Ring-opening of monocyclopropanated *N*-Boc-pyrroles

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Für meine Mama und Papa

„I dream of painting and then I paint my dream "

Vincent Van Gogh

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Abbreviations

Å	angstrom	EtOAc	ethyl acetate
Ac	acetyl	g	gram(s)
ACN	acetonitrile	GABA	γ-aminobutyric acid
AIBN	aza-*iso*butyronitrile	h	hour(s)
Ar	aryl	HPLC	high-performance liquid
atm.	Atmosphere	HRMS	high-resolution mass spectrometry
Boc	*tert*-butoxycarbonyl	Hz	Hertz
brine	saturated NaCl solution	*iPr*	*iso*-propyl
Bu	butyl	IR	infrared
BuLi	butyl lithium	L	liter; ligand
°C	degrees Celsius	M	molar
calcd.	calculated	μ	micro
cm^{-1}	wavenumber(s)	max	maximum
d	day(s)	Me	methyl
DBU	1,8-diazabicyclo [5.4.0] undec-7-ene	MeOH	methanol
DCM	dichloromethane	MHz	megahertz
DMF	dimethyl formamide	min	minute(s)
DMS	dimethyl sulfide	mL	milliliter
DMSO	dimethylsulfoxide	mm	millimeter
d.r.	diastereomeric ratio	mmol	millimole(s)
ed.	edition	mp	melting point
EDG	electron-donating group	Ms	mesyl
ee	enantiomeric excess	NBS	*N*-bromosuccinimide
e.g.	*exempli gratia*, for example	NMR	nuclear magnetic resonance
eq	equation	Nu	nucleophile
equiv	equivalent(s)	n.d.	not detected
ESI	electrospray ionization	PG	protection group
Et	ethyl	pH	proton log units
et al.	and others (co-authors)	Ph	phenyl
etc.	etcetera	ppm	part per million
Et_3N	trimethylamine	Piv	pivaloyl
EWG	electron-withdrawing group	PE	petroleum ether

quant	quantitative
rac	racemic
R_f	retention factor (in chromatography)
r.t	room temperature
sat.	saturated
*t*Bu	*tert*-butyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	tri*iso*propylsilyl
TLC	thin layer chromatography
TON	turnover number
TOF	turnover frequency
t_R	retention time
Ts	tosyl
vs	versus
UV	ultraviolet
wt%	weight percent

A. Introduction

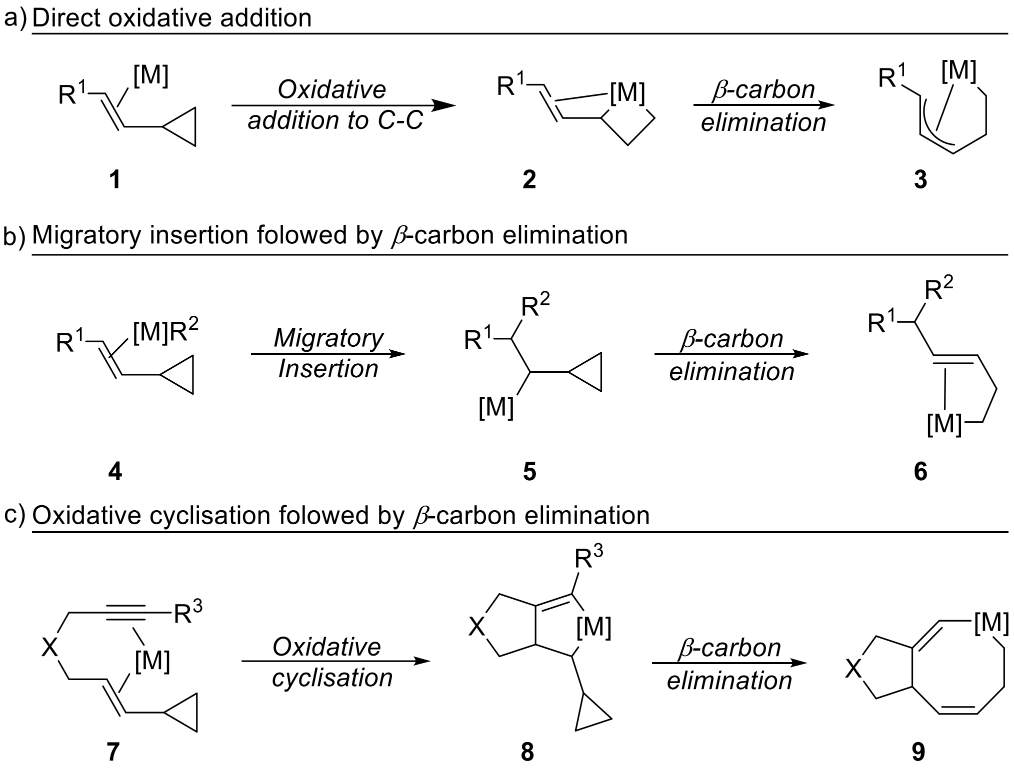
1. Introduction: Transition-metal-catalyzed ring-opening of non-activated vinyl cyclopropanes

Vinylcyclopropanes (VCPs) are not only important structural elements that constitute the skeleton of many biologically active and drug-related compounds,[1–4] but also one of the most versatile building blocks in organic synthesis.[5–7] Over the past few decades, VCPs have been successfully employed to develop various synthetic methodologies and to access complex targets in total synthesis.[8–15]

In general, VCPs can undergo different types of rearrangement processes: a) ring-opening;[16,17] b) *cis–trans* isomerization;[18–23] c) ring-expansion to generate cyclopentenes or methylcyclobutenes.[24–30] These transformations can proceed through thermal, photochemical, or catalytic pathways.[7,31] The driving force for ring opening of VCPs is the strain relief associated with the three-membered ring fragmentation.[32] The unique reactivities of VCPs also arise from both the high *p*-character of C–C σ-bonds of the cyclopropane ring and the overlap of these σ-bonds with the π-orbitals of the vinyl group.

A donor-acceptor substitution pattern along the vinylcyclopropane moiety, i.e. activated VCPs, greatly facilitates the ring-opening of the cyclopropanes. This strategy was broadly exploited in organic synthesis.[32] However, transition-metal catalysis[33–36] offers a powerful technique to achieve ring opening chemistry also for non-activated VCPs.[3–5] The development of transition-metal-catalyzed methodologies that allow highly selective C–H or C–C bond cleavage of VCPs is therefore a conceptually most intriguing, but underexplored area in synthetic organic chemistry.[37] In this chapter, we will discuss the ring opening of non-activated vinylcyclopropanes catalyzed by transition metals, such as palladium,[38–47] zirconium,[48–50] platinum,[51] iron,[52–55] gold,[56–60] rhodium,[61–81] ruthenium,[61,82–86] nickel [37,87–89] and cobalt. [92]

The fundamental mechanistic pathways for ring-opening reactions catalyzed by metal complexes are illustrated in Scheme 1. Direct oxidative addition of a metal to the C-C cyclopropane bond constitutes the most direct approach for ring-opening (Scheme 1 a). This approach can deliver metalacyclobutanes **2** or σ-alkyl π-allyl complexes **3**. Another approach to achieve such a C-C bond activation is via migratory insertion of a metal complex onto the VCP alkene moiety leading to **4**, followed by a formal [1,3] metal migration with concurrent C-C-bond cleavage to give rise to an α-cyclopropyl organometallic species **5**. In a similar fashion, the oxidative cyclization of an alkene alkyne complex **7** to a metallacyclopentene **8** also sets the stage for cyclopropane bond cleave via a *β*-carbon elimination, which results in an intermediate **9** (Scheme 1 c).

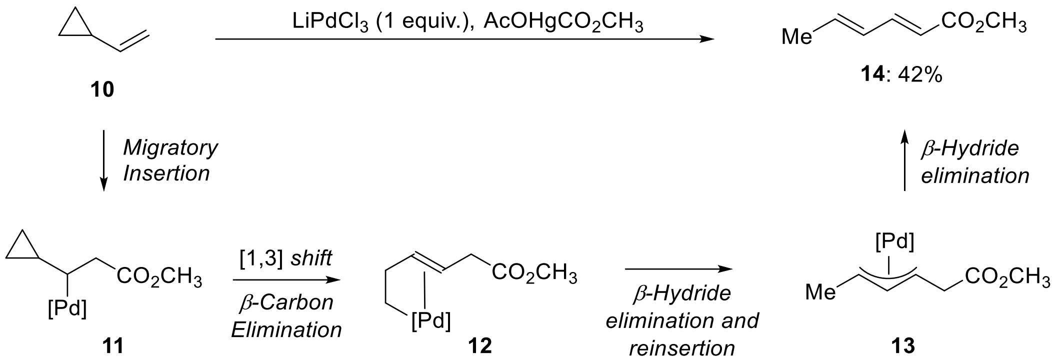


M= Pd, Zr, Pt, Fe, Au, Rh, Ru, Ni

Scheme 1. Mechanistic pathways of transition-metal-catalyzed ring opening of non-activated vinyl cyclopropanes.

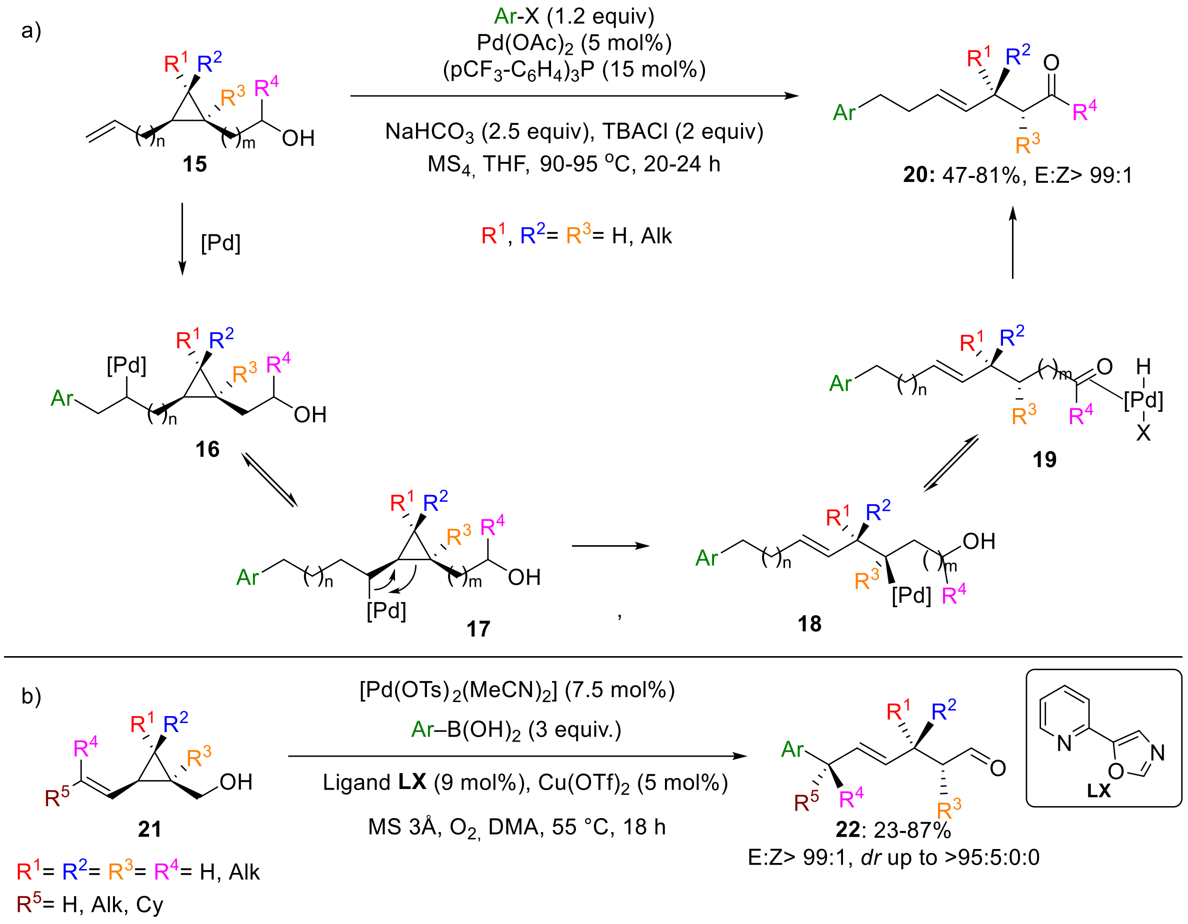
Palladium-Catalyzed Reactions.

Selective ring opening of VCPs mediated by transition-metal "chain-walking" is mostly dominated by the utilization of palladium complexes.[38–46] Pioneering work in this area was done by Heck and Fischetti who reported the synthesis of diene **14** via ring-opening carboesterification of non-activated VCP **10** (Scheme 2).[38] The proposed mechanism for this reaction involves transmetalation of the methoxycarbonyl group of $AcOHgCO_2CH_3$ to a $[Pd^{II}]$ species followed by migratory insertion with VCP **10**. The resulting α-cyclopropyl-organopalladium **11** undergoes a *β*-carbon elimination delivering a primary alkyl palladium **12** which upon *β*-hydride elimination and hydride insertion to the terminal position rearranges to the allyl palladium complex **13**. Through a final *β*-hydride elimination of this complex the diene **14** was obtained in 42% yield.



Scheme 2. Early evidence of palladium-catalyzed ring-opening reactions of VCP and "chain-walking".

Moving to a catalytic manifold, efforts have been subsequently devoted to exploit the ability of palladium to migrate over the hydrocarbon chain to build up complex structures.[38–42] Marek and co-workers developed an elegant approach to access diverse open-chain molecules by palladium-catalyzed Mizoroki–Heck intermolecular arylation of vinyl substituted cyclopropanes **15**. Notably, the homologues with a remote alkene moiety could also be employed (Scheme 3 a).[42] Mechanistic studies suggested that the reaction is initiated by the migratory insertion of ArPdX to the terminal olefin upon which a series of β-hydride elimination and reinsertion events take place to arrive at the organopalladium complex **17**, at which point the Pd-migration with concurrent C–C ring opening delivers **18**. The chain walking process then resumes until the strategically placed hydroxyl group can terminate the reaction by β-hydride elimination to yield thermodynamically favored carbonyl compound **19**.

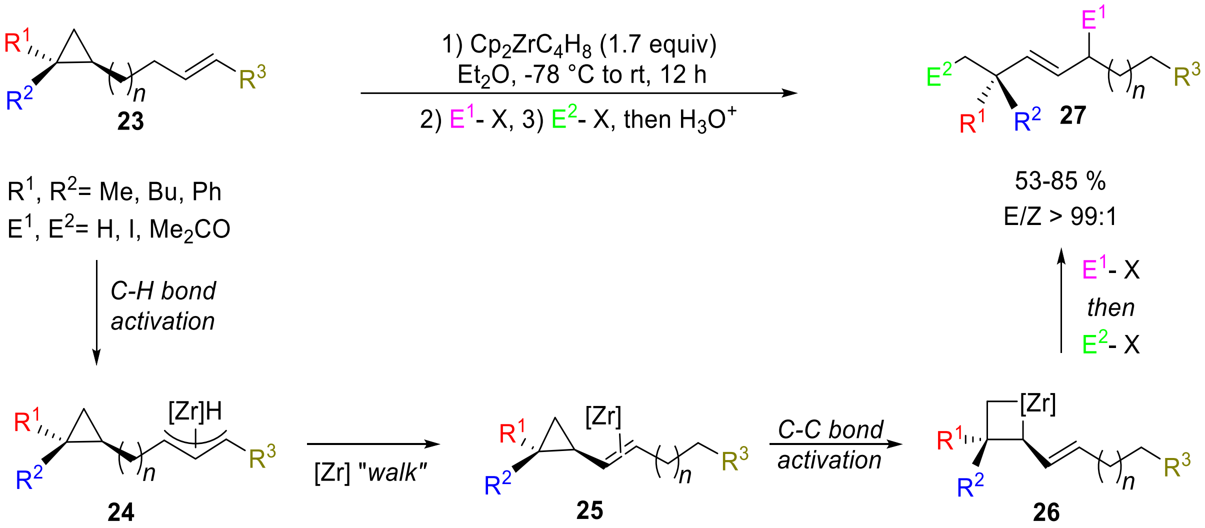


Scheme 3. The ring opening of VCPs triggered by palladium chain walk process.

In 2018, the same group reported a related palladium-catalyzed oxidative Heck reaction. Hydroxyl directed migratory insertion arylpalladium intermediates into VCP **21** followed by *β*-carbon elimination and chain walking mechanism afforded products **22** with high regio and diastereoselectivity (Scheme 3b).[43] The reaction showed high functional group tolerance delivering desired products in moderate to good yields.

Stoichiometric Zirconium-mediated Reactions.

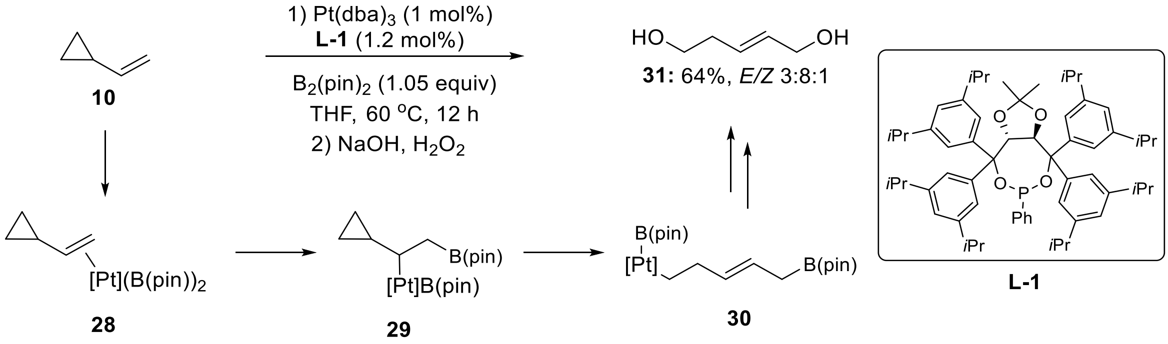
The C–C combied with a C–H-bond activation of VCPs is possible through stoichiometric zirconocene complexes (Scheme 4).[48–50] One such example was reported by Marek and co-workers in 2013, in which the overall process involves a ring-opening difunctionalization of VCPs using two distinct electrophiles. The reaction is initiated via an allylic C–H-insertion by zirconocene, upon which a zirconium walk from **24** to **25** occurs. For here, a direct oxidative addition into the proximal cyclopropane C–C bond to give the zirconacyclobutane **26** takes place, which undergoes a sequential reaction with two electrophiles starting at the allylic position. Overall the products **27** are obtained with excellent regio and diastereoselectivity.



Scheme 4. Zirconium-mediated selective C–C ring opening of cyclopropanes.

Platinum-Catalyzed Reactions.

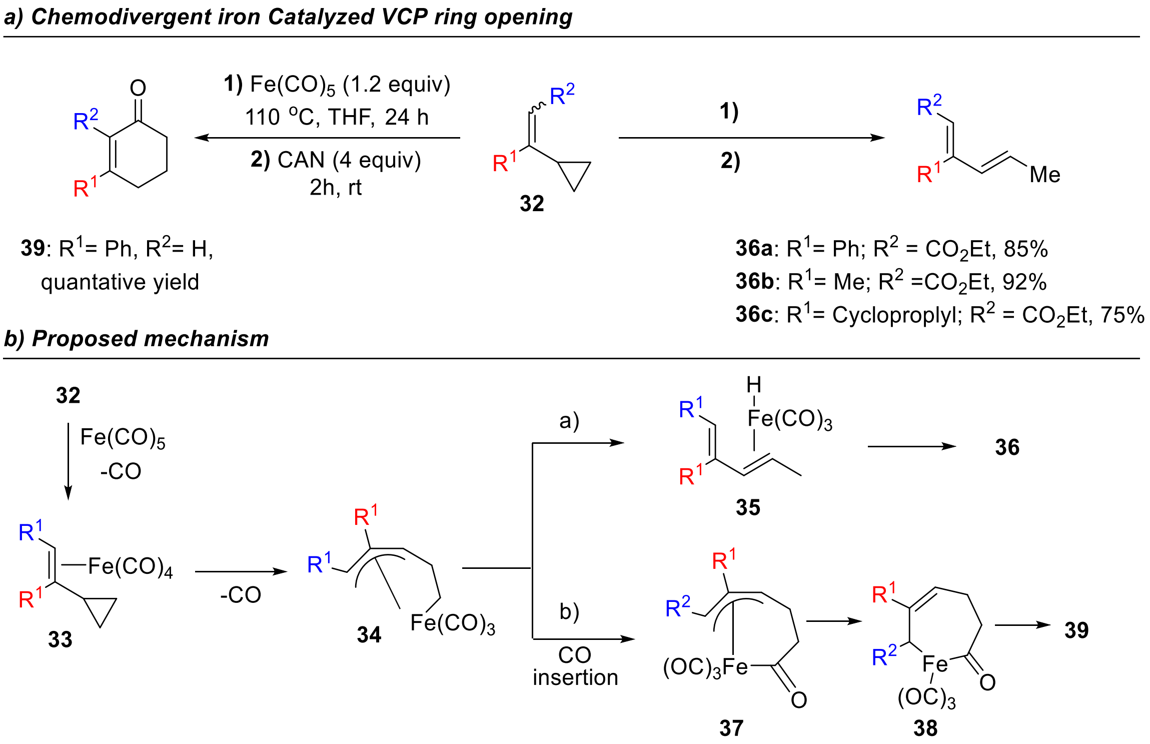
While studying platinum-catalyzed enantioselective diborylations of alkenes and, Moken and co-workers also investigated this reaction with VCP **10**.[51] After workup with hydrogen peroxide under basic conditions the diol **31** was obtained, suggesting the intermediacy of the *α*-cyclopropyl organoplatinum complex **29**, which, analogous to palladium, undergoes a *β*-carbon elimination to afford the primary alkyl platinum complex **30**. The latter undergoes a reductive elimination to afford the diborylated product which is subsequently oxidized to the corresponding diol **31**.



Scheme 5. Platinum-catalyzed enantioselective ring-opening of VCPs.

Stoichiometric Iron-Mediated Reactions.

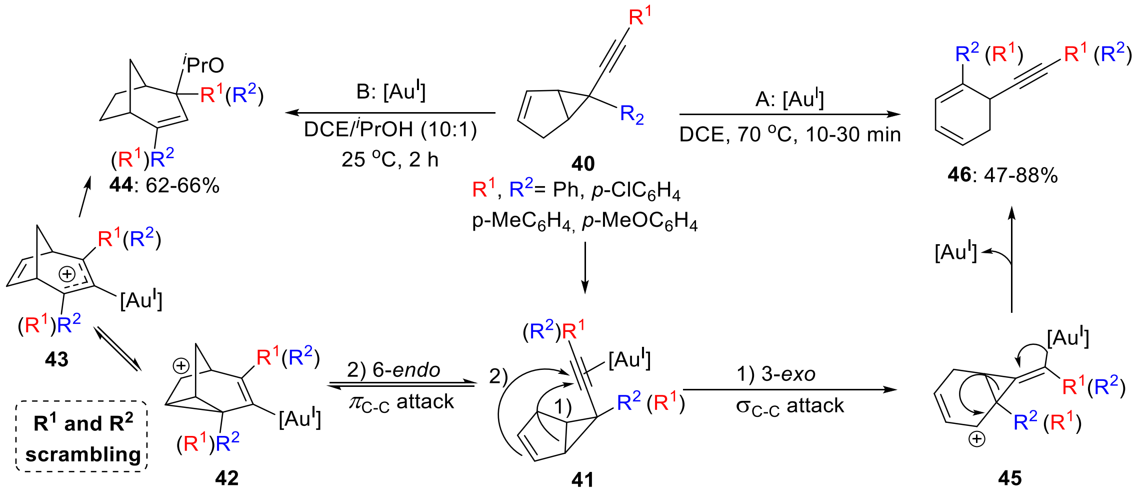
Schulze and co-workers presented iron-mediated ring-opening of non-activated VCPs leading to either *α,β*-unsaturated ketones or conjugated dienes (Scheme 6).[52] The nature of this chemodivergent transformation was mainly influenced by the electronic properties of the alkene moiety of VCPs **32**. Thus, when electron poor alkenes were employed the VCP ring opening led to conjugated dienes **36** (Scheme 6b). Conversely, electron neutral alkenes led to the formation of *α*, *β*-unsaturated ketones **39**. The postulated mechanism for this reaction starts CO dissociation and direct oxidative addition to the cyclopropyl C–C bond leading to the σ-alkyl π-allyl complex **33**. Depending upon on the electronic nature of the π-allyl moiety, the mechanism diverges to either one of the following two mechanisms: a) for electron withdrawing substituents at the π-allyl **35**, the reaction proceed through *β*-hydride elimination affording the corresponding conjugated diene **36**; b) for electron neutral substituents at the π-allyl, the reaction proceeds through a CO insertion and reductive elimination to afford a *β*,*γ*-unsaturated ketone which isomerizes *in situ* to the corresponding *α*,*β*-unsaturated one **39**.



Scheme 6. Iron-promoted ring-opening of non-activated VCPs.

Gold-Catalyzed Reactions.

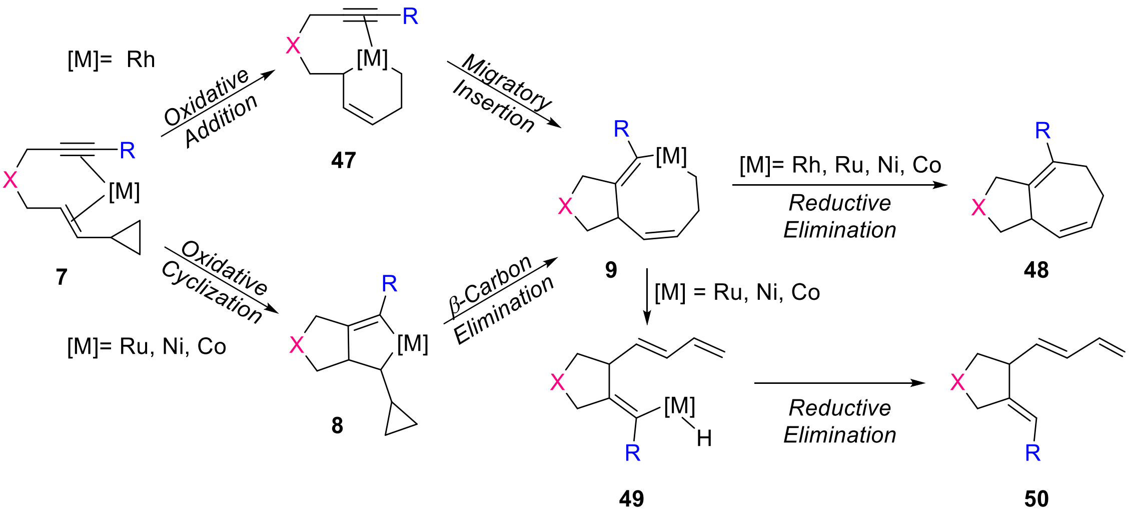
In 2011, Barluenga and co-workers reported a gold(I)-catalyzed, chemodivergent, ring-opening reaction of alkynylcyclopropanes **40** (Scheme 7).[58] In the absence of an alcohol as a cosolvent, the selective cleavage of the non-activated C–C bond resulted in the formation of alkynylcyclohexadienes **46** in 47–88% yield. On the other hand, when an alcohol was added the bicyclic compounds **44** were obtained instead. Curiously, the reaction led to scrambling between the substituents R^1 and R^2 employed in the starting material on both products **44** and **46**. The mechanistic rationale for this reaction started with the coordination of [Au^I] species to form **41**. This intermediate scrambles R^1 and R^2 via a reversible 6-*endo-dig* cyclisation and cation rearrangement (**42** and **43**). In the absence of an alcohol, the reaction proceeds through an irreversible 3-*exo-dig* nucleophilic attack of the $\sigma_{C–C}$ bond connecting the two bridgehead carbons of the bicycle. The ring opening of non-activated C–C bond results on the formation of intermediate **45**, which eliminates [Au^I] leading to the dihidrobenzenes **46**. If, however, an alcohol is used as cosolvent, the cationic intermediates **42** are trapped and, upon protodemetallation of the resulting alkenylgold(I) complex, lead to the formation of the bicyclic compounds **44**.



Scheme 7. Gold (I)-catalyzed ring-opening of VCPs.

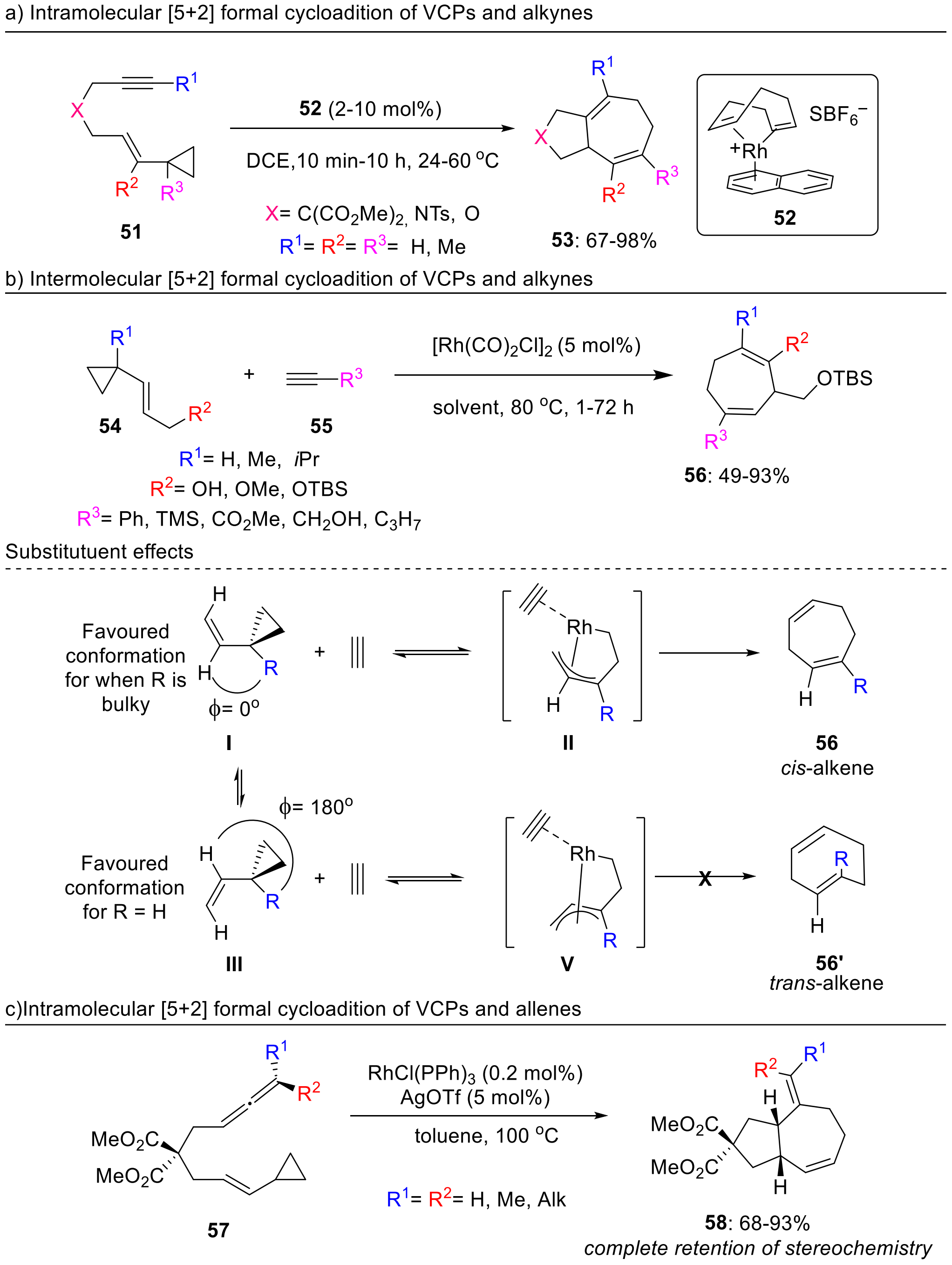
Rhodium-, Ruthenium-, Nickel and Cobalt-Catalyzed Reactions.

Perhaps the most popular application of VCPs is on rhodium catalyzed formal cycloaddition reactions.[90] In 1995, Wender and co-workers reported the first such rhodium catalyzed ring-opening [5+2]-intramolecular cycloaddition of VCPs and alkynes.[61] This versatile strategy was since extended to other systems and found application in total synthesis of natural products.[63] Some of these developments will be herein discussed to illustrate modern implementations thereof.[62–64,66–70] The general mechanistic picture of ring opening and subsequent cycloaddition for these reactions is illustrated in Scheme 8. Coordination of VCPs and alkynes to the transition metal can lead to either direct C–C activation via oxidative addition (**47**) or oxidative cyclization leading to an α-cyclopropyl organometalic species (**8**). Regardless of the first step, the same metalacyclooctadiene **9** is achieved on the second step, through either *β*-carbon elimination in the case of **8** or migratory insertion in the case of **47**. The metallacyclooctadiene **9** can then follow two mechanistic pathways: reductive elimination, affording cycloheptadienes **48**, or *β*-hydride elimination affording an alkylmetalhydride **49** that delivers the corresponding triene **50** upon reductive elimination.



Scheme 8. Different mechanistic routes of ring-opening processes delivering cycloadducts and dienes.

In 2002, Wender developed a general procedure for rhodium-catalyzed ring-opening and subsequent [5+2]-cycloaddition of non-activated VCPs delivering multifunctionalized hexahydroazulenes and heterocyclic derivatives thereof (Scheme 9a).[64] In comparison with other rhodium catalysts like the Wilkinson's catalyst ($[RhCl(PPh_3)_3]$), where longer time and



a) Intramolecular [5+2] formal cycloadition of VCPs and alkynes

b) Intermolecular [5+2] formal cycloadition of VCPs and alkynes

Substitutuent effects

c)Intramolecular [5+2] formal cycloadition of VCPs and allenes

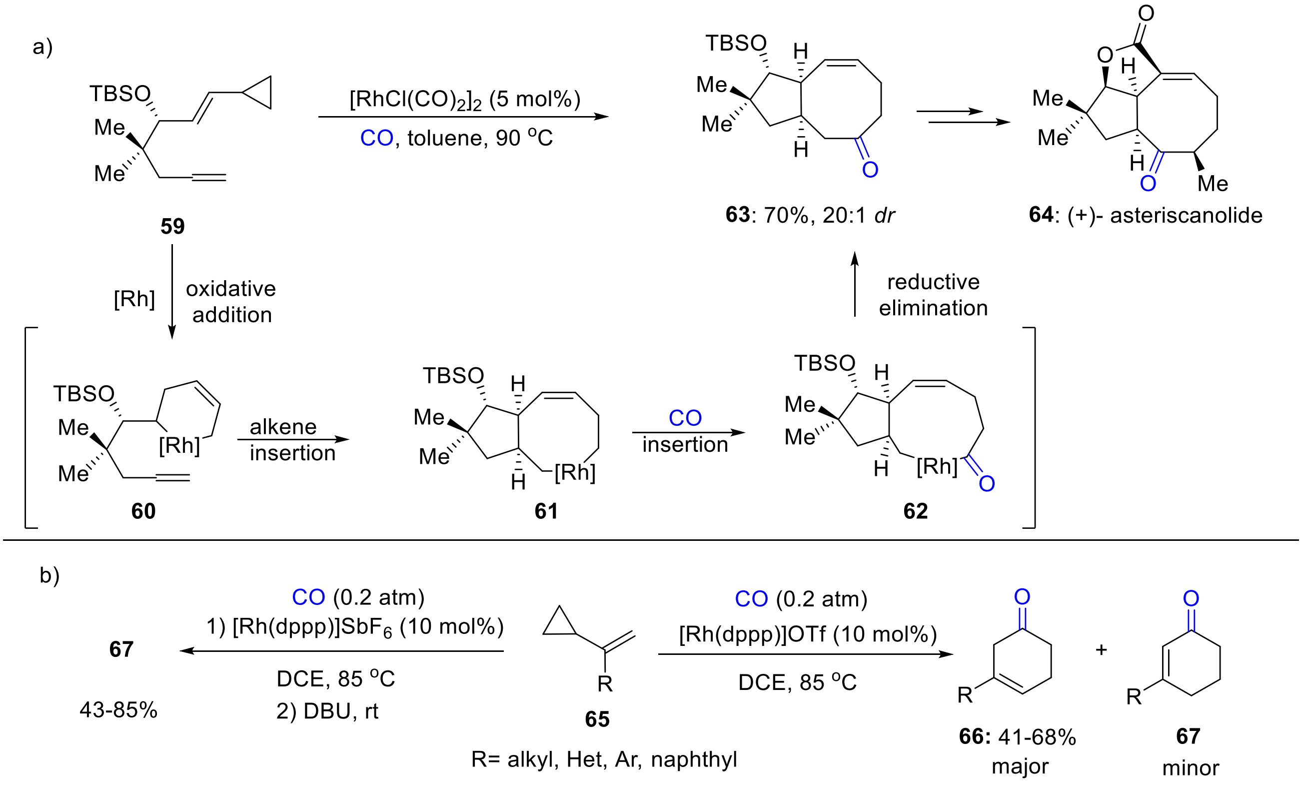
Scheme 9. The inter- and intramolecular [5+2]-cycloadditions of VCPs with different π-systems.

harsher reaction condition was required, **52** was found the most general and powerful rhodium complex for inter- and intramolecular [5+2]-transformations, providing the desired product **53** in excellent yields.

The same group reported the intermolecular [5+2]-transformation of non-activated VCPs with different alkynes in the presence of $[Rh(CO)_2Cl]_2$ providing cycloheptadiene **56** in 49–93% yields (Scheme 9b).[66] Curiously, unsubstituted VCPs required longer reaction time and delivered reduced yields in this transformation, when compared to VCPs containing a quaternary carbon. This was attributed to steric effects that destabilize conformation **I** over **III** (Scheme 9b). This facilitates the C–C bond cleavage that leads to the *Z*-allyl intermediate **II**, which, as opposed to the E-allyl intermediate **IV**, is able to deliver the desired cyclodienes **56**.

Wender and co-workers also presented intramolecular [5+2]-cycloadditions between vinyl cyclopropanes and allenes, using Wilkinson's catalyst (Scheme 9c).[67,68] The *cis* fused system **58** were formed as major in 68-93% yield. Moreover, cycloaddition of chiral allenes proceeded with complete axial to central chirality transfer.

In 2007, Yu and co-workers presented the rhodium-catalyzed [5+2+1]-cycloaddition reaction of VCPs and CO (Scheme 10a).[72] The oxidative addition of the rhodium(I)-catalyst onto **59** generated rhodacyclohexene intermediate **60**. The subsequent migratory insertion



Scheme 10. Rhodium-catalyzed [5+2+1] and [5+1] cycloaddition of VCPs with CO.

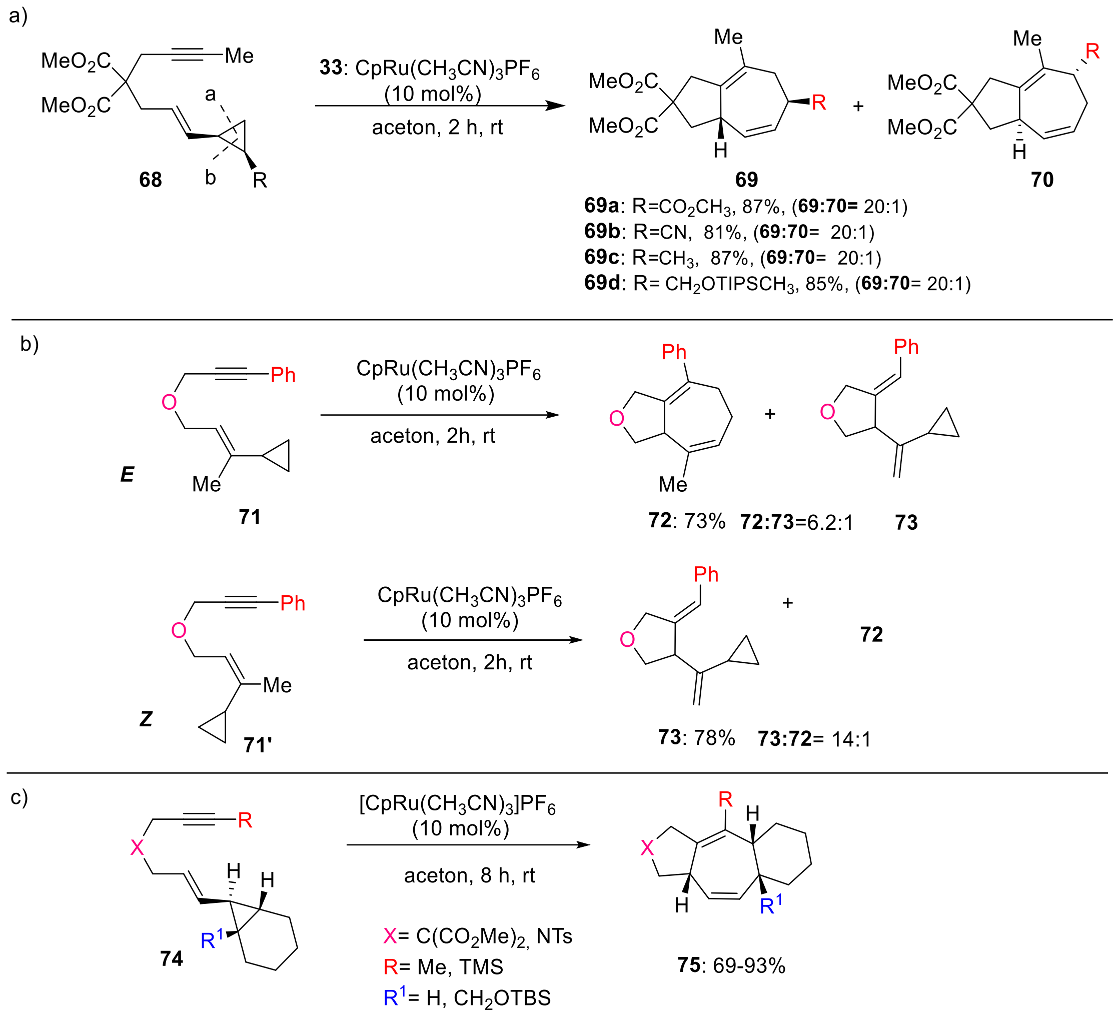
into the alkene moiety led to **61**. Next, the CO insertion process formed the intermediate **62**. Finally, reductive elimination of **63** resulted on the 8-membered heterocyclic compound **63** in high diastereosselectivity (20:1). The reaction scope employed various substituted VCPs demonstrating high functional group tolerance. This two component rhodium-catalyzed reaction is now widely employed in total synthesis to deliver complex natural products like (+)-asteriscanolide **64.**[77]

In 2011, the same group reported rhodium-catalyzed [5+1] cycloaddition of non-activated VCP **65** and CO (Scheme 10b).[78] The cycloaddition of VCPs in the presence of [Rh(dppp)]OTf catalyst delivered a mixture of regioisomers **66** and **67**, where **60** was identified as a major product in 41–68% yields. On the other hand, the selective ring-opening and [5+1]-cycloaddition could also be employed on the synthesis of **67** when [Rh(dppp)]SbF$_6$ was used as catalyst and the reaction was further treated with DBU. In this case, high yields and selectivities could be obtained.

Ruthenium-catalyzed formal [5+2]-cycloadditions of VCPs are efficient routes for natural product synthesis offering short and atom-economical ways to deliver complex polycyclic structures with excellent yields and stereo and regiocontrol.[61,82,83,85,86] Trost and co-workers reported one such reaction in high yields, regio- and diastereoselectivity (Scheme 11a).[82] The mechanistic proposal for this reaction involves oxidative cyclization followed by *β*-carbon elimination (Scheme 8). Both electronic and steric factors influenced the selective ring-opening of the cyclopropyl ring. *Cis*-cyclopropanes bearing electron-withdrawing substitution led to **69** as a single isomer. In contrast, *trans*-cyclopropanes delivered mixture of the two isomers **69** and **70**.

When different diastereoisomers were applied to the ruthenium-catalyzed [5+2]-cycloaddition of Scheme 11 b, contrasting results have been observed. Cycloaddition product **72** was obtained in 73% yield, when *E* isomer was employed. In contrast, the use of *Z* olefin provided diene **73** as a major product in 78% yield.

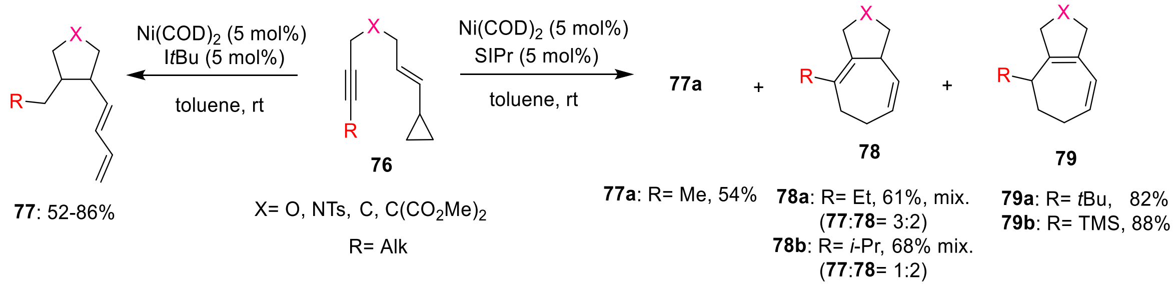
The construction of fused tricyclic seven membered ring **75** was reported utilizing the same ruthenium catalyzed [5+2]-cycloaddition methodology (Scheme 11c). Despite of the steric hindrance on the cyclopropyl ring, the tryclyclic products were obtained in good to excellent yields and diastereoselectivity.[82]



Scheme 11. Ruthenium-catalyzed intramolecular [5+2]-cycloadditions of VCPs.

In 2004, Louie reported the nickel-catalyzed ring-opening of non-activated VCPs **76** furnishing various heterocyclic adducts (Scheme 12).[87] The selective, high yielding, preparation of cyclopentadienes **77** was achieved in the presence of 1,3-di-tertbutylimidazolidene (I*t*Bu). In addition, striking steric effects of the alkynyl substitution, R in **41**, in the presence of bulky ligand (SIPr) were observed. Thus, if a sterically unhindered alkyne is employed, like when R = Me in **76**, cyclopentane **77a** was observed. On the other hand, a mixture of **77** and **78** was obtained after introducing more sterically hindered groups like Et or ^{i}Pr in the substrate **76**. Finally, a large group substitution on alkynyl led to sole bicyclic seven-membered ring **79**.

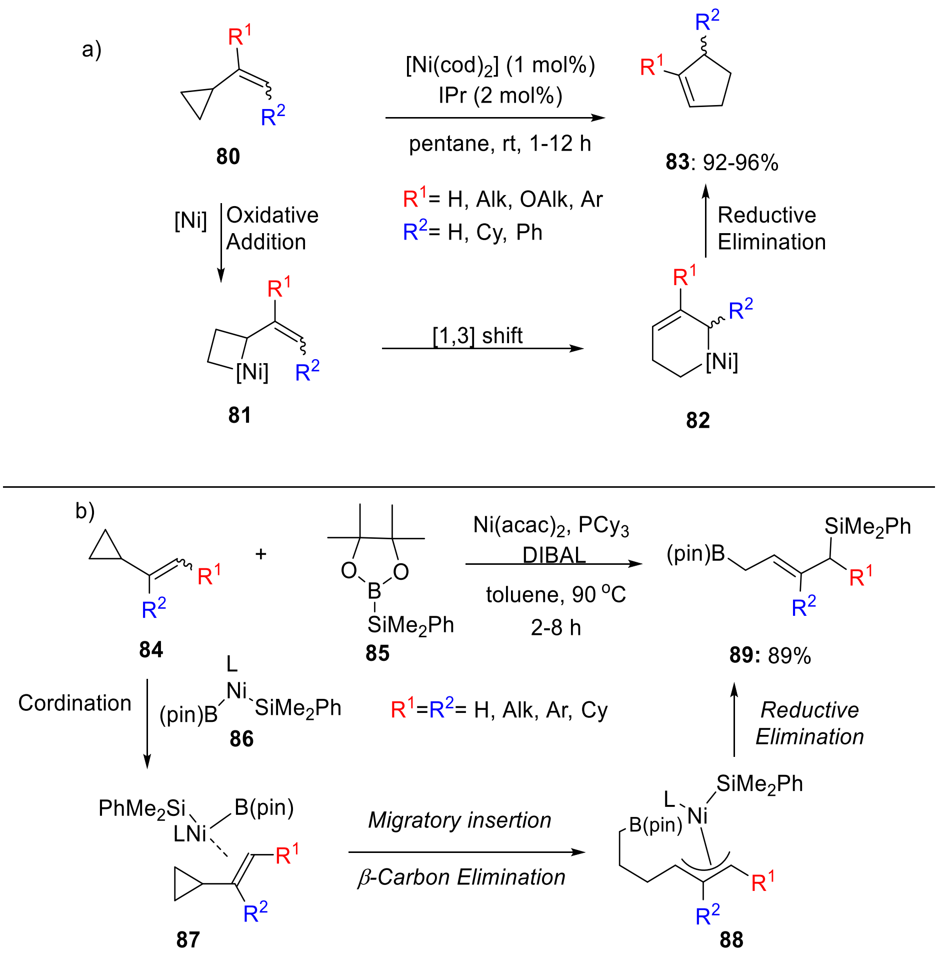
A plausible mechanism for this transformation is illustrated in Scheme 8. According to which, nickel-catalyzed transformation of cyclopropylenyne **8** would generate a nickelacyclooctadiene **9** (see Scheme 8), much to the liken of the rhodium and ruthenium intermediates previously discussed. *β*-Hydride followed by reductive elimination would then lead to the triene **77** (**49** in Scheme 8).[88] In contrast, if both ligand and substituent R in **76** are bulky, *β*-Hydride would be unfavored, and reductive elimination would lead to the bicyclic seven-membered heterocycle **78**, which isomerizes *in situ* to afford **79**.



Scheme 12: Nickel catalyzed ring opening and subsiqent cycloadiition of VCPs.

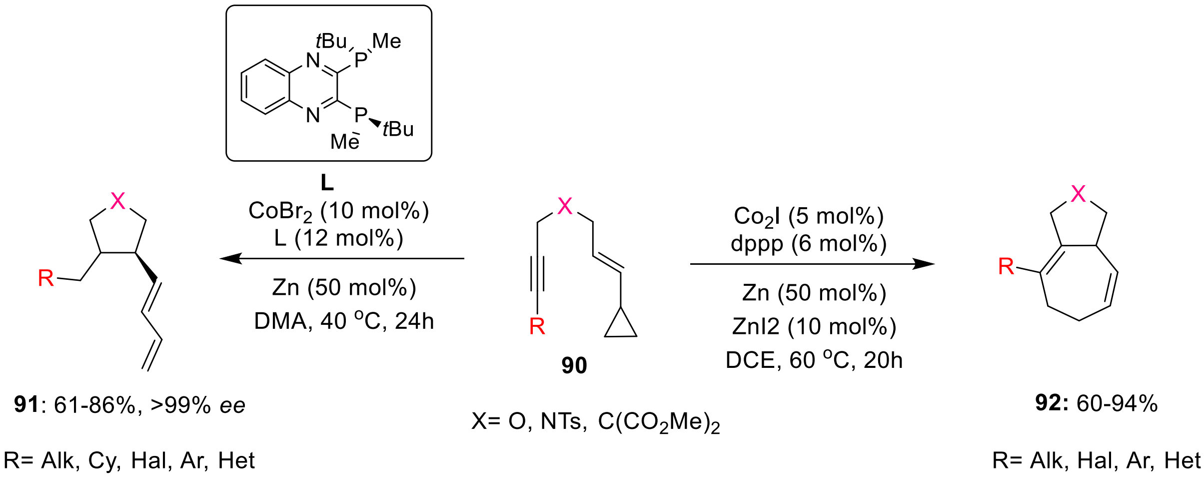
The same group also reported nickel-catalyzed ring-opening and further isomerization of activated and non-activated VCPs.[89] The resulting cyclopentene products are a core structure of many biological systems (Scheme 13 a).[91] The ligand choice was crucial in performing the isomerization step and no reaction was observed in its absence. Thus, the combination of Ni(0) and a sterically hindered N-heterocyclic carbene (NHC) led to satisfactory results. Moreover, the substitution pattern of the alkene moiety of VCPs was crucial for the reaction rate. While 1,1-disubstituted alkenes led to the desired products **83** in good yield, trisubstituted as well as 1,2–dissubstituted olefins reacted sluggishly or not at all. The proposed mechanism starts with the oxidative addition of nickel complex to the VCP forming the nickelacyclobutane **81**, a [1,3]-metal-shift would then provide nickelacyclohexene **82**, which in turn would undergo reductive elimination to generate the five-membered carbocycle **83**.

Suginome and Ito reported the nickel-catalyzed ring-opening silaboration of non-activated VCP **80** yielding products **89** in high regio- and stereoselective (Scheme 13).[37] The proposed mechanism involves coordination of cyclopropane into nickel complex **86** leading to intermediate **87**. Subsequent migratory insertion and *β*-carbon elimination leads to the allyl nickel complex **88**, which would then undergo reductive elimination to deliver the final product **89** as the exclusive regioisomer.



Scheme 13. Nickel-catalyzed ring opening and cycloaddition.

In 2018, Yoshikai and co-workers, reported a cobalt catalyzed intramolecular reaction between non-activated VCP and alkynes delivering bicyclic hexahydroazulenes and heterocyclic derivatives thereof with high chemo-, regio- and stereoselectivity (Scheme 14).[92] In the examples illustrated in Scheme 14, ligand- and substituent-controlled selective transformations of VCPs were achieved. In this work Yoshikai demonstrated that the choice of solvent and cobalt complex allows control over two competitive pathways, [5+2]-cycloadditions and homo-ene reactions (Scheme 14). Thus, utilizing the noncoordinating solvent 1,2-dichloroethane in combination with diphosphine ligand led to cyclopentane products **91** in excellent yields and enantioselectivities. While, the weakly coordinating solvent dimethylacetamide resulted in [5+2]-cycloadducts **92** with high yields.



Scheme 14. Cobalt-catalyzed, solvent-controled, ring opening of VCPs.

In summary, the unique ability of transition metals to cleave a non-activated C–C bond on a VCP ring is a valuable transformation in organic chemistry. Moreover, the selectivity in these reactions can be tuned by the appropriate selection of, metal complexes, ligands, substrate substituent patterns, and solvents. This flexibility allows for a richness of mechanistic pathways and, perhaps more importantly, synthetic applications. For this reason, the synthesis of VCP containing molecules and their further transformation are highly desirable in synthetic chemistry and natural product synthesis.

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B. Main Part

1- Heck cross-coupling arylation of monocyclopropanated heterocycles

1.1 Introduction: The synthesis of cyclopropanes

Cyclopropane subunit is one of the most occurring moieties in organic synthesis.[1,2] Cyclopropane-based molecules are widely utilized as versatile synthetic building blocks in organic transformations for the synthesis of complex structures. [2,3] Besides, they are a rather kinetically inert and resistant to bond cleavage unless activated. The substitution of three-membered ring systems with donor and acceptor groups results in the tremendous increase of its reactivity.[4a,4b] In early 70s and 80s of last century, pioneering studies of Wenkert and Reissig demonstrated the first synthesis of donor–acceptor (D–A) cyclopropanes.[4] Generally, two possibilities of donor and acceptor groups substitution at the cyclopropane ring are known: vicinal **I** and geminal **II**. The highly polarized chemical bond between a vicinally substituted cyclopropane ring with donor and acceptor groups respectively promoted heterolytically cleavage giving rise to 1,3-zwitterion synthons: this process is known as "push-pull" effect. The positive charge in the resulting 1,3-zwitterionic structure is stabilized by the donor group and the negative charge is stabilized by the acceptor.[4 d, 4e, 4? -i] On the contrary, a geminal substitution with donor and acceptor groups **II** is less popular in synthetic chemistry but very often utilized in medicinal chemistry since they display important structural motifs.[5]

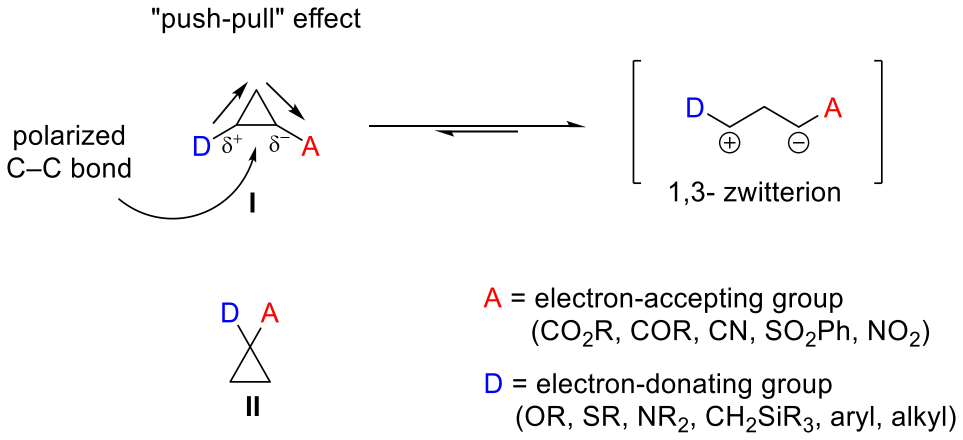
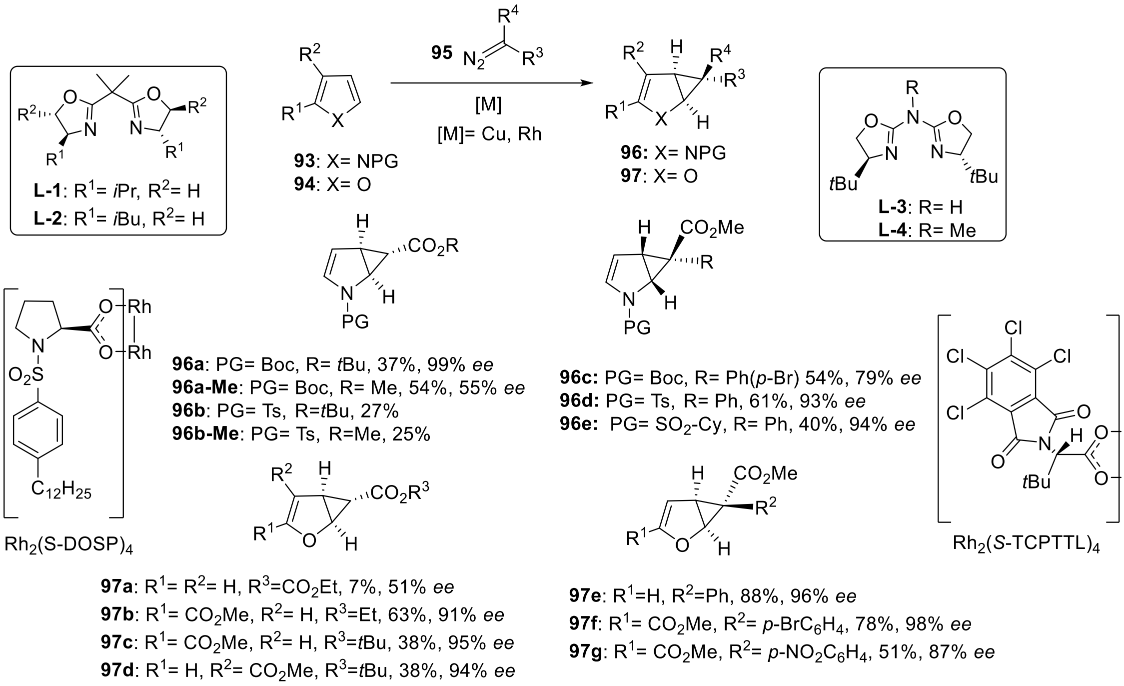


Figure 1. *"Push–pull"* effect on in vicinally positioned D-A cyclopropanes **I** and geminal cyclopropanes **II**.

Over the past few decades, the area of donor–acceptor cyclopropanes has been massively expanded leading to various transformations such as rearrangements, cycloadditions and ring-opening reactions.[6-15] The high importance of heterocyclic moieties in natural product synthesis attracted many synthetic chemists to develop a general methodology for cyclopropanated heterocycles construction. Among all reported methods,[16-26] the transition-metal-catalyzed cyclopropanation of olefinic bonds using diazo compounds as a carbene source is one of the best developed and employed transformations.[1a, 27, 28]



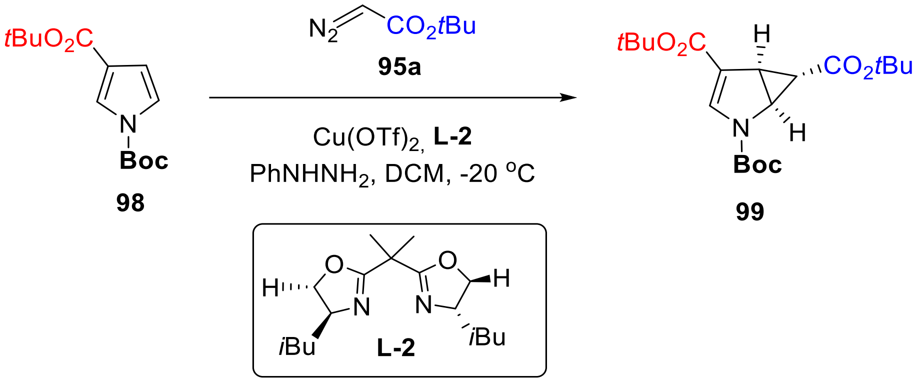
Scheme 15. Previous synthesis of enantioselective synthesis of monocyclopropanated pyrroles.

This method was used to facilitate the synthesis of various highly functionalized enantiomerically enriched heterocyclic cyclopropanes bearing donor–acceptor groups on the cyclopropyl unit. [29-31] Wenkert [29] and Fowler[30] studied highly diastereoselective cyclopropanations to access similar types of cycloadducts such as **96** and **97**, although only few examples of enantioselective cyclopropanations[31] have been realized by that time. Over the last decade, Reiser and Davies studied the general methods of heterocycles cyclopropanation with diazo esters in the presence of metal complexes illustrated in Scheme 15. Copper/aza-bis(oxazoline) ligands complexes catalyzed reaction between pyrroles and acceptor-substituted diazo esters delivered cyclopropanated pyrroles **96a-Me** in lower enantioselectivity and moderate yields, while more sterically hindered diazoester, bearing *t*Bu substitution, gave rise to **96a** in excellent enantiomeric excess >99% and 37% yield (Scheme 15).[32-37] The same catalytic system was employed in 2- and 3- ester-substituted furans, delivering **97b**–**c** cyclopropanes with excellent enantioselectivity (91–95% *ee*), albeit in moderate yields (38–61%).[35–37] Alternatively rhodium complexes, Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-TCPTTL)$_4$ also demonstrated remarkably efficiency for the cyclopropanation of substituted furans, using a diversity of aryl diazoesters.[32, 37] Recently, Davies and co-workers reported the ability of aryldiazoacetates to absorb visible light, to proceed photolysis by blue light irradiation in the presence of various trapping reagents such as styrene, carboxylic acids, amines, alkanes and arenes.[38] The developed general procedure was applied to give an easy excess to the highly functionalized cyclopropanated pyrroles[38] and furans[15] in excellent yields, under mild conditions. (**96**, **97**, Scheme 15) Although, it should be mentioned that this method does not apply for the synthesis of enantiomerically pure products.

The demonstrated cyclopropanated pyrroles, which contain a vinyl cyclopropane unit, are ideal intermediates for further ring opening transformations delivering valuable nitrogen containing heterocycles, which will be discussed in the following sections.[39,40,44,45] Therefore, the synthesis of new stereoselective substituted-cyclopropanated pyrroles have attracted continuously attention.

1.2 The synthesis of new 3-substituted cyclopropanated pyrroles.

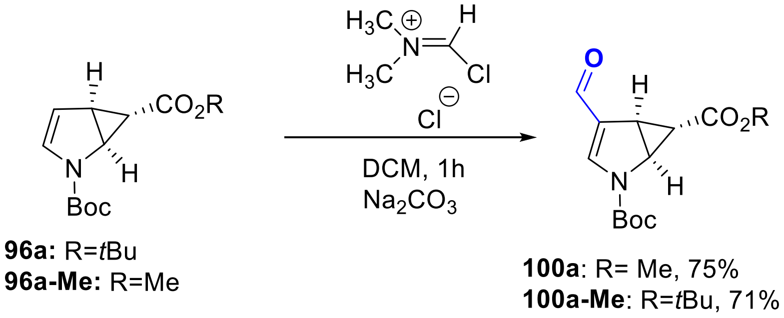
To expand the scope of these useful building blocks, Cu(II)-catalyzed cyclopropanation between 1*H*-pyrrole-1,3-dicarboxylate **98** and diazo ester **95a** was investigated (Scheme 16). Different reaction conditions were tested in order to obtain the desired 3-substituted pyrroles. In the absence of a ligand, very low yield of product **99** was observed (5%). Instead, the combination of Cu(OTf)$_2$ catalyst with ligand **L-2** led to an important increase in the product yield.



Scheme 16. The cyclopropanation of **98** with diazo ester.

Low reaction temperature and slow addition rate of diazo acetate were also important for the efficiency of cyclopropanation, furnishing the desired 3- substituted cyclopropanated pyrrole **99** in 42% yield. However, further investigation of enantioselective 3-substituted cyclopropane **99** formation in the presence of other chiral ligands is required.

Considering the importance of formyl and acetyl substitution, which can be later transformed to various functional groups, the direct formylation and acetylation of cyclopropanated pyrroles was investigated (Scheme 17).



Scheme 17. The synthesis of formyl substituted cyclopropanated pyrroles.

The formyl substituted cyclopropanated pyrroles synthesis in the presence of *in situ* generated Vilsmeier reagent (VR) is widely utilized for the formylation of activated aromatic and heteroaromatic compounds.[42]

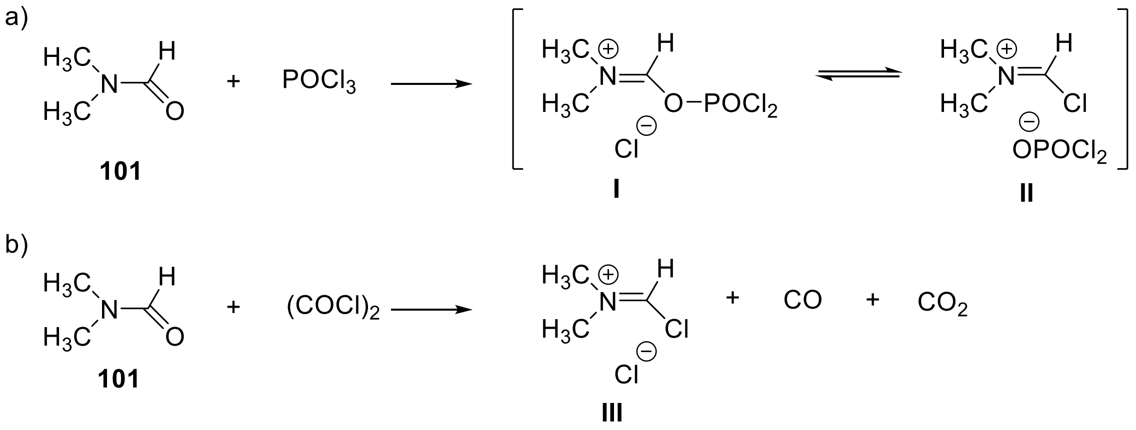
In the first attempt of the preparation of Vilsmeier reagent from N, N-dimethylformamide (DMF) and phosphoryl trichloride ($POCl_3$), the decomposition of the starting material was detected, either under the reflux or at room temperature (Table 1, entry 1 and 2). However, the *in situ* generation of the Vilsmeier reagent from oxalyl chloride and DMF led to the desired products **100a** and **100a-Me** in high yields and with high selectivity.

Table 1. The conditions for formylation of cyclopropanes.[a]

Entry	Conditions	Yields % **100a/100a-Me**
1.	DMF, $POCl_3$, 0 °C; DCE, reflux, 30 min	trace
2.	DMF, $POCl_3$, 0 °C; rt, DCE, 3 h	19 (**100a**)[b]
3.	DMF, $(COCl)_2$, 0 °C; rt, DCE, 1h, Na_2CO_3	75/ 71 [b]

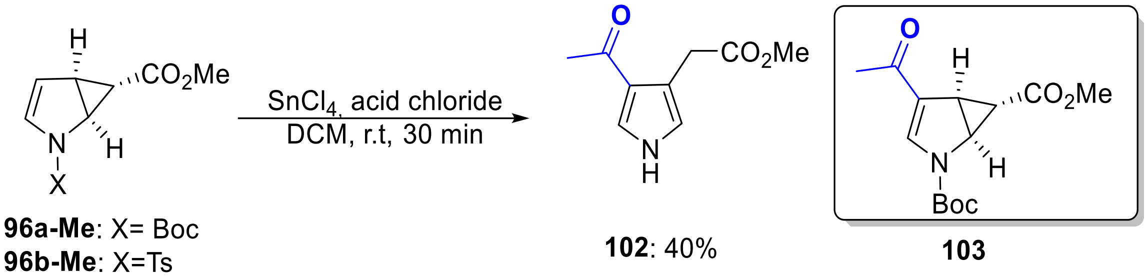
a) DMF (1 mL), DCM (4 mL), oxalyl chloride (0,6 mmol, 1.2 equiv), at 0 °C, **96a, 96a-Me** (0.5 mmol), 1 h; b) isolated yield based

The reactivity of the Vilsmeier reagent was crucial for desired selective transformation.[44] It is known, that VR prepared from $POCl_3$ and DMF shows very high reactivity (Scheme 18 a), which supposedly caused the ring opening of cyclopropane and its further decomposition, while the second method of VR generation (Scheme 18 b) provides milder condition allowing the selective formylation of **96a**.



Scheme 18. The *in-situ* generation of Vilsmeier reagent.

Having the formylated cyclopropane products **100a** and **100a-Me**, next the acylation of **96a-Me** was investigated. The employment of an acid chloride in the presence of base led to the undesired ring opening reaction of **96a-Me** (Table 2, entry 1). Thus, another procedure was followed: the Friedel crafts acylation[46] of **96a-Me** in the presence of various Lewis acids was screened. No reaction was observed in the presence of a Lewis Acid Sc(OTf)$_3$ and acetyl chloride in DCM, while tin(VI) chloride (Table 2, entry 3) resulted in deprotection and further undesired ring opening of cyclopropane ring delivering compound **102** in 40% yield (Scheme 19). Based on this result, we assumed that deprotection of Boc group proceeded in acidic condition leading to the undesired ring opening, for that purpose we switched the NBoc group to a NTs **96b-Me**. However, in this derivative the same undesired ring opening was observed. The use of other synthetic methods is required for the desired acylated cyclopropane formation.



Scheme 19. Further attempts to synthesis formyl and acetyl cyclopropanated pyrroles.

Table 2. Further attempts to synthesis compound **103**.

Entry	Conditions	Yields % **103**
1.	Acid chloride (1.5 equiv), K_2CO_3 (2 equiv), ACN, rt to 50 °C	trace
2.	Sc(OTf)$_3$, Acid chloride, DCM, rt, 3 h	trace
3.	SnCl$_4$, Acid chloride, DCM, r.t, 30 min	n.d.

1.3 The ring opening of cyclopropanated pyrroles

Ring opening reactions of donor-acceptor-substituted cyclopropanes is the most fundamental transformation for three membered ring systems.[6–8] The combination of release of cyclopropane ring strain (approx. 27 kcal/mol) as well as matched electronics along the donor–acceptor substituted carbon–carbon bond gives rise to heterolytic cleavage of the latter, generating a 1,3-dipole intermediate that can undergo manifold follow-up transformations such as cycloadditions, rearrangements, pericyclic reactions or reactions with electrophiles and nucleophiles.[9–12]

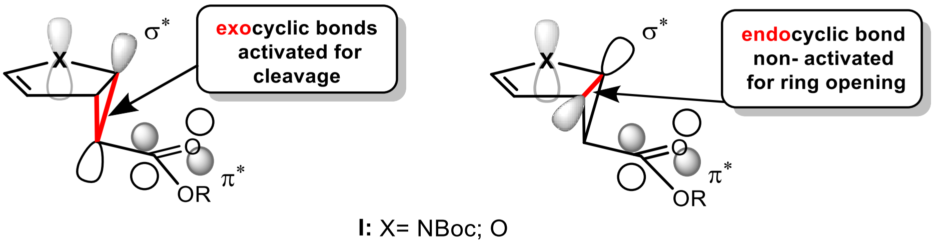
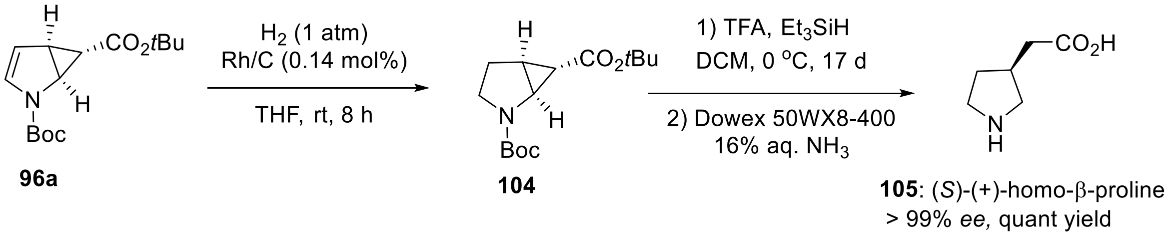


Figure 2. Exo- and endo-bond cleavage in monocyclopropanated pyrroles and furans **I**.

The cyclopropanated heterocycles **I** [13-15,33,30] (Figure 2) are ideal starting materials for ring-opening process. This ring opening can happen at the exocyclic carbon-carbon cyclopropane bonds, due to the donor lone pair of the heteroatom / π-C–C bond and the π*-acceptor orbital of the carbonyl ester acceptor group are aligned in parallel with the σ*-C–C-orbital, which facilitates the push-pull effect between these groups. Consequently, both reaction pathways have been demonstrated in various synthetic applications.[13, 14]

In 2017, Reiser and co-workers reported the methodology of activated exocyclic C–C bond cleavage of cyclopropanated pyrroles delivering enantioselective homo-β-proline **105** in quantitative yields (Scheme 20).[33 a]



Scheme 20. The ring cleavage of activated exocyclic C–C bond in **96a**.

Rh/C catalyzed hydrogenation of **96a** at atmospheric pressure provided **104** in quantitative yield. The intermediate **104** suffered the ring-opening through the activated exocyclic bond and deprotection of the Boc group under TFA/Et_3SiH conditions resulting in **105** in excellent yield and enantioselectivity.[43]

In contrast, the ring-opening of the non-activated, endocyclic cyclopropane bond in **96a** is challenging given that the respective σ^*-C–C-orbital is orthogonal to the donor atom in the five-membered ring. Such ring-opening cleavage would be the most important from synthetic point of view, since it would open up the possibility for regio- and stereoselective synthesis of valuable six membered nitrogen and oxygen containing heterocycles.

The synthesis of dihydropyridines and pyran derivatives has obtained much attention due to valuable synthetic and biological applications (Figure 3).[44, 45] 1,2-dihydropyridines are important structure motives as they can easily give access to a highly functionalized pyridines, which are in a high demand in current materials, agrochemicals and pharmaceuticals, albeit challenging in preparation due to the selective functionalization of pyridine moieties.[45f]

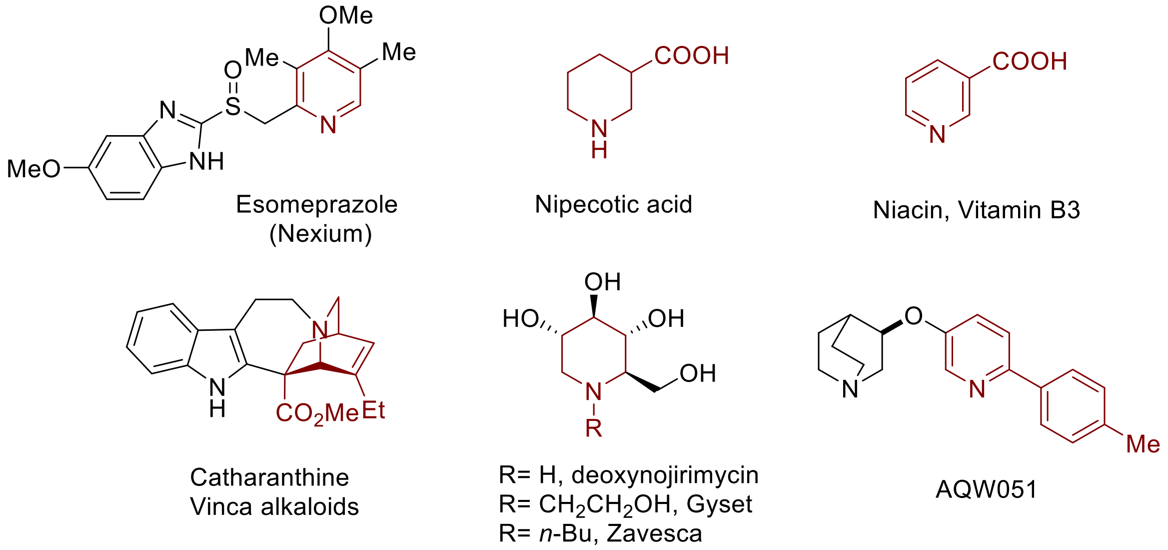
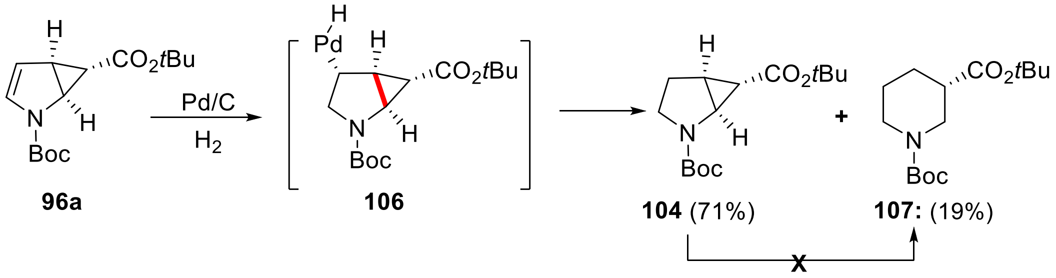


Figure 3. Alkaloids, azasugars and drug candidates based on pyridine moiety.

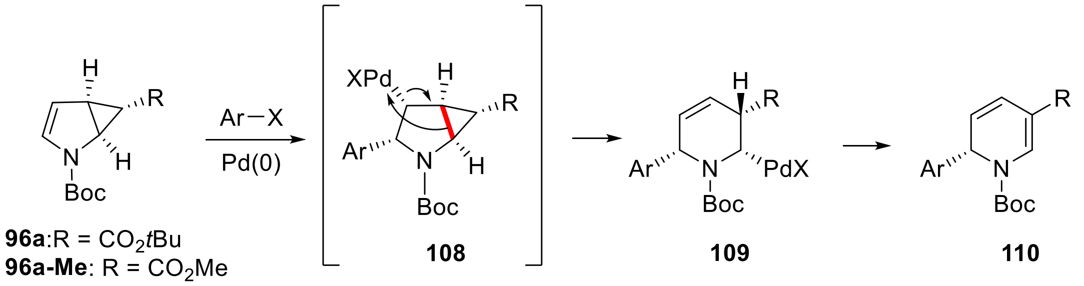
1.4 Reaction design based on early observation of the desired ring opening

The first indication that endocyclic ring-opening indeed would have occurred, was detected during the hydrogenation of **96a**, being readily available in diastereo- and enantiopure form, next to the expected adduct **104** gave rise to piperidine **107** as a minor byproduct (Scheme 21).[43] Since piperidine **107** could not be generated from **104** neither under the reaction conditions nor under harsher conditions (e.g. changing from atmospheric hydrogen pressure to 60 bar) or switching to various transition metals like platinum, iridium or rhodium catalysts, we summarized that **104** is not on the reaction pathway to **107**. Instead, we proposed that intermediate **106**, generated after hydropalladation of **96a**, underwent the expected reductive elimination **104**, is also able proceed endocyclic ring opening (Scheme 21).



Scheme 21. Hydrogenation of **96a**.

Therefore, we assumed that the desired ring expansion of **96a, 96a-Me** to dihydropyridines should become possible via an organopalladium intermediate of type **108** in which reductive elimination of Pd(0) but also β-hydride elimination of HPdX would be facilitated (Scheme 22). Instead, migration of PdX with concurrent cyclopropane ring opening, which has been described in a few previous cases,[47, 48] could occur leading to **109**. In order to close the catalytic cycle, a trans-β-hydride elimination of HPdX occurred obtaining **110**. This process is feasible with the assistance of the neighboring nitrogen donor via a base mediated elimination of the fairly acidic H^+, being allylic and next to an ester group R, and $[PdX]^-$.[49]



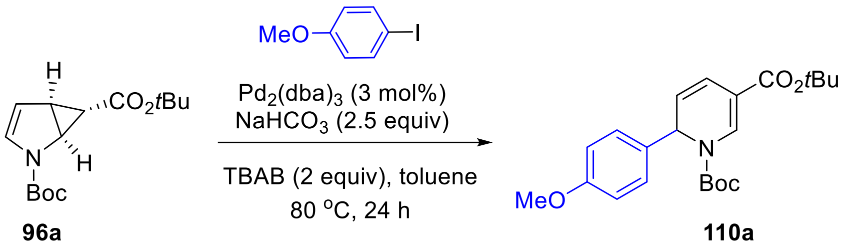
Scheme 22. Heck arylation of **96a, 96b** with concurrent endocyclic cyclopropane bond cleavage.

Herein, we report that palladium catalyzed Heck-coupling reactions of cyclopropanated pyrroles provided the desired ring expansion with concurrent stereoselective introduction of an aryl or heteroaryl moiety from the *exo*-face of the bicyclic system. In this way, 6-aryl-1,6-dihydropyridine-3-carboxylates can be accessed, and they can be further transformed with high diastereoselectivity to tetrahydropyridines or nipecotic acid derivatives as well as to *ortho*-arylated pyridines.[15]

1.4.1 Optimization studies

Based on previous described reports of palladium-catalyzed Heck-coupling reaction with dihydrofurans and allylated cyclopropanes,[50] it was carried out a search of the suitable reaction conditions. We started our studies with the reaction between **96a** and *p*-methoxyiodobenzene (Table 3). Different reaction conditions including various palladium sources, solvents and reaction temperature were screened (Table 3). The employment of $Pd(PPh_3)_4$ in THF and $NaHCO_3$/TBACl yielded the product in only 10%, while the reactions in the presence of $Pd_2(dba)_3$ $CHCl_3$ and $Pd_2(dba)_3$ showed much better product yields (Table 3, entry 6 and 7). The influence of different solvents was also important for successful ring opening. Thus, the reaction carried in ethylene glycol resulted with no product formation, whereas benzene and toluene increased the yield delivering product in 66% and 67% yields, respectively (Table 3, entries 12 and 13). The combination of inorganic base ($NaHCO_3$) and *tert*-butyl ammonium bromide (TBAB) successfully increased the product yield. In the following reaction the role of *tert*-butyl ammonium bromide was very important. TBAB acts as a solid-liquid phase-transfer agent, it can also act as a stabilizing additive to increase the lifetime of underligated Pd(0) species to match slower oxidative addition rates with less reactive substrates.[51] $Pd_2(dba)_3$ was identified as a suitable catalyst in combination with tetrabutylammonium bromide (TBAB, 2 equiv), $NaHCO_3$ as base (2.5 equiv) and toluene as solvent to cleanly form **110a**. While typically the alkene component is employed in excess (3–5 equiv) in Heck couplings, employing **96a** and iodobenzene in equimolar amounts nevertheless gave an appreciable yield (61%, Table 3, entry 20) of **110a**. Considering that one of the substrates might be more valuable in a given transformation, employing the excess of iodobenzene yielded in 74% yield (Table 3, entry 21), while the excess of **96a** provided **110a** in 81% yield (Table 3, entry 22). Expectedly, the absence of a palladium source did not deliver the desired product **110a** (Table 3, entry 23).

Table 3. Optimization of the reaction conditions.

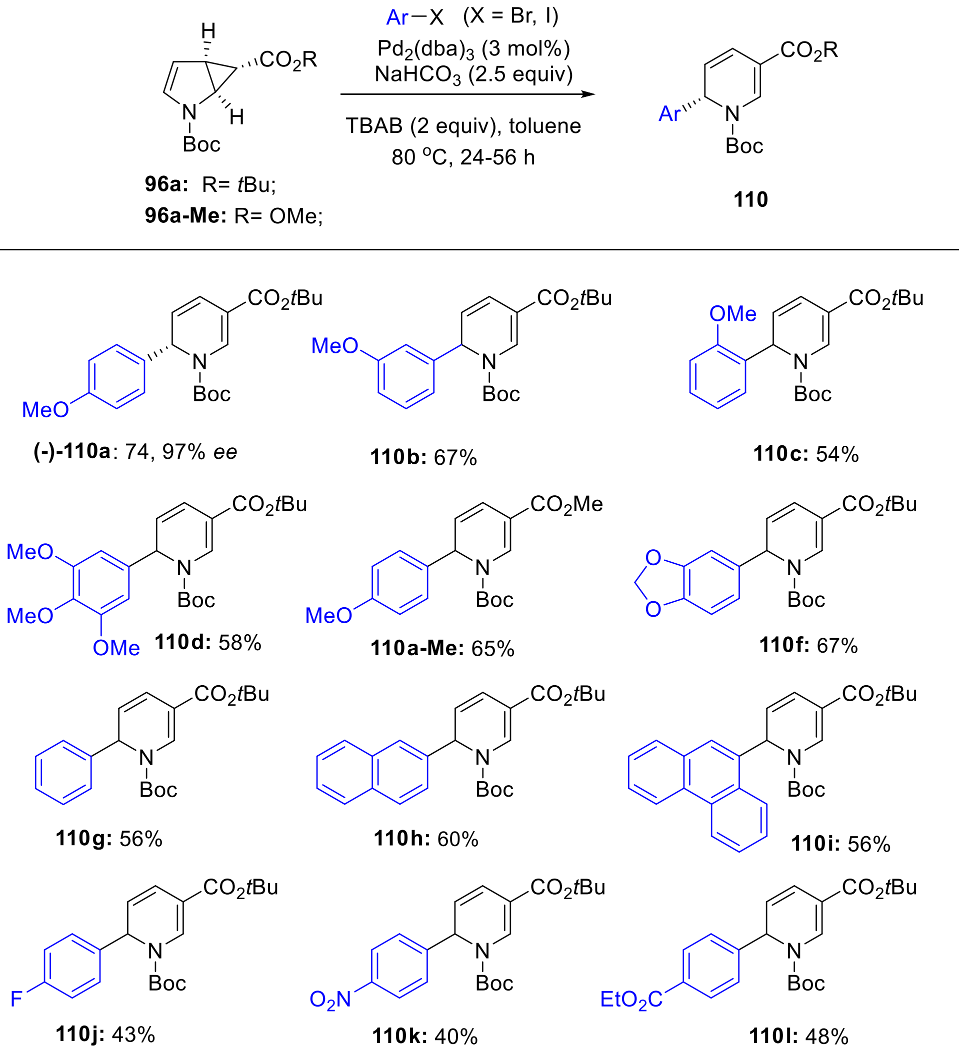


Entry	Catalyst	Solvent	Base/Additive	Yield (%)**110a** [a,b]
1	Pd(OAc)$_2$	THF	NaHCO$_3$/TBACl	30
2	PdCl$_2$	THF	NaHCO$_3$/TBACl	35
3	Pd(dba)$_2$	THF	NaHCO$_3$/TBACl	45
4	Pd(PPh$_3$)$_2$Cl$_2$	THF	NaHCO$_3$/TBACl	43
5	Pd(PPh$_3$)$_4$	THF	NaHCO$_3$/TBACl	10
6	Pd$_2$ (dba)$_3$*CHCl$_3$	THF	NaHCO$_3$/TBACl	48
7	Pd$_2$ (dba)$_3$	THF	NaHCO$_3$/TBACl	50
8	Pd$_2$ (dba)$_3$	DMF	NaHCO$_3$/TBACl	65
9	Pd$_2$ (dba)$_3$	Dioxane	NaHCO$_3$/TBACl	55
10	Pd$_2$ (dba)$_3$	(CH$_2$OH)$_2$	NaHCO$_3$/TBACl	-
11	Pd$_2$ (dba)$_3$	Benzene	NaHCO$_3$/TBACl	66
12	Pd$_2$ (dba)$_3$	Toluene	NaHCO$_3$/TBACl	67
13	Pd$_2$ (dba)$_3$	Toluene	Na$_2$CO$_3$ TBACl	68
14	Pd$_2$ (dba)$_3$	Toluene	NaHCO$_3$/No TBACl	30
15	Pd$_2$(dba)$_3$	Toluene	DIPEA/TBACl	67
16	Pd$_2$(dba)$_3$	Toluene	Proton Sponge /TBACl	29
17	Pd$_2$(dba)$_3$	Toluene	TEA/TBACl	64
18	Pd$_2$(dba)$_3$	Toluene	DMAP/TBACl	34
19	Pd$_2$(dba)$_3$	Toluene	NaHCO$_3$/p-NO$_2$PhCO$_2$H	21
20	Pd$_2$(dba)$_3$	Toluene	NaHCO$_3$/TBAB	61[c]
21	**Pd$_2$(dba)$_3$**	**Toluene**	**NaHCO$_3$/TBAB**	**74**[d]
22	**Pd$_2$(dba)$_3$**	**Toluene**	**NaHCO$_3$/TBAB**	**81**[e]
23	No Catalyst	Toluene	NaHCO$_3$/TBAB	-

a) *Condition I*: **96a** (0.5 mmol), Ar–I (0.75 mmol, 1.5 equiv), catalyst (3 mol%), base (2.5 equiv), additive (2 equiv), solvent (1.5 mL), N$_2$, 80 °C, 24 h, yield based on **96a**; b) NMR yield using diphenylmethane as internal standard; c) **96a** (1 equiv)/Ar–I (1 equiv); d) isolated yield based on **96a**; e) *Condition II*: Ar–I (0.5 mmol, 1 equiv), **96a** (1.5 mmol, 3 equiv), catalyst (3 mol%), base (2.5 equiv), additive (2 equiv), solvent (1.5 mL), N_2, 80 ºC, 24 h, isolated yield based on Ar–I.

