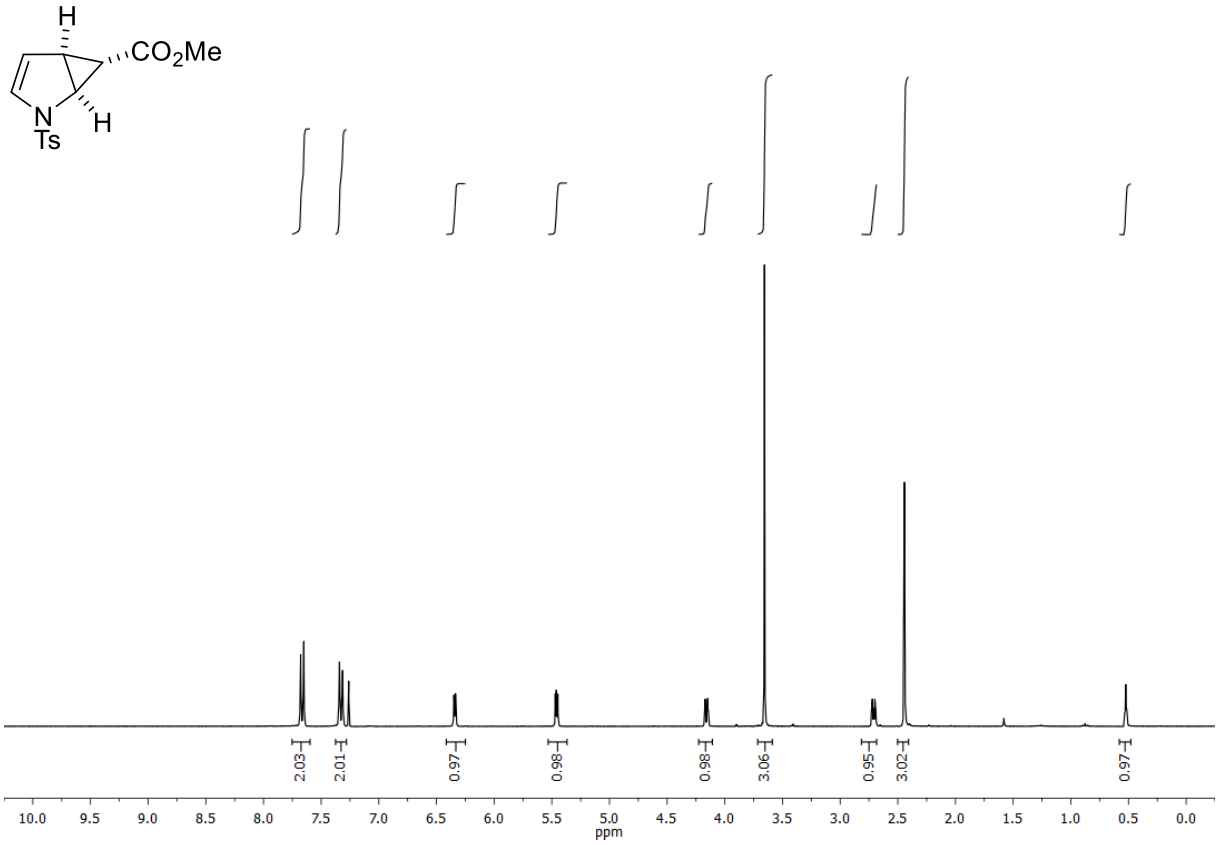
Compound **3-*t*Bu ^{1}H-NMR** ($CDCl_3$)



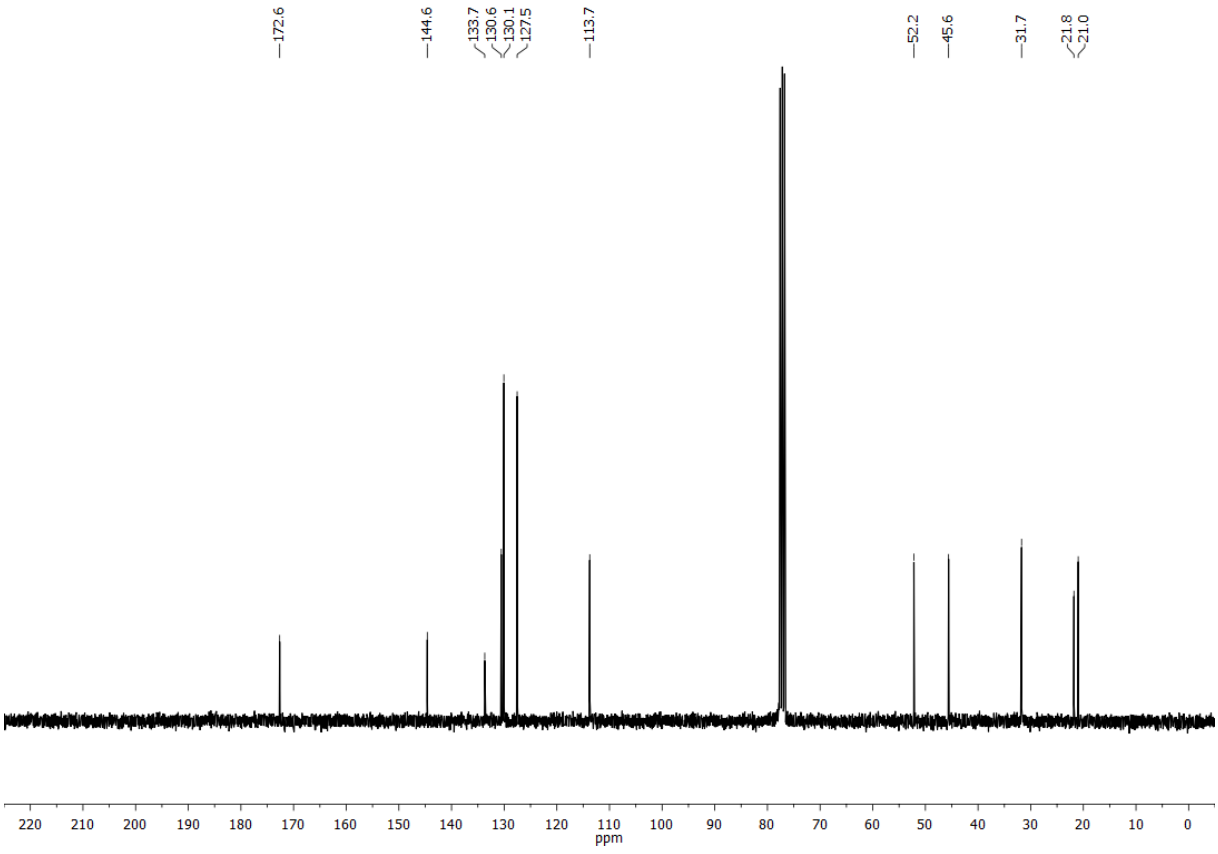
Compound **3-*t*Buv ^{13}C-NMR** ($CDCl_3$)



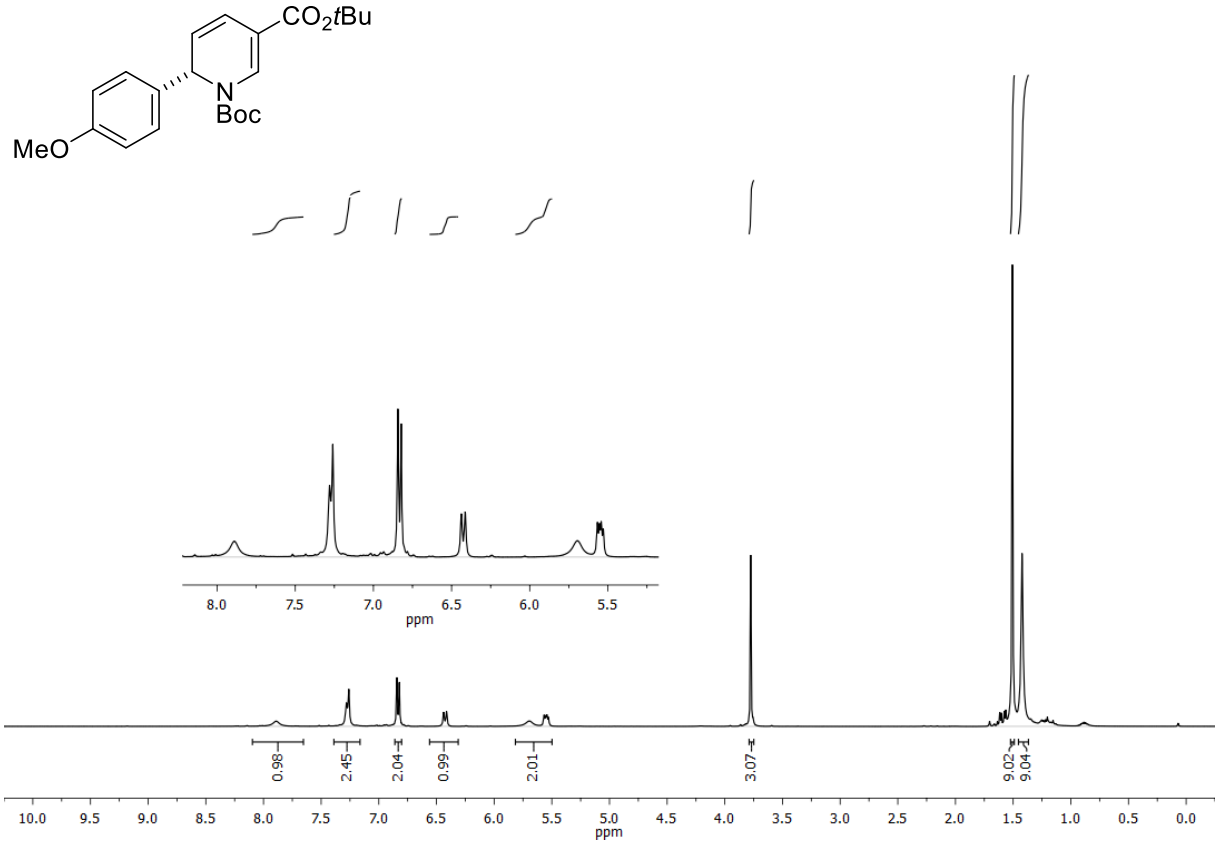
Compound **3-Ts-Me ^{1}H-NMR** ($CDCl_3$)



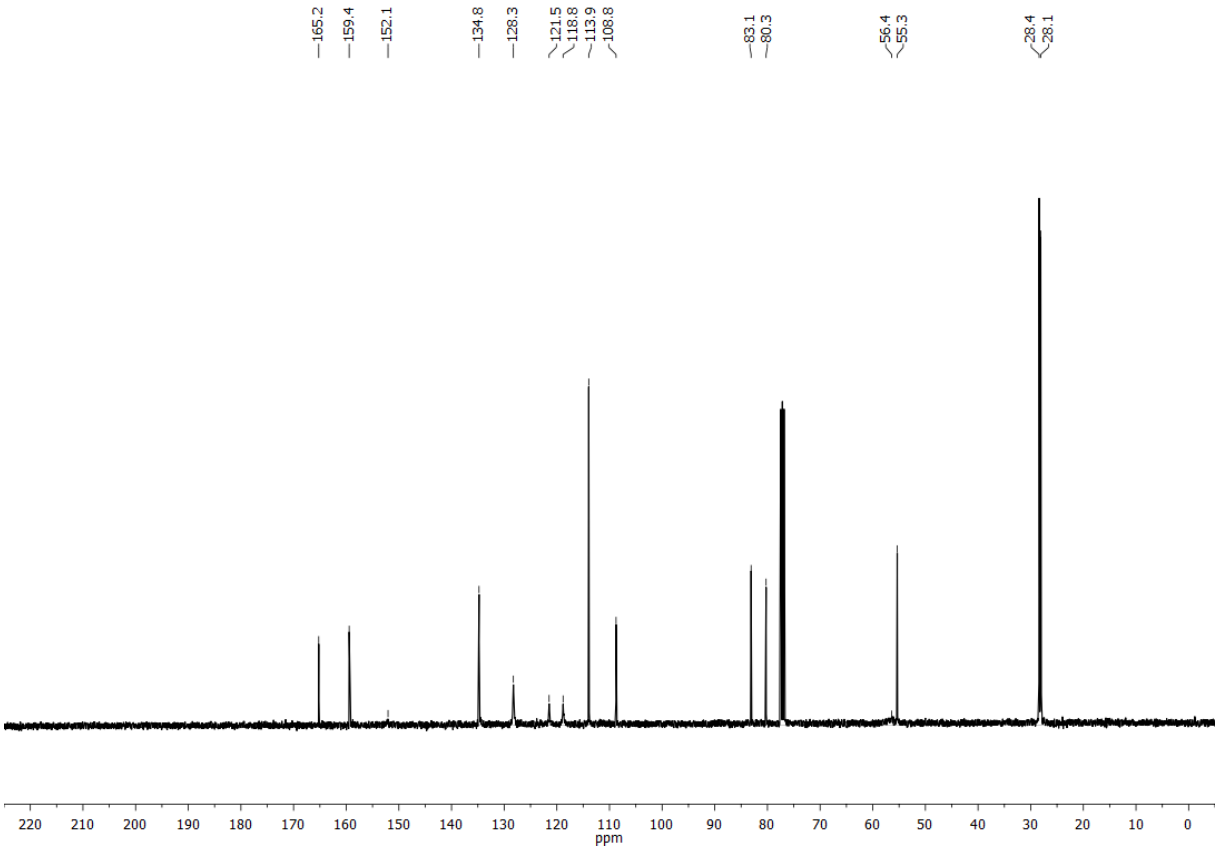
Compound **3-Ts-Me ^{13}C-NMR** ($CDCl_3$)



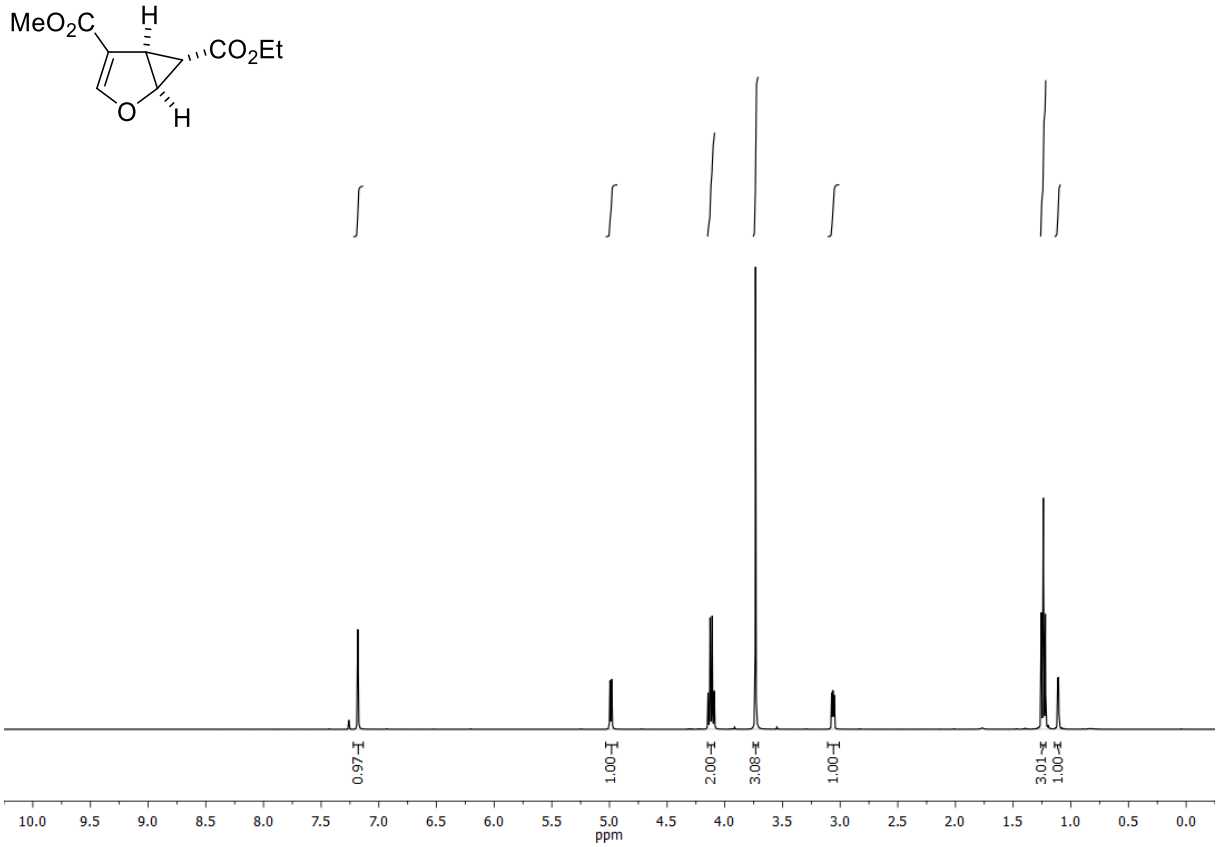
Compound **14a** ^{1}**H-NMR** ($CDCl_3$)



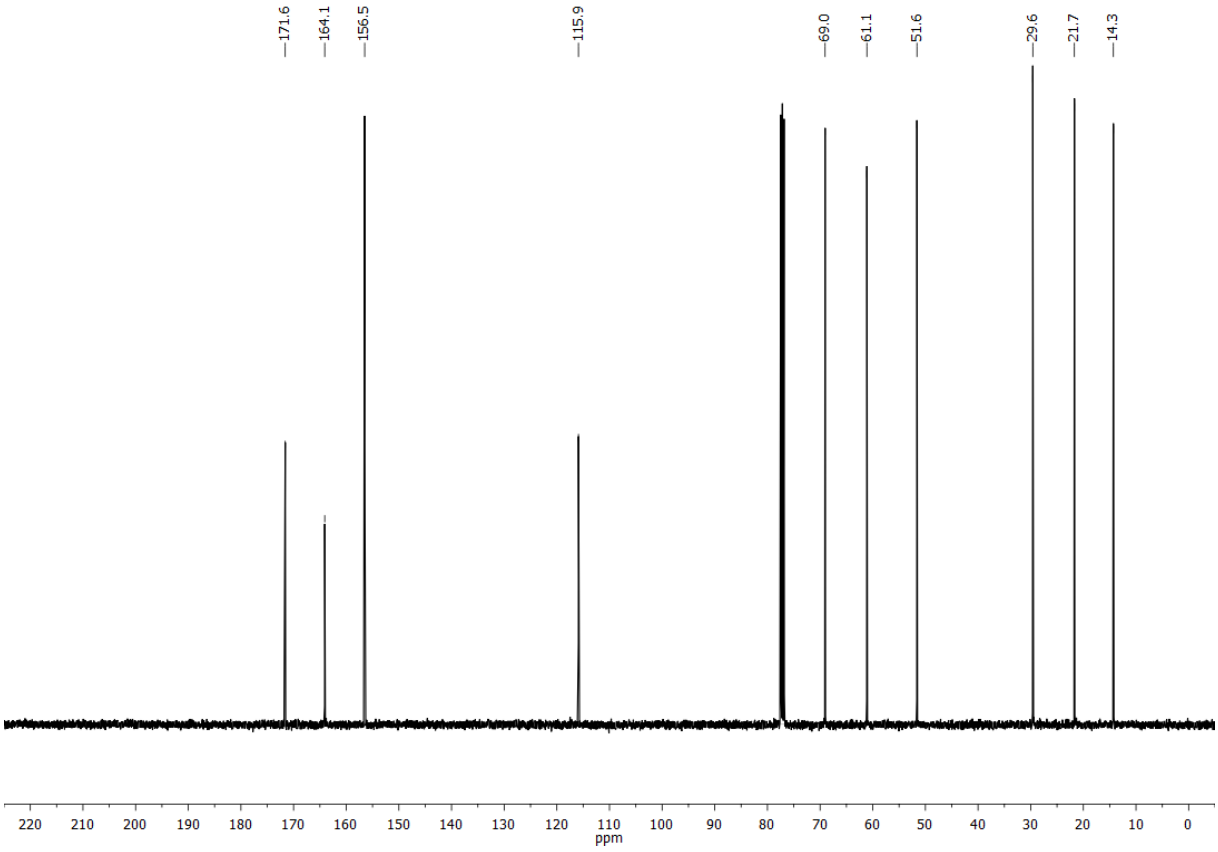
Compound **14a** ^{13}**C-NMR** ($CDCl_3$)



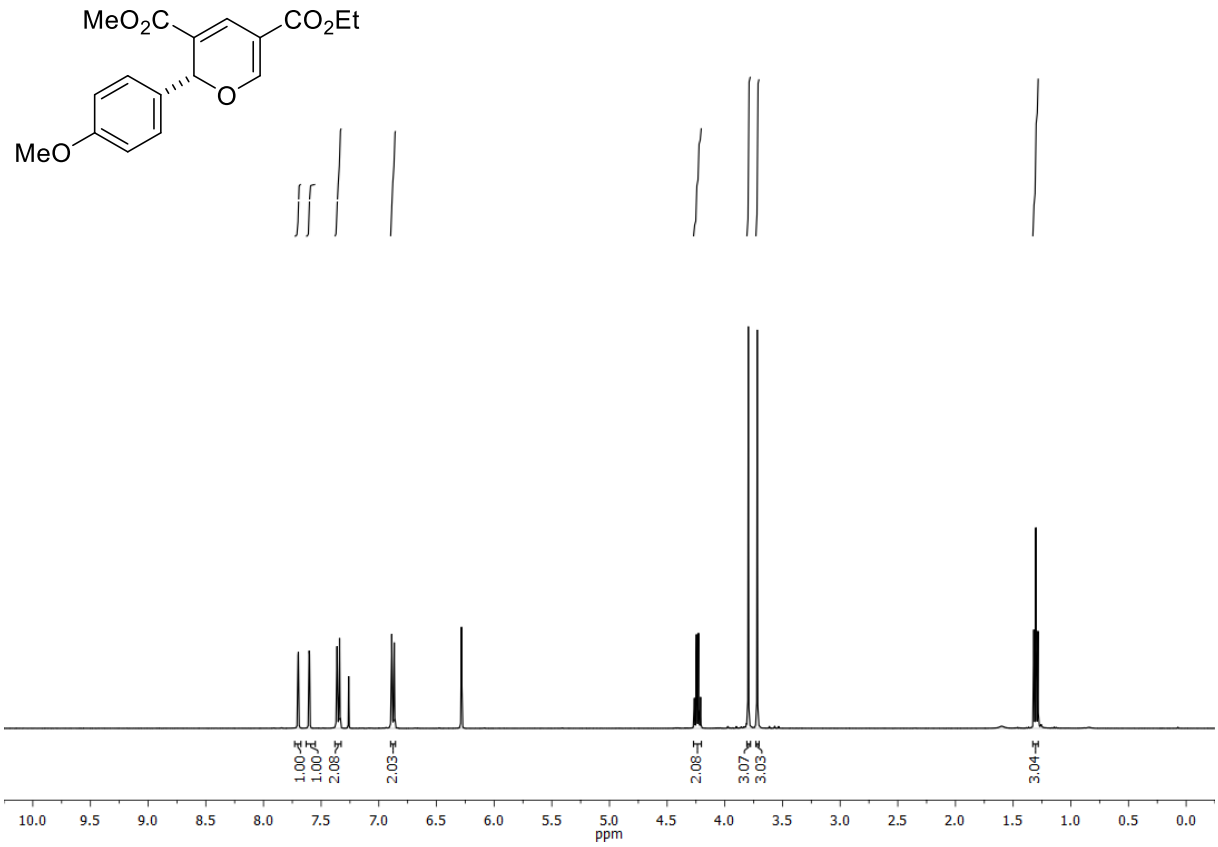
Compound 15 ^{1}H-NMR ($CDCl_3$)



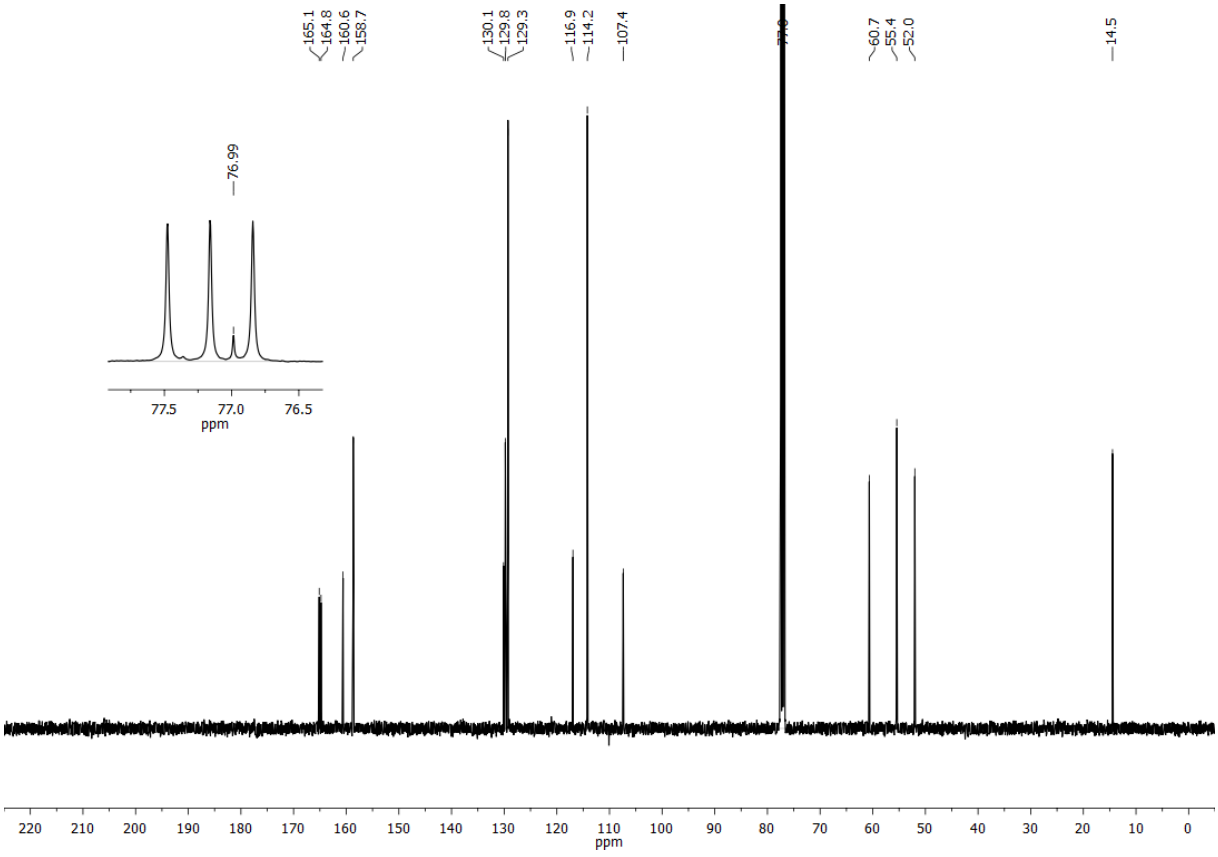
Compound **15 ^{13}C-NMR** ($CDCl_3$)



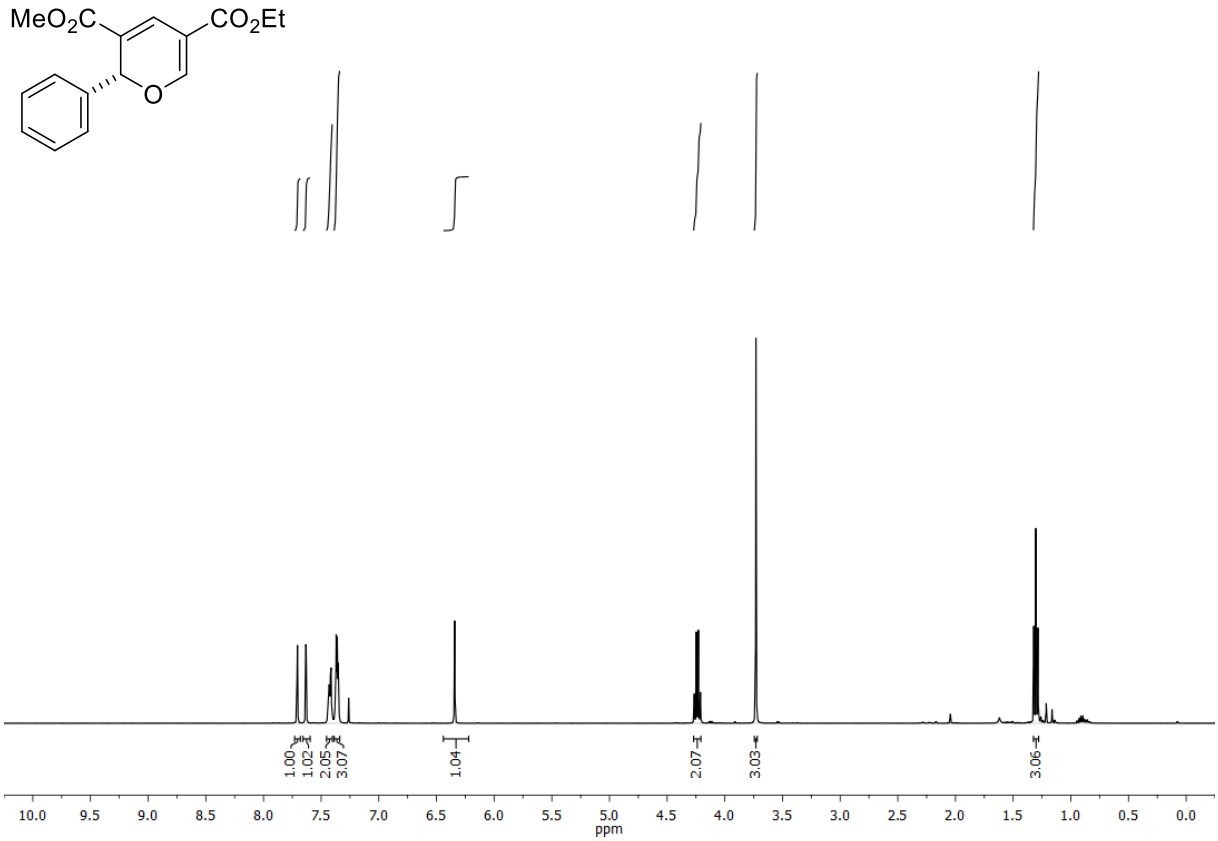
Compound **16a** ^{1}**H-NMR** ($CDCl_3$)



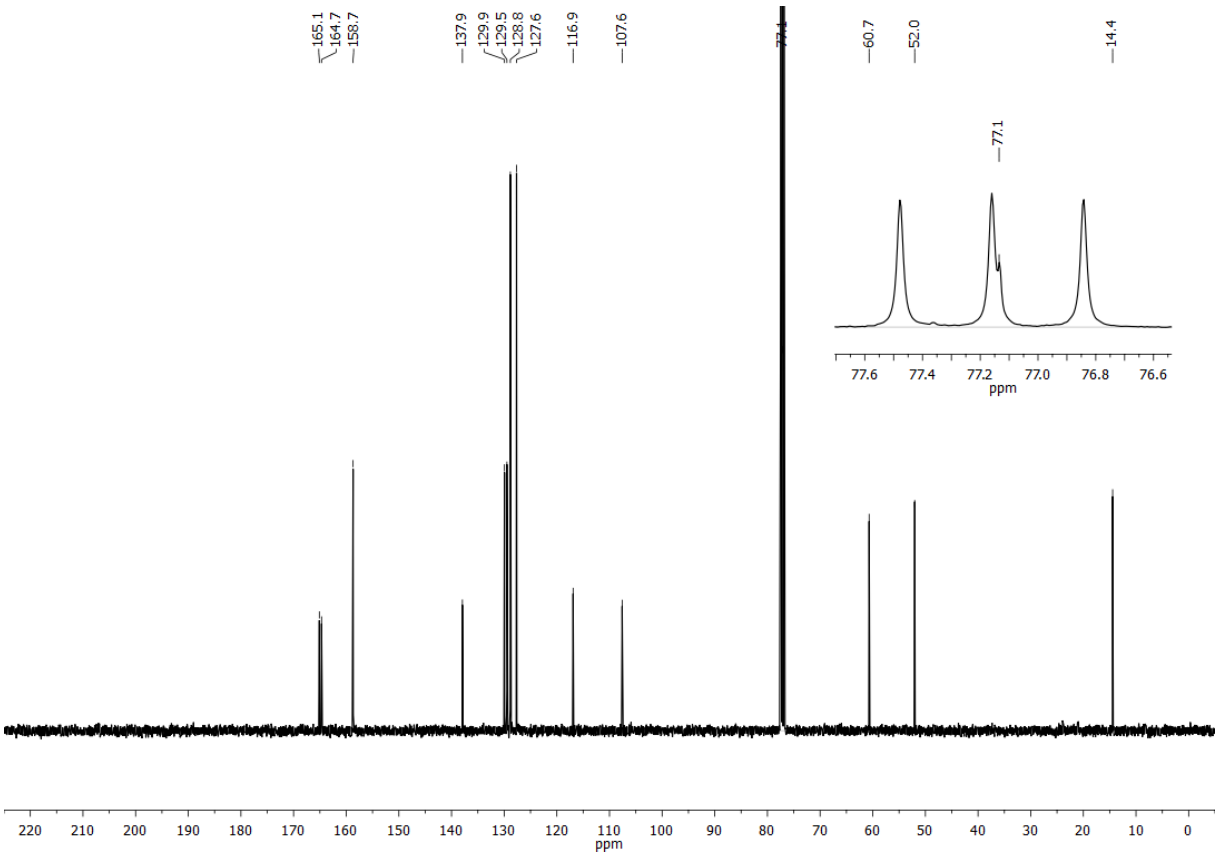
Compound **16a** ^{13}**C-NMR** ($CDCl_3$)



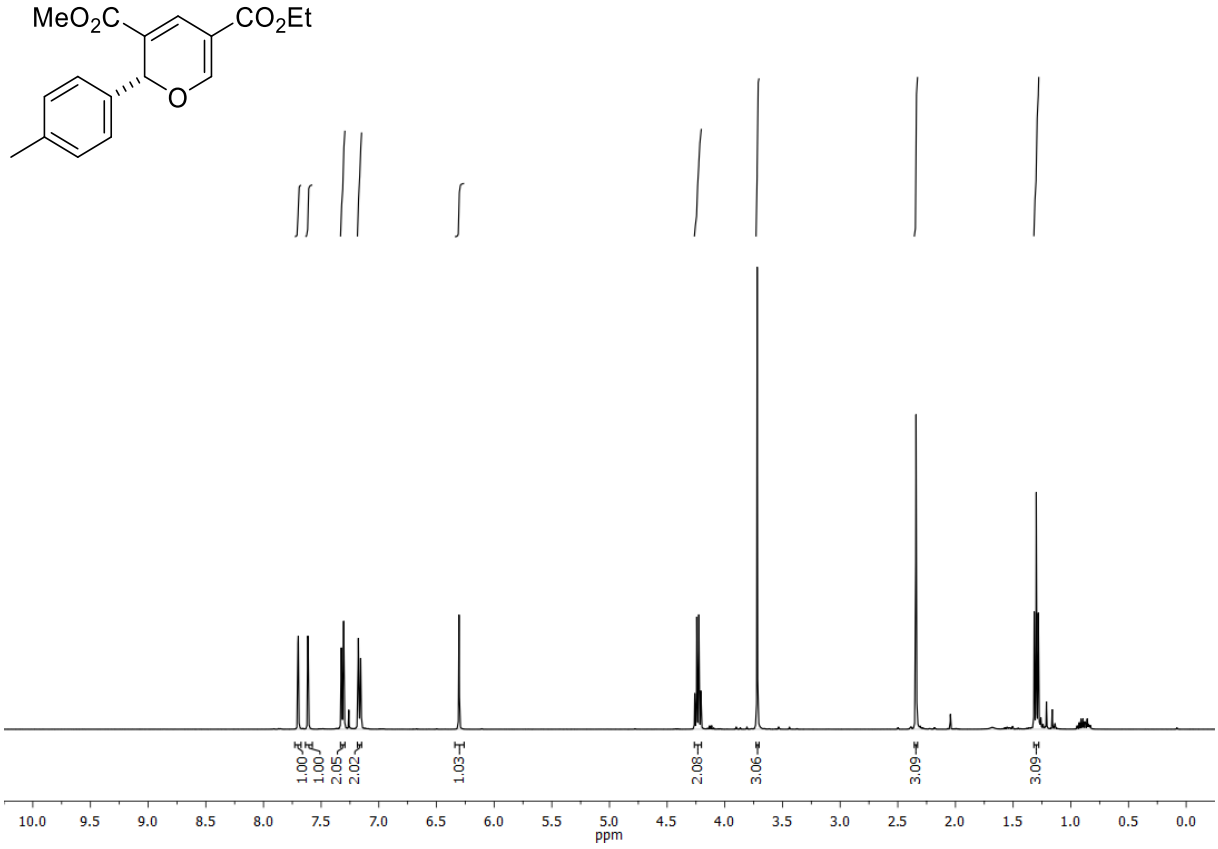
Compound **16b** ^{1}**H-NMR** ($CDCl_3$)



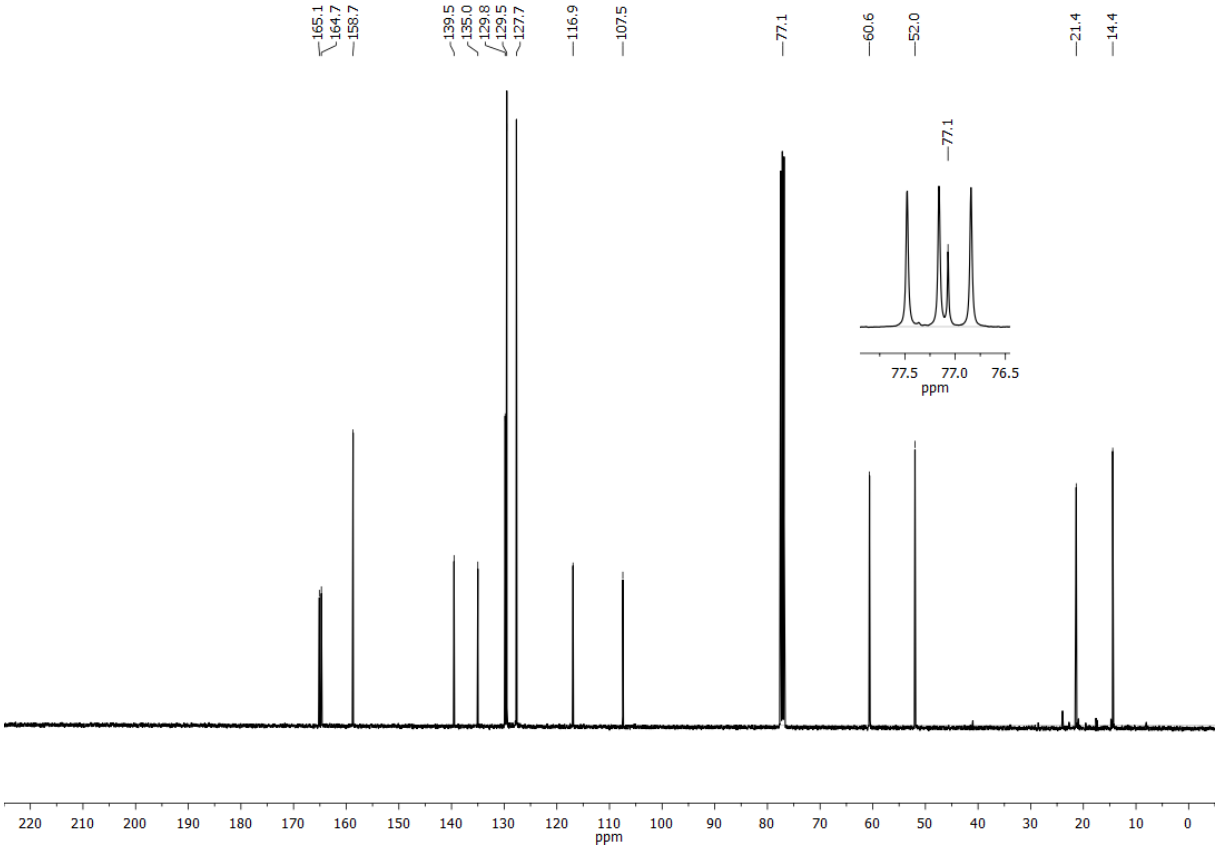
Compound **16b** ^{13}**C-NMR** ($CDCl_3$)



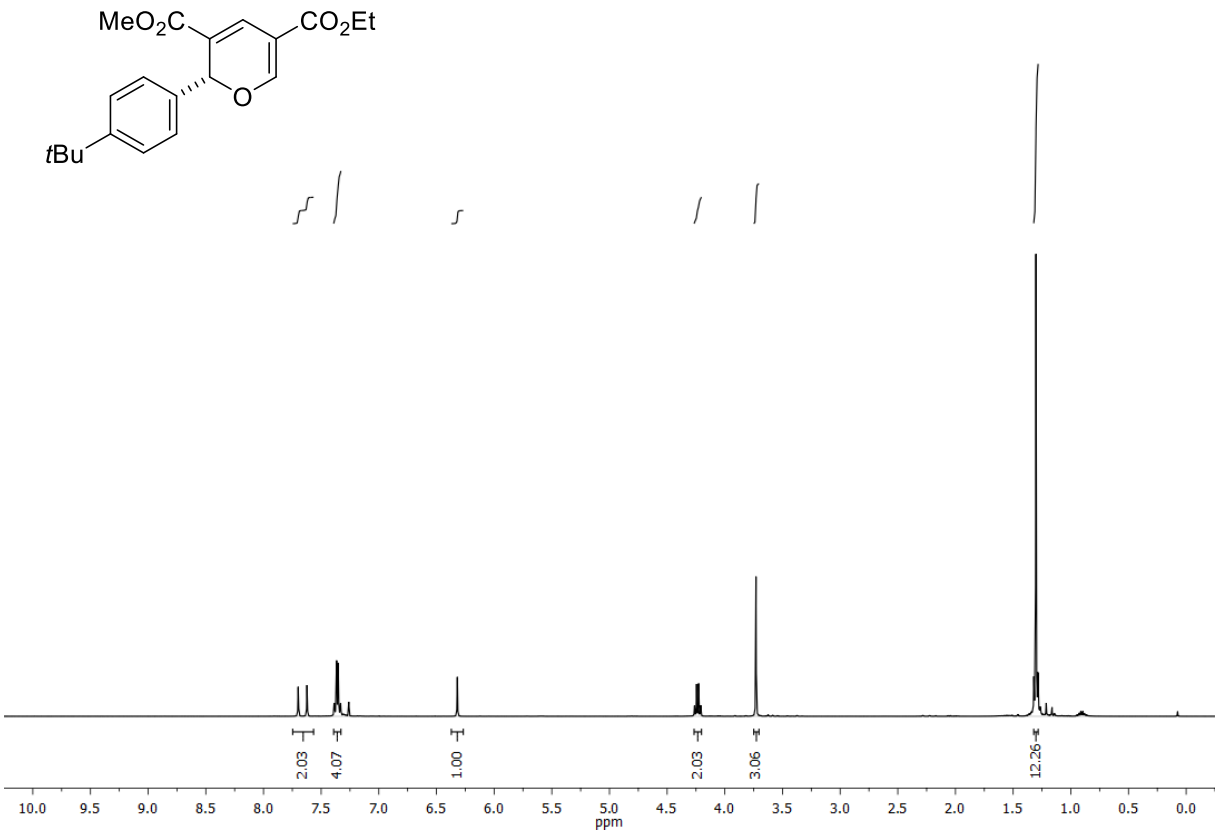
Compound **16c** ^{1}**H-NMR** ($CDCl_3$)



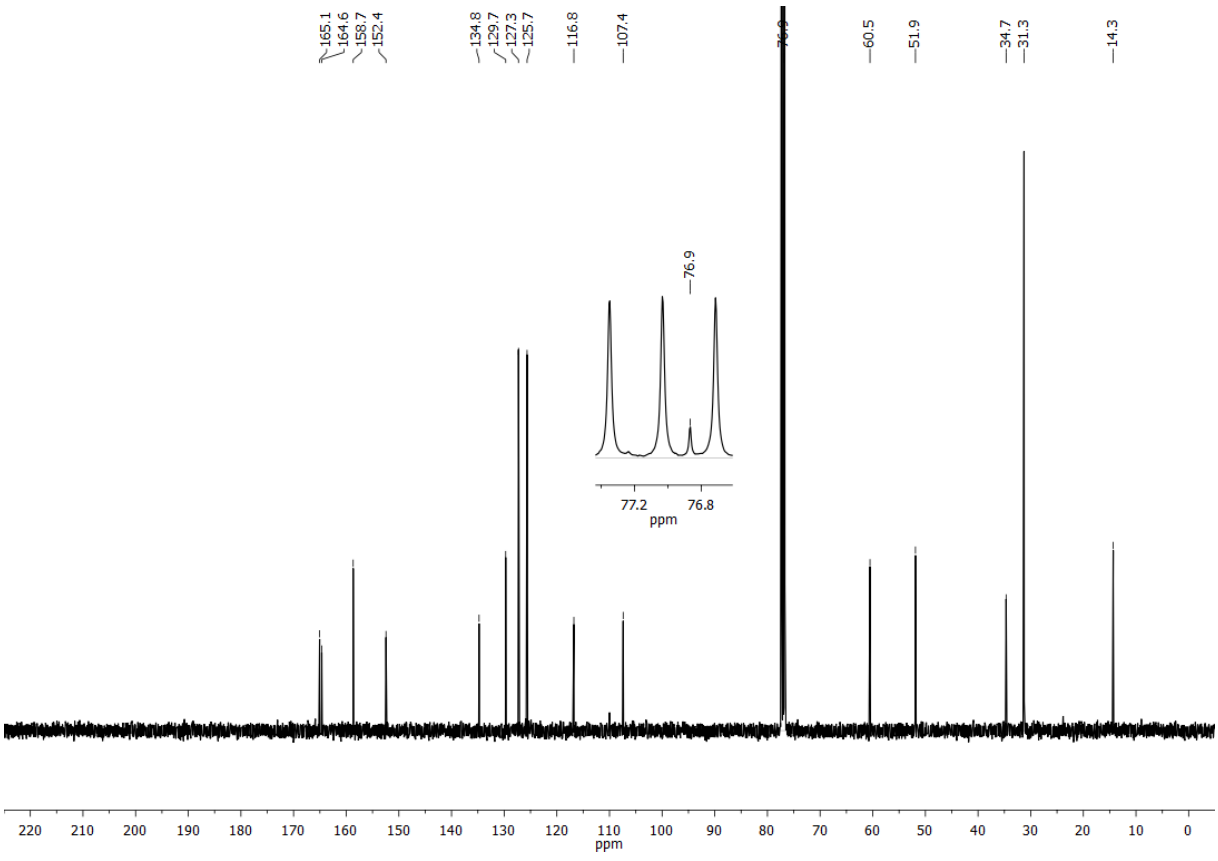
Compound **16c** ^{13}**C-NMR** ($CDCl_3$)



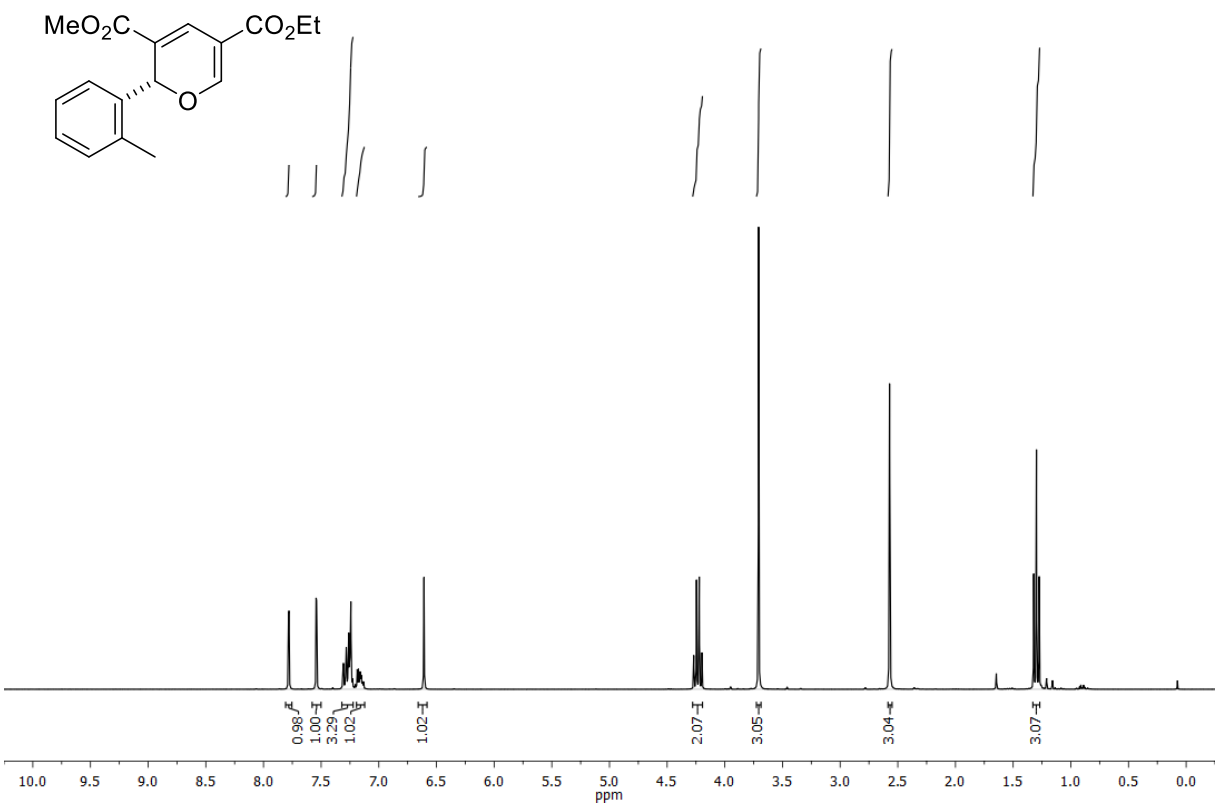
Compound **16d** ^{1}**H-NMR** ($CDCl_3$)



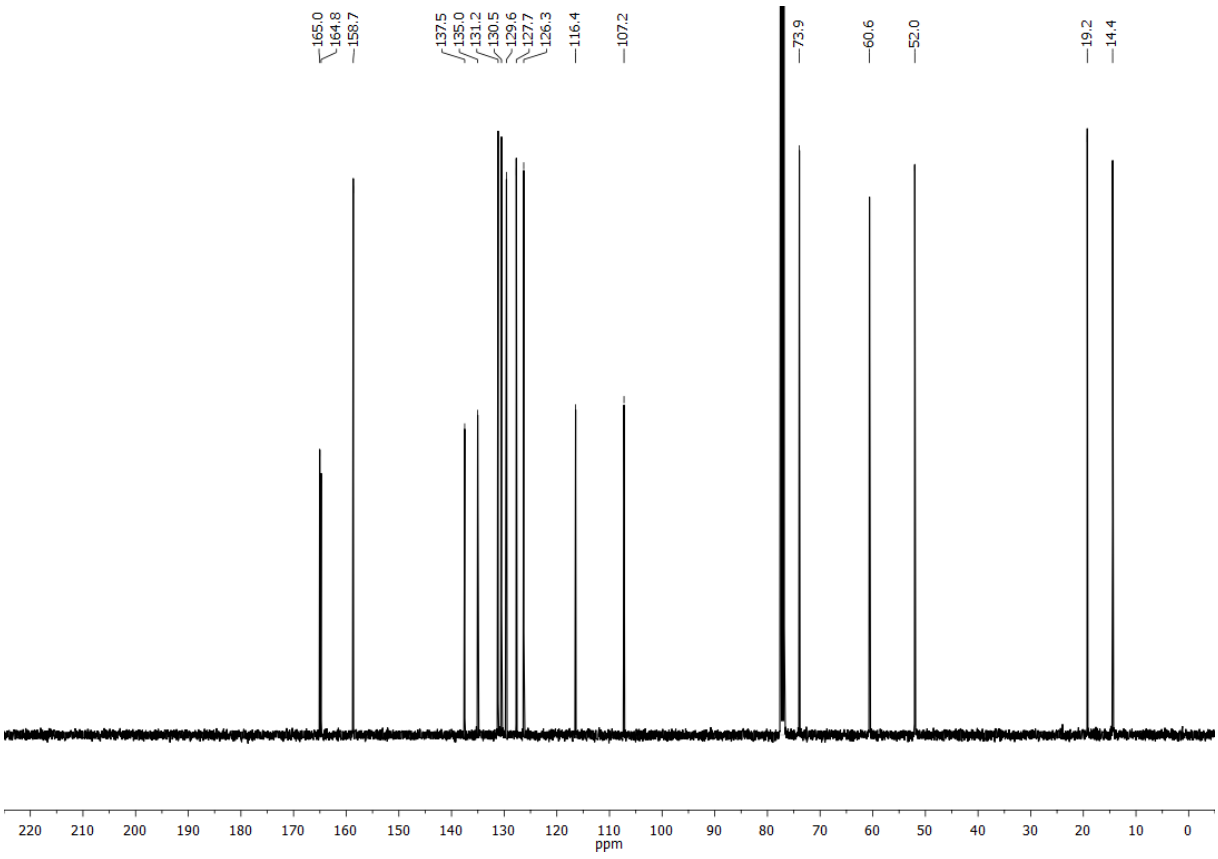
Compound **16d** ^{13}**C-NMR** ($CDCl_3$)



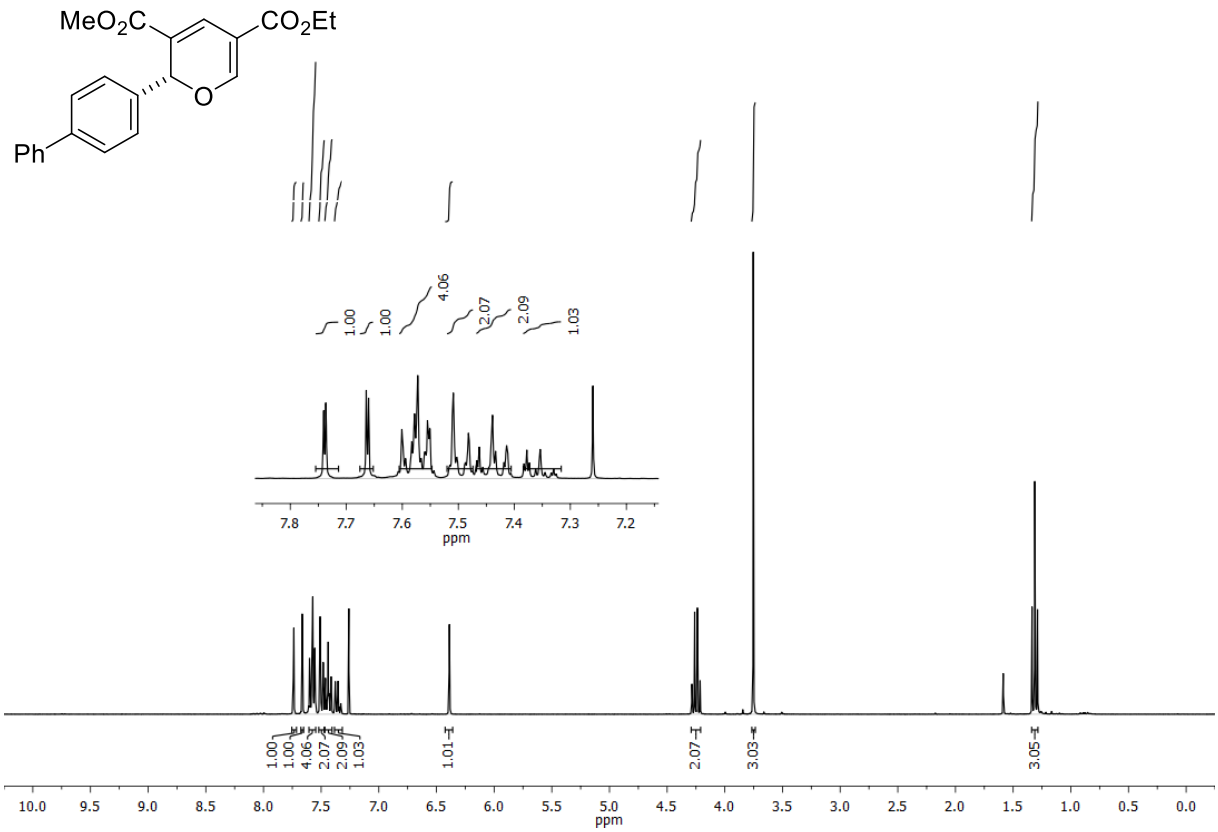
Compound **16e** ^{1}**H-NMR** ($CDCl_3$)



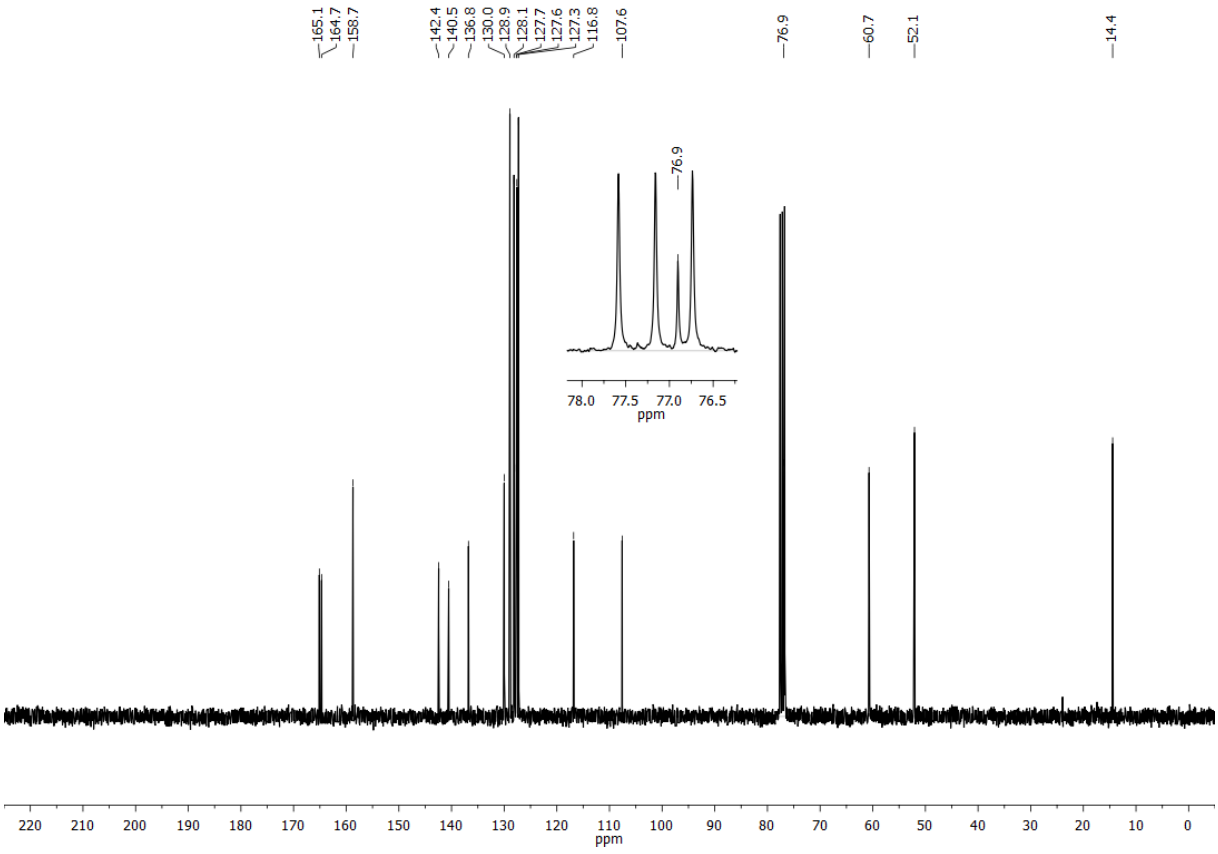
Compound **16e** ^{13}**C-NMR** ($CDCl_3$)



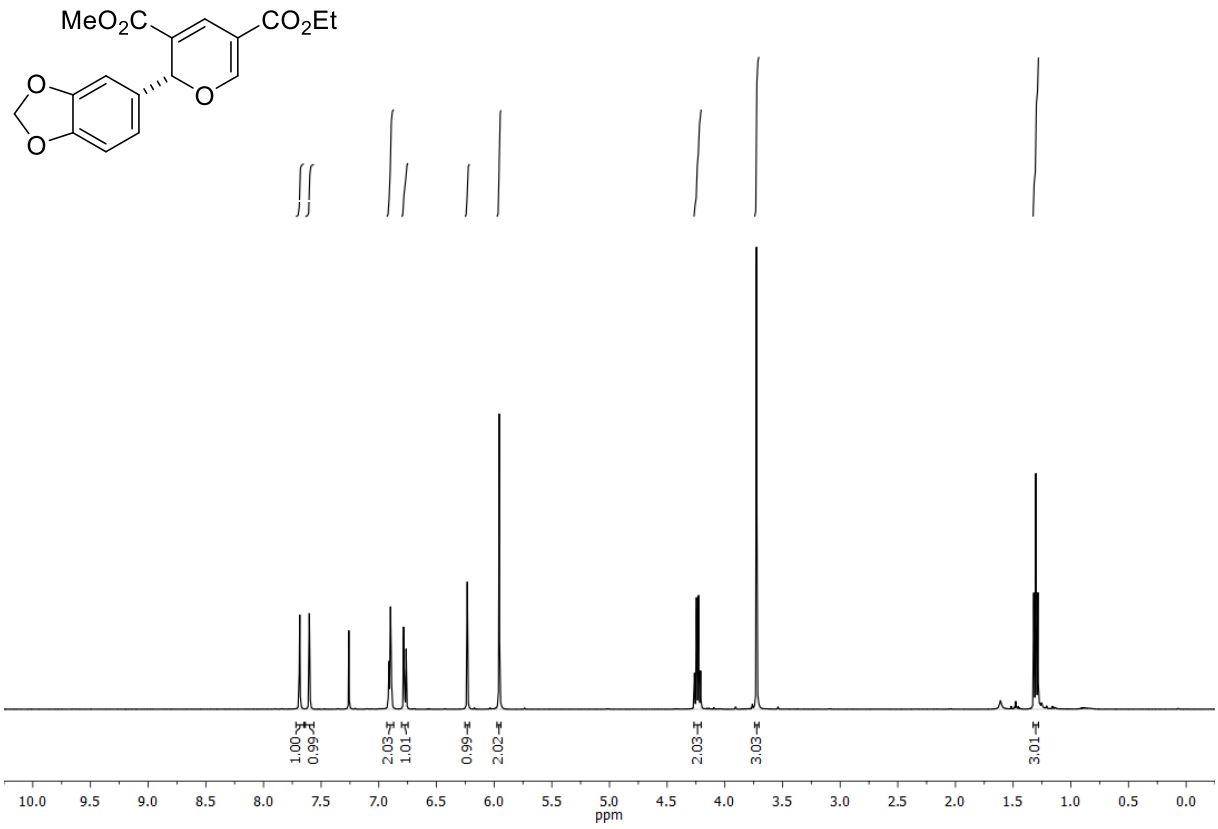
Compound **16f** ^{1}**H-NMR** ($CDCl_3$)



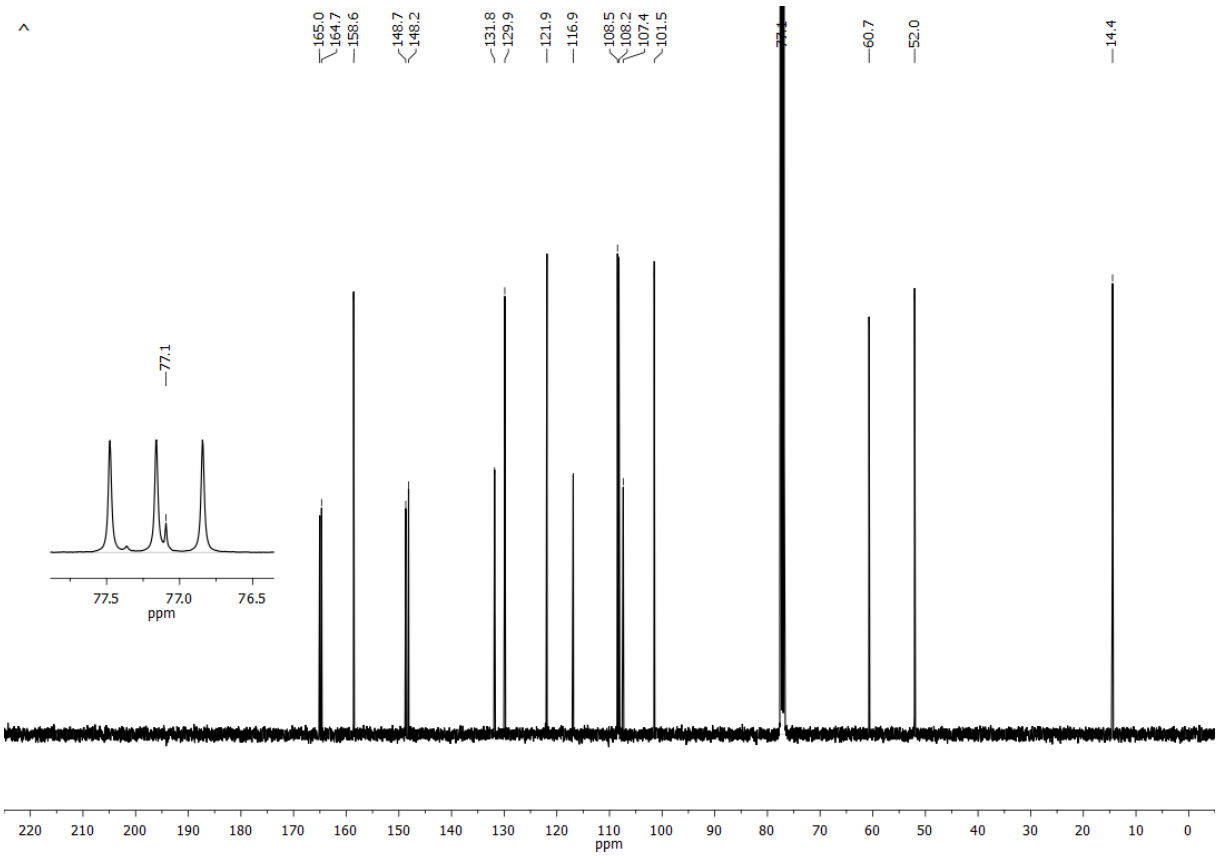
Compound **16f** ^{13}**C-NMR** ($CDCl_3$)



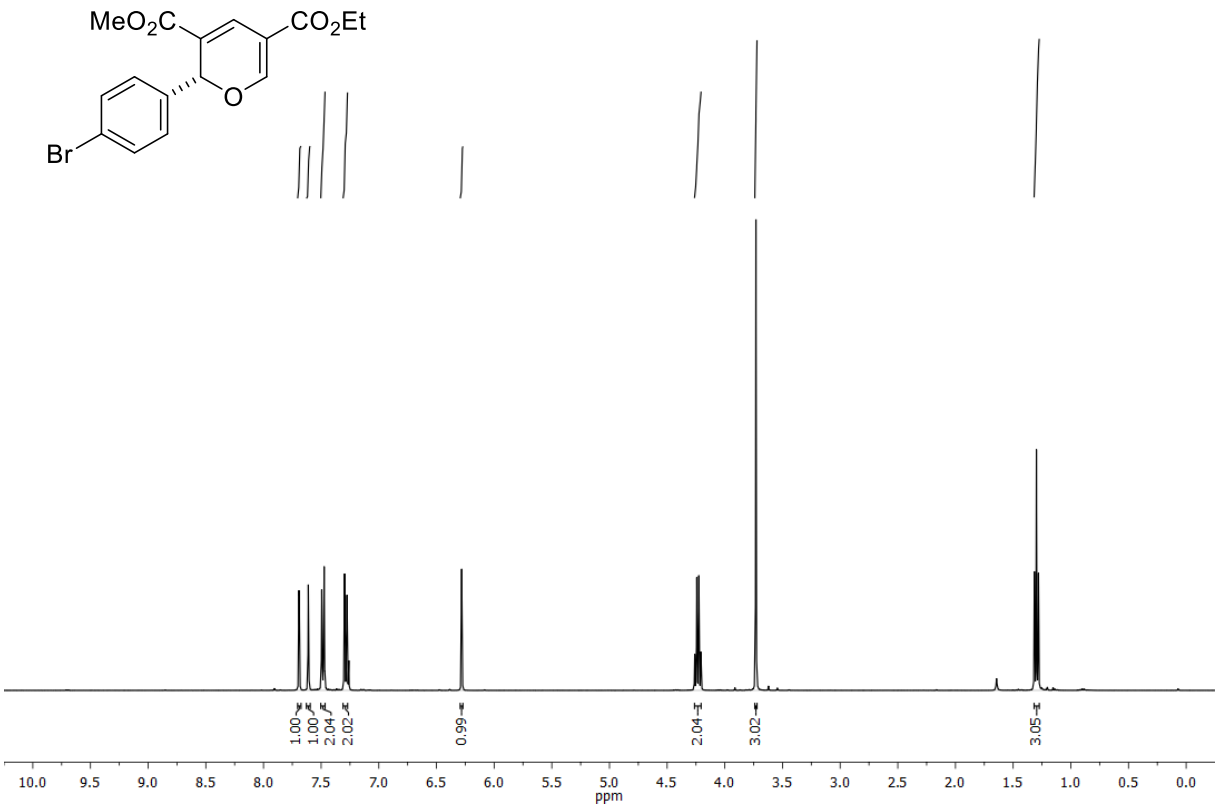
Compound **16g** ^{1}**H-NMR** ($CDCl_3$)



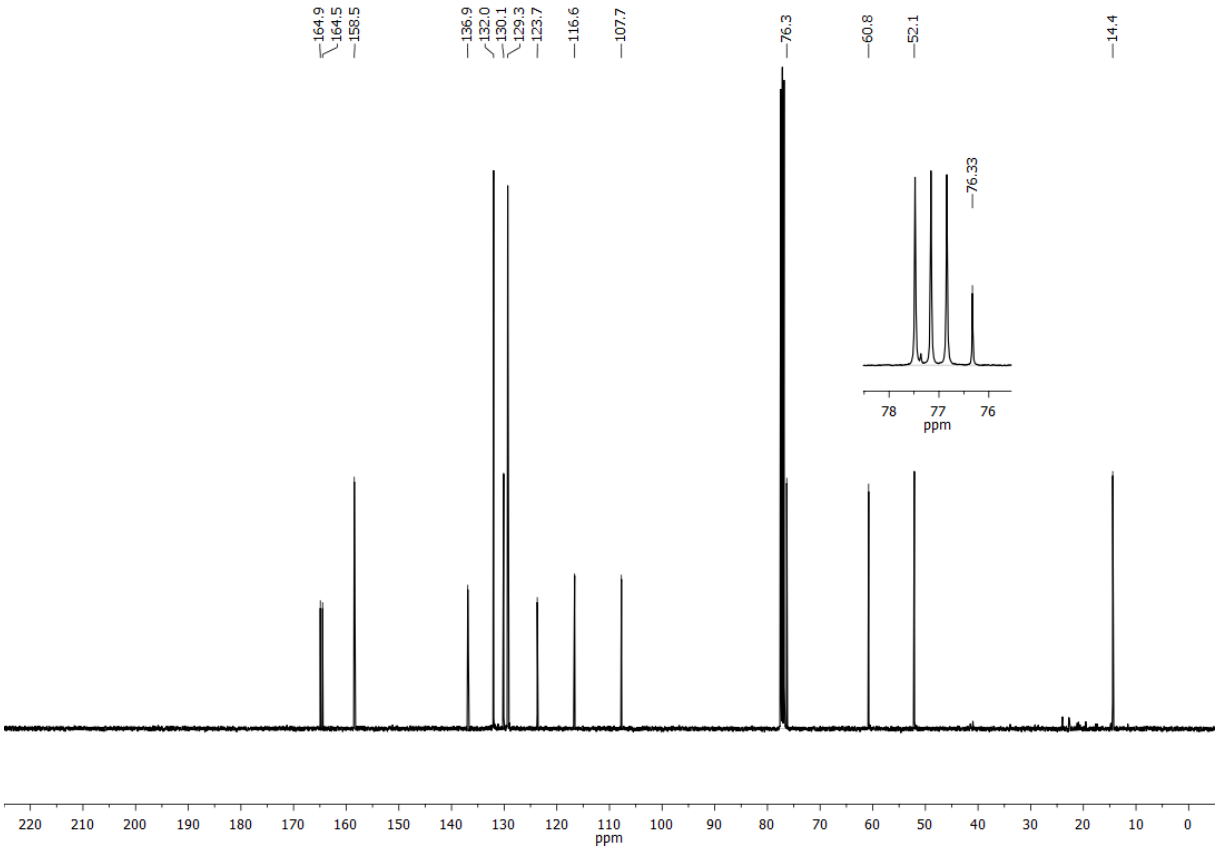
Compound **16g** ^{13}**C-NMR** ($CDCl_3$)



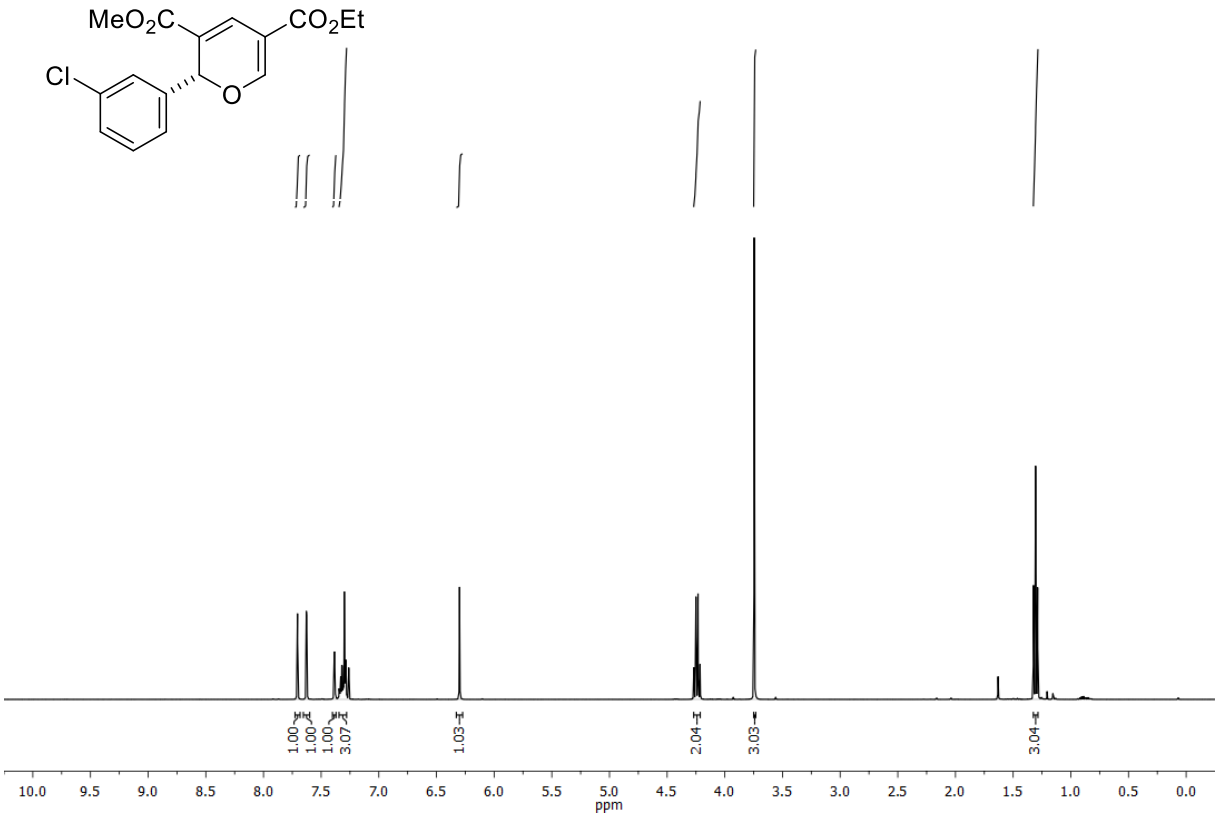
Compound **16h** ^{1}**H-NMR** ($CDCl_3$)



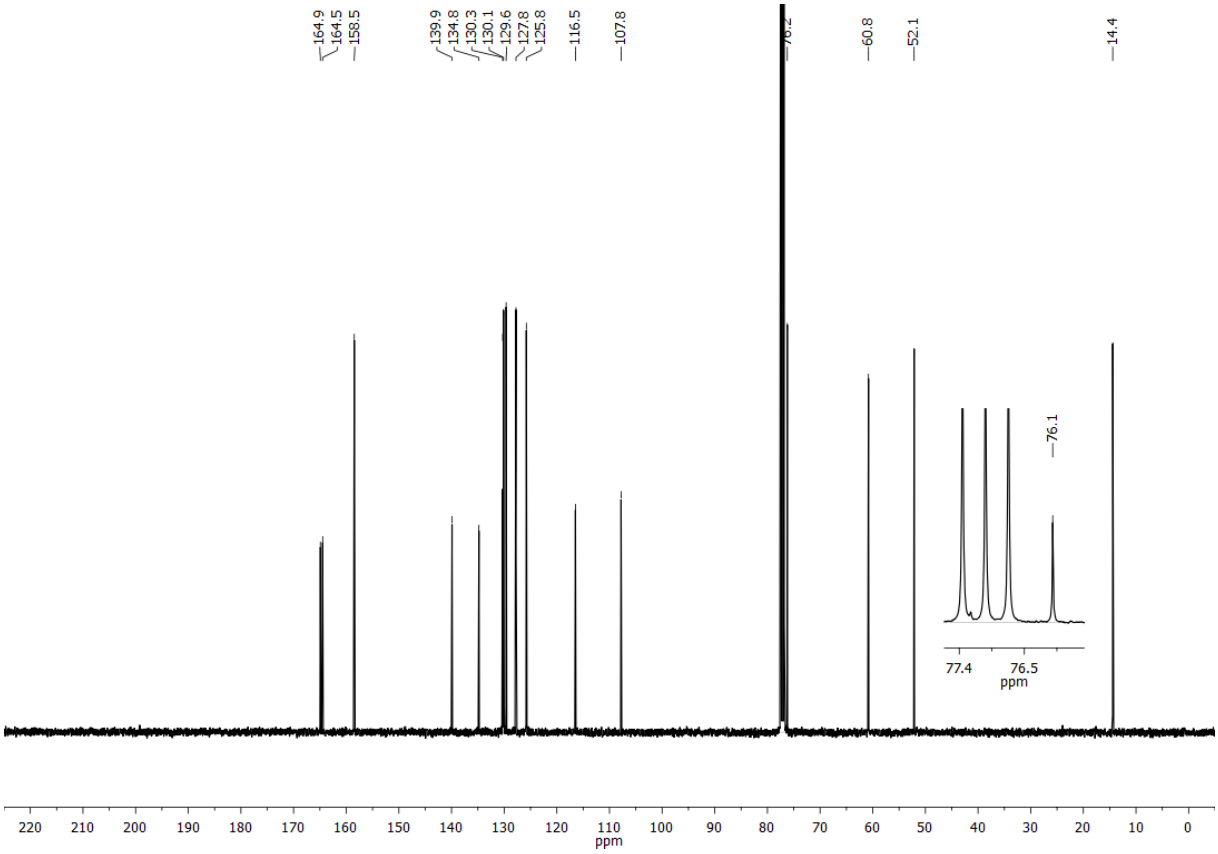
Compound **16h** ^{13}**C-NMR** ($CDCl_3$)



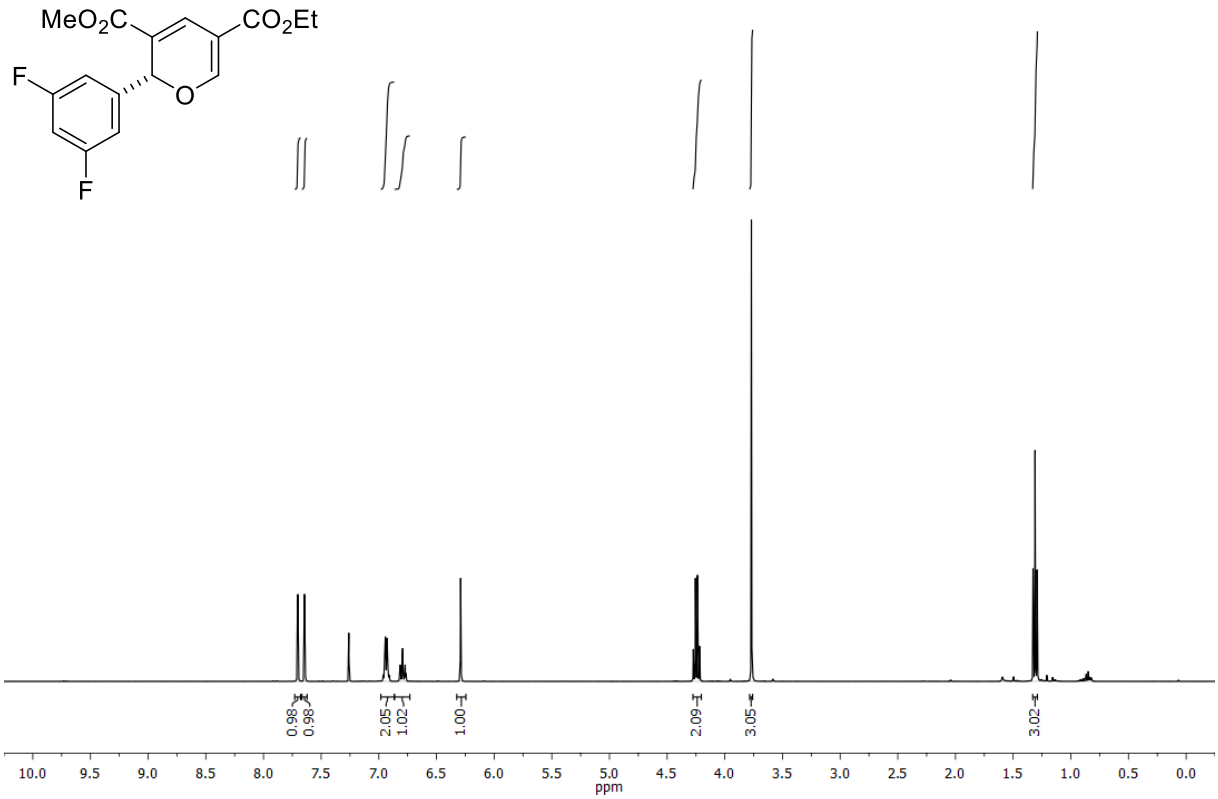
Compound **16i** ^{1}**H-NMR** ($CDCl_3$)



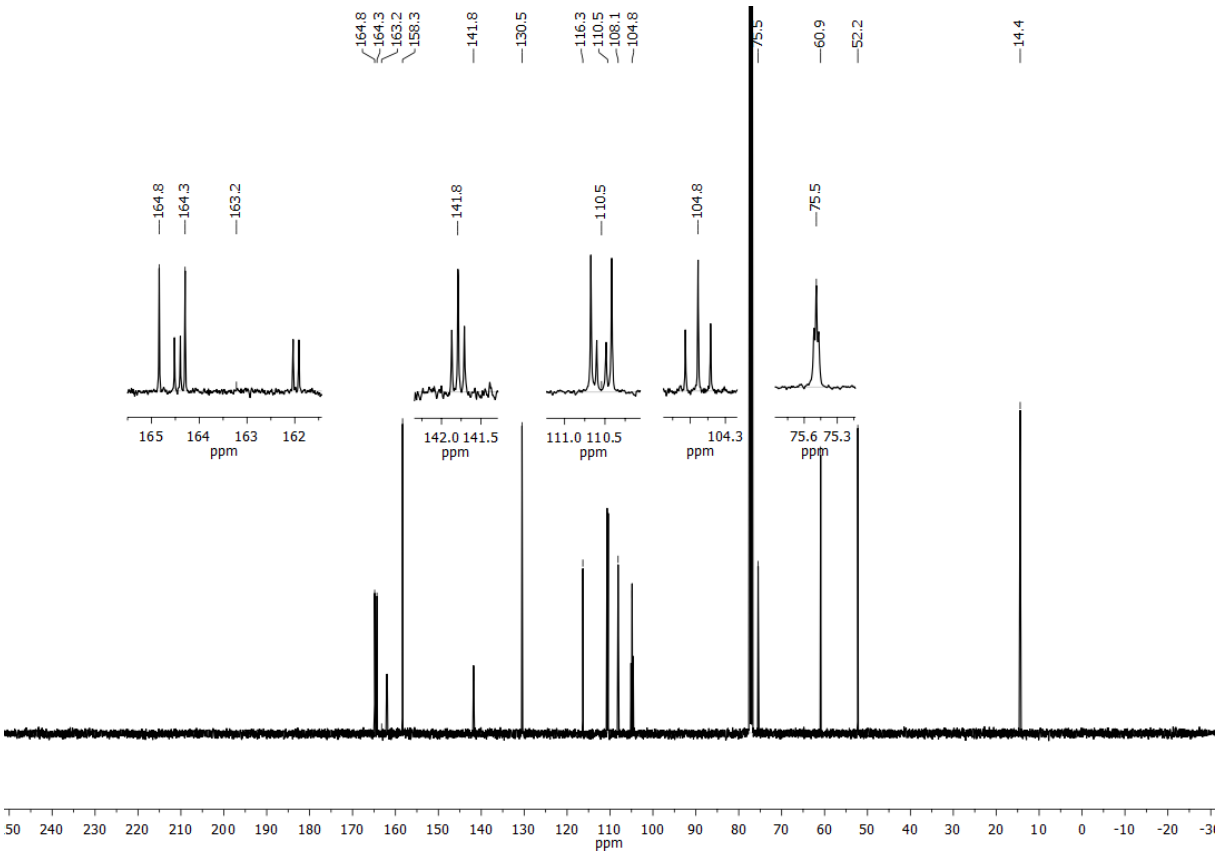
Compound **16i** ^{13}**C-NMR** ($CDCl_3$)



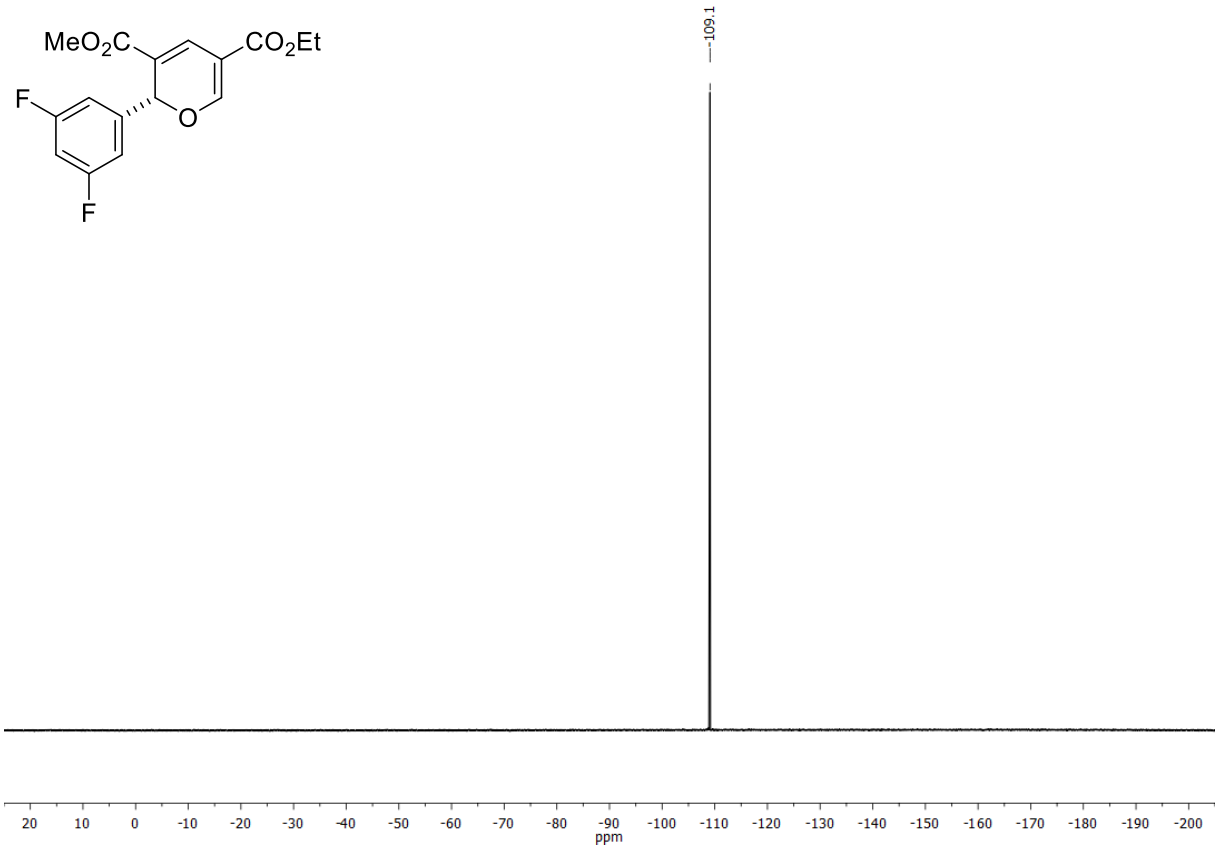
Compound **16j** ^{1}**H-NMR** ($CDCl_3$)



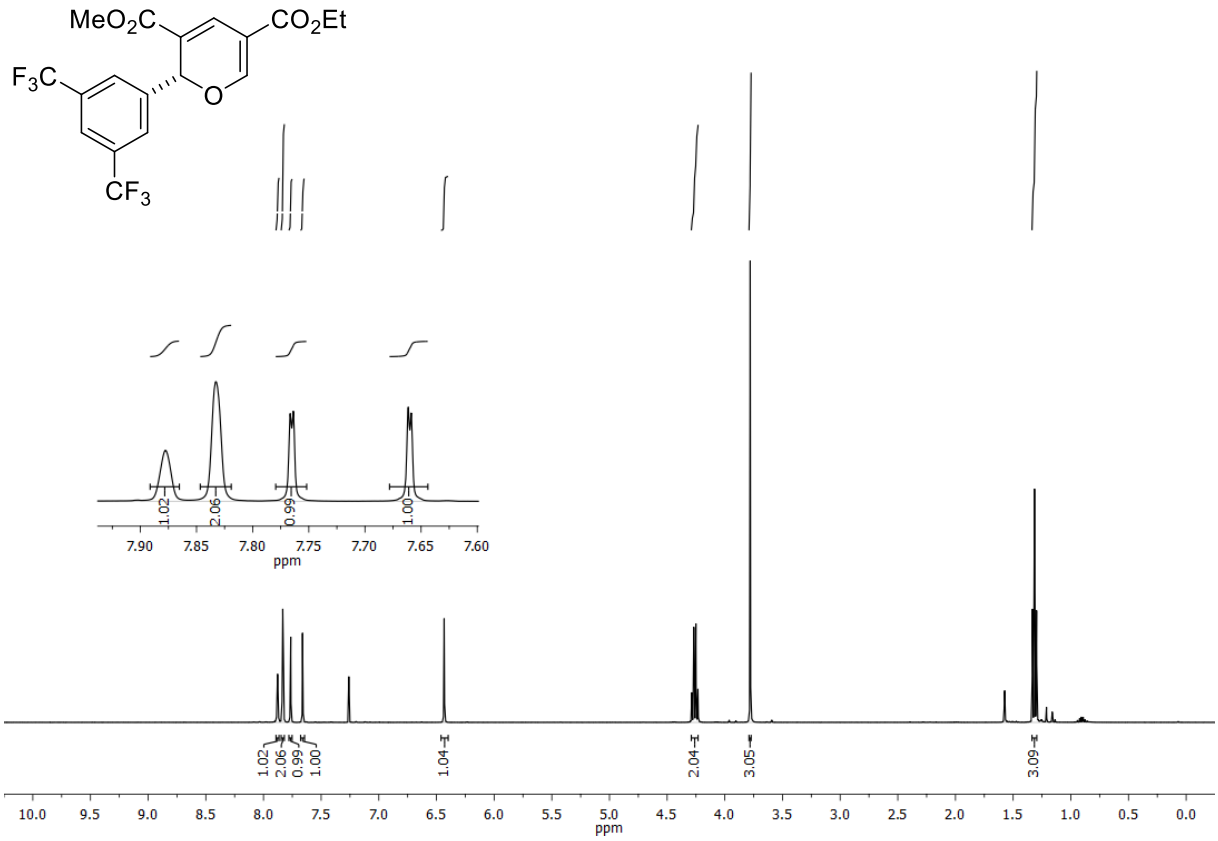
Compound **16j** ^{13}**C-NMR** ($CDCl_3$)



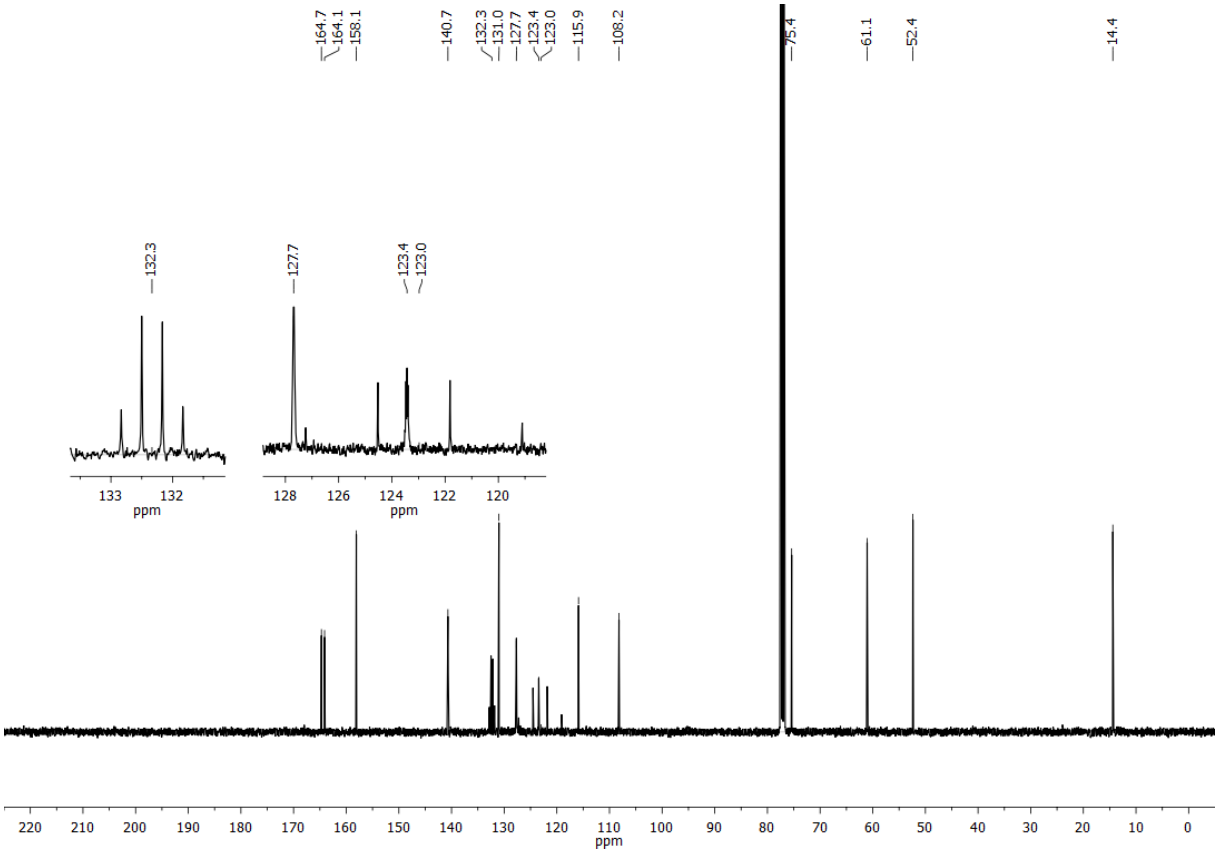
Compound **16j** **^{19}F-NMR** ($CDCl_3$)



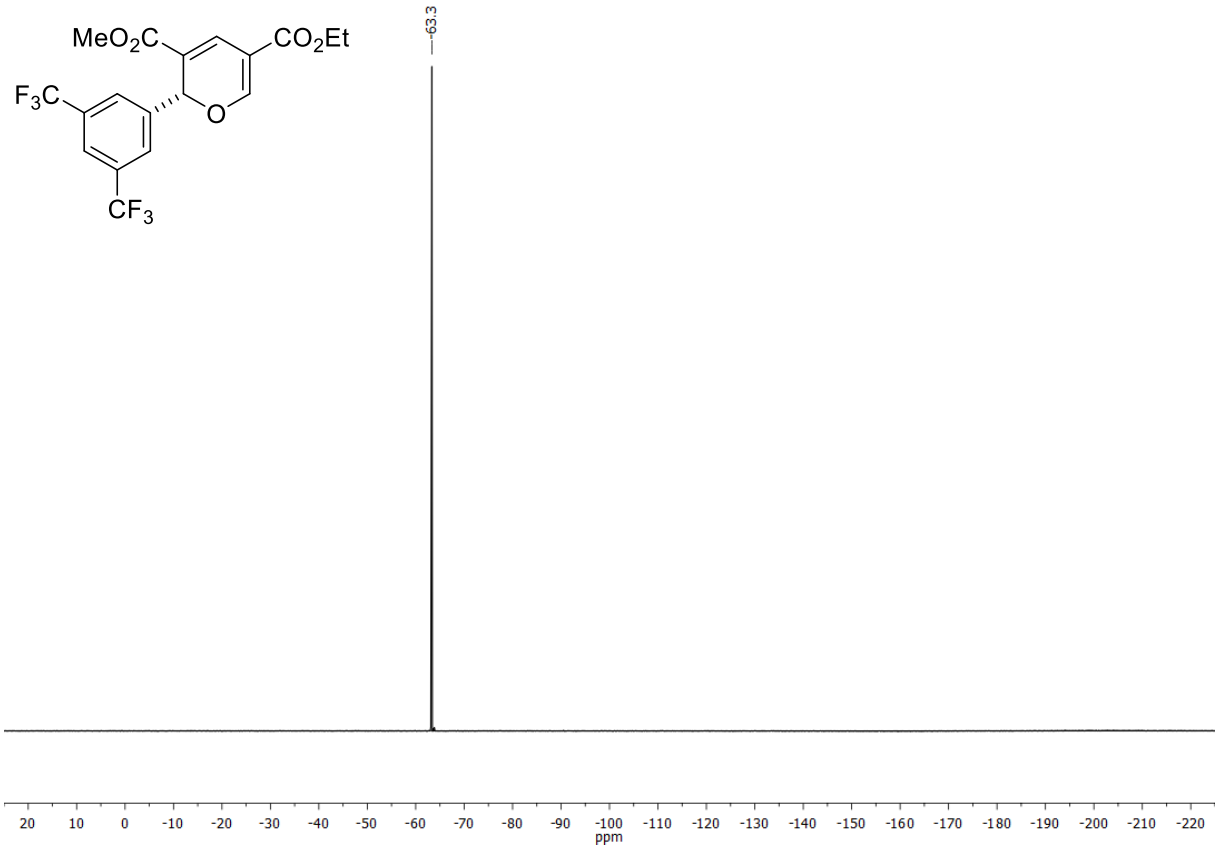
Compound **16k** ^{1}**H-NMR** ($CDCl_3$)



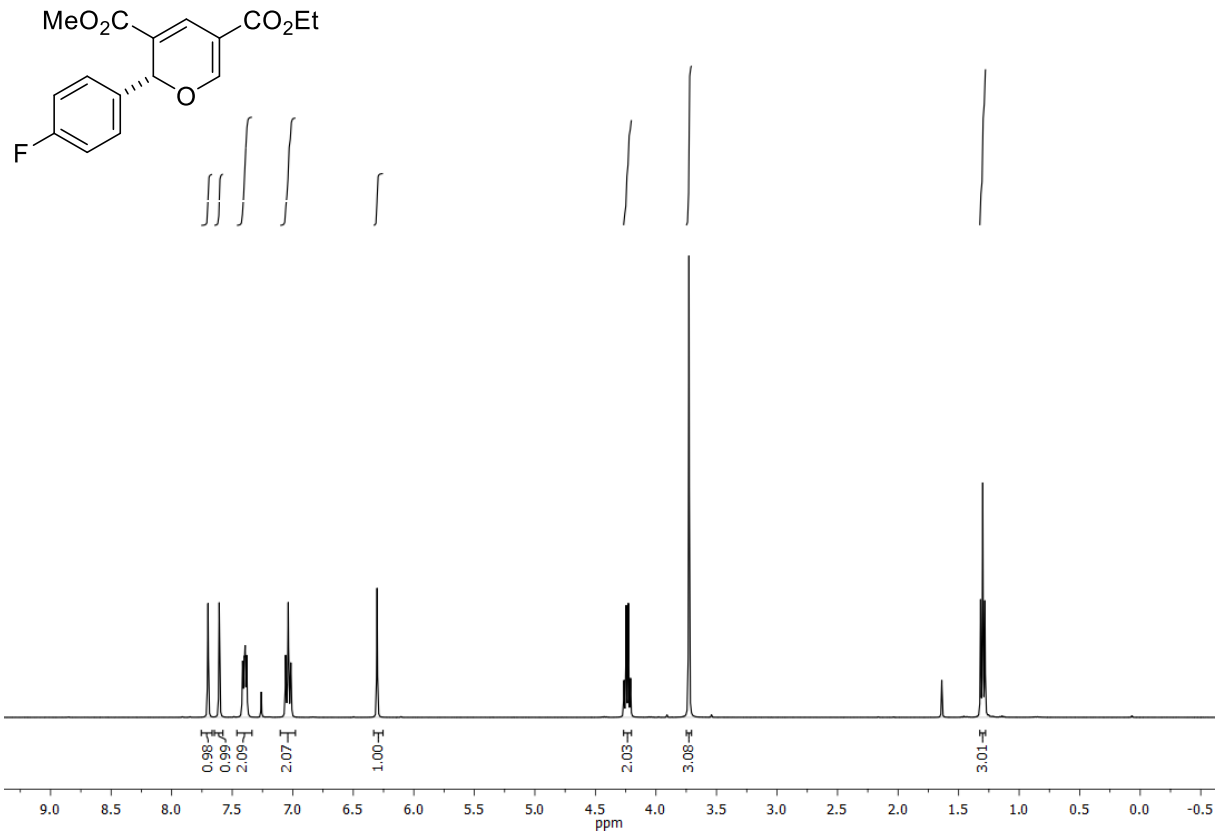
Compound **16k** ^{13}**C-NMR** ($CDCl_3$)



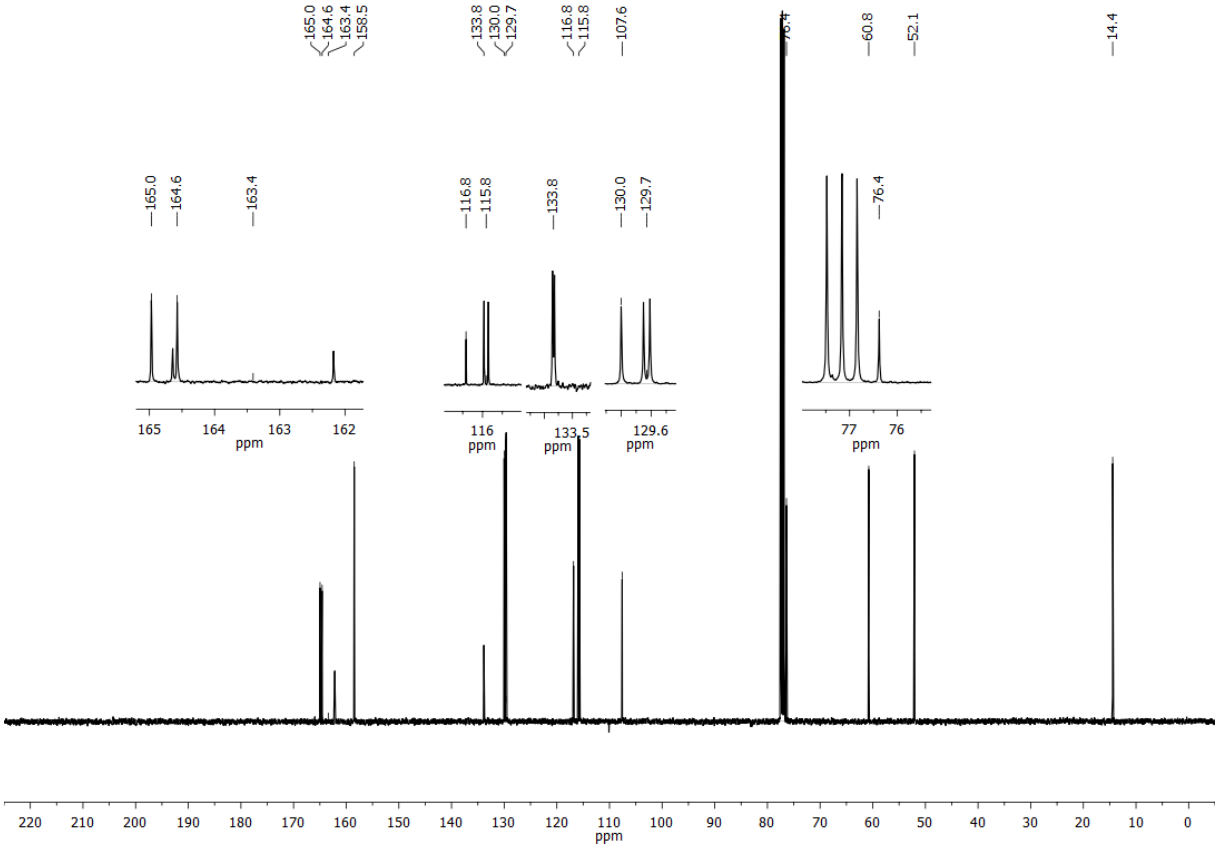
Compound **16k** **^{19}F-NMR** ($CDCl_3$)



