THE UNIVERSITY OF CHICAGO

TRANSITION METAL-CATALYZED FUNCTIONALIZATION OF C−H AND C−C BONDS

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YAN XU

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LIST OF ABBREVIATIONS

Ac	Acetyl
Acac	acetylacetonate
Ad	Adamantyl
Ar	Aryl
BARF	Tetrakis(perfluorophenyl)borate
BINAP	2,2'-bis(Diphenylphosphino)-1,1'-binaphthalene
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
Bz	Benzoyl
COD	1,5-Cyclooctadienyl
COE	Cyclooctene
Cp	Cyclopentadienyl
Cp*	1,2,3,4,5-Pentamethylcyclopentadienyl
Cy	Cyclohexyl
δ	Chemical shift
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DMF	*N*,*N*-Dimethylformamide
DMPU	*N, N'*-Dimethylpropyleneurea
DMSO	Dimethylsulphoxide
DPEphos	(Oxydi-2,1-phenylene)bis(diphenylphosphine)

dppb	1,4-bis(Diphenylphosphino)butane
dppe	1,2-bis(Diphenylphosphino)ethane
dppf	1,1'-bis(Diphenylphosphino)ferrocene
dppp	1,3-bis(Diphenylphosphino)propane
dppm	1,1-bis(Diphenylphosphino)methane
dr	Diastereomeric ratio
DG	Directing group
DTBMP	2,6-Di-tert-butyl-4-methylpyridine
ee	Enantiomeric excess
Et	Ethyl
equiv	Equivalent
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HPLC	High performance liquid chromatography
HRMS	High-resolution mass spectrometry
IBX	2-Iodoxybenzoic acid
IMes	1,3-Dimesitylimidazol-2-ylidene
i-Pr	Isopropyl
IR	Infrared
KPS	Potassium persulfate
m	Meta
mCPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
Mes	Mesityl
MOM	Methoxymethyl
Ms	Methanesulphonyl

M.S.	Molecular Sieve
MW	Microwave
m/z	Mass charge ratio
nbd	2,5-Norbornadiene
NBS	*N*-Bromosuccinimide
n-Bu	*normal*-Butyl
NFSI	*N*-Fluorobenzenesulfonimide
NHC	*N*-Heterocyclic Carbene
NIS	*N*-Iodosuccinimide
NMR	Nuclear magnetic resonance
n-Pr	*normal*-Propyl
Ns	Nitrobenzenesulphonyl
o	Ortho
Oxone	$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$
p	Para
PCC	Pyridinium chlorochromate
Ph	Phenyl
Phth	Phthaloyl
Pin	Pinacolyl
Piv	Pivaloyl
Py	Pyridyl
rr	Regioisomeric ratio
rt	Room temperature
TBS	*tert*-Butyldimethylsilyl
t-Bu	*tert*-Butyl

Tf	Trifluoromethanesulphonyl
Tfa	Trifluoroacetyl
THF	Tetrahydrofuran
TIPS	Tri-*iso*-propylsilyl
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
Tol	Tolyl
Ts	*para*-Toluenesulphonyl

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Yan Xu

University of Chicago

July 2018

CHAPTER 1

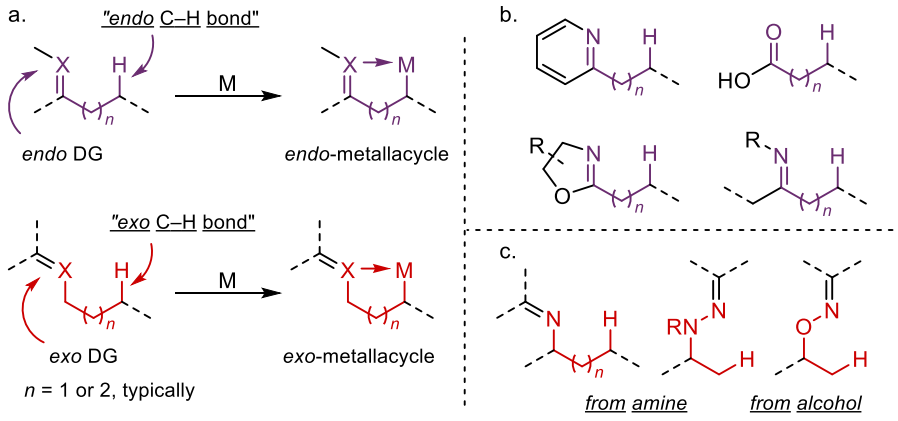
sp^3 C–H Activation via exo-Type Directing Groups

1.1 Introduction

Site-selective functionalization of inert aliphatic C–H bonds has become an increasingly important tool, as it shows promise for streamlining synthesis of complex organic molecules.[1] Among various approaches, cyclometalation aided by an adjacent directing group (DG) is frequently utilized to activate C–H bonds with excellent site-selectivity control. Given that the majority of coordinating groups bear a π-bond moiety,[1b,i] the DGs can be divided into two categories: *endo*-DG that features an endocyclic π-bond after C–H metalation and *exo*-DG that features an exocyclic π-bond instead (Scheme 1.1a). The C–H activations assisted by *endo*-DGs have been widely explored.[2] While highly efficient, these C–H activations usually require functional groups (FGs) with double bonds already built in, such as pyridines,[2a] oxazolines,[2b] carboxylic acids,[2c] and ketone derivatives[2a,2d-f] (Scheme

1.1b). In contrast, reactions via an *exo*-directing mode were historically less developed, but have received considerable attentions recently. Compared to their *endo* counterparts, the *exo*-DGs are typically derived from more flexible FGs, such as alcohols and aliphatic amines, which open the door for developing new site-selective C–H functionalization (Scheme 1.1c). To better describe the challenges and achievements of this field, this mini-review is divided into two parts, with (i) a brief introduction of the "*endo* effect" from the organometallic viewpoint and (ii) the discussion of stoichiometric and catalytic transformations in functionalizing unactivated C(sp^3)–H bonds *via* *exo*-type DGs. Reactions with C(sp^2)–H or activated C(sp^3)–H bonds will not be included in this chapter.

Scheme 1.1 Comparison between *endo*- and *exo*-DGs

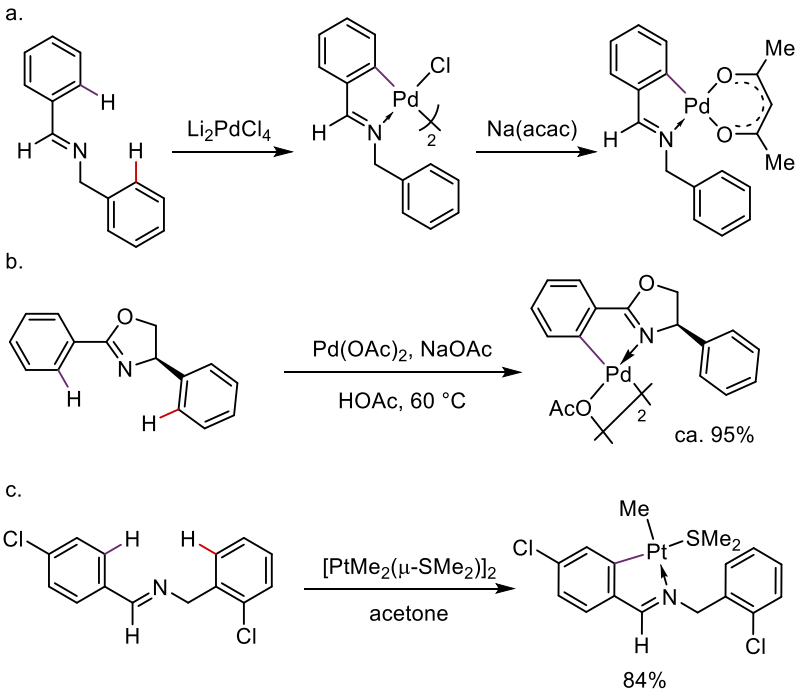


1.2 *Endo* vs *Exo*: the "*Endo* Effect"

C–H cyclometalation can be highly regioselective when C–H bonds are available for activation through either *endo* or *exo* directing mode.[3] The selective activation of "*endo* C–H bonds" over "*exo* C–H bonds", which has been widely referred to as "*endo* effect", has been

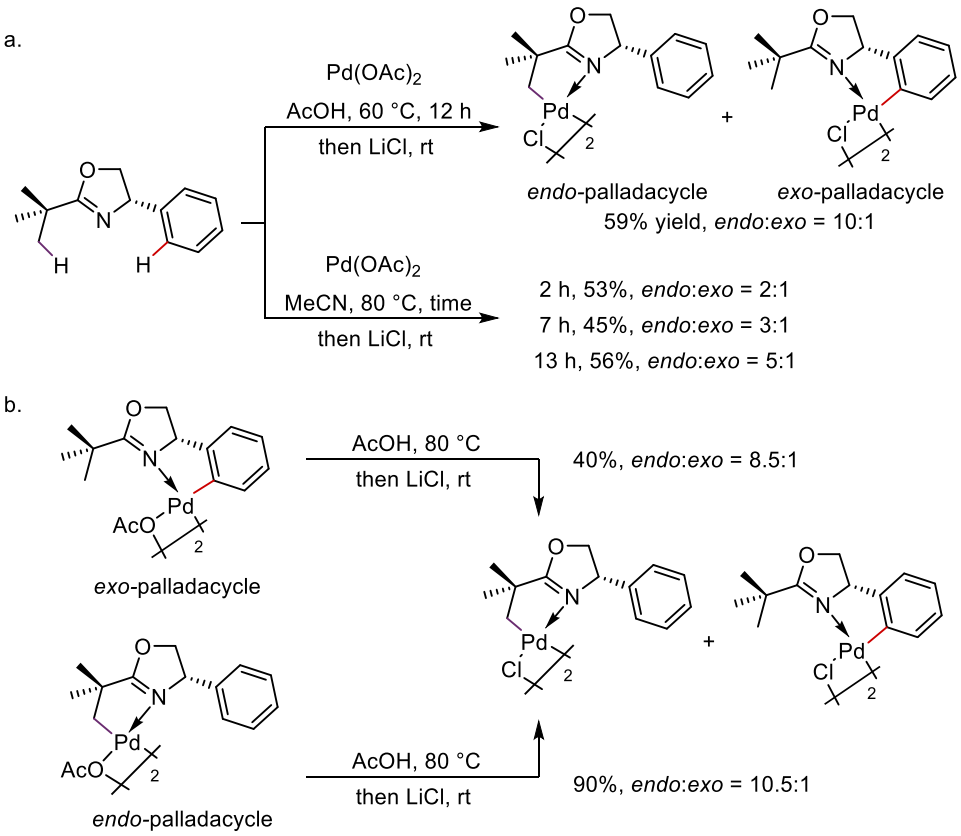
observed with various types of DGs, such as imines and oxazolines.[4] For example, treating *N*-benzylbenzaldimine with Li_2PdCl_4 led to a chloro-bridged *endo*-palladacycle, which underwent ligand exchange to give the monomer whose structure was unambiguously assigned by X-ray diffraction (Scheme 1.2a).[5] In nearly a quantitative yield, *endo*-metallacycle was also formed exclusively when 4-phenyl-2-oxazoline was treated with stoichiometric $Pd(OAc)_2$ (Scheme 1.2b).[6] Such tendency was also observed for other transition metals, such as platinum (Scheme 1.2c).[7] It is worth pointing out that the *endo* effect is not restricted to C–H metalation reactions. In the case of oxidative addition of *ortho*-brominated *N*-benzylbenzaldimine to Pd(0), the *endo*-complex was formed preferentially as well.[8] While the detailed reason for this *endo* effect is yet to be fully elucidated, studies have suggested that a combination of structural factors, e.g. bond angle, distortion of the C=N π-bond, the planarity of the metallocycle etc., makes the *endo*-complexes derived from imines or oxazolines more thermodynamically stable than their *exo* counterparts.[9]

Scheme 1.2 *Endo* Preference in Regioselective C–H Metalation



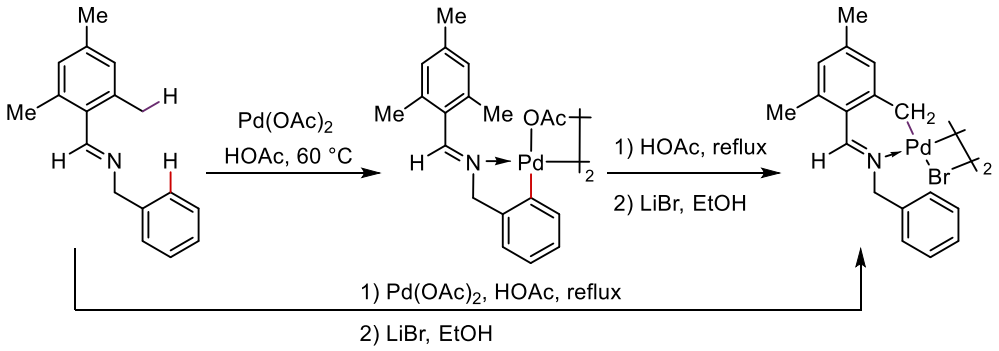
The preference for *endo* activation can be very strong in certain cases that it permits activation of an *endo* C(sp^3)–H bond in presence of a more reactive *exo* C(sp^2)–H bonds. The reaction between 2-*tert*-butyl-4-phenyl-2-oxazoline and $Pd(OAc)_2$ stands for an impressive example (Scheme 1.3).[9a] Under various reaction conditions, the *endo* sp^3 palladated complex was obtained as the major product with up to 10:1 regioselectivity (Scheme 1.3a). In addition, treatment of the pure *exo*-complex under AcOH at 80 ^oC led to a 8.5:1 mixture of the *endo*- and *exo*-isomers. Treatment of the pure *endo*-complex under the same reaction conditions led to a similar 10.5:1 mixture of isomers (Scheme 1.3b). These experiments suggest that (i) there is equilibrium between the *exo* and *endo* isomers, and (ii) the *endo* sp^3 C–H palladation is thermodynamically favoured at least in these cases.

Scheme 1.3 Selective Activation Of *endo* C(sp^3)–H Bonds over *exo* C(sp^2)–H Bonds



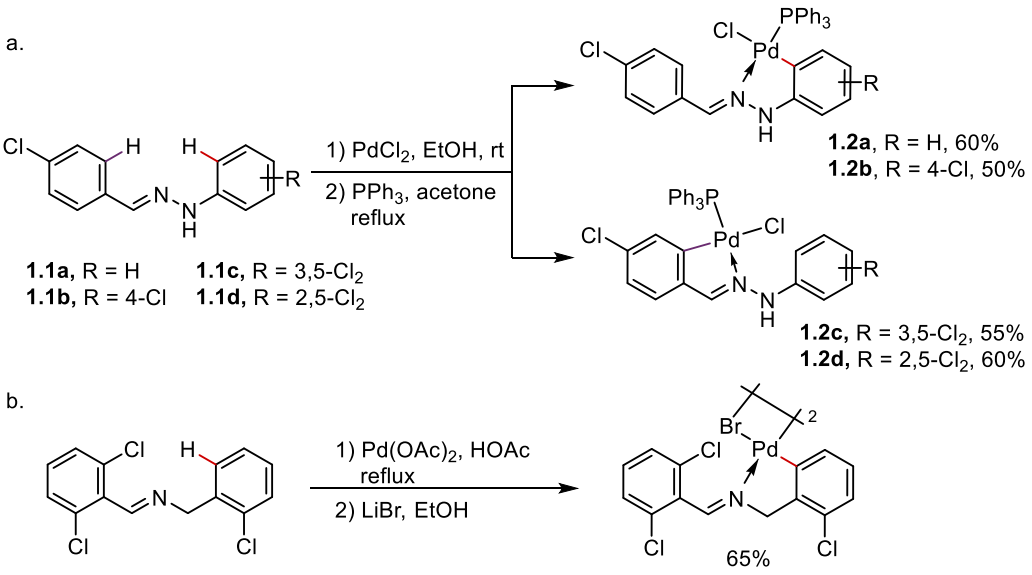
It appears that, in some cases, the *exo*-complex is the kinetic product, which can be isolated and then isomerized to the more thermodynamically stable *endo*-complex. As one example, a five-membered *exo*-palladacycle was obtained by reacting *N*-mesitylbenzylideneamine with $Pd(OAc)_2$ under mild reaction conditions at 60 ^{o}C, which was further transformed to a more stable *endo* palladacycle in refluxing acetic acid (Scheme 1.4).[10]

Scheme 1.4 Isomerization of *exo*-Metallocycles to *endo*-Metallocycles



Under a strong electronic or steric bias, the *exo*-metallacycle can sometimes become the major product. For instance, *exo*-palladacycles were obtained at room temperature for the reaction of benzaldehyde phenylhydrazones **1.1a** and **1.1b** with $PdCl_2$, likely due to the large difference in electron density between the *endo*- and *exo*- rings as a result of the highly electron-donating amine moiety. As expected, when more electron-withdrawing (and also sterically demanding) chlorine substituents were introduced at the *ortho*- and *meta*- positions of the phenylhydrazine rings (**1.1c** and **1.1d**), only the *endo*-metallacycles were obtained (Scheme 1.5a).[11] Besides, the *exo*-metalation can also be accomplished by blocking the *endo* reaction sites. For example, when both *endo* C–H bonds of *N*-benzylbenzaldimine were replaced by chlorine atoms, the *exo*-palladacycle was formed exclusively (Scheme 1.5b).[12]

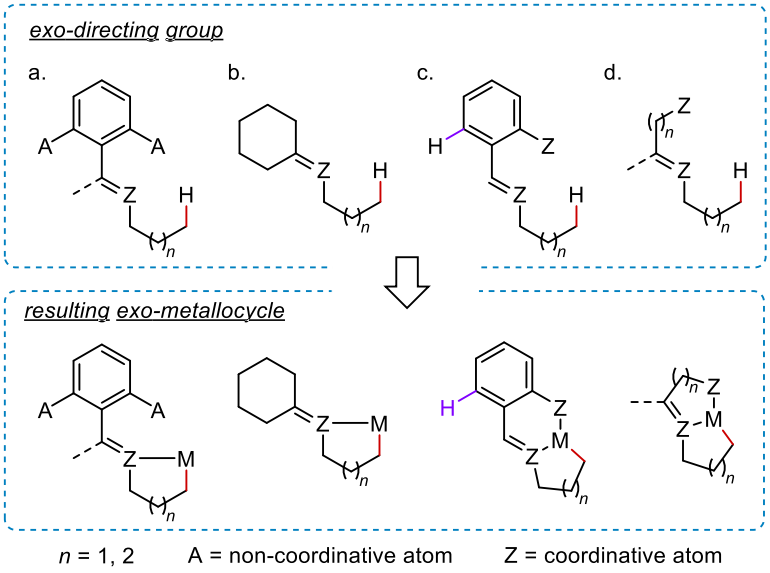
Scheme 1.5 *exo*-Metallocycle Formation Promoted by (a) Electronic Bias, and (b) Blocking of *endo* Reaction Sites



1.3 sp^3 C–H Activation *via Exo*-type DGs

To outcompete the *endo* preference, two general strategies are commonly applied in the design of *exo*-DGs for sp^3 C–H activation: (i) blocking or obviating potential *endo* reaction sites (Schemes 1.6a and 1.6b) and/or (ii) adding an extra coordinating entity at a proper position of the *endo* side to enable chelation (Schemes 1.6c and 1.6d). In the latter case, formation of an additional 5- or 6-membered metallacycle inhibits the activation of *endo* C–H bonds (if any) and may further promote the *exo* metalation due to the increased structural rigidity.

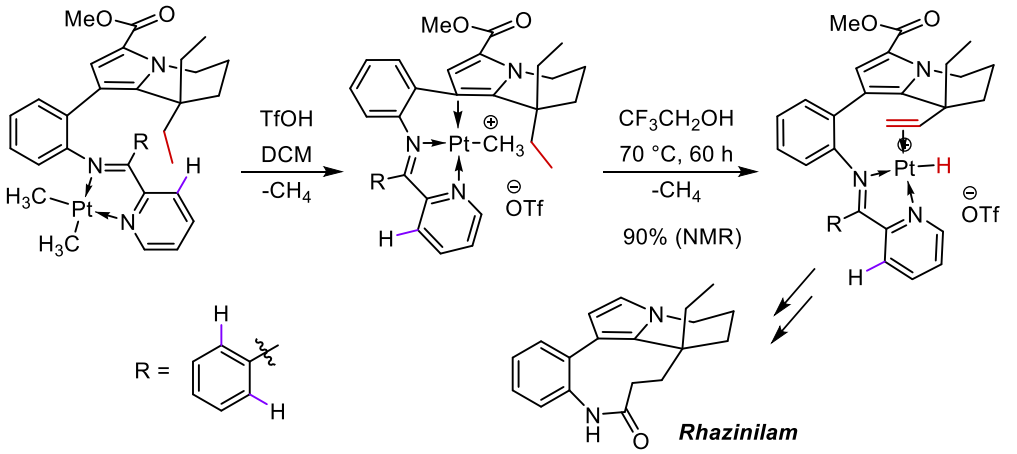
Scheme 1.6 General Strategies in the Design of *exo*-Directing Groups



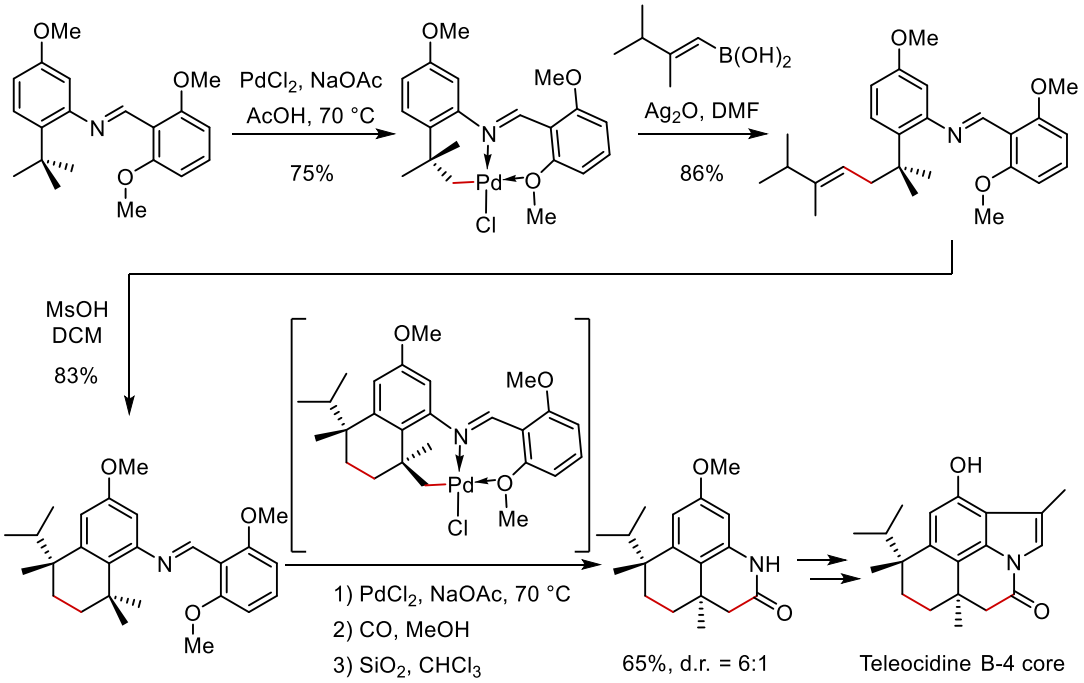
1.3.1 Reactions with Stoichiometric Metals

In 2000 and 2002, two seminal stoichiometric examples were reported by Sames and coworkers in the synthesis of Rhazinilam[13] and the core of Teleocidin B4[14]. In Scheme 1.7, the C–H platation of a remote ethyl group was promoted by a phenylpyridyl ketimine-type DG using stoichiometric cationic Pt(II), followed by β-hydride elimination to afford an alkene–Pt(II)–H complex. The *endo* C(sp^2)–H bonds at the phenyl and pyridyl groups were untouched. In Scheme 1.8, *exo*-palladacycles were obtained through the activation of *tert*-butyl groups when treating 2-*tert*-butylaniline-derived 2,6-bismethoxybenzaldimines with $PdCl_2$ in acetic acid. The two *ortho*-OMe substituents not only blocked the *endo* reaction sites, but also served as additional directing groups. Alkenylation and carbonylation products were further furnished in high yields by treating the resulting Pd complexes with a vinyl boronic acid and CO/MeOH, respectively.

Scheme 1.7 Pt-mediated Dehydrogenation of a Remote Ethyl Group



Scheme 1.8 Pd-mediated C(sp^3)–H Alkenylation and Carbonylation of 2-*tert*-Butylanilines

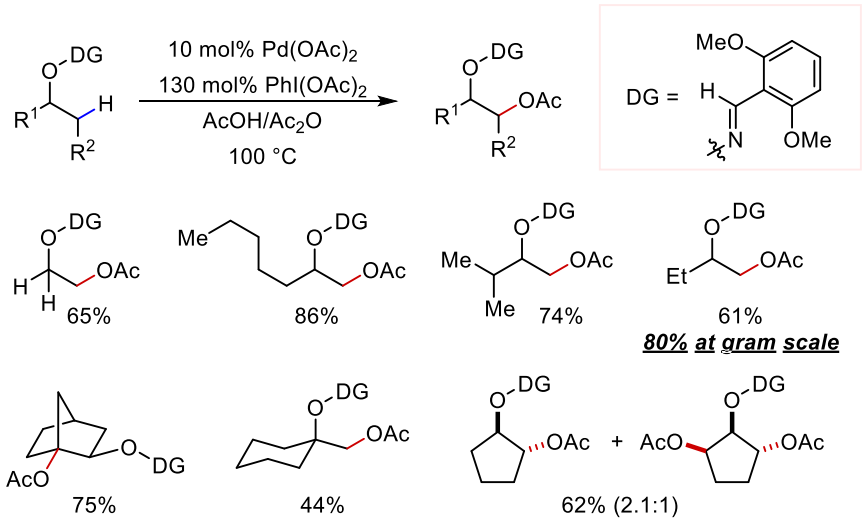


1.3.2 Catalytic Reactions

In 2012, Dong and co-workers reported a Pd-catalyzed β-C(sp^3)–H acetoxylation reaction of masked alcohols using PIDA as the oxidant (Scheme 1.9). [15] A 2,6-bismethoxybenzaldoxime protecting group was used as an *exo*-DG and to mask the hydroxyl

group of the alcohol. The *ortho*-OMe groups once again were found indispensible, as they blocked the *endo* reaction sites and served as potential secondary coordination sites. Methyl, cyclic methylene, and even bridgehead methine C–H bonds were readily acetoxylated in a group of primary, secondary, and tertiary alcohol derivatives, providing chemically differentiated 1,2-diols after orthogonal deprotection. It is worthy to mention that the DG can be conveniently removed using zinc and acetic acid.

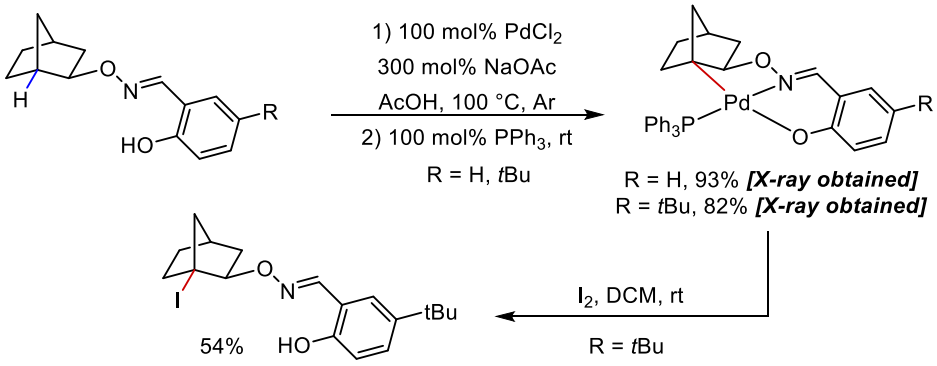
Scheme 1.9 Pd-Catalyzed β C–H Acetoxylation of Masked Alcohols



The mechanism was investigated by the same team in 2016 to elucidate the unusual activation of bridgehead C–H bonds.[16] With a salicylaldehyde-derived *exo*-DG, the C–H cyclopalladation occurred smoothly at the bridgehead position, furnishing a [6,5]-fused palladacycle (Scheme 1.10). Further treatment of the complex with iodine led to iodination at the bridgehead position in a moderate yield. The previously used 2,6-bismethoxybenzaldoxime DG, on the other hand, was found incompatible in the

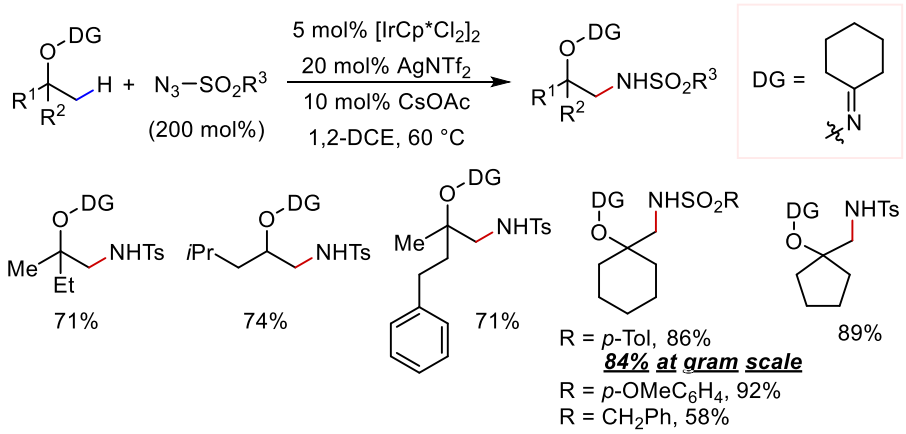
stoichiometric study, due to an elimination to yield 2,6-bismethoxybenzonitrile when no oxidant was applied.

Scheme 1.10 C−H Cyclopalladation at Bridgehead Positions Enabled by an *exo*-DG



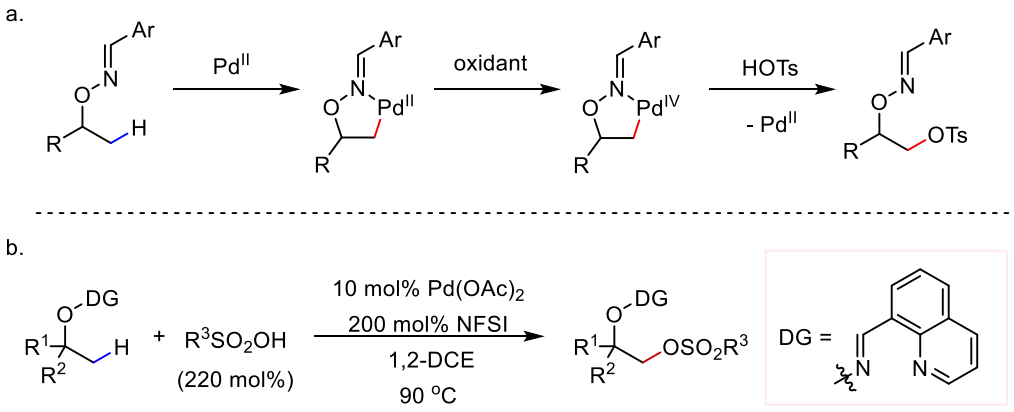
An Ir(III)-catalyzed β-C(sp^3)–H amidation reaction of masked alcohols was reported in 2014 by Chang and coworkers using sulfonyl azides as the amine source (Scheme 1.11).[17] A cyclohexyl ketoxime-type DG was introduced on the free alcohol to facilitate the C–H activation through formation of a five-membered *exo*-iridacycle. A range of primary, secondary, and tertiary alcohols can be readily amidated at β methyl positions using different sulfonyl azides, furnishing β-amino alcohols after removal of the DG through reductive cleavage of the N–O bond using $LiAlH_4$.

Scheme 1.11 Ir-Catalyzed β-C–H Amidation of Masked Alcohols

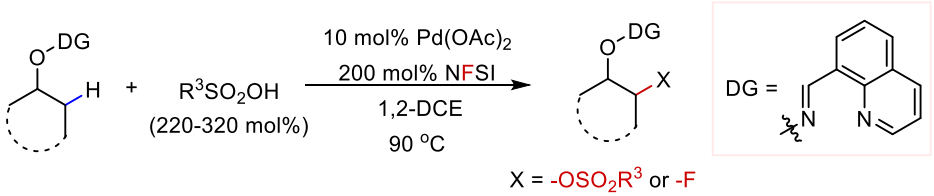


In 2015, a Pd-catalyzed β-C(sp^3)–H sulfonyloxylation reaction of masked alcohols was reported by Dong and coworkers, using NFSI as the oxidant and sulfonic acids as the source of sulfonyloxy groups (Scheme 12).[18] An 8-quinolinecarbaldoxime-type *exo*-DG, which can be installed through a one- or two-pot procedure from the free alcohol, was found optimal. The proposed mechanism following a Pd(II)-Pd(IV) cycle is depicted in scheme 12a, and the reaction proceeds through (i) β C–H palladation to form a five-membered *exo*-palladacycle, (ii) oxidation to generate Pd(IV), and (iii) reductive elimination to yield the product and regenerate the Pd(II) catalyst. Interestingly, competing β-C–H fluorination occurred along with the β-sulfonyloxylation at cyclic methylenes of masked cyclohexanols (Scheme 1.13). The detail of this work will be discussed further in Chapter 3.

Scheme 1.12 Pd-Catalyzed β C–H Sulfonyloxylation of Masked Alcohols

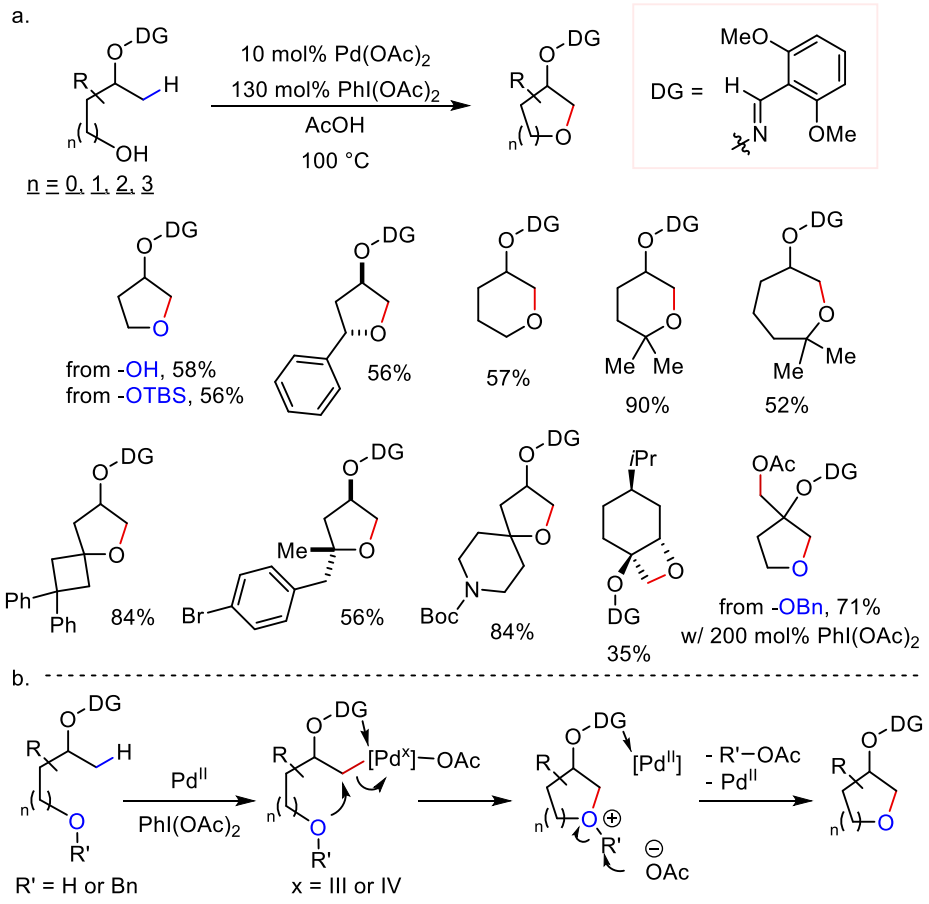


Scheme 1.13 Pd-Catalyzed β-C–H Fluorination/Sulfonyloxylation of Masked Cyclohexanols



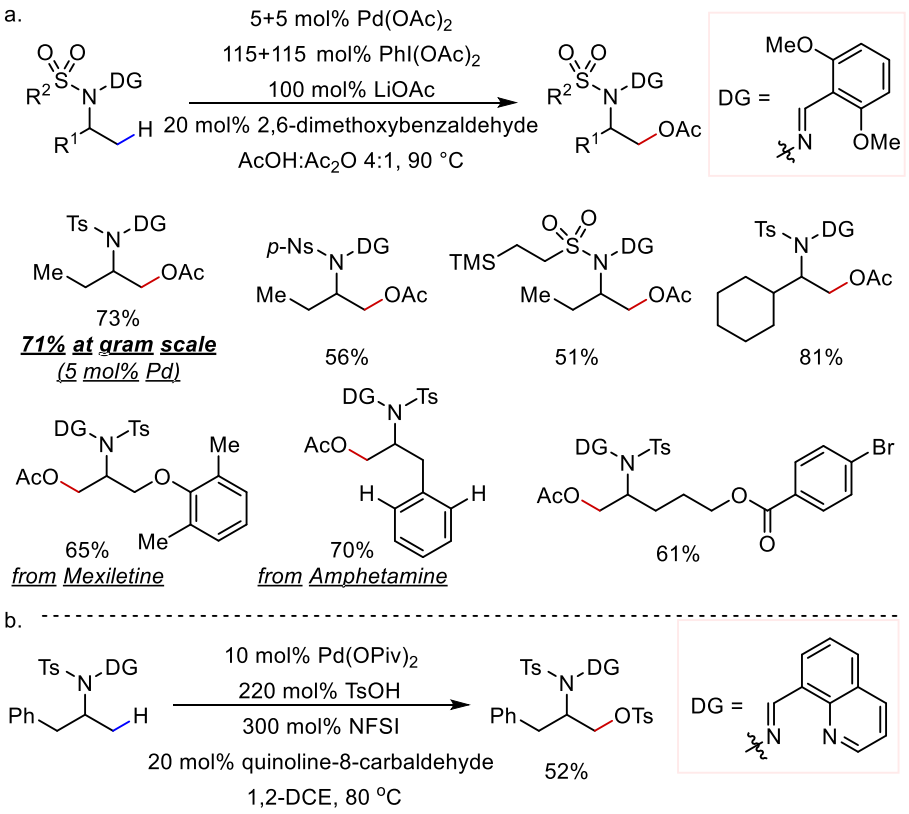
A Pd-catalyzed intramolecular β-C(sp^3)–H etherification reaction with internal hydroxyl nucleophiles was reported by Dong and coworkers in 2015 (Scheme 1.14).[19] Directed by an oxime-masked alcohol, various aliphatic cyclic ethers with 4- to 7-membered rings were readily formed through dehydrogenative annulation at β-methyl positions. Tethered primary, secondary, and tertiary hydroxyl groups can all be used as nucleophiles as well as TBS- and Bn-protected alcohols (Scheme 1.14a). The reaction was proposed to begin with β-C–H palladation, followed by oxidation to form a hypervalent Pd species and then S_N2-type reductive elimination to furnish the ether product (Scheme 1.14b).

Scheme 1.14 Pd-Catalyzed β C–H Etherification with Internal Hydroxyl Nucleophiles



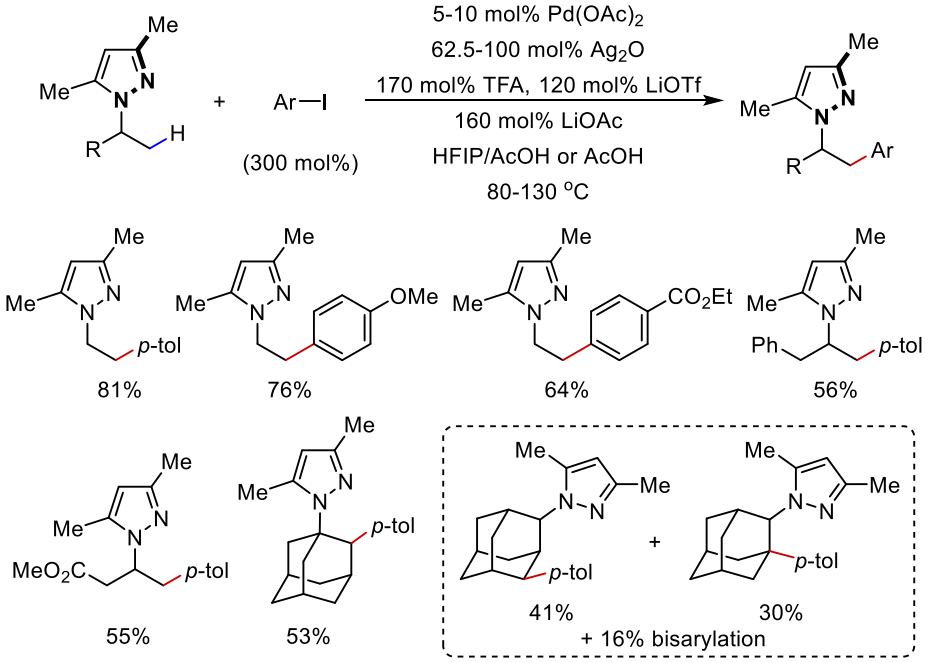
Apart from using alcohol-based substrates, in 2016 Dong and co-workers reported a Pd-catalyzed β-C(sp^3)–H oxygenation reaction of sulfonyl-protected primary amines (Scheme 1.15).[20] A removable hydrazone-based *exo*-DG, which was introduced through a one-pot procedure on the free amine, was capable of promoting the β-C–H activation through formation of a five-membered *exo*-palladacycle. Similar to the case of oxime-based DGs, 2,6-bismethoxyphenyl- and 8-quinolinyl-derived hydrazones were used for the β-acetoxylation (Scheme 1.15a) and the β-tosyloxylation (Scheme 1.15b), respectively. A wide range of primary amines with different skeletons and FGs, including those equipped with removable sulfonyl protecting groups (such as *p*-nosyl and SES), were readily oxidized at the β-methyl C–H bonds. The β-OTs could be further derivatized through S_N2 reactions. The DG can be readily removed through cleavage of the N–N bond using zinc and acetic acid.

Scheme 1.15 Pd-Catalyzed β C–H Oxygenation of Protected Amines



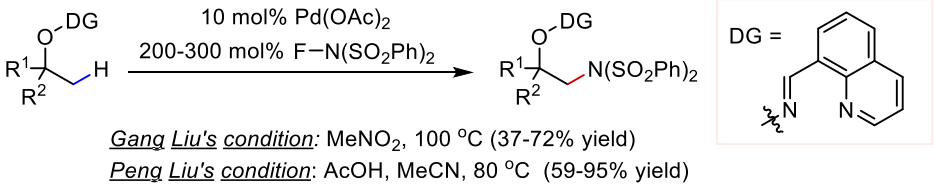
In 2017, Daugulis and coworkers reported a Pd-catalyzed β-C(sp^3)–H arylation promoted by a pyrazole DG (Scheme 1.16).[21] Aryl iodides were used as the aryl source, and a high yield was achieved when combining LiOTf/TFA/LiOAc and Ag_2O as the additives. Methyl and some methylene/methine C–H bonds were arylated with good tolerance of FGs. Upon ozonolysis, the pyrazole motif can be converted to an amide moiety.

Scheme 1.16 Pd-Catalyzed β-C–H Arylation of 1-Alkyl-1*H*-Pyrazoles



In 2017, Liu[22a] and Liu[22b] independently reported the Pd-catalyzed β-sulfonimidation of masked alcohols using NFSI as the oxidant and the nitrogen source (Scheme 1.17). The 8-quinolyl-derived aldoxime was found to be the optimal *exo* DG in each work. Methyl C(sp^3)–H bonds in various skeletons can be activated with tolerance of many FGs, such as free alcohols, olefins, primary alkyl chlorides and tosylates. 1,2-Amino alcohol derivatives were furnished upon removal of the DG and the sulfonyl group.

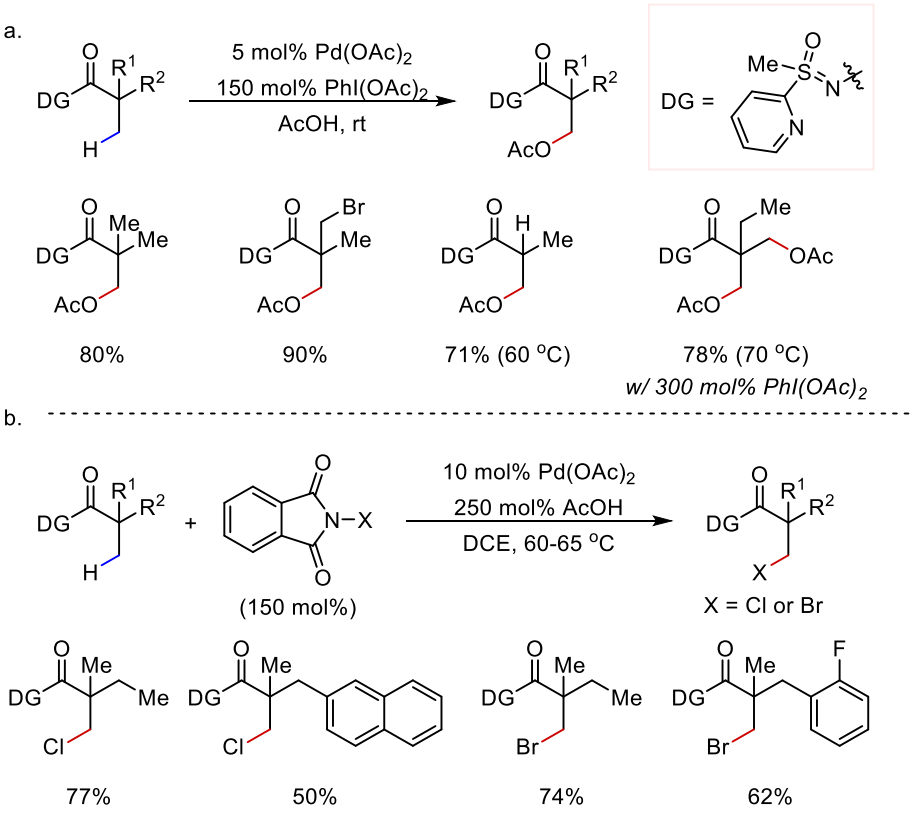
Scheme 1.17 Pd-Catalyzed β C–H Sulfonimidation of Masked Alcohols



An unique *S*-methyl-*S*-2-pyridylsulfoximine-based DG,[23] developed by Sahoo group, was found to be another effective *exo*-type DG that promotes the C(sp^3)–H activation (Scheme 1.18).[23b-c] Various primary β C–H bonds of sulfoximine-*N*-amides, which typically

derived from corresponding carboxylic acids or acyl chlorides, underwent facile acetoxylation[23b] (Scheme 1.18a) or halogenation[23c] (Scheme 1.18b) under Pd catalysis by using $PhI(OAc)_2$ or *N*-halophthalimide as the oxidant, respectively. A group of FGs were found compatible. The DG can be removed and recycled from the products through hydrolysis, furnishing free carboxylic acids in high yield.

Scheme 1.18 Pd-Catalyzed β C–H Acetoxylation/Halogenation of Sulfoximine-*N*-Amides

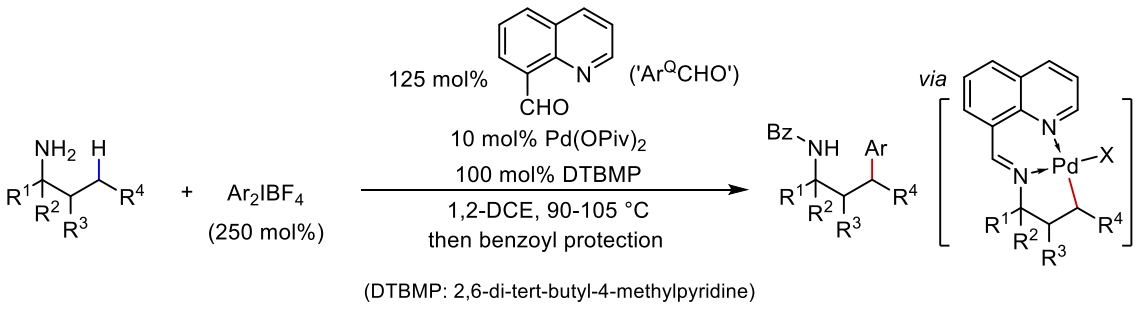


While significant progress has been made in the C–H activation using amide-,[24] sulfonamide-,[25] hydrazone-,[20] and urea-type DGs,[26] extra synthetic steps are required for the DG installation and removal. Hence, direct employment of free amine as the substrates became an ideal approach.[27] In 2016, the Dong,[28] Ge,[29] Yu,[30] and Murakami[31] groups independently reported the Pd-catalyzed γ-C(sp^3)–H arylation of free primary amines using 8-

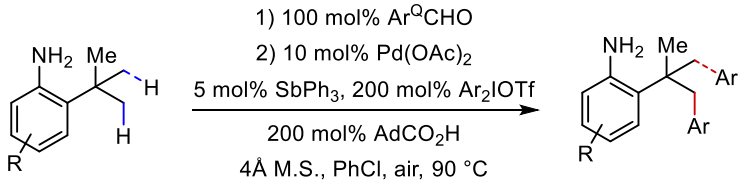
formylquinoline, glyoxylic acid, 2-hydroxynicotinaldehyde, and 3,5-di-*tert*-butylsalicylaldehyde as transient DGs (TDGs), respectively.

The 8-formylquinoline was first used by Dong and co-workers.[28] Through *in situ* condensation with free primary amines, an imine was formed, which promoted the γ-C–H activation as an *exo*-DG via formation of a [6,5]-fused palladacycle. By coupling with bisaryliodonium salts, methyl and methylene (cyclic and acyclic) C–H bonds at the γ-position were readily arylated (Scheme 1.19). The δ-arylation of 2-*tert*-butylanilines was also achieved under modified reaction conditions (Scheme 1.20). The detail of this work will be discussed further in Chapter 4.

Scheme 1.19. Pd-Catalyzed γ-C–H Arylation of Free Primary Amines using 8-Formylquinoline as the Transient Directing Group

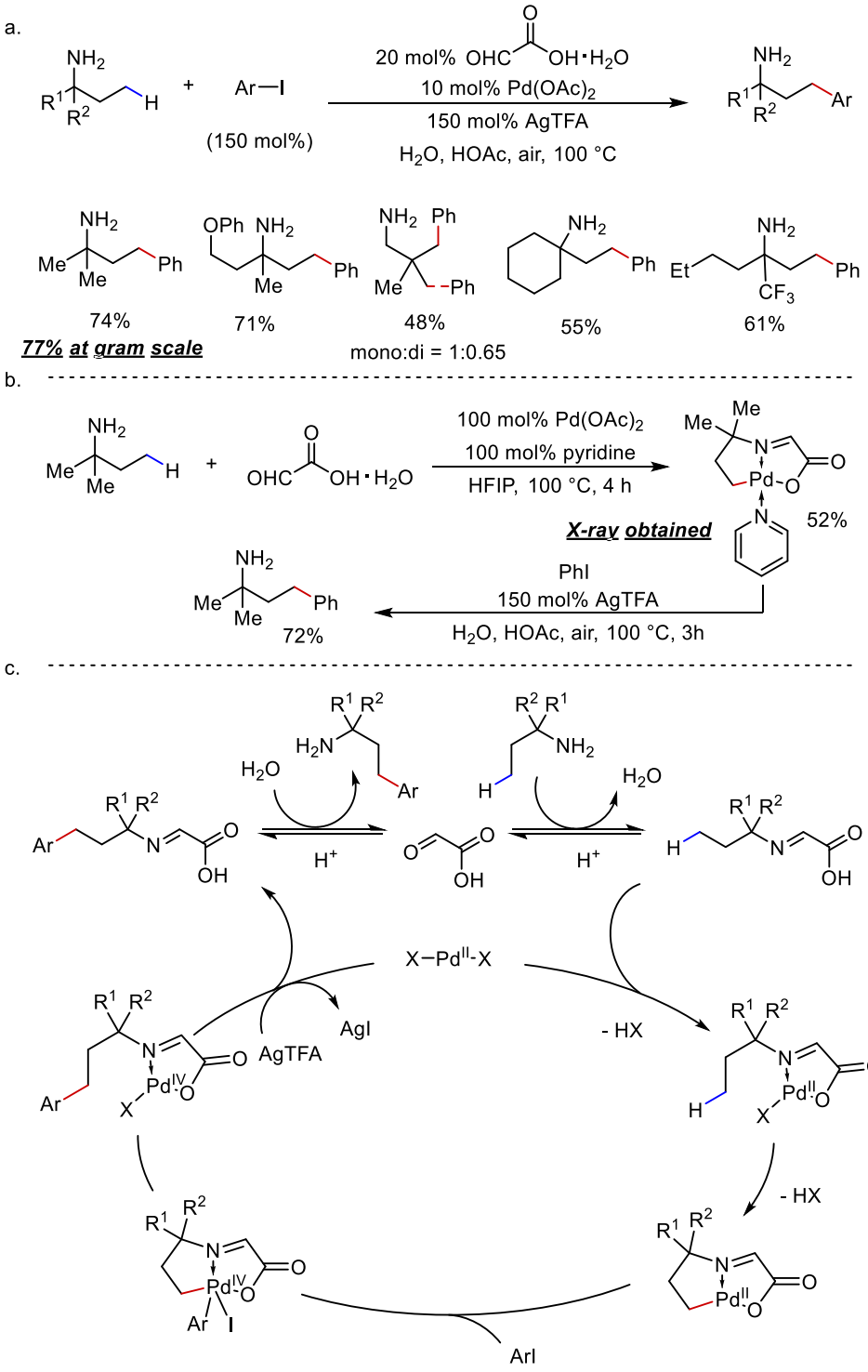


Scheme 1.20 Pd-Catalyzed δ C–H Arylation of 2-*tert*-Butylanilines



Ge and co-workers identified the glyoxylic acid monohydrate as another optimal TDG (Scheme 1.21).[29] By using 20 mol% of the TDG and 10 mol% of $Pd(OAc)_2$ as the catalyst, γ-arylated amines were furnished and directly isolated in high yields from a large number of primary amines and aryl iodides in the presence of stoichiometric silver salt (Scheme 1.21a). Amines with a secondary α carbon were found incompatible due to α-oxidation and the lack of Thorpe–Ingold effect. A C–H palladated complex that featured a [5,5]-fused palladacycle was obtained by reacting *tert*-amylamine with glyoxylic acid and stoichiometric $Pd(OAc)_2$. Further treatment of this complex with arylation condition yielded γ-arylated *tert*-amylamine as the product (Scheme 1.21b). A detailed reaction mechanism was proposed accordingly (Scheme 1.21c).

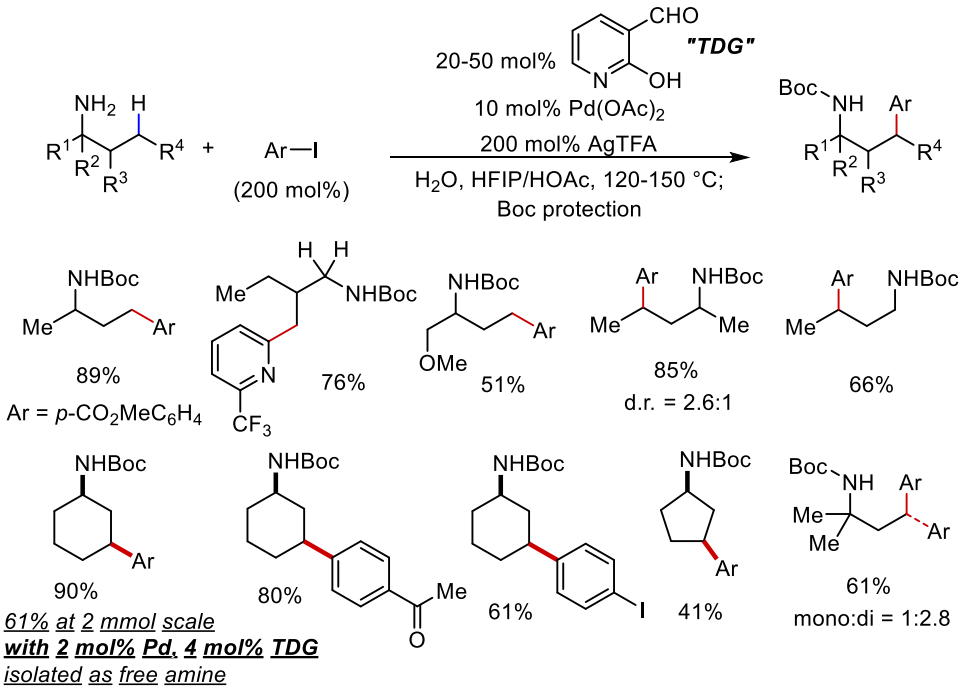
Scheme 1.21 Pd-Catalyzed γ C–H Arylation of Free Primary Amines using Glyoxylic Acid as the Transient Directing Group



Yu and coworkers discovered that the same type of reactions could also be achieved by using 20-50 mol% 2-hydroxynicotinaldehyde as the TDG (Scheme 1.22).[30] A range of different aryl and heteroaryl iodides were readily coupled with primary amines through the activation of γ-methyl and methylene C–H bonds. Various FGs were well tolerated. In one

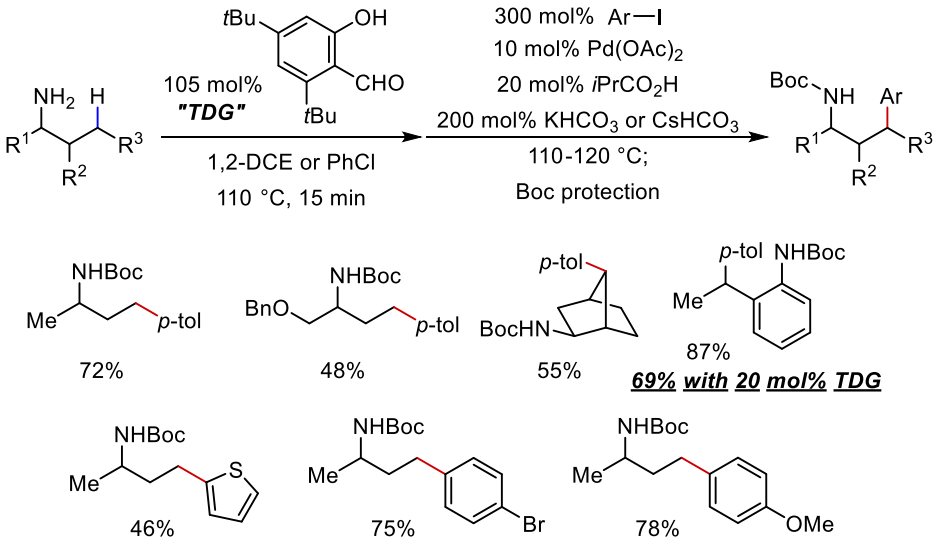
example, unprotected γ-arylated cyclohexylamine product was obtained in 61% yield on a 2 mmol scale when only 4 mol% TDG and 2 mol% of Pd were employed.

Scheme 1.22 Pd-Catalyzed γ C–H Arylation of Free Primary Amines using 2-Hydroxynicotinaldehyde As The Transient Directing Group



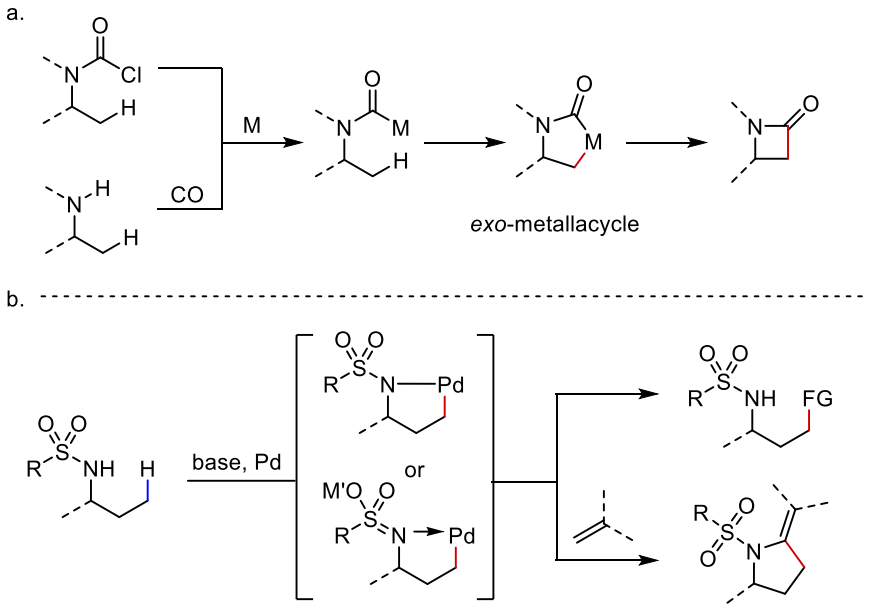
3,5-Di-*tert*-butylsalicylaldehyde was found to be another effective TDG by Murakami and co-workers (Scheme 1.23).[31] Pre-condensation between the amine substrates and the TDG was carried out at 110 °C for 15 min before the addition of the rest of reagents. Various aryl iodides and unprotected primary amines were compatible. The feasibility of using the DG in a catalytic fashion was also demonstrated in one example with 2-ethylaniline as the substrate.

Scheme 1.23 Pd-Catalyzed γ C–H Arylation of Free Primary Amines using 3,5-Di-*tert*-Butylsalicylaldehyde As The Transient Directing Group



Two other types of sp^3 C–H activation *via* the formation of *exo*-metallocycles are also worthy to be mentioned, although the DGs or the directing motifs applied in these reactions may not strictly qualify as typical *exo*-DGs (Scheme 1.24). In the first case, a carbamoyl-metal species is generated from either (i) oxidative addition of acyl chlorides,[32] or (ii) carbonylation of free amines.[27c,33] Upon cyclometalation at the β C–H bond, an *exo*-metallocycle is formed, which further transforms to β-lactams through reductive elimination[32,33] (Scheme 1.24a). A similar reaction mode was also reported with vinyl bromides through sequential oxidative addition / C–H metalation to induce intramolecular C(sp^3)–H activation and the subsequent formation of C–C bonds.[1o,34] In the second scenario, it is sometimes proposed that the deprotonation of sulfonamide under basic condition generates a sulfonaimine motif, which promotes the cyclopalladation at the γ-position as an *exo*-DG.[25,35] Further transformations of this intermediate lead to various C–C bond forming reactions (Scheme 1.24b). Given the space limitation, these two types of reactions will not be discussed in details.

Scheme 1.24 Other Types of C(sp^3)–H Activation *via* the Formation of *exo*-Metallocycles



1.4 Conclusions and Outlook

The *exo*-type DGs have emerged as a powerful tool in functionalization of unactivated sp^3 C–H bonds particularly in alcohol or amine-containing compounds. A range of novel directing modes and unconventional site selectivity have therefore been disclosed using *exo*-type DGs, such as in the β–functionalization of masked alcohols, and in the β- and γ-functionalization of amines. It is anticipated that applications of these distinct methods in complex molecule syntheses would appear more frequently in the future work. Functionalization of other classes of compounds beyond alcohols and amines using such an *exo*-directing mode will continue to be discovered. In addition, to form larger metallacycles with the activation of more remote C–H bonds through incorporation with other transition metals and/or evolution of the *exo*-DGs continuously represents an exciting direction of

research. Finally, developing various, more powerful and efficient transient *exo*-DGs is expected to gain more attention in the ongoing studies.

(Some contents of this chapter were published in *Chem. Sci.* **2018**, *9*, 1424)

1.6 References

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CHAPTER 2

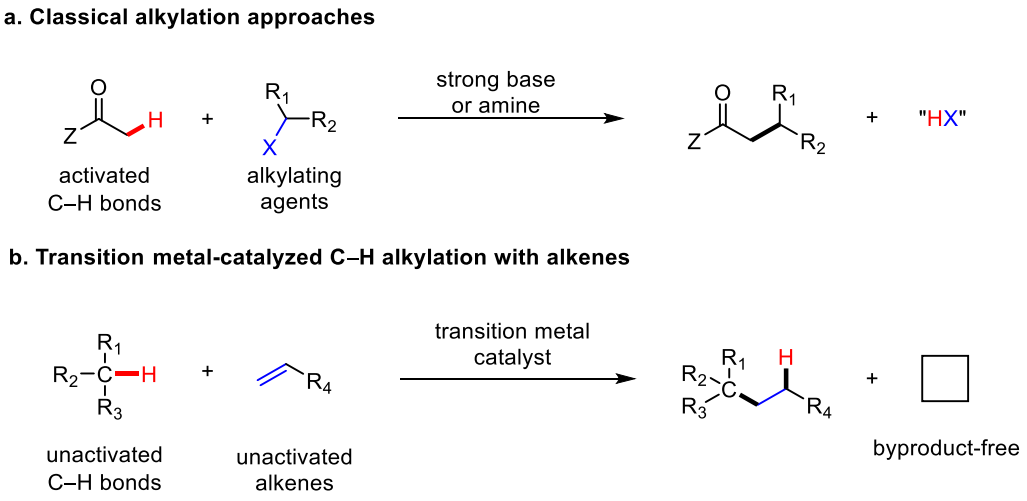
Transition Metal-Catalyzed Alkylation of sp^3 C−H Bonds Using Alkenes

2.1 Introduction

Carbon−carbon (C−C) bond construction is the foundation of pure and applied organic chemistry, as organic molecules are essentially any molecule that contains carbons. The alkylation reaction of C(sp^3)–H bonds, such as the coupling between an alkylating agent and a nucleophile, has been employed numerous times in the synthesis of compounds for various purposes, and is arguably one of the most important types of reactions that construct C−C bond (Scheme 2.1). Conventionally, the nucleophiles for these alkylation reactions are generated from activated C(sp^3)–H bonds, such as the α C(sp^3)–H bonds of carbonyl compounds, through the use of strong bases or amines. Besides, reactive alkylating agents, such as alkyl halides, are generally required. While

efficiency, these transformations, in many cases, are still concerned about the availability of the nucleophiles and the alkylating agents, as well as the compatibility of the acid/base-involved reaction conditions with other reactive functional groups (Scheme 2.1a). With the advance of transition metal catalysis, in the recent decade, a new alkylation approach arose by splitting an C(sp^3)–H bond and then adding them across an unactivated alkenes (Scheme 2.1b). Compared to the traditional approaches, the new methods employ unactivated C(sp^3)–H bonds as substrates and cheaper olefins as alkylating agents, and in principle, could be performed in redox-neutral, strong acid/base-free conditions without the formation of any by-product. Good functional group compatibility is further expected, especially when considering the reactivity of alkenes is *ortho*gonal to many functional groups. In this section, the transition metal-catalyzed alkylation of C(sp^3)–H bonds using alkenes will be reviewed in detailed. The alkylation reactions of activated C(sp^3)–H bonds, as well as the reactions using more reactive allenes, conjugated enynes or Micheal acceptors, will not be discussed.

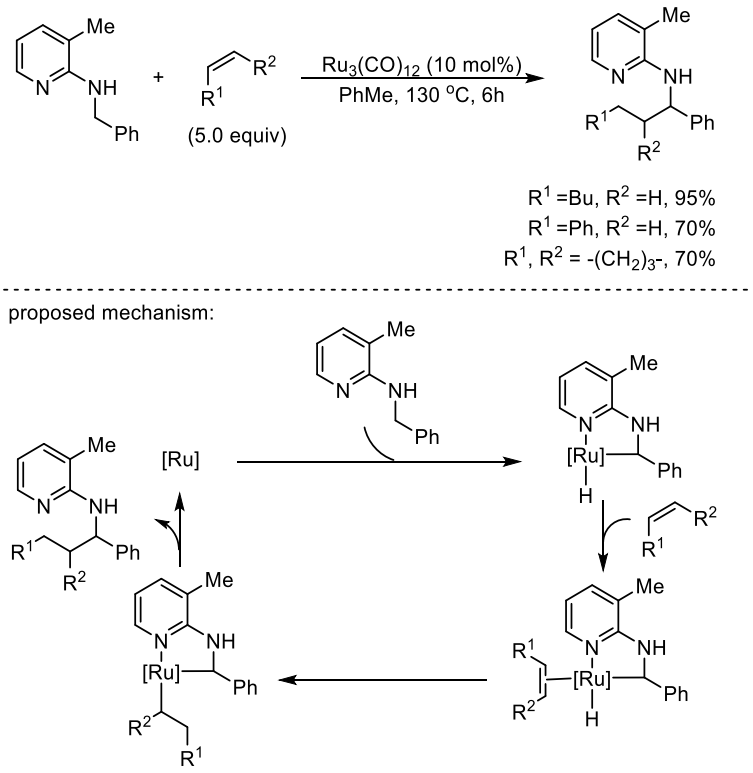
Scheme 2.1 Alkylation of sp^3 C–H Bonds



2.2 Directing Group Assisted Alkylation

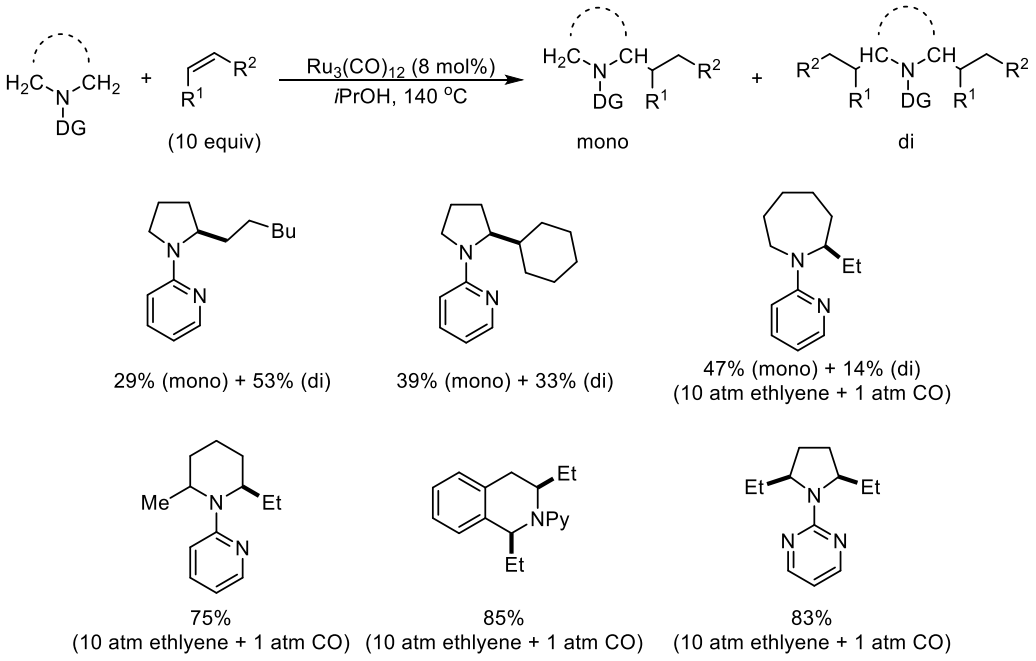
The first Ru-catalyzed alkylation of benzylic C–H bonds was reported by Jun in 1998 (Scheme 2.2).[1] Using a $Ru_3(CO)_{12}$ catalyst, *N*-benzyl-*N*-(3-methyl-2-pyridyl)amine could react with both terminal and cyclic alkenes with good yields. The reaction mechanism was proposed as follows: pyridine-directed oxidative addition of the Ru(0) catalyst into the benzylic C–H bond to form a 5-membered metallacycle complex, followed by coordination of an olefin, hydride-insertion and reductive elimination to form the desired alkylation product and regenerate the Ru(0) catalyst. It is noteworthy that the methyl group at the 3-position of the pyridine is required, which may retard the free rotation of the benzyl group around the amine and help the benzylic C–H bond to approach the metal center after coordination.

Scheme 2.2 Ru-Catalyzed C–H Alkylation of 2-(Benzylamino)pyridines



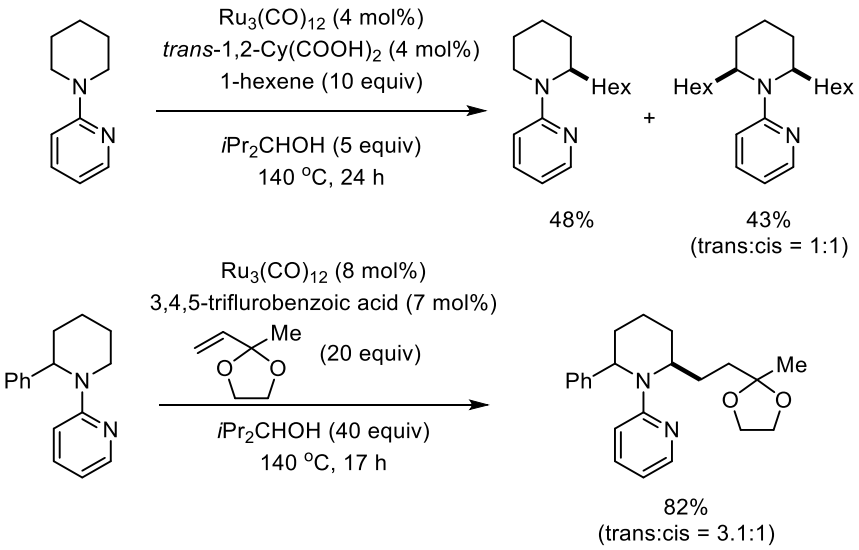
Later, the reaction was expanded to regular aliphatic C–H bonds adjacent to nitrogen atoms by Murai (Scheme 2.3).[2] Cyclic amines were found to be more reactive than acyclic ones, and both the pyridine and the pyrimidine moiety could serve as effective directing groups. Systematic studies revealed that electron-withdrawing substituents on the pyridine ring as well as substitution adjacent to the sp^2 nitrogen decreased the catalyst reactivity. The presence of CO in some cases was not essential, but was able to keep the reaction clean, putatively by suppressing catalyst decomposition. Although a detailed reaction mechanism was not clear, an H/D exchange experiment between the substrates and the alkenes indicated that the C–H cleavage was reversible, suggesting that C–H bond cleavage is not the rate-determining step.

Scheme 2.3 Ru-Catalyzed Alkylation of α-to-Nitrogen C–H Bonds



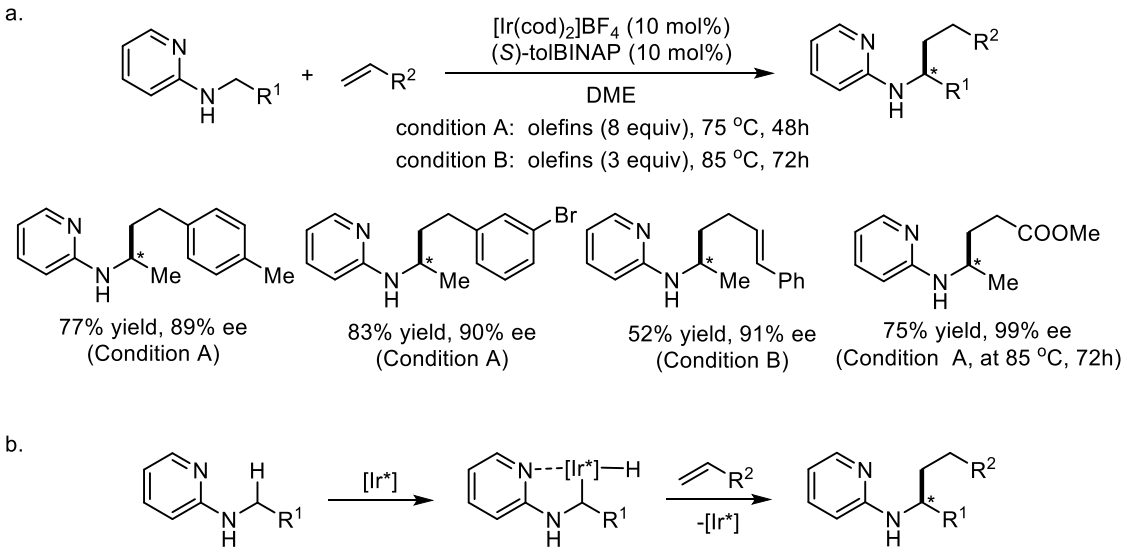
Expanding on the same catalytic system, Maes found that using a hindered alcohol solvent and a catalytic amount of a carboxylic acid promoter allowed for a directed Ru-catalyzed C–H bond alkylation of piperidines, which are less-reactive substrates compared to the corresponding five-membered cyclic amines (Scheme 2.4).[3,4] The hindered alcohol was proposed to promote the formation of the key H–Ru^{II}–OOCR intermediate. Upon alkene insertion and coordination to the substrate, the resulting Ru-bound carboxylate was expected to undergo the C–H bond cleavage through a concerted metalation-deprotonation (CMD) mechanism to give a bis-alkyl Ru complex, which then undergoes reductive elimination to give the product.

Scheme 2.4 Ru-Catalyzed C–H Alkylation of Piperidines



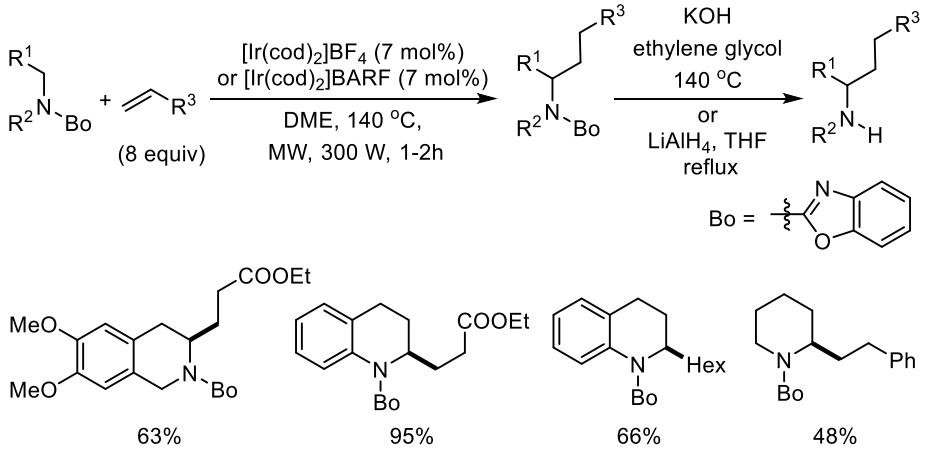
In 2011, Shibata and coworkers reported an enantioselective alkylation of 2-(alkylamino)pyridines with a chiral Ir catalyst.[5,6] Various acyclic amines can undergo the transformation smoothly with different olefins, and tol-BINAP was found to provide the highest enantioselectivities (Scheme 2.5a). An Ir-hydride-mediated mechanism was proposed for this reaction (Scheme 2.5b).

Scheme 2.5 Ir-catalyzed Enantioselective C–H Alkylation of 2-(Alkylamino)pyridines



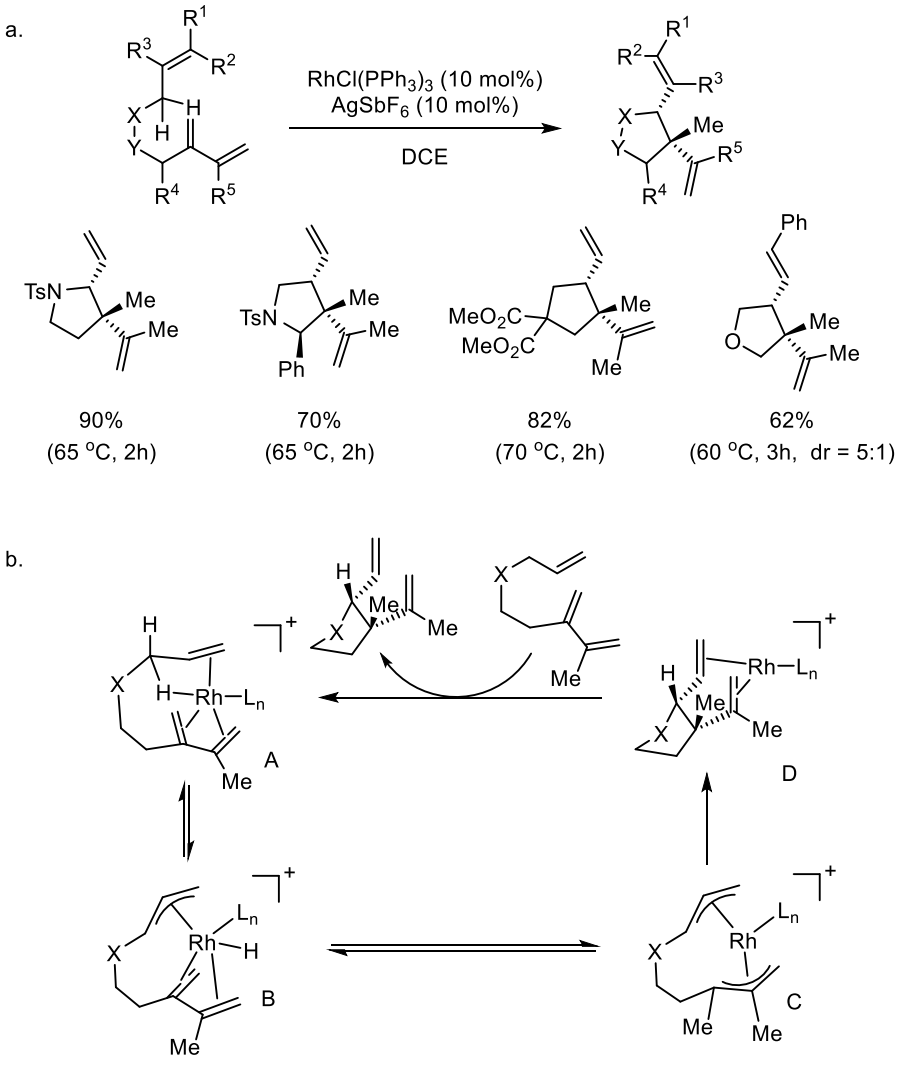
By taking advantage of benzoxazole as a removable directing group, Opatz later reported a similar Ir-catalyzed transformation.[7] Moderate to high yields and good selectivities for monoalkylation were observed for both six-membered cyclic amines and open-chain amine substrates, while the five-membered cyclic analogue provided mixtures of mono- and multi-alkylated products (Scheme 2.6). The benzoxazole group can be removed by treatment with KOH in ethylene glycol at 140 °C or with $LiAlH_4$ in refluxing THF.

Scheme 2.6 Ir-catalyzed C–H Alkylation of 2-(Alkylamino)benzoxazoles



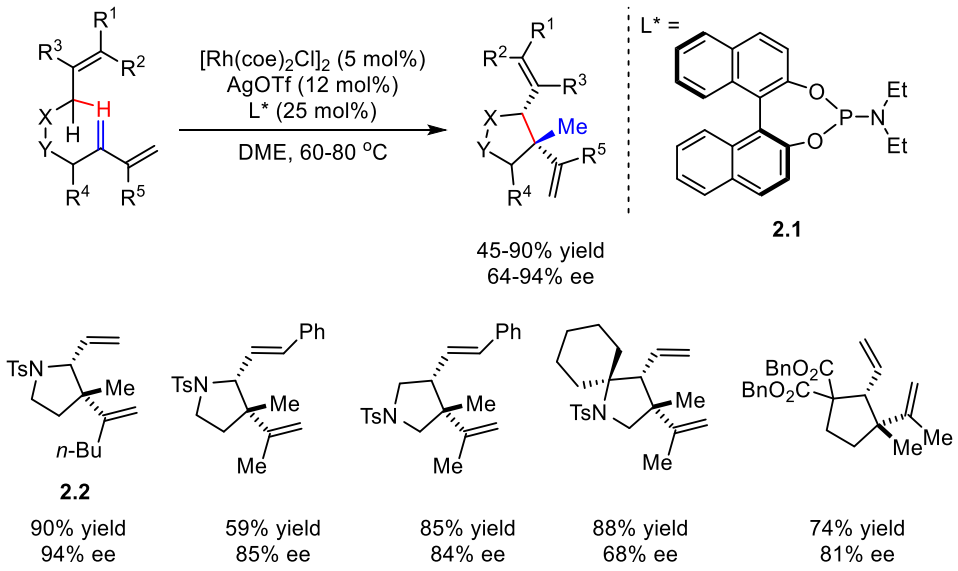
Allylic C–H bonds also proved to be good substrates in the conjugated diene-assisted allylic C–H alkylation reaction reported by Yu in 2010.[8] Using a cationic Rh(I) catalyst, a variety of polysubstituted tetrahydrofurans, tetrahydropyrroles and cyclopentanes were synthesized from tethered ene-2-dienes. The reaction proceeded with good diastereoselectivity (Scheme 2.7a). The mechanism was explored by DFT calculations.[9] It was found that coordination with the diene moiety promotes an intermolecular C–H activation, and the resulting Rh–H inserts into the diene to give a bisallyl Rh complex, which then undergoes reductive elimination to give the product (Scheme 2.7b).

Scheme 2.7 Rh-catalyzed Conjugated Diene-assisted Allylic C–H Alkylation



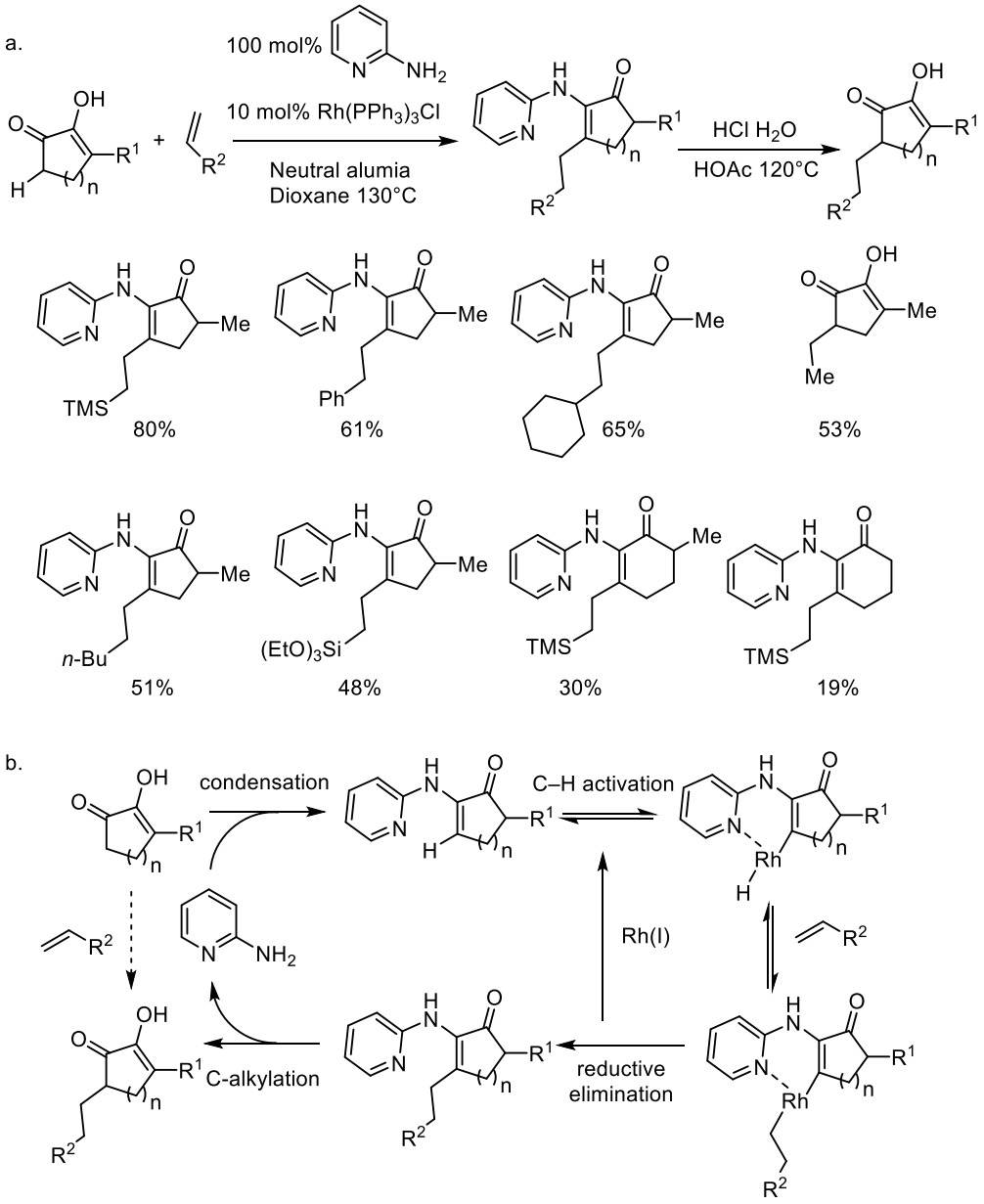
In 2011, Yu and coworkers found that chiral phosphoramidates **2.1** enabled an enantioselective version of this reaction with high diastereomeric-control (Scheme 2.8).[10] Interestingly, the chiral diene product **2.2** proved to be an efficient ligand for Rh(I)-catalyzed asymmetric 1,4-additions.[11]

Scheme 2.8 Rh-catalyzed Enantioselective assisted Allylic C–H Alkylation



In 2012, Dong and coworkers reported an intermolecular C–H alkylation of 1,2-diketones with simple alkyl and aryl olefins (Scheme 2.9a).[12] The reaction starts with condensation between the diketone and 2-aminopyiridine to give the corresponding enamine. The pyridine then directs oxidative addition of Rh to give a Rh(III)-hydride species. The Rh-hydride undergoes migratory insertion into the olefin to give the key intermediate, which then reductively eliminates to yield the alkylation product (Scheme 2.9b). Unfortunately, condensation between the diketone and aminopyridine was not reversible under the reaction conditions and an additional step to hydrolyze the directing group was needed.

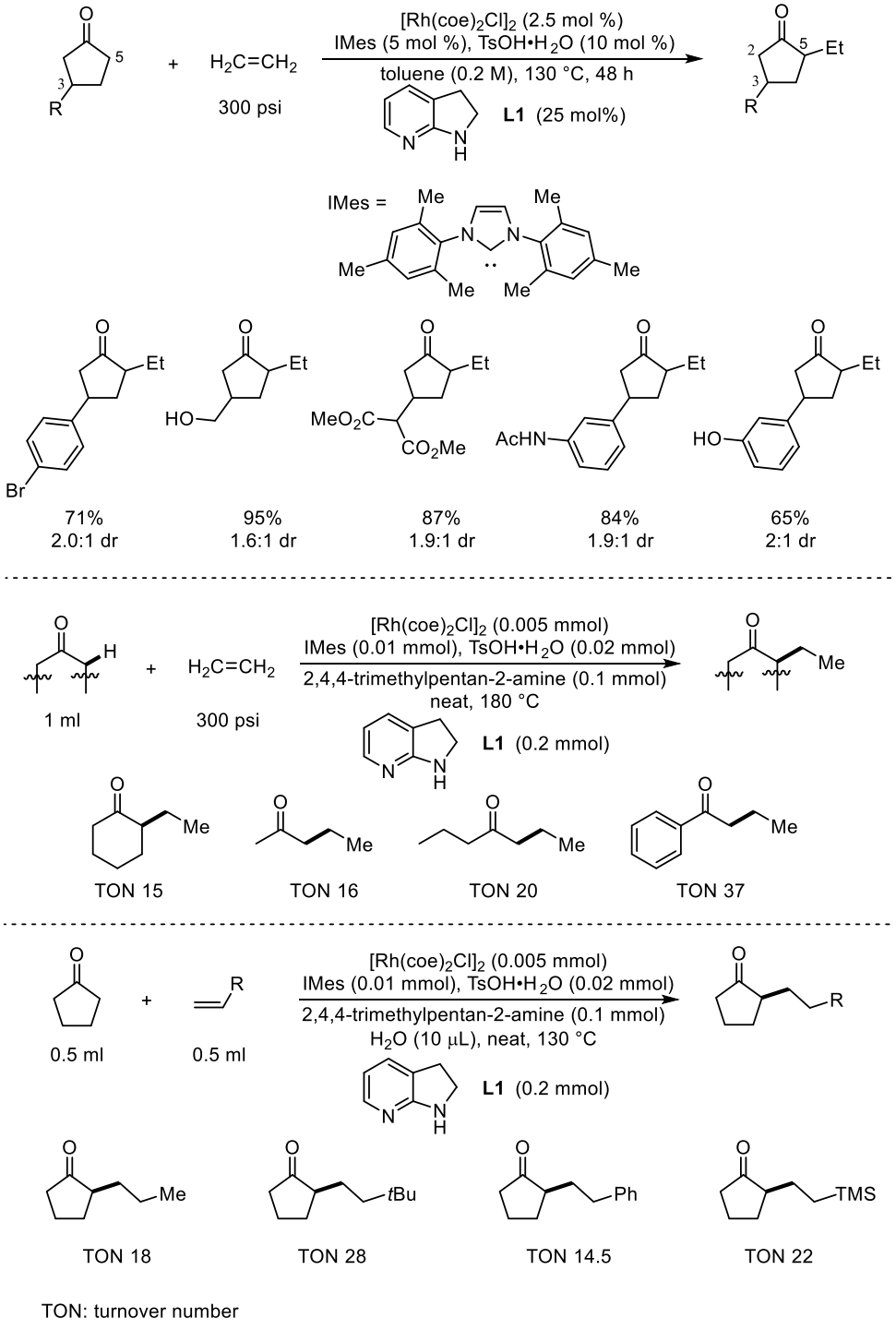
Scheme 2.9 Rh-catalyzed C–H Alkylation of 1,2-Diketones



In 2014, a direct alkylation of regular ketones with simple olefins was achieved by using 7-azaindoline as the bifunctional catalyst.[13] While Wilkinson's catalyst gave low reactivity, use of a NHC ligand significantly enhanced the efficiency. Various 3-substitued cyclopentanones can be smoothly coupled with ethylene regioselectively at the less hindered C5 position. A number of functional groups, including free alcohols, phenols, amines, esters, amides, nitriles, thioethers and arylbromides were tolerated. While less efficient, other cyclic

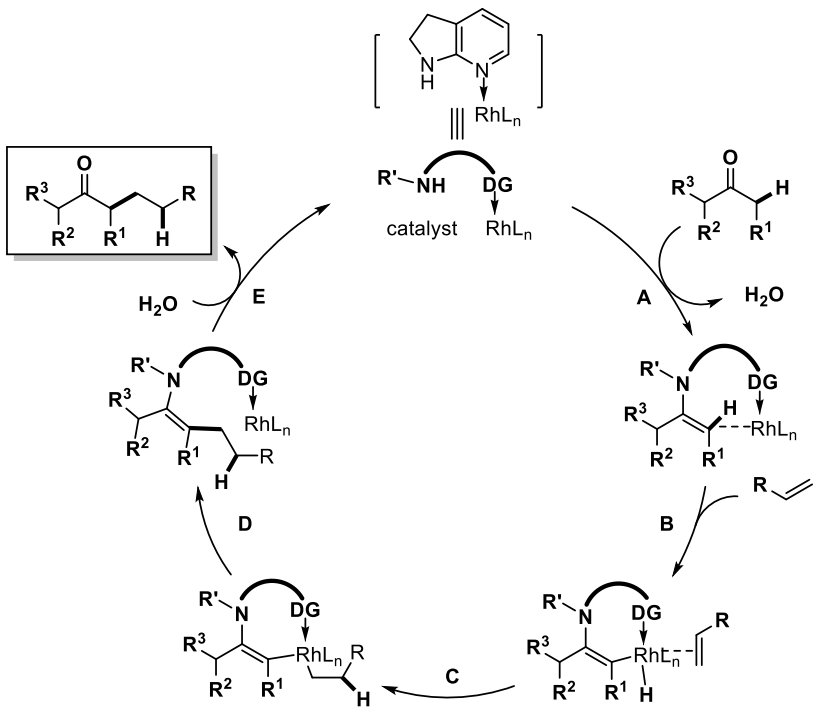
and acyclic ketones as well as several α-olefins can also be used as substrates under modified conditions (Scheme 2.10).

Scheme 2.10 Rh- and 7-Azaindoline-catalyzed C–H Alkylation of Regular Ketones



The mechanism was proposed to proceed with initial condensation of the amine with the ketone to form an enamine intermediate (step A, Scheme 2.11). Coordination of the Rh(I) catalyst by the pyridine moiety facilitates insertion into the enamine vinyl C–H bond to generate a metal-hydride species (step B), which further undergoes olefin migratory insertion (step C) and reductive elimination (step D) to give an alkylated enamine. Hydrolysis gives the α-alkylation product and regenerates the catalyst (step E).

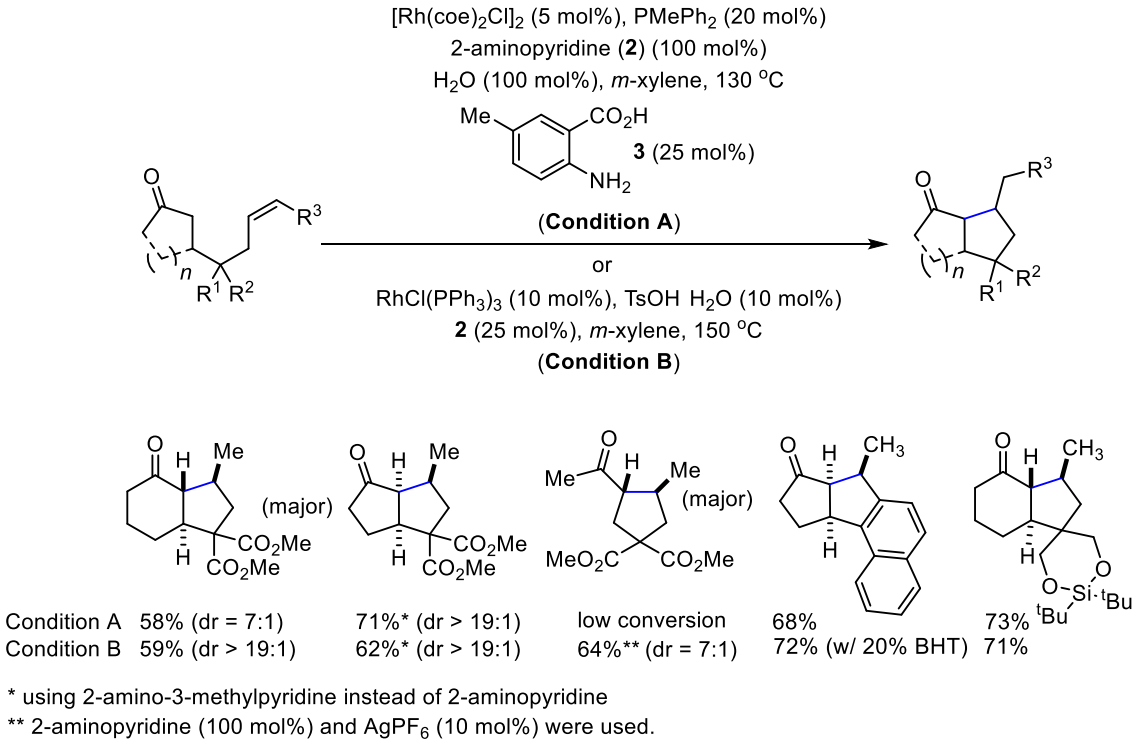
Scheme 2.11 Proposed Mechanism for the Rh- and 7-Azaindoline-catalyzed C–H Alkylation



A catalytic intramolecular ketone–olefin coupling was reported in 2015.[14] Taking advantage of a similar dual-activation mode, a bifunctional ligand, such as 2-aminopyridine, was used to form enamines with ketones and promote C–H coupling with the pendent olefin. While the rhodium catalysts are more effective for the formation of five-membered rings, a ruthenium-based system was discovered to afford the six-membered ring products. In

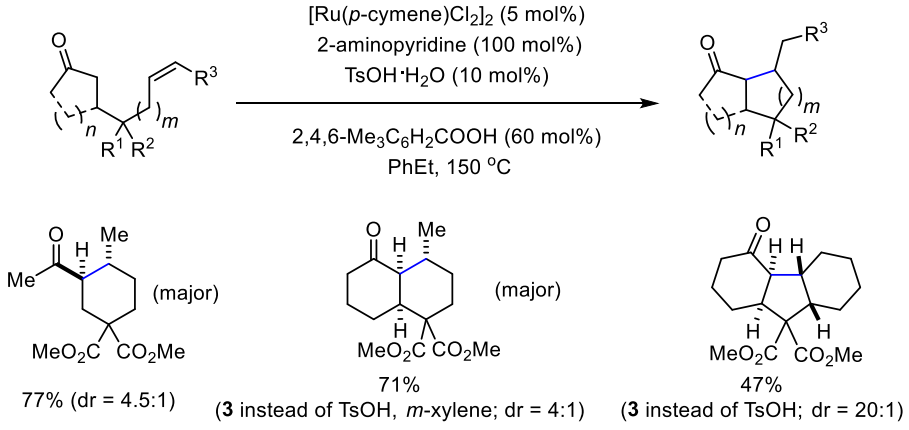
addition, this alkylation reaction can be conducted under both pH- and redox-neutral conditions, which makes it complementary to previously developed Conia-ene-type reactions. For example, a number of acid-sensitive functional groups, such as ketal, silyl ethers and aryl olefins, are tolerated in this reaction (Scheme 2.12 and 2.13).

Scheme 2.12 Rh-catalyzed Intramolecular C–H Alkylation of Ketones with Tethered Olefins



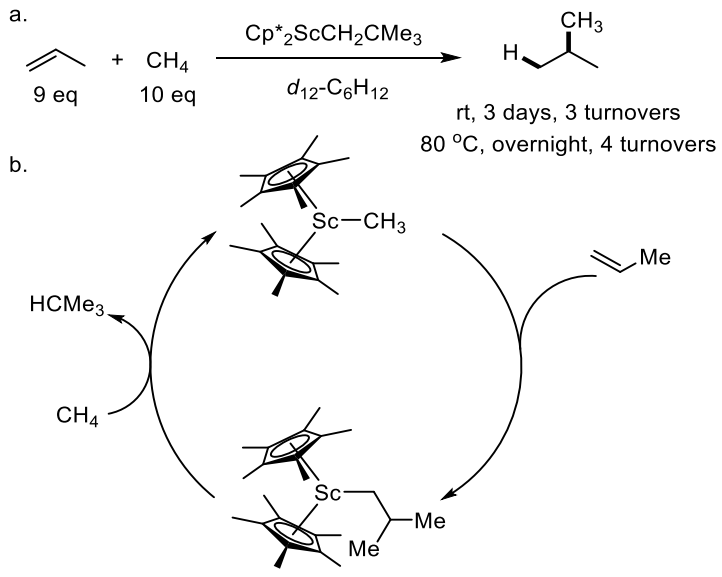
* using 2-amino-3-methylpyridine instead of 2-aminopyridine
** 2-aminopyridine (100 mol%) and $AgPF_6$ (10 mol%) were used.

Scheme 2.13 Ru-catalyzed Intramolecular C–H Alkylation of Ketones with Tethered Olefins



The first example of the rare-earth metal-catalyzed alkylation of simple alkanes with olefins was reported by Tilley in 2003.[15] The scandium alkyl species $Cp^*_2ScCH_2CMe_3$ was synthesized by the addition of a pentane solution of $LiCH_2CMe_3$ into Cp^*_2ScCl at low temperature, forming a very reactive organometallic complex which enabled a hydromethylation reaction between propene and methane (9 and 10 equiv, respectively) in cyclohexane, albeit in low TONs (Scheme 2.14a). The proposed reaction mechanism is depicted in Scheme 2.14b, involving a σ-bond metathesis between the $Cp^*_2ScCH_2CMe_3$ and methane with subsequent olefin insertion. Unfortunately, other olefins, such as 2-butene, 1-hexene, 1-butene, 2-methylpropene and norbornylene, failed to react with methane, even at elevated temperatures.

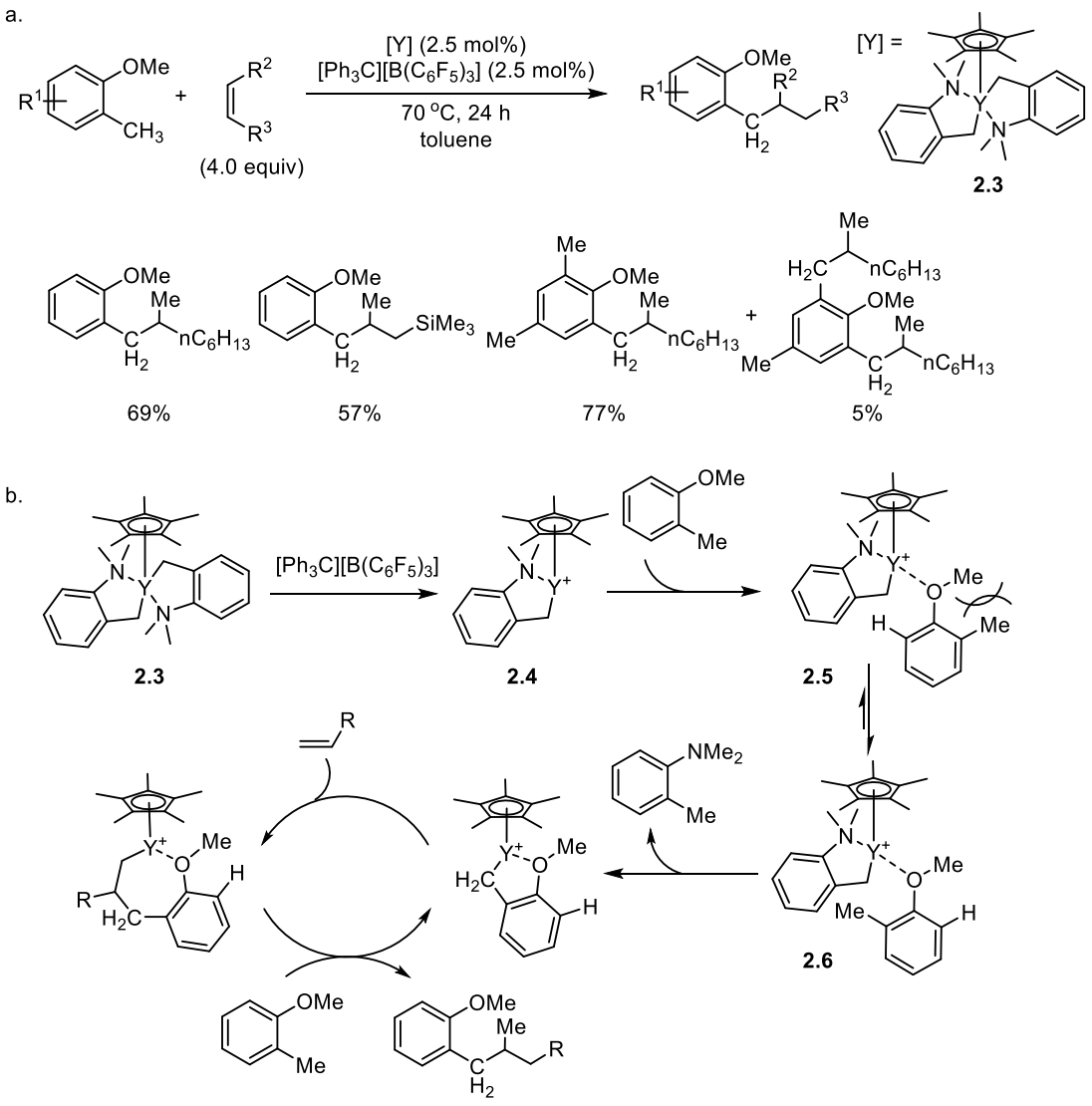
Scheme 2.14 Sc-catalyzed Hydromethylation of Propene with Methane



Another interesting rare-earth metal-catalyzed benzylic C–H alkylation with olefins was reported in 2012 by Hou.[16] Through combination of a half-sandwich dialkyl yttrium species and an equal equivalent of $[Ph_3C][B(C_6F_5)_4]$, the alkylation of various 2-

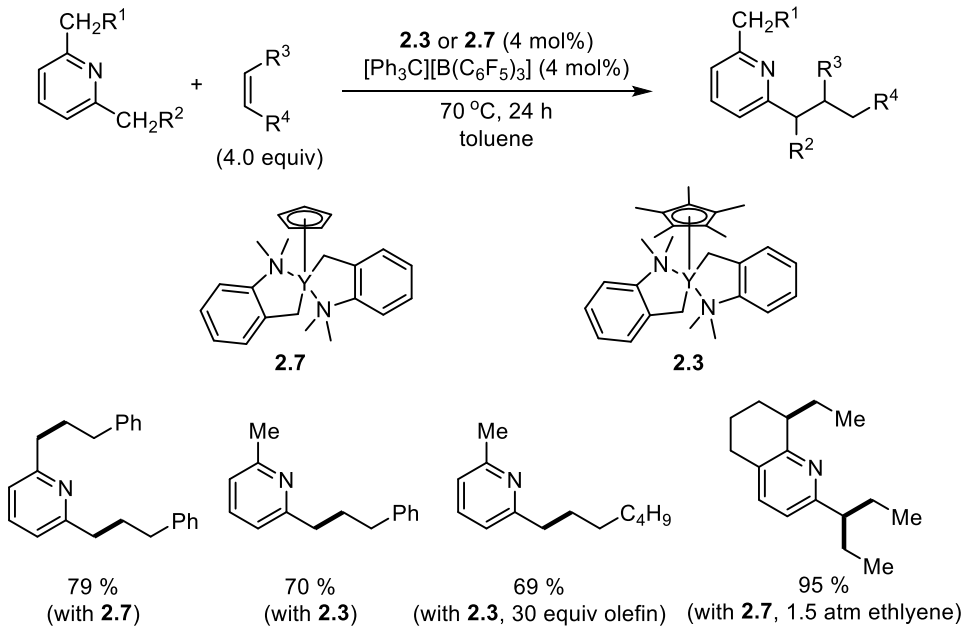
methylanisoles took place smoothly to generate the branched products in good yields (Scheme 2.15a). The mechanism was proposed to involve the following sequence of steps: (i) coordination of the ether oxygen to the cationic monoalkyl metal species **2.4** (generated in situ from the reaction between the dialkyl pre-catalyst **2.3** and $[Ph_3C][B(C_6F_5)_4]$); (ii) ligand-directed C–H metallation through σ-bond metathesis; (iii) olefin insertion into the Y-alkyl bond; and (iv) deprotonation of another 2-methylanisole substrate to generate the mono-alkyl catalyst. The selectivity for the sp^3 benzylic C–H bond over aromatic sp^2 C–H bonds is potentially due to the unfavorable steric interaction in intermediate **2.5**. If sterically allowed, the C–H activation at the *ortho*-sp^2 C–H bond would still be preferred (Scheme 2.15b).

Scheme 2.15 Y-catalyzed Benzylic C–H Alkylation of 2-Methylanisoles



Reactions of simple olefins with the benzylic C–H bonds of alkyl pyridines were also achieved by the same group.[17] The reaction mechanism is similar to the previous case. The $[C_5H_5YR_2]$ (**2.7**) catalyst was found to afford multi-alkylation products, while the more sterically demanding complex, $[C_5Me_5YR_2]$ (**2.3**), favored monoalkylation products. Interestingly, the methylene C–H bonds on the benzylic position can also smoothly participate in the reaction (Scheme 2.16).

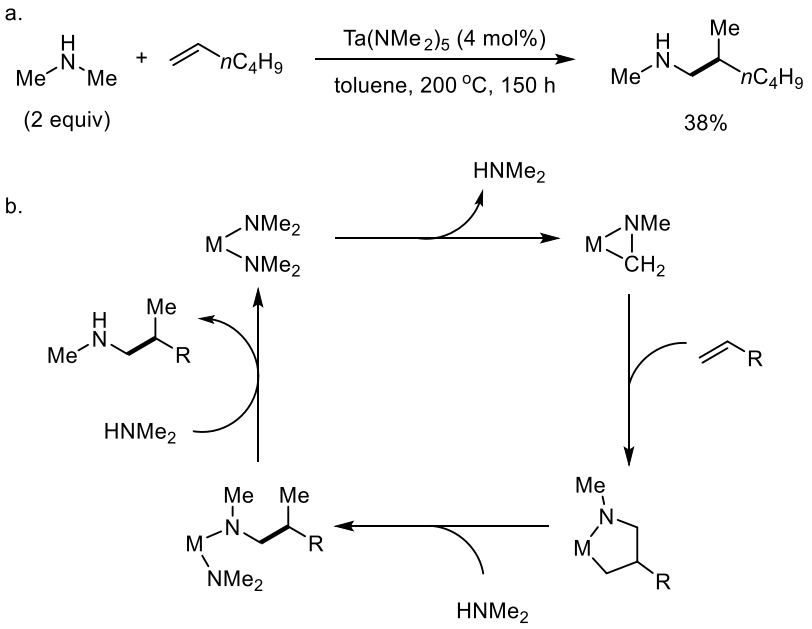
Scheme 2.16 Y-catalyzed Benzylic C–H Alkylation of 2-Alkylpyridines



2.3 Hydroaminoalkylation

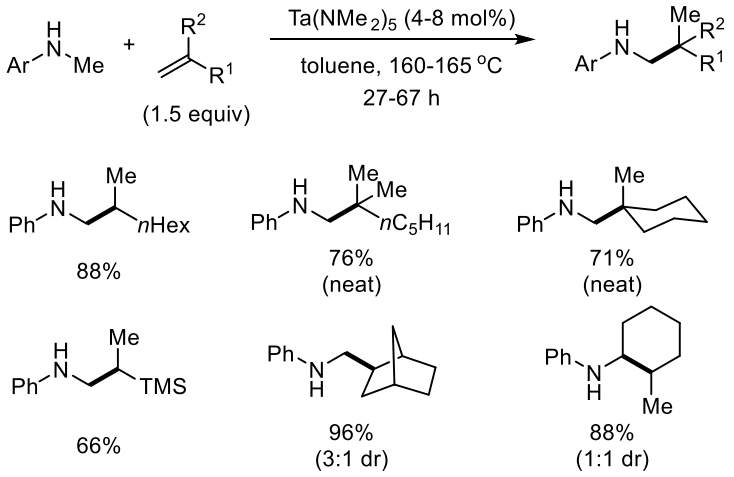
Over 30 years ago, Maspero[18] and Nugent[19] reported early examples of a direct α-alkylation of dialkylamines with simple olefins in the presence of homoleptic dimethylamido complexes of groups IV and V transition metals. After testing a series of niobium, tungsten and tantalum complexes as catalysts, the best result was achieved with $Ta(NMe_2)_5$. Heating dimethyl amine and 1-hexene at 200 ºC for 150 hours produced 38% of the branched hydroaminoalkylation product (Scheme 2.17a). A mechanism was proposed by Nugent as follows: (i) formation of the azametallacyclopropane (η^2-imine complex) via reversible C–H metalation of the dimethylamido ligand (amine elimination), (ii) insertion of the olefin to give a five-membered metallocycle, (iii) protonation, and, finally, (iv) ligand exchange with another amine moiety to release the product and start a new catalytic cycle (Scheme 2.17b).

Scheme 2.17 Early Examples of Transition Metals-catalyzed α-Alkylation of Dialkylamines



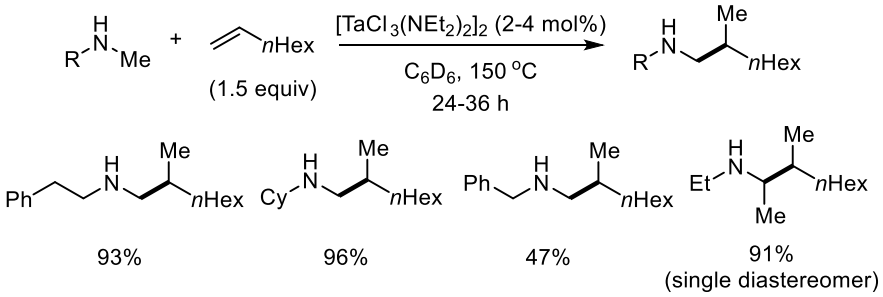
This reaction was revisited by Herzon and Hartwig in 2007, leading to the development an efficient catalytic hydroaminoalkylation reaction of *N*-alkyl arylamines with simple olefins.[20] Given that the corresponding zirconocene-η^2-imine complex forms faster from *N*-alkyl arylamido species rather than dialkylamido species,[21] it was hypothesized that the desired hydroaminoalkylation reaction would proceed more efficiently with *N*-alkyl arylamine substrates. Indeed, the expected hydroaminoalkylation products were formed in generally good yields within a shorter reaction period (27-62 h) at lower temperatures (160-165 ºC). Both mono- and 1,1-disubstituted olefins were suitable coupling partners; however, unstrained 1,2-disubstituted olefins could not be utilized (Scheme 2.18).

Scheme 2.18 $Ta(NMe_2)_5$-catalyzed Hydroaminoalkylation with *N*-alkyl Arylamines



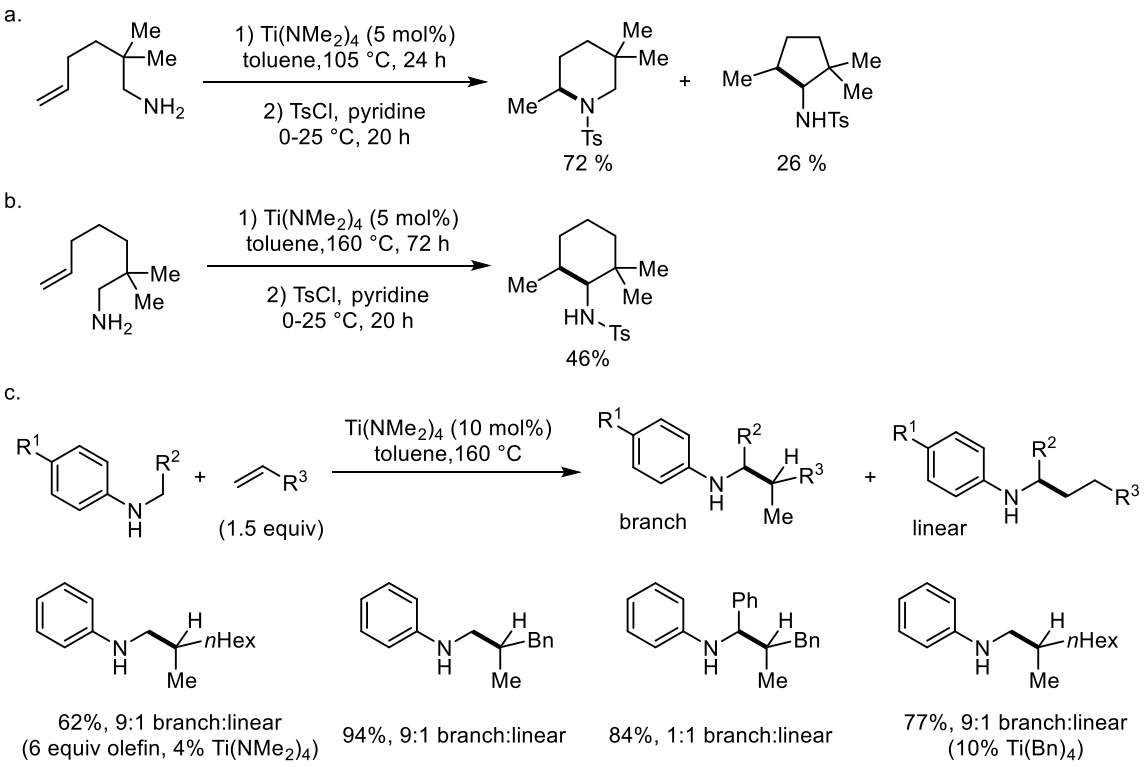
Later, more reactive hydroaminoalkylation reaction with dialkylamines was reported by the same group utilizing a less electron-rich chloroamido complex $[TaCl_3(NEt_2)_2]_2$ as the pre-catalyst.[22] The addition of olefins to the α-C–H bonds of both methyl and ethyl groups proceeded efficiently in good to excellent yields. Interestingly, *N*-methylbenzylamine reacted selectively at the methyl position, despite the existence of the more acidic benzylic C–H bond (**Scheme 2.19**). Further investigation demonstrated that the chloroamido complex $[TaCl_3(NMePh)_2]_2$ can catalyze the hydroaminoalkylation reaction with *N*-alkyl arylamines effectively at 90 °C, while the previously reported $Ta(NMe_2)_5$ catalyst showed no activity at this temperature. A preliminary mechanistic study implied that formation of the metallacyclopropane (η^2-imine complex) was the turnover-limiting step under the current conditions.

Scheme 2.19 $[TaCl_3(NEt_2)_2]_2$-catalyzed Hydroaminoalkylation with Dialkylamines



In 2009, a Ti-catalyzed hydroaminoalkylation reaction was reported by Doye and coworkers.[23] The reaction was uncovered during their study of the intramolecular hydroamination of 1-amino-5-hexenes, where aminocyclopentanes were formed as a side product (Scheme 2.20a). 1-Amino-6-heptenes were selected as the substrates to suppress the undesired hydroamination reaction, which would lead to an unfavorable seven-membered ring. Indeed, the hydroaminoalkylation product was isolated in 46% yield (Scheme 2.20b). Expansion to an intermolecular reaction between secondary amines and alkenes was successful, involing the activation of C–H bonds at methyl or benzylic positions (Scheme 2.20c). Further investigation showed that tetrabenzyltitanium ($Ti(Bn)_4$) was also an effective catalyst for these transformations, including the hydroaminoalkylation of styrene.[24]

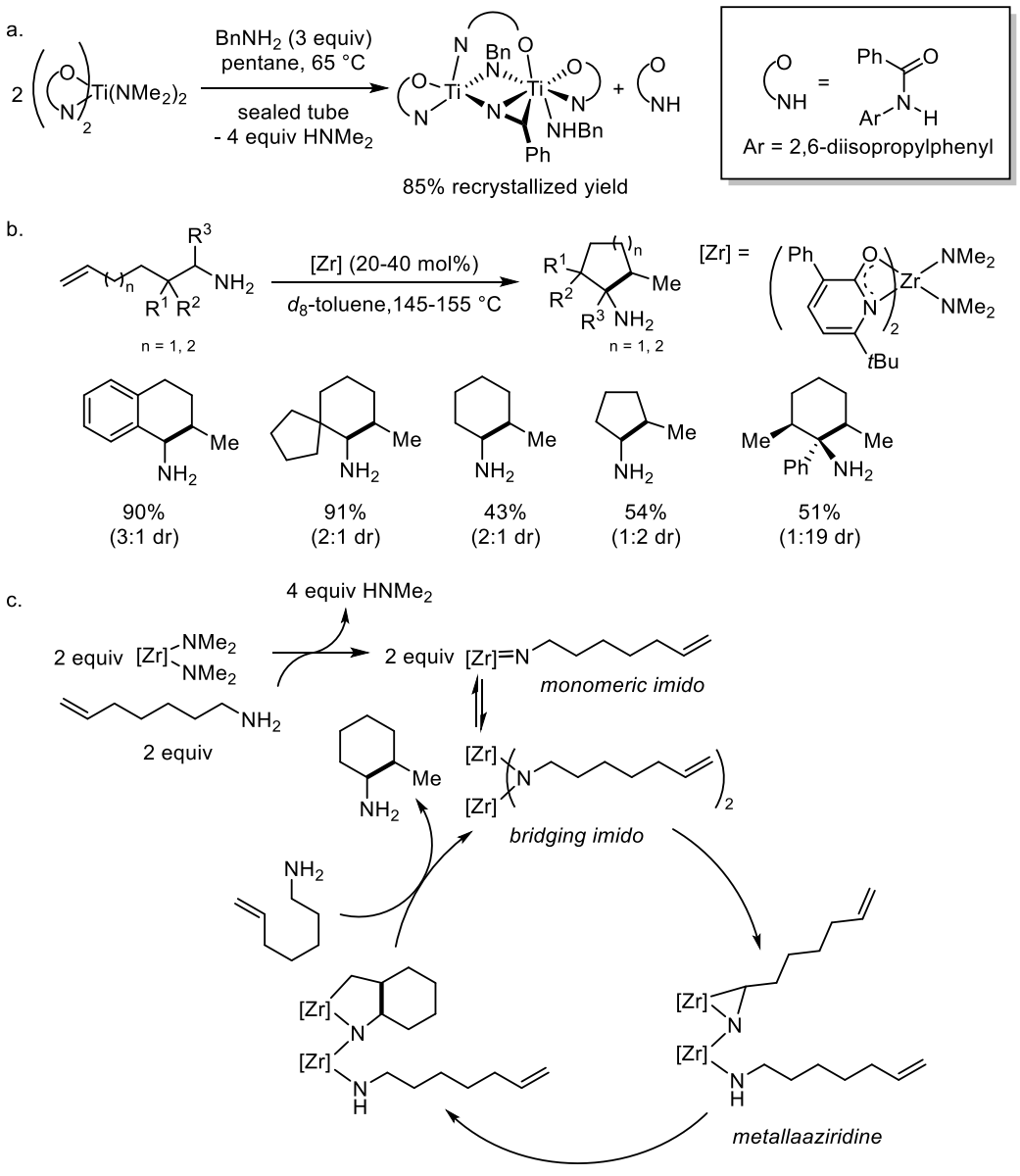
Scheme 2.20 $Ti(NMe_2)_4$-catalyzed Hydroaminoalkylation with Primary/Secondary Amines



In the same year, Schafer and coworkers isolated a metallaaziridine-bridged bimetallic titanium complex through stoichiometric treatment of the *N*,*O*-chelating amidate titanium complex with primary amines (Scheme 2.21a).[25] Importantly, this bimetallic species showed catalytic activity towards intramolecular hydroaminoalkylation reactions. Shifting to a larger zirconium metal center and a less sterically demanding 2-pyridonate ligand, the catalytic reactivity was significantly improved. Both 1-amino-5-hexenes and 1-amino-6-heptenes could be used as substrates, without requirement of *gem*-disubstituents to promote the Thorpe-Ingold effect. Importantly, this reaction allowed the formation of quarternary carbon centers (Scheme 2.21b). Interestingly, when using secondary aminoalkene substrates, no consumption of the substrate was observed, which indicated that in this case the Zr-imido species might be a requisite intermediate to generate the key bridging metallaaziridine dimer complex. A simplified mechanism was proposed (Scheme 2.21c). Improvement of the

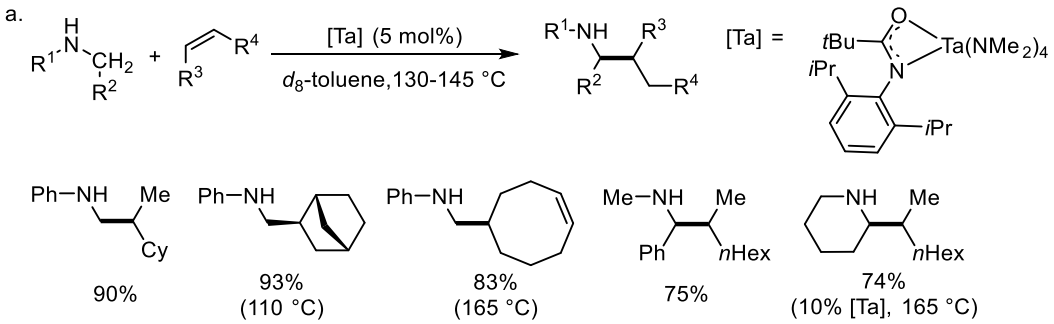
substrate scope and yields were further reported by the same group through the use of a similar 2-pyridonate titanium complex in 2013.[26] In 2015, a well-defined azazirconocyclopropane and azazirconocyclopentane were characterized and reported by Basset and coworkers as key intermediate for a silica-supported Zr-catalyzed hydroaminoalkylation reactions.[27]

Scheme 2.21 Zirconium 2-Pyridonate-catalyzed Intramolecular Hydroaminoalkylation of Alkenyl Primary Amines

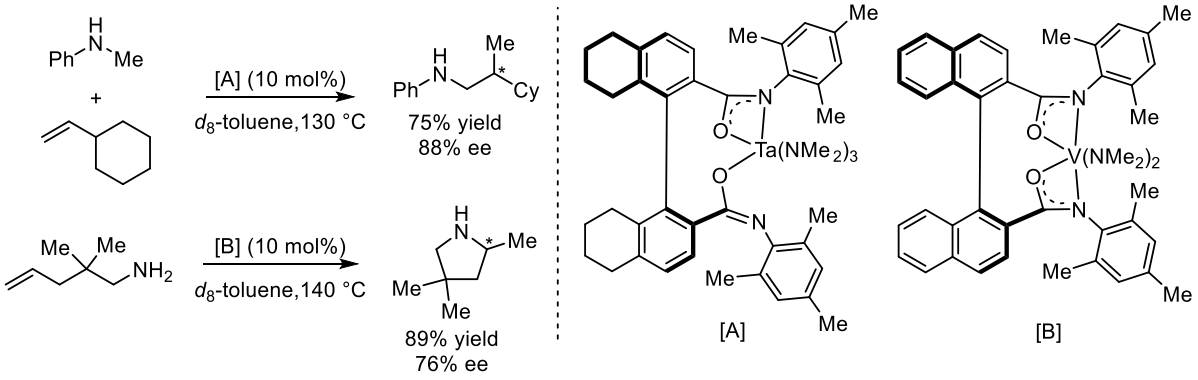


Schafer and coworkers developed group V transition metal-based (e.g. tantalum) catalysts also using a steric bulky *N*,*O*-chelating ligand (Scheme 2.22a).[28] Enantioselective transformations were also achieved by using a chiral pre-catalyst **XX**, which represented the first examples of catalytic asymmetric hydroaminoalkylation (Scheme 2.22b). Further improvement of the catalytic enantioselective hydroaminoalkylation was achieved by Zi and coworkers (Scheme 2.23).[29,30]

Scheme 2.22 Tantalum Amidate-catalyzed Hydroaminoalkylation with Secondary Amines

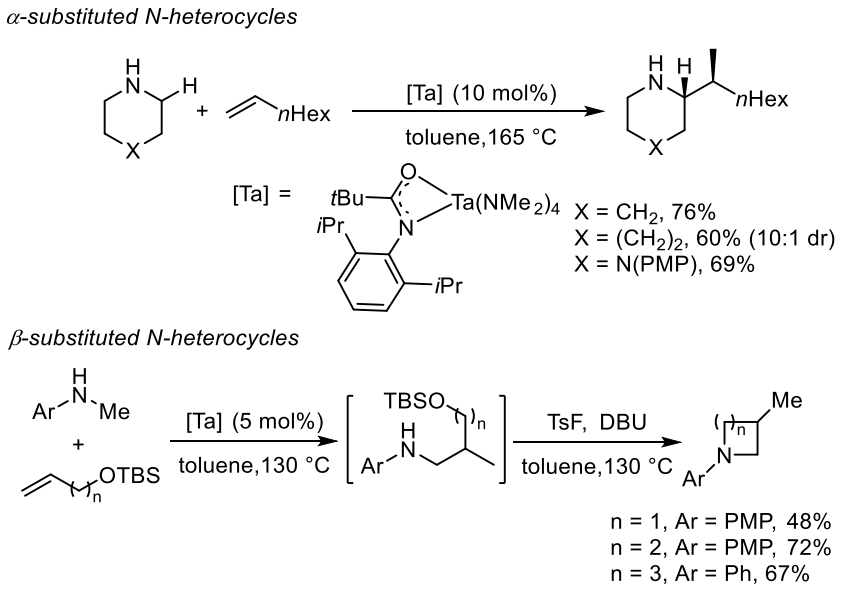


Scheme 2.23 Ta- and V-catalyzed Enantioselective Hydroaminoalkylation



This catalytic system has also been used for the synthesis of α- and *β*-substituted *N*-heterocycles by Schafer and coworkers (Scheme 2.24).[31] This approach provids an alternative disconnection for the general access of various azetidines, pyrrolidines, piperidines and azepanes.

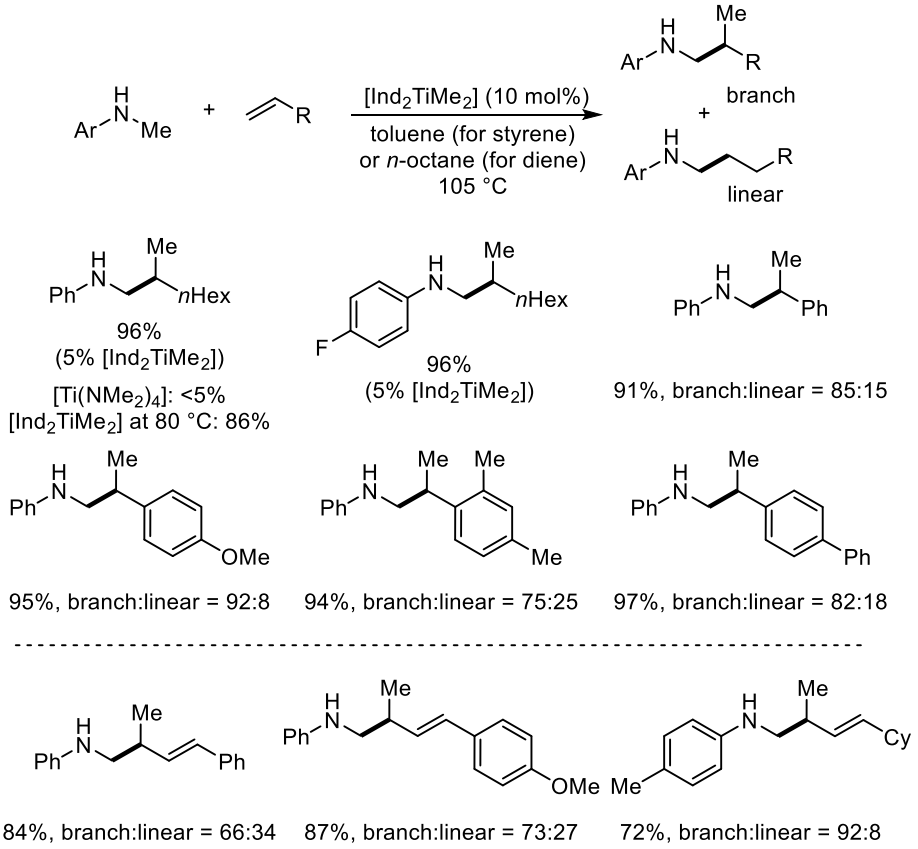
Scheme 2.24 α- and *β*-Substituted *N*-heterocycles Synthesis through Tantalum Amidate-catalyzed Hydroaminoalkylation



In 2010, Doye developed an $(Ind)_2TiMe_2$ catalyst, which efficiently catalyzed the intermolecular hydroaminoalkylation reaction between *N*-alkyl arylamines and terminal

olefins at temperature as low as 80 °C. The lowered reaction temperature provided access to thermo-sensitive olefin substrates, such as styrenes[32] and 1,3-dienes[33], which are susceptible to polymerization under relative harsher conditions (130-165 °C). Among the aryl olefins tested, this catalytic system was particularly efficient for electron-rich and less hindered ones (Scheme 2.25). Intramolecular α-alkylation of *N*-alkyl arylamines also occured smoothly with the same catalyst.

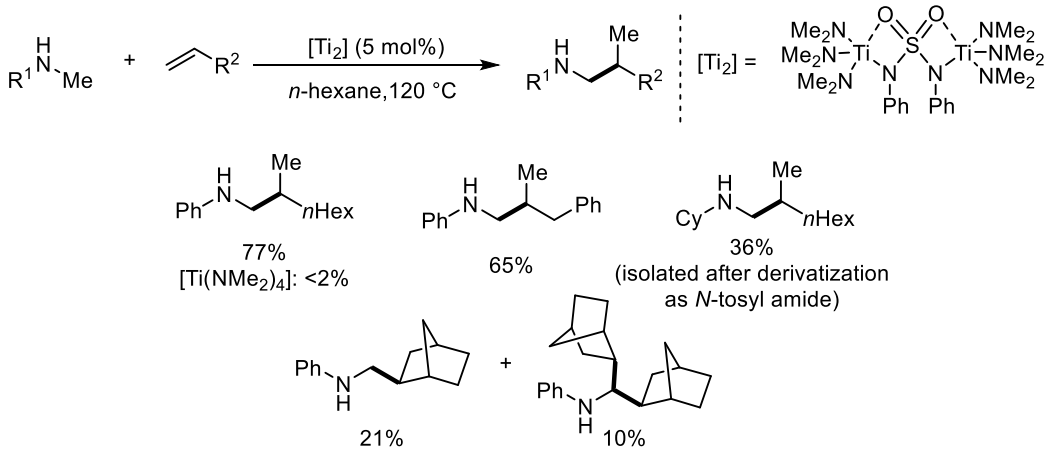
Scheme 2.25 $(Ind)_2TiMe_2$-catalyzed Hydroaminoalkylation with *N*-methyl Arylamines



A new dinuclear titanium sulfamide complex was reported by the same group in 2012, which also catalyzed the intermolecular hydroaminoalkylation.[34] For example, heating *N*-methylaniline and 1-octene with 5 mol% of the dinuclear catalyst at 120 °C for 48 hours afforded the expected hydroaminoalkylation product in 77% yield, while the previous

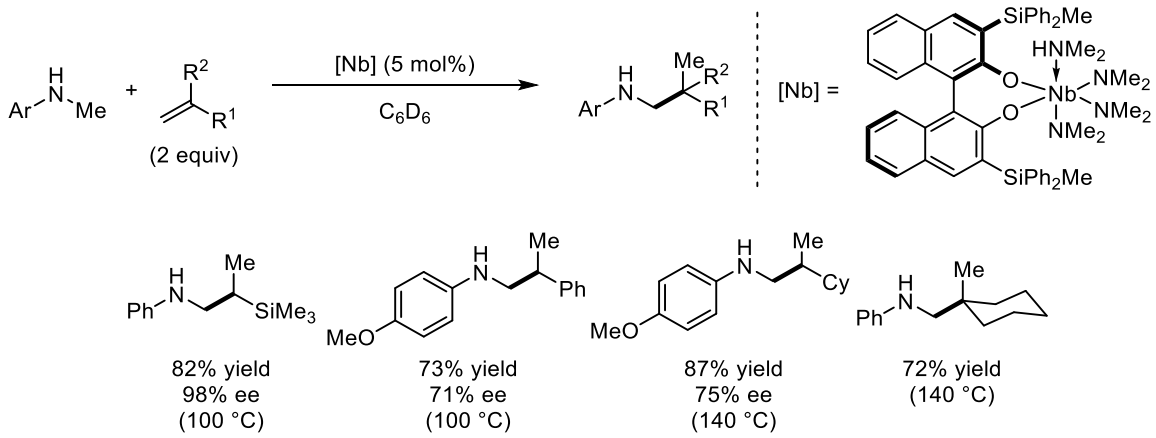
$Ti(NMe_2)_4$ catalyst provided less than 2% yield of the product under identical conditions. Although the reaction temperature (120 ^oC) was higher than the one with the $(Ind)_2TiMe_2$ catalyst (105 ^oC), it was worthy to mention that this Ti catalyst enabled hydroaminoalkylation with a dialkylamine, albeit in 36% yield (Scheme 2.26).

Scheme 2.26 Titanium Sulfamide-catalyzed Hydroaminoalkylation with Secondary Amines



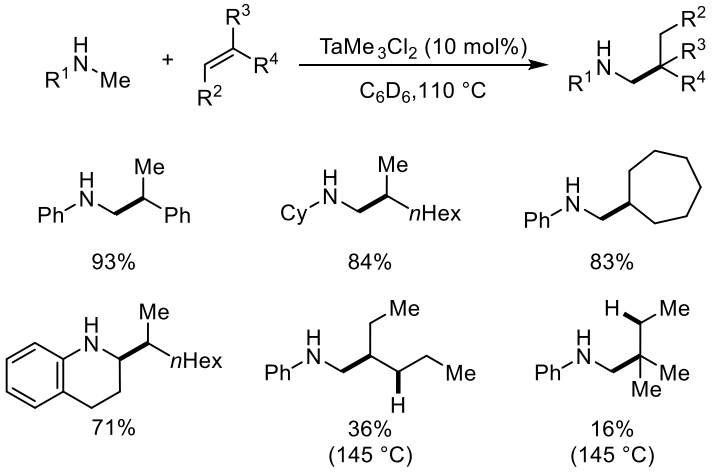
In 2012, Hultzsch and coworkers found that the binaphtholate complexes of group V metals can catalyzed intermolecular hydroaminoalkylation of simple alkenes with secondary amines in high regio- and enantioselectivity (Scheme 31).[35] A detailed mechanistic study, supported by a series of kinetic and isotope effect studies, was conducted, demonstrating that (i) the reaction was first order in amine and the catalyst, (ii) the formation of the metallaaziridine was a fast reversible nondissociative process, and (iii) the overall rate determining step occurred during the amine exchange or the alkene insertion (which was in contrast with the previous mechanistic study of group IV transition metals).

Scheme 2.27 Niobium-catalyzed Enantioselective Hydroaminoalkylation with *N*-methyl Arylamines



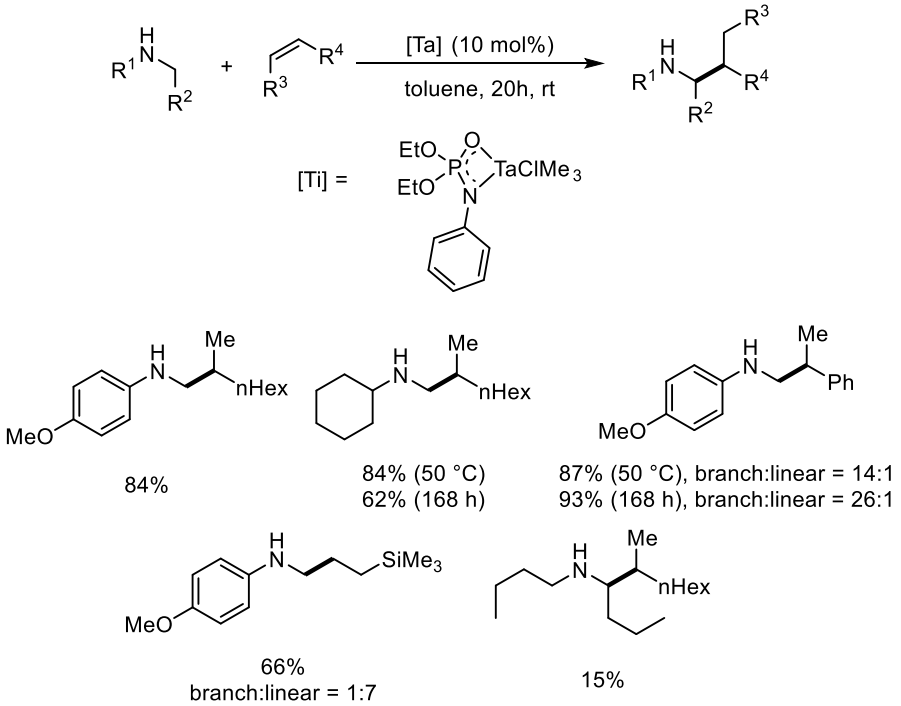
In 2013, Schafer and coworkers discovered that using $TaMe_3Cl_2$ as the catalyst, reduced reaction temperature and a broader substrate scope was achieved in the hydroaminoalkylation reactions.[36] It was proposed that the reactive catalytic species was generated in situ from the elimination of CH_4 from the $TaMe_3Cl_2$ pre-catalyst to form a tantalazirdine intermediate. Various α-olefins including styrene derivatives can be efficiently coupled in high regioselectivity. Remarkably, sterically demanding 1,2-disubstituted- and trisubstituted acyclic alkenes could also be coupled, albeit in lower yields (Scheme 2.28).

Scheme 2.28 $TaMe_3Cl_2$-catalyzed Hydroaminoalkylation with Secondary Amines



Later, a more reactive Ta-based catalyst was also developed by Schafer and coworkers. The new catalyst contains a bulky phosphoramidate ligand together with a chloride ligand, which dramatically increased the catalyst reactivity, providing alkylations at room temperature.[37] Challenging substrates, such as styrenes and dialkyl amines, can be coupled using this catalyst. Interestingly, due to the β-silicon effect, linear product was obtained primarily when vinyltrimethylsilane was employed (Scheme 2.29). This transformation can also be realized under solvent-free conditions.

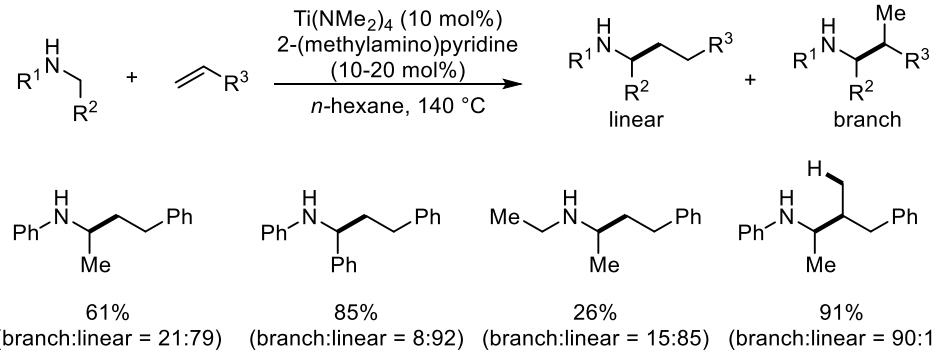
Scheme 2.29 Room Temperature Hydroaminoalkylation Catalyzed by Tantalum Phosphoramidate



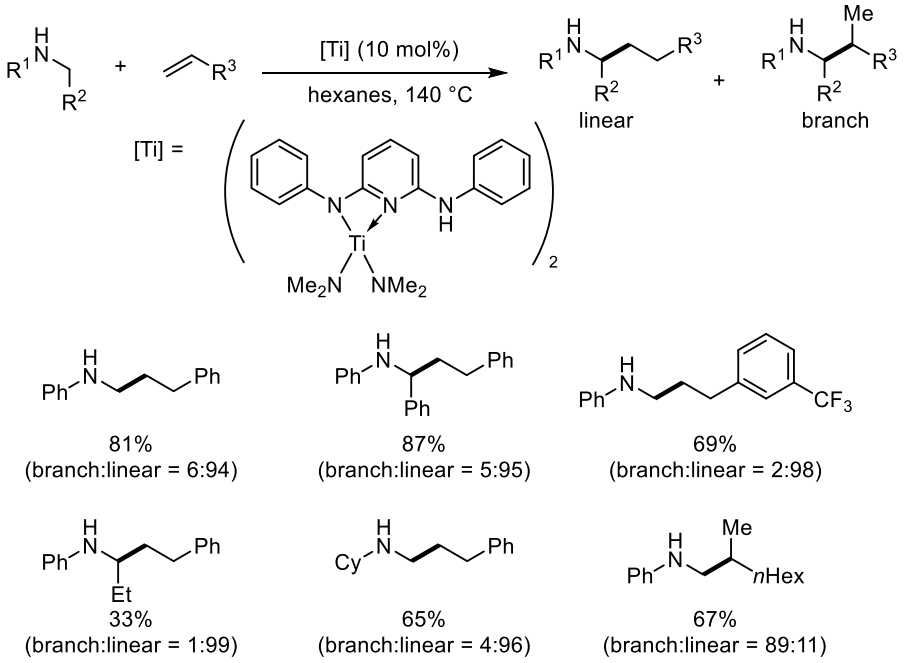
In 2013, a Ti-catalyzed hydroaminoalkylation reaction was reported by Doye and coworkers using an in situ generated catalyst from 2-(methylamino)pyridine and $Ti(NMe_2)_4$ complex. Up to 92:8 linear selectivity was achieved using styrenes, while branch products

were still formed as major products with alkyl olefins (Scheme 2.30).[38] This catalytic system was also successful for intramolecular hydroaminoalkylation reactions with enhanced activity compared to the simple $Ti(NMe_2)_4$ catalyst.[39] Further improvement on the linear selectivity with styrenes was achieved later by the same group using a new Ti catalyst with 2,6-bis(phenylamino)pyridinato ligands (Scheme 2.31).[40] Interesting, they also found that by using the commercially available $Ta(NMe_2)_5$ catalyst, the regioselectivity of the hydroaminoalkylation reactions of styrenes was reversed, providing the branched regioisomers almost exclusively.[41]

Scheme 2.30 $Ti(NMe_2)_4$/2-(Methylamino)pyridine-catalyzed Hydroaminoalkylation

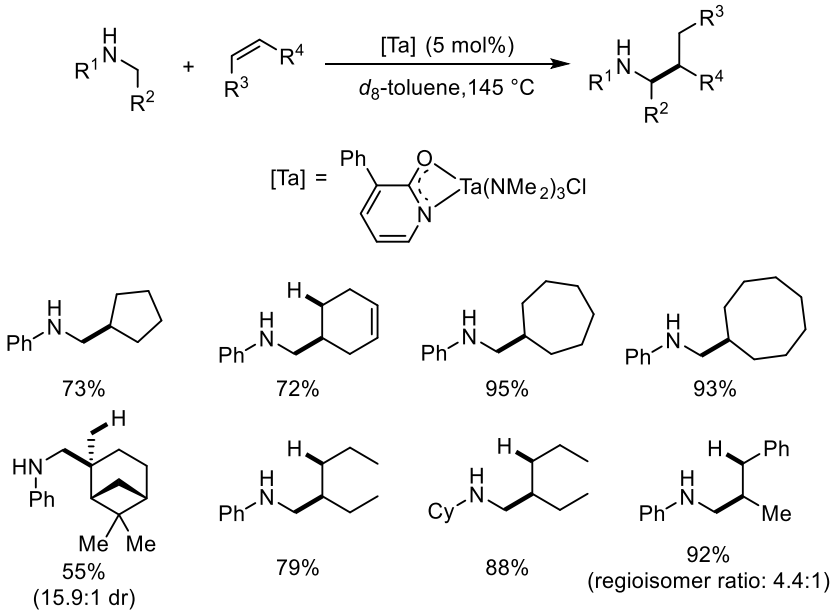


Scheme 2.31 Titanium 2,6-Bis(phenylamino)pyridinate-catalyzed Hydroaminoalkylation

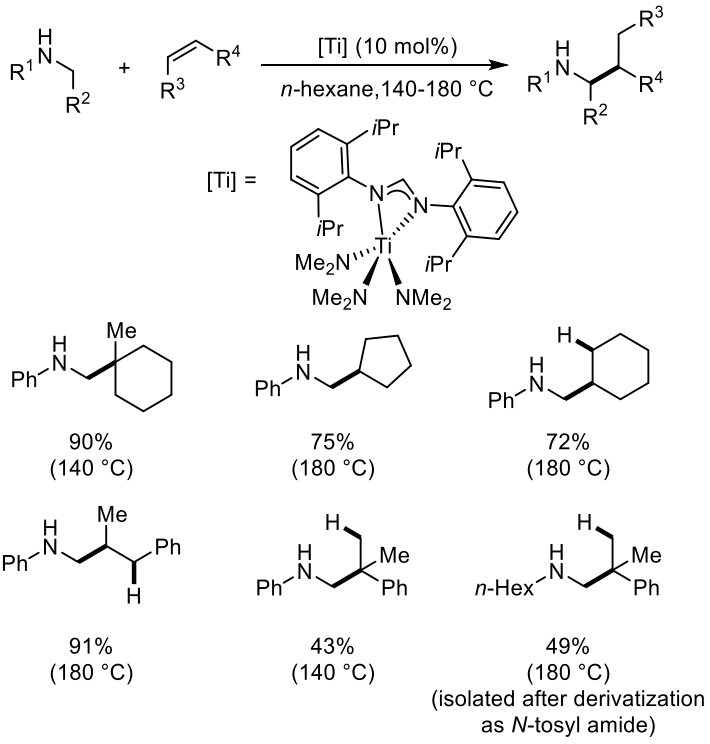


Besides styrenes, another challenging type of substrates in the hydroaminoalkylation was sterically demanding 1,1- and 1,2-disubstituted alkenes. A seminal solution was found by Schafer and coworkers in 2014, initiated by a systematic survey on catalysts bearing different electronic and steric properties. While the electron-withdrawing and sterically demanding Ta-catalyst are highly effective for terminal alkenes (as shown before), the Ta catalyst with the combination of electron-withdrawing and sterically less-hindered chloride and 2-pyridonate ligands turned out to be effective for sterically demanding alkenes. Both aryl and alkyl amines can be readily employed in this transformation (Scheme 2.32).[42] In 2015, a Ti-catalyzed hydroaminoalkylation reaction of sterically demanding alkenes with secondary amines was also reported by Doye and coworkers (Scheme 2.33).[43]

Scheme 2.32 Ta-catalyzed Hydroaminoalkylation of Sterically Demanding Alkenes



Scheme 2.33 Ti-catalyzed Hydroaminoalkylation of Sterically Demanding Alkenes

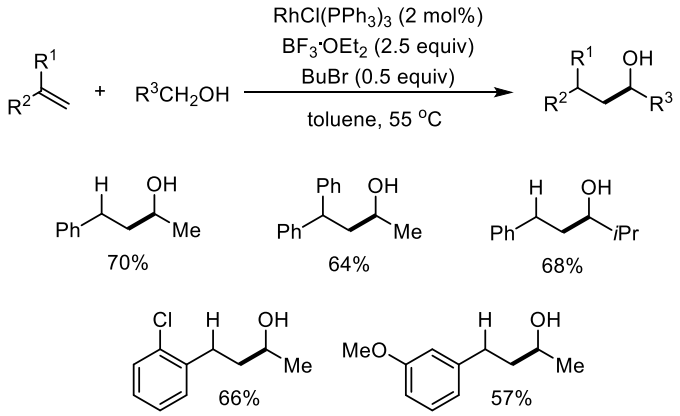


2.4 Hydrohydroxyalkylation

In contrast to hydroaminoalkylation, the hydrohydroxyalkylation reaction was less studied. During the study of the hydroaminoalkylation reaction by Nugent and coworkers in

1983, they found that Zr(IV), Nb(V) and Ta(V) could all catalyze the H-D exchange on the β-position of ethanol.[44] However, no olefin insertion product was observed. The first transition metal catalyzed hydrohydroxyalkylation was reported by the Tu group in 2005.[45] Taking advantage of a cooperative Lewis acid promoter and Wilkinson's catalyst, primary alcohols could couple with olefins smoothly. Bromobutane was used to suppress undesired Friedel-Crafts reaction between the olefins and the aromatic solvent (Scheme 2.34). Olefins bearing strong electron-withdrawing groups, such as 2-nitrostyrene, were unreactive under these conditions. On the other hand, highly electron-rich 2- or 4-methoxy styrenes led to a complex mixture.

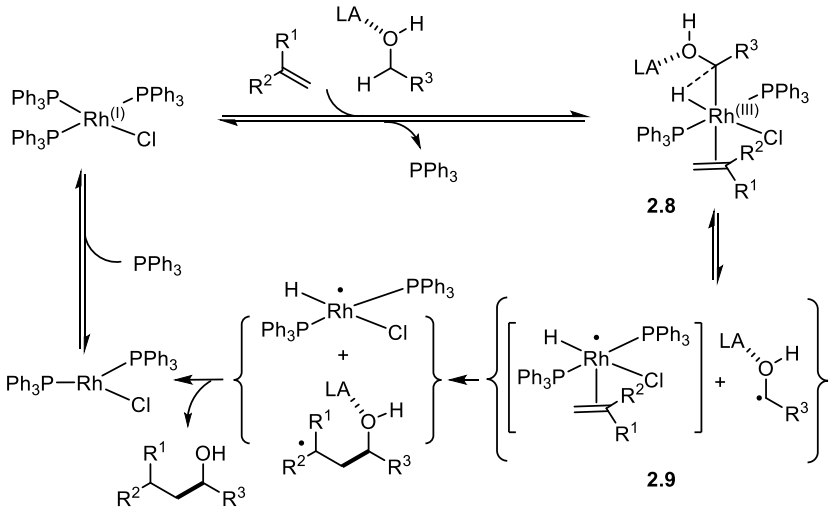
Scheme 2.34 Rh-catalyzed α-Alkylation of Primary Alcohols



Radical scavengers (1,4-benzoquinone, TEMPO, and $FeCl_3$) were found to completely inhibit the reaction. In addition, crossover experiments between deuterated and undeuterated alcohols led to a statistical distribution of the labels amongst the products, indicating a possible radical reaction mechanism. Based on these observations, a tentative mechanism was proposed. The Lewis acid-promoted oxidative addition of the alcohol α C–H bond to the Rh(I) species gives Rh(III) complex **2.8**, which would then be converted into a

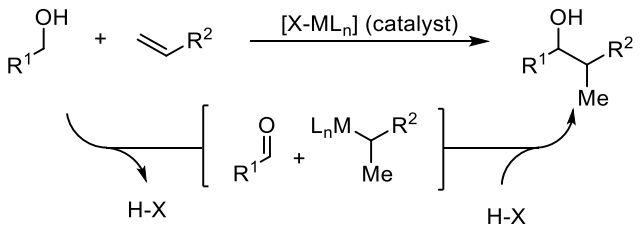
radical pair **2.9**. Subsequently, a Kharasch-type radical reaction was proposed to occur to give the hydrohydroxyalkylation product and regenerate the Rh(I) catalyst (Scheme 2.35). Same transformation has also been achieved using $FeCl_3$.[46] When using $Pd(OAc)_2/PPh_3$ as the catalyst instead of the Wilkinson's complex, a domino alkene dimerization happens after the initial alcohol-olefin coupling.[47]

Scheme 2.35 Proposed Mechanism for the Rh-catalyzed α-Alkylation of Primary Alcohols



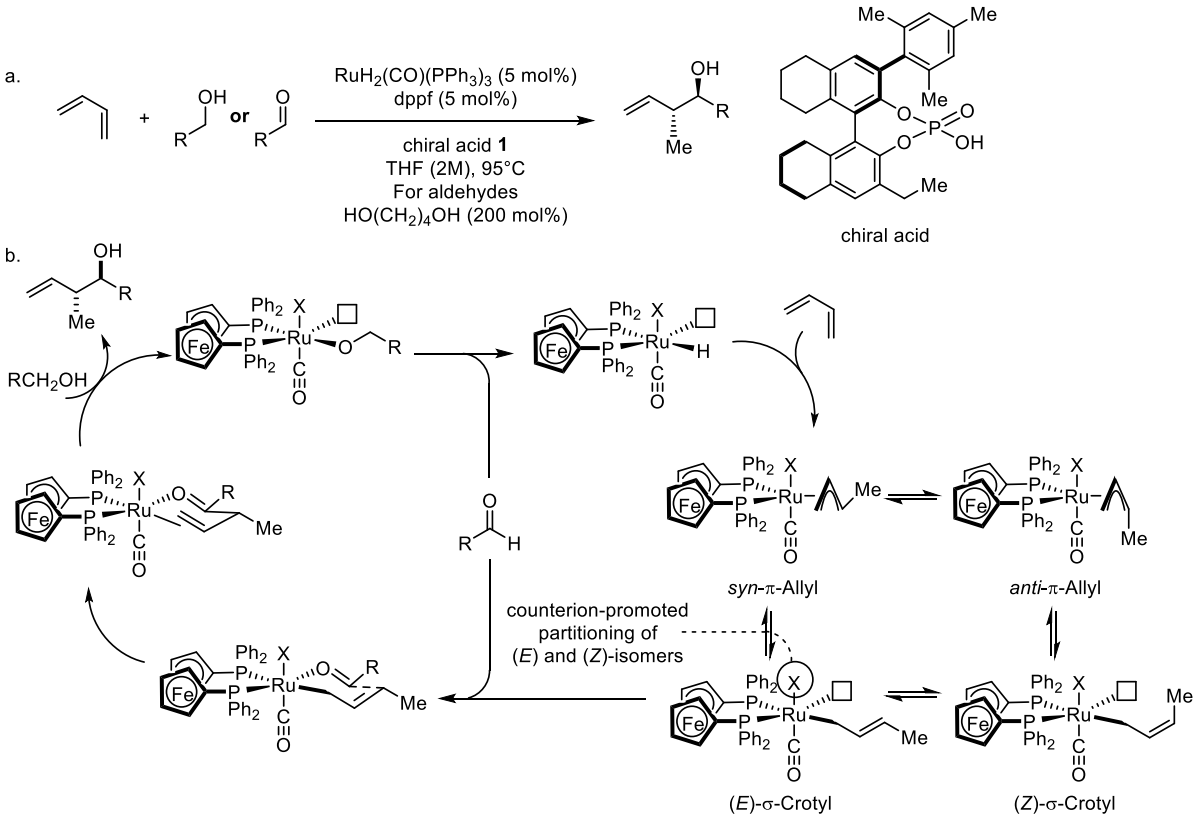
Using transition metal-mediated transfer hydrogenation, Krische and coworkers developed a series of C–C bond forming reactions at alcohol α-position with unsaturated compounds, including olefins, allenes, conjugated dienes and enynes (Scheme 2.36).[48-50] Given that this area has been recently reviewed,[48-51] only the corresponding hydrohydroxyalkylations are discussed here.

Scheme 2.36 Basic Reaction Scheme for Transition Metal-mediated Transfer Hydrogenation



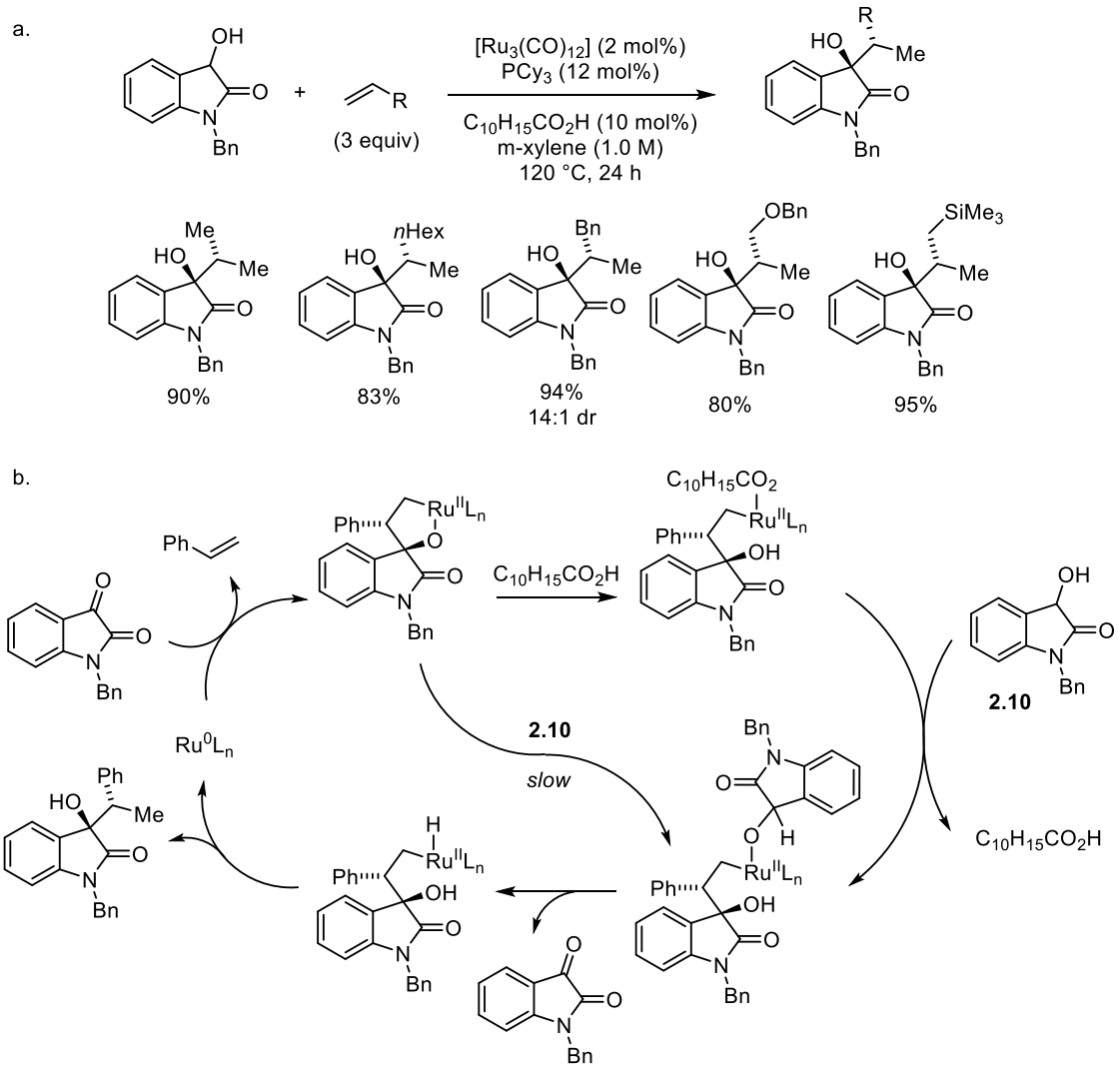
As an example, in 2012, the enantioselective coupling between primary alcohols and conjugated dienes was accomplished by Krische and coworkers using a Ru catalyst and a chiral phosphinic acid (Scheme 2.37).[52] The crotylated product was obtained in high enantio and diastereoselectivity. Regarding the mechanism, the coordination of the Ru(II) catalyst to an alcohol generates a corresponding aldehyde and a Ru(II)-hydride through β-hydride elimination. Controlled by the chirality on the phosphric acid, the following diene insertion selectively generates the (*E*)-σ-crotylruthenium isomer, which further undergoes a formal carbonyl addition through a closed Zimmerman−Traxler-type transition state to yield the hydrohydroxyalkylation product (Scheme 2.37b).

Scheme 2.37 Ru-catalyzed Enantioselective α-Alkylation of Primary Alcohol



As an another example, the coupling between simple olefins and 3-hydroxy-2-oxindoles was reported in 2013.[53] The reaction gave excellent branched selectivity favoring the *anti*-product (Scheme 2.38a). A cyclo-metallation pathway was proposed. The Ru(0) catalyst undergoes direct cyclometallation with the in situ generated isatin and the olefin to give a 5-membered ruthenacycle. The Ru−O bond can be hydrolyzed by the acid additive and then 3-hydroxy-2-oxindole substrate, followed by β-H elimination to give the isatin intermediate and a Ru(II)-hydride species. Further C–H reductive elimination gives the hydrohydroxylalkylation product and regenerates the Ru(0) catalyst (Scheme 2.38b).

Scheme 2.38 Ru-catalyzed α-Alkylation of 3-Hydroxy-2-oxindoles



2.5 Conclusions and Outlook

The field of transition metal-catalyzed alkylation of sp^3-C−H bonds using alkenes has been rapidly growing over the last two decades. The advantage of C−H alkylation with olefins is clear from the atom-efficiency, redox-economy and synthetic streamline compared with traditional synthetic methods. However, the scope of the sp^3-C−H bonds that can be coupled with olefins is still one of the major limitations: To date, the majority of the transformations still have to use relatively activated C−H bonds as the substrates, such as at

benzylic, allylic, or α-to-nitrogen positions. Only in scattered examples, the unactivated C−H bonds can be coupled with olefins. Thus, the development of efficient catalytic systems that couple unactivated C−H bonds with olefins will be highly desirable. The achievement of this goal, on the other hand, is expected to rely heavily on the design of new site-selective control strategies. Currently, a majority of the methodologies available require chelation assistance, which is considered as a directing group strategy. However, conveniently linked directing groups, such as pyridines, dramatically limited the synthetic application. A promising strategy to this problem is by adopting temporary directing group strategy, where an additive can reversibly bond with a substrate and induce a directing effect, improving both the reactivity and selectivity greatly. Furthermore, it is worthnoting that the olefin scope for these transformations is also relatively limited. More reactive ono-substituted olefins are commonly used, while sterically hindered internal olefins are often found to be challaging substrates. How to efficiently couple these multi-substituted olefins in a regioselective manner is another question to be solved. The conquer of these challenges would make this transformation a truly useful tool for the organic synthesis.

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CHAPTER 3

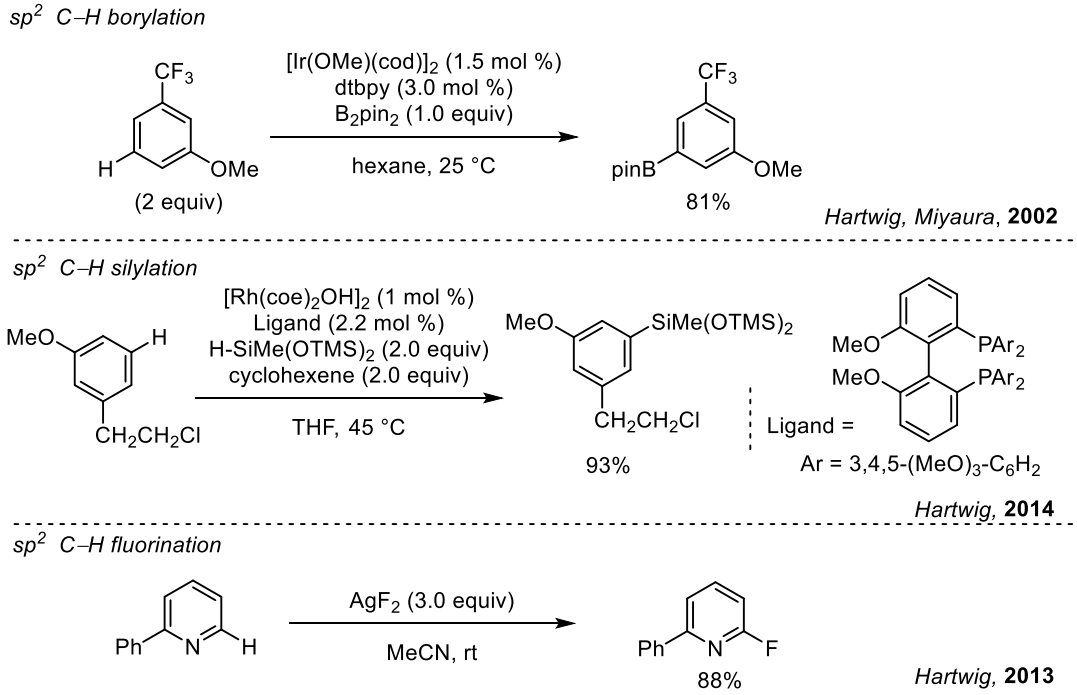
Pd-Catalyzed Diverse sp^3 C−H Functionalization through Alcohol *β*-Sulfonyloxylation

3.1 Introduction

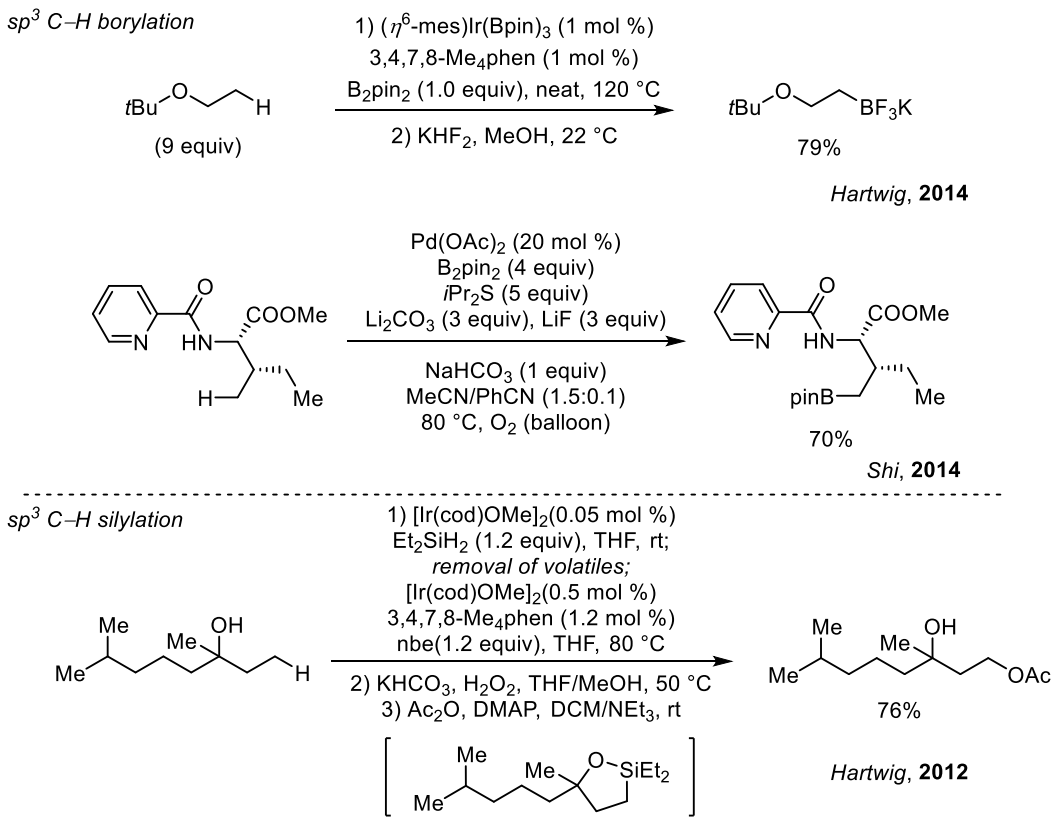
Modern drug discovery relies heavily on rapid preparation and testing of a panel of closely related analogues. Consequently, strategies allowing for diverse derivatization of a late-stage intermediate are advantageous over individual parallel syntheses in searching for lead compounds[1-3]. During the past decade, site-selective carbon-hydrogen bond (C−H) functionalization has become an attractive tool for derivatizing complex synthetic intermediates[4-8], because it allows direct conversion of an inert C−H bond into new FGs[9-17]. However, one main obstacle of utilizing C−H functionalization for late-stage diversification is that only a limited range of FGs can be introduced, which are often substrate and/or reaction-condition dependent. Moreover, each of these reactions generally requires intensive reaction-condition (catalyst) optimizations and/or specific directing group (DG) design. To

overcome such limitations, perhaps a more practical approach is to first install a latent FG site-selectively through C−H activation and then branch out to other FGs through reliable chemistry. For instance, C−H borylation[18-22], silylation[18,23,24] and fluorination[25] of arenes serve as seminal examples of diverse functionalization of an sp^2 C−H bond through transformations of aromatic boranes, silanes and fluorides (Scheme 3.1). In contrast, for unactivated (non-benzylic, -allylic, -α-to-a-heteroatom or -strained) sp^3 C−H bonds, while the corresponding C−H borylation and silylation have been elegantly demonstrated (Scheme 3.2), the diversification becomes more challenging due to significantly reduced reactivity of alkyl boranes and silanes towards electrophiles[32].

Scheme 3.1 Selected Examples for Borylation, Silylation and Fluorination of sp^2 C−H Bonds

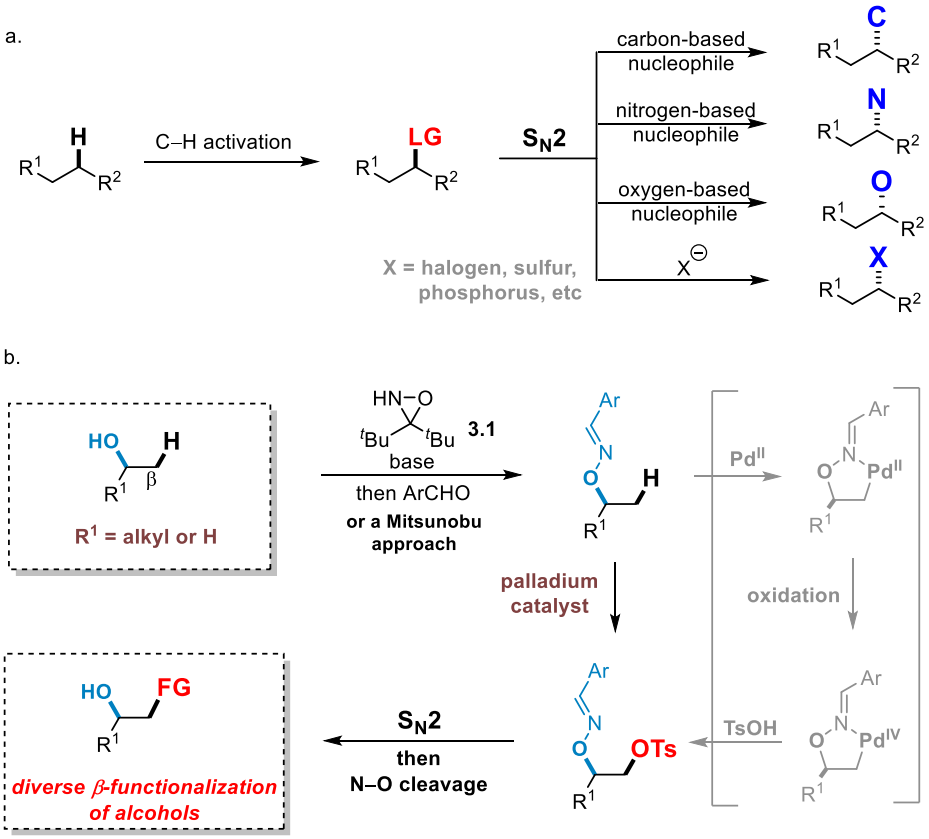


Scheme 3.2 Selected Examples for Borylation and Silylation of sp^3 C−H Bonds



To enable diverse functionalization of an sp^3 position that lacks pre-activation, we sought an alternative strategy that is to directly replace a C−H bond with a good leaving group (LG) in a late-stage intermediate, and subsequently employ S_N2 reactions, as a single type of transformation, for preparing derivatives or analogues (Figure 3.1a). Given the general reliability of S_N2 reactions and broad availability of various nucleophiles, we expect that this LG approach would be appealing and suitable for late-stage diversification at inert sp^3-hybridized positions. Clearly, success of this approach requires efficient methods for site-selective introduction of a good LG via C−H functionalization.

Figure 3.1 A LG-based Strategy for Late-stage Diversification using C−H Activation



Alkyl halides (RX) and alkyl sulfonates (e.g. ROTs; Ts, *p*-toluenesulfonyl) are typical substrates for S_N2 reactions. Although radical-mediated halogenation of unactivated aliphatic substrates efficiently provides secondary and tertiary chlorides and bromides[33-35], they generally do not give the more reactive primary products and the site-selectivity is normally controlled by the inherent steric/electronic bias of the substrates. The palladium-catalyzed oxazoline- and amide-directed C−H halogenation, pioneered by Yu[36-38] and Sahoo[39], can exclusively form primary alkyl halides, albeit restrained to neopentyl-type electrophiles. While scattered substitution examples with the resulting neopentyl halides were shown, they are not typically considered as good substrates for S_N2 reactions. We foresaw the advantage of using alkyl sulfonates as the S_N2 substrates due to their increased thermal/light stability

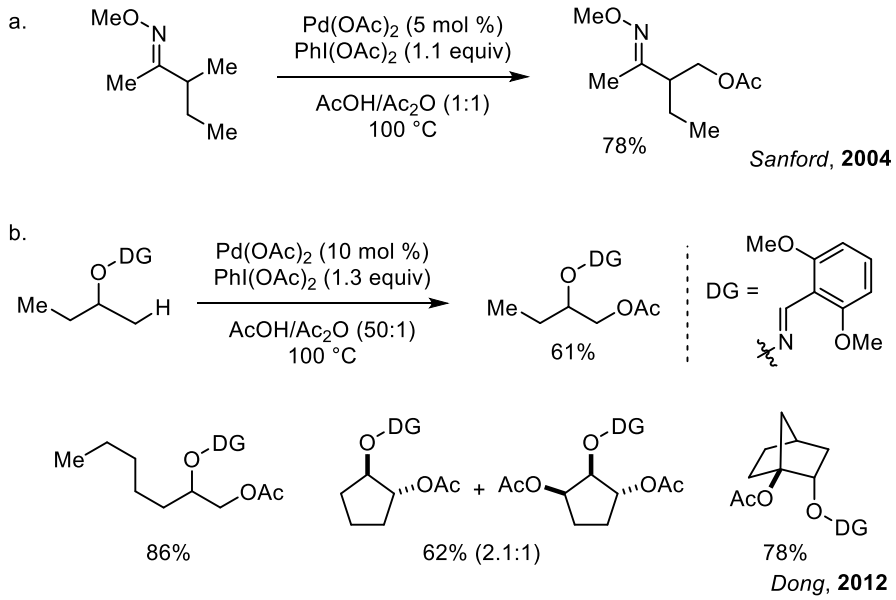
and resistance to radical-triggered side-reactions compared to alkyl halides, and pursued a catalytic system that provides site-and chemoselective installation of a sulfonyloxy group onto chemically inert positions. Considering the ubiquity of hydroxyl groups in bioactive molecules and the frequency for use as synthetic handles, herein we describe a palladium-catalyzed C−H oxidation reaction that can selectively install a sulfonyloxy group at the β-position of masked alcohols[40], which can be applied to diverse β-functionalization of hydroxyl-containing compounds (Figure 3.1b).

To install a sulfonyloxy group (e.g. OTs) through activating an inert sp^3 C−H bond at alcohol β-position, a number of challenges can be envisioned. First, a recent mechanistic study by Sanford and coworkers demonstrated that C(sp^3)–O reductive elimination can occur from a Pd^{IV} intermediate with diverse oxygen nucleophiles, including the OTs anion, through a nucleophilic attack pathway[41]. However, considering the complexity of a catalytic system and the exceedingly low nucleophilicity of the OTs anion, the proposed tosyloxylation may suffer from the competition from other potential nucleophiles or side reactions (e.g. β-hydrogen elimination) with the hypervalent Pd intermediate[42]. Second, due to the high reactivity of sterically unhindered alkyl tosylates, product stability during the reaction must be considered, which requires relatively mild catalytic conditions. Third, compatibility between the OTs group and the vicinal protected alcohol moiety (including the deprotection conditions) is another concern. An intriguing question is, by properly choosing the DG and deprotection conditions, can the alcohol moiety be revealed without affecting the OTs group?

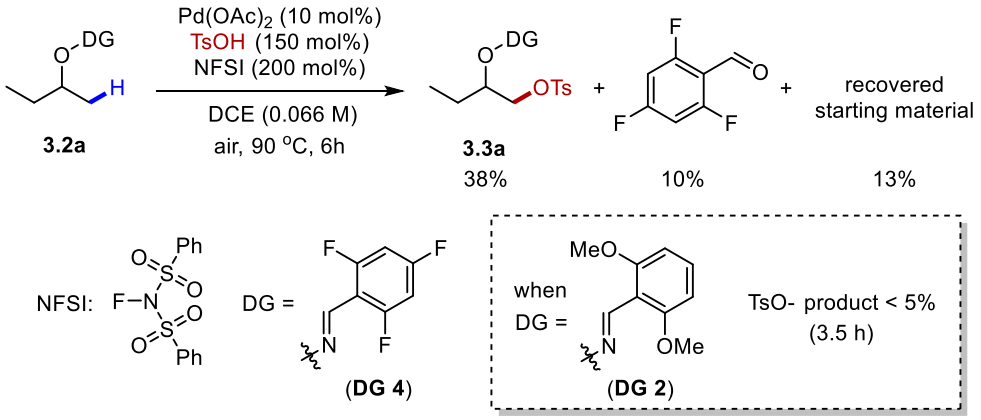
3.2 Results and Discussion

Oximes are reported to serve as DGs to facilitate the activation of sp^3 C−H bonds (Scheme 3.3a).[43] In 2012, our group discovered oximes can also serve as both a protected alcohol and an *exo*-type DG for sp^3 C−H activation, enabling synthesis of chemically differentiated 1,2-diols from mono-alcohols (Scheme 3.3b).[44] Following the same *exo*-directing strategy, our original plan is to study the sp^3 C−H fluorination reaction by using similar type of the oxime DGs with electrophilic fluorinating agents. Surprisingly, while no success was achieved with the desired fluorination reaction, a C−H tosyloxylation product was observed when TsOH was used as an additive and a 2,4,6-trifluorobenzaldehyde-derived oxime (**DG 2**) was used as the DG. After screening of different oxidants, solvents and Pd sources, a 38% yield of the C−H tosyloxylation product (**3.3a**) could be obtained by treating the 2-butanol-derived oxime (**3.2a**) with 10 mol% $Pd(OAc)_2$, TsOH, and NFSI in DCE at 90 ^oC for 6 hours. We hypothesized that, although TsO^- is a poor nucleophile, using TsOH as the reagent, nucleophiles with a significantly higher pKa value than TsOH (such as F^-, $N(SO_2Ph)_2^-$ or OAc^-) would mostly exist in their protonated forms and thus be less competitive towards S_N2 reactions. Interestingly, the 2,6-dimethoxyphenyl-derived **DG 4**, which showed high reactivity in our previous work[44], only provided a trace amount of product **3.3a** along with significant decomposition of the starting material (Scheme 3.4).

Scheme 3.3 Previous Studies on Oxime-directed sp^3 C−H Activation



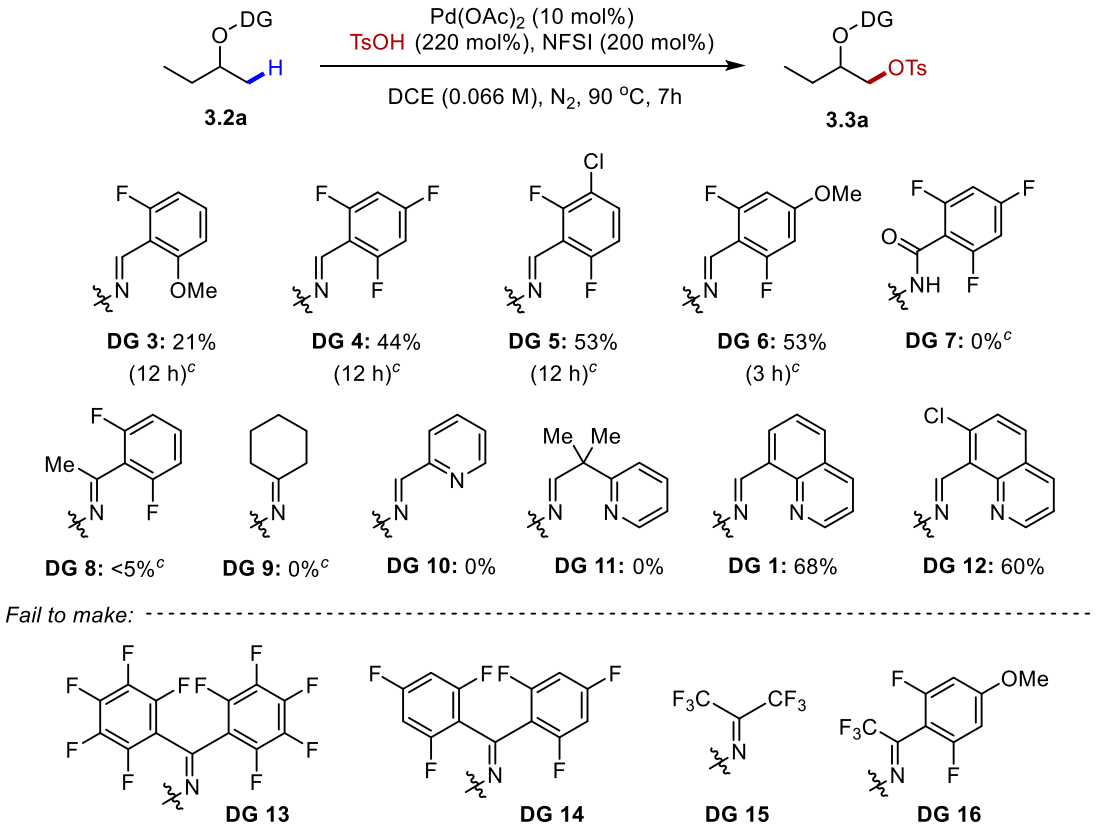
Scheme 3.4 Initial Hit of the Reactivity



Further optimization focused on the evolution of the directing group (Scheme 3.5). As shown in Scheme 3.4, one of the major decomposition pathways for **3.2** is through hydrolysis, leading to the formation of the corresponding aldehyde. We envisioned that such a process, which is proposed to start with the nucleophilic addition of water to the iminyl carbon, might be suppressed by increasing the electronic density of the arene. A group of DGs was then synthesized and equipped onto the 2-butanol substrate (**DGs 3** to **6**). Indeed, while the replacement of the fluorine atom at the *ortho* position decreased the yield (**DG 3**), the

replacement of the fluorine atom at the *para* position with either a *meta*-Cl or a *para*-OMe substituent increased the stability of the oxime, and therefore led to higher yields (53%, **DGs 5** and **6**). To further increase the stability of the directing motif, we synthesized the corresponding *ortho*-fluorinated benzamide (**DG 7**) and acetophenone-derived oxime (**DG 8**). However, complete or significant loss of reactivity was observed. Noting that for **DG 8,** one of the major side pathways is the oxidation at the ketone α C−H bonds, a group of *ortho*- and/or α-fluorinated ketones were prepared. However, possibly duo to increased steric hindrance, the oxime preparations through condensation were unfruitful, leading to either aromatic nucleophilic substitution products (for **DGs 13** and **14**), or no conversion (for **DGs 15** and **16**). The cyclohexanone oxime also showed no reactivity (**DG 9**). Finally, a group of pyridine-based DGs were synthesized and tested (**DGs 1**, **10** to **12**). The 8-quinolinecarboxaldehyde oxime (**DG 1**) was identified as the best DG, possibly due to its enhanced stability and good directing ability. It is interesting to observe that **DGs 10** and **11** with similar chelating moieties as **DG 1** showed almost no reactivity. A chlorine atom was introduced on the 7-position of the quinoline, which was designed to block the potential competing sp^2 C−H activation site and to retard the free rotation of the quinoline ring to enforce coordination. However, a lower yield was observed (60%, **DG 12**).

Scheme 3.5 Optimization of the Directing Groups[a,b]

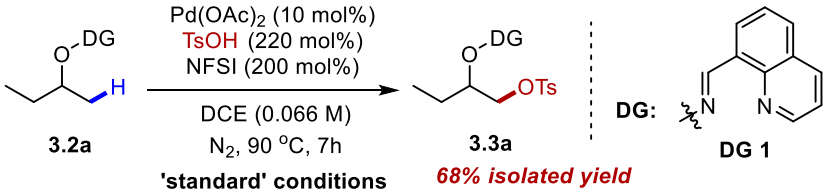


[a] Reaction conditions: **2a** (0.1 mmol), TsOH (0.22 mmol), $Pd(OAc)_2$ (0.01 mmol), NFSI (0.2 mmol), DCE (1.5 ml), 90 °C, 7h. [b] NMR yields using 1-fluoronaphthalene or 1,1,2,2-tetrachloroethane as the internal standard. [c] The reactions were conducted under air, and 150 mol% TsOH was used.

After establishing the optimal reaction condition, the influence of each reaction parameter was then examined through control experiments (Table 3.1). Using oxidants other than NSFI also provided the desired product (entries 1-3), but giving either lower conversions or more unidentifiable byproducts. No product was observed in the absence of oxidant or the palladium catalyst (entries 4 and 5). Dichloroethane (DCE) proved to be an optimal solvent, although chlorobenzene worked almost equally well (entry 9). It is noteworthy that, while slower, this reaction can be performed at *lower temperatures* (entries 10 and 11). Another

attractive feature is that *both moisture and air can be tolerated* for this transformation (entries 13 and 14).

Table 3.1 Control Experiments from the 'Standard' Condition[a]

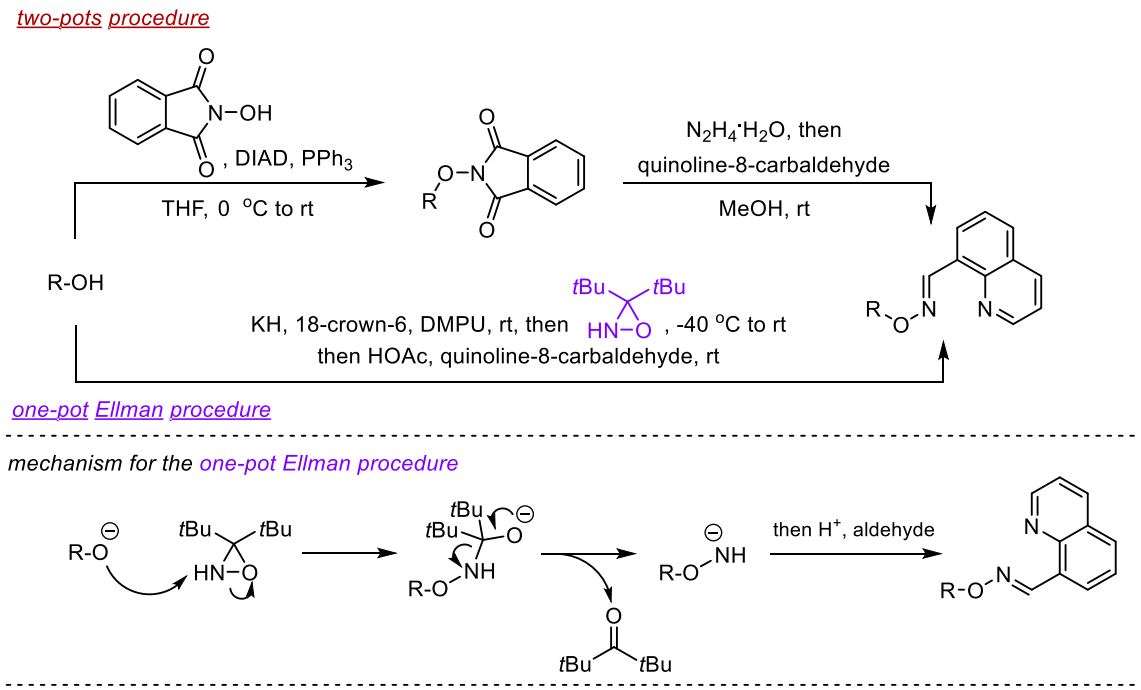


entry	variations from the 'standard' conditions	yield of **3a** (%)[b]	unreacted **2a** (%)[b]
1	**KPS** instead of **NFSI**	34	40
2	**Oxone** instead of **NFSI**	47	18
3	**$PhI(OAc)_2$** instead of **NFSI**	48[d]	<5
4	w/o **NFSI**	0	84
5	w/o **$Pd(OAc)_2$**	0	>99
6	**150 mol%** TsOH instead of **220 mol%** TsOH	48	24
7	**$CHCl_3$** instead of **DCE**	33	46
8	**PhCl** instead of **DCE**	66	0
9	**110 °C** instead of **90 °C**[e]	55	0
10	**70 °C** instead of **90 °C**[f]	60	8
11	**50 °C** instead of **90 °C**[g]	44	23
12	+ 100 mol% **H_2O**	62	0
13	under **air** atmosphere	63	9

[a] Reaction conditions: **3.2a** (0.1 mmol), TsOH (0.22 mmol), $Pd(OAc)_2$ (0.01 mmol), NFSI (0.2 mmol), DCE (1.5 ml), 90 °C, 7h. [b] NMR yields using 1-fluoronaphthalene or 1,1,2,2-tetrachloroethane as the internal standard. Besides **3.2a** and **3.3a**, the remaining materials are mainly unidentifiable decomposition products. [c] The reactions were conducted under air, and 150 mol% TsOH was used. [d] Isolated yields. [e] **3.2a** was all consumed within 2 h. [f] Reaction time was 24 h. [g] Reaction time was 138 h. For full experimental details, see the **Experimental Section**.

We next move our attention to the substrate scope study. The directing group can be installed onto the free alcohols using either the Ellman's procedure (one pot)[45] or the previously demonstrated Mitsunobu procedure (two pots)[44] (Scheme 3.6).

Scheme 3.6 General Procedure for DG Installation



The substrate scope was then examined (Table 3.2). A variety of methyl C−H bonds at the β-position of primary, secondary and tertiary alcohols can be efficiently tosyloxylated. Ditosyloxylations were observed for substrates with more than one available methyl group (**3.3b** and **3.3i**). Different substitution patterns near the reaction center were well-tolerated, including sterically demanding cyclohexyl and isopropyl moieties (**3.3e** and **3.3g**), and a potentially coordinative methoxy group (**3.3d**). Aromatic rings with electron-donating or withdrawing groups were compatible, including heteroarenes and polyarenes such as thiophene and naphthalene (**3.3v** and **3.3u**). Many FGs, such as aryl-halides (**3.3k**-**3.3m**), nitroarenes (**3.3o**), nitriles (**3.3s**), esters (**3.3j**-**3.3x**), cyclopropanes (**3.3h**), and even

unprotected aryl aldehydes (**3.3r**), remain untouched. In addition, simple terminal olefins and α,β-unsaturated esters can also be tolerated (**3.3x** and **3.3w**).

Table 3.2 Study of the Substrate Scope[a]

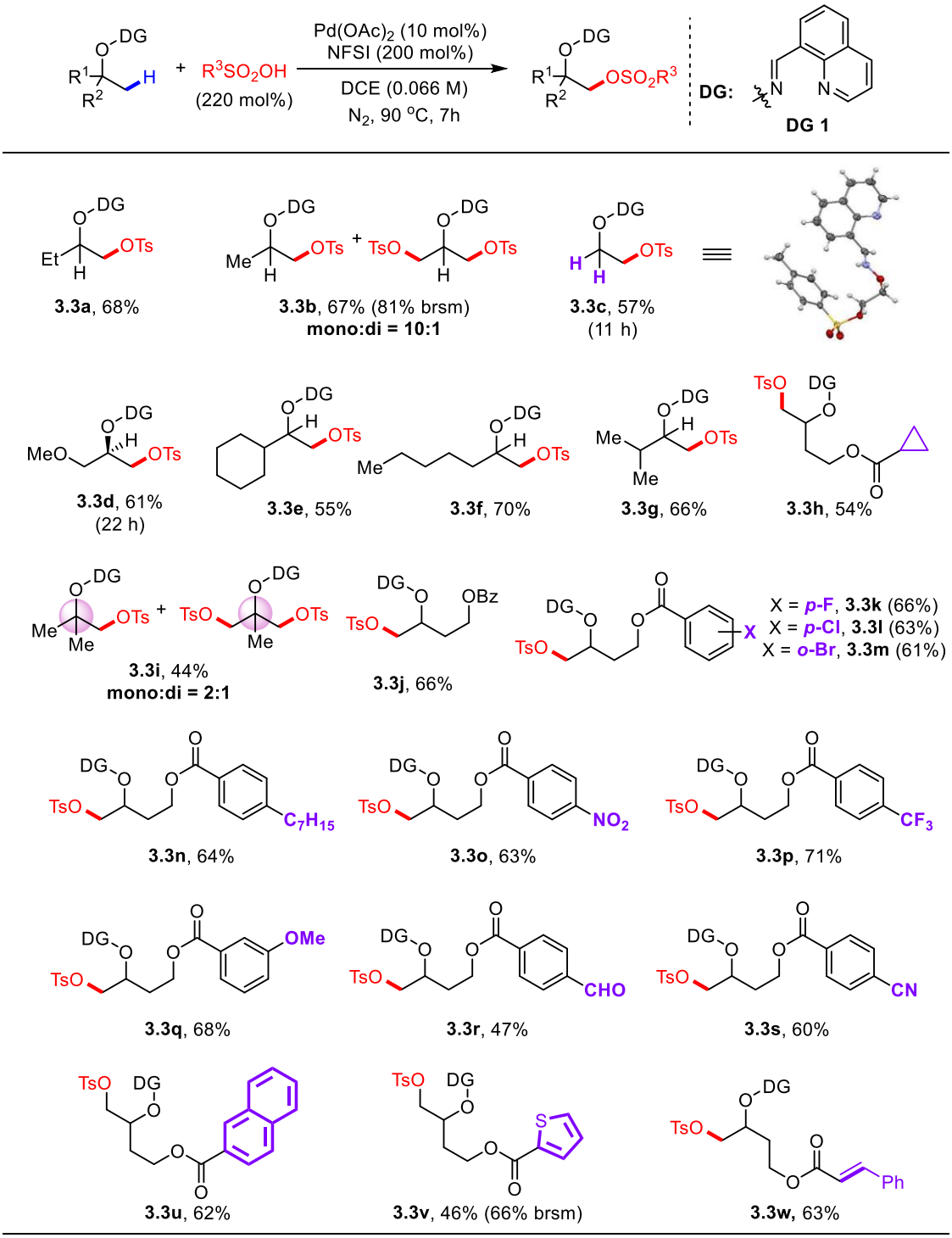
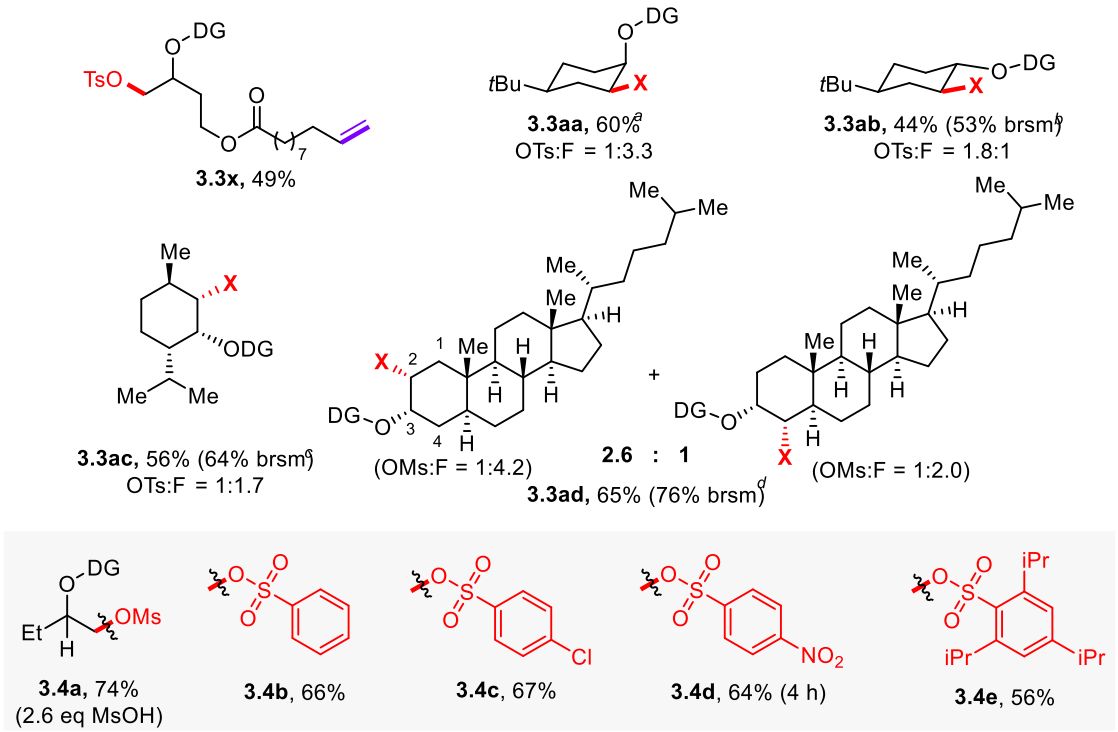


Table 3.2 Study of the Substrate Scope[a] (Continued)

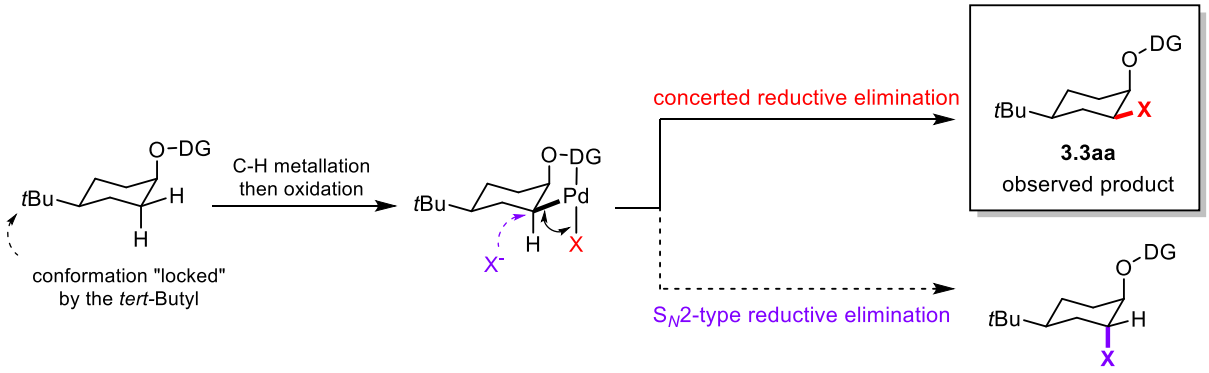


[a] General reaction conditions: oxime substrate (0.15 mmol), TsOH (0.33 mmol), $Pd(OAc)_2$ (0.015 mmol), NSFI (0.3 mmol), DCE (2.2 ml), 90 °C, 7h. All yields are isolated yields. [b] 10 h, 20 mol% $Pd(OAc)_2$. [c] 3.2 equiv TsOH, PhCl, 10.5 h. [d] 3.2 equiv TsOH, 4 h. [e] 2.6 equiv MsOH, 8.5 h, 20 mol% $Pd(OAc)_2$.

Moreover, this reaction is not limited to methyl groups: unactivated methylene C−H bonds can also be functionalized (**3.3aa** and **3.3ab**). Interestingly, unlike the reactions with methyls, a competing fluorination reaction occurred when activating a cyclic methylene though the exact reason remains unclear. The tosyloxylation-fluorination ratios varied with different substrate configurations; after careful assignment, C−H functionalization at the equatorial position was found predominating in all these cases. The stereochemical outcome with the conformationally rigid substrate **3.3aa** suggests a plausible concerted reductive elimination pathway when forming the sterically hindered product, for a simple S_N2 pathway

would require palladation at the axial position which is beyond the reach of the DG. However, a double stereo-inversion pathway cannot be excluded at this stage (Scheme 3.7). More complex substrates, such as those derived from menthol and cholesterol, also provided the desired methylene-functionalized products (**3.3ac** and **3.3ad**). Detailed mechanistic studies of these reactions and efforts on improving the chemoselectivity are under way in our laboratory.

Scheme 3.7 Conformational Analysis of the Reductive Elimination Pathways

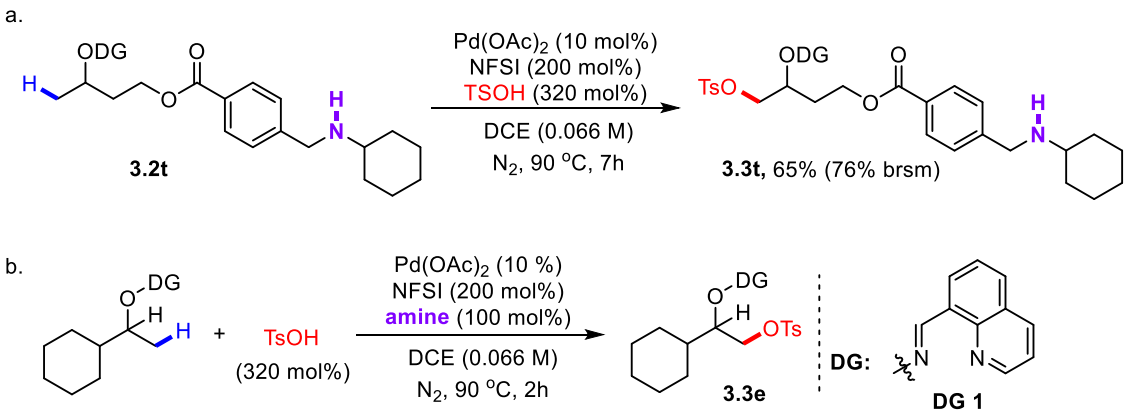


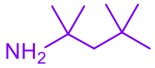
Besides the OTs group, other sulfonyloxy groups can also be efficiently installed. For example, use of aliphatic methylsulfonic acid gave the mesylated (OMs) product (Table 3.2, **3.4a**) in 74% yield. Aromatic sulfonic acids bearing different electronic and steric properties, including the highly bulky triisopropylphenylsulfonic acid, all reacted smoothly suggesting a general reaction feature (**3.4b** to **3.4e**). This provides options of installing tunable LGs through C−H activation for the subsequent S_N2 reactions.

Encouraged by an outside reviewer of this work, we then investigated whether free amines, which are commonly found in bio-important molecules, could be tolerated in this transformation. Accordingly, **3.2t** was synthesized and tested. To our delight, the free amine

was found compatible during the reaction when additional one equivalent of the acid was added (Scheme 3.8a). It is likely that the amines can be "*in situ*" protected as the corresponding ammonium salts, which prevents further reactions with the oxidant and/or the electrophiles. After completion of the reaction, the reaction media was basified, and **3.3t** could be isolated through regular chromatography technique. A "robust test" was then conducted, and further confirmed the compatibility of a group of primary and secondary aliphatic amines (Scheme 3.8b). Unfortunately, anilines were not tolerated due to oxidative decompositions.

Scheme 3.8 Study of Amine Compatibility



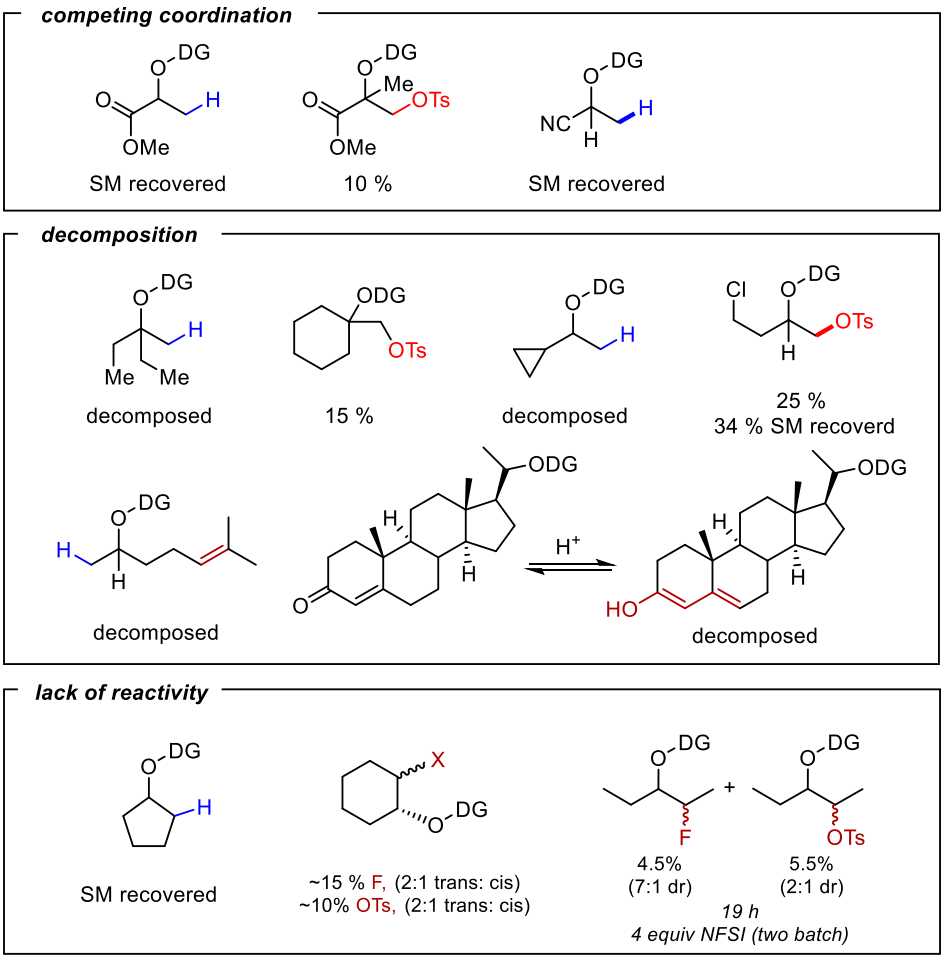
entry	amine	TsO-product yield[a]	amine recovery yield
1	without amine	55%[b]	--
2		57%	88%[c]
3	Cy_2NH	58%	97%[a]
4	morphline	61%	>99%[d]

[a] isolated yield. [b] TsOH (2.2 eq), 7h (as **Standard condition**). [c] GC yield. [d] isolated as benzoylated derivative.

Three types of substrates were found incompatible in this transformation (Scheme 3.9). Total or significant loss of the reactivity was observed when competing coordinative

sites exists, such as a nitrile group or an α ester. Some tertiary alcohols were found as unsuccessful substrates, due to significant E1 elimination under strong acidic conditions. A cyclopropyl group attached on the α position could not be tolerated, same as a primary chloride. Electron rich alkenes would suffer from oxidative decompositions and thus not tolerated. Methlyene activation was generally challenging for this transformation: For cyclic methylenes, 25% combined yield was observed for the simple cyclohexanol-derived substrate, while no desired product was detected for the cyclopentanol counterpart. The linear methylene was also found difficult to be activated under current conditions.

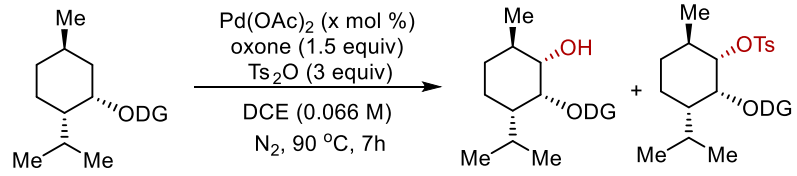
Scheme 3.9 Examples of Failed Substrates



Using menthol as a model substrate, a brief investigation was conducted aiming to suppress the fluorine incorporation during the β C−H oxygenation of substituted cyclohexanols. It is found that by using Oxone in replacement of NFSI as the oxidant and Ts_2O as the tosyl source, a mixture of the –OTs and the –OH products could be furnished. However, after extensive condition screening, we were not able to turn over the catalytic circle. As shown in Scheme 3.10a, while a Pd loading of 10 mol% provided a 10% yield of the –OTs product, a Pd loading of 30 mol% produced 20% of the –OH product and 13% of the –OTs product. We currently suspected that the formation of the tri-dentate intermediate could be the reason of the turnover problem (Scheme 3.10b).

Scheme 3.10 Preliminary Investigation on β C−H Oxygenation of Menthols

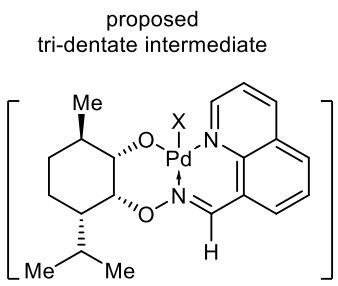
a.



entry[a]	Pd loading	SM	Pro-OH	Pro-OTs
1	10 mol %	60	0	10
2	20 mol %	35	13	9
3	30 mol %	29	20	13

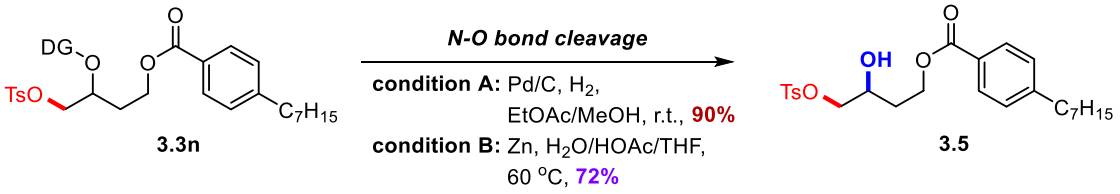
[a] oxone = 2 $KHSO_5$ + $KHSO_4$ + K_2SO_4

b.