1.4.2 Substrate scope

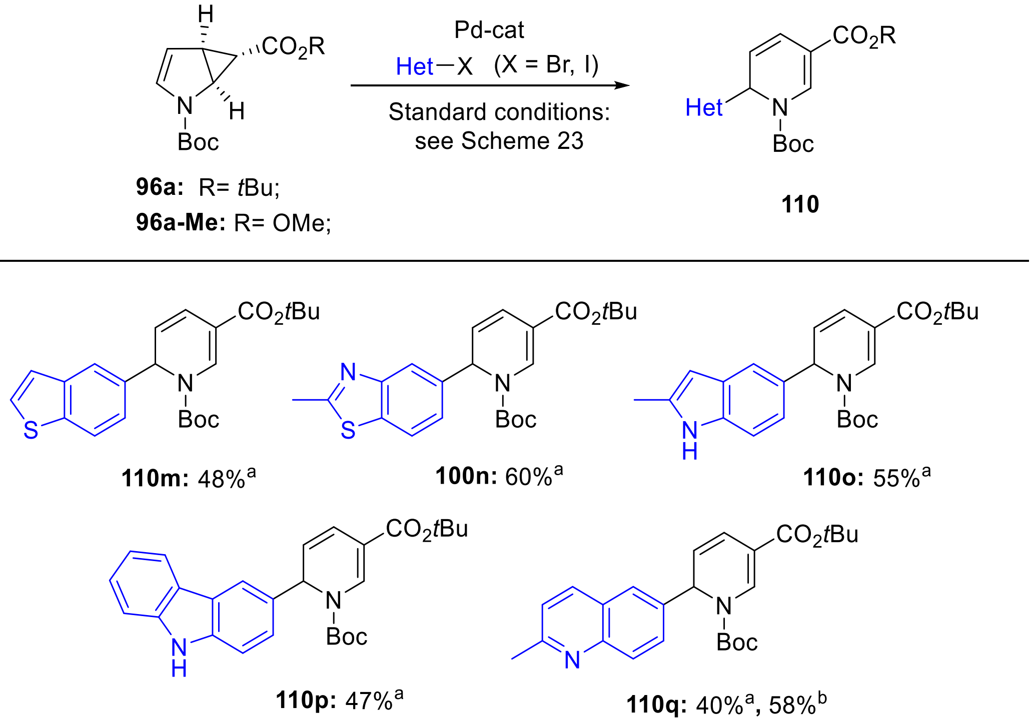
With the optimized reaction conditions in hand, we next explored the generality of the reaction scope (Scheme 9). Both aryl iodides (for **110a–110c, 110e-Me, 110g, 110h**–**110l, 110r**) and aryl bromides (for **110d**, **110f**, **110i**, **110m**–**110q)** could be efficiently coupled with **96** to deliver the desired dihydropyridines **110**. The electron rich aryl halides such as like *p*-methoxy benzene and 1-bromo-3,4-(methylenedioxy) benzene gave higher yields 74% and 67% respectively (**110a** and **110f**), while electron deficient (**110j**–**l**) and electron neutral ones with a phenyl,



Scheme 23. Substrate scope for the synthesis of 2,5-disubstituted-1,2-dihydropyridines.

naphthyl or phenanthryl moiety (**110g–110i)** also performed well in the coupling/ring-opening cascade. It should be noted that coupling of monocyclopropnated pyrrole with *p*-NO$_2$ benzene iodide was carried out at 65 °C, while higher temperature resulted in aromatized product formation.

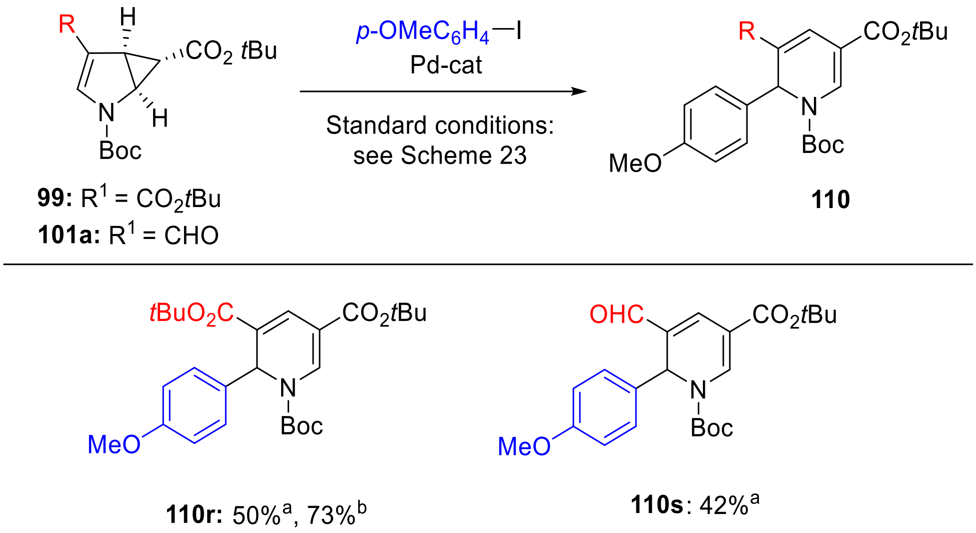
Notable, as demonstrated with the synthesis of (–)-**110a** (proof of absolute stereochemistry *via* (+)-**122**, vide infra), using enantiopure (–)-**110a** (97% *ee*)**,** this transformation proceeds with perfect chirality transfer, in which the Heck-arylation occurs from the convex face of the bicycle.



Scheme 24. Substrate scope for the synthesis of 2,5-disubstituted-1,2-dihydropyridines: a) *Condition I* (Table 3^a); b) *Condition II* (Table 3^b).

Considering the high importance of functionalization of heteroarenes, different heteroaromatic moieties were successfully incorporated forming **110m-110q** in moderate yields. The increase of yields was observed, thus employing *Condition II* (for more details see Experimental section) furnishing **100q** in 58% yield.

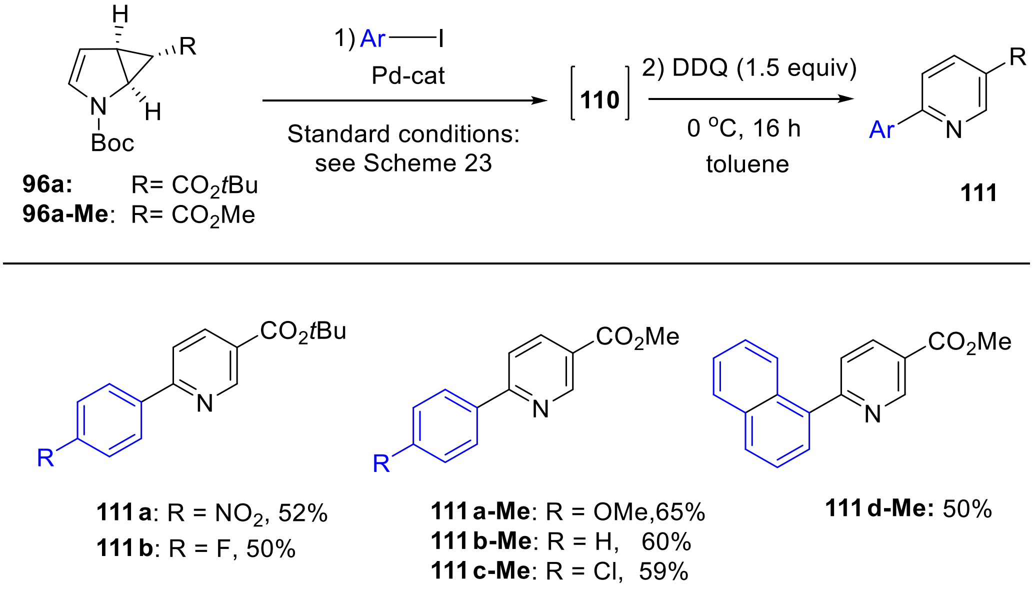
Encouraged by these positive results, we added one more level of complexity to this sequence with the introduction of an ester or a formyl group into the 3-position of the cyclopropanated pyrrole. Despite steric hindrance, the construction of 2,3,5-trisubstituted-1,2-dihydropyridines product with moderate to good yields was obtained (Scheme 25). In this case as well the



Scheme 25. Substrate scope for the synthesis of 2,5-disubstituted-1,2-dihydropyridines: a) *Condition I* (Table 3[a]); b) *Condition II* (Table 3[b]).

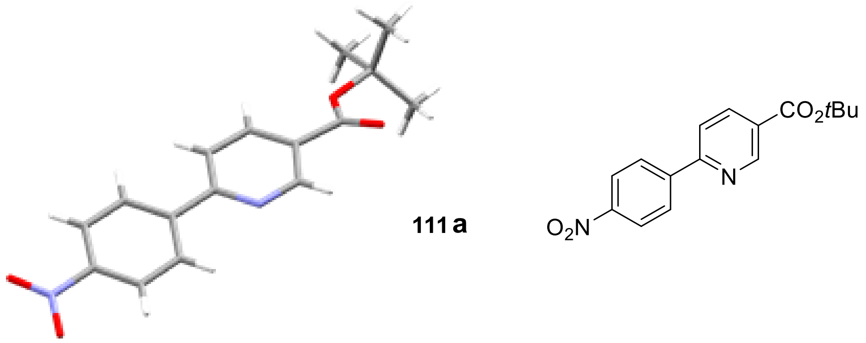
increase of yields was observed, while employing *Condition II* (for more details see Experimental section) resulting **100r** in 73% yield.

It is known that pyridines are the most widespread heteroarene found in FDA approved drugs that contain a nitrogen heterocycle.[40] They are also a key structure of many valuable molecules utilized in agrochemicals, materials, and ligands for metal catalysts.[52–54] As a consequence of its importance, direct methods that selectively functionalize pyridine moieties are in high



Scheme 26. One-pot synthesis of pyridines from monocyclopropanated pyrroles 1 and aryl halides.

demand in the pharmaceutical sciences and beyond. However, they possess considerable challenges for their preparation. Classical electrophilic aromatic substitution reactions on pyridines as well as metalation-trapping sequences usually require harsh reaction conditions. Recent development in transition metal catalyzed C−H activation methodology afforded a series of selective reactions at the 2-, 3- and 4-position, respectively.[44] The 2-arylated dihydropyridines[46,47] **110** are obviously suitable starting materials for this scaffold, nevertheless, ideally a one-pot synthesis of such pyridines from **96** would be desirable. Indeed, after the Heck coupling to **110**, simple addition of powerful oxidant DDQ to the reaction mixture gave rise to the desired 2-arylpyridines **111** (Scheme 26). Yields of **111** were in some cases even improved in comparison to the synthesis of the corresponding dihydropyridines **110**, for example, **111a** (X-ray structure is illustrated in Figure 4) and **111b**, pointing towards the lability of the latter to a certain extent.



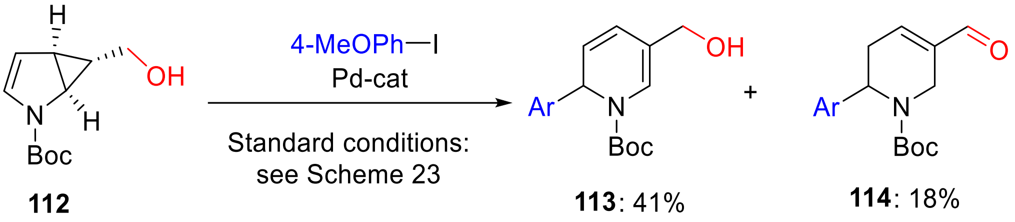
111a

Figure 4: Single crystal X-ray structure of **111a** (C = grey, H = white, O = red, N = blue).

The expanding of the scope for the Heck cross-coupling reaction of monocyclopropanated furans **97** and aryl iodides delivering 2-arylated 2*H*−pyran was also investigated. [15]

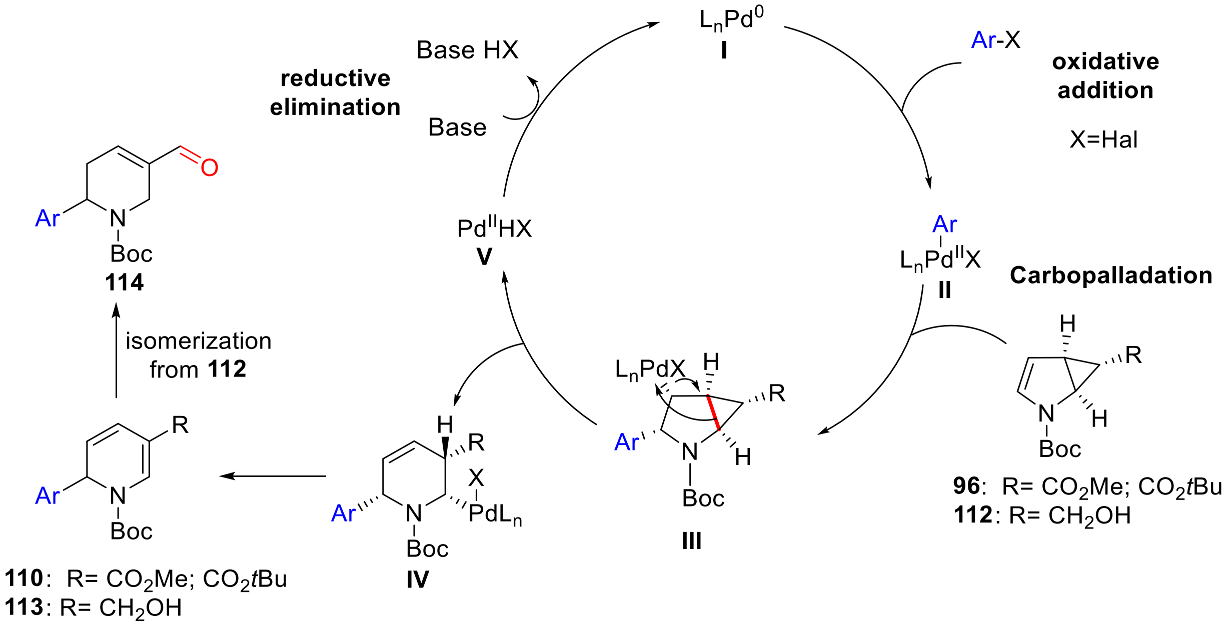
1.4.3 Mechanistic discussion

The developed synthesis of cyclopropane ring opening triggered by palladium Heck cross-coupling is an elegant method that showed high tolerance toward functionalization on aryl ring as well on cyclopropyl unit bearing acceptor or donor substituents. Thus, the cyclopropanated pyrrole derivative **112** bearing an electron donor group on cyclopropyl ring was subjected to the reaction conditions described in Scheme 23. Substrate **112** cleanly underwent the ring-opening reaction, proving that an acceptor substituent for the assumed base induced *trans*-β-hydride elimination is not necessary for desired product formation **113**.



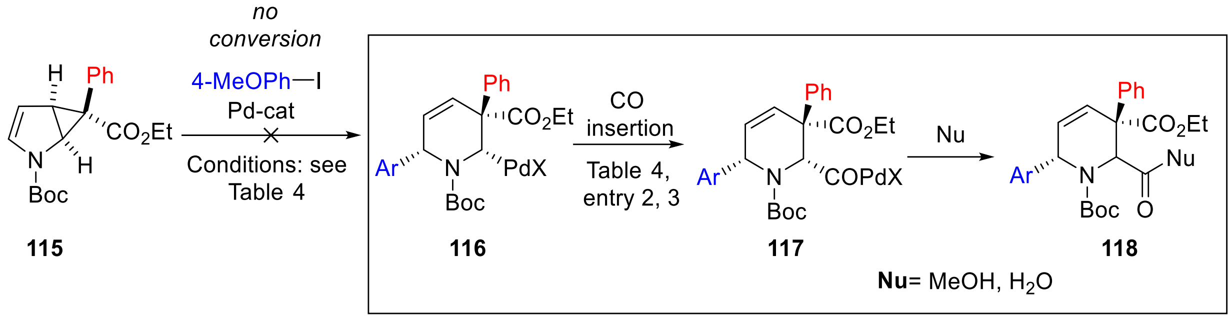
Scheme 27. Ring opening of cyclopropanated pyrrole bearing electron donating group.

Based on the previous reports[48,51] as well as the obtained results the proposed reaction mechanism for the palladium catalyzed endocyclic bond cleavage of cyclopropanated derivatives (Scheme 27). The oxidative insertion of the aryl halide to $L_nPd(0)$ **I** generated the $L_nPd(II)ArX$ species **II** following carbometallation: from which the migratory insertion on **96/112**, occurred to deliver intermediate **III**. A facile and rapid migration of the metal over the alkyl chain through successive 1,3-hydrogen shifts subsequently led to the selective endocyclic ring-fragmentation of **III** providing intermediate **IV**, which underwent trans-*β*-hydride elimination to form ring opening products (**110** and **113)**. The carbopalladation of the C−C double bond takes place from the sterically less encumbered face of **96**, which is a key point for desired transformation. Besides the expected product **113**, as a result of a formal chain walk of palladium with concurrent double bond isomerization the thermodynamically favoured conjugated carbonyl compound **114** was also observed.



Scheme 28. Proposed catalytic cycle.

To further shed light on the mechanism and the substrate prerequisites, we subjected the cyclopropane derivatives **115** to the standard reaction conditions (Table 4, entry 1). No conversion was observed with these substrates, which is consistent with the formation of the organopalladium intermediate **IV** that cannot close the catalytic cycle by *β*-hydride elimination.



Scheme 29. Attempts of carbonylative Heck reactions.

To achieve the ring opening cleavage of substrate **115**, carbonylative Heck reactions were next attempted.[56, 57] There is no doubt that *β*-hydride elimination is facilitated by the presence of the double bond; thus, the absence of *β*-hydride would make the mentioned process impossible. However, **116** can be a suitable intermediate for further CO insertion to generate **117** followed by nucleophile attack to form intermediate **118** (Scheme 29). Unfortunately, neither conversion of **115** was observed at rt or T= 80 ºC, nor if higher reaction temperature (T = 110 ºC) and longer reaction time were used, instead the decomposition of **115** was observed (Table 4, entry 2, 3 and 4). Further studies employing other synthetic methods are required in order to make the desired transformation occur.

Table 4. Conditions for desired ring opening of **115**.

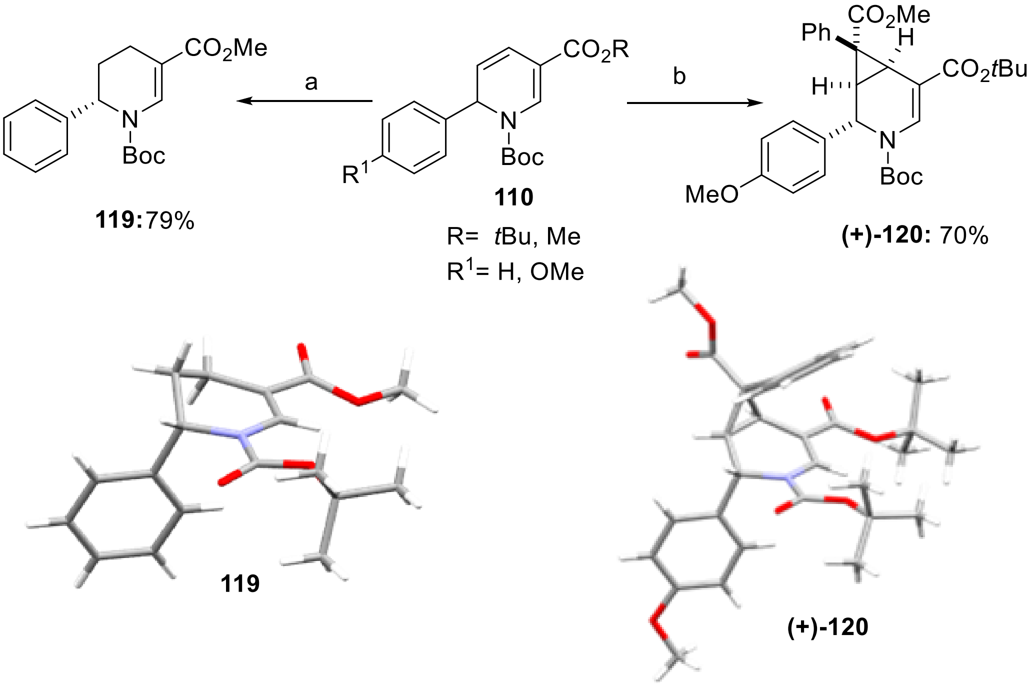
Entry	Conditions	Yield (%)[b] **118**
1.	Standard condition: see Scheme 23	n.d
2.	4-OMePh-I (1.5 equiv), $Pd_2(dba)_3$ (5 mol%), $NaHCO_3$ (1.5 equiv), MeOH, CO (1 atm), rt-60 °C, 48h	n.d
3.	4-OMePh-I (1.5 equiv), $Pd_2(dba)_3$ (5 mol%), $NaHCO_3$ (1.5 equiv), MeOH, CO (1 atm), 110 °C, 48h	traces
4.	4-OMePh-I (1.5 equiv), $Pd_2(dba)_3$ (5 mol%), $NaHCO_3$ (1.5 equiv), DMF/H_2O= 1:2, CO (1 atm), rt-60 °C, 48h	n.d

a) **115** (164 mg, 0.5 mmol), 4-iodoanisole (175 mg, 0.75 mmol, 1.5 equiv), catalyst (3 mol%), base (2.5 equiv), additive (2 equiv), solvent (1.5 mL), CO (1 atm), N_2; b) determined by NMR

1.4.4 Application of 1,2-dihydropyridines.

Dihydropyridines constitute versatile synthetic building blocks.[58-59] Thus, representative transformations were carried out,[15] which all proceeded with remarkable diastereoselectivity. Compounds **110a-Me** was selectively hydrogenated to afford tetrahydropyridines **119**. In addition, cyclopropanation of (–)-**110a** with methyl phenyldiazoacetate in the presence of $Rh_2(OAc)_4$ as catalyst give rise to bicycle (+)-**120** as a single stereoisomer. The crystal structure of (+)-**120** proved the absolute stereochemistry (–)-**110**.

Further transformations leading to nipecotic acid deriative, as well as dihydroxylation of **110a** to provide corresponding syn-diol and bromohydrin products were also realized.[15]



Scheme 30. Transformations of 1,2-dihydropyridines derivatives.

Conditions: a) H_2 (balloon), Pd/C (10 wt%), MeOH, 25 °C, 16 h; c) methyl phenyldiazoacetate (1.5 equiv), $Rh_2(OAc)_4$ (1 mol%), hexanes, 25 ^{O}C, 2 h.

1.5 Conclusion

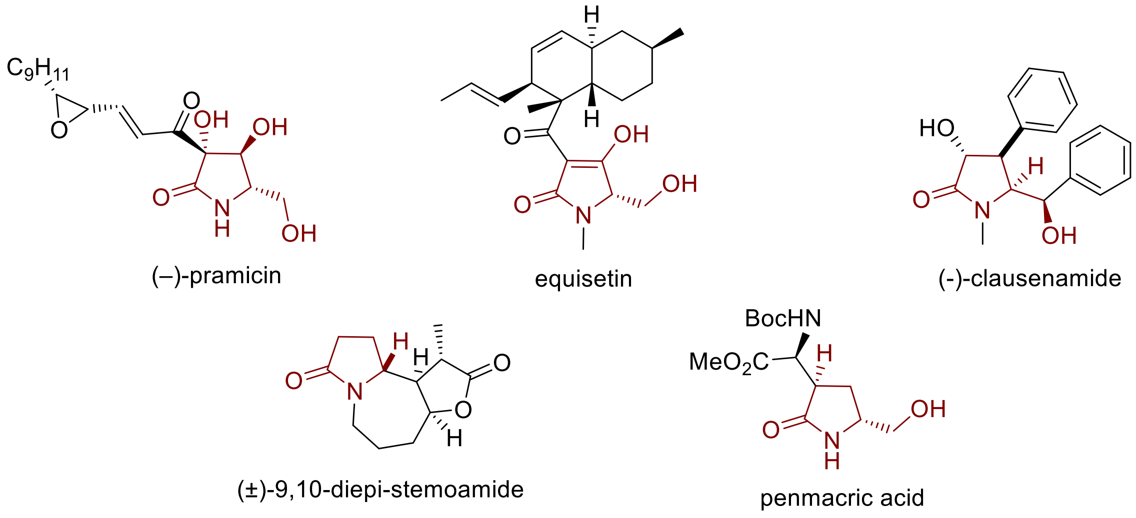
In conclusion, a highly regio- and diastereoselective palladium-catalyzed Heck cross-coupling of monocyclopropanated heterocycles with hetero/aryl halides with concurrent ring opening of the non-activated cyclopropane bond has been realized. Almost all literature known reports demonstrate activated exocyclic bond cleavage of cyclopropane. In turn, the new elegant method of palladium-catalyzed Heck-coupling ring opening of non-activated C−C bond of cyclopropane was demonstrated.

The developed method offers generous functional group tolerance in both heterocyclic cyclopropane moieties or aryl/heteroaryl groups giving an access to the highly functionalized 6-membered N-heterocycles such as dihydropyridines and pyridines widely occurring in numerous natural and synthetic products, which are highly desirable in pharmaceutical sciences and beyond. The design of this reaction will open up new avenues in the chemistry of donor–acceptor cyclopropanes. The further scope extension and mechanistic studies of palladium-catalyzed Heck cross-coupling of monocyclopropanated heterocycles are currently ongoing in our group.

2. Synthesis of 5-substituted 3-pyrrolidin-2-ones via photoredox catalysis

2.1 Introduction: Bioactivity and the synthesis of pyrrolidone derivatives.

5-substituted 3-pyrrolidin-2-ones have special significance since they constitute a core structure of many compounds displaying marvelous biological and pharmacological activities:[60–62] for example (–)-pramicin[63, 64] demonstrated good antimicrobial activity against *Candida parapsilosis*, as well as good antibacterial activity against *Bacillus subtilis*; equisetin- is known as an antibiotic, as well as it has a significant cytotoxic and phytotoxic activities; penmacric acid- shows significant anti-inflammatory activity against acute inflammation, (±)-9,10-diepi-stemoamide- used as an anticough agent and also for the treatment of respiratory diseases such as asthma and tuberculosis (Figure 5).[65]



(–)-pramicin

equisetin

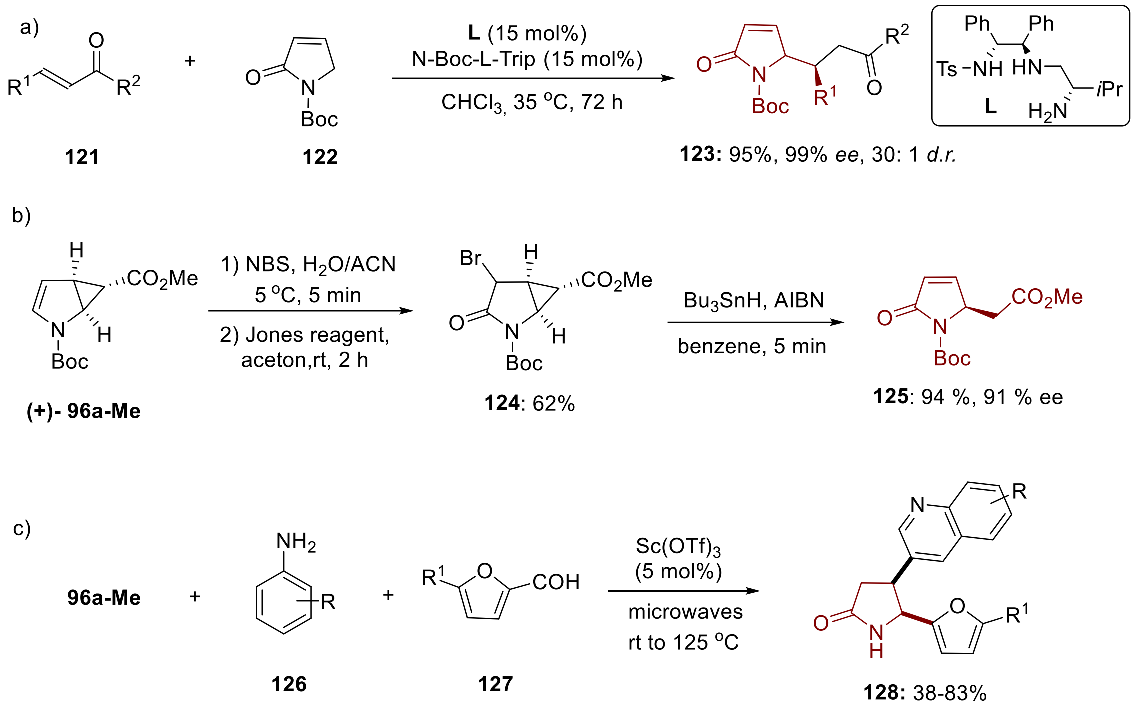
(-)-clausenamide

(±)-9,10-diepi-stemoamide

penmacric acid

Figure 5. Natural products that contain the fragments of 5-substituted 3-pyrrolidin-2-one derivatives.

The stereoselective transformations of pyrrolidin-2-ones continue to be rare, both in the field of organocatalytic synthesis and organometallic catalysis.[66,67] The insufficiency of reactions is partially due to the challenges in the chemoselective activation of the α, β-unsaturated vinylogous system either as a donor or as an acceptor in chemical reactions.[66] Satisfactory results were demonstrated in the report of Ye and co-workers (Scheme 31 a).[67] The highly diastereo- and enantioselective synthesis of 5-substituted 3-pyrrolidin-2-ones was performed by direct organocatalytic asymmetric vinylogous Michael reaction of *α*,*β*-unsaturated γ-butyrolactam **121** with *α*,*β*-unsaturated ketones **121**. The corresponding Michael products **123** could be obtained with excellent enantio- (95% to 99% *ee*) and diastereoselectivity (4:1–30:1 *d.r.*) but also in excellent yields (75–90%).



Scheme 31. The synthesis of 2-pyrolidones.

Reiser and co-workers reported exocyclic ring opening cleavage of cyclopropane **124** by radical chain process furnishing enantioselective 5-substituted 3-pyrrolidin-2-one (Scheme 31 b).[33b] Enantiopure **96a-Me** was utilized as suitable intermediate for the synthesis of corresponding compound **124**, since the direct employment of **96a-Me** in above mentioned process resulted in undesired transformation. Firstly, the corresponding bromohydrin was obtained, from **96a-Me** in the presence of NBS in water. Next, oxidative addition using Jones reagent furnished **124** in 62% yield. The ring opening of exocyclic bond cleavage of **124** was realized by radical chain process employing Bu_3SnH and AIBN delivering product **125** in 94% yield and 91% *ee*. The compound **125** was then subjected to further functionalization, obtaining various substituted pyrrolidine-2-ones. Besides, the enantioselective synthesis of natural product (S)-vigabatrin was demonstrated.

Reiser and co-workers have also carried out the Lewis-acid-catalyzed a multicomponent approach to access *cis*-4,5-disubstituted pyrrolidinones **128** under microwave (mw) irradiation (Scheme 18 c).[13c] The reaction includes several processes: a Povarov reaction of aromatic imines generated from **126** and **127**, following the Lewis acid promoted exocyclic ring opening of **96a-Me**, and finally 1,4-furan ring migration occurred subsequently resulting with the quinoline formation. The synthesized products **128** were obtained in high yields and excellent stereoselectivity.

2.2 General concepts of visible-light photoredox catalysis and ATRA reactions

The first discovery of photochemical reactions have been realized at the beginning of the twenty century by pioneer Italian photochemist of Armenian origin Giacomo Ciamician.[68] During the last couple of decades, this fascinating discovery had a number of potential applications, emerging the area of photochemistry and photoredox-catalysis as a powerful tool in synthetic organic chemistry.[69] Significant energy efficiency, simple setup, mild reaction conditions as well as replacing toxic or expensive reagents are important features of this class of reactions.[70,71,72] The photoredox catalyzed reactions have been applied in numerous applications in both industry and academia for the preparations of natural products,[69,73] drugs[74] and functional materials.[75]

The basic principle of photoredox-catalysis is the promotion of an electron transfer to or from a substrate, subsequently forming reactive species, which usually followed by the extrusion of a leaving group generating neutral radical. The subsequent formed neutral radical acts as the active species which initiates a chemical transformation.

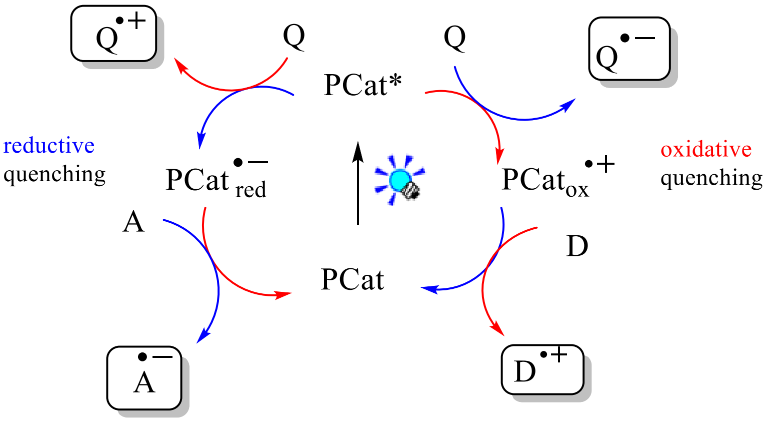


Figure 6. Photoredox catalysis including reductive or oxidative pathways.

The photoredox-catalysis undergoes two different electron-transfer pathways; both the “quenching” and the “regenerative” electron transfer can be efficient to give an access to desired chemical transformation. Ideally, the two electron-transfer processes are related by the substrates or intermediates of the catalyzed reaction and therefore do not require any sacrificial electron donor or acceptor, this type of photocatalytic cycles are called redox-neutral.[69] In turn, the photocatalyst can be quenched by a sacrificial electron donor or an electron acceptor and the reduced or oxidized photocatalyst can act as an oxidant or reductant.

Visible-light-mediated atom transfer radical addition (ATRA) is one attractive methods of chemical transformation in photoredox-catalysis.[76,77] Visible-light-catalyzed ATRA reactions starts with an electron transfer from a photocatalyst (PC=photocatalyst, such as Cu, Ru, or Ir based transition-metal complexes) to **129** (Figure 7). Excited state of photocatalysts **I*** can generate radical R$^\cdot$ upon one-electron reduction of **130**. The R$^\cdot$ radical can react with the olefin **130** furnishing radical **131**, which can get oxidized by PC$^+$ to form carbocation **132** with parallel regeneration of the photocatalyst. To form the final product **133**, cation **132** recombines with X$^-$.[69b]

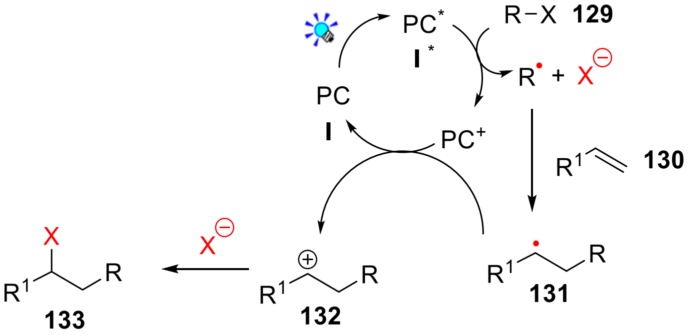
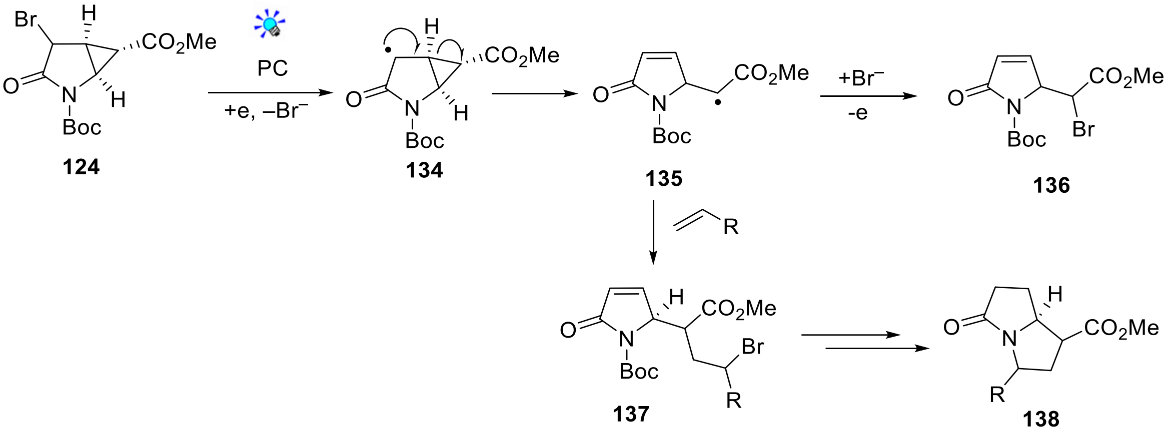


Figure 7. Visible-light-mediated atom transfer radical addition process.

2.3 The initial attempts of pyrrolidizines alkaloids synthesis

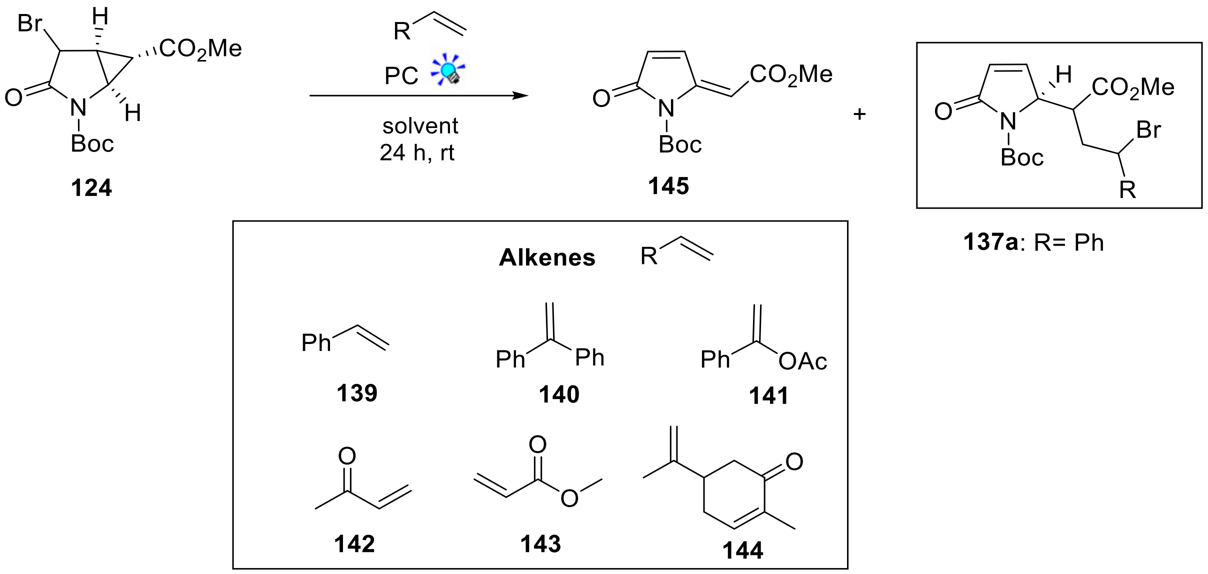
Initially, we hypothesized that cyclopropane ring opening processes can be mediated by visible light (ATRA reactions), which we believed would lead to a new way for the synthesis of pyrrolidizines derivatives, a class of important compounds in drug development.



Scheme 32. The proposed approach to synthesis of novel pyrrolidizines alkaloids.

We proposed that electron transfer from PC to **124** would proceed the extrusion of Br^- subsequently generating radical **134**, which will be a key step for ring opening process furnishing **135** radical intermediate. Further, recombination of Br^- could give rise to **136**, which is a valuable building block for the construction of complex molecules. In addition, radical **135** could be trapped by various olefins to furnish **137**, which can be used as an intermediate for the synthesis of pyrrolidizines alkaloids.

Based on previous observations, we commenced our study utilizing various photocatalysts and reaction conditions to carry out the desired transformation (Scheme 33). The reaction of substrate **124** with styrene in the presence of *fac*-$Ir(ppy)_3$ photocatalyst failed to provide desired product **137a** (Table 5, entry 1). The irradiation of photochemical reactions in the presence of $[Cu(dap)_2]Cl$ and $[Ru(bpy)_3]Cl_2$ catalysts also was unsuccessful. Next, the photoredox reaction of **124** with electron-neutral, or electron rich alkenes such as like diphenylethylene **140** and α-acetoxystyrene **141**, as well as with Michael acceptors as, methylvinyl ketone **142**, methyl acrylates **143** and *D*-Carvon **144** was tested. In all attempts, the formation of the **137** type of



Scheme 33. Photocatalytic study of **124** with the tested alkenes.

Table 5. Photocatalytic conditions of **124** with the styrene.[a]

Entry	Photocatalyst	Conditions	Yield (%)[b] **137a**
1.	*fac*-Ir(ppy)$_3$ (2 mol%)	**139** (5 equiv), ACN, LED$_{450\ \text{nm}}$	n. d.
2.	[Cu(dap)$_2$ Cl] (2 mol%)	**139** (5 equiv), ACN, LED$_{530\ \text{nm}}$	trace
3.	[Ru(bpy)$_3$] Cl$_2$(2 mol%)	**139** (5 equiv), ACN, LED$_{450\ \text{nm}}$	trace
4.	*fac*-Ir(ppy)$_3$ (2 mol%)	**139** (5 equiv), ACN /H$_2$O (1:1), LED$_{450\ \text{nm}}$	trace
5.	*fac*-Ir(ppy)$_3$ (2 mol%)	**139** (5 equiv), LiBr, DMF/H$_2$O (1 eq.), LED$_{450\ \text{nm}}$	trace

a) **124** (166 mg, 0.5 mmol), **139** (280 mL, 2.5 mmol, 5 equiv), catalyst (2 mol%), additive (2 equiv), solvent (1.5 mL), LED$_{450\ \text{nm}}$ or LED$_{530\ \text{nm}}$ N$_2$, rt, 24 h; b) determined by NMR

products were not observed. Instead compound **145** formed, while oxidative quenching cycle was employed. In the presence *fac*-Ir(ppy)$_3$ the substrate **124** was fully converted forming five-member ring **145** (X-ray structure of **145** is illustrated in Figure 8), although desired ATRA type products **136** or **137** were not observed (Scheme 33).

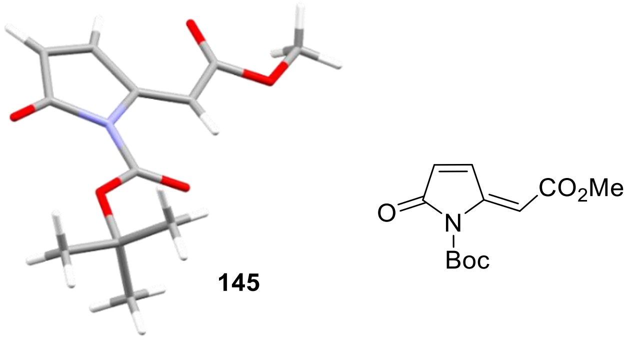
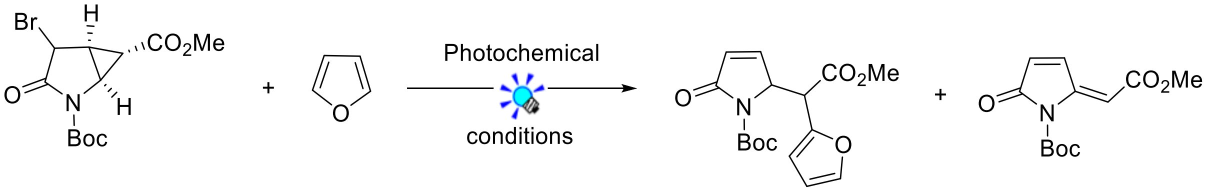


Figure 8. Single crystal X-ray structure of **145** (C = grey, H = white, O = red, N = blue).

2.4 Synthesis of trapping products

To carry out the formation of trapping products from **124** via photoredox catalysis, electron enriched heterocycles were screened under photocatalytic condition illustrated in Scheme 34. To our delight, ring opening of **124** with electron-rich heterocycles via oxidative photoredox catalysis resulted in the formation of δ-substituted α, β-unsaturated γ-lactams. However, the formation of compound **145** was also observed.



124 **146a** **147a** **145**

Scheme 34. Photoredox catalysis between **124** and furan.

Table 6. Screening of photocatalyst.^{a}

Entry	Photocatalyst	Convertion (%) ^{b}	*d.r.* (%)	Yields (%) ^{b}
		124	**147**$^{b)}$	**147/145**
1.	*fac*-Ir(ppy)$_3$ (2 mol%)	80	2:1	30/40
2.	Ir(dtbbpy)(ppy)$_2$PF$_6$ (2 mol%)	80	2:1	25/37
3.	[Ru(bpy)$_3$] Cl$_2$ (2 mol%)	80	-	trace
4.	Eosyn Y (5 mol%)^{d}	70	-	trace
5.	*fac*-Ir(ppy)$_3$ (2 mol%) $^{c)}$	85	2:1	41/35

a) **124** (166 mg, 0.5 mmol), **146a** (5 equiv), catalyst (2 mol%), ACN (1.5 mL), LED$_{450\ nm}$, N$_2$, rt, 12 h; b) determined by NMR; c) **146a** (10 equiv); d) LED$_{530\ nm}$.

To proceed a selective products formation, different photochemical conditions were screened. *fac*-Ir(ppy)$_3$ was found a suitable photocatalyst. Based on the obtained results, we realized that photoinduced ring opening of **124** and subsequent generation of **145** is a very fast process. In order to proceed the selective formation of desired product **147**, more equivalents of furan were added in the presence of *fac*-Ir(ppy)$_3$, indeed resulting in the rise of product yields (Table 6, entry 5). The other reaction parameters: solvent, base and reaction were also tested (Table 7). The investigation revealed that DMF was the most effective solvent to promote the reaction delivering product in 45% yield (Table 7, entry 4), while the use of other solvents such as acetonitrile, 1,2-dichloroethane or dimethyl sulfoxide, resulted in lower yields. In addition, the employment of a base in the photochemical reaction induced a rise of the yields of product **147**, and at the same time the amount of generated compound **145** was decreased (Table 7, entries

Table 7. Screening of base, solvent and reaction temperature.[a]

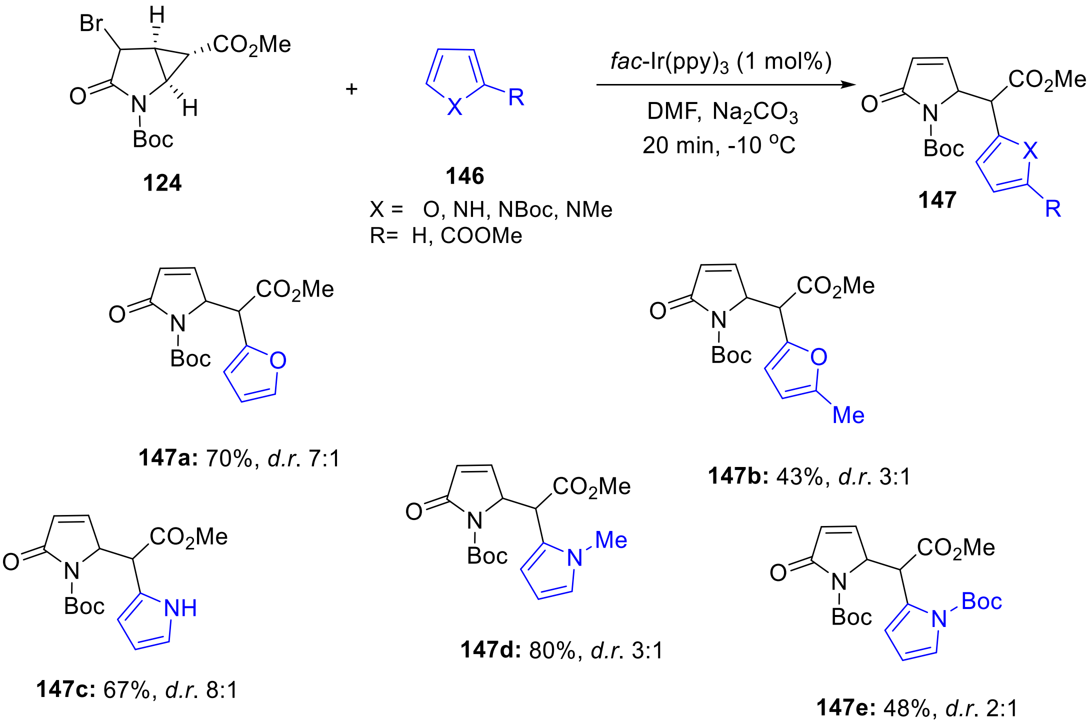
Entry	Solvent	Base	Temperature (°C)	Conversion (%) [b] **124**	*d.r.* (%) **147**[b)]	Yields (%) [b] **147**/ **145**
1.	DCM	-	24	70	-	trace
2.	DMSO	-	24	85	2:1	40/ 31
3.	DMF	-	24	90	2:1	45/ 30
4.	DMF	KH_2PO_4	24	95	2:1	47/ 29
5.	DMF-	K_2CO_3	24	95	2:1	49/ 28
6.	DMF	Na_2CO_3	24	100	2:1	50/ 27
7.	DMF-	Cs_2CO_3	24	90	2:1	46/ 30
8.	DMF	Na_2CO_3	24	100	2:1	55/ 24 [c)]
9.	DMF	Na_2CO_3	24	100	1:1	55/ 35 [e)]
10.	DMF	Na_2CO_3	0	100	5:1	65/ 15
11.	DMF	Na_2CO_3	-10	100	7:1	70/ -
12.	DMF	Na_2CO_3	-20	100	7:1	70/ -
13.	DMF	Na_2CO_3	-10	100	7:1	70[f)]/ -
14. [g)]	DMF	Na_2CO_3	24	-	-	-
15. [h)]	DMF	Na_2CO_3	24	-	-	-

a) **124** (166 mg, 0.5 mmol), **146a** (10 equiv), catalyst (2 mol%), base (2 equiv), solvent (1.5 mL), LED$_{450\,nm}$, N_2, rt, 12 h; b) determined by NMR; c) **146a** (15 equiv); e) under O_2; f) catalyst (1 mol%); g) no PC, h) no light.

4-8). Indeed, a better yield of **147** was obtained when Na_2CO_3 was used (Table 7, entry 7). The employment of more:15 equivalents of furan resulted in 55% product yield.

Considering the unsatisfied low diastereomeric ratio of product **147** (2:1) at ambient temperature and the formation of undesired compound **145,** the reaction was performed at lower temperatures. It was found that low temperature was crucial for obtaining high diastereoselectivities (Table 6, entries 11, 12, 13). Under these conditions product **147** was obtained exclusively in 70% yield and *d.r.* = 7:1 (entry 11). The yield was retained upon treatment with only 1 mol % of *fac*-Ir(ppy)$_3$ (entry 13). Control experiments confirmed that the ring opening of **147** is indeed a photochemically mediated process: if either the photocatalyst (entry 14) or the light source (entry 15) were omitted, no yields of desired product were observed. Thus, the combinations of 15 equiv of furan, 1 mol % of *fac*-Ir(ppy)$_3$, 1.2 equiv of Na_2CO_3 in DMF at -10 ^{o}C under the blue irradiation for 20 minutes are the optimal conditions for this transformation**.**

2.4.1 Substrate scope



124

146

147

147a: 70%, *d.r.* 7:1

147b: 43%, *d.r.* 3:1

147c: 67%, *d.r.* 8:1

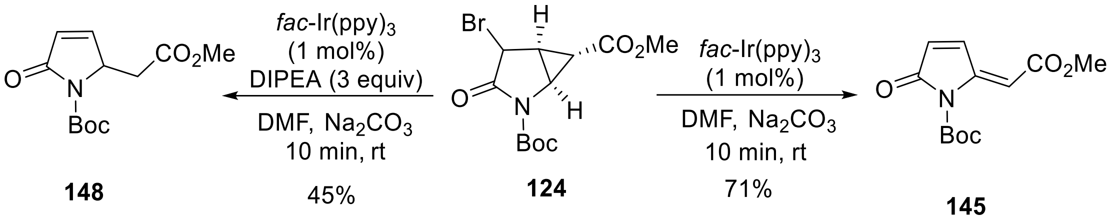
147d: 80%, *d.r.* 3:1

147e: 48%, *d.r.* 2:1

Scheme 35. The synthesis of 5-Substituted 3-pyrrolidin-2-ones via photoredox catalysis.

Under the optimized conditions (Table 7 entry 13), the substrate scope of the photochemical transformation was investigated (Scheme 35). It has to be noticed that the reaction was significantly affected by the electronic effects of substituents. Thus, using *N*-methylpyrrole as a reagent resulted **147d** in high yields, although low diastereoselectivity (3:1 *d.r.*), while *N*-pyrrole give rise to **147c** in good yield and high diastereoselectivity (8:1 *d.r.*). The employment of N-Boc protected pyrrole led to the compound **147e** in low yields and low diastereoselectivities, presumablydue to the nature of electron withdrawing Boc substitution and its steric hindrance. A 2-methylpyrrole derivative furnished the product **147b** in 43% yield, 3:1 *d.r.* Finally, the use of furan generated **147a** in 70% yield and 7:1 *d. r.* The cristal structure is required to determine the absolute configuration of obtained products.

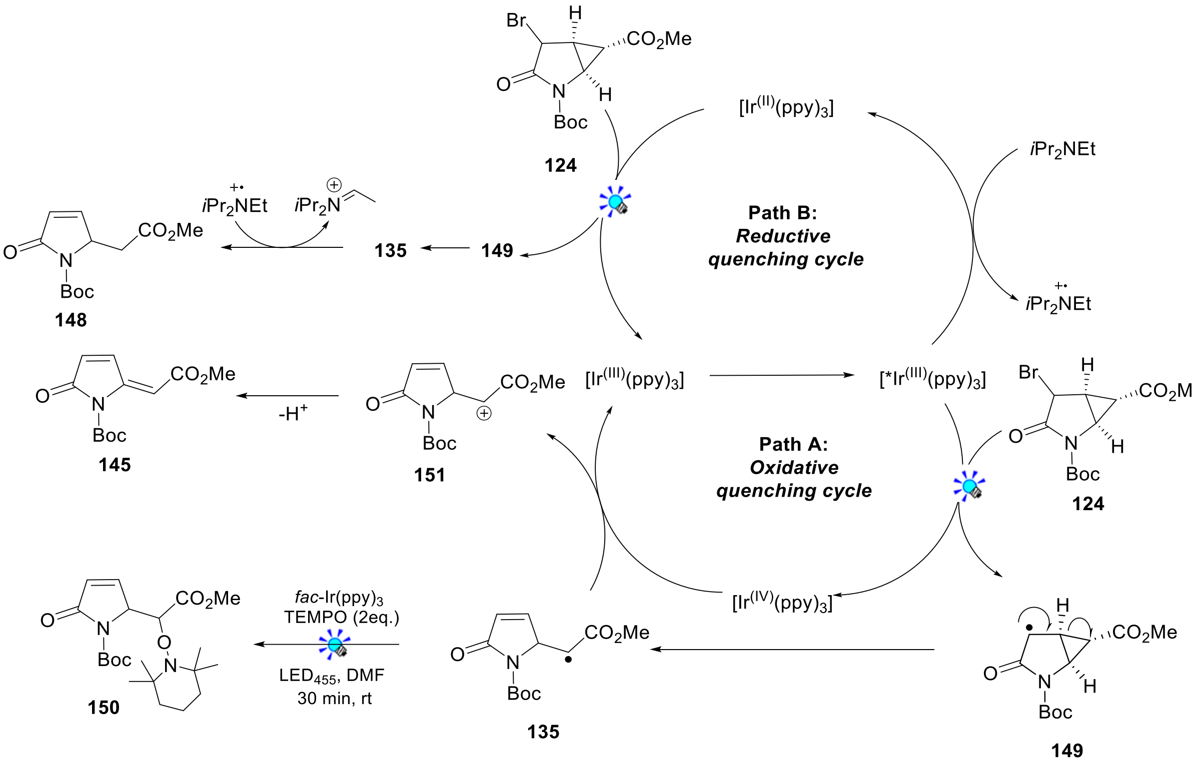
The use of other heterocycles such as thiophen, benzofuran, indole, imidazole was also investigated. Unfortunately, no desired products were observed in these cases.



Scheme 36. The photoreaction of **124** through the oxidative and reductive quenching cycles.

Investigation of the oxidative quenching cycle of the ring opening of **124** employing 1 mol % of *fac*-Ir(ppy)$_3$, 1.2 equiv of Na$_2$CO$_3$ in DMF at -10 ^{o}C under blue irradiation resulted compound **145** in 71% yield. In turn, the photoreaction of **124** through the reductive quenching cycle, using DIPEA as a sacrificial electron donor led to the compound **148** in 45% yield, showing the efficiency oxidative quenching cycle.

2.4.2 Proposed mechanism



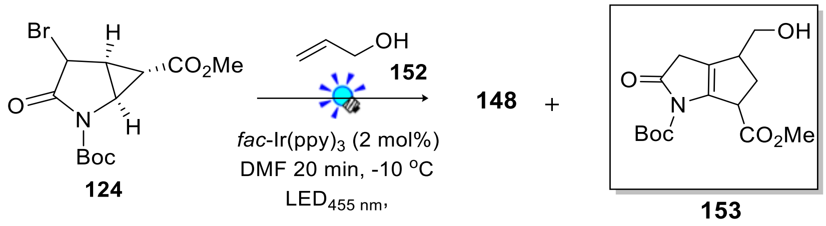
Scheme 37. Proposed mechanism for photocatalyzed reductive and oxidative cycles.

Path A: *Oxidative quenching cycle*: A plausible mechanism for the formation of product **145**, involving oxidative quenching cycles has been proposed. Single electron transfer from the excited Ir(ppy)$_3$ to **124** led after cyclopropane ring-opening to the radical **150.** Oxidation of this radical by the oxidized form of the photocatalyst to the corresponding cation **151** followed by deprotonation, which yields the product **145** and recover the photocatalyst in its initial state completing the catalytic cycle. The mechanism of the formation of radical **135** has been proved by utilizing well known radical marker TEMPO with targeting substrate **124** and *fac*-Ir(ppy)$_3$ in DMF under visible light irradiation. After 30 minutes the TEMPO trapped intermediate **150** was detected (see the Experimental section for more details).

Path B: *Reductive quenching cycle*: The proposed mechanism pathway of formation product **148** involves generation of the reduced form of the photocatalyst via reduction of its excited state with DIPEA (as a sacrificial electron donor). Next the reduced photocatalyst transfers an electron to the substrate **124** inducing cyclopropane ring-opening and forming the same key intermediate as in the pathway A the radical **135**, which is directly converted to the product **148** via abstraction of hydrogen atom from DIPEA

2.3.4 Further transformation attempts

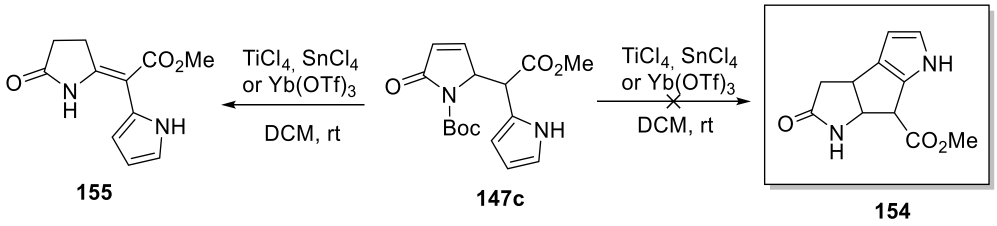
Next, we were intrigued to facilitate the cascade photocatalytic cyclization between substrate **124** and allyl alcohol **154** (the substrates which contains hydrogen source) to form cyclized pyrrolidone type product **153** (Scheme 38). The structural analogues of **153** are known to be human glutamate transporters EAAT1, EAAT2, and EAAT3, and *i*Glu receptors.[78] Pharmacological characterization of those Glu analogues has provided important information about the binding mode of Glu to Glu receptors and transporters, as well as the structural requirements for Glu receptor agonist/antagonist activity, Glu transporter substrate/inhibitor activity, and subtype selectivity.[78] Unfortunately, no desired product was detected in this transformation, while the formation of reductive product 3,4-didehydropyroglutamic esters **148**



Scheme 38. The formation of isomerized product.

was obtained. We believed that the allylic alcohol **152**, which acts as sacrificial electron donor by giving a hydrogen in the following photochemical reaction formed **148** (Scheme 38).

Having developed a new approach to a variety of 5-substituted 3-pyrrolidin-2-one derivatives by photoredox catalysis, we then devoted our efforts to exploring further transformations, aiming synthesize tricyclic ring systems, which are important skeletons of many biologically active compounds. The treatment of **147c** with Lewis acid failed to give the desired adduct **154**, instead the isomerizes product **155** was observed in 45% yields (Scheme 39).



Scheme 39. The formation of isomerized product

2.5 Conclusion

In summary, the exocyclic ring-opening of α-bromoketone via photoredox catalysis delivering pyrrolidone derivatives was studied. Upon irradiation the formation of exclusively Michael acceptor **145** was obtained through oxidative quenching from substrate **124**. Moreover, the corresponding ring opening radical generated from **124** was trapped with electron rich heterocycles providing 5-substituted 3-pyrrolidin-2-one derivatives, despite the limited substratescope, the formed products were obtained in good yields and in some case with high *d.r.* ratio. On the other hand, photochemical ring opening of **124** through the reductive quenching cycle delivered **148**, in lower yields than the previously reported.[33b] Despite of this fact, it was an alternative method to avoid the employment of replacing hazardous reagent (AIBN).

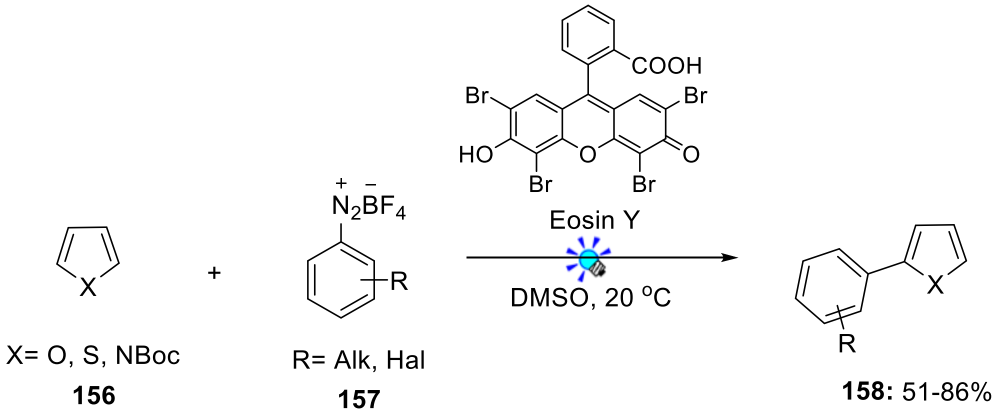
The synthesized 5-substituted 3-pyrrolidin-2-ones can serve as valuable intermediates in a number of biologically active compounds and might be of importance in natural product synthesis due to their potential utility towards construction of complex molecules.

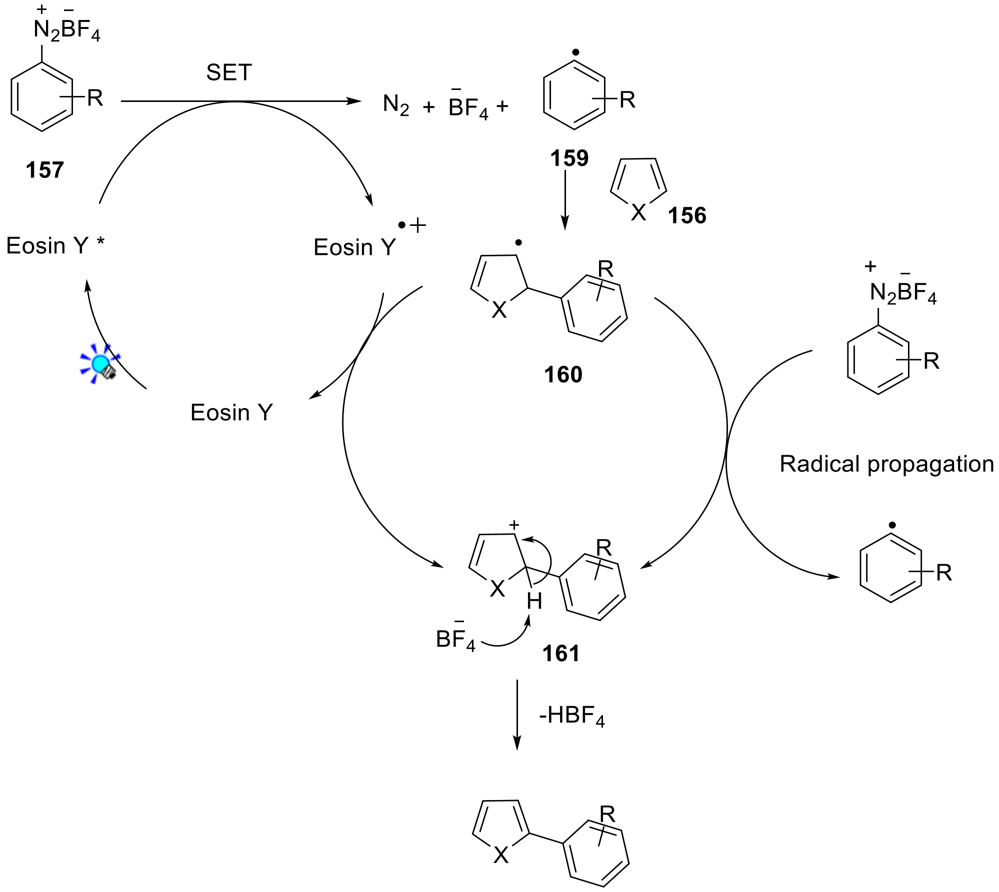
3. Photoredox mediated direct arylsulfonylation of cyclopropanated pyrrole derivatives

3.1 Literature synthesis of arylated and arylsulfonylated heterocycles.

Arylated pyrrolidines are structural key motifs present in many natural and synthetic useful molecules.[80] The core structure of some medicinally important synthetic molecules is built on arylated pyrrolidine. As an example, CCK antagonist (RP 66803)[80h] and angiotensin-converting enzyme (ACE) inhibitor[80i, j] having potential trypanosomal activity should be noted. Apart from their pharmacological applications, enantioenriched arylated pyrrolidine frameworks are important intermediates in organic synthesis.[81] The widespread utilization of arylated pyrrolidine derivatives, in both medicinal chemistry and organic synthesis, demands the development of novel and applicable methods for their preparation. Over the years diverse procedures have been reported for the aryl−heteroaryl bonds construction.[82] One of the recent methods of aryl−heteroaryl bonds construction is the direct arylation of heteroarenes by C−H bond activation via photoredox catalysis. In this section we aimed to develop a photochemical method of cyclopropane arylation employing different aryl sources.

In 2012, König and co-workers developed a metal-free method for the visible-light-mediated direct C−H arylation of heteroarenes **156** with aryl diazonium salts **157** (Scheme 40).[83] As photoredox catalyst, it was employed the organic dye Eosin Y, which allows the reaction to occur at room temperature without using a transition-metal catalyst or base, and delivering arylated heteroarene products **158** in high yields. The aryl radical **159** was formed





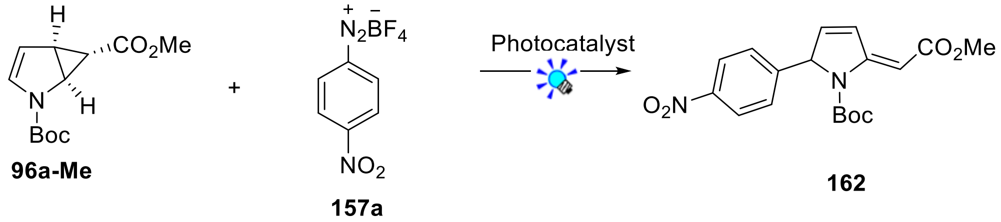
158

Scheme 40. Literature known visible light mediated direct arylation of heterocycles.

by SET from the excited state of eosin Y to aryl diazonium salt **157**, which followed the addition of aryl radical **159** to heterocyclic compound **156** forming radical intermediate **160**. Next, radical **160** transformed to carbocation intermediate **161** by two possible pathways: *i*) oxidation of the radical intermediate **160** by the eosin Y radical cation to give **161** and *ii*) the oxidation of **160** by aryl diazonium salt **157** in a radical chain transfer mechanism. The coupling product **158** was resulted after deprotonation of intermediate **161**, regenerating the aromatic system.

3.2 Synthesis of 3-substituted arylated cyclopropane

Utilizing the above-mentioned strategy,[83] we commenced our study with the reaction between *N*-carbomethoxypyrrole **96a-Me** and diazonium salt **157a** under photochemical conditions aiming to form the arylated coupling product **162** (Scheme 41).



Scheme 41. Proposed C-H arylation of cyclopropanated pyrrole with aryl diazonium salts.

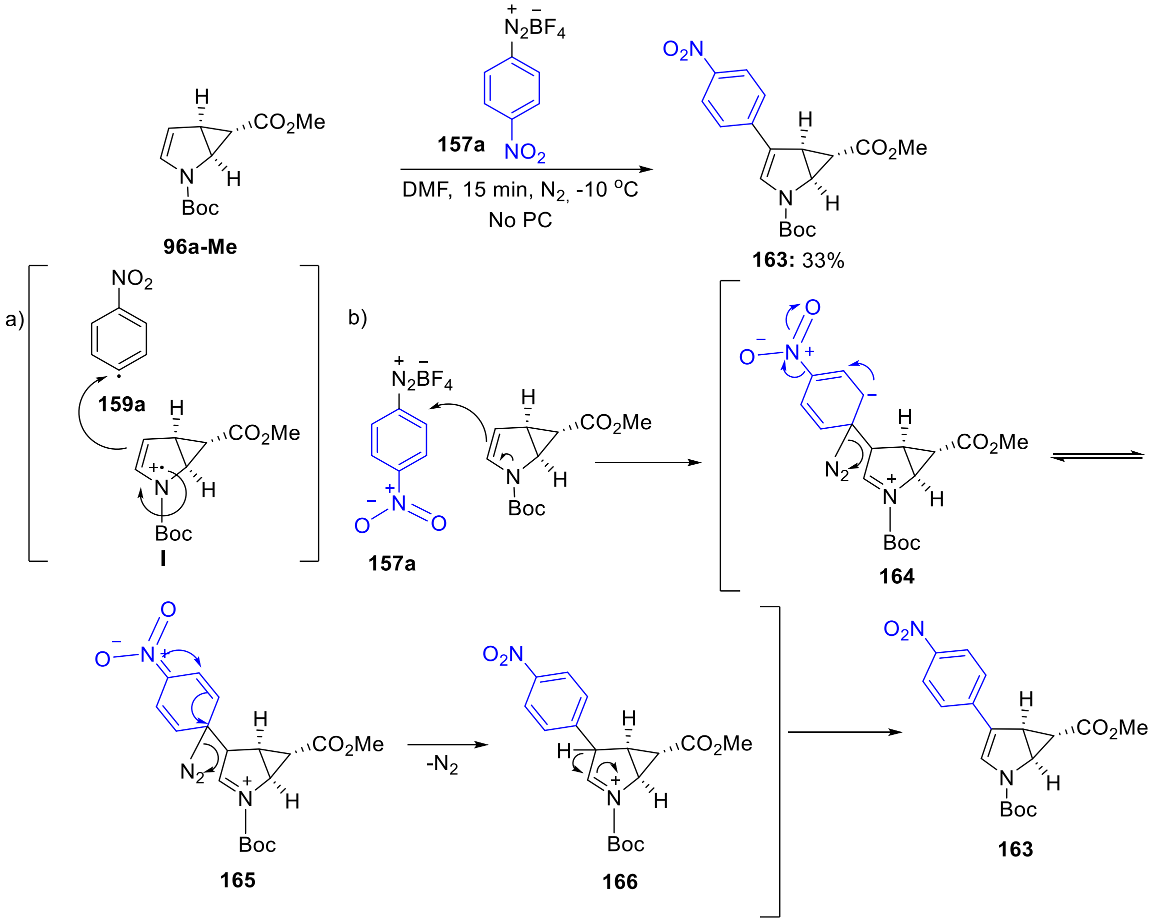
The photochemical reaction between **96a-Me** and *p*- nitrobenzenediazonium tetrafluoroborate **157a** in the presence of Eosin Y in DMSO resulted in unclear reaction mixture. Targeting to proceed the direct C−H arylation of cyclopropanated **96a-Me** substrate with aryl diazonium salts using various photocatalytic conditions was then investigated, but the reactions failed to give the desired products (Table 8, entries 1-3). However, an immediate color change was observed after mixing the substrate **96a-Me** with diazonium salt in DMSO at room temperature after 5 minutes in the absence of any photocatalysts and LED source.

Table 8. Screening of base, solvent and reaction temperature.[a]

Entry	Conditions	Yields (%) [b] **163**
1.	Eosin Y (5 mol%), DMSO, 20 °C, LED $_{530\ nm}$	traces
2.	[Ru(bpy)$_3$] Cl$_2$ (2 mol%), DMSO, 20 °C, LED $_{435\ nm}$	traces
3.	*fac*-Ir(ppy)$_3$(2 mol%), DMSO, 20 °C, LED $_{435\ nm}$	traces
4	No PC, DMSO, 20 °C, 10 min	13
5.	No PC, DMF, 20 °C, 10 min	15
6.	No PC, DMF, 0 °C, 10 min	20
7.	No PC, DMF, -10 °C, 10 min	33
8.	No PC, DMF, -10 °C, 10 min	31[c]
9.	NaOAc (1.1 equiv), ACN, 20 °C, 2 h	traces
10.	Cu(OTf)$_2$ (0.15 equiv), ACN, 2 h	traces

a) **96a-Me** (120 mg, 0.5 mmol), **157a** (177 mg, 0.75 mmol, 1.5 equiv), solvent (1.5 mL), N$_2$, 24 h; b) determined by NMR; c) in the dark.

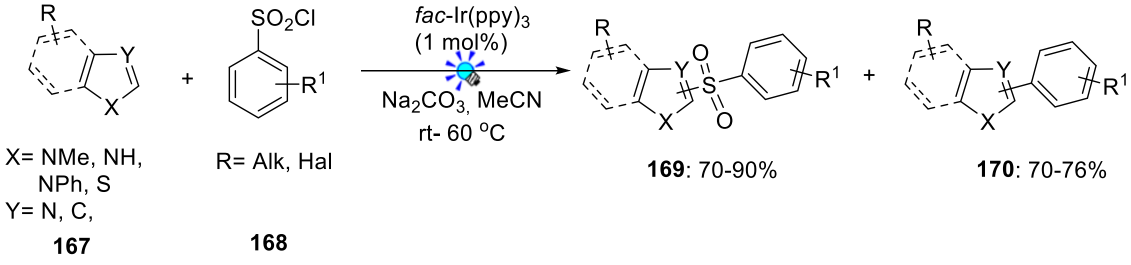
After the purification of the resulting mixture, the formation of compound **163** was isolated in 13% yield. Since the chemical process was exothermic, the lower reaction temperature favored the reaction and when the reaction was performed at -10 °C in DMF, the product **163** was provided in 33 % yield (Table 8, entries 5−7). Further attempts to increase reaction yields by transition-metal-free Meerwein arylation[84] and classical copper-catalyzed addition of an aryl diazonium salt[85] to a cyclopropanated pyrroles only led to decomposition of the substrate. Firstly, we proposed that the reaction might proceed by nucleophilic attack of enamine to the aryl radical **159a**, which was formed in DMF solution after dinitrogen extrusion (Scheme 41 a). However, we found out that it is an unlikely process, while experimental data showed that the same reaction with electron-donating substitution on aryl fragment did not afford the desired adducts (unclean crude reaction was observed).



Scheme 42. C−H arylation of **96a-Me** with aryl diazonium salts.

Thus, we proposed that formation of product **163**, was plausibly promoted due to the electron-withdrawing effect of nitro group at *para*-position of the aryldiazonium salt **157a** (Scheme 42 b), which is known to be a very active reagent that stabilizes the aromatic ring by mesomeric effect. As a result, the nucleophilic aromatic substitution is favored and consequent electrophilic addition at the C3-position of substrate **96a-Me** delivers **164**. The following extrusion of N_2 and further deprotonation furnishes the final product **163**.

In 2018, Reiser and co-workers published a visible-light-mediated temperature controlled arylation or arylsulfonylation of heterocyclic compounds (Scheme 43).[84] Alternatively to aryldiazonium salt, in this work arylsulfonyl chloride was utilized as a reagent. This starting material has several advantages, they are biocompatible, relatively cheap, commercially available and arylsulfonyl chlorides can be stored for longer periods of time under ambient conditions.[85] In this work the importance of the temperature for the selective visible light mediated C−C or C−S bond formation was demonstrated. Thus, at room temperature (23 °C) the selective C2-sulfonylation into **167** was realized, resulting **169** in 70−90% yields. While, at higher temperature (45 °C), the exclusive C2-arylation products **170** were obtained in 70−76% yields.

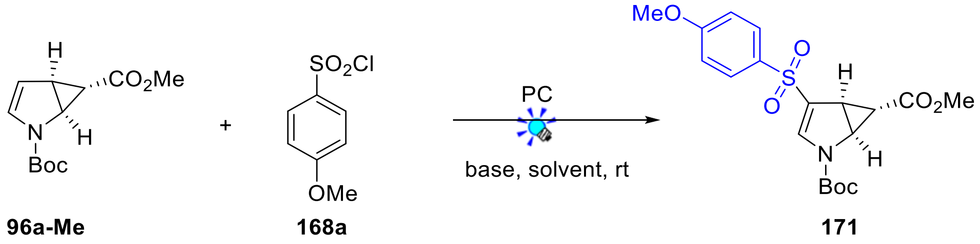


Scheme 43. Known temperature control, selective sulfonylation or arylation of heterocycles via photoredox catalysis.

3.3. Synthesis of 3-substituted arylsulfonylated cyclopropanes.

3.3.1 Optimization studies

Intrigued by this observation, we next investigated the visible-light photocatalyzed cross-coupling reactions between arylsulfonyl chloride and substrate **168a**. Thus, the reaction at 50 °C did not yield the desired cross-coupling arylated product resulting in a unclear reaction mixture. In turn, the photochemical reaction between substrate **96a-Me** and 4-methoxybenzenesulfonyl chloride **168a** at room temperature gave rise to arylsulfonylation **171** product. Surprisingly, no ring opening was observed, albeit compound **171** can serve as a building block for further transformation. To optimize reaction conditions, different photocatalysts and reaction conditions were screened. During the photochemical reaction between **96a-Me** and **168a**, *fac*-Ir(ppy)$_3$ and Ru(bpy)$_3$Cl$_2$ showed almost the same efficiency (Table 9, entries 1 and 4). Therefore, the less expensive Ru(bpy)$_3$Cl$_2$ was chosen as optimal catalyst. Switching the solvent did not give satisfying results (Table 8, entries 5−7), while the employment of K$_2$HPO$_4$ promoted the formation of arylsulfonylated product in 45% yield (entry 11).



Scheme 44. The synthesis of 3-subsitituted arylsulfonylated cyclopropane.

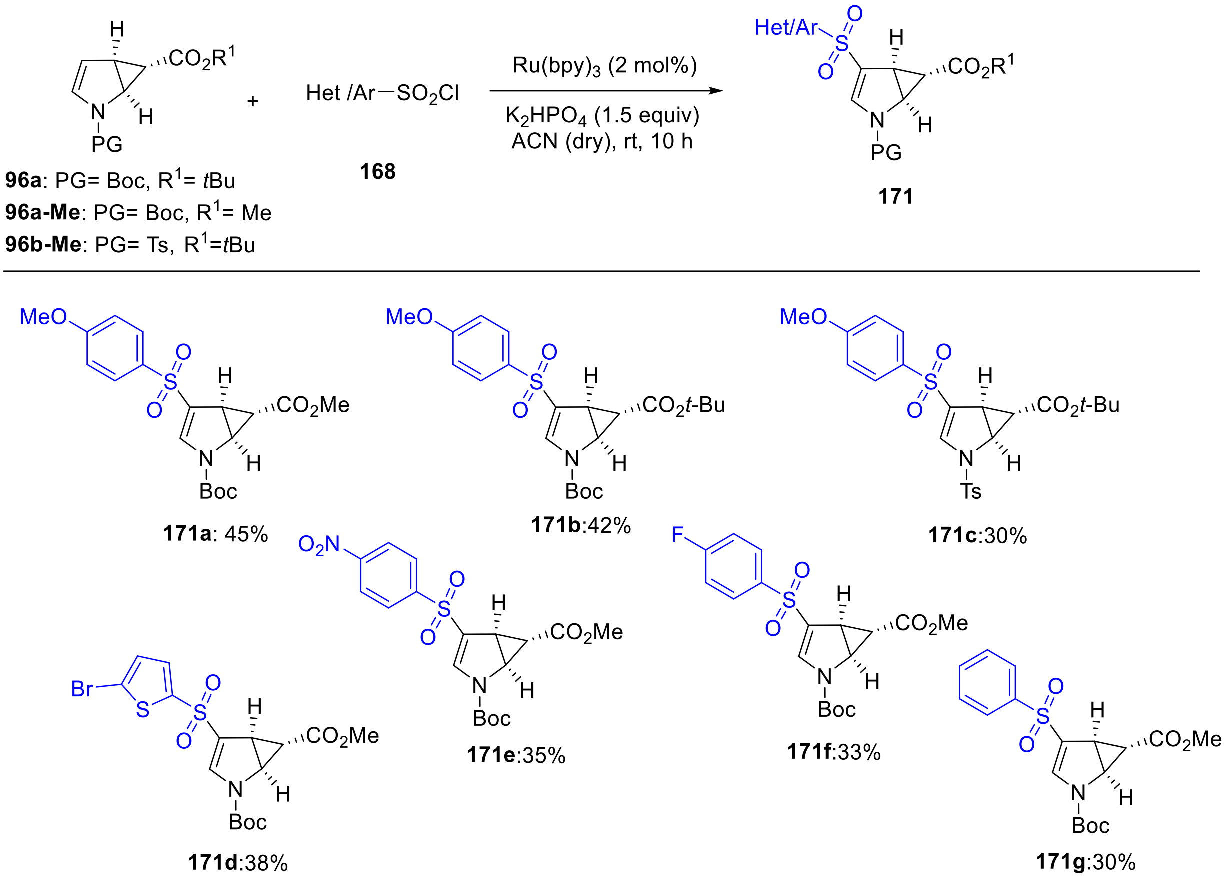
Table 9. Optimization reaction.[a]

Entry	Photocatalyst	Base	Solvent	Yields (%)[b] **171**
1.	*fac*-Ir(ppy)$_3$ (2 mol%)	Na$_2$CO$_3$	ACN	33
2.	Ir(dtbbpy)(ppy)$_2$PF$_6$ (2 mol%)	Na$_2$CO$_3$	ACN	16
3.	Ir[p-F(t-Bu)-ppy]$_3$ (2 mol%)	Na$_2$CO$_3$	ACN	17
4	[Ru(bpy)$_3$] Cl$_2$ (2 mol%)	Na$_2$CO$_3$	ACN	32
5.	[Ru(bpy)$_3$] Cl$_2$ (2 mol%)	Na$_2$CO$_3$	DCM	20
6.	[Ru(bpy)$_3$] Cl$_2$ (2 mol%)	Na$_2$CO$_3$	DMSO	23
7.	[Ru(bpy)$_3$] Cl$_2$ (2 mol%)	Na$_2$CO$_3$	DMF	30
8.	[Ru(bpy)$_3$] Cl$_2$ (2 mol%)	NaHCO$_3$	ACN	39
9.	[Ru(bpy)$_3$] Cl$_2$ (2 mol%)	K$_2$CO$_3$	ACN	33
10.	[Ru(bpy)$_3$] Cl$_2$ (2 mol%)	Cs$_2$CO$_3$	ACN	25
11.	[Ru(bpy)$_3$] Cl$_2$ (2 mol%)	K$_2$HPO$_4$	ACN	45
12	[Ru(bpy)$_3$] Cl$_2$ (2 mol%)[c]	K$_2$HPO$_4$	ACN	-
13.	No PC	K$_2$HPO$_4$	ACN	-

a) **96a-Me** (120 mg, 0.5 mmol), **168a** (135 mg, 0.65 mmol, 1.3 equiv), base (1.5 equiv), solvent (1.5 mL), N$_2$, 24 h; b) determined by NMR; c) no light.

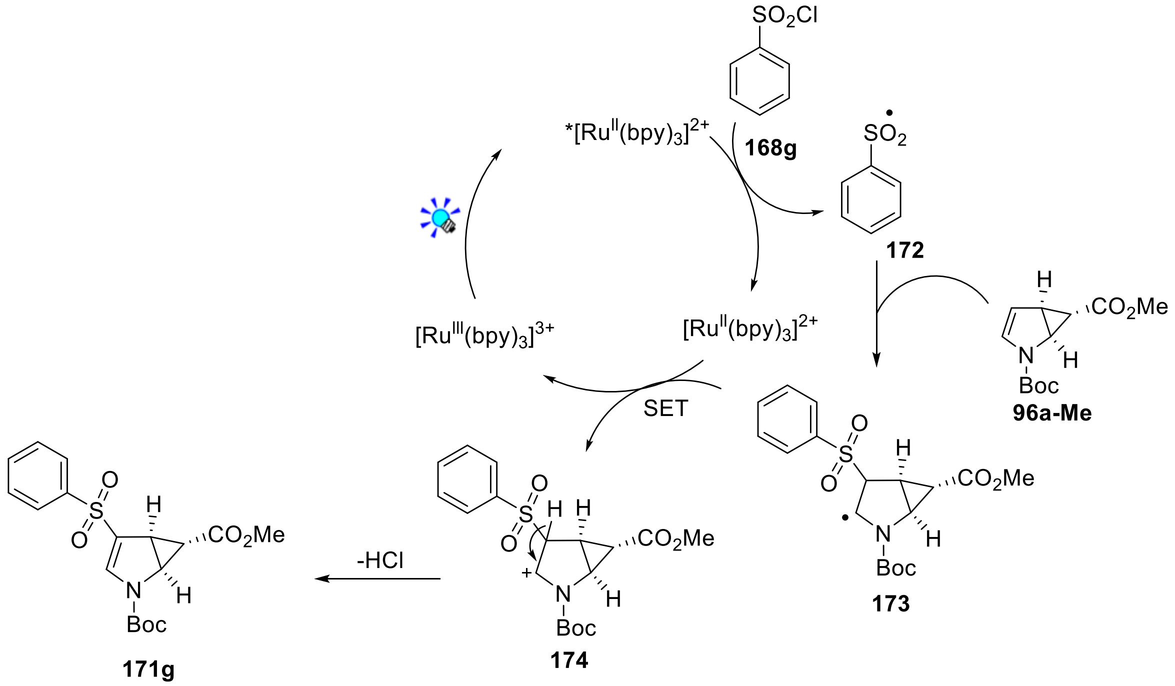
3.3.2 Substrate scope and proposed mechanism of 3-substituted arylsulfonylated cyclopropanes

The substrate scope of the photochemical transformation was then investigated (Scheme 44). The reaction was affected by the electronic effects of the substituents on the arylsulfonyl chlorides. The arylsulfonyl chlorides bearing electron-withdrawing (**171e**, **171f**) or neutral groups (**171g**) showed slightly lower yields than those bearing electron- donating (**171a**, **171b**). Electronic effects of the protecting groups at the nitrogen atom also influenced the efficiency of the photochemical process. The more electron withdrawing group Ts afforded **171c** only in 30%, while switching to Boc group **171b** delivered the product in 42% yield.



Scheme 45. The direct arylsulfonylation of cyclopropanated pyrrole derivatives.

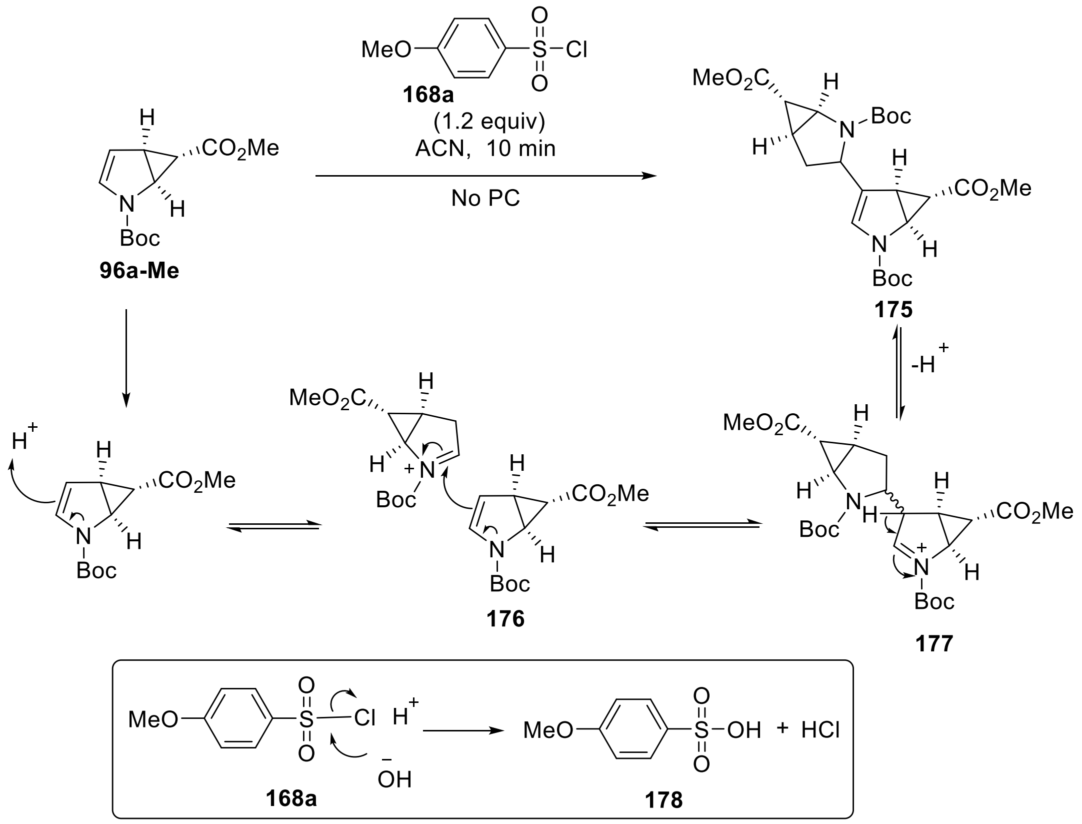
Based on previous literature reports,[82–90] a plausible mechanism for the direct arylsulfonylation was proposed (Scheme 45). The irradiation of $[Ru(bpy)_3]Cl_2$ with visible light promotes metal-to-ligand charge transfer state of the photocatalyst generating $[Ru(bpy)_3]Cl_2$*. A single electron transfer from the excited $[Ru(bpy)_3]Cl_2$* to the arylsulfonyl chloride **168g** affords $[Ru(bpy)_3]Cl_2$ and the arylsulfonyl radical **172**. The coupling of **172** with a cyclopropanated pyrrole **96a-Me** at C3-position would generate the radical on the C2 position **173**, which is favored due to the effective stabilization by nitrogen. Subsequently **173** would transform into the corresponding carbocation intermediate **174** by oxidation with the oxidized photocatalyst which in turn regenerates the catalyst. Deprotonation of carbocation intermediate **174** resulted the desired 3-arylsulfonyl substituted pyrrole. The base K_2HPO_4 was employed in the reaction to neutralize the hydrogen chloride generated as a byproduct in the reaction. The cyclopropane cleavage was not observed, which could be explained in terms of unfavored radical addition at the C2-position, generating a non-stabilized primary radical.



Scheme 46. Proposed mechanism.