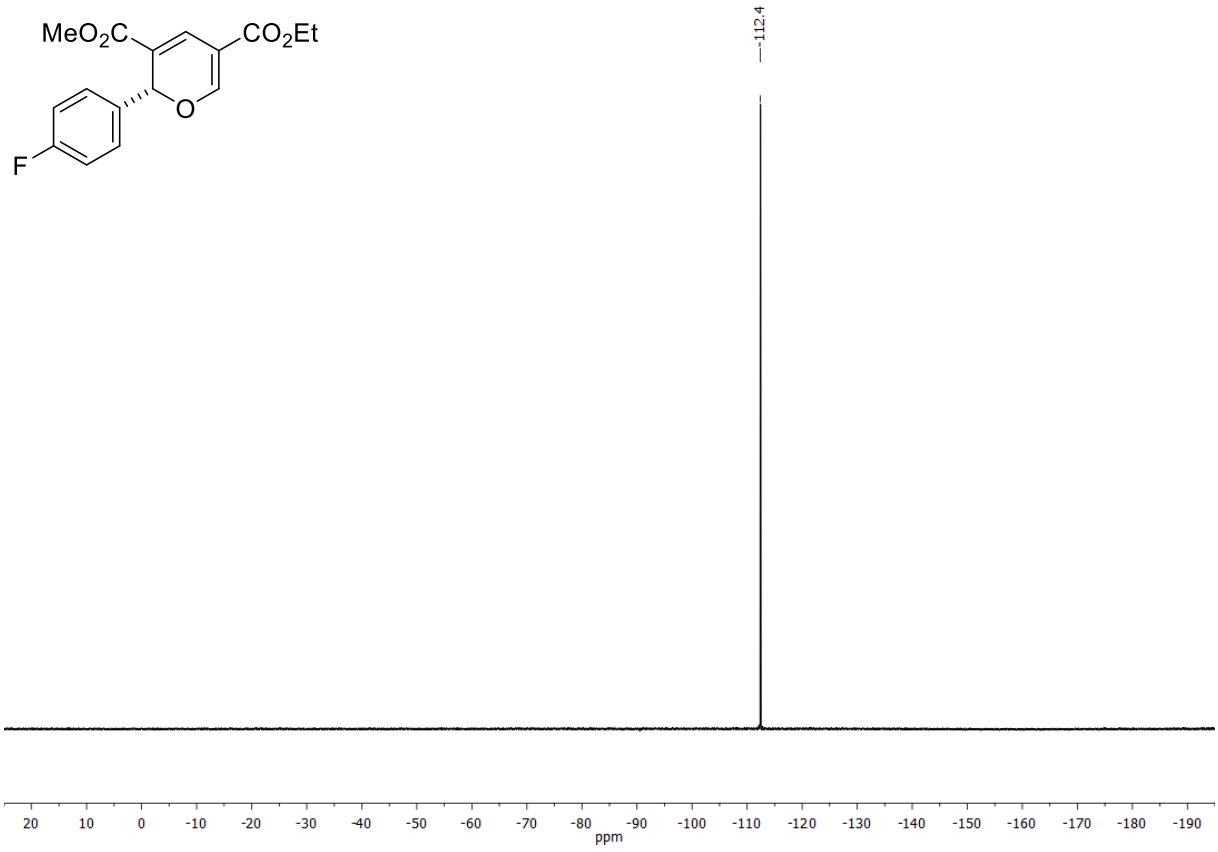
Compound **16l** ^{1}**H-NMR** ($CDCl_3$)



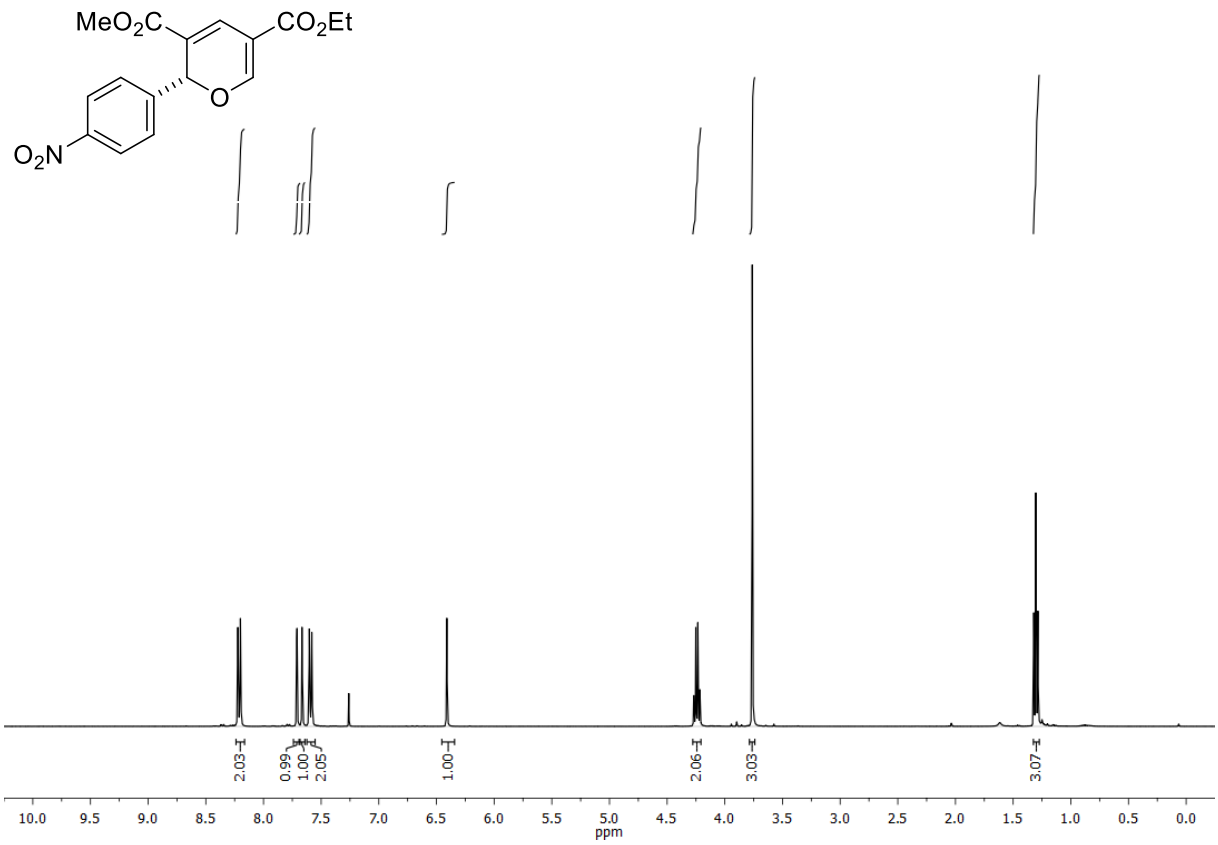
Compound **16l** ^{13}**C-NMR** ($CDCl_3$)



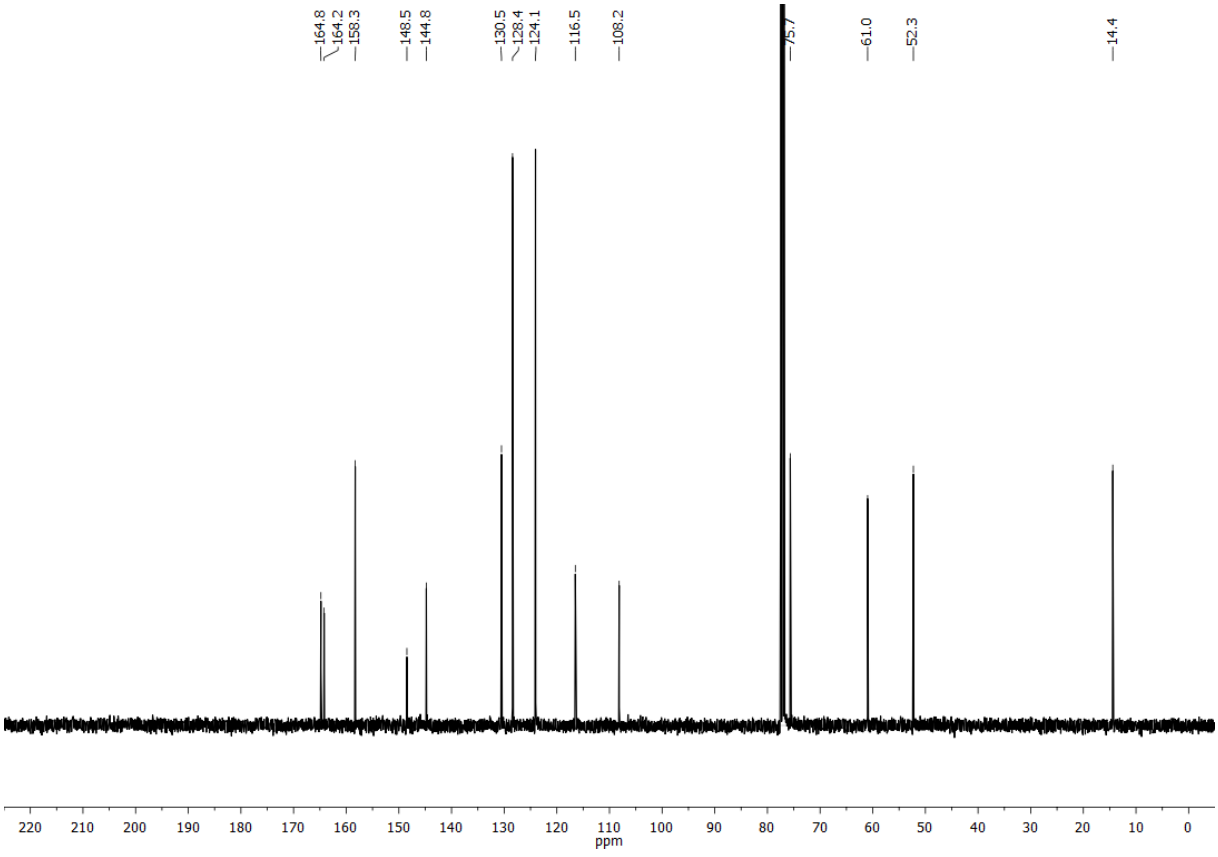
Compound **16l** **^{19}F-NMR** ($CDCl_3$)



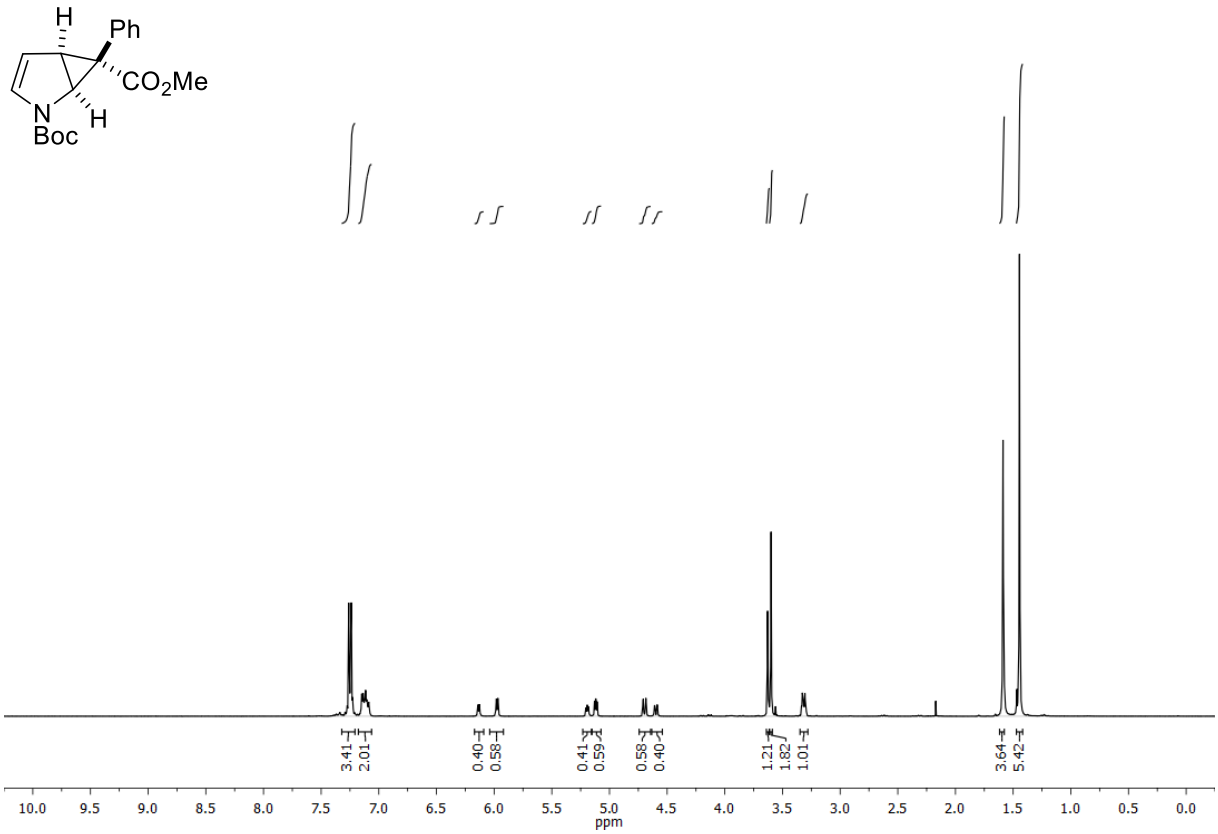
Compound **16m** ^{1}**H-NMR** ($CDCl_3$)



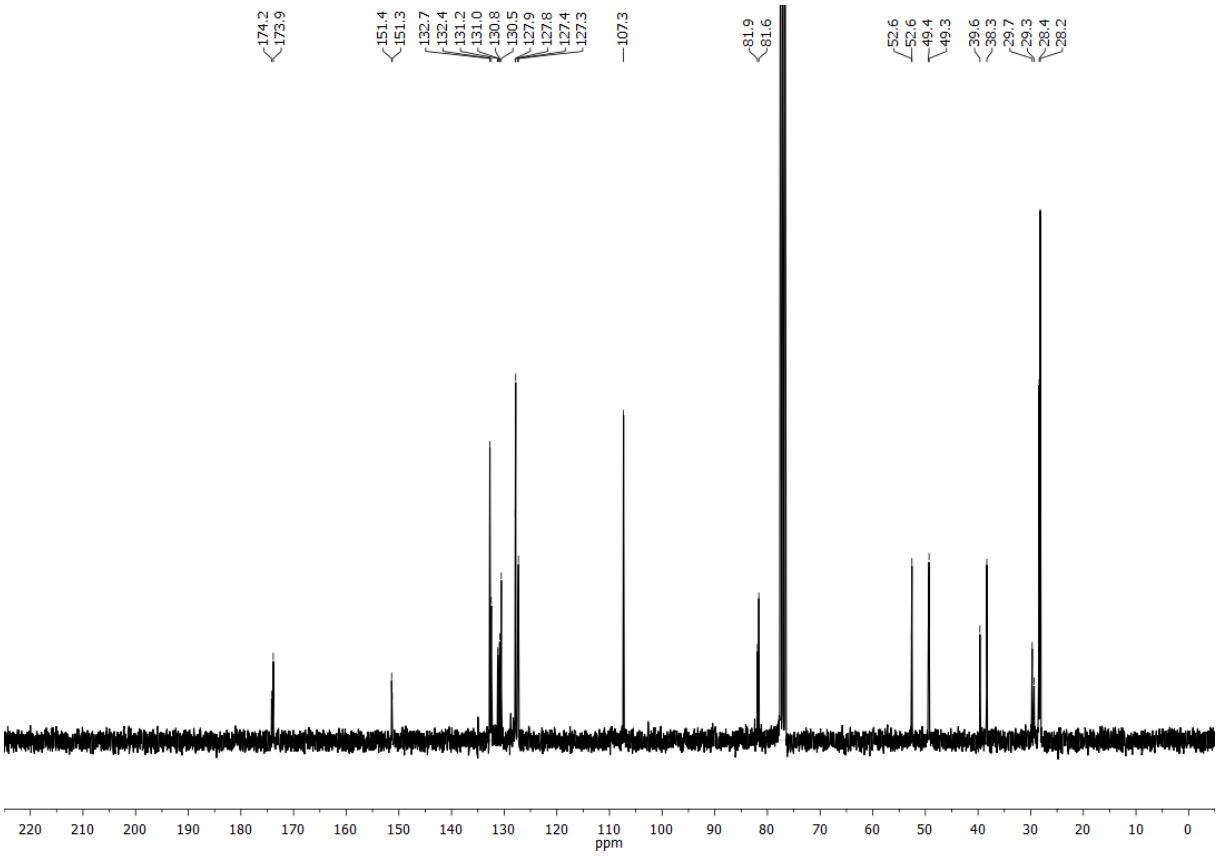
Compound **16m** ^{13}**C-NMR** ($CDCl_3$)



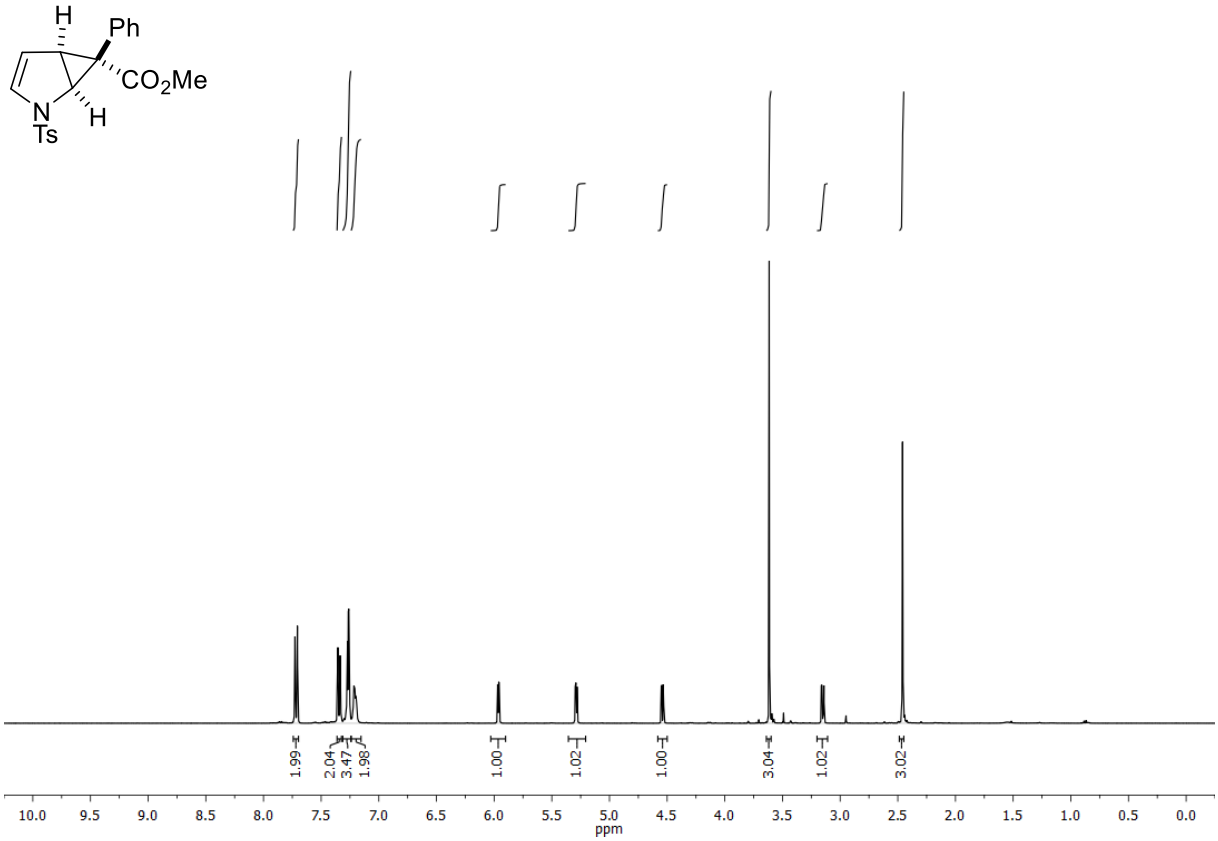
Compound **17-Boc** ^{1}**H-NMR** ($CDCl_3$)



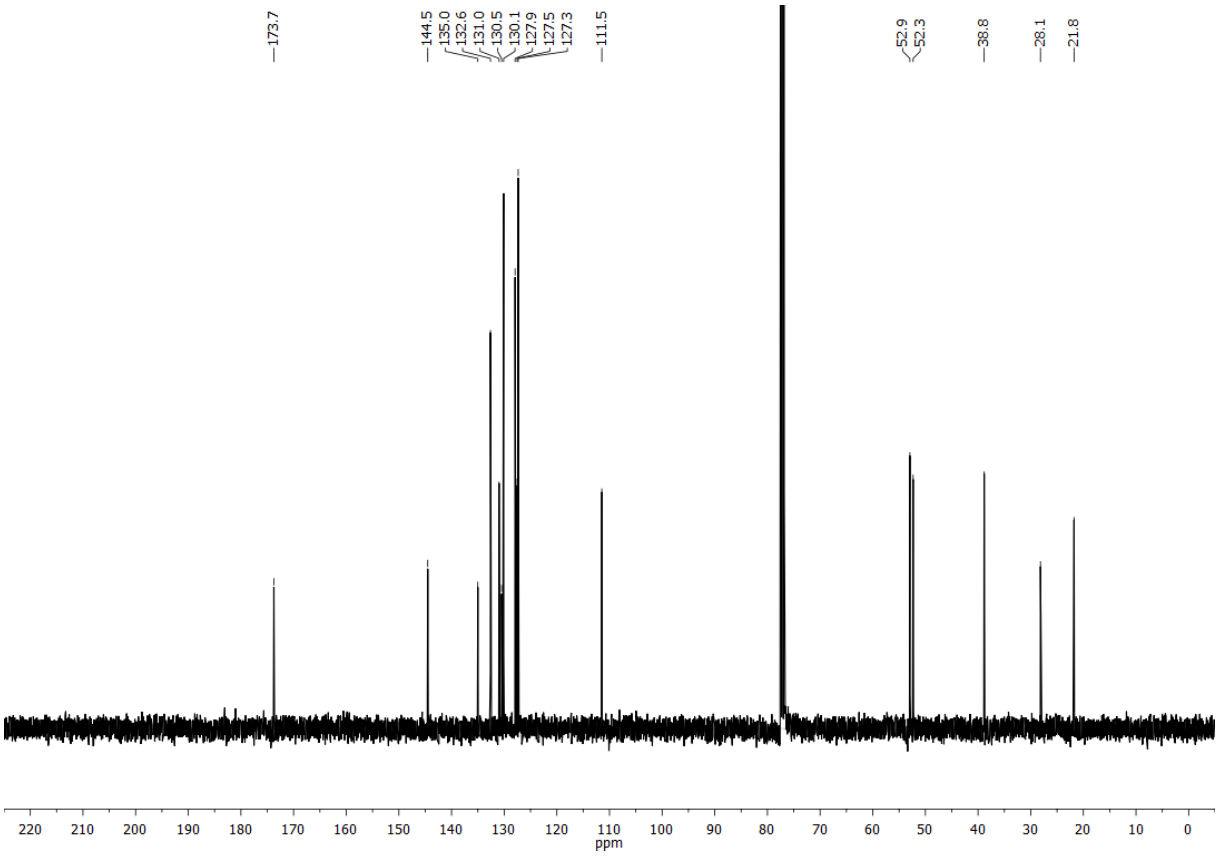
Compound **17-Boc** ^{13}**C-NMR** ($CDCl_3$)



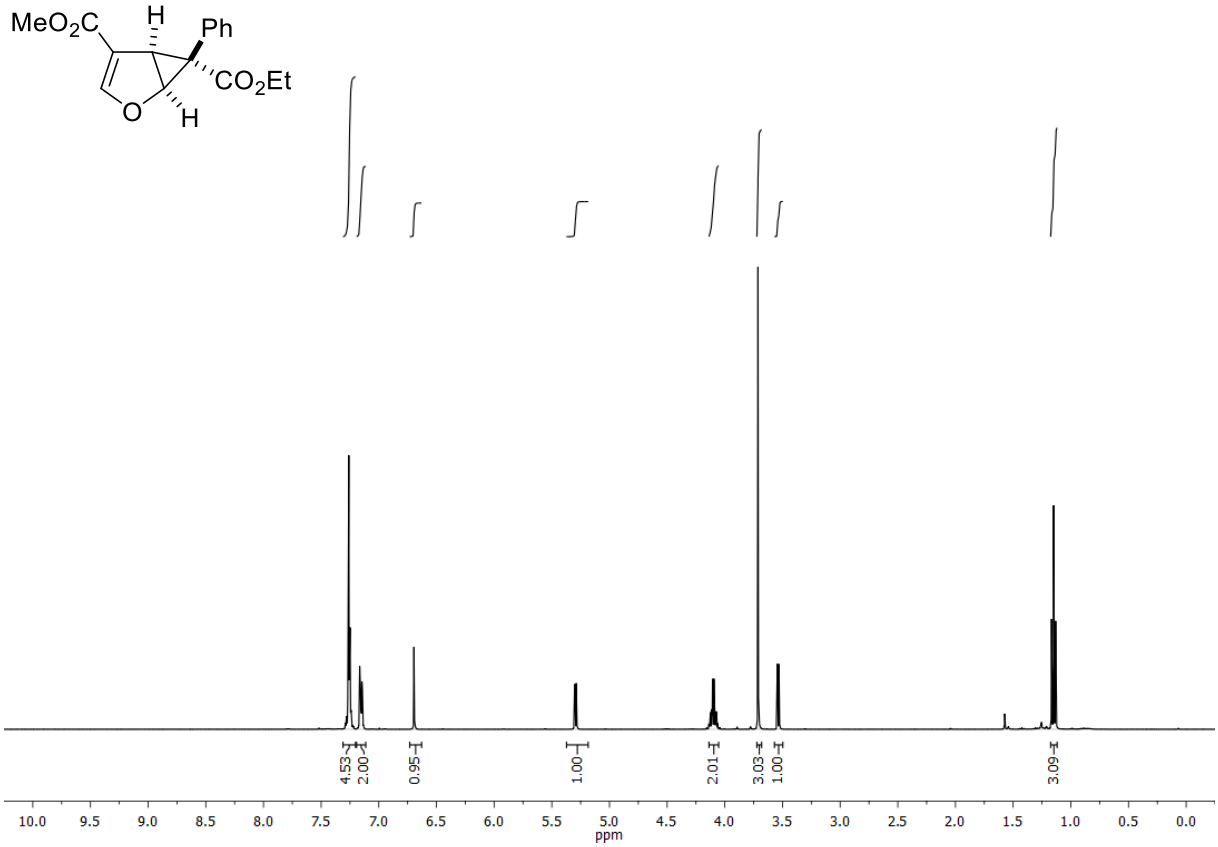
Compound **17-Ts ^{1}H-NMR** ($CDCl_3$)



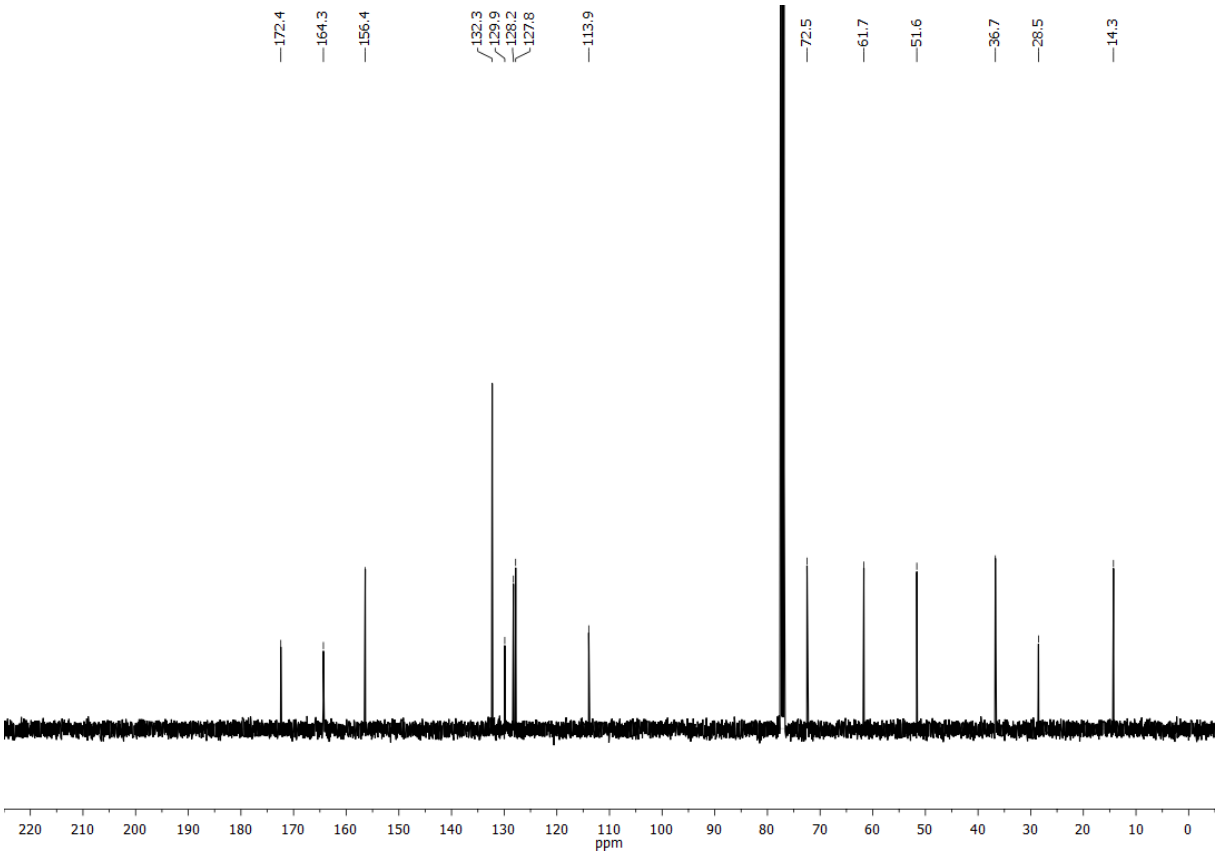
Compound **17-Ts ^{13}C-NMR** ($CDCl_3$)



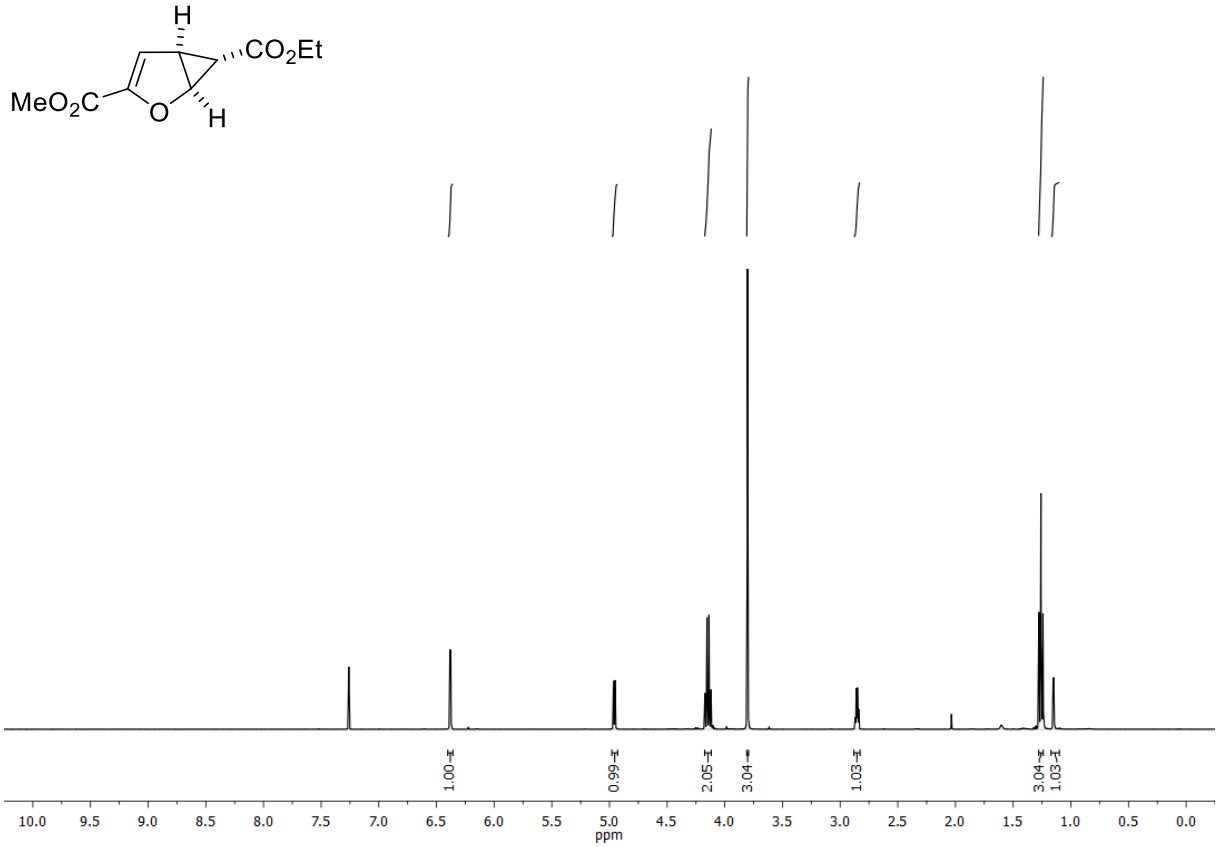
Compound **18** **^{1}H-NMR** ($CDCl_3$)



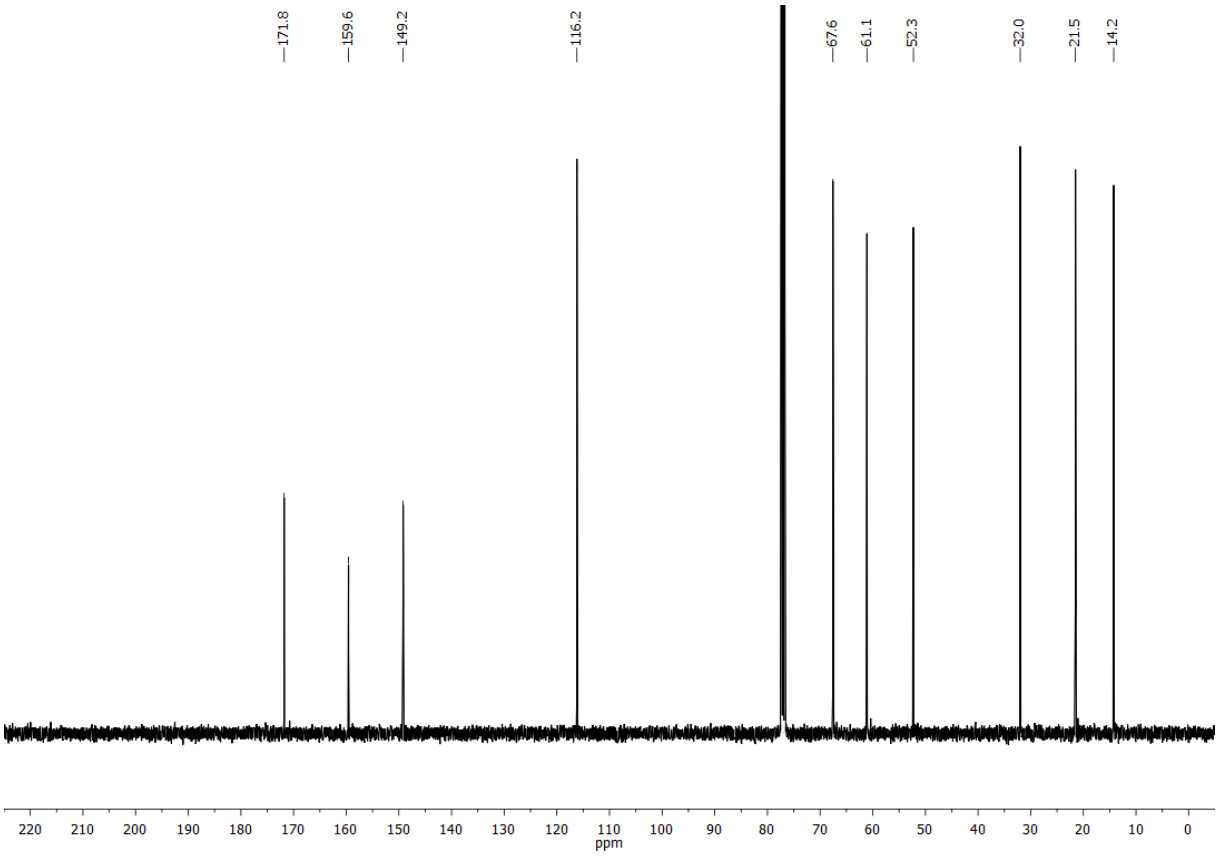
Compound **18** **^{13}C-NMR** ($CDCl_3$)



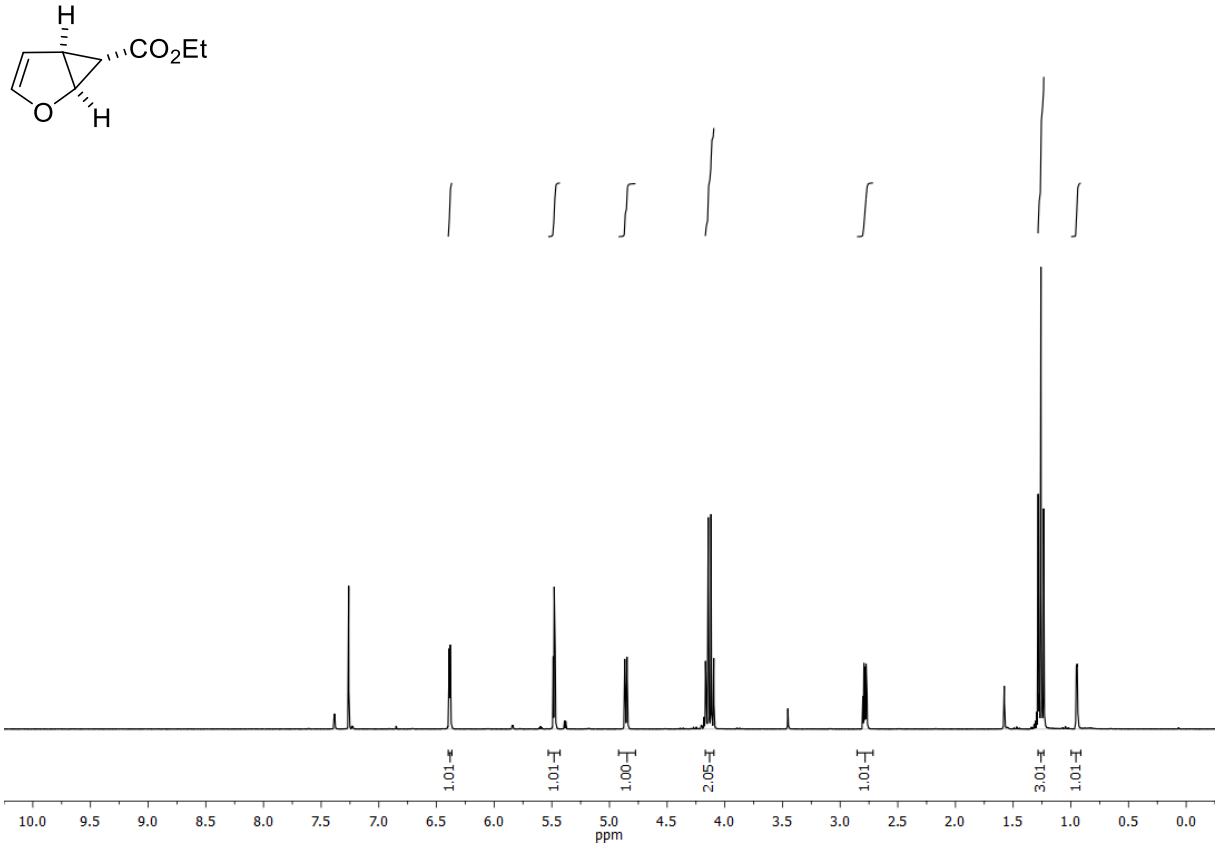
Compound **30** ^{1}**H-NMR** ($CDCl_3$)



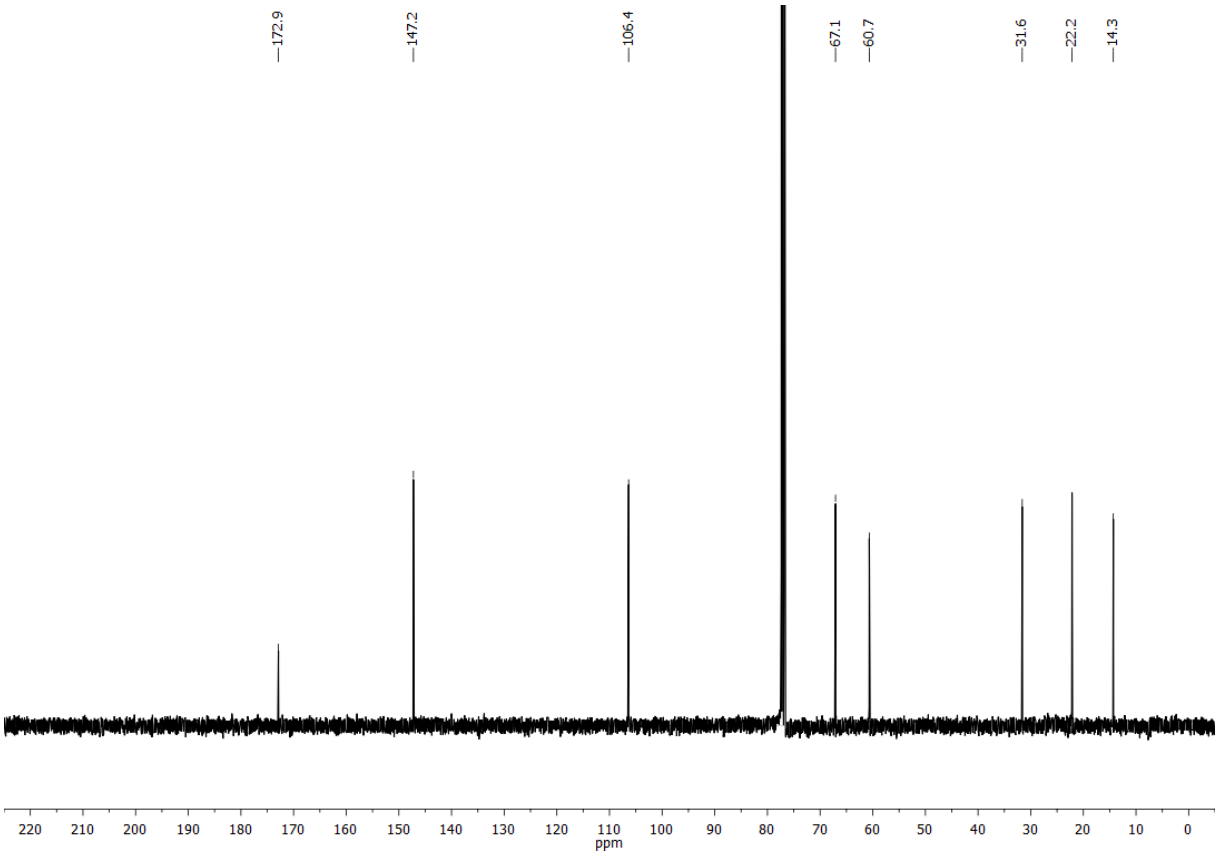
Compound **30** ^{13}**C-NMR** ($CDCl_3$)



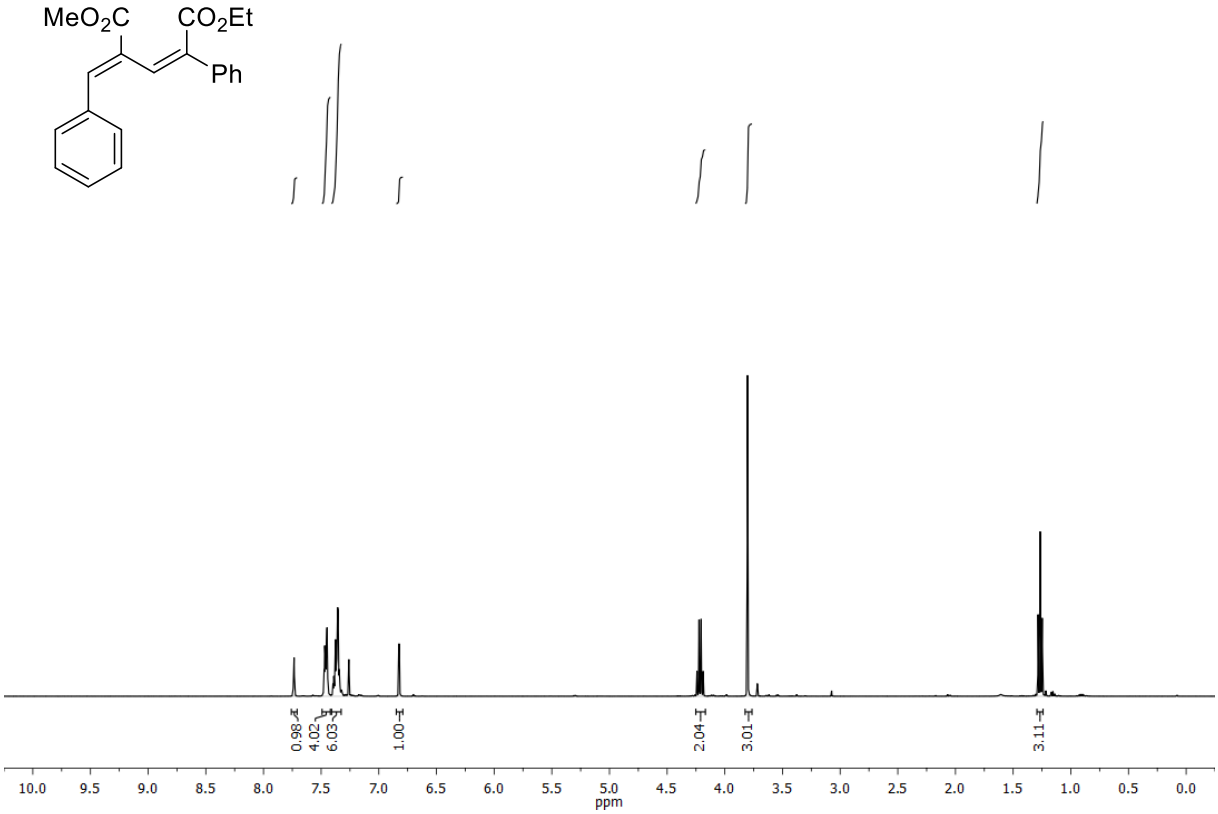
Compound **32** **^{1}H-NMR** ($CDCl_3$)



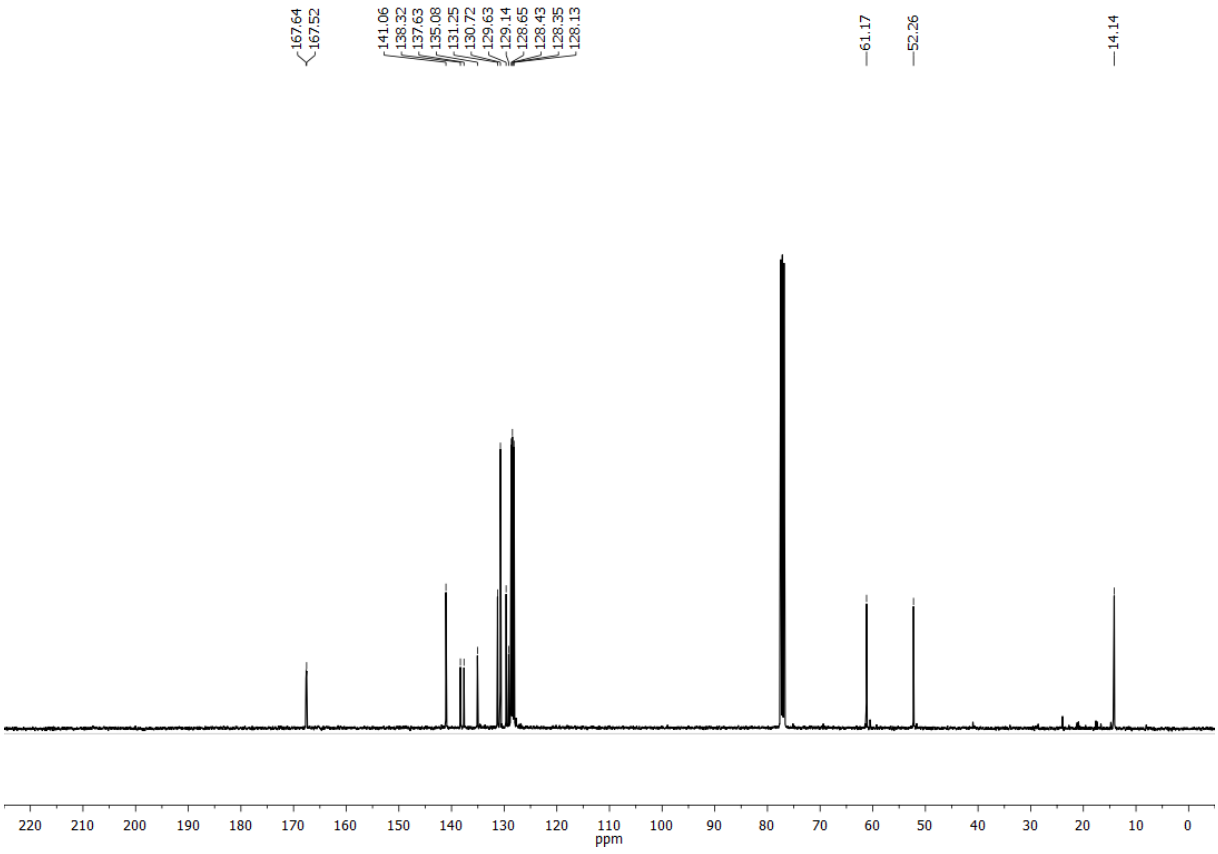
Compound **32** **^{13}C-NMR** ($CDCl_3$)



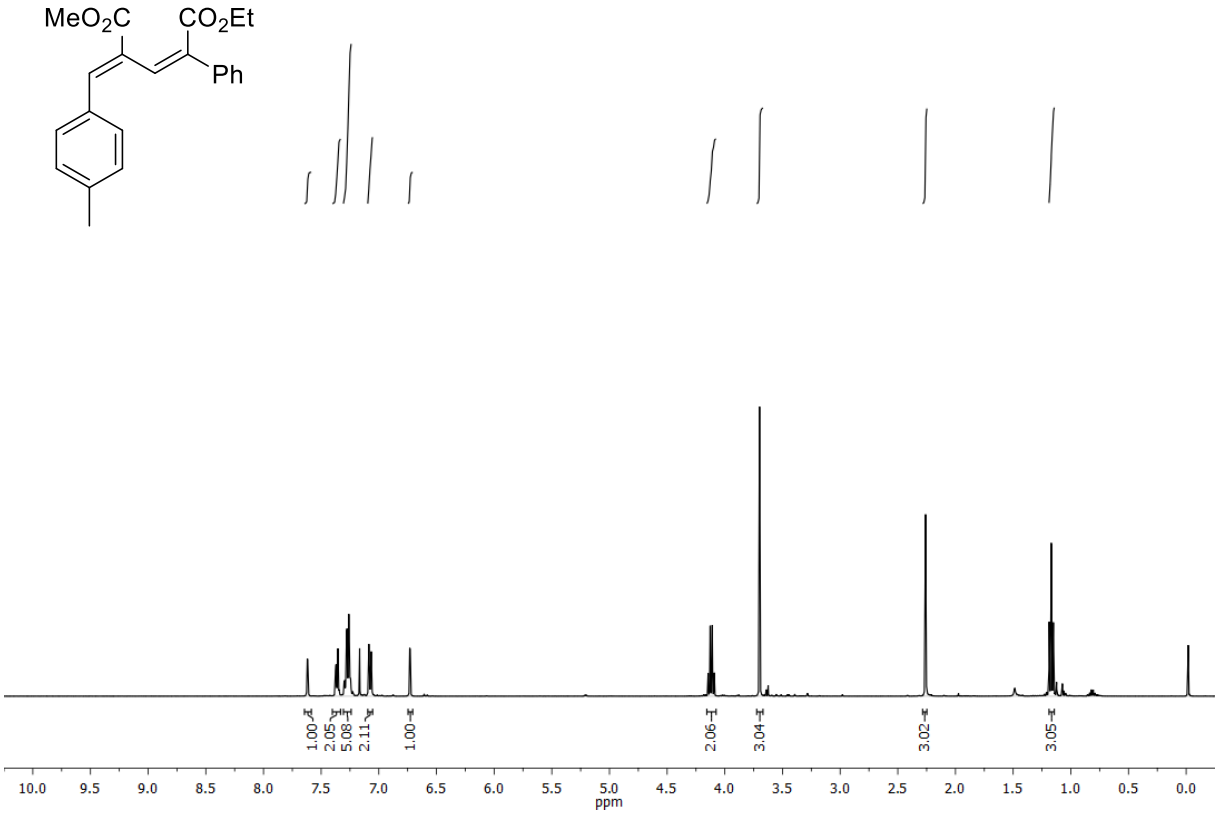
Compound **44a** **^{1}H-NMR** ($CDCl_3$)



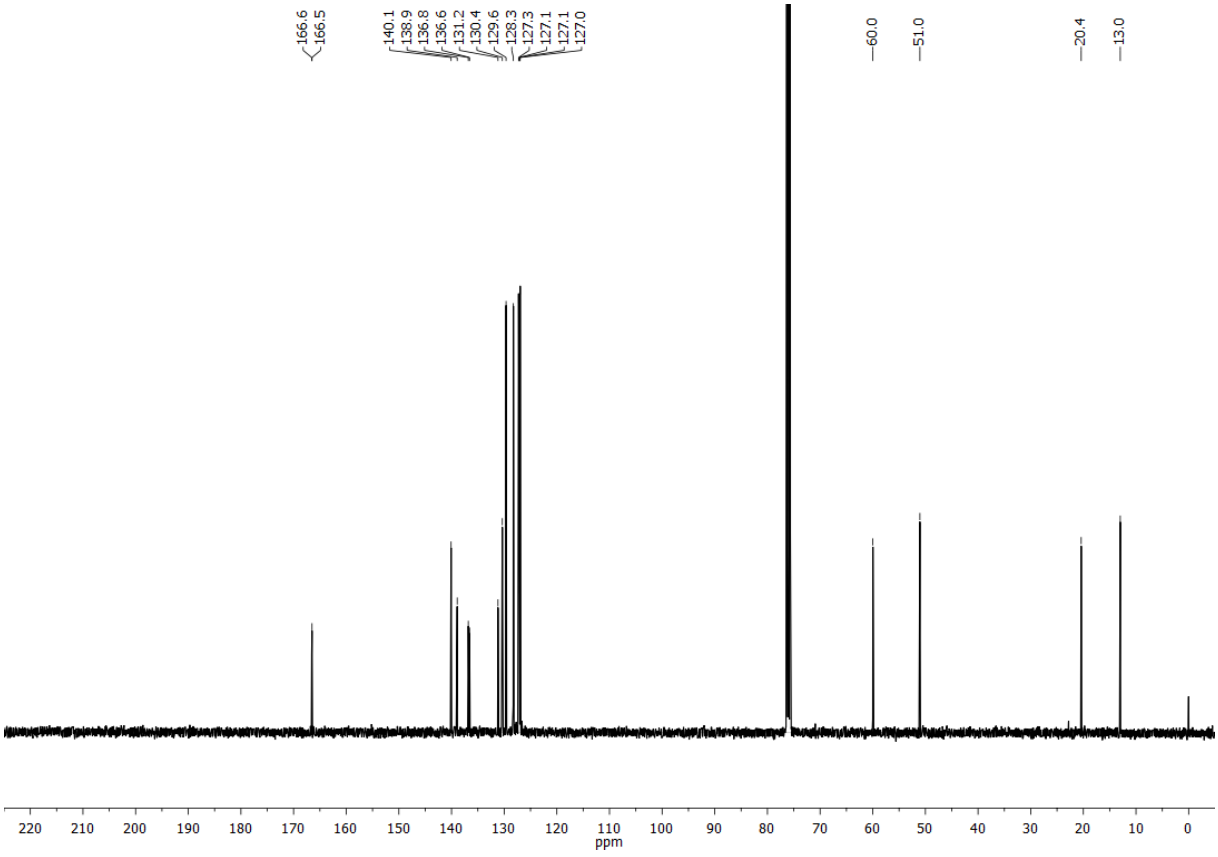
Compound **44a** **^{13}C-NMR** ($CDCl_3$)



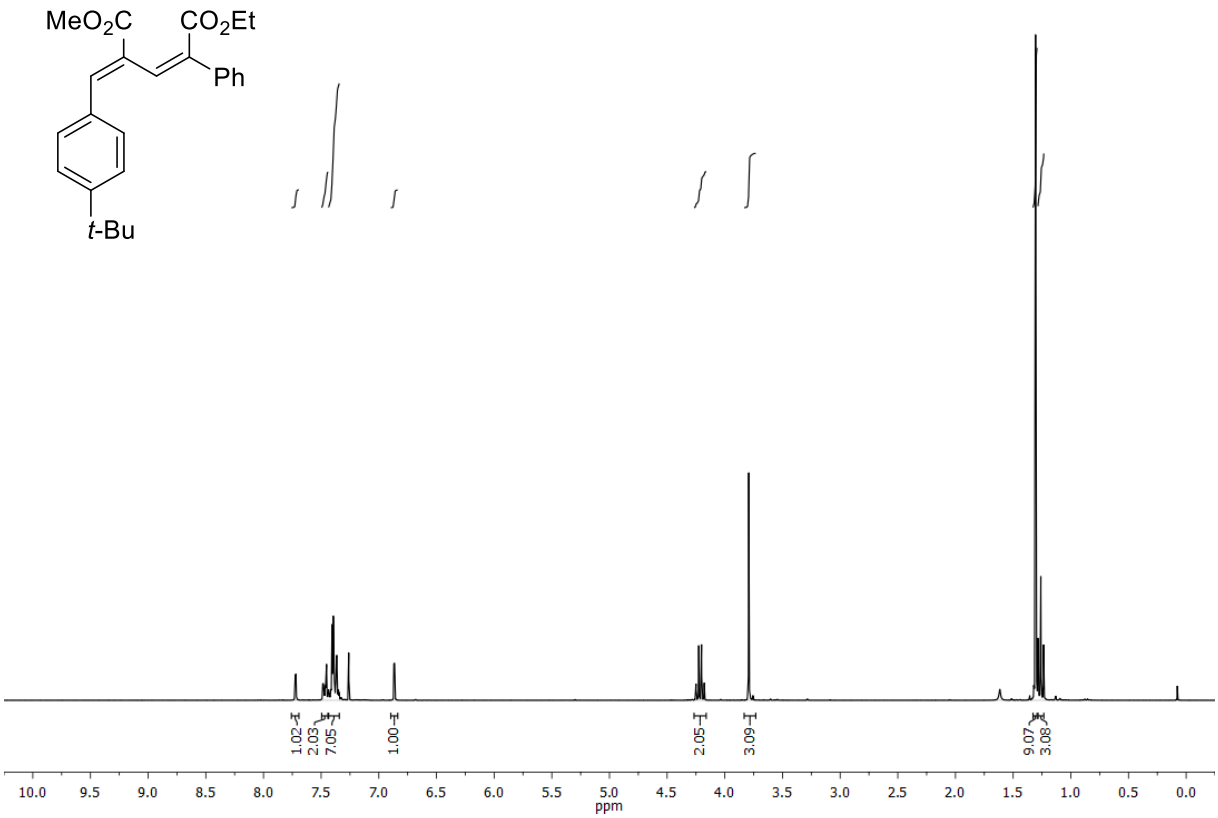
Compound **44b** ^{1}**H-NMR** ($CDCl_3$)



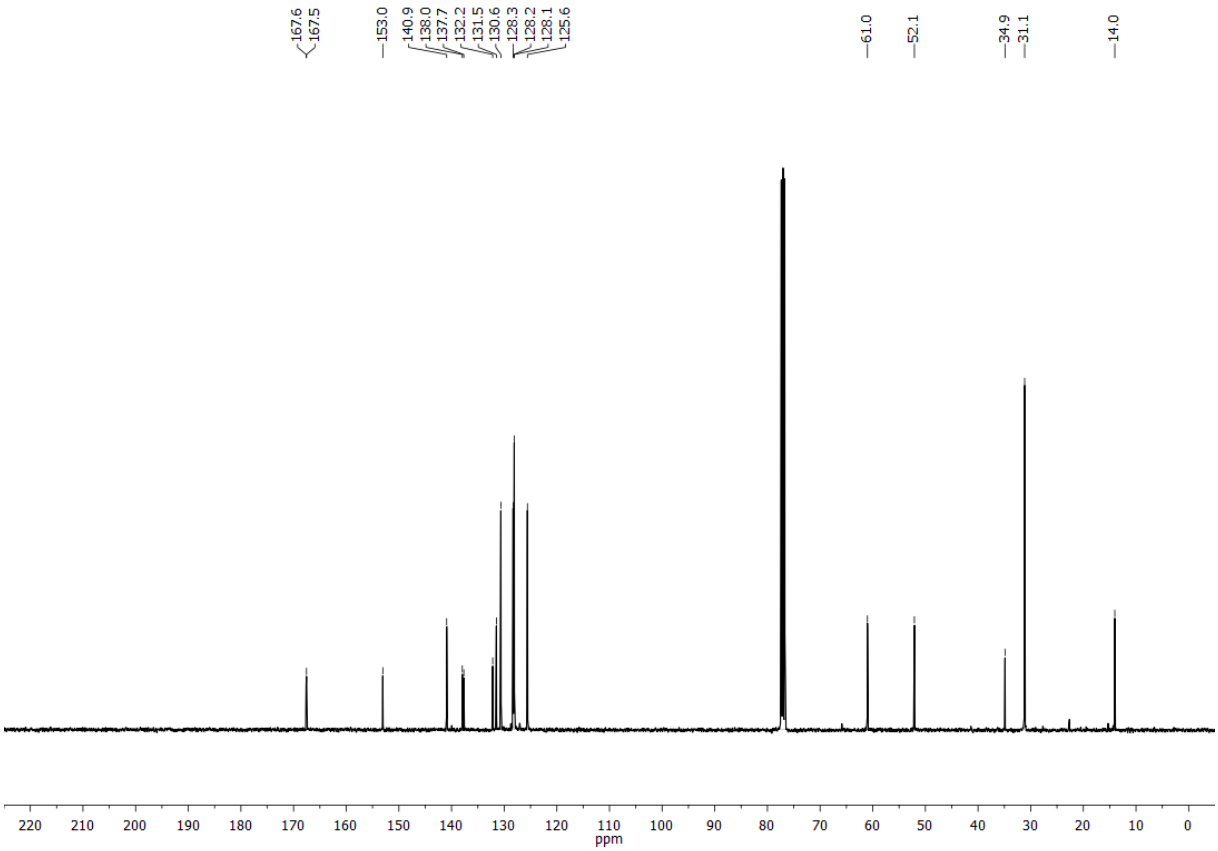
Compound **44b** ^{13}**C-NMR** ($CDCl_3$)



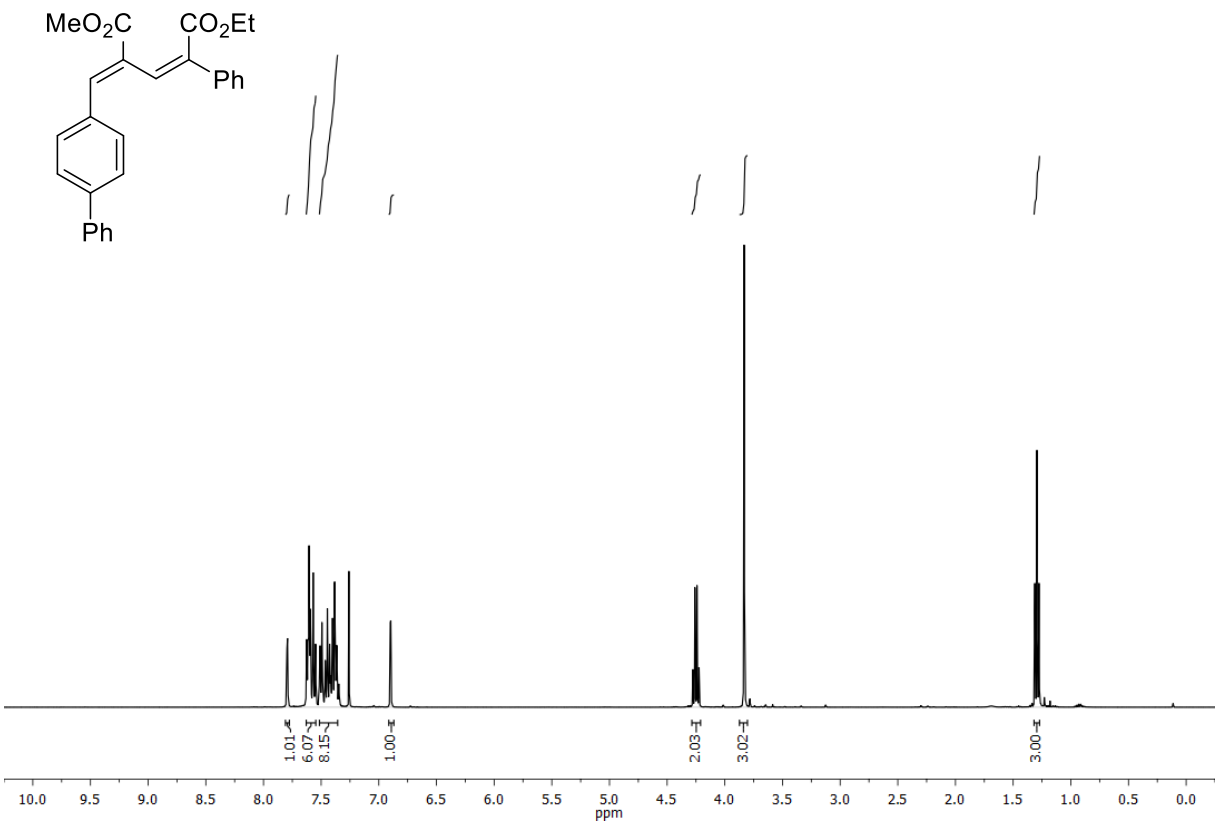
Compound **44c** ^{1}**H-NMR** ($CDCl_3$)



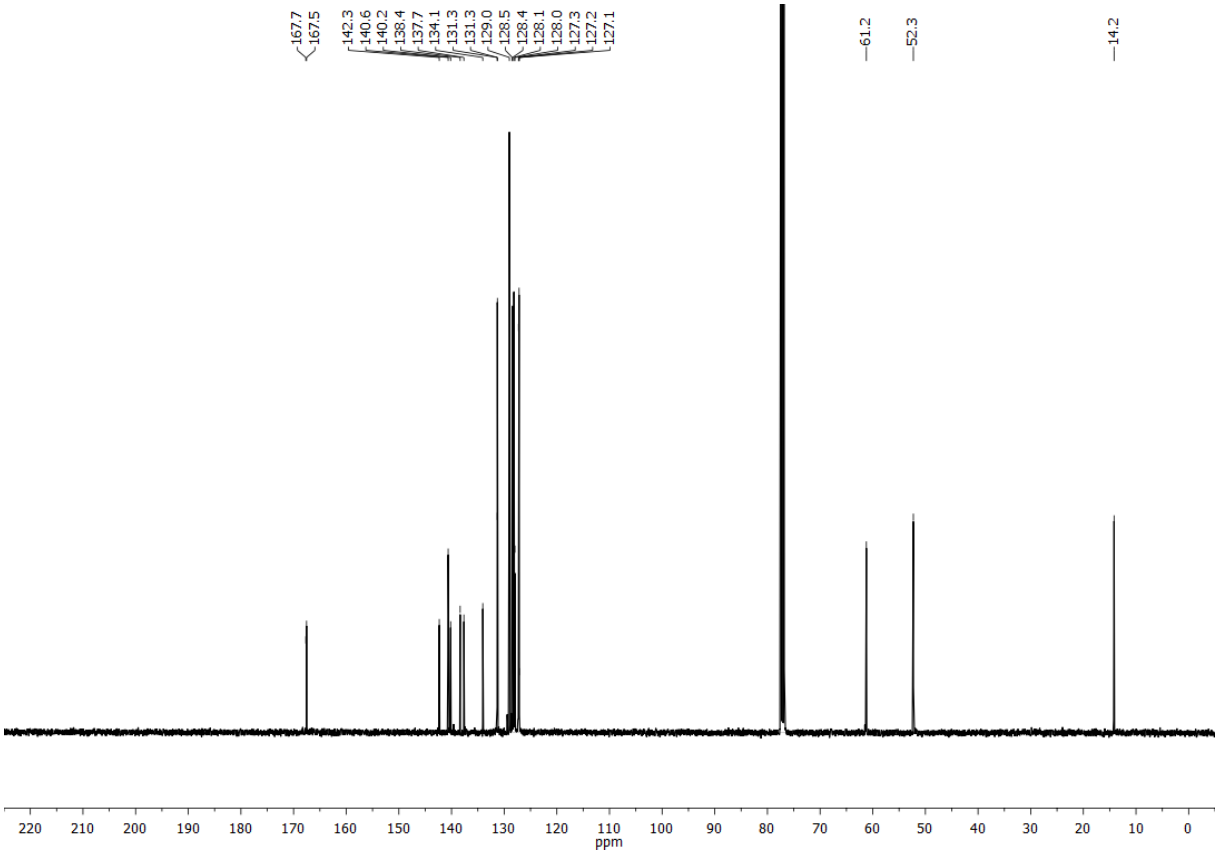
Compound **44c** ^{13}**C-NMR** ($CDCl_3$)



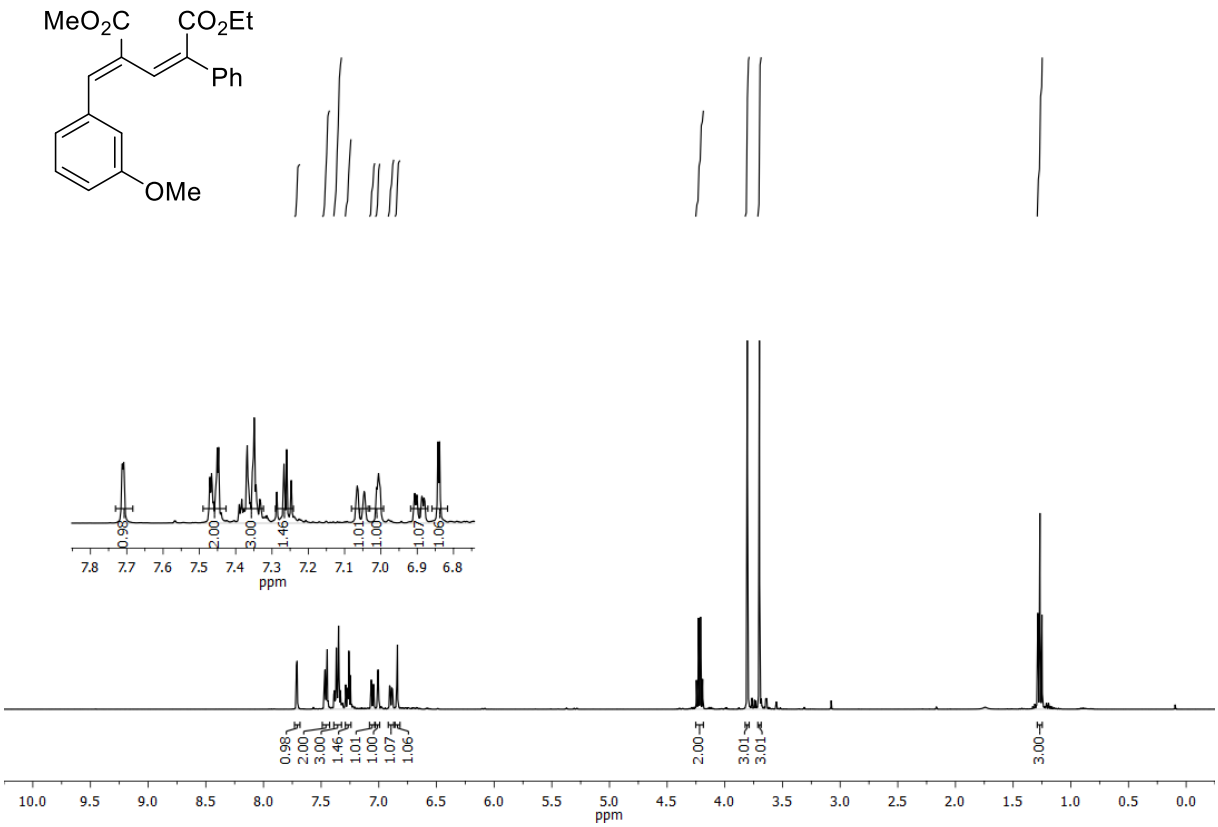
Compound **44d** ^{1}**H-NMR** ($CDCl_3$)



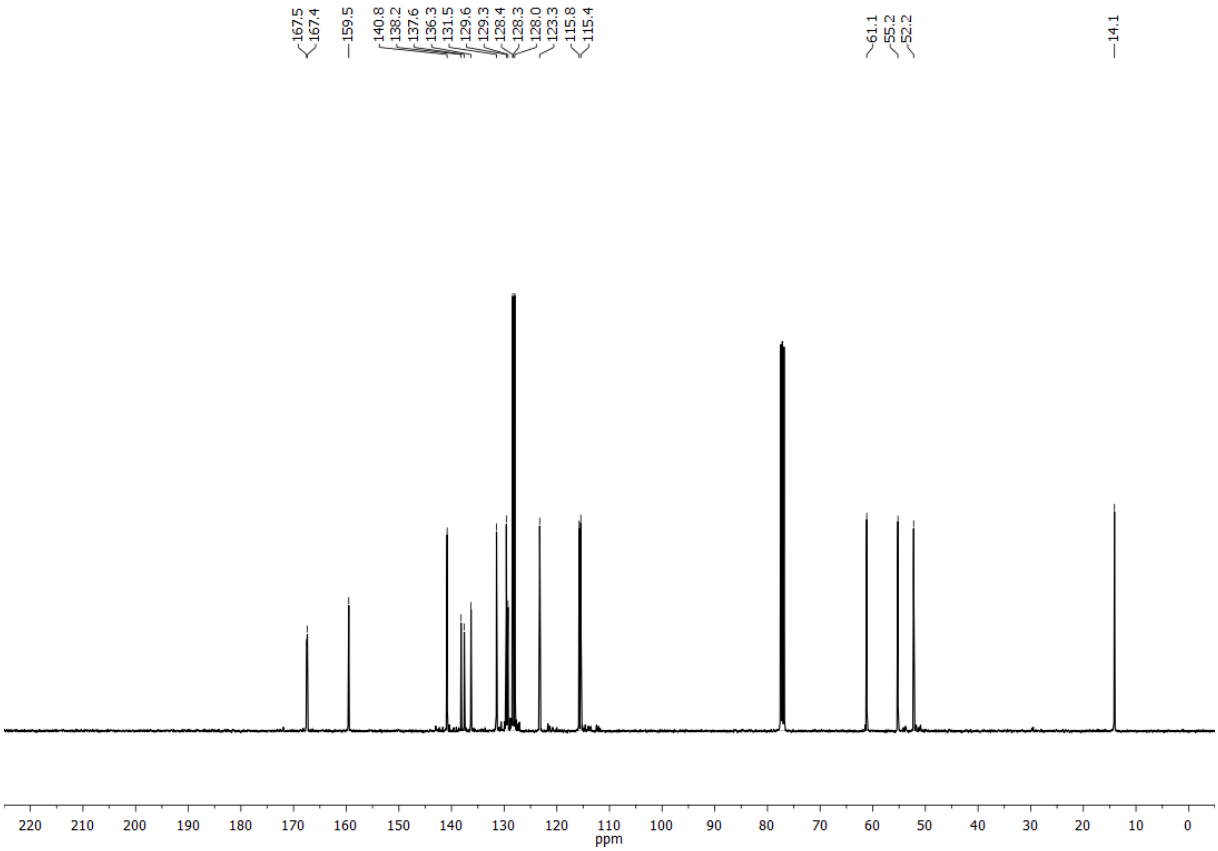
Compound **44d** ^{13}**C-NMR** ($CDCl_3$)



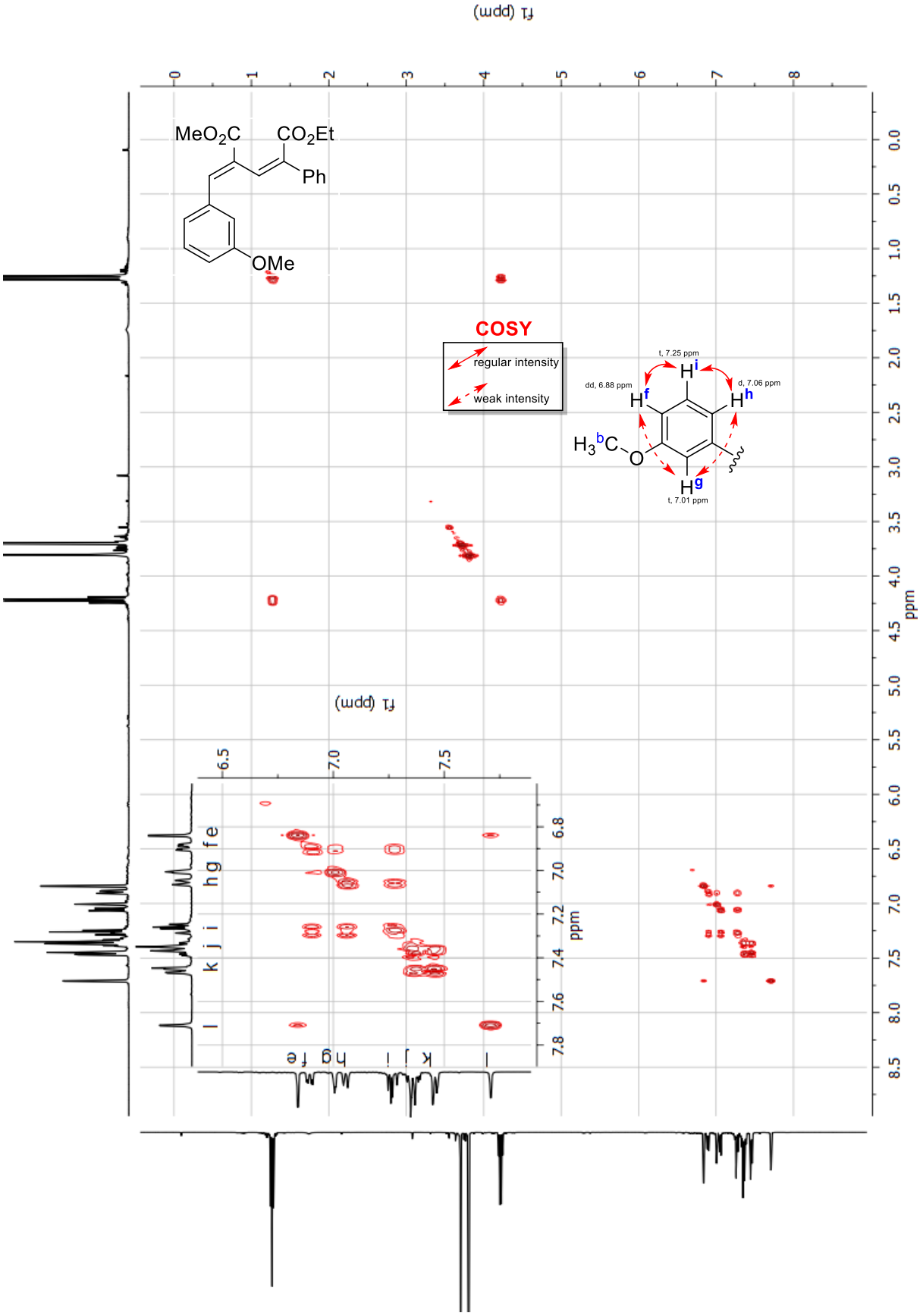
Compound **44e** **^{1}H-NMR** ($CDCl_3$)



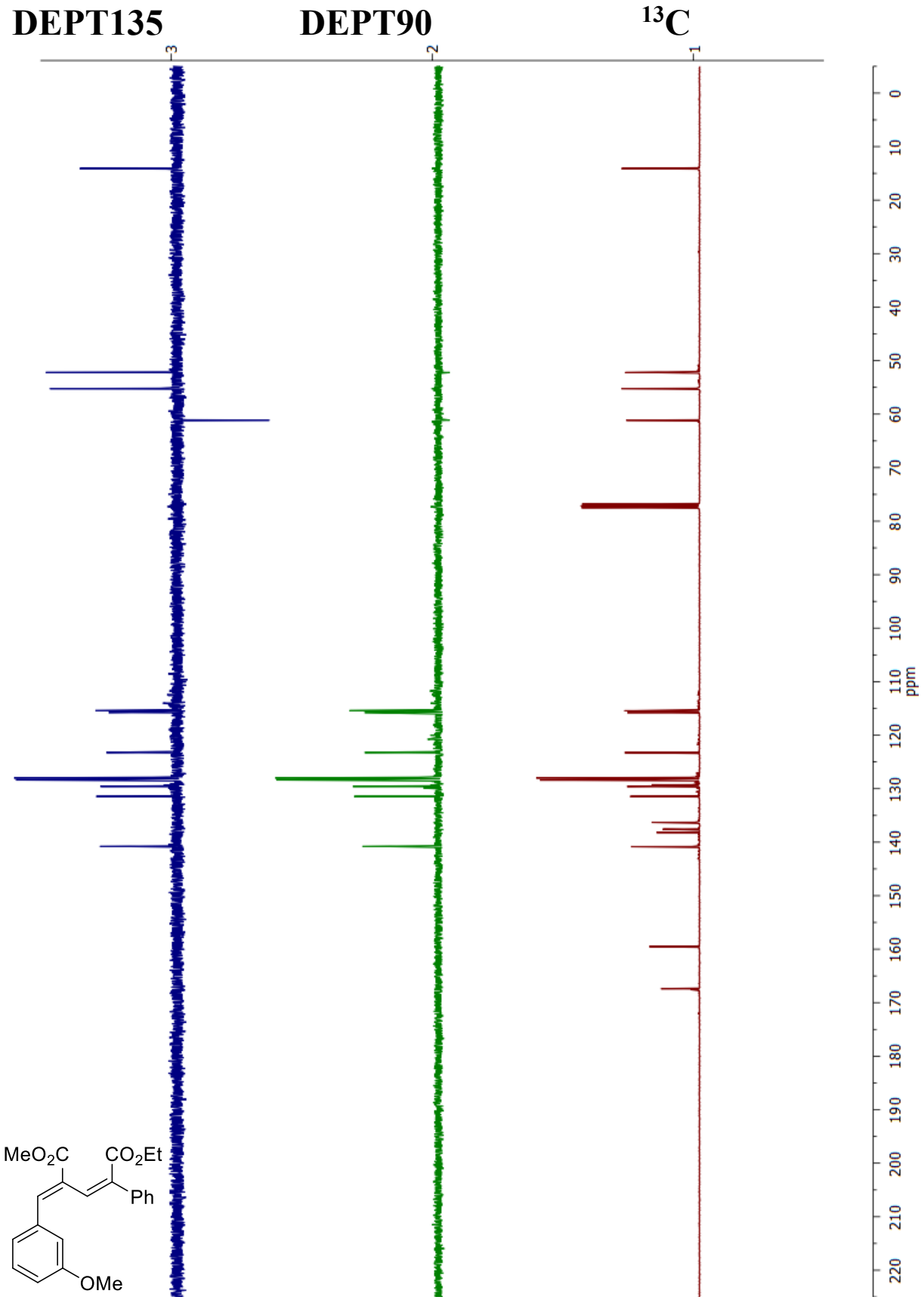
Compound **44e** **^{13}C-NMR** ($CDCl_3$)



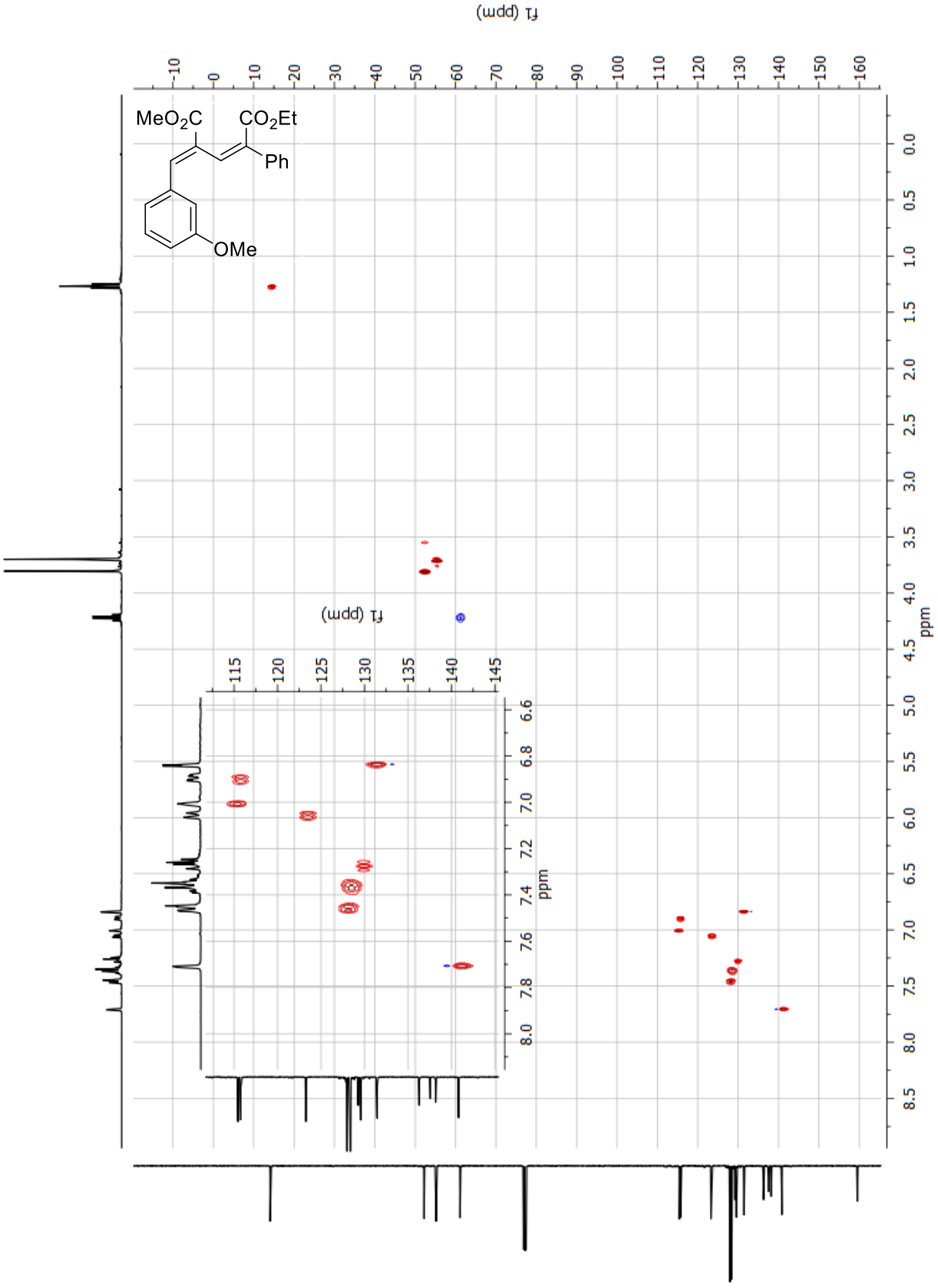
Compound **44e - COSY**



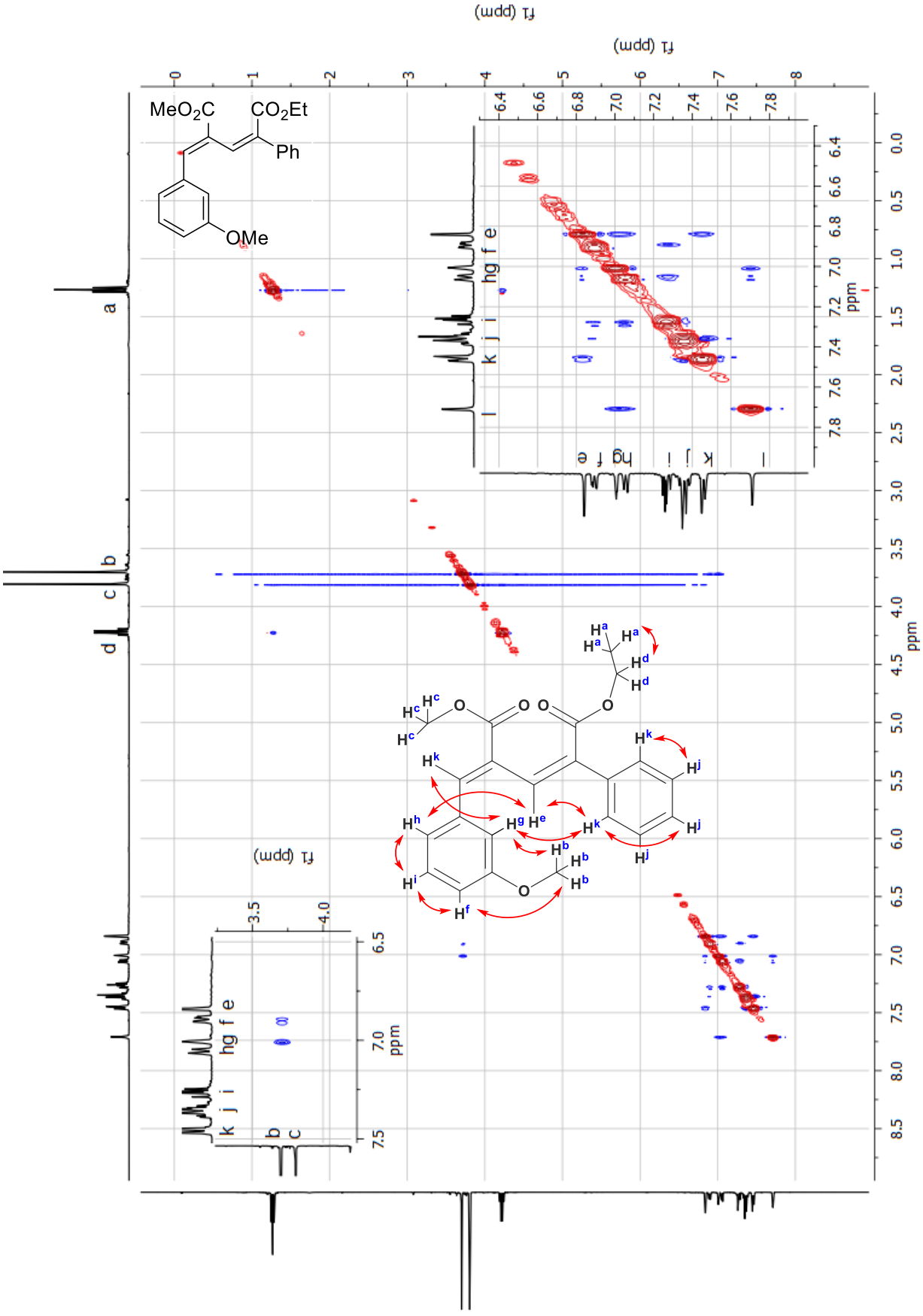
Compound **44e – DEPT135 – DEPT90 – ^{13}C-NMR**



Compound **44e - HSQC**



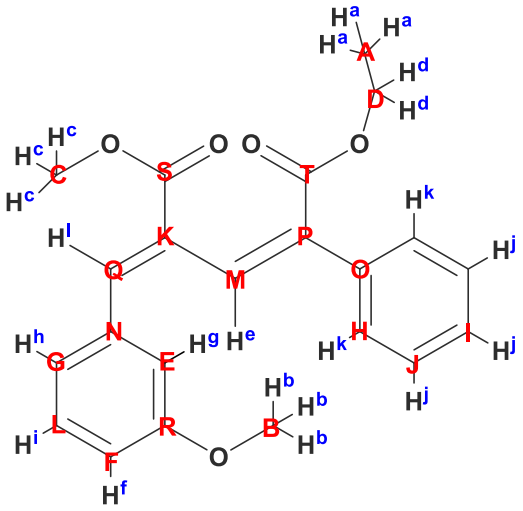
Compound **44e - NOESY**

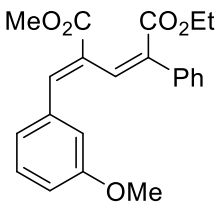


Compound **44e** – **^{1}H-NMR/^{13}C-NMR signal assignment**

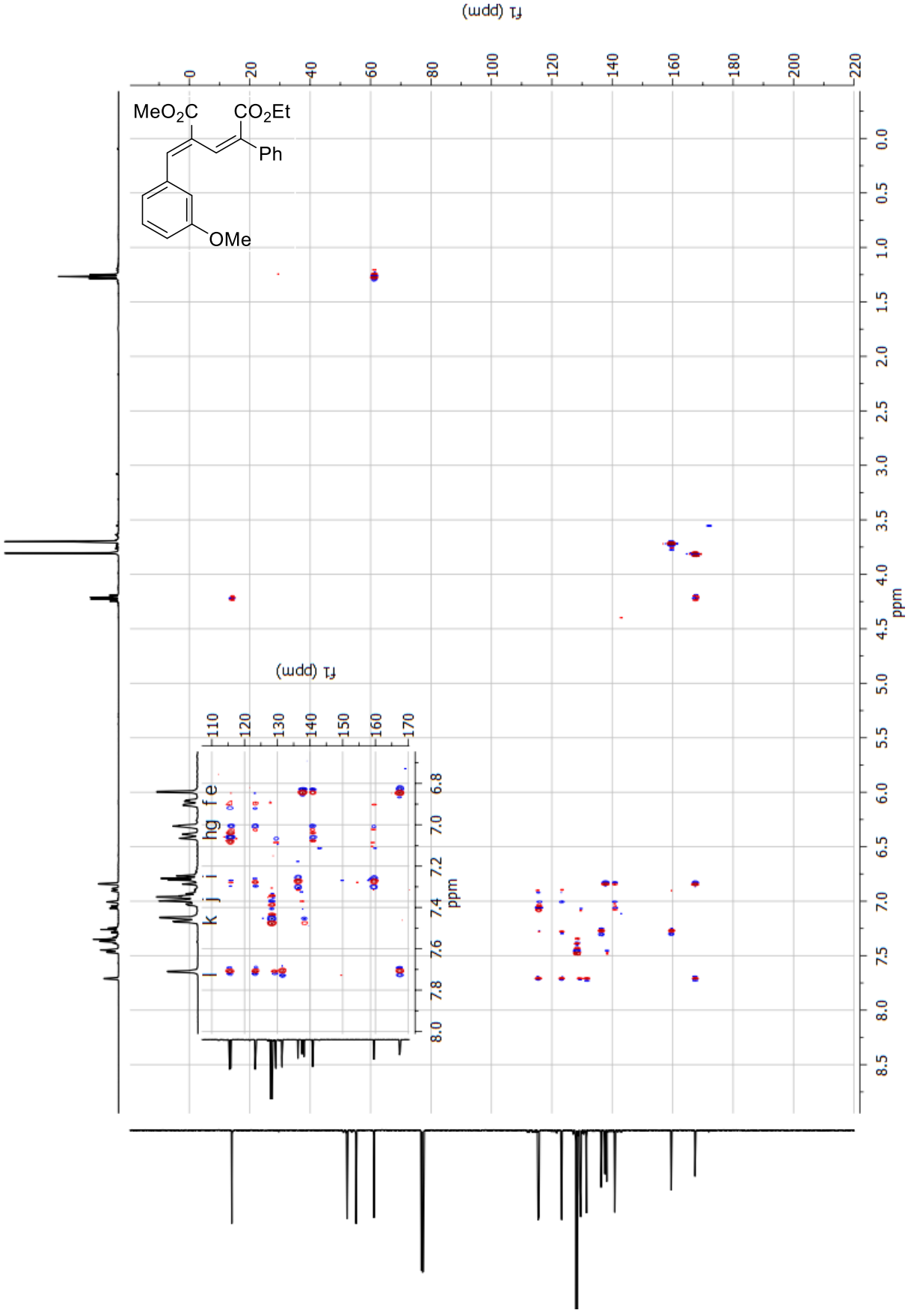
proton NMR Signal, chemical shift [ppm]	**HMBC long range coupling to CARBON:**
e, 6.84	^{3}J to **S** and/or **T** (ester groups, signals too close together), **Q**, **O**
f, 6,88	^{3}J to **G**, **E**, **B**
g, 7.01	^{3}J to **F**, **Q**, **G**, **B**; ^{2}J to **R**
h, 7.06	^{3}J to **Q**, **E**; ^{2}J to **L**
i, 7.27	^{3}J to **N**, **R**; ^{2}J to **G**, **F**
j, 7.35	$^{2/3}$J to **O**, further coupling to **J**, **H** and/or **K** (carbons in phenyl group, poor resolution, signals too close together)
k, 7.45	^{3}J to **P**, $^{2/3}$J to **I**, **J**
l, 7.71	^{3}J to **S**, **M**, **G**, **E**; ^{2}J to **K**

Signal	**Chemical shift [ppm]**	**Assignment**
A	14.1	CH_3
B	52.2	CH_3
C	55.2	CH_3
D	61.1	CH_2
E	115.4	CH
F	115.8	CH
G	123.3	CH
H	128.0	CH
I	128.3	CH
J	128.4	CH
K	129.3	q
L	129.6	CH
M	131.5	CH
N	136.3	q
O	137.6	q
P	138.2	q
Q	140.8	CH
R	159.5	q
S	167.4	q
T	167.5	q

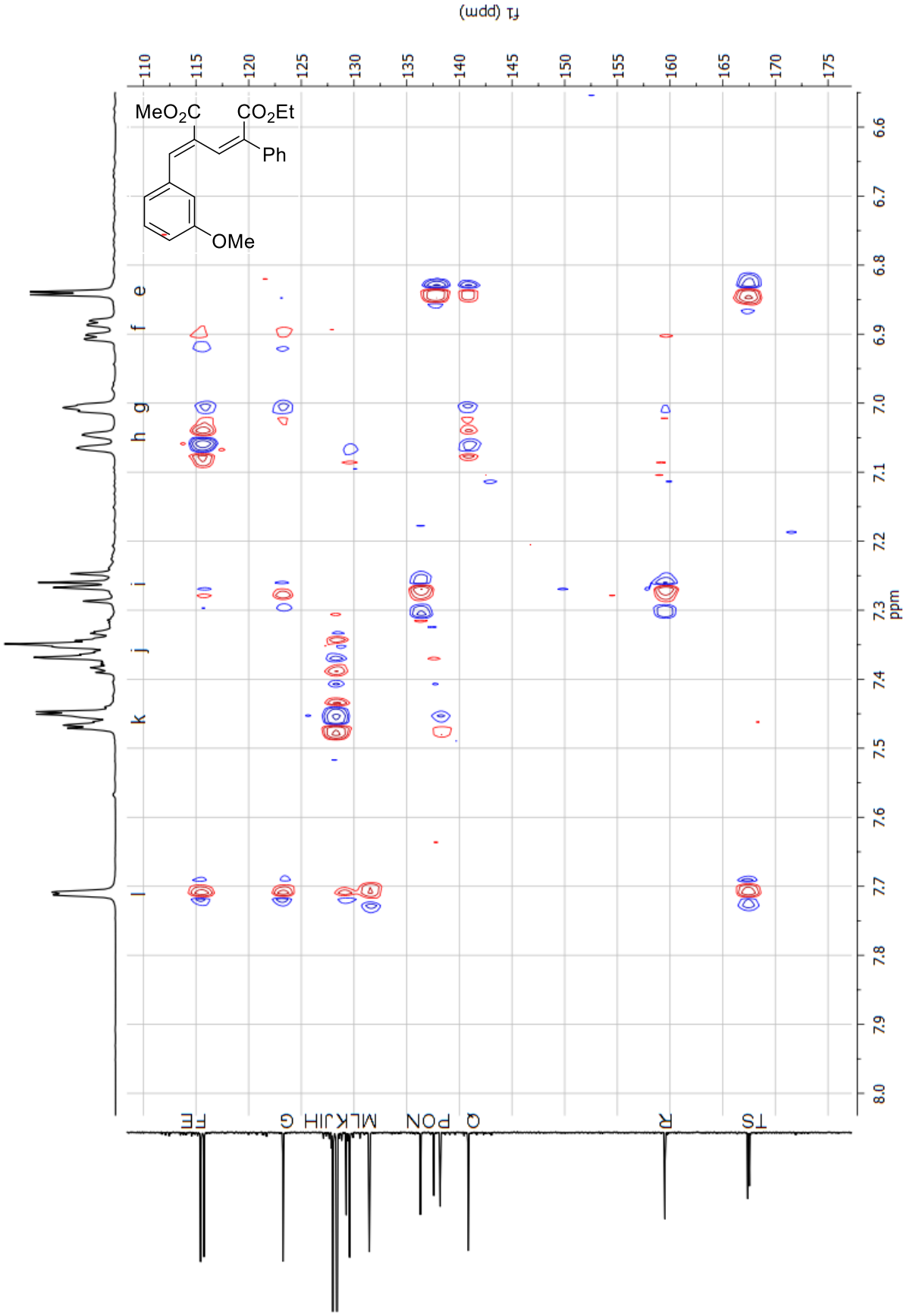




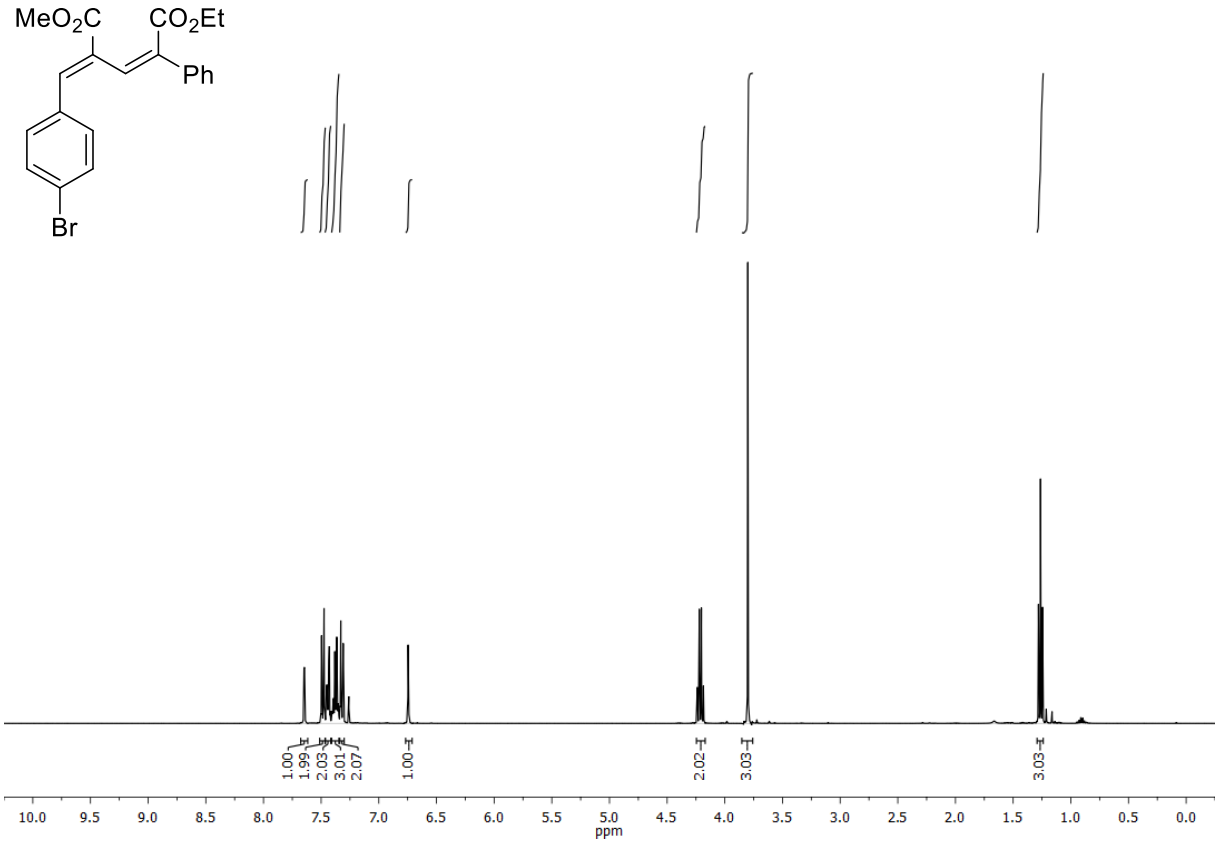
Compound **44e - HMBC**



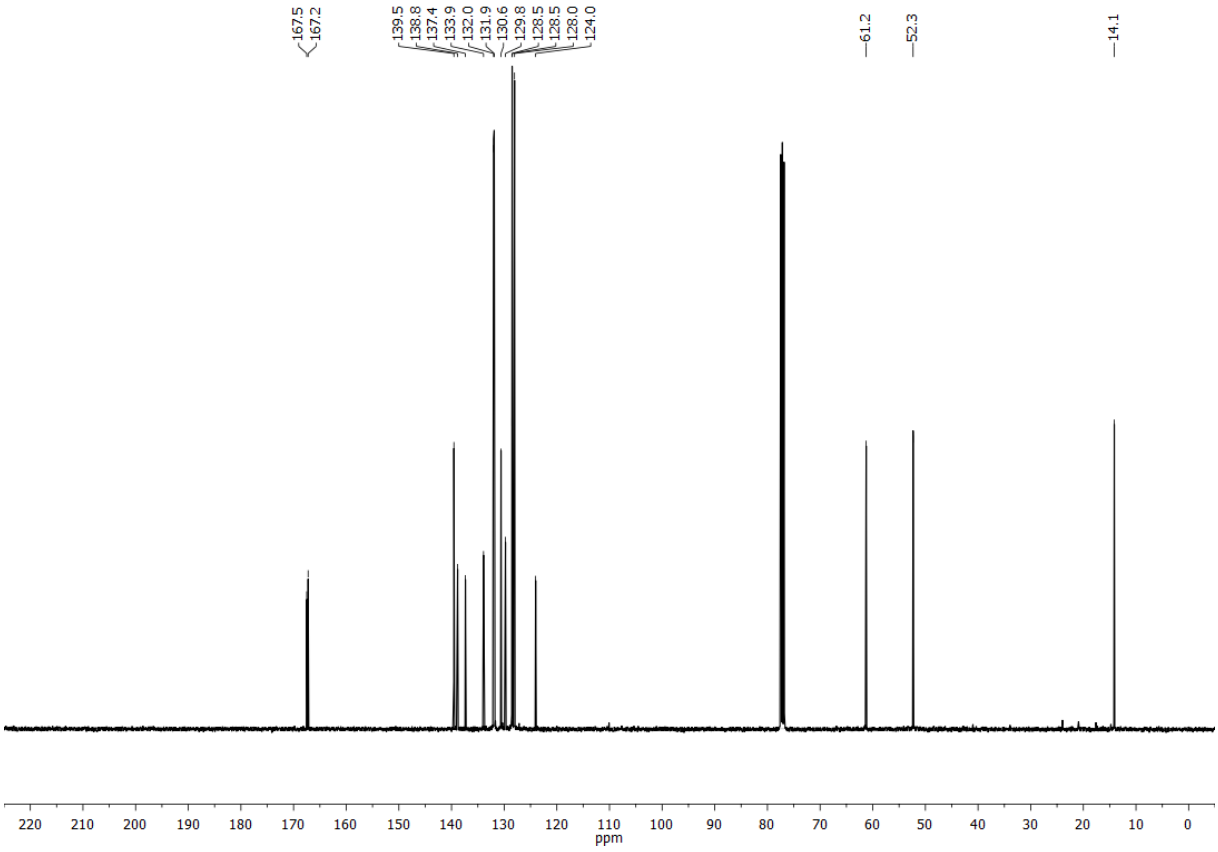
Compound **44fe– HMBC – cut-out**



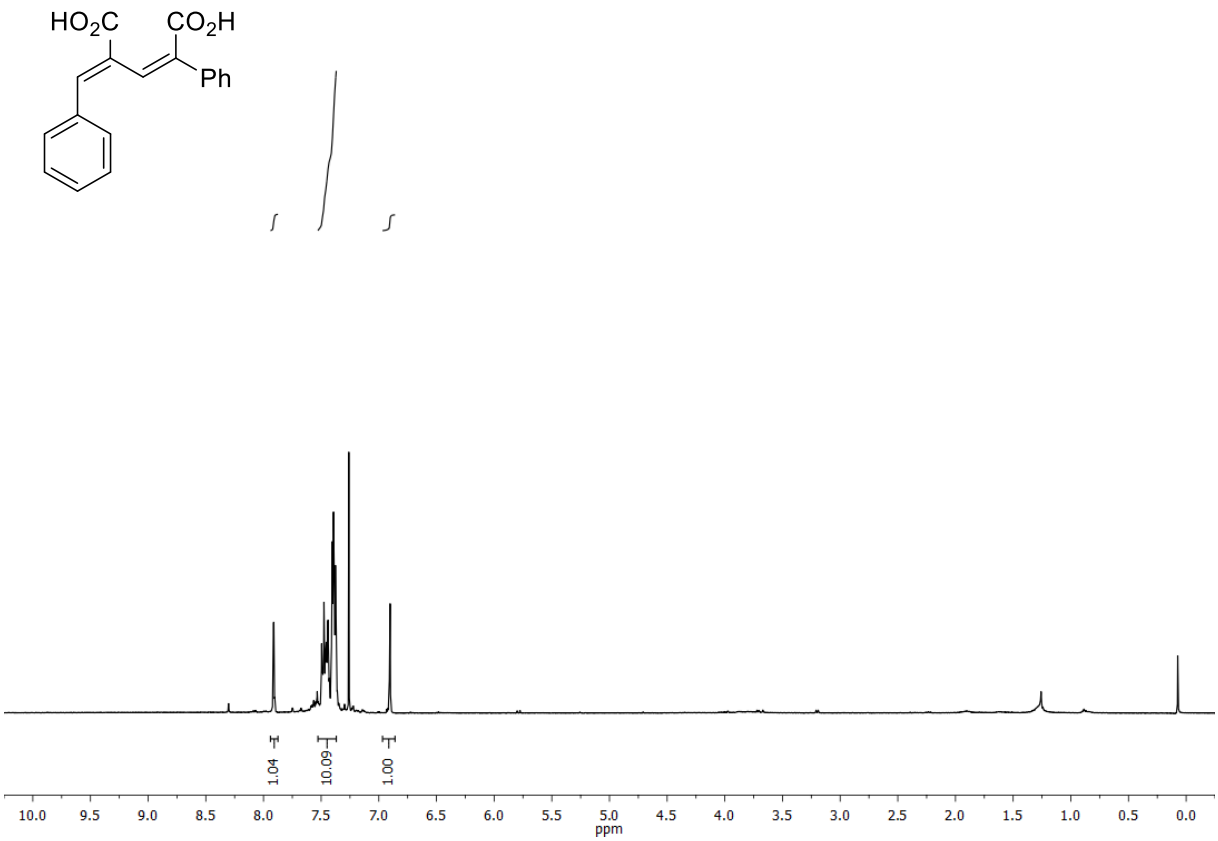
Compound **44f** ^{1}**H-NMR** ($CDCl_3$)