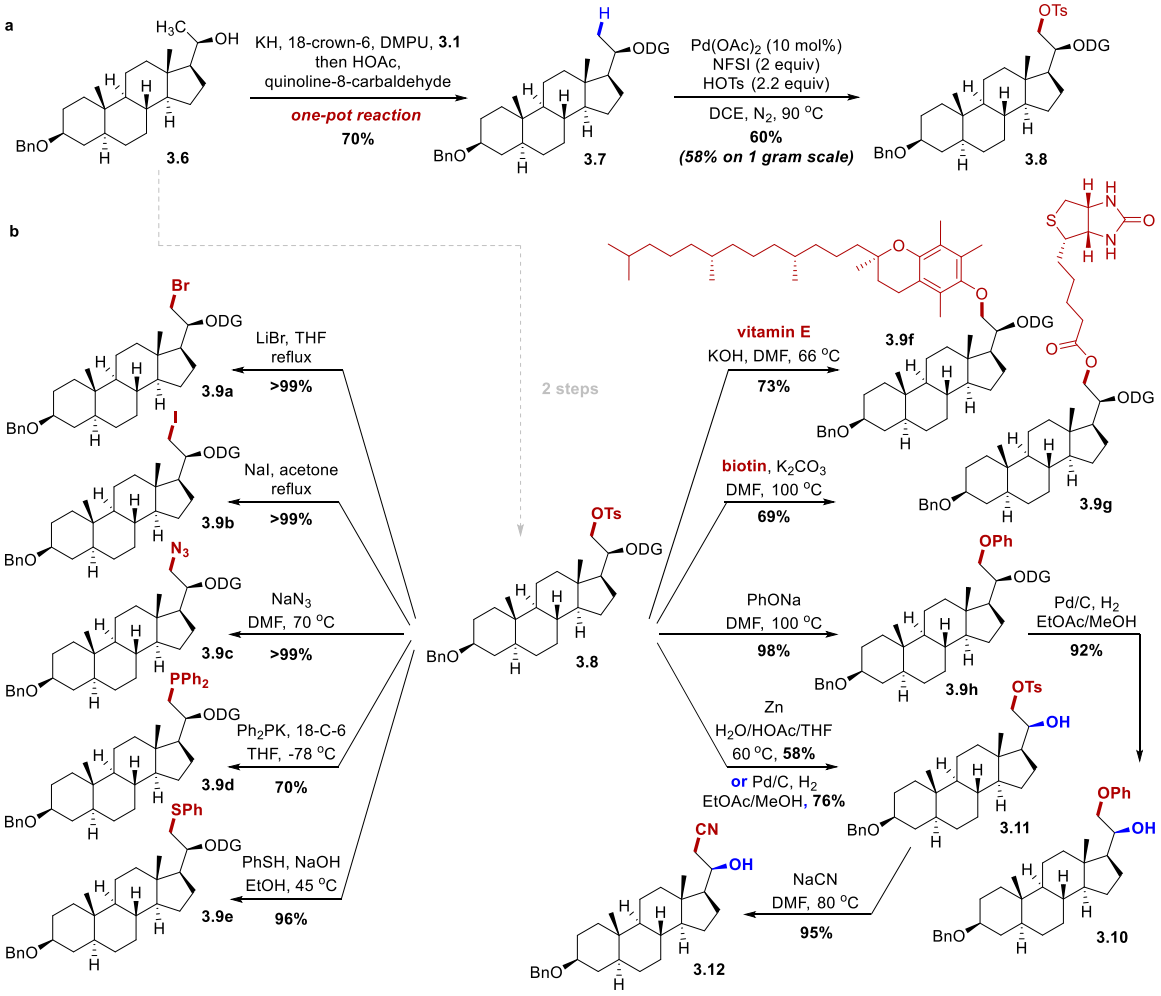
Regards the removal of the DG, the N−O bond of the DG could be easily cleaved either under catalytic hydrogenation conditions or using zinc and acetic acid, furnishing free alcohols in high yield without the formation of significant amounts of epoxides (Scheme 3.11).

Figure 3.2 Removal of the DG



Finally, application of this LG-based strategy to late-stage diversification was demonstrated on a steroid intermediate (Figure 3.3). The mono-protected 2H-pregnanediol (**3.6**) was prepared in three steps from commercially available *Pregnenolone*. The DG can be efficiently installed in one pot using Ellman's oxaziridine 3.**1**[45]. The sp^3 C−H tosyloxylation occurred smoothly at the inert C21 position providing tosylate **3.8** in 60% yield (58% on a gram-scale), which serves as a common intermediate for diversification (Figure 3.3a). The subsequent nucleophilic substitution reactions rapidly prepared a variety of *2H-pregnanediol* derivatives through forming C−C, C−O, C−N, C−X, C−S and C−P bonds. In particular, biologically interesting molecules, such as *biotin* and *vitamin E*, can be directly coupled giving the corresponding conjugated compounds. It is noteworthy that sulfide and phosphine FGs are nontrivial to be introduced directly using common C−H activation methods due to their strong coordination ability to transition metals and sensitivity to oxidants. This LG-based strategy can overcome such a limitation affording sulfide **3.9e** and phosphine **3.9d** by employing tosylates as a convenient handle. We further illustrate that the DG can be removed under mild conditions either before or after substitution reactions. Interestingly, the Pd/C-catalyzed hydrogenation conditions can chemoselectively cleave the oxime N−O bond instead of removing the benzyl protecting group (Figure 3.3b).

Figure 3.3 Late-Stage Diversification via a LG-based Strategy



3.3 Conclusions

In conclusion, the present study provides a convenient and efficient approach for diverse functionalization of alcohol-containing compounds through β-sulfonyloxylation. As the hydroxyl group is widely found in bioactive molecules and synthetic intermediates, this LG-based approach is expected to streamline the preparation of complex pharmaceutical analogues, and ultimately contribute to expediting the search for lead compounds.

(Some contents of this chapter were published in *Nat. Chem*. **2015**, *7*, 829)

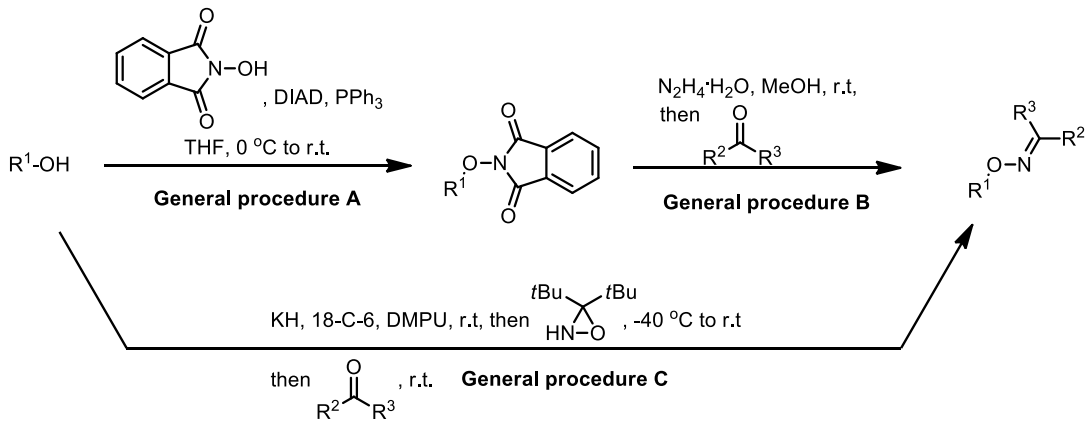
3.4 Experimental

Unless otherwise noted, all experiments were carried out under air atmosphere. 1,2-dichloroethane (DCE), chlorobenzene (PhCl), 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one (DMPU) and *N*,*N*-dimethylformamide (DMF) were distilled over CaH_2. Toluene and tetrahydrofuran (THF) were distilled over sodium. Anhydrous 4-methylbenzenesulfonic acid (*p*-TsOH) was obtained from corresponding monohydrate by removal of H_2O at 60 °C under *vacuo*. The other reagents and solvents were directly used from the supplier without further purification unless noted. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plate (silica gel 60, F254, EMD chemical). The vials (1 dram, 15×45 mm with PTFE lined cap attached) were purchased from Qorpak and dried in an oven overnight and cooled in air. Optical rotations were determined using an Anton Paar MCP 200 polarimeter. Infrared spectra were recorded on a Nicolet iS5 FT-IR Spectrometer using neat thin film technique. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+Na]^+$ or $[M+H]^+$. Nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR, ^{19}F NMR) were recorded with Varian Gemini (400 MHz, ^{1}H at 400 MHz, ^{13}C at 100 MHz, ^{19}F at 376 MHz) or Varian Unity+ (300 MHz, ^{1}H at 300 MHz, ^{13}C at 75 MHz) unless noted. For $CDCl_3$ solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; $CHCl_3$ δ H (7.26 ppm) and $CDCl_3$ δ C (77.16 ppm). For C_6D_6 solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; C_6D_6 δ H (7.16 ppm) and C_6D_6 δ C (128.06 ppm). Coupling constants are reported in Hertz (Hz). Data for ^{1}H NMR and ^{19}F NMR

spectra are reported as follows: chemical shift (ppm, referenced to protium: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet (quintet), dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet, coupling constant (Hz), and integration).

Preparation and characterization of starting materials

Scheme 3.12 General Procedure for Substrates Preparation



General procedure A: To a solution of alcohol (5 mmol, 1.0 equiv), *N*-hydroxyphthalimide (978 mg, 6 mmol, 1.2 equiv) and PPh_3 (1.572 g, 6 mmol, 1.2 equiv) in 20 mL THF was added diisopropyl azodicarboxylate (1.2 mL, 6 mmol, 1.2 equiv) dropwise at 0 °C. Then the reaction was allowed to warm to room temperature and stirred overnight. Upon done, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel to give the title compounds. *All the yields are not optimized.*

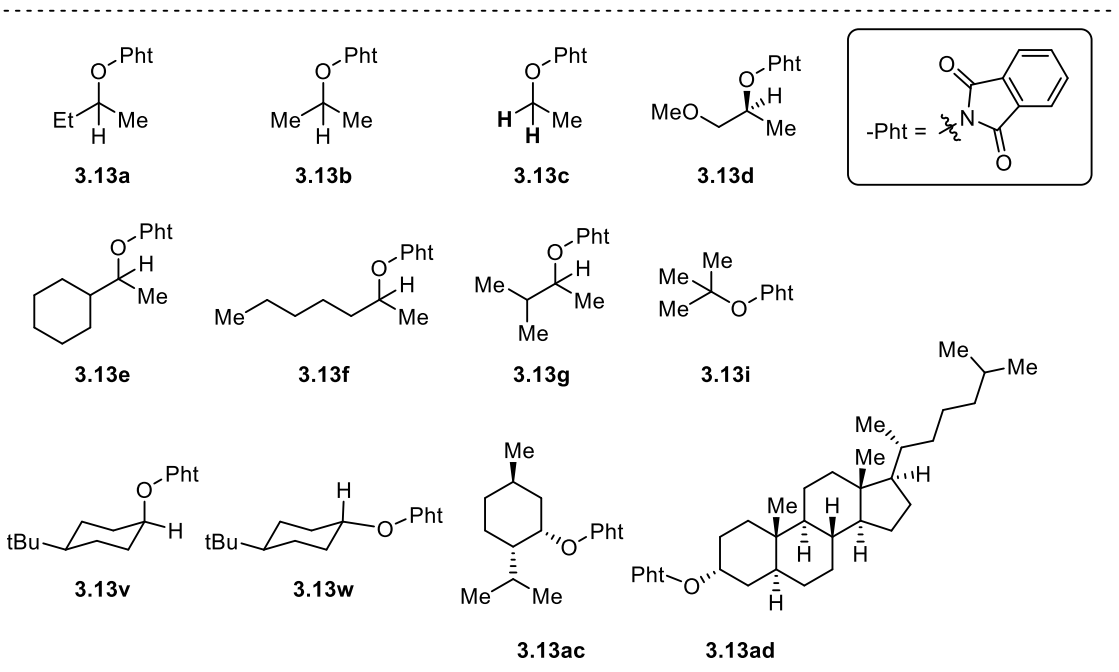
General procedure B: To a solution of *N*-alkoxyphthalimide (1.1 equiv) in MeOH (5 mL/mmol) was added hydrazine monohydrate (1.15 equiv) at room temperature. The reaction was monitored by TLC and usually completed in 30 min. Then aldehyde or ketone (1.0 equiv) was added. The reaction was monitored by TLC. After 0.5 h the mixture was filtered to remove precipitate if formed and then the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel to give the title compounds. *All the yields are not optimized*

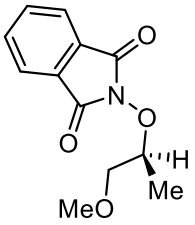
General procedure C: The following procedure is a modified procedure from the literature[45]. To a suspension of KH (1.5 equiv.) and 18-crown-6 (0.1 equiv.) in DMPU (3ml/1mmol alcohol) was added alcohol (1.0 equiv) under N_2 atmosphere at room temperature. After stirring at room temperature for 1h and no gas evolution was observed, the resulting solution was slowly added into a DMPU solution (1.5ml/1mmol alcohol) of 3,3'-di-*tert*-butyl oxziridine **3.1** (2.5 equiv) at -40 °C (*3,3'-di-tert-butyl oxziridine **3.1** was prepared according to the same literature*). Upon done, the reaction was warmed to room temperature and stirred for another 1.5 h. Several drops of HOAc were added in, followed by the addition of aldehyde (1.3 equiv.). The mixture was stirred for 0.5 h, and then diluted with 1M NaOH, extracted with EtOAc and washed with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give the title compounds.

Preparation and characterization of *N*-alkoxyphthalimides

3.13a, 3.13b, 3.13c, 3.13e, 3.13f, 3.13g, 3.13i, 3.13ac were prepared according to the reported literature[44]. **3.13d, 3.13v, 3.13w, 3.13ad** were prepared according to **General procedure A**.

Scheme 3.13 Structures of *N*-alkoxyphthalimides Synthesized for this Study

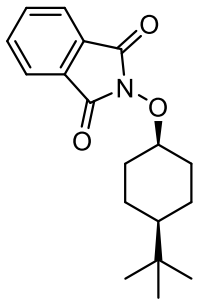




3.13d

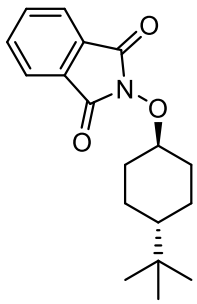
(*S*)-2-((1-methoxypropan-2-yl)oxy)isoindoline-1,3-dione (3.13d): The titled compound was prepared according to **General Procedure A** using (*R*)-1-methoxypropan-2-ol as starting material. Yellowish oil. Yield 95%. R_f = 0.35 (Hex/EA= 5:1). IR (KBr)

2984.79, 2934.89, 2875.88, 1788.29, 1732.08, 1380.80, 1189.99 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 2H), 7.77 – 7.69 (m, 2H), 4.62 – 4.47 (m, 1H), 3.71 – 3.62 (m, 1H), 3.53 – 3.48 (m, 1H), 3.31 (s, 3H), 1.37 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.05, 134.47, 129.07, 123.55, 82.66, 75.21, 59.29, 16.00. HRMS: calcd. $[M+H]^+$ 236.09174 Found: 236.09180. $[a]_D^{20}$ = 11.5 (c 0.85, $CHCl_3$).



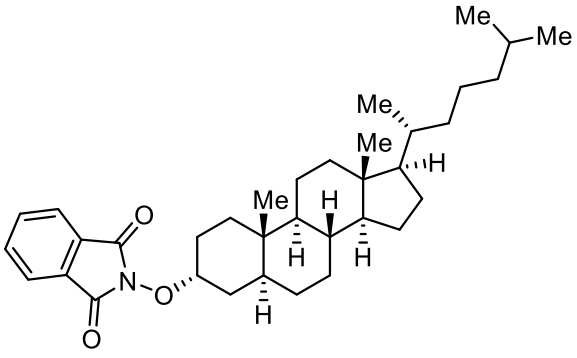
3.13v

2-(((1*s*,4*s*)-4-(*tert*-butyl)cyclohexyl)oxy)isoindoline-1,3-dione (3.13v): Colorless oil. Yield 72%. Rf = 0.3 (Hex/EA= 5:1). IR (KBr) 2956.67, 2863.48, 1793.81, 1733.03, 1469.67, 1382.55, 1368.37, 1190.10 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.76 (m, 2H), 7.71 (ddd, *J* = 5.7, 2.8, 1.3 Hz, 2H), 4.44 (d, *J* = 2.3 Hz, 1H), 2.15 (d, *J* = 13.2 Hz, 2H), 1.72 – 1.40 (m, 6H), 1.06 – 0.99 (m, 1H), 0.88 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.39, 134.45, 129.20, 123.45, 82.47, 47.77, 32.74, 29.88, 27.61, 21.37. HRMS: calcd. $[M+Na]^+$ 324.15701 Found: 324.15730.



3.13w

2-(((1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl)oxy)isoindoline-1,3-dione (13w): white solid. m.p. = 120-121 °C. Yield 70%. Rf = 0.3 (Hex/EA= 5:1). IR (KBr) 2948.56, 2861.45, 1781.65, 1739.11, 1465.62, 1354.19, 1186.04 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.79 (m, 2H), 7.76 – 7.70 (m, 2H), 4.14 (tt, *J* = 11.4, 4.4 Hz, 1H), 2.18 (ddd, *J* = 8.0, 2.9, 1.2 Hz, 2H), 1.85 (dd, *J* = 6.7, 3.1 Hz, 2H), 1.61 – 1.44 (m, 2H), 1.11 – 0.94 (m, 3H), 0.83 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.43, 134.49, 129.09, 123.56, 86.64, 47.12, 32.37, 31.30, 27.71, 25.36. HRMS: calcd. $[M+Na]^+$ 324.15701 Found: 324.15730.



3.13ad

2-(((3*R*,5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)isoindoline-1,3-dione (3.13ad): White solid. m.p. = 165-166°C. Yield 88%. R_f = 0.5 (Hexane:Ethyl acetate = 20:1).

IR (KBr) 2932, 2867, 1789, 1734, 1467, 1445, 1376, 1188, 1123 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.76 – 7.70 (m, 2H), 4.43 (d, *J* = 2.2 Hz, 1H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 1.9 Hz, 3H), 0.85 (d, *J* = 1.9 Hz, 3H), 0.79 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.41, 134.43, 129.20, 123.47, 83.36, 56.57, 56.35, 54.01, 42.69, 40.09, 39.64, 39.36, 36.30, 35.97, 35.87, 35.63, 32.56, 32.26, 32.01, 28.57, 28.39, 28.13, 25.26, 24.33, 24.00, 22.97, 22.70, 20.92, 18.80, 12.21, 11.36. HRMS: calcd. $[M+Na]^+$ 556.37610 Found: 556.37610.

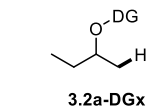
Preparation and characterization of oxime substrates

3.2a-DG2 was prepared according to the reported literature[44]. **3.2a-DG1, 3.2a-DG3, 3.2a-DG4, 3.2a-DG5, 3.2a-DG6, 3.2a-DG10, 3.2a-DG12, 3.2b, 3.2c, 3.2d, 3.2e, 3.2f, 3.2g, 3.2i, 3.2v, 3.2w, 3.2ac,** and **3.2ad** were prepared according to **General procedure B**. **3.2a-DG1** can also be prepared according to **General procedure C**. **3.2a-DG7**, **3.2a-DG8**, **3.2a-DG9, 3.2h, 3.2j to 3.2u, 3.2x, 3.2y,** and **3.2z** were prepared according to the following procedures.

Quinoline-8-carbaldehyde was prepared according to a slightly modified procedure from the literature[46]: A 500 ml round bottom flask was charged with 8-methylquinoline (10 g, 70 mmol, 1.0 equiv), *N*-bromosuccinimide (37.4 g, 210 mmol, 3.0 equiv), 2,2'-azobis(2-methylpropionitrile) (1 g, 6 mmol, 0.085 equiv.) and 1,2-dicholoethane (120 ml). The mixture was allowed to heat to reflux for 5 hours and then cool to room temperature. The mixture was diluted by DCM (1 L) and neutralized by 1M NaOH (400 ml). The organic layer was

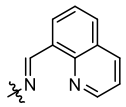
separated, and washed by 1M NaOH, water and brine. The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then refluxed with 750 ml of water for 5 hours under N_2. Upon done, the mixture was cooled to room temperature, neutralized by 1M NaOH (500 ml), extracted with diethyl ether and washed with water and brine. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give the title compounds as a white solid (6.6 g, 60%).

Scheme 3.14 Structures of Oxime Substrates Synthesized for this Study

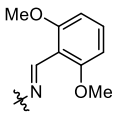


3.2a-DGx

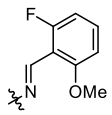
DG =



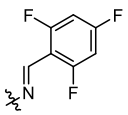
DG 1



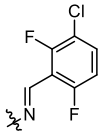
DG 2



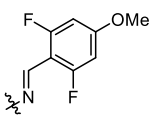
DG 3



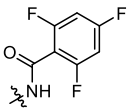
DG 4



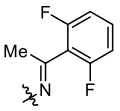
DG 5



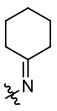
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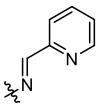
DG 7



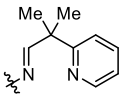
DG 8



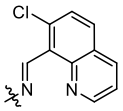
DG 9



DG 10



DG 11



DG 12



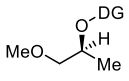
3.2a



3.2b

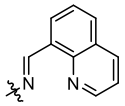


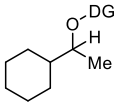
3.2c



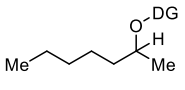
3.2d

DG =

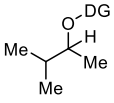




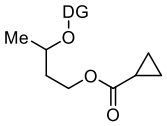
3.2e



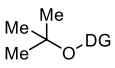
3.2f



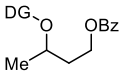
3.2g



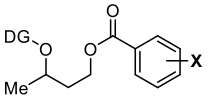
3.2h



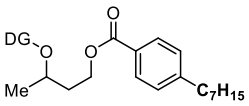
3.2i



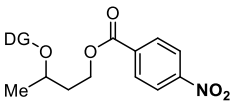
3.2j



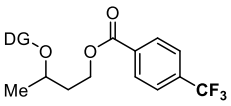
X = ***p*-F**, **3.2k**
X = ***p*-Cl**, **3.2l**
X = ***o*-Br**, **3.2m**



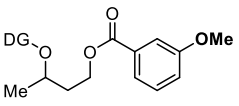
3.2n



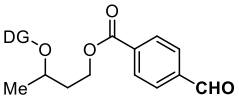
3.2o



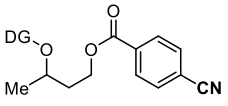
3.2p



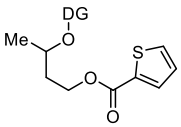
3.2q



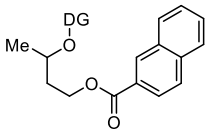
3.2r



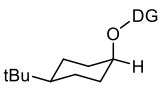
3.2s



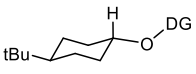
3.2t



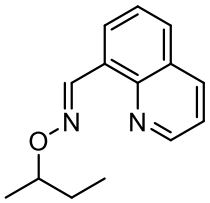
3.2u



3.2v

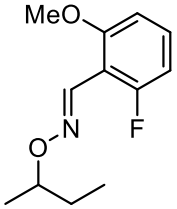


3.2w



3.2a-DG1

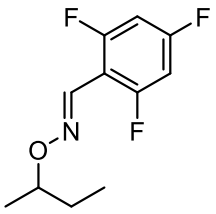
(*E*)-quinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime (3.2a-DG1): Colorless oil. Yield 88%. R_f = 0.7 (Hex/EA= 5:1). IR (KBr) 2979.86, 2934.89, 2881.50, 1588.76, 1501.64, 1051.99, 962.06, 995.78 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.91 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.26 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.82 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.36 – 4.26 (m, 1H), 1.83 – 1.71 (m, 1H), 1.65-1.55 (m, 1H), 1.31 (d, *J* = 6.3 Hz, 3H), 0.98 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.02, 146.03, 145.51, 136.28, 130.77, 129.24, 128.39, 126.50, 126.10, 121.44, 80.96, 28.73, 19.48, 9.92. HRMS: calcd. $[M+H]^+$ 229.13354 Found: 229.1335. **2a-DG1** can also be prepared according to **General procedure C** on 2.08 mmol scale as colorless oil (0.303 g, 64%).



3.2a-DG3

(*E*)-2-fluoro-6-methoxybenzaldehyde *O*-(sec-butyl) oxime (3.2a-DG3): Yellowish oil. Yield 81%. R_f = 0.3 (Hex/EA= 10:1). IR (KBr) 2971.43, 2934.89, 2881.50, 1616.86, 1473.54, 1445.43, 1245.90 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 0.8 Hz, 1H), 7.24

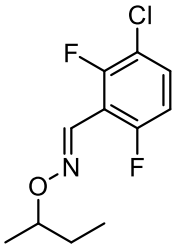
(td, *J* = 8.4, 6.3 Hz, 1H), 6.75-6.65 (m, 2H), 4.29 (h, *J* = 6.3 Hz, 1H), 3.85 (s, 3H), 1.81 – 1.70 (m, 1H), 1.57 (dqd, *J* = 14.8, 7.4, 6.4 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.00 (d, *J* = 254.4 Hz), 158.88 (d, *J* = 6.9 Hz), 141.06 (d, *J* = 3.4 Hz), 130.36 (d, *J* = 10.9 Hz), 109.92 (d, *J* = 14.3 Hz), 108.65 (d, *J* = 22.2 Hz), 106.45 (d, *J* = 3.1 Hz), 80.67, 56.11, 28.45, 19.15, 9.68. ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.65 (dd, *J* = 9.9, 6.3 Hz, 1F). HRMS: calcd. $[M+H]^+$ 248.10573 Found: 248.10590.



3.2a-DG4

(*E*)-2,4,6-trifluorobenzaldehyde *O*-(*sec*-butyl) oxime (3.2a-DG4): Colorless oil. Yield 59%. R_f = 0.6 (Hex/EA= 10:1). IR (KBr) 3398.31, 2940.52, 2358.78, 2339.11, 1644.96, 1614.05, 1498.83, 1442.62 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 6.70 (t, *J* = 8.4 Hz, 2H), 4.28 (dd, *J* = 12.6, 6.3 Hz, 1H), 1.74 (dqd, *J* = 13.8, 7.5, 6.3 Hz, 1H), 1.57 (dqd, *J* = 13.7, 7.4, 6.2 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.76 (dt, *J* = 252.4, 15.3 Hz, 1C), 161.28 (ddd, *J* = 257.1, 14.8, 9.6 Hz, 2C), 137.93 (d, *J* = 1.9 Hz, 1C), 107.38 (td, *J* = 15.3, 4.9 Hz, 1C), 100.95 (ddd, *J* = 26.7, 25.7, 3.3 Hz, 2C), 81.54, 28.53, 19.25, 9.80. ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.96 (tt, *J* = 8.7, 7.5 Hz, 1F), -107.86 – -108.04 (m, 2F). HRMS: calcd. $[M+H]^+$ 232.09438, Found: 232.09440.

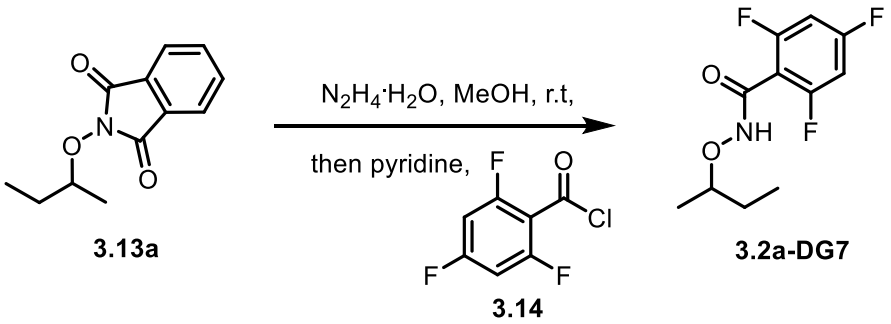
(*E*)-3-chloro-2,6-difluorobenzaldehyde *O*-(*sec*-butyl) oxime (2a-DG5): Yellowish oil. Yield 81%. R_f = 0.5 (Hex/EA= 10:1). IR (KBr) 2974.24, 2937.70, 2884.31, 1619.67, 1481.97, 1026.70 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.33 (ddd, *J* = 9.0, 8.0, 5.5 Hz, 1H), 6.90 (td, *J* = 9.2, 1.8 Hz, 1H), 4.31 (h, *J* = 6.3 Hz, 1H), 1.76 (dqd, *J* = 13.8, 7.5, 6.3 Hz, 1H), 1.64 – 1.55 (m, 1H), 1.29 (d, *J* = 6.3 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ carbon signals were found at 160.52, 160.46, 157.97, 157.91, 157.41, 157.34, 154.84, 154.77, 138.11, 130.56, 130.46, 117.52, 117.38, 117.34, 112.55, 112.51, 112.32, 112.28, 112.14, 111.99, 111.84, 81.84, 28.53, 19.26, 9.81. ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.00 (ddd, *J* = 7.9, 4.2, 1.8 Hz, 1F), -112.61 – -112.71 (m, 1F). HRMS: calcd. $[M+H]^+$ 248.06483 Found: 248.06470.



3.2a-DG5

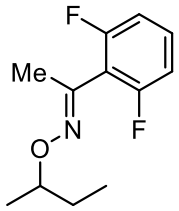
(*E*)-2,6-difluoro-4-methoxybenzaldehyde *O*-(*sec*-butyl) oxime (3.2a-DG6): Yellowish oil. Yield 74%. R_f = 0.3 (Hex/EA= 10:1). IR (KBr) 3016.39, 2977.05, 2940.52, 2878.69, 1633.72, 1504.45, 1442.62, 1153.16 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s,

1H), 6.47 (d, *J* = 10.2 Hz, 2H), 4.27 (h, *J* = 6.3 Hz, 1H), 3.80 (s, 3H), 1.80 – 1.69 (m, 1H), 1.62 – 1.52 (m, 1H), 1.27 (d, *J* = 6.3 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.73 (dd, *J* = 253.9, 10.2 Hz), 161.43 (t, *J* = 14.2 Hz), 138.92, 103.27 (t, *J* = 15.6 Hz), 98.77 – 98.30 (m), 81.10, 56.03, 28.57, 19.30, 9.84. ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.98 – -110.08 (m, 2F). HRMS: calcd. $[M+H]^+$ 244.11437 Found: 244.11460.



***N*-(*sec*-butoxy)-2,4,6-trifluorobenzamide (3.2a-DG7):** To a solution of 2-(*sec*-butoxy)isoindoline-1,3-dione (**13a**) (1 equiv., 4 mmol, 0.876g) in MeOH (20 mL) was added hydrazine monohydrate (1.1 equiv., 220 mg) at room temperature. The reaction was stirred at room temperature for 30 min. Then pyridine (1.2 equiv., 379 mg) was added into the mixture. After cooling to 0 °C, 2,4,6-trifluorobenzoyl chloride (**14**) (1.1 equiv., 0.856 g) was added dropwise, and the resulting mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (DCM:EA = 40:1) on silica gel to give the *N*-(*sec*-butoxy)-2,4,6-trifluorobenzamide (**3.2a-DG7**) as a white solid (0.80 g, 78%). m.p.= 89-90 °C. R_f = 0.4 (DCM/EA= 30:1). IR (KBr) 3187.82, 2979.86, 2361.59, 1670.26, 1639.34, 1442.62, 1122.25 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (br, 0.15H), 8.68 (br, 0.85H), 6.67 (t, *J* = 8.2 Hz,

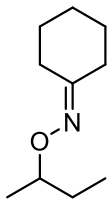
2H), 4.12 – 3.92 (m, 1H), 3.62 (br, 1H), 1.81 – 1.63 (m, 1H), 1.53 (tt, *J* = 14.3, 7.2 Hz, 1H), 1.25 (d, *J* = 6.2 Hz, 2.55H), 1.06 (br, 0.45H), 0.94 (t, *J* = 7.5 Hz, 2.55H), 0.63 (br, 0.45H). ^{13}C NMR (101 MHz, $CDCl_3$) δ carbon signals were found at 165.36, 165.20, 165.06, 162.83, 162.68, 162.55, 162.28, 162.22, 162.13, 162.04, 159.76, 159.65, 159.61, 159.51, 157.82, 101.36, 101.33, 101.09, 101.07, 100.84, 100.81, 83.94, 27.42, 17.82, 9.62. ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.18 (p, *J* = 8.3 Hz, 0.84F), -103.65 (br, 0.15F), -107.40 (t, *J* = 7.9 Hz, 1.70F), -108.14 (br, 0.30F). HRMS: calcd. $[M+H]^+$ 270.07123 Found: 270.07140.



3.2a-DG8

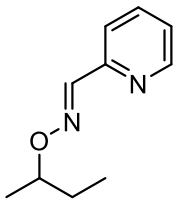
(*E*)-1-(2,6-difluorophenyl)ethanone *O*-(*sec*-butyl) oxime (3.2a-DG8): was prepared according to a modified procedure of **General procedure B** (*after adding the corresponding ketone, the reaction mixture was heated to reflux for 1h instead of stirring at room temperature*) and isolated as a ca. 5:1 E/Z isomer. Colorless oil. Yield 77 %. R_f = 0.7 (Hex/EA= 10:1). IR (KBr) 2979.86, 2932.08, 2875.88, 1628.10, 1467.92, 1245.90, 995.78 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 1H), 7.01 – 6.79 (m, 2H), 4.25 (h, *J* = 6.3 Hz, 0.82H), 4.13 (dd, *J* = 12.5, 6.3 Hz, 0.17H), 2.19-2.17 (m, 3H), 1.74 (dqd, *J* = 13.6, 7.5, 6.1 Hz, 0.82H), 1.64 – 1.53 (m, 1.17H), 1.44 (td, *J* = 7.6, 3.7 Hz, 0.17H), 1.27 (d, *J* = 6.3 Hz, 2.5H), 1.16 (d, *J* = 6.3 Hz, 0.5H), 0.95 (t, *J* = 7.5 Hz, 2.5H), 0.83 (t, *J* = 7.5 Hz, 0.5H). ^{13}C NMR (101 MHz, $CDCl_3$) major isomer: δ 160.74 (dd, *J* = 250.4, 7.1 Hz), 146.61, 130.00

(t, J = 10.3 Hz), 112.00 – 111.59 (m), 80.98, 28.66, 19.36, 16.34 (t, J = 1.7 Hz), 9.75. ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.91 (d, J = 44.2 Hz, 0.16F), -112.80 (t, J = 6.6 Hz, 0.86F). HRMS: calcd. $[M+H]^+$ 228.11945 Found: 228.11950.



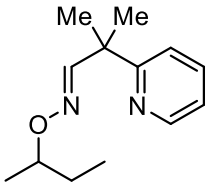
3.2a-DG9

Cyclohexanone *O*-(*sec*-butyl) oxime (3.2a-DG9): was prepared according to a modified procedure of **General procedure B** (*after adding the corresponding ketone, the reaction mixture was heated to reflux for 1h instead of stirring at room temperature*). Colorless oil. Yield 36%. R_f = 0.6 (Hex/EA= 10:1). IR (KBr) 2971.43, 2934.89, 2859.02, 1644.96, 1453.86, 1369.56, 1133.49, 995.78 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 – 3.98 (m, 1H), 2.53 – 2.37 (m, 2H), 2.19 (dd, J = 7.1, 5.5 Hz, 2H), 1.71 – 1.55 (m, 7H), 1.53 – 1.42 (m, 1H), 1.18 (d, J = 6.3 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.62, 79.31, 32.48, 28.58, 27.25, 26.06, 25.94, 25.47, 19.28, 9.78. HRMS: calcd. $[M+H]^+$ 170.15394 Found: 170.15390.



3.2a-DG10

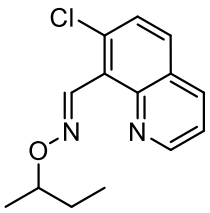
(*E*)-picolinaldehyde *O*-(*sec*-butyl) oxime (3.2a-DG10): Colorless oil. Yield 84%. R_f = 0.5 (Hex/EA= 5:1). IR (KBr) 2974.24, 2929.27, 2881.50, 1591.57, 1467.92, 1434.19, 1001.41 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.8 Hz, 1H), 8.15 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.67 (td, *J* = 7.9, 1.7 Hz, 1H), 7.23 (ddd, *J* = 7.3, 4.9, 1.0 Hz, 1H), 4.39 – 4.20 (m, 1H), 1.83 – 1.70 (m, 1H), 1.59 (tt, *J* = 13.8, 6.9 Hz, 1H), 1.29 (d, *J* = 6.3 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.31, 149.70, 148.56, 136.43, 123.76, 120.92, 81.62, 28.56, 19.34, 9.82.HRMS: calcd. $[M+H]^+$ 179.11789 Found: 179.11790.



3.2a-DG11

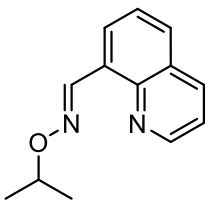
(*E*)-2-methyl-2-(pyridin-2-yl)propanal *O*-(*sec*-butyl) oxime (3.2a-DG11): Colorless oil. Yield 65%. R_f = 0.6 (Hex/EA= 5:1). IR (KBr) 3064.49, 2977.05, 2929.27, 2878.69, 1591.57, 1479.16, 999.42, 947.45 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 – 8.51 (m, 1H), 7.70 – 7.56 (m, 2H), 7.27 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.12 (ddt, *J* = 7.4, 4.8, 1.2 Hz, 1H), 4.21 – 4.04 (m, 1H), 1.74 – 1.66 (m, 1H), 1.59 – 1.41 (m, 7H), 1.21 (d, *J* = 6.3 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.19, 155.56, 149.11, 136.49,

121.51, 120.73, 79.99, 43.75, 28.54, 26.14, 19.16, 9.85. HRMS: calcd. $[M+H]^+$ 221.16484 Found: 221.16460.



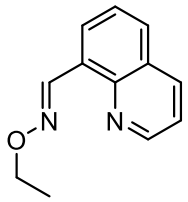
3.2a-DG12

(*E*)-7-chloroquinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime (3.2a-DG12): Colorless oil. Yield 91%. R_f = 0.5 (Hex/EA= 5:1). IR (KBr) 2971.43, 2932.08, 2881.50, 1614.05, 1597.19, 1490.40, 1130.68, 947.45 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 8.95 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.13 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.40 – 4.31 (m, 1H), 1.90 – 1.79 (m, 1H), 1.70 – 1.57 (m, 1H), 1.36 (d, *J* = 6.3 Hz, 3H), 1.00 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.89, 147.67, 144.62, 136.10, 134.31, 129.38, 129.05, 128.72, 126.78, 121.59, 81.06, 28.69, 19.39, 9.87. HRMS: calcd. $[M+H]^+$ 285.07651 Found: 285.07680.



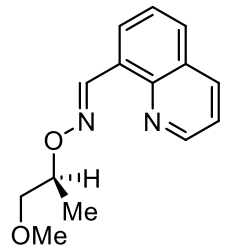
3.2b

(*E*)-quinoline-8-carbaldehyde *O*-isopropyl oxime (3.2b): Colorless oil. Yield 74%. R_f = 0.4. IR (KBr) 3036, 2974, 2929, 1616,1586, 1574, 1497, 1467 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.89 (dd, J = 4.2, 1.8 Hz, 1H), 8.27 (dd, J = 7.3, 1.4 Hz, 1H), 8.08 (dd, J = 8.3, 1.8 Hz, 1H), 7.78 (dd, J = 8.2, 1.4 Hz, 1H), 7.56 – 7.48 (m, 1H), 7.36 (dd, J = 8.3, 4.2 Hz, 1H), 4.55 (hept, J = 6.3 Hz, 1H), 1.36 (d, J = 6.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.93, 145.90, 145.57, 136.15, 130.57, 129.23, 128.25, 126.37, 126.01, 121.36, 75.81, 21.86. HRMS: calcd. $[M+H]^+$ 215.11789 Found: 215.11770.



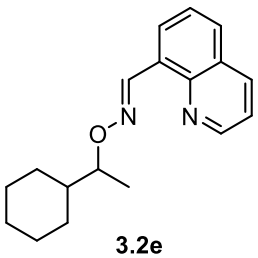
3.2c

(*E*)-quinoline-8-carbaldehyde *O*-ethyl oxime (3.2c): Colorless oil. Yield 70%. R_f = 0.4. IR (KBr) 3037, 2977, 2931, 2879, 1616, 1586, 1574, 1496, 1483 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.89 (dd, J = 4.2, 1.8 Hz, 1H), 8.25 (dt, J = 5.3, 2.6 Hz, 1H), 8.09 (dd, J = 8.3, 1.8 Hz, 1H), 7.79 (dd, J = 8.2, 1.4 Hz, 1H), 7.52 (t, J = 7.7 Hz, 1H), 7.37 (dd, J = 8.3, 4.2 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.97, 146.02, 145.90, 136.17, 130.29, 129.38, 128.26, 126.37, 126.10, 121.39, 77.48, 77.16, 76.84, 69.87, 14.80. HRMS: calcd. $[M+Na]^+$ 223.08418 Found: 223.08390.



3.2d

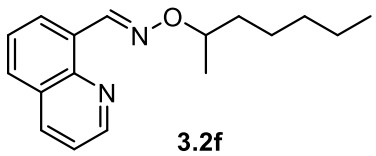
(*S*)-quinoline-8-carbaldehyde *O*-(1-methoxypropan-2-yl) oxime (3.2d): Colorless oil. Yield 84%. R_f = 0.4 (Hex/EA= 5:1). IR (KBr) 2982.67, 2920.84, 2878.69, 1588.45, 1496.02, 1111.01, 970.49, 799.06 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.91 (td, *J* = 4.1, 1.7 Hz, 1H), 8.27 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.14 (dt, *J* = 6.7, 3.4 Hz, 1H), 7.89 – 7.79 (m, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.63 – 4.51 (m, 1H), 3.65 (dd, *J* = 10.4, 5.8 Hz, 1H), 3.55 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.43 (s, 3H), 1.36 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.08, 146.44, 146.02, 136.24, 130.46, 129.44, 128.35, 126.45, 126.24, 121.47, 78.58, 75.34, 59.48, 16.96. HRMS: calcd. $[M+Na]^+$ 267.11040 Found: 267.11050. $[a]_D^{20}$ = 31.2 (c 1.73, $CHCl_3$).



3.2e

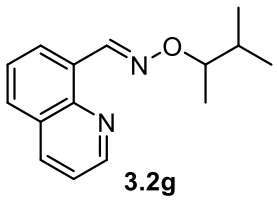
(*E*)-quinoline-8-carbaldehyde *O*-(1-cyclohexylethyl) oxime (3.2e): Colorless oil. Yield 86%. R_f = 0.7 (Hex/EA= 5:1). IR (KBr) 3053.91, 2978.95, 2930.33, 2849.30, 1591.22, 1500.06, 1447.38, 961.17 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.92 (ddd, *J* = 4.1, 1.6, 1.2 Hz, 1H), 8.28 (d, *J* = 7.3 Hz, 1H), 8.22 – 8.08 (m, 1H), 7.82 (d, *J* = 8.1 Hz, 1H),

7.55 (t, *J* = 7.7 Hz, 1H), 7.41 (ddd, *J* = 8.3, 4.2, 0.9 Hz, 1H), 4.19 (p, *J* = 6.1 Hz, 1H), 1.93 (s, 1H), 1.83 – 1.58 (m, 5H), 1.37 – 0.99 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.98, 145.98, 145.21, 136.27, 130.79, 129.16, 128.39, 126.50, 126.04, 121.42, 83.90, 42.65, 29.21, 28.39, 26.83, 26.47, 26.45, 16.95. HRMS: calcd. $[M+Na]^+$ 305.16243 Found: 305.16270.



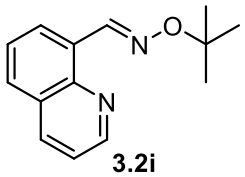
3.2f

(*E*)-quinoline-8-carbaldehyde *O*-heptan-2-yl oxime (3.2f): Colorless oil. Yield 85%. R_f = 0.7 (Hex/EA/DCM = 10:1:3). IR (KBr) 3017.45, 2960.72, 2934.38, 2857.40, 1597.30, 1498.03, 1378.50, 971.30 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 9.37 (s, 1H), 8.97 – 8.85 (m, 1H), 8.26 (d, *J* = 7.3 Hz, 1H), 8.13 (dt, *J* = 8.5, 4.4 Hz, 1H), 7.81 (t, *J* = 7.1 Hz, 1H), 7.54 (dd, *J* = 10.0, 5.4 Hz, 1H), 7.40 (dt, *J* = 12.2, 4.2 Hz, 1H), 4.44 – 4.28 (m, 1H), 1.83 – 1.68 (m, 1H), 1.56 – 1.28 (m, 10H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.02, 146.01, 145.45, 136.28, 130.76, 129.23, 128.39, 126.50, 126.10, 121.45, 79.86, 35.93, 32.12, 25.36, 22.80, 20.11, 14.24. HRMS: calcd. $[M+H]^+$ 271.18049 Found: 271.18050.



3.2g

(*E*)-quinoline-8-carbaldehyde *O*-(3-methylbutan-2-yl) oxime (3.2g): Colorless oil. Yield 69%. R_f = 0.5. IR (KBr) 2961, 2930, 1587, 1496, 1468, 1385, 1368, 1107 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.92 (dd, J = 4.2, 1.8 Hz, 1H), 8.29 (dd, J = 7.3, 1.4 Hz, 1H), 8.14 (dd, J = 8.3, 1.8 Hz, 1H), 7.82 (dd, J = 8.2, 1.4 Hz, 1H), 7.55 (t, J = 7.7 Hz, 1H), 7.41 (dd, J = 8.3, 4.2 Hz, 1H), 4.24 – 4.17 (m, 1H), 2.02 (dtd, J = 13.7, 6.8, 5.8 Hz, 1H), 1.28 (d, J = 6.4 Hz, 3H), 0.99 (dd, J = 13.8, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.86, 145.82, 145.17, 136.16, 130.59, 129.12, 128.26, 126.36, 125.89, 121.32, 84.19, 32.32, 18.74, 17.62, 16.13. HRMS: calcd. $[M+H]^+$ 243.14919 Found: 243.14880.

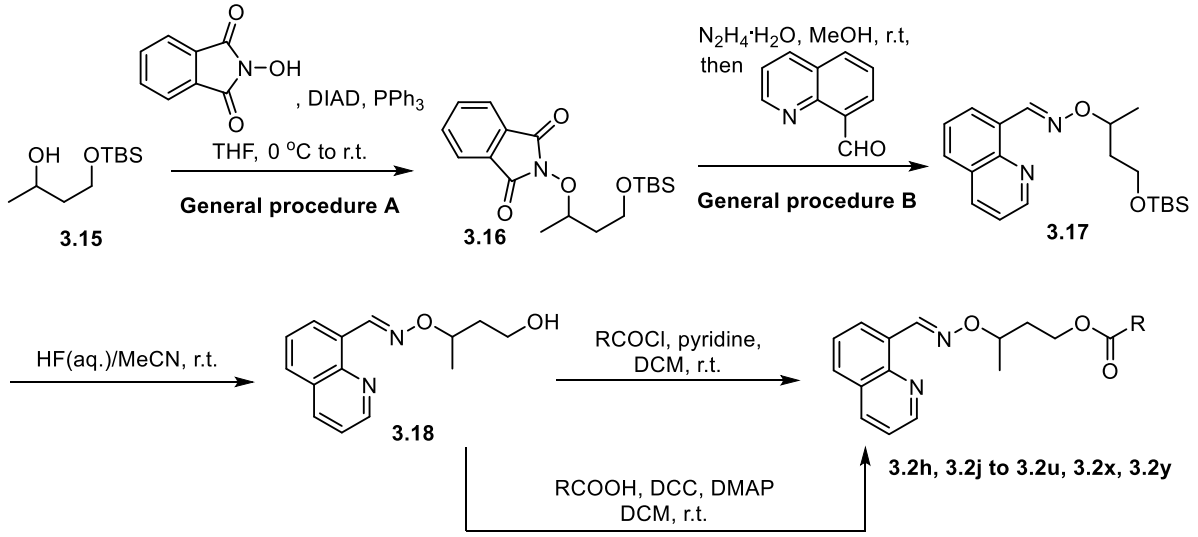


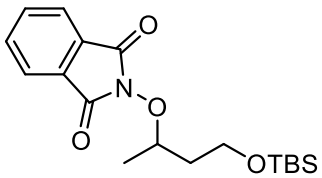
3.2i

(*E*)-quinoline-8-carbaldehyde *O*-(tert-butyl) oxime (3.2i): Colorless oil.Yield 70%. R_f=0.4. IR (KBr) 32976, 2928, 1587, 1497, 1467, 1387, 1362, 1192 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.89 (dd, J = 4.2, 1.8 Hz, 1H), 8.30 (dd, J = 7.3, 1.4 Hz, 1H), 8.09 (dd, J = 8.3, 1.8 Hz, 1H), 7.78 (dd, J = 8.2, 1.4 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.36 (dd, J = 8.3, 4.2 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.87, 145.90, 144.80, 136.14, 131.02, 128.98, 128.27, 126.38, 125.89, 121.30, 79.08, 27.82. HRMS: calcd. $[M+H]^+$ 229.13354 Found: 229.13330.

3.2h, 3.2j to 3.2u, 3.2x, and **3.2y** were prepared according to the following procedures.

Scheme 3.15 General Procedures for the Synthesis of **3.2h, 3.2j** to **3.2u, 3.2x,** and **3.2y**

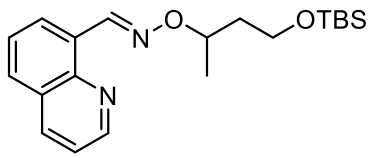




3.16

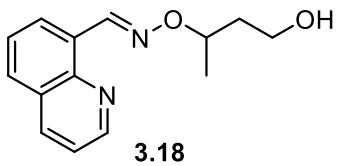
2-((4-((*tert*-Butyldimethylsilyl)oxy)butan-2-yl)oxy)isoindoline-1,3-dione (3.16): was prepared according to **General procedure A** using 4-((*tert*-butyldimethylsilyl)oxy)butan-2-ol (**3.15**) as starting material (**3.15** was prepared according to known literature[47]). Colorless oil. Yield 70%. R_f = 0.7 (Hex/EA= 2:1). IR (KBr) 3466, 2960, 2856, 1743, 1471, 1375, 1254, 1193, 1094 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.1 Hz, 2H), 4.53 (dd, *J* = 12.6, 6.3 Hz, 1H), 3.92 – 3.73 (m, 2H), 2.08 (dd, *J* = 14.1, 6.4 Hz, 1H), 1.80 (dd, *J* = 14.0, 6.4 Hz, 1H), 1.38 (d, *J* = 6.3 Hz,

3H), 0.88 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) 164.48, 134.53, 129.15, 123.59, 82.34, 59.68, 38.30, 26.05, 19.29, 18.40, -5.22, -5.27. HRMS: calcd. $[M+Na]^+$ 372.16015 Found: 372.16050.



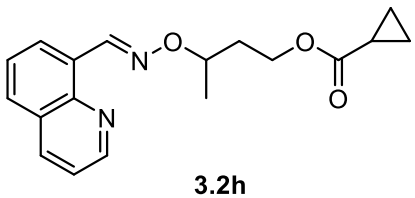
3.17

(*E*)-quinoline-8-carbaldehyde *O*-(4-((tert-butyldimethylsilyl)oxy)butan-2-yl) oxime (3.17): was prepared according to **General procedure B.** Colorless oil. Yield 72%. R_f = 0.8 (Hex/EA= 5:1). IR (KBr) 2960.19, 2932.08, 2856.21, 1584.99, 1501.83, 1474.11, 1091.33, 959.25, 832.79 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.93 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.28 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.84 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.60 – 4.46 (m, 1H), 3.80 (ddd, *J* = 6.9, 6.1, 2.4 Hz, 2H), 2.07 – 1.95 (m, 1H), 1.85 – 1.73 (m, 1H), 1.37 (d, *J* = 6.3 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.03, 145.99, 145.53, 136.31, 130.68, 129.27, 128.39, 126.51, 126.13, 121.46, 76.84, 60.09, 39.08, 26.13, 20.49, 18.50, -5.11, -5.14. HRMS: calcd. $[M+Na]^+$ 381.19687 Found: 381.19710.



3.18

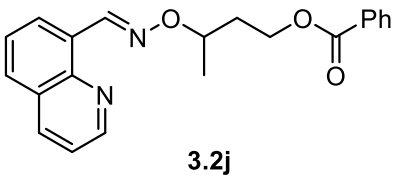
(*E*)-quinoline-8-carbaldehyde *O*-(4-hydroxybutan-2-yl) oxime (3.18): 1.5 mL 50% HF aqueous solution was added into a MeCN (7 mL) solution of quinoline-8-carbaldehyde *O*-(4-((tert-butyldimethylsilyl)oxy)butan-2-yl) oxime **(3.17)** (1 equiv., 1.5 mmol, 540 mg) at room temperature. The mixture was stirred for 20 min, and then diluted with 1M NaOH (40 mL), extracted with EtOAc and washed with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane:EA = 10:1) to give the title compounds as colorless oil (340 mg, 98%). R_f = 0.65 (Hex/EA= 5:1). IR (KBr) 3374.00, 2976.93, 2926.28, 1585.14, 1493.98, 1370.40, 1052.34, 955.09 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ9.36 (s, 1H), 8.92 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.21 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.84 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.68 – 4.52 (m, 1H), 3.93 – 3.75 (m, 2H), 2.55 (s, 1H), 1.97 – 1.89 (m, 2H), 1.39 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.16, 146.28, 145.94, 136.36, 130.17, 129.63, 128.42, 126.49, 126.47, 121.55, 78.05, 60.15, 39.10, 20.50. HRMS: calcd. $[M+Na]^+$ 267.11040 Found: 267.11050.



3.2h

(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)butyl cyclopropanecarboxylate (2h): The cyclopropanecarbonyl chloride (**3.19**) (1.33 equiv., 98 mg) was slowly added into a DCM solution (7 mL) of quinoline-8-carbaldehyde *O*-(4-hydroxybutan-2-yl) oxime **(3.18)** (1

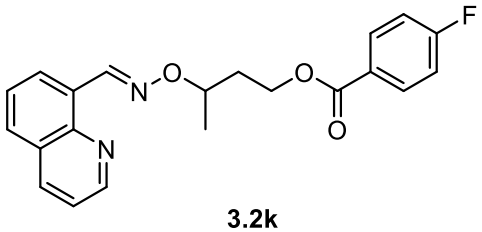
equiv., 0.7 mmol, 170 mg) and pyridine (2 equiv., 111 mg) at room temperature. The mixture was stirred for 1 h, and then diluted with 1M NaOH (10 mL), extracted with DCM and washed with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane:EA:DCM = 15:1:1) to give the title compounds as colorless oil (184 mg, 84%). R_f = 0.3 (Hex/EA/DCM = 10:1:3). IR (KBr) 3027.63, 2970.93, 1729.27, 1498.83, 1380.80, 1181.26 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.92 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.27 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.84 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.57 – 4.48 (m, 1H), 4.26 (ddd, *J* = 7.1, 6.4, 2.2 Hz, 2H), 2.10 (ddt, *J* = 14.0, 7.7, 6.3 Hz, 1H), 1.99 – 1.90 (m, 1H), 1.61 (ddd, *J* = 9.3, 6.3, 4.0 Hz, 1H), 1.39 (d, *J* = 6.4 Hz, 3H), 1.05 – 0.96 (m, 2H), 0.88 – 0.79 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.05, 150.08, 145.99, 136.31, 130.47, 129.43, 128.38, 126.49, 126.18, 121.50, 76.64, 61.67, 35.00, 20.28, 13.08, 8.52. HRMS: calcd. $[M+H]^+$ 335.13661 Found: 335.13680.



3.2j

(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)butyl benzoate (3.2j): The benzyl chloride (**20**) (1.33 equiv., 56 mg) was slowly added into a DCM solution (3 mL) of quinoline-8-carbaldehyde *O*-(4-hydroxybutan-2-yl) oxime **(3.18)** (1 equiv., 0.3 mmol, 72 mg) and pyridine (2 equiv., 47 mg) at room temperature. The mixture was stirred for 1 h, and then

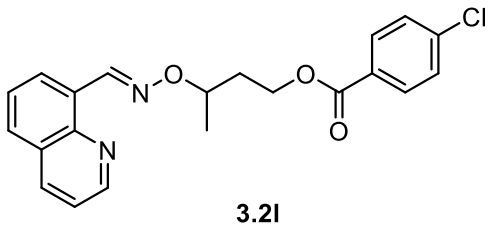
diluted with 1M NaOH (10 mL), extracted with DCM and washed with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane:EA:DCM = 15:1:1) to give the title compounds as colorless oil (70 mg, 67%). R_f = 0.35 (Hex/EA/DCM = 8:1:1). IR (KBr) 3074.88, 2977.05, 2923.65, 1718.03, 1501.64, 1282.44, 1116.63, 956.44 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.93 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.26 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.11 – 8.02 (m, 2H), 7.85 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.54 (dt, *J* = 5.1, 4.5 Hz, 2H), 7.43 (ddd, *J* = 8.4, 5.8, 2.8 Hz, 3H), 4.63 (ddd, *J* = 7.6, 6.3, 5.0 Hz, 1H), 4.58 – 4.45 (m, 2H), 2.23 (ddd, *J* = 12.3, 7.7, 6.1 Hz, 1H), 2.15 – 2.04 (m, 1H), 1.44 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.75, 150.08, 146.07, 136.33, 132.95, 130.58, 129.74, 129.44, 128.45, 128.40, 126.51, 126.23, 121.50, 110.15, 76.74, 62.19, 35.09, 20.35. HRMS: calcd. $[M+Na]^+$ 371.13661 Found: 371.13680.



3.2k

(*E*)-3-(((Quinolin-8-ylmethylene)amino)oxy)butyl 4-fluorobenzoate (3.2k): The 4-fluorobenzyl chloride (**3.21**) (1.33 equiv., 211 mg) was slowly added into a DCM solution (10 mL) of quinoline-8-carbaldehyde *O*-(4-hydroxybutan-2-yl) oxime **(3.18)** (1 equiv., 1 mmol, 244 mg) and pyridine (2 equiv., 158 mg) at room temperature. The mixture was stirred for 1 h, and then diluted with 1M NaOH (10 mL), extracted with DCM and washed with

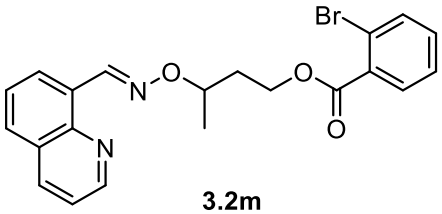
water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane:EA:DCM = 15:1:1) to give the title compounds as yellowish oil (311 mg, 85%). R_f = 0.4 (Hex/EA/DCM = 8:1:1). IR (KBr) 3066.98, 2974.24, 2929.27, 1712.41, 1616.86, 1507.26, 1282.44, 1117.23, 957.84 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.92 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.25 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.10 – 8.02 (m, 2H), 7.83 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.13 – 7.03 (m, 2H), 4.66 – 4.57 (m, 1H), 4.56 – 4.44 (m, 2H), 2.21 (dt, *J* = 12.3, 7.1 Hz, 1H), 2.12 – 2.02 (m, 1H), 1.43 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ carbon signal was found at 167.05, 165.75, 164.53, 150.07, 146.05, 145.95, 136.29, 132.28, 132.19, 130.37, 129.46, 128.36, 126.78, 126.75, 126.45, 126.13, 121.50, 115.66, 115.44, 76.69, 62.30, 34.99, 20.33. ^{19}F NMR (376 MHz, $CDCl_3$) δ -106.03 (tt, *J* = 8.4, 5.5 Hz, 1F). HRMS: calcd. $[M+Na]^+$ 389.12719 Found: 389.12720.



3.2l

(*E*)-3-(((Quinolin-8-ylmethylene)amino)oxy)butyl 4-chlorobenzoate (3.2l): The 4-chlorobenzyl chloride (**3.22**) (1.33 equiv., 230 mg) was slowly added into a DCM solution (10 mL) of quinoline-8-carbaldehyde *O*-(4-hydroxybutan-2-yl) oxime **(3.18)** (1 equiv., 1 mmol, 244 mg) and pyridine (2 equiv., 158 mg) at room temperature. The mixture was stirred

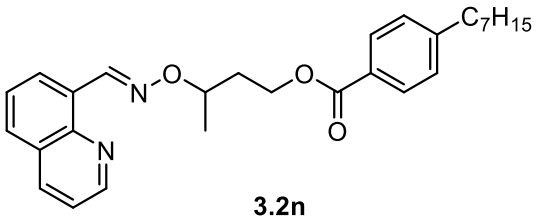
for 1 h, and then diluted with 1M NaOH (10 mL), extracted with DCM and washed with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane:EA:DCM = 15:1:1) to give the title compounds as a white solid (332 mg, 87%). m.p.= 67-69 °C. R_f = 0.3 (Hex/EA/DCM = 8:1:1). IR (KBr) 2968.62, 2929.27, 1723.65, 1594.38, 1276.81, 1108.20 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.93 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.25 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.02 – 7.96 (m, 2H), 7.85 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.41 – 7.36 (m, 2H), 4.61 (ddd, *J* = 7.7, 6.3, 4.8 Hz, 1H), 4.51 (td, *J* = 6.5, 1.6 Hz, 2H), 2.22 (ddd, *J* = 14.3, 6.1, 1.6 Hz, 1H), 2.10 (ddd, *J* = 14.4, 7.2, 4.8 Hz, 1H), 1.43 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.88, 150.10, 146.09, 145.98, 139.36, 136.32, 131.13, 130.39, 129.49, 128.99, 128.79, 128.39, 126.48, 126.16, 121.53, 76.71, 62.45, 34.99, 20.34. HRMS: calcd. $[M+Na]^+$ 405.82938 Found: 405.09760.



3.2m

(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)butyl 2-bromobenzoate (3.2m): The 2-bromobenzyl chloride (**3.23**) (1.33 equiv., 292 mg) was slowly added into a DCM solution (10 mL) of quinoline-8-carbaldehyde *O*-(4-hydroxybutan-2-yl) oxime **(3.18)** (1 equiv., 1 mmol, 244 mg) and pyridine (2 equiv., 158 mg) at room temperature. The mixture was stirred

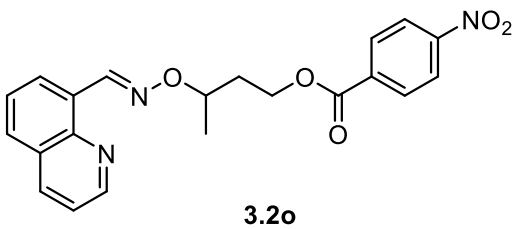
for 1 h, and then diluted with 1M NaOH (10 mL), extracted with DCM and washed with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane:EA:DCM = 15:1:1) to give the title compounds as yellowish oil (346 mg, 81%). R_f = 0.3 (Hex/EA/DCM = 8:1:1). IR (KBr) 3071.41, 2979.86, 2929.27, 1732.08, 1591.57, 1293.68, 1254.33, 1136.30, 962.06 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.92 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.27 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.91 – 7.77 (m, 2H), 7.67 – 7.61 (m, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.32 (dqd, *J* = 15.0, 7.4, 1.7 Hz, 2H), 4.68 – 4.59 (m, 1H), 4.54 (dd, *J* = 7.1, 6.2 Hz, 2H), 2.31 – 2.20 (m, 1H), 2.10 (ddd, *J* = 14.4, 7.2, 4.8 Hz, 1H), 1.43 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.36, 150.08, 146.07, 145.98, 136.31, 134.40, 132.55, 131.47, 130.40, 129.46, 128.37, 127.26, 126.49, 126.19, 121.75, 121.50, 76.59, 62.89, 34.93, 20.34. HRMS: calcd. $[M+Na]^+$ 449.04710 Found: 449.04720.



3.2n

(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)butyl 4-heptylbenzoate (3.2n): The 4-heptylbenzoyl chloride (**3.24**) (1.33 equiv., 292 mg) was slowly added into a DCM solution (10 mL) of quinoline-8-carbaldehyde *O*-(4-hydroxybutan-2-yl) oxime **(3.18)** (1 equiv., 1 mmol, 244 mg) and pyridine (2 equiv., 158 mg) at room temperature. The mixture was stirred

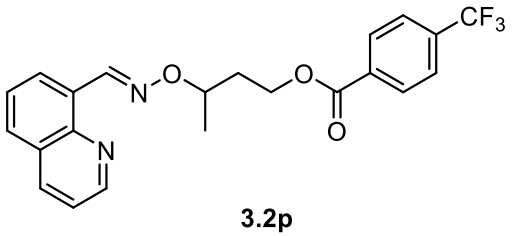
for 1 h, and then diluted with 1M NaOH (10 mL), extracted with DCM and washed with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane:EA:DCM = 15:1:1) to give the title compounds as colorless oil (380 mg, 85%). R_f = 0.35 (Hex/EA/DCM = 8:1:1). IR (KBr) 3033.26, 2957.38, 2923.65, 2850.59, 1718.03, 1614.05, 1279.63, 1113.82 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.93 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.26 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.98 – 7.92 (m, 2H), 7.84 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 4.67 – 4.59 (m, 1H), 4.55 – 4.46 (m, 2H), 2.71 – 2.57 (m, 2H), 2.23 (ddt, *J* = 13.8, 7.6, 6.2 Hz, 1H), 2.12 – 2.04 (m, 1H), 1.65-1.55 (m, 2H), 1.43 (d, *J* = 6.4 Hz, 3H), 1.37 – 1.19 (m, 8H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.85, 150.08, 148.56, 146.03, 146.01, 136.31, 130.47, 129.78, 129.43, 128.52, 128.39, 127.99, 126.50, 126.22, 121.50, 76.76, 61.98, 36.15, 35.10, 31.92, 31.31, 29.35, 29.28, 22.79, 20.34, 14.24. HRMS: calcd. $[M+H]^+$ 469.24616 Found: 469.24600.



3.2o

(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)butyl 4-nitrobenzoate (3.2o): The 4-nitrobenzoyl chloride (**3.25**) (1.33 equiv., 248 mg) was slowly added into a DCM solution (10 mL) of quinoline-8-carbaldehyde *O*-(4-hydroxybutan-2-yl) oxime **(3.18)** (1 equiv., 1

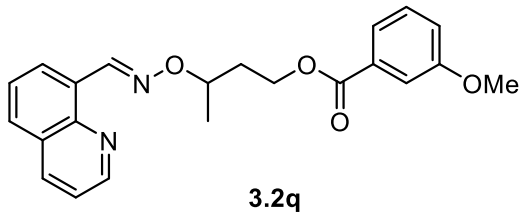
mmol, 244 mg) and pyridine (2 equiv., 158 mg) at room temperature. The mixture was stirred for 1 h, and then diluted with 1M NaOH (10 mL), extracted with DCM and washed with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane:EA:DCM = 15:1:1) to give the title compounds as a white solid (281 mg, 72%). m.p.= 92-94 °C. R_f = 0.3 (Hex/EA/DCM = 8:1:1). IR (KBr) 2982.67, 2932.08, 1729.27, 1605.77, 1535.36, 1355.50, 1282.44, 1108.20 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.91 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.30 – 8.05 (m, 6H), 7.85 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.67 – 4.54 (m, 3H), 2.30 – 2.19 (m, 1H), 2.18 – 2.09 (m, 1H), 1.44 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.81, 150.49, 150.12, 146.11, 145.91, 136.34, 135.92, 130.83, 130.27, 129.56, 128.38, 126.45, 126.08, 123.60, 121.57, 76.77, 63.19, 34.83, 20.34. HRMS: calcd. $[M+Na]^+$ 416.12169 Found: 416.12190.



3.2p

(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)butyl 4-(trifluoromethyl)benzoate (3.2p): The 4-trifluoromethylbenzoyl chloride (**3.26**) (1.33 equiv., 278 mg) was slowly added into a DCM solution (10 mL) of quinoline-8-carbaldehyde *O*-(4-hydroxybutan-2-yl) oxime **(3.18)** (1 equiv., 1 mmol, 244 mg) and pyridine (2 equiv., 158 mg) at room temperature. The

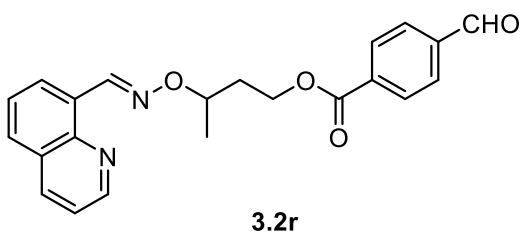
mixture was stirred for 1 h, and then diluted with 1M NaOH (10 mL), extracted with DCM and washed with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane:EA:DCM = 15:1:1) to give the title compounds as colorless oil (373 mg, 90%). R_f = 0.4 (Hex/EA/DCM = 8:1:1). IR (KBr) 3061.02, 2977.05, 2934.89, 1729.27, 1588.45, 1417.33, 1330.21, 1279.63, 1133.49 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.91 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.25 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.18-8.13 (m, 3H), 7.84 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.72 – 7.63 (m, 2H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.67 – 4.53 (m, 3H), 2.24 (ddt, *J* = 13.9, 7.8, 6.1 Hz, 1H), 2.17 – 2.08 (m, 1H), 1.44 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.33, 149.93, 145.94, 145.78, 136.15, 134.22 (d, *J* = 32.6 Hz), 133.57 (q, *J* = 1.0 Hz), 130.17, 129.95, 129.34, 128.22, 126.29, 125.96, 125.30 (q, *J* = 3.8 Hz), 123.61 (q, *J* = 272.6 Hz), 121.36, 76.54, 62.61, 34.76, 20.17. ^{19}F NMR (376 MHz, $cdcl_3$) δ -63.10 (s, 3F). HRMS: calcd. $[M+Na]^+$ 439.12400 Found: 439.12420.



3.2q

(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)butyl 3-methoxybenzoate (3.2q): The 3-methyloxybenzoyl chloride (**3.27**) (1.33 equiv., 227 mg) was slowly added into a DCM solution (10 mL) of quinoline-8-carbaldehyde *O*-(4-hydroxybutan-2-yl) oxime **(3.18)** (1

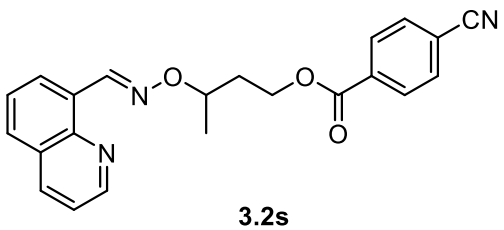
equiv., 1 mmol, 244 mg) and pyridine (2 equiv., 158 mg) at room temperature. The mixture was stirred for 1 h, and then diluted with 1M NaOH (10 mL), extracted with DCM and washed with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane:EA:DCM = 15:1:1) to give the title compounds as yellowish oil (303 mg, 80%). R_f = 0.3 (Hex/EA/DCM = 8:1:1). IR (KBr) 3038.88, 2977.05, 2932.08, 1718.03, 1585.95, 1493.21, 1285.25, 1229.04, 1046.37 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.92 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.26 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.84 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.60 – 7.51 (m, 2H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.08 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 4.62 (ddd, *J* = 7.6, 6.3, 5.0 Hz, 1H), 4.57 – 4.47 (m, 2H), 3.83 (s, 3H), 2.28 – 2.19 (m, 1H), 2.10 (ddd, *J* = 14.4, 7.2, 4.9 Hz, 1H), 1.44 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.60, 159.61, 150.06, 146.03, 145.97, 136.29, 131.84, 130.41, 129.46, 129.43, 128.36, 126.47, 126.17, 122.13, 121.48, 119.46, 114.12, 76.71, 62.28, 55.54, 35.04, 20.34. HRMS: calcd. $[M+Na]^+$ 401.14718 Found: 401.14720.



3.2r

(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)butyl 4-formylbenzoate (3.2r): Dicyclohexylcarbodiimide (DCC) (1.16 equiv., 168 mg) and 4-dimethylaminopyridine

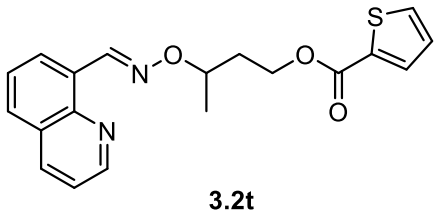
(DMAP) (0.416 equiv., 37 mg) was added into a DCM solution (14 mL) of quinoline-8-carbaldehyde *O*-(4-hydroxybutan-2-yl) oxime **(3.18)** (1 equiv., 0.7 mmol, 170 mg) and 4-formylbenzoic acid (**3.28**) (1.16 equiv., 123 mg) at room temperature. The mixture was stirred at room temperature overnight and then filtered to remove precipitate before concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane:EA:DCM = 10:1:3) to give the title compounds as colorless oil (184 mg, 70%). R_f = 0.25 (Hex/EA/DCM = 8:1:1). IR (KBr) 3061.02, 2968.62, 2929.27, 1726.46, 1712.41, 1494.90, 1279.63, 1206.56, 1108.20 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 9.38 (s, 1H), 8.92 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.25 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.23 – 8.17 (m, 2H), 8.15 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.94 – 7.88 (m, 2H), 7.84 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.68 – 4.53 (m, 3H), 2.24 (ddt, *J* = 14.0, 7.8, 6.1 Hz, 1H), 2.18 – 2.08 (m, 1H), 1.44 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.81, 165.68, 150.10, 146.11, 145.95, 139.14, 136.33, 135.52, 130.34, 130.33, 129.61, 129.51, 128.38, 126.47, 126.14, 121.53, 76.68, 62.83, 34.93, 20.35. HRMS: calcd. $[M+H]^+$ 377.14959 Found: 377.14980.



3.2s

(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)butyl 4-cyanobenzoate (3.2s): The 4-cyanobenzyl chloride (**3.29**) (1.33 equiv., 154 mg) was slowly added into a DCM solution (7

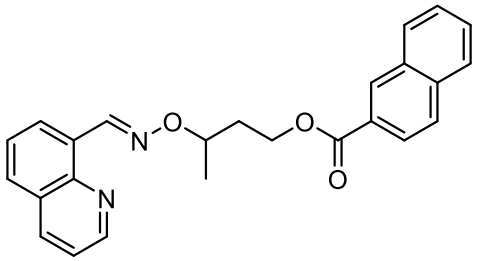
mL) of quinoline-8-carbaldehyde *O*-(4-hydroxybutan-2-yl) oxime **(3.18)** (1 equiv., 0.7 mmol, 170 mg) and pyridine (2 equiv., 111 mg) at room temperature. The mixture was stirred for 1 h, and then diluted with 1M NaOH (10 mL), extracted with DCM and washed with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane:EA:DCM = 15:1:1) to give the title compounds as colorless oil (240 mg, 92%). R_f = 0.3 (Hex/EA/DCM = 8:1:3). IR (KBr) 3061.36, 2982.67, 2929.27, 2235.13, 1720.84, 1498.36, 1285.25, 1105.39 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ9.36 (s, 1H), 8.92 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.24 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.15 (ddd, *J* = 8.6, 7.5, 1.8 Hz, 3H), 7.88 – 7.82 (m, 1H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.66 – 4.50 (m, 3H), 2.22 (ddd, *J* = 12.2, 7.9, 6.2 Hz, 1H), 2.12 (ddd, *J* = 14.5, 7.3, 4.6 Hz, 1H), 1.44 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.06, 150.11, 146.12, 145.94, 136.35, 134.35, 132.28, 130.29, 130.23, 129.55, 128.39, 126.46, 126.10, 121.58, 118.17, 116.31, 76.69, 63.04, 34.86, 20.34. HRMS: calcd. $[M+H]^+$ 374.14992 Found: 374.15000.



3.2t

(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)butyl thiophene-2-carboxylate (3.2t): The thiophene-2-carbonyl chloride (**30**) (1.33 equiv., 137 mg) was slowly added into a DCM solution (7 mL) of quinoline-8-carbaldehyde *O*-(4-hydroxybutan-2-yl) oxime **(3.18)** (1

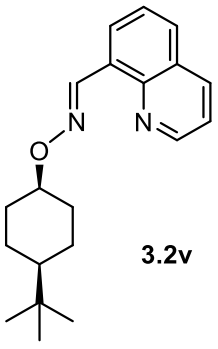
equiv., 0.7 mmol, 170 mg) and pyridine (2 equiv., 111 mg) at room temperature. The mixture was stirred for 1 h, and then diluted with 1M NaOH (10 mL), extracted with DCM and washed with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane:EA:DCM = 15:1:1) to give the title compounds as colorless oil (210 mg, 85%). R_f = 0.3 (Hex/EA/DCM = 10:1:3). IR (KBr) 3078.22, 2974.24, 2929.27, 1712.41, 1420.14, 1259.95, 1099.77 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.92 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.26 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.82 (ddd, *J* = 5.9, 5.0, 1.3 Hz, 2H), 7.60 – 7.51 (m, 2H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.08 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.64 – 4.55 (m, 1H), 4.49 (ddd, *J* = 7.3, 6.3, 3.0 Hz, 2H), 2.21 (ddt, *J* = 13.8, 7.6, 6.2 Hz, 1H), 2.08 (ddd, *J* = 14.3, 7.2, 4.9 Hz, 1H), 1.43 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.39, 150.07, 146.06, 145.98, 136.30, 134.13, 133.47, 132.37, 130.42, 129.44, 128.37, 127.81, 126.49, 126.20, 121.49, 76.65, 62.37, 35.03, 20.33. HRMS: calcd. $[M+H]^+$ 355.11109 Found: 355.11180.



3.2u

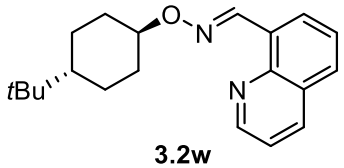
(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)butyl 2-naphthoate (3.2u): The 2-naphthoyl chloride (**3.31**) (1.33 equiv., 177 mg) was slowly added into a DCM solution (7

mL) of quinoline-8-carbaldehyde *O*-(4-hydroxybutan-2-yl) oxime **(3.18)** (1 equiv., 0.7 mmol, 170 mg) and pyridine (2 equiv., 111 mg) at room temperature. The mixture was stirred for 1 h, and then diluted with 1M NaOH (10 mL), extracted with DCM and washed with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane:EA:DCM = 15:1:1) to give the title compounds as colorless oil (237 mg, 85%). R_f = 0.4 (Hex/EA/DCM = 8:1:1). IR (KBr) 3064.17, 2971.43, 2926.46, 1723.65, 1496.02, 1290.87, 1195.32 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.91 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.62 (s, 1H), 8.27 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.08 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.96 – 7.92 (m, 1H), 7.89 – 7.82 (m, 3H), 7.60 – 7.50 (m, 3H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.67 (ddd, *J* = 7.6, 6.3, 4.9 Hz, 1H), 4.64 – 4.55 (m, 2H), 2.28 (ddd, *J* = 12.4, 7.8, 6.2 Hz, 1H), 2.21 – 2.11 (m, 1H), 1.47 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.91, 150.06, 146.07, 145.98, 136.29, 135.61, 132.61, 131.16, 130.43, 129.51, 129.44, 128.37, 128.27, 128.22, 127.86, 127.79, 126.68, 126.48, 126.19, 125.43, 121.48, 76.81, 62.35, 35.11, 20.38. HRMS: calcd. $[M+Na]^+$ 421.15226 Found: 421.15230.



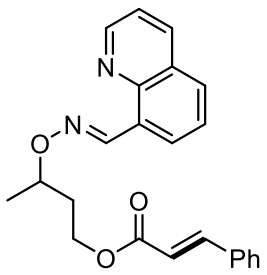
3.2v

(*E*)-quinoline-8-carbaldehyde *O*-((1*s*,4*s*)-4-(*tert*-butyl)cyclohexyl) oxime (3.2v): White solid, m.p.= 87-89 °C. Yield 84 %. R_f = 0.6 (Hex/EA/DCM = 10:1:3). IR (KBr) 3017.45, 2946.54, 2867.53, 1587.17, 1498.03, 1366.35, 971.30 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.97 – 8.90 (m, 1H), 8.31 (d, *J* = 7.3 Hz, 1H), 8.19 – 8.12 (m, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.49 (s, 1H), 2.22 (d, *J* = 12.5 Hz, 2H), 1.60 – 1.46 (m, 4H), 1.46 – 1.33 (m, 2H), 1.05 (t, *J* = 11.6 Hz, 1H), 0.87 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.99, 145.96, 145.36, 136.38, 130.72, 129.23, 128.43, 126.54, 126.06, 121.45, 77.40, 48.09, 32.77, 30.73, 27.73, 21.71. HRMS: calcd. $[M+H]^+$ 311.21179 Found: 311.21100.



3.2w

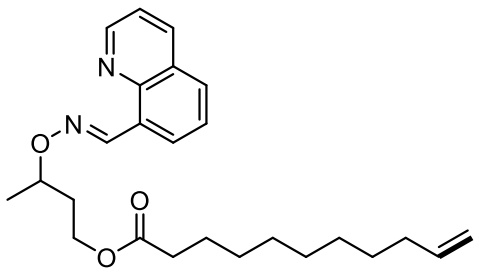
(*E*)-quinoline-8-carbaldehyde *O*-((1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl) oxime (3.2w): White solid, m.p.= 127-129 °C. Yield 86%. R_f = 0.6 (Hex/EA/DCM = 10:1:3). IR (KBr) 3047.31, 2946.14, 2861.83, 1583.14, 1498.83, 1363.93, 953.63 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.92 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.26 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.84 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.15 (tt, *J* = 11.3, 4.3 Hz, 1H), 2.32 – 2.23 (m, 2H), 1.86 (dd, *J* = 13.4, 2.9 Hz, 2H), 1.43 – 1.32 (m, 2H), 1.19 – 1.02 (m, 3H), 0.88 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.05, 146.04, 145.81, 136.28, 130.71, 129.29, 128.38, 126.51, 126.18, 121.47, 82.44, 47.56, 32.50, 27.84, 25.71. HRMS: calcd. $[M+H]^+$ 311.21179 Found: 311.21190.



3.2x

3-(((*E*)-(quinolin-8-ylmethylene)amino)oxy)butyl cinnamate (3.2x): The cinnamoyl chloride (1.33 equiv., 55.5 mg) was slowly added into a DCM solution (2.5 mL) of quinoline-8-carbaldehyde *O*-(4-hydroxybutan-2-yl) oxime **(3.18)** (1 equiv., 0.25 mmol, 61 mg) and pyridine (2 equiv., 40 mg) at room temperature. The mixture was stirred for 10 h, and then diluted with 1M NaOH (3 mL), extracted with DCM and washed with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane:EA:DCM = 15:1:1) to give the title compounds as colorless oil (84 mg, 90%). R_f = 0.3 (Hex/EA/DCM = 10:1:3). IR (KBr) 3068, 2970, 2930, 1712, 1637, 1498, 1315, 1177 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.91 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.28 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.84 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.69 (d, *J* = 16.0 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.40 – 7.34 (m, 3H), 6.45 (d, *J* = 16.0 Hz, 1H), 4.64 – 4.53 (m, 1H), 4.48 – 4.35 (m, 2H), 2.18 (ddt, *J* = 13.9, 7.7, 6.2 Hz, 1H), 2.03 (dtd, *J* = 11.9, 7.1, 4.9 Hz, 1H), 1.42 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.15, 150.08, 146.03, 145.99, 144.80, 136.30, 134.58,

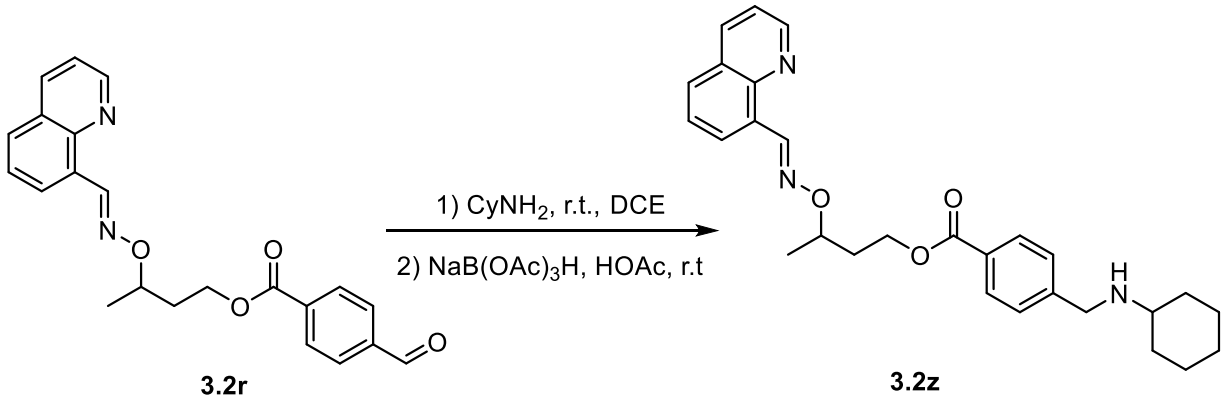
130.44, 130.33, 129.44, 128.97, 128.38, 128.20, 126.49, 126.20, 121.49, 118.36, 76.70, 61.78, 35.03, 20.31. HRMS: calcd. $[M+Na]^+$ 397.15230 Found: 397.15220.



3.2y

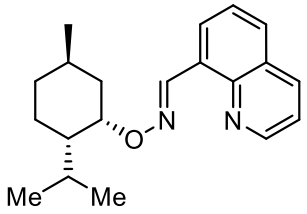
(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)butyl undec-10-enoate (3.2y): The undec-10-enoyl chloride (1.33 equiv., 108 mg) was slowly added into a DCM solution (4 mL) of quinoline-8-carbaldehyde *O*-(4-hydroxybutan-2-yl) oxime **(3.18)** (1 equiv., 0.4 mmol, 100 mg) and pyridine (2 equiv., 64 mg) at room temperature. The mixture was stirred for 11 h, and then diluted with 1M NaOH (5 mL), extracted with DCM and washed with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane:EA:DCM = 15:1:1) to give the title compounds as colorless oil (132 mg, 80%). R_f = 0.3 (Hex/EA/DCM = 10:1:3). IR (KBr) 3078, 2930, 2853, 1739, 1589, 1496, 1461, 1173 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.92 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.26 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.85 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.03 – 4.88 (m, 2H), 4.57 – 4.46 (m, 1H), 4.25 (dd, *J* = 10.0, 3.9 Hz, 2H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.13 – 1.90 (m, 4H), 1.64 – 1.60 (m, 2H), 1.41 – 1.25 (m, 13H). ^{13}C NMR (101 MHz, $CDCl_3$) δ

174.07, 150.09, 145.99, 139.33, 136.32, 130.46, 129.44, 128.39, 126.49, 126.18, 121.50, 114.26, 76.63, 61.45, 34.98, 34.53, 33.93, 29.43, 29.36, 29.28, 29.20, 29.02, 25.13, 20.28. HRMS: calcd. $[M+Na]^+$ 433.24620 Found: 433.24610.



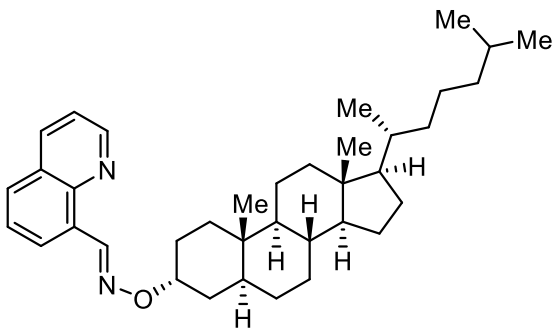
(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)butyl 4-((cyclohexylamino)methyl)benzoate (3.2z): The titled compound was prepared by reductive amination. The aldehyde **3.2r** (1 equiv., 0.265 mmol, 100 mg) was added into a DCE solution (2 mL) of cyclohexylamine (2.2 equiv., 60 mg) at room temperature. The mixture was stirred for 3 h, followed by the addition of $NaB(OAc)_3H$ (170 mg) and HOAc (36 μL). The mixture was stirred for additional 3 h at the same temperature. After concentrated under reduced pressure, the residue was purified by flash column chromatography on silica gel (Hexane:EA:NEt_3 = 5:1:0.12) to give the title compounds as colorless oil (110 mg, 90%). R_f = 0.1 (Hexane:EA:NEt_3 = 3:1:0.1). IR (KBr) 2926, 2851, 1717, 1275, 1106, 956, 792, 755 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.93 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.26 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.05 – 7.97 (m, 2H), 7.84 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J*

= 8.3, 4.2 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 2H), 4.67 – 4.56 (m, 1H), 4.56 – 4.44 (m, 2H), 3.86 (s, 2H), 2.45 (tt, *J* = 10.2, 3.7 Hz, 1H), 2.29 – 2.18 (m, 1H), 2.08 (dtd, *J* = 12.0, 7.0, 5.0 Hz, 1H), 1.96 – 1.84 (m, 2H), 1.79 – 1.68 (m, 2H), 1.63 – 1.58 (m, 1H), 1.44 (t, *J* = 6.3 Hz, 3H), 1.24 – 1.06 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.71, 150.08, 146.47, 146.05, 146.01, 136.31, 130.46, 129.88, 129.43, 129.08, 128.39, 128.02, 126.50, 126.21, 121.49, 76.74, 62.09, 56.28, 50.80, 35.08, 33.70, 26.29, 25.13, 20.34. HRMS: calcd. $[M+Na]^+$ 482.24140 Found: 482.24160.



3.2ac

(*E*)-quinoline-8-carbaldehyde *O*-((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) oxime (3.2ac): White solid. m.p.= 81-82 °C. Yield 90%. R_f = 0.5 (Hexane:Ethyl acetate = 25:1). IR (KBr) 2945, 2922, 2867, 2842, 1586, 1495, 1455, 1383, 1366 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.94 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.32 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.83 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.65 (d, *J* = 2.6 Hz, 1H), 2.26 (ddd, *J* = 13.8, 6.0, 3.5 Hz, 1H), 1.82 – 1.69 (m, 4H), 1.49 – 1.37 (m, 1H), 1.08 – 1.00 (m, 2H), 0.99 (t, *J* = 4.5 Hz, 3H), 0.96 – 0.90 (m, 4H), 0.86 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.79, 145.74, 144.75, 136.23, 130.62, 128.95, 128.29, 126.40, 125.81, 121.26, 79.40, 47.33, 39.61, 35.16, 29.16, 26.01, 25.21, 22.46, 21.24, 20.93. HRMS: calcd. $[M+Na]^+$ 333.19370 Found: 333.19420.

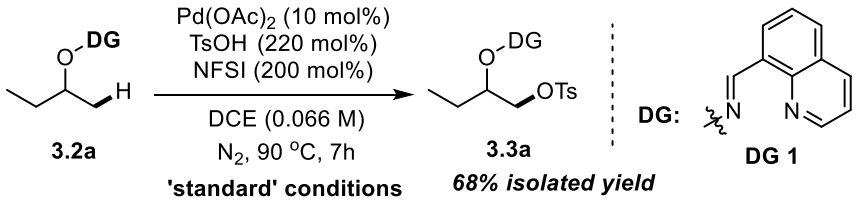


3.2ad

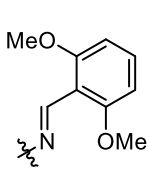
(*E*)-quinoline-8-carbaldehyde *O*-((3*R*,5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl) oxime (3.2ad): White solid. m.p.= 69-70°C. Yield 80%. R_f = 0.6 (Hexane:Ethyl acetate = 10:1). IR (KBr) 2929, 2865, 2361, 2343, 1497, 1466, 1383, 1363, 1306 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.94 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.30 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.83 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.50 (d, *J* = 2.5 Hz, 1H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 1.9 Hz, 3H), 0.86 (d, *J* = 1.9 Hz, 3H), 0.83 (s, 3H), 0.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.99, 145.97, 145.37, 136.33, 130.73, 129.21, 128.42, 126.52, 126.05, 121.44, 78.21, 56.70, 56.37, 54.35, 42.74, 40.22, 39.68, 36.33, 35.98, 35.92, 35.68, 33.02, 32.83, 32.15, 28.79, 28.42, 28.16, 26.06, 24.36, 24.00, 22.99, 22.73, 20.96, 18.82, 12.24, 11.63. HRMS: calcd. $[M+H]^+$ 543.43090 Found: 543.43110.

Reaction condition optimization for Pd-catalyzed C-H tosyloxylation

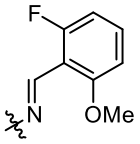
Table 3.3 Selected Optimization of Reaction Conditions



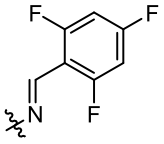
entry	variations from the 'standard' conditions	yield of **3.2a** (%)[b]	unreacted **3.1a** (%)[b]
1	**DG 2-DG 13** instead of **DG 1**	listed below	listed below
2	KPS instead of **NFSI**	34	40
3	Oxone instead of **NFSI**	47	18
4	$PhI(OAc)_2$ instead of **NFSI**	48[d]	<5
5	w/o **NFSI**	0	84
6	w/o **$Pd(OAc)_2$**	0	>99
7	150 mol% TsOH instead of **220 mol% TsOH**	48	24
8	$CHCl_3$ instead of **DCE**	33	46
9	PhCl instead of **DCE**	66	0
10	110 °C instead of **90 °C**[e]	55	0
11	70 °C instead of **90 °C**[f]	60	8
12	50 °C instead of **90 °C**[g]	44	23
13	+ 100 mol% H_2O	62	0
14	under air atmosphere	63	9



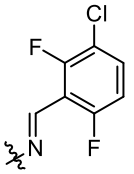
DG 2: <5% (3.5 h)



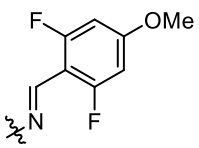
DG 3: 21% (12 h)[c]



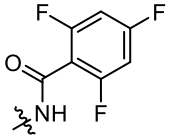
DG 4: 44% (12 h)[c]



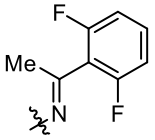
DG 5: 53% (12 h)[c]



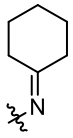
DG 6: 53% (3 h)[c]



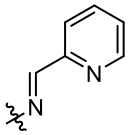
DG 7: 0%[c]



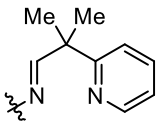
DG 8: < 5%[c]



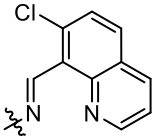
DG 9: 0%[c]



DG 10: 0%



DG 11: 0%



DG 12: 60%

[a] Reaction conditions: **3.2a** (0.1 mmol), TsOH (0.22 mmol), $Pd(OAc)_2$ (0.01 mmol), *N*-fluorobenzenesulfonimide (0.2 mmol), DCE (1.5 ml), 90 °C, 7h. [b] NMR yields using 1-fluoronaphthalene or 1,1,2,2-tetrachloroethane as the internal standard. Besides **3.2a** and **3.3a**, the remaining materials are mainly unidentifiable decomposition products. [c] The reactions were conducted under air, and 150 mol% TsOH was used. [d] Isolated yields. [e] **3.2a** was all consumed within 2 h. [f] Reaction time was 24 h. [g] Reaction time was 138 h.

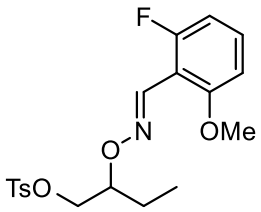
"Standard condition": An 4 mL vial was charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 0.1 equiv.), TsOH (37.8 mg, 0.22 mmol, 2.2 equiv.), *N*-fluorobenzenesulfonimide (63 mg, 0.2 mmol, 2.0 equiv.), 1,2-dichloroethane (1.5 ml) and quinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime **(3.2a)** (22.8 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 7 hours under stirring. The vial was then allowed to cool to room temperature. Na_2CO_3 (90 mg) and 1,10-phenanthroline (3.6 mg) was then added in to quench the reaction, and the mixture was further stirred at room temperature for 36 h. The mixture was filtered through a small plug of Celite to remove the precipitate and washed with dichloromethane. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane/ethyl acetate/DCM = 20:1:5) to give the desired product **3.3a** as yellowish oil (27.2 mg, 68% yield). R_f = 0.4 (Hex/EA/DCM = 10:1:3). IR (KBr) 3063.56, 2969.66, 2878.24, 1600.82, 1492.11, 1363.62, 1175.84, 955.94 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.94 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.08 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.86 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.17 (dd, *J* = 8.6, 0.6 Hz, 2H), 4.37 – 4.21 (m, 3H), 2.12 (s, 3H),

1.84 – 1.62 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.11, 146.46, 145.81, 144.67, 136.33, 132.83, 129.85, 129.76, 129.66, 128.32, 128.14, 126.36, 126.10, 121.55, 81.59, 70.21, 23.32, 21.40, 9.80. HRMS: calcd. $[M+H]^+$ 399.13731 Found: 399.13800.

Entry 1 (DG2): An 4 mL vial was charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 0.1 equiv.), TsOH (25.8 mg, 0.15 mmol, 1.5 equiv.), *N*-fluorobenzenesulfonimide (63 mg, 0.2 mmol, 2.0 equiv.), 1,2-dichloroethane (1.5 ml) and oxime substrate **3.2a-DG2** (23.7 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was sealed again and heated in a pie-block at 90 °C for 3.5 hours under stirring. The vial was then allowed to cool to room temperature. Trace amounts of product was detected by LC-MS.

Entry 1 (DG3 to DG8): An 4 mL vial was charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 0.1 equiv.), TsOH (25.8 mg, 0.15 mmol, 1.5 equiv.), *N*-fluorobenzenesulfonimide (63 mg, 0.2 mmol, 2.0 equiv.), 1,2-dichloroethane (1.5 ml) and oxime substrate (0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and heated in a pie-block at 90 °C for 12 hours (unless noted otherwise) under stirring. The vial was then allowed to cool to room temperature. The solvent was then removed in *vacuo* before 1-fluoronaphthalene (0.15 mmol, 21.9 mg) was added. The yield of the desired product was determined by ^{19}F NMR using 1-fluoronaphthalene as the internal standard.

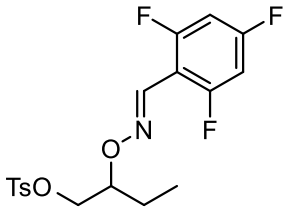
For the isolation of the desired product, an 4 mL vial was charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 0.1 equiv.), TsOH (25.8 mg, 0.15 mmol, 1.5 equiv.), *N*-fluorobenzenesulfonimide (63 mg, 0.2 mmol, 2.0 equiv.), 1,2-dichloroethane (1.5 ml) and oxime substrate (0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 12 hours (unless noted otherwise) under stirring. The vial was then allowed to cool to room temperature. The solvent was removed in *vacuo* and the residue was further purified with flash column chromatography (hexane/ethyl acetate = 10:1) to give the title product.



3.3a-DG3

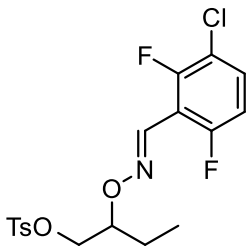
(*E*)-2-(((2-fluoro-6-methoxybenzylidene)amino)oxy)butyl 4-methylbenzenesulfonate (3.3a-DG3): isolated as a mixture of *E*/*Z* isomer (*E*/*Z* = 6.5:1). Colorless oil. R_f = 0.2 (Hex/EA= 5:1). IR (KBr) 2972.88, 2930.33, 2883.74, 1613.51, 1572.99, 1473.72, 1366.35, 1181.99 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.82 – 7.72 (m, 2H), 7.34 – 7.22 (m, 3H), 6.75 – 6.65 (m, 2H), 4.29 – 4.16 (m, 3H), 3.88 – 3.80 (m, 3H), 2.44 (s, 0.40H), 2.29 (s, 2.60H), 1.82 – 1.60 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 2.60H), 0.88 (t, *J* = 7.4 Hz, 0.40H). ^{13}C NMR (101 MHz, $CDCl_3$) δ carbon signal was found at 162.42, 159.88, 159.07, 159.00, 144.67, 142.49, 142.46, 132.94, 131.07, 130.96, 129.89, 129.75,

128.21, 128.12, 109.52, 109.38, 108.90, 108.68, 106.65, 106.62, 81.66, 81.49, 70.10, 70.02, 56.30, 56.13, 23.43, 23.17, 21.81, 21.61, 9.82, 9.48. ^{19}F NMR (376 MHz, $CDCl_3$) δ -106.84 (s, 0.12F), -109.98 (d, *J* = 6.0 Hz, 0.88F). HRMS: calcd. $[M+Na]^+$ 418.10950 Found: 418.11000.



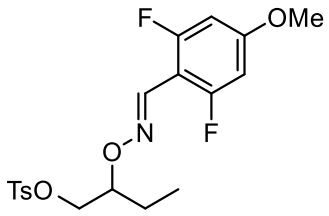
3.3a-DG4

(*E*)-2-(((2,4,6-trifluorobenzylidene)amino)oxy)butyl 4-methylbenzenesulfonate (3.3a-DG4): isolated as a mixture of *E*/*Z* isomer (*E*/*Z* = 9:1). Colorless oil. R_f = 0.3 (Hex/EA= 10:1). IR (KBr) 3100.51, 2972.88, 2930.33, 1645.92, 1613.51, 1443.33, 1362.30, 1181.99 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.69 (t, *J* = 8.5 Hz, 2H), 4.26 – 4.18 (m, 2.70H), 4.11 (t, *J* = 4.6 Hz, 0.30H), 2.43 (s, 0.3H), 2.32 (s, 2.7H), 1.78 – 1.57 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 2.7H), 0.87 (t, *J* = 7.5 Hz, 0.3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ carbon signal was found at 164.27, 164.12, 162.61, 162.52, 162.46, 162.37, 161.90, 161.75, 161.59, 160.04, 159.95, 159.90, 159.80, 144.75, 139.21, 139.19, 132.97, 129.87, 129.74, 129.51, 129.14, 128.16, 128.10, 128.03, 106.87, 106.82, 106.72, 106.67, 106.57, 106.52, 101.28, 101.25, 101.02, 100.98, 100.76, 100.73, 82.08, 69.88, 23.08, 21.59, 9.71. ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.79 – -103.84 (m, 0.12F), -104.64 – -104.91 (m, 0.94F), -105.42 (dd, *J* = 16.5, 8.3 Hz, 0.06F), -107.26 (t, *J* = 7.9 Hz, 1.88F). HRMS: calcd. $[M+Na]^+$ 424.08010 Found: 424.08060.



3.3a-DG5

(*E*)-2-(((3-chloro-2,6-difluorobenzylidene)amino)oxy)butyl 4-methylbenzenesulfonate (3.3a-DG5): isolated as a mixture of *E*/*Z* isomer (*E*/*Z* = 15:1). Colorless oil. R_f = 0.3 (Hex/EA= 5:1). IR (KBr) 3074.17, 2970.85, 2938.44, 1726.96, 1615.53, 1465.62, 1366.35, 1181.99 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.83 – 7.72 (m, 2H), 7.35 (ddd, *J* = 9.0, 8.0, 5.5 Hz, 1H), 7.25 – 7.21 (m, 2H), 6.88 (td, *J* = 9.2, 1.8 Hz, 1H), 4.28 – 4.05 (m, 3H), 2.43 (s, 0.2H), 2.30 (s, 2.8H), 1.80 – 1.61 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 2.8H), 0.88 (t, *J* = 7.5 Hz, 0.2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ carbon signals were found at 160.47, 160.42, 157.92, 157.87, 157.34, 157.27, 154.76, 154.69, 144.79, 139.41, 139.40, 133.02, 131.09, 131.05, 130.99, 129.77, 128.99, 128.23, 128.08, 112.60, 112.56, 112.37, 112.33, 82.37, 69.86, 23.12, 21.61, 9.76.^{19}F NMR (376 MHz, $CDCl_3$) δ -107.27 (d, *J* = 9.6 Hz, 0.03F), -108.16 (dd, *J* = 10.9, 6.6 Hz, 0.03F), -110.18 (ddd, *J* = 8.0, 3.5, 1.7 Hz, 0.97F), -112.15 (ddd, *J* = 9.3, 5.4, 3.6 Hz, 0.97F). HRMS: calcd. $[M+Na]^+$ 440.05050 Found: 440.05100.



3.3a-DG6

(*E*)-2-(((2,6-difluoro-4-methoxybenzylidene)amino)oxy)butyl 4-methylbenzenesulfonate (3.3a-DG6): isolated as a mixture of *E*/*Z* isomer (*E*/*Z* = 15:1). Colorless oil. R_f = 0.4 (Hex/EA= 5:1). IR (KBr) 3106.58, 2974.90, 2940.46, 1637.82, 1506.13, 1447.38, 1362.30, 1179.97, 1147.55 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 0.14H), 7.25 (d, *J* = 8.0 Hz, 1.86H), 6.47 (d, *J* = 10.1 Hz, 2H), 4.27 – 4.10 (m, 3H), 3.83 – 3.80 (m, 3H), 2.44 (s, 0.2H), 2.32 (s, 2.8H), 1.78 – 1.61 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ carbon signals were found at 163.04, 162.94, 161.98, 161.84, 161.70, 160.51, 160.41, 144.71, 140.08, 133.06, 129.74, 128.22, 98.70, 98.41, 81.74, 70.03, 56.10, 23.14, 21.63, 9.78. ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.58 (d, *J* = 9.6 Hz, 0.06F), -109.39 (d, *J* = 10.2 Hz, 0.94F). HRMS: calcd. $[M+Na]^+$ 436.10010 Found: 436.10060.

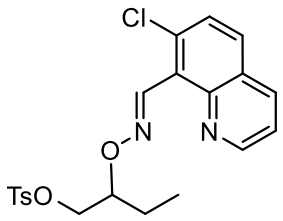
Entry 1 (DG9): An 4 mL vial was charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 0.1 equiv.), TsOH (25.8 mg, 0.15 mmol, 1.5 equiv.), *N*-fluorobenzenesulfonimide (63 mg, 0.2 mmol, 2.0 equiv.), 1,2-dichloroethane (1.5 ml) and oxime substrate **3.2a-DG9** (16.9mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and heated in a pie-block at 90 °C for 12 hours under stirring. The vial was then allowed to cool to room temperature. No desired product was detected by TLC or ^1H NMR analysis.

*(*For **DG2 to DG9**, using 1.5 equiv. of TsOH instead of 2.2 equiv. TsOH is due to the non-basicity of the directing group.)*

Entry 1 (DG10 and DG11): An 4 mL vial was charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 0.1 equiv.), (37.8 mg, 0.22 mmol, 2.2 equiv.), *N*-fluorobenzenesulfonimide (63 mg, 0.2 mmol, 2.0 equiv.), 1,2-dichloroethane (1.5 ml) and oxime substrate (0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 7 hours under stirring. The vial was then allowed to cool to room temperature. Na_2CO_3 (90 mg) and 1,10-phenanthroline (3.6 mg) was then added in to quench the reaction, and the mixture was further stirred at room temperature for 36 h. No desired product was detected by TLC analysis of the crude mixture.

Entry 1 (DG12): An 4 mL vial was charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 0.1 equiv.), TsOH (37.8 mg, 0.22 mmol, 2.2 equiv.), *N*-fluorobenzenesulfonimide (63 mg, 0.2 mmol, 2.0 equiv.), 1,2-dichloroethane (1.5 ml) and 7-chloroquinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime **(3.2a-DG12)** (26.3 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 7 hours under stirring. The vial was allowed to cool to room temperature. The solvent was removed in *vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yield of the desired product was determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard.

For the isolation of the desired product, an 4 mL vial was charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 0.1 equiv.), TsOH (25.8 mg, 0.15 mmol, 1.5 equiv.), *N*-fluorobenzenesulfonimide (63 mg, 0.2 mmol, 2.0 equiv.), 1,2-dichloroethane (1.5 ml) and 7-chloroquinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime **(3.2a-DG12)** (26.3 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was sealed again and heated in a pie-block at 90 °C for 7 hours under stirring. The vial was then allowed to cool to room temperature. Na_2CO_3 (90 mg) and 1,10-phenanthroline (3.6 mg) was added in to quench the reaction, and the mixture was further stirred at room temperature for 36 h. The mixture was filtered through a small plug of Celite to remove the precipitate and washed with dichloromethane. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane/ethyl acetate/DCM = 20:1:5) to give the title product as colorless oil.



3.3a-DG12

(*E*)-2-((((7-chloroquinolin-8-yl)methylene)amino)oxy)butyl 4-methylbenzenesulfonate (3.3a-DG12): Colorless oil. R_f = 0.3 (Hex/EA/DCM = 10:1:3). IR (KBr) 3031.63, 2976.93, 2928.31, 1601.35, 1491.95, 1364.32, 1179.97, 963.20 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.93 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.8

Hz, 1H), 7.84 – 7.78 (m, 2H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 4.35 – 4.26 (m, 3H), 2.20 (s, 3H), 1.85 – 1.70 (m, 2H), 1.00 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.84, 147.37, 146.04, 144.65, 136.16, 134.19, 132.92, 129.78, 129.48, 129.36, 128.22, 127.64, 126.69, 121.73, 81.67, 70.26, 23.28, 21.53, 9.81. HRMS: calcd. $[M+Na]^+$ 455.08030 Found: 455.08070,

Entry 2: An 4 mL vial was charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 0.1 equiv.), TsOH (37.8 mg, 0.22 mmol, 2.2 equiv.), potassium persulfate (54 mg, 0.2 mmol, 2.0 equiv.), 1,2-dichloroethane (1.5 ml) and quinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime **(3.2a)** (22.8 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 7 hours under stirring. The vial was allowed to cool to room temperature. The solvent was then removed in *vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yield of the desired product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard (^{1}H NMR yield: 34%, unreacted **3.2a:** 40%).

Entry 3: An 4 mL vial was charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 0.1 equiv.), TsOH (37.8 mg, 0.22 mmol, 2.2 equiv.), Oxone® (74 mg, 0.12 mmol, 1.2 equiv.), 1,2-dichloroethane (1.5 ml) and quinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime **(3.2a)** (22.8 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then

sealed again and heated in a pie-block at 90 °C for 7 hours under stirring. The vial was allowed to cool to room temperature. The solvent was then removed in *vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yield of the desired product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard (^{1}H NMR yield: 47%, unreacted **3.2a:** 18%).

Entry 4: An 4 mL vial was charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 0.1 equiv.), TsOH (37.8 mg, 0.22 mmol, 2.2 equiv.), $PhI(OAc)_2$ (64 mg, 0.2 mmol, 2.0 equiv.), 1,2-dichloroethane (1.5 ml) and quinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime **(3.2a)** (22.8 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 7 hours under stirring. The vial was allowed to cool to room temperature. Na_2CO_3 (90 mg) and 1,10-phenanthroline (3.6 mg) was then added in to quench the reaction, and the mixture was further stirred at room temperature for 36 h. The mixture was filtered through a small plug of Celite to remove the precipitate and washed with dichloromethane. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane/ethyl acetate/DCM = 20:1:5) to give the desired product in 48% yield.

Entry 5: An 4 mL vial was charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 0.1 equiv.), TsOH (37.8 mg, 0.22 mmol, 2.2 equiv.), 1,2-dichloroethane (1.5 ml) and quinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime **(3.2a)** (22.8 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and

purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 7 hours under stirring. The vial was allowed to cool to room temperature. The solvent was then removed in *vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yield of the desired product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard (^{1}H NMR yield: 0%, unreacted **3.2a:** 84%).

Entry 6: An 4 mL vial was charged with TsOH (37.8 mg, 0.22 mmol, 2.2 equiv.), *N*-fluorobenzenesulfonimide (63 mg, 0.2 mmol, 2.0 equiv.), 1,2-dichloroethane (1.5 ml) and quinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime **(3.2a)** (22.8 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 7 hours under stirring. The vial was then allowed to cool to room temperature. The solvent was then removed in *vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yield of the desired product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard (^{1}H NMR yield: 0%, unreacted **3.2a:** >99%).

Entry 7: An 4 mL vial was charged with $Pd(OAc)_2$ (3.5 mg, 0.015 mmol, 0.1 equiv.), TsOH (25.8 mg, 0.15 mmol, 1.5 equiv.), *N*-fluorobenzenesulfonimide (63 mg, 0.2 mmol, 2.0 equiv.), 1,2-dichloroethane (1.5 ml) and quinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime **(3.2a)** (22.8 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 7 hours under stirring. The vial

was allowed to cool to room temperature. The solvent was then removed in *vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yield of the desired product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard (^{1}H NMR yield: 48%, unreacted **3.2a:** 24%).

Entry 8: An 4 mL vial was charged with $Pd(OAc)_2$ (3.5 mg, 0.015 mmol, 0.1 equiv.), TsOH (37.8 mg, 0.22 mmol, 2.2 equiv.), *N*-fluorobenzenesulfonimide (63 mg, 0.2 mmol, 2.0 equiv.), $CHCl_3$ (1.5 ml) and quinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime **(3.2a)** (22.8 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 7 hours under stirring. The vial was allowed to cool to room temperature. The solvent was then removed in *vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yield of the desired product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard (^{1}H NMR yield: 33%, unreacted **3.2a:** 46%).

Entry 9: An 4 mL vial was charged with $Pd(OAc)_2$ (3.5 mg, 0.015 mmol, 0.1 equiv.), TsOH (37.8 mg, 0.22 mmol, 2.2 equiv.), *N*-fluorobenzenesulfonimide (63 mg, 0.2 mmol, 2.0 equiv.), PhCl (1.5 ml) and quinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime **(3.2a)** (22.8 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 7 hours under stirring. The vial was then allowed to cool to room temperature. The solvent was then removed in *vacuo* before 1,1,2,2-

tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yield of the desired product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard (^{1}H NMR yield: 66%, unreacted **3.2a:** 0%).

Entry 10: An 4 mL vial was charged with $Pd(OAc)_2$ (3.5 mg, 0.015 mmol, 0.1 equiv.), TsOH (37.8 mg, 0.22 mmol, 2.2 equiv.), *N*-fluorobenzenesulfonimide (63 mg, 0.2 mmol, 2.0 equiv.), 1,2-dichloroethane (1.5 ml) and quinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime **(3.2a)** (22.8 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 110 °C for 2 hours under stirring. The vial was then allowed to cool to room temperature. The solvent was then removed in *vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yield of the desired product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard (^{1}H NMR yield: 55%, unreacted **3.2a:** 0%).

Entry 11: An 4 mL vial was charged with $Pd(OAc)_2$ (3.5 mg, 0.015 mmol, 0.1 equiv.), TsOH (37.8 mg, 0.22 mmol, 2.2 equiv.), *N*-fluorobenzenesulfonimide (63 mg, 0.2 mmol, 2.0 equiv.), 1,2-dichloroethane (1.5 ml) and quinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime **(3.2a)** (22.8 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 70 °C for 24 hours under stirring. The vial was allowed to cool to room temperature. The solvent was then removed in *vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yield of the desired

product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard (^{1}H NMR yield: 60%, unreacted **3.2a:** 8%).

Entry 12: An 4 mL vial was charged with $Pd(OAc)_2$ (3.5 mg, 0.015 mmol, 0.1 equiv.), TsOH (37.8 mg, 0.22 mmol, 2.2 equiv.), *N*-fluorobenzenesulfonimide (63 mg, 0.2 mmol, 2.0 equiv.), 1,2-dichloroethane (1.5 ml) and quinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime **(3.2a)** (22.8 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 50 °C for 138 hours under stirring The vial was allowed to cool to room temperature. The solvent was then removed in *vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yield of the desired product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard (^{1}H NMR yield: 44%, unreacted **3.2a:** 23%).

Entry 13: An 4 mL vial was charged with $Pd(OAc)_2$ (3.5 mg, 0.015 mmol, 0.1 equiv.), TsOH (37.8 mg, 0.22 mmol, 2.2 equiv.), *N*-fluorobenzenesulfonimide (63 mg, 0.2 mmol, 2.0 equiv.), 1,2-dichloroethane (1.5 ml), H_2O (1.8 mg, 0.1 mmol, 1.0 equiv.) and quinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime **(3.2a)** (22.8 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 7 hours under stirring. Then, the vial was allowed to cool to room temperature. The solvent was then removed in *vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yield of the desired product was determined by ^{1}H NMR

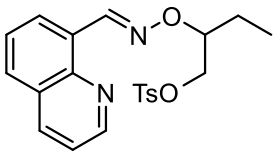
using 1,1,2,2-tetrachloroethane as the internal standard (^{1}H NMR yield: 62%, unreacted **3.2a:** 0%).

Entry 14: An 4 mL vial was charged with $Pd(OAc)_2$ (3.5 mg, 0.015 mmol, 0.1 equiv.), TsOH (37.8 mg, 0.22 mmol, 2.2 equiv.), *N*-fluorobenzenesulfonimide (63 mg, 0.2 mmol, 2.0 equiv.), 1,2-dichloroethane (1.5 ml) and quinoline-8-carbaldehyde *O*-(*sec*-butyl) oxime **(3.2a)** (22.8 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and heated in a pie-block at 90 °C for 7 hours under stirring. The vial was allowed to cool to room temperature. The solvent was then removed in *vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yield of the desired product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard (^{1}H NMR yield: 63%, unreacted **3.2a:** 9%).

Typical procedure for substrate scope research

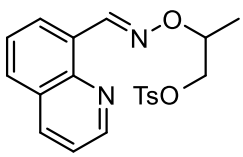
Unless stated otherwise, an 4 mL vial was charged with $Pd(OAc)_2$ (3.5 mg, 0.015 mmol, 0.1 equiv.), sulfonic acid (0.33 mmol, 2.2 equiv.), *N*-fluorobenzenesulfonimide (95 mg, 0.3 mmol, 2.0 equiv.), 1,2-dichloroethane (2.2 ml) and oxime substrate (0.15 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 7 hours (unless noted otherwise in **Table 3.2**) under stirring. The vial was then allowed to cool to room temperature. Na_2CO_3 (150 mg) and 1,10-phenanthroline (5.1 mg) was then added in to quench the reaction, and the mixture was

further stirred at room temperature for 36 h. The mixture was filtered through a small plug of Celite to remove the precipitate and washed with dichloromethane. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane/ethyl acetate/DCM, typically 20:1:5 or 10:1:3) to give the title product.



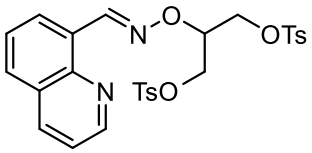
3.3a

(*E*)-2-(((quinolin-8-ylmethylene)amino)oxy)butyl 4-methylbenzenesulfonate (3.3a): Yellowish oil. Yield 68%. R_f = 0.4 (Hex/EA/DCM = 10:1:3). IR (KBr) 3063.56, 2969.66, 2878.24, 1600.82, 1492.11, 1363.62, 1175.84, 955.94 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.94 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.08 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.86 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.17 (dd, *J* = 8.6, 0.6 Hz, 2H), 4.37 – 4.21 (m, 3H), 2.12 (s, 3H), 1.84 – 1.62 (m, 2H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.11, 146.46, 145.81, 144.67, 136.33, 132.83, 129.85, 129.76, 129.66, 128.32, 128.14, 126.36, 126.10, 121.55, 81.59, 70.21, 23.32, 21.40, 9.80. HRMS: calcd. $[M+H]^+$ 399.13731 Found: 399.13800.



3.3b

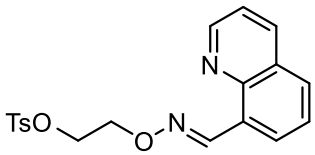
(*E*)-2-(((quinolin-8-ylmethylene)amino)oxy)propyl 4-methylbenzenesulfonate (3.3b): Yellowish oil. Yield 61 %. R_f = 0.3 (Hex/EA/DCM = 10:1:3). IR (KBr) 2984.49, 2927.66, 1598.35, 1501.99, 1363.62, 1195.61, 1180.78 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.92 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.12 (ddd, *J* = 8.6, 7.8, 1.5 Hz, 2H), 7.85 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 4.52 (qd, *J* = 6.6, 2.0 Hz, 1H), 4.23 (d, *J* = 4.5 Hz, 2H), 2.15 (s, 3H), 1.34 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.13, 146.65, 145.85, 144.73, 136.32, 132.86, 129.84, 129.80, 129.71, 128.32, 128.14, 126.37, 126.17, 121.57, 76.39, 71.50, 21.46, 16.14. HRMS: calcd. $[M+Na]^+$ 407.10360 Found: 407.10400.



3.3b'

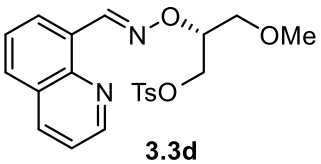
(*E*)-2-(((quinolin-8-ylmethylene)amino)oxy)propane-1,3-diyl bis(4-methylbenzenesulfonate) (3.3b'): Yellowish oil. Yield 6%. R_f = 0.1 (Hex/EA/DCM = 10:1:3). IR (KBr) 2958.69, 2928.31, 2855.37, 1745.19, 1460.25, 1364.32, 1169.20 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.95 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.01 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.88 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.81 – 7.63 (m, 4H),

7.53 (t, *J* = 7.7 Hz, 1H), 7.47 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 4H), 4.56 (p, *J* = 5.0 Hz, 1H), 4.37 – 4.17 (m, 4H), 2.25 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.29, 147.97, 145.88, 145.16, 136.39, 132.49, 130.17, 130.02, 129.21, 128.37, 128.22, 126.39, 126.38, 121.71, 77.71, 67.17, 21.61. HRMS: calcd. $[M+H]^+$ 577.10736 Found: 577.10730.



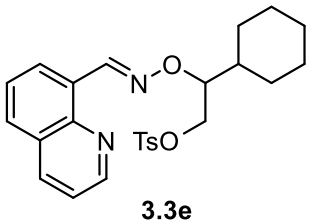
3.3c

(*E*)-2-(((quinolin-8-ylmethylene)amino)oxy)ethyl 4-methylbenzenesulfonate (3.3c): Colorless oil. Yield 57%. R_f = 0.3 (Hex/EA/DCM = 10:1:3). IR (KBr) 3044.80, 2927.66, 1593.41, 1499.52, 1366.09, 1178.31, 1094.30, 928.76 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.93 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.09 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.86 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 4.37 (s, 4H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.19, 147.21, 145.85, 144.79, 136.34, 132.86, 129.87, 129.82, 129.59, 128.33, 128.16, 126.38, 126.23, 121.61, 71.28, 68.48, 21.43. HRMS: calcd. $[M+H]^+$ 393.08795 Found: 393.08820.



3.3d

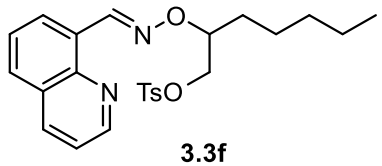
(*R*,*E*)-3-methoxy-2-(((quinolin-8-ylmethylene)amino)oxy)propyl 4-methylbenzenesulfonate (3.3d): Yellowish oil. Yield 61%. R_f = 0.2 (Hex/EA/DCM = 10:1:3). IR (KBr) 2982.40, 2922.72, 2824.00, 1598.35, 1501.99, 1361.15, 1180.78, 1096.77 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.92 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.11 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.92 – 7.83 (m, 1H), 7.83 – 7.72 (m, 2H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.24 – 7.13 (m, 2H), 4.62 – 4.47 (m, 1H), 4.35 (qd, *J* = 10.6, 4.7 Hz, 2H), 3.74 – 3.56 (m, 2H), 3.36 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.19, 147.46, 145.90, 144.80, 136.31, 132.80, 129.88, 129.84, 129.65, 128.34, 128.21, 126.38, 126.30, 121.61, 79.51, 70.51, 68.50, 59.54, 21.51. HRMS: calcd. $[M+H]^+$ 415.13222 Found: 415.13180. $[a]_D^{20}$ = 19.2 (c 1.56, $CHCl_3$).



3.3e

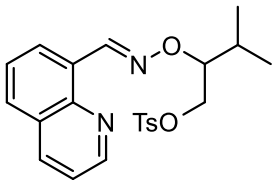
(*E*)-2-cyclohexyl-2-(((quinolin-8-ylmethylene)amino)oxy)ethyl 4-methylbenzenesulfonate (3.3e): Yellowish oil. Yield 55%. R_f = 0.4 (Hex/EA/DCM = 10:1:3). IR (KBr) 3040.00, 2925.19, 2851.06, 1595.88, 1497.05, 1450.10, 1363.62, 1363.62, 1180.78 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.94 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.06 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.88 – 7.83 (m, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 4.32 (qd, *J* = 10.7, 4.2 Hz, 2H), 4.17 – 4.05 (m, 1H), 2.05 (s, 3H), 1.88 (d, *J* = 12.9 Hz, 1H),

1.85-1.60 (m, 5H), 1.29 – 1.02 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.09, 146.07, 145.79, 144.60, 136.36, 132.83, 129.91, 129.72, 129.59, 128.34, 128.18, 126.39, 126.07, 121.55, 84.72, 68.98, 37.99, 28.93, 28.76, 26.42, 26.10, 25.96, 21.35. HRMS: calcd. $[M+H]^+$ 453.18426 Found: 453.18470.



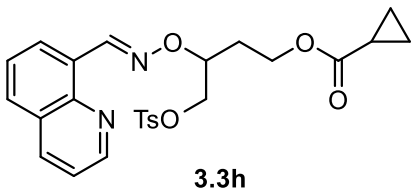
3.3f

(*E*)-2-(((quinolin-8-ylmethylene)amino)oxy)heptyl 4-methylbenzenesulfonate (3.3f): Yellowish oil. Yield 70%. R_f = 0.4 (Hex/EA/DCM = 10:1:3). IR (KBr) 3030.40, 2957.31, 2856.01, 1600.82, 1501.99, 1455.04, 1368.57, 1180.78 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.96 – 8.86 (m, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 8.07 (d, *J* = 7.3 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 4.45 – 4.16 (m, 3H), 2.09 (s, 3H), 1.79 – 1.69 (m, 1H), 1.66 – 1.57 (m, 1H), 1.48 – 1.20 (m, 6H), 0.87 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.12, 146.41, 145.82, 144.66, 136.35, 132.86, 129.89, 129.76, 129.65, 128.34, 128.17, 126.39, 126.12, 121.57, 80.39, 70.58, 31.78, 30.12, 25.04, 22.62, 21.40, 14.14. HRMS: calcd. $[M+H]^+$ 441.18426 Found: 441.18440.



3.3g

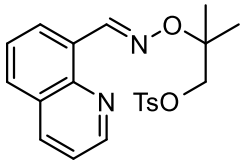
(*E*)-3-methyl-2-(((quinolin-8-ylmethylene)amino)oxy)butyl 4-methylbenzenesulfonate (3.3g): Yellowish oil. Yield 66 %. R_f = 0.4 (Hex/EA/DCM = 10:1:3). IR (KBr) 2962.25, 2875.77, 1724.80, 1595.88, 1494.58, 1472.34, 1358.68, 1175.84 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.93 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.12 – 8.02 (m, 1H), 7.85 (d, *J* = 7.3 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 4.38 – 4.26 (m, 2H), 4.08 (dt, *J* = 8.2, 4.3 Hz, 1H), 2.17 – 2.02 (m, 4H), 1.04 – 0.92 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.09, 146.14, 145.78, 144.63, 136.36, 132.83, 129.86, 129.73, 129.62, 128.34, 128.16, 126.39, 126.07, 121.55, 85.38, 69.15, 28.63, 21.36, 18.72, 18.44. HRMS: calcd. $[M+H]^+$ 413.15296 Found: 413.15320.



3.3h

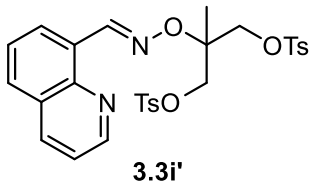
(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)-4-(tosyloxy)butyl cyclopropanecarboxylate (3.3h): Yellowish oil. Yield 54%. R_f = 0.15 (Hex/EA/DCM = 10:1:3). IR (KBr) 3017.45, 2958.69, 1724.93, 1595.27, 1362.30, 1179.97 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.93 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.8 Hz, 1H),

8.06 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.86 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.82 – 7.74 (m, 2H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.51 (td, *J* = 8.7, 4.4 Hz, 1H), 4.31 (qd, *J* = 10.7, 4.3 Hz, 2H), 4.27 – 4.15 (m, 2H), 2.16 – 2.03 (m, 4H), 2.03 – 1.95 (m, 1H), 1.59 (tt, *J* = 8.0, 4.6 Hz, 1H), 1.03 – 0.94 (m, 2H), 0.87 – 0.80 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.86, 150.18, 147.05, 145.81, 144.80, 136.34, 132.70, 129.86, 129.80, 129.60, 128.32, 128.16, 126.35, 126.19, 121.61, 77.27, 70.32, 60.72, 29.59, 21.39, 12.96, 8.64, 8.63. HRMS: calcd. $[M+H]^+$ 483.15844 Found: 483.15910.



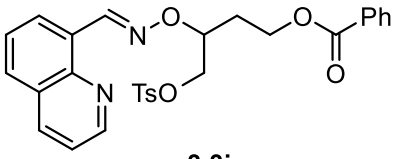
3.3i

(*E*)-2-methyl-2-(((quinolin-8-ylmethylene)amino)oxy)propyl 4-methylbenzenesulfonate (3.3i): Colorless oil. Yield 29%. R_f = 0.4 (Hex/EA/DCM = 10:1:3). IR (KBr) 2982.40, 2925.19, 1598.35, 1499.52, 1358.68, 1180.78, 913.93 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.93 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.01 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.86 (s, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.11 (dd, *J* = 8.0, 0.5 Hz, 2H), 4.17 (s, 2H), 2.10 (s, 3H), 1.36 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.12, 145.95, 145.87, 144.58, 136.30, 132.88, 130.24, 129.72, 129.48, 128.33, 128.15, 126.34, 126.06, 121.54, 78.84, 73.91, 23.08, 21.44. HRMS: calcd. $[M+Na]^+$ 421.11925 Found: 421.11970.



3.3i'

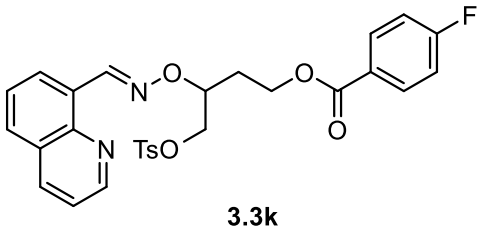
(*E*)-2-methyl-2-(((quinolin-8-ylmethylene)amino)oxy)propane-1,3-diyl bis(4-methylbenzenesulfonate) (3.3i'): Yellowish oil. Yield 15%. R_f = 0.2 (Hex/EA/DCM = 10:1:3). IR (KBr) 3061.02, 2958.69, 2928.31, 2855.37, 1603.38, 1459.54, 1364.32, 1198.20, 1184.02 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.94 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.89 (ddd, *J* = 9.5, 7.8, 1.4 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 4H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.23 – 7.14 (m, 4H), 4.16 (d, *J* = 2.6 Hz, 4H), 2.23 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.27, 147.32, 145.79, 145.04, 136.37, 132.43, 130.05, 129.95, 129.51, 128.33, 128.18, 128.13, 126.32, 121.68, 79.34, 70.23, 21.61, 18.54. HRMS: calcd. $[M+Na]^+$ 591.12301 Found: 591.12340.



3.3j

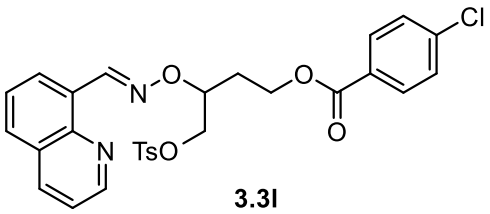
(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)-4-(tosyloxy)butyl benzoate (3.3j): Yellowish oil. Yield 66%. R_f = 0.35 (Hex/EA/DCM = 10:1:3). IR (KBr) 3063.56, 2954.84, 1719.42, 1593.41, 1501.99, 1361.15, 1269.95 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.93 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.07 – 7.99 (m, 3H), 7.87 – 7.83 (m, 1H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.52 (dt, *J* = 12.8, 7.6 Hz, 2H), 7.46 – 7.38 (m, 3H), 7.14 (d, *J* = 8.1 Hz, 2H), 4.61 (td, *J* = 8.6, 4.3 Hz, 1H), 4.55 – 4.43 (m, 2H), 4.36 (qd, *J* =

10.7, 4.3 Hz, 2H), 2.27 – 2.13 (m, 2H), 2.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.48, 150.16, 147.10, 145.79, 144.82, 136.31, 133.07, 132.64, 130.16, 129.86, 129.80, 129.68, 129.53, 128.46, 128.29, 128.14, 126.32, 126.18, 121.59, 77.31, 70.32, 61.24, 29.68, 21.37. HRMS: calcd. $[M+H]^+$ 519.15844 Found: 519.15830.



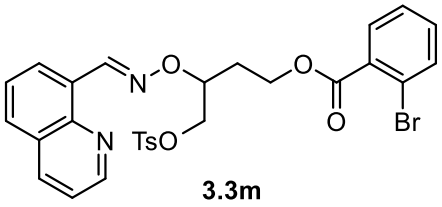
3.3k

(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)-4-(tosyloxy)butyl 4-fluorobenzoate (3.3k): Yellowish oil. Yield 66%. R_f = 0.25 (Hex/EA/DCM = 10:1:3). IR (KBr) 3073.44, 2959.78, 1721.89, 1600.82, 1506.93, 1363.62, 1279.62 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.92 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.08 – 8.00 (m, 3H), 7.85 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 8.7 Hz, 2H), 4.59 (td, *J* = 8.6, 4.2 Hz, 1H), 4.54 – 4.40 (m, 2H), 4.41 – 4.31 (m, 2H), 2.27 – 2.13 (m, 2H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ carbon signal was found at 167.08, 165.50, 164.55, 150.16, 147.11, 145.76, 144.84, 136.32, 132.63, 132.28, 132.18, 129.89, 129.80, 129.48, 128.29, 128.12, 126.43, 126.40, 126.30, 126.14, 121.60, 115.69, 115.47, 77.36, 70.27, 61.43, 29.64, 21.36. ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.72 (tt, *J* = 8.6, 5.5 Hz, 1F). HRMS: calcd. $[M+H]^+$ 537.14902 Found: 537.14920.



3.3l

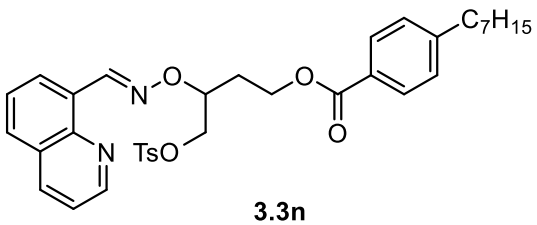
(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)-4-(tosyloxy)butyl 4-chlorobenzoate (3.3l): Yellowish oil. Yield 63%. R_f = 0.2 (Hex/EA/DCM = 10:1:3). IR (KBr) 3072.35, 2962.25, 2932.21, 1716.95, 1598.35, 1363.62, 1274.67, 1089.36 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.92 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.08 – 8.02 (m, 1H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.88 – 7.83 (m, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 4.59 (td, *J* = 8.6, 4.3 Hz, 1H), 4.53 – 4.42 (m, 2H), 4.39 – 4.30 (m, 2H), 2.26 – 2.13 (m, 2H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.60, 150.17, 147.12, 145.74, 144.84, 139.45, 136.32, 132.62, 131.07, 129.89, 129.81, 129.45, 128.78, 128.61, 128.29, 128.12, 126.30, 126.14, 121.60, 77.37, 70.25, 61.56, 29.61, 21.37. HRMS: calcd. $[M+H]^+$ 553.11946 Found: 553.11930.



3.3m

(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)-4-(tosyloxy)butyl 2-bromobenzoate (3.3m): Yellowish oil. Yield 61%. R_f = 0.25 (Hex/EA/DCM = 10:1:3). IR (KBr) 3068.50, 2957.31, 1734.25, 1593.41, 1363.62, 1291.97, 1175.84 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ

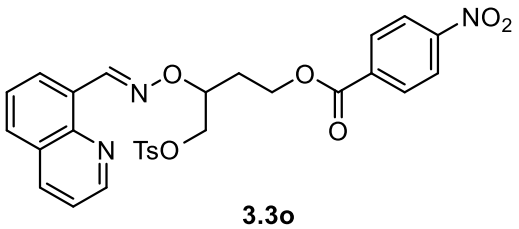
9.23 (s, 1H), 8.95 – 8.87 (m, 1H), 8.15 (dd, *J* = 8.2, 1.1 Hz, 1H), 8.05 (d, *J* = 7.3 Hz, 1H), 7.87 – 7.83 (m, 1H), 7.82 – 7.73 (m, 3H), 7.62 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 4.68 – 4.59 (m, 1H), 4.56 – 4.43 (m, 2H), 4.34 (qd, *J* = 10.7, 4.2 Hz, 2H), 2.28 – 2.13 (m, 2H), 2.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.10, 150.15, 147.15, 145.77, 144.80, 136.31, 134.36, 132.70, 132.63, 131.46, 129.86, 129.80, 129.51, 128.30, 128.11, 127.27, 126.32, 126.19, 121.66, 121.58, 77.22, 70.29, 61.92, 29.58, 21.37. HRMS: calcd. $[M+H]^+$ 597.06895 Found: 597.06880.



3.3n

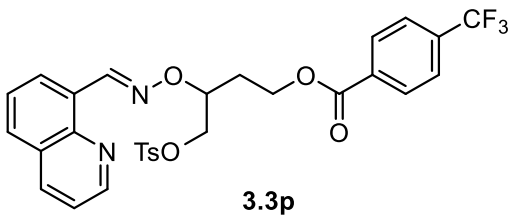
(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)-4-(tosyloxy)butyl 4-heptylbenzoate (3.3n): Yellowish oil. Yield 64%. R_f = 0.3 (Hex/EA/DCM = 10:1:3). IR (KBr) 2966.04, 2935.07, 2848.59, 1721.89, 1608.20, 1366.09, 1274.67, 1185.72 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.92 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.05 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.85 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.76 (t, *J* = 12.6 Hz, 2H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 4.61 (td, *J* = 8.6, 4.4 Hz, 1H), 4.53 – 4.30 (m, 4H), 2.73 – 2.51 (m, 2H), 2.28 – 2.12 (m, 2H), 2.07 (s, 3H), 1.66 – 1.54 (m, 2H), 1.34 – 1.20 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.56, 150.13, 148.69, 147.05, 145.77, 144.78,

136.30, 132.66, 129.82, 129.78, 129.73, 129.54, 128.51, 128.28, 128.12, 127.59, 126.30, 126.17, 121.56, 77.34, 70.34, 61.01, 36.08, 31.84, 31.22, 29.69, 29.27, 29.20, 22.72, 21.35, 14.19. HRMS: calcd. $[M+H]^+$ 617.26799 Found: 617.26760.



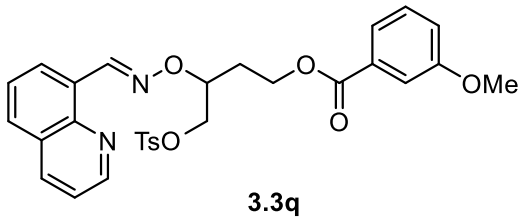
3.3o

(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)-4-(tosyloxy)butyl 4-nitrobenzoate (3.3o): Colorless gel. Yield 63%. R_f = 0.1 (Hex/EA/DCM = 10:1:3). IR (KBr) 3119.92, 2964.77, 2922.23, 2257.74, 1726.96, 1595.27, 1356.22, 1285.31 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.91 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.17 (dd, *J* = 17.9, 9.0 Hz, 5H), 8.04 – 8.00 (m, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 2H), 4.65 – 4.50 (m, 3H), 4.35 (d, *J* = 4.4 Hz, 2H), 2.32 – 2.14 (m, 2H), 2.09 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 164.58, 150.48, 150.20, 147.17, 145.71, 144.92, 136.34, 135.53, 132.60, 130.79, 129.97, 129.84, 129.35, 128.29, 128.12, 126.29, 126.09, 123.56, 121.65, 77.48, 70.17, 62.41, 29.52, 21.38. HRMS: calcd. $[M+H]^+$ 564.14352 Found: 564.14330.



3.3p

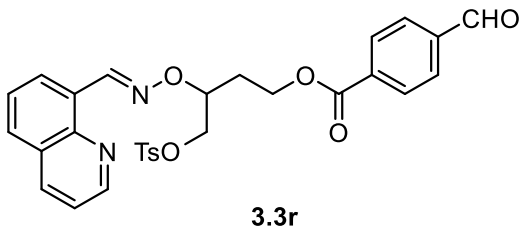
(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)-4-(tosyloxy)butyl 4-(trifluoromethyl)benzoate (3.3p): Yellowish oil. Yield 71%. R_f = 0.3 (Hex/EA/DCM = 10:1:3). IR (KBr) 3072.35, 2964.72, 1729.31, 1600.82, 1366.09, 1336.44, 1272.20 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.92 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.18 – 8.09 (m, 3H), 8.03 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.85 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.15 (d, *J* = 8.1 Hz, 2H), 4.64 – 4.57 (m, 1H), 4.57 – 4.47 (m, 2H), 4.40 – 4.31 (m, 2H), 2.30 – 2.16 (m, 2H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.26, 150.18, 147.17, 145.73, 144.88, 136.36, 134.43 (q, *J* = 32.3 Hz), 133.39, 132.64, 130.10, 129.93, 129.82, 129.41, 128.31, 128.13, 126.30, 126.16, 125.46 (q, *J* = 3.6 Hz), 123.7 (q, *J* = 273.7 Hz), 121.63, 77.41, 70.24, 61.94, 29.59, 21.36. ^{19}F NMR (376 MHz, $cdcl_3$) δ -63.08 (s, 3F). HRMS: calcd. $[M+H]^+$ 587.14582 Found: 587.14570.



3.3q

(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)-4-(tosyloxy)butyl 3-methoxybenzoate (3.3q): Yellowish oil. Yield 68%. R_f = 0.2 (Hex/EA/DCM = 10:1:3). IR

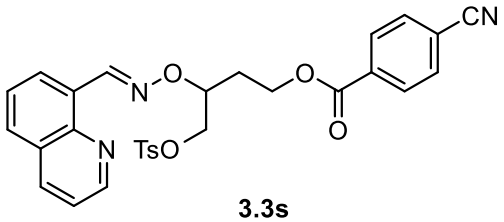
(KBr) 3074.88, 2958.69, 2928.31, 2255.71, 1720.88, 1599.32, 1491.95, 1364.32 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.92 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.05 (d, *J* = 7.2 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.11 – 7.05 (m, 1H), 4.60 (td, *J* = 8.5, 4.2 Hz, 1H), 4.47 (ddd, *J* = 10.0, 9.5, 5.5 Hz, 2H), 4.40 – 4.30 (m, 2H), 3.82 (s, 3H), 2.28 – 2.12 (m, 2H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.35, 159.61, 150.15, 147.09, 145.78, 144.81, 136.30, 132.65, 131.46, 129.85, 129.80, 129.52, 129.48, 128.29, 128.13, 126.31, 126.17, 122.08, 121.58, 119.57, 114.10, 77.33, 70.31, 61.35, 55.52, 29.68, 21.36. HRMS: calcd. $[M+H]^+$ 549.16900 Found: 549.16920.



3.3r

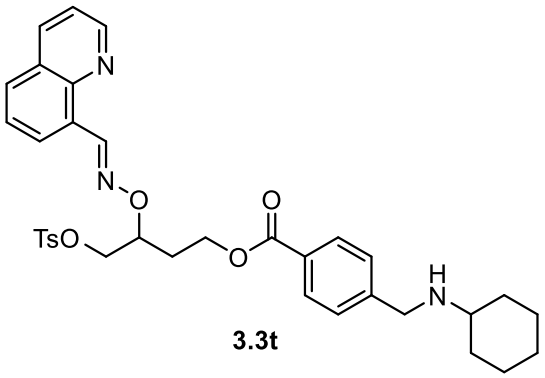
(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)-4-(tosyloxy)butyl 4-formylbenzoate (3.3r): Yellowish oil. Yield 47%. R_f = 0.1 (Hex/EA/DCM = 10:1:3). IR (KBr) 3061.02, 2966.80, 2920.20, 2853.13, 1706.70, 1599.32, 1496.00, 1275.18 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.06 (s, 1H), 9.21 (s, 1H), 8.95 (s, 1H), 8.22 – 8.13 (m, 3H), 8.05 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.92 – 7.89 (m, 2H), 7.87 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.82 – 7.74 (m, 2H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.17 (dd, *J* = 8.5, 0.6 Hz, 2H), 4.68 – 4.59 (m, 1H), 4.59 – 4.45 (m, 2H), 4.41 – 4.32 (m, 2H), 2.30 – 2.22 (m, 1H), 2.22 – 2.14 (m, 1H), 2.11

(s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.49, 165.28, 149.97, 147.03, 145.31, 144.67, 139.04, 136.37, 134.98, 132.56, 130.13, 129.74, 129.65, 129.39, 129.17, 128.17, 127.96, 127.88, 126.23, 121.45, 77.28, 70.07, 61.81, 29.47, 21.22. HRMS: calcd. $[M+H]^+$ 547.15335 Found: 547.15330.



3.3s

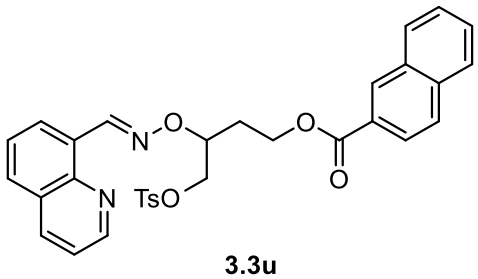
(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)-4-(tosyloxy)butyl 4-cyanobenzoate (3.3s): Yellowish oil. Yield 60%. R_f = 0.25 (Hex/EA/DCM = 10:2:3). IR (KBr) 3057.56, 2958.69, 2932.82, 2235.45, 1722.90, 1597.30, 1493.98, 1358.24, 1279.23 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.93 (d, *J* = 2.7 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.3 Hz, 1H), 8.09 (dd, *J* = 5.0, 3.6 Hz, 2H), 8.03 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.86 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.69 – 7.64 (m, 2H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.60 (dd, *J* = 8.8, 4.3 Hz, 1H), 4.51 (ddq, *J* = 11.3, 7.8, 5.7 Hz, 2H), 4.37 – 4.31 (m, 2H), 2.30 – 2.23 (m, 1H), 2.20 – 2.15 (m, 1H), 2.10 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.82, 150.18, 147.19, 145.67, 144.88, 136.41, 133.99, 132.68, 132.25, 130.19, 129.96, 129.83, 129.37, 128.32, 128.12, 126.32, 126.18, 121.66, 118.04, 116.39, 77.46, 70.18, 62.22, 29.58, 21.38. HRMS: calcd. $[M+H]^+$ 544.15369 Found: 544.15400.



3.3t

(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)-4-(tosyloxy)butyl 4-((cyclohexylamino)methyl)benzoate (3.3t): The reaction was stopped at 3 hour. Colorless oil. Yield 49%. *A procedure which is slightly different from the standard procedure was employed*. An 4 mL vial was charged with $Pd(OAc)_2$ (3.5 mg, 0.075 mmol, 0.1 equiv.), TsOH (0.24 mmol, 3.2 equiv.), *N*-fluorobenzenesulfonimide (48 mg, 0.15 mmol, 2.0 equiv.), 1,2-dichloroethane (1.1 ml) and oxime substrate (34.5 mg, 0.075 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 6 hours under stirring. The vial was allowed to cool to room temperature. Pyridine (80 μL) and *N*-ethyldiisopropylamine (160 μL) was added, and the resulting mixture was directly loaded on a silica gel column and further purified with flash column chromatography (hexane/ethyl acetate/*N*-ethyldiisopropylamine = 5:1:0.12 to hexane/ethyl acetate/*N*-ethyldiisopropylamine = 3:2:0.1) to give the title tosyloxylated product as yellowish oil (30.5 mg, 65%) and the recycled starting material as colorless oil (5.3 mg, 15%). R_f = 0.1 (hexane/ethyl acetate/*N*-ethyldiisopropylamine = 3:1:0.1). IR (KBr) 2926, 2852, 1717, 1449, 1362, 1274, 1189, 1176 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.93 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.05 (d, *J* = 6.7 Hz, 1H), 7.97 (d,

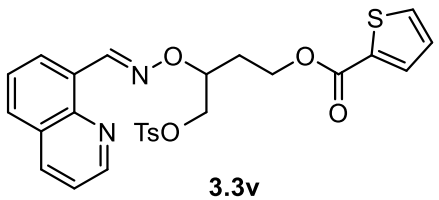
J = 8.2 Hz, 2H), 7.91 – 7.83 (m, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 4.60 (dq, *J* = 8.6, 4.2 Hz, 1H), 4.56 – 4.30 (m, 4H), 3.86 (s, 2H), 2.52 – 2.39 (m, 1H), 2.26 – 2.12 (m, 2H), 2.09 (s, 3H), 2.03 (br, 1H), 1.90 (d, *J* = 11.9 Hz, 2H), 1.76 – 1.68 (m, 2H), 1.60 (d, *J* = 10.0 Hz, 1H), 1.25 – 1.05 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.44, 150.18, 147.12, 146.13, 145.84, 144.81, 136.33, 132.72, 129.89, 129.85, 129.83, 129.61, 128.83, 128.18, 128.15, 126.36, 126.23, 121.61, 77.35, 70.34, 61.19, 56.19, 50.51, 33.43, 29.72, 26.20, 25.07, 21.41. HRMS: calcd. $[M+Na]^+$ 652.24520 Found: 652.24510.



3.3u

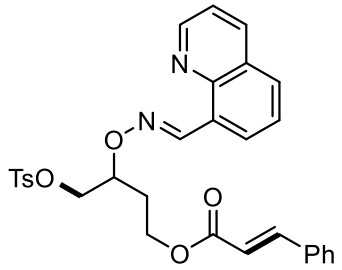
(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)-4-(tosyloxy)butyl 2-naphthoate (3.3u): Yellowish oil. Yield 62%. R_f = 0.2 (Hex/EA/DCM = 10:1:3). IR (KBr) 3070.12, 2968.82, 2924.25, 1716.83, 1601.35, 1498.03, 1368.37, 1289.36 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.93 (s, 1H), 8.59 (s, 1H), 8.15 (d, *J* = 8.1 Hz, 1H), 8.05 (dd, *J* = 13.7, 4.7 Hz, 2H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.84 (dd, *J* = 8.2, 3.2 Hz, 3H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.57 (t, *J* = 7.1 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.43 (dd, *J* = 8.2, 3.8 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 4.69 (dd, *J* = 7.9, 3.7 Hz, 1H), 4.60 – 4.50 (m, 2H), 4.40 (qd, *J* = 10.8, 4.2 Hz, 2H), 2.33 – 2.18 (m, 2H), 2.08 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.64, 150.10, 147.13, 145.54, 144.79, 136.49, 135.61, 132.75, 132.56, 131.17, 129.84, 129.80, 129.49, 129.43,

128.33, 128.31, 128.23, 128.13, 127.80, 127.42, 126.70, 126.38, 125.30, 122.86, 121.57, 77.59, 70.40, 61.46, 29.77, 21.36. HRMS: calcd. $[M+H]^+$ 569.17409 Found: 569.17360.



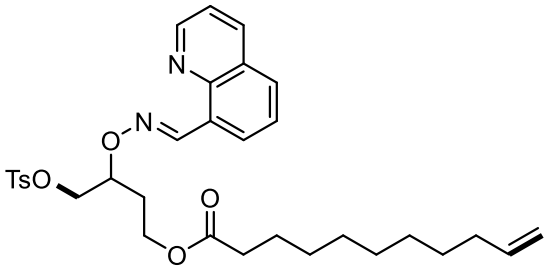
3.3v

(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)-4-(tosyloxy)butyl thiophene-2-carboxylate (3.3v): Yellowish oil. Yield 46%. R_f = 0.15 (Hex/EA/DCM = 10:1:3). IR (KBr) 3106.06, 3061.02, 2958.69, 2920.20, 1710.75, 1599.32, 1425.10, 1362.30, 1267.08 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.93 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.05 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.86 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.84 – 7.74 (m, 3H), 7.56 – 7.49 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.15 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.08 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.58 (td, *J* = 8.7, 4.5 Hz, 1H), 4.50 – 4.39 (m, 2H), 4.35 (qd, *J* = 10.7, 4.3 Hz, 2H), 2.23 (dd, *J* = 14.7, 5.8 Hz, 2H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.24, 150.28, 147.24, 145.93, 144.93, 136.44, 133.81, 133.74, 132.79, 132.68, 129.97, 129.93, 129.68, 128.42, 128.27, 127.98, 126.46, 126.33, 121.71, 77.39, 70.44, 61.52, 29.79, 21.51. HRMS: calcd. $[M+H]^+$ 525.11486 Found: 525.11530.



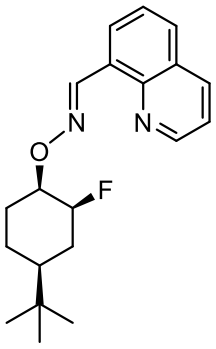
3.3w

3-(((*E*)-(quinolin-8-ylmethylene)amino)oxy)-4-(tosyloxy)butyl cinnamate (3.3w): The reaction was stopped at 4 hour. Colorless oil. Yield 63%. R_f = 0.1 (Hex/EA/DCM = 10:1:3). IR (KBr) 3062, 2960, 1710, 1633, 1493, 1360, 1175 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.92 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.07 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.86 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.82 – 7.76 (m, 2H), 7.68 (d, *J* = 16.0 Hz, 1H), 7.55 – 7.47 (m, 3H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.37 (dd, *J* = 4.1, 2.4 Hz, 3H), 7.21 – 7.14 (m, 2H), 6.43 (d, *J* = 16.0 Hz, 1H), 4.57 (dq, *J* = 8.7, 4.4 Hz, 1H), 4.49 – 4.30 (m, 4H), 2.27 – 2.02 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.90, 150.19, 147.10, 145.84, 145.10, 144.82, 136.33, 134.45, 132.72, 130.42, 129.86, 129.83, 129.61, 128.98, 128.33, 128.22, 128.18, 126.36, 126.22, 121.61, 117.99, 77.38, 70.34, 60.86, 29.66, 21.41. HRMS: calcd. $[M+Na]^+$ 567.15600 Found: 567.15600.



3.3x

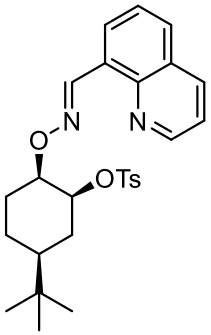
(*E*)-3-(((quinolin-8-ylmethylene)amino)oxy)-4-(tosyloxy)butyl undec-10-enoate (3.3x): *The reaction was stopped at 3 hour.* Colorless oil. Yield 49%. R_f = 0.2 (Hex/EA/DCM = 10:1:3). IR (KBr) 3076, 2930, 2853, 1741, 1601, 1493, 1493, 1366, 1192, 1179 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.94 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.06 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.87 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.82 – 7.72 (m, 2H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.23 – 7.11 (m, 2H), 5.79 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.04 – 4.83 (m, 2H), 4.50 (td, *J* = 8.7, 4.4 Hz, 1H), 4.35 – 4.16 (m, 4H), 2.28 (t, *J* = 7.6 Hz, 2H), 2.17 – 1.89 (m, 7H), 1.64 – 1.57 (m, 2H), 1.44 – 1.17 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.84, 150.21, 147.05, 145.85, 144.80, 139.32, 136.35, 132.74, 129.87, 129.82, 129.63, 128.35, 128.19, 126.37, 126.19, 121.63, 114.26, 77.27, 70.32, 60.52, 34.40, 33.91, 29.59, 29.41, 29.33, 29.26, 29.19, 29.00, 25.06, 21.42. HRMS: calcd. $[M+Na]^+$ 603.24990 Found: 603.24970.



3.3aa-F

(±)-(*E*)-quinoline-8-carbaldehyde *O*-((1*R*,2*S*,4*S*)-4-(*tert*-butyl)-2-fluorocyclohexyl) oxime (3.3aa-F): The crude material was determined to be a single diastereomer by LC-MS analysis and was isolated as a single diastereomer as determined by ^1H NMR analysis. The

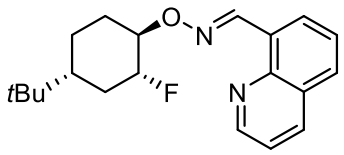
configuration of the titled compound is determined by NOE(1D) and 2D NMR studies, see *VII: NMR Spectrum (Part B).* Colorless oil. Yield 46%. R_f = 0.6 (Hex/EA/DCM = 10:1:3). IR (KBr) 3013.39, 2962.75, 2869.56, 1587.17, 1496.00, 1374.45, 1044.23, 1005.74 cm^{-1}. ^1H NMR (499 MHz, $CDCl_3$) δ 9.50 (s, 1H), 8.94 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.31 (dd, *J* = 7.3, 1.0 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.85 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.81 (d, *J* = 3.2 Hz, 1H), 4.62 (dddd, *J* = 46.4, 12.0, 4.7, 3.3 Hz, 1H), 2.33 (ddd, *J* = 14.1, 7.5, 3.3 Hz, 1H), 1.99 (s, 1H), 1.78 (qd, *J* = 12.1, 7.0 Hz, 1H), 1.54 – 1.31 (m, 3H), 1.16 (t, *J* = 12.2 Hz, 1H), 0.92 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.05, 146.35, 145.96, 136.38, 130.30, 129.49, 128.42, 126.52, 126.30, 121.48, 93.19 (d, *J* = 181.5 Hz), 78.75 (d, *J* = 15.4 Hz), 46.43 (d, *J* = 9.1 Hz), 32.64, 28.65 (d, *J* = 6.2 Hz), 28.43 (d, *J* = 17.8 Hz), 27.76, 20.16. ^{19}F NMR (376 MHz, $CDCl_3$) δ -179.30 – -179.64 (m, 1F). HRMS: calcd. $[M+H]^+$ 329.20237 Found: 329.20270.



3.3aa-OTs

(±)-(1*S*,2*R*,5*S*)-5-(*tert*-butyl)-2-(((*E*)-(quinolin-8-ylmethylene)amino)oxy)cyclohexyl 4-methylbenzenesulfonate (3.3aa-OTs): The crude material was determined to be a 12:1 mixture of diastereomers by LC-MS analysis and was

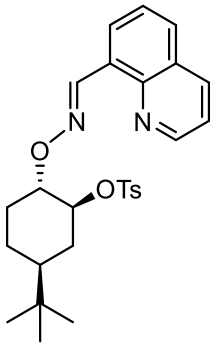
isolated as a > 20:1 mixture of diastereomers as determined by ^{1}H NMR analysis. The configuration of the titled compound is determined by NOE(1D) and 2D NMR studies, see *VII: NMR Spectrum (Part B).* Colorless oil. Yield 14%. R_f = 0.35 (Hex/EA/DCM = 10:1:3). IR (KBr) 3039.73, 2962.75, 2867.53, 1741.14, 1601.35, 1498.03, 1370.40, 1181.9 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6) δ 9.86 (s, 1H), 8.58 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.34 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.42 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.30 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 6.70 (dd, *J* = 8.3, 4.1 Hz, 1H), 6.65 – 6.59 (m, 2H), 4.99 – 4.79 (m, 2H), 2.23 (ddd, *J* = 14.2, 6.5, 3.5 Hz, 1H), 1.94 (dd, *J* = 13.2, 8.9 Hz, 2H), 1.63 (s, 3H), 1.31 – 1.21 (m, 1H), 1.14 (dd, *J* = 13.0, 3.2 Hz, 1H), 1.08 – 1.00 (m, 1H), 0.89 – 0.82 (m, 1H), 0.69 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 150.00, 146.37, 146.29, 143.61, 136.46, 135.77, 130.90, 129.64, 129.33, 128.57, 126.40, 126.16, 121.35, 82.29, 78.58, 46.70, 32.39, 29.20, 29.11, 27.46, 20.97, 19.99. HRMS: calcd. $[M+Na]^+$ 481.21556 Found: 481.21500.



3.3ab-F

(±)-(*E*)-quinoline-8-carbaldehyde *O*-((1*R*,2*R*,4*R*)-4-(*tert*-butyl)-2-fluorocyclohexyl) oxime (3.3ab-F): The crude material was determined to be a single diastereomer by LC-MS analysis and was isolated as a single diastereomer as determined by ^{1}H NMR analysis. The configuration of the titled compound is determined by NOE(1D) and 2D NMR studies, see *VII: NMR Spectrum (Part B).* Colorless oil. Yield 16%. R_f = 0.6 (Hex/EA/DCM = 10:1:3). IR (KBr) 3041.76, 2956.67, 2869.56, 1591.22, 1498.03, 1370.40,

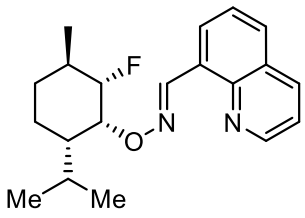
1066.52, 1040.18 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.92 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.27 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.85 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.64 (dddd, *J* = 51.2, 11.2, 9.0, 5.2 Hz, 1H), 4.29 (tdd, *J* = 11.6, 9.0, 5.2 Hz, 1H), 2.38 – 2.21 (m, 2H), 1.83 – 1.75 (m, 1H), 1.49 – 1.31 (m, 2H), 1.22 – 1.07 (m, 2H), 0.91 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 150.06, 146.45, 146.41, 135.75, 131.22, 129.30, 128.48, 126.40, 126.12, 121.33, 93.26 (d, *J* = 179.7 Hz), 85.02 (d, *J* = 16.6 Hz), 45.69 (d, *J* = 8.9 Hz), 33.04 (d, *J* = 17.5 Hz), 32.02, 30.01 (d, *J* = 7.2 Hz), 27.53, 24.93. ^{19}F NMR (376 MHz, c_6d_6) δ -178.57 (d, *J* = 51.1 Hz, 1F). HRMS: calcd. $[M+Na]^+$ 351.18431 Found: 351.18440.



3.3ab-OTs

(±)-(1*S*,2*S*,5*S*)-5-(*tert*-butyl)-2-(((*E*)-(quinolin-8-ylmethylene)amino)oxy)cyclohexyl 4-methylbenzenesulfonate (3.3ab-OTs): The crude material was determined to be a 7:1 mixture of diastereomers by LC-MS analysis and was isolated as a 9:1 mixture of diastereomers as determined by ^{1}H NMR analysis. The configuration of the titled compound is determined by NOE(1D) and 2D NMR studies, see *VII: NMR Spectrum (Part B).* Colorless oil. Yield 28%. R_f = 0.4 (Hex/EA/DCM = 10:1:3). IR

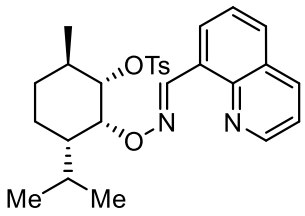
(KBr) 3041.76, 2962.75, 2865.50, 1597.30, 1496.00, 1364.32, 1177.94, 1068.54 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6) δ 9.42 (s, 0.1H), 9.30 (s, 0.9H), 8.62 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.31 (dd, *J* = 7.3, 1.4 Hz, 0.9H), 8.24 – 8.20 (m, 0.1H), 7.98 (d, *J* = 8.3 Hz, 1.8H), 7.92 (d, *J* = 8.3 Hz, 0.2H), 7.47 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.31 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.79 (s, 1H), 6.71 (d, *J* = 7.9 Hz, 1.8H), 6.57 (d, *J* = 8.0 Hz, 0.2H), 5.35 (s, 0.1H), 4.89 (ddd, *J* = 11.4, 9.5, 5.1 Hz, 0.9H), 4.25 (ddd, *J* = 11.3, 9.2, 4.9 Hz, 0.9H), 3.99 (ddd, *J* = 12.4, 4.7, 2.8 Hz, 0.1H), 2.60 (ddt, *J* = 12.4, 5.3, 2.7 Hz, 1H), 2.19 – 2.06 (m, 1H), 1.64 (s, 2.7H), 1.56 (s, 0.3H), 1.40 – 1.26 (m, 3H), 0.91 (ddt, *J* = 18.1, 12.2, 3.0 Hz, 1H), 0.75 (s, 1H), 0.67 (s, 9H). ^{13}C NMR (151 MHz, C_6D_6) (for major isomer) δ 149.94, 146.18, 145.77, 143.61, 135.95, 135.84, 130.88, 129.57, 129.31, 128.50, 128.35, 126.48, 126.05, 121.36, 83.61, 83.22, 46.19, 34.42, 32.08, 30.68, 27.48, 24.80, 20.98. HRMS: calcd. $[M+Na]^+$ 503.19750 Found: 503.19780.



3.3ac-F

(*E*)-quinoline-8-carbaldehyde *O*-((1*R*,2*S*,3*R*,6*S*)-2-fluoro-6-isopropyl-3-methylcyclohexyl) oxime (3.3ac-F): 3.2 equiv. TsOH was used and the reaction was stopped at 4 h. The titled compound was isolated as a single diastereomer as determined by ^{1}H NMR analysis (*along with trace amount (<5%) of another unknown fluorinated product which was not the diastereomer of the titled compound based on ^{1}H and ^{19}F NMR analysis*). Colorless

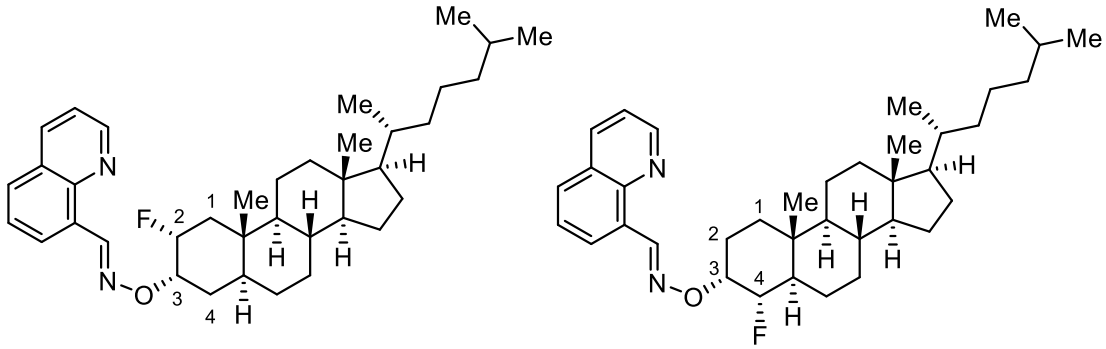
oil. Yield 35%. R_f = 0.4 (Hexane:Ethyl acetate = 25:1). IR (KBr) 2954, 2927, 2870, 1735, 1587, 1496, 1458, 1387 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 10.02 (s, 1H), 8.61 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.49 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.42 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.26 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.10 (t, *J* = 7.7 Hz, 1H), 6.70 (dd, *J* = 8.3, 4.1 Hz, 1H), 5.24 – 5.18 (m, 1H), 3.86 (ddd, *J* = 47.2, 10.9, 2.8 Hz, 1H), 2.22 (tdd, *J* = 10.9, 6.6, 4.3 Hz, 1H), 1.82 (ddt, *J* = 13.4, 9.0, 6.7 Hz, 1H), 1.60 – 1.50 (m, 1H), 1.43 – 1.34 (m, 2H), 1.08 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.83 – 0.74 (m, 1H), 0.74 – 0.62 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ carbon signals were found at 149.92, 145.90, 144.93, 136.39, 130.37, 129.24, 128.39, 126.56, 126.25, 121.40, 99.92, 98.10, 81.28, 81.12, 47.91, 47.86, 32.47, 32.38, 32.14, 31.96, 28.73, 24.26, 21.27, 21.11, 17.95, 17.92. ^{19}F NMR (376 MHz, $CDCl_3$) δ -167.44 – -167.89 (m, 1F). HRMS: calcd. $[M+Na]^+$ 351.18430 Found: 351.18450.



3.3ac-OTs

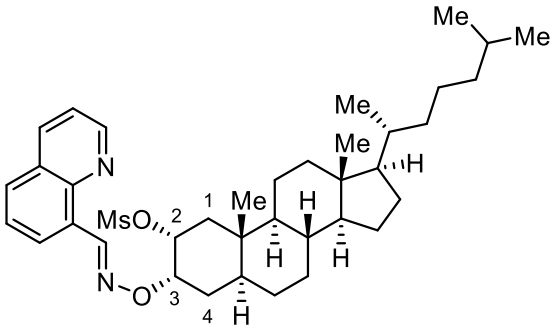
(1*S*,2*R*,3*S*,6*R*)-3-isopropyl-6-methyl-2-(((*E*)-(quinolin-8-ylmethylene)amino)oxy)cyclohexyl 4-methylbenzenesulfonate (3.3ac-OTs): 3.2 equiv. TsOH was used and the reaction was stopped at 4 h. The titled compound was isolated as a single diastereomer as determined by 1D and 2D NMR analysis. Colorless oil. Yield 21%. R_f = 0.1 (Hexane:Ethyl acetate = 25:1). IR (KBr) 2957, 2928, 1496, 1458, 1364, 1188, 1176, 1097 cm^{-1}. ^1H NMR (500 MHz, C_6D_6) δ 9.89 (s, 1H), 8.58 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.49 (dd,

J = 7.3, 1.3 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.44 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.32 (dd, *J* = 5.5, 2.6 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 6.70 (dd, *J* = 8.3, 4.1 Hz, 1H), 6.59 (dd, *J* = 8.6, 0.7 Hz, 2H), 5.32 (s, 1H), 4.46 (dd, *J* = 11.2, 2.6 Hz, 1H), 2.19 – 2.07 (m, 1H), 1.84 – 1.67 (m, 4H), 1.56 – 1.50 (m, 1H), 1.42 – 1.29 (m, 2H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.90 – 0.85 (m, 1H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.78 – 0.68 (m, 1H). ^{13}C NMR (101 MHz, C_6D_6) δ 149.90, 146.33, 145.28, 143.56, 136.06, 135.77, 131.07, 129.45, 129.12, 128.18, 127.94, 126.60, 126.40, 121.27, 88.21, 81.87, 48.10, 33.14, 31.85, 29.07, 24.12, 21.16, 21.07, 21.02, 18.66. HRMS: calcd. $[M+Na]^+$ 503.19750 Found: 503.19790.

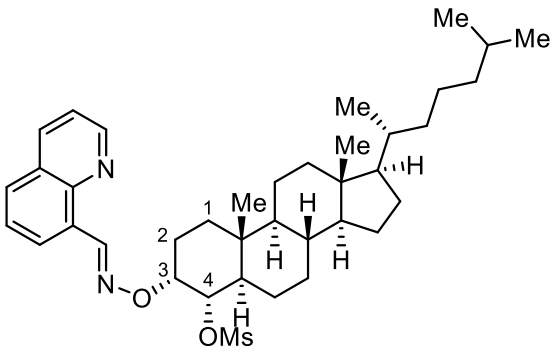


2-F-3.3ad and 4-F-3.3ad: 2.6 equiv. MsOH was used and the reaction was stopped at 8.5 h. The titled compounds were isolated as an inseparable mixture with a ratio of 3:1. The stereochemistry was determined by 1D and 2D NMR analysis. Colorless oil. Yield 50%. R_f = 0.5 (Hexane:Ethyl acetate = 10:1). IR (KBr) 2932, 2866, 1496, 1466, 1381, 1047, 1009, 996 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6) δ 10.11 (m, *J* = 4.0 Hz, 1H), 8.58 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.49 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.42 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.29 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.13 (dd, *J* = 7.8, 3.1 Hz, 1H), 6.70 (dd, *J* = 8.3, 4.1 Hz, 1H), 5.09 – 4.95 (m, 1H), 4.60 (dddd,

J = 45.68, 11.99, 4.97, 3.58 Hz, 0.75H), 4.31 (ddd, *J* = 46.8, 11.6, 3.3 Hz, 0.25H), 1.03 (d, 3H), 0.95 (d, 3H), 0.93 (d, 3H), 0.66 (d, 3H), 0.62 (d, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ carbon signals were found at 149.98, 146.39, 146.36, 135.77, 131.11, 131.07, 129.29, 126.43, 126.13, 121.31, 93.09, 91.28, 90.88, 89.08, 80.09, 79.94, 79.79, 56.75, 56.48, 56.36, 54.14, 46.57, 46.33, 45.27, 45.11, 44.83, 42.92, 42.81, 40.26, 40.21, 39.97, 39.60, 39.43, 39.08, 38.59, 38.25, 37.87, 37.80, 37.42, 37.32, 36.71, 36.32, 36.25, 35.64, 35.56, 35.35, 34.88, 32.74, 32.68, 32.02, 31.93, 31.39, 30.25, 29.13, 28.72, 28.45, 27.85, 25.37, 24.51, 24.48, 24.40, 23.09, 22.84, 22.71, 22.67, 21.68, 21.36, 21.20, 19.05, 12.76, 12.74, 12.38. ^{19}F NMR (376 MHz, C_6D_6) δ -185.66 – -186.18 (m, 0.75 F), -196.07 (dd, *J* = 46.9, 5.4 Hz, 0.25F). HRMS: calcd. $[M+Na]^+$ 583.40340 Found: 583.40350.



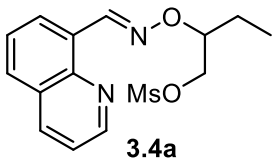
2-OMs-3.3ad



4-OMs-3.3ad

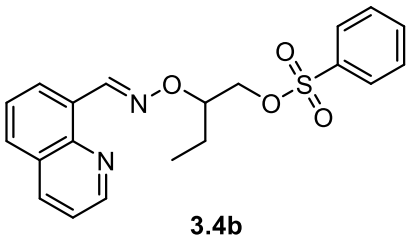
2-OMs-3.3ad and 4-OMs-3.3ad: The titled compounds were isolated as an inseparable mixture with a ratio of 1.5:1. The stereochemistry was determined by 1D and 2D NMR analysis. Colorless oil. Yield 15%. R_f = 0.2 (Hexane:Ethyl acetate = 10:1). IR (KBr) 2928, 2866, 1466, 1458, 1355, 1176, 1047, 1018 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6) δ 10.10 (s, 1H), 8.59 (td, *J* = 4.0, 1.8 Hz, 1H), 8.44 (d, *J* = 7.3 Hz, 1H), 7.42 (ddd, *J* = 8.3, 5.2, 1.8 Hz,

1H), 7.30 (ddd, *J* = 8.1, 4.7, 1.3 Hz, 1H), 7.13 (dd, *J* = 8.6, 4.4 Hz, 1H), 6.69 (dt, *J* = 8.3, 4.2 Hz, 1H), 5.18 (dd, *J* = 5.5, 3.0 Hz, 0.4H), 5.15 – 5.05 (m, 1.2H), 4.88 (dd, *J* = 11.7, 3.2 Hz, 0.4H), 2.41 (d, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.64 (d, Hz, 6H), 0.30 (s, 3H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 150.16, 146.39, 146.31, 145.93, 145.92, 136.48, 136.45, 130.07, 130.04, 129.71, 129.68, 128.48, 126.54, 126.14, 126.10, 121.61, 121.59, 82.87, 79.64, 79.45, 79.22, 56.53, 56.44, 56.34, 56.33, 54.33, 54.23, 44.28, 42.74, 42.63, 40.04, 39.98, 39.67, 39.62, 39.45, 38.55, 38.41, 37.73, 36.32, 35.96, 35.16, 34.88, 32.80, 31.84, 31.53, 31.26, 29.86, 28.39, 28.17, 27.56, 25.64, 24.34, 24.29, 24.00, 22.99, 22.72, 21.19, 21.03, 18.82, 18.81, 14.28, 12.89, 12.76, 12.24. HRMS: calcd. $[M+Na]^+$ 659.38530 Found: 659.38550.



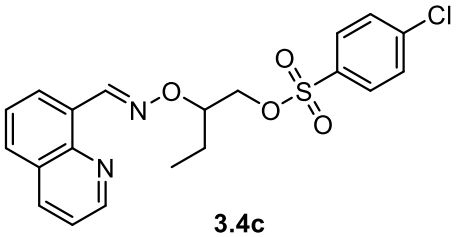
3.4a

2-(((Quinolin-8-ylmethylene)amino)oxy)butyl methanesulfonate (3.4a): Yellowish oil. Yield 74 %. R_f = 0.2 (Hex/EA/DCM = 10:1:3). IR (KBr) 2972.13, 2932.08, 1590.94, 1494.58, 1358.68, 1178.31, 958.41 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.93 – 8.90 (m, 1H), 8.26 (d, *J* = 7.3 Hz, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.44 (dd, *J* = 7.8, 3.7 Hz, 1H), 4.54 – 4.38 (m, 3H), 3.04 (s, 3H), 1.91 – 1.73 (m, 2H), 1.06 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.19, 147.08, 145.93, 136.38, 129.90, 129.80, 128.39, 126.46, 126.31, 121.61, 81.96, 70.20, 37.72, 23.46, 9.84. HRMS: calcd. $[M+H]^+$ 323.10601 Found: 323.10610.



3.4b

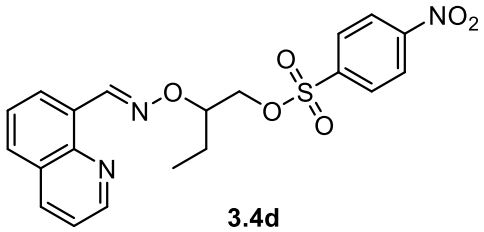
(*E*)-2-(((quinolin-8-ylmethylene)amino)oxy)butyl benzenesulfonate (3.4b): Yellowish oil. Yield 66 %. R_f = 0.4 (Hex/EA/DCM = 10:1:3). IR (KBr) 3072.35, 2972.13, 2937.05, 1588.87, 1499.52, 1452.57, 1195.61, 958.41 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.93 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.09 (d, *J* = 7.3 Hz, 1H), 7.96 – 7.88 (m, 2H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.49 – 7.35 (m, 4H), 4.30 (s, 3H), 1.81 – 1.67 (m, 2H), 0.98 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.10, 146.64, 145.80, 136.37, 135.91, 133.68, 129.81, 129.72, 129.18, 128.32, 128.06, 126.38, 126.22, 121.56, 81.56, 70.43, 23.37, 9.76. HRMS: calcd. $[M+H]^+$ 385.12166 Found: 385.12180.



3.4c

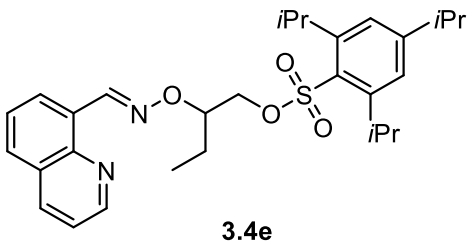
(*E*)-2-(((quinolin-8-ylmethylene)amino)oxy)butyl 4-chlorobenzenesulfonate (3.4c): Yellowish oil. Yield 67 %. R_f = 0.4 (Hex/EA/DCM = 10:1:3). IR (KBr) 2967.19, 2878.24, 1588.47, 1497.05, 1366.09, 1185.72, 955.94 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ

9.23 (s, 1H), 8.95 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.06 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.88 – 7.79 (m, 3H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.37 – 7.30 (m, 2H), 4.37 – 4.24 (m, 3H), 1.84 – 1.66 (m, 2H), 1.00 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.18, 146.67, 145.78, 140.34, 136.41, 134.43, 129.85, 129.63, 129.53, 129.49, 128.41, 126.38, 126.09, 121.60, 81.52, 70.71, 23.30, 9.84. HRMS: calcd. $[M+H]^+$ 419.08269 Found: 419.08280.



3.4d

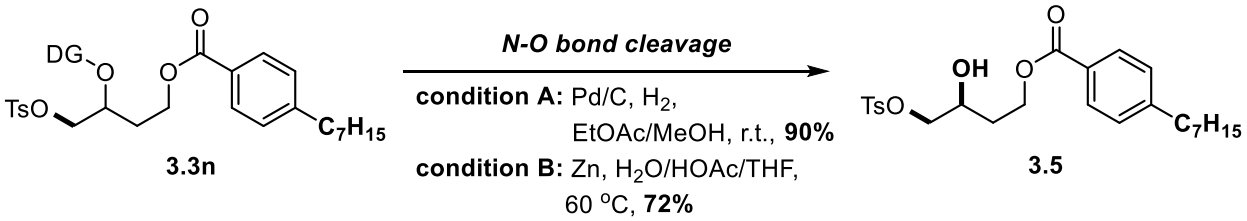
(*E*)-2-(((quinolin-8-ylmethylene)amino)oxy)butyl 4-nitrobenzenesulfonate (3.4d): Yellowish oil. Yield 64%. R_f = 0.3 (Hex/EA/DCM = 10:1:3). IR (KBr) 3108.61, 3066.07, 2974.90, 2934.38, 1690.49, 1607.43, 1534.50, 1504.11, 1350.14 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.98 – 8.90 (m, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 8.15 – 8.08 (m, 2H), 8.06 (ddd, *J* = 6.8, 2.7, 1.3 Hz, 2H), 8.00 (d, *J* = 7.3 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.54 – 7.43 (m, 2H), 4.51 – 4.44 (m, 1H), 4.42 – 4.34 (m, 1H), 4.33 – 4.25 (m, 1H), 1.85 – 1.65 (m, 2H), 1.01 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.38, 150.32, 146.43, 145.47, 141.82, 136.50, 130.12, 129.43, 129.21, 128.39, 126.23, 125.78, 124.22, 121.78, 81.49, 71.62, 23.15, 9.90. HRMS: calcd. $[M+H]^+$ 430.10674 Found: 430.10660.



3.4e

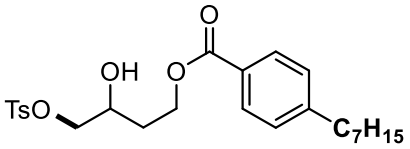
(*E*)-2-(((quinolin-8-ylmethylene)amino)oxy)butyl 2,4,6-triisopropylbenzenesulfonate (3.4e): Yellowish oil. Yield 56%. R_f = 0.2 (Hex/EA/DCM = 10:1:3). IR (KBr) 2964.77, 2867.53, 1595.27, 1461.56, 1350.14, 1177.94, 961.17 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.91 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.22 – 8.10 (m, 2H), 7.84 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.15 (s, 2H), 4.42 – 4.27 (m, 3H), 4.19 (dt, *J* = 13.5, 6.7 Hz, 2H), 2.81 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.85 – 1.74 (m, 2H), 1.27 (dd, *J* = 6.7, 1.8 Hz, 12H), 1.17 (dd, *J* = 6.9, 2.7 Hz, 6H), 1.03 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.66, 150.96, 150.10, 146.65, 145.93, 136.29, 130.01, 129.66, 129.51, 128.33, 126.38, 126.24, 123.79, 121.52, 81.82, 68.97, 34.25, 29.77, 24.91, 24.87, 23.68, 23.58, 23.56, 9.77. HRMS: calcd. $[M+H]^+$ 511.26251 Found: 511.26290.

Removal of the directing group



Condition A: An EtOAc (2.1 mL)/MeOH (0.35 mL) suspension of Pd/C (10% w/w) (150 mg) and **3.3n** (30 mg, 0.049 mmol, 1.0 equiv.) was stirred under a hydrogen atmosphere (balloon pressure) and monitored by TLC. After 2.5 hours, the mixture was filtered through a small plug of Celite to remove the precipitate and washed with dichloromethane. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane: ethyl acetate: DCM = 10:1:3) to give the desired product **5** as colorless oil (20.2 mg, 90%).

Condition B: The following procedure is a modified procedure of known literature[2]. To a solution of **3.3n** (40 mg, 0.065 mmol, 1 equiv) in 1 mL AcOH-THF-Water (3:1:1), Zinc powder (35 mg, 0.65 mmol, 10 equiv) was added in one portion at room temperature. Then the mixture was stirred at 60 ^{o}C and monitored by TLC. After 2.5 hours, the mixture was filtered through a small plug of silica gel to remove the precipitate and washed with dichloromethane. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane: ethyl acetate: DCM = 10:1:3) to give the desired product **5** as colorless oil (21.6 mg, 72%).

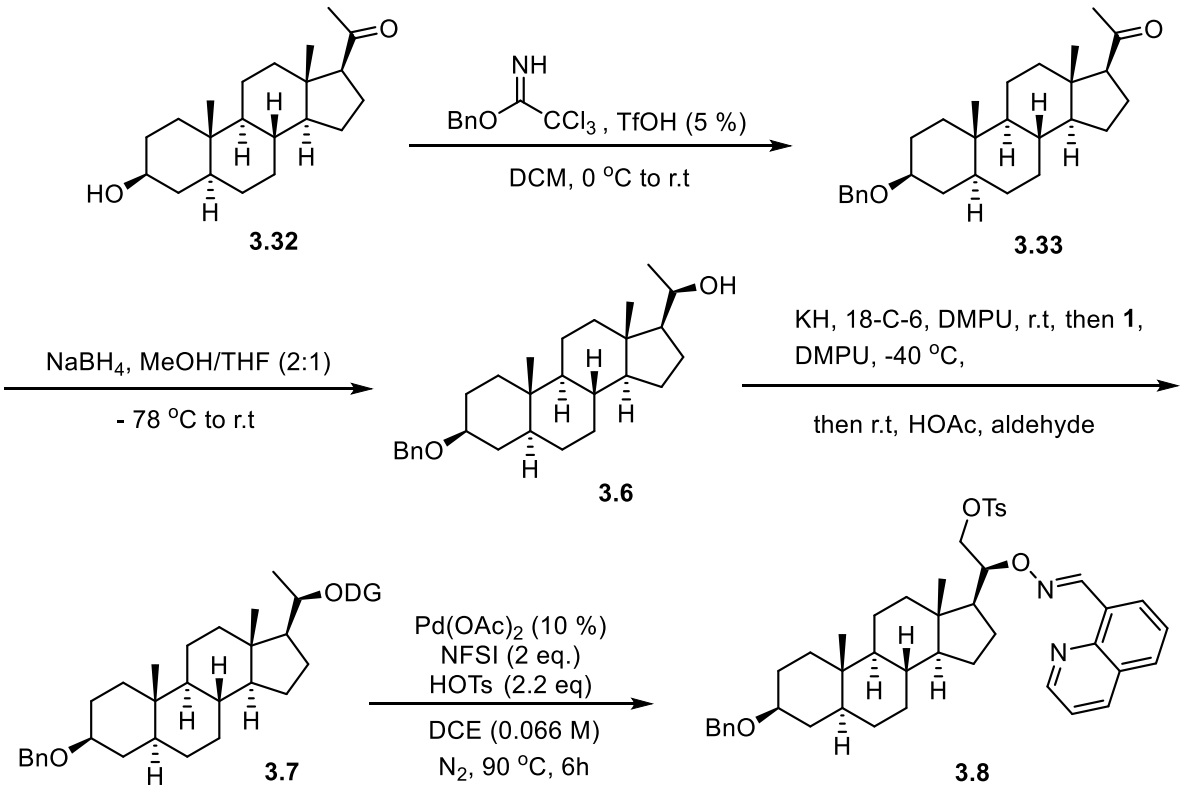


3.5

3-Hydroxy-4-(tosyloxy)butyl 4-heptylbenzoate (3.5): Colorless oil. R_f = 0.1 (Hex/EA/DCM = 10:1:3). IR (KBr) 3499.77, 2965.81, 2923.65, 2856.21, 1712.41, 1614.05,

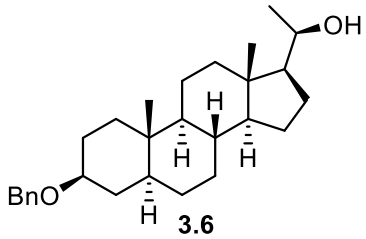
1366.74, 1279.63, 1181.26 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.86 (m, 2H), 7.82 – 7.72 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 4.52 (ddd, *J* = 11.3, 9.0, 4.6 Hz, 1H), 4.47 – 4.32 (m, 1H), 4.13 – 3.92 (m, 3H), 2.71 – 2.61 (m, 2H), 2.56 (d, *J* = 4.2 Hz, 1H), 2.44 (s, 3H), 1.97 – 1.89 (m, 1H), 1.87 – 1.77 (m, 1H), 1.62 (dt, *J* = 14.9, 7.4 Hz, 2H), 1.32 – 1.24 (m, 8H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.99, 149.06, 145.27, 132.72, 130.11, 129.81, 128.66, 128.13, 127.40, 73.65, 66.66, 60.92, 36.18, 32.40, 31.92, 31.30, 29.35, 29.27, 22.79, 21.81, 14.23. HRMS: calcd. $[M+Na]^+$ 485.19683 Found: 485.19700.

Late-stage functionalization of steroids and removal of the directing group



1-((3*S*,5*S*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-(benzyloxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)ethanone (3.33): 3.32 was prepared from commercial available 3*β*-hydroxypregn-5-en-20-one (*Pregnenolone*) according to known literature[48]. To a DCM (55 mL) solution of **3.32** (3.18 g, 10 mmol, 1.0 equiv.) was added a DCM (6 mL) solution of benzyl 2,2,2-trichloroacetimidate (5.06g, 20 mmol, 2.0 equiv.). After cooling to 0 °C, a DCM (2 mL) solution of TfOH (75 mg, 0.5 mmol, 0.05 equiv.) was slowly added into the mixture. The reaction mixture was stirred at 0 °C for 20 minutes. Then, the reaction was allowed to warm to room temperature and stirred for 4 hours. The reaction was cool to 0 °C for again, and then diluted with buffer solution (pH = 7), extracted with DCM and washed

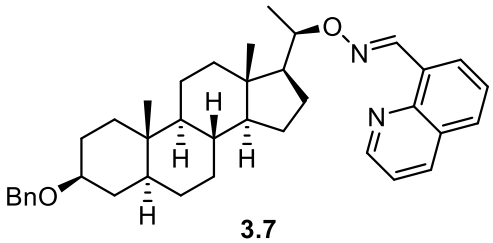
with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Toluene:EA = 30:1) to give the title compounds as a white solid (2.72 g, 66%). m.p.= 149-153 °C. R_f = 0.3 (Hex/EA= 10:1). IR (KBr) 3033.30, 2934.38, 2849.30, 1704.67, 1449.41, 1354.19, 1096.90 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 4H), 7.29 – 7.26 (m, 1H), 4.55 (d, *J* = 2.1 Hz, 2H), 3.34 (tt, *J* = 11.1, 4.7 Hz, 1H), 2.51 (t, *J* = 9.0 Hz, 1H), 2.11 (s, 3H), 0.81 (s, 3H), 0.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.83, 139.32, 128.46, 127.68, 127.49, 78.06, 69.93, 64.01, 56.87, 54.44, 45.00, 44.42, 39.25, 37.18, 36.00, 35.63, 34.93, 32.20, 31.66, 28.88, 28.41, 24.56, 22.94, 21.38, 13.60, 12.44. HRMS: calcd. $[M+H]^+$ 409.31011 Found: 409.31010.



3.6

(1*R*)-1-((3*S*,5*S*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-(benzyloxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)ethanol (3.6): To a MeOH (12 mL)/THF (6 mL) solution of **3.33** (125 mg, 0.3 mmol, 1.0 equiv.) was added $NaBH_4$ (46 mg, 0.9 mmol, 3.0 equiv.) at -78 °C. Then, the reaction was allowed to slowly warm to room temperature and stirred for 13 hours. The reaction was diluted with water, extracted with DCM and washed with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column

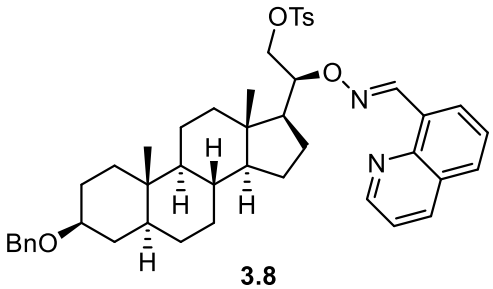
chromatography on silica gel (Hexane:EA = 10:1) to give the title compounds as a white solid (83 mg, 66%). m.p.= 110.5-112 °C. R_f = 0.65 (Hex/EA= 3:1). IR (KBr) 3398.31, 2932.36, 2962.75, 2853.35, 1453.46, 1374.45, 1098.93 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 4H), 7.29 – 7.26 (m, 1H), 4.55 (d, *J* = 1.2 Hz, 2H), 3.76 – 3.67 (m, 1H), 3.33 (ddd, *J* = 15.8, 11.1, 4.7 Hz, 1H), 2.02 (dt, *J* = 12.2, 3.1 Hz, 1H), 1.91 (d, *J* = 12.7 Hz, 1H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.82 (s, 3H), 0.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.33, 128.45, 127.67, 127.45, 78.14, 70.71, 69.91, 58.73, 56.10, 54.53, 45.01, 42.66, 40.29, 37.15, 35.98, 35.47, 34.98, 32.29, 28.96, 28.41, 25.78, 24.60, 23.74, 21.25, 12.74, 12.45. HRMS: calcd. $[M+H]^+$ 411.32576 Found: 411.32440.



3.7

(*E*)-quinoline-8-carbaldehyde *O*-((1*R*)-1-((3*S*,5*S*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-(benzyloxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)ethyl) oxime (3.7): The following procedure is according to **General procedure C.** To a suspension of KH (240 mg, 1.5 equiv.) and 18-crown-6 (105mg, 0.1 equiv.) in DMPU (12 mL) was added alcohol **3.6** (1.62 g, 3.9 mmol, 1.0 equiv.) under N_2 atmosphere at room temperature. After stirring at room temperature for 1h and no gas evolution was observed, the resulting solution was slowly added into a DMPU solution (6 mL) of 3,3'-di-tert-butyl oxziridine **3.1** (1.53 g, 2.5 equiv.) at -40 °C (*3,3'-di-tert-butyl oxziridine was prepared*

according to the reported literature[1]). Upon done, the reaction was warmed to room temperature and stirred for another 1.5 h. 0.3 mL HOAc were added in, followed by the addition of quinoline-8-carbaldehyde (800 mg, 1.3 equiv). The mixture was stirred for 0.5 h, and then diluted with 1M NaOH, extracted with EtOAc and washed with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane:EA = 20:1) to give the title compounds as a white solid (1.53 g, 70%). m.p.= 66-70 °C. R_f = 0.3 (Hex/EA= 10:1). IR (KBr) 2934.38, 2863.52, 1593.25, 1498.03, 1368.37, 1100.96, 965.22 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.93 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.30 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.83 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.38 – 7.28 (m, 4H), 7.27 – 7.23 (m, 1H), 4.55 (d, *J* = 1.5 Hz, 2H), 4.32 (dq, *J* = 12.2, 6.1 Hz, 1H), 3.34 (td, *J* = 11.1, 5.5 Hz, 1H), 2.18 – 2.12 (m, 1H), 1.90 (d, *J* = 12.4 Hz, 1H), 1.30 (d, *J* = 6.1 Hz, 3H), 0.80 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.98, 145.93, 144.73, 139.37, 136.34, 130.85, 129.14, 128.45, 128.43, 127.70, 127.46, 126.52, 125.97, 121.43, 82.11, 78.21, 69.91, 56.13, 55.25, 54.69, 45.05, 42.86, 39.73, 37.15, 36.01, 35.59, 35.02, 32.40, 29.03, 28.44, 25.91, 24.67, 21.30, 20.26, 12.86, 12.45. HRMS: calcd. $[M+H]^+$ 565.37886 Found: 565.37870.



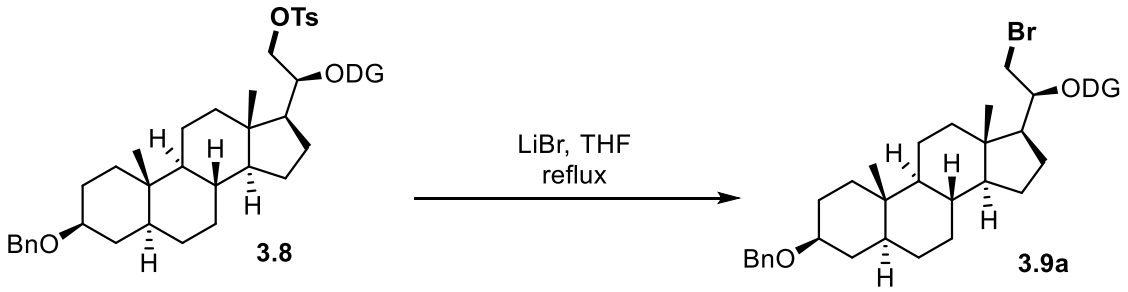
3.8

(2*S*)-2-((3*S*,5*S*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-(benzyloxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-(((*E*)-(quinolin-8-ylmethylene)amino)oxy)ethyl 4-methylbenzenesulfonate (3.8): A 4 mL vial was charged with $Pd(OAc)_2$ (3.5 mg, 0.015 mmol, 0.1 equiv.), TsOH (56.8 mg, 0.33 mmol, 2.2 equiv.), *N*-fluorobenzenesulfonimide (95 mg, 0.3 mmol, 2.0 equiv.), 1,2-dichloroethane (2.2 ml) and oxime substrate **3.7** (84.7 mg, 0.15 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 6 hours under stirring. The vial was allowed to cool to room temperature. Na_2CO_3 (150 mg) and 1,10-phenanthroline (5.1 mg) was then added in to quench the reaction, and the mixture was further stirred at room temperature for 36 h. The mixture was filtered through a small plug of Celite to remove the precipitate and washed with dichloromethane. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane/ethyl acetate/DCM = 10:1:3) to give the title product **3.8** as yellowish solid (66.6 mg, 60%). m.p.= 73-77 °C. R_f = 0.3 (Hex/EA/DCM = 10:1:3). IR (KBr) 3036.77, 2932.36, 2853.35, 1607.43, 1500.06, 1451.44, 1362.30, 1179.60 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, *J* = 11.3 Hz, 1H), 8.99 – 8.92 (m, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.02 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.85 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.79 – 7.66 (m, 2H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 8.3,

4.2 Hz, 1H), 7.41 – 7.28 (m, 4H), 7.28 – 7.23 (m, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 4.55 (d, *J* = 1.9 Hz, 2H), 4.41 (dd, *J* = 10.7, 2.2 Hz, 1H), 4.30 – 4.23 (m, 1H), 4.18 (dd, *J* = 10.7, 3.6 Hz, 1H), 3.32 (td, *J* = 11.1, 5.5 Hz, 1H), 2.03 (dd, *J* = 10.0, 7.2 Hz, 1H), 1.87 (s, 3H), 0.78 (s, 3H), 0.71 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.06, 145.69, 145.56, 144.41, 139.29, 136.33, 132.66, 129.94, 129.57, 129.50, 128.40, 128.33, 128.16, 127.63, 127.41, 126.34, 125.87, 121.52, 82.83, 78.09, 70.58, 69.86, 55.70, 54.50, 48.60, 44.90, 42.80, 39.37, 37.05, 35.90, 35.54, 34.92, 32.24, 28.90, 28.37, 24.86, 24.58, 21.17, 21.13, 12.65, 12.37. HRMS: calcd. $[M+H]^+$ 735.38262 Found: 735.38160.

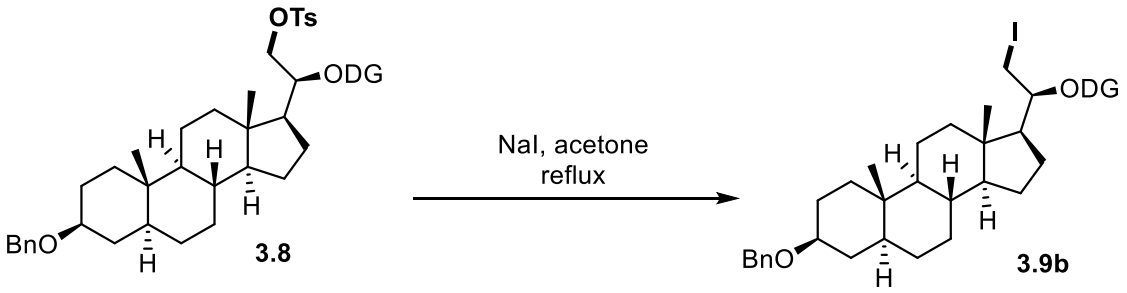
Gram scale preparation of 3.8

A 40 mL vial was charged with $Pd(OAc)_2$ (42 mg, 0.1 equiv.), TsOH (0.68g, 2.2 equiv.), *N*-Fluorobenzenesulfonimide (1.14 g, 2.0 equiv.), 1,2-dichloroethane (26 ml) and substrate **3.7 (**1.02 g, 1.8 mmol, 1.0 equiv.). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 6 hours under stirring. The vial was allowed to cool to room temperature. Na_2CO_3 (1.8 g) and 1,10-phenanthroline (65 mg) was then added in to quench the reaction, and the mixture was further stirred at room temperature for 36 h. The mixture was filtered through a small plug of Celite to remove the precipitate and washed with dichloromethane. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane: ethyl acetate: DCM = 10:1:3) to give the tosyloxylated product **8** as a yellowish solid (0.758 g, 58%).



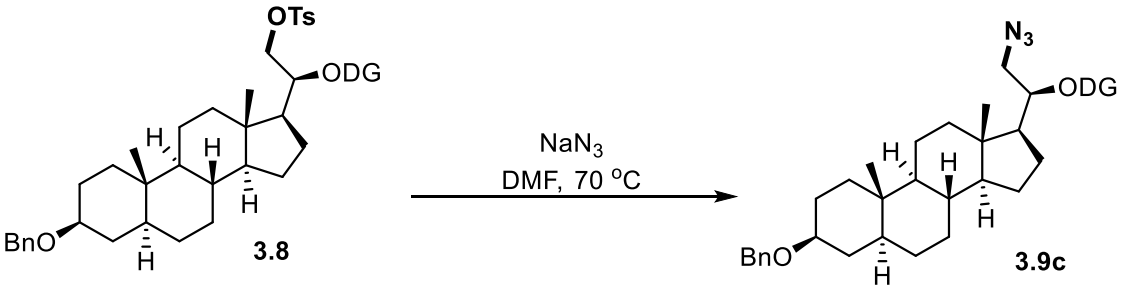
(*E*)-quinoline-8-carbaldehyde *O*-((1*S*)-1-((3*S*,5*S*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-(benzyloxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-bromoethyl) oxime (3.9a): A 4 mL vial was charged with **3.8** (37 mg, 0.05 mmol, 1 equiv.), LiBr (18 mg, 4 equiv.) and THF **(**0.5 mL). The vial was sealed with a PTFE lined cap and heated to reflux for 72 hours. Then, the vial was allowed to cool to room temperature. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane: ethyl acetate: DCM = 10:1:3) to give the titled compound **3.9a** as colorless oil (32.1 mg, >99%). R_f = 0.7 (Hex/EA= 10:1:3). IR (KBr) 3038.88, 2929.27, 2850.59, 1591.57, 1498.83, 1453.86, 1091.33 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.94 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.30 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.85 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.38 – 7.30 (m, 4H), 7.29-7.23 (m, 1H), 4.55 (d, *J* = 1.3 Hz, 2H), 4.31 (dt, *J* = 10.4, 3.3 Hz, 1H), 3.98 (dd, *J* = 11.1, 2.8 Hz, 1H), 3.58 (dd, *J* = 11.1, 3.6 Hz, 1H), 3.42 – 3.24 (m, 1H), 2.12 (dd, *J* = 9.1, 2.6 Hz, 1H), 0.80 (d, *J* = 3.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.11, 146.29, 145.97, 139.37, 136.30, 130.30, 129.59, 128.44, 128.42, 127.67, 127.44, 126.42, 126.08, 121.51, 83.33, 78.17, 69.92, 55.85, 54.62, 51.20, 45.01, 42.84, 39.49, 37.14,

35.98, 35.61, 35.00, 32.32, 28.98, 28.43, 24.94, 24.61, 21.26, 13.22, 12.43. HRMS: calcd. $[M+Na]^+$ 665.27131 Found: 665.27070.



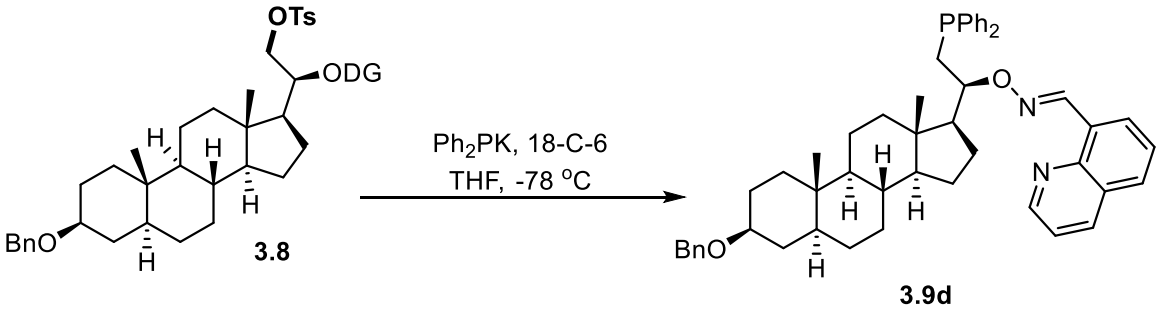
(*E*)-quinoline-8-carbaldehyde *O*-((1*S*)-1-((3*S*,5*S*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-(benzyloxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-iodoethyl) oxime (3.9b): A 4 mL vial was charged with **3.8** (37 mg, 0.05 mmol, 1 equiv.), NaI (30 mg, 4 equiv.) and acetone **(**1 mL). The vial was sealed with a PTFE lined cap and heated to reflux for 18 hours. The vial was allowed to cool to room temperature. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane: ethyl acetate: DCM = 10:1:3) to give the titled compound **3.9b** as yellowish oil (35.0 mg, >99%). R_f = 0.6 (Hex/EA/DCM = 10:1:3). IR (KBr) 3030.45, 2934.89, 2850.59, 1593.02, 1504.45, 1096.96, 908.67, 737.24 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.94 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.30 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.86 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.40 – 7.28 (m, 4H), 7.28 – 7.23 (m, 1H), 4.55 (d, *J* = 1.4 Hz, 2H), 3.78 (ddd, *J* = 9.8, 9.3, 3.1 Hz, 2H), 3.43 – 3.27 (m, 2H), 2.12 (dd, *J* = 9.1, 2.6 Hz, 1H), 0.80 (d, *J* = 2.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.10, 146.37, 145.94, 139.34, 136.31, 130.27,

129.58, 128.44, 128.41, 127.67, 127.44, 126.42, 126.06, 121.51, 82.38, 78.14, 69.90, 55.83, 54.58, 53.26, 44.99, 42.81, 39.46, 37.12, 35.96, 35.57, 34.98, 32.30, 28.96, 28.41, 24.89, 24.57, 21.23, 13.79, 13.59, 12.42. HRMS: calcd. $[M+Na]^+$ 713.25744 Found: 713.25680.



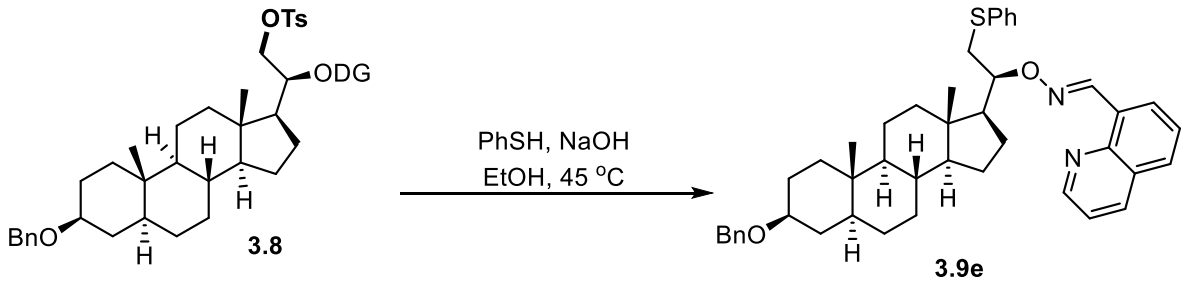
(*E*)-quinoline-8-carbaldehyde *O*-((1*S*)-2-azido-1-((3*S*,5*S*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-(benzyloxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)ethyl) oxime (3.9c): A 4 mL vial was charged with **3.8** (37 mg, 0.05 mmol, 1 equiv.), NaN_3 (13 mg, 4 equiv.) and DMF **(**1 mL). The vial was sealed with a PTFE lined cap and heated to 70 °C for 18 hours under stirring. The vial was allowed to cool to room temperature. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane: ethyl acetate: DCM = 10:1:3) to give the titled compound **3.9c** as colorless oil (30.6 mg, >99%). R_f = 0.5 (Hex/EA/DCM = 10:1:3). IR (KBr) 3038.88, 2932.08, 2853.40, 2105.85, 1501.64, 1456.67, 1094.15 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.94 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.32 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.86 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.39 – 7.29 (m, 4H), 7.27 (dd, *J* = 7.5, 4.6 Hz, 1H), 4.55 (d, *J* = 1.3 Hz, 2H), 4.38 (ddd, *J* = 10.8, 4.6, 2.9 Hz, 1H), 3.77 (dd, *J* = 13.2, 2.8 Hz, 1H), 3.40 – 3.28 (m, 2H), 2.13 (dd, *J* =

9.2, 2.5 Hz, 1H), 1.97 – 1.87 (m, 2H), 0.80 (s, 3H), 0.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.12, 146.17, 145.95, 139.33, 136.29, 130.23, 129.61, 128.43, 128.42, 127.67, 127.44, 126.42, 126.06, 121.51, 84.74, 78.14, 69.90, 55.88, 54.58, 53.36, 50.13, 44.98, 42.96, 39.51, 37.10, 35.96, 35.58, 34.98, 32.31, 28.96, 28.40, 25.26, 24.68, 21.25, 12.84, 12.42. HRMS: calcd. $[M+H]^+$ 606.38026 Found: 606.37950.



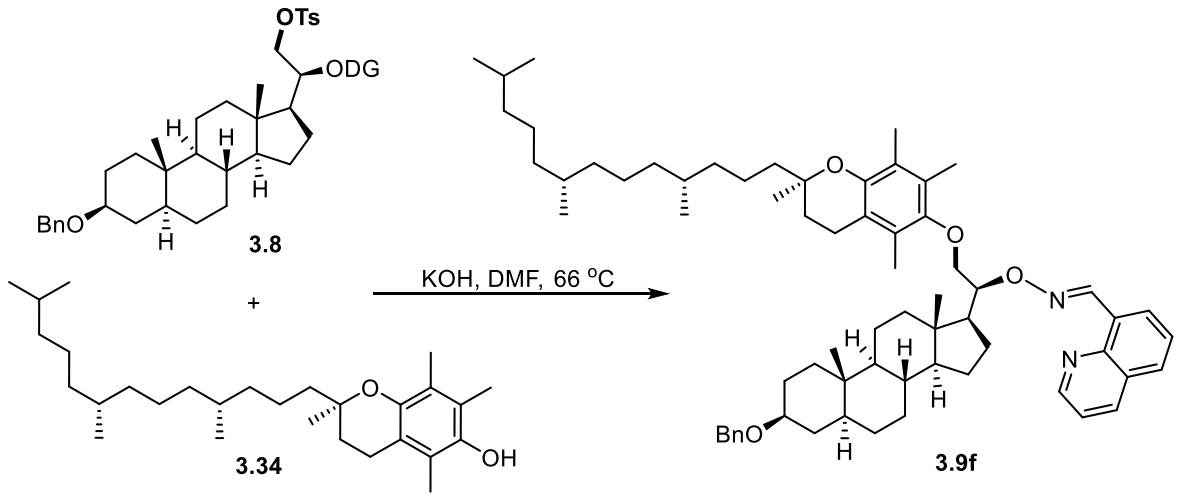
(*E*)-quinoline-8-carbaldehyde *O*-((1*S*)-1-((3*S*,5*S*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-(benzyloxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-(diphenylphosphino)ethyl) oxime (3.9d): To a THF solution of Ph_2PK (0.5 M, 0.12 mL, 1.2 equiv) was slowly added a THF solution (0.6 mL) of **3.8** (37 mg, 0.05 mmol, 1 equiv.) and 18-C-6 (16 mg, 1.2 equiv.) at -78 °C. Then, the reaction was allowed to warm to room temperature slowly, and further stirred overnight. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane: ethyl acetate: DCM = 10:1:3) to give the titled compound **3.9d** as yellowish oil (15.1 mg, 72%). R_f = 0.6 (Hex/EA/DCM = 10:1:3). IR (KBr) 3058.55, 2934.89, 2847.78, 1591.57, 1498.83, 1439.81, 1096.96, 956.44 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.91 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.19 – 8.09 (m, 2H), 7.81 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.50 – 7.38

(m, 5H), 7.38 – 7.28 (m, 4H), 7.28 – 7.26 (m, 1H), 7.25 – 7.18 (m, 4H), 7.17 – 7.10 (m, 2H), 4.58 – 4.46 (m, 3H), 3.37 – 3.28 (m, 1H), 2.61 (dt, *J* = 14.4, 3.6 Hz, 1H), 2.50 (dd, *J* = 14.5, 7.0 Hz, 1H), 2.15-2.03 (m, 2H), 1.89 (d, *J* = 8.5 Hz, 1H), 1.85-1.74 (m, 1H), 0.78 (s, 3H), 0.72 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ carbon signals were found at 149.83, 145.85, 144.77, 140.04, 139.94, 139.60, 139.49, 139.41, 136.20, 133.52, 133.36, 132.90, 132.75, 130.81, 129.01, 128.44, 128.41, 128.34, 128.32, 128.28, 128.27, 128.23, 128.08, 127.68, 127.44, 126.39, 125.94, 121.32, 83.99, 83.90, 78.22, 69.91, 56.00, 54.67, 54.36, 54.29, 45.06, 43.16, 39.61, 37.16, 35.99, 35.60, 35.03, 34.55, 34.42, 32.36, 29.03, 28.44, 26.10, 24.73, 21.30, 12.89, 12.43. HRMS: calcd. $[M+H]^+$ 749.42305 Found: 749.42220.



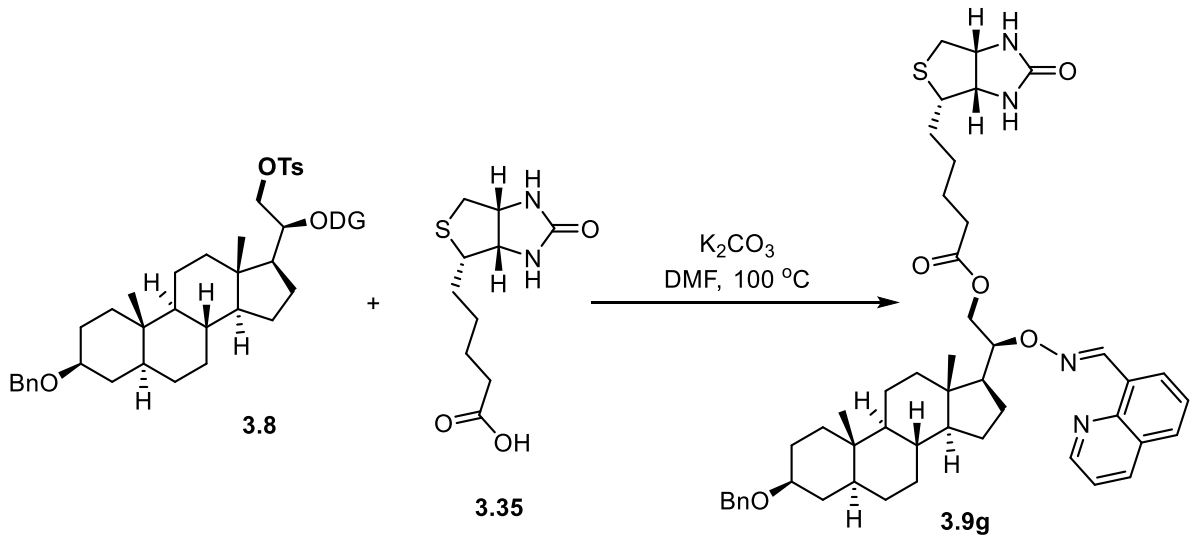
(*E*)-quinoline-8-carbaldehyde *O*-((1*S*)-1-((3*S*,5*S*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-(benzyloxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-(phenylthio)ethyl) oxime (3.9e): A 4 mL vial was charged with PhSH (11 mg, 2 equiv.), NaOH (4 mg, 2 equiv.) and EtOH **(**1 mL). The vial was sealed with a PTFE lined cap and heated to 40 °C for 0.5 hours under stirring before **3.8** (37 mg, 0.05 mmol, 1 equiv.) was added into the mixture. The reaction was stirred at the same temperature for another 16 hours. The vial was allowed to cool to room temperature. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane: ethyl

acetate: DCM = 10:1:3) to give the titled compound **3.9e** as colorless oil (32.2 mg, 96%). R_f = 0.7 (Hex/EA/DCM = 10:1:3). IR (KBr) 3064.17, 3038.88, 2937.70, 2850.59, 1583.14, 1493.21, 1091.33, 737.24 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.93 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.27 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.84 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.37 – 7.29 (m, 4H), 7.26 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.23 – 7.16 (m, 2H), 7.09 – 7.03 (m, 1H), 4.59 – 4.46 (m, 3H), 3.48 (dd, *J* = 13.3, 3.5 Hz, 1H), 3.31 (ddd, *J* = 18.8, 12.2, 5.9 Hz, 2H), 2.14 – 2.08 (m, 1H), 0.80 (s, 3H), 0.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.98, 145.89, 145.52, 139.34, 137.76, 136.26, 130.53, 129.47, 129.33, 128.78, 128.43, 128.37, 127.67, 127.44, 126.42, 126.01, 125.67, 121.43, 84.25, 78.16, 69.89, 55.88, 54.60, 52.19, 44.99, 43.09, 39.54, 38.48, 35.96, 35.57, 34.98, 32.32, 28.98, 28.41, 25.53, 24.70, 21.26, 12.92, 12.42. HRMS: calcd. $[M+Na]^+$ 695.36417 Found: 695.36320.