3.3.3 Formation of dimer

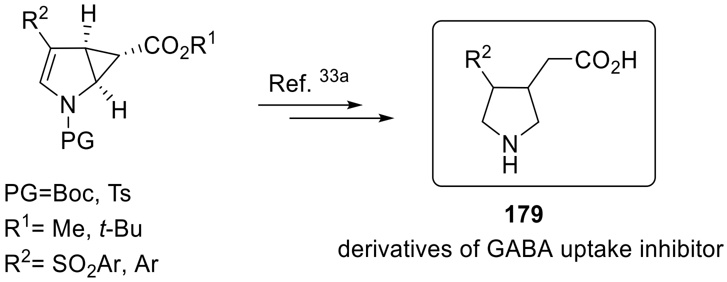
It is important to note that the reaction set up was crucial for the desired direct arylsulfonylation. The efficient transformation requires first irradiation of photocatalyst with aryl sulfonyl chloride **168** and a base following the addition of **96a-Me**. Otherwise, the mixture of **96a-Me** and aryl sulfonyl chloride in ACN gives rise to the quick formation of dimer **175** (3:1 *d.r.*), no photocatalyst and irradiation is required for this transformation (Scheme 46). The generation of dimers was already described upon treatment under acidic condition with TFA[36] or gold(I) catalysis.[92] The possible explanation is that aryl sulfonyl chloride under moisturizing conditions generates aryl sulphonyl acid **179** and acid chloride, even small amount of any of these acids will facilitate acid catalyze dimerization.



Scheme 47. Proposed mechanism for the acid-catalyzed dimerization of enecarbamate.

It is known that enamides display two opposing reaction pathways, they can undergo reactions with both electrophiles and nucleophiles. The protonation of **96a-Me** would give rise to the iminium species **176** which act as electrophiles for the dimer formation. A second molecule of **96a-Me** then acts as nucleophile and attacks the iminium ion to generate **176**. The elimination of H^+ will close catalytic cycle resulting in dimer **175**. The resulting product **175** containing 1,3-diamine framework, can be used as an intermediate in natural product synthesis[93] and medicinal chemistry.[94] The generation of acidic condition can also explain the low yields of arylsulfonylated products, since acidic condition beside dimerization can also promote undesired ring opening of the cyclopropanated substrates.

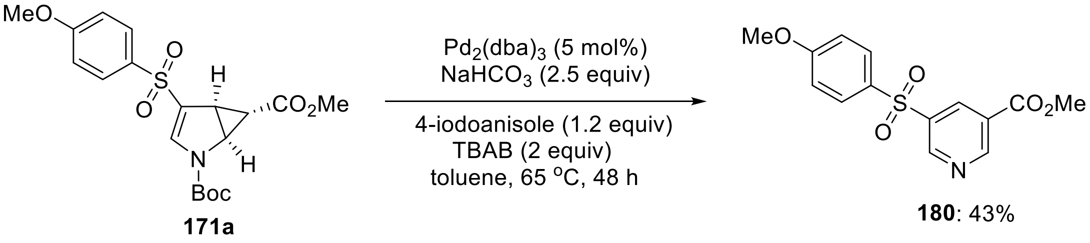
3.4. Application of arylated and arylsulfonylated cyclopropanes.



Scheme 48. Aryl and arylsulfonylated products as a suitable intermediate for the synthesis of homo-β-proline derivatives.

3-substituted aryl and arylsulfonylated products can serve as a suitable intermediate for the synthesis of new drug candidates such as homo-β-proline derivatives, GABA uptake inhibitors, utilizing in the treatment of neurological and psychiatric disorders, such as anxiety, Parkinson's disease, epilepsy and some forms of schizophrenia (Scheme 47).[95]

The synthesized arylsulfonylated products are an interesting building blocks for further transformation, allowing to access an important 6-membered nitrogen containing heterocycles (Scheme 48). The palladium catalyzed reaction between **171a** with 4-iodoanisole was conducted to obtain coupling product, albeit the ring opening reaction resulted in pyridine product **180** in 43%, with no desired coupling product formation. Albeit, product **180** is a valuable intermediate, which contains a key structure of many biological active compounds and drug candidates.[44]



Scheme 49. Ring expansion furnishing pyridine derivative.

3.5 Conclusion

The visible-light-mediated reaction between aryl sulfonyl chloride and targeting cyclopropanated pyrrole derivatives resulted in direct arylsulfonylation. The reaction set up is very important for desired transformation to take place. Thus, photoredox catalysis gave rise to C−S bond formation, while employing acidic conditions led to dimerization. In addition, the formation of direct arylated cyclopropane was also achieved. The synthesized products constitute convenient scaffolds for the synthesis of valuable five- and six-membered heterobiaryls, which are important structural motifs frequently found in natural products, pharmaceuticals and functional materials.[96,97]

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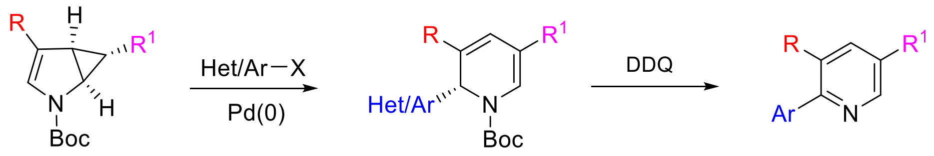
C. Summary

In this thesis the importance of monocyclopropanated pyrroles as a valuable intermediate for the design of highly functionalized five- and six-membered nitrogen containing heterocycles has been shown. Previously, the ring-opening of rather activated exocyclic carbon-carbon bond of cyclopropanes was realized, while the cleavage of non-activated carbon-carbon bond was challenging in the area for the long time. In the first part of the thesis we put our efforts to develop the general method of desired ring expansion on cyclopropane ring system (Scheme 49).



R = H, CO_2Alkyl, CHO
R^1 = CO_2Alkyl, CH_2OH

110: 41-81% yield

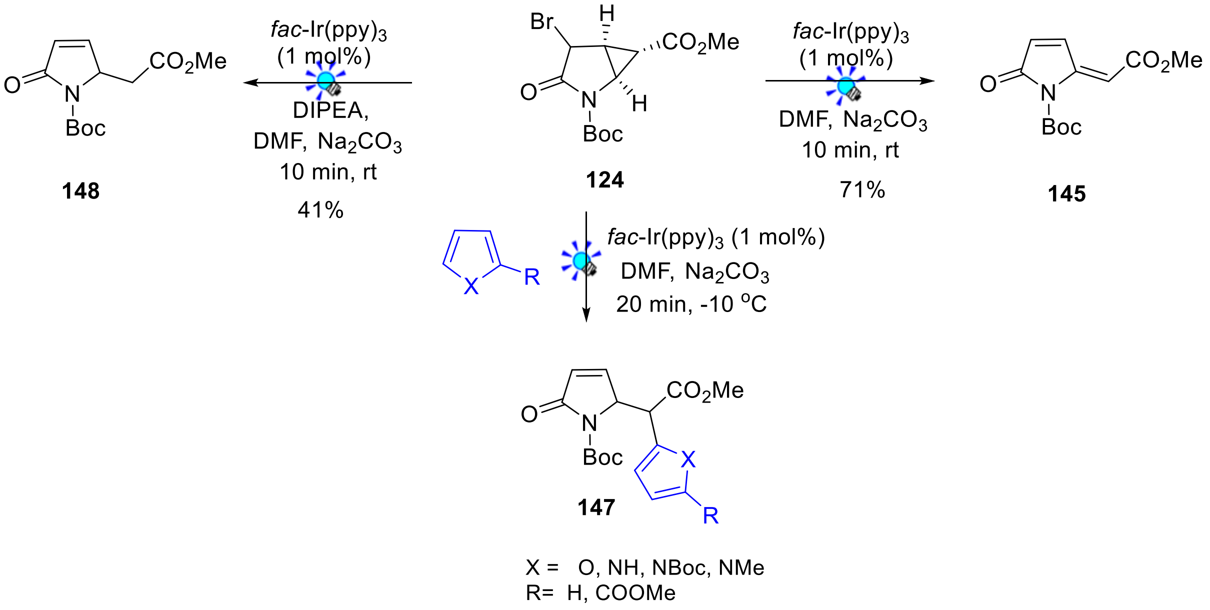
111

- **perfect transfer of chirality**
- **facile access to functionalized pyridines and piperidines**

Scheme 49. Palladium catalyzed ring-opening of the non-activated cyclopropanes delivering valuable six-membered heterocycles.

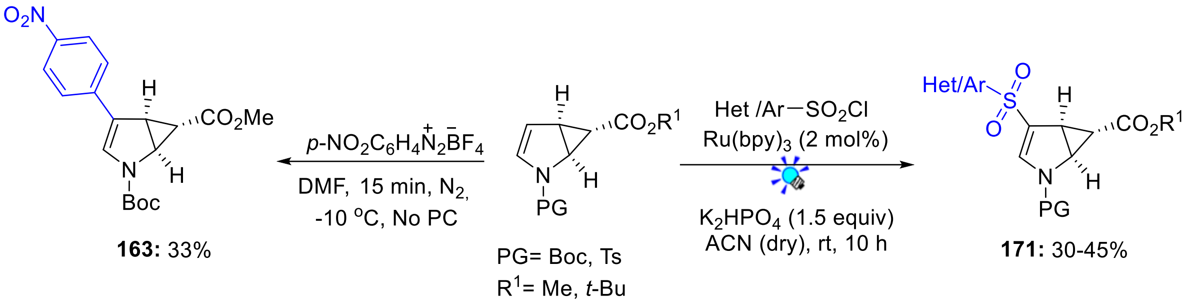
Delightfully, highly regio- and diastereoselective palladium-catalyzed Heck cross-coupling of monocyclopropanated pyrroles with hetero/aryl halides with concurrent ring-opening of the non-activated cyclopropane bond has been realized, delivering highly functionalized dihydropyridines and pyridines. The developed general method demonstrated the wide scope of transformation between cycloadducts and various aryl and heteroaryl substrates. Despite steric hindrance the introduction of an ester or a formyl group into the 3-position of the cyclopropanated pyrrole also proceed well in cross-coupling reaction delivering highly functionalized dihydropyridines. Notable, employing enantiopure cyclopropanated pyrrole, this transformation occurred with perfect chirality transfer, in which the Heck-arylation occurs from the convex face of the bicycle. In addition, a one-pot synthesis of biaryl pyridine was realized: starting from the Heck coupling to dihydropyridine, the subsequent addition of oxidant (DDQ) to the reaction mixture resulted in desired 2-arylpyridines, which are very important pharmacophores, albeit challenging in the preparation. Pleasantly, the substitution of alcohol on cyclopropyl group, instead of classical donor-acceptor group, also provide the desired transformation, presenting the generosity of developed palladium catalyzed Heck cross-coupling method. Finally, the transformations of corresponding dihydropyridines as a suitable intermediate was demonstrated.

In the second section of the thesis, the visible light mediated ring opening of α-bromoketone **124** furnishing valuable five membered nitrogen containing pyrrolidone derivatives was demonstrated (Scheme 50).



Scheme 50. The visible light mediated ring opening of *α*-bromoketone.

The irradiation of **124** thorough the oxidative quenching cycle provided the fast ring-opening, delivering product **145**. In turn, the photochemical reaction of **124** through the reductive quenching cycle, in the presence of DIPEA as an electron donor facilitated compound **148**. Finally, the trapping products **147** were formed utilizing oxidative quenching cycle between substrate **124** and electron enriched heterocycles. The synthesized 5-substituted 3-pyrrolidin-2-one derivatives are important intermediates and highly desirable in natural product synthesis and medicinal chemistry.

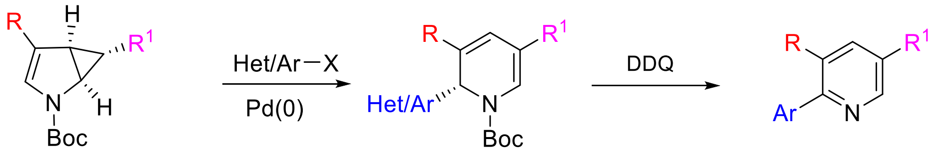


Scheme 51. Direct arylation and arylsulfonylation of cycloadducts.

Visible-light-promoted catalyzed reaction between cyclopropanated pyrrole derivatives and arylsulfonyl chlorides gave rise to the construction of sulfur containing products **171** through the simple C–S bond-formation, which was discussed in the third section of the thesis (Scheme 51). In addition, the direct C–H arylation of cyclopropanated pyrroles with nitrobenzenediazonium tetrafluoroborate substrate in DMF was obtained, delivering arylated cyclopropane **163**. The provided aryl and arylsulfonylated cyclopropanes can serve a as building block for further transformation to construct complex structure molecules.

D. Zusammenfassung

Die vorliegende Arbeit beschreibt die Anwendung einfach-cyclopropanierter Pyrrole als Ausgangsmaterial zur Synthese von funktionalisierten fünf- und sechsgliedrigen Stickstoff-Heterocyclen. Während die Ringöffnung aktivierter exocyclischer C–C-Bindungen in Cyclopropanen bekannt ist, stellt der Bruch der unaktivierten C–C-Bindung, und damit die Ringerweiterung, schon lange eine Herausforderung dar. Im ersten Teil der Arbeit wird eine Methode für ebendiese Ringerweiterung beschrieben (Schema 49).



R = H, CO_2Alkyl, CHO
R^1 = CO_2Alkyl, CH_2OH

110: 41-81% Ausbeute

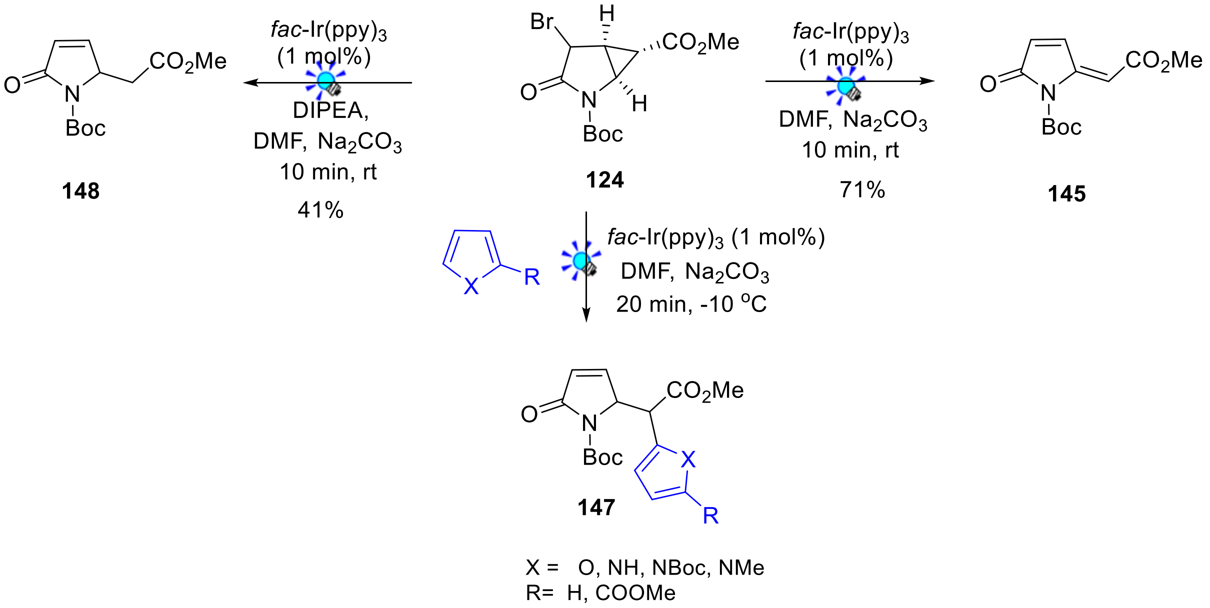
111

- **Perfekter Chiralitätstransfer**
- **Leichter Zugang zu funktionalisierten Pyridinen, Piperidinen und Pyranen**

Schema 49. Die Palladium katalysierte Ringöffnung eines Cyclopropans an der inaktivierten Bindung setzt einen wertvollen sechs-gliedrigen Heterozyklus frei.

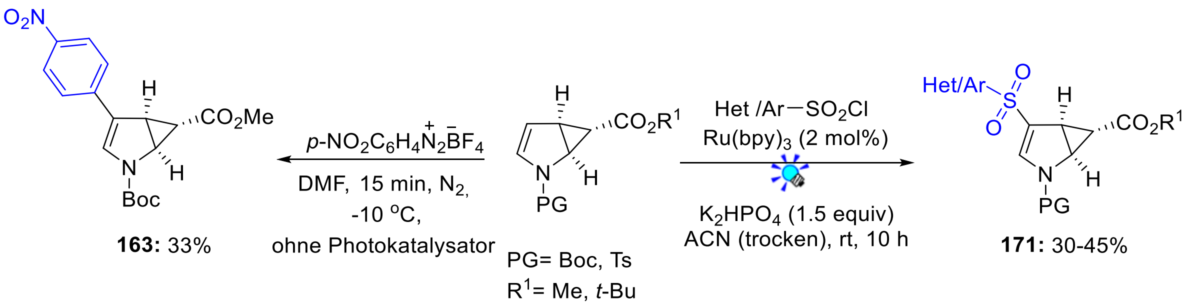
Zu unserer Freude konnte eine regio- und diastereoselektive palladiumkatalysierte Heck-Kopplung von monocyclopropanierten Pyrrolen mit (hetereo)arylhalogeniden und damit einhergehender Ringerweiterung durchgeführt werden, um hochfunktionalisierte Dihydropyridine und Pyridine darzustellen. Die entwickelten Reaktionsbedingungen ermöglichen die Umsetzung einer großen Bandbreite sowohl von Cycloaddukten als auch Aryl- und Heteroarylhalogeniden. Trotz erhöhten sterischen Anspruchs hinderte die Einführung eines Esters oder einer Formylgruppe in 3-Position des Pyrrols die Reaktivität in der Kreuzkupplung nicht und ermöglichte die Darstellung hochfunktionalisierter Dihydropyridine. Bei Verwendung von enantiomerenreinem cyclopropaniertem Pyrrol wurde ein vollständiger Übertrag der Chiralität beobachtet, da die Heck-Reaktion nur von der convexen Seite des Bicyclus stattfinden kann. Weiterhin wurde eine Ein-Topf Synthese von Arylpyridinen entwickelt, wobei die aus der Heckkupplung erhaltenen Dihydropyridine durch Addition eines Oxidans (DDQ) zu den erwarteten 2-Arylpyridinen umgesetzt wurden, welche einen sonst schwer darzustellenden Pharmakophor darstellen. Erfreulicherweise konnte auch ein Alkohol an der Cyclopropylgruppe, statt des klassischen Donor-Akzeptor-Systems, verwendet werden, was die Substratbreite der entwickelten Palladiumkatalysierten Heckkupplung hervorhebt. Zuletzt wurden weitere Transformationen der Dihydropyridine unternommen, um ihren Nutzen als Intermediate bei der Naturstoffsynthese zu zeigen.

Im zweiten Teil dieser Arbeit wurde die durch sichtbares Licht mediierte Ringöffnung von α-Bromoketon **124** zu wertvollen fünfgliedrigen Pyrrolidinderivaten gezeigt.



Schema 50. Ringöffnung eines α-Bromoketons ausgelöst durch sichtbares Licht.

Die Umsetzung von **124** durch den oxidativen Cyclus eines Photokatalysators ergab eine schnelle Ringöffnung die zu Produkt **145** führte. Alternativ führte die photochemische Umsetzung in Gegenwart von DIPEA als Elektronendonor im reduktiven Cyclus eines Photokatalysators zu **148**. Zuletzt wurden die Additionsprodukte **147** unter Nutzung des oxidativen Cyclus in Gegenwart elektronenreicher Heterocyclen gewonnen.



Schema 51. Arylierung und arylsulfonylierung von Cycloadditionsproducten.

Die Photoreaktion zwischen cyclopropanierten Pyrrolen und Arylsulfonylchloriden führte zu den schwefelhaltigen Produkten **171** durch die Addition eines Schwefelradikals, welche im dritten teil der vorliegenden Arbeit behandelt wird. Zusätzlich wurde eine Arylierung der cyclopropanierten Pyrrole durch Umsetzung mit Nitrobenzoldiazoniumtetrafluoroborat in DMF erreicht, was zu Produkt **163** führte. Die erhaltenen Aryl- und Arylsulfonylcyclopropane können als Ausgangsmaterialien für weitere Umsetzungen dienen, um Moleküle mit anspruchsvoller Struktur zu erhalten.

E. Experimental Part

1. General Information

Commercially available chemicals were used as received, without any further purification. All reactions were carried out in oven 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. Solvents for column chromatography were distilled prior to use. The reported yields are referred to the isolated compounds unless otherwise stated.

Chromatography

Analytical thin layer chromatography was performed with TLC precoated aluminium sheets (Merck silica gel 60 F254, 0.25 mm layer thickness). Visualization was done with UV light ($\lambda =$ 254 nm) and staining with vanillin (6 g vanillin in 100 mL EtOH and 5 mL H_2SO_4), sodium permanganate (1 g $KMnO_4$ and 2 g Na_2CO_3 in 100 mL H_2O), PMA (1 g ceric ammonium sulphate and 2.5 g ammonium molybdate in 10 mL H_2SO_4 and 90 mL H_2O) or anisaldehyde (5 mL *p*-anisaldehyde in 5 mL H_2SO_4 and 100 mL EtOH) followed by heating. Column chromatography was performed with silica gel (Merck, Geduran 60, 0.063 - 0.200 mm particle size). Flash column chromatography was performed with silica gel (Merck, Geduran 60, 0.040–0.063 mm particle size)

^{1}H-, ^{13}C- and ^{19}F-NMR

NMR-spectra were recorded on a FT-NMR-spectrometer of the type BRUKER Avance 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C, 282 MHz for ^{19}F), BRUKER Avance III 400 “Nanobay” (400 MHz for ^{1}H, 100 MHz for ^{13}C, 386 MHz for ^{19}F) or BRUKER Avance III 600 (600 MHz for ^{1}H, 151 MHz for ^{13}C, 565 MHz for ^{19}F) at ambient temperature. All spectra were recorded in $CDCl_3$ unless otherwise stated. Chemical shift δ for ^{1}H-NMR were reported in ppm relative to the signal of $CDCl_3$ at 7.26 ppm. Spectra were evaluated in 1st order and coupling constants *J* were reported in Hz. Splitting patterns for the spin multiplicity in the spectra are given as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of a doublet, ddd = doublet of a doublet of a doublet, dt = doublet of a triplet, b = broad and m = multiplet. Chemical shift δ for ^{13}C-NMR were reported in ppm relative to the signal of $CDCl_3$ at 77.2 ppm.

IR-Spectroscopy

ATR-IR spectroscopy was carried out on a Biorad Excalibur FTS 3000 spectrometer, equipped with a Specac Golden Gate Diamond Single Reflection ATR-System. Solid and liquid compounds were measured neatly and the wave numbers are reported as cm-1. 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.

Gas Chromatography

Gas chromatography was performed on a Fisons GC 8000 Series with a flame ionization detector (FID). DB1 (100% Dimethylpolysiloxan, 30 m, ID 0.25 mm, 0.25 μm Film) was used as stationary phase.

Mass Spectroscopy

Mass spectroscopy was performed using a Jeol AccuTOF GCX, Agilent Q-TOF 6540 UHD at the Central Analytical Laboratory (University of Regensburg). High-resolution mass spectra were measured using atmospheric pressure chemical ionization (APCI), chemical ionization (CI), electron ionization (EI), electrospray ionization (ESI), field desorption (FD) or field ionization (FI) with a quadrupole time-of-flight (Q-TOF) detector.

Analytical high-performance liquid chromatography (HPLC)

Analytical high-performance liquid chromatography (HPLC) was conducted on a Varian 920-LC chromatograph equipped with Diode Array detector. Phenomenex Lux Cellulose-1 and 2 served as chiral stationary phase and mixtures of *n*-heptane and *i*-PrOH were used for elution.

Optical rotations

Optical rotations [α] were determined using Perkin Elmer 241 polarimeter at λ = 589 nm (sodium-d-line) in a 1.0 dm measuring cell and the specified solvent.

Melting Point

Melting point measurements were carried out on a SRS MPA 100 OptiMelt at a heating rate of 1 °C/min.

X-ray

X-ray analysis of single crystals was performed using a Agilent Technologies SuperNova, Agilent Technologies Gemini R Ultra, Agilent GV 50 or Rigaku GV 50 at the Central Analytical Laboratory (University of Regensburg). The ellipsoid contour percent probability level is set to 50%. The structure was solved with the ShelXT (Sheldrick, 2015) structure solution program, using the Intrinsic Phasing solution method. The model was refined with version 2016/6 of ShelXL (Sheldrick, 2015) using Least Squares minimisation.

Light Sources

Photochemical reactions were performed using a LED-plate or a LED-stick.

Green LED-plate LED530 six green light emitting diodes (3 W, λ max = 530 nm, produced by LUXEON Lumiled, purchased from Conrad Electronic SE) mounted on a heat sink. A LUMOtech LEDlight 1 -20 VA Universal was used as power supply unit.

Blue LED-plate LED455 six blue light emitting diodes (3 W, λ max = 455 nm, produced by LUXEON Lumiled, purchased from Conrad Electronic SE) mounted on a heat sink. A LUMOtech LEDlight 1 -20 VA Universal was used as power supply unit.

Green LED-stick LED530 One green light emitting diode Cree XP-E (3 W, λ max = 520-535 nm).

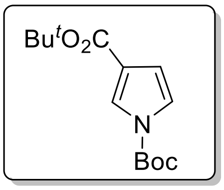
Blue LED-stick LED455 One blue light emitting diode Cree XP-E (3 W, λ max = 450-465 nm).

2. Synthesis of Literature Known Compounds and Reagents

Following compounds were synthesized according to literature known procedures or were on stock in the laboratories of the *Reiser group:*

Tert-butyl diazoacetate,[2] methyl diazoacetate,[3] methyl phenyldiazoacetate,[4] (-)-(*S*,*S*)-bis(4-isopropyloxazoline),[5] *tert*-butyl-1*H*-pyrrole-1-carboxylate[6], di-*tert*-butyl 1*H*-pyrrole-1,3-dicarboxylate,[7] *tert*-butyl *N*-hydroxycarbamate,[8] compounds **96a**,[9] **(-)-96a**,[9] **96a-Me,**[10], **112**,[11] **115**, [12] **124**[13], **96b**[17] were prepared following the previously reported procedures and their analytical data were consistent with those published in the literature.

Di-*tert*-butyl 1*H*-pyrrole-1,3-dicarboxylate (I):

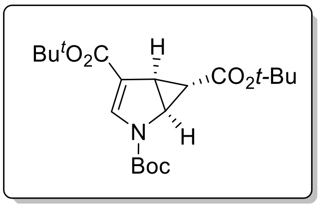


To a solution of *tert*-butyl 1*H*-pyrrole-3-carboxylate (1.34 g, 8 mmol) and DMAP (98 mg, 0.8 mmol, 0.1 equiv) in DCM (40 mL) was added portion wise di-*tert*-butyl dicarbonate (2.27 g, 10.4 mmol, 1.3 equiv) at 25 °C under an atmosphere of nitrogen. The reaction mixture was stirred at the same temperature for 16 h and then the solvent was removed *in vacuo*. Column chromatography eluting with PE/EtOAc afforded **I** as yellowish crystals (1.96 g, 92%). **R*f*** = 0.75 (PE/EtOAc = 10:1); **Mp** = 73-75 °C.

^{1}H NMR (300 MHz, CDCl$_3$) *δ:* 7.73 – 7.70 (m, 1H), 7.15 (dd, *J* = 3.3, 2.2 Hz, 1H), 6.52 (dd, *J* = 3.3, 1.6 Hz, 1H), 1.58 (s, 9H), 1.52 (s, 9H); **^{13}C NMR (75 MHz, CDCl$_3$)** *δ:* 163.5, 148.1, 124.4, 121.3, 120.4, 112.1, 84.8, 80.4, 28.3, 27.9; **IR** (neat, cm^{-1}): 2951, 1700, 1710, 1351, 1250, 1171, 997, 650; **HRMS (ESI):** *m/z* calculated for $C_{14}H_{21}NO_4$ $(M+H)^+$: 267.1471. Found 267.1369.

2.1. Synthesis of 3-substituted cyclopropanated pyrroles.

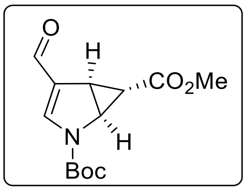
Tri-*tert*-butyl-2-azabicyclo [3.1.0] hex-3-ene-2,4,6-tricarboxylate (99):



According to literature procedure,[8] in a flame dried Schlenk flask under N_2-atmosphere $Cu(OTf)_2$ (20 mg, 56 µmol, 0.01 equiv) and (-)-(*S,S*)-bis(4-isopropyloxazoline) (30 mg, 0.112 mmol, 0.02 equiv) were dissolved in anhydrous CH_2Cl_2 (10 mL) at room temperature and stirred for 1 hour at the same temperature. In a second flask under nitrogen atmosphere di-*tert*-butyl 1*H*-pyrrole-1,3-dicarboxylate (**I**) (1.5 g, 5.6 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and the resulting solution was cooled down to -20 °C by the use of a cryostat. The Cu/ligand mixture was added *via* a syringe to this flask and phenylhydrazine (6 µL, 0.056 mmol, 0.01 equiv) was added dropwise. *Tert*-butyl diazoacetate (11.4 wt% solution in anhydrous CH_2Cl_2, 1.42 g; 11.2 mmol, 2 equiv) was added *via* a syringe pump (addition rate:1 drop/20 s). After completion of the addition, the reaction mixture was stirred for additional 6 h at -20 ^{o}C and subsequently filtered through a pad of basic alumina and washed with CH_2Cl_2 (200 mL. The residue obtained after removal of solvents was subjected to column chromatography (silica gel, PE/EtOAc) to afford **99** as a white solid (900 mg, 42%). **R*f*** = 0.65 (PE/EtOAc = 10:1); **Mp** = 163-165 ^{o}C.; $[\alpha]_D^{20}$ -115.894. (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.37 – 7.05 (m, 1H), 4.50 – 4.11 (m, 1H), 3.01 (s, 1H), 1.51 (s, 9H), 1.48 (s, 9H), 1.43 (s, 9H), 0.93 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 171.4, 163.8, 150.4, 137.4 + 137.0, 117.6, 83.2, 81.2, 80.7, 44.6, 29.9 + 29.0, 28.3, 28.2, 28.2, 23.0 (*signal doubling due to rotamers*); **IR** (neat, cm^{-1}): 2985, 1692, 1587, 1412, 1367, 1136, 1025, 831, 760; **HRMS (ESI)**: *m/z* calculated for $C_{20}H_{31}NO_6$ $(M+H)^+$: 382.2151. Found 382.2227.

2-(*Tert*-butyl) 6-methyl 4-formyl-2-azabicyclo [3.1.0] hex-3-ene-2,6-dicarboxylate(101a- Me):

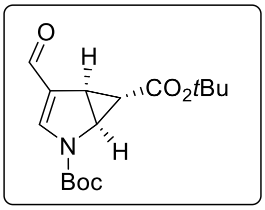


Method A: According literature procedure[14], phosphorus oxychloride (1 mmol) was added dropwise to DMF (1 mmol) at 10 °C in a period of 3 min and the mixture was stirred for 20 min. To the cooled mixture (5 °C) was added ethylene dichloride (2 ml) and then a solution of **96a-Me** (165 mg, 0.75 mmol) in ethylene dichloride (1.5 ml) over a period of 30 min. The solution was stirred at 0-5 ^{0}C for 1 h and refluxed for 15 min. After work-up with aqueous sodium acetate, the combined organic layer was dried on Na_2SO_4. The resulting solution was purified by column chromatography (silica gel, PE/EA 4:1), to afford **101a-Me** as a yellowish oil (50 mg, 25%). $\mathbf{R_f}$ = 0.14 (PE/EtOAc = 2:1).

Method B: According literature procedure[15] to a solution of DMF (1 mL) in CH_2Cl_2 (4 mL) at 0 °C was added oxalyl chloride (51 μL, 0,6 mmol, 1.2 equiv) dropwise. The solution was stirred at 0 °C for 10 min. To the resultant white suspension was added the **96a-Me** (120 mg, 0,5 mmol, 1 equiv) shown above in CH_2Cl_2 (1 mL). The solution was warmed to room temperature and stirred for 1 h. The mixture was quenched with saturated aqueous Na_2CO_3 (30 mL) and stirred vigorously for 15 min. The resultant solution was extracted with CH_2Cl_2 and dried (Na_2SO_4). The residue obtained after removal of solvents was subjected to column chromatography (silica gel, PE/EtOAc= 3:1) to afford **101a-Me** as a white solid (100 mg, 75%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.54 (s, 1H), 7.39 (s, 1H), 4.46 (s, 1H), 3.69 (s, 3H), 3.18 (dd, *J* = 6.7, 2.8 Hz, 1H), 1.54 (s, 9H), 1.06 (s, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 184.55, 172.12, 149.64, 144.23, 126.79, 84.38, 52.19, 44.84, 28.07, 26.87, 21.85; **IR** (neat, cm^{-1}):2981, 1718, 1662, 1408, 1358, 1278, 1144, 980, 730. **HRMS (ESI)**: *m/z* calculated for $C_{22}H_{29}NO_5$ $(M+H)^+$ 267.1107; Found 267.1189

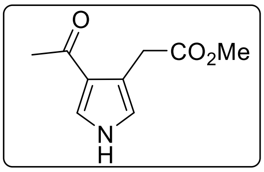
Di-*tert*-butyl-4-formyl-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (101a):



Following ***Method B***, **101a** was prepared from **96a** (140 mg, 0.5 mmol). The residue obtained after removal of solvents was subjected to column chromatography (silica gel, PE/EtOAc= 3:1) to afford **101a** as a white solid (110 mg, 71%). **R*f*** = 0.2 (PE/EtOAc = 2:1); **Mp**= 157-159 °C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.54 (s, 1H), 7.34 (s, 1H), 4.40 (s, 1H), 3.27 – 2.96 (m, 1H), 1.55 (s, 9H), 1.44 (s, 9H), 0.96 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.6, 170.7, 149.8, 144.0, 127.0, 84.1, 81.5, 44.6, 28.1, 28.0, 26.3, 22.9; **HRMS (ESI):** *m/z* calculated for $C_{16}H_{23}NO_5$ $(M+H)^+$: 310.1576. Found 310.1576.

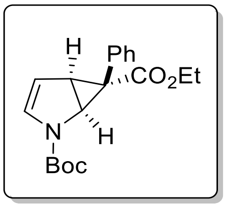
Methyl 2-(4-acetyl-1*H*-pyrrol-3-yl) acetate (102):



According to the literature,[18] to a stirring solution of **96a-Me** (120 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) under nitrogen at 0 °C was added. acetyl chloride (0.7 mL, 1 mmol) in a single portion via syringe and then $SnCl_4$ (0.4 mL, 1.2 mmol was added in small portions to the suspension. The mixture was stirred for 30 at room temperature. After being quenched with ice and water (30 mL), the mixture was filtered to remove inorganic precipitates, and the organic material was extracted with ethyl acetate (50 mL) and was dried over Na_2SO_4. The resulting solution was purified by column chromatography (silica gel, PE/EA 3:1), to afford **102** as a brownish solid (75 mg, 40%). **Mp**= 68-70 °C. **R*f*** = 0.23 (PE/EA = 10:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.49 (s, 1H), 6.85 – 6.81 (m, 1H), 6.12 – 6.08 (m, 1H), 3.73 (s, 2H), 3.69 (s, 3H), 2.39 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 187.7, 170.3, 131.8, 117.7, 110.3, 52.3, 33.2, 25.2; **IR** (neat, cm^{-1}):3272, 3239, 1736, 1617, 1488, 1412, 1222, 1162, 1259, 793. **HRMS (ESI)**: *m/z* calculated for $C_{22}H_{29}NO_5$ (M+H)$^+$ 182.0739; Found 182.0741

2-(*Tert*-butyl) 6-ethyl -6-phenyl-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (115):



Compound **115** was synthesized according to a literature procedure.[16] A flame dried 30 mL Schlenck tube equipped with a magnetic stirring bar was charged with *tert*-butyl-1*H*-pyrrole-1-carboxylate (3.34 mL, 10 mmol, 5 equiv), ethyl 2-diazo-2-phenylacetate (380 mg, 2 mmol, 1.0 equiv) and anhydrous DCM (15 mL). The deeply orange-colored reaction mixture was stirred and irradiated with blue light (LED, λ = 455 nm) for 24 hours giving a reddish-colored solution. After complete consumption of the diazo ester (monitoring by TLC) the solvent was removed in vacuuo and the product was isolated by flash column chromatography (PE/EtOAc= 10:1) affording **115** (430 mg, 65%) as a white solid. **R*f*** = (PE/EtOAc = 3:1) = 0.6; **Mp** = 90 – 93 °C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 6.3 Hz, 2H), 7.19 – 7.07 (m, 2H), 6.08 (dd, *J* = 63.4, 3.8 Hz, 1H), 5.25 – 5.12 (m, 1H), 4.67 (dd, *J* = 47.0, 6.8 Hz, 1H), 4.20 – 4.03 (m, 2H), 3.39 – 3.28 (m, 1H), 1.62 (s, 4H), 1.48 (s, 5H), 1.22 – 1.09 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.2, 151.4, 132.6, 131.3, 130.4, 127.7, 127.1, 107.4, 81.5, 61.1, 49.2, 39.2, 38.0, 28.1, 14.1; **HRMS** (+APCI): calcd. for $C_{19}H_{23}NO_4$ [M+H]+ 330.1627 found 330.1628.

3. General Procedures for Pd-Catalyzed 1,2-Dihydropyridines Preparation (*GP-1a, GP-1b*):

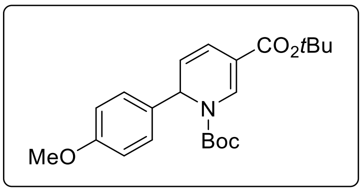
General procedure 96a (GP-96a): Conditions I

An oven dried 10 mL Schlenk flask equipped with a magnetic stirring bar was charged with a monocyclocpropanated *N*-Boc pyrrole **96a,** (-)-**96a**, **96a-Me** or **99** (0.5 mmol, 1 equiv), (hetero)aryl halide (1.5 mmol), $Pd_2(dba)_3$ (14 mg, 3 mol%), $NaHCO_3$ (105 mg, 1.25 mmol, 2.5 equiv), and tetrabutylammonium bromide (TBAB) (322 mg, 1 mmol, 2 equiv) followed by addition of dry toluene (1.5 mL). The resulting mixture was degassed by "pump-freeze-thaw" cycles (×3), then stirred for 5 min at room temperature and subsequently placed on a pre-heated oil bath at 80 °C for 24–56 h. After completion of the reaction (as monitored by TLC), the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (15 mL) and filtered through a pad of Celite. The obtained filtrates were concentrated under reduced pressure and subjected to column chromatography using PE/ EtOAc, as eluent to afford products **110a-110s**.

General procedure 99 (GP-99): Conditions II

An oven dried 10 mL Schlenk flask equipped with a magnetic stirring bar was charged with (hetero)aryl halide (0.5 mmol, 1 equiv), monocyclocpropanated *N*-Boc pyrrole **96a** (1.5 mmol, 3 equiv), $Pd_2(dba)_3$ (14 mg, 3 mol%), $NaHCO_3$ (105 mg, 1.25 mmol, 2.5 equiv), and tetrabutylammonium bromide (TBAB) (322 mg, 1 mmol, 2 equiv) followed by addition of dry toluene (1.5 mL). The resulting mixture was degassed by "pump-freeze-thaw" cycles (×3), then stirred for 5 min at room temperature and subsequently placed on a pre-heated oil bath at 80 °C for 24–56 h. After completion of the reaction (as monitored by TLC), the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (15 mL) and filtered through a pad of Celite. The obtained filtrates were concentrated under reduced pressure and subjected to column chromatography using PE/ EtOAc, as eluent to afford products **110a, 110q** and **110r**. Yield based on aryl halide.

Di-*tert*-butyl 6-(4-methoxyphenyl) pyridine-1,3(6*H*)-dicarboxylate (110a):

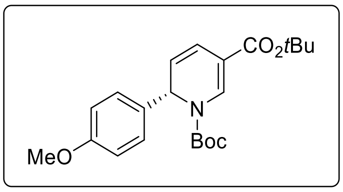


Following *GP-96a- Conditions I,* **110a** was prepared from **96a** (141 mg, 0.5 mmol, 1 equiv) and 4-iodoanisole (175 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel; PE/EtOAc= 10:1) to afford **110a** as a yellowish oil (143 mg, 74% yield. $\mathbf{R}_f$ = 0.40 (PE/EtOAc = 10:1). Reaction time was 24 hours.

Following *GP-99- Conditions II,* **110a** was prepared from **96a** (420 mg, 1.5 mmol, 3 equiv) and 4-iodoanisole (117 mg, 0.5 mmol, 1 equiv) to afford **110a** (157 mg, 81% yield. Yield based on aryl halide). Reaction time was 24 hours.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.89 (br s, 1H), 7.31 – 7.25 (m, 2H), 6.86 – 6.79 (m, 2H), 6.42 (d, *J* = 9.9 Hz, 1H), 5.69 (br s, 1H), 5.54 (dd, *J* = 9.9, 5.2 Hz, 1H), 3.76 (s, 3H), 1.50 (s, 9H), 1.42 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 165.1, 159.3, 152.2, 134.7, 134.2, 128.1, 121.4, 118.7, 113.8, 108.6, 83.0, 80.1, 56.5, 55.2, 28.3, 28.0; **IR** (neat, cm^{-1}): 2880, 1770, 1500, 1450, 1356, 1250, 1150, 977, 850; **HRMS (ESI)**: *m/z* calculated for $C_{22}H_{29}NO_5$ $(M+H)^+$: 388.2046. Found 388.2120. **HPLC analysis** (CHIRALPAK-IA, *n*-heptane/*i*-PrOH 9:1, flow 0.5 mL/min): t_r= 4.044 min (**(+)-110a**), t_r= 4.296 min (**(-)-110a**).

Di-*tert*-butyl (*S*)-6-(4-methoxyphenyl)pyridine-1,3(6*H*)-dicarboxylate ((-)-110a):

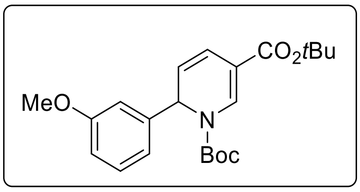


Following *GP-96a- Conditions I,* (–)-**110a** was prepared from (–)-**96a** (141 mg, 0.5 mmol; 97% *ee*) and 4-iodoanisole (175 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel; PE/EtOAc= 10:1) to afford **(-)-110a** as a yellowish oil (143 mg, 74%). $\mathbf{R}_f$ = 0.40 (PE/ EtOAc=10:1). Reaction time was 24 hours.

NMR and IR data were identical with those reported for the racemate; **HRMS (ESI)**: *m/z* calculated for $C_{22}H_{29}NO_5$ $(M+H)^+$: 388.2046. Found 388.2128; **HPLC analysis**

(CHIRALPAK-IA, *n*-heptane/*i*-PrOH 9:1, flow 0.5 mL/min): t_r= **4.296 min** (major peak); *ee* (97% *ee*); $[\alpha]_D^{20}$ –268.4 (*c* 1.0, $CHCl_3$).

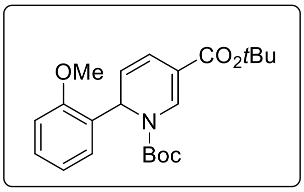
Di-*tert*-butyl 6-(3-methoxyphenyl) pyridine-1,3(6*H*)-dicarboxylate (110b):



Following *GP-96a- Conditions I,* **110b** was prepared from **96a** (141 mg, 0.5 mmol) and 3-iodoanisole (175 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc =10:1) to afford **110b** as a yellow oil (128 mg, 67% yield). **R*f*** = 0.40 (PE/EtOAc = 10:1). Reaction time was 36 hours.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.94 (br s, 1H), 7.28 – 7.20 (m, 1H), 6.95 – 6.76 (m, 3H), 6.40 (d, *J* = 9.8 Hz, 1H), 5.72 (br s, 1H), 5.57 (dd, *J* = 9.8, 5.1 Hz, 1 H), 3.77 (s, 3H), 1.50 (s, 9H), 1.41 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.0, 159.9, 152.2, 144.0, 134.9, 129.7, 121.2, 119.0, 118.7, 112.9, 112.3, 108.6, 83.1, 80.2, 57.6, 55.3, 28.3, 28.0; **IR** (neat, cm^{-1}): 2978, 2973, 1722, 1699, 1587, 1390, 1244, 1125, 1080, 1010, 849, 752; **HRMS (ESI):** *m/z* calculated for $C_{22}H_{29}NO_5$ $(M+H)^+$: 388.2046. Found 388.1952.

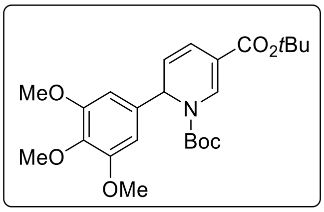
Di-*tert*-butyl 6-(2-methoxyphenyl) pyridine-1,3(6*H*)-dicarboxylate (110c):



Following *GP-96a- Conditions I,* **110c** was prepared from **96a** (141 mg, 0.5 mmol) and 2-iodoanisole (175 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc =10:1) to afford **110b** as a yellow oil (106 mg, 54% yield). **R*f*** = 0.4 (PE/ EtOAc =10:1). Reaction time was 36 hours.

^{1}H NMR (300 MHz, $CDCl_3$) *δ:* 8.07 (br s, 1H), 7.24 – 7.17 (m, 2H), 6.93 – 6.82 (m, 2H), 6.23 (dt, *J*=10.0, 1.4, 1H), 6.12 (d, *J* = 4.4 Hz, 1H), 5.65 (br s, 1H), 3.83 (s, 3H), 1.50 (s, 9H), 1.30 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ:* 165.2, 154.2, 152.3, 135.1, 132.3, 128.5, 125.7, 121.2, 121.1, 117.7, 110.2, 108.1, 82.7, 80.0, 55.3, 52.6, 28.3, 27.8. **IR** (neat, cm^{-1}): 2974, 1722, 1367, 1233, 1140, 1025, 846, 749; **HRMS (ESI):** *m/z* calculated for $C_{22}H_{29}NO_5$ $(M+H)^+$: 388.2046. Found 388.1942.

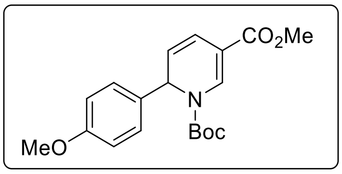
Di-*tert*-butyl 6-(3,4,5-trimethoxyphenyl) pyridine-1,3(6*H*)-dicarboxylate (110d):



Following *GP-96a- Conditions I,* **110d** was prepared from **96a** (141 mg, 0.5 mmol) and 5-bromo-1,2,3-trimethoxybenzene (185 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/EA=10:1) to afford **110d** as a yellow oil (129 mg, 58% yield). **R*f*** = 0.25 (PE/EA=10:1). Reaction time was 36 hours.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.89 (br s, 1H), 6.59 – 6.42 (m, 3H), 5.73 (br s, 1H), 5.58 (dd, *J*=9.7, 5.2, 1H), 3.82 (s, 9H), 1.50 (s, 9H), 1.44 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) 165.1, 153.4, 152.3, 138.4, 137.8, 134.8, 120.9, 119.4, 108.9, 103.8, 83.2, 80.3, 60.9, 56.2, 56.2, 56.17, 28.3, 28.1; **IR** (neat, cm^{-1}): 2974, 2937, 1699, 1367, 1237, 1125, 1039, 1006, 849, 752; **HRMS (ESI)**: *m/z* calculated for $C_{24}H_{33}NO_7$ $(M+H)^+$: 448.2257. Found 448.2178.

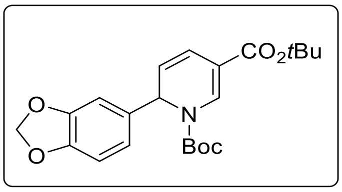
1-(*Tert*-butyl) 3-methyl 6-(4-methoxyphenyl)pyridine-1,3(6*H*)-dicarboxylate (110a-Me):



Following *GP-96a- Conditions I,* **110a-Me** was prepared from **96a-Me** (120 mg, 0.5 mmol) 4-iodoanisole (175 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/EtOAc=10:1) to afford **110a-Me** as a yellow oil (112 mg, 65% yield). **R*f*** = 0.38 (PE/EtOAc=10:1). Reaction time was 24 hours.

^{1}H NMR (400 MHz, CDCl3) δ 7.96 (s, 1H), 7.28 – 7.215 (m, 2H), 6.85 – 6.79 (m, 2H), 6.46 (d, 1H), 5.71 (s, 1H), 5.59-5.53 (m, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 1.43 (s, 9H); **^{13}C NMR** (101 MHz, CDCl3) δ 166.2, 159.4, 152.1, 135.5, 134.2, 128.1, 121.6, 118.4, 113.8, 107.1, 83.2, 56.2, 55.2, 51.4, 28.0; **IR** (neat, cm^{-1}) 2981, 1703, 1587, 1513, 1338, 1237, 1144, 1032, 853, 771, 730; **HRMS (ESI)**: m/z calculated for $C_{19}H_{23}NO_5$ (M+H)$^+$: 346,1649; Found 346,1651 (M+H)$^+$.

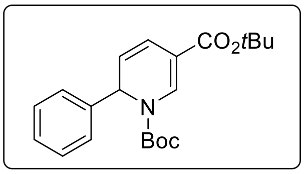
Di-*tert*-butyl 6-(benzo[d][1,3] dioxol-5-yl)pyridine-1,3(6*H*)-dicarboxylate (110f):



Following *GP-96a- Conditions I,* **110f** was prepared from **96a** (141 mg, 0.5 mmol) and 1-bromo-3,4-(methylenedioxy) benzene (150 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc=10:1) to afford **110f** as a yellow oil (134 mg, 67% yield). **R*f*** = 0.55 (PE/ EtOAc=10:1). Reaction time was 24 hours.

^{1}H NMR (400 MHz, CDCl3) *δ:* 7.88 (br s, 1H), 6.88 – 6.69 (m, 3H), 6.41 (d, *J* = 9.8 Hz, 1H), 5.92 – 5.89 (m, 2H), 5.65 (br s, 1H), 5.52 (dd, *J*=9.8, 5.2, 1H), 1.49 (s, 9H), 1.43 (s, 9H). **^{13}C NMR** (101 MHz, CDCl3) *δ* 165.0, 152.1, 147.9, 147.3, 136.1, 134.7, 121.2, 120.2, 118.9, 108.6, 108.1, 107.5, 101.1, 83.1, 80.2, 56.6, 28.3, 28.0; **IR** (neat, cm^{-1}): 2978, 2933, 1699, 1487, 1367, 1237, 1140, 1036, 752; **HRMS (ESI):** *m/z* calculated for $C_{22}H_{27}NO_6$ $(M+H)^+$: 402.1838. Found 402.1734.

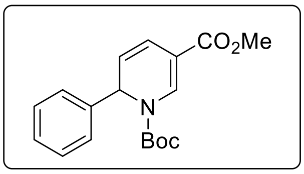
Di-*tert*-butyl 6-phenylpyridine-1,3(6*H*)-dicarboxylate (110g):



Following *GP-96a- Conditions I,* **110g** was prepared from **96a** (141 mg, 0.5 mmol) and iodobenzene (153 mg, 84 mL, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc= 30:1) to afford **110g** as a yellow oil (100 mg, 56% yield). $\mathbf{R}_f$ = 0.45 (PE/ EtOAc = 10:1). Reaction time was 36 hours.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.88 (br s, 1H), 7.26 – 7.13 (m, 5H), 6.34 (d, *J* = 9.8 Hz, 1H), 5.67 (br s, 1H), 5.51 (dd, *J*=9.8, 5.2, 1H), 1.45 (s, 9H), 1.33 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 164.7, 151.8, 148.8, 147.6, 134.7, 127.3, 124.1, 120.2, 119.8, 108.8, 83.9, 80.7, 56.4, 28.3, 28.0; **IR** (neat, cm^{-1}): 2978, 1699, 1341, 1244, 1129, 1077, 909, 726, 697; **HRMS (ESI)**: *m/z* calculated for $C_{21}H_{27}NO_4$ $(M+H)^+$: 358.1940. Found 358.2013.

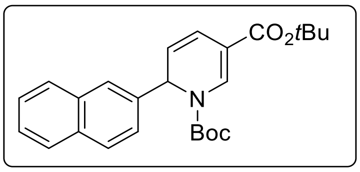
1-(*Tert*-butyl) 3-methyl 6-phenylpyridine-1,3(6*H*)-dicarboxylate (110g-Me):



Following *GP-96a- Conditions I,* **110g-Me** was prepared from **96a-Me** (120 mg, 0.5 mmol) and iodobenzene (153 mg, 84 μL, 0.75 mmol, 1.5 equiv). The product isolated after column chromatography contained impurities which could be removed after its conversion to **111b-Me**. $\mathbf{R}_f$ = 0.45, (PE/ EtOAc= 10:1); NMR yield = 57%. Reaction time was 36 hours.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.02 (br s, 1H), 7.35– 7.24 (m, 5H), 6.45 (d, *J* = 9.7 Hz, 1H), 5.75 (br s, 1H), 5.61 (dd, *J* = 9.7, 5.2 Hz, 1H), 3.77 (s, 3H), 1.41 (s, 9H); **HRMS (ESI)**: m/z calculated for $C_{18}H_{21}NO_4$ $(M+H)^+$: 316.1471; Found 316.1401.

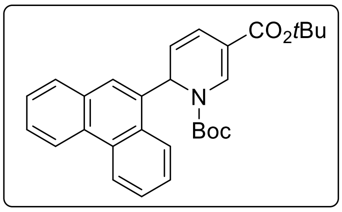
Di-*tert*-butyl 6-(naphthalen-1-yl) pyridine-1,3(6*H*)-dicarboxylate (110h):



Following *GP-96a- Conditions I,* **110h** was prepared from **96a** (141 mg, 0.5 mmol) and 1-iodonaphthalene (190 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc =30:1) to afford **110h** as a yellowish oil (122 mg, 60% yield). **R*f*** = 0.70 (PE/ EtOAc = 10:1). Reaction time was 36 hours.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.20 (br s, 1H), 8.13 – 8.05 (m, 1H), 7.90 – 7.85 (m, 1H), 7.81 – 7.76 (m, 1H), 7.59 – 7.42 (m, 4H), 6.57 (br s, 1H), 6.30 (d, *J* = 9.9 Hz, 1H), 5.72 (dd, *J* = 9.9, 4.5 Hz, 1H), 1.54 (s, 9H), 1.15 (br s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.2, 152.3, 140.4, 135.3, 133.7, 129.0, 128.7, 128.1, 126.6, 126.0, 125.8, 122.9, 122.3, 121.3, 118.1, 107.7, 83.1, 80.3, 54.8, 28.4, 27.8; **IR** (neat, cm^{-1}): 2978, 2933, 1699, 1595, 1367, 1244, 1125, 1010, 809, 730; **HRMS (ESI):** *m/z* calculated for $C_{25}H_{29}NO_4$ $(M+H)^+$: 408.2097. Found 408.2181.

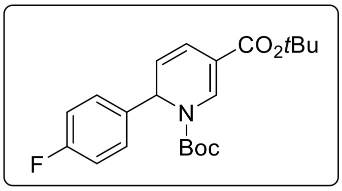
Di-*tert*-butyl 6-(phenanthren-9-yl) pyridine-1,3(6*H*)-dicarboxylate (110i):



Following *GP-96a- Conditions I,* **110i** was prepared from **96a** (141 mg, 0.5 mmol) and 9-bromophenanthrene (192 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc, 20:1) to afford **110i** as a yellow oil (128 mg, 56% yield). **R*f*** = 0.37 (PE/EtOAc = 10:1). Reaction time was 48 hours.

^{1}H NMR (400 MHz, CDCl$_3$) *δ:* 8.82 – 8.74 (m, 1H), 8.70 – 8.62 (m, 1H), 8.32 (br s, 1H), 8.20 – 8.10 (m, 1H), 7.92 – 7.84 (m, 1H), 7.77 – 7.56 (m, 5H), 6.62 (br s, 1H), 6.35 (d, *J* = 10.0 Hz, 1H), 5.88 – 5.76 (m, 1H), 1.57 (s, 9H), 1.18 (br s, 9H). **^{13}C NMR** (101 MHz, CDCl$_3$) *δ:* 165.2, 152.3, 138.4, 135.3, 131.8, 130.8, 130.1, 128.8, 128.2, 127.1, 126.8, 126.7, 126.6, 123.5, 123.4, 122.9, 122.5, 121.0, 118.4, 107.8, 83.2, 80.4, 54.9, 28.4, 27.8; **IR** (neat, cm^{-1}): 2974, 1714, 1367, 1233, 1140, 950, 905, 846, 723; **HRMS (ESI)**: *m/z* calculated for $C_{29}H_{31}NO_4$ $(M+H)^+$: 458.2253. Found 458.2147.

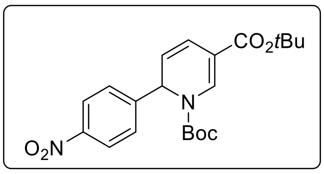
Di-*tert*-butyl 6-(4-fluorophenyl) pyridine-1,3(6*H*)-dicarboxylate (110j):



Following *GP-96a- Conditions I,* **110j** was prepared from **96a** (141 mg, 0.5 mmol) and 4-fluoroiodobenzene (167 mg, 86 μL, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc= 40:1) to afford **110j** as a yellowish oil (80 mg, 43% yield). **R*f*** = 0.35 (PE/EtOAc= 10:1). Reaction time was 36 hours.

^{1}H NMR (400 MHz, CDCl$_3$) *δ:* 7.89 (br s, 1H), 7.35 – 7.28 (m, 2H), 7.02 – 6.94 (m, 2H), 6.43 (d, *J* = 9.8 Hz, 1H), 5.73 (br s, 1H), 5.54 (dd, *J*=9.8, 5.2, 1H), 1.50 (s, 9H), 1.41 (s, 9H). **^{13}C NMR** (101 MHz, CDCl$_3$) *δ:* 165.0, 163.7, 152.0, 134.7, 128.6, 121.0, 119.2, 115.6, 115.3, 108.7, 83.3, 80.3, 56.4, 28.3, 28.0; **IR** (neat, cm^{-1}): 2978, 1714, 1509, 1367, 1230, 1140, 905, 834; **HRMS (ESI)**: *m/z* calculated for $C_{21}H_{26}FNO_4$ $(M+H)^+$: 376.1846. Found 376.1742.

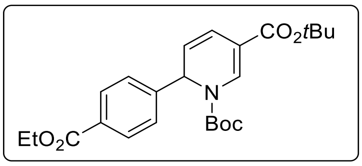
Di-*tert*-butyl 6-(4-nitrophenyl) pyridine-1,3(6*H*)-dicarboxylate (110k):



Following *GP-96a- Conditions I*, (reaction temperature 65 °C), **110k** was prepared from **96a** (141 mg, 0.5 mmol) and 1-iodo-4-nitrobenzene (186 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/EtOAc = 30:1) to afford **110k** as a yellow oil (80 mg, 40% yield). **R*f*** = 0.25 (PE/EtOAc = 10:1). Reaction time was 56 hours.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.22 – 8.14 (m, 2H), 7.92 (br s, 1H), 7.55 – 7.45 (m, 2H), 6.46 (d, *J* = 9.8 Hz, 1H), 5.87 (br s, 1H), 5.55 (dd, *J*=9.8, 5.2, 1H), 1.51 (s, 9H), 1.42 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 164.7, 151.8, 148.8, 147.6, 134.7, 127.3, 124.1, 120.2, 119.8, 108.8, 83.9, 80.7, 56.4, 28.3, 28.0; **IR** (neat, cm^{-1}): 2978, 1699, 1520, 1345, 1244, 1140, 1006, 849, 730; **HRMS (ESI)**: *m/z* calculated for $C_{21}H_2N_2O_6$ $(M+H)^+$: 403.1791. Found 403.1184.

Di-*tert*-butyl 6-(4-(ethoxycarbonyl) phenyl)pyridine-1,3(6*H*)-dicarboxylate (110l):

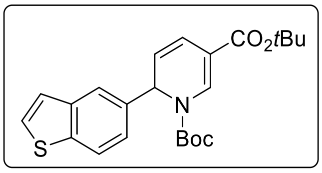


Following *GP-96a- Conditions I,* **110l** was prepared from **96a** (141 mg, 0.5 mmol) and ethyl 4-iodobenzoate (207 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc =10:1) to afford **110l** as a yellow oil (102 mg, 48 % yield). **R*f*** = 0.4 (PE/ EtOAc =10:1). Reaction time was 48 hours.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.07 – 7.92 (m, 3H), 7.44 – 7.34 (m, 2H), 6.41 (d, *J* = 9.8 Hz, 1H), 5.78 (br s, 1H), 5.61 – 5.50 (m, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.51 (s, 9H), 1.40 (s, 9H), 1.37 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 166.3, 164.9, 151.9, 147.1, 134.8, 130.1, 129.8, 126.2, 120.6, 119.4, 108.7, 83.5, 80.4, 61.0, 57.8, 28.3, 28.0, 14.4; **IR** (neat, cm$^-$

^{1}): 2978, 1699, 1367, 1271, 1244, 1140, 909, 849, 1006, 767, 730; **HRMS (ESI)**: *m/z* calculated for $C_{24}H_{31}NO_6$ $(M+H)^+$: 430.2151. Found 430.2215.

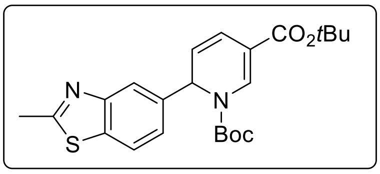
Di-*tert*-butyl 6-(benzo[b]thiophen-5-yl) pyridine-1,3(6*H*)-dicarboxylate (110m):



Following *GP-96a- Conditions I,* **110m** was prepared from **96a** (141 mg, 0.5 mmol) and 5-bromo-1-benzothiophene (159 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc= 40:1) to afford **110m** as a yellow oil (100 mg, 48% yield). **R*f*** = 0.30 (PE/ EtOAc= 10:1). Reaction time was 48 hours.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97 (br s, 1H), 7.88 – 7.75 (m, 2H), 7.47 – 7.29 (m, 3H), 6.46 (d, *J* = 9.9 Hz, 1H), 5.88 (br s, 1H), 5.63 (dd, *J*=9.9, 5.2, 1H), 1.53 (s, 9H), 1.41 (br s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 165.2, 152.2, 139.8, 139.4, 138.7, 134.9, 127.0, 124.0, 123.2, 122.7, 121.6, 121.4, 118.8, 108.6, 83.2, 80.3, 57.5, 28.3, 28.0; **IR** (neat, cm^{-1}) 2978, 2933, 1695, 1341, 1237, 1125, 1010, 735; **HRMS (ESI)**: *m/z* calculated for $C_{23}H_{27}NO_4S$ $(M+H)^+$: 414.1661. Found 414.1737.

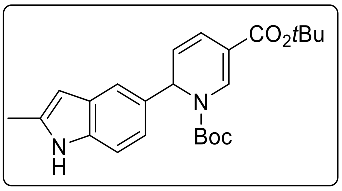
Di-*tert*-butyl 6-(2-methylbenzo[d]thiazol-5-yl) pyridine-1,3(6*H*)-dicarboxylate (110n):



Following *GP-96a- Conditions I,* **110n** was prepared from **96a** (141 mg, 0.5 mmol) and 5-bromo-2-methyl benzothiazole (170 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc = 30:1) to afford **110n** as a yellowish oil (128 mg, 60% yield). **R*f*** = 0.35 (PE/ EtOAc=10:1). Reaction time was 48 hours.

^{1}H NMR (400 MHz, CDCl$_3$) *δ:* 8.00 – 7.87 (m, 2H), 7.78 – 7.70 (m, 1H), 7.40 – 7.31 (m, 1H), 6.43 (d, *J*=9.8, 1H), 5.86 (br s, 1H), 5.60 (dd, *J*=9.8, 5.2, 1H), 2.79 (s, 3H), 1.50 (s, 9H), 1.44 (br s, 9H); **^{13}C NMR** (101 MHz, CDCl$_3$) *δ:* 167.7, 164.9, 153.7, 152.1, 140.4, 135.2, 134.7, 123.4, 121.5, 121.1, 120.3, 119.1, 108.8, 83.2, 80.2, 57.8, 28.3, 28.0, 20.2; **IR** (neat, cm^{-1}): 2978, 2933, 1695, 1341, 1241, 1125, 1010, 812, 730. **HRMS (ESI)**: *m/z* calculated for $C_{23}H_{28}N_2O_4S$ (M+H)$^+$: 429.1770. Found 429.1847.

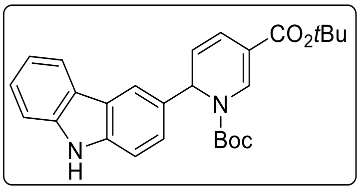
Di-*tert*-butyl 6-(2-methyl-1*H*-indol-5-yl) pyridine-1,3(6*H*)-dicarboxylate (110o):



Following *GP-96a- Conditions I,* **110o** was prepared from **96a** (141 mg, 0.5 mmol) and 5-brom-1-methyl-1*H*-indol (158 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc= 40:1) to afford **110o** as a yellow oil (110 mg, 55% yield). **R*f*** = 0.30 (PE/ EtOAc=10:1). Reaction time was 48 hours.

^{1}H NMR 7.97 (br s, 1H), 7.60 (br s, 1H), 7.33 – 7.21 (m, 1H), 7.07 – 6.99 (m, 1H), 6.50 – 6.39 (m, 2H), 5.86 (br s, 1H), 5.64 (dd, *J*=9.8, 5.2, 1H), 3.76 (s, 3H), 1.54 (s, 9H), 1.42 (s, 9H); **^{13}C NMR** (101 MHz, CDCl$_3$) *δ:* 165.4, 152.3, 136.5, 134.9, 133.5, 129.3, 128.4, 122.2, 120.8, 119.3, 118.2, 109.3, 108.6, 101.2, 82.7, 79.9, 57.7, 32.9, 28.2, 28.0; **IR** (neat, cm^{-1}): 2978, 1692, 1367, 1244, 1125, 1077, 905, 726, **HRMS (ESI)**: *m/z* calculated for $C_{24}H_{30}N_2O_4$ (M+H)$^+$: 411.2206. Found 411.2093.

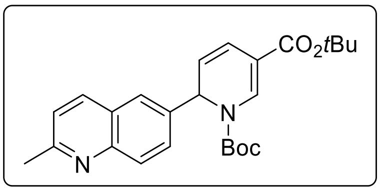
Di-*tert*-butyl 6-(9*H*-carbazol-3-yl) pyridine-1,3(6*H*)-dicarboxylate (110p):



Following *GP-96a- Conditions I,* **110p** was prepared from **96a** (141 mg, 0.5 mmol) and 2-bromo-9*H*-carbazole (184 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc= 30:1) to afford **110p** as a yellowish oil (105 mg, 47% yield). $\mathbf{R}_f$ = 0.30 (PE/ EtOAc= 10:1). Reaction time was 48 hours.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.37 – 7.93 (m, 4H), 7.46 – 7.35 (m, 3H), 7.30 – 7.17 (m, 2H), 6.49 (d, *J*=9.7, 1H), 5.92 (br s, 1H), 5.67 (dd, *J*=9.7, 5.1, 1H), 1.58 (s, 9H), 1.41 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.4, 152.3, 140.7, 140.0, 139.8, 135.0, 125.9, 123.0, 123.0, 121.9, 120.3, 120.3, 119.4, 118.4, 118.0, 110.7, 108.7, 108.6, 83.2, 80.4, 58.1, 28.3, 27.9; **IR** (neat, cm^{-1}): 3391, 2974, 1707, 1587, 1367, 1241, 1133, 1010, 905, 849, 775; **HRMS (ESI)**: *m/z* calculated for $C_{27}H_{30}N_2O_4$ $(M+H)^+$: 447.2206. Found 447.2283.

Di-*tert*-butyl 6-(2-methylquinolin-6-yl) pyridine-1,3(6*H*)-dicarboxylate (110q):

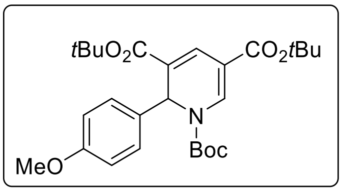


Following *GP-96a- Conditions I,* **110q** was prepared from **96a** (141 mg, 0.5 mmol, 1 equiv) and 6-bromo-2-methylquinoline (167 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc= 20:1) to afford **110q** as a yellow oil (85 mg, 40% yield). $\mathbf{R}_f$ = 0.25 (PE/ EtOAc= 10:1). Reaction time was 56 hours.

Following *GP-99- Conditions II,* **110q** was prepared from **99a** (420 mg, 1.5 mmol, 3 equiv) and 6-bromo-2-methylquinoline (111 mg, 0.5 mmol, 1 equiv) to afford **110q** (123 mg, 58% yield. Yield based on aryl halide). Reaction time was 56 hours.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.05 – 7.89 (m, 3H), 7.71 – 7.60 (m, 2H), 7.25 – 7.19 (m, 1H), 6.43 (d, *J*=9.9, 1H), 5.88 (s, 1H), 5.59 (dd, *J*=9.8, 5.2, 1H), 2.63 (s, 3H), 1.44 (s, 9H), 1.29 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.0, 159.2, 152.0, 147.5, 139.3, 136.3, 134.8, 129.3, 128.3, 126.2, 124.8, 122.3, 120.9, 119.1, 108.5, 83.3, 80.3, 57.0, 28.3, 27.9, 25.3; **IR** (neat, cm^{-1}): 2978, 1695, 1367, 1244, 1140, 1080, 976, 730; **HRMS (ESI)**: *m/z* calculated for $C_{25}H_{30}N_2O_4$ $(M+H)^+$: 423.2206. Found 423.2278.

Tri-*tert*-butyl 2-(4-methoxyphenyl) pyridine-1,3,5(2*H*)-tricarboxylate (110r):

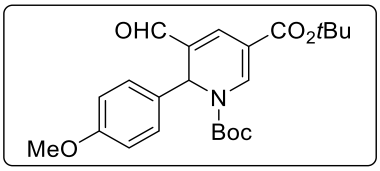


Following *GP-96a- Conditions I,* **110r** was prepared from **99** (190 mg, 0.5 mmol, 1 equiv) and 4-iodoanisole (175 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc= 30:1) to afford **110r** as a yellowish oil (120 mg, 50 % yield). **R*f*** = 0.55 (PE/ EtOAc =10:1). Reaction time was 56 hours.

Following *GP-99- Conditions II*, **110r** was prepared from **99** (570 mg, 1.5 mmol, 3 equiv) and 4-iodoanisole (117 mg, 0.5 mmol, 1 equiv) to afford **110r** (178 mg, 73% yield. Yield based on aryl halide). Reaction time was 56 hours.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.06 (br s, 1H), 7.51 (d, *J*=1.3, 1H), 7.32 – 7.24 (m, 2H), 6.80 – 6.71 (m, 2H), 6.14 (br s, 1H), 3.74 (s, 3H), 1.50 (s, 9H), 1.44 (s, 9H), 1.38 (s, 9H); **^{13}C NMR** (101 MHz, CD_3CN) δ 165.0, 164.8, 160.6, 152.4, 139.3, 134.1, 129.4, 129.0, 124.2, 114.6, 109.3, 84.9, 81.7, 81.4, 55.8, 55.7, 28.4, 28.2, 28.0; **IR** (neat, cm^{-1}) 2978, 1699, 1513, 1457, 1367, 1244, 1133, 1032, 909, 846, 767, 730; **HRMS (ESI):** *m/z* calculated for $C_{27}H_{37}NO_7$ $(M+H)^+$: 488.2570. Found 488.2658.

Di-*tert*-butyl 5-formyl-6-(4-methoxyphenyl)pyridine-1,3(6*H*)-dicarboxylate (110s):



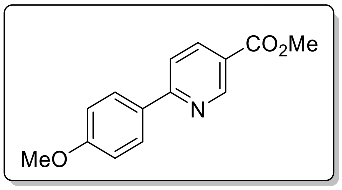
Following *GP-96a- Conditions I*, **110s** was prepared from **100a** (100 mg, 0.32 mmol) and 4-iodoanisole (115 mg, 0.48 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc= 5:1) to afford **110s** as a yellowish oil (55 mg, 42% yield). **R*f*** = 0.65 (PE/ EtOAc= 2:1). Reaction time was 36 hours.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.43 (s, 1H), 8.32 (s, 1H), 7.37 (d, *J* = 1.2 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.20 (s, 1H), 3.76 (s, 3H), 1.55 (s, 9H), 1.45 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 189.7, 164.0, 159.7, 141.5, 138.2, 133.3, 131.3, 128.4, 127.7, 113.8, 107.9, 84.8, 81.3, 55.3, 54.3, 28.4, 28.0; **HRMS (ESI)**: *m/z* calculated for $C_{23}H_{29}NO_6$ $(M+H)^+$: 416.1995. Found 416.9999.

3.1 General Procedure for One-Pot Synthesis of Pyridines (*GP-2*).

The toluene solution from dihydropyridine formation (see *GP-96a*) was cooled to 0 °C in an ice bath and stirred at this temperature for 5 min before DDQ (283.75 mg, 1.25 mmol, 2.5 equiv) was added. The mixture was stirred at 0 ºC for an additional hour and then allowed to warm to room temperature overnight. After complete consumption of the starting material (as monitored by TLC), the reaction solution was thoroughly washed with $NaHCO_3$, brine and the aqueous phases were extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and filtered. The obtained solution was concentrated and subjected to column chromatography using PE/EtOAc as eluent to afford products **111a-111e**.

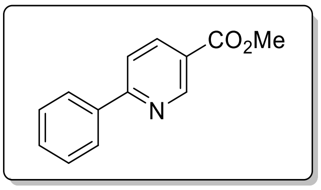
Methyl 6-(4-methoxyphenyl) nicotinate (111a-Me):



Following *GP-2*, **111a-Me** was prepared from **96a-Me** (120 mg, 0.5 mmol) and 4-iodoanisole (175 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc= 30:1) to afford **111a-Me** as a beige solid (77.5 mg, 65% yield); **R*f*** = 0.25 (PE/ EtOAc =10:1). **Mp** = 161-165 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 9.22 (d, *J* = 2.1 Hz, 1H), 8.28 (dd, *J* = 8.4, 2.1 Hz, 1H), 8.05 – 8.00 (m, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.04 – 6.96 (m, 2H), 3.95 (s, 3H), 3.87 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 166.1, 161.4, 160.6, 151.0, 137.8, 130.9, 128.9, 123.5, 119.0, 114.4, 55.5, 52.3; **IR** (neat, cm^{-1}): 2952, 1714, 1591, 1472,1431, 1248, 1110, 1017, 827, 782, 738; **HRMS (ESI):** *m/z* calculated for $C_{14}H_{13}NO_3$ $(M+H)^+$: 244.0895. Found 244.0974.

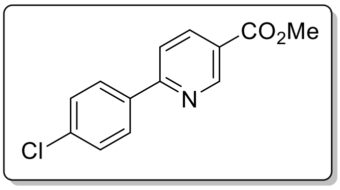
Methyl 6-phenylnicotinate (111b-Me):



Following *GP-2*, **111b-Me** was prepared from **96a-Me** (120 mg, 0.5 mmol) and iodobenzene (153 mg, 84 mL, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc = 30:1) to afford **111b-Me** as a beige solid (64 mg, 60% yield); **R*f*** = 0.35 (PE/ EtOAc =10:1). **Mp** = 155-157 °C.

^{1}H NMR (400 MHz, CDCl$_3$) *δ:* 9.28 (d, *J* = 2.0 Hz, 1H), 8.34 (dd, *J* = 8.3, 2.0 Hz, 1H), 8.10 – 8.02 (m, 2H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.55 – 7.44 (m, 3H), 3.97 (s, 3H). **^{13}C NMR** (101 MHz, CDCl$_3$) *δ:* 166.0, 161.0, 151.0, 138.4, 138.0, 130.0, 129.0, 127.4, 124.3, 119.9, 52.4; **IR** (neat, cm^{-1}): 2944, 1714, 1591, 1285, 1199, 1114, 1077, 846, 749, 697; **HRMS (ESI):** *m/z* calculated for $C_{13}H_{11}NO_2$ (M+H)$^+$: 214.0790. Found 214.0868.

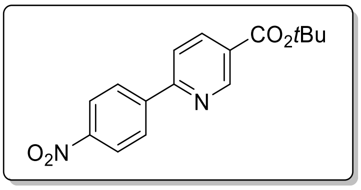
Methyl 6-(4-chlorophenyl) nicotinate (111c):



Following *GP-2*, **111c-Me** was prepared from **96a-Me** (120 mg, 0.5 mmol) and 1-chloro-4-iodobenzene (178 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc = 30:1) to afford **111c-Me** as a brownish solid (73 mg, 59% yield). **R*f*** = 0.4 (PE/ EtOAc = 10:1). **Mp** = 125-128 °C.

^{1}H NMR (400 MHz, CDCl$_3$) *δ:* 9.26 (dd, *J*=2.2, 1.0, 1H), 8.34 (dd, *J* = 8.3, 2.2 Hz, 1H), 8.04 – 7.98 (m, 2H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.49 – 7.44 (m, 2H), 3.97 (s, 3H), **^{13}C NMR** (101 MHz, CDCl$_3$) *δ:* 165.8, 159.7, 151.1, 138.1, 136.7, 136.3, 129.2, 128.7, 124.5, 119.7, 52.5; **IR** (neat, cm^{-1}): 2929, 1699, 1595, 1472, 1367, 1293, 1210, 842, 782; **HRMS (ESI):** *m/z* calculated for $C_{13}H_{10}ClNO_2$ (M+H)$^+$: 248.0400. Found 248.0476.

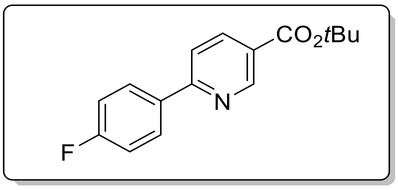
***Tert*-butyl 6-(4-nitrophenyl) nicotinate (111a):**



Following *GP-2*, **111a** was prepared from **96a** (141 mg, 0.5 mmol) and 1-iodo-4-nitrobenzene (186 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc = 30:1) to afford **111a** as a yellow solid (80 mg, 53% yield). **R*f*** = 0.32 (PE/ EtOAc =10:1); **Mp** = 103-105 °C.

^{1}H NMR (400 MHz, CDCl$_3$) *δ:* 9.27 (s, 1H), 8.43 – 8.30 (m, 3H), 8.24 (d, *J* = 8.8 Hz, 2H), 7.83 (d, *J* = 8.5 Hz, 1H), 1.64 (s, 9H). **^{13}C NMR** (101 MHz, CDCl$_3$) *δ:* 164.1, 157.8, 151.3, 138.2, 128.4, 128.2, 127.3, 124.5, 124.2, 120.6, 82.5, 28.3; **IR** (neat, cm^{-1}): 2987, 1710, 1513, 1252, 1341, 1107, 1017, 838, 745; **HRMS (ESI):** *m/z* calculated for $C_{16}H_{16}N_2O_4$ (M+H)$^+$: 301.1110. Found 301.1195

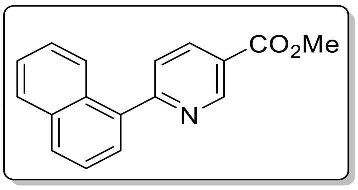
***Tert*-butyl 6-(4-fluorophenyl)nicotinate (111b):**



Following *GP-2*, **111b** was prepared from **96a** (141 mg, 0.5 mmol) and 4-fluoroiodobenzene (167 mg, 86 mL, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc = 20:1,) to afford **111b** as a yellow solid (69 mg, 50% yield). **R*f*** = 0.35 (PE/ EtOAc =10:1); **Mp** = 110-112 °C.

^{1}H NMR (600 MHz, CDCl$_3$) *δ:* 9.21 (dd, *J*=2.2, 0.9, 1H), 8.29 (dd, *J*=8.3, 2.2, 1H), 8.09 – 8.02 (m, 2H), 7.74 (dd, *J*=8.3, 0.9, 1H), 7.21 – 7.15 (m, 2H), 1.62 (s, 9H); **^{13}C NMR** (151 MHz, CDCl$_3$) *δ:* 164.5, 164.1, 159.4, 151.0, 138.0, 134.6, 129.4, 126.0, 119.5, 116.0, 82.1, 28.3; **^{19}F NMR** (377 MHz, CDCl$_3$) *δ:* -111.96; **IR** (neat, cm^{-1}) 2952, 1714, 1587, 1289, 1244, 1107, 1017, 838, 745; **HRMS (ESI):** *m/z* calculated for $C_{16}H_{16}N_2O_4$ (M+H)$^+$: 273.1165. Found 273.1200.

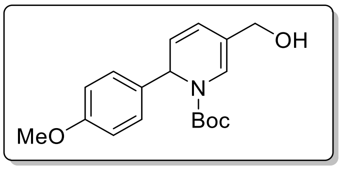
Methyl 6-(naphthalen-1-yl) nicotinate (111d-Me):



Following *GP-2*, **111d-Me** was prepared from **96a** (120 mg, 0.5 mmol) and1-iodonaphthalene (190 mg, 0.75 mmol, 1.5 equiv). The crude product was purified by column chromatography (silica gel, PE/ EtOAc= 20:1,) to afford **111d-Me** as a yellow solid (69 mg, 50% yield). $\mathbf{R}_{\boldsymbol{f}}$ = 0.5 (PE/ EtOAc =10:1); **Mp** = 87-90 °C.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 9.42 – 9.37 (m, 1H), 8.41 (dd, *J*=8.1, 2.2, 1H), 8.13 – 8.07 (m, 1H), 7.97 – 7.89 (m, 2H), 7.70 – 7.61 (m, 2H), 7.59 – 7.45 (m, 3H), 4.00 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.8, 163.1, 150.7, 137.5, 137.5, 133.9, 130.8, 129.7, 128.5, 127.9, 126.8, 126.1, 125.3, 125.2, 124.6, 124.2, 52.4; **IR** (neat, cm^{-1}): 2952, 1718, 1595, 1438, 1282, 1125, 1021, 770, 764; **HRMS (ESI):** *m/z* calculated for $C_{17}H_{13}NO_2$ $(M+H)^+$: 264.0946. Found 264.1023.

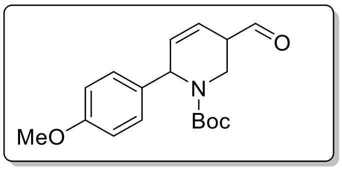
Tert -Butyl -5-(hydroxymethyl)-2-(4-methoxyphenyl)pyridine-1(2*H*)-carboxylate (113):



Following *GP-99a- Conditions I*, **112** (100 mg, 0.5 mmol) and 4-iodoanisole (175 mg, 0.75 mmol, 1.5 equiv) were reacted to yield after column chromatography (silica gel, PE/ EtOAc= 2:1) **113** as a yellowish oil (65 mg, 41% yield) and **114** as a yellowish oil (28 mg, 18% yield). Reaction time was 48 hours.

R*f* = 0.30 (PE/ EtOAc= 2:1). **^{1}H NMR** (400 MHz, Acetonitrile-*d*$_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 31.0 Hz, 1H), 6.05 (d, *J* = 9.1 Hz, 1H), 5-79-5.61 (m, 2H), 4.06 – 3.95 (m, 2H), 3.76 (s, 3H), 2.79 (s, 1H), 1.44 (s, 9H); **^{13}C NMR** (101 MHz, CD_3CN) δ 160.1, 135.8, 128.7, 124.4, 124.0, 123.6, 122.8, 122.4, 114.6, 82.1, 79.1, 62.8, 55.8, 28.3 (*signal doubling due to rotamers*); **HRMS (ESI)**: *m/z* calculated for $C_{18}H_{23}NO_4$ $(M+H)^+$: 318.1627. Found 318.1706.

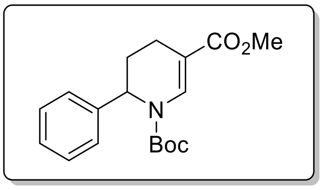
Tert-Butyl-3-formyl-6-(4-methoxyphenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (114):



114: R*f* = 0.5 (PE/ EtOAc= 2:1).**^{1}H NMR** (400 MHz, Acetonitrile-*d*$_3$) δ 9.39 (s, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.09 (dd, *J* = 4.9, 2.8 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 5.59 (d, *J* = 5.1 Hz, 1H), 4.37 (d, *J* = 18.6 Hz, 1H), 3.75 (s, 3H), 3.29 (d, *J* = 17.9 Hz, 1H), 2.88 (dd, *J* = 7.7, 4.7 Hz, 2H), 1.47 (s, 9H); **^{13}C NMR** (101 MHz, CD_3CN) δ 192.4, 159.4, 155.2, 147.7, 138.5, 132.7, 128.3, 114.3, 80.4, 78.7, 55.4, 30.4, 29.6, 28.1; **HRMS (ESI)**: *m/z* calculated for $C_{18}H_{23}NO_4$ $(M+H)^+$: 318.1627. Found 318.1626.

3.2 Derivatization Reactions

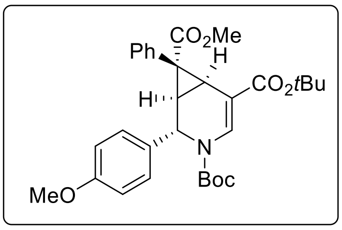
1-(*tert*-Butyl) 3-methyl 6-phenyl-5,6-dihydropyridine-1,3(4*H*)-dicarboxylate (119):



Pd/C (10 wt.%) (7 mol%, 37 mg) was added to **110g-Me** (0.5 mmol, 158 mg) dissolved in dry THF (1 mL) and the resulting suspension was intensively stirred at 25 °C under H_2 (balloon) for 3 hours. After that time, the mixture was filtered over a plug of Celite, concentrated under reduced pressure, and purified by column chromatography (silica gel, PE/EtOAc) to afford **119** as a white solid (123 mg, 77% yield). **Mp** = 118-120 °C; **R*f*** = 0.58 (PE/EA= 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.33 (br s, 1H), 7.37 – 7.17 (m, 3H), 7.10 – 7.04 (m, 2H), 5.32 (s, br 1H), 3.73 (s, 3H), 2.38 (d, *J*=16.6, 1H), 2.12 – 2.02 (m, 1H), 2.02 – 1.89 (m, 1H), 1.89 – 1.75 (m, 1H), 1.37 (br s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 167.9, 151.9, 141.3, 135.9, 128.5, 127.0, 125.1, 107.5, 82.5, 55.2, 51.3, 27.9, 27.2, 16.5; **IR** (neat, cm^{-1}): 2952, 1725, 1692, 1636, 1312, 1244, 1133, 764, 680; **HRMS (ESI):** *m/z* calculated for $C_{18}H_{23}NO_4$ $(M+H)^+$: 318.1627. Found 318.1699.

3,5-Di-*tert*-butyl 7-methyl (1*R*,2*S*,6*S*,7*R*)-2-(4-methoxyphenyl)-7-phenyl-3-azabicyclo-[4.1.0]hept-4-ene-3,5,7-tricarboxylate ((+)-122):



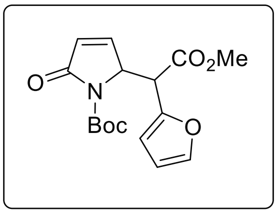
A solution of methyl phenyldiazoacetate (48 mg, 0.272 mmol, 1.5 equiv) in dry petroleum ether (1.2 mL) was added using a syringe pump (addition rate:1 drop/10 s) to a vigorously stirred mixture of dihydropyridine (-)-**110a** (70 mg, 0.181 mmol) and $Rh_2(OAc)_4$ (2.4 mg, 5.4 µmol, 3 mol%) in the same solvent (1.2 mL) at 25 °C under an atmosphere of nitrogen. After the addition was completed, the resulting mixture was left for additional 30 min and then the solvent was evaporated. Column chromatography eluting with Et_2O/PE afforded **(+)-122** as colorless crystals (71 mg, 70%). **R*f*** = 0.41 (20% EtOAc/PE); **Mp**= 150-151 °C; $[\alpha]_D^{20}$= +51.9 °(*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, DMF, 80 oC) δ: 7.47 (s, 1H), 7.40 – 7.26 (m, 7H), 7.00 – 6.95 (m, 2H), 5.64 (s, 1H), 3.83 (s, 3H), 3.61 (s, 3H), 2.92 (dd, J = 9.8, 0.9 Hz, 1H), 2.71 (dd, J = 9.8, 0.7 Hz, 1H), 1.59 (s, 9H), 1.29 (s, 9H); **^{13}C NMR** (101 MHz, C_6D_6, 70 °C) δ: 172.1, 166.4, 159.9, 150.8, 135.1, 134.9, 133.8, 131.2, 128.6, 128.1, 127.6, 114.6, 108.2, 81.8, 79.8, 54.9, 52.0, 50.9, 40.95, 36.6, 28.4, 27.9, 24.2; **IR** (neat, cm-1): 2974, 2937, 1718, 1689, 1644, 1510, 1368, 1234, 1170, 1141, 988, 705; **HRMS** (ESI): calculated for $C_{31}H_{37}NO_7Na$ (M+Na)+ 558.2462. Found 558.2466.

4. General Procedure of 5-Substituted 3-Pyrrolidin-2-ones synthesis *(GP-3):*

An oven dried 10 mL Schleck flask equipped with a magnetic stir bar and septum was charged with heteroarene **146** (15 equiv.), Na_2CO_3 (106 mg, 1 mmol, 2 equiv) and (*fac*-Ir(ppy)$_3$ (3,27 mg, 1.00 mol %) in 2 mL dry DMF, then substrate **124** (167 mg, 0.5 mmol, 1 equiv.) was added. The resulting suspension was deoxygenated by three freeze-pump-thaw cycles (3x). The reaction mixture was irradiated with blue light emitting diode (LED, λmax= 455nm) at -10 °C for 20 minutes. After complete conversion of starting materials (monitored by TLC analysis), the reaction mixture was saturated with brine solution (15 mL) and the product was extracted with ethyl acetate (3x15 mL), the combined organic layers were dried over Na_2SO_4 and concentrated, the residue was purified by column chromatography on silicagel using PE/ EtOAc, as eluent to afford products **147a-147e**.

***Tert*-butyl-2-((*R*)-1-(furan-2-yl)-2-methoxy-2-oxoethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (147a, 147´a):**

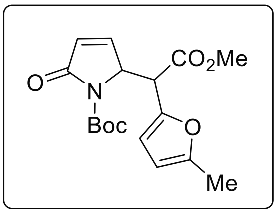


Following *GP-3*, **147a** and **147´a** was prepared from **124** (100 mg, 0,3 mmol) and furan (15 equiv, 3 mmol, 0.217 mL). The crude product was purified by column chromatography (silica gel, PE/ EtOAc= 10:1) to afford both **147a** and **147´a** as a dark yellow oil (69mg, 70% yield). **147a** - **R*f*** = 0.4 and **147´a** - **R*f*** = 0.3 (PE/ EtOAc= 10:1). The diastereomeric ratio was determined by NMR (7:1) **147a** major and **147´a** minor *d.r.*

147a: **^{1}H NMR** (300 MHz, CDCl3) δ 7.44 (dd, J = 6.2, 2.1 Hz, 1H), 7.25 (d, J = 0.7 Hz, 1H), 6.25 (dd, J = 3.2, 1.9 Hz, 1H), 6.10 – 6.07 (m, 1H), 5.95 (dd, J = 6.2, 1.6 Hz, 1H), 5.13 – 5.09 (m, 1H), 4.93 (d, J = 4.3 Hz, 1H), 3.78 (s, 3H), 1.59 (s, 9H); **^{13}C NMR** (75 MHz, CDCl3) δ 169.8, 168.40 , 149.51 , 148.31 , 145.82, 142.82 , 127.61, 110.41, 110.23, 83.55, 62.14, 52.71 , 45.30, 28.11; IR (neat, cm-1): 3116, 2981, 1781, 1736, 1707, 1502, 1438, 1356, 1315, 1252, 1151, 987, 935, 834, 749. **HRMS (ESI)**: exact m/z calculated for $C_{16}H_{19}NO_6$ (M+H)+ : 322,1212; Found 322,1216 (M+H)+.