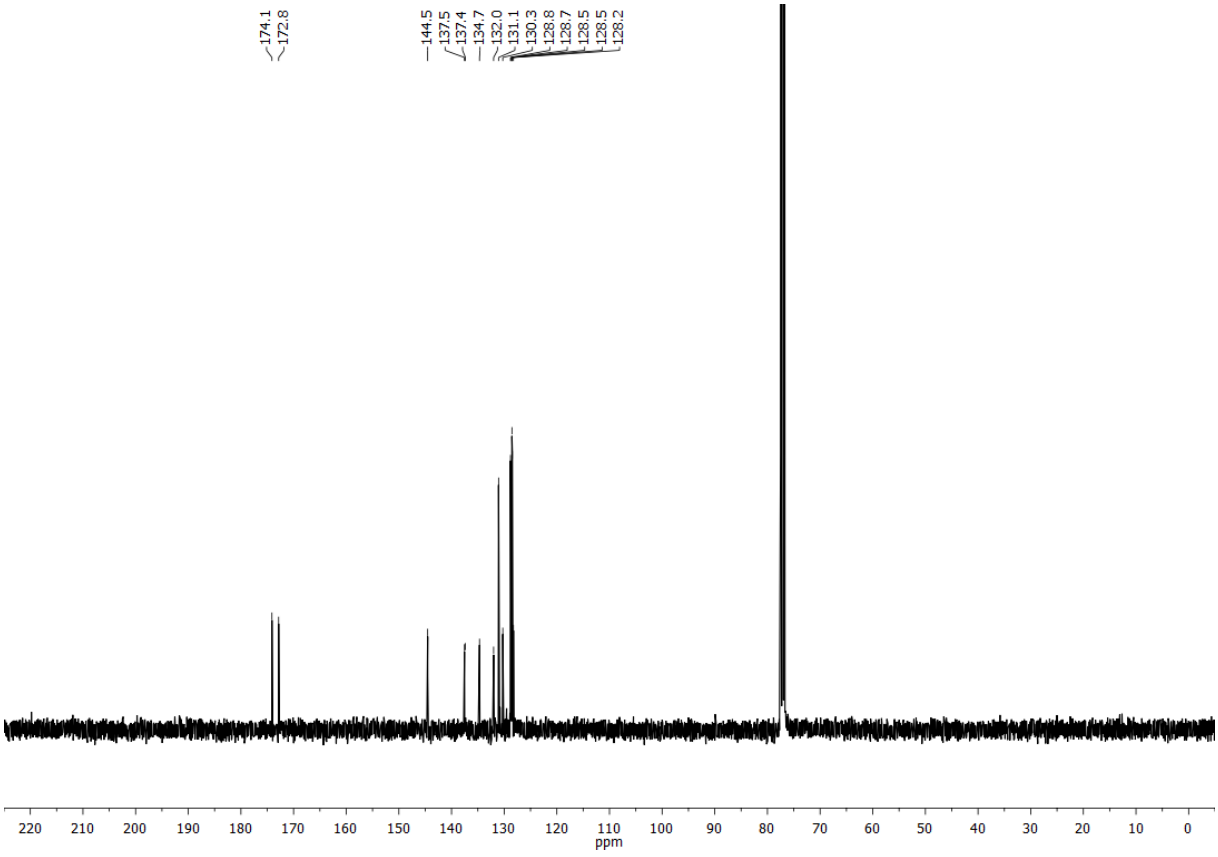
Compound **44f** ^{13}**C-NMR** ($CDCl_3$)



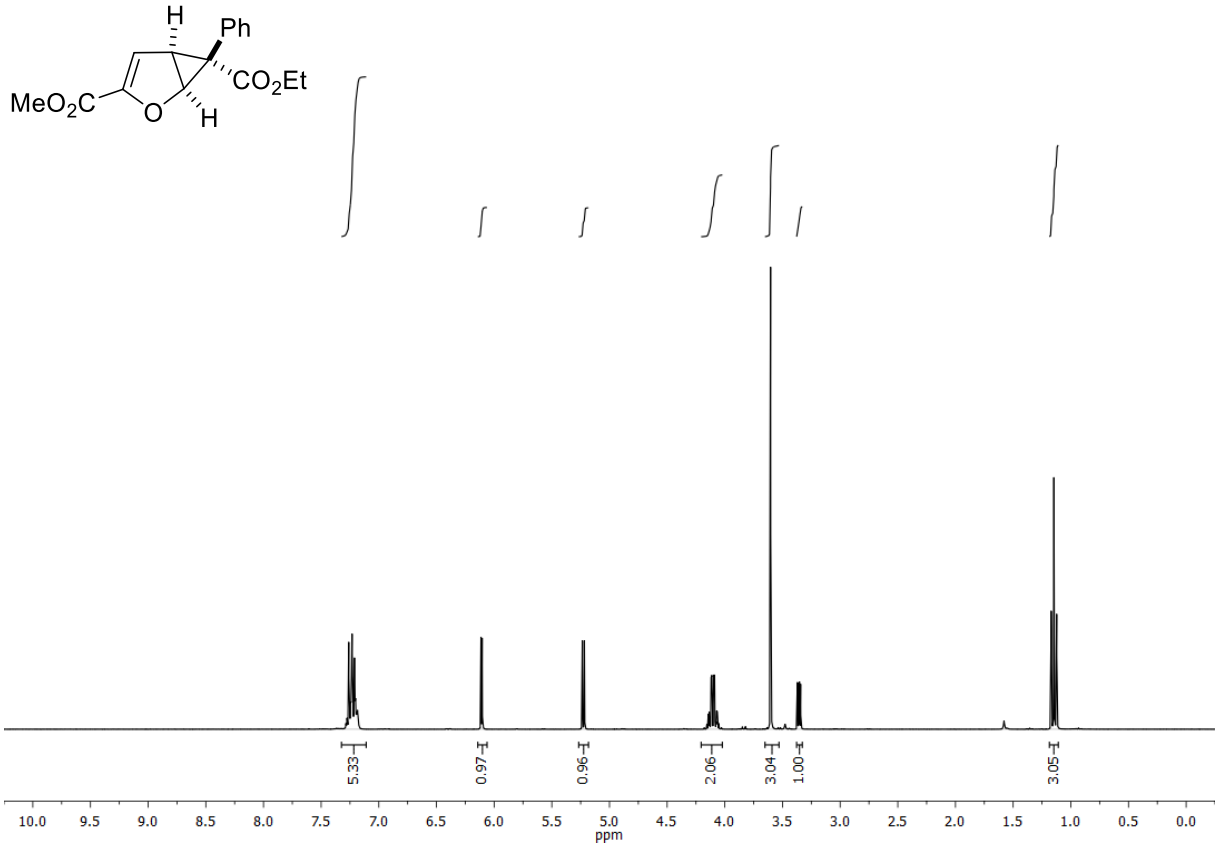
Compound **45** **^{1}H-NMR** ($CDCl_3$)



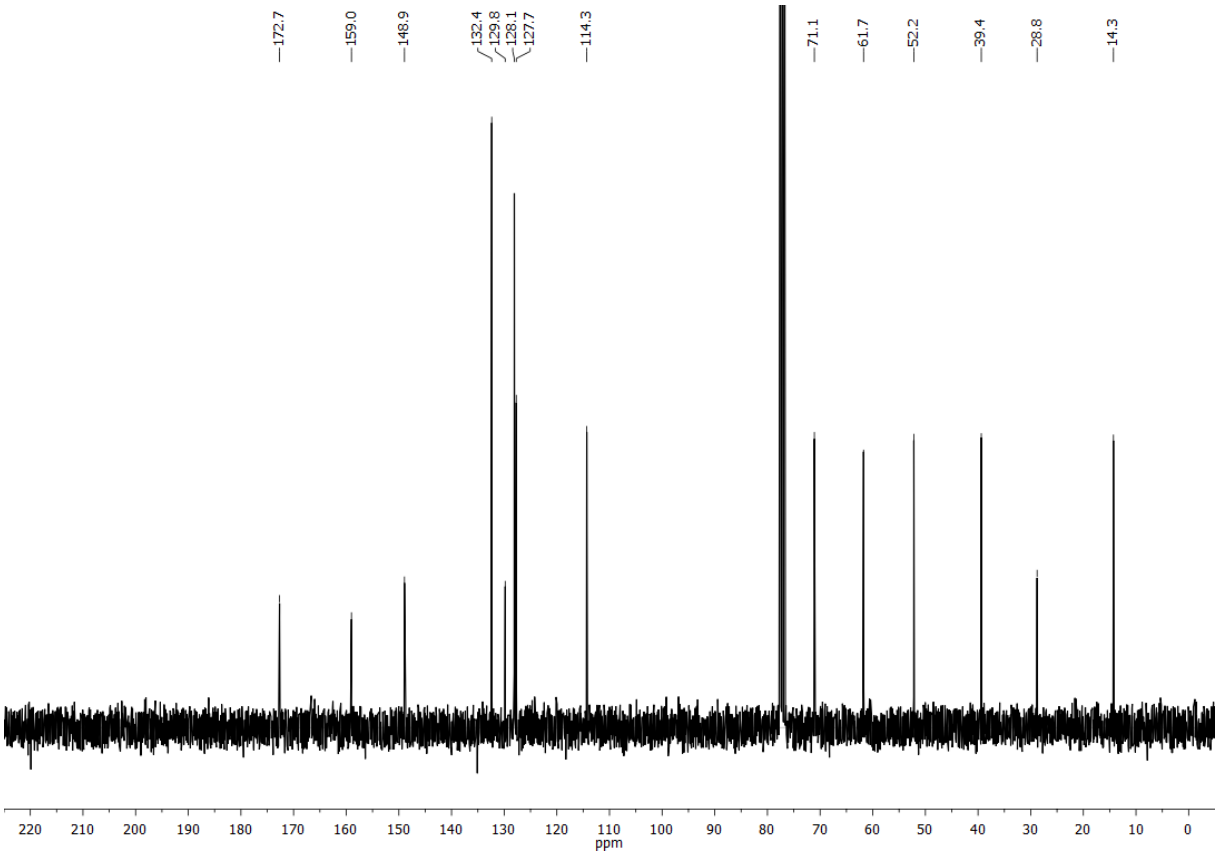
Compound **45** **^{13}C-NMR** ($CDCl_3$)



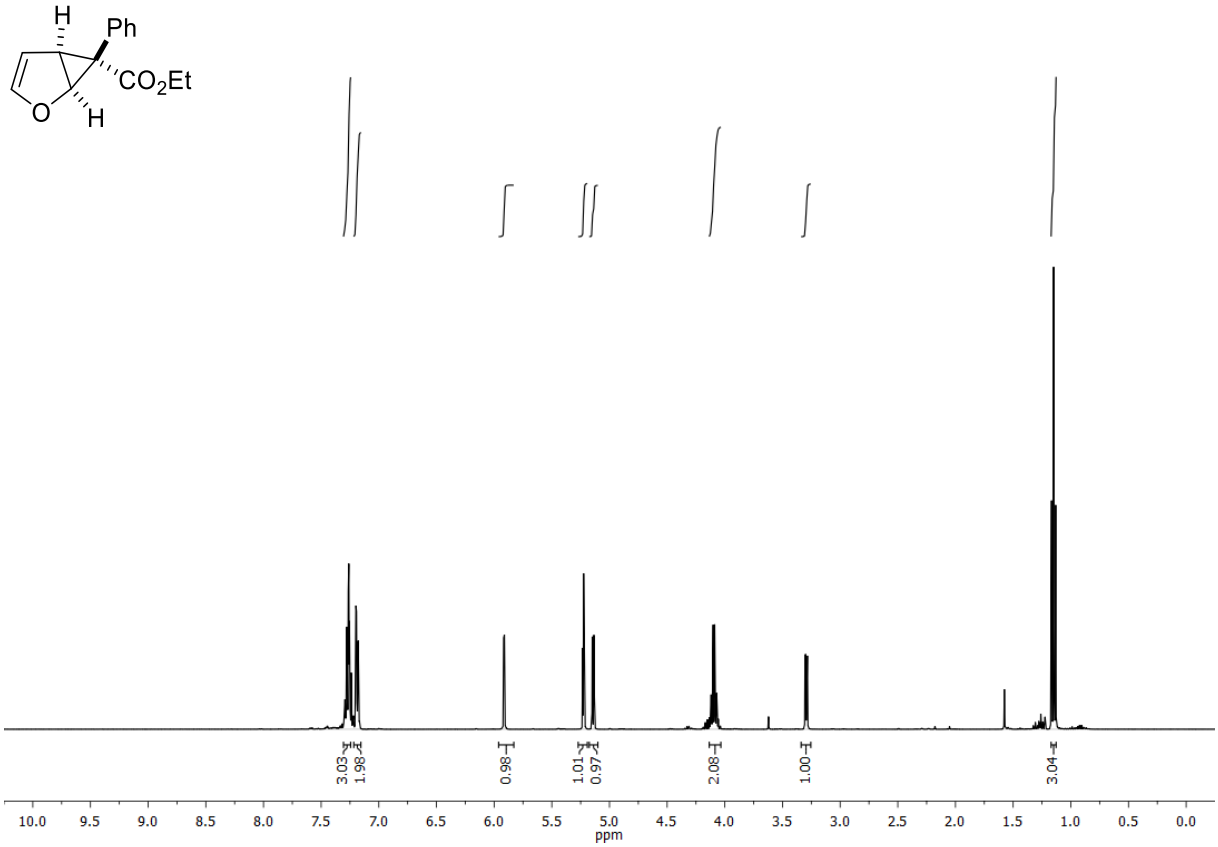
Compound **47** **^{1}H-NMR** ($CDCl_3$)



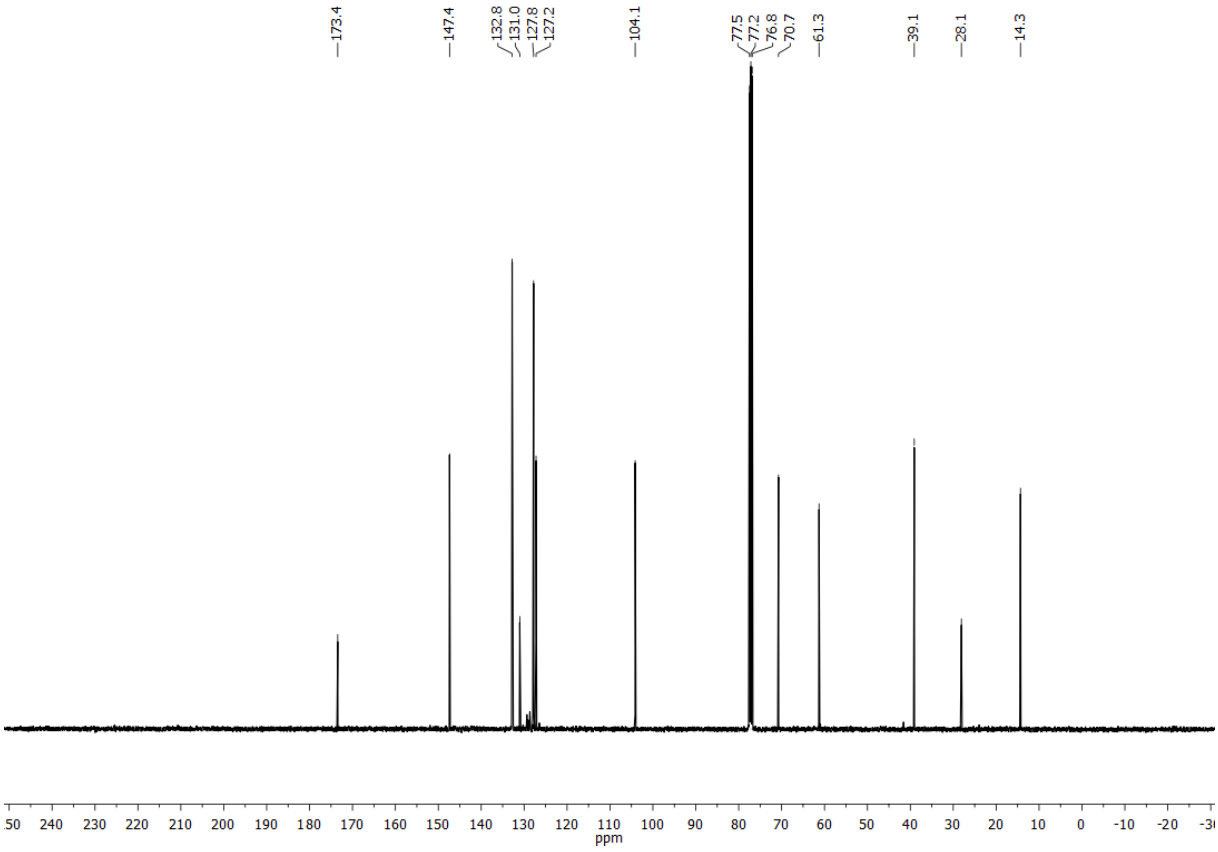
Compound 47 **^{13}C-NMR** ($CDCl_3$)



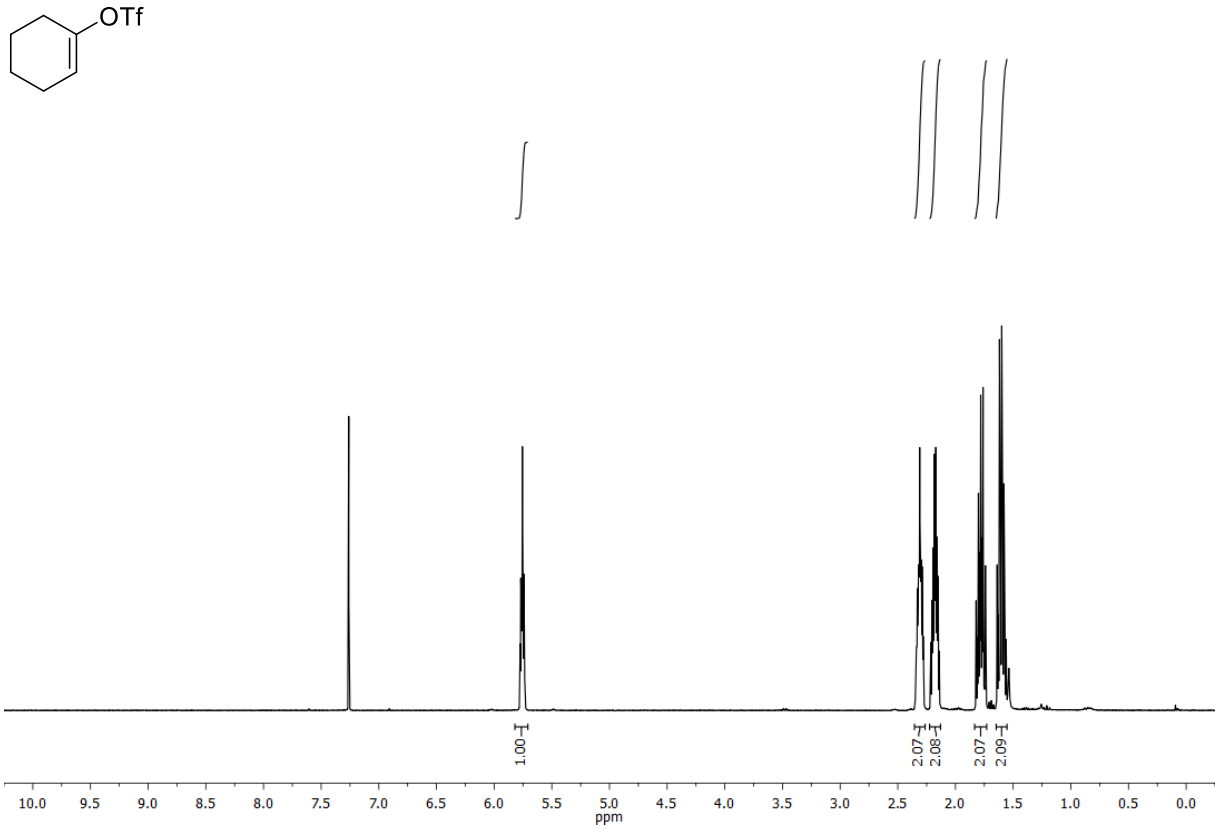
Compound **48** **^{1}H-NMR** ($CDCl_3$)



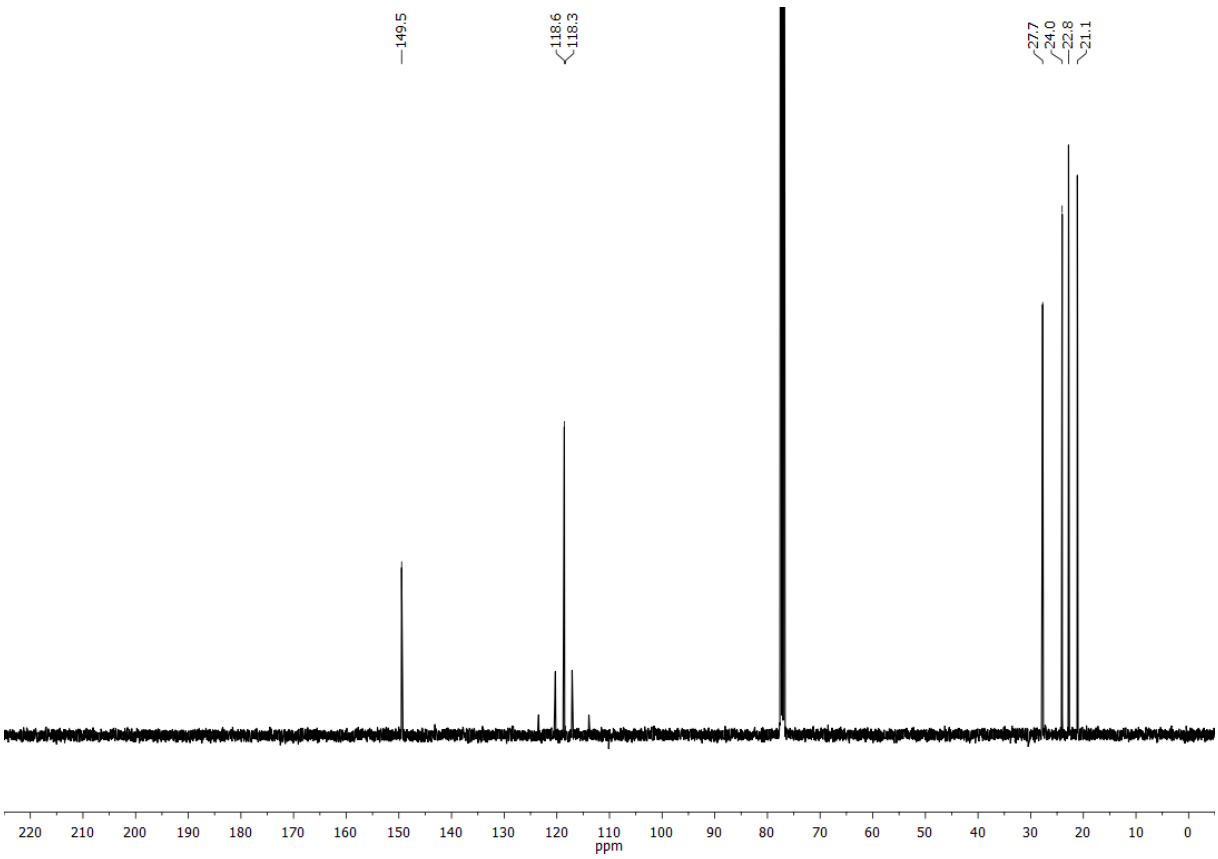
Compound **48** **^{13}C-NMR** ($CDCl_3$)



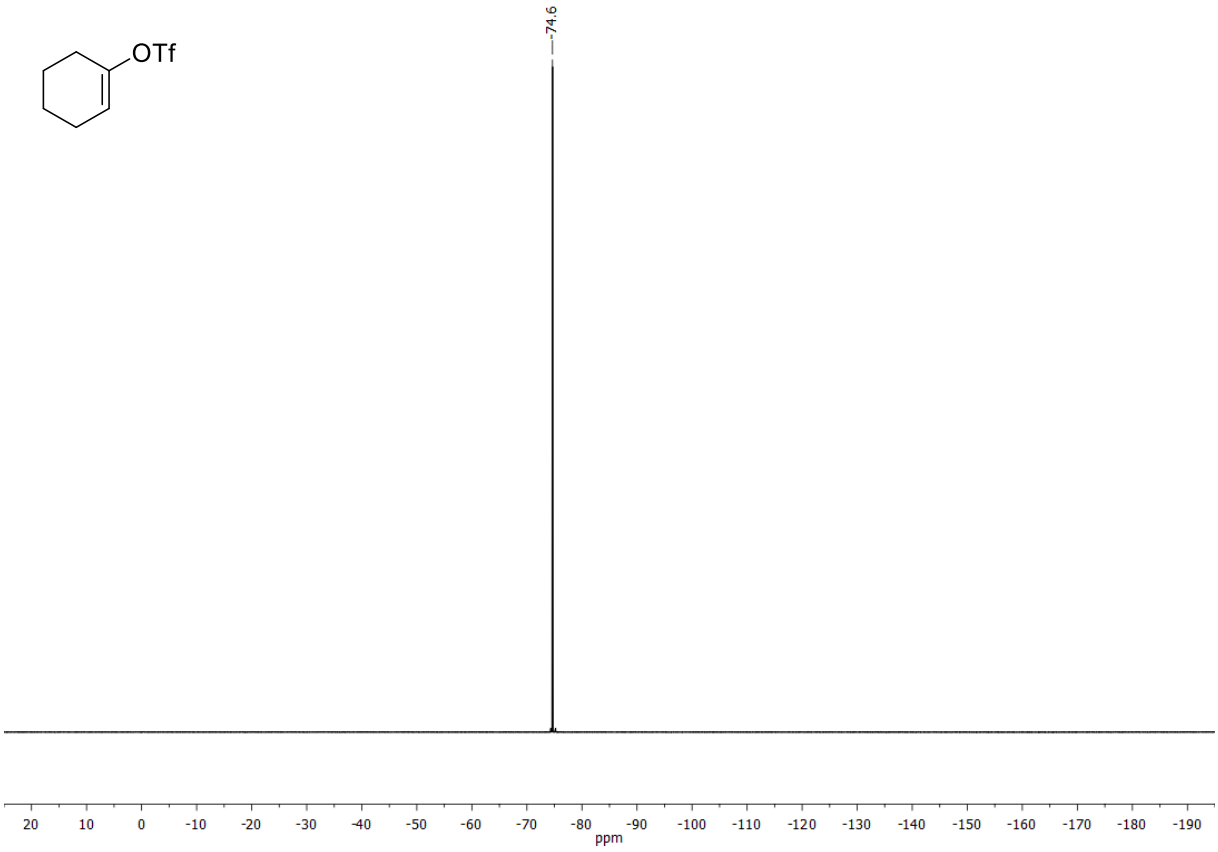
Compound **65a** ^{1}**H-NMR** ($CDCl_3$)



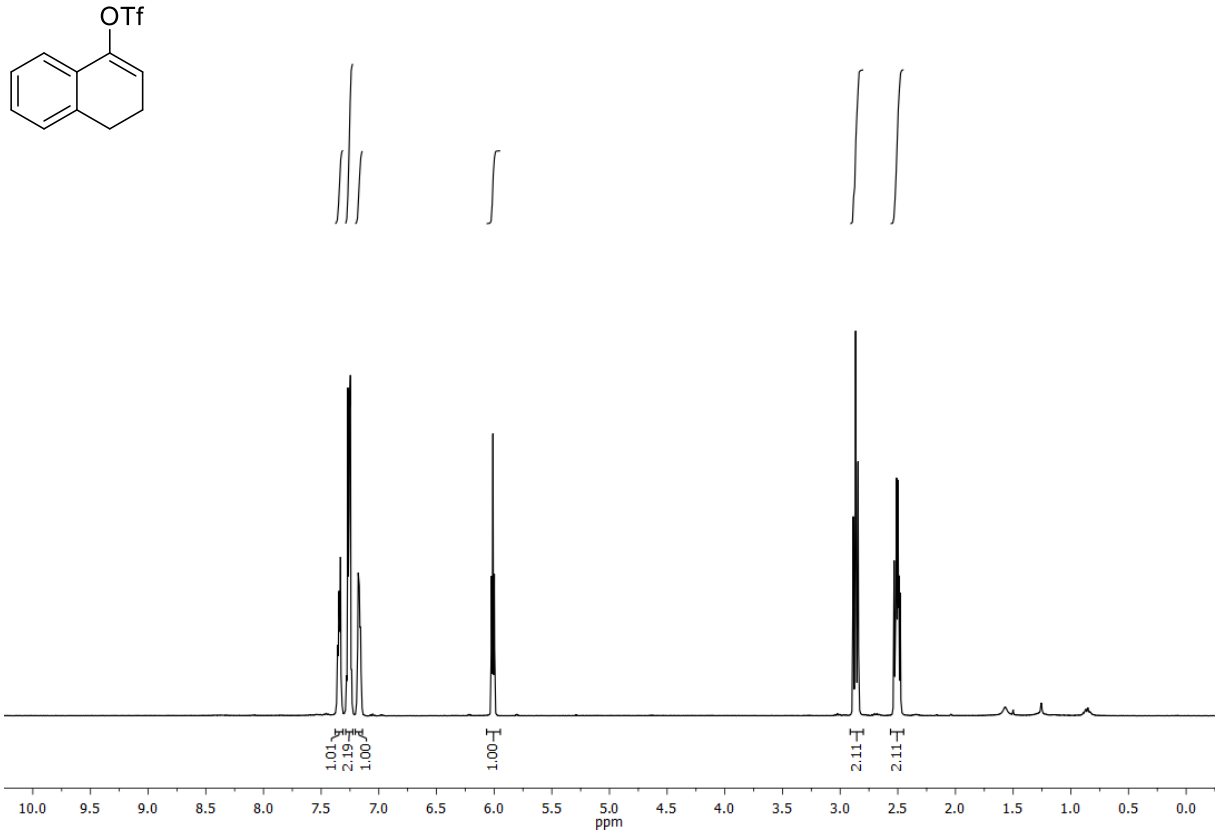
Compound **65a** ^{13}**C-NMR** ($CDCl_3$)



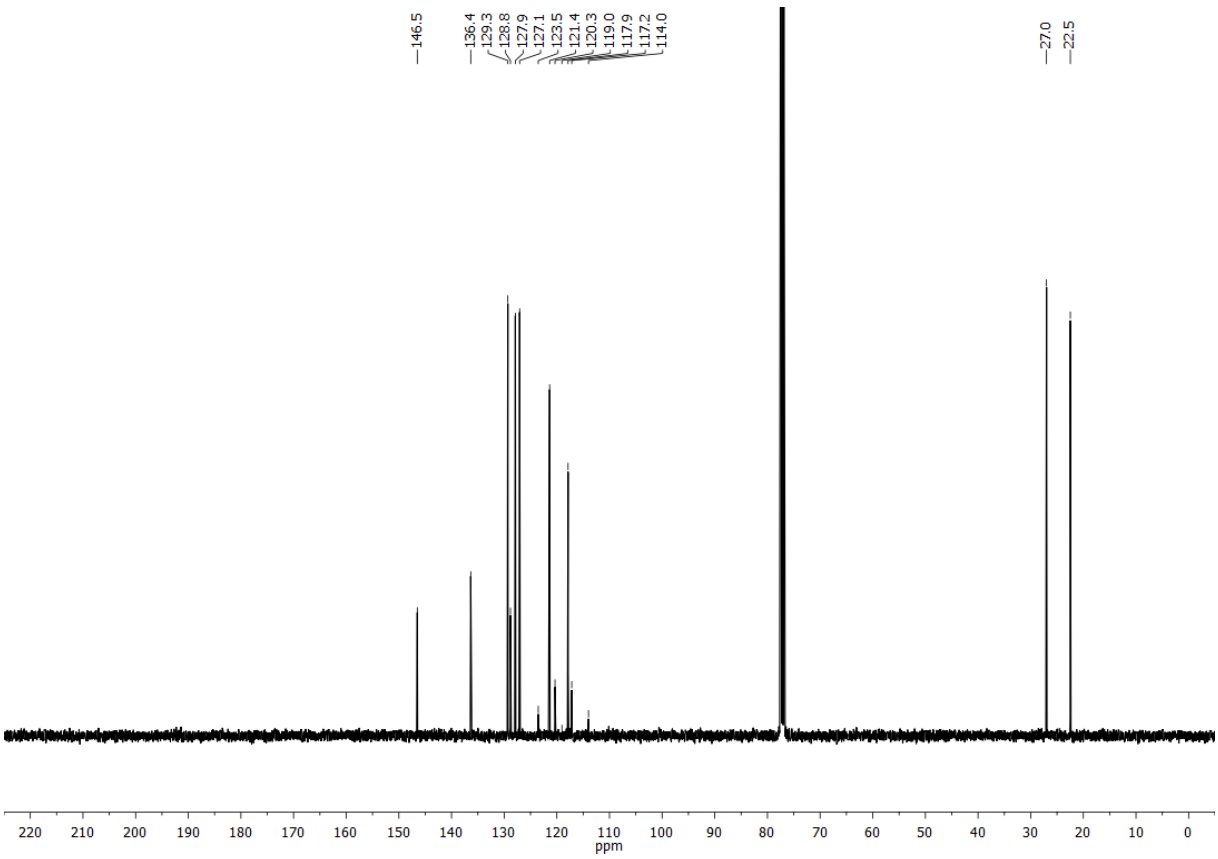
Compound **65a** ^{19}**F-NMR** ($CDCl_3$)



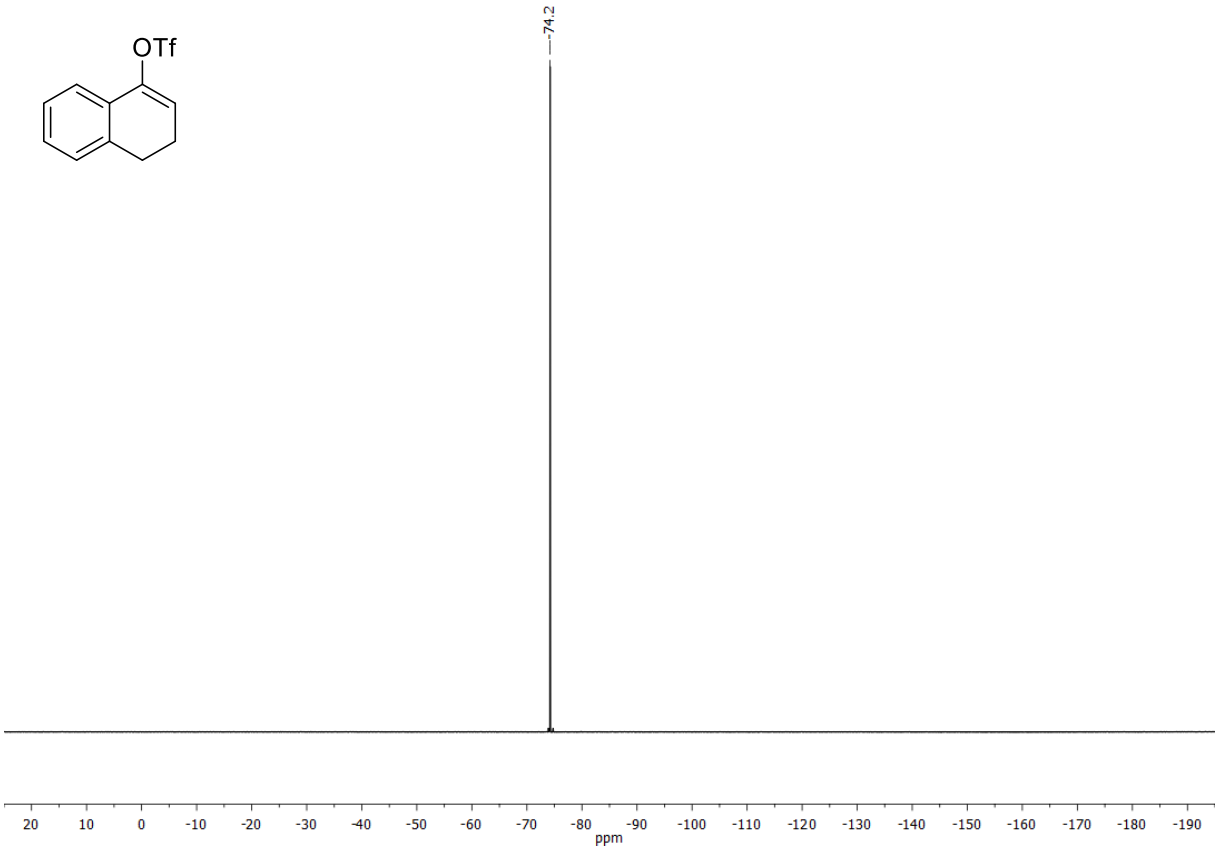
Compound **65b** ^{1}**H-NMR** ($CDCl_3$)



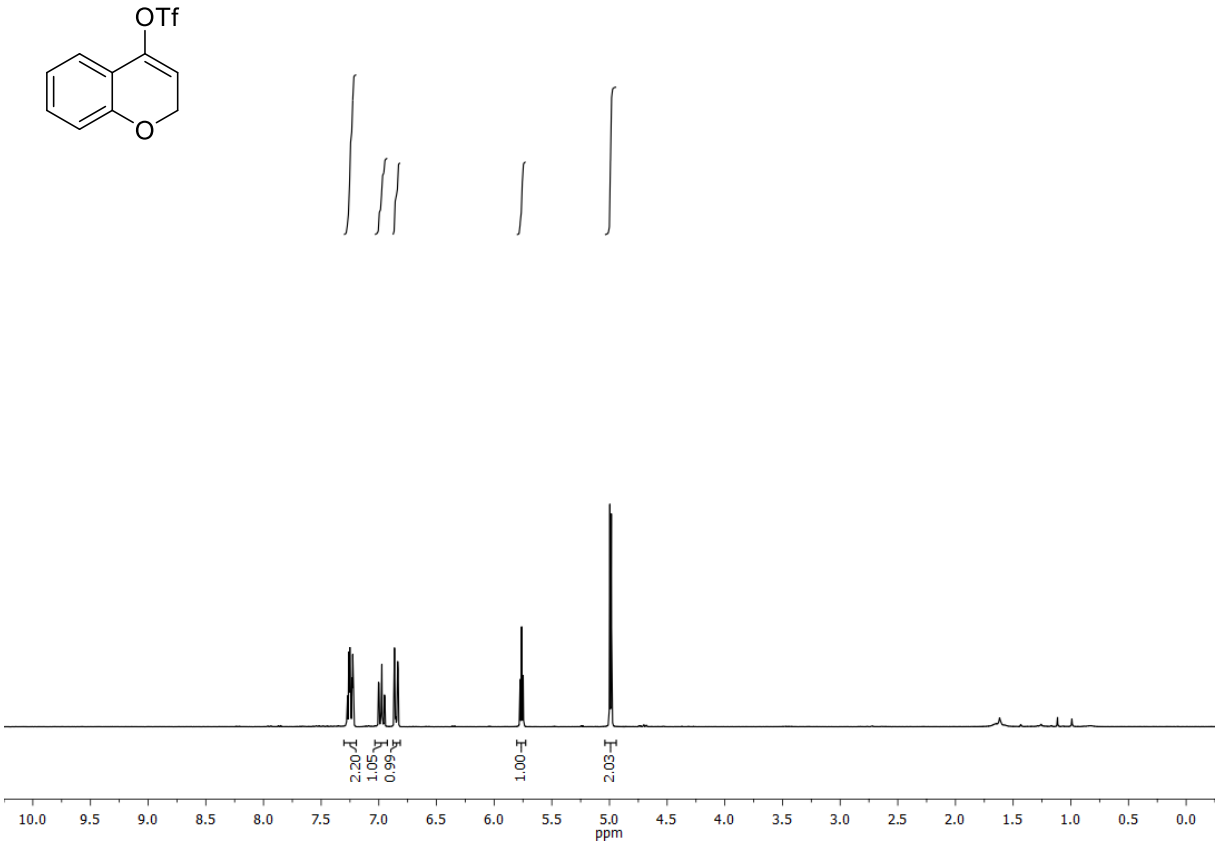
Compound **65b** ^{13}**C-NMR** ($CDCl_3$)



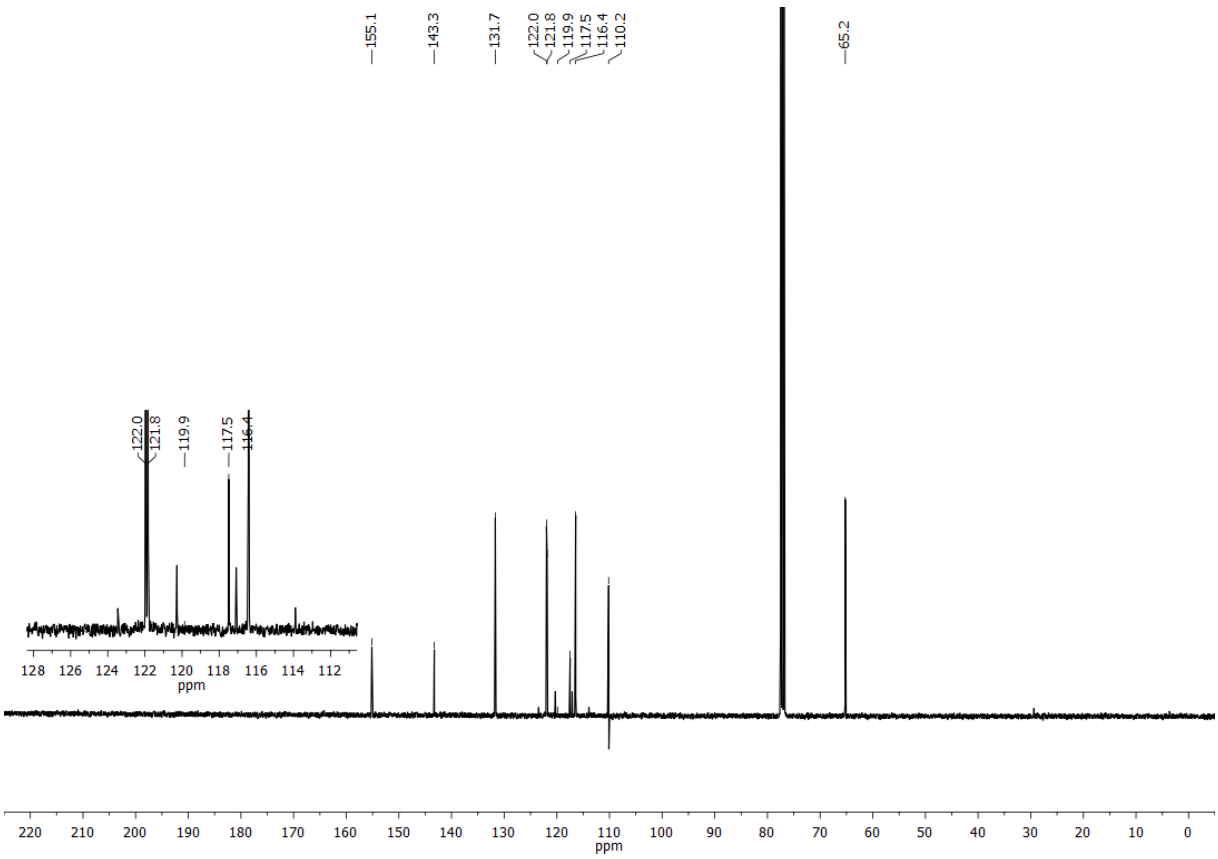
Compound **65b** ^{19}**F-NMR** ($CDCl_3$)



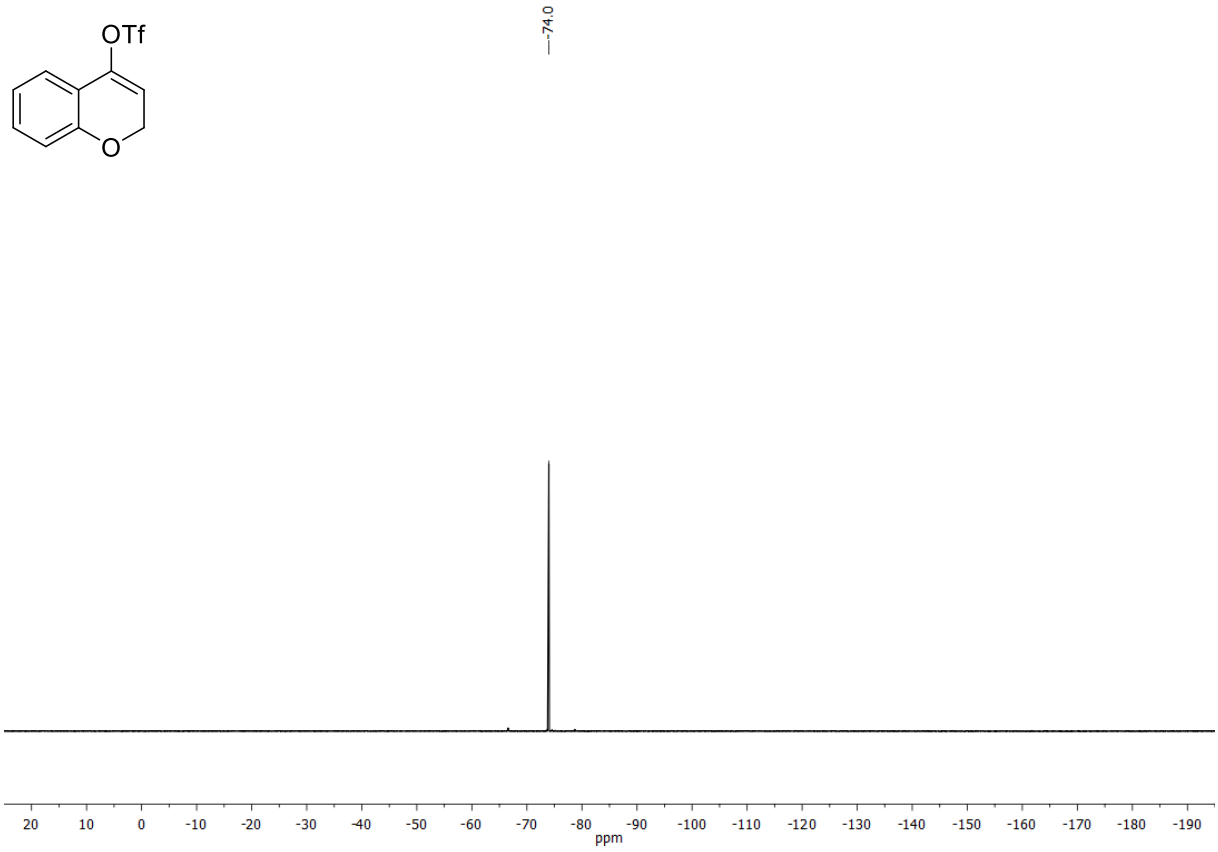
Compound **65c** ^{1}**H-NMR** ($CDCl_3$)



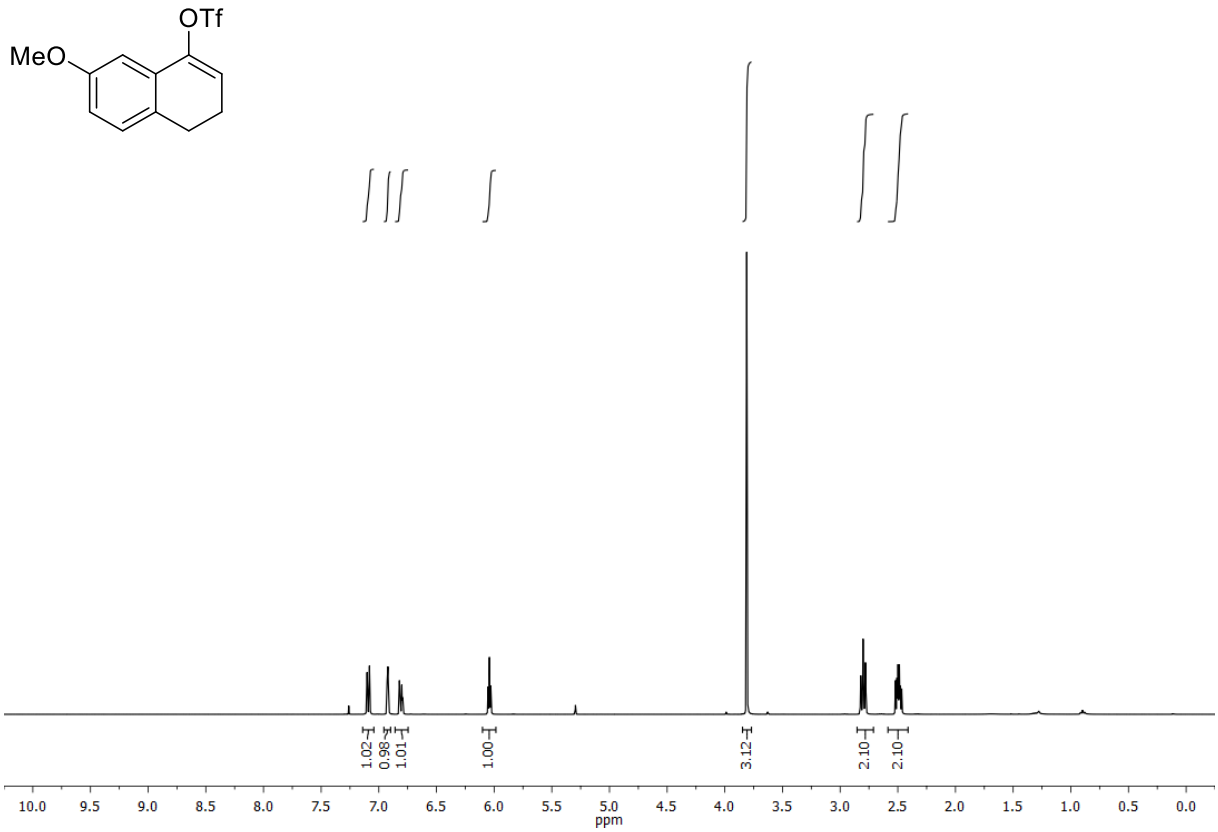
Compound **65c** ^{13}**C-NMR** ($CDCl_3$)



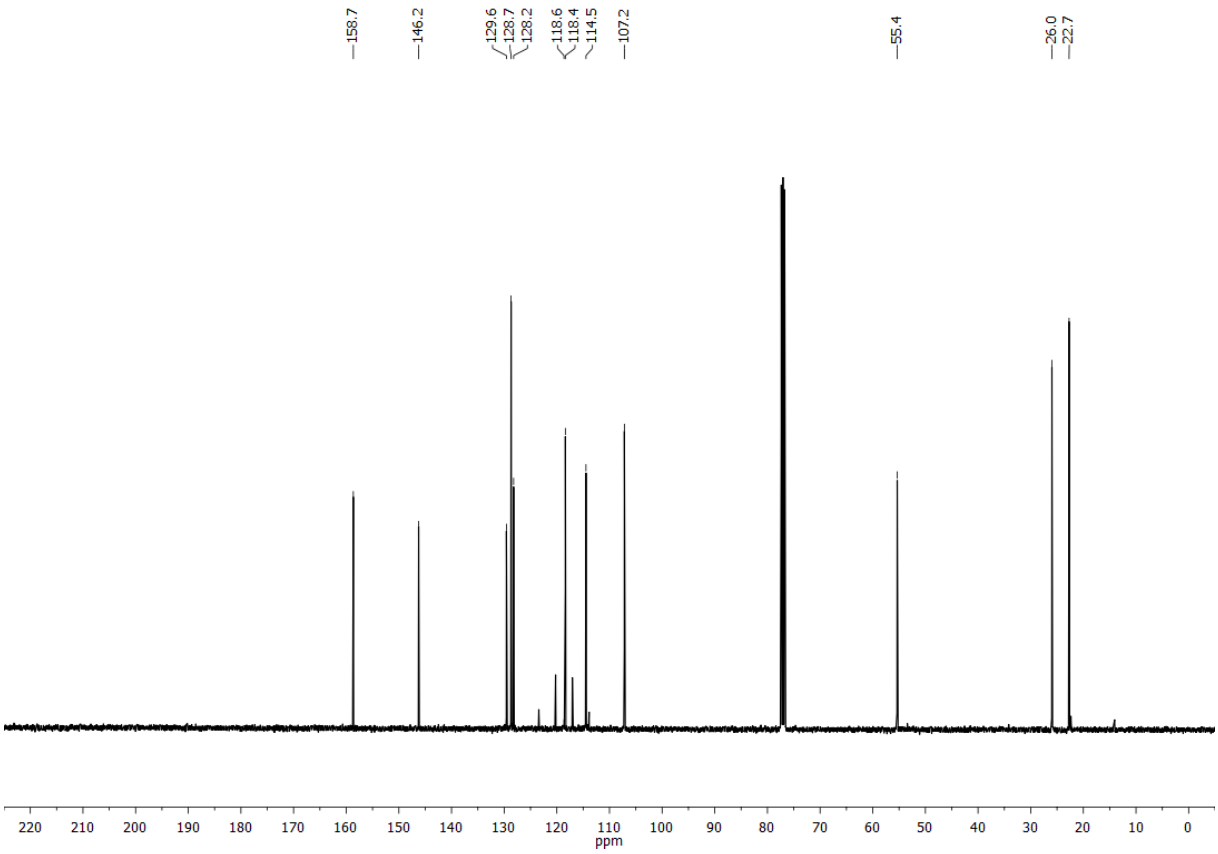
Compound **65c** ^{19}**F-NMR** ($CDCl_3$)



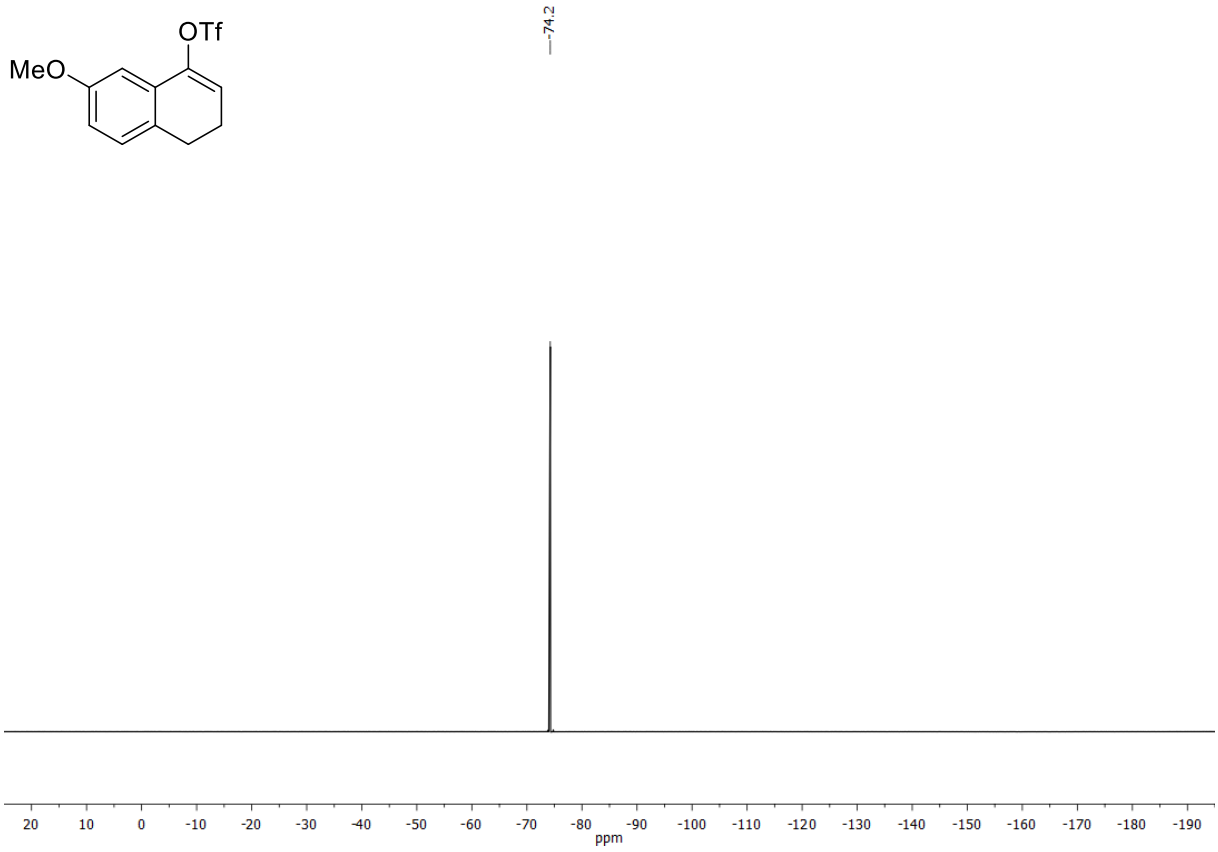
Compound **65d** ^{1}**H-NMR** ($CDCl_3$)



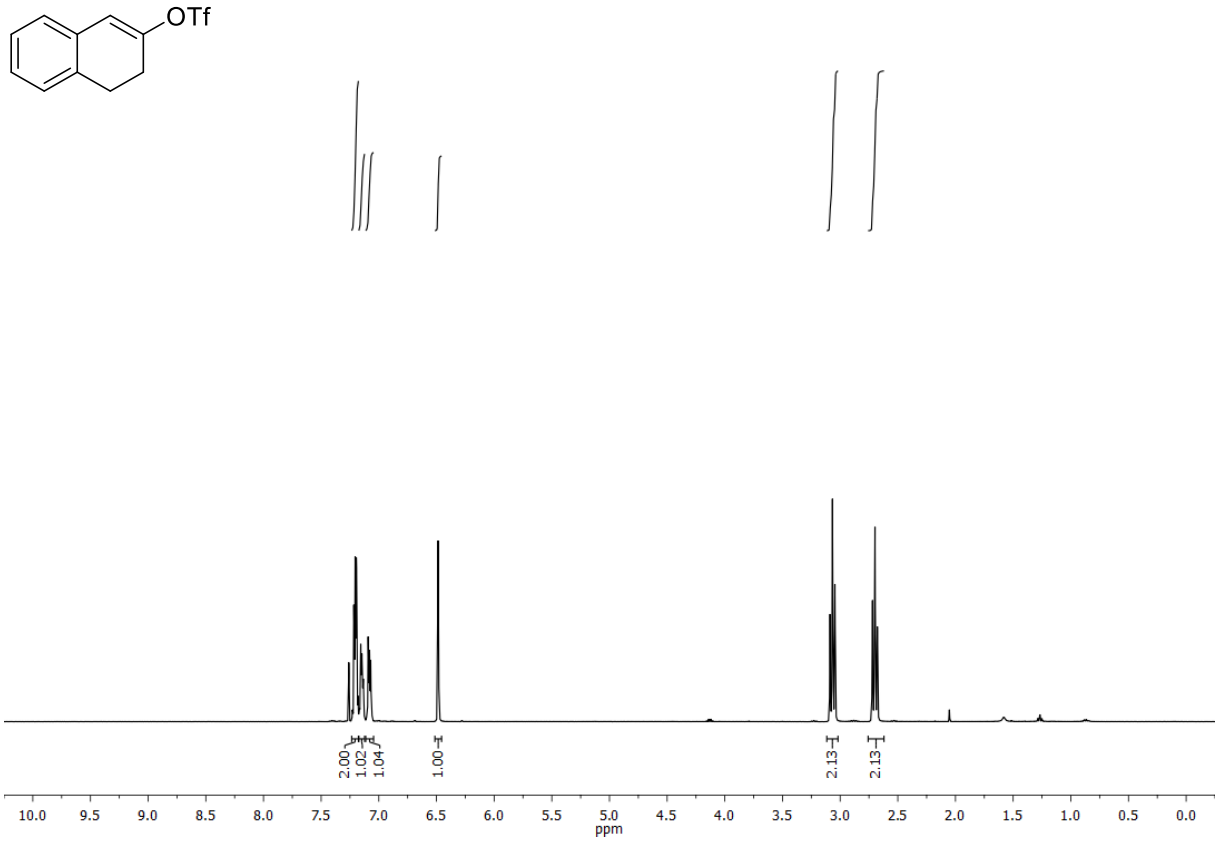
Compound **65d** ^{13}**C-NMR** ($CDCl_3$)



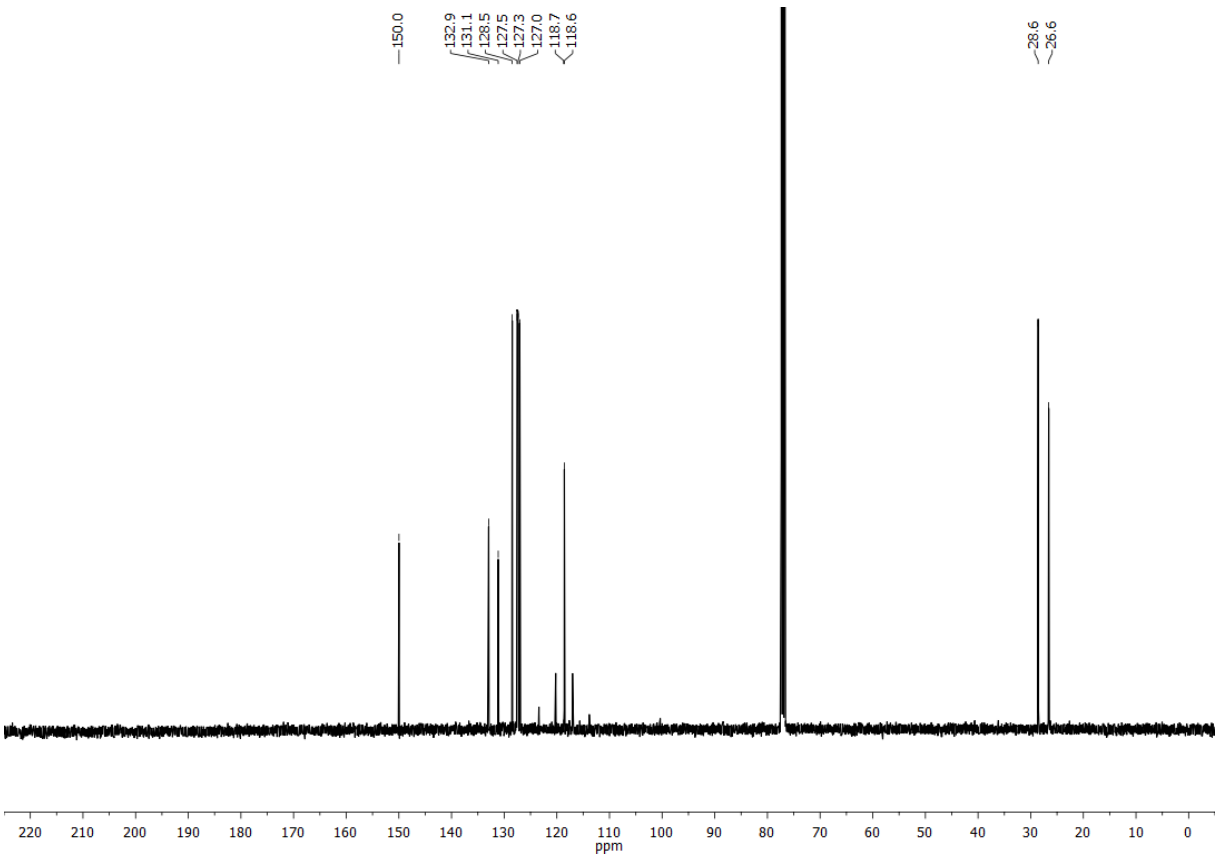
Compound **65d** ^{19}**F-NMR** ($CDCl_3$)



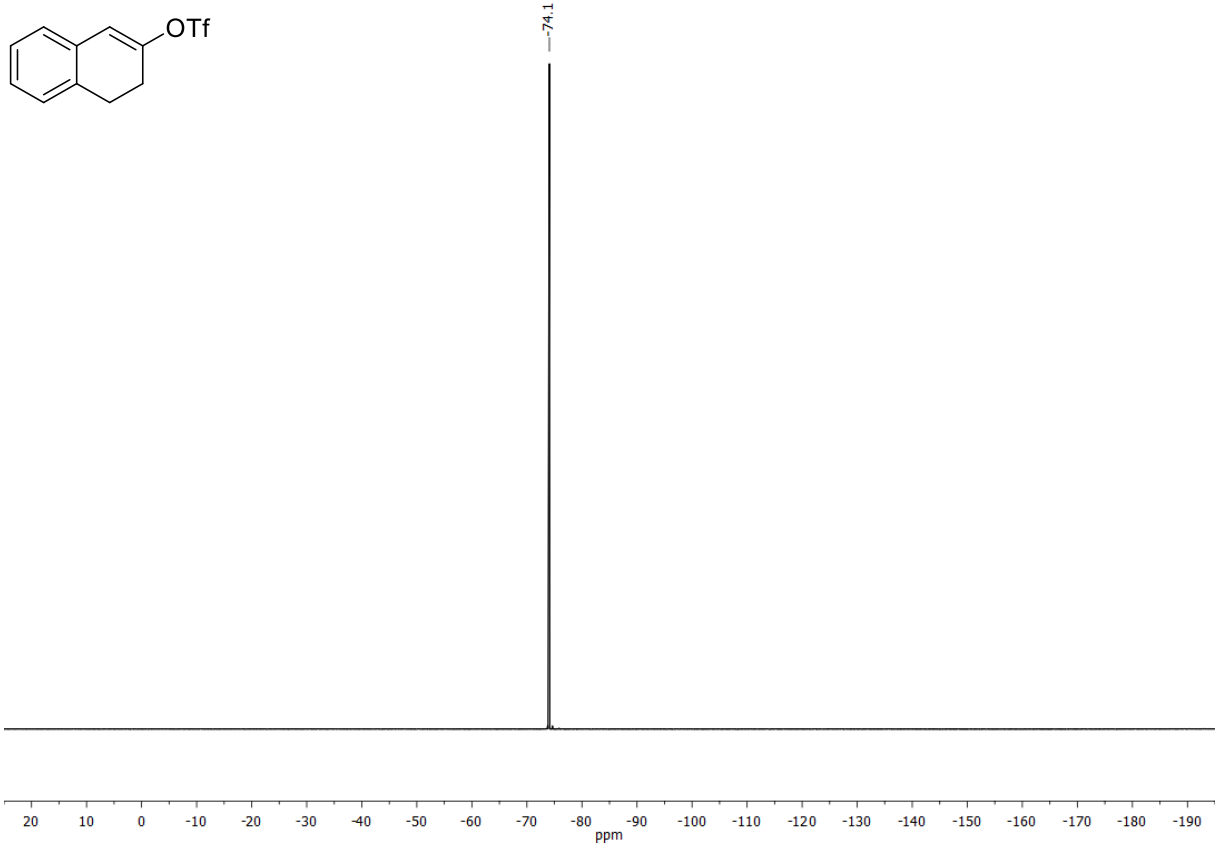
Compound **65e** ^{1}**H-NMR** ($CDCl_3$)



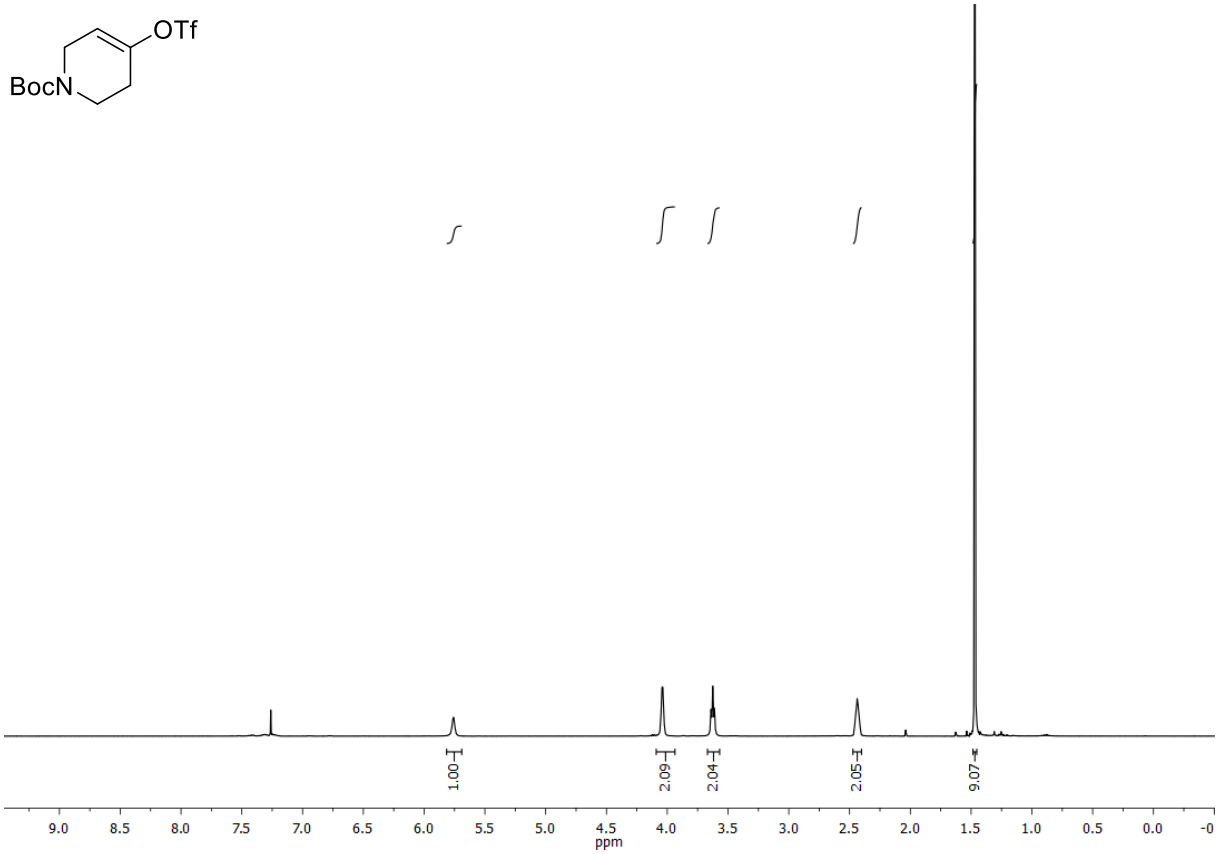
Compound **65e** ^{13}**C-NMR** ($CDCl_3$)



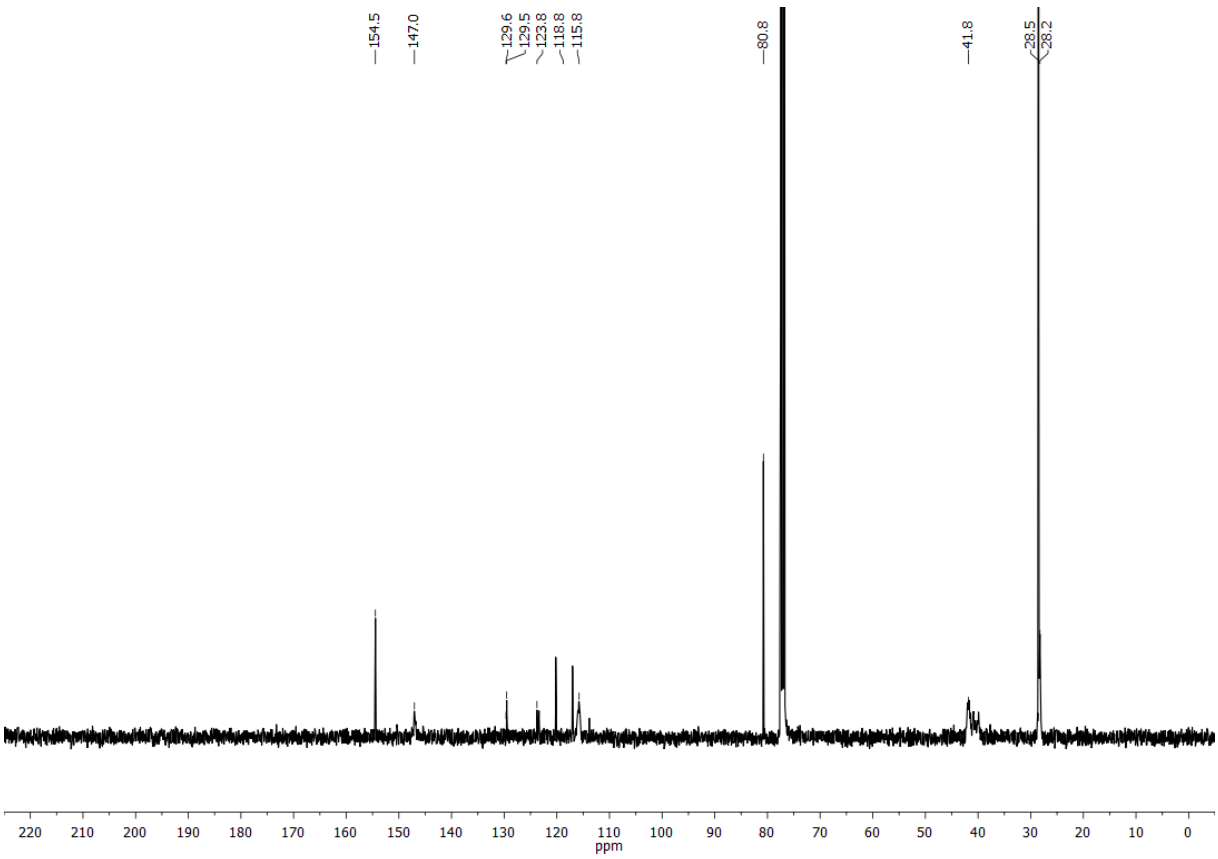
Compound **65e** **^{19}F-NMR** ($CDCl_3$)



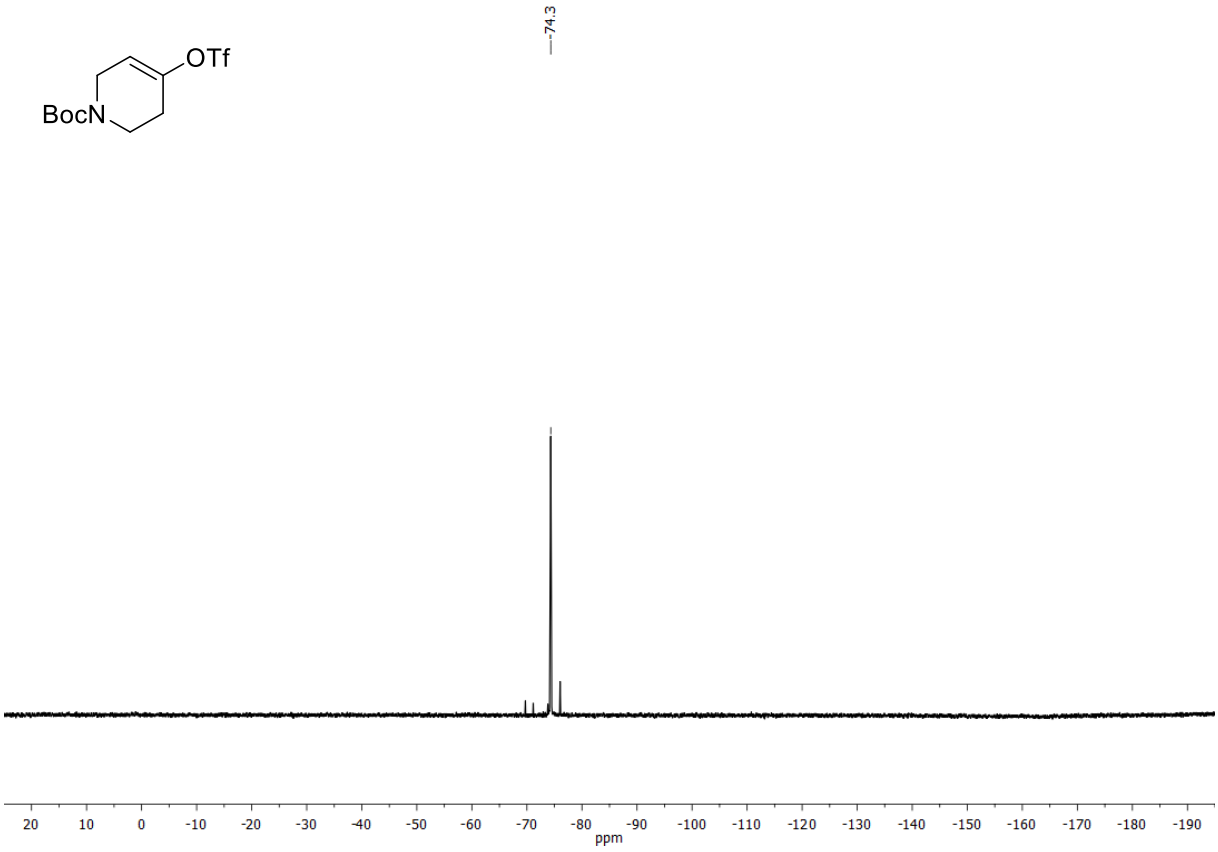
Compound **65f** ^{1}**H-NMR** ($CDCl_3$)



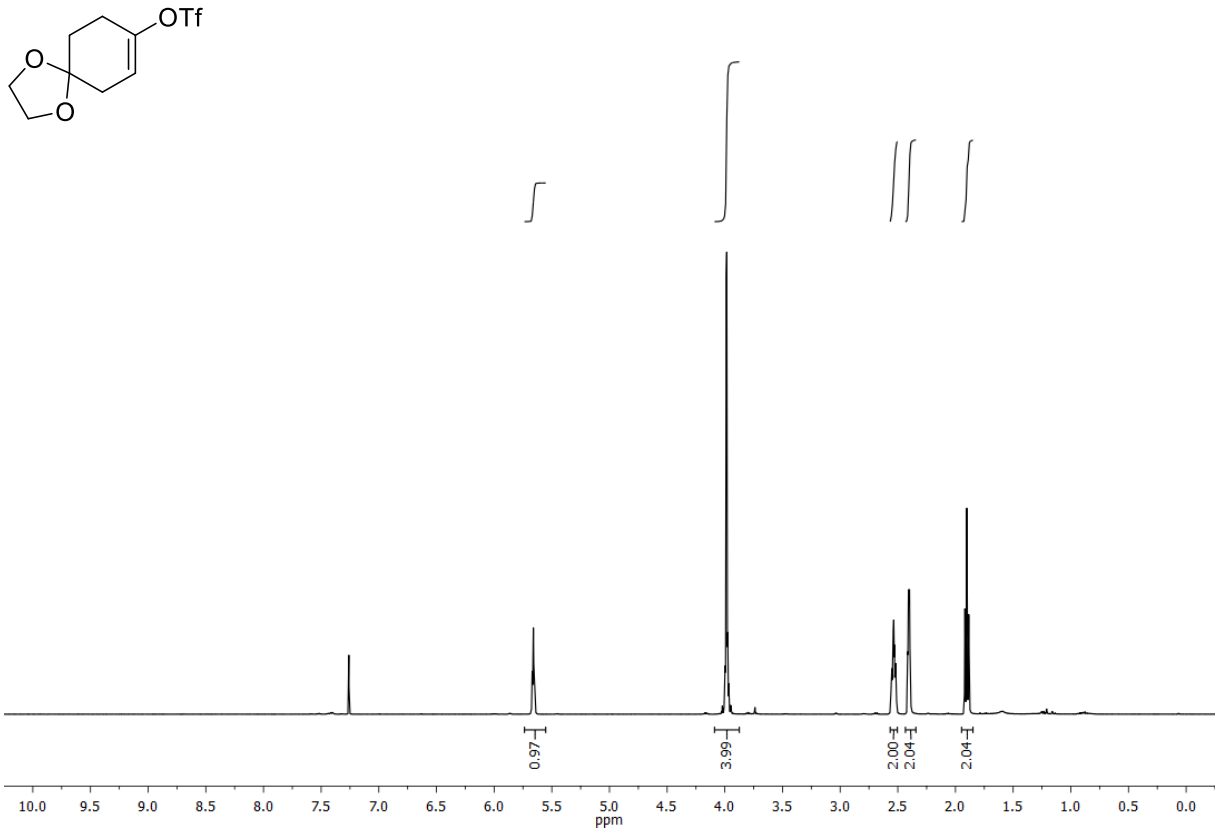
Compound **65f** ^{13}**C-NMR** ($CDCl_3$)



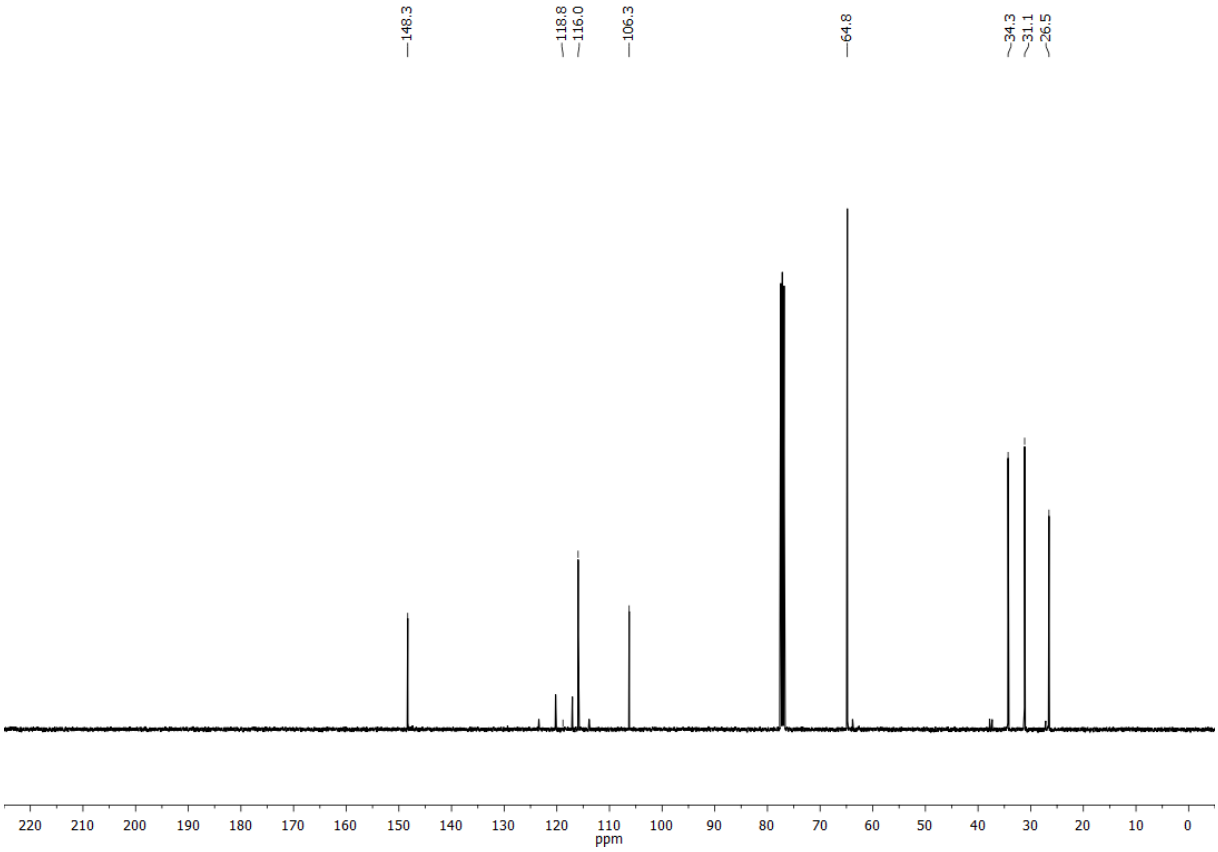
Compound **65f** ^{19}**F-NMR** ($CDCl_3$)



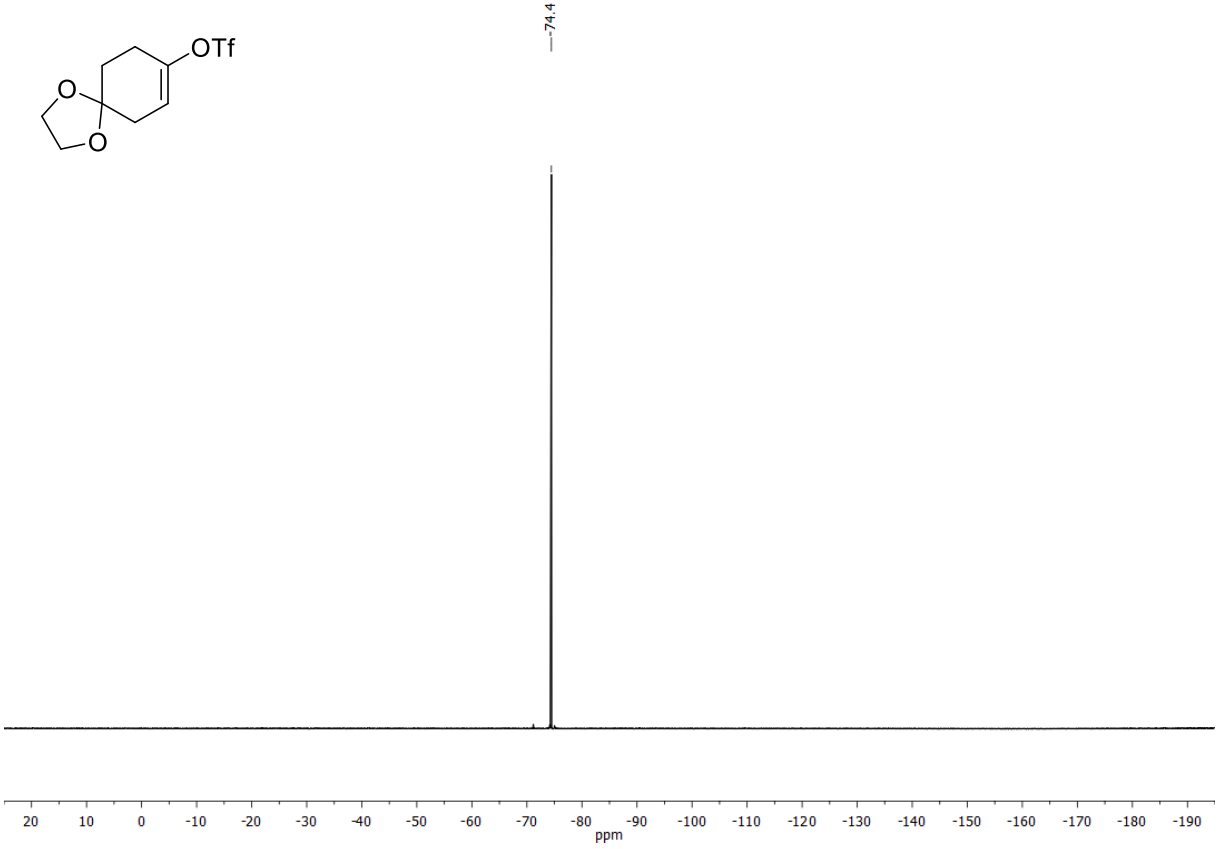
Compound **65g** ^{1}**H-NMR** ($CDCl_3$)



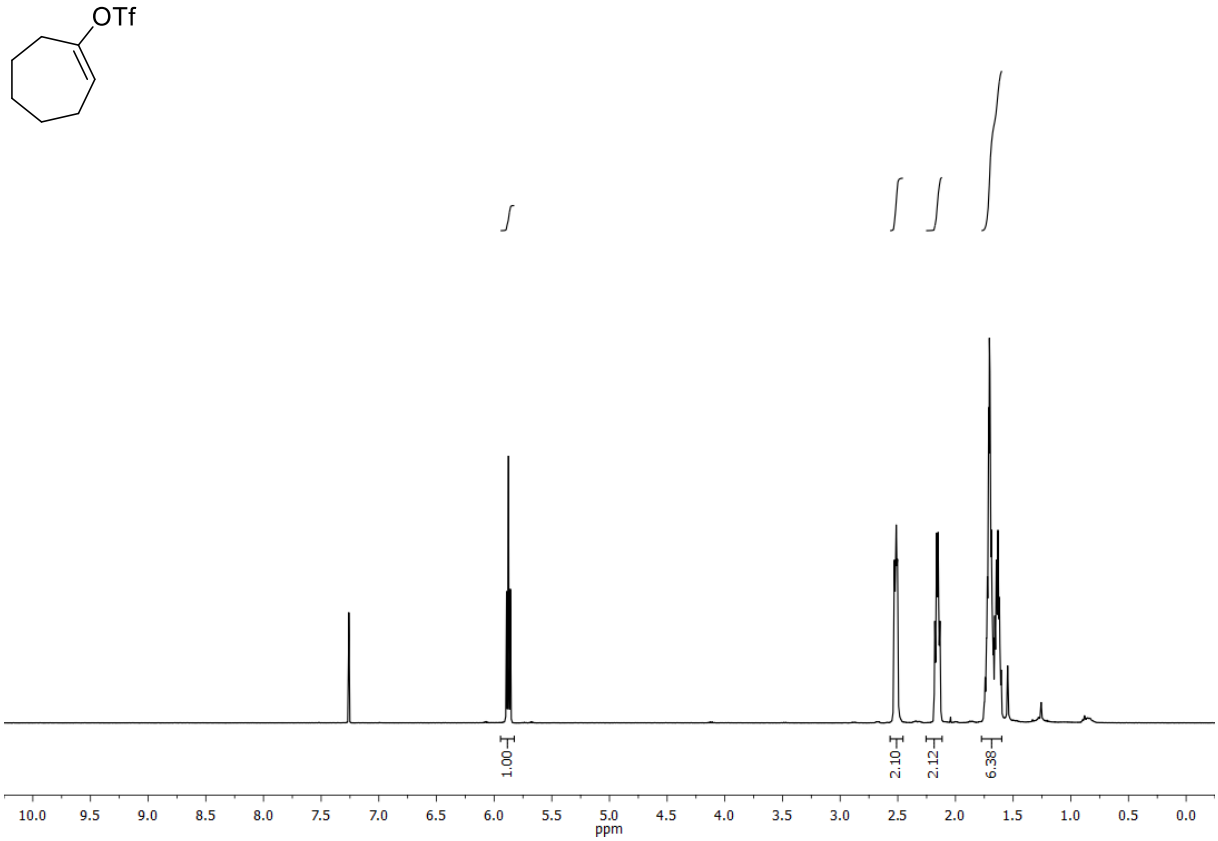
Compound **65g** ^{13}**C-NMR** ($CDCl_3$)



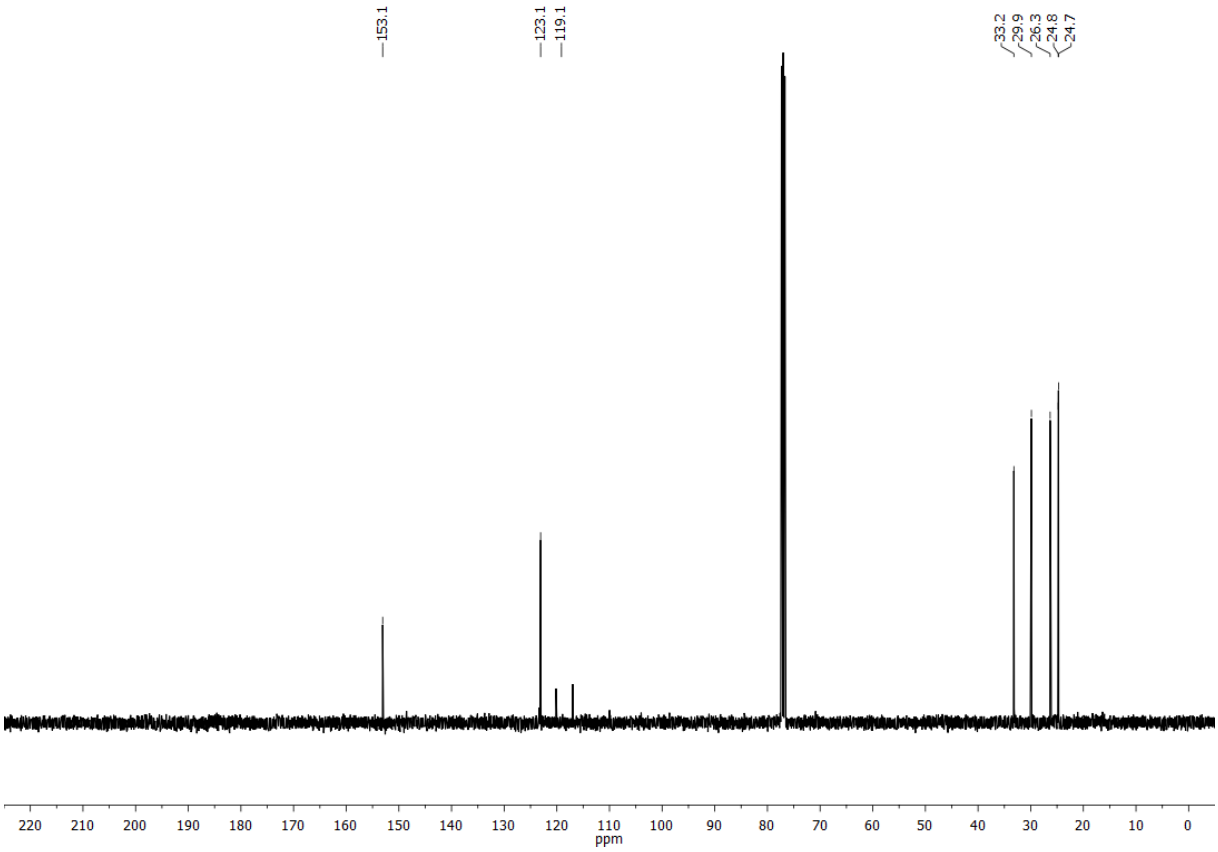
Compound **65g** ^{19}**F-NMR** ($CDCl_3$)



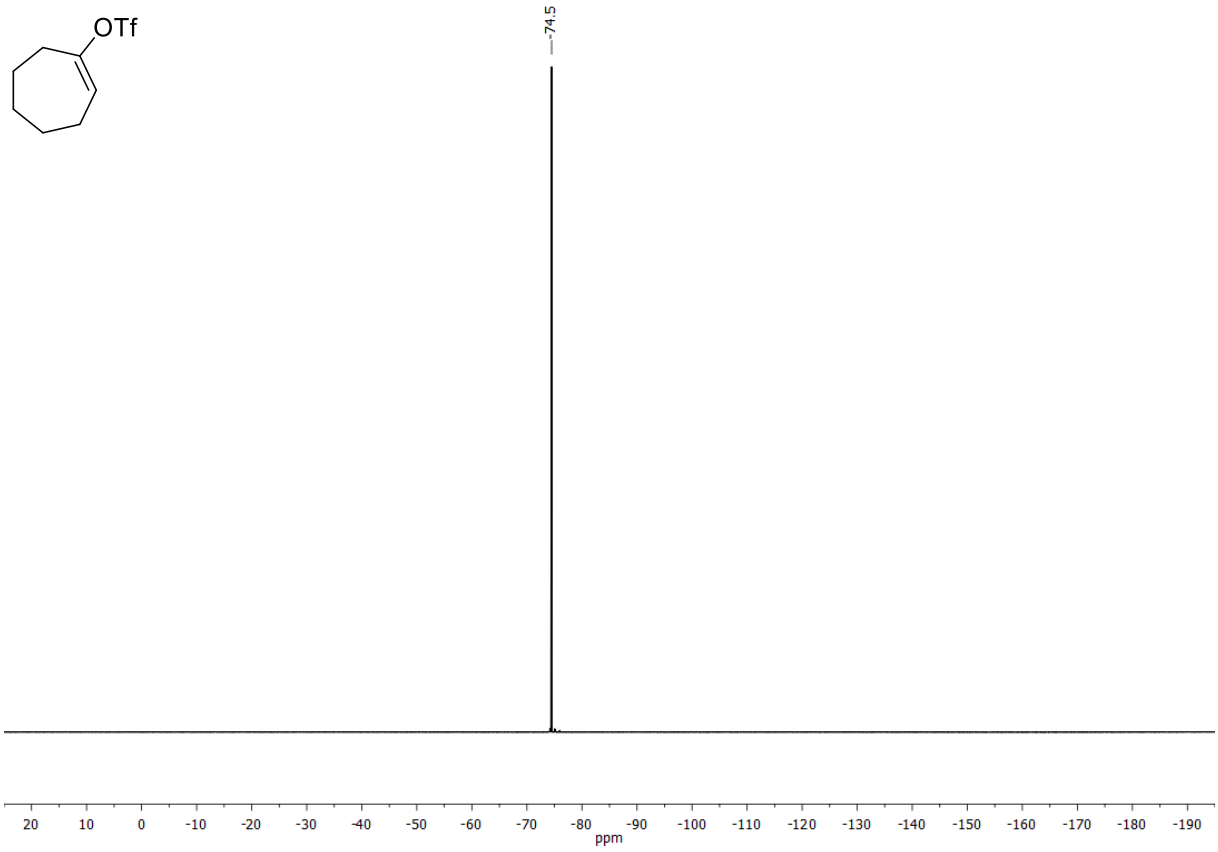
Compound **65h** ^{1}**H-NMR** ($CDCl_3$)



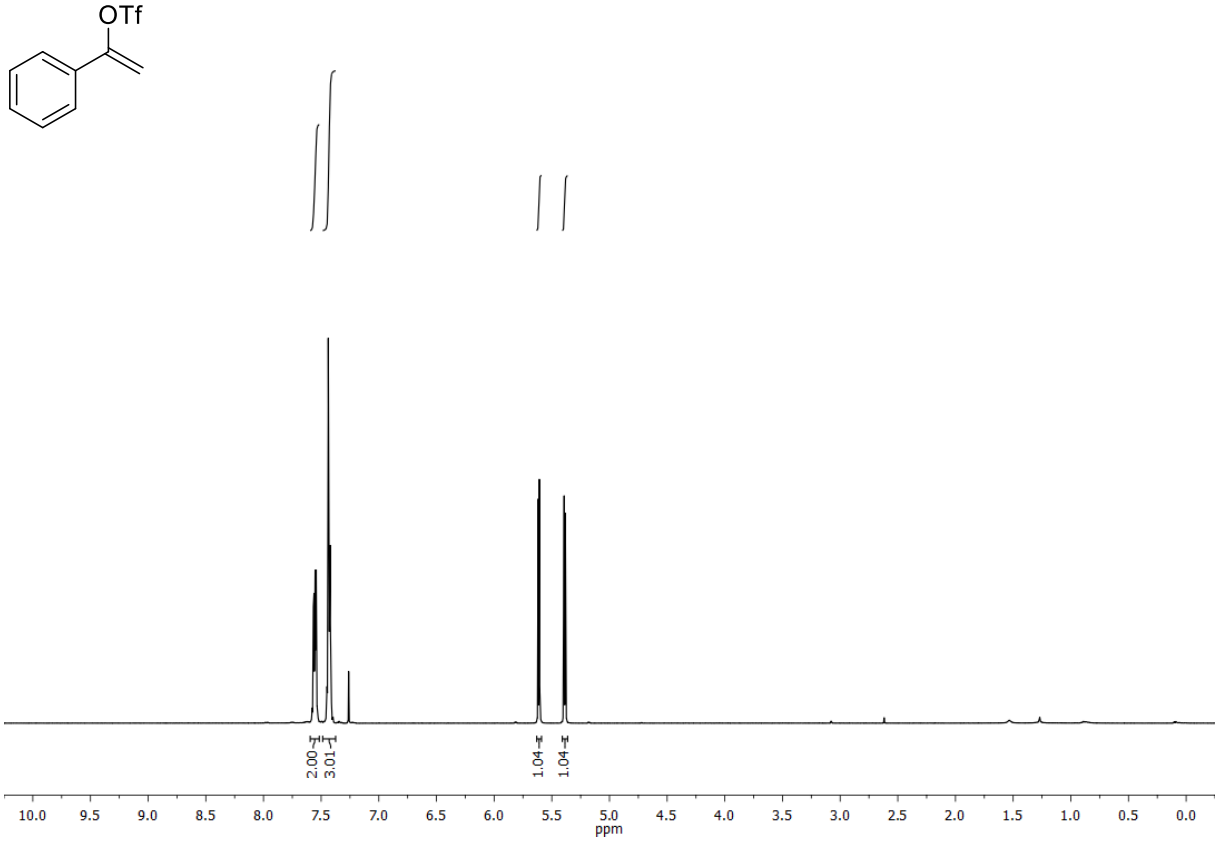
Compound **65h** ^{13}**C-NMR** ($CDCl_3$)



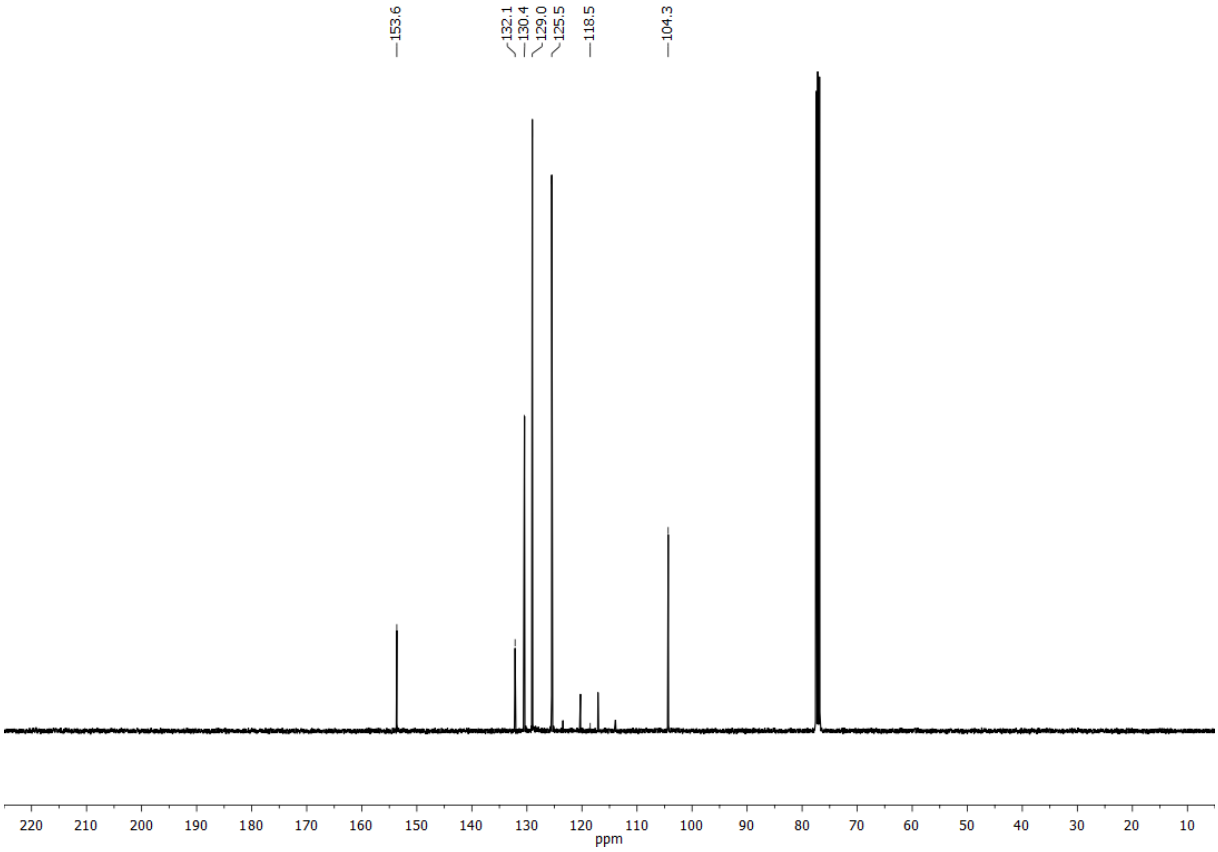
Compound **65h** ^{19}**F-NMR** ($CDCl_3$)