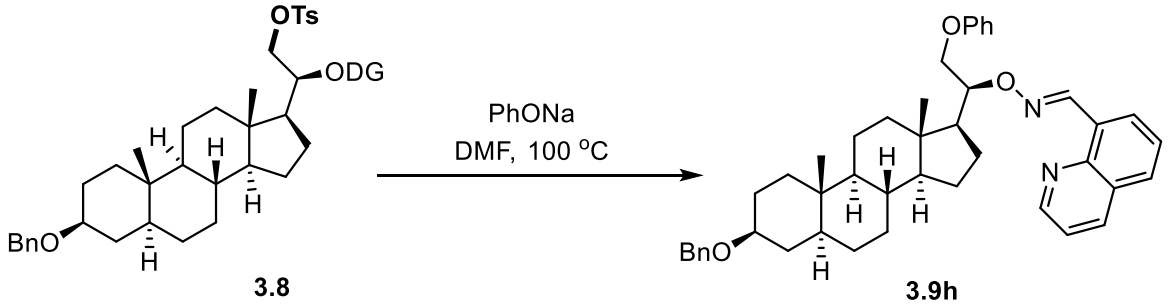
(*E*)-quinoline-8-carbaldehyde *O*-((1*S*)-1-((3*S*,5*S*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-(benzyloxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-(((*R*)-

2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)ethyl) oxime (3.9f): A 4 mL vial was charged with **3.8** (18.5 mg, 0.025 mmol, 1 equiv.), KOH (1.7 mg, 1.2 equiv.), Vitamin E **3.34** (11 mg, 1 equiv.) and DMF **(**0.5 mL). The vial was sealed with a PTFE lined cap and stirred at room temperature for 1 hour before heated to 66 °C for 6 hours. The vial was allowed to cool to room temperature. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane: ethyl acetate: DCM = 10:1:3) to give the titled compound as colorless oil (18.0 mg, 73%). R_f = 0.5 (Hex/EA/DCM = 10:1:3). IR (KBr) 3041.69, 2932.08, 2864.64, 1588.76, 1453.86, 1377.99, 1257.14, 1088.52 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.95 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.30 (dd, *J* = 7.4, 1.3 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.84 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.37 – 7.30 (m, 4H), 7.28 – 7.26 (m, 1H), 4.55 (d, *J* = 1.2 Hz, 2H), 4.49 (dt, *J* = 11.1, 3.3 Hz, 1H), 3.94 (d, *J* = 3.3 Hz, 2H), 3.40 – 3.27 (m, 1H), 2.51 (t, *J* = 6.7 Hz, 2H), 2.23 – 2.10 (m, 8H), 2.03 (s, 3H), 1.19 (s, 3H), 0.87 (s, 3H), 0.85 (s, 3H), 0.84 (s, 3H), 0.83 (s, 3H), 0.83 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.03, 148.39, 147.77, 146.03, 145.24, 139.42, 136.26, 130.82, 129.20, 128.45, 128.19, 127.69, 127.44, 126.48, 126.18, 125.92, 122.79, 121.44, 117.54, 85.56, 78.24, 74.80, 73.70, 69.93, 55.93, 54.70, 49.48, 45.07, 43.09, 40.22, 39.64, 39.53, 37.63, 37.60, 37.56, 37.44, 37.18, 36.03, 35.68, 35.06, 32.94, 32.84, 32.42, 31.48, 29.06, 28.47, 28.13, 25.64, 24.95, 24.58, 23.98, 22.87, 22.78, 21.38, 21.16, 20.78, 19.90, 19.80, 12.85, 12.83, 12.46, 11.97, 11.90. HRMS: calcd. $[M+Na]^+$ 1015.72623. Found: 1015.72350.



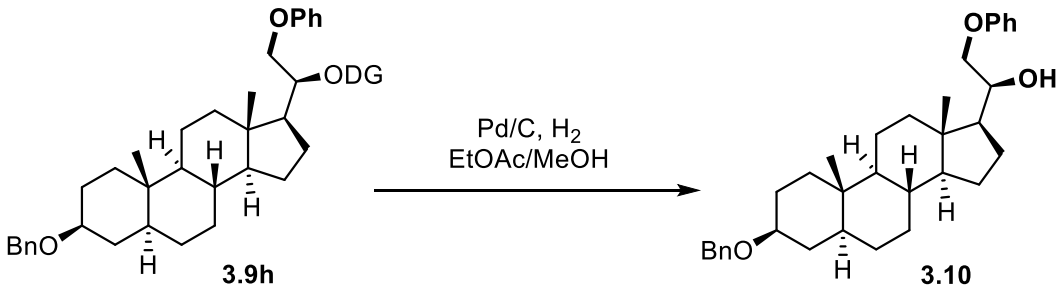
(2*S*)-2-((3*S*,5*S*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-(benzyloxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-(((*E*)-(quinolin-8-ylmethylene)amino)oxy)ethyl 5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanoate (3.9g): A 4 mL vial was charged with **3.8** (18.5 mg, 0.025 mmol, 1 equiv.), K_2CO_3 (14 mg, 4 equiv.), Biotin **3.35** (12.2 mg, 2 equiv.) and DMF **(**0.5 mL). The vial was sealed with a PTFE lined cap and heated to 100 °C for 4 hours. The vial was allowed to cool to room temperature. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane: ethyl acetate: DCM = 10:1:3) to give the titled compound as colorless oil (13.9 mg, 69%). R_f = 0.25 (DCM/MeOH = 20:1). IR (KBr) 3238.41, 3069.79, 2926.46, 2856.21, 1715.22, 1453.86, 1094.15, 734.88 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.94 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.29 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.86 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.40 – 7.29 (m, 4H), 7.26 – 7.22 (m, 1H), 5.60 (s, 1H), 5.01 (s, 1H), 4.54 (d, *J* = 1.6 Hz, 2H), 4.50 – 4.36 (m, 3H), 4.25 (dd, *J* = 11.8, 5.0 Hz, 1H), 4.18 (ddd, *J* = 7.7, 4.6, 1.2 Hz, 1H), 3.37 – 3.26 (m, 1H), 3.09 – 2.98 (m, 1H), 2.80 (dd, *J* = 12.8, 4.9 Hz, 1H), 2.66 (d, *J* = 12.8

Hz, 1H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.08 (d, *J* = 11.9 Hz, 1H), 1.95-1.82 (m, 2H), 0.78 (d, *J* = 4.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.89, 163.34, 150.13, 145.83, 145.38, 139.33, 136.43, 130.23, 129.55, 128.44, 128.42, 127.68, 127.45, 126.55, 126.08, 121.56, 83.64, 78.15, 69.91, 65.24, 61.86, 60.10, 55.82, 55.51, 54.58, 49.72, 45.00, 42.97, 40.69, 39.54, 37.12, 35.97, 35.59, 34.97, 33.97, 32.33, 28.97, 28.41, 28.27, 28.13, 25.22, 24.84, 24.73, 21.28, 12.82, 12.42. HRMS: calcd. $[M+Na]^+$ 829.43331 Found: 829.43260.



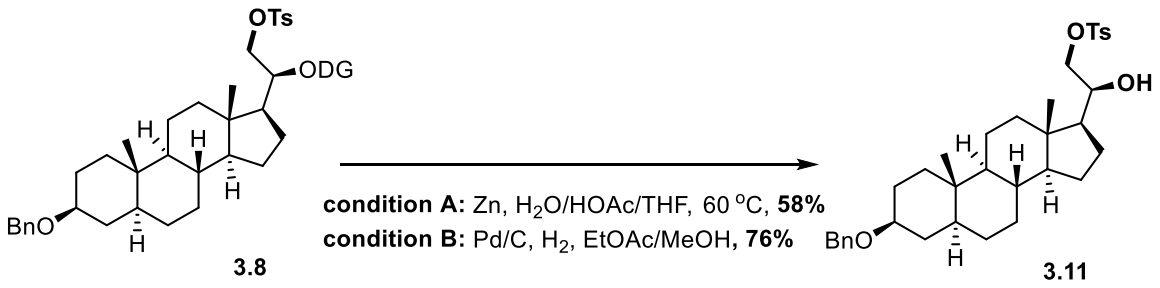
(*E*)-quinoline-8-carbaldehyde *O*-((1*S*)-1-((3*S*,5*S*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-(benzyloxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-phenoxyethyl) oxime (3.9h): A 4 mL vial was charged with **3.8** (37 mg, 0.05 mmol, 1 equiv.), NaOPh (11.6 mg, 2 equiv.) and DMF **(**1 mL). The vial was sealed with a PTFE lined cap and heated to 100 °C for 13 hours. The vial was allowed to cool to room temperature. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane: ethyl acetate: DCM = 10:1:3) to give the titled compound as colorless oil (32.2 mg, 98%). R_f = 0.6 (Hex/EA/DCM = 10:1:3). IR (KBr) 3036.07, 2932.08, 2859.02, 1605.62, 1496.02, 1456.67, 1243.09, 1094.15 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.92 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.29 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.14 (dd,

J = 8.3, 1.8 Hz, 1H), 7.84 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.38 – 7.30 (m, 4H), 7.30 – 7.24 (m, 3H), 6.99 – 6.89 (m, 3H), 4.60 – 4.51 (m, 3H), 4.37 (dd, *J* = 10.4, 3.0 Hz, 1H), 4.15 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.39 – 3.30 (m, 1H), 2.15 (ddd, *J* = 24.0, 13.0, 5.5 Hz, 2H), 1.91 (d, *J* = 10.3 Hz, 1H), 0.82 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.33, 150.04, 145.94, 145.71, 139.36, 136.26, 130.50, 129.42, 129.38, 128.44, 128.39, 127.68, 127.44, 126.42, 126.01, 121.45, 120.67, 114.94, 84.24, 78.18, 69.90, 69.17, 55.85, 54.66, 49.93, 45.02, 42.96, 39.60, 37.14, 35.99, 35.65, 35.00, 32.36, 29.00, 28.43, 25.13, 24.74, 21.32, 12.87, 12.44. HRMS: calcd. $[M+Na]^+$ 679.38701 Found: 679.38670.



(1*S*)-1-((3*S*,5*S*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-(benzyloxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-phenoxyethanol (3.10): An EtOAc (1.8 mL)/MeOH (0.3 mL) suspension of Pd/C (10% w/w) (125 mg) and **3.9h** (25 mg, 0.038 mmol, 1.0 equiv.) was stirred under a hydrogen atmosphere (balloon pressure) and monitored by TLC. After 4 hours, the mixture was filtered through a small plug of Celite to remove the precipitate and washed with dichloromethane. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane: ethyl acetate:

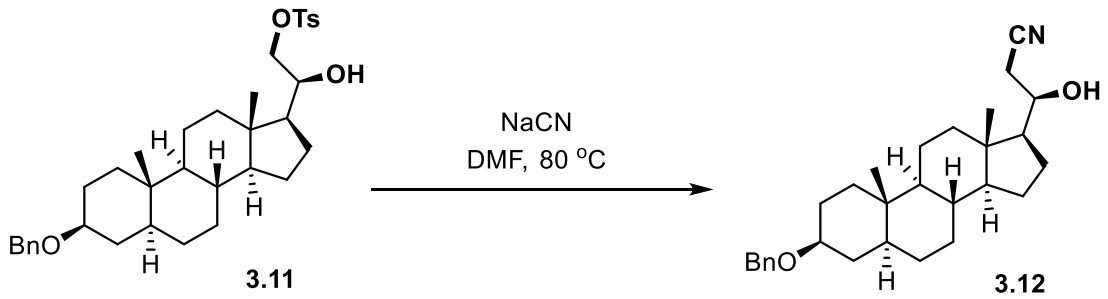
DCM = 10:1:3) to give the desired product **3.10** as a white solid (17.5 mg, 92%). m.p.= 155-157 °C. R_f = 0.35 (Hex/EA/DCM = 10:1:3). IR (KBr) 3584.07, 3558.78, 3437.94, 3061.36, 3030.45, 2940.52, 2853.40, 1600.00, 1496.02, 1453.86, 1240.28 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 4H), 7.31 – 7.25 (m, 3H), 6.99 – 6.93 (m, 1H), 6.93 – 6.88 (m, 2H), 4.56 (d, *J* = 0.8 Hz, 2H), 3.99 (dd, *J* = 9.2, 2.3 Hz, 1H), 3.98 – 3.88 (m, 1H), 3.78 (dd, *J* = 9.2, 7.0 Hz, 1H), 3.40 – 3.29 (m, 1H), 2.22 (d, *J* = 4.4 Hz, 1H), 2.16 (dt, *J* = 12.3, 3.1 Hz, 1H), 1.93 (d, *J* = 10.5 Hz, 1H), 0.83 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.90, 139.40, 129.63, 128.45, 127.68, 127.46, 121.21, 114.80, 78.17, 72.92, 72.15, 69.93, 55.95, 54.68, 52.40, 45.07, 43.07, 39.91, 37.19, 36.04, 35.61, 35.03, 32.41, 28.99, 28.44, 25.00, 24.85, 21.27, 12.59, 12.47. HRMS: calcd. $[M+Na]^+$ 525.33392 Found: 525.33400.



(2*S*)-2-((3*S*,5*S*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-(benzyloxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-hydroxyethyl 4-methylbenzenesulfonate (3.11):

Condition A: To a solution of **3.8** (47.1 mg, 0.063 mmol, 1 equiv) in 1 mL AcOH-THF-Water (3:1:1), Zinc powder (35 mg, 0.65 mmol, 10 equiv) was added in one portion at room temperature. Then the mixture was stirred at 60 °C and monitored by TLC. After 2.5 hours, the mixture was filtered through a small plug of silica gel to remove the precipitate and washed with dichloromethane. The solvent was then removed in *vacuo* and the residue was

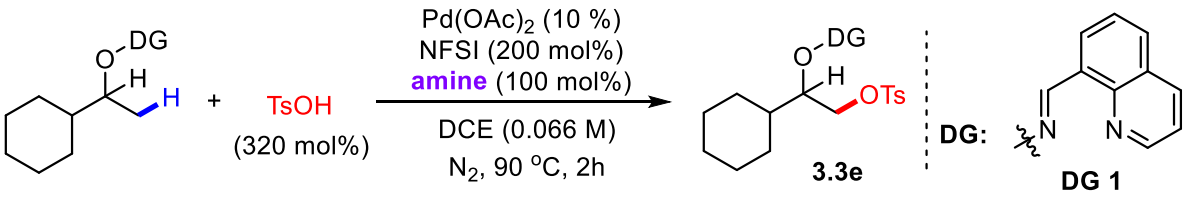
further purified with flash column chromatography (hexane: ethyl acetate: DCM = 10:1:3) to give the desired product **3.11** as a yellowish solid (21.6 mg, 58%). **Condition B:** An EtOAc (1.4 mL)/MeOH (0.25 mL) suspension of Pd/C (10% w/w) (100 mg) and **3.8** (23.6 mg, 0.032 mmol, 1.0 equiv.) was stirred under a hydrogen atmosphere (balloon pressure) and monitored by TLC. After 3.5 hours, the mixture was filtered through a small plug of Celite to remove the precipitate and washed with dichloromethane. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane: ethyl acetate: DCM = 10:1:3) to give the desired product **3.11** as a yellowish solid (14.0 mg, 76%). m.p.= 139-141°C. R_f = 0.65 (Hex/EA/DCM = 3:1:1). IR (KBr) 3550.35, 3432.32, 2932.08, 2856.21, 1602.81, 1456.67, 1361.12, 1172.83, 1102.58 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.29 (m, 6H), 7.28 – 7.25 (m, 1H), 4.55 (d, *J* = 0.9 Hz, 2H), 4.06 (dd, *J* = 10.0, 2.1 Hz, 1H), 3.84 (dd, *J* = 10.0, 6.3 Hz, 1H), 3.74 (dd, *J* = 9.1, 5.1 Hz, 1H), 3.39 – 3.26 (m, 1H), 2.45 (s, 3H), 2.03 (dt, *J* = 6.3, 3.4 Hz, 1H), 1.96 – 1.85 (m, 2H), 0.80 (s, 3H), 0.70 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.14, 139.30, 132.77, 130.06, 128.44, 128.09, 127.67, 127.46, 78.09, 74.39, 72.39, 69.90, 55.74, 54.49, 51.77, 44.96, 42.98, 39.74, 37.12, 35.96, 35.49, 34.95, 32.26, 28.90, 28.38, 24.79, 24.68, 21.81, 21.16, 12.45, 12.42. HRMS: calcd. $[M+Na]^+$ 603.31147 Found: 603.31110.

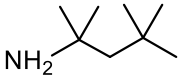


(3*R*)-3-((3*S*,5*S*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-(benzyloxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-3-hydroxypropanenitrile (3.12): A 2 mL vial was charged with **3.8** (14 mg, 0.024 mmol, 1 equiv.), NaCN (4.8 mg, 4 equiv.) and DMF **(**0.4 mL). The vial was sealed with a PTFE lined cap and heated to 80 °C for 14 hours. Then, the vial was allowed to cool to room temperature. The solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane: ethyl acetate: DCM = 10:1:3) to give the titled compound as a white solid (10.0 mg, 95%). m.p. = 171-173 °C. R_f = 0.1 (Hex/EA= 5:1). IR (KBr) 3469.22, 2930.33, 2861.45, 2247.61, 1455.49, 1356.22, 1100.96, 1070.57 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 4H), 7.29 – 7.26 (m, 1H), 4.55 (d, *J* = 0.9 Hz, 2H), 3.86 (dtd, *J* = 9.9, 6.2, 3.6 Hz, 1H), 3.34 (tt, *J* = 11.1, 4.7 Hz, 1H), 2.59 (dd, *J* = 16.7, 3.6 Hz, 1H), 2.39 (dd, *J* = 16.8, 6.1 Hz, 1H), 2.03 – 1.96 (m, 1H), 1.92 (d, *J* = 11.2 Hz, 1H), 1.82 (d, *J* = 6.4 Hz, 1H), 0.82 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.30, 128.47, 127.69, 127.49, 117.90, 78.07, 70.47, 69.95, 55.89, 55.64, 54.40, 44.95, 42.90, 39.90, 37.13, 35.98, 35.46, 34.96, 32.18, 28.87, 28.39, 26.30, 25.38, 24.55, 21.17, 12.73, 12.44. HRMS: calcd. $[M+H]^+$ 436.3216 Found: 436.3216.

Robust test for amine compatibility

Table 3.4 Robust Test for Amine Compatibility



entry	amine	TsO-product yield[a]	amine recovery yield
1	without amine	55%[b]	--
2		57%	88%[c]
3	Cy_2NH	58%	97%[a]
4	morphline	61%	>99%[d]

[a] isolated yield. [b] TsOH (2.2 eq), 7h. [c] GC yield. [d] isolated as benzoylated derivative.

Entry 2: an 4 mL vial was charged with $Pd(OAc)_2$ (3.5 mg, 0.015 mmol, 0.1 equiv.), TsOH (82.6 mg, 0.48 mmol, 3.2 equiv.), oxime substrate (35.7 mg, 0.15 mmol, 1.0 equiv.), 2,4,4-trimethylpentan-2-amine (19.3 mg, 0.15 mmol, 1.0 equiv.), and 1,2-dichloroethane (2.2 ml). The mixture was stirred at room temperature for 1-2 min before *N*-fluorobenzenesulfonimide (95 mg, 0.3 mmol, 2.0 equiv.) was added. The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 2 hours. The vial was then allowed to cool to room temperature and the solvent was removed in *vacuo*. Pyridine (0.2 ml) and dodecane (17.0 mg, as internal standard) was added, and the mixture was further stirred at room temperature for additional 5 min to fully mix. A very small portion (ca. 5 μL) of the resulting solution was taken out for GC analysis, and the

residue was directly loaded on a silica gel column and further purified with flash column chromatography (hexane/ethyl acetate/DCM, 20:1:5 to 10:1:3) to give the title tosyloxylated product as yellowish oil (37.9 mg, 57%).

GC analysis: After the pyridine (0.2 ml) and dodecane (17.0 mg, as internal standard) was added and fully mixed with the reaction residue, ca. 5 μL of the resulting solution was taken out into a GC vial, followed by the addition of *tert*-butylamine (50 μL) and diethyl ether (0.8 ml). The resulting solution was directly used for GC analysis. *GC instrument conditions:* inlet temperature: 250 °C, detector temperature: 300 °C, hydrogen flow: 40 mL/min, air flow: 400 mL/min, column + makeup flow: 30 mL/min. Method: 50 °C hold for 5 min, followed by a temperature increase of 10 °C/min to 280 °C, hold 0 min (total run time: 28 min). Working curve was made with 2,4,4-trimethylpentan-2-amine and dodecane (as internal standard). Retention times were as follows: 2,4,4-trimethylpentan-2-amine (4.84) and dodecane (12.67).

Entry 3: an 4 mL vial was charged with $Pd(OAc)_2$ (3.5 mg, 0.015 mmol, 0.1 equiv.), TsOH (82.6 mg, 0.48 mmol, 3.2 equiv.), oxime substrate (35.9 mg, 0.15 mmol, 1.0 equiv.), dicyclohexylamine (27.3 mg, 0.15 mmol, 1.0 equiv.), and 1,2-dichloroethane (2.2 ml). The mixture was stirred at room temperature for 1-2 min before *N*-fluorobenzenesulfonimide (95 mg, 0.3 mmol, 2.0 equiv.) was added. The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 2 hours. The vial was

then allowed to cool to room temperature and the solvent was removed in *vacuo.* Pyridine (0.2 ml) was added, and the mixture was directly loaded on a silica gel column and further purified with flash column chromatography (hexane/ethyl acetate = 10:1 to hexane/ethyl acetate/$HNEt_2$ = 1:1:0.03) to give the title tosyloxylated product as yellowish oil (38.7 mg, 58%) and the recycled dicyclohexylamine as colorless oil (26.4 mg, 97%).

Entry 4 an 4 mL vial was charged with $Pd(OAc)_2$ (3.5 mg, 0.015 mmol, 0.1 equiv.), TsOH (82.6 mg, 0.48 mmol, 3.2 equiv.), oxime substrate (36.2 mg, 0.15 mmol, 1.0 equiv.), morpholine (13.3 mg, 0.15 mmol, 1.0 equiv.), and 1,2-dichloroethane (2.2 ml). The mixture was stirred at room temperature for 1-2 min before *N*-fluorobenzenesulfonimide (95 mg, 0.3 mmol, 2.0 equiv.) was added. The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 90 °C for 2 hours. The vial was then allowed to cool to room temperature. Pyridine (72 μL, 6 equiv.) and benzoyl chloride (105 μL, 6 equiv.) was added followed by the addition of *N*-ethyldiisopropylamine (260 μL, 10 equiv.). The resulting mixture was allowed to stir at room temperature for 30 min, and the solvent was then removed in *vacuo* and the residue was further purified with flash column chromatography (hexane/ethyl acetate/DCM = 20:1:5 to hexane/ethyl acetate = 4:1) to give the title tosyloxylated product as yellowish oil (41.5 mg, 61%) and the phenyl(piperidin-1-yl)methanone as colorless oil (29.0 mg, > 99%).

X-Ray data for 3.3c and 3.6

X-Ray structure for **3.3c:**

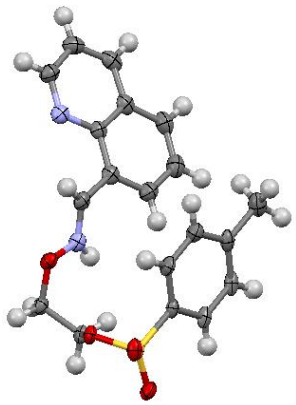


Table 3.5 Crystal Data and Structure Refinement for **3.3c**

Empirical formula	C19 H19 N2 O4 S	
Formula weight	371.42	
Temperature	133(2) K	
Wavelength	1.54184 Å	
Crystal system	orthorhombic	
Space group	P b c a	
Unit cell dimensions	a = 21.5264(5) Å	α= 90°.
	b = 7.0928(2) Å	β= 90°.
	c = 23.3930(8) Å	γ = 90°.
Volume	3571.70(18) $Å^3$	
Z	8	
Density (calculated)	1.381 Mg/m^3	
Absorption coefficient	1.848 mm^{-1}	
F(000)	1560	
Crystal size	0.230 x 0.120 x 0.060 mm	
Theta range for data collection	3.779 to 74.229°.	
Index ranges	-21<=h<=25, -5<=k<=8, -21<=l<=28	
Reflections collected	11052	

Independent reflections	3548 [R(int) = 0.0310]
Completeness to theta = 67.684°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00 and 0.707
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3548 / 66 / 315
Goodness-of-fit on F^2	1.124
Final R indices [I>2sigma(I)]	R1 = 0.0675, wR2 = 0.1742
R indices (all data)	R1 = 0.0744, wR2 = 0.1784
Extinction coefficient	n/a
Largest diff. peak and hole	0.754 and -0.660 e.$Å^{-3}$

X-Ray structure for **3.6:**

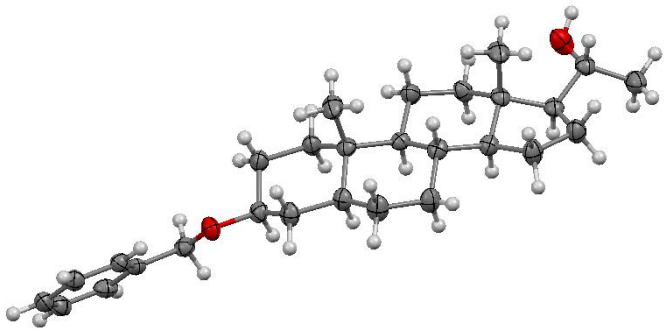


Table 3.6 Crystal Data and Structure Refinement for **3.6**

Empirical formula	C28 H42 O2
Formula weight	410.61
Temperature	140(2) K
Wavelength	1.54184 Å

Crystal system	monoclinic	
Space group	P 21	
Unit cell dimensions	a = 15.21431(7) Å	α = 90°.
	b = 19.23139(10) Å	β = 97.2270(4)°.
	c = 16.42940(7) Å	γ = 90°.
Volume	4768.93(4) $Å^3$	
Z	8	
Density (calculated)	1.144 Mg/m^3	
Absorption coefficient	0.529 mm^{-1}	
F(000)	1808	
Crystal size	0.300 x 0.200 x 0.130 mm	
Theta range for data collection	3.555 to 76.543°.	
Index ranges	-18<=h<=18, -23<=k<=19, -20<=l<=20	
Reflections collected	57757	
Independent reflections	17039 [R(int) = 0.0229]	
Completeness to theta = 67.684°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.822	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	17039 / 721 / 1097	
Goodness-of-fit on F^2	1.098	
Final R indices [I>2sigma(I)]	R1 = 0.0341, wR2 = 0.0957	
R indices (all data)	R1 = 0.0347, wR2 = 0.0968	
Absolute structure parameter	-0.04(4)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.266 and -0.199 $e.Å^{-3}$	