147´a: **^{1}H NMR** (300 MHz, Chloroform-d) δ 7.48 – 7.40 (m, 1H), 7.29 (dd, J = 6.2, 2.0 Hz, 1H), 6.44 – 6.37 (m, 2H), 6.13 (dd, J = 6.2, 1.6 Hz, 1H), 5.01 – 4.95 (m, 1H), 4.87 (d, J = 4.5 Hz, 1H), 3.65 (s, 3H), 1.60 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.61, 168.22, 149.33, 148.01, 147.51, 142.81, 127.32, 110.73, 109.31, 83.61, 62.83, 52.51, 46.12, 28.11; **IR** (neat, cm-1): 3112, 2978, 1736, 1628, 1438, 1356, 1315, 1252, 1103, 1151, 1047, 842, 805, 745; **HRMS (ESI)**: exact m/z calculated for $C_{16}H_{19}NO_6$ (M+H)+ : 322.1212; Found 322.1216 (M+H)+.

***Tert*-butyl -2-((*R*)-2-methoxy-1-(5-methylfuran-2-yl)-2-oxoethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (147b, 147´b):**

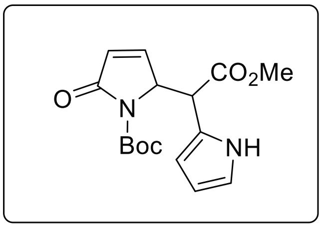


Following *GP-3*, **147b** and **147´b** was prepared from **124** (100 mg, 0,3 mmol) and 2-methylfuran (15 equiv, 3 mmol, 0.265 mL). The crude product was purified by column chromatography (silica gel, PE/ EtOAc= 10:1) to afford both **147b** and **147´b** as a brawn oil (44 mg, 43% yield). **147b- R*f*** = 0.5 and **147´b- R*f*** = 0.4 (PE/ EtOAc= 10:1). The *diastereomeric ratio* was determined by NMR (3:1) **147b** major and **147´b** minor *dr*.

147b: **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.45 (dd, *J* = 6.2, 2.1 Hz, 1H), 5.97 (dd, *J* = 6.2, 1.6 Hz, 1H), 5.95 (d, *J* = 3.1 Hz, 1H), 5.81 (dd, *J* = 3.0, 0.8 Hz, 1H), 5.09 (m, *J* = 6.2 Hz, 1H), 4.87 (d, *J* = 4.4 Hz, 1H), 3.77 (s, 3H), 2.16 (d, *J* = 0.5 Hz, 3H), 1.59 (d, *J* = 3.8 Hz, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.1, 168.5, 152.4, 149.5, 148.4, 143.8, 127.5, 111.0, 106.4, 83.4, 62.1, 52.6, 45.3, 28.1, 13.51; **IR** (neat, cm^{-1}): 3104, 2981,1781, 1736, 1707, 1628, 1561, 1438, 1356, 1319, 1282, 1252, 1155, 939, 872, 797, 693. **HRMS (ESI):** exact m/z calculated for $C_{16}H_{19}NO_6$ (M+H)$^+$: 336,1369; Found 336,1372 (M+H)$^+$.

147´b: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 6.2, 2.0 Hz, 1H), 6.26 (d, *J* = 3.1 Hz, 1H), 6.13 (dd, *J* = 6.2, 1.7 Hz, 1H), 5.95 (dd, *J* = 3.0, 1.0 Hz, 1H), 4.99 – 4.92 (m, 1H), 4.82 (d, *J* = 4.5 Hz, 1H), 3.64 (s, 3H), 2.29 (s, 3H), 1.60 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.7, 168.3, 152.6, 149.3, 148.3, 145.5, 127.1, 110.0, 106.6, 83.5, 62.9, 52.4, 46.1, 28.1, 13.6; **IR** (neat, cm^{-1}): 3354, 2929, 2855, 1774, 1736, 1628, 1438, 1319, 1282, 1252, 1103, 1051, 946, 842, 797, 749; **HRMS (ESI):** exact m/z calculated for $C_{16}H_{19}NO_6$ $(M+H)^+$: 336,1369; Found 336,1372 $(M+H)^+$.

***Tert*-butyl-2-((*R*)-2-methoxy-2-oxo-1-(1*H*-pyrrol-2-yl)ethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (147c, 147´c):**



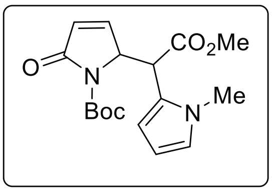
Following *GP-3*, **147c** and **147´c** was prepared from **124** (100 mg, 0,3 mmol) and furan (15 equiv, 3 mmol, 0.217 mL). The crude product was purified by column chromatography (silica gel, PE/ EtOAc= 10:1) to afford both **147c** and **147´c** as a dark yellow oil (66 mg, 67% yield). **147c- R*f*** = 0.25 and **147´c-R*f*** = 0.2 (PE/ EtOAc= 10:1). The *diastereomeric ratio* was determined by NMR (8:1) **147c** major and **147´c** minor *d.r*.

147c: **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.53 (s, 1H), 7.27 – 7.24 (m, 1H), 6.66 (dd, J = 4.1, 2.7 Hz, 1H), 6.07 (dd, J = 5.9, 2.8 Hz, 1H), 5.95 (dd, J = 6.2, 1.5 Hz, 1H), 5.87 (t, J = 3.6 Hz, 1H), 5.03 – 4.94 (m, 1H), 4.76 (d, J = 4.5 Hz, 1H), 3.80 (s, 3H), 1.60 (s, 9H);**^{13}C NMR (75 MHz, $CDCl_3$)** δ 168.6, 168.2, 149.3, 148.0, 147.5, 142.8, 127.3, 110.7, 109.3, 83.6, 62.8, 52.5, 46.1, 28.1; **IR** (neat, cm^{-1}): 3112, 2978, 1736, 1628, 1438, 1356, 1315, 1252, 1103, 1151, 1047, 842, 805, 745**; HRMS (ESI):** exact m/z calculated for $C_{16}H_{19}NO_6$ $(M+H)^+$: 322.1212; Found 322.1216 $(M+H)^+$.

147´c: **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.15 (s, 1H), 7.03 (dd, *J* = 6.2, 2.0 Hz, 1H), 6.79 (dd, *J* = 4.1, 2.6 Hz, 1H), 6.21 – 6.14 (m, 1H), 6.09 (dd, *J* = 6.2, 1.6 Hz, 2H), 4.91 (d, *J* = 5.4 Hz, 1H), 4.82 (dt, *J* = 5.4, 1.9 Hz, 1H), 3.66 (s, 3H), 1.61 (s, 9H); **^{13}C NMR** (75 MHz,

$CDCl_3$) δ 169.8, 168.4 , 149.5 , 148.3 , 145.8, 142.8 , 127.6, 110.4, 110.2, 83.5, 62.1, 52.7 , 45.3, 28.1; **IR** (neat, cm^{-1}): 3116, 2981, 1781, 1736, 1707, 1502, 1438, 1356, 1315, 1252, 1151, 987, 935, 834, 749. **HRMS (ESI)**: exact m/z calculated for $C_{16}H_{19}NO_6$ $(M+H)^+$: 322,1212; Found 322,1216 $(M+H)^+$.

***Tert*-butyl-2-((*R*)-2-methoxy-1-(1-methyl-1*H*-pyrrol-2-yl)-2-oxoethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (147d, 147´d):**

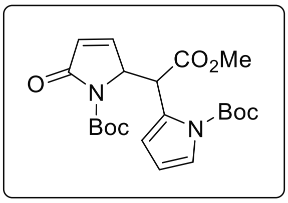


Following *GP-3*, **147d** and **147´d** was prepared from **124** (100 mg, 0,3 mmol) and N-Methylpyrrole (15 equiv, 3 mmol, 0.265 mL). The crude product was purified by column chromatography (silica gel, PE/ EtOAc= 10:1) to afford both **147d** and **147´d** as a brawn oil (80 mg, 80% yield). **147d- R*f*** = 0.4 and **147´d - R*f*** = 0.3 (PE/ EtOAc= 10:1). The *diastereomeric ratio* was determined by NMR (3:1) **147d** major and **147´d** minor *dr*.

147d: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 6.2, 2.0 Hz, 1H), 6.51 – 6.45 (m, 1H), 6.00 (dd, *J* = 6.2, 1.6 Hz, 1H), 5.98 – 5.95 (m, 1H), 5.80 (dd, *J* = 3.7, 1.6 Hz, 1H), 5.10 (dt, *J* = 3.8, 1.8 Hz, 1H), 4.80 (d, *J* = 3.9 Hz, 1H), 3.71 (s, 3H), 3.48 (s, 3H), 1.57 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.5, 168.5, 150.3, 149.6, 127.6, 123.2, 109.5, 107.9, 83.6, 62.8 , 52.5, 42.8, 33.6, 28.1; **IR** (neat, cm^{-1}): 2981, 1781, 1936, 1703, 1606, 1487, 1457, 1315, 1252, 1215, 10054, 834, 715; **HRMS (ESI):** exact m/z calculated for $C_{17}H_{22}N_2O_5$ $(M+H)^+$ 335,1529; Found 335,1531 $(M+H)^+$.

147´d: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (dt, *J* = 6.5, 3.3 Hz, 1H), 6.67 – 6.62 (m, 1H), 6.27 (dd, *J* = 3.6, 1.6 Hz, 1H), 6.12 (dd, *J* = 6.0, 2.3 Hz, 1H), 4.88 (d, *J* = 4.7 Hz, 1H), 4.74 – 4.64 (m, 1H), 3.70 (s, 3H), 3.62 (s, 3H), 1.60 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.1, 168.7, 150.1, 148.7, 127.6, 124.5, 123.3, 109.3, 107.0, 83.6, 63.0, 52.2, 43.6, 34.0, 28.1; **IR** (neat, cm^{-1}): 2922, 2851, 1781, 1736, 1703, 1606, 1457, 1315, 1252, 1155, 1051, 1107, 998, 842, 716; **HRMS (ESI):** exact m/z calculated for $C_{17}H_{22}N_2O_5$ $(M+H)^+$:335,1529; Found 335, 1531 $(M+H)^+$.

Tert-butyl 2-(1-(1-(*tert*-butoxycarbonyl)-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)-2-methoxy 2-oxoethyl)-1*H*-pyrrole-1-carboxylate (147e, 147´e):

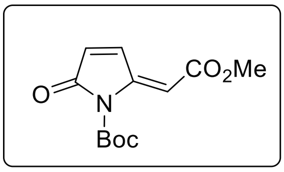


Following *GP-3*, **147e** and **147´e** was prepared from **124** (100 mg, 0,3 mmol) and N-Boc-pyrrole (15 equiv, 3 mmol, 0.5 mL). The crude product was purified by column chromatography (silica gel, PE/ EtOAc= 10:1) to afford both **147e** and **147´e** as a brawn oil (60 mg, 48% yield). **147e- R$_f$**= 0.4 and **147´e- R$_f$**= 0.3 (PE/ EtOAc= 10:1). The *diastereomeric ratio* was determined by NMR (2:1) **147e** major and **147´e** minor *d.r*.

147e: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 (dd, *J* = 6.1, 2.2 Hz, 1H), 7.14 – 7.05 (m, 1H), 6.04 (t, *J* = 3.4 Hz, 1H), 5.99 (dd, *J* = 3.3, 1.7 Hz, 1H), 5.85 (dd, *J* = 6.1, 1.5 Hz, 1H), 5.41 (d, *J* = 4.2 Hz, 1H), 5.31 – 5.23 (m, 1H), 3.71 (s, 3H), 1.58 (s, 9H), 1.54 (s, 9H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 170.9, 168.9, 149.3, 149.1, 126.2, 125.6, 122.7, 116.5, 110.1, 84.1, 83.1, 63.0, 52.2, 44.7, 28.1, 27.9, 27.9; **IR** (neat, cm^{-1}): 2981, 1781, 1736, 1435, 1367, 1315, 1248, 1155, 1062, 913, 842, 723; **HRMS (ESI):** exact m/z calculated for C$_{21}$H$_{28}$N$_2$O$_7$ (M+H)$^+$: 421,1897; Found 421,1898 (M+H)$^+$.

147´e: **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.24 (dt, *J* = 3.5, 1.8 Hz, 2H), 6.29 (dd, *J* = 3.0, 1.3 Hz, 1H), 6.15 (t, *J* = 3.4 Hz, 1H), 6.11 (dd, *J* = 6.2, 1.5 Hz, 1H), 5.29 – 5.26 (m, 1H), 5.24 (d, *J* = 5.0 Hz, 1H), 3.62 (s, 3H), 1.57 (s, 9H), 1.55 (s, 9H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 169.7, 169.0, 149.3, 149.1, 148.3, 127.6, 127.4, 122.4, 113.8, 110.2, 84.3, 83.4, 62.0, 52.1, 45.9, 28.1, 27.9; **IR** (neat, cm^{-1}): 2981, 1781, 1736, 1479, 1367, 1312, 1252, 1151, 1118, 914, 842, 771; **HRMS (ESI):** exact m/z calculated for C$_{21}$H$_{28}$N$_2$O$_7$ (M+H)$^+$: 421,1897; Found 421, 1898 (M+H)$^+$.

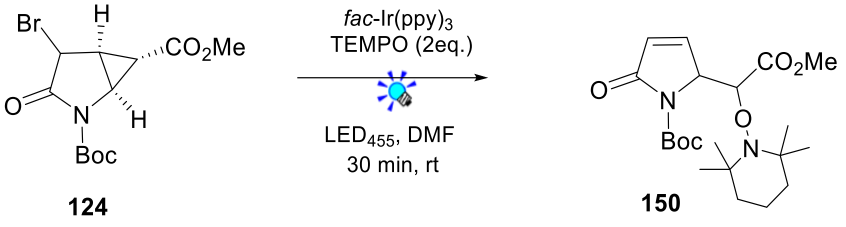
***Tert*-butyl (*E*)-2-(2-methoxy-2-oxoethylidene)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (145):**



An oven dried 10 mL Schleck flask equipped with a magnetic stirring bar was charged with substrate **124** (167 mg, 0.5 mmol), *fac*-Ir(ppy)$_3$ (3,27 mg, 0.005 mmol, 1.00 mol %) in 2 mL dry DMF. The resulting suspension was deoxygenated by three freeze-pump-thaw cycles. The reaction mixture was irradiated with blue light emitting diode (LED, λmax= 455nm) at room temperature for 10 min. After complete conversion of starting materials, the reaction mixture was saturated with brine solution (15 mL) and the product was extracted with ethyl acetate (3x15 mL), the combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure and subjected to column chromatography using PE/ EtOAc= 10:1 as an eluent to afford **145** (90 mg, 71% yield) as a white solid, **Mp**= 125-127 °C, **R*f*** = 0.6 (PE/ EtOAc= 10:1).

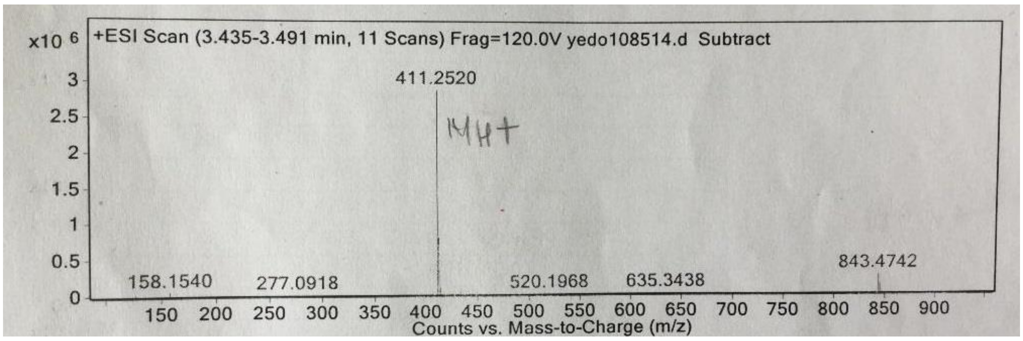
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 6.2, 0.6 Hz, 1H), 6.93 – 6.68 (m, 1H), 6.20 (ddd, *J* = 6.2, 1.6, 0.6 Hz, 1H), 3.71 (t, *J* = 8.8 Hz, 3H), 1.53 (t, *J* = 5.6 Hz, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.1, 166.2, 148.6, 147.5, 138.1, 125.9, 106.5, 84.9, 77.4, 77.0, 76.6, 51.9, 28.0; **IR** (neat, cm^{-1}): 2985, 1759, 1632, 1453, 1297, 1133, 987, 823, 730; **HRMS (ESI):** exact m/z calculated for $C_{12}H_{15}NO_5$ $(M+H)^+$: 254,0950; Found 254,1024 $(M+H)^+$.

The experimental procedure for capturing radicals 150.

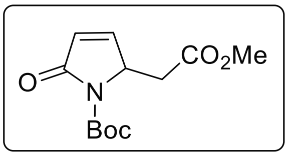


M. Wt =410.25

An oven dried 10 mL Schleck flask equipped with a magnetic stirring bar was charged with substrate **124** (167 mg, 0.5 mmol), *fac*-Ir(ppy)$_3$ (3,27 mg, 0.005 mmol, 1.00 mol %) and TEMPO (2 equiv) in 2 mL dry DMF. The resulting suspension was deoxygenated by three freeze-pump-thaw cycles (3x). The reaction mixture was irradiated with blue light emitting diode (LED, λmax= 455nm) at room temperature. After 30 minutes of irradiation, a TEMPO trapped compound **150** was detected by mass spectra.



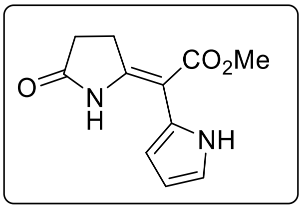
Tert-butyl 2-(2-methoxy-2-oxoethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (148):



An oven dried 10 mL Schleck flask equipped with a magnetic stirring bar was charged with substrate **124** (167 mg, 0.5 mmol), *fac*-Ir(ppy)$_3$ (3,27 mg, 0.005 mmol, 1.00 mol %) and DIPEA (1.5 mmol, 3 equiv) in 2 mL dry DMF. The resulting suspension was deoxygenated by three freeze-pump-thaw cycles (3x). The reaction mixture was irradiated with blue light emitting diode (LED, λmax= 455nm) at room temperature for 10 min. After complete conversion of starting materials, the reaction mixture was saturated with brine solution (15 mL) and the product was extracted with ethyl acetate (3x15 mL), the combined organic layer was dried over Na_2SO_4, was concentrated under reduced pressure and subjected to column chromatography using PE/ EtOAc= 10:1 as a eluent to afford **148** a yellowish oil in 45% yield. **R*f*** = 0.3 (PE/ EtOAc= 10:1).

^{1}H NMR (300 MHz, CDCl3): *δ* 1.56 (s, 9H), 2.43 (dd, *J*) 10.0, 16.1 Hz, 1H), 3.33 (dd, *J*) 4.0, 16.1 Hz, 1H), 3.71 (s, 3H), 4.88 (ddd, *J*) 1.9, 3.8, 10.0 Hz, 1H), 6.12 (dd, *J*) 1.6, 6.1 Hz, 1H), 7.34 (dd, *J*) 2.0, 6.1 Hz, 1H). **^{13}C NMR** (75 MHz, CDCl3): *ä* 28.1, 36.5, 52.1, 58.7, 83.6, 127.0, 149.3, 149.9, 168.6, 170.4.

Methyl (*E*)-2-(5-oxopyrroli*di*n-2-ylidene)-2-(1*H*-pyrrol-2-yl)acetate (155):



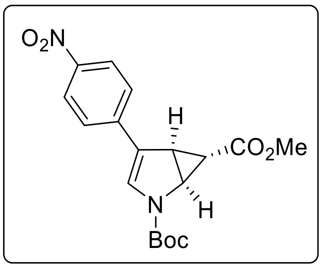
To a solution of **147c** (50 mg, 0.15 mmol, 1 equiv) in DCM (1 mL) at 0 °C slowly was added $SnCl_4$ (9 µL, 0.07 mmol, 0.5 equv) and stirred vigorously for 5 minutes. After the reaction mixture was quenched with water. The resultant solution was extracted with DCM, $NaHCO_3$ brine solution and was dried (Na_2SO_4). The residue obtained after removal of solvents was subjected to column chromatography (silica gel, PE/EtOAc= 3:1) to afford **155** as a yellowish oil (15 mg, 45%); **R*f*** = 0.3 (PE/ EtOAc) = 1:1.

^{1}H NMR (600 MHz, Chloroform-d) δ 10.28 (s, 1H), 8.48 (s, 1H), 6.81 (s, 1H), 6.24 (s, 1H), 6.07 (s, 1H), 3.77 (s, 3H), 2.97-2.85 (m, 2H), 2.56 – 2.42 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 177.63, 168.03, 156.98, 124.01, 117.64, 109.21, 108.40, 96.78, 77.23, 77.02, 76.81, 52.02, 28.07, 27.46; **HRMS (ESI)**: exact m/z calculated for $C_{11}H_{12}N_2O_3$ $(M+H)^+$: 221,0840; Found 221,0830 $(M+H)^+$;

5. General Procedure for arylation and arylsulfonylation of cyclopropanes

5.1 Procedure for arylsulfonylation of cyclopropane 96a-Me

2-(*Tert*-butyl) 6-methyl-4-(4-nitrophenyl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (163):



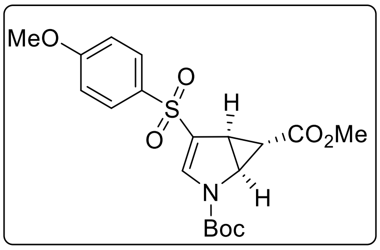
An oven dried 10 mL Schleck flask equipped with a magnetic stir bar was charged with substrate **96a-Me** (120 mg, 0.5 mmol) in 2 mL dry DMF. Then 4-nitrobenzenediazonium tetrafluoroborate (236 mg, 1mmol, 2 equiv) was added at -10 °C portion wise and resulting mixture was stirred for 15 minutes (note that longer reaction time give rise to decomposition of product). The resulting mixture was saturated with brine solution (15 mL) and the product was extracted with ethyl acetate (3x15 mL), the combined organic layer was dried over Na_2SO_4 and concentrated, the residue was purified by column chromatography (silica gel, PE/EtOAc= 10:1, was treated with 1 % TEA) to afford product **163** (58 mg, 33%) as a yellow oil. **R*f*** = 0.6 (PE/EtOAc = 3:1).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.19 (d, *J* = 8.9 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 63.2 Hz, 1H), 4.50 (d, *J* = 45.7 Hz, 1H), 3.75 (s, 3H), 3.24 – 3.09 (m, 1H), 1.56 (s, 9H), 1.21 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.93, 150.5, 146.0, 140.0, 128.1, 124.8, 124.2, 122.1, 83.1, 52.2, 44.5, 29.7, 28.2, 22.4; **HRMS** (+APCI): calcd. for $C_{18}H_{20}N_2O_6$ [M+H]+ 361.1321, Found 361.1327.

5.2 General Procedure for arylsulfonylation of cyclopropanes (*GP-4*)

An oven dried 10 mL Schlenk flask was charged with benzenesulfonyl chloride (1 mmol, 2 equiv), K_2HPO_4 (174 mg, 1mmol, 2 equiv) and $Ru(bpy)_3$ (7.48 mg, 2 mol %) in 1 mL dry acetonitrile. The resulting suspension was degassed by “pump-freeze-thaw” cycles (×3). The reaction mixture was irradiated with blue light emitting diode (LED, λmax = 455 nm) and then substrate **96a, 96a-Me** or **96b-Me** was added under positive nitrogen atmosphere. After complete conversion of starting materials (monitored by TLC analysis), the reaction mixture was saturated with brine solution (15 mL) and the product was extracted with ethyl acetate (3x15 mL), the combined organic layers were dried over Na_2SO_4 and concentrated, the residue was purified by column chromatography on silicagel using PE/ EtOAc, as eluent to afford products **171a-171g**.

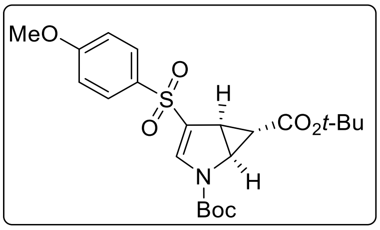
2-(*Tert*-butyl) 6-methyl -4-((4-methoxyphenyl)sulfonyl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (171a):



Following *GP-4*, **171a** was prepared from **96a-Me** (120 mg, 0.5 mmol) and 4-methoxybenzenesulfonyl chloride (206.65 mg, 1 mmol, 2 equiv). The crude product was purified by column chromatography (silica gel, PE/EA=10:1) to afford **171a** as a yellowish oil (91 mg, 45% yield). **R*f*** = 0.3 (PE/EA = 5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.8 Hz, 1H), 7.28 (s, 1H), 6.98 (t, *J* = 12.6 Hz, 1H), 4.45 (s, 1H), 3.87 (s, 3H), 3.67 (s, 3H), 2.96 (d, *J* = 5.2 Hz, 1H), 1.52 (s, 9H), 0.97 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.92, 163.63, 149.91, 137.01, 131.88, 129.59, 124.32, 114.60, 84.22, 55.71, 52.27, 45.41, 28.06, 20.78; **IR** (neat, cm-1): 2881, 1719, 1576, 1498, 1371, 1256, 1133, 1088, 976, 834, 670; **HRMS** (ESI): *m/z* calculated for $C_{19}H_{23}NO_7S$ $(M+H)^+$: 410,1195 ; Found 410,1538 $(M+H)^+$

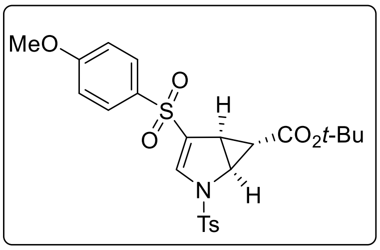
Di-*tert*-butyl -4-((4-methoxyphenyl)sulfonyl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (171b):



Following *GP-4*, **171b** was prepared from **96a** (140 mg, 0.5 mmol) and 4-iodoanisole (206 mg, 1 mmol, 2 equiv). The crude product was purified by column chromatography (silica gel; PE/EtOAc= 7:1,) to afford **171b** as a yellowish oil (97 mg, 42%). **R*f*** = 0.37 (PE/ EtOAc=5:1)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 – 7.82 (m, 2H), 7.24 (s, 1H), 7.03 – 6.98 (m, 2H), 4.40 (s, 1H), 3.88 (s, 3H), 2.88 (s, 1H), 1.51 (s, 9H), 1.41 (s, 9H), 0.83 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.5, 163.5, 149.9, 136.7, 131.9, 129.5, 124.4, 114.5, 84.0, 81.6, 55.6, 45.0, 28.0, 28.0, 21.9; **IR** (neat, cm-1): 2978, 1714, 1576, 1330, 1297, 1136, 1092, 946, 833, 730, 670; **HRMS (ESI)**: *m/z* calculated for $C_{22}H_{29}NO_7S$ $(M+H)^+$: 452,1665; Found 452.1675 $(M+H)^+$

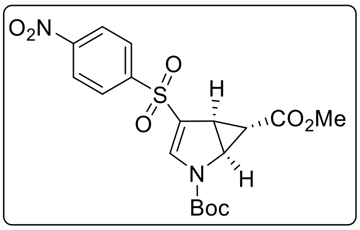
Tert-butyl-4-((4-methoxyphenyl)sulfonyl)-2-tosyl-2-azabicyclo[3.1.0]hex-3-ene-6-carboxylate (171c):



Following *GP-4***,** **171c** was prepared from **96b-Me** (120 mg, 0.5 mmol) and 4-Methoxybenzenesulfonyl chloride (206.65 mg, 1 mmol, 2 equiv). The crude product was purified by column chromatography (silica gel, PE/EA=10:1) to afford **171c** as a yellowish oil (74 mg, 30% yield). **R*f*** = 0.3 (PE/EA) = 5:1.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 (d, *J* = 8.8 Hz, 2H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.9 Hz, 2H), 4.20 (d, *J* = 6.9 Hz, 1H), 4.00 (s, 2H), 2.90 (dd, *J* = 6.9, 2.9 Hz, 1H), 2.59 (s, 3H), 1.51 (s, 9H), 0.45 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.9, 163.7, 145.5, 137.2, 133.1, 131.2, 130.4, 129.7, 127.3, 127.0, 114.6, 81.8, 55.7, 45.6, 28.9, 28.0, 21.7, 20.4; ; **IR** (neat, cm-1): 2974, 2929, 1703, 1576, 1494, 1367, 1133, 1010, 905, 831, 723, 663; **HRMS (ESI)**: *m/z* calculated for $C_{24}H_{27}NO_7S_2$ $(M+H)^+$: 506.1229; Found 506. 1237 $(M+H)^+$.

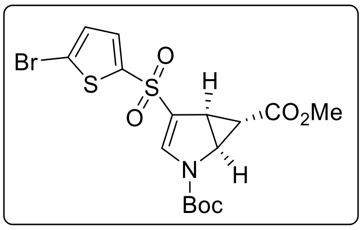
2-(*Tert*-butyl) 6-methyl-4-((4-nitrophenyl)sulfonyl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (171e):



Following *GP-4***, 171e** was prepared from **96a-Me** (120 mg, 0.5 mmol) and 4-nitrobenzenesulfonyl chloride (222 mg, 1 mmol, 2 equiv). The crude product was purified by column chromatography (silica gel, PE/EA=10:1) to afford **171e** as a yellowish oil (75 mg, 35% yield). **R*f*** = 0.25 (PE/EA = 5:1).

^{1}H NMR (400 MHz, Chloroform-d) δ 8.39 (d, J = 8.8 Hz, 2H), 8.10 (d, J = 8.8 Hz, 2H), 7.43 (s, 1H), 4.49 (s, 1H), 3.68 (s, 3H), 3.02 (dd, J = 7.0, 2.7 Hz, 1H), 1.52 (s, 9H), 0.93 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.4, 167.8, 150.4, 146.2, 139.6, 133.5, 128.6, 123.5, 121.6, 84.9, 52.4, 45.5, 28.0, 20.3; **IR** (neat, cm-1): 2881, 1722, 1569, 1371, 1338, 1282, 1140, 1088, 853, 730; **HRMS (ESI)**: *m/z* calculated for $C_{18}H_{20}N_2O_8S$ $(M+H)^+$: 425.0940; Found 425.0957 $(M+H)^+$.

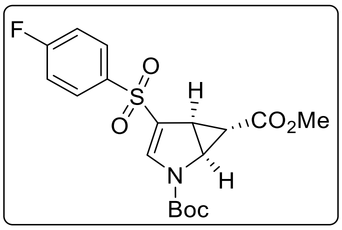
2-(*Tert*-butyl) 6-methyl -4-((5-bromothiophen-2-yl)sulfonyl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (171d):



Following *GP-4***, 171d** was prepared from **96a-Me** (120 mg, 0.5 mmol) and 5-Bromothiophene-2-sulfonyl chloride (262 mg, 1 mmol, 2 equiv). The crude product was purified by column chromatography (silica gel, PE/EA=7:1) to afford **171d** as a yellowish oil (95 mg, 37% yield). **R*f*** = 0.2 (PE/EA = 5:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 (d, *J* = 3.9 Hz, 1H), 7.31 (s, 1H), 7.10 (d, *J* = 4.0 Hz, 1H), 4.46 (s, 1H), 2.95 (d, *J* = 5.7 Hz, 1H), 1.52 (s, 9H), 1.43 (s, 9H), 0.90 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 206.9, 170.3, 149.7, 142.8, 133.1, 130.8, 123.3, 121.7, 84.4, 81.9, 45.1, 30.9, 28.0, 28.0, 21.8; **IR** (neat, cm-1): 2978, 1722, 1572, 1334, 1133, 1084, 969, 769, 670; **HRMS (ESI)**: *m/z* calculated for $C_{19}H_{24}BrNO_6S_2$ $(M+H)^+$: 506.0228; Found 506.0228 $(M+H)^+$.

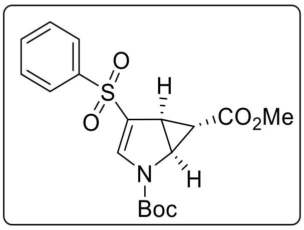
2-(*Tert*-butyl) 6-methyl-4-((4-fluorophenyl)sulfonyl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (171f):



Following *GP-4*, **171f** was prepared from **96a-Me** (120 mg, 0.5 mmol) and 4-iodoanisole (206 mg, 0.1 mmol, 2 equiv). The crude product was purified by column chromatography (silica gel; PE/EtOAc= 10:1) to afford **171f** as a colorless oil (65 mg, 33%). **R*f*** = 0.5 (PE/ EtOAc=5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 1H), 7.34 (s, 1H), 7.25 (m, 2H), 4.49 (s, 1H), 3.69 (s, 3H), 2.99 (dd, 1H), 1.53 (s, 9H), 1.27 (s, 1H), 0.97 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.7, 166.8, 164.3, 149.6, 137.8, 136.5, 130.2, 130.1, 123.2, 116.8, 116.5, 84.4, 52.3, 45.4, 31.8, 28.0, 20.6; **HRMS (ESI)**: *m/z* calculated for $C_{18}H_{20}FNO_6S$ $(M+H)^+$: 398.0998 ; Found 398.1068 $(M+H)^+$.

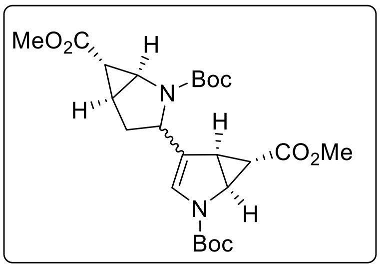
2-(*Tert*-butyl) 6-methyl -4-(phenylsulfonyl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (171g):



Following *GP-4***, 171g** was prepared from **96a-Me** (120 mg, 0.5 mmol) and benzenesulfonyl chloride (0.128 mL, 1 mmol, 2 equiv). The crude product was purified by column chromatography (silica gel, PE/EA=5:1) to afford **171g** as a yellowish oil (60 mg, 30% yield). $\mathbf{R}_f$ = 0.11 (PE/EA = 10:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 (d, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.06 (s, 1H), 4.19 (s, 1H), 3.39 (s, 3H), 2.75 – 2.68 (m, 1H), 1.24 (s, 9H), 0.68 (s, 1H); **^{13}C NMR** (101 MHz, CDCl3) δ 171.7, 149.7, 140.3, 137.7, 133.4, 129.3, 127.2, 123.4, 84.3, 52.2, 45.4, 28.0, 20.6; **IR** (neat, cm-1):2981, 1722, 1572, 1371, 1136, 1088, 976, 719, 669; **HRMS (ESI)**: *m/z* calculated for $C_{18}H_{21}NO_6S$ $(M+H)^+$: 380.1090; Found 380.1091 $(M+H)^+$.

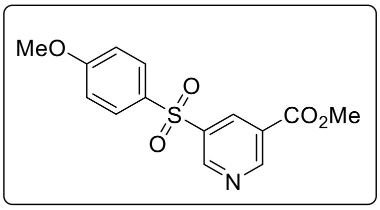
2-(*Tert*-butyl)6-methyl-2-(tert-butoxycarbonyl)-6-(methoxycarbonyl)-2-azabicyclo [3.1.0]hexan-3-yl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (177):



An 10 mL Schlenk flask equipped with a magnetic stirring bar was charged with **96a-Me** (120 mg, 0.5 mmol, 1.0 equiv) in acetonitrile (2 ml). The resulting mixture was stirred for 10 min at room temperature. After completion of the reaction (as monitored by TLC), the resulting mixture was saturated with brine solution (15 mL) and the product was extracted with ethyl acetate (3x15 mL), the combined organic layer was dried over Na_2SO_4 and concentrated, the residue was purified by column chromatography (silica gel; PE/EtOAc= 10:1) to afford **181** as a colorless oil (51 mg, 33 % yield. $\mathbf{R_f}$ = 0.30 (PE/EtOAc = 10:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.47 – 6.23 (m, 1H), 4.43 – 4.19 (m, 2H), 3.82 – 3.74 (m, 2H), 3.66 (s, 6H), 2.79 – 2.69 (m, 1H), 2.21 – 2.13 (m, 2H), 1.67 – 1.63 (m, 1H), 1.47 (s, 9H), 1.42 (s, 9H), 1.07 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.10, 171.09, 155.01, 150.90, 149.21, 124.62, 83.85, 80.66, 57.067, 51.81, 51.71, 51.71, 45.41, 34.82, 28.23, 28.26, 27.97, 24.93, 22.25;

Methyl 5-(4-methoxyphenyl)sulfonyl)nicotinate (181):



An oven dried 10 mL Schlenk flask equipped with a magnetic stirring bar was charged with a monocyclocpropanated *N*-Boc pyrrole **171a** (204 mg, 0.5 mmol, 1 equiv), $Pd_2(dba)_3$ (14 mg, 3 mol%), 4-iodoanisole (0.6 mmol, 1.2 equiv), $NaHCO_3$ (105 mg, 1.25 mmol, 2.5 equiv), and tetrabutylammonium bromide (TBAB) (322 mg, 1 mmol, 2 equiv) followed by addition of dry toluene (1.5 mL). The resulting mixture was degassed by "pump-freeze-thaw" cycles (×3), then stirred for 5 min at room temperature and subsequently placed on a pre-heated oil bath at 80 °C for 48 h. After completion of the reaction (as monitored by TLC), the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (15 mL) and filtered through a pad of Celite. The crude product was purified by column chromatography (silica gel; PE/EtOAc= 10:1) to afford **181** as a colorless oil (51 mg, 33 % yield. **R_f** = 0.30 (PE/EtOAc = 10:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.28 (d, *J* = 31.9 Hz, 1H), 8.74 (d, *J* = 2.1 Hz, 1H), 7.99 – 7.72 (m, 2H), 7.08 – 6.85 (m, 2H), 3.98 (s, 3H), 3.86 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.14, 154.02, 151.62, 139.27, 135.95, 131.58, 130.26, 126.45, 115.00, 77.37, 77.05, 76.73, 55.80, 52.97; **IR** (neat, cm^{-1}): 2952, 1714, 1591, 1472,1431, 1248, 1110, 1017, 827, 782, 738; **HRMS (ESI):** *m/z* calculated for $C_{14}H_{13}NO_3S$ $(M+H)^+$: 308.0514. Found 308.0523.

6. References

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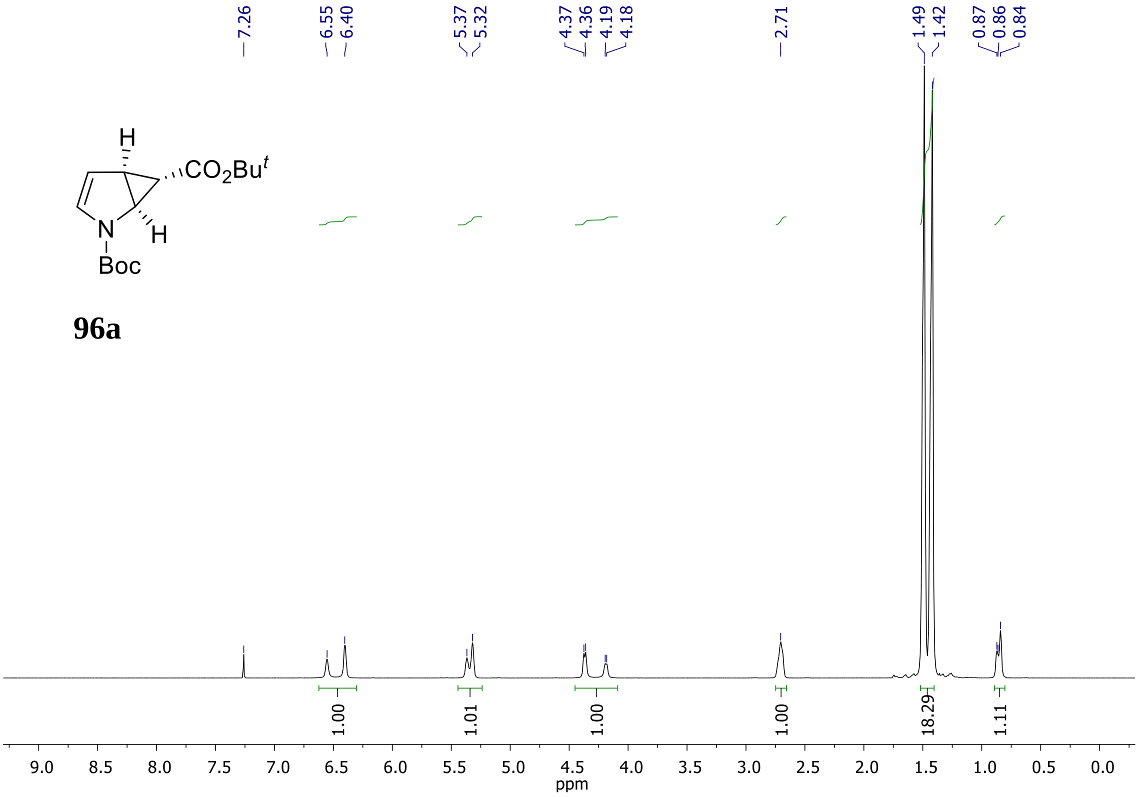
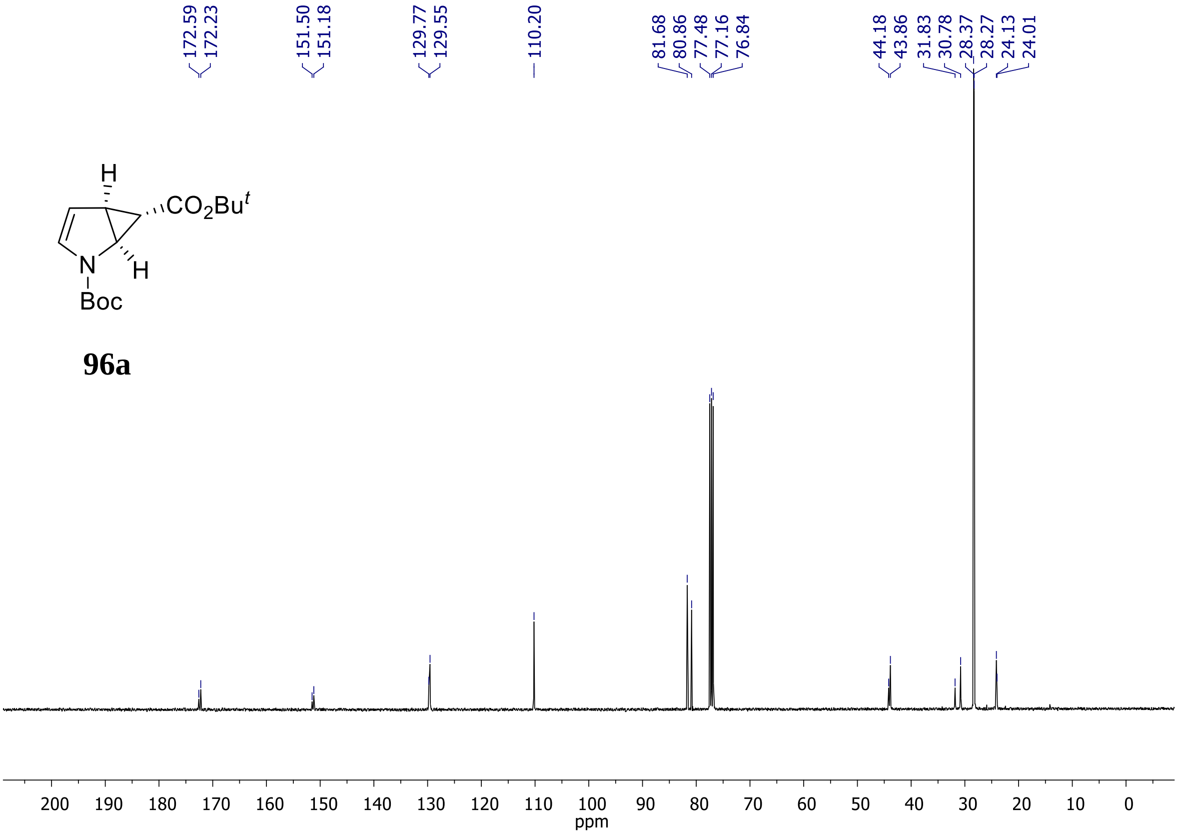
F Appendix

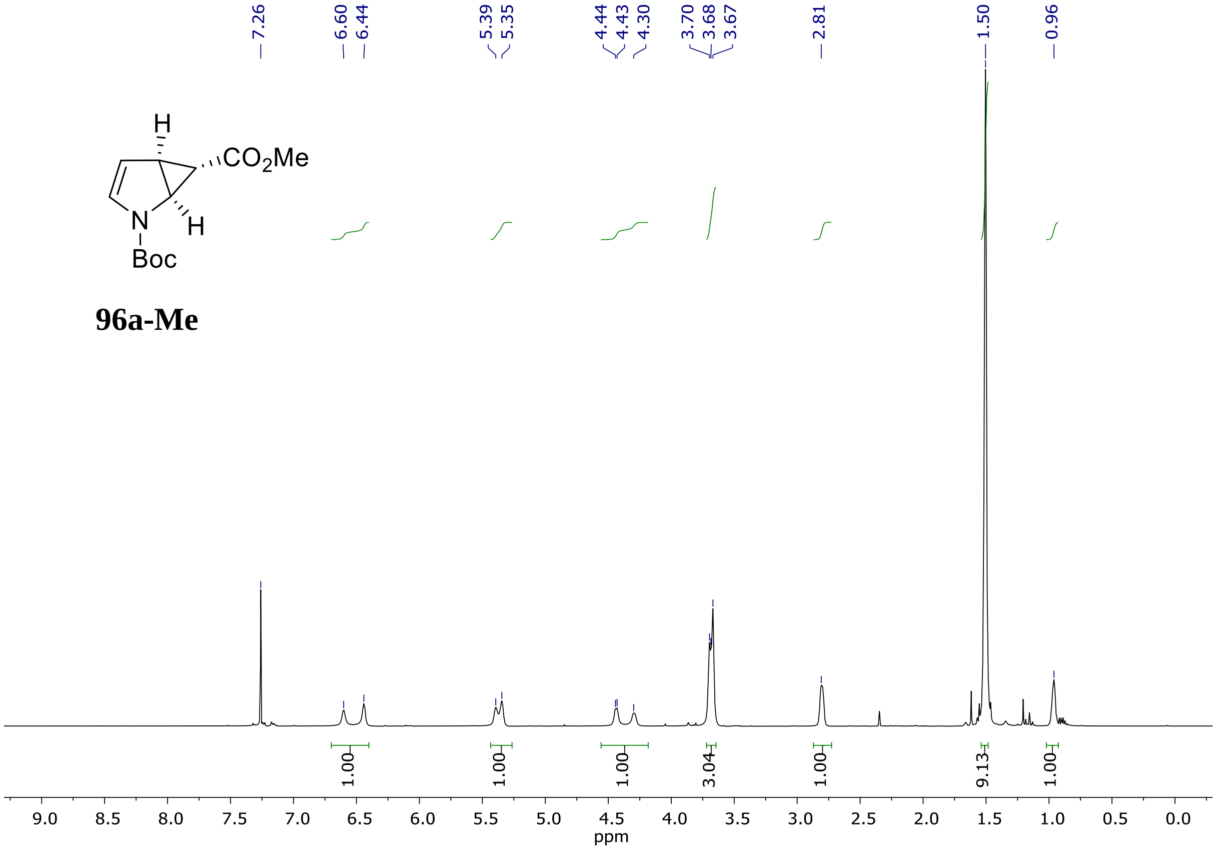
1. Copies of NMR spectra



^{1}H NMR (400 MHz, CDCl$_3$)

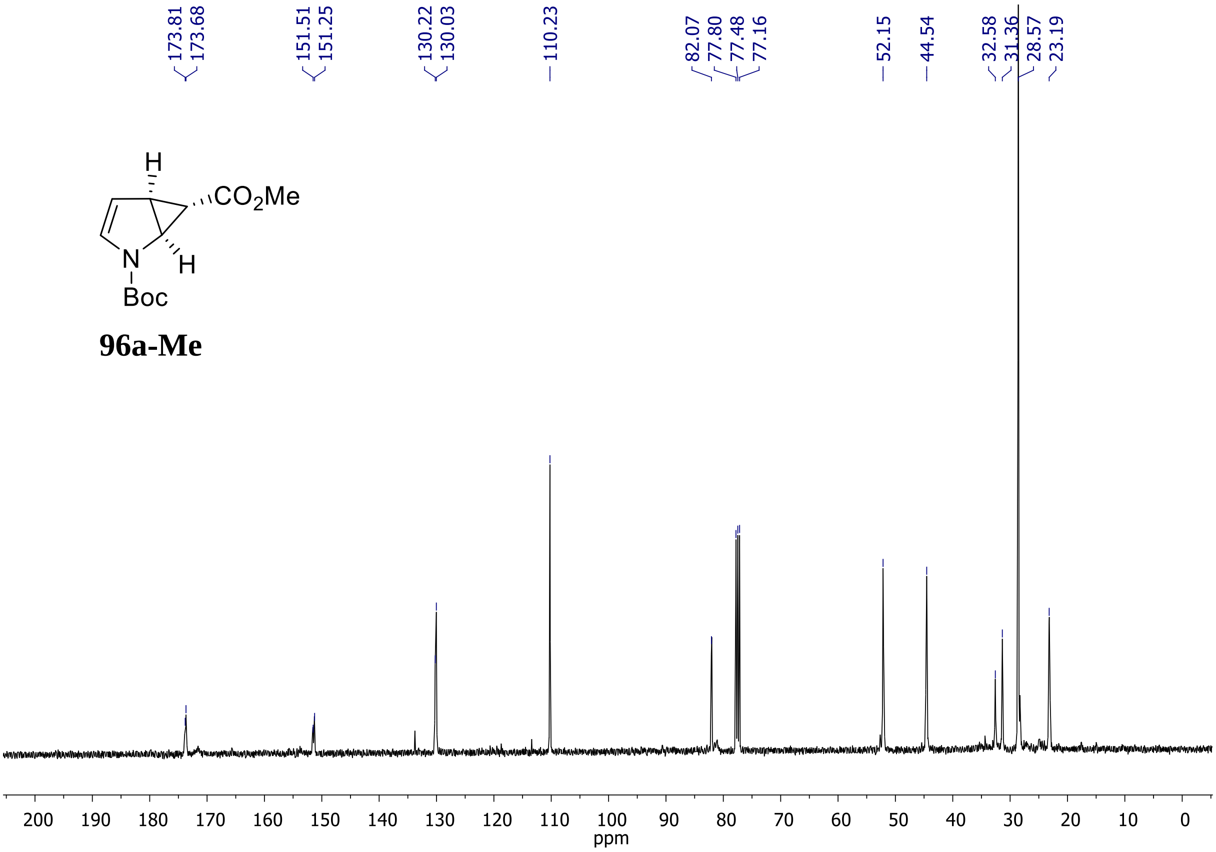


^{13}C NMR (101 MHz, CDCl$_3$)



96a-Me

^{1}H NMR (400 MHz, CDCl$_3$)



96a-Me

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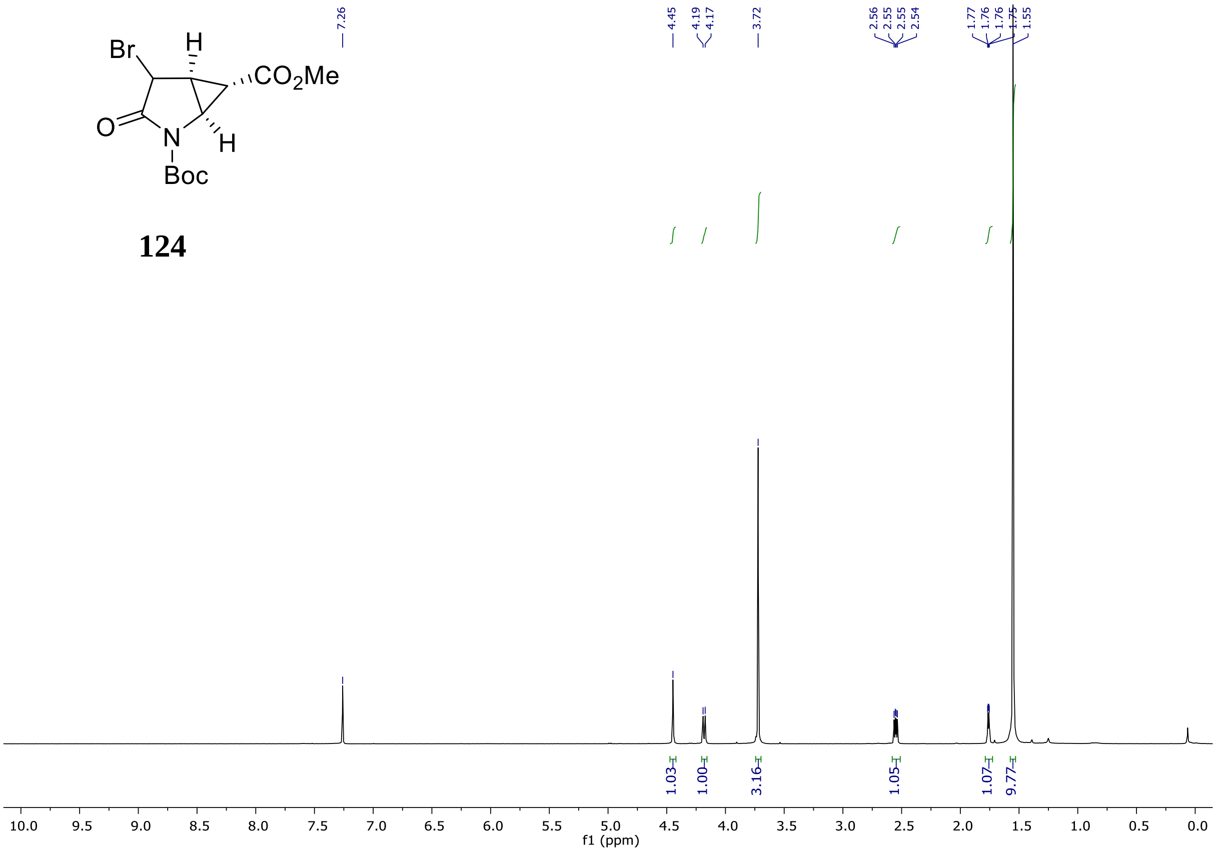
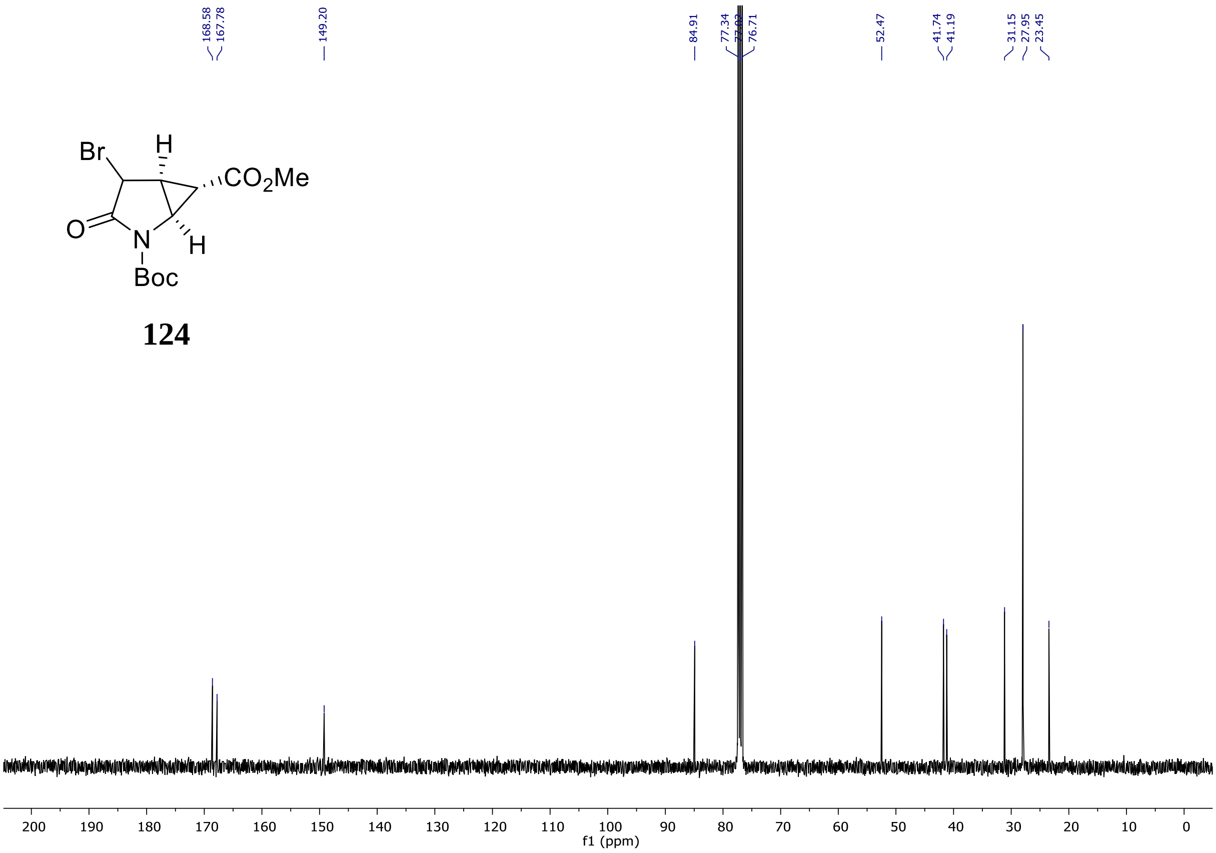


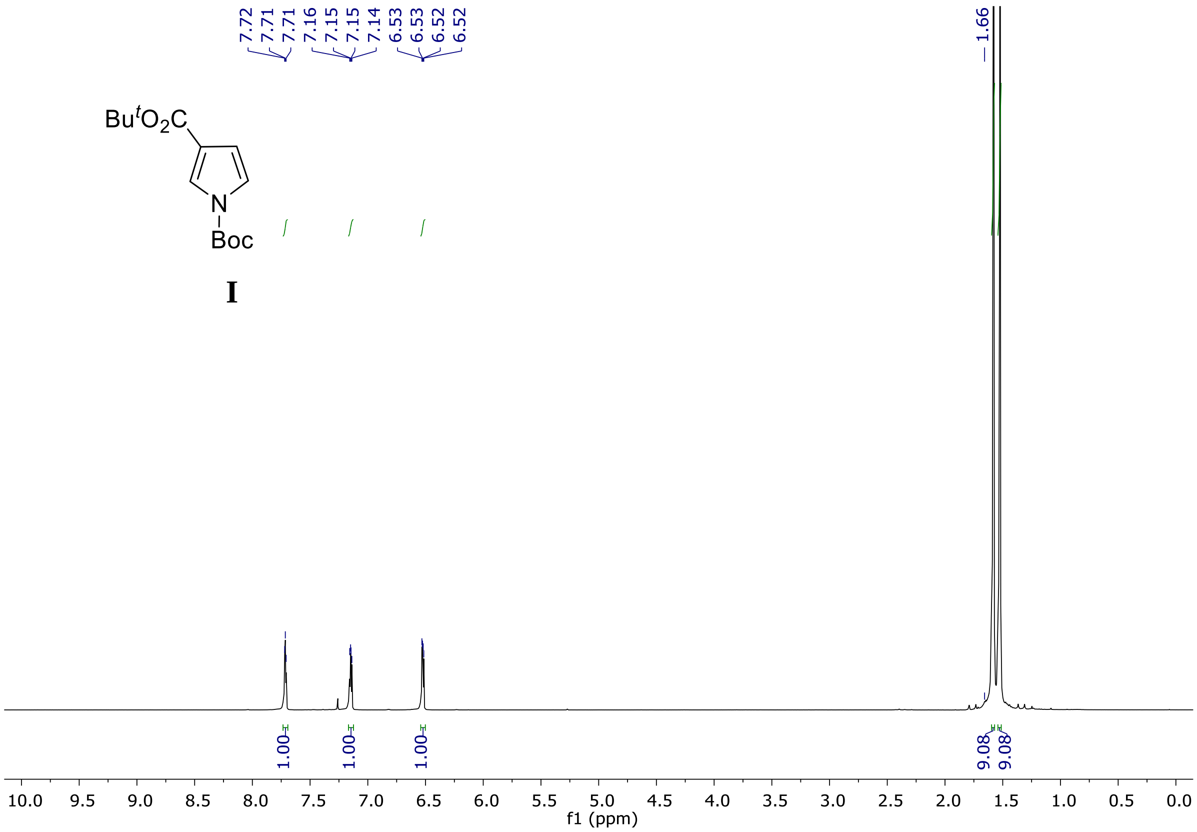
124

^{1}H NMR (400 MHz, CDCl$_3$)



124

^{13}C NMR (101 MHz, CDCl$_3$)



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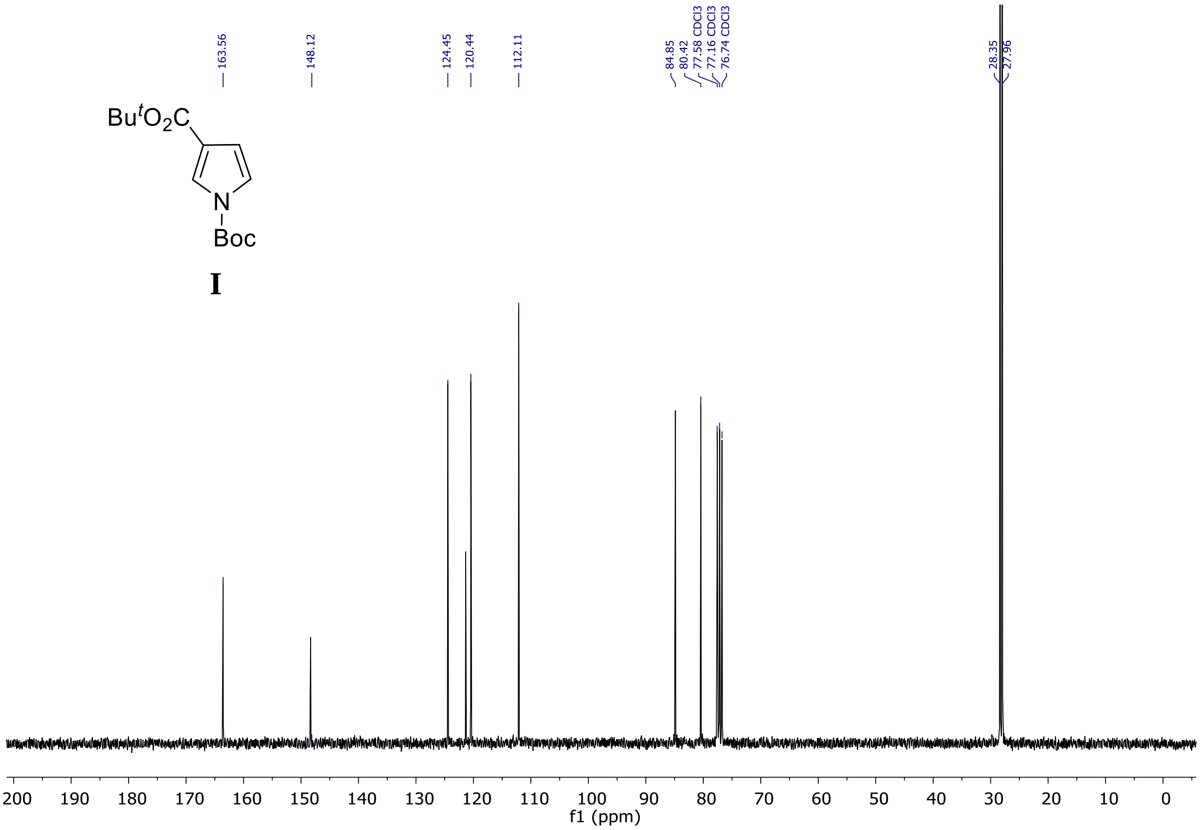
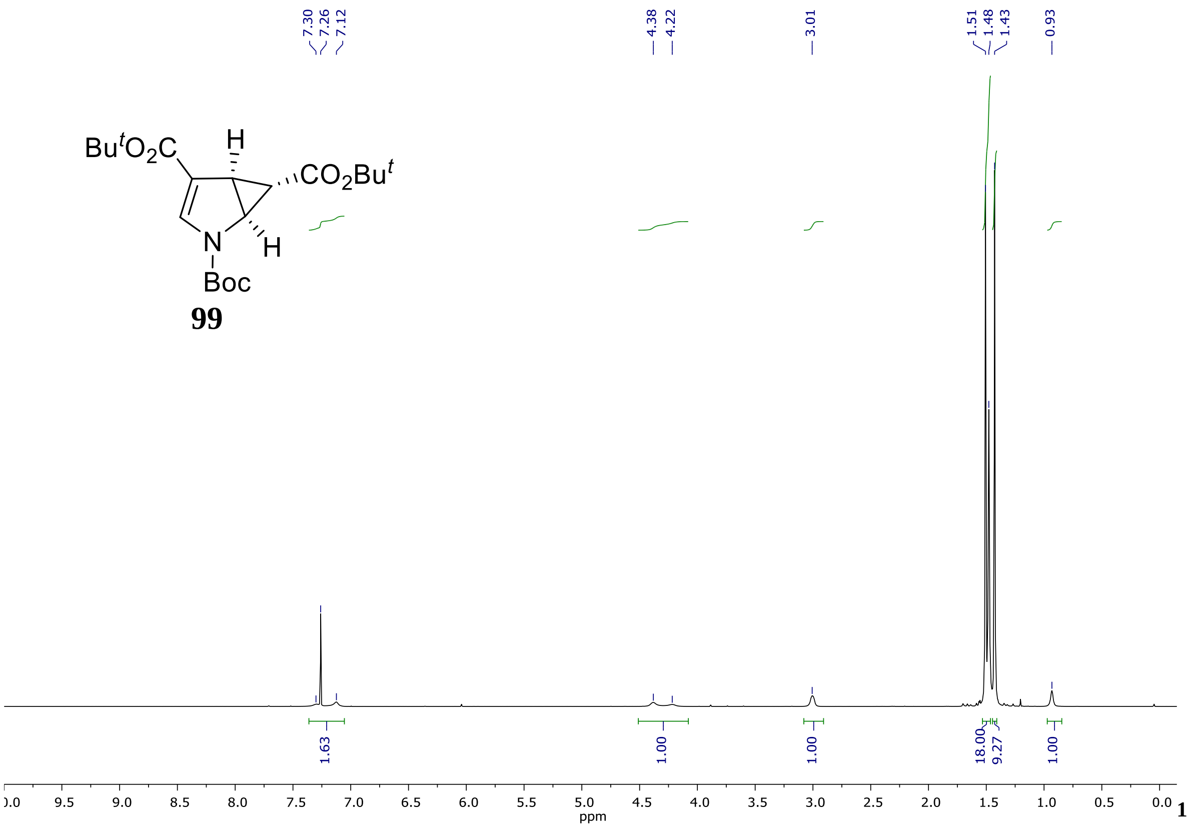
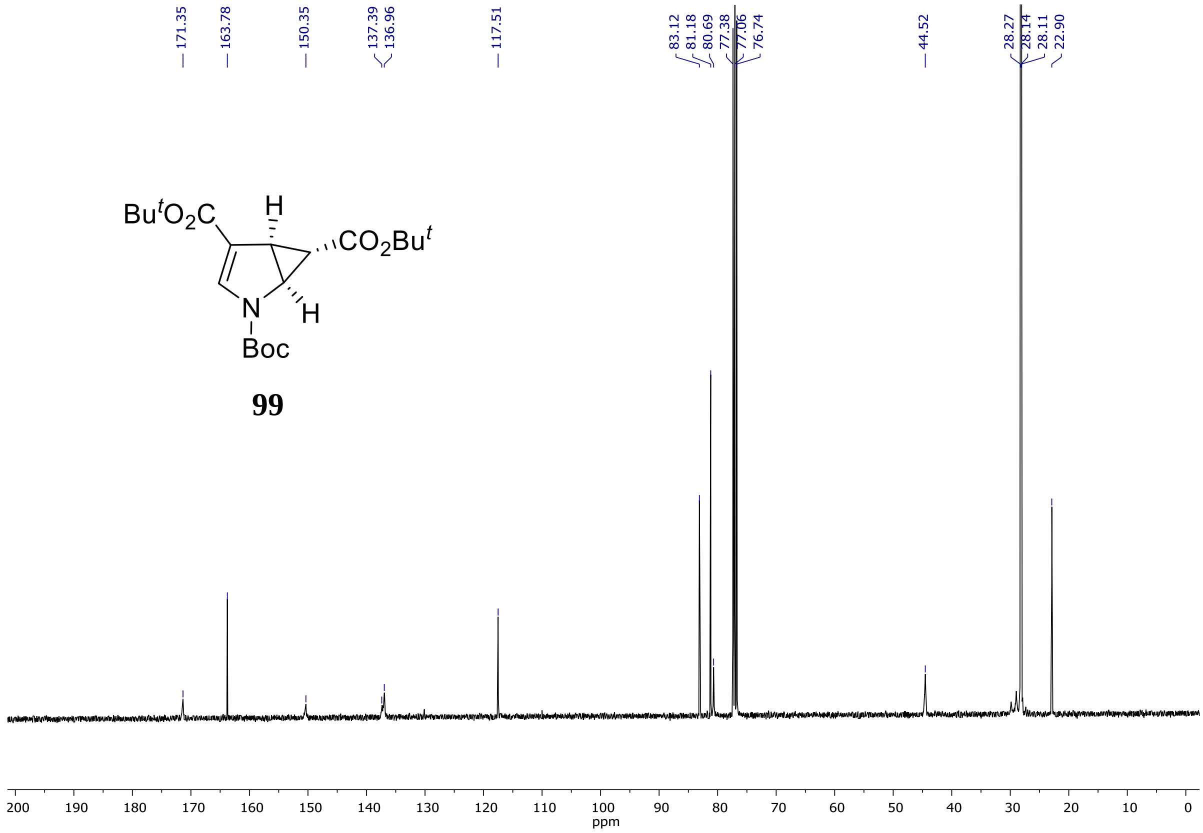


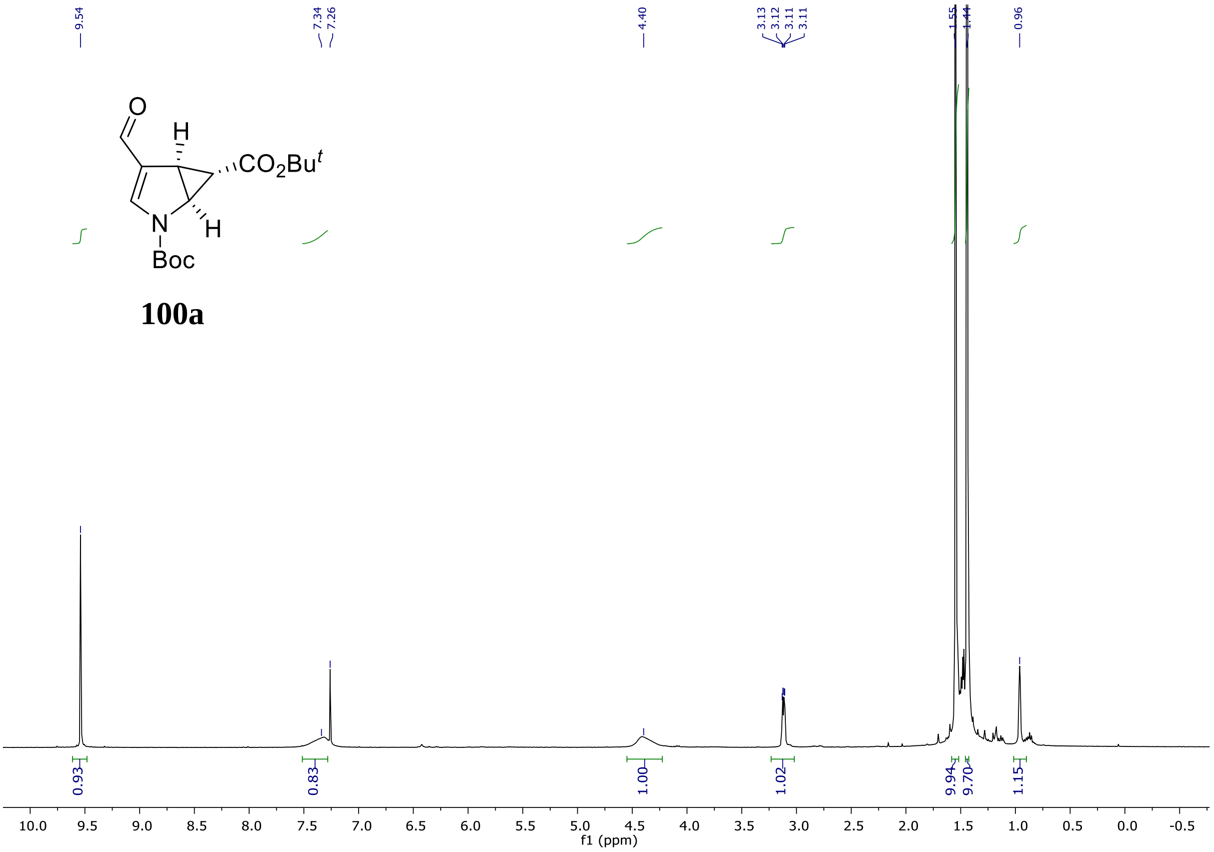
^{13}C NMR (75 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



^{13}C NMR (101 MHz, CDCl$_3$)



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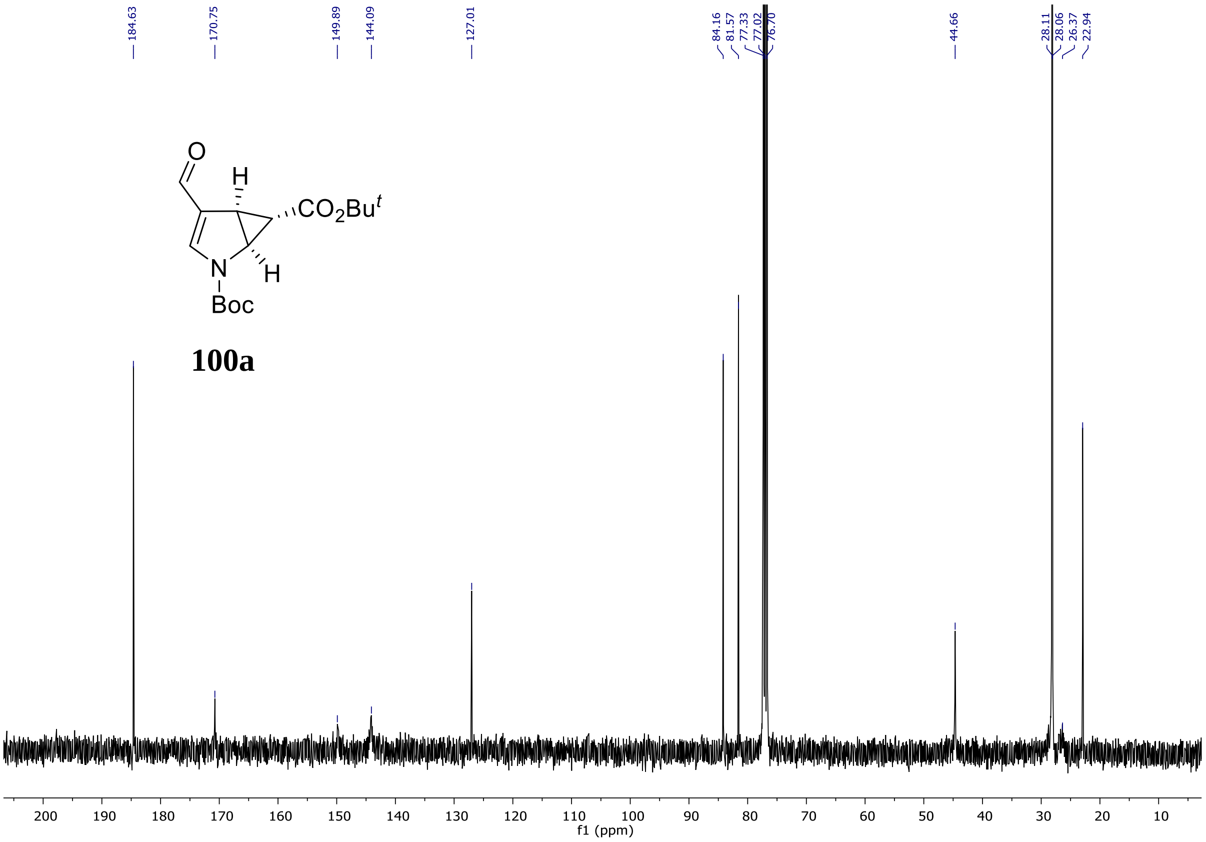
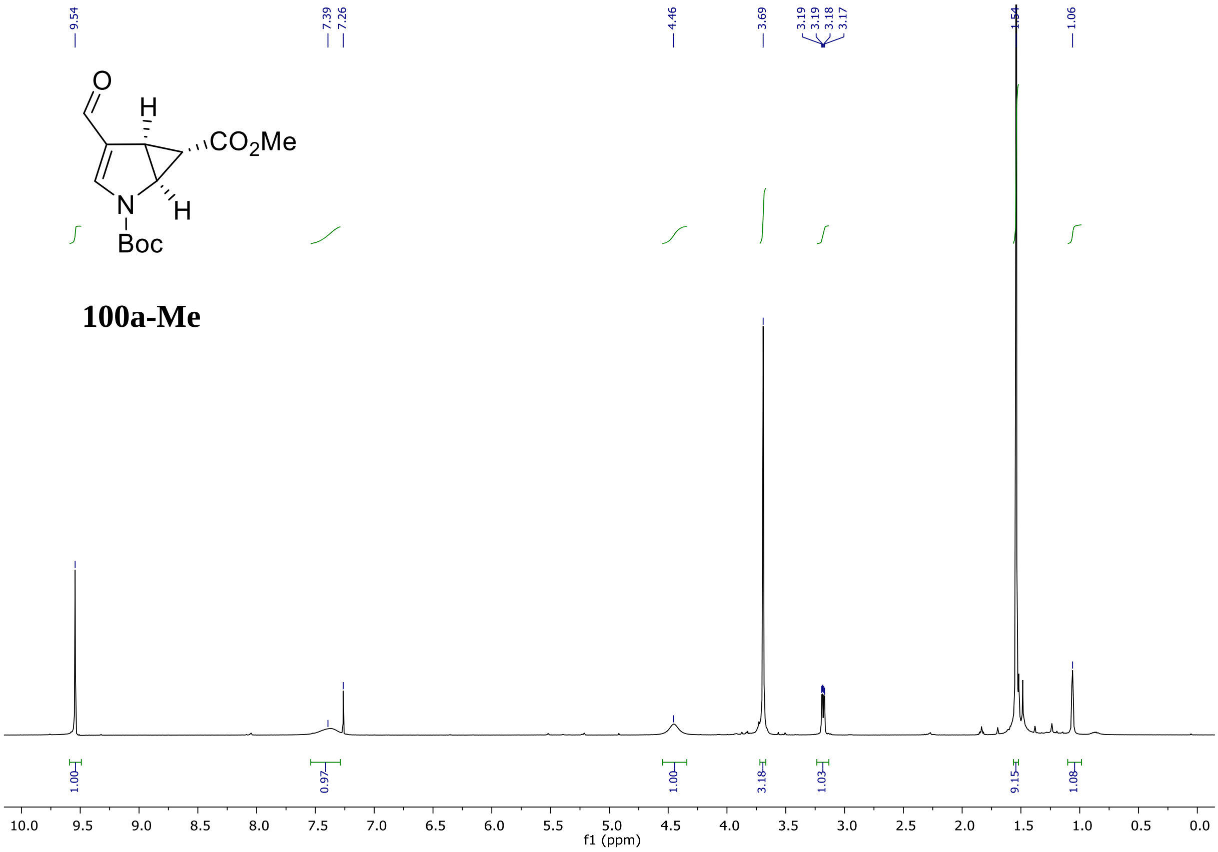
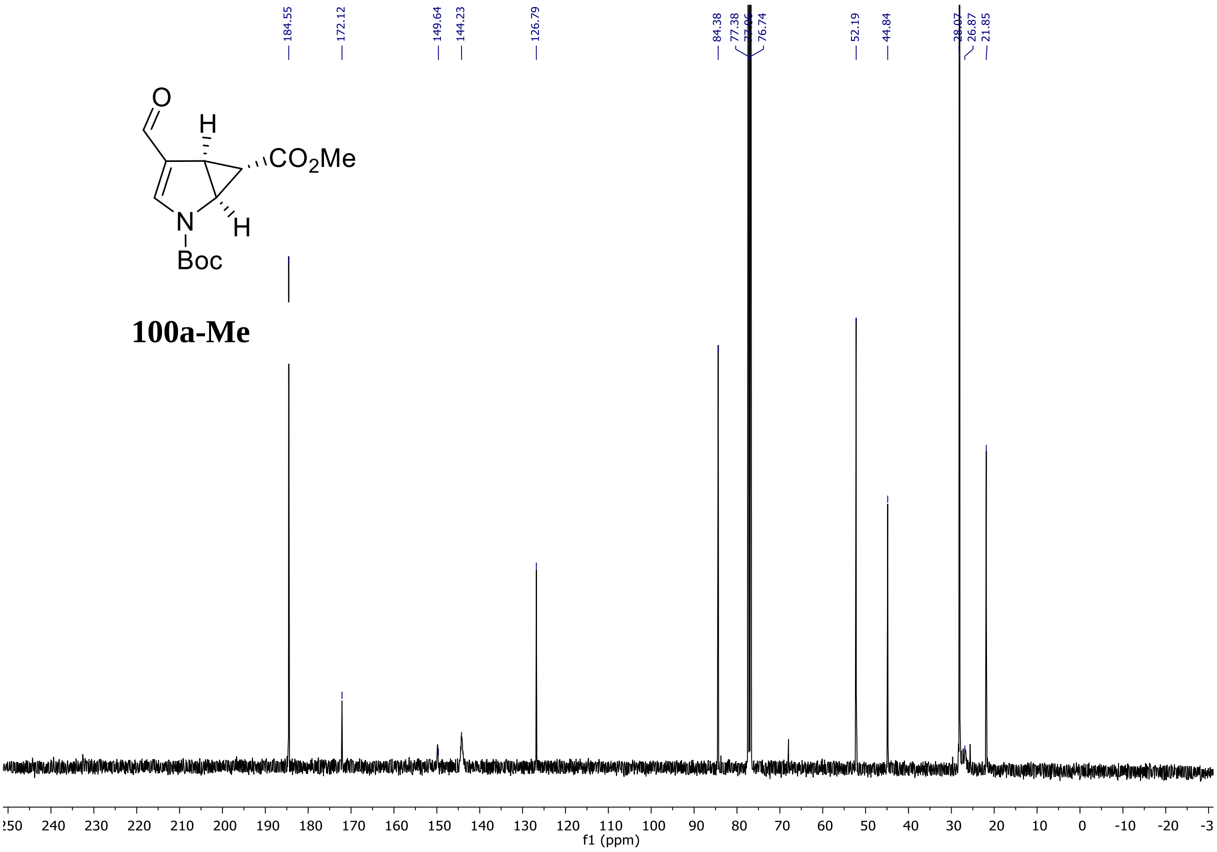


^{13}C NMR (101 MHz, CDCl$_3$)



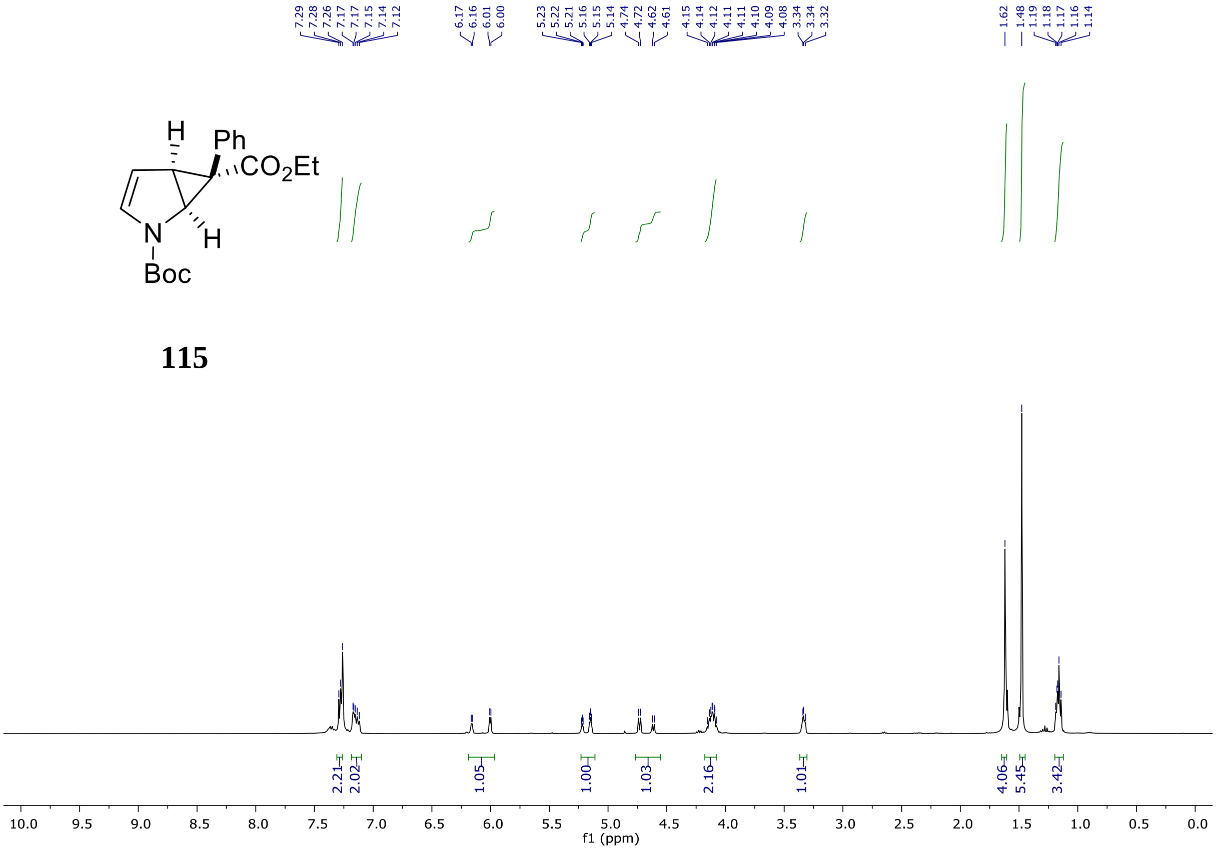
100a-Me

^{1}H NMR (400 MHz, CDCl$_3$)



100a-Me

^{13}C NMR (101 MHz, CDCl$_3$)



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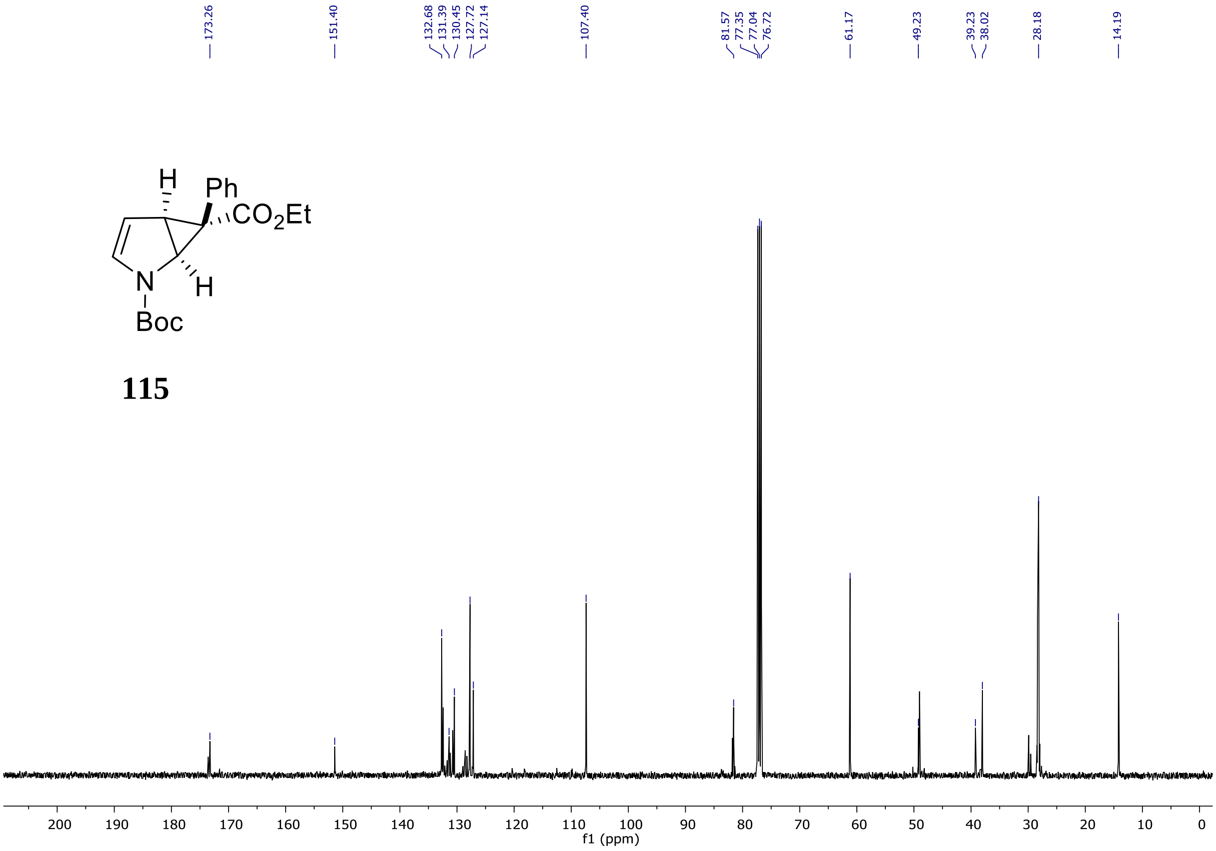