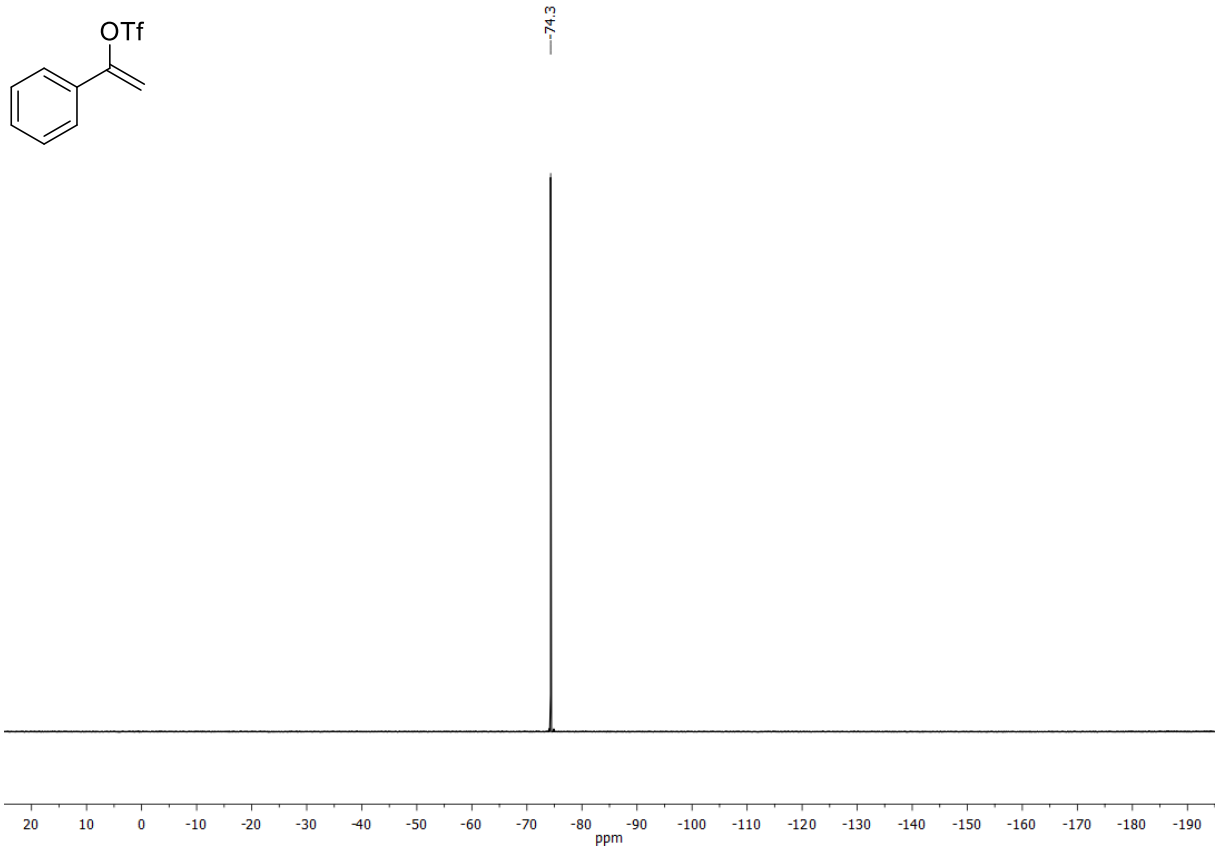
Compound **65i** ^{1}**H-NMR** ($CDCl_3$)



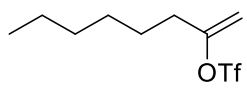
Compound **65i** ^{13}**C-NMR** ($CDCl_3$)

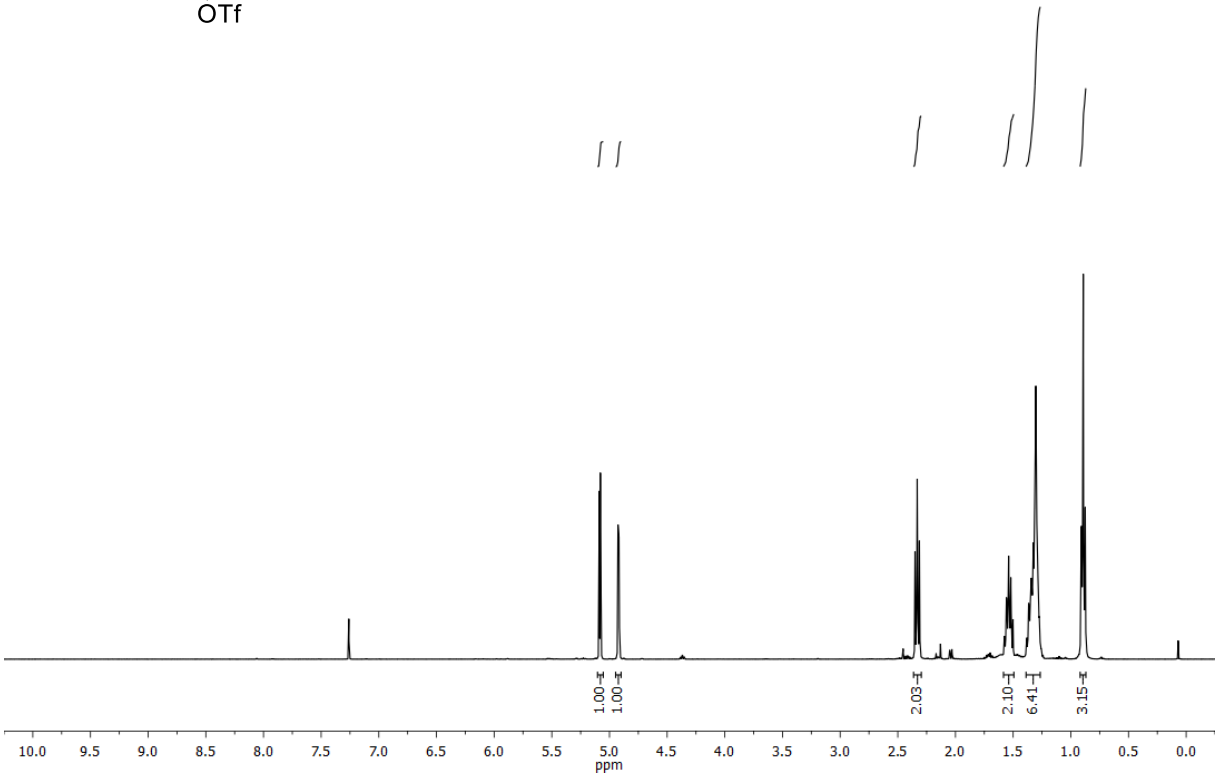


Compound **65i** ^{19}**F-NMR** ($CDCl_3$)

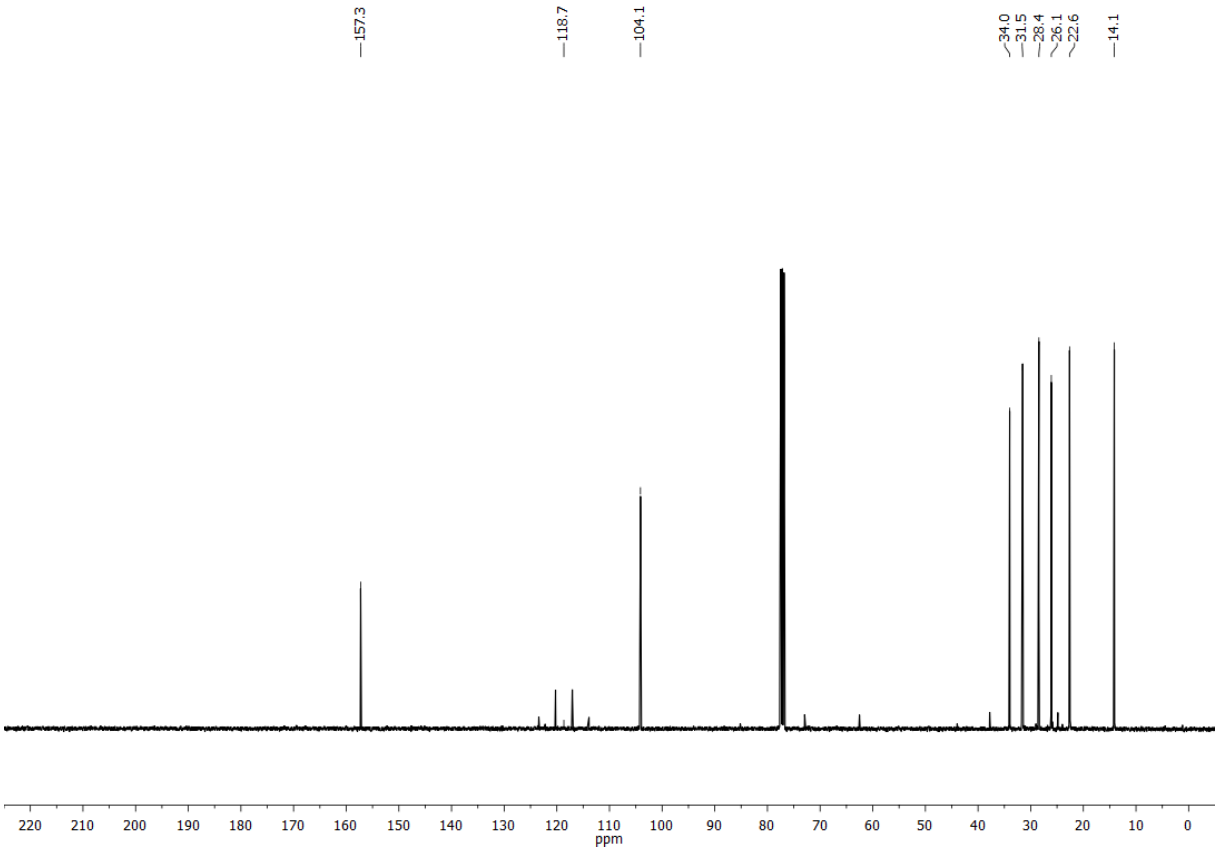


Compound **65j** ^{1}**H-NMR** ($CDCl_3$)

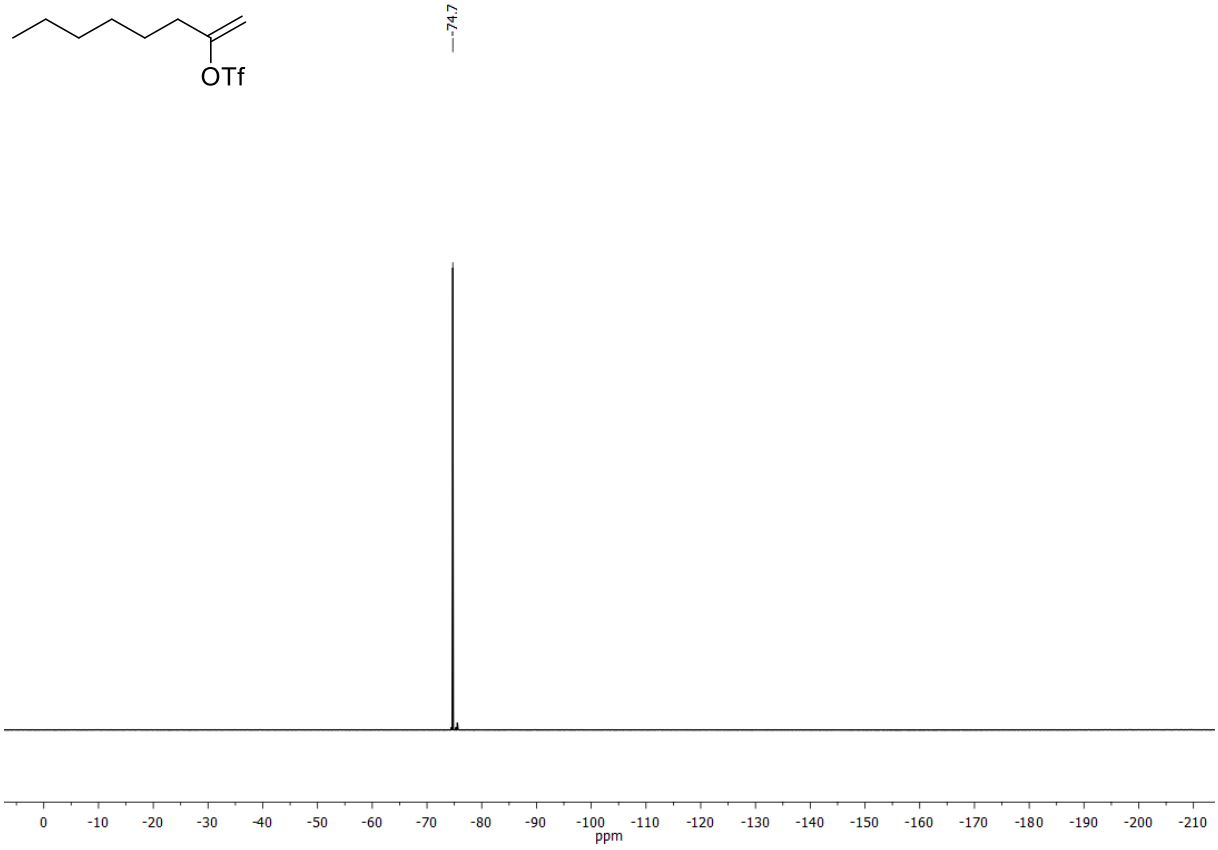




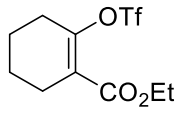
Compound **65j** ^{13}**C-NMR** ($CDCl_3$)

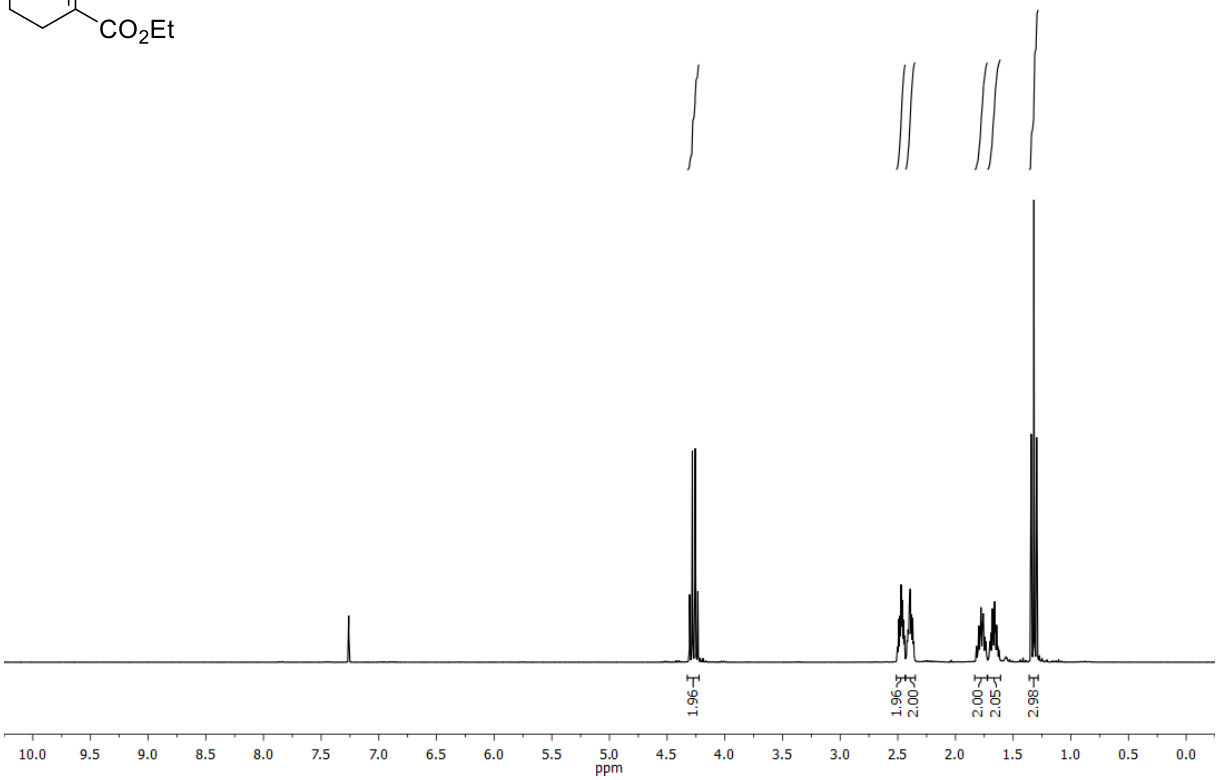


Compound **65j** **^{19}F-NMR** ($CDCl_3$)

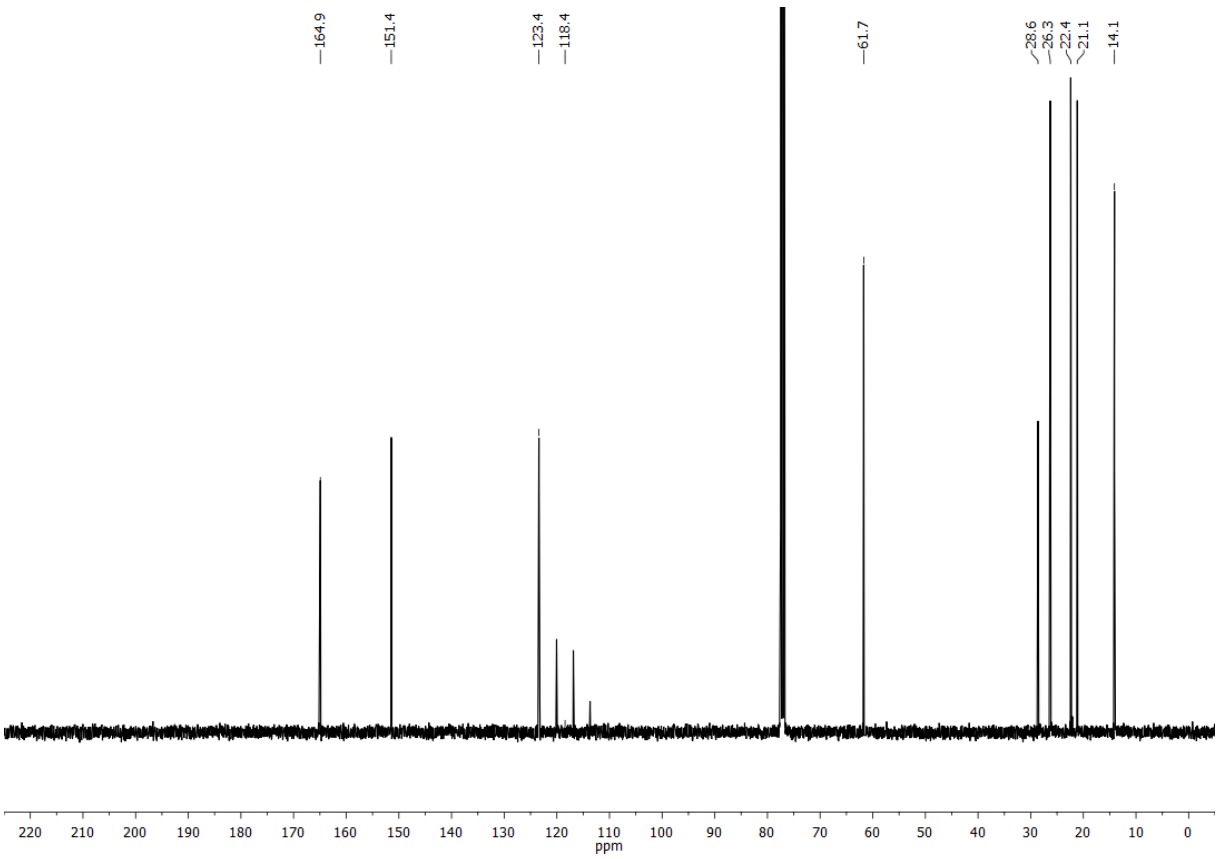


Compound **65k** ^{1}**H-NMR** ($CDCl_3$)

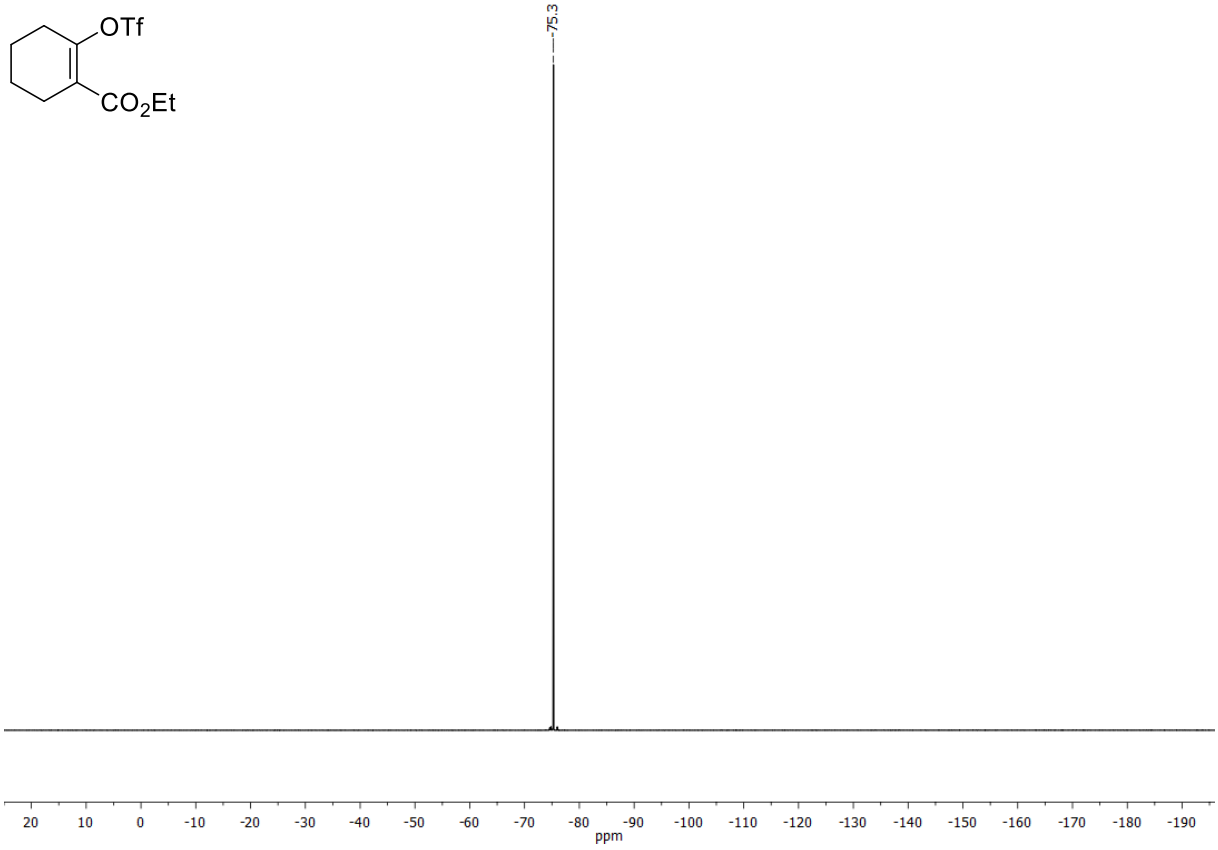




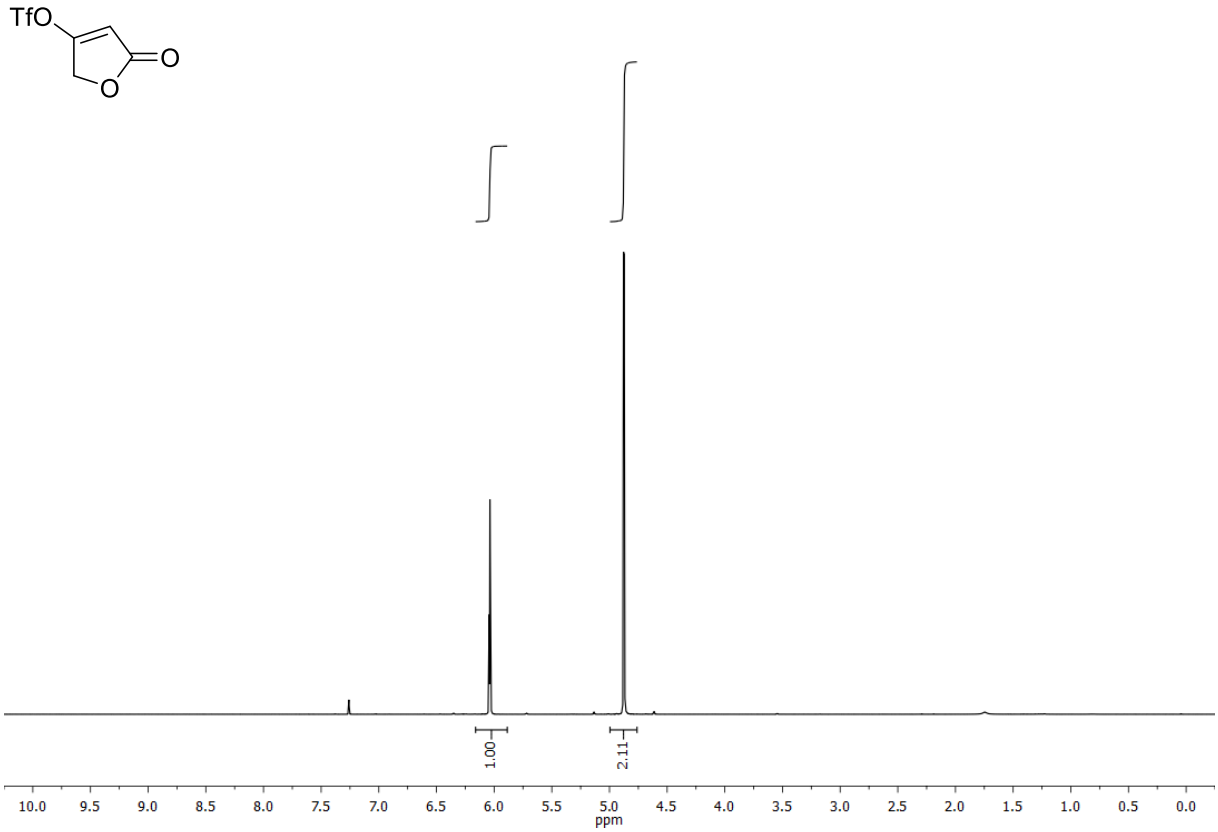
Compound **65k** ^{13}**C-NMR** ($CDCl_3$)



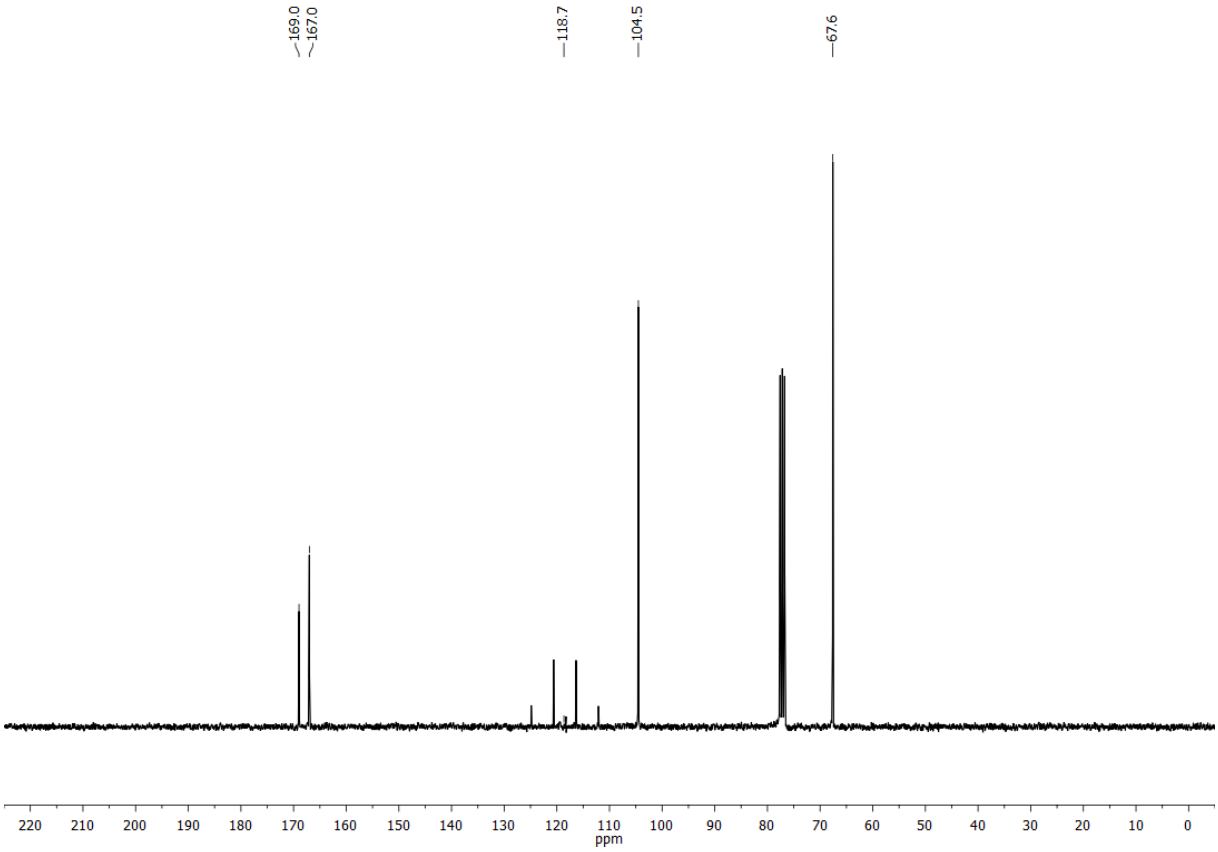
Compound **65k** ^{19}**F-NMR** ($CDCl_3$)



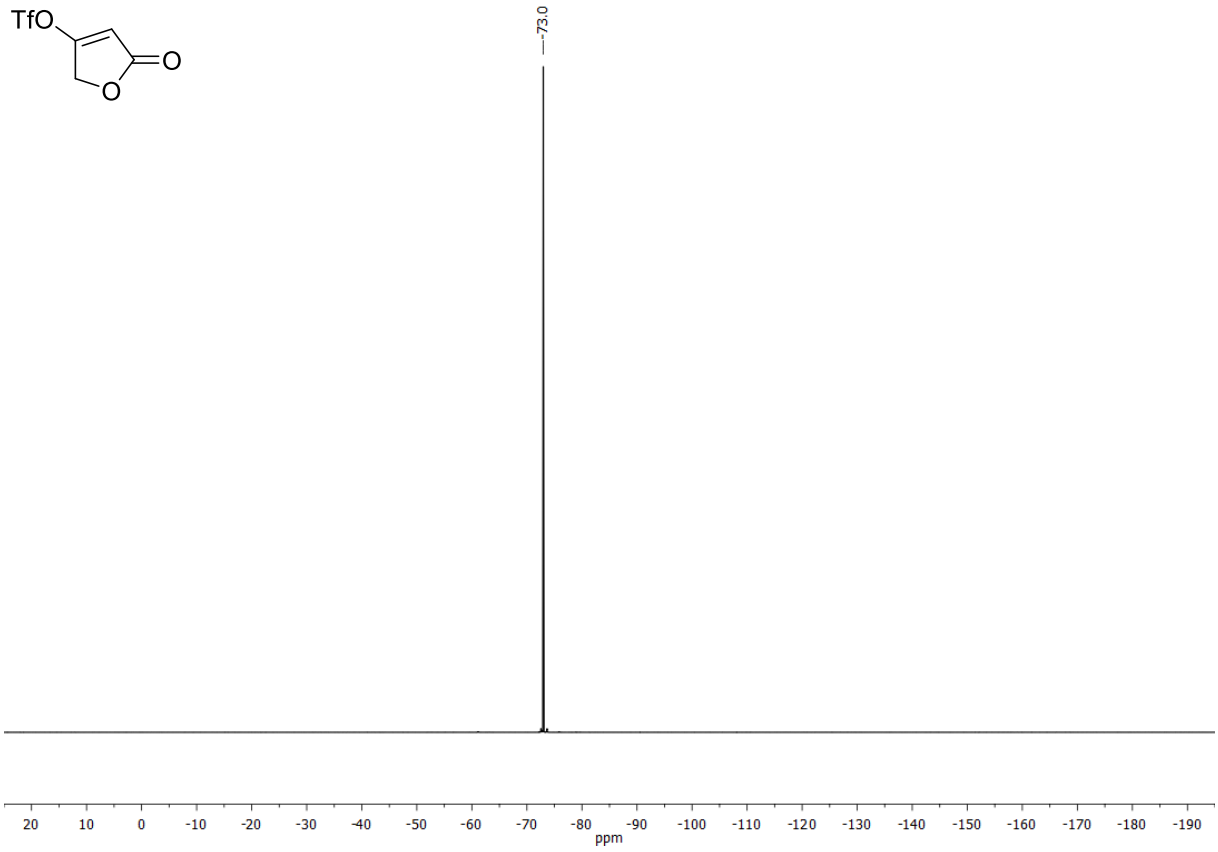
Compound **65l** ^{1}**H-NMR** ($CDCl_3$)



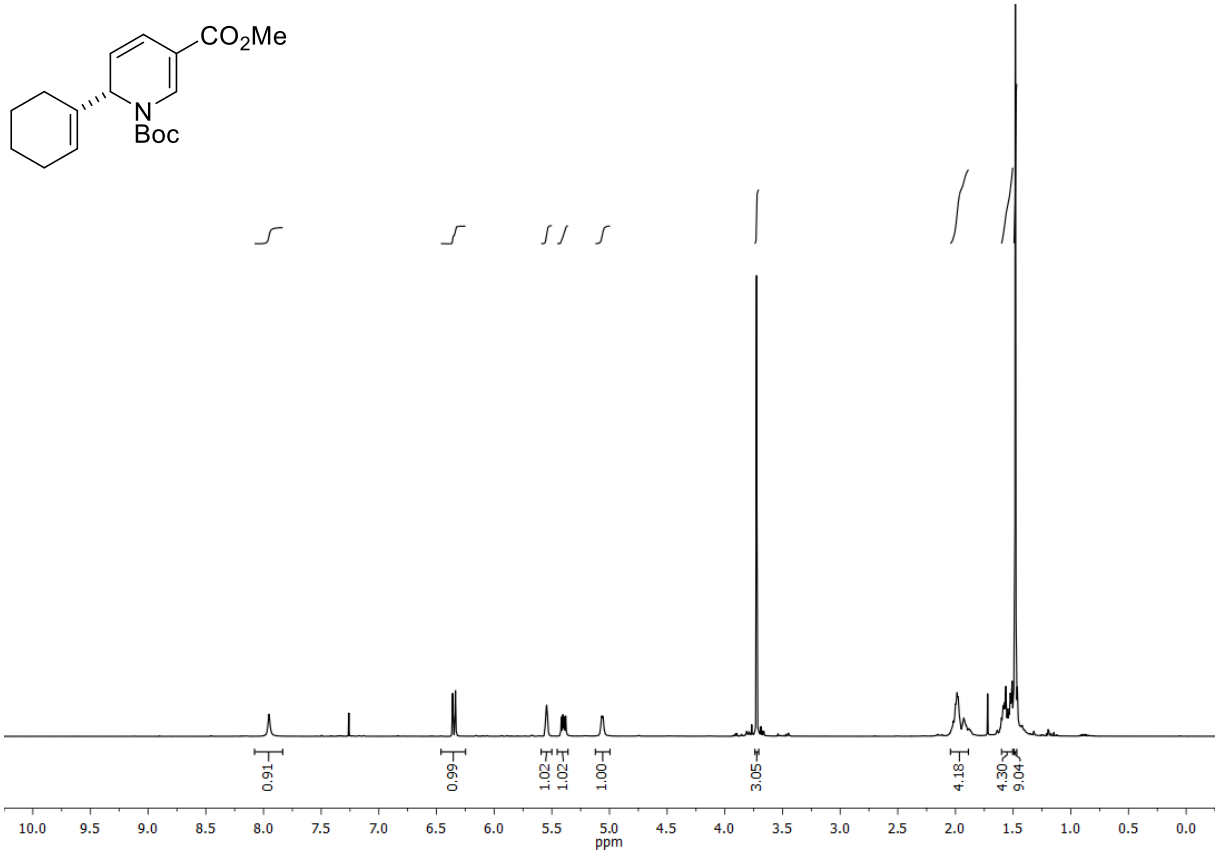
Compound **65l** ^{13}**C-NMR** ($CDCl_3$)



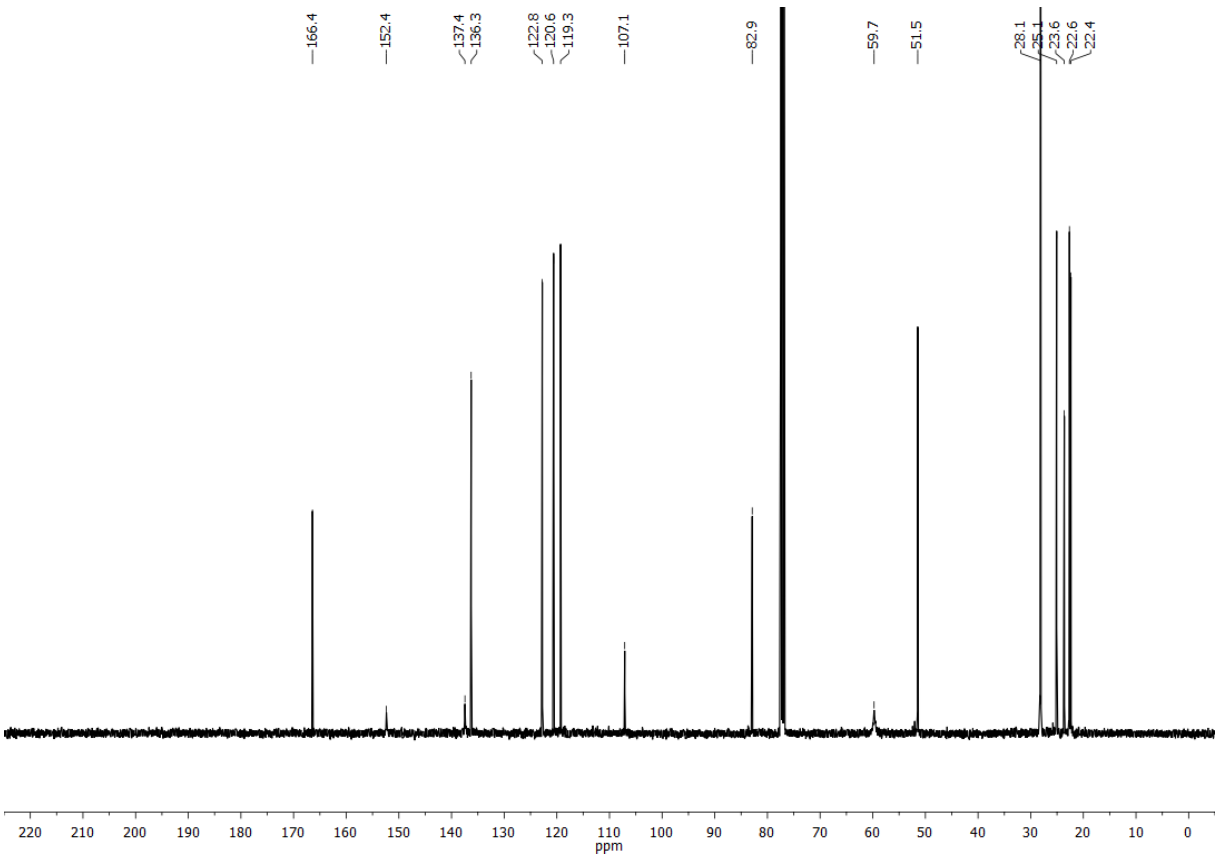
Compound **65l** ^{19}**F-NMR** ($CDCl_3$)



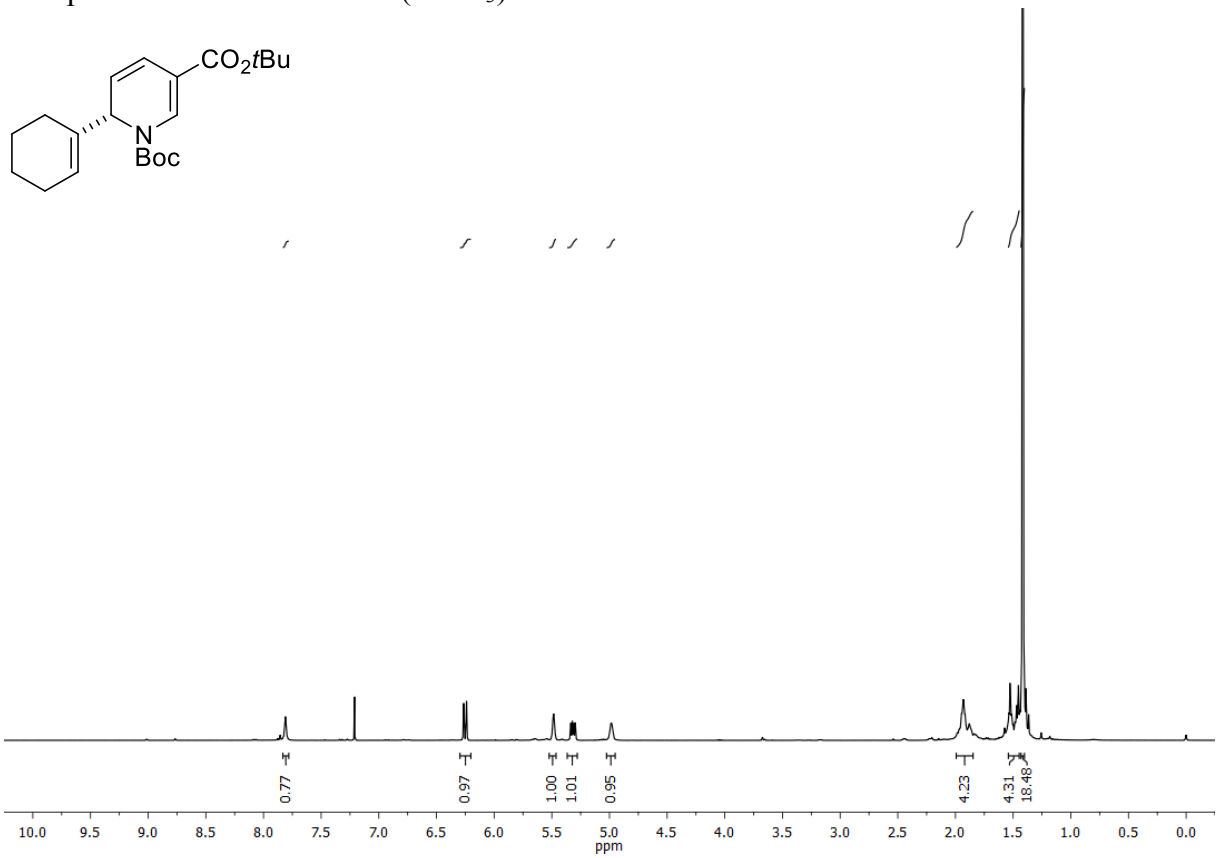
Compound **66a-Me ^{1}H-NMR** ($CDCl_3$)



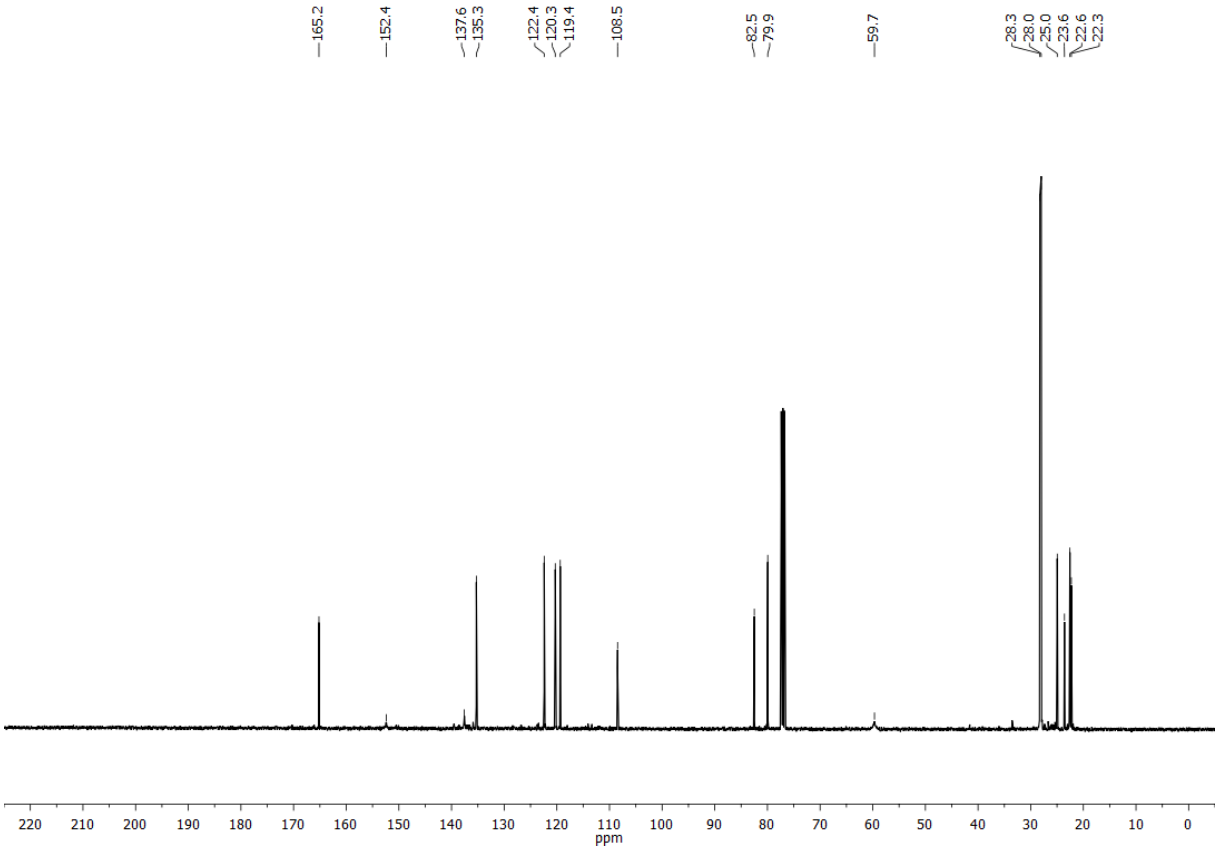
Compound **66a-Me ^{13}C-NMR** ($CDCl_3$)



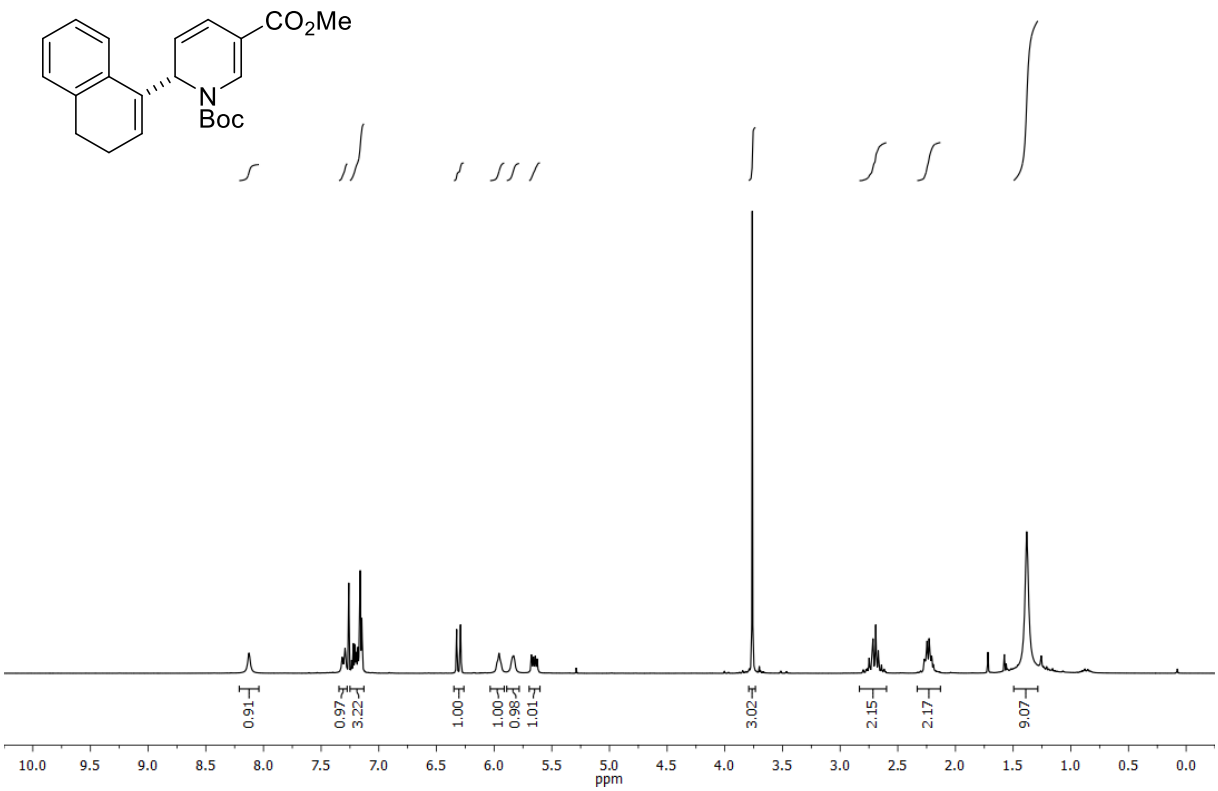
Compound **66a-*t*Bu ^{1}H-NMR** ($CDCl_3$)



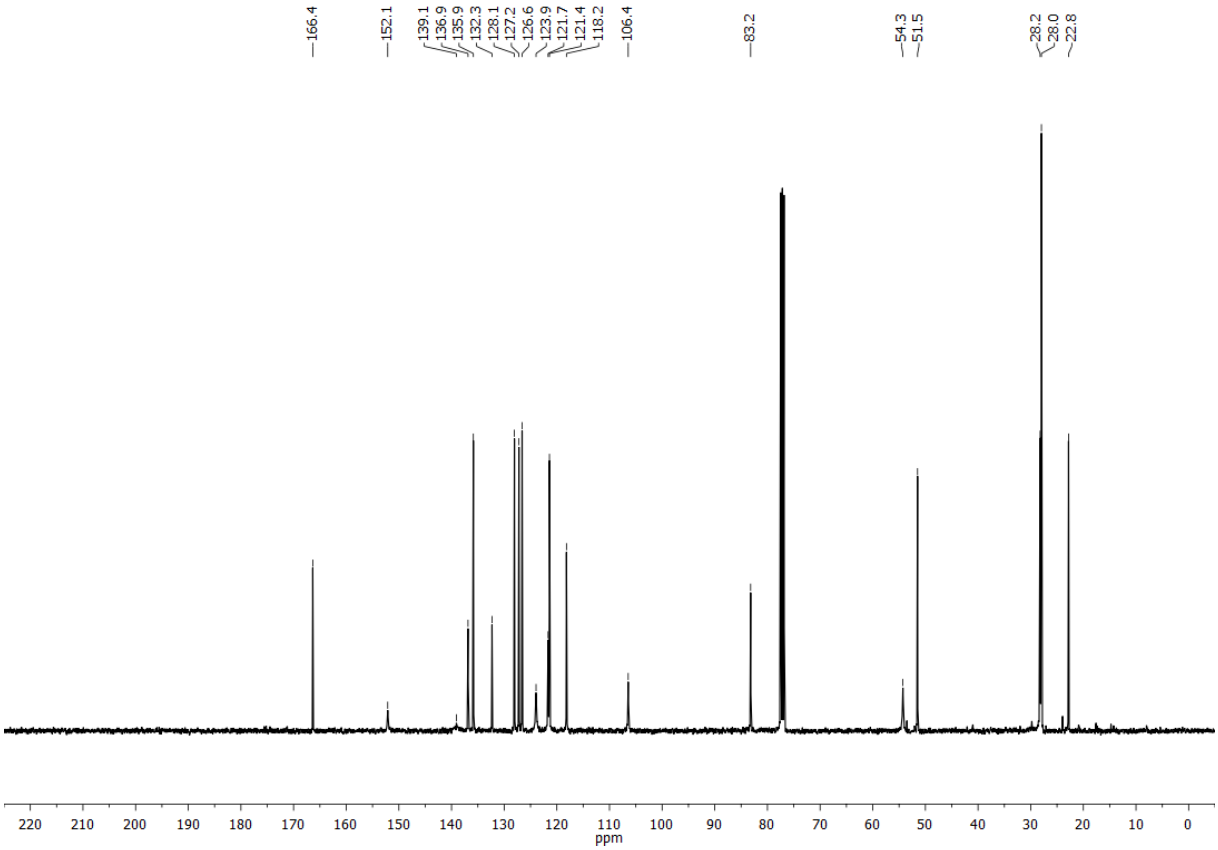
Compound **66a-*t*Bu ^{13}C-NMR** ($CDCl_3$)



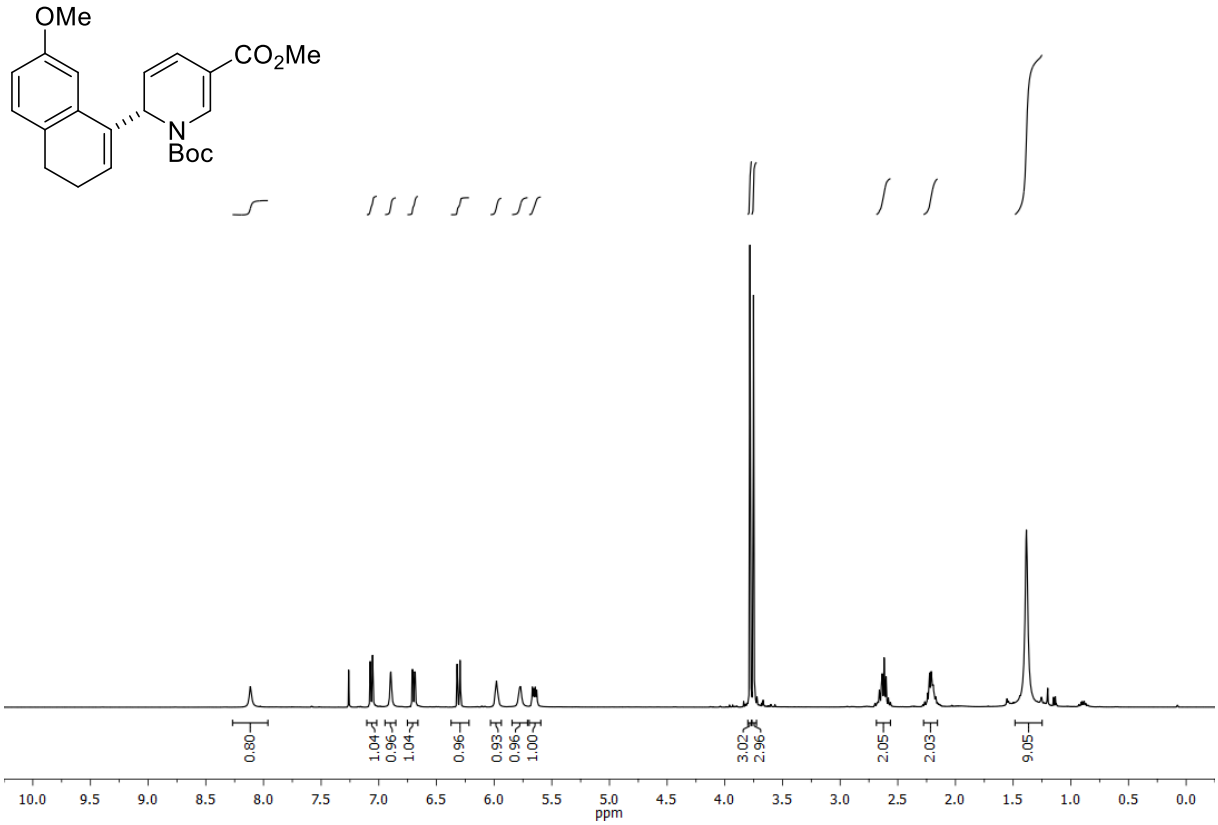
Compound **66b-Me ^{1}H-NMR** ($CDCl_3$)



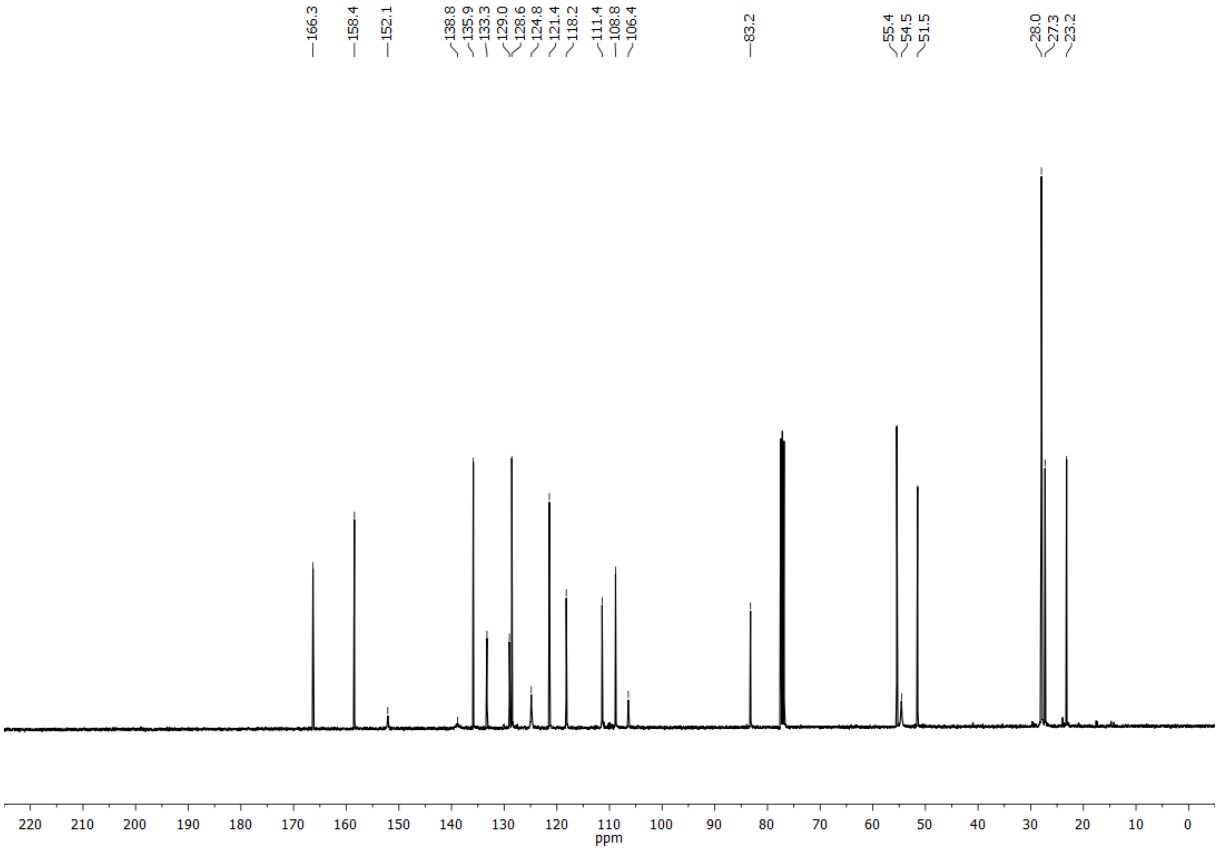
Compound **66b-Me ^{13}C-NMR** ($CDCl_3$)



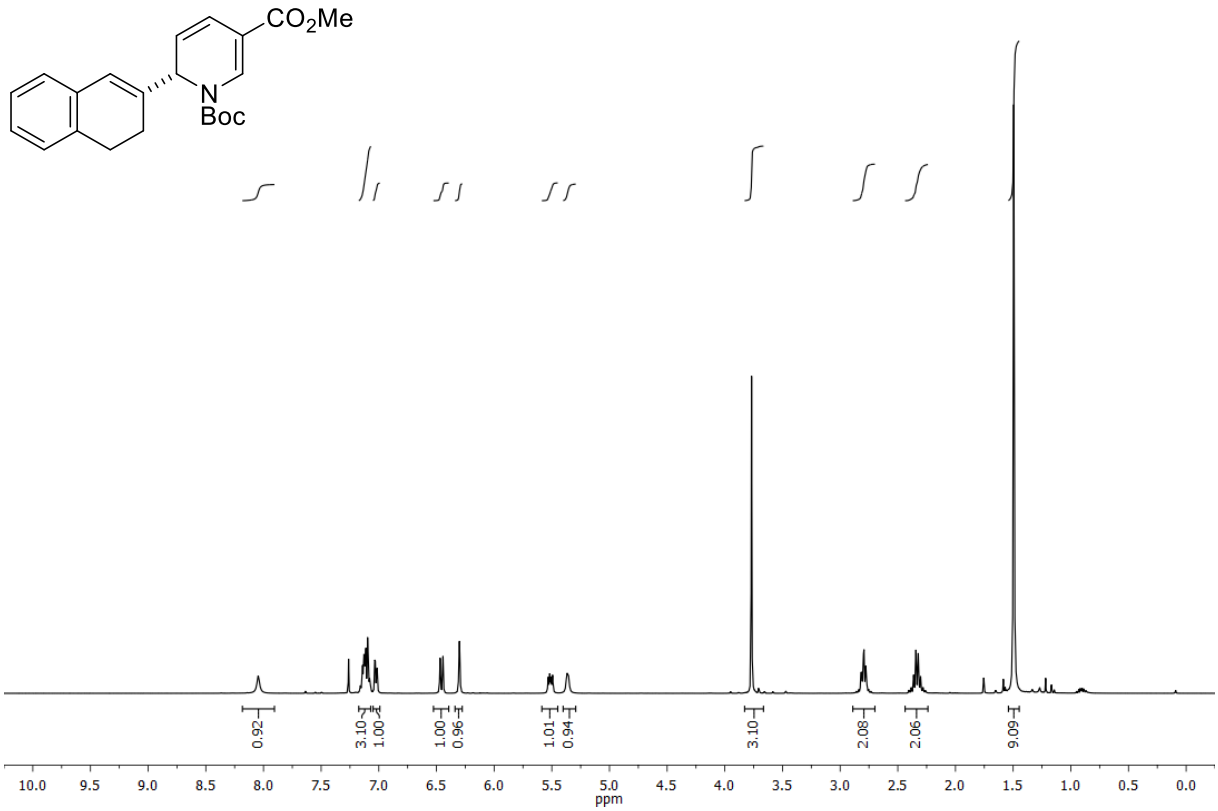
Compound **66d-Me ^{1}H-NMR** ($CDCl_3$)



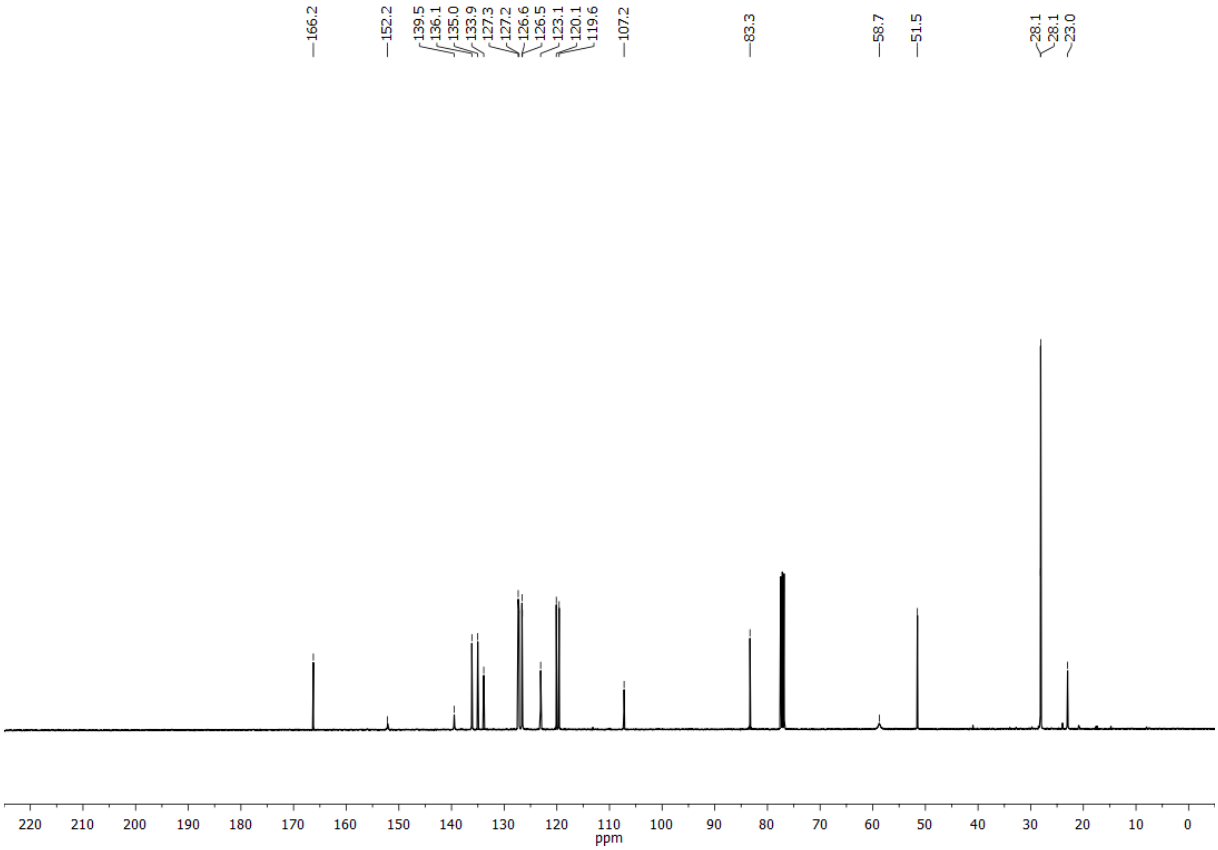
Compound **66d-Me ^{13}C-NMR** ($CDCl_3$)



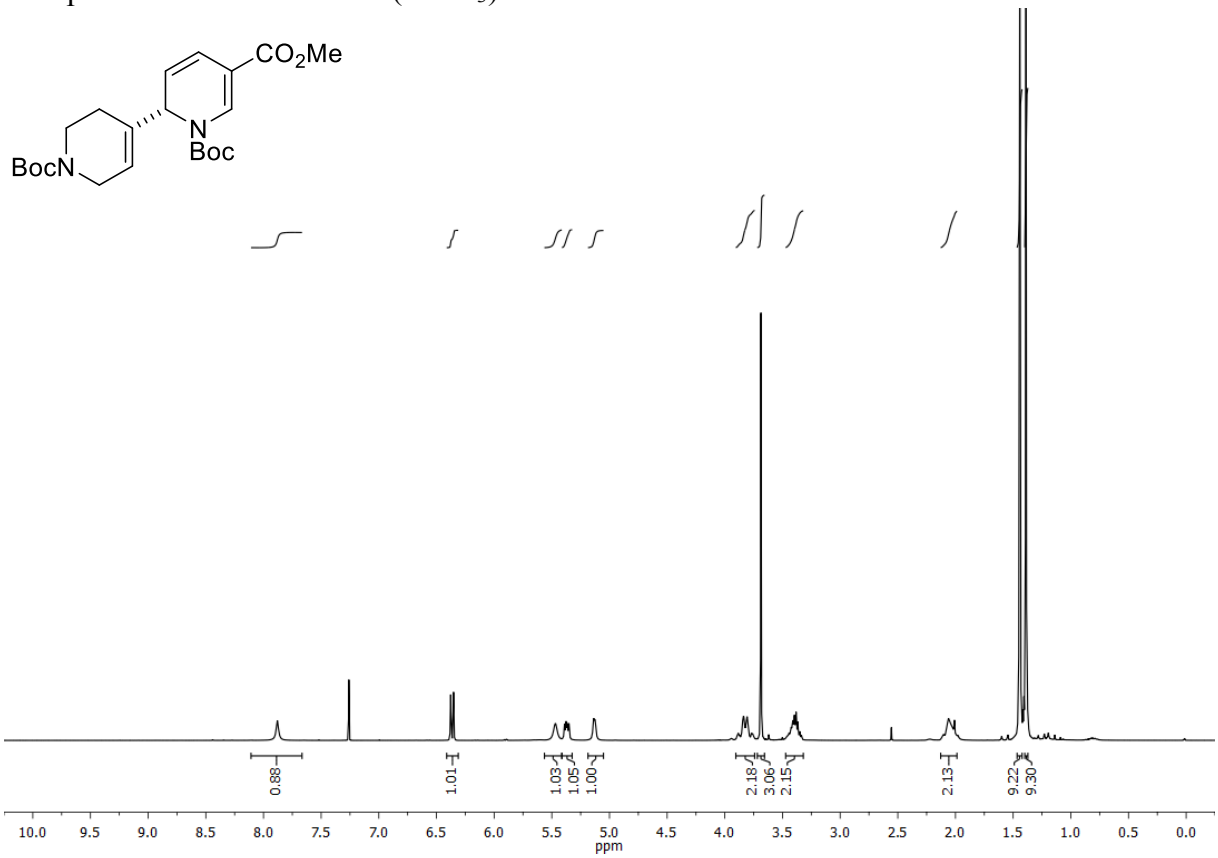
Compound **66e-Me ^{1}H-NMR** ($CDCl_3$)



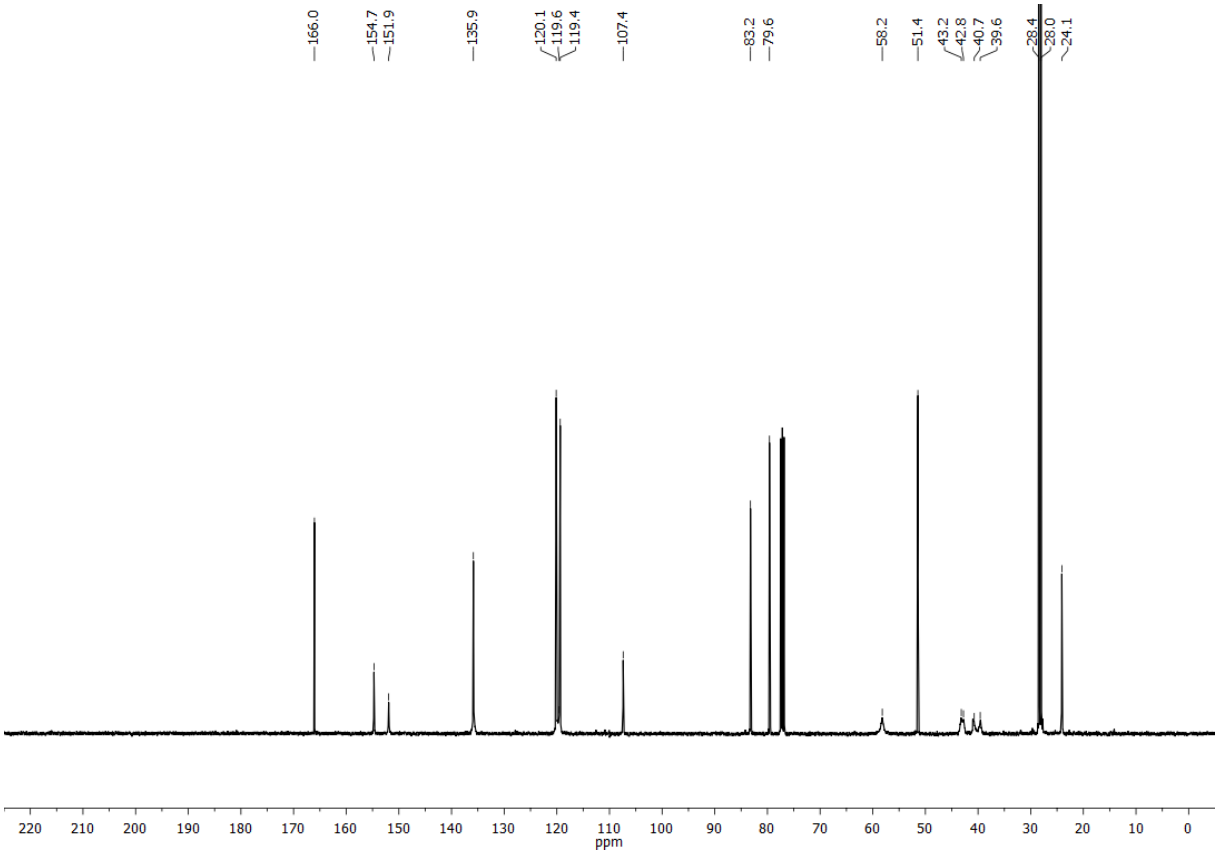
Compound **66e-Me ^{13}C-NMR** ($CDCl_3$)



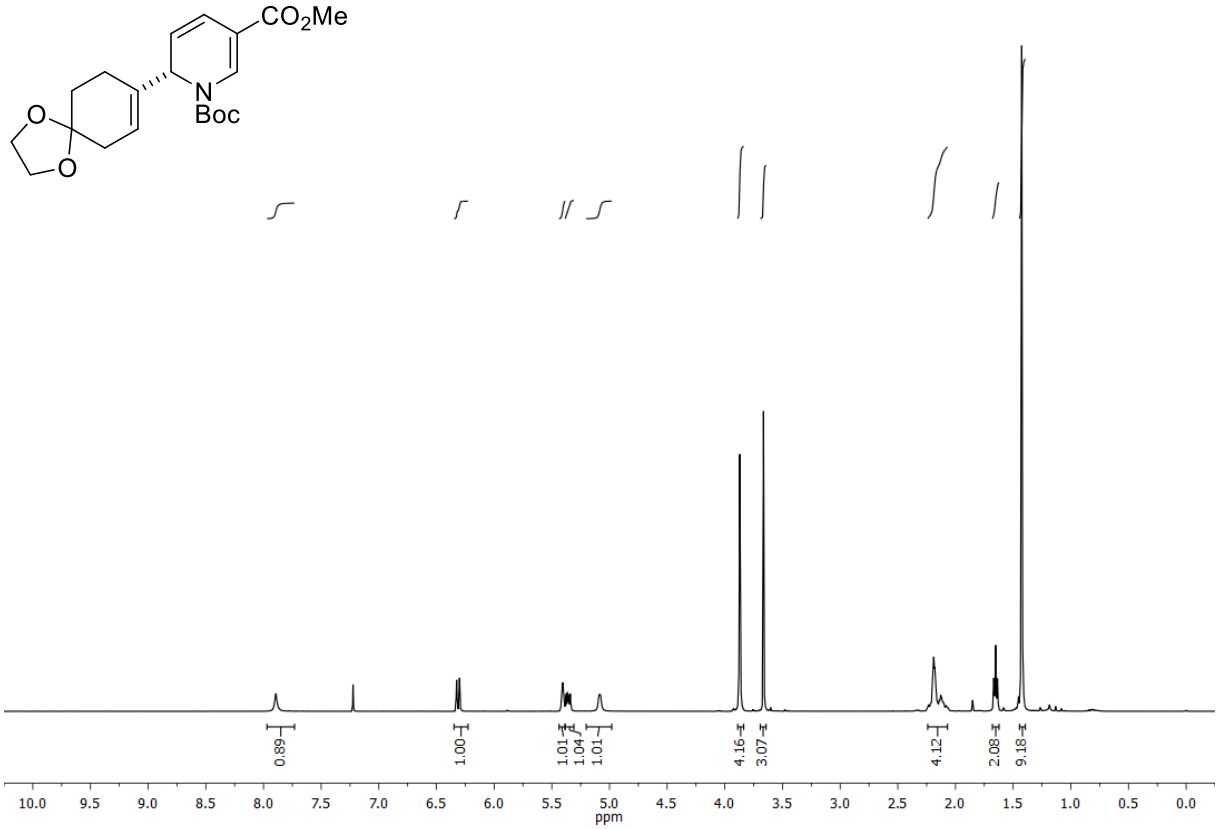
Compound **66f-Me ^{1}H-NMR** ($CDCl_3$)



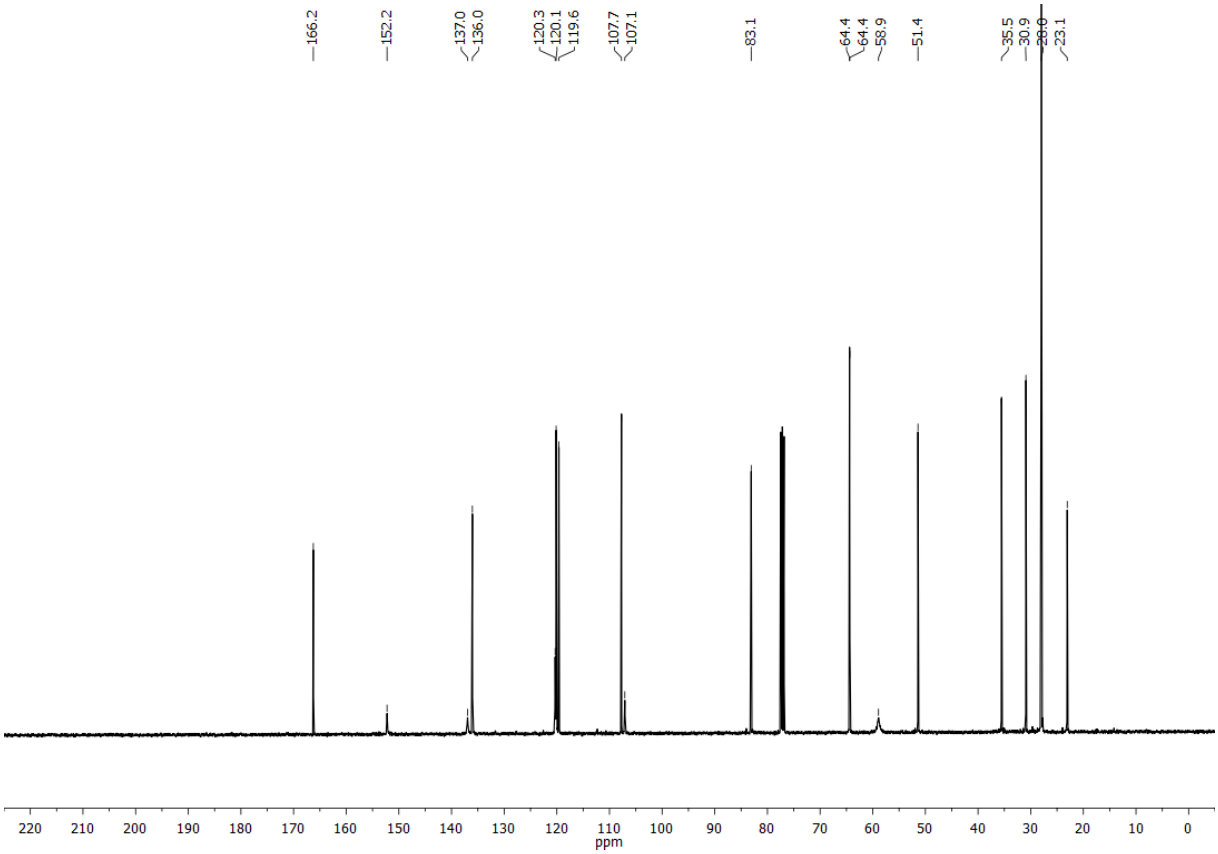
Compound **66f-Me ^{13}C-NMR** ($CDCl_3$)



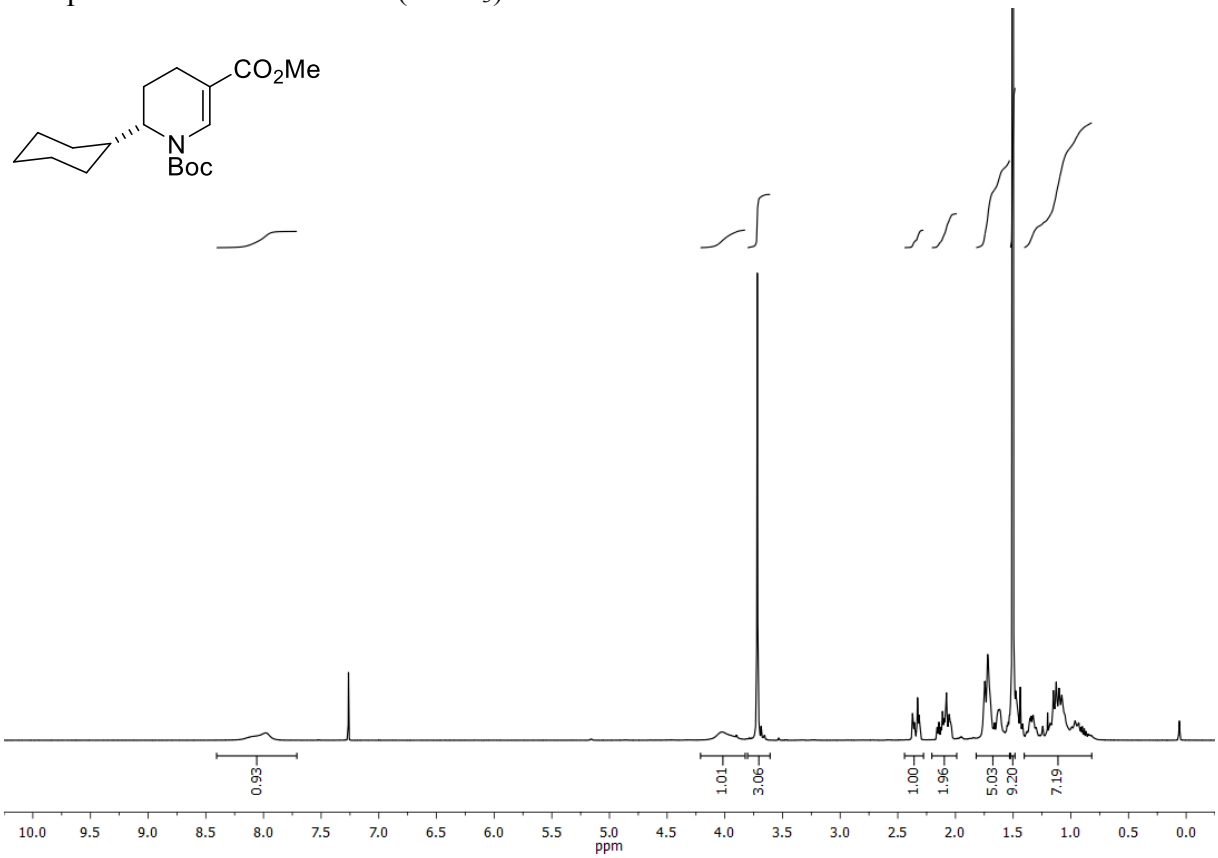
Compound **66g-Me ^{1}H-NMR** ($CDCl_3$)



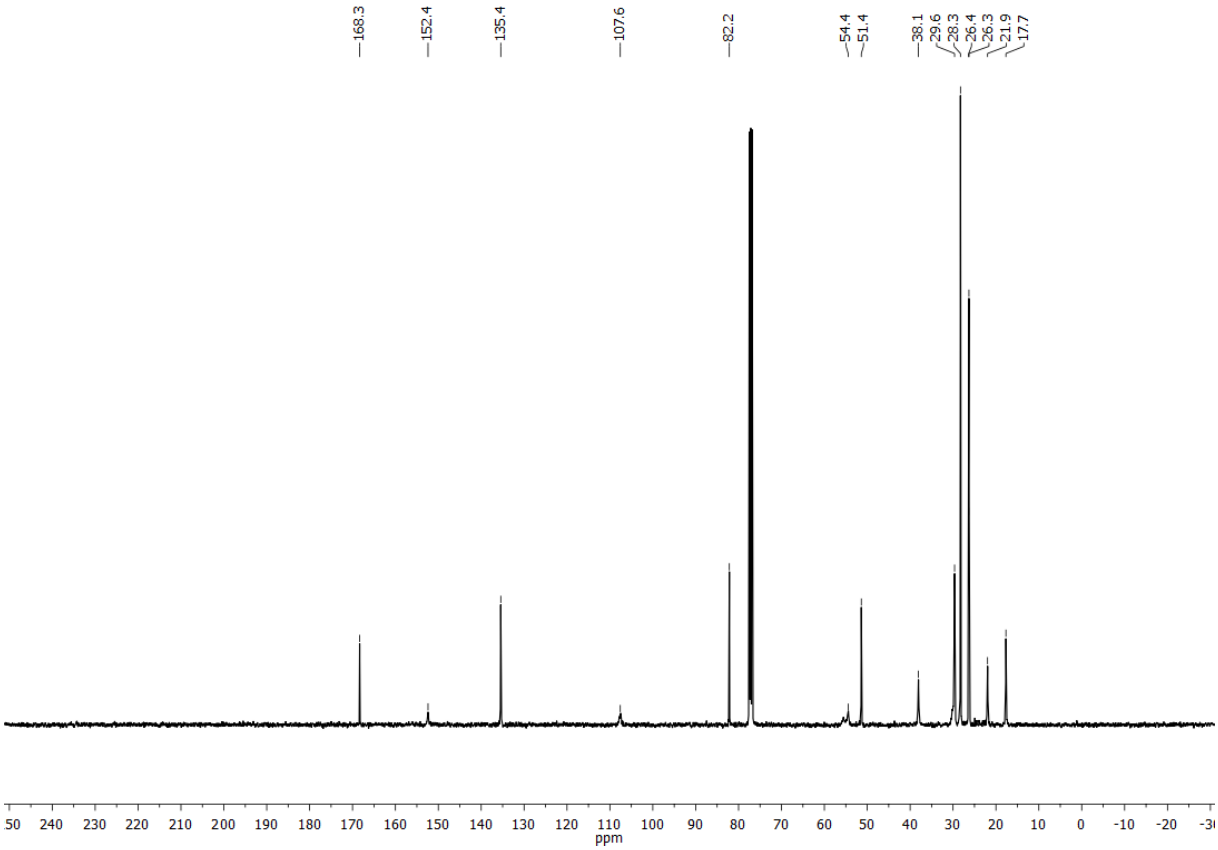
Compound **66g-Me ^{13}C-NMR** ($CDCl_3$)



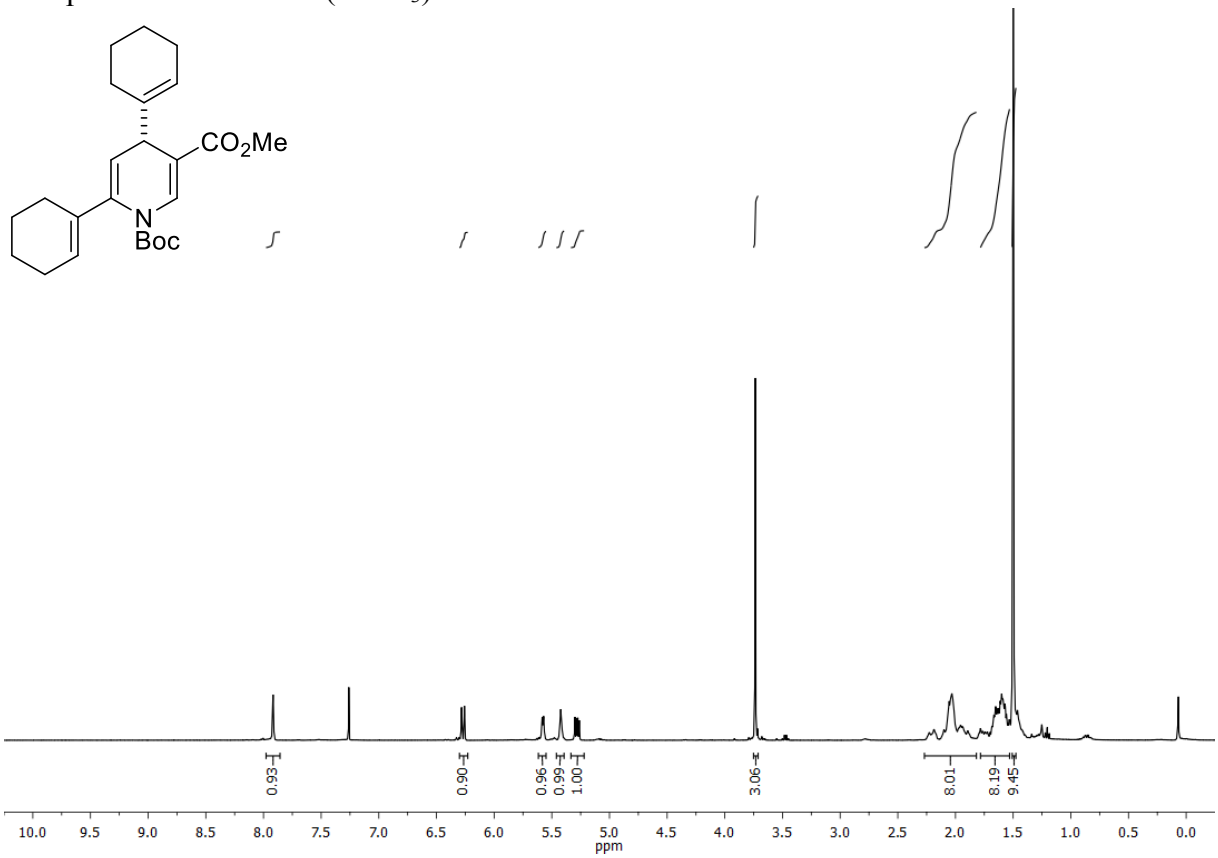
Compound **67a-Me** ^{1}**H-NMR** ($CDCl_3$)



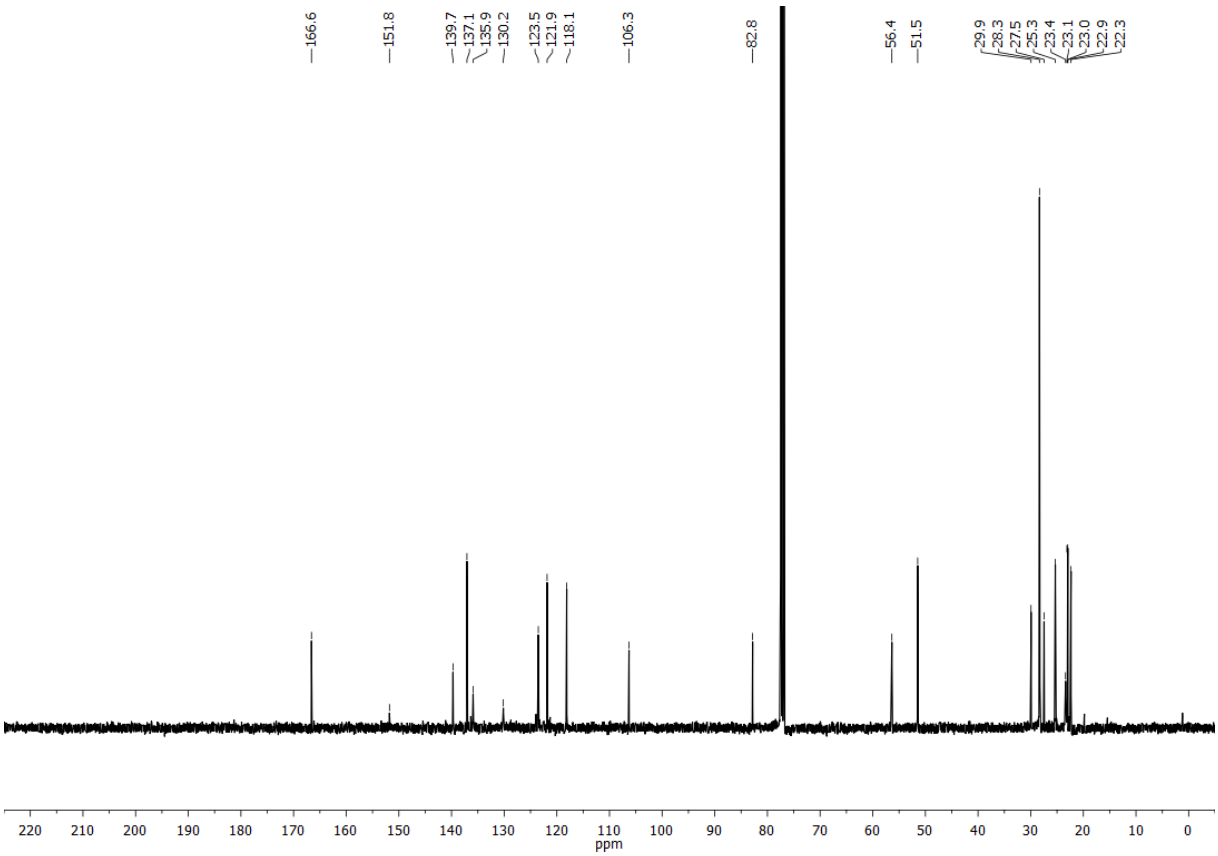
Compound **67a-Me** ^{13}**C-NMR** ($CDCl_3$)



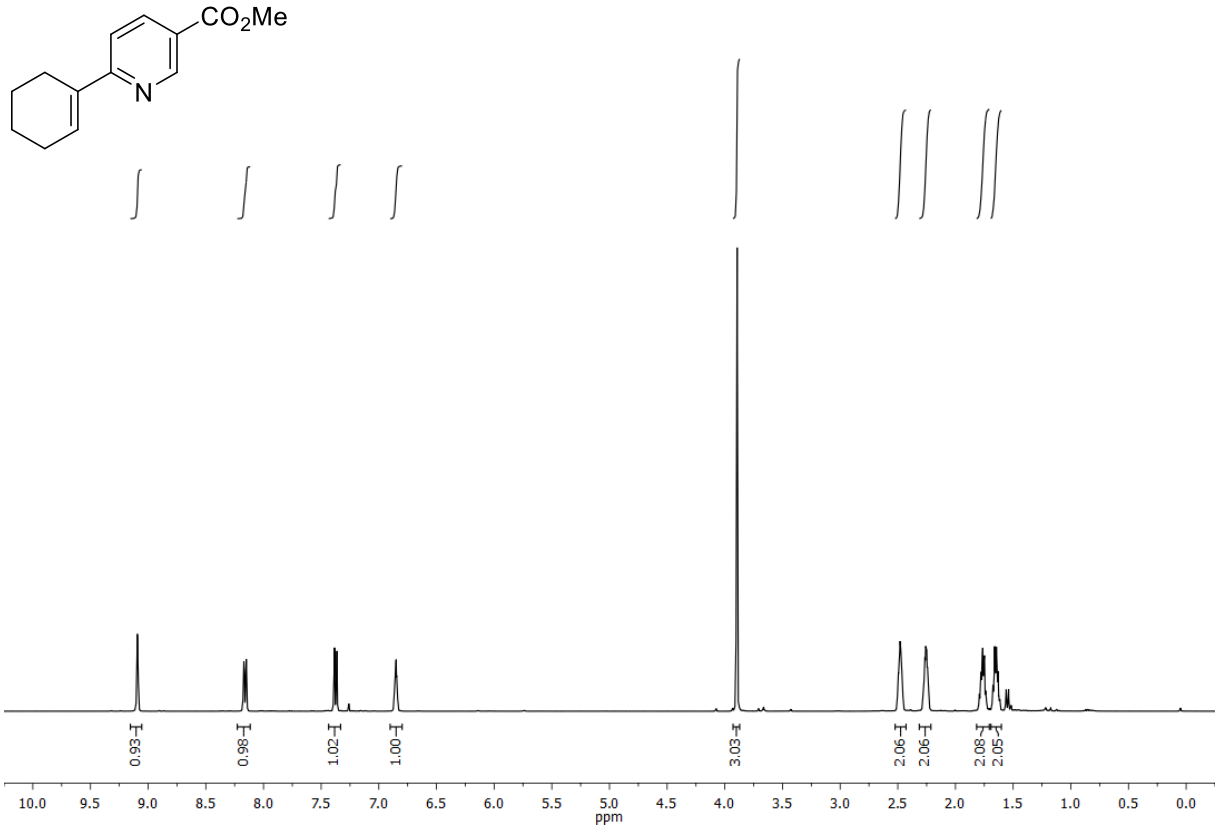
Compound **73** **^{1}H-NMR** ($CDCl_3$)



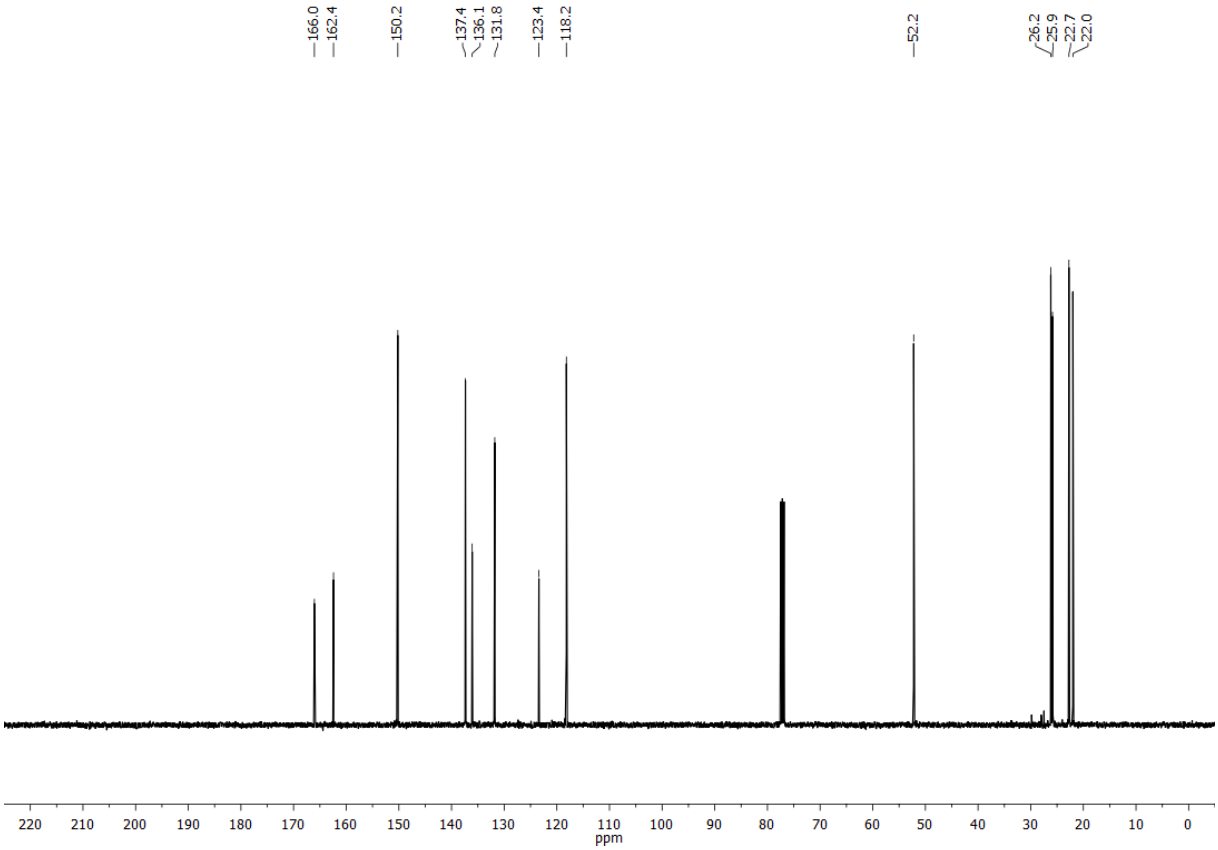
Compound **73** **^{13}C-NMR** ($CDCl_3$)



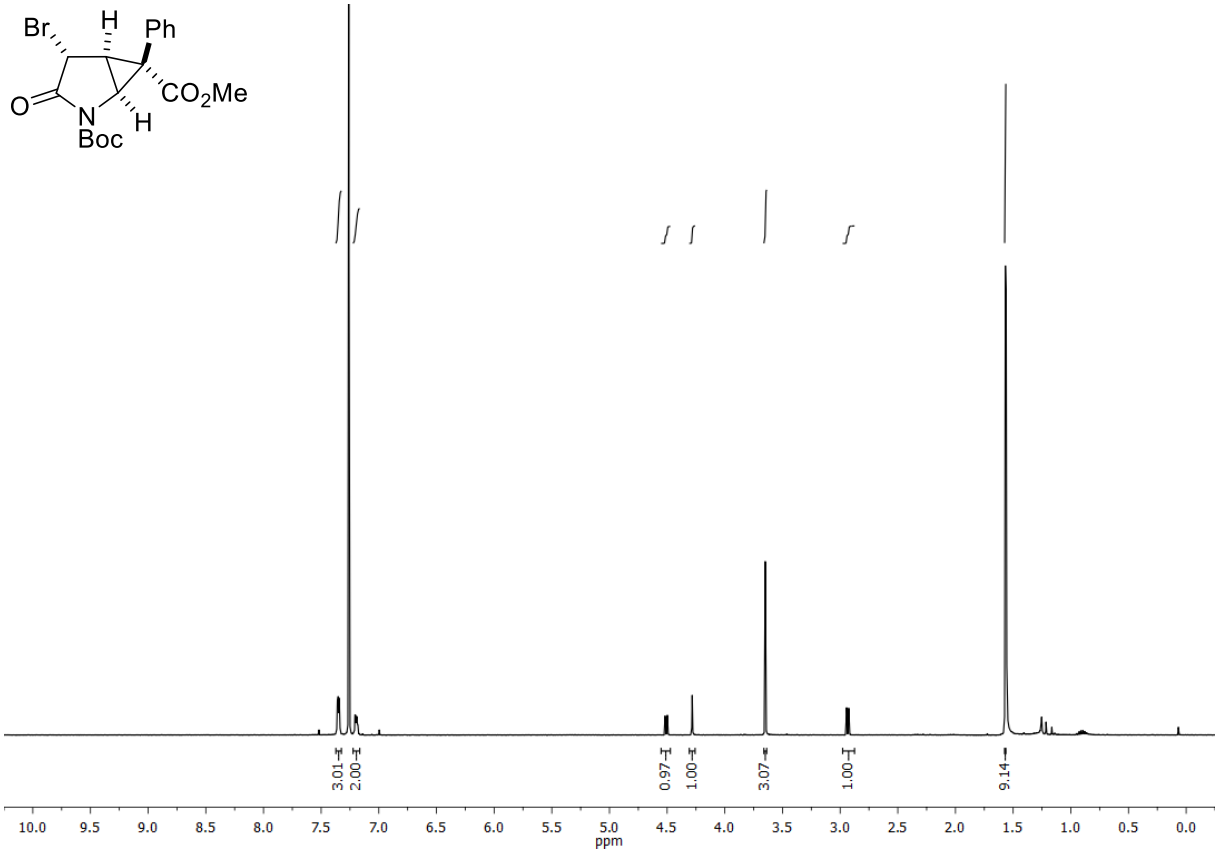
Compound **74** **^{1}H-NMR** ($CDCl_3$)



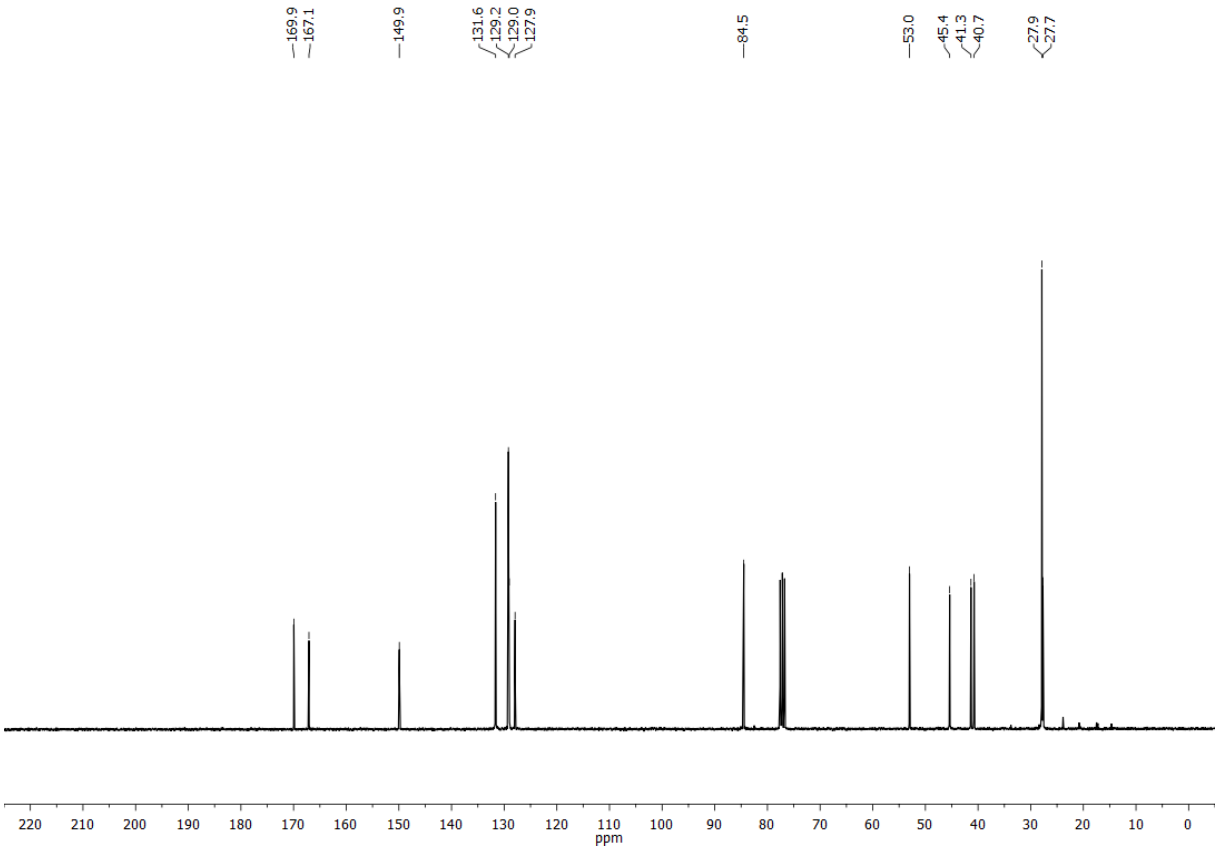
Compound 74 **^{13}C-NMR** ($CDCl_3$)



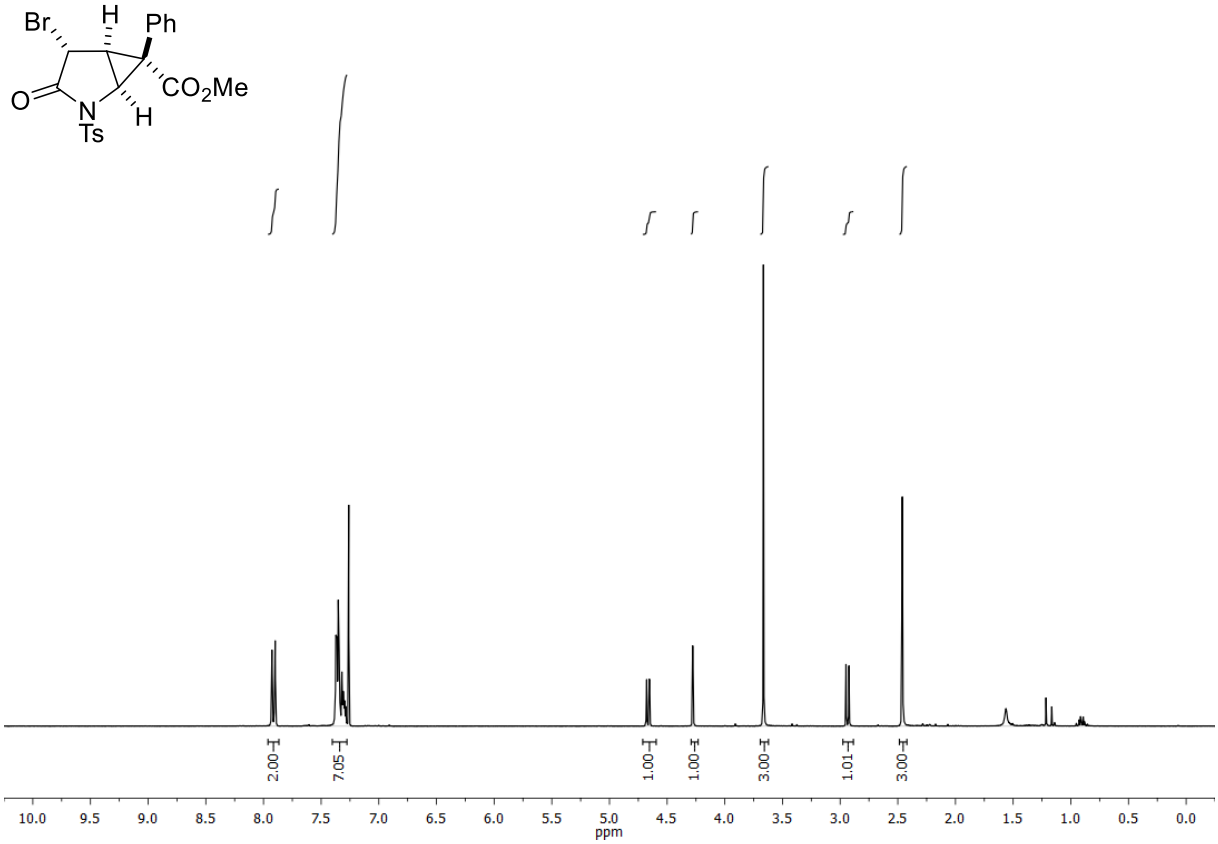
Compound **79-Boc** ^{1}**H-NMR** ($CDCl_3$)