3.5 ^{1}H-NMR and ^{13}C-NMR spectra

Figure 3.4 ^{1}H-NMR Spectrum of **3.13d**

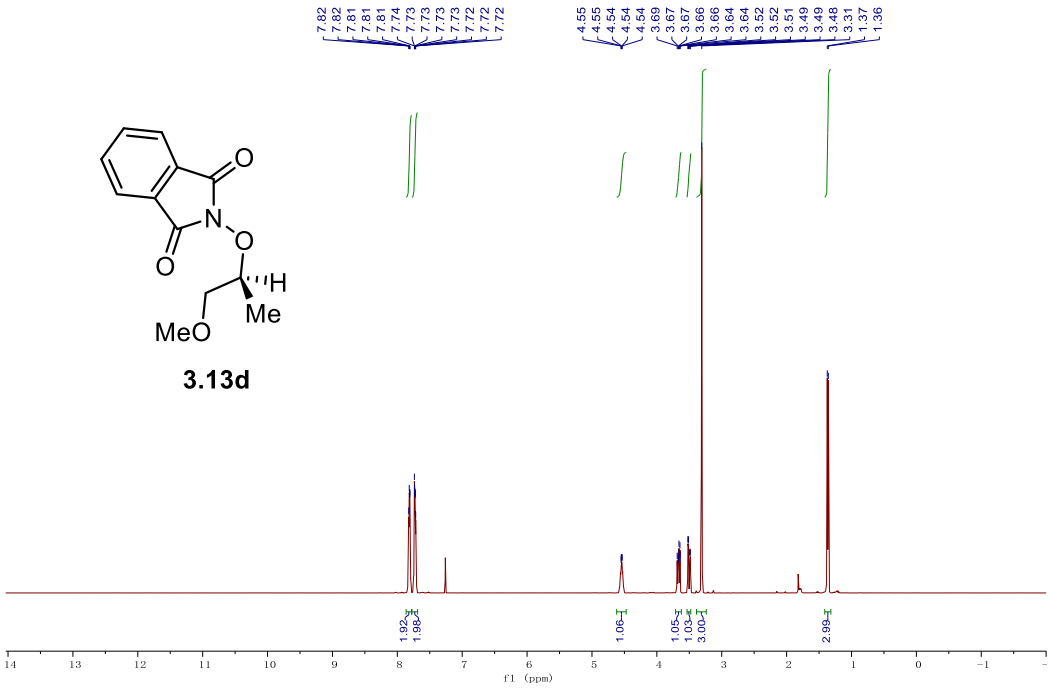


Figure 3.5 ^{13}C-NMR Spectrum of **3.13d**

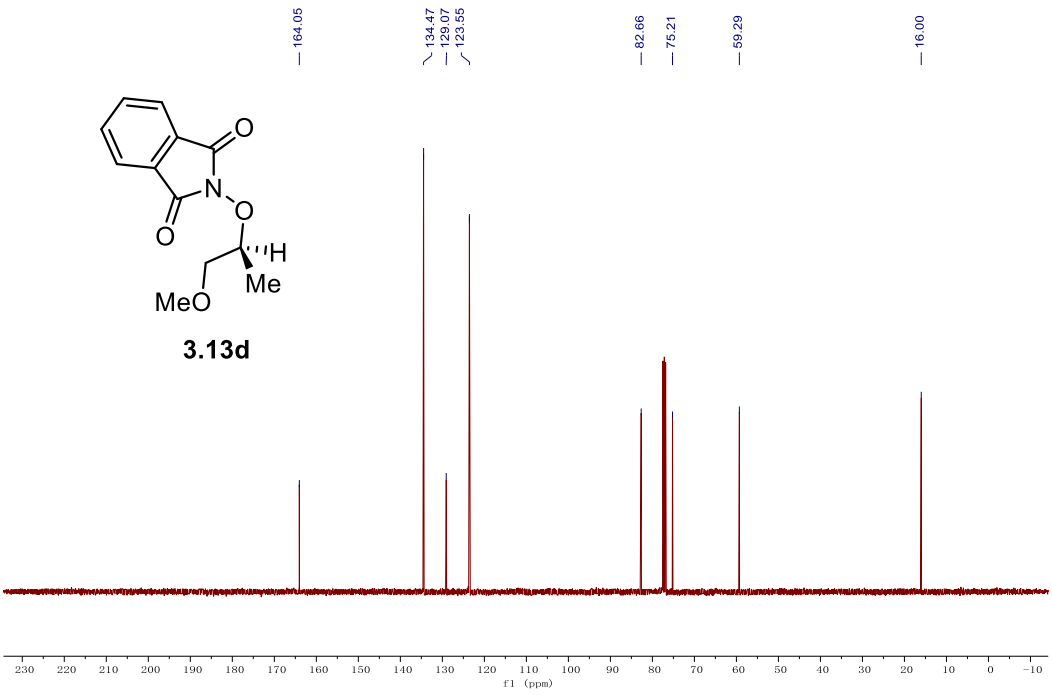


Figure 3.6 ^{1}H-NMR Spectrum of **3.13v**

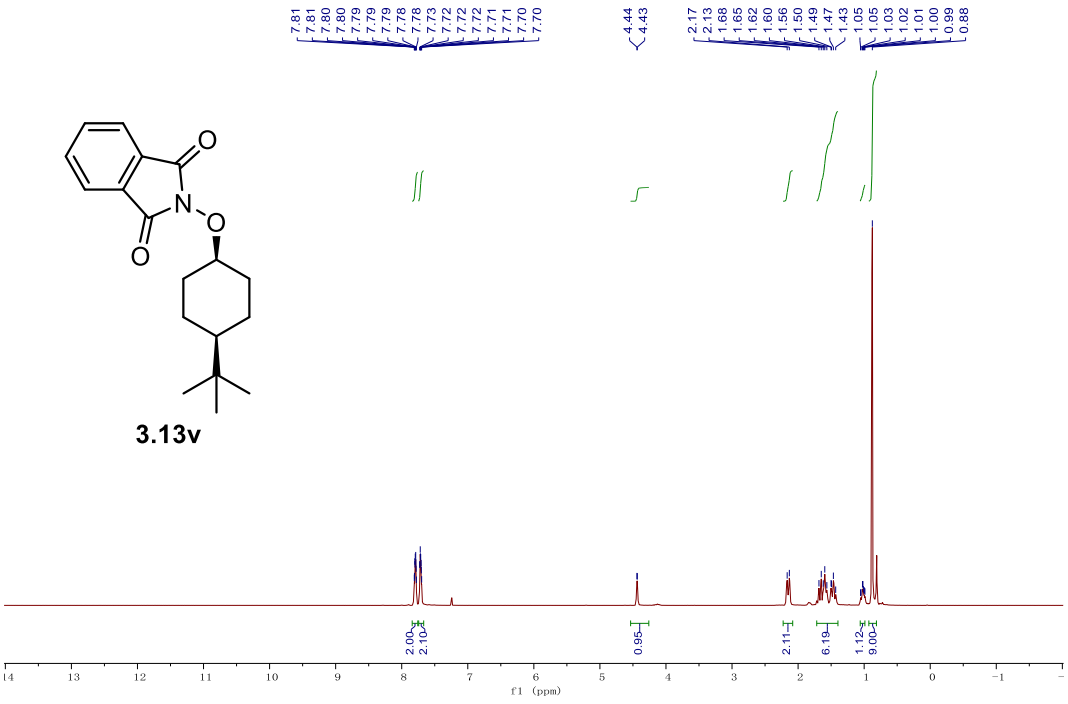


Figure 3.7 ^{13}C-NMR Spectrum of **3.13v**

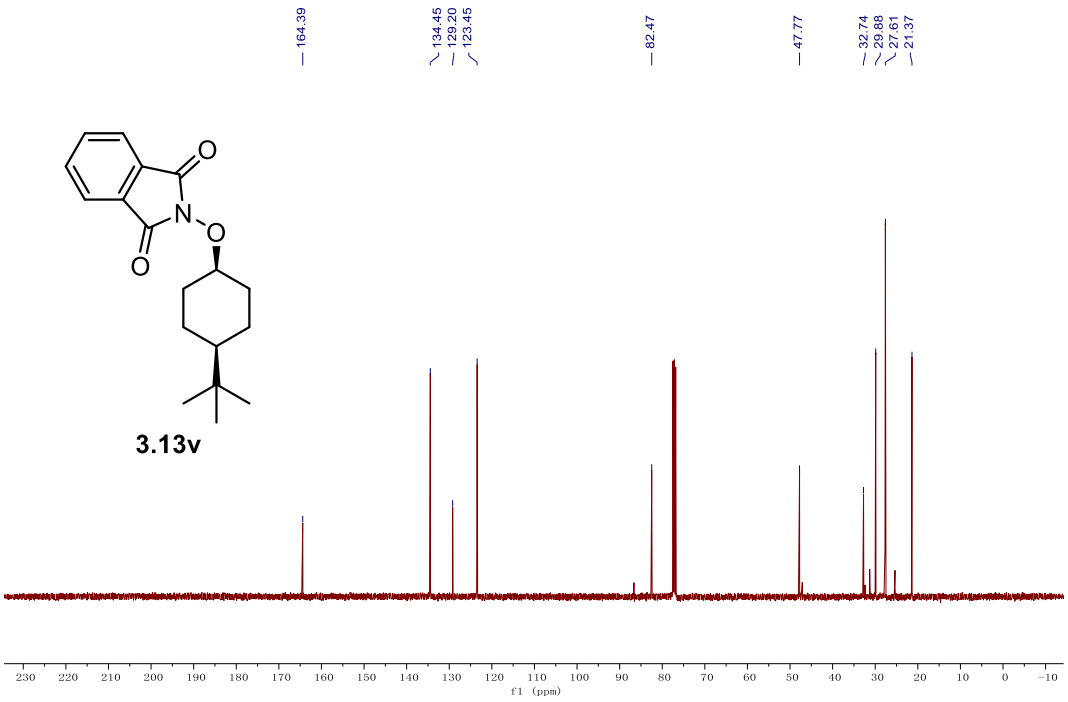


Figure 3.8 ^{1}H-NMR Spectrum of **3.13w**

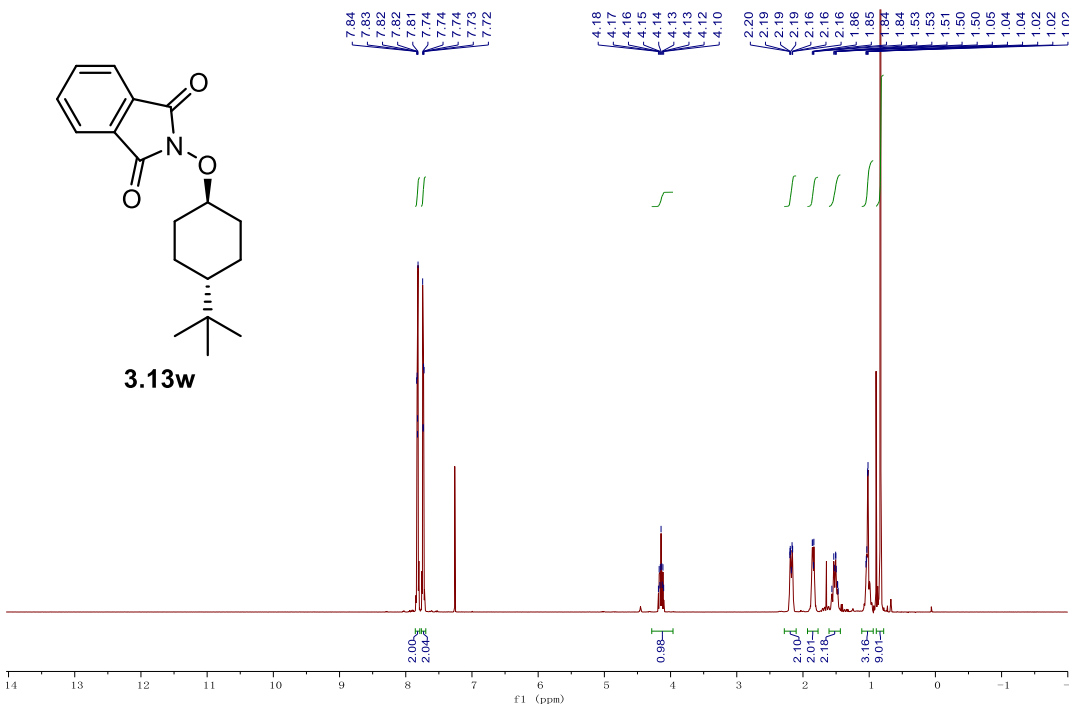


Figure 3.9 ^{13}C-NMR Spectrum of **3.13w**

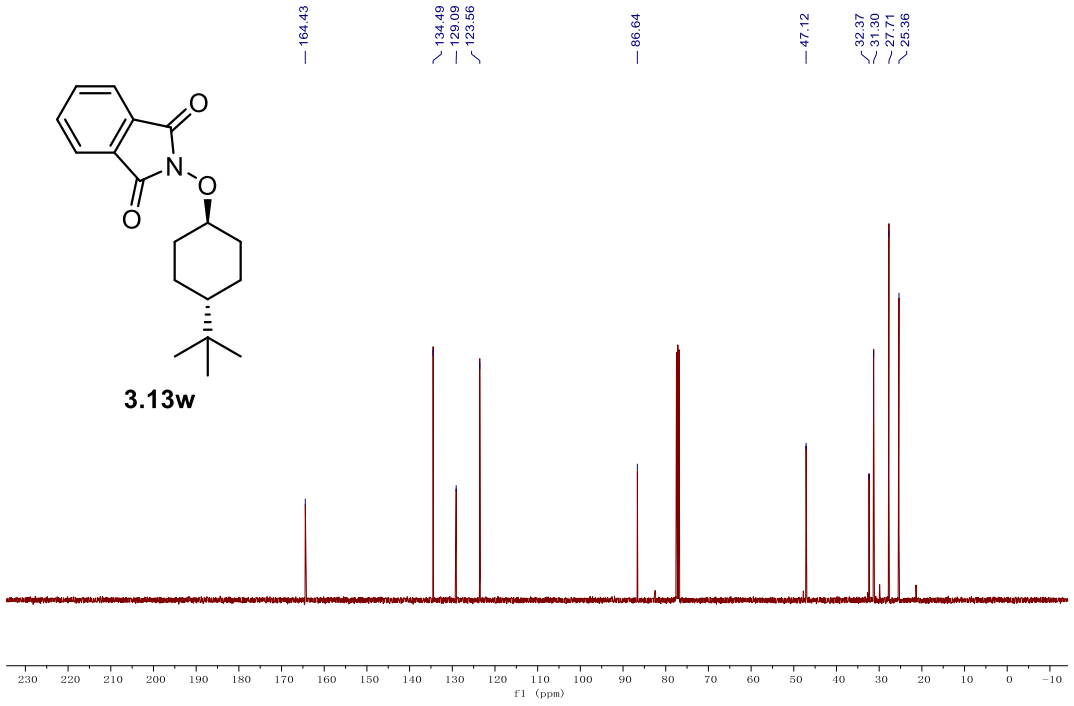


Figure 3.10 ^{1}H-NMR Spectrum of **3.2a-DG1**

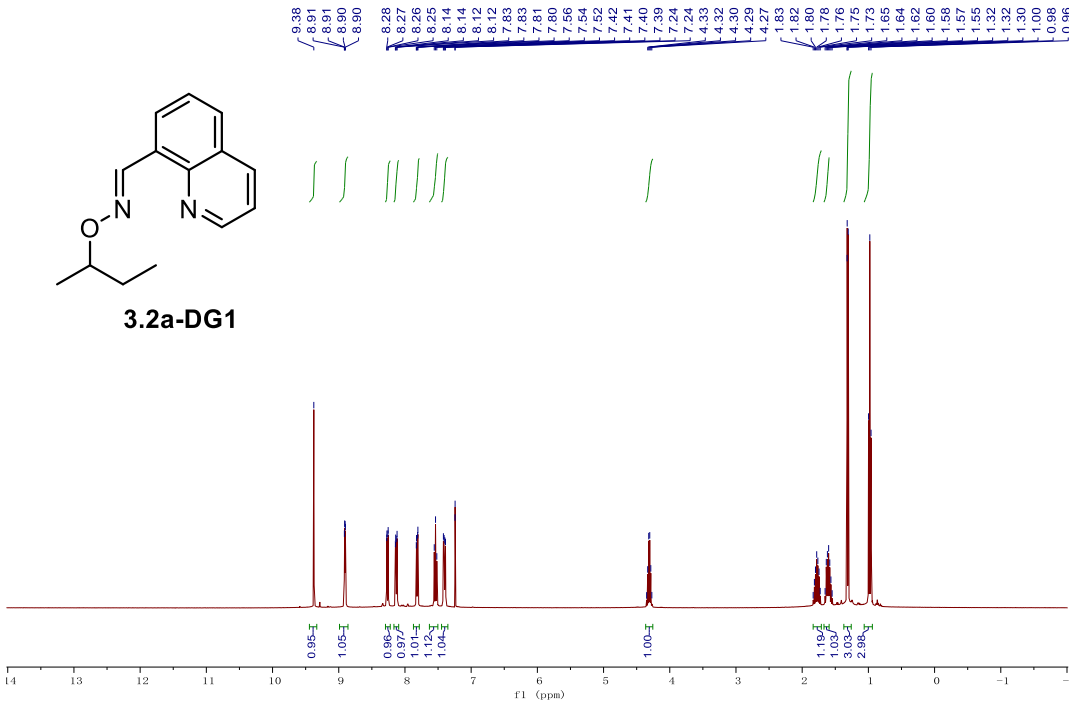


Figure 3.11 ^{13}C-NMR Spectrum of **3.2a-DG1**

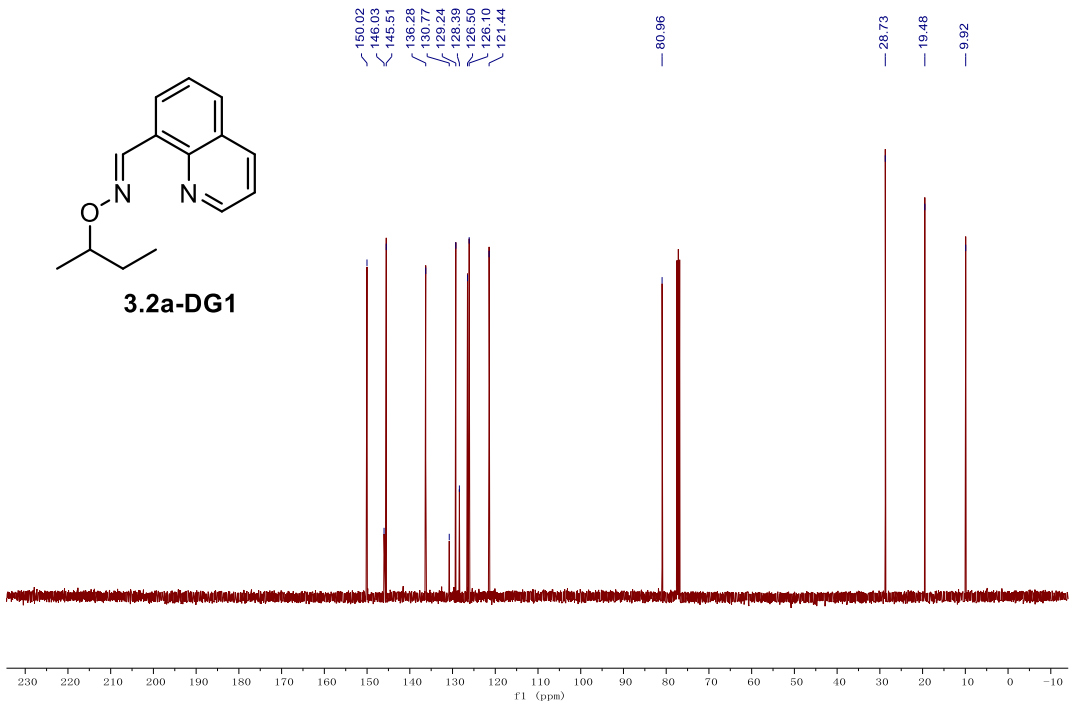


Figure 3.12 ^{1}H-NMR Spectrum of **3.2a-DG3**

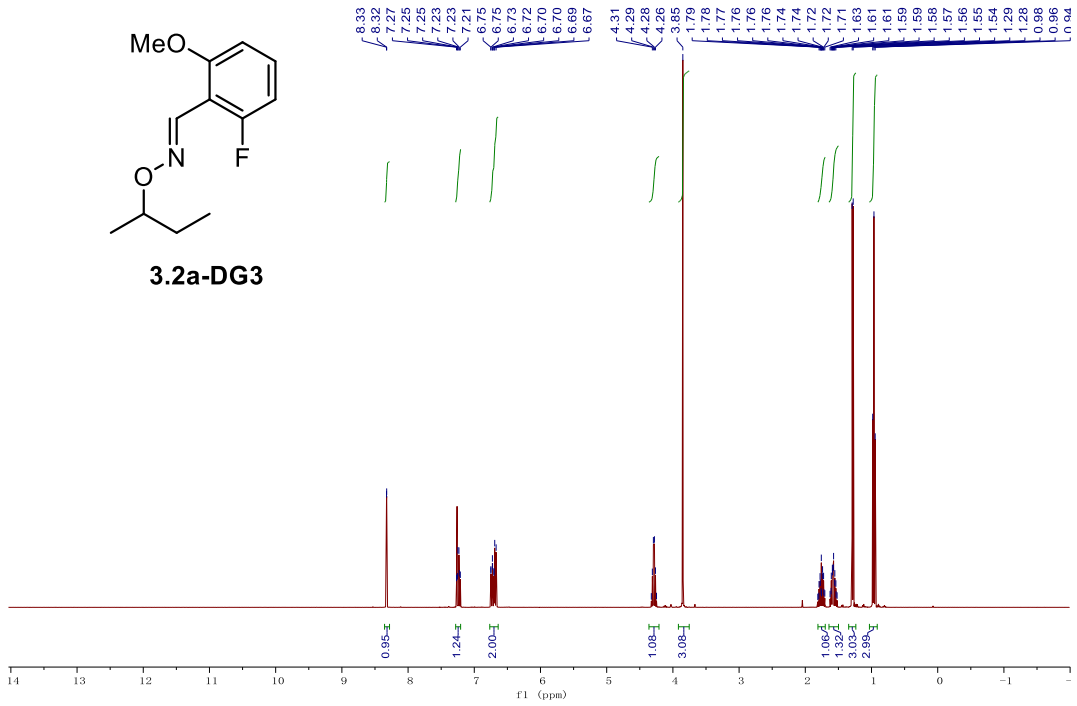


Figure 3.13 ^{13}C-NMR Spectrum of **3.2a-DG3**

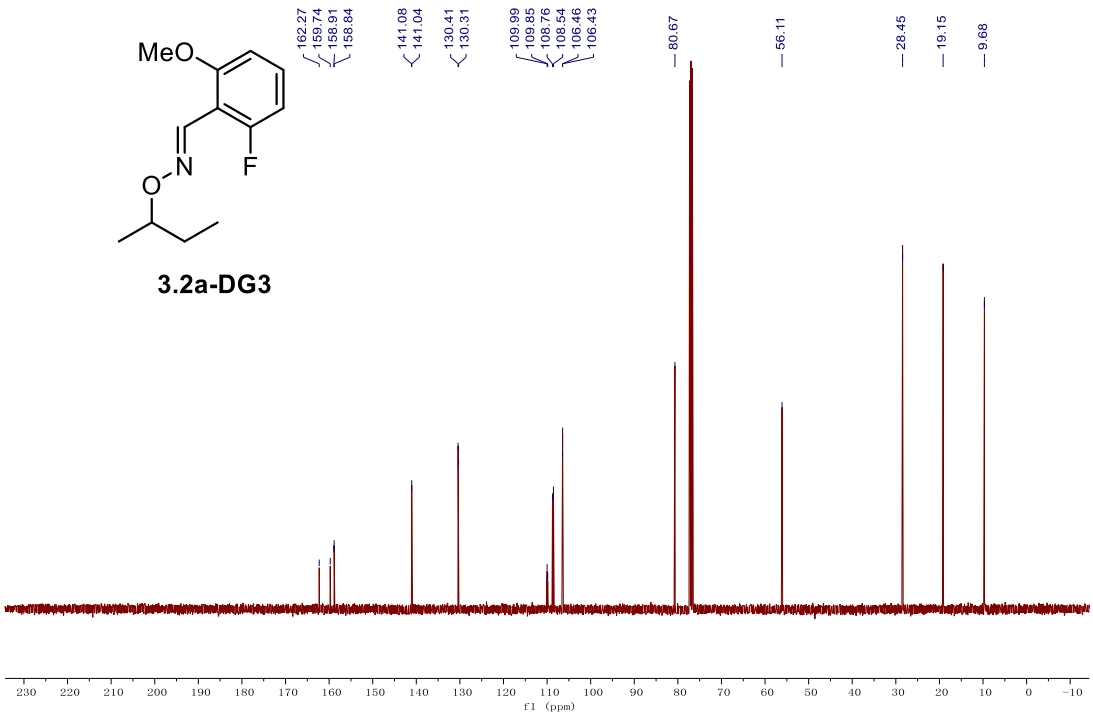


Figure 3.14 ^{19}F-NMR Spectrum of **3.2a-DG3**

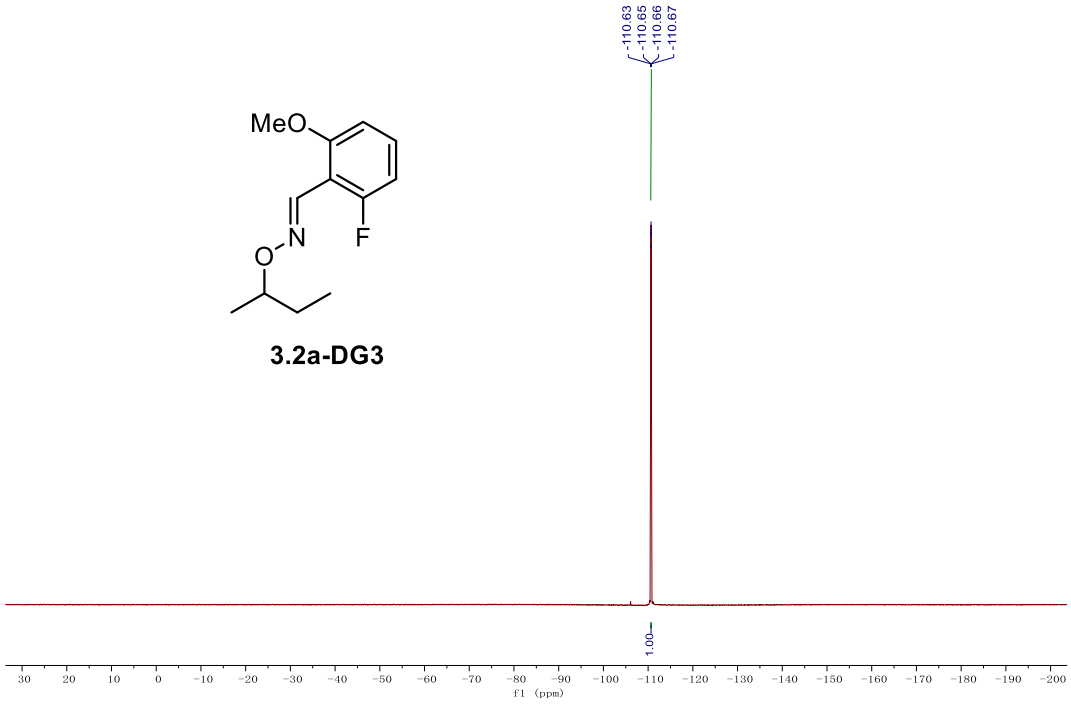


Figure 3.15 ^{1}H-NMR Spectrum of **3.2a-DG4**

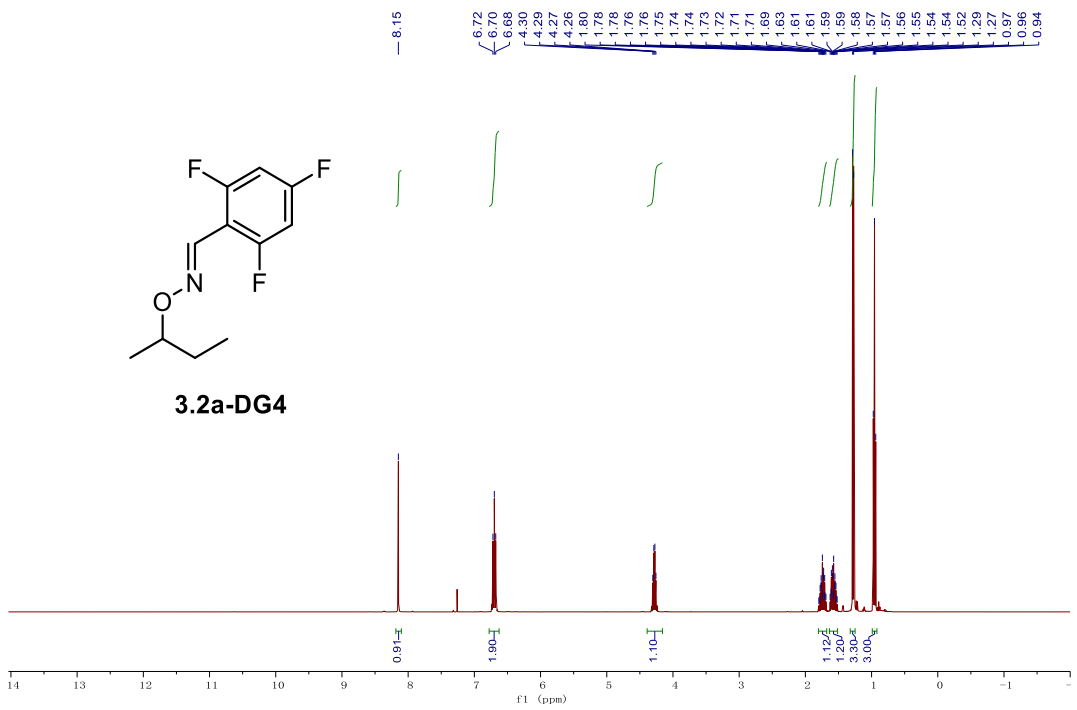


Figure 3.16 ^{13}C-NMR Spectrum of **3.2a-DG4**

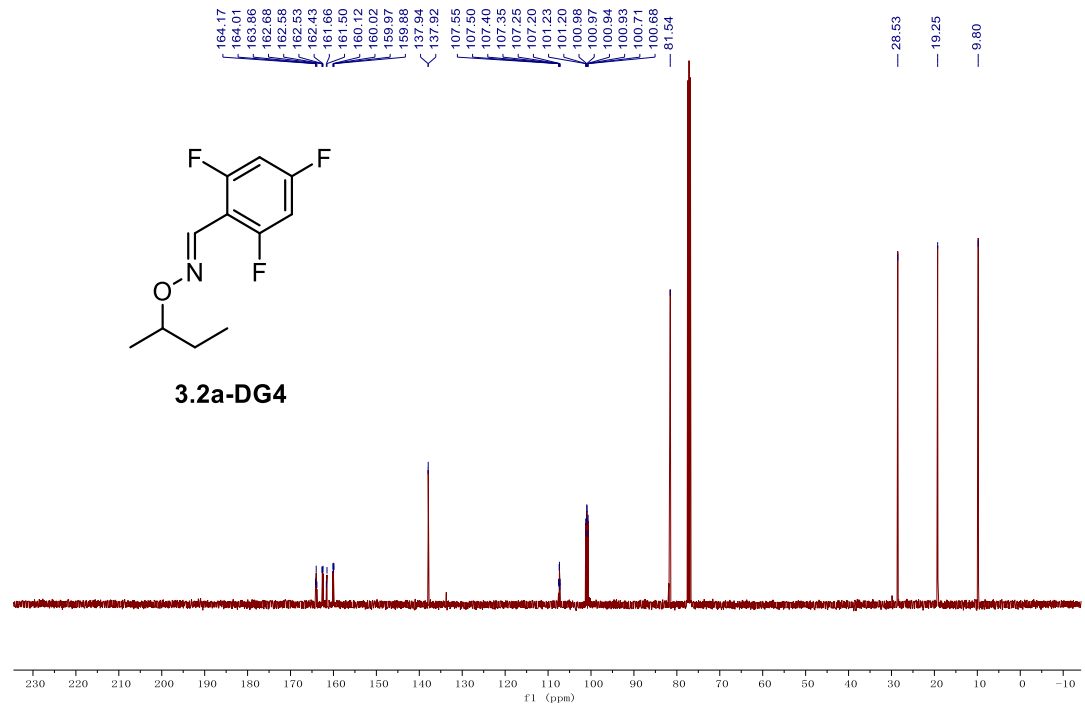


Figure 3.17 ^{19}F-NMR Spectrum of **3.2a-DG4**

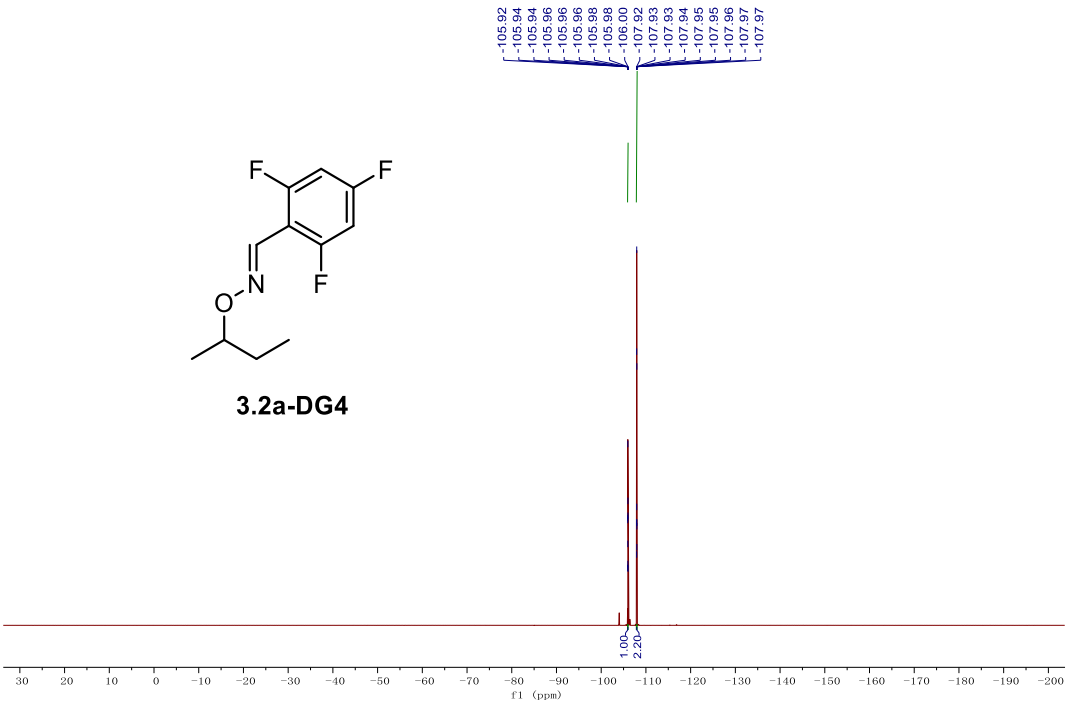


Figure 3.18 ^{1}H-NMR Spectrum of **3.2a-DG5**

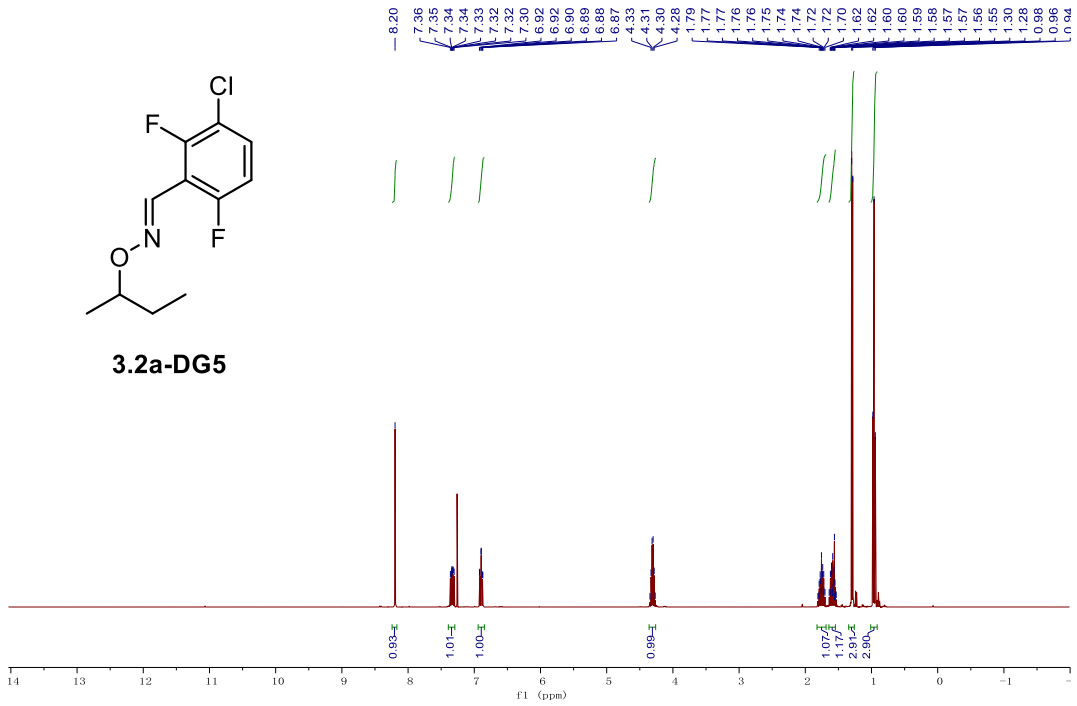


Figure 3.19 ^{13}C-NMR Spectrum of **3.2a-DG5**

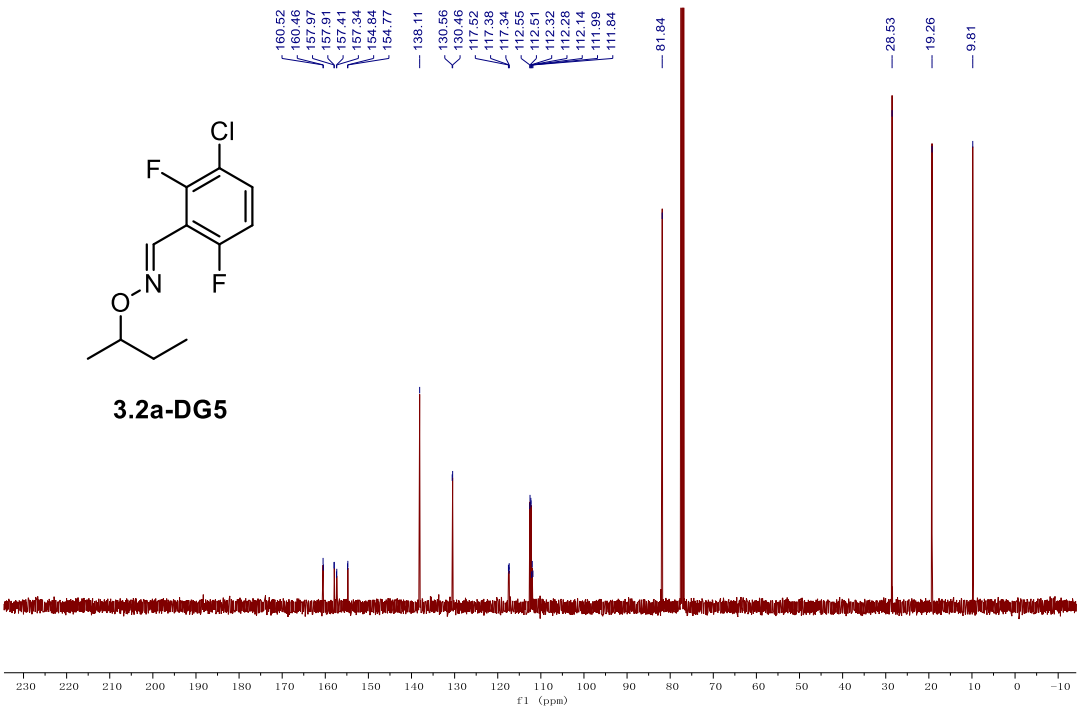


Figure 3.20 ^{19}F-NMR Spectrum of **3.2a-DG5**

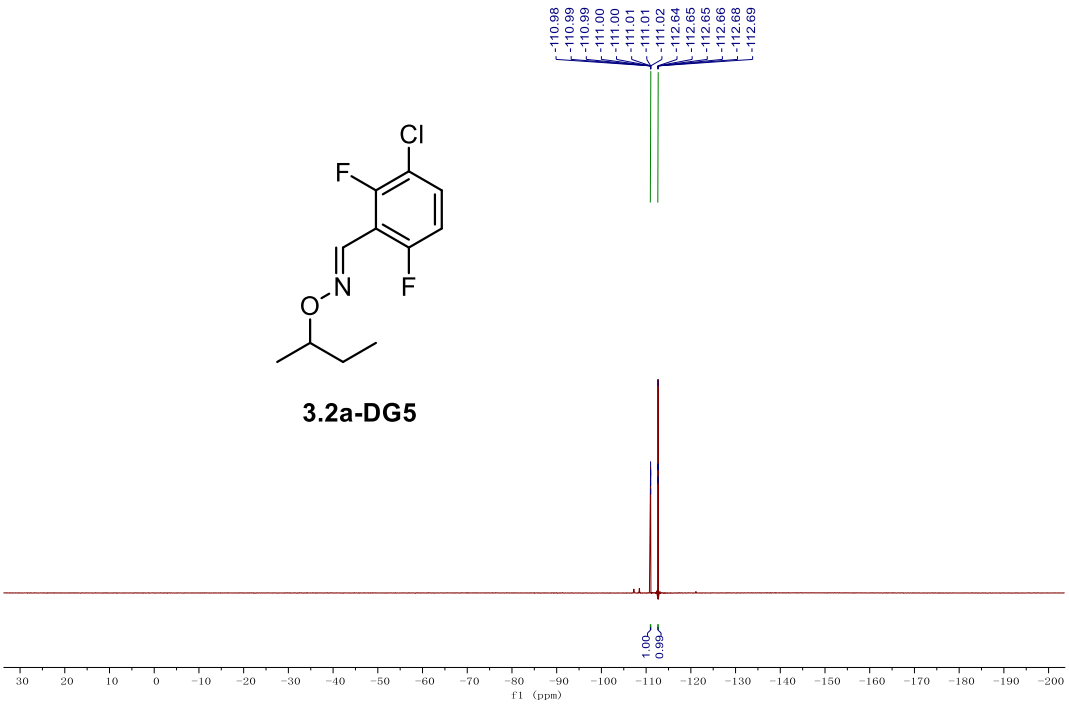


Figure 3.21 ^{1}H-NMR Spectrum of **3.2a-DG6**

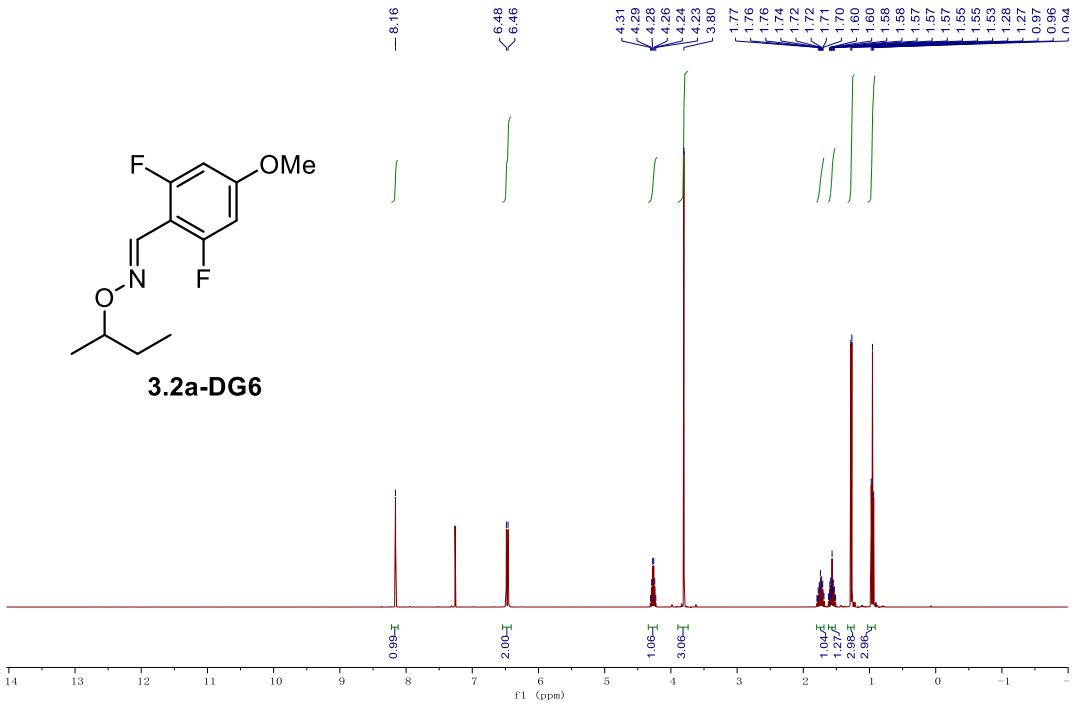


Figure 3.22 ^{13}C-NMR Spectrum of **3.2a-DG6**

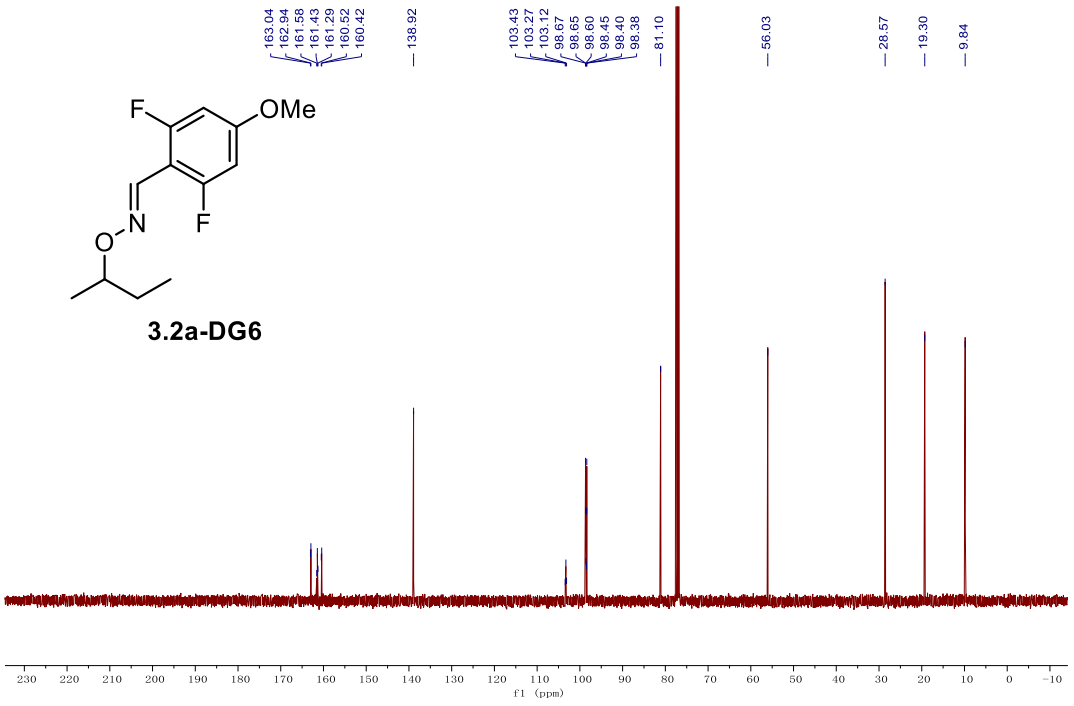


Figure 3.23 ^{19}F-NMR Spectrum of **3.2a-DG6**

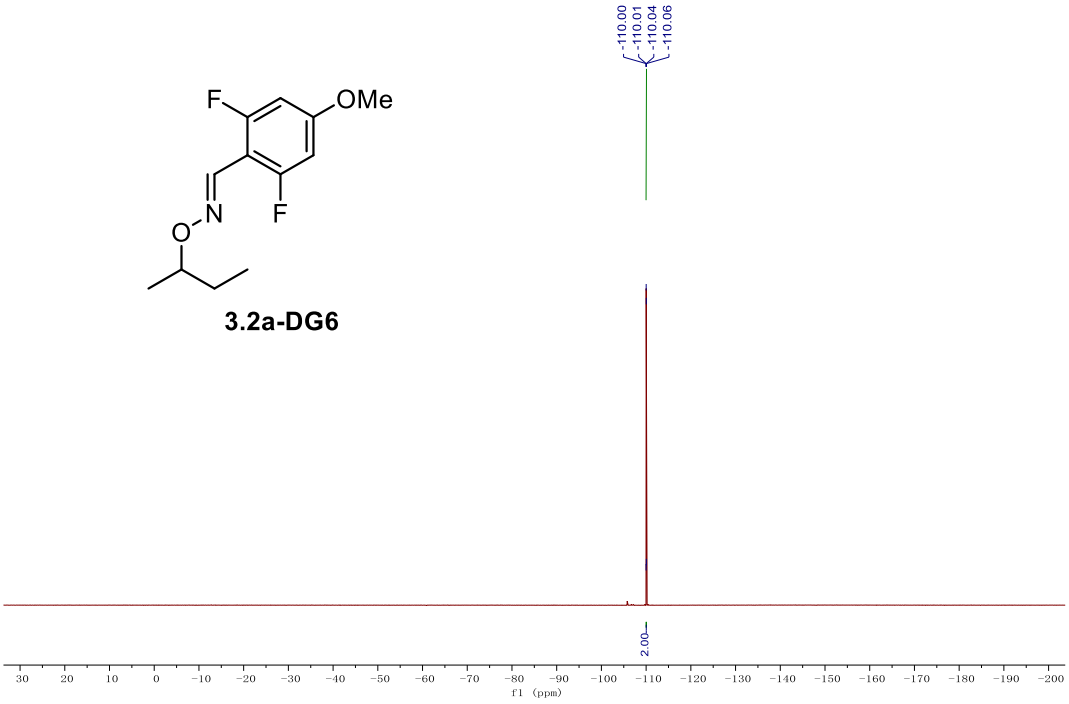


Figure 3.24 ^{1}H-NMR Spectrum of **3.2a-DG7**

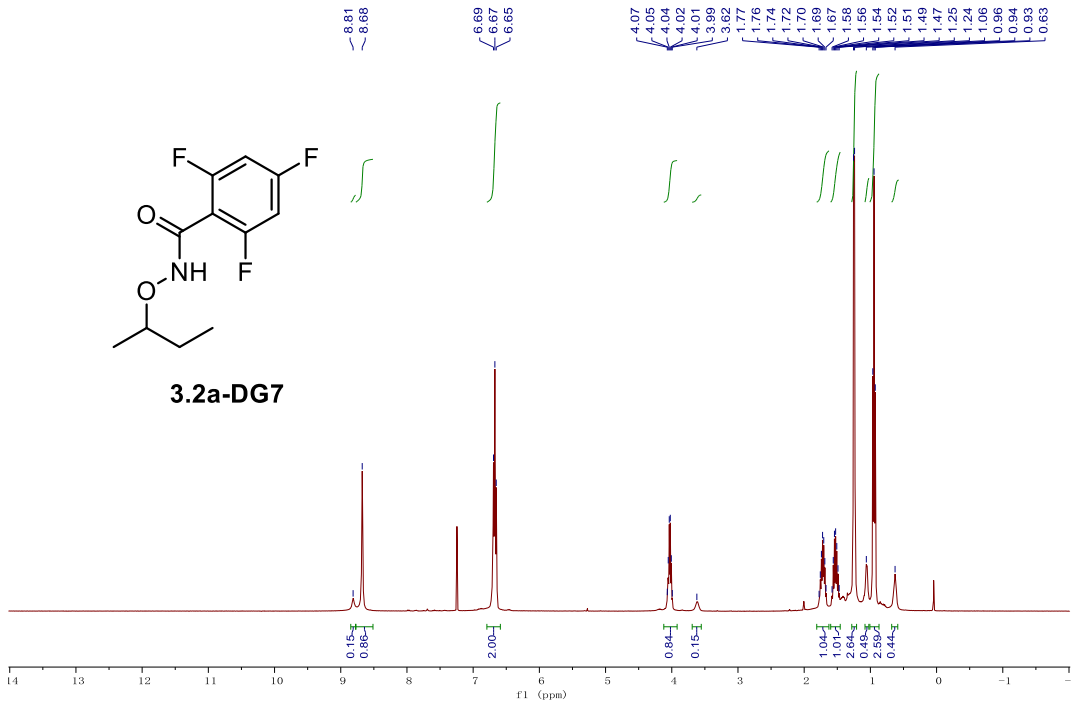


Figure 3.25 ^{13}C-NMR Spectrum of **3.2a-DG7**

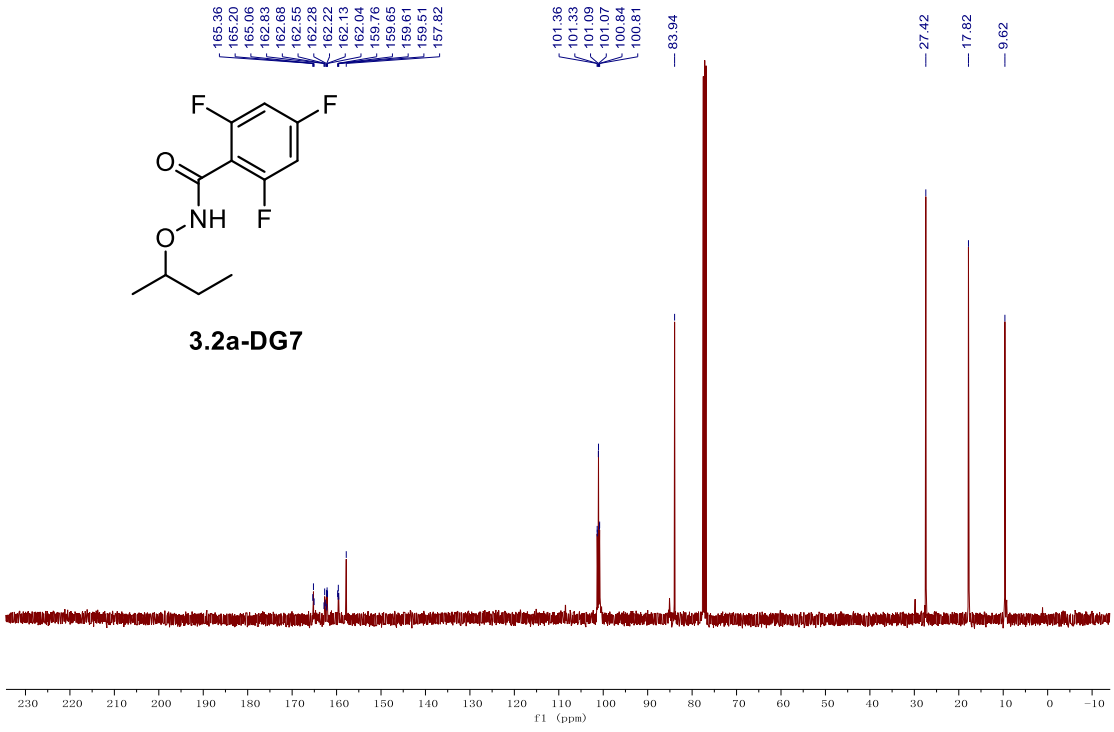


Figure 3.26 ^{19}F-NMR Spectrum of **3.2a-DG7**

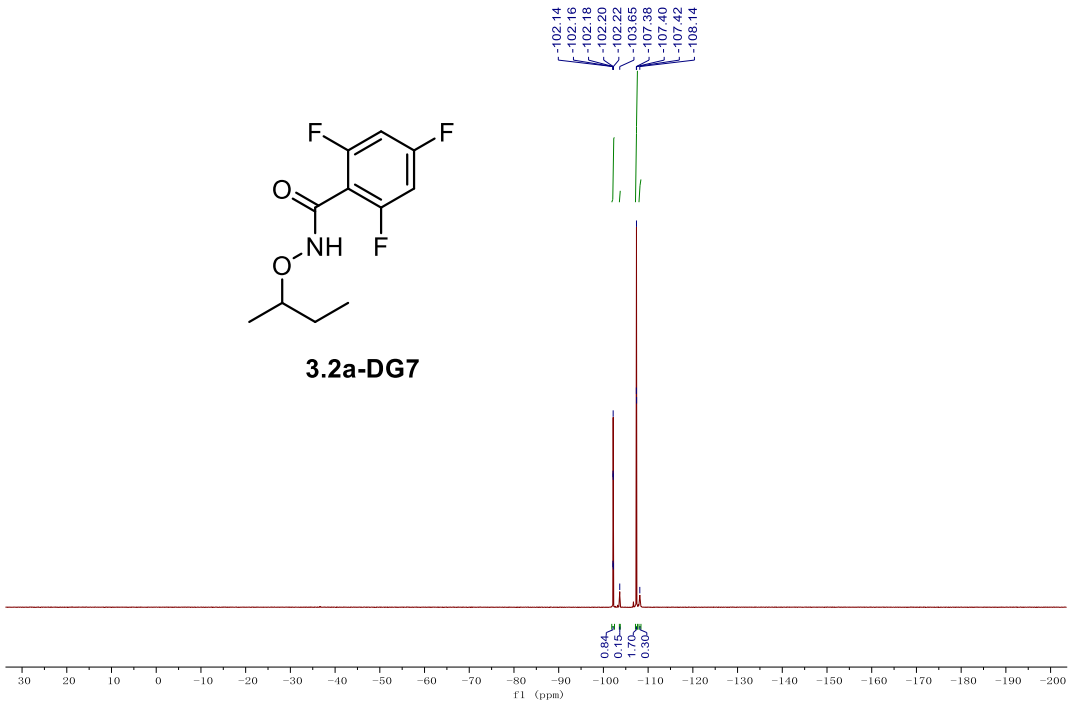


Figure 3.27 ^{1}H-NMR Spectrum of **3.2a-DG8**

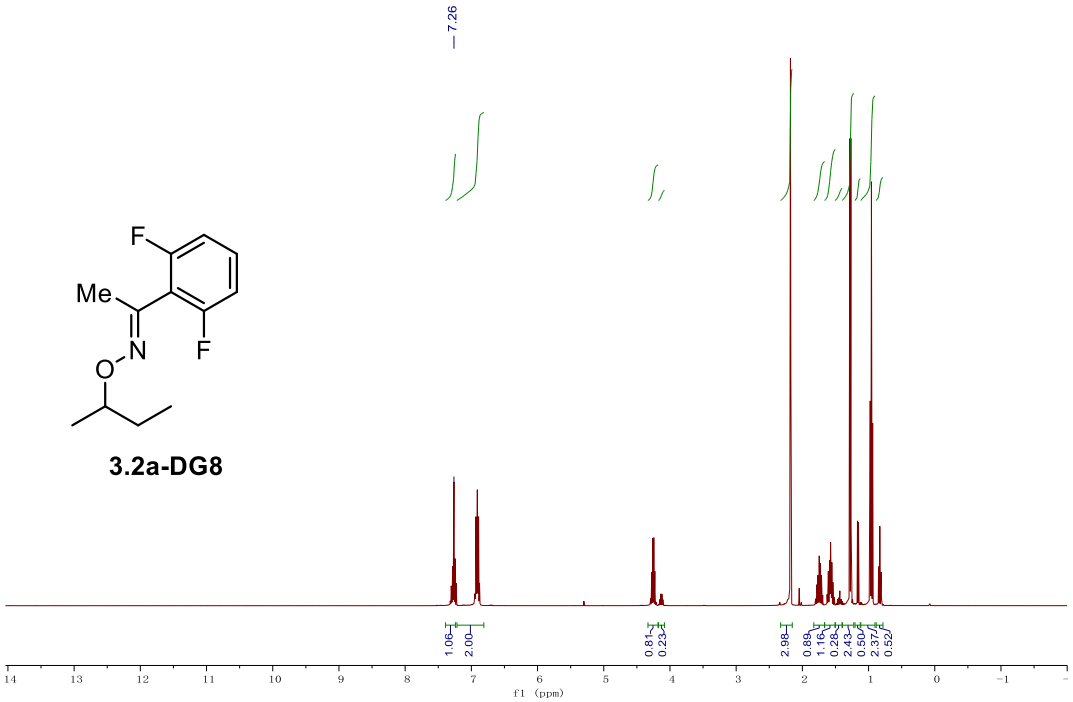


Figure 3.28 ^{13}C-NMR Spectrum of **3.2a-DG7**

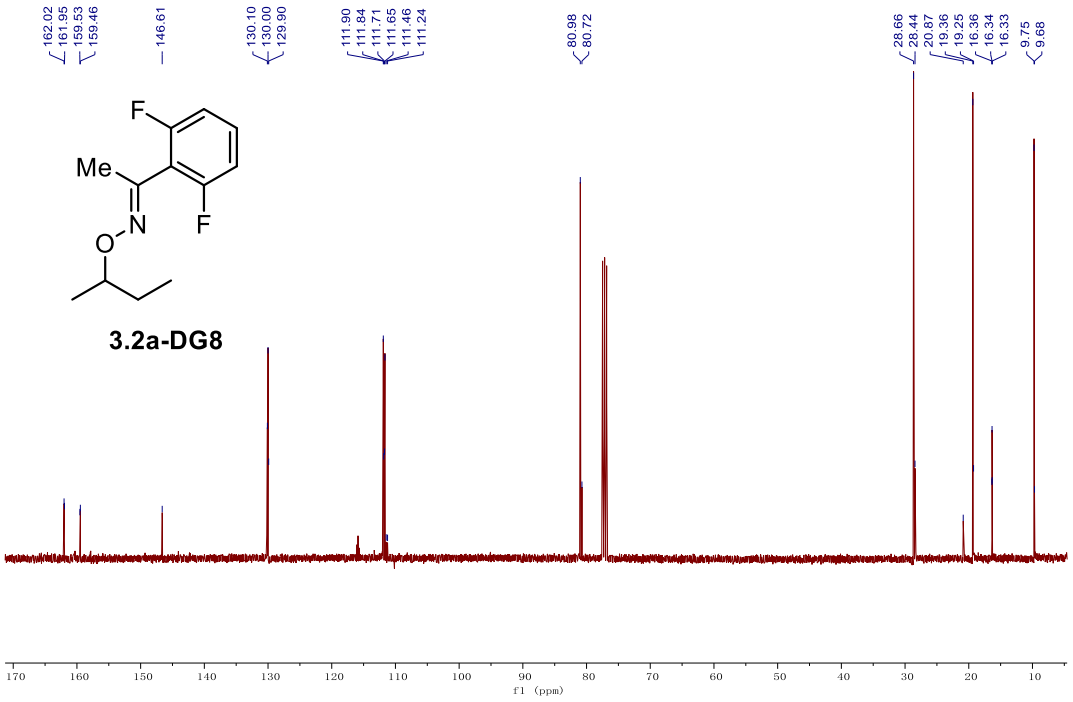


Figure 3.29 ^{19}F-NMR Spectrum of **3.2a-DG8**

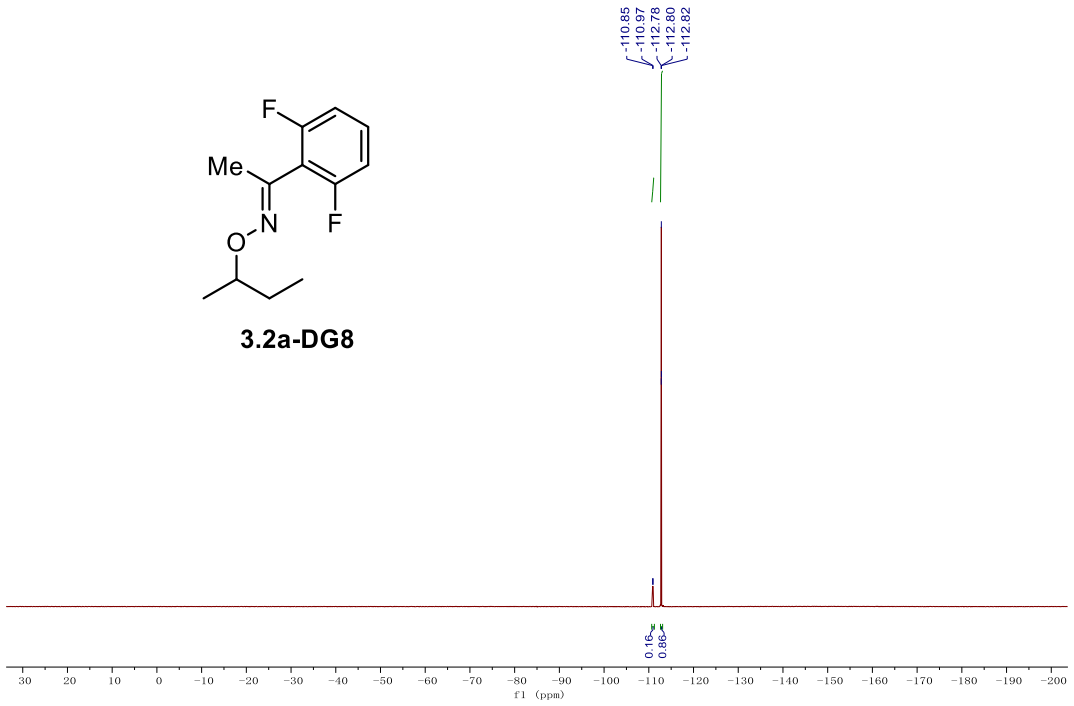


Figure 3.30 ^{1}H-NMR Spectrum of **3.2a-DG9**

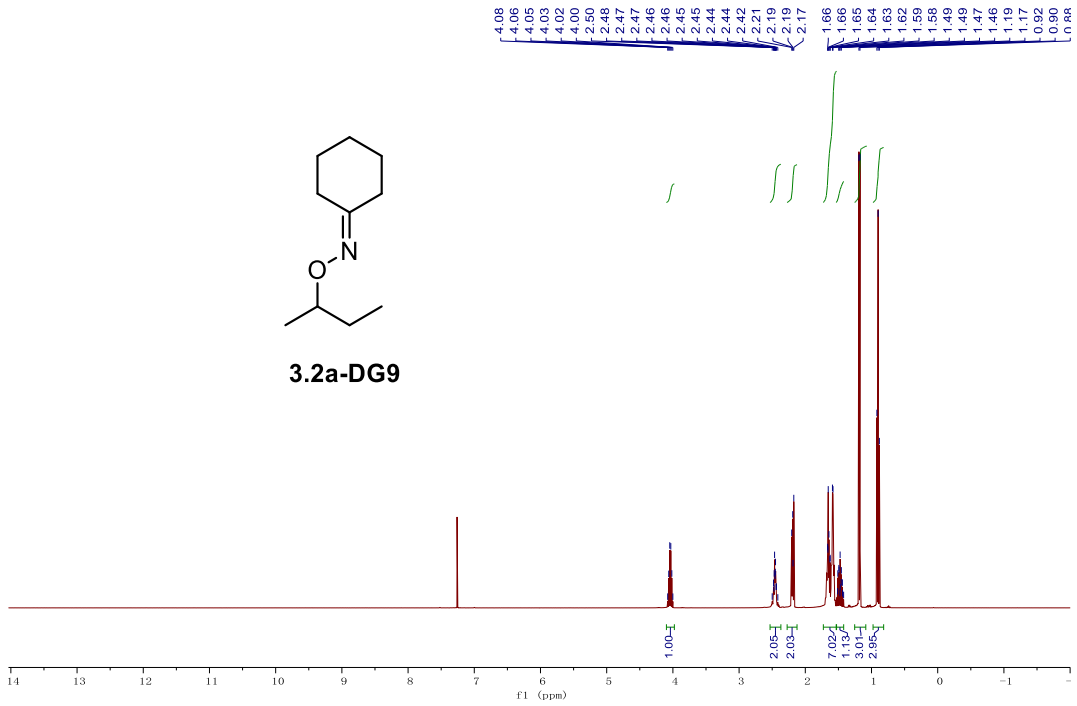


Figure 3.31 ^{13}C-NMR Spectrum of **3.2a-DG9**

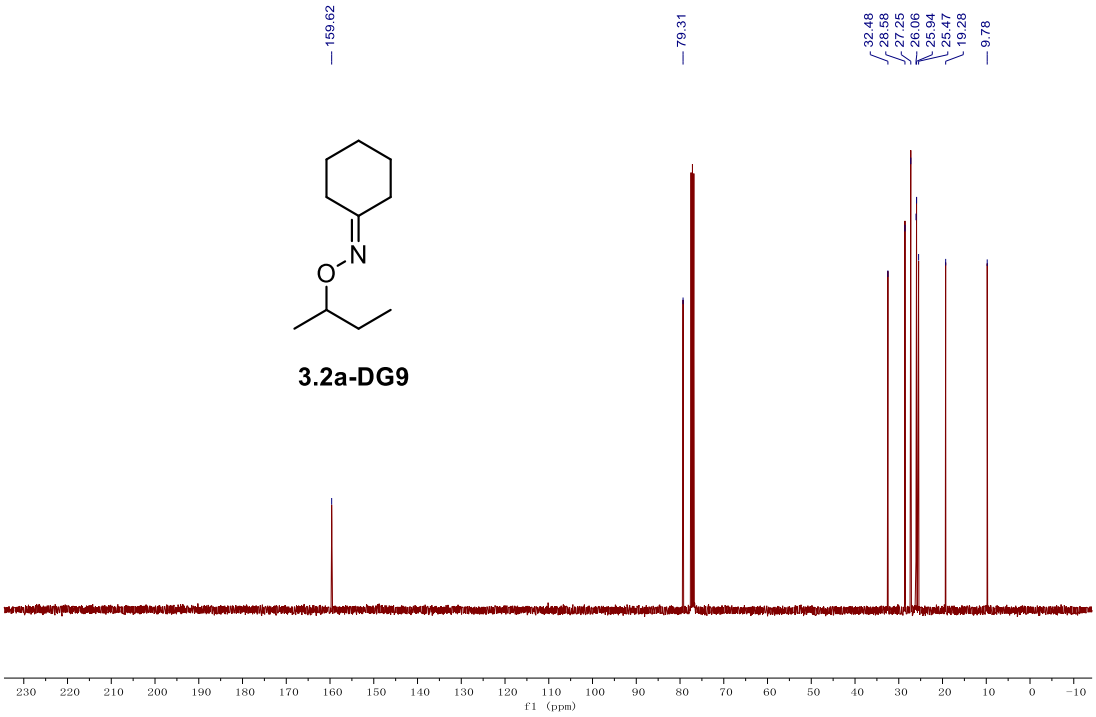


Figure 3.32 ^{1}H-NMR Spectrum of **3.2a-DG10**

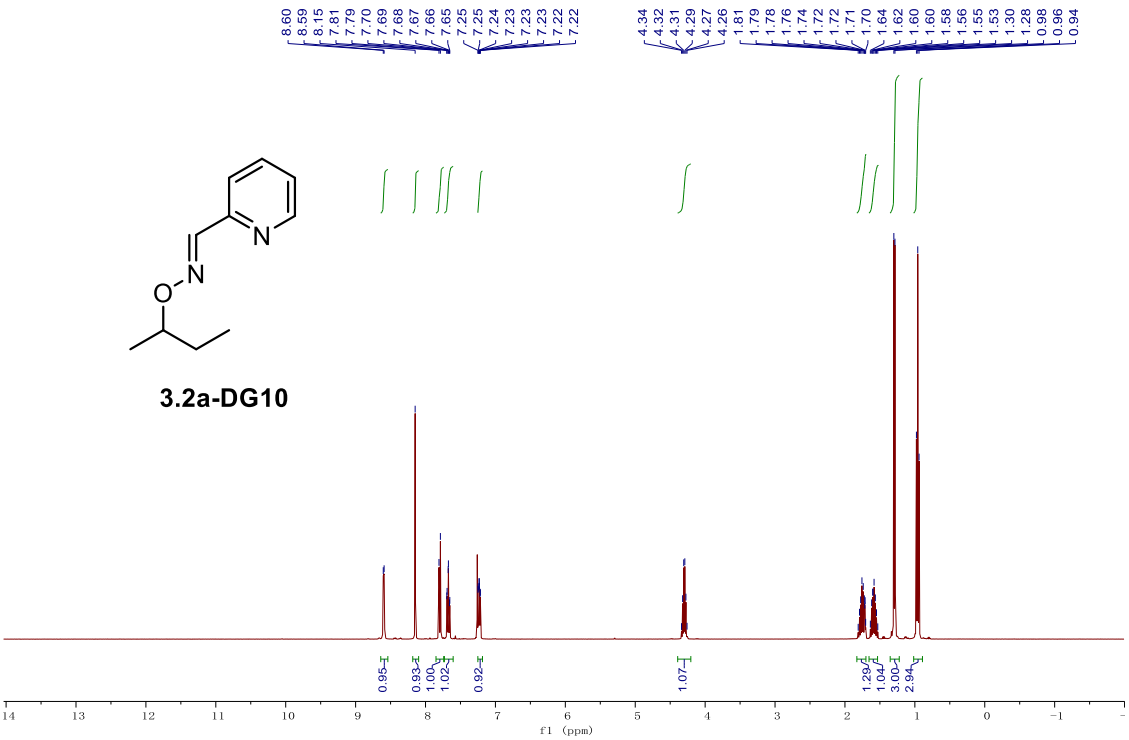


Figure 3.33 ^{13}C-NMR Spectrum of **3.2a-DG10**

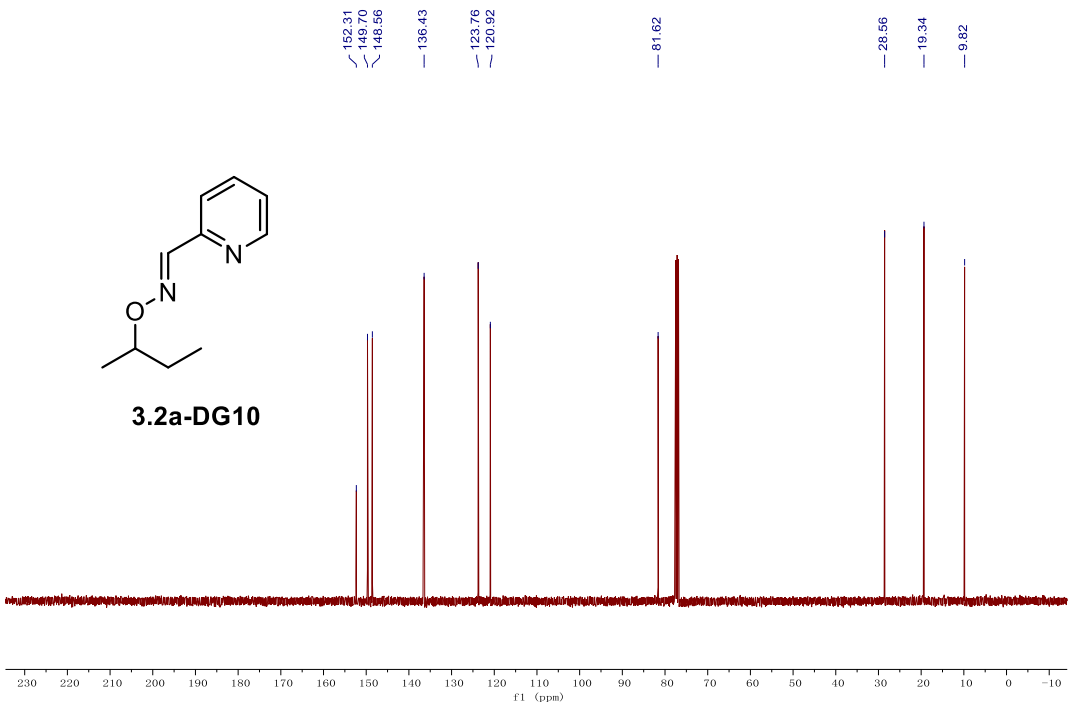


Figure 3.34 ^{1}H-NMR Spectrum of **3.2a-DG11**

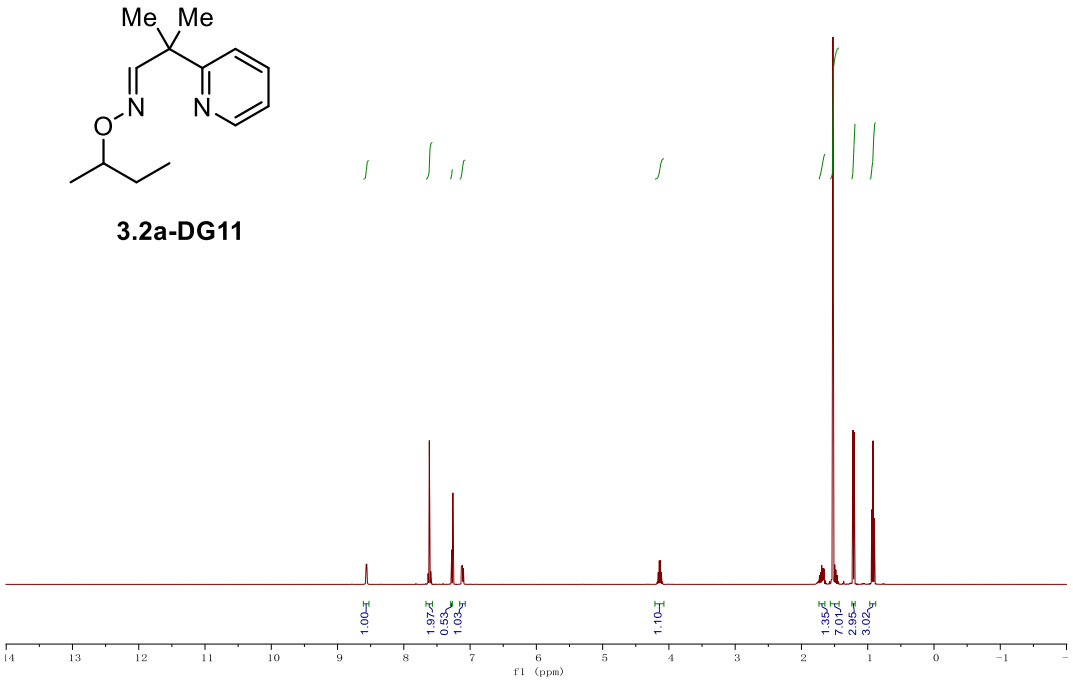


Figure 3.35 ^{13}C-NMR Spectrum **of 3.2a-DG11**

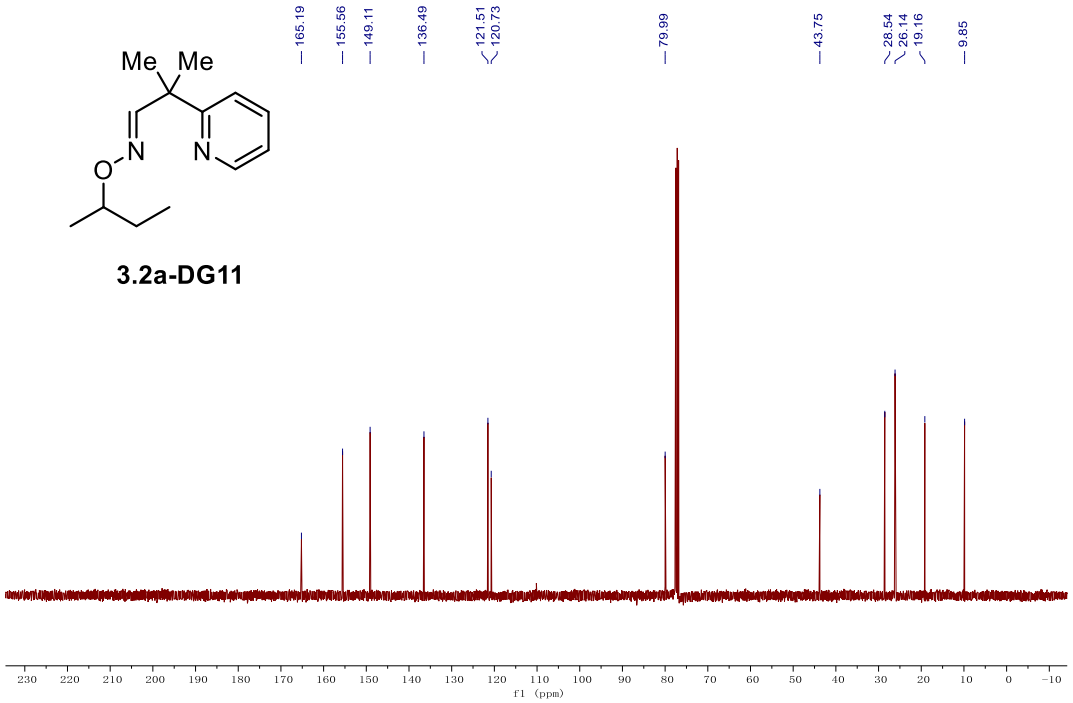


Figure 3.36 ^{1}H-NMR Spectrum of **3.2a-DG12**

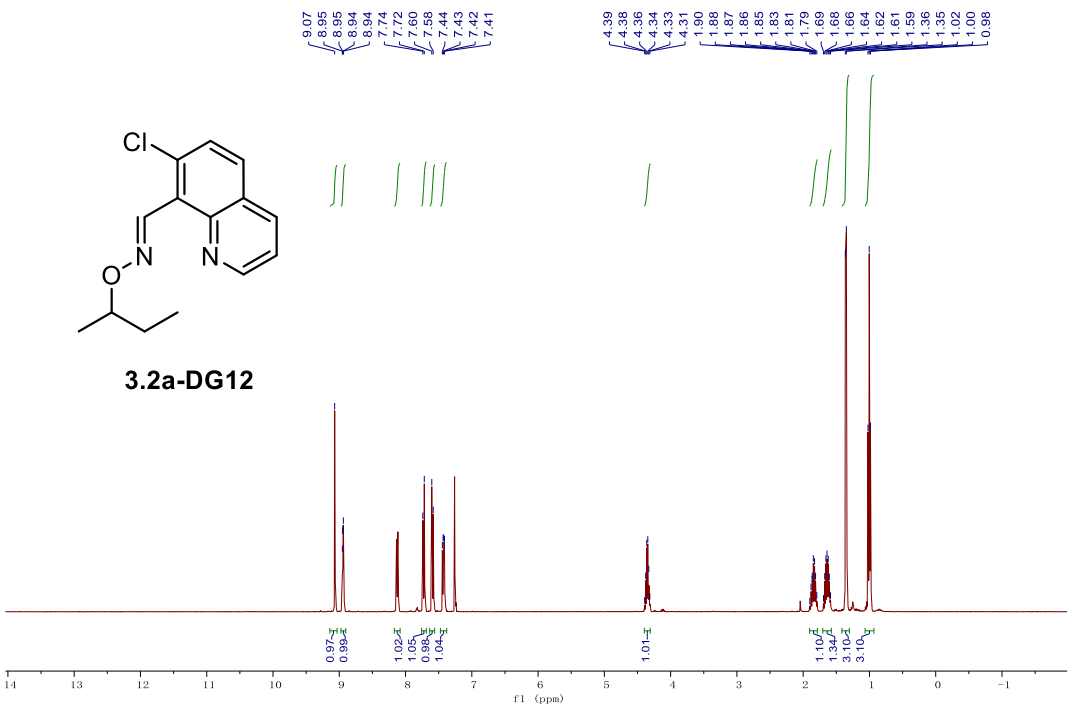


Figure 3.37 ^{13}C-NMR Spectrum of **3.2a-DG12**

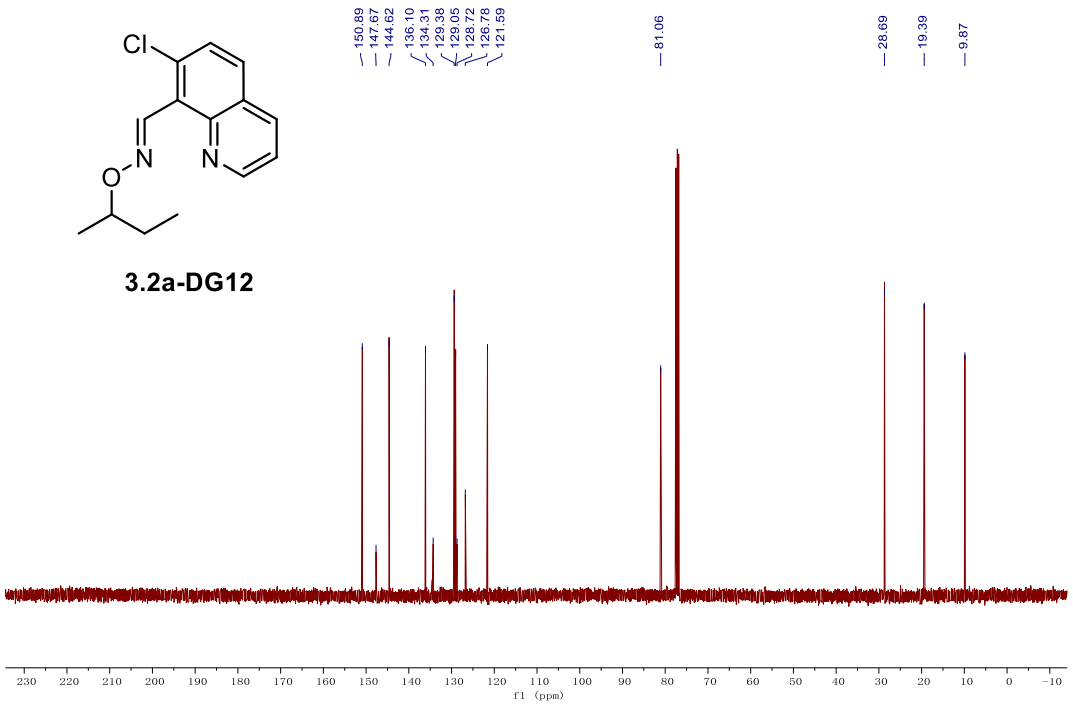


Figure 3.38 ^{1}H-NMR Spectrum of **3.2b**

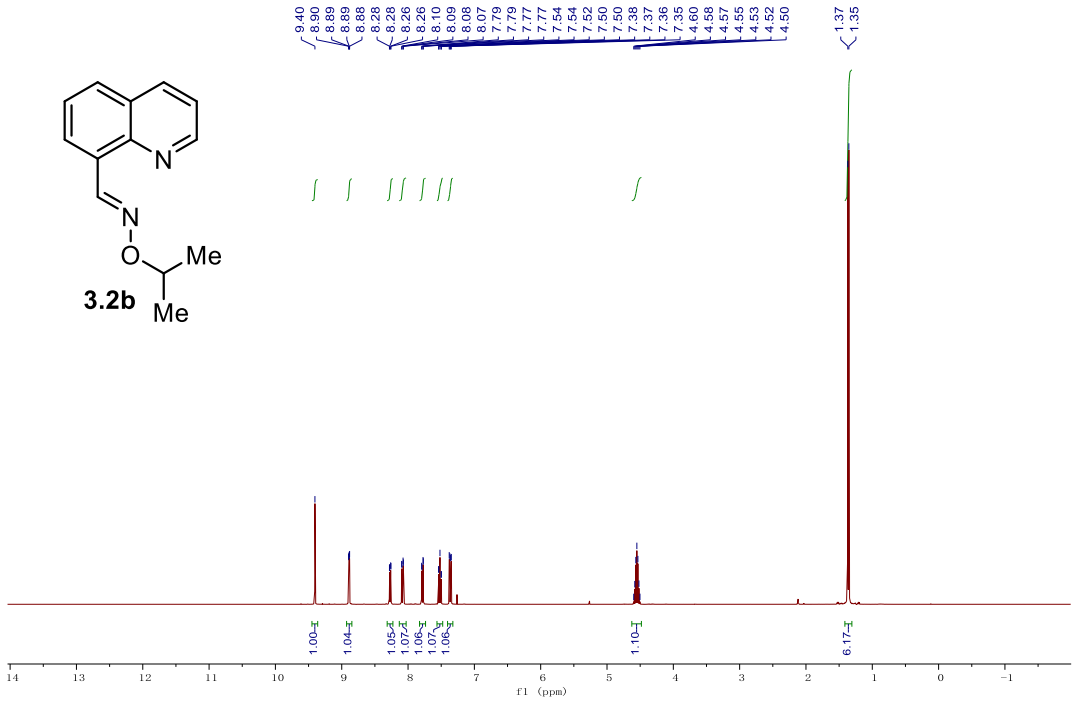


Figure 3.39 ^{13}C-NMR Spectrum of **3.2b**

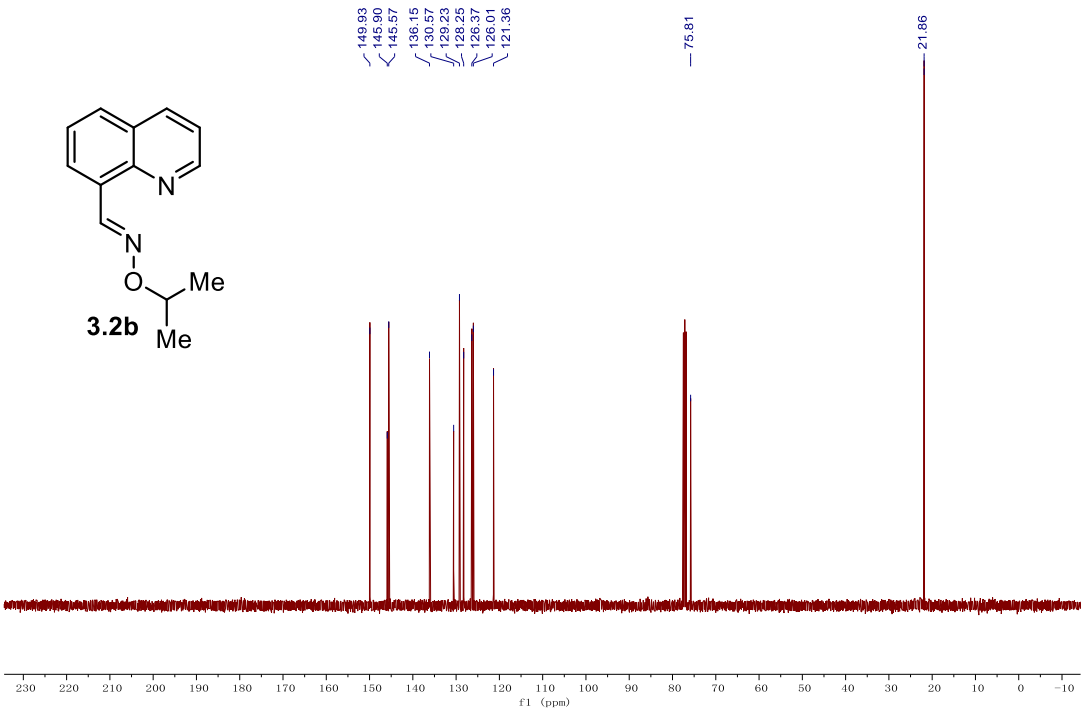


Figure 3.40 ^{1}H-NMR Spectrum of **3.2c**

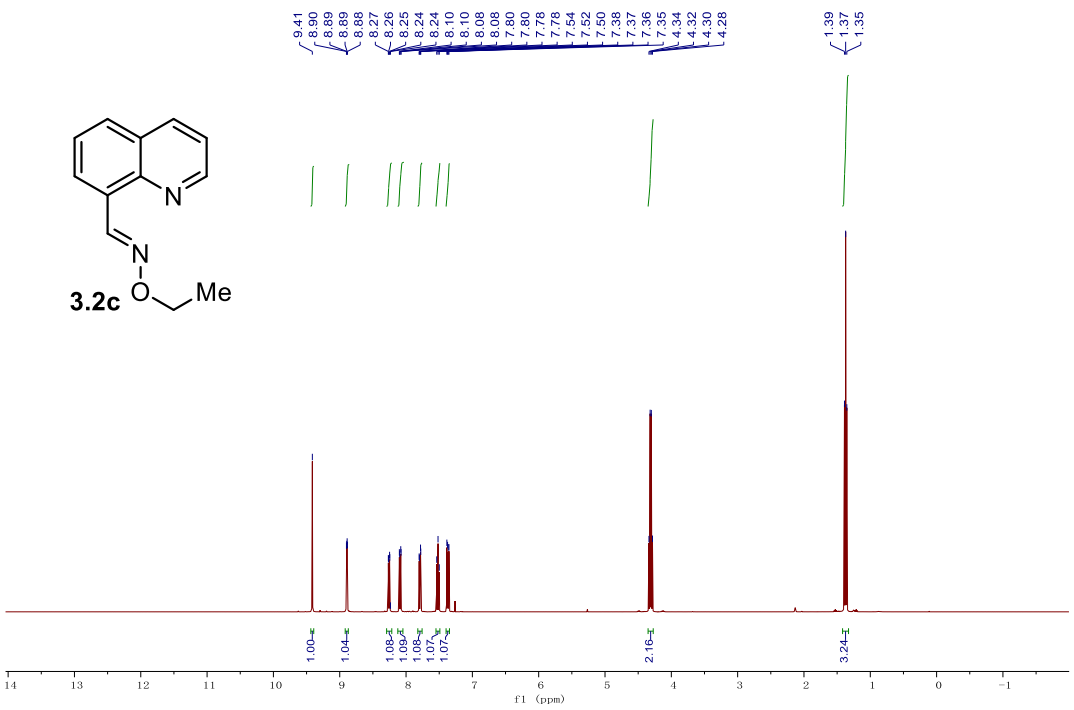


Figure 3.41 ^{13}C-NMR Spectrum of **3.2c**

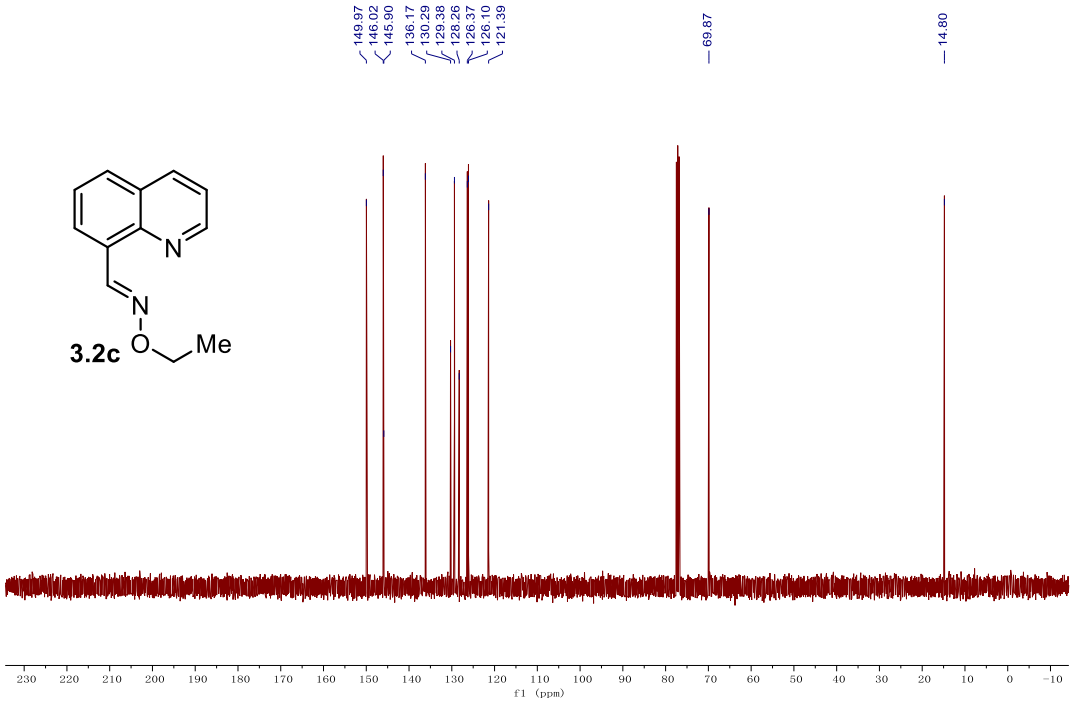


Figure 3.42 ^{1}H-NMR Spectrum of **3.2d**

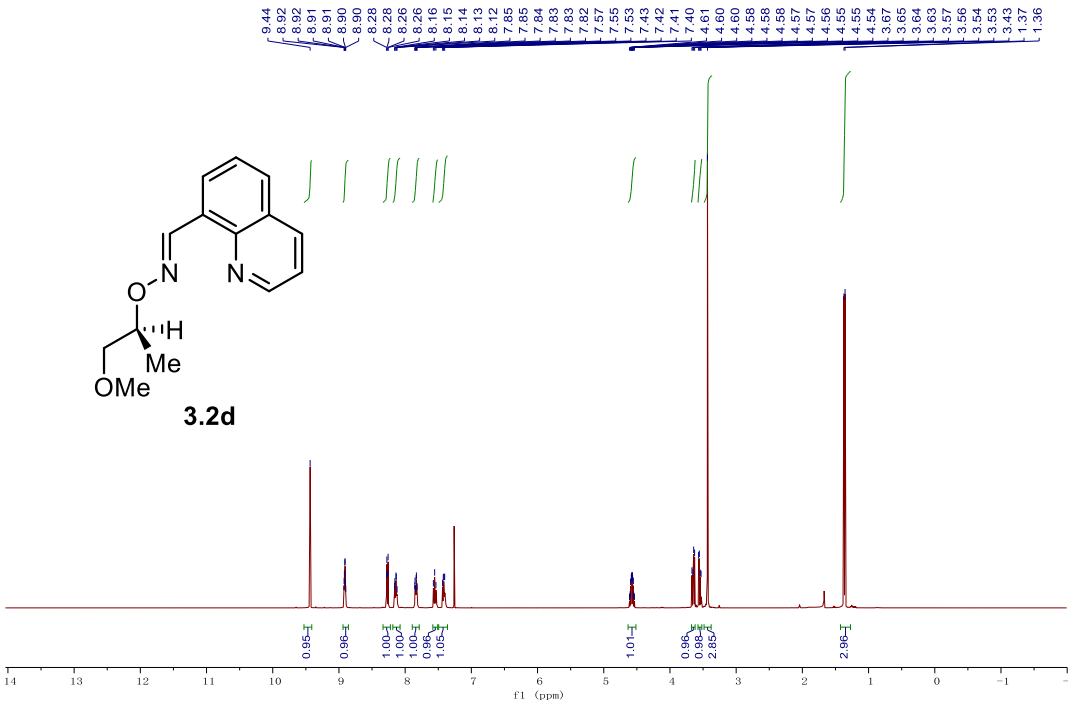


Figure 3.43 ^{13}C-NMR Spectrum of **3.2d**

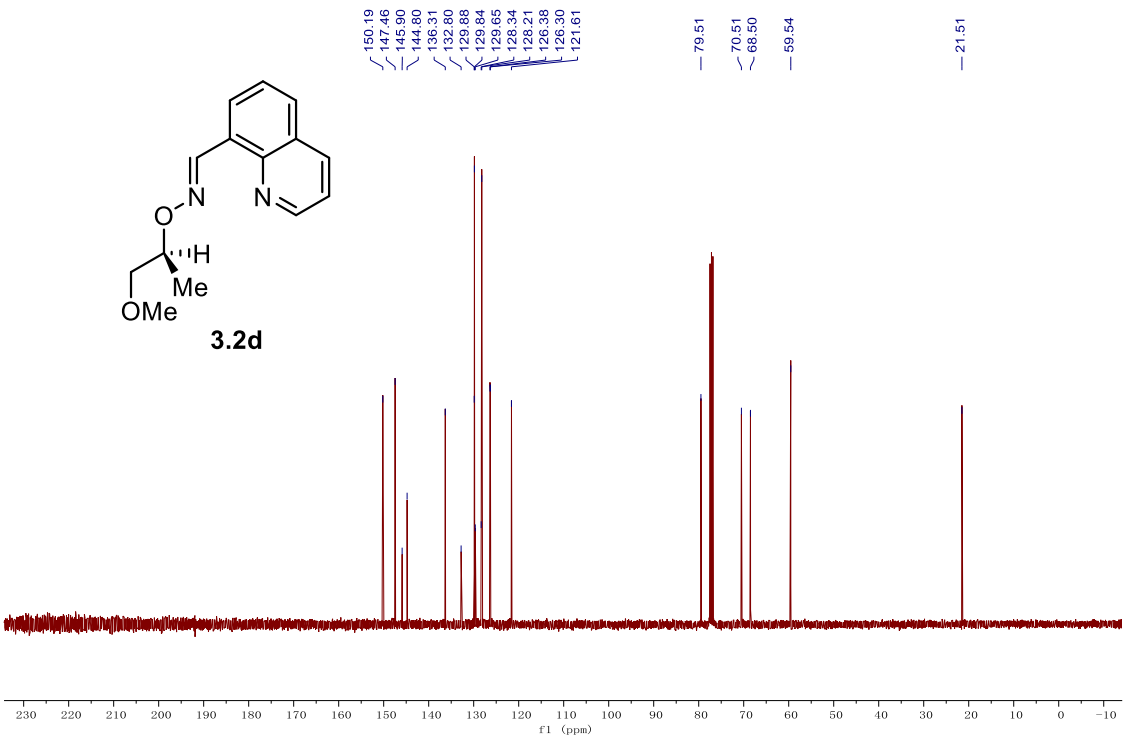


Figure 3.44 ^{1}H-NMR Spectrum of **3.2e**

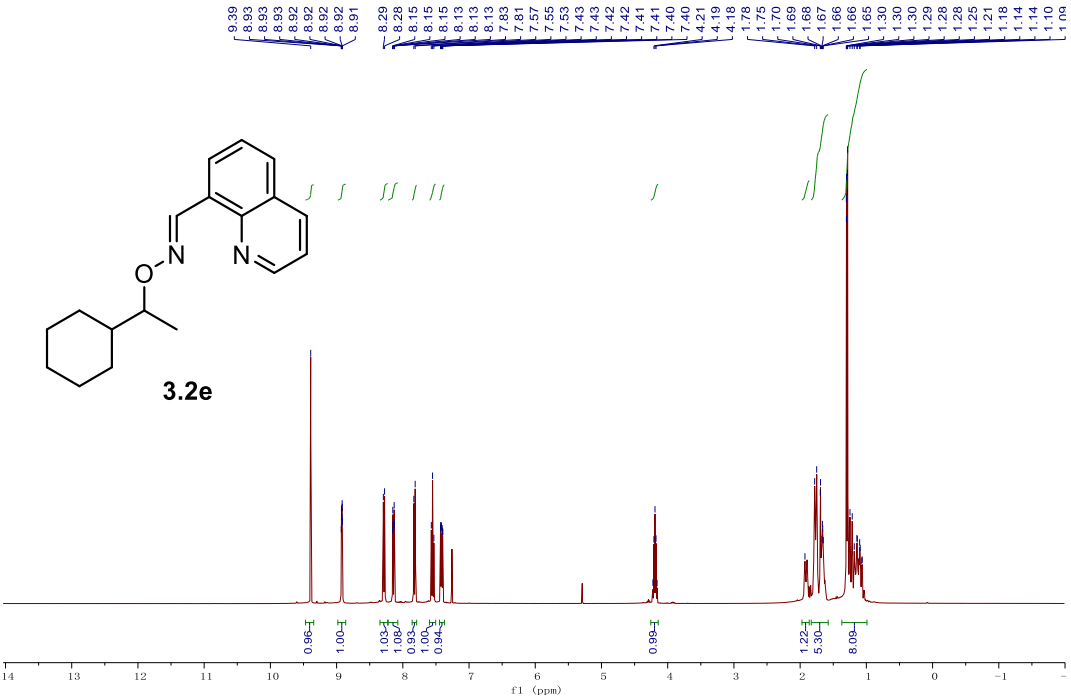


Figure 3.45 ^{13}C-NMR Spectrum of **3.2e**

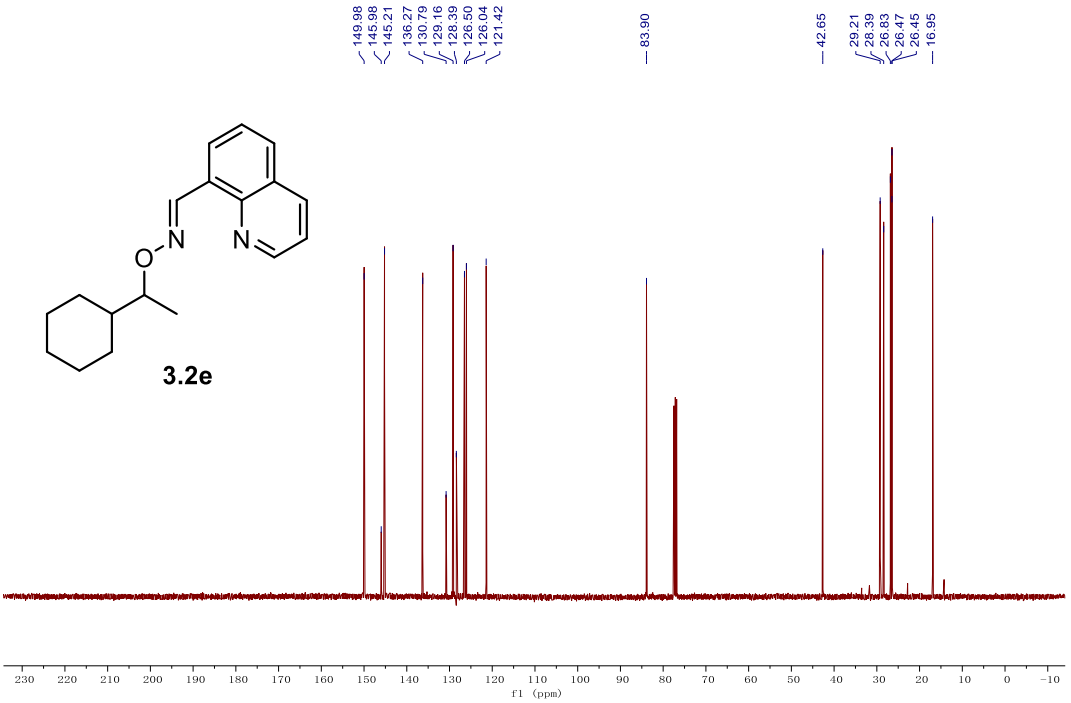


Figure 3.46 ^{1}H-NMR Spectrum of **3.2f**

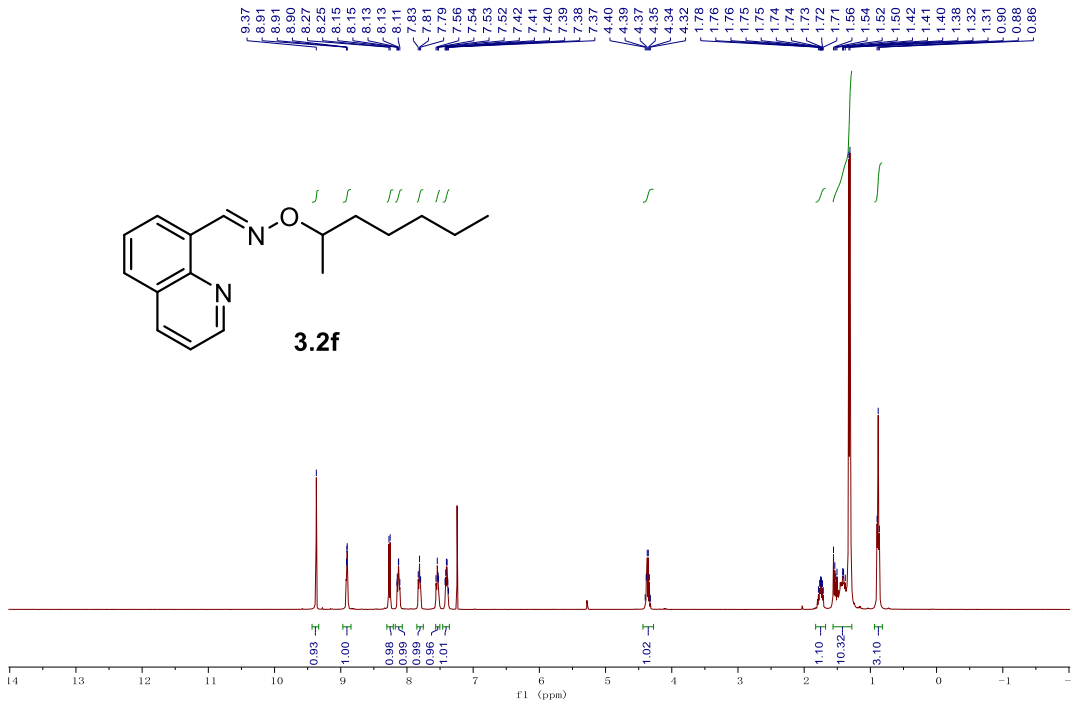


Figure 3.47 ^{13}C-NMR Spectrum of **3.2f**

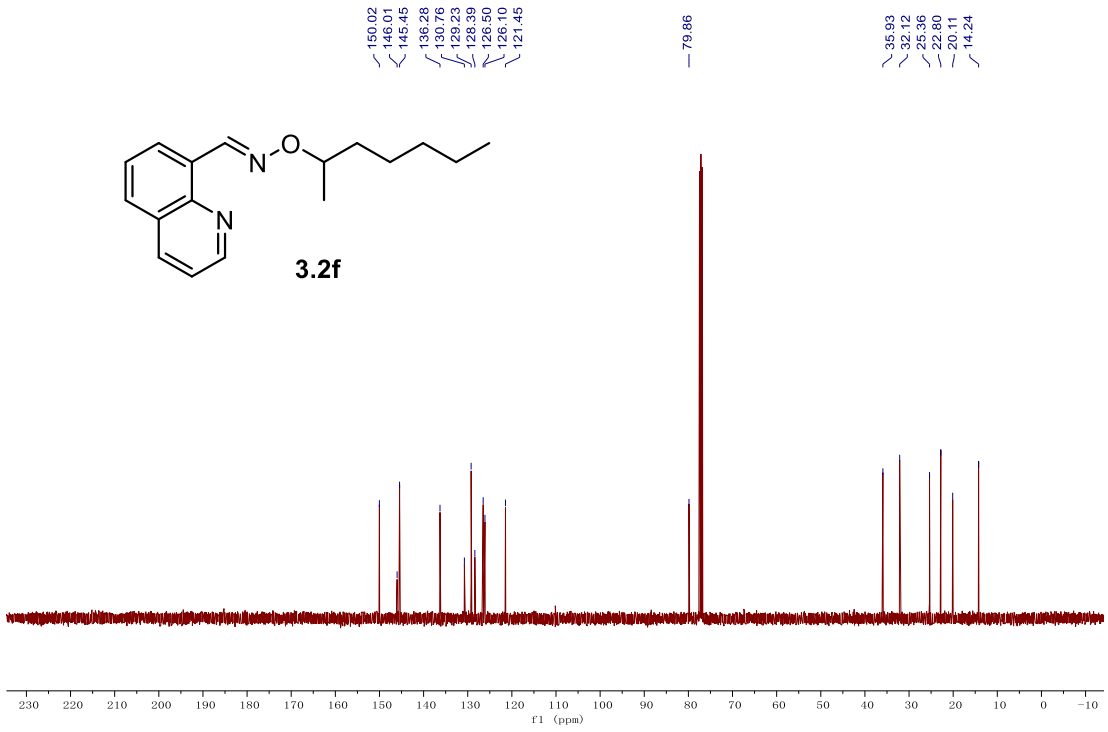


Figure 3.48 ^{1}H-NMR Spectrum of **3.2g**

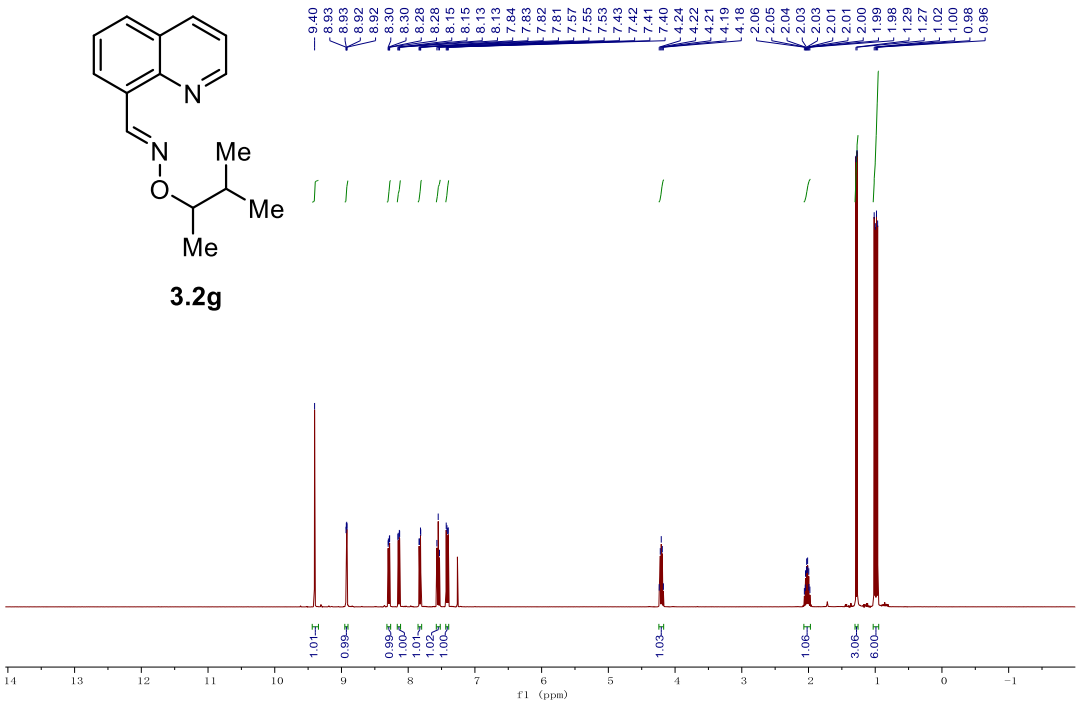


Figure 3.49 ^{13}C-NMR Spectrum of **3.2g**

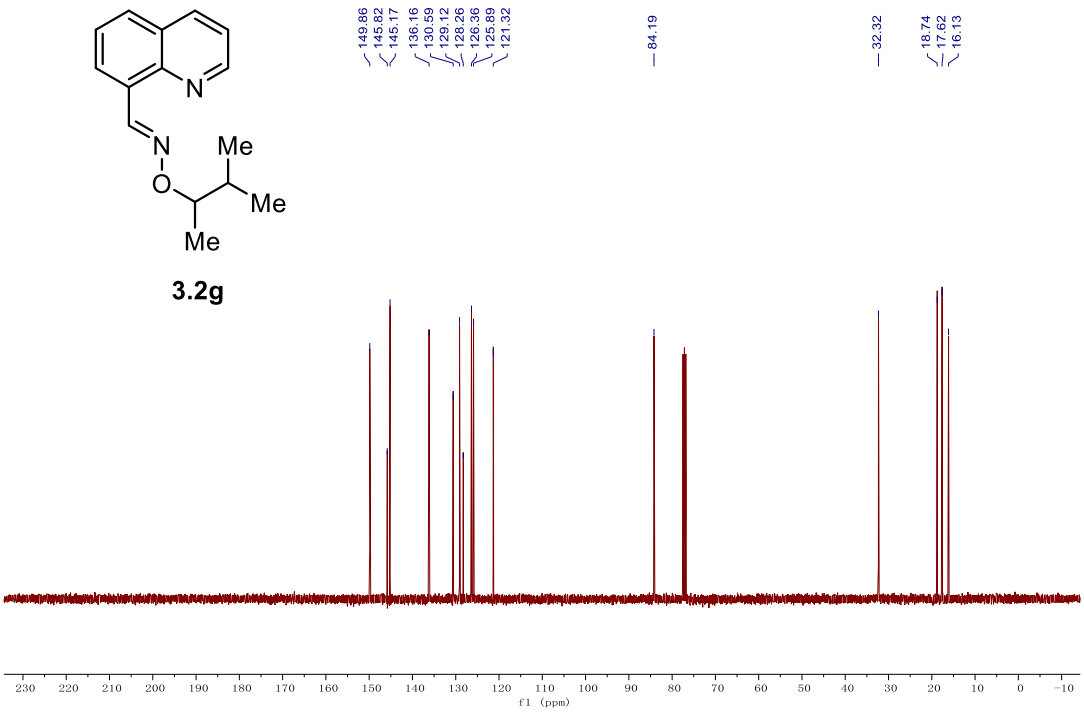


Figure 3.50 ^{1}H-NMR Spectrum of **3.2i**

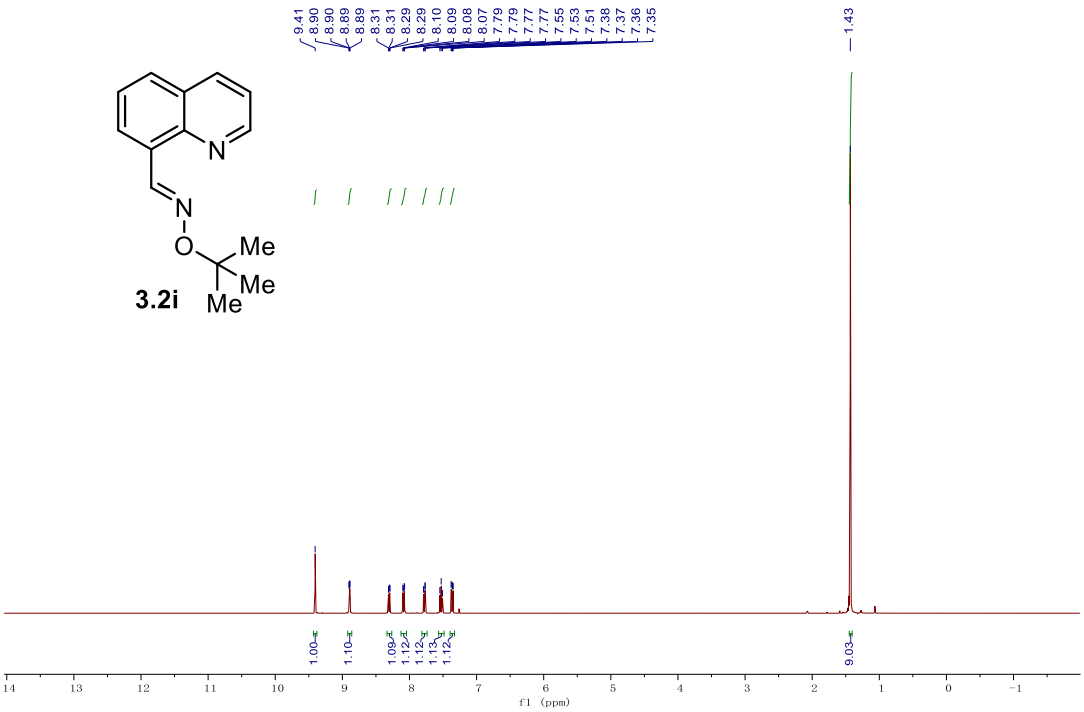


Figure 3.51 ^{13}C-NMR Spectrum of **3.2i**

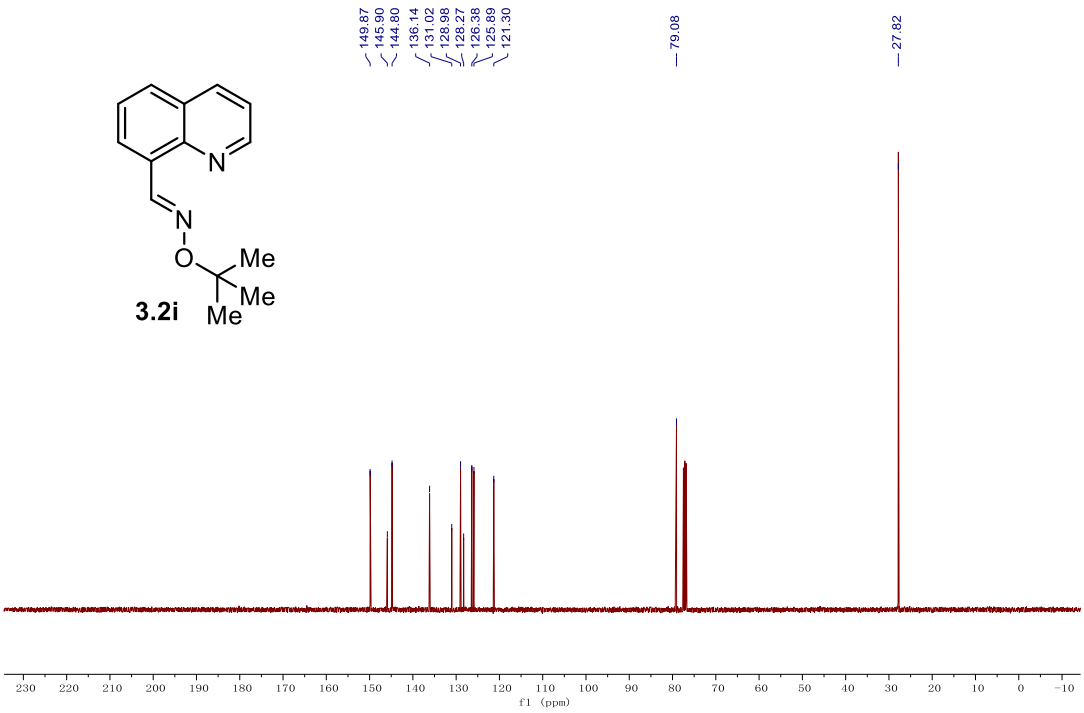


Figure 3.52 ^{1}H-NMR Spectrum of **3.16**

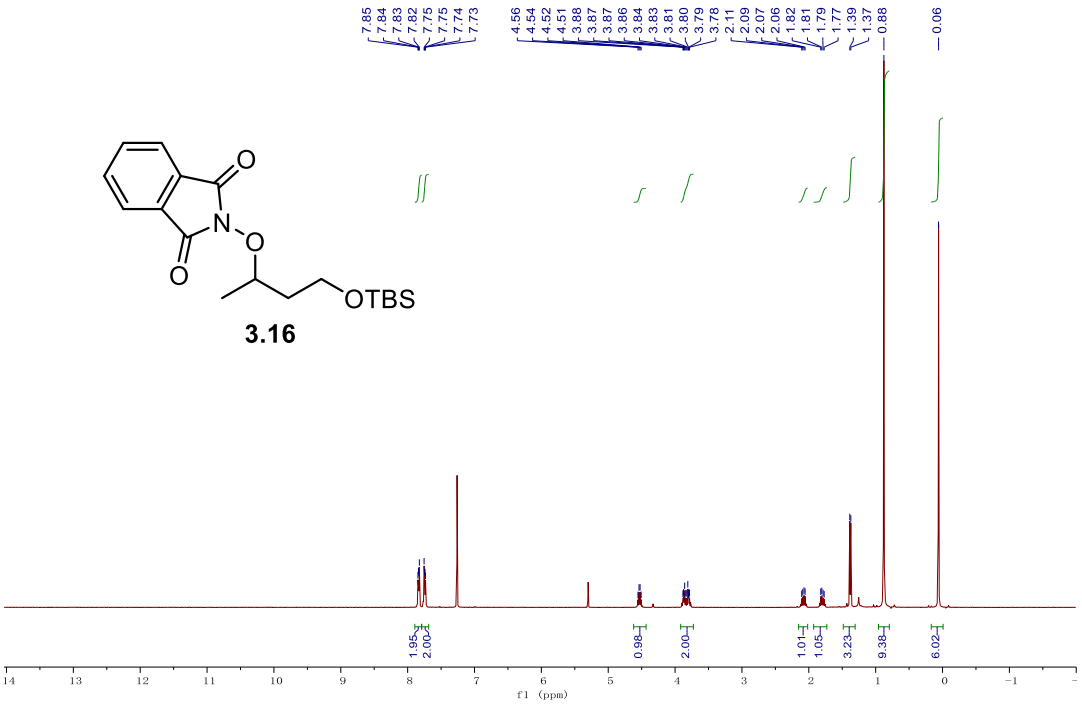


Figure 3.53 ^{13}C-NMR Spectrum of **3.16**

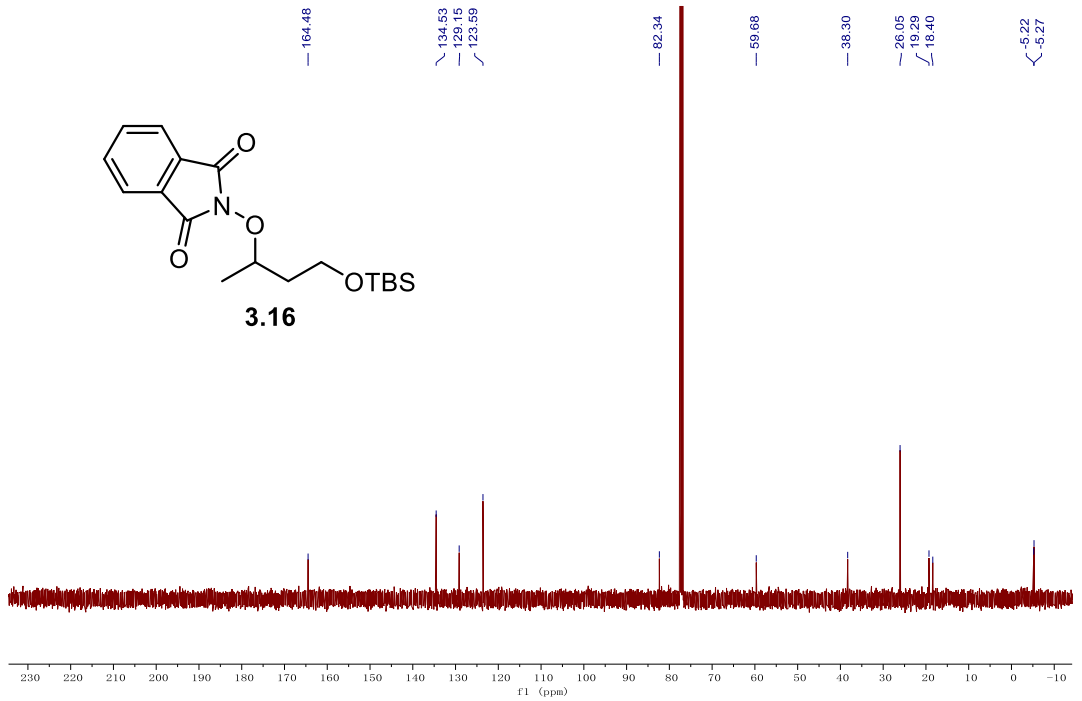


Figure 3.54 ^{1}H-NMR Spectrum of **3.17**

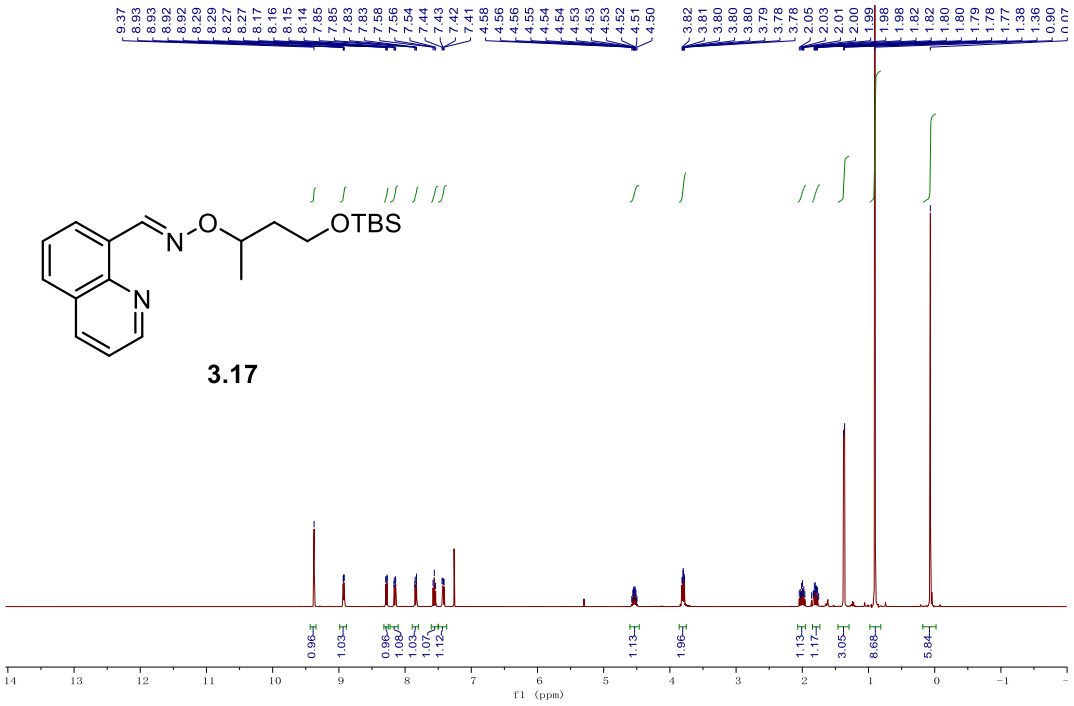


Figure 3.55 ^{13}C-NMR Spectrum of **3.17**

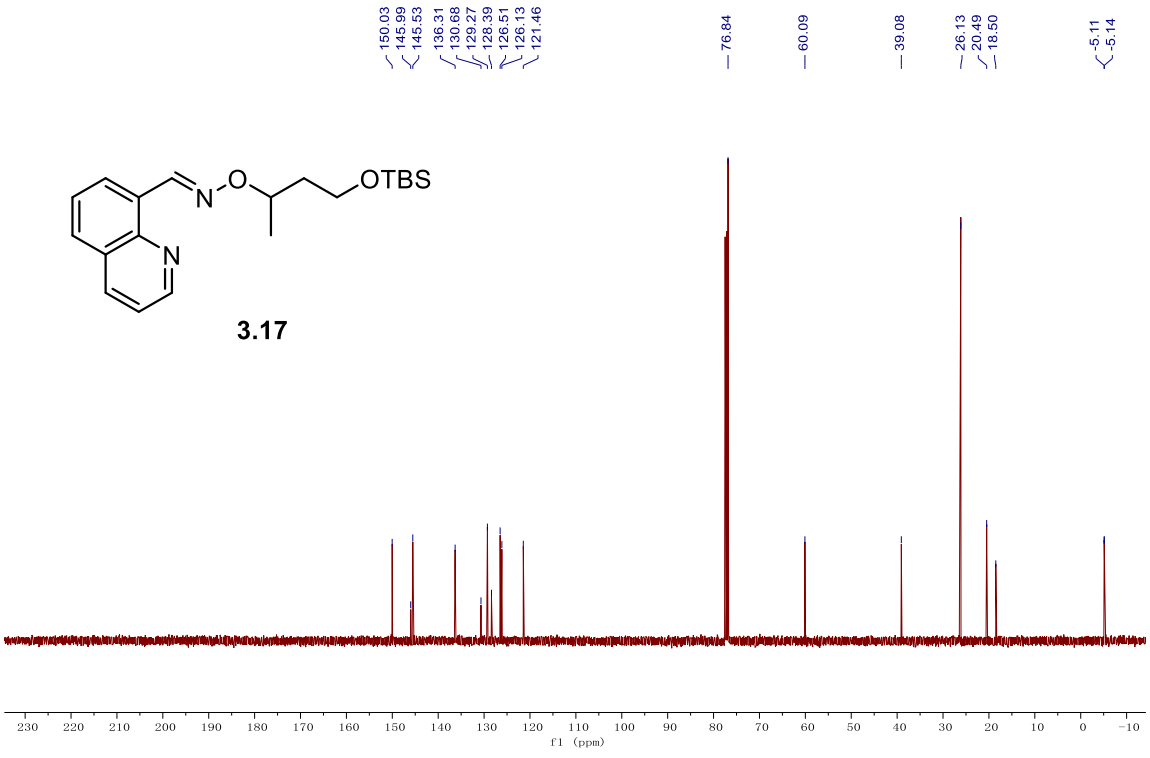


Figure 3.56 ^{1}H-NMR Spectrum of **3.18**

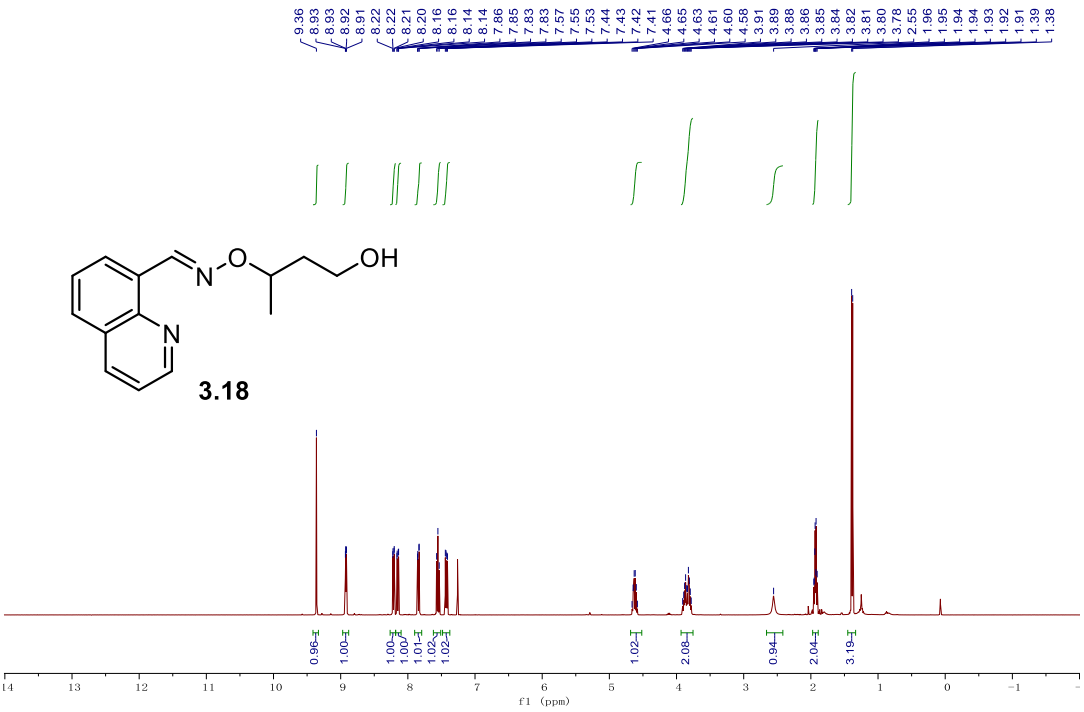


Figure 3.57 ^{13}C-NMR Spectrum of **3.18**

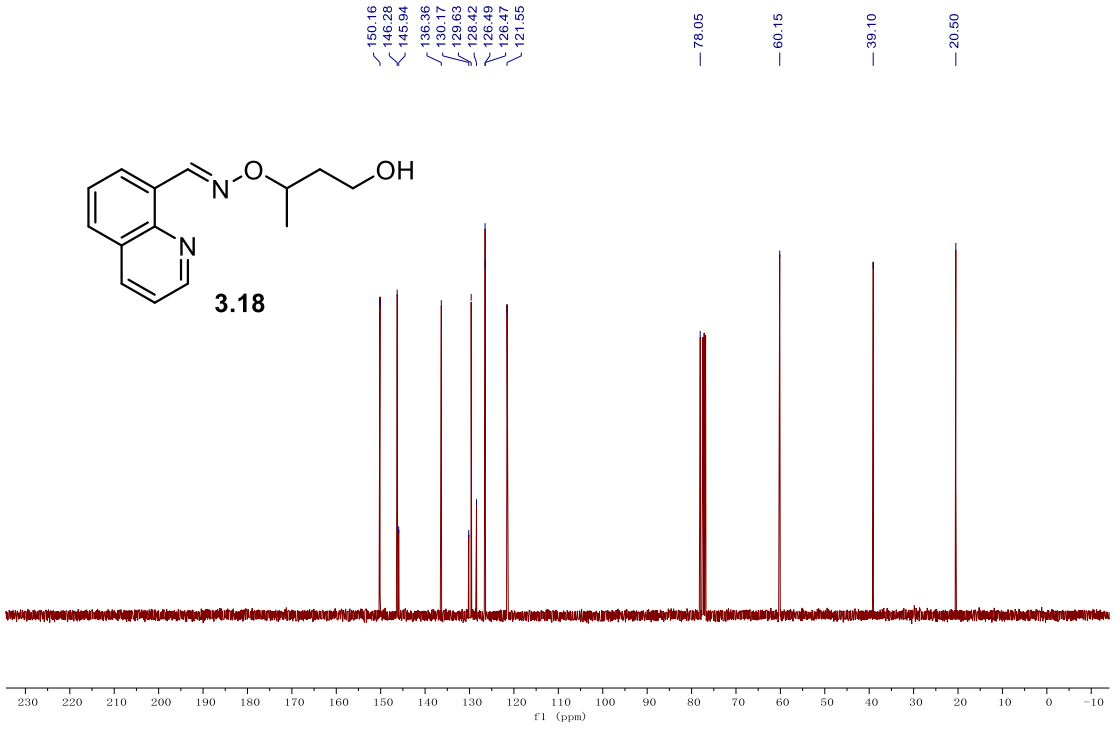


Figure 3.58 ^{1}H-NMR Spectrum of **3.2h**

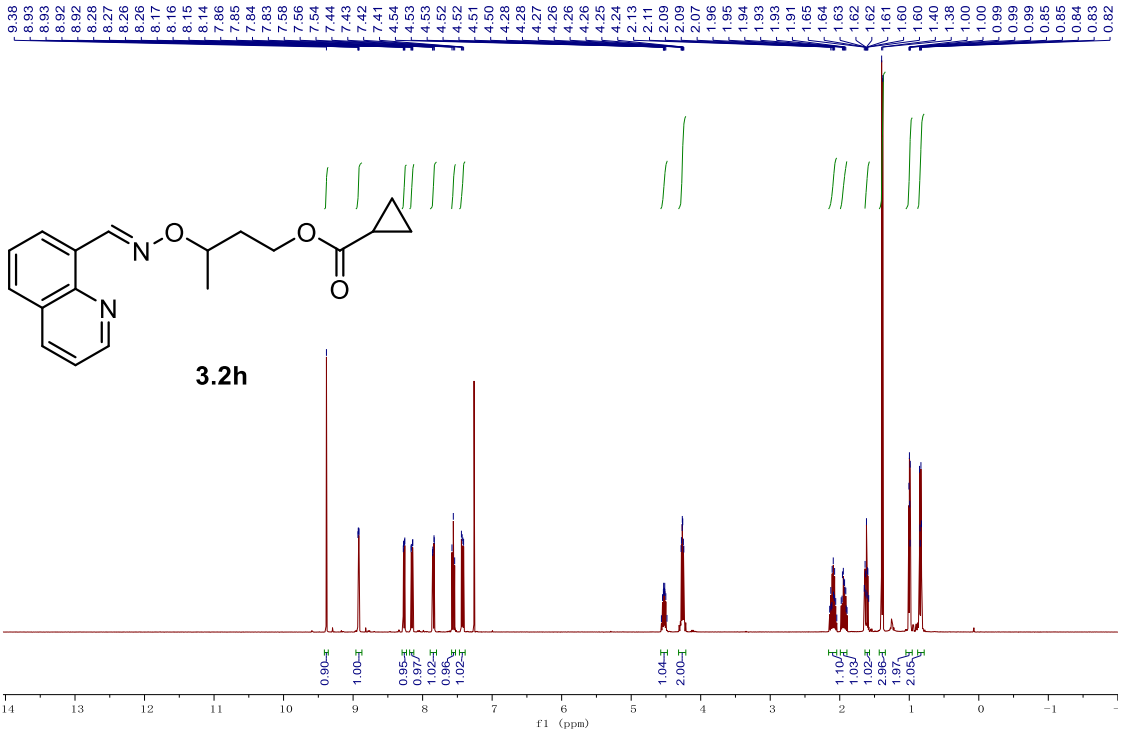


Figure 3.59 ^{13}C-NMR Spectrum of **3.2h**

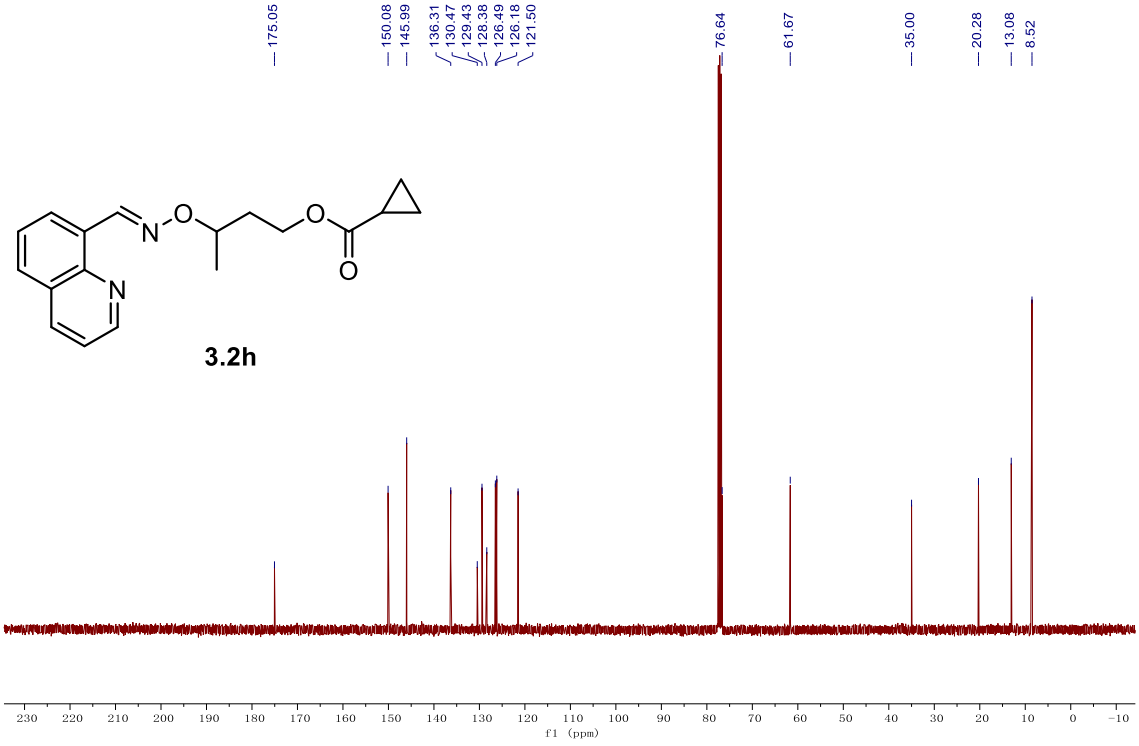


Figure 3.60 ^{1}H-NMR Spectrum of **3.2j**

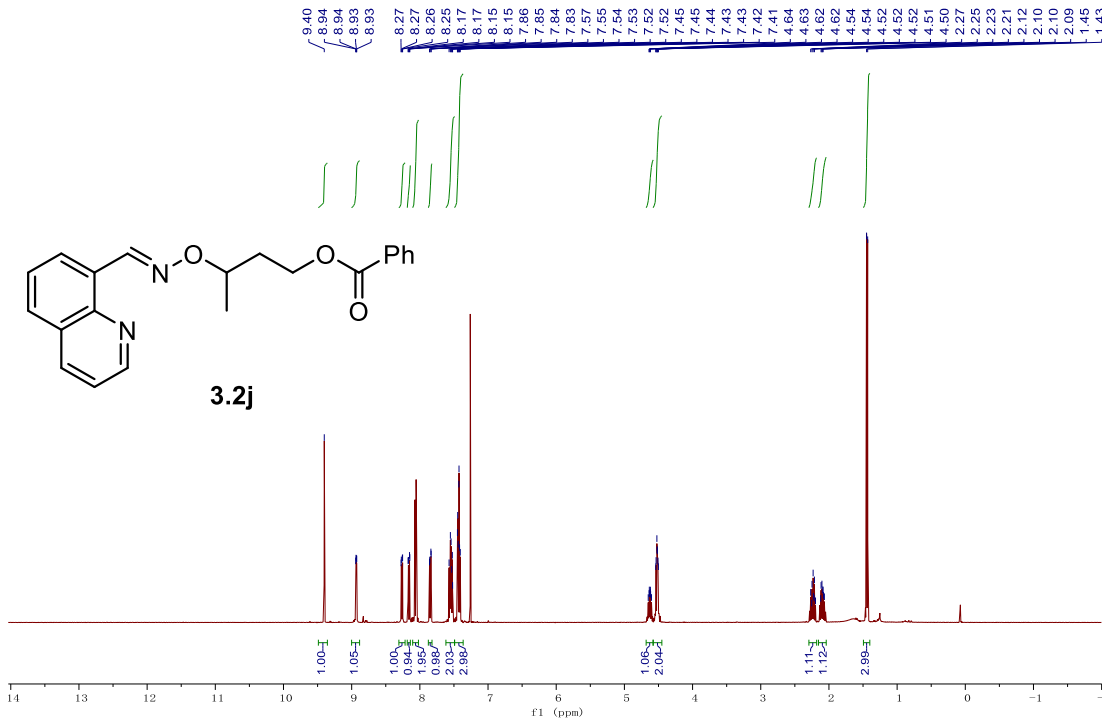


Figure 3.61 ^{13}C-NMR Spectrum of **3.2j**

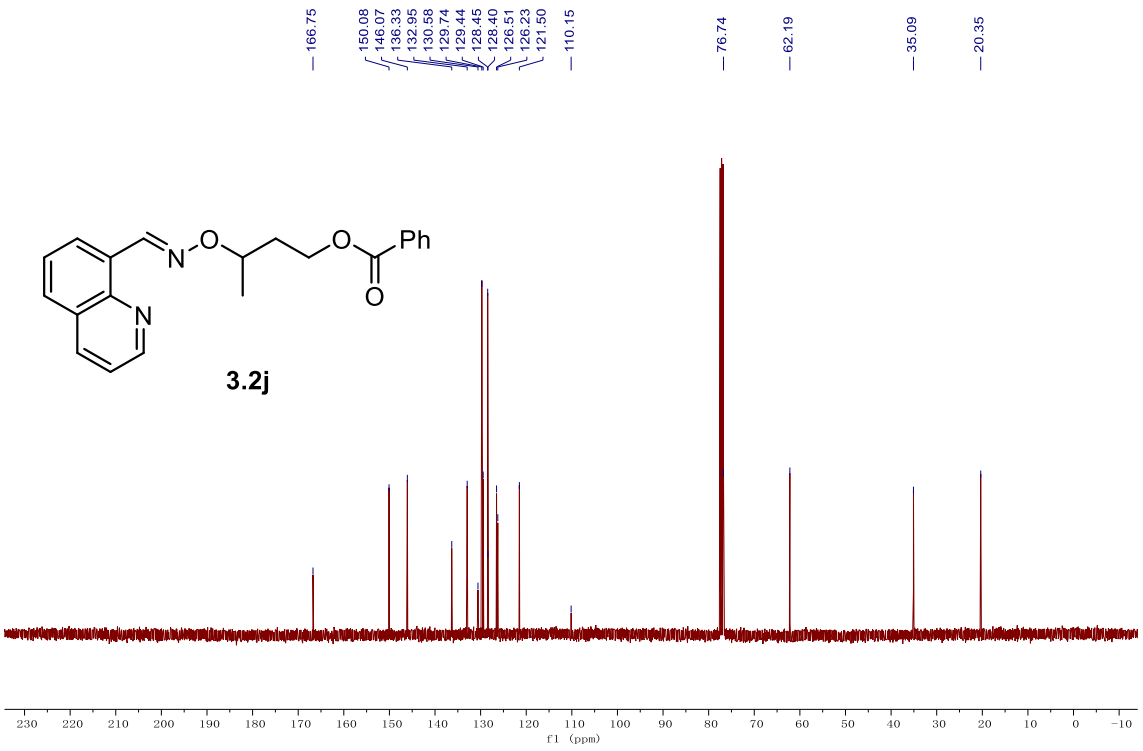


Figure 3.62 ^{1}H-NMR Spectrum of **3.2k**

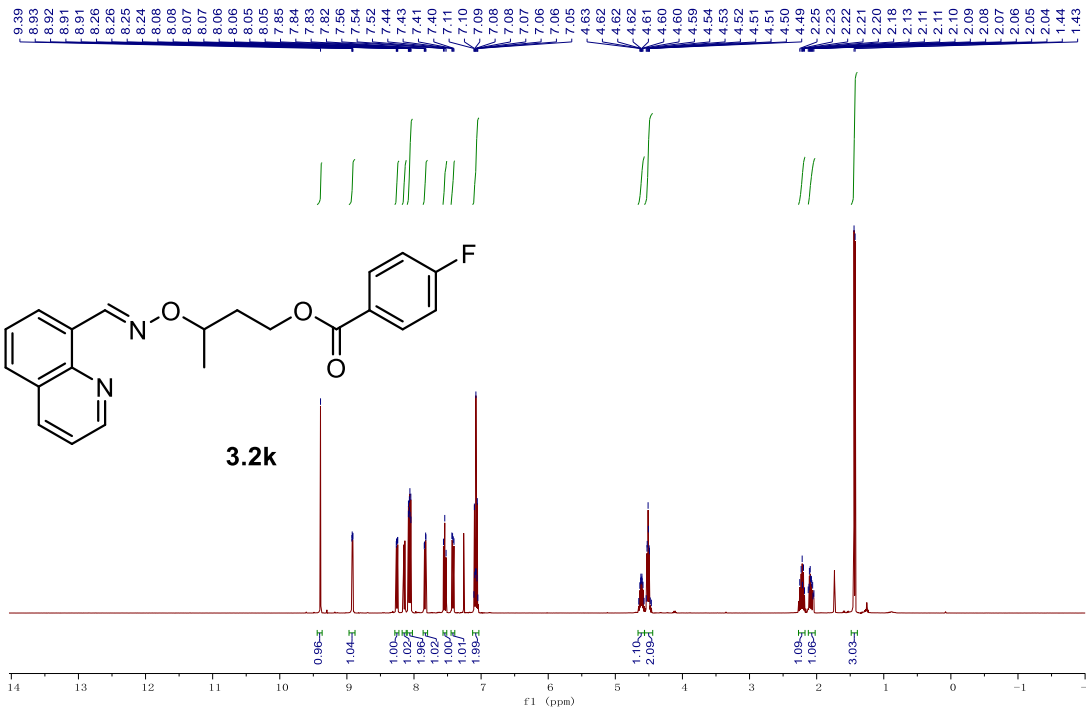


Figure 3.63 ^{13}C-NMR Spectrum of **3.2k**

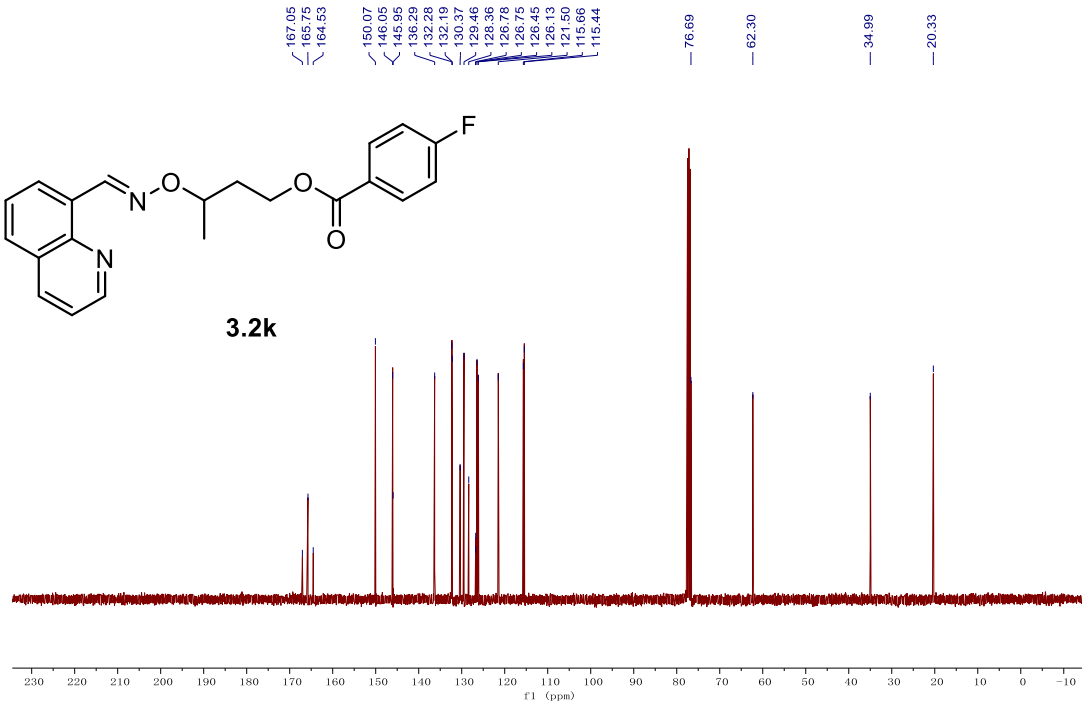


Figure 3.64 ^{19}F-NMR Spectrum of **3.2k**

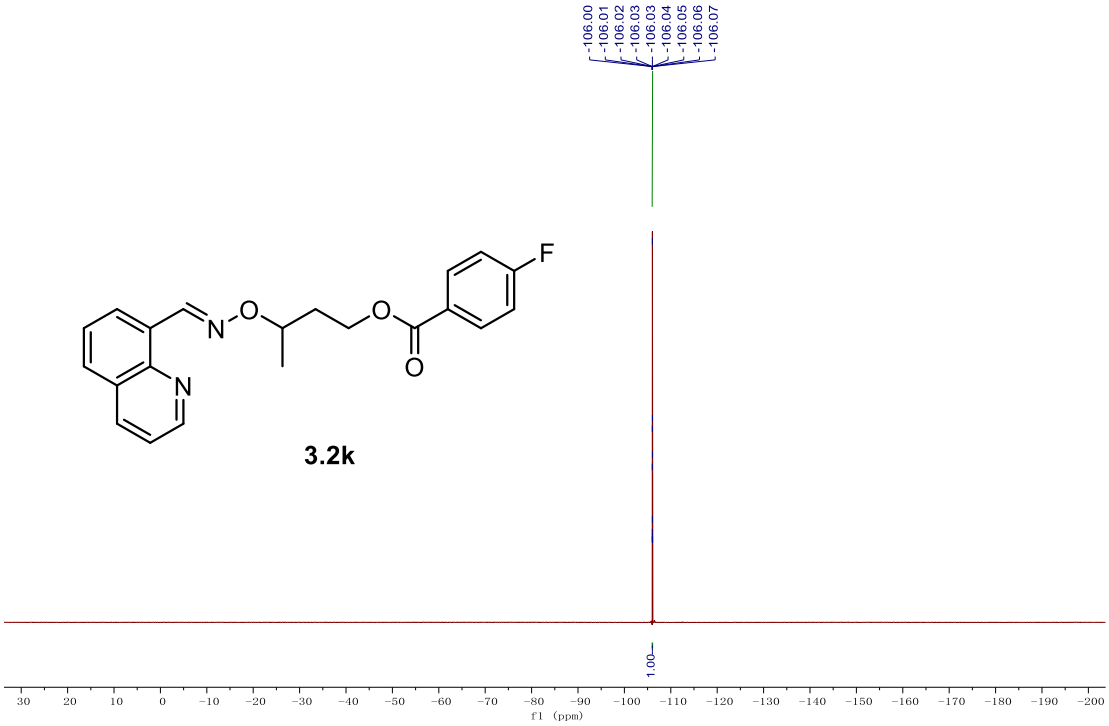


Figure 3.65 ^{1}H-NMR Spectrum of **3.2l**

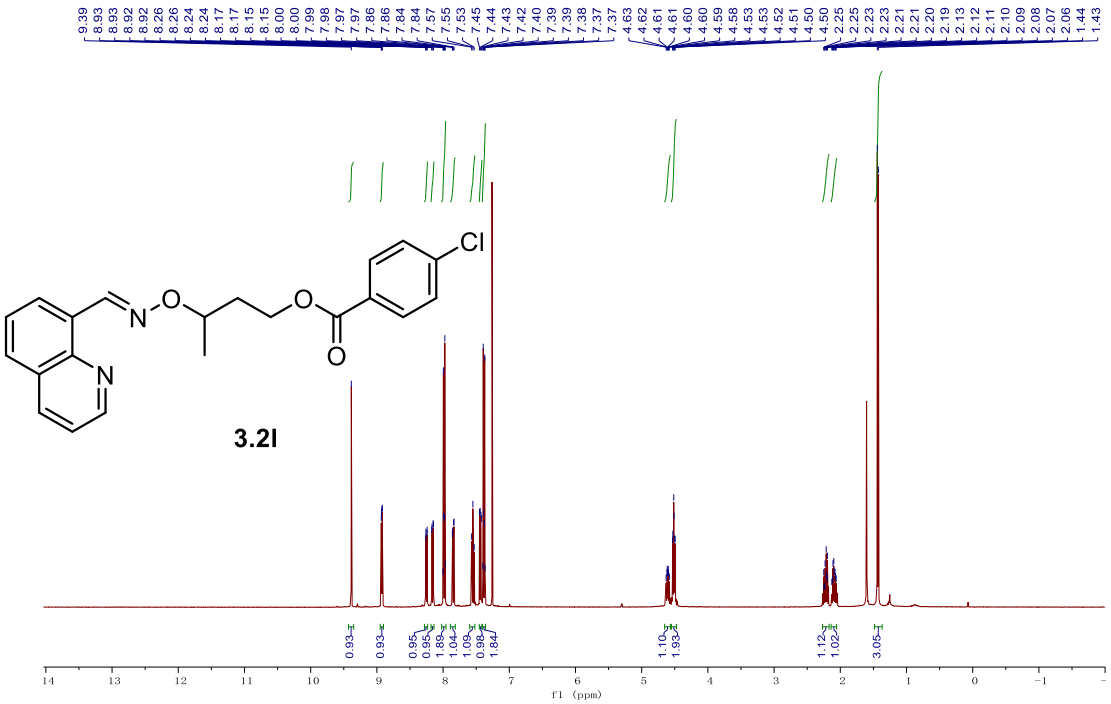


Figure 3.66 ^{13}C-NMR Spectrum of **3.2l**

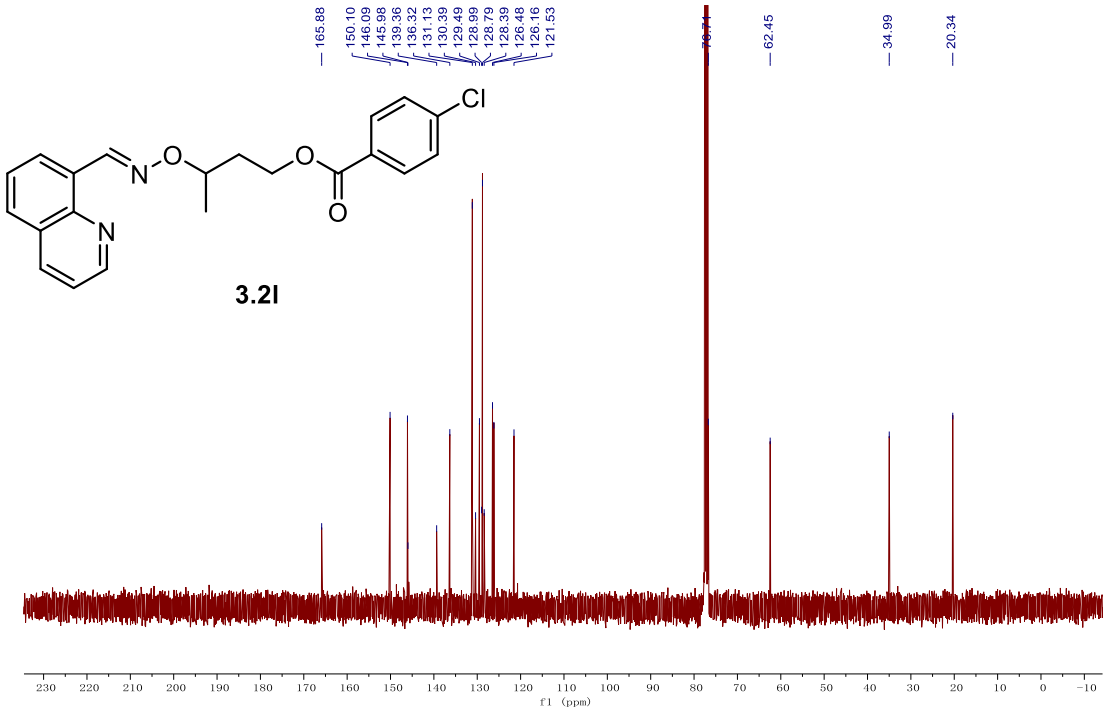


Figure 3.67 ^{1}H-NMR Spectrum of **3.2m**

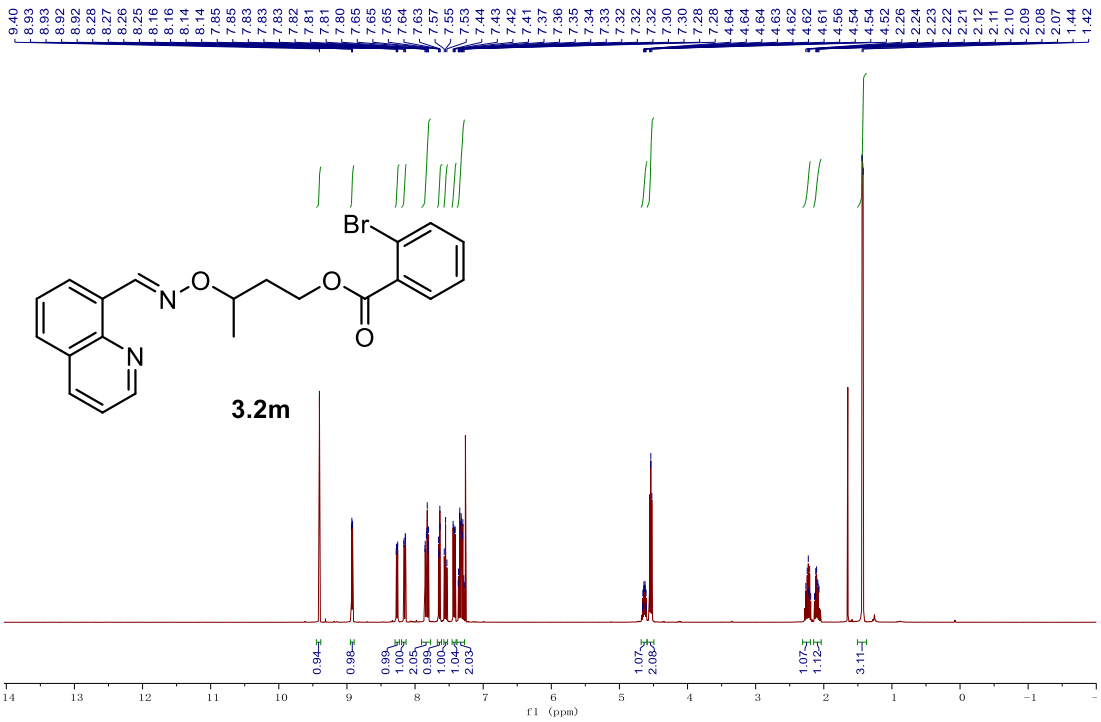


Figure 3.68 ^{13}C-NMR Spectrum of **3.2m**

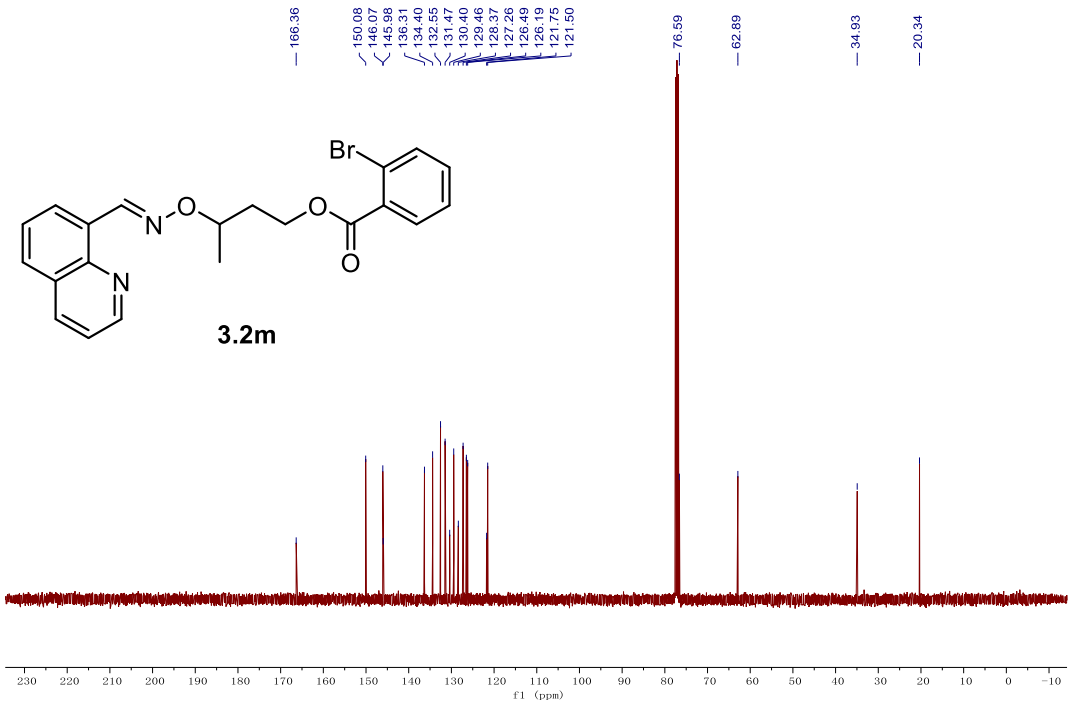


Figure 3.69 ^{1}H-NMR Spectrum of **3.2n**

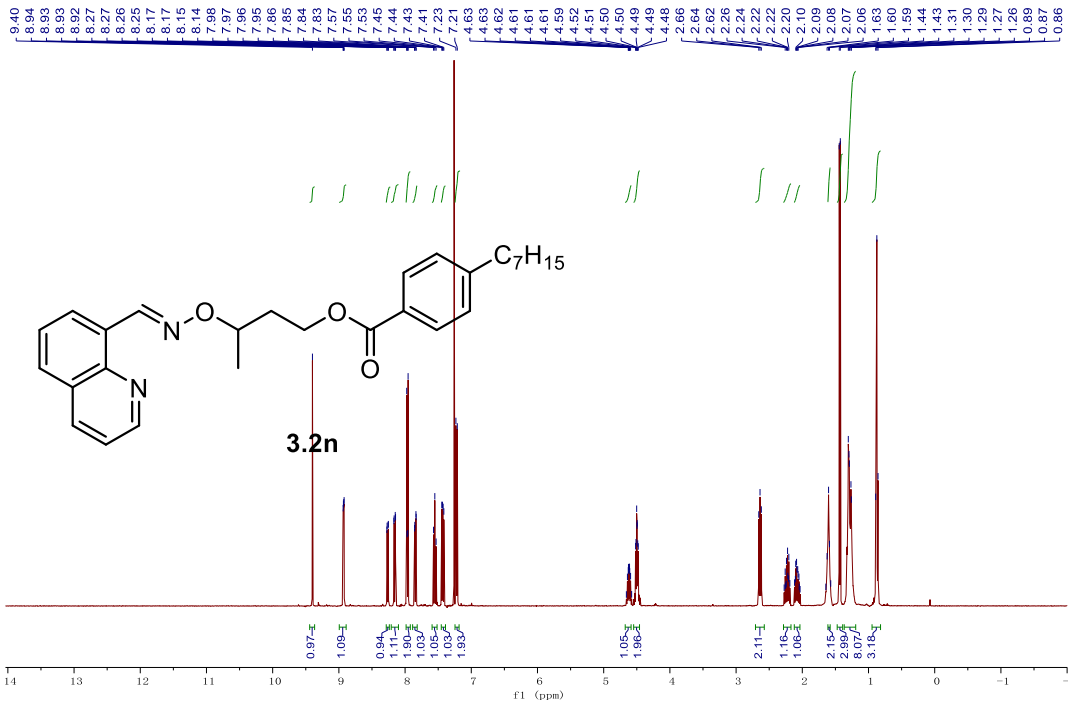


Figure 3.70 ^{13}C-NMR Spectrum of **3.2n**

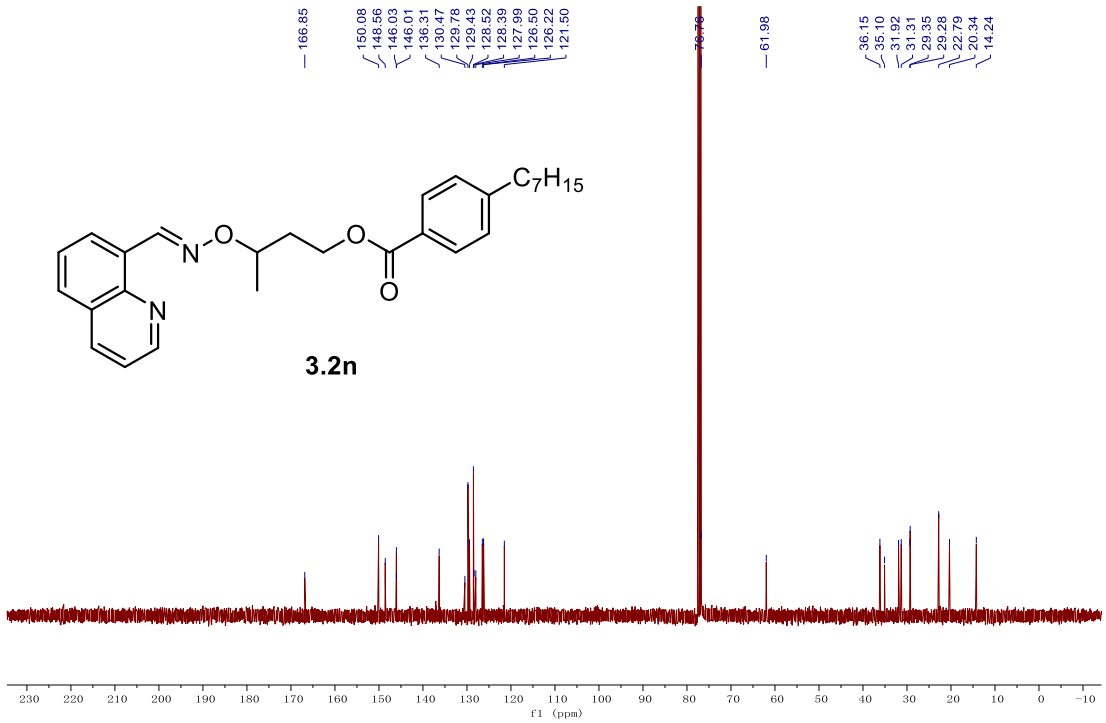


Figure 3.71 ^{1}H-NMR Spectrum of **3.2o**

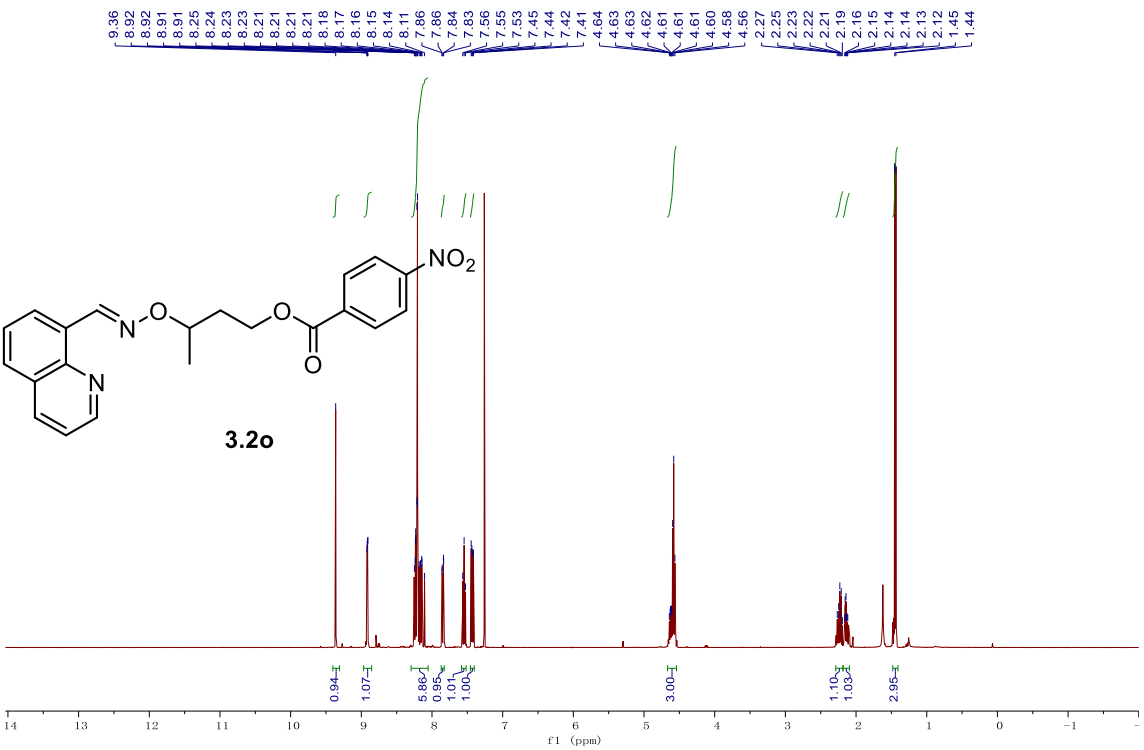


Figure 3.72 ^{13}C-NMR Spectrum of **3.2o**

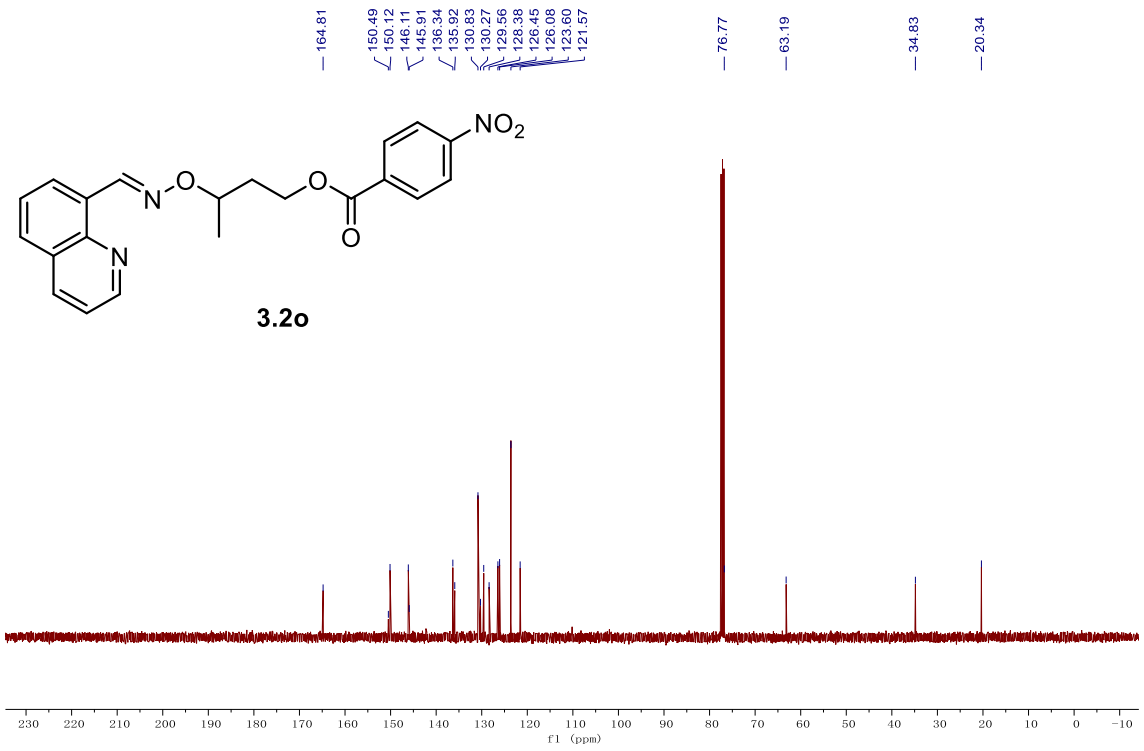


Figure 3.73 ^{1}H-NMR Spectrum of **3.2p**

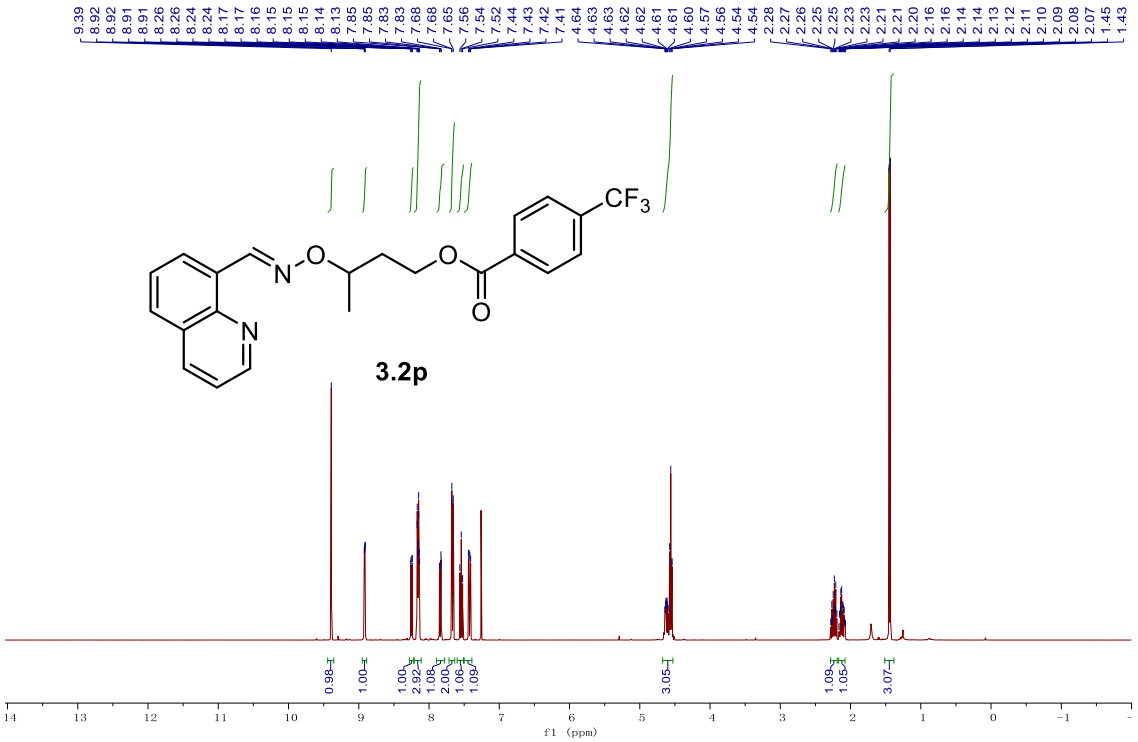


Figure 3.74 ^{13}C-NMR Spectrum of **3.2p**

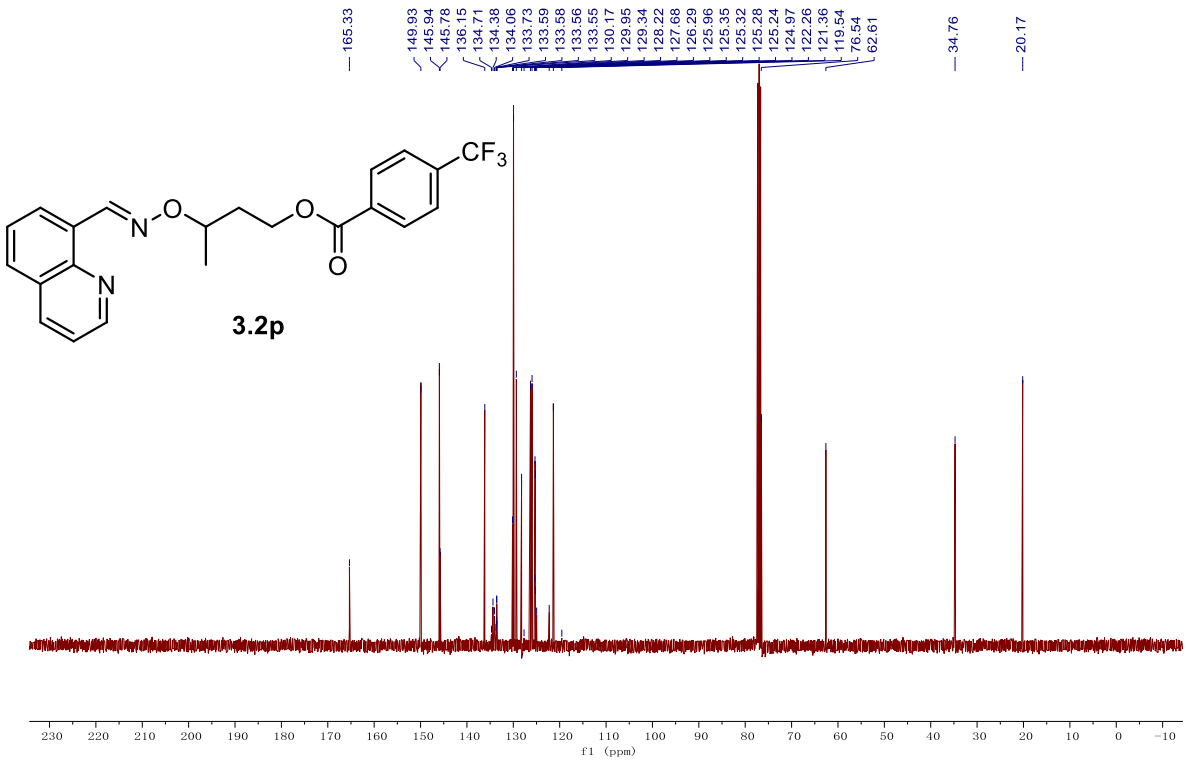


Figure 3.75 ^{19}F-NMR Spectrum of **3.2p**

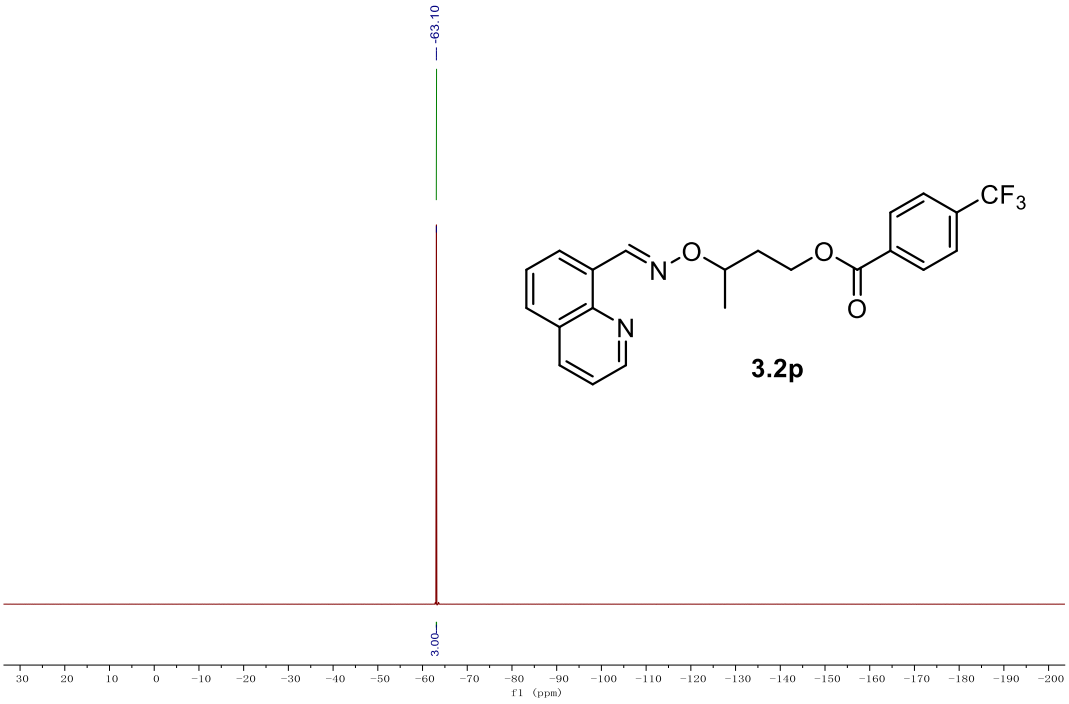


Figure 3.76 ^{1}H-NMR Spectrum of **3.2q**

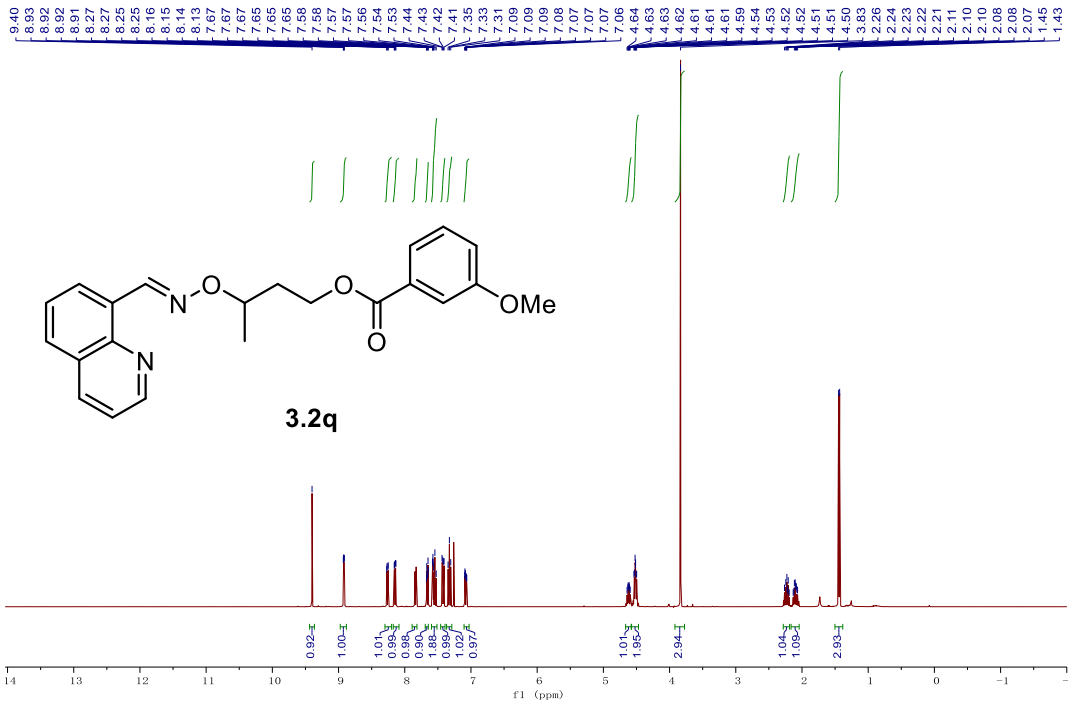


Figure 3.77 ^{13}C-NMR Spectrum of **3.2q**

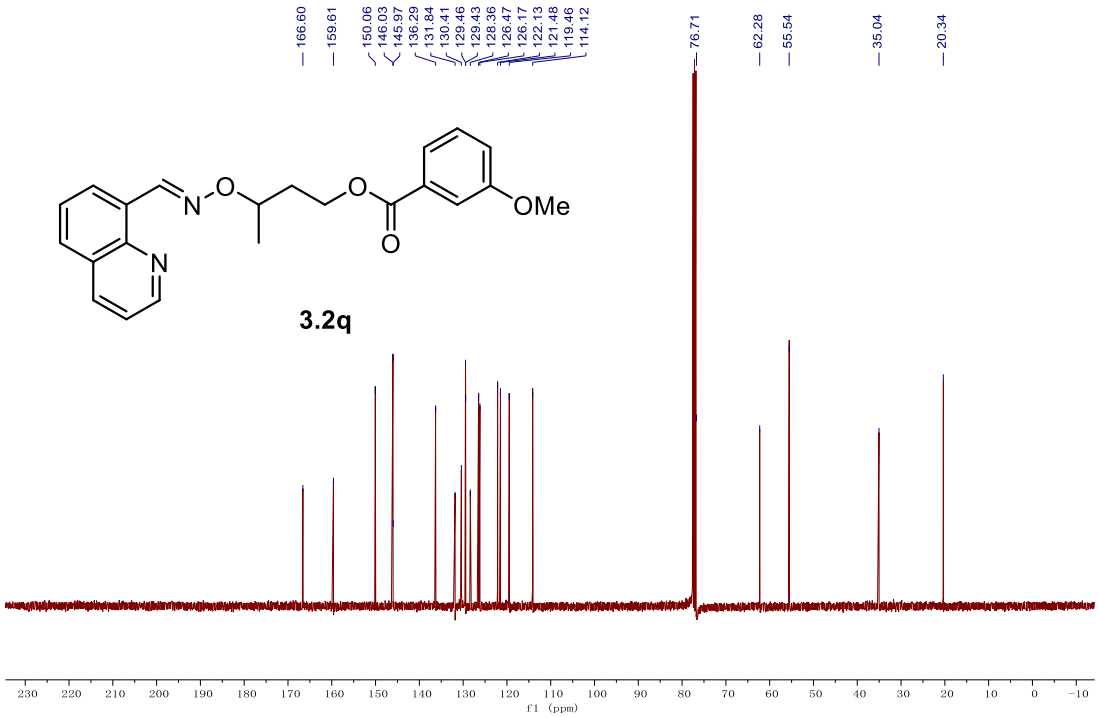


Figure 3.78 ^{1}H-NMR Spectrum of **3.2r**

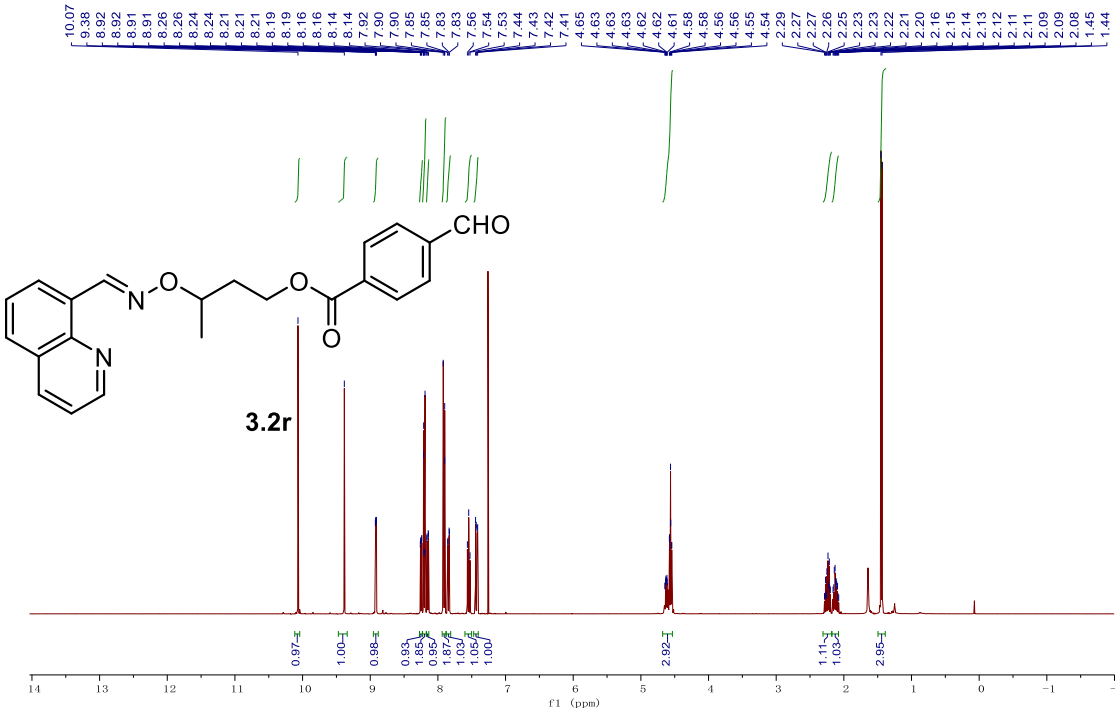


Figure 3.79 ^{13}C-NMR Spectrum of **3.2r**

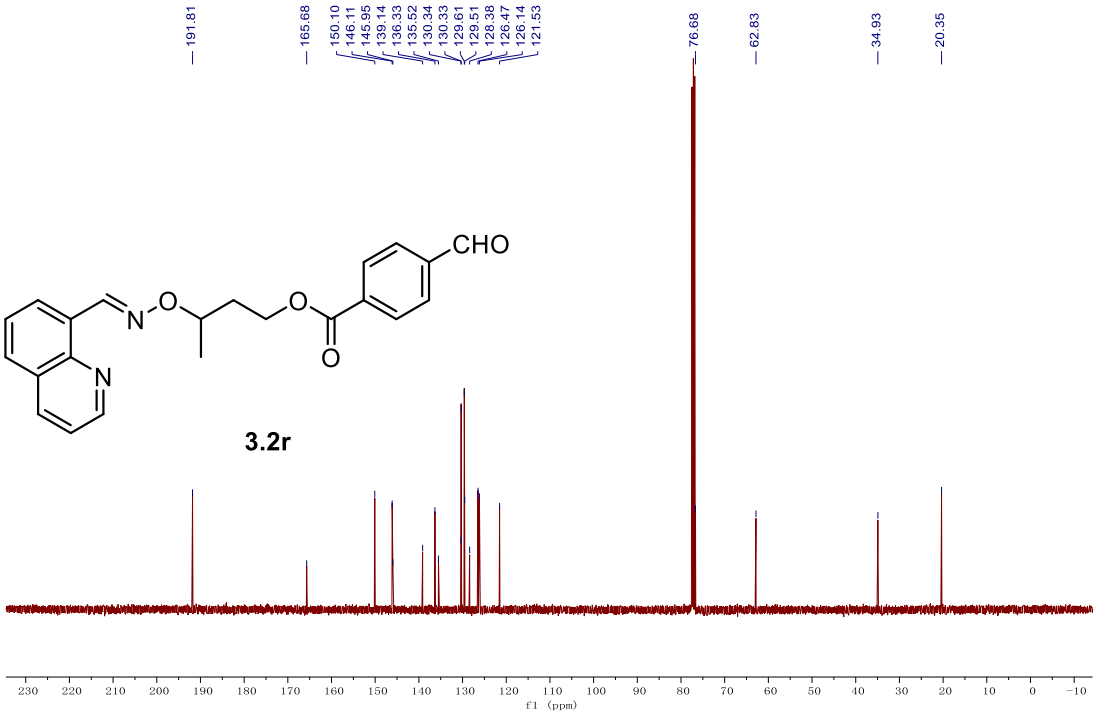


Figure 3.80 ^{1}H-NMR Spectrum of **3.2s**

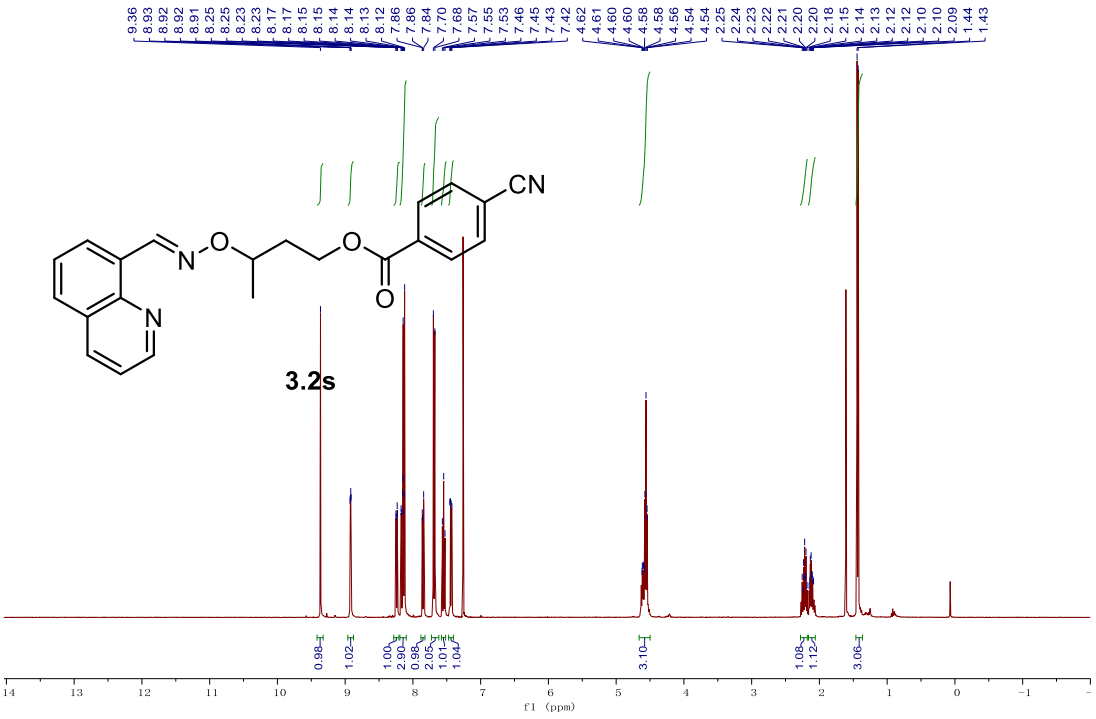


Figure 3.81 ^{13}C-NMR Spectrum of **3.2s**

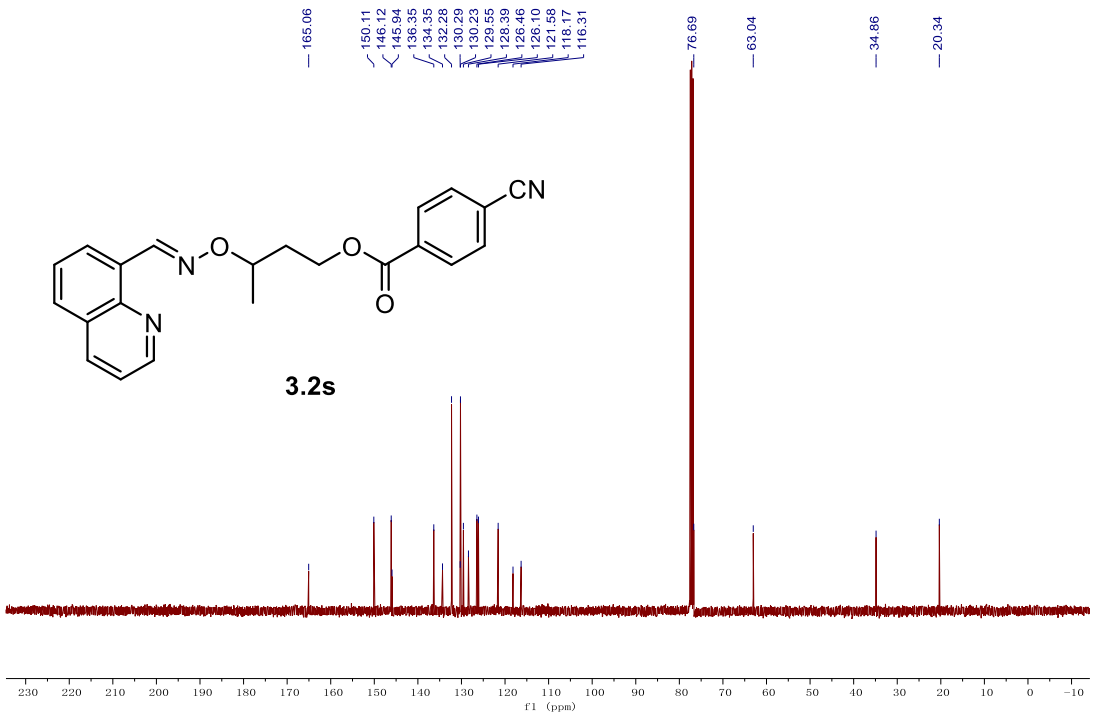


Figure 3.82 ^{1}H-NMR Spectrum of **3.2t**

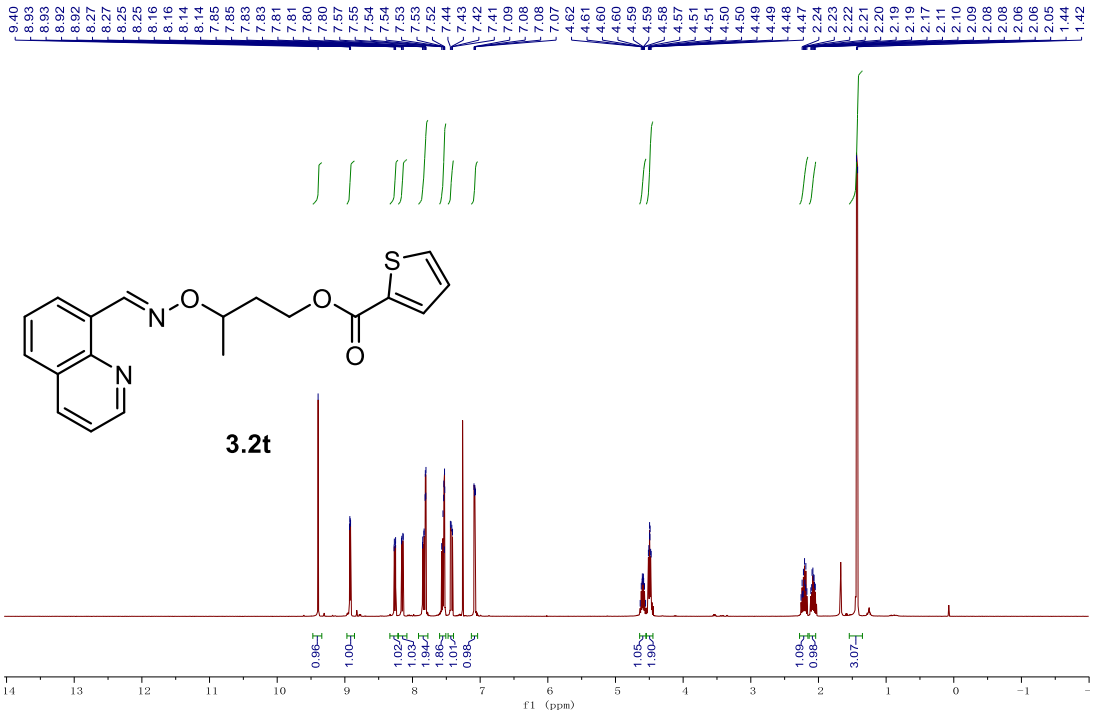


Figure 3.83 ^{13}C-NMR Spectrum of **3.2t**

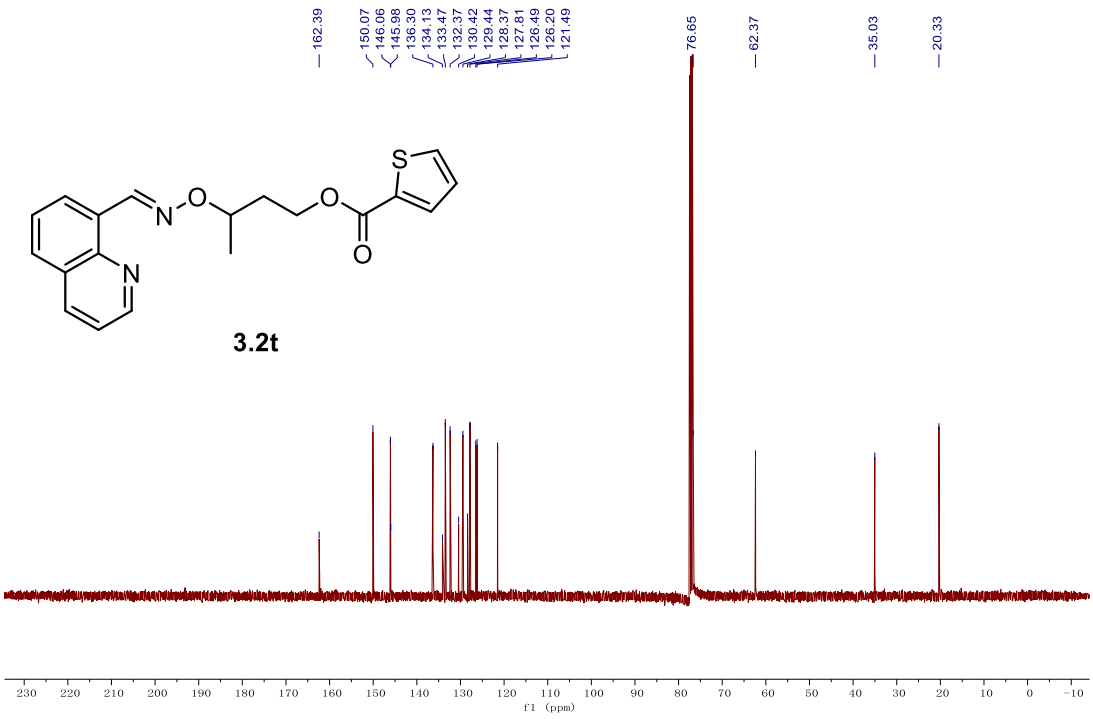


Figure 3.84 ^{1}H-NMR Spectrum of **3.2u**

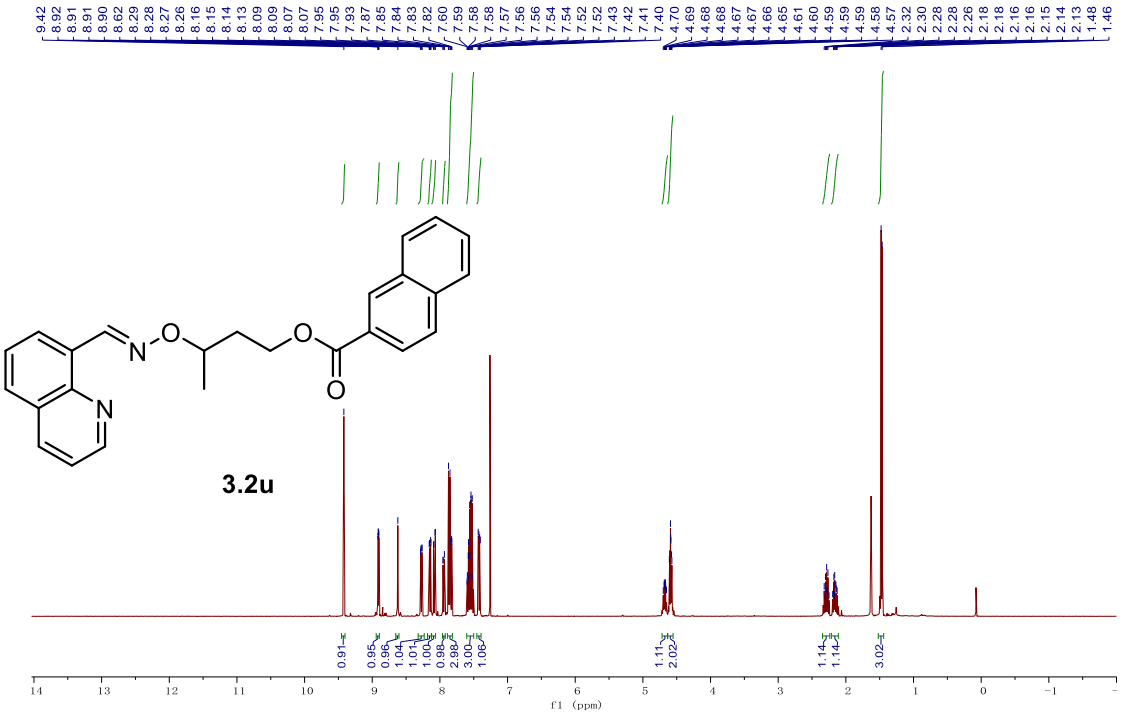


Figure 3.85 ^{13}C-NMR Spectrum of **3.2u**

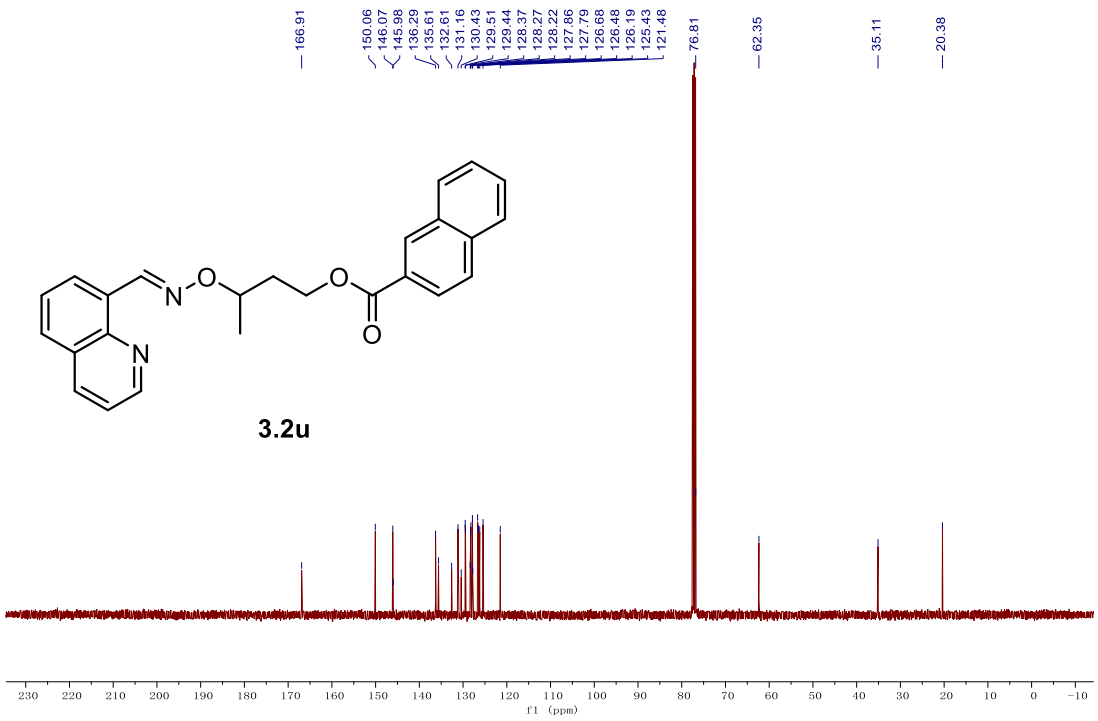


Figure 3.86 ^{1}H-NMR Spectrum of **3.2v**

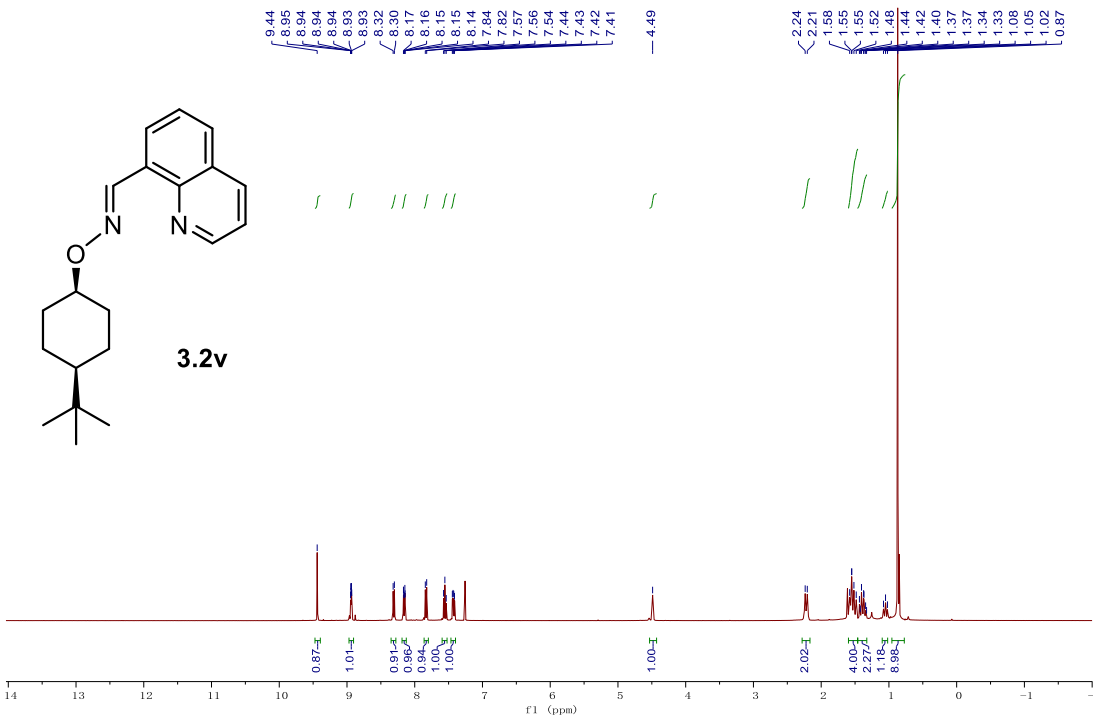


Figure 3.87 ^{13}C-NMR Spectrum of **3.2v**

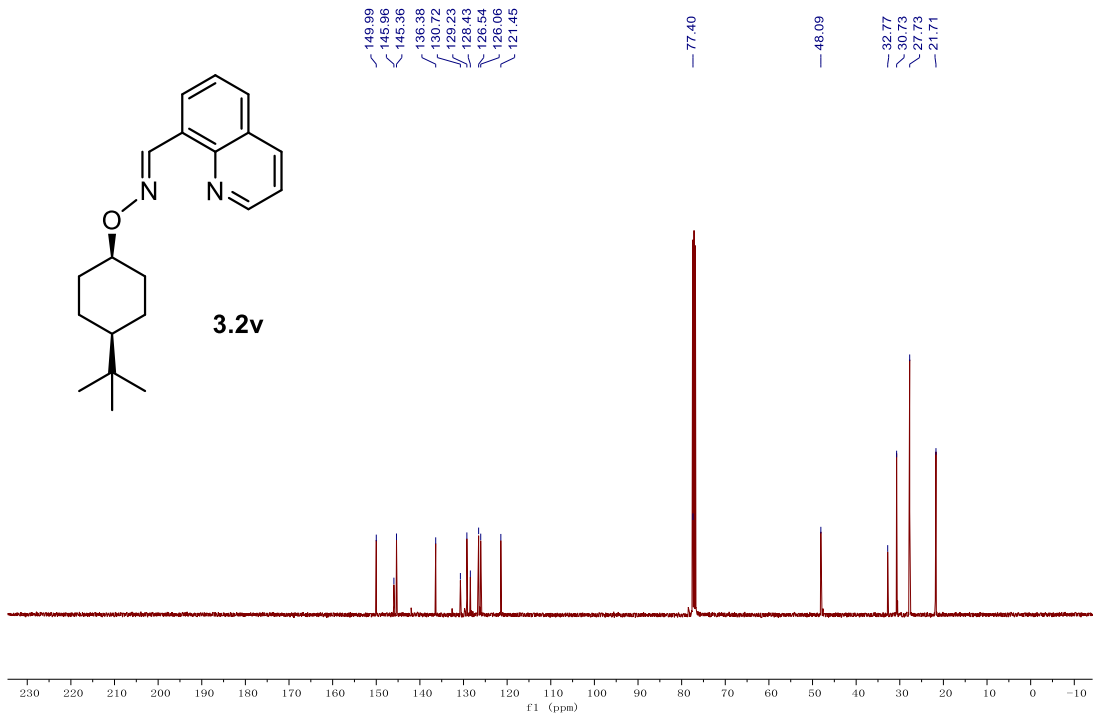


Figure 3.88 ^{1}H-NMR Spectrum of **3.2w**

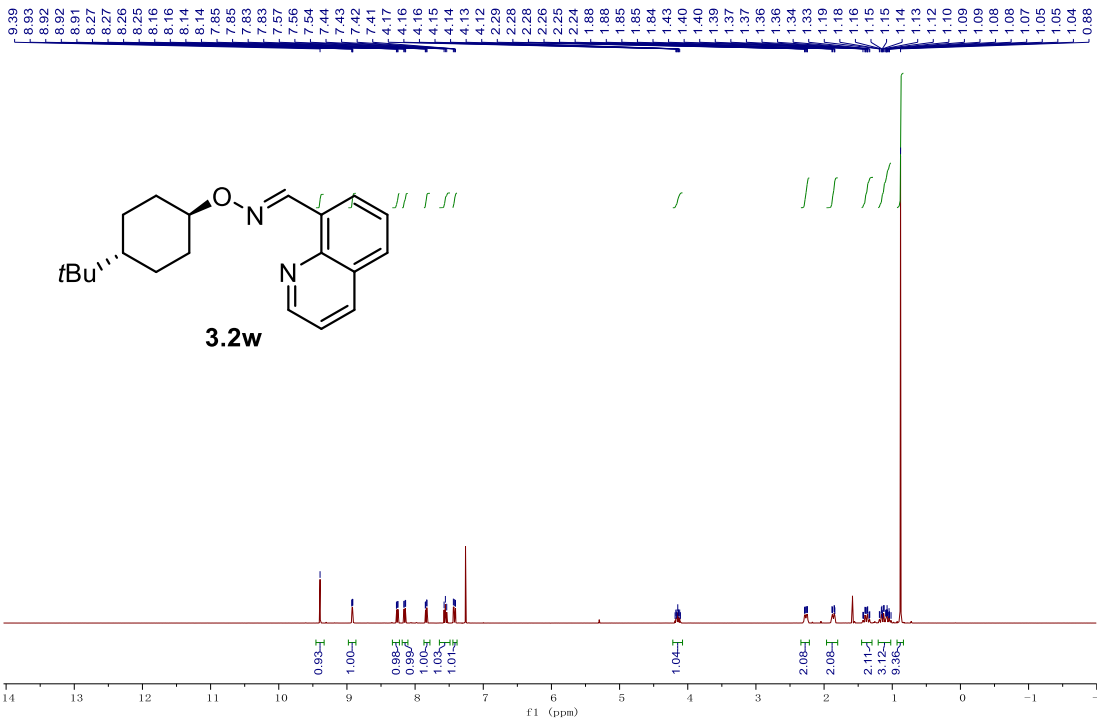


Figure 3.89 ^{13}C-NMR Spectrum of **3.2w**

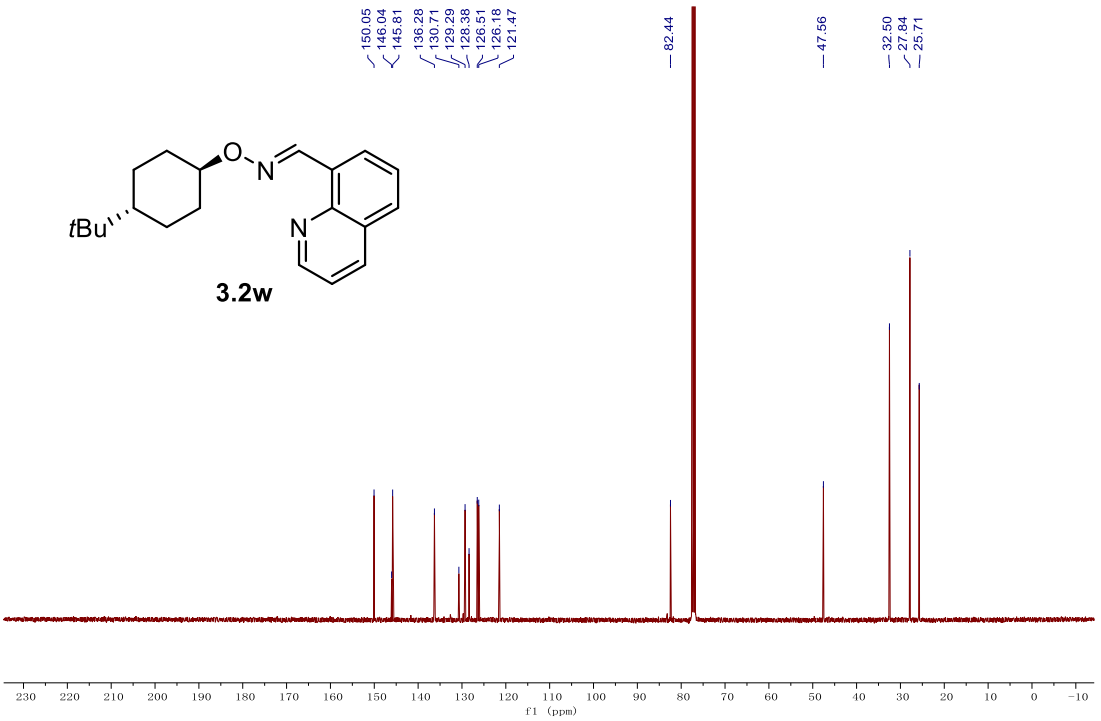


Figure 3.90 ^{1}H-NMR Spectrum of **3.2x**

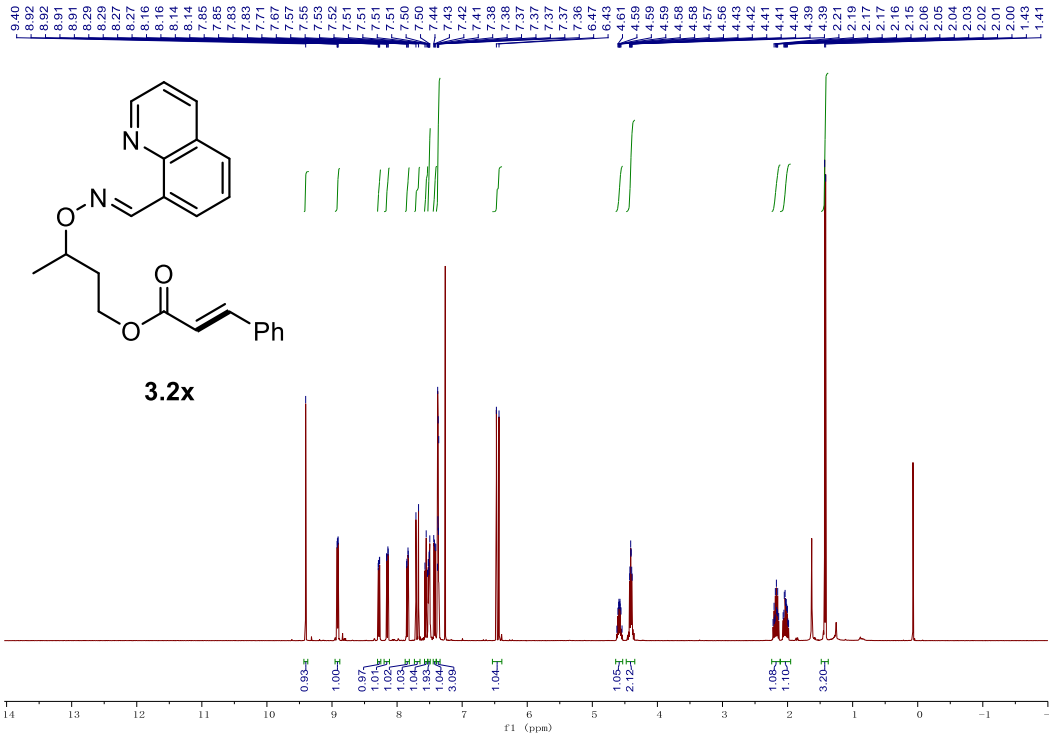


Figure 3.91 ^{13}C-NMR Spectrum of **3.2x**

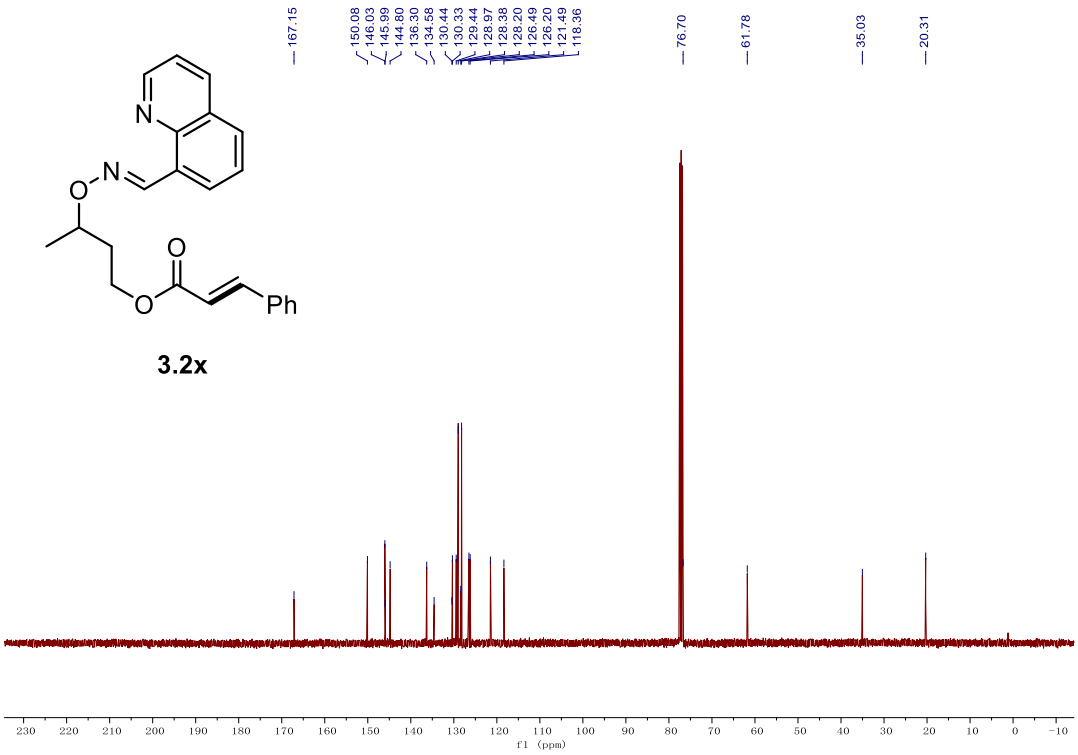


Figure 3.92 ^{1}H-NMR Spectrum of **3.2y**

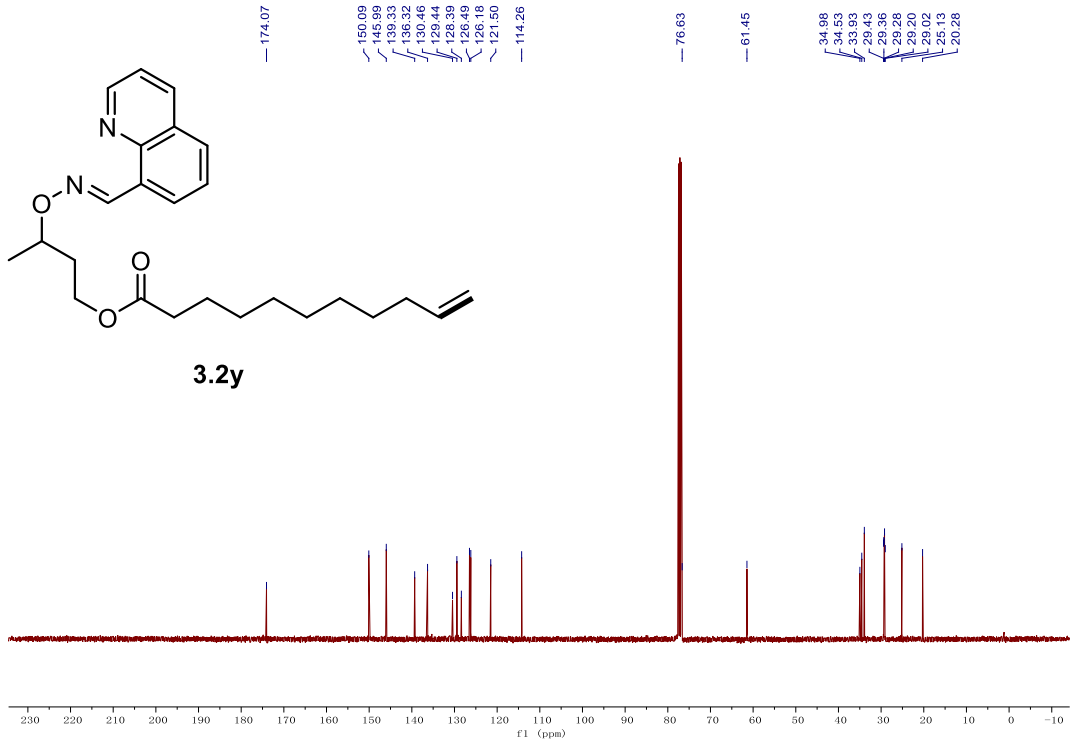


Figure 3.93 ^{13}C-NMR Spectrum of **3.2y**

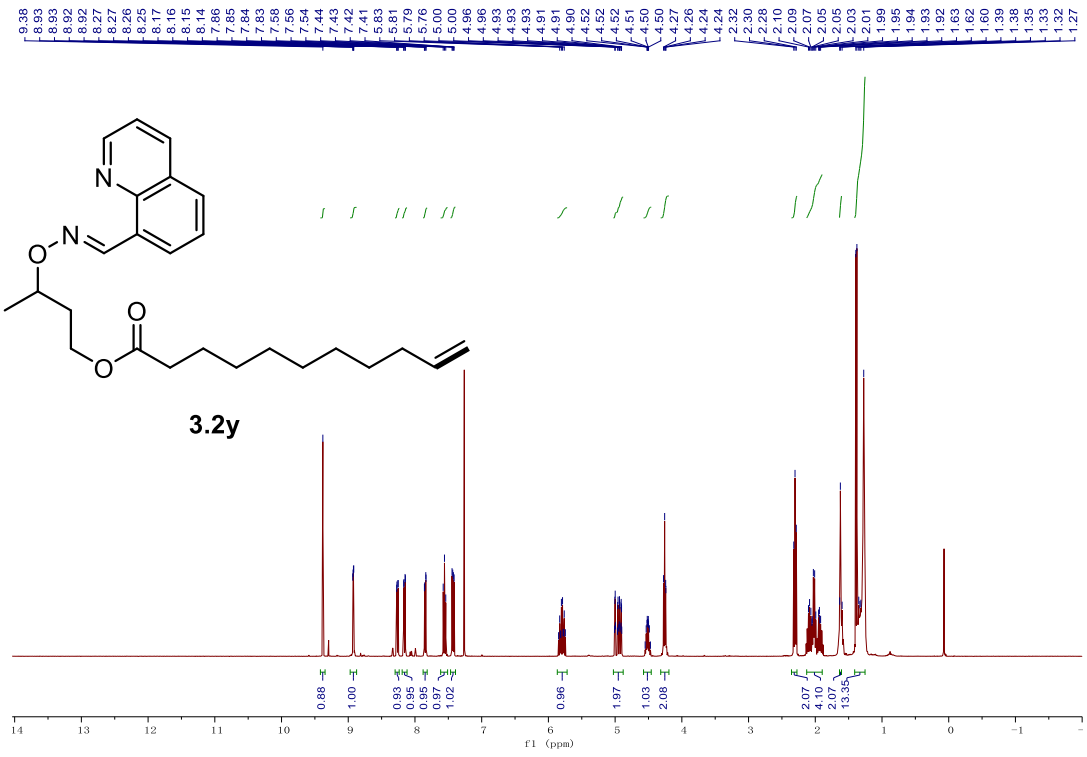


Figure 3.94 ^{1}H-NMR Spectrum of **3.2z**

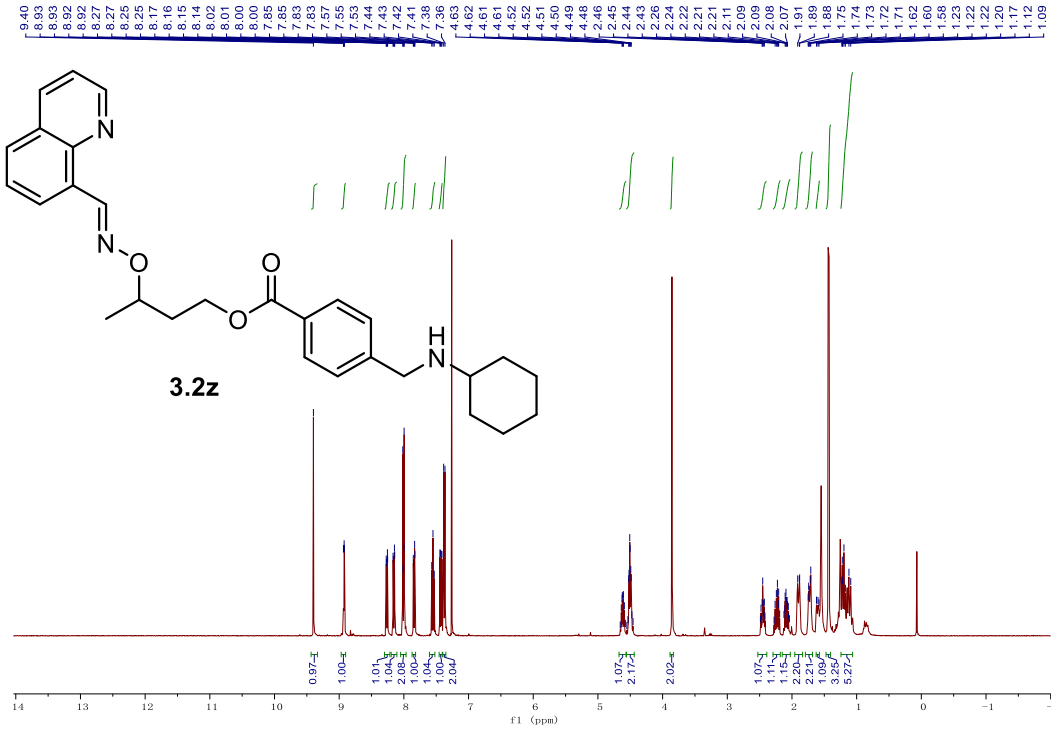


Figure 3.95 ^{13}C-NMR Spectrum of **3.2z**

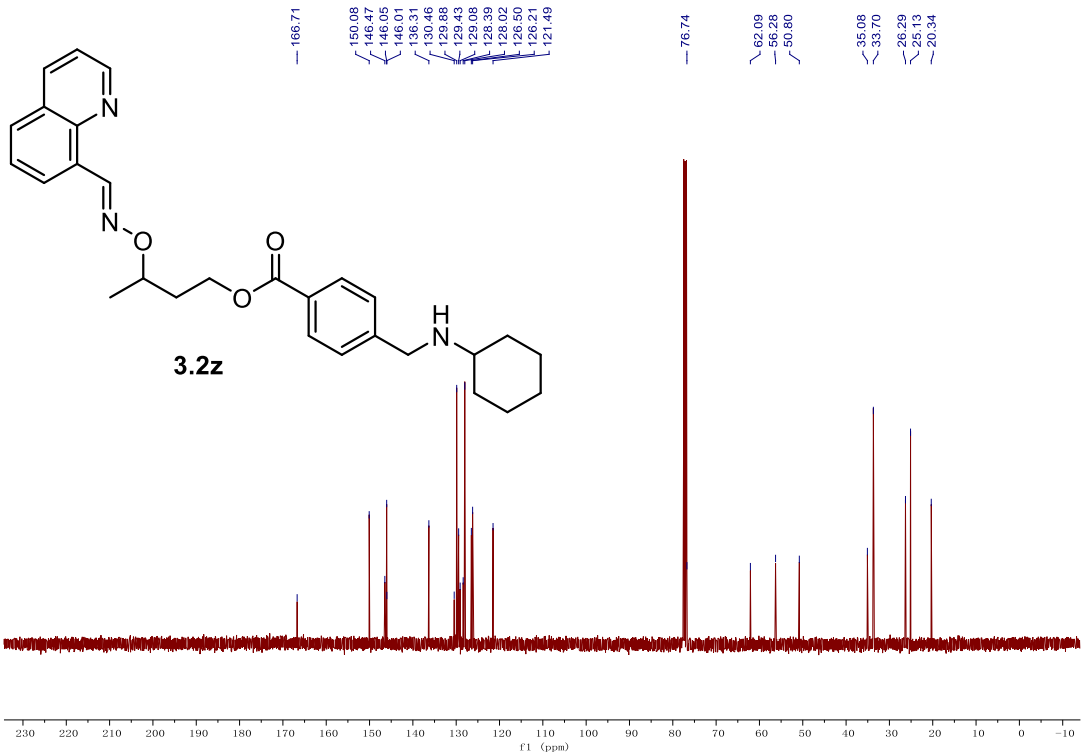


Figure 3.96 ^{1}H-NMR Spectrum of **3.2ac**

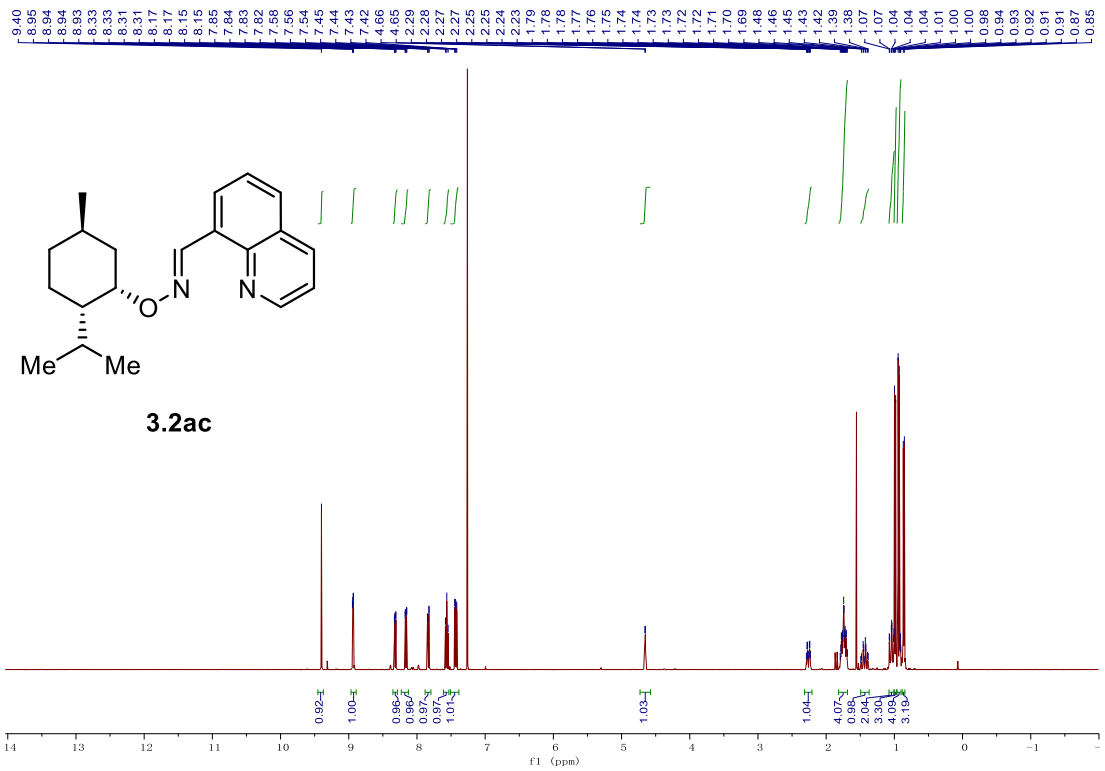


Figure 3.97 ^{13}C-NMR Spectrum of **3.2ac**

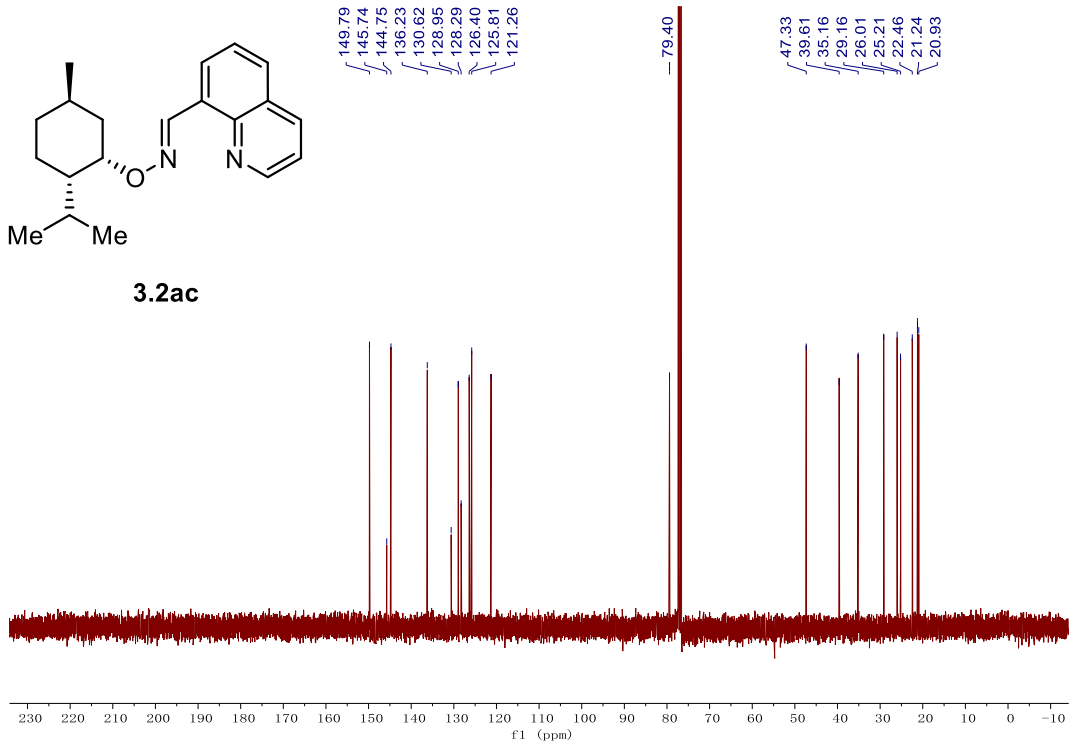


Figure 3.98 ^{1}H-NMR Spectrum of **3.2ad**

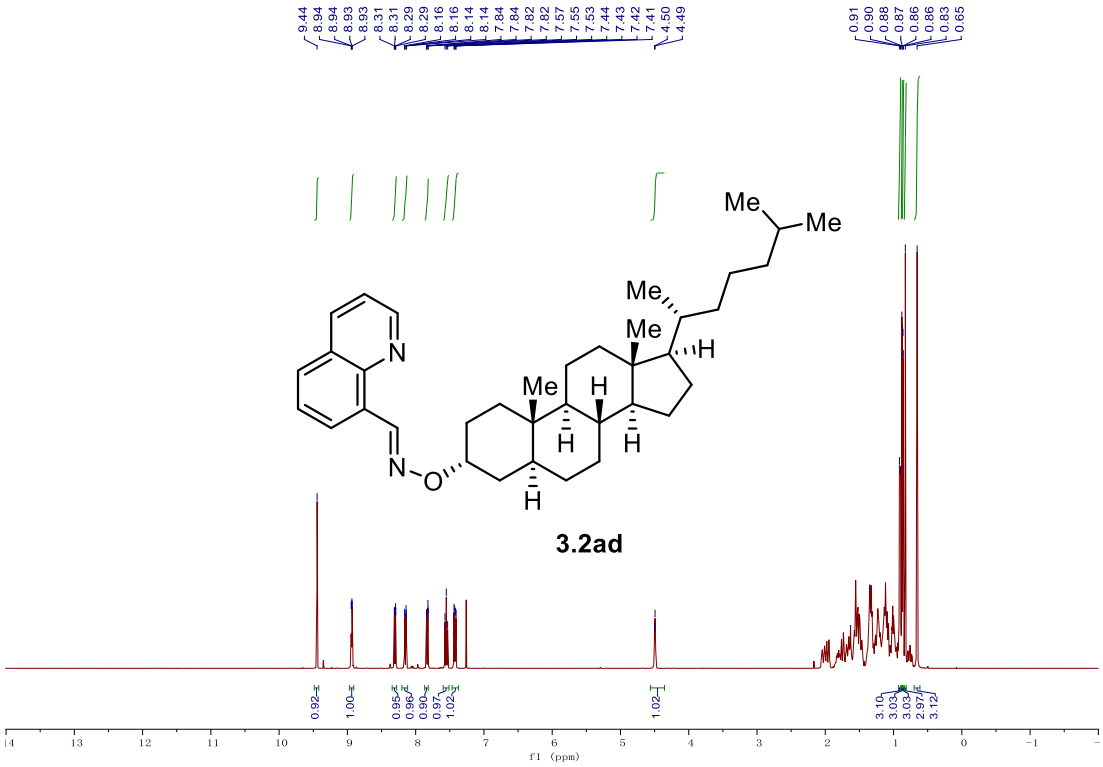


Figure 3.98b ^{13}C-NMR Spectrum of **3.2ad**

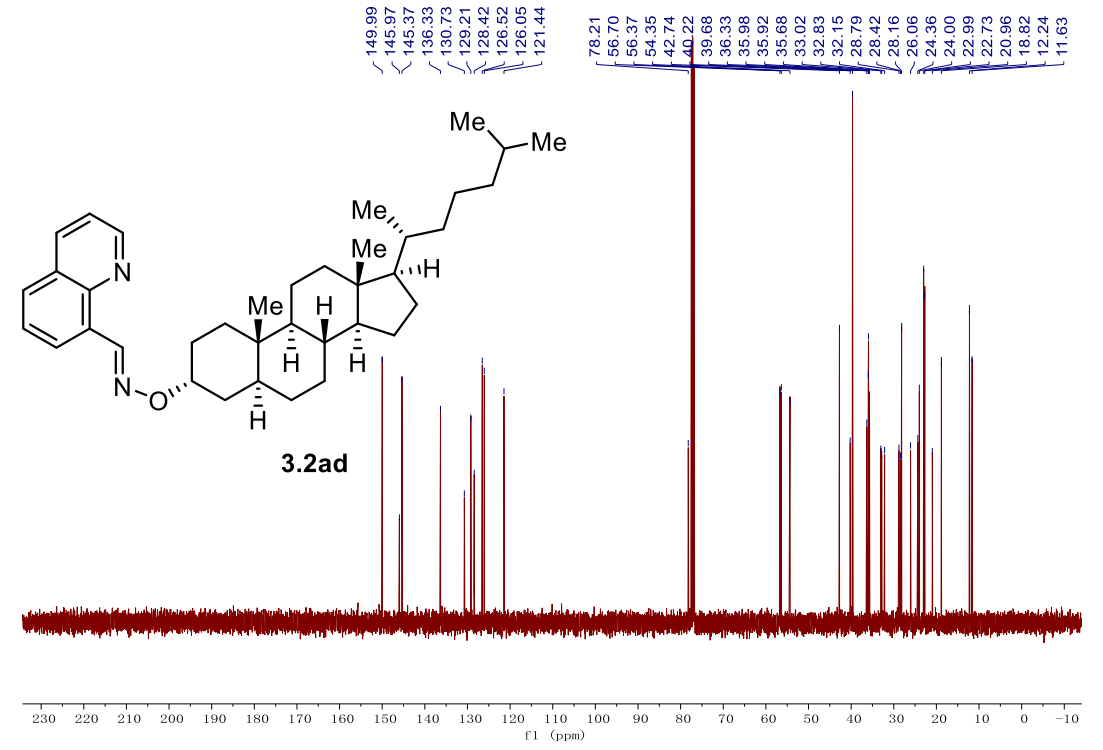


Figure 3.99 ^{1}H-NMR Spectrum of **3.3a-DG3**

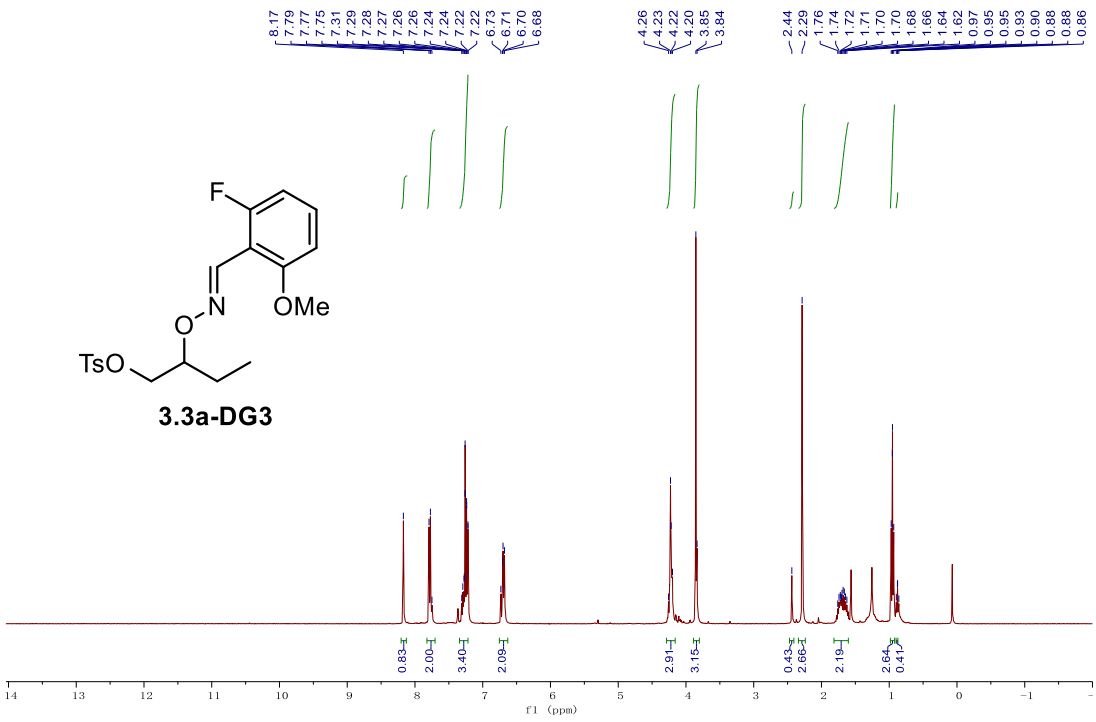


Figure 3.100 ^{13}C-NMR Spectrum of **3.3a-DG3**

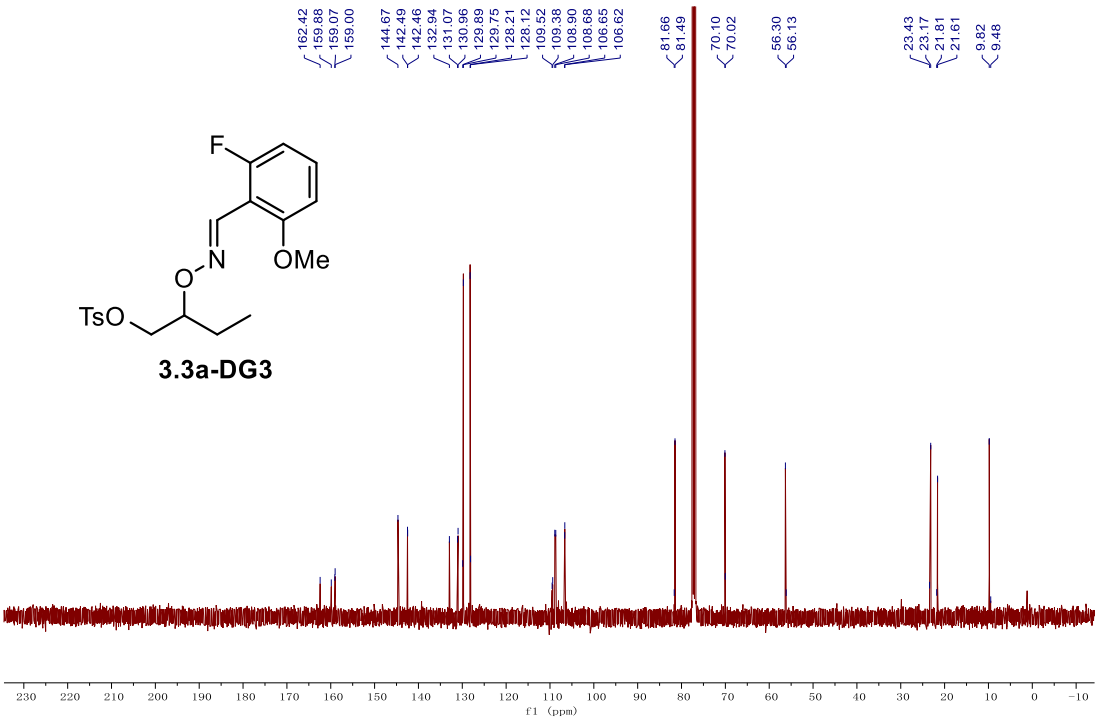


Figure 3.101 ^{19}F-NMR Spectrum of **3.3a-DG3**

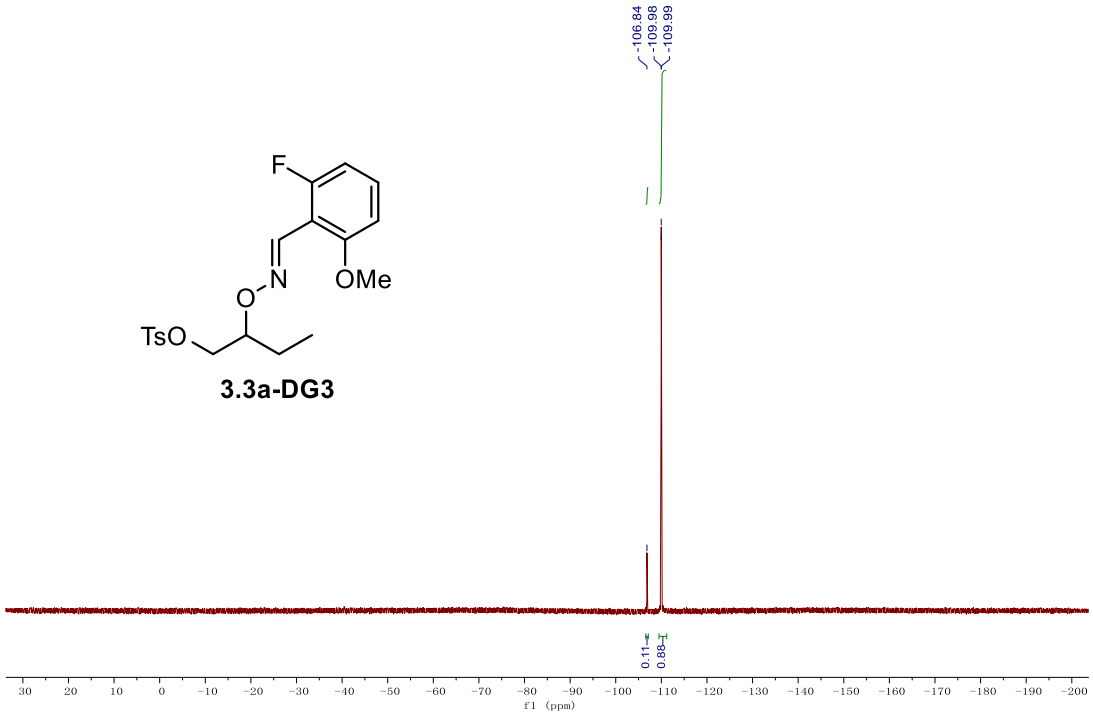


Figure 3.102 ^{1}H-NMR Spectrum of **3.3a-DG4**

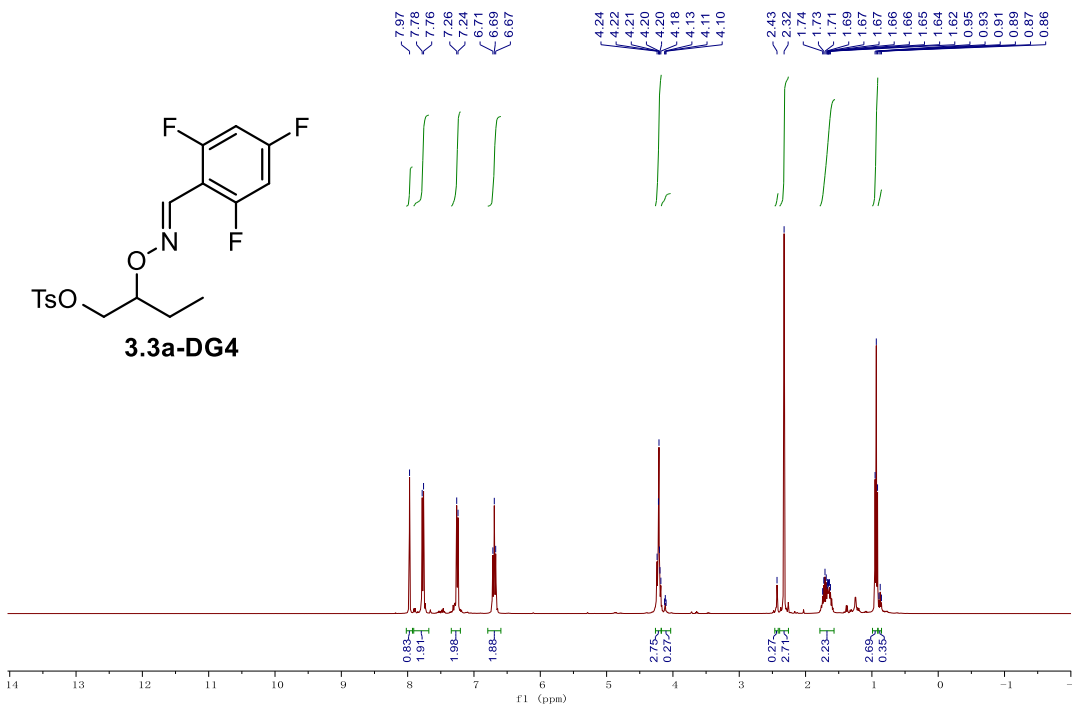


Figure 3.103 ^{13}C-NMR Spectrum of **3.3a-DG4**

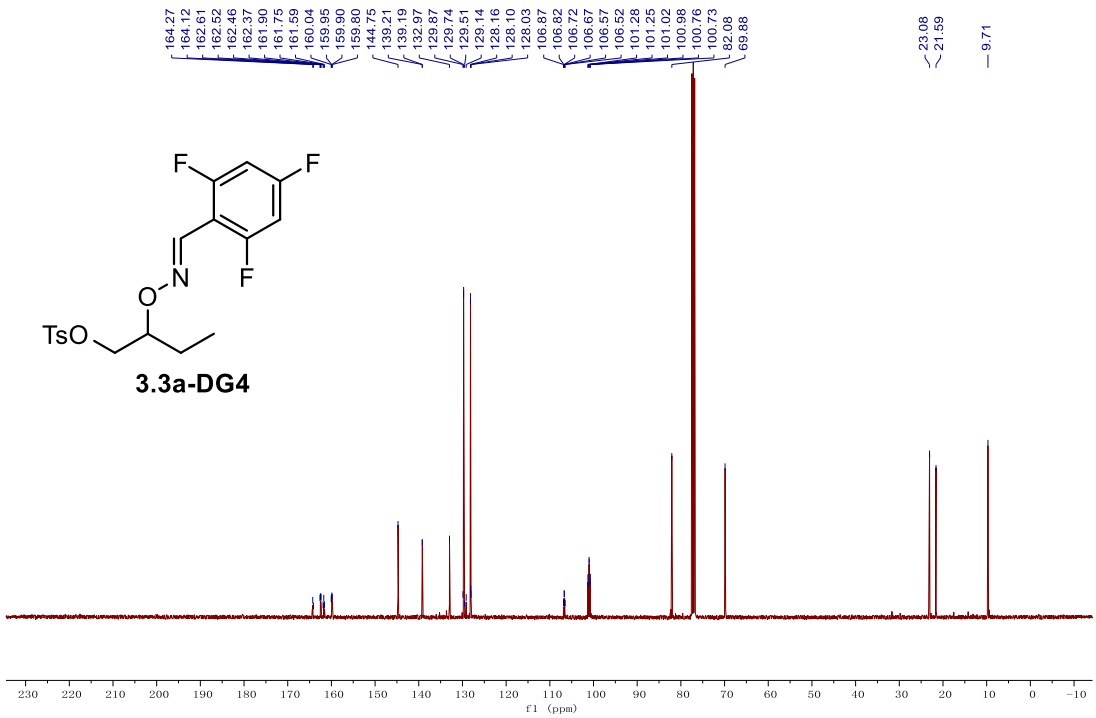


Figure 3.104 ^{19}F-NMR Spectrum of **3.3a-DG4**

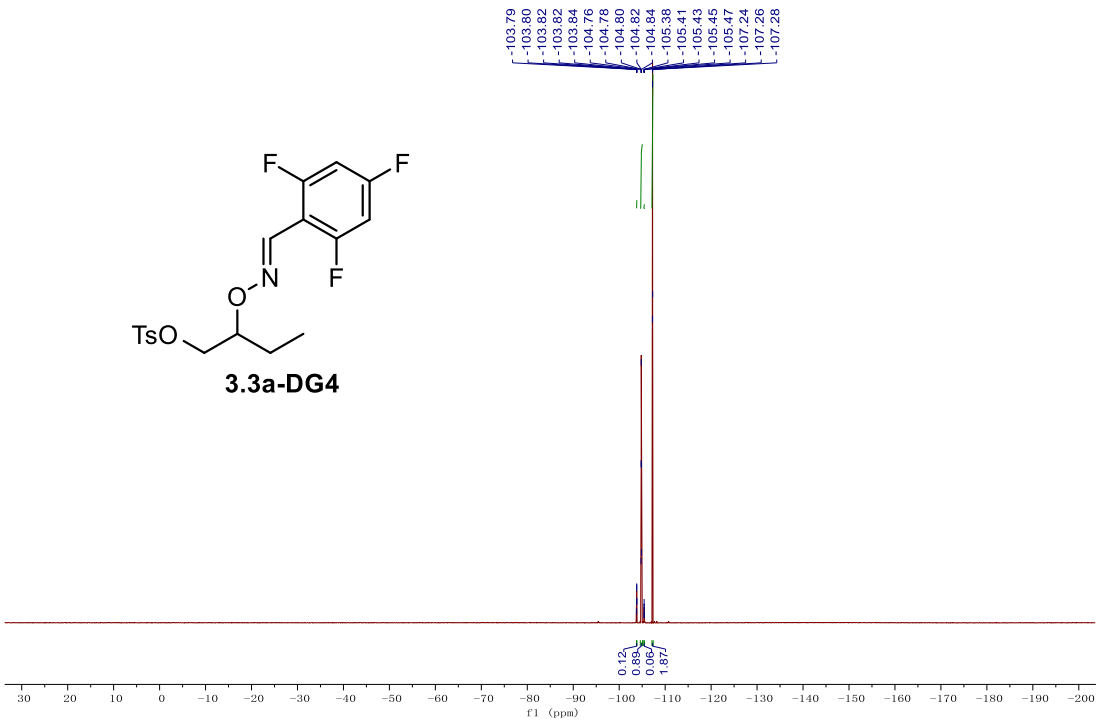


Figure 3.105 ^{1}H-NMR Spectrum of **3.3a-DG5**

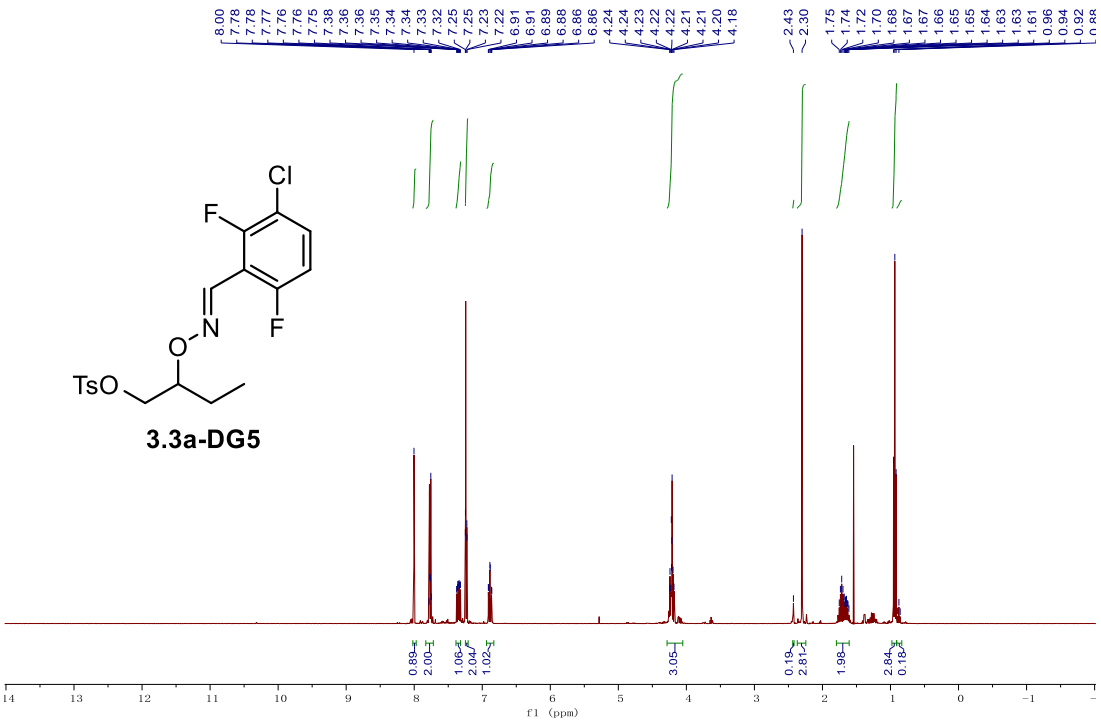


Figure 3.106 ^{13}C-NMR Spectrum of **3.3a-DG5**

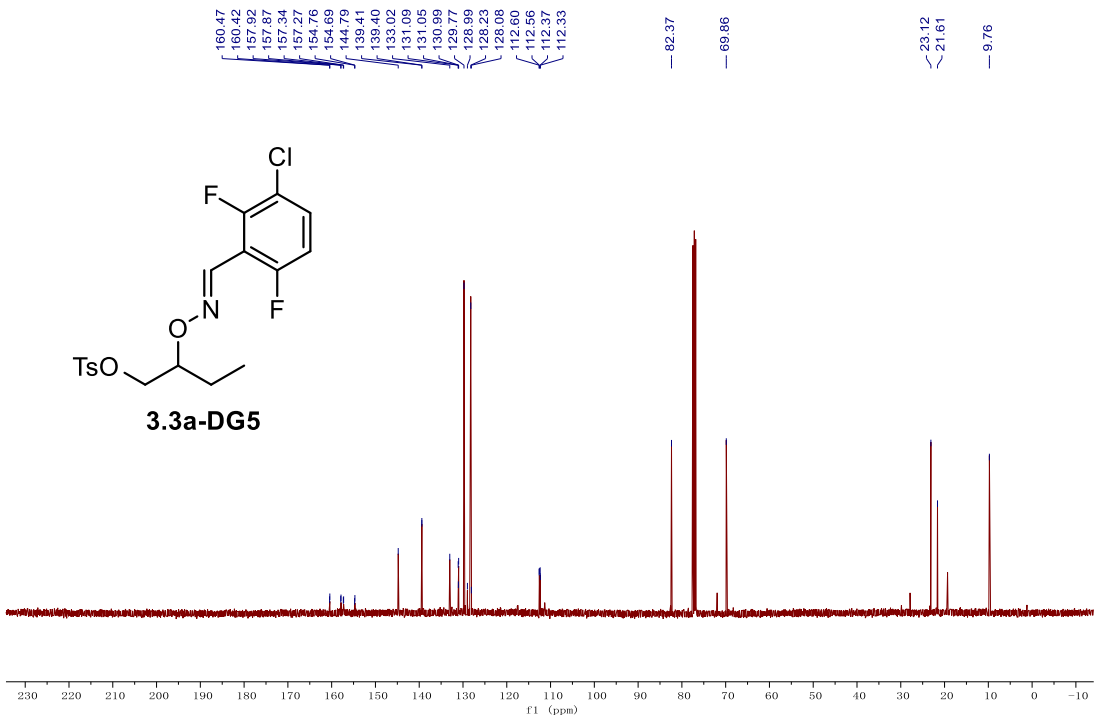


Figure 3.107 ^{19}F-NMR Spectrum of **3.3a-DG5**

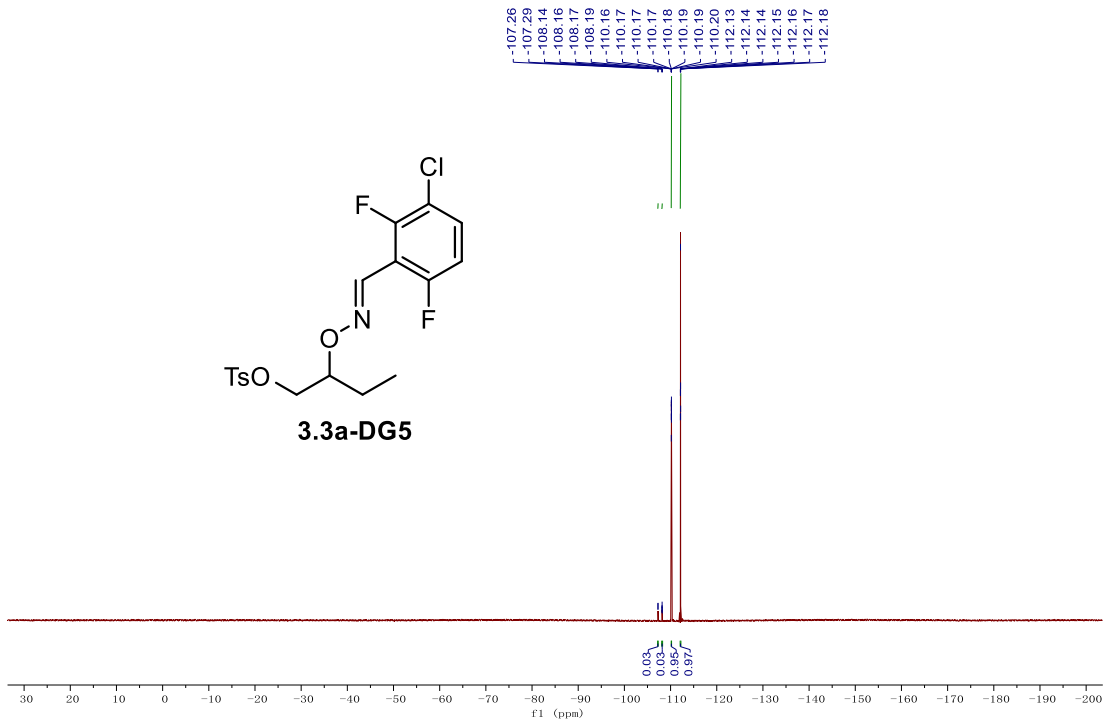


Figure 3.108 ^{1}H-NMR Spectrum of **3.3a-DG6**

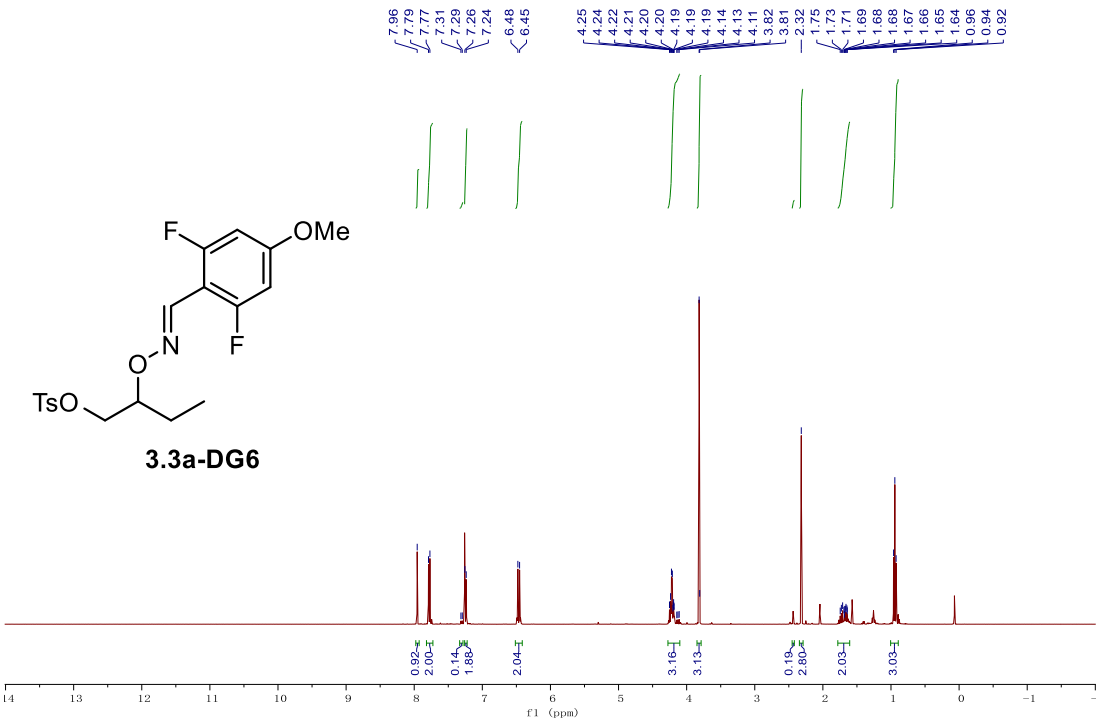


Figure 3.109 ^{13}C-NMR Spectrum of **3.3a-DG6**

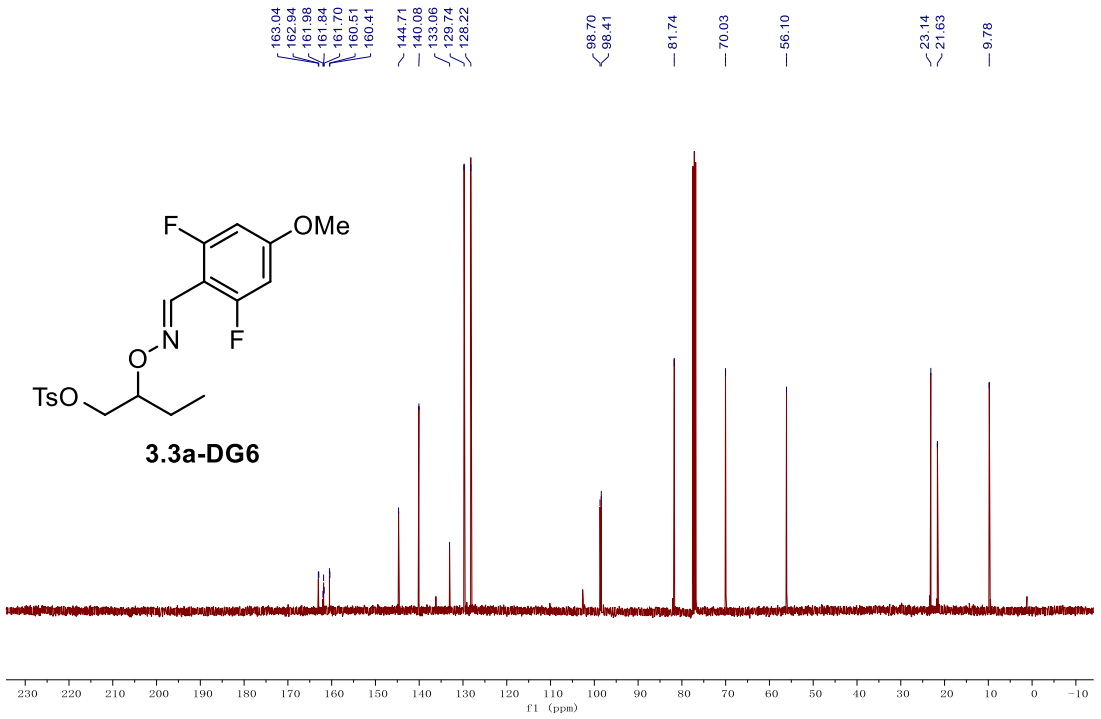


Figure 3.110 ^{19}F-NMR Spectrum of **3.3a-DG6**

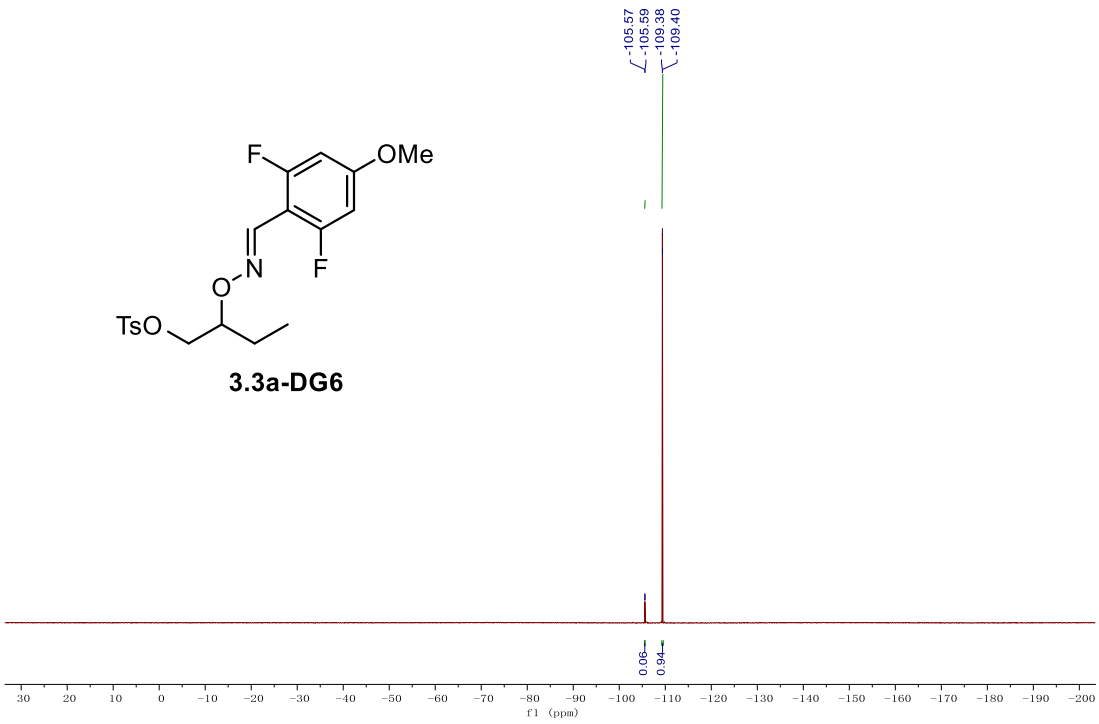


Figure 3.111 ^{1}H-NMR Spectrum of **3.3a-DG12**

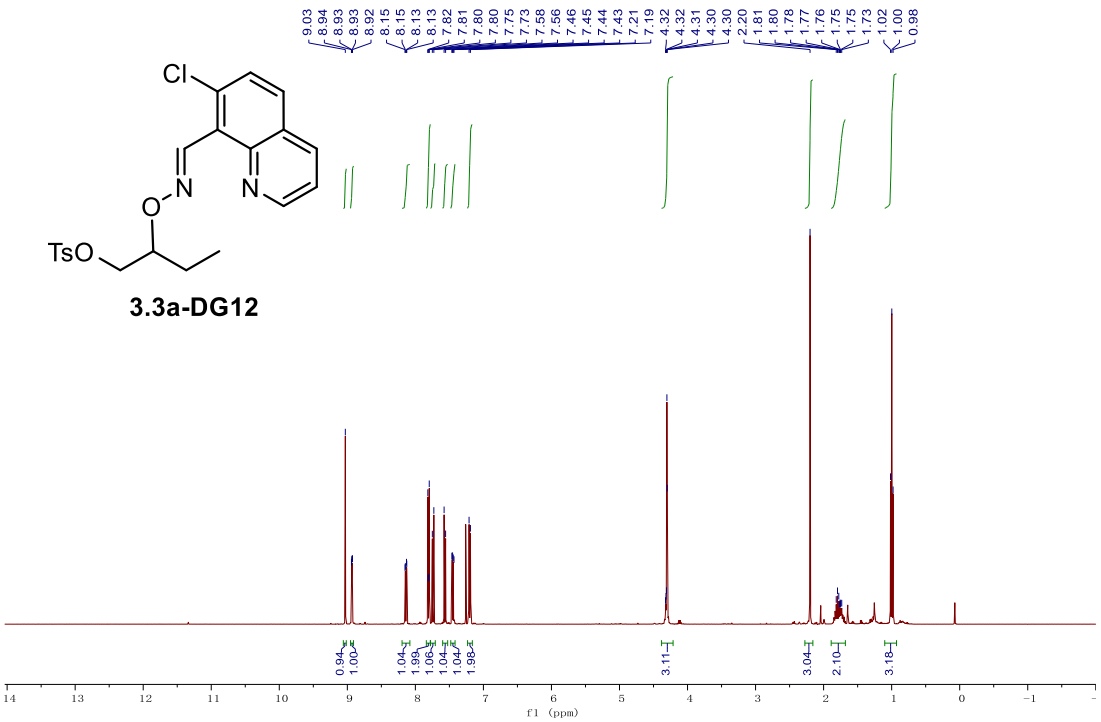


Figure 3.112 ^{13}C-NMR Spectrum of **3.3a-DG12**

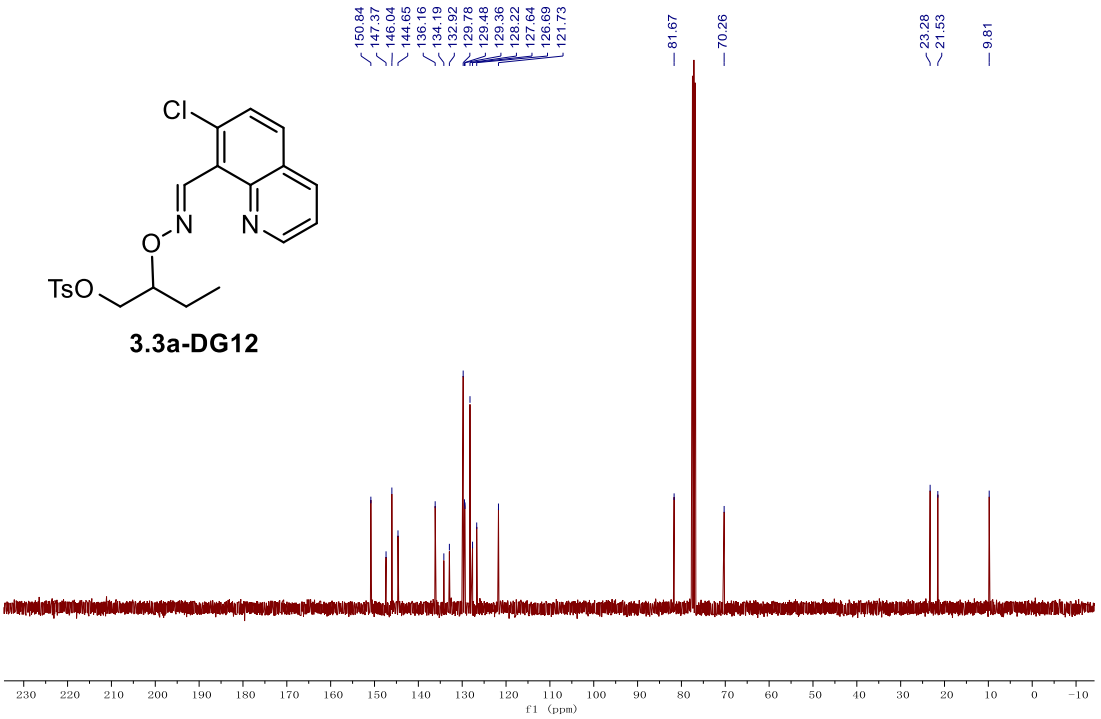


Figure 3.113 ^{1}H-NMR Spectrum of **3.3a**

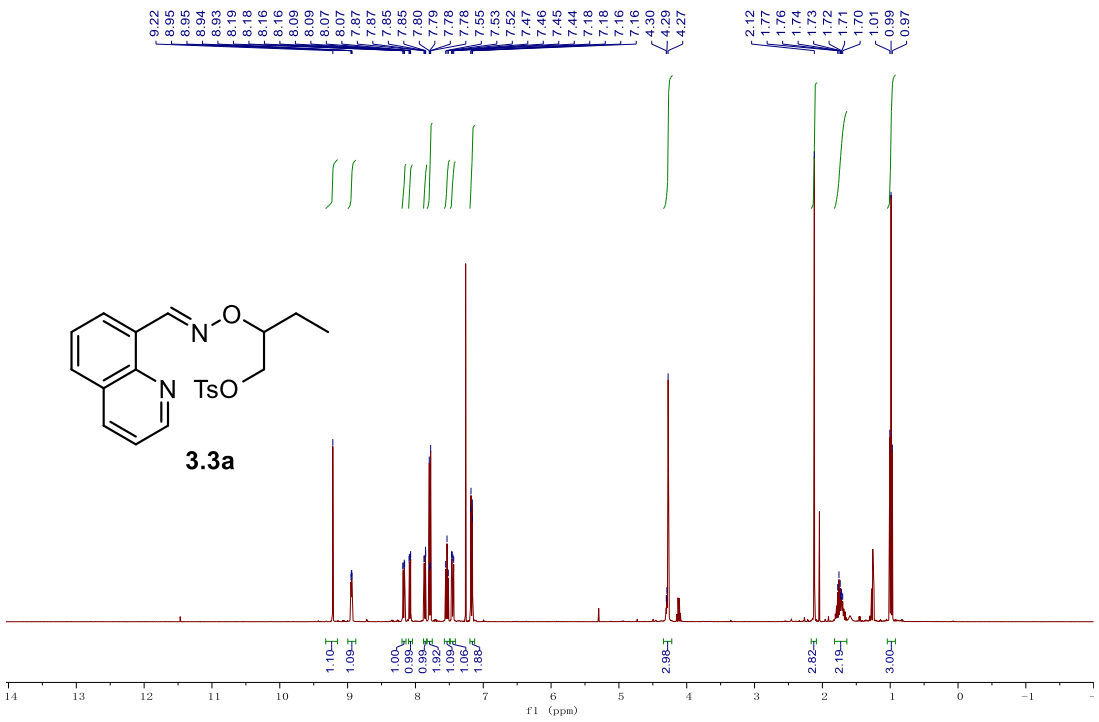


Figure 3.114 ^{13}C-NMR Spectrum of **3.3a**

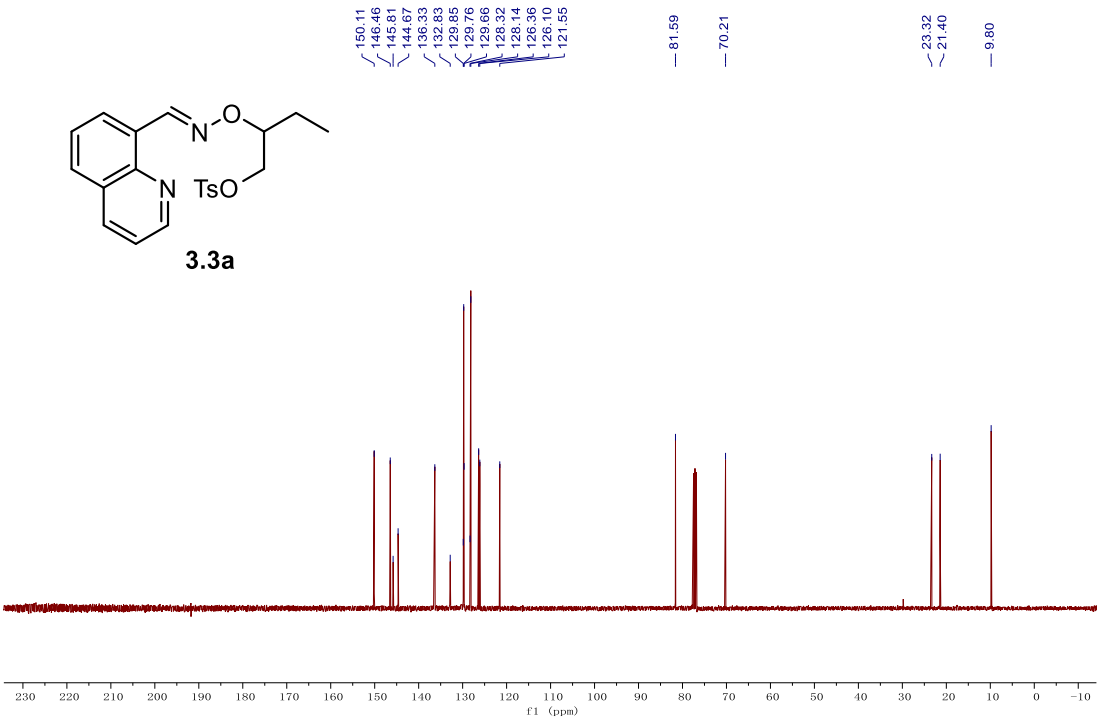


Figure 3.115 ^{1}H-NMR Spectrum of **3.3b**

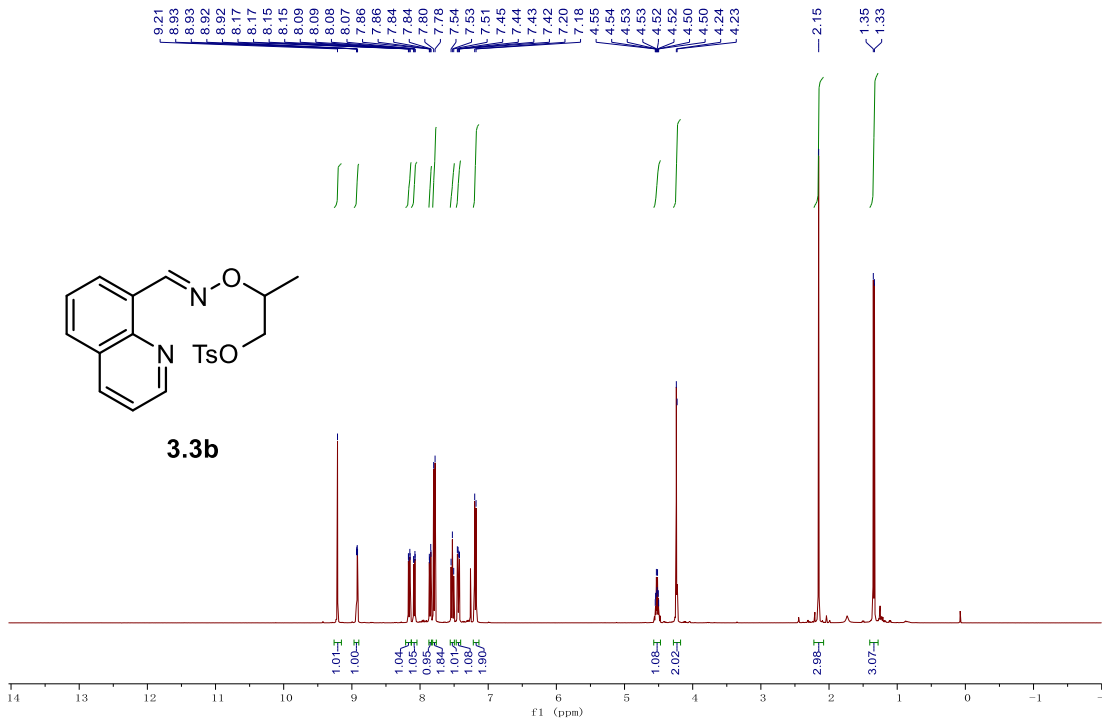


Figure 3.116 ^{13}C-NMR Spectrum of **3.3b**

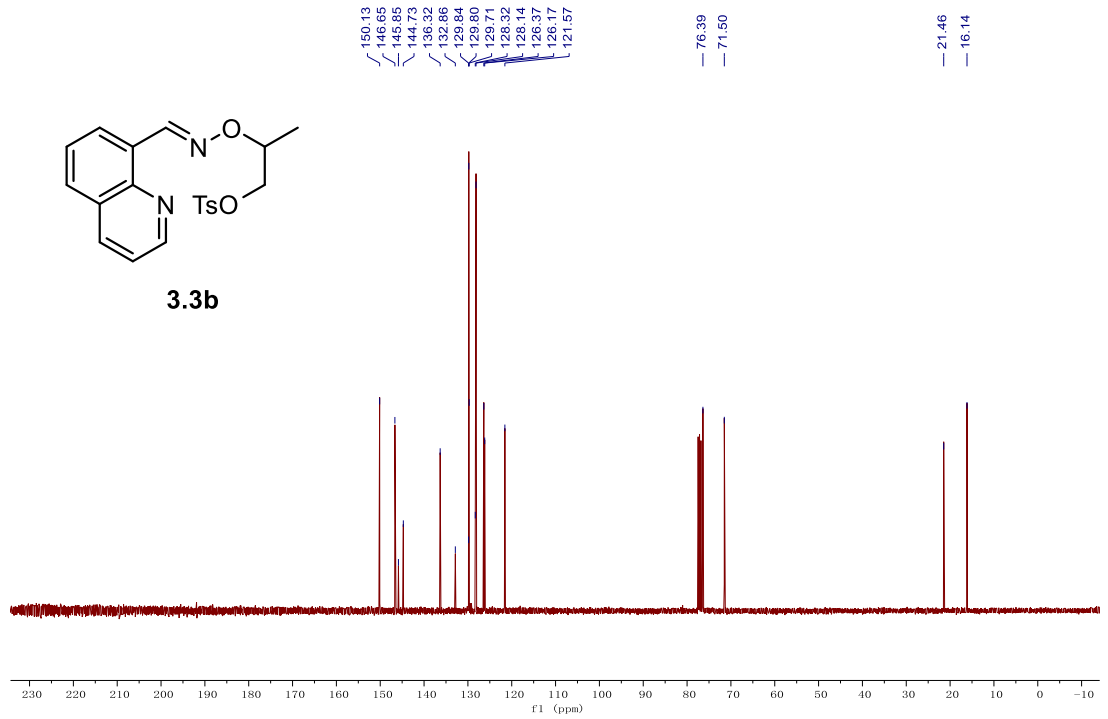


Figure 3.117 ^{1}H-NMR Spectrum of **3.3b'**

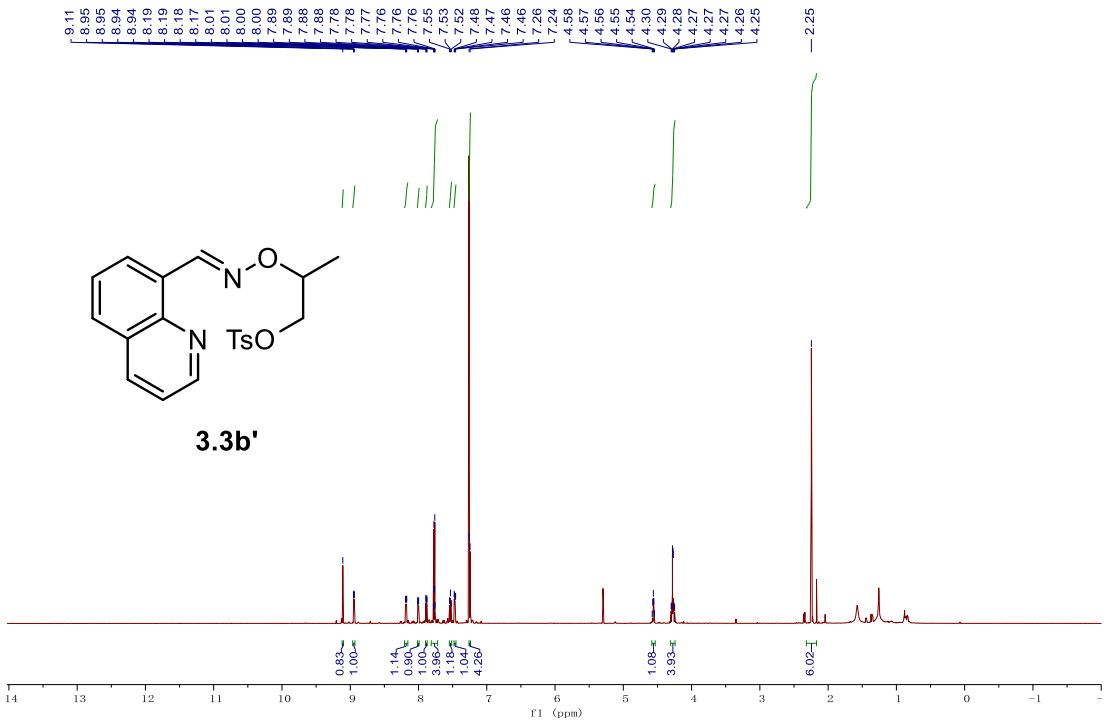


Figure 3.118 ^{13}C-NMR Spectrum of **3.3b'**

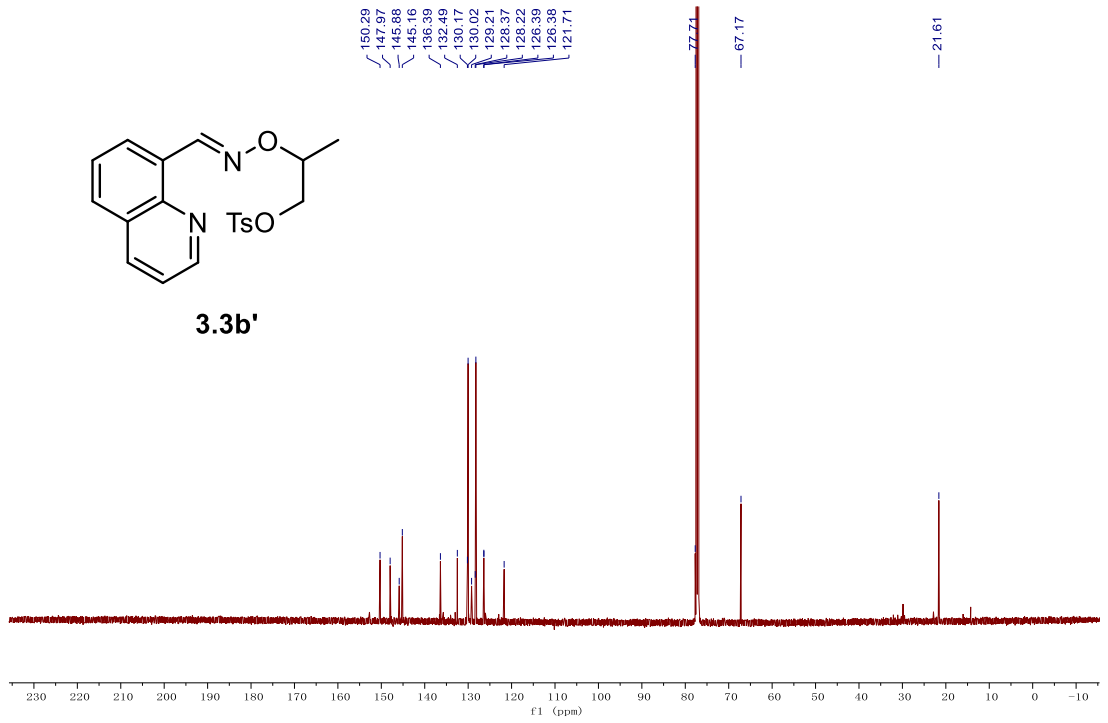


Figure 3.119 ^{1}H-NMR Spectrum of **3.3c**

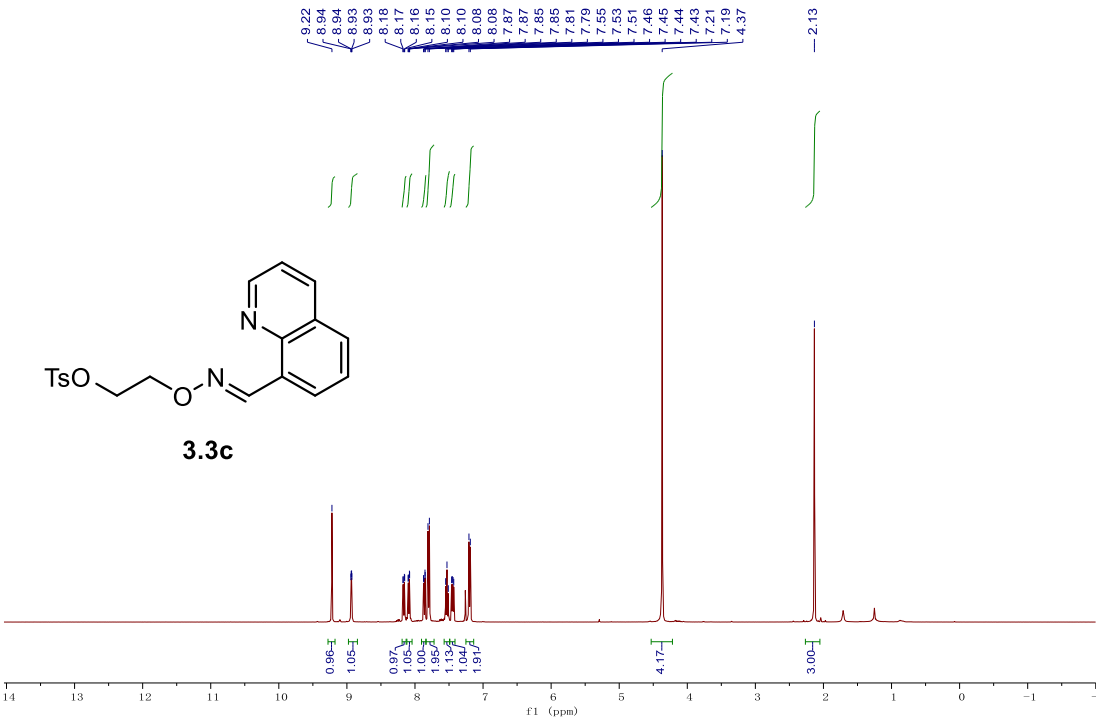


Figure 3.120 ^{13}C-NMR Spectrum of **3.3c**

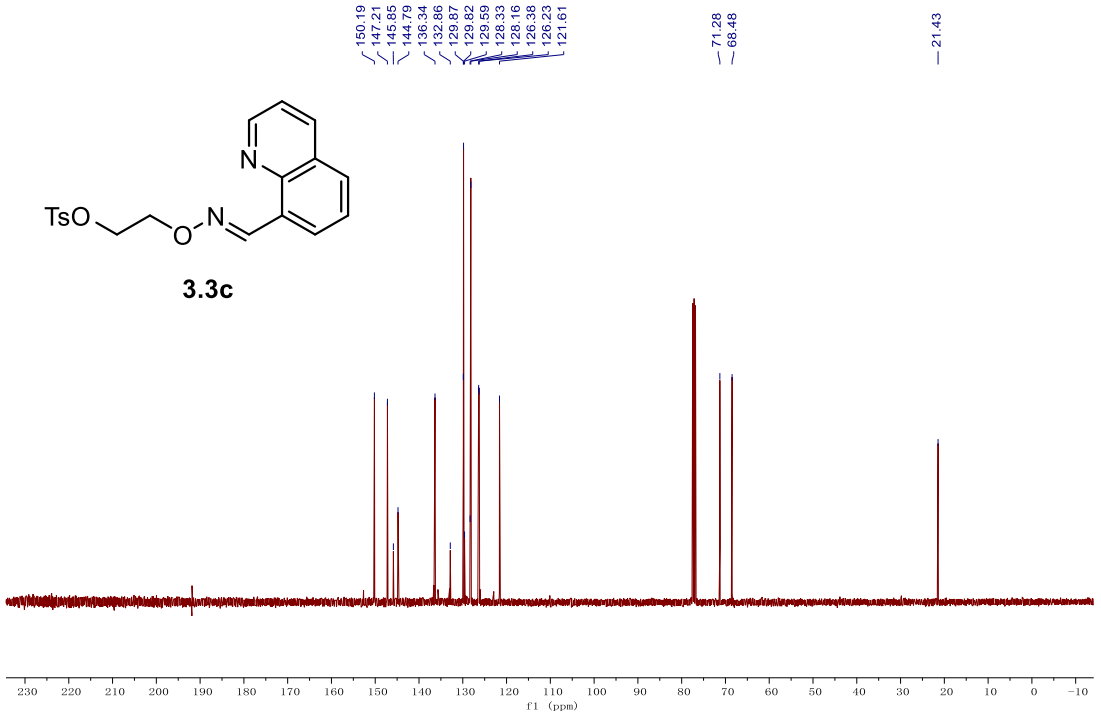


Figure 3.121 ^{1}H-NMR Spectrum of **3.3d**

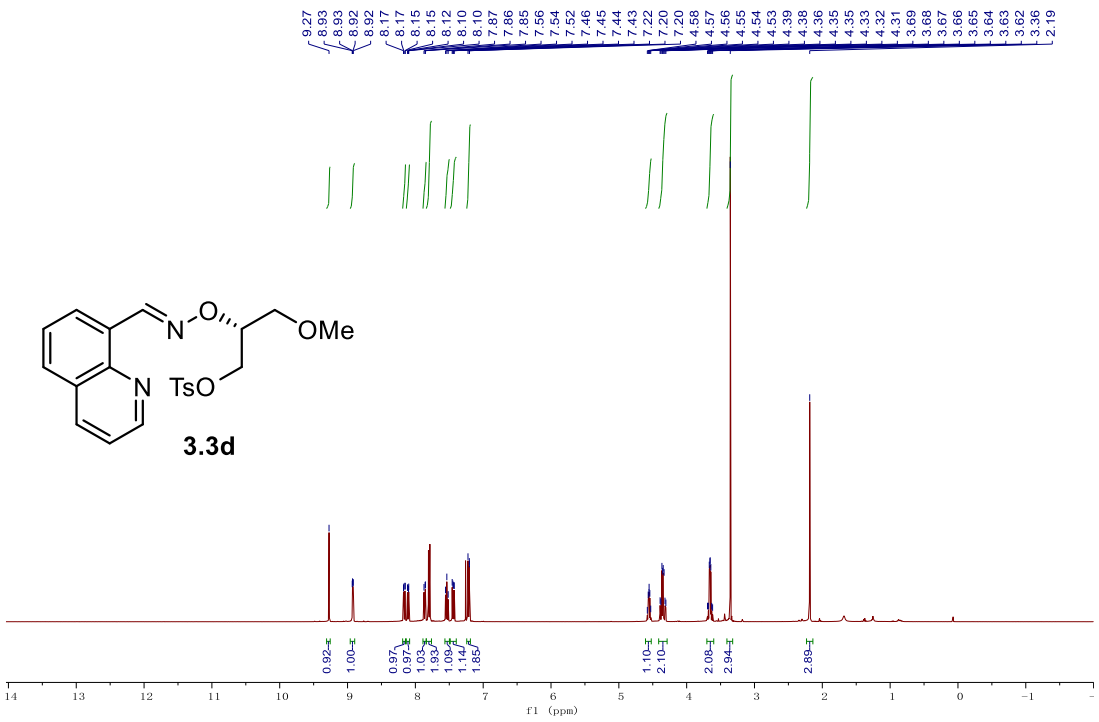


Figure 3.122 ^{13}C-NMR Spectrum of **3.3d**

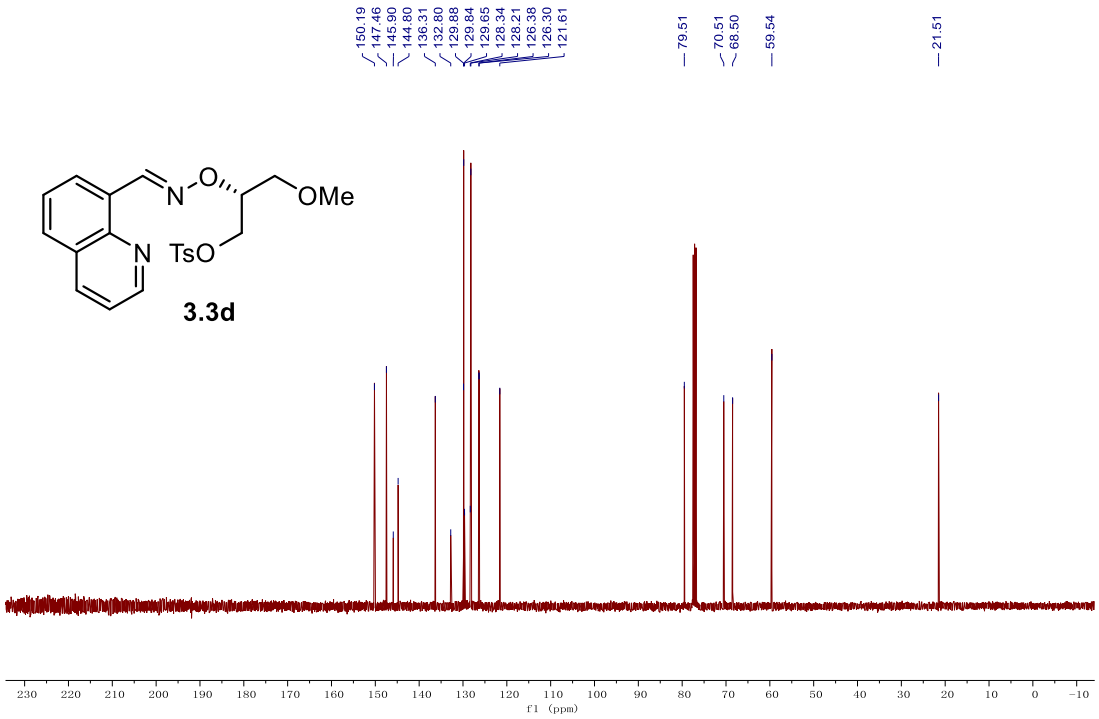


Figure 3.123 ^{1}H-NMR Spectrum of **3.3e**

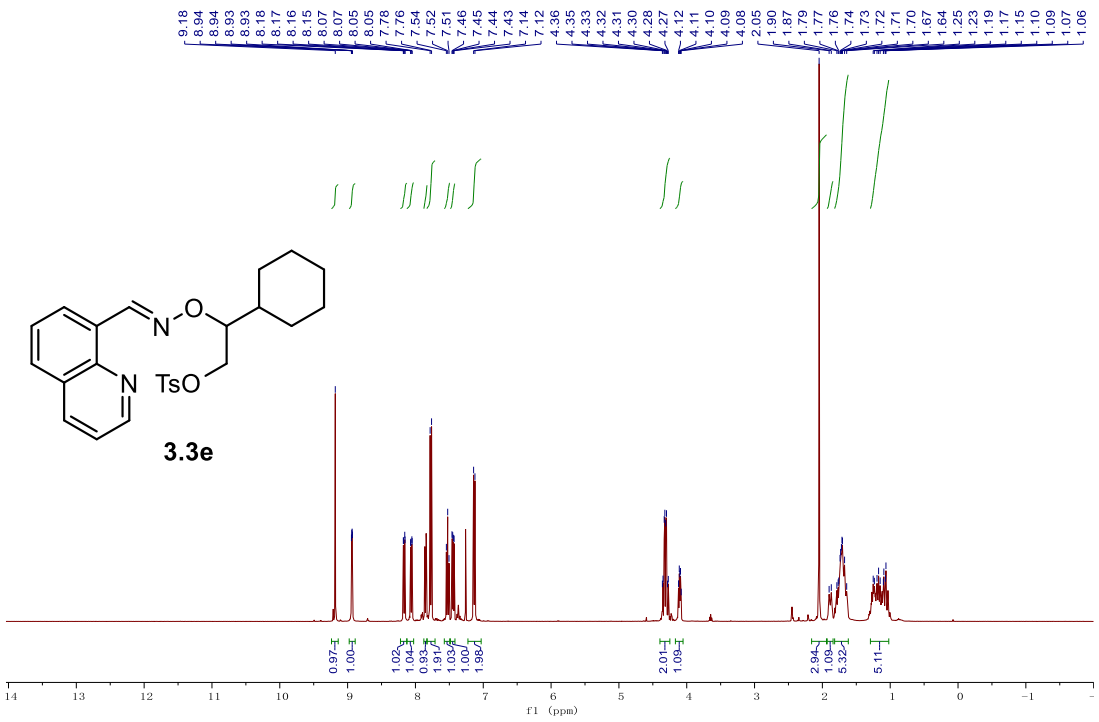


Figure 3.124 ^{13}C-NMR Spectrum of **3.3e**

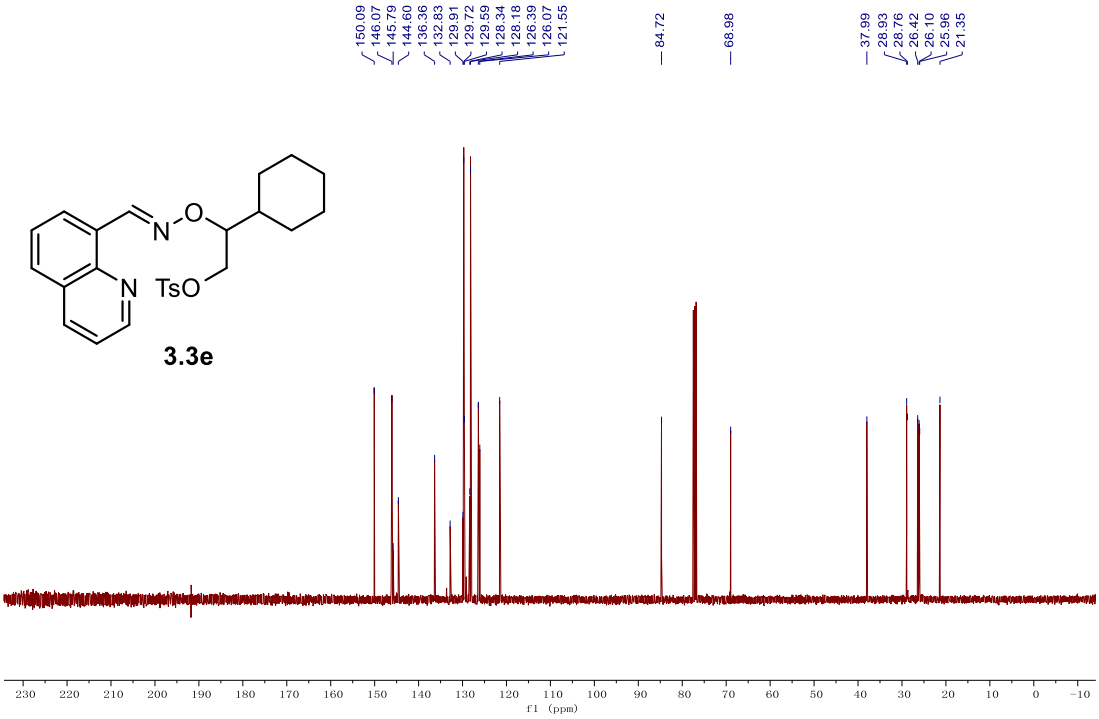


Figure 3.125 ^{1}H-NMR Spectrum of **3.3f**

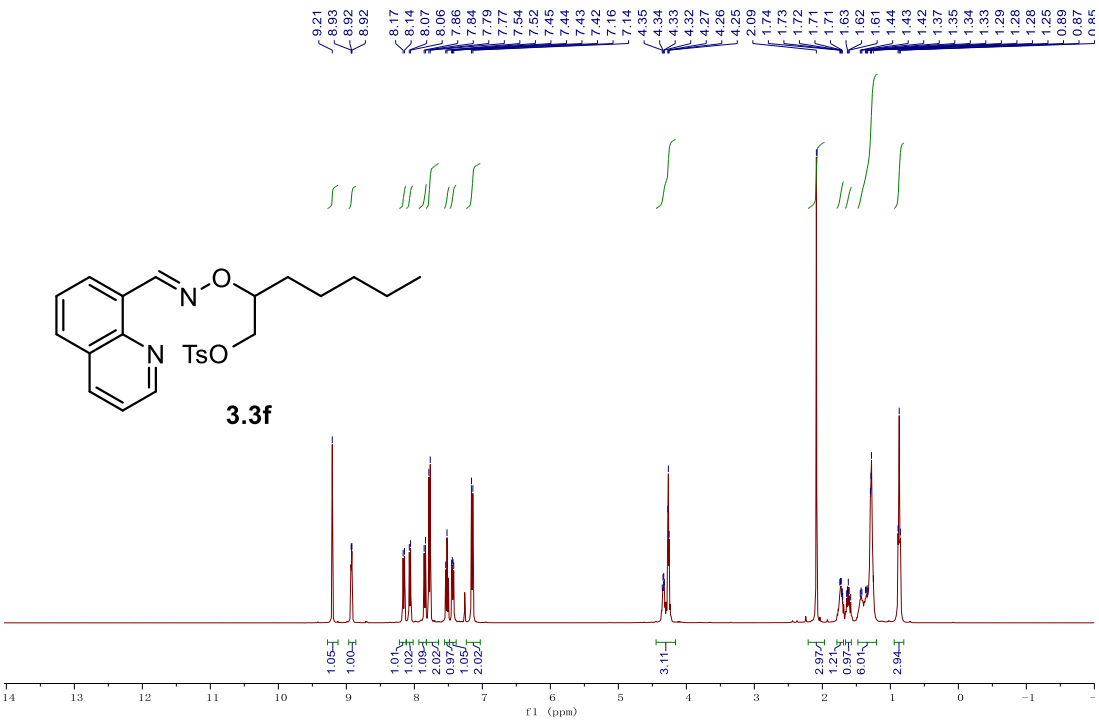


Figure 3.126 ^{13}C-NMR Spectrum of **3.3f**

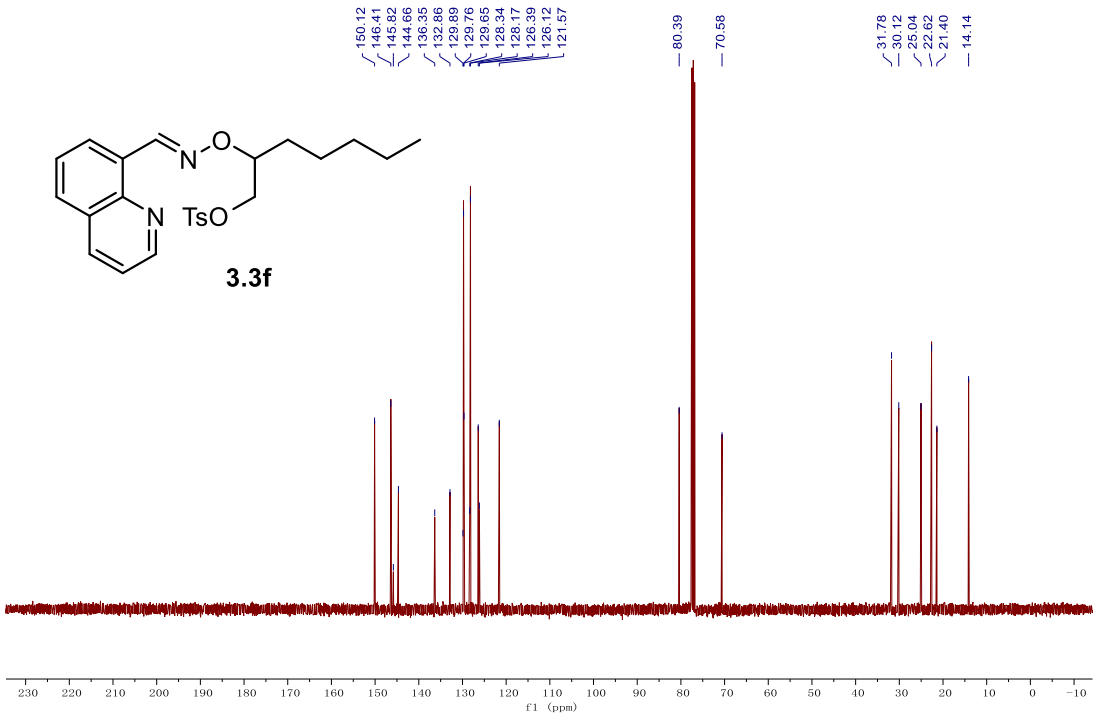


Figure 3.127 ^{1}H-NMR Spectrum of **3.3g**

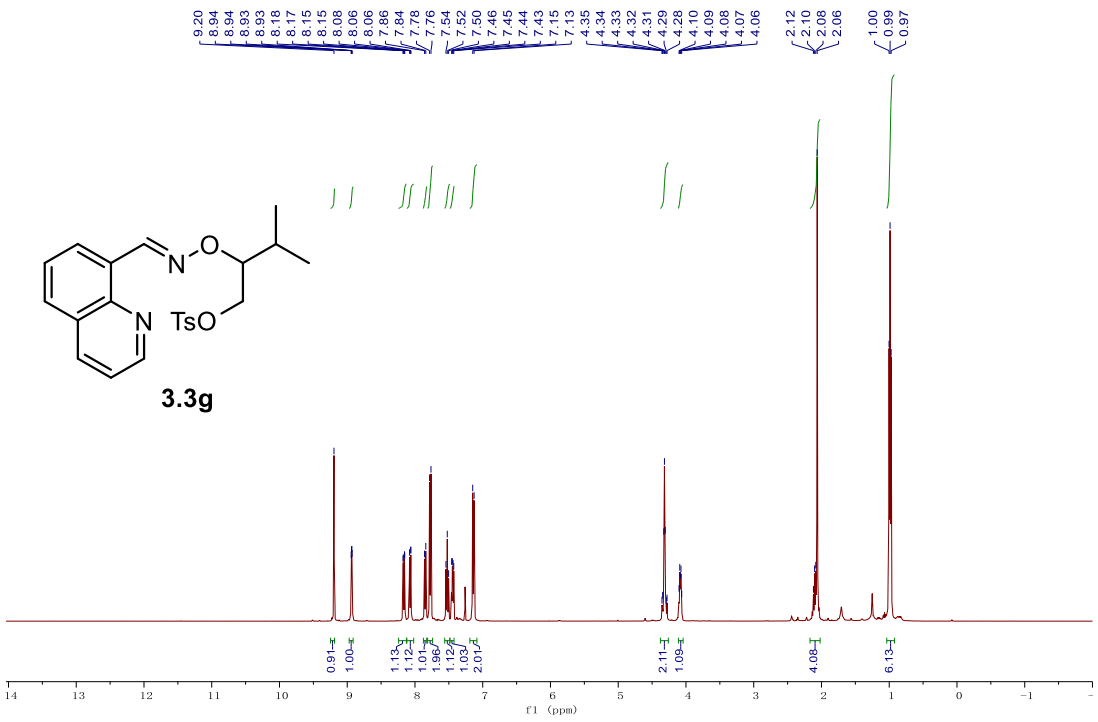


Figure 3.128 ^{13}C-NMR Spectrum of **3.3g**

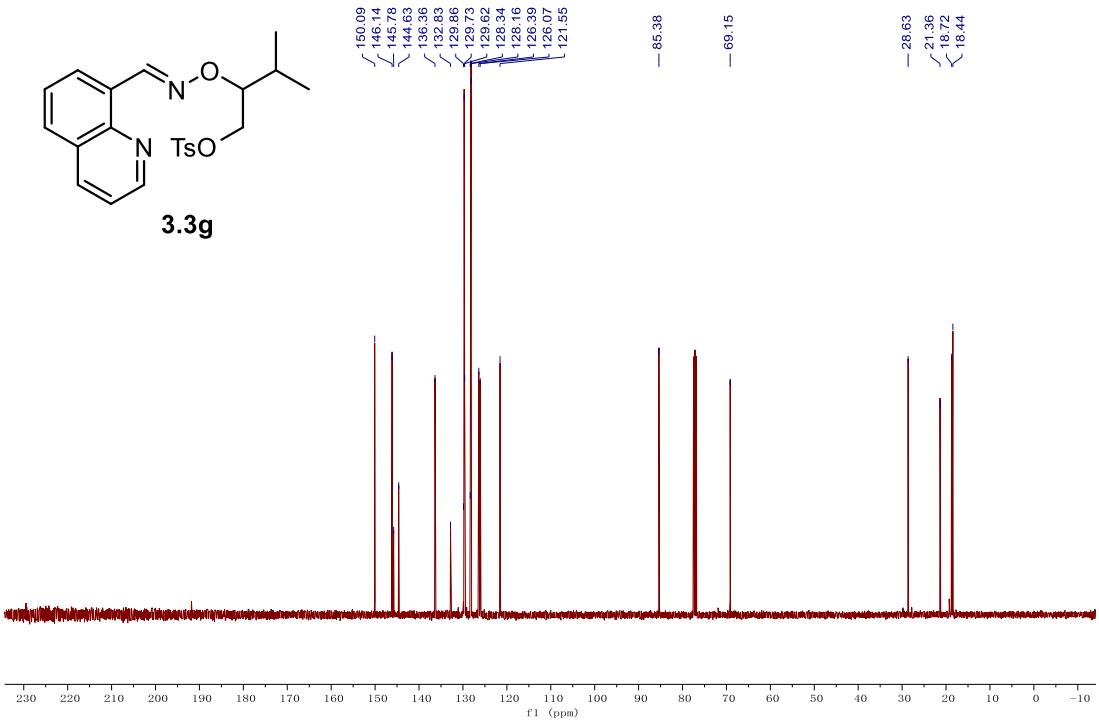


Figure 3.129 ^{1}H-NMR Spectrum of **3.3h**

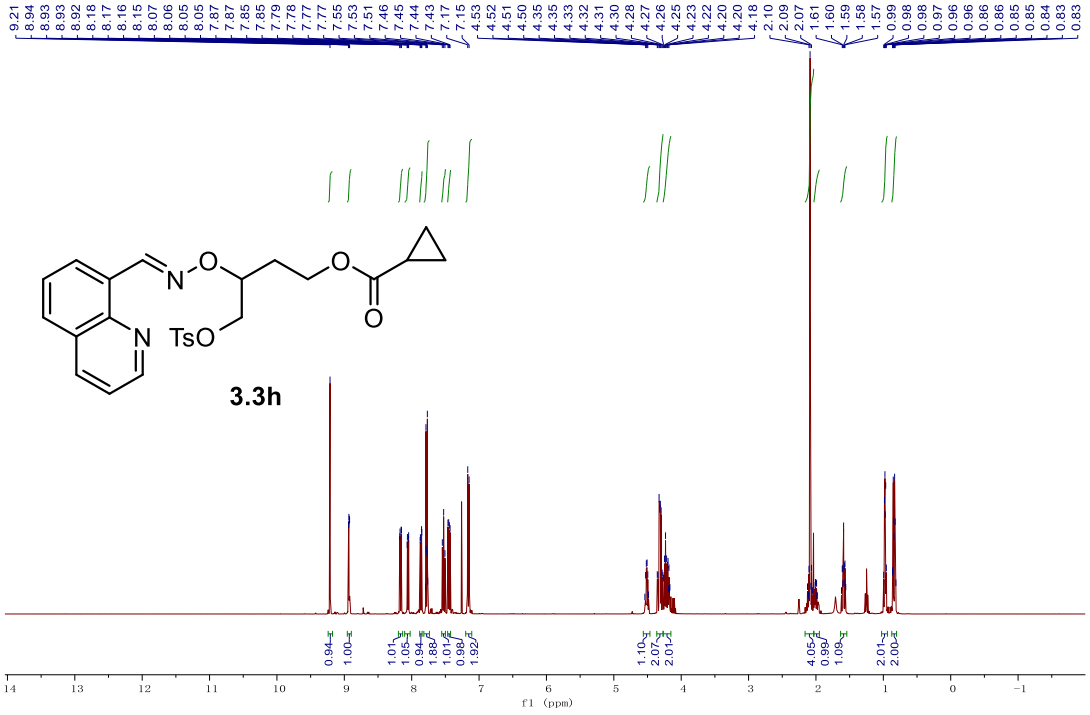


Figure 3.130 ^{13}C-NMR Spectrum of **3.3h**

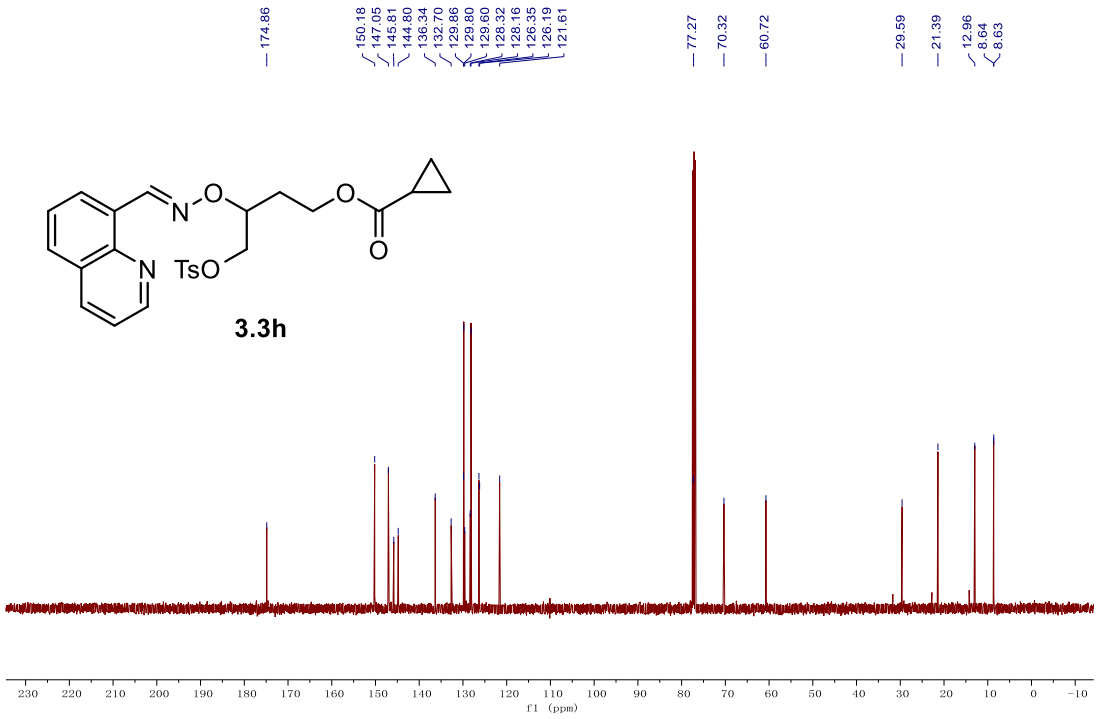


Figure 3.131 ^{1}H-NMR Spectrum of **3.3i**

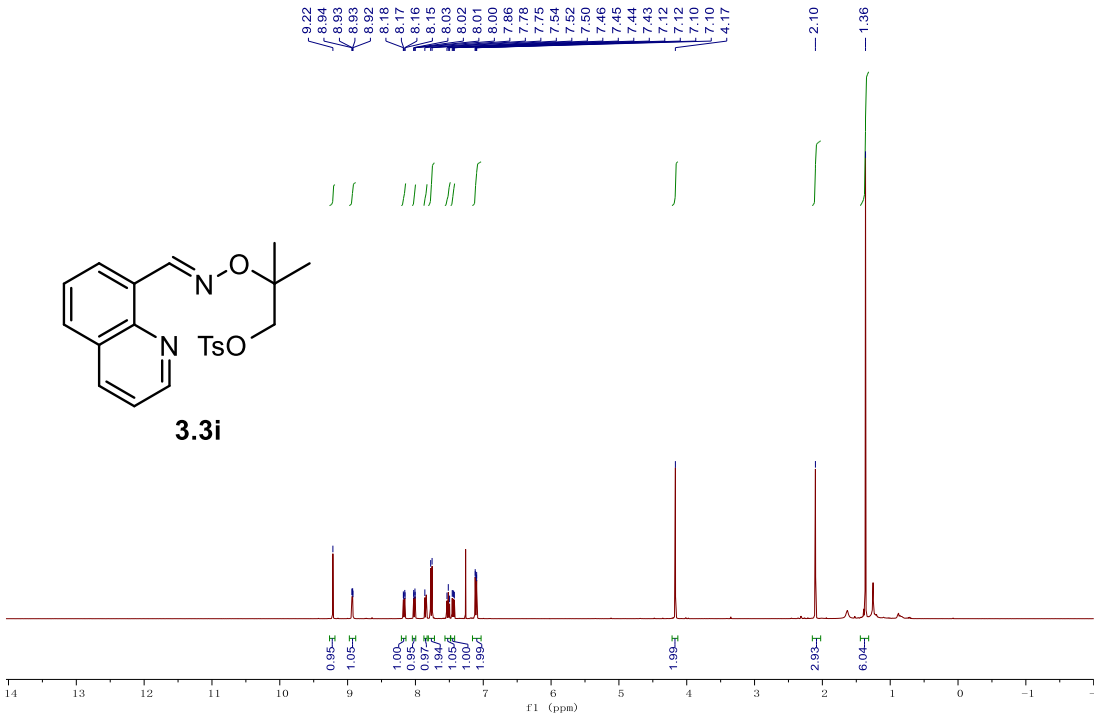


Figure 3.132 ^{13}C-NMR Spectrum of **3.3i**

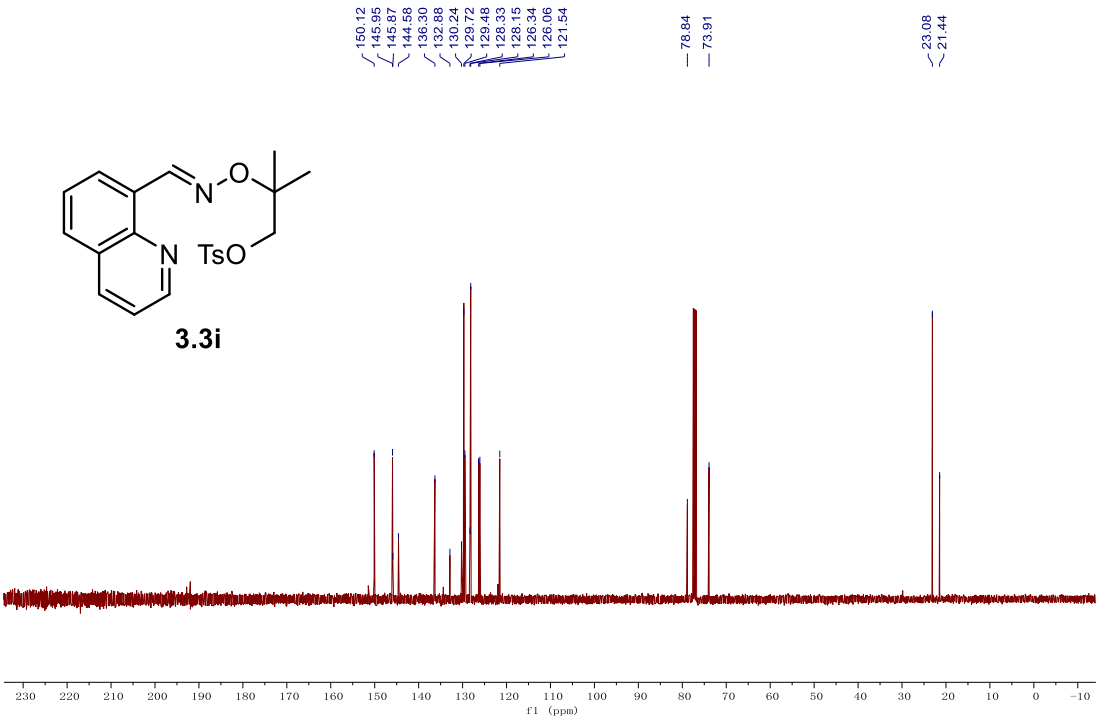


Figure 3.133 ^{1}H-NMR Spectrum of **3.3i'**

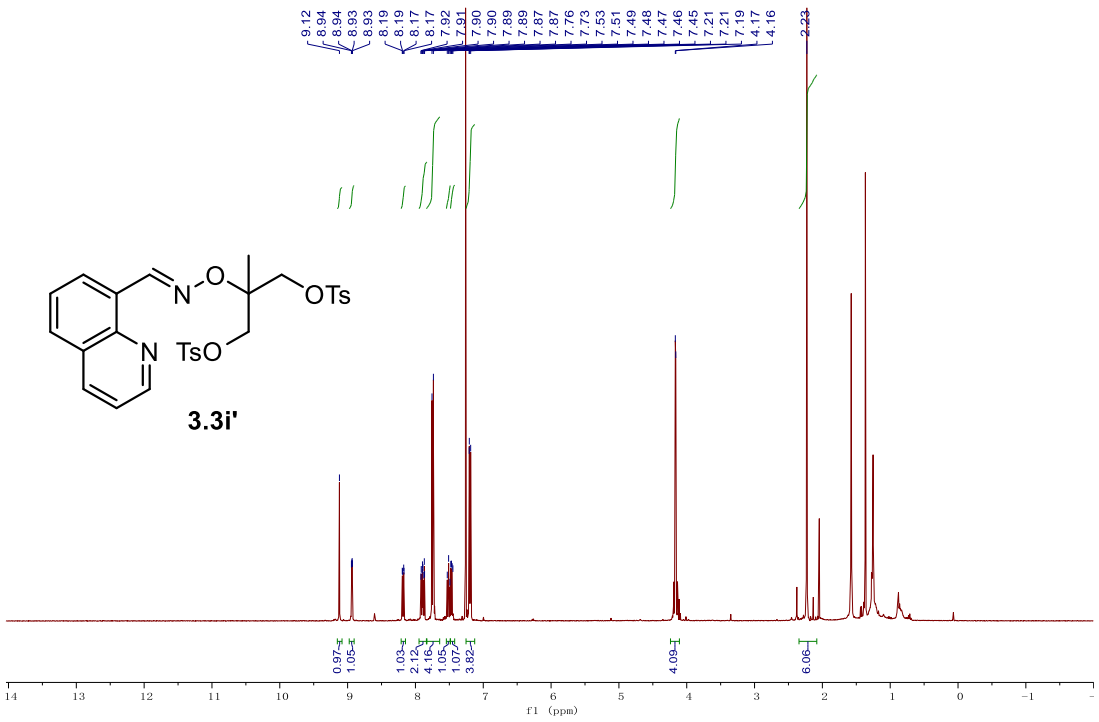


Figure 3.134 ^{13}C-NMR Spectrum of **3.3i'**

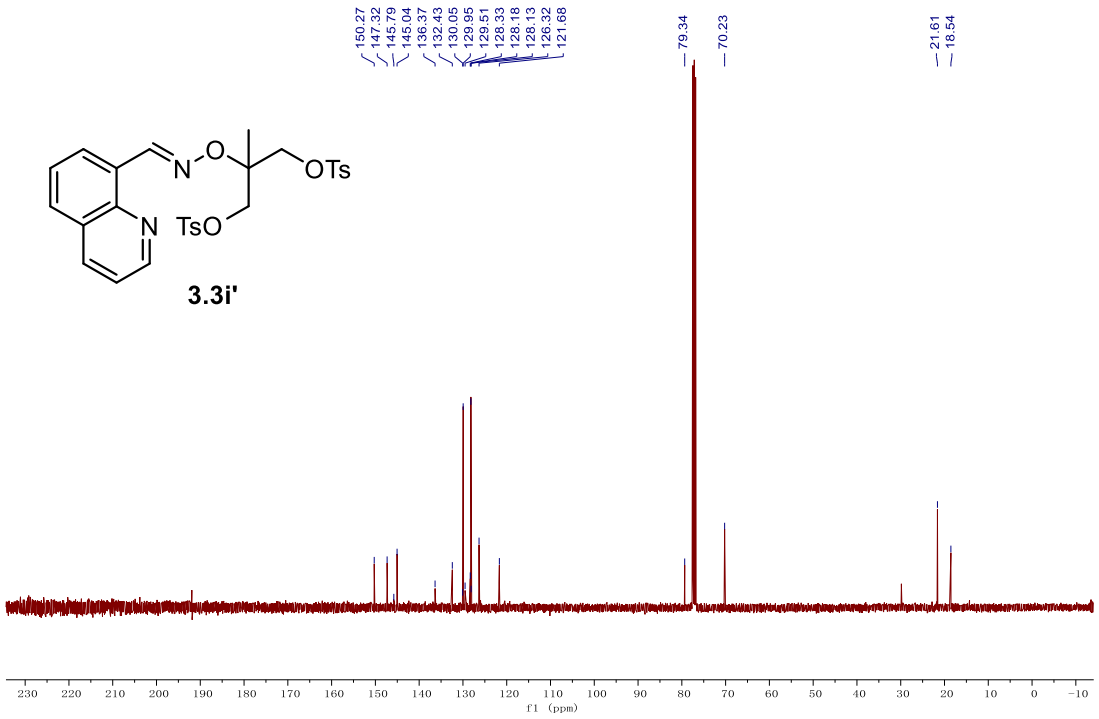


Figure 3.135 ^{1}H-NMR Spectrum of **3.3j**

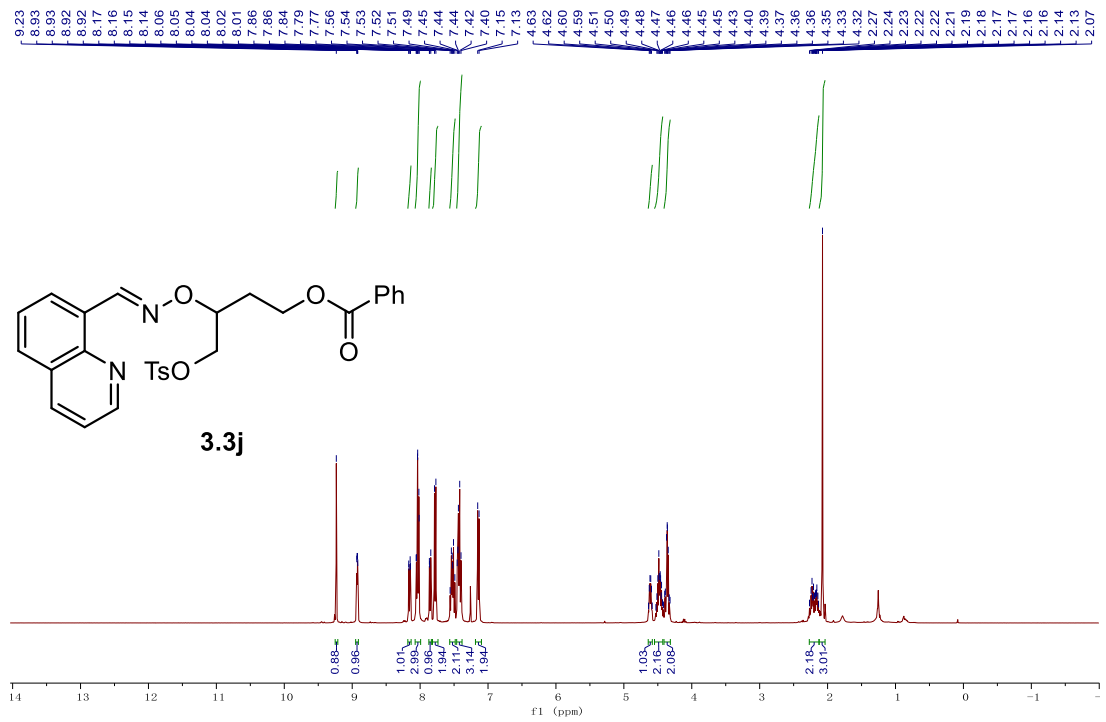


Figure 3.136 ^{13}C-NMR Spectrum **of 3.3j**

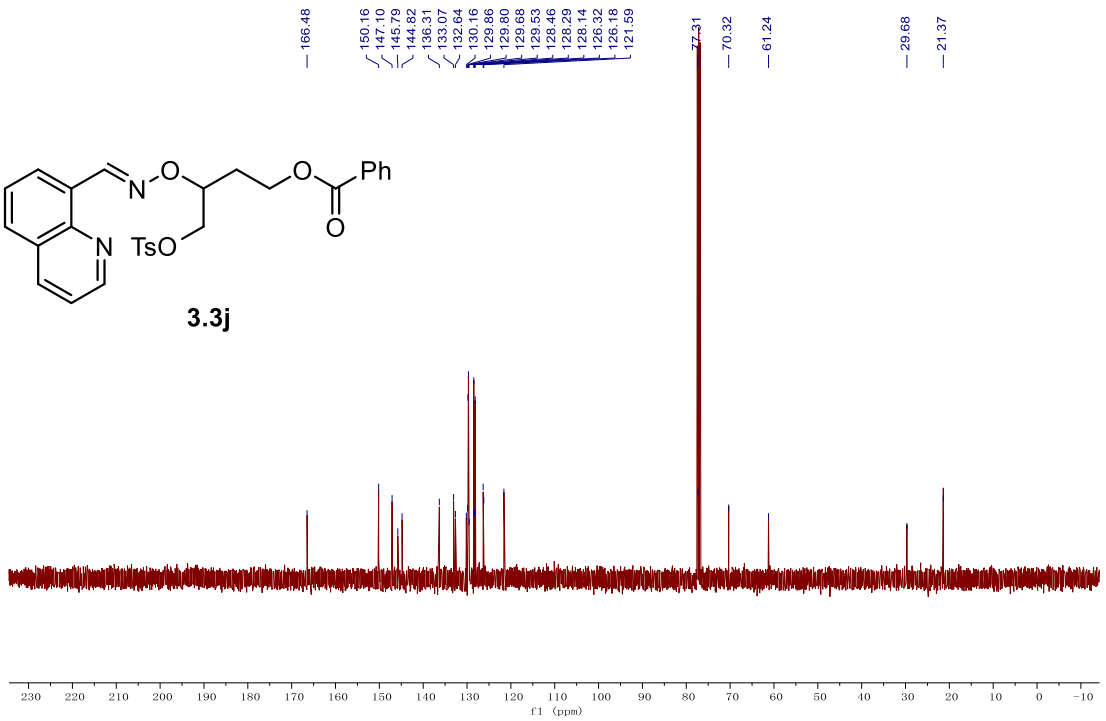


Figure 3.137 ^{1}H-NMR Spectrum of **3.3k**

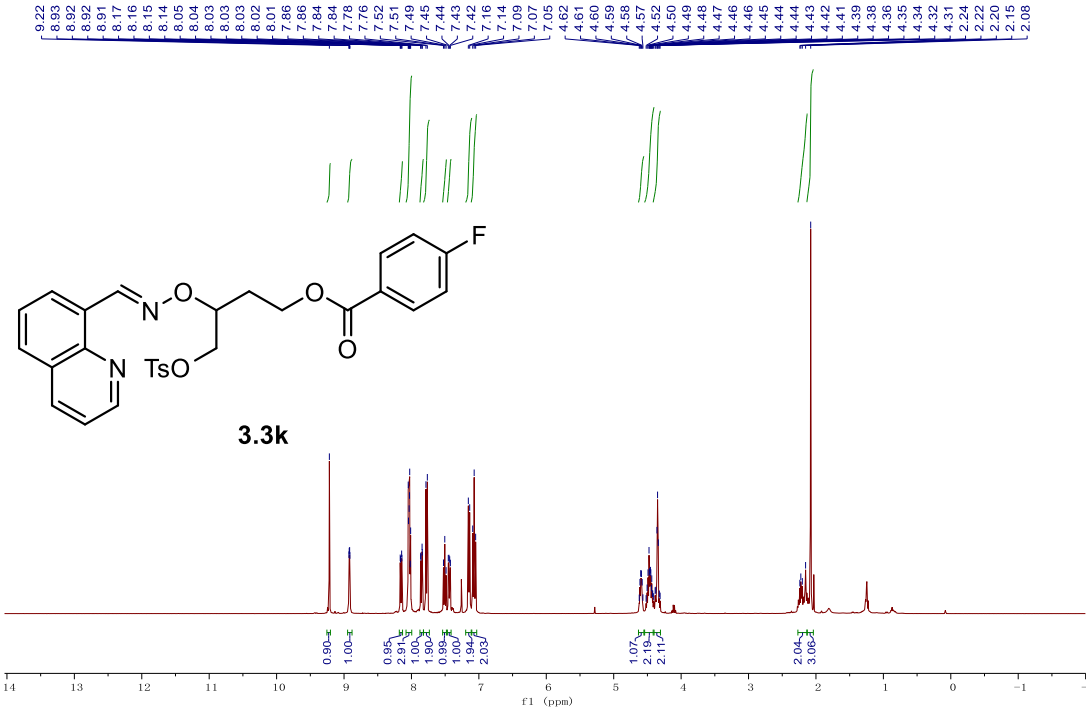


Figure 3.138 ^{13}C-NMR Spectrum of **3.3k**

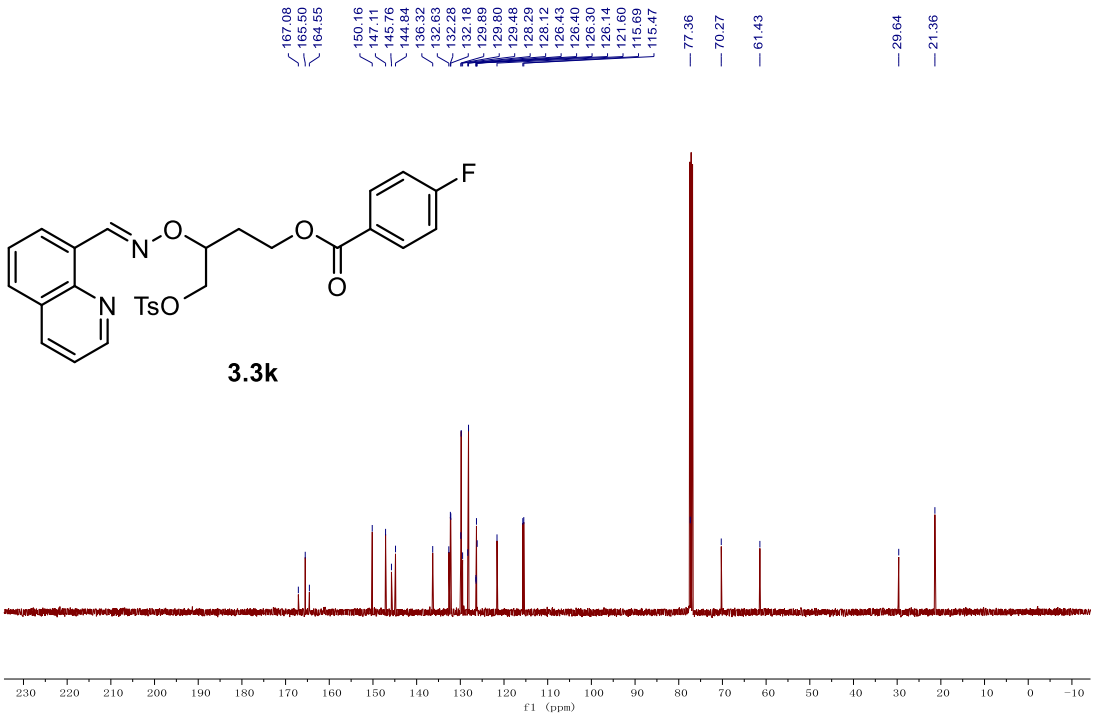


Figure 3.139 ^{19}F-NMR Spectrum of **3.3k**

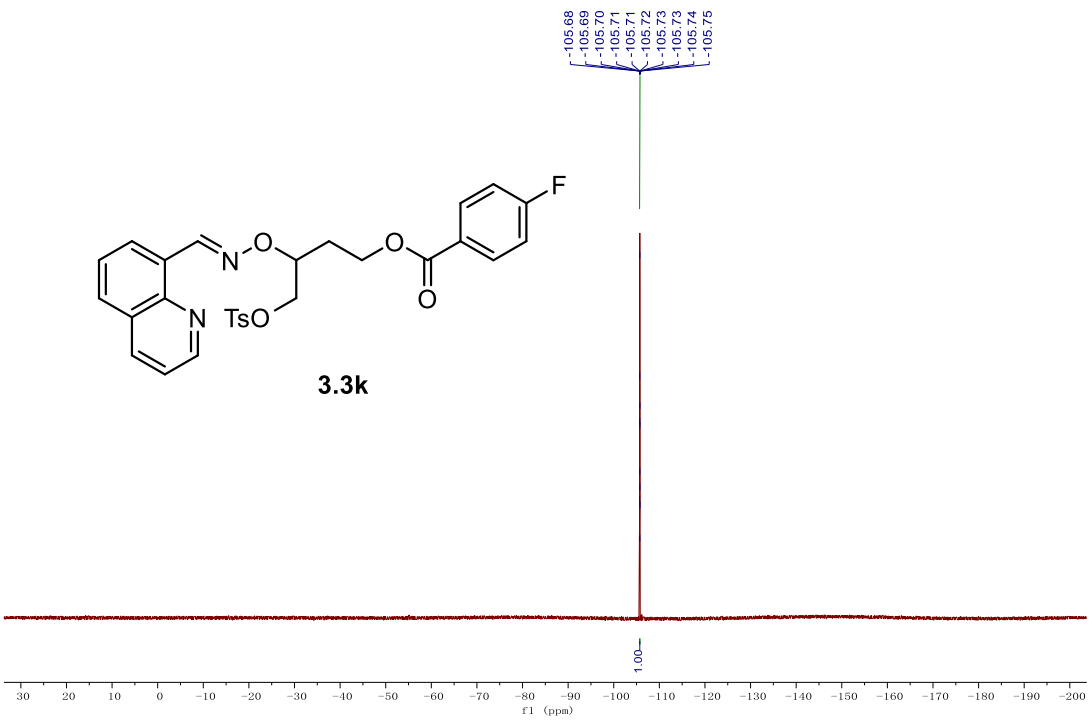


Figure 3.140 ^{1}H-NMR Spectrum of **3.3l**

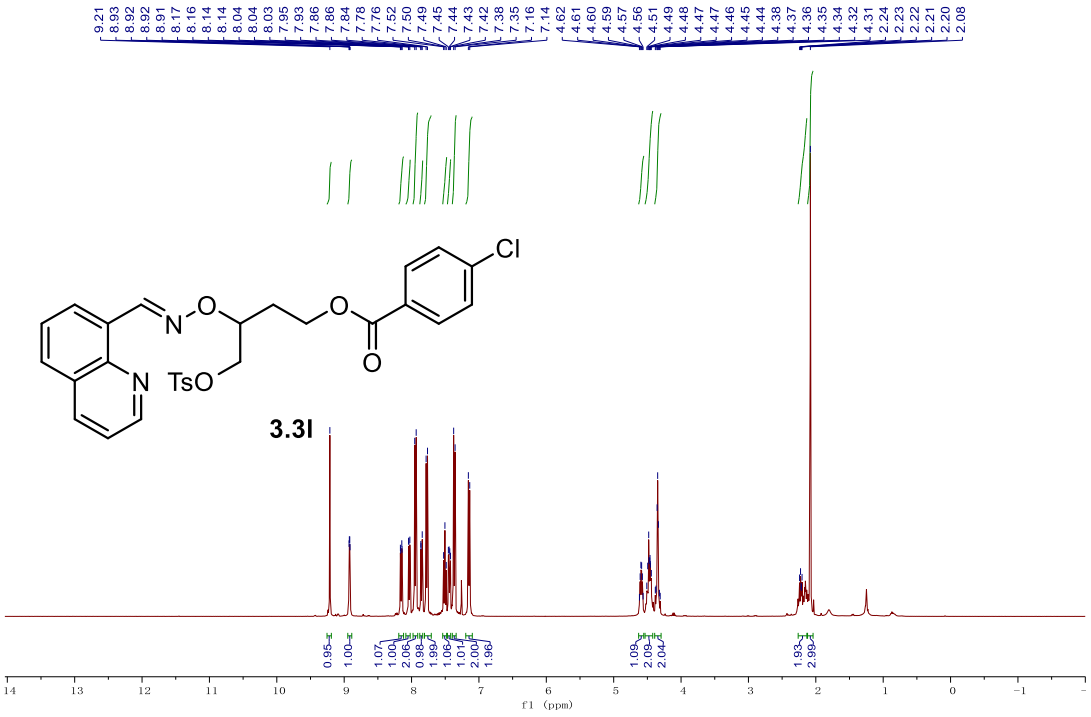


Figure 3.141 ^{13}C-NMR Spectrum of **3.3l**

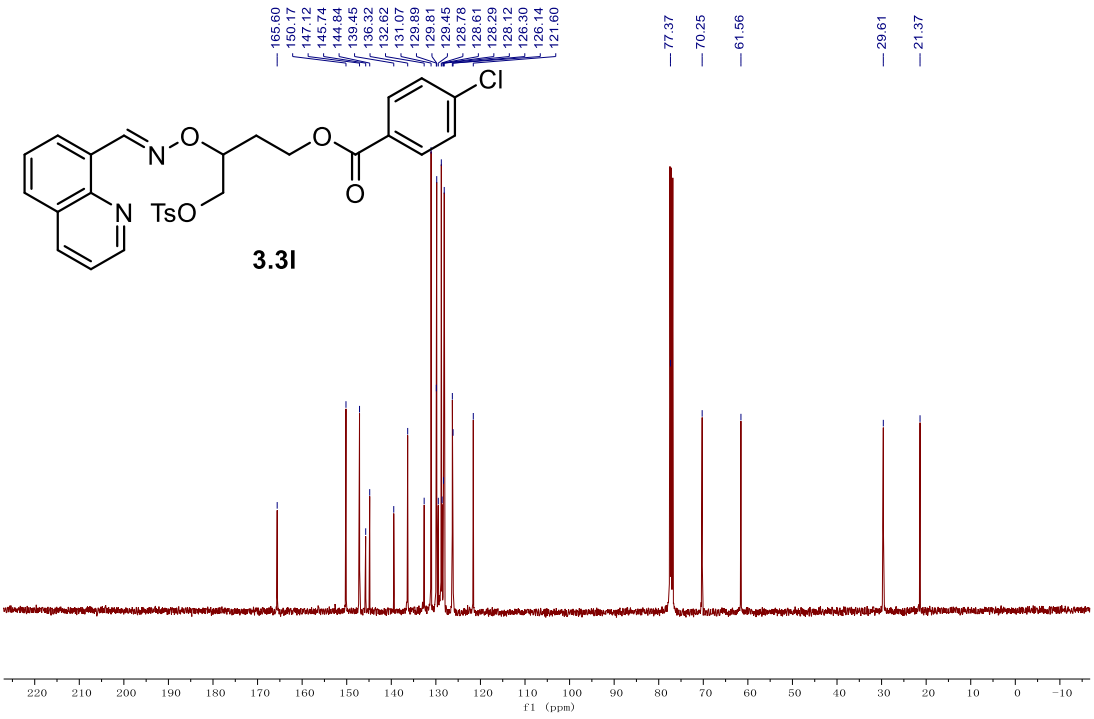


Figure 3.142 ^{1}H-NMR Spectrum of **3.3m**

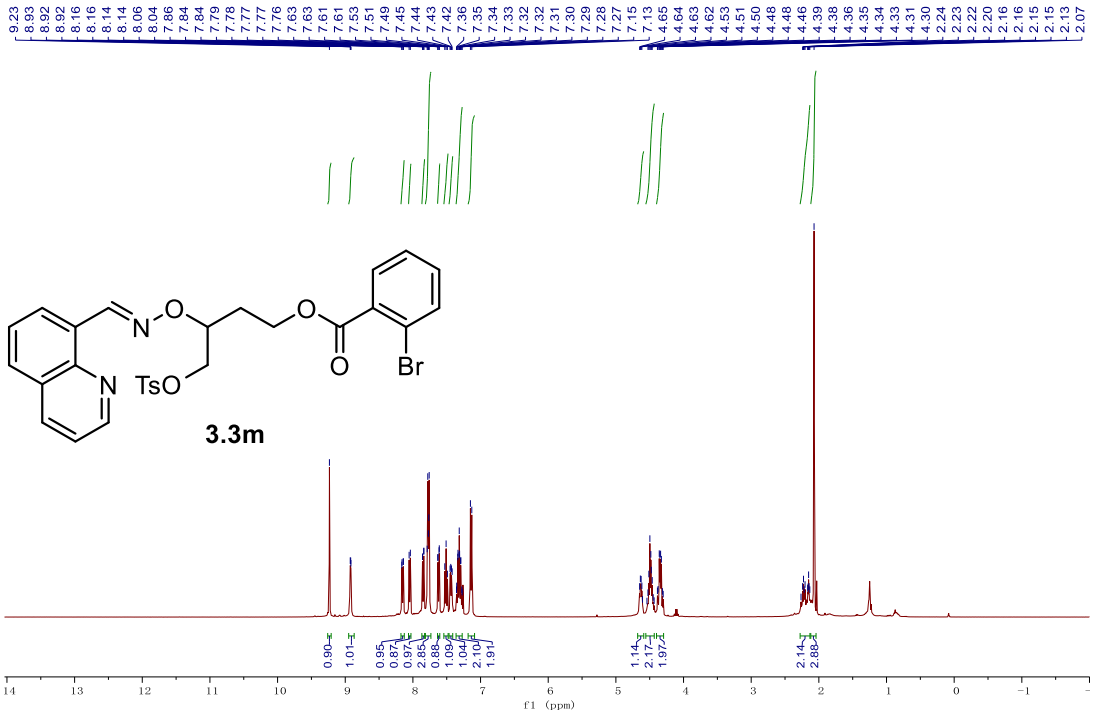


Figure 3.143 ^{13}C-NMR Spectrum of **3.3m**

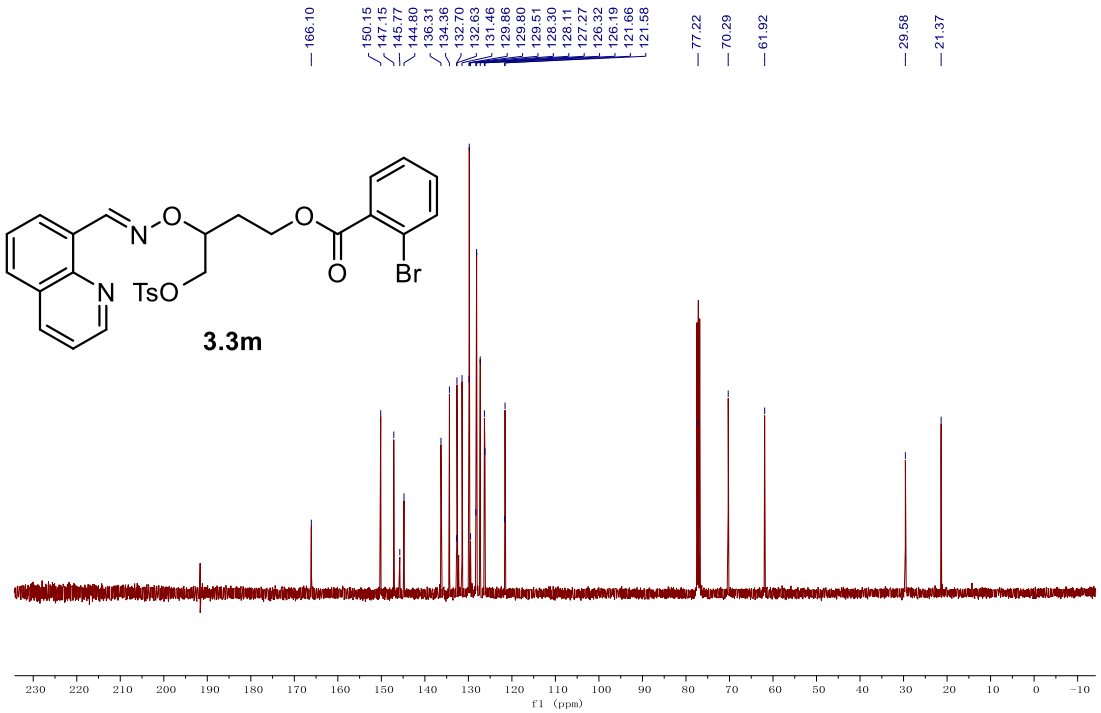


Figure 3.144 ^{1}H-NMR Spectrum of **3.3n**

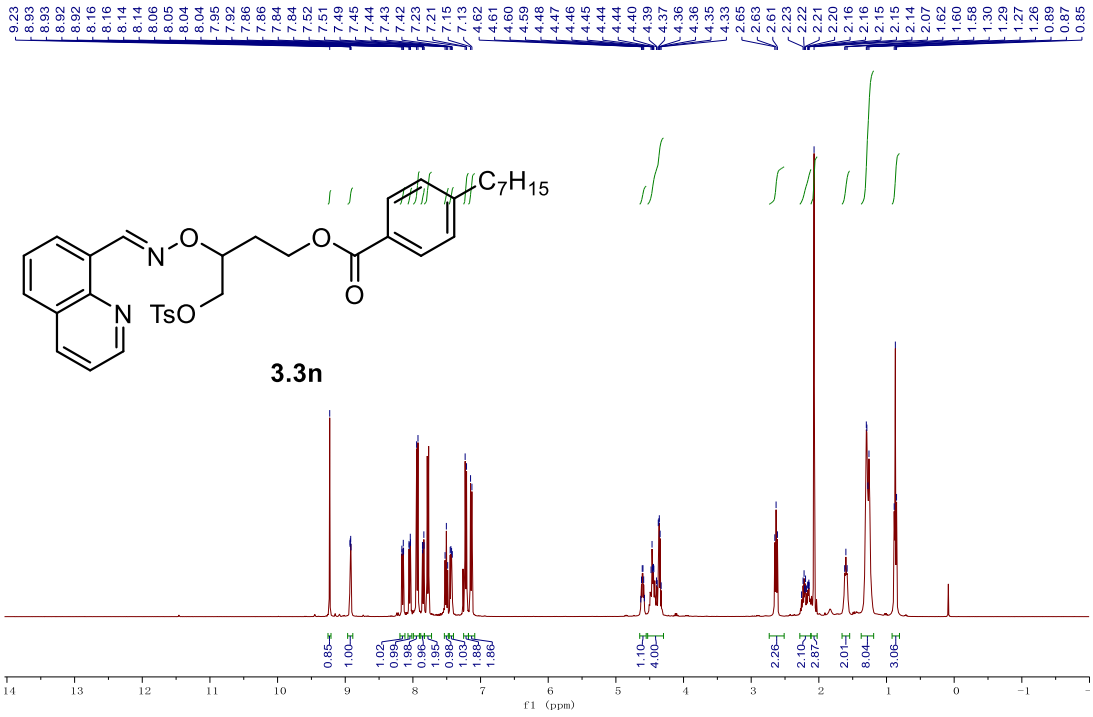


Figure 3.145 ^{13}C-NMR Spectrum of **3.3n**

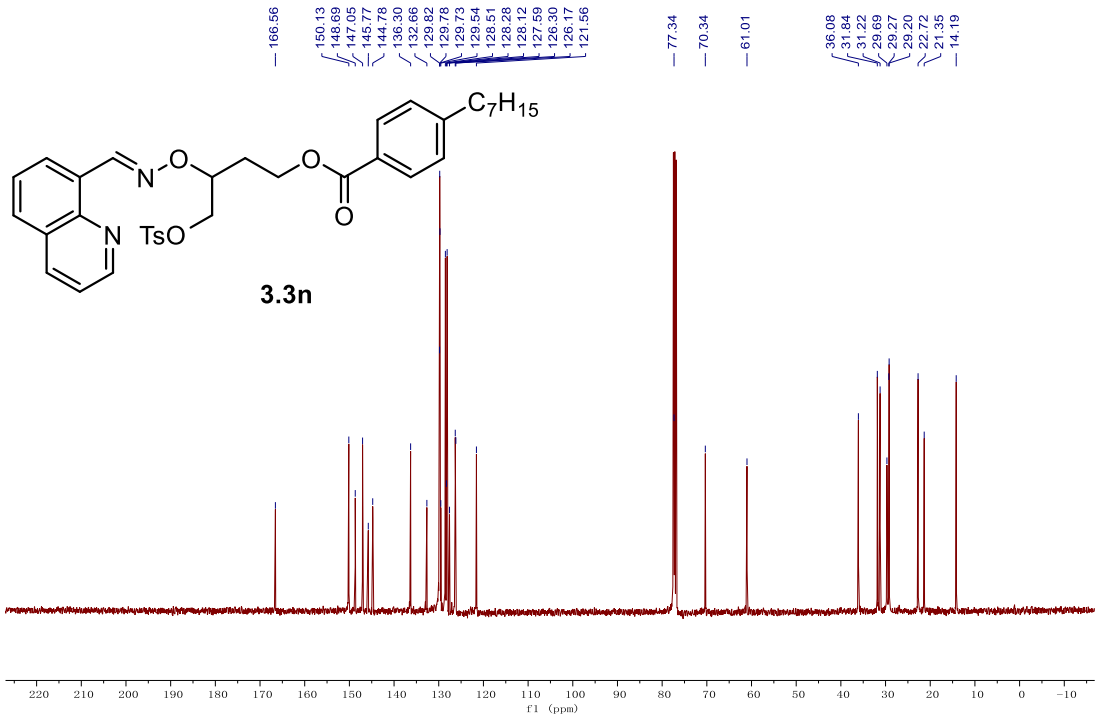


Figure 3.146 ^{1}H-NMR Spectrum of **3.3o**

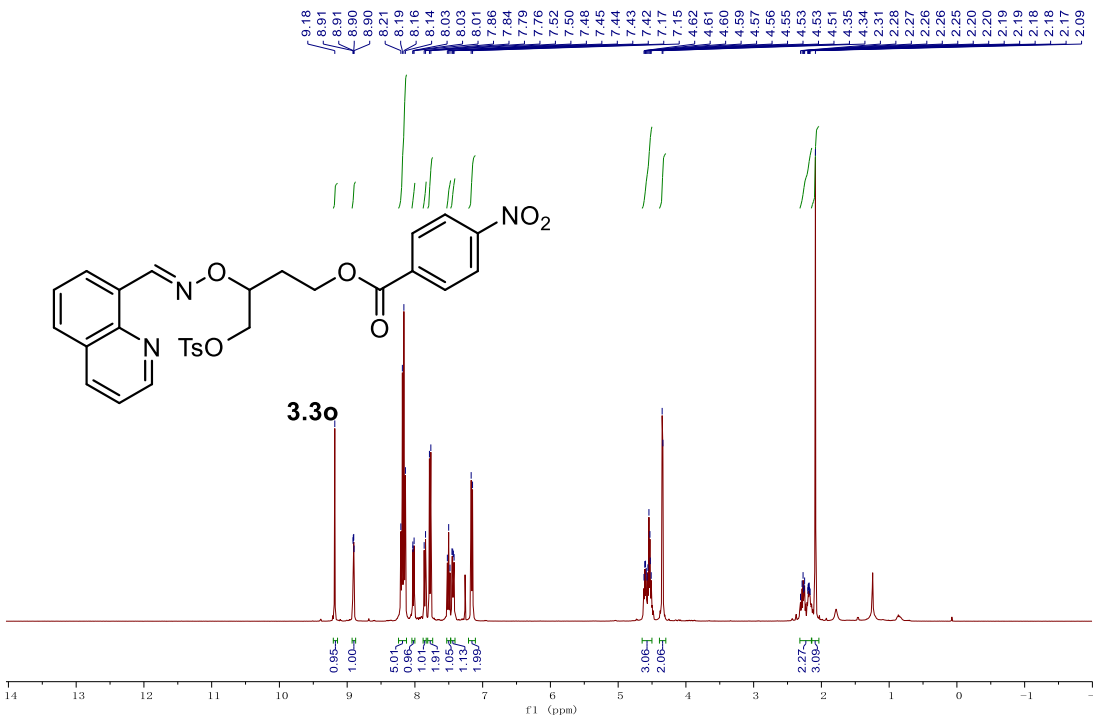


Figure 3.147 ^{13}C-NMR Spectrum of **3.3o**

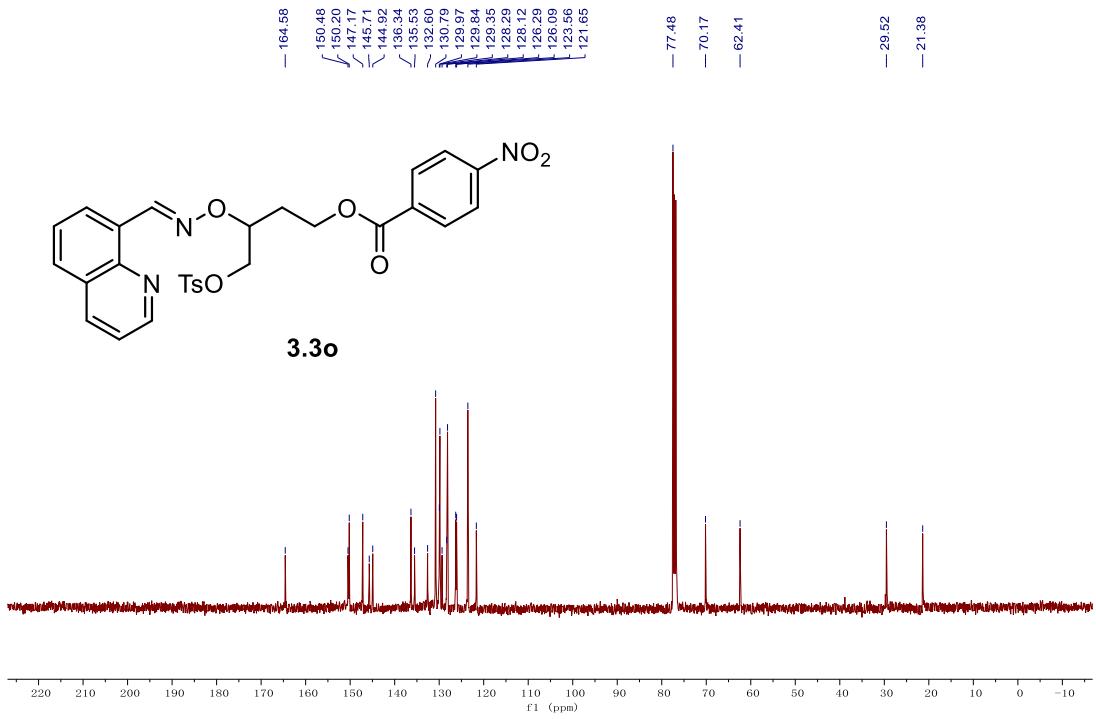


Figure 3.148 ^{1}H-NMR Spectrum of **3.3p**

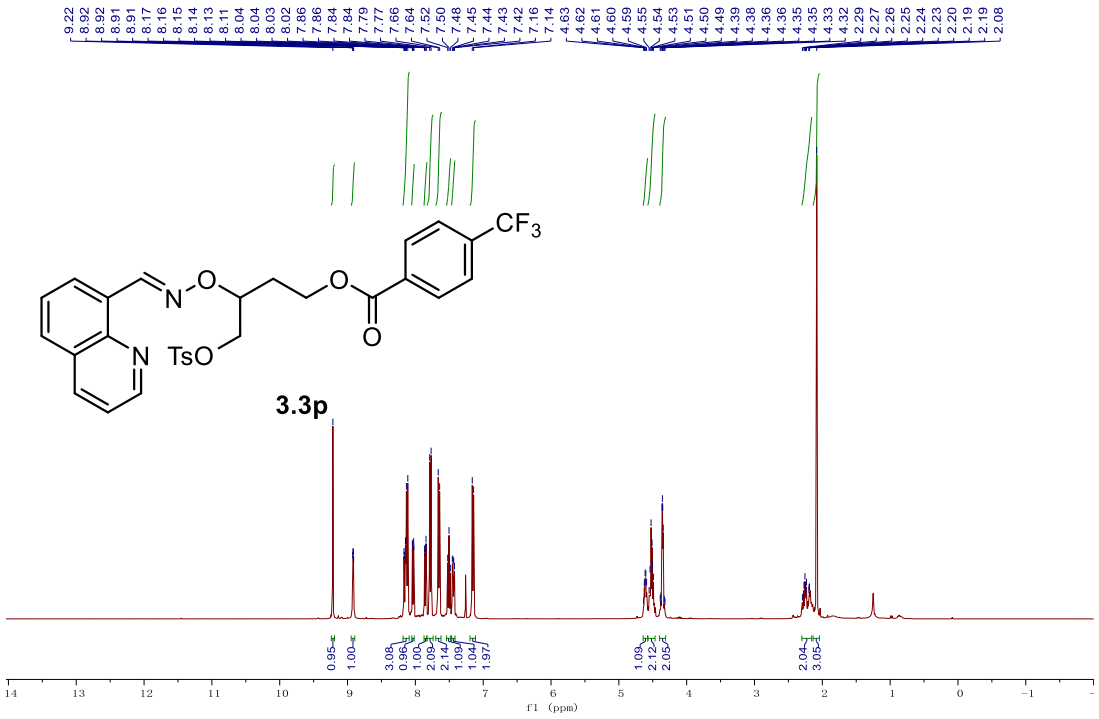


Figure 3.149 ^{13}C-NMR Spectrum of **3.3p**

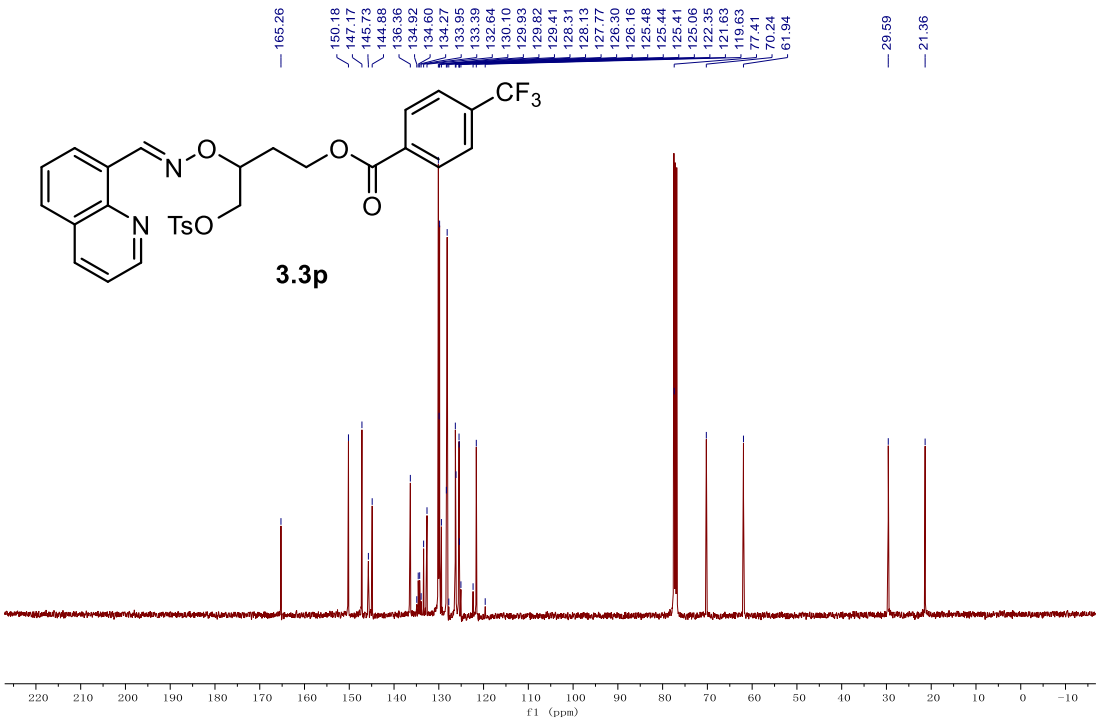


Figure 3.150 ^{19}F-NMR Spectrum of **3.3p**

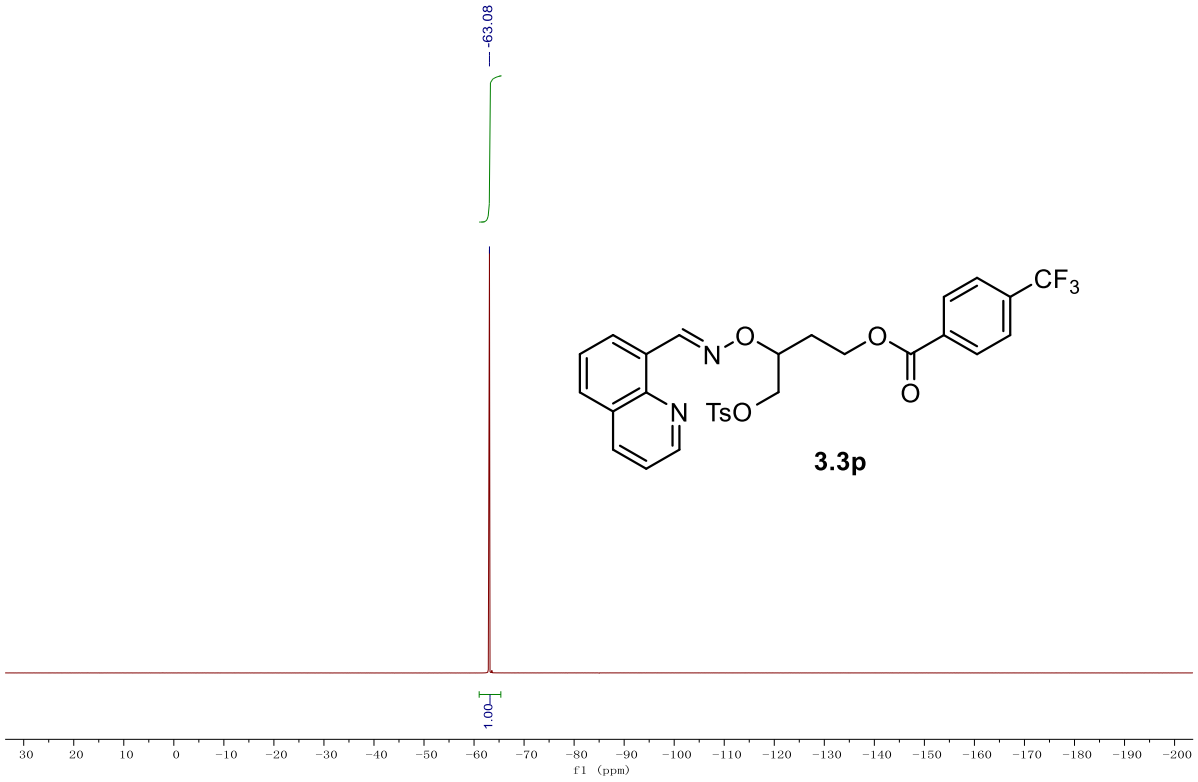


Figure 3.151 ^{1}H-NMR Spectrum of **3.3q**

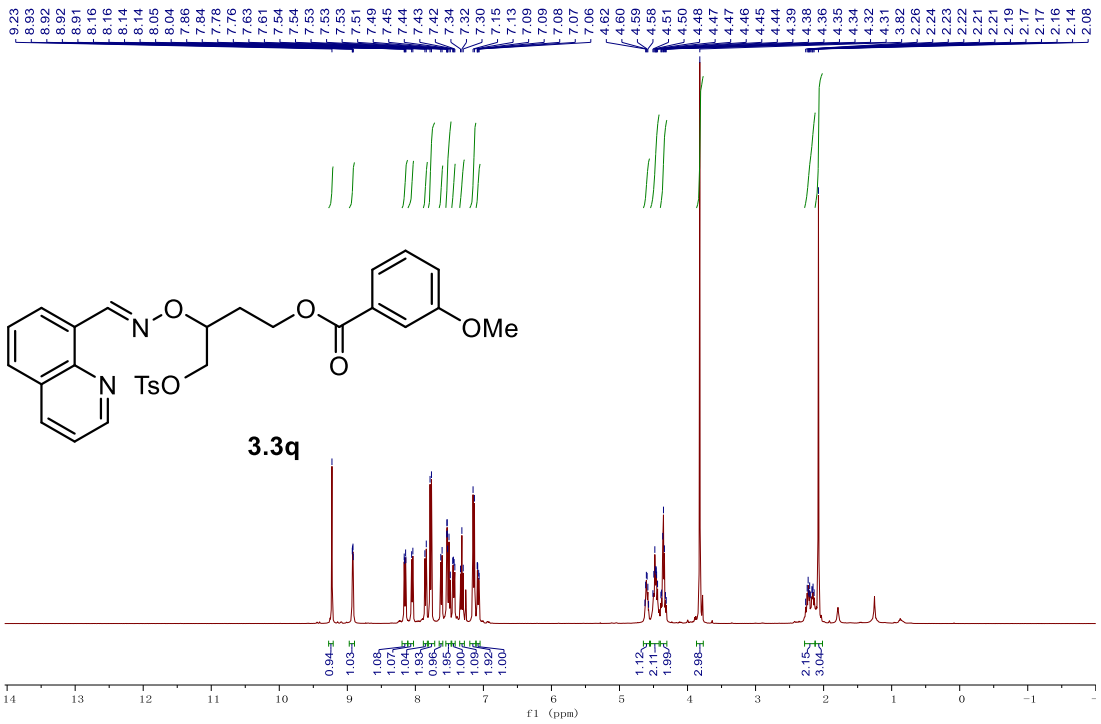


Figure 3.152 ^{13}C-NMR Spectrum of **3.3q**

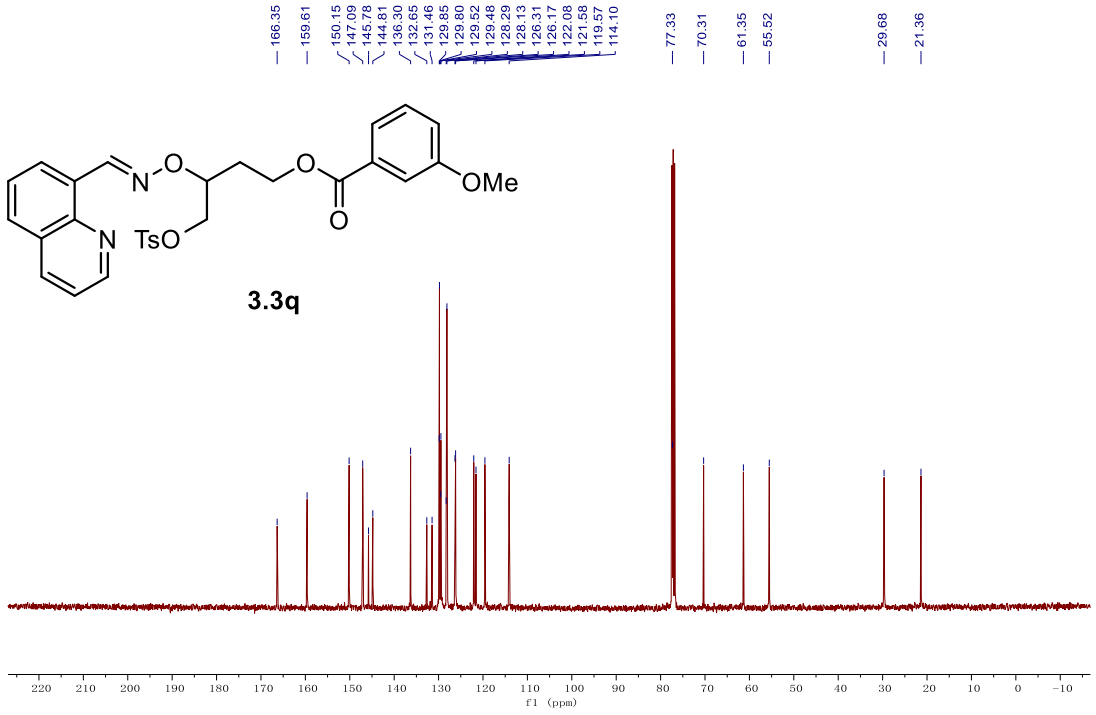


Figure 3.153 ^{1}H-NMR Spectrum of **3.3r**

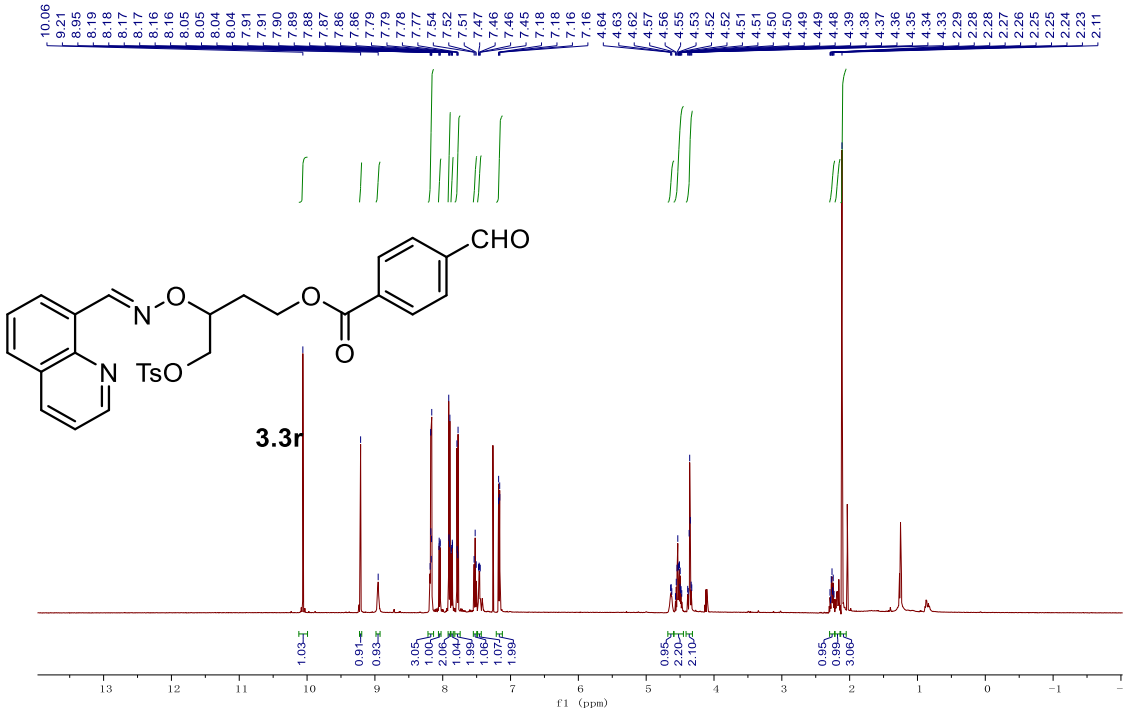


Figure 3.154 ^{13}C-NMR Spectrum of **3.3r**

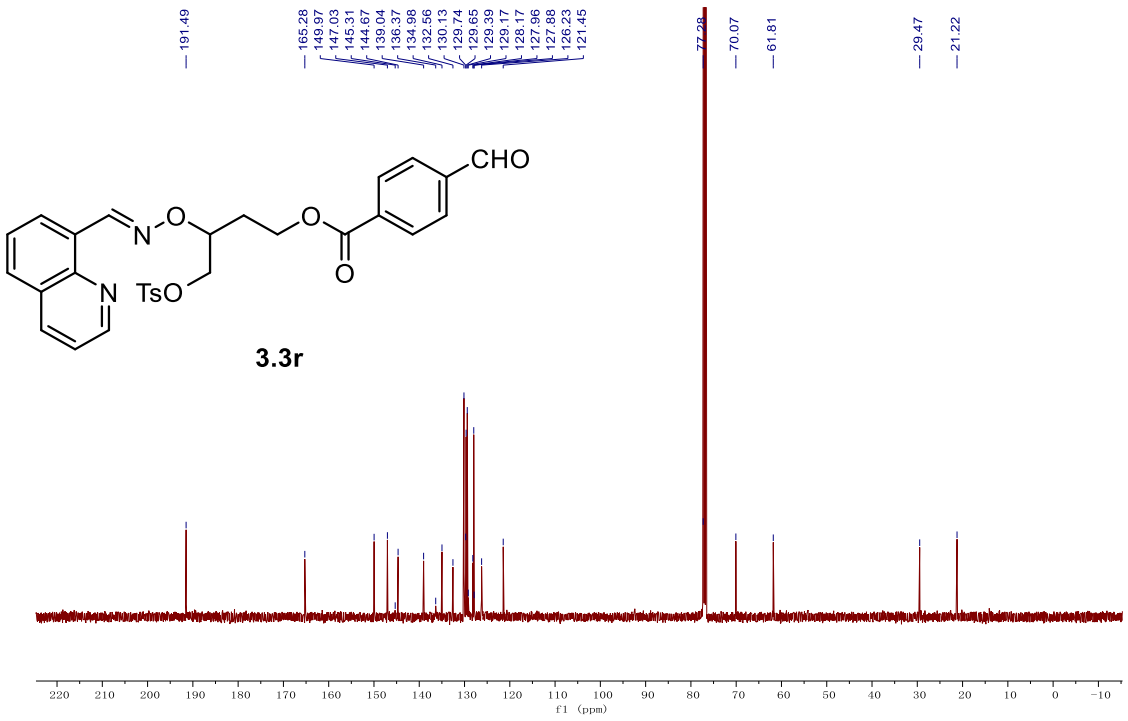


Figure 3.155 ^{1}H-NMR Spectrum of **3.3s**

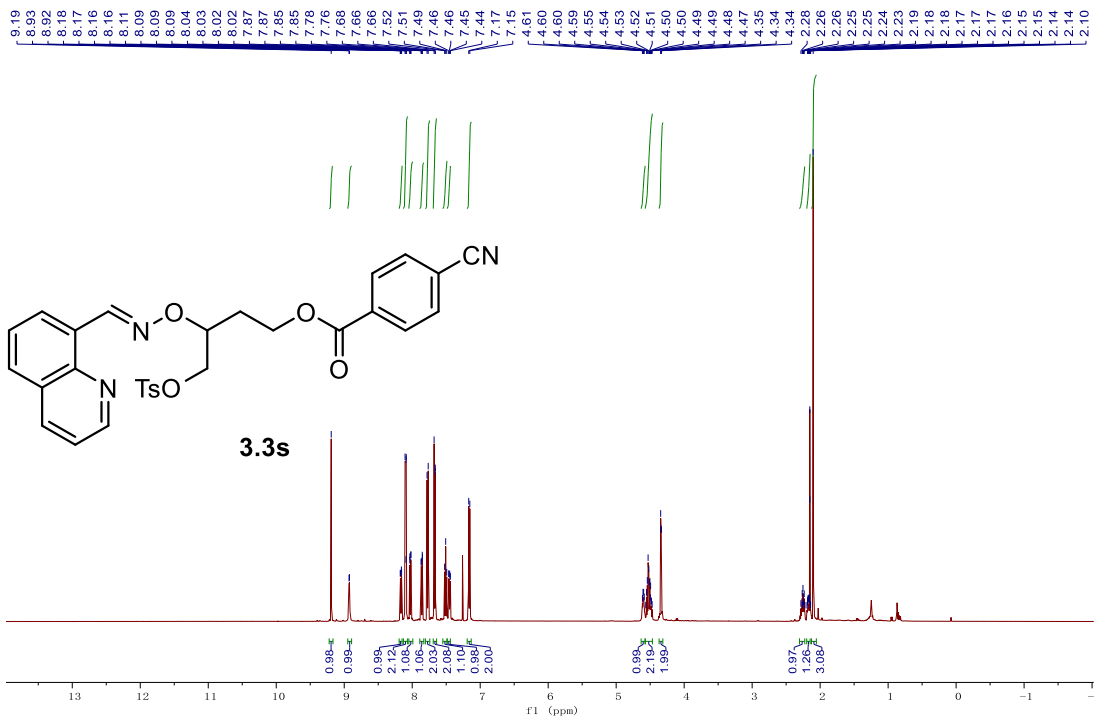


Figure 3.156 ^{13}C-NMR Spectrum of **3.3s**

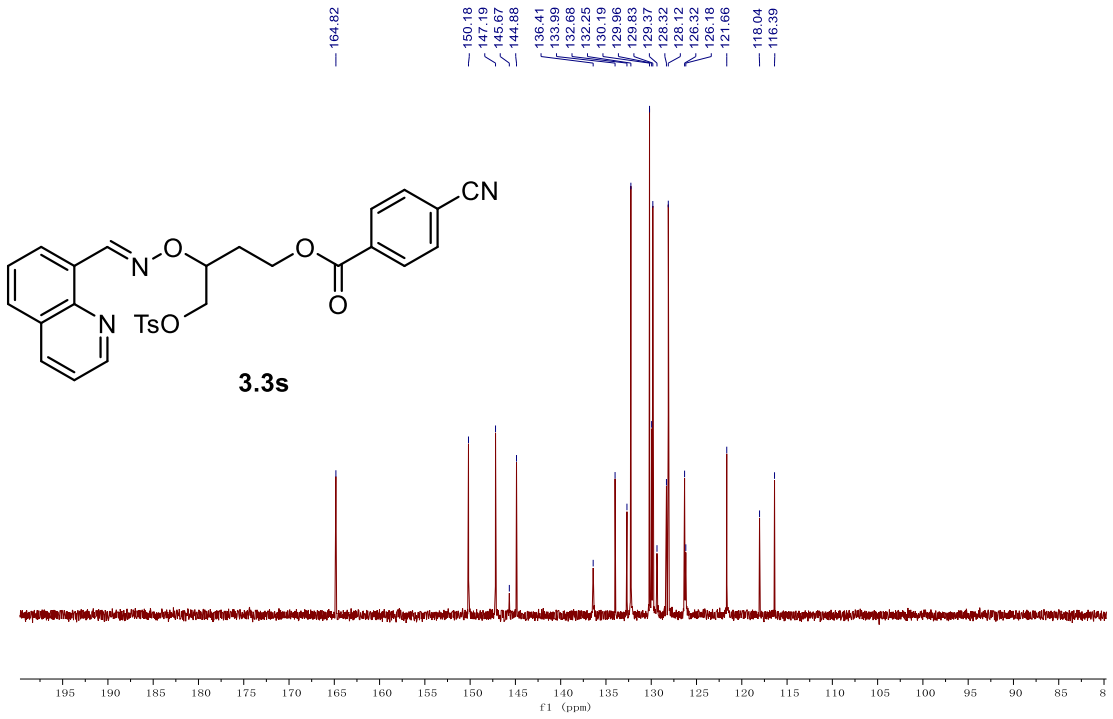


Figure 3.157 ^{1}H-NMR Spectrum of **3.3t**

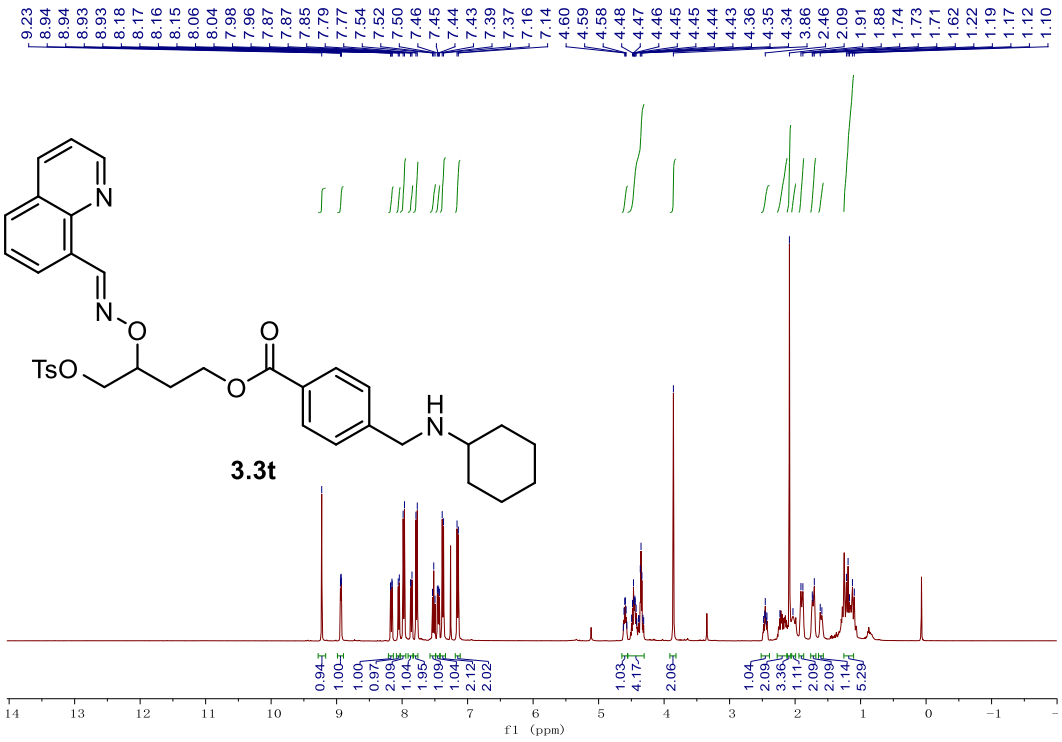


Figure 3.158 ^{13}C-NMR Spectrum of **3.3t**

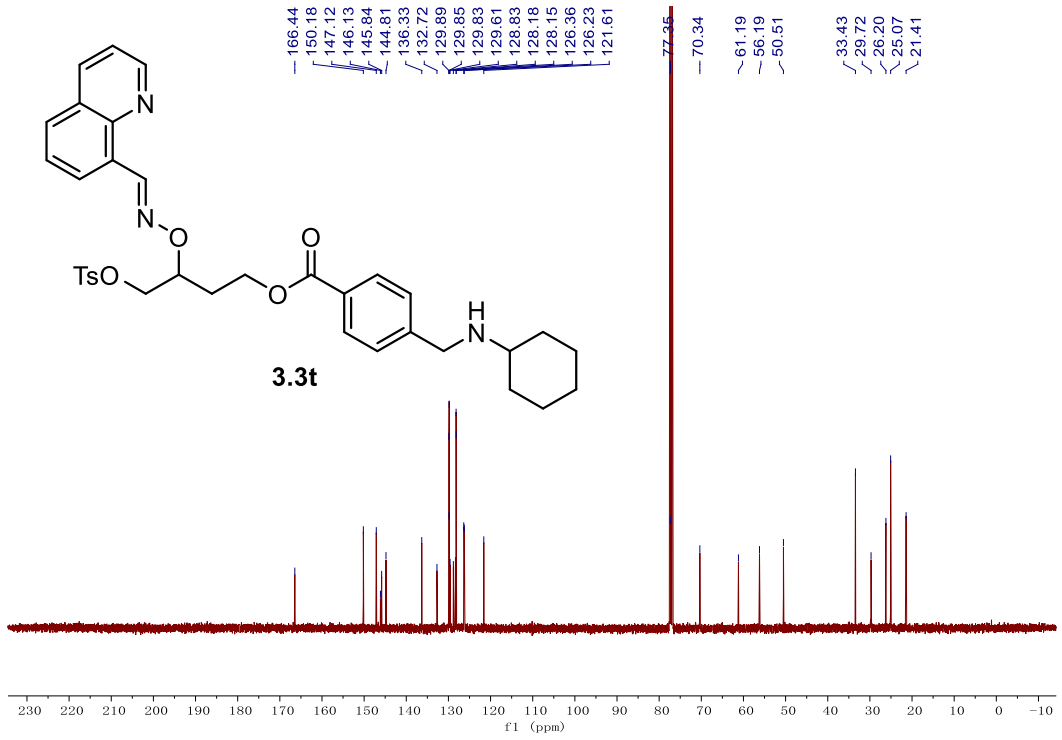


Figure 3.159 ^{1}H-NMR Spectrum of **3.3v**

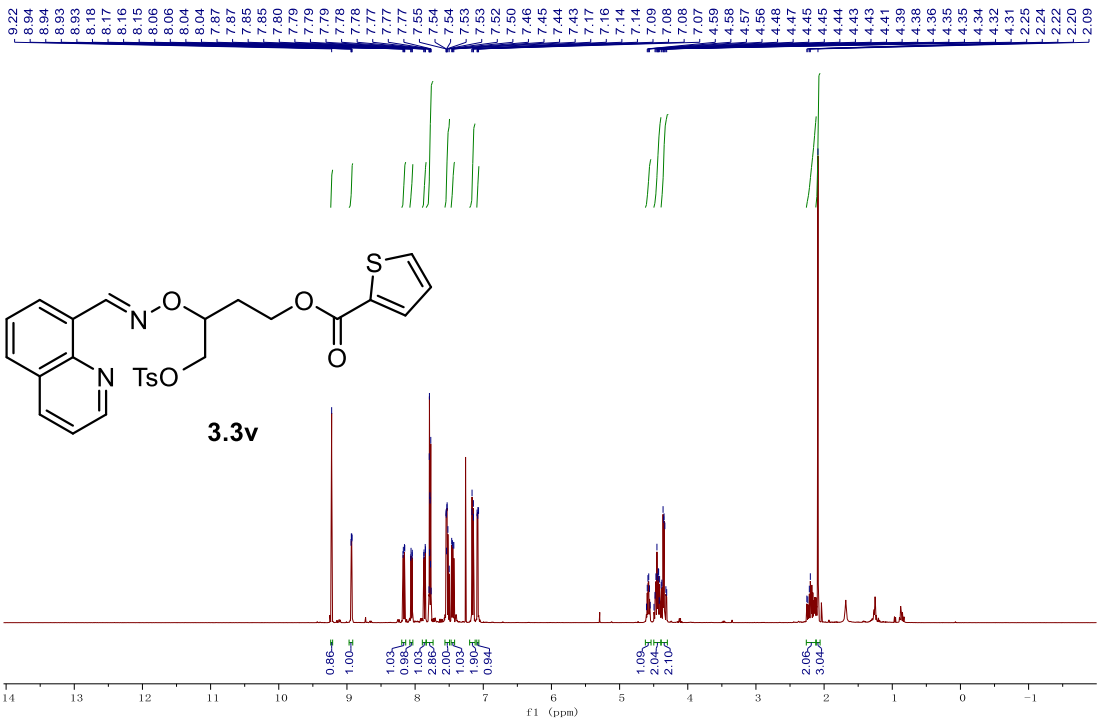


Figure 3.160 ^{13}C-NMR Spectrum of **3.3v**

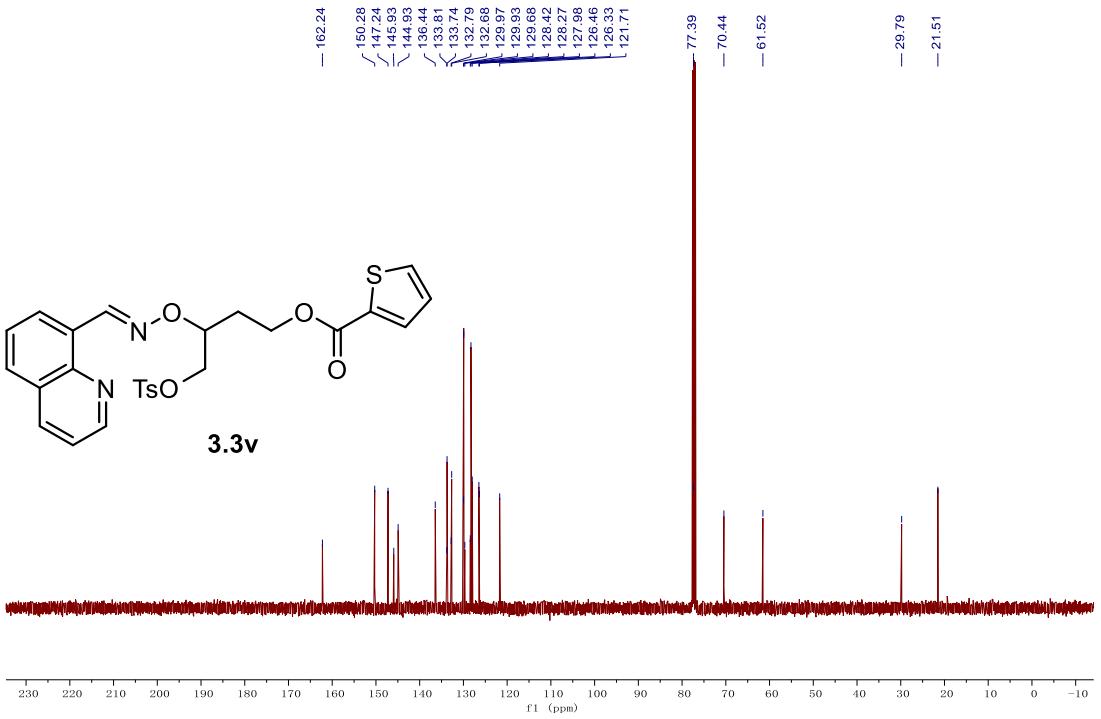


Figure 3.161 ^{1}H-NMR Spectrum of **3.3w**

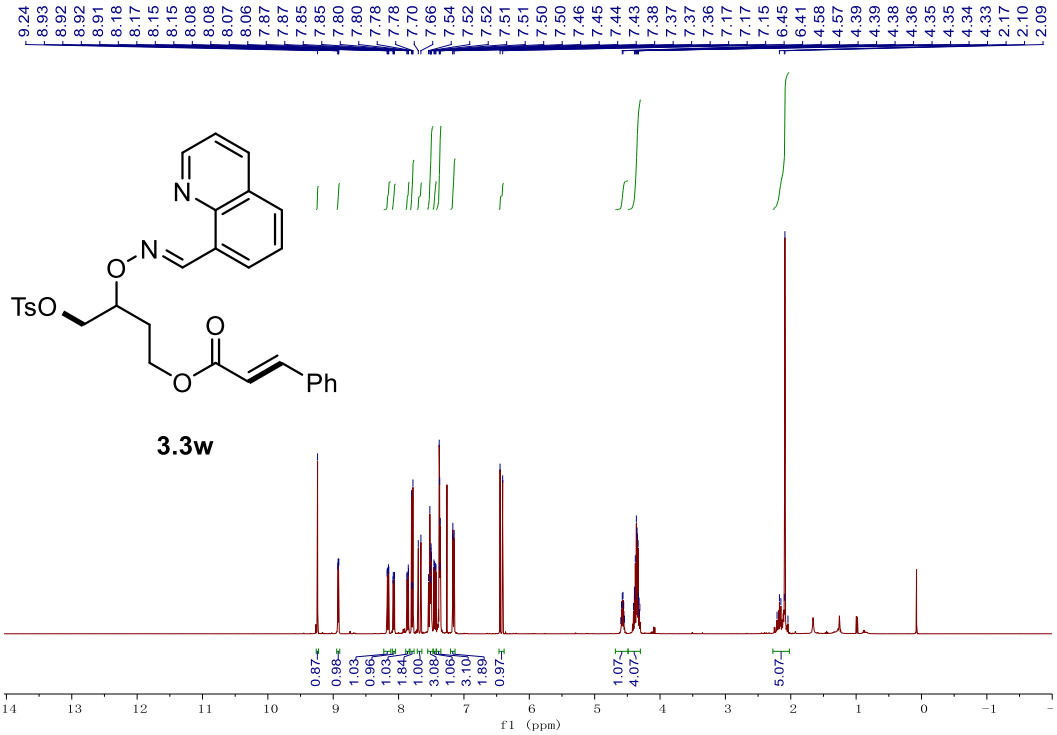


Figure 3.162 ^{13}C-NMR Spectrum of **3.3w**

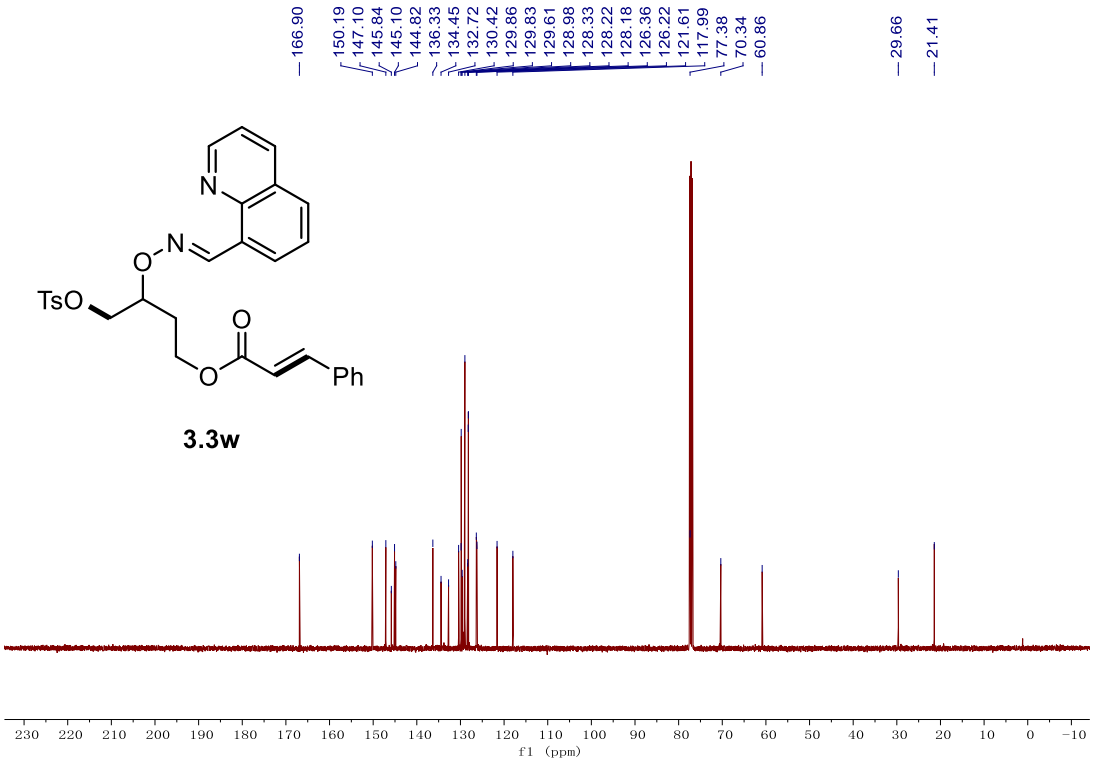


Figure 3.163 ^{1}H-NMR Spectrum of **3.3u**

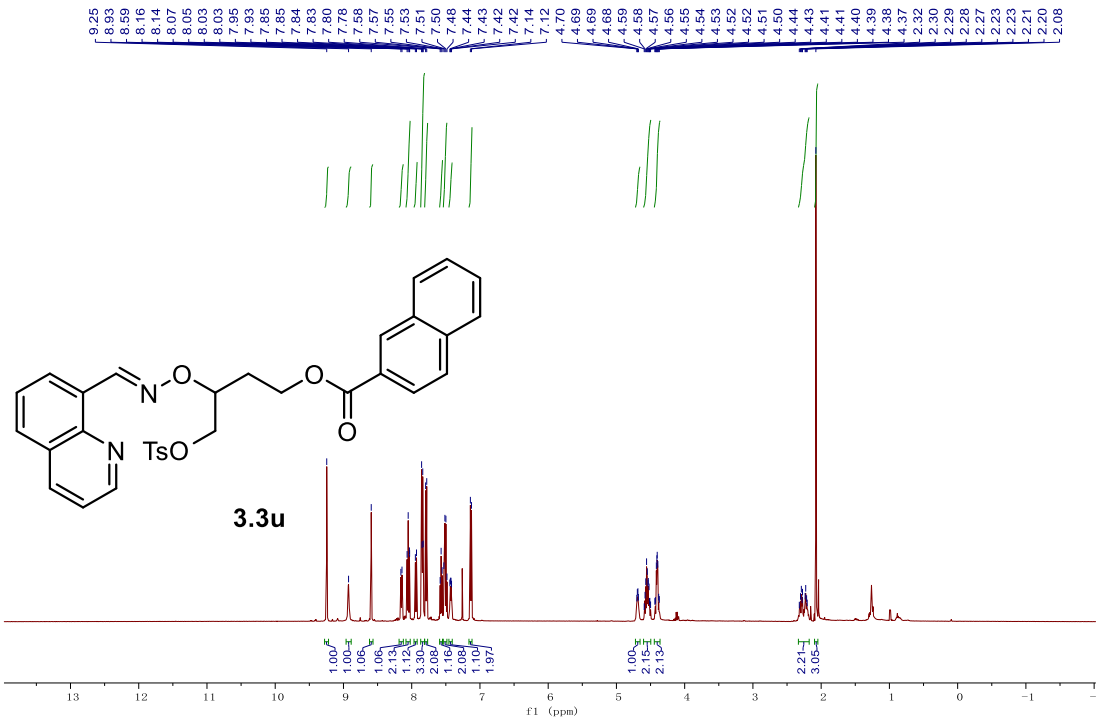


Figure 3.164 ^{13}C-NMR Spectrum of **3.3u**

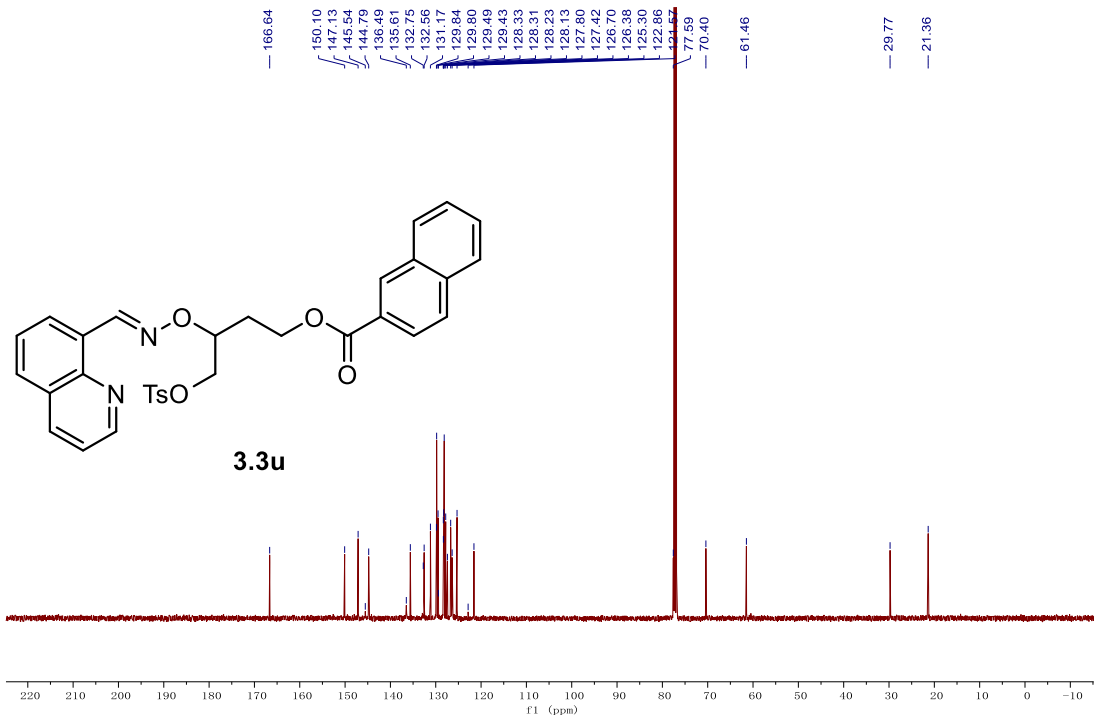


Figure 3.165 ^{1}H-NMR Spectrum of **3.3x**