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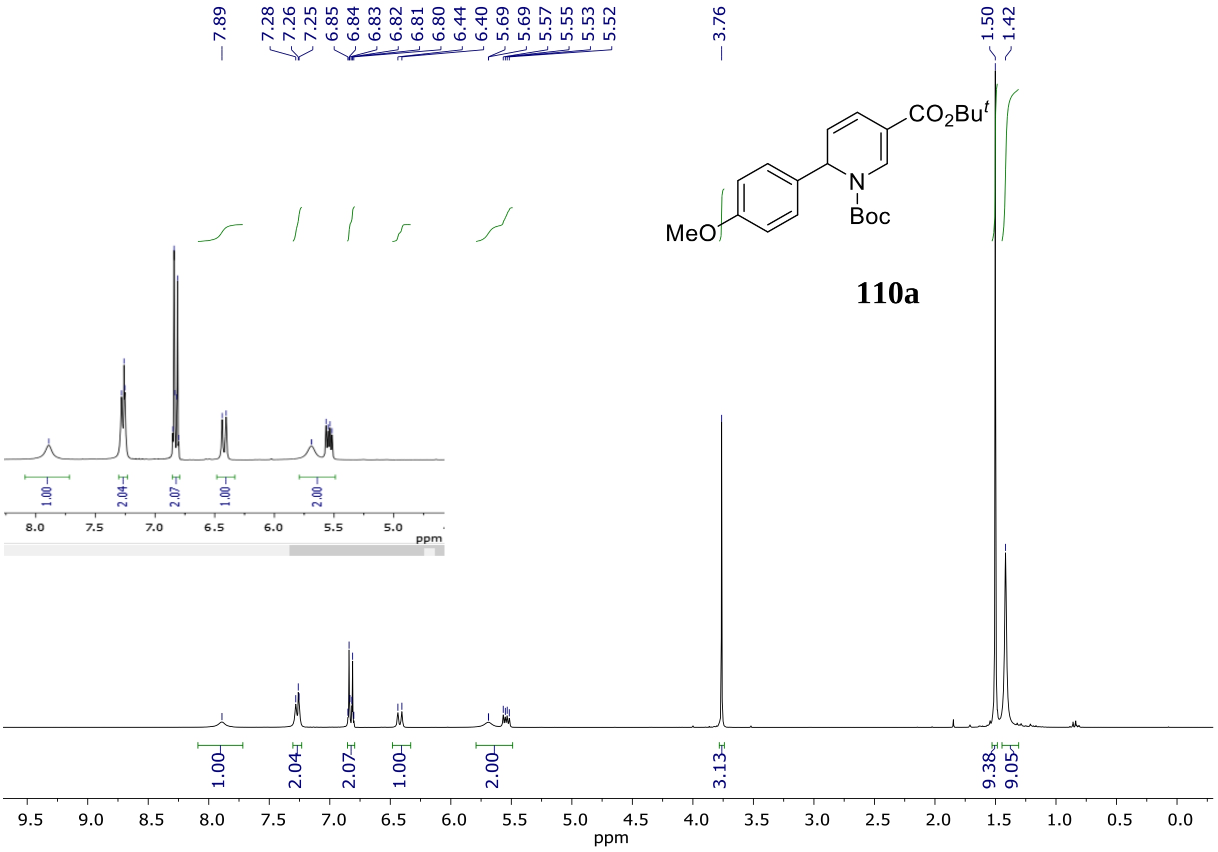
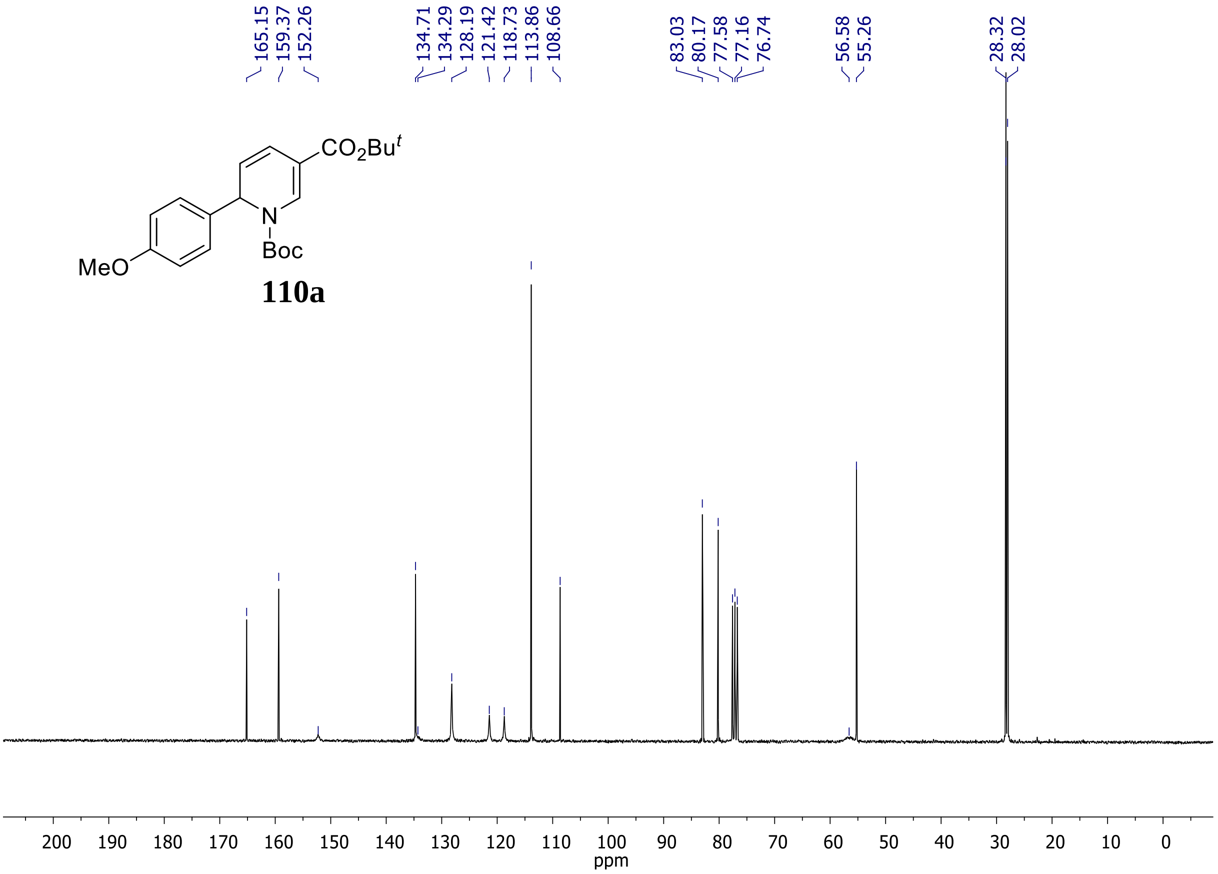


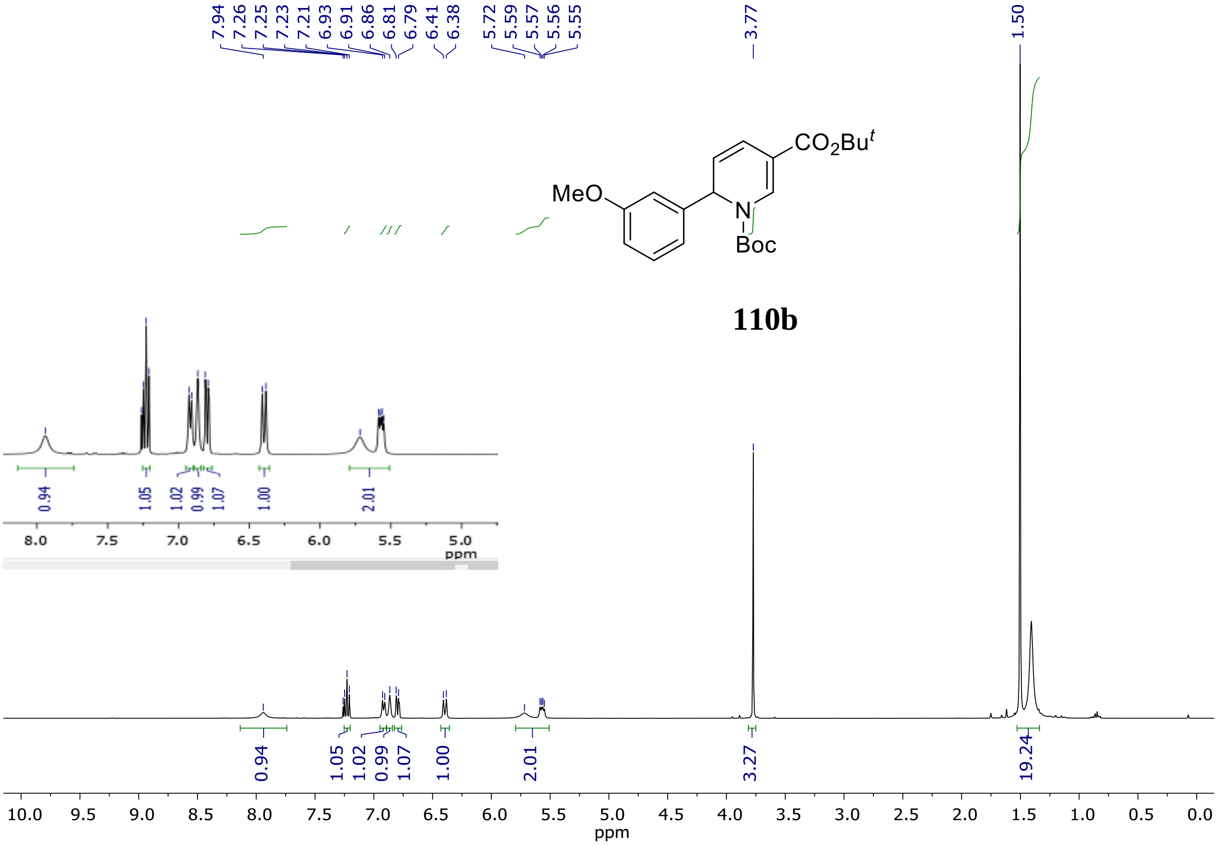
110a

^{1}H NMR (300 MHz, CDCl$_3$)



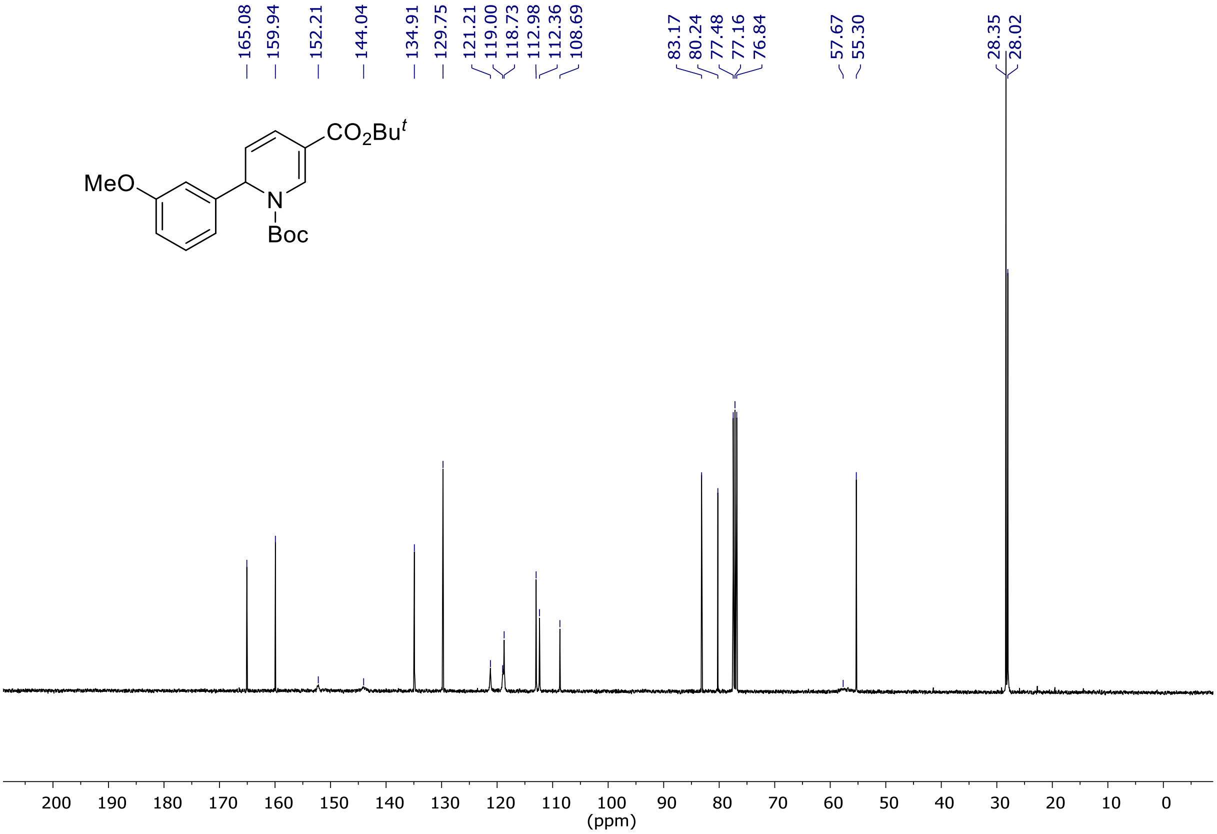
110a

^{13}C NMR (75 MHz, CDCl$_3$)

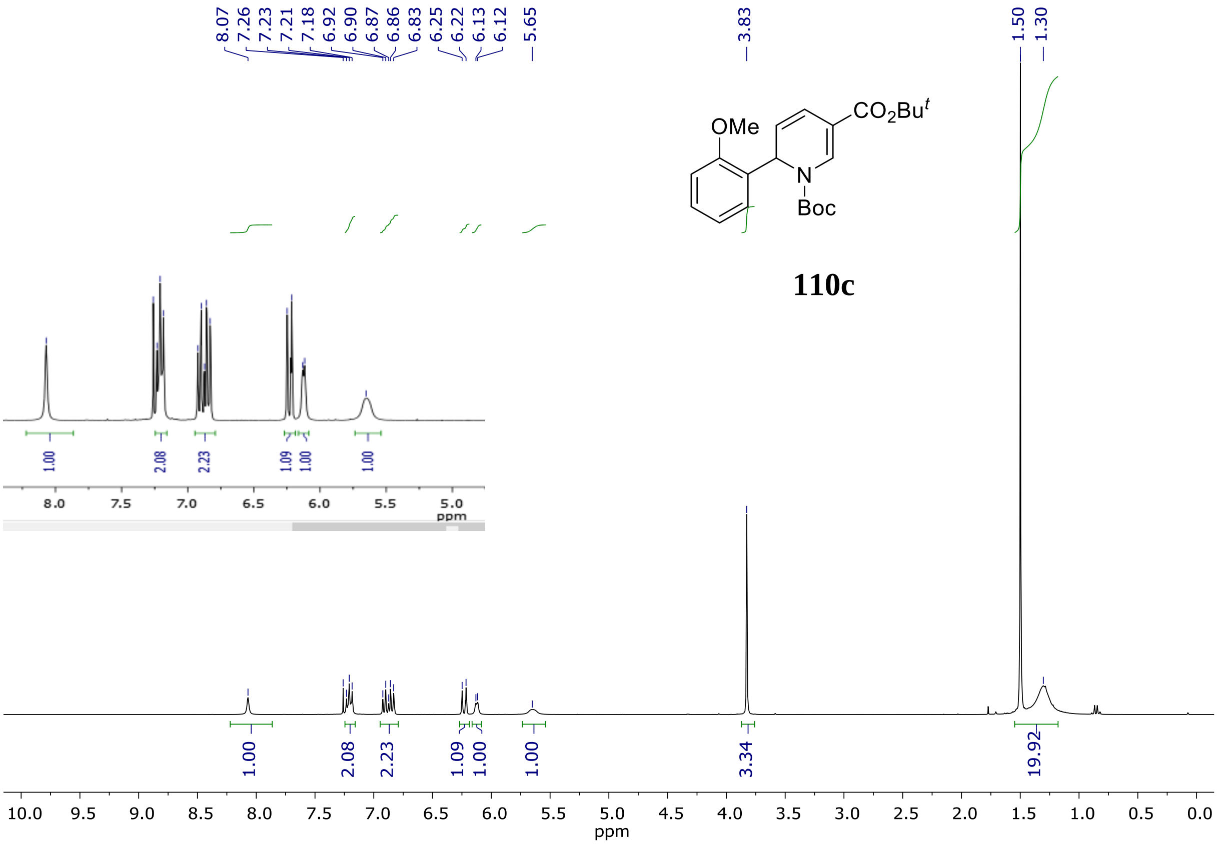


110b

^1H NMR (400 MHz, $CDCl_3$)

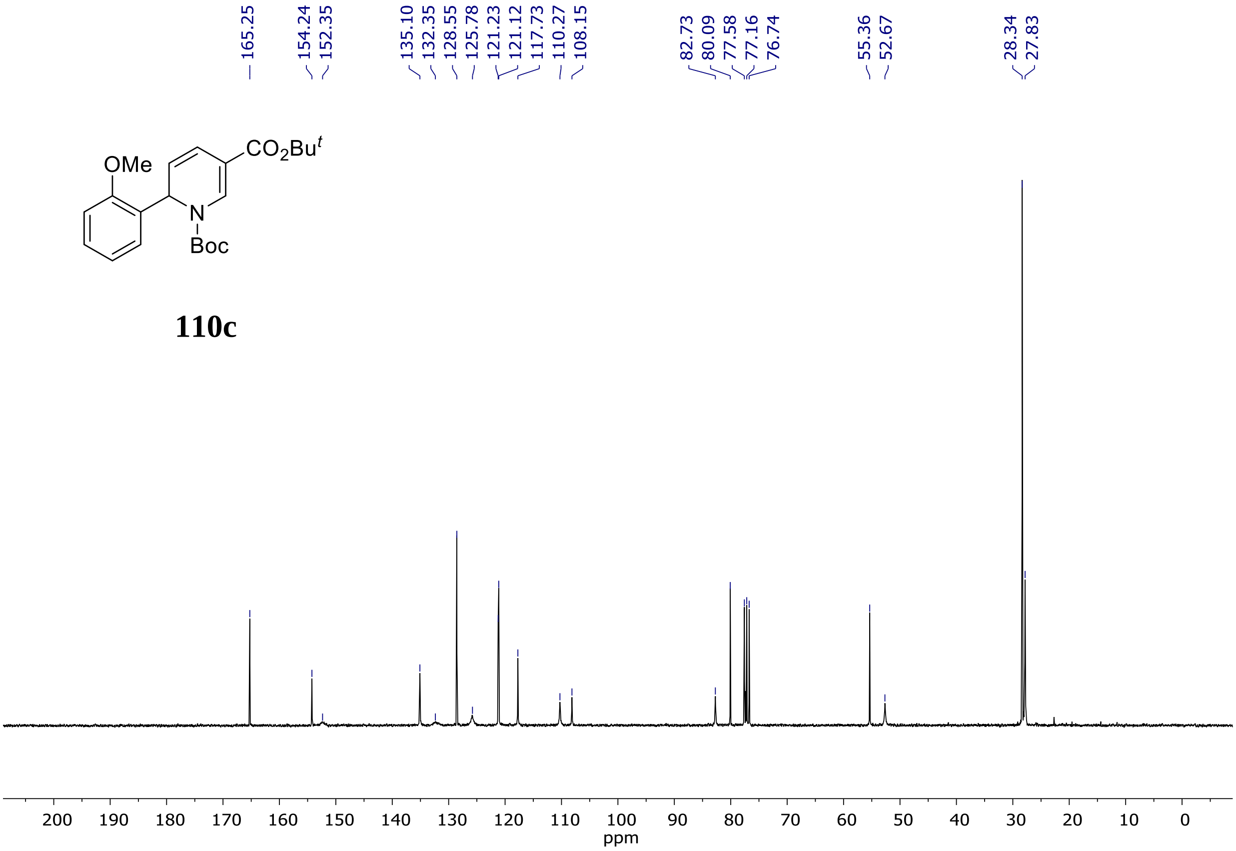


^{13}C NMR (101 MHz, $CDCl_3$)



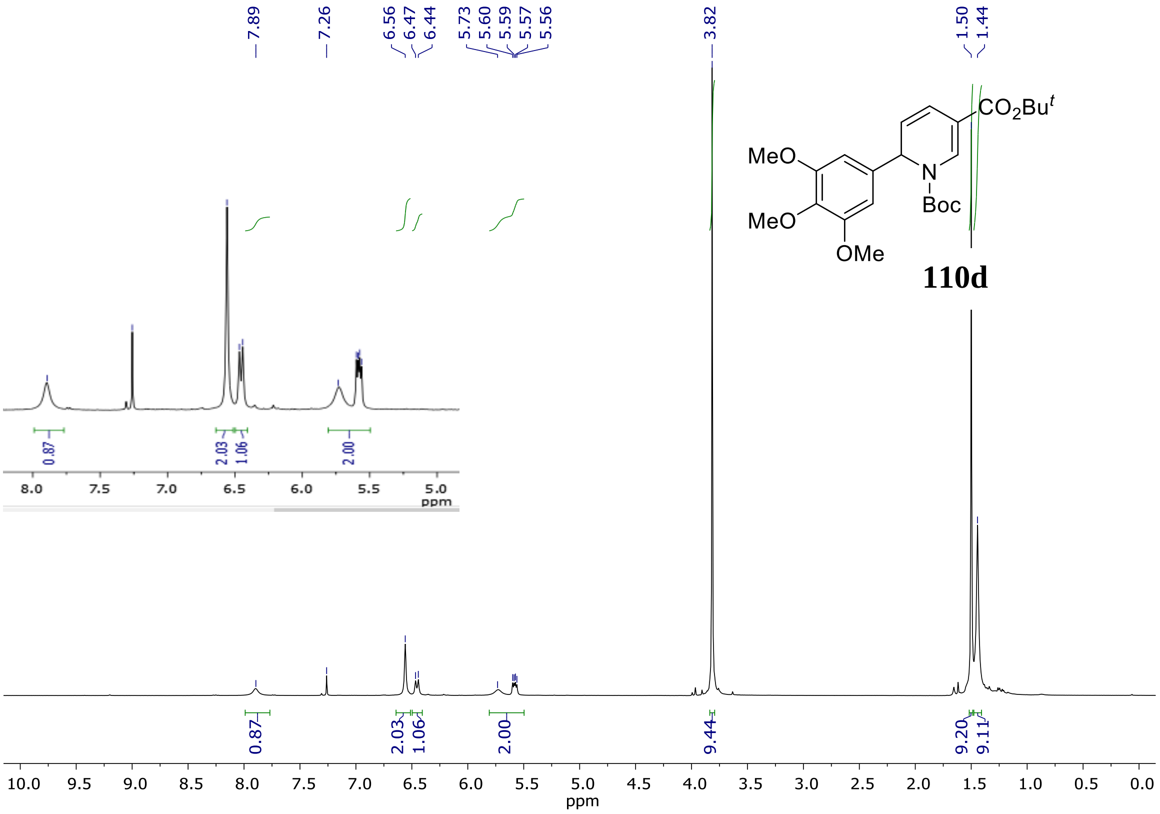
110c

^{1}H NMR (300 MHz, CDCl$_3$)

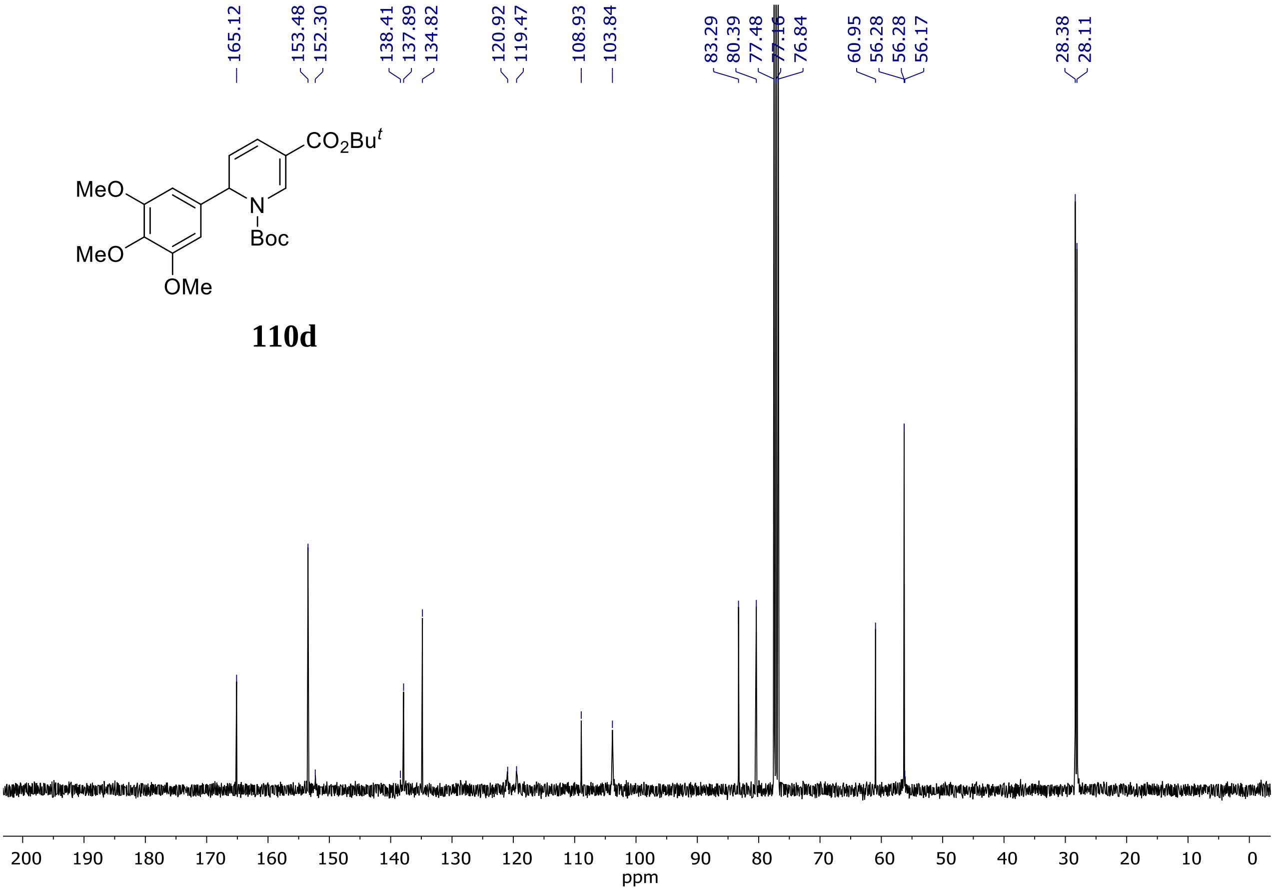


110c

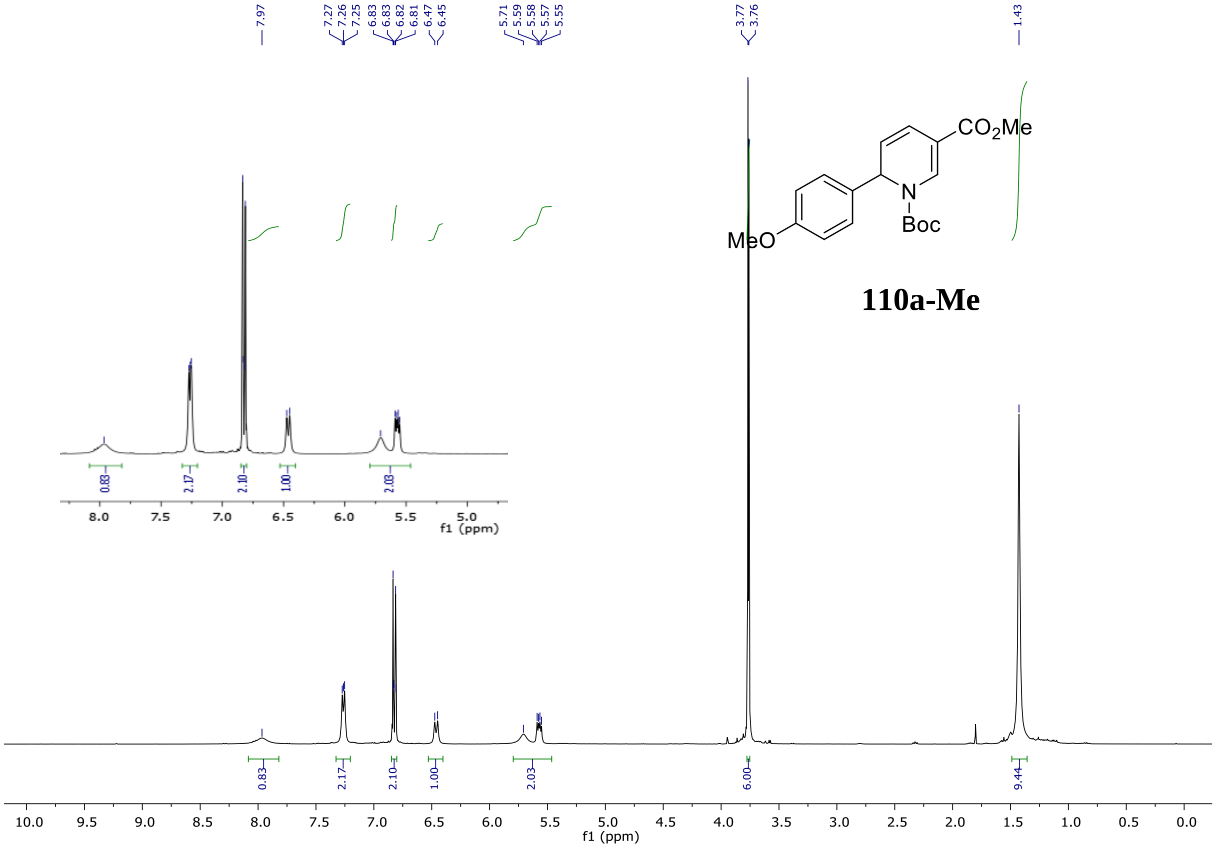
^{13}C NMR (75 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)

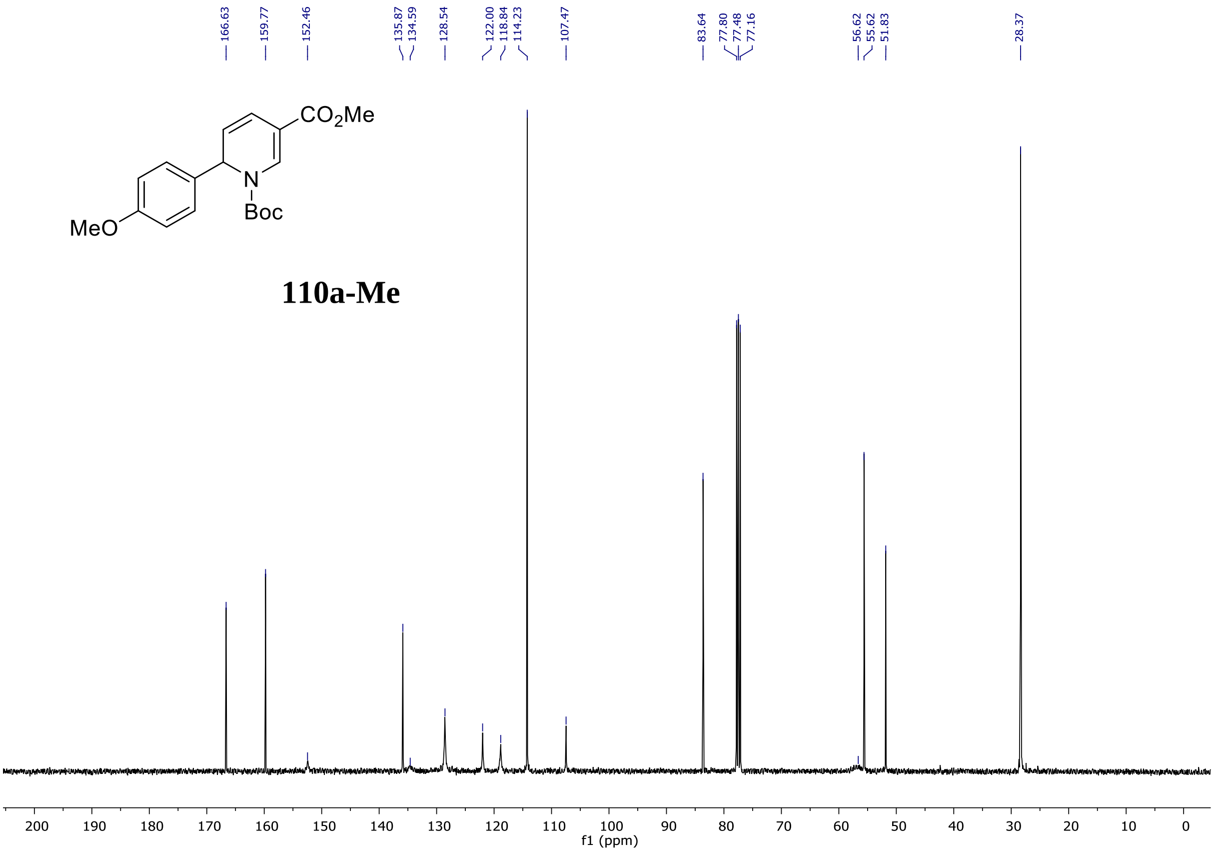


^{13}C NMR (101 MHz, CDCl$_3$)



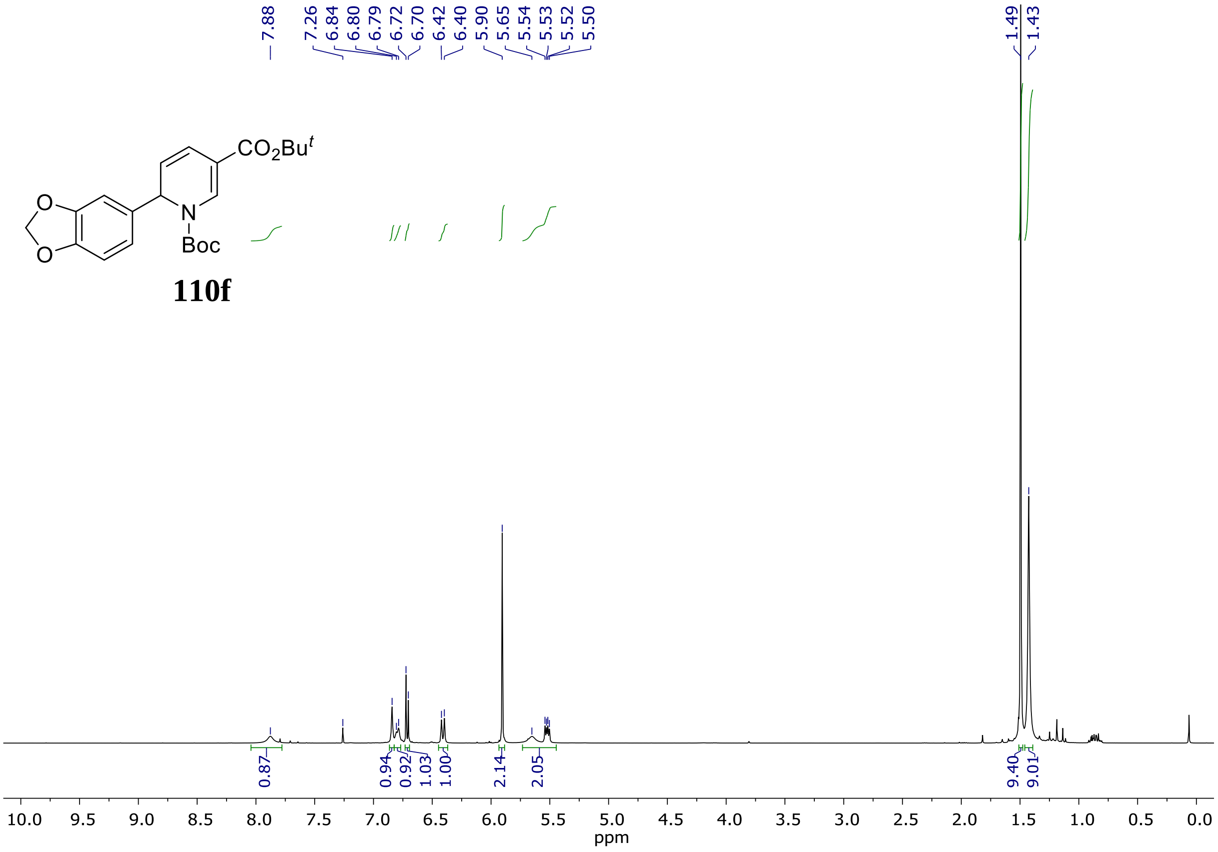
110a-Me

^{1}H NMR (400 MHz, CDCl$_3$)

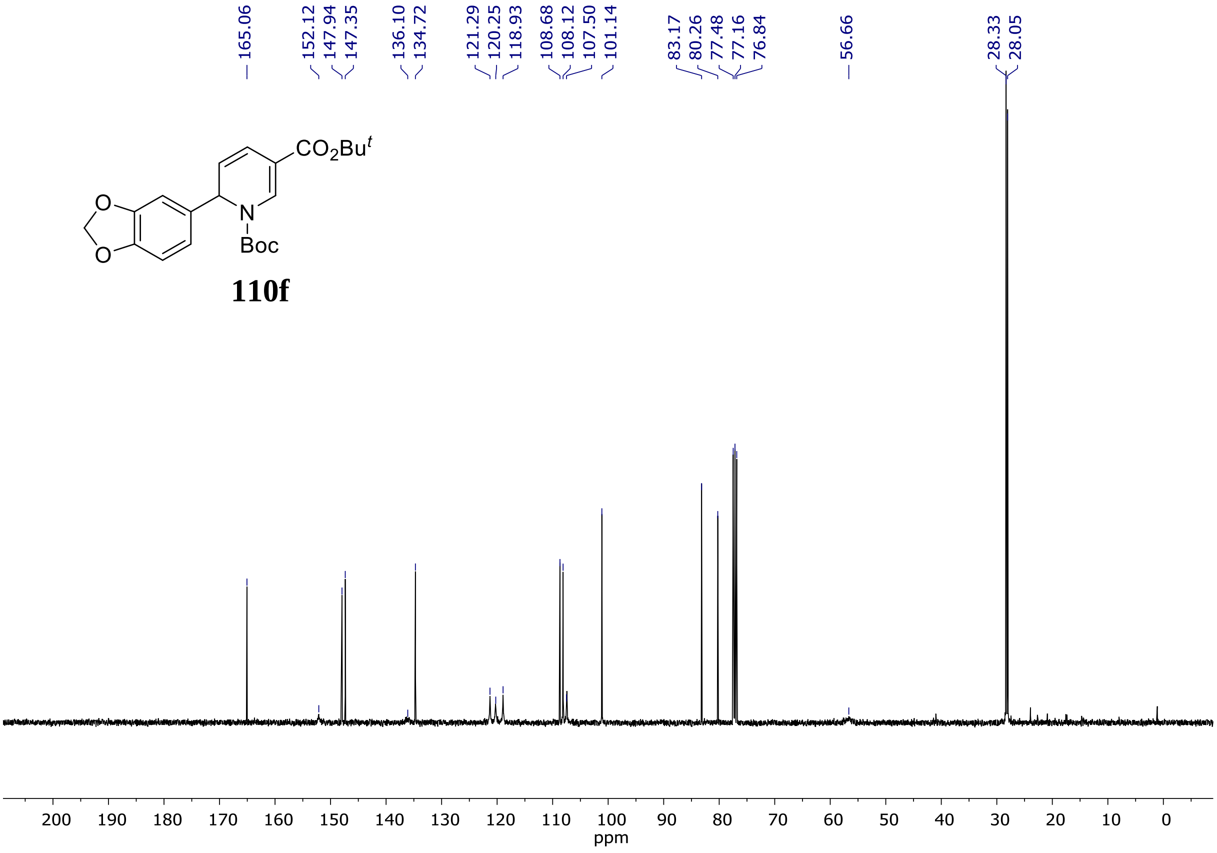


110a-Me

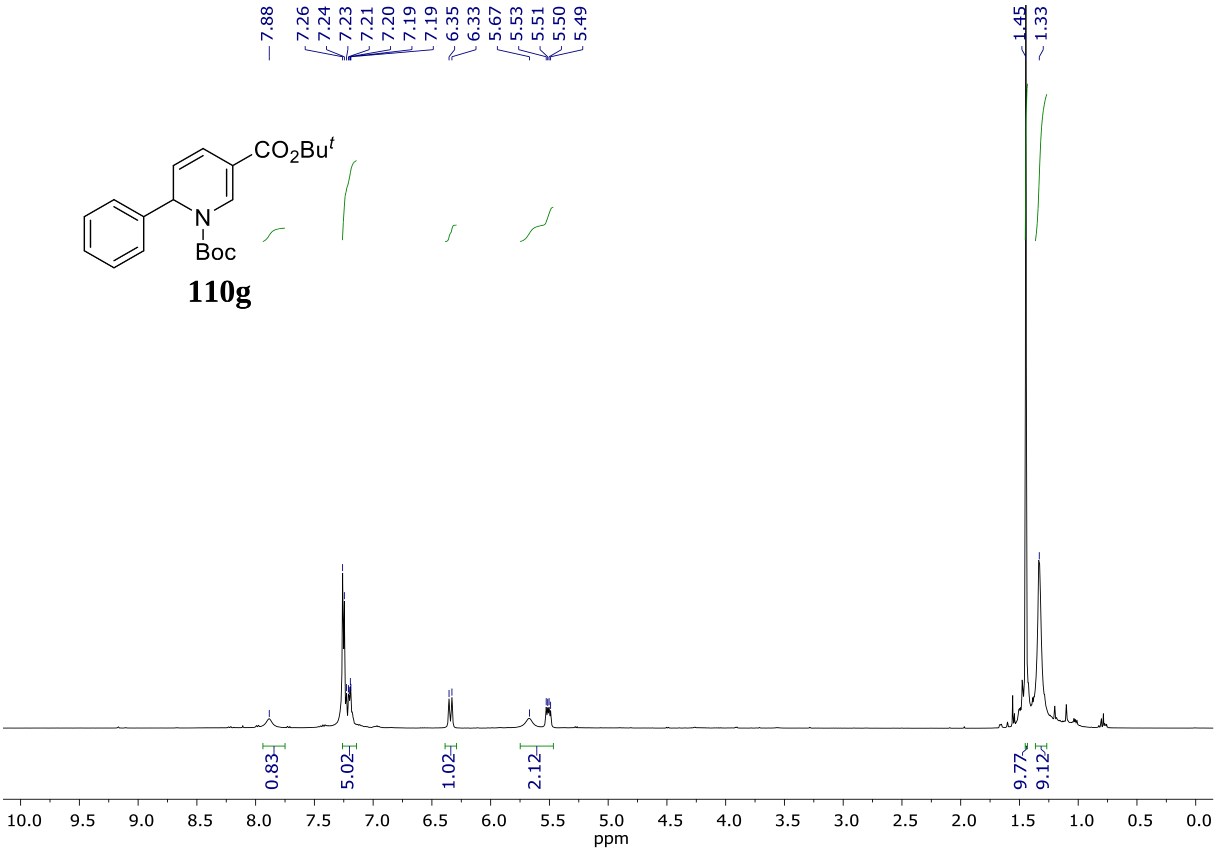
^{13}C NMR (101 MHz, CDCl$_3$)



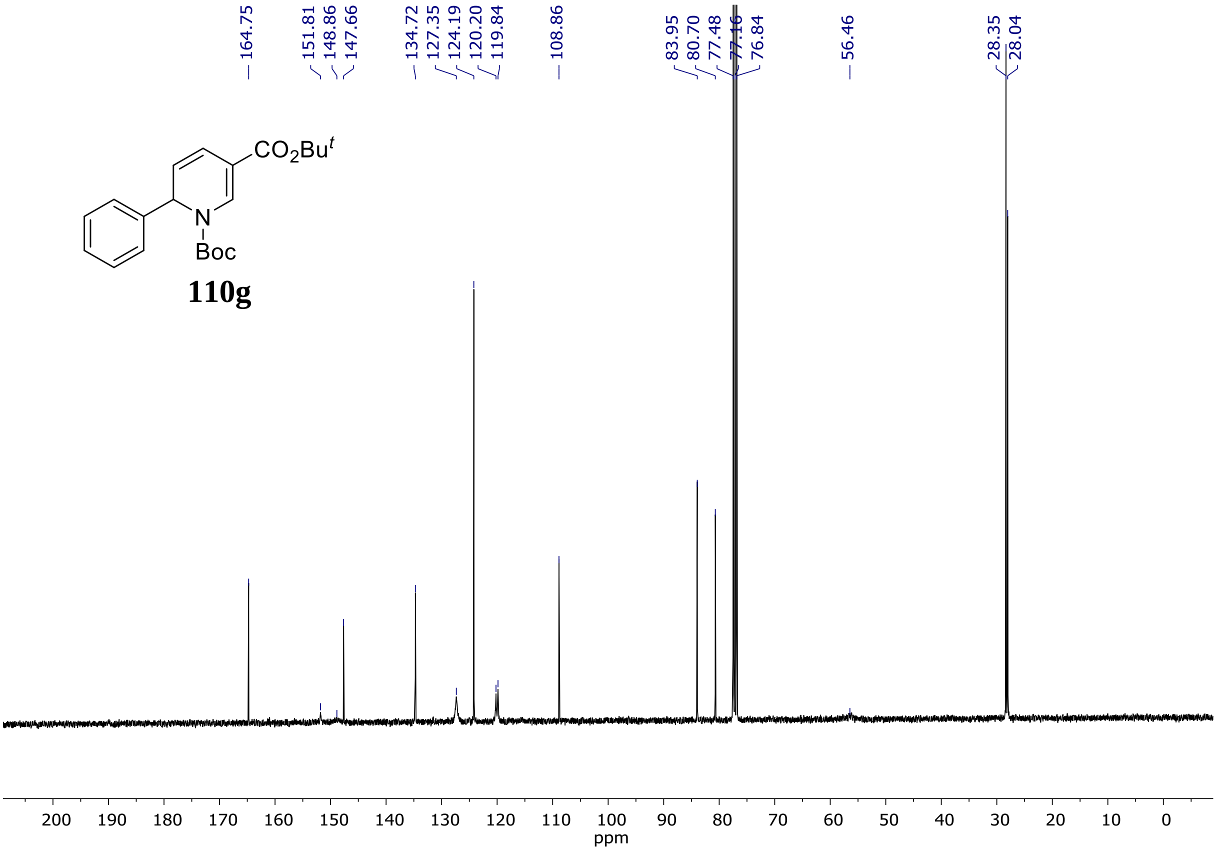
^{1}H NMR (400 MHz, CDCl$_3$)



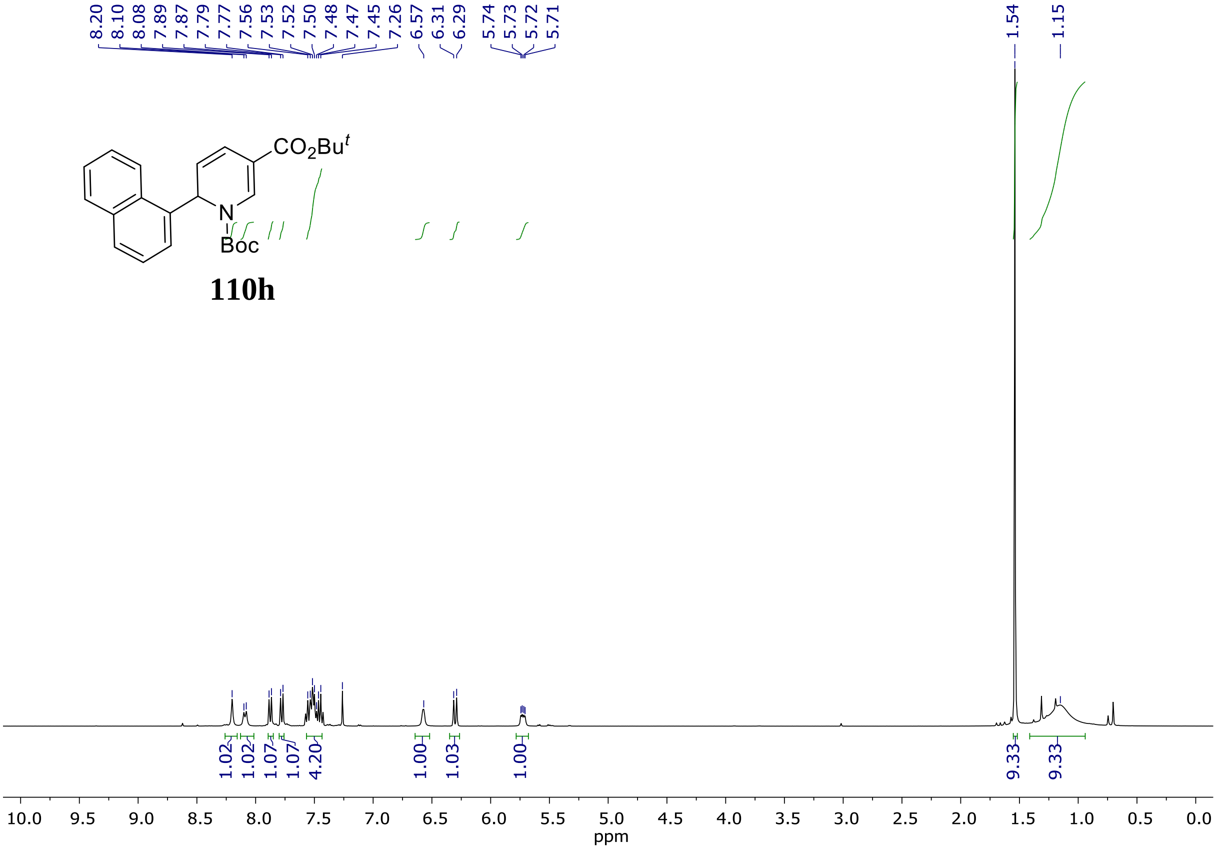
^{13}C NMR (101 MHz, CDCl$_3$)



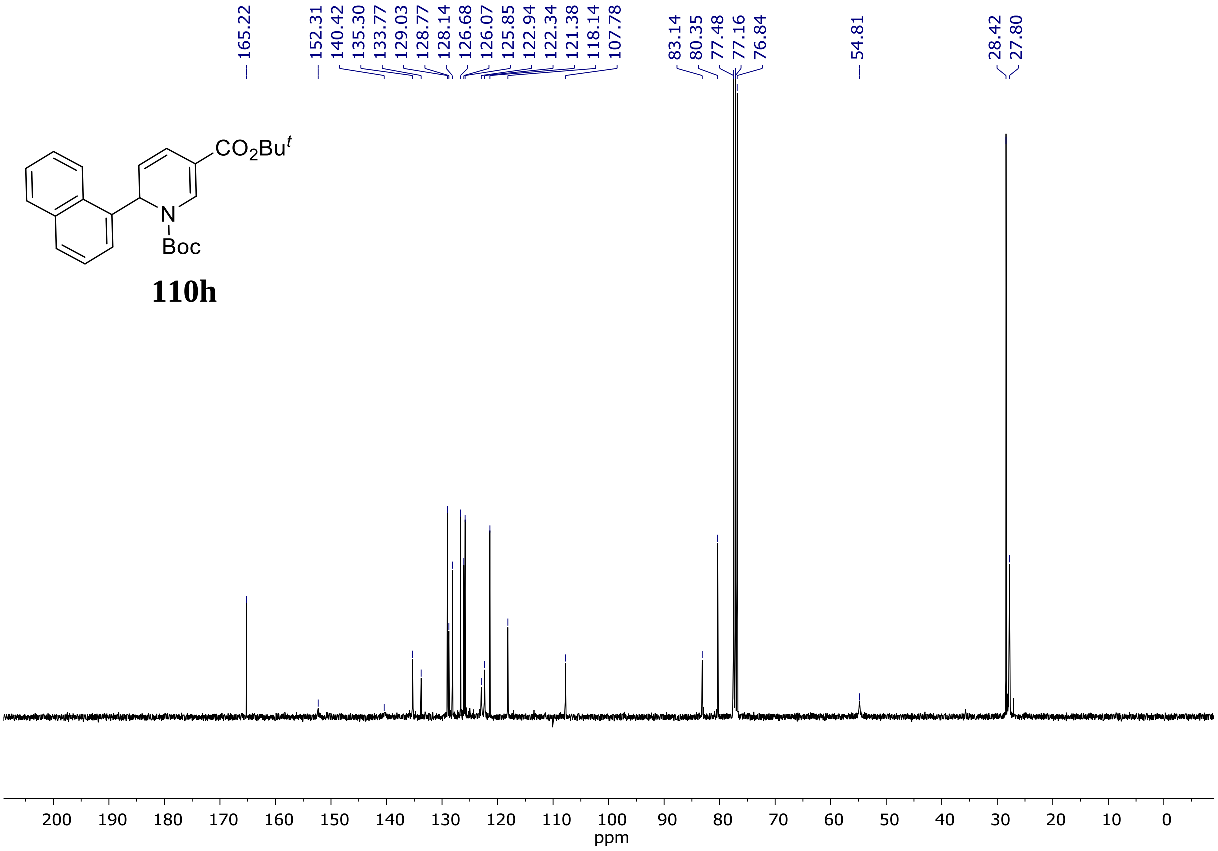
^{1}H NMR (400 MHz, CDCl$_3$)



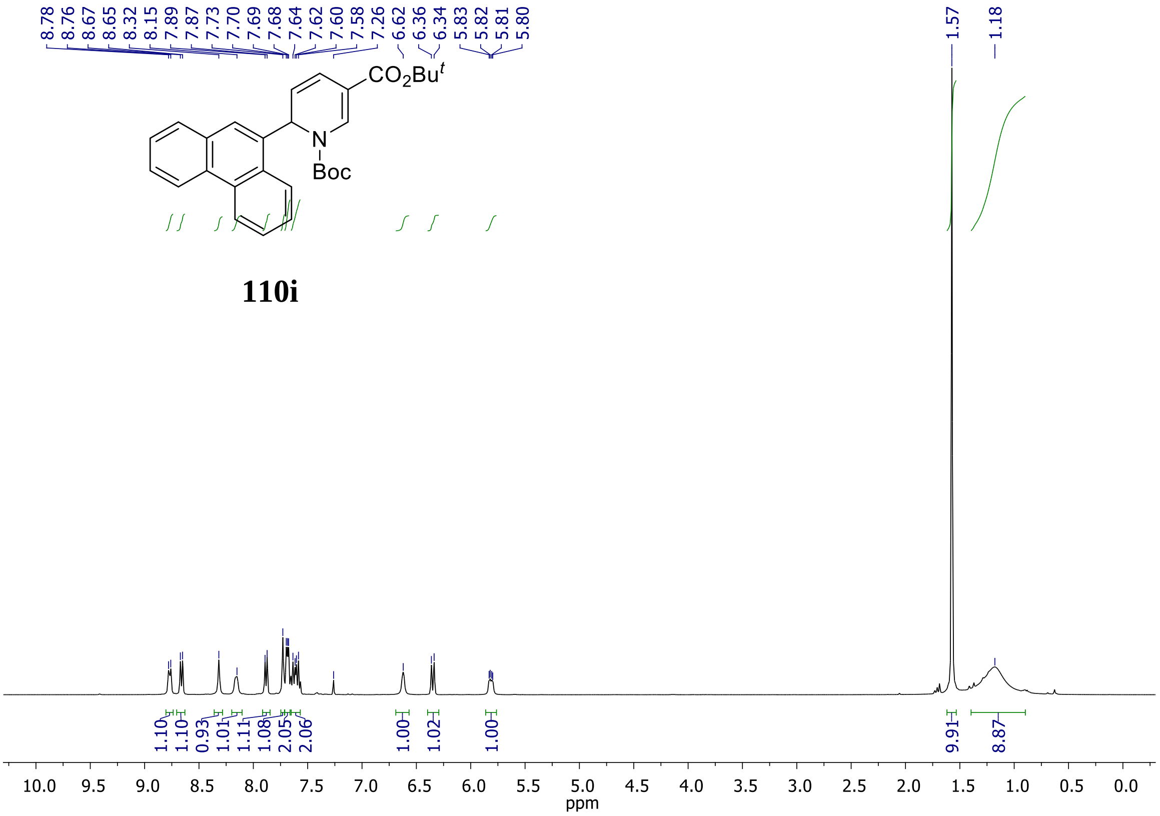
^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)

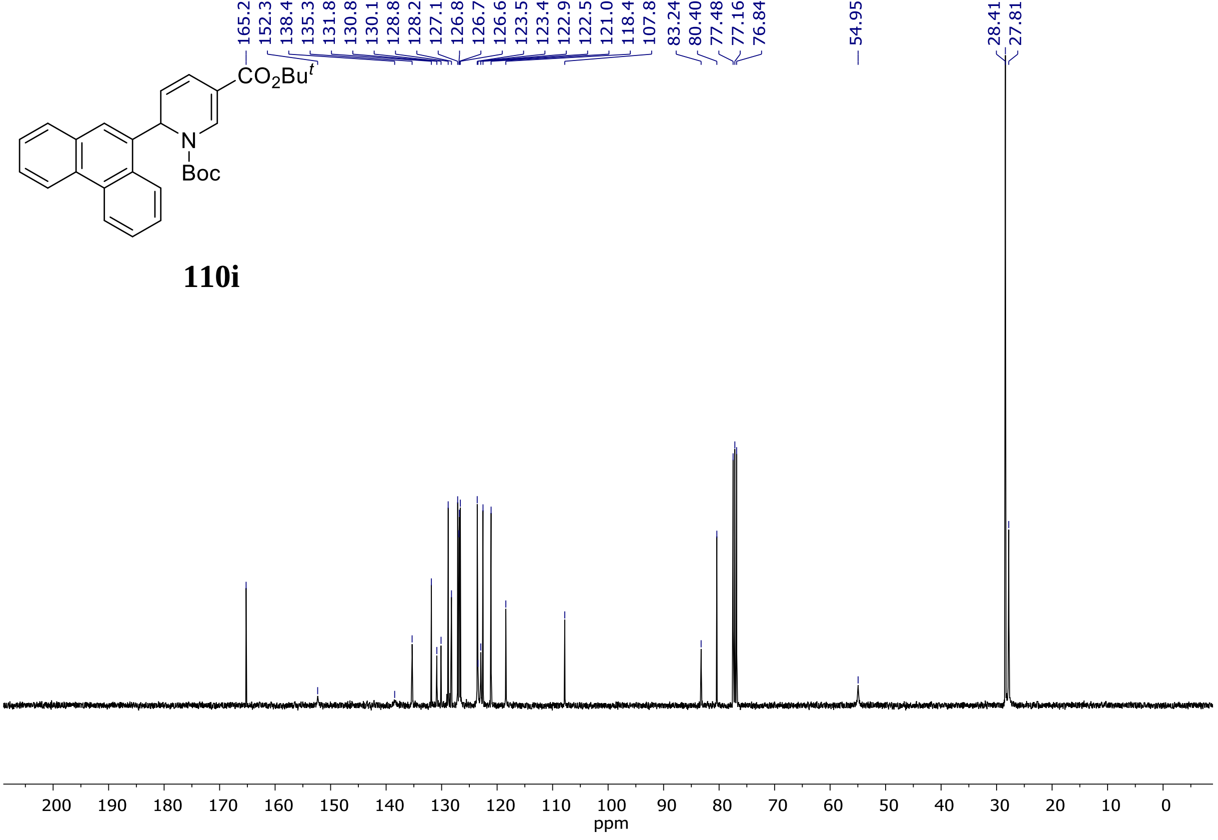


^{13}C NMR (101 MHz, CDCl$_3$)



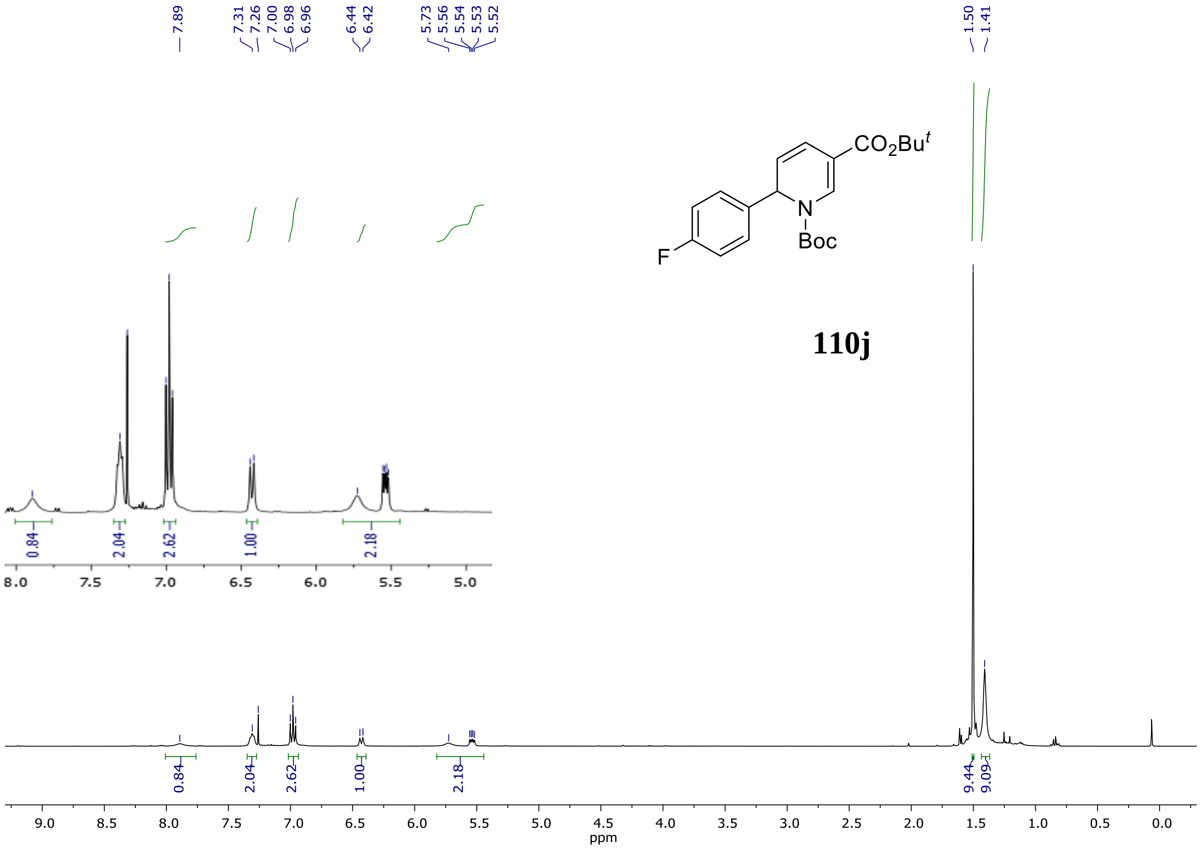
110i

^{1}H NMR (400 MHz, CDCl$_3$)

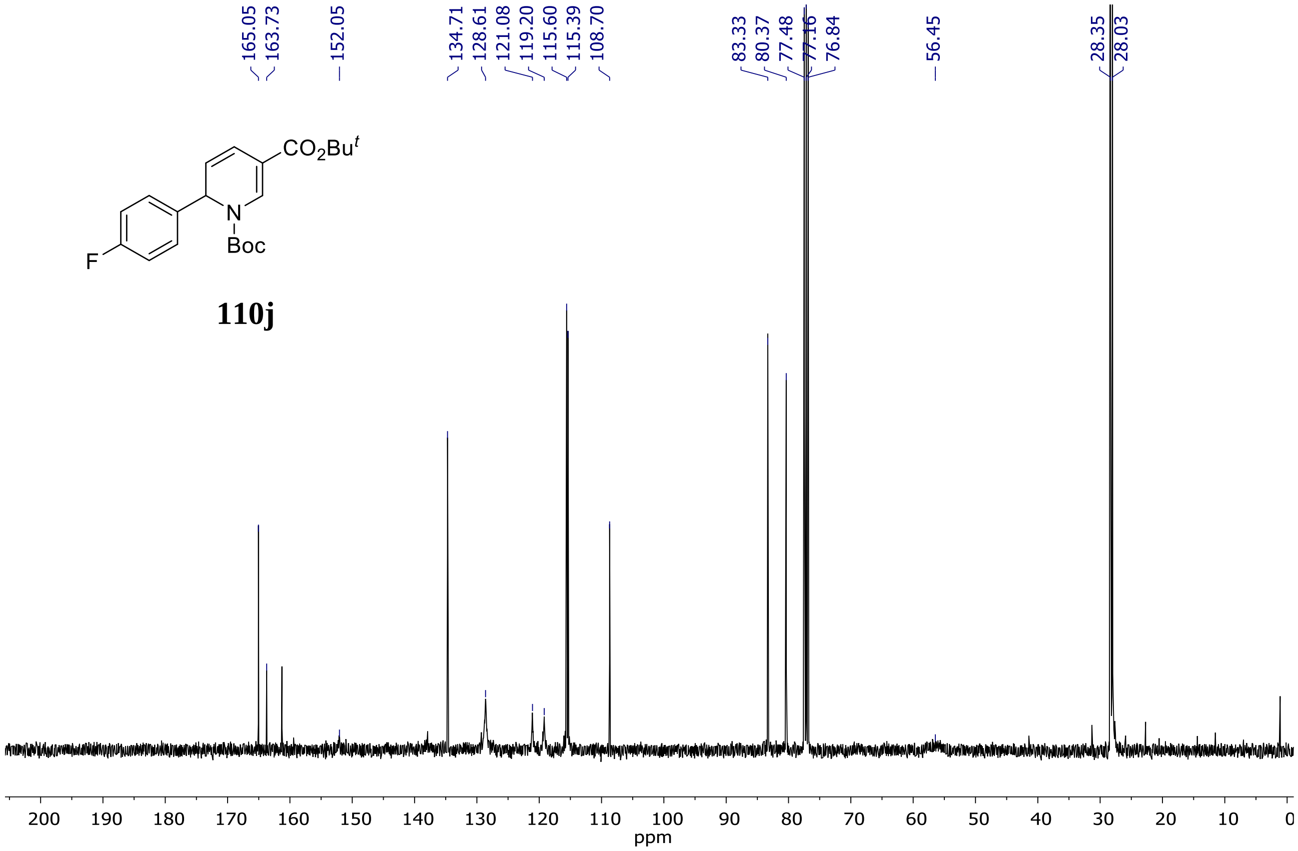


110i

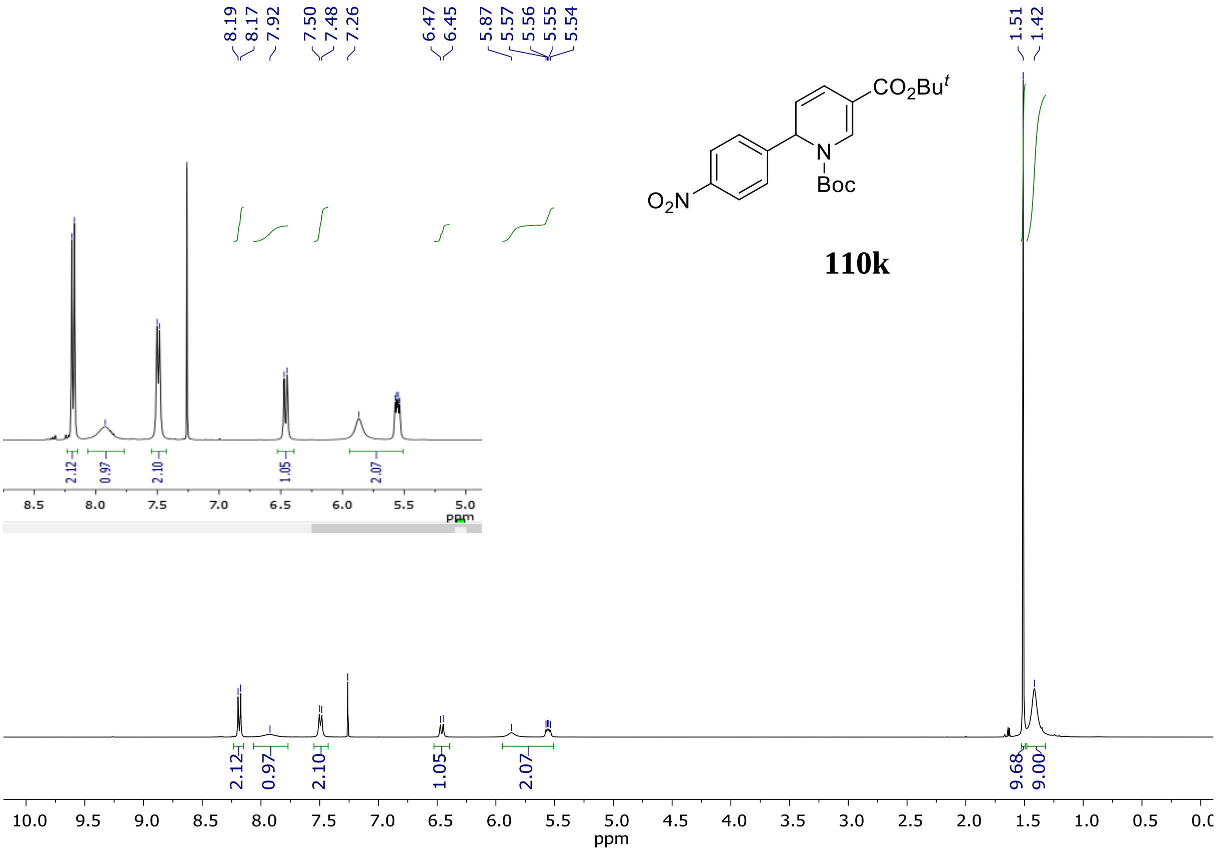
^{13}C NMR (101 MHz, CDCl$_3$)



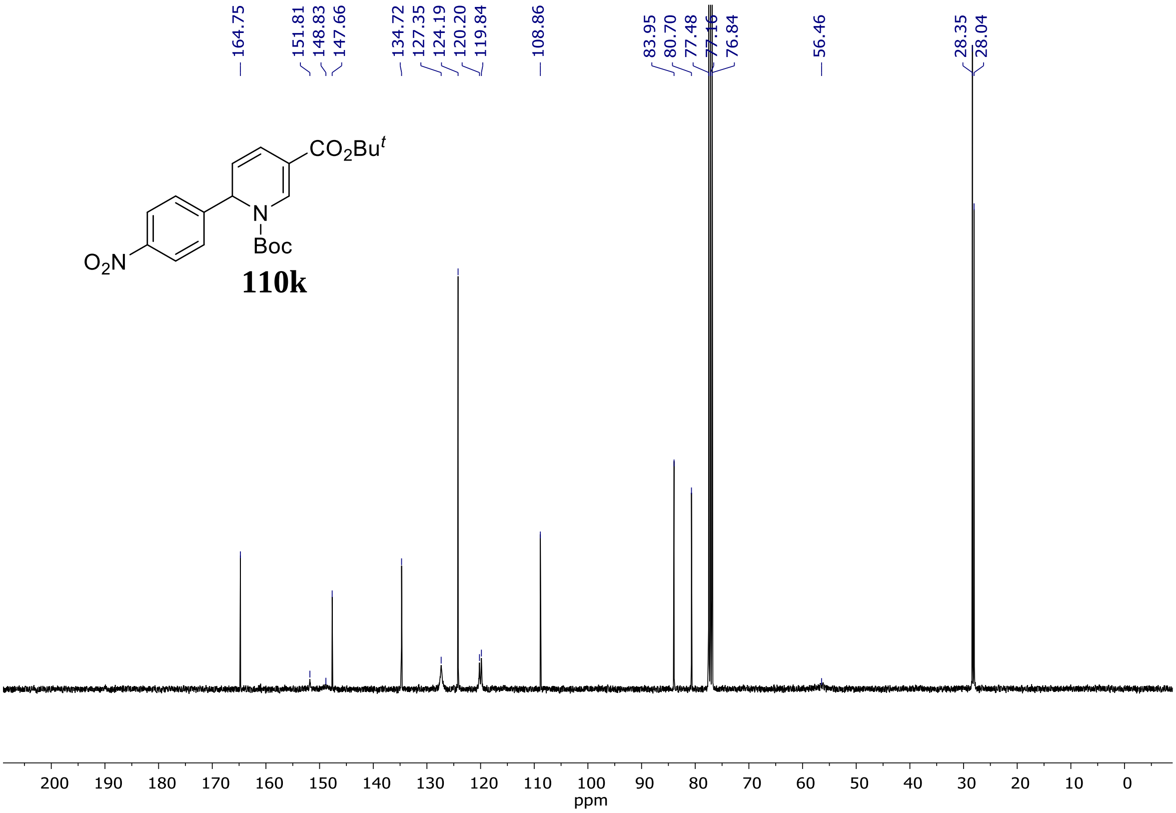
^{1}H NMR (400 MHz, CDCl$_3$)



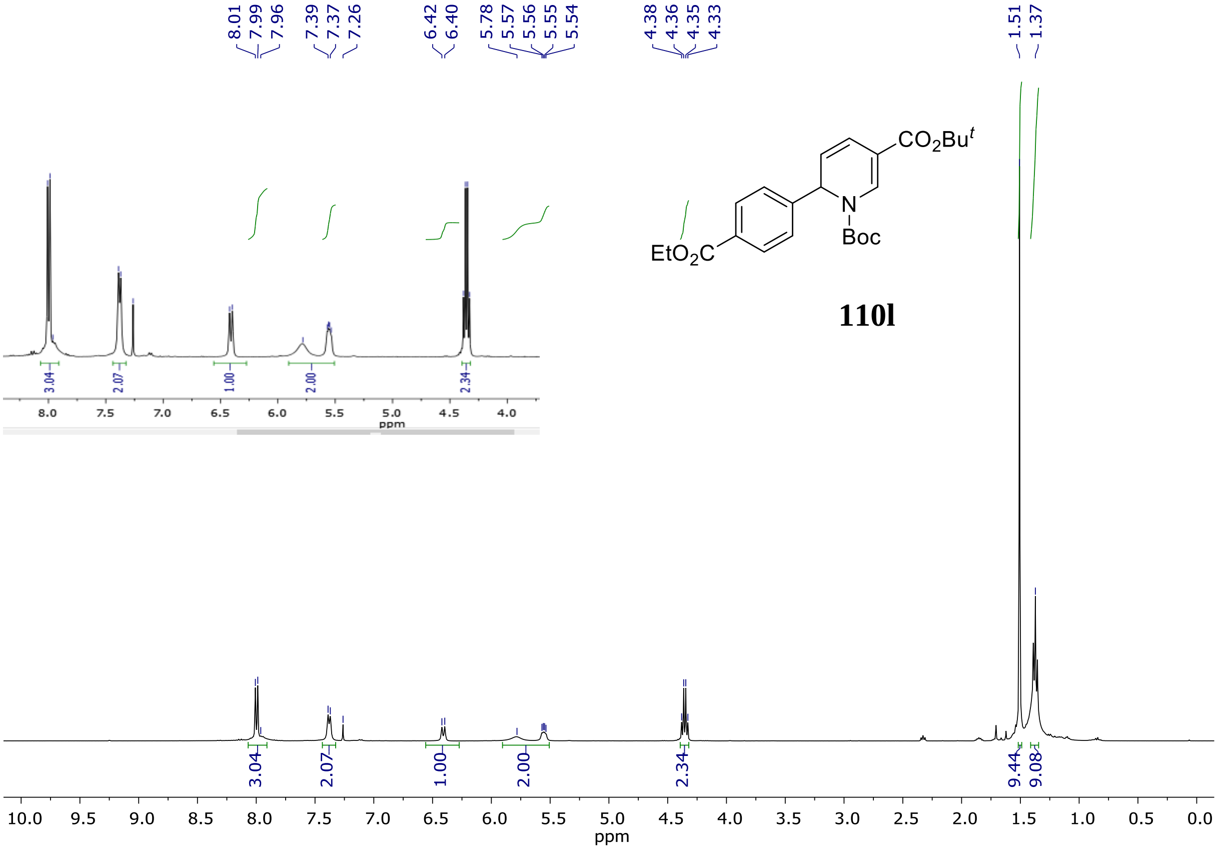
^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)

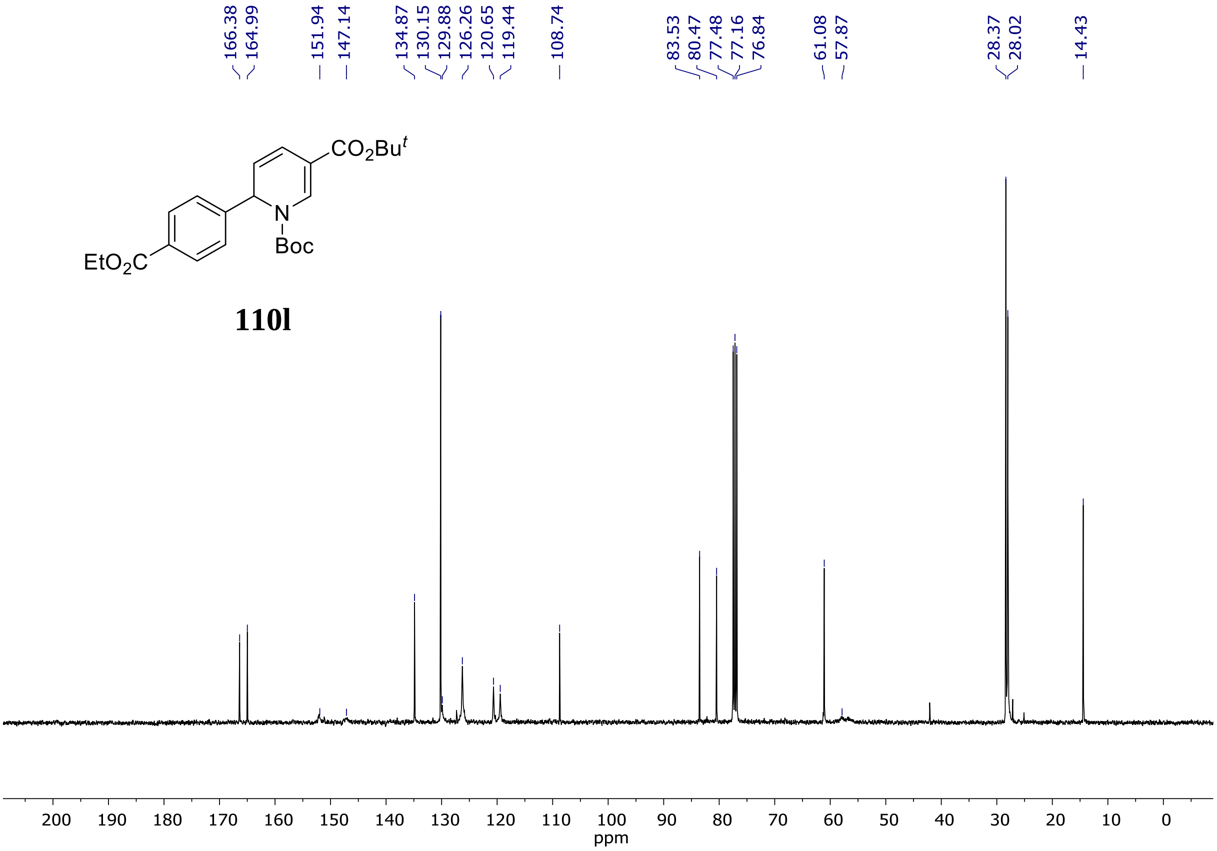


^{13}C NMR (101 MHz, CDCl$_3$)



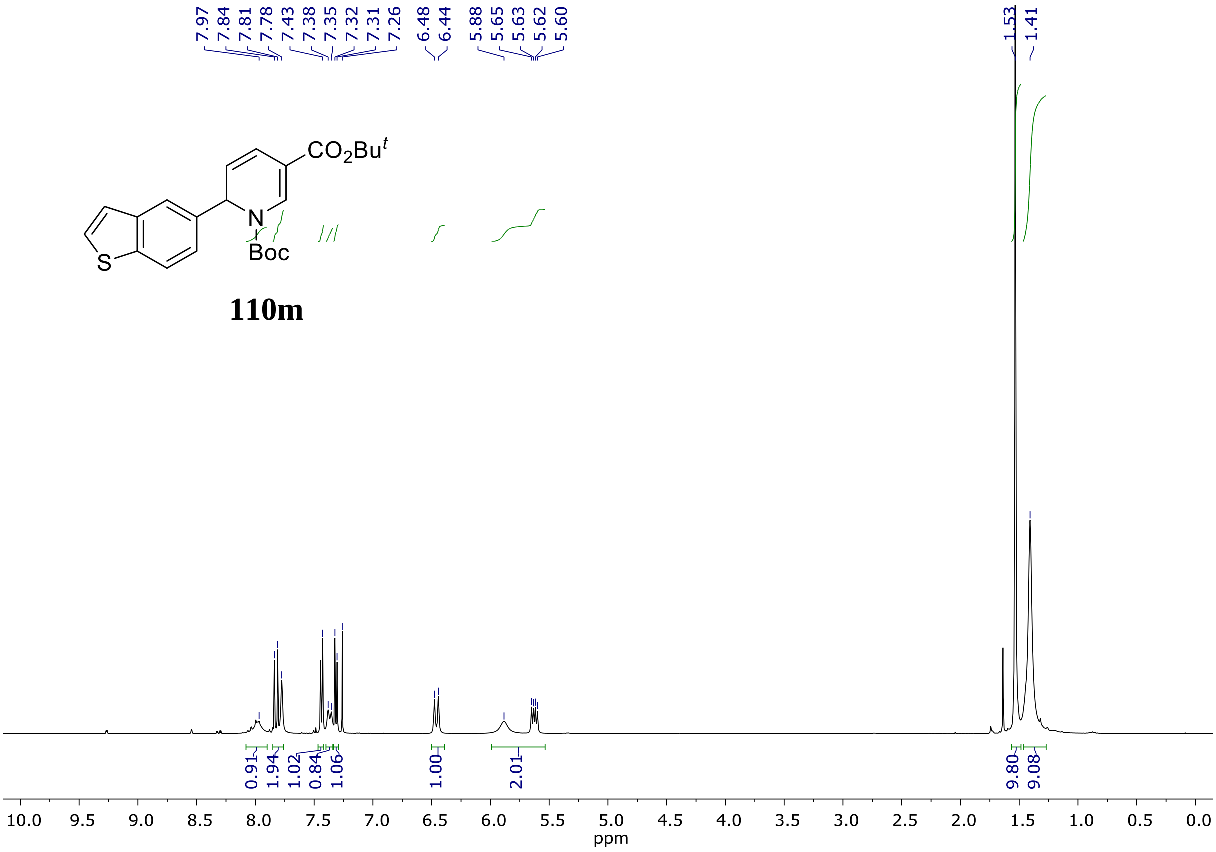
110l

^{1}H NMR (400 MHz, CDCl$_3$)



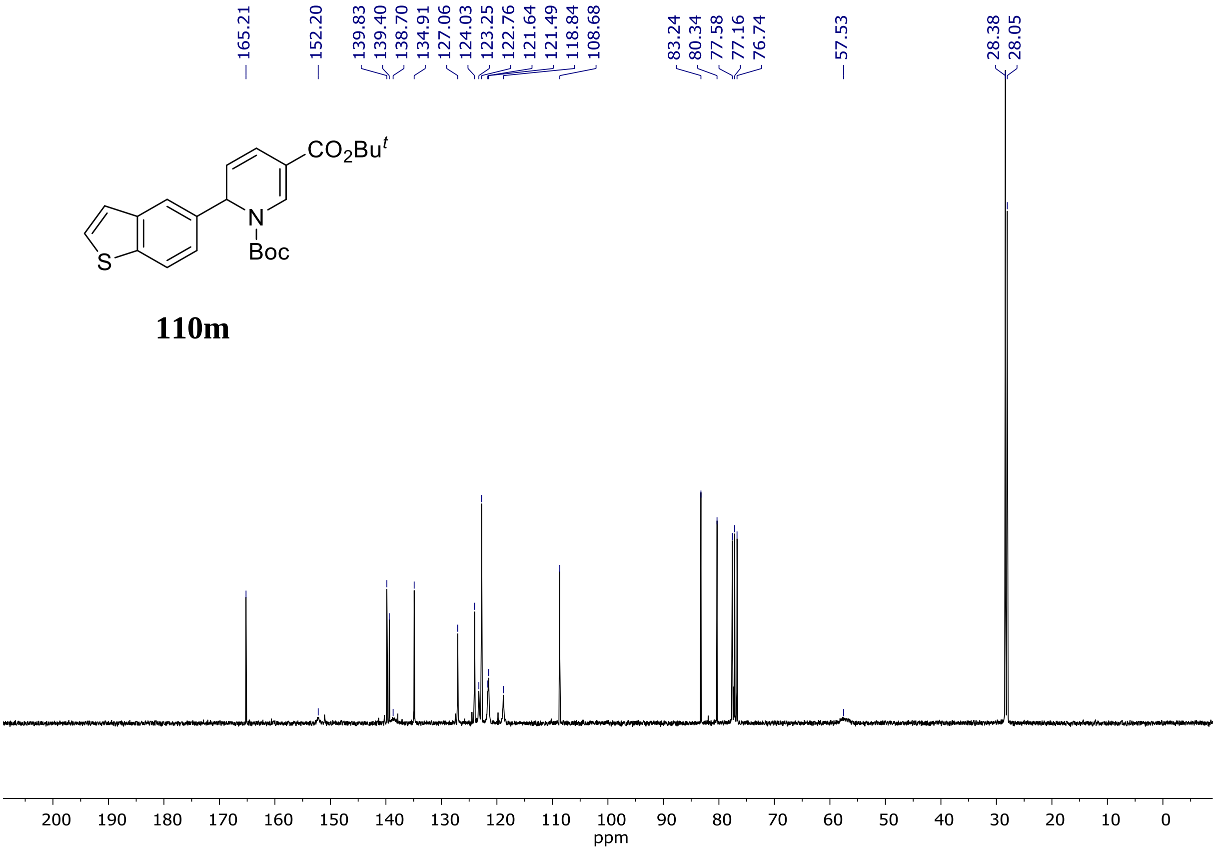
110l

^{13}C NMR (101 MHz, CDCl$_3$)



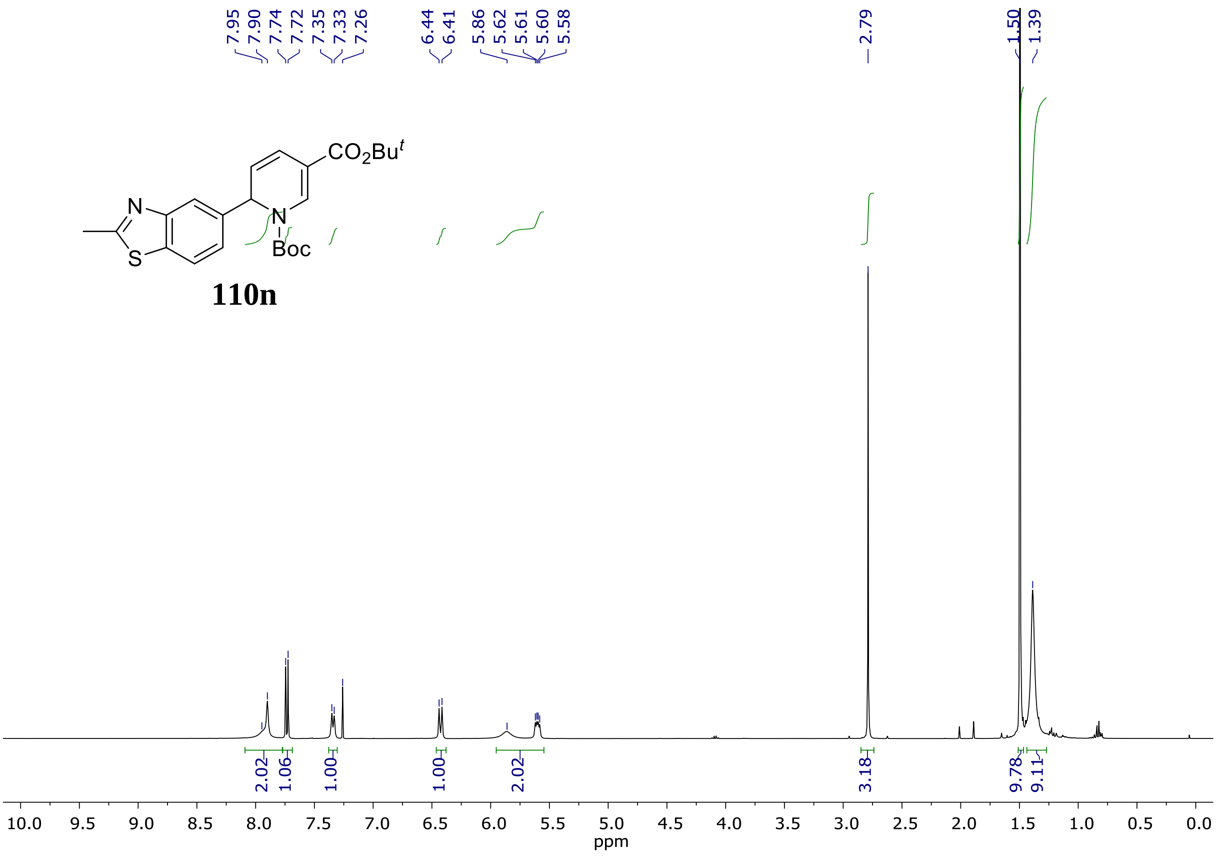
110m

^{1}H NMR (300 MHz, CDCl$_3$)