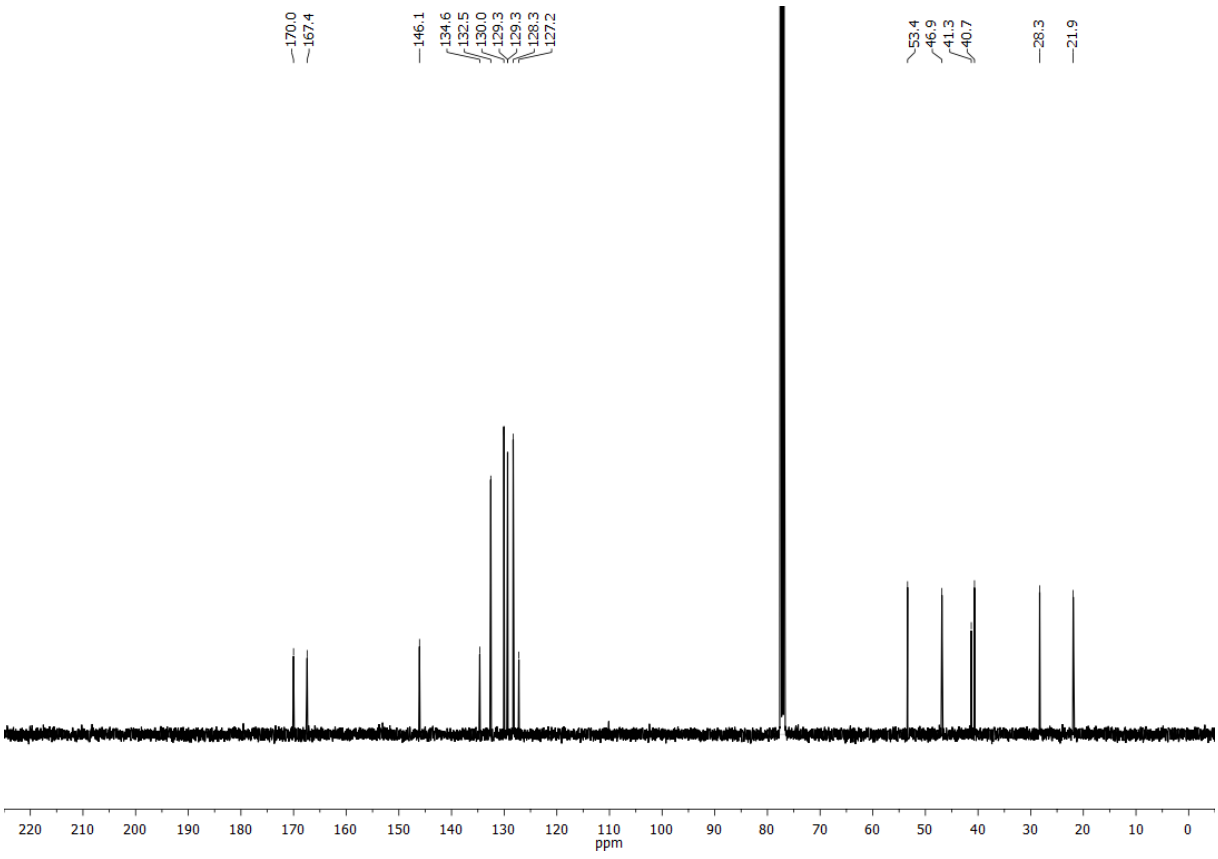
Compound **79-Boc** ^{13}**C-NMR** ($CDCl_3$)



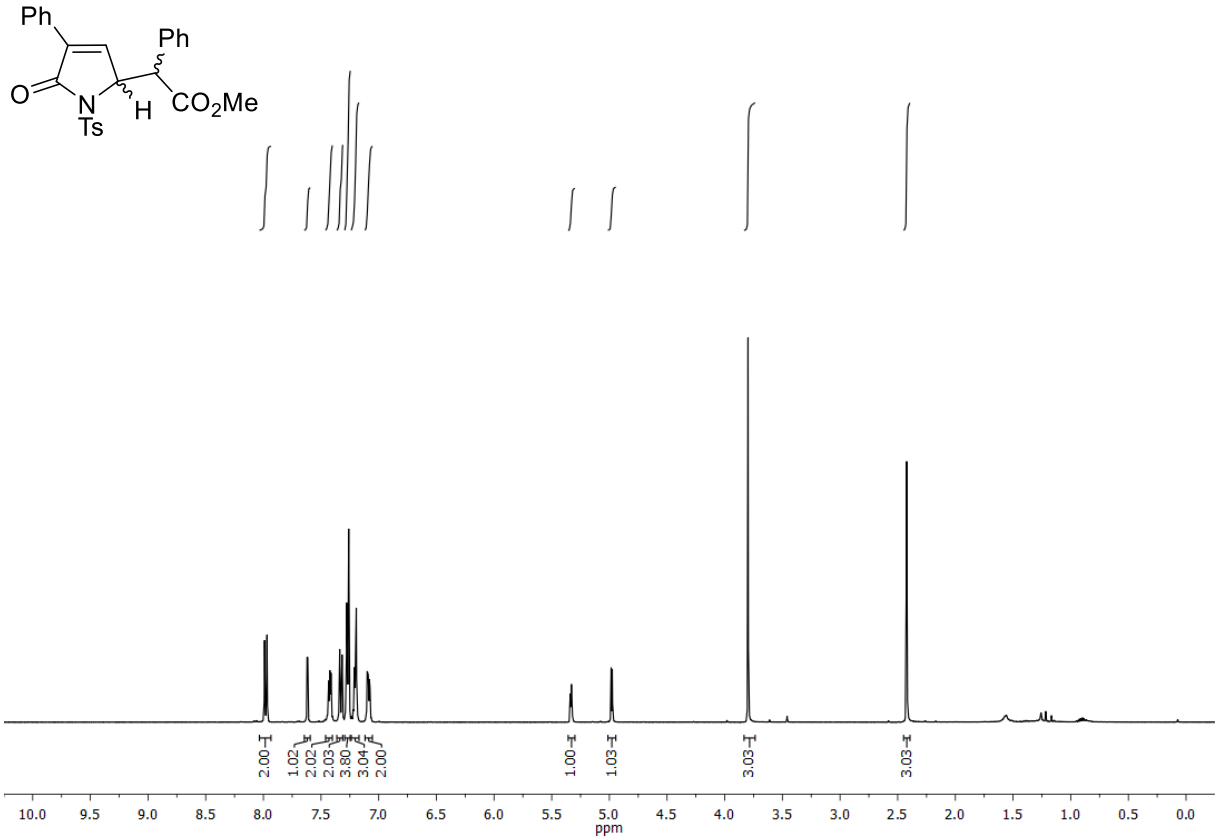
Compound **79-Ts ^{1}H-NMR** ($CDCl_3$)



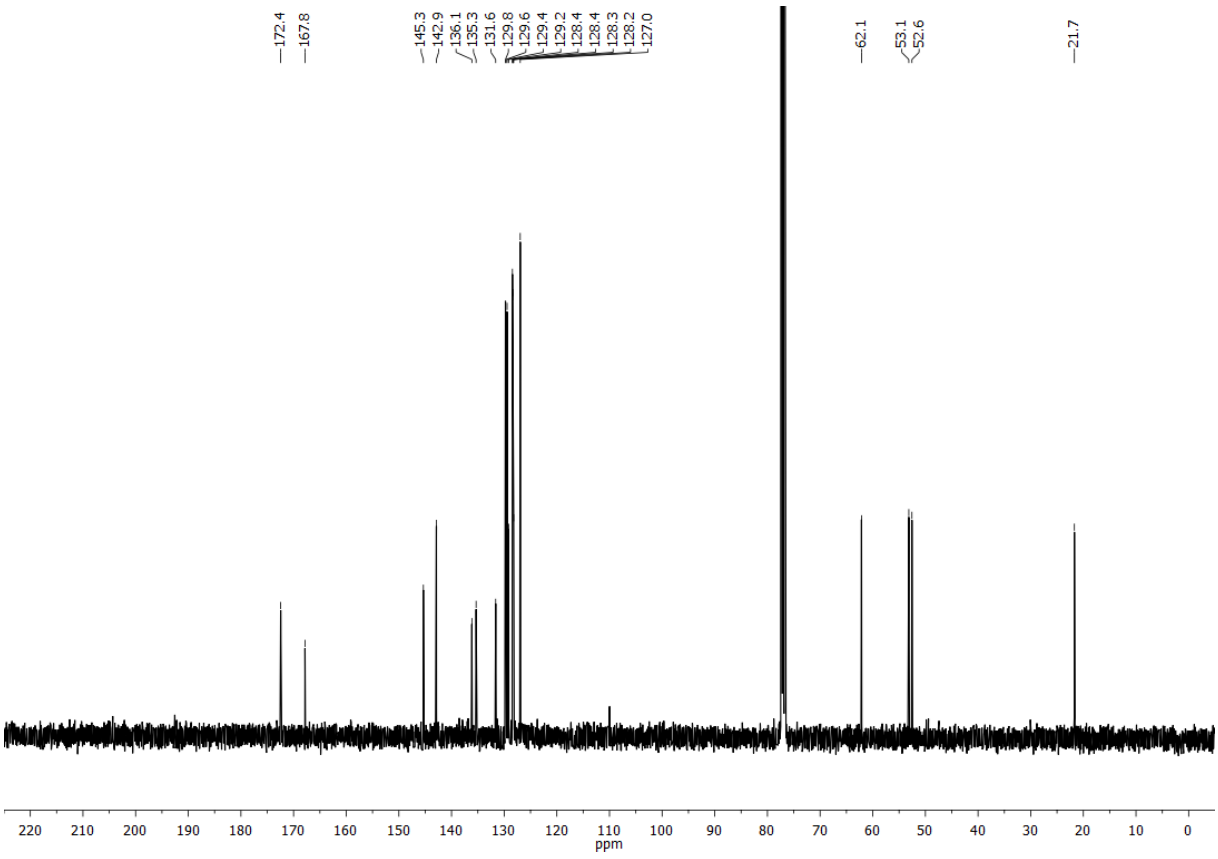
Compound **79-Ts ^{13}C-NMR** ($CDCl_3$)



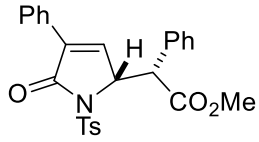
Compound **86 (major)** ^{1}**H-NMR** ($CDCl_3$)

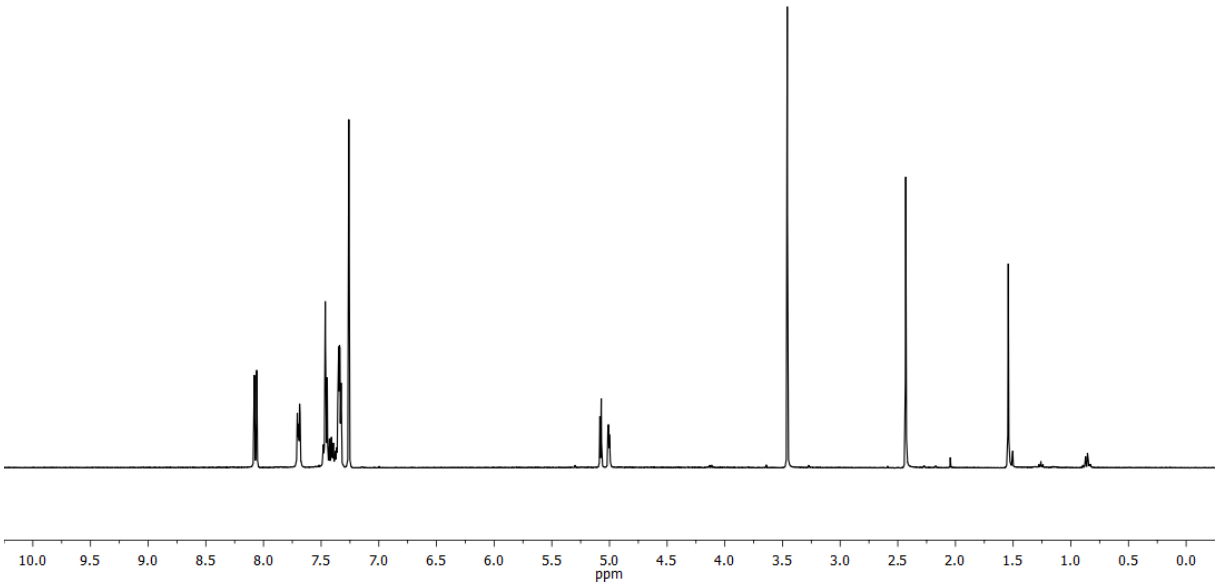


Compound **86 (minor)** ^{13}**C-NMR** ($CDCl_3$)

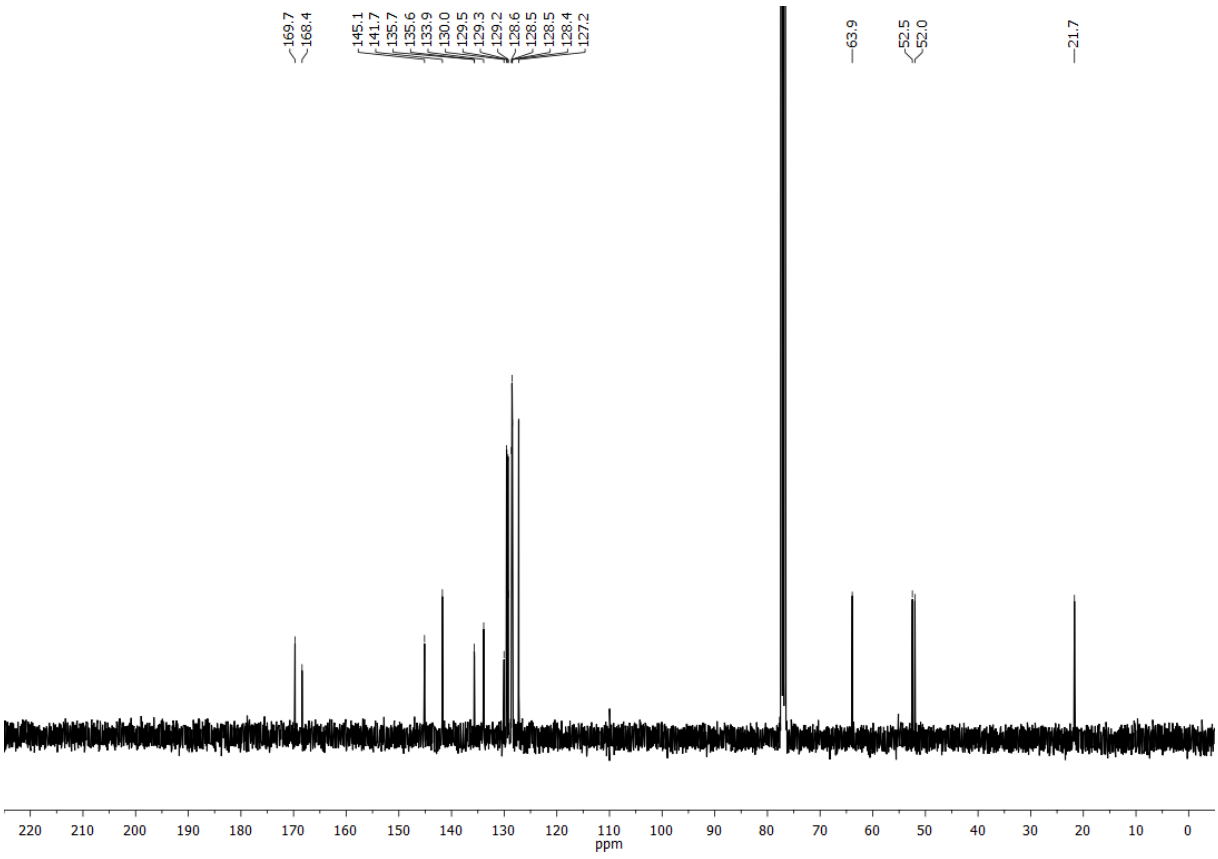


Compound **86 (minor)** ^{1}**H-NMR** ($CDCl_3$)

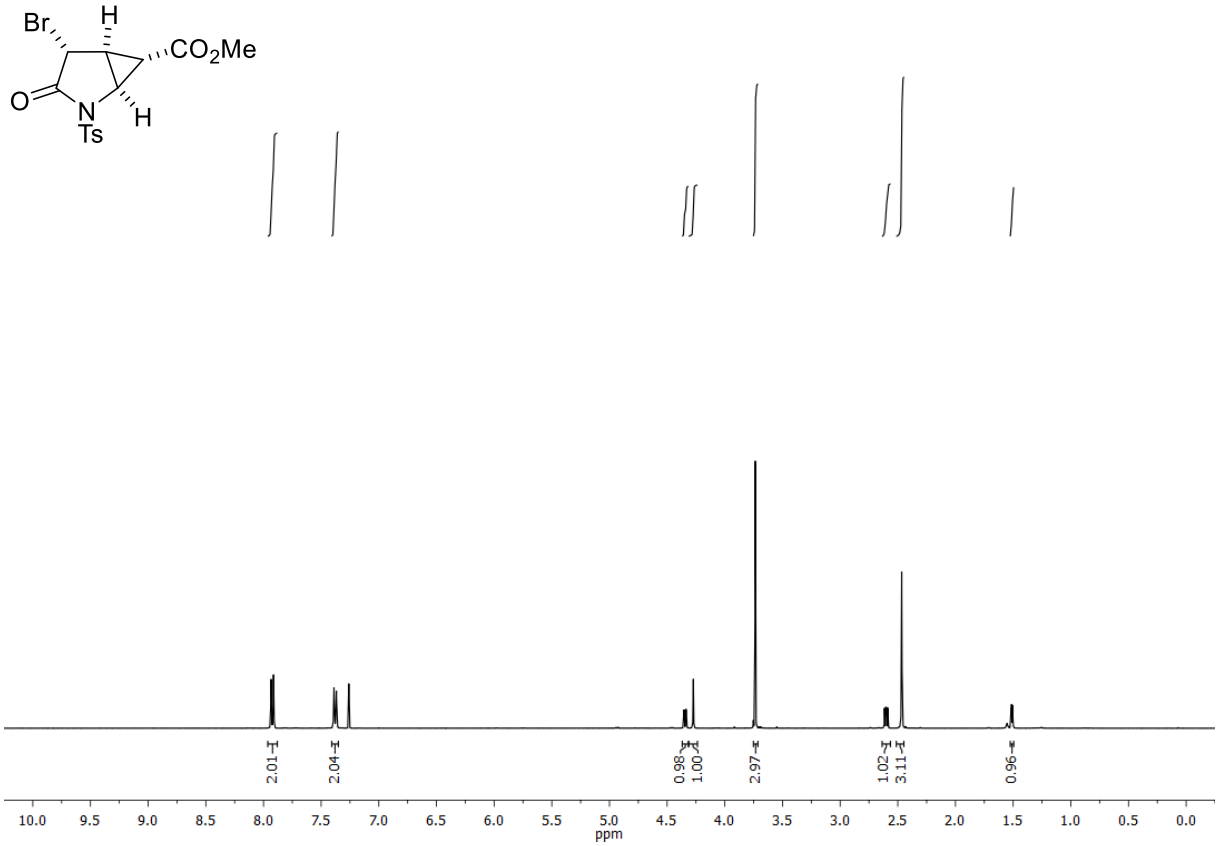




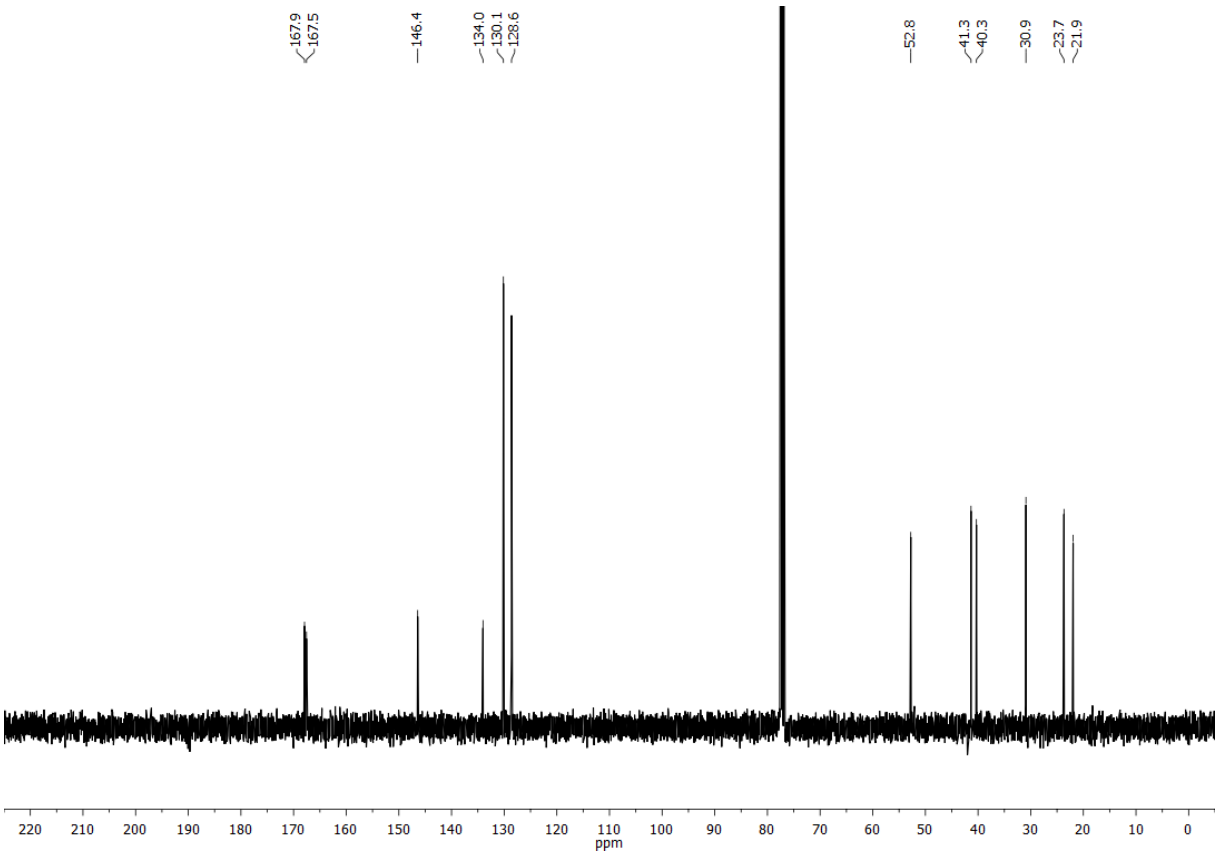
Compound **86 (minor)** ^{13}**C-NMR** ($CDCl_3$)



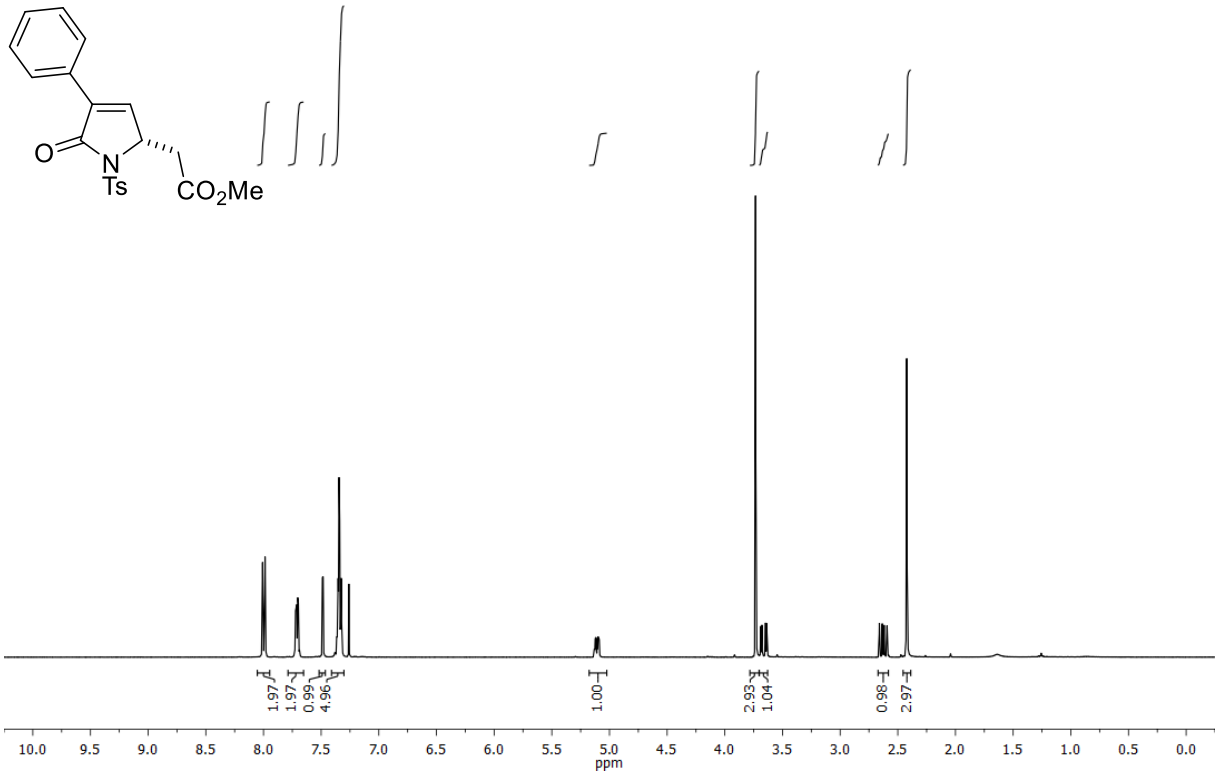
Compound **87** **^{1}H-NMR** ($CDCl_3$)



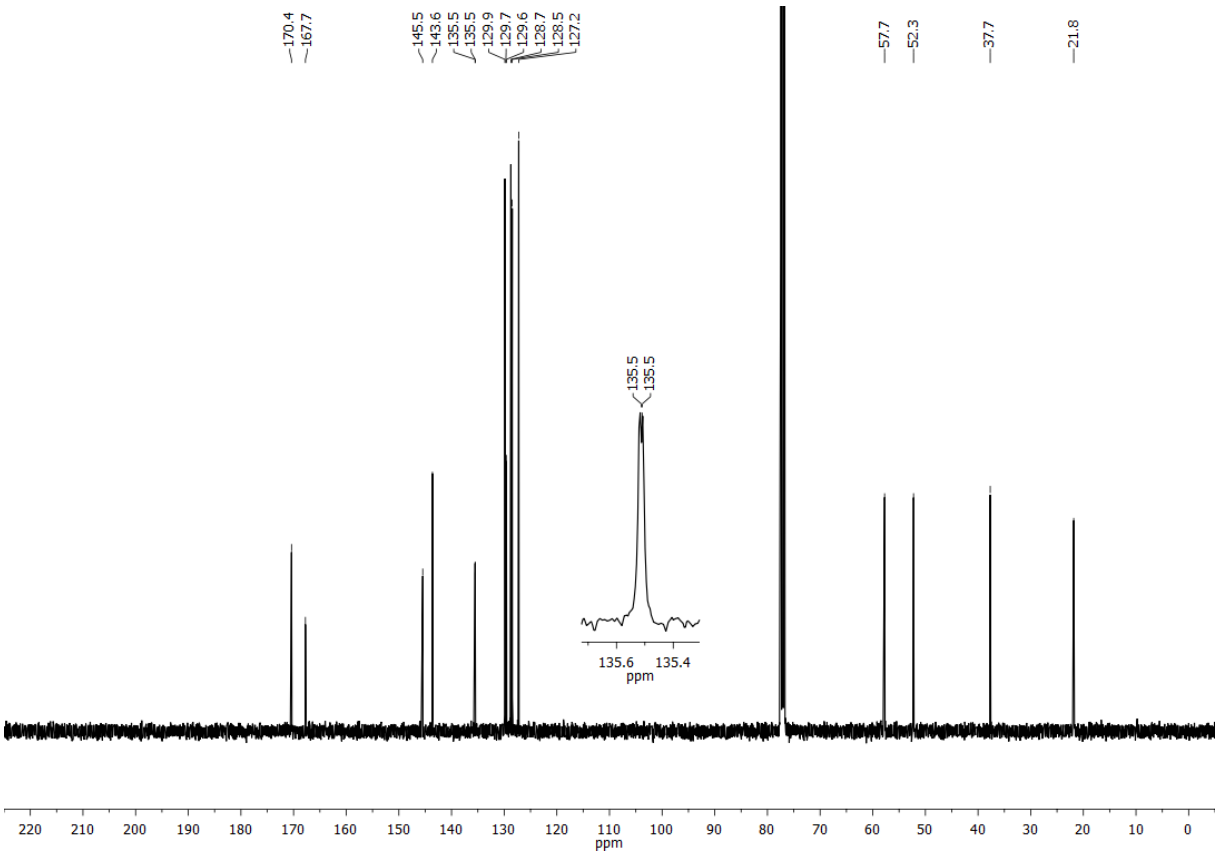
Compound **87** **^{13}C-NMR** ($CDCl_3$)



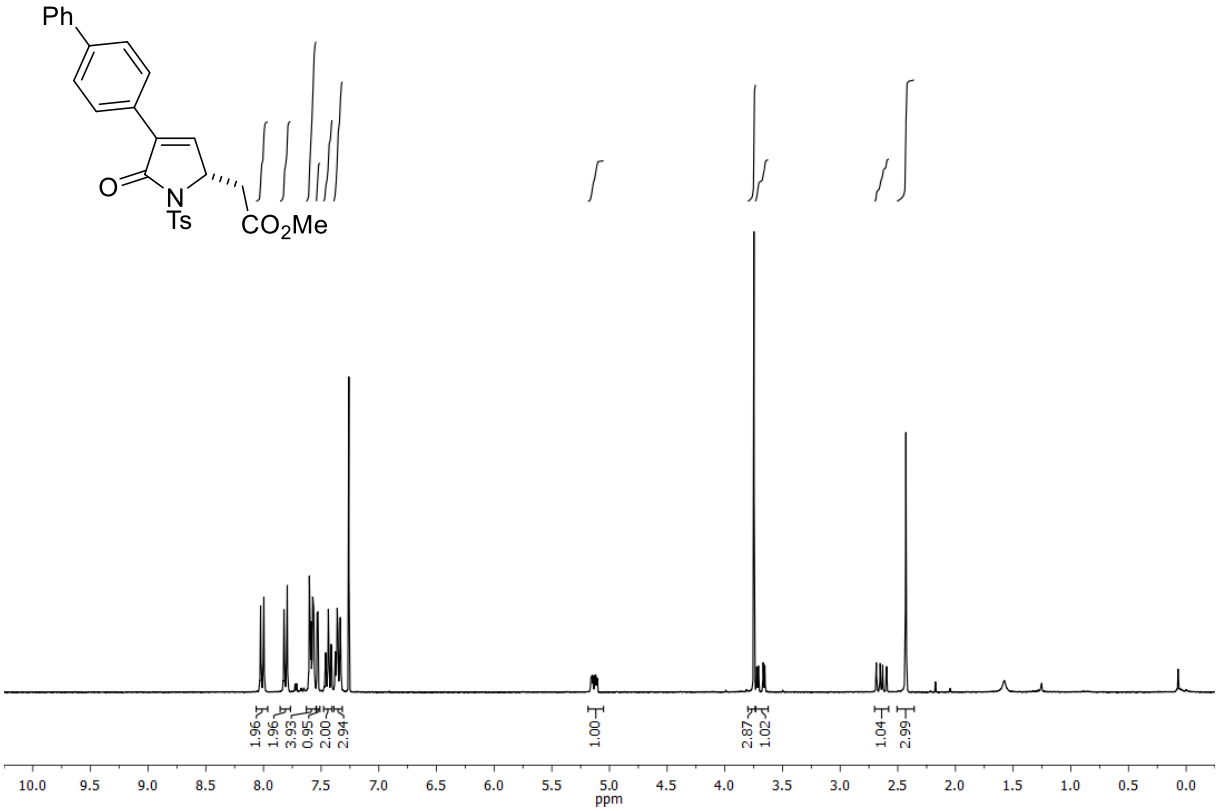
Compound **88a** ^{1}**H-NMR** ($CDCl_3$)



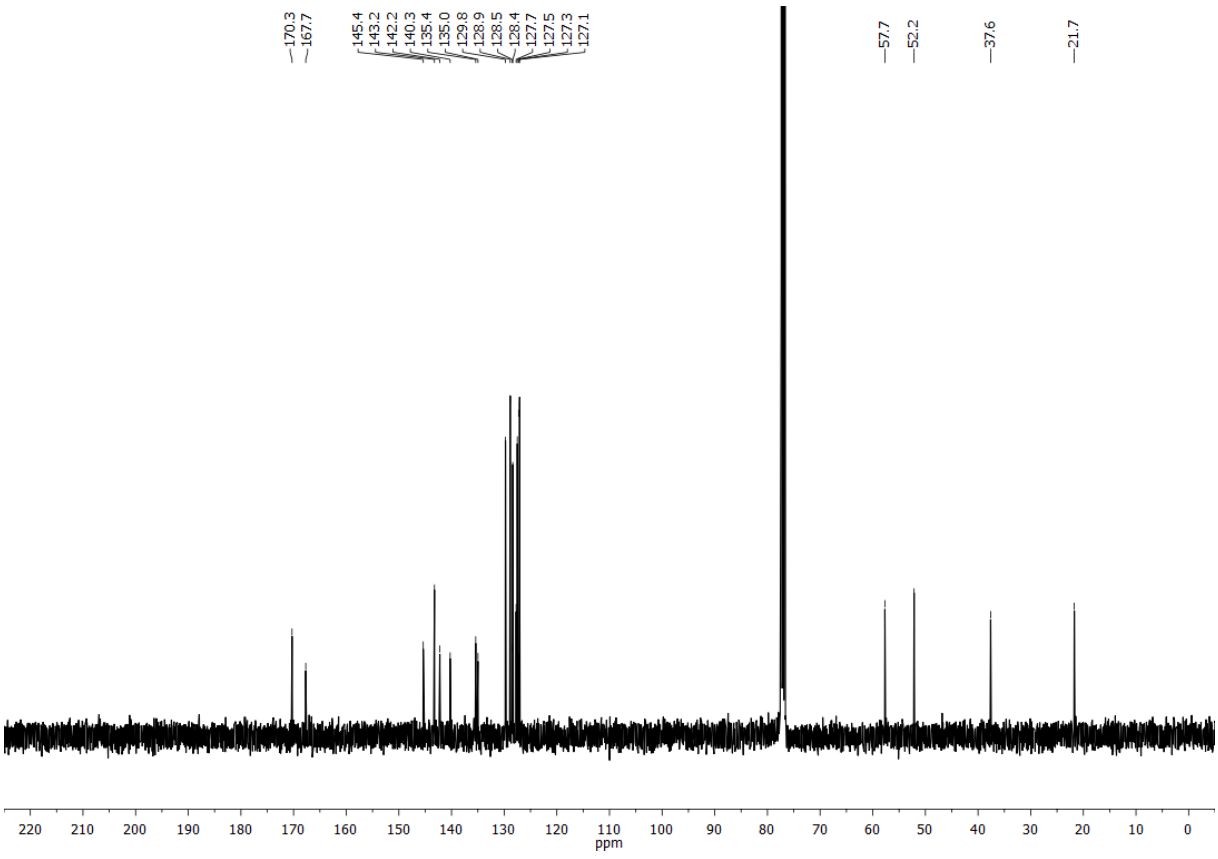
Compound **88** ^{13}**C-NMR** ($CDCl_3$)



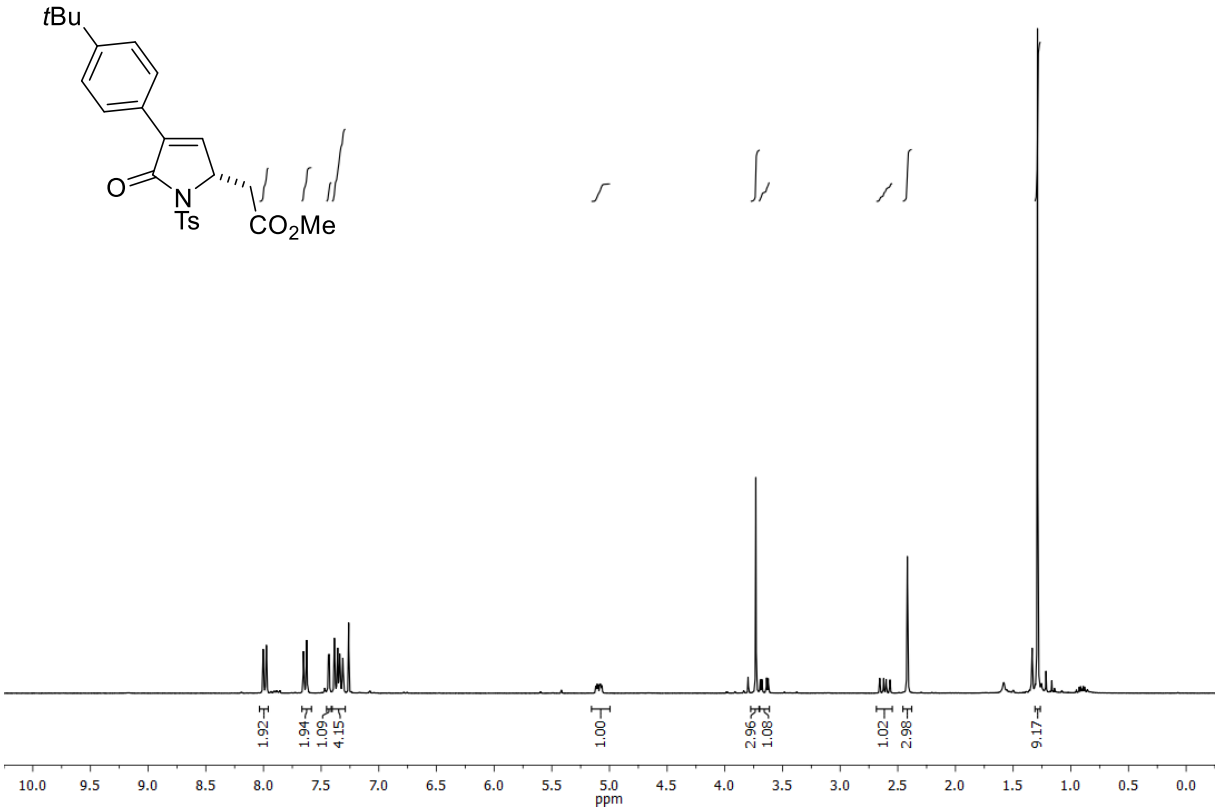
Compound **88b** **^{1}H-NMR** ($CDCl_3$)



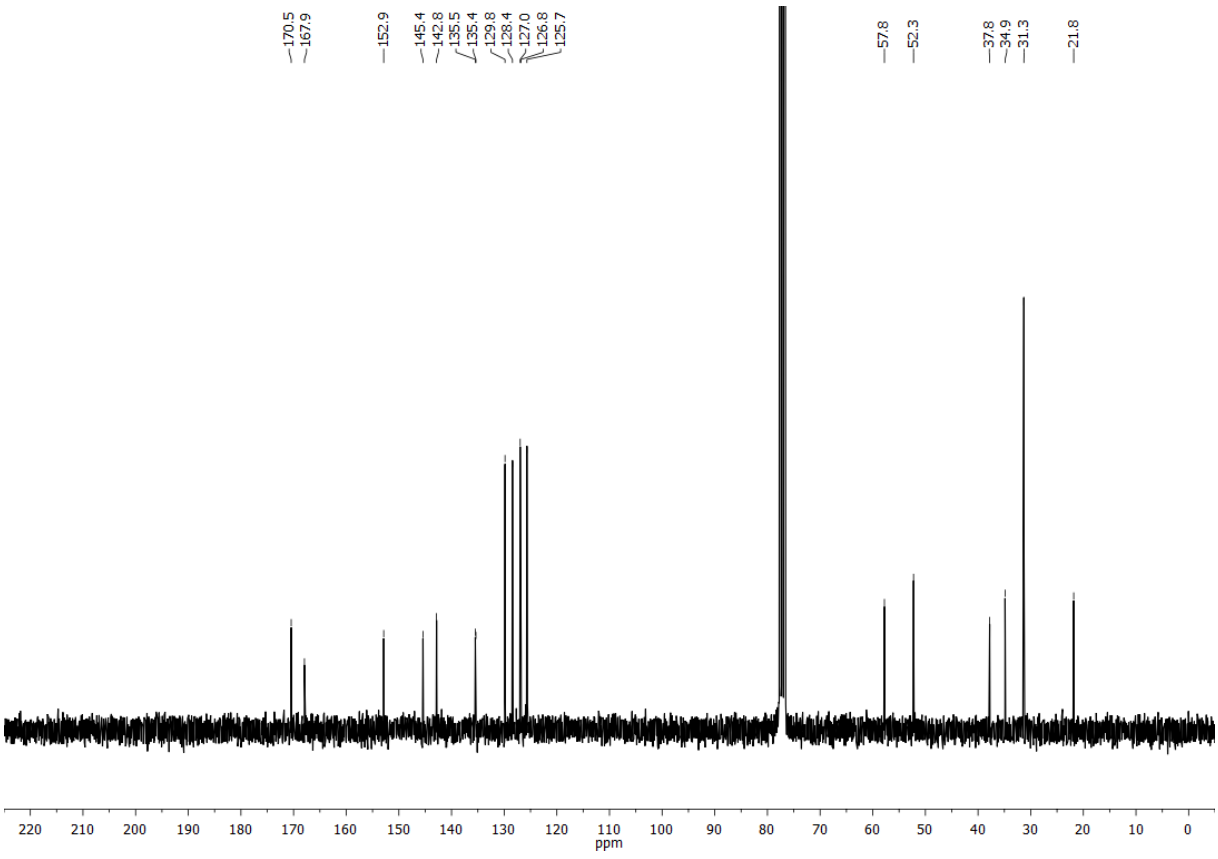
Compound **88b** **^{13}C-NMR** ($CDCl_3$)



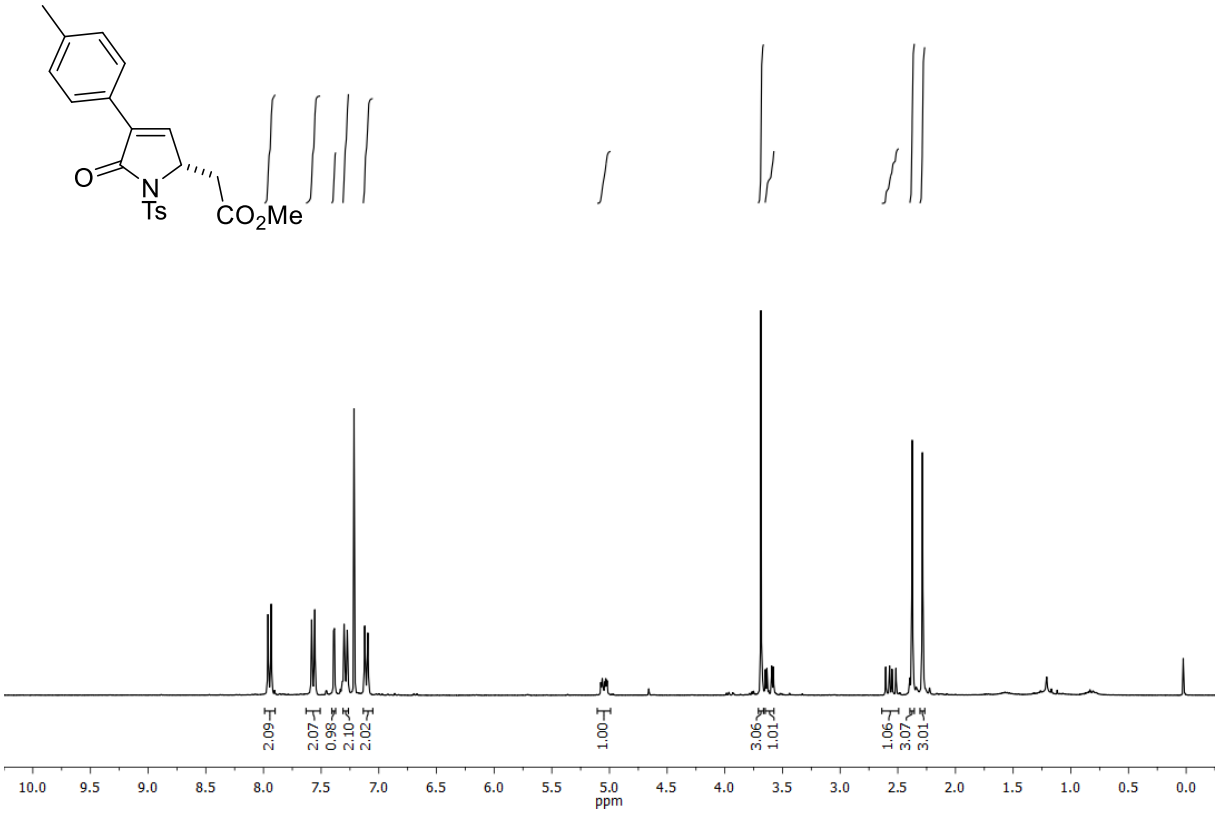
Compound **88c** **^{1}H-NMR** ($CDCl_3$)



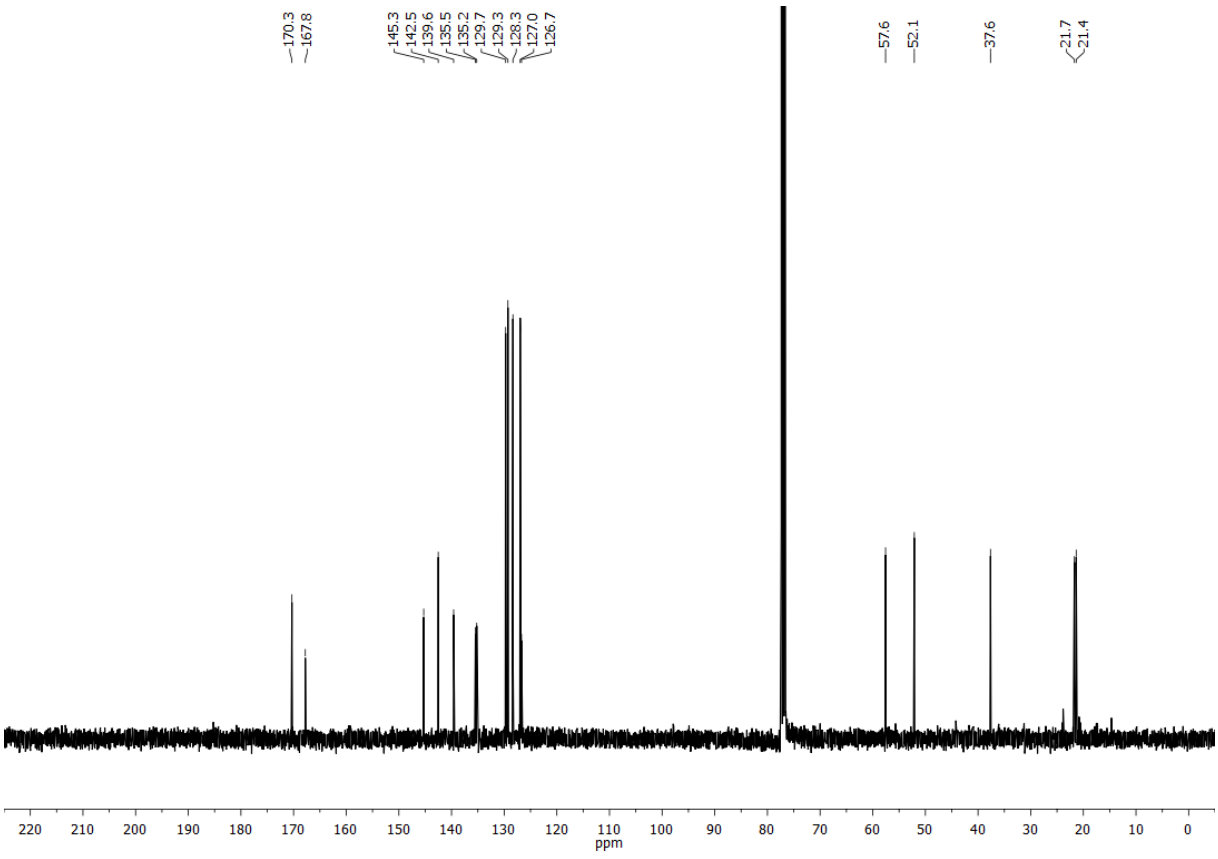
Compound **88c** **^{13}C-NMR** ($CDCl_3$)



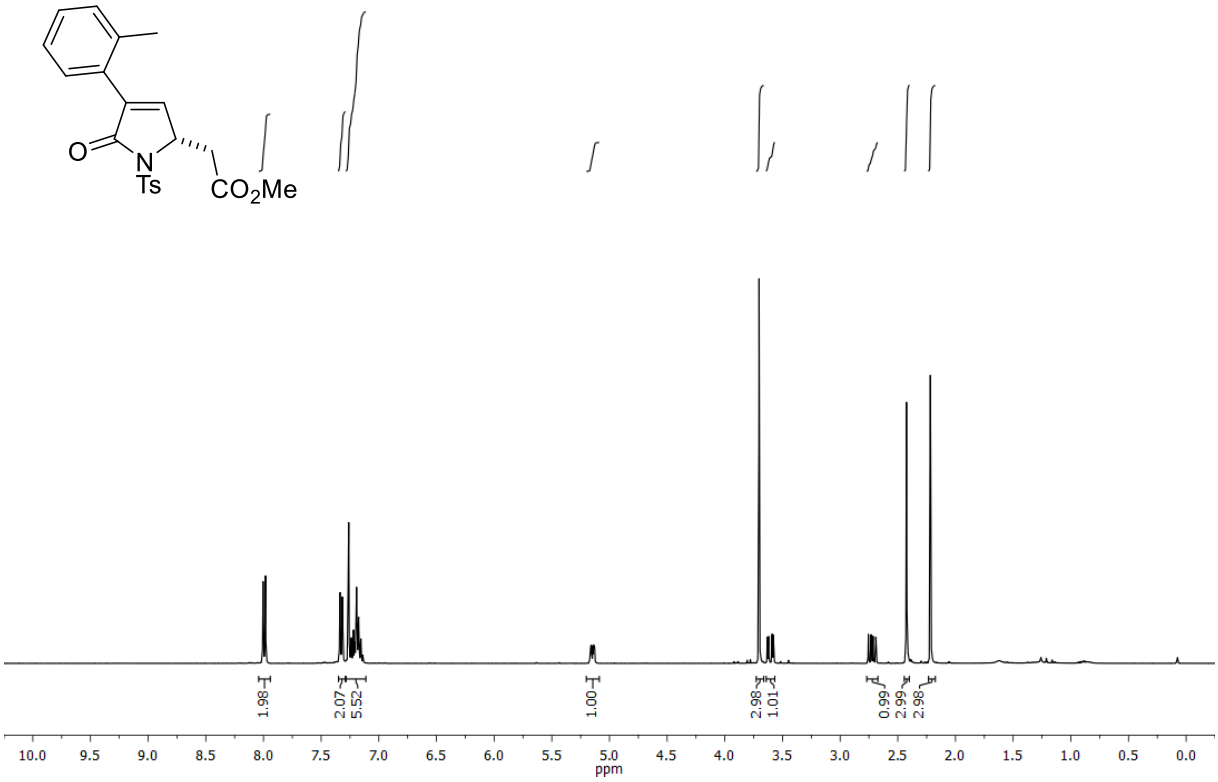
Compound **88d** **^{1}H-NMR** ($CDCl_3$)



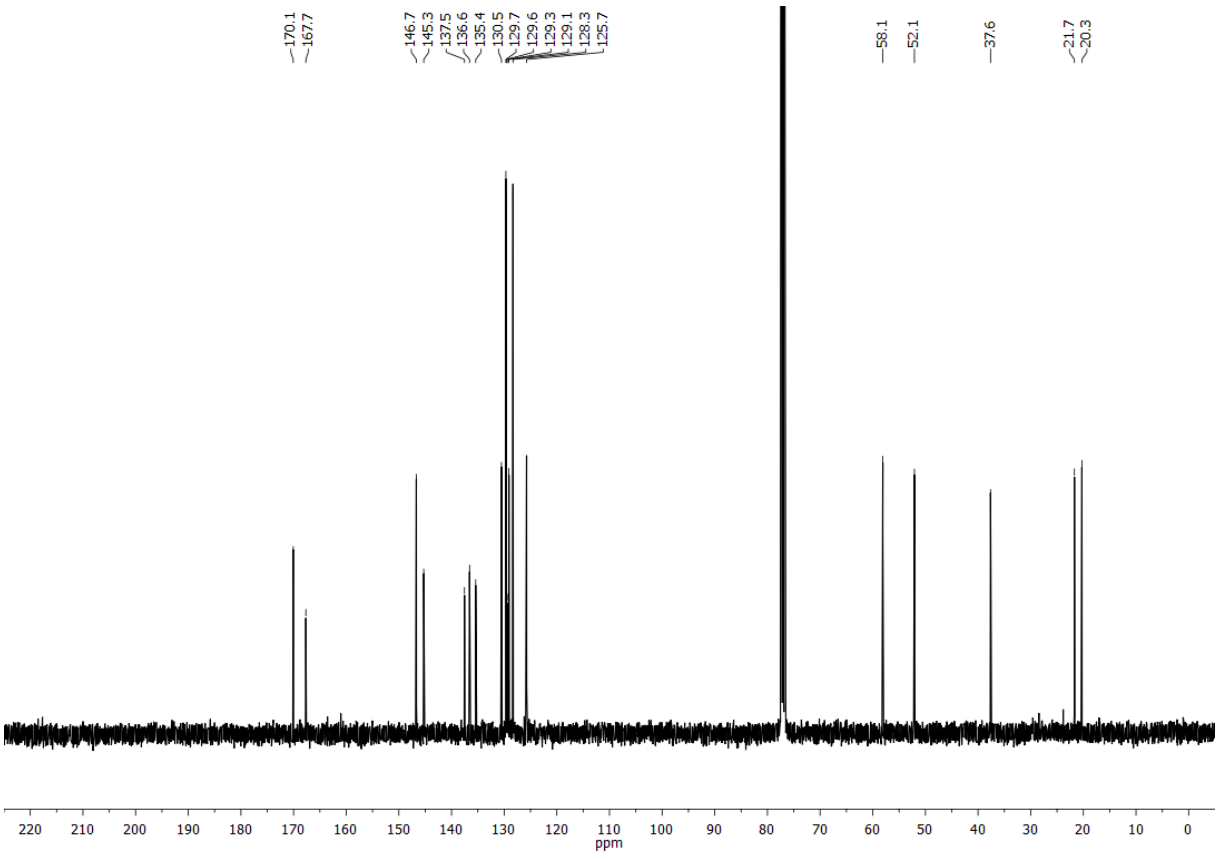
Compound **88d** **^{13}C-NMR** ($CDCl_3$)



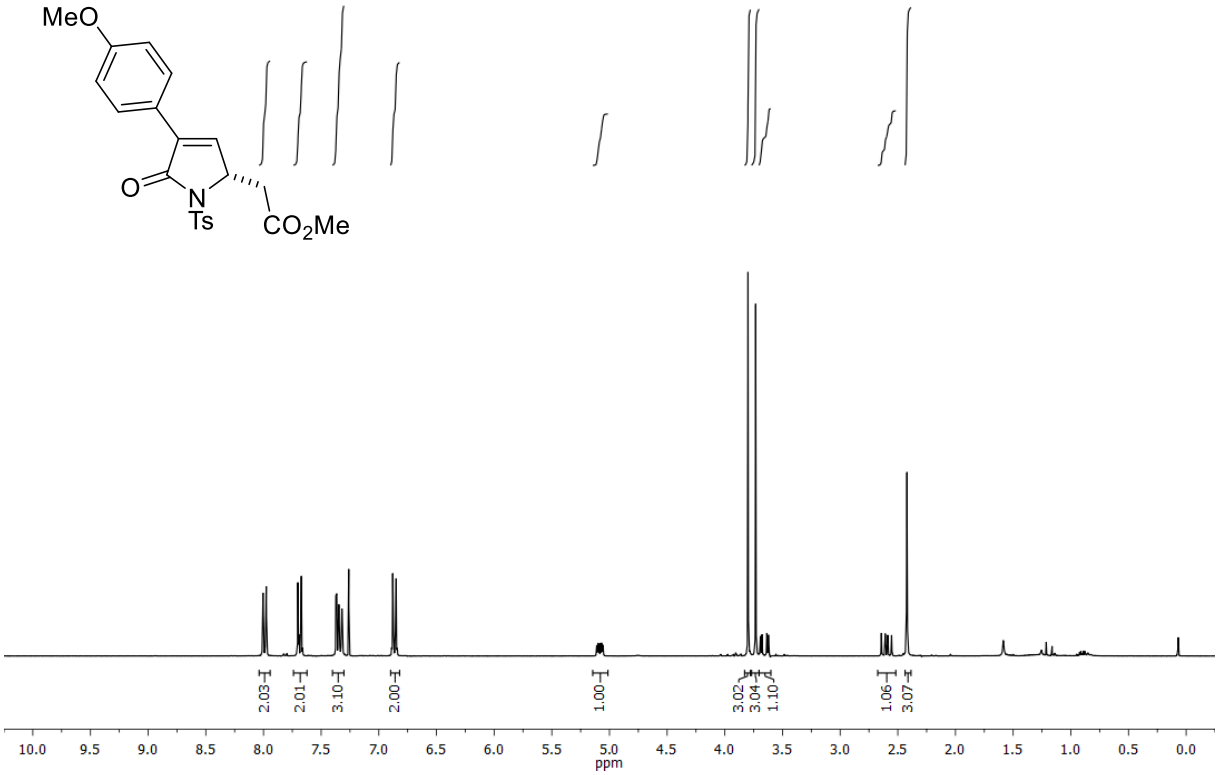
Compound **88e** ^{1}**H-NMR** ($CDCl_3$)



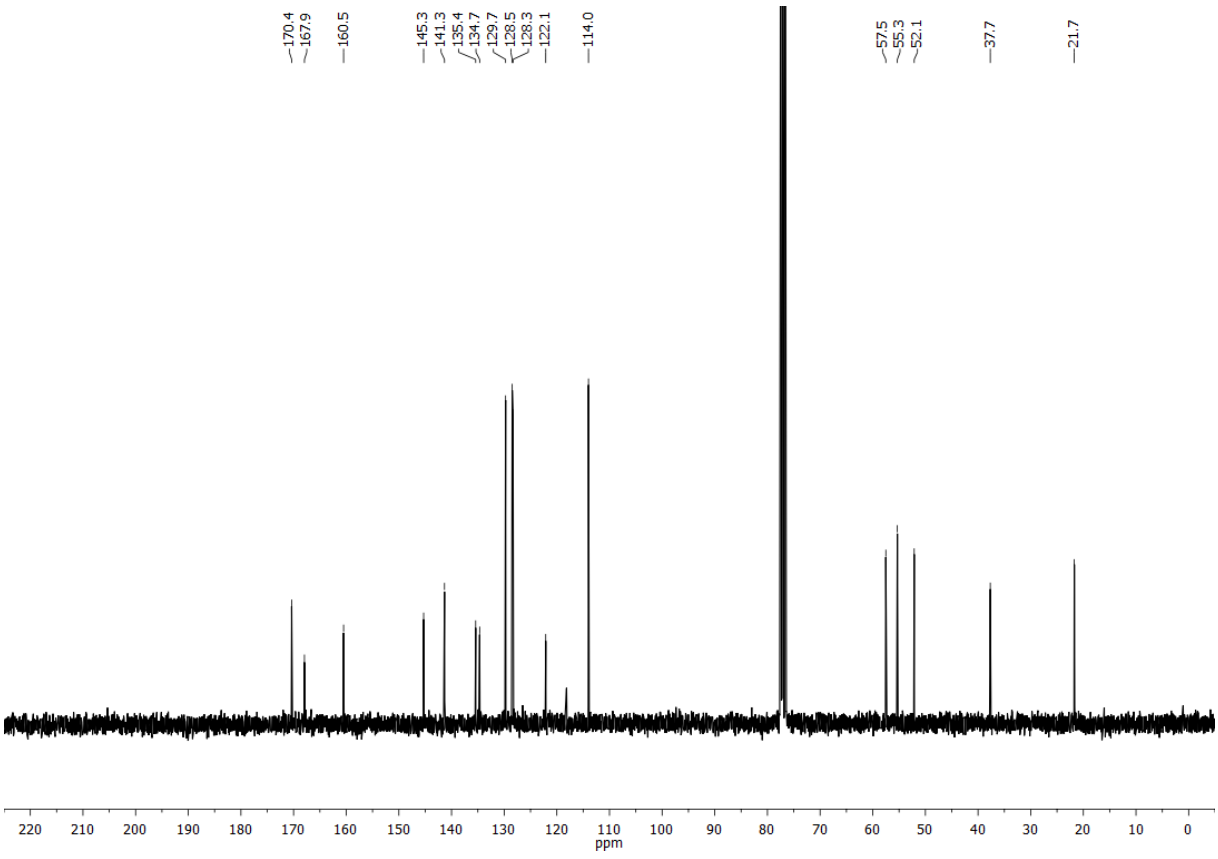
Compound **88e** ^{13}**C-NMR** ($CDCl_3$)



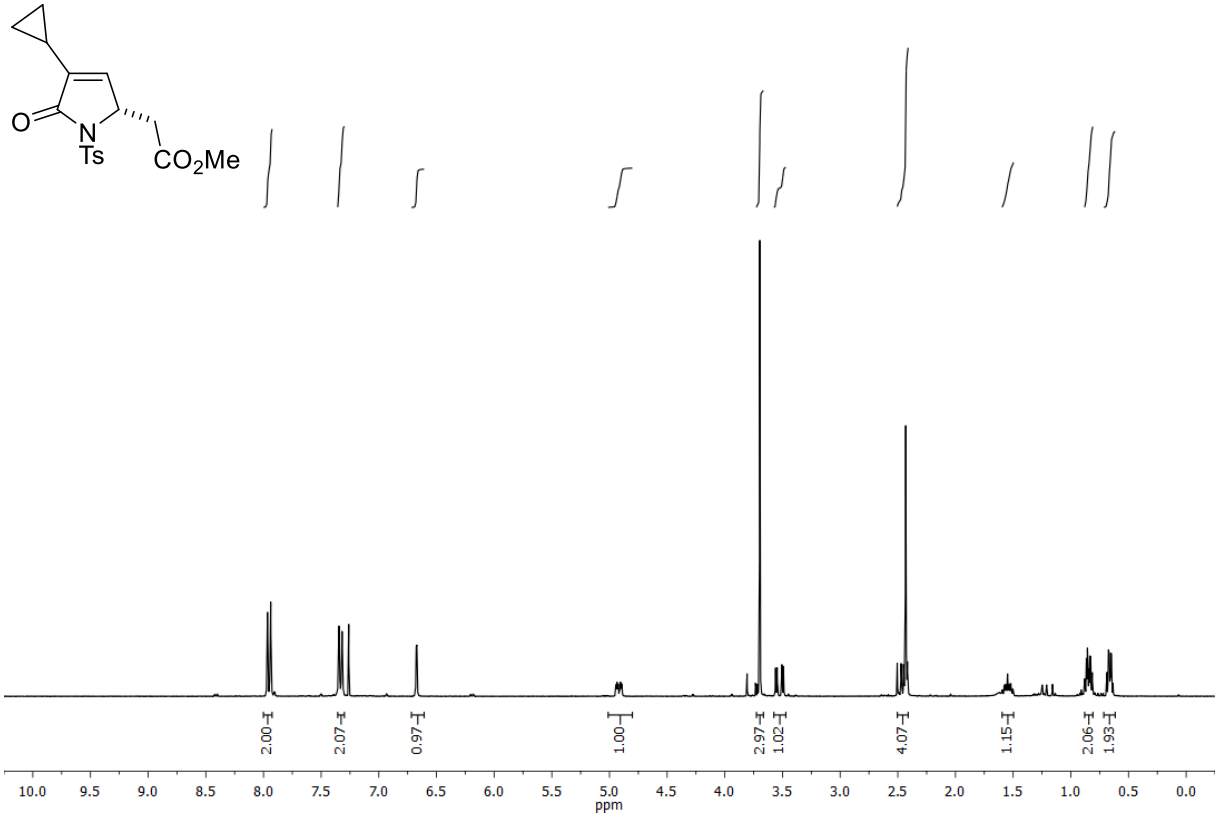
Compound **88f** ^{1}**H-NMR** ($CDCl_3$)



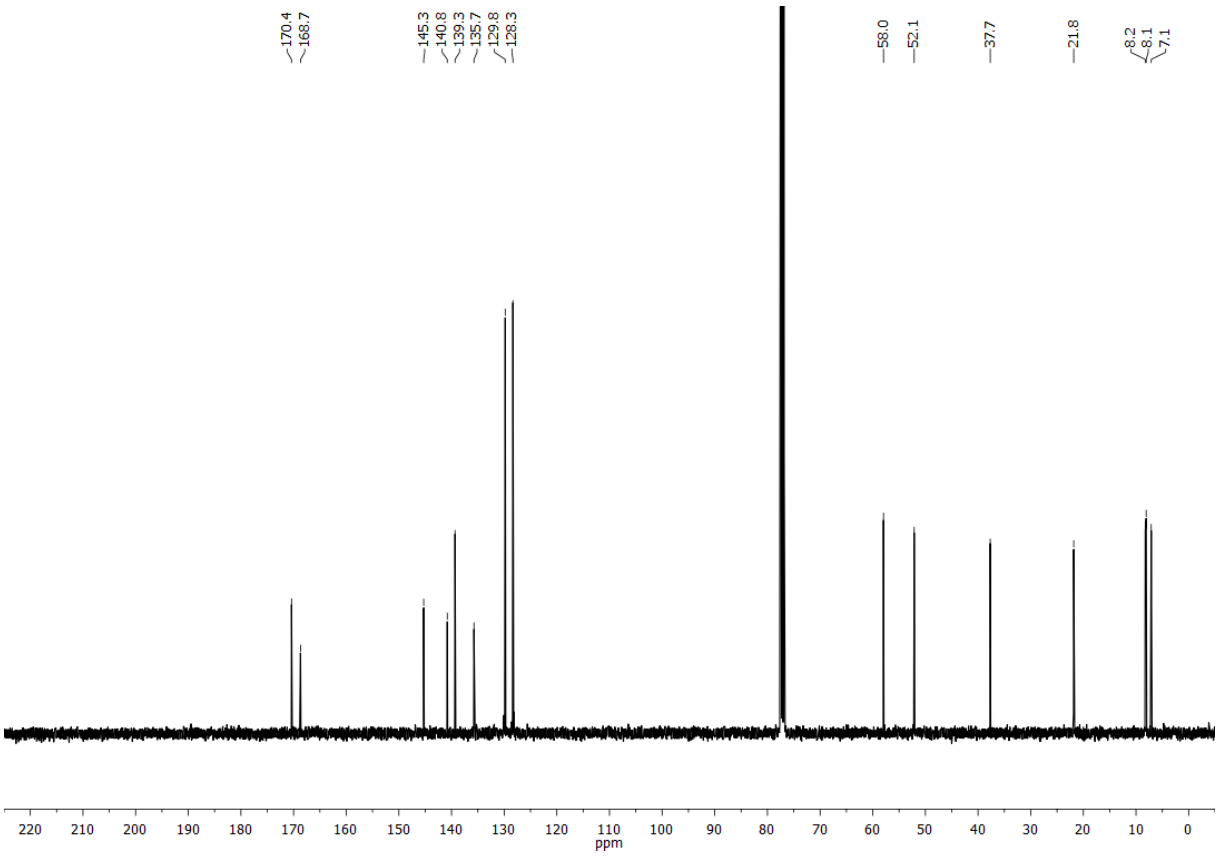
Compound **88f** ^{13}**C-NMR** ($CDCl_3$)



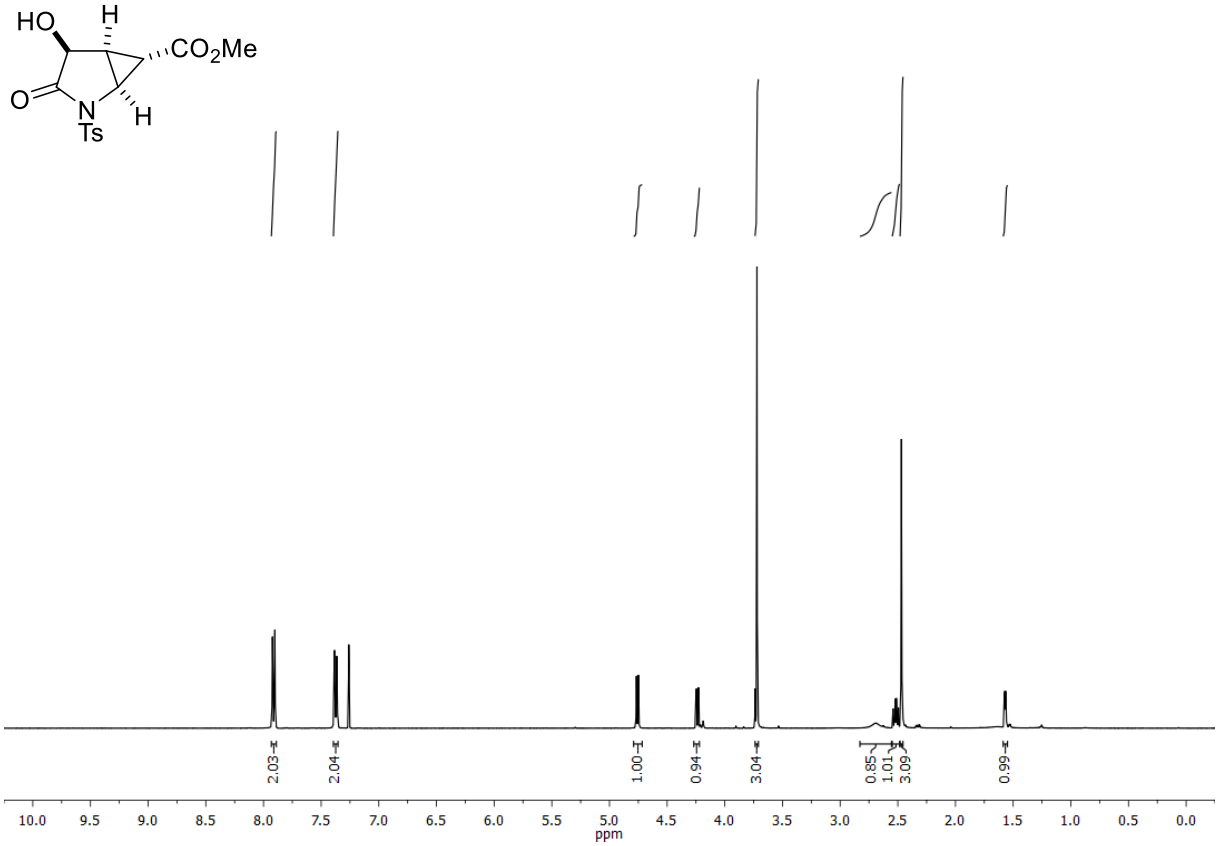
Compound **88g** ^{1}**H-NMR** ($CDCl_3$)



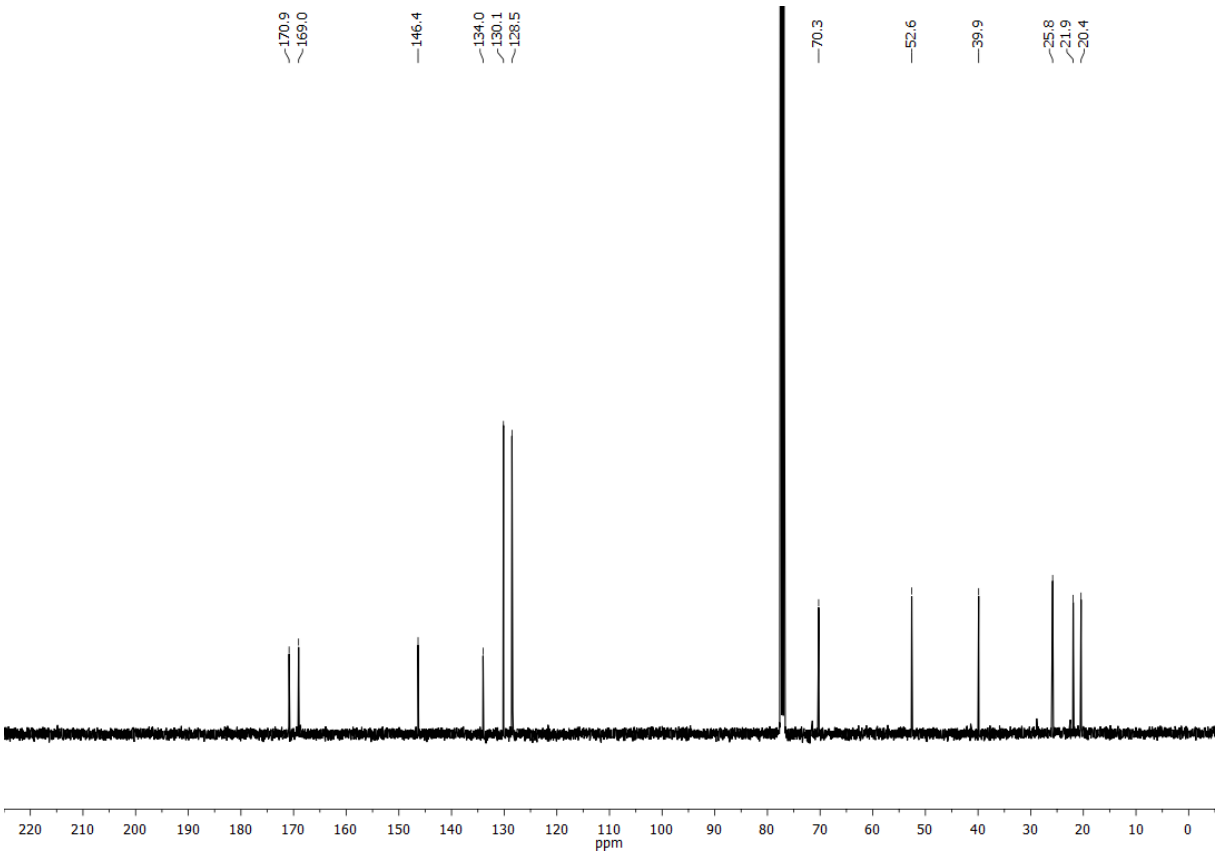
Compound **88g** ^{13}**C-NMR** ($CDCl_3$)



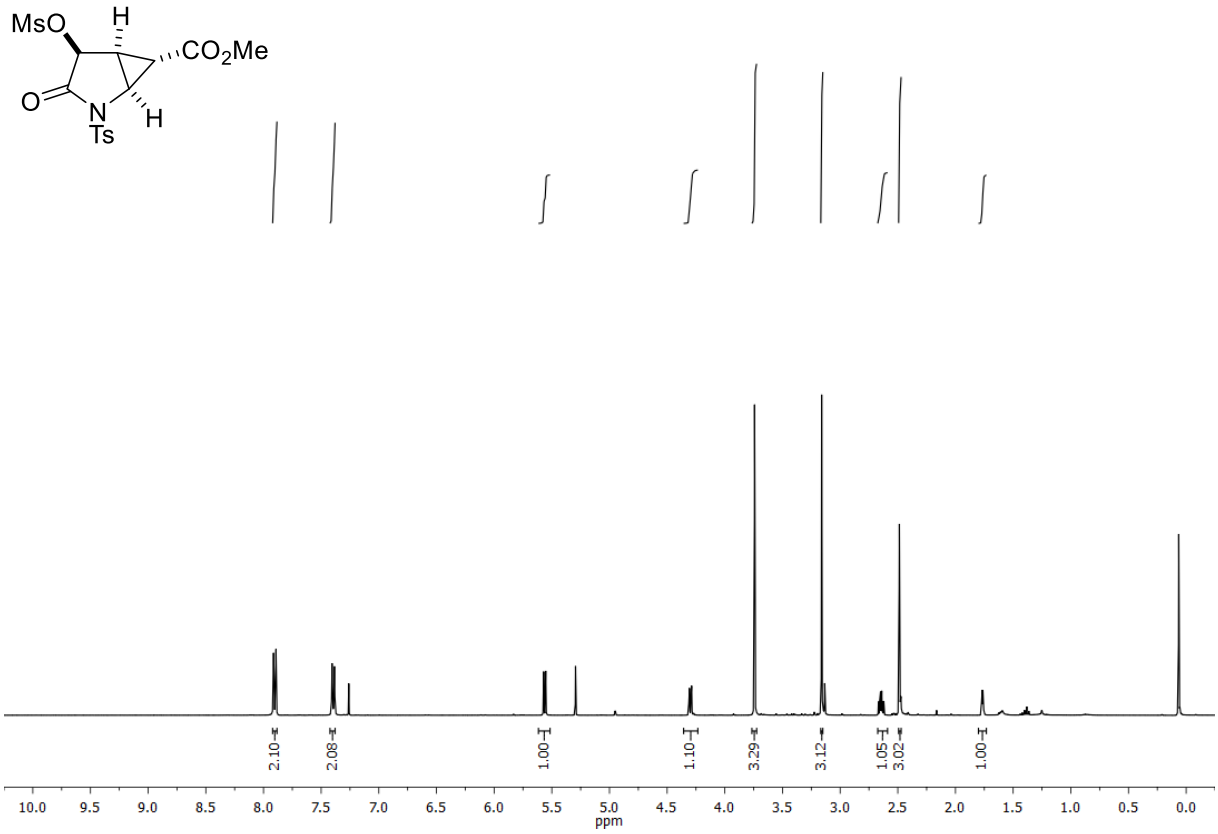
Compound **104** **^{1}H-NMR** ($CDCl_3$)



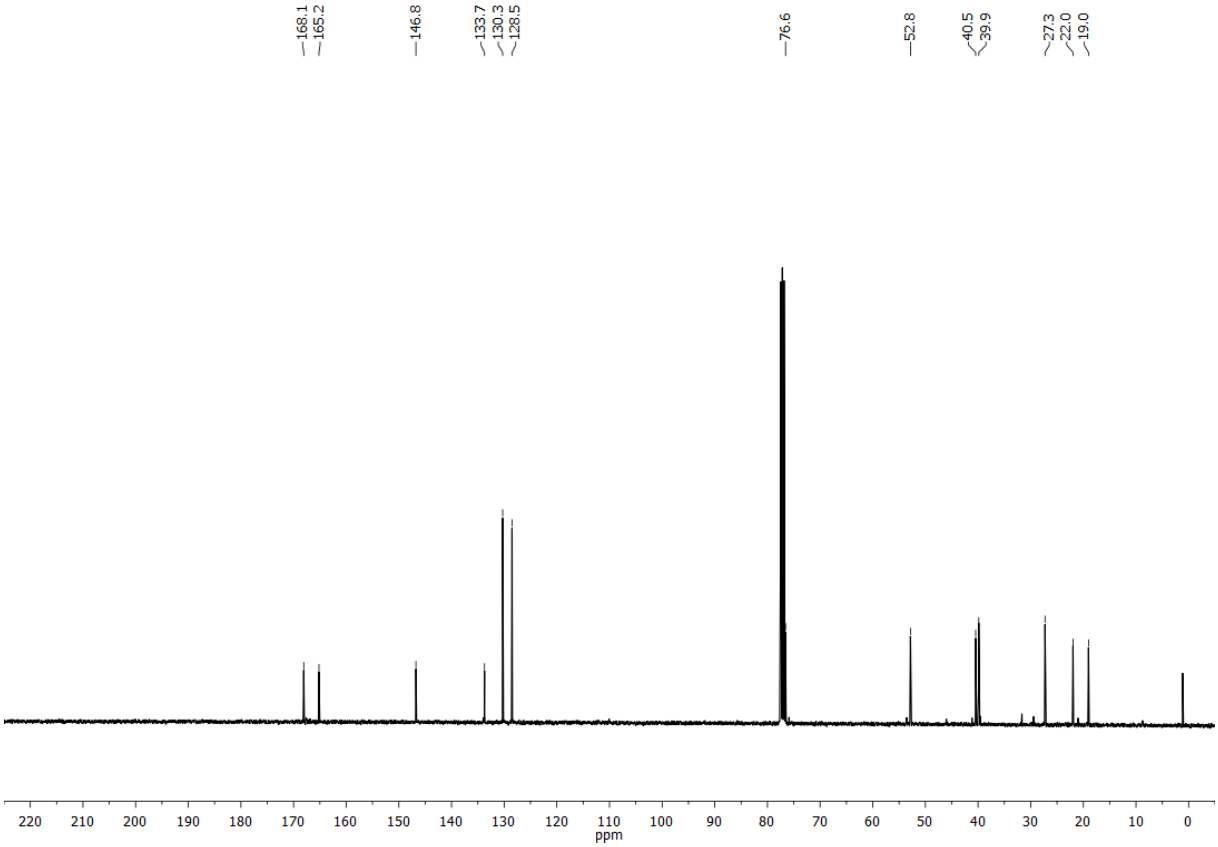
Compound **104** **^{13}C-NMR** ($CDCl_3$)



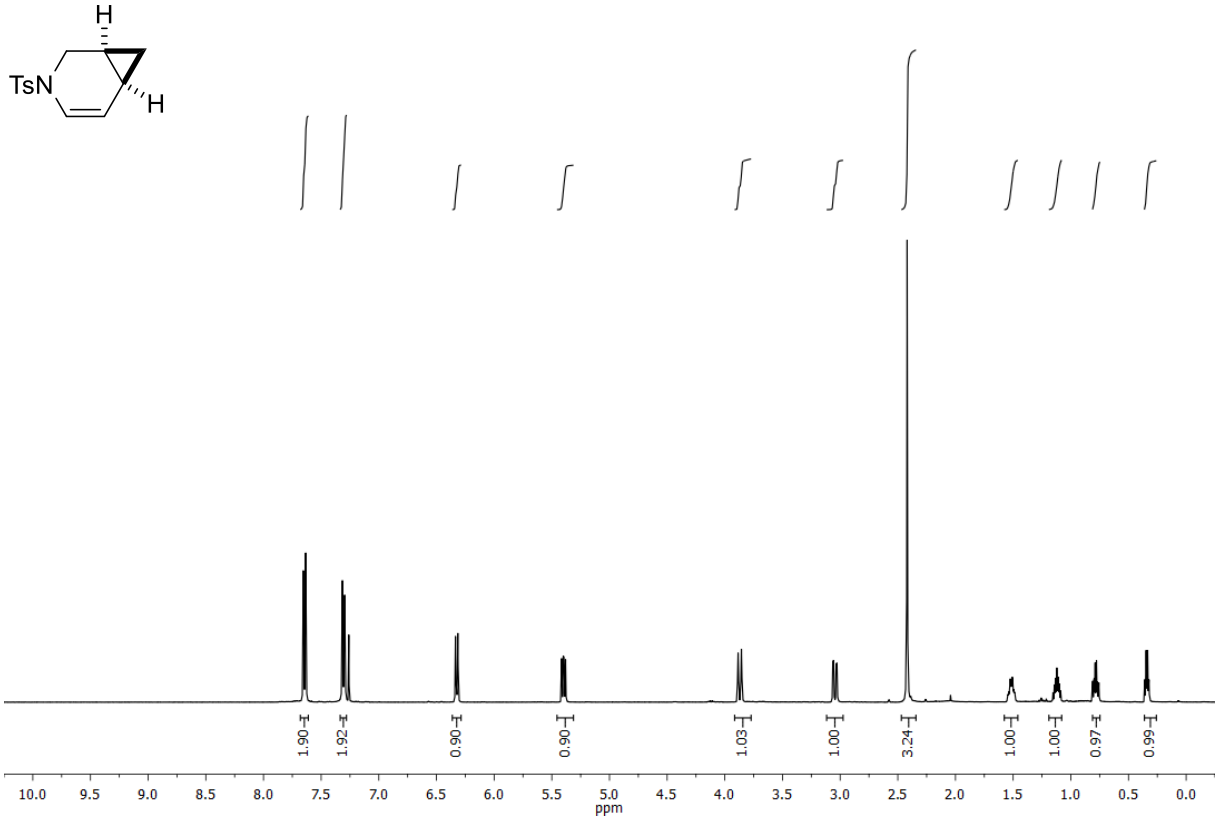
Compound **105** ^{1}**H-NMR** ($CDCl_3$)



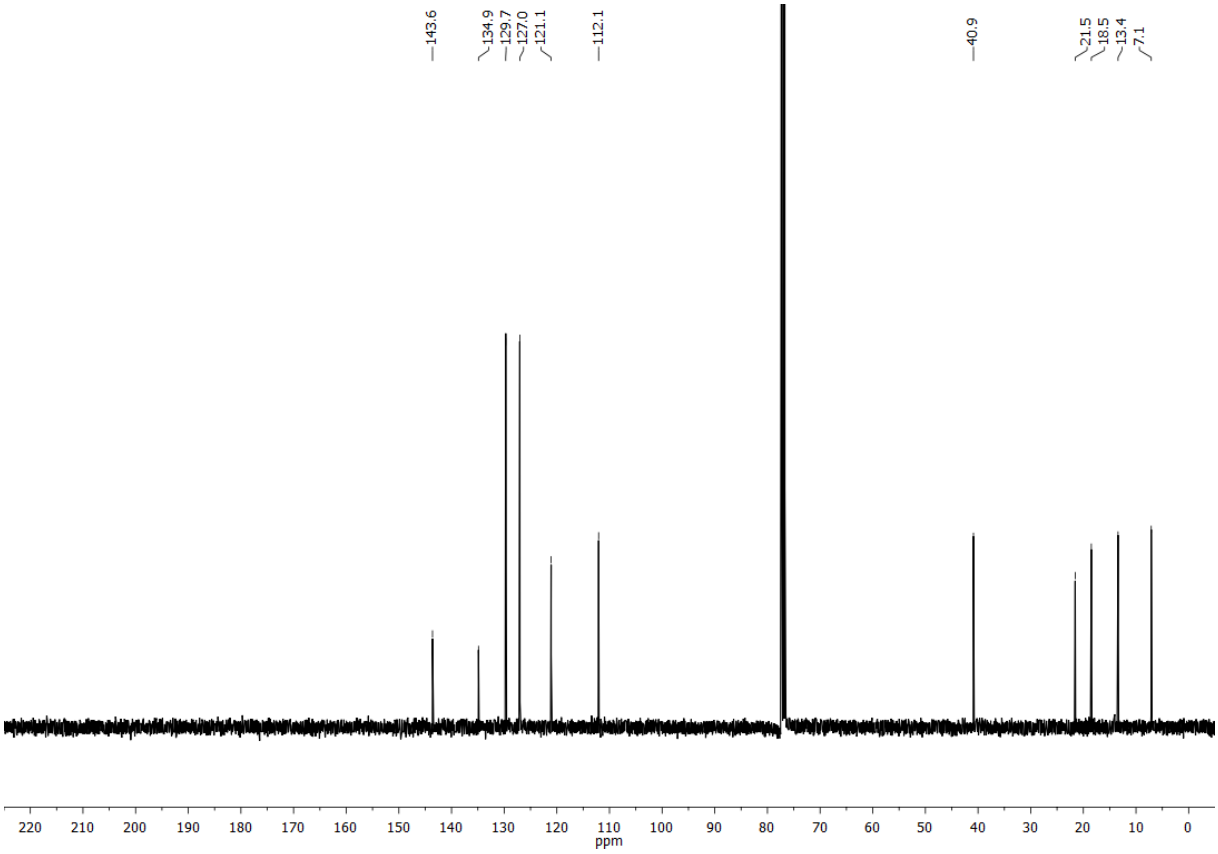
Compound **105** ^{13}**C-NMR** ($CDCl_3$)



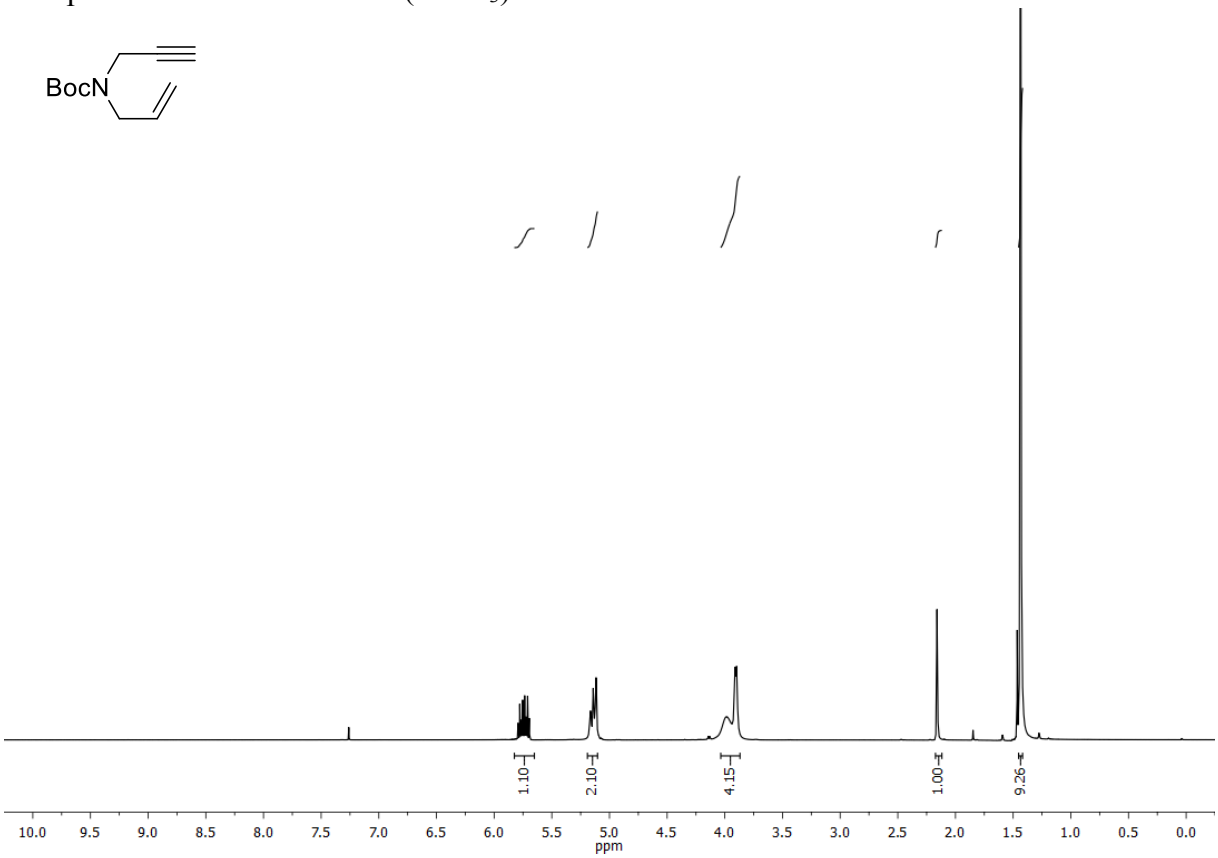
Compound **114-Ts ^{1}H-NMR** ($CDCl_3$)



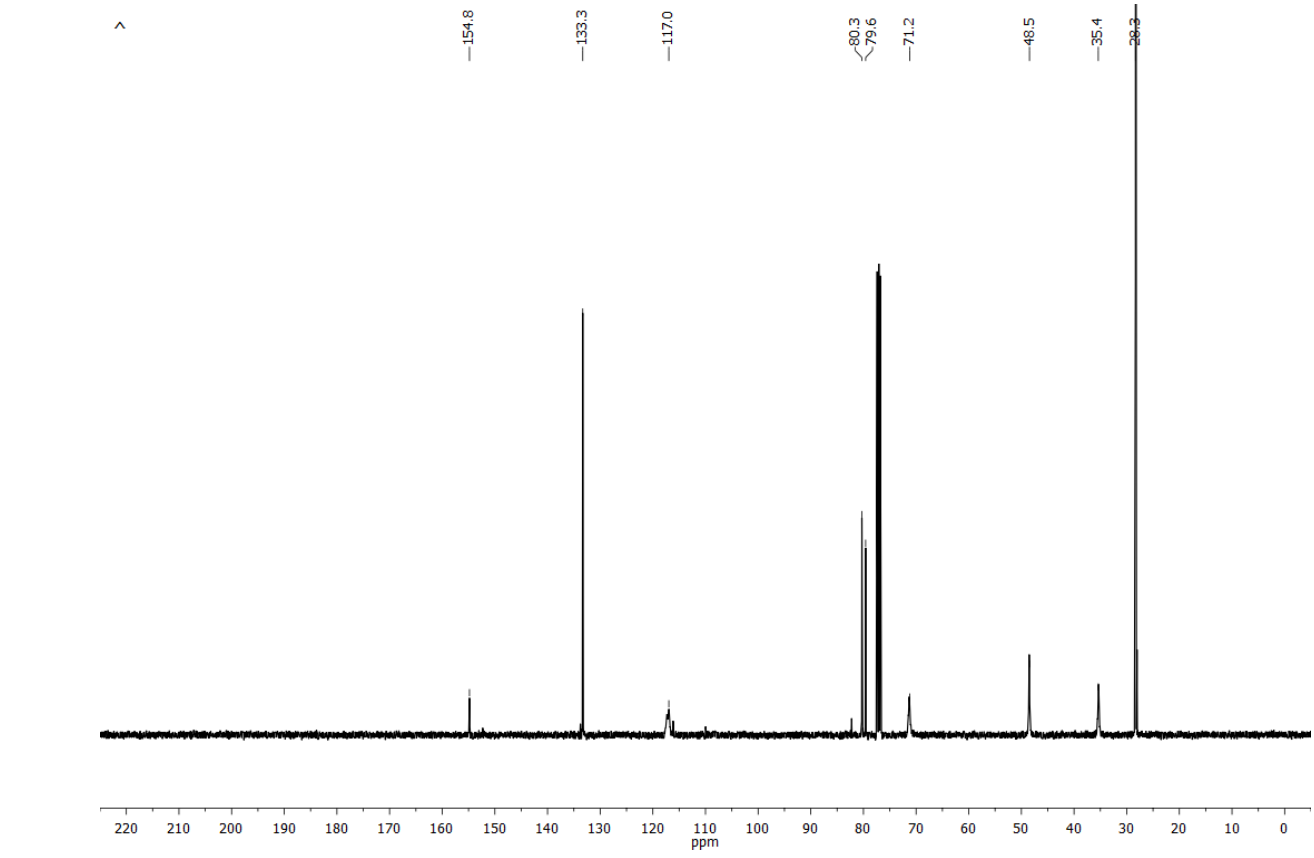
Compound **114-Ts ^{13}C-NMR** ($CDCl_3$)



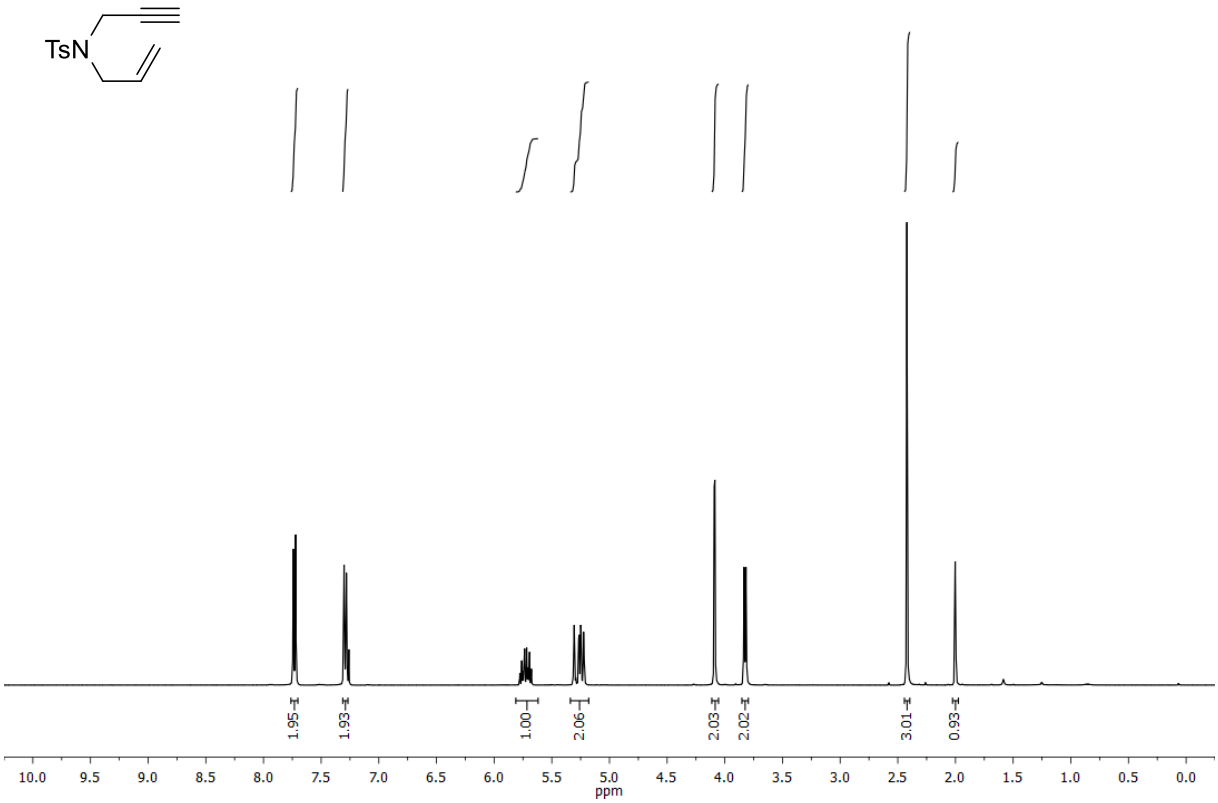
Compound **115-Boc ^{1}H-NMR** ($CDCl_3$)



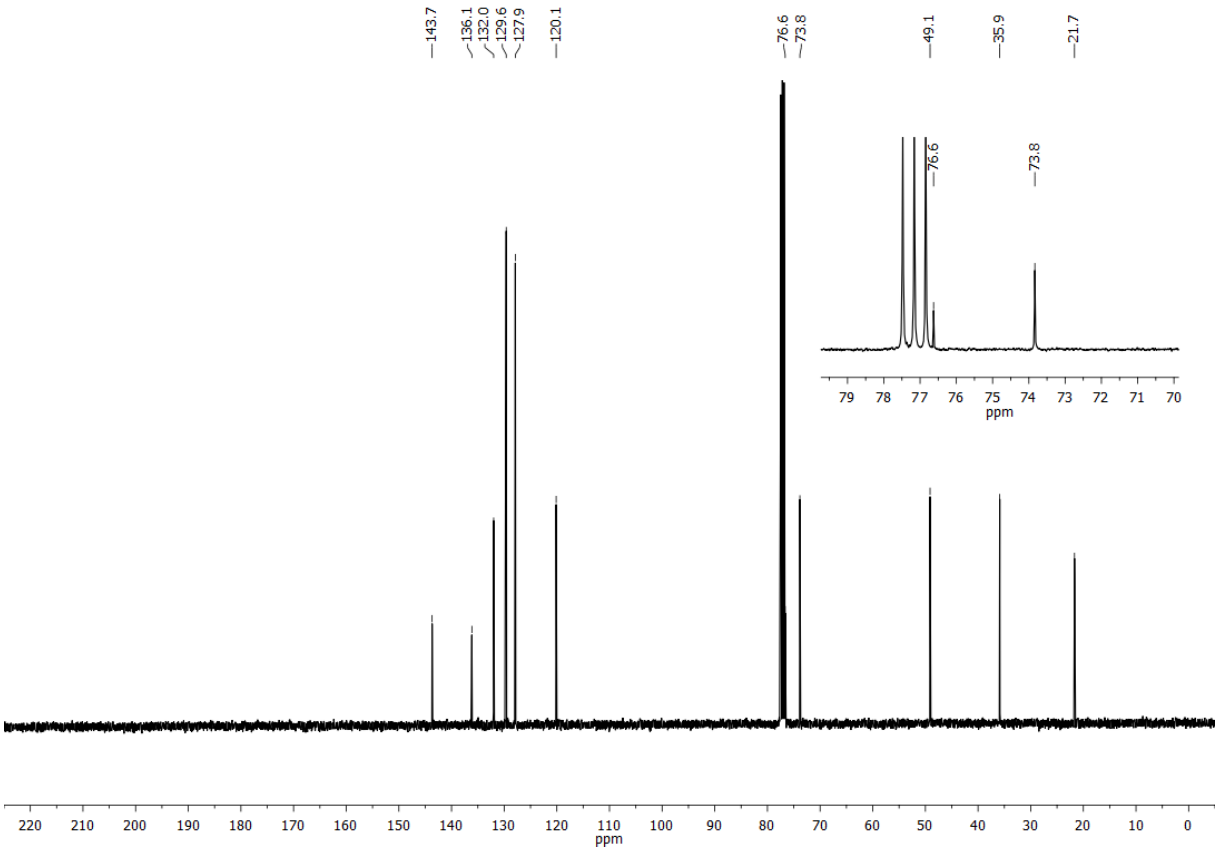
Compound **115-Boc ^{13}C-NMR** ($CDCl_3$)



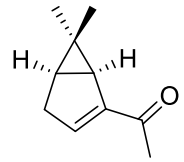
Compound **115-Ts** ^{1}**H-NMR** ($CDCl_3$)



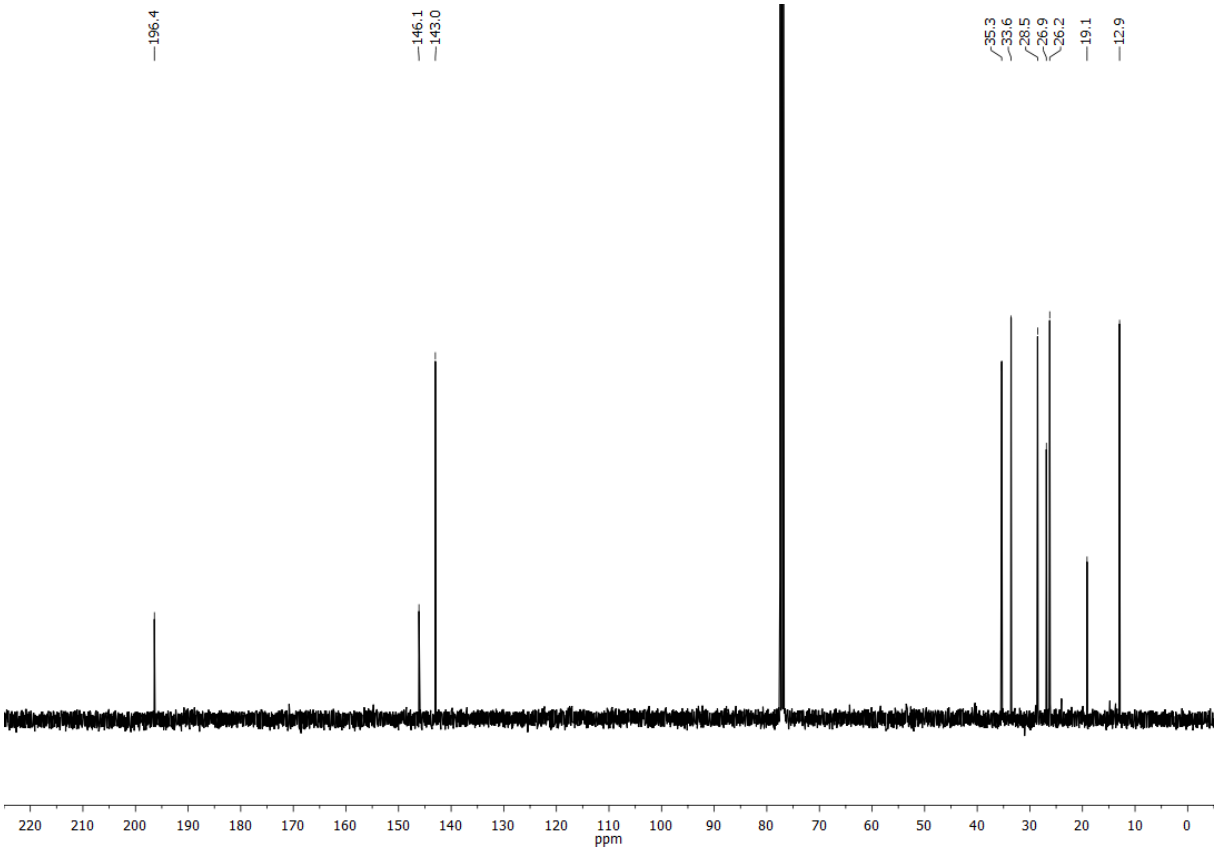
Compound **115-Ts** ^{13}**C-NMR** ($CDCl_3$)