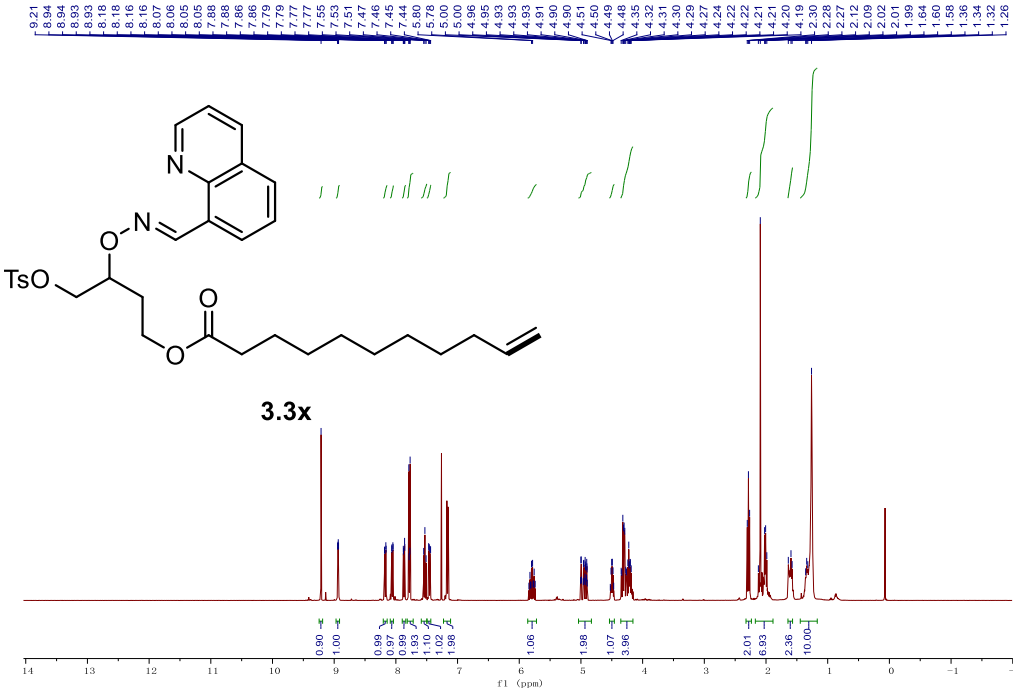


Figure 3.166 ^{13}C-NMR Spectrum of **3.3x**

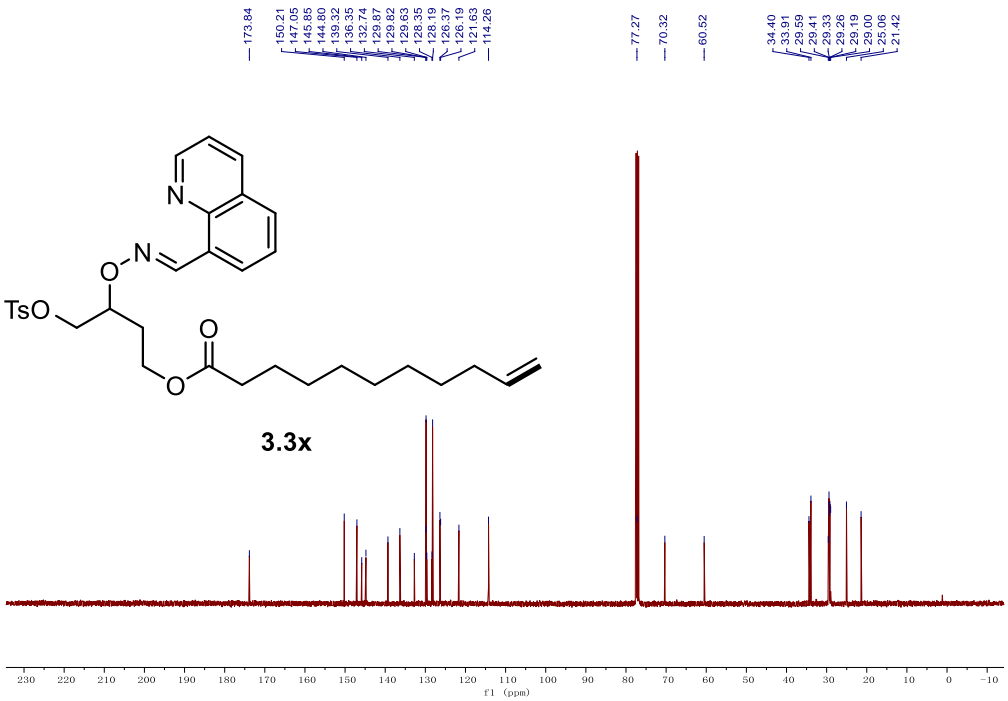


Figure 3.167 ^{1}H-NMR Spectrum of **3.3aa-F**

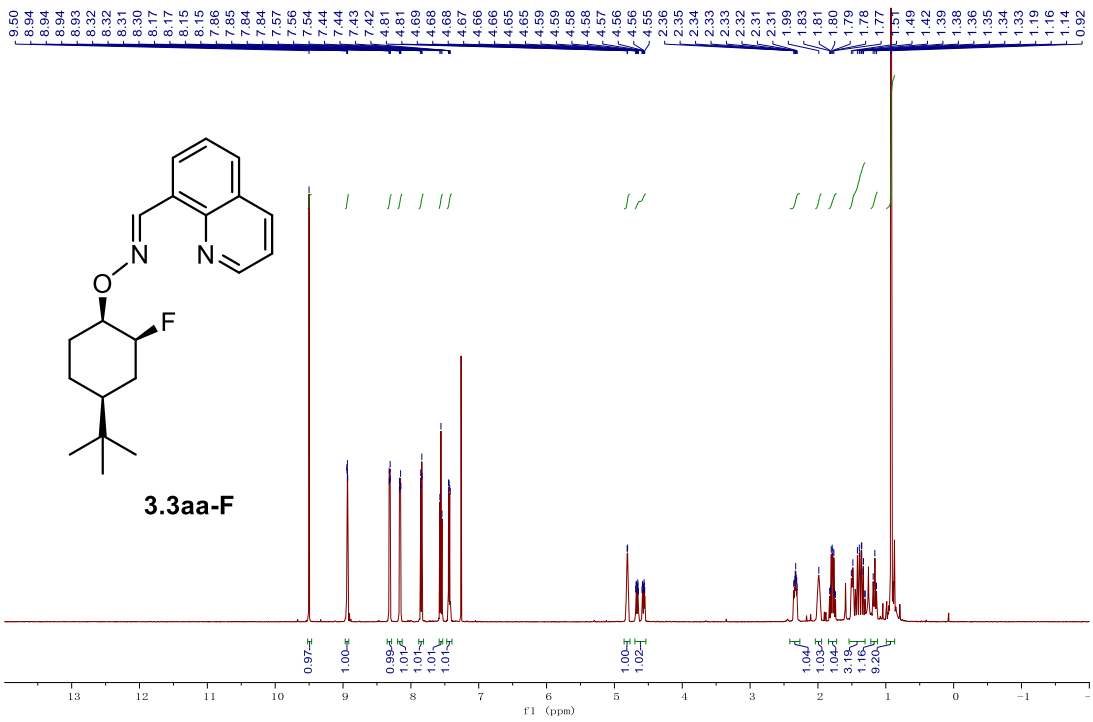


Figure 3.168 ^{13}C-NMR Spectrum of **3.3aa-F**

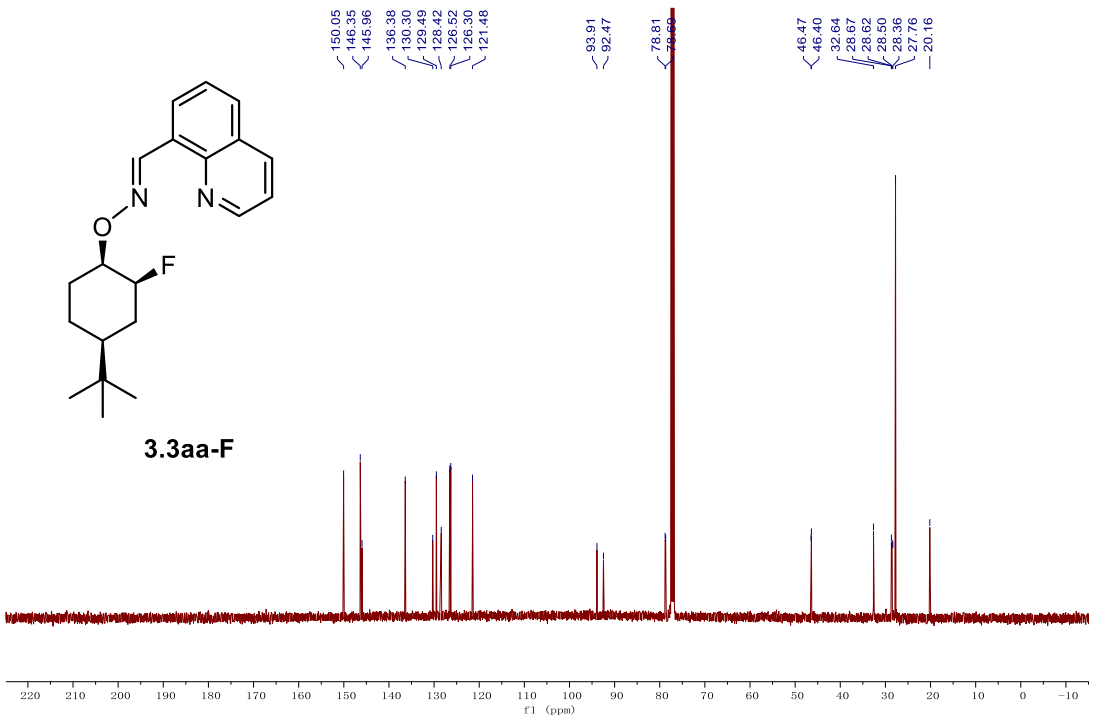


Figure 3.169 ^{19}F-NMR Spectrum of **3.3aa-F**

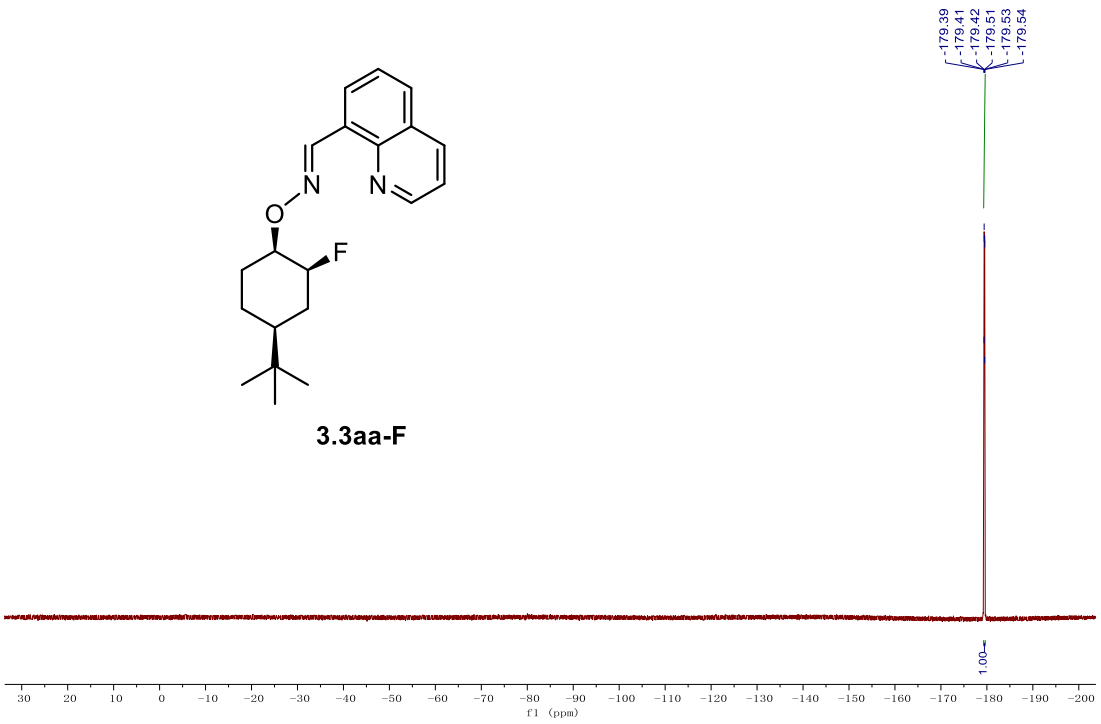


Figure 3.170 ^{1}H-NMR Spectrum of **3.3aa-OTs**

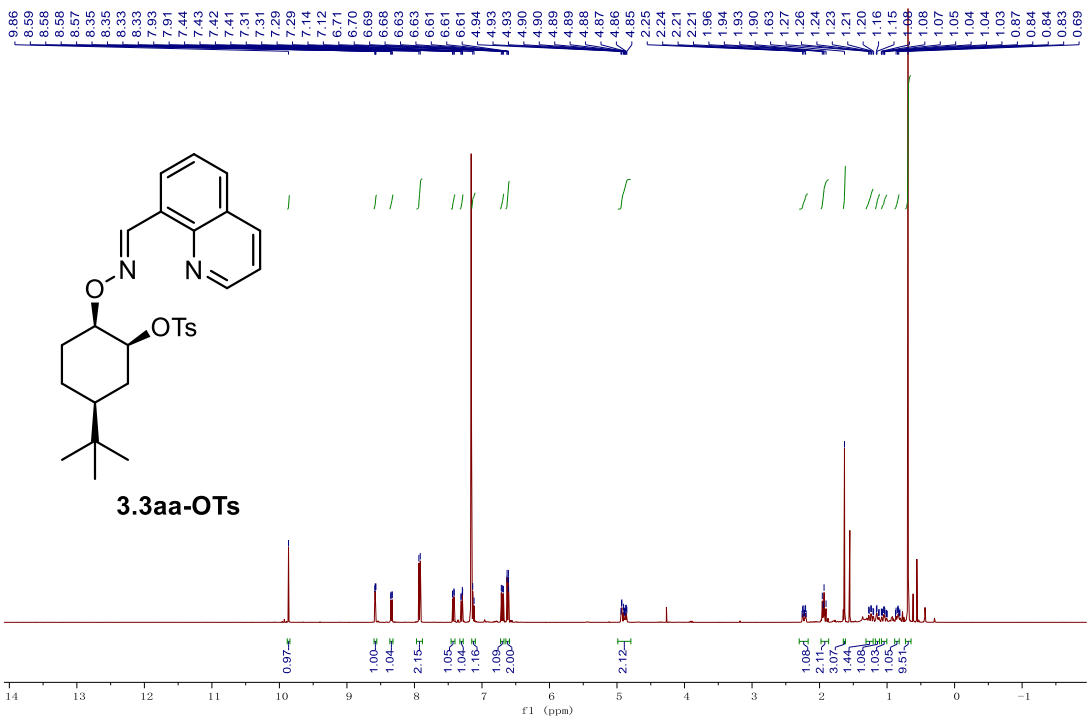


Figure 3.171 ^{13}C-NMR Spectrum of **3.3aa-OTs**

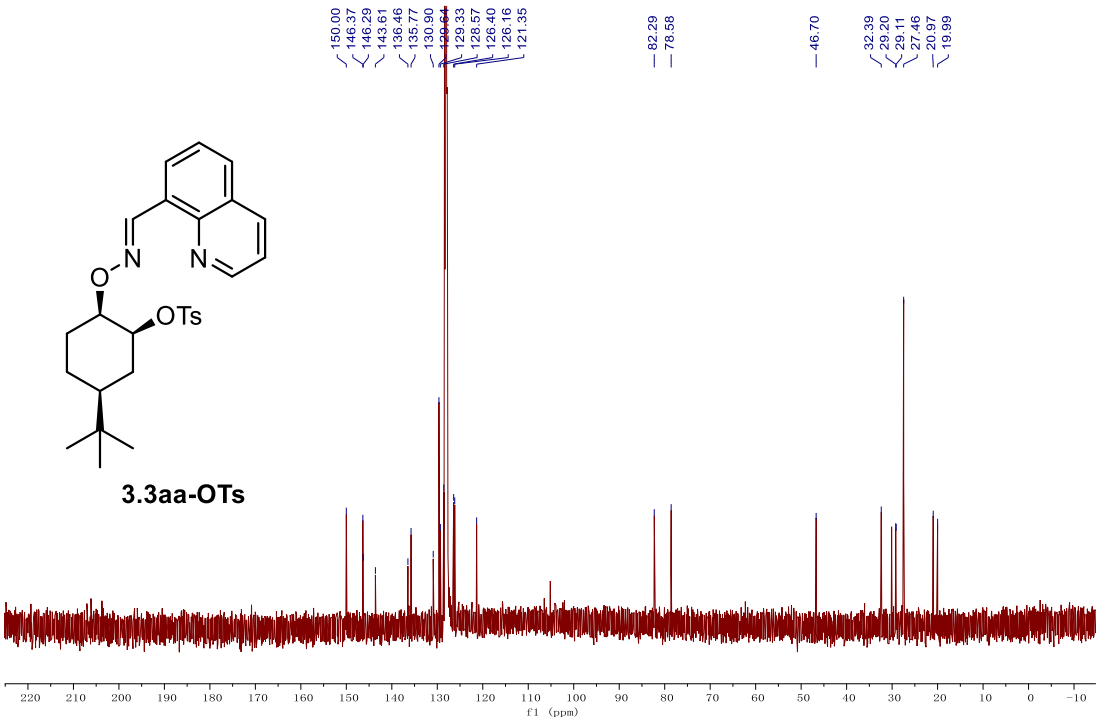


Figure 3.172 ^{1}H-NMR Spectrum of **3.3ab-F**

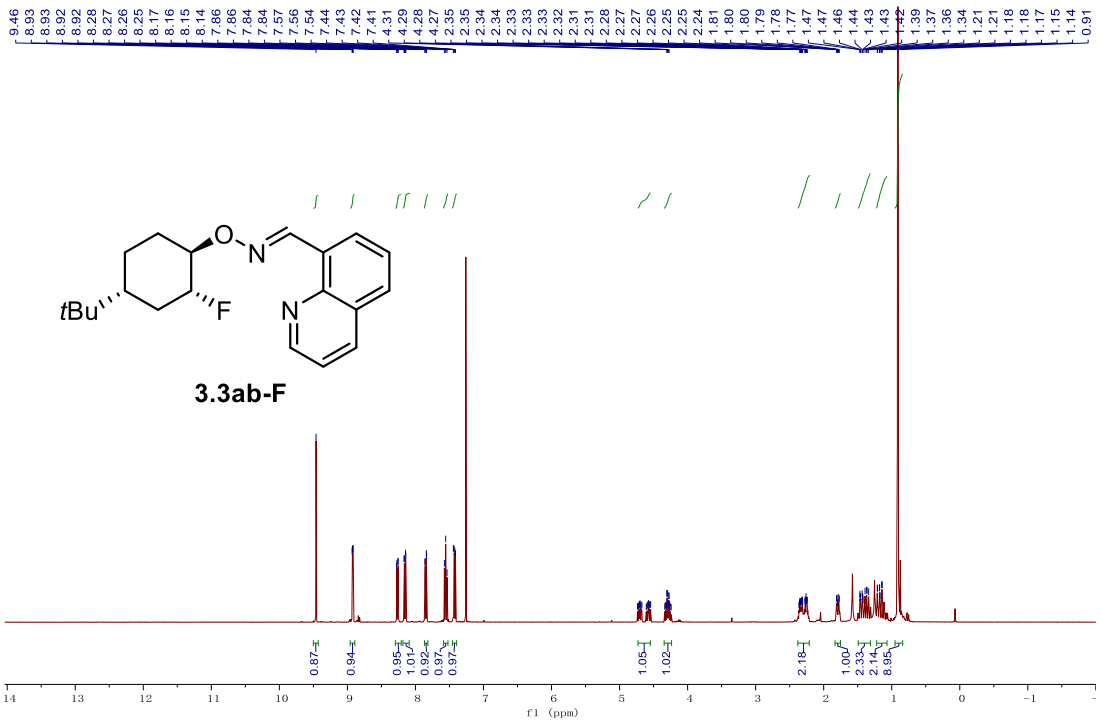


Figure 3.173 ^{13}C-NMR Spectrum of **3.3ab-F**

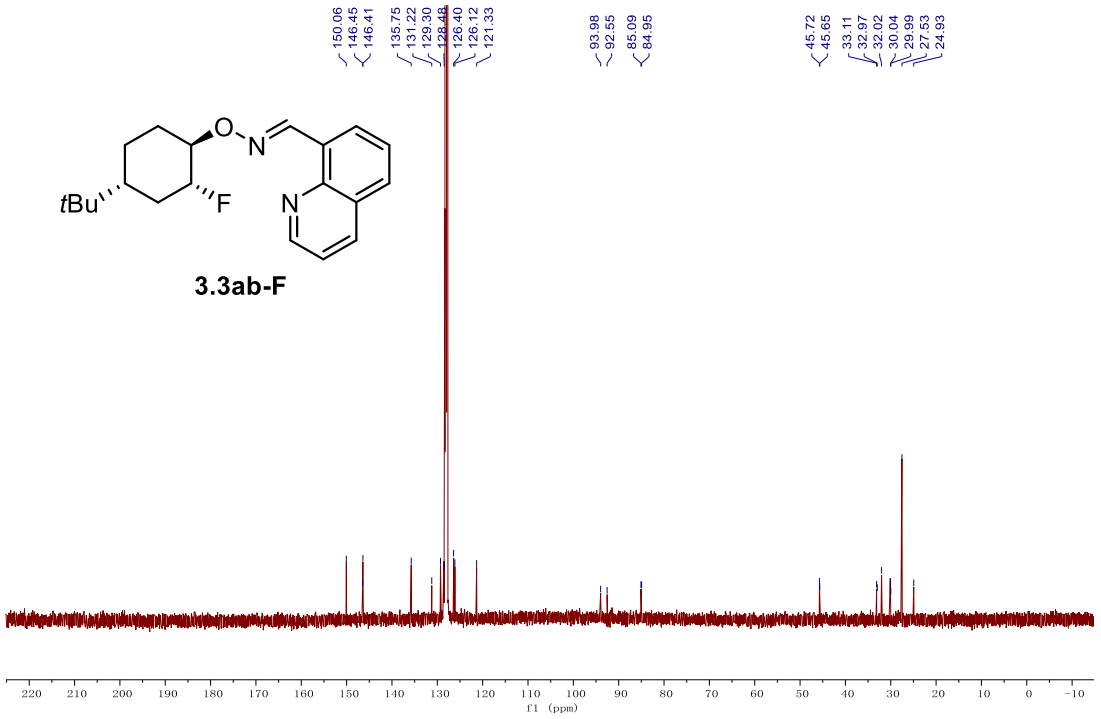


Figure 3.174 ^{19}F-NMR Spectrum of **3.3ab-F**

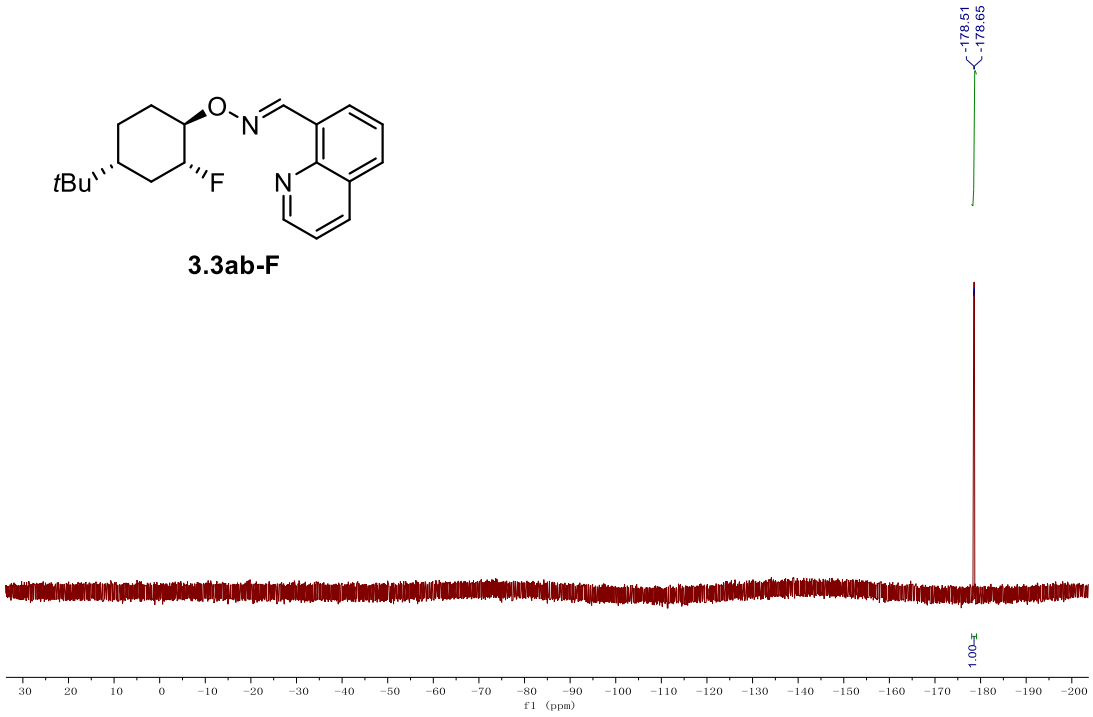


Figure 3.175 ^{1}H-NMR Spectrum of **3.3ab-OTs**

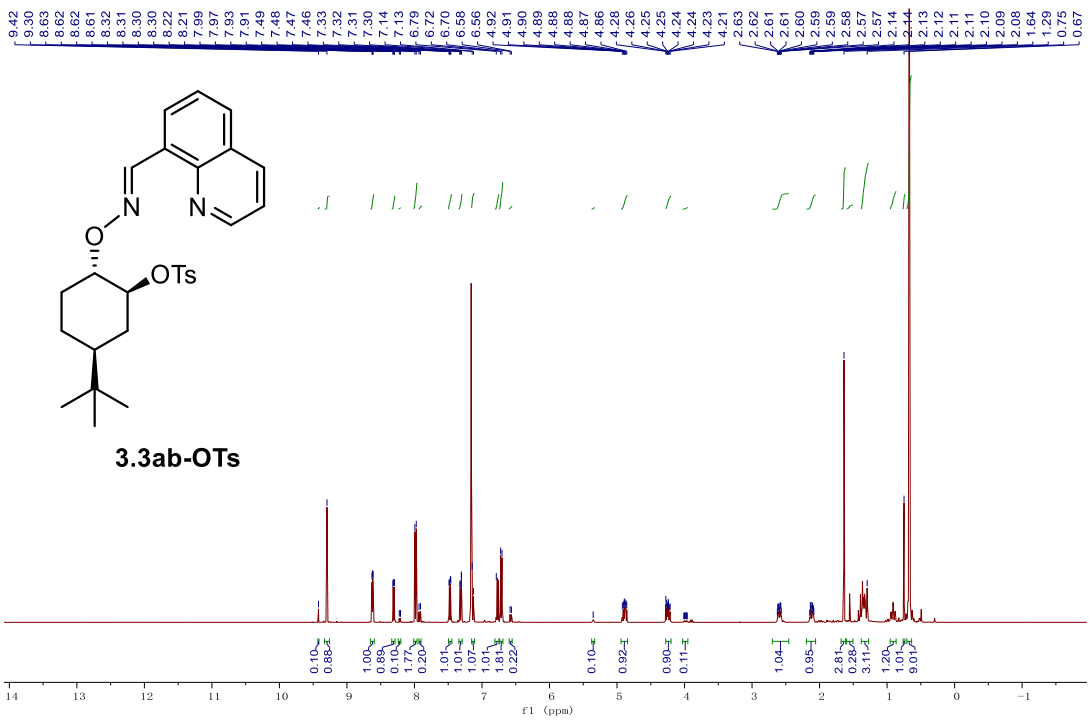


Figure 3.176 ^{13}C-NMR Spectrum of **3.3ab-OTs**

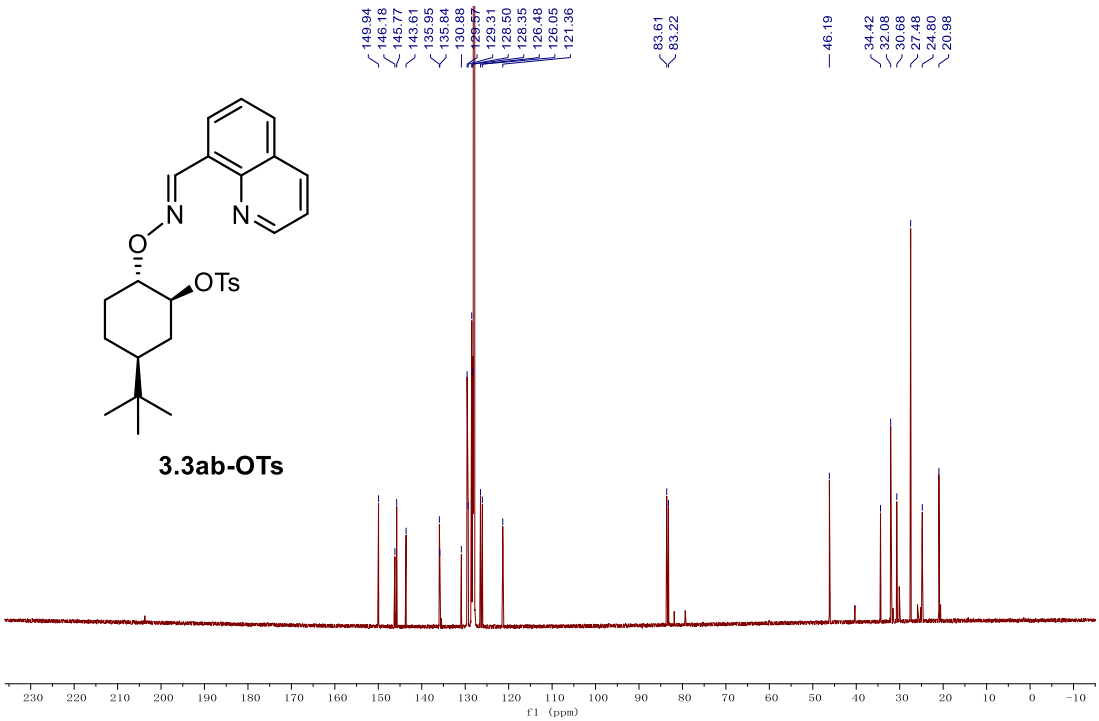


Figure 3.177 ^{1}H-NMR Spectrum of **3.3ac-F**

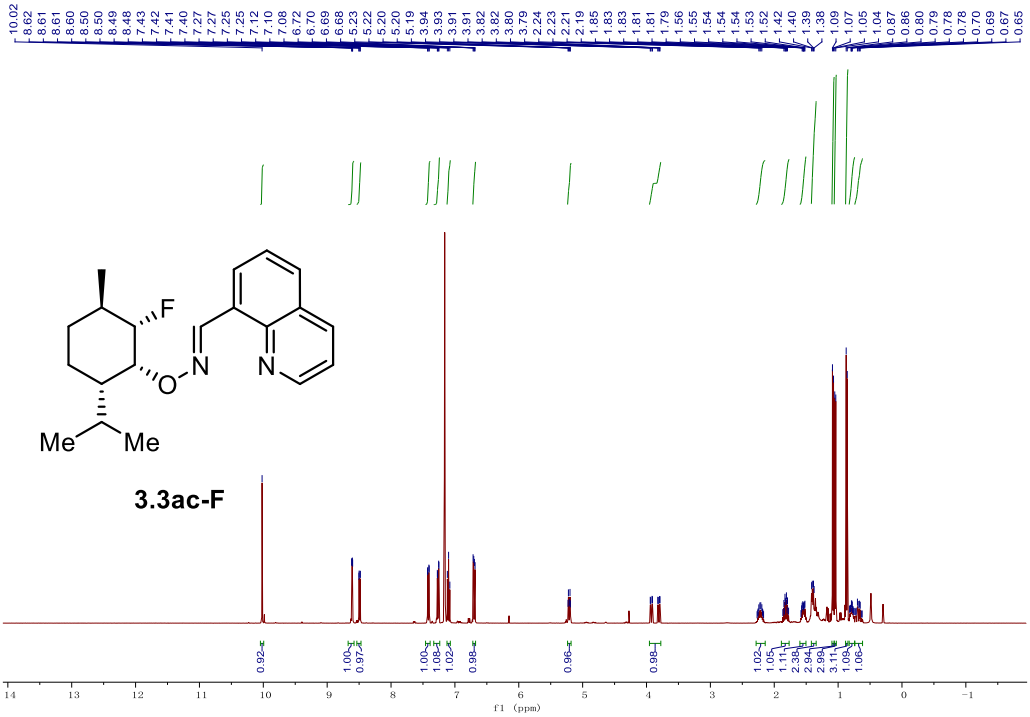


Figure 3.178 ^{13}C-NMR Spectrum of **3.3ac-F**

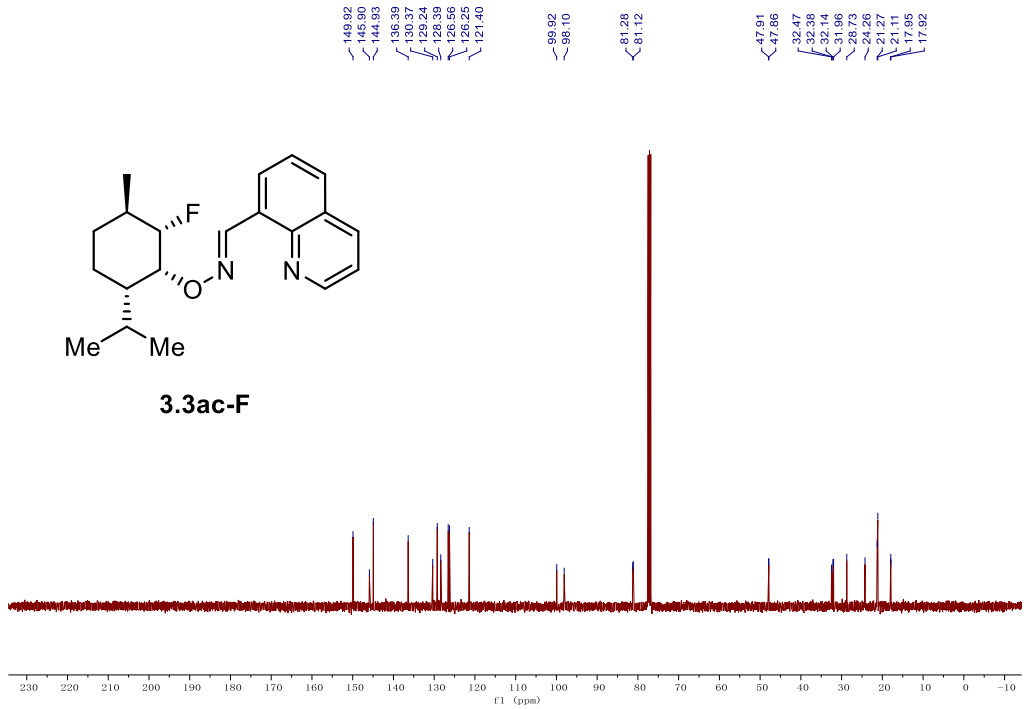


Figure 3.179 ^{19}F-NMR Spectrum of **3.3ac-F**

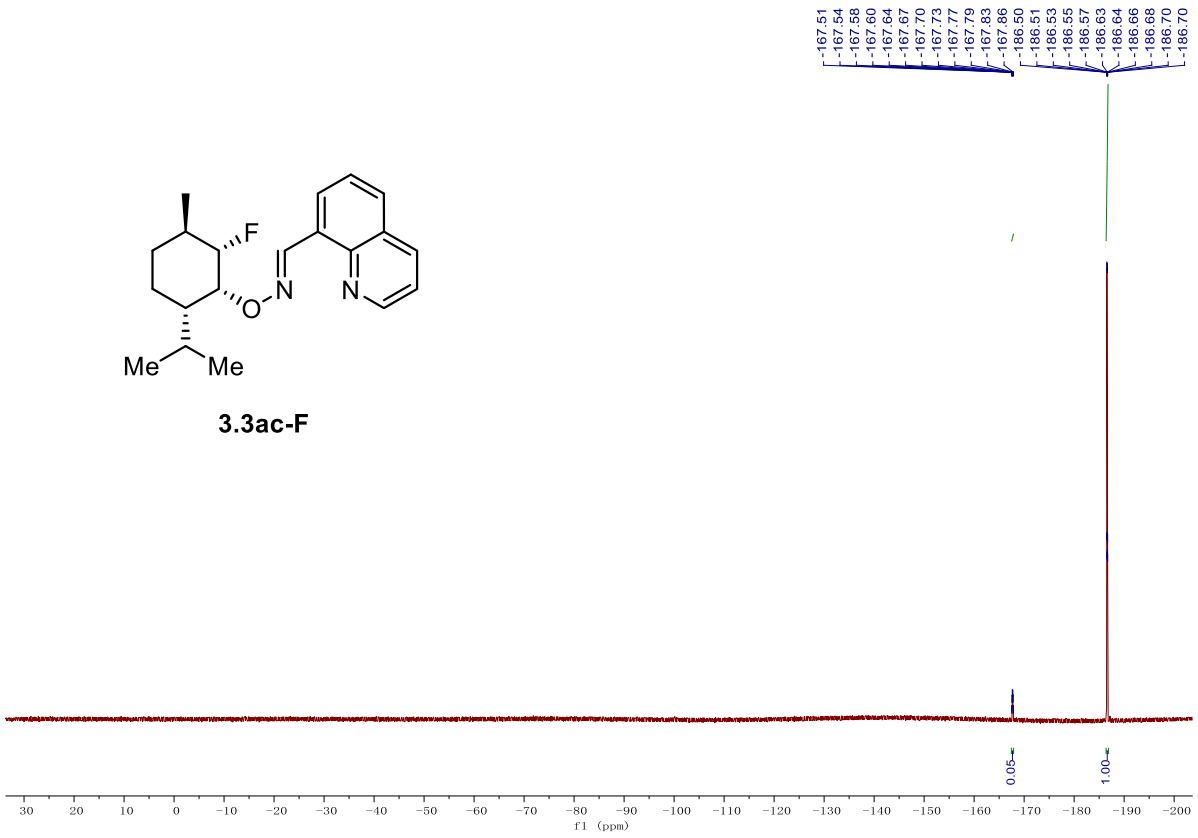


Figure 3.180 ^{1}H-NMR Spectrum of **3.3ac-OTs**

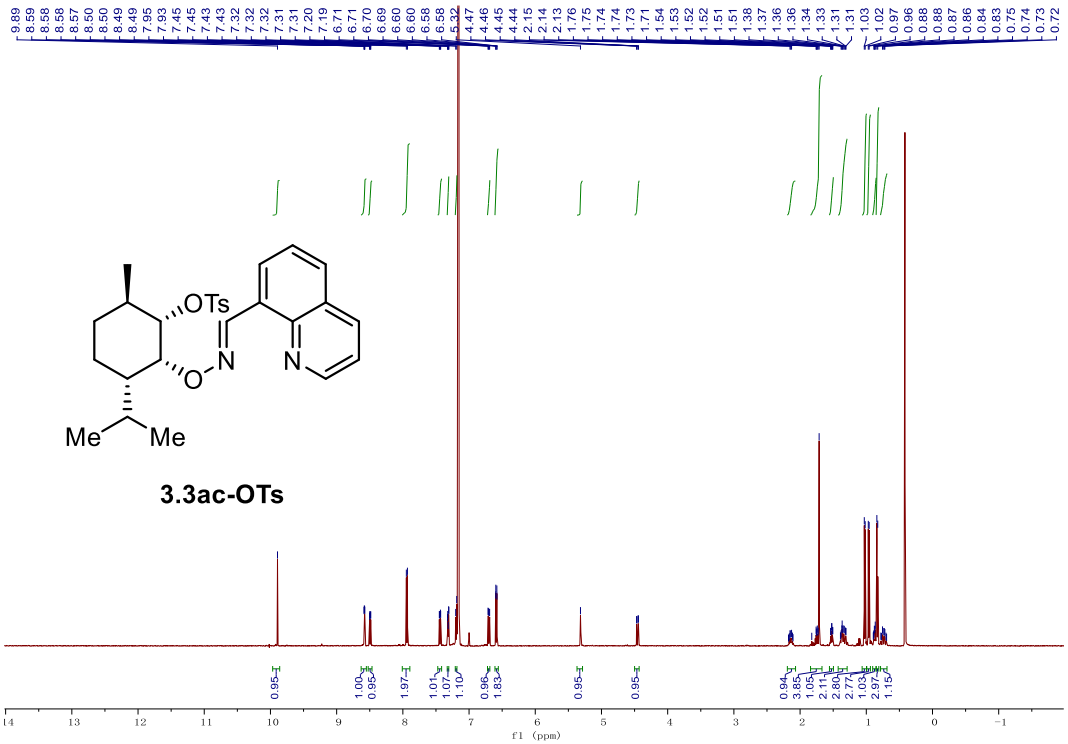


Figure 3.181 ^{13}C-NMR Spectrum of **3.3ac-OTs**

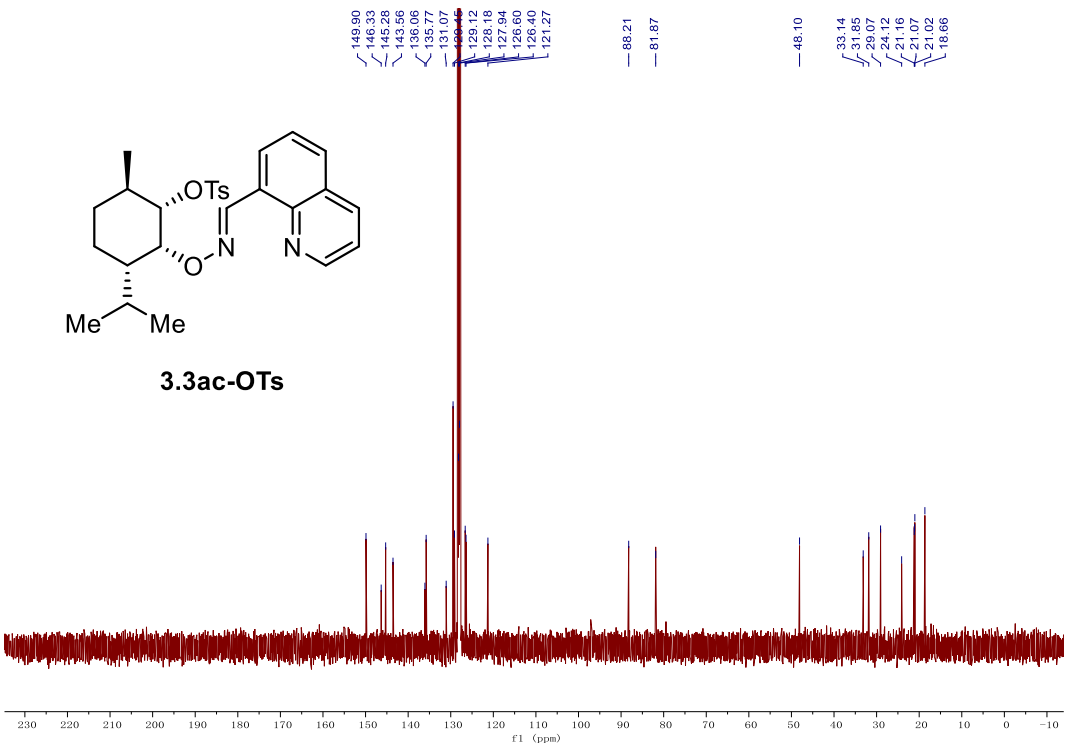


Figure 3.182 ^{1}H-NMR Spectrum of **2-F-3.3ad** and **4-F-3.3ad**

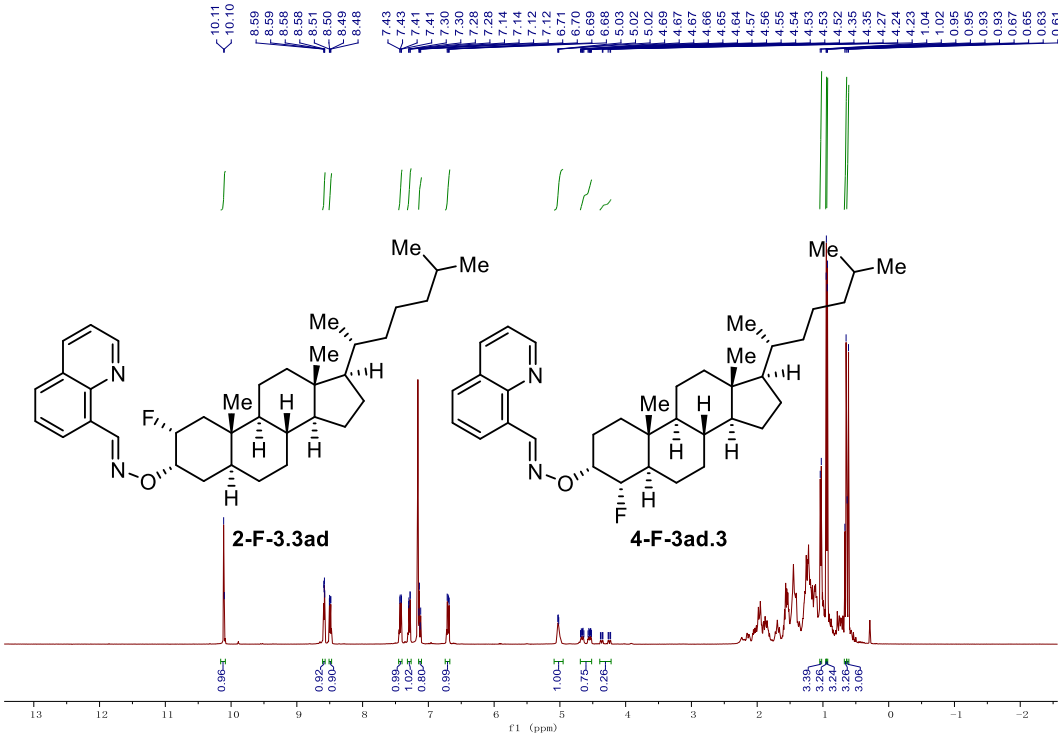


Figure 3.183 ^{13}C-NMR Spectrum of **2-F-3.3ad** and **4-F-3.3ad**

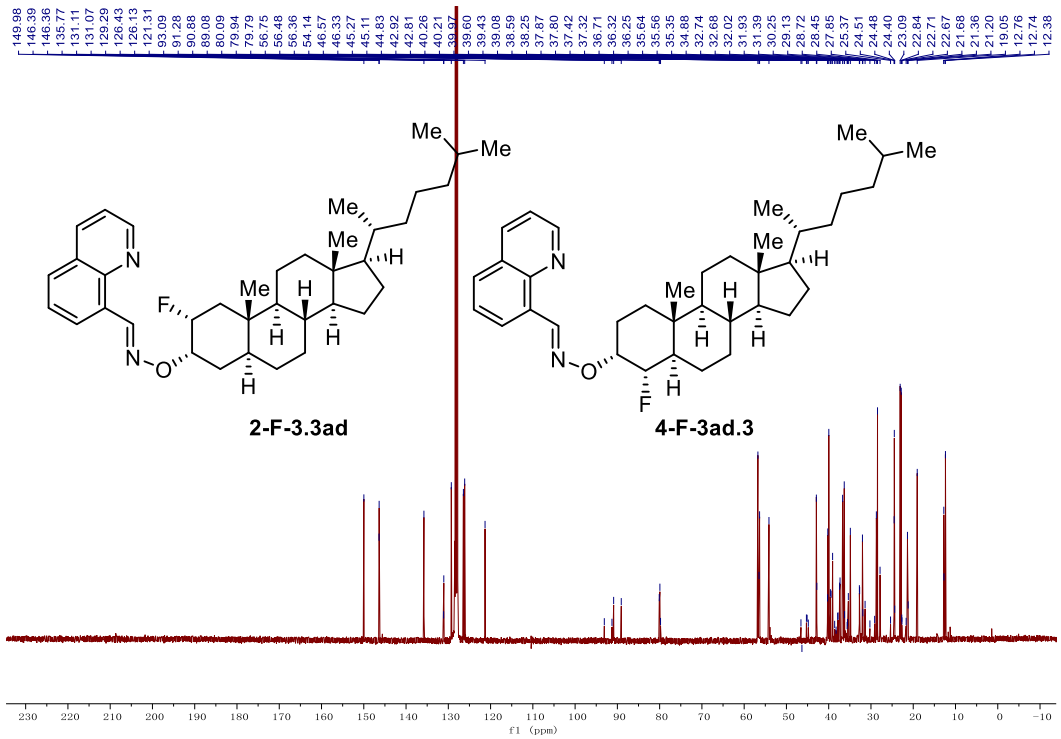


Figure 3.184 ^{19}F-NMR Spectrum of **2-F-3.3ad** and **4-F-3.3ad**

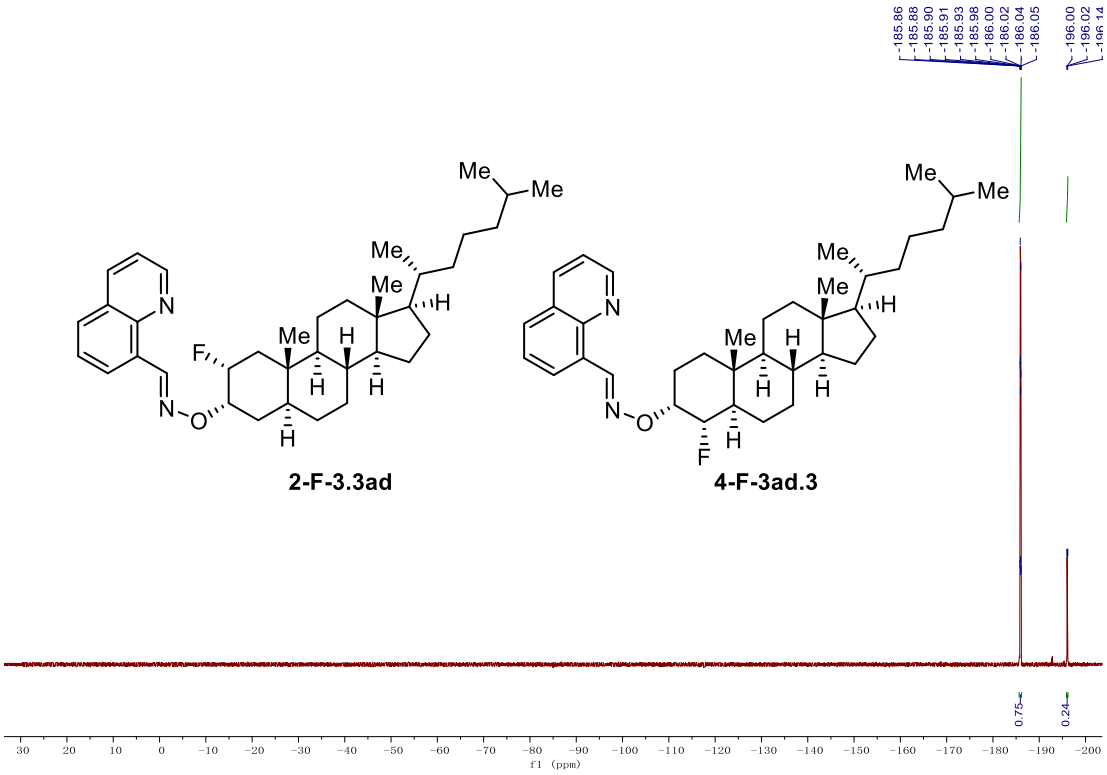


Figure 3.185 ^{1}H-NMR Spectrum of **2-OMs-3.3ad** and **4-OMs-3.3ad**

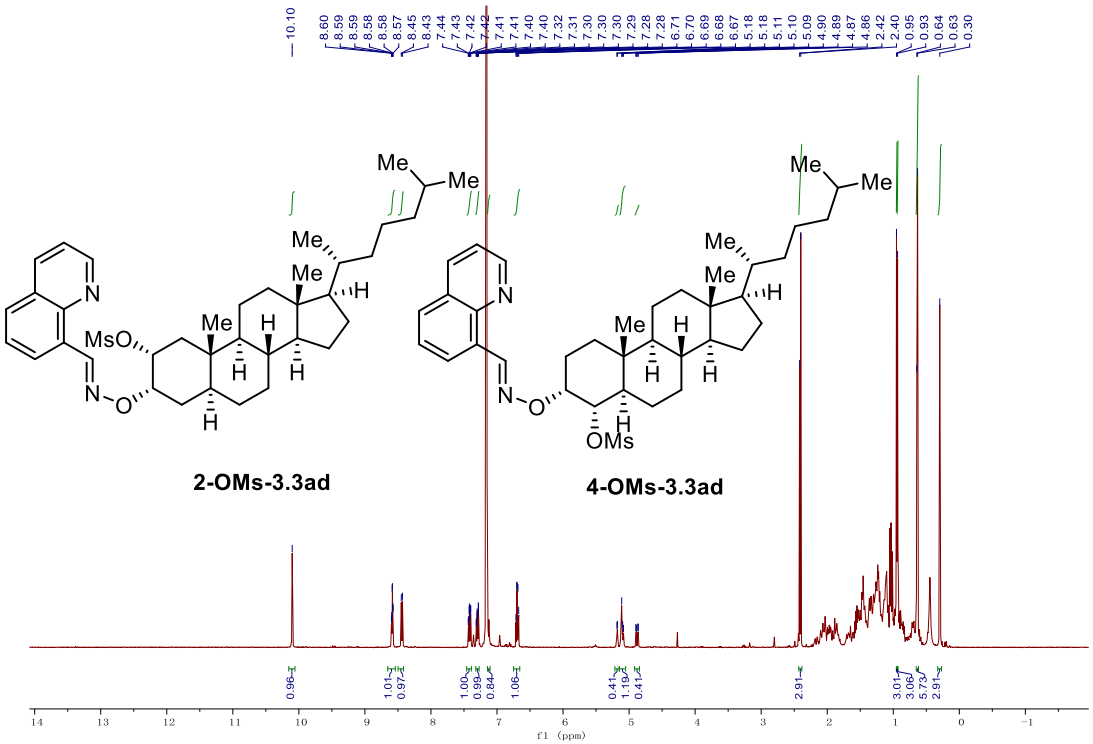


Figure 3.186 ^{13}C-NMR Spectrum of **2-OMs-3.3ad** and **4-OMs-3.3ad**

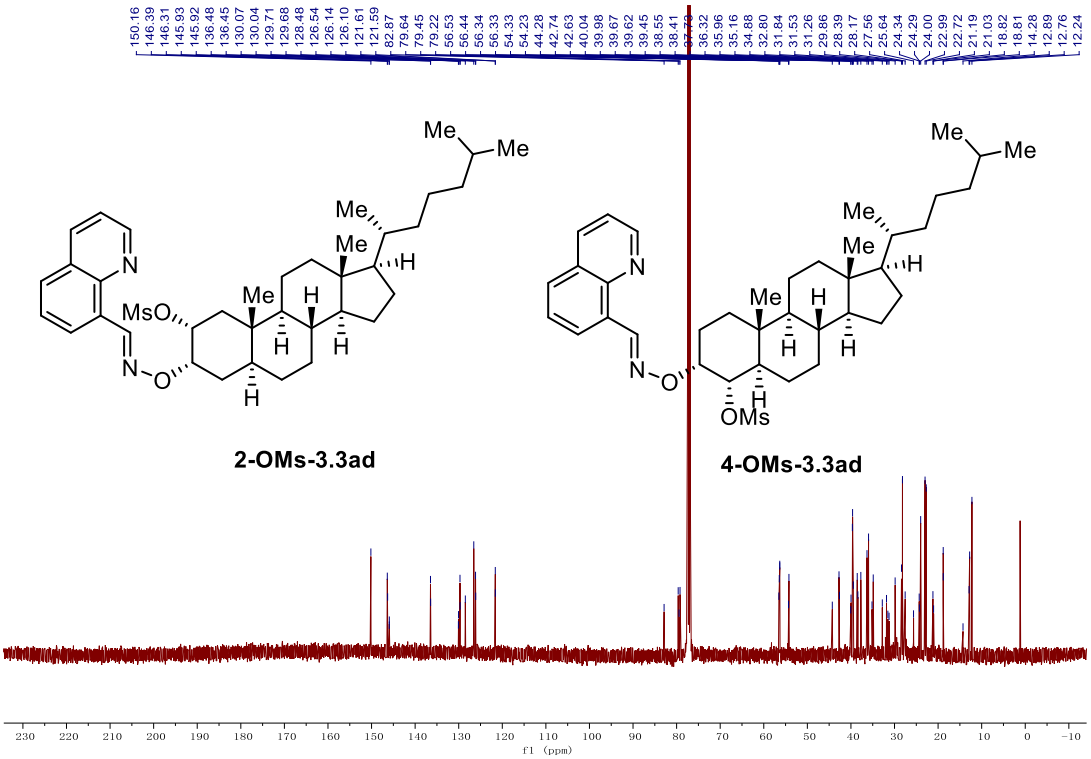


Figure 3.187 ^{1}H-NMR Spectrum of **3.4a**

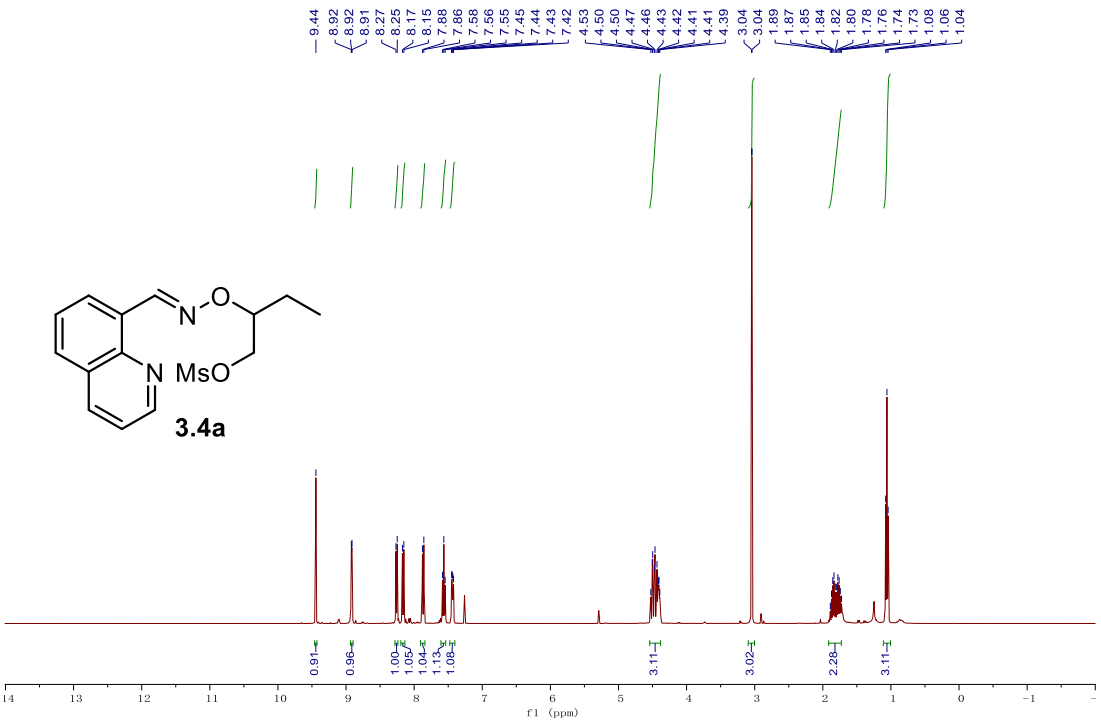


Figure 3.188 ^{13}C-NMR Spectrum of **3.4a**

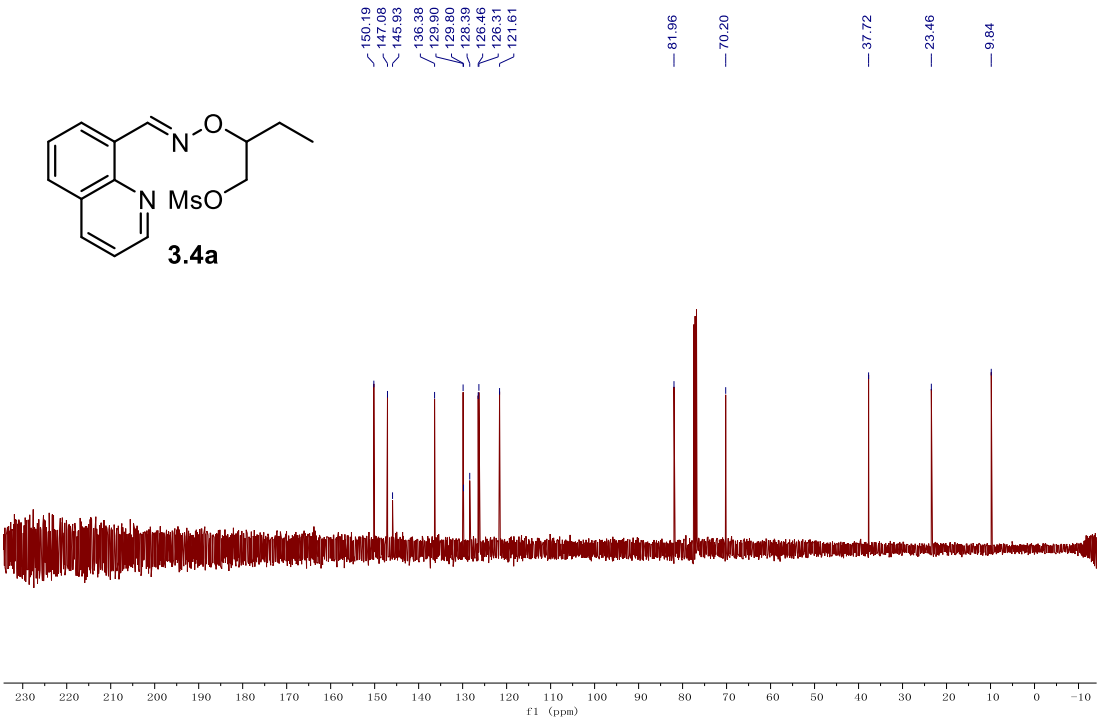


Figure 3.189 ^{1}H-NMR Spectrum of **3.4b**

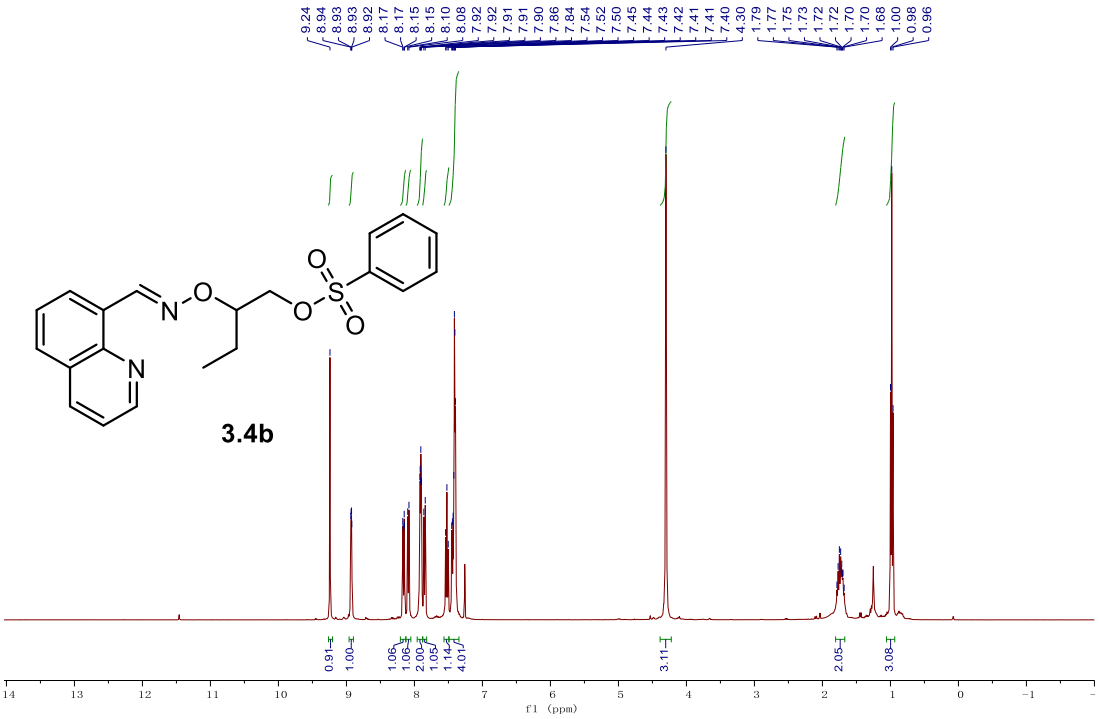


Figure 3.190 ^{13}C-NMR Spectrum of **3.4b**

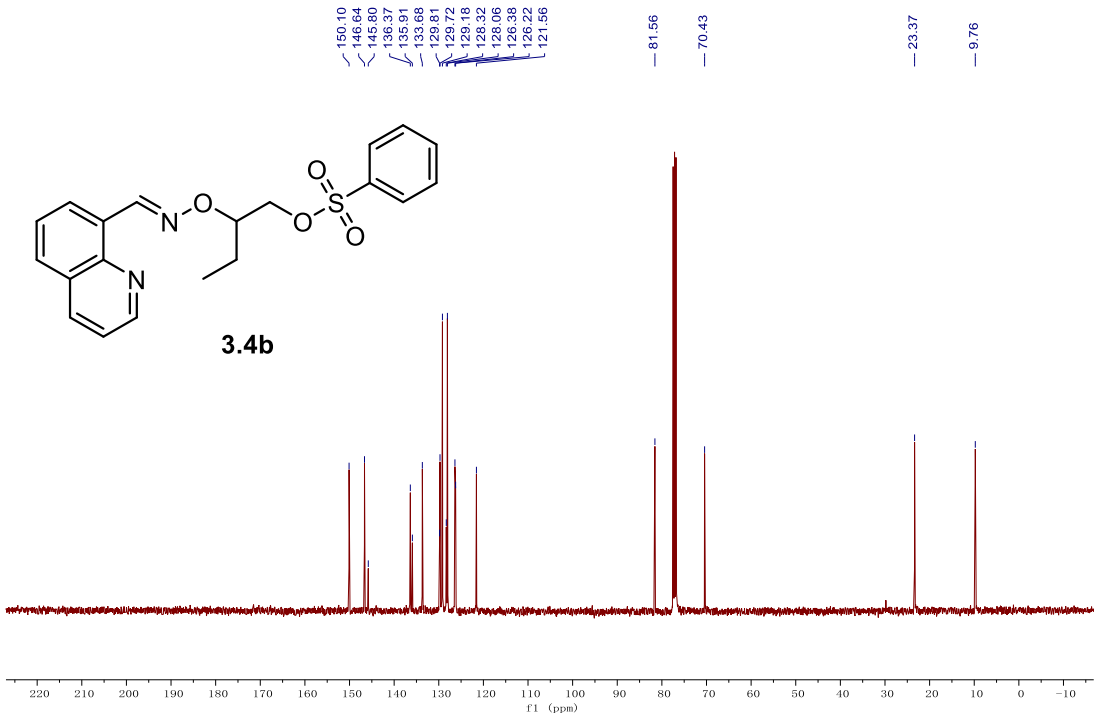


Figure 3.191 ^{1}H-NMR Spectrum of **3.4c**

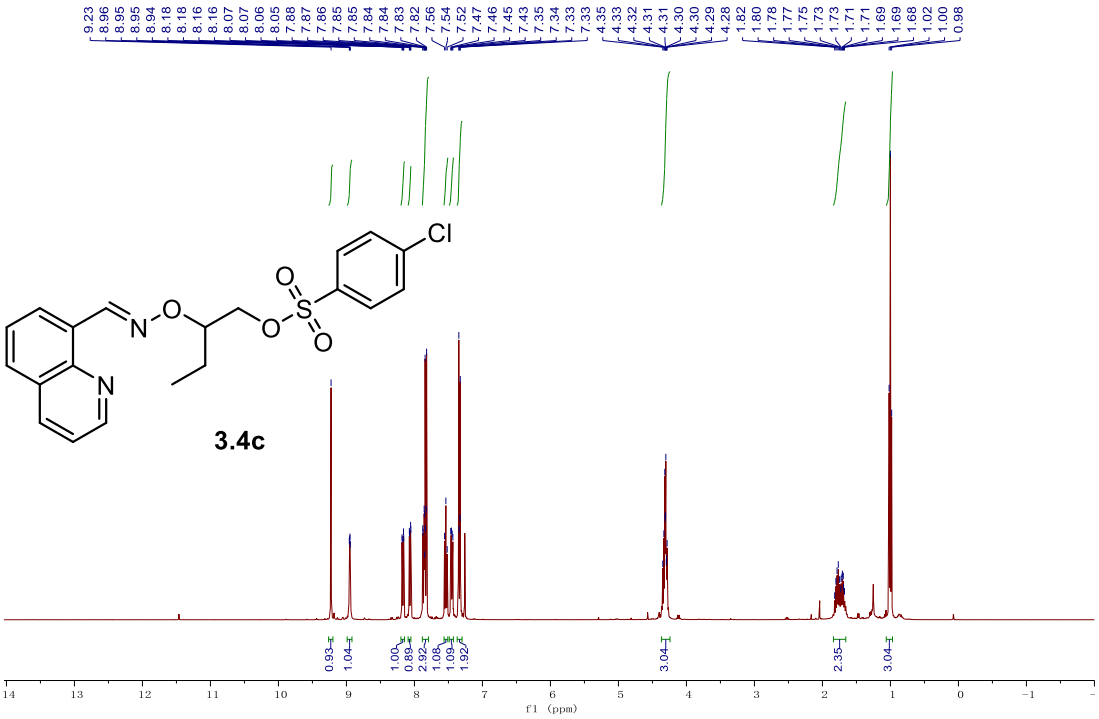


Figure 3.192 ^{13}C-NMR Spectrum of **3.4c**

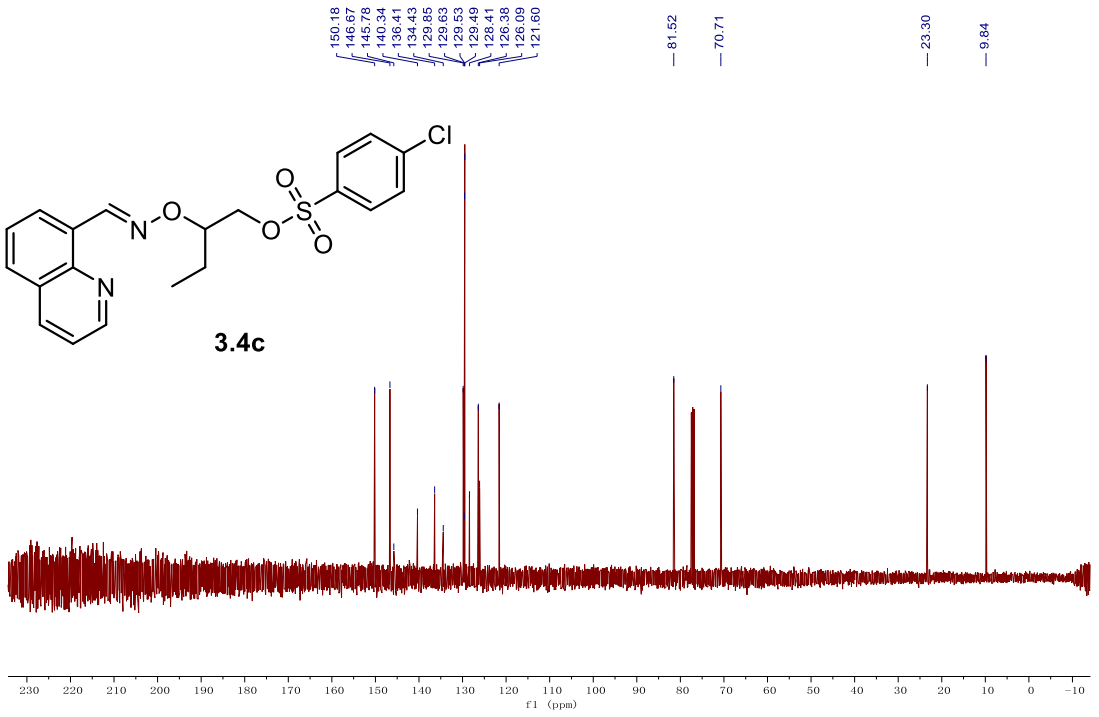


Figure 3.193 ^{1}H-NMR Spectrum of **3.4d**

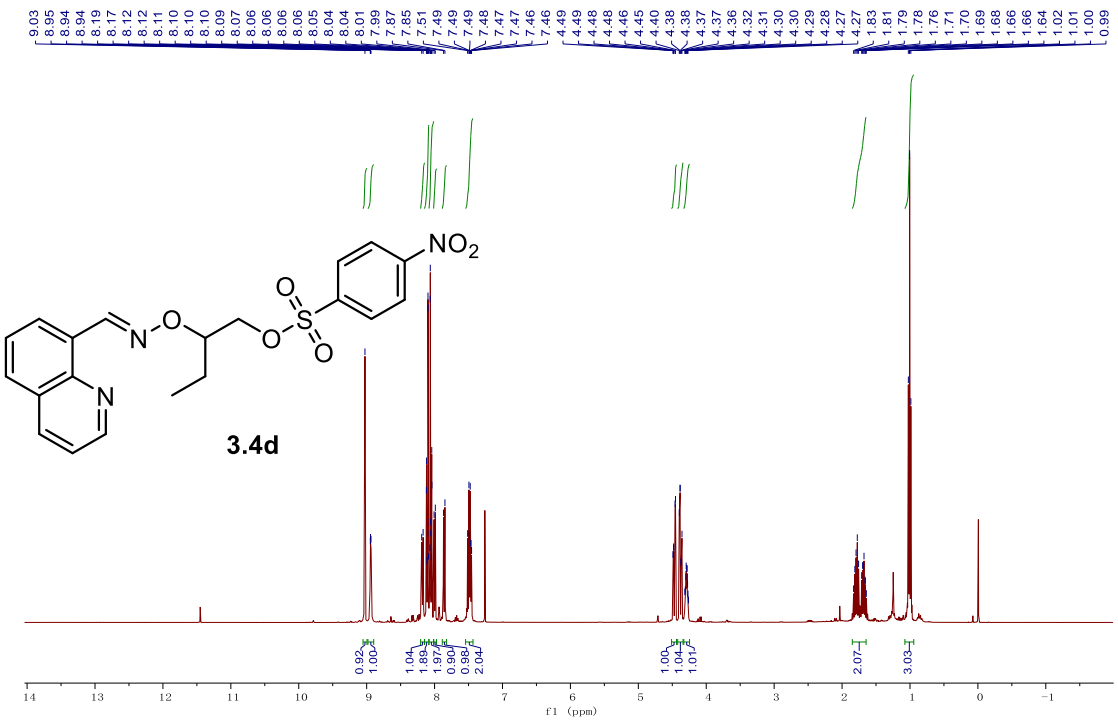


Figure 3.194 ^{13}C-NMR Spectrum of **3.4d**

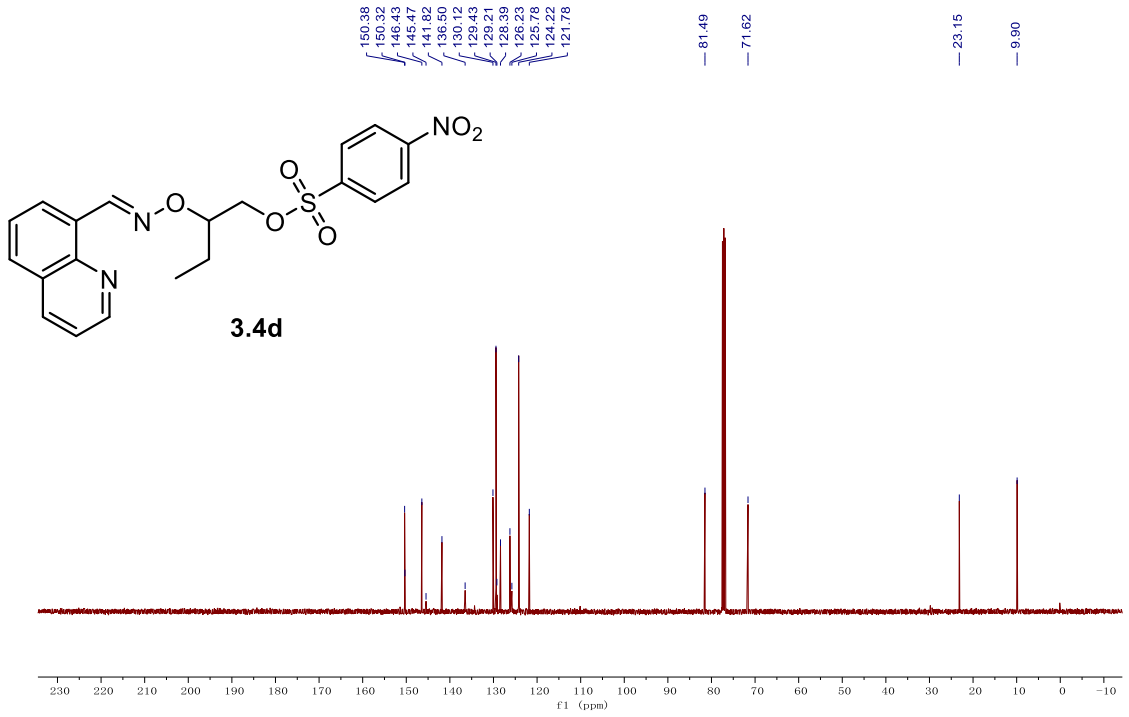


Figure 3.195 ^{1}H-NMR Spectrum of **3.4e**

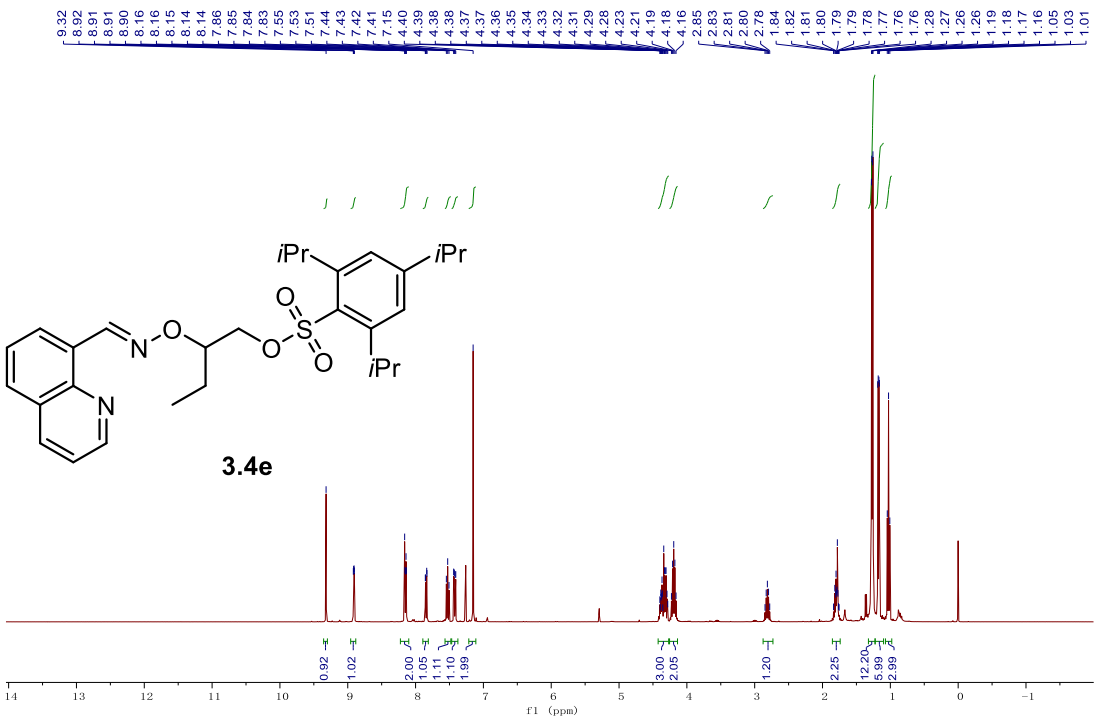


Figure 3.196 ^{13}C-NMR Spectrum of **3.4e**

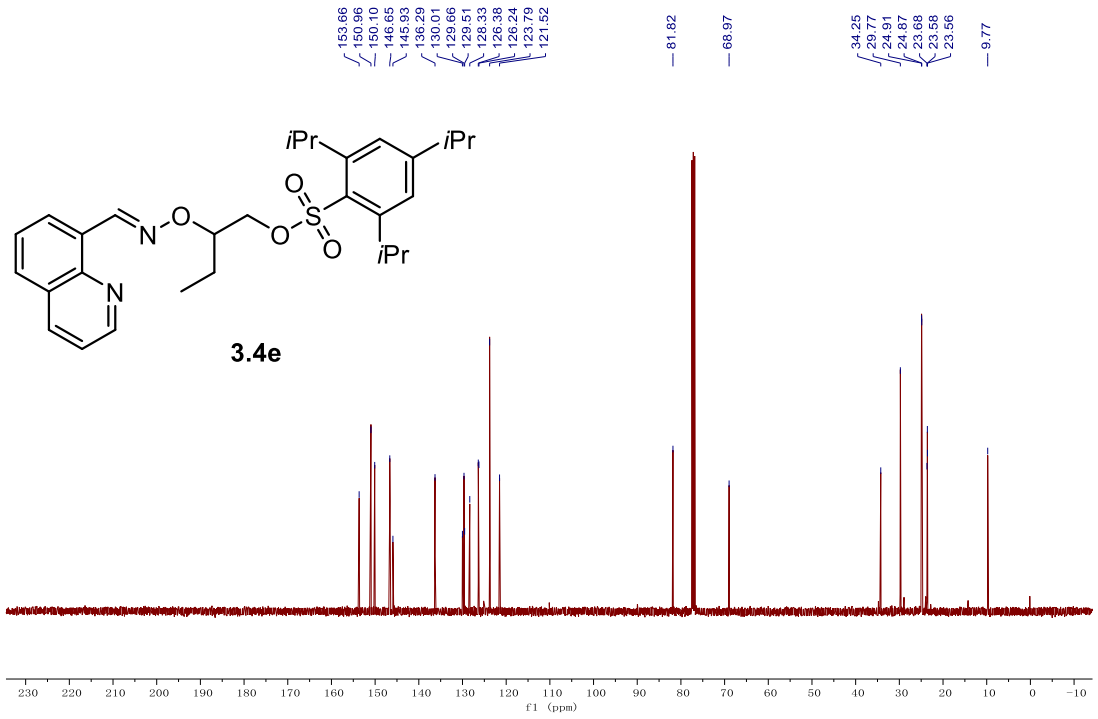


Figure 3.197 ^{1}H-NMR Spectrum of **3.5**

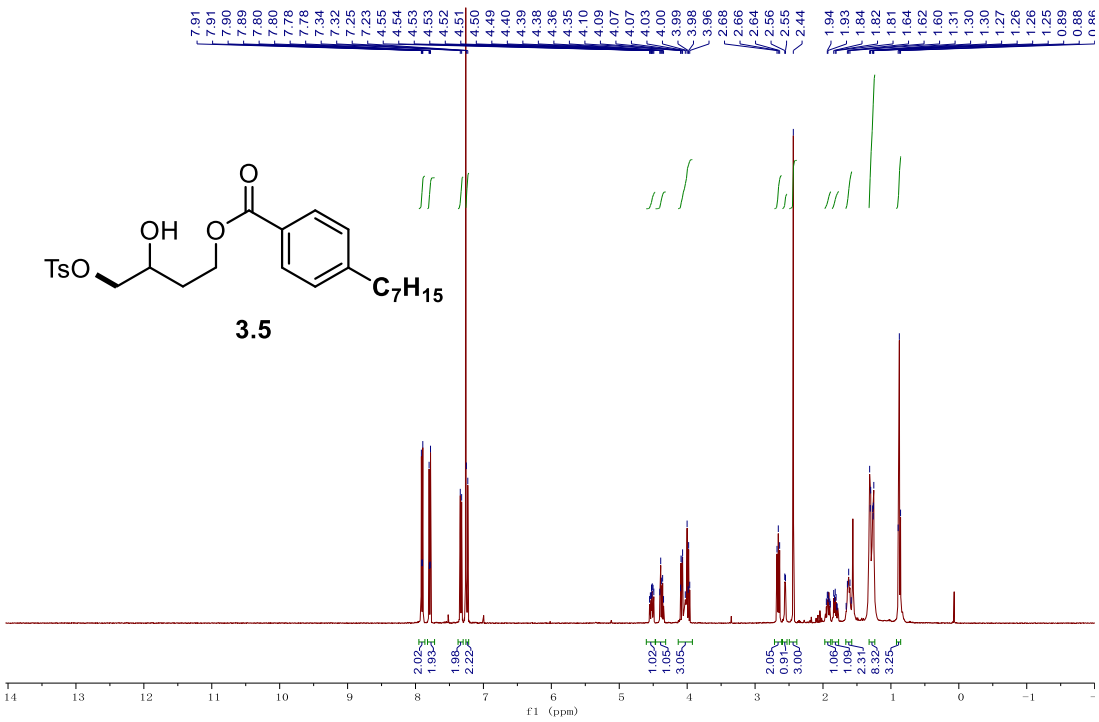


Figure 3.198 ^{13}C-NMR Spectrum of **3.5**

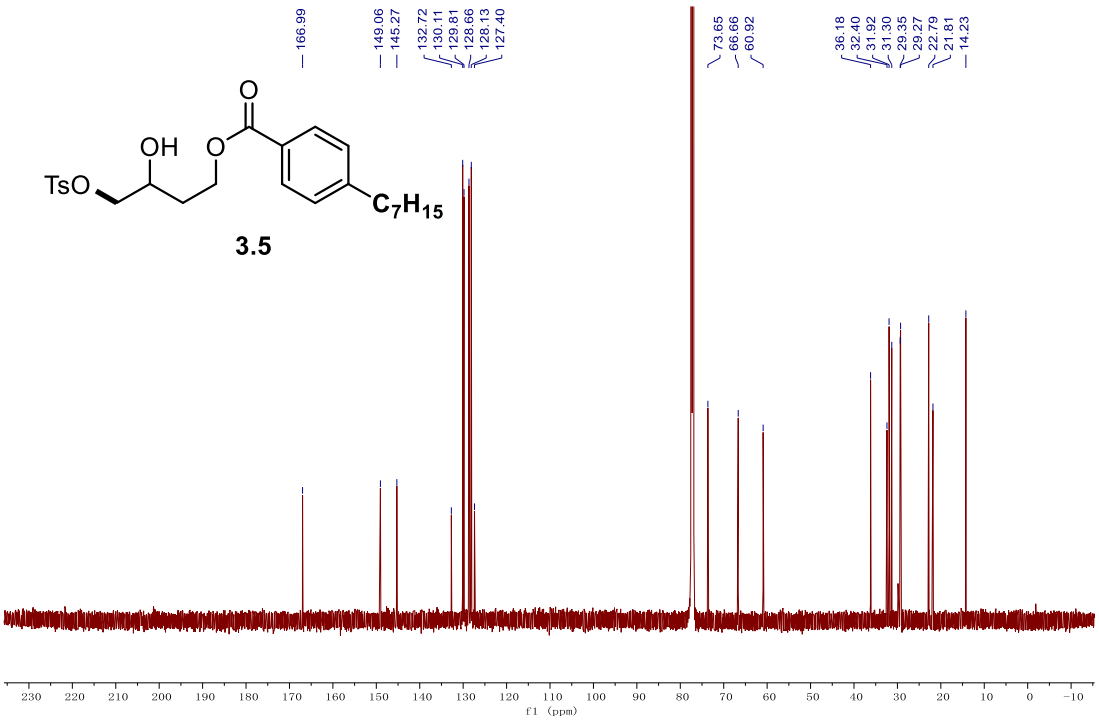


Figure 3.199 ^{1}H-NMR Spectrum of **3.33**

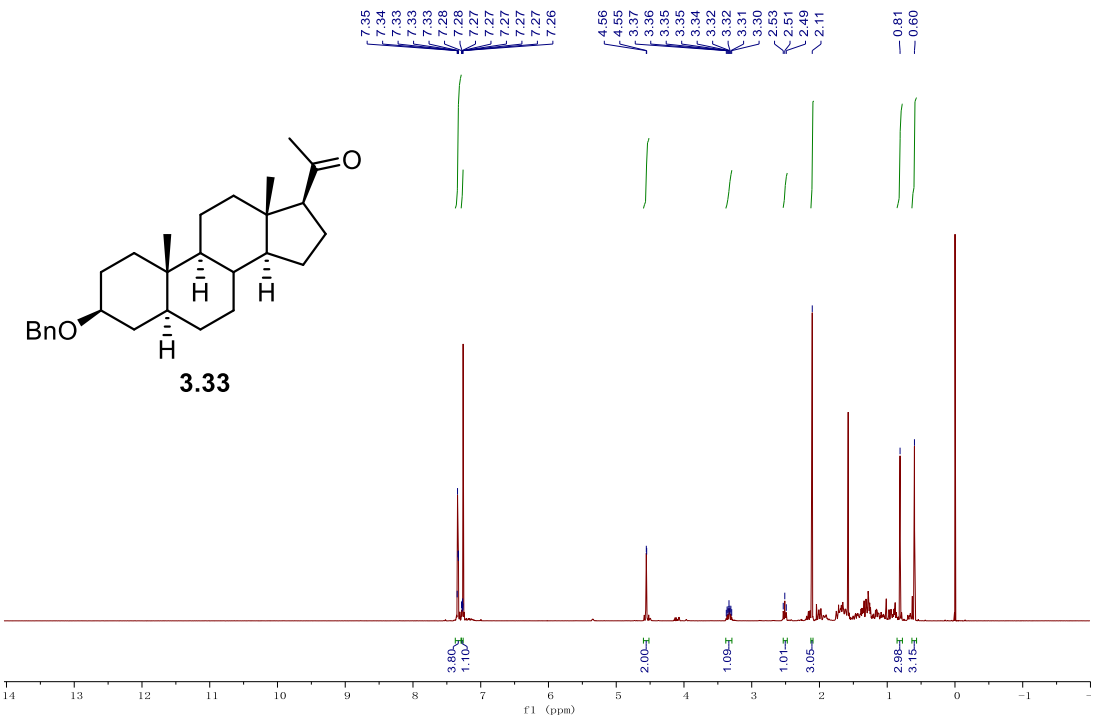


Figure 3.200 ^{13}C-NMR Spectrum of **3.33**

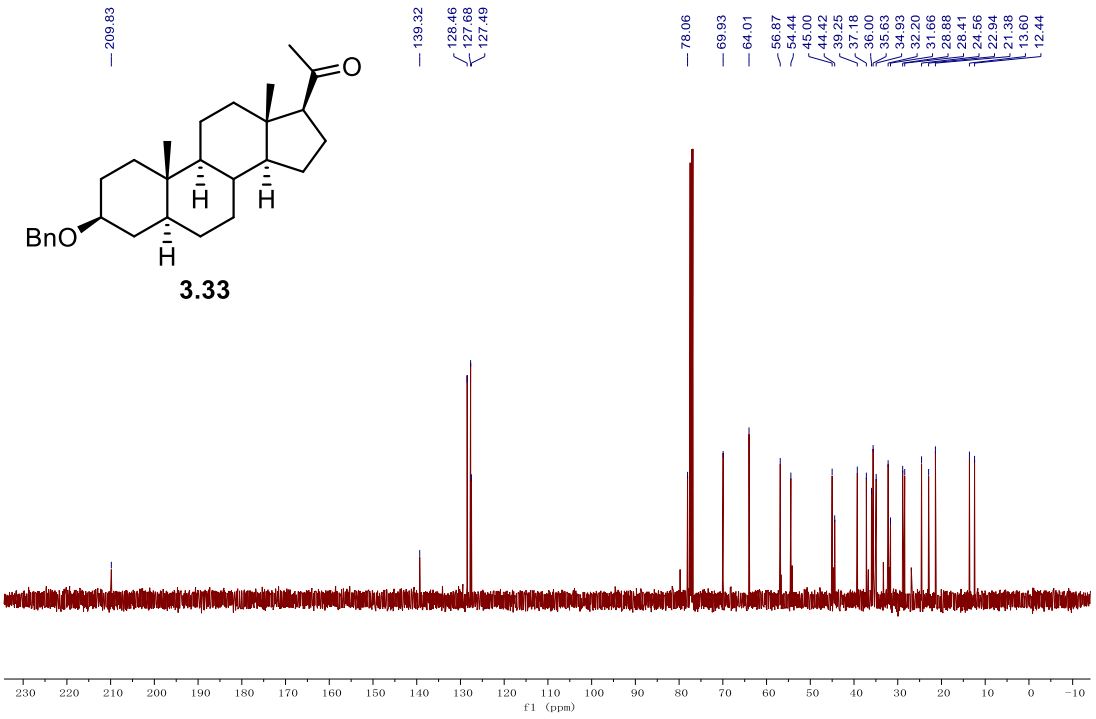


Figure 3.201 ^{1}H-NMR Spectrum of **3.6**

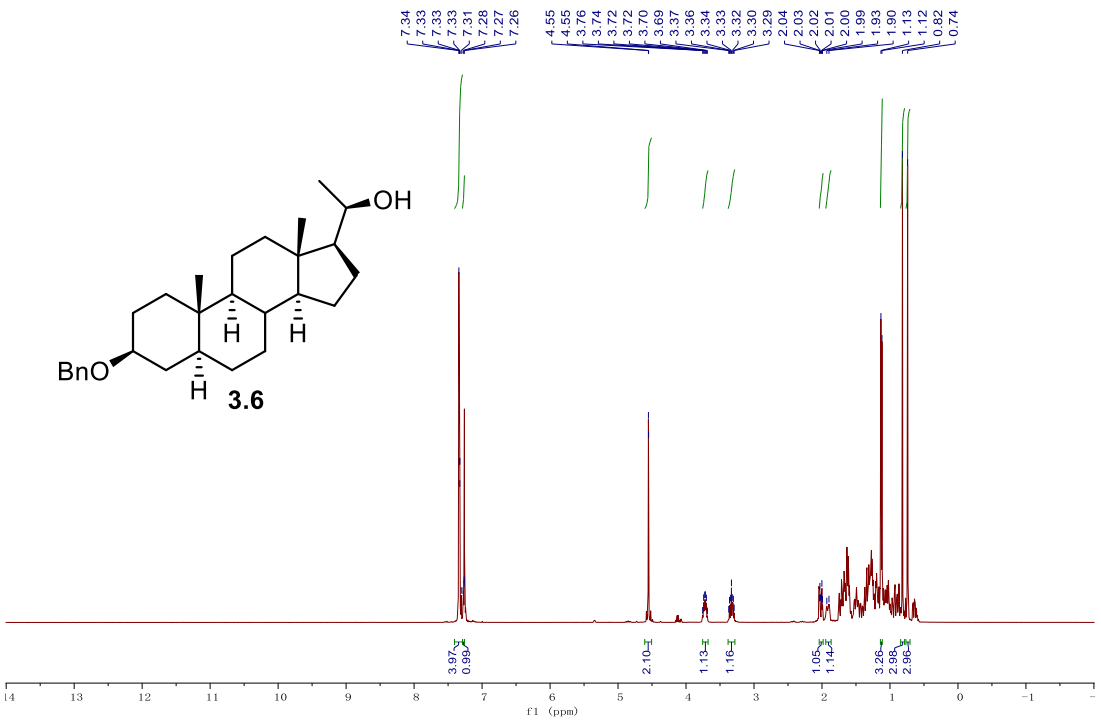


Figure 3.202 ^{13}C-NMR Spectrum of **3.6**

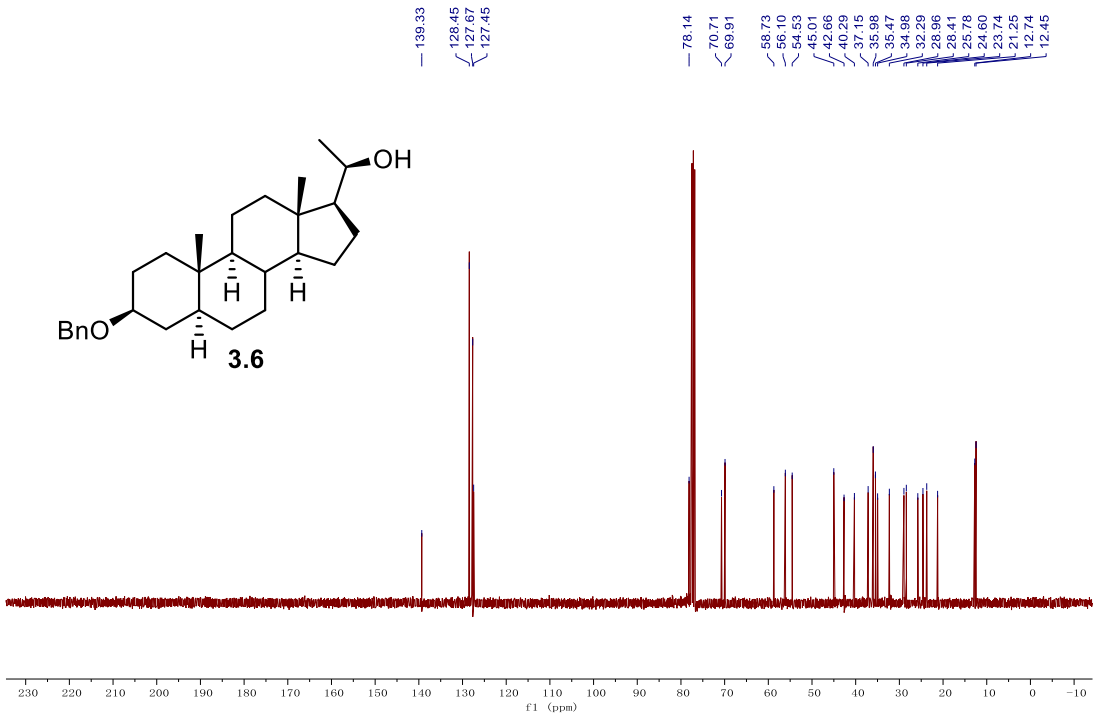


Figure 3.203 ^{1}H-NMR Spectrum of **3.7**

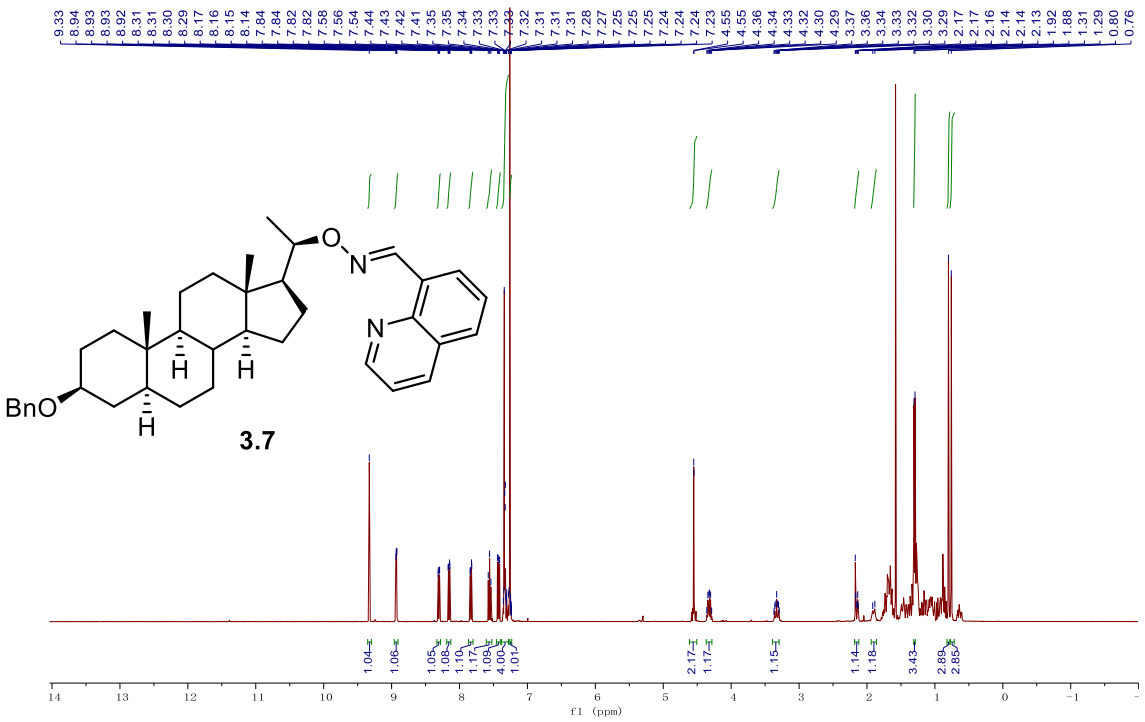


Figure 3.204 ^{13}C-NMR Spectrum of **3.7**

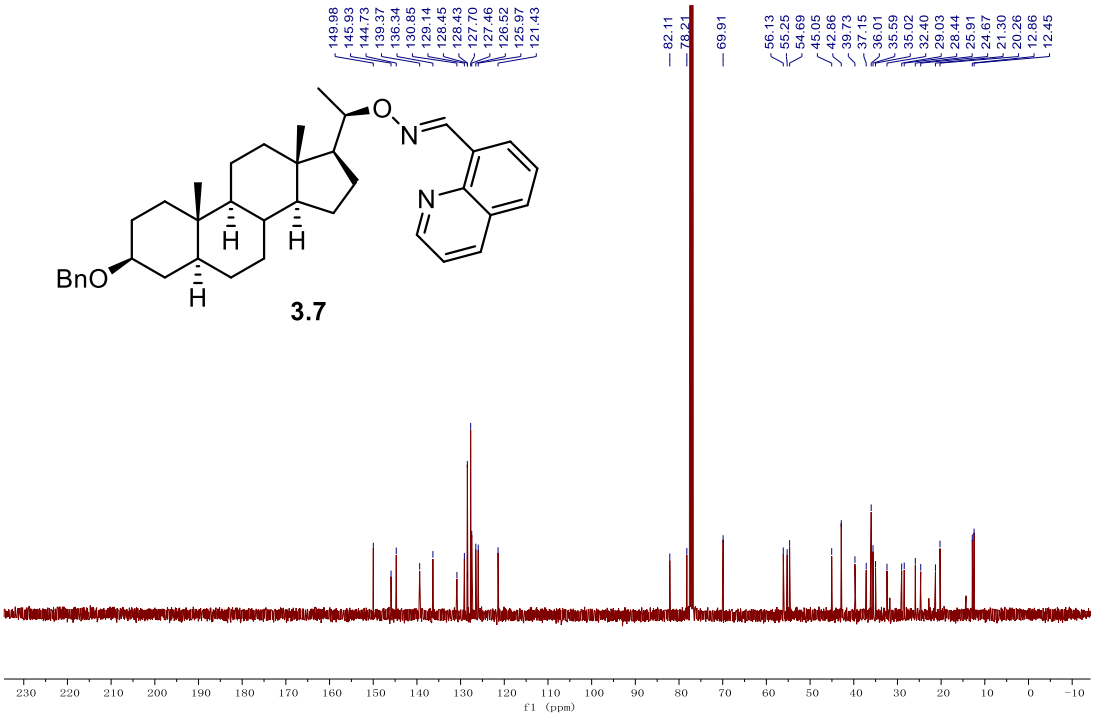


Figure 3.205 ^{1}H-NMR Spectrum of **3.8**

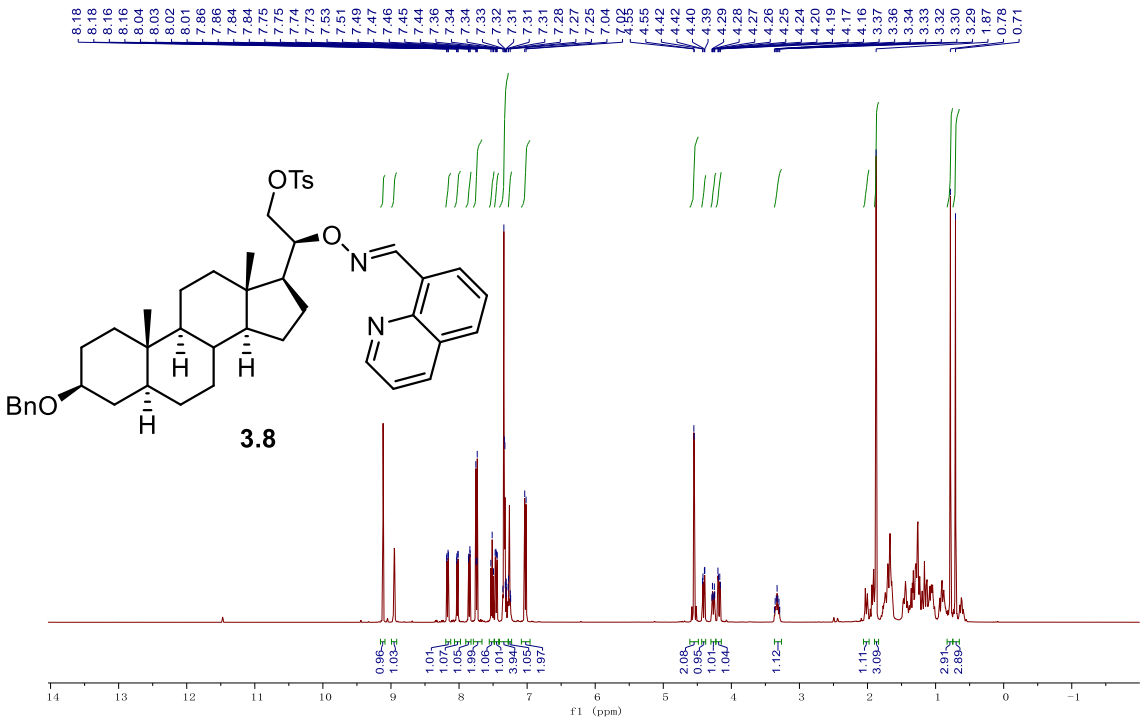


Figure 3.206 ^{13}C-NMR Spectrum of **3.8**

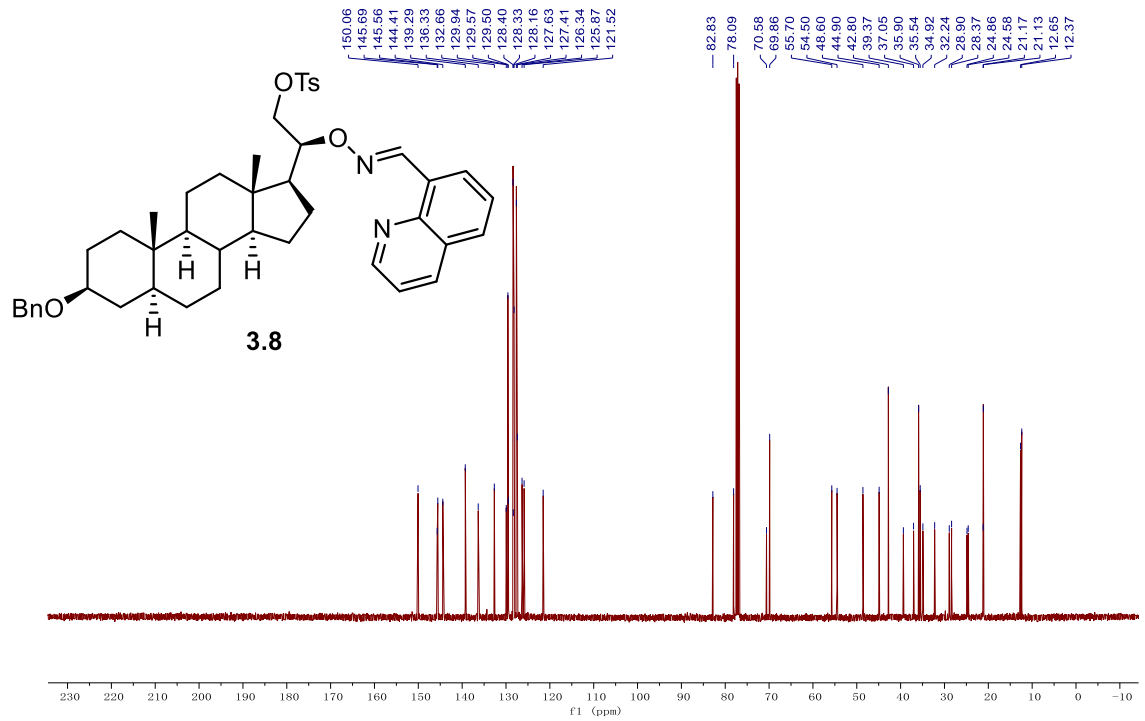


Figure 3.207 ^{1}H-NMR Spectrum of **3.9a**

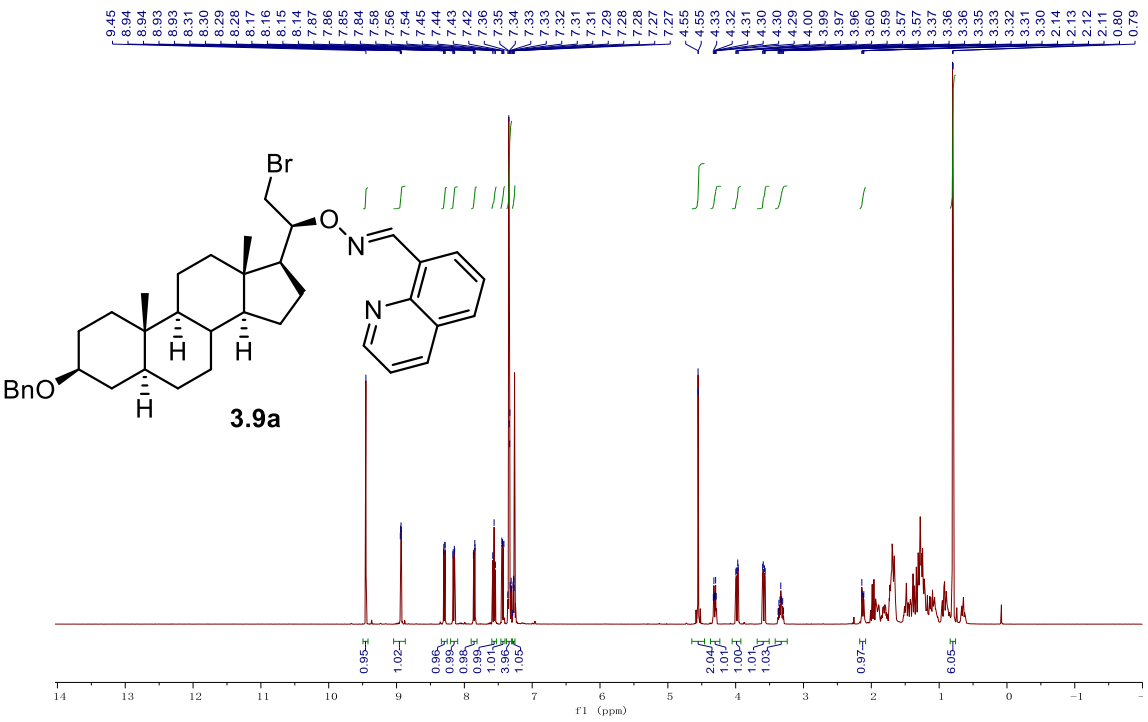


Figure 3.208 ^{13}C-NMR Spectrum of **3.9a**

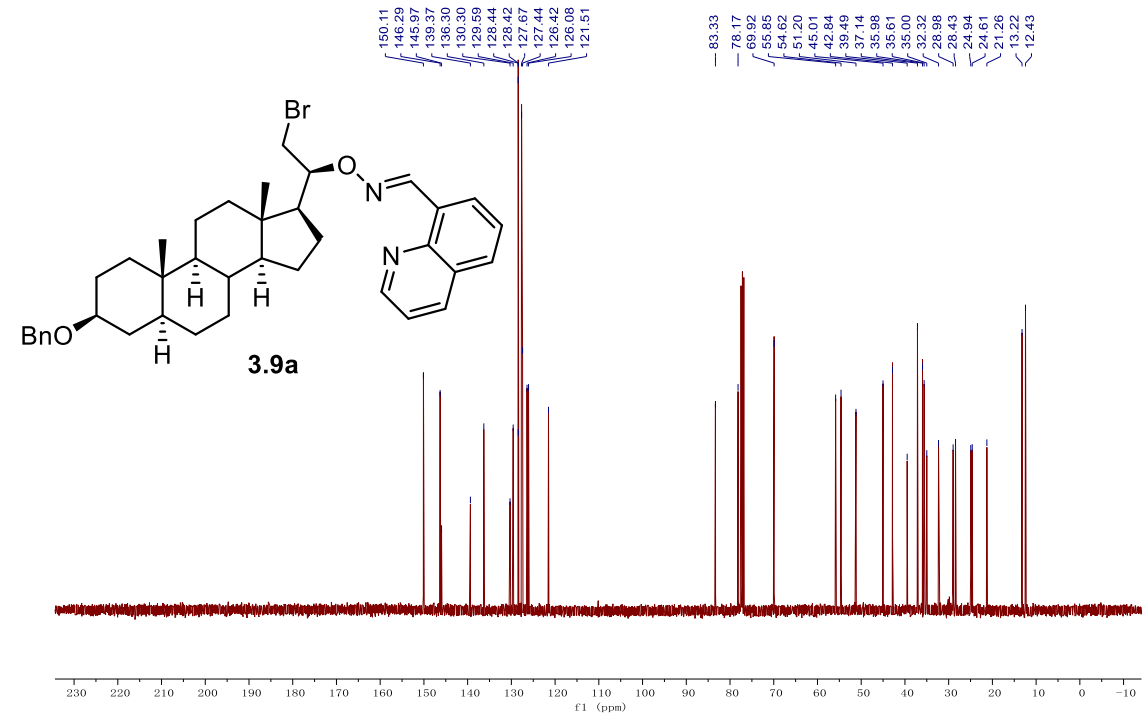


Figure 3.209 ^{1}H-NMR Spectrum of **3.9b**

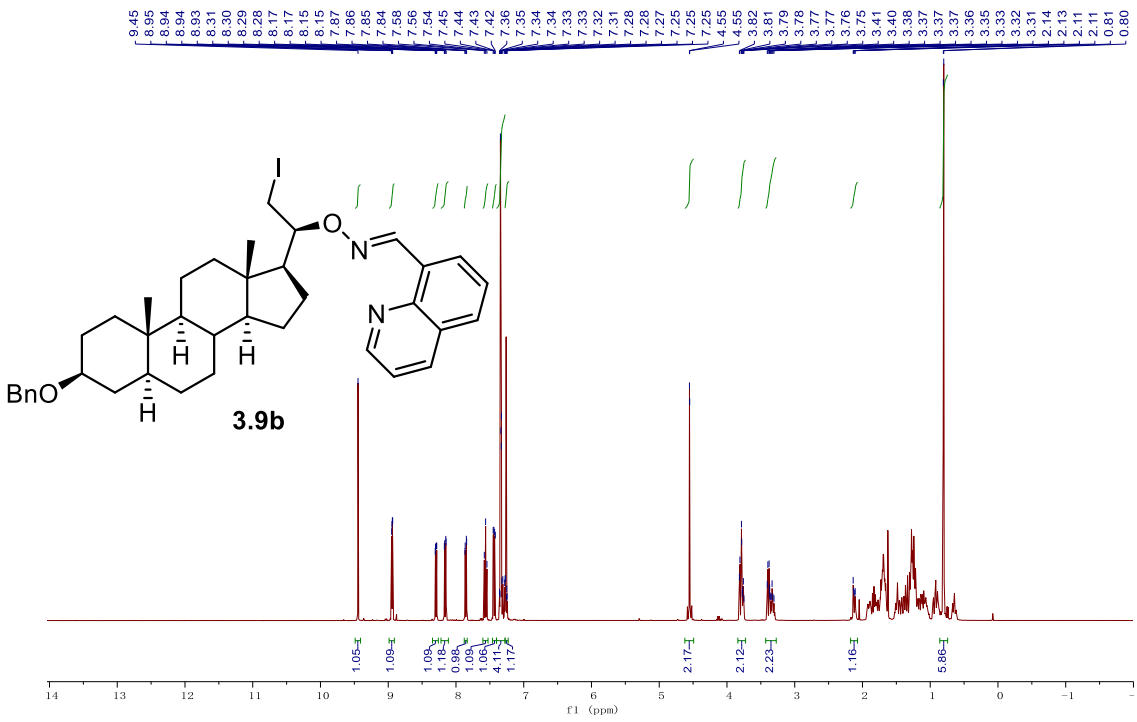


Figure 3.210 ^{13}C-NMR Spectrum of **3.9b**

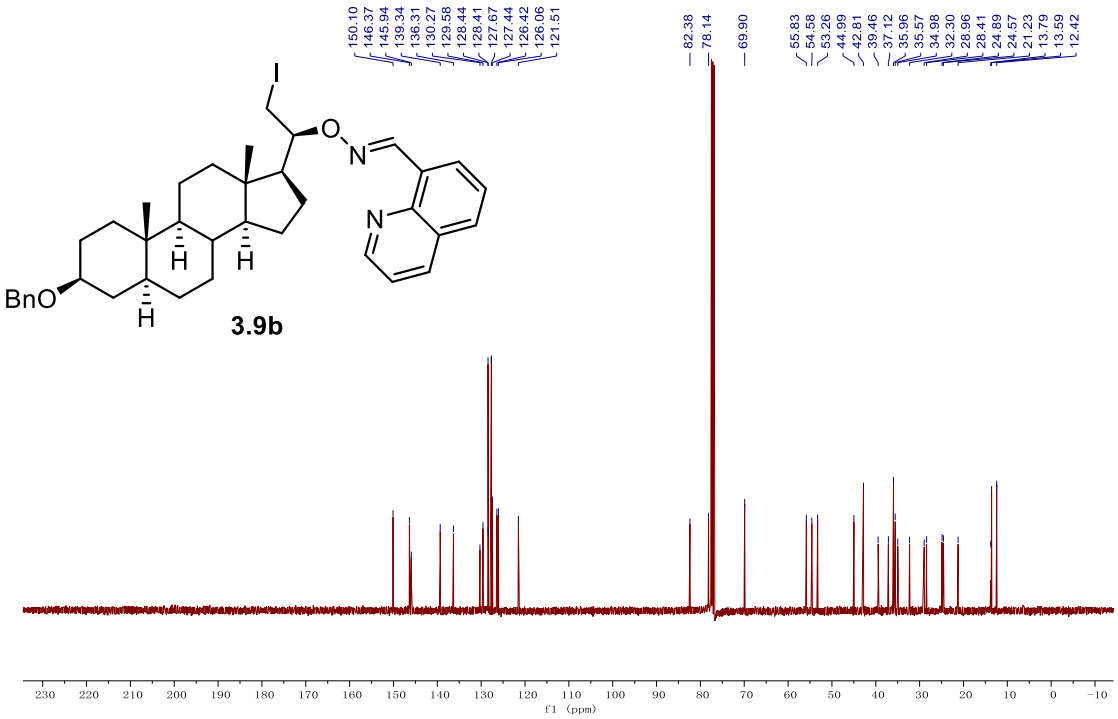


Figure 3.211 ^{1}H-NMR Spectrum of **3.9c**

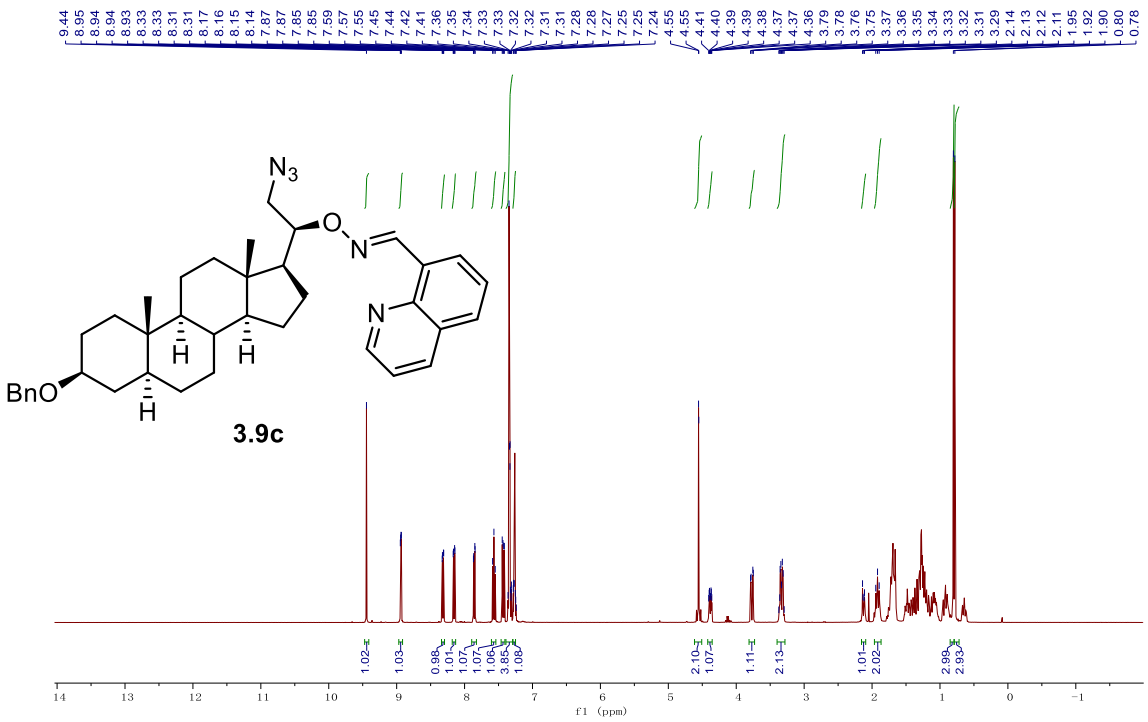


Figure 3.212 ^{13}C-NMR Spectrum of **3.9c**

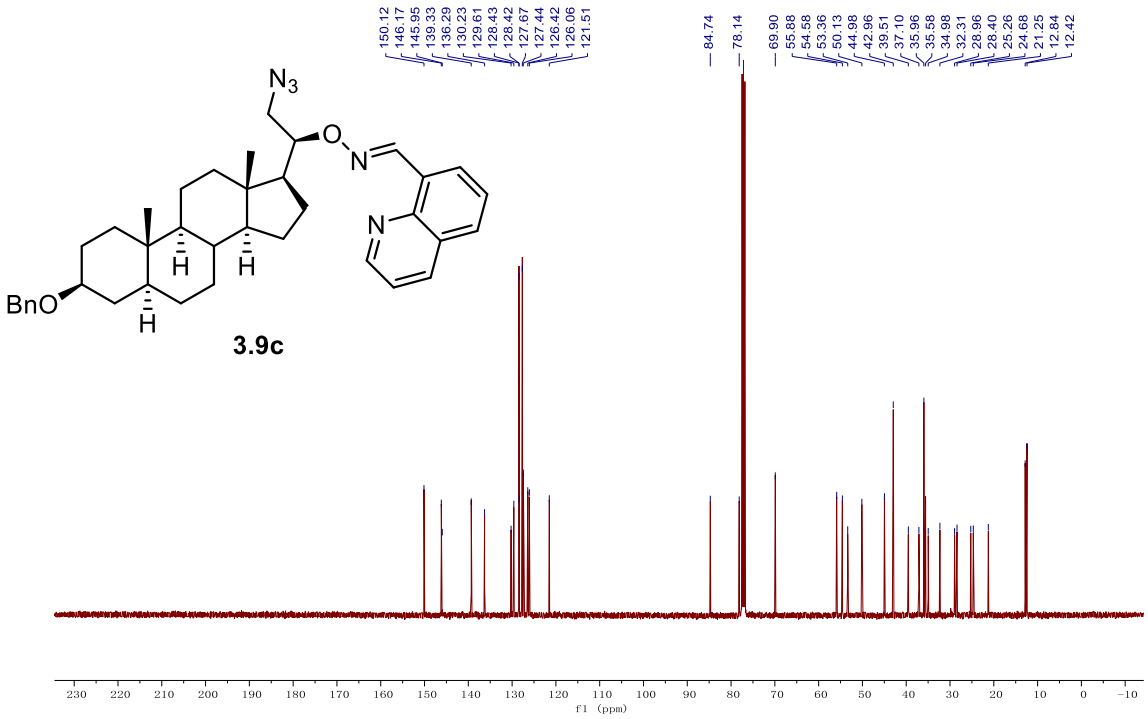


Figure 3.213 ^{1}H-NMR Spectrum of **3.9d**

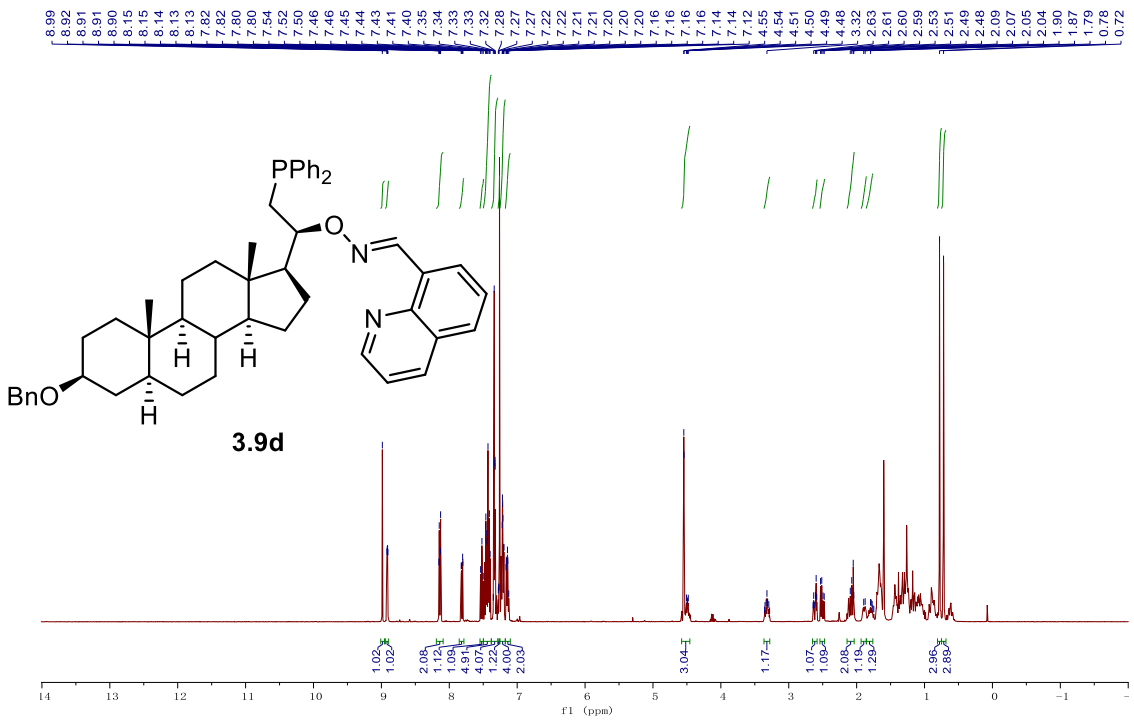


Figure 3.214 ^{13}C-NMR Spectrum of **3.9d**

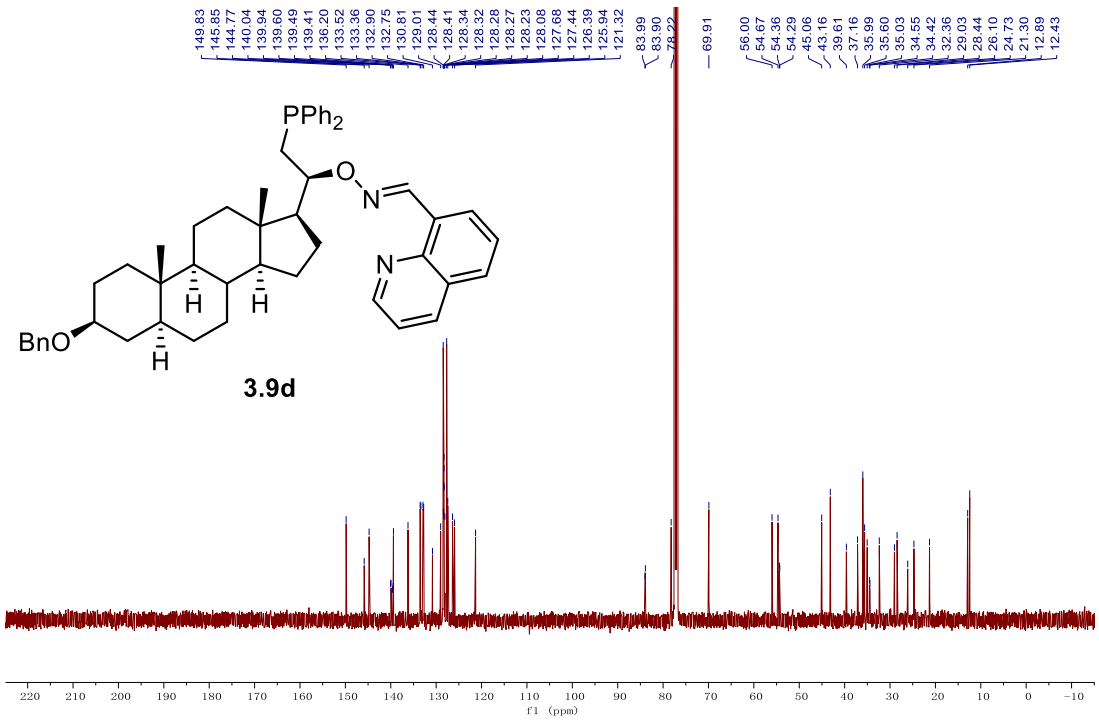


Figure 3.215 ^{1}H-NMR Spectrum of **3.9e**

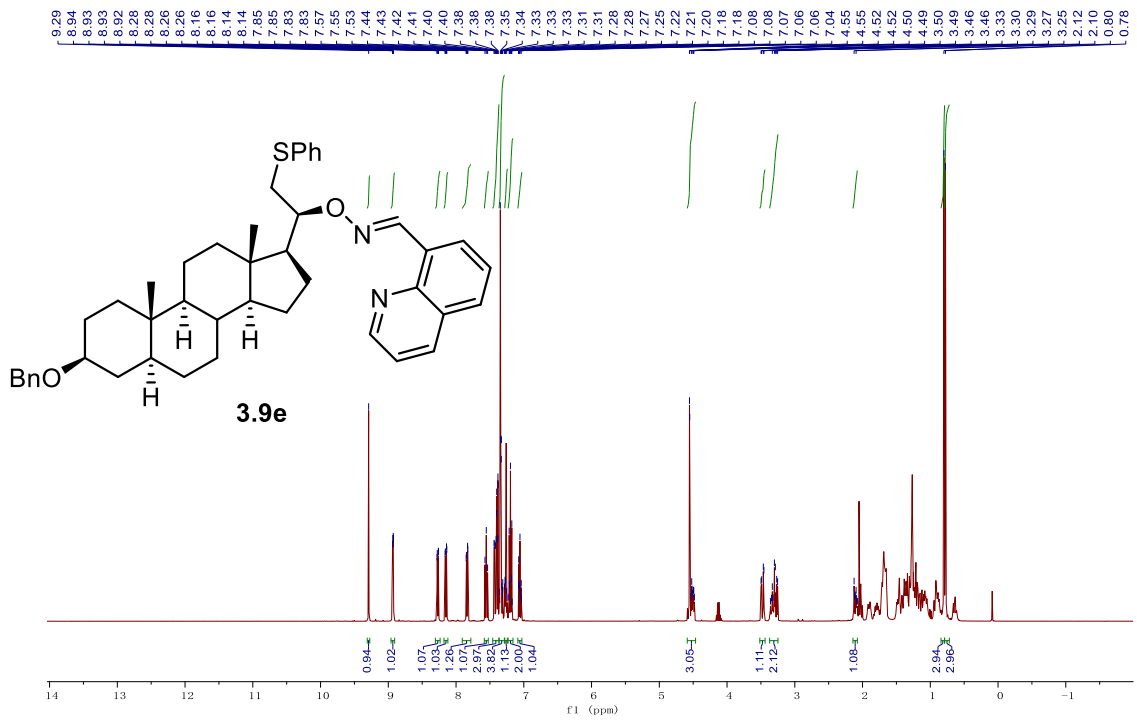


Figure 3.216 ^{13}C-NMR Spectrum of **3.9e**

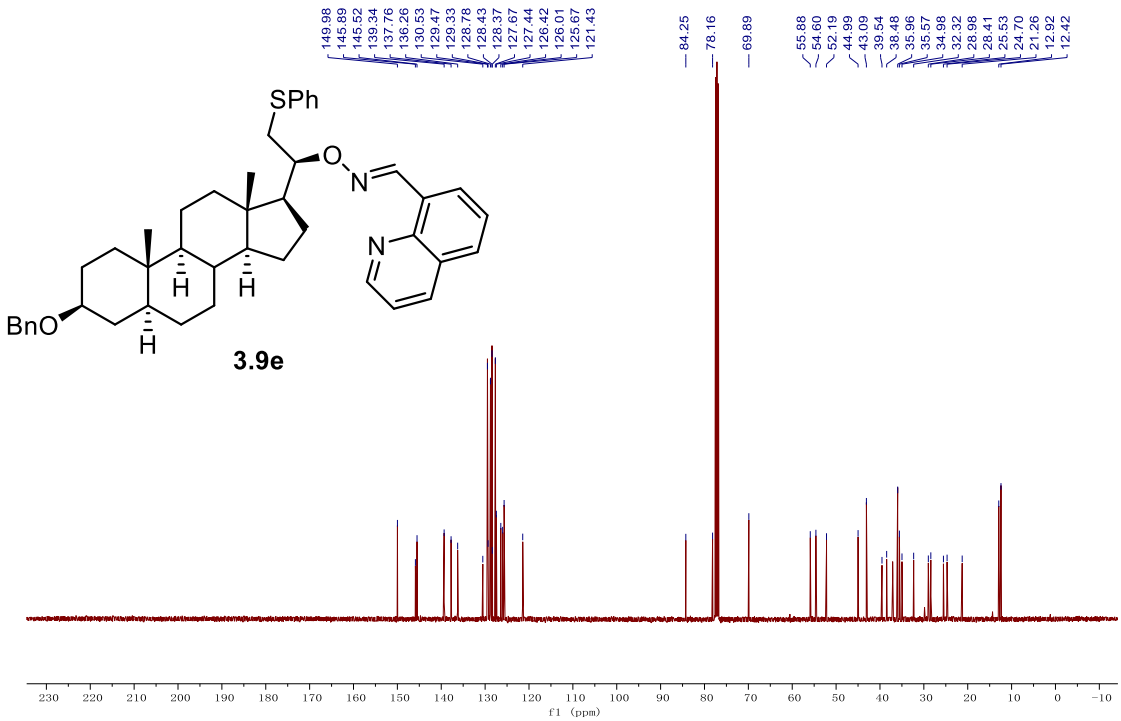


Figure 3.217 ^{1}H-NMR Spectrum of **3.9f**

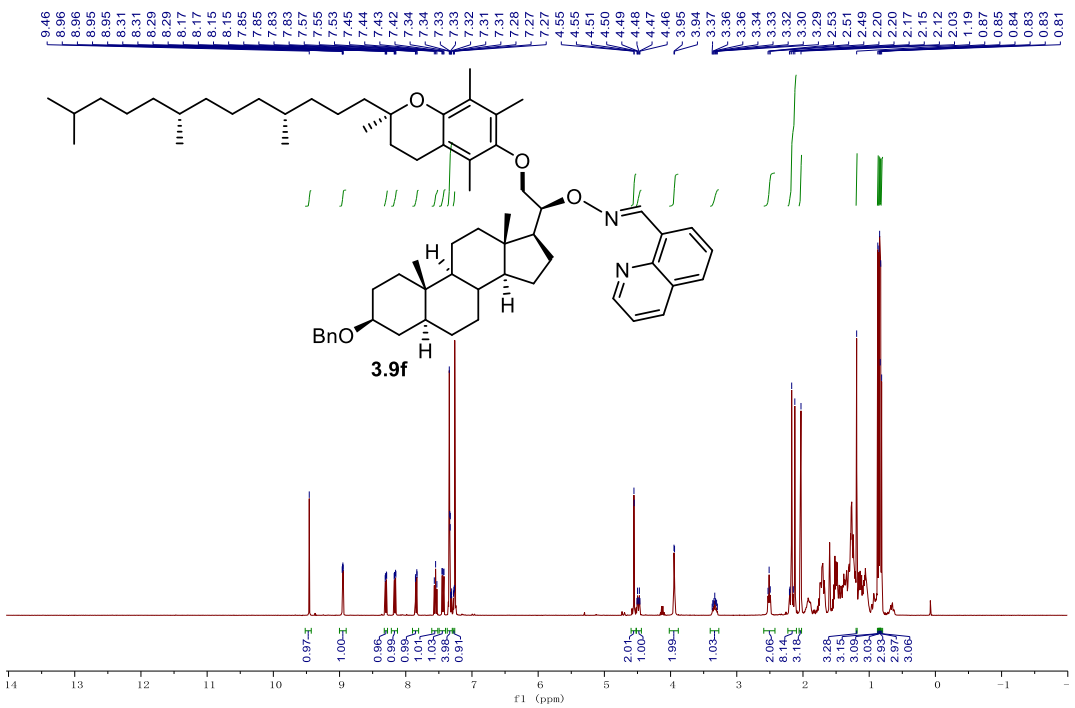


Figure 3.218 ^{13}C-NMR Spectrum of **3.9f**

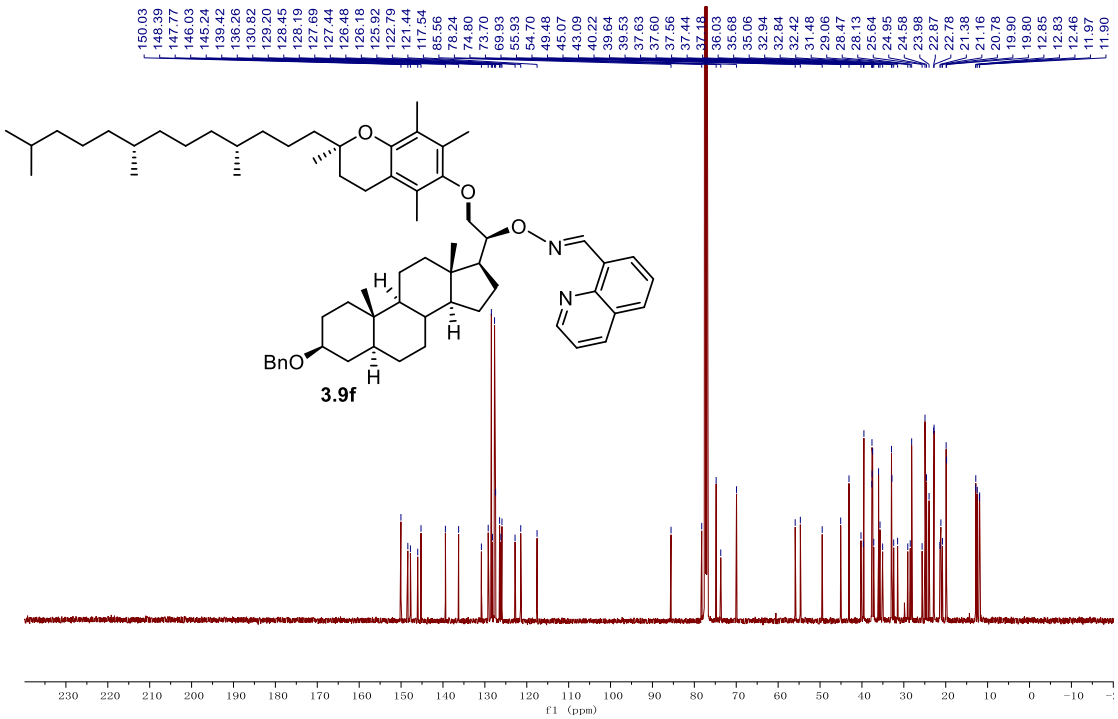


Figure 3.219 ^{1}H-NMR Spectrum of **3.9g**

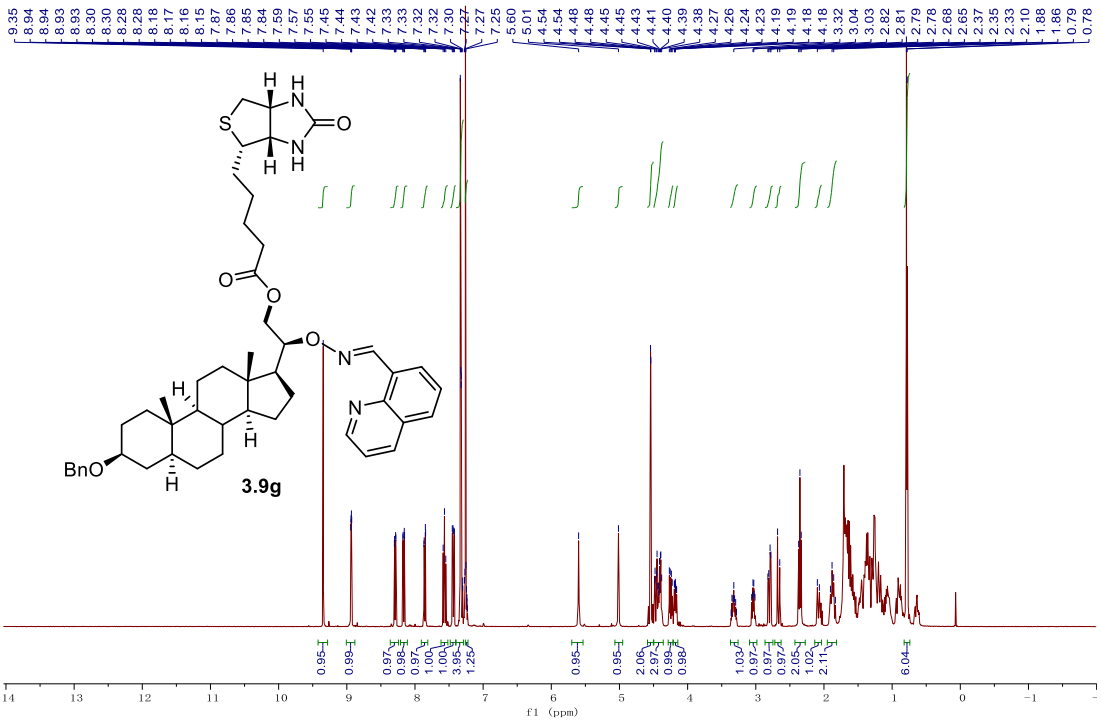


Figure 3.220 ^{13}C-NMR Spectrum of **3.9g**

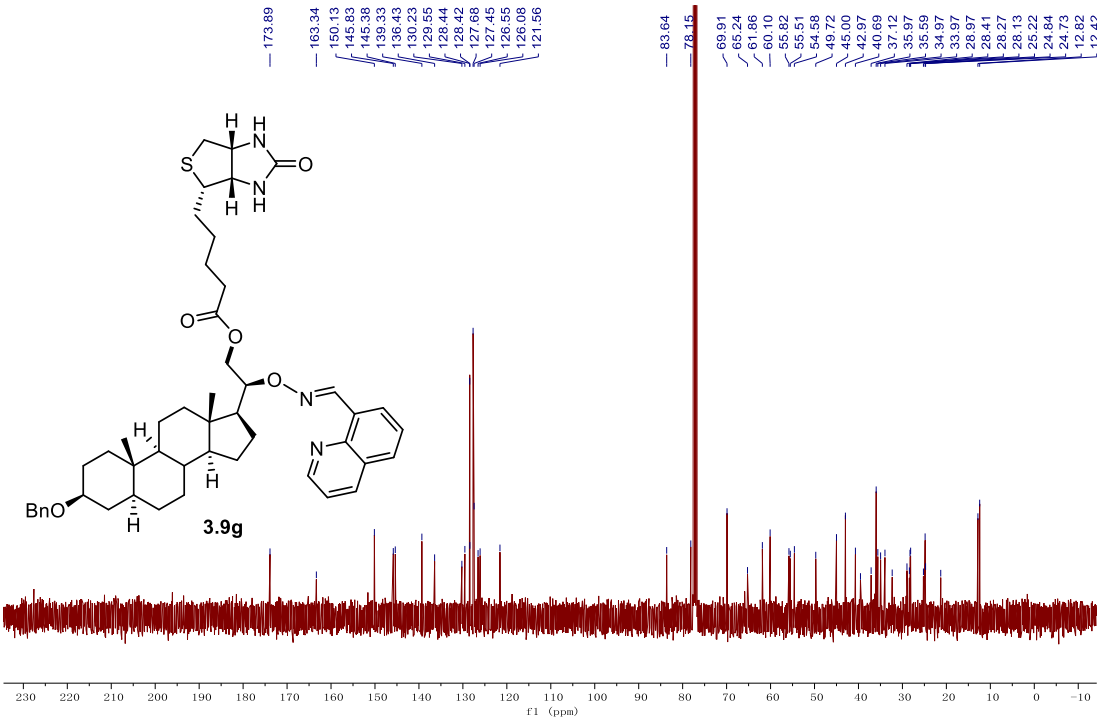


Figure 3.221 ^{1}H-NMR Spectrum of **3.9h**

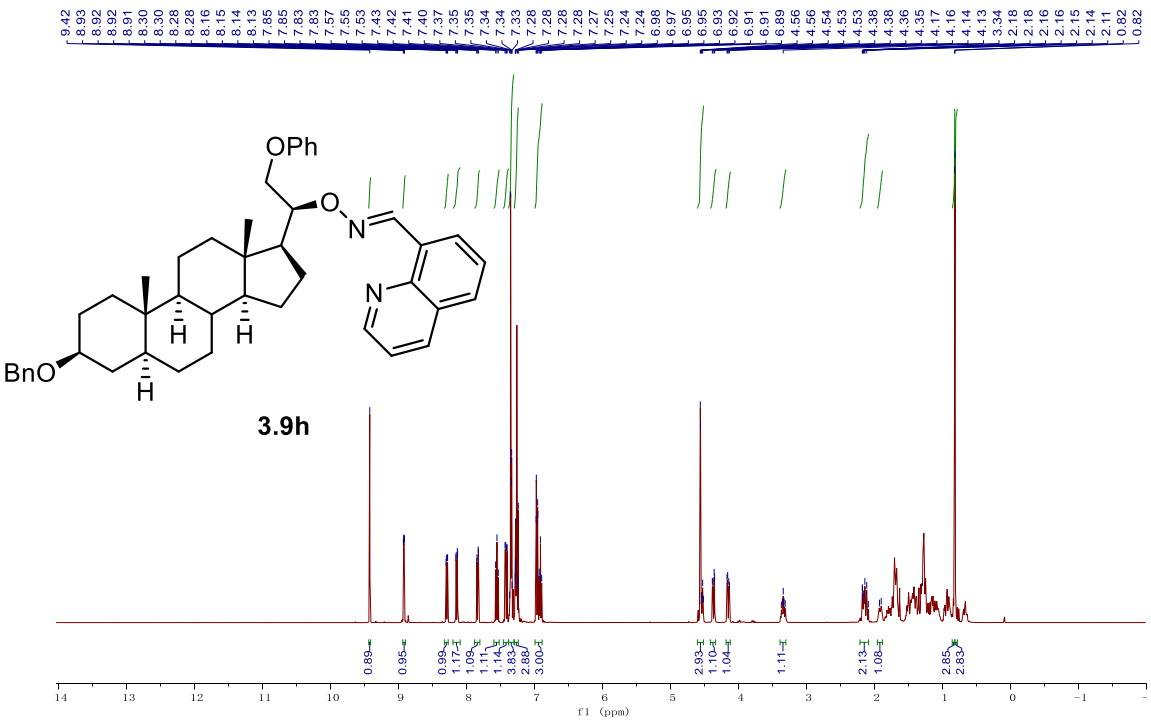


Figure 3.222 ^{13}C-NMR Spectrum of **3.9h**

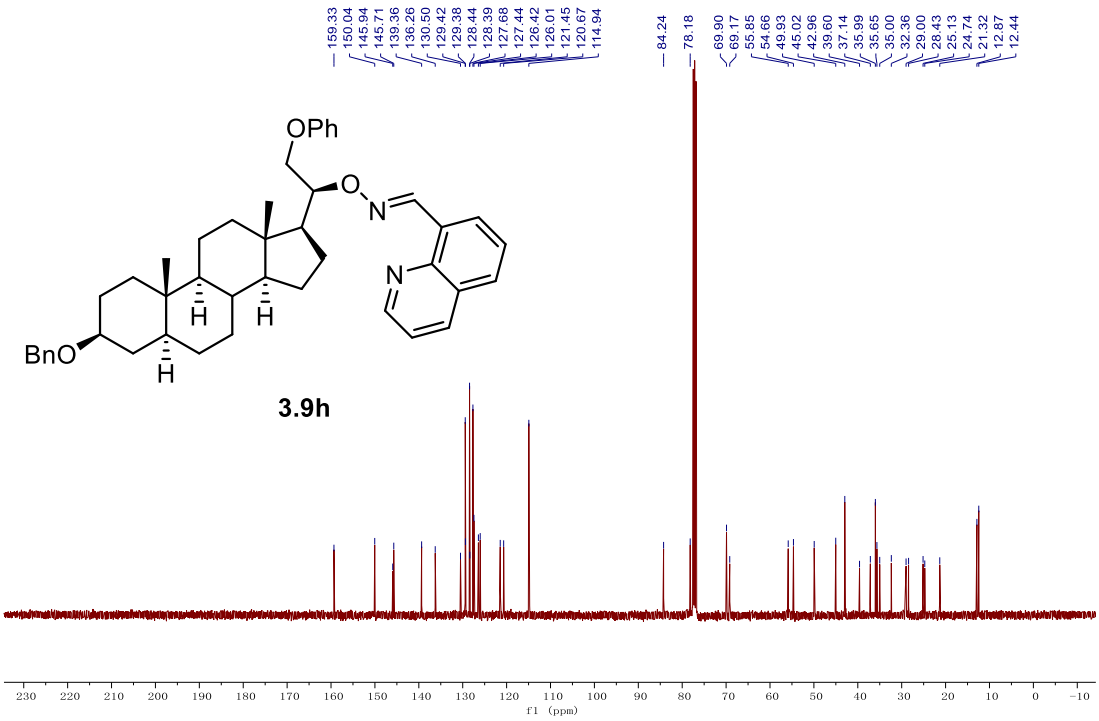


Figure 3.223 ^{1}H-NMR Spectrum of **3.10**

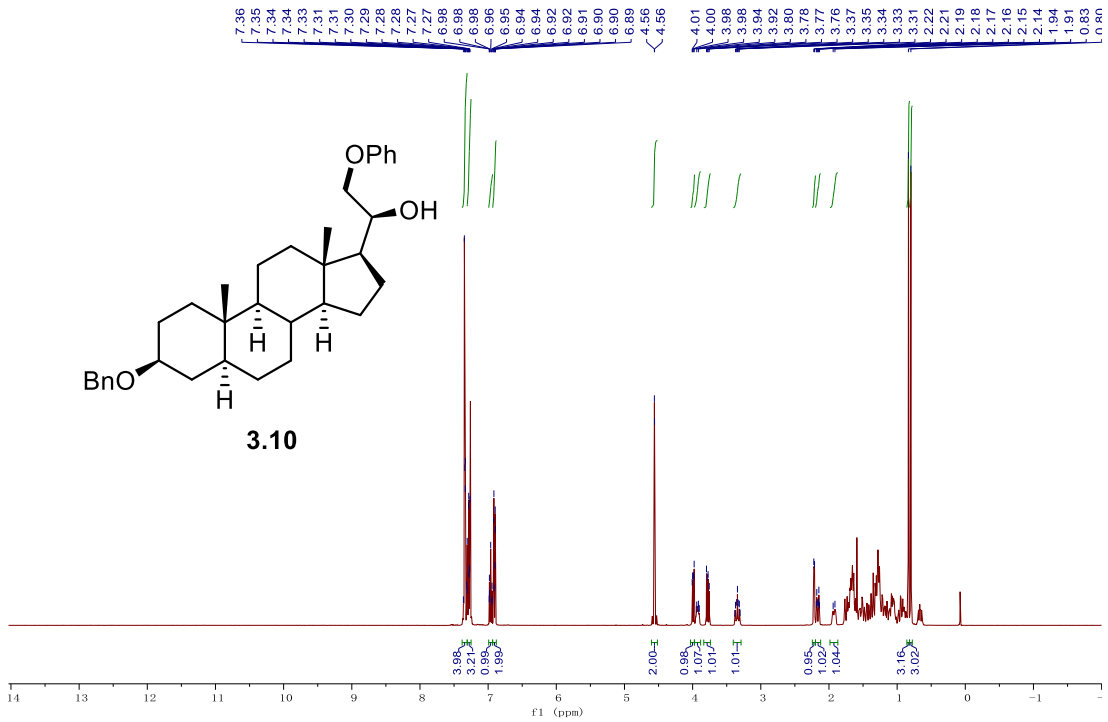


Figure 3.224 ^{13}C-NMR Spectrum of **3.10**

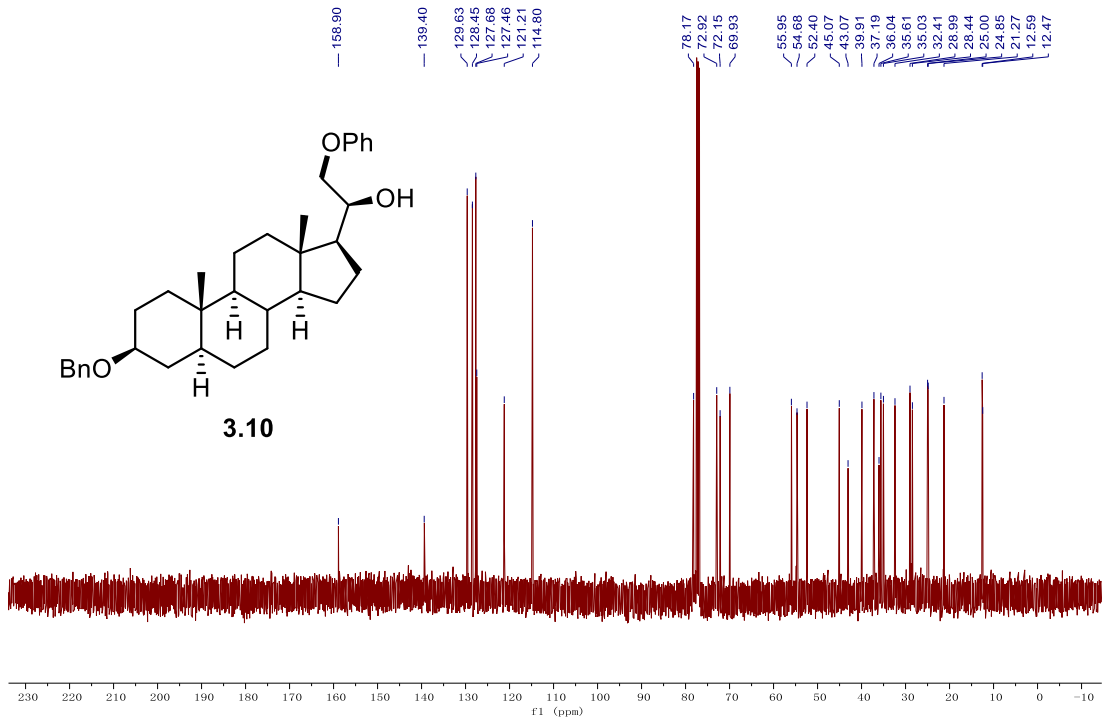


Figure 3.225 ^{1}H-NMR Spectrum of **3.11**

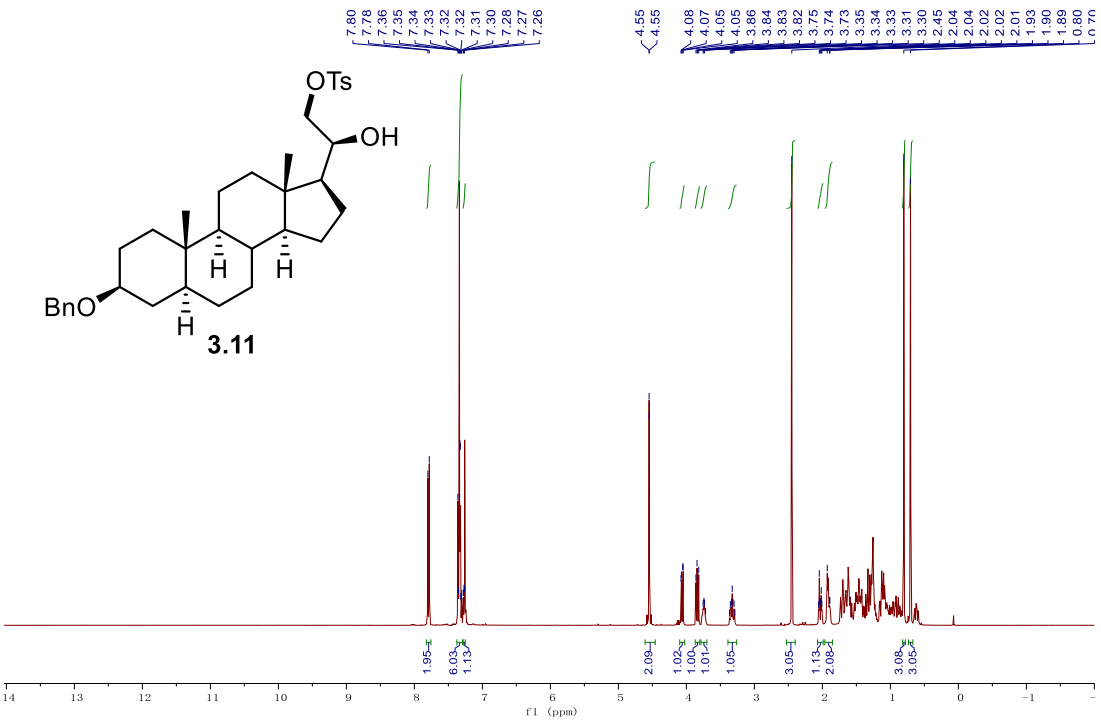


Figure 3.226 ^{13}C-NMR Spectrum of **3.11**

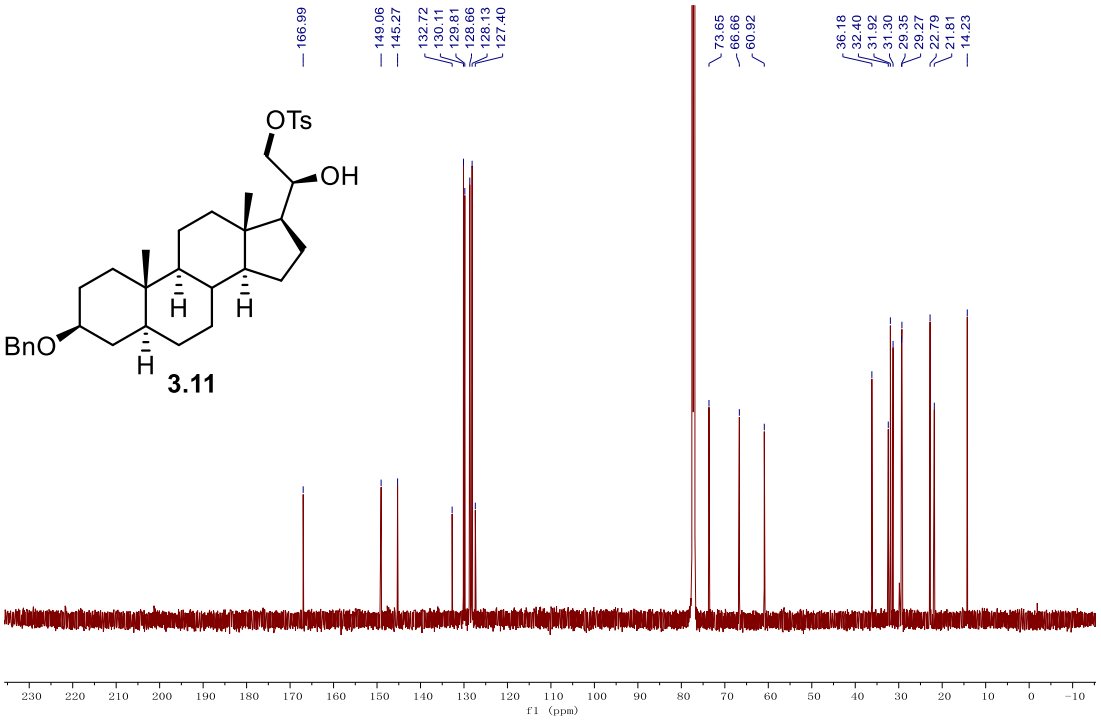


Figure 3.227 ^{1}H-NMR Spectrum of **3.12**

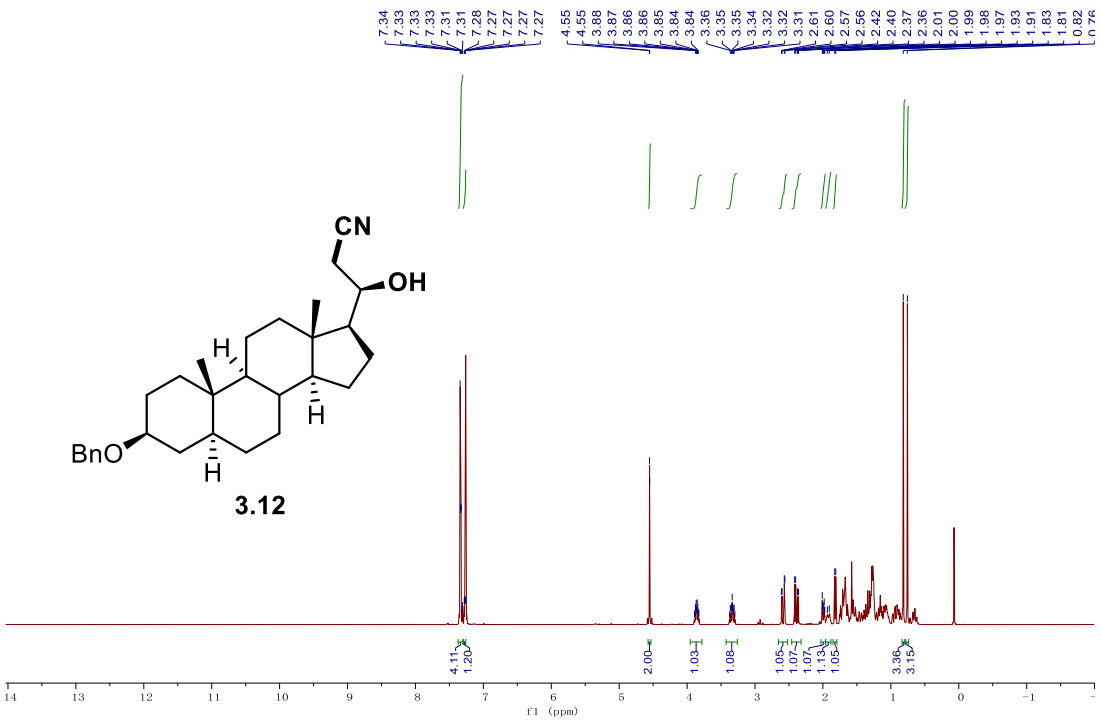


Figure 3.228 ^{13}C-NMR Spectrum of **3.12**

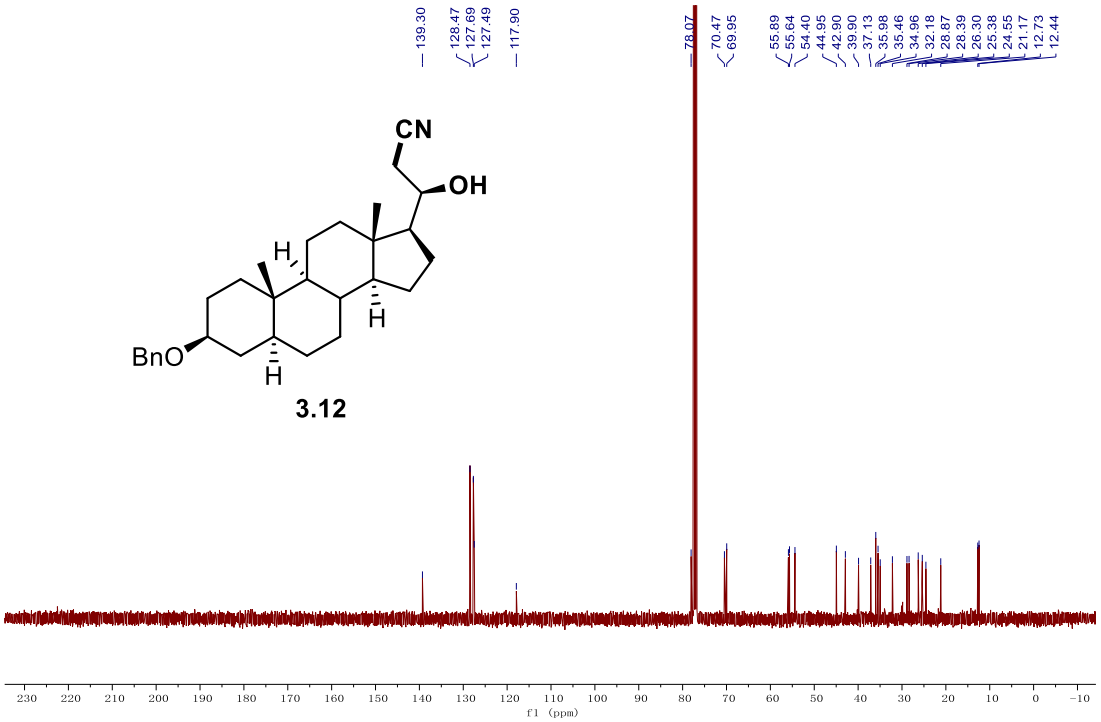


Figure 3.229 ^{1}H-NMR Spectrum of **3.13ad**

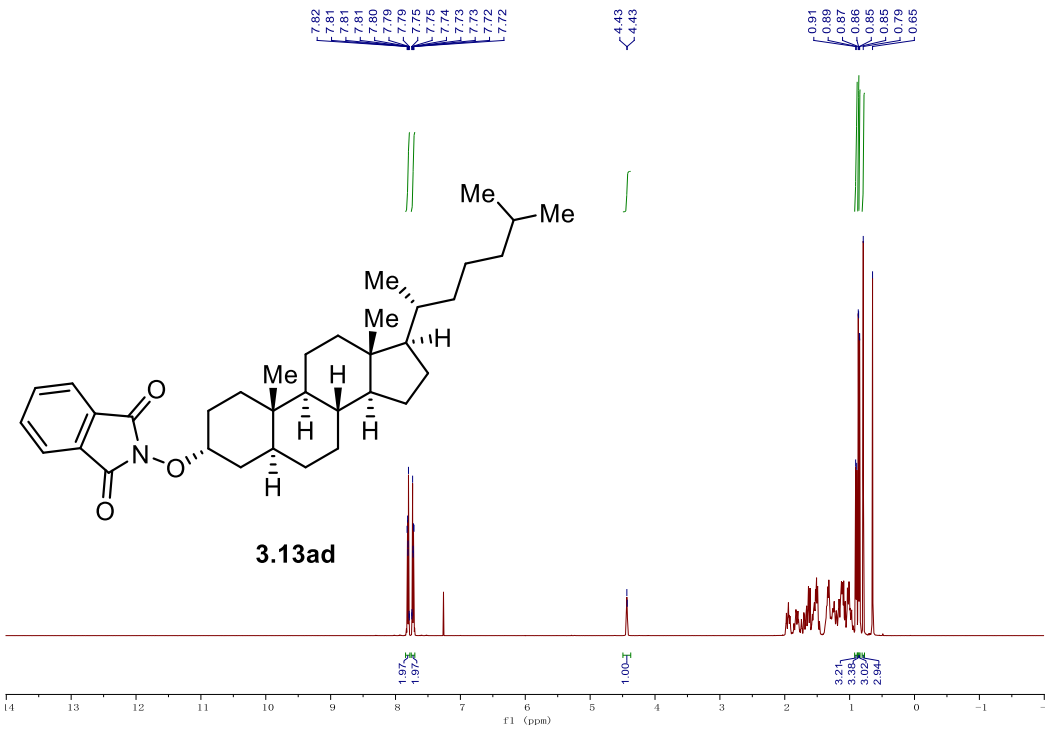


Figure 3.230 ^{13}C-NMR Spectrum of **3.13ad**

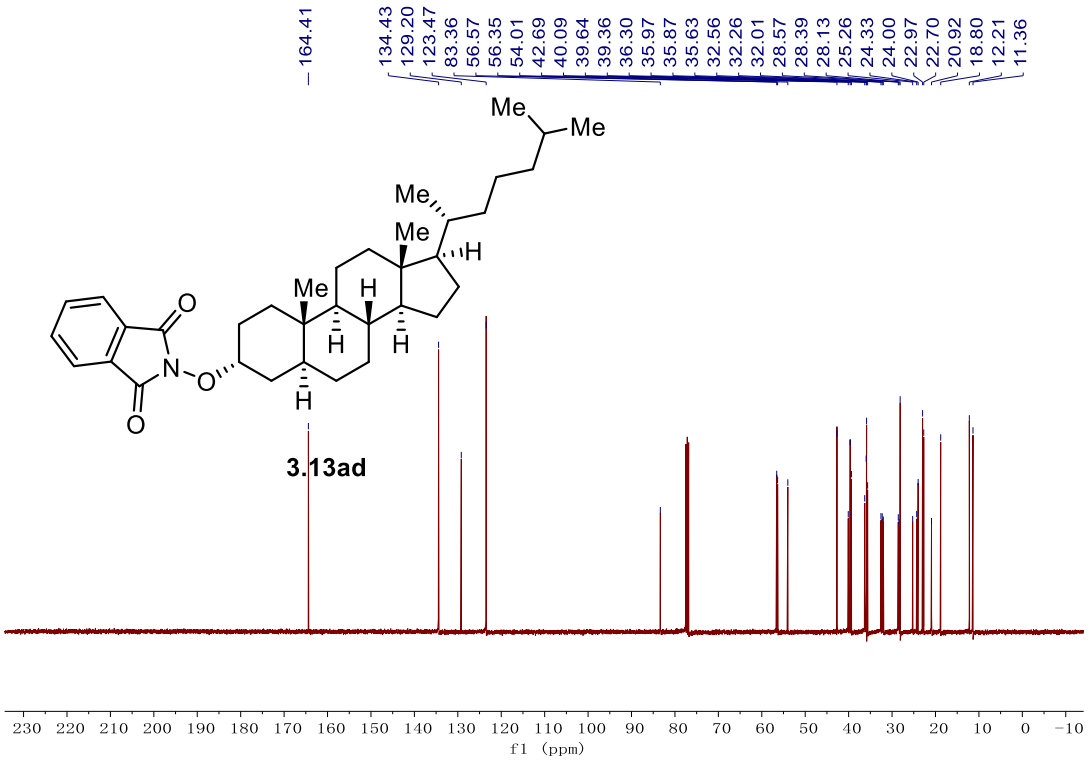


Figure 3.231 NOE(1D) Spectrum of **3.3aa-F**

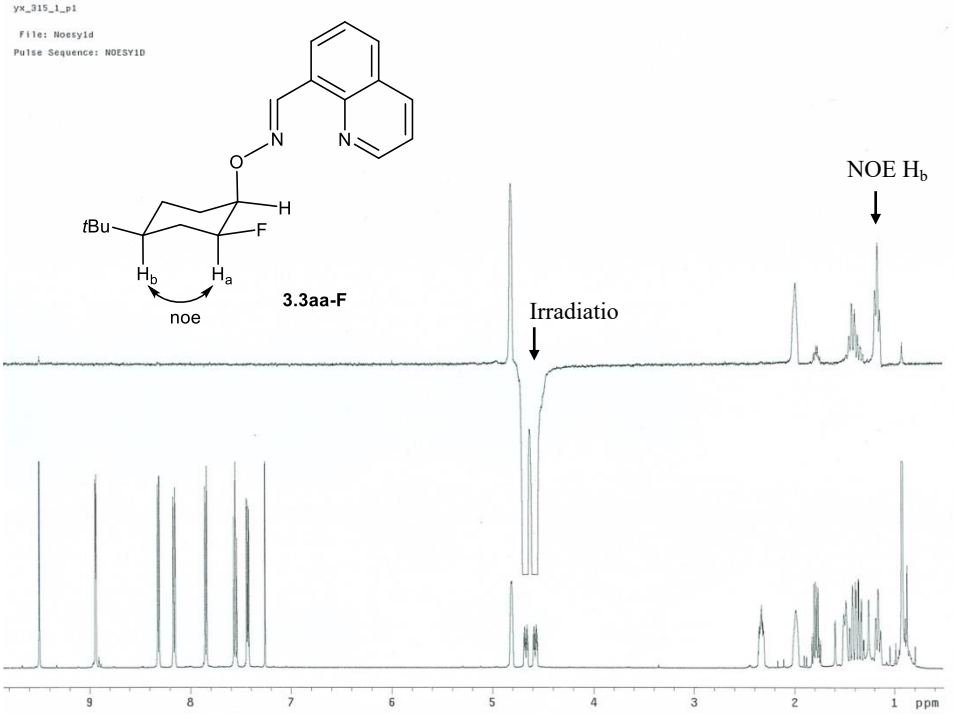


Figure 3.232 COSY Spectrum of **3.3aa-F**

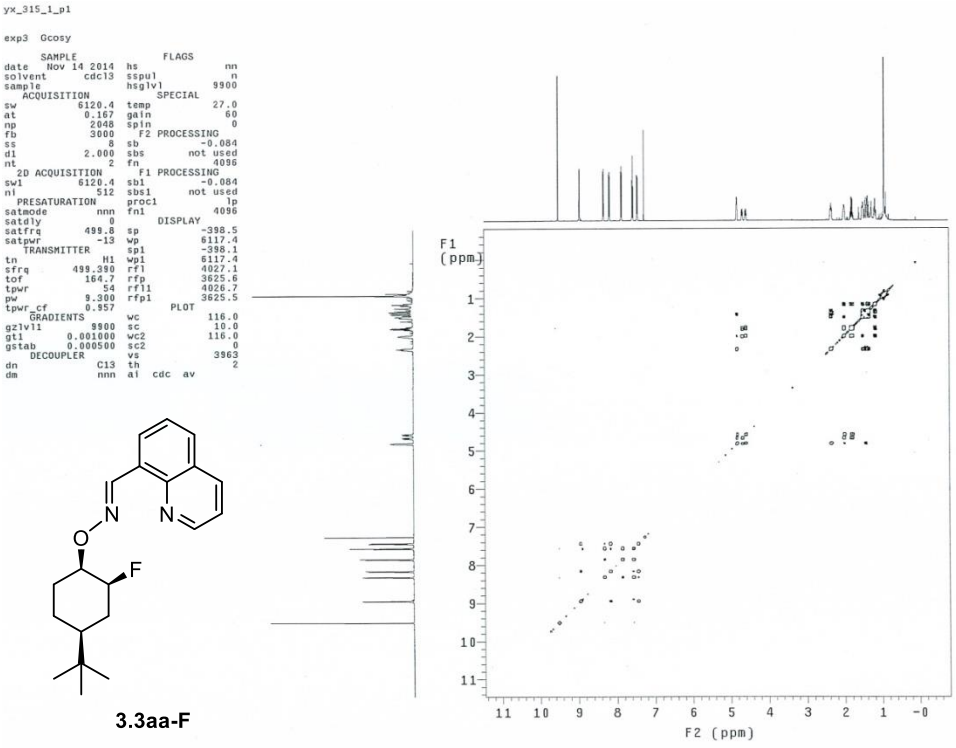


Figure 3.233 NOE(1D) Spectrum of **3.3aa-OTs**

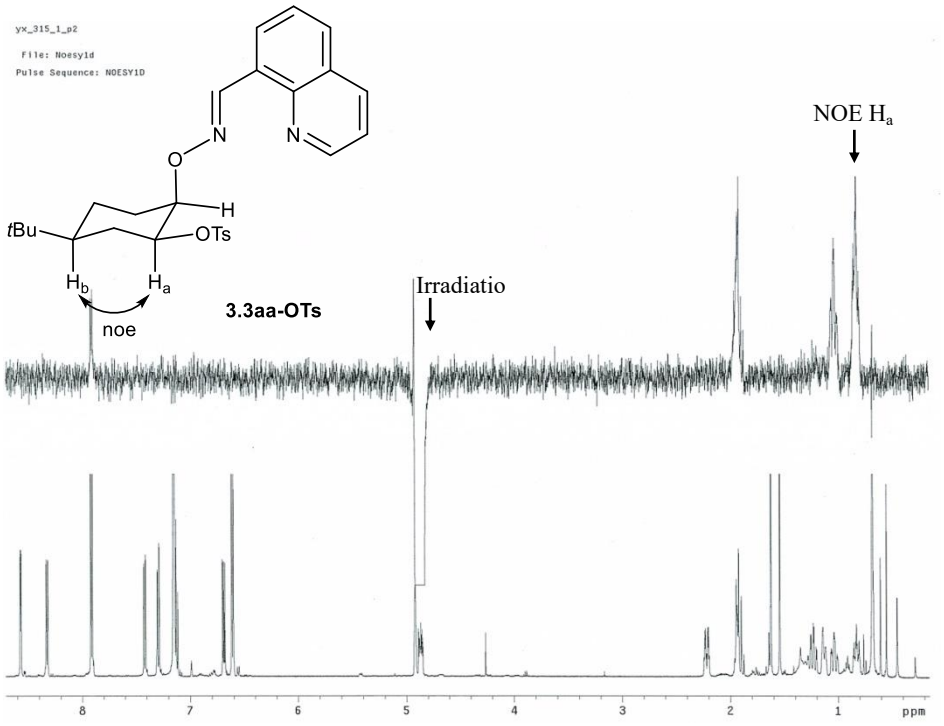


Figure 3.234 COSY Spectrum of **3.3aa-OTs**

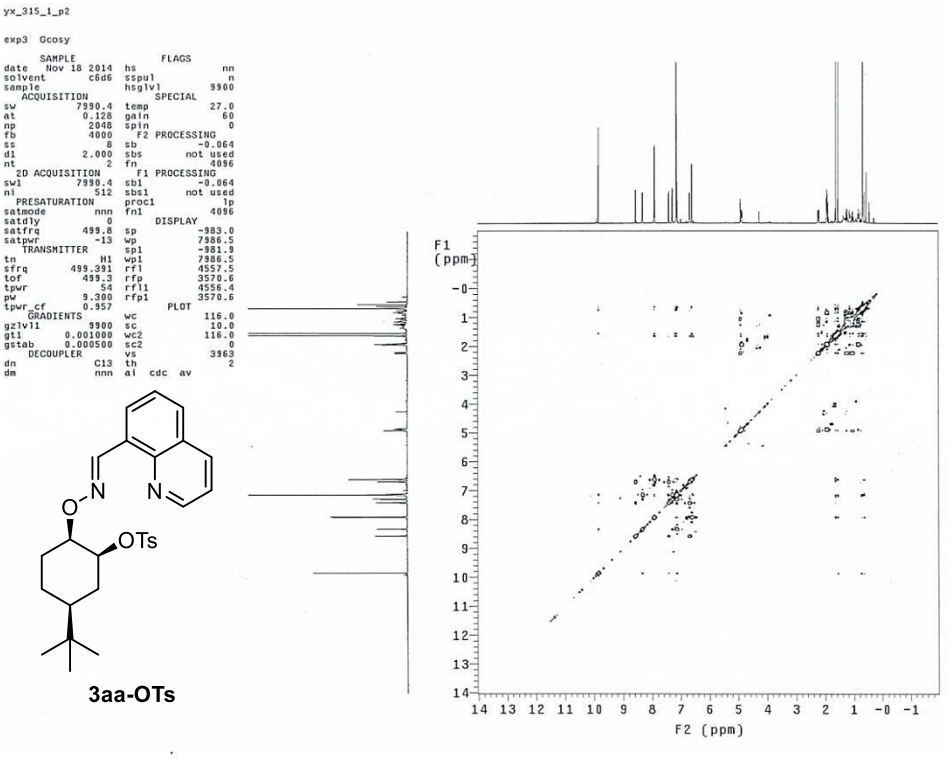


Figure 3.235 NOE(1D) Spectrum of **3.3ab-F**

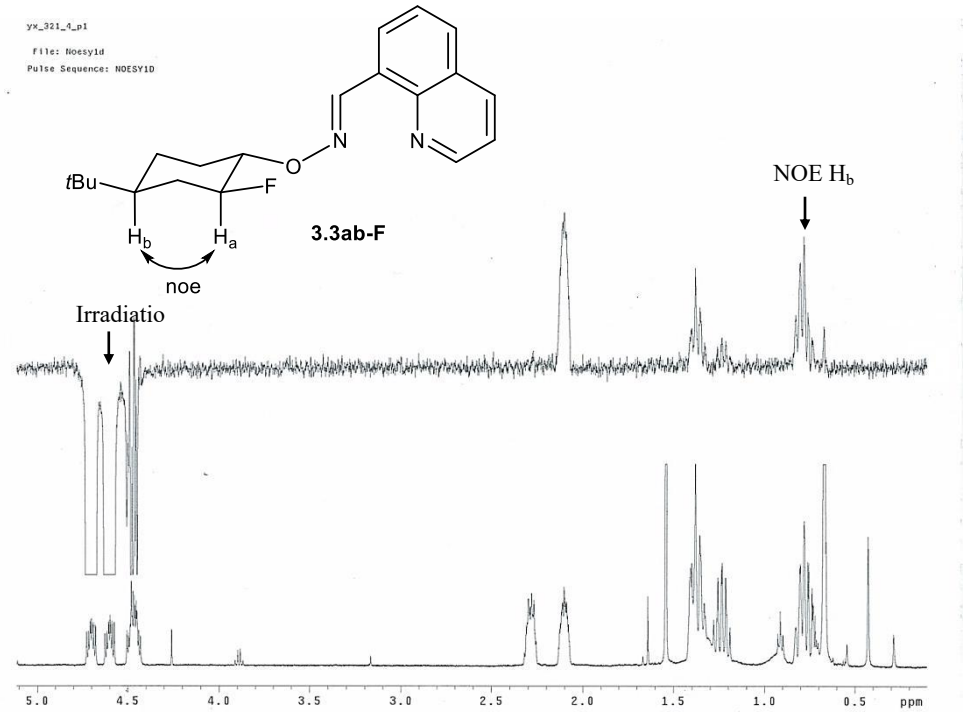


Figure 3.236 COSY Spectrum of **3.3ab-F**

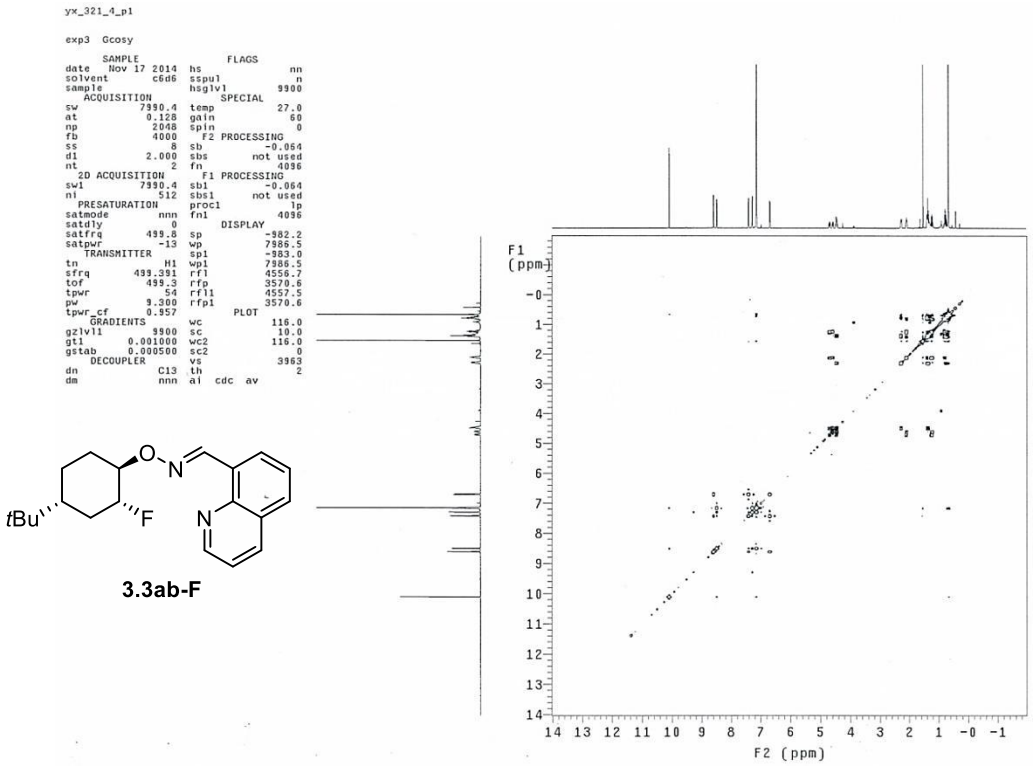


Figure 3.237 NOE(1D) Spectrum of **3.3ab-OTs** (for the Major Isomer)

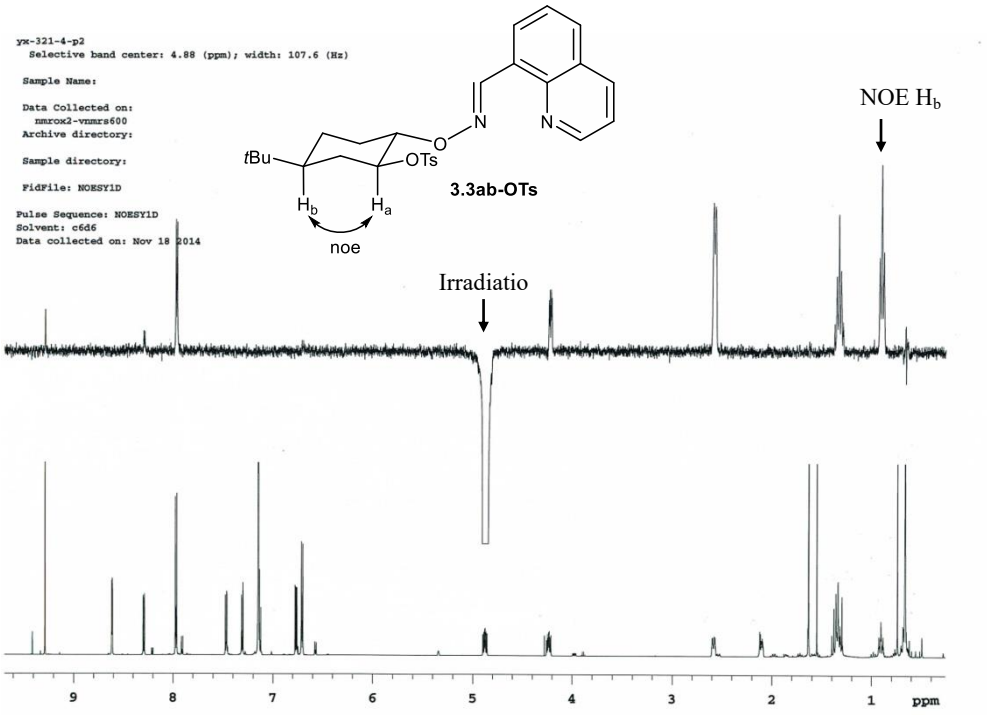
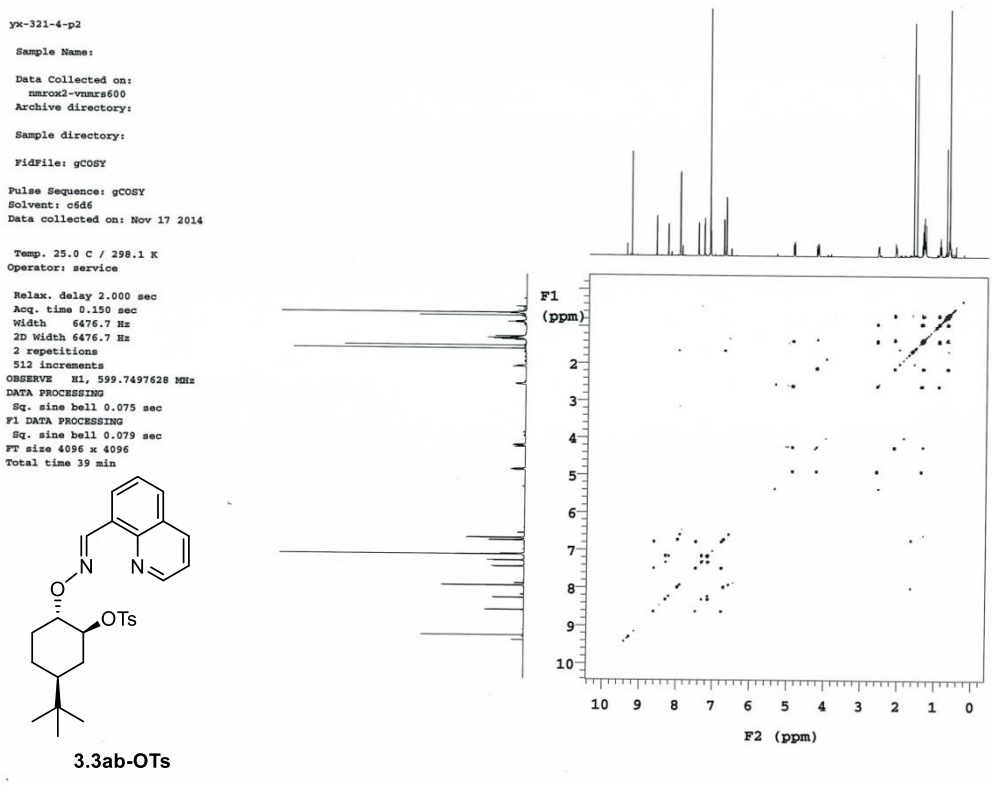


Figure 3.238 COSY Spectrum of **3.3ab-OTs** (for the Major Isomer)



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CHAPTER 4

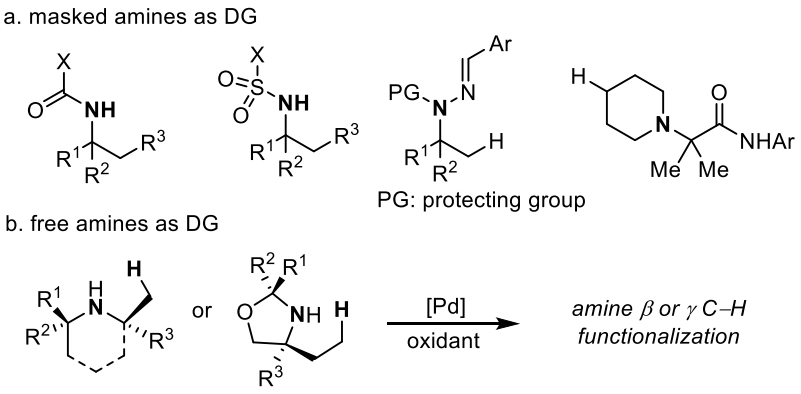
Pd-Catalyzed sp^3 C−H Arylation of Free Primary Amines

4.1 Introduction

Amines are commonly found in approved drugs, agrochemicals and other biologically important molecules.[1,2] While it remains an ongoing challenge, site-selective functionalization of amine unactivated C−H bonds[3] would offer a straightforward approach to access various derivatives and analogues, which should consequently impact pharmaceutical and agrochemical development. During the past decade, significant progress has been achieved for transition metal-catalyzed functionalization of unactivated aliphatic C−H bonds in amines by using directing group (DG) strategies,[4] in which the amine moiety is often masked as amides,[5,6] sulfonamides,[7] hydrazones,[8] and ureas,[9] or tethered with another DG[10] (Scheme 4.1a). Although highly effective, these tactics typically require additional steps for installation and removal of the DG component. An ideal approach would directly employ a

free amine as the DG. Recently, elegant work by Gaunt and coworkers disclosed the first examples of free amine-directed catalytic activation of primary C−H bonds (Scheme 4.1b), whereas use of bulky disubstituted amine substrates appears to be important.[11] It is likely that the main difficulties of directly using a free amine as DG comes from the lack of back bonding when coordinating with transition metals as well as the susceptibility of amines to both oxidants and electrophiles.[12] Stimulated by the aforementioned challenge, we sought the use of an *in situ* generated *exo*-type DG for direct C−H activation of free primary amines. In this chapter, a new palladium-catalyzed direct arylation of unactivated aliphatic C−H bonds of free primary amines was discovered. By taking advantages of an *exo*-imine-type of directing group (DG) that can be generated and removed *in situ*, a range of unprotected aliphatic amines could undergo site-selective arylation at the γ position.

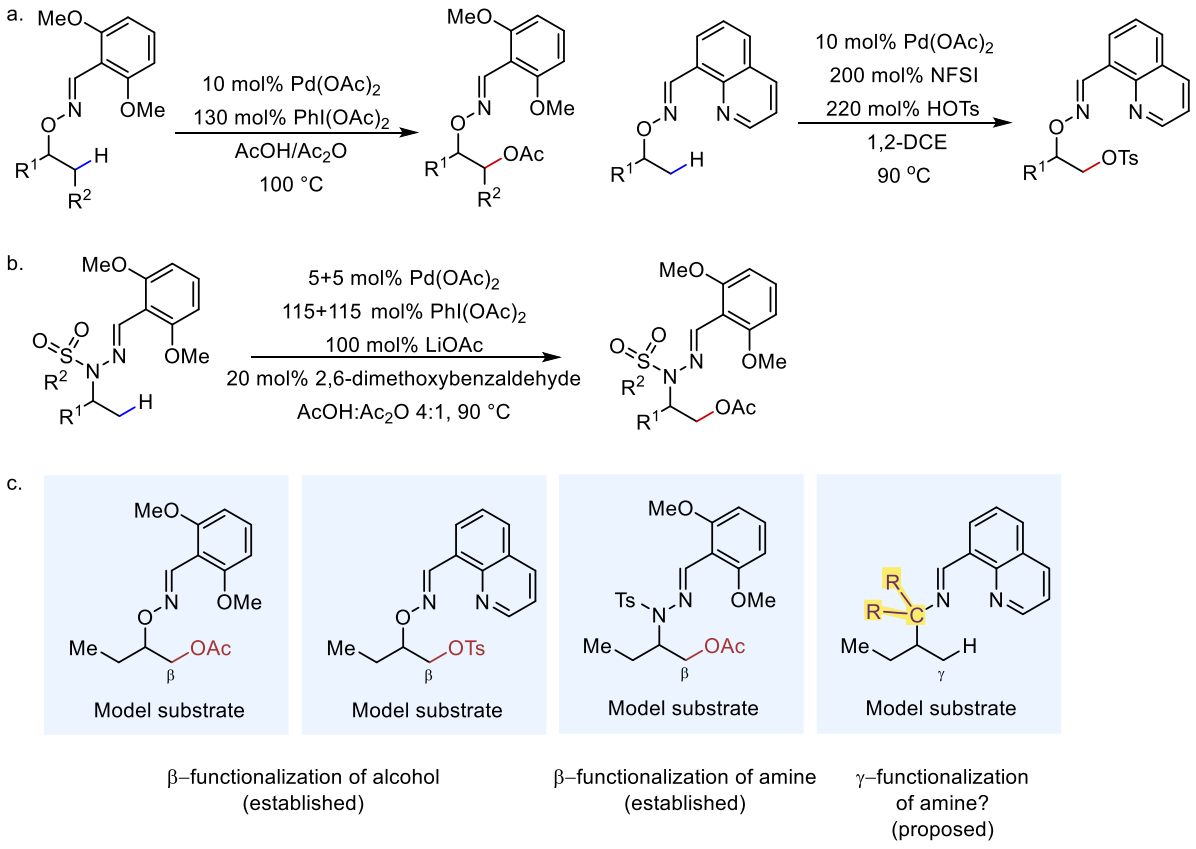
Scheme 4.1 Known DG-based Strategies for Amine C(sp^3)−H Functionalization



4.2 Results and Discussion

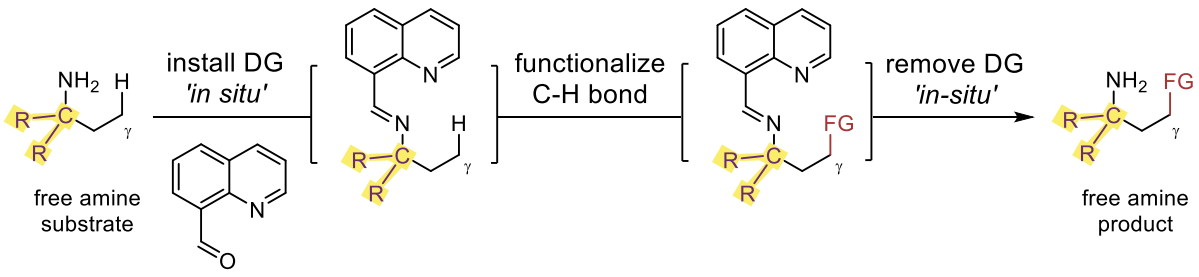
Our laboratory has previously employed an *exo*-directing mode to realize catalytic functionalization of unactivated aliphatic C−H bonds with oximes[13] (Scheme 4.2a) and hydrazones[8] (Scheme 4.2b). In each case, the iminyl group functioned as a nitrogen-based directing arm, and was 'anchored' onto the aliphatic chain through either an oxygen or a nitrogen atom as a linker. Thus, an intriguing question is whether a regular imine can be employed as an effective *exo*-DG for sp^3 C−H activation, in which case the 'linker' would be a carbon atom (Scheme 4.2c).

Scheme 4.2 Established and Proposed *exo*-DG Strategies for C(sp^3)−H activation



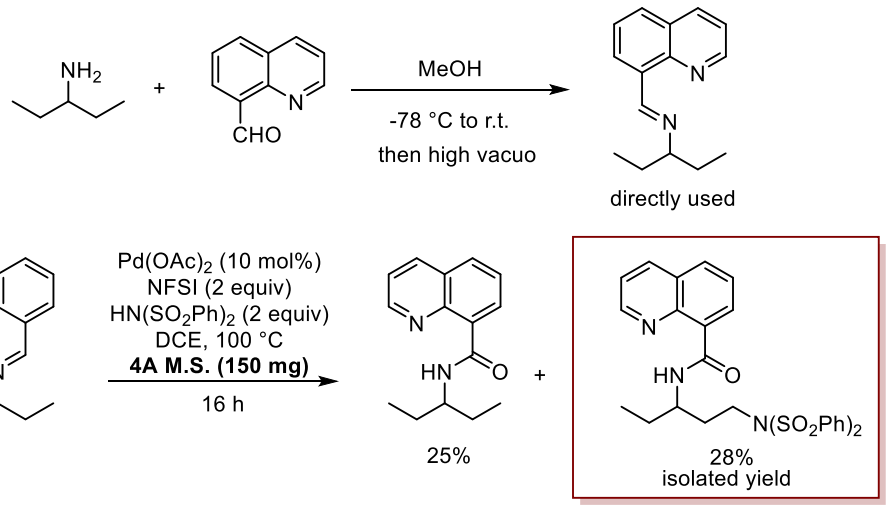
Compared to oximes and hydrazones, *N*-alkyl imines are generally more labile towards hydrolysis; however, successful realization of such a transformation would allow free amines to be used as substrates for remote C−H functionalization through *in situ* formation and removal of the imine DG (Scheme 4.3).[14-16] Seminal examples using aniline-derived imines as *exo*-DGs were reported by Sames and coworkers in the total synthesis of rhazinilam[17] and the core of teleocidin B4,[18] involving stoichiometric platinum and palladium for dehydrogenation, vinylation and carbonylation reactions (see Chapter 1 for details).

Scheme 4.3 *in situ* Formation and Removal of the Imine DGs



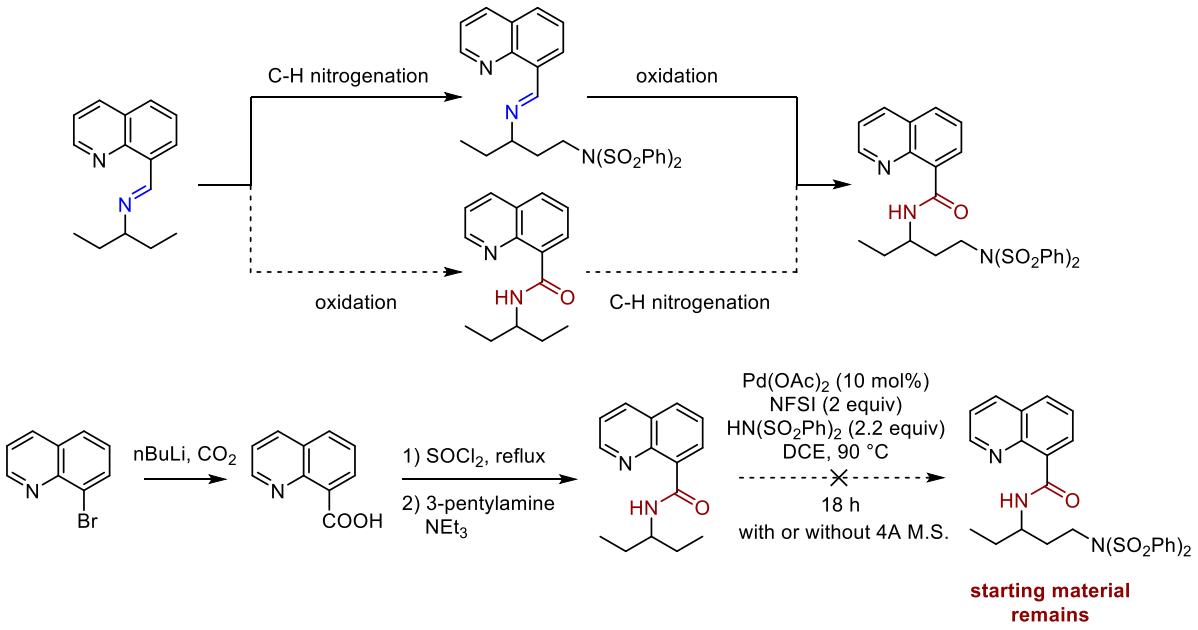
We initiated our study by treating a pre-condensed imine substrate with the tosyloxylation condition ($Pd(OAc)_2$, NFSI, TsOH) that was developed in the previous Chapter (see Chapter 3). Unfortunately, the imine susbtrate was majorly decomposed under such a strong acidic condition and no desired product was ever observed. To our delight, by replacing the TsOH with a less acidic $HN(SO_2Ph)_2$, the γ-nitrogenation product was observed in 28% yield. However, the imine motif was also oxidized into an amide.

Scheme 4.4 the Initial Hit of the Reactitity



Given that amides were commonly used as directing groups to promote sp^3 C−H activation, two reaction pathways were proposed. In the first case, the oxidation of the imine occurred after the C−H nitrogenation, in which the imine indeed served as the directing group. Alternatively, the oxidation took place first, tranfering the imine into an amide, and was then followed by an amide-directed C−H activation. To further distinguish between the two pathways, the corresponding amide was synthesized and treated with the identical reaction condition. No γ-nitrogenation product was observed, which strongly suggested that an imine, instead of an amide, served as the directing group in this transformation (Scheme 4.5).

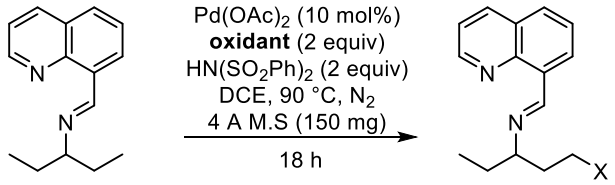
Scheme 4.5 Proposed Reaction Pathways for the γ C−H Nitrogenation



To avoid imine oxidation, a group of oxidants that are weaker then NFSI but still captable for Pd(II)-Pd(IV) oxidation was sequentially tested. To our delight, a trace amount of arylation product was observed when MesI(*p*-tol)OTf was used as the oxidant (Scheme 4.6a). A working hypothesis of the arylation mechanism was depicted in Scheme 4.6b through concerted metalation-deprotonation (CMD) followed by oxidation with the aryl electrophile and then reductive elimination.

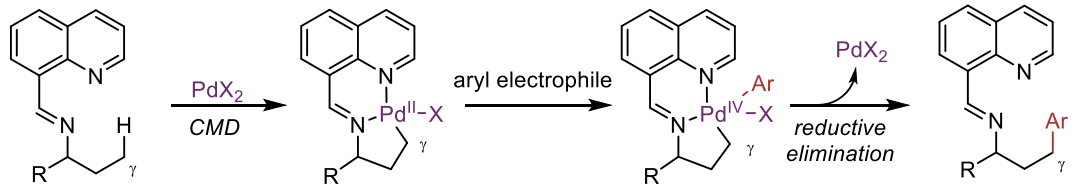
Scheme 4.6 Discovery of the γ C−H Arylation Reaction

a.



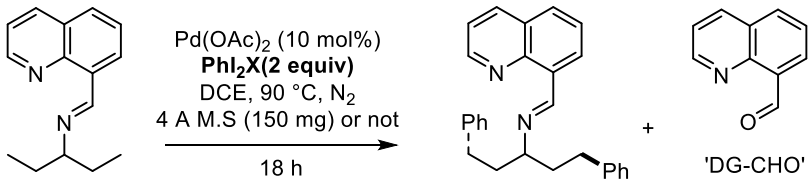
entry	oxidant	result
1	Togni reagent	>80% sm remains
2	IBX	messy
3	oxone	67% sm remains
4	KPS	45% sm remains
5	MesI(*p*-tol)OTf	trace arylation product, 56% sm remains

b. working hypothesis of the arylation mechanism



A group of different aryl iodonium salts was then synthesized and tested. With aryl iodonium salts, $HN(SO_2Ph)_2$ was in general found unnecessary and harmful to the reactions. The Ph_2IX salt was found more reactive than the MesI(Ph)X and led to higher conversions. A detailed screening was performed for Ph_2IX salts with different counter anions. While significant difference was not observed among these salts, the Ph_2INTf_2 was found the best, affording 52% overall yield and very satisfying mass balance (Scheme 4.7).

Scheme 4.7 Screening of Different Aryl Iodonium Salts



entry	Oxidant	M.S.	rsm*	mono-pro*	di-pro*	DG-CHO	yield	*brsm*
1	Ph_2IOTf	+	37+7	28+4	3+1	11	36	*64*
2	Ph_2IBF_4	+	18	38	9	10	47	*57*
3	Ph_2IPF_6	+	40	40	--	3	40	*67*
4	Ph_2INTf_2	+	35	38	10	3	48	*74*
5	Ph_2IOTf	-	35+12	28+8	5+1	--	42	*79*
6	Ph_2IBF_4	-	35	38	11	--	49	*77*
7	Ph_2IPF_6	-	30+5	33+5	9+2	--	49	*77*
8	**Ph_2INTf_2**	-	38+7	34+6	10+2	--	52	*95*

* x+y, x: as protonated imine, y: as protonated amine or unprotonated imine. rsm: recycled starting material

Noting that one equivalent of strong acid was generated during the course of the reaction, we hypothesized that the addition of a proper base might neutralize the acid, liberate the directing pyridine from its protonated form, and thus promote the full conversion of the starting material. Extensive screening over a variety of inorganic and organic bases was performed. However, most of the commonly used bases showed no or negative effects to the reaction. Interestingly, the conversion could be improved by using insoluable $Ca(OH)_2$ or $Ba(OH)_2$. Further improvement was achieved by using the bulkyl non-coordinative 2,6-di-*tert*-butylpyridine (**4.2**). A brief screening over acidic additives and ligands was also performed. Unfortunately no positive result was obtained (Scheme 4.8).