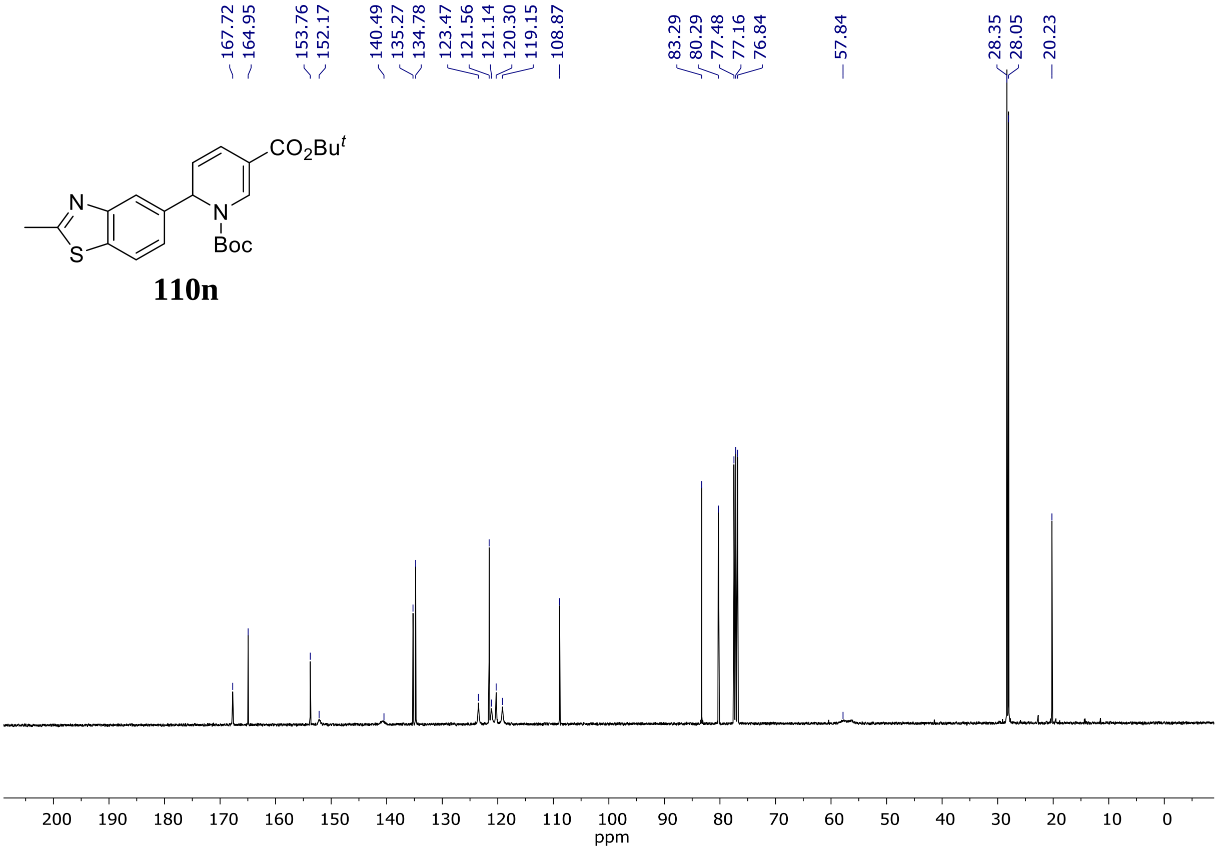


110m

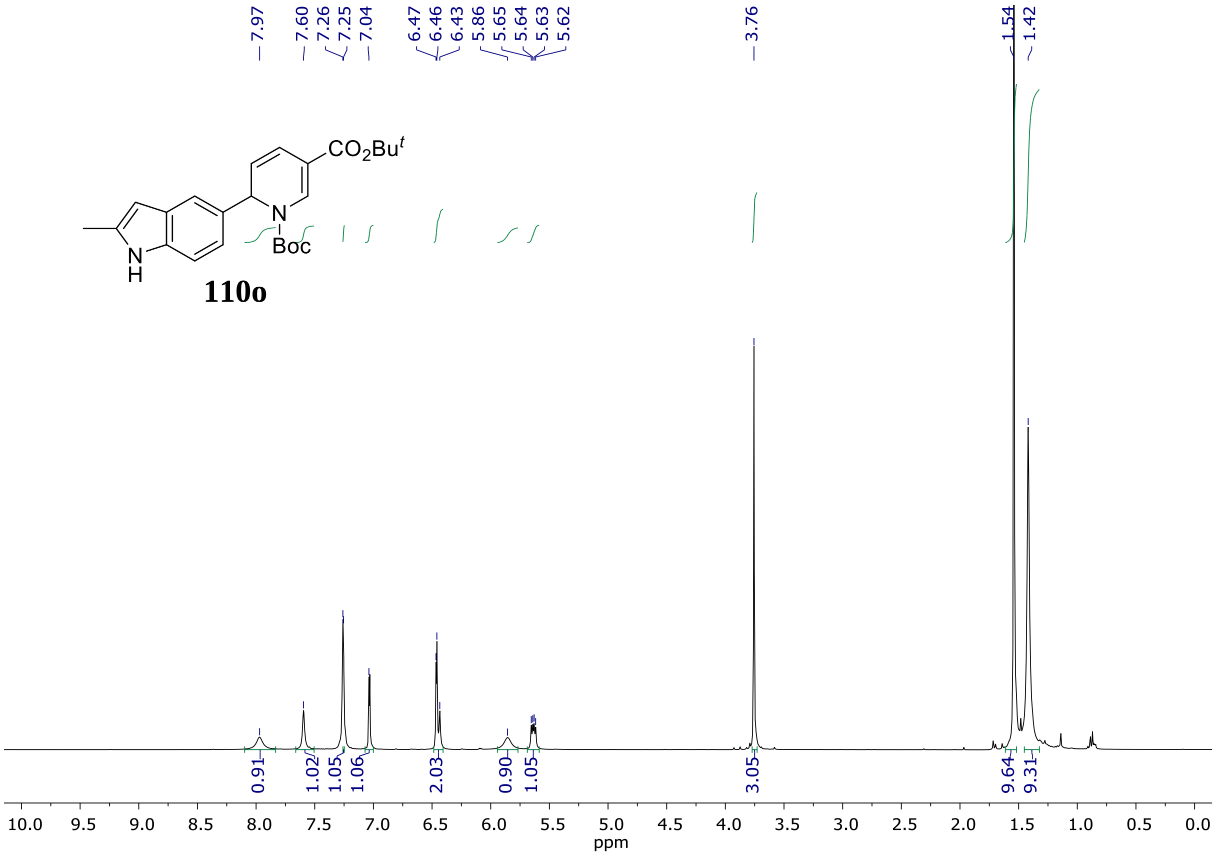
^{13}C NMR (75 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)

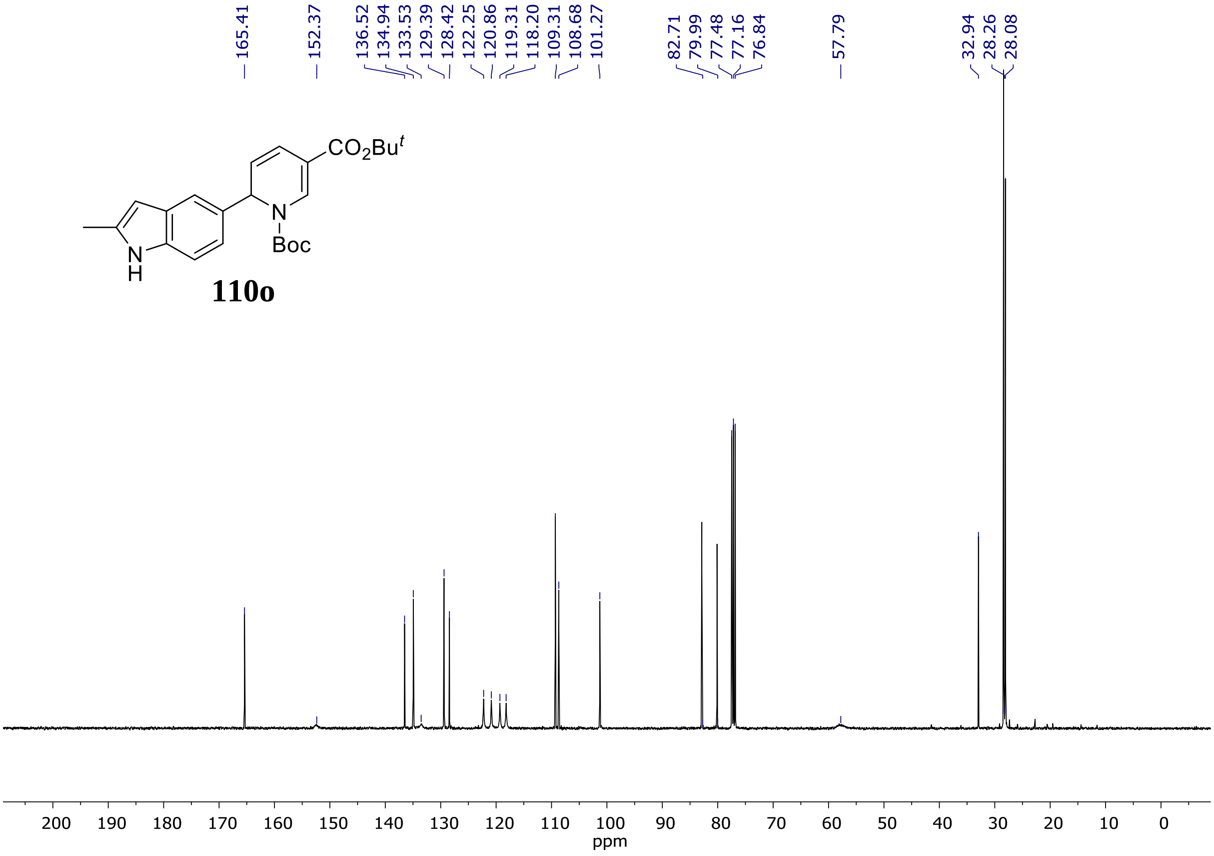


^{13}C NMR (101 MHz, CDCl$_3$)



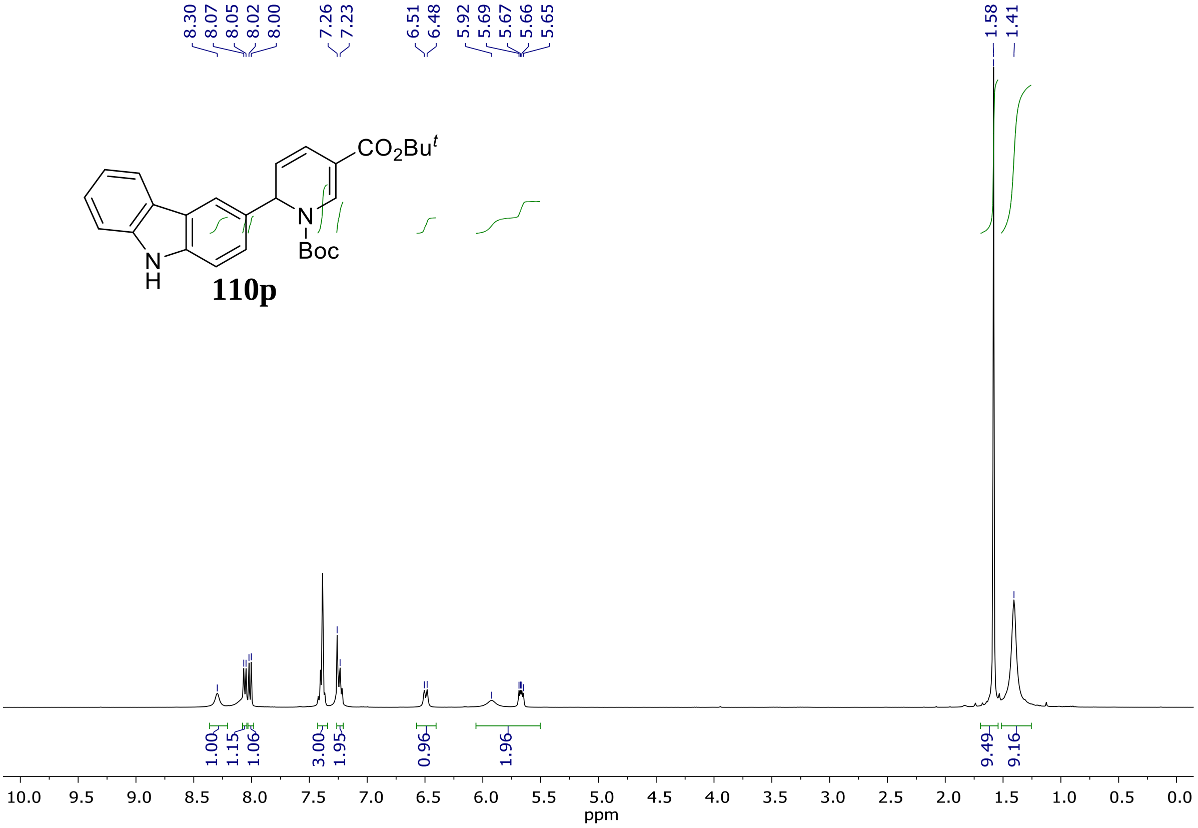
110o

^{1}H NMR (400 MHz, CDCl$_3$)

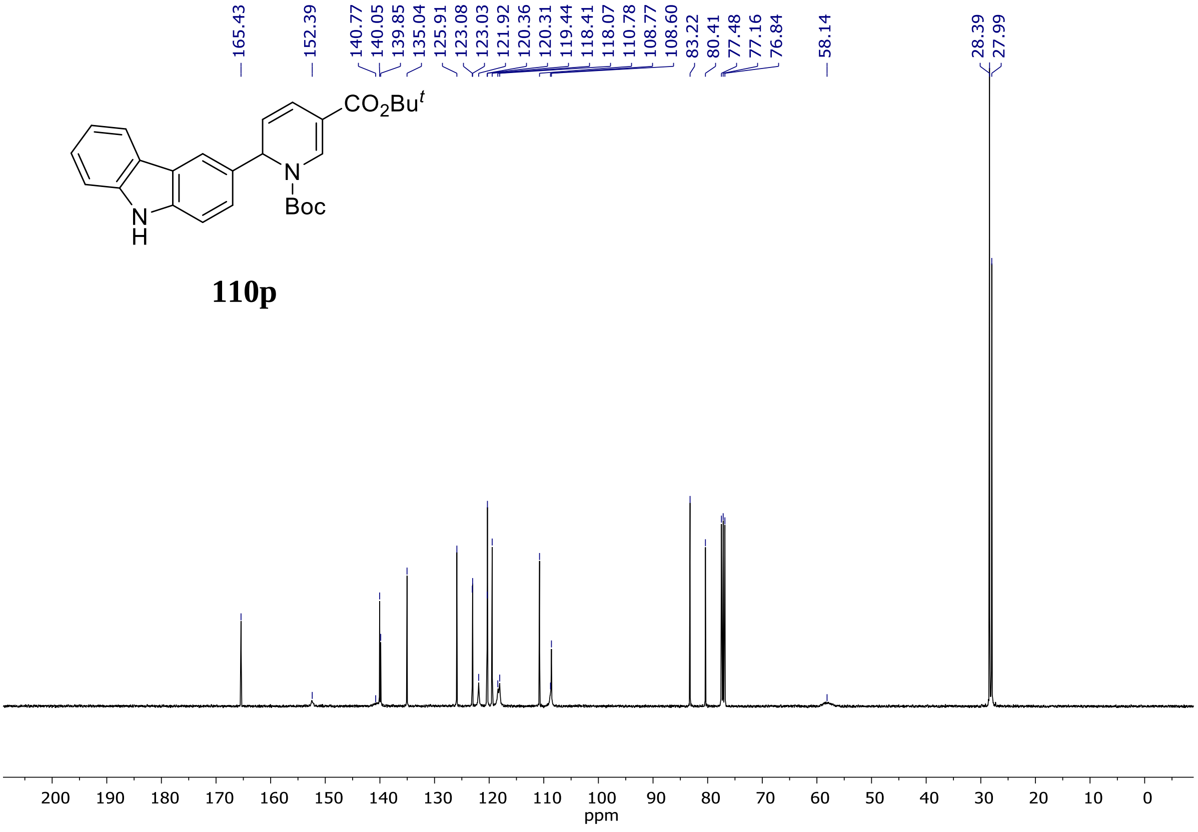


110o

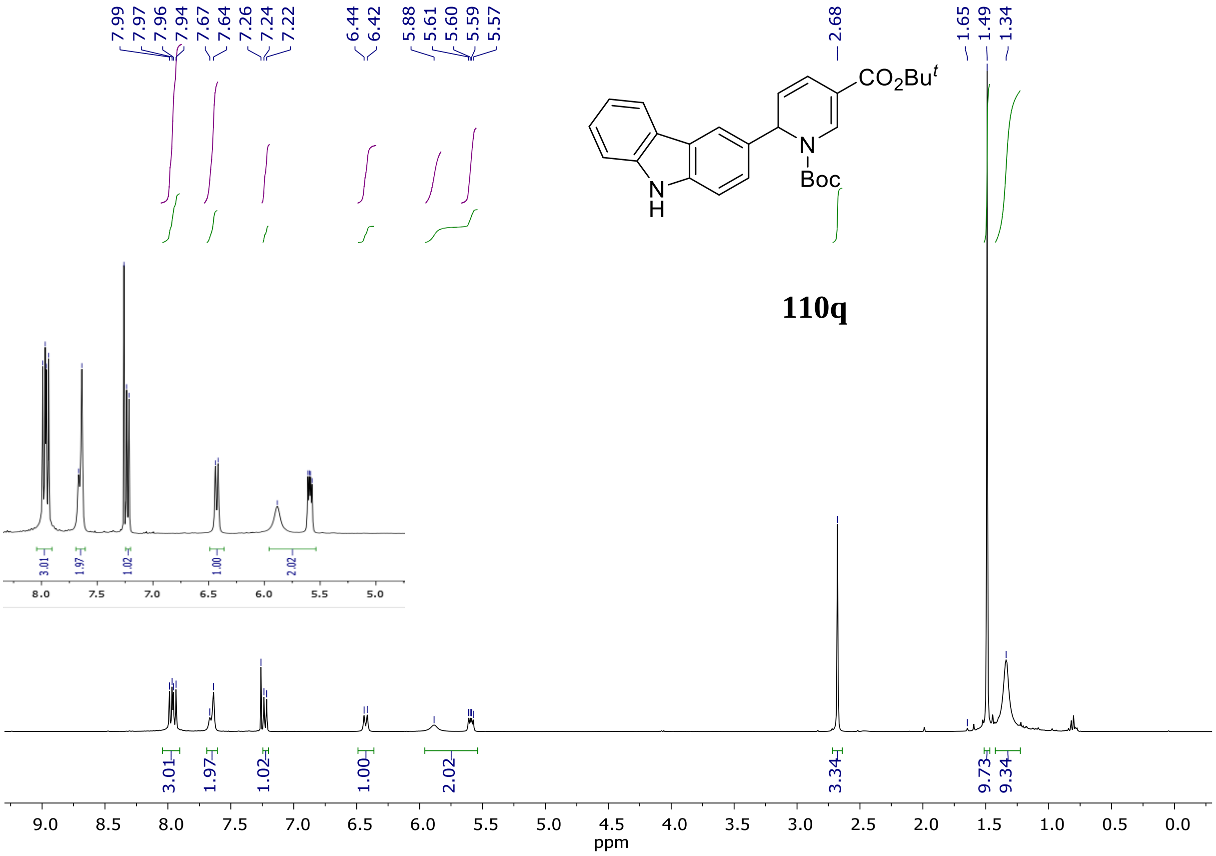
^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)

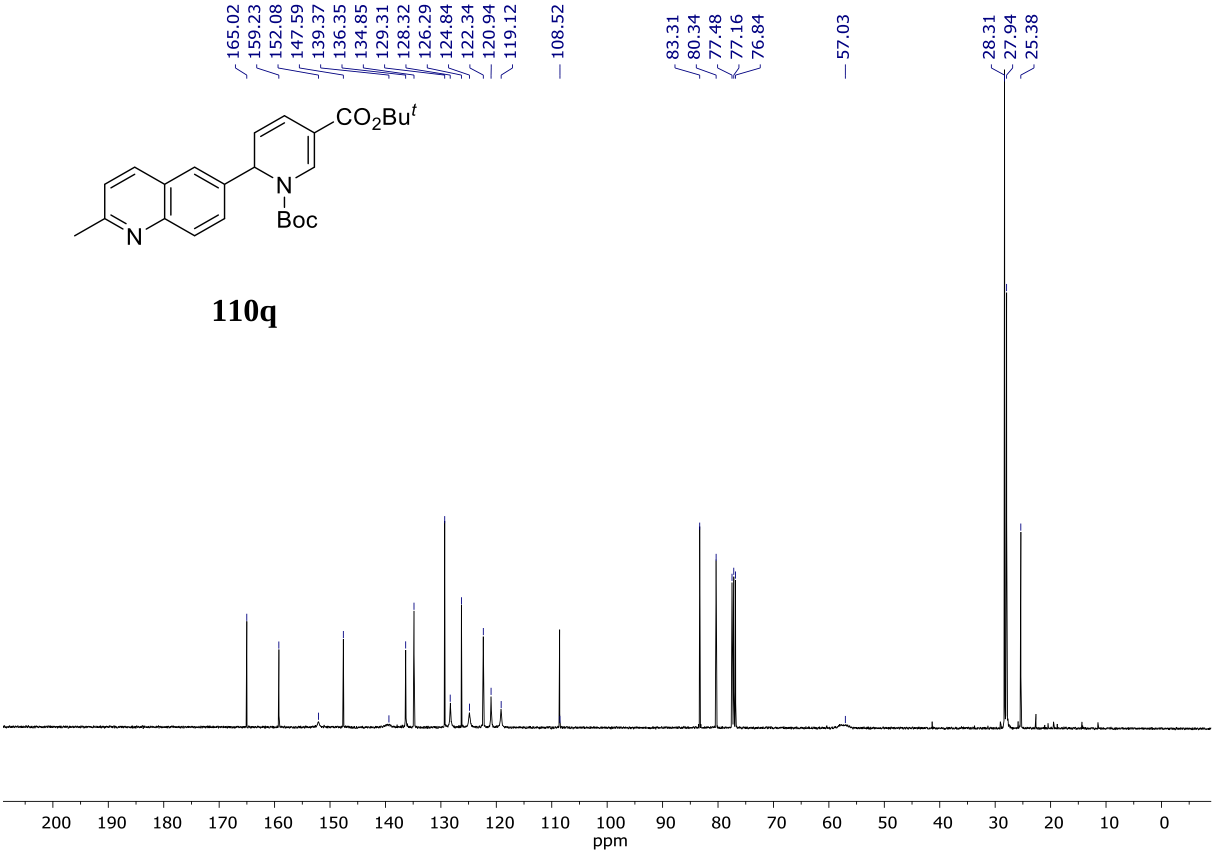


^{13}C NMR (101 MHz, CDCl$_3$)



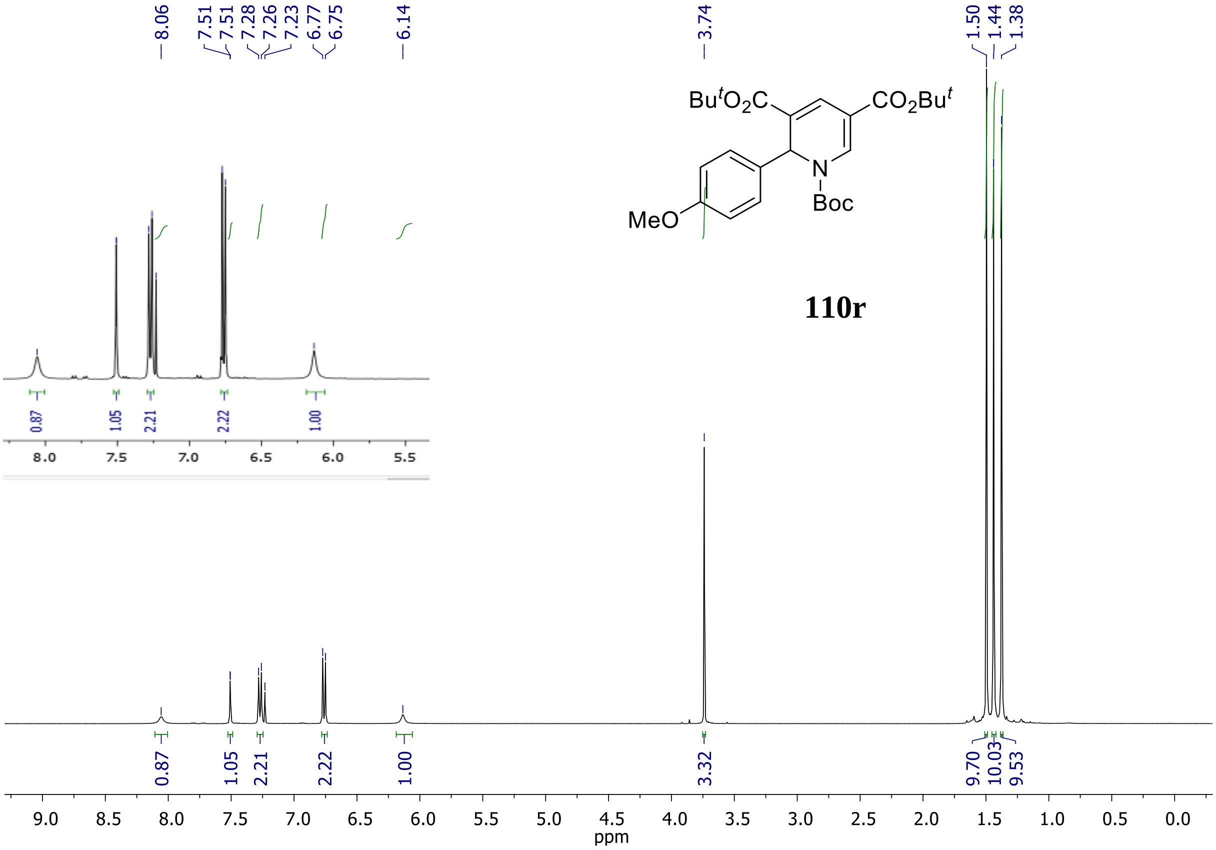
110q

^{1}H NMR (400 MHz, CDCl$_3$)

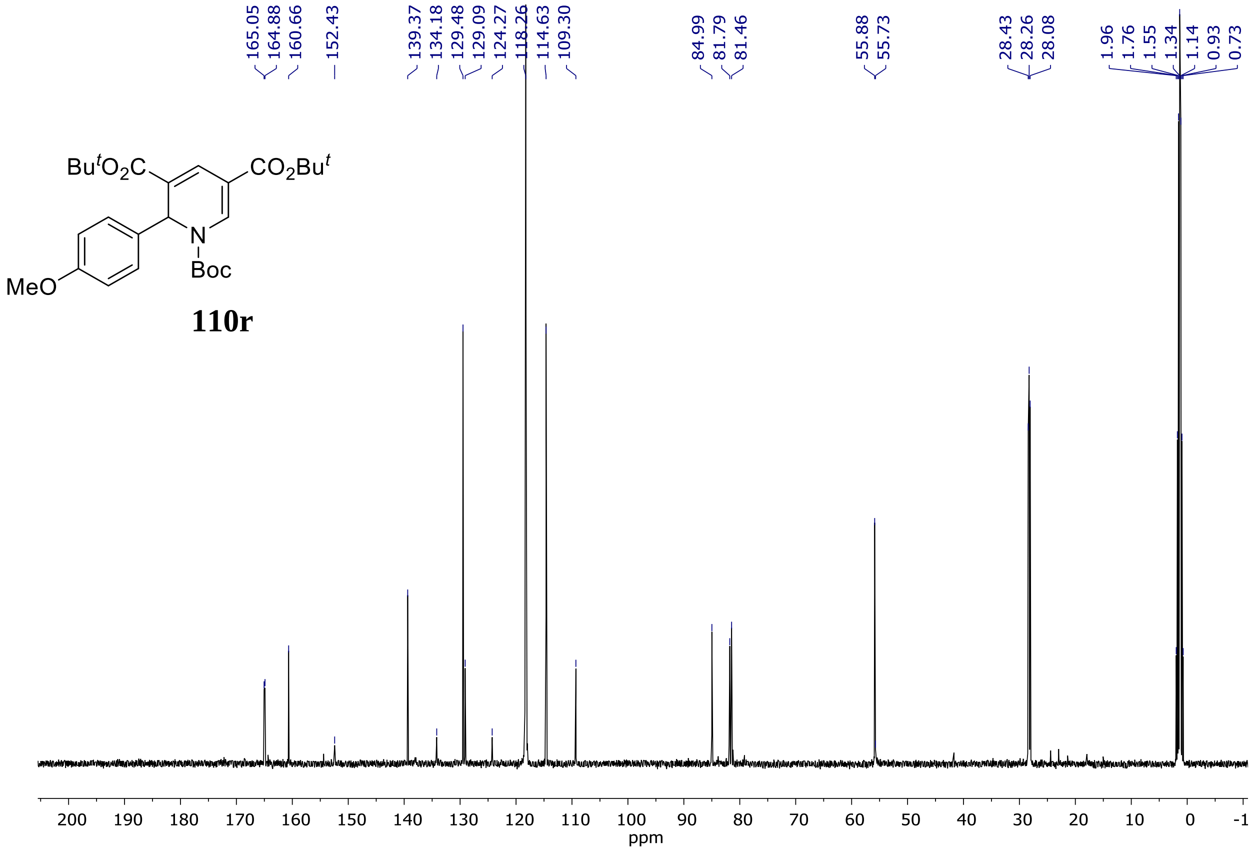


110q

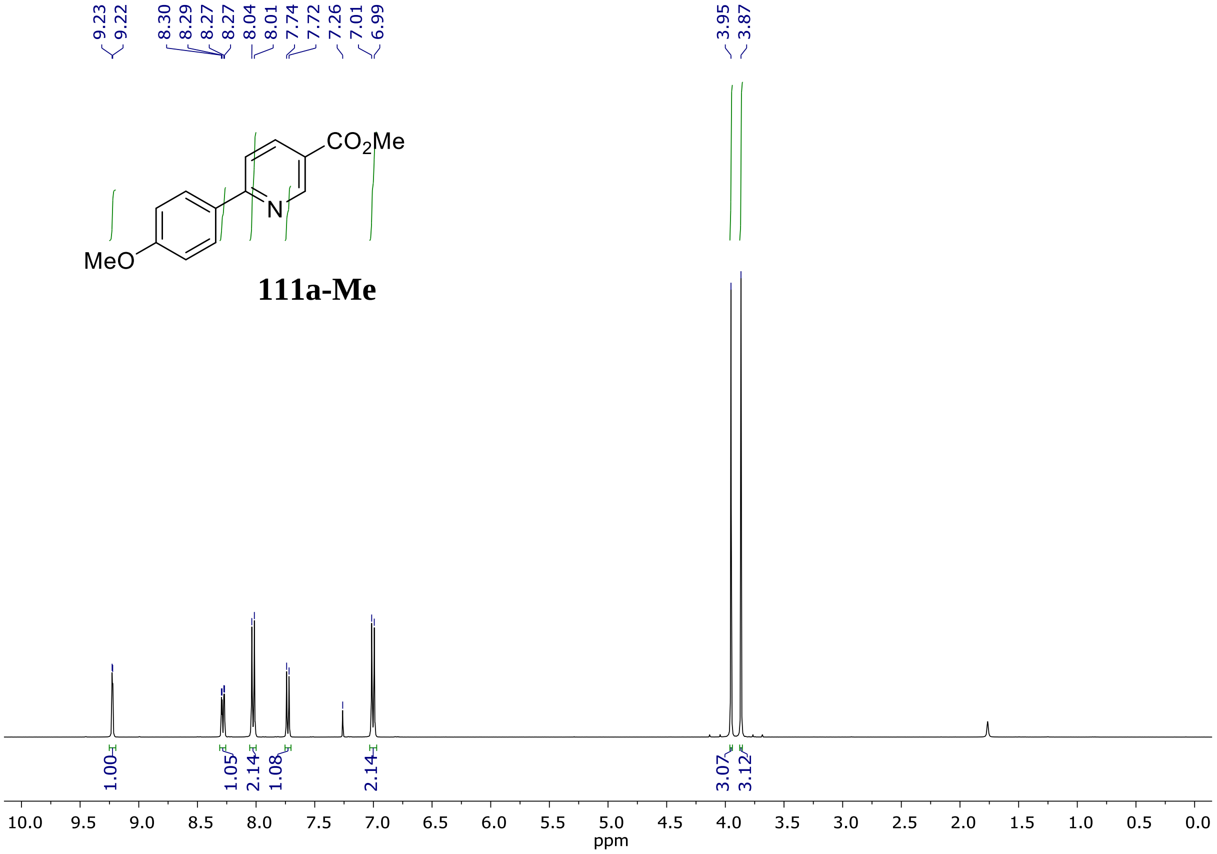
^{13}C NMR (101 MHz, CDCl$_3$)



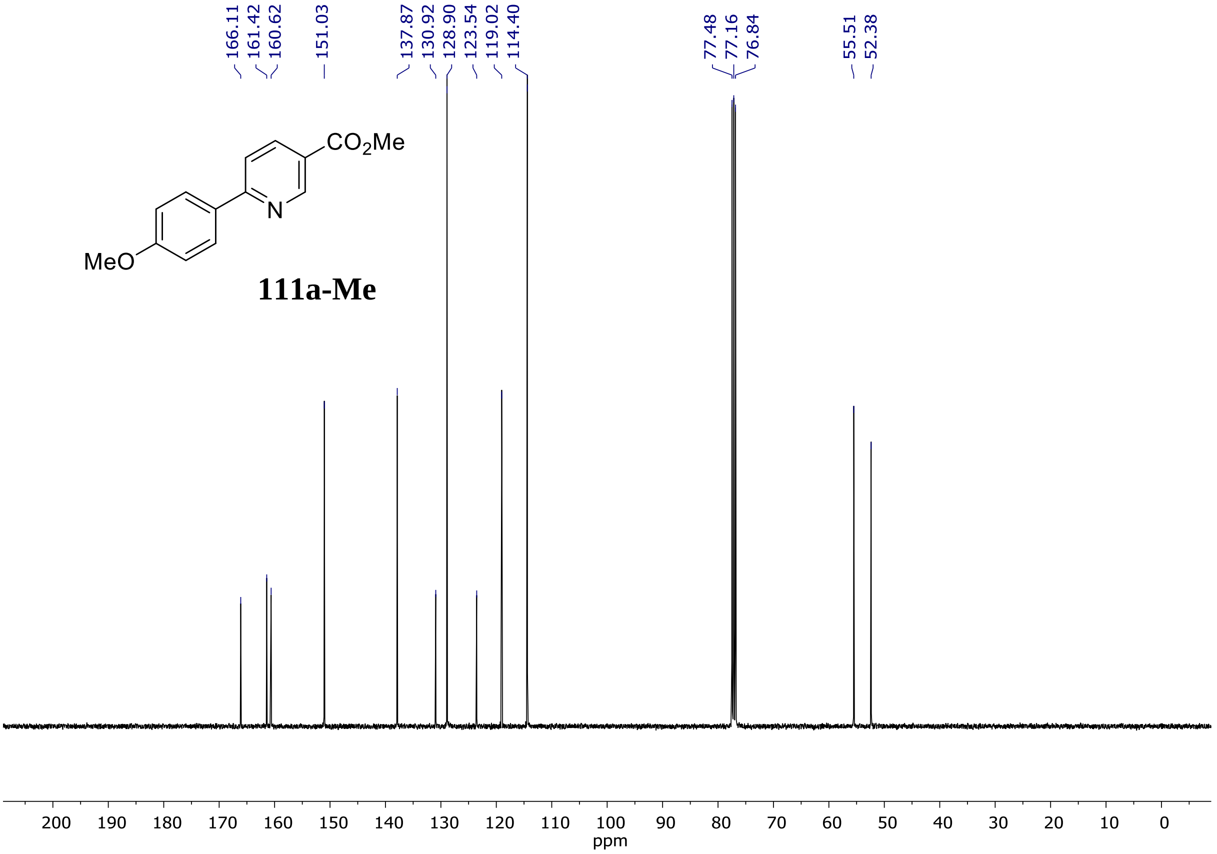
^{1}H NMR (400 MHz, CDCl$_3$)



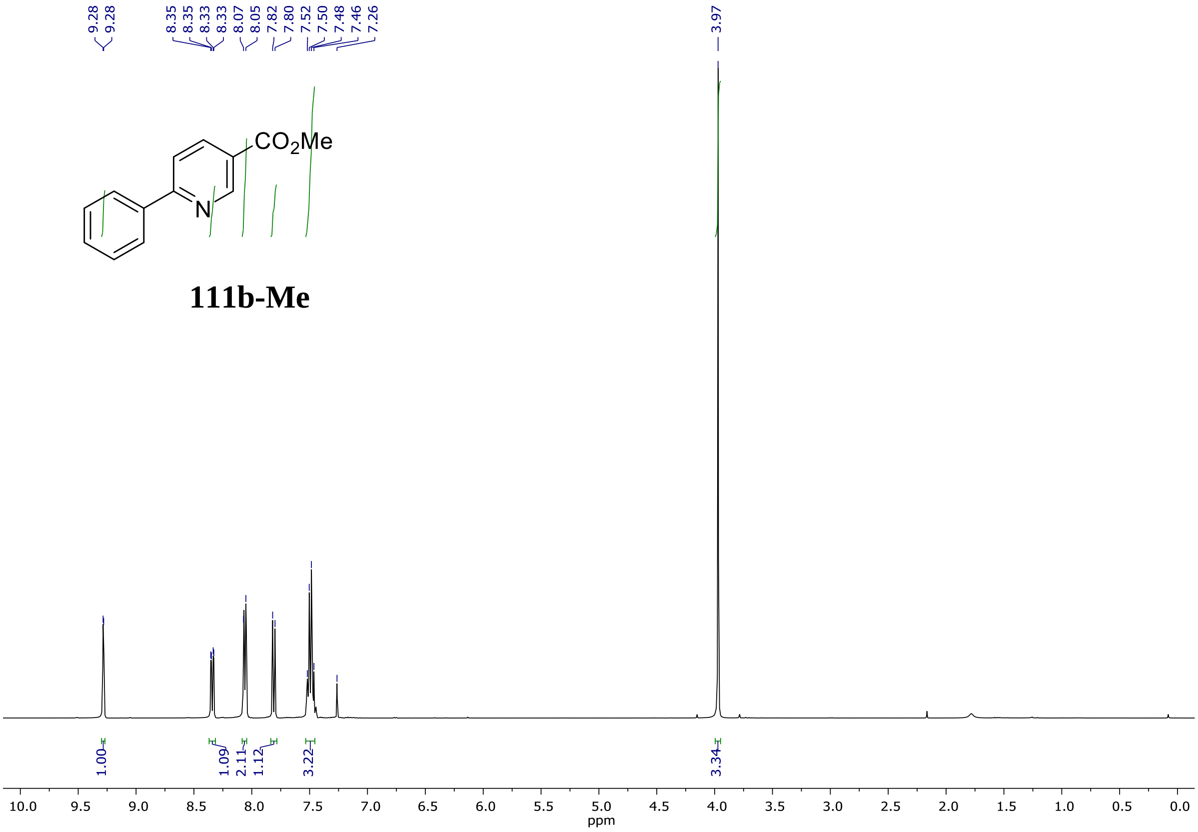
^{13}C NMR (101 MHz, CD$_3$CN)



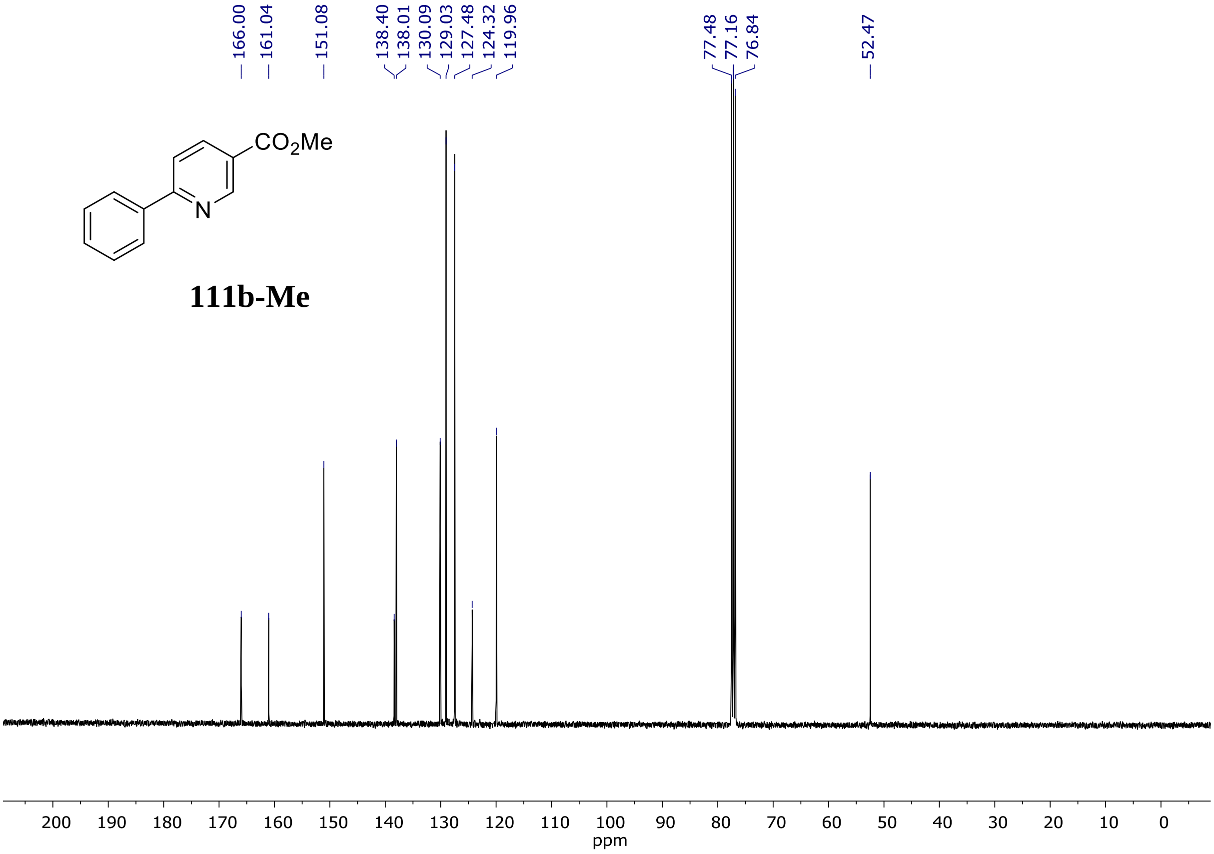
^{1}H NMR (400 MHz, CDCl$_3$)



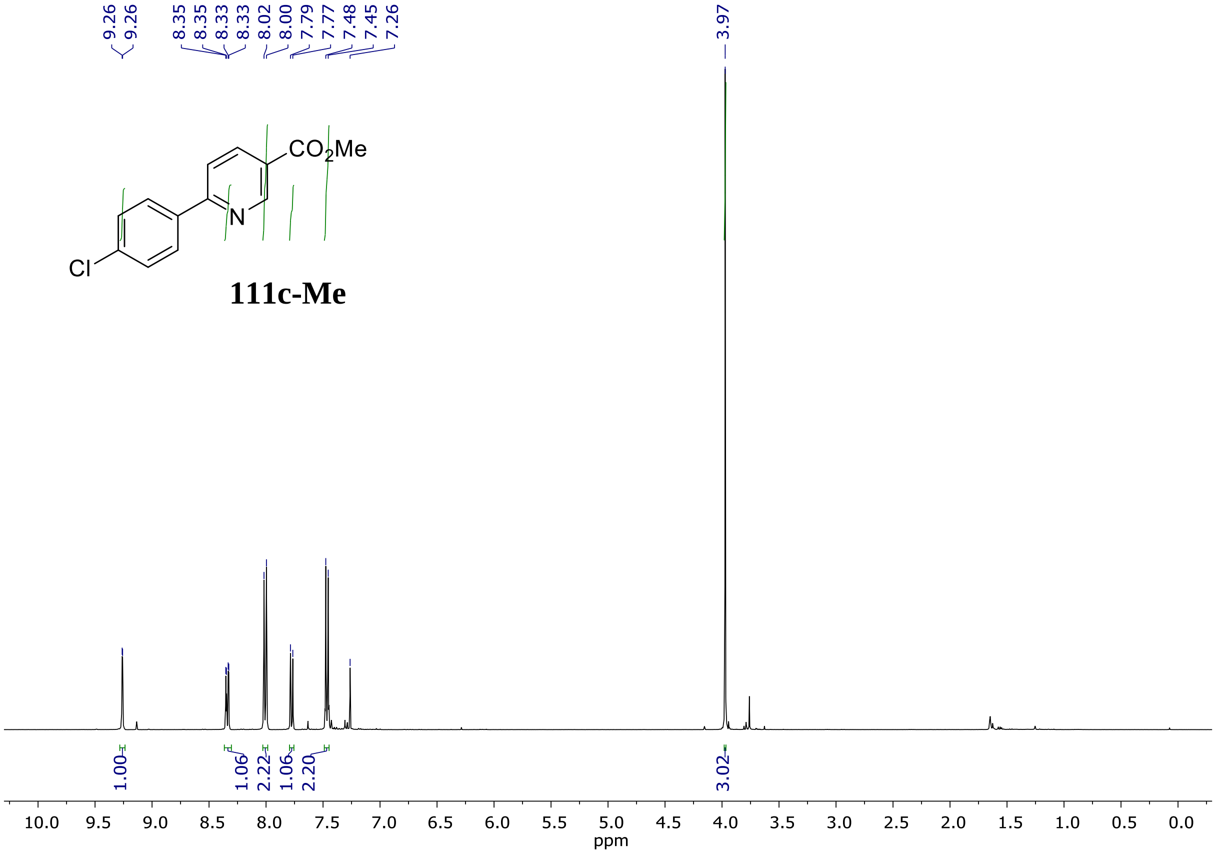
^{13}C NMR (101 MHz, CDCl$_3$)



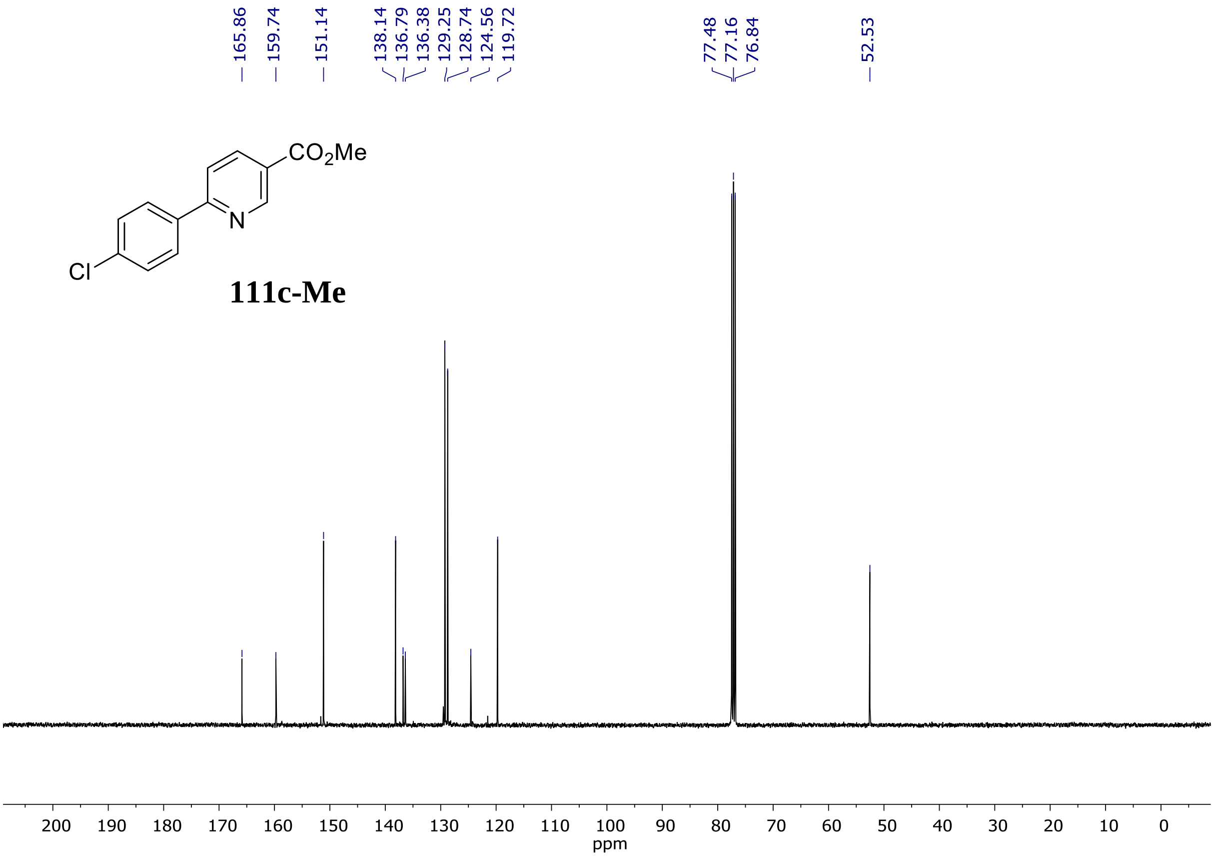
^{1}H NMR (400 MHz, CDCl$_3$)



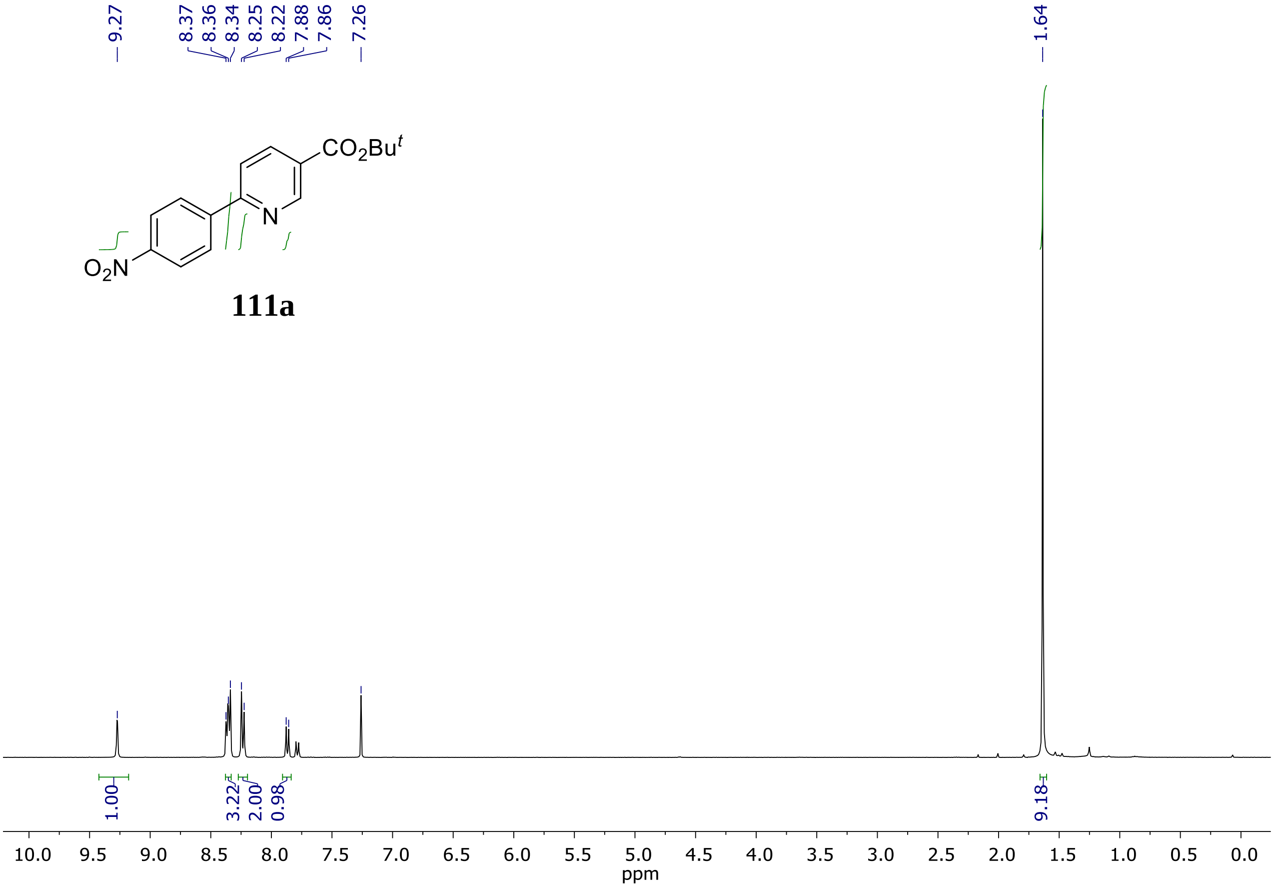
^{13}C NMR (101 MHz, CDCl$_3$)



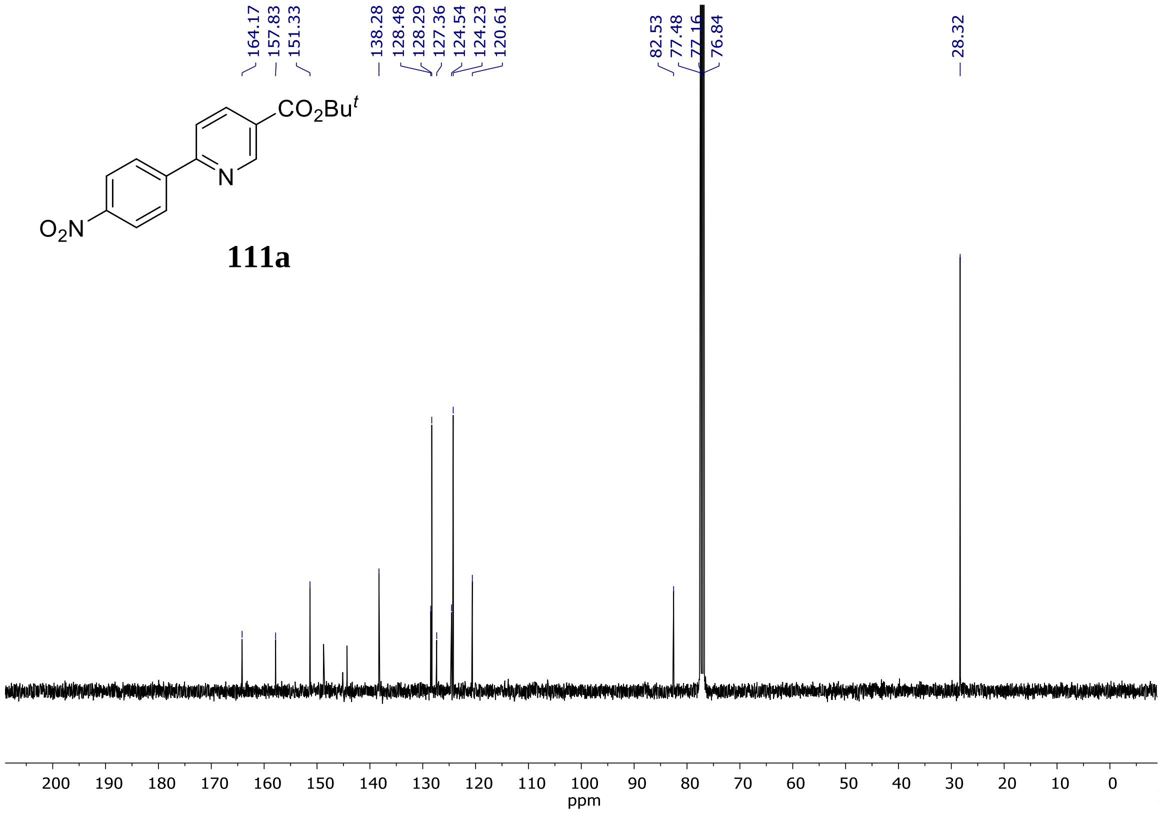
^{1}H NMR (400 MHz, CDCl$_3$)



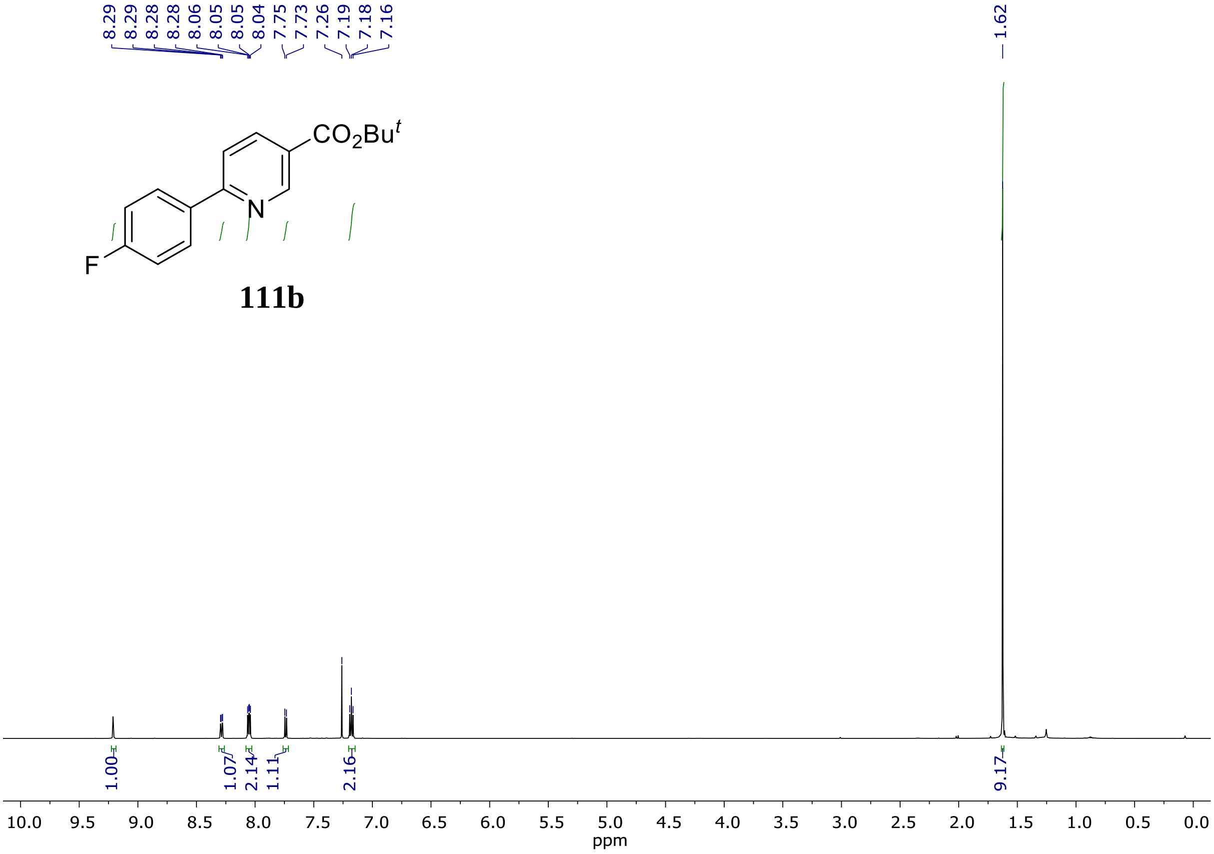
^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)

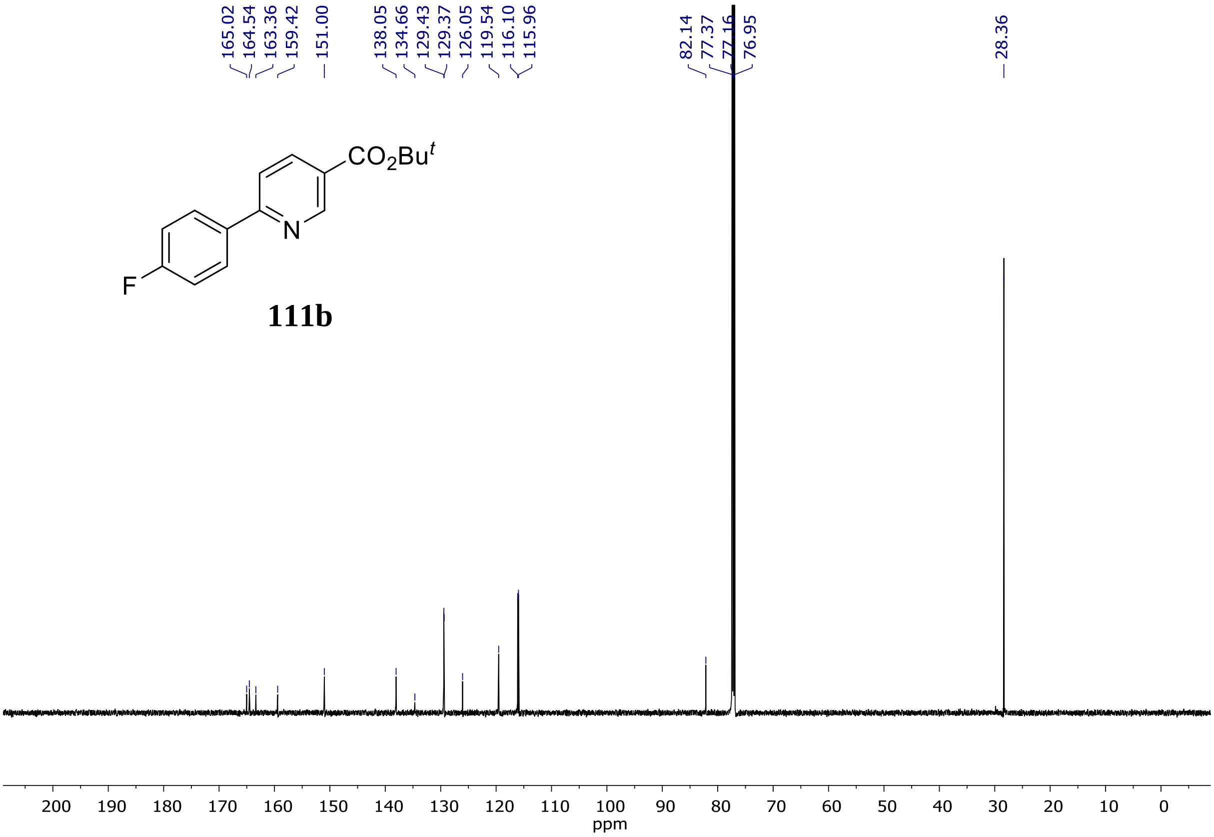


^{13}C NMR (101 MHz, CDCl$_3$)



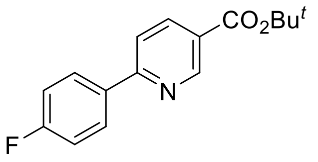
111b

^{1}H NMR (600 MHz, CDCl$_3$)

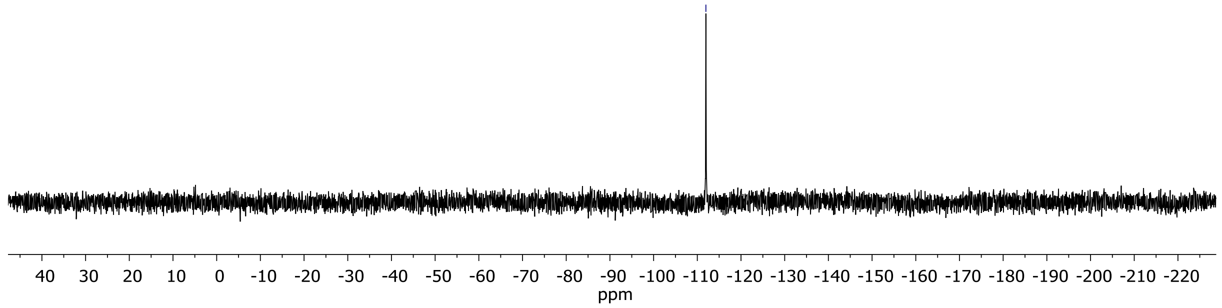


111b

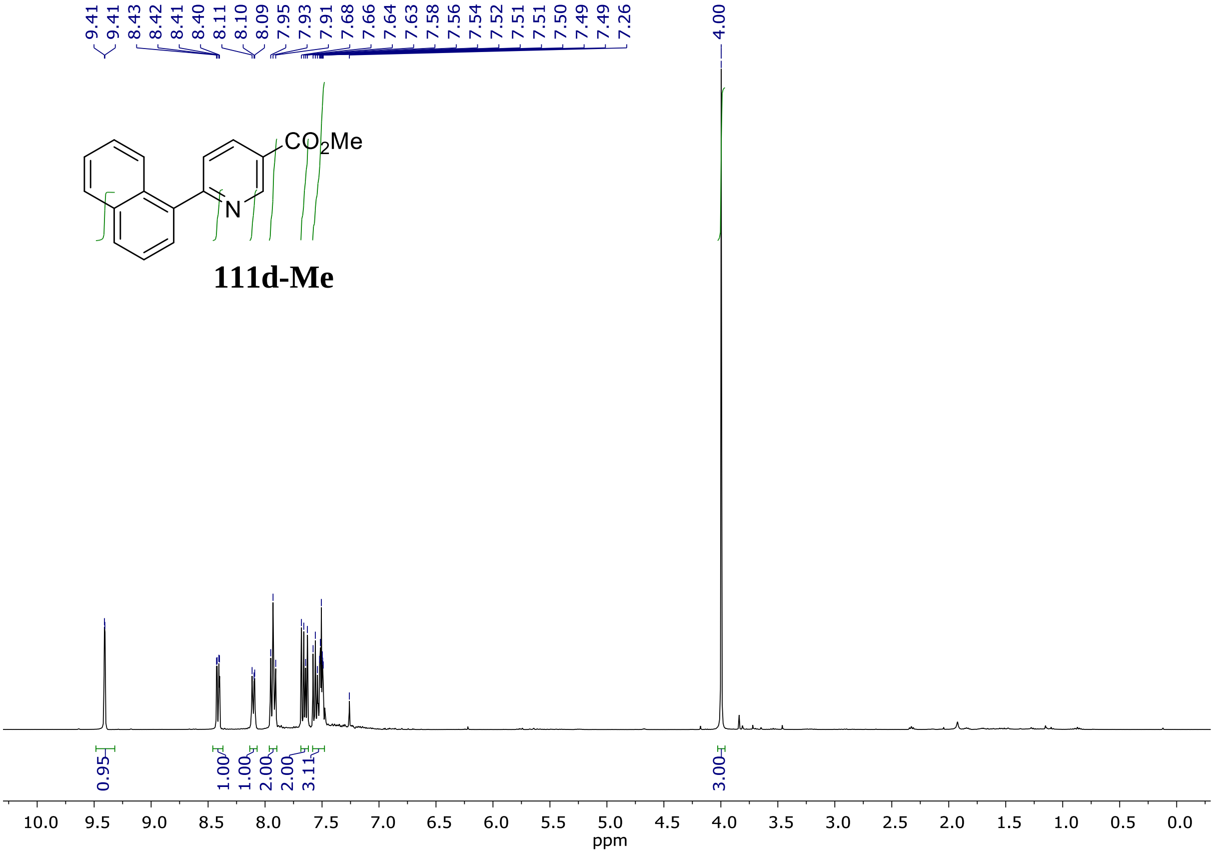
^{13}C NMR (151 MHz, CDCl$_3$)



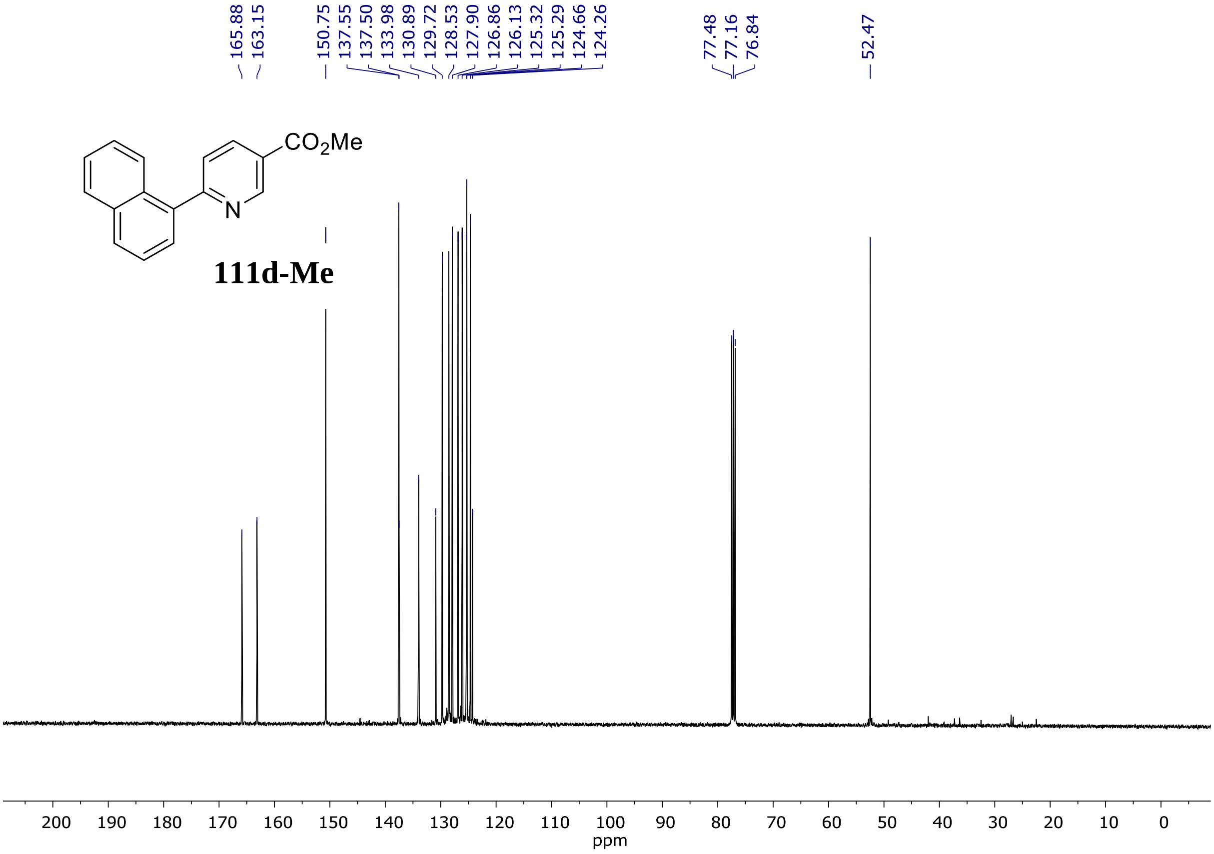
111b



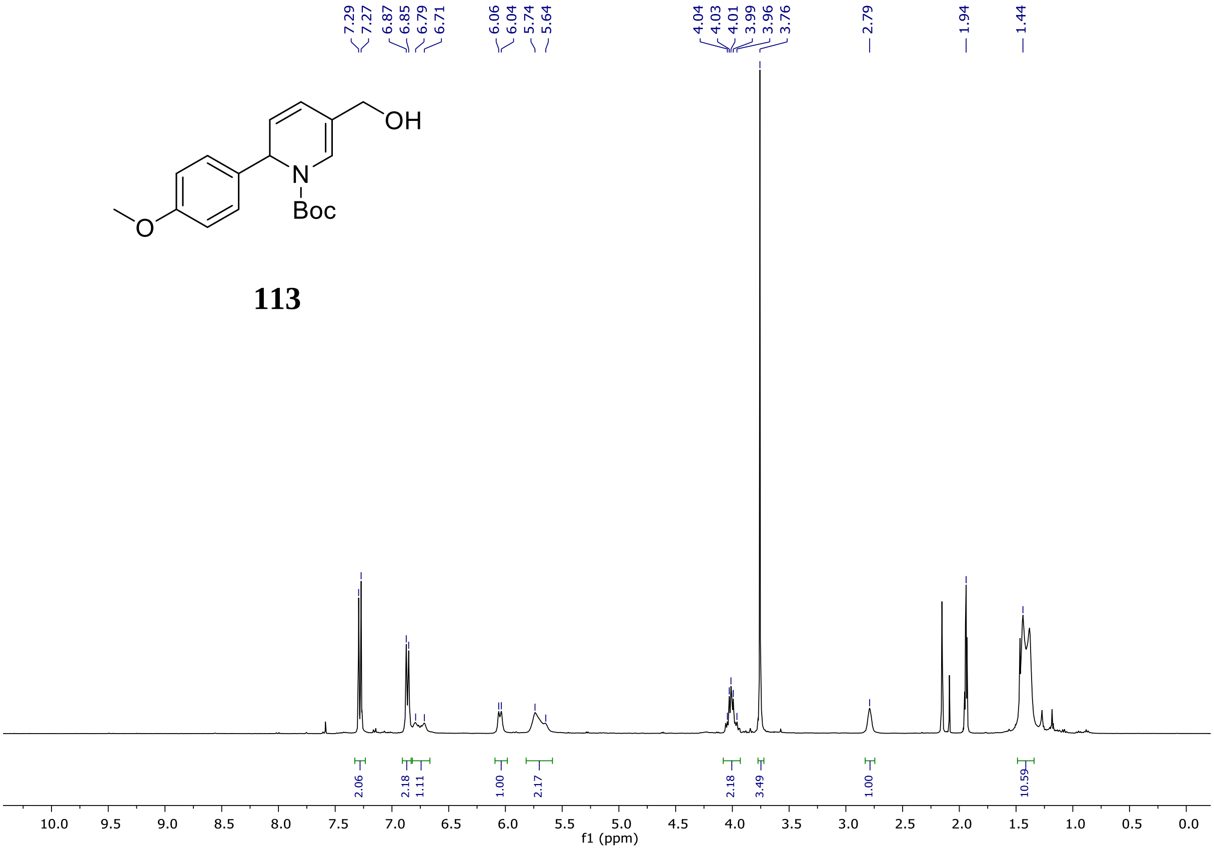
^{19}F NMR (377 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)

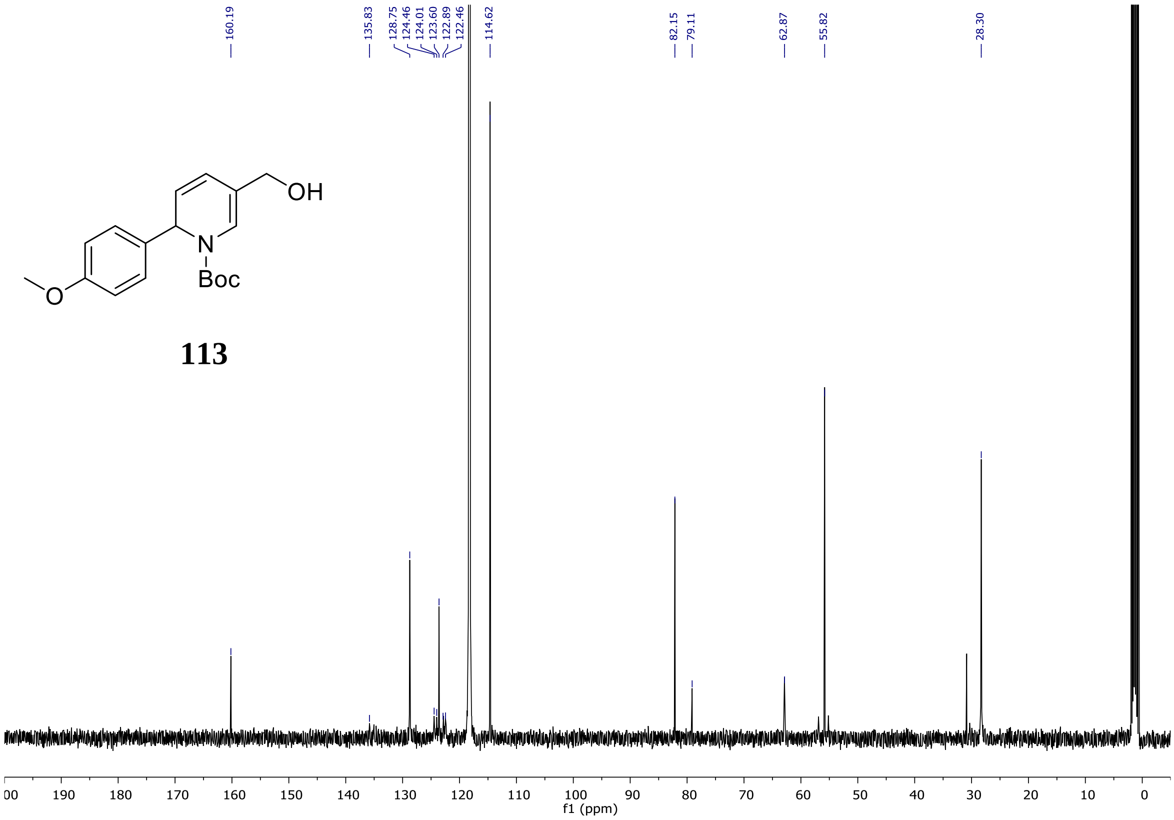


^{13}C NMR (101 MHz, CDCl$_3$)



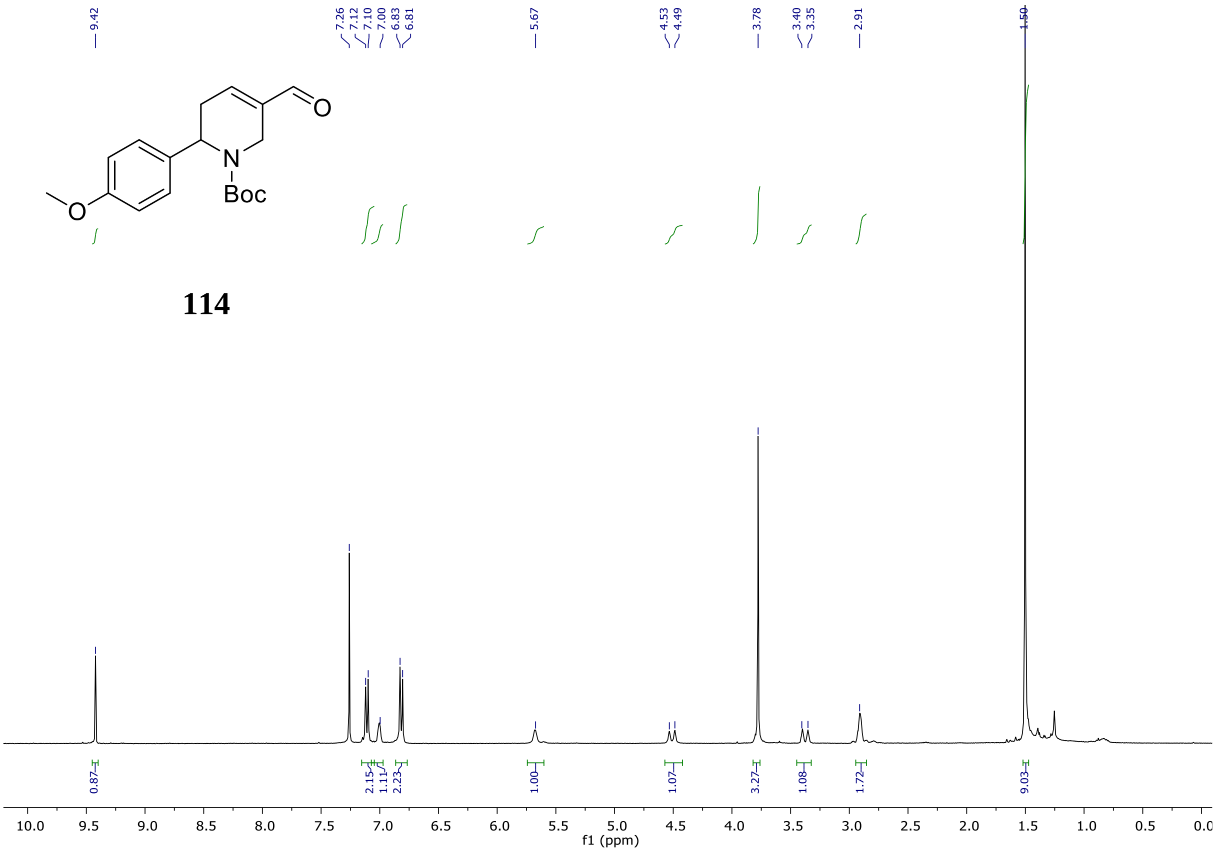
113

^{1}H NMR (400 MHz, CD$_3$CN)



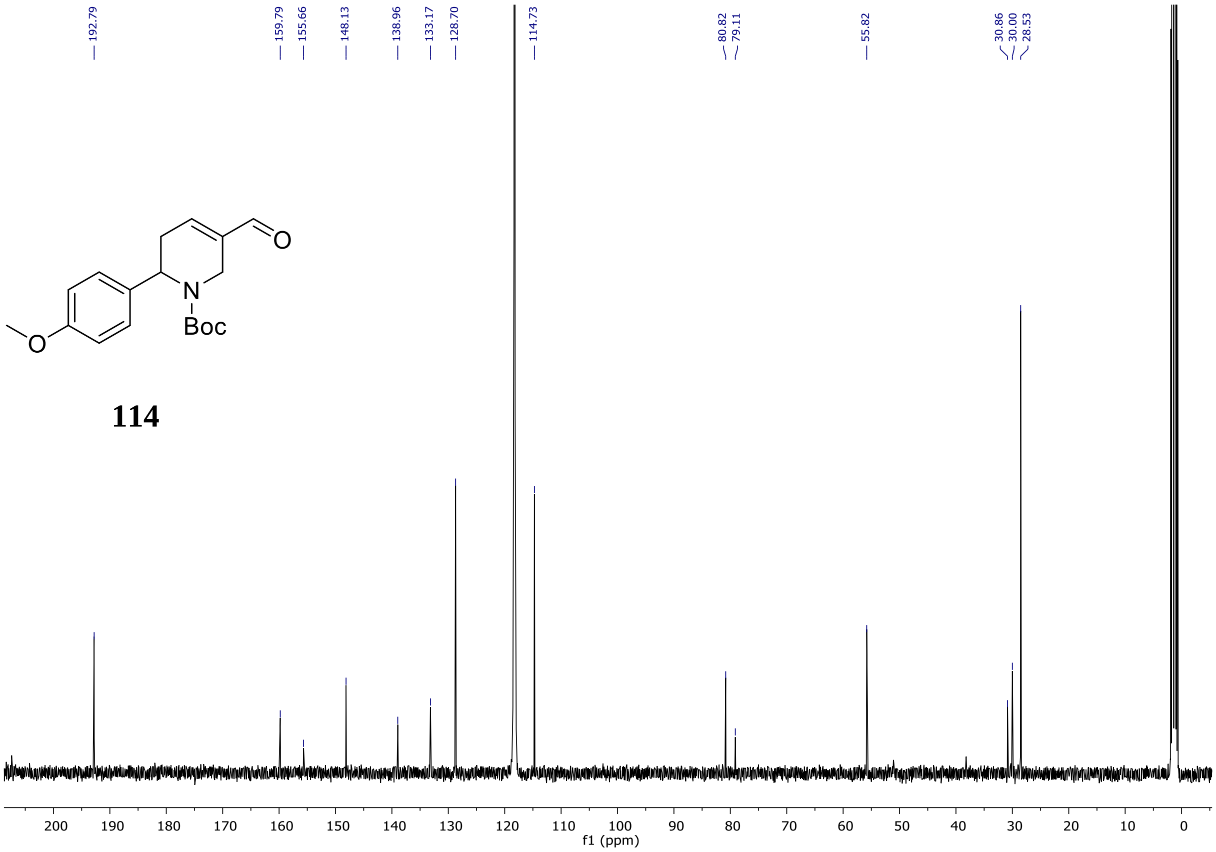
113

^{13}C NMR (101 MHz, CD$_3$CN)



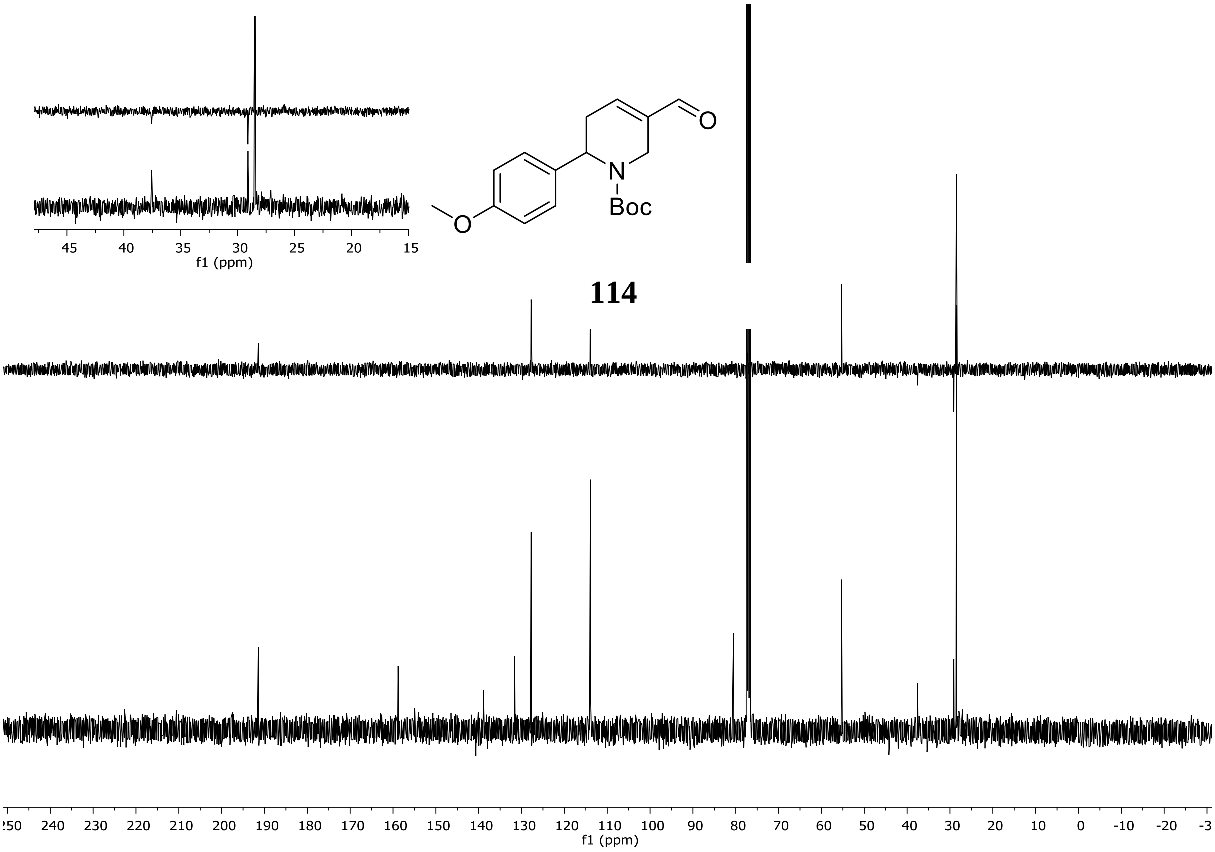
114

^{1}H NMR (400 MHz, CD$_3$CN)



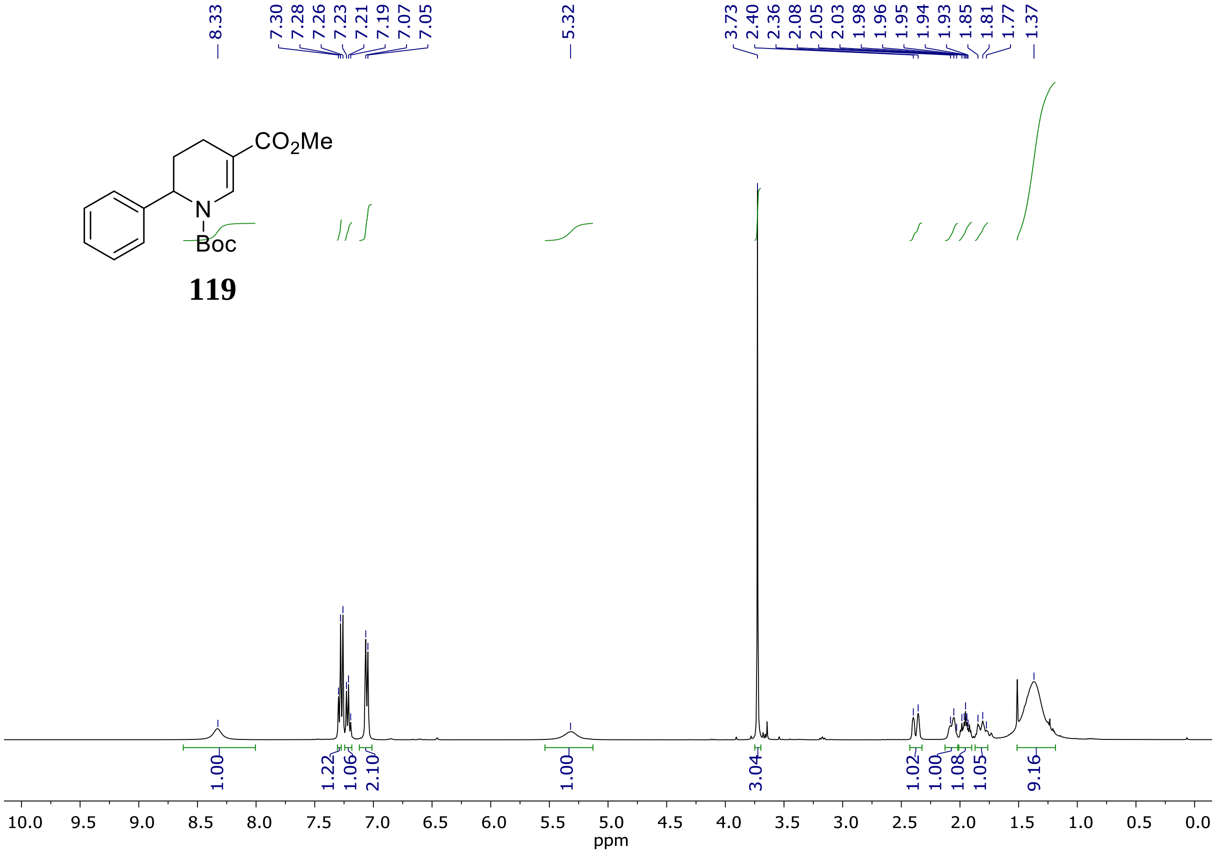
114

^{13}C NMR (101 MHz, CD$_3$CN)



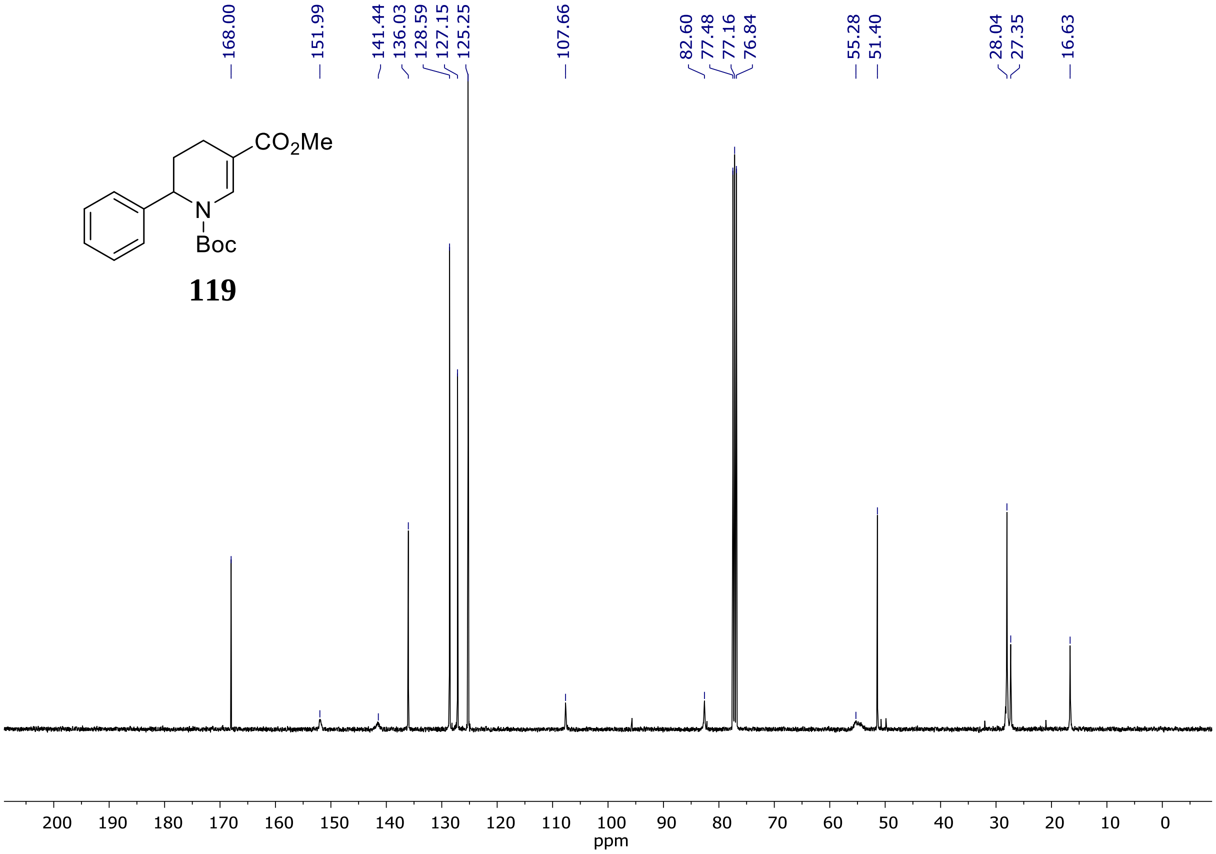
114

^{1}H NMR (400 MHz, CD$_3$CN) ^{13}C NMR (101 MHz, CD$_3$CN)