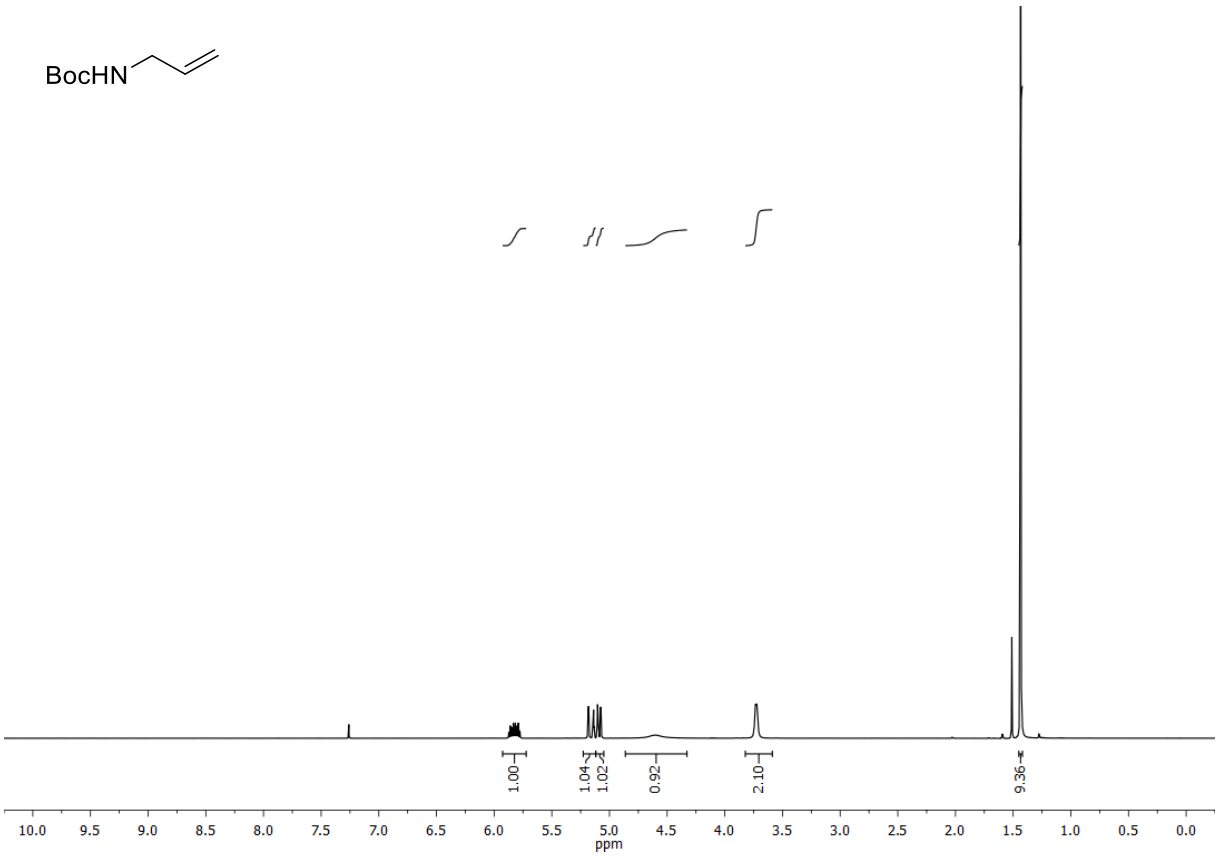
Compound **(+)-116 ^{1}H-NMR** ($CDCl_3$)



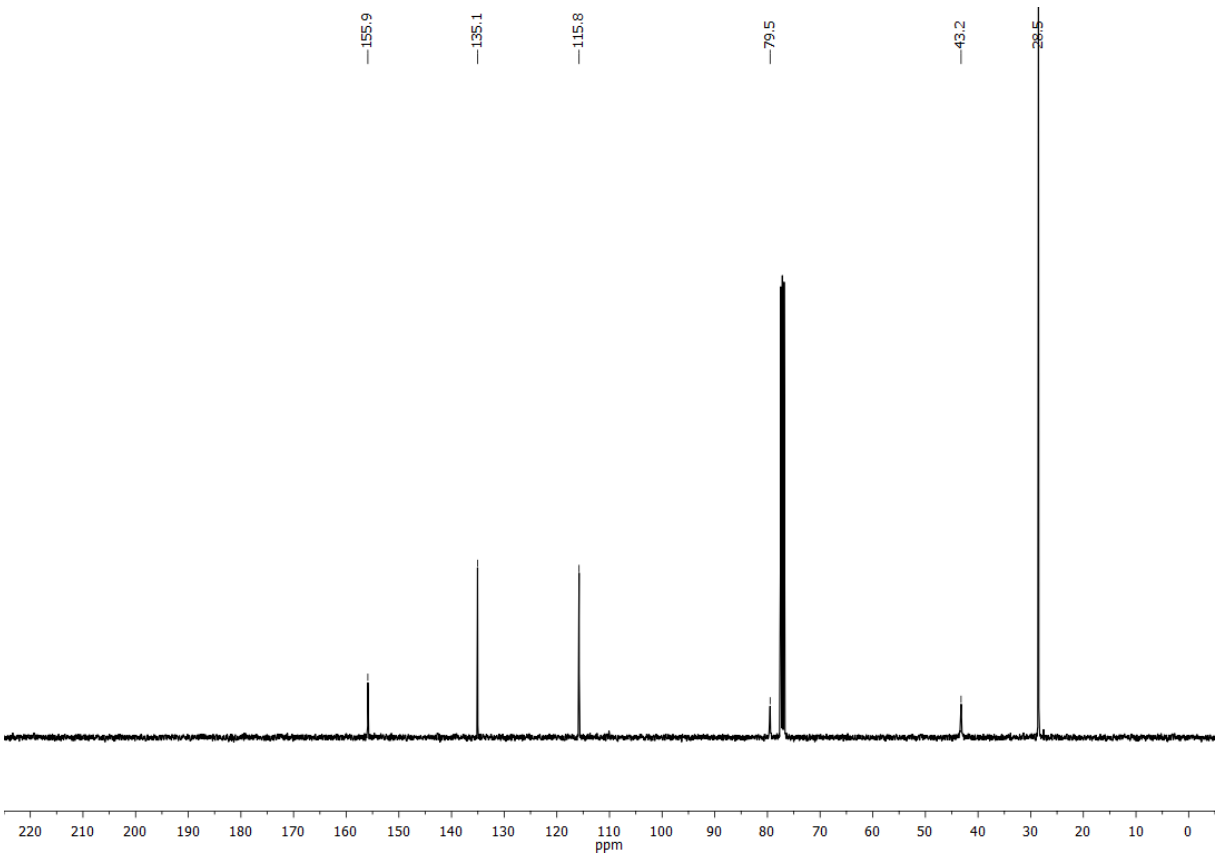
Compound **(+)-116 ^{13}C-NMR** ($CDCl_3$)



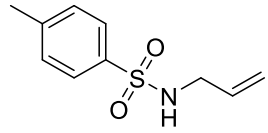
Compound **119-Boc ^{1}H-NMR** ($CDCl_3$)

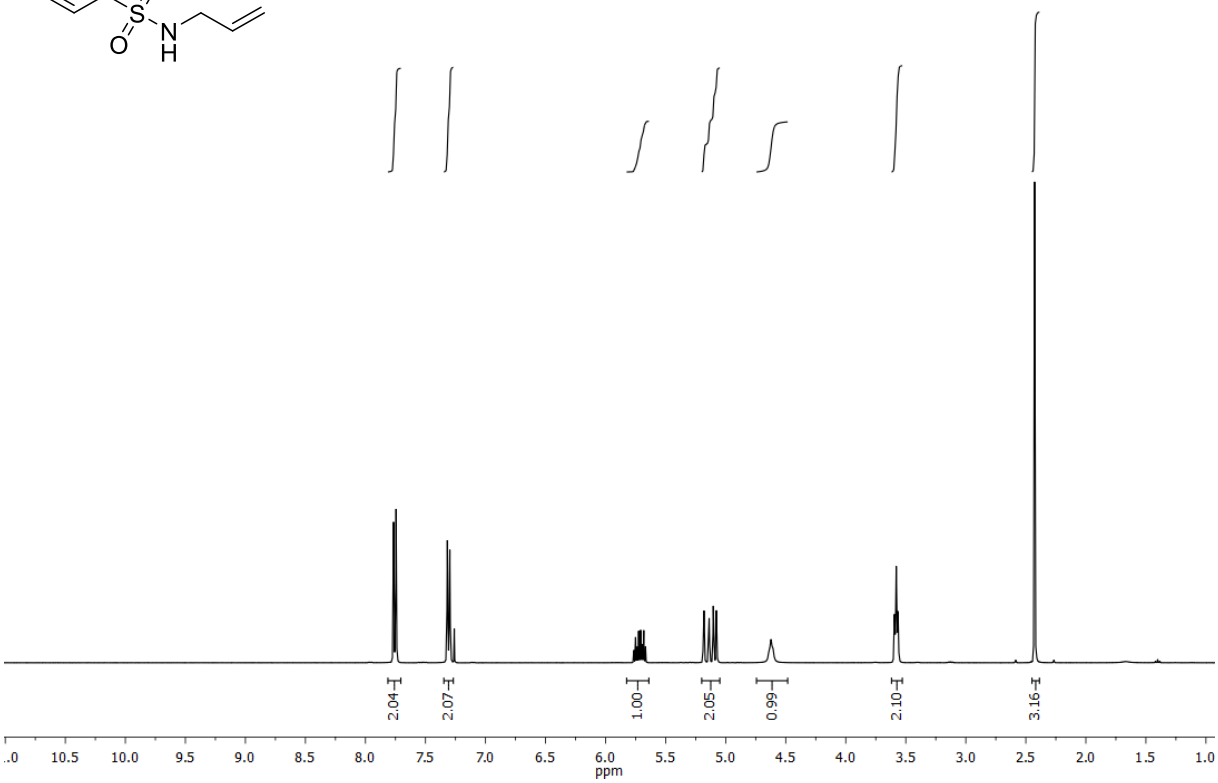


Compound **119-Boc ^{13}C-NMR** ($CDCl_3$)

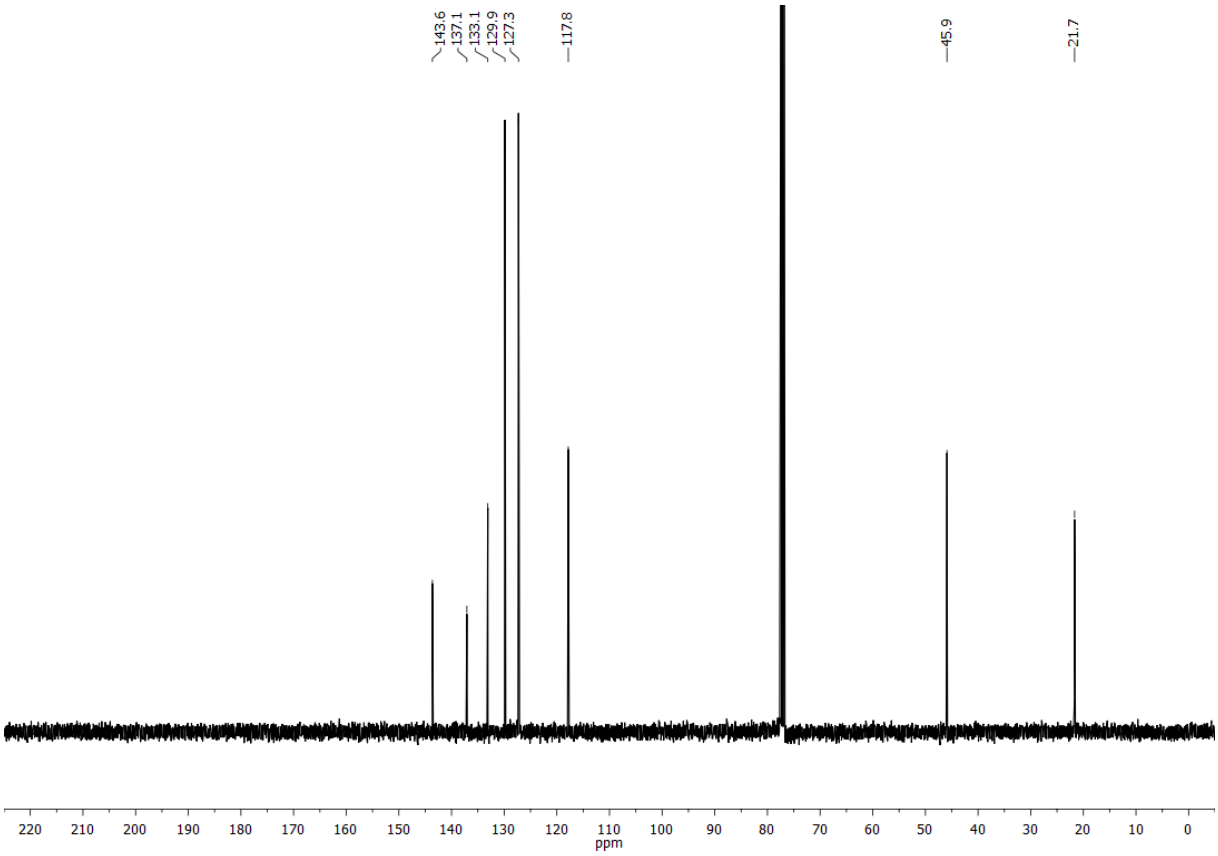


Compound **119-Ts ^{1}H-NMR** ($CDCl_3$)

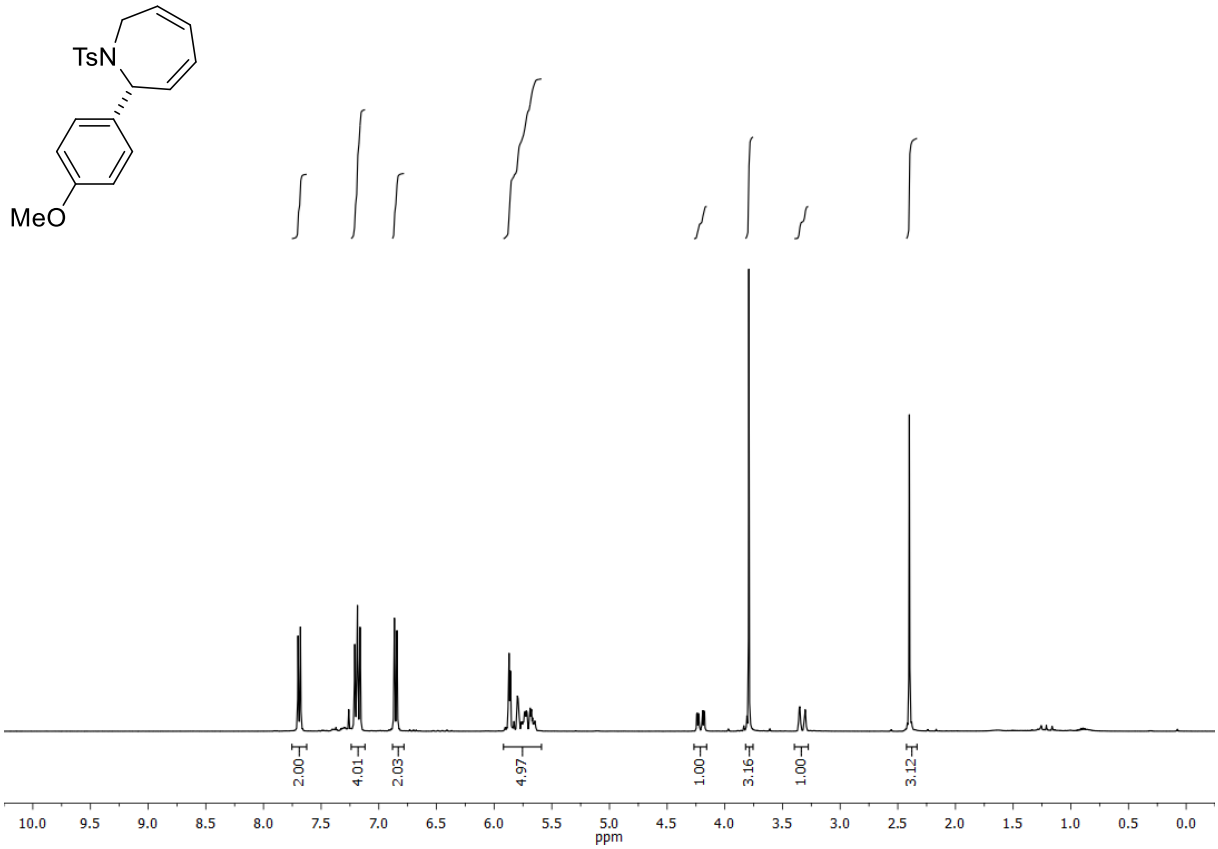




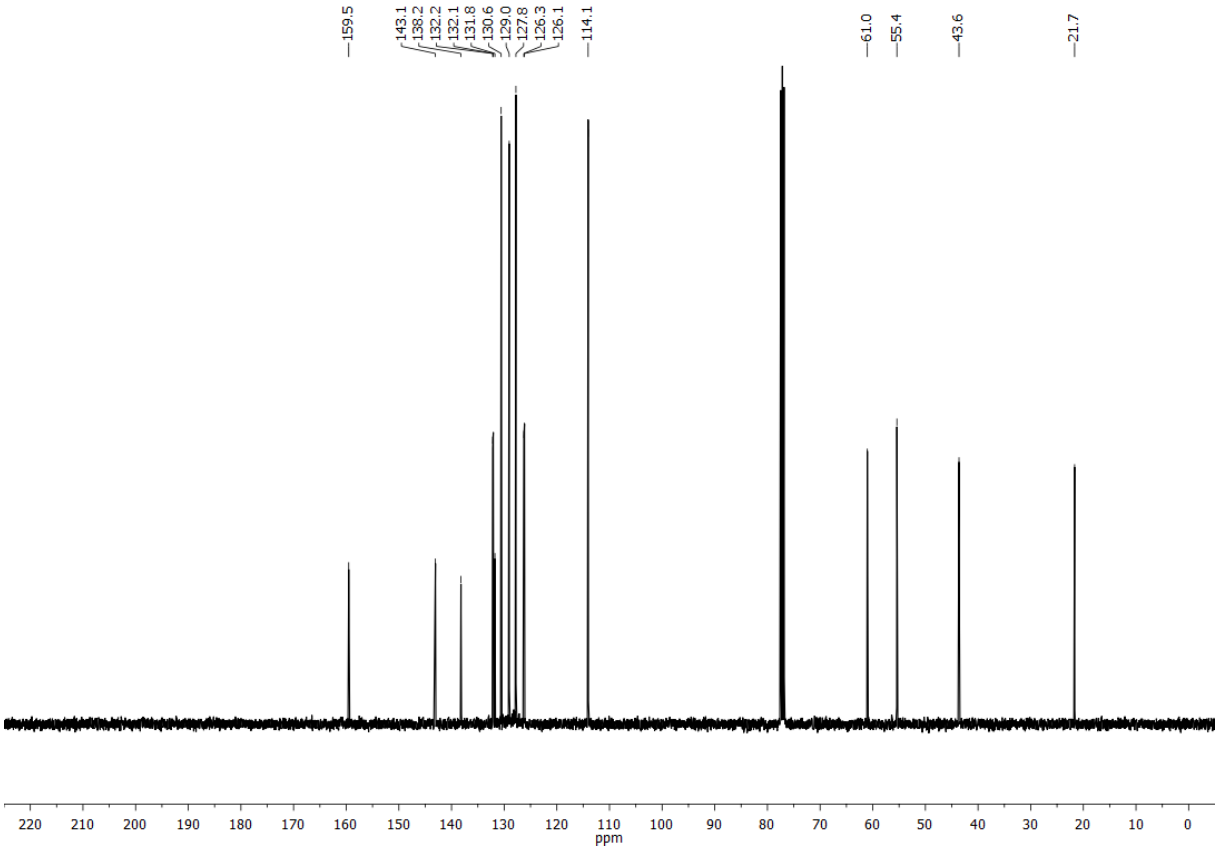
Compound **119-Ts ^{13}C-NMR** ($CDCl_3$)



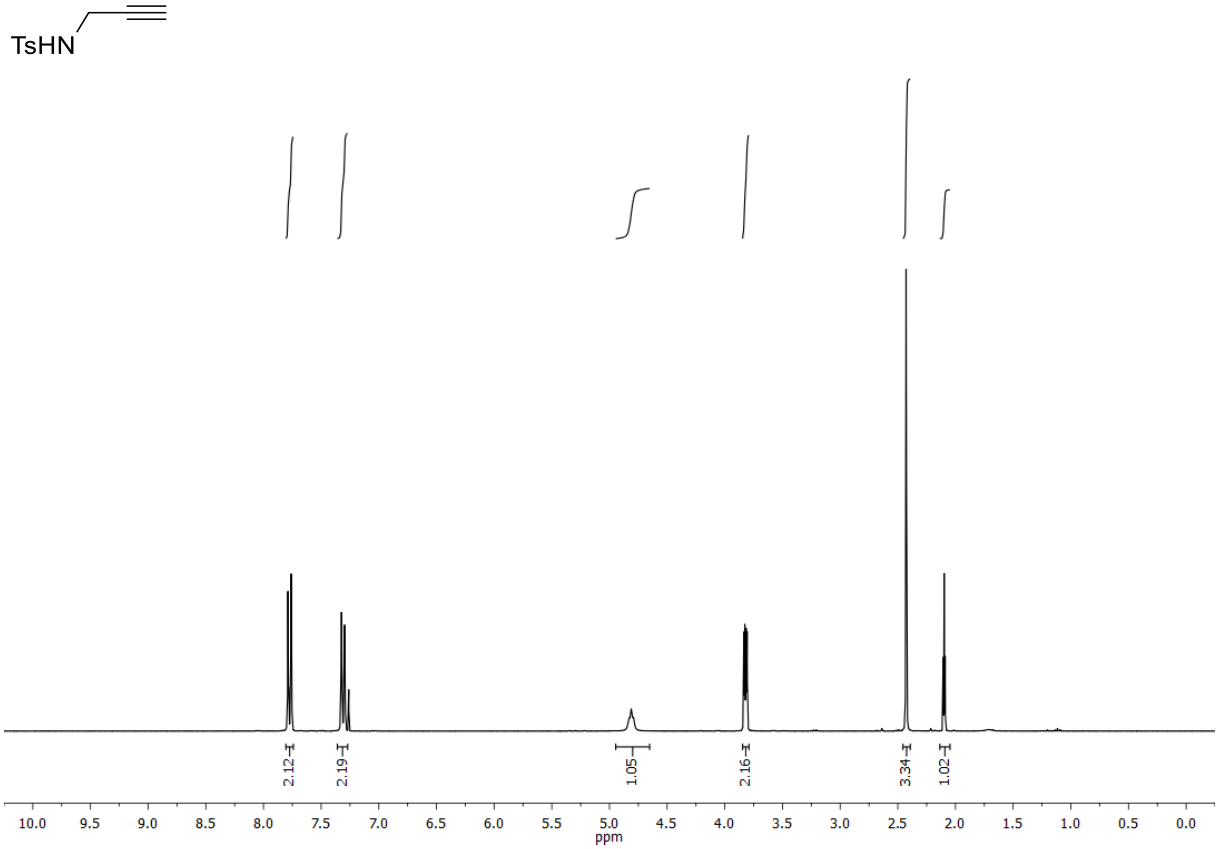
Compound **123** **^{1}H-NMR** ($CDCl_3$)



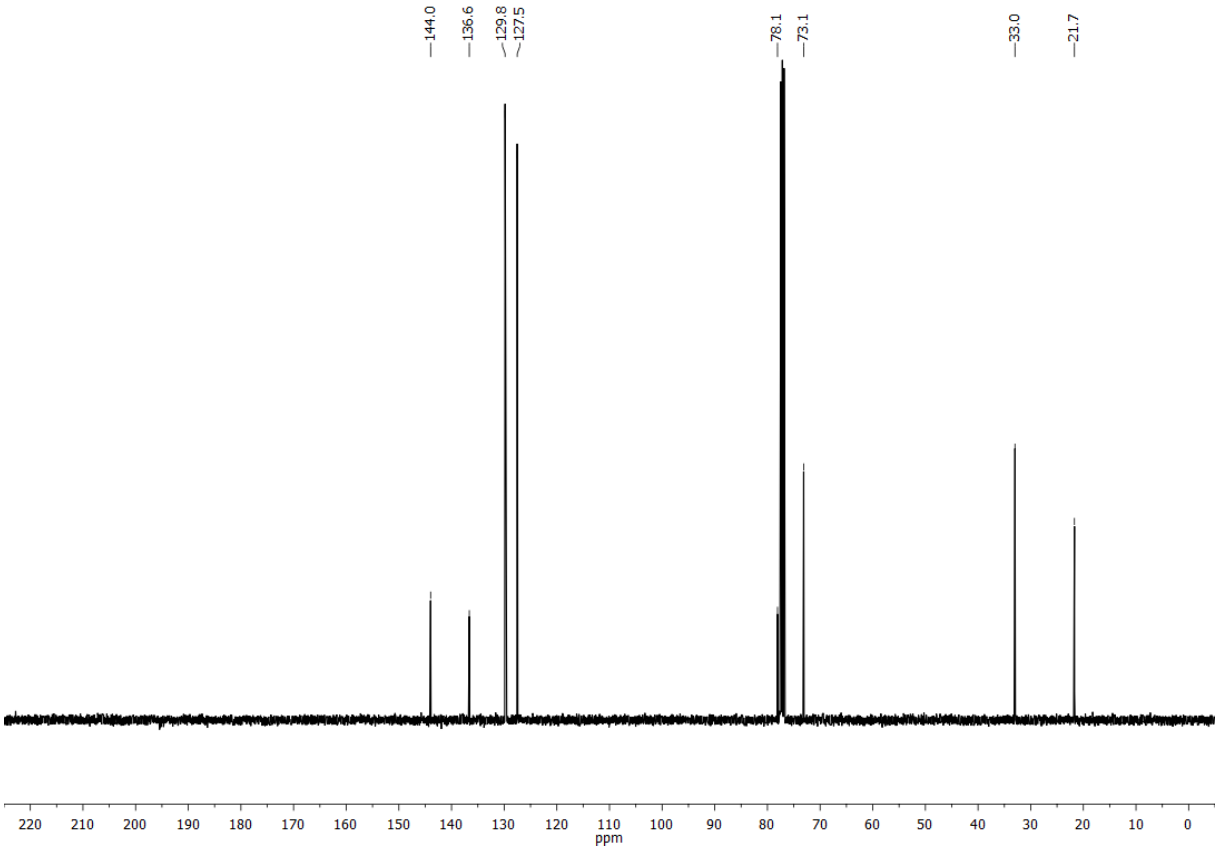
Compound **123** **^{13}C-NMR** ($CDCl_3$)



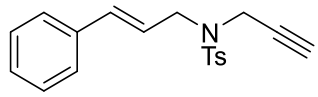
Compound **124** ^{1}**H-NMR** ($CDCl_3$)

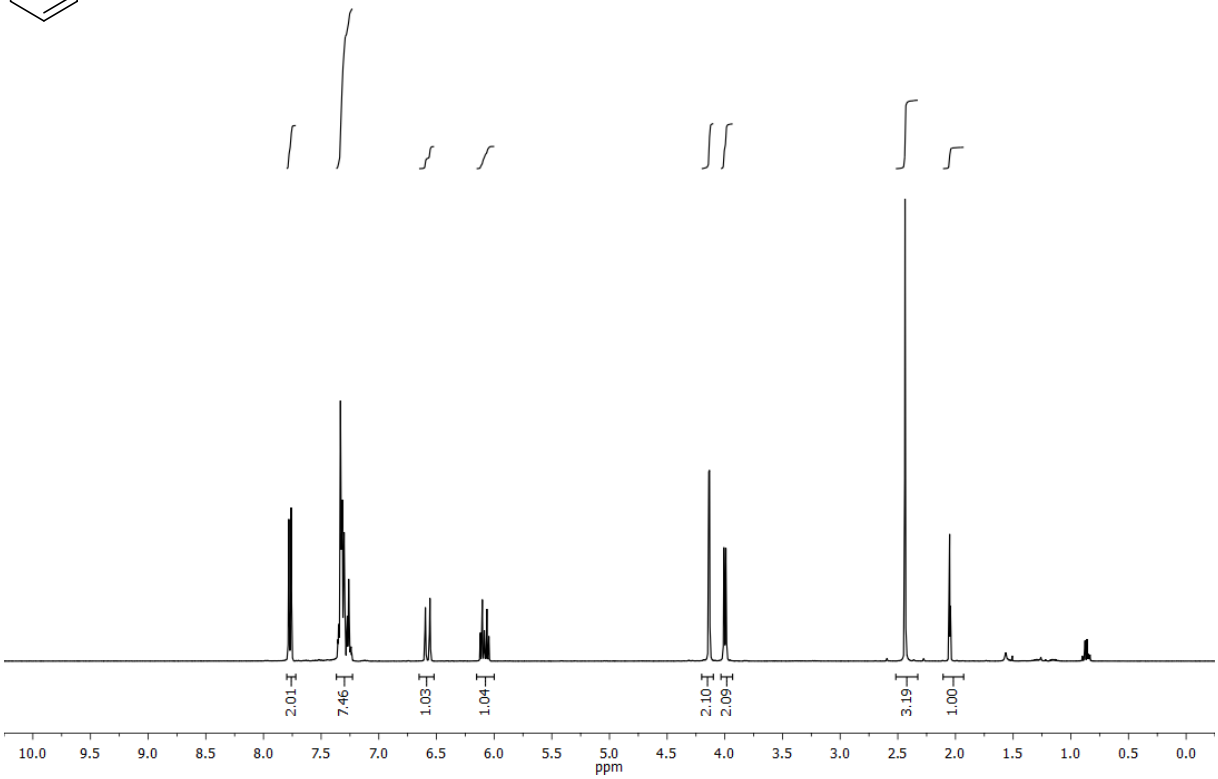


Compound **124** ^{13}**C-NMR** ($CDCl_3$)

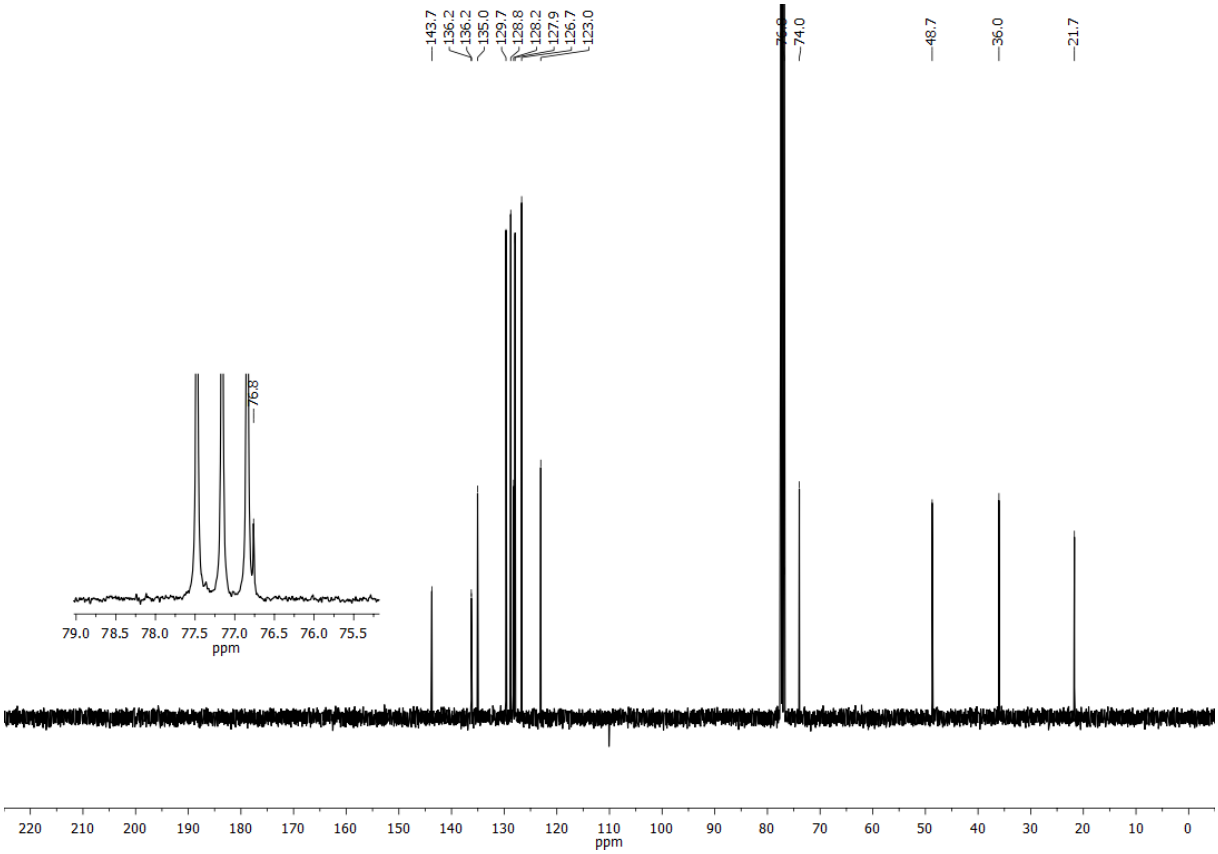


Compound **125** **^{1}H-NMR** ($CDCl_3$)

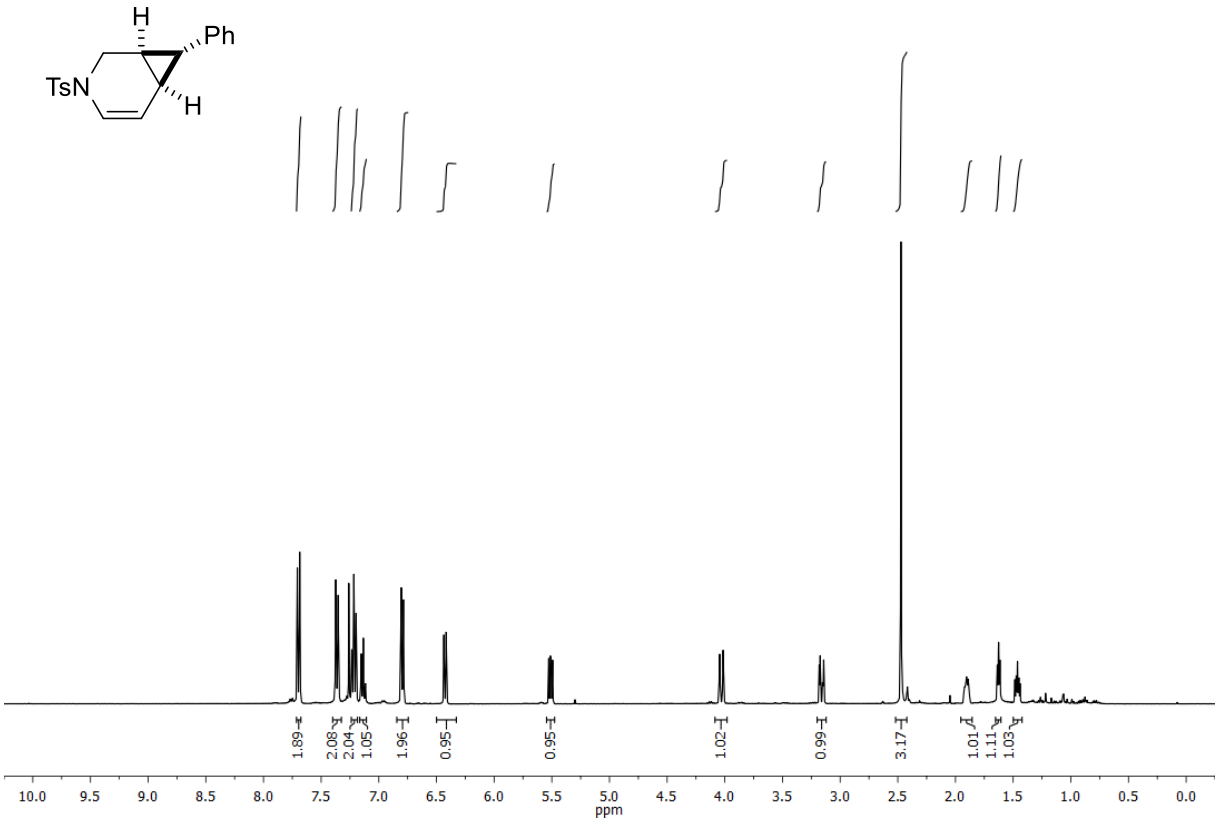




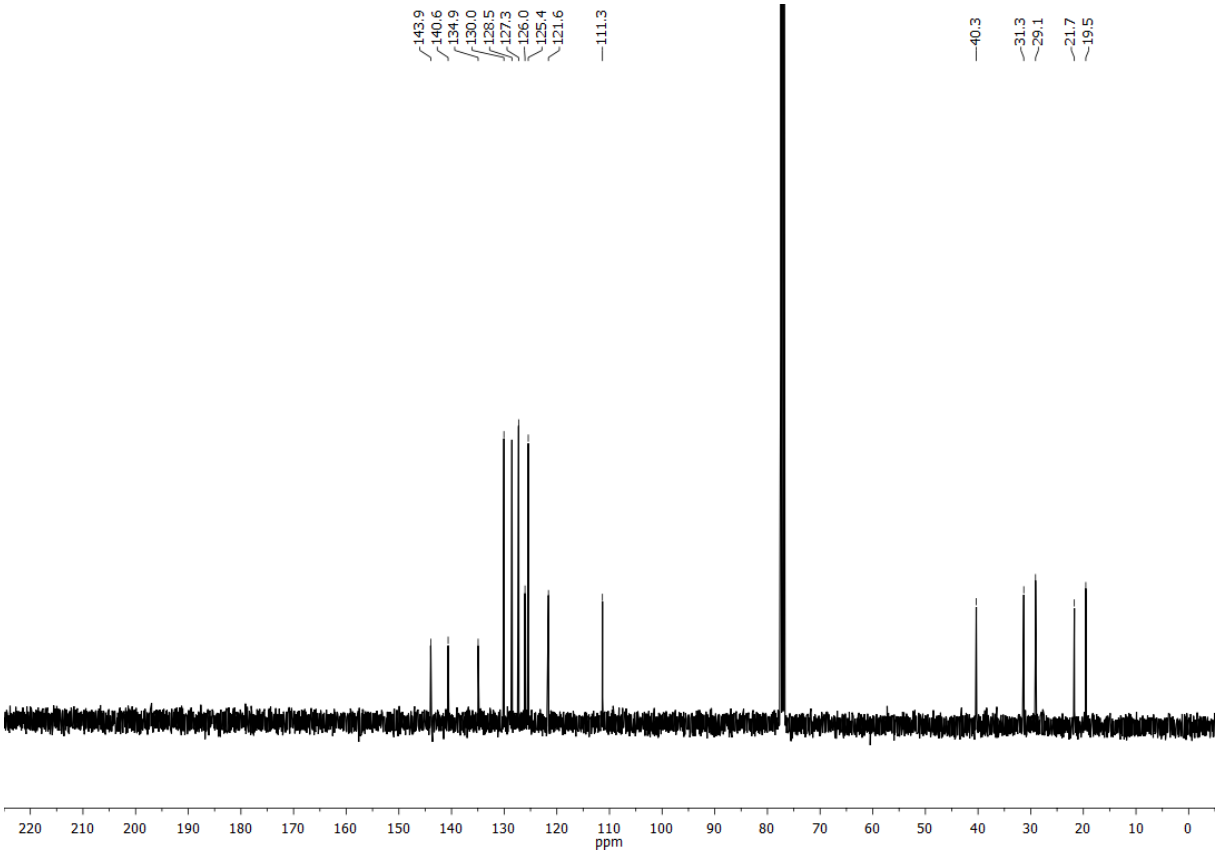
Compound **125** **^{13}C-NMR** ($CDCl_3$)



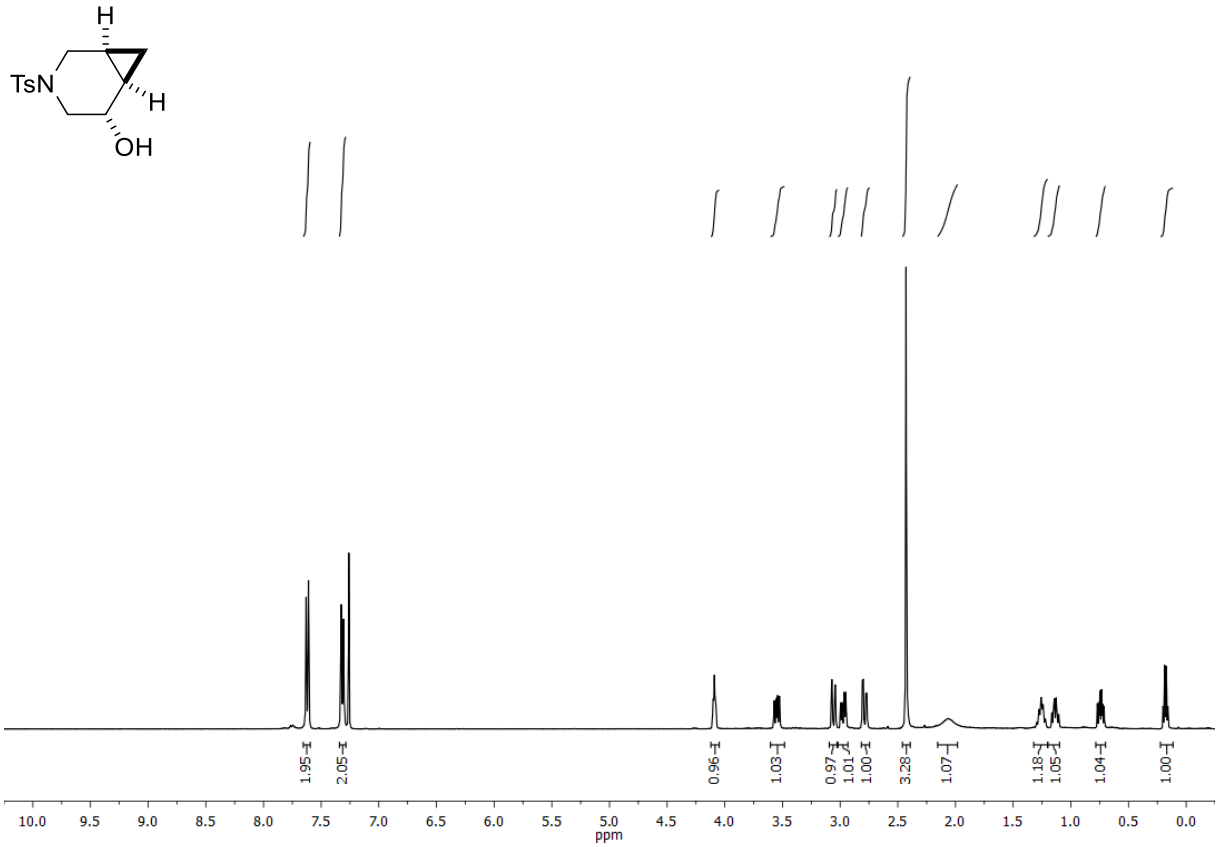
Compound **126** ^{1}**H-NMR** ($CDCl_3$)



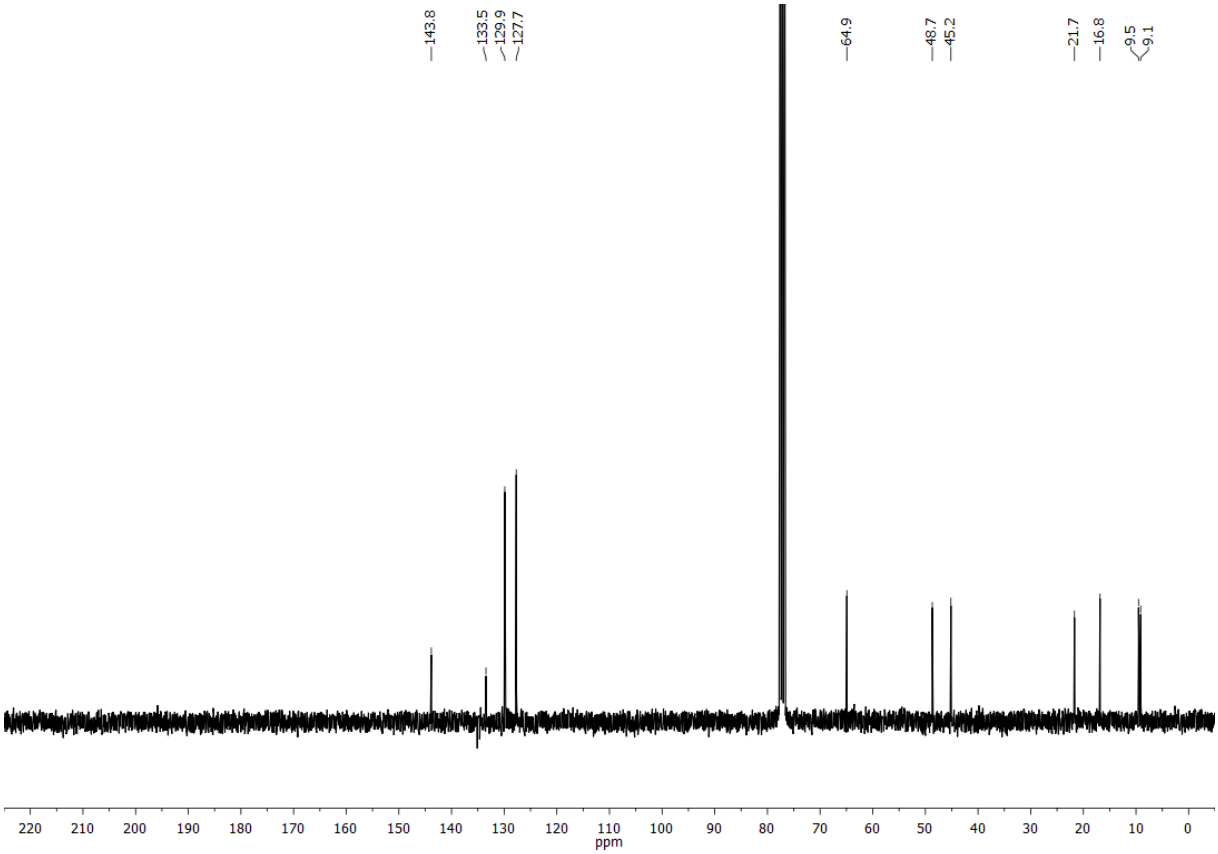
Compound **126** ^{13}**C-NMR** ($CDCl_3$)



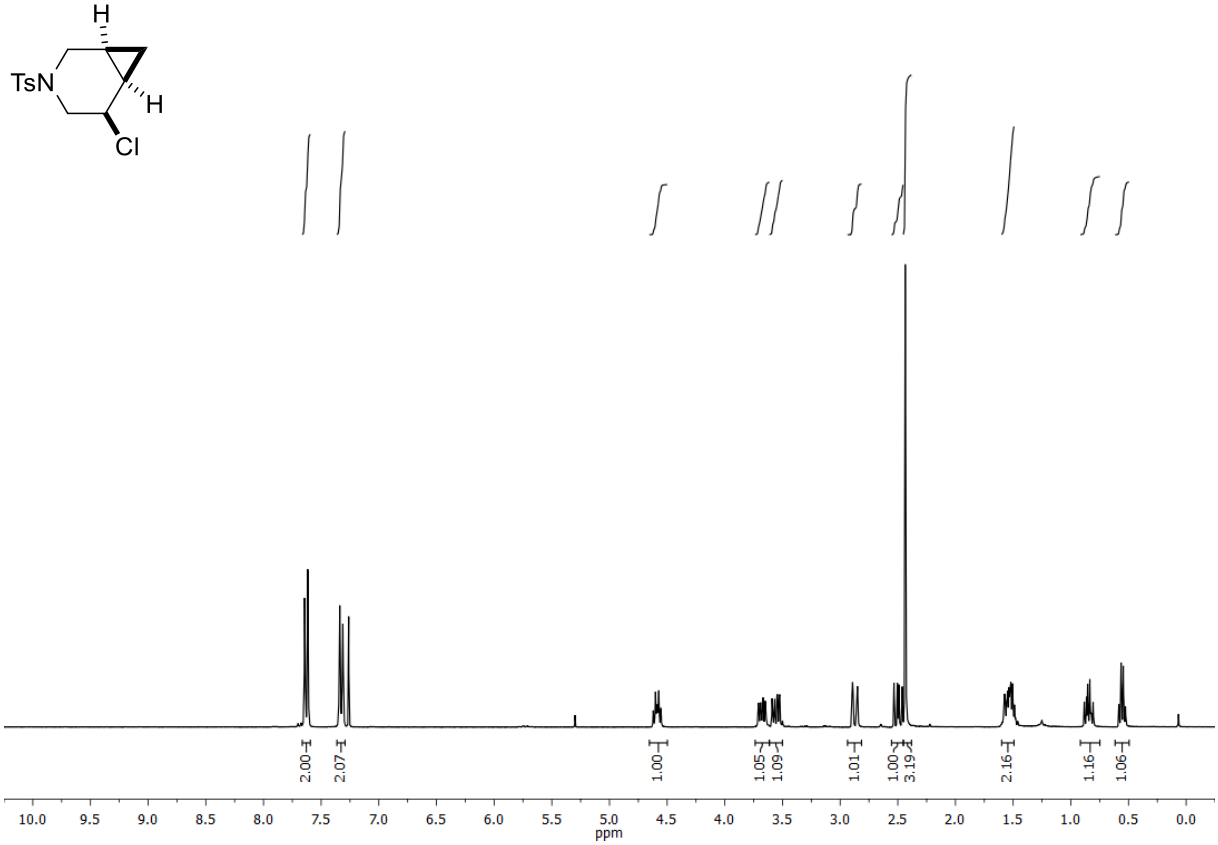
Compound **128** **^{1}H-NMR** ($CDCl_3$)



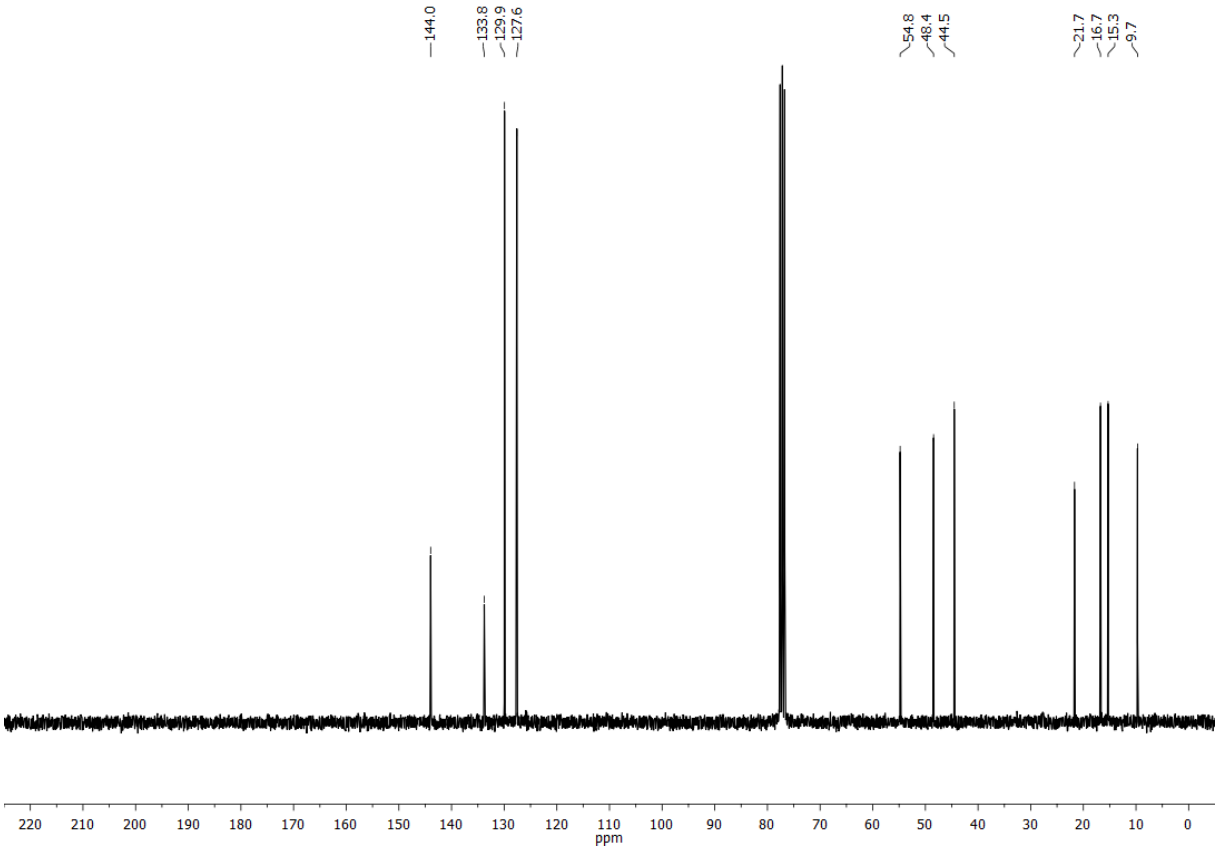
Compound **128** **^{13}C-NMR** ($CDCl_3$)



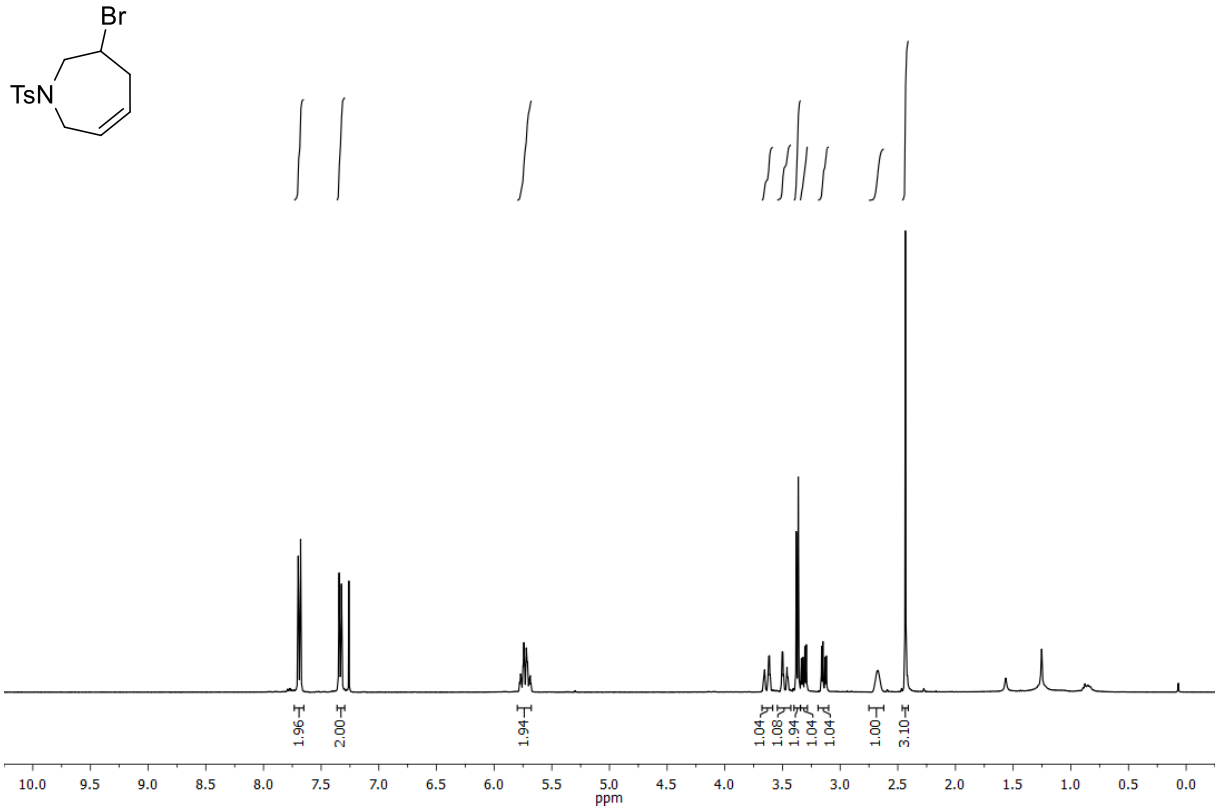
Compound **132** ^{1}**H-NMR** ($CDCl_3$)



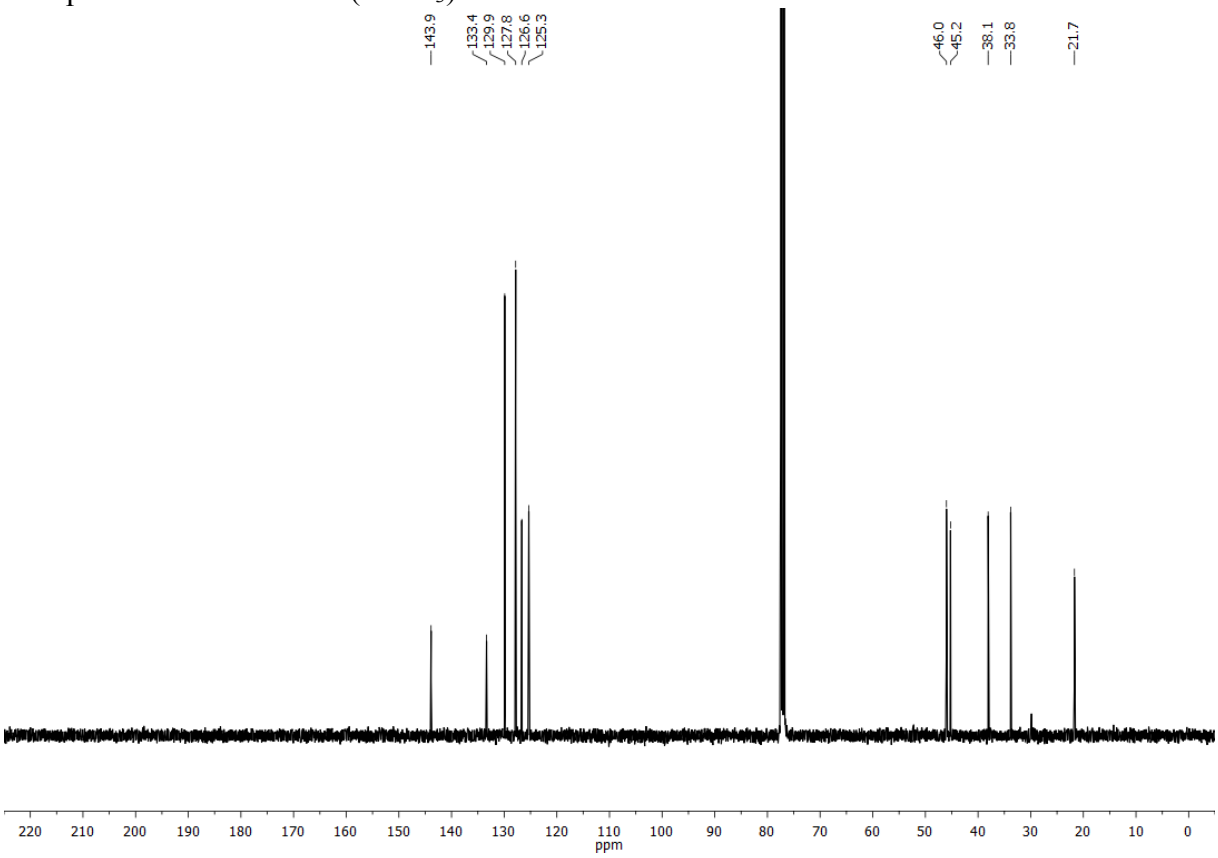
Compound **132** ^{13}**C-NMR** ($CDCl_3$)



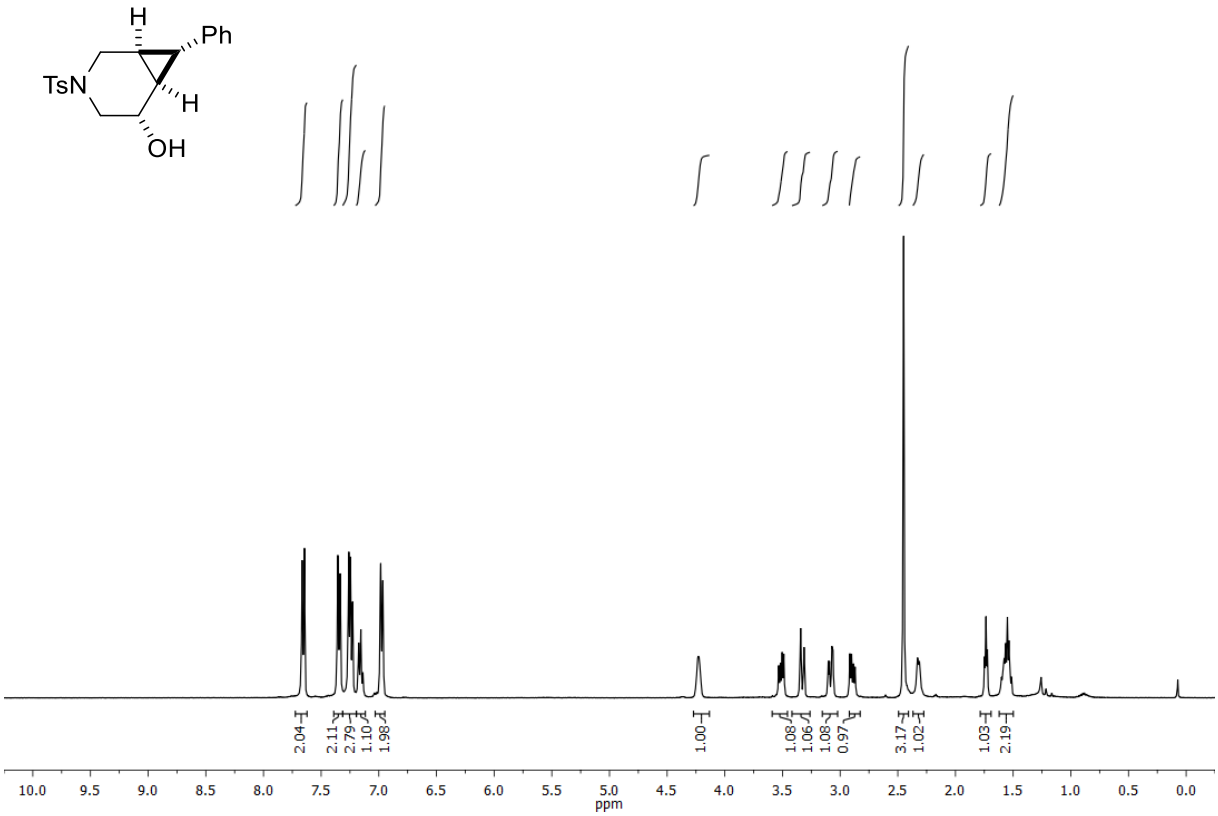
Compound **136** **^{1}H-NMR** ($CDCl_3$)



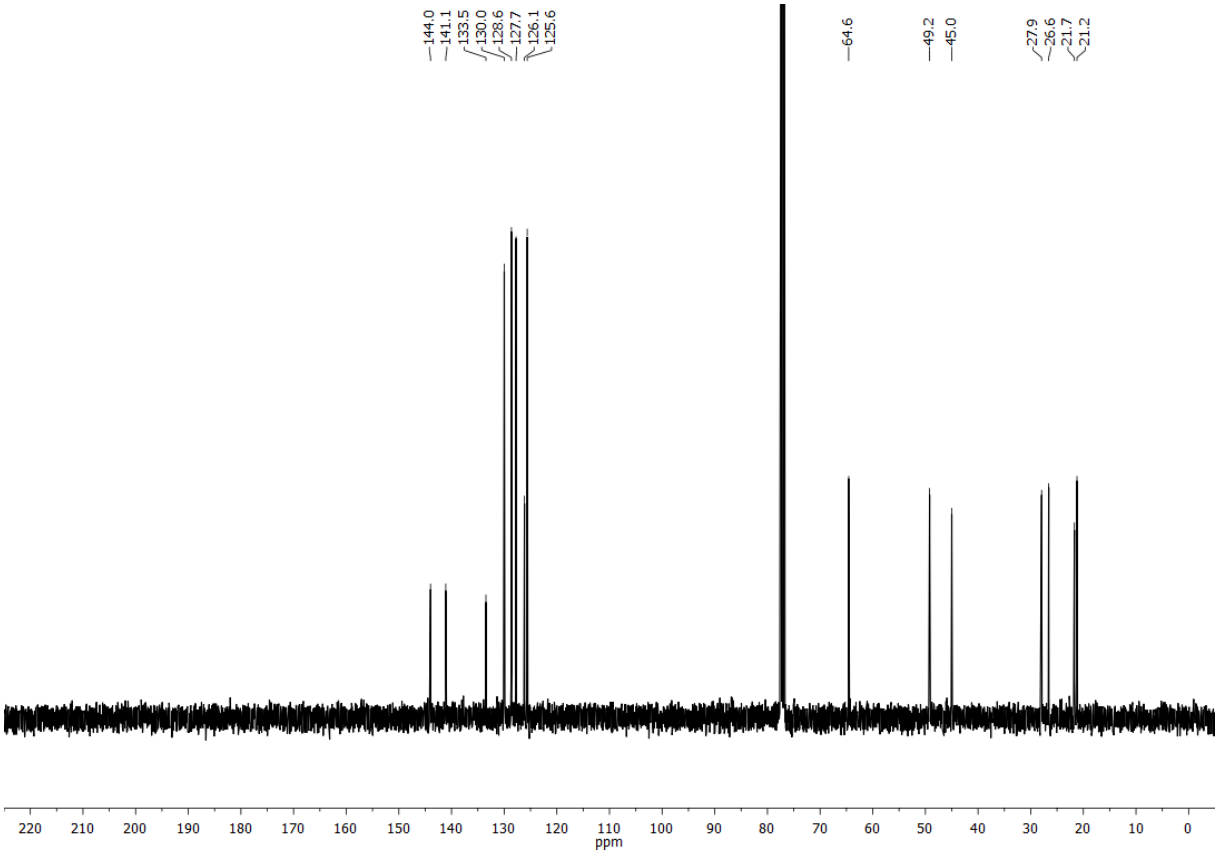
Compound **136** **^{13}C-NMR** ($CDCl_3$)



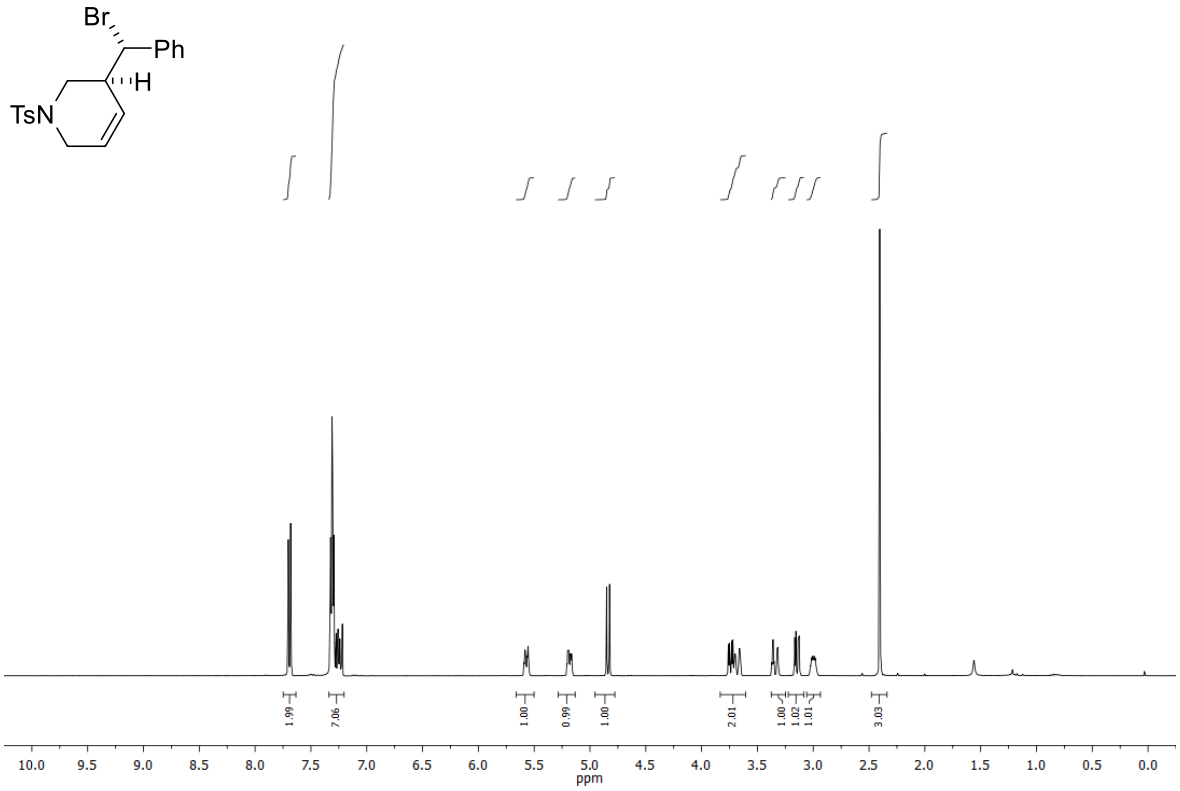
Compound 1**38** **^{1}H-NMR** ($CDCl_3$)



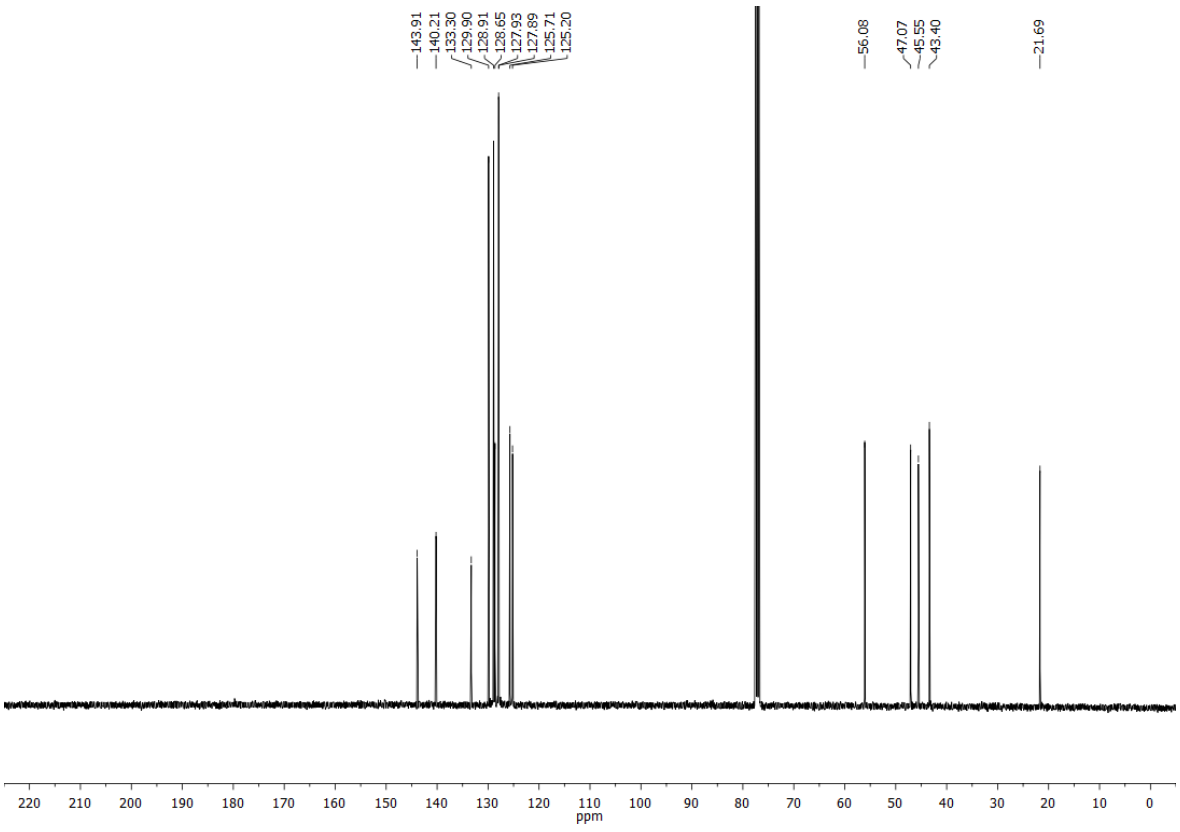
Compound **138** **^{13}C-NMR** ($CDCl_3$)



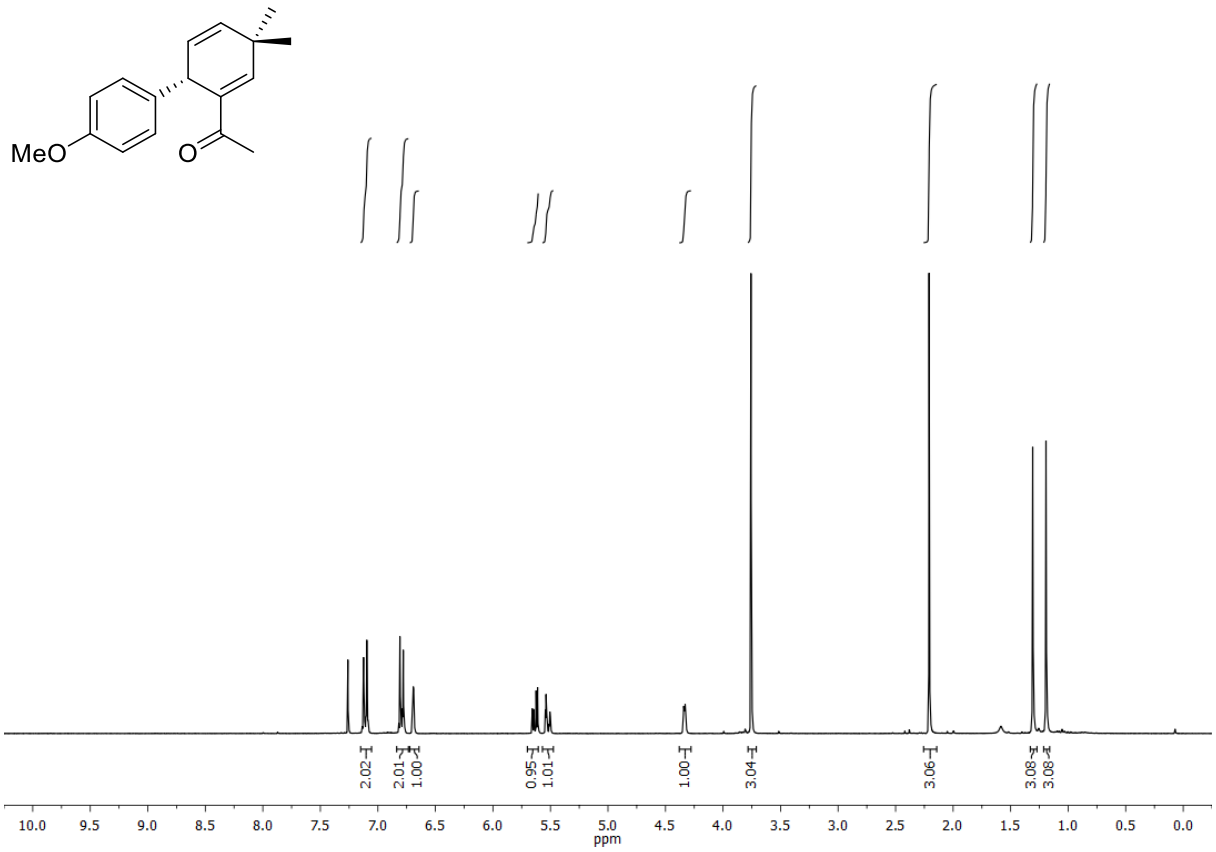
Compound **140** **^{1}H-NMR** ($CDCl_3$)



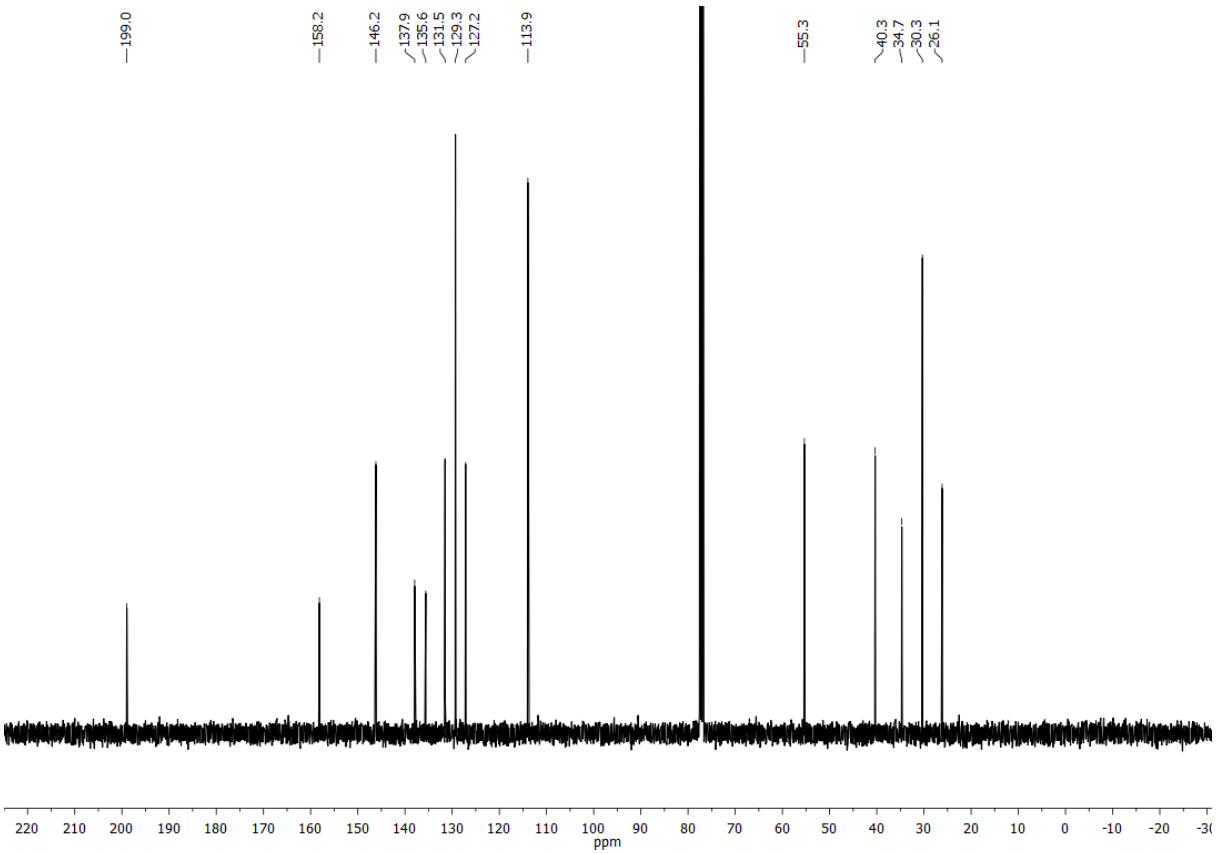
Compound **140** **^{13}C-NMR** ($CDCl_3$)



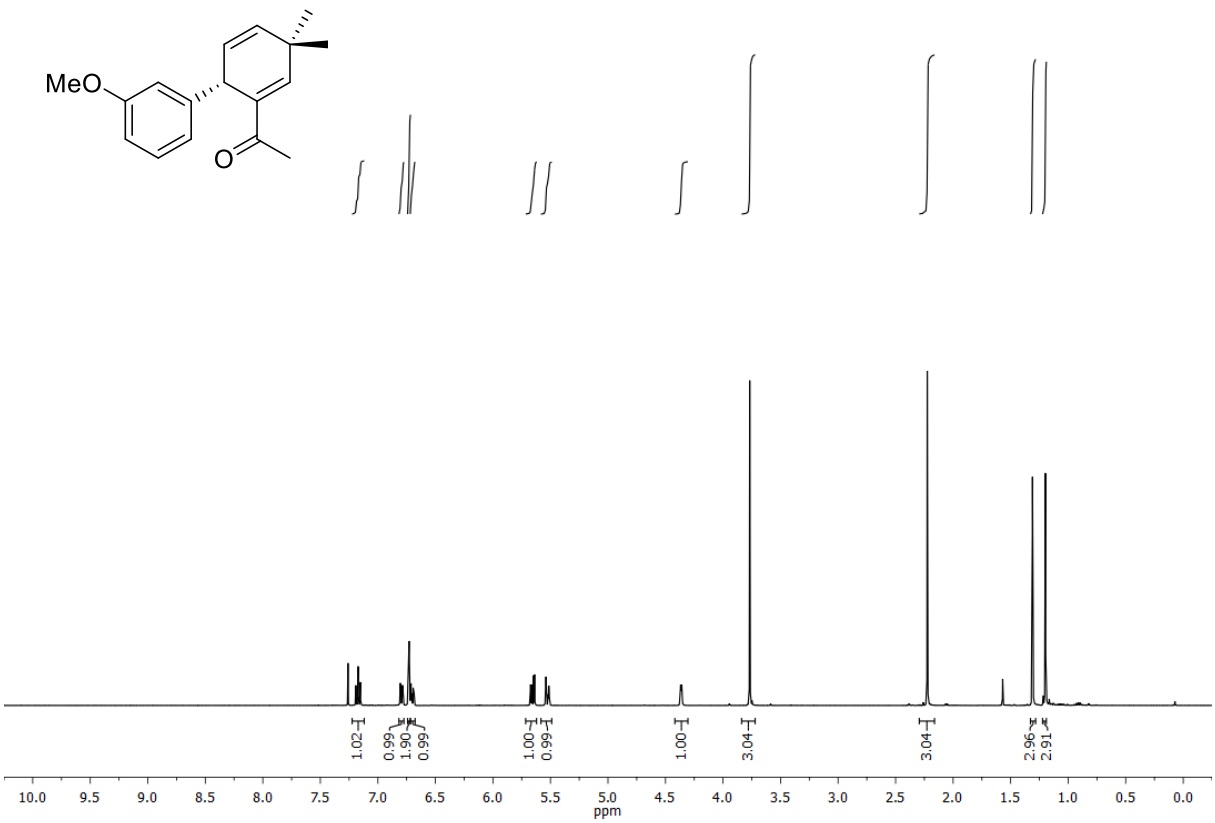
Compound **(-)-147a ^{1}H-NMR** ($CDCl_3$)



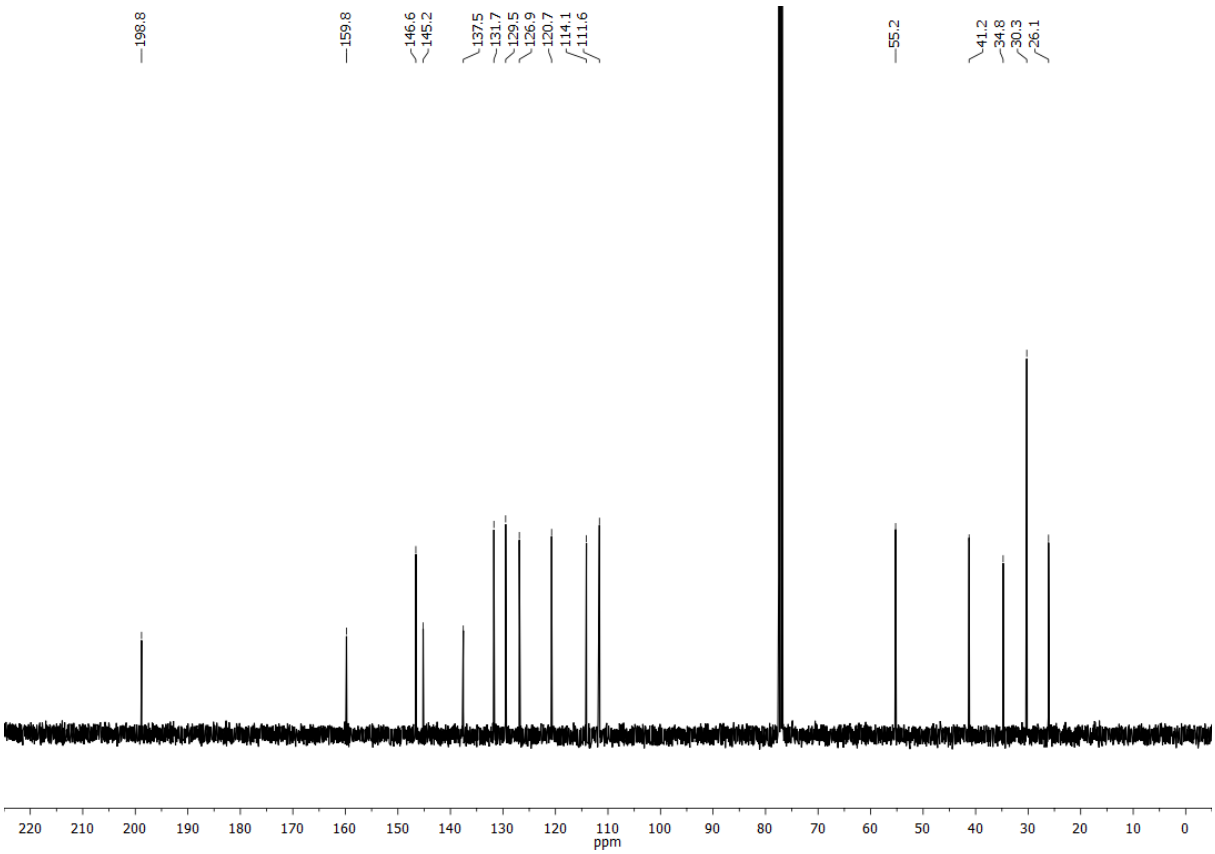
Compound **(-)-147a ^{13}C-NMR** ($CDCl_3$)



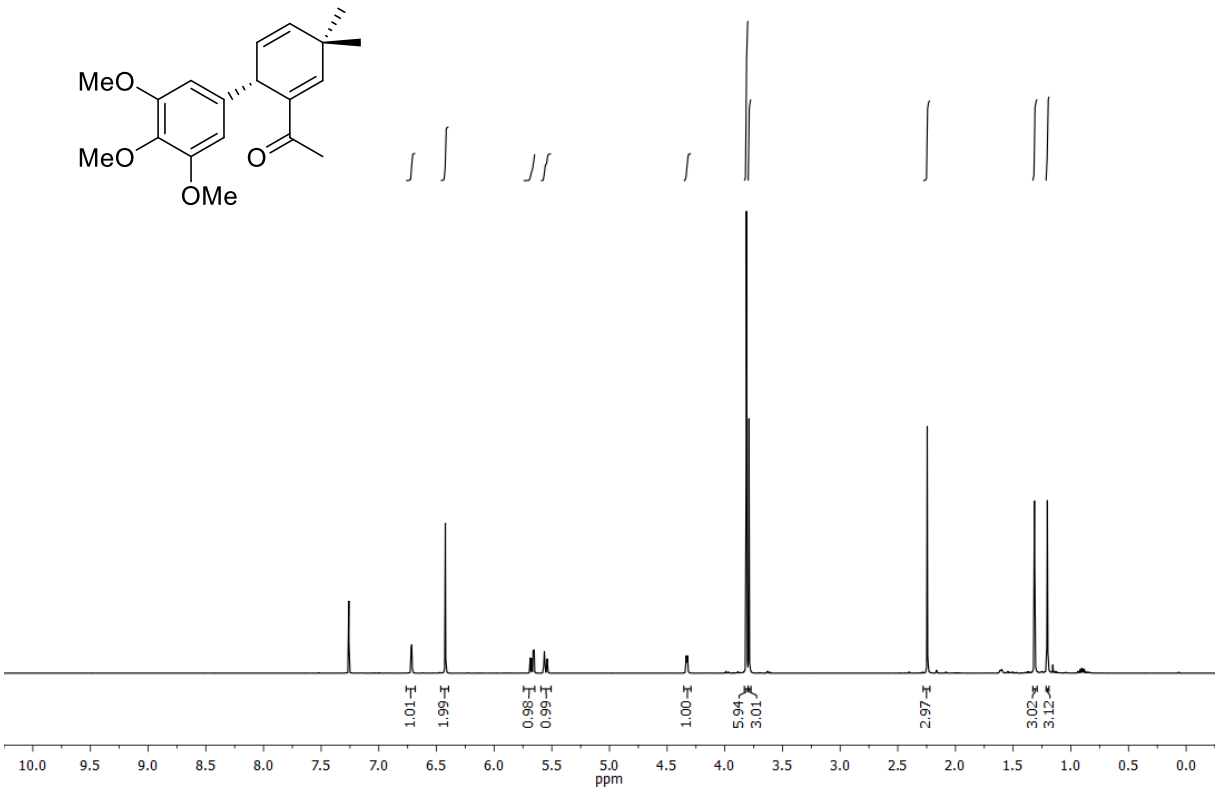
Compound **(-)-147b ^{1}H-NMR** ($CDCl_3$)



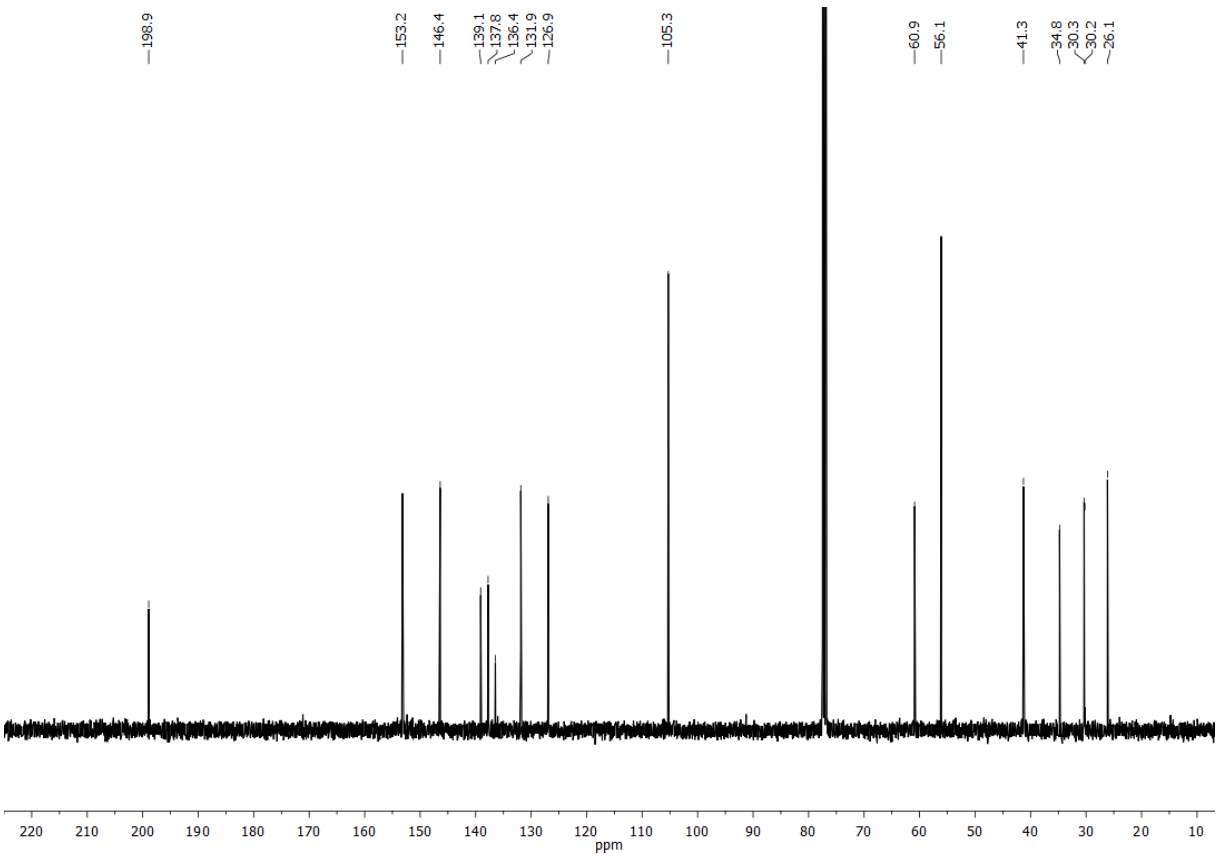
Compound **(-)-147b ^{13}C-NMR** ($CDCl_3$)



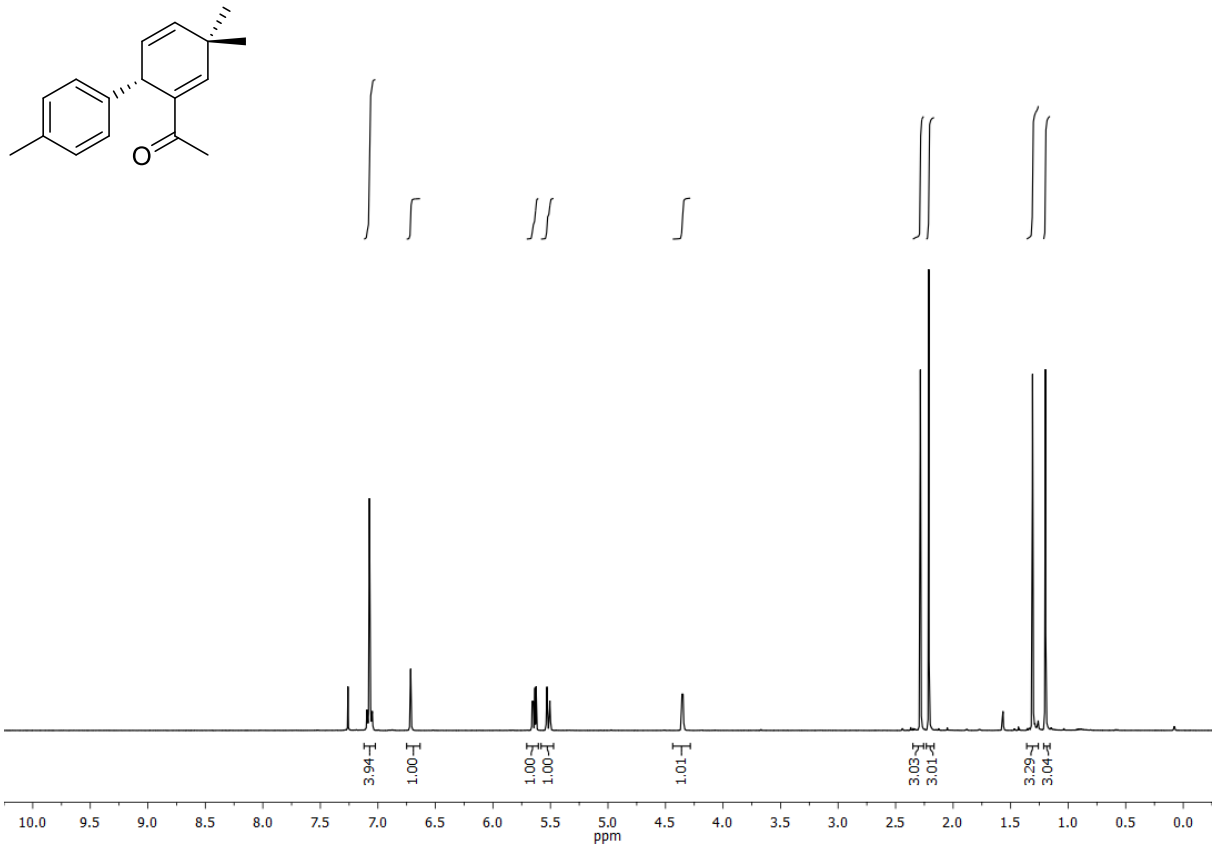
Compound **(-)-147d ^{1}H-NMR** ($CDCl_3$)



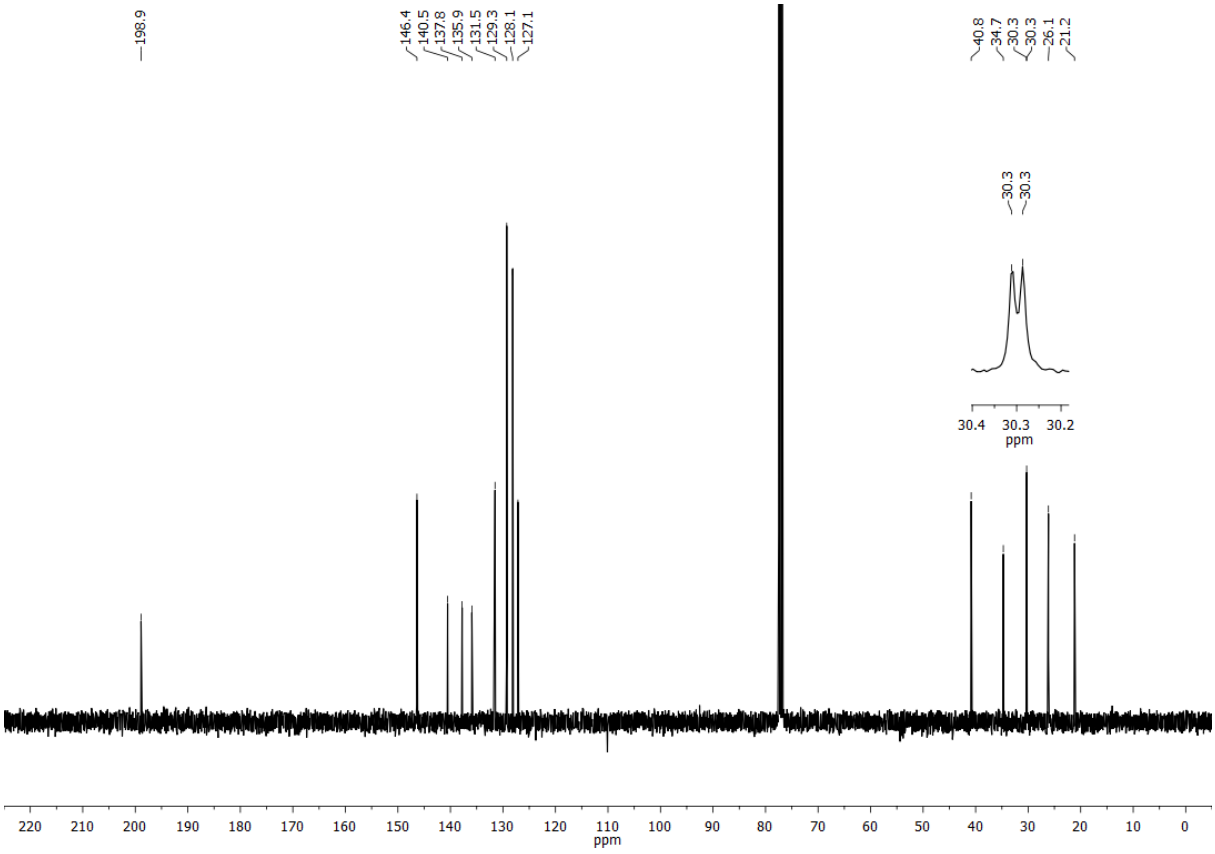
Compound **(-)-147d ^{13}C-NMR** ($CDCl_3$)



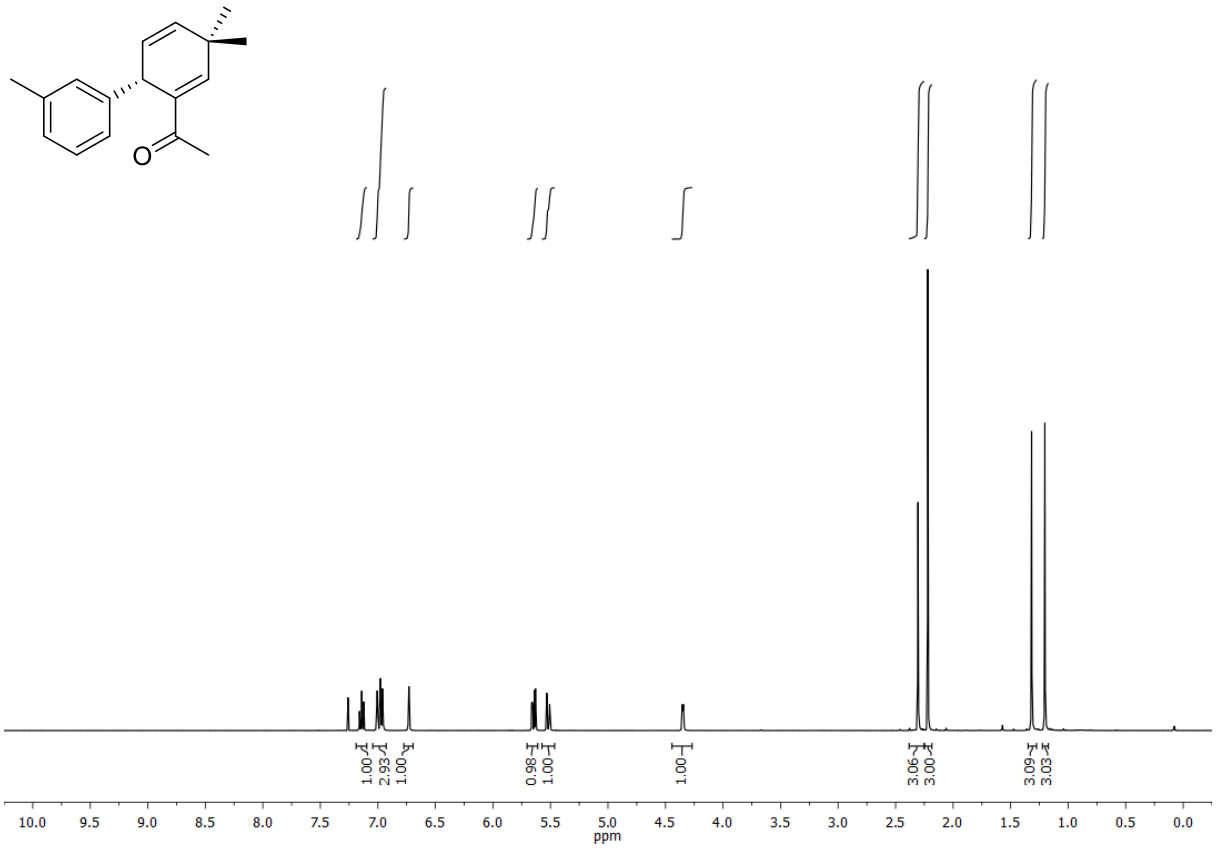
Compound **(-)-147e ^{1}H-NMR** ($CDCl_3$)



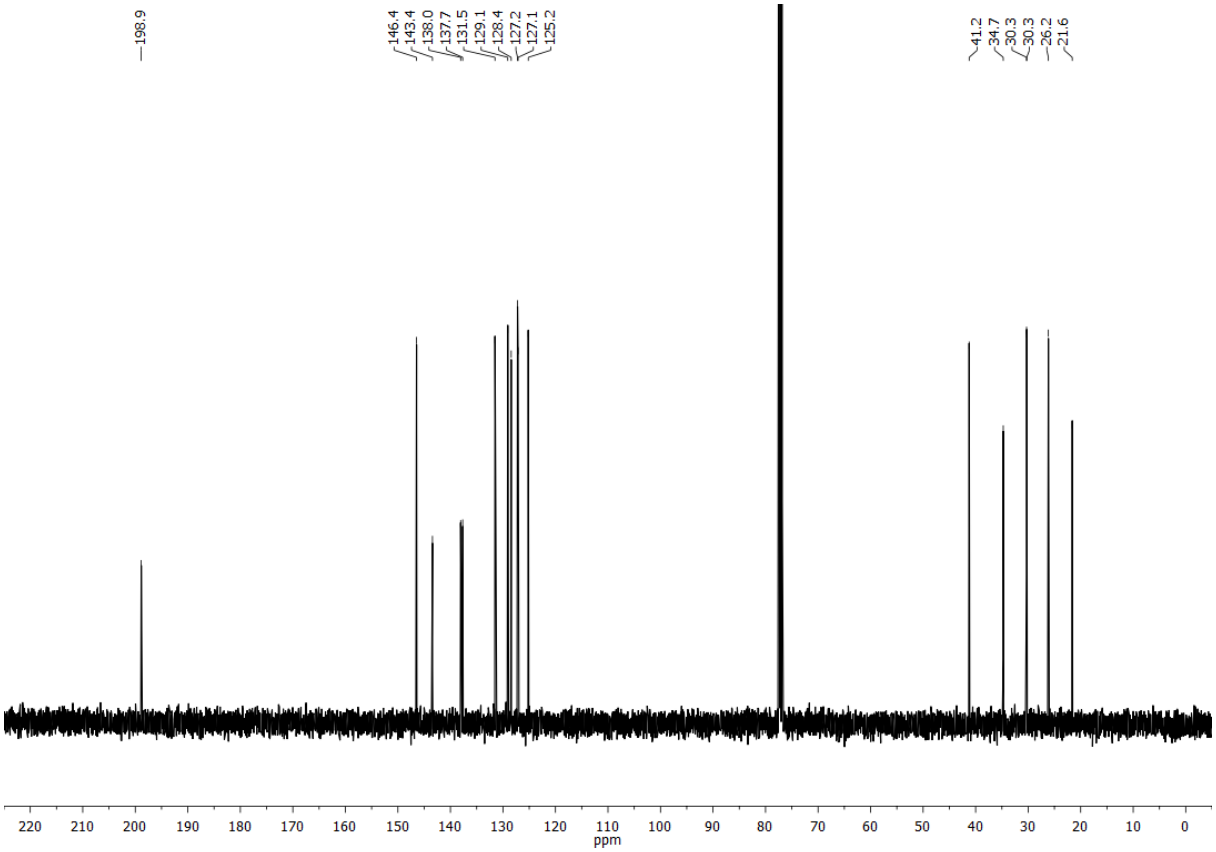
Compound **(-)-147e ^{13}C-NMR** ($CDCl_3$)



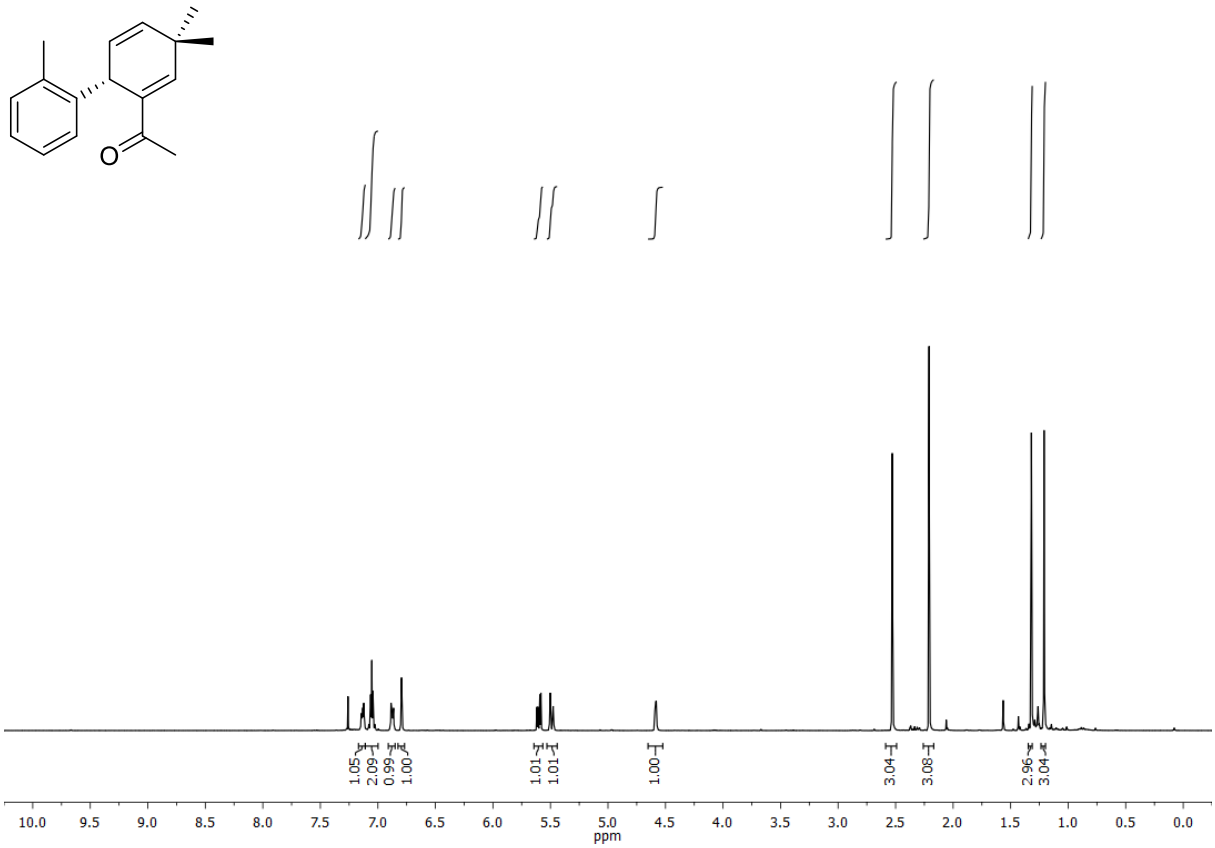
Compound **(-)-147f** ^{1}**H-NMR** ($CDCl_3$)