Scheme 4.8 Screening of Different Bases, Acids and Ligands

Base Screened:

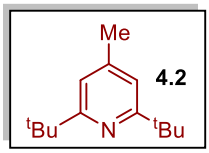
no or negative effect:

LiOAc·	KOAc	$CaCO_3$	KF	MgO	Pyridine	
NaOAc	Li_2CO_3	Ag_2CO_3	KH_2PO_4	CaO	TMP	NaOTs
KOAc	Na_2CO_3	$NaHCO_3$	K_2HPO_4	LiOH	*N*-Me-TMP	KOTs
AgOAc	K_2CO_3	NaF	K_3PO_4	$Mg(OH)_2$	Hunig base	
CsOPiv	Cs_2CO_3	CsF	NaO^{t}Bu	Pyridine	2,6-lutidine	

positive effect:

$Ca(OH)_2$

$Ba(OH)_2$



Acid Screened:

no or negative effect: PivOH AcOH PhCOOH MesCOOH AdCOOH $(BnO)_2PO_2H$

Ligand Screened:

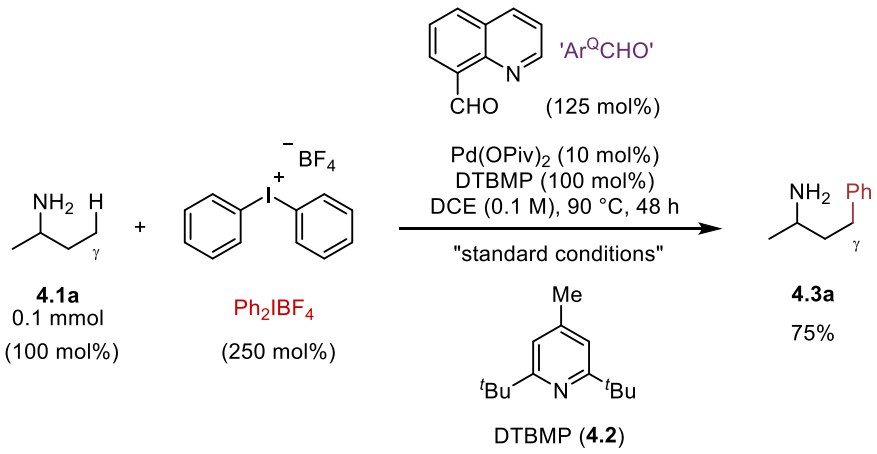
no or negative effect: BQ $AsPh_3$ $SbPh_3$ Ac-Gly-OH Ac-Val-OH MeCN DMF

The optimal condition was finally identified using simple 2-butylamine **4.1a** as a model substrate. Quinoline-8-carbaldehyde (Ar^QCHO) was still employed as the additive to *in situ* generate the imine DG. After further examining a range of palladium precatalysts and solvent combinations, the desired γ-arylation product (**4.3a**) can be obtained in 75% yield when using $Pd(OPiv)_2$ as the precatalyst, Ph_2IBF_4 as the aryl electrophile, base **4.2** as an additive, and dichloroethane (DCE) as the solvent (entry 1, Table 4.1). It is worth noting that the C−H arylation occurred site-selectively at the γ-position; no β arylation was observed, likely due to the preference of forming 5-membered palladacycle.

A series of control experiments were subsequently conducted (Table 4.1). In the absence of either the palladium precatalyst or quinoline-8-carbaldehyde, no desired product was observed (entries 2 and 3). The yield significantly diminished when the reaction was run under air or at a lower temperature (entries 4 and 5). Use of $Pd(OAc)_2$ instead of $Pd(OPiv)_2$ gave comparable results (entry 6). As shown previously, the counterion of the iodonium salts slightly affects the efficiency of this transformation, with the BF_4 one proven to be optimal

under this condition (entries 7 and 8). DCE was proved to be the best solvent (entries 10 and 11). The reaction was tolerant of the stoichiometric addition of water (entry 12).

Table 4.1 Optimal Conditions and Control experiments for the γ-Arylation of Amine **4.1a**



Entry	Variations from the "standard conditions"	Yield of **4.3a** [%][a,b]	Unreacted **4.1a** [%][a,b]
1	**none**	**75**	**10**
2	no $Pd(OPiv)_2$	0	73
3	no Ar^QCHO	0	50
4	under air	36	18
5	at 70 °C	< 10	74
6	$Pd(OAc)_2$ instead of $Pd(OPiv)_2$	71	7
7	Ph_2IOTf instead of Ph_2IBF_4	61	24
8	Ph_2IPF_6 instead of Ph_2IBF_4	65	18
9	$Ba(OH)_2$ instead of **2**	56	23
10	in $CHCl_3$	41	29
11	in PhCl	24	54
12	H_2O (1 equiv) was added	70	15

[a] Determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard. [b] Sum of the protonated amine and the corresponding imine condensed with Ar^QCHO.

With the optimized conditions in hand, the substrate scope of the γ-arylation was explored (Table 4.2). While arylated free amine products can be isolated upon workup of the reaction (*vide infra*, Scheme 4.10), for ease of isolation and also due to the volatility of the alkyl amines, all of the products were isolated here as the benzoylamide derivatives. Aryl groups with various electronic properties were installed under the reaction conditions (**4.4a-**

h). In addition, primary, secondary and tertiary alkyl amines are all suitable substrates for this reaction (**4.4i-l**). Moreover, a number of functional groups were found compatible, including electron-rich arenes (**4.4g**, **4.4q** and **4.4r**), benzyl ethers (**4.4o**, **4.4s**, and **4.4t**), methylenedioxy (**4.4r**), cyano (**4.4s**) and nitro (**4.4t**) groups. It is noteworthy that aryl chlorides (**4.4p**), bromides (**4.4c**), and iodides (**4.4d**), although known to undergo Pd-catalyzed arylation reactions,[5-7] are tolerated with this catalytic system, allowing them to be used as a handle for further functionalization. Remarkably, both cyclic and acyclic methylene C−H bonds can be arylated with good efficacies (**4.4u-w**).

Table 4.2 Substrate Scope with Various Alkyl Amines[a]

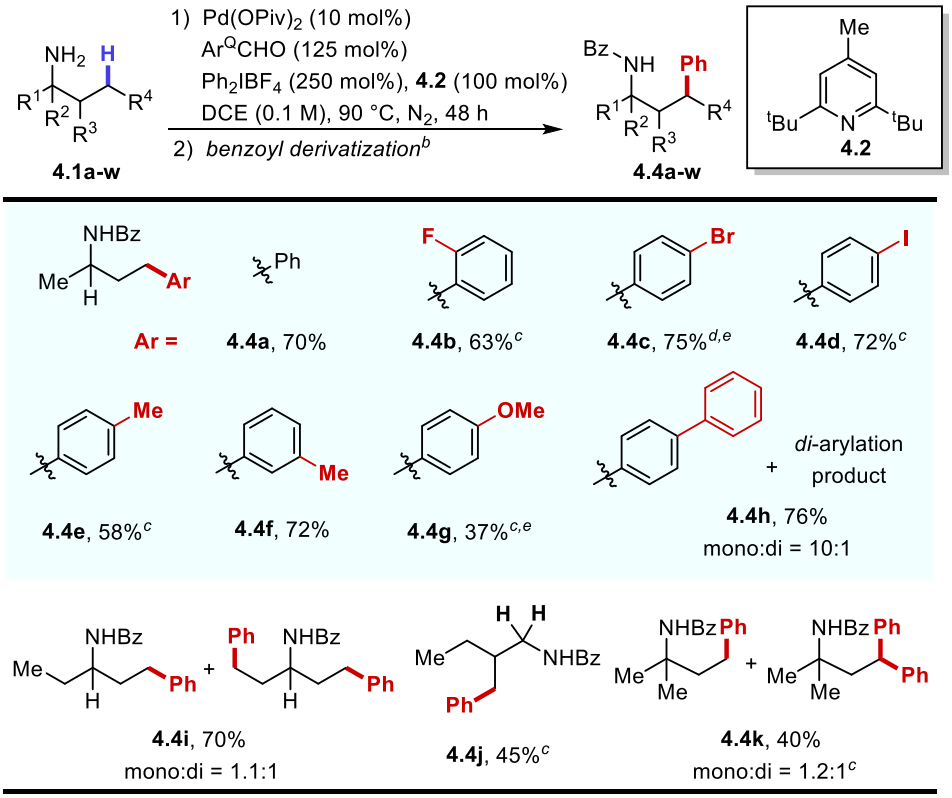
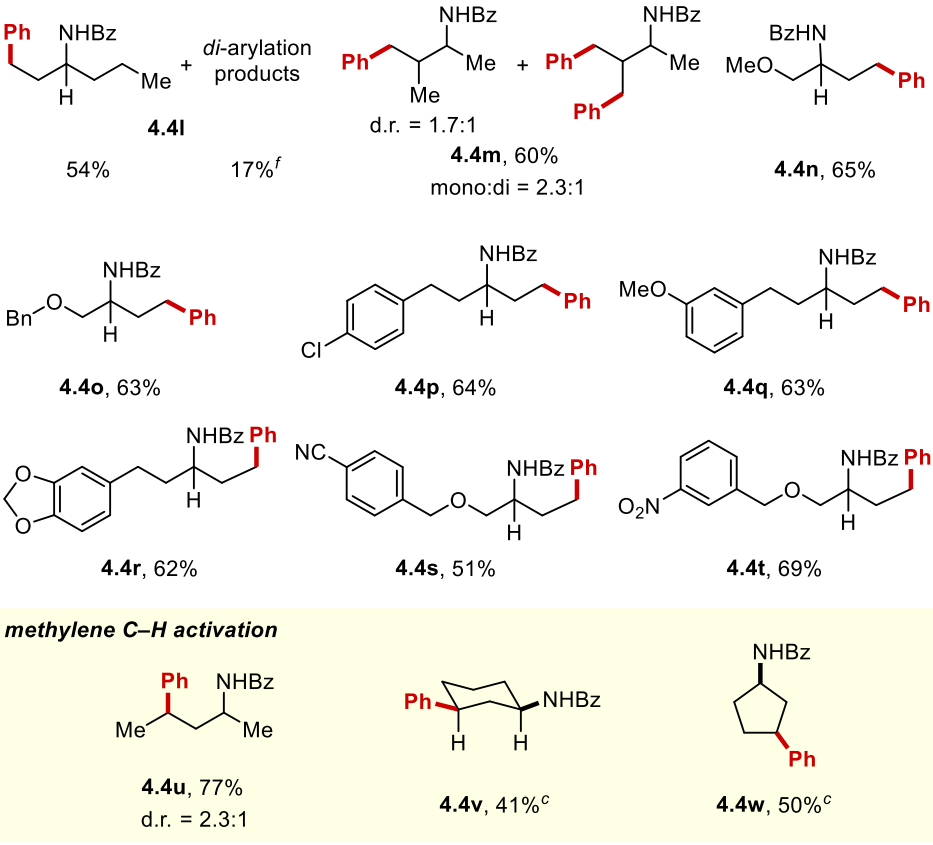


Table 4.2 Substrate Scope with Various Alkyl Amines[a] (Continued)

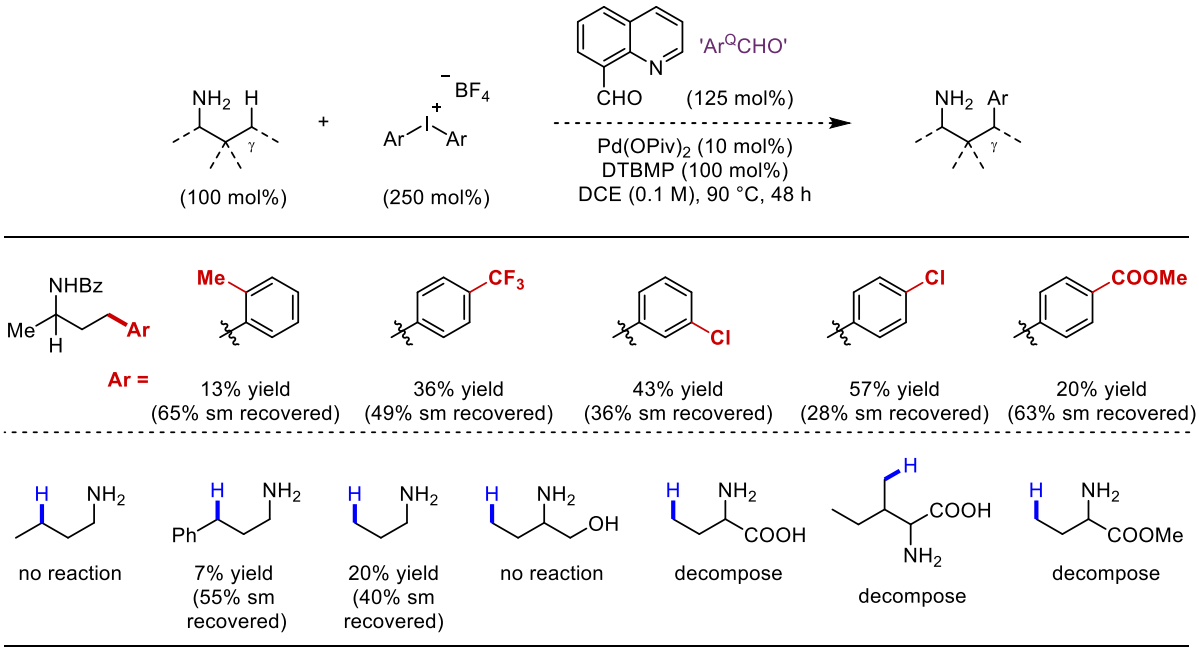


[a] All yields are isolated yields. Unless otherwise noted, the *gem* diarylation products were less than 5%. [b] Benzoylation procedure: $MeONH_3Cl$ (4.0 equiv.), NEt_3 (0.3 mL), r.t., 2h, then Bz_2O (8.8 equiv.), r.t., 12h. [c] 100 ºC. [d] 105 ºC. [e] 64h. [f] 1,1-and 1,5-diarylation products were isolated with a ratio of 1:4. The d.r. for the 1,5-diarylation products is 3:1.

Not very surprisingly, bis(aryl)iodonium salts bearing *ortho* substitution reacted poorly due to increased steric. However, interestingly, several other aryl electrophiles with no *ortho* substitutions could not perform very well in the reactions as well. While the detailed reason remained unknown, we suspected that the moderate conversions observed in these reactions were caused by the poor solubility of the corresponding iodonium salts (Table 4.3).

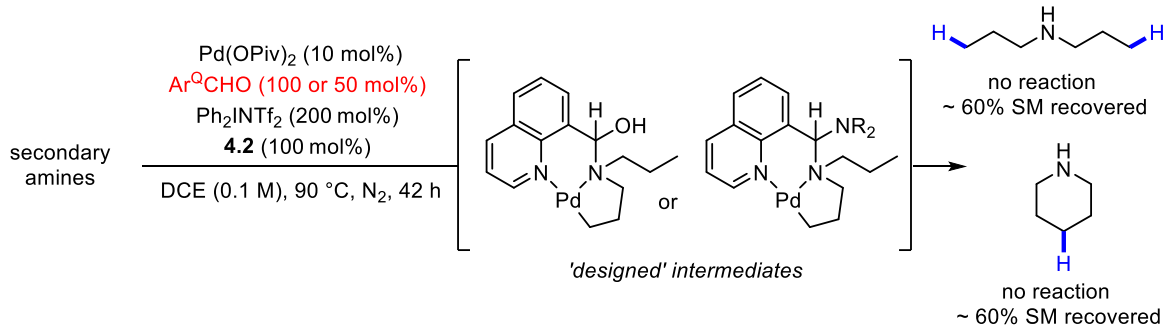
Amines bearing primary α-carbons generally demonstrated decreased reactivities, possibily duo to the increased flexibility around the carbon skeletons. Besides, β-amino acids or β-amino alcohols were not compatible, leading to totally decomposition or no reaction.

Table 4.3 Examples of Failed Substrates



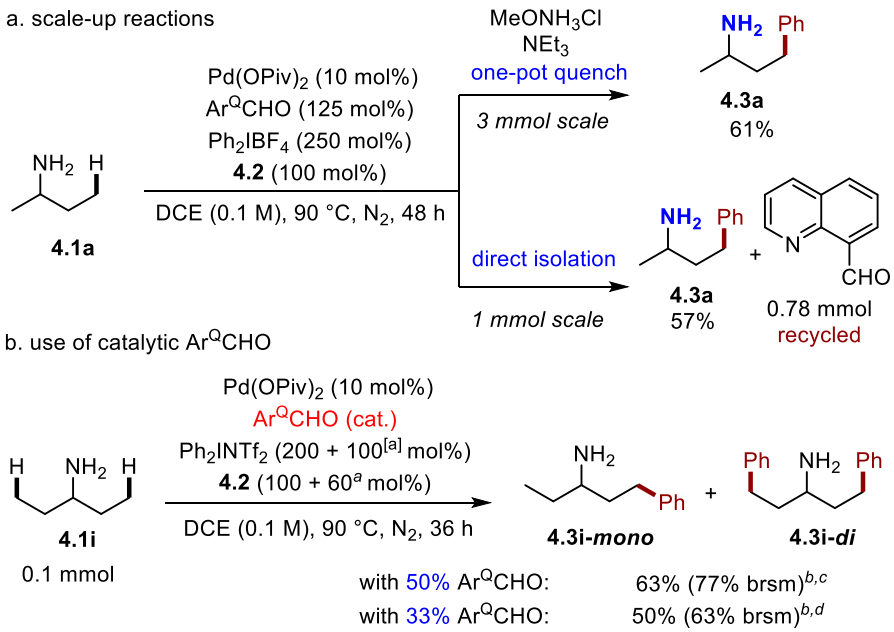
The feasibility of using secondary amines as substrates was briefly examined (Scheme 4.9). Though imine could not be formed, we envisioned that the alkyl nitrogen atoms on a hemiaminal or an aminal might be capable to serve as the directing group. Following the assumption, both linear and cyclic secondary amines were tested. However, no desired product was observed.

Scheme 4.9 Screening of Different Bases, Acids and Ligands



Nevertheless, the isolation of the free amine products proved to be feasible. For example, after a simple workup with methoxyamine, free amine product **4.3a**, though volatile, was isolated in 61% yield on a 3 mmol scale. In addition, direct isolation of **4.3a** from the reaction mixture (without methoxyamine workup) was also viable by chromatography, affording **4.3a** with only slightly decreased yield meanwhile recycling of most $Ar^{Q}CHO$ (Scheme 4.10a). Furthermore, due to the reversibility of imine formation, the use of a catalytic amount of $Ar^{Q}CHO$ was examined. To our delight, moderate catalytic activity was observed, suggesting that imine formation and hydrolysis are compatible under the C−H arylation conditions (Scheme 4.10b). In these cases, the oxidant and base was added in two batches to achieve higher yield.

Scheme 4.10 Further Study on the C−H γ-Arylation



[a] A second batch of the oxidant and base was added at 18h. [b] Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard. The product was observed as a mixture of the protonated amine and the corresponding imine after condensation with Ar^{Q}CHO. [c] mono:di = 1:1.4. [d] mono:di = 1:1.5.

4.3 Conclusions

In summary, we have developed a palladium-catalyzed direct arylation of sp^3 C−H bonds of free primary amines. Using an *in situ* generated imine *exo*-DG, a range of unactivated aliphatic C−H bonds, including methyl, cyclic and acyclic methylene groups, are activated site-selectively. Given the ubiquity of amine functional groups, it is expected that this method would pontentially streamline syntheses of nitrogen-containing compounds. The *in situ*-DG strategy through dynamic covalent interaction should have broader implications beyond the amine C−H activation.

(Some contents of this chapter were published in *Angew. Chem. Int. Ed.*, **2016**, *55*, 9084)

4.4 Experimental

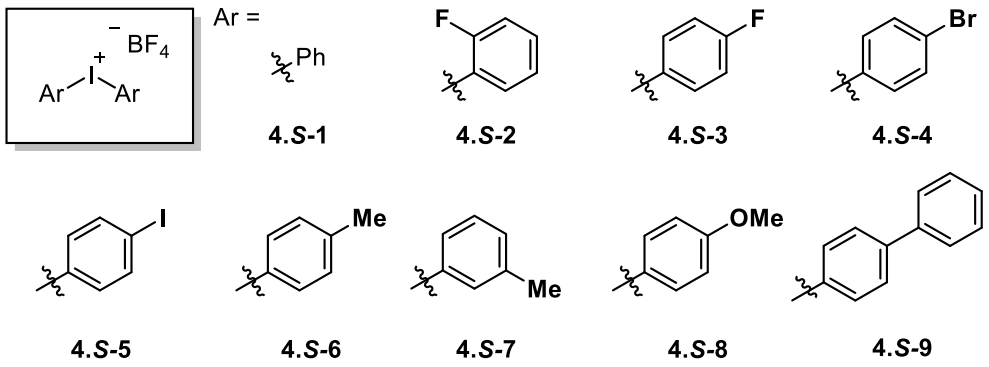
Unless otherwise noted**,** ^{1}H, gCOSY and ^{13}C spectra were recorded on a Varian Inova 400 MHz MHz NMR spectrometer and processed using MestReNova by Mestrelab Research S.L. Proton (^{1}H) chemical shifts are reported in parts per million (δ) with respect to tetramethylsilane (TMS, δ=0), and referenced internally with respect to the protio solvent impurity. Carbon (^{13}C) chemical shifts are reported in parts per million (δ) with respect to tetramethylsilane (TMS, δ=0), and referenced internally with respect to the carbon signal of the solvent. Fluorine (^{19}F) chemical shifts are reported in parts per million (δ) and referenced internally with respect to hexafluorobenzene included in an insert tube (C_6F_6, δ=-164.9). Deuterated NMR solvents were obtained from Cambridge Isotope Laboratories, Inc., Andover, MA, and used without further purification. Mass spectra were recorded on an Agilent 6530 LC Q-TOF mass spectrometer using electrospray ionization with fragmentation voltage set at 115 V and processed with an Agilent MassHunter Operating System. X-ray diffraction data were collected at 100(2) K on a Bruker-Nonius Kappa CCD or Agilent SuperNova AtlasS2 CCD. All other materials were obtained from Aldrich Chemical Company, St. Louis, MO, Combi-Blocks, San Diego, or TCI, Tokyo, Japan and were used as received.

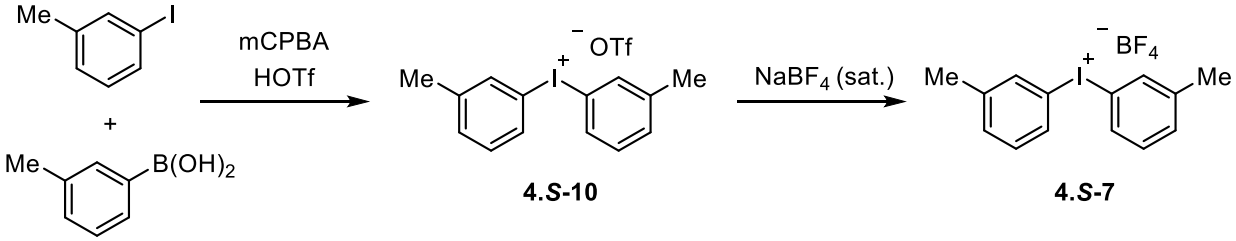
Synthesis of iodonium reagents

The iodonium compounds **4.*S*-1** through **4.*S*-6**[19a] and **4.*S*-8**[19a] and **4.*S*-9**[19b] were prepared according to the previously reported literatures. The iodonium reagents **4.*S*-7** was

prepared according to the following procedures. The others are commercially available and were used as received.

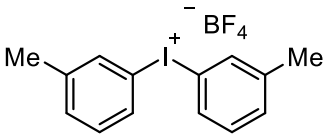
Scheme 4.11 Structures of Iodonium Tetrafluoroborates Synthesized for this Study





Bis(3-(methylphenyl)iodonium Triflate (4.*S*-10): Modifying a known procedure, 3-iodotoluene (2.18 g, 10.0 mmol) was added to DCM (50 mL) along with 70% 3-chloroperoxybenzoic acid (2.70 g, 11.0 mmol), followed by $BF_3{\cdot}OEt_2$ (1.5 mL, 12.5 mmol). After stirring for 1 h, reaction was cooled to 0 ºC, followed by addition of *p*-tolylboronic acid (1.50 g, 11.0 mmol). After 30 min the reaction was warmed to room temperature, and stirring continued. After 1 h the reaction was re-cooled to 0 ºC, followed by drop-wise addition of HOTf (0.90 mL, 10.2 mmol). Reaction was allowed to warm to room temperature, followed by evaporation of volatiles *in vacuo*. The residue was triturated with Et_2O (20 mL) and

cooling to − 20 ºC. The resulting solid was filtered and rinsed with additional Et_2O, then dried to give product as a white solid that was consistent with the previously reported data[20] (2.58 g, 56%). ^{1}H NMR (400 MHz; DMSO-d_6): δ 8.09 (s, 2H), 8.03 (d, J = 7.9 Hz, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 7.8 Hz), 2.34 (s, 3H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 141.8, 135.3, 132.7, 132.2, 131.5, 116.2, 20.8.



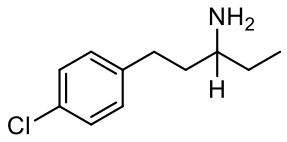
4.*S*-7

Bis(3-(methylphenyl)iodonium tetrafluoroborate (4.*S*-7)[19c]: 4.*S*-10 (900 mg, 2.0 mmol) was dissolved in 50 mL DCM. Saturated aqueous $NaBF_4$ solution (50 mL) was then added, and the mixture was vigorously stirred for 3 h. The organic phase was separated and the water phase was extracted twice with DCM. The combined organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give the tetrafluoroborate product **4.*S*-7** as a white solid (550 mg, 70%).

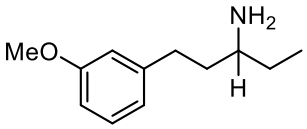
Synthesis of the amine substrates

The amines **4.1p**, **4.1q**, **4.1r**, **4.1s** and **4.1t** were prepared according to the following procedures. The remaining substrates were purchased and used as received.

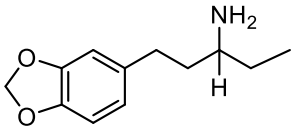
Scheme 4.12 Structures of Amine Substrates Synthesized for this Study



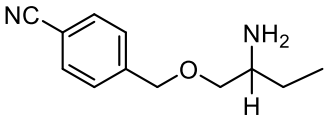
4.1p



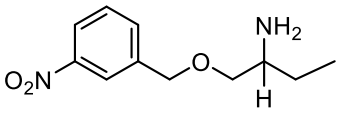
4.1q



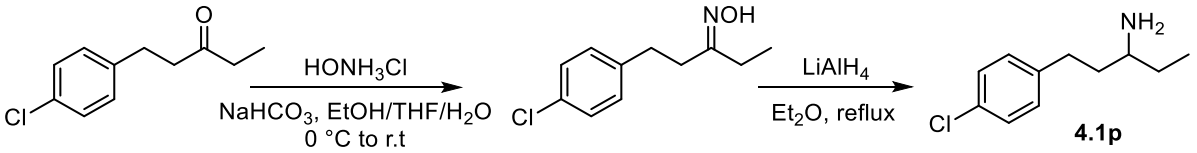
4.1r



4.1s



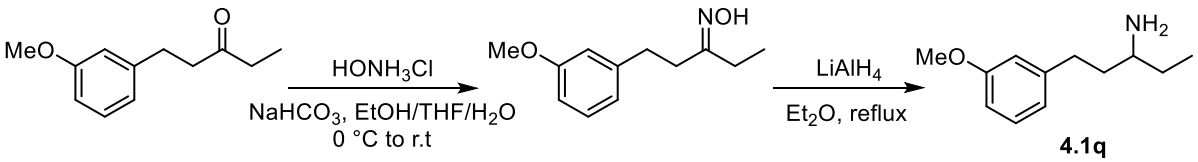
4.1t



4.1p

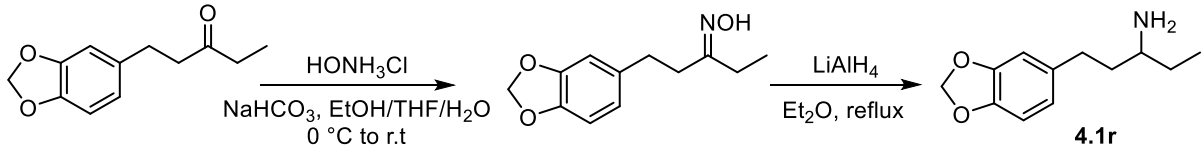
1-(4-Chlorophenyl)pentan-3-amine (4.1p): Following a slightly modified procedure,[21] 1-(4-chlorophenyl)pentan-3-one[22] (400 mg, 2 mmol) was combined with hydroxylamine hydrochloride (280 mg, 2 mmol) in mixed solvent of EtOH/THF/H_2O (2.4 mL/1.2 mL/ 0.6 mL), followed by batchwise addition of $NaHCO_3$ at 0 ºC. The reaction was then stirred at room temperature overnight. The mixture was filtered and the filter cake was washed with EtOAc. The filtrate was diluted with EtOAc (8 mL) and washed by H_2O (2 mL) and brine (2 mL). The organic phase was dried over $MgSO_4$ and then concentrated *in vacuo*. The crude oxime was directly used for next step without further purification. At 0 ºC, to a stirred suspension of $LiAlH_4$ (152 mg, 4 mmol) in dry Et_2O (8 mL) was added the oxime (422 mg, 2 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and heated at reflux for 6 h. Then the reaction mixture was cooled to 0 ºC and carefully quenched via sequential addition of H_2O (1 mL), 10% aqueous NaOH (1 mL) and H_2O (2 mL). After stirred at room temperature for 15 min, the mixture was filtered and the filter cake was

washed with Et_2O. The filtrate was dried over $MgSO_4$ and then concentrated *in vacuo*. The crude mixture was then purified by column chromatography over silica (5:1:1 hexanes/EtOAc/DCM to 3:1:1:0.25 hexanes/EtOAc/DCM/NEt_3) to give the product as a colorless oil (290 mg, 74%). R_f = 0.2 (Hex/EA/DCM/NEt_3 = 3:1:1:0.2). IR (KBr) 3365, 2931, 1574, 1492, 1093, 819 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 2H), 7.14 – 7.09 (m, 2H), 2.76 – 2.57 (m, 3H), 1.76 – 1.66 (m, 1H), 1.57 – 1.44 (m, 2H), 1.36 – 1.23 m, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.80, 131.27, 129.58, 128.31, 52.09, 39.11, 31.86, 30.69, 10.23. HRMS: calcd. 198.10440 $[M+H]^+$ Found: 198.10500.



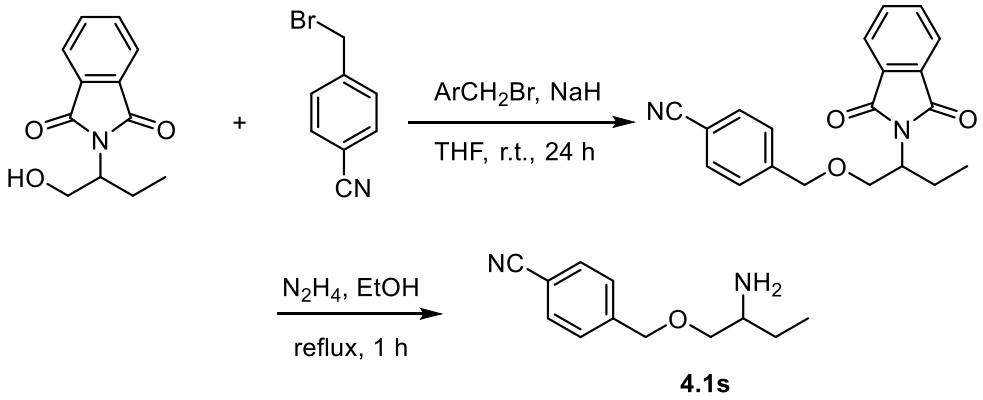
1-(3-Methoxyphenyl)pentan-3-amine (1q): Following a slightly modified procedure,[21] 1-(3-methoxyphenyl)pentan-3-one[22] (400 mg, 2 mmol) was combined with hydroxylamine hydrochloride (280 mg, 2 mmol) in mixed solvent of EtOH/THF/H_2O (2.4 mL/1.2 mL/ 0.6 mL), followed by batchwise addition of $NaHCO_3$ at 0 ºC. The reaction was then stirred at room temperature overnight. The mixture was filtered and the filter cake was washed with EtOAc. The filtrate was diluted with EtOAc (8 mL) and washed by H_2O (2 mL) and brine (2 mL). The organic phase was dried over $MgSO_4$ and then concentrated *in vacuo*. The crude oxime was directly used for next step without further purification. At 0 ºC, to a stirred suspension of $LiAlH_4$ (152 mg, 4 mmol) in dry Et_2O (6 mL) was added the oxime (414 mg, 2 mmol) in dry Et_2O (4 mL) dropwise. The reaction mixture was allowed to warm to

room temperature and heated at reflux for 6 h. Then the reaction mixture was cooled to 0 ºC and carefully quenched via sequential addition of H_2O (1 mL), 10% aqueous NaOH (1 mL) and H_2O (2 mL). After stirred at room temperature for 15 min, the mixture was filtered and the filter cake was washed with Et_2O. The filtrate was dried over $MgSO_4$ and then concentrated *in vacuo*. The crude mixture was then purified by column chromatography over silica (5:1:1 hexanes/EtOAc/DCM to 3:1:1:0.25 hexanes/EtOAc/DCM/NEt_3) to give the product as a colorless oil (280 mg, 73%). R_f = 0.15 (Hex/EA/DCM/NEt_3 = 2:1:1:0.2). IR (KBr) 3362, 2935, 1584, 1455, 1261, 779 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.8 Hz, 1H), 6.82 – 6.76 (m, 1H), 6.77 – 6.70 (m, 2H), 3.80 (s, 3H), 2.80 – 2.54 (m, 3H), 1.79 – 1.71 (m, 1H), 1.62 – 1.46 (m, 2H), 1.38 – 1.24 (m, 3H), 0.93 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.60, 144.10, 129.27, 120.75, 114.10, 110.96, 55.11, 52.29, 39.19, 32.67, 30.70, 10.32. HRMS: calcd. 194.15390 $[M+H]^+$ Found: 194.15430.



1-(Benzo[*d*][1,3]dioxol-5-yl)pentan-3-amine (4.1r): Following a slightly modified procedure,[21] 1-(benzo[d][1,3]dioxol-5-yl)pentan-3-one[22] (412 mg, 2 mmol) was combined with hydroxylamine hydrochloride (280 mg, 2 mmol) in mixed solvent of EtOH/THF/H_2O (2.4 mL/1.2 mL/ 0.6 mL), followed by batchwise addition of $NaHCO_3$ at 0 ºC. The reaction was then stirred at room temperature overnight. The mixture was filtered and the filter cake was washed with EtOAc. The filtrate was diluted with EtOAc (8 mL) and washed by H_2O (2

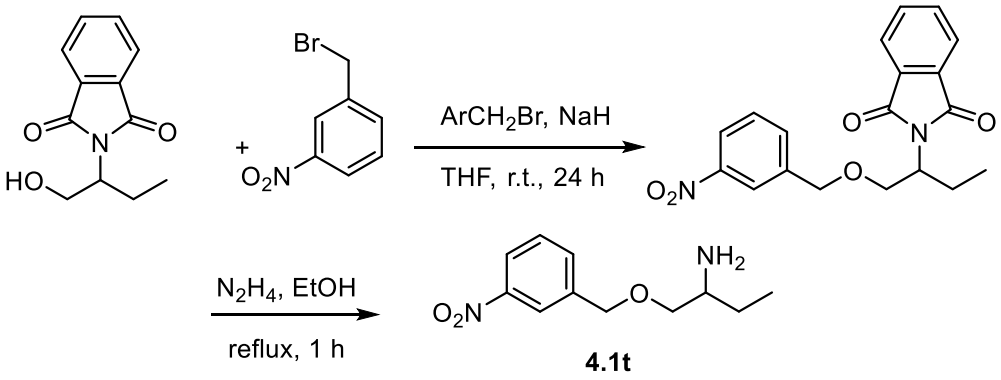
mL) and brine (2 mL). The organic phase was dried over $MgSO_4$ and then concentrated *in vacuo*. The crude oxime was directly used for next step without further purification. At 0 ºC, to a stirred suspension of $LiAlH_4$ (152 mg, 4 mmol) in dry Et_2O (6 mL) was added the oxime (442 mg, 2 mmol) in dry Et_2O (4 mL) dropwise. The reaction mixture was allowed to warm to room temperature and heated at reflux for 6 h. Then the reaction mixture was cooled to 0 ºC and carefully quenched via sequential addition of H_2O (1 mL), 10% aqueous NaOH (1 mL) and H_2O (2 mL). After stirred at room temperature for 15 min, the mixture was filtered and the filter cake was washed with Et_2O. The filtrate was dried over $MgSO_4$ and then concentrated *in vacuo*. The crude mixture was then purified by column chromatography over silica (5:1:1 hexanes/EtOAc/DCM to 3:1:1:0.25 hexanes/EtOAc/DCM/NEt_3) to give the product as a colorless oil (310 mg, 75%). R_f = 0.15 (Hex/EA/DCM/NEt_3 = 2:1:1:0.2). IR (KBr) 3364, 2930, 1489, 1442, 1246, 810 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.75 – 6.68 (m, 2H), 6.67 – 6.62 (m, 1H), 5.91 (s, 2H), 2.73 – 2.61 (m, 2H), 2.55 (ddd, *J* = 13.8, 10.1, 6.3 Hz, 1H), 1.74 – 1.66 (m, 1H), 1.57 – 1.45 (m, 2H), 1.39 – 1.26 (m, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.51, 145.48, 136.27, 120.95, 108.79, 108.10, 100.71, 52.16, 39.53, 32.34, 30.72, 10.32. HRMS: calcd. 208.13320 $[M+H]^+$ Found: 208.13310.



4.1s

4-((2-Aminobutoxy)methyl)benzonitrile (4.1s): 2-(1-hydroxybutan-2-yl)isoindoline-1,3-dione[23] (660 mg, 3 mmol) was combined with 4-(bromomethyl)benzonitrile (620 mg, 3.15 mmol) in THF (6 mL), followed by addition of NaH at room temperature. The reaction was then stirred at room temperature for 24h. The mixture was loaded on a small plug of silica gel and first washed with hexanes/EtOAc (10:1) to remove the remaining 4-(bromomethyl)benzonitrile and then eluted with EtOAc to afford a solution of crude product. After concentrated *in vacuo*, the crude product was directly used for next step without further purification. At room temperature, the crude product from last step (500 mg, ca. 1.5 mmol) in EtOH (3 mL) was added hydrazine monohydrate (300 mg, 6 mmol). The reaction mixture was heated at reflux for 1h. Then the reaction mixture was cooled to 0 ºC and filtered. The filtrate was dried over $MgSO_4$ and then concentrated *in vacuo*. The crude mixture was then purified by column chromatography over silica (5:1:1 hexanes/EtOAc/DCM to 3:1:1:0.25 hexanes/EtOAc/DCM/NEt_3) to give the product as a colorless oil (140 mg, 46%). R_f = 0.15 (Hex/EA/DCM/NEt_3 = 2:1:1:0.2). IR (KBr) 3370, 2963, 2228, 1461, 1098, 819 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 4.57 (s, 2H), 3.48 (dd, *J* = 9.0, 3.8 Hz, 1H), 3.28 (dd, *J* = 9.0, 7.6 Hz, 1H), 2.96 – 2.90 (m, 1H), 1.52 – 1.41 (m, 3H), 1.35 – 1.28 (m, 1H), 0.94 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.97, 132.18, 127.62, 118.81, 111.23, 76.02, 72.16, 52.43, 27.00, 10.44. HRMS: calcd. 205.13350 $[M+H]^+$ Found: 205.13400.

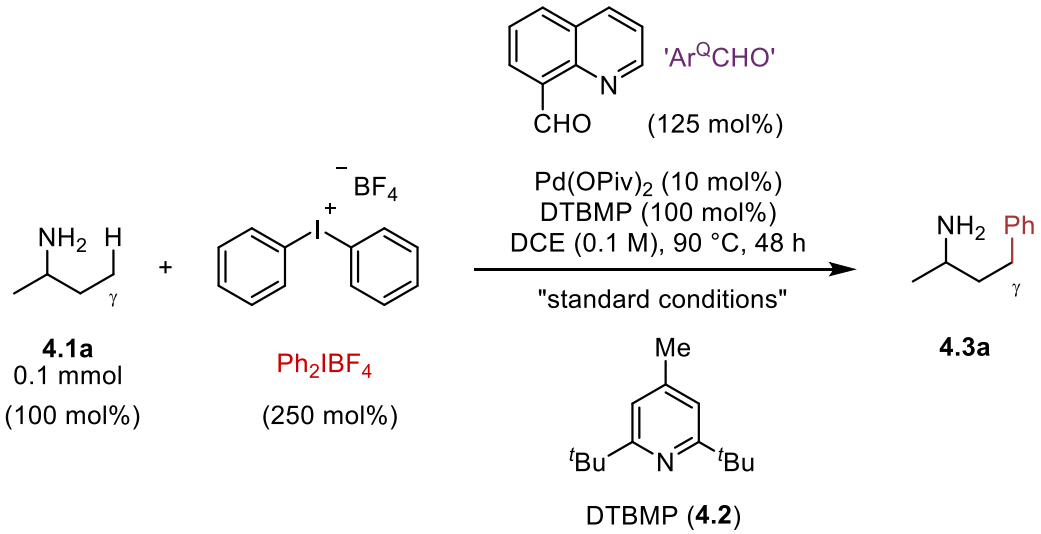


4.1t

1-((3-Nitrobenzyl)oxy)butan-2-amine (4.1t): 2-(1-hydroxybutan-2-yl)isoindoline-1,3-dione[23] (660 mg, 3 mmol) was combined with 1-(bromomethyl)-3-nitrobenzene (680 mg, 3.15 mmol) in THF (6 mL), followed by addition of NaH at room temperature. The reaction was then stirred at room temperature for 24h. The mixture was loaded on a small plug of silica gel and first washed with hexanes/EtOAc (10:1) to remove the remaining 4-(bromomethyl)benzonitrile and then eluted with EtOAc to afford a solution of crude product. After concentration *in vacuo*, the crude product was directly used for the next step without further purification. At room temperature, the crude product from last step (354 mg, ca. 1 mmol) in EtOH (2 mL) was added hydrazine monohydrate (200 mg, 4 mmol). The reaction mixture was heated at reflux for 1 h. Then the reaction mixture was cooled to 0 ºC and filtered. The filtrate was dried over $MgSO_4$ and then concentrated *in vacuo*. The crude mixture was then purified by column chromatography over silica (5:1:1 hexanes/EtOAc/DCM to 3:1:1:0.25 hexanes/EtOAc/DCM/NEt_3) to give the product as a

colorless oil (160 mg, 71%). R_f = 0.2 (Hex/EA/DCM/NEt_3 = 2:1:1:0.2). IR (KBr) 3370, 2963, 1529, 1349, 1098, 732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 4.61 (s, 2H), 3.50 (dd, *J* = 9.0, 3.8 Hz, 1H), 3.30 (dd, *J* = 9.0, 7.6 Hz, 1H), 2.99 – 2.91 (m, 1H), 1.52 – 1.44 (m, 3H), 1.38 – 1.27 (m, 1H), 0.95 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.30, 140.63, 133.24, 129.31, 122.53, 122.16, 76.05, 71.90, 52.42, 27.01, 10.45. HRMS: calcd. 225.12340 $[M+H]^+$ Found: 225.12290.

Typical procedure for control experiments for the γ-arylation

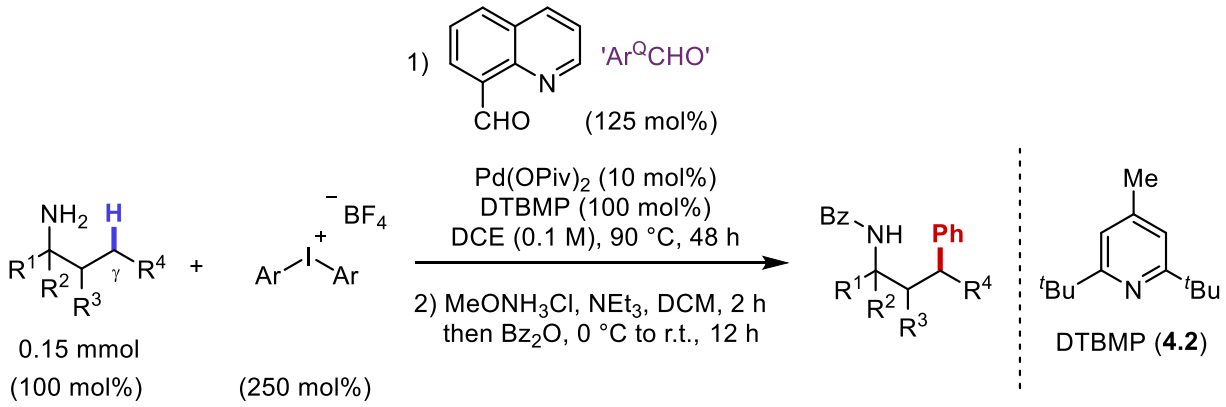


"Standard conditions": A 4 mL vial was charged with $Pd(OPiv)_2$ (3.1 mg, 0.01 mmol, 0.10 equiv), quinoline-8-carbaldehyde (19.6 mg, 0.125 mmol, 1.25 equiv), 2,6-di-^{t}butyl-4-methylpyridine **2** (20.5 mg, 0.1 mmol, 1.0 equiv), and DCE (1.0 mL), followed by the addition of 2-butylamine **1a** (7.3 mg, 0.1 mmol, 1.0 equiv) and Ph_2IBF_4 (92 mg, 0.25 mmol, 2.5 equiv). The vial was sealed with a PTFE lined cap and transferred into a glove

box. After opening and purging under N_2 atmosphere for 5 min, the vial was then sealed again and heated in a pie-block at 90 °C under stirring for 48h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yield of the desired product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard.

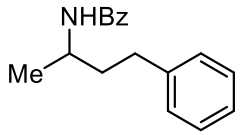
All control experiments were conducted at 0.1 mmol scale, and changes were made on the **"standard conditions"** described above according to Table 4.1.

Typical procedure for substrate scope study



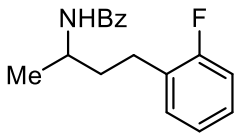
A 4 mL vial was charged with $Pd(OPiv)_2$ (4.6 mg, 0.015 mmol, 0.10 equiv), quinoline-8-carbaldehyde (29.4 mg, 0.1875 mmol, 1.25 equiv), 2,6-di-^{t}butyl-4-methylpyridine **4.2** (30.8 mg, 0.15 mmol, 1.0 equiv), and DCE (1.5 mL), followed by the addition of amine substrate (0.15 mmol, 1.0 equiv) and Ar_2IBF_4 (0.375 mmol, 2.5 equiv). The vial was sealed with a PTFE lined cap and transferred into a glove box. After opening and

purging under N_2 atmosphere for 5 min, the vial was then sealed again and heated in a pie-block at 90 °C under stirring for 48h (unless otherwise noted). After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. Methoxyamine hydrochloride (50 mg, 0.6 mmol, 4.0 equiv), NEt_3 (0.3 mL), and DCM (5 mL) were added to the residue and the mixture was stirred at RT for 2h, followed by the addition of benzoic anhydride (300 mg) in DCM (1 ml) at 0 °C. The mixture was stirred at room temperature for an additional 12h, and concentrated under *vacuo* and further purified by flash column chromatography over silica (hexane/ethyl acetate/DCM) to give the arylation products.



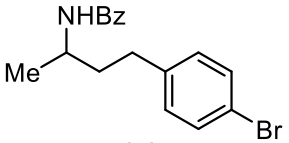
4.4a

***N*-(4-phenylbutan-2-yl)benzamide (4.4a):** Colorless oil (26.2 mg, 70% yield, 78% *brsm* yield as 2.6 mg starting material was recovered as its benzoylamide derivative). R_f = 0.4 (Hex/EA/DCM = 5:1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.64 (m, 2H), 7.51 – 7.46 (m, 1H), 7.45 – 7.37 (m, 2H), 7.31 – 7.26 (m, 2H), 7.26 – 7.13 (m, 3H), 5.88 (d, *J* = 8.5 Hz, 1H), 4.34 – 4.24 (m, 1H), 2.80 – 2.69 (m, 2H), 1.97 – 1.85 (m, 2H), 1.29 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.77, 141.70, 134.83, 131.28, 128.48, 128.32, 126.75, 125.91, 45.70, 38.58, 32.50, 21.08. HRMS: calcd. 254.15390 $[M+H]^+$ Found: 254.15450. The spectra matches the reported literature.[24]



4.4b

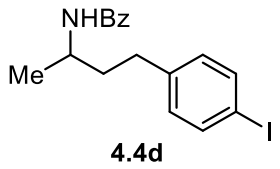
***N*-(4-(2-fluorophenyl)butan-2-yl)benzamide (4.4b):** Colorless oil (25.6 mg, 63% yield, 80% *brsm* yield as 5.6 mg starting material was recovered as its benzoylamide derivative). R_f = 0.4 (Hex/EA/DCM = 5:1:2). IR (KBr) 3299, 2969, 1635, 1540, 1491, 913 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.70 (m, 2H), 7.53 – 7.46 (m, 1H), 7.46 – 7.39 (m, 2H), 7.24 – 7.13 (m, 2H), 7.08 – 6.96 (m, 2H), 5.93 (d, *J* = 8.4 Hz, 1H), 4.33 – 4.23 (m, 1H), 2.83 – 2.67 (m, 2H), 1.92 – 1.83 (m, 2H), 1.29 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.89, 161.03 (d, *J* = 244.5 Hz), 134.86, 131.33, 130.60 (d, *J* = 5.0 Hz), 128.52, 128.50 (d, *J* = 15.6 Hz), 127.69 (d, *J* = 8.0 Hz), 126.77, 124.08 (d, *J* = 3.5 Hz), 115.23 (d, *J* = 22.1 Hz), 45.67, 37.33 (d, *J* = 1.2 Hz), 25.93 (d, *J* = 2.6 Hz), 21.10. ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.96. HRMS: calcd. 272.14450 $[M+H]^+$ Found: 272.14540.



4.4c

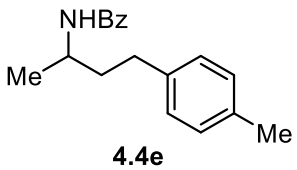
***N*-(4-(4-bromophenyl)butan-2-yl)benzamide (4.4c):** White solid (37.2 mg, 75% yield, 88% *brsm* yield as 4.2 mg starting material was recovered as its benzoylamide derivative). R_f = 0.5 (Hex/EA/DCM = 5:1:2). M.P. = 137 – 139 ^oC. IR (KBr) 3298, 2927, 1634, 1540, 1488, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 2H), 7.52 – 7.47 (m, 1H), 7.46 – 7.35 (m, 4H), 7.12 – 7.04 (m, 2H), 5.85 (d, *J* = 8.6 Hz, 1H), 4.32 – 4.22 (m,

1H), 2.74 – 2.64 (m, 2H), 1.92 – 1.81 (m, 2H), 1.28 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.79, 140.64, 134.71, 131.51, 131.39, 130.10, 128.55, 126.72, 119.68, 45.52, 38.50, 31.97, 21.12. HRMS: calcd. 332.06450 $[M+H]^+$ Found: 332.06510.



4.4d

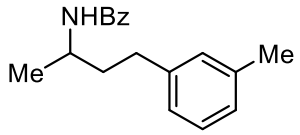
***N*-(4-(4-iodophenyl)butan-2-yl)benzamide (4.4d):** White solid (40.8 mg, 72% yield, 84% *brsm* yield as 3.6 mg starting material was recovered as its benzoylamide derivative). R_f = 0.35 (Hex/EA/DCM = 5:1:2). M.P. = 158 – 160 ^{o}C. IR (KBr) 3297, 2968, 1631, 1544, 1485, 805 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 2H), 7.64 – 7.54 (m, 2H), 7.53 – 7.47 (m, 1H), 7.46 – 7.40 (m, 2H), 7.01 – 6.89 (m, 2H), 5.87 (d, J = 8.6 Hz, 1H), 4.30 – 4.23 (m, 1H), 2.72 – 2.61 (m, 2H), 1.91 – 1.81 (m, 2H), 1.27 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.77, 141.34, 137.48, 134.69, 131.38, 130.45, 128.55, 126.72, 90.96, 45.53, 38.41, 32.06, 21.11. HRMS: calcd. 380.05060 $[M+H]^+$ Found: 380.05030.



4.4e

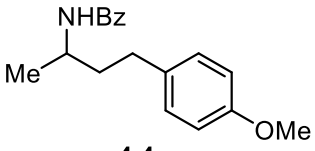
***N*-(4-(p-tolyl)butan-2-yl)benzamide (4.4e):** White solid (23.1 mg, 58% yield, 69% *brsm* yield as 4.2 mg starting material was recovered as its benzoylamide derivative). R_f =

0.45 (Hex/EA/DCM = 5:1:2). M.P. = 131 – 133 ^{o}C. IR (KBr) 3323, 2965, 1633, 1534, 1451, 807 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.64 (m, 2H), 7.51 – 7.45 (m, 1H), 7.44 – 7.37 (m, 2H), 7.09 (s, 4H), 5.88 (d, *J* = 8.4 Hz, 1H), 4.33 – 4.22 (m, 1H), 2.77 – 2.63 (m, 2H), 2.31 (s, 3H), 1.94 – 1.84 (m, 2H), 1.28 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.72, 138.61, 135.40, 134.84, 131.25, 129.17, 128.45, 128.20, 126.75, 45.71, 38.60, 32.01, 21.06, 20.96. HRMS: calcd. 268.16960 $[M+H]^+$ Found: 268.16990.



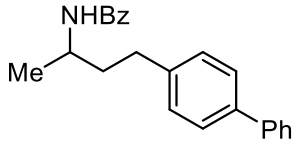
4.4f

***N*-(4-(*m*-tolyl)butan-2-yl)benzamide (4.4f):** White solid (28.7 mg, 72% yield, 79% *brsm* yield as 2.4 mg starting material was recovered as its benzoylamide derivative). R_f = 0.45 (Hex/EA/DCM = 5:1:2). M.P. = 110 – 112 ^{o}C. IR (KBr) 3301, 2969, 1633, 1538, 1490, 913 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.62 (m, 2H), 7.52 – 7.45 (m, 1H), 7.44 – 7.35 (m, 2H), 7.17 (td, *J* = 7.4, 0.9 Hz, 1H), 7.04 – 6.96 (m, 3H), 5.89 (d, *J* = 8.4 Hz, 1H), 4.34 – 4.23 (m, 1H), 2.76 – 2.64 (m, 2H), 2.30 (s, 3H), 1.96 – 1.84 (m, 2H), 1.29 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.73, 141.69, 138.08, 134.83, 131.27, 129.15, 128.46, 128.40, 126.74, 126.66, 125.30, 45.82, 38.55, 32.41, 21.35, 21.06. HRMS: calcd. 268.16960 $[M+H]^+$ Found: 268.17010.



4.4g

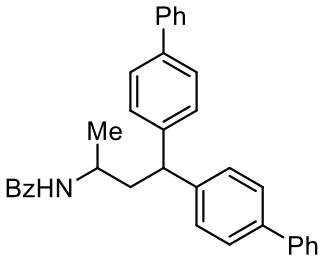
***N*-(4-(4-methoxyphenyl)butan-2-yl)benzamide (4.4g):** White wax (15.6 mg, 37% yield, 54% *brsm* yield as 8.5 mg starting material was recovered as its benzoylamide derivative). R_f = 0.25 (Hex/EA/DCM = 5:1:2). IR (KBr) 3306, 2933, 1634, 1540, 1512, 1245, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 2H), 7.51 – 7.46 (m, 1H), 7.44 – 7.38 (m, 2H), 7.21 – 7.04 (m, 2H), 6.91 – 6.76 (m, 2H), 5.86 (d, *J* = 8.5 Hz, 1H), 4.32 – 4.22 (m, 1H), 3.77 (s, 3H), 2.73 – 2.64 (m, 2H), 1.92 – 1.82 (m, 2H), 1.28 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.73, 157.83, 134.85, 133.72, 131.28, 129.23, 128.47, 126.75, 113.90, 55.23, 45.65, 38.76, 31.55, 21.09. HRMS: calcd. 284.16450 $[M+H]^+$ Found: 284.16510.



4.4h-*mono*

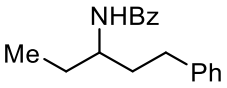
***N*-(4-([1,1'-biphenyl]-4-yl)butan-2-yl)benzamide (4.4h-*mono*):** Colorless oil (34.0 mg, 69% yield, 75% *brsm* yield as 2.1 mg starting material was recovered as its benzoylamide derivative). R_f = 0.40 (Hex/EA/DCM = 5:1:2). IR (KBr) 3320, 2969, 1632, 1539, 1489, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.62 (m, 2H), 7.61 – 7.50 (m, 4H), 7.50 – 7.28 (m, 8H), 5.89 (d, *J* = 8.5 Hz, 1H), 4.38 – 4.28 (m, 1H), 2.84 – 2.73 (m, 2H), 2.05 – 1.86 (m, 2H), 1.31 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.76, 140.93,

140.85, 138.93, 134.80, 131.30, 128.77, 128.69, 128.50, 127.24, 127.04, 126.96, 126.73, 45.75, 38.49, 32.14, 21.12. HRMS: calcd. 330.18520 $[M+H]^+$ Found: 330.18610.



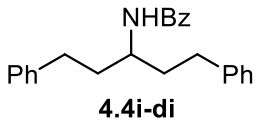
4.4h-*di*

***N*-(4,4-di([1,1'-biphenyl]-4-yl)butan-2-yl)benzamide (4.4h-*di*):** Colorless oil (5.0 mg, 7% yield, 8% *brsm* yield as 2.1 mg starting material was recovered as its benzoylamide derivative). R_f = 0.42 (Hex/EA/DCM = 5:1:2). IR (KBr) 3318, 2927, 1632, 1542, 1486, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 10H), 7.45 – 7.37 (m, 9H), 7.34 – 7.29 (m, 4H), 5.79 (d, *J* = 8.3 Hz, 1H), 4.35 – 4.28 (m, 1H), 4.20 (t, *J* = 7.5 Hz, 1H), 2.56 – 2.49 (m, 1H), 2.40 – 2.33 (m, 1H), 1.33 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.59, 143.96, 143.33, 140.74, 139.40, 134.61, 131.25, 128.69, 128.43, 128.13, 128.09, 127.52, 127.50, 127.13, 126.99, 126.64, 47.81, 45.08, 42.50, 21.19. HRMS: calcd. 482.24780 $[M+H]^+$ Found: 482.24810.



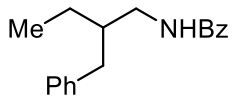
4.4i-*mono*

***N*-(1-phenylpentan-3-yl)benzamide (4.4i-*mono*):** The reaction was conducted in 0.2 mmol scale. Colorless oil (20.0 mg, 37% yield, 44% *brsm* yield as 6.3 mg starting material was recovered as its benzoylamide derivative). R_f = 0.4 (Hex/EA/DCM = 5:1:2). IR (KBr) 3307, 2927, 1634, 1538, 1029, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.64 (m, 2H), 7.54 – 7.47 (m, 1H), 7.46 – 7.38 (m, 2H), 7.32 – 7.25 (m, 2H), 7.24 – 7.14 (m, 3H), 5.80 (d, *J* = 9.1 Hz, 1H), 4.22 – 4.13 (m, 1H), 2.77 – 2.69 (m, 2H), 2.01 – 1.92 (m, 1H), 1.87 – 1.78 (m, 1H), 1.77 – 1.65 (m, 1H), 1.61 – 1.50 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.19, 141.91, 134.92, 131.31, 128.53, 128.47, 128.33, 126.75, 125.89, 51.08, 36.56, 32.43, 28.14, 10.28. HRMS: calcd. 268.16960 $[M+H]^+$ Found: 268.17050.



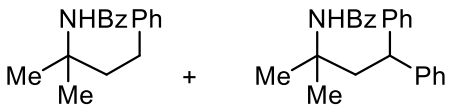
4.4i-di

***N*-(1,5-diphenylpentan-3-yl)benzamide (4.4i-*di*):** The reaction was conducted in 0.2 mmol scale. Colorless oil (22.8 mg, 33% yield, 39% *brsm* yield as 6.3 mg starting material was recovered as its benzoylamide derivative). R_f = 0.42 (Hex/EA/DCM = 5:1:2). IR (KBr) 3241, 2918, 1627, 1535, 1052, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.58 (m, 2H), 7.52 – 7.47 (m, 1H), 7.44 – 7.38 (m, 2H), 7.30 – 7.26 (m, 4H), 7.22 – 7.15 (m, 6H), 5.80 (d, *J* = 9.2 Hz, 1H), 4.37 – 4.29 (m, 1H), 2.73 (t, *J* = 8.0 Hz, 4H), 2.07 – 1.81 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.05, 141.74, 134.71, 131.37, 128.50, 128.33, 126.76, 125.94, 49.73, 37.08, 32.40. HRMS: calcd. 344.20090 $[M+H]^+$ Found: 344.20190.



4.4j

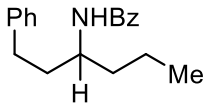
***N*-(2-benzylbutyl)benzamide (4.4j):** Colorless oil (18.1 mg, 45% yield, 66% *brsm* yield as 9.1 mg starting material was recovered as its benzoylamide derivative). R_f = 0.35 (Hex/EA/DCM = 5:1:2). IR (KBr) 3306, 2927, 1637, 1542, 1491, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.50 (m, 2H), 7.49 – 7.43 (m, 1H), 7.40 – 7.34 (m, 2H), 7.33 – 7.28 (m, 2H), 7.25 – 7.16 (m, 3H), 5.88 (br, 1H), 3.58 (ddd, *J* = 13.7, 6.6, 5.3 Hz, 1H), 3.31 (ddd, *J* = 13.7, 7.1, 5.3 Hz, 1H), 2.79 (dd, *J* = 13.8, 6.1 Hz, 1H), 2.57 (dd, *J* = 13.8, 8.2 Hz, 1H), 2.01 – 1.86 (m, 1H), 1.48 – 1.40 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.21, 140.69, 134.59, 131.24, 129.05, 128.63, 128.40, 126.69, 126.13, 43.35, 42.05, 39.34, 25.11, 11.20. HRMS: calcd. 268.16960 $[M+H]^+$ Found: 268.17020.



4.4k-mono **4.4k-di**

The reaction was conducted on 0.1 mmol scale. ***N*-(2-methyl-4-phenylbutan-2-yl)benzamide (4.4k-*mono*) and *N*-(2-methyl-4,4-diphenylbutan-2-yl)benzamide (4.4k-*di*)** were isolated as an inseparable mixture (12.2 mg, colorless oil)**.** The yield of each compound was calculated based on the NMR analysis of the mixture (**4.4k-*mono*:** 5.9 mg, 22% yield, 44% *brsm* yield as 9.6 mg starting material was recovered as its benzoylamide derivative; **4.4k-*di*:** 6.3 mg, 18% yield, 36% *brsm* yield as 9.6 mg starting material was recovered as its

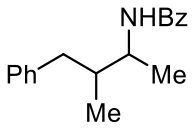
benzoylamide derivative). R_f = 0.65 (Hex/EA/DCM = 5:1:2). IR (KBr) 3324, 2969, 1644, 1525, 1291, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) (mono:di = 0.52 : 0.48) δ 7.67 – 7.62 (m, 1H), 7.49 – 7.31 (m, 4H), 7.28 – 7.22 (m, 5H), 7.20 – 7.08 (m, 2.4H), 5.87 (br, 0.52H), 5.73 (br, 0.48H), 4.21 (t, *J* = 7.0 Hz, 0.48H), 2.71 – 2.59 (m, 2H), 2.22 – 2.14 (m, 1.04H), 1.53 (s, 2.88H), 1.51 (s, 3.12H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were found at δ 166.82, 166.45, 145.34, 142.11, 135.76, 135.21, 131.10, 130.83, 128.92, 128.46, 128.45, 128.42, 128.05, 127.68, 126.63, 126.44, 126.35, 125.80, 54.41, 54.19, 47.57, 46.42, 41.92, 30.81, 27.47, 27.19. HRMS: **4.4k-*mono*** calcd. 268.16960 $[M+H]^+$ Found: 268.16990. **4.4k-*di*** calcd. 344.20090 $[M+H]^+$ Found: 344.20160.



4.4l

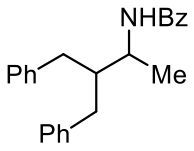
***N*-(1-phenylhexan-3-yl)benzamide (4.4l):** The reaction was conducted on 0.097 mmol scale. Colorless oil (14.7 mg, 54% yield). The 1,1-and 1,5-diarylation products were isolated with a ratio of 1:4 as an inseparable mixture (6.0 mg, 17% yield). The d.r. for the 1,5-diarylation products is 3:1 determined by NMR analysis of the crude isolated mixture. R_f = 0.4 (Hex/EA/DCM = 5:1:2). IR (KBr) 3296, 2955, 1633, 1538, 1030, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.66 (m, 2H), 7.52 – 7.47 (m, 1H), 7.45 – 7.40 (m, 2H), 7.29 – 7.26 (m, 2H), 7.23 – 7.14 (m, 3H), 5.79 (d, *J* = 9.2 Hz, 1H), 4.35 – 4.14 (m, 1H), 2.75 – 2.71 (m, 2H), 1.98 – 1.91 (m, 1H), 1.87 – 1.76 (m, 1H), 1.57 – 1.37 (m, 4H), 0.94 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.07, 141.93, 134.90, 131.29, 128.52, 128.46, 128.33,

126.75, 125.87, 49.54, 37.60, 37.09, 32.41, 19.20, 14.04. HRMS: calcd. 282.18520 $[M+H]^+$ Found: 282.18600.



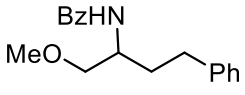
4.4m-*mono*

***N*-(3-methyl-4-phenylbutan-2-yl)benzamide (4.4m-*mono*)** were isolated as an inseparable mixture of diastereomers (Colorless oil, 17.7 mg, 42% yield, d.r. = 1.7:1, 63% *brsm* yield as 9.4 mg starting material was recovered as its benzoylamide derivative)**.** The d.r. ratio was determined based on the NMR analysis of the crude mixture. R_f = 0.35 (Hex/EA/DCM = 5:1:2). IR (KBr) 3319, 2972, 1636, 1541, 1057, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) (d.r. = 0.65 : 0.35) δ 7.71 – 7.66 (m, 1.35H), 7.61 – 7.57 (m, 0.65H), 7.51 – 7.46 (m, 1H), 7.44 – 7.37 (m, 2H), 7.32 – 7.26 (m, 2H), 7.23 – 7.17 (m, 3H), 5.95 (d, *J* = 8.7 Hz, 0.65H), 5.87 (d, *J* = 9.1 Hz, 0.35H), 4.36 – 4.17 (m, 1H), 2.89 – 2.80 (m, 1H), 2.49 – 2.40 (m, 1H), 2.15 – 2.01 (m, 1H), 1.29 – 1.22 (m, 3H), 0.97 (d, *J* = 6.9 Hz, 1.05H), 0.91 (d, *J* = 6.8 Hz, 1.95H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were found at δ 166.72, 140.58, 134.91, 134.87, 131.31, 131.26, 129.13, 129.04, 128.52, 128.46, 128.37, 126.75, 126.72, 126.01, 125.95, 49.60, 49.19, 40.09, 39.85, 39.77, 39.45, 17.45, 17.16, 15.99, 15.01. HRMS: calcd. 268.16960 $[M+H]^+$ Found: 268.17060.



4.4m-*di*

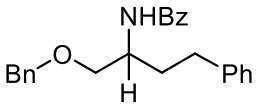
***N*-(3-benzyl-4-phenylbutan-2-yl)benzamide (4.4m-*di*):** Colorless oil (9.5 mg, 18% yield, 27% *brsm* yield as 9.4 mg starting material was recovered as its benzoylamide derivative). R_f = 0.4 (Hex/EA/DCM = 5:1:2). IR (KBr) 3315, 2928, 1637, 1541, 1073, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 1H), 7.34 – 7.27 (m, 7H), 7.26 – 7.18 (m, 7H), 5.75 (d, *J* = 8.7 Hz, 1H), 4.40 – 4.32 (m, 1H), 2.79 (dd, *J* = 13.8, 6.2 Hz, 1H), 2.70 (d, *J* = 7.1 Hz, 2H), 2.64 (dd, *J* = 13.7, 8.2 Hz, 1H), 2.52 – 2.44 (m, 1H), 1.30 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.99, 141.08, 140.18, 134.44, 131.14, 129.12, 129.02, 128.83, 128.58, 128.22, 126.64, 126.24, 126.17, 48.14, 46.50, 38.63, 35.91, 16.42. HRMS: calcd. 344.20090 $[M+H]^+$ Found: 344.20200.



4.4n

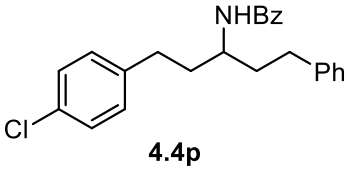
***N*-(1-methoxy-4-phenylbutan-2-yl)benzamide (4.4n):** Colorless oil (16.7 mg, 65% yield). R_f = 0.2 (Hex/EA/DCM = 5:1:2). IR (KBr) 3306, 2925, 1636, 1539, 1125, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.71 (m, 2H), 7.53 – 7.48 (m, 1H), 7.46 – 7.39 (m, 2H), 7.30 – 7.26 (m, 2H), 7.24 – 7.14 (m, 3H), 6.37 (d, *J* = 8.8 Hz, 1H), 4.44 – 4.28 (m, 1H), 3.58 – 3.46 (m, 2H), 3.37 (s, 3H), 2.78 – 2.70 (m, 2H), 2.05 – 1.97 (m, 2H). ^{13}C NMR (101 MHz,

$CDCl_3$) δ 166.96, 141.69, 134.63, 131.40, 128.50, 128.41, 128.34, 126.90, 125.88, 74.13, 59.20, 49.27, 33.73, 32.57. HRMS: calcd. 284.16450 $[M+H]^+$ Found: 284.16540.



4.4o

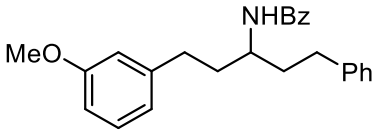
***N*-(1-(benzyloxy)-4-phenylbutan-2-yl)benzamide (4.4o):** Colorless oil (33.7 mg, 63% yield). R_f = 0.35 (Hex/EA/DCM = 5:1:2). IR (KBr) 3306, 2924, 1636, 1539, 1091, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.64 (m, 2H), 7.52 – 7.47 (m, 1H), 7.45 – 7.40 (m, 2H), 7.36 – 7.26 (m, 7H), 7.24 – 7.14 (m, 3H), 6.39 (d, *J* = 8.9 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.41 – 4.34 (m, 1H), 3.65 – 3.58 (m, 2H), 2.74 – 2.66 (m, 2H), 2.09 – 1.98 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.95, 141.68, 137.96, 134.63, 131.38, 128.49, 128.46, 128.41, 128.36, 127.81, 127.74, 126.89, 125.88, 73.30, 71.46, 49.35, 33.75, 32.56. HRMS: calcd. 360.19580 $[M+H]^+$ Found: 360.19680.



4.4p

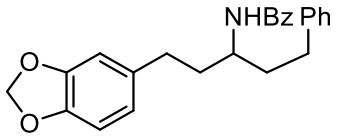
***N*-(1-(4-chlorophenyl)-5-phenylpentan-3-yl)benzamide (4.4p):** White wax (36.3 mg, 64% yield). R_f = 0.55 (Hex/EA/DCM = 5:1:2). IR (KBr) 3296, 2923, 1633, 1538, 1492, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.55 (m, 2H), 7.54 – 7.47 (m, 1H), 7.46 –

7.39 (m, 2H), 7.29 – 7.25 (m, 2H), 7.25 – 7.21 (m, 2H), 7.21 – 7.15 (m, 3H), 7.14 – 7.08 (m, 2H), 5.79 (d, *J* = 9.2 Hz, 1H), 4.34 – 4.25 (m, 1H), 2.76 – 2.67 (m, 4H), 2.04 – 1.79 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.07, 141.60, 140.12, 134.59, 131.67, 131.46, 129.70, 128.56, 128.53, 128.32, 126.72, 125.99, 49.52, 37.10, 37.09, 32.39, 31.80. HRMS: calcd. 378.16190 $[M+H]^+$ Found: 378.16270.



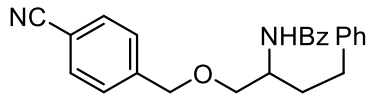
4.4q

***N*-(1-(3-methoxyphenyl)-5-phenylpentan-3-yl)benzamide (4.4q):** Colorless oil (35.1 mg, 63% yield). R_f = 0.4 (Hex/EA/DCM = 5:1:2). IR (KBr) 3296, 2946, 1633, 1538, 1489, 1260, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.60 (m, 2H), 7.53 – 7.47 (m, 1H), 7.45 – 7.37 (m, 2H), 7.29 – 7.26 (m, 2H), 7.23 – 7.16 (m, 4H), 6.84 – 6.67 (m, 3H), 5.86 (d, *J* = 9.1 Hz, 1H), 4.37 – 4.28 (m, 1H), 3.77 (s, 3H), 2.72 (q, *J* = 8.2 Hz, 4H), 2.05 – 1.80 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.05, 159.69, 143.39, 141.73, 134.68, 131.35, 129.46, 128.48, 128.32, 126.75, 125.92, 120.66, 114.05, 111.28, 55.12, 49.74, 37.09, 36.91, 32.46, 32.39. HRMS: calcd. 374.21150 $[M+H]^+$ Found: 374.21110.



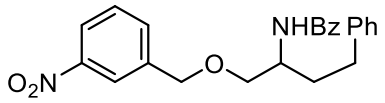
4.4r

***N*-(1-(benzo[*d*][1,3]dioxol-5-yl)-5-phenylpentan-3-yl)benzamide (4.4r):** White solid (36.0 mg, 62% yield). R_f = 0.4 (Hex/EA/DCM = 5:1:2). M.P. = 132 – 134 ^{o}C. IR (KBr) 3296, 2923, 1633, 1489, 1245, 913 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.61 (m, 2H), 7.54 – 7.47 (m, 1H), 7.45 – 7.38 (m, 2H), 7.31 – 7.26 (m, 2H), 7.22 – 7.15 (m, 3H), 6.75 – 6.64 (m, 2H), 6.63 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.92 – 5.87 (m, 2H), 5.83 (d, *J* = 9.1 Hz, 1H), 4.34 – 4.25 (m, 1H), 2.72 (t, *J* = 7.9 Hz, 2H), 2.65 (t, *J* = 7.8 Hz, 2H), 2.05 – 1.77 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.02, 147.62, 145.67, 141.72, 135.53, 134.68, 131.36, 128.49, 128.32, 126.74, 125.94, 121.02, 108.77, 108.23, 100.75, 49.60, 37.30, 37.07, 32.38, 32.15. HRMS: calcd. 388.19070 $[M+H]^+$ Found: 388.19170.



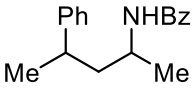
4.4s

***N*-(1-((4-cyanobenzyl)oxy)-4-phenylbutan-2-yl)benzamide (4.4s):** White wax (29.5 mg, 51% yield). R_f = 0.2 (Hex/EA/DCM = 5:1:2). IR (KBr) 3316, 2925, 2228, 1638, 1535, 1092, 744 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.66 (m, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.55 – 7.49 (m, 1H), 7.46 – 7.38 (m, 4H), 7.30 – 7.26 (m, 2H), 7.21 – 7.17 (m, 3H), 6.28 (d, *J* = 8.8 Hz, 1H), 4.60 (d, *J* = 13.0 Hz, 1H), 4.54 (d, *J* = 13.0 Hz, 1H), 4.44 – 4.36 (m, 1H), 3.64 (d, *J* = 3.8 Hz, 2H), 2.81 – 2.64 (m, 2H), 2.07 – 2.01 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.03, 143.48, 141.42, 134.42, 132.25, 131.57, 128.57, 128.51, 128.32, 127.73, 126.83, 126.04, 118.71, 111.47, 72.31, 72.27, 49.27, 33.62, 32.55. HRMS: calcd. 385.19110 $[M+H]^+$ Found: 385.19140.



4.4t

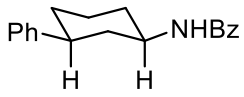
***N*-(1-((3-nitrobenzyl)oxy)-4-phenylbutan-2-yl)benzamide (4.4t):** Colorless oil (41.8 mg, 69% yield). R_f = 0.25 (Hex/EA/DCM = 5:1:2). IR (KBr) 3306, 2926, 1637, 1529, 1349, 1094, 803 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.19 (m, 1H), 8.16 – 8.12 (m, 1H), 7.75 – 7.70 (m, 2H), 7.65 – 7.60 (m, 1H), 7.53 – 7.48 (m, 2H), 7.46 – 7.40 (m, 2H), 7.31 – 7.26 (m, 2H), 7.23 – 7.16 (m, 3H), 6.33 (d, *J* = 8.8 Hz, 1H), 4.64 (d, *J* = 12.5 Hz, 1H), 4.58 (d, *J* = 12.5 Hz, 1H), 4.45 – 4.37 (m, 1H), 3.66 (d, *J* = 3.8 Hz, 2H), 2.78 – 2.72 (m, 2H), 2.09 – 2.02 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.04, 148.32, 141.41, 140.19, 134.40, 133.29, 131.53, 129.40, 128.57, 128.49, 128.33, 126.84, 126.01, 122.71, 122.21, 72.27, 71.96, 49.23, 33.58, 32.53. HRMS: calcd. 405.18090 $[M+H]^+$ Found: 405.18140.



4.4u

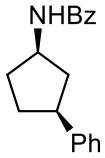
***N*-(4-phenylpentan-2-yl)benzamide (4.4u):** isolated as an inseparable mixture of diastereomers (colorless oil, 30.8 mg, 77% yield). The d.r. for the products is 2.3:1 determined by NMR analysis of the crude isolated mixture. R_f = 0.4 (Hex/EA/DCM = 5:1:2). IR (KBr) 3306, 2965, 1633, 1540, 1491, 913 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) (d.r. = 0.72 : 0.28) δ 7.60 – 7.53 (m, 2H), 7.49 – 7.44 (m, 1H), 7.42 – 7.34 (m, 2H), 7.33 – 7.27 (m, 2H),

7.25 – 7.14 (m, 3H), 5.80 – 5.74 (m, 1H), 4.31 – 4.05 (m, 1H), 2.97 – 2.88 (m, 0.72H), 2.88 – 2.79 (m, 0.28H), 1.99 – 1.91 (m, 0.28H), 1.90 – 1.85 (m, 1.44H), 1.80 – 1.74 (m, 0.28H), 1.33 – 1.29 (m, 3H), 1.25 – 1.20 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were found at δ 166.66, 166.37, 147.06, 146.87, 134.78, 134.72, 131.20, 131.19, 128.70, 128.64, 128.37, 127.03, 126.78, 126.70, 126.26, 126.12, 45.18, 45.16, 44.78, 44.42, 37.52, 36.62, 23.22, 22.67, 21.62, 20.85. HRMS: calcd. 268.16960 $[M+H]^+$ Found: 268.16970.



4.4v

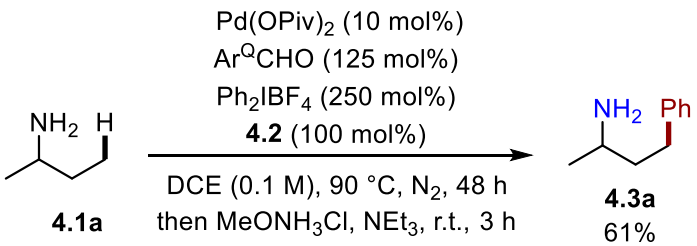
***N*-((1*R*,3*S*)-3-phenylcyclohexyl)benzamide (4.4v):** White solid (16.6 mg, 41% yield, 72% *brsm* yield as 12.7 mg starting material was recovered as its benzoylamide derivative). R_f = 0.3 (Hex/EA/DCM = 5:1:2). M.P. = 190 – 192 ^{o}C. IR (KBr) 3292, 2928, 1633, 1541, 1325, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.71 (m, 2H), 7.53 – 7.46 (m, 1H), 7.45 – 7.39 (m, 2H), 7.33 – 7.27 (m, 2H), 7.24 – 7.16 (m, 3H), 5.96 (d, *J* = 8.2 Hz, 1H), 4.16 (tdt, *J* = 11.9, 8.1, 4.0 Hz, 1H), 2.74 (tt, *J* = 12.1, 3.4 Hz, 1H), 2.35 – 2.25 (m, 1H), 2.21 – 2.14 (m, 1H), 2.00 – 1.89 (m, 2H), 1.66 – 1.54 (m, 1H), 1.47 – 1.35 (m, 2H), 1.26 – 1.20 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.66, 146.07, 134.92, 131.31, 128.53, 128.41, 126.78, 126.73, 126.16, 49.19, 43.10, 41.05, 33.09, 32.98, 25.13. HRMS: calcd. 280.16960 $[M+H]^+$ Found: 280.16990. The stereochemistry was determined by analysis of the coupling constants.



4.4w

***N*-((1*R*,3*S*)-3-phenylcyclopentyl)benzamide (4.4w):** White wax (19.8 mg, 50% yield, 76% *brsm* yield as 9.6 mg starting material was recovered as its benzoylamide derivative). R_f = 0.3 (Hex/EA/DCM = 5:1:2). IR (KBr) 3305, 2955, 1633, 1538, 1313, 913 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.72 (m, 2H), 7.53 – 7.47 (m, 1H), 7.46 – 7.40 (m, 2H), 7.34 – 7.26 (m, 4H), 7.24 – 7.17 (m, 1H), 6.15 (d, *J* = 7.1 Hz, 1H), 4.68 – 4.48 (m, 1H), 3.23 – 3.14 (m, 1H), 2.64 (dt, *J* = 13.2, 6.9 Hz, 1H), 2.38 – 2.28 (m, 1H), 2.22 – 2.14 (m, 1H), 1.91 – 1.81 (m, 1H), 1.78 – 1.71 (m, 1H), 1.64 – 1.60 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.12, 144.85, 134.69, 131.36, 128.53, 128.44, 126.88, 126.80, 126.13, 51.21, 43.79, 41.83, 32.87, 31.94. HRMS: calcd. 266.15390 $[M+H]^+$ Found: 266.15460. The stereochemistry was determined by 1D NOE analysis (*vide infra*).

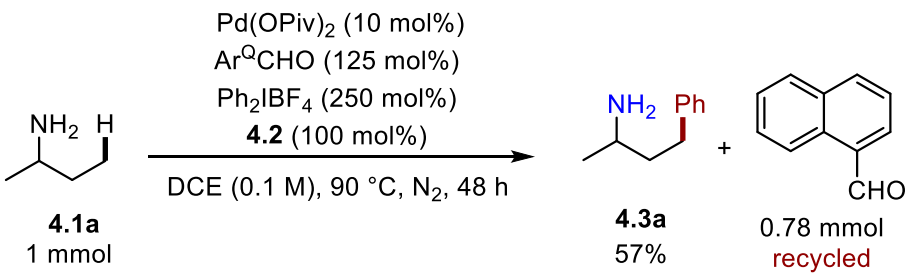
Scale-up reactions



4.1a **4.3a** 61%

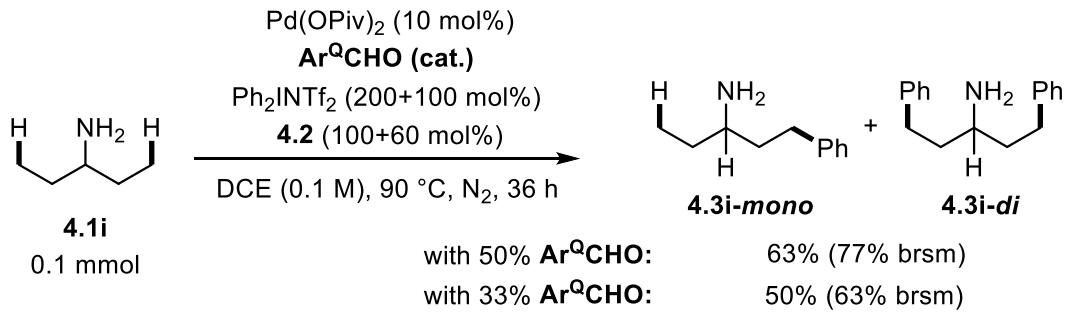
A 50 ml sealed vessel was charged with $Pd(OPiv)_2$ (93 mg, 0.3 mmol, 0.1 equiv), quinoline-8-carbaldehyde (588 mg, 3.75 mmol, 1.25 equiv), 2,6-di-*tert*-butyl-4-

methylpyridine **4.2** (615 mg, 3 mmol, 1.0 equiv) and DCE (30 mL), followed by the addition of 2-butylamine **4.1a** (219 mg, 3 mmol, 1.0 equiv) and Ph_2IBF_4 (2.76 g, 7.5 mmol, 2.5 equiv). The vessel was sealed and transferred into a glove box. After opening and purging under N_2 atmosphere for 8 min, the vial was then sealed again and heated in a pre-heated oil bath at 90 °C under stirring for 48h. After cooling to room temperature, the vessel was opened in air and methoxyamine hydrochloride (1 g, 12 mmol, 4.0 equiv) and NEt_3 (6 mL) were added to the reaction mixture. The mixture was stirred at RT for an additional 3h, filtered, and concentrated under *vacuo* (*due to the volatility of the products, the vacuum applied here is around 50 Torr*) and further purified by flash column chromatography over silica (5:1:2 hexanes/EtOAc/DCM, then 1:2:1:0.25 hexanes/EtOAc/DCM/NEt_3) to give the free amine product **4.3a** as a yellow oil that matched the literature reported data[25] (271 mg, 61%). R_f = 0.15 (Hex/EA/DCM/NEt_3 = 1:2:1:0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.25 – 7.13 (m, 3H), 2.92 (h, *J* = 6.3 Hz, 1H), 2.72 – 2.55 (m, 2H), 1.73 – 1.59 (m, 2H), 1.40 (br, 2H), 1.11 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.23, 128.28, 128.26, 125.66, 46.48, 41.76, 32.77, 23.95.



A 40 mL vial was charged with $Pd(OPiv)_2$ (31 mg, 0.1 mmol, 0.10 equiv), quinoline-8-carbaldehyde (196 mg, 1.25 mmol, 1.25 equiv), 2,6-di-*tert*-butyl-4-methylpyridine **4.2** (205 mg, 1 mmol, 1.0 equiv) and DCE (10 mL), followed by the addition of 2-butylamine **4.1a** (73 mg, 0.1 mmol, 1.0 equiv) and Ph_2IBF_4 (920 mg, 2.5 mmol, 2.5 equiv). The vial was sealed with a PTFE lined cap and transferred into a glove box. After opening and purging under N_2 atmosphere for 5 min, the vial was then sealed again and heated in a pie-block at 90 °C under stirring for 48h. After cooling to room temperature, the reaction mixture was mixed with 1M aqueous HCl (25 mL). After stirred at room temperature for 15 min, the mixture was transferred to a separate funnel and the organic phase was discarded. The water phase was extracted with DCM (5 mL) and the organic phase was discarded. Then the water phase was basified by 4M aqueous NaOH until pH > 12. The water phase was extracted with DCM (4 x 15 mL). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo* (*due to the volatility of the products, the vacuum applied here is around 50 Torr*). The residue was further purified by flash column chromatography over silica (5:1:2 hexanes/EtOAc/DCM, then 1:2:1:0.25 hexanes/EtOAc/DCM/NEt_3) to afford the recycled Ar^QCHO as a white solid (124 mg, 0.78 mmol) and the free amine product **4.3a** as a yellow oil (84.3 mg, 57%).

Use of catalytic Ar^QCHO



Use of 50 mol% catalytic Ar^{Q}CHO: A 4 mL vial was charged with $Pd(OPiv)_2$ (3.1 mg, 0.01 mmol, 0.10 equiv), quinoline-8-carbaldehyde (7.9 mg, 0.05 mmol, 0.5 equiv), 2,6-di-*tert*-butyl-4-methylpyridine **4.2** (20.5 mg, 0.1 mmol, 1.0 equiv) and DCE (1.0 mL), followed by the addition of 3-pentylamine **4.1i** (8.7 mg, 0.1 mmol, 1.0 equiv) and Ph_2IBF_4 (74 mg, 0.2 mmol, 2.0 equiv). The vial was sealed with a PTFE lined cap and transferred into a glove box. After opening and purging under N_2 atmosphere for 5 min, the vial was then sealed again and heated in a pie-block at 90 °C under stirring for 18h. After cooling to room temperature, the second batch of Ph_2IBF_4 (37 mg, 0.1 mmol, 1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine **4.2** (12.3 mg, 0.06 mmol, 0.6 equiv) was added to the reaction mixture under air. The vial was sealed again and transferred into a glove box. After opening and purging under N_2 atmosphere for 5 min, the vial was then sealed and heated at 90 °C for additional 18h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yield of the desired product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard (^{1}H NMR yield of **4.3i-*mono***: 26%, ^{1}H NMR yield of **4.3i-*di***: 37%, unreacted **4.1i:** 18%).

Use of 33 mol% catalytic $Ar^{Q}CHO$: A 4 mL vial was charged with $Pd(OPiv)_2$ (3.1 mg, 0.01 mmol, 0.10 equiv), quinoline-8-carbaldehyde (5.2 mg, 0.033 mmol, 0.33 equiv), 2,6-di-*tert*-butyl-4-methylpyridine **4.2** (20.5 mg, 0.1 mmol, 1.0 equiv) and DCE (1.0 mL), followed by the addition of 3-pentylamine **4.1i** (8.7 mg, 0.1 mmol, 1.0 equiv) and Ph_2IBF_4 (74 mg, 0.2 mmol, 2.0 equiv). The vial was sealed with a PTFE lined cap and transferred into a glove box. After opened and purged under N_2 atmosphere for 5 min, the vial was then sealed again and heated in a pie-block at 90 °C under stirring for 18h. After cooling to room temperature, the second batch of Ph_2IBF_4 (37 mg, 0.1 mmol, 1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine **4.2** (12.3 mg, 0.06 mmol, 0.6 equiv) was added to the reaction mixture under air. The vial was sealed again and transferred into a glove box. After opening and purging under N_2 atmosphere for 5 min, the vial was then sealed and heated at 90 °C for additional 18h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yield of the desired product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard (^{1}H NMR yield of **4.3i-*mono***: 20%, ^{1}H NMR yield of **4.3i-*di***: 30%, unreacted **4.1i:** 20%).