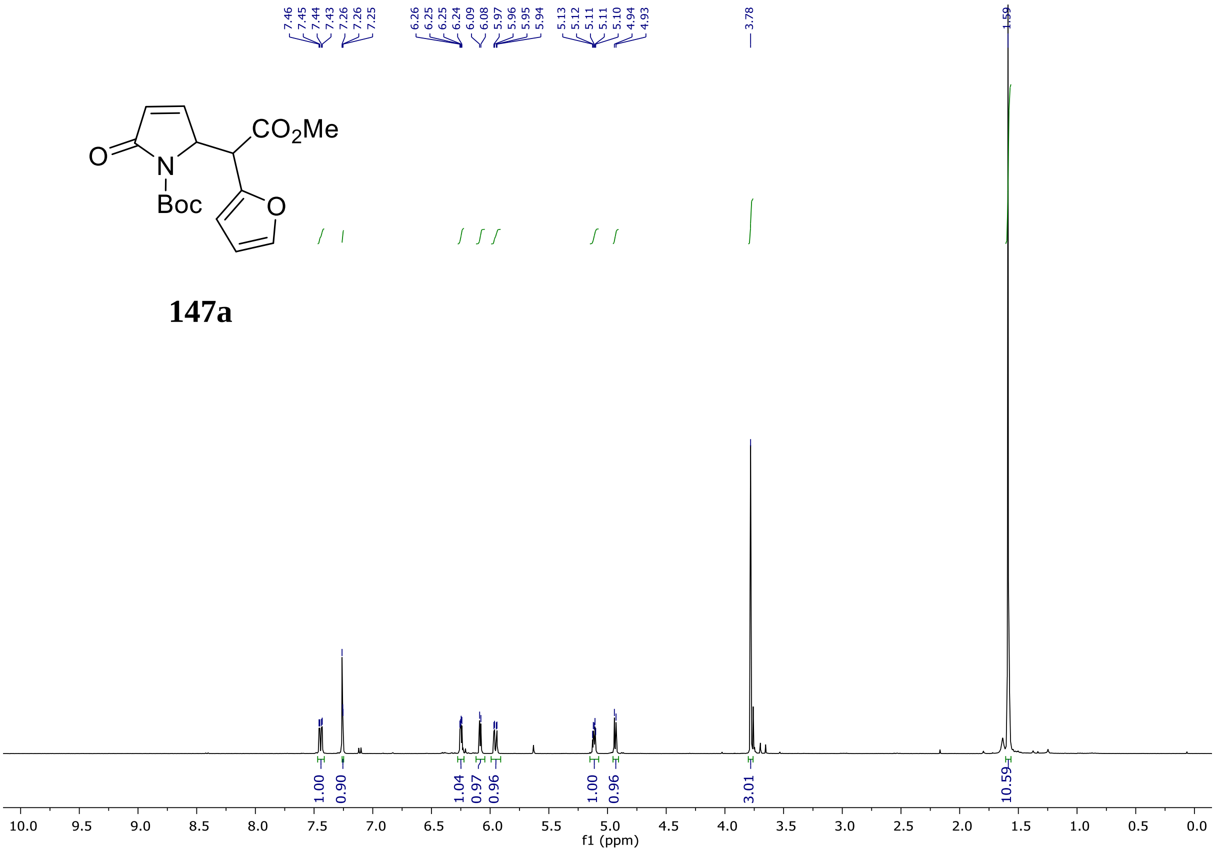
119

^{1}H NMR (400 MHz, CDCl$_3$)



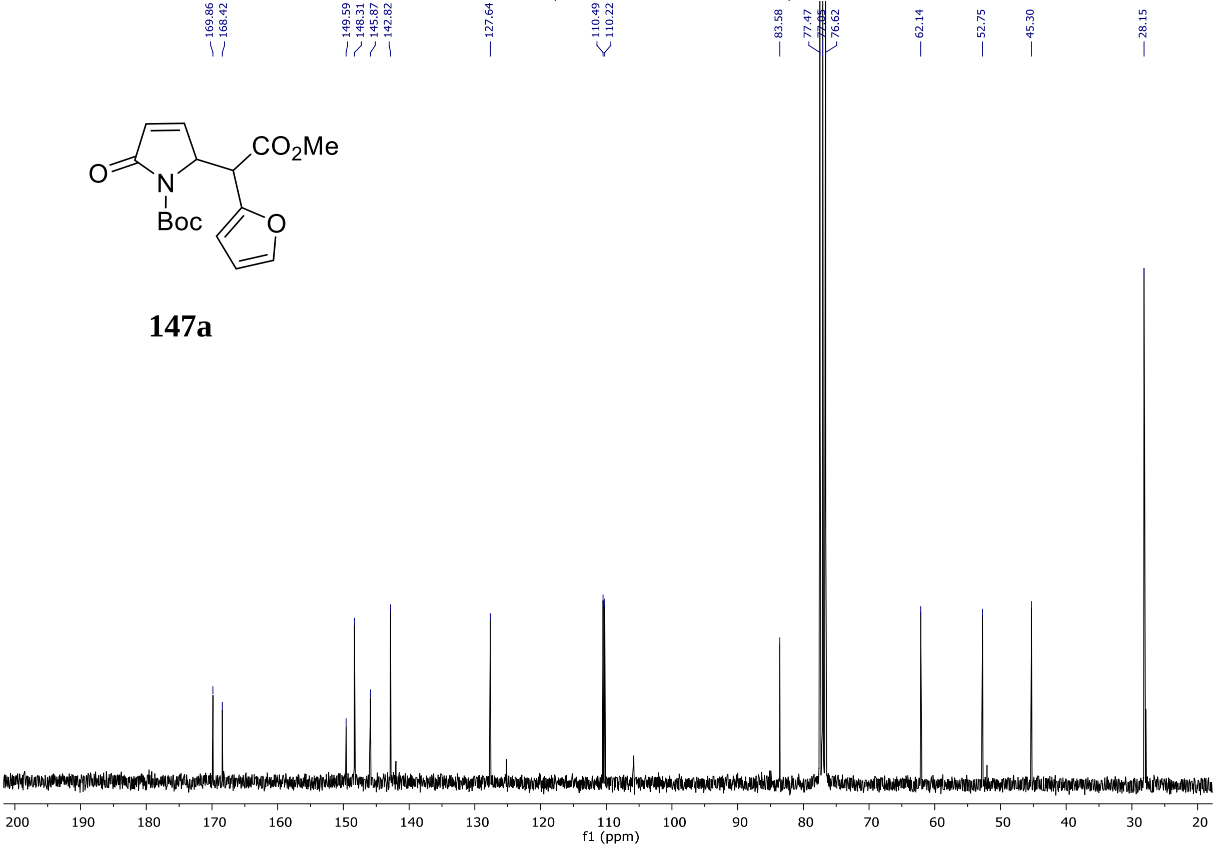
119

^{13}C NMR (101 MHz, CDCl$_3$)



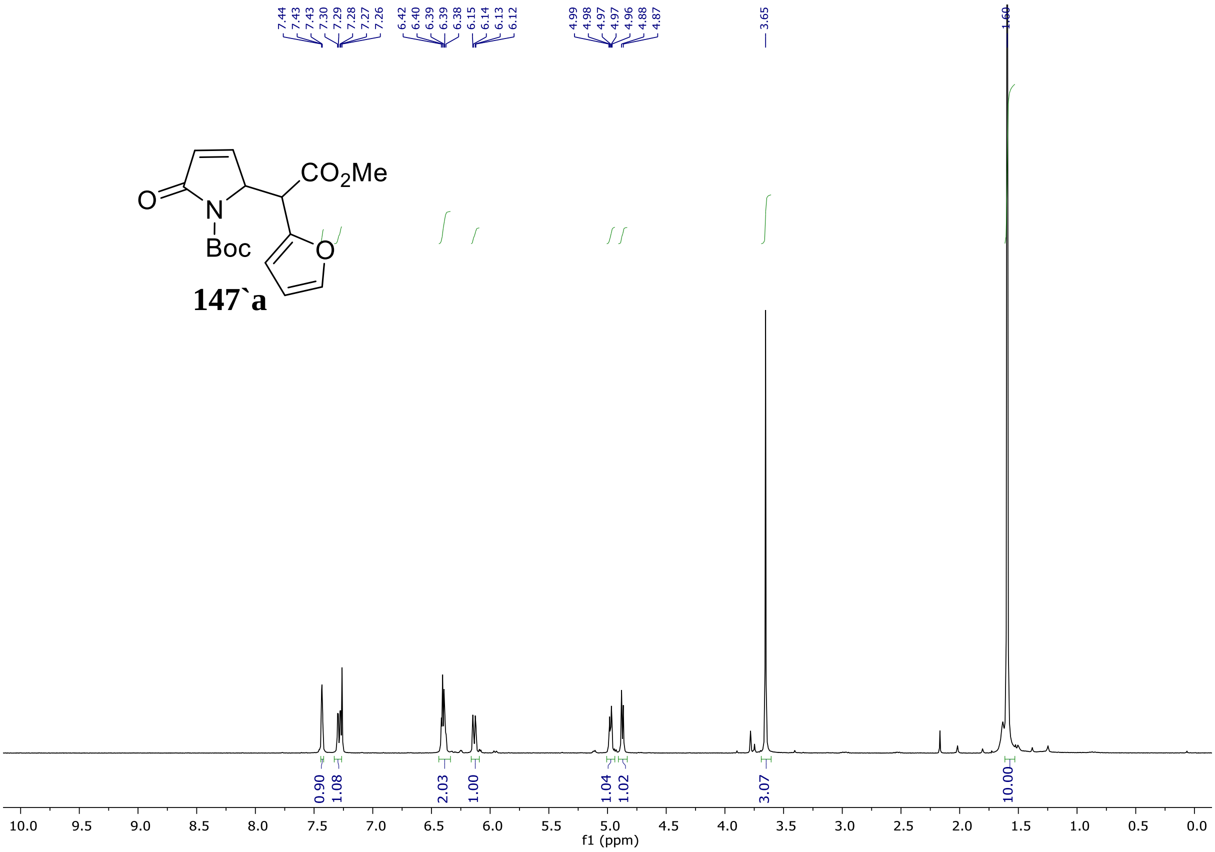
147a

^{1}H NMR (400 MHz, CDCl$_3$)

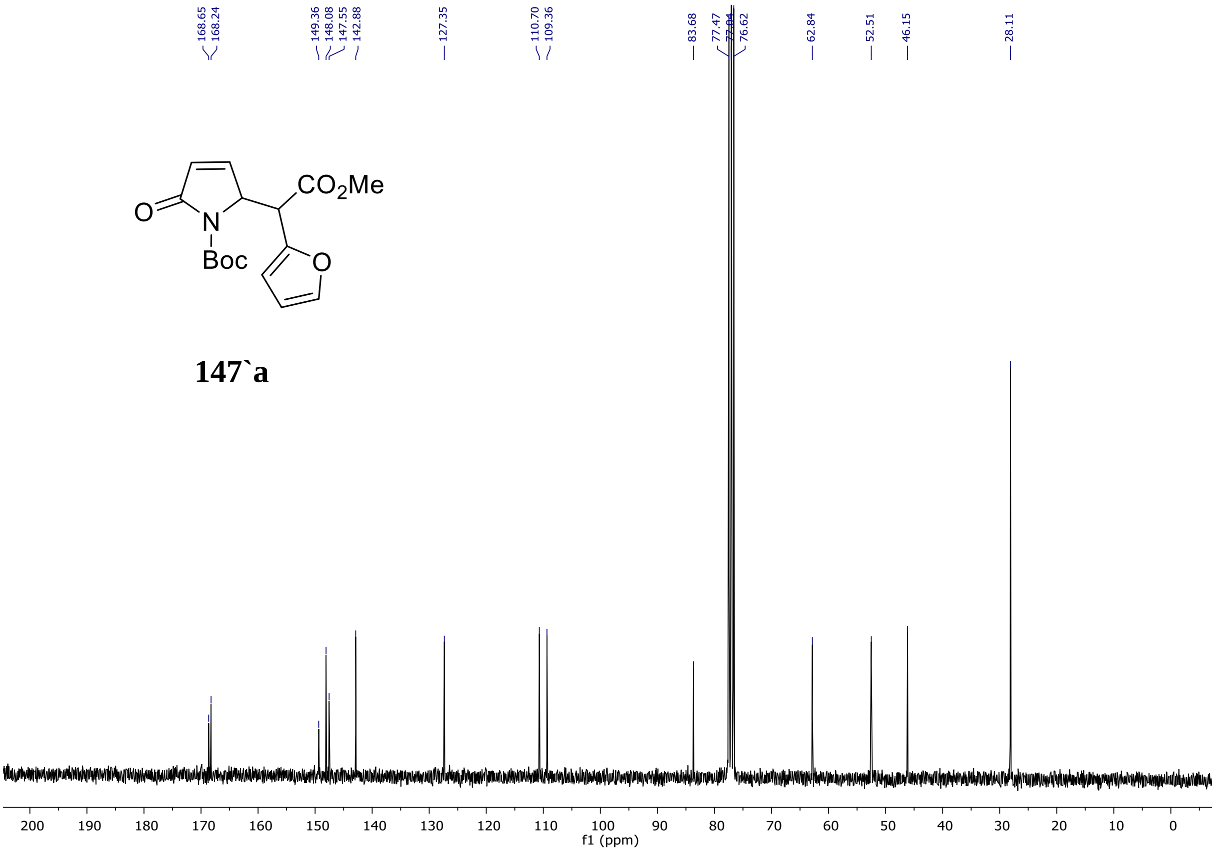


147a

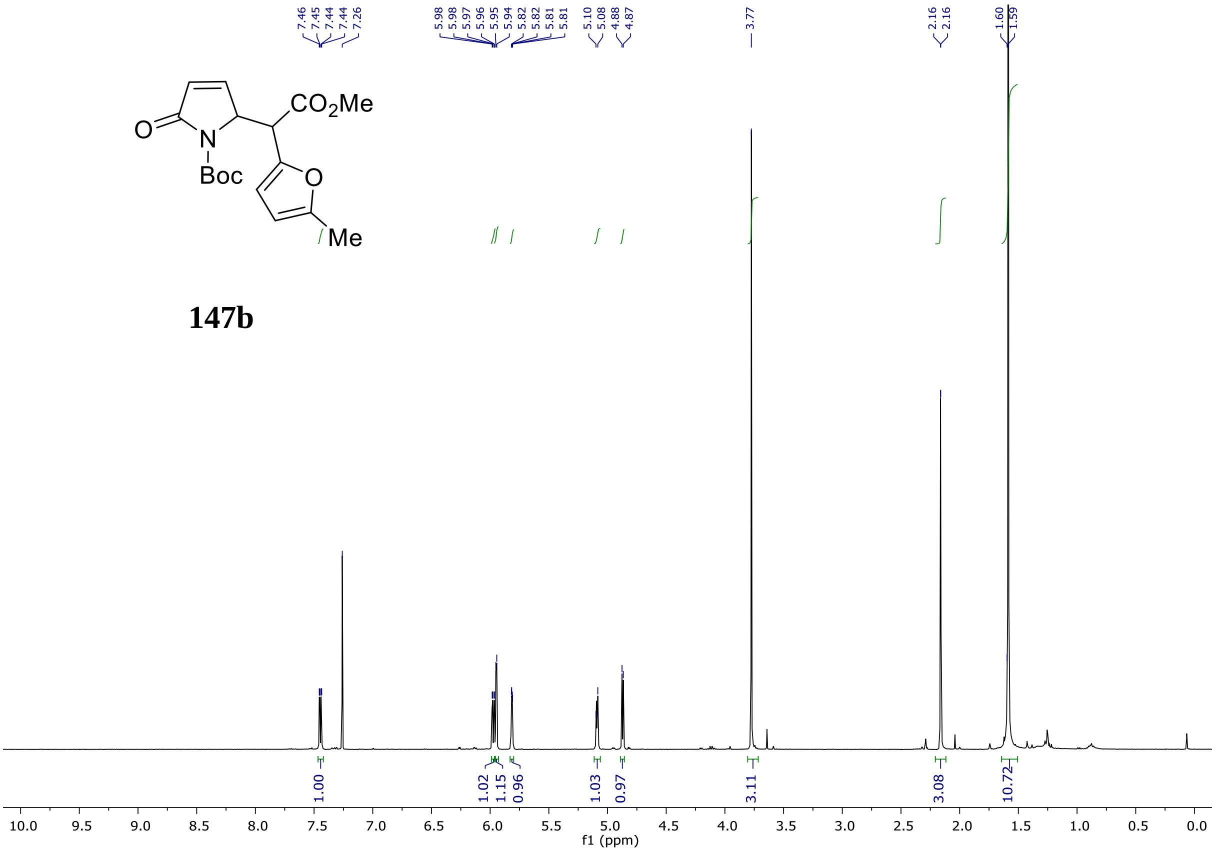
^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)

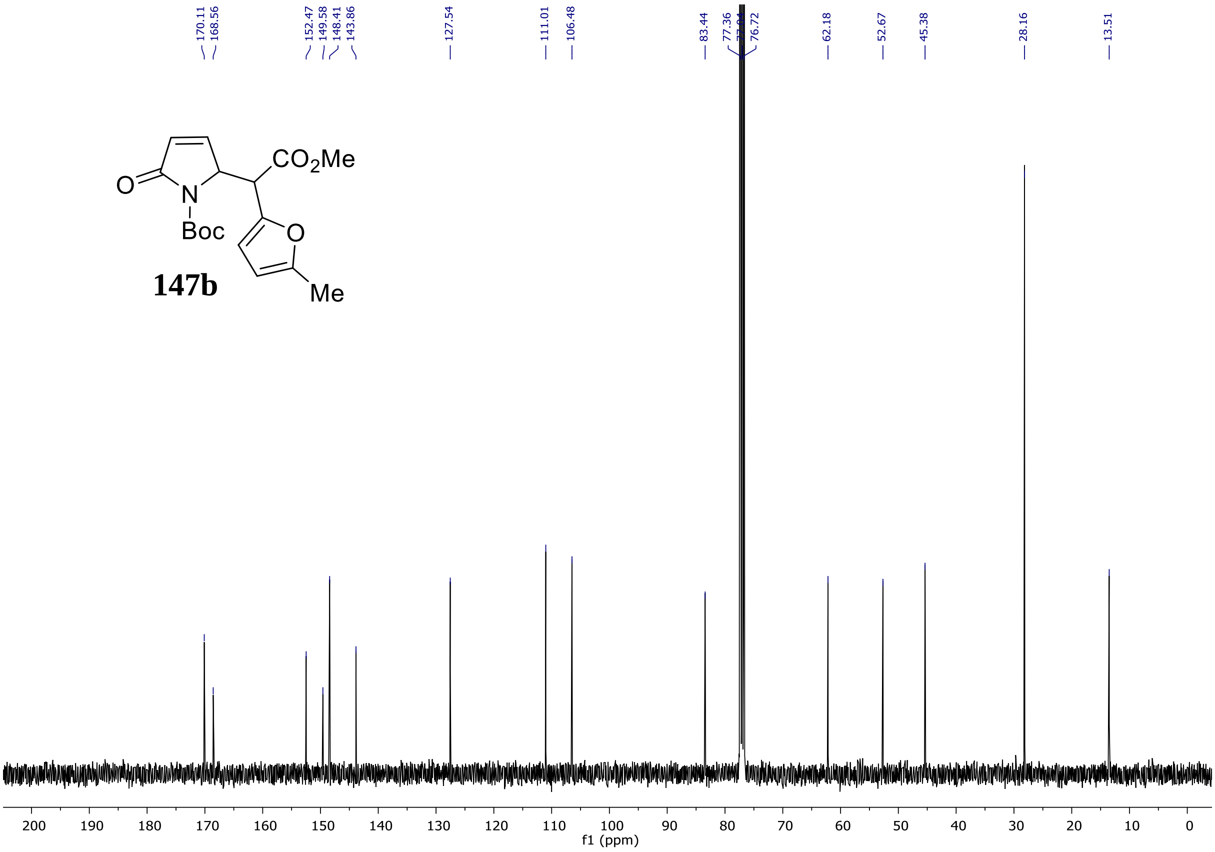


^{13}C NMR (101 MHz, CDCl$_3$)



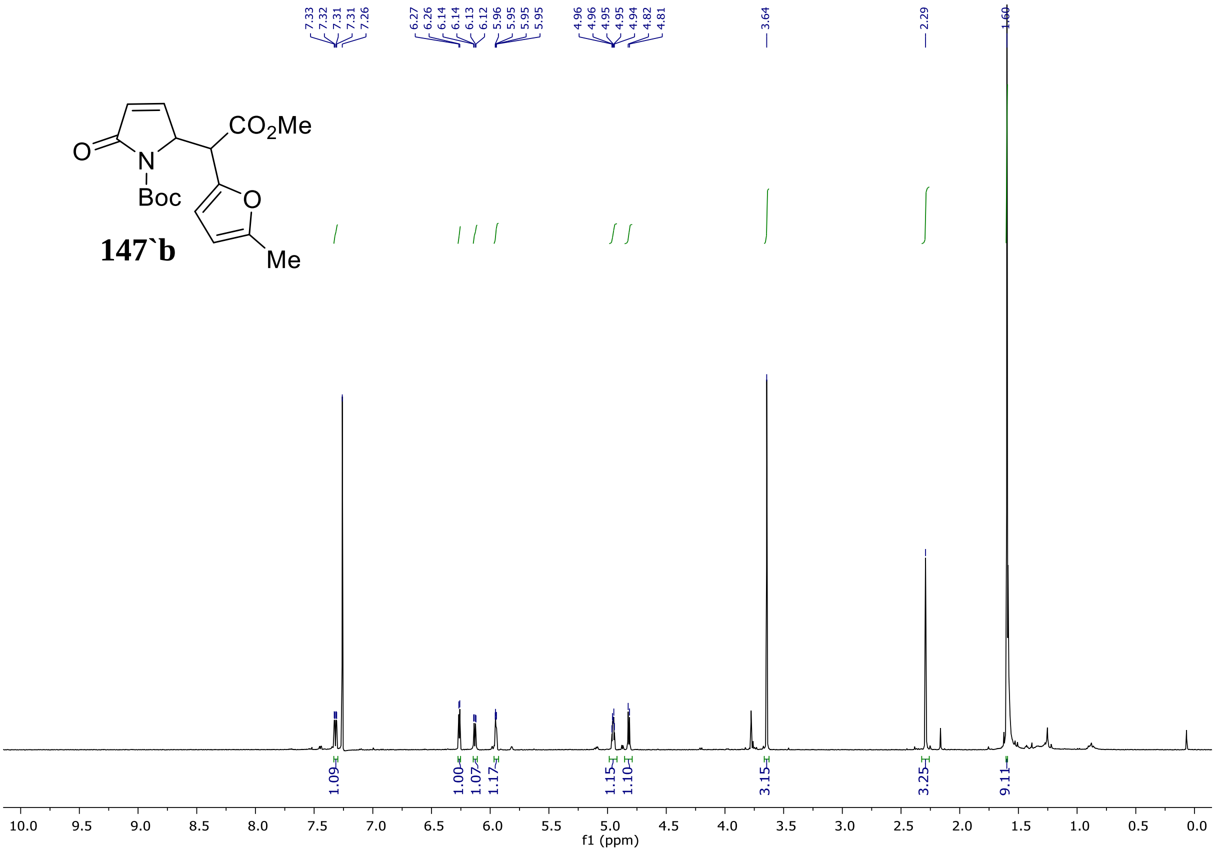
147b

^{1}H NMR (400 MHz, CDCl$_3$)

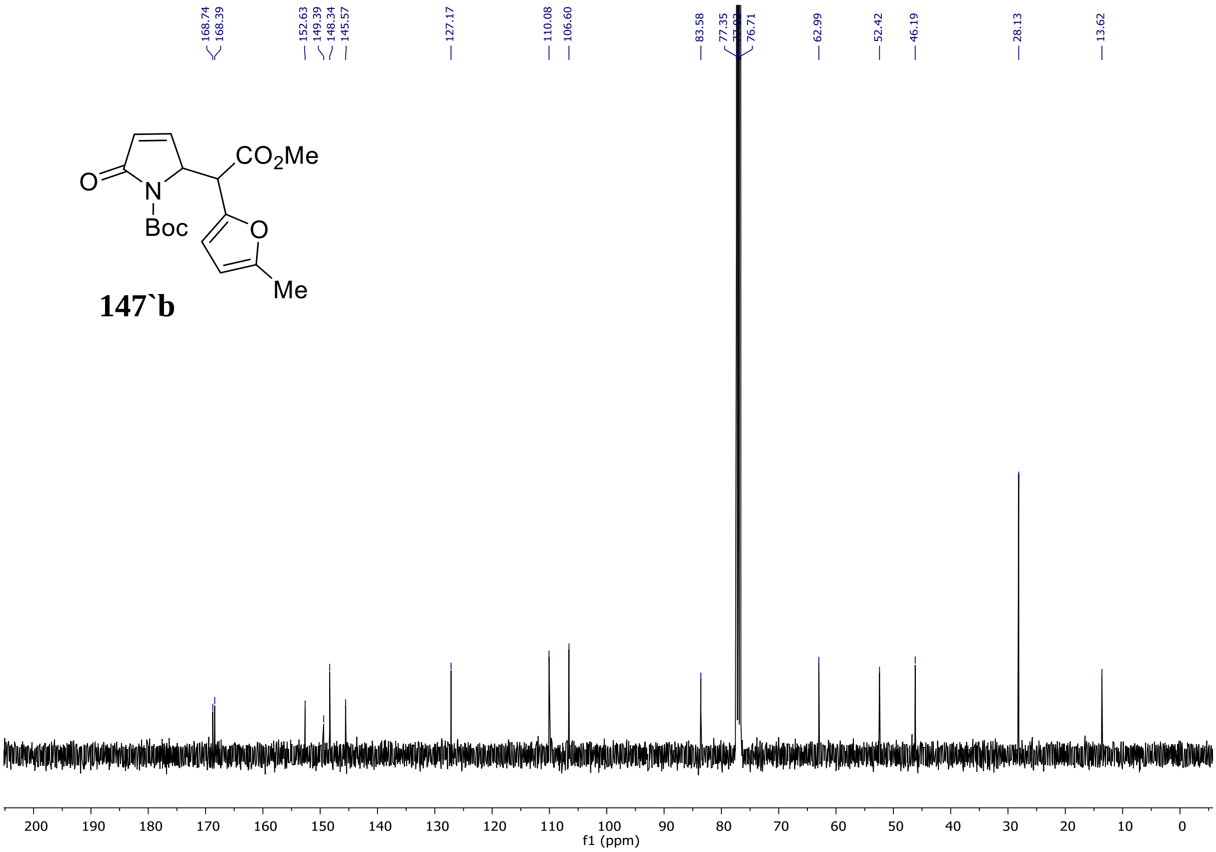


147b

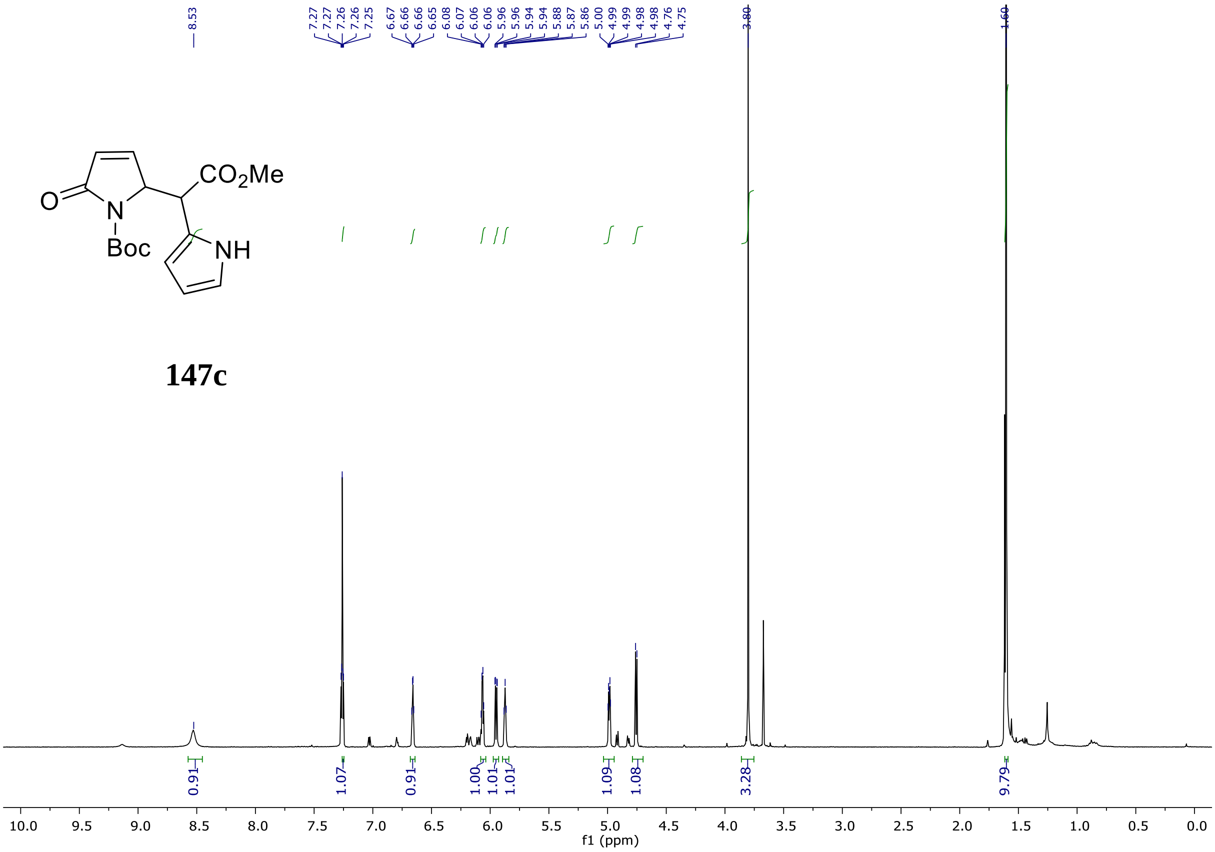
^{13}C NMR (101 MHz, CDCl$_3$)



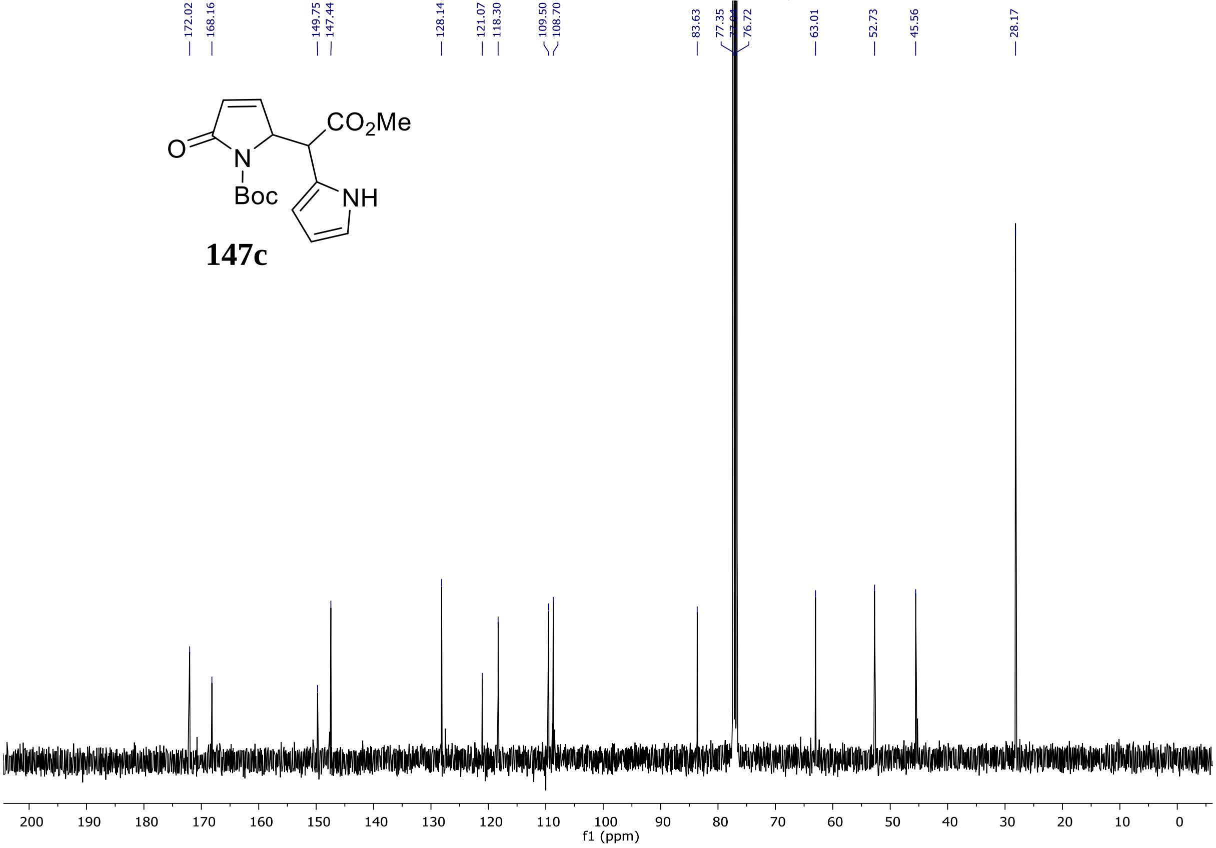
^{1}H NMR (400 MHz, CDCl$_3$)



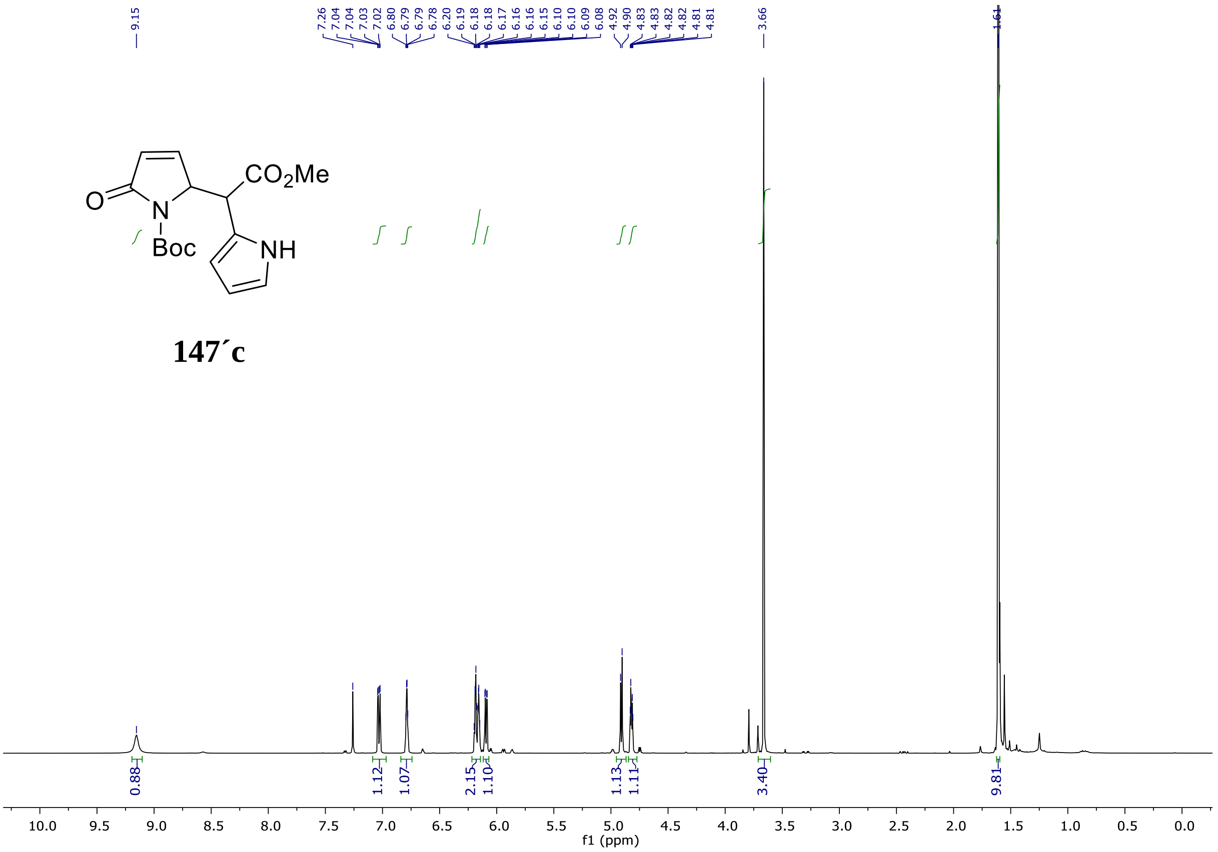
^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)

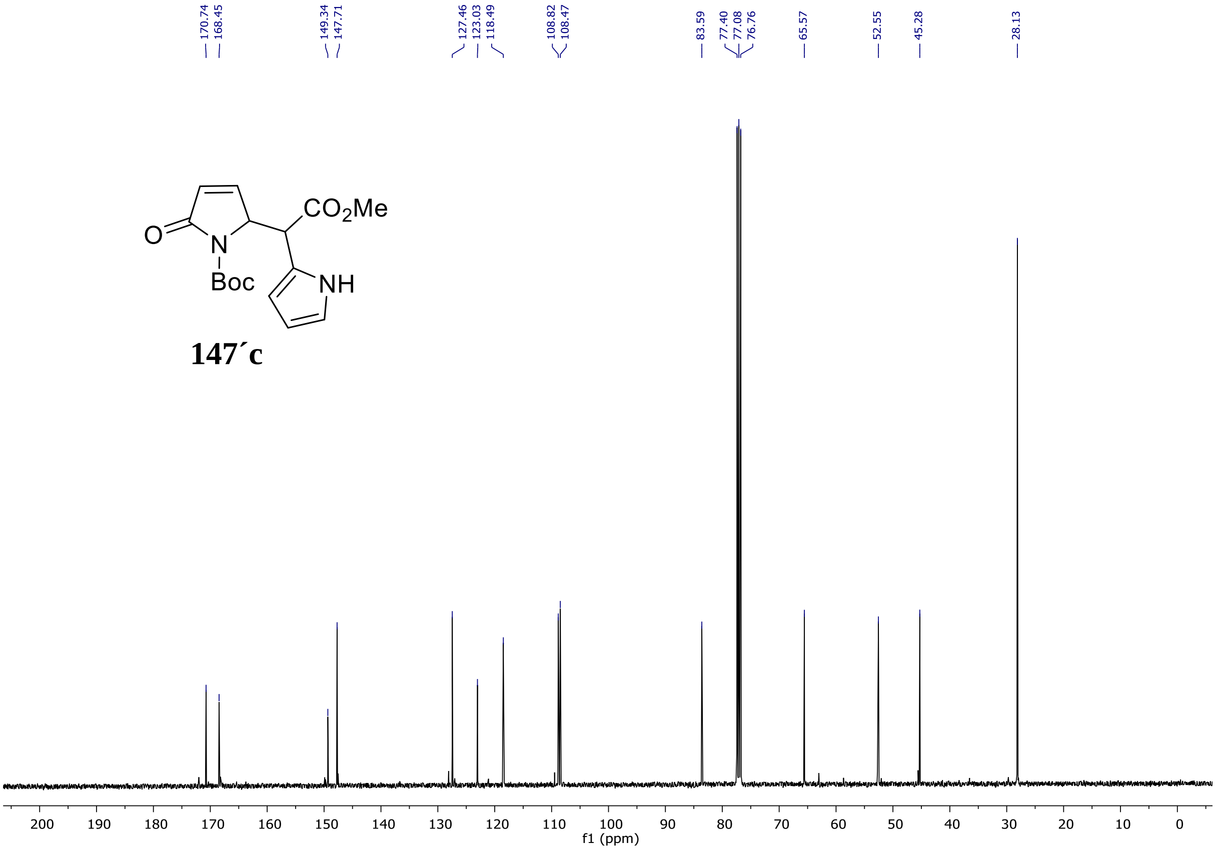


^{13}C NMR (101 MHz, CDCl$_3$)



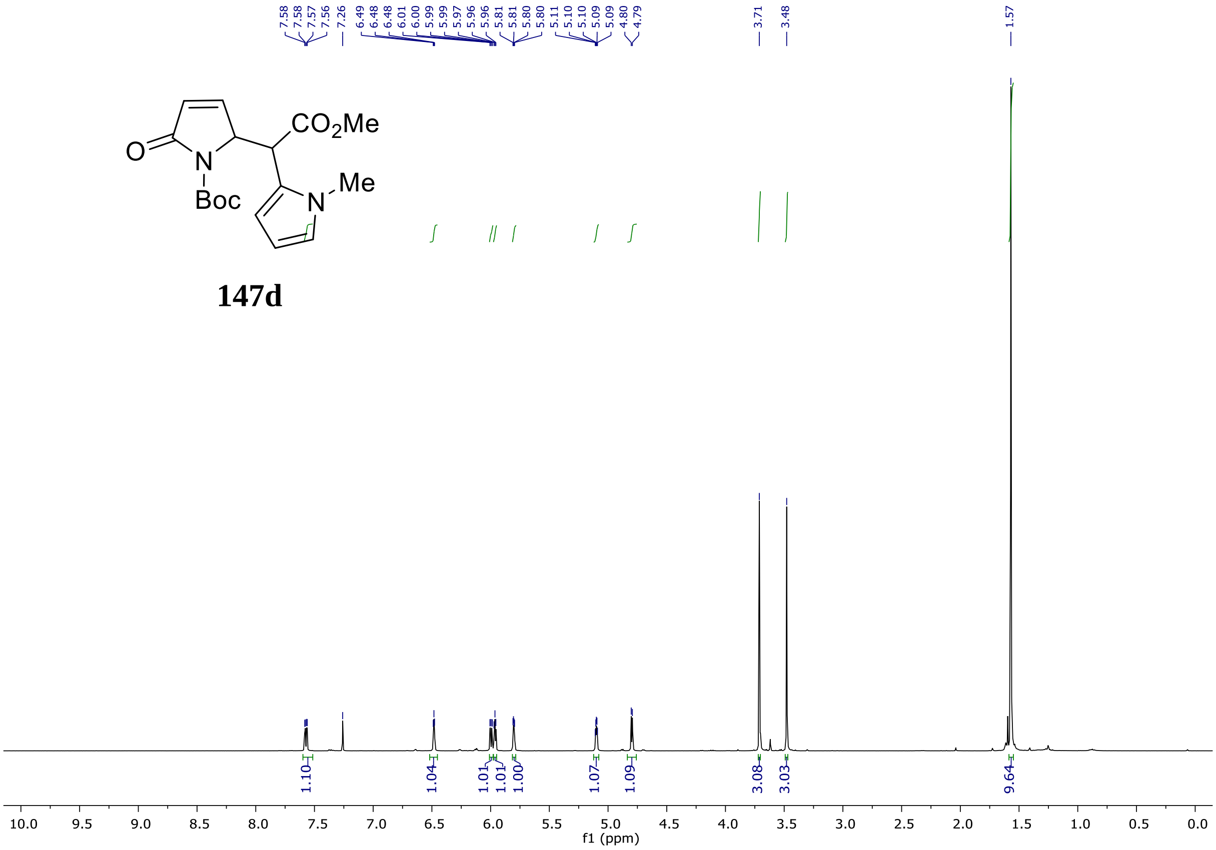
147´c

^{1}H NMR (400 MHz, CDCl$_3$)

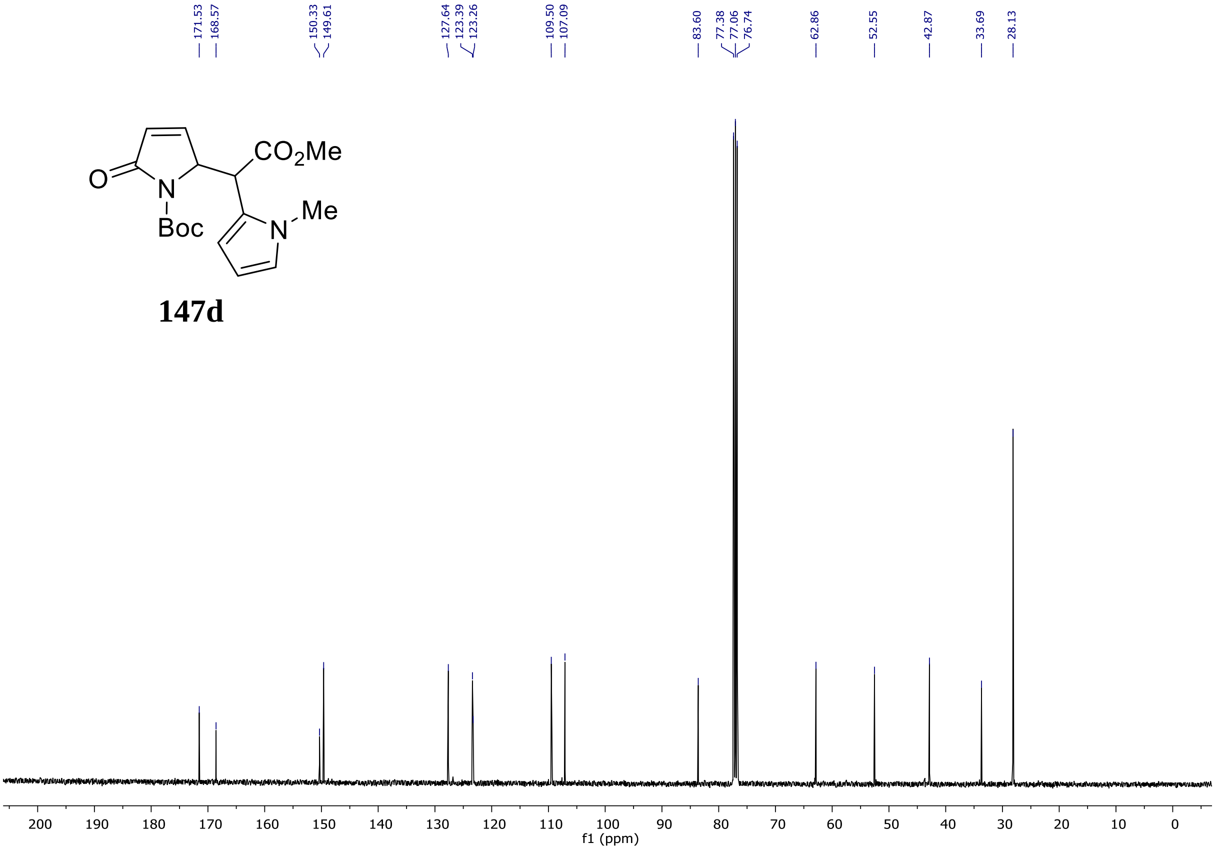


147´c

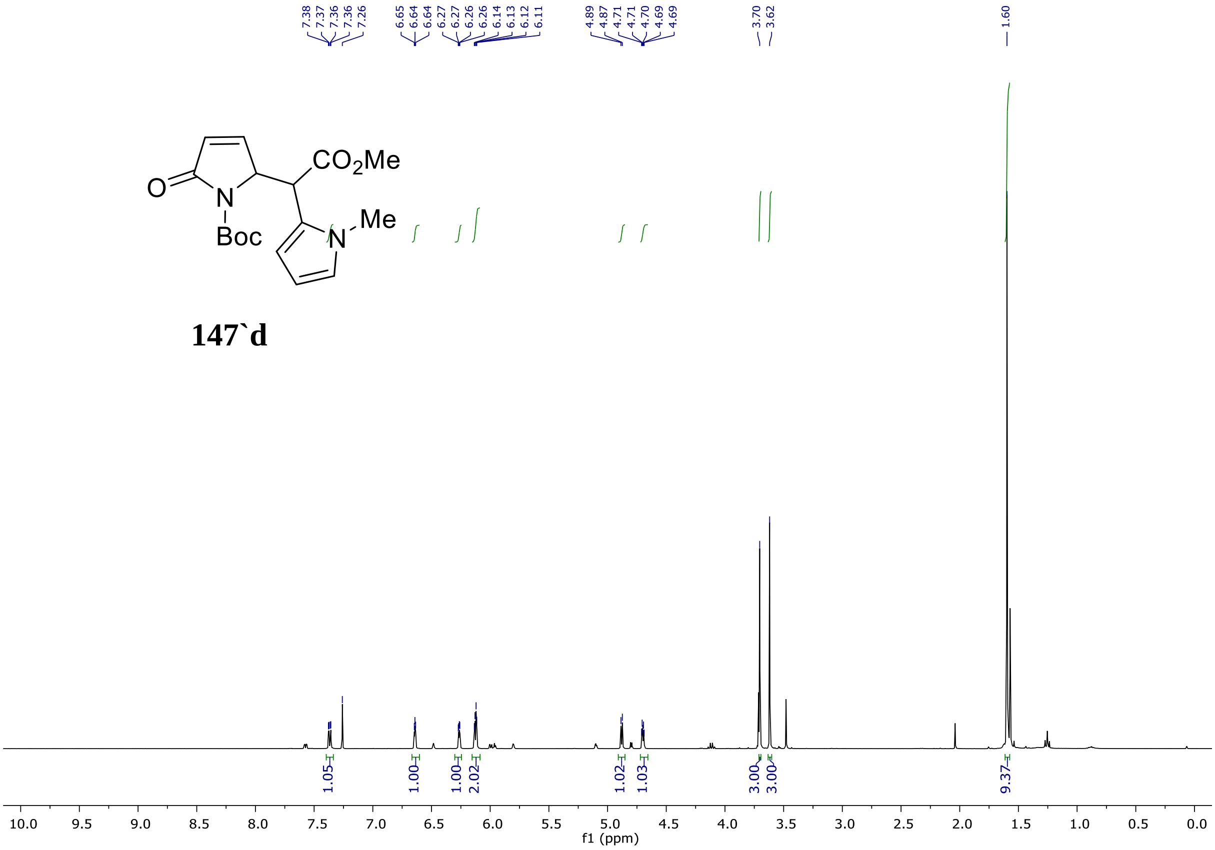
^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)

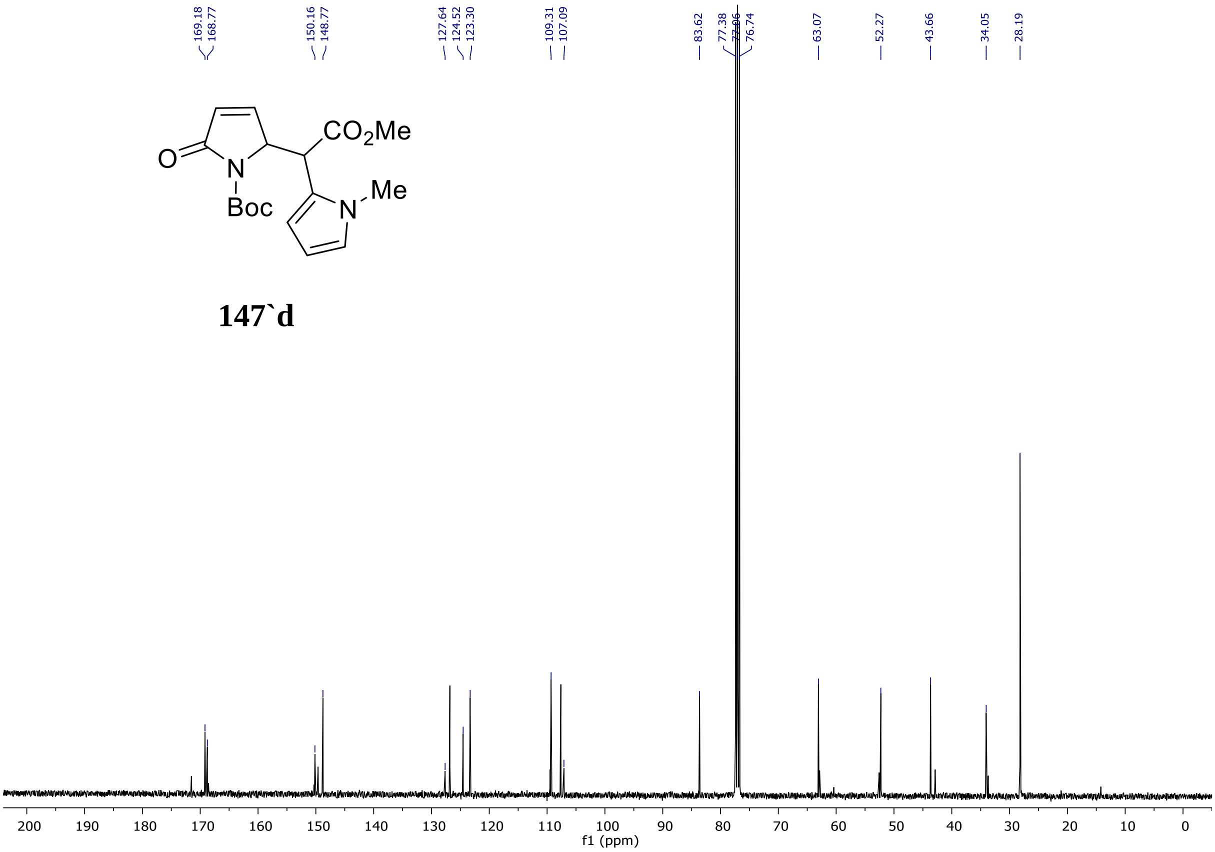


^{13}C NMR (101 MHz, CDCl$_3$)



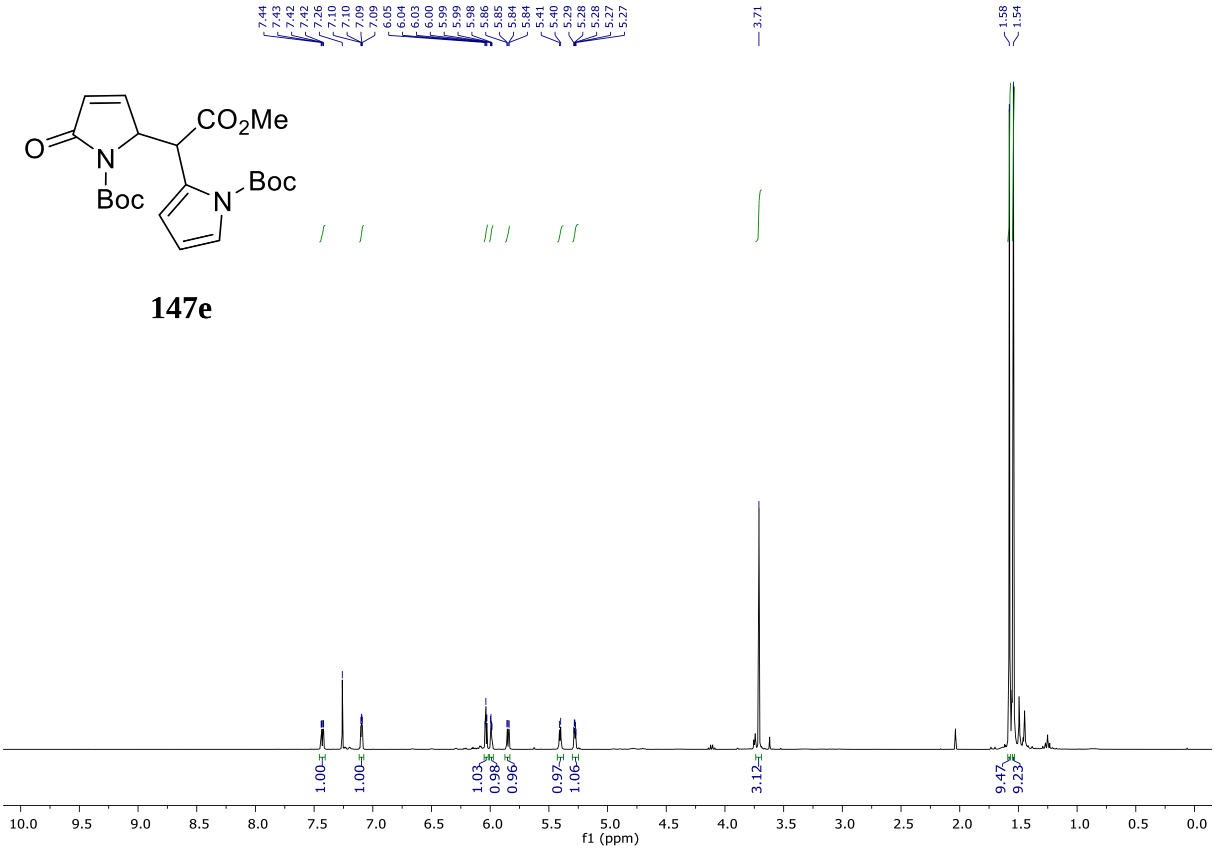
147`d

^{1}H NMR (400 MHz, CDCl$_3$)

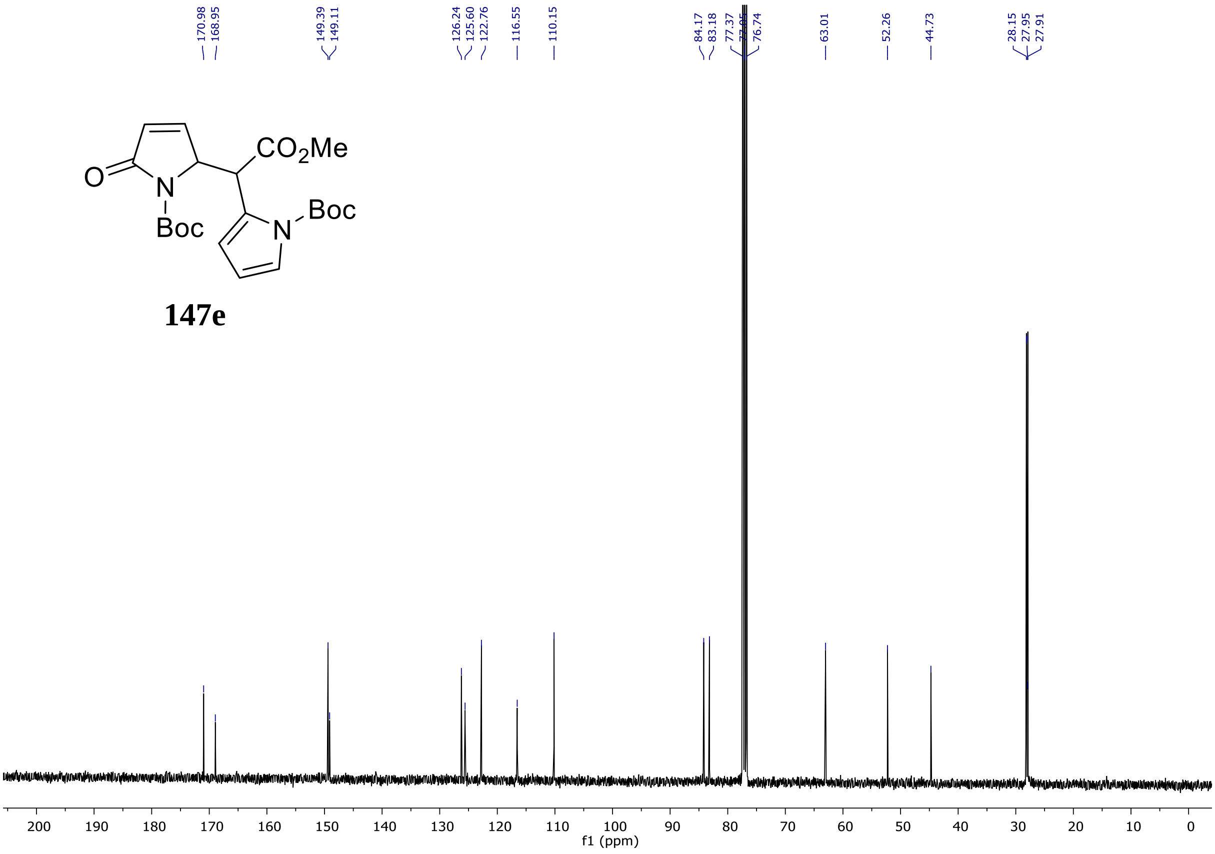


147`d

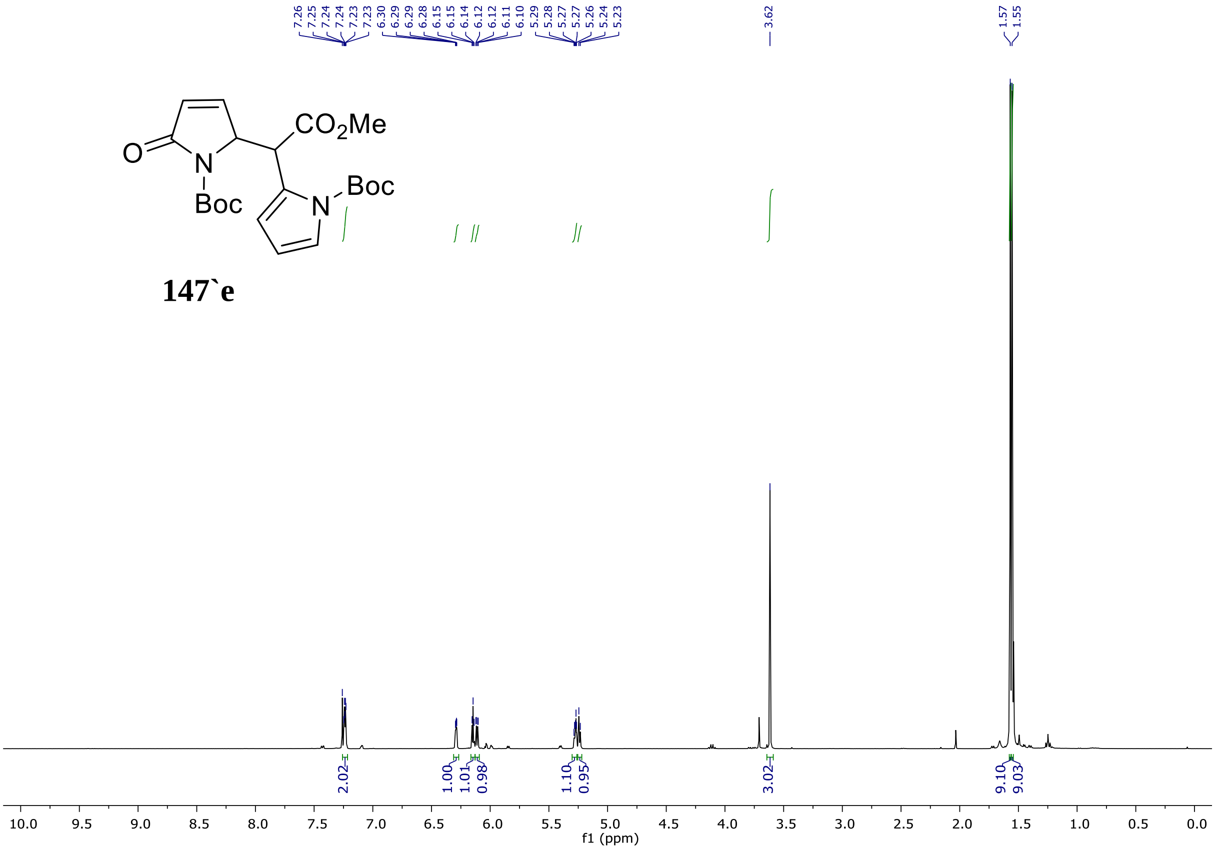
^{13}C NMR (101 MHz, CDCl$_3$)



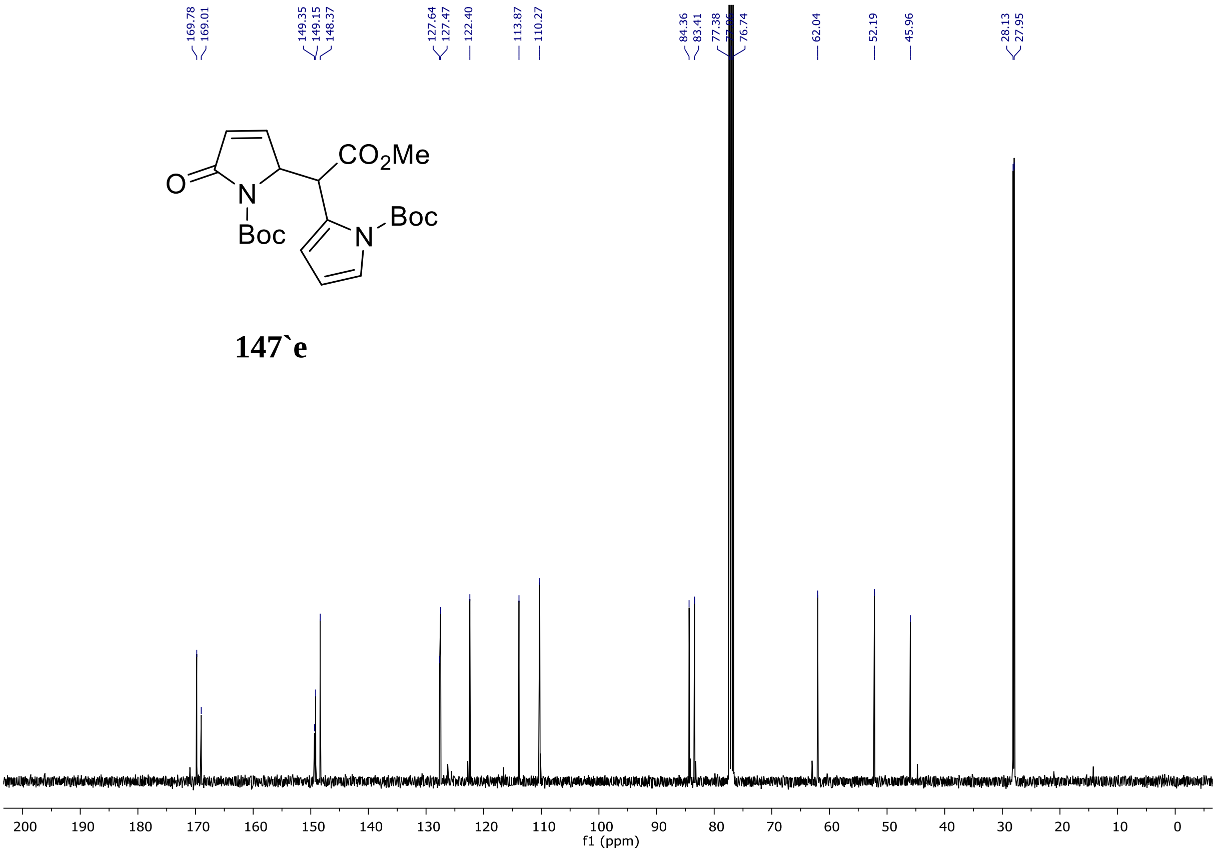
^{1}H NMR (400 MHz, CDCl$_3$)



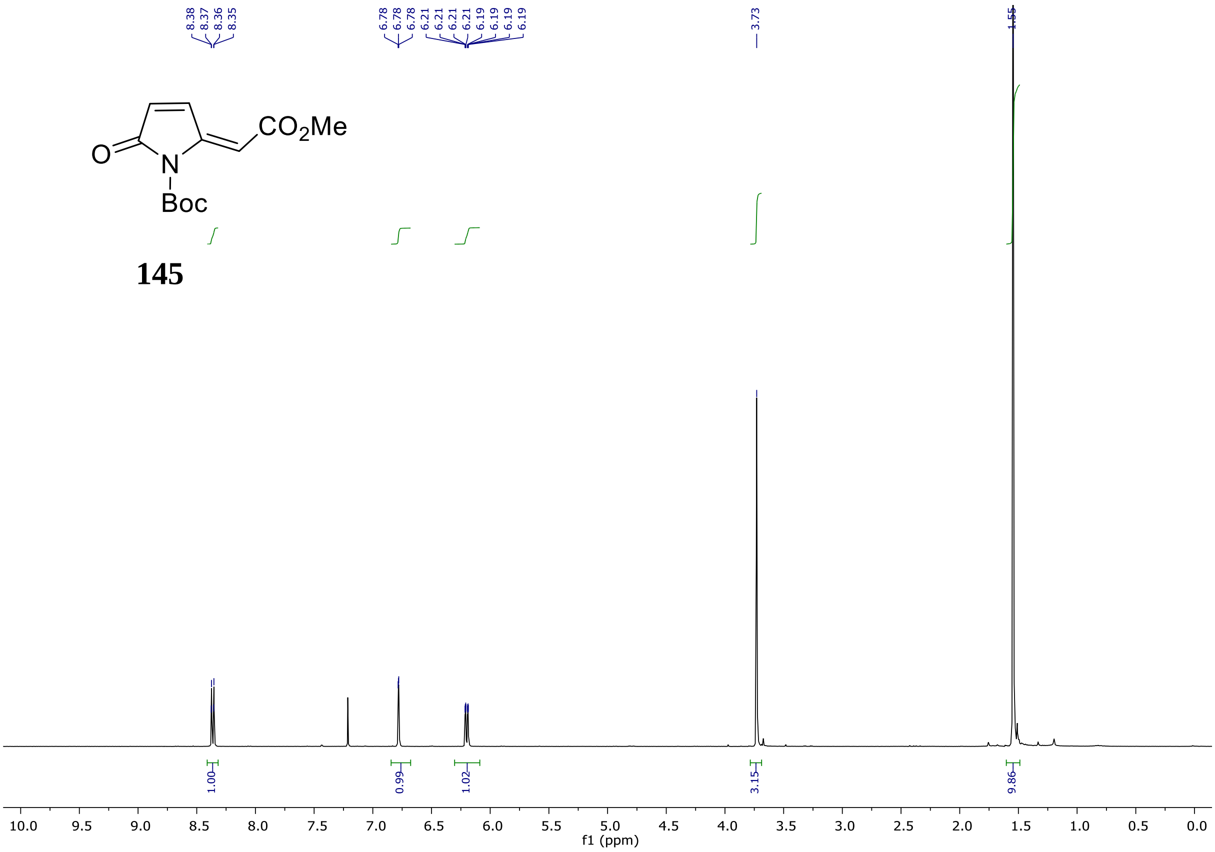
^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)

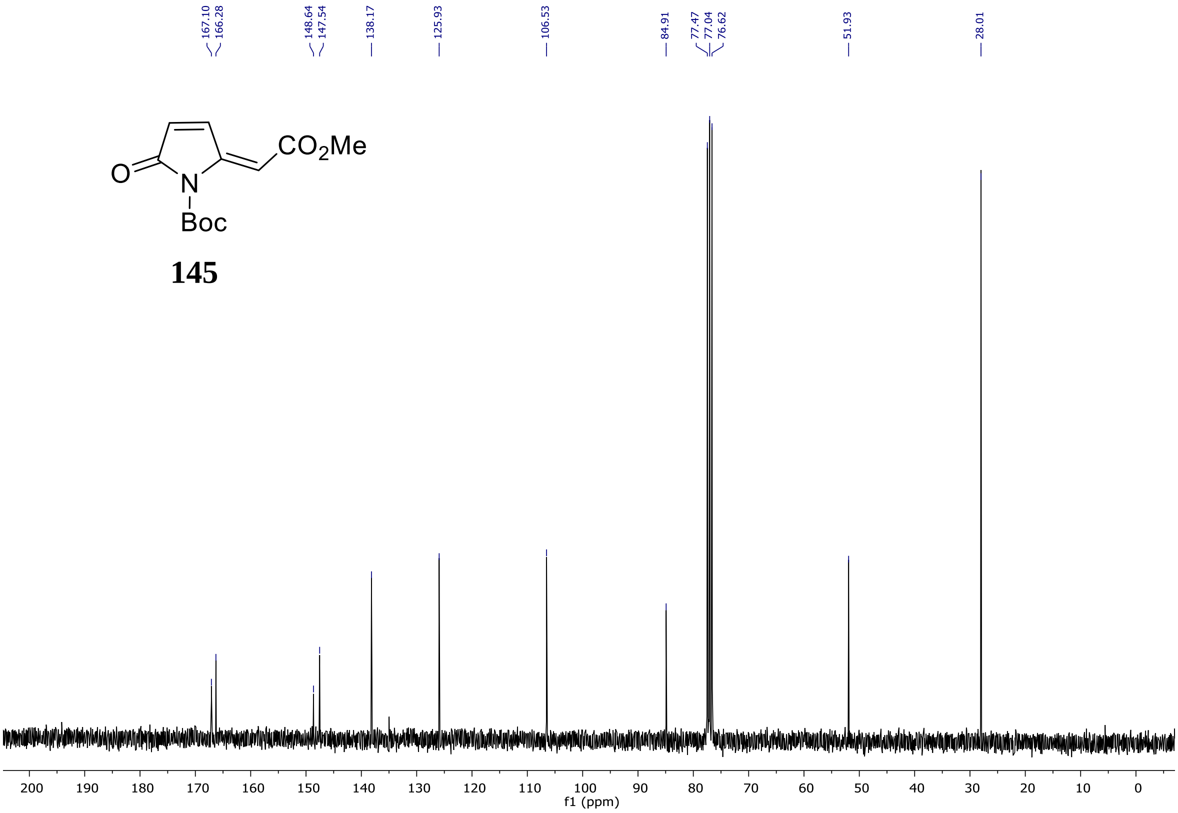


^{13}C NMR (101 MHz, CDCl$_3$)



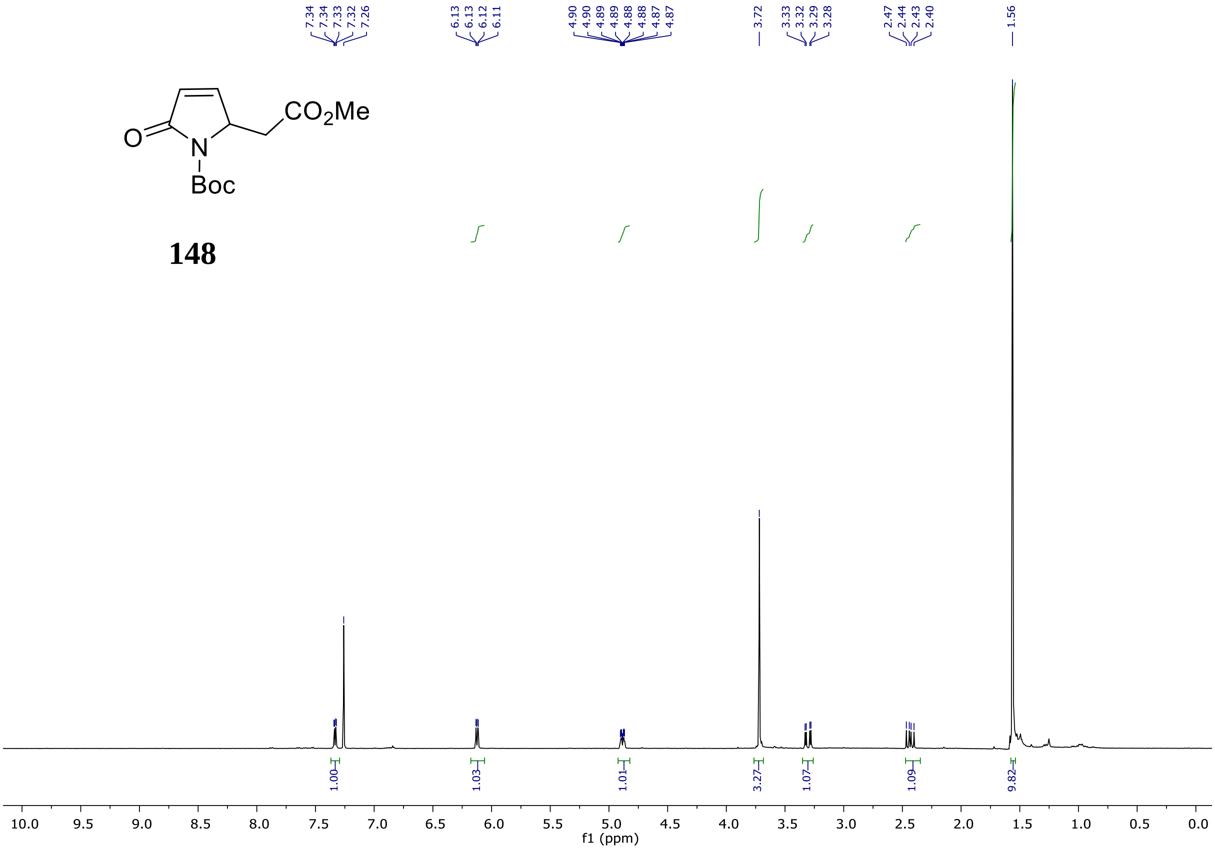
145

^{1}H NMR (400 MHz, CDCl$_3$)



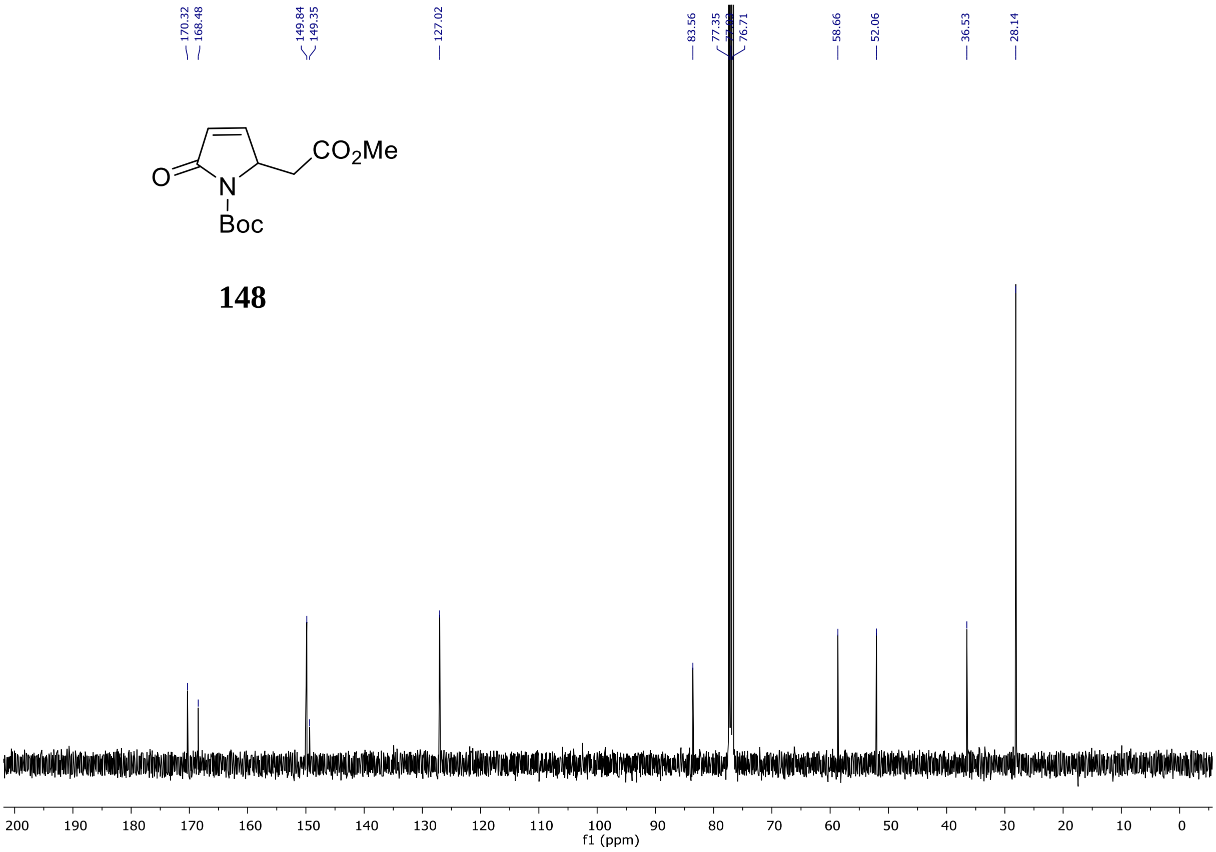
145

^{13}C NMR (101 MHz, CDCl$_3$)



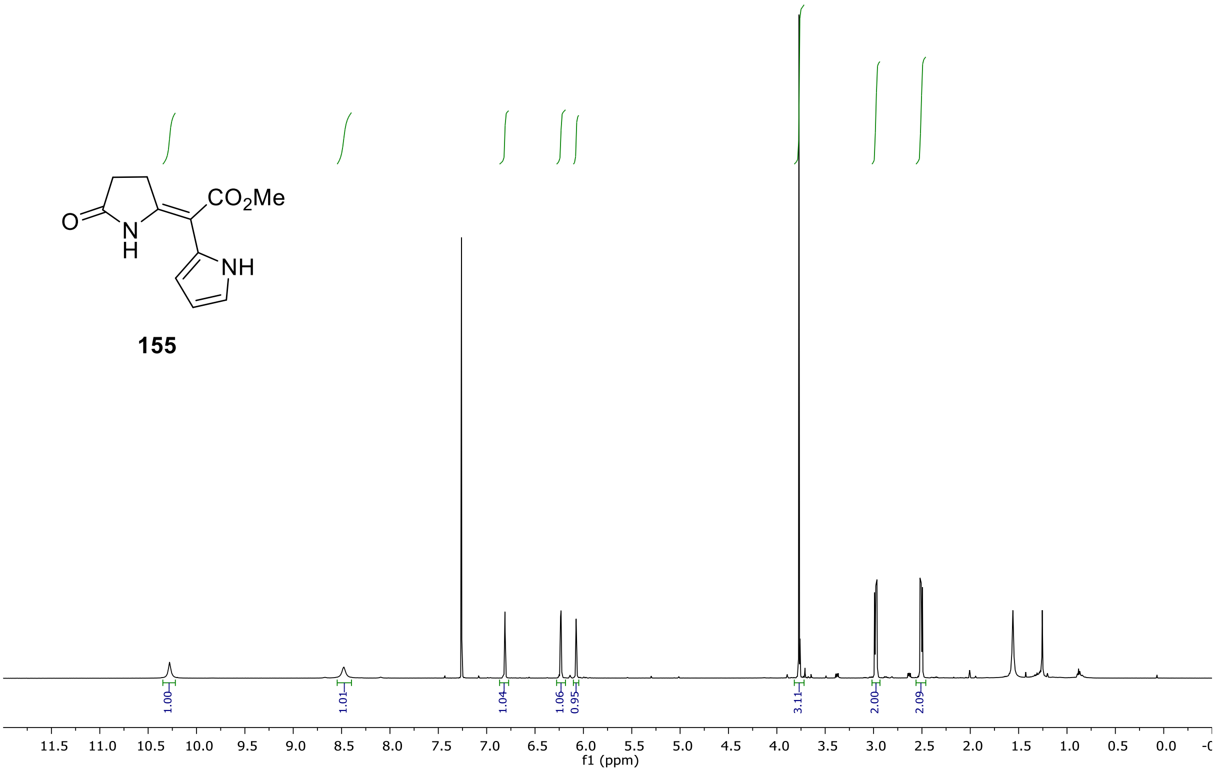
148

^{1}H NMR (400 MHz, CDCl$_3$)

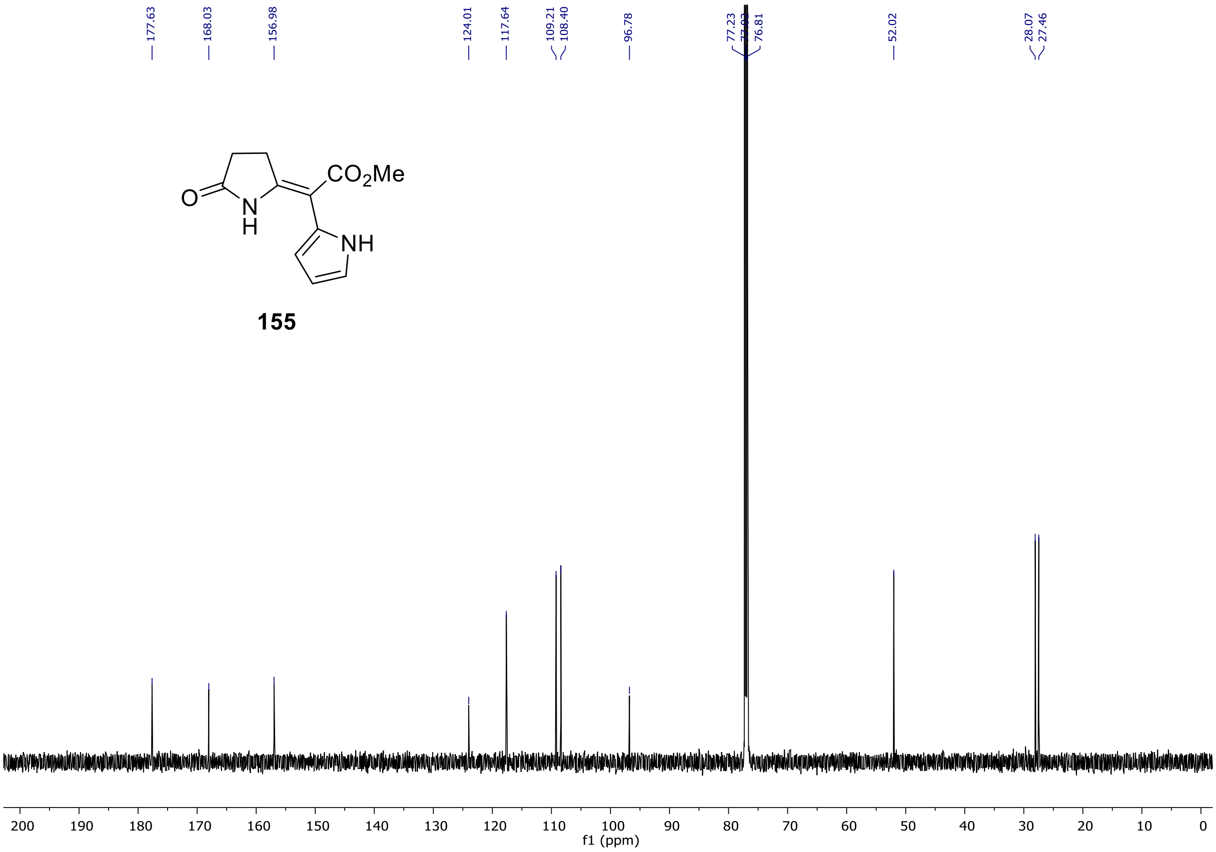


148

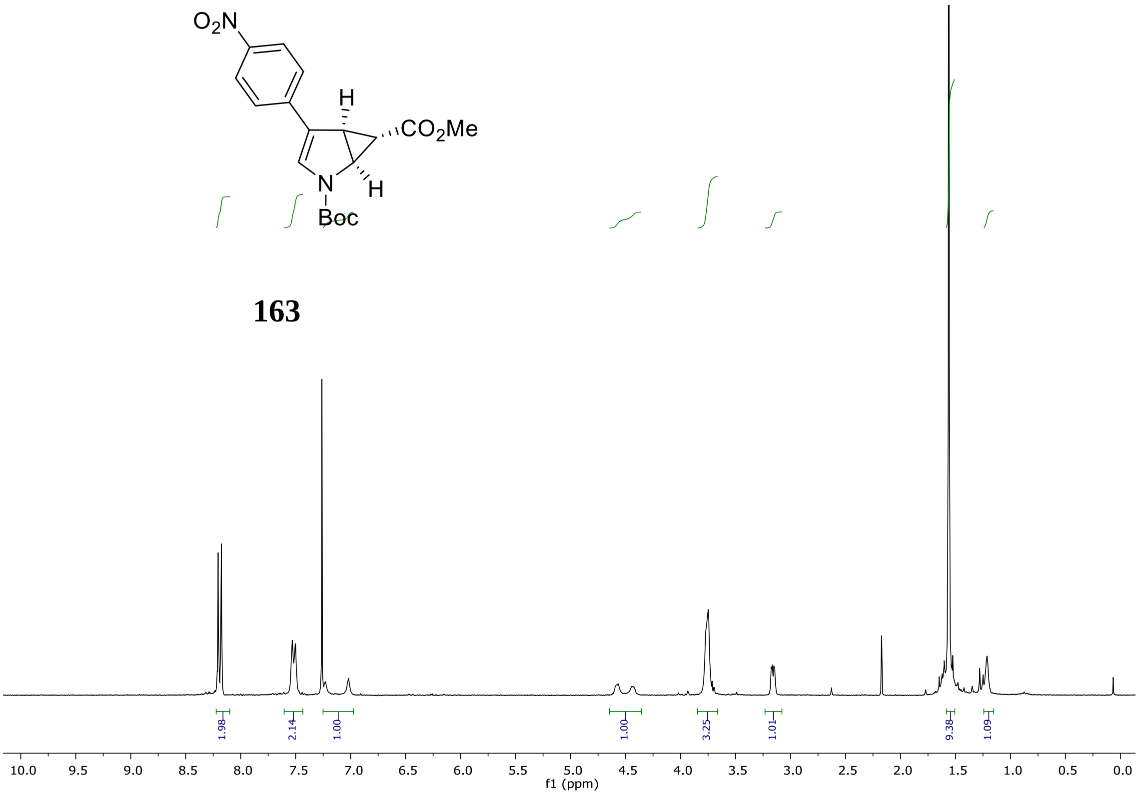
^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (600 MHz, CDCl$_3$)

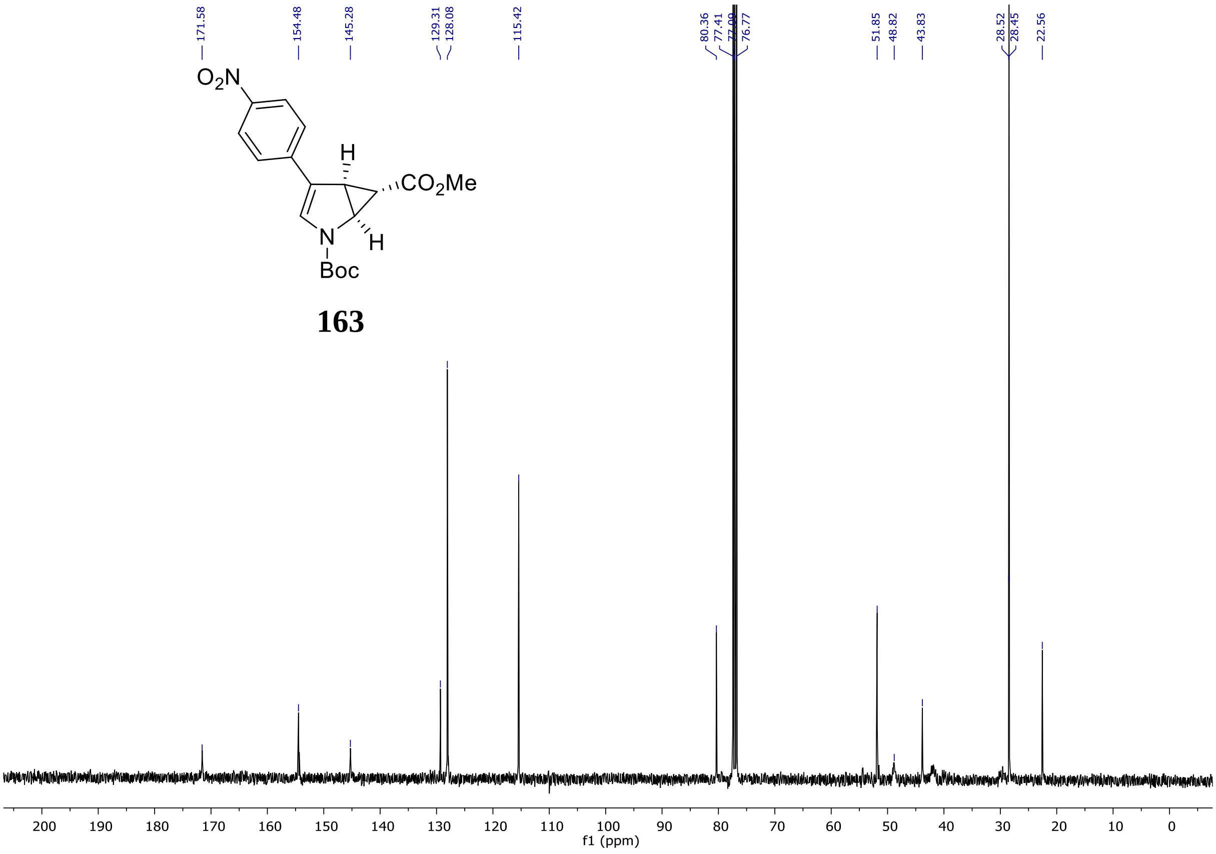


^{13}C NMR (101 MHz, CDCl$_3$)