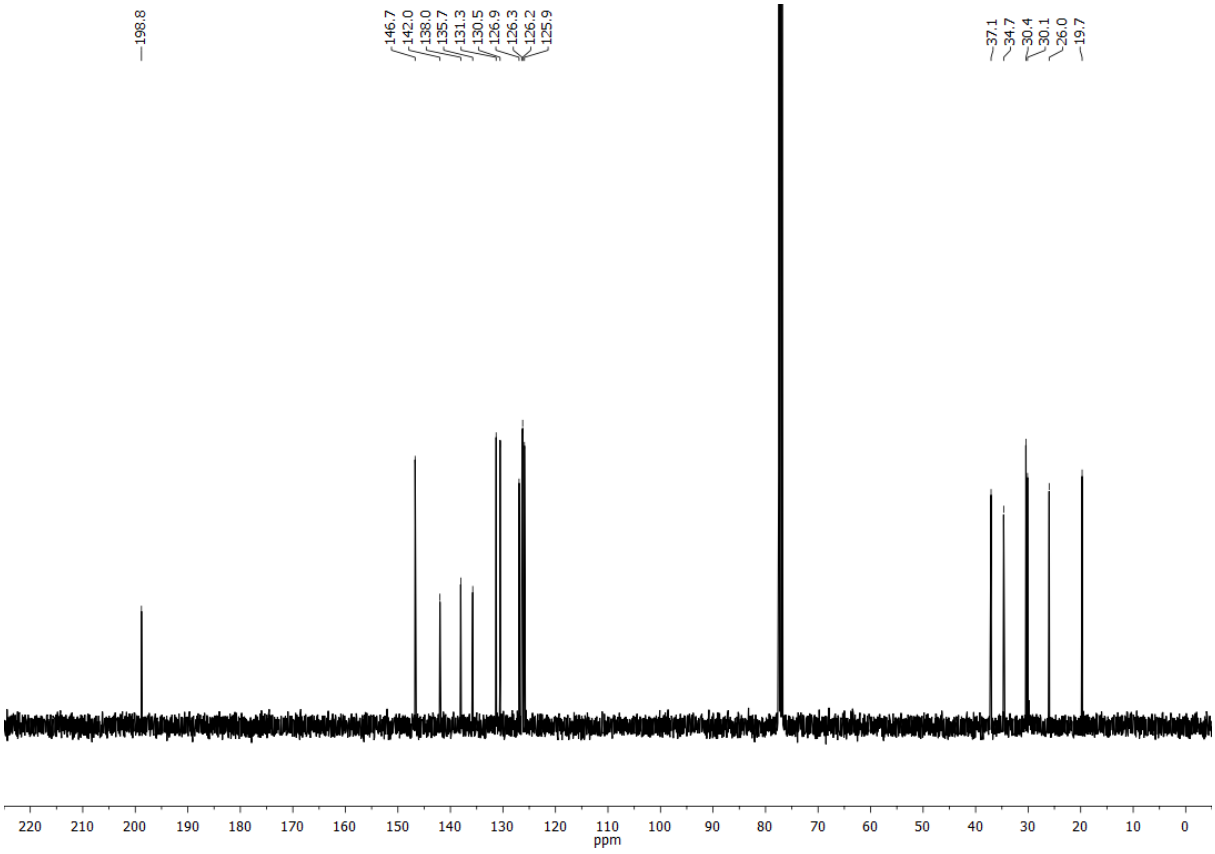
Compound **(-)-147f** ^{13}**C-NMR** ($CDCl_3$)



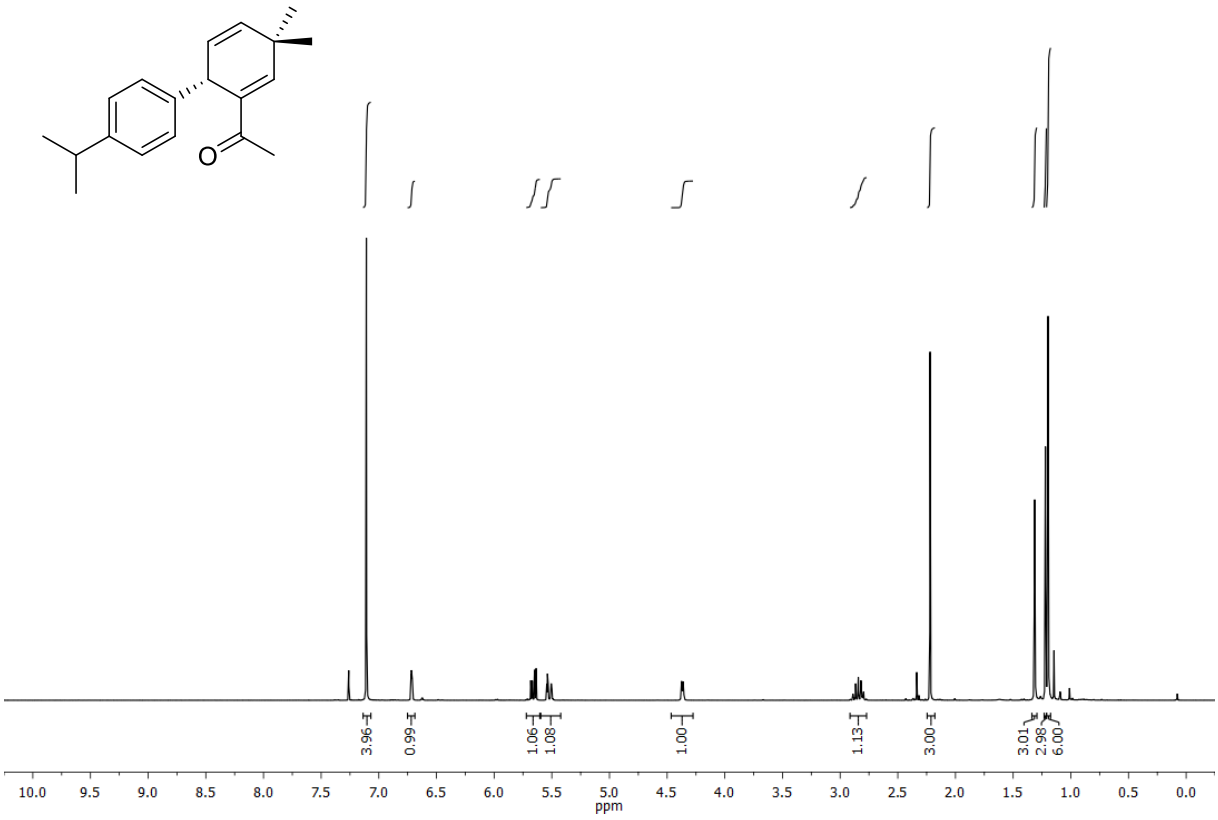
Compound **(-)-147g ^{1}H-NMR** ($CDCl_3$)



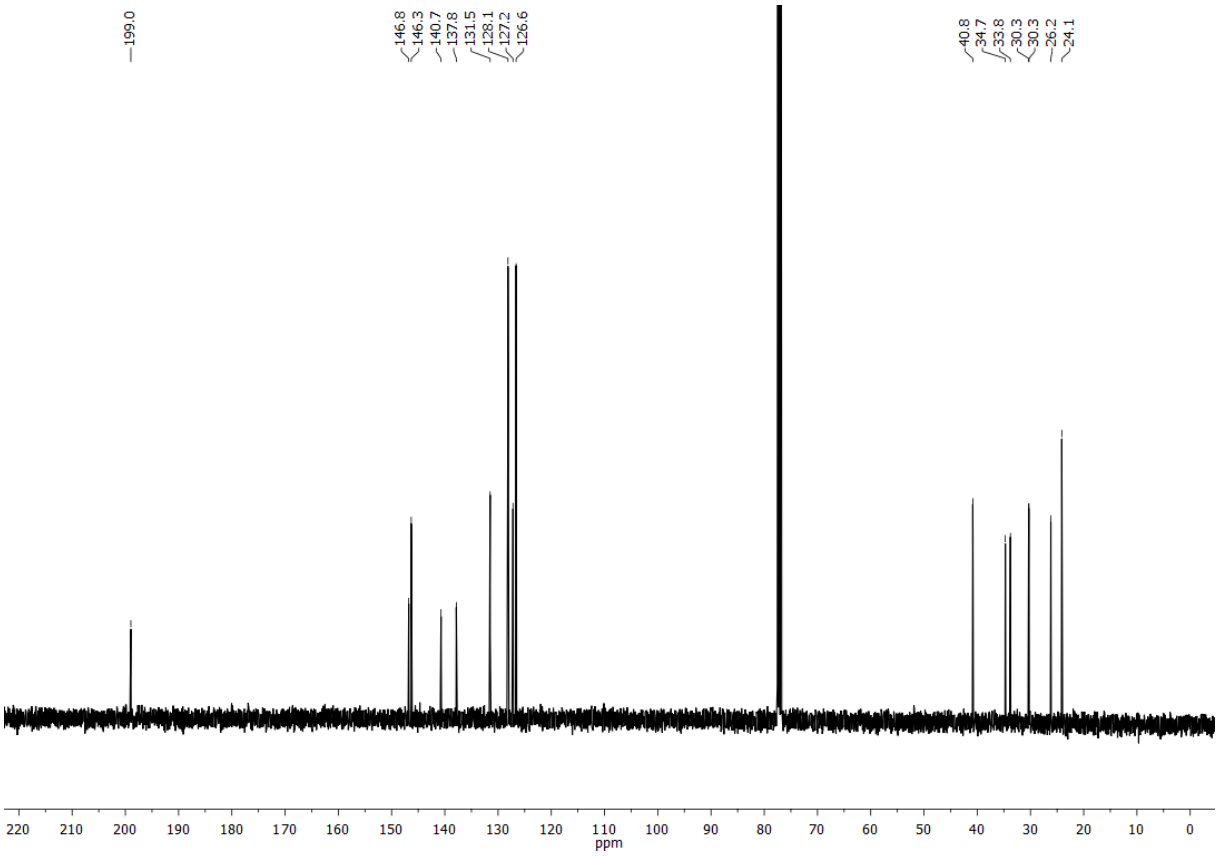
Compound **(-)-147g ^{13}C-NMR** ($CDCl_3$)



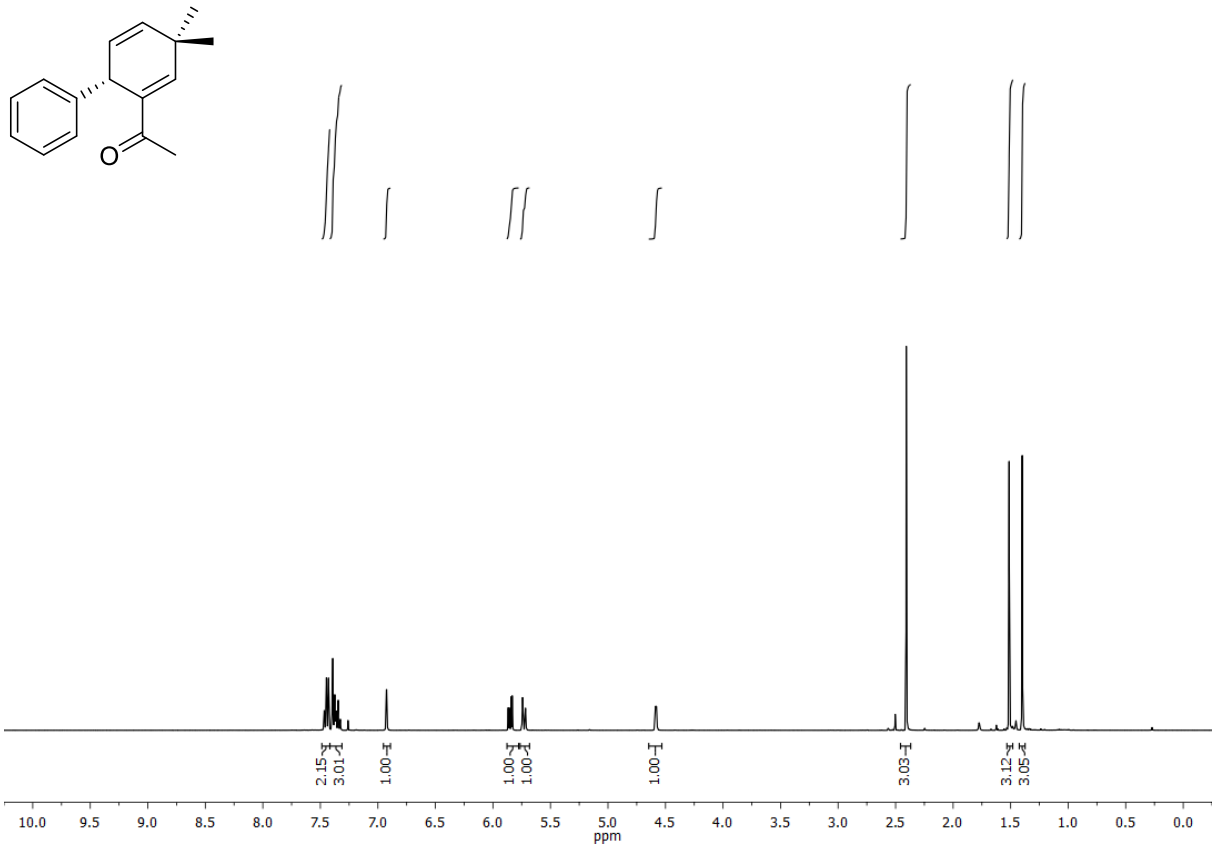
Compound **(-)-147h ^{1}H-NMR** ($CDCl_3$)



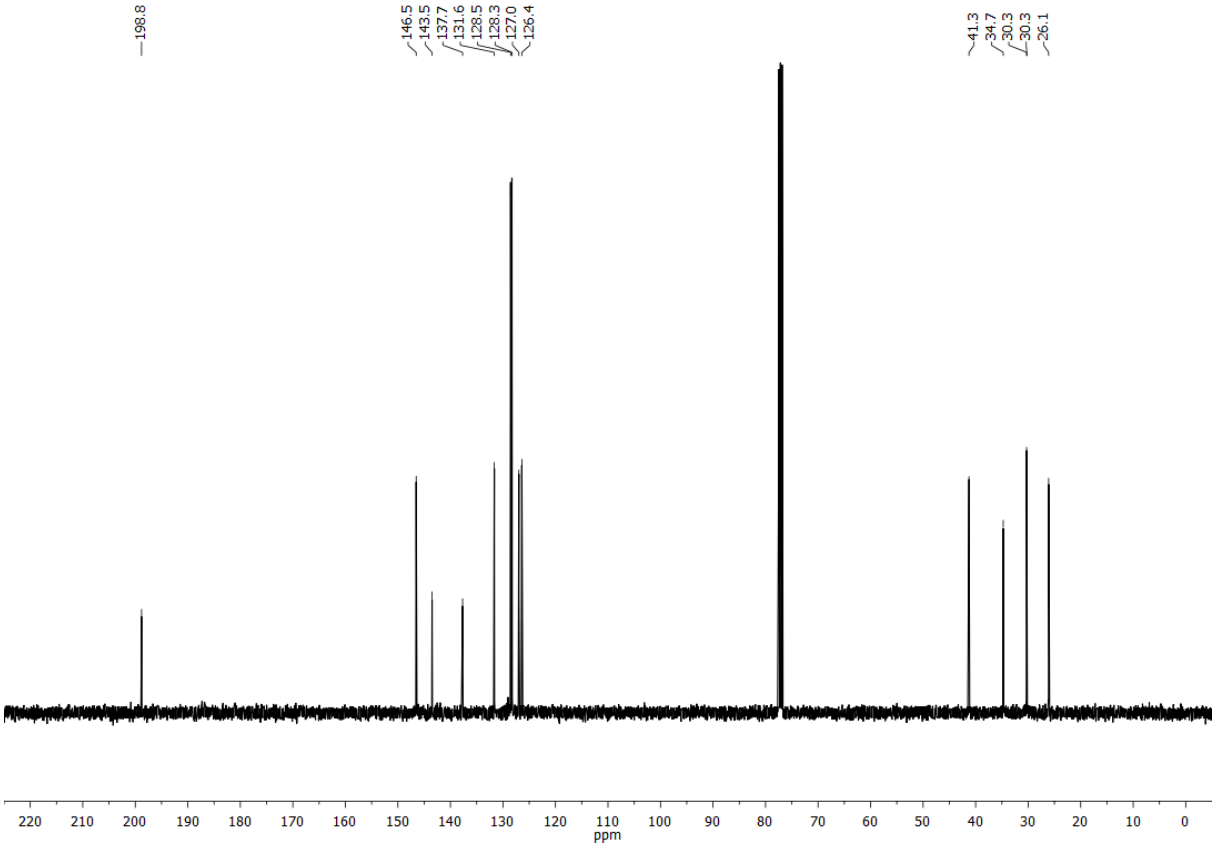
Compound **(-)-147h ^{13}C-NMR** ($CDCl_3$)



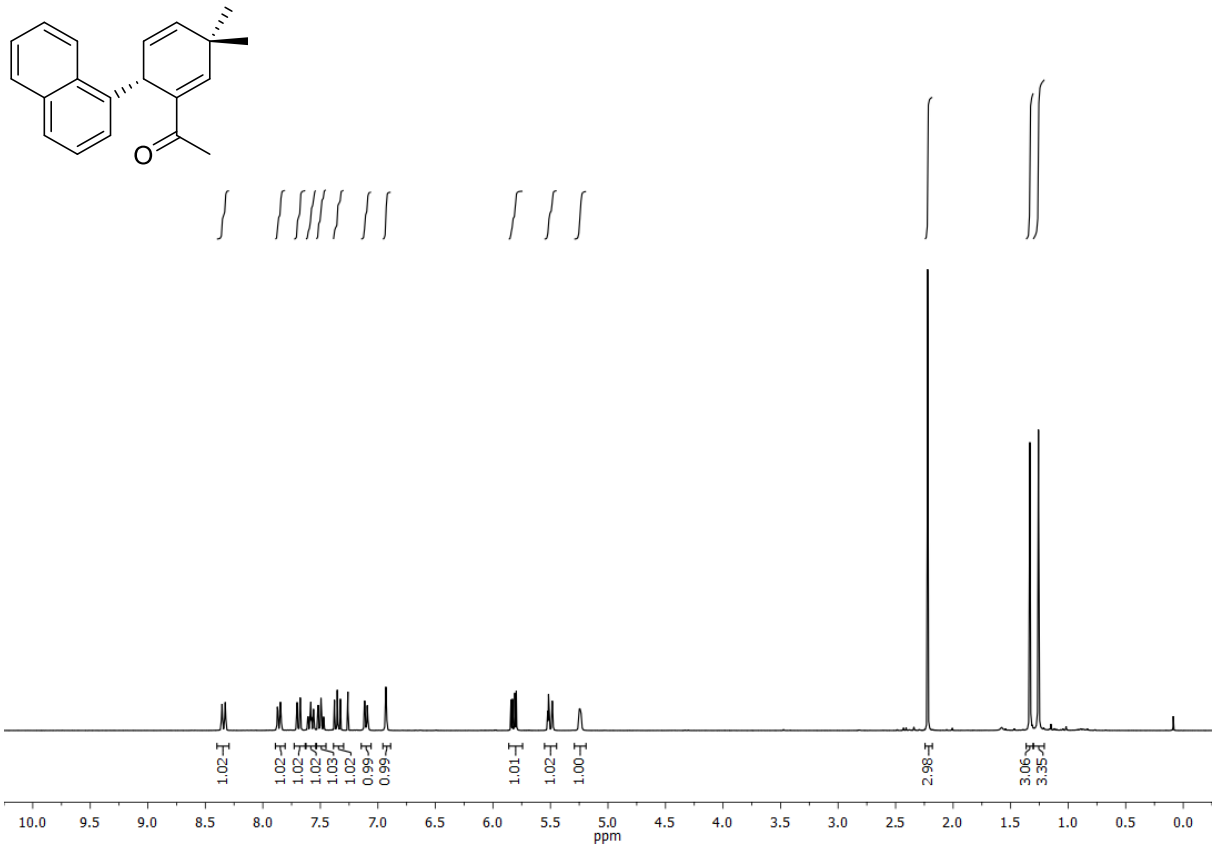
Compound **(-)-147i ^{1}H-NMR** ($CDCl_3$)



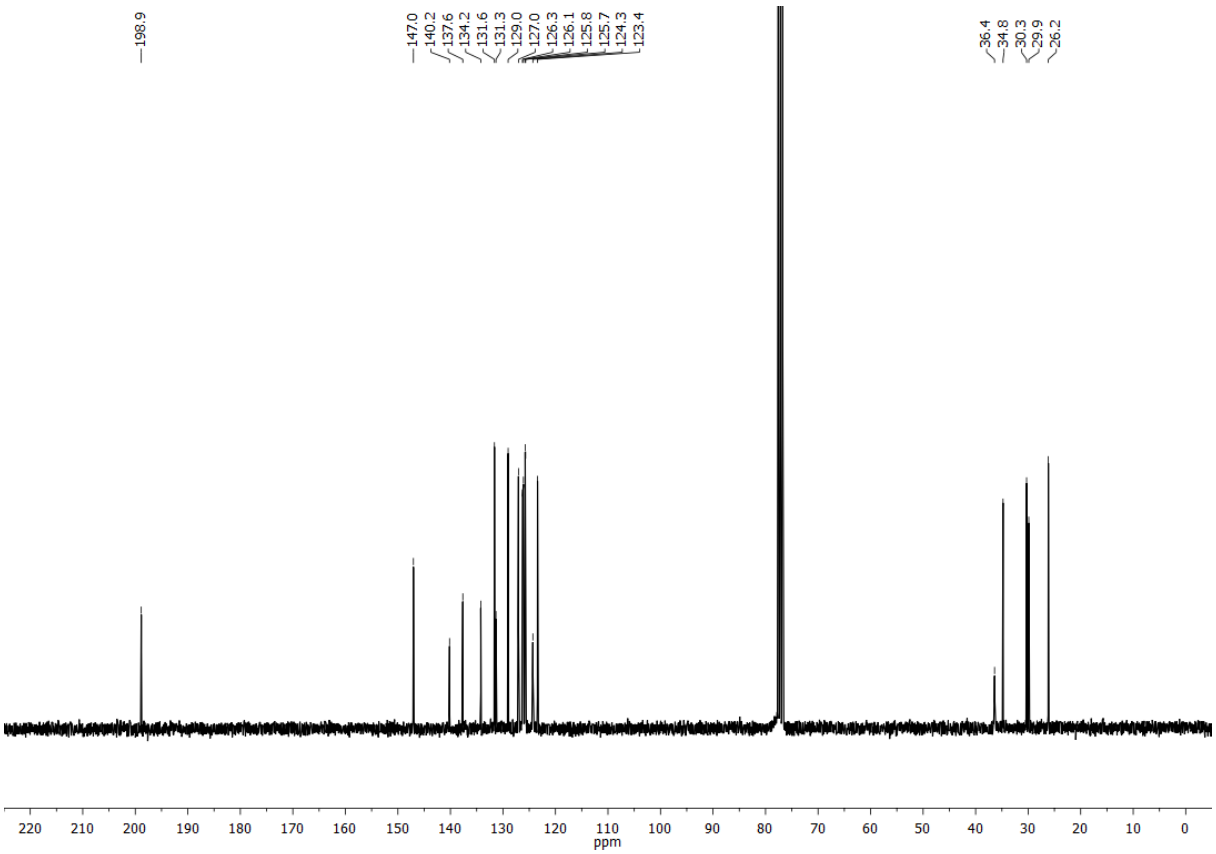
Compound **(-)-147i ^{13}C-NMR** ($CDCl_3$)



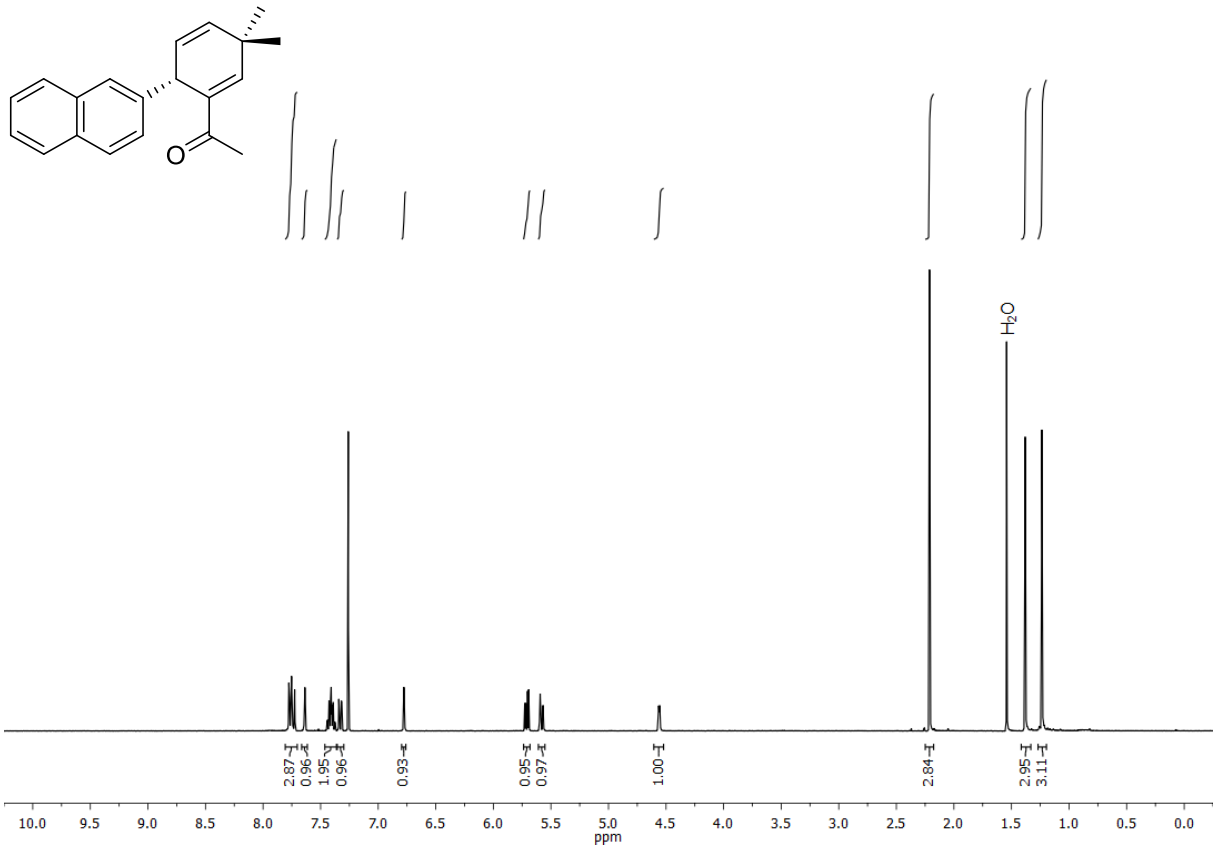
Compound **(-)-147j ^{1}H-NMR** ($CDCl_3$)



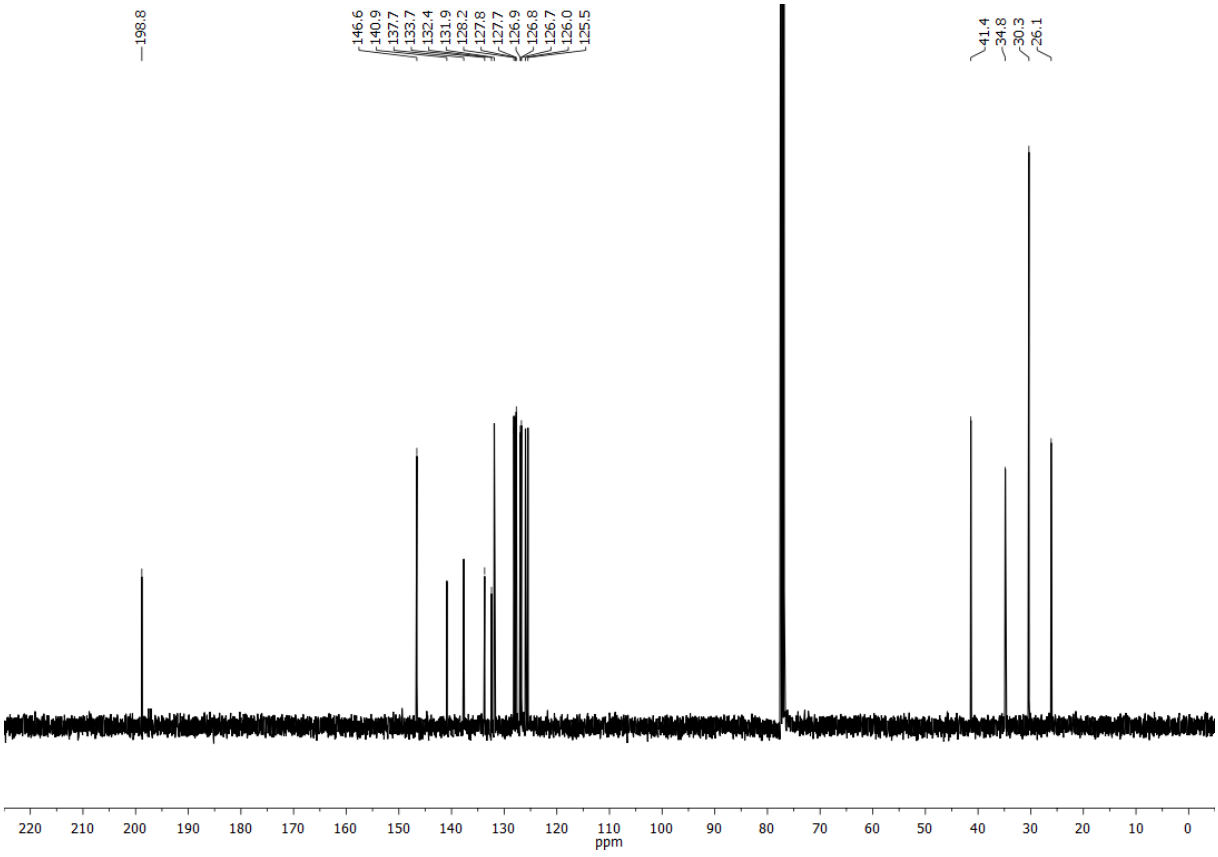
Compound **(-)-147j ^{13}C-NMR** ($CDCl_3$)



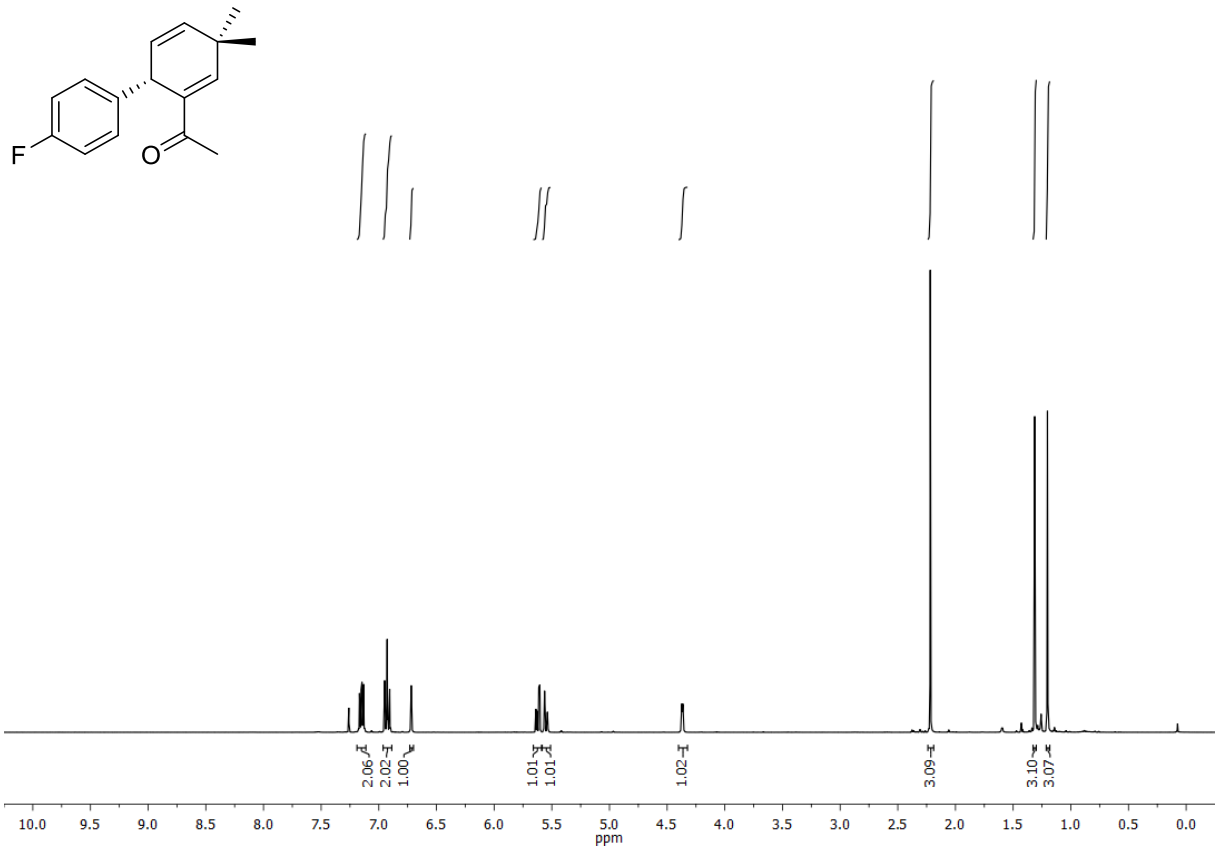
Compound **(-)-147k ^{1}H-NMR** ($CDCl_3$)



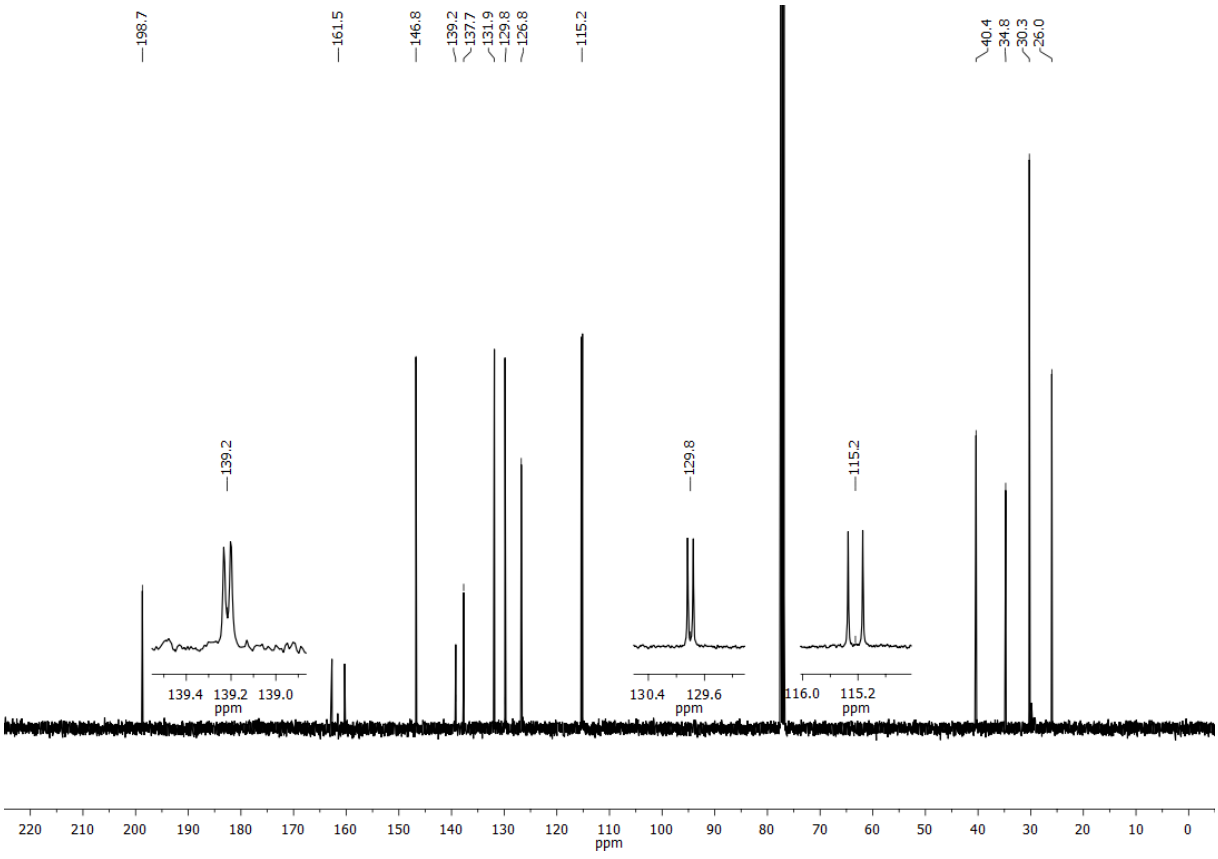
Compound **(-)-147k ^{13}C-NMR** ($CDCl_3$)



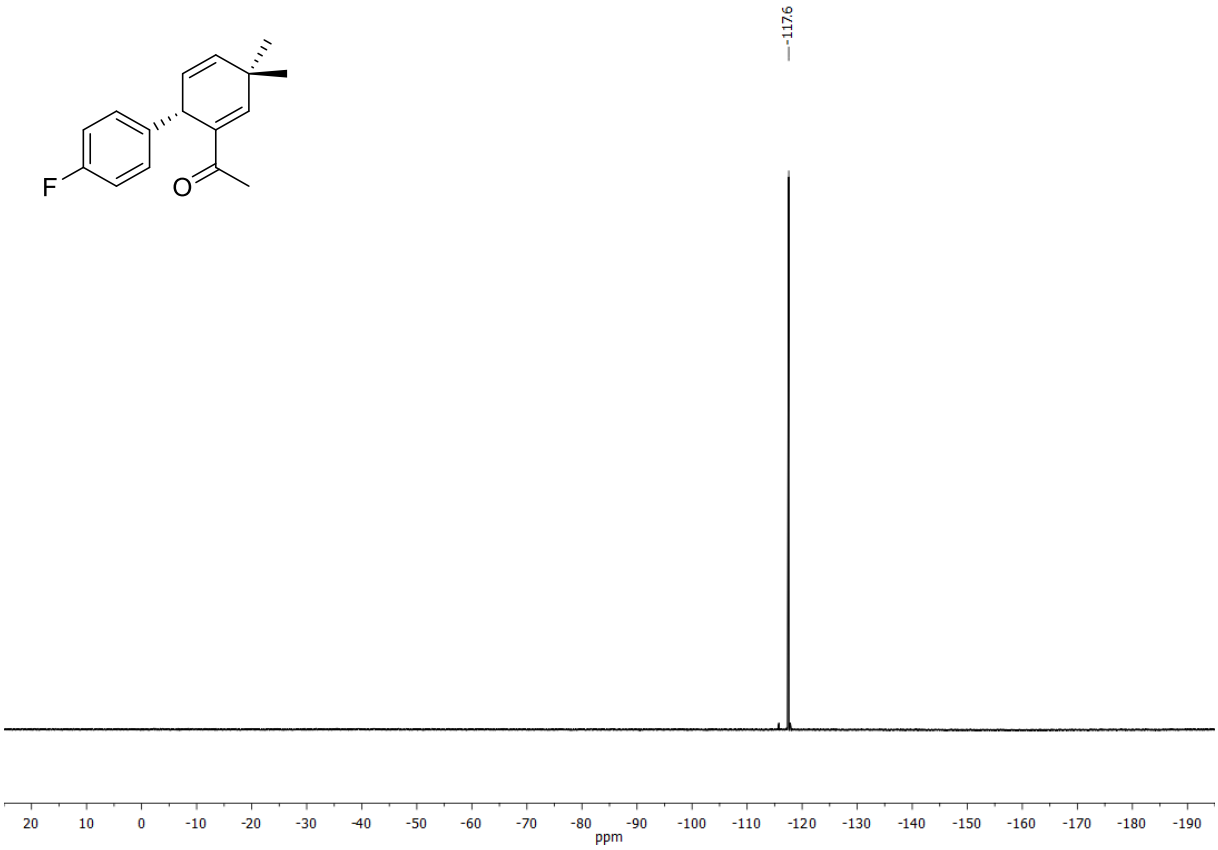
Compound **(-)-147l** ^{1}**H-NMR** ($CDCl_3$)



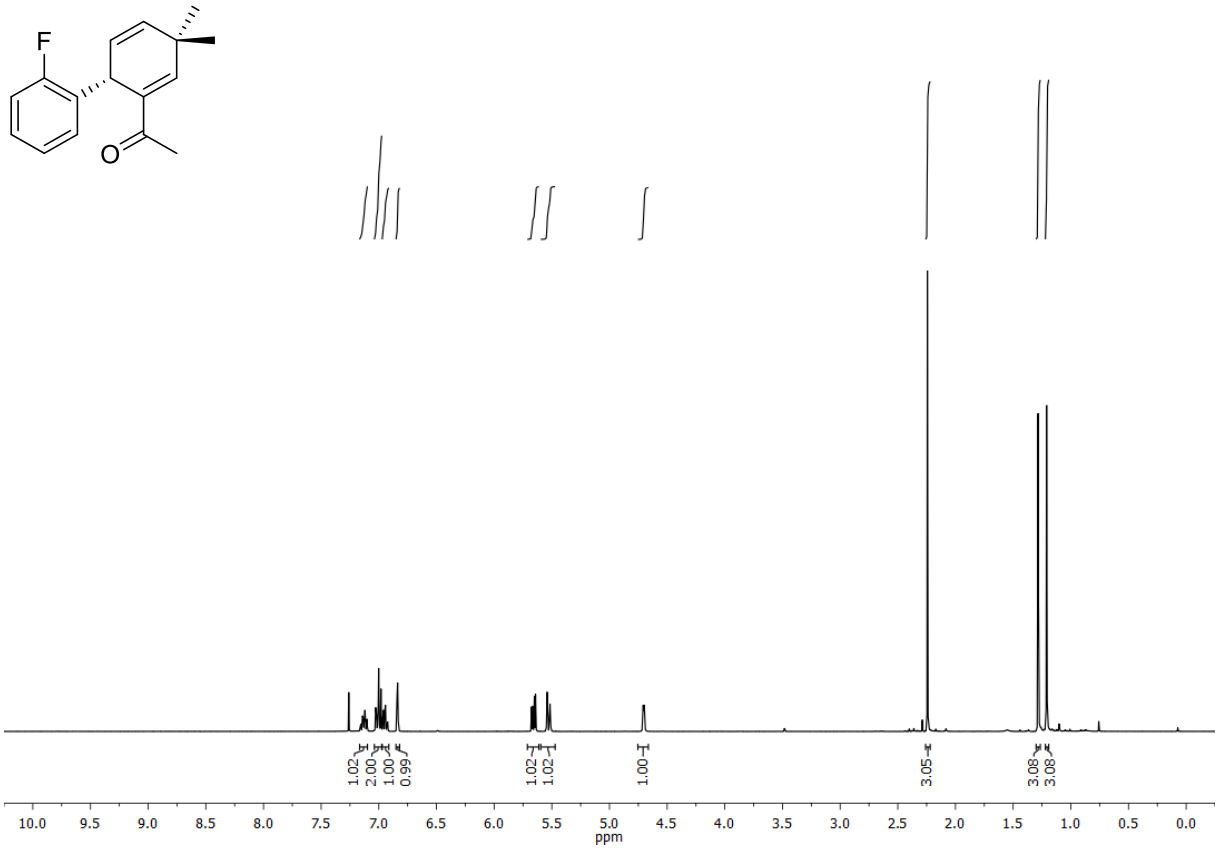
Compound **(-)-147l** ^{13}**C-NMR** ($CDCl_3$)



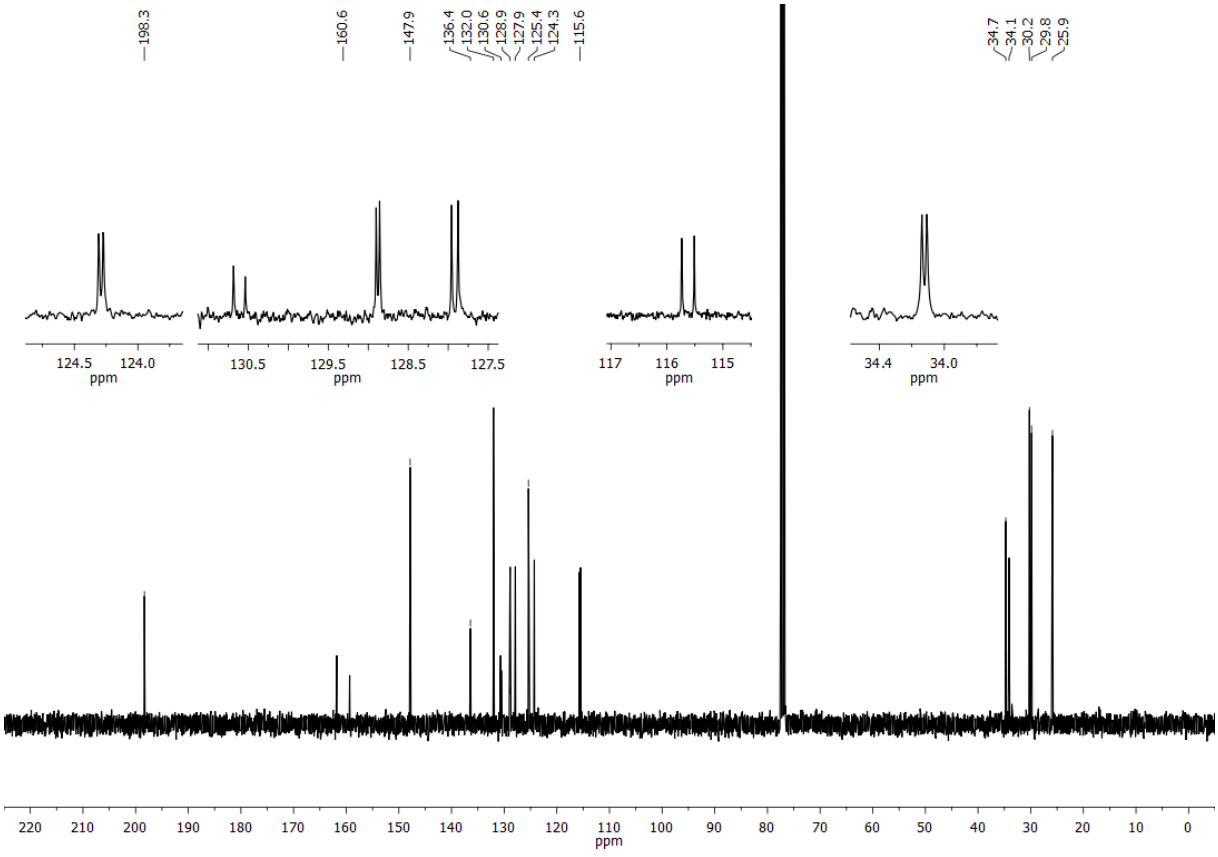
Compound **(-)-147l** ^{19}**F-NMR** ($CDCl_3$)



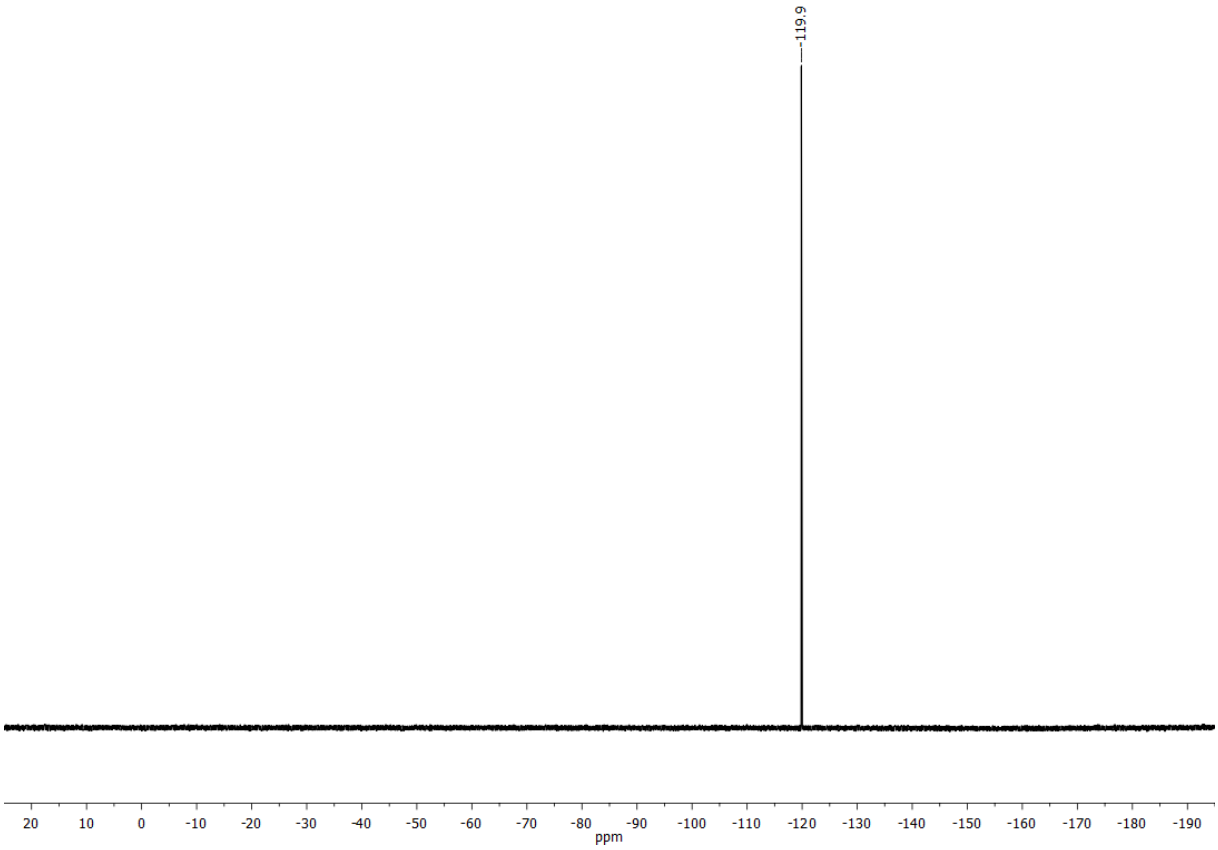
Compound **(-)-147m ^{1}H-NMR** ($CDCl_3$)



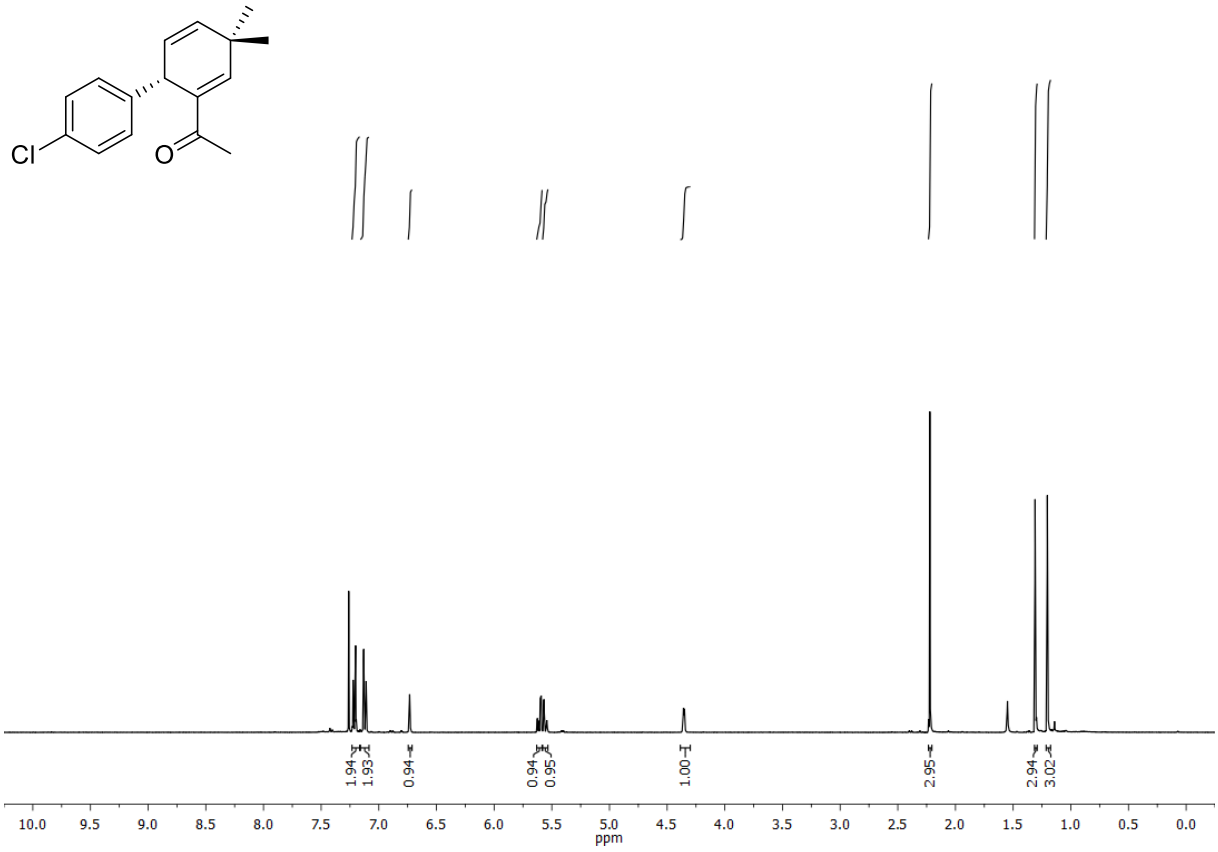
Compound **(-)-147m ^{13}C-NMR** ($CDCl_3$)



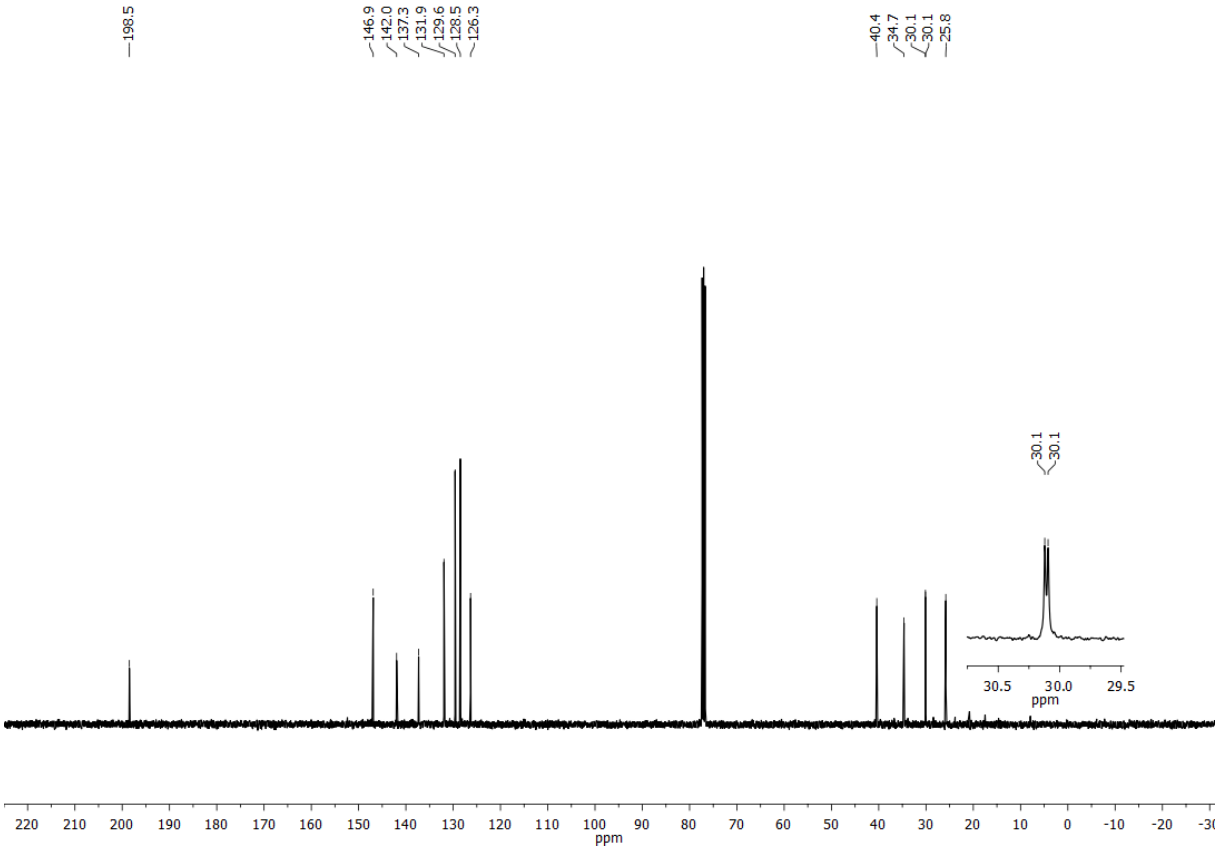
Compound **(-)-147m ^{19}F-NMR** ($CDCl_3$)



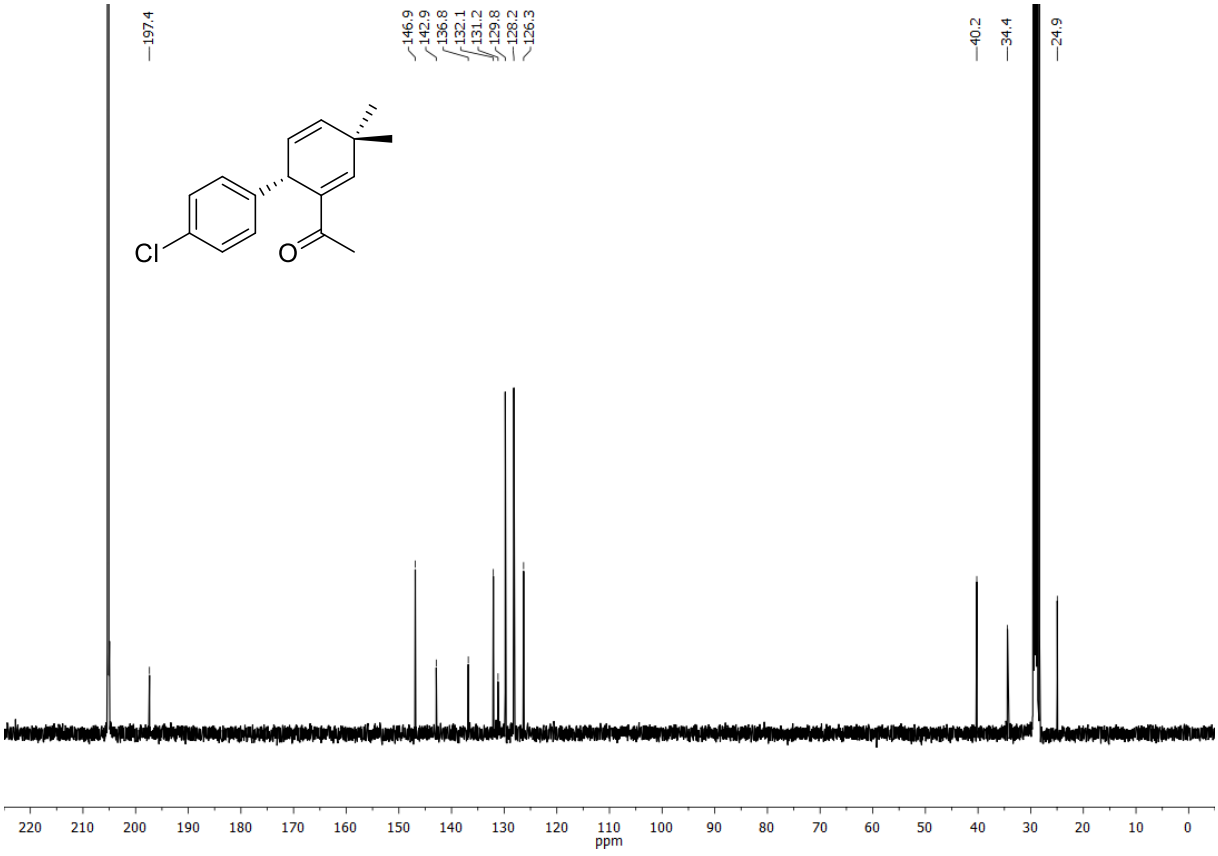
Compound **(-)-147n ^{1}H-NMR** ($CDCl_3$)



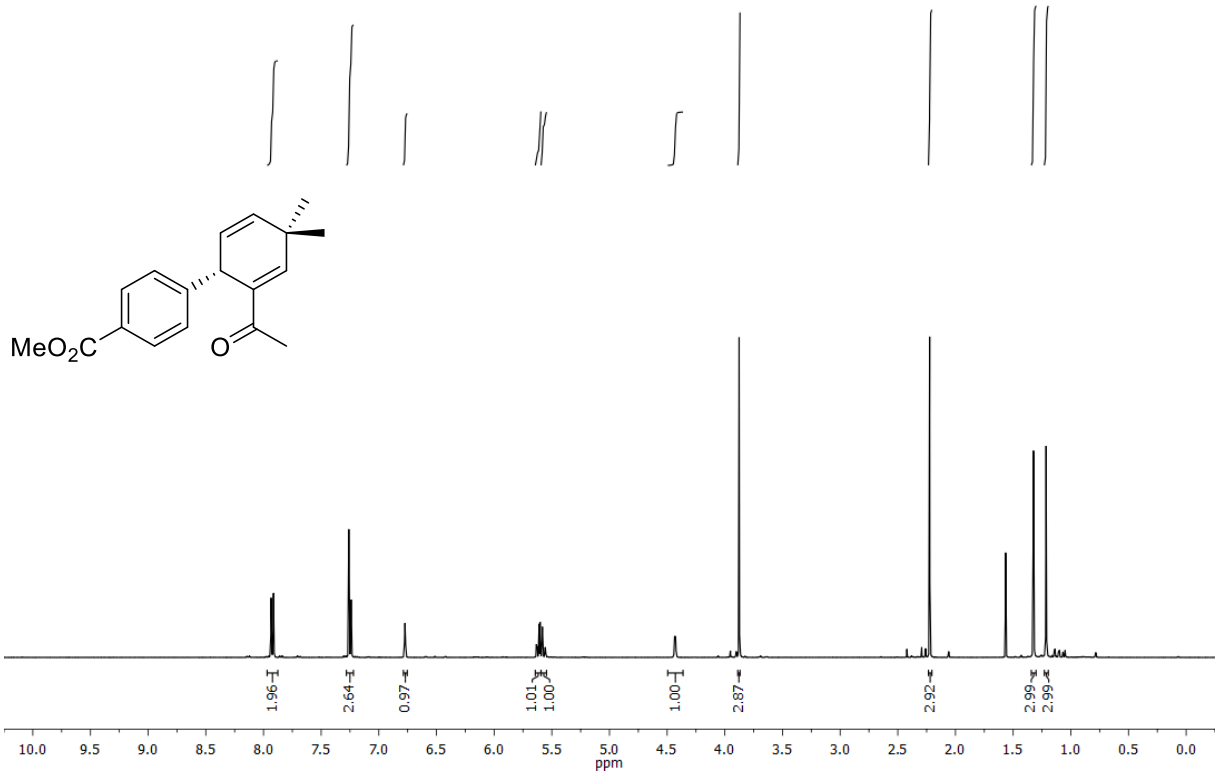
Compound **(-)-147n ^{13}C-NMR** ($CDCl_3$)



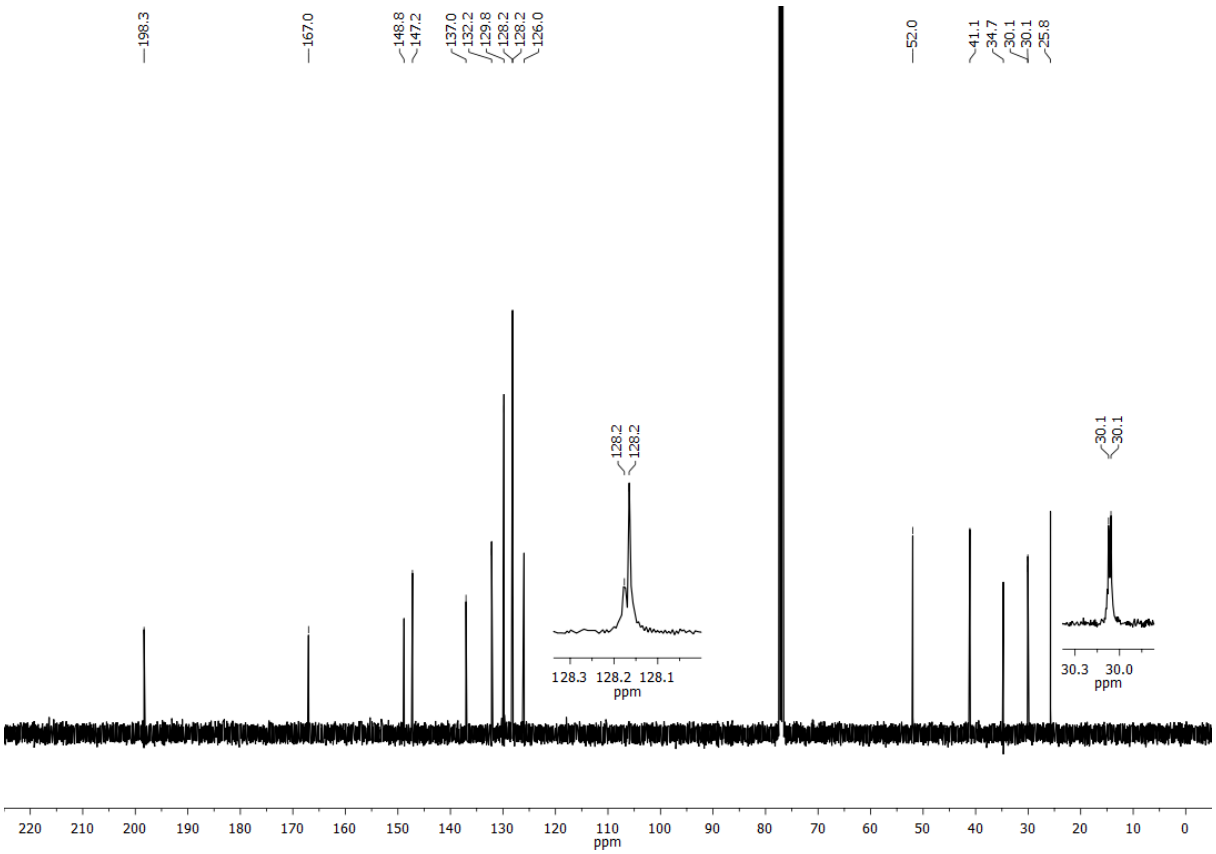
Compound **(-)-147n** ^{13}**C-NMR** (acetone-d6)



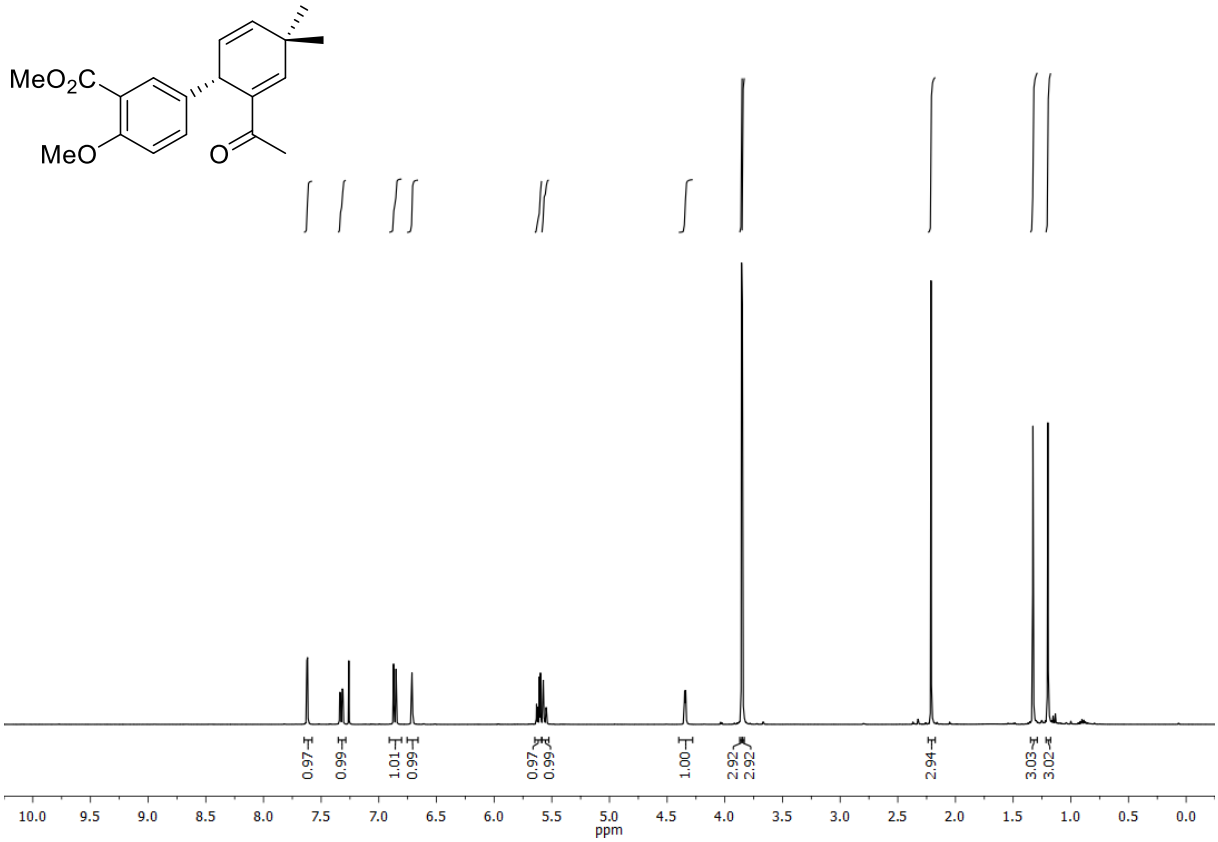
Compound **(-)-147o ^{1}H-NMR** ($CDCl_3$)



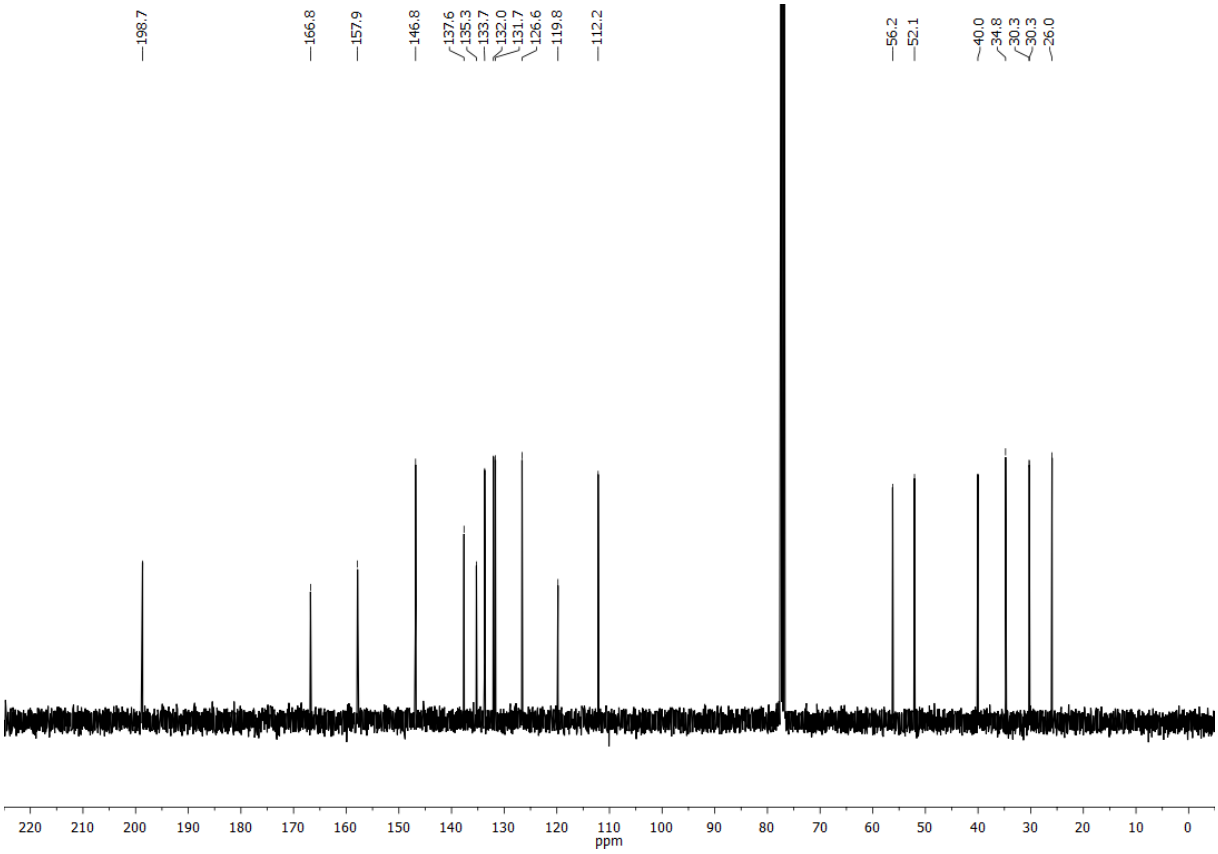
Compound **(-)-147o ^{13}C-NMR** ($CDCl_3$)



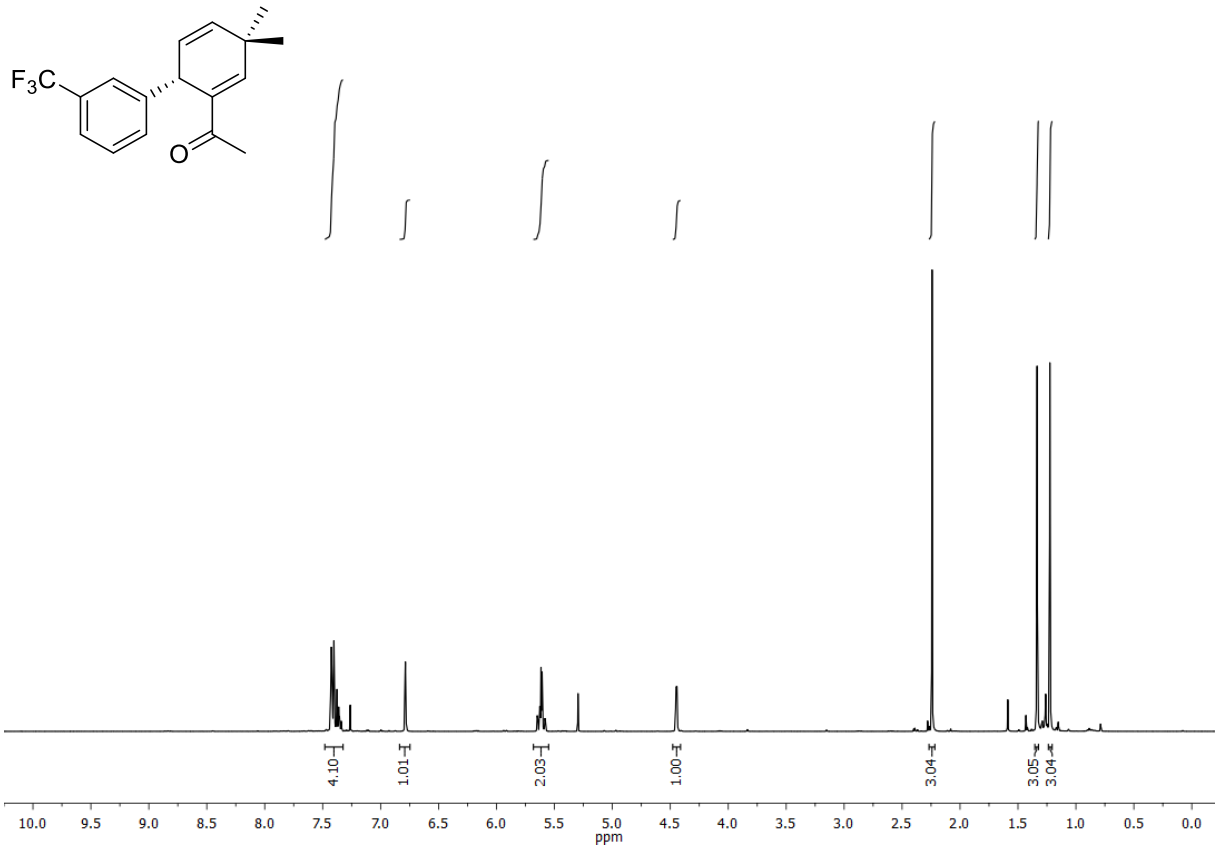
Compound **(-)-147q** ^{1}**H-NMR** ($CDCl_3$)



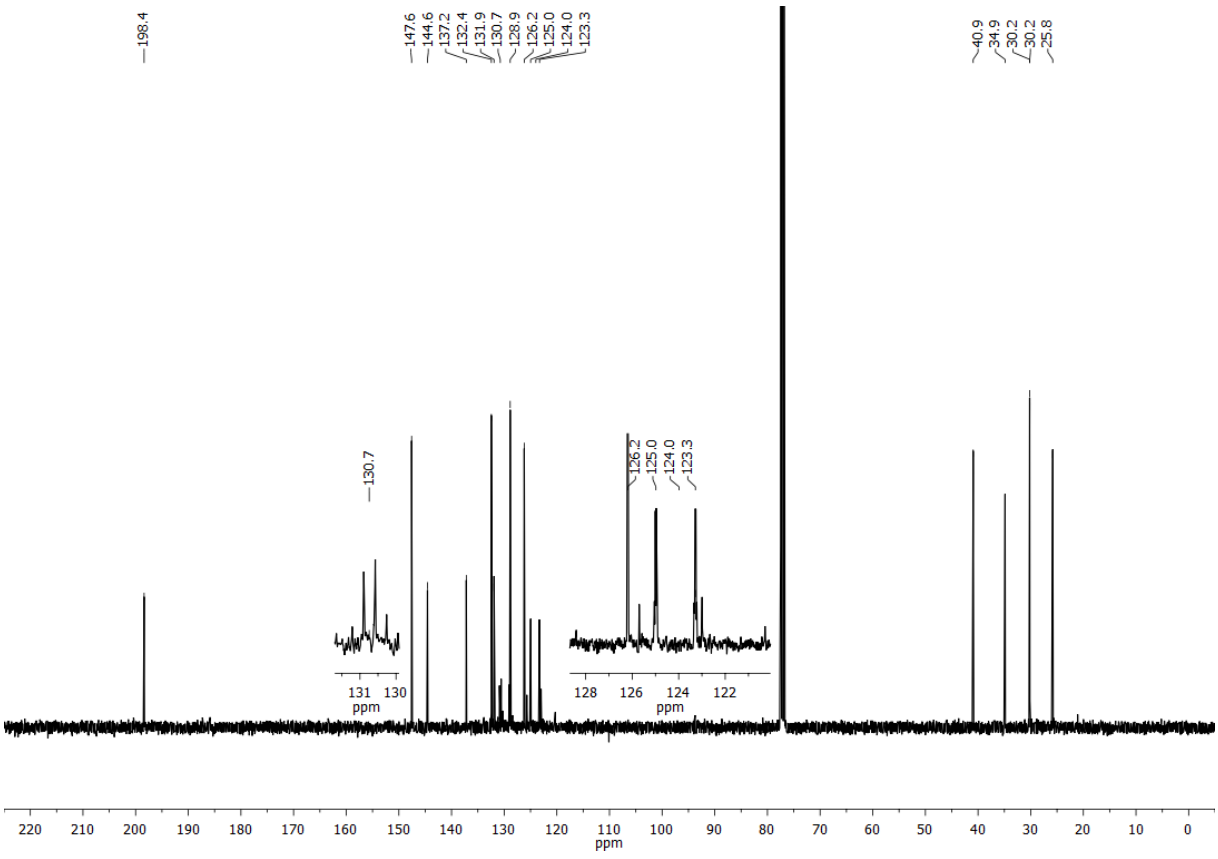
Compound **(-)-147q** ^{13}**C-NMR** ($CDCl_3$)



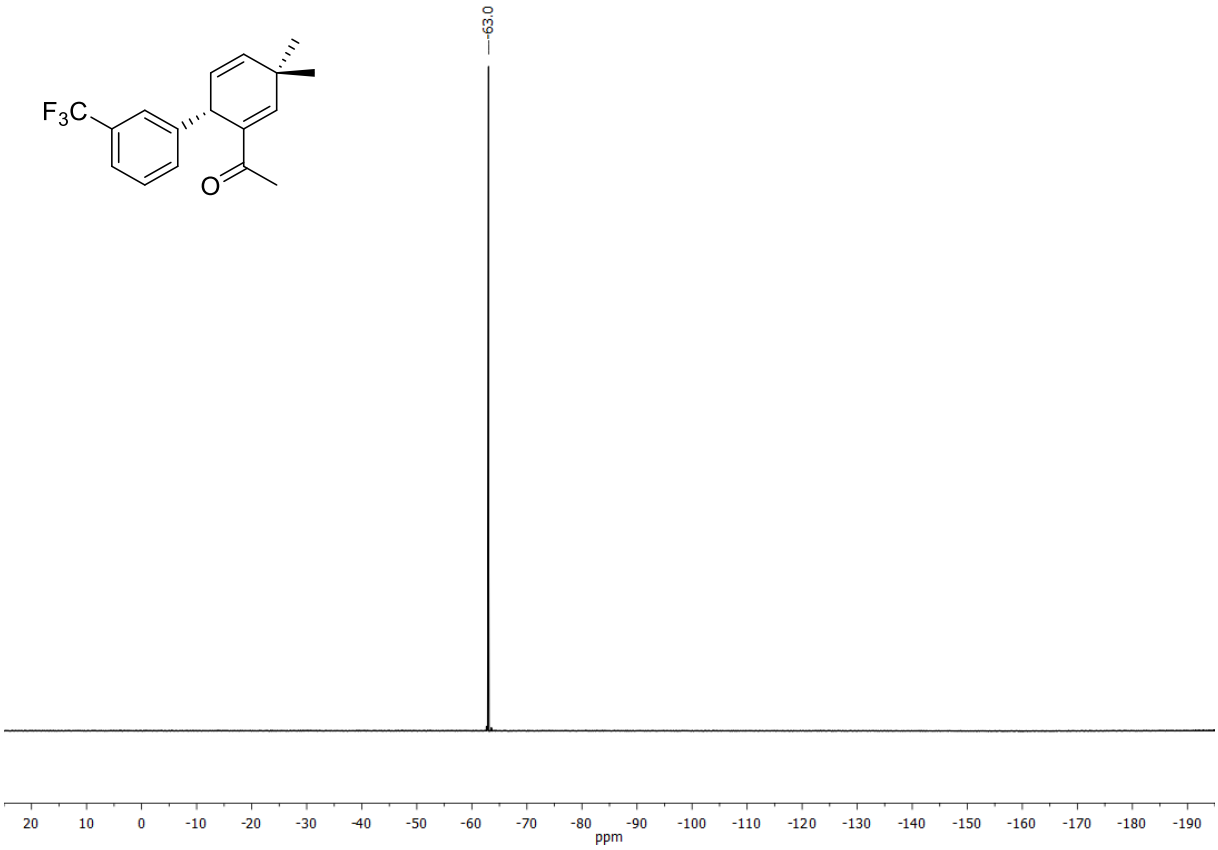
Compound **(-)-147s ^{1}H-NMR** ($CDCl_3$)



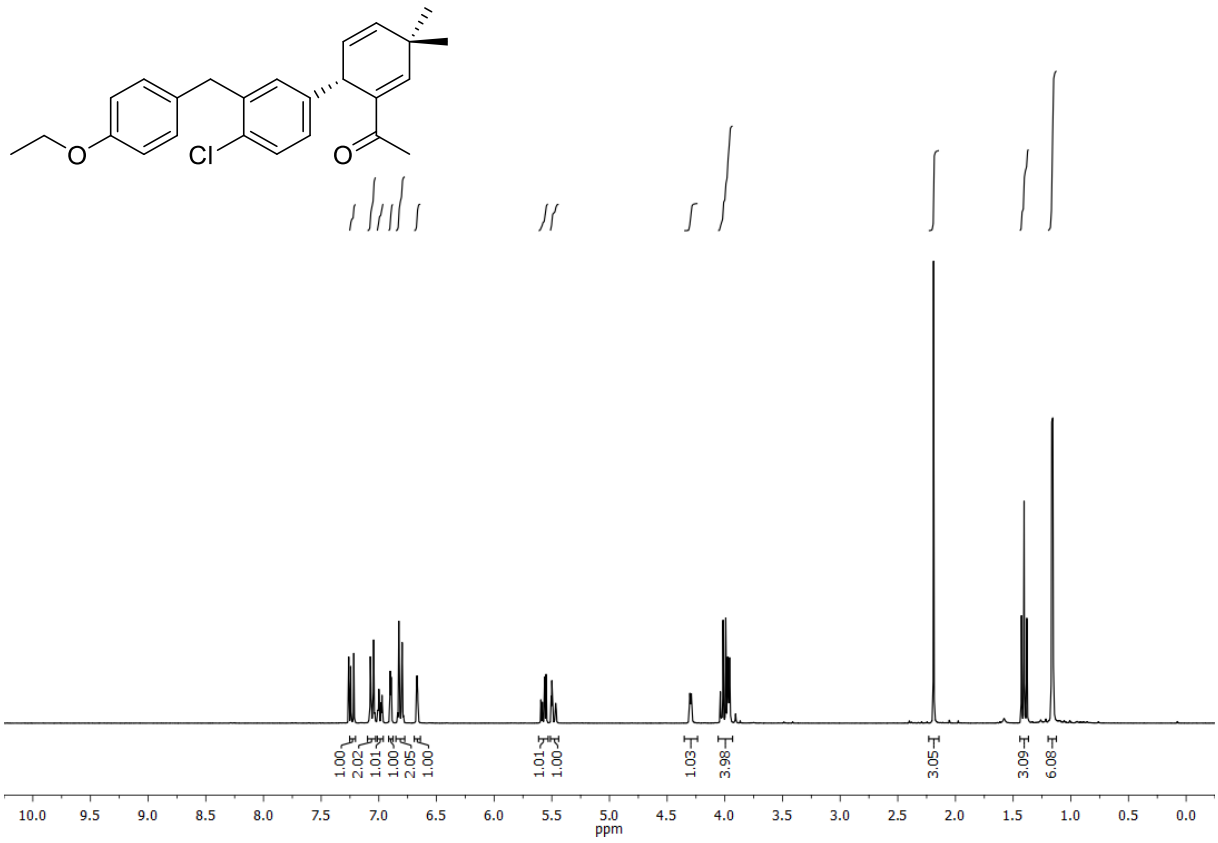
Compound **(-)-147s ^{13}C-NMR** ($CDCl_3$)



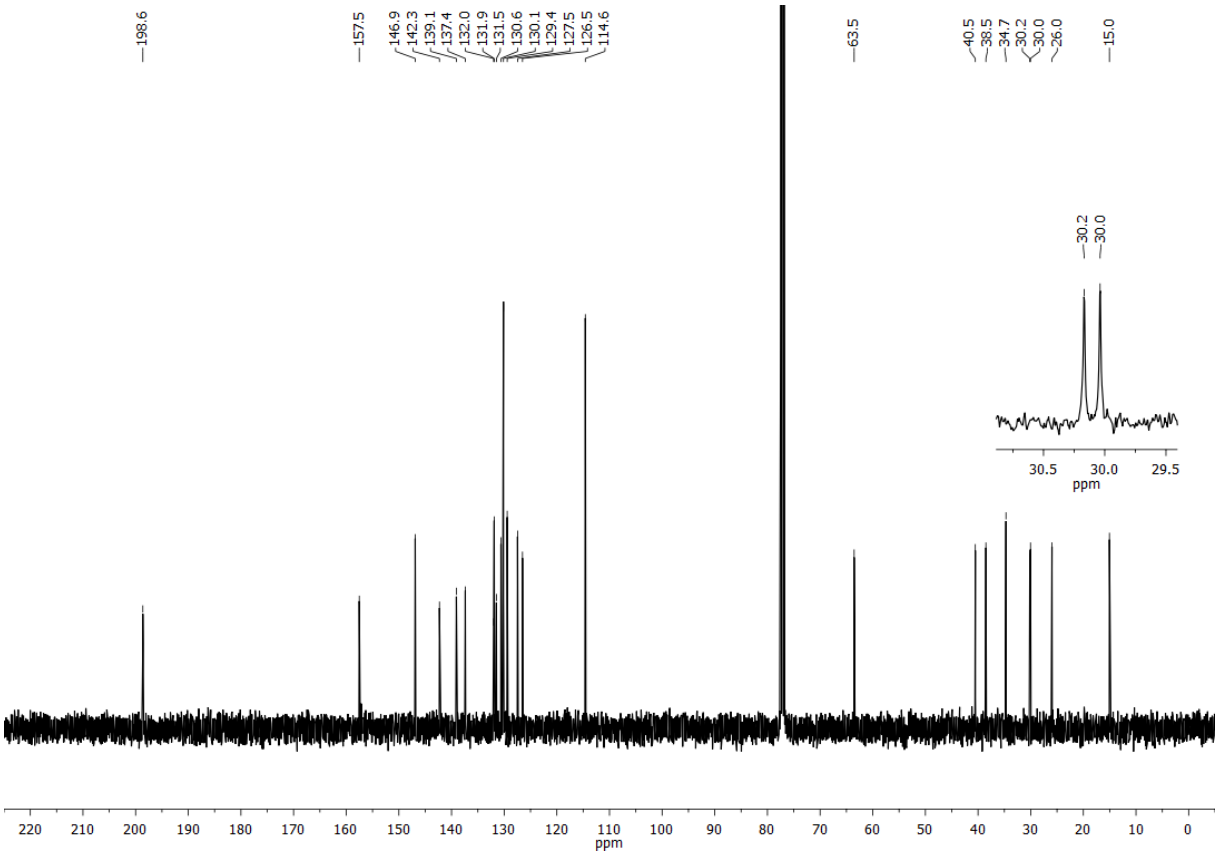
Compound **(-)-147s** ^{19}**F-NMR** ($CDCl_3$)



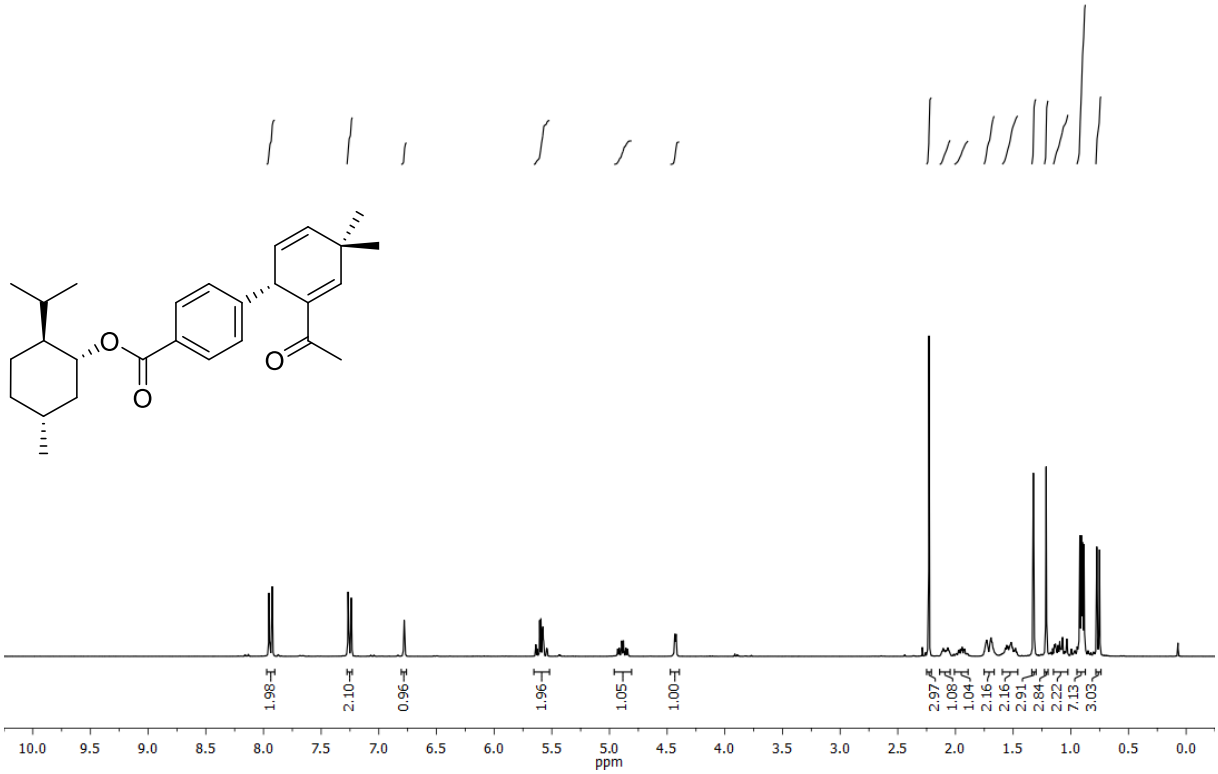
Compound **(-)-147t ^{1}H-NMR** ($CDCl_3$)



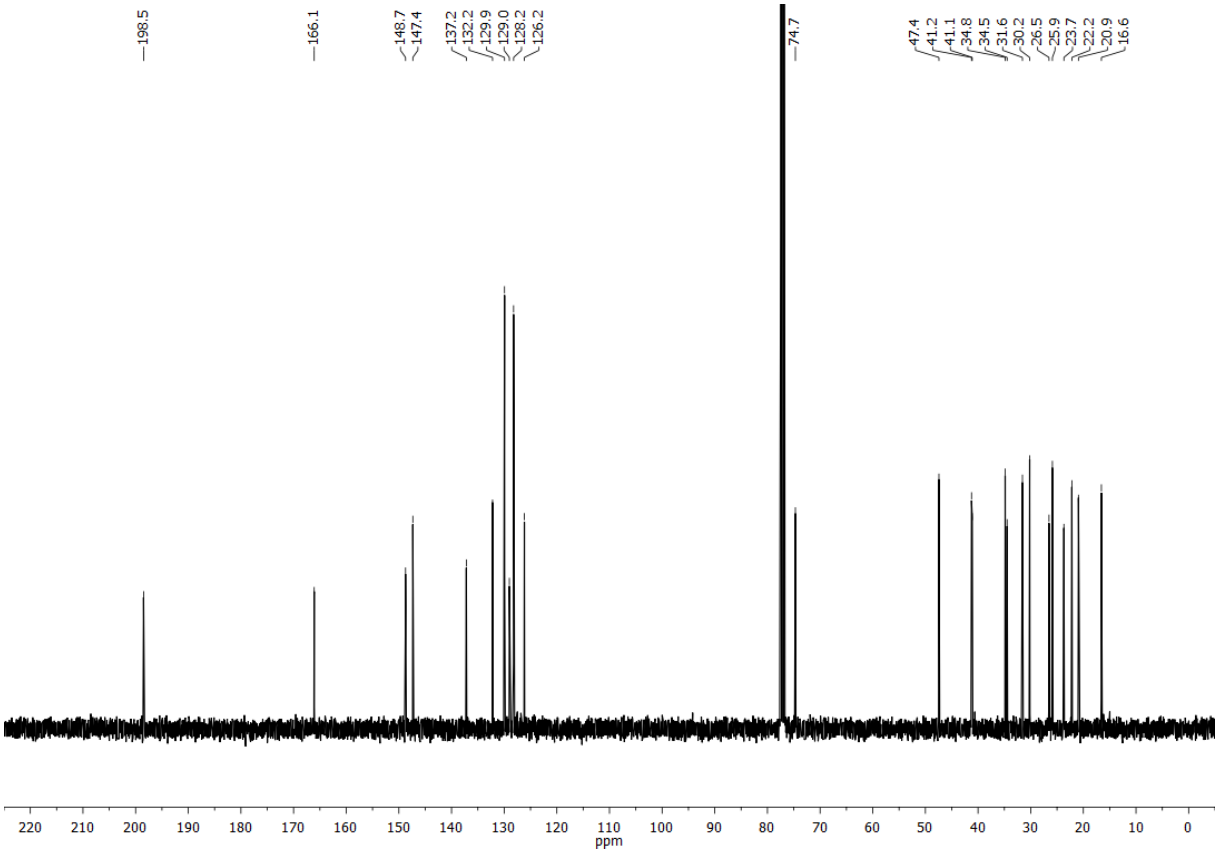
Compound **(-)-147t ^{13}C-NMR** ($CDCl_3$)



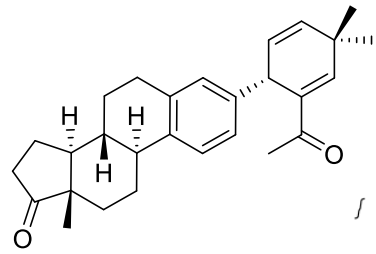
Compound **(-)-147u ^{1}H-NMR** ($CDCl_3$)



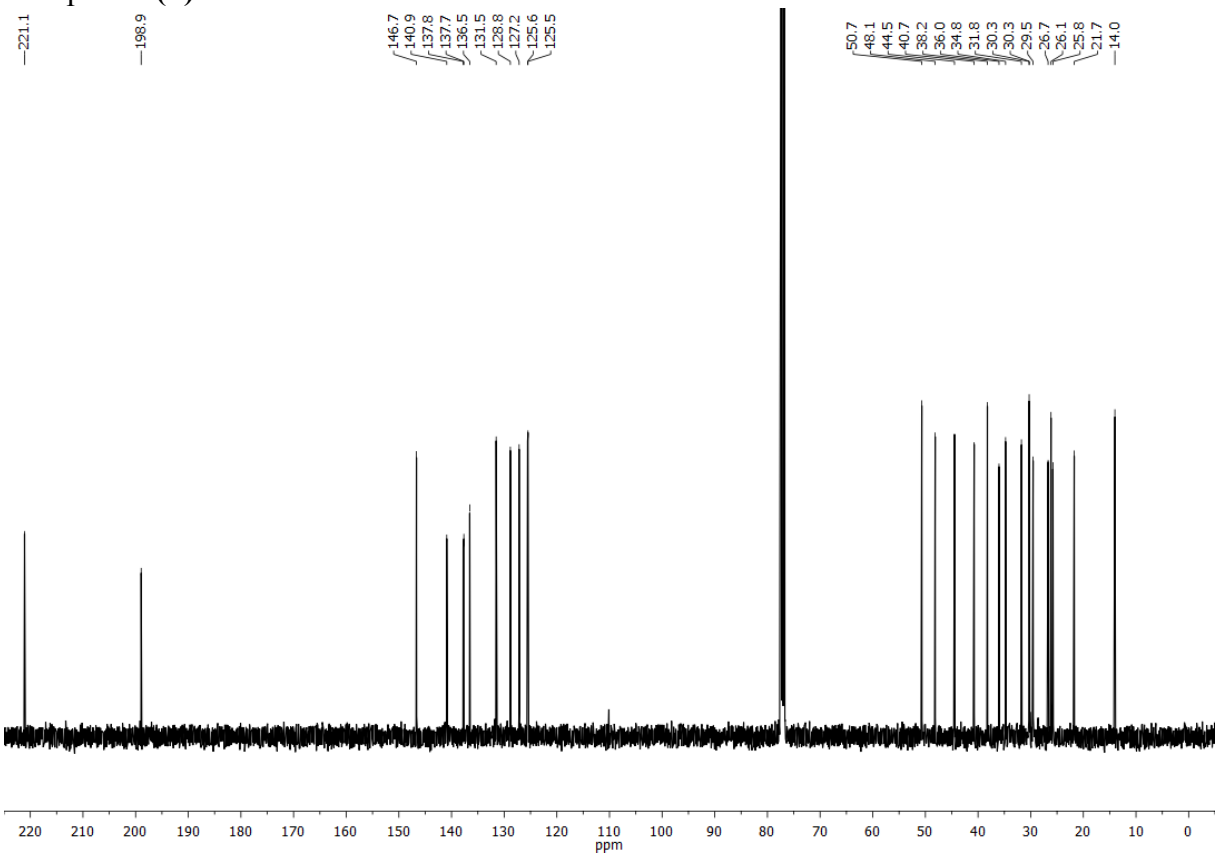
Compound **(-)-147u ^{13}C-NMR** ($CDCl_3$)



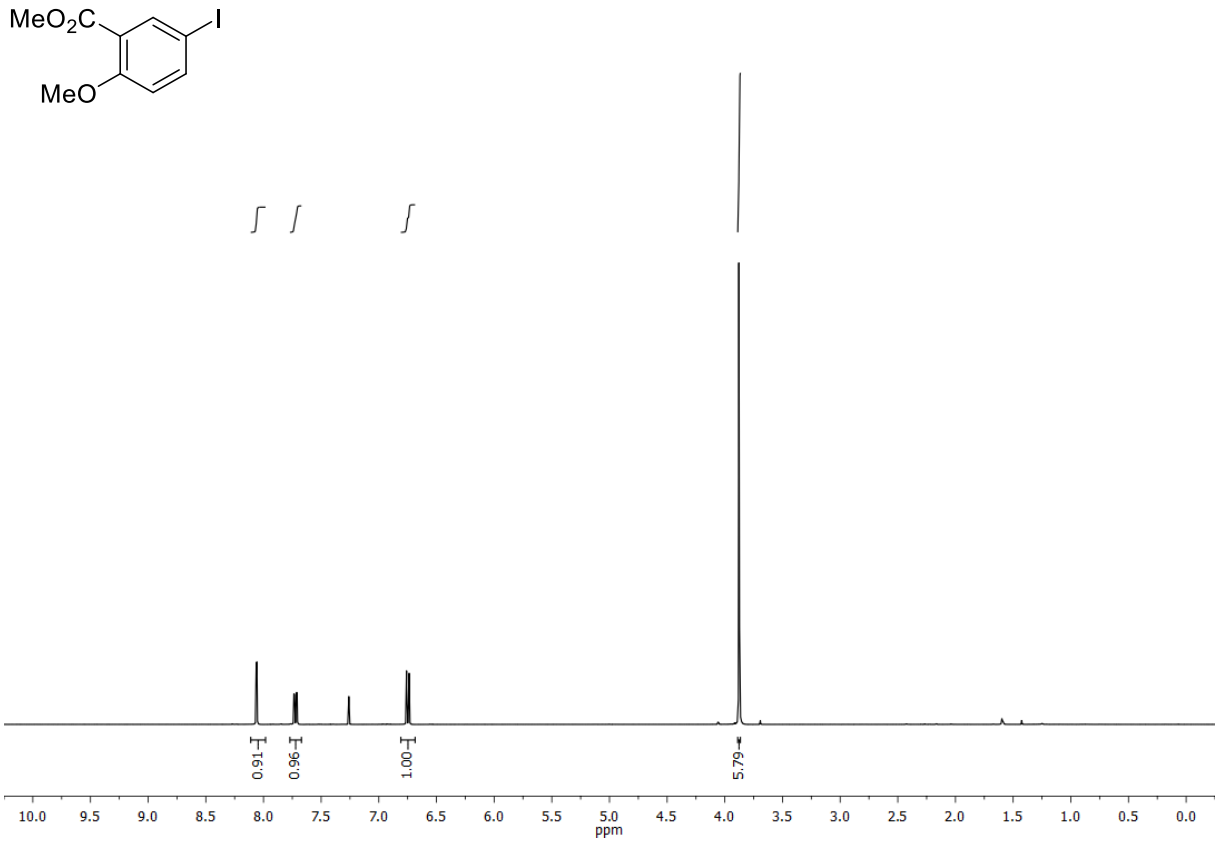
Compound **(+)-147v ^{1}H-NMR** ($CDCl_3$)