4.5 ^{1}H-NMR and ^{13}C-NMR spectra

Figure 4.1 ^{1}H-NMR Spectrum of **4.4a**

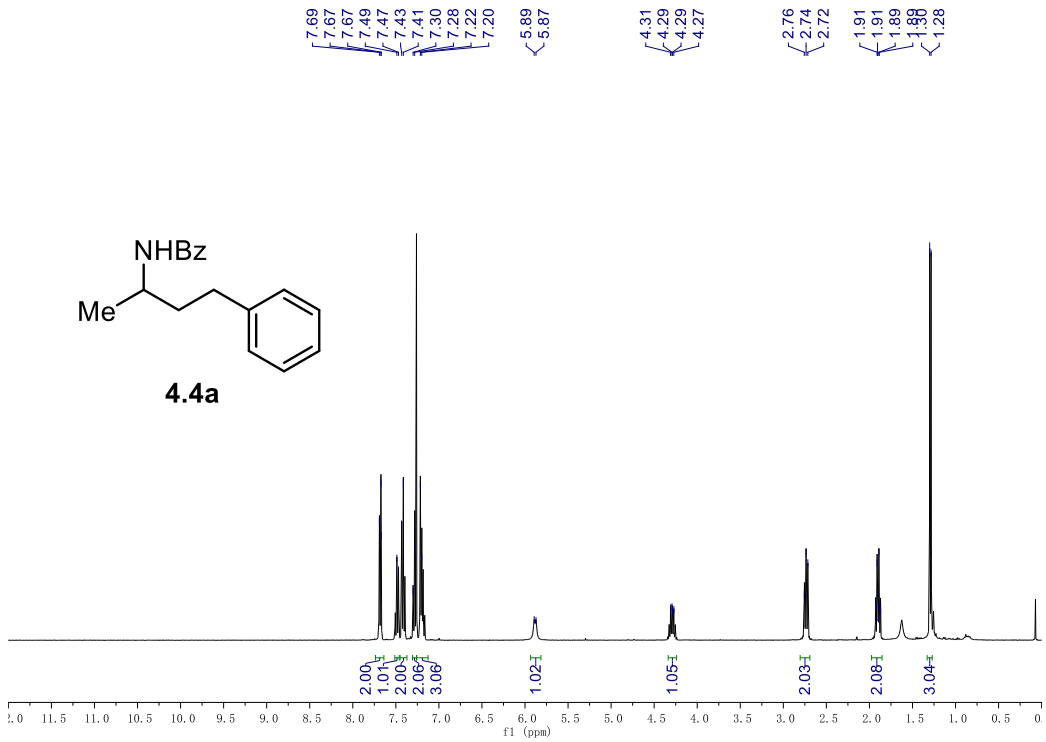


Figure 4.2 ^{13}C-NMR Spectrum of **4.4a**

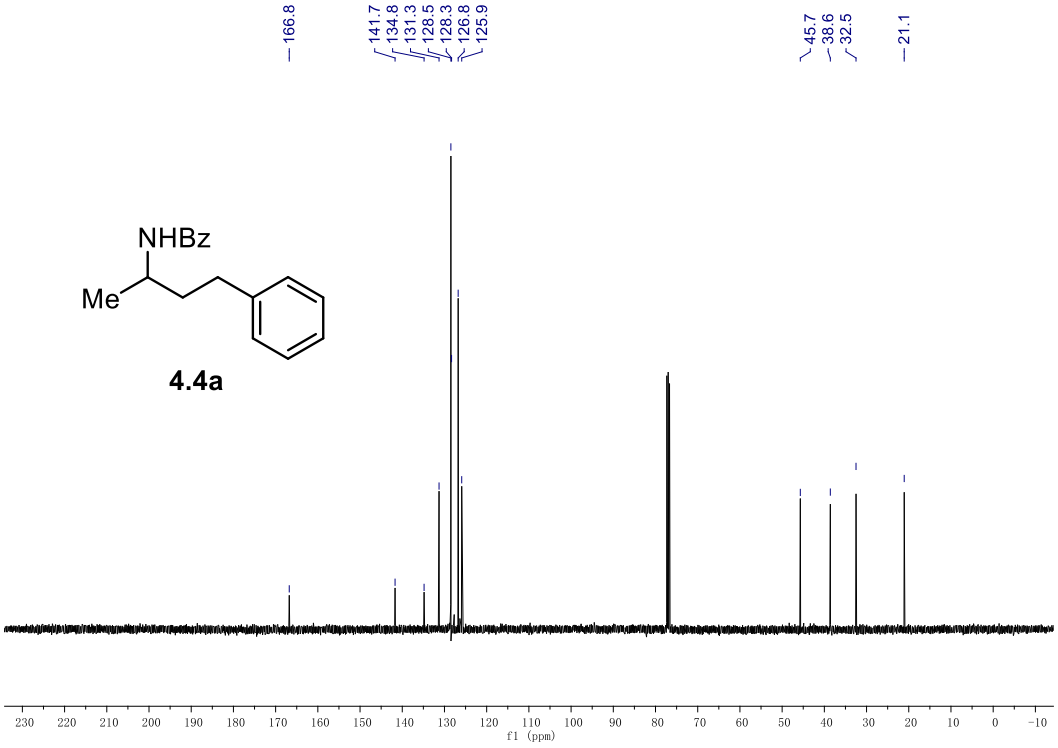


Figure 4.3 ^{1}H-NMR Spectrum of **4.4b**

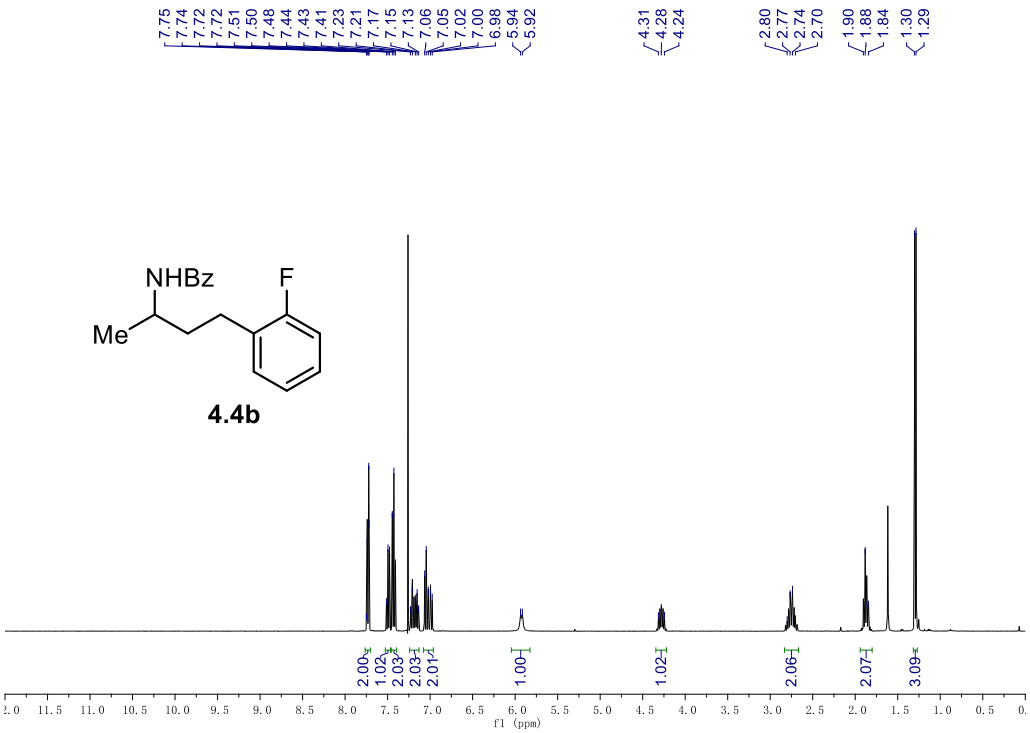


Figure 4.4 ^{13}C-NMR Spectrum of **4.4b**

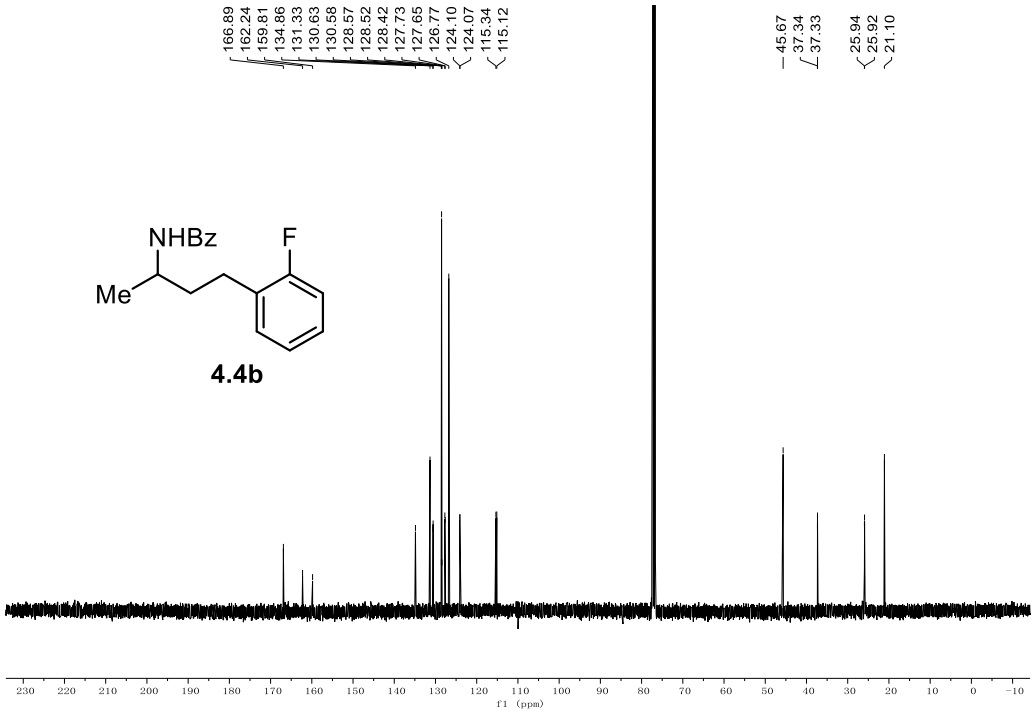


Figure 4.5 ^{1}H-NMR Spectrum of **4.4c**

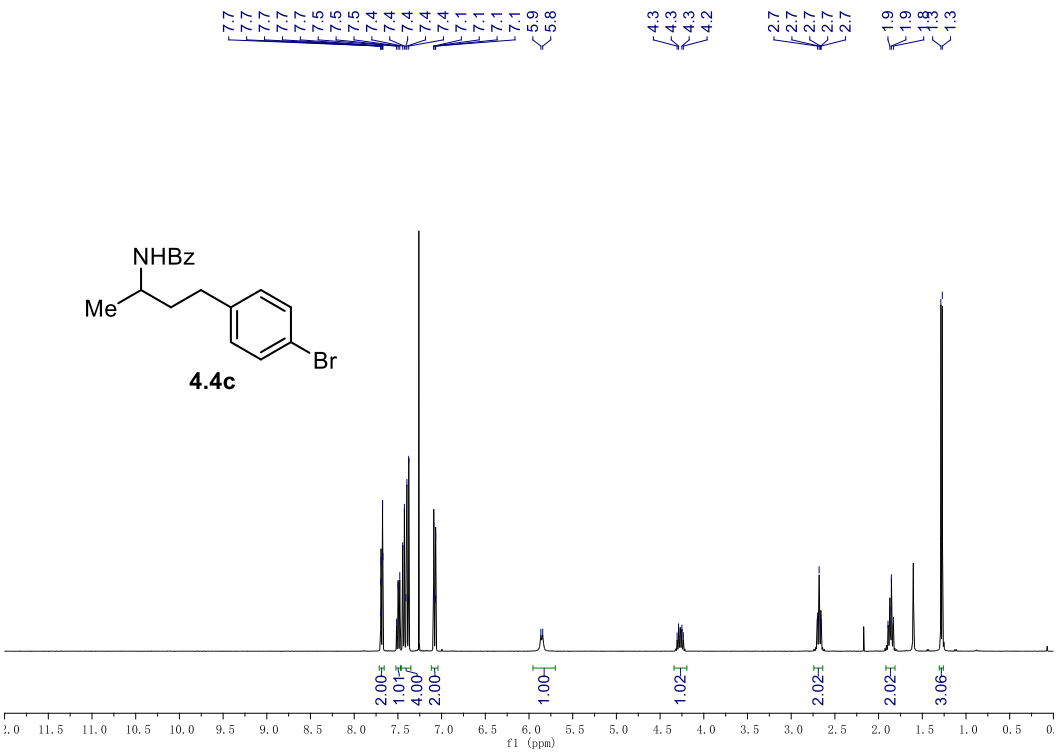


Figure 4.6 ^{13}C-NMR Spectrum of **4.4c**

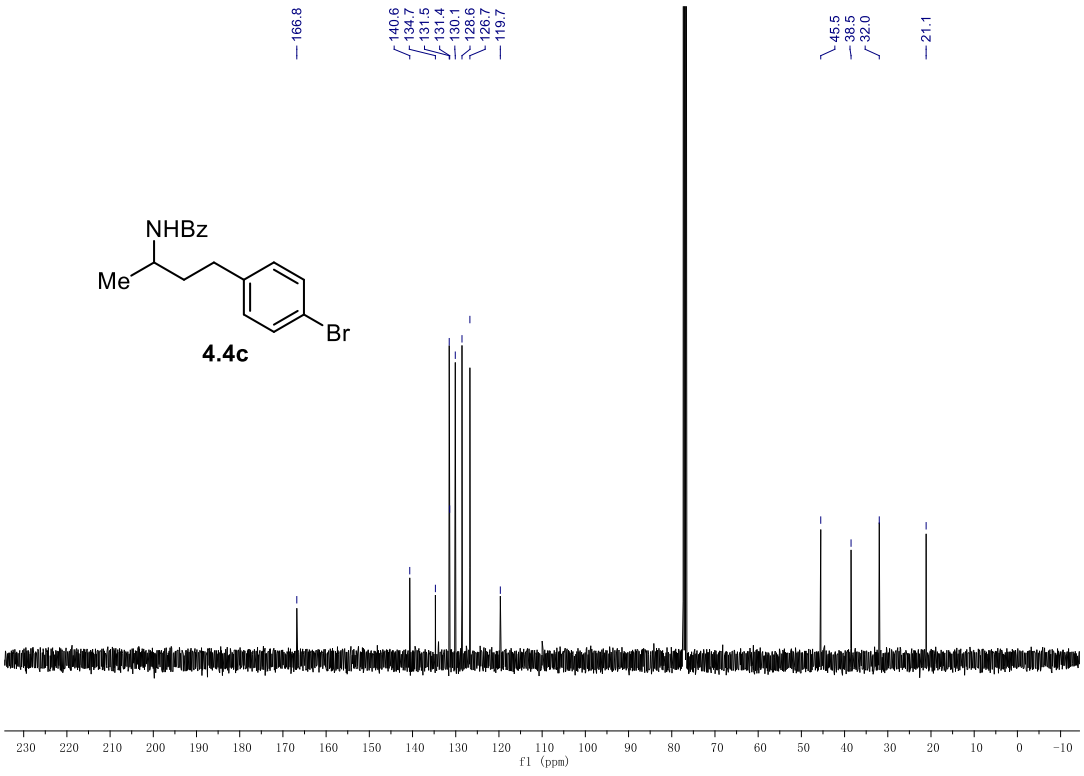


Figure 4.7 ^{1}H-NMR Spectrum of **4.4d**

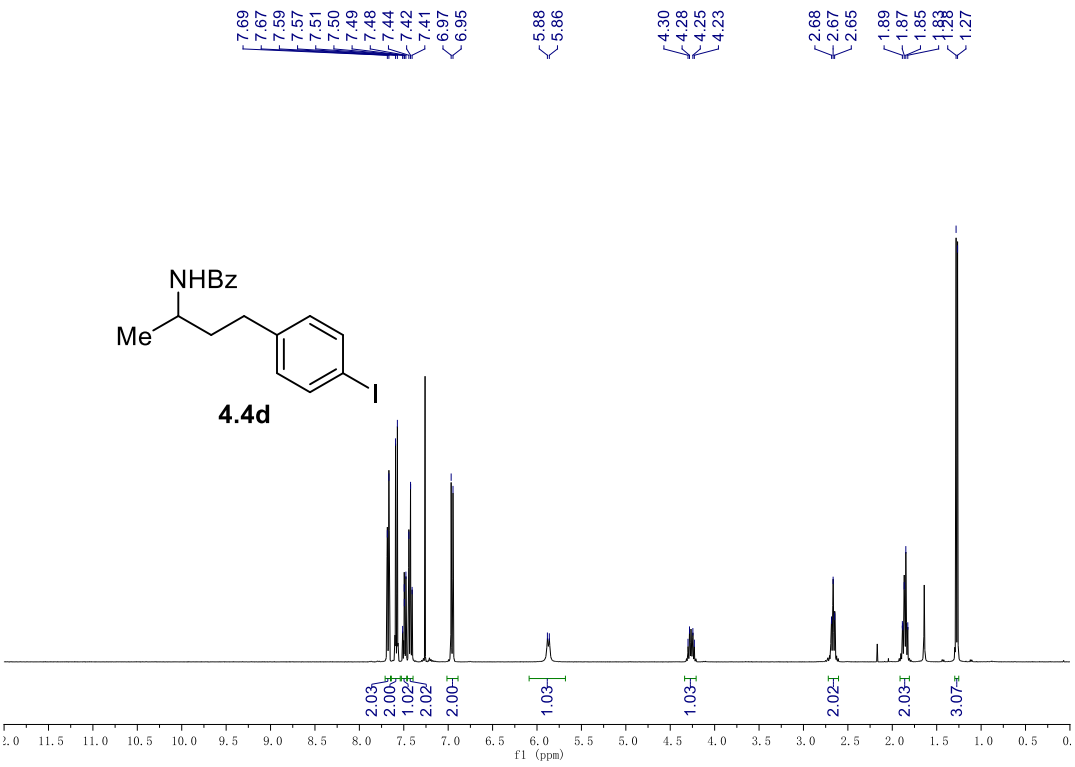


Figure 4.8 ^{13}C-NMR Spectrum of **4.4d**

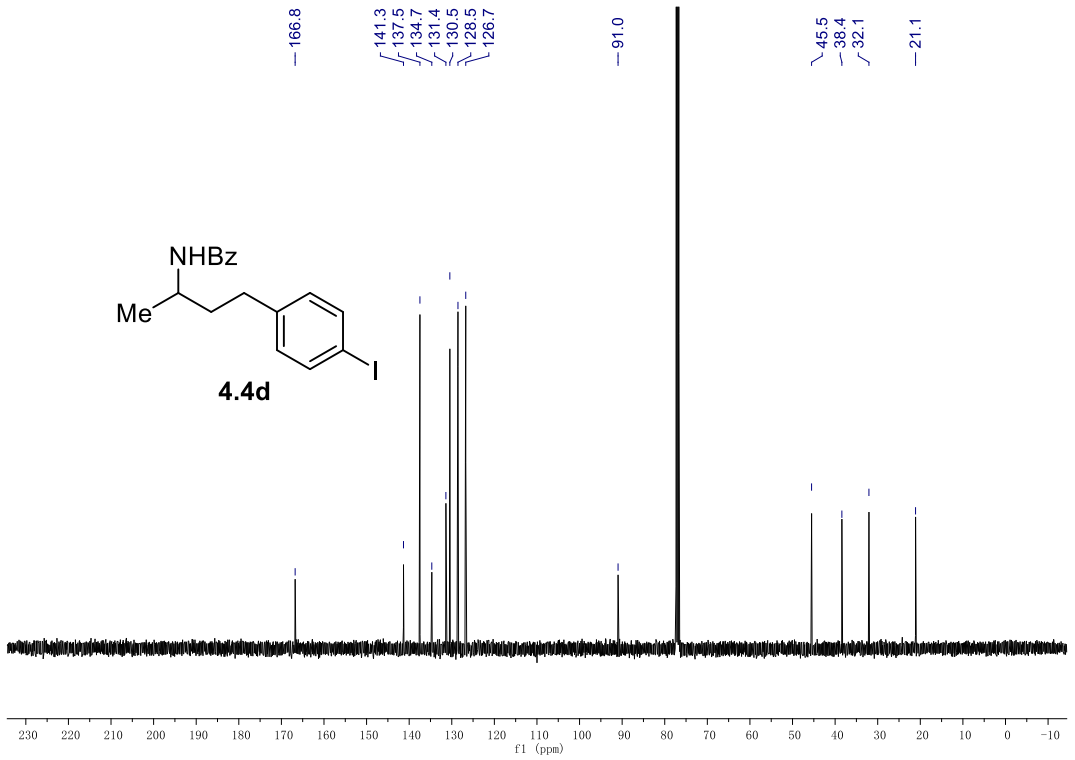


Figure 4.9 ^{1}H-NMR Spectrum of **4.4e**

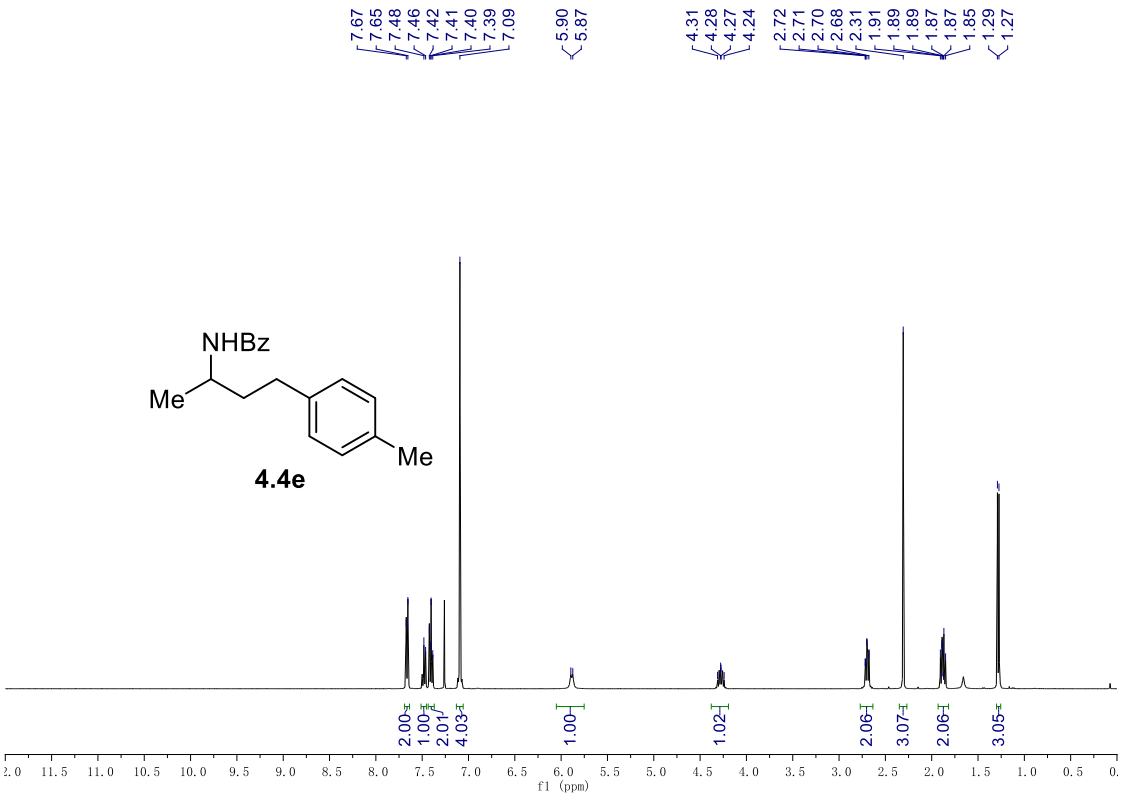


Figure 4.10 ^{13}C-NMR Spectrum of **4.4e**

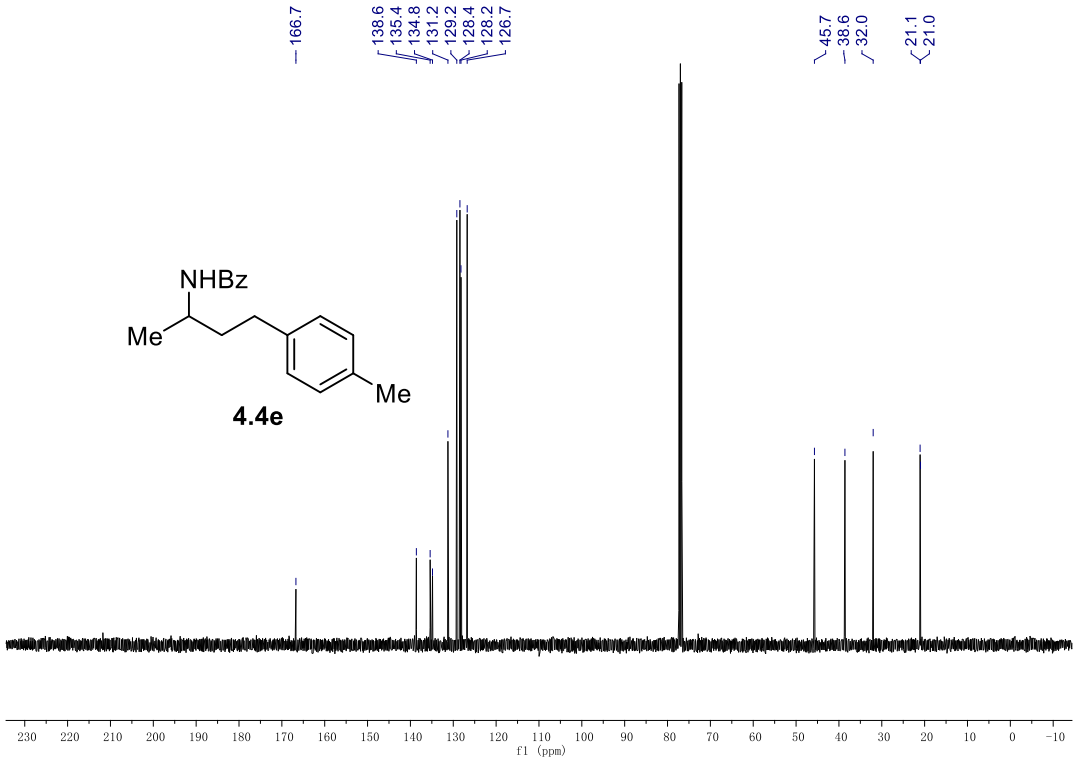


Figure 4.11 ^{1}H-NMR Spectrum of **4.4f**

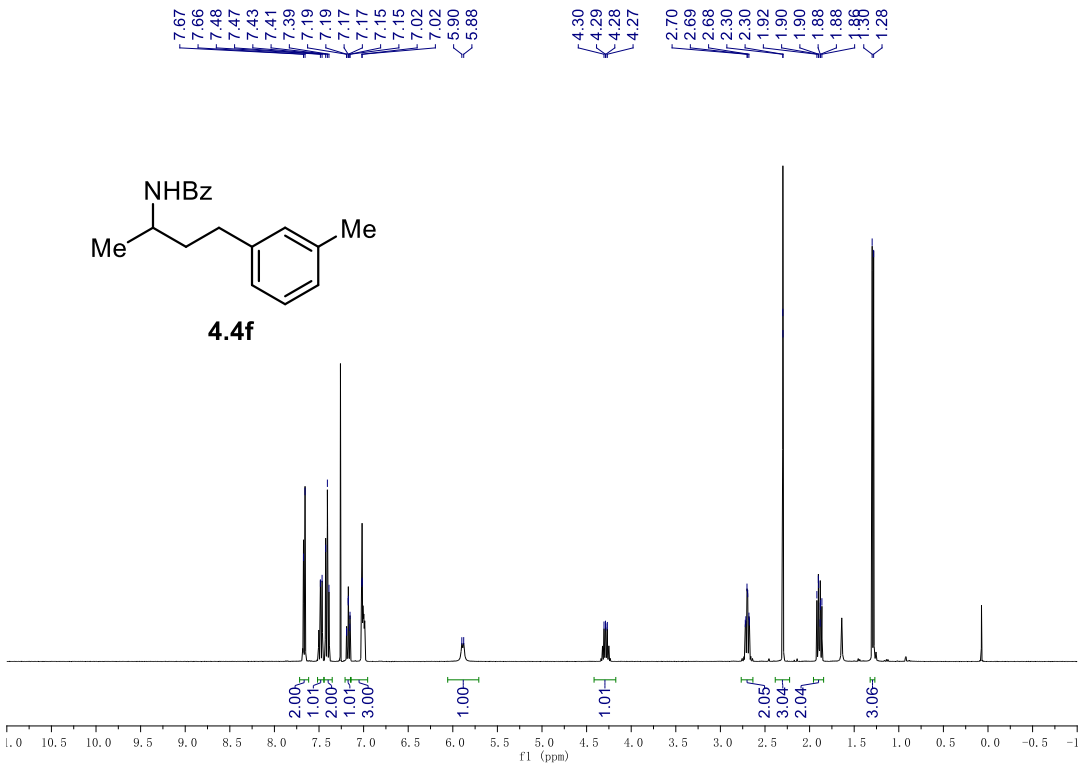


Figure 4.12 ^{13}C-NMR Spectrum of **4.4f**

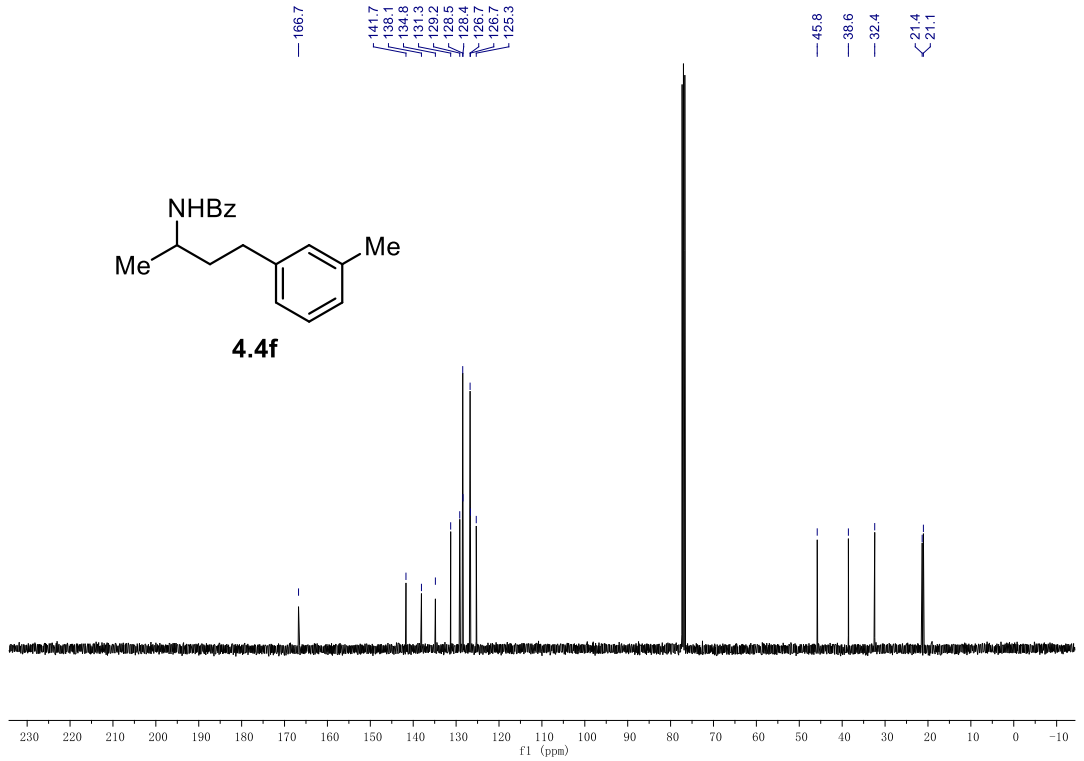


Figure 4.13 ^{1}H-NMR Spectrum of **4.4g**

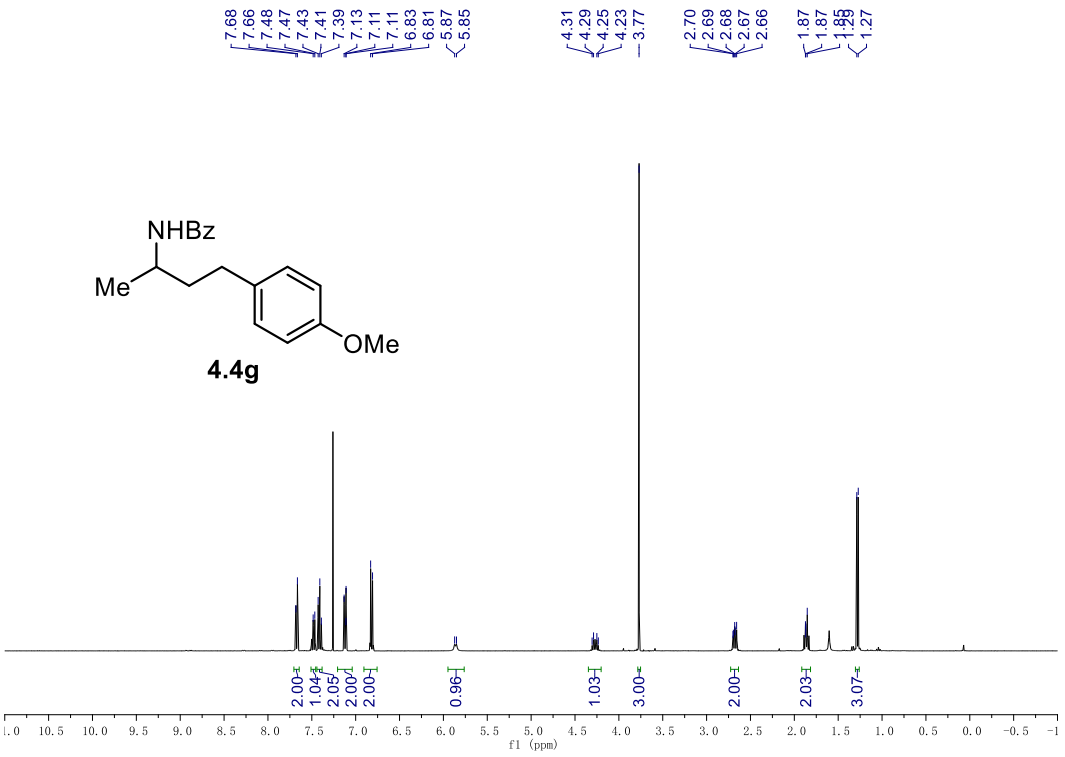


Figure 4.14 ^{13}C-NMR Spectrum of **4.4g**

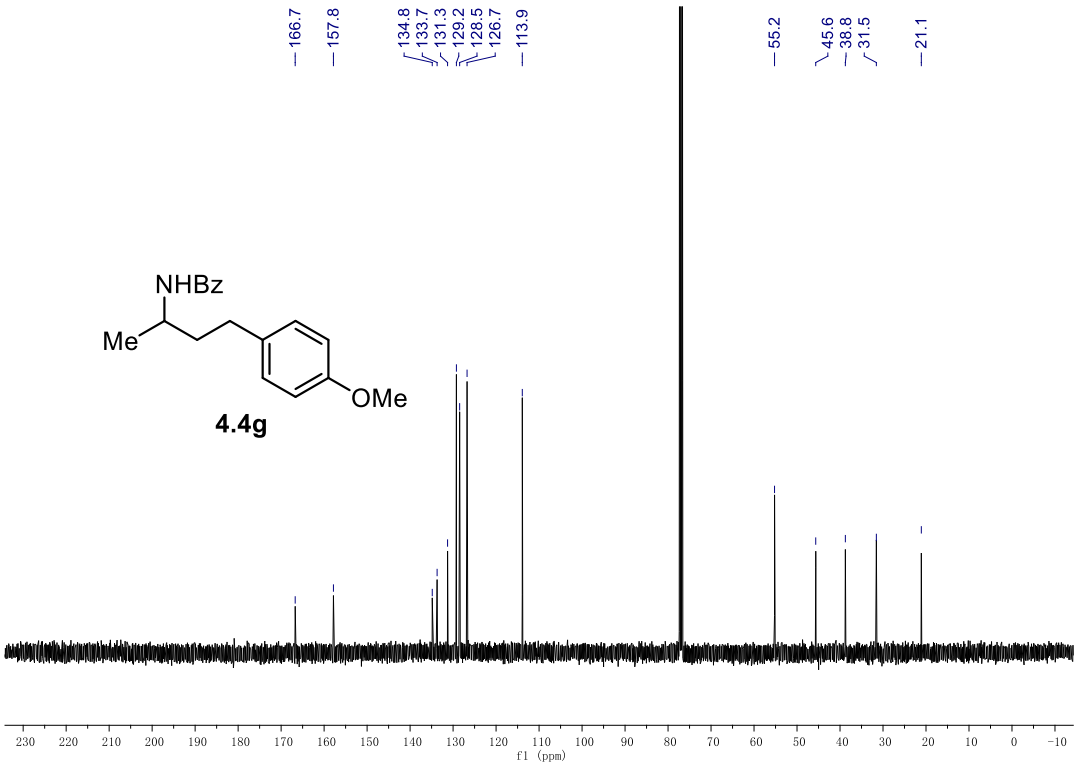


Figure 4.15 ^{1}H-NMR Spectrum of **4.4h-mono**

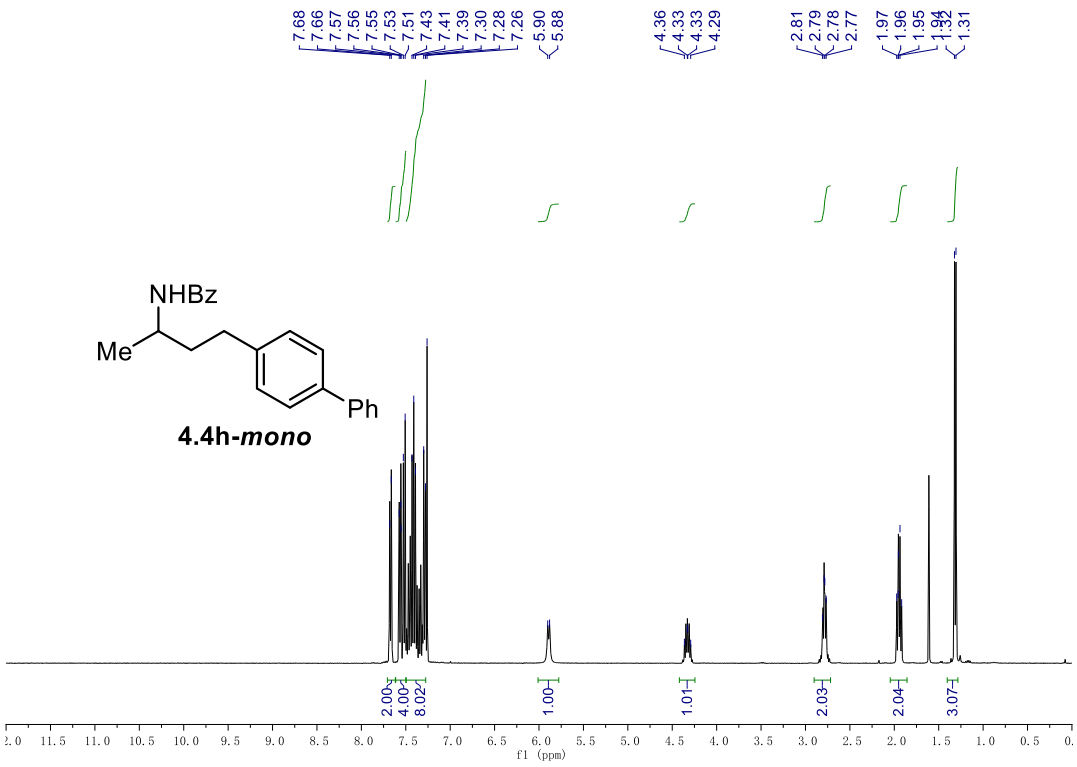


Figure 4.16 ^{13}C-NMR Spectrum of **4.4h-mono**

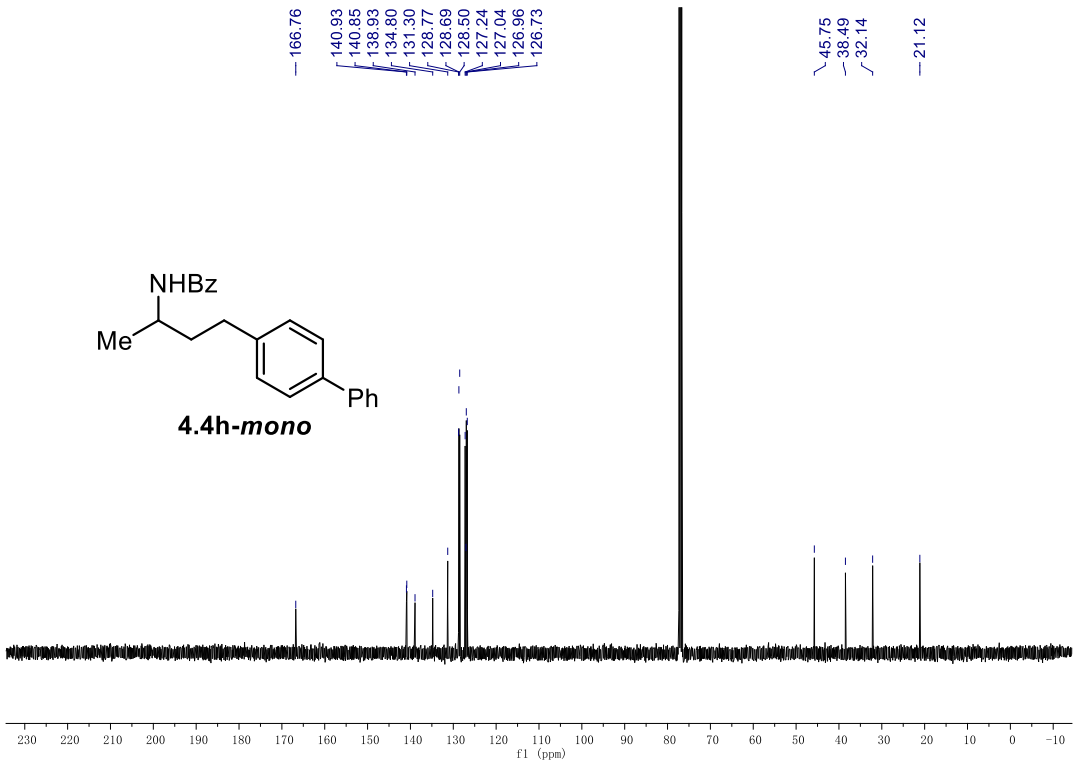


Figure 4.17 ^{1}H-NMR Spectrum of **4.4h-di**

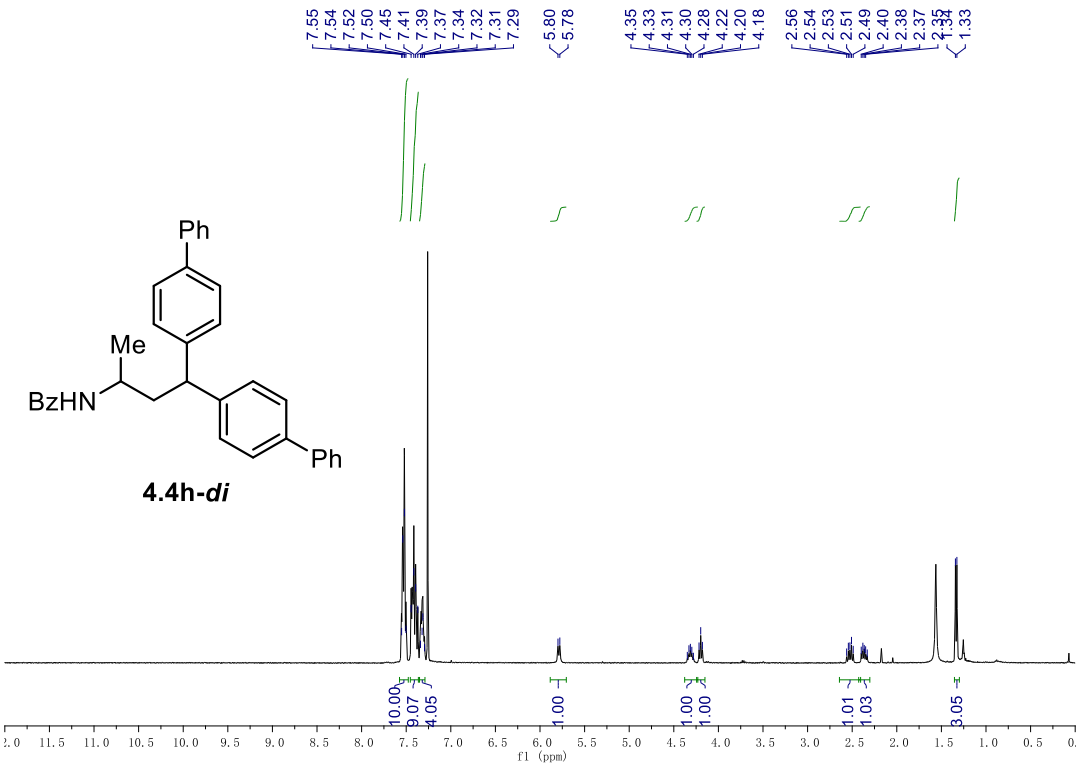


Figure 4.18 ^{13}C-NMR Spectrum of **4.4h-di**

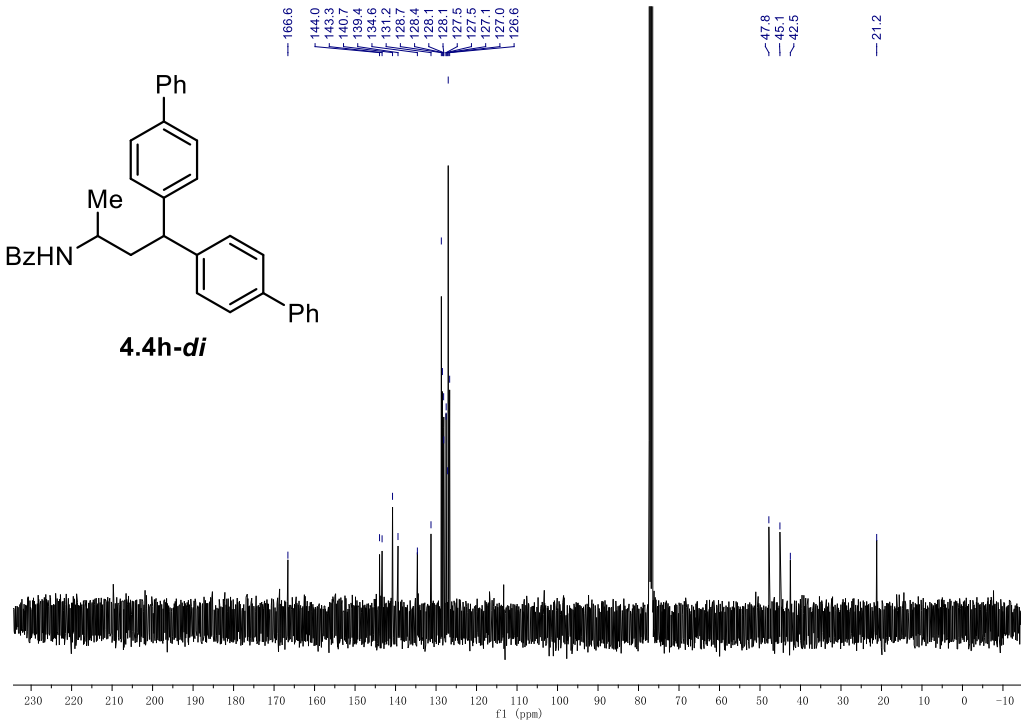


Figure 4.19 ^{1}H-NMR Spectrum of **4.4i-mono**

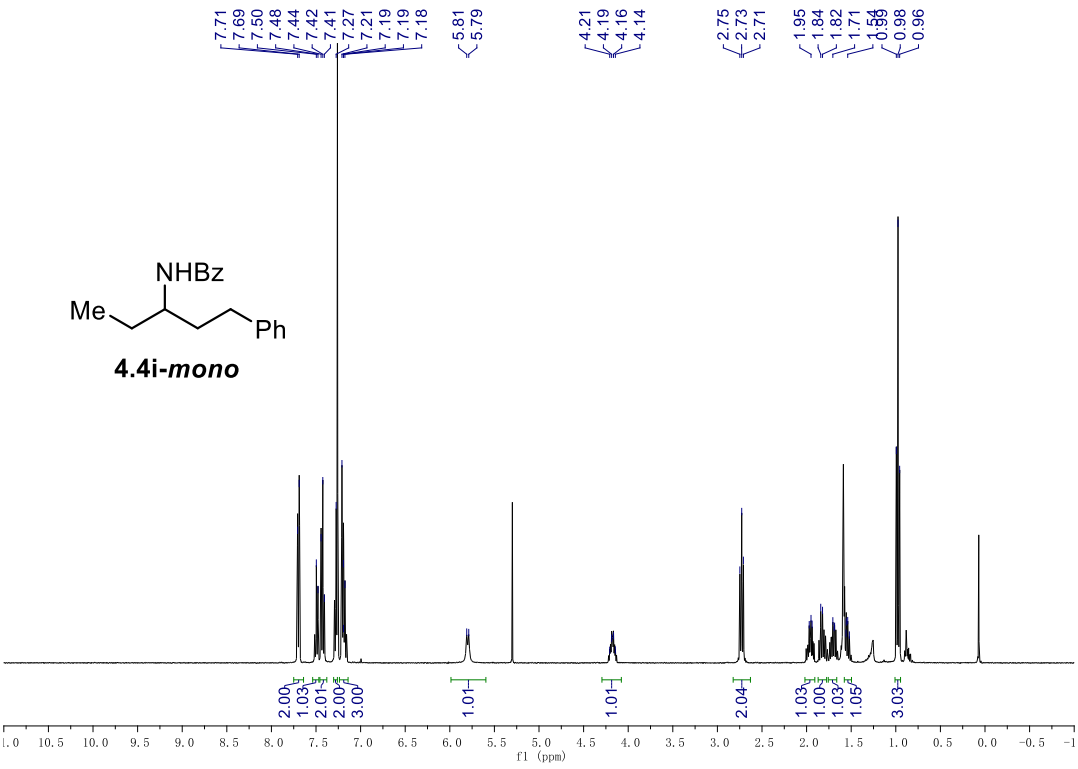


Figure 4.20 ^{13}C-NMR Spectrum of **4.4i-mono**

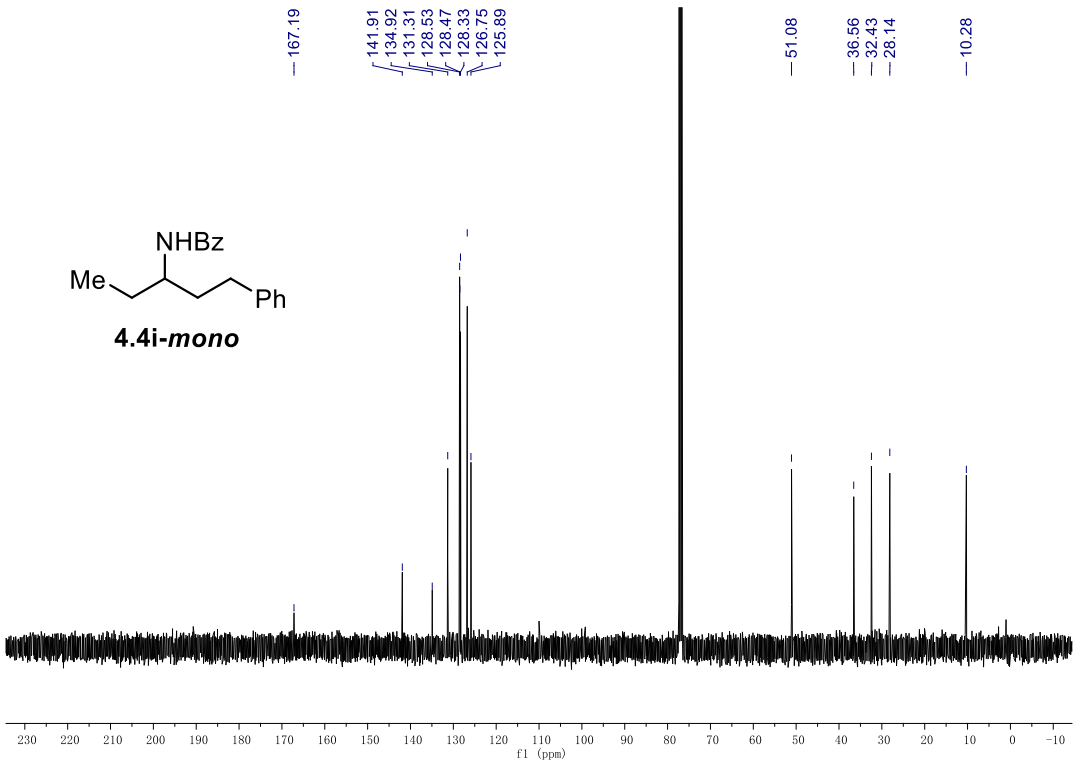


Figure 4.21 ^{1}H-NMR Spectrum of **4.4i-di**

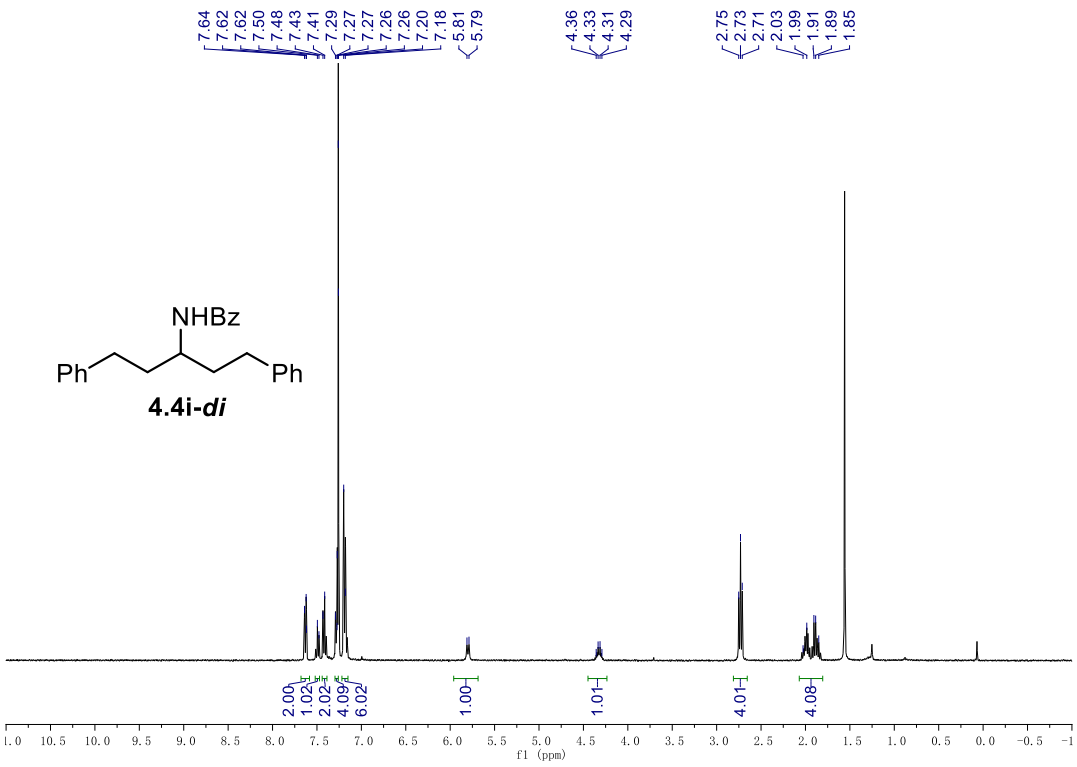


Figure 4.22 ^{13}C-NMR Spectrum of **4.4i-di**

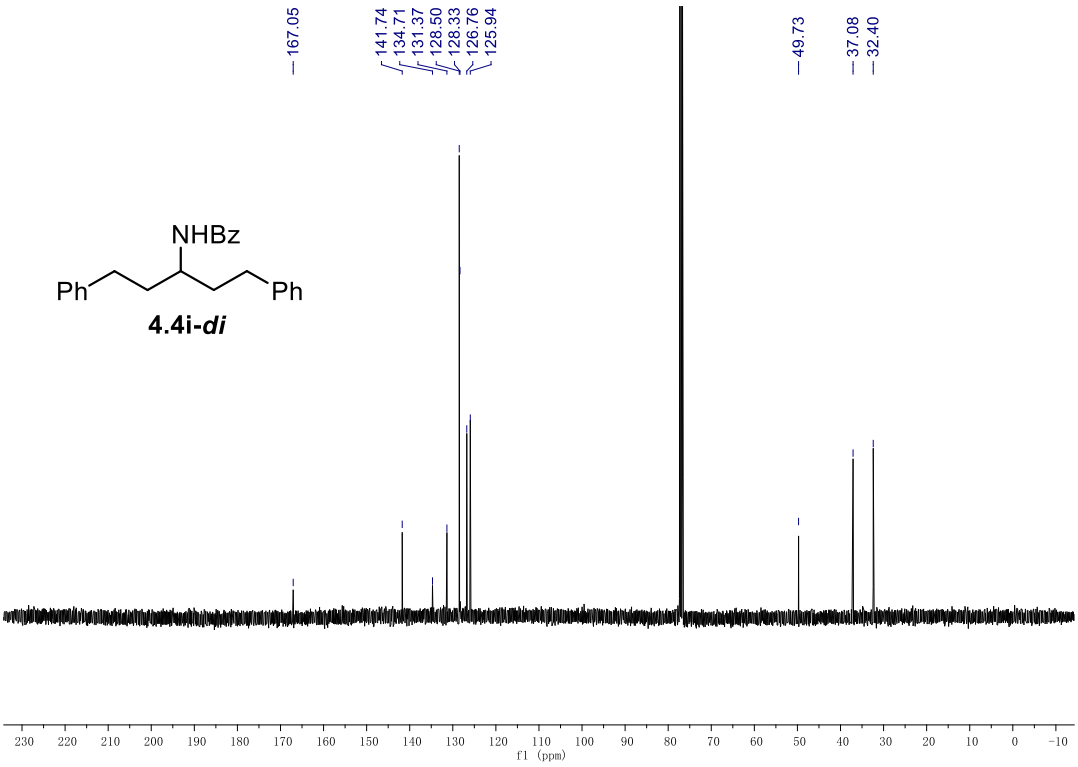


Figure 4.23 ^{1}H-NMR Spectrum of **4.4j**

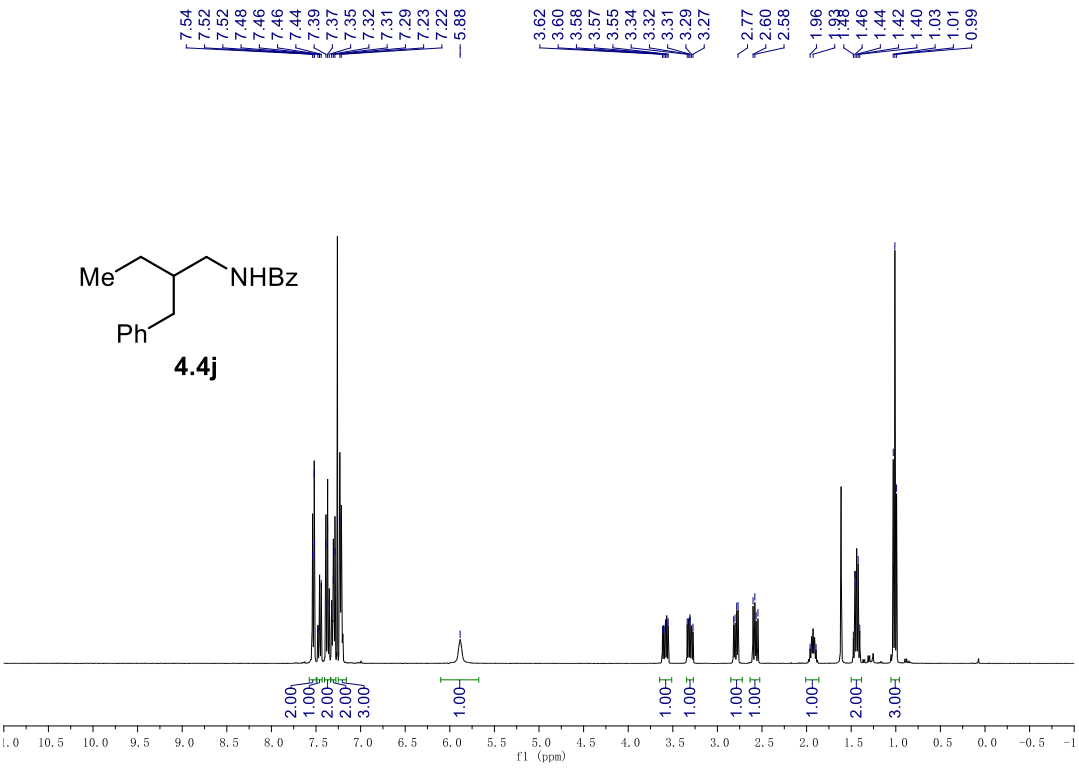


Figure 4.24 ^{13}C-NMR Spectrum of **4.4j**

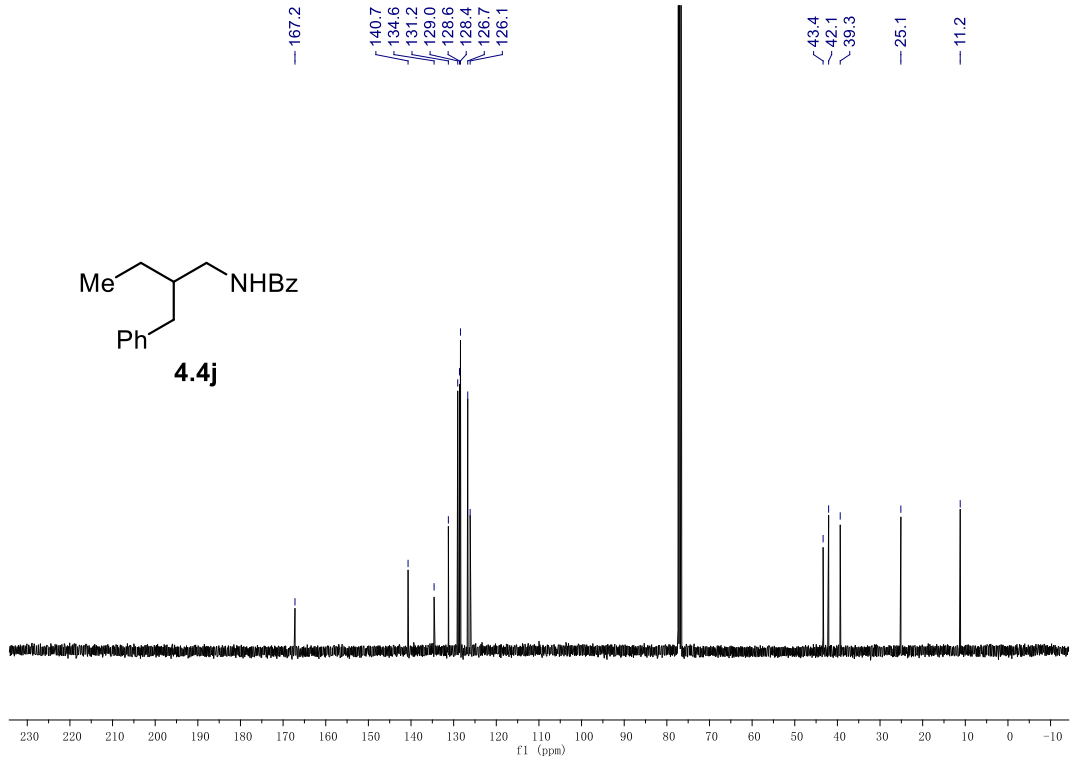


Figure 4.25 ^{1}H-NMR Spectrum of **4.4k-mono** and **4.4k-di**

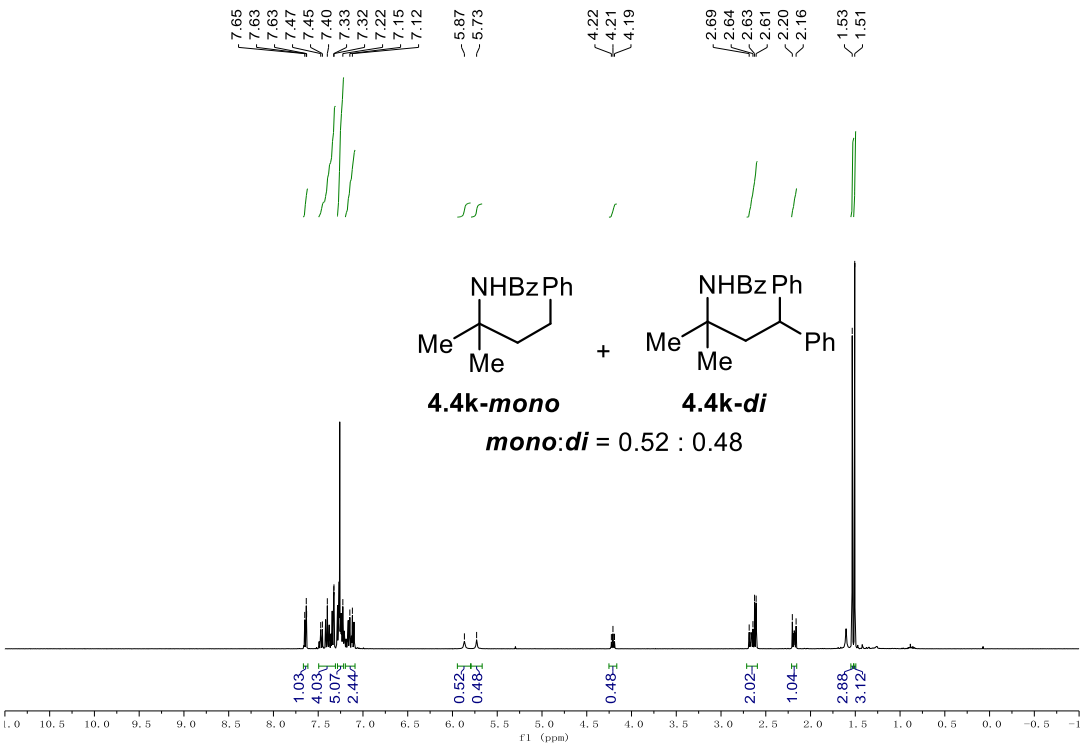


Figure 4.26 ^{13}C-NMR Spectrum of **4.4k-mono** and **4.4k-di**

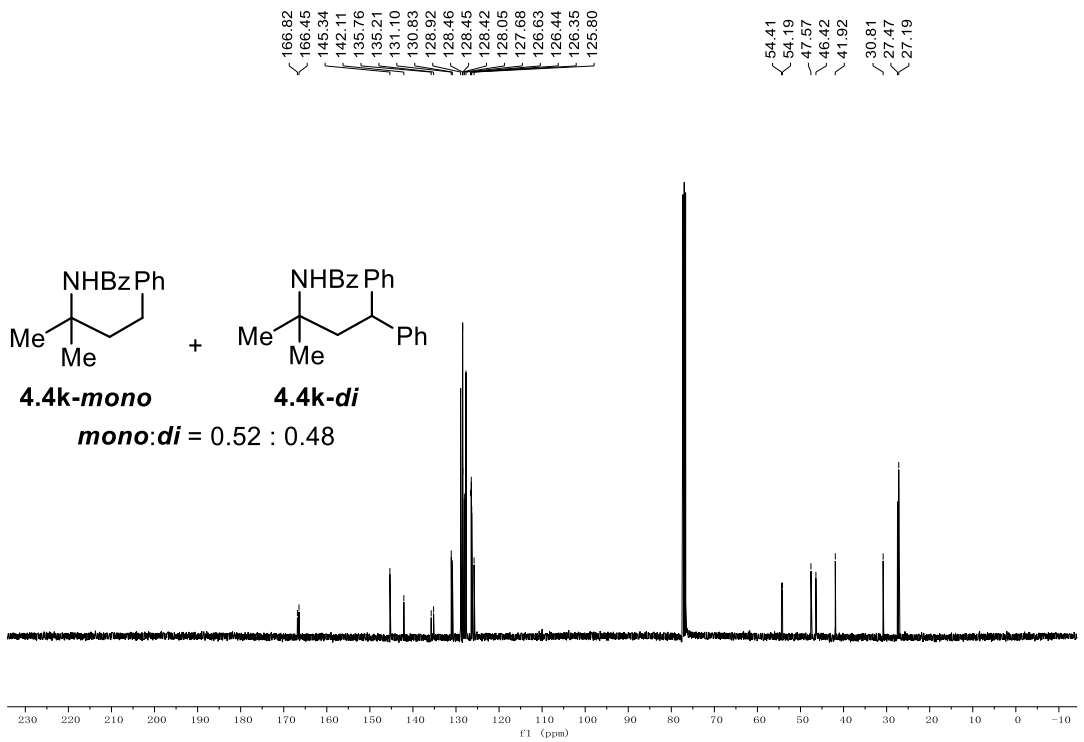


Figure 4.27 ^{1}H-NMR Spectrum of **4.4l**

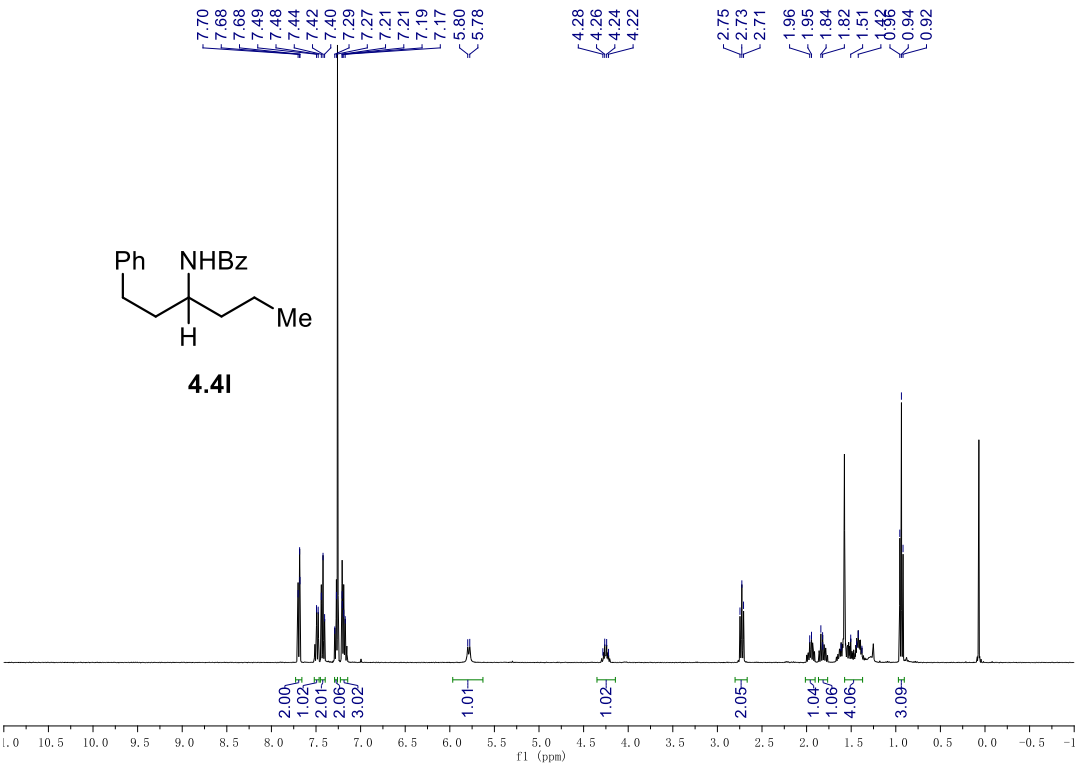


Figure 4.28 ^{13}C-NMR Spectrum of **4.4l**

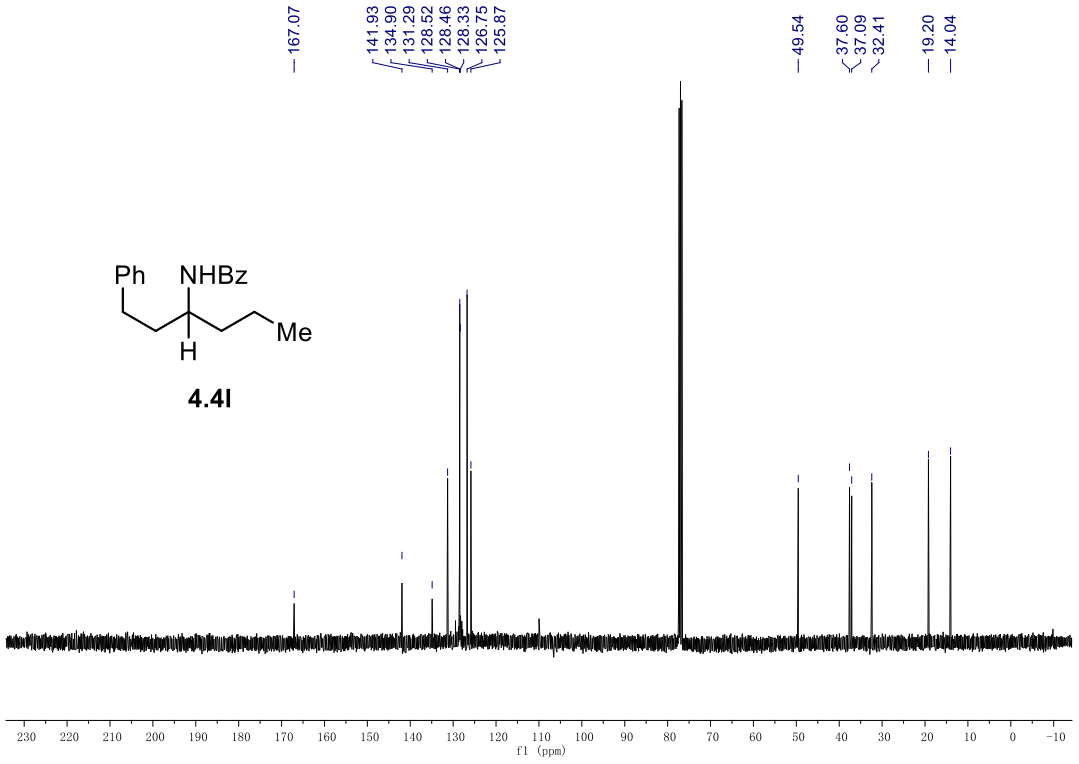


Figure 4.29 1H-NMR Spectrum of **4.4m-mono**

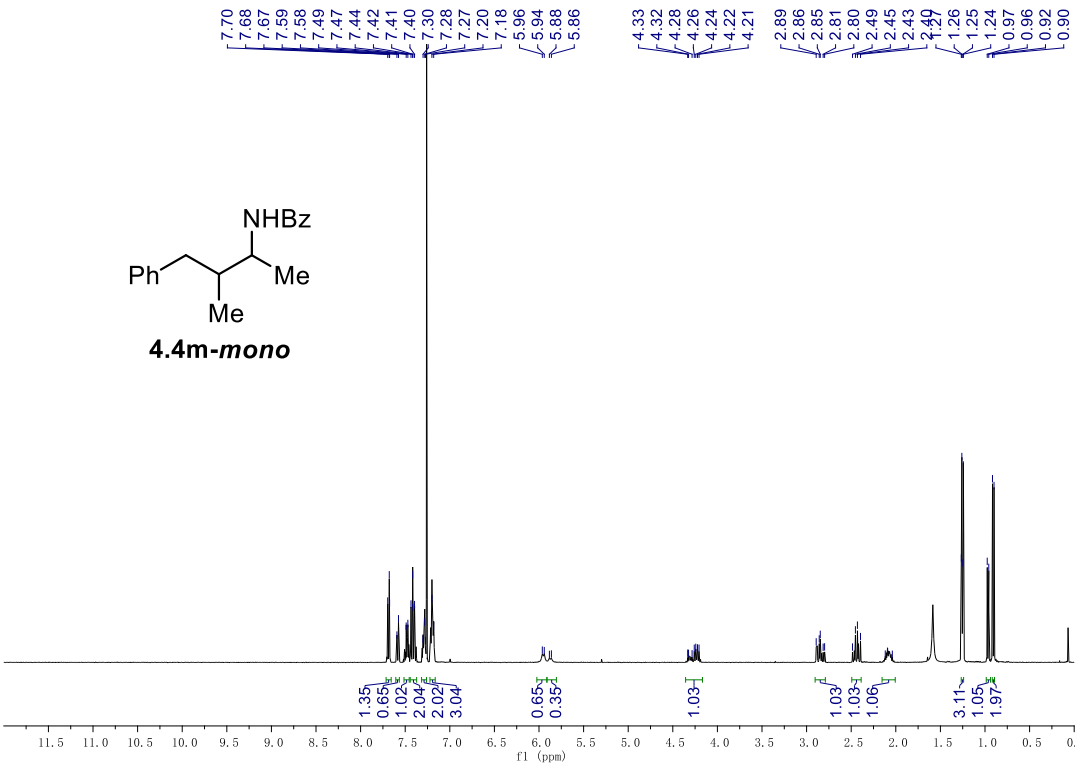


Figure 4.30 ^{13}C-NMR Spectrum of **4.4m-mono**

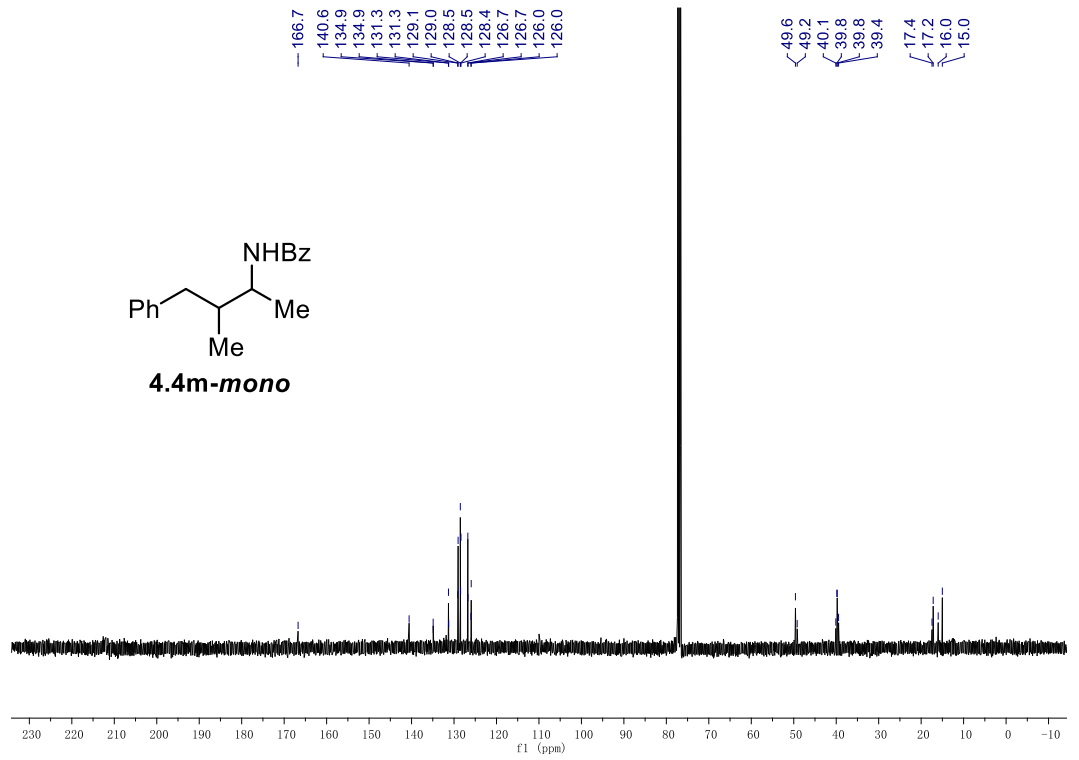


Figure 4.31 ^{1}H-NMR Spectrum of **4.4m-di**

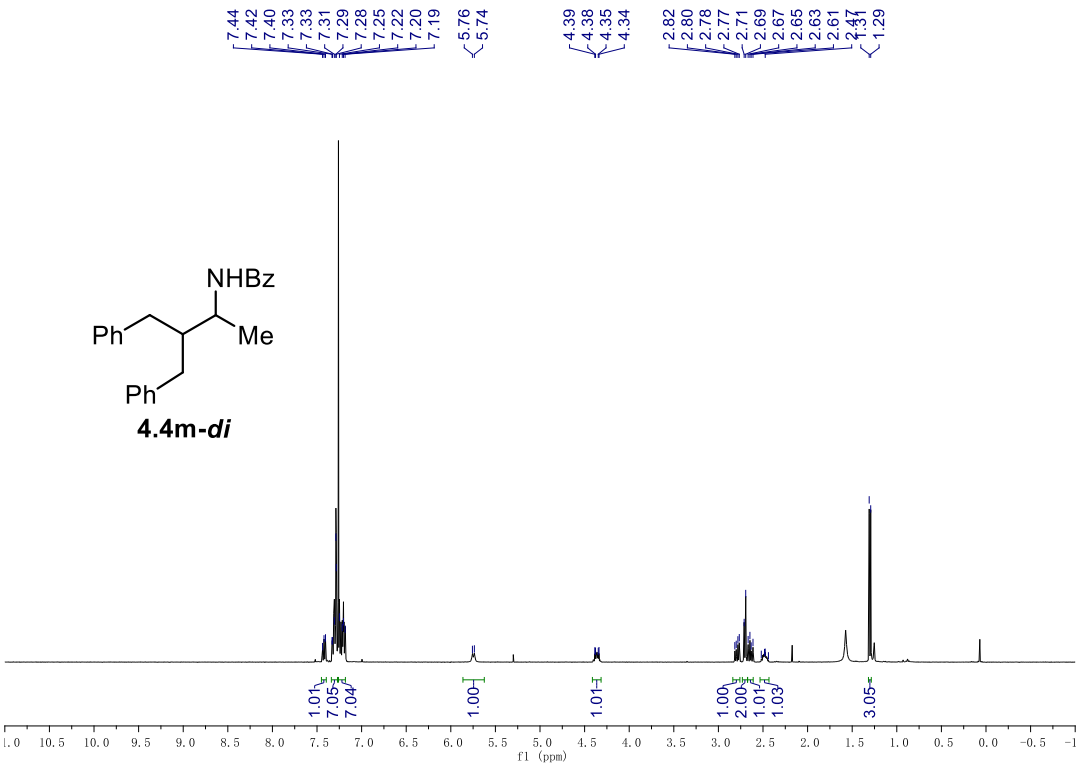


Figure 4.32 ^{13}C-NMR Spectrum of **4.4m-di**

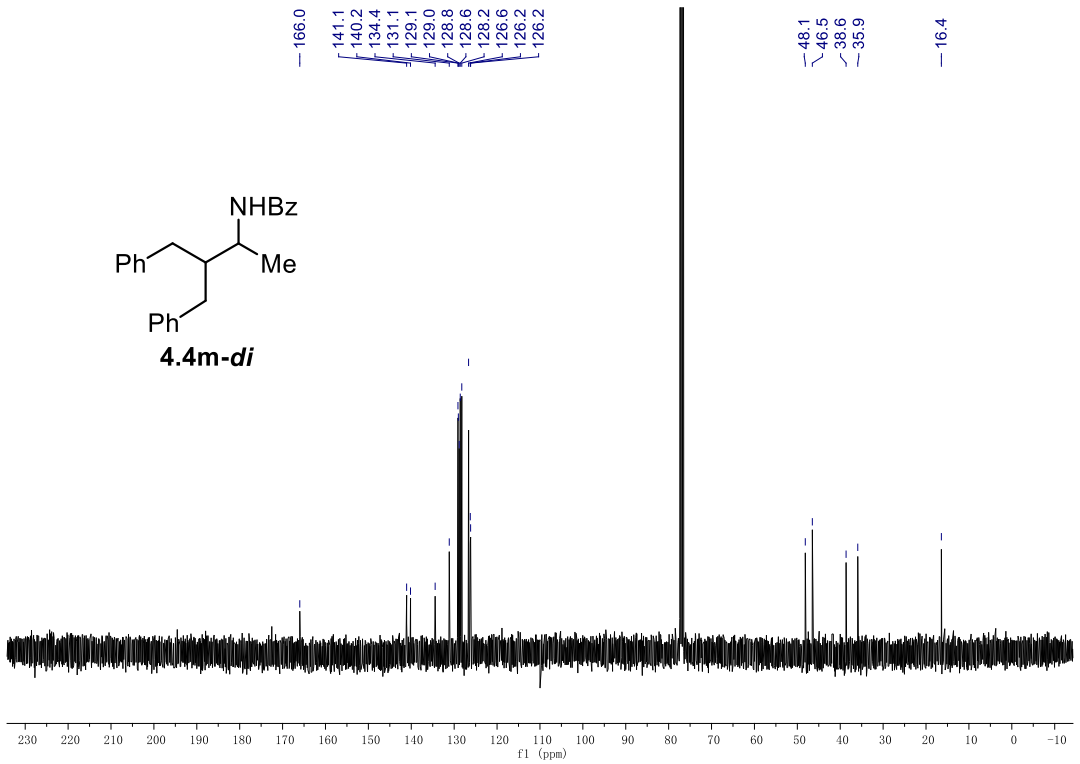


Figure 4.33 ^{1}H-NMR Spectrum of **4.4n**

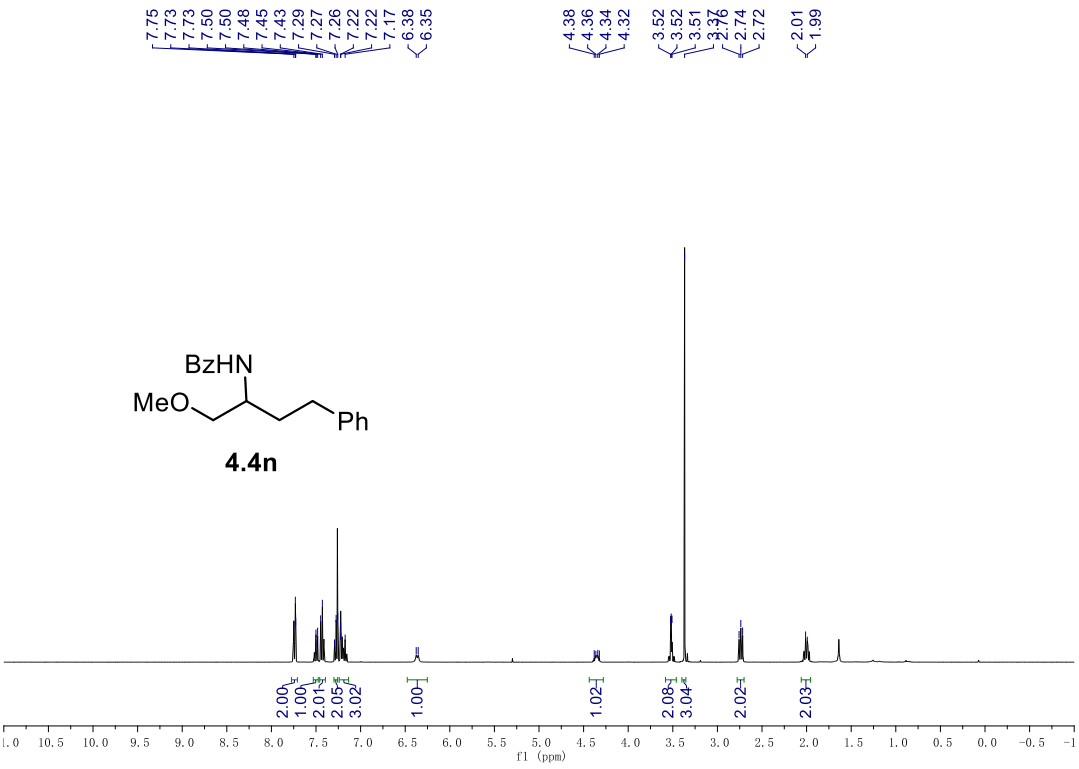


Figure 4.34 ^{13}C-NMR Spectrum of **4.4n**

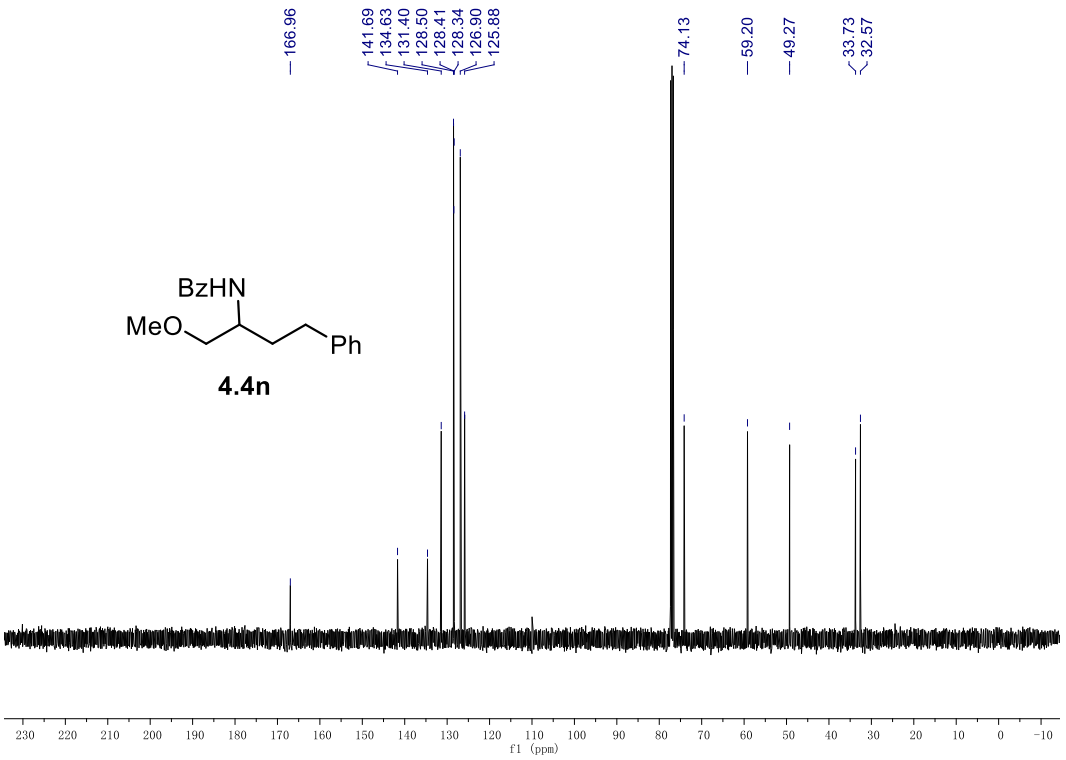


Figure 4.35 ^{1}H-NMR Spectrum of **4.4o**

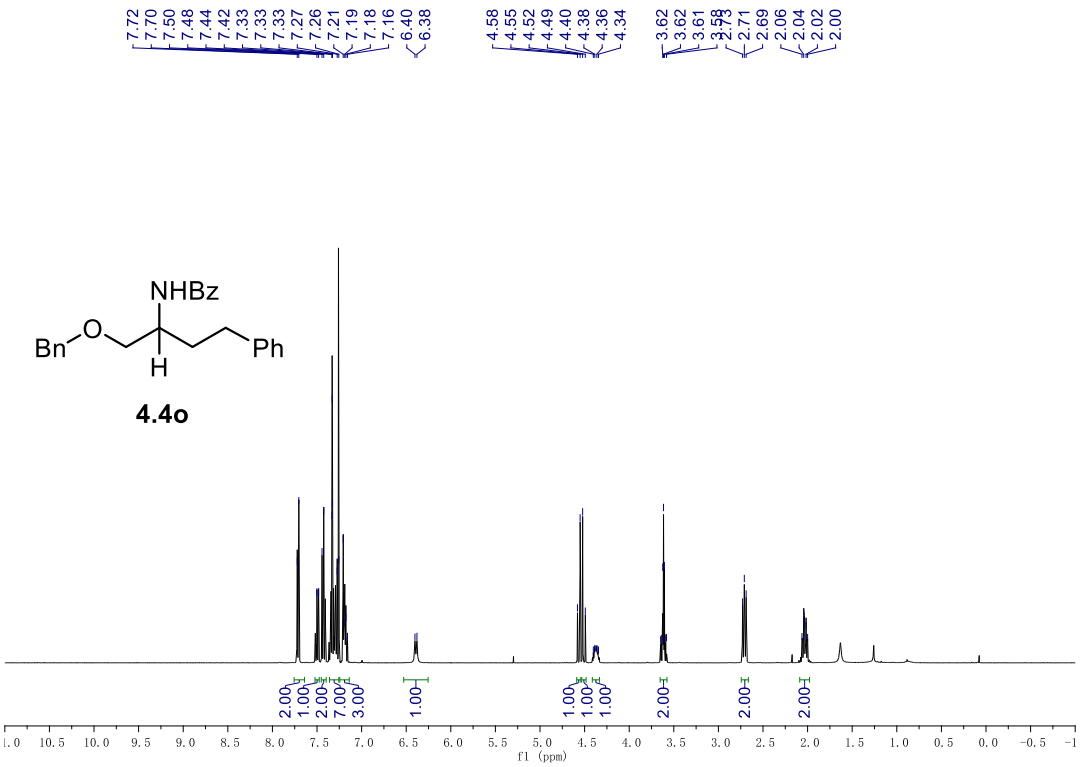


Figure 4.36 ^{13}C-NMR Spectrum of **4.4o**

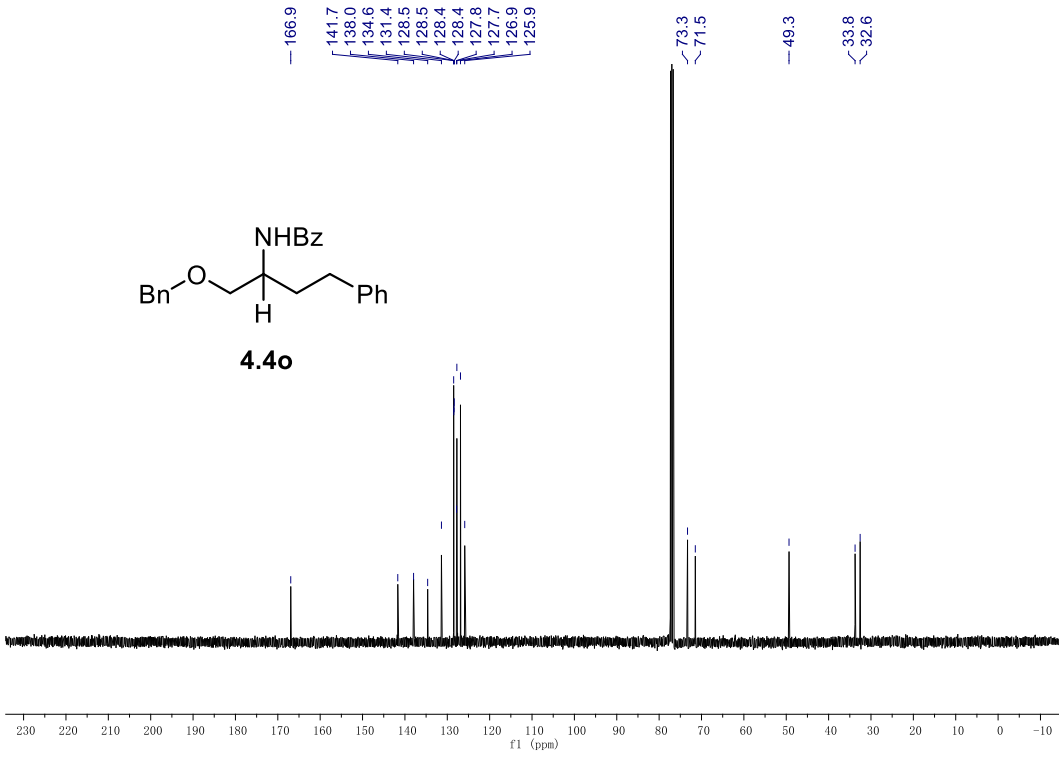


Figure 4.37 ^{1}H-NMR Spectrum of **4.4p**

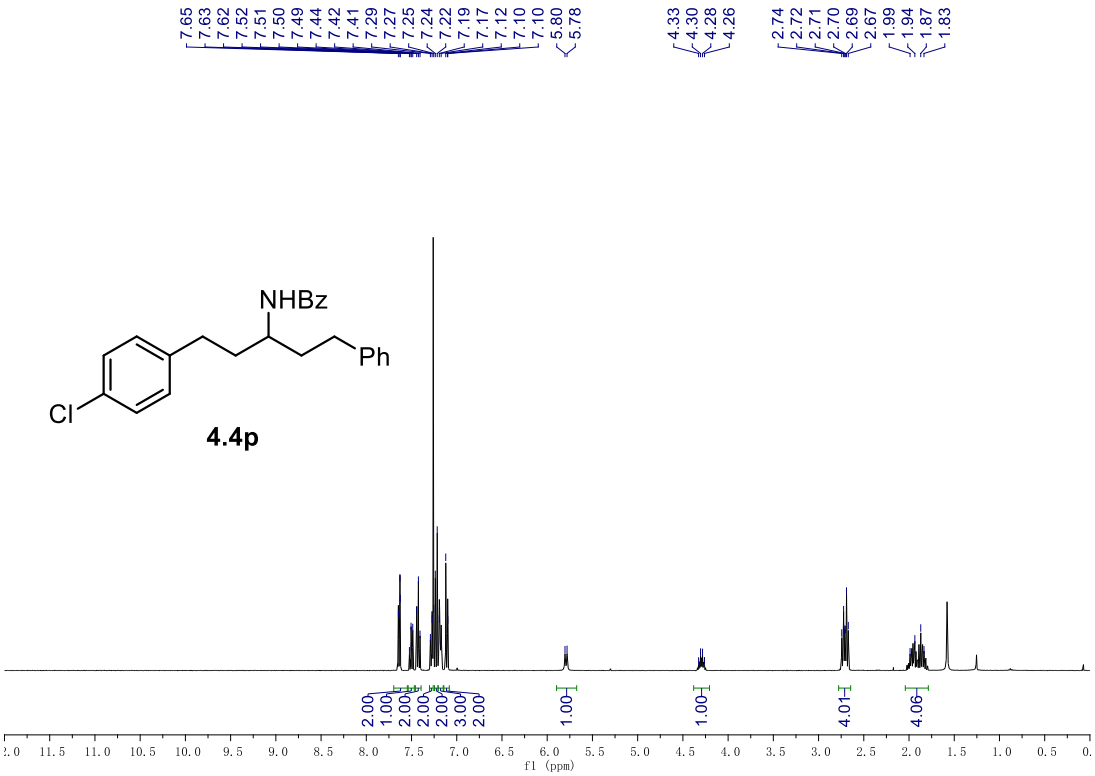


Figure 4.38 ^{13}C-NMR Spectrum of **4.4p**

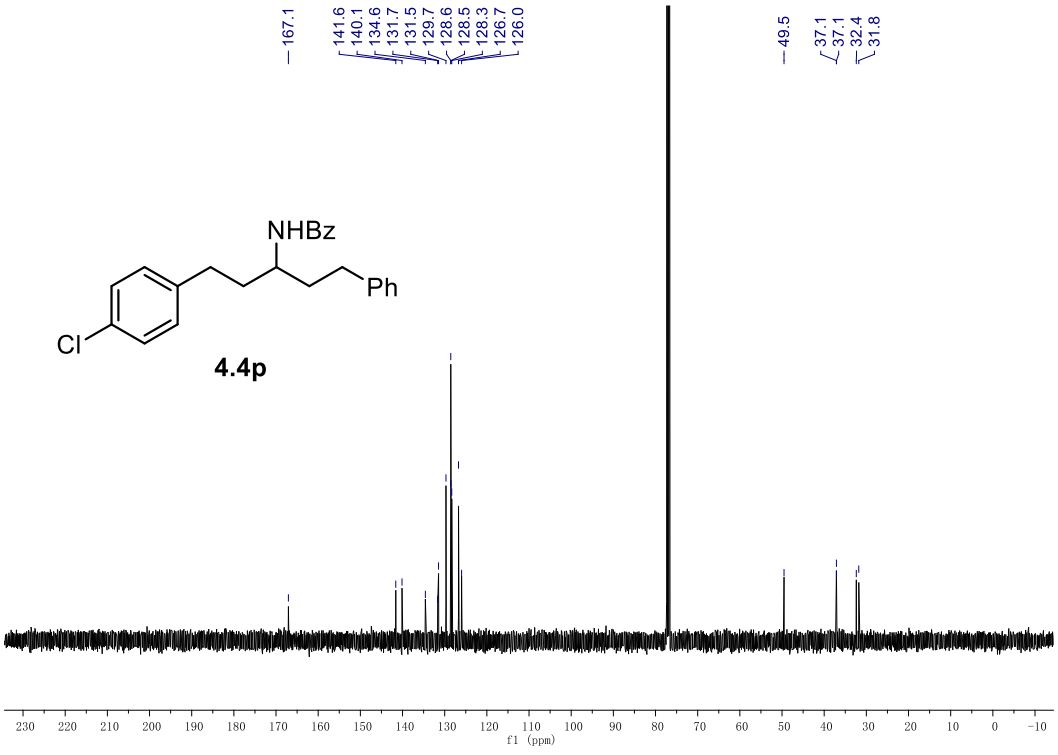


Figure 4.39 ^{1}H-NMR Spectrum of **4.4q**

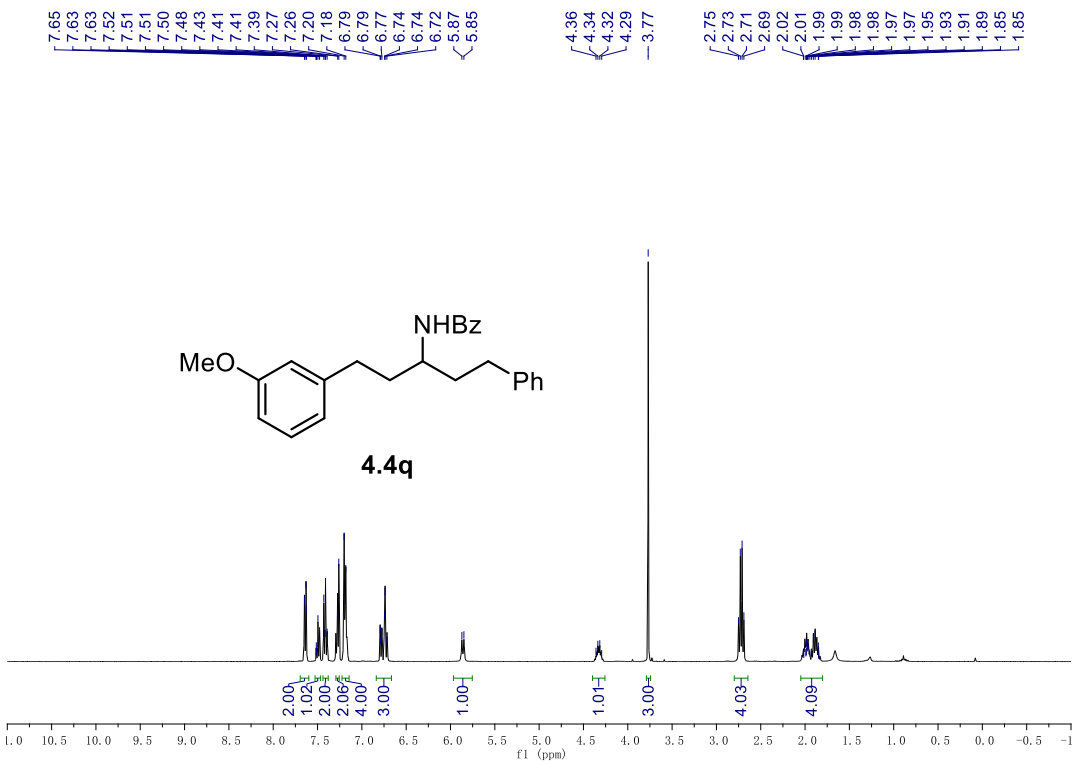


Figure 4.40 ^{13}C-NMR Spectrum of **4.4q**

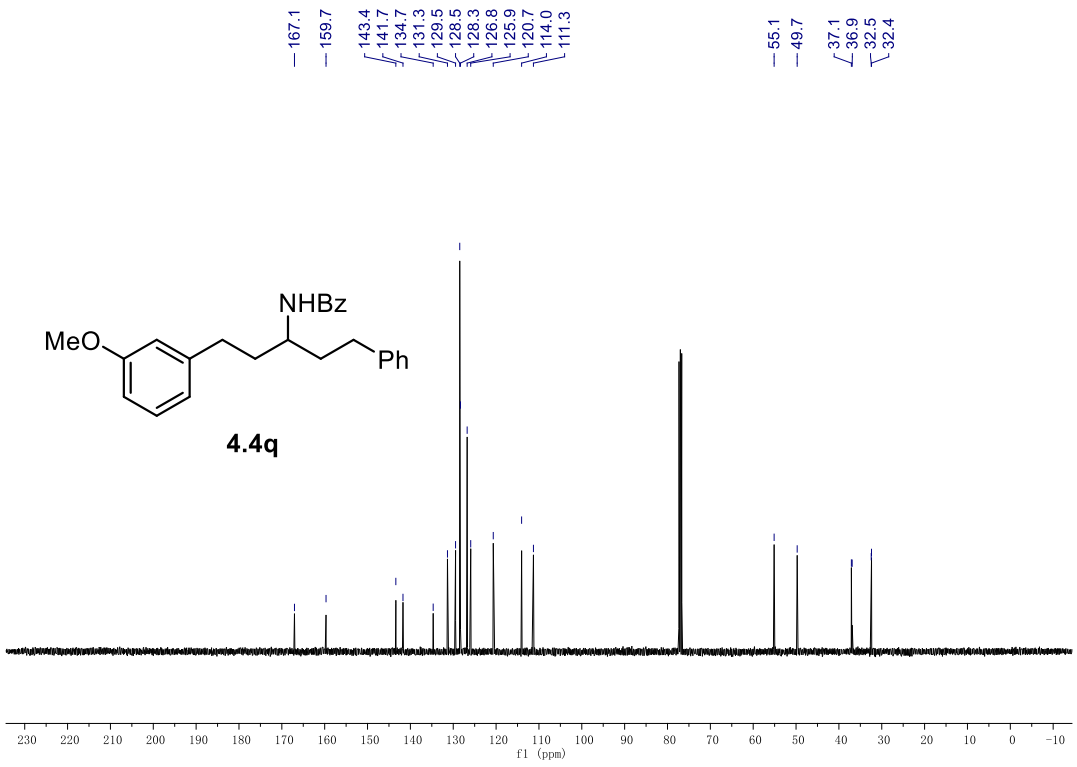


Figure 4.41 ^{1}H-NMR Spectrum of **4.4r**

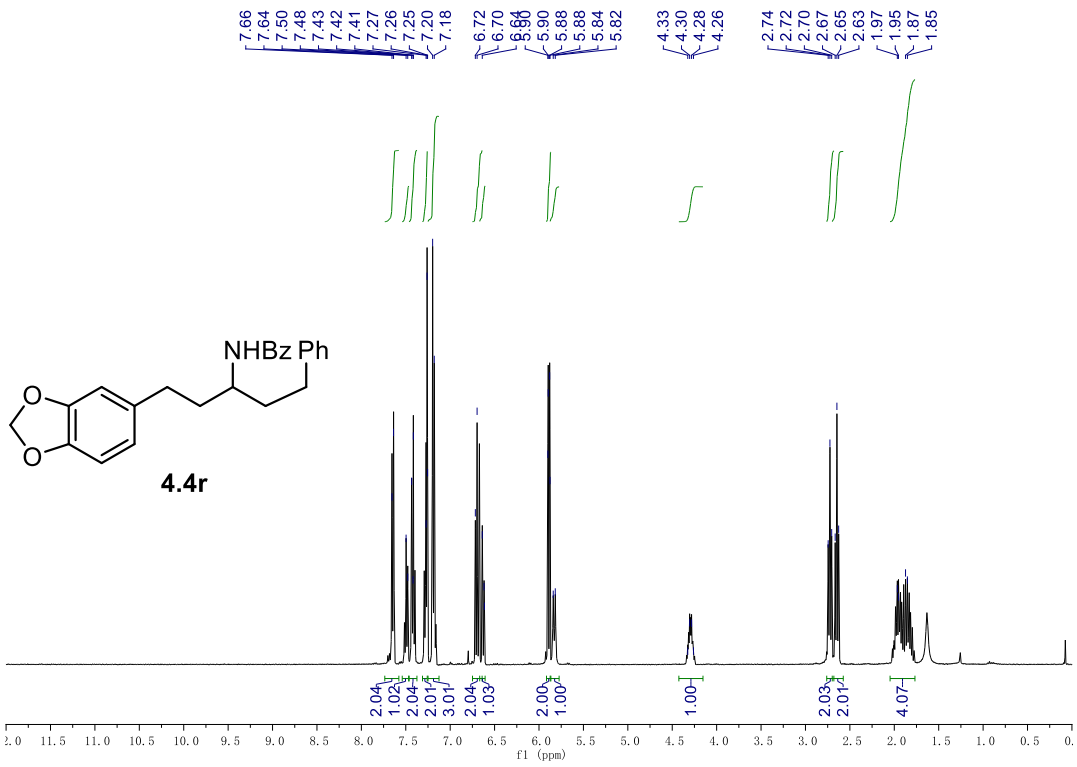


Figure 4.42 ^{13}C-NMR Spectrum of **4.4r**

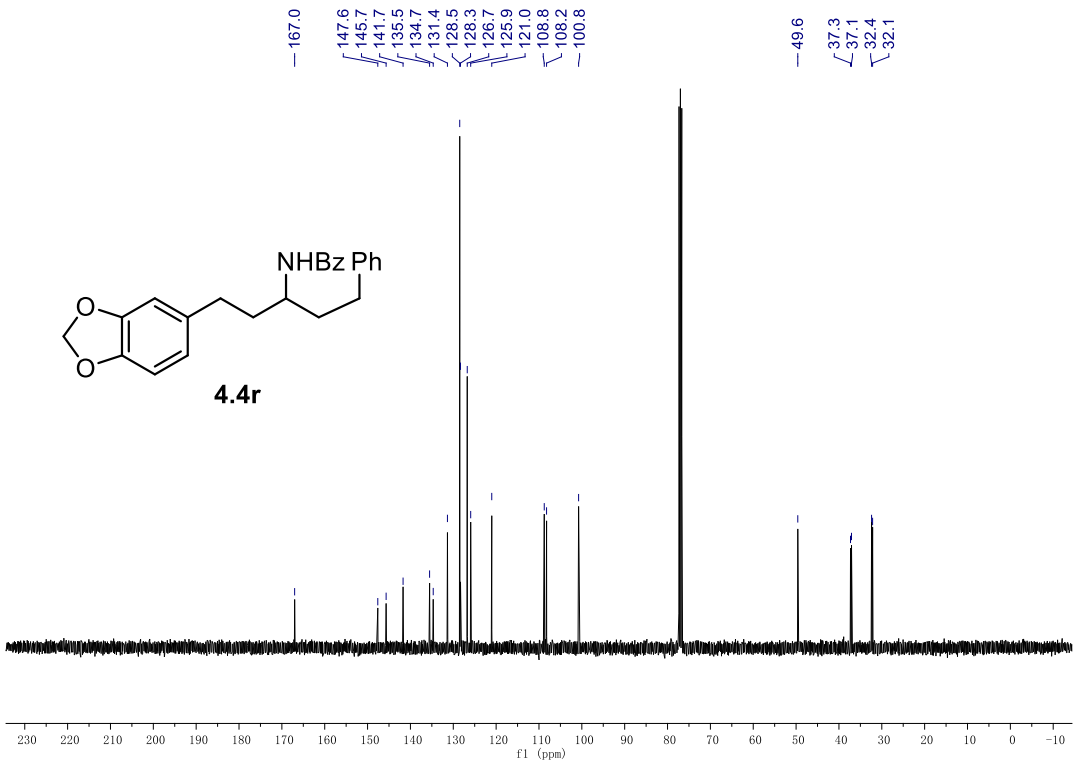


Figure 4.43 ^{1}H-NMR Spectrum of **4.4s**

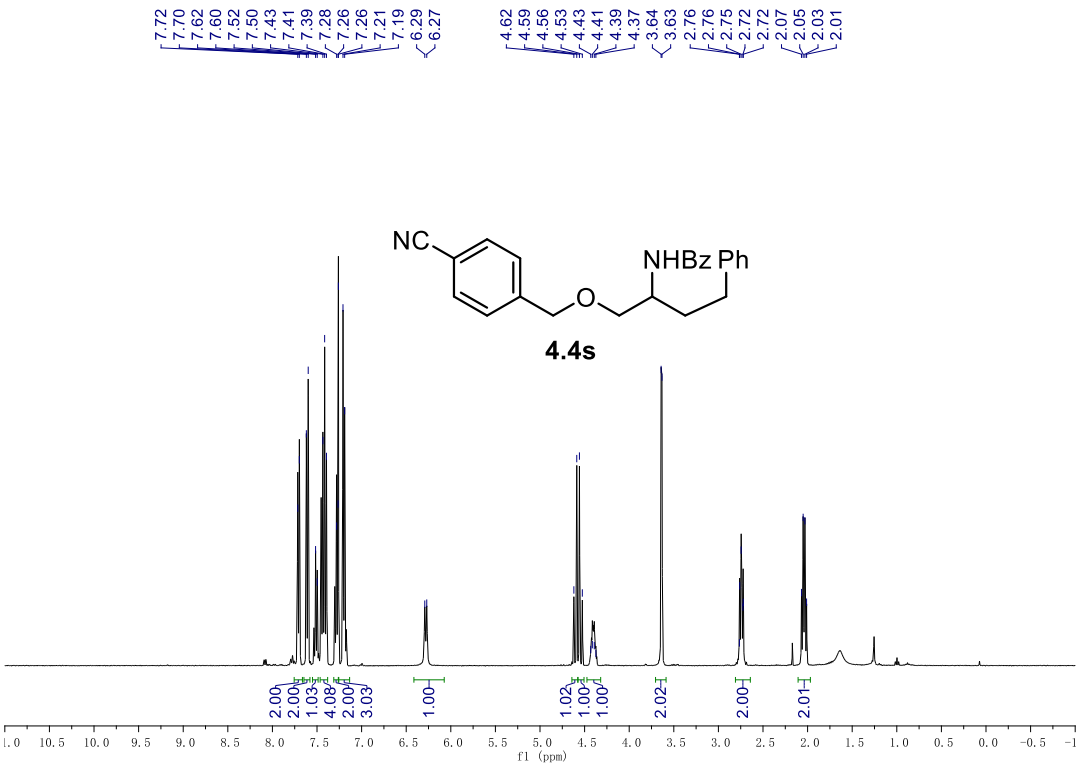


Figure 4.44 ^{13}C-NMR Spectrum of **4.4s**

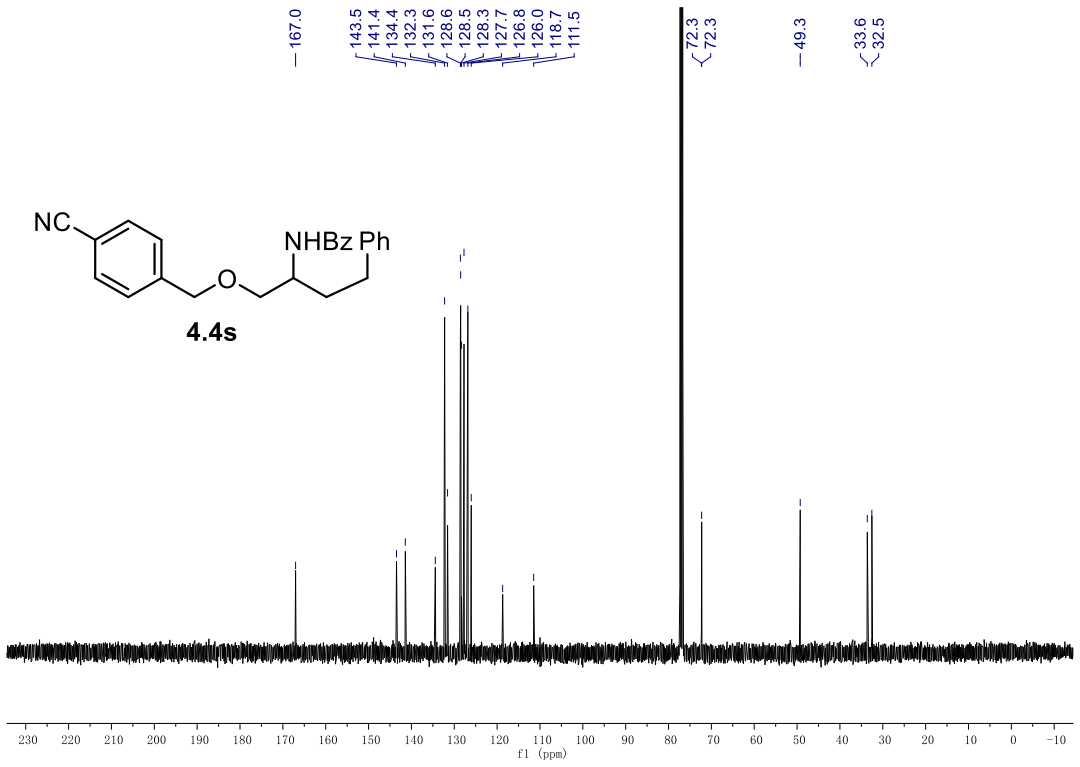


Figure 4.45 ^{1}H-NMR Spectrum of **4.4t**

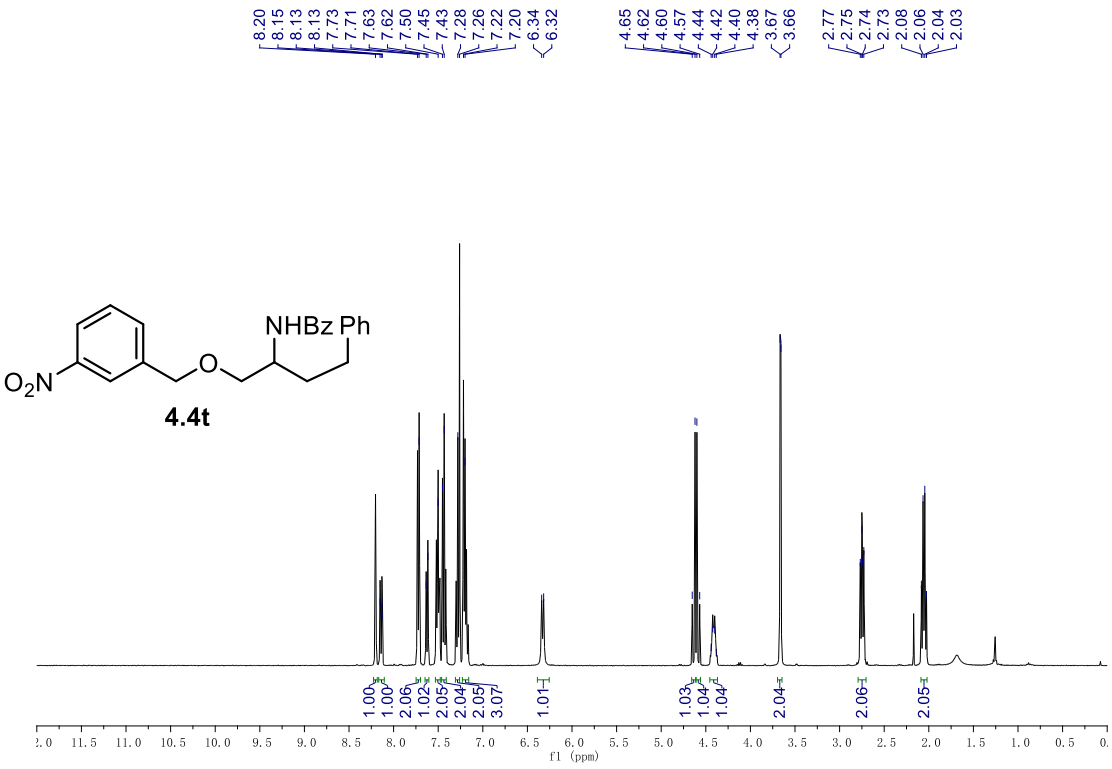


Figure 4.46 ^{13}C-NMR Spectrum of **4.4t**

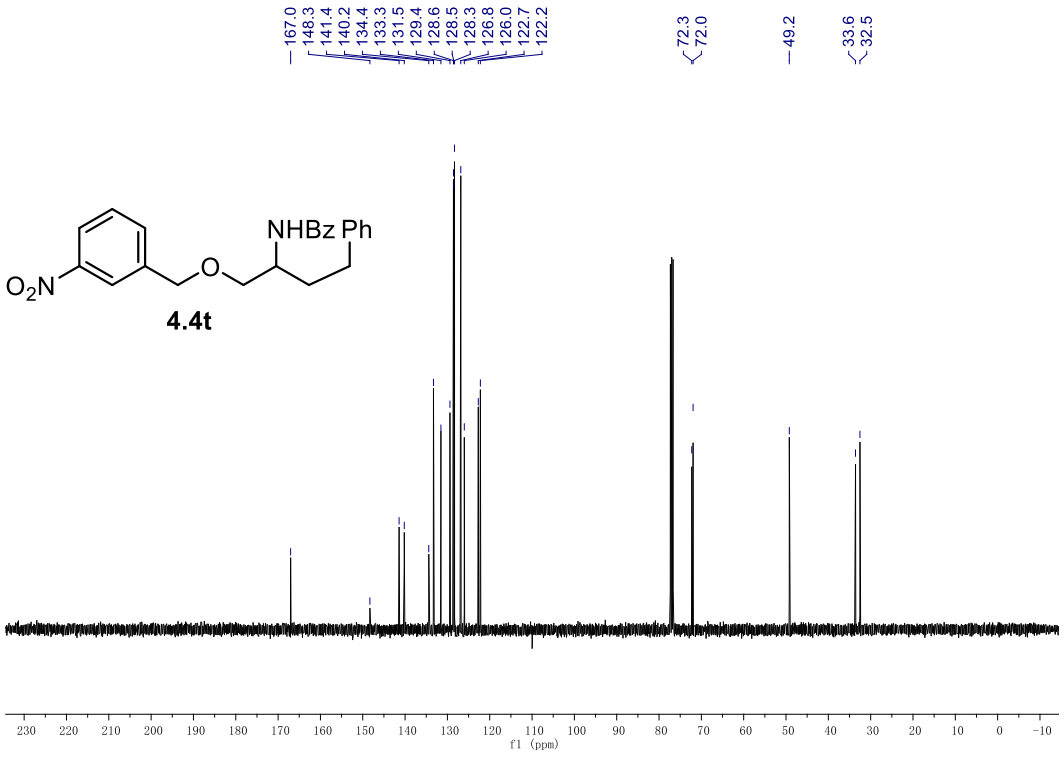


Figure 4.47 ^{1}H-NMR Spectrum of **4.4u**

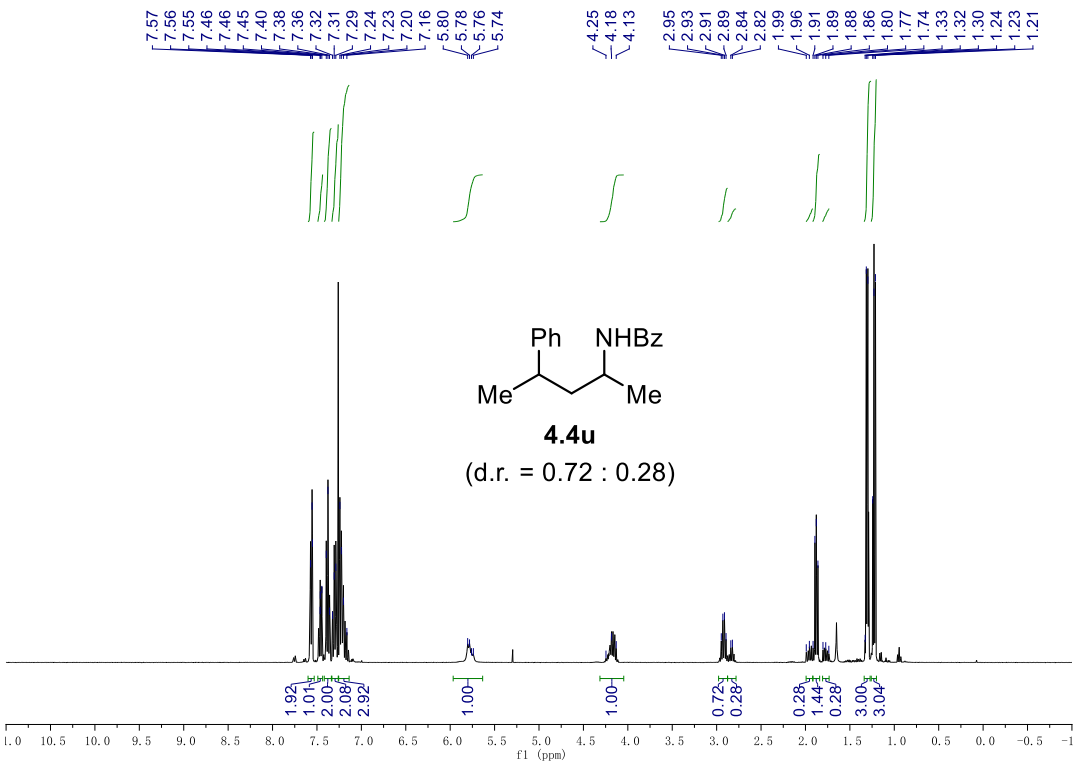


Figure 4.48 ^{13}C-NMR Spectrum of **4.4u**

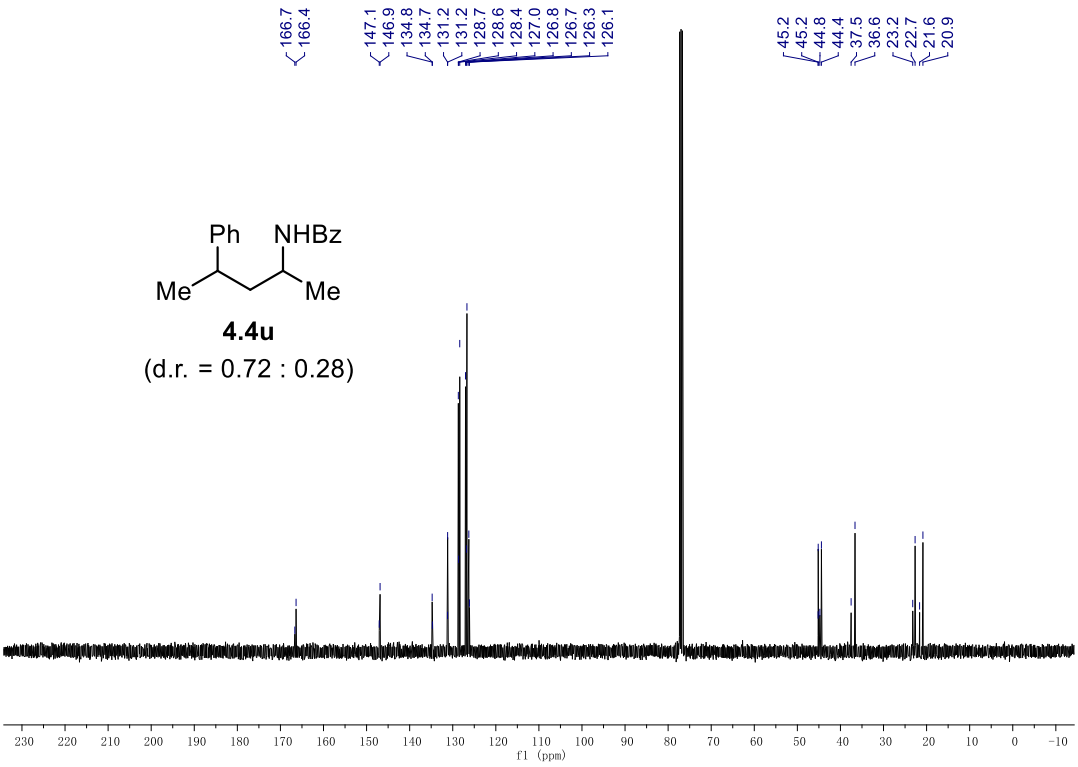


Figure 4.49 ^{1}H-NMR Spectrum of **4.4v**

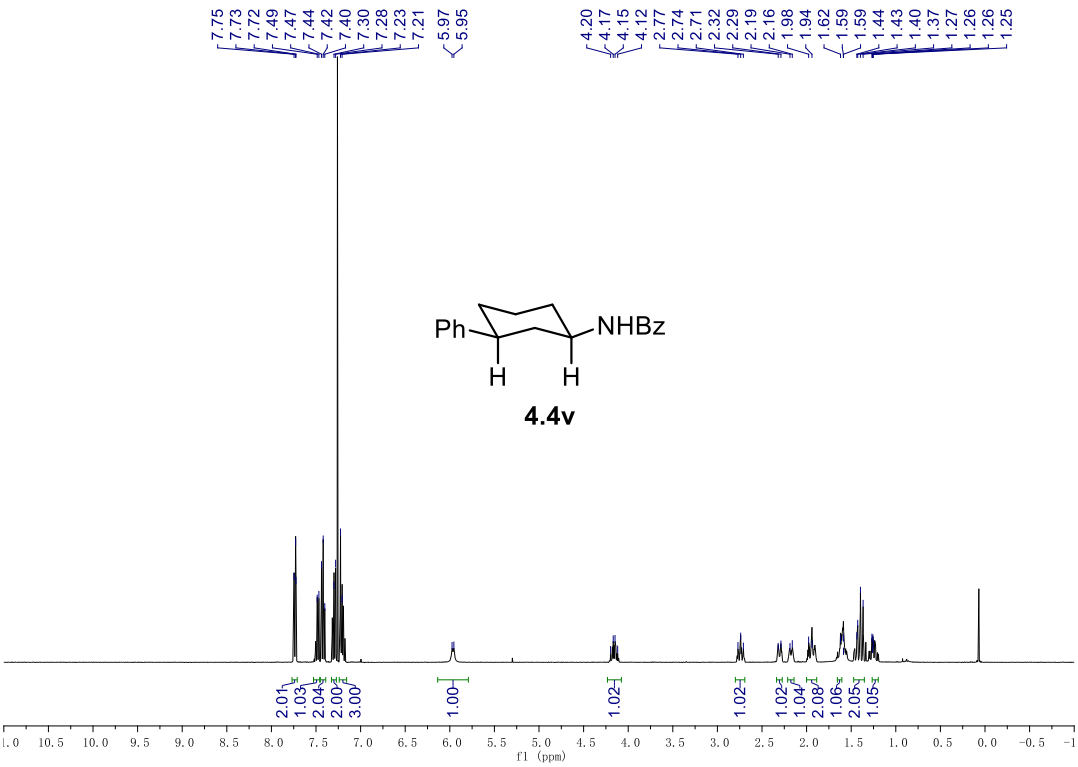


Figure 4.50 ^{13}C-NMR Spectrum of **4.4v**

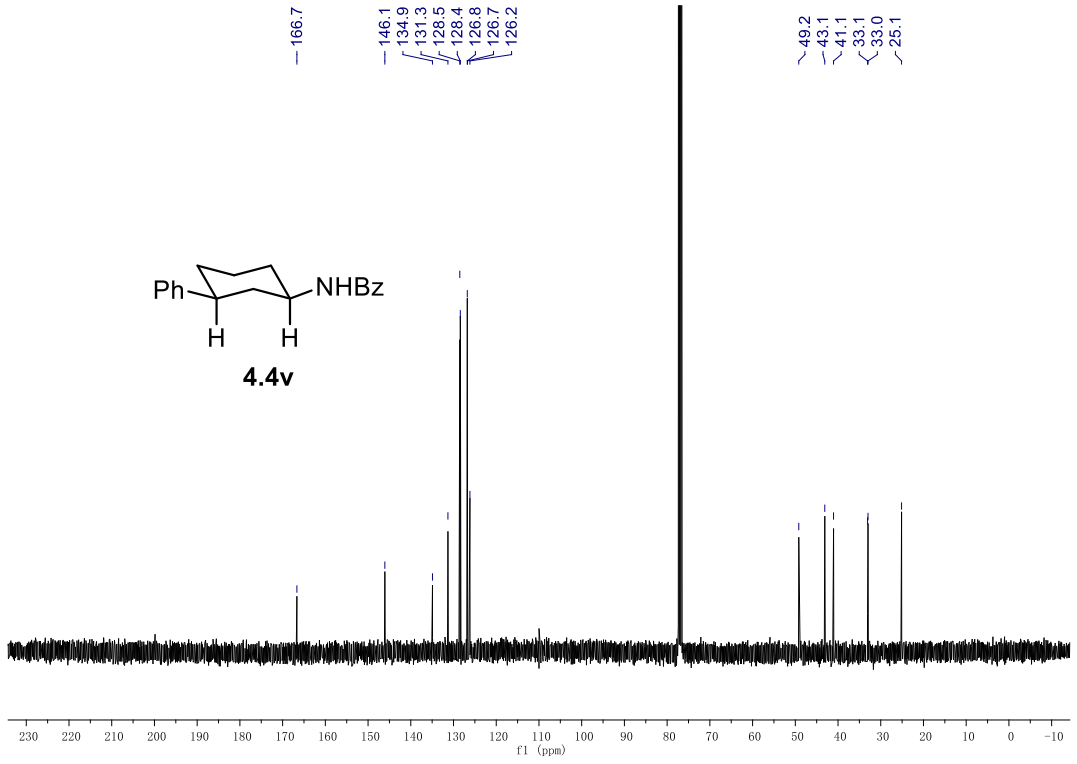


Figure 4.51 ^{1}H-NMR Spectrum of **4.4w**

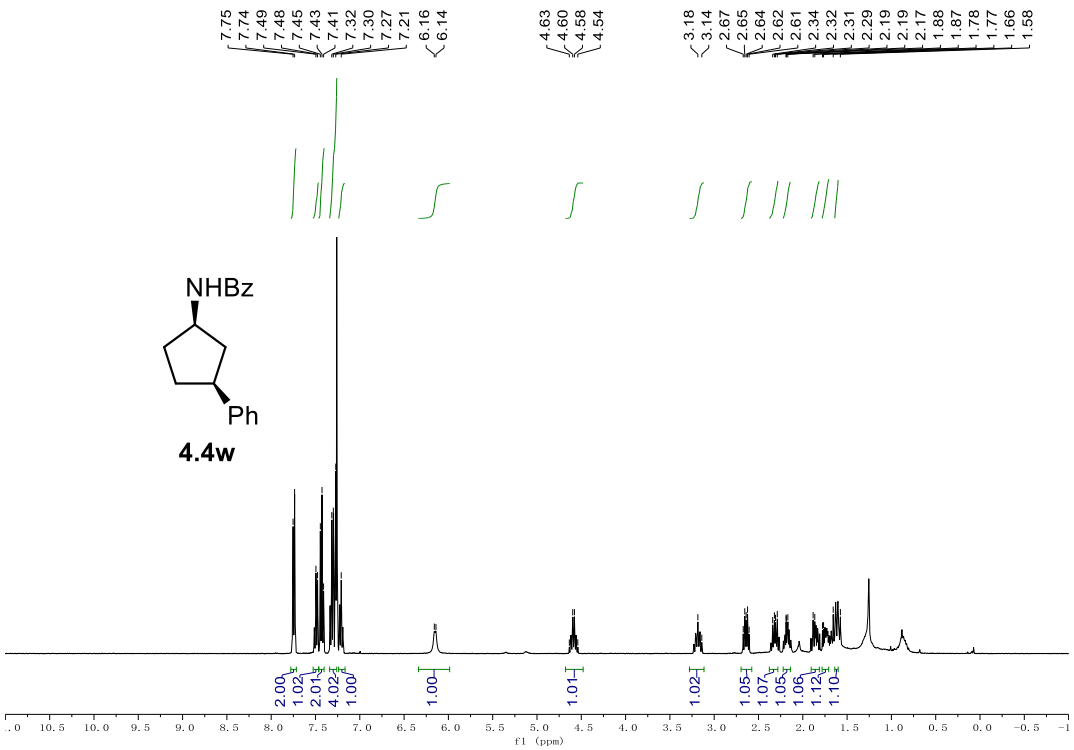


Figure 4.52 ^{13}C-NMR Spectrum of **4.4w**

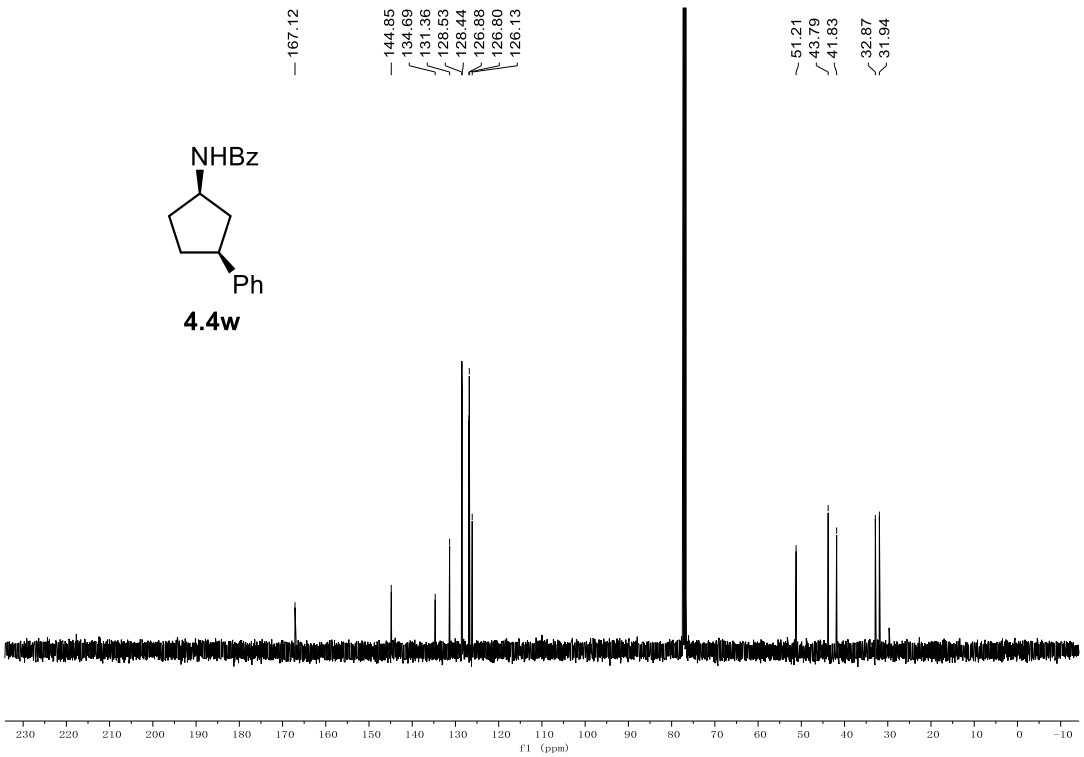


Figure 4.53 ^{1}H-NMR Spectrum of **4.1p**

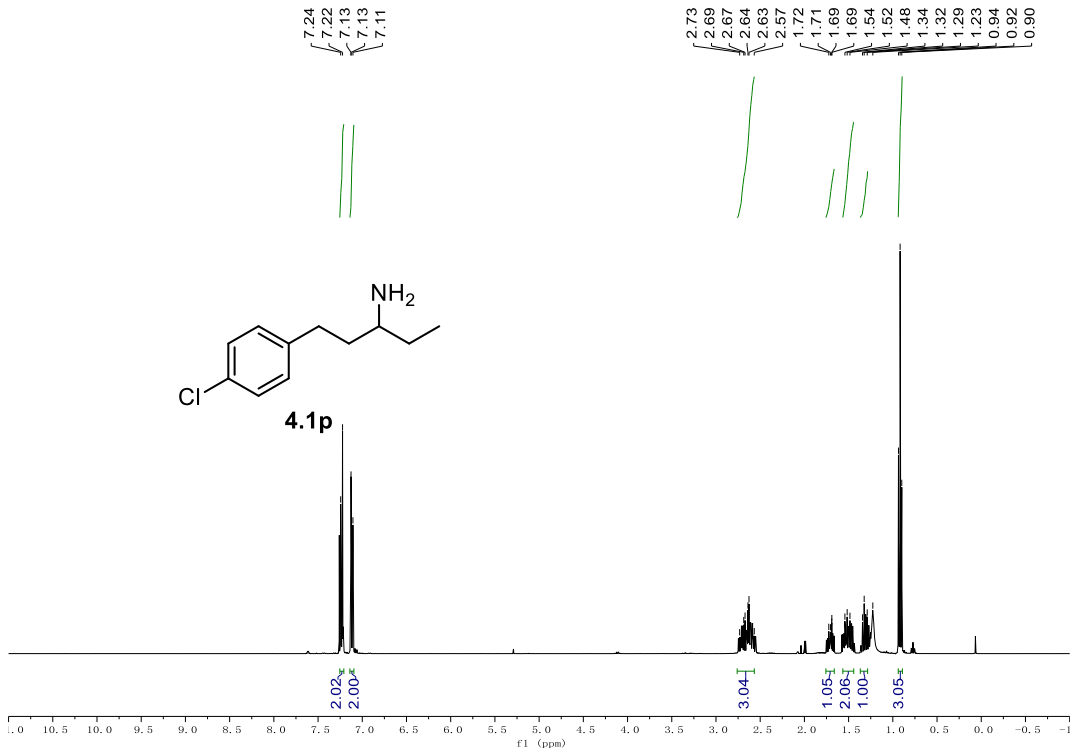


Figure 4.54 ^{13}C-NMR Spectrum of **4.1p**

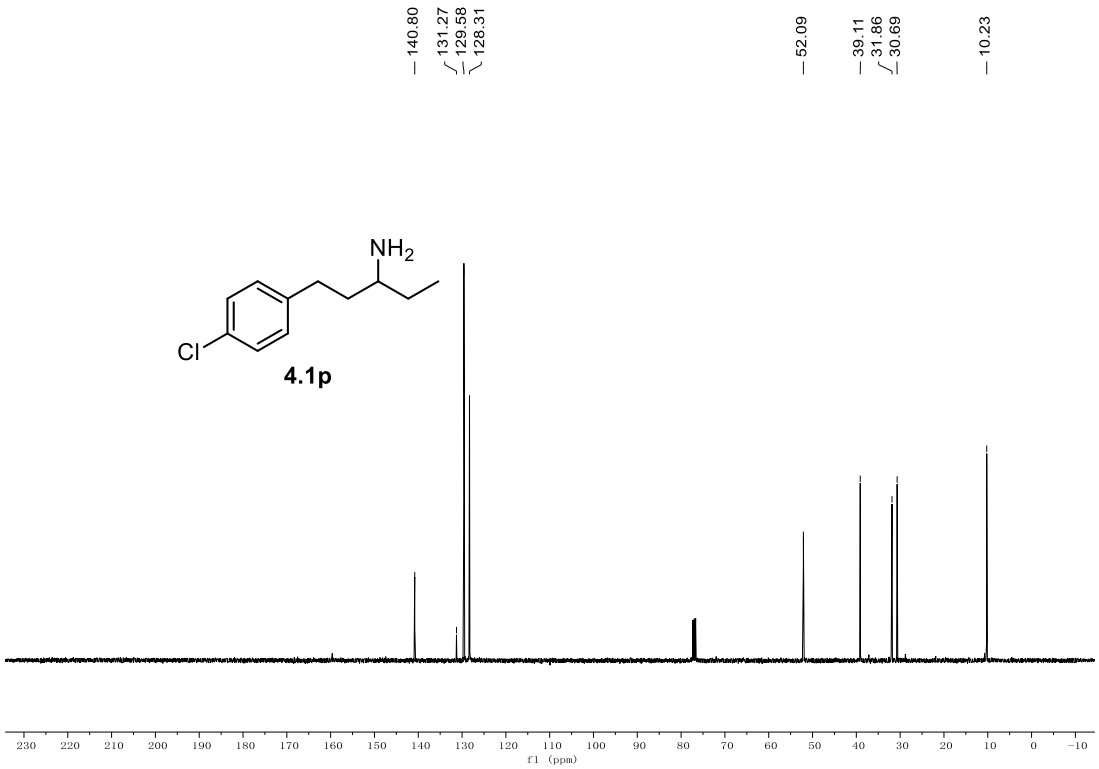


Figure 4.55 ^{1}H-NMR Spectrum of **4.1q**

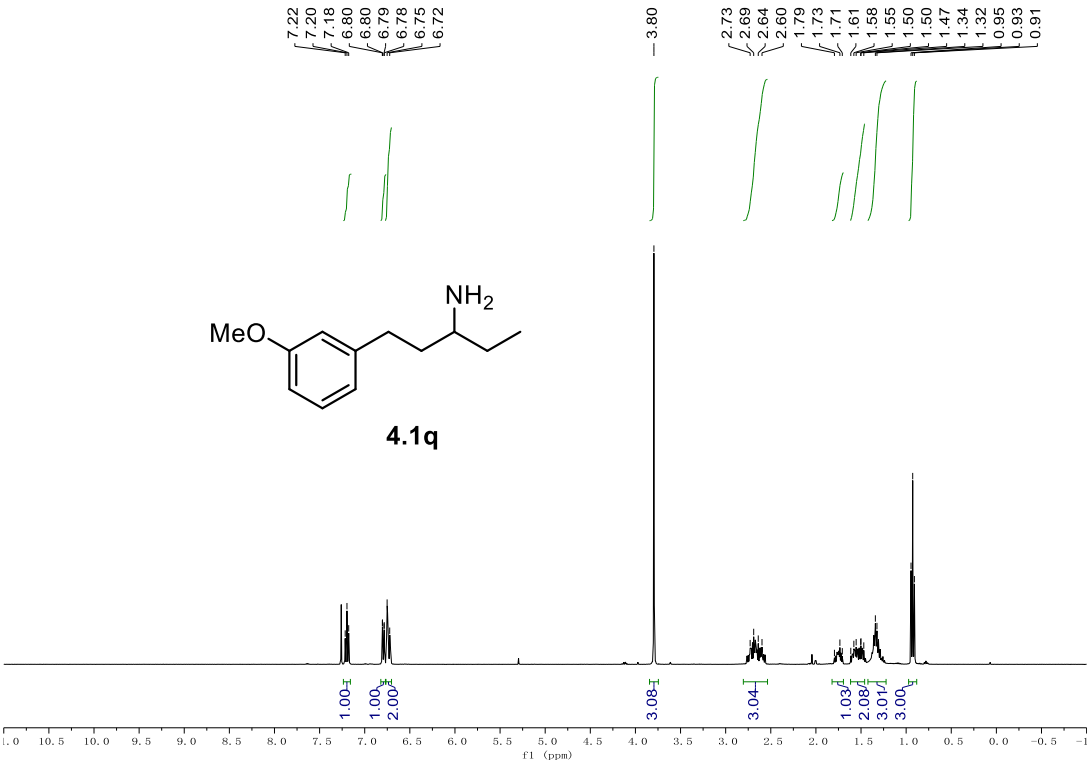


Figure 4.56 ^{13}C-NMR Spectrum of **4.1q**

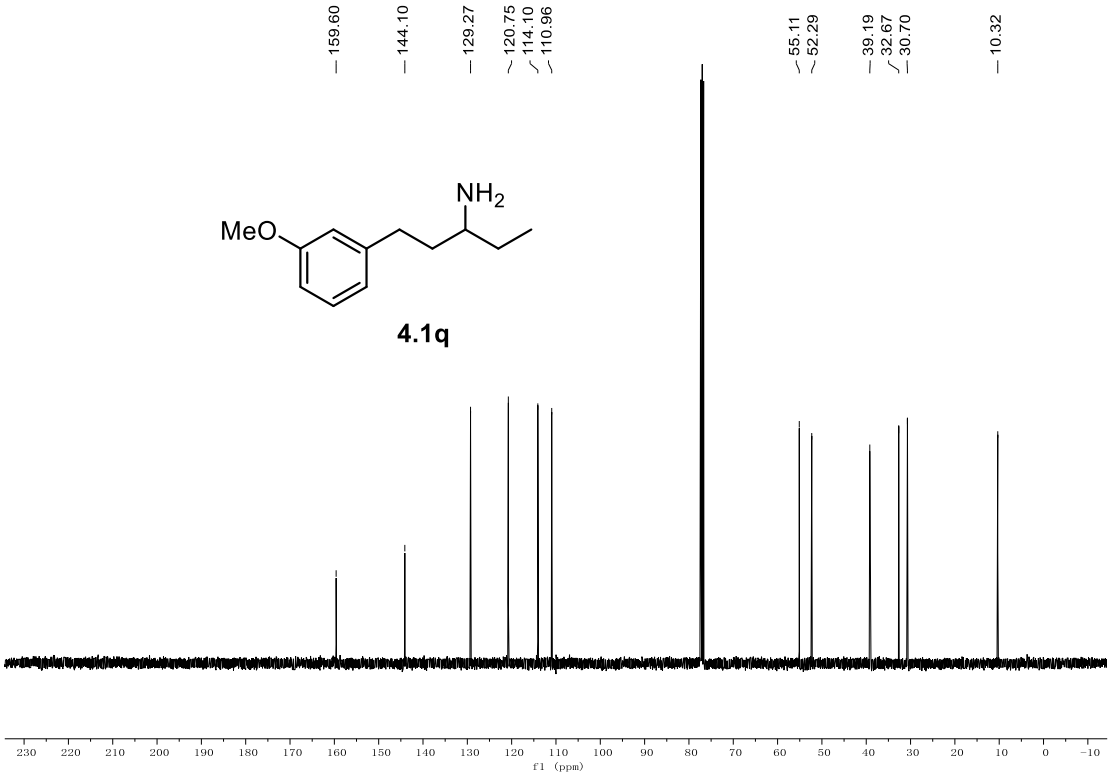


Figure 4.57 ^{1}H-NMR Spectrum of **4.1r**

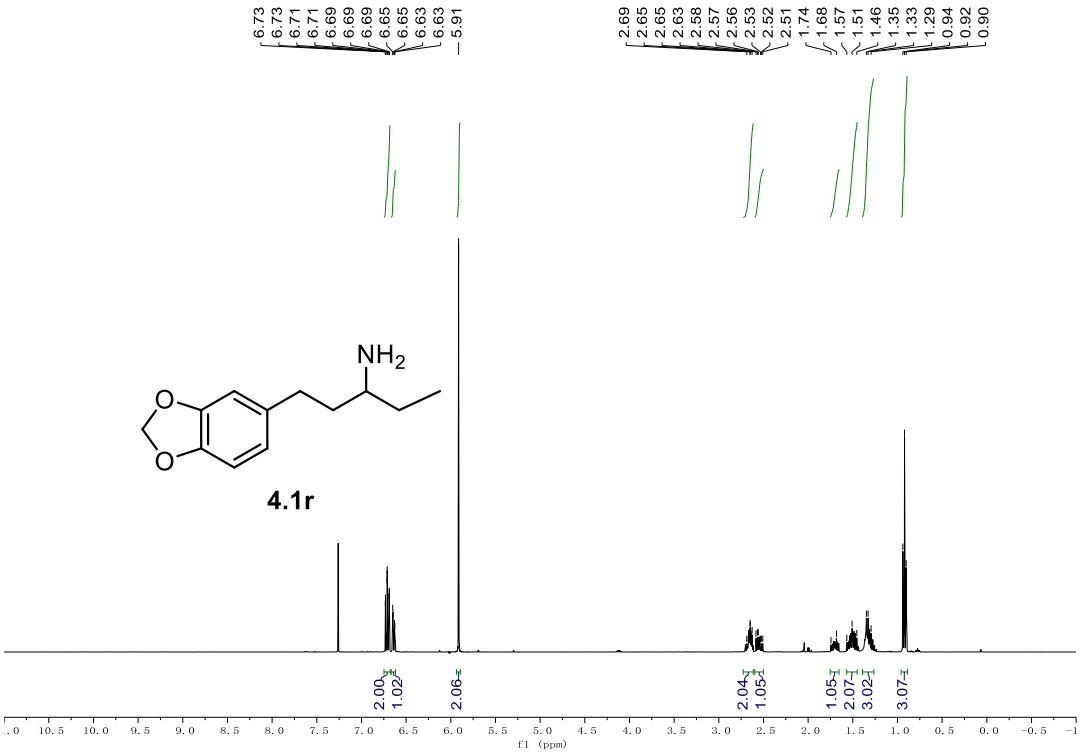


Figure 4.58 ^{13}C-NMR Spectrum of **4.1r**

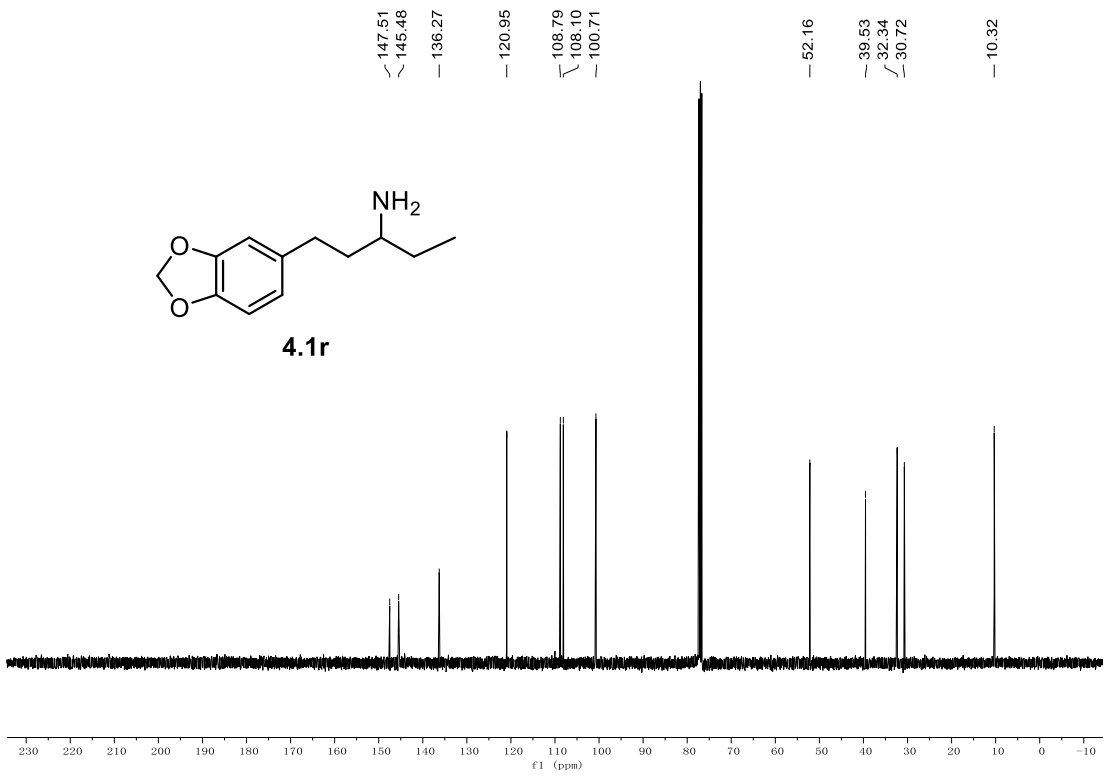


Figure 4.59 ^{1}H-NMR Spectrum of **4.1s**

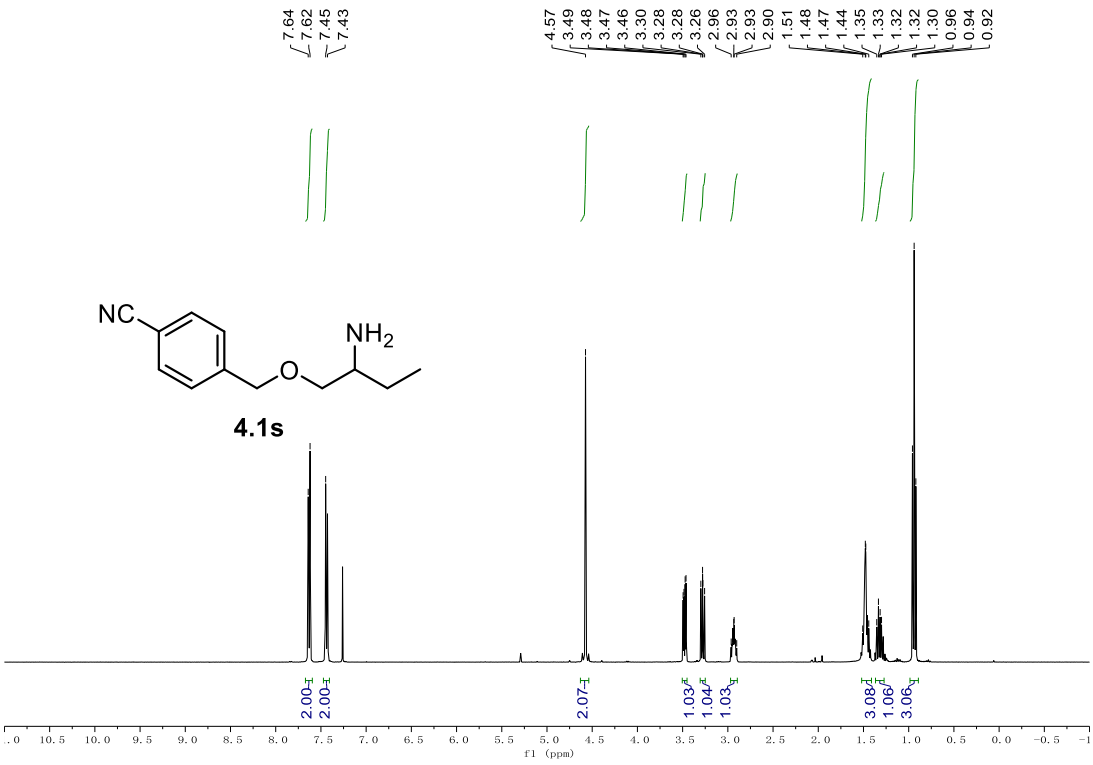


Figure 4.60 ^{13}C-NMR Spectrum of **4.1s**

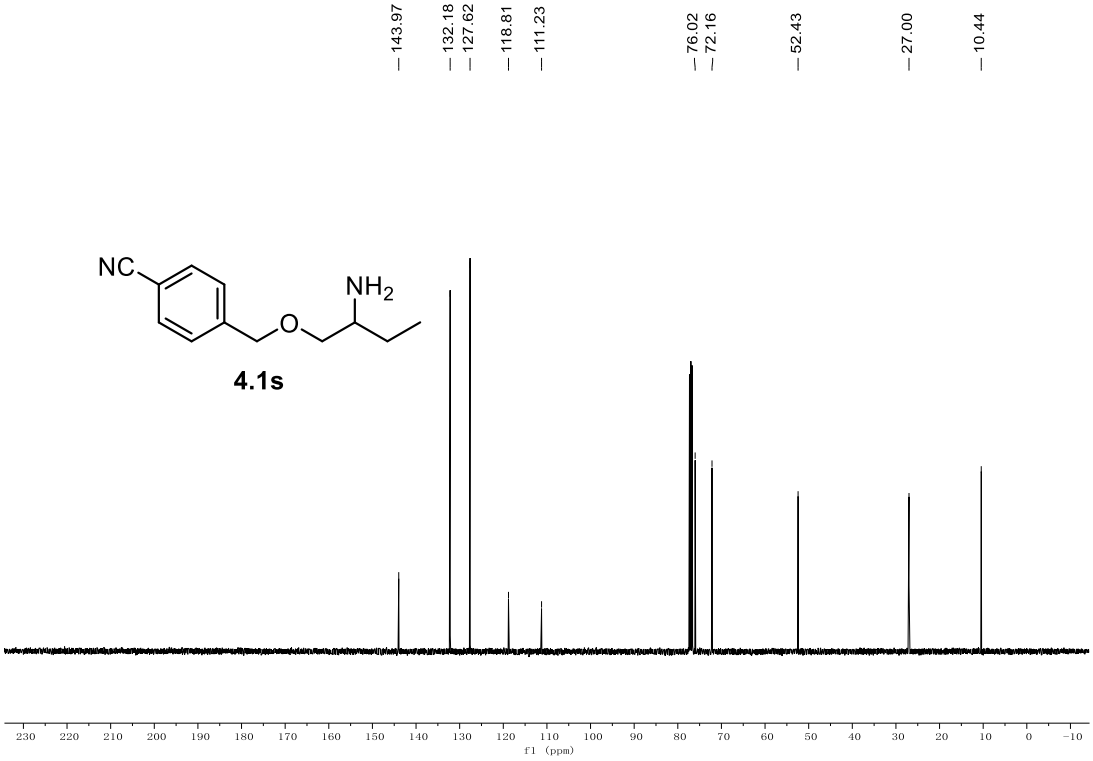


Figure 4.61 ^{1}H-NMR Spectrum of **4.1t**

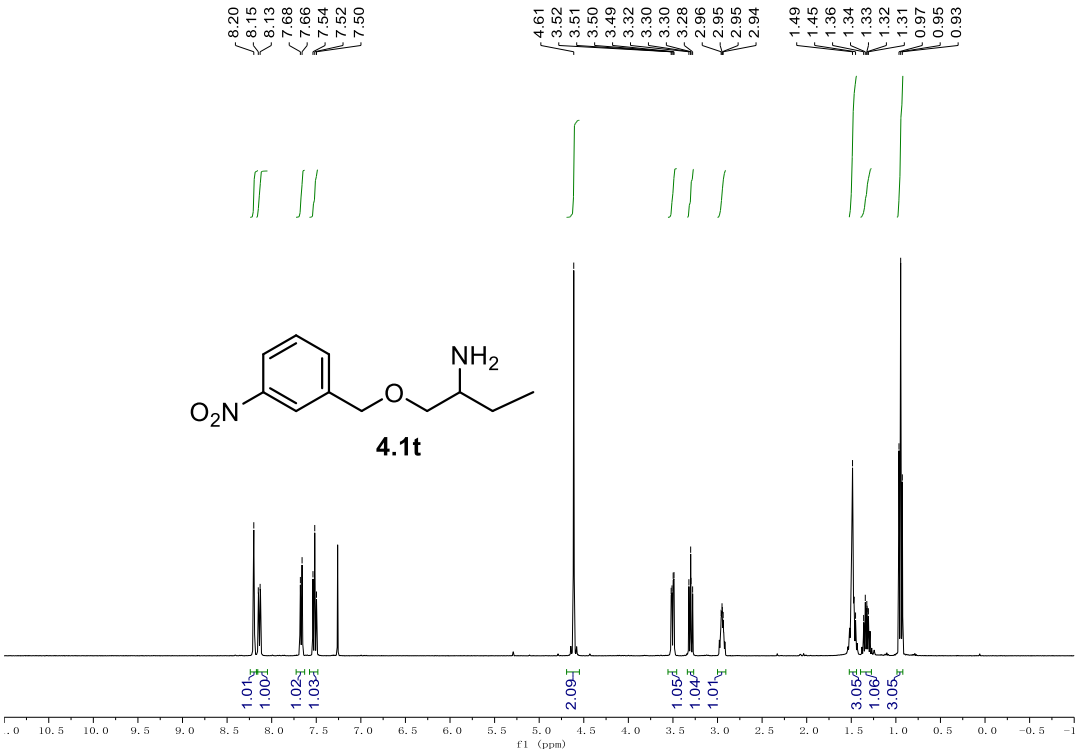


Figure 4.62 ^{13}C-NMR Spectrum of **4.1t**

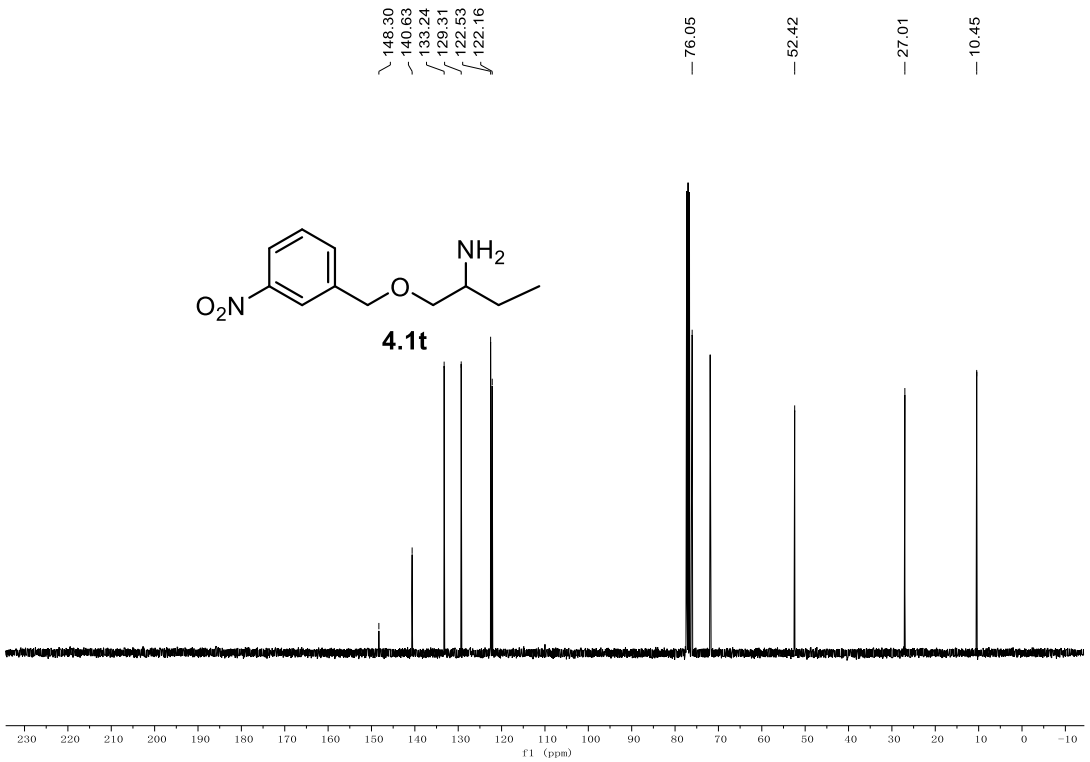
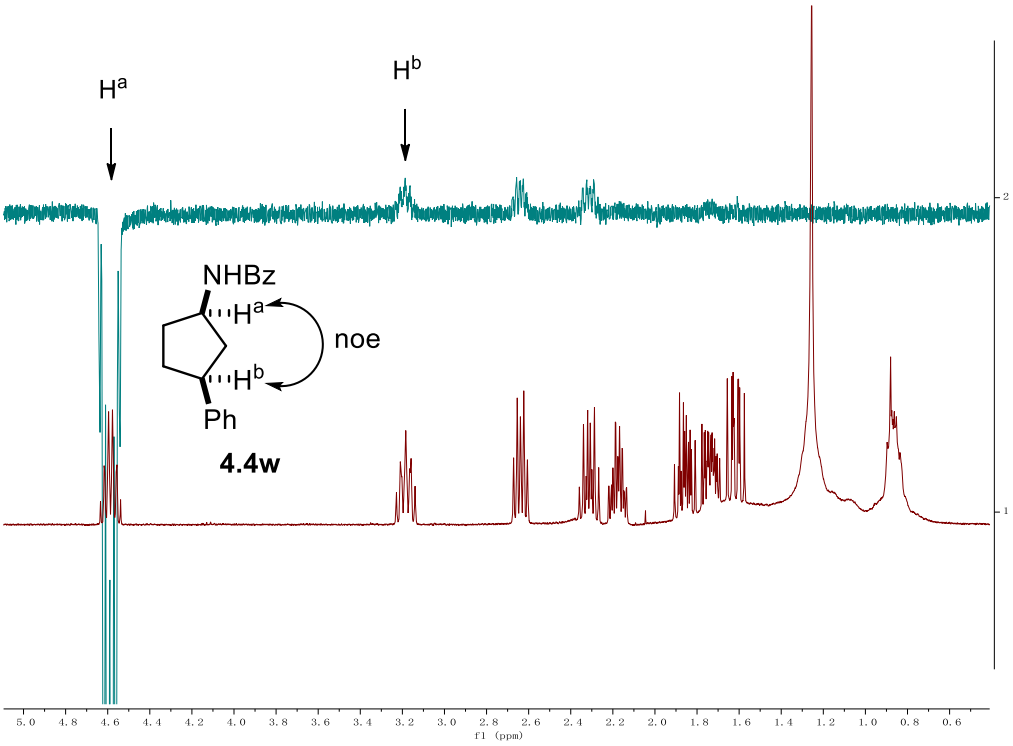


Figure 4.63 1D NOE spectrum of **4.4w**



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CHAPTER 5

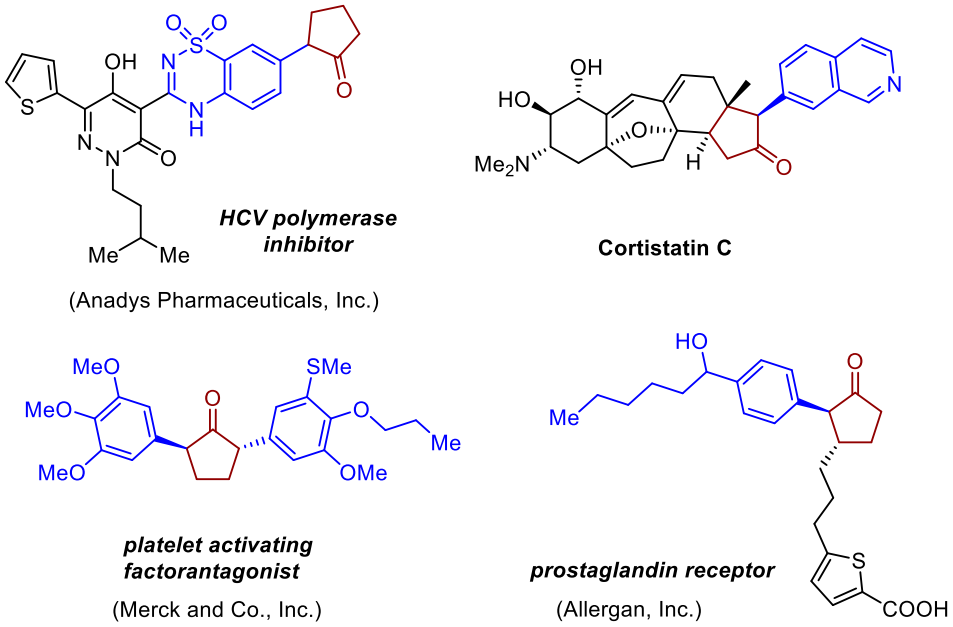
Pd/Amine-Catalyzed α-Arylation of Cyclopentanones

5.1 Introduction

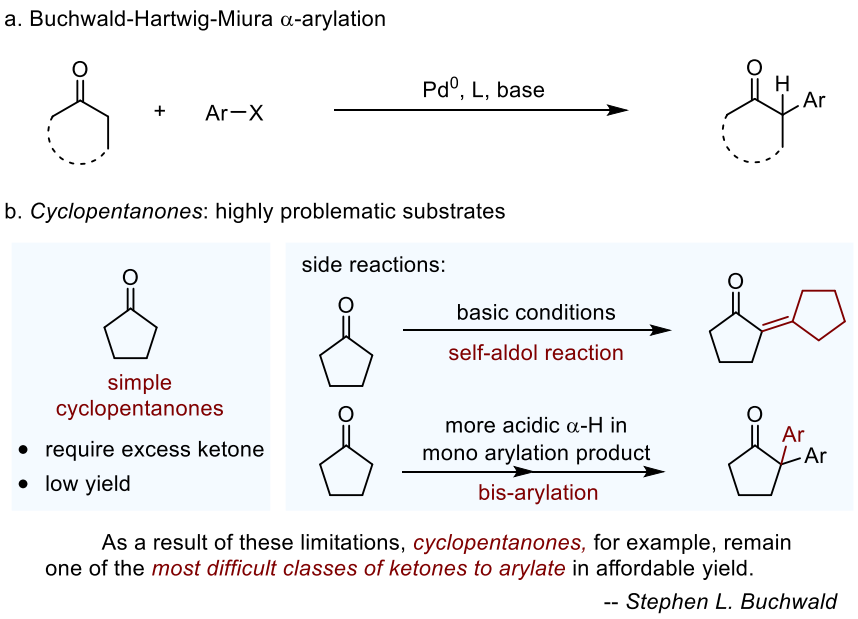
The Buchwald−Hartwig−Miura (BHM) arylation represents a cornerstone in functionalizing carbonyl compounds through transition metal-catalyzed cross-coupling with aryl halides.[1,2] While broad substrate scope has been established for this transformation, simple or less substituted cyclopentanones have been known as problematic substrates[3] despite that α-arylated cyclopentanones are widely found in pharmaceuticals and bio-active compounds (Figure 5.1). The challenge is attributed to several severe side reactions of cyclopentanones, such as self-aldol condensation[3a,c] and multi-arylation,[3b] due to the basic reaction media and more acidic α-hydrogens in singly arylated products (Scheme 5.1).[4] Consequently, only scattered examples[5] have been reported using either excess[6] or specialized cyclopentanones.[3a,7] More often, indirect multi-step approaches are employed to

access α-arylated cyclopentanones.[8-10] Thus, a general solution to the "cyclopentanone-arylation" problem remains to be discovered.

Figure 5.1 Representative Examples of Bioactive α-Arylated Cyclopentanones

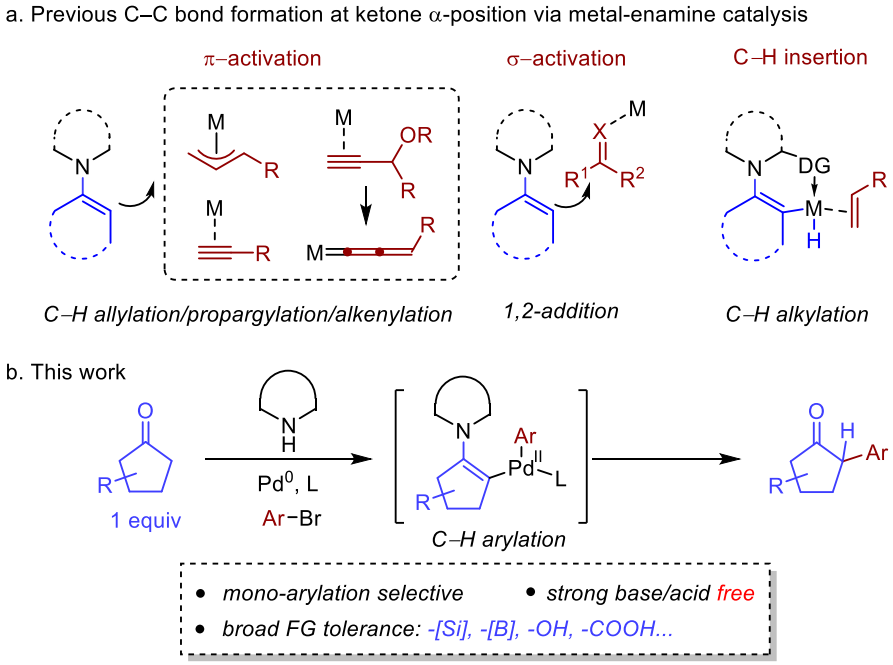


Scheme 5.1 Challenges for α-Arylation of Simple or Less Substituted Cyclopentanones



On the other hand, merging transition-metal and enamine catalysis has enabled a number of powerful C−C bond forming transformations at the α-position of carbonyl compounds.[11,12] The mode of activation generally includes 1) nucleophilic attack of enamines to metal-activated allyl, benzylic, propargyl and alkynyl electrophiles; 2) 1,2 or 1,4-addition to polar π-bonds activated by Lewis acidic metals (Scheme 5.2a).[11e] In addition, we recently reported a directed C−H insertion/metalation approach for ketone α-alkylation[13a-c] and alkenylation[13d] with olefins and alkynes. Moreover, through combining enamine and copper catalysis, elegant trifluoromethylation,[14a] arylation,[14b] and vinylation[14c] of more reactive aldehyde substrates were reported by MacMillan using hypervalent iodonium salts. In this chapter, a new reaction mode for the metal/enamine cooperative catalysis was designed and developed, for the first time enabling the direct mono α-C−H arylation of normal cyclopentanones using readily available aryl bromide (Scheme 5.2b).

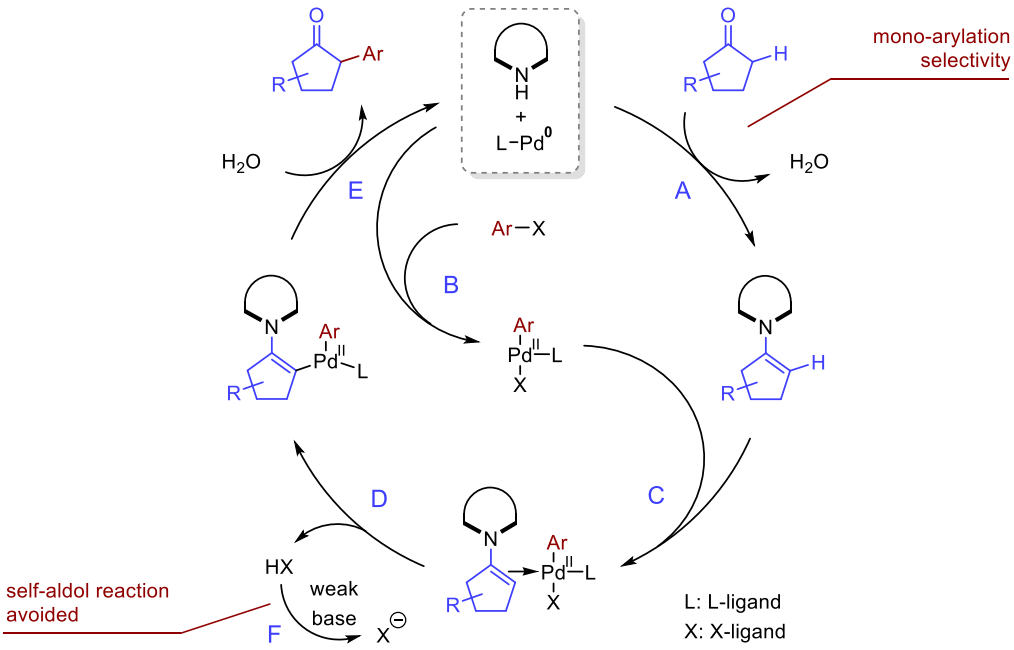
Scheme 5.2 C−C Bond Formation at Ketone α-Positions via Metal-Enamine Catalysis



5.2 Results and Discussion

To address the α-arylation challenge of cyclopentanones, a Pd-enamine cooperative catalysis strategy was conceived (Figure 5.2). Starting with a secondary amine and a Pd(0) catalyst, an enamine and a X-Pd(II)-aryl species could be formed respectively with cyclopentanone and the aryl halide (Steps A and B). Subsequently, C−H metalation of the enamine would afford an enaminyl aryl-Pd(II) intermediate (Steps C and D),[15] which could undergo reductive elimination and hydrolysis to provide the arylated ketone and regenerate the catalysts (Step E). This strategy would avoid strong bases (or acids), thus self-aldol should be less favorable. In addition, over arylation could be minimized because enamine formation is highly sensitive to the sterics of the ketone substrate. Due to the redox-neutral and pH-mild conditions, good chemoselectivity and functional group (FG) tolerance was further expected.

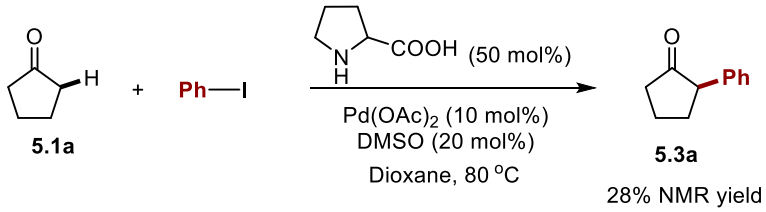
Figure 5.2 Proposed Strategy



The challenges of the proposed strategy are 2-fold: 1) catalyzed by Pd, amines are known to reduce aryl halides to arenes[16] or cross couple to form anilines;[17] thus, the compatibility between the two catalytic processes would be one concern. 2) The kinetics of forming the enamine and X-Pd(II)-aryl species need to match each other. Otherwise, known side reactions, such as enamine-aldol,[18] ketone dehydrogenation[19] and aryl dimerization,[20] can compete.

The original reactivity was disclosed by Dr. Zhongxing Huang during his study toward β C−H arylation of cyclic ketones. By treating cyclohexanone (**5.1a**) with $Pd(OAc)_2$, proline and phenyl iodide, 2-phenyl cyclohexanone (**5.3a**) was formed in 28% NMR yield.

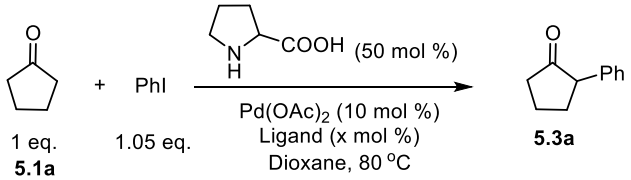
Scheme 5.3 Original Discovery of the Reactivity



After some brief screening of solvents, concentration, and additives, a series of phosphine and NHC ligands were then examined (Table 5.1). Among all ligands tested, tri(*ortho*-tolyl)phosphine was found most effective, leading to a 34% yield out of a 76% conversion (entry 18). The simple triphenyl phosphine is found non-effective (entry 1-2), while bi-dentate and phosphite ligands in general gave poor yields. Among the catalog of electron-rich bulky mono-dentate ligands that are considered to accelerate the oxidation addition of aryl halides as well as the C−C reductive elimination, only tri-*tert*-butyl

phosphine (entry 14) and Sphos (entry 30) gave comparable yields. The tri(*ortho*-tolyl)phosphine was then chosen for further optimization.

Table 5.1 Screening of Ligands for Ketone α C–H Arylation



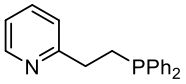
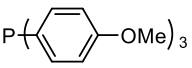
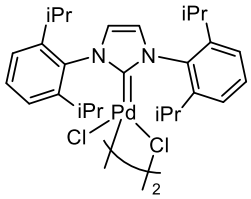
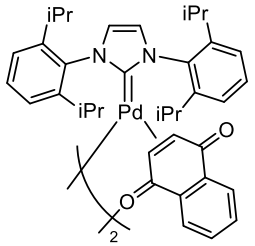
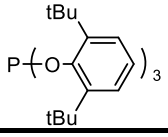
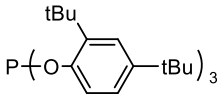
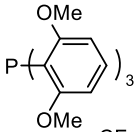
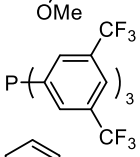
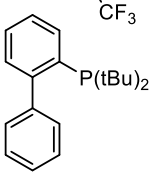
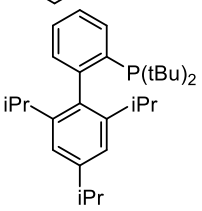
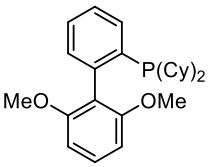
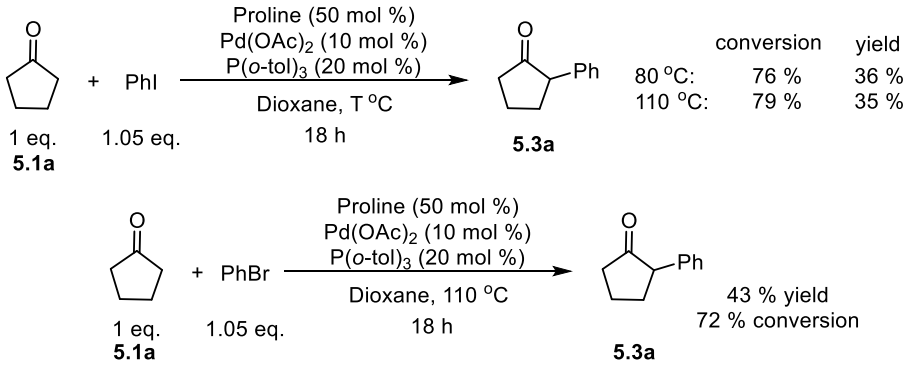
Entry	Ligand	equiv.	conversion	yield
1	$Pd(PPh_3)_4$ *instead of* $Pd(OAc)_2$	10 %	24 %	0 %
2	PPh_3	20 %	34 %	9 %
3	$P(2\text{-furyl})_3$	20 %	71 %	13 %
4	dppm	15 %	16 %	0 %
5	dppe	15 %	22 %	0 %
6	dppp	15 %	29 %	0 %
7	dppb	15 %	29 %	0 %
8	dppf	15 %	64 %	21 %
9	DPEphos	15 %	39 %	trace
10	BINAP	15 %	38 %	trace
11		15 %	33 %	0 %
12	$P(Me)_3$	20 %	37 %	0 %
13	$P(i\text{Pr})_3$	20 %	35 %	0 %
14	$P(t\text{Bu})_3$	20 %	85 %	31 %
15	PCy_3	20 %	31 %	0 %
16	DCyPPF	20 %	88 %	23 %
17	$AsPh_3$	20 %	72 %	17 %
18	$P(o\text{-tol})_3$	20 %	76 %	34 %
19	$P(C_6F_5)_3$	20 %	51 %	17 %
20		20 %	55 %	18 %
21		5 %	36 %	0 %
22		5 %	51 %	18 %
23	$P(OCH_2CF_3)_3$	20 %	71 %	19 %
24		20 %	40 %	12 %

Table 5.1 Screening of Ligands for Ketone α C−H Arylation (continued)

Entry	Ligand	equiv.	conversion	yield
25		20 %	--	0 %
26		20 %	--	0 %
27		20 %	65 %	23 %
28		10 %	65 %	24 %
29		10 %	68 %	27 %
30		10 %	81 %	34 %

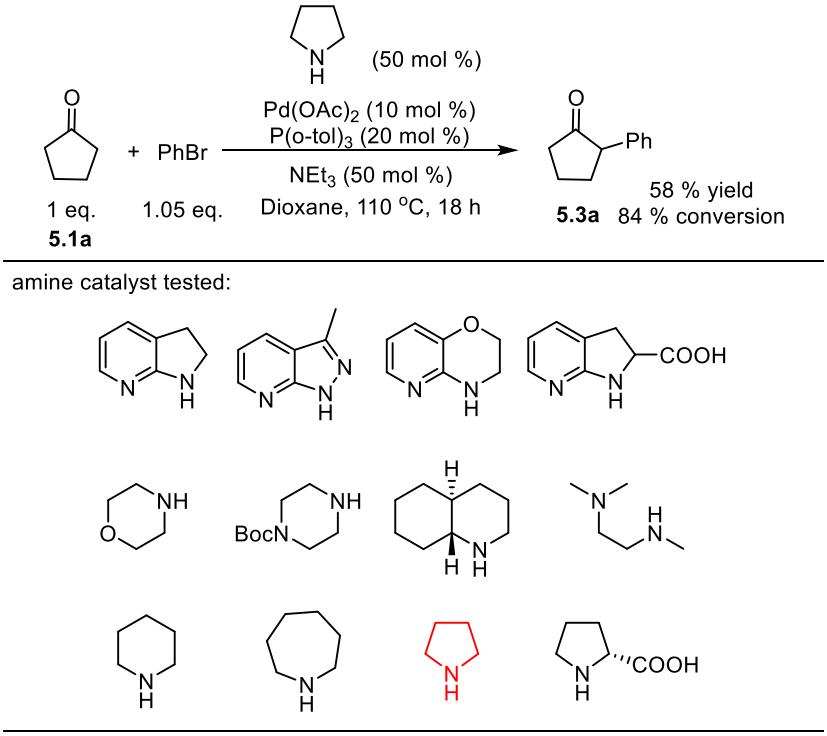
With the concern that the iodine anions generated in the reaction system might gradually poison the catalyst due to poor solubility of stable PdI_2, aryl bromides were tested. Indeed, at elevated temperature (110 ^{o}C), higher yield (43%) was observed (Scheme 5.4).

Scheme 5.4 Aryl Iodides vs. Aryl Bromides



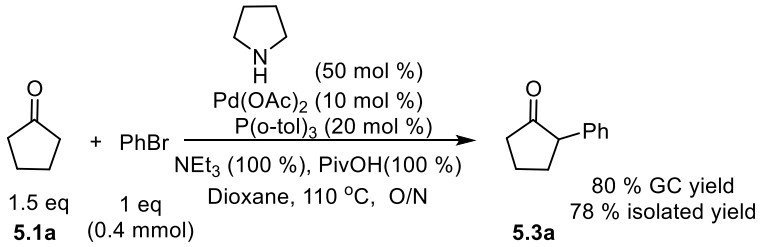
A variety of secondary amines were then tested as amine catalysts. Simple pyrrolidine was found a better catalyst than the previous proline. By further adding NEt_3 as an additive, 58% yield could be obtained. Less than 10% of the product was observed with other amine catalysts (Scheme 5.5).

Scheme 5.5 Screening of Amine Catalysts for Ketone α C−H Arylation



By further playing with the additives and the equivalency of the starting materials, **5.3a** could be obtained in 78% yield by using 1 equivalent of NEt_3 and PivOH as an additive combination and 1.5 equivalent of the cyclopentanone as the starting material. However, in order to demonstrate a more appealing and practical chemistry, we expected to 1) further lower the loading of the catalyst, and 2) use the ketone as the limiting reagent (Scheme 5.6).

Scheme 5.6 Two Challenges to be Solved for this Study

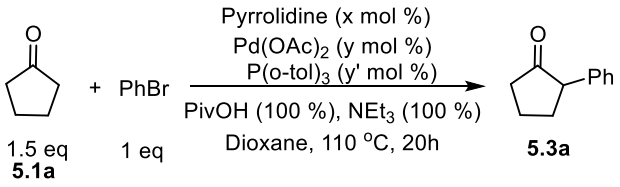


Challenge 1: can the catalyst loading be lowered?

Challenge 2: can ketone be used as limiting reagent?

A set of control experiments were conducted to test the lowest loading for the Pd and amine catalysts that did not affect the yield. While a Pd loading of 5 mol% still furnished the **5.3a** in 77% yield, **5.3a** was only obtained in 50% yield when the amine loading was decreased by half (Scheme 5.7).

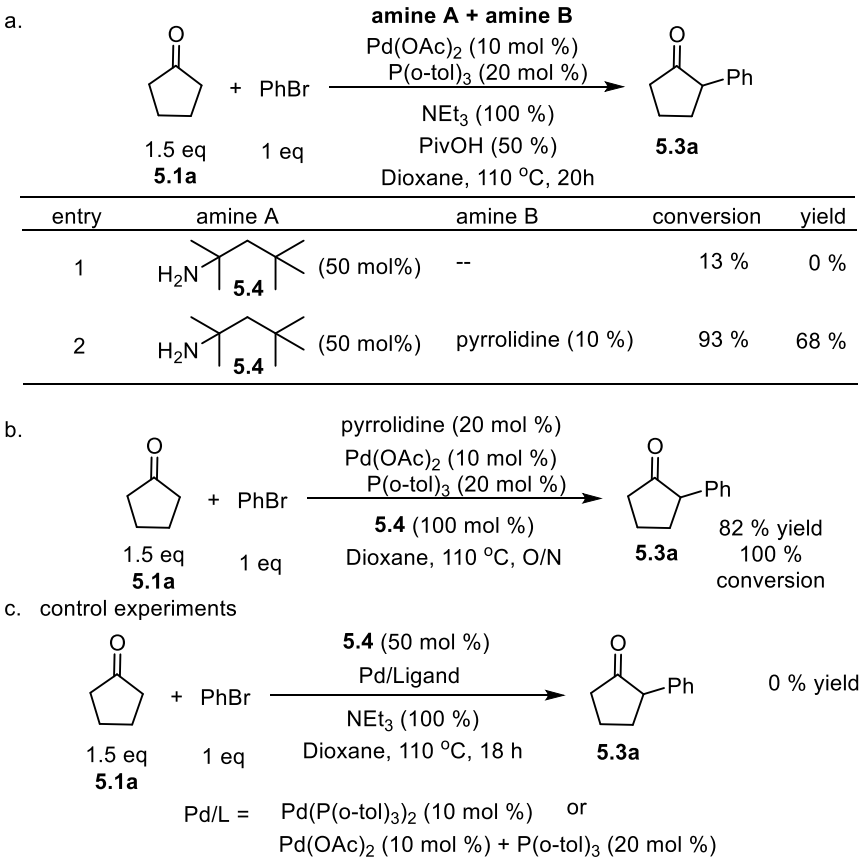
Scheme 5.7 Test on the Loading of the Pd and Amine Catalysts



	conv.	yield
[amine] = 50 % **[Pd]** = 10 %, **[PAr$_3$]** = 20 %	100 %	78 %
[amine] = 50 % **[Pd]** = 5 %, **[PAr$_3$]** = 10 %	100 %	77 %
[amine] = 25 % **[Pd]** = 5 %, **[PAr$_3$]** = 10 %	60 %	50 %

Interestingly, with the addition of 1,1,3,3-tetramethylbutylamine (**5.4**), the loading of the pyrrolidine catalyst could be dramatically decreased. While the **5.4** itself demonstrated no catalytic activity (Scheme 5.8a, entry 1, and Scheme 5.8c), with the addition of 50 mol% of **5.4,** a 68% yield was obtained with only 10 mol% of pyrrolidine catalyst (Scheme 5.8a, entry 2). Upon optimization, the yield could be further improved to 82% yield using 20 mol% of pyrrolidine as the amine catalyst and 100 mol% of **5.4** as an additive (Scheme 5.8b).

Scheme 5.8 Discovery of Amine 5.4 as an Effective Additive



A lower yield was observed when cyclopentanone was used as the limiting reagent (Scheme 5.9). By a thorough screening of weak bases that could neutralize the "HBr" generated from the reaction (*vide supra*, Figure 5.2, Step F), we were delighted to find that the yield could be improved to 75% by using a combination of 100 mol% of NaOAc as the weak base and 30 mol% of **5.4** as an additive (Table 5.2, entry 10)**.** Interestingly, lowering the Pd loading down to 2.5 mol% further increased the yield up to 85% (Table 5.3, entry 11).

Scheme 5.9 Using Cyclopentanone as the Limiting Reagent

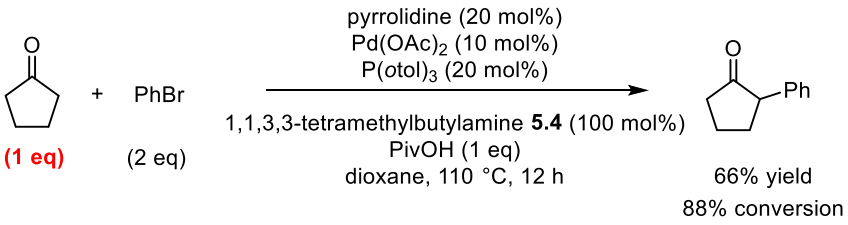
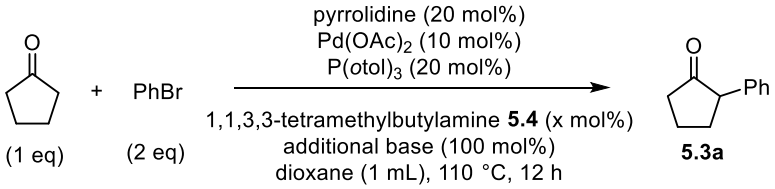
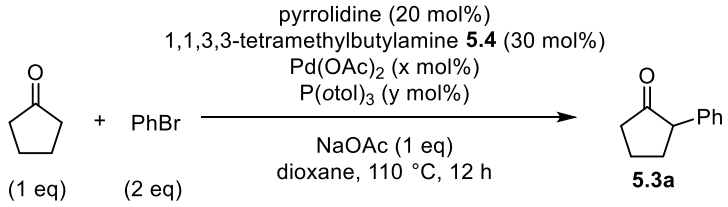


Table 5.2 Screening of Weak Bases for Ketone α C–H Arylation



entry	loading of **5.4**	additional base	yield	conversion	brsm
1	50%	--	35	60	58
2	0%	NEt_3	14	48	30
3	0%	--	0	28	0
4	0%	$NaHCO_3$	50	74	67
5	0%	Na_2CO_3	21	48	45
6	0%	PivOCs	0	26	0
7	30%	$NaHCO_3$	57	82	70
8	30%	Na_2CO_3	52	80	65
9	30%	PivOCs	0	30	0
10	30%	NaOAc	75	94	80
11	30%	KOTfa	35	65	54

Table 5.3 Screening of the Pd loading for Ketone α C−H Arylation

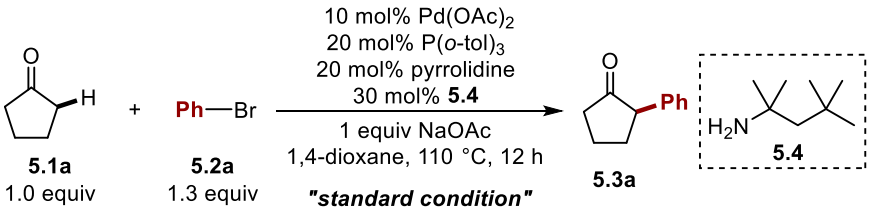


entry	condition	yield
w/ 10% Pd, 20% PAr_3		
1	**w/o change**	**74**
2	pyrrolidine = 25%	79
3	pyrrolidine = 30%	81
4	Pd = $Pd(OPiv)_2$	76
5	Pd = $Pd(OTfa)_2$	68
w/ 5% Pd, 10% PAr_3		
6	**w/o change**	**79**
7	pyrrolidine = 15%	72
8	amine **5.4** = 50%	81
9	amine **5.4** = 20%	75

entry	condition	yield
w/ 2.5% Pd, 5% PAr_3		
10	**w/o change**	**82**
11	pyrrolidine = 30%	85
12	pyrrolidine = 40%	79
13	Pd = $Pd(OPiv)_2$	85
w/ 1% Pd, 2% PAr_3		
14	**w/o change**	**76**
15	pyrrolidine = 30%	76
16	pyrrolidine = 30% amine **5.4** = 50%	80
[Best Pd loading: 2.5% [Best amine catalyst loading: 30%]		

After identifying the optimal condition, a set of control experiments were then conducted (Table 5.4). Both the pyrrolidine[22] and $Pd(OAc)_2$ were found indispensible (entries 2 and 3). Among various ligands, P(*o*-tol)$_3$ was still the best, although P(*t*-Bu)$_3$ worked almost equally well (entries 4-8). Amine **5.4** was found to be an important additive, although its role remained to be defined (entries 10 and 11).[13b] While NaOAc proved to be optimal, other weak bases, such as $NaHCO_3$, are also effective (entries 12-14). Near neutral conditions can be adopted when NaOAc was replaced with a 1:1 amine **5.4**/PivOH buffer (entry 15). Lower temperatures are also possible albeit requiring longer reaction time (entries 16 and 17). In addition, 1 equiv of PhBr can be used without significant loss of yield (entry 20). Finally, high compatibilty with water (entry 22) and moderate tolerance of air (entry 23) were observed.

Table 5.4 Control Experiments from the 'Standard' Condition



Entry	Variations from the reaction conditions of eq 1	Yield of **5.3a** [%][a]
1	none	75
2	no pyrrolidine	0
3	no $Pd(OAc)_2$	0
4	no P(*o*-tol)$_3$	9
5	PPh_3 instead of P(*o*-tol)$_3$	48
6	P(1-napthyl)$_3$ instead of P(*o*-tol)$_3$	58
7	P(*t*-Bu)$_3$ instead of P(*o*-tol)$_3$	73
8	P(*i*-Pr)$_3$ instead of P(*o*-tol)$_3$	0
9	$Pd^0[P(o\text{-tol})_3]_2$ instead of $Pd(OAc)_2$/P(*o*-tol)$_3$	77
10	no amine **5.4**	59
11	NEt_3 instead of amine **5.4**	54
12	no NaOAc	27
13	$NaHCO_3$ instead of NaOAc	57
14	Na_2CO_3 instead of NaOAc	52
15	amine **5.4** (1 equiv)/PivOH (1 equiv) instead of amine **5.4** (30 mol%)/NaOAc (1 equiv)	67
16	**80 °C**, 26h[b]	**75**
17	**60 °C**, 48h, with P(*t*-Bu)$_3$[b]	60
18	with 5 mol% $Pd(OAc)_2$/10 mol% P(*o*-tol)$_3$	79
19	with 2.5 mol% $Pd(OAc)_2$/5 mol% P(*o*-tol)$_3$	82
20	***with 2.5 mol% Pd(OAc)$_2$/5 mol% P(o-tol)$_3$***[b]	***85(80)***
21	PhBr = 1 equiv[c]	80
22	H_2O (1 equiv) was added[c]	**74**
23	under **air**[c]	50

[a] GC yield determined using dodecane as the internal standard. [b] 30 mol% pyrrolidine was used. [c] Change was made based on entry 20.

The substrate scope was subsequently examined (Table 5.5). Various aryl bromides with different electronic properties were efficiently coupled in good to excellent yields. Substitutions at *ortho*, *meta* or *para* positions were all tolerated. FGs, such as aryl chlorides (**5.3j**), fluorides (**5.3n**), esters (**5.3g** and **5.3h**), nitriles (**5.3o**), amides (**5.3i**, **5.3q** and **5.3u**), thioethers (**5.3d**) and even a tocopherol moiety (**5.3y**), were compatible. Substrates bearing

enolizable protons, such as methyl sulfones (**5.3r**), or FGs that are sensitive to nucleophiles, e.g. benzophenones (**5.3t**) and Weinreb amides (**5.3q**), all worked well. Remarkably, *free* carboxylic acids (**5.3p**) and alcohols (**5.3x**) remained intact. In addition, this transformation is highly chemoselective to cyclopentanones; for example, the methyl aryl ketone (**5.3s**) was well tolerated, which is likely attributed to the rate difference in enamine formation.[23] Encouragingly, aryl silanes (**5.3w**) and boronic esters (**5.3v**), well known partners for Pd-catalyzed cross couplings, remained untouched due to the lack of strong bases. Furthermore, both electron-rich and -deficient heteroarenes and polyarenes, such as unprotected indole (**5.5a**), pyridine (**5.5b**), benzothiophene (**5.5c**) and naphthalene (**5.5d**), can also be introduced. Altogether, this aylation method offers a distinct and complementary feature from the BHM reaction.

Table 5.5 Scope of Aryl Bromides

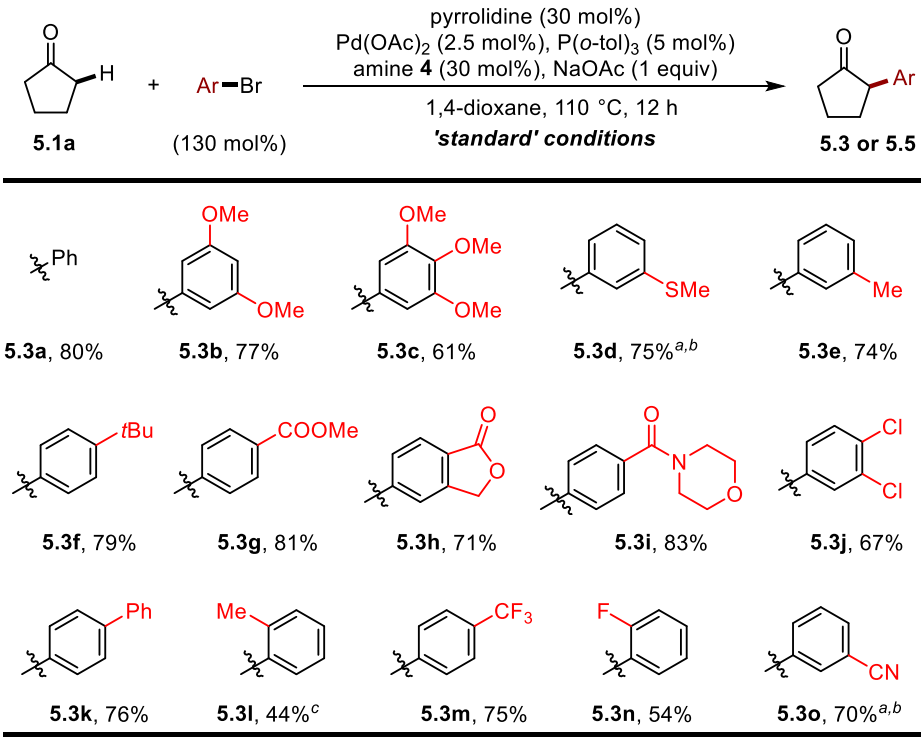
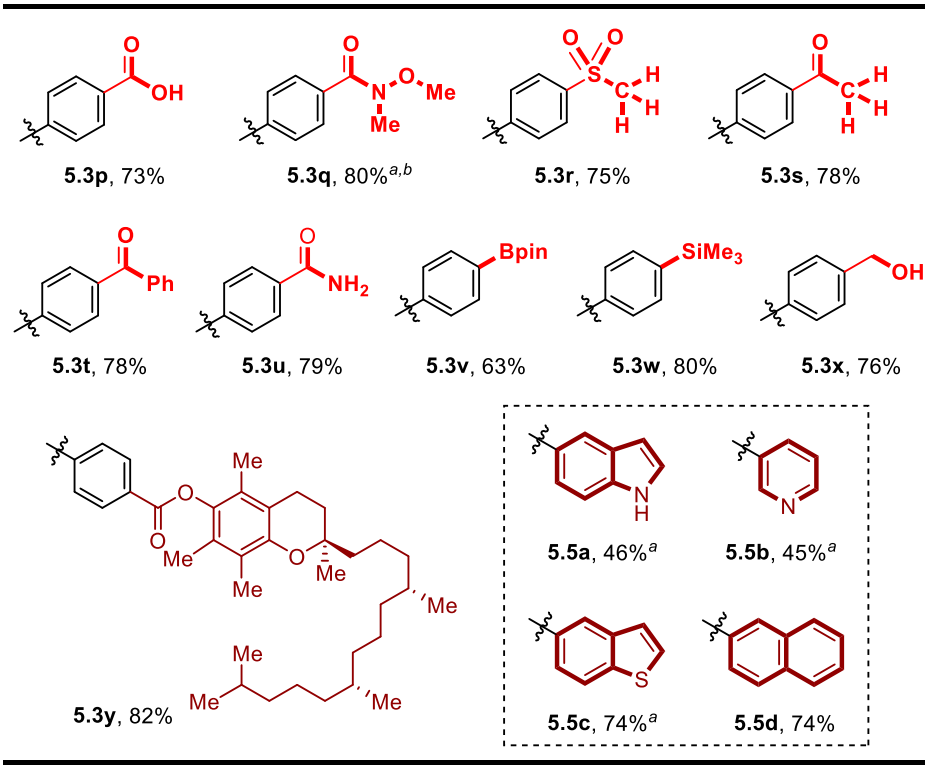


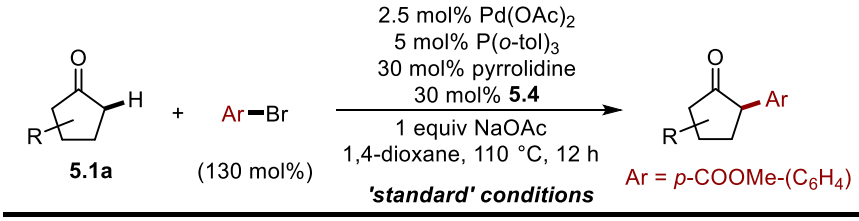
Table 5.5 Scope of Aryl Bromides (continued)

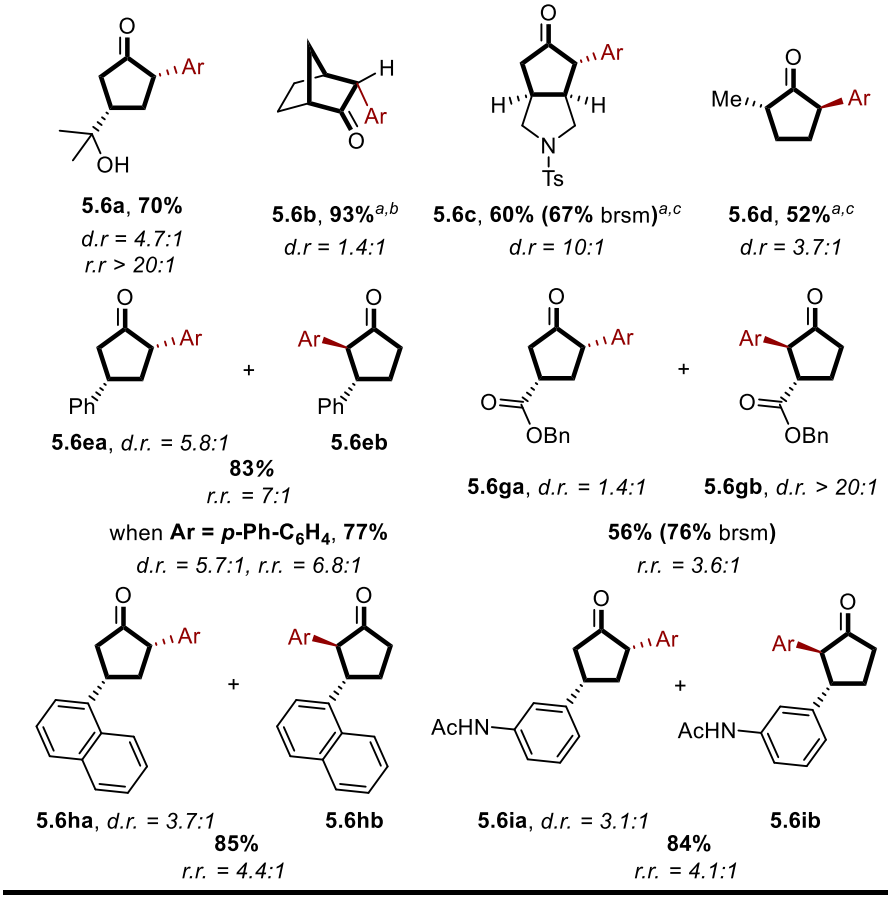


[a] With 10 mol% $Pd(OAc)_2$, 20 mol% P(*o*-tol)$_3$. [b] 24 h. [c] With 2 equiv of ArBr, 18 h.

Cyclopentanones with different substitution patterns were tested (Table 5.5).[24] Substitutions at α- or β-positions, including alkyl, aryl and carbonyl groups, were all tolerated. Both bridged (**5.6b**) and fused cycles (**5.6c**) are suitable substrates. Interestingly, tertiary alcohol moiety was also competent (**5.6a**). For substrates with an existing stereocenter, moderate to good diastereoselectivity was observed. The thermodynamically more stable isomers were favoured, which is likely controlled by the rapid keto-enol tautomerization under the reaction conditions.

Table 5.6 Scope of Cyclopentanones



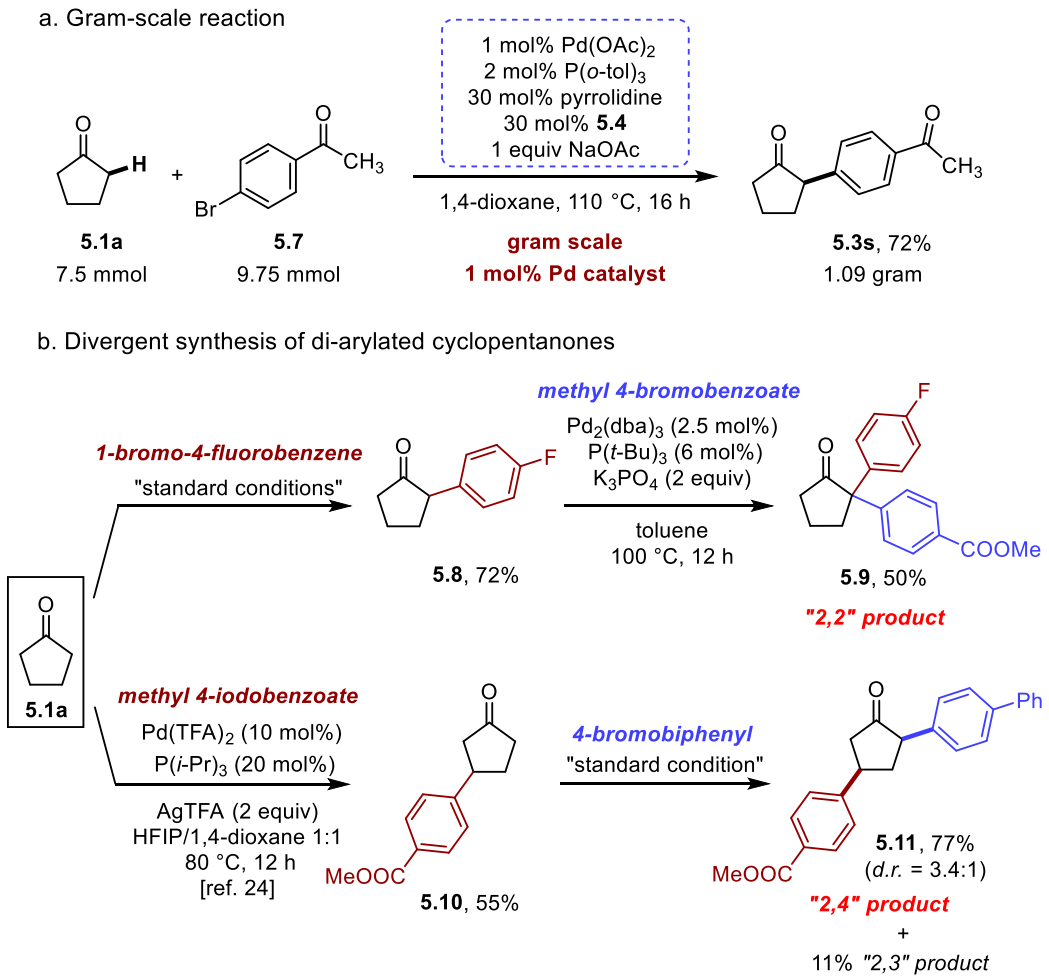


[a] With 10 mol% $Pd(OAc)_2$, 20 mol% P(*o*-tol)$_3$, and 50 mol% of pyrrolidine. [b] 18 h. [c] Without **5.4**, 24 h.

A gram-scale preparation was demonstrated with *1 mol% Pd* (Scheme 5.10a). Given the relatively low costs of each reagent used and tolerance of moisture/air, this protocol is expected to be practical for larger scales. Further applications were illustrated in the synthesis of multi-arylated cyclopentanones (Scheme 5.10b), which were challenging to prepare. While the previous attempt only offered the bis-arylated product in spite of using excess

cyclopentanones,[4] under the current conditions the mono-arylated product was smoothly obtained. Further conversion to the 2,2-diarylated product (**5.9**) was achieved with a regular BHM reaction. In contrast, using our previously developed β-arylation methods,[25] followed by this α-arylation protocol, the 2,4-diarylated compound (**5.11**) can be rapidly synthesized in two steps from cyclopentanones.

Scheme 5.10 Synthetic Applications



5.3 Conclusions

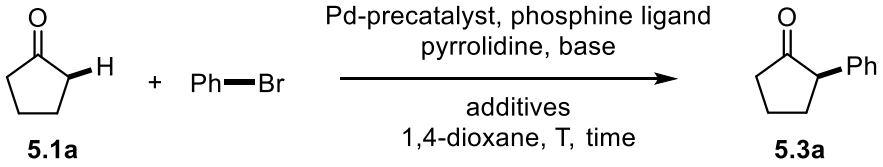
In conclusion, the long-standing challenge of mono-α-arylation of cyclopentanones is addressed via Pd-amine cooperative catalysis in this chapter. This method is scalable and chemoselective with broad functional group tolerance. Application to controlled sequential arylation of cyclopentanones has been also demonstrated.

(Some contents of this chapter were published in *Angew. Chem., Int. Ed.* **2016**, *55*, 2559)

5.4 Experimental

Unless otherwise noted, all experiments were carried out under air atmosphere. 1,4-dioxane were distilled over Na. The other reagents and solvents were directly used from the supplier without further purification unless noted. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plate (silica gel 60, F254, EMD chemical). The vials (1 dram, 15×45 mm with PTFE lined cap attached) were purchased from Qorpak and used directly. Optical rotations were determined using an Anton Paar MCP 200 polarimeter. Infrared spectra were recorded on a Nicolet iS5 FT-IR Spectrometer using neat thin film technique. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+Na]^+$ or $[M]^+$. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded with Varian Gemini (400 MHz, ^{1}H at 400 MHz, ^{13}C at 101 MHz) unless noted. For $CDCl_3$ solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; $CHCl_3$ δ H (7.26 ppm) and $CDCl_3$ δ C (77.16 ppm). For C_6D_6 solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; C_6D_6 δ H (7.16 ppm) and C_6D_6 δ C (128.06 ppm). Coupling constants are reported in Hertz (Hz). Data for ^{1}H NMR and ^{19}F NMR spectra are reported as follows: chemical shift (ppm, referenced to protium: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet (quintet), dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet, coupling constant (Hz), and integration).

Typical procedure for reaction condition screening

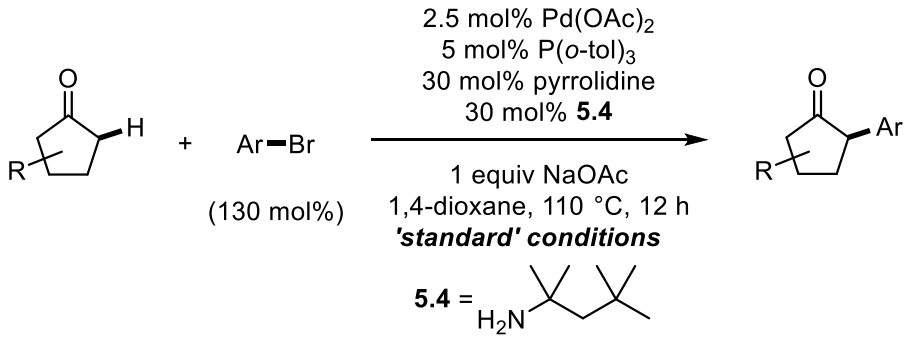


5.1a **5.3a**

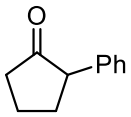
The reaction was run at a 0.2 mmol scale based on the limiting reagent. A 4 mL vial was charged with palladium salt, phosphine ligand, base, cyclopentanone, bromobenzene, pyrrolidine, additives and 1 mL 1,4-dioxane. The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 110 °C for 12 hours (unless noted otherwise) under stirring. Then the mixture was allowed to cool to room temperature. Diethyl ether (1 mL) and appropriate amount of dodecane (~20 mg) was added to the reaction as internal standard and the mixture was stirred for an additional 5 min to fully mix. ~0.3 mL of the resulting mixture was filtered through a small plug of silica gel, eluted with diethyl ether. The filtrate was directly used for GC analysis

** For reactions using P(t-Bu)$_3$ as the phosphine ligand, the P(t-Bu)$_3$ was added into the reaction vial after the reaction vial was transferred into a glove box and purged under N_2 atmosphere for 5 min.*

Typical procedure for substrate scope study



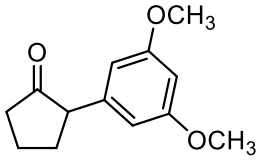
A 4 mL vial was charged with $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol, 0.025 equiv), P(*o*-tol)$_3$ (4.6 mg, 0.015 mmol, 0.05 equiv), NaOAc (24.6 mg, 0.3 mmol, 1.0 equiv), cyclopentanones (0.3 mmol, 1.0 equiv), aryl bromides (0.39 mmol, 1.3 equiv), pyrrolidine (7.7 μL, 0.09 mmol, 0.3 equiv), 1,1,3,3-tetramethylbutylamine **5.4** (15 μL, 0.09 mmol, 0.3 equiv) and 1,4-dioxane (1.5 mL). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min. The vial was then sealed again and heated in a pie-block at 110 °C under stirring for 12 hours, before cooled to room temperature. The mixture was filtered through a small plug of silica gel, eluted with ethyl acetate. The solvent was removed in *vacuo* and flash column chromatography (hexane/ethyl acetate or hexane/acetone) of the residue gave the arylation product.



5.3a

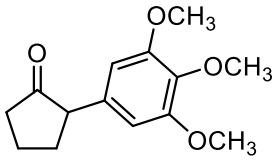
2-Phenylcyclopentanone (5.3a): Colorless oil (38.3 mg, 80% yield). R_f = 0.5 (Hex/EA = 5:1). IR (KBr) 3032, 2971, 2930, 1737, 1494, 1451, 1141 cm^{-1}. ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.31 – 7.22 (m, 1H), 7.22 – 7.16 (m, 2H), 3.43 – 3.23 (m, 1H), 2.56 – 2.43 (m, 2H), 2.36 – 2.24 (m, 1H), 2.21 – 2.06 (m, 2H), 2.01 – 1.86 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.24, 138.55, 128.73, 128.27, 127.03, 55.48, 38.59, 31.90, 21.01. HRMS: calcd. 160.0888 $[M]^+$ Found: 160.0887. The spectroscopic data are in accordance with those previously reported in the literature.[26]



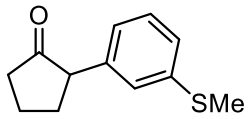
5.3b

2-(3,5-Dimethoxyphenyl)cyclopentanone (5.3b): Colorless oil (48.9 mg, 77% yield). R_f = 0.3 (Hex/EA = 5:1). IR (KBr) 3003, 2965, 2841, 1745, 1601, 1462, 1431.18, 1208, 1158 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 6.61 (dd, *J* = 2.2, 0.5 Hz, 2H), 6.56 (t, *J* = 2.3 Hz, 1H), 3.47 (s, 6H), 2.92 (dd, *J* = 11.2, 8.3 Hz, 1H), 2.12 – 1.97 (m, 2H), 1.91 – 1.71 (m, 2H), 1.65 – 1.53 (m, 1H), 1.40 – 1.27 (m, 1H). ^{13}C NMR (101 MHz, C_6D_6) δ 214.96, 161.52, 141.43, 107.01, 98.97, 54.92, 54.87, 38.16, 31.44, 20.83. HRMS: calcd. 220.1099 $[M]^+$ Found: 220.1098.



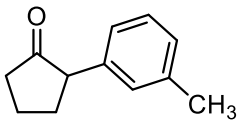
5.3c

2-(3,4,5-Trimethoxyphenyl)cyclopentanone (5.3c): Colorless oil (45.2 mg, 61% yield). R_f = 0.1 (Hex/EA = 5:1). IR (KBr) 2969, 2940, 1741, 1593, 1508, 1455, 1419, 1248, 1127 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 6.42 (s, 2H), 3.84 (s, 3H), 3.47 (s, 6H), 2.84 (dd, *J* = 11.4, 8.2 Hz, 1H), 2.11 – 1.92 (m, 2H), 1.83 (ddd, *J* = 18.4, 10.7, 8.8 Hz, 1H), 1.77 – 1.64 (m, 1H), 1.64 – 1.51 (m, 1H), 1.40 – 1.22 (m, 1H). ^{13}C NMR (101 MHz, C_6D_6) δ carbon signals were observed at 215.19, 154.18, 138.65, 134.37, 106.50, 60.54, 60.53, 56.02, 56.01, 54.88, 38.18, 31.71, 20.84. HRMS: calcd. 250.1205 $[M]^+$ Found: 250.1211.



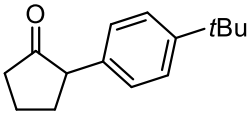
5.3d

2-(3-(Methylthio)phenyl)cyclopentanone (5.3d): The reaction was conducted with 10 mol% $Pd(OAc)_2$, 20 mol% P(*o*-tol)$_3$ for 24 h. Colorless oil (46.4 mg, 75% yield). R_f = 0.35 (Hex/EA = 5:1). IR (KBr) 2968, 2922, 2874, 1741, 1593, 1480, 1145 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.23 (m, 1H), 7.15 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 7.09 (t, *J* = 1.9 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 3.30 (dd, *J* = 11.0, 8.6 Hz, 1H), 2.54 – 2.44 (m, 5H), 2.37 – 2.26 (m, 1H), 2.22 – 2.05 (m, 2H), 2.00 – 1.89 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.81, 139.22, 138.82, 129.13, 126.64, 125.22, 125.08, 55.30, 38.56, 31.83, 20.97, 16.02. HRMS: calcd. 206.0765 $[M]^+$ Found: 206.0766.



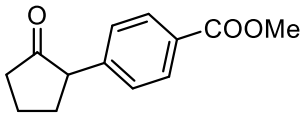
5.3e

2-(*m*-Tolyl)cyclopentanone (5.3e): Colorless oil (38.6 mg, 74% yield). R_f = 0.55 (Hex/EA = 5:1). IR (KBr) 3028, 2963, 2870, 1741, 1616, 1494, 1144 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 7.13 (d, *J* = 7.5 Hz, 1H), 7.02 – 6.88 (m, 3H), 2.84 (dd, *J* = 11.4, 8.3 Hz, 1H), 2.15 (s, 3H), 2.05 – 1.87 (m, 2H), 1.78 (ddd, *J* = 18.4, 10.7, 8.8 Hz, 1H), 1.63 (dtd, *J* = 12.5, 11.2, 6.5 Hz, 1H), 1.54 – 1.46 (m, 1H), 1.32 – 1.20 (m, 1H). ^{13}C NMR (101 MHz, C_6D_6) δ 215.29, 139.28, 138.00, 129.41, 128.61, 127.69, 125.64, 54.82, 38.21, 31.72, 21.48, 20.87. HRMS: calcd. 174.1045 $[M]^+$ Found: 174.1046.



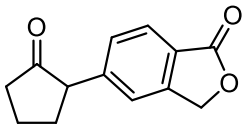
5.3f

2-(4-(*tert*-Butyl)phenyl)cyclopentanone (5.3f): Colorless oil (51.1 mg, 79% yield). R_f = 0.5 (Hex/EA = 5:1). IR (KBr) 2967, 2906, 2874, 1743, 1520, 1466, 1271 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.31 (m, 2H), 7.19 – 7.07 (m, 2H), 3.41 – 3.23 (m, 1H), 2.57 – 2.43 (m, 2H), 2.37 – 2.23 (m, 1H), 2.22 – 2.07 (m, 2H), 1.97 – 1.88 (m, 1H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.49, 149.71, 135.39, 127.83, 125.63, 54.99, 38.53, 34.52, 31.81, 31.44, 20.97. HRMS: calcd. 216.1514 $[M]^+$ Found: 216.1516.



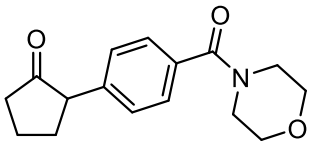
5.3g

Methyl 4-(2-oxocyclopentyl)benzoate (5.3g): Colorless oil (52.8 mg, 81% yield). R_f = 0.25 (Hex/EA = 5:1). IR (KBr) 2959, 2880, 1747, 1725, 1609, 1437, 1289, 1113 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 8.15 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 2H), 3.52 (s, 3H), 2.73 (dd, *J* = 11.2, 8.2 Hz, 1H), 2.03 – 1.90 (m, 1H), 1.83 – 1.65 (m, 2H), 1.54 – 1.40 (m, 2H), 1.26 – 1.14 (m, 1H). ^{13}C NMR (101 MHz, C_6D_6) δ 214.26, 166.68, 144.24, 130.01, 129.33, 128.61, 54.71, 51.62, 37.99, 31.09, 20.75. HRMS: calcd. 218.0943 $[M]^+$ Found: 218.0945.



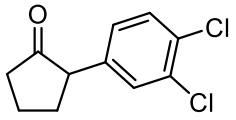
5.3h

5-(2-Oxocyclopentyl)isobenzofuran-1(3*H*)-one (5.3h): Colorless oil (48.3 mg, 71% yield). R_f = 0.3 (Hex/EA/DCM = 2:1:1). IR (KBr) 2971, 2880, 1761, 1620, 1451, 1360 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.78 (m, 1H), 7.34 (d, *J* = 7.8 Hz, 2H), 5.27 (s, 2H), 3.45 (dd, *J* = 11.5, 8.3 Hz, 1H), 2.61 – 2.45 (m, 2H), 2.38 – 2.26 (m, 1H), 2.26 – 2.07 (m, 2H), 2.04 – 1.90 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.62, 170.95, 147.13, 145.32, 129.33, 125.83, 124.47, 121.98, 69.60, 55.61, 38.37, 31.62, 20.85. HRMS: calcd. 239.06790 $[M+Na]^+$ Found: 239.06770.



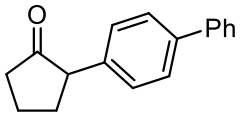
5.3i

2-(4-(Morpholine-4-carbonyl)phenyl)cyclopentanone (5.3i): Colorless oil (67.8 mg, 83 % yield). R_f = 0.1 (Hex/EA/DCM = 2:1:1). IR (KBr) 3487, 2971, 2920, 2861, 1741, 1630, 1433, 1277 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 3.90 – 3.35 (m, 8H), 3.32 (dd, *J* = 11.0, 8.5 Hz, 1H), 2.54 – 2.41 (m, 2H), 2.33 – 2.21 (m, 1H), 2.20 – 2.02 (m, 2H), 1.99 – 1.86 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.48, 170.22, 140.42, 133.79, 128.37, 127.43, 66.90, 55.11, 48.25, 42.65, 38.43, 31.67, 20.83. HRMS: calcd. 296.12570 $[M+Na]^+$ Found: 296.12600.



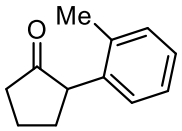
5.3j

2-(3,4-Dichlorophenyl)cyclopentanone (5.3j): Colorless oil (45.9 mg, 67% yield). R_f = 0.4 (Hex/EA = 5:1). IR (KBr) 2969, 2878, 1741, 1476, 1405, 1141, 1030 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 7.10 (d, *J* = 2.1 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.61 (dd, *J* = 8.4, 2.1 Hz, 1H), 2.46 (dd, *J* = 11.7, 8.1 Hz, 1H), 1.95 – 1.83 (m, 1H), 1.70 – 1.55 (m, 2H), 1.41 – 1.32 (m, 1H), 1.28 – 1.17 (m, 1H), 1.17 – 1.05 (m, 1H). ^{13}C NMR (101 MHz, C_6D_6) δ 213.69, 139.10, 132.72, 131.08, 130.48, 130.36, 128.01, 53.54, 37.70, 30.69, 20.53. HRMS: calcd. 228.0109 $[M]^+$ Found: 228.0107.



5.3k

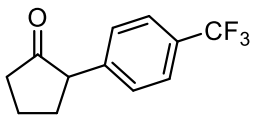
2-([1,1'-Biphenyl]-4-yl)cyclopentanone (5.3k): White solid (53.7 mg, 76% yield). m.p.= 121-123 °C. R_f = 0.5 (Hex/EA = 5:1). IR (KBr) 3030, 2965, 2873, 1743, 1490, 1453, 1141 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.53 (m, 4H), 7.47 – 7.41 (m, 2H), 7.37 – 7.32 (m, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 3.38 (dd, *J* = 11.1, 8.7 Hz, 1H), 2.65 – 2.46 (m, 2H), 2.42 – 2.26 (m, 1H), 2.26 – 2.10 (m, 2H), 2.11 – 1.88 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.18, 141.00, 139.99, 137.56, 128.85, 128.66, 127.49, 127.31, 127.20, 55.20, 38.54, 31.86, 21.00. HRMS: calcd. 236.1201 $[M]^+$ Found: 236.1204. The spectroscopic data are in accordance with those previously reported in the literature.[27]



5.3l

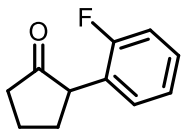
2-(*o*-Tolyl)cyclopentanone (5.3l): The reaction was conducted with 2 equiv of ArBr for 18 h. Colorless oil (22.9 mg, 44% yield). R_f = 0.6 (Hex/EA = 5:1). IR (KBr) 3026, 2963, 2876, 1741, 1496, 1265, 1148 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.12 (m, 3H), 7.03 – 6.98 (m, 1H), 3.53 (ddd, *J* = 11.6, 8.1, 1.3 Hz, 1H), 2.55 – 2.44 (m, 2H), 2.39 – 2.26 (m, 4H), 2.23 – 2.14 (m, 1H), 2.09 – 1.90 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.87, 137.65, 136.88, 130.66, 127.45, 127.01, 126.39, 53.13, 38.83, 31.82, 21.17, 20.05. HRMS:

calcd. 174.1045 $[M]^+$ Found: 174.1045. The spectroscopic data are in accordance with those previously reported in the literature.[28]



5.3m

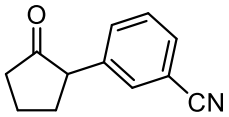
2-(4-(Trifluoromethyl)phenyl)cyclopentanone (5.3m): Colorless oil (50.4 mg, 75% yield). R_f = 0.4 (Hex/EA = 5:1). IR (KBr) 2969, 2886, 1747, 1624, 1419, 1334, 1170, 1123 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 3.39 (dd, *J* = 11.6, 8.3 Hz, 1H), 2.61 – 2.44 (m, 2H), 2.31 (ddd, *J* = 18.7, 10.7, 8.7 Hz, 1H), 2.24 – 2.07 (m, 2H), 2.03 – 1.91 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.01, 142.42 (q, *J* = 1.3 Hz), 129.27 (q, *J* = 32.5 Hz), 128.63, 125.58 (q, *J* = 3.8 Hz), 124.29 (q, *J* = 271.9 Hz), 55.19, 38.41, 31.55, 20.91. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.57 (s, 1F). HRMS: calcd. 228.0762 $[M]^+$ Found: 228.0765.



5.3n

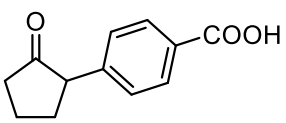
2-(2-Fluorophenyl)cyclopentanone (5.3n): Colorless oil (28.4 mg, 54% yield). R_f = 0.65 (Hex/EA = 5:1). IR (KBr) 2973, 2890, 1745, 1494, 1455, 1233 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.20 (m, 1H), 7.16 – 7.01 (m, 3H), 3.46 (dd, *J* = 11.9, 8.6 Hz, 1H),

2.53 – 2.43 (m, 2H), 2.37 (ddd, *J* = 19.0, 11.2, 8.5 Hz, 1H), 2.24 – 2.14 (m, 1H), 2.12 – 2.03 (m, 1H), 2.00 – 1.87 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were observed at δ 217.65, 162.23, 159.78, 130.52, 130.48, 128.90, 128.81, 126.64, 126.49, 124.37, 124.34, 115.89, 115.67, 51.04, 38.14, 31.62, 31.60, 21.35. ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.96 (dt, *J* = 11.2, 6.1 Hz, 1F). HRMS: calcd. 178.0794 $[M]^+$ Found: 178.0795.



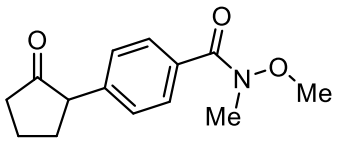
5.3o

3-(2-Oxocyclopentyl)benzonitrile (5.3o): The reaction was conducted with 10 mol% $Pd(OAc)_2$, 20 mol% P(*o*-tol)$_3$ for 24 h. Colorless oil (38.7 mg, 70% yield). R_f = 0.2 (Hex/EA = 5:1). IR (KBr) 2965, 2880, 2229, 1743, 1486, 1267, 1141 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dt, *J* = 6.5, 1.9 Hz, 1H), 7.50 (br, 1H), 7.48 – 7.41 (m, 2H), 3.35 (dd, *J* = 11.9, 8.4 Hz, 1H), 2.61 – 2.46 (m, 2H), 2.37 – 2.25 (m, 1H), 2.24 – 2.15 (m, 1H), 2.14 – 2.04 (m, 1H), 2.03 – 1.91 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.44, 139.67, 132.91, 131.75, 130.69, 129.41, 118.88, 112.70, 54.68, 38.25, 31.18, 20.79. HRMS: calcd. 185.0841 $[M]^+$ Found: 185.0840.



5.3p

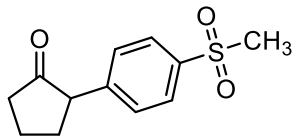
4-(2-Oxocyclopentyl)benzoic acid (5.3p): The reaction was conducted with 3 equiv NaOAc. After the reaction is done, the mixture was concentrated under reduced pressure. Trifluoroacetic acid (123 μL, 1.6 mmol) was added, and the resulting mixture was directly purified by flash column chromatography on silica gel (Hex:EA:HOAc = 10:1:0.2 to Hex:EA:HOAc = 5:1:0.4) to give the title compound as a white solid (44.6 mg, 73% yield). m.p.= 157 – 159 °C. R_f = 0.25 (Hex/EA/HOAc = 2:1:0.15). IR (KBr) 2965, 2878, 1741, 1680, 1425, 1287, 1127 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 10.87 (br, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 3.41 (dd, *J* = 11.2, 8.4 Hz, 1H), 2.61 – 2.46 (m, 2H), 2.32 (ddd, *J* = 18.9, 10.7, 8.6 Hz, 1H), 2.24 – 2.08 (m, 2H), 2.04 – 1.90 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.26, 172.05, 144.65, 130.56, 128.43, 128.05, 55.46, 38.50, 31.55, 20.95. HRMS: calcd. 227.06790 $[M+Na]^+$ Found: 227.06710.



5.3q

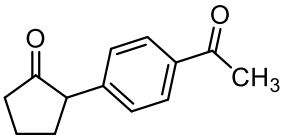
***N*-methoxy-*N*-methyl-4-(2-oxocyclopentyl)benzamide (5.3q):** The reaction was conducted with 10 mol% $Pd(OAc)_2$, 20 mol% P(*o*-tol)$_3$ for 24 h. White solid (59.1 mg, 80% yield). m.p.= 70-72 °C. R_f = 0.25 (Hex/EA/DCM = 3:1:1). IR (KBr) 3500, 2971, 2940, 1747, 1634, 1455, 1421, 1385 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 3.54 (s, 3H), 3.39 – 3.27 (m, 4H), 2.57 – 2.39 (m, 2H), 2.35 – 2.22 (m, 1H), 2.21 – 2.02 (m, 2H), 1.99 – 1.88 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.46,

169.60, 141.19, 132.53, 128.61, 127.84, 61.15, 55.11, 38.53, 33.89, 31.65, 20.90. HRMS: calcd. 270.11010 $[M+Na]^+$ Found: 270.11040.



5.3r

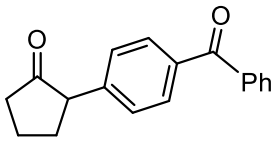
2-(4-(Methylsulfonyl)phenyl)cyclopentanone (5.3r): White solid (53.0 mg, 75% yield). m.p.= 86-88 °C. R_f = 0.1 (Hex/EA/DCM = 3:1:1). IR (KBr) 3019, 2967, 2880, 1745, 1601, 1409, 1409, 1299 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 3.41 (dd, *J* = 11.7, 8.3 Hz, 1H), 3.01 (s, 3H), 2.60 – 2.45 (m, 2H), 2.30 (ddd, *J* = 18.8, 10.7, 8.6 Hz, 1H), 2.24 – 2.06 (m, 2H), 2.04 – 1.89 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.55, 144.72, 139.02, 129.25, 127.65, 55.23, 44.62, 38.33, 31.40, 20.83. HRMS: calcd. 261.05560 $[M+Na]^+$ Found: 261.05530.



5.3s

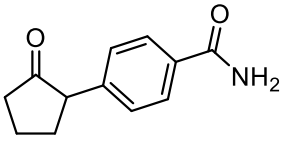
2-(4-Acetylphenyl)cyclopentanone (5.3s): White solid (47.1 mg, 78% yield). m.p.= 79-81 °C. R_f = 0.2 (Hex/EA = 5:1). IR (KBr) 2969, 2882, 1741, 1680, 1417, 1362, 1265 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 3.38 (dd, *J* = 11.5, 8.5 Hz, 1H), 2.58 – 2.45 (m, 5H), 2.37 – 2.25 (m, 1H), 2.23 – 2.07 (m, 2H), 2.02 –

1.89 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.04, 197.80, 143.91, 135.80, 128.65, 128.44, 55.35, 38.40, 31.47, 26.67, 20.89. HRMS: calcd. 225.08860 $[M+Na]^+$ Found: 225.08860.



5.3t

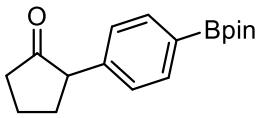
2-(4-Benzoylphenyl)cyclopentanone (5.3t): Colorless wax (61.6 mg, 78% yield). R_f = 0.2 (Hex/EA = 5:1). IR (KBr) 3060, 2967, 2882, 1747, 1660, 1451, 1320, 1283 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.71 (m, 4H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 3.41 (dd, *J* = 11.2, 8.4 Hz, 1H), 2.64 – 2.45 (m, 2H), 2.32 (ddd, *J* = 18.9, 10.7, 8.5 Hz, 1H), 2.26 – 2.10 (m, 2H), 2.06 – 1.90 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.19, 196.36, 143.28, 137.70, 136.18, 132.42, 130.47, 130.06, 128.33, 128.20, 55.39, 38.49, 31.62, 20.94. HRMS: calcd. 287.10430 $[M+Na]^+$ Found: 287.10450.



5.3u

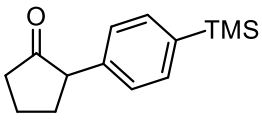
4-(2-Oxocyclopentyl)benzamide (5.3u): White solid (48.3 mg, 79% yield). m.p.= 153-155 °C. R_f = 0.1 (Hex/EA/DCM = 1:1:1). IR (KBr) 3386, 3188, 2965, 2878, 1743, 1636, 1403 cm^{-1}. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.41 (br, 1H), 7.30 (d,

J = 8.3 Hz, 2H), 6.62 (br, 1H), 3.47 (dd, J = 11.3, 8.3 Hz, 1H), 2.55 – 2.44 (m, 1H), 2.44 – 2.25 (m, 2H), 2.23 – 2.09 (m, 2H), 2.03 – 1.89 (m, 1H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 216.79, 168.92, 143.91, 133.58, 129.17, 128.36, 55.67, 38.67, 32.41, 21.46. HRMS: calcd. 226.08380 $[M+Na]^+$ Found: 226.08360.



5.3v

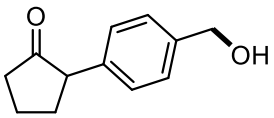
2-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopentanone (5.3v): White solid (53.8 mg, 63% yield). m.p.= 140-142 °C. R_f = 0.35 (Hex/EA = 5:1). IR (KBr) 2975, 2878, 1743, 1616, 1403, 1366, 1144 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.1 Hz, 2H), 7.24 – 7.14 (m, 2H), 3.34 (dd, J = 11.1, 8.7 Hz, 1H), 2.56 – 2.42 (m, 2H), 2.38 – 2.23 (m, 1H), 2.23 – 2.08 (m, 2H), 2.01 – 1.88 (m, 1H), 1.33 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.84, 141.81, 135.18, 127.66, 83.84, 55.63, 38.57, 31.80, 24.95, 21.01. HRMS: calcd. 286.1740 $[M]^+$ Found: 286.1747.



5.3w

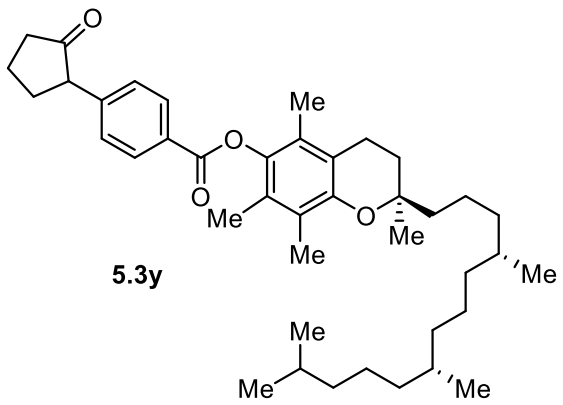
2-(4-(Trimethylsilyl)phenyl)cyclopentanone (5.3w): Colorless oil (55.4 mg, 80% yield). R_f = 0.55 (Hex/EA = 5:1). IR (KBr) 3019, 2959, 2894, 1737, 1403, 1249, 1111 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 3.34 (dd, *J* = 10.7, 8.5 Hz, 1H), 2.62 – 2.46 (m, 2H), 2.31 (ddd, *J* = 18.9, 10.9, 8.6 Hz, 1H), 2.23 – 2.07 (m, 2H), 2.02 – 1.87 (m, 1H), 0.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.14, 139.05, 138.84, 133.73, 127.62, 55.47, 38.53, 31.77, 20.98, -1.02. HRMS: calcd. 232.1283 $[M]^+$ Found: 232.1284.



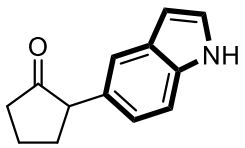
5.3x

2-(4-(Hydroxymethyl)phenyl)cyclopentanone (5.3x): Colorless oil (43.0 mg, 76% yield). R_f = 0.2 (Hex/EA = 2:1). IR (KBr) 3402, 2963, 2878, 1739, 1516, 1403, 1148 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6) δ 7.23 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 4.42 (s, 2H), 2.82 (dd, *J* = 11.4, 8.3 Hz, 1H), 2.12 – 1.93 (m, 2H), 1.93 – 1.86 (m, 1H), 1.76 (ddd, *J* = 18.6, 10.8, 8.8 Hz, 1H), 1.61 (dtd, *J* = 12.4, 11.3, 6.5 Hz, 1H), 1.55 – 1.45 (m, 1H), 1.30 – 1.19 (m, 1H). ^{13}C NMR (101 MHz, C_6D_6) δ 216.02, 140.48, 138.07, 128.52, 127.22, 64.79, 54.71, 38.15, 31.61, 20.82. HRMS: calcd. 190.0994 $[M]^+$ Found: 190.0997.



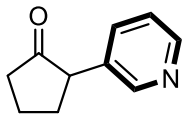
5.3y

(*R*)-2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl 4-(2-oxocyclopentyl)benzoate (5.3y): Isolated as a mixture of diastereomers (d.r. not determined). Colorless wax (167.5 mg, 82% yield). R_f = 0.4 (Hex/EA = 5:1). IR (KBr) 2957, 2918, 2921, 2874, 2256, 1733, 1607, 1458, 1281, 1239 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 3.45 (dd, *J* = 11.3, 8.6 Hz, 1H), 2.68 – 2.49 (m, 4H), 2.38 – 2.29 (m, 1H), 2.28 – 2.16 (m, 2H), 2.14 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.00 – 1.92 (m, 1H), 1.91 – 1.77 (m, 2H), 1.70 – 1.00 (m, 24H), 1.00 – 0.68 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were observed at δ 217.07, 165.03, 149.54, 144.26, 140.70, 130.56, 128.52, 128.36, 127.01, 125.24, 123.20, 117.56, 75.17, 55.55, 40.50, 39.71, 39.48, 38.45, 37.56, 37.40, 32.91, 32.86, 32.78, 31.62, 31.37, 31.16, 28.09, 24.93, 24.57, 24.31, 23.81, 22.85, 22.76, 21.15, 20.97, 20.75, 19.88, 19.79, 13.15, 12.30, 11.97. HRMS: calcd. 639.43840 $[M+Na]^+$ Found: 639.43760.



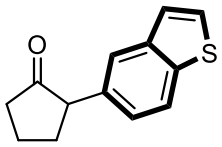
5.5a

2-(1*H*-indol-5-yl)cyclopentanone (5.5a): The reaction was conducted with 10 mol% $Pd(OAc)_2$, 20 mol% P(*o*-tol)$_3$ for 12 h. Colorless oil (27.5 mg, 46% yield). R_f = 0.25 (Hex/EA = 3:1). IR (KBr) 3402, 2965, 2874, 1731, 1478, 1419, 1348, 1156 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.46 (s, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.15 (t, *J* = 2.8 Hz, 1H), 7.00 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.50 (t, *J* = 2.6 Hz, 1H), 3.43 (dd, *J* = 10.7, 8.5 Hz, 1H), 2.62 – 2.44 (m, 2H), 2.34 (ddd, *J* = 18.8, 10.9, 8.6 Hz, 1H), 2.24 – 2.13 (m, 2H), 2.03 – 1.90 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.53, 135.00, 129.92, 128.25, 124.71, 122.46, 120.07, 111.36, 102.58, 55.75, 38.64, 32.59, 21.02. HRMS: calcd. 222.08890 $[M+Na]^+$ Found: 222.08860.



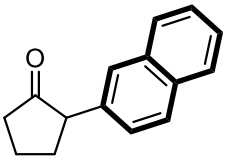
5.5b

2-(Pyridin-3-yl)cyclopentanone (5.5b): The reaction was conducted with 10 mol% $Pd(OAc)_2$, 20 mol% P(*o*-tol)$_3$ for 12 h. Colorless oil (21.8 mg, 45% yield). R_f = 0.15 (Hex/EA/DCM = 2:1:1). IR (KBr) 3406, 2969, 2886, 1741, 1488, 1427, 1148 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.45 (d, *J* = 2.2 Hz, 1H), 7.53 (dt, *J* = 8.2, 2.0 Hz, 1H), 7.30 – 7.22 (m, 1H), 3.33 (dd, *J* = 11.8, 8.4 Hz, 1H), 2.60 – 2.46 (m, 2H), 2.36 – 2.24 (m, 1H), 2.24 – 2.15 (m, 1H), 2.15 – 2.04 (m, 1H), 2.04 – 1.92 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.91, 149.59, 148.32, 135.73, 134.00, 123.57, 52.90, 38.30, 31.34, 20.94. HRMS: calcd. 162.09130 $[M+H]^+$ Found: 162.09110.



5.5c

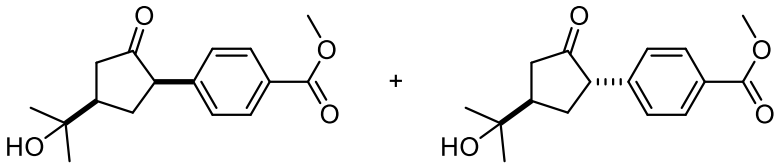
2-(Benzo[*b*]thiophen-5-yl)cyclopentanone (5.5c): The reaction was conducted with 10 mol% $Pd(OAc)_2$, 20 mol% P(*o*-tol)$_3$ for 12 h. Yellowish solid (47.6 mg, 74% yield). m.p.= 102-105 °C. R_f = 0.35 (Hex/EA = 5:1). IR (KBr) 3103, 2963, 2878, 1743, 1439, 1267, 1160 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 1H), 7.66 (d, *J* = 1.7 Hz, 1H), 7.43 (d, *J* = 5.4 Hz, 1H), 7.30 (dd, *J* = 5.4, 0.8 Hz, 1H), 7.18 (dd, *J* = 8.4, 1.8 Hz, 1H), 3.45 (dd, *J* = 11.0, 8.8 Hz, 1H), 2.62 – 2.47 (m, 2H), 2.34 (ddd, *J* = 18.8, 10.8, 8.7 Hz, 1H), 2.25 – 2.10 (m, 2H), 2.05 – 1.89 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.35, 140.05, 138.48, 134.65, 126.93, 124.72, 123.84, 123.10, 122.72, 55.42, 38.56, 32.21, 20.99. HRMS: calcd. 239.05010 $[M+Na]^+$ Found: 239.04990.



5.5d

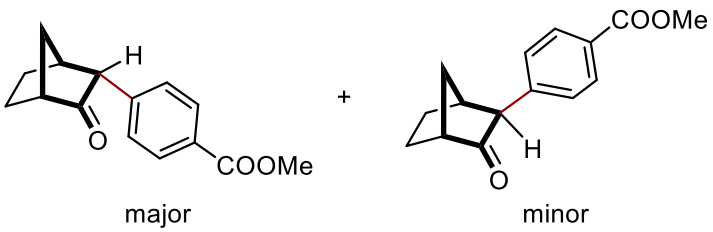
2-(Naphthalen-2-yl)cyclopentanone (5.5d): White solid (46.4 mg, 74% yield). m.p.= 83-86 °C. R_f = 0.55 (Hex/EA = 5:1). IR (KBr) 3056, 2961, 2874, 1737, 1512, 1453, 1405, 1143, 815 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 7.70 – 7.62 (m, 3H), 7.55 (d, *J* = 1.6 Hz, 1H), 7.33 – 7.22 (m, 3H), 2.98 (dd, *J* = 11.5, 8.2 Hz, 1H), 2.03 (dddt, *J* = 18.6, 8.4, 2.8, 1.4 Hz, 1H), 1.93 (dddt, *J* = 12.5, 8.3, 6.3, 2.1 Hz, 1H), 1.81 (ddd, *J* = 18.6, 10.8, 8.8 Hz, 1H), 1.68 (dtd, *J* = 12.6, 11.3, 6.4 Hz, 1H), 1.51 (dddt, *J* = 15.3, 9.0, 6.5, 2.5 Hz, 1H), 1.34 – 1.22

(m, 1H). ^{13}C NMR (101 MHz, C_6D_6) δ 215.19, 136.74, 134.04, 132.99, 128.39, 128.05, 128.03, 127.09, 127.07, 126.26, 125.84, 54.88, 38.22, 31.45, 20.88. HRMS: calcd. 210.1045 $[M]^+$ Found: 210.1046.



5.6a

5.6a: The reaction was carried out on a 0.3 mmol scale. The crude material was determined to be a 4.7:1 mixture of diastereomers by ^{1}H NMR analysis and was isolated as an inseparable 4.8:1 mixture of diastereomers as determined by ^{1}H NMR analysis. Colorless oil. Yield: 57.1 mg (70%). R_f = 0.2 (Hex/EA = 3:2). ^{1}H NMR (400 MHz, $CDCl_3$) (major : minor = 0.84 : 0.16) δ 8.09 – 7.94 (m, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 3.90 (s, 3H), 3.72 (dd, *J* = 9.8, 5.0 Hz, 0.16H, minor diastereomer), 3.49 (dd, *J* = 13.1, 8.3 Hz, 0.84H, major diastereomer), 2.58 – 2.22 (m, 4.16H), 2.12 – 2.02 (m, 0.84H, major diastereomer), 1.35 (br, 1H), 1.33 (s, 3H), 1.30 (s, 2.52H, major diastereomer), 1.28 (s, 0.48H, minor diastereomer). ^{13}C NMR (101 MHz, $CDCl_3$) major diastereomer δ 215.73, 167.06, 143.42, 129.96, 128.95, 128.39, 70.66, 56.71, 52.24, 45.21, 40.17, 32.44, 29.02, 28.18. minor diastereomer δ 217.26, 167.01, 144.42, 130.10, 128.81, 127.80, 71.50, 53.98, 52.24, 44.84, 40.28, 31.48, 29.02, 28.23. IR (KBr) 3502, 2977, 2890, 1743, 1721, 1289, 1115, 915 cm^{-1}. HRMS: calcd. 299.12540 $[M+Na]^+$ Found: 299.12570.

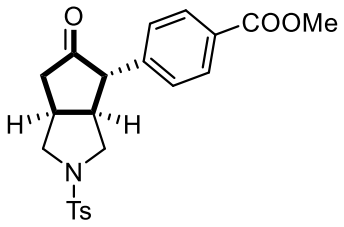


5.6b

The reaction was conducted on a 0.3 mmol scale with 10 mol% $Pd(OAc)_2$, 20 mol% P(*o*-tol)$_3$ and 50 mol% of pyrrolidine for 18 h. The crude material was determined to be a 1.4:1 mixture of diastereomers by ^{1}H NMR analysis and the isolated ratio of the diastereomers was 1.4:1. Yield: 68.3 mg (93%).

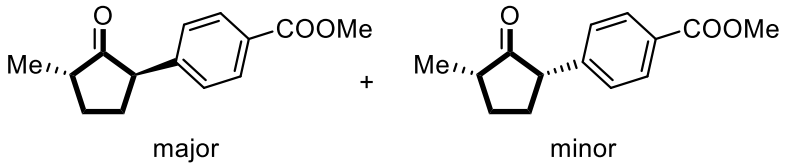
5.6b-major: Colorless oil. R_f = 0.2 (Hex/EA = 5:1). IR (KBr) 2957, 2880, 1745, 1727, 1611, 1433, 1283, 1184, 1113 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 3.89 (s, 3H), 3.49 (d, *J* = 4.9 Hz, 1H), 2.89 (br, 1H), 2.78 (d, *J* = 4.8 Hz, 1H), 1.96 – 1.86 (m, 2H), 1.75 – 1.68 (m, 1H), 1.55 (tdd, *J* = 11.2, 4.5, 1.8 Hz, 2H), 1.45 – 1.31 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.95, 167.02, 141.94, 129.84, 128.76, 128.53, 58.53, 52.22, 51.14, 41.93, 36.97, 24.42, 22.03. HRMS: calcd. 267.09920 $[M+Na]^+$ Found: 267.09940.

5.6b-minor: Colorless oil. R_f = 0.25 (Hex/EA = 5:1). IR (KBr) 2955, 2880, 1749, 1723, 1435, 1283, 1188, 1113 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 3.90 (s, 3H), 3.15 (d, *J* = 3.5 Hz, 1H), 2.92 (br, 1H), 2.68 (d, *J* = 3.3 Hz, 1H), 2.06 – 1.88 (m, 3H), 1.74 – 1.60 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.08, 167.05, 142.39, 129.87, 128.57, 127.85, 58.55, 52.22, 49.62, 41.29, 35.14, 28.17, 24.69. HRMS: calcd. 267.09920 $[M+Na]^+$ Found: 267.09940.



5.6c

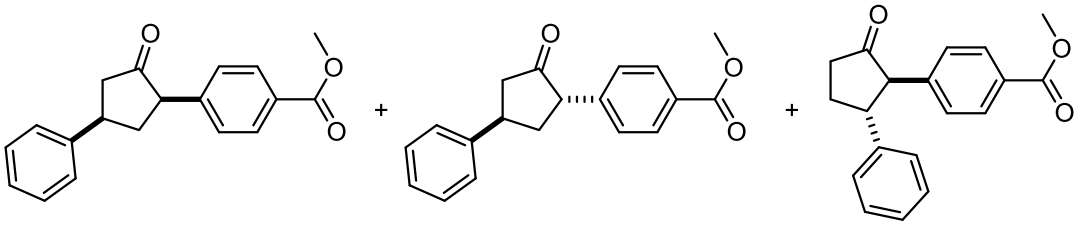
5.6c: The reaction was conducted on a 0.2 mmol scale with 10 mol% $Pd(OAc)_2$, 20 mol% P(*o*-tol)$_3$, 50 mol% of pyrrolidine and without 1,1,3,3-tetramethylbutylamine (amine **4**) for 24 h. The crude material was determined to be a 10:1 mixture of diastereomers by ^{1}H NMR analysis and was isolated as an inseparable 9:1 mixture of diastereomers as determined by ^{1}H NMR analysis. Colorless wax (49.3 mg, 60% yield). Recovered starting material: 6.1 mg (11%). R_f = 0.7 (Hex/EA = 2:3). IR (KBr) 2955, 2867, 1743, 1721, 1437, 1344, 1283, 1160, 1115 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) major diastereomer δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.37 – 7.33 (m, 2H), 7.04 (d, *J* = 8.2 Hz, 2H), 3.89 (s, 3H), 3.58 (dd, *J* = 10.3, 8.7 Hz, 1H), 3.39 (dd, *J* = 10.5, 1.9 Hz, 1H), 3.33 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.15 (dd, *J* = 10.3, 6.8 Hz, 1H), 3.06 (d, *J* = 9.7 Hz, 1H), 3.00 – 2.89 (m, 2H), 2.60 (dd, *J* = 19.3, 8.6 Hz, 1H), 2.46 – 2.38 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.16, 166.78, 144.23, 141.88, 133.01, 130.27, 130.05, 129.50, 128.61, 127.79, 58.57, 53.47, 52.40, 52.35, 47.82, 42.33, 36.62, 21.74. HRMS: calcd. 436.11890 $[M+Na]^+$ Found: 436.11920.



major minor

5.6d

5.6d: The reaction was conducted on a 0.3 mmol scale with 10 mol% $Pd(OAc)_2$, 20 mol% P(*o*-tol)$_3$, 50 mol% of pyrrolidine and without 1,1,3,3-tetramethylbutylamine (amine **4**) for 24 h. The crude material was determined to be a 3.7:1 mixture of diastereomers by ^{1}H NMR analysis and was isolated as an inseparable 3:1 mixture of diastereomers as determined by ^{1}H NMR analysis. Colorless oil (36.4 mg, 52% yield). R_f = 0.5 (Hex/EA = 5:1). IR (KBr) 2963, 2932, 2874, 1741, 1722, 1435, 1283, 1184, 1111 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) (major : minor = 0.7 : 0.3) δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.21 (m, 2H), 3.88 (s, 3H), 3.50 (t, *J* = 8.6 Hz, 0.3H), 3.33 (dd, *J* = 12.2, 8.3 Hz, 0.7H), 2.54 – 2.17 (m, 3.3H), 2.07 – 1.95 (m, 0.7H), 1.77 (dt, *J* = 12.0, 6.1 Hz, 0.3H), 1.54 (qd, *J* = 12.0, 6.0 Hz, 0.7H), 1.18 (d, *J* = 6.8 Hz, 2.1H), 1.14 (d, *J* = 7.4 Hz, 0.9H). ^{13}C NMR (101 MHz, $CDCl_3$) major isomer δ 218.50, 167.06, 144.27, 129.95, 128.78, 128.21, 54.97, 52.20, 45.07, 29.95, 29.72, 14.67 minor isomer δ 219.30, 167.03, 144.29, 129.99, 128.75, 128.20, 54.50, 52.20, 42.74, 29.32, 28.85, 15.54. HRMS: calcd. 255.09920 $[M+Na]^+$ Found: 255.09910.



5.6ea-major **5.6ea-minor** **5.6eb**

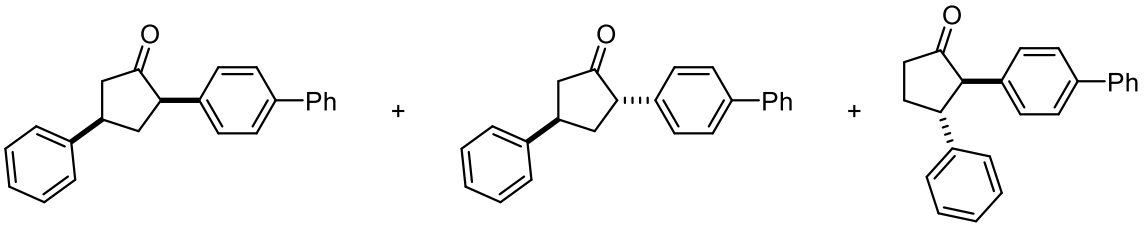
The reaction was carried out on a 0.3 mmol scale. The crude material was determined to be a 5.8:1.1:1 mixture of the above isomers by ^{1}H NMR analysis and the isolated ratio of

the isomers was 5.5:1:1. Yield: 72.1 mg (83%). **6.6eb** and fractions of **6ea-major** can be obtained as their pure form.

5.6ea-major: White solid. m.p. = 84 – 86 °C. R_f = 0.33 (Hex/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.01 (m, 2H), 7.41 – 7.27 (m, 7H), 3.91 (s, 3H), 3.64 (dd, *J* = 13.0, 7.8 Hz, 1H), 3.51 (tdd, *J* = 12.4, 7.4, 5.8 Hz, 1H), 2.99 – 2.84 (m, 2H), 2.52 (dd, *J* = 18.5, 12.3 Hz, 1H), 2.28 (q, *J* = 12.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.88, 166.97, 142.98, 142.24, 130.01, 129.07, 128.93, 128.35, 127.13, 126.87, 56.72, 52.23, 46.06, 39.95, 39.32. IR (KBr) 3028, 2955, 1741, 1725, 1433, 1281, 1109 cm^{-1}. HRMS: calcd. 317.11480 $[M+Na]^+$ Found: 317.11480

5.6ea-minor: Isolated as an inseparable mixture with **6ea-major**. R_f = 0.33 (Hex/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.42 – 7.26 (m, 7H), 3.91 (s, 3H), 3.80 – 3.65 (m, 2H), 2.82 (dd, *J* = 18.7, 8.1 Hz, 1H), 2.77 – 2.65 (m, 2H), 2.64 – 2.55 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.52, 166.96, 143.53, 143.19, 130.11, 128.98, 128.96, 128.00, 127.00, 126.88, 52.59, 52.26, 45.20, 38.92, 38.66.

5.6eb: Colorless wax. R_f = 0.2 (Hex/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.87 (m, 2H), 7.29 – 7.24 (m, 2H), 7.22 – 7.17 (m, 1H), 7.17 – 7.12 (m, 2H), 7.12 – 7.07 (m, 2H), 3.86 (s, 3H), 3.56 – 3.46 (m, 2H), 2.77 – 2.67 (m, 1H), 2.56 – 2.44 (m, 2H), 2.21 – 2.07 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.70, 167.00, 142.44, 141.17, 129.96, 129.06, 128.90, 128.87, 127.25, 127.12, 63.06, 52.21, 50.69, 38.94, 29.60. IR (KBr) 3032, 2961, 2886, 1717, 1611, 1437, 1289, 1190, 1111 cm^{-1}. HRMS: calcd. 317.11480 $[M+Na]^+$ Found: 317.11490.



5.6fa-major **5.6fa-minor** **5.6fb**

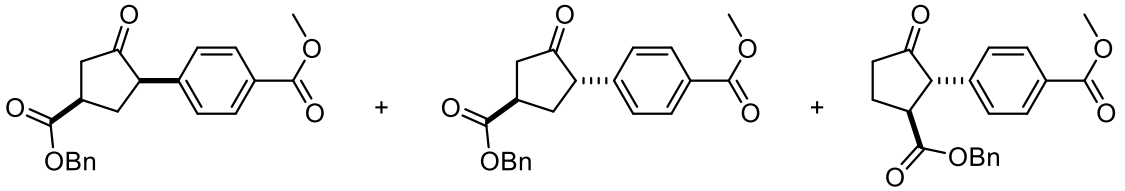
The reaction was carried out on a 0.3 mmol scale. The crude material was determined to be a 5.7:1.1:1 mixture of the above isomers by ^{1}H NMR analysis and the isolated ratio of the isomers was 5.5:1:1. Yield: 71.5 mg (77%). **5.6fa-major** and **5.6fb** can be obtained as their pure form.

5.6fa-major: Colorless wax. R_f = 0.4 (Hex/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.55 (m, 4H), 7.46 – 7.29 (m, 10H), 3.63 (dd, *J* = 13.2, 8.2 Hz, 1H), 3.52 (tdd, *J* = 12.5, 7.5, 5.7 Hz, 1H), 2.98 – 2.87 (m, 2H), 2.53 (dd, *J* = 18.5, 12.3 Hz, 1H), 2.31 (q, *J* = 12.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.99, 142.55, 140.96, 140.25, 136.90, 128.93, 128.89, 128.73, 127.59, 127.39, 127.24, 127.08, 126.94, 56.64, 46.20, 40.02, 39.64. IR (KBr) 3056, 3030, 2961, 1737, 1492, 1405, 1143 cm^{-1}. HRMS: calcd. 335.14060 $[M+Na]^+$ Found: 335.14070

5.6fa-minor: Isolated as an inseparable mixture with the remaining ketone starting material. Colorless wax. R_f = 0.5 (Hex/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.56 (m, 4H), 7.47 – 7.30 (m, 10H), 3.77 (p, *J* = 7.1 Hz, 1H), 3.67 (t, *J* = 8.2 Hz 1H), 2.84 (ddd, *J* = 18.6, 8.2, 1.0 Hz, 1H), 2.78 – 2.55 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.54, 143.48,

140.85, 140.07, 137.41, 128.91, 128.89, 128.33, 127.62, 127.40, 127.19, 126.92, 126.90, 52.41, 45.29, 39.03, 38.88.

5.6fb: Colorless wax. R_f = 0.3 (Hex/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.45 (m, 4H), 7.41 (dd, *J* = 8.2, 7.2 Hz, 2H), 7.35 – 7.27 (m, 3H), 7.26 – 7.21 (m, 3H), 7.13 (d, *J* = 7.9 Hz, 2H), 3.64 – 3.50 (m, 2H), 2.80 – 2.67 (m, 1H), 2.60 – 2.45 (m, 2H), 2.22 – 2.05 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.72, 141.70, 140.92, 140.03, 136.16, 129.16, 128.82, 128.81, 127.46, 127.30, 127.23, 127.16, 127.08, 62.55, 50.46, 38.92, 29.76. IR (KBr) 3058, 3030, 2967, 2932, 1745, 1490, 1405, 1129 cm^{-1}. HRMS: calcd. 335.14060 $[M+Na]^+$ Found: 335.14050



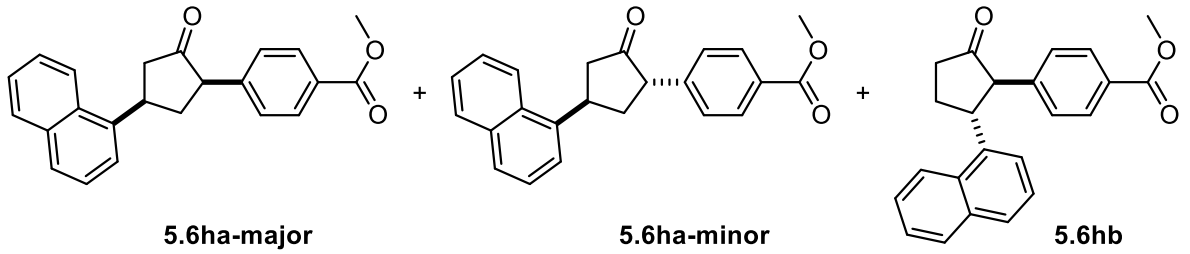
5.6ga-major **5.6ga-minor** **5.6gb**

The reaction was carried out on a 0.3 mmol scale. The crude material was determined to be a 2.1:1.5:1 mixture of the above isomers by ^{1}H NMR analysis. The isolated ratio of the isomers was 2.4:1.6:1 while the **5.6ga-major** and **5.6ga-minor** was isolated as an inseparable mixture of diastereomers (**5.6gb** can be obtained as its pure form). Yield: 59.0 mg (56%). Recovered starting material: 15.4 mg (24%).

5.6ga-major and **5.6ga-minor:** Isolated as an inseparable mixture. Colorless oil. R_f = 0.3 (Hex/EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) (major : minor = 0.7 : 0.3) δ 8.03 – 7.98 (m,

2H), 7.48 – 7.28 (m, 5H), 7.28 – 7.22 (m, 2H), 5.20 (s, 2H), 3.90 (s, 3H), 3.67 (t, *J* = 9.7 Hz, 0.3H), 3.50 (dd, *J* = 13.1, 8.1 Hz, 0.7H), 3.37 (ddd, *J* = 11.8, 7.4, 3.6 Hz, 0.3H), 3.24 (tdd, *J* = 11.5, 8.3, 6.3 Hz, 0.7H), 2.88 – 2.64 (m, 2.7H), 2.57 (dd, *J* = 19.0, 9.0 Hz, 0.3H), 2.45 (ddd, *J* = 13.5, 10.9, 7.6 Hz, 0.3H), 2.32 (q, *J* = 12.6 Hz, 0.7H). ^{13}C NMR (101 MHz, $CDCl_3$) major isomer δ 212.95, 173.43, 166.93, 142.19, 135.58, 130.08, 129.30, 128.84, 128.67, 128.42, 128.36, 67.20, 55.71, 52.28, 41.35, 39.14, 34.70 minor isomer δ 214.18, 174.42, 166.93, 142.77, 135.56, 130.11, 129.17, 128.87, 128.73, 128.46, 128.16, 67.27, 52.63, 52.28, 40.93, 38.30, 34.16. IR (KBr) 3036, 2955, 2886, 1749, 1725, 1283, 1188, 1115 cm^{-1}. HRMS: calcd. 375.12030 $[M+Na]^+$ Found: 375.12080

5.6gb: Colorless oil. R_f = 0.27 (Hex/EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.36 – 7.27 (m, 3H), 7.19 (t, *J* = 6.5 Hz, 4H), 5.11 (s, 2H), 3.91 (s, 3H), 3.77 (d, *J* = 11.7 Hz, 1H), 3.32 (td, *J* = 11.4, 6.4 Hz, 1H), 2.71 – 2.59 (m, 1H), 2.54 – 2.36 (m, 2H), 2.24 – 2.09 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$)δ 213.81, 173.13, 166.91, 141.70, 135.45, 130.14, 129.41, 128.73, 128.57, 128.25, 67.09, 58.83, 52.29, 49.26, 37.95, 24.95. IR (KBr) 3036, 2955, 2886, 1749, 1725, 1283, 1188, 1115 cm^{-1}. HRMS: calcd. 375.12030 $[M+Na]^+$ Found: 375.12070.



5.6ha-major **5.6ha-minor** **5.6hb**

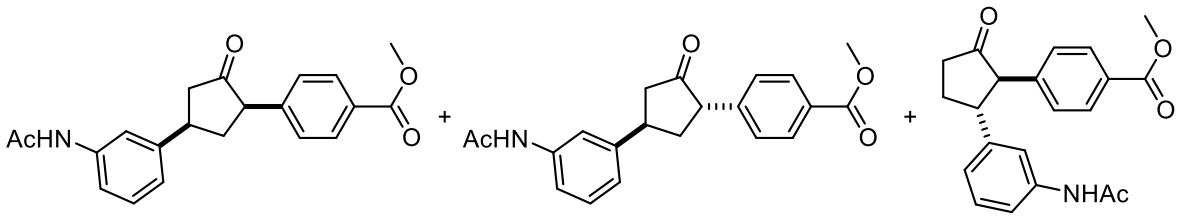
The reaction was carried out on a 0.3 mmol scale. The crude material was determined to be a 3.7:1:1.1 mixture of the above isomers by ^{1}H NMR analysis and the isolated ratio of the isomers was 3:1.1:1. Yield: 87.8 mg (85%). **5.6hb** and fractions of **5.6ha-major** can be obtained as their pure form.

5.6ha-major: Colorless wax. R_f = 0.3 (Hex/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.3 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 2H), 7.96 – 7.89 (m, 1H), 7.86 – 7.78 (m, 1H), 7.62 – 7.49 (m, 4H), 7.37 (d, *J* = 8.4 Hz, 2H), 4.27 (tdd, *J* = 12.3, 7.1, 5.5 Hz, 1H), 3.92 (s, 3H), 3.79 (dd, *J* = 12.9, 7.8 Hz, 1H), 3.10 (ddd, *J* = 18.4, 7.2, 1.4 Hz, 1H), 3.00 (dddd, *J* = 12.8, 7.7, 5.3, 2.3 Hz, 1H), 2.62 (dd, *J* = 18.5, 12.4 Hz, 1H), 2.47 (q, *J* = 12.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.69, 166.99, 142.99, 137.81, 134.11, 131.95, 130.04, 129.25, 129.11, 128.39, 127.79, 126.47, 125.96, 125.73, 123.08, 122.04, 56.64, 52.25, 46.05, 38.33, 35.97. IR (KBr) 3050, 2951, 2884, 1747, 1721, 1437, 1279, 1117 cm^{-1}. HRMS: calcd. 367.13050 $[M+Na]^+$ Found: 367.13060

5.6ha-minor: R_f = 0.3 (Hex/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 2H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.85 – 7.80 (m, *J* = 1H), 7.63 – 7.43 (m, 4H), 7.32 (d, *J* = 8.2 Hz, 2H), 4.50 (br, 1H), 3.92 (s, 3H), 3.64 (t, *J* = 9.4 Hz, 1H), 3.06 – 2.89 (m, 2H), 2.85 – 2.70 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.69, 166.90, 143.40, 138.62, 134.22, 131.40, 129.99, 129.25, 128.89, 128.13, 127.75, 126.49, 125.97, 125.33, 123.21, 122.23, 52.29, 52.17, 44.91, 37.73, 34.13.

5.6hb: Colorless oil. R_f = 0.25 (Hex/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.00 (m, 1H), 7.90 – 7.84 (m, 3H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.52 – 7.40 (m, 4H), 7.21 (d, *J* =

8.2 Hz, 2H), 4.44 (td, *J* = 12.0, 5.9 Hz, 1H), 3.95 (d, *J* = 12.4 Hz, 1H), 3.84 (s, 3H), 2.85 – 2.71 (m, 2H), 2.71 – 2.56 (m, 1H), 2.13 – 2.00 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.29, 166.93, 141.94, 137.06, 134.15, 131.88, 129.94, 129.23, 129.04, 128.79, 127.72, 126.35, 125.86, 125.67, 122.73, 122.48, 61.08, 52.17, 44.88, 38.77, 30.41. IR (KBr) 3047, 2954, 1741, 1719, 1435, 1281, 1186, 1115 cm^{-1}. HRMS: calcd. 367.13050 $[M+Na]^+$ Found: 367.13070.



5.6ia-major **5.6ia-minor** **5.6ib**

The reaction was conducted on a 0.3 mmol scale. The crude material was determined to be a 3.1:1:1 mixture of the above isomers by ^{1}H NMR analysis and the isolated ratio of the isomers was 3.4:1:1. Yield: 86.8 mg (84%). **5.6ib** and fractions of **5.6ia-major** can be obtained as their pure form.

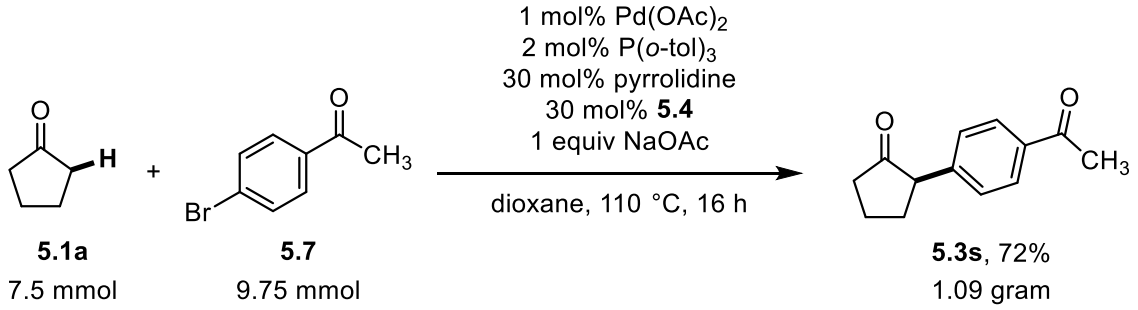
5.6ia-major: Colorless wax. R_f = 0.5 (Hex/EA = 2:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.3 Hz, 2H), 7.63 (s, 1H), 7.41 (br, 1H), 7.33 – 7.28 (m, 4H), 7.09 – 7.04 (m, 1H), 3.91 (s, 3H), 3.61 (dd, *J* = 13.0, 7.8 Hz, 1H), 3.48 (tdd, *J* = 12.4, 7.5, 5.7 Hz, 1H), 2.97 – 2.81 (m, 2H), 2.49 (dd, *J* = 18.5, 12.3 Hz, 1H), 2.25 (q, *J* = 12.5 Hz, 3H), 2.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.76, 168.57, 167.03, 143.35, 142.88, 138.53, 130.01, 129.50, 129.06, 128.37, 122.68, 118.48, 118.43, 56.70, 52.26, 45.99, 39.95, 39.15, 24.79. IR (KBr)

3301, 3151, 3042, 2955, 1719, 1672, 1551, 1437, 1285, 1115 cm^{-1}. HRMS: calcd. 374.13630 $[M+Na]^+$ Found: 374.13680

5.6ia-minor: R_f = 0.5 (Hex/EA = 2:3). ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.55 (s, 1H), 7.35 – 7.28 (m, 4H), 7.24 (br, 1H), 7.02 (dt, *J* = 6.3, 2.0 Hz, 1H), 3.91 (s, 3H), 3.75 – 3.63 (m, 2H), 2.85 – 2.54 (m, 4H), 2.19 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.40, 168.48, 166.98, 144.32, 143.47, 138.48, 130.12, 129.56, 128.99, 128.00, 122.65, 118.48, 118.36, 52.59, 52.28, 45.21, 38.94, 38.57, 24.84.

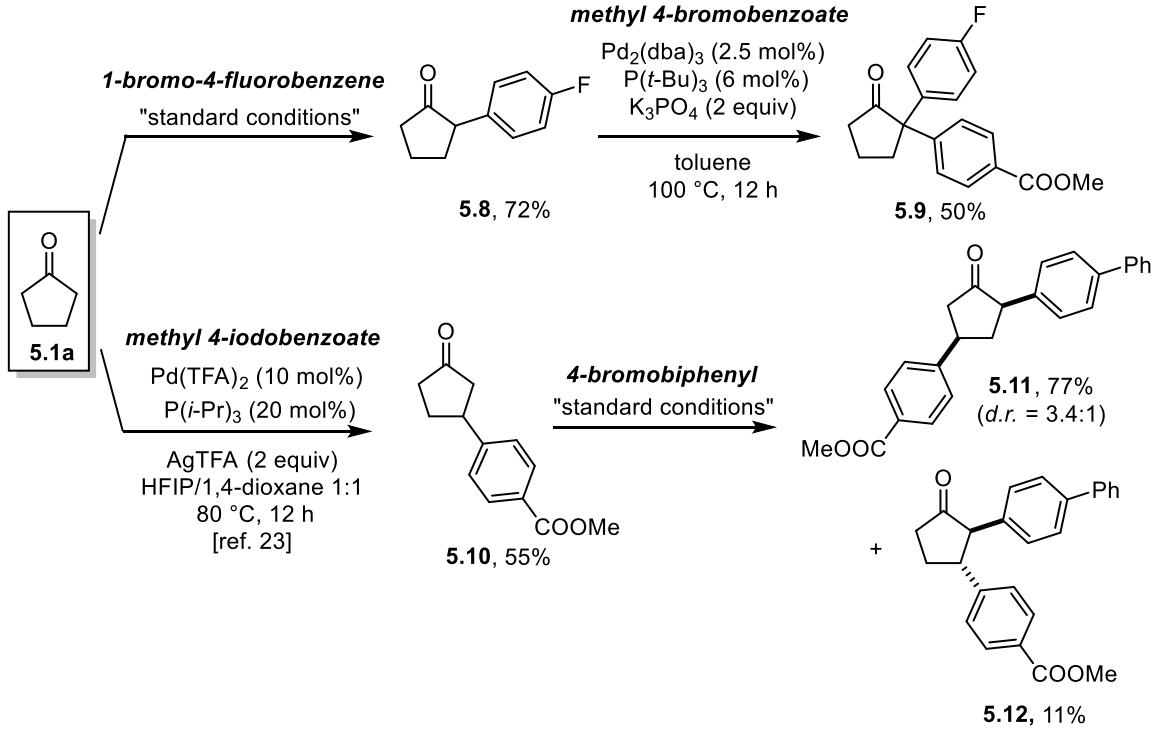
5.6ib: Colorless wax. R_f = 0.4 (Hex/EA = 2:3). ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.2 Hz, 2H), 7.52 (s, 1H), 7.25 – 7.18 (m, 2H), 7.16 – 7.08 (m, 3H), 6.90 (d, *J* = 6.5 Hz, 1H), 3.87 (s, 3H), 3.59 – 3.44 (m, 2H), 2.72 (dd, *J* = 17.1, 8.4 Hz, 1H), 2.59 – 2.43 (m, 2H), 2.19 – 2.07 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.49, 168.42, 167.04, 142.31, 138.44, 130.32, 129.97, 129.44, 129.07, 128.91, 126.27, 123.07, 118.42, 62.85, 52.22, 50.64, 38.83, 29.71, 24.85. IR (KBr) 3315, 2961, 2928, 2857, 1743, 1723, 1672, 1557, 1437, 1287, 1107 cm^{-1}. HRMS: calcd. 374.13630 $[M+Na]^+$ Found: 374.13640

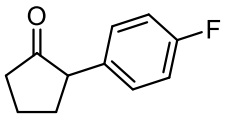
Gram-scale reaction



An 100 mL Schlenk flask was charged with $Pd(OAc)_2$ (17 mg, 0.075 mmol, 0.01 equiv), P(*o*-tol)$_3$ (46 mg, 0.15 mmol, 0.02 equiv), NaOAc (0.61 g, 7.5 mmol, 1.0 equiv) and 1-(4-bromophenyl)ethanone **7** (1.94 g, 9.75 mmol, 1.3 equiv), and then degassed with N_2. 1,4-dioxane (37.5 mL) was added in, followed by cyclopentanone (631 mg, 7.5 mmol, 1.0 equiv), pyrrolidine (193 μL, 2.25 mmol, 0.3 equiv) and 1,1,3,3-tetramethylbutylamine **5.4** (0.375 mL, 2.25 mmol, 0.3 equiv). The flask was then heated in an oil bath at 110 °C under stirring for 16 hours, before cooled to room temperature. The mixture was filtered through a small plug of silica gel, eluted with ethyl acetate. The solvent was removed in *vacuo* and flash column chromatography (Hex/EA = 10:1) of the residue gave the arylation product **5.3s** as a yellowish solid (1.09g, 72% yield).

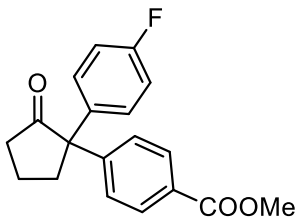
Divergent synthesis of di-arylated cyclopentanones





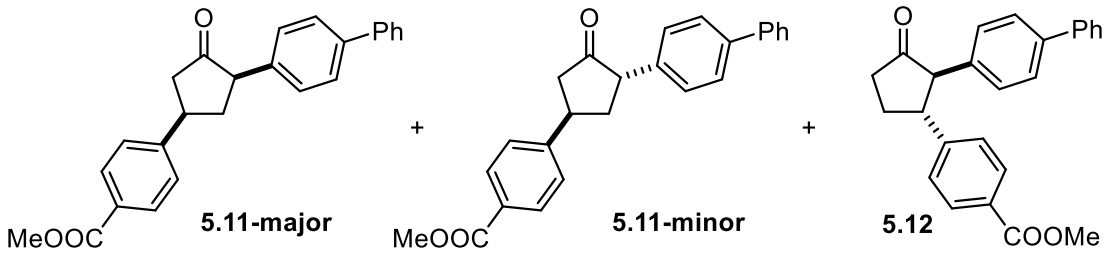
5.8

2-(4-Fluorophenyl)cyclopentanone (5.8): An 4 mL vial was charged with $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol, 0.025 equiv), P(*o*-tol)$_3$ (4.6 mg, 0.015 mmol, 0.05 equiv), NaOAc (24.6 mg, 0.3 mmol, 1.0 equiv), cyclopentanone (25.2 mg, 0.3 mmol, 1.0 equiv), 1-bromo-4-fluorobenzene (68.3 mg, 0.39 mmol, 1.3 equiv), pyrrolidine (7.7 μL, 0.09 mmol, 0.3 equiv), 1,1,3,3-tetramethylbutylamine **5.4** (15 μL, 0.09 mmol, 0.3 equiv) and 1,4-dioxane (1.5 mL). The vial was sealed with a PTFE lined cap and transferred into a glove box. After opened and purged under N_2 atmosphere for 5 min, the vial was then sealed again and heated in a pie-block at 110 °C under stirring for 12 hours before cooled to room temperature. The mixture was filtered through a small plug of silica gel and eluted with ethyl acetate. The solvent was then removed in *vacuo* and flash column chromatography (Hex/EA = 20:1) of the residue gave the titled product as yellowish oil (37.9 mg, 72% yield). R_f = 0.55 (Hex/EA = 5:1). IR (KBr) 2967, 2879, 1741, 1512, 1407, 1227, 1164, 1148 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.02 (t, *J* = 8.7 Hz, 2H), 3.30 (dd, *J* = 11.5, 8.3 Hz, 1H), 2.56 – 2.42 (m, 2H), 2.36 – 2.23 (m, 1H), 2.21 – 2.12 (m, 1H), 2.12 – 2.00 (m, 1H), 2.00 – 1.87 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ carbon signals were observed at 217.90, 217.89, 163.14, 160.70, 134.09, 134.06, 129.75, 129.67, 115.63, 115.41, 54.67, 38.36, 31.83, 20.86. ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.12 (tt, *J* = 8.7, 5.4 Hz, 1F). HRMS: calcd. 178.0794 $[M]^+$ Found: 178.0792. The spectroscopic data are in accordance with those previously reported in the literature.[27]



5.9

Methyl 4-(1-(4-fluorophenyl)-2-oxocyclopentyl)benzoate (5.9): An 4 mL vial was charged with $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol, 0.025 equiv), K_3PO_4 (85 mg, 0.4 mmol, 2.0 equiv), **5.8** (35.6 mg, 0.2 mmol, 1.0 equiv), methyl 4-bromobenzoate (86 mg, 0.4 mmol, 2.0 equiv) and toluene (0.7 mL). The vial was sealed with a PTFE lined cap and transferred into a glove box. The vial was opened and purged under N_2 atmosphere for 5 min, followed by the addition of P(*t*-Bu)$_3$ (2.4 mg, 0.012 mmol, 0.06 equiv),. The vial was then sealed again and heated in a pie-block at 100 °C under stirring for 12 hours. The mixture was cooled to room temperature, filtered through a small plug of silica gel and eluted with ethyl acetate. The solvent was removed in *vacuo* and flash column chromatography (Hex/EA = 15:1) of the residue gave the titled product as colorless oil (31 mg, 50% yield). R_f = 0.3 (Hex/EA = 5:1). IR (KBr) 2957, 2888, 1741, 1723, 1508, 1439, 1283, 1233, 1111 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.20 (dd, *J* = 8.8, 5.1 Hz, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 3.90 (s, 3H), 2.70 (hept, *J* = 6.7 Hz, 2H), 2.48 (t, *J* = 7.5 Hz, 2H), 1.96 (p, *J* = 7.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ carbon signals were observed at 217.08, 166.87, 163.13, 160.68, 147.65, 137.05, 137.02, 129.85, 129.81, 129.73, 128.86, 128.09, 115.69, 115.48, 62.06, 52.28, 38.30, 38.25, 18.98. HRMS: calcd. 335.10540 $[M+Na]^+$ Found: 335.10550.



An 4 mL vial was charged with $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol, 0.025 equiv), P(*o*-tol)$_3$ (4.6 mg, 0.015 mmol, 0.05 equiv), NaOAc (24.6 mg, 0.3 mmol, 1.0 equiv), **5.10** (65.5 mg, 0.3 mmol, 1.0 equiv) (***5.10*** *was prepared according to known literature*[4]), 4-bromobiphenyl (91 mg, 0.39 mmol, 1.3 equiv), pyrrolidine (7.7 μL, 0.09 mmol, 0.3 equiv), 1,1,3,3-tetramethylbutylamine **5.4** (15 μL, 0.09 mmol, 0.3 equiv) and 1,4-dioxane (1.5 mL). The vial was sealed with a PTFE lined cap and transferred into a glove box. After opened and purged under N_2 atmosphere for 5 min, the vial was then sealed again and heated in a pie-block at 110 °C under stirring for 12 hours before cooled to room temperature. The mixture was filtered through a small plug of silica gel and eluted with ethyl acetate. The filtrate was concentrated under *vacuo* and further purified by flash column chromatography (Hex/EA = 15:1) to give the titled products. The isolated ratio of the above isomers was 5.2:1.55:1. Yield: 97.4 mg (88%). All of the three isomers can be isolated as their pure form.

5.11-major: White solid. m.p.= 125-127 °C. R_f = 0.4 (Hex/EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.1 Hz, 2H), 7.64 – 7.55 (m, 4H), 7.46 – 7.39 (m, 4H), 7.39 – 7.29 (m, 3H), 3.93 (s, 3H), 3.64 (dd, *J* = 13.0, 7.8 Hz, 1H), 3.57 (dt, *J* = 12.0, 5.7 Hz, 1H), 3.09 – 2.80 (m, 2H), 2.53 (dd, *J* = 18.4, 12.2 Hz, 1H), 2.31 (q, *J* = 12.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.25, 166.95, 147.80, 140.89, 140.35, 136.60, 130.24, 129.03, 128.90, 128.70, 127.61, 127.43, 127.23, 127.01, 56.50, 52.29, 45.84, 40.03, 39.39. IR (KBr)

3030, 3005, 1743, 1719, 1490, 1279, 1263, 1111 cm^{-1}. HRMS: calcd. 393.14610 $[M+Na]^+$ Found: 393.14590.

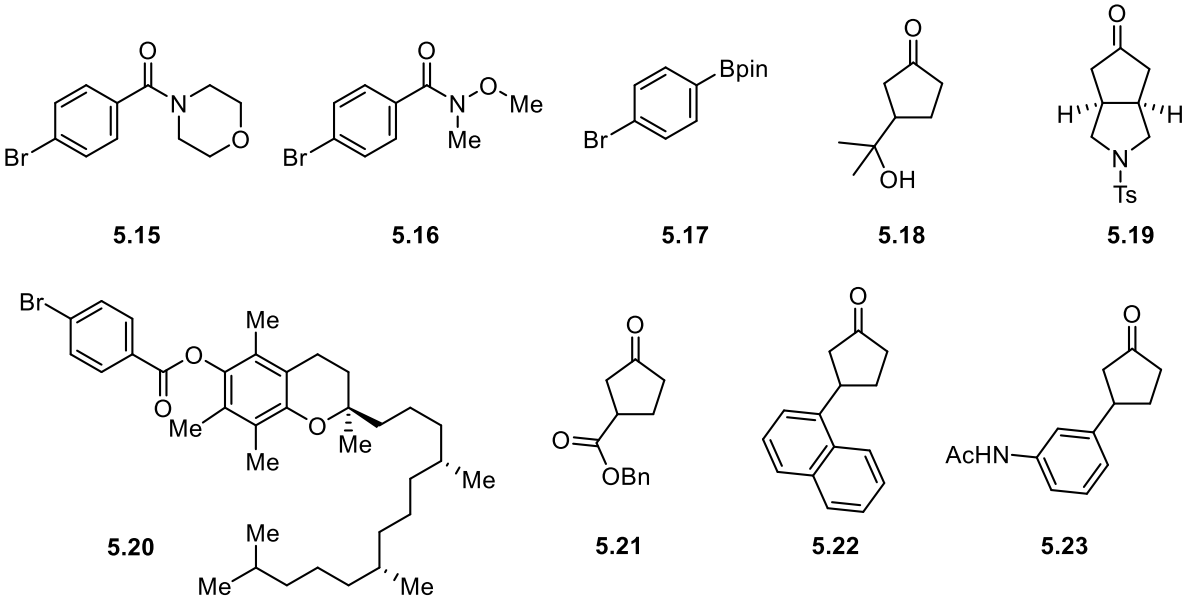
5.11-minor: White solid. m.p.= 121-123 °C. R_f = 0.5 (Hex/EA = 3:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.3 Hz, 2H), 7.57 (dd, *J* = 8.3, 1.6 Hz, 4H), 7.49 – 7.29 (m, 7H), 3.93 (s, 3H), 3.81 (p, *J* = 7.3 Hz, 1H), 3.68 (t, *J* = 7.9 Hz, 1H), 2.86 (dd, *J* = 18.6, 8.2 Hz, 1H), 2.73 (dd, *J* = 12.8, 6.3 Hz, 2H), 2.59 (dt, *J* = 13.3, 7.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.82, 166.94, 148.75, 140.79, 140.22, 137.11, 130.25, 128.92, 128.27, 127.69, 127.47, 127.20, 127.01, 52.40, 52.31, 45.02, 39.19, 38.64. IR (KBr) 3032, 2953, 1747, 1719, 1613, 1488, 1435, 1279 cm^{-1}. HRMS: calcd. 393.14610 $[M+Na]^+$ Found: 393.14640.

5.12: Colorless wax. R_f = 0.35 (Hex/EA = 3:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.57 – 7.47 (m, 4H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.31 (dd, *J* = 11.4, 7.9 Hz, 3H), 7.09 (d, *J* = 8.2 Hz, 2H), 3.89 (s, 3H), 3.61 (td, *J* = 12.1, 5.3 Hz, 1H), 3.53 (d, *J* = 12.6 Hz, 1H), 2.81 – 2.70 (m, 1H), 2.61 – 2.48 (m, 2H), 2.23 – 2.09 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.98, 166.95, 147.00, 140.81, 140.27, 135.71, 130.16, 129.11, 129.08, 128.84, 127.57, 127.37, 127.33, 127.17, 62.61, 52.24, 50.65, 38.79, 29.39. IR (KBr) 3034, 2949, 1747, 1719, 1490, 1435, 1279, 1186, 1117 cm^{-1}. HRMS: calcd. 393.14610 $[M+Na]^+$ Found: 393.14600.

Preparation of starting materials

The aryl bromides **15**,[30] **16**,[31] **17**,[32] **20**[33] and the compounds **18**,[34] **19**,[35] **21**,[36] **22**,[37] **23**[38] are prepared according to the previously reported literatures. The others are commercially available and were used as received.

Scheme 5.11 Structures of Substrates Synthesized for this Study



X-ray data for 5.6fa-major

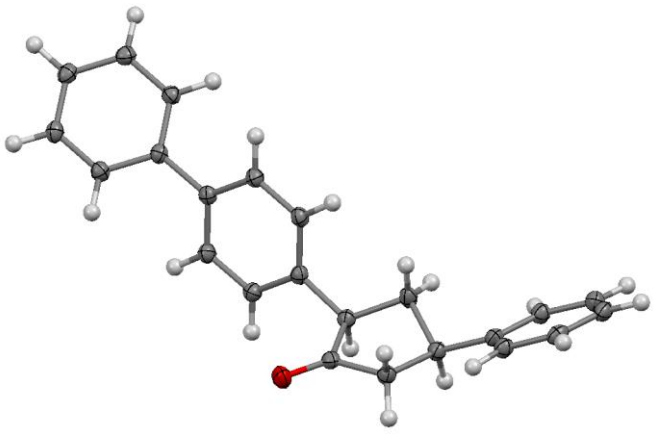


Table 5.7 Crystal Data and Structure Refinement for **5.6fa-major**

Empirical formula	C23 H20 O	
Formula weight	312.39	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 16.3044(17) Å	α = 90°.
	b = 5.8274(5) Å	β = 108.937(5)°.
	c = 17.635(3) Å	γ = 90°.
Volume	1584.9(3) $Å^3$	
Z	4	
Density (calculated)	1.309 Mg/m^3	
Absorption coefficient	0.078 mm^{-1}	
F(000)	664	
Crystal size	0.690 x 0.260 x 0.150 mm^3	
Theta range for data collection	1.479 to 32.007°.	
Index ranges	-23<=h<=23, -7<=k<=8, -24<=l<=26	
Reflections collected	26720	
Independent reflections	5247 [R(int) = 0.0541]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.9012	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5247 / 0 / 297	
Goodness-of-fit on F^2	1.047	
Final R indices [I>2sigma(I)]	R1 = 0.0472, wR2 = 0.1235	
R indices (all data)	R1 = 0.0573, wR2 = 0.1303	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.311 and -0.250 $e.Å^{-3}$	