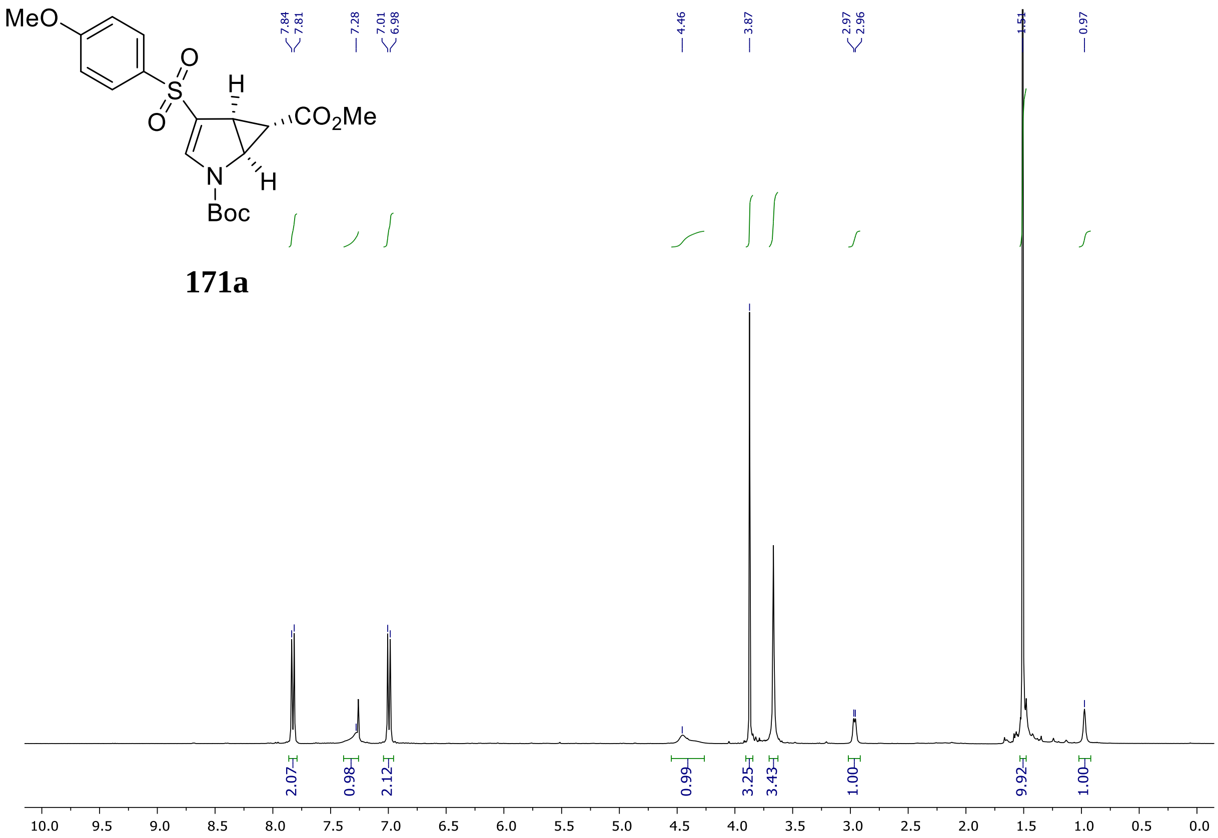
163

^{1}H NMR (300 MHz, CDCl$_3$)



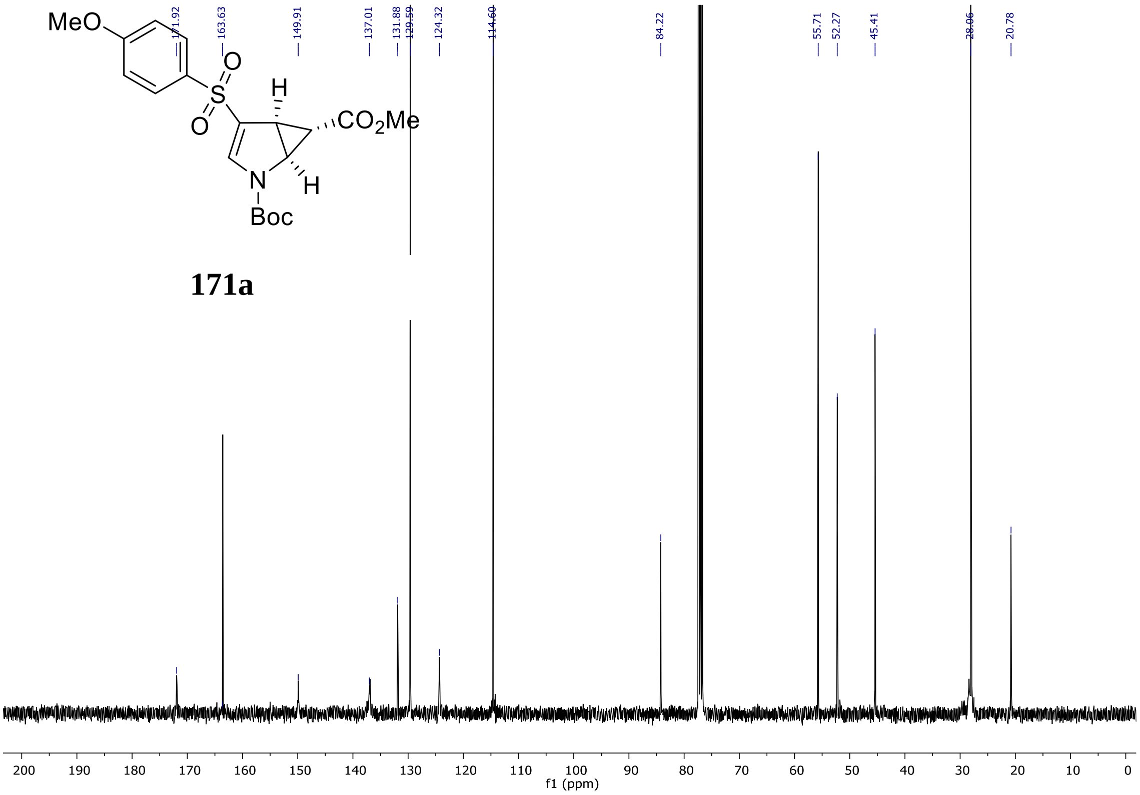
163

^{13}C NMR (101 MHz, CDCl$_3$)



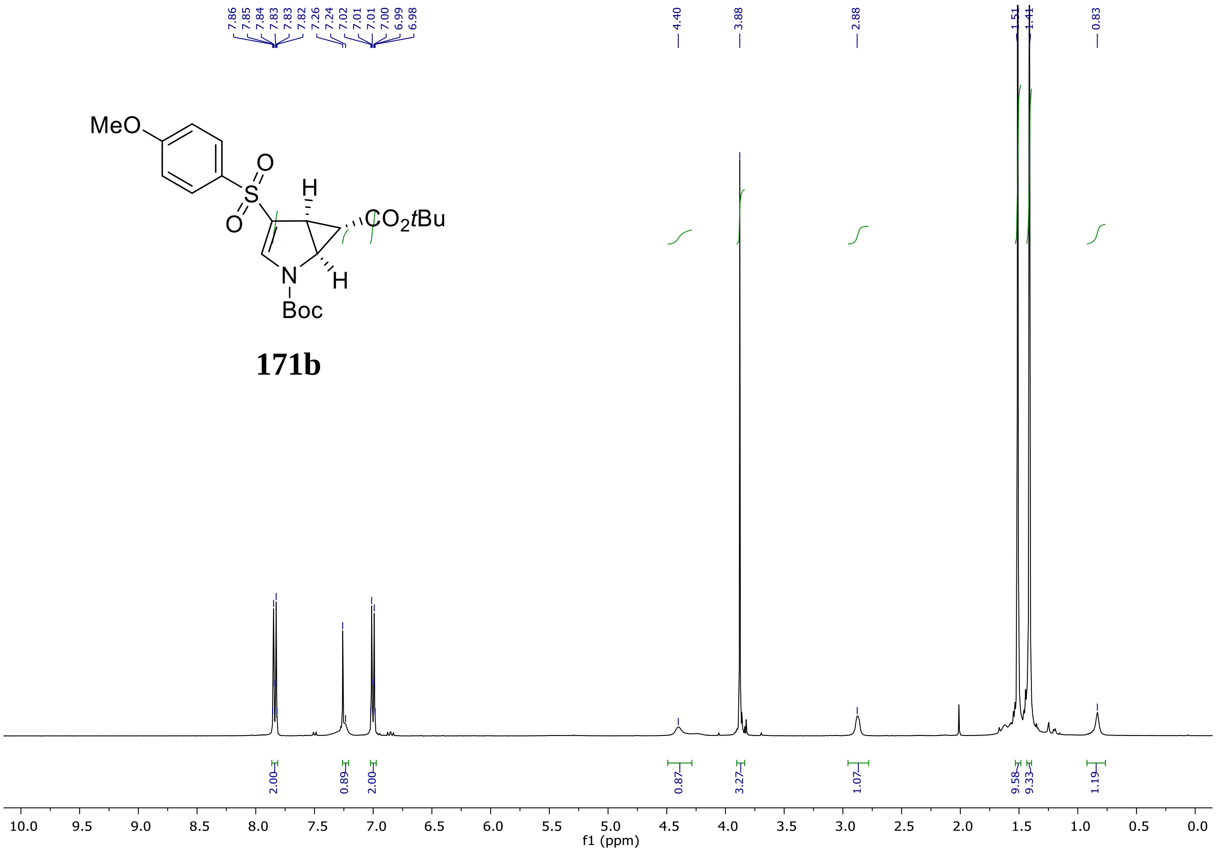
171a

^{1}H NMR (400 MHz, CDCl$_3$)



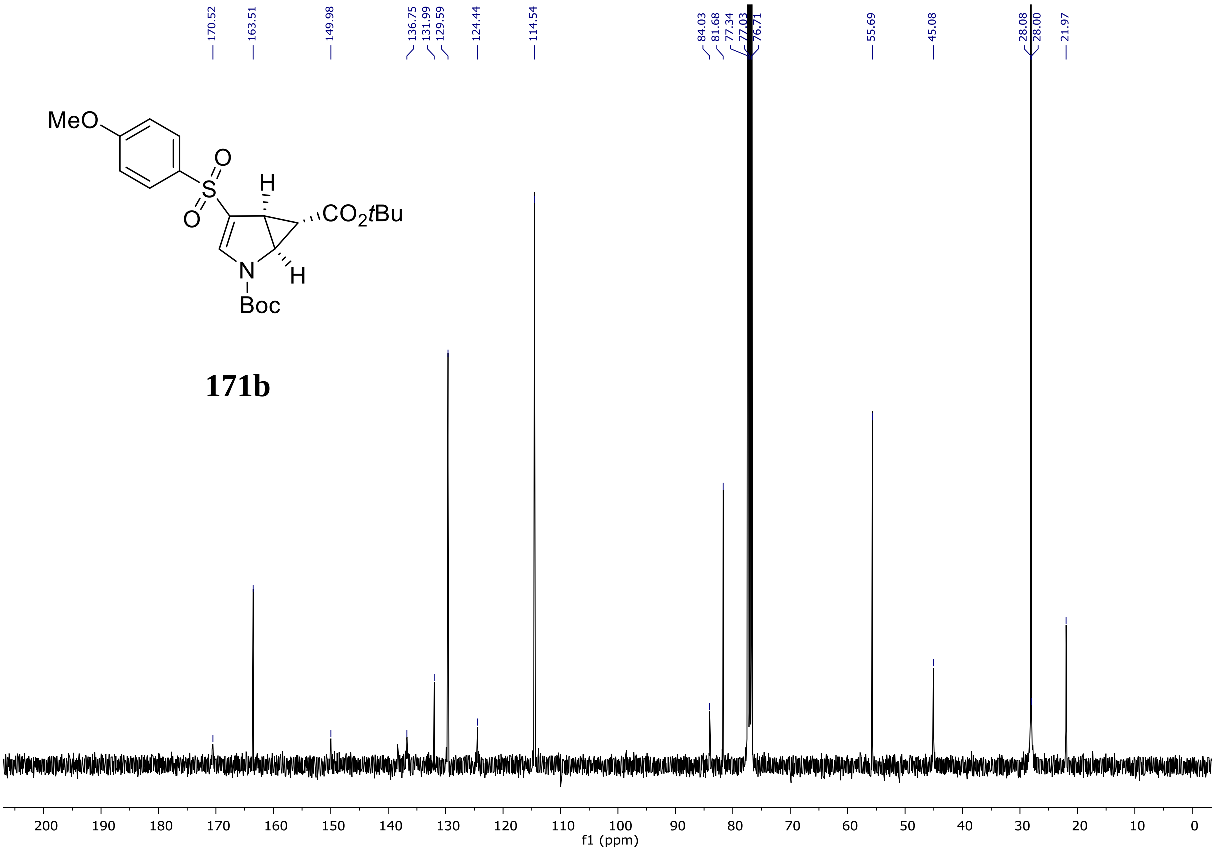
171a

^{13}C NMR (101 MHz, CDCl$_3$)



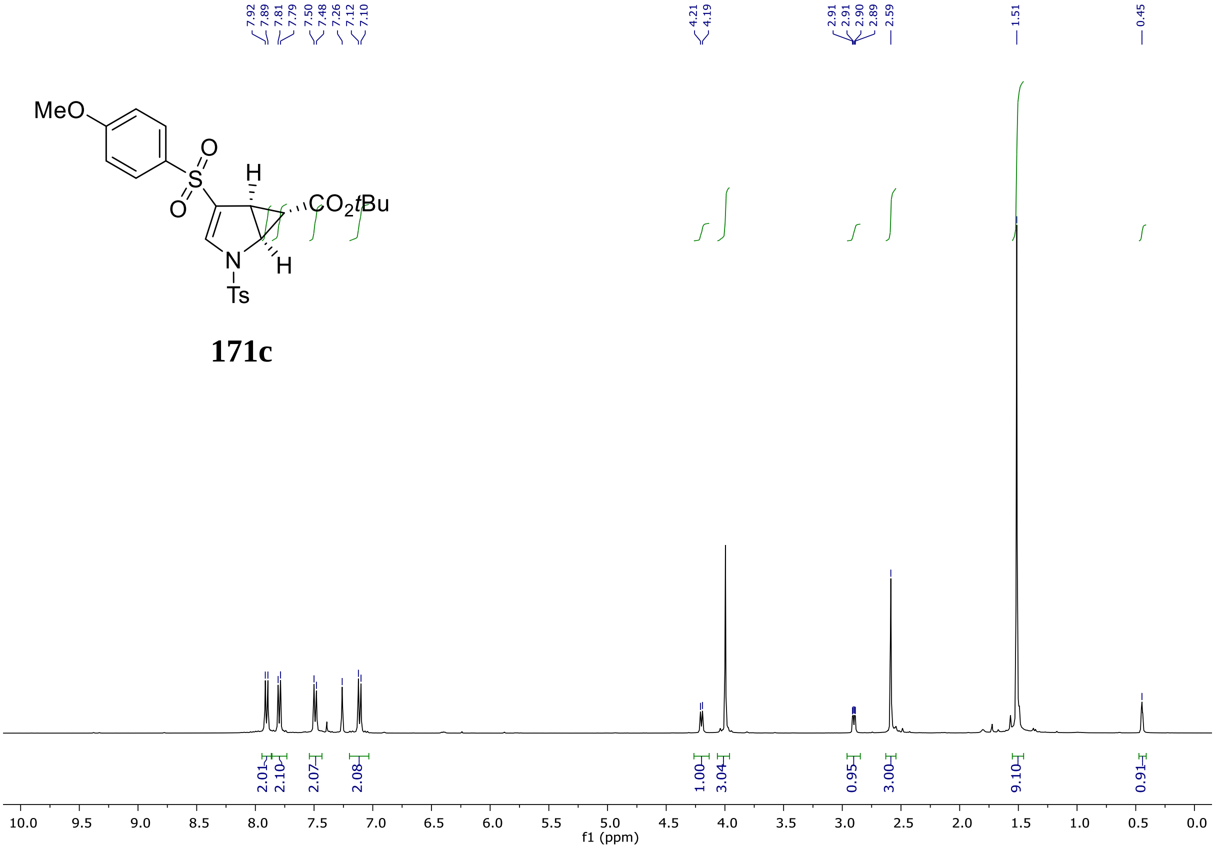
171b

^{1}H NMR (400 MHz, CDCl$_3$)



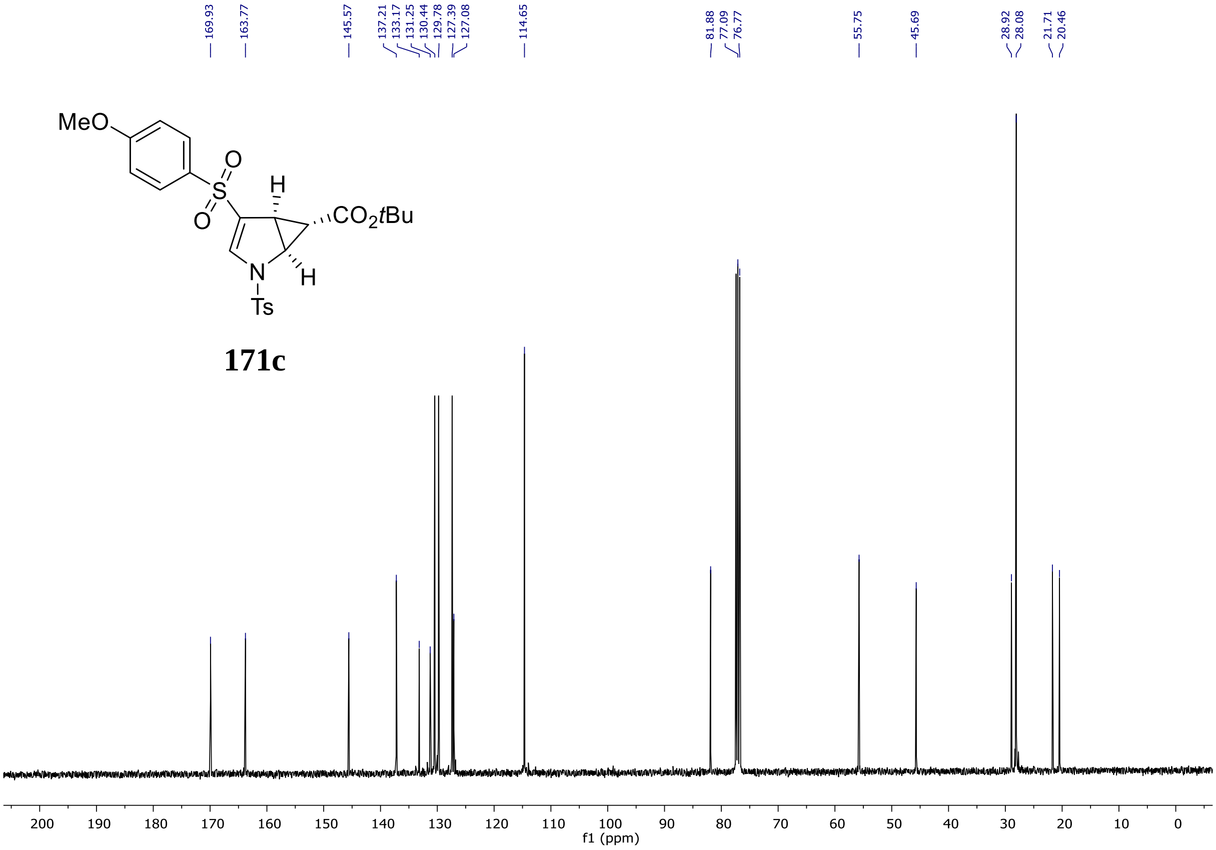
171b

^{13}C NMR (101 MHz, CDCl$_3$)



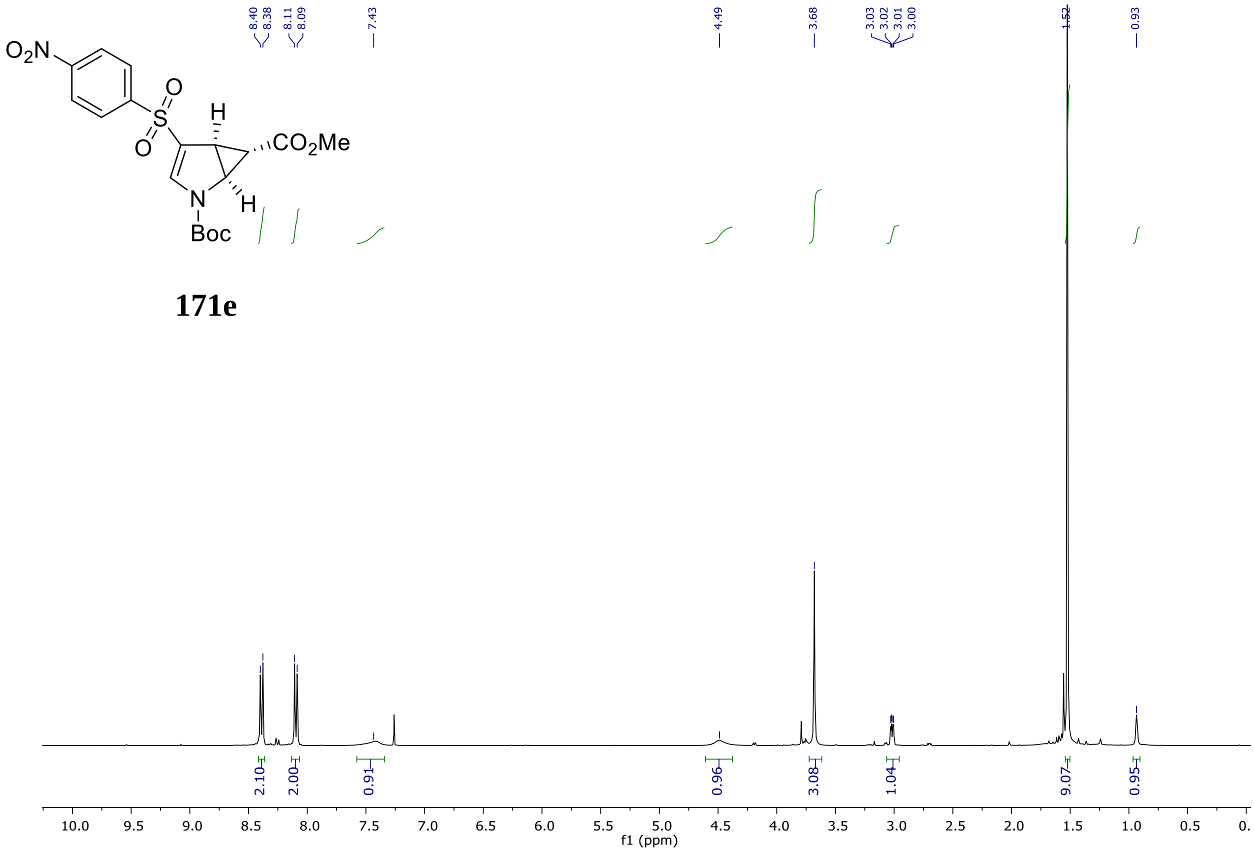
171c

^{1}H NMR (400 MHz, CDCl$_3$)

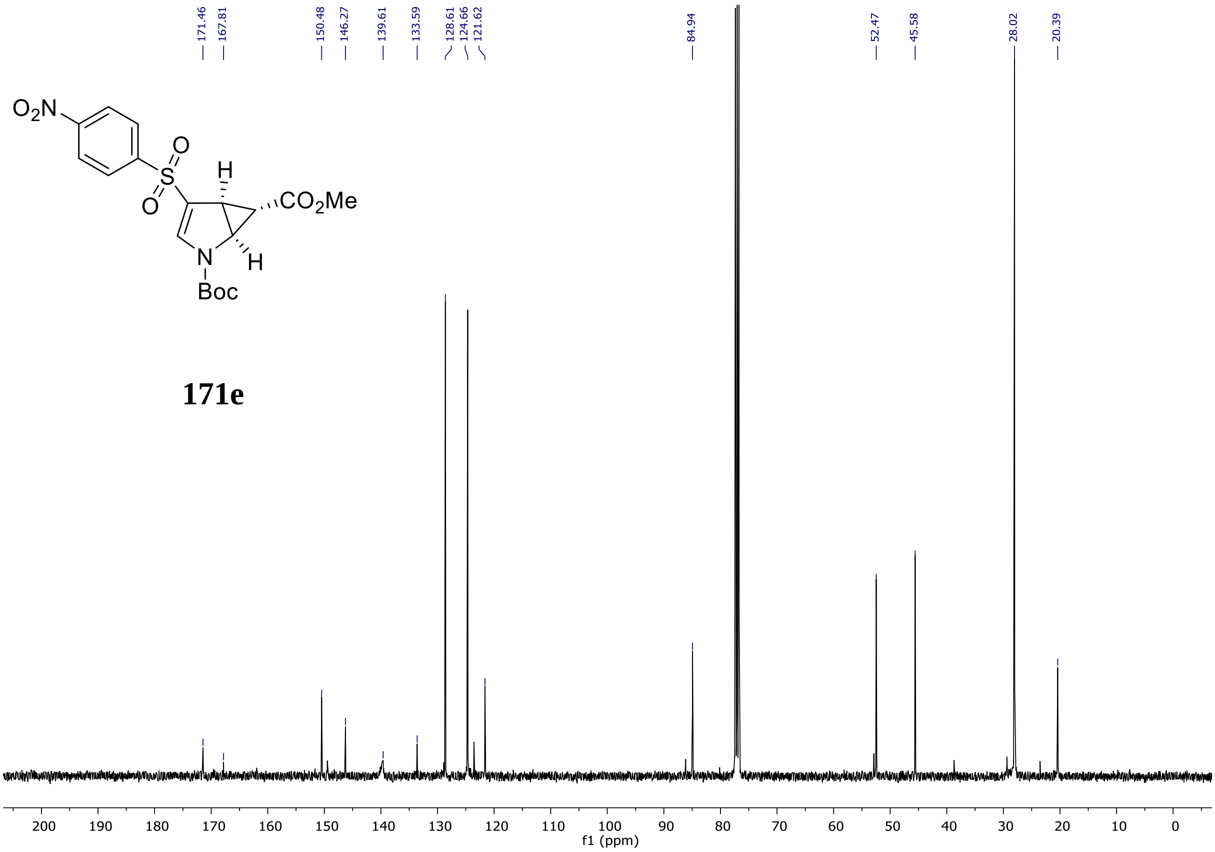


171c

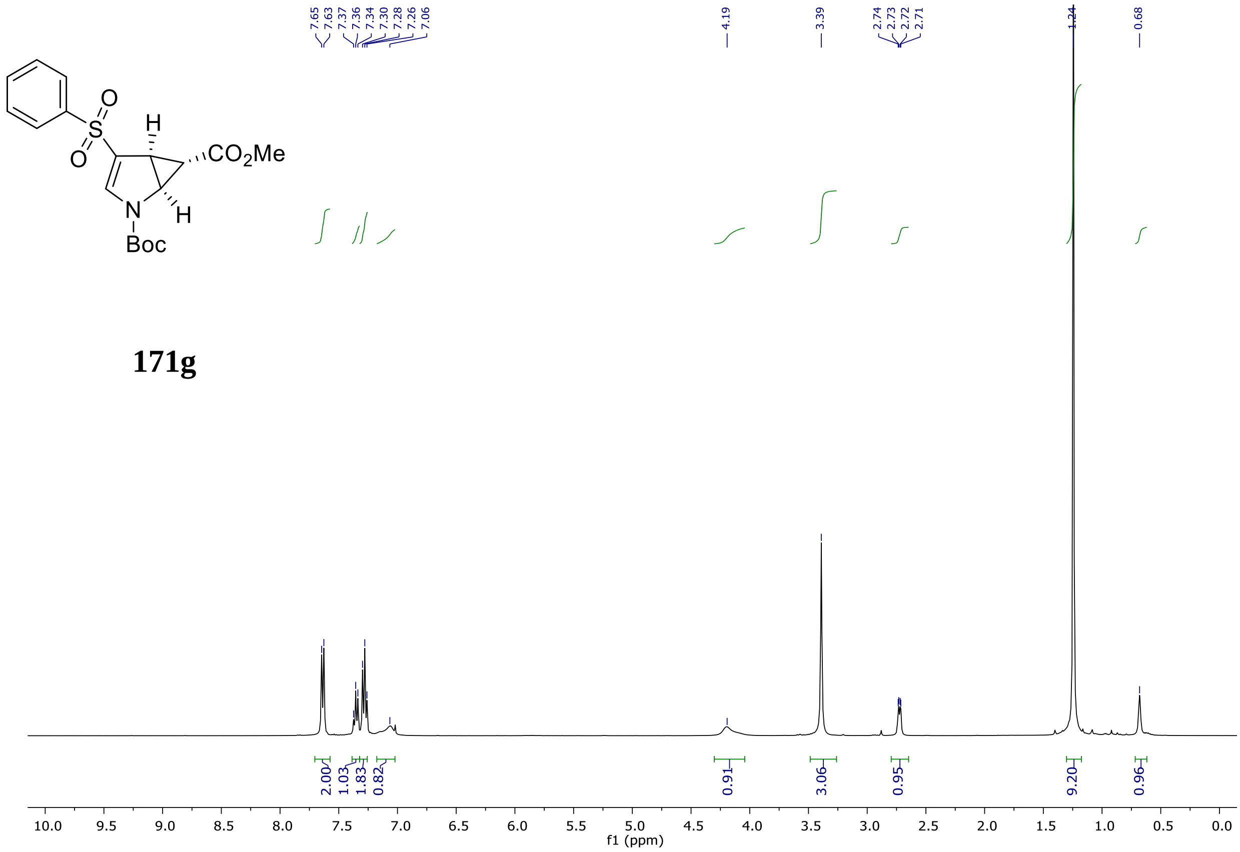
^{13}C NMR (101 MHz, CDCl$_3$)



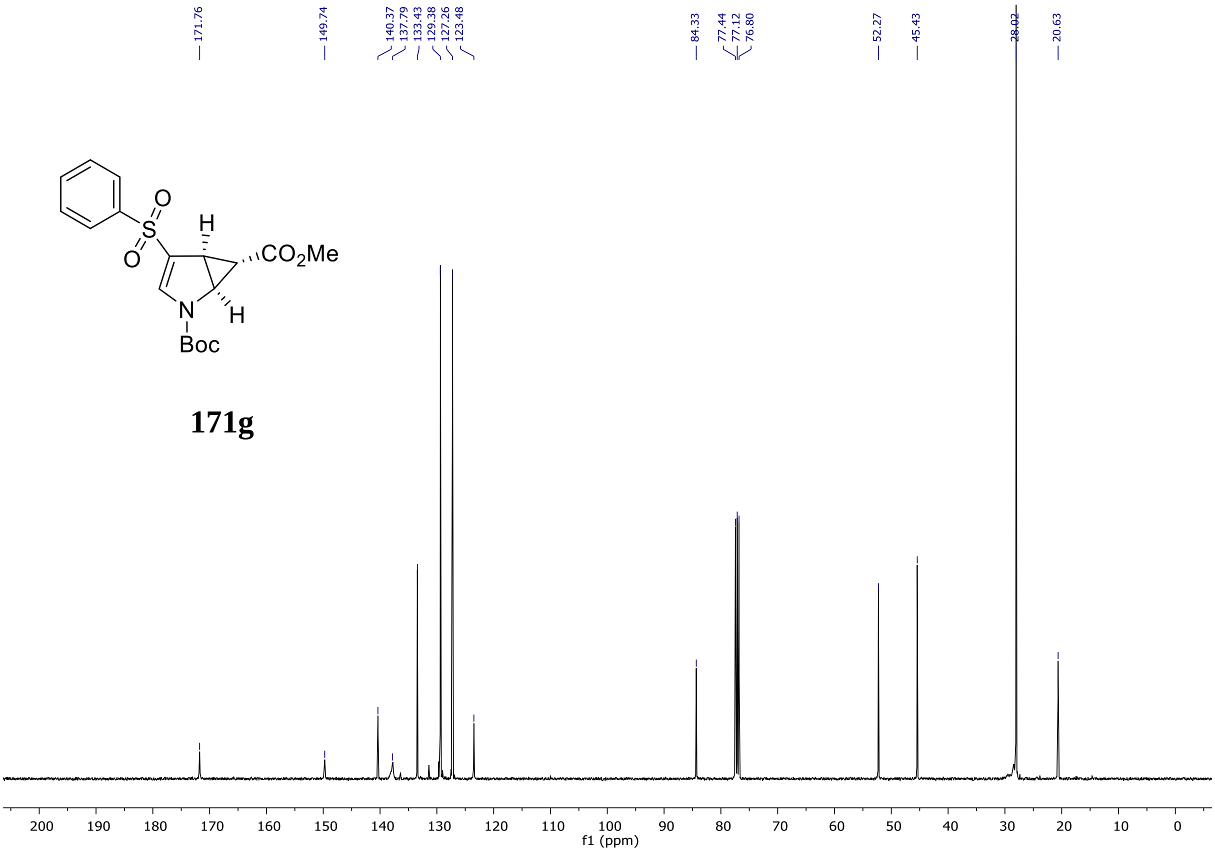
^{1}H NMR (400 MHz, CDCl$_3$)



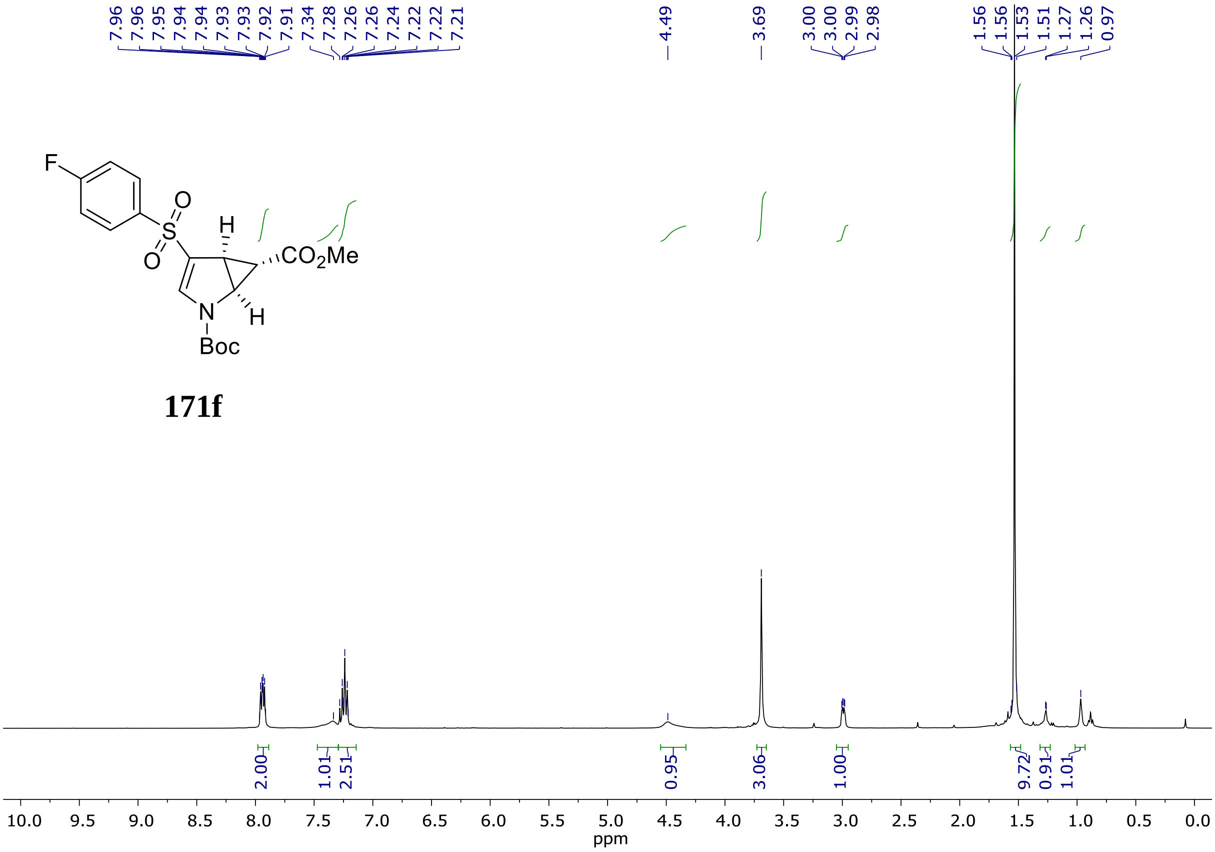
^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)

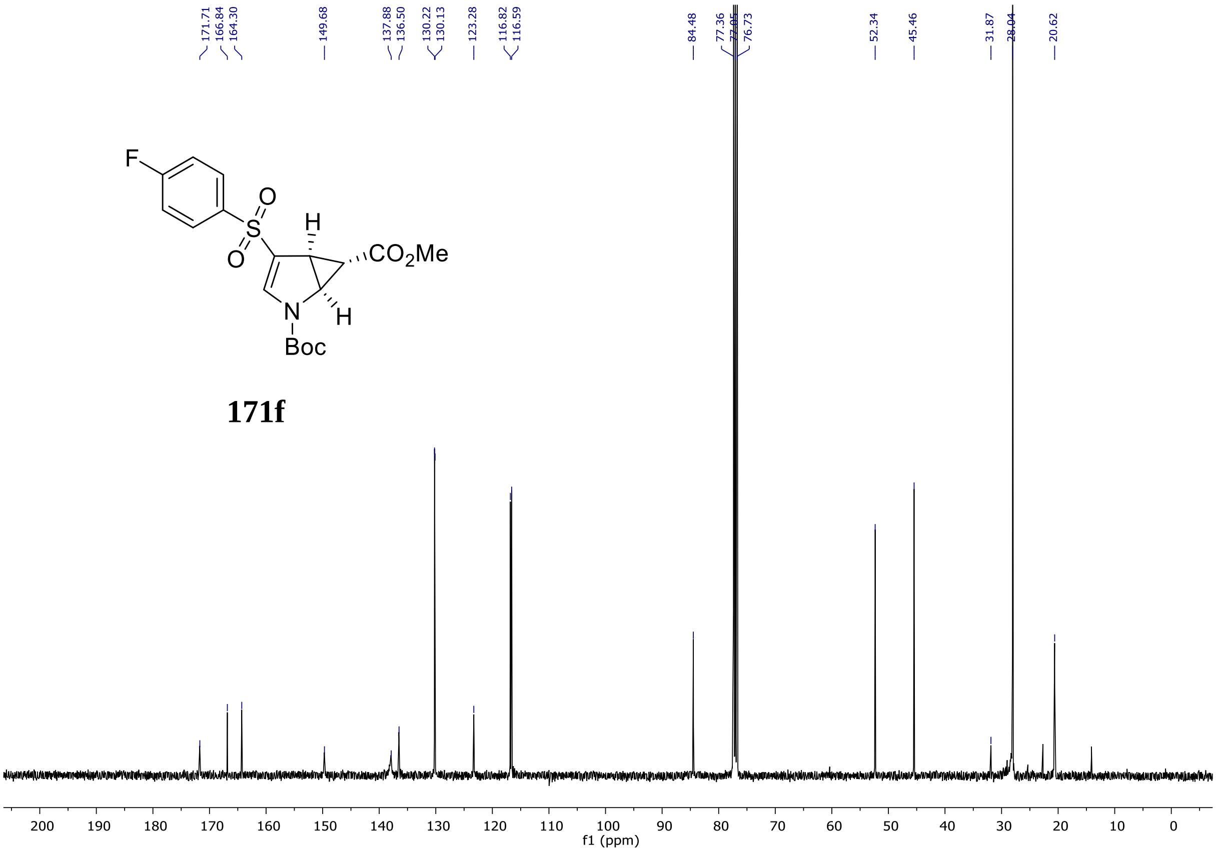


^{13}C NMR (101 MHz, CDCl$_3$)



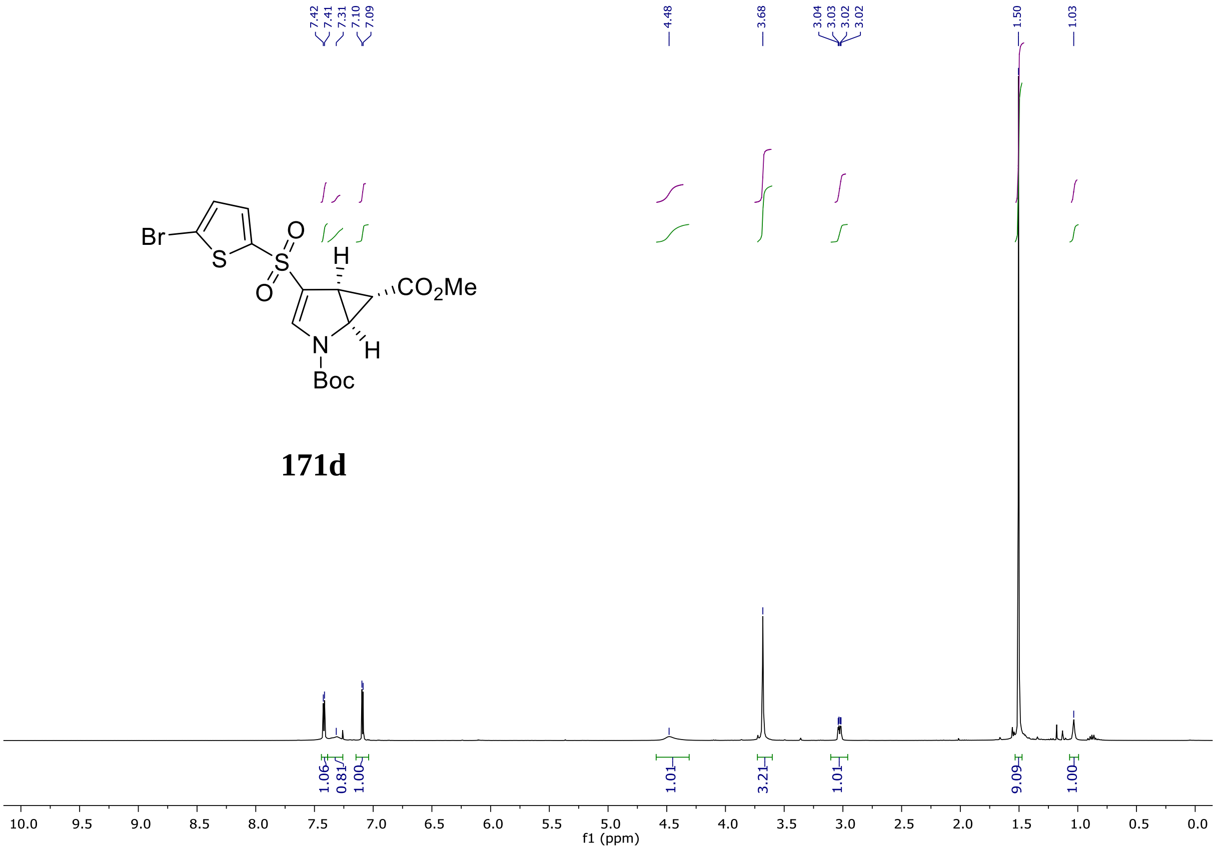
171f

^{1}H NMR (400 MHz, CDCl$_3$)

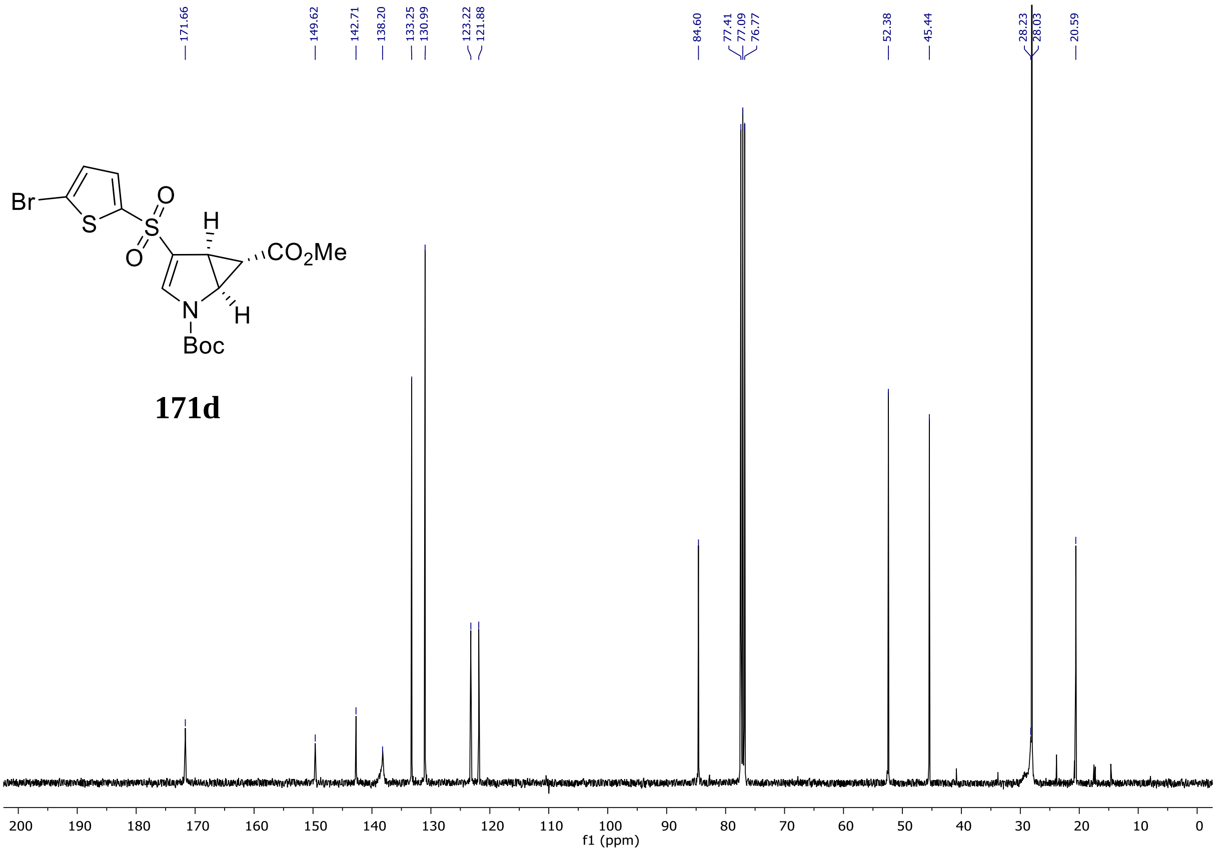


171f

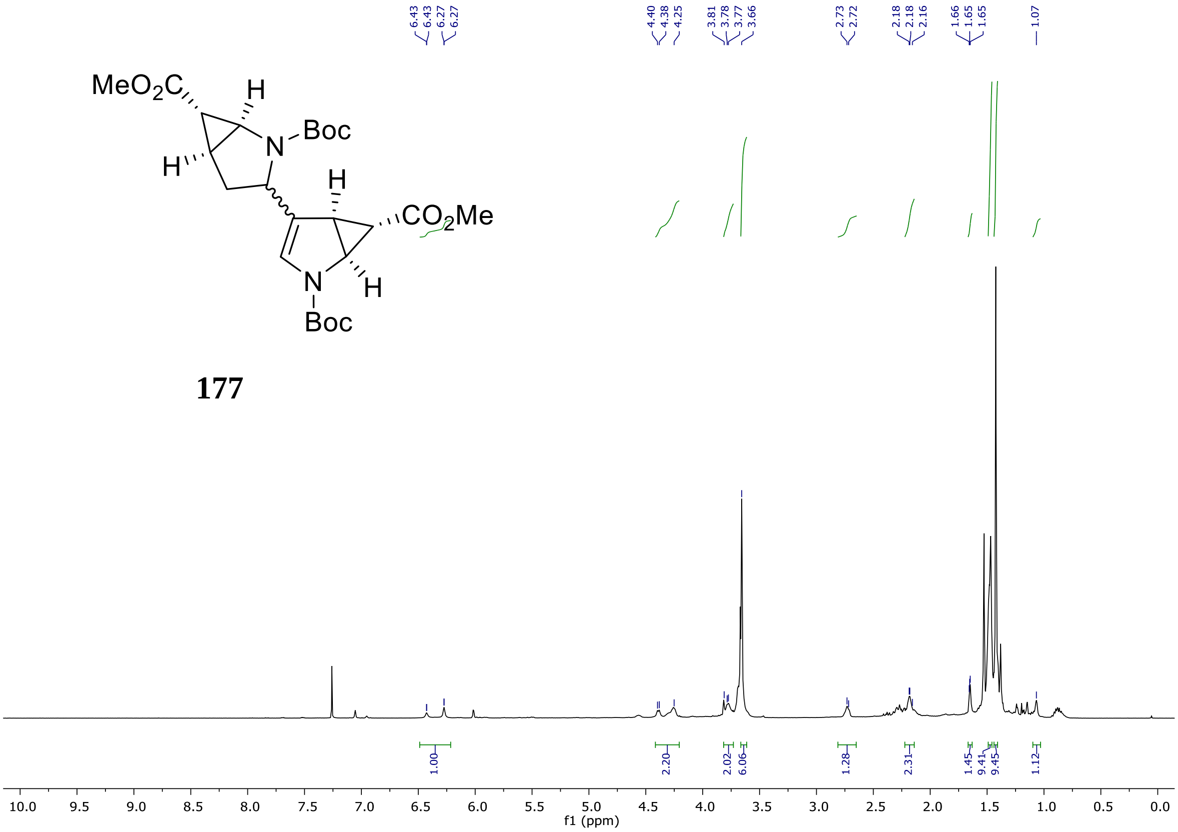
^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)

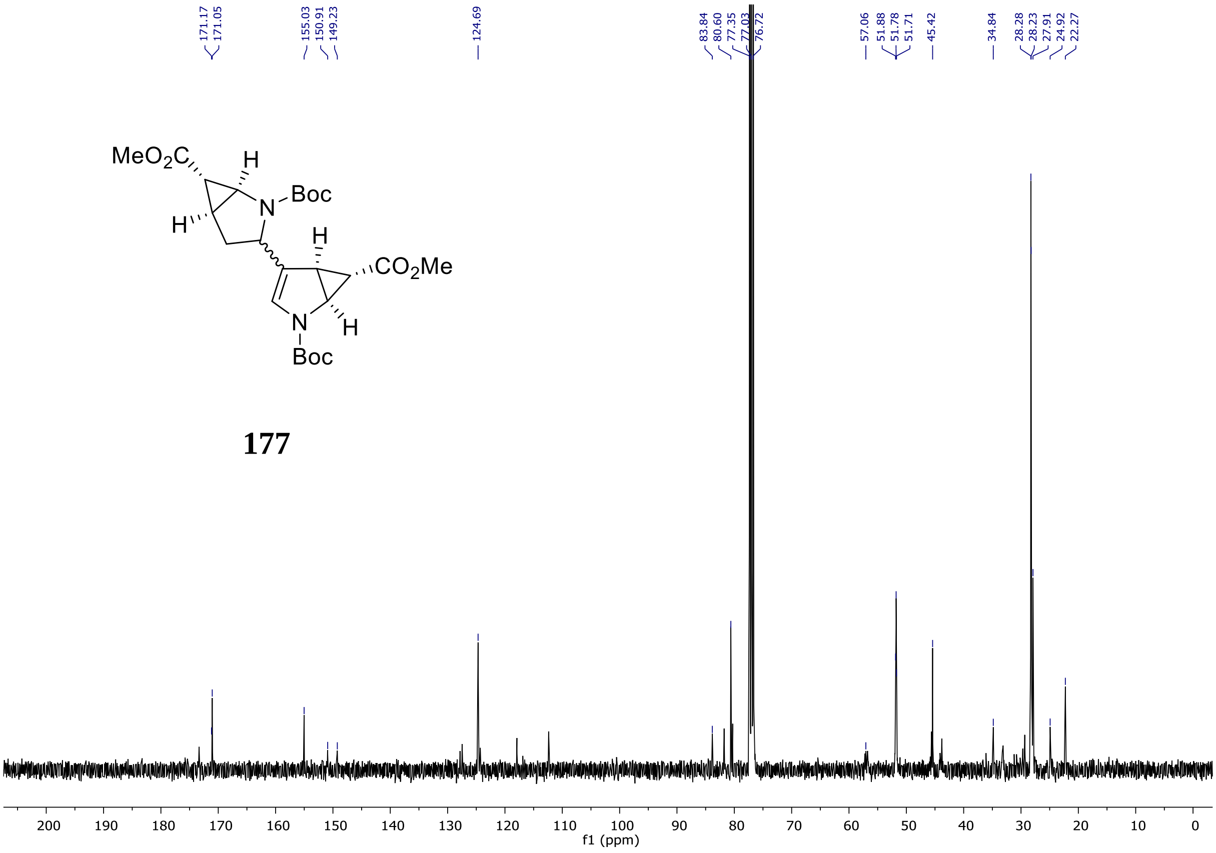


^{13}C NMR (101 MHz, CDCl$_3$)



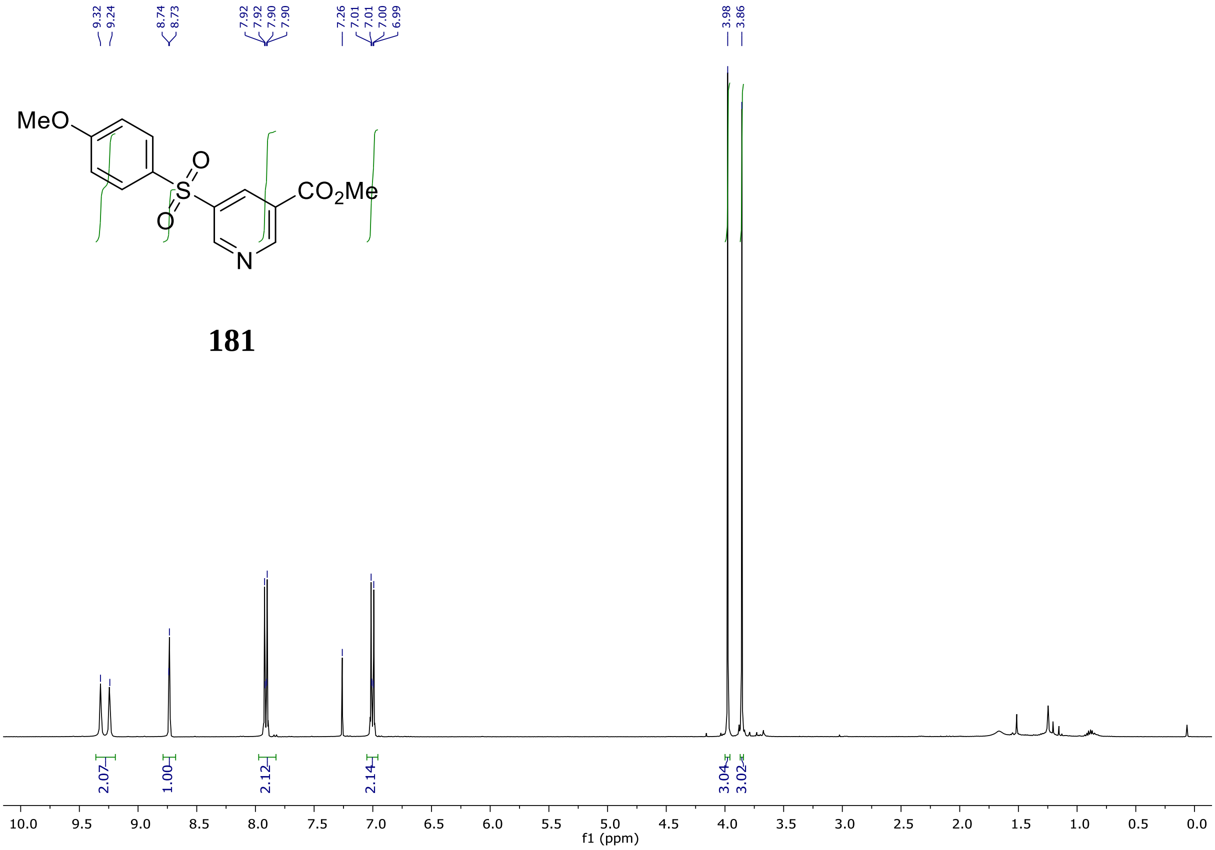
177

^{1}H NMR (300 MHz, CDCl$_3$)



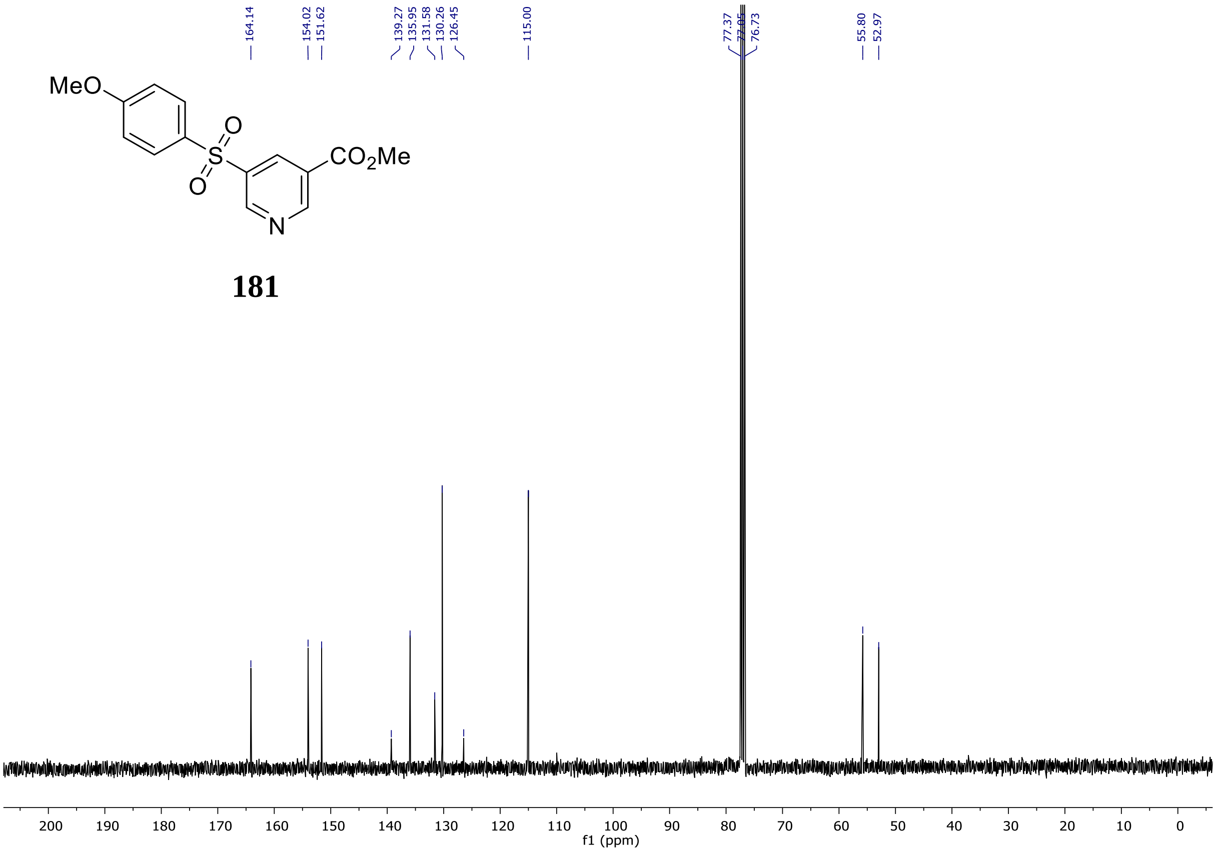
177

^{13}C NMR (101 MHz, CDCl$_3$)



181

^{1}H NMR (300 MHz, CDCl$_3$)

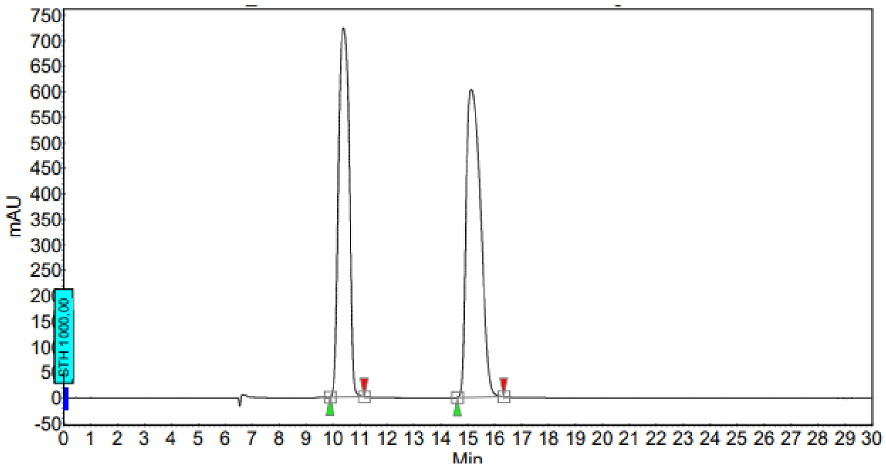


181

^{13}C NMR (101 MHz, CDCl$_3$)

2. HPLC chromatograms

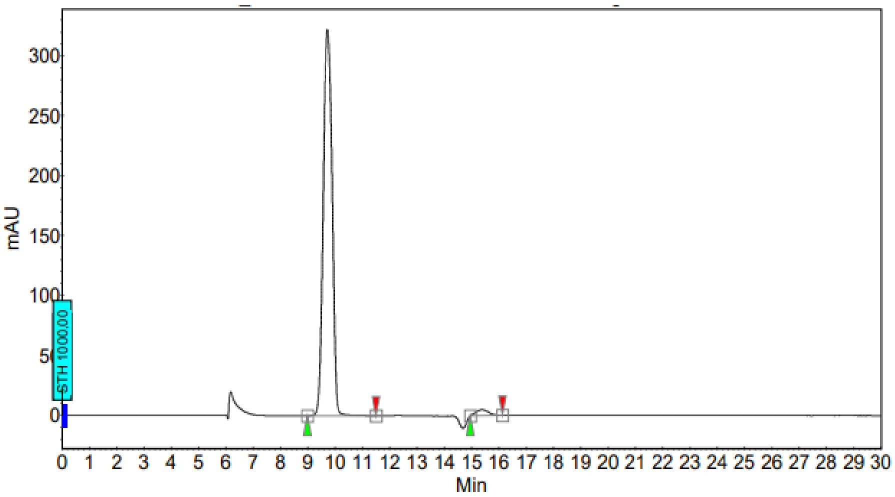
Data for 96a:



Peak Results:

Index	Time (min)	Area (mAU·min)	Area (%)
1	10.39	332.5	46.876
2	15.13	376.9	53.124
Total		709.4	100.00

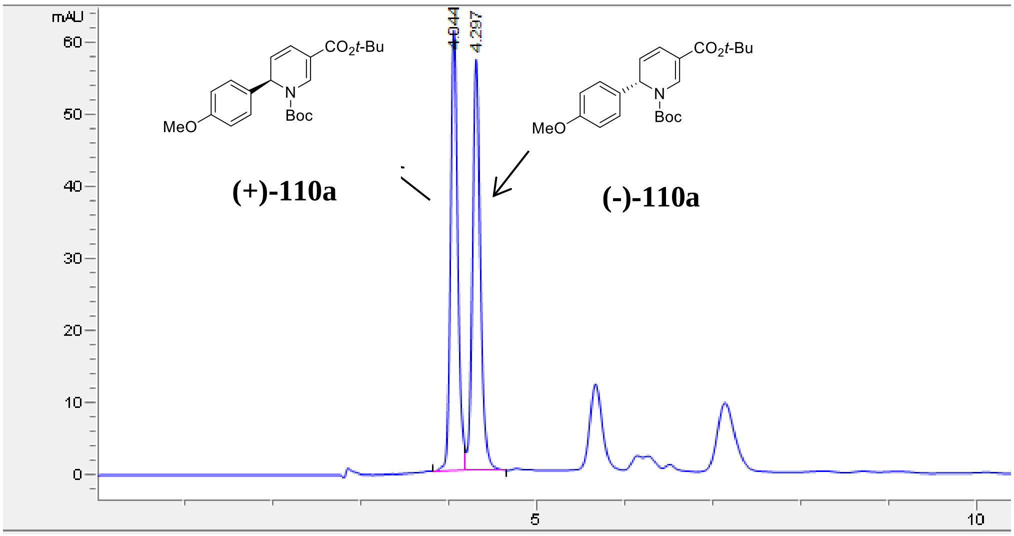
Data for (-)-96a:



Peak Results:

Index	Time (min)	Area (mAU·min)	Area (%)
1	9.72	121.5	98.67
2	15.38	2.7	1.33
Total		124.1	

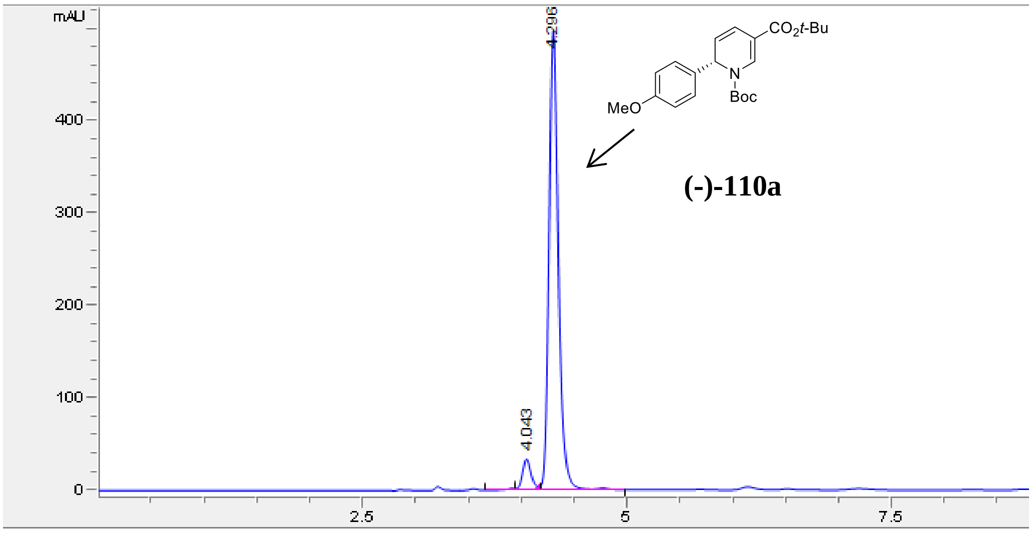
Data for 110a:



Peak Results:

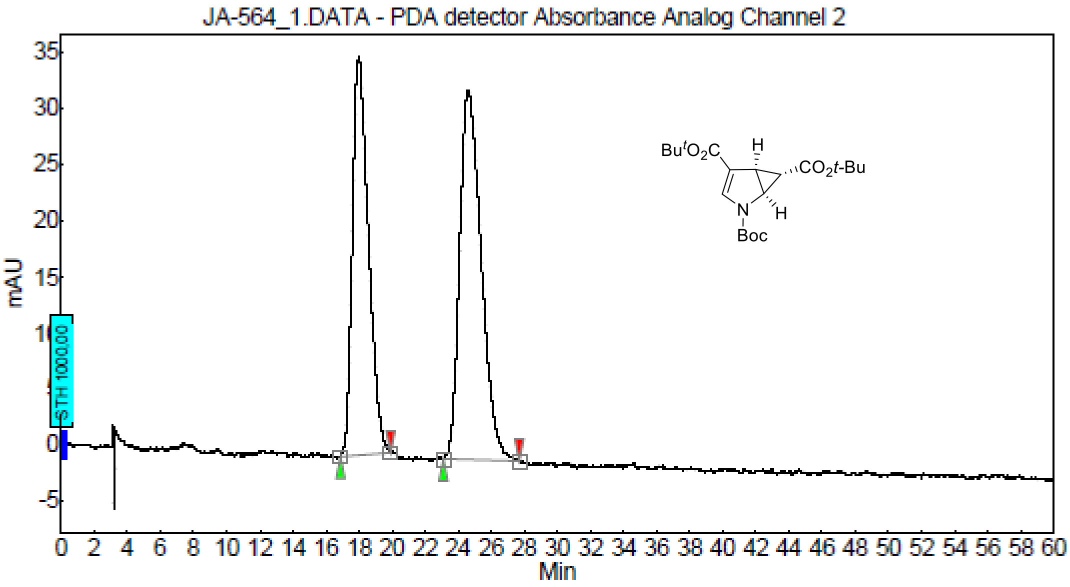
Index	Time (min)	Area (mAU·s)	Area (%)
1	4.04	320.90115	49.99
2	4.30	321.02954	50.01
Total		641.93069	

Data for 110a:



Peak Results:

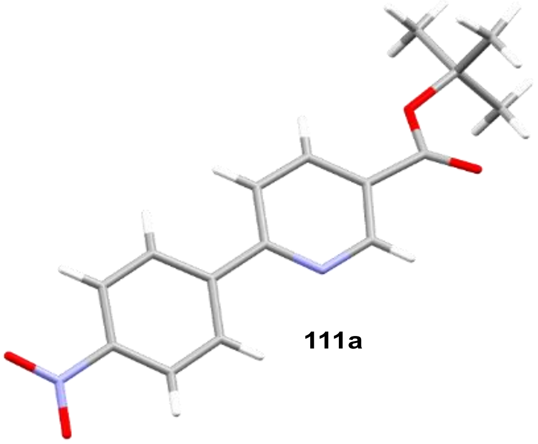
Index	Time (min)	Area (mAU.s)	Area (%)
1	4.04	156.29250	1.60
2	4.30	2976.55981	98.39
Total		3132.85231	



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	17,97	44,53	35,5	40,1	44,533
2	UNKNOWN	24,60	55,47	32,9	49,9	55,467
Total			100,00	68,4	89,9	100,000

2. X-ray crystallography data



111a

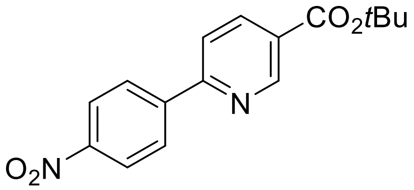


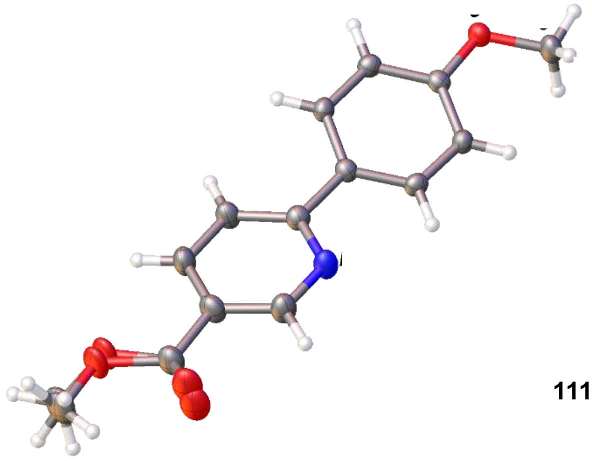
Table 1. Crystal data and structure refinement for **111a**.

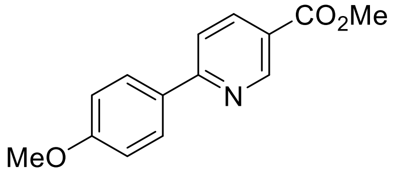
Compound	**R002**
Identification code	JA-487-2
Formula	$C_{16}H_{16}N_2O_4$
$D_{calc.}$/ g cm^{-3}	1.3795
μ /mm^{-1}	0.833
Formula Weight	300.32
Colour	clear colourless
Shape	plate
Size/mm^3	0.25×0.16×0.07
T/K	123.00(10)
Crystal System	triclinic
Space Group	*P*-1
a/Å	5.8128(3)
b/Å	10.1519(4)
c/Å	12.5413(4)
α/°	83.613(3)
β/°	89.482(3)
γ/°	79.429(4)
V/Å^3	722.95(5)
Z	2
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu K□
Θ_{min}/°	3.55
Θ_{max}/°	74.26
Measured Refl.	14758
Independent Refl.	2872
Reflections Used	2541

R_{int}	0.0405
Parameters	202
Restraints	0
Largest Peak	0.2678
Deepest Hole	-0.2222
GooF	1.0538
wR_2 (all data)	0.1074
wR_2	0.1030
R_1 (all data)	0.0418
R_1	0.0375

Reflection Statistics

Total reflections (after filtering)	14758	Unique reflections	2872
Completeness	0.973	Mean I/*s*	21.71
hkl_{max} collected	(7, 12, 15)	hkl_{min} collected	(-7, -12, -15)
hkl_{max} used	(7, 12, 15)	hkl_{min} used	(-7, -12, 0)
Lim d_{max} collected	100.0	Lim d_{min} collected	0.77
d_{max} used	12.46	d_{min} used	0.8
Friedel pairs	2439	Friedel pairs merged	1
Inconsistent equivalents	5	R_{int}	0.0405
R_{sigma}	0.022	Intensity transformed	0
Omitted reflections	0	Omitted by user (OMIT hkl)	0
Multiplicity	(1420, 1264, 953, 808, 551, 247, 62, 6)	Maximum multiplicity	14
Removed systematic absences	0	Filtered off (Shel/OMIT)	0





111a-Me

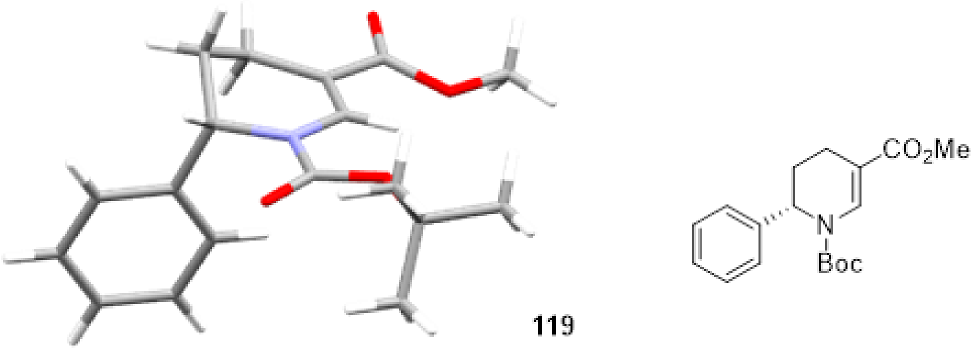
Table 2. Crystal data and structure refinement for **111a-Me.**

Compound	**test_Kopie**
Formula	$C_{14}H_{13}NO_3$
$D_{calc.}$/ g cm^{-3}	1.362
μ /mm^{-1}	0.793
Formula Weight	243.25
Colour	clear colourless
Shape	prism
Size/mm^3	0.20×0.17×0.10
T/K	123.00(10)
Crystal System	orthorhombic
Flack Parameter	-0.04(5)
Hooft Parameter	-0.02(5)
Space Group	$Pca2_1$
a/Å	6.15130(10)
b/Å	7.10860(10)
c/Å	27.1285(4)
α/°	90
β/°	90
γ/°	90
V/Å^3	1186.25(3)
Z	4
Z'	1
Wavelength/Å	1.54184
Radiation type	CuK□
Θ_{min}/°	3.258
Θ_{max}/°	73.385
Measured Refl.	12129

Independent Refl.	2356
Reflections with I > 2(I)	2304
R_{int}	0.0225
Parameters	198
Restraints	19
Largest Peak	0.160
Deepest Hole	-0.141
GooF	1.055
wR_2 (all data)	0.0757
wR_2	0.0749
R_1 (all data)	0.0285
R_1	0.0278

Reflection Statistics

Total reflections (after filtering)	13391	Unique reflections	2356
Completeness	0.986	Mean I	39.98
hkl_{max} collected	(7, 8, 33)	hkl_{min} collected	(-7, -8, -33)
hkl_{max} used	(7, 8, 33)	hkl_{min} used	(0, 0, -33)
Lim d_{max} collected	100.0	Lim d_{min} collected	0.77
d_{max} used	13.56	d_{min} used	0.8
Friedel pairs	3213	Friedel pairs merged	0
Inconsistent equivalents	0	R_{int}	0.0225
R_{sigma}	0.0141	Intensity transformed	0
Omitted reflections	0	Omitted by user (OMIT hkl)	0
Multiplicity	(3930, 2579, 978, 291, 41)	Maximum multiplicity	14
Removed systematic absences	1262	Filtered off (Shel/OMIT)	0



119

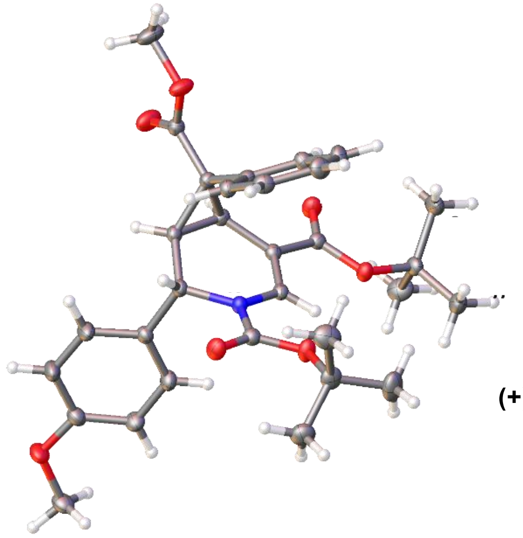
Table 3. Crystal data and structure refinement for **119.**

Compound	**Q138**
Formula	$C_{18}H_{23}NO_4$
$D_{calc.}$/ g cm^{-3}	1.266
μ /mm^{-1}	0.726
Formula Weight	317.37
Colour	clear colourless
Shape	prism
Size/mm^3	0.15×0.09×0.04
T/K	122.96(13)
Crystal System	monoclinic
Space Group	$P2_1/n$
a/Å	5.7268(2)
b/Å	18.8102(6)
c/Å	15.4599(5)
$\alpha/^\circ$	90
$\beta/^\circ$	91.124(3)
$\gamma/^\circ$	90
V/Å^3	1665.05(10)
Z	4
Z'	1
Wavelength/Å	1.54184
Radiation type	CuK□
$\Theta_{min}/^\circ$	3.701
$\Theta_{max}/^\circ$	73.883
Measured Refl.	9719
Independent Refl.	3341
Reflections Used	2817
R_{int}	0.0341
Parameters	212
Restraints	0
Largest Peak	0.192

Deepest Hole	-0.201
GooF	1.054
wR_2 (all data)	0.0977
wR_2	0.0920
R_1 (all data)	0.0457
R_1	0.0375

Reflection Statistics

Total reflections (after filtering)	9908	Unique reflections	3341
Completeness	0.989	Mean I	17.62
hkl_{max} collected	(7, 21, 19)	hkl_{min} collected	(-6, -23, -18)
hkl_{max} used	(7, 23, 19)	hkl_{min} used	(-7, 0, 0)
Lim d_{max} collected	100.0	Lim d_{min} collected	0.77
d_{max} used	11.94	d_{min} used	0.8
Friedel pairs	1235	Friedel pairs merged	1
Inconsistent equivalents	16	R_{int}	0.0341
R_{sigma}	0.0326	Intensity transformed	0
Omitted reflections	0	Omitted by user (OMIT hkl)	0
Multiplicity	(4180, 1596, 628, 148, 12)	Maximum multiplicity	10
Removed systematic absences	189	Filtered off (Shel/OMIT)	0



(+)-120

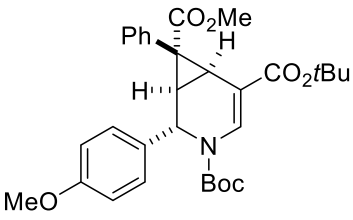


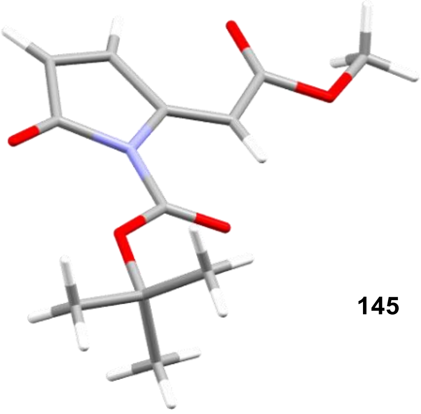
Table 4. Crystal data and structure refinement for (+)-**120**.

Compound	**R110**
Formula	$C_{31}H_{37}NO_7$
$D_{calc.}$/ g cm^{-3}	1.235
μ /mm^{-1}	0.710
Formula Weight	535.61
Colour	clear colourless
Shape	prism
Size/mm^3	0.28×0.20×0.15
T/K	123.00(10)
Crystal System	monoclinic
Space Group	$P2_1/c$
a/Å	8.79163(14)
b/Å	31.2432(5)
c/Å	10.6264(2)
α /°	90
β /°	99.3024(17)
γ /°	90
V/Å^3	2880.47(9)
Z	4
Z'	1
Wavelength/Å	1.54184
Radiation type	CuK□
Θ_{min}/°	4.447
Θ_{max}/°	74.206
Measured Refl.	32161

Independent Refl.	5795
Reflections with I > 2(I)	5472
R_{int}	0.0200
Parameters	360
Restraints	0
Largest Peak	0.270
Deepest Hole	-0.237
GooF	1.039
wR_2 (all data)	0.0879
wR_2	0.0864
R_1 (all data)	0.0371
R_1	0.0353

Reflection Statistics

Total reflections (after filtering)	32516	Unique reflections	5795
Completeness	0.99	Mean I	47.45
hkl_{max} collected	(10, 39, 13)	hkl_{min} collected	(-10, -38, -11)
hkl_{max} used	(10, 38, 13)	hkl_{min} used	(-10, 0, 0)
Lim d_{max} collected	100.0	Lim d_{min} collected	0.77
d_{max} used	10.49	d_{min} used	0.8
Friedel pairs	7276	Friedel pairs merged	1
Inconsistent equivalents	3	R_{int}	0.02
R_{sigma}	0.0114	Intensity transformed	0
Omitted reflections	0	Omitted by user (OMIT hkl)	0
Multiplicity	(9183, 6062, 2276, 915, 131, 11)	Maximum multiplicity	16
Removed systematic absences	355	Filtered off (Shel/OMIT)	0



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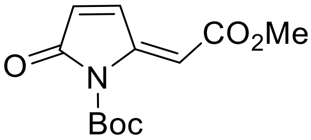

Table 5. Crystal data and structure refinement for **145**.

Compound	**JA-6**
CCDC	n/a
Formula	$C_{12}H_{15}NO_5$
$D_{calc.}$/ g cm^{-3}	1.401
μ /mm^{-1}	0.927
Formula Weight	253.25
Colour	clear colourless
Shape	plate
Max Size/mm	0.46
Mid Size/mm	0.32
Min Size/mm	0.09
T/K	122.98(10)
Crystal System	monoclinic
Space Group	$P2_1/m$
a/Å	12.2037(2)
b/Å	6.76442(12)
c/Å	15.3457(3)
α/°	90
β/°	108.595(2)
γ/°	90
V/Å^3	1200.67(4)
Z	4
Z'	1
Θ_{min}/°	3.822
Θ_{max}/°	73.884
Measured Refl.	23955
Independent Refl.	2643
Reflections Used	2460
R_{int}	0.0259
Parameters	215

Restraints	0
Largest Peak	0.273
Deepest Hole	-0.206
GooF	1.032
wR_2 (all data)	0.1001
wR_2	0.0984
R_1 (all data)	0.0353
R_1	0.0336

Reflection Statistics

Total reflections (after filtering)	23978	Unique reflections	2643
Completeness	0.995	Mean I	51.73
hklsub>max</sub> collected	(15, 8, 19)	hklsub>min</sub> collected	(-15, -8, -18)
hkl$_{max}$ used	(14, 8, 19)	hkl$_{min}$ used	(-15, 0, 0)
Lim d$_{max}$ collected	100.0	Lim d$_{min}$ collected	0.77
d$_{max}$ used	11.57	d$_{min}$ used	0.8
Friedel pairs	3802	Friedel pairs merged	1
Inconsistent equivalents	14	R$_{int}$	0.0259
R$_{sigma}$	0.0096	Intensity transformed	0
Omitted reflections	0	Omitted by user (OMIT hkl)	0
Multiplicity	(1845, 2268, 2153, 1213, 563, 297, 120, 73, 25, 4)	Maximum multiplicity	27
Removed systematic absences	23	Filtered off (Shel/OMIT)	0

4. Curriculum vitae

Julietta Yedoyan

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Education

Since 10/2015-	***Graduate student***, Faculty of Chemistry and Pharmacy, Institute of Organic Chemistry, University of Regensburg, Regensburg, Germany
09/2007-05/2012	**MSc in Pharmacology**, Faculty of Chemistry, Department of Pharmaceutical-Chemistry, Yerevan State University, Yerevan, Armenia
09/1997-05/2007	Secondary school in Vanadzor, Armenia

Past Employments/ Research Visits

03/2019	***Intern***, Merck KGaA, Darmstadt, Germany
05/2015-10/2015	***Research Assistant***, Department of Organic Chemistry, University of Texas at San Antonio, San Antonio, USA
04/2013-01/2015	***Research Assistant***, Laboratory of Biomimetic Catalysis, Armbiotechnology Scientific and Production Center, Yerevan, Armenia
03/2012-03/2013	***Intern***, Gedeon Richter Pharmaceuticals, Yerevan, Armenia
10/2011-03/2012	***Exchange student***, Department of Organic Chemistry, Rostock University, Rostock, Germany

Research Scholarships/ Travel Grants

05/2019-06/2019	Bayerische Chancengleichheits: ***Research scholarship***
10/2018	GDCh: ***Travel grant***, Frontiers in Chemistry, Yerevan, Armenia
10/2018-03/2019	IQN- MC: ***Research scholarship***, University of Regensburg
07/2017	DAAD: ***Travel grant***, 67th Lindau Nobel Laureate Meeting, Lindau
09/2016	GDCh: ***Travel grant***, ACS 252nd National Meeting, Philadelphia, PA, USA
10/2016	DAAD: ***Travel grant***, 27th European Summer Academy, Bonn, Brussels, Luxemburg
10/2015-09/2018	DAAD: ***Research scholarship,*** University of Regensburg
05/2015-10/2015	Calouste Gulbenkian ***Research scholarship***, UTSA, USA
06/2014	Calouste Gulbenkian ***Travel grant***, FACS XV conference, Avignon, France
01/2014-10/2014	ISTC- 13RB-043 ***Research scholarship***, Armbiotechnology SPC, Armenia

List of scientific publications

1. **Yedoyan J.** ; Angnes A. R.; Reiser, O. „ Transition-Metal-Catalyzed Ring-Opening of Non-activated Vinyl Cyclopropanes" Manuscript in preparation.
2. **Yedoyan J.** ; Wurzer N.; Klimczak U.; Ertl T.; Reiser, O. „ *Regio- and Stereoselective Synthesis of Functionalized Dihydropyridines, Pyridines and 2H-Pyrans Triggered by Heck Coupling of Monocyclopropanated Heterocycles*" *Angew. Chem. Int. Ed. Engl***.** **2019**, *58*, 3594-3598*; Angew. Chem.* **2019**, *131*, 3632-3636.
3. Cheng, Q.-Q.; Yu, Y.; **Yedoyan, J**.; Doyle, M. P. "Vinyldiazo reagents and metal catalysts: a versatile toolkit for heterocycle and carbocycle construction" *ChemCatChem* **2018**, *9*, DOI: 10.1002/cctc.201701346.
4. Cheng, Q.-Q.; **Yedoyan, J**.; Arman, H.; Doyle, M. P. "Dirhodium(II)-catalyzed annulation of enoldiazoacetamides with α-diazoketones: an efficient and highly selective approach to fused and bridged ring systems" *Angew. Chem., Int. Ed.* **2016**, *55*, 5573–5576; *Angew. Chem.* **2016**, *128*, 5663–5666.

   Highlighted on the Inside Cover of *Angew. Chem., Int. Ed.* **2016**, *55*(18); *Angew. Chem.* **2016**, *128*(18).

   Highlighted in *ChemInform* **2016**, *47*, 36-144.

5. Cheng, Q.-Q.; **Yedoyan, J**.; Arman, H.; Doyle, M. P. "Copper-catalyzed divergent addition reactions of enoldiazoacetamides with nitrones" *J. Am. Chem. Soc.* **2016**, *138*, 44–47.

   Highlighted in *Synfacts* **2016**, *12*, 391.

   Highlighted as the Editors' Choice in *ChemInform* **2016**, *47*, 22-021.

6. V. O. Iaroshenko, Gevogyan A., Mkrtchyan S., Arakelyan K., Grigoryan T., **Yedoyan J**., Villingera A. and Langer P. "Transition-Metal-Catalyzed Arylation of Nitroimidazoles and Further Transformations of Manipulable Nitro Group" *J. Org. Chem.*, **2015**, 80 (4), 2103–2119.

Press release

- **Süddeutsche Zeitung**, 67. LINDAUER NOBELPREISTRÄGERTAGUNG (Nr. 147, Thursday, 29. Juni 2017)
- **"Women in Research"**, https://womeninresearchblog.wordpress.com/2017/05/31/julietta-armenia/

Language skills

Armenian	Native speaker
Englisch	Fluent
Russian	Fluent
German	Good

Membership

2015-2019	Chemical Photocatalysis - GRK 1626
2016-2019	Gesellschaft Deutscher Chemiker
2016	American Chemical Society

Professional References

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My Ph.D. program would not be possible without the generous financial support of DAAD Foundation in the science and beyond, giving me the chance to participate in various scientific and social activities such as 27th European Summer Academy and of course for the great honor to join the 67th Lindau Nobel Laureate Meeting as one of the DAAD scholars. I would also like to thank the committee of DAAD who believed in me and gave me this unique opportunity to make my dreams come true as well as Dr. Thomas Prahl and Elena Schmid for their support and great discussions and for the opportunity to give annual talks at DAAD orientation seminars in Bonn. I am also very grateful to GDCh, and DFG-GRK-1626 for their travel grants to participate at scientific conferences and events. I also sincerely appreciate to Bayerische Chancengleichheits-Stipendien for the research grant to finish my doctoral study.

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H. Declaration

Herewith I declare that this present PhD 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 acknowledgement of collaborative research.

Regensburg, 27.05.2019

Julietta Yedoyan

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