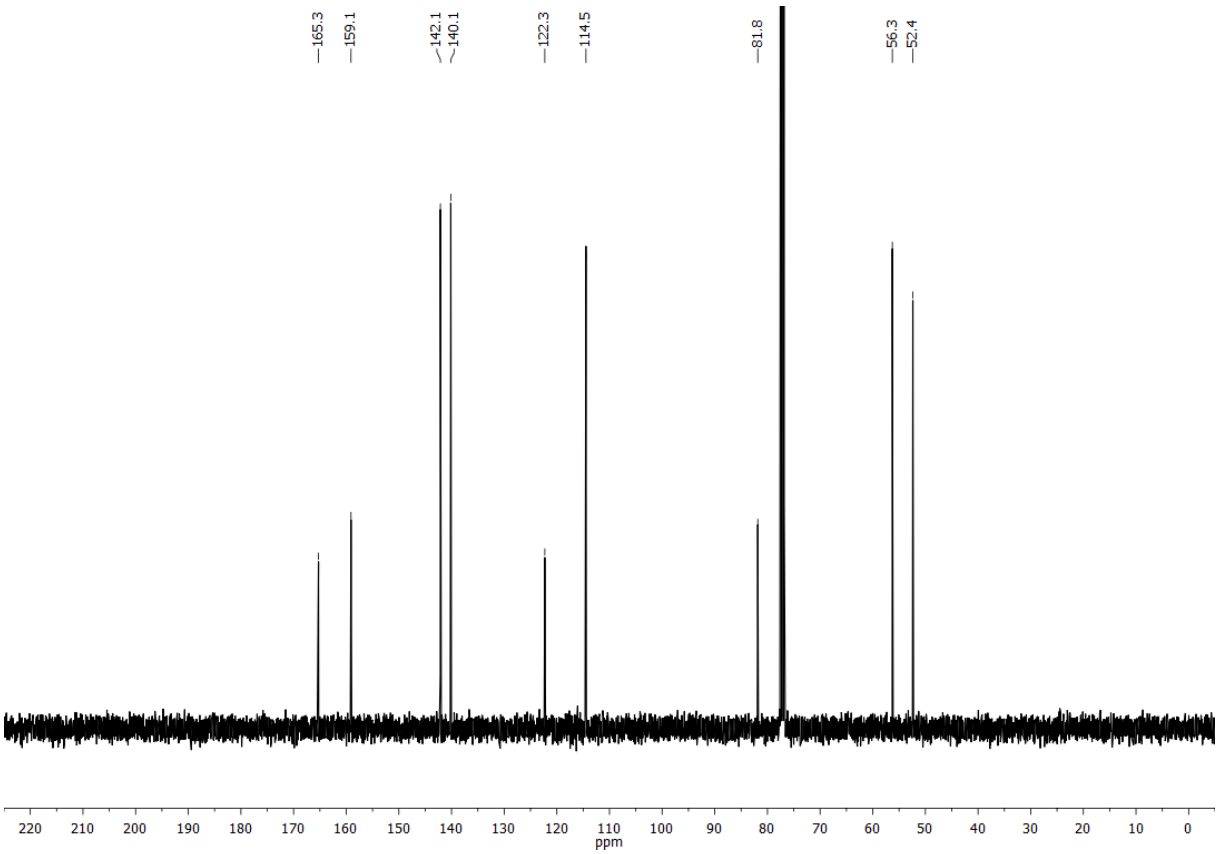
Compound **(+)-147v ^{13}C-NMR**



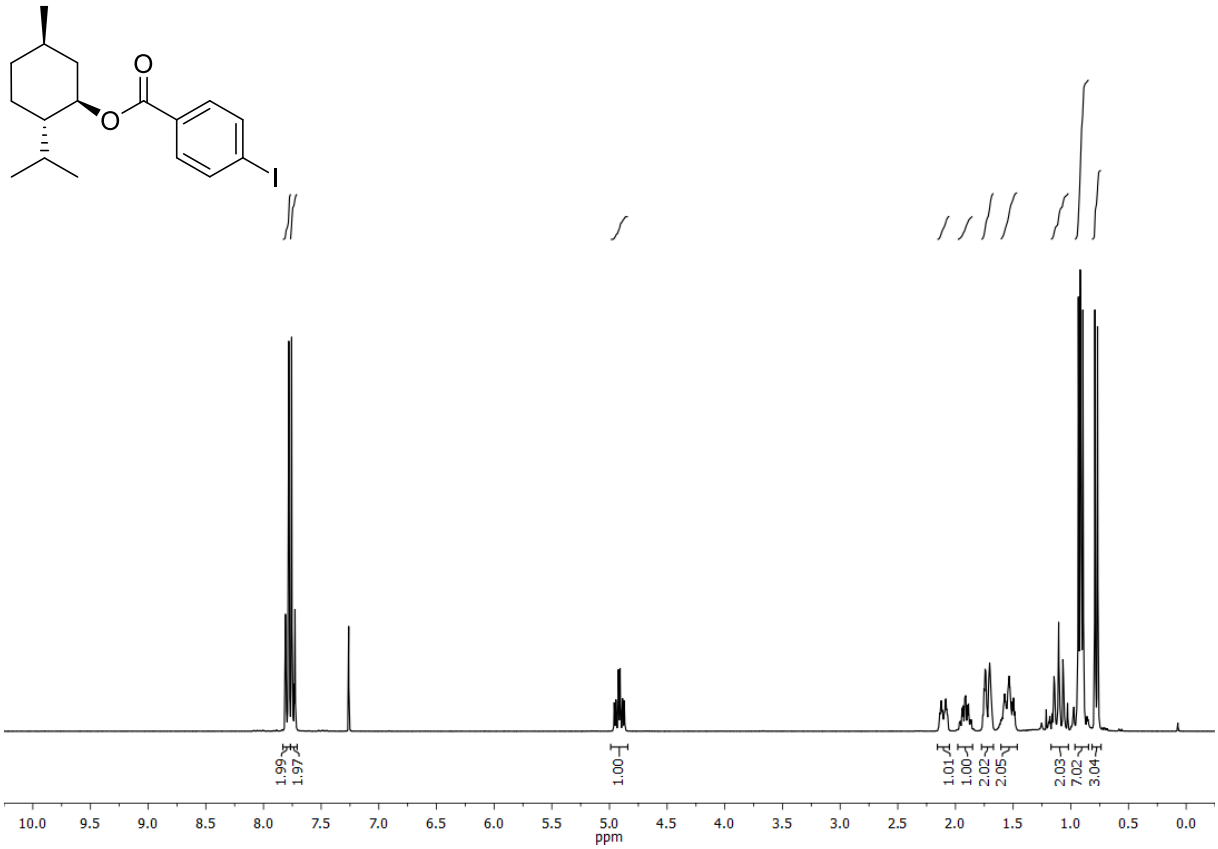
Compound **149q** ^{1}**H-NMR** ($CDCl_3$)



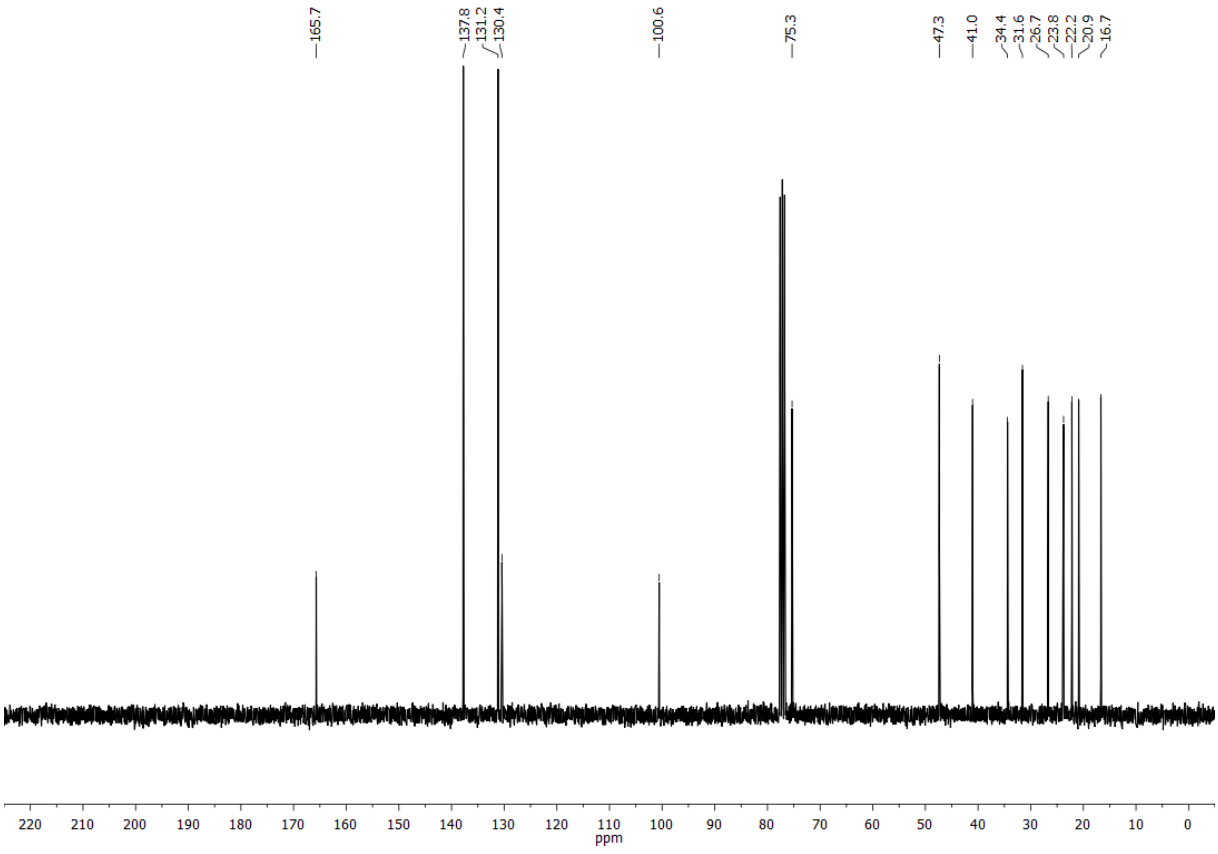
Compound **149q** ^{13}**C-NMR** ($CDCl_3$)



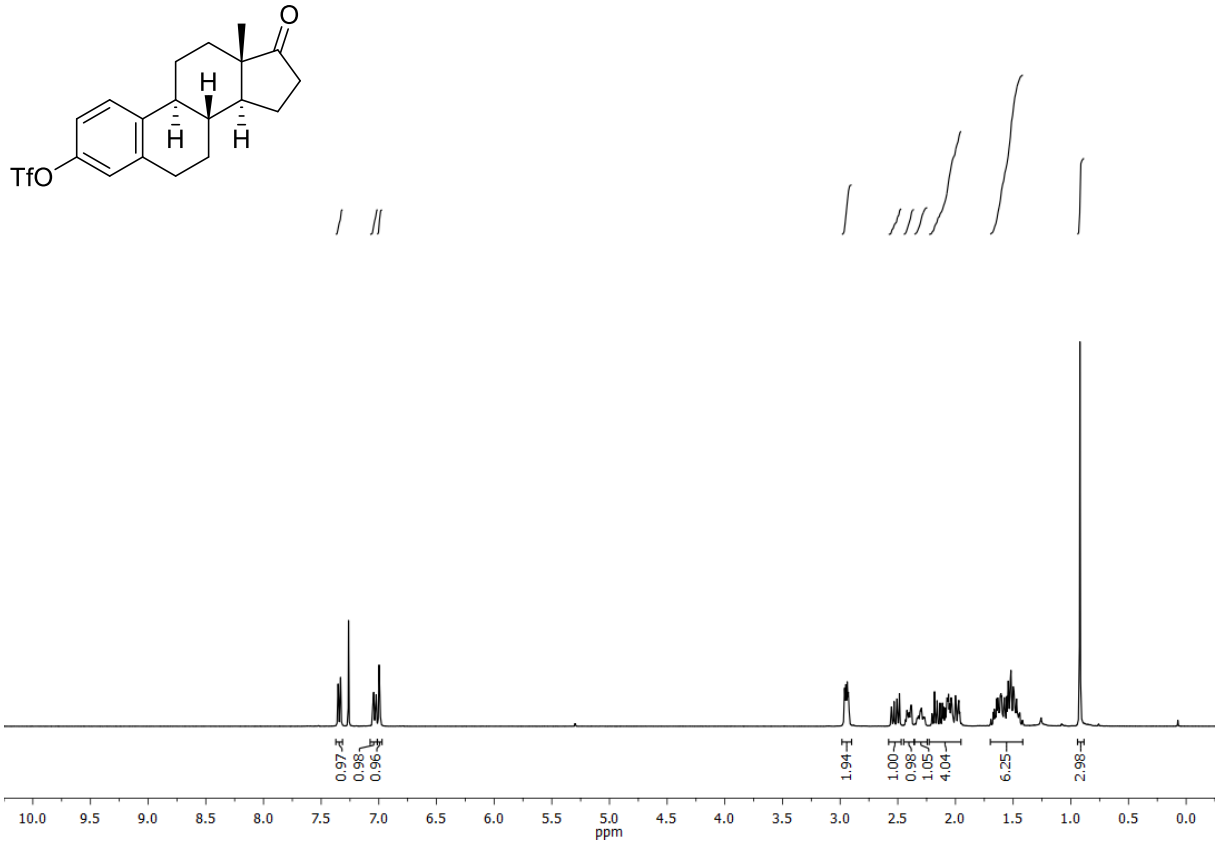
Compound **149u** ^{1}**H-NMR** ($CDCl_3$)



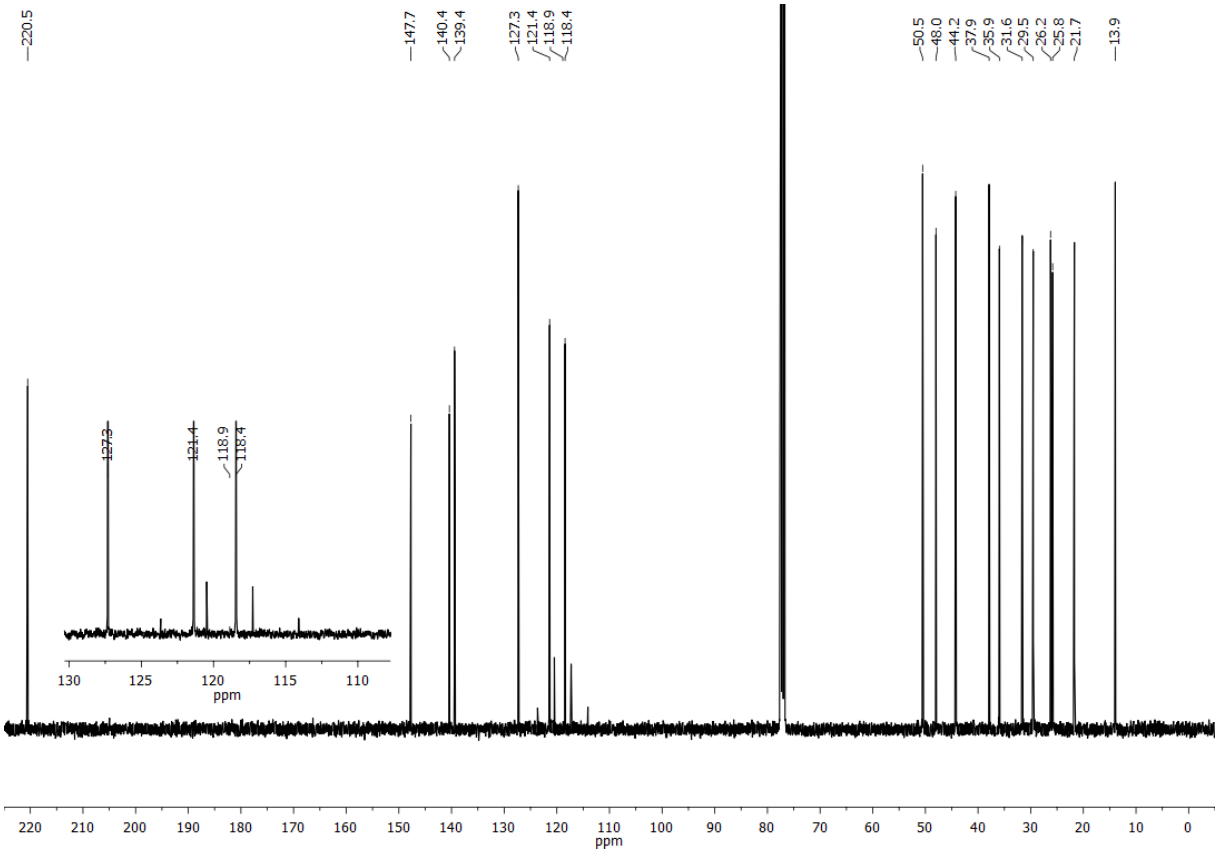
Compound **149u** ^{13}**C-NMR** ($CDCl_3$)



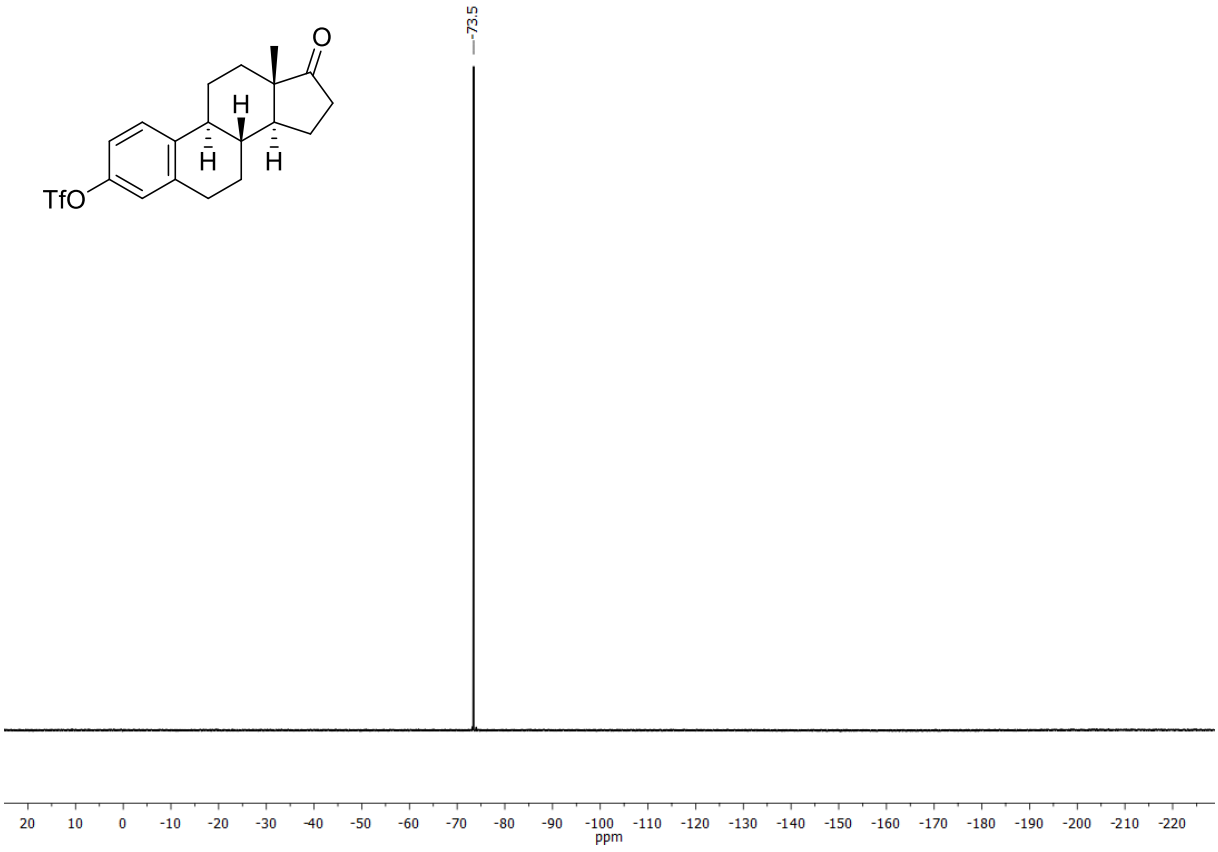
Compound **153** **^{1}H-NMR** ($CDCl_3$)



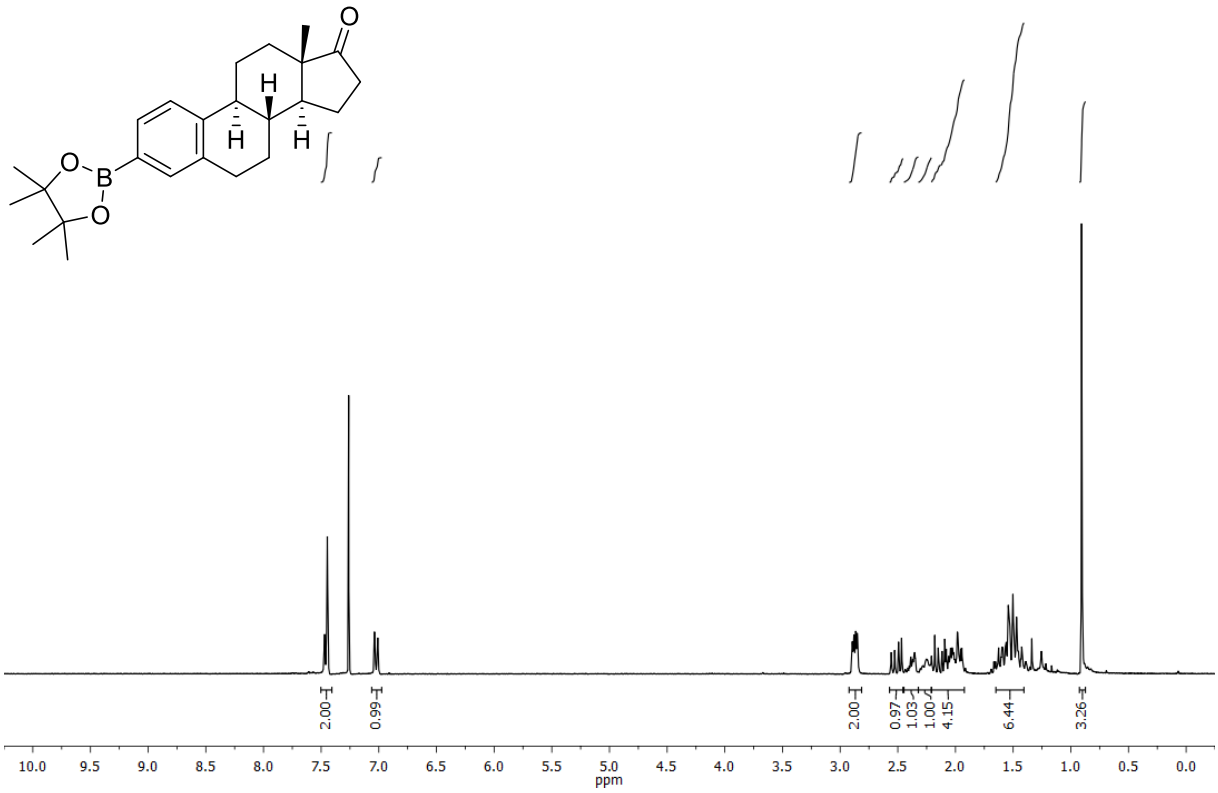
Compound **153** **^{13}C-NMR** ($CDCl_3$)



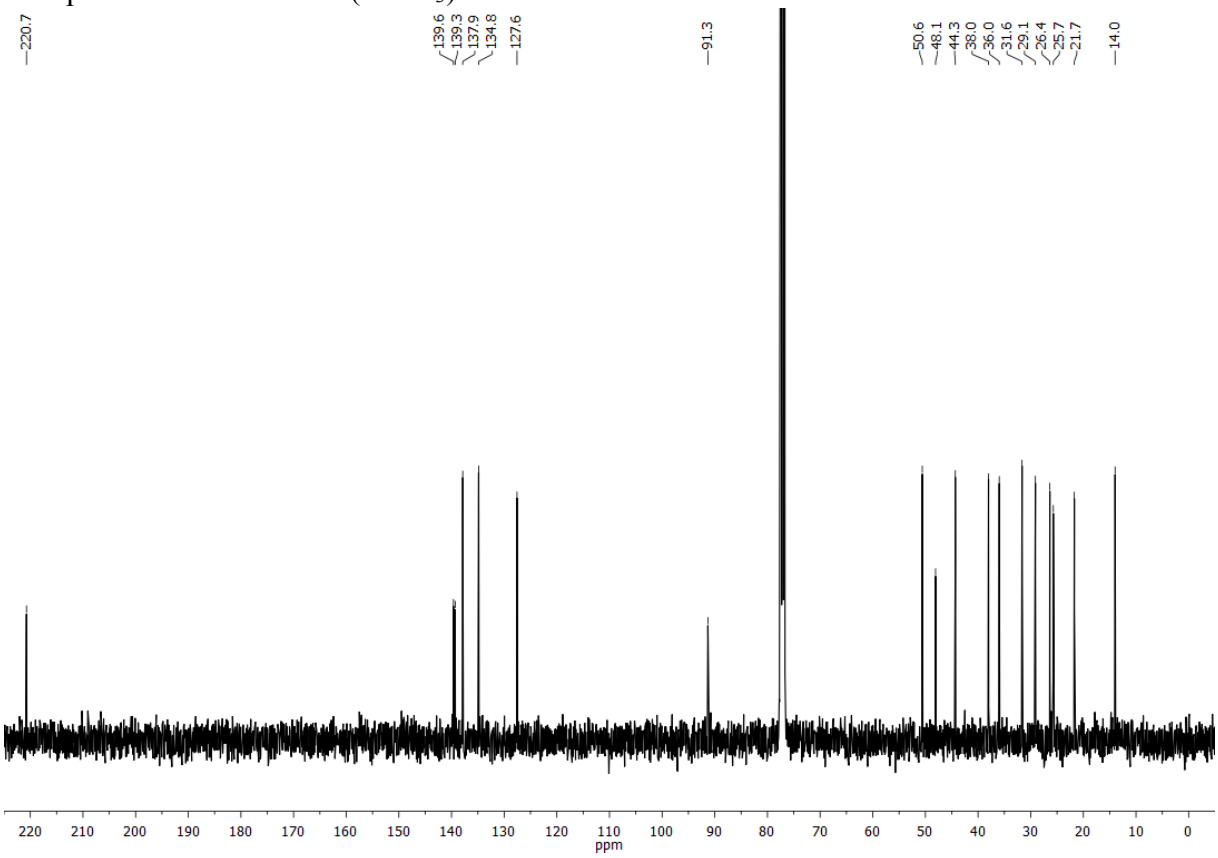
Compound **153** **^{19}F-NMR** ($CDCl_3$)



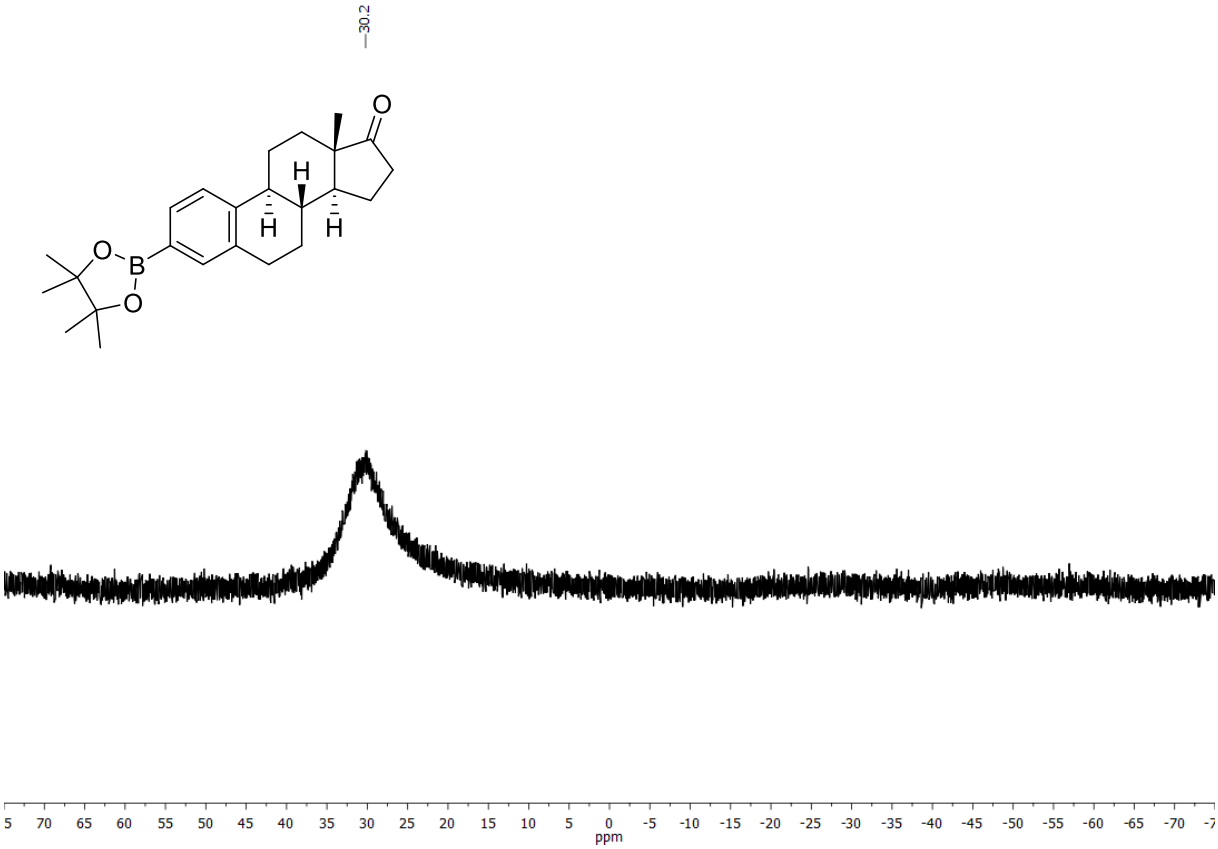
Compound **154** **^{1}H-NMR**



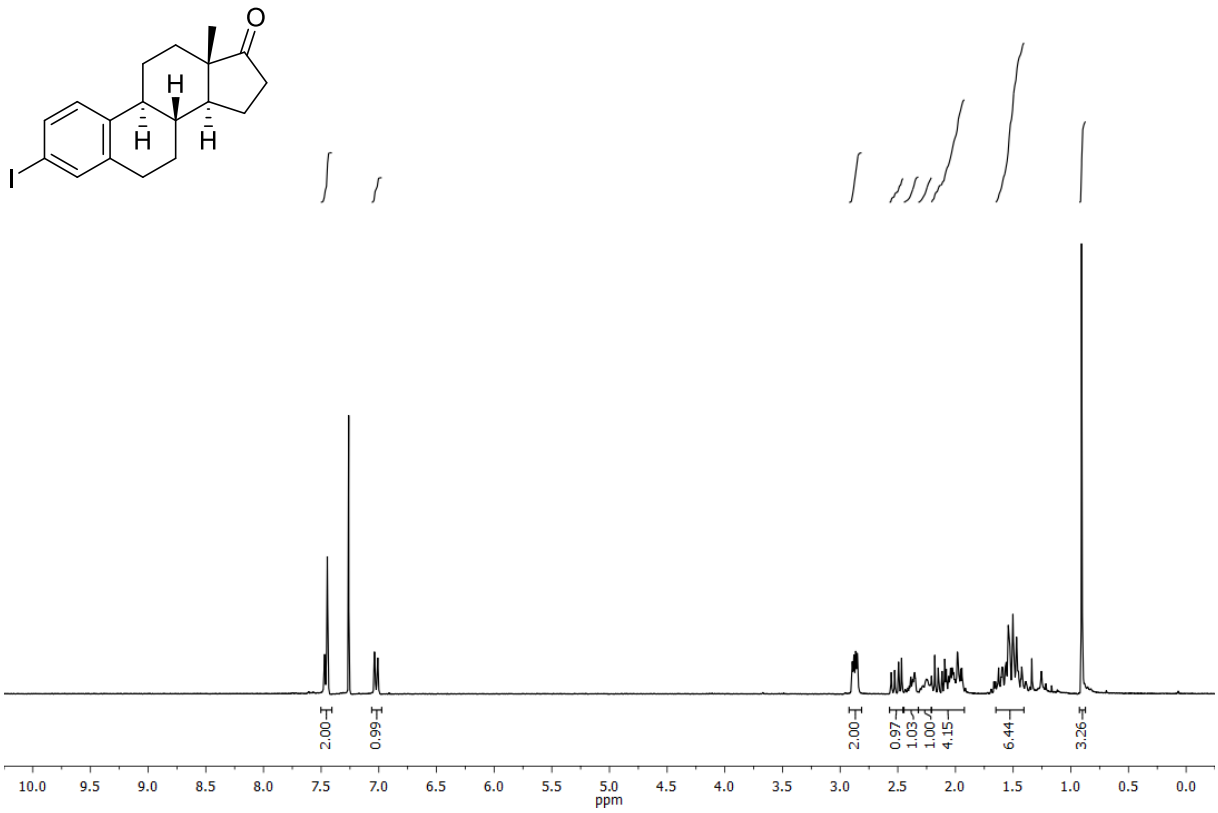
Compound **154** **^{13}C-NMR** ($CDCl_3$)



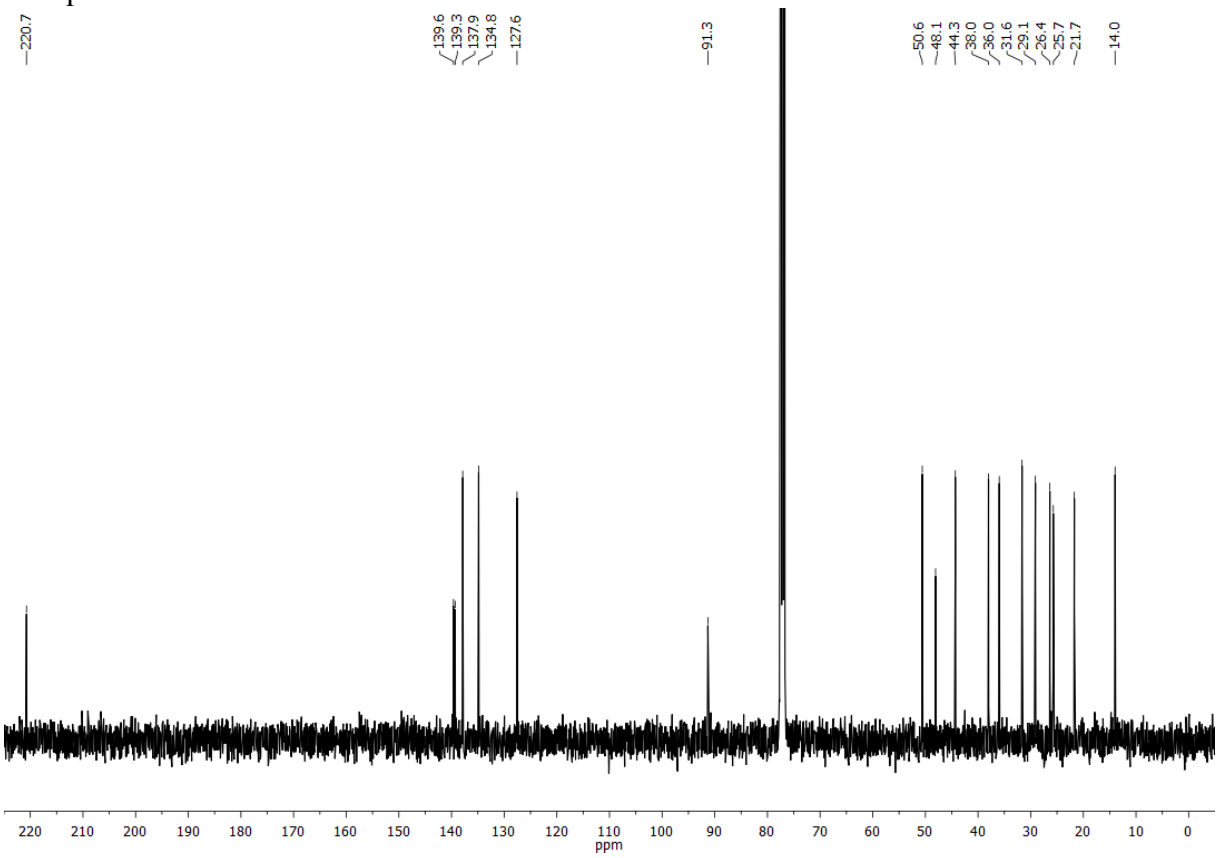
Compound **154** ^{11}**B-NMR** ($CDCl_3$)



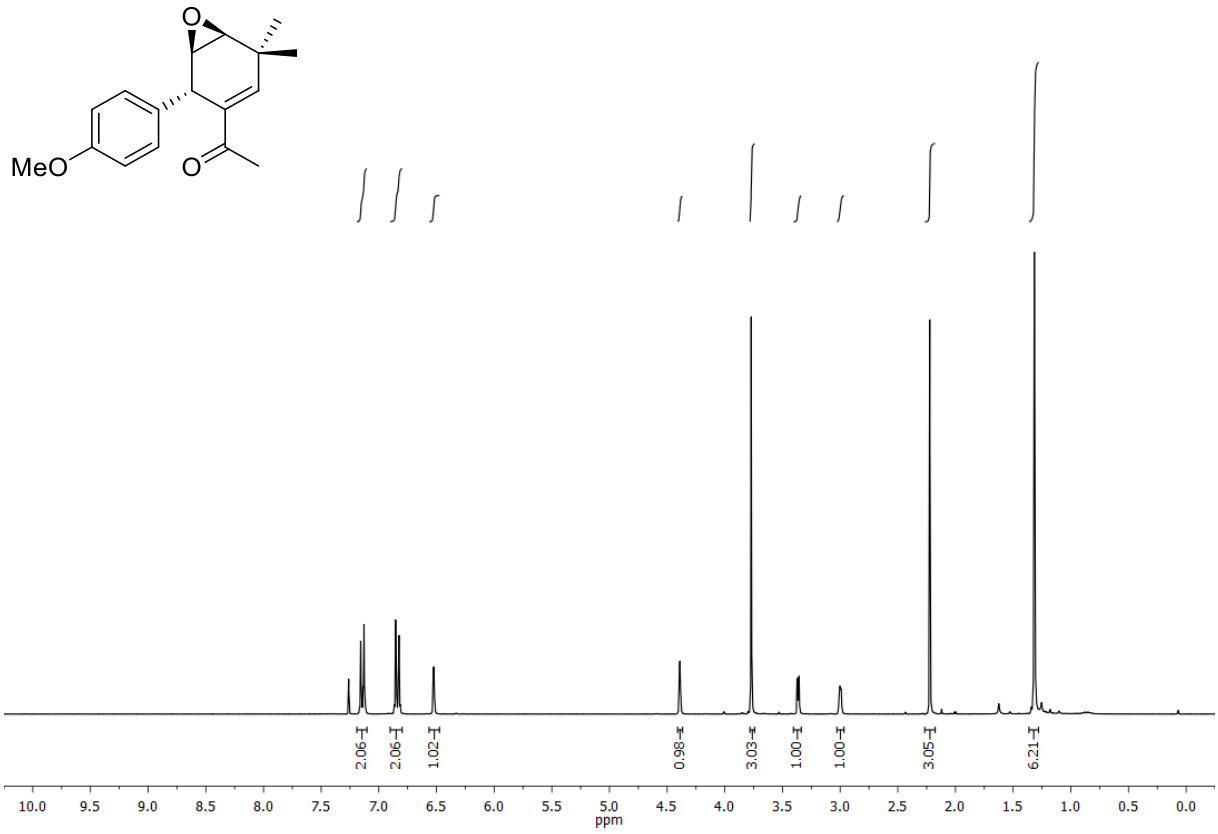
Compound **149v** ^{1}**H-NMR** ($CDCl_3$)



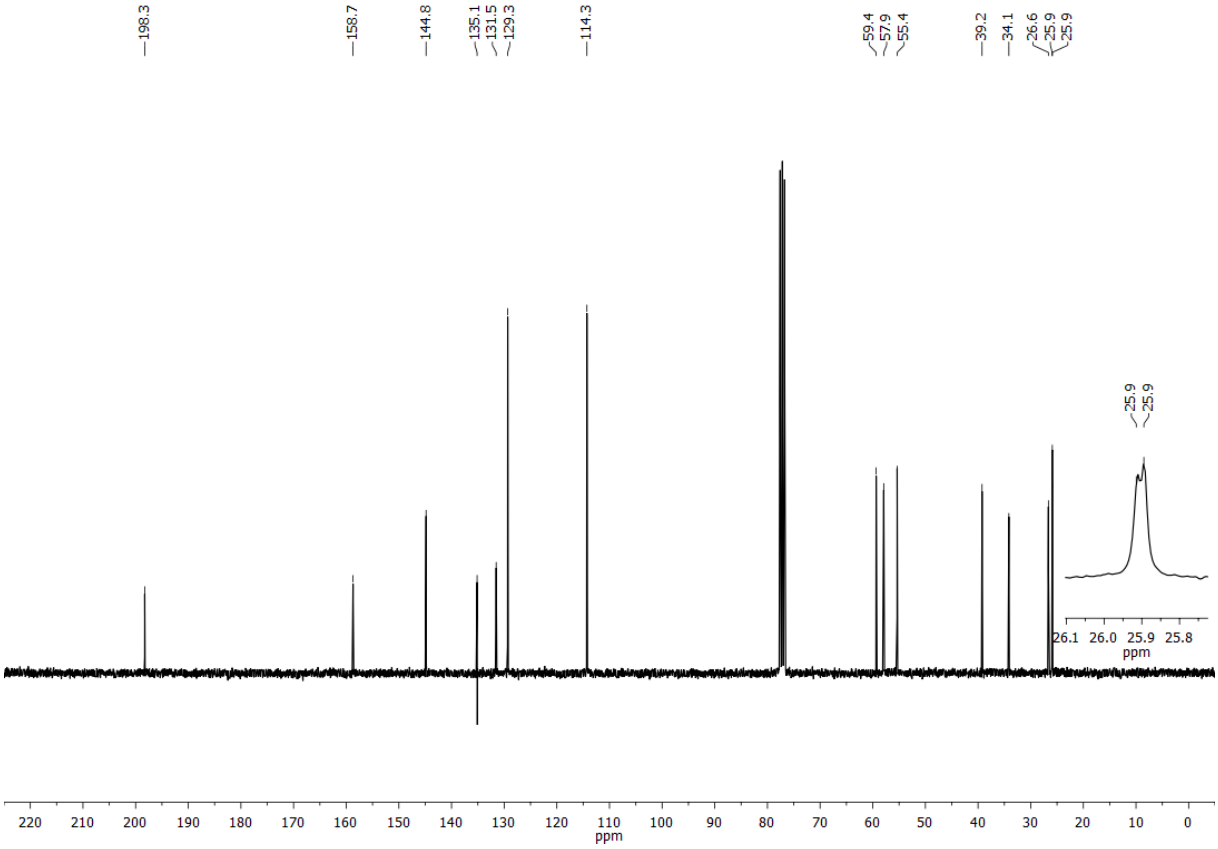
Compound **149v** ^{13}**C-NMR**



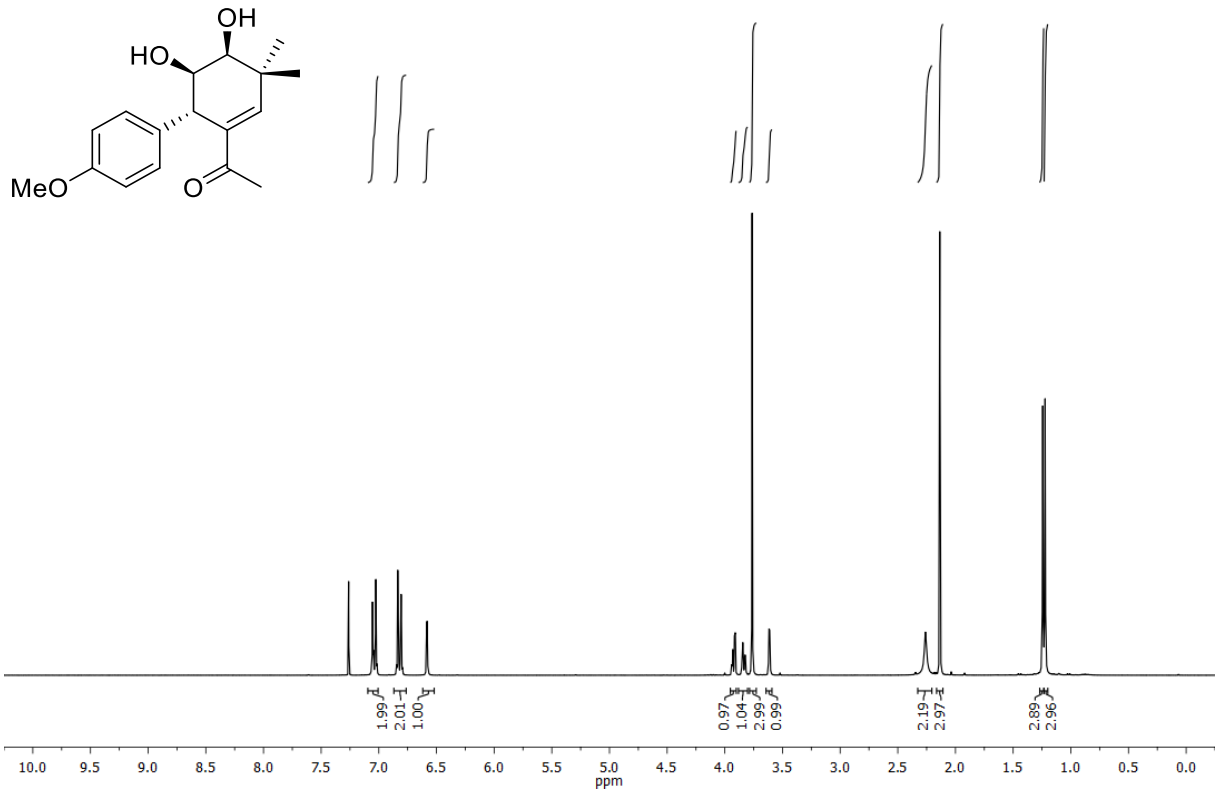
Compound **(+)-155** ^{1}**H-NMR** ($CDCl_3$)



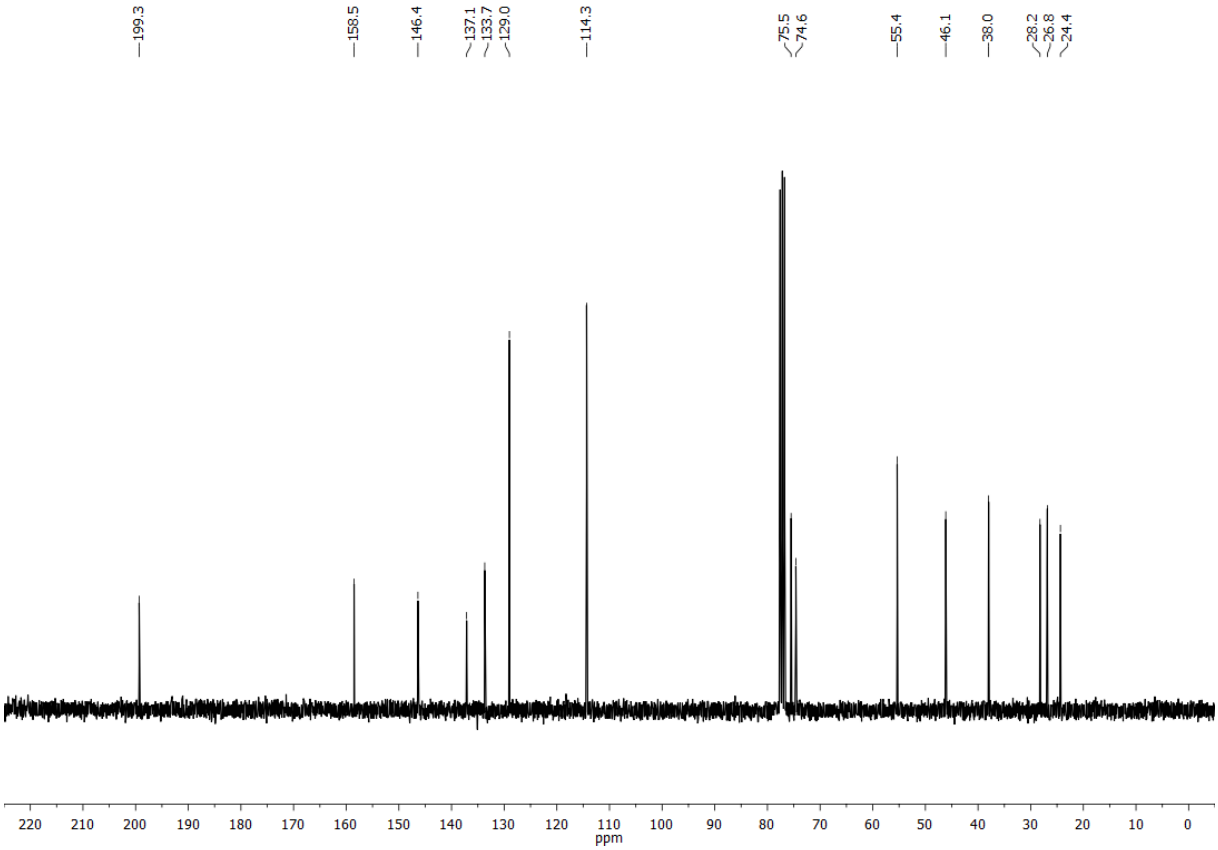
Compound **(+)-155** ^{13}**C-NMR** ($CDCl_3$)



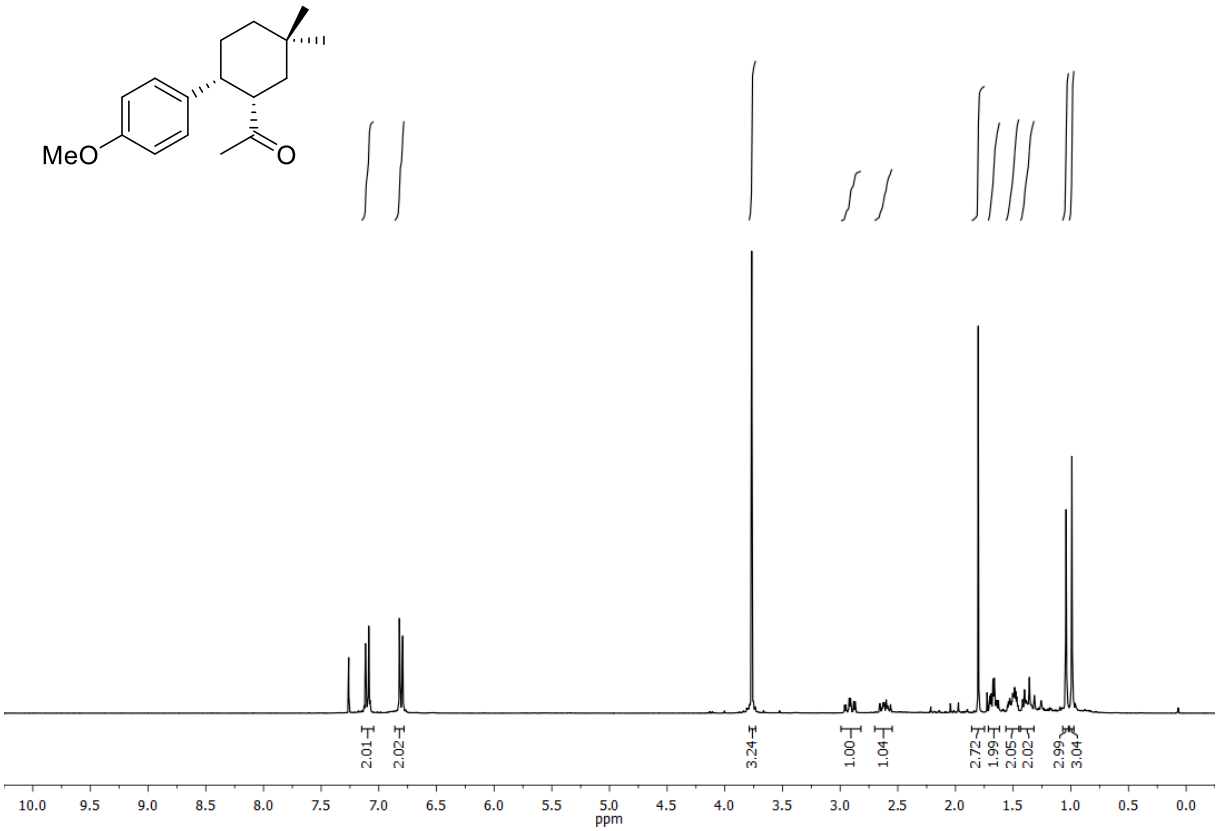
Compound **(+)-157** ^{1}H-NMR ($CDCl_3$)



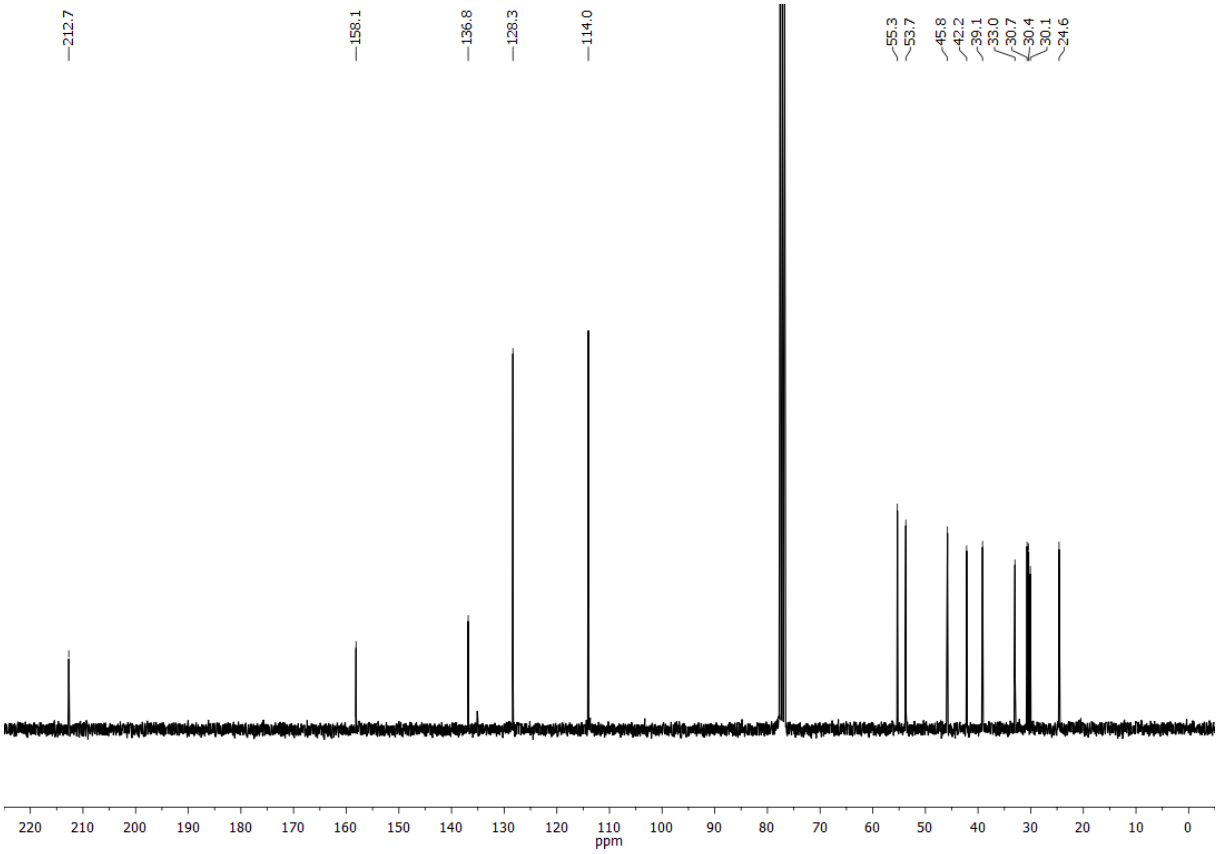
Compound **(+)-157** **^{13}C-NMR** ($CDCl_3$)



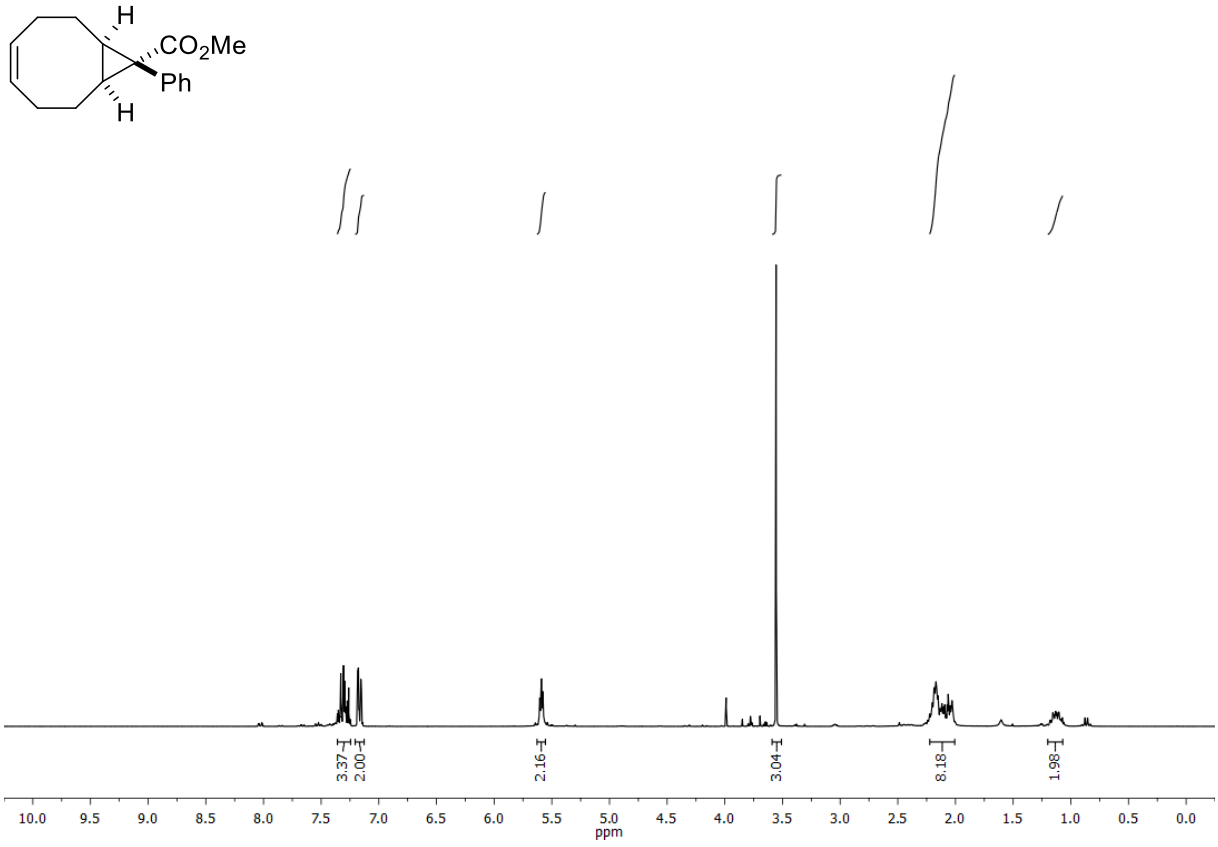
Compound **(-)-156** ^{1}**H-NMR** ($CDCl_3$)



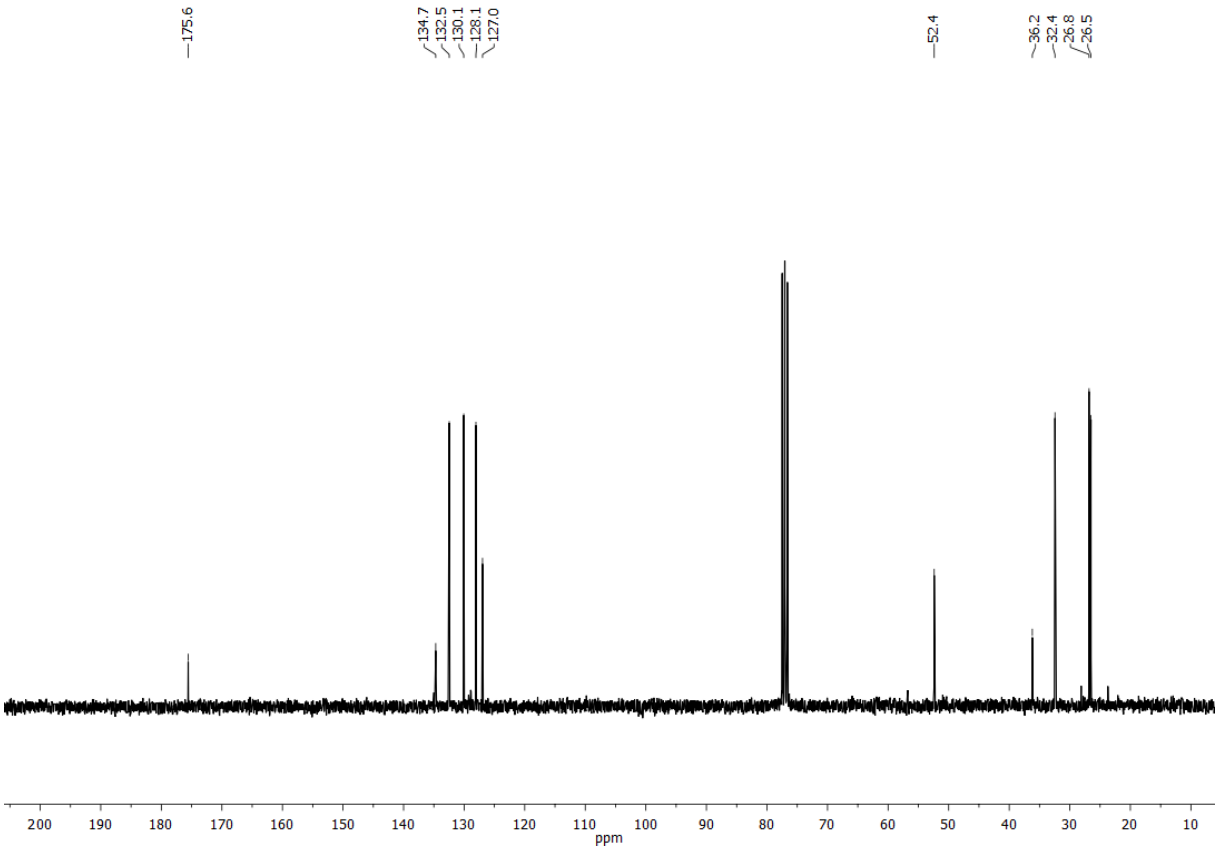
Compound **(-)-156** ^{13}**C-NMR** ($CDCl_3$)



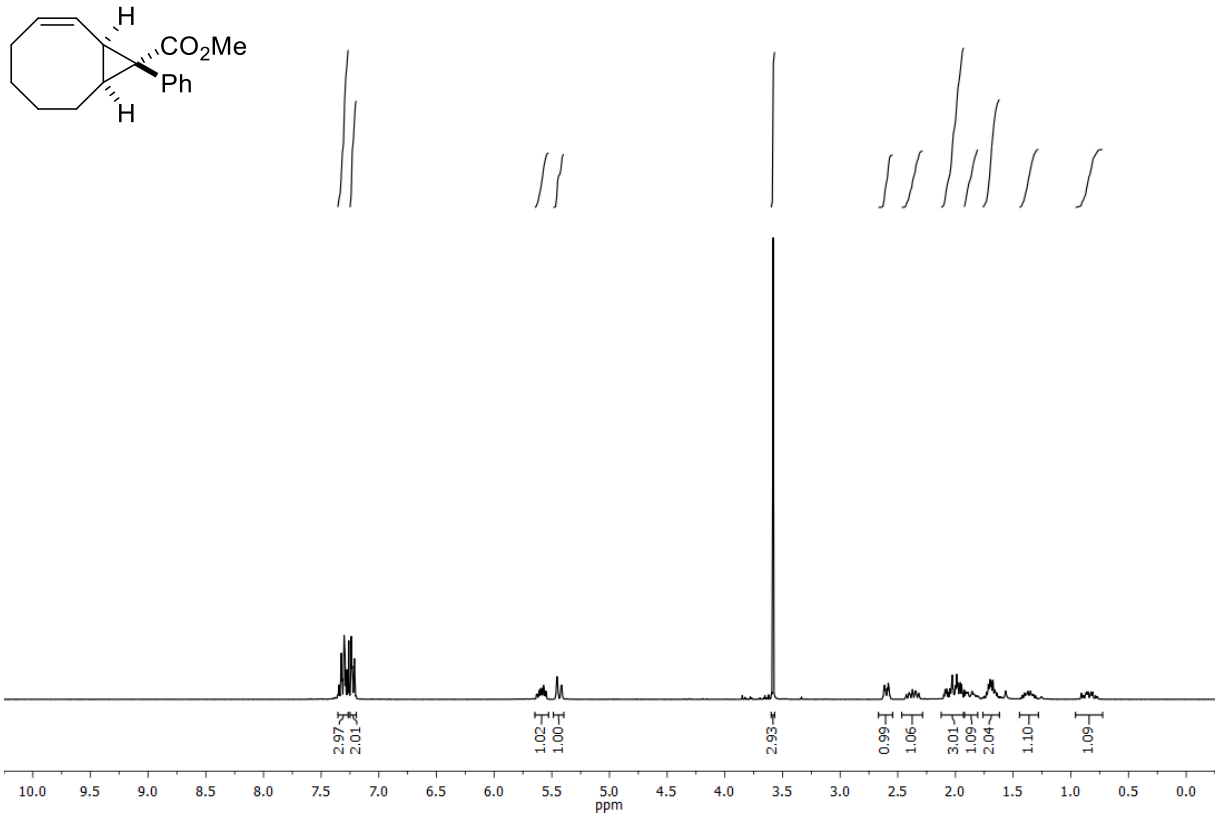
Compound **160** ^{1}**H-NMR** ($CDCl_3$)



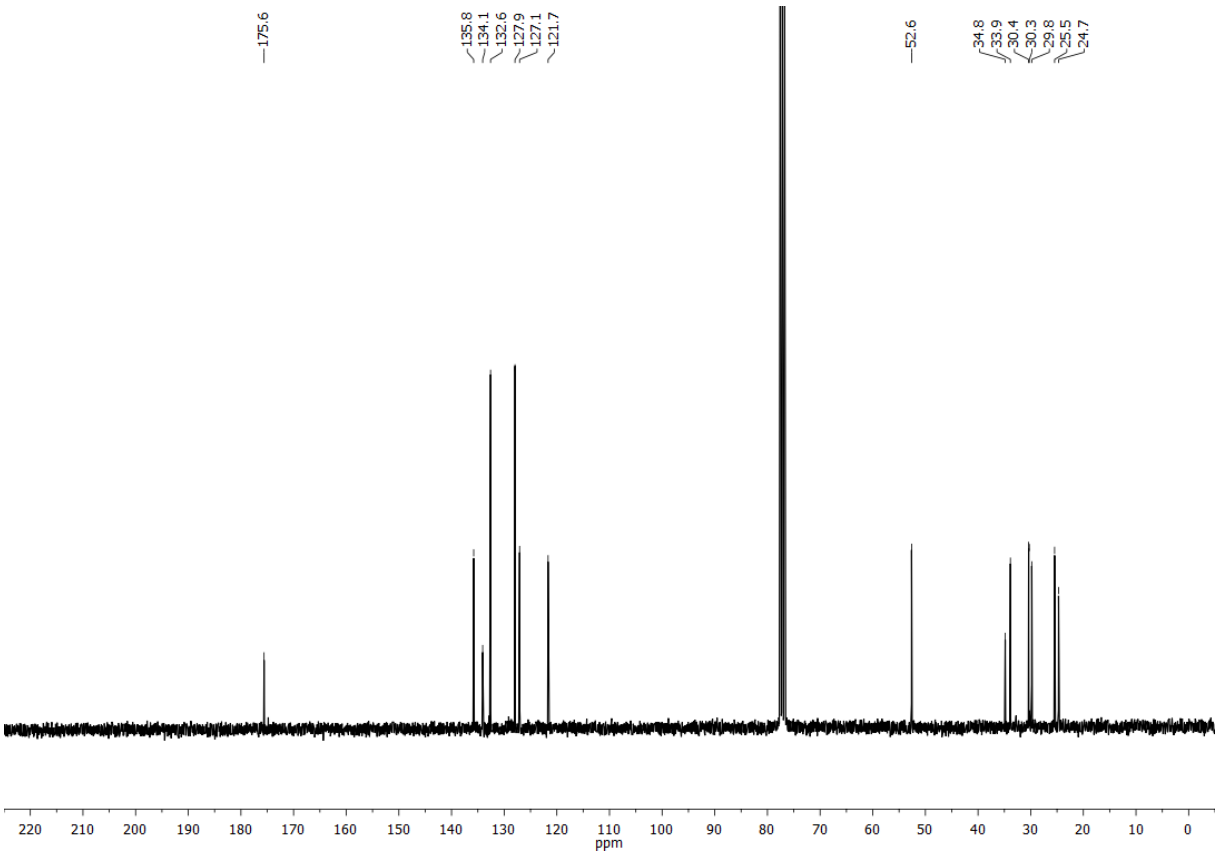
Compound **160** ^{13}**C-NMR** ($CDCl_3$)



Compound **162** **^{1}H-NMR** ($CDCl_3$)



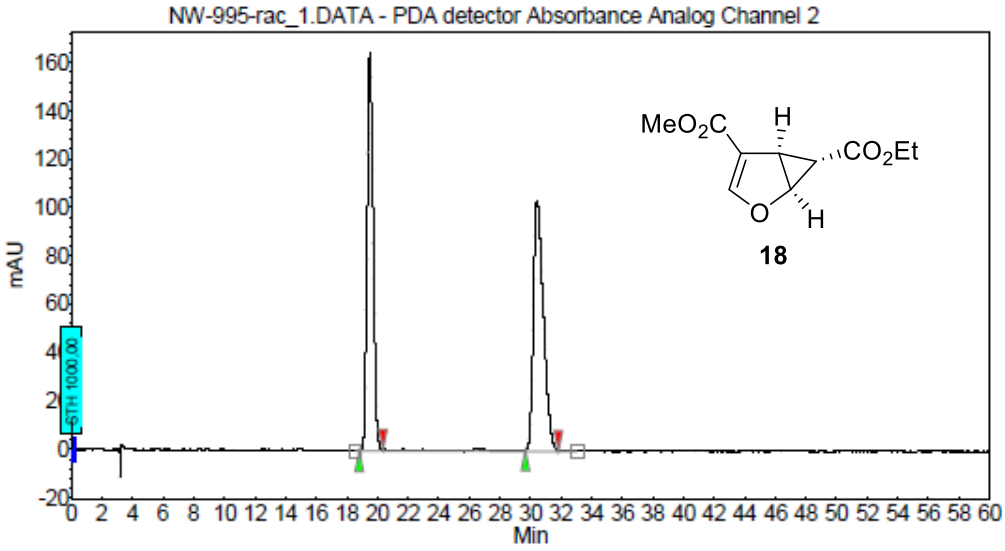
Compound **162** **^{13}C-NMR** ($CDCl_3$)



2. Chiral HPLC data

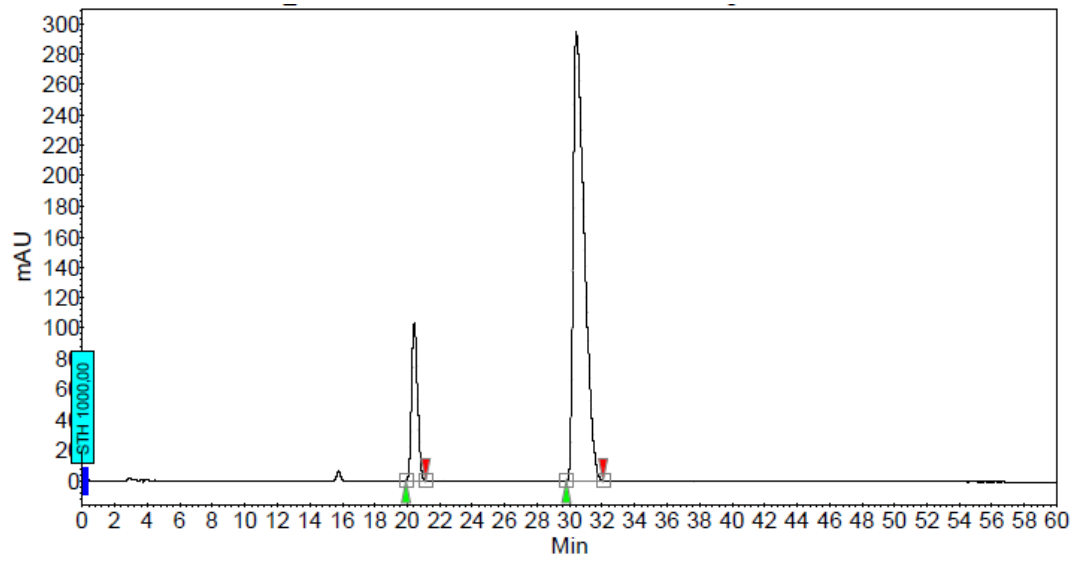
Column : Phenomenex Lux Cellulose-2, 4.6 x 250 mm, 5 µm

Eluents : A = *n*-Heptane 99%, B = *i*-Propanol 1%; **Flow** : 1.0 ml/min; λ : 254 nm



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	19,50	48,92	164,8	76,8	48,924
2	UNKNOWN	30,43	51,08	103,6	80,2	51,076
Total			100,00	268,4	157,0	100,000



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	20,44	15,66	103,5	43,3	15,660
2	UNKNOWN	30,42	84,34	294,8	233,3	84,340
Total			100,00	398,4	276,7	100,000

3. X-ray crystallography data

Table S 4. Crystallography data I.

Compound	16a	17-Boc	17-Ts	18	45
CCDC	2088173	/	/	/	2022177
Formula	$C_{17}H_{18}O_6$	$C_{18}H_{21}NO_4$	$C_{20}H_{19}NO_4S$	$C_{16}H_{16}O_5$	$C_{18}H_{14}O_4$
$D_{calc.}$/ g cm^{-3}	1.377	1.297	1.370	1.337	1.364
μ/mm^{-1}	0.876	0.748	1.824	0.601	0.794
Formula Weight	318.31	315.36	369.42	288.29	294.29
Colour	clear colourless	clear colourless	clear colourless	clear colourless	clear light yellow
Shape	prism	prism	prism	prism	prism
Size/mm^3	0.14×0.08×0.05	0.15×0.14×0.13	0.11×0.07×0.07	0.31×0.21×0.09	0.33×0.15×0.10
T/K	123.01(10)	123.00(10)	123.00(10)	123.00(10)	123.00(10)
Crystal System	triclinic	triclinic	monoclinic	triclinic	triclinic
Space Group	P-1	P-1	$P2_1/n$	P-1	P-1
a/Å	7.2743(4)	8.2017(2)	13.3737(3)	5.7900(2)	10.9933(2)
b/Å	10.4582(7)	9.0589(3)	6.62897(15)	8.6794(2)	11.0860(2)
c/Å	11.7037(7)	12.2322(3)	20.6853(5)	14.2867(4)	11.8874(3)
α/°	65.313(6)	100.632(2)	90	92.420(2)	82.9525(18)
β/°	85.025(5)	105.929(2)	102.362(2)	90.164(2)	87.9032(18)
γ/°	71.891(5)	105.715(2)	90	93.429(2)	85.5601(18)
V/Å^3	767.96(9)	807.71(4)	1791.31(7)	716.02(4)	1432.94(6)
Z	2	2	4	2	4
Z'	1	1	1	1	2
Wavelength/Å	1.54184	1.54184	1.54184	1.39222	1.54184
Radiation type	CuK$_\alpha$	CuK$_\alpha$	CuK$_\alpha$	?	CuK$_\alpha$
Θ_{min}/°	4.163	3.914	3.614	2.795	3.748
Θ_{max}/°	73.661	76.434	74.618	60.047	74.255
Measured Refl.	15818	27927	15592	15553	32892
Independent Refl.	3045	3365	3624	2809	5767
Reflections with I > 2(I)	2604	3097	3169	2601	5212
R_{int}	0.0475	0.0253	0.0358	0.0313	0.0325
Parameters	211	212	237	192	407
Restraints	0	0	0	0	0
Largest Peak	0.225	0.244	0.311	0.188	0.602
Deepest Hole	-0.216	-0.231	-0.409	-0.226	-0.402
GooF	1.128	1.043	1.027	1.033	1.034
wR_2 (all data)	0.1199	0.0842	0.0876	0.0944	0.1217
wR_2	0.1151	0.0817	0.0834	0.0922	0.1177
R_1 (all data)	0.0533	0.0355	0.0390	0.0379	0.0494
R_1	0.0454	0.0326	0.0330	0.0357	0.0451

Table S 5. Crystallography data II.

Compound	74	79-Boc	79-Ts	86 (minor)
CCDC	**2088174**	/	/	/
Formula	$C_{13}H_{15}NO_2$	$C_{18}H_{20}BrNO_5$	$C_{20}H_{18}BrNO_5S$	$C_{26}H_{23}NO_5S$
$D_{calc.}$/ g cm^{-3}	1.307	1.553	1.620	1.356
μ/mm^{-1}	0.515	3.447	4.259	1.164
Formula Weight	217.26	410.26	464.32	461.51
Colour	clear colourless	clear colourless	colourless	clear colourless
Shape	prism	prism	prism	plate
Size/mm^3	0.19×0.14×0.13	0.21×0.17×0.12	0.20×0.18×0.10	0.34×0.17×0.06
T/K	122.97(13)	123.01(10)	123.01(10)	123.00(10)
Crystal System	monoclinic	monoclinic	triclinic	monoclinic
Space Group	$P2_1/n$	$P2_1/c$	P-1	$P2_1/n$
a/Å	11.2637(2)	6.49370(10)	7.4885(3)	14.67621(16)
b/Å	5.81620(10)	24.6606(4)	9.5522(3)	17.48970(18)
c/Å	17.3002(4)	10.9675(2)	14.5200(5)	27.1133(3)
α/°	90	90	84.272(3)	90
β/°	102.970(2)	92.146(2)	83.774(3)	102.9420(11)
γ/°	90	90	67.511(3)	90
V/Å^3	1104.45(4)	1755.09(5)	952.07(6)	6782.73(14)
Z	4	4	2	12
Z'	1	1	1	3
Wavelength/Å	1.39222	1.54184	1.54184	1.39222
Radiation type	Cu K	Cu K$_\alpha$	Cu K$_\alpha$	Cu K
Θ_{min}/°	3.868	3.585	5.021	2.736
Θ_{max}/°	60.092	73.007	76.561	60.089
Measured Refl.	11769	19704	22400	73434
Independent Refl.	2205	3470	3962	13567
Reflections with I > 2(I)	1971	3404	3794	11976
R_{int}	0.0220	0.0214	0.0351	0.0338
Parameters	169	230	255	898
Restraints	106	0	0	0
Largest Peak	0.241	0.538	0.404	0.300
Deepest Hole	-0.273	-0.693	-0.386	-0.435
GooF	1.066	1.064	1.041	1.046
wR_2 (all data)	0.1186	0.0588	0.0592	0.0972
wR_2	0.1138	0.0585	0.0584	0.0935
R_1 (all data)	0.0477	0.0244	0.0238	0.0421
R_1	0.0432	0.0240	0.0225	0.0361

Table S 6. Crystallography data III.

Compound	88a	104	123	132
CCDC	/	/	/	/
Formula	$C_{20}H_{19}NO_5S$	$C_{14}H_{15}NO_6S$	$C_{20}H_{21}NO_3S$	$C_{13}H_{16}ClNO_2S$
$D_{calc.}$/ g cm^{-3}	1.409	1.465	1.324	1.440
μ/mm^{-1}	1.865	2.233	1.765	3.996
Formula Weight	385.42	325.33	355.44	285.78
Colour	clear colourless	clear colourless	clear light yellow	clear colourless
Shape	prism	plate	prism	prism
Size/mm^3	0.46×0.32×0.28	0.21×0.08×0.03	0.14×0.14×0.05	0.17×0.14×0.10
T/K	123.00(10)	123.00(10)	123.01(10)	123.01(10)
Crystal System	monoclinic	monoclinic	monoclinic	orthorhombic
Flack Parameter	/	0.013(11)	/	0.418(15)
Hooft Parameter	/	-0.003(7)	/	0.417(3)
Space Group	$P2_1/c$	$P2_1$	$P2_1/n$	$P2_12_12_1$
a/Å	17.7927(3)	9.3002(2)	12.46610(10)	6.19721(5)
b/Å	5.62378(12)	15.5856(3)	10.33940(10)	12.54839(11)
c/Å	18.2894(3)	10.9289(2)	14.0681(2)	16.95174(15)
α/°	90	90	90	90
β/°	96.8070(16)	111.361(2)	100.4530(10)	90
γ/°	90	90	90	90
V/Å^3	1817.19(6)	1475.31(5)	1783.17(3)	1318.252(19)
Z	4	4	4	4
Z'	1	2	1	1
Wavelength/Å	1.54184	1.54184	1.54184	1.54184
Radiation type	Cu K$_\alpha$	Cu K$_\alpha$	Cu K$_\alpha$	Cu K$_\alpha$
Θ_{min}/°	4.870	4.344	4.363	4.384
Θ_{max}/°	72.758	72.942	73.155	73.186
Measured Refl.	17836	16187	19760	22228
Independent Refl.	3578	5694	3488	2626
Reflections with I > 2(I)	3361	5464	3254	2607
R_{int}	0.0462	0.0261	0.0192	0.0289
Parameters	246	403	228	165
Restraints	0	1	0	0
Largest Peak	0.493	0.263	0.266	0.186
Deepest Hole	-0.429	-0.267	-0.403	-0.188
GooF	1.060	1.015	1.058	1.060
wR_2 (all data)	0.1131	0.0807	0.0852	0.0580
wR_2	0.1111	0.0790	0.0838	0.0579
R_1 (all data)	0.0428	0.0318	0.0326	0.0213
R_1	0.0406	0.0300	0.0307	0.0212

Table S 7. Crystallography data IV.

Compound	140	(-)-147q	(-)-156	162
CCDC	/	**2088175**	**2088175**	/
Formula	$C_{19}H_{20}BrNO_2S$	$C_{19}H_{22}O_4$	$C_{17}H_{24}O_2$	$C_{17}H_{20}O_2$
$D_{calc.}$/ g cm^{-3}	1.537	1.253	1.158	1.249
μ/mm^{-1}	4.389	0.706	0.576	0.631
Formula Weight	406.33	314.36	260.36	256.33
Colour	clear colourless	clear colourless	clear colourless	clear colourless
Shape	needle-shaped	irregular-shaped	prism-shaped	prism-shaped
Size/mm^3	0.13×0.04×0.02	0.39×0.35×0.25	0.23×0.13×0.07	0.15×0.05×0.03
T/K	123.00(10)	123.01(10)	122.98(10)	122.9(4)
Crystal System	monoclinic	orthorhombic	monoclinic	monoclinic
Flack Parameter	/	0.06(8)	0.08(13)	/
Hooft Parameter	/	0.05(7)	0.07(10)	/
Space Group	$P2_1/c$	$P2_12_12_1$	$P2_1$	$P2_1/c$
a/Å	19.9914(5)	7.70490(10)	5.7986(4)	11.0298(3)
b/Å	5.58860(10)	9.7402(2)	8.1719(6)	16.1088(4)
c/Å	16.1098(4)	22.1970(3)	15.8328(10)	7.8923(2)
α/°	90	90	90	90
β/°	102.609(2)	90	95.315(6)	103.633(3)
γ/°	90	90	90	90
V/Å^3	1756.44(7)	1665.82(5)	747.02(9)	1362.77(6)
Z	4	4	2	4
Z'	1	1	1	1
Wavelength/Å	1.54184	1.54184	1.54184	1.54184
Radiation type	Cu K$_\alpha$	Cu K$_\alpha$	Cu K$_\alpha$	Cu K$_\alpha$
Θ_{min}/°	2.265	4.958	5.613	4.124
Θ_{max}/°	74.621	66.649	67.290	74.719
Measured Refl.	6255	11073	7059	19386
Independent Refl.	6255	2932	2573	2759
Reflections with I > 2(I)	5741	2850	2491	2429
R_{int}	.	0.0306	0.0283	0.0265
Parameters	298	213	176	183
Restraints	0	0	1	7
Largest Peak	0.333	0.121	0.213	0.766
Deepest Hole	-0.613	-0.171	-0.216	-0.566
GooF	1.063	1.071	1.057	1.041
wR_2 (all data)	0.0877	0.0730	0.1017	0.1320
wR_2	0.0860	0.0722	0.1004	0.1277
R_1 (all data)	0.0346	0.0298	0.0384	0.0569
R_1	0.0315	0.0289	0.0374	0.0509

4. Computational data

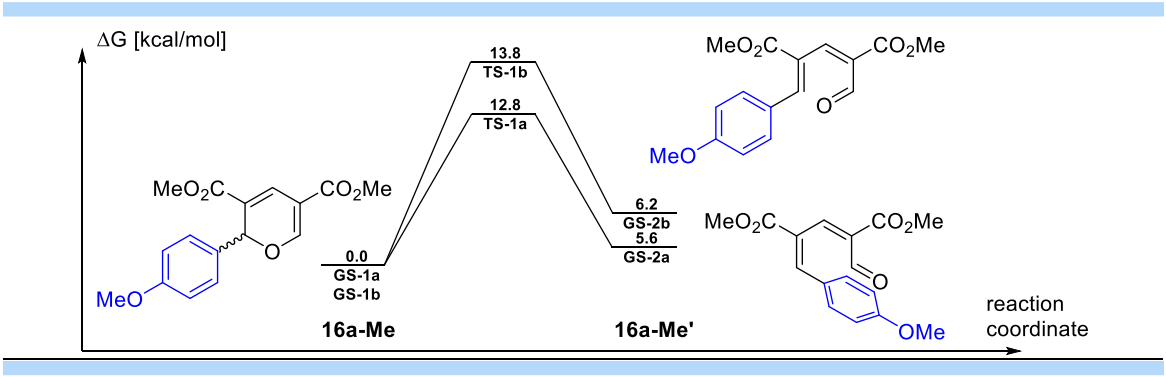
All calculations have been run with the Gaussian09.E01 software package.[69]

The stationary points have been confirmed to be either minimum energy structures or saddle points of first order (transition states) by frequency analysis under the harmonic oscillator approximation. The minimum energy structures were all free from imaginary frequencies, whereas the transition states exhibit a single imaginary frequency that was verified as the correct reaction coordinate of the elementary step of interest by visualization in GaussView 6.1.1. Calculations were run for 298.15 K and THF as solvent.

The reported energies are Gibb's free energies including zero-point correction and values are given in kcal/mol.

Rendered structures have been obtained by the freeware CVLY View.[70]

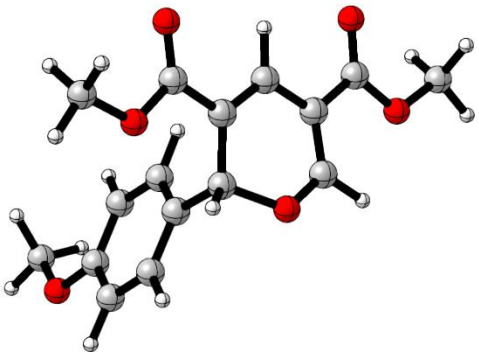
For calculations we investigated the 6π-electrocyclic ring opening of **16-Me** to its ring-opened open-chained aldehyde **16-Me'**. Since this disrotatory process can furnish two E/Z isomers as products, both pathways were calculated.



Scheme S 2. Calculated energy profile for racemization of model substrate **16-Me**.

[69] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y. ; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. ; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, G. ; Voth, G. A. ; Salvador, P. ; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D. ; Farkas, O. ; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J., Gaussian, Inc., Wallingford CT, **2013**.

[70] CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, **2009** (www.cylview.org).

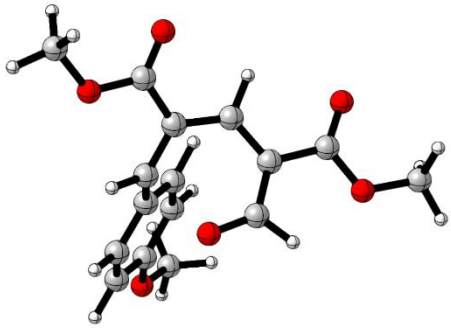


GS-1a **(16-Me)**

0			1
C	3.474107	-1.259427	-0.118781
C	3.017284	-1.817273	1.087333
C	1.697417	-1.635530	1.477961
C	0.801113	-0.899755	0.685170
C	1.266230	-0.355333	-0.514961
C	2.591989	-0.525063	-0.923346
H	3.707897	-2.391523	1.696677
H	1.352440	-2.073213	2.411139
H	0.591203	0.203484	-1.154707
H	2.918396	-0.090899	-1.860142
O	4.779605	-1.490750	-0.424448
C	5.297208	-0.946512	-1.641943
H	5.233878	0.147600	-1.644186
H	6.343923	-1.250382	-1.680223
H	4.767262	-1.349992	-2.512257
C	-0.613441	-0.691341	1.170993
H	-0.888663	-1.507464	1.837478
C	-0.877708	1.689041	1.586325
H	-0.605856	2.492251	2.262966
C	-1.488963	1.891849	0.382137
C	-1.987375	0.731985	-0.320361
H	-2.677229	0.872013	-1.145303
C	-1.639386	-0.511451	0.077691
O	-0.626560	0.486356	2.087164
C	-1.769784	3.239035	-0.134678
C	-1.487832	5.571490	0.198989
H	-0.991670	6.203205	0.935536
H	-1.062203	5.738388	-0.793332
H	-2.560276	5.779586	0.180592
O	-1.242614	4.217433	0.632385
O	-2.406573	3.460346	-1.155513
C	-2.196418	-1.692127	-0.607247
O	-2.964095	-1.660421	-1.558560
O	-1.748910	-2.842238	-0.058613
C	-2.217484	-4.065561	-0.662362
H	-1.913774	-4.112717	-1.710798
H	-1.746690	-4.867205	-0.093769
H	-3.305555	-4.134701	-0.590046

Zero-point correction= 0.297939 (Hartree/Particle)
Thermal correction to Energy= 0.319014
Thermal correction to Enthalpy= 0.319958
Thermal correction to Gibbs Free Energy= 0.245590
Sum of electronic and zero-point Energies= -1070.519827
Sum of electronic and thermal Energies= -1070.498752
Sum of electronic and thermal Enthalpies= -1070.497807
Sum of electronic and thermal Free Energies= -1070.572176

	E (Thermal)	CV	S
	KCal/Mol	Cal/Mol-Kelvin	Cal/Mol-Kelvin
Total	200.184	77.078	156.522



TS-1a

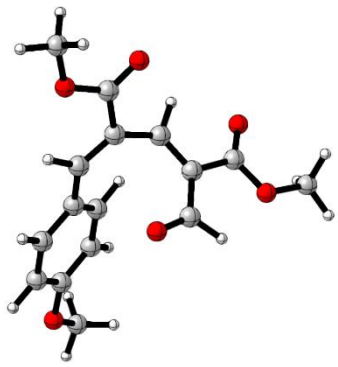
0			1
C	3.475031	-1.352759	-0.001576
C	2.918468	-1.983680	1.129065
C	1.552012	-1.953783	1.327540
C	0.693712	-1.286058	0.420196
C	1.267293	-0.685026	-0.719086
C	2.637207	-0.711284	-0.934819
H	3.578346	-2.487562	1.827381
H	1.124897	-2.435296	2.202076
H	0.629060	-0.207260	-1.453072
H	3.045656	-0.249099	-1.824546
O	4.816424	-1.430045	-0.117556
C	5.453579	-0.804957	-1.242221
H	5.258683	0.272297	-1.252271

H	6.520464	-0.983867	-1.108831
H	5.118575	-1.256883	-2.181622
C	-0.719605	-1.269091	0.690775
H	-1.061575	-2.042510	1.372395
C	-0.526581	1.421876	1.636704
H	-0.340156	2.306041	2.259894
C	-0.906077	1.677759	0.280506
C	-1.631694	0.720696	-0.449446
H	-2.293117	1.088285	-1.229289
C	-1.709741	-0.628879	-0.112655
O	-0.472057	0.302684	2.197807
C	-0.858708	3.046284	-0.254688
C	-0.208885	5.297052	0.134392
H	0.256540	5.850781	0.950008
H	0.413213	5.348023	-0.762620
H	-1.199552	5.703775	-0.082919
O	-0.310663	3.938862	0.604670
O	-1.241559	3.366160	-1.374236
C	-2.905374	-1.379298	-0.540929
O	-3.785958	-0.941403	-1.269412
O	-2.918614	-2.644160	-0.057713
C	-4.066874	-3.445990	-0.400908
H	-4.129067	-3.580405	-1.483382
H	-3.906374	-4.405094	0.091486
H	-4.984654	-2.979603	-0.034622

Zero-point correction= 0.294416 (Hartree/Particle)
Thermal correction to Energy= 0.315746
Thermal correction to Enthalpy= 0.316691
Thermal correction to Gibbs Free Energy= 0.242081
Sum of electronic and zero-point Energies= -1070.499390
Sum of electronic and thermal Energies= -1070.478059
Sum of electronic and thermal Enthalpies= -1070.477115
Sum of electronic and thermal Free Energies= -1070.551725

	E (Thermal)	CV	S
	KCal/Mol	Cal/Mol-Kelvin	Cal/Mol-Kelvin
Total	198.134	77.399	157.030

imaginary frequency = -233.4835 cm-1



GS-2a **(16-Me')**

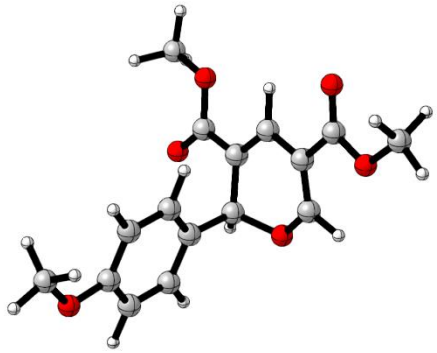
0			1
C	3.775132	-0.779354	-0.026893
C	3.319104	-1.845759	0.767671
C	1.974832	-2.177824	0.769660
C	1.032830	-1.441385	0.015246
C	1.515898	-0.400345	-0.798979
C	2.864577	-0.066639	-0.828114
H	4.034962	-2.400122	1.365707
H	1.630328	-3.006039	1.382234
H	0.834631	0.145105	-1.440624
H	3.199903	0.730680	-1.479502
O	5.104080	-0.525132	0.025258
C	5.628760	0.553325	-0.759378
H	5.176865	1.507381	-0.467122
H	6.698347	0.575791	-0.549102
H	5.468480	0.376045	-1.828371
C	-0.358092	-1.832587	0.092695
H	-0.517562	-2.870140	0.372693
C	-0.370098	1.369606	1.455636
H	-0.159961	2.360462	1.888334
C	-1.083489	1.393848	0.163022
C	-1.599121	0.306752	-0.480727
H	-2.260022	0.541160	-1.312123
C	-1.489724	-1.114101	-0.174528
O	-0.042887	0.357272	2.063617
C	-1.383581	2.715824	-0.464359
C	-1.233499	5.072754	-0.238346
H	-0.845737	5.763188	0.510222
H	-0.702861	5.196746	-1.185106
H	-2.303093	5.234502	-0.389758
O	-0.996658	3.754287	0.301693
O	-1.908695	2.861574	-1.557379
C	-2.802647	-1.812041	-0.251623
O	-3.856085	-1.236019	-0.491800
O	-2.732821	-3.138160	-0.025802

C	-3.986993	-3.852078	-0.033487
H	-4.461309	-3.779815	-1.014932
H	-3.729216	-4.887462	0.188485
H	-4.658236	-3.453857	0.731108

Zero-point correction= 0.294837 (Hartree/Particle)
Thermal correction to Energy= 0.317256
Thermal correction to Enthalpy= 0.318200
Thermal correction to Gibbs Free Energy= 0.240225
Sum of electronic and zero-point Energies= -1070.508704
Sum of electronic and thermal Energies= -1070.486285
Sum of electronic and thermal Enthalpies= -1070.485341
Sum of electronic and thermal Free Energies= -1070.563316

	E (Thermal)	CV	S
	KCal/Mol	Cal/Mol-Kelvin	Cal/Mol-Kelvin
Total	199.081	79.694	164.112

no imaginary frequencies



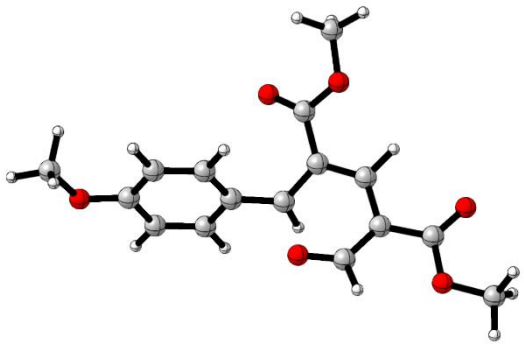
GS-1b (16-Me)

0			1
C	3.698019	-0.954132	-0.118130
C	3.622100	-0.464685	1.196924
C	2.439710	0.097186	1.659267
C	1.307388	0.187105	0.832563
C	1.398214	-0.296920	-0.475223
C	2.579447	-0.867017	-0.958002
H	4.498807	-0.527753	1.833661
H	2.391099	0.476350	2.676662
H	0.544333	-0.225187	-1.140746
H	2.615335	-1.229841	-1.977629
O	4.894917	-1.485778	-0.487560
C	5.029568	-1.991493	-1.818888
H	4.874506	-1.199560	-2.560468
H	6.052491	-2.362678	-1.892114
H	4.328870	-2.813862	-2.002813
C	0.028857	0.760511	1.395708
H	0.269752	1.464154	2.191753
C	-1.578197	-1.056118	1.460115
H	-1.844393	-1.969197	1.981789
C	-2.156496	-0.662310	0.287225
C	-1.876806	0.675488	-0.183963
H	-2.508281	1.095200	-0.957988
C	-0.883234	1.399553	0.377737
O	-0.691806	-0.323366	2.121770
C	-3.148987	-1.490333	-0.412487
C	-4.282141	-3.573988	-0.472843
H	-5.275998	-3.120684	-0.448019
H	-3.997354	-3.782308	-1.506863
H	-4.268734	-4.490762	0.116284
O	-3.314128	-2.705503	0.152114
O	-3.760841	-1.127371	-1.408001
C	-0.579747	2.792935	0.017999
O	0.292639	3.457588	0.563982
O	-1.353720	3.269052	-0.977599
C	-1.105200	4.631515	-1.380937
H	-1.278976	5.315610	-0.546790
H	-0.079498	4.742792	-1.740855
H	-1.813412	4.826987	-2.185903

Zero-point correction= 0.297997 (Hartree/Particle)
Thermal correction to Energy= 0.319068
Thermal correction to Enthalpy= 0.320012
Thermal correction to Gibbs Free Energy= 0.245733
Sum of electronic and zero-point Energies= -1070.519966
Sum of electronic and thermal Energies= -1070.498895
Sum of electronic and thermal Enthalpies= -1070.497951
Sum of electronic and thermal Free Energies= -1070.572229

	E (Thermal)	CV
S		
	KCal/Mol	Cal/Mol-Kelvin
Cal/Mol-Kelvin		
Total	200.218	77.039
156.332		

no imaginary frequencies



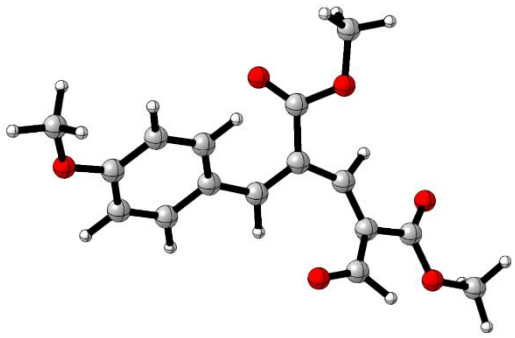
TS-1b

0			1
C	4.274555	-0.901723	0.090798
C	3.603244	-1.548710	1.144505
C	2.241870	-1.360846	1.308269
C	1.515610	-0.501372	0.454300
C	2.201457	0.122088	-0.605453
C	3.561672	-0.071643	-0.796132
H	4.167079	-2.194237	1.809581
H	1.722612	-1.870019	2.115250
H	1.658473	0.753478	-1.299462
H	4.059941	0.416353	-1.624136
O	5.601013	-1.142774	-0.000102
C	6.347896	-0.511099	-1.049297
H	6.296283	0.579454	-0.964783
H	7.378162	-0.840760	-0.913940
H	5.986812	-0.828607	-2.033159
C	0.095367	-0.353828	0.658476
H	-0.312917	-0.990921	1.439003
C	-1.939559	-1.659840	-0.591755
H	-2.482048	-2.408723	-1.179652
C	-2.698225	-0.622400	0.010178
C	-2.081024	0.629211	0.237617
H	-2.724953	1.501934	0.218868
C	-0.710810	0.806237	0.352136
O	-0.679848	-1.737274	-0.600343
C	-4.166332	-0.682920	0.022088
C	-6.083414	-2.027297	-0.376684
H	-6.485234	-1.880861	0.628854
H	-6.540268	-1.309894	-1.062818
H	-6.271503	-3.046401	-0.714808
O	-4.649199	-1.884857	-0.374386
O	-4.896956	0.234209	0.377253
C	-0.133887	2.166426	0.308661
O	0.974834	2.489771	0.711721
O	-1.007586	3.069496	-0.198178
C	-0.594285	4.449133	-0.144900
H	-0.420145	4.759132	0.888667
H	0.315242	4.600646	-0.731181
H	-1.421151	5.014078	-0.575490

Zero-point correction= 0.295121 (Hartree/Particle)
Thermal correction to Energy= 0.316204
Thermal correction to Enthalpy= 0.317148
Thermal correction to Gibbs Free Energy= 0.243400
Sum of electronic and zero-point Energies= -1070.498414
Sum of electronic and thermal Energies= -1070.477331
Sum of electronic and thermal Enthalpies= -1070.476387
Sum of electronic and thermal Free Energies= -1070.550135

	E (Thermal)	CV
S		
	KCal/Mol	Cal/Mol-Kelvin
Cal/Mol-Kelvin		
Total	198.421	76.867
155.216		

imaginary frequency = -248.8410 cm-1



GS-2b (16-Me')

0			1
C	4.506381	-0.886944	0.136718
C	3.733067	-1.809389	0.865170

C	2.360983	-1.649967	0.935459
C	1.710669	-0.551628	0.320653
C	2.504336	0.347084	-0.422025
C	3.879340	0.187287	-0.522080
H	4.227943	-2.643907	1.350753
H	1.765986	-2.375201	1.483164
H	2.040793	1.167630	-0.954641
H	4.453878	0.889021	-1.113290
O	5.837410	-1.119744	0.109161
C	6.678251	-0.225209	-0.632499
H	6.614551	0.792981	-0.234581
H	7.692309	-0.605067	-0.506810
H	6.413496	-0.229741	-1.695223
C	0.274480	-0.476674	0.427408
H	-0.195211	-1.417042	0.684245
C	-2.432987	-1.759568	-0.935023
H	-3.271025	-2.210451	-1.490584
C	-2.824032	-0.624486	-0.086919
C	-2.017493	0.423271	0.299925
H	-2.573298	1.290519	0.647580
C	-0.587949	0.587128	0.275806
O	-1.295986	-2.191257	-1.114231
C	-4.278086	-0.431374	0.184596
C	-6.449663	-1.369244	-0.012779
H	-6.655801	-1.304185	1.058070
H	-6.861210	-0.494805	-0.522118
H	-6.871817	-2.284609	-0.426969
O	-5.028606	-1.465841	-0.247265
O	-4.760055	0.533779	0.759757
C	-0.119824	2.009214	0.271091
O	0.839781	2.449770	0.880550
O	-0.937423	2.787298	-0.467722
C	-0.646472	4.202362	-0.471279
H	-0.700797	4.604347	0.543062
H	0.346480	4.385009	-0.888651
H	-1.413236	4.652284	-1.101339

Zero-point correction= 0.294854 (Hartree/Particle)
Thermal correction to Energy= 0.317265
Thermal correction to Enthalpy= 0.318209
Thermal correction to Gibbs Free Energy= 0.239148
Sum of electronic and zero-point Energies= -1070.506576
Sum of electronic and thermal Energies= -1070.484165
Sum of electronic and thermal Enthalpies= -1070.483221
Sum of electronic and thermal Free Energies= -1070.562281

	E (Thermal)	CV	S
	KCal/Mol	Cal/Mol-Kelvin	Cal/Mol-Kelvin
Total	199.087	79.613	166.397

no imaginary frequencies

5. Curriculum Vitae

PERSONAL DATA	
Name	Nikolai Wurzer
Date and place of birth	[redacted]
Nationality	German
E-mail	[redacted]

EDUCATION	
10/2018 – 09/2021	**PhD Thesis** at the University of Regensburg under the supervision of Prof. Dr. Oliver Reiser *"Palladium-catalyzed ring opening of fused bicyclic vinyl-cyclopropanes"*
09/2018	**Graduation**: Master of Science
06/2018 – 08/2018	**Research Project** at Emory University in Atlanta, GA, USA under the supervision of Prof. Dr. Huw M. L. Davies "*Rh(II)-Catalyzed Monocyclopropanation of Pyrroles and Its Application to the Synthesis Pharmaceutically Relevant Compounds*"
01/2016 – 09/2018	**Master Thesis** at the University of Regensburg under the supervision of Prof. Dr. Oliver Reiser "*Palladium-catalyzed ring-opening of cyclopropanated furans and enantioselective cyclopropanation of pyrroles*"
10/2016 – 09/2018	**Studies in Chemistry (M. Sc.)**, University of Regensburg
07/2016	**Graduation:** Bachelor of Science
04/2016 – 05/2016	**Bachelor Thesis** at the University of Regensburg under the supervision of Prof. Dr. Oliver Reiser "*Cyclopropanierung von Heterozyklen und deren Anwendung für die Synthese eines Homo-β-Prolin-Derivates*"
09/2013 – 07/2016	**Studies in Chemistry (B. Sc.)**, University of Regensburg
09/2005 – 06/2013	[redacted]

AWARDS AND SCHOLARSHIPS

04/2019 – 03/2021	Kekulé fellowship for PhD candidates Stiftung Stipendien-Fonds des Verbandes der chemischen Industrie e.V.
06/2017	Graduation award of the Dr. Alfons Paulus foundation for best bachelor graduation

LIST OF PUBLICATIONS

- **N. Wurzer**, U. Klimczak, T. Babl, S. Fischer, R. A. Angnes, D. Kreutzer, A. Pattanaik, J. Rehbein*, Oliver Reiser***,** *ACS Catal.* **2021**, *11*, 12019 - 12028: "*Heck-Type Coupling of Fused Bicyclic Vinylcyclopropanes: Synthesis of 1,2-Dihydropyridines, 2,3-Dihydro-1H-azepines, 1,4-Cyclohexadienes, and 2H-Pyrans*" (doi:10.1021/acscatal.1c02564).
- J. Fu†, **N. Wurzer**†, V. Lehner, O. Reiser*****, H. M. L. Davies*****, *Org. Lett.* **2019**, *21*, 6102 – 6106: "*Rh(II)-Catalyzed Monocyclopropanation of Pyrroles and Its Application to the Synthesis of Pharmaceutically Relevant Compounds*" (†shared first authorship; doi:10.1021/acs.orglett.9b02250).
- J. Yedoyan, **N. Wurzer**, U. Klimczak, T. Ertl, O. Reiser*, *Angew. Chem. Int. Ed. Engl.* **2019**, *58*, 3594 – 3598: "*Regio- and Stereoselective Synthesis of Functionalized Dihydropyridines, Pyridines and 2H-Pyrans: Heck Coupling of Monocyclopropanated Heterocycles"* (doi:10.1002/anie.201813716).

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Weiterhin möchte ich mich bei [redacted] bedanken, der mit seiner Expertise über Synthesen, praktisches Arbeiten und Technik immer eine große Unterstützung war. Auch gilt mein Dank den technischen Angestellten [redacted] und [redacted] für ihre tatkräftige Unterstützung bei der Synthese von Startmaterialien im großen Maßstab, beim Trocknen von Lösemitteln, sowie HPLC Messungen.

Auch möchte ich den Mitarbeitern der zentralen Analytik [redacted] und [redacted] für die Hilfe bei der Aufnahme von NMR Spektren und der Durchführung von Massenspektroskopien danken. Besonders den Mitarbeitern der Röntgenstrukturanalyse [redacted] und [redacted] möchte ich dafür danken, dass sie immer stets bemüht waren die perfekten Einkristalle in meinen zahlreichen Proben zu finden.

Auch möchte ich mich bei meinen Laborkollegen [redacted] und [redacted] für angenehme Arbeitsatmophäre bedanken. Auch den restlichen Mitarbeiten des Arbeitskreises [redacted] und [redacted] möchte ich für die angenehme und entspannte Arbeitsatmosphäre danken.

Gleicher Dank gilt auch unseren ehemaligen Mitarbeitern und Gästen [redacted]

und [redacted]

Für die fachliche Unterstützung und zahlreiche anregende Diskussionen möchte ich mich auch bei unseren äußerst talentierten Post-Docs [redacted] und [redacted] bedanken.

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Abschließend möchte ich mich von ganzen Herzen bei meiner Familie und meinen Freunden, von welchen ich seit jeher Rückhalt und bedingungslose Unterstützung erfahren habe, bedanken!

H. Declaration

Herewith I declare that this present thesis is a presentation of my original work prepared single-handed. Wherever contributions from others are involved, all of them are marked clearly, with reference to the literature, license, and acknowledgment of collaborative research.

Regensburg, December 9th, 2021

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Nikolai Wurzer