5.5 ^{1}H-NMR and ^{13}C-NMR spectra

Figure 5.3 ^{1}H-NMR Spectrum of **5.3a**

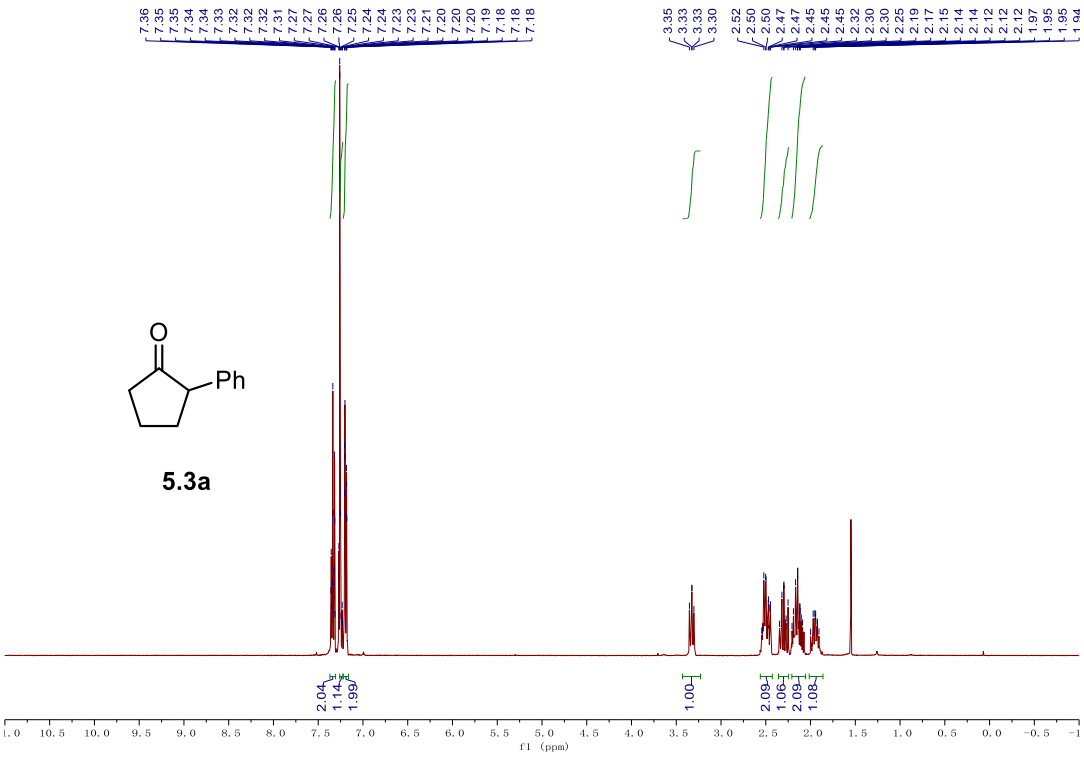


Figure 5.4 ^{13}C-NMR Spectrum of **5.3a**

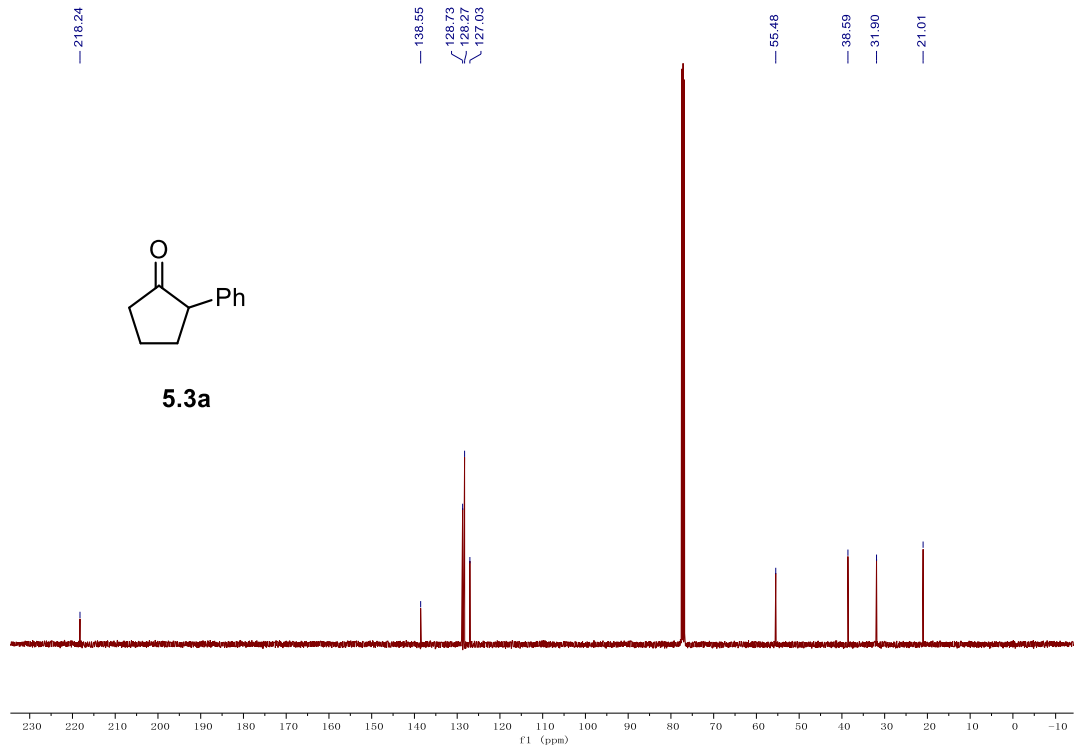


Figure 5.5 ^{1}H-NMR Spectrum of **5.3b**

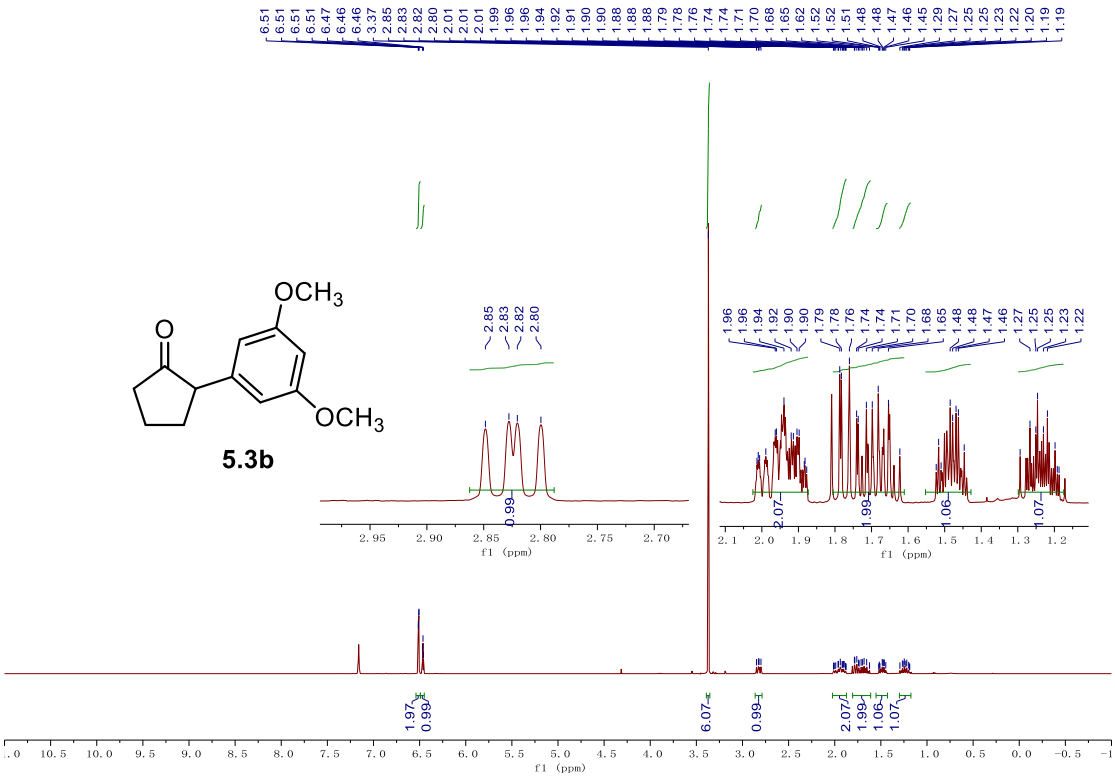


Figure 5.6 ^{13}C-NMR Spectrum of **5.3b**

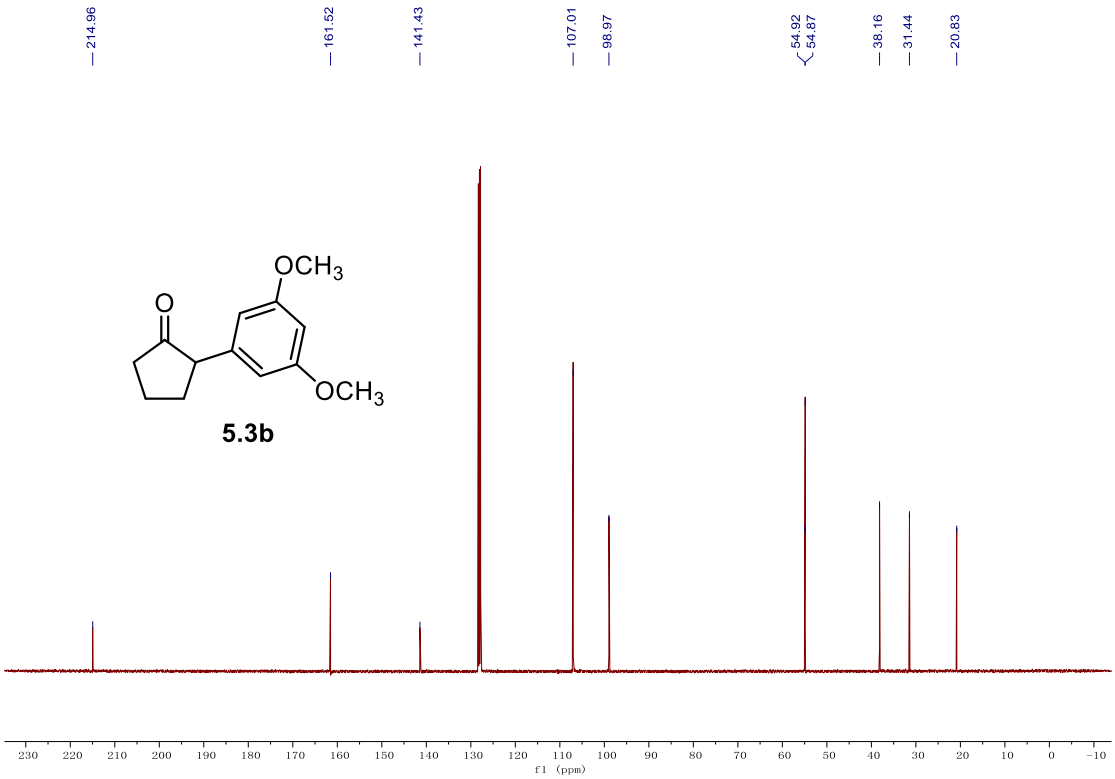


Figure 5.7 ^{1}H-NMR Spectrum of **5.3c**

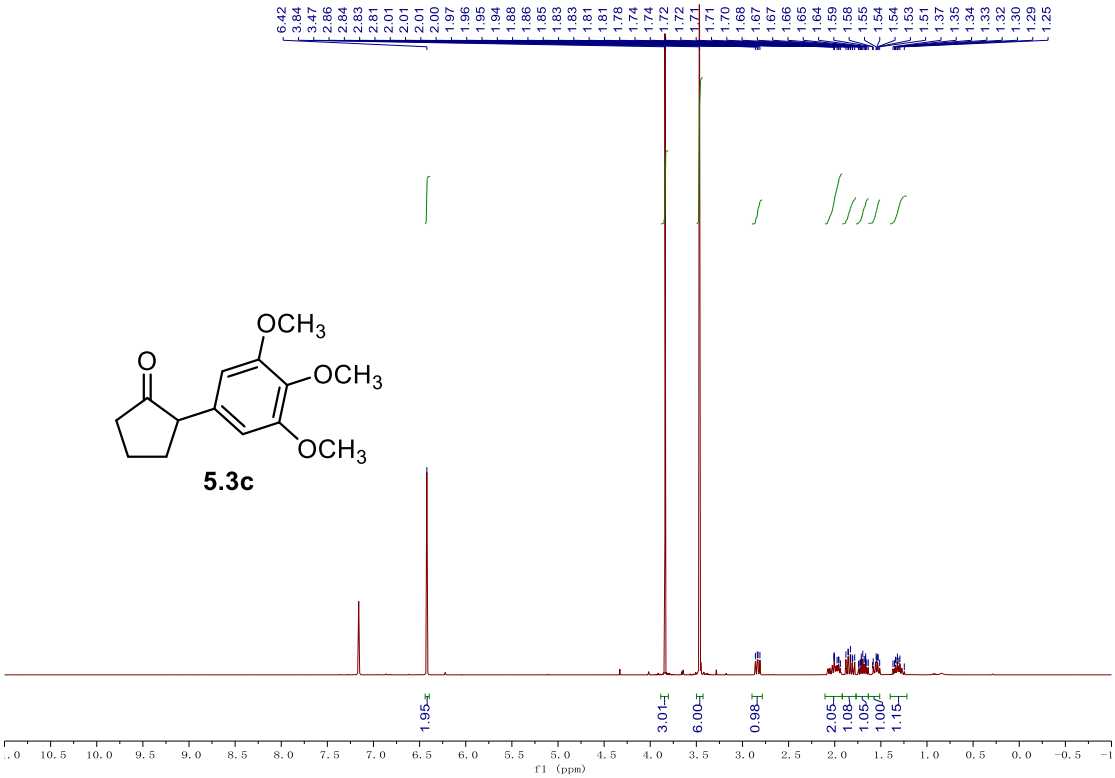


Figure 5.8 ^{13}C-NMR Spectrum of **5.3c**

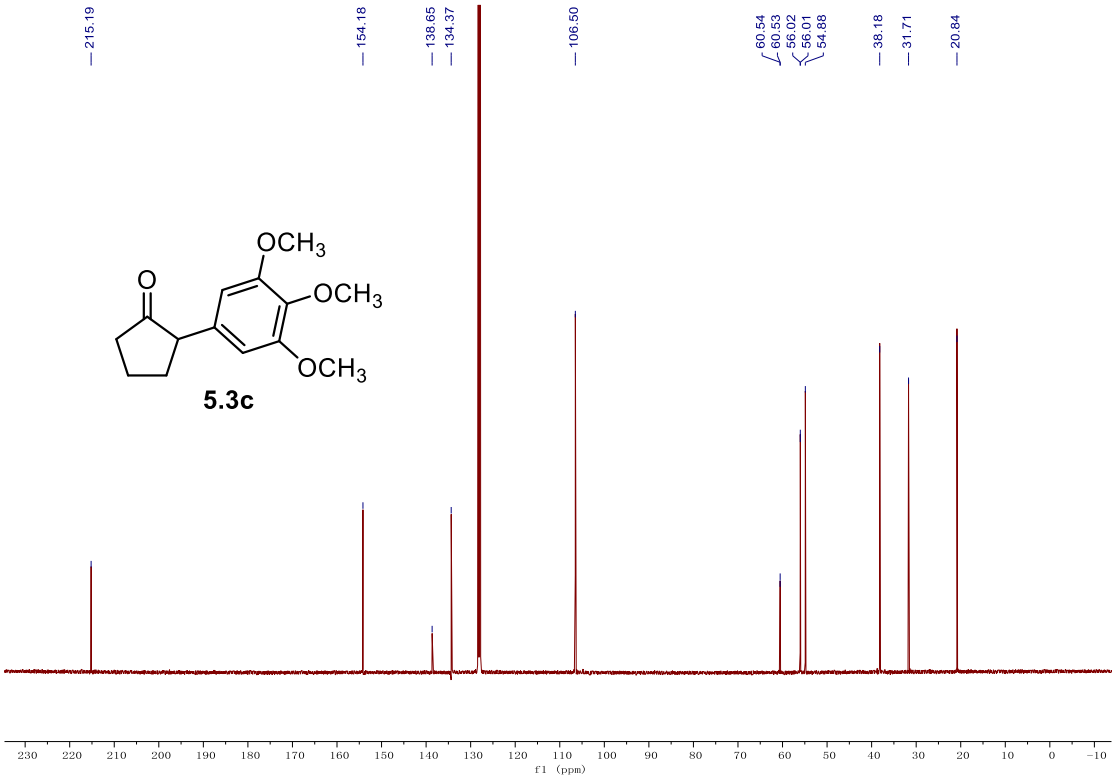


Figure 5.9 ^{1}H-NMR Spectrum of **5.3d**

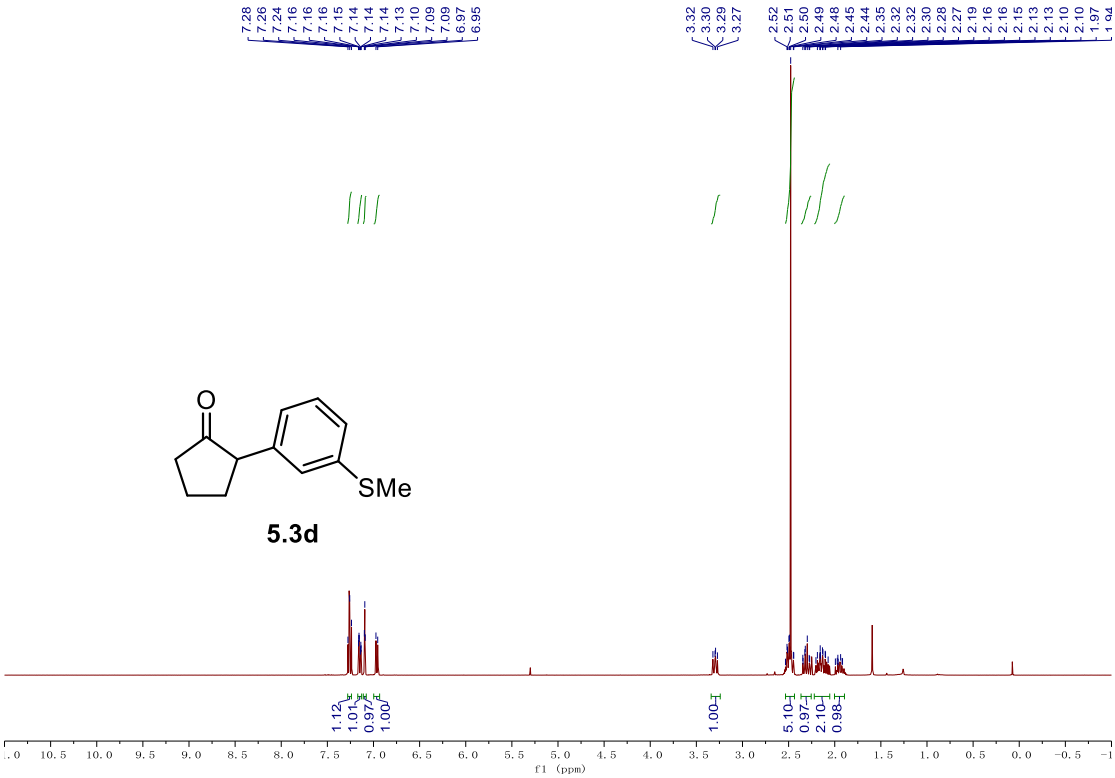


Figure 5.10 ^{13}C-NMR Spectrum of **5.3d**

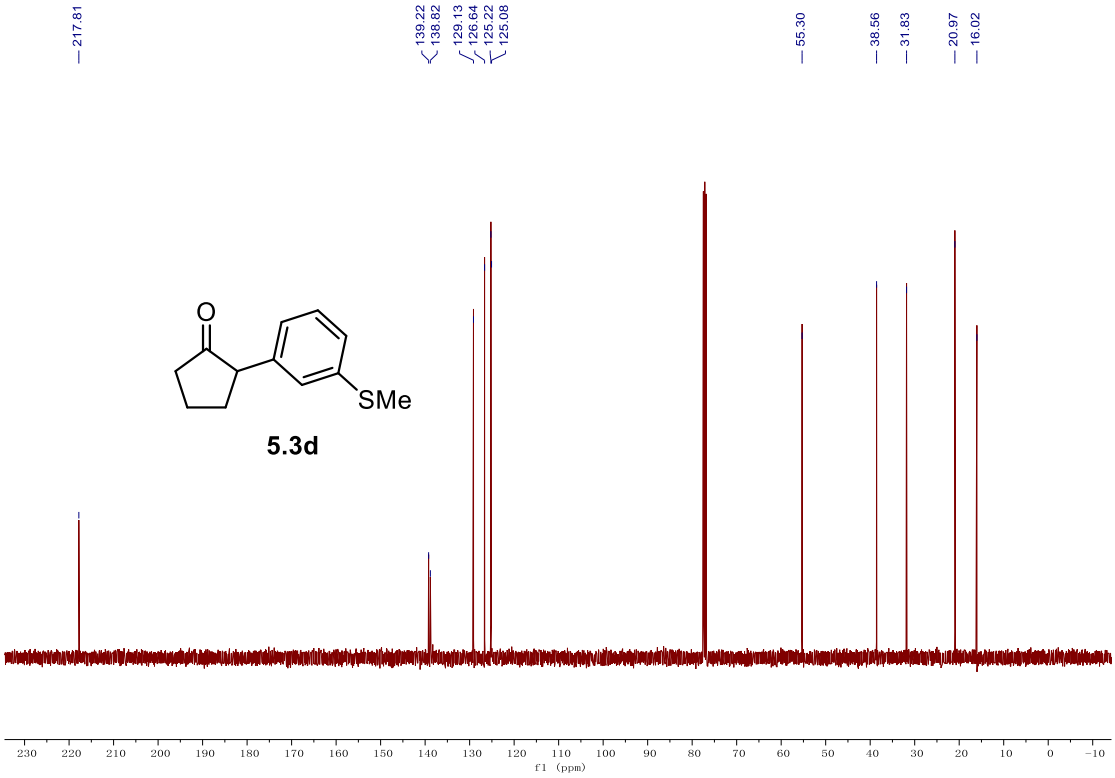


Figure 5.11 ^{1}H-NMR Spectrum of **5.3e**

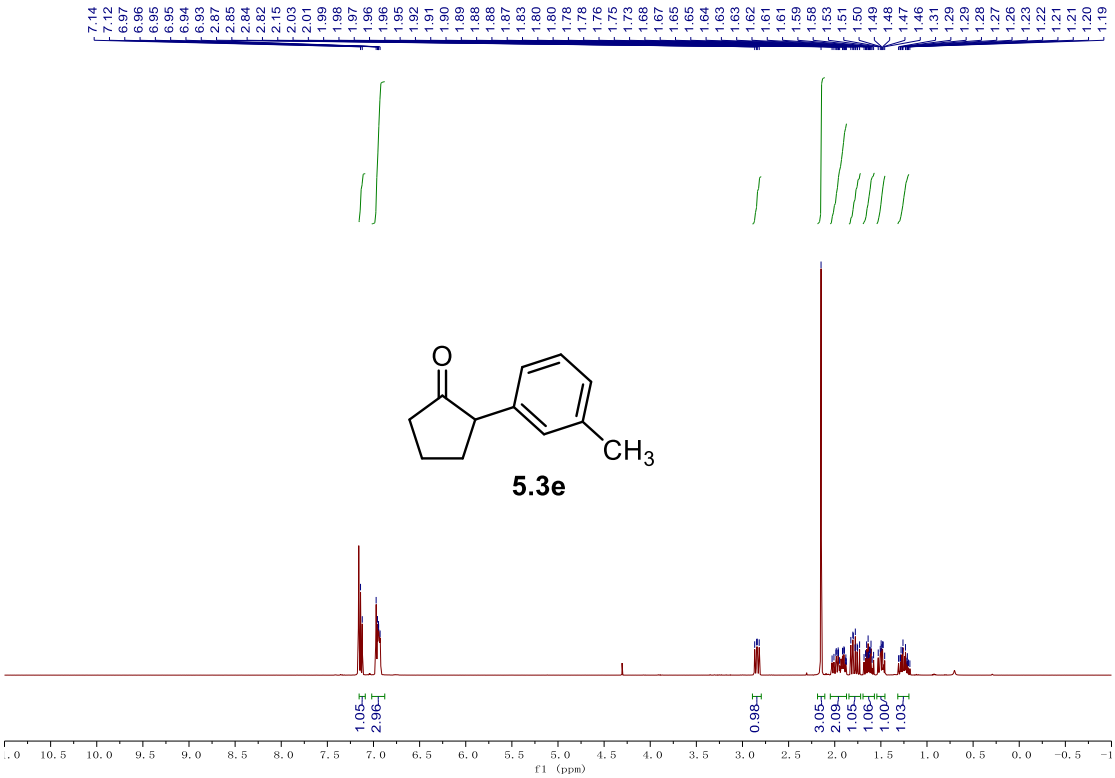


Figure 5.12 ^{13}C-NMR Spectrum of **5.3e**

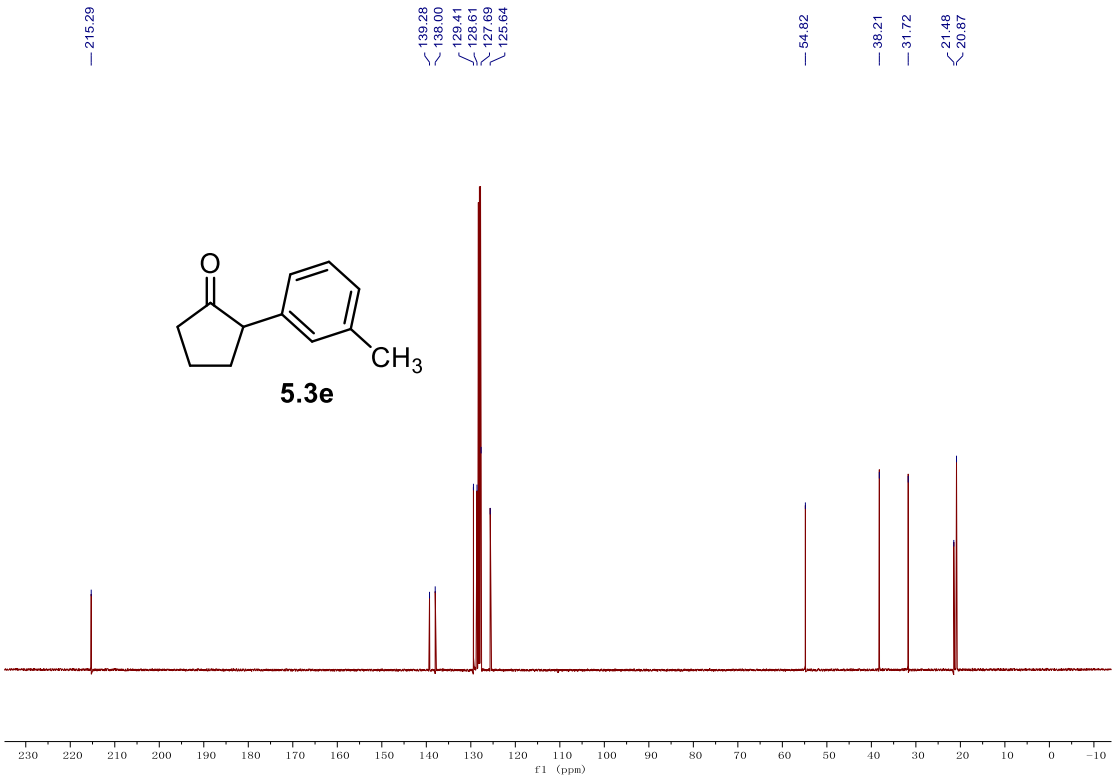


Figure 5.13 ^{1}H-NMR Spectrum of **5.3f**

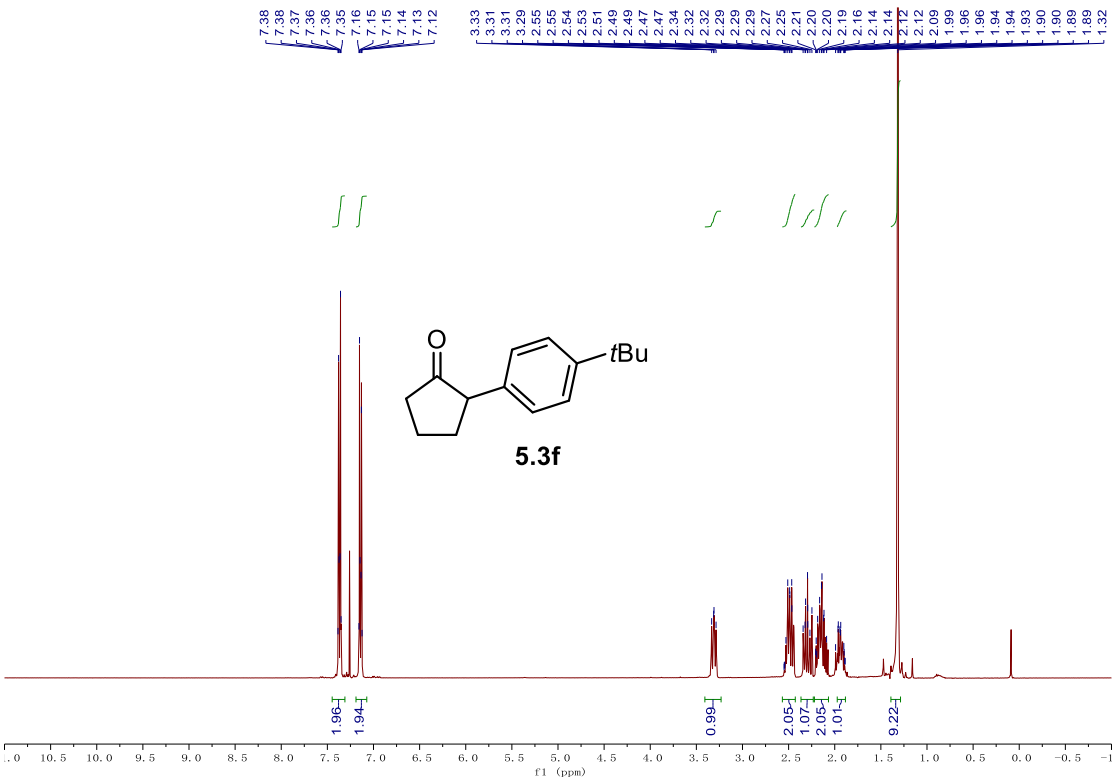


Figure 5.14 ^{13}C-NMR Spectrum of **5.3f**

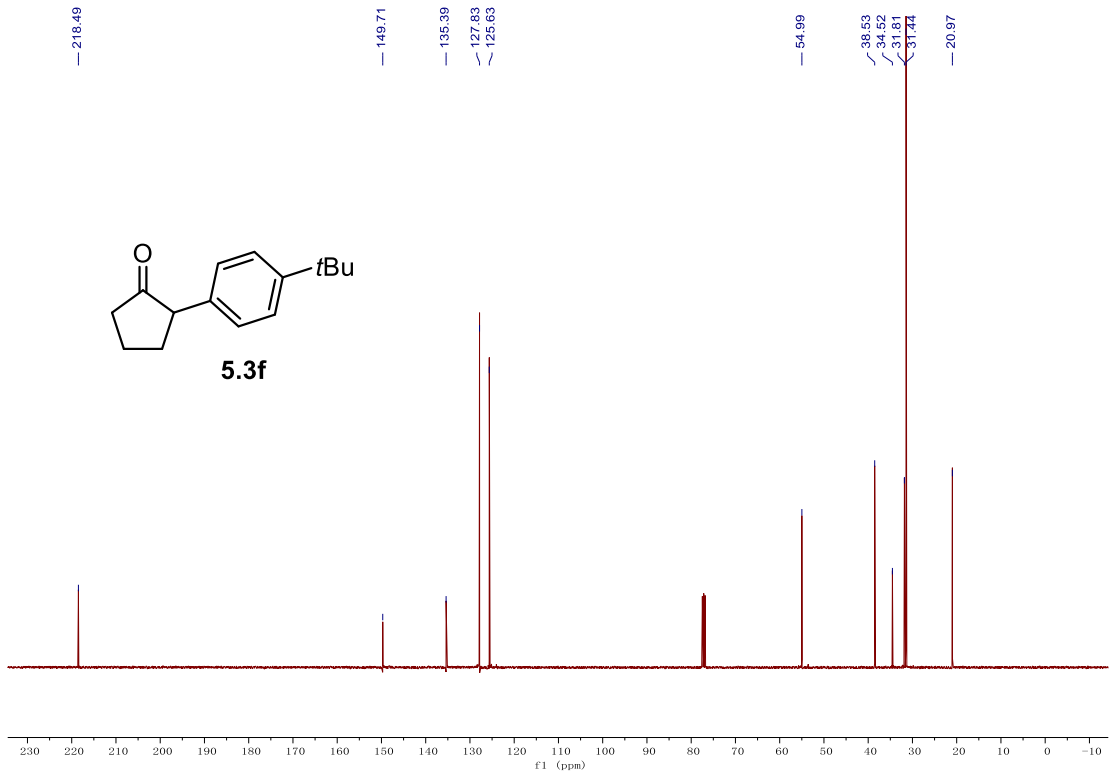


Figure 5.15 ^{1}H-NMR Spectrum of **5.3g**

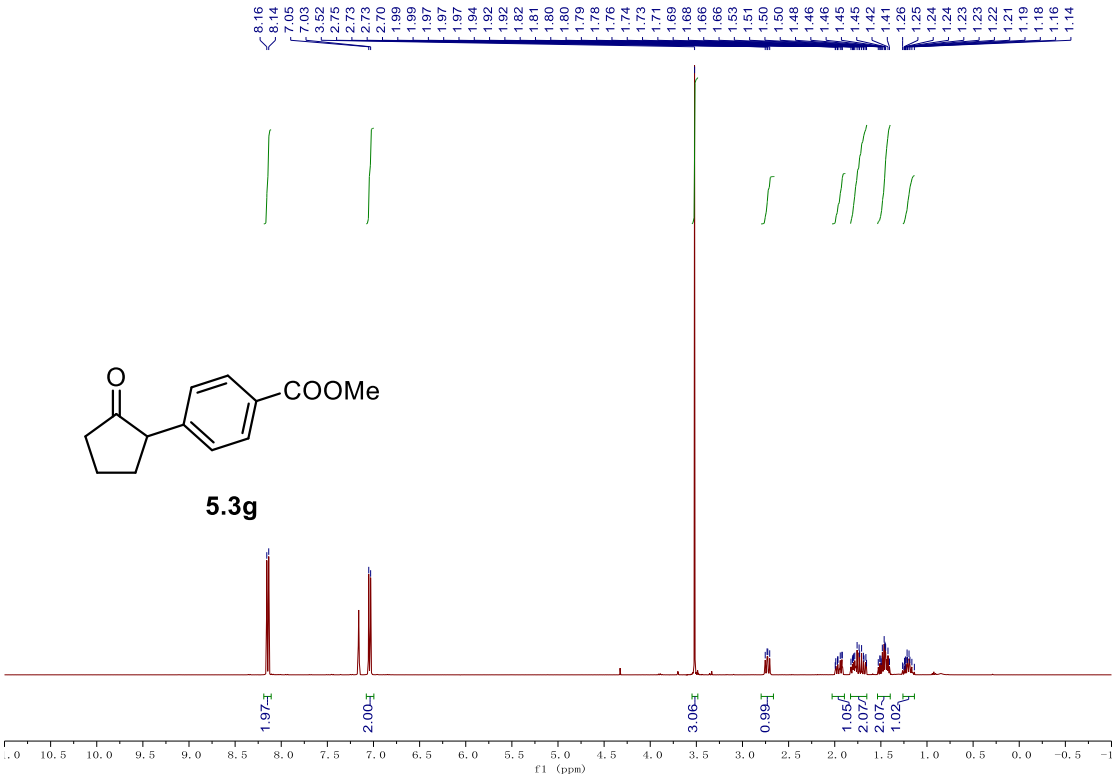


Figure 5.16 ^{13}C-NMR Spectrum of **5.3g**

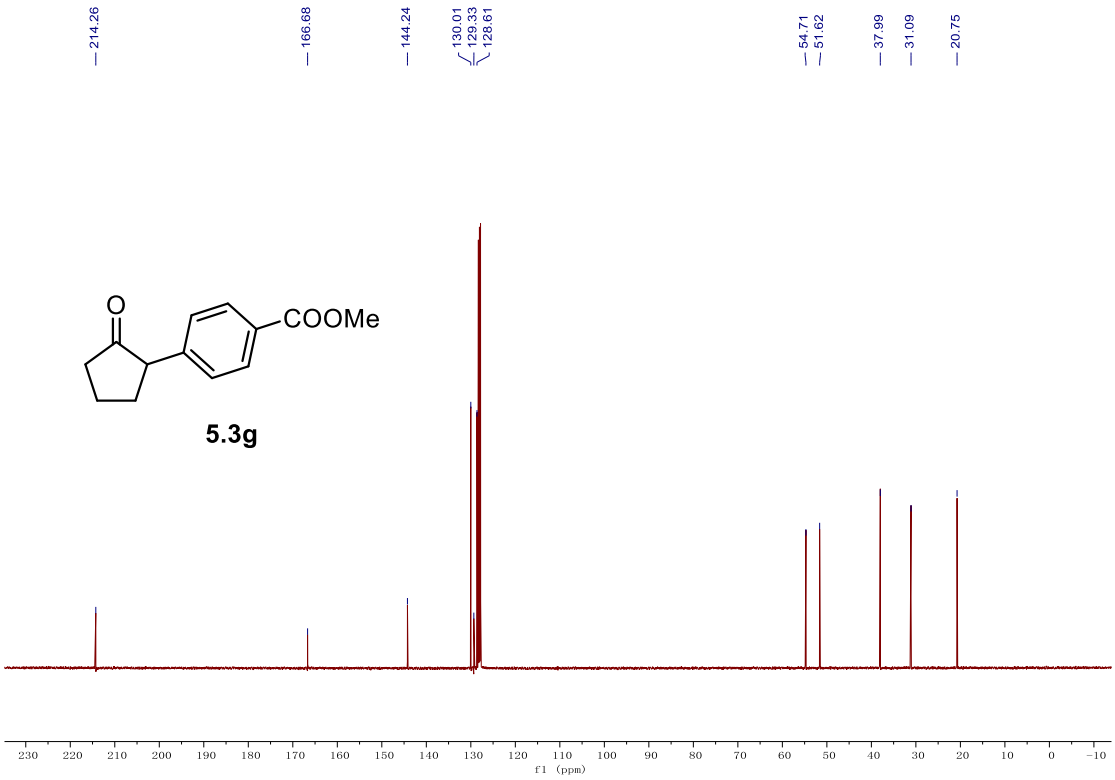


Figure 5.17 ^{1}H-NMR Spectrum of **5.3h**

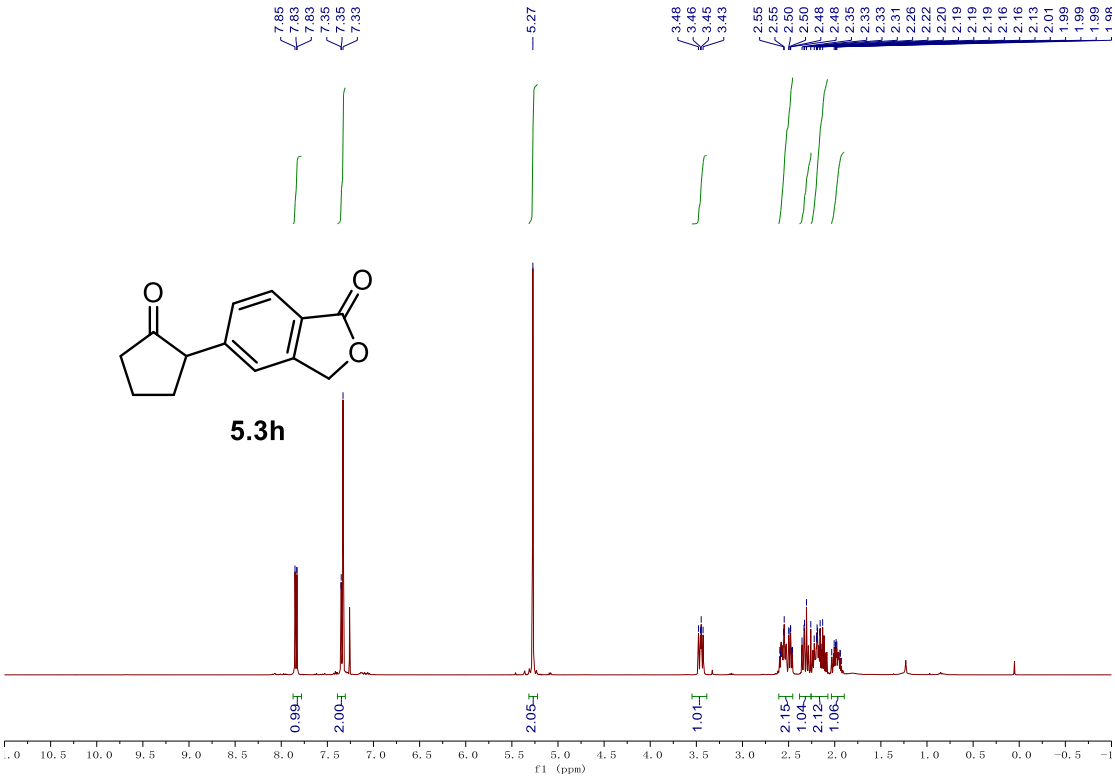


Figure 5.18 ^{13}C-NMR Spectrum of **5.3h**

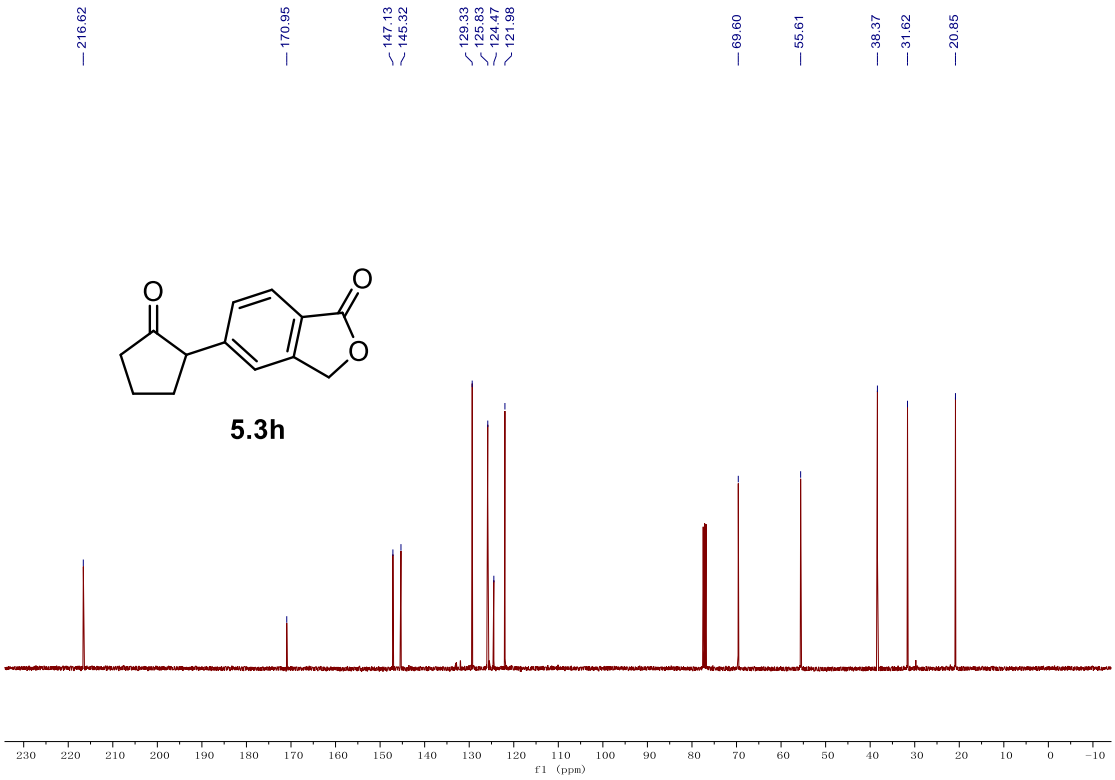


Figure 5.19 ^{1}H-NMR Spectrum of **5.3i**

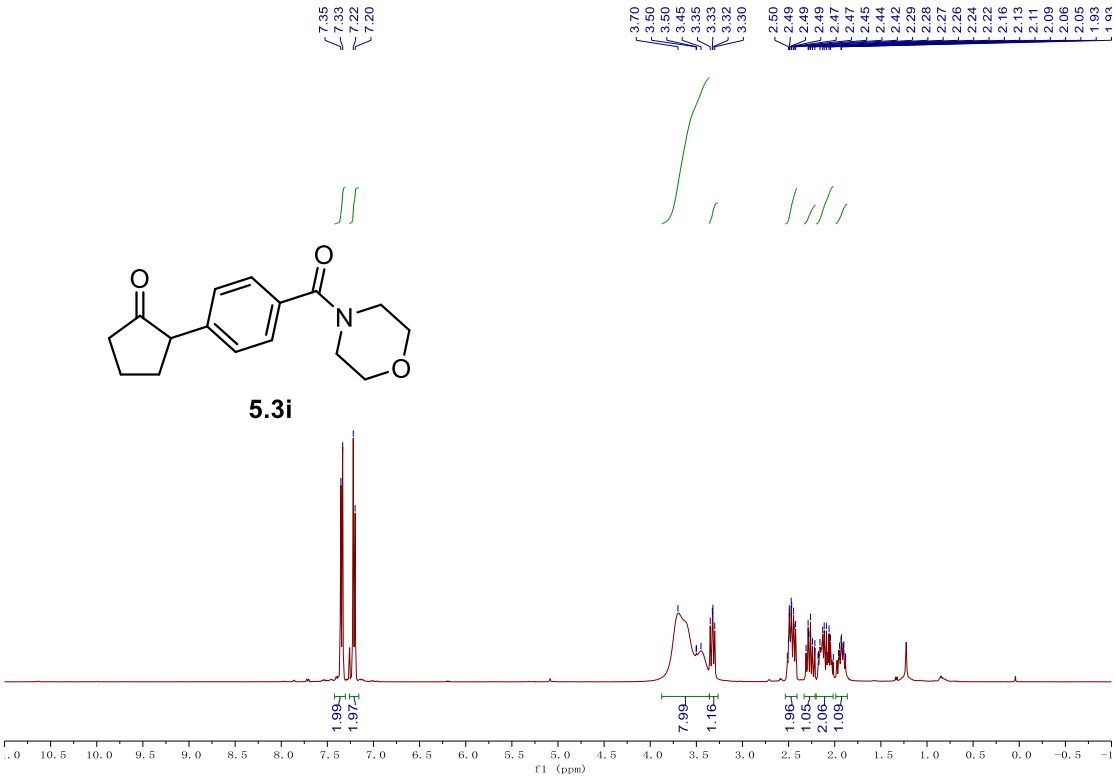


Figure 5.20 ^{13}C-NMR Spectrum of **5.3i**

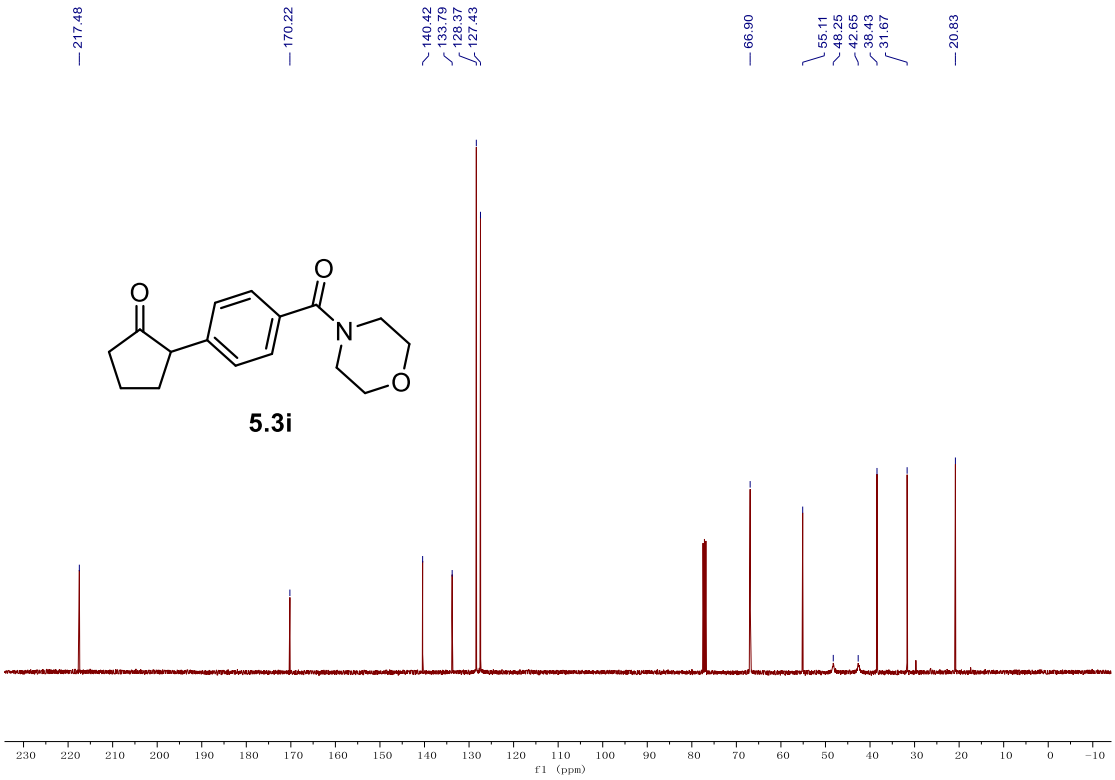


Figure 5.21 ^{1}H-NMR Spectrum of **5.3j**

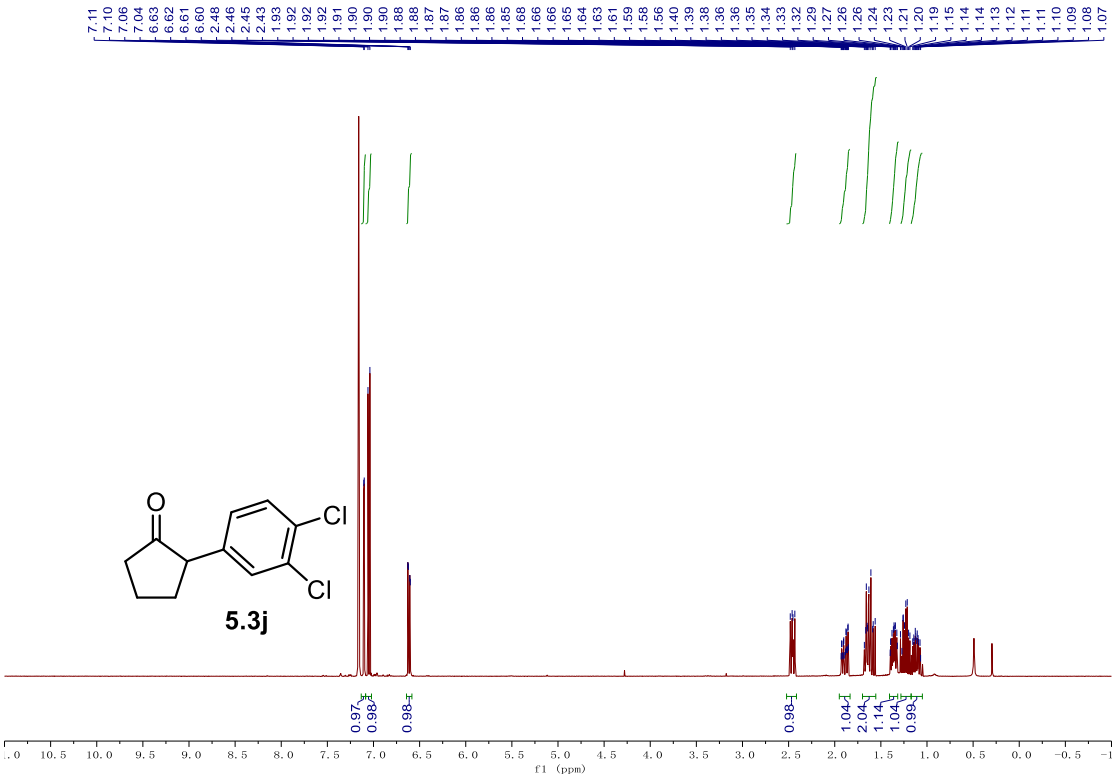


Figure 5.22 ^{13}C-NMR Spectrum of **5.3j**

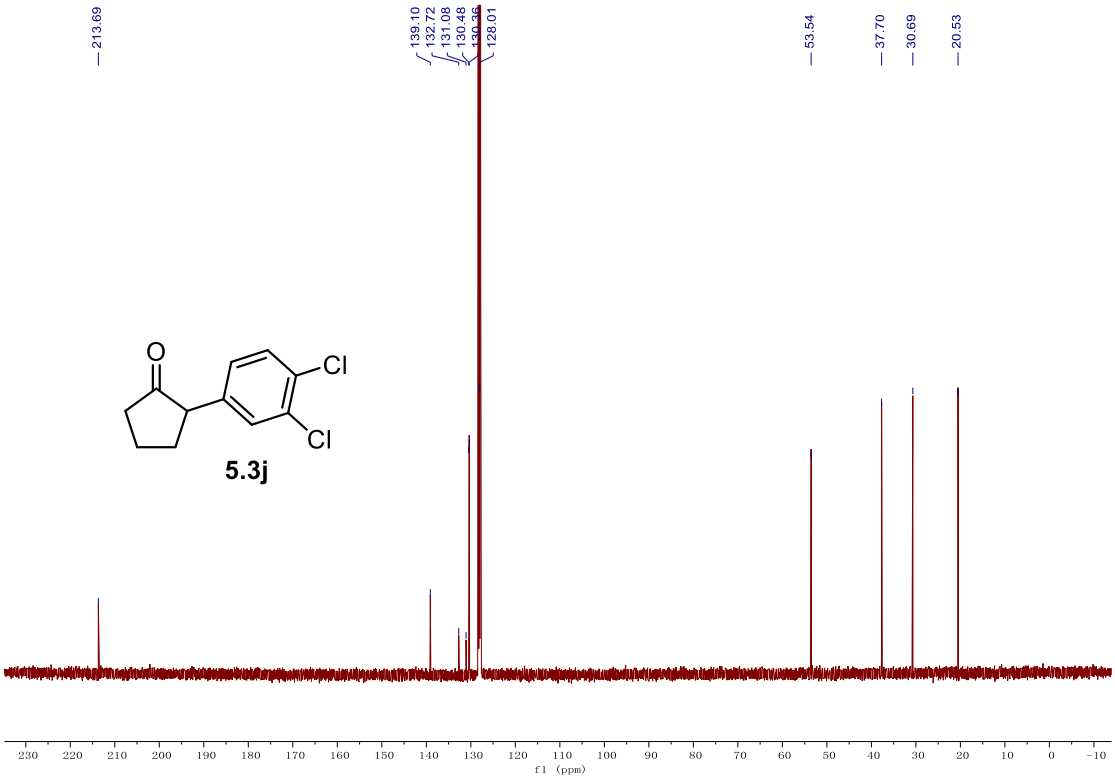


Figure 5.23 ^{1}H-NMR Spectrum of **5.3k**

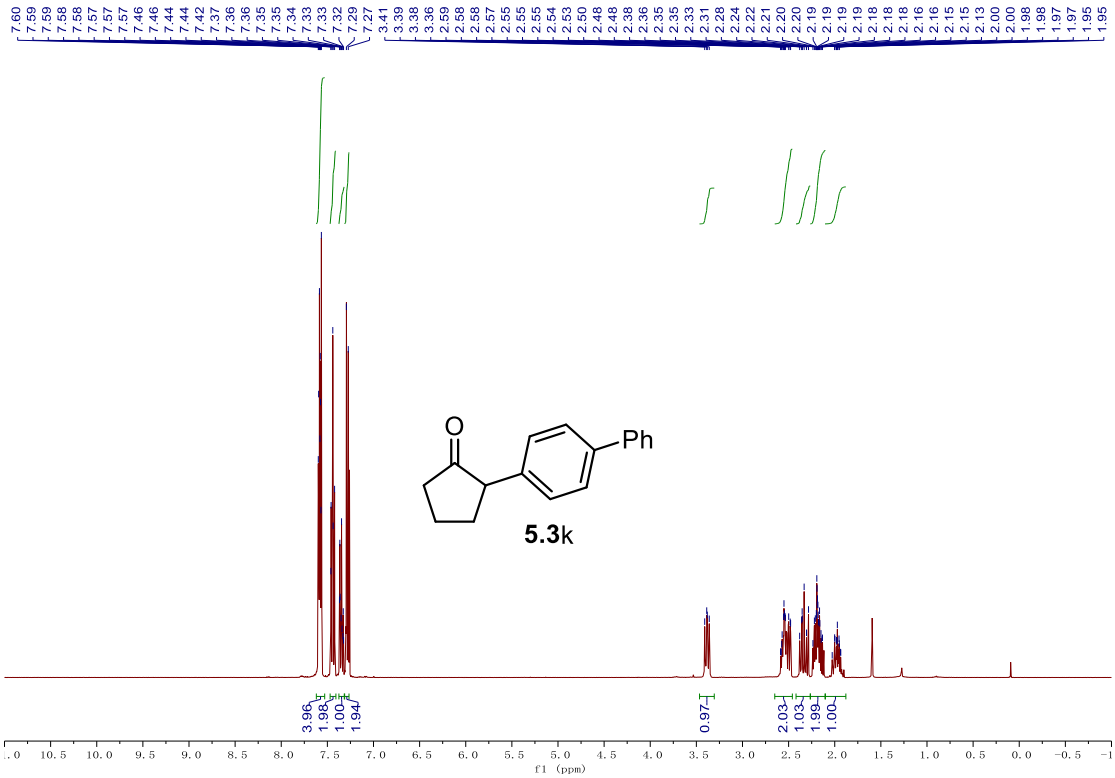


Figure 5.24 ^{13}C-NMR Spectrum of **5.3k**

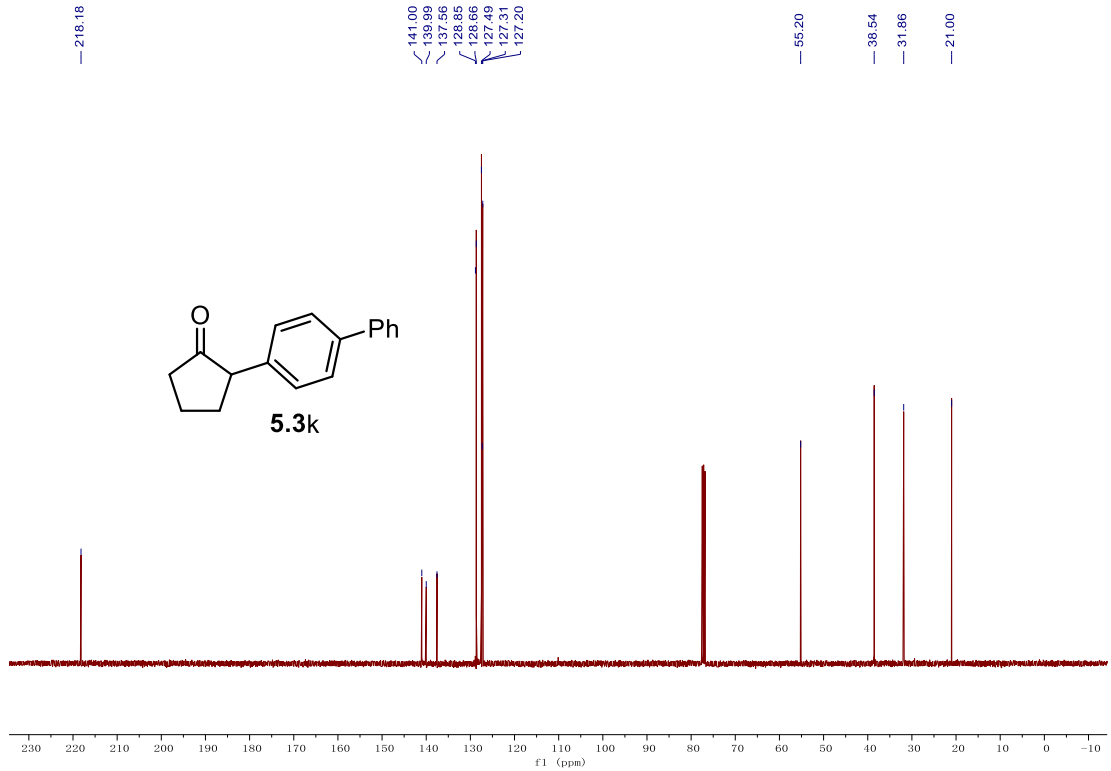


Figure 5.25 ^{1}H-NMR Spectrum of **5.3l**

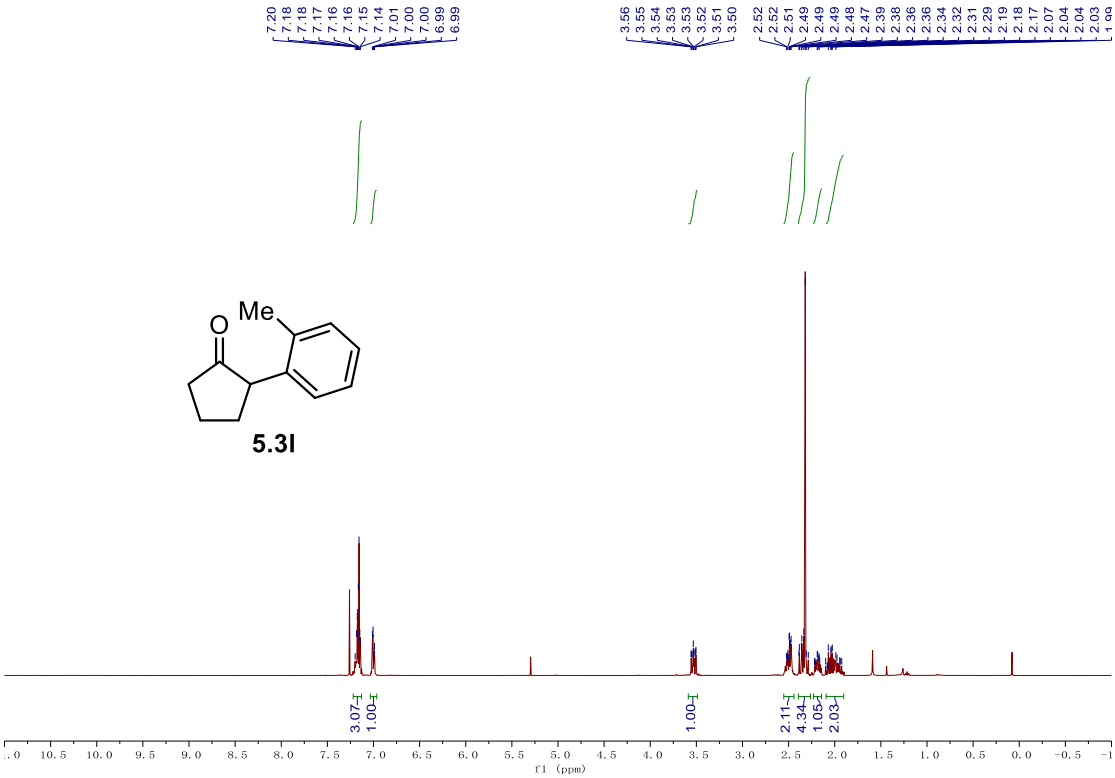


Figure 5.26 ^{13}C-NMR Spectrum of **5.3l**

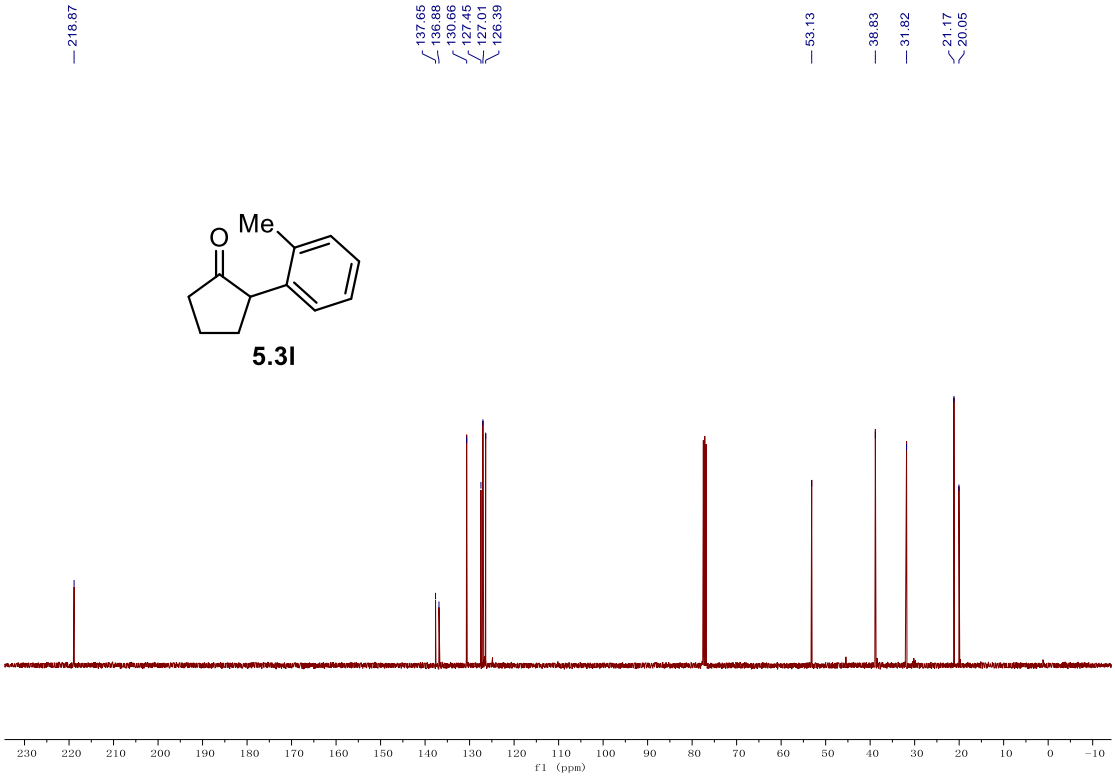


Figure 5.27 ^{1}H-NMR Spectrum of **5.3m**

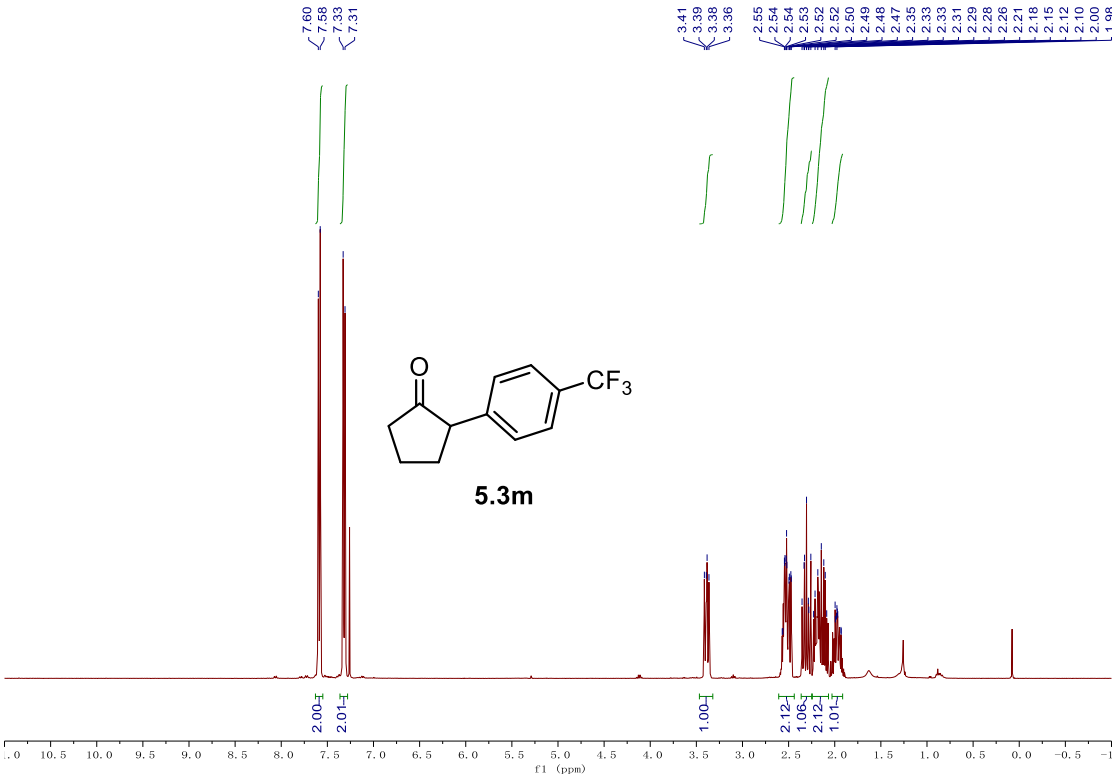


Figure 5.28 ^{13}C-NMR Spectrum of **5.3m**

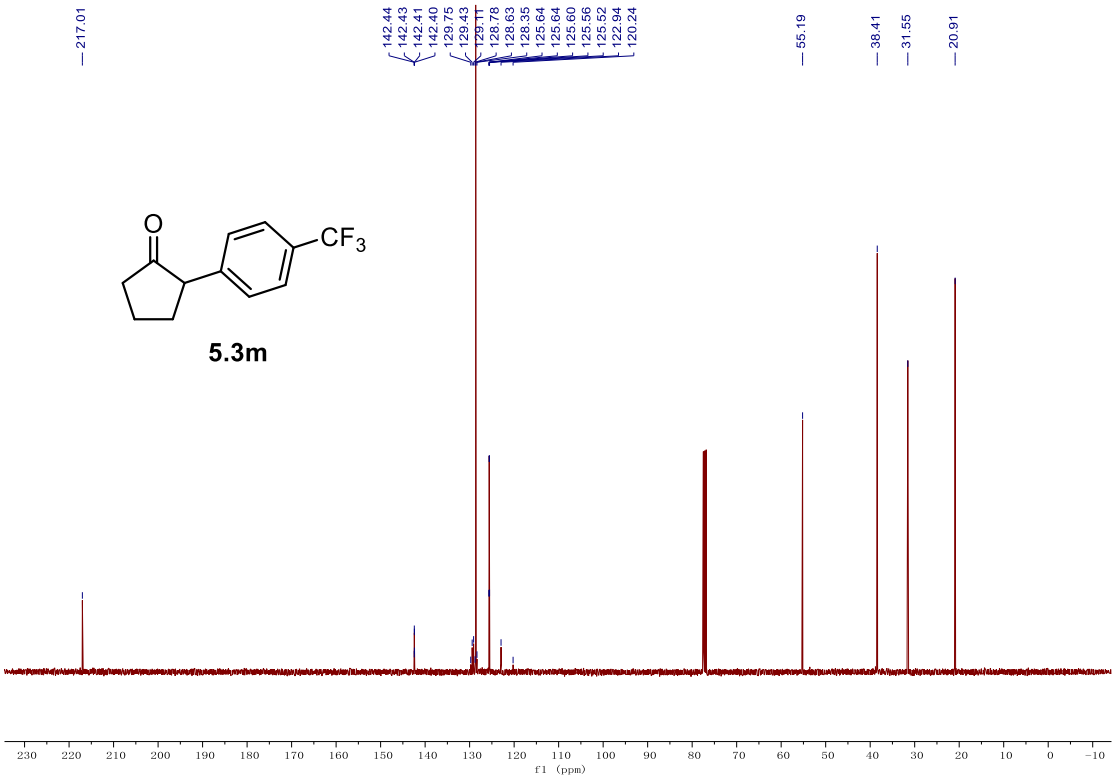


Figure 5.29 ^{19}F-NMR Spectrum of **5.3m**

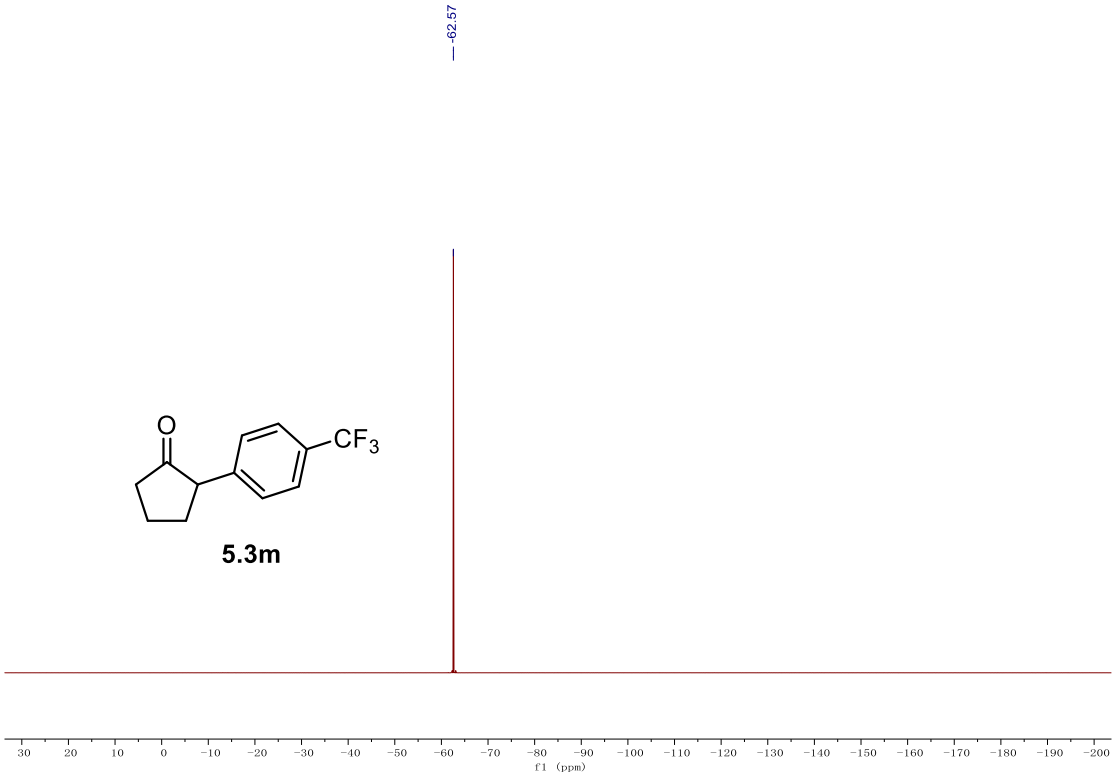


Figure 5.30 ^{1}H-NMR Spectrum of **5.3n**

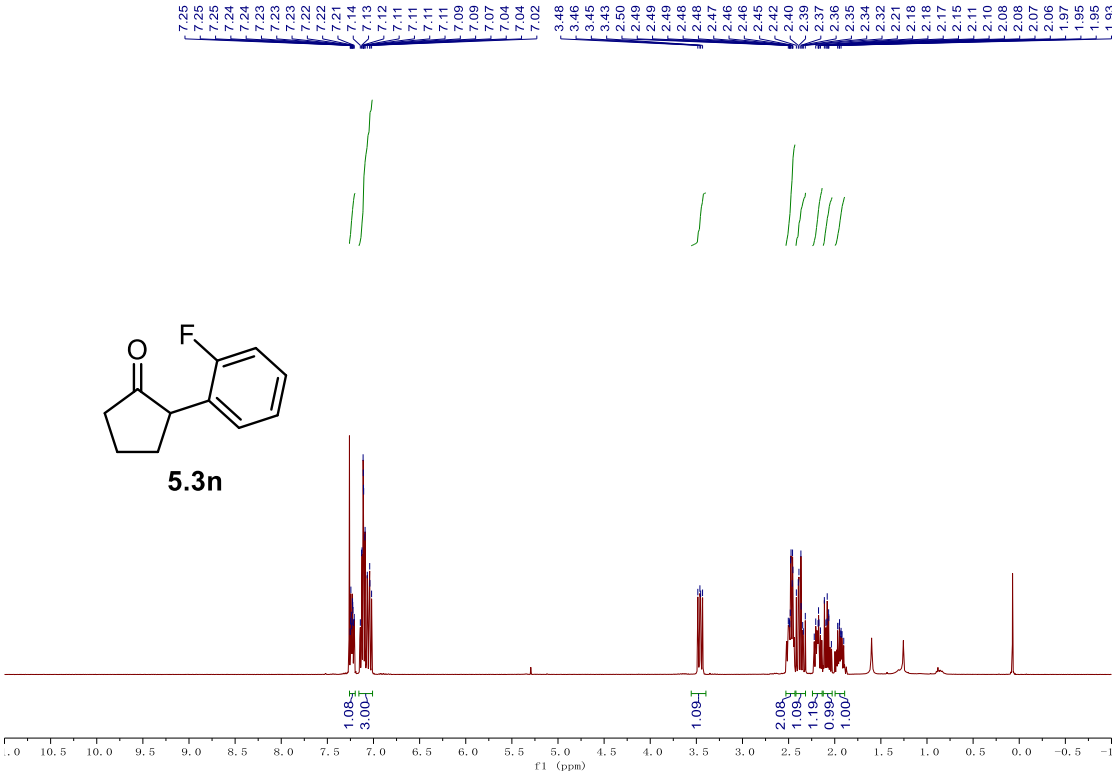


Figure 5.31 ^{13}C-NMR Spectrum of **5.3n**

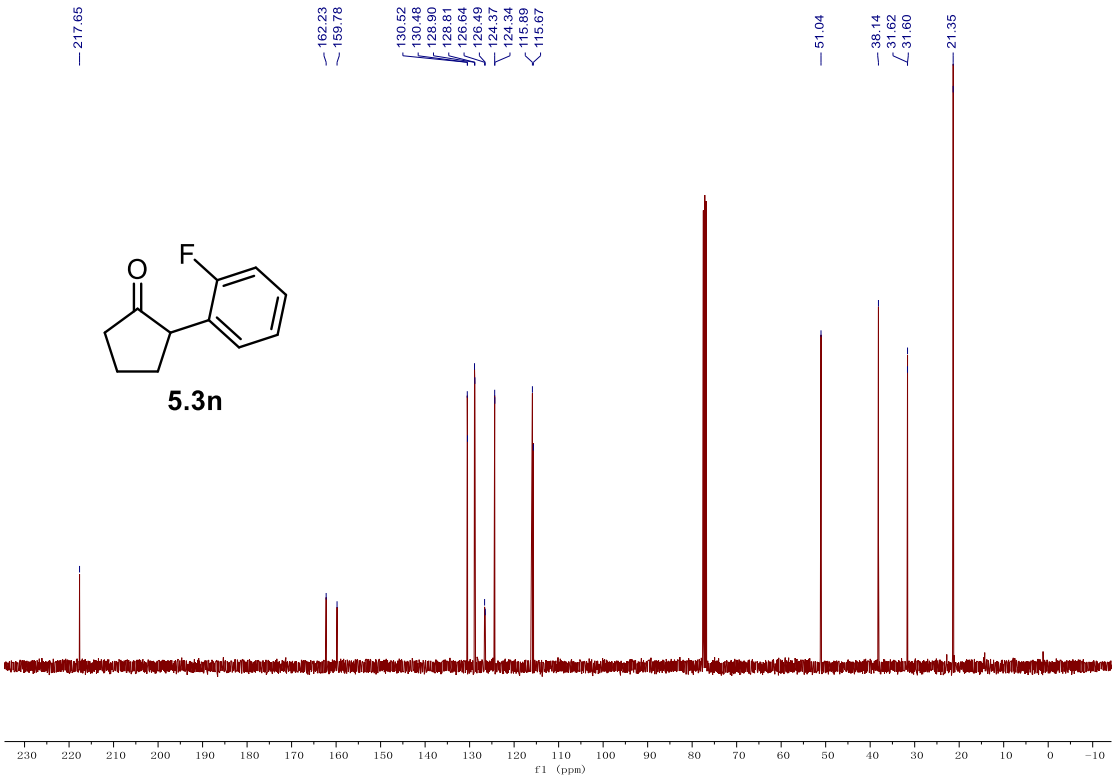


Figure 5.32 ^{19}F-NMR Spectrum of **5.3n**

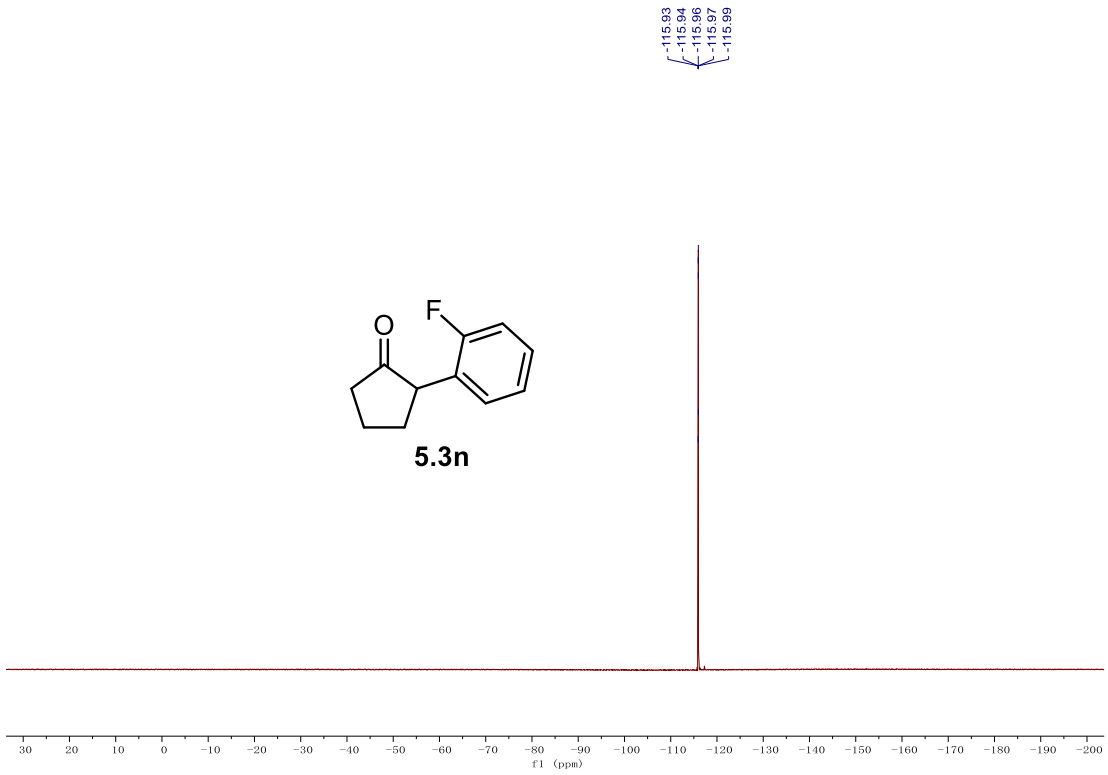


Figure 5.33 ^{1}H-NMR Spectrum of **5.3o**

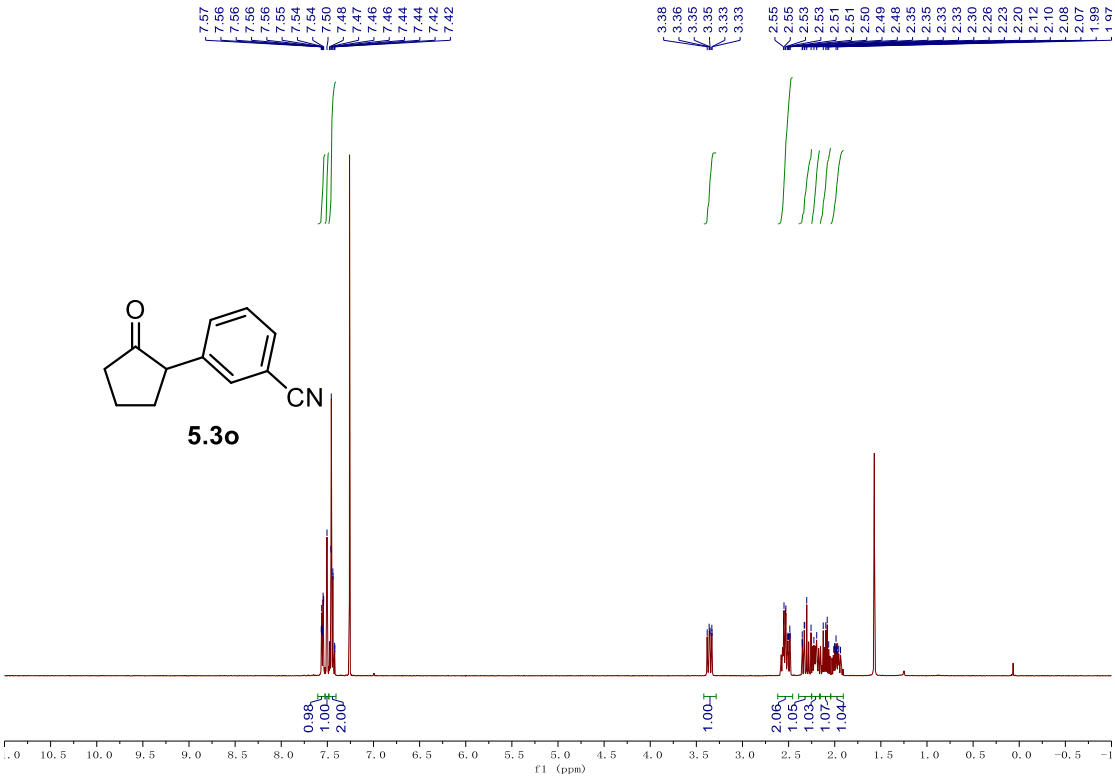


Figure 5.34 ^{13}C-NMR Spectrum of **5.3o**

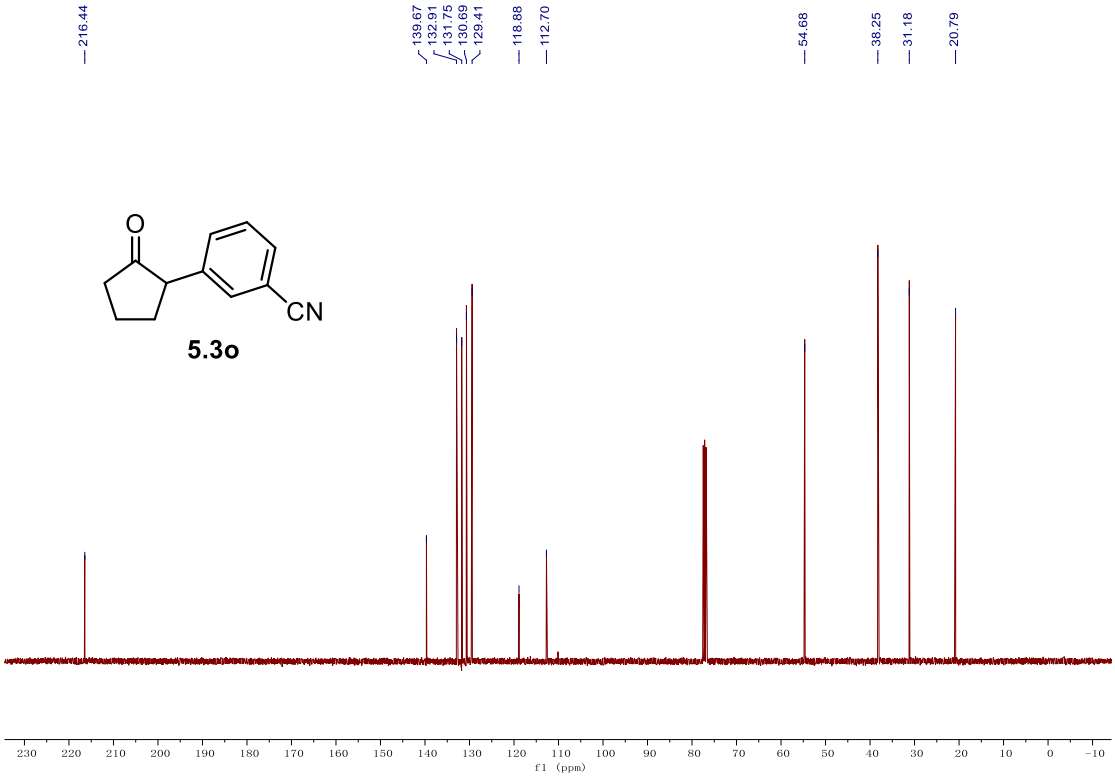


Figure 5.35 ^{1}H-NMR Spectrum of **5.3p**

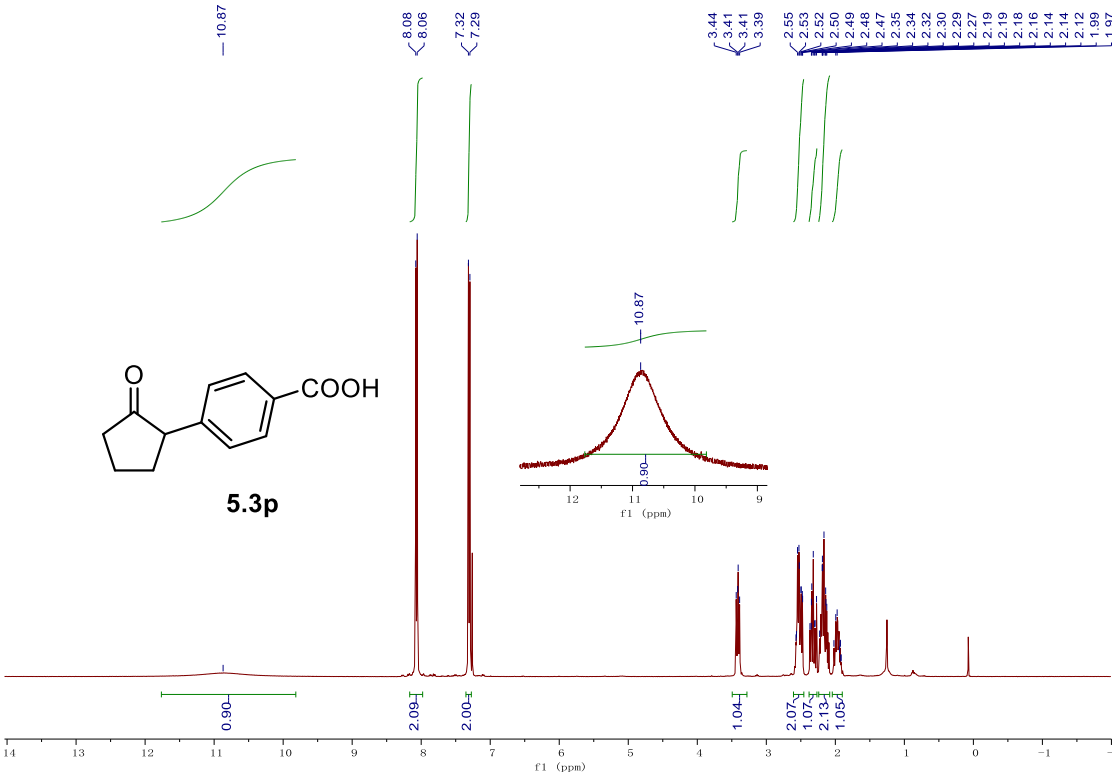


Figure 5.36 ^{13}C-NMR Spectrum of **5.3p**

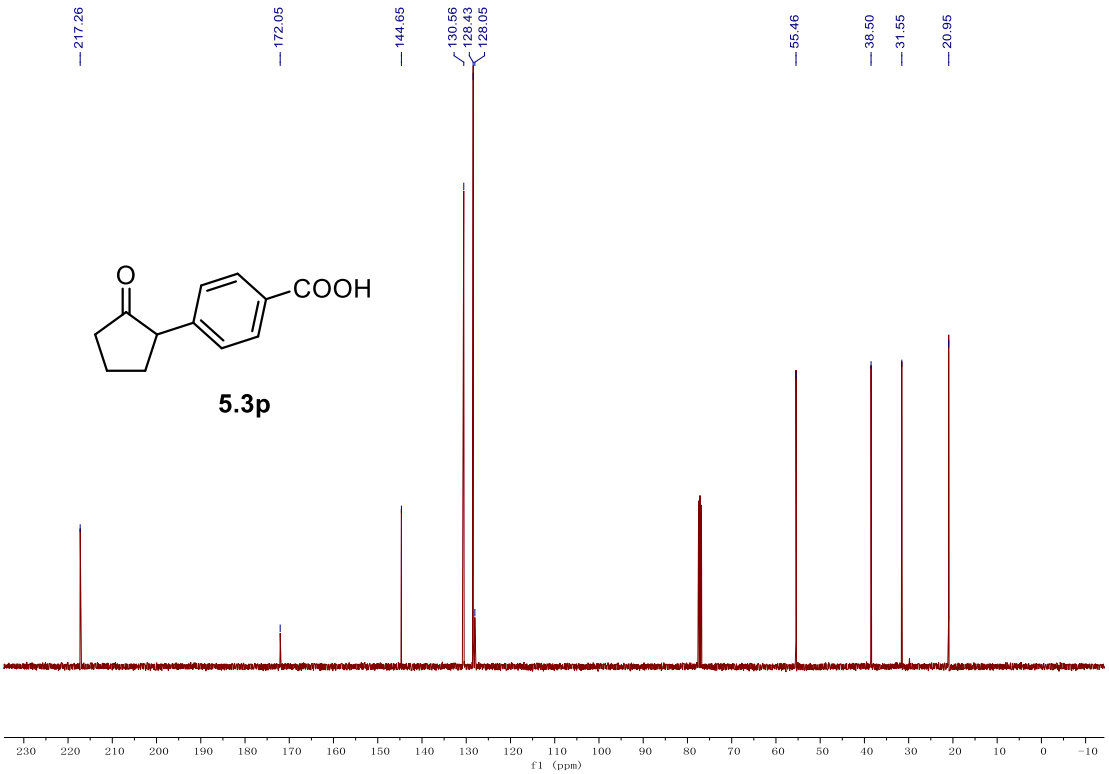


Figure 5.37 ^{1}**H**-NMR Spectrum of **5.3q**

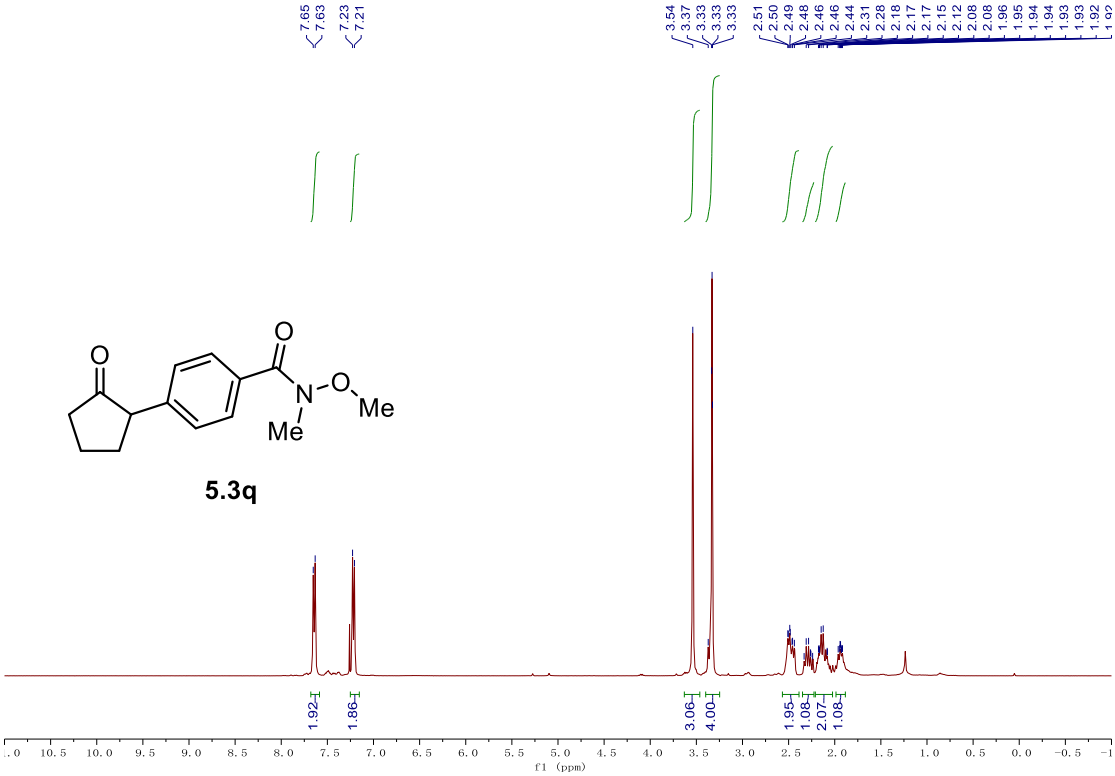


Figure 5.38 ^{13}C-NMR Spectrum of **5.3q**

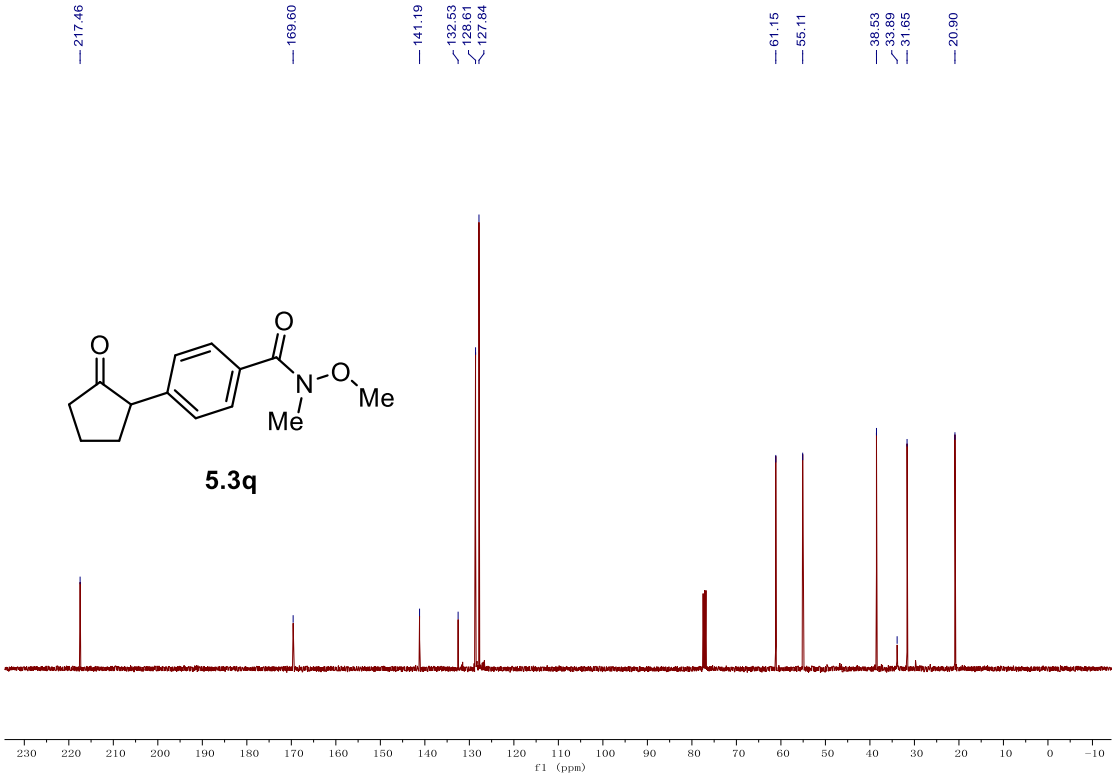


Figure 5.39 ^{1}H-NMR Spectrum of **5.3r**

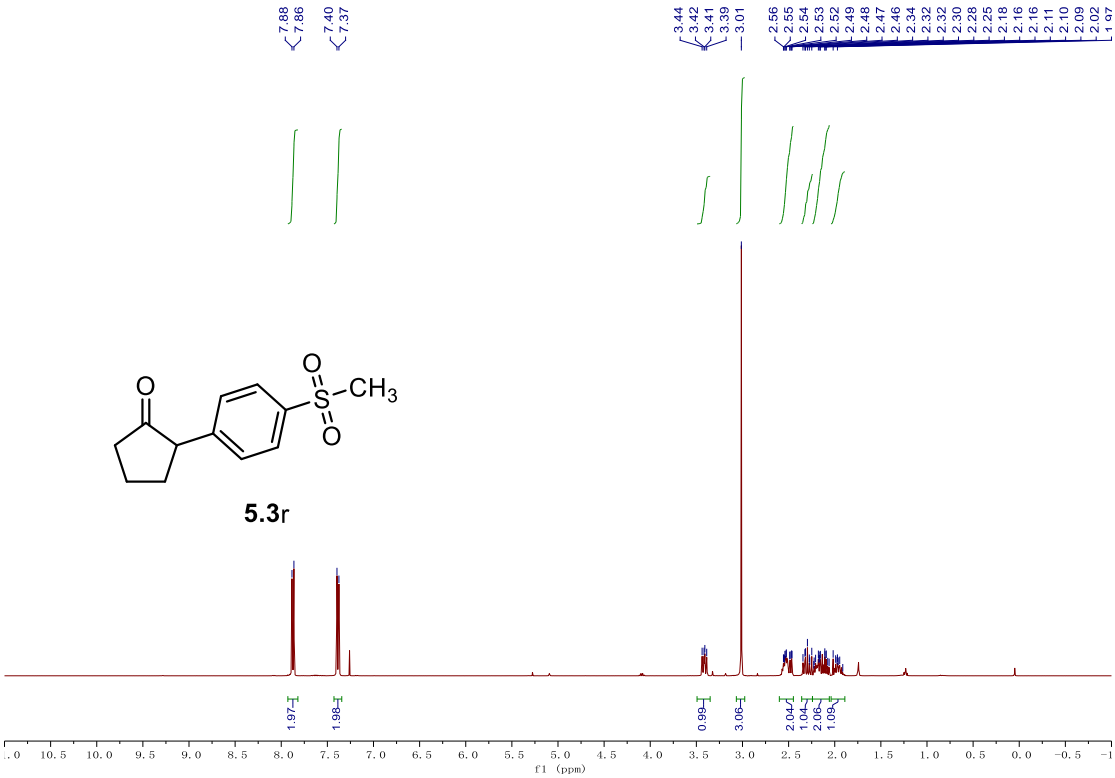


Figure 5.40 ^{13}C-NMR Spectrum of **5.3r**

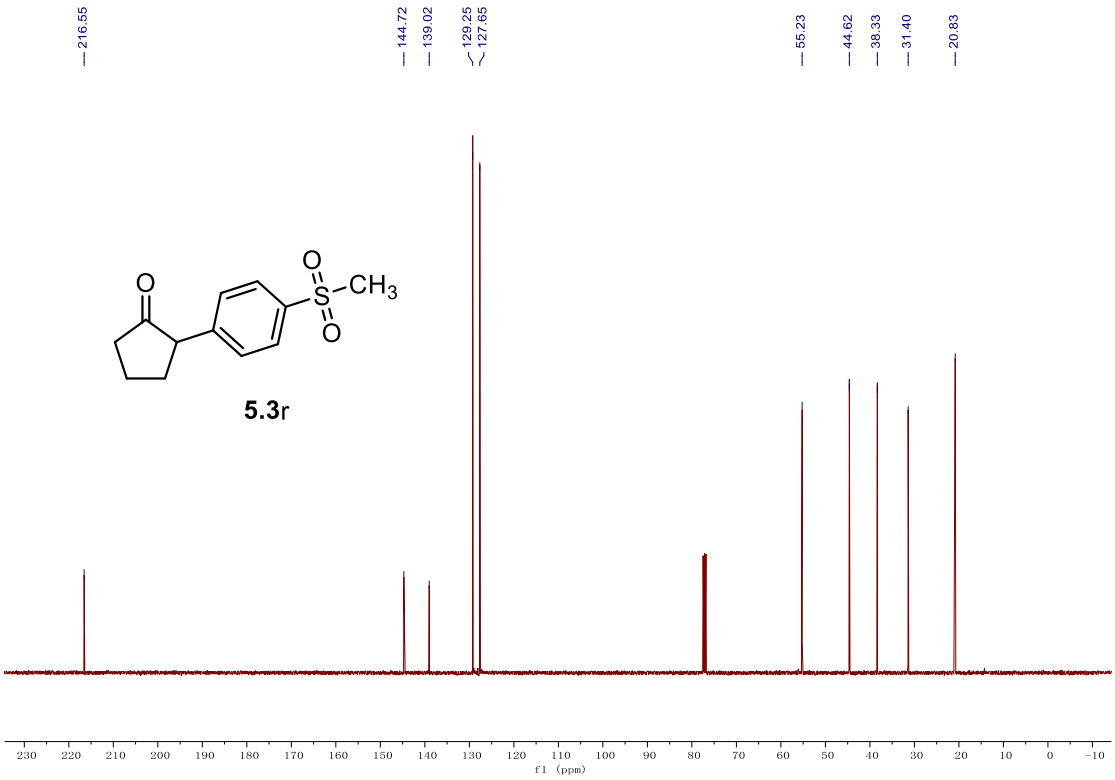


Figure 5.41 ^{1}H-NMR Spectrum of **5.3s**

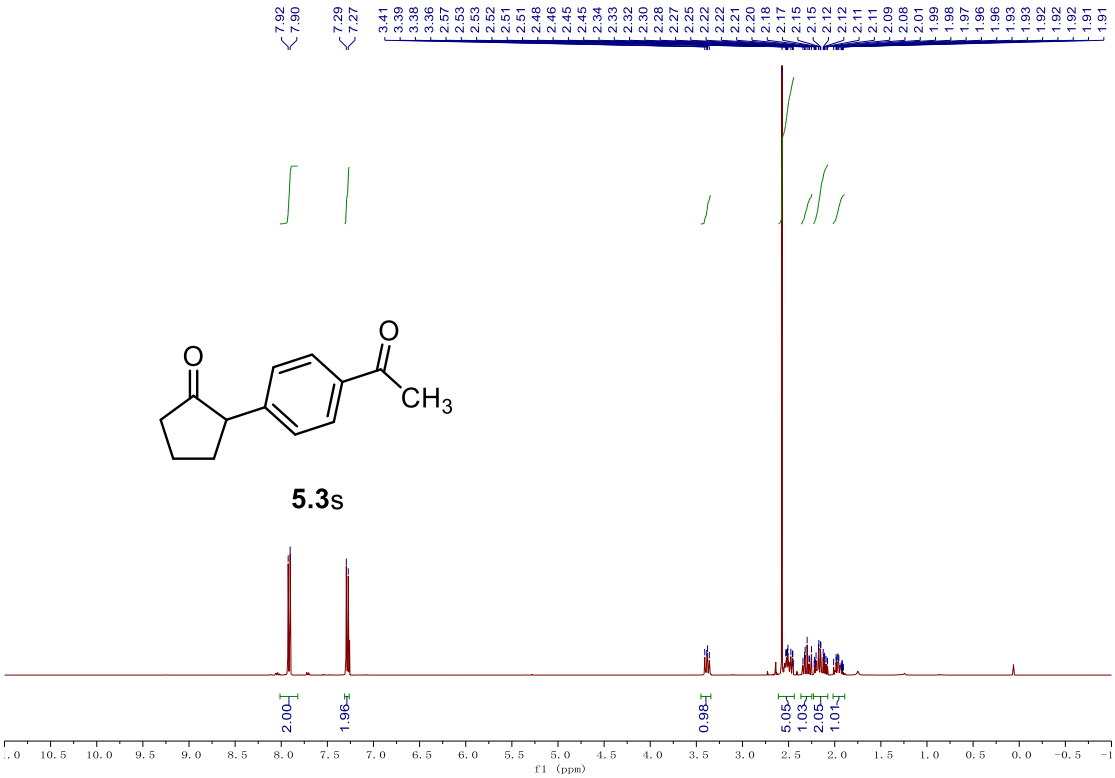


Figure 5.42 ^{13}C-NMR Spectrum of **5.3s**

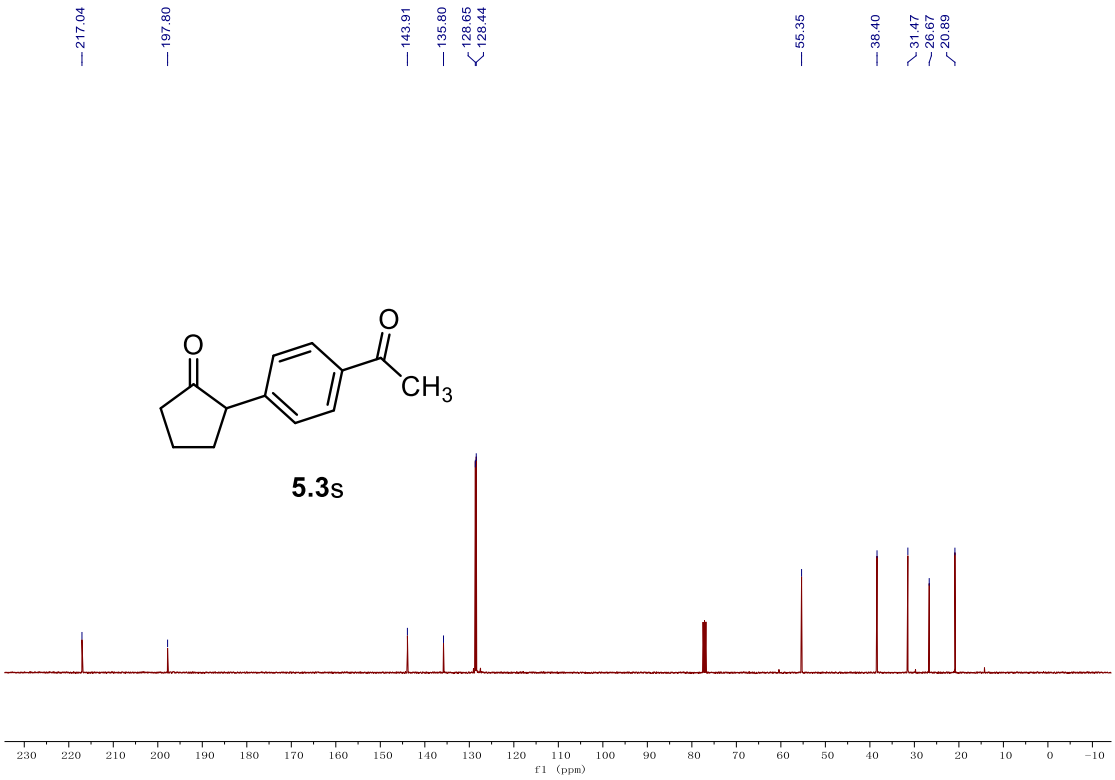


Figure 5.43 ^{1}H-NMR Spectrum of **5.3t**

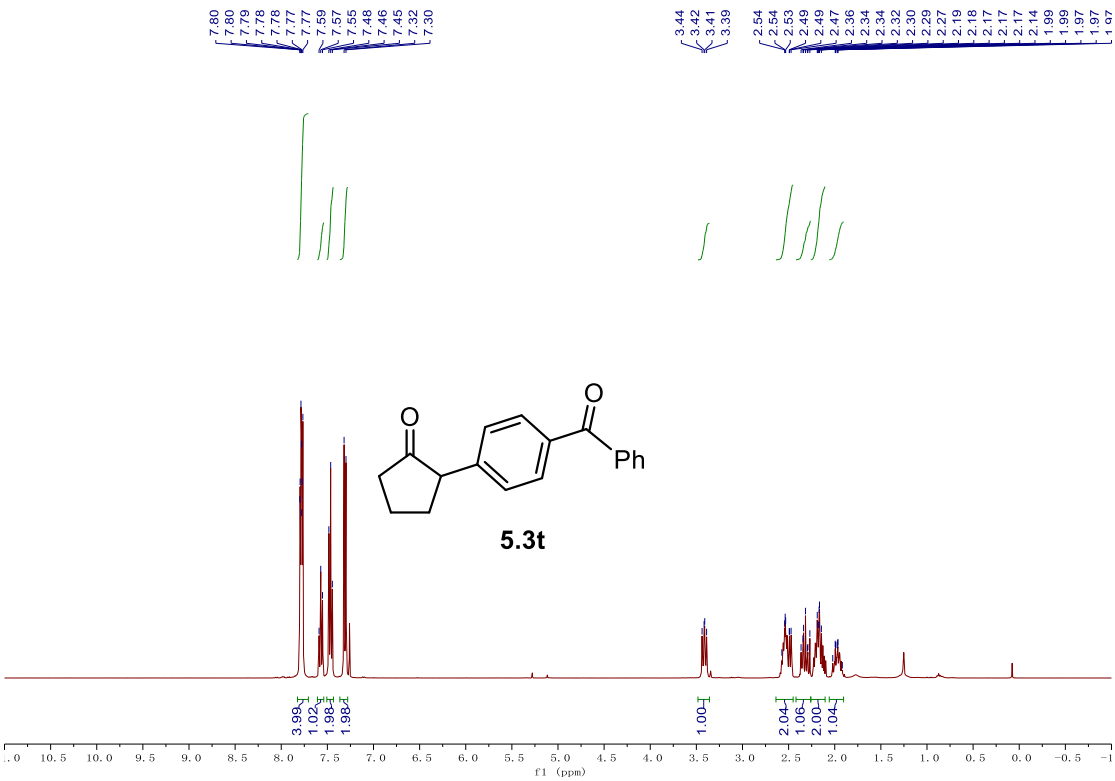


Figure 5.44 ^{13}C-NMR Spectrum of **5.3t**

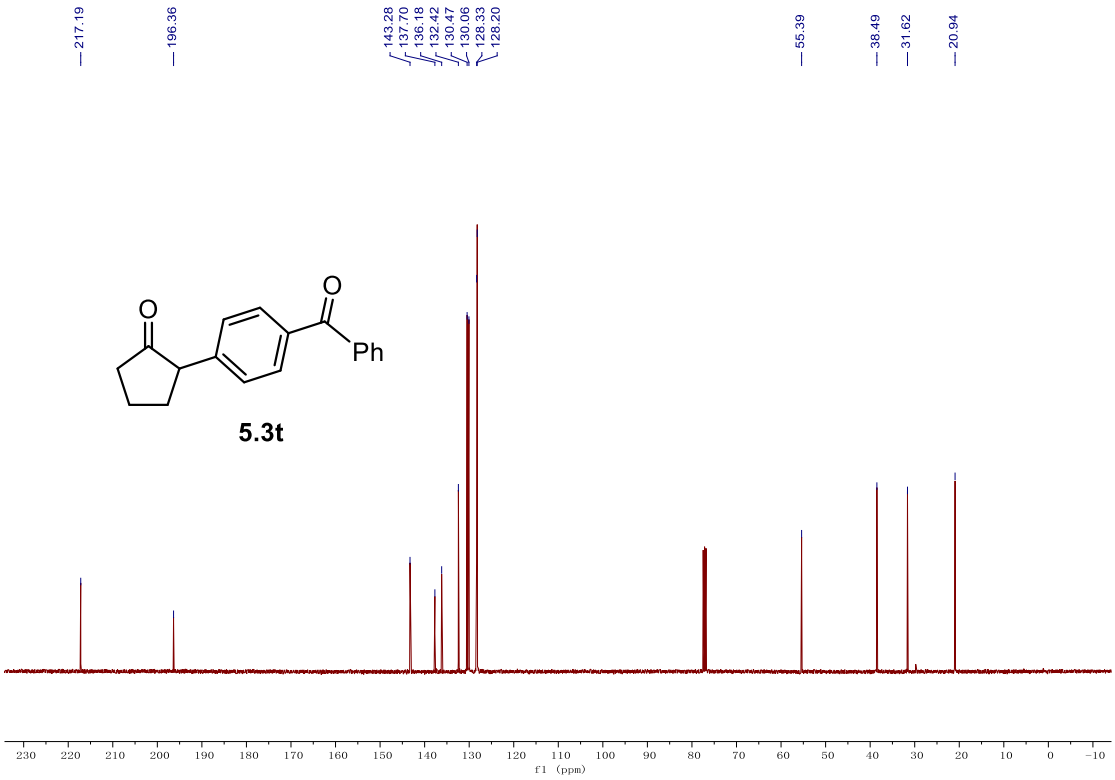


Figure 5.45 ^{1}H-NMR Spectrum of **5.3u**

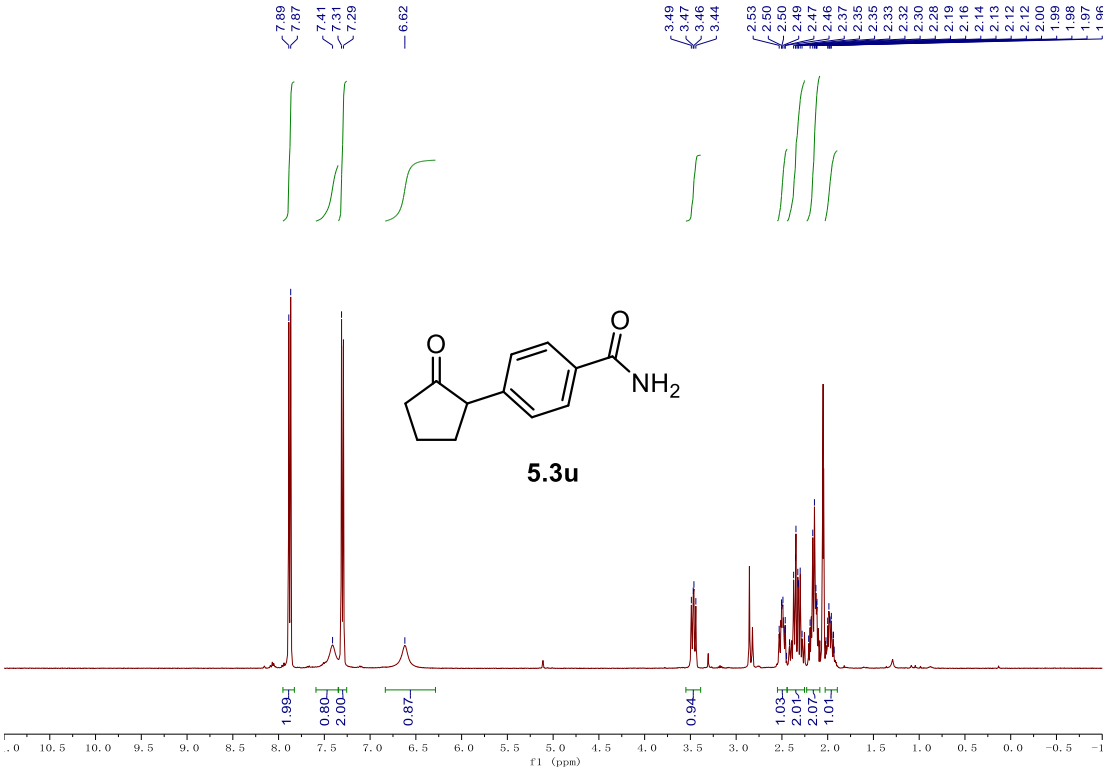


Figure 5.46 ^{13}C-NMR Spectrum of **5.3u**

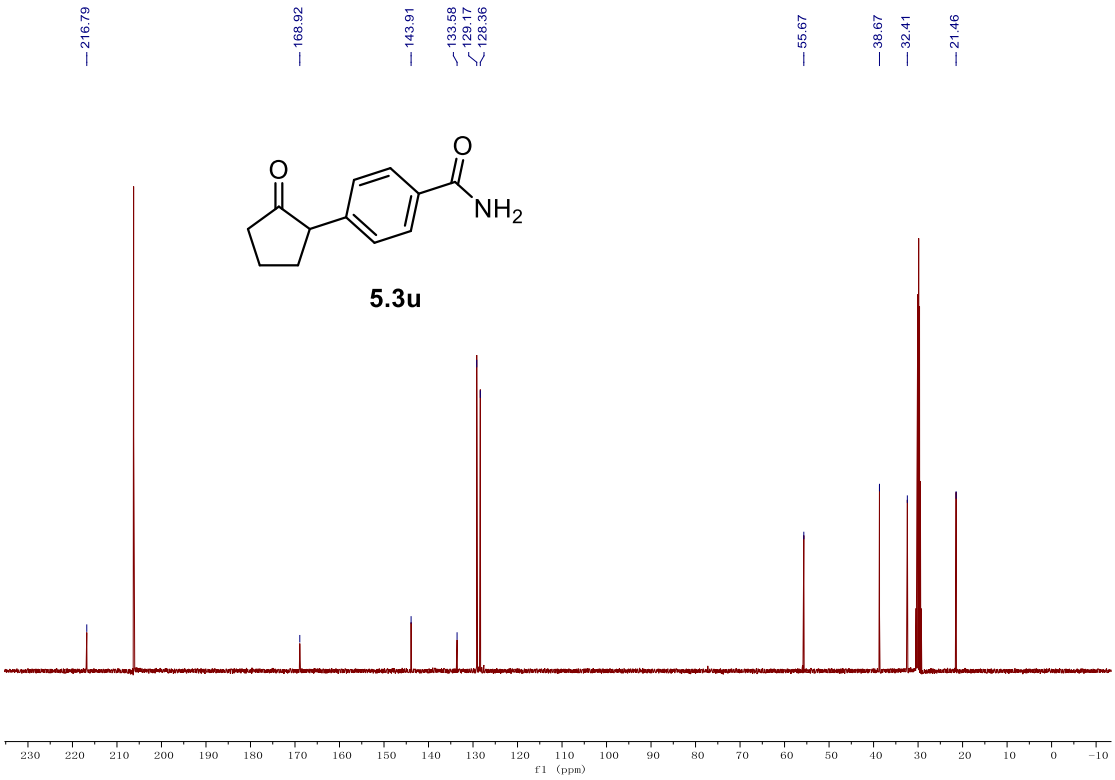


Figure 5.47 ^{1}H-NMR Spectrum of **5.3v**

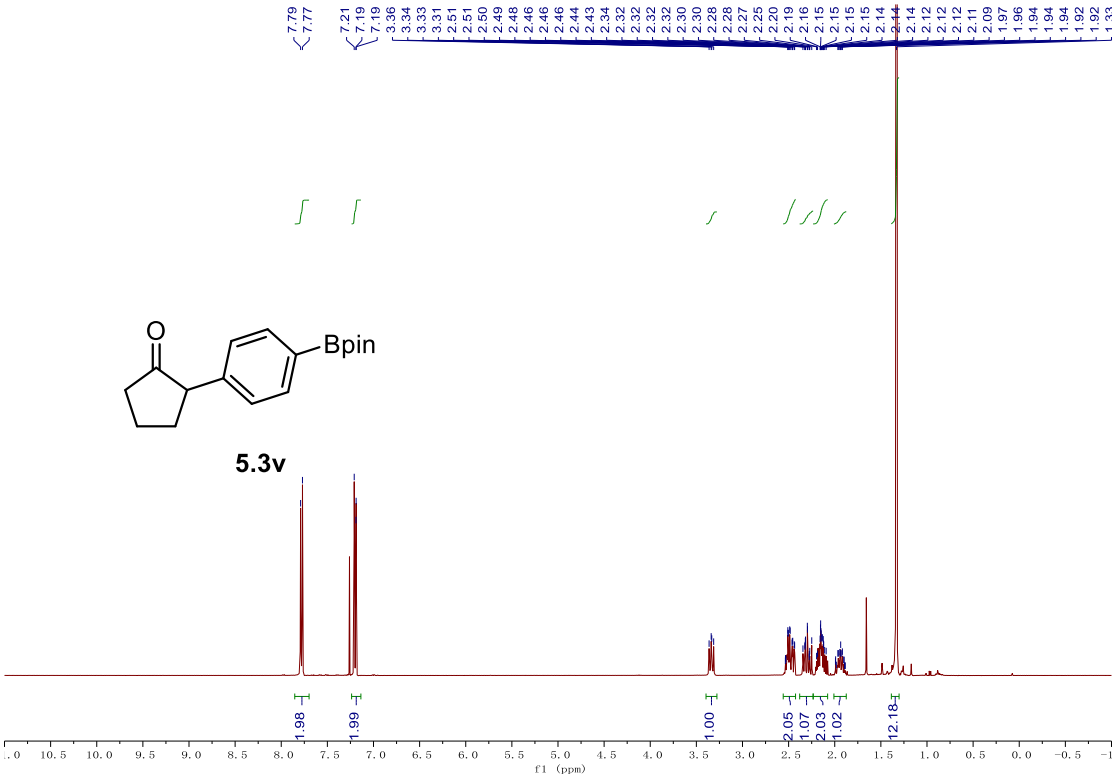


Figure 5.48 ^{13}C-NMR Spectrum of **5.3v**

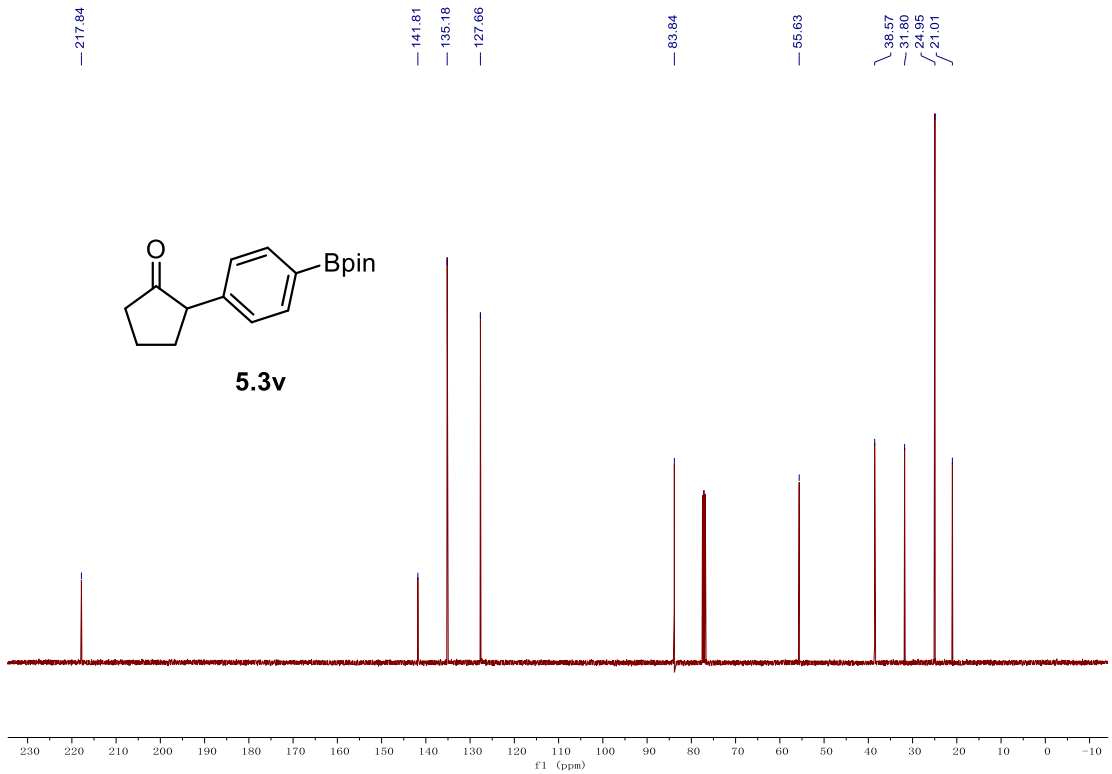


Figure 5.49 ^{1}H-NMR Spectrum of **5.3w**

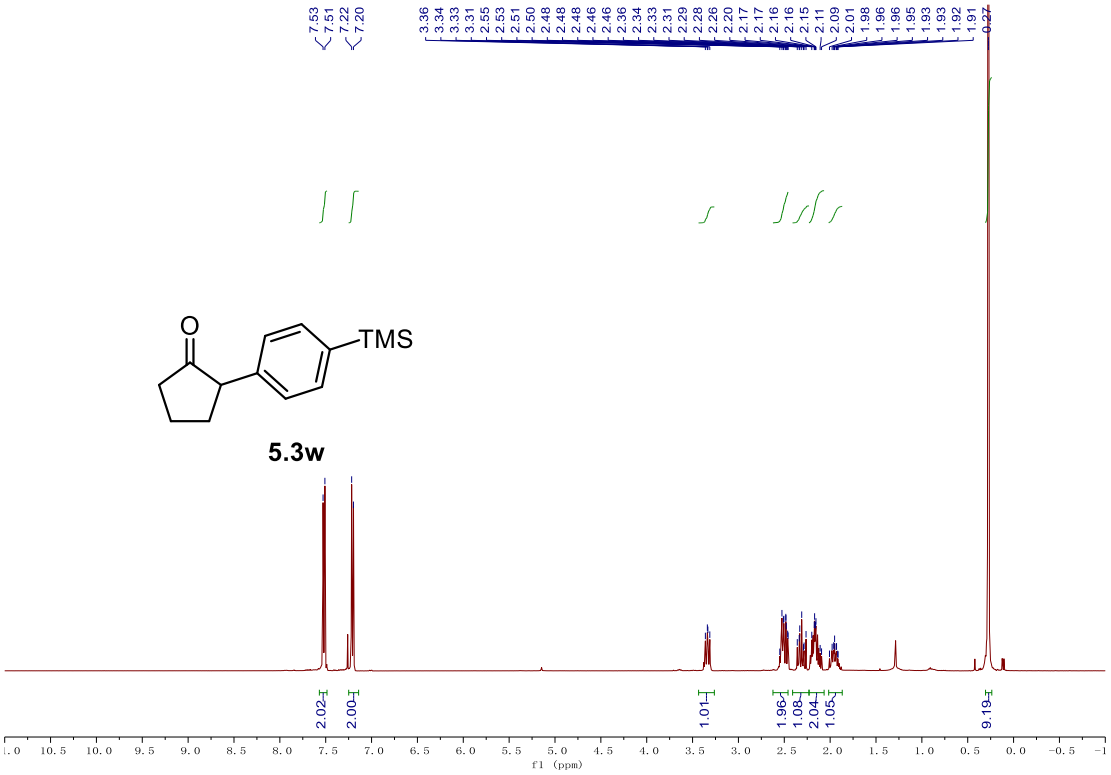


Figure 5.50 ^{13}C-NMR Spectrum of **5.3w**

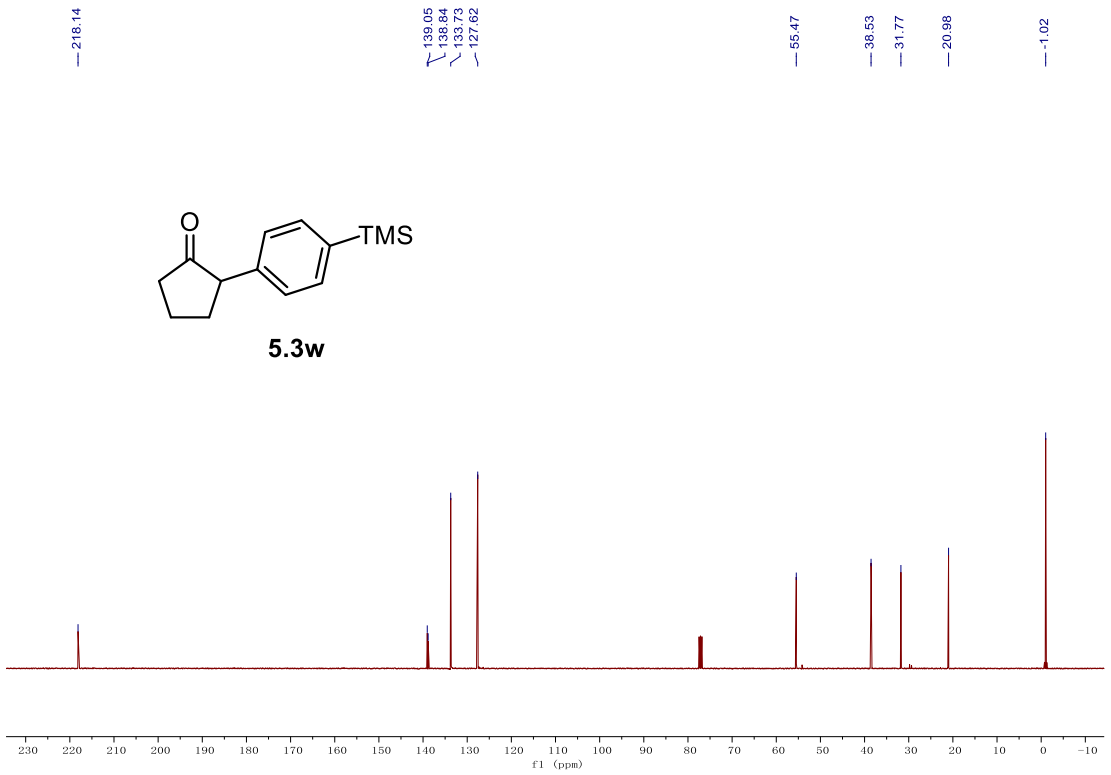


Figure 5.51 ^{1}H-NMR Spectrum of **5.3x**

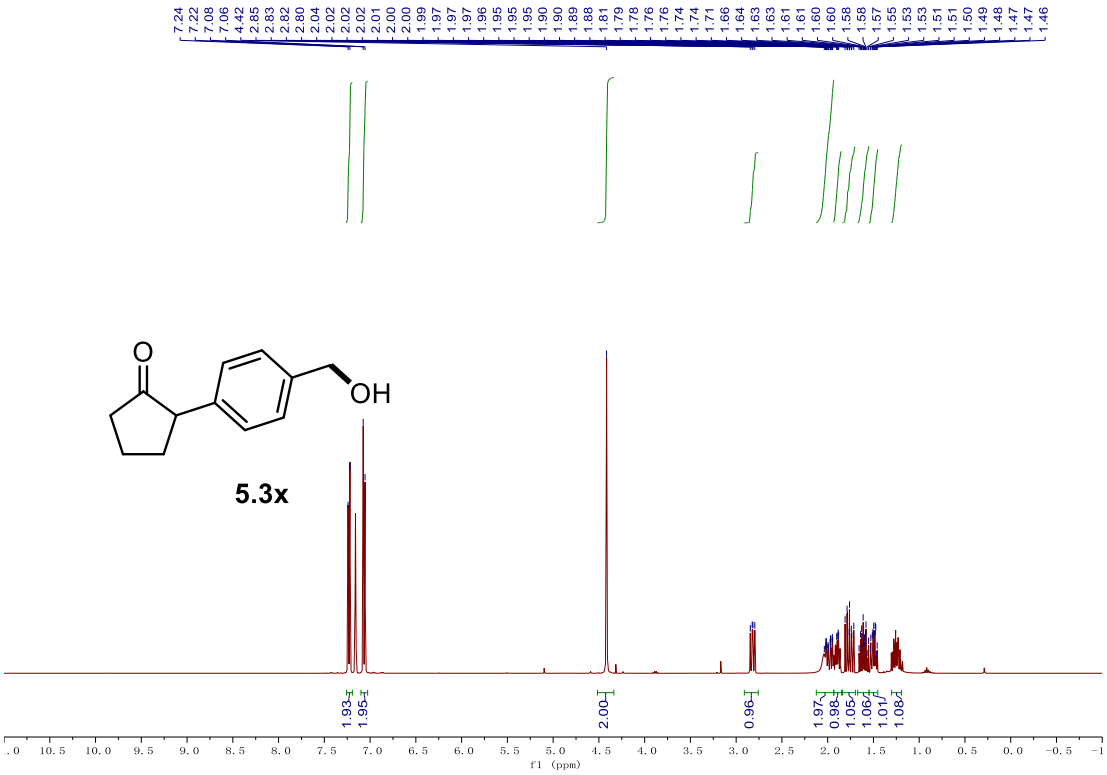


Figure 5.52 ^{13}C-NMR Spectrum of **5.3x**

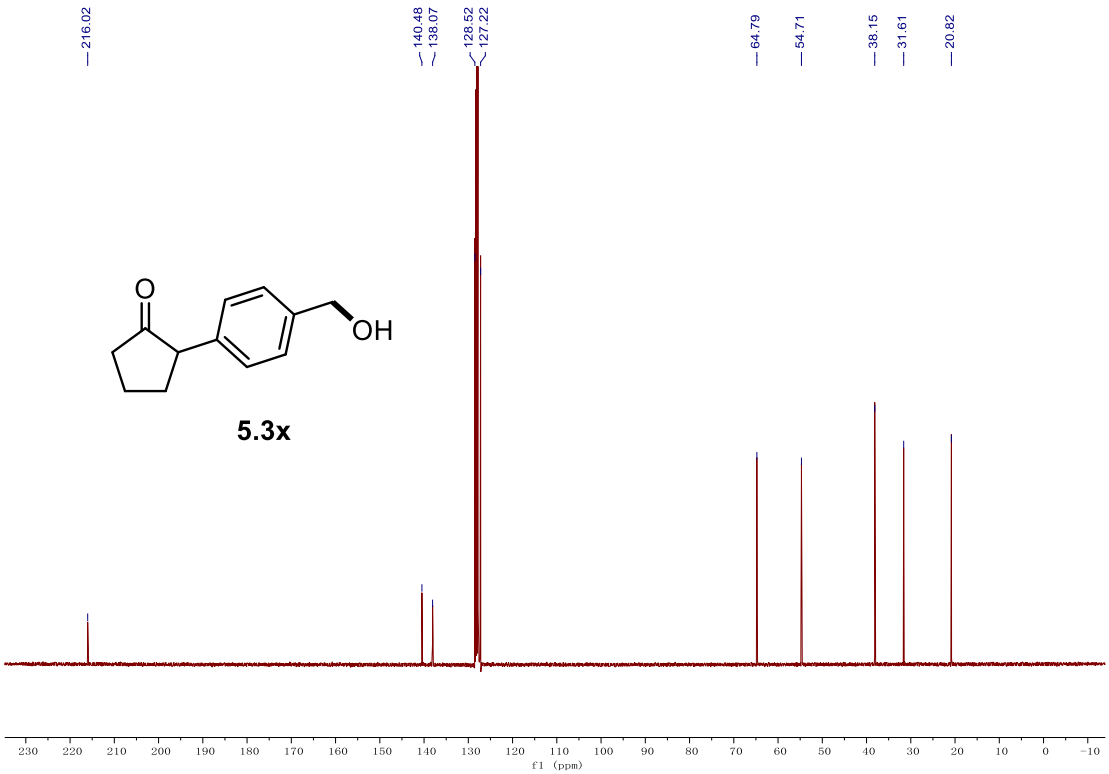


Figure 5.53 ^{1}H-NMR Spectrum of **5.3y**

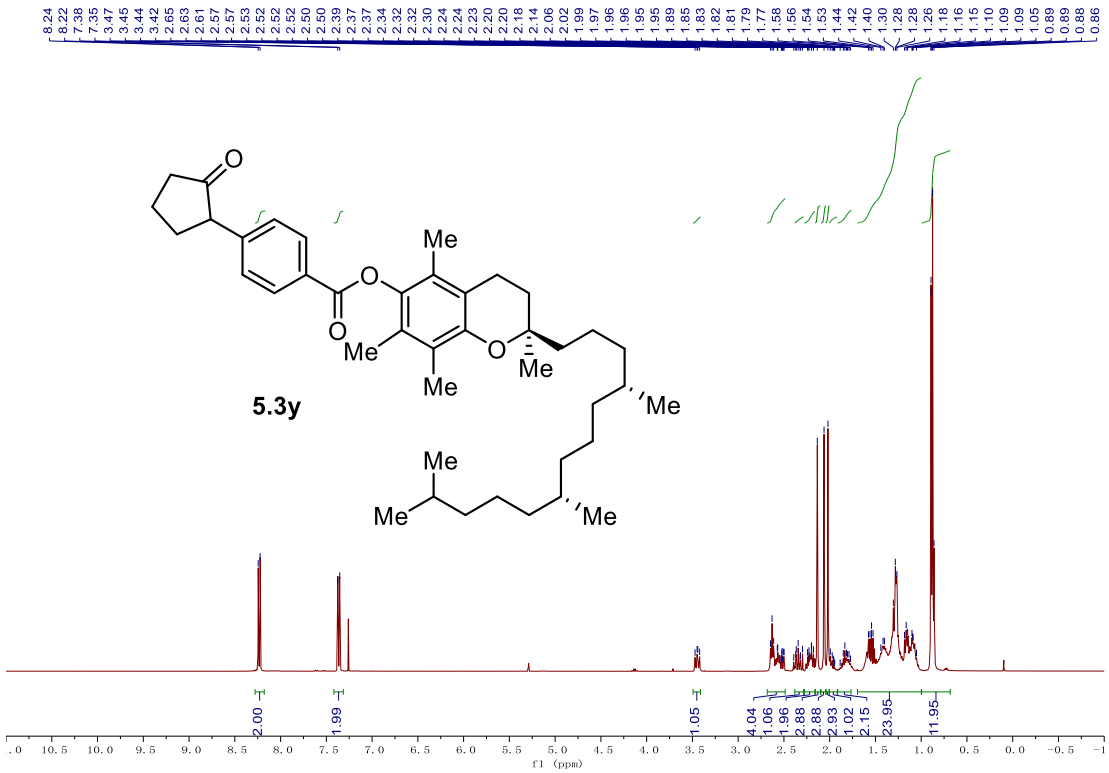


Figure 5.54 ^{13}C-NMR Spectrum of **5.3y**

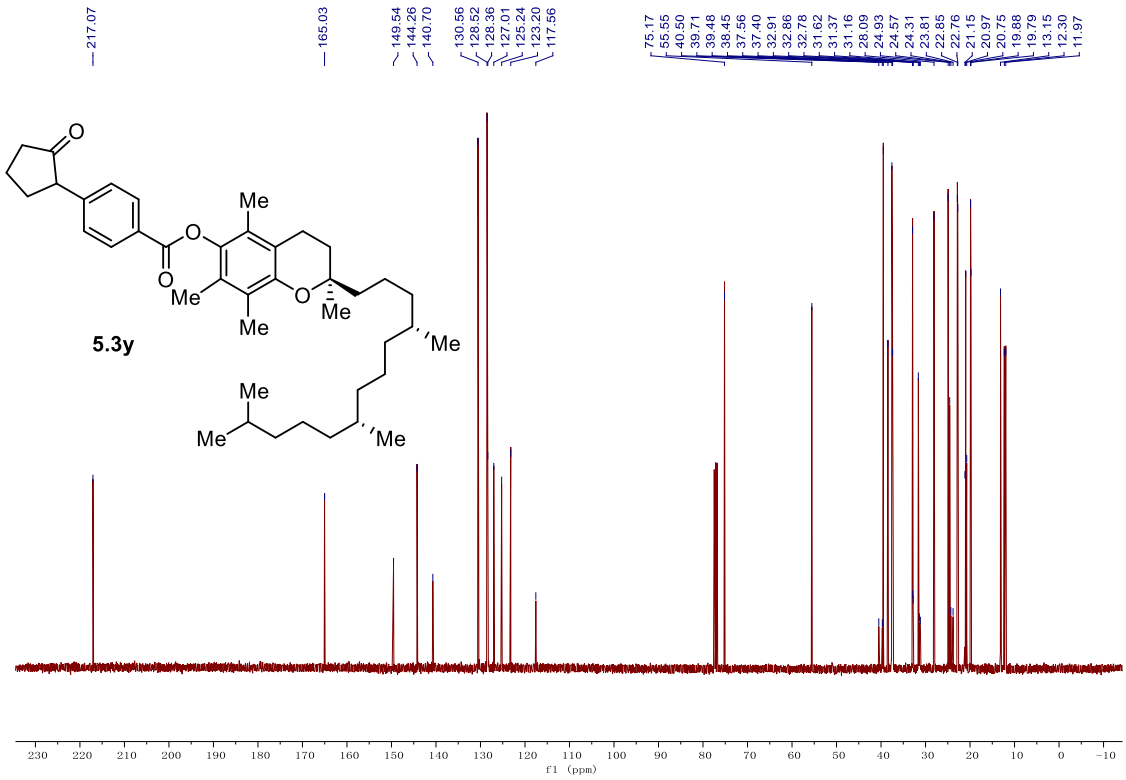


Figure 5.55 ^{1}H-NMR Spectrum of **5.5a**

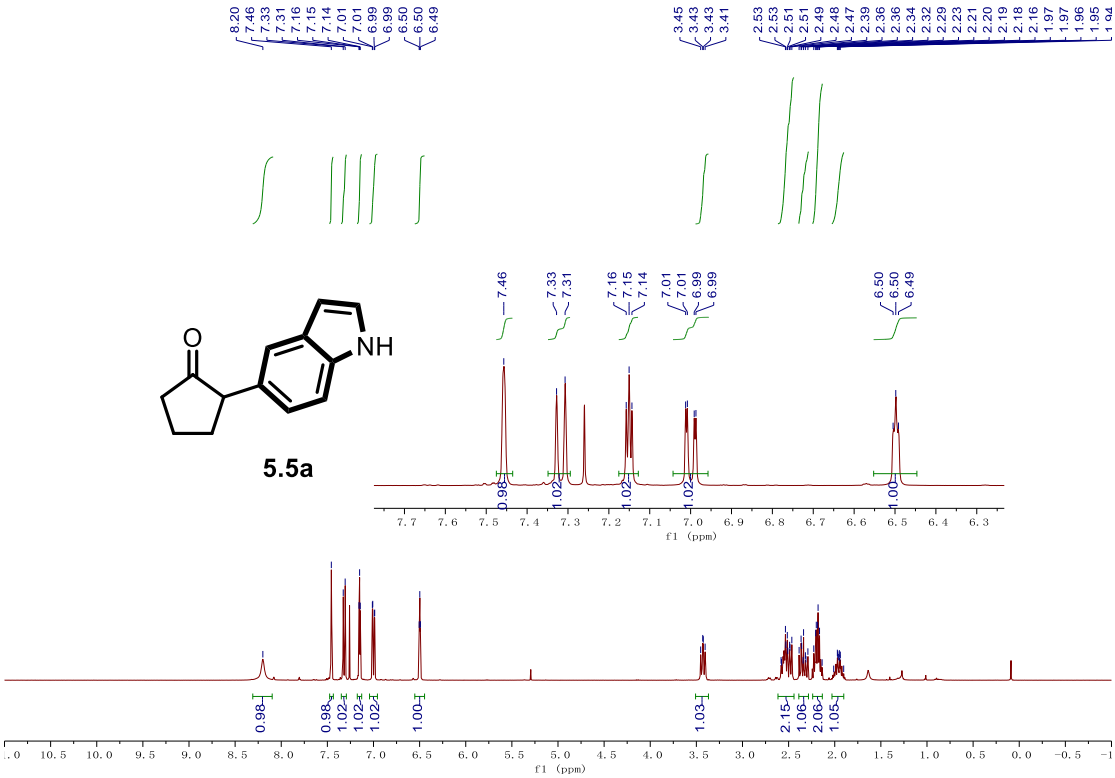


Figure 5.56 ^{13}C-NMR Spectrum of **5.5a**

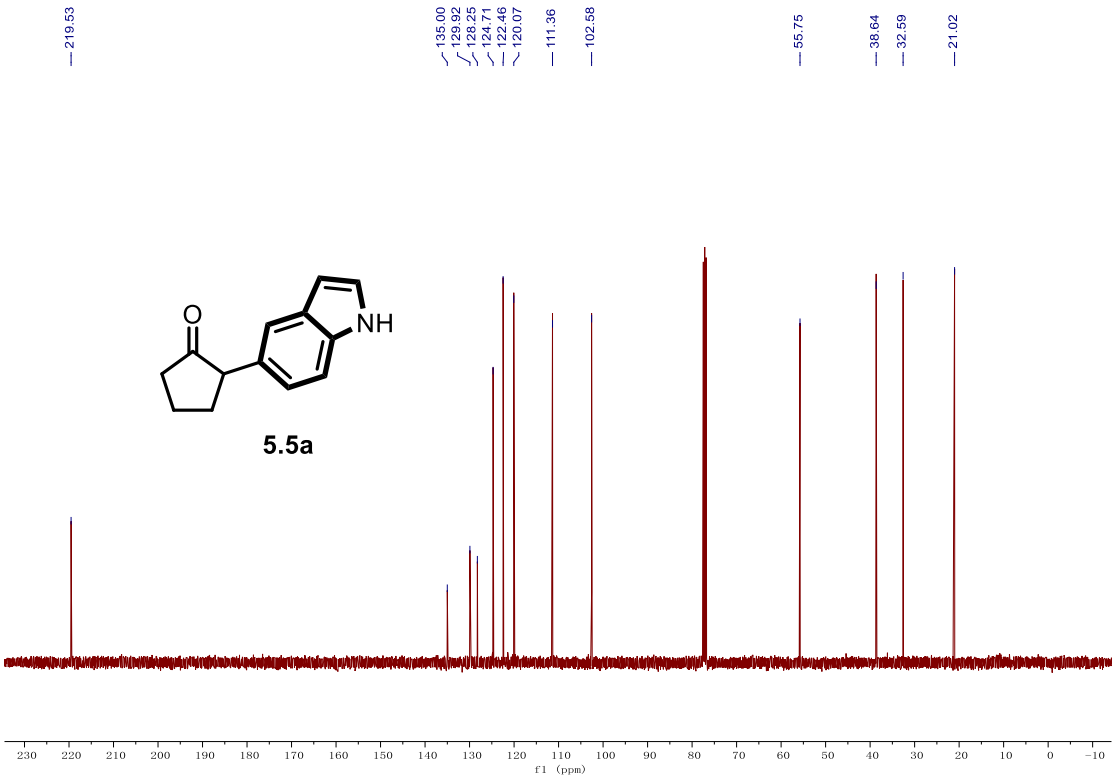


Figure 5.57 ^{1}H-NMR Spectrum of **5.5b**

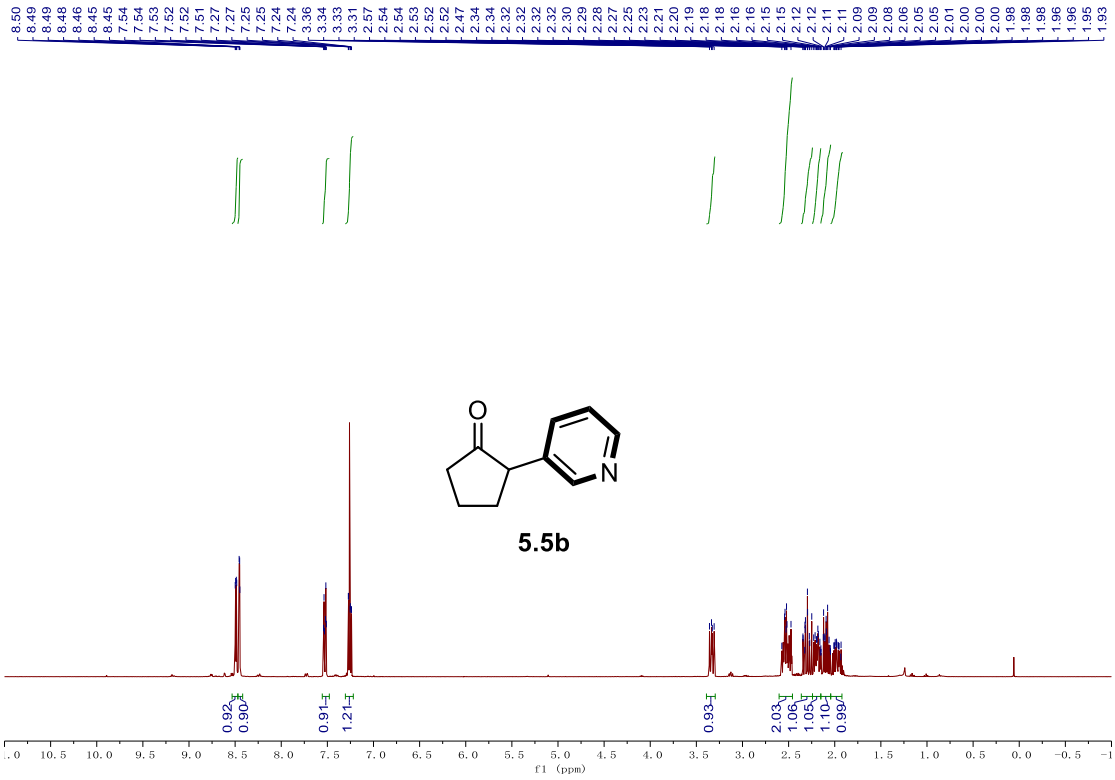


Figure 5.58 ^{13}C-NMR Spectrum of **5.5b**

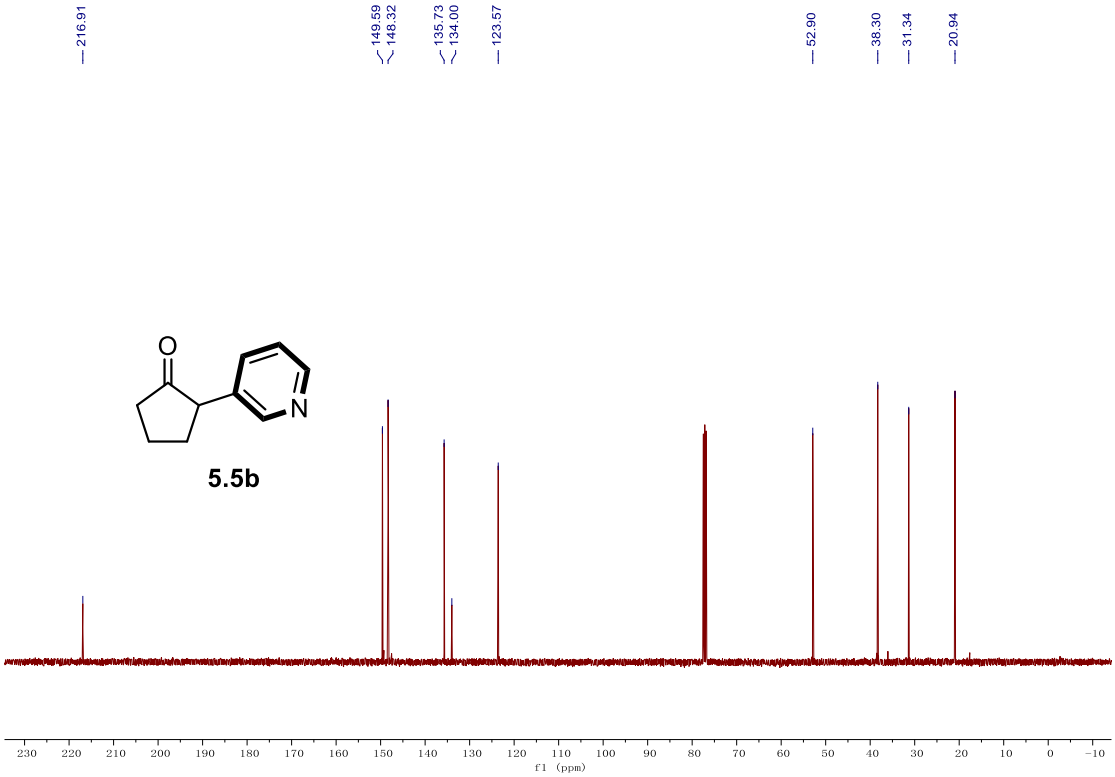


Figure 5.59 ^{1}H-NMR Spectrum of **5.5c**

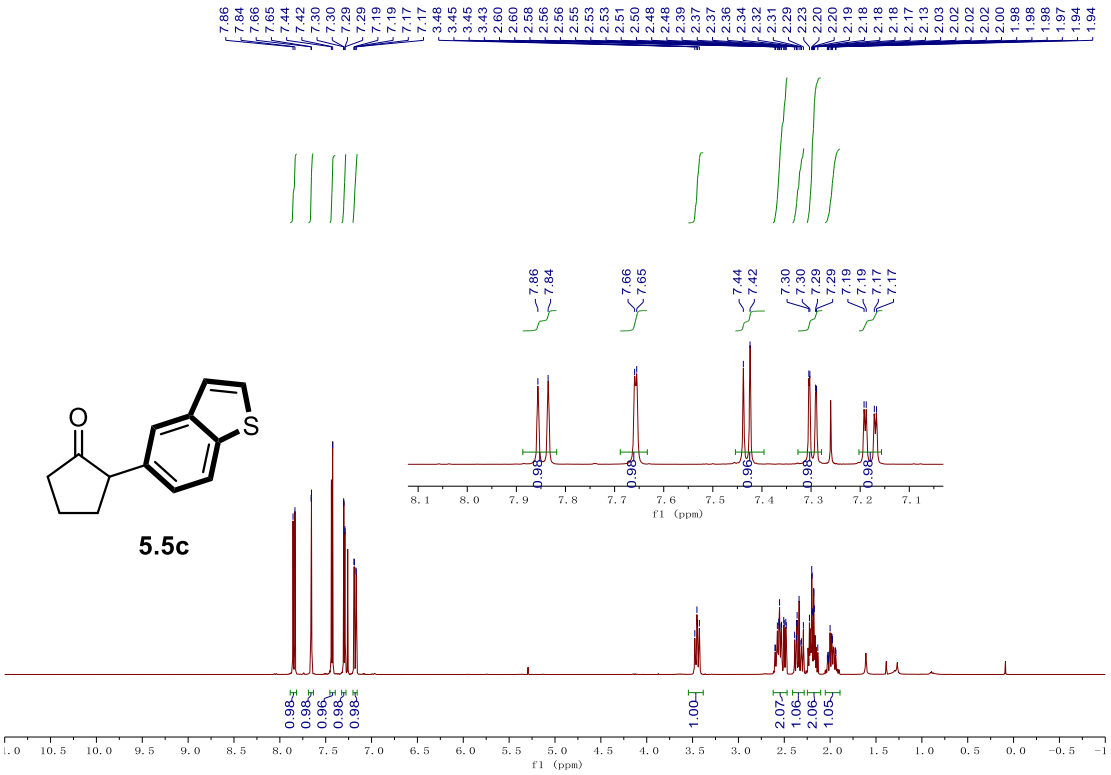


Figure 5.60 ^{13}C-NMR Spectrum of **5.5c**

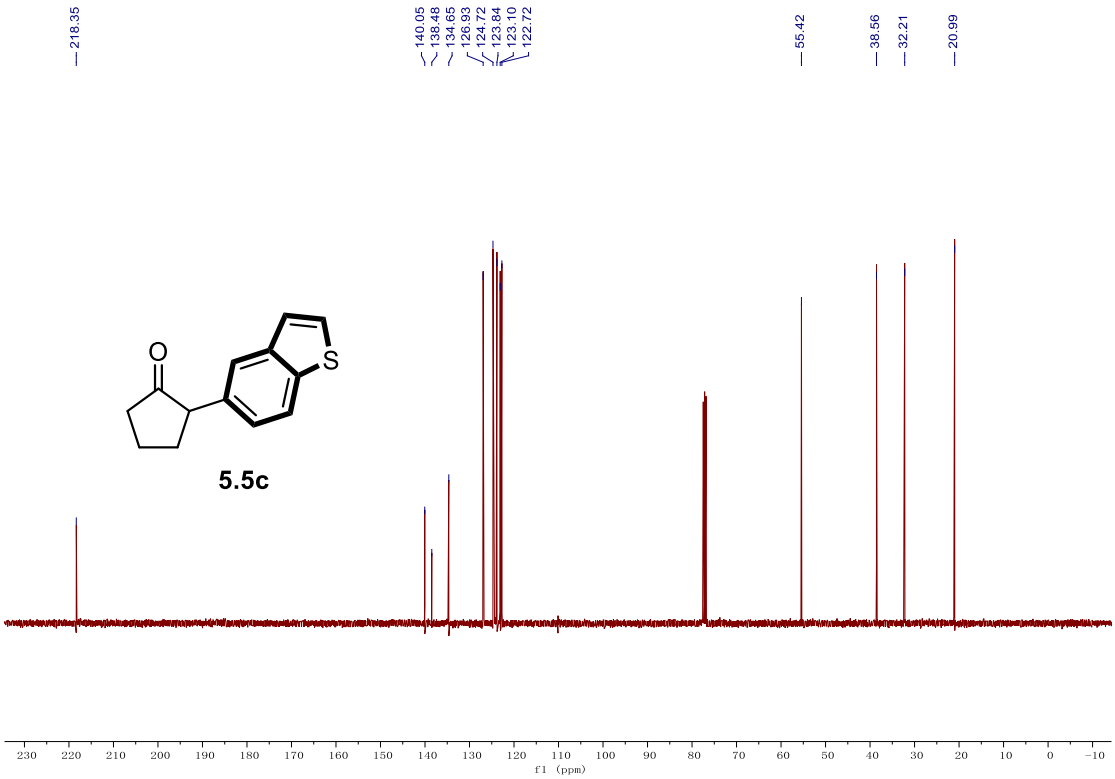


Figure 5.61 ^{1}H-NMR Spectrum of **5.5d**

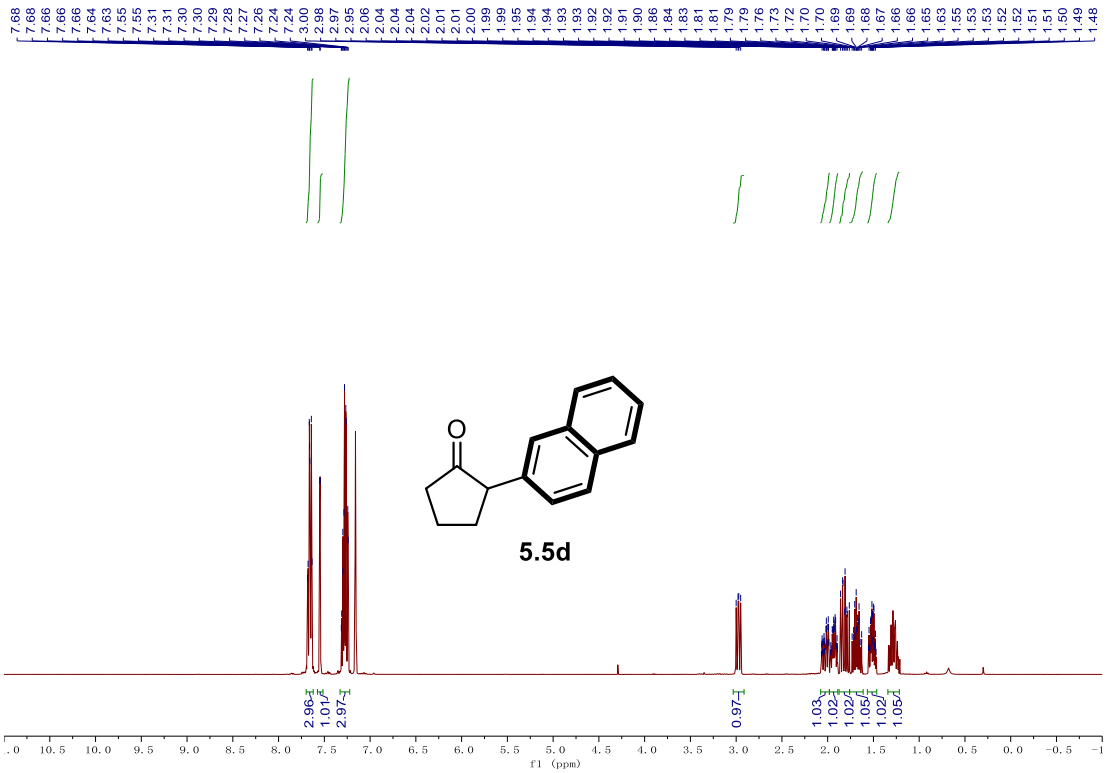


Figure 5.62 ^{13}C-NMR Spectrum of **5.5d**

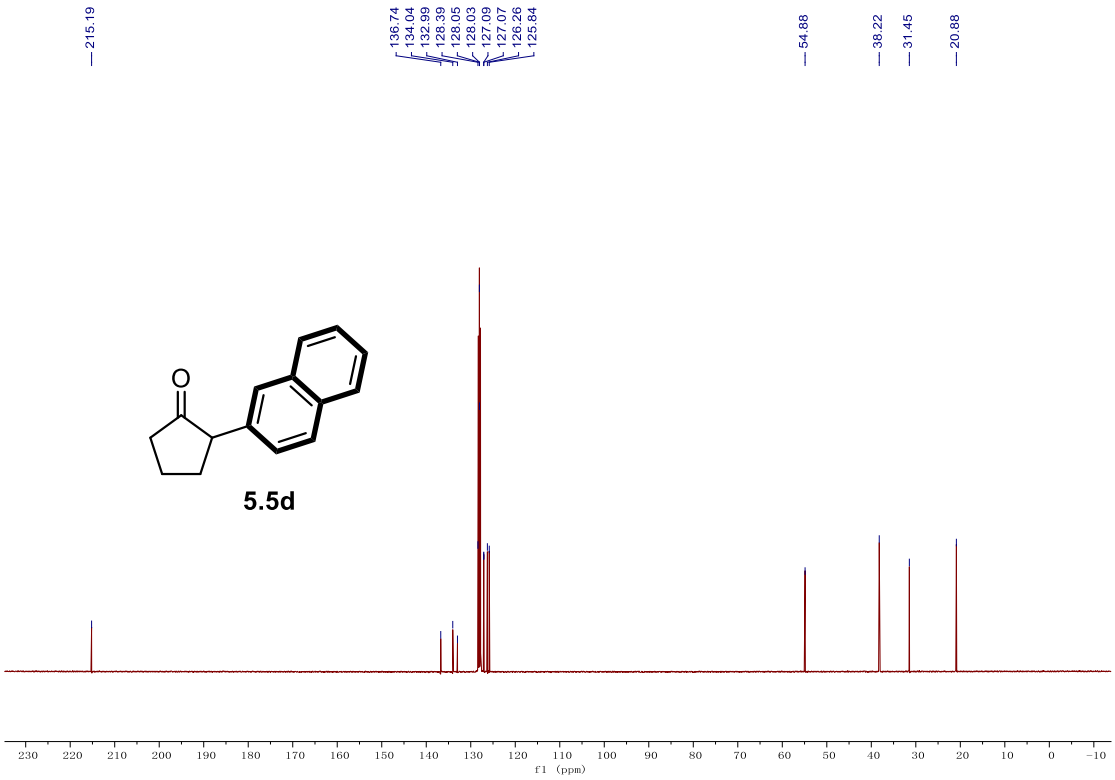


Figure 5.63 ^{1}H-NMR Spectrum of **5.6a**

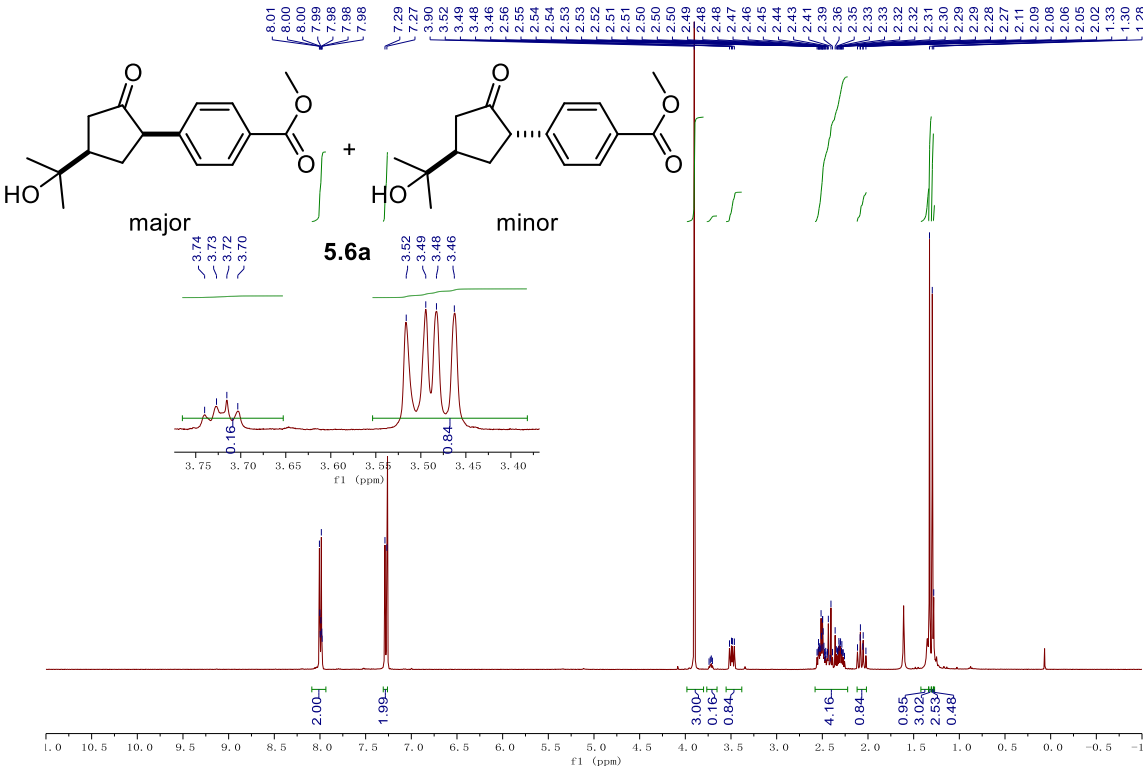


Figure 5.64 ^{13}C-NMR Spectrum of **5.6a**

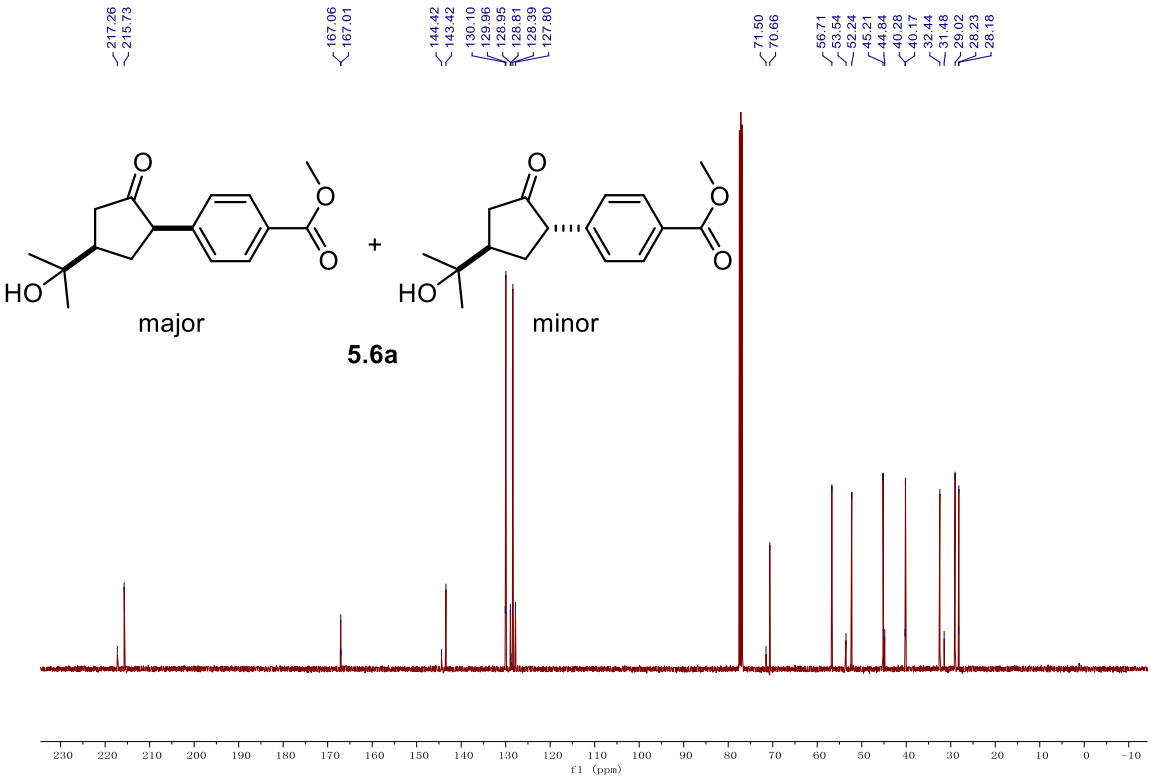


Figure 5.65 ^{1}H-NMR Spectrum of **5.6b-major**

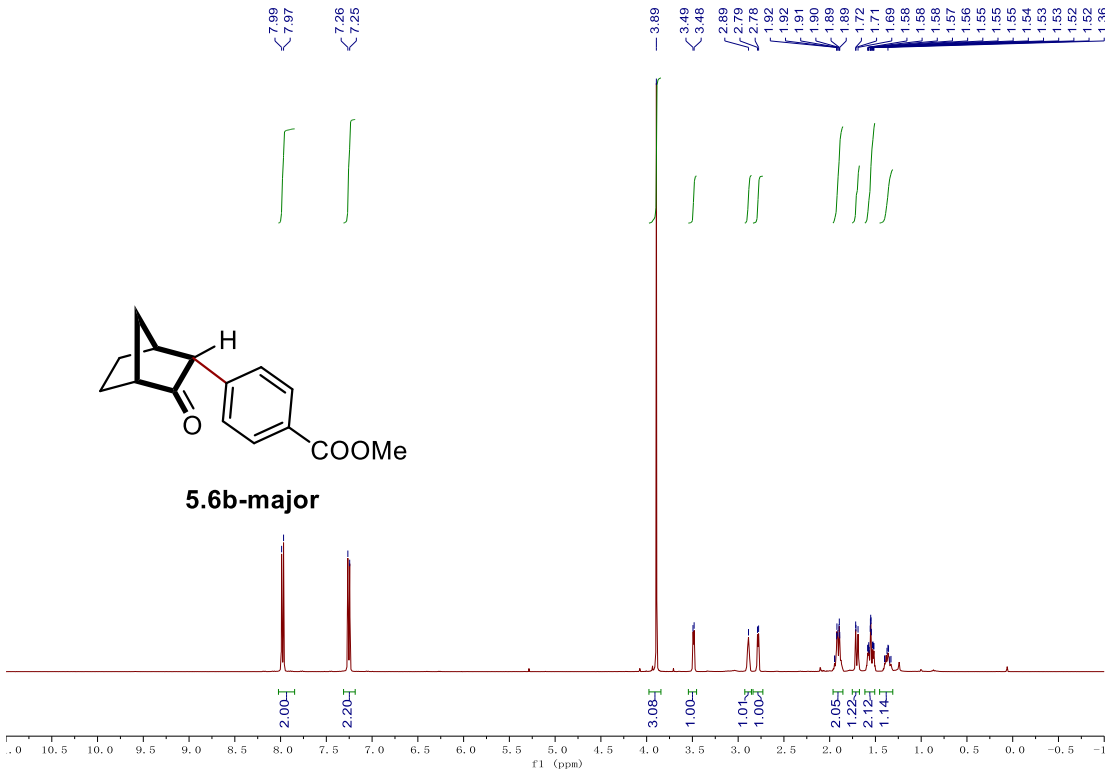


Figure 5.66 ^{13}C-NMR Spectrum of **5.6b-major**

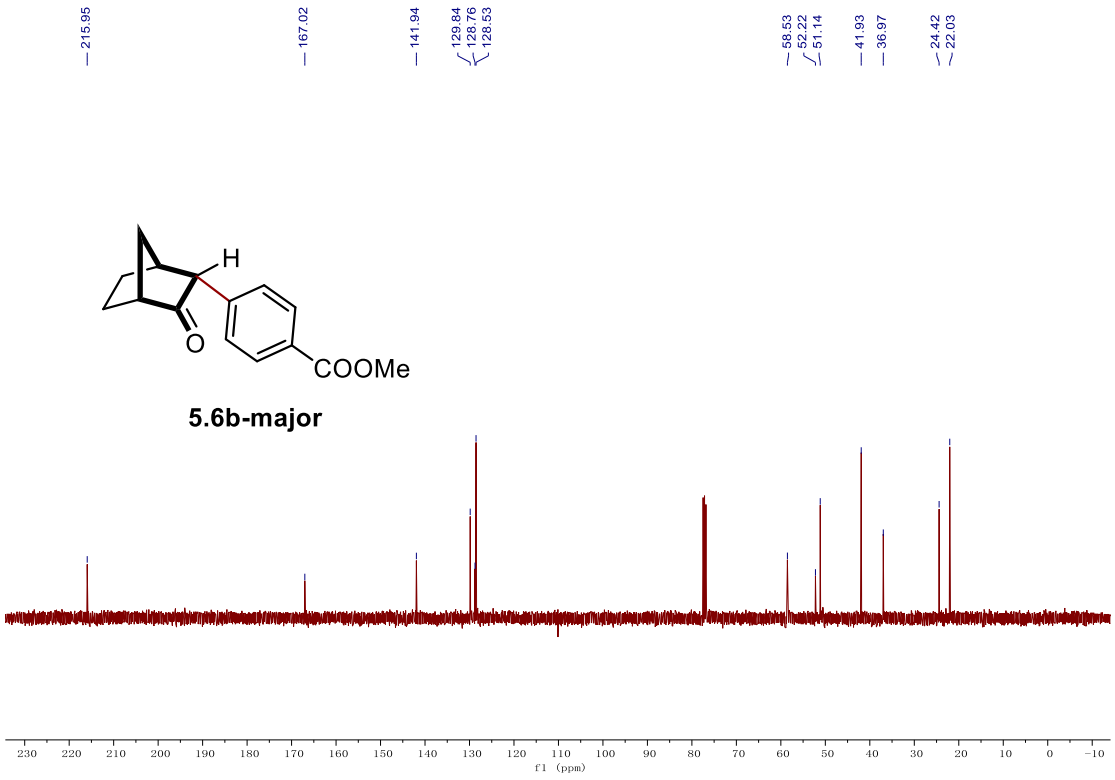


Figure 5.67 ^{1}H-NMR Spectrum of **5.6b-minor**

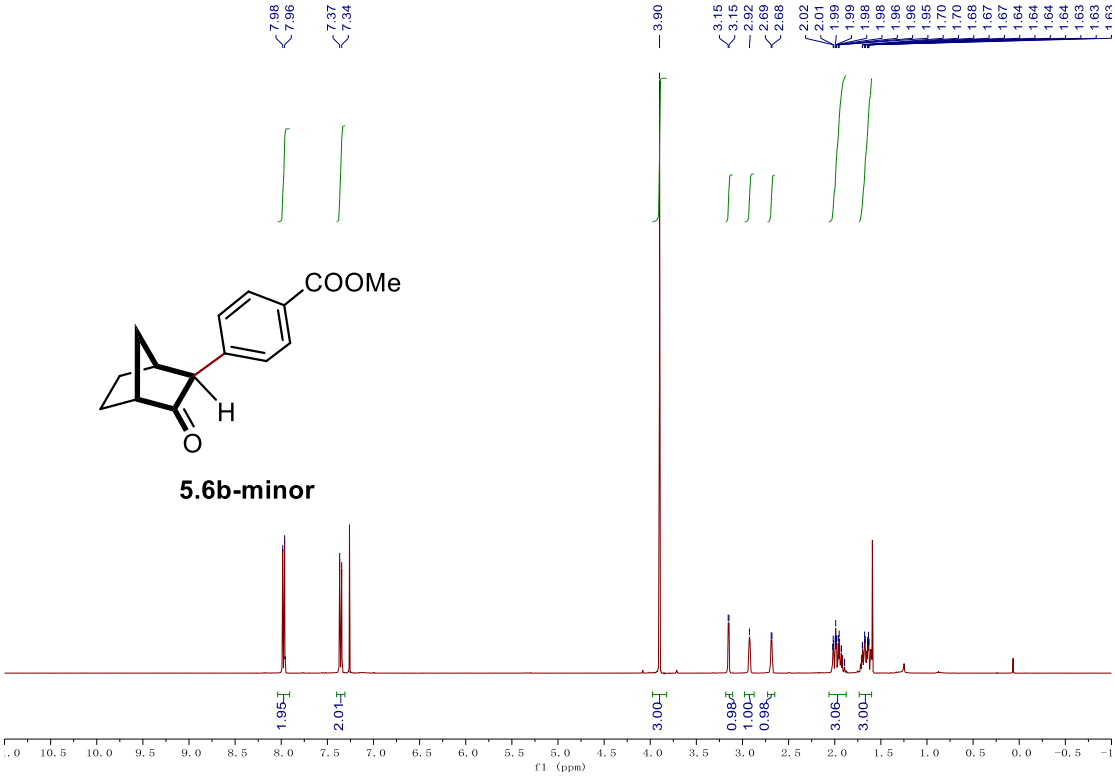


Figure 5.68 ^{13}C-NMR Spectrum of **5.6b-minor**

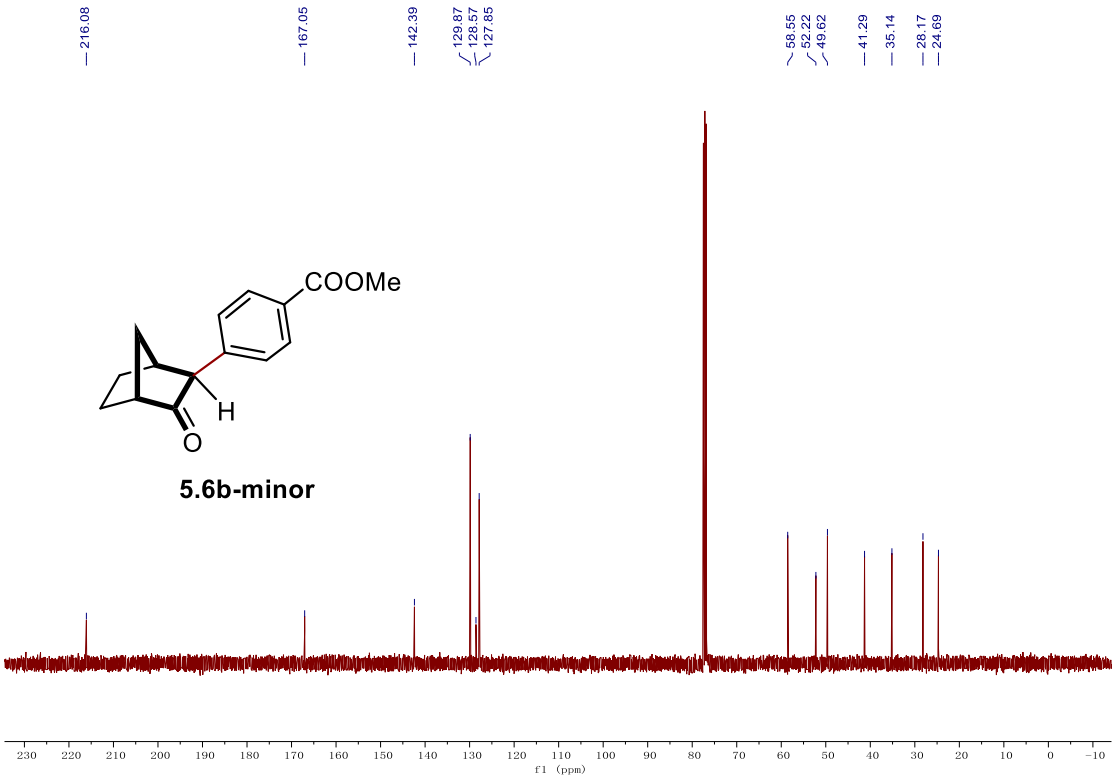


Figure 5.69 NOESY(1D) (CD_3CN) Spectrum of **5.6b-major**

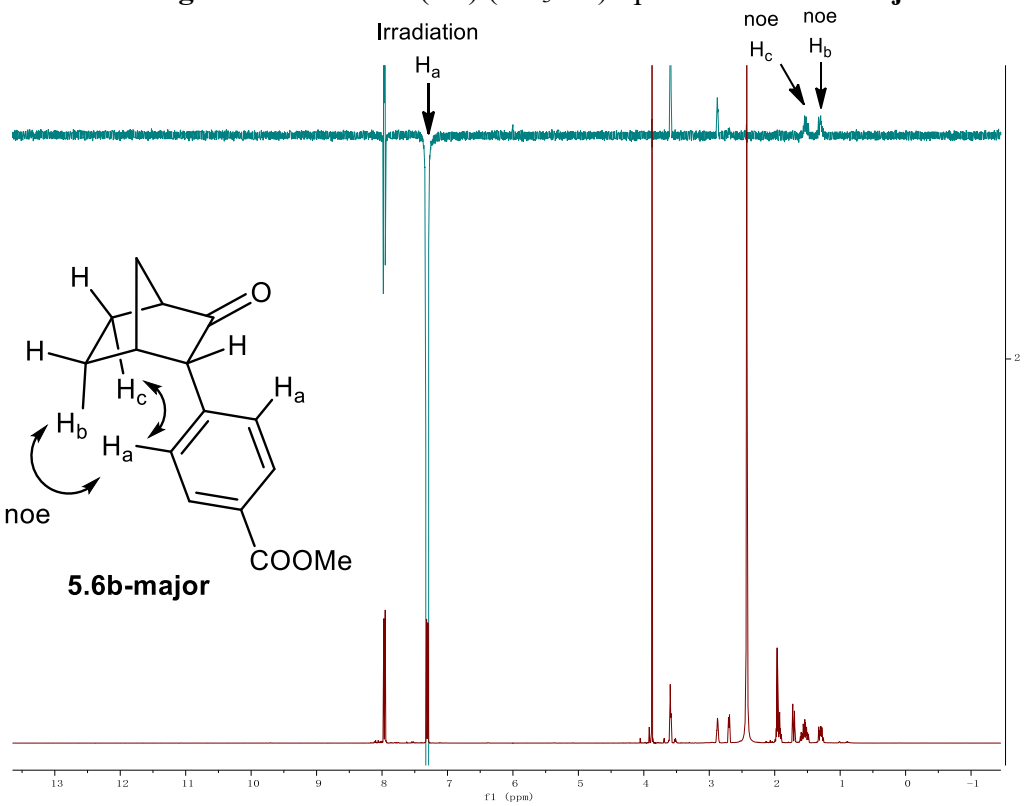


Figure 5.70 COSY (CD_3CN) Spectrum of **5.6b-major**

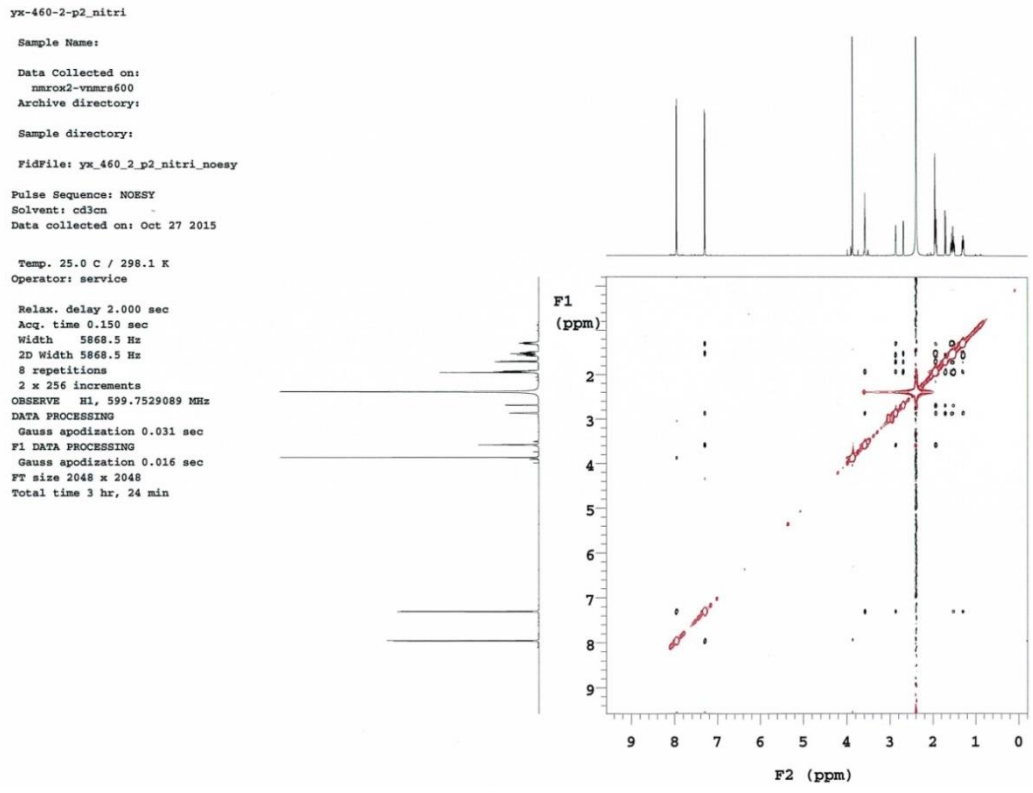


Figure 5.70 COSY (CD_3CN) Spectrum of **5.6b-major** (continued)

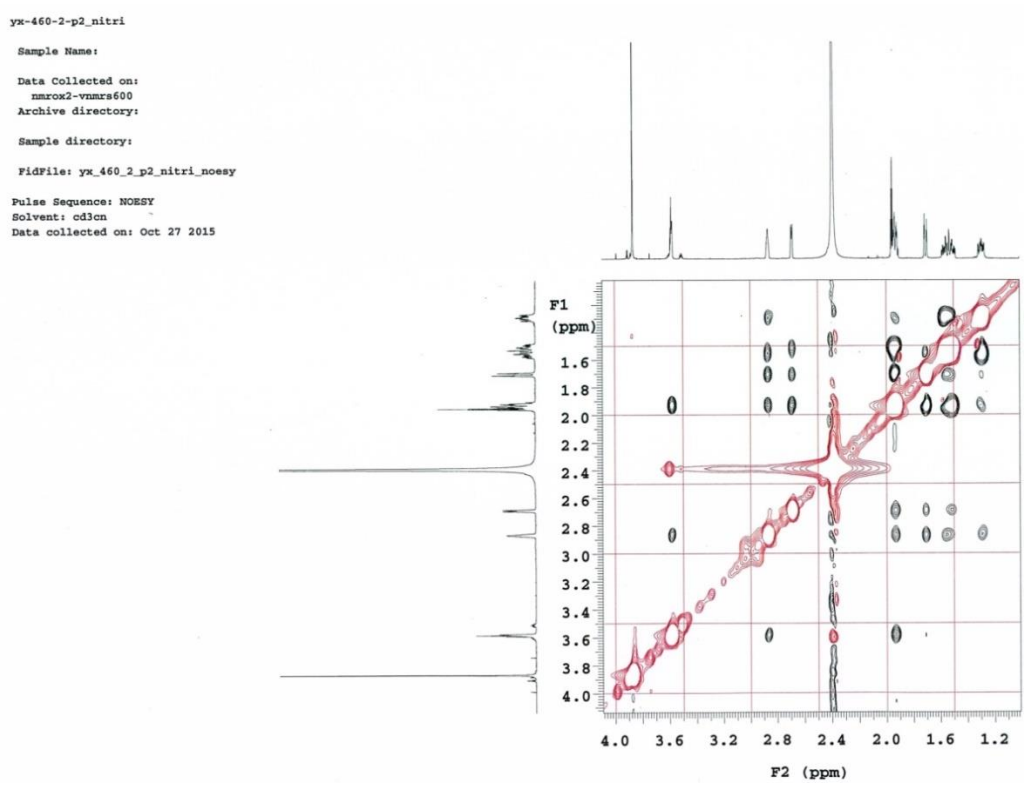


Figure 5.71 HSQC (CD_3CN) Spectrum of **5.6b-major**

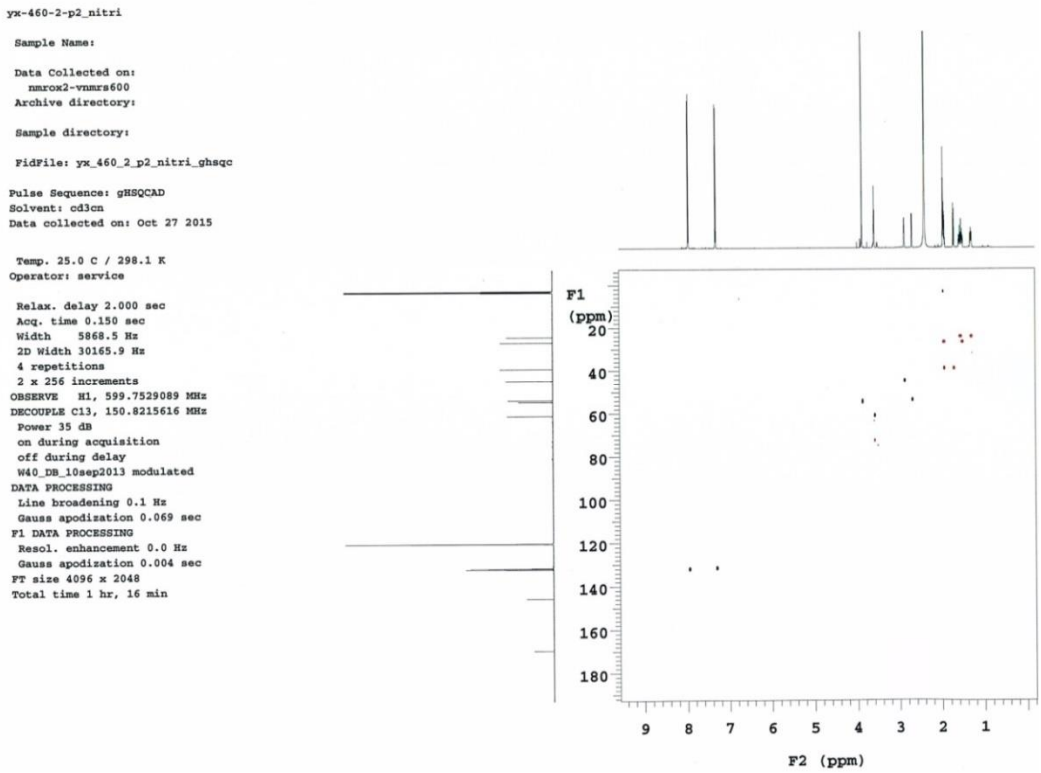


Figure 5.71 HSQC (CD_3CN) Spectrum of **5.6b-major** (continued)

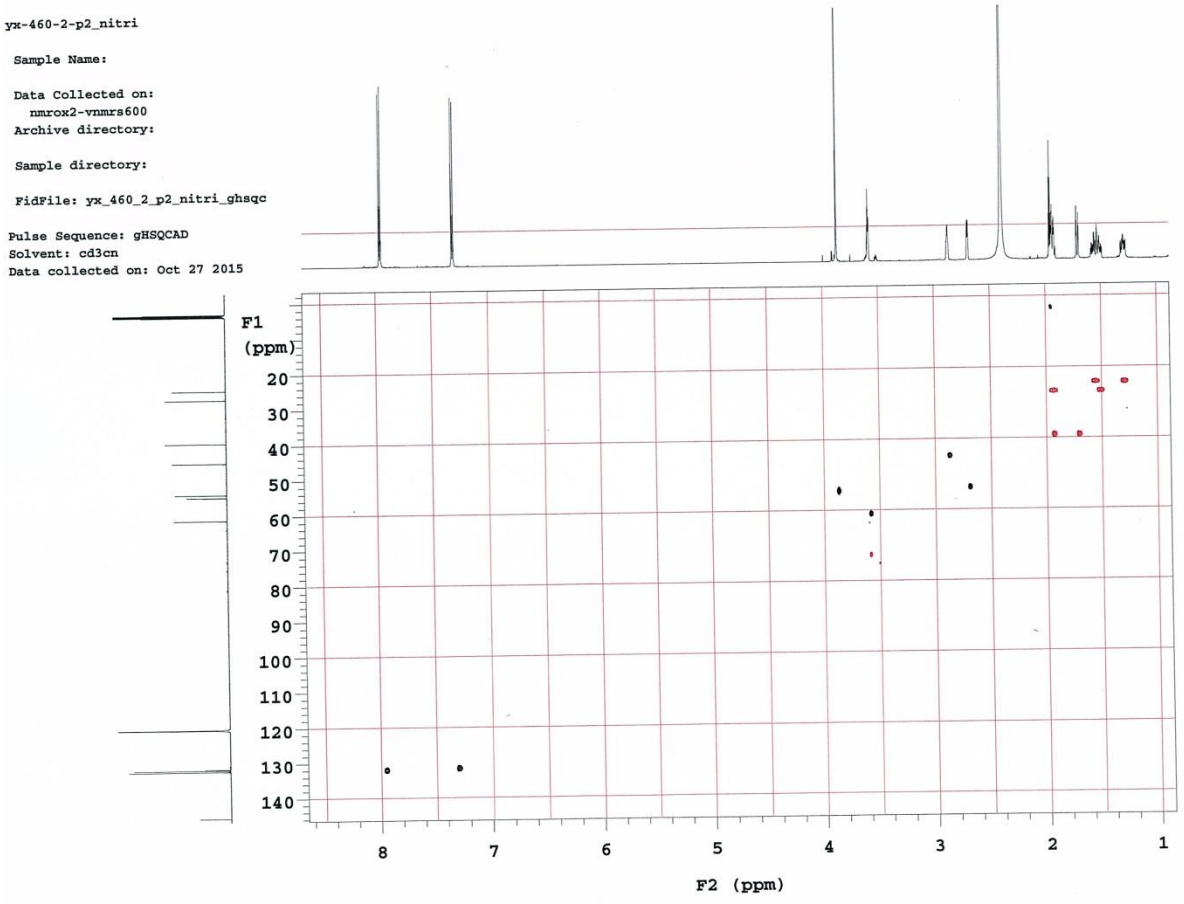


Figure 5.72 ^{1}H-NMR Spectrum of **5.6c**

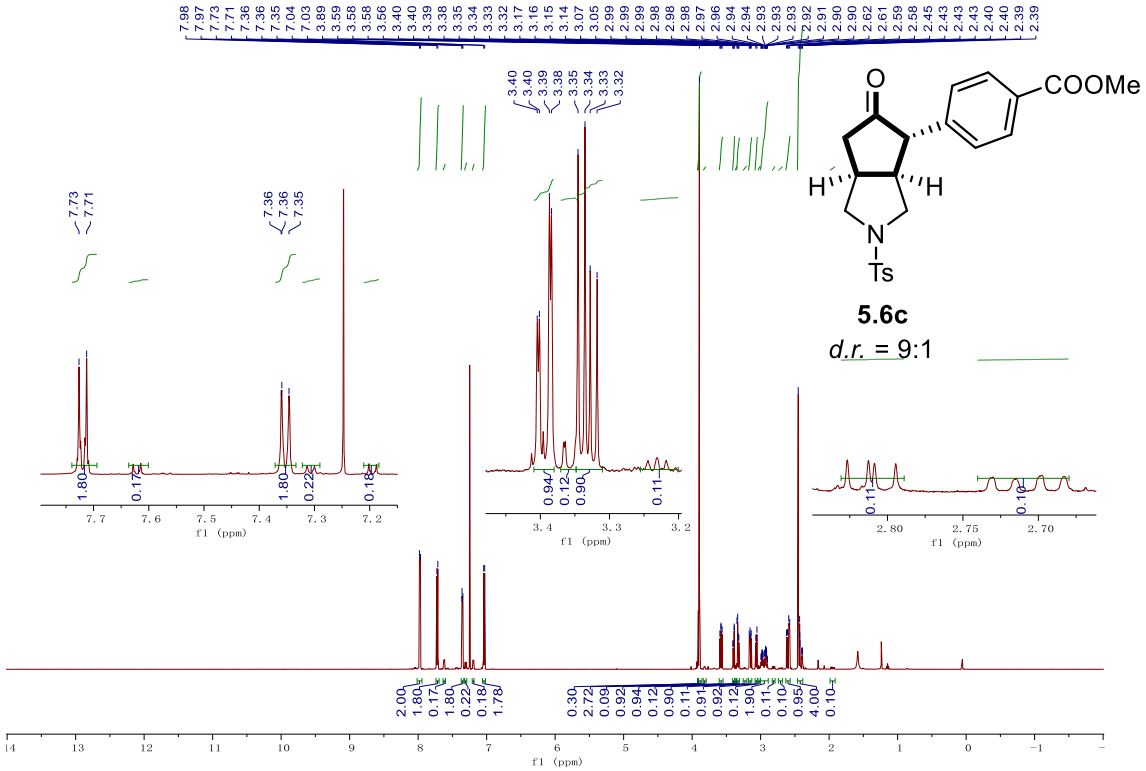


Figure 5.73 ^{13}C-NMR Spectrum of **5.6c**

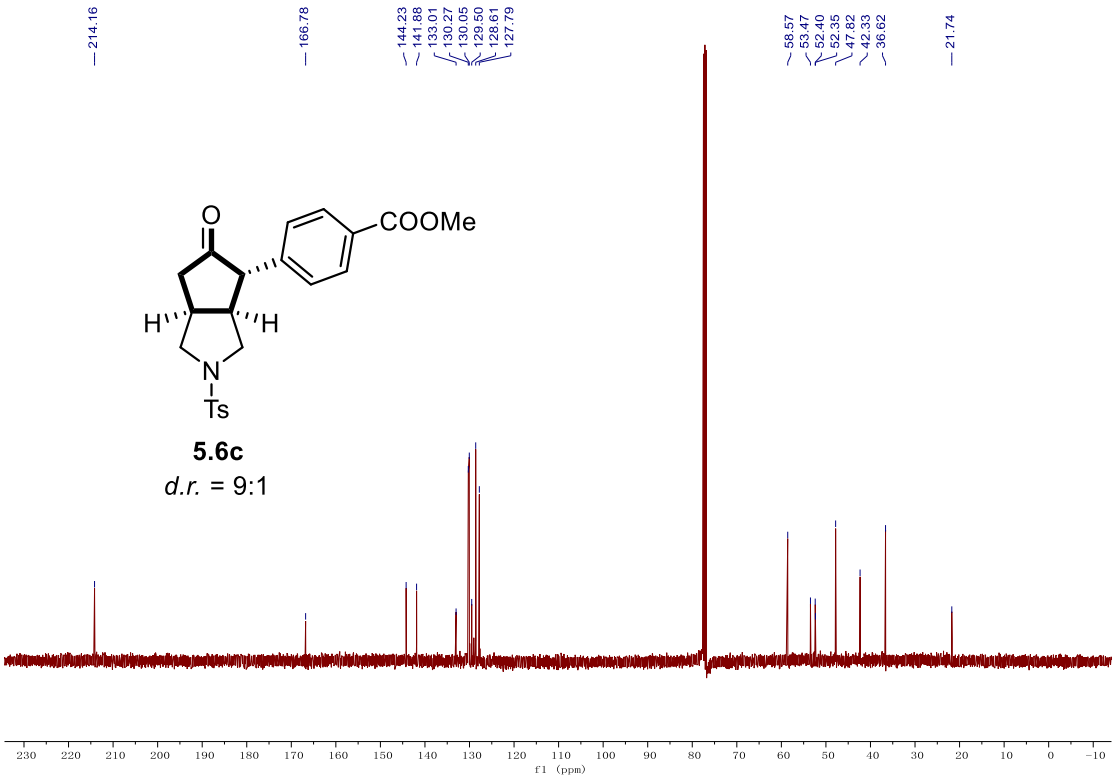


Figure 5.74 NOESY(1D) ($CDCl_3$) Spectrum of **5.6c-major**

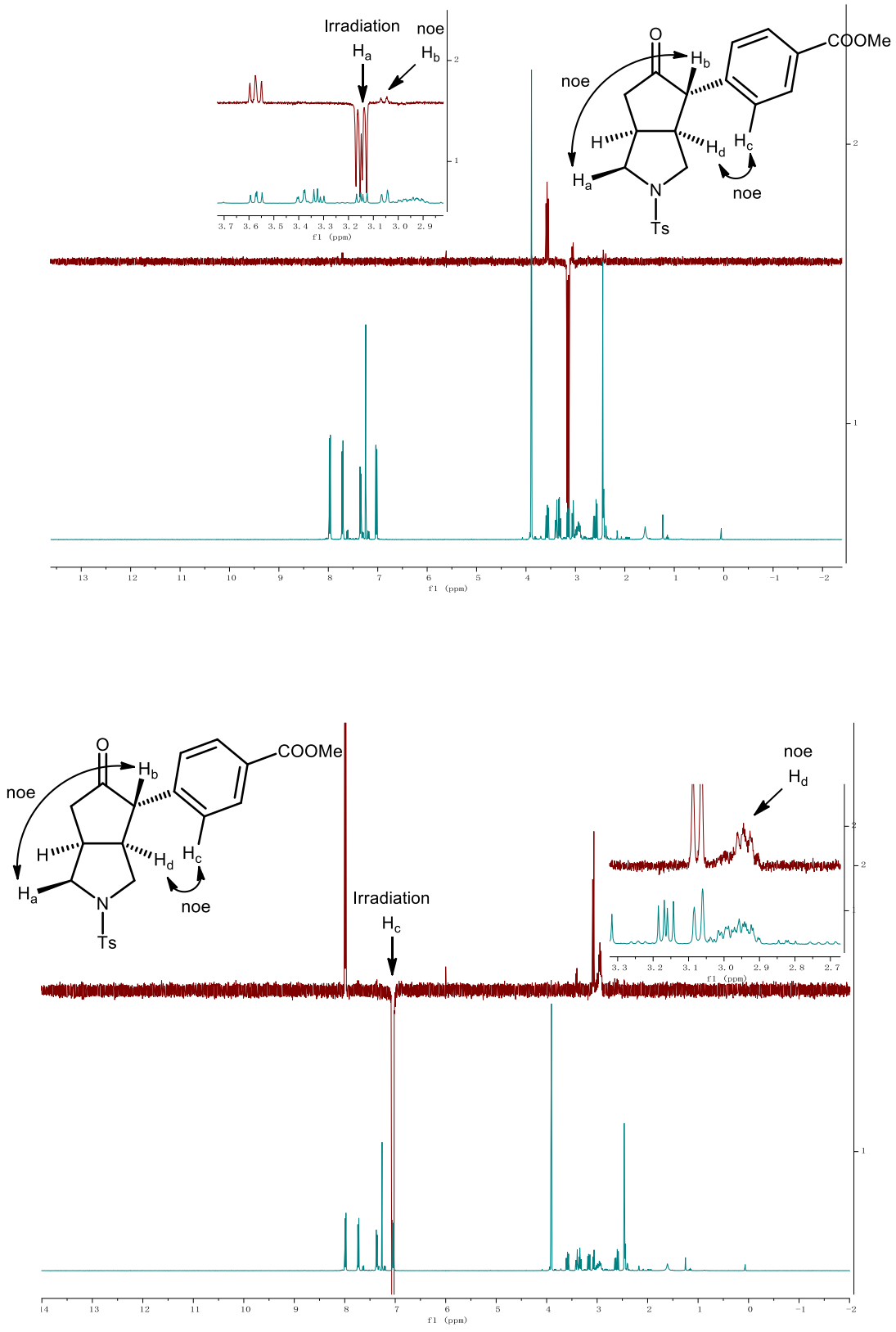
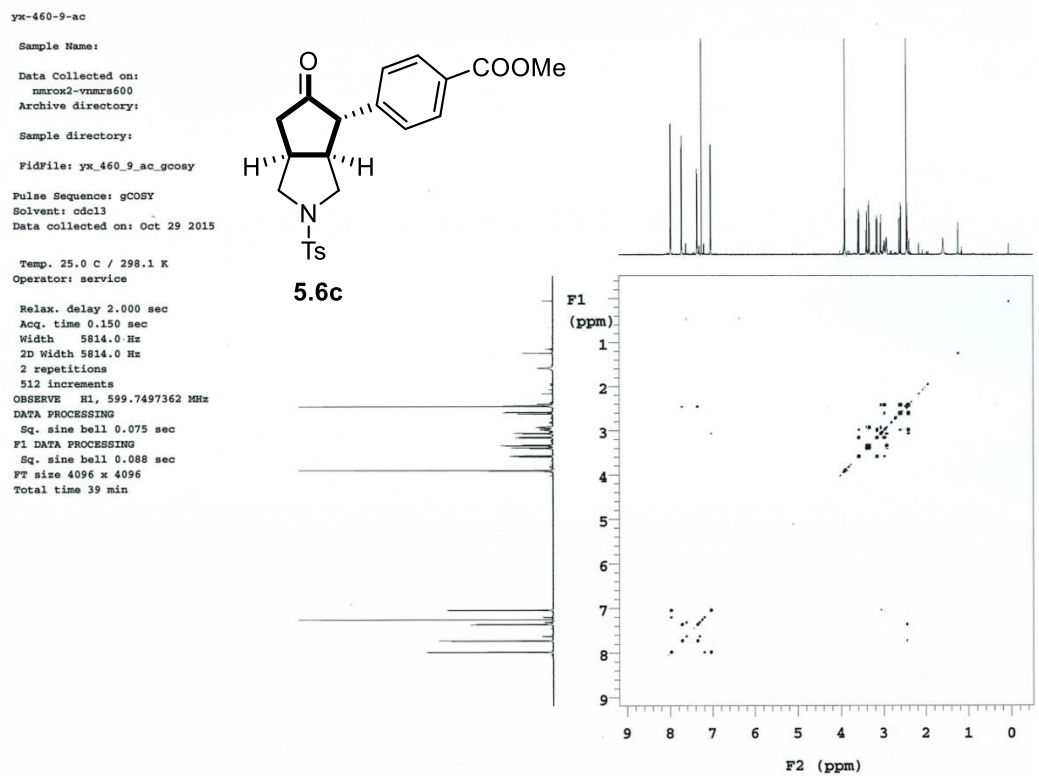


Figure 5.75 COSY ($CDCl_3$) Spectrum of **5.6c-major**



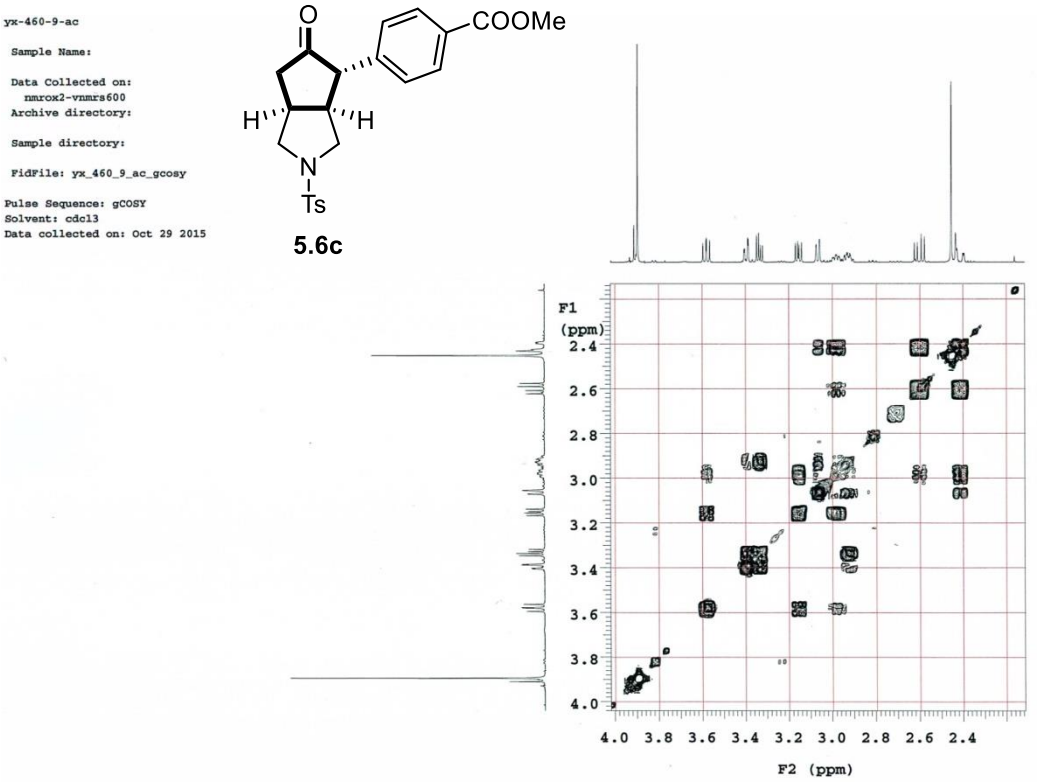


Figure 5.76 ^{1}H-NMR Spectrum of **5.6d**

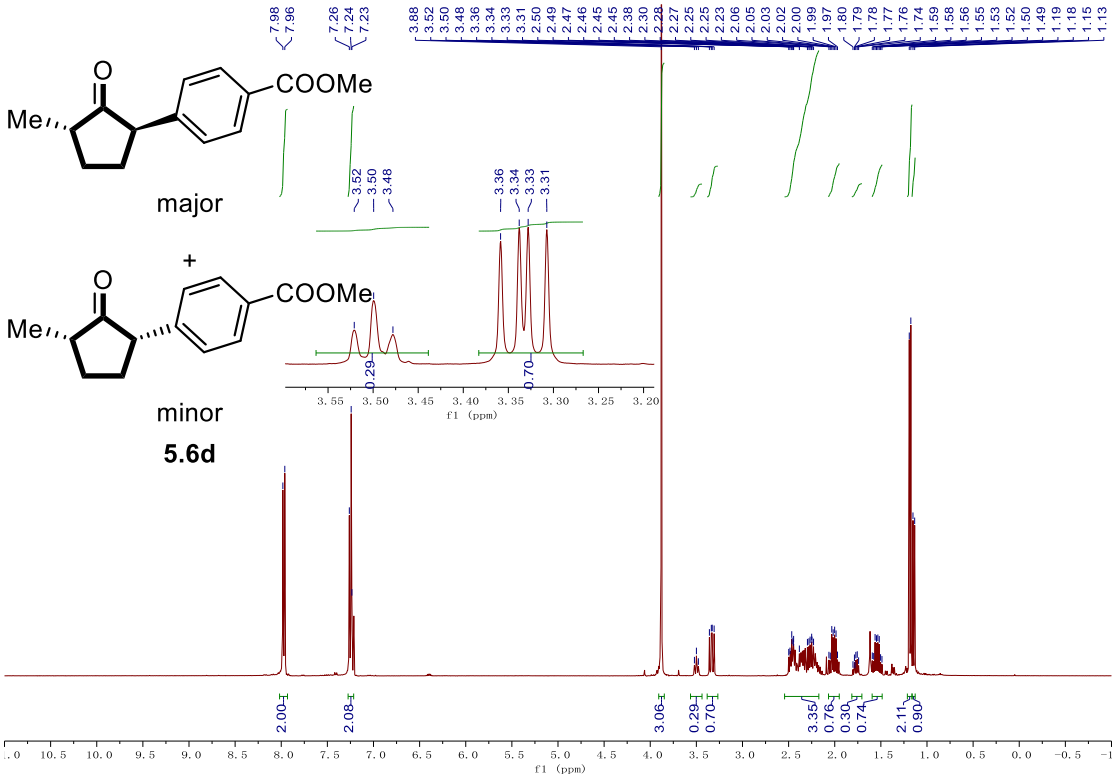


Figure 5.77 ^{13}C-NMR Spectrum of **5.6d**

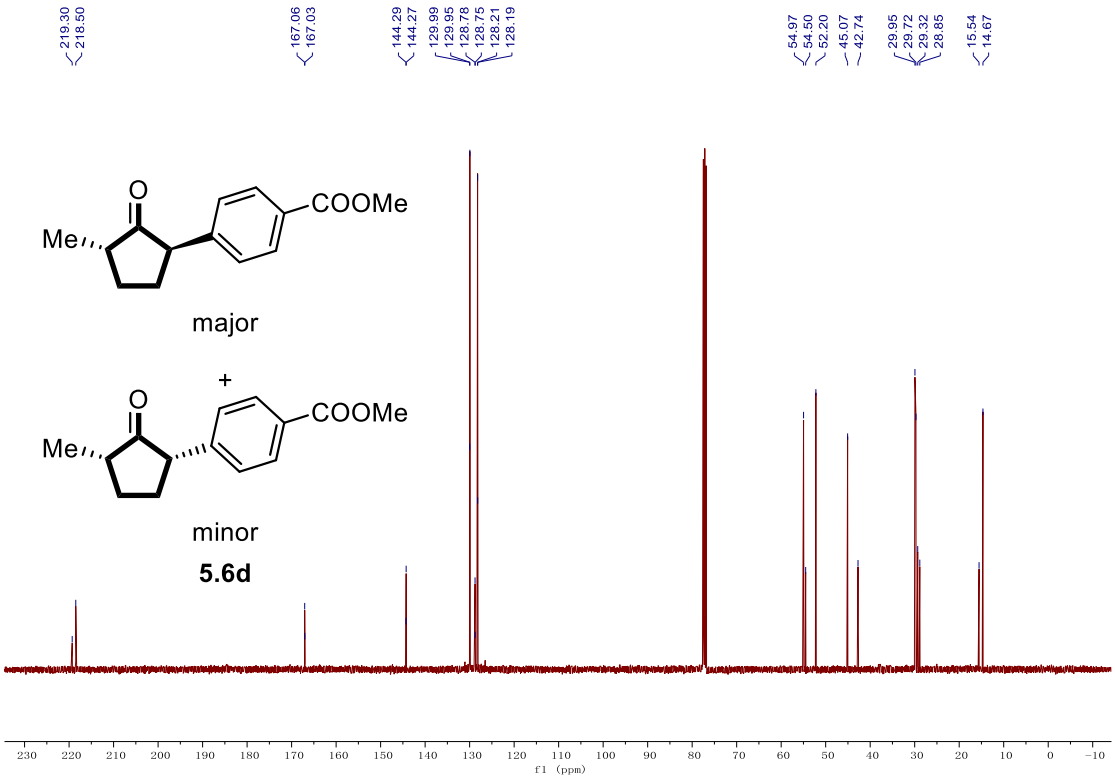
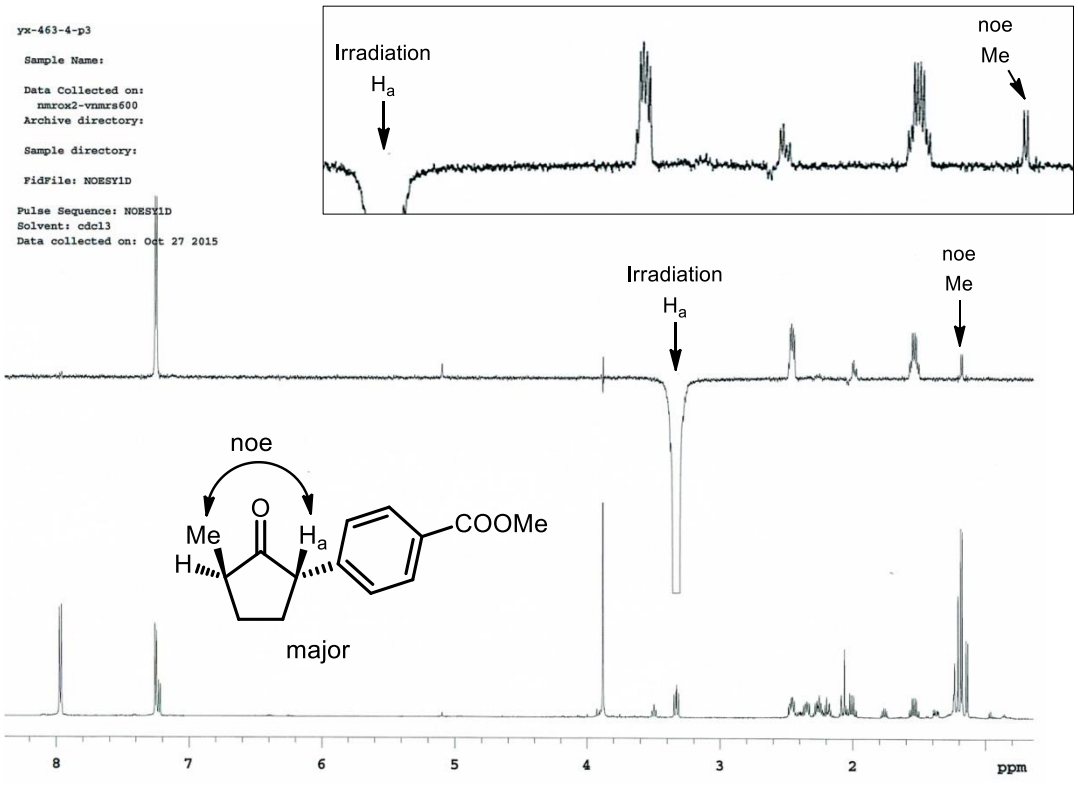


Figure 5.78 NOESY(1D) ($CDCl_3$) Spectrum of **5.6d-major** and **5.6d-minor**



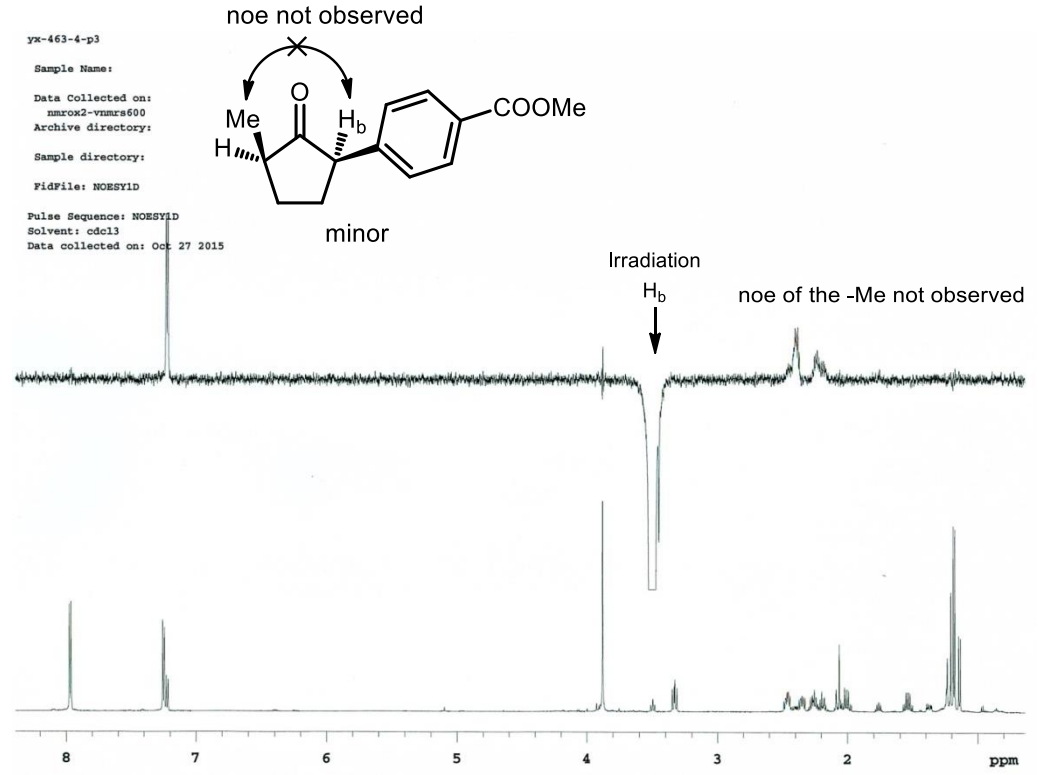


Figure 5.79 ^{1}H-NMR Spectrum of **5.6ea-major**

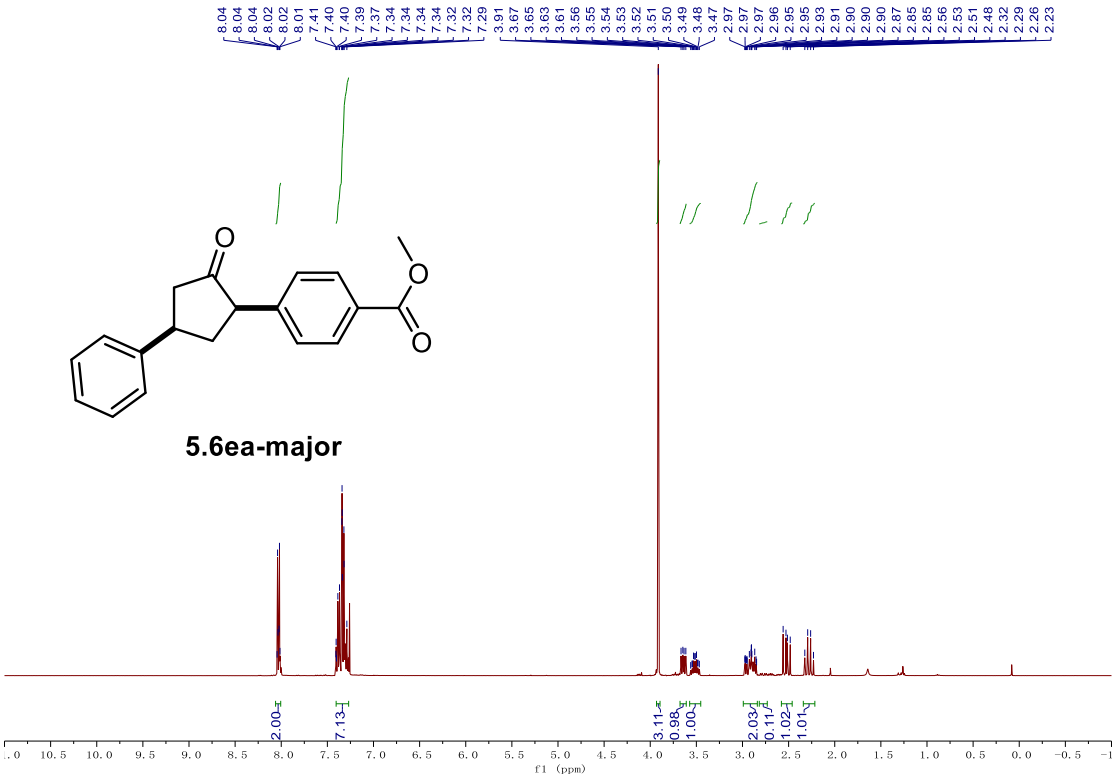


Figure 5.80 ^{13}C-NMR Spectrum of **5.6ea-major**

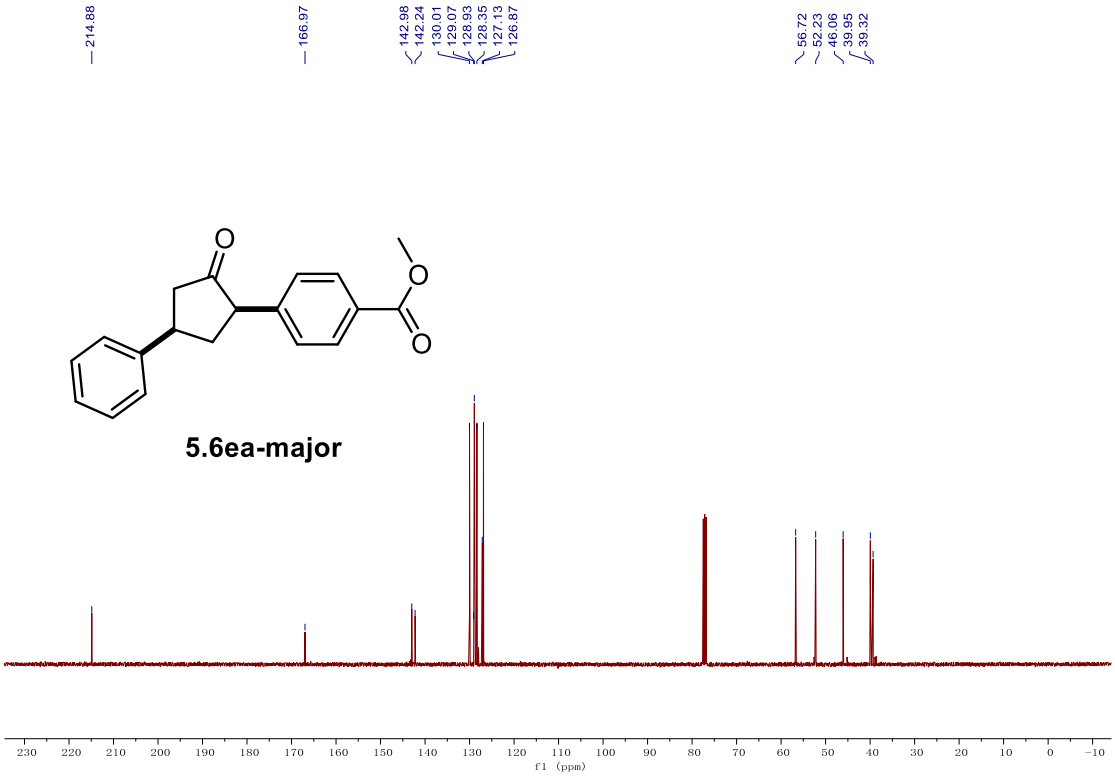


Figure 5.81 ^{1}H-NMR Spectrum of **5.6eb**

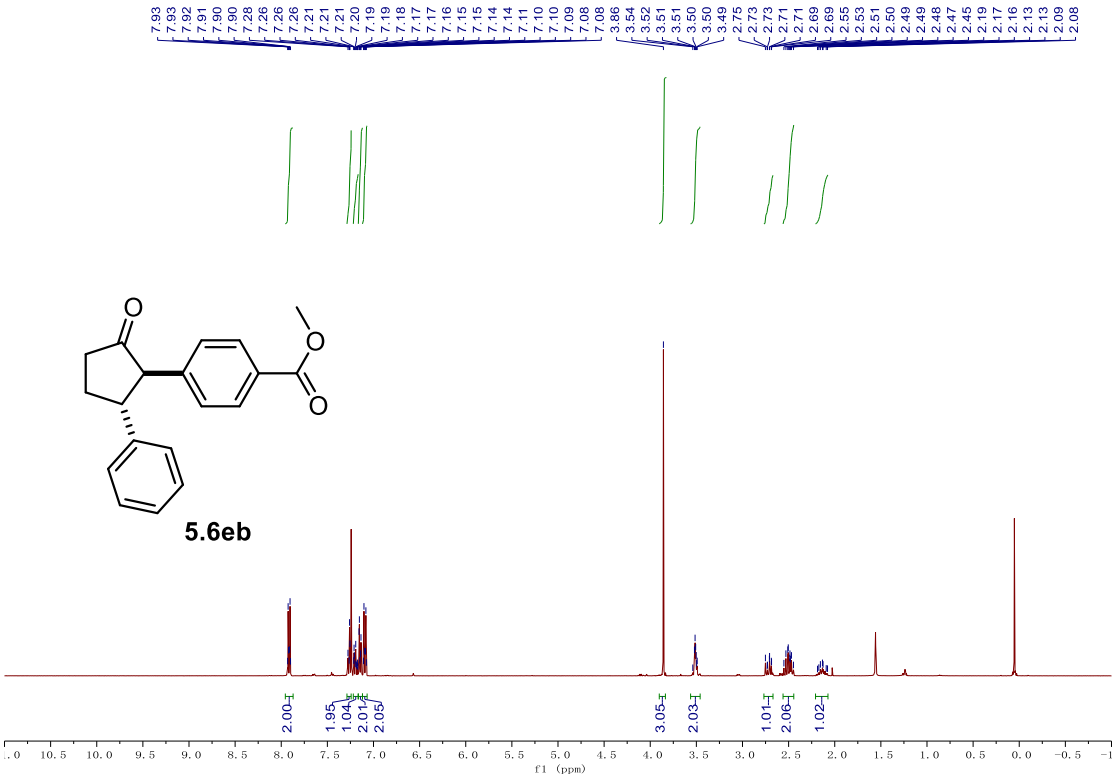


Figure 5.82 ^{13}C-NMR Spectrum of **5.6eb**

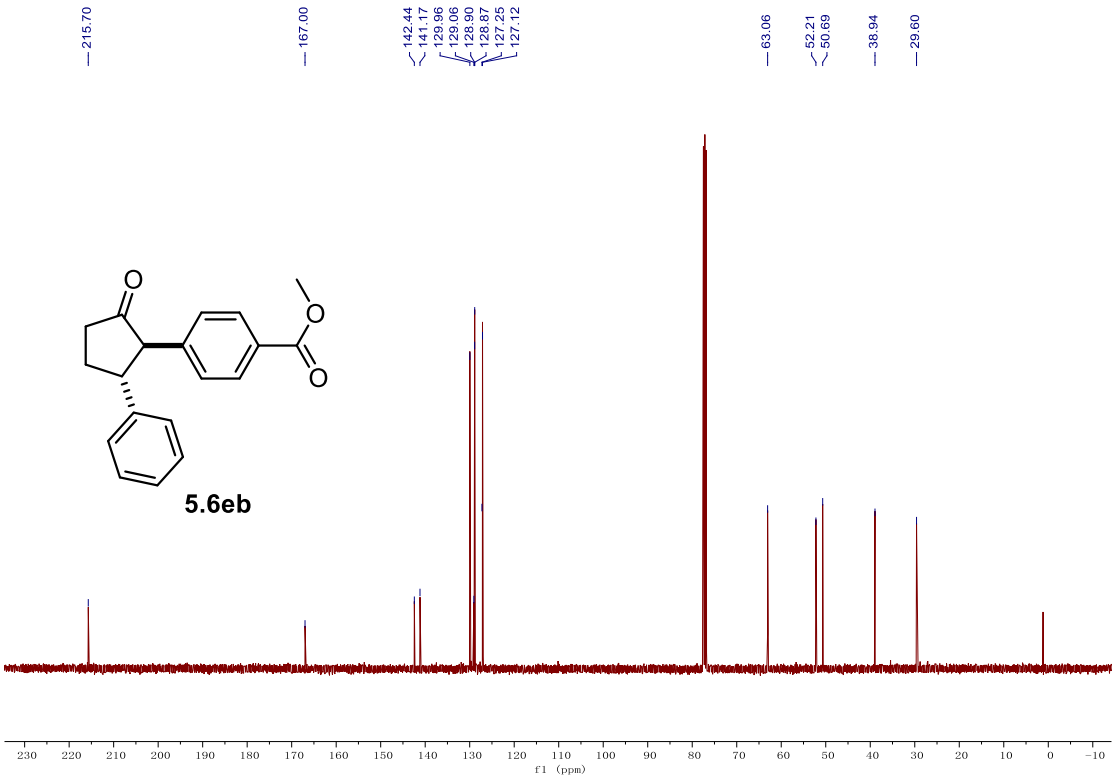


Figure 5.83 ^{1}H-NMR Spectrum of **5.6fa-major**

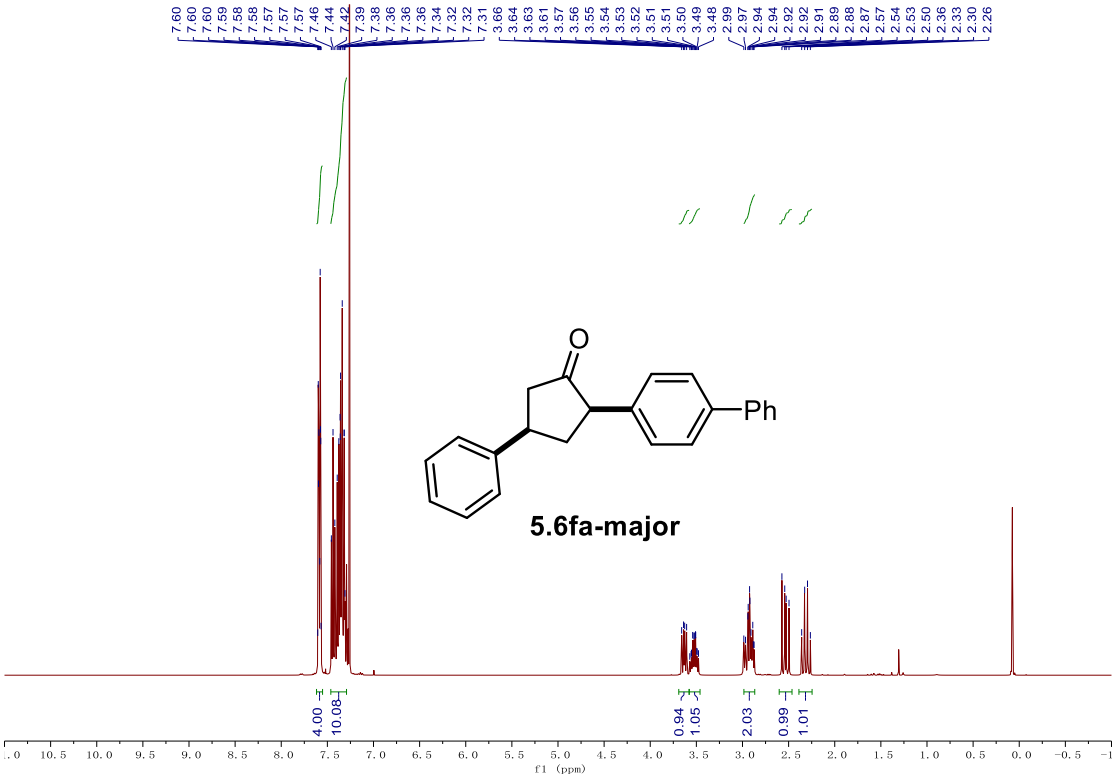


Figure 5.84 ^{13}C-NMR Spectrum of **5.6fa-major**

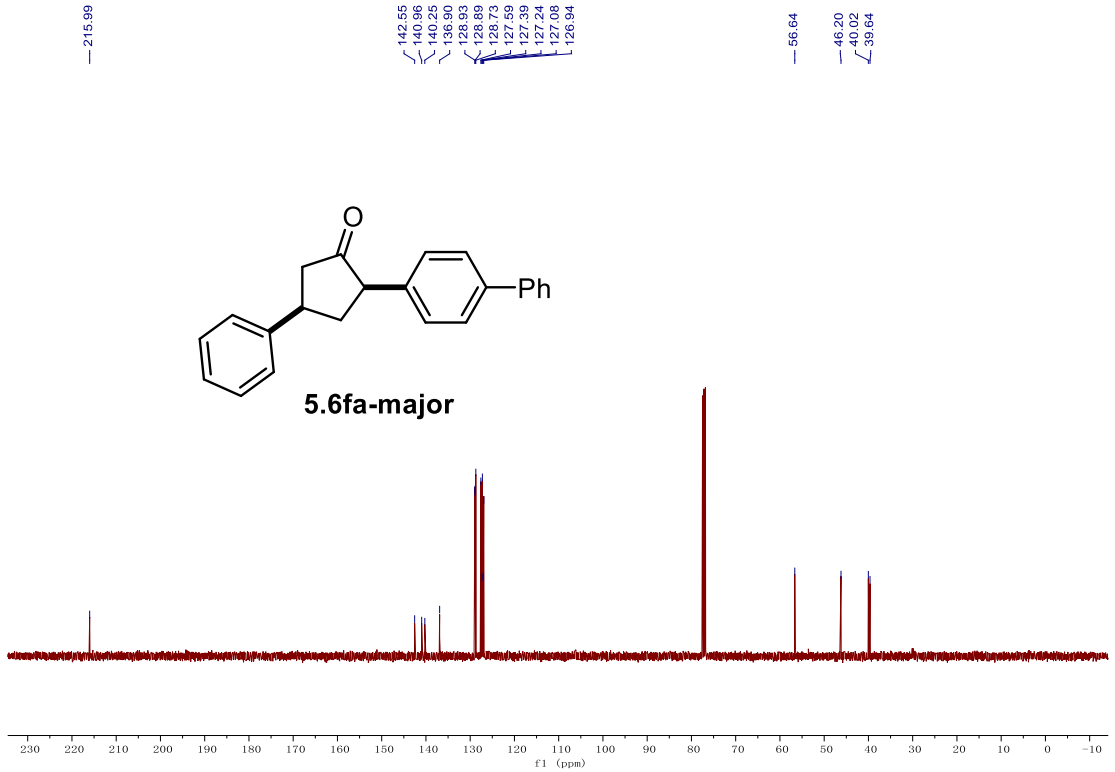


Figure 5.85 ^{1}H-NMR Spectrum of **5.6fb**

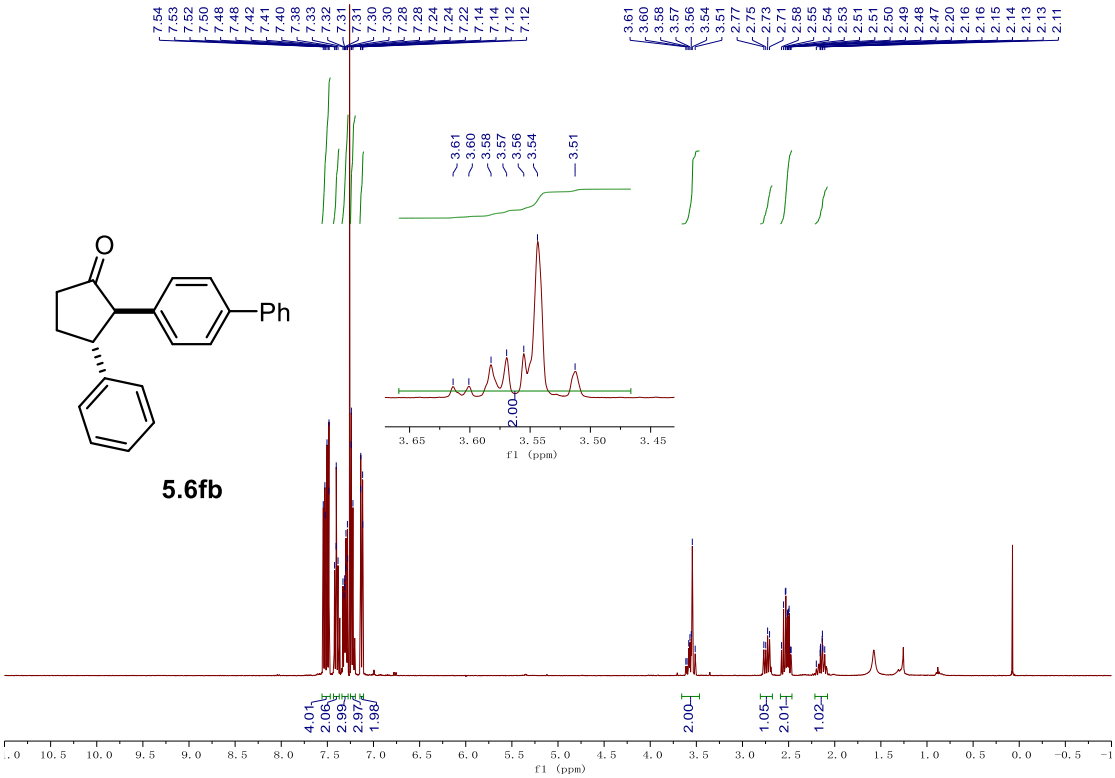


Figure 5.86 ^{13}C-NMR Spectrum of **5.6fb**

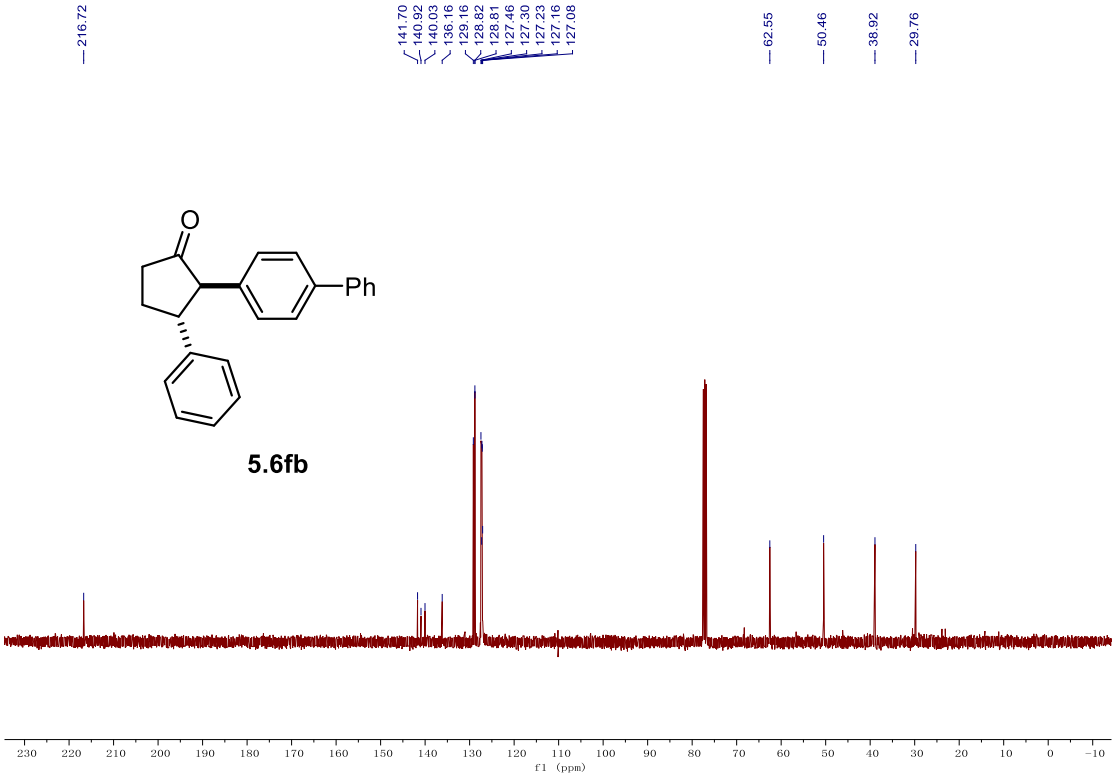


Figure 5.87 ^{1}H-NMR Spectrum of **5.6ga-minor**

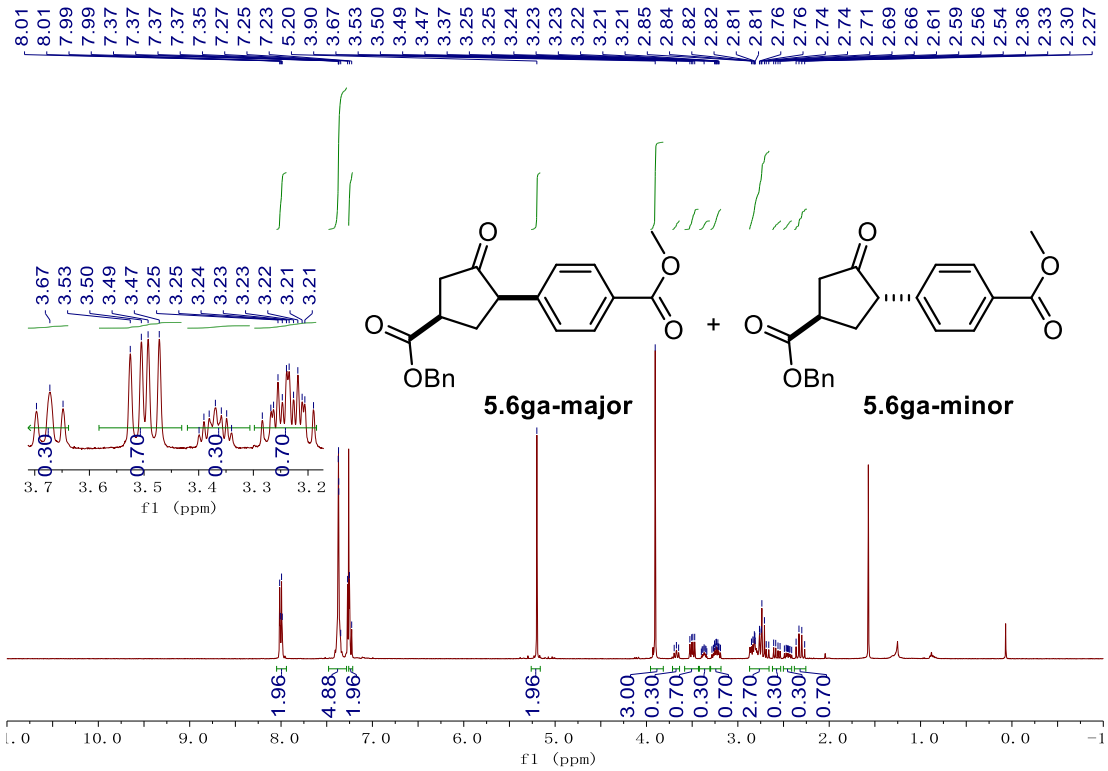


Figure 5.88 ^{13}C-NMR Spectrum of **5.6ga-minor**

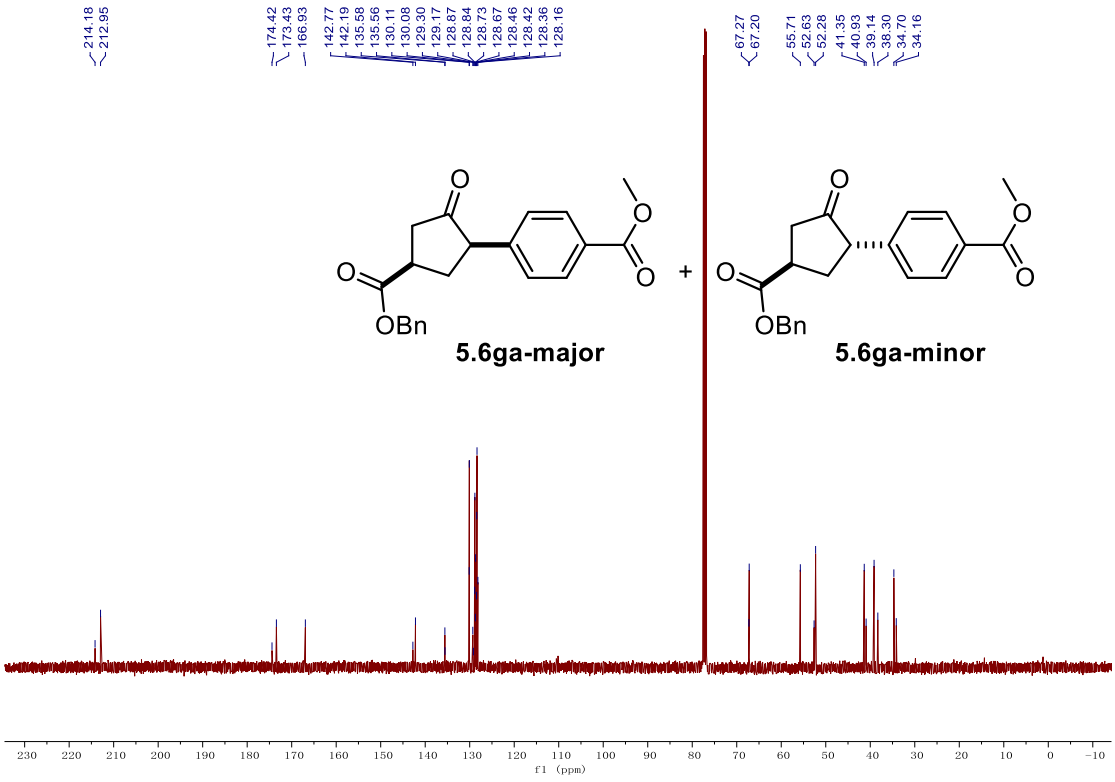


Figure 5.89 ^{1}H-NMR Spectrum of **5.6gb**

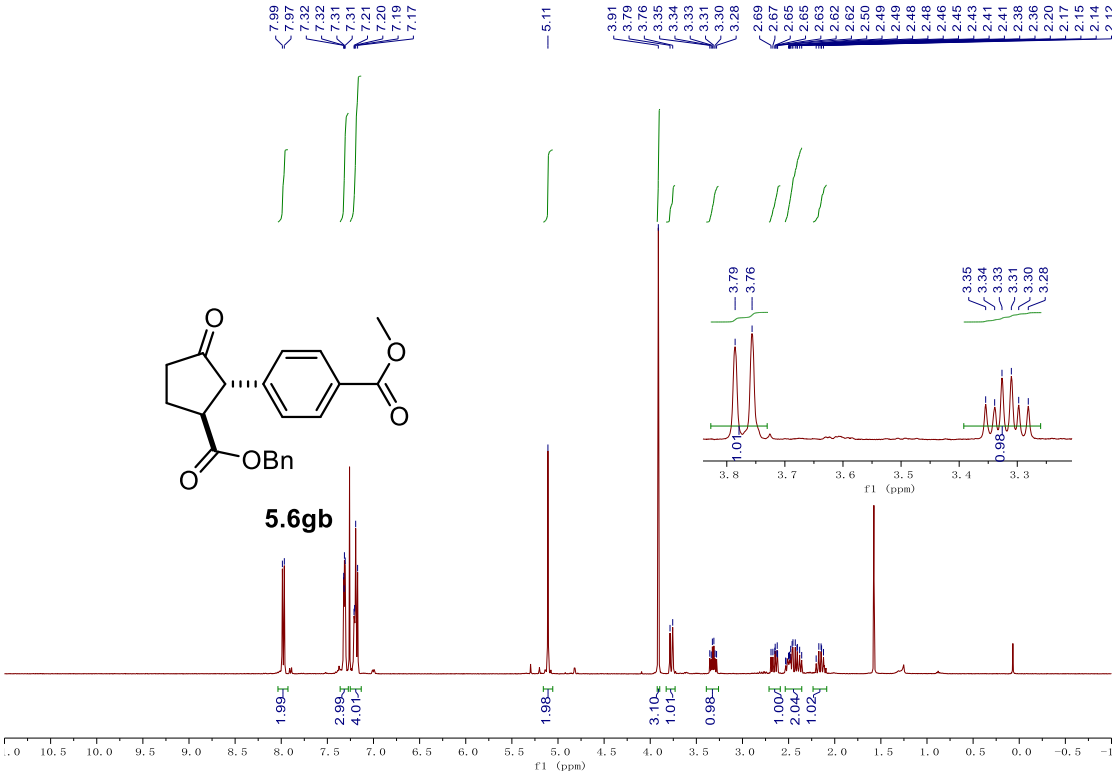


Figure 5.90 ^{13}C-NMR Spectrum of **5.6gb**

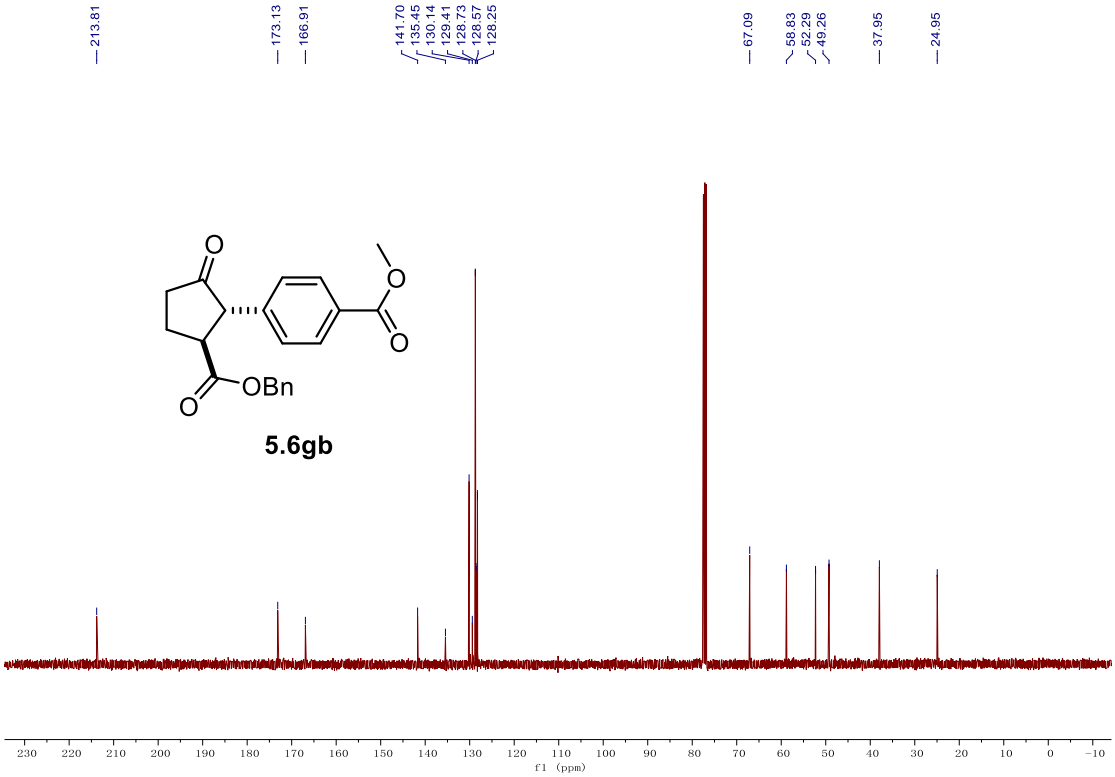


Figure 5.91 ^{1}H-NMR Spectrum of **5.6ha-major**

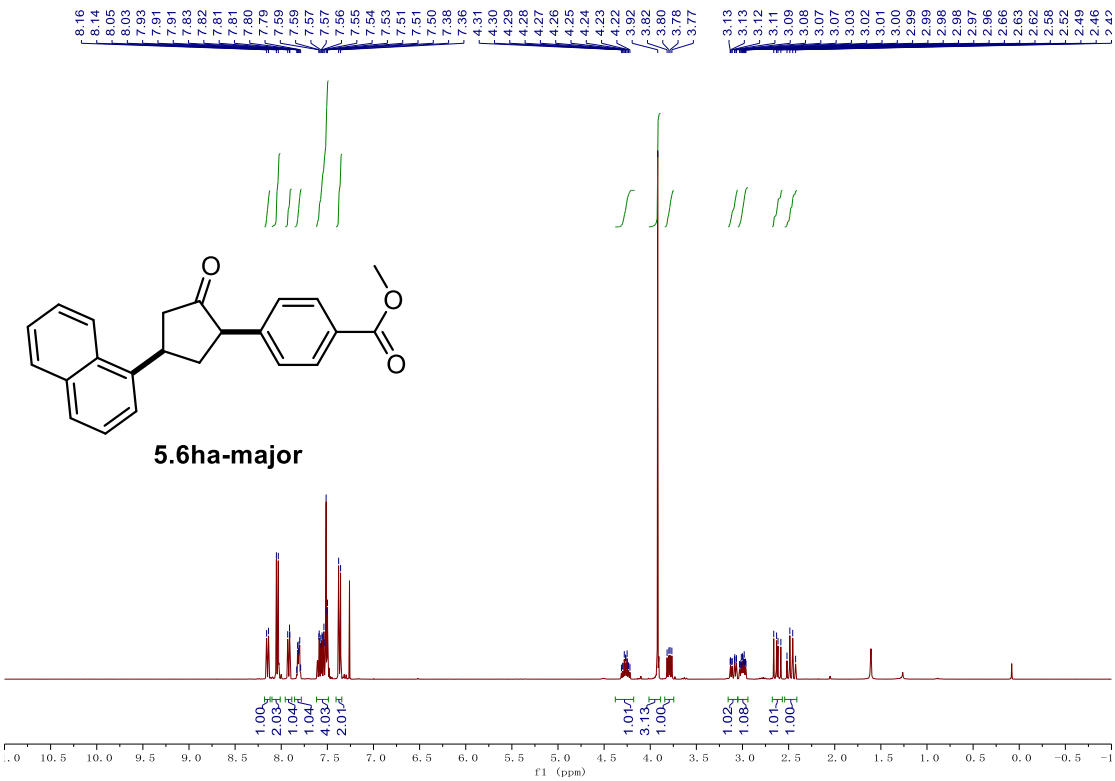


Figure 5.92 ^{13}C-NMR Spectrum of **5.6ha-major**

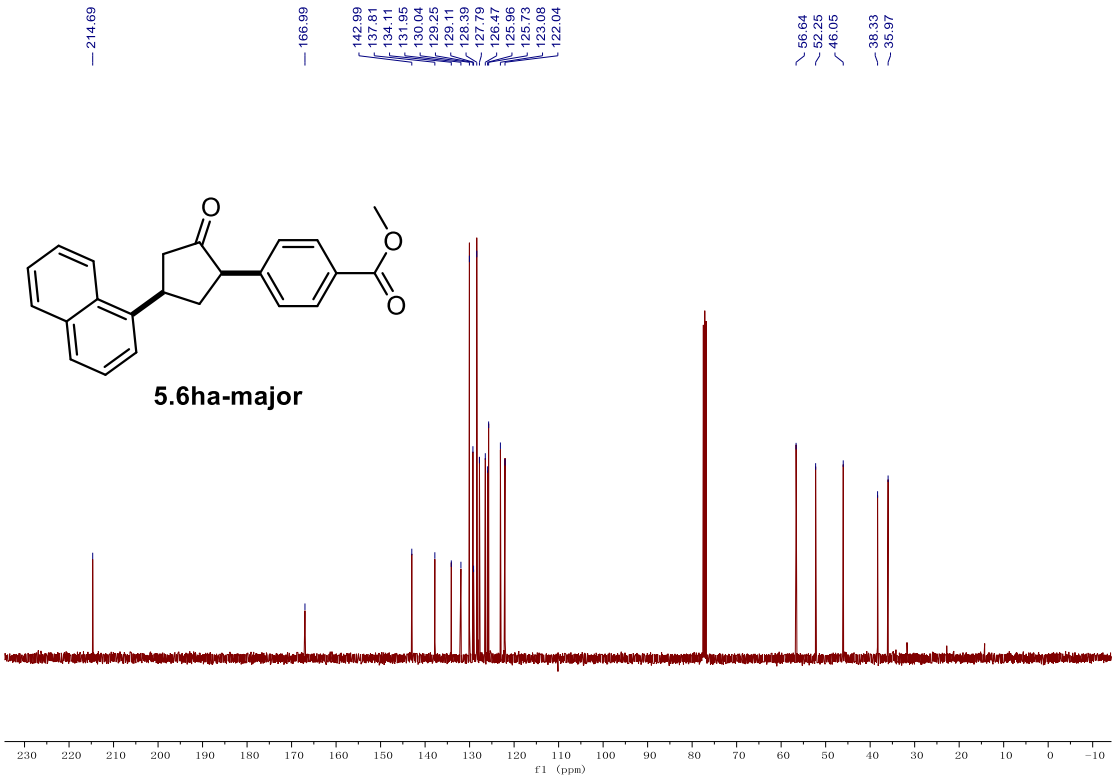


Figure 5.93 ^{1}H-NMR Spectrum of **5.6hb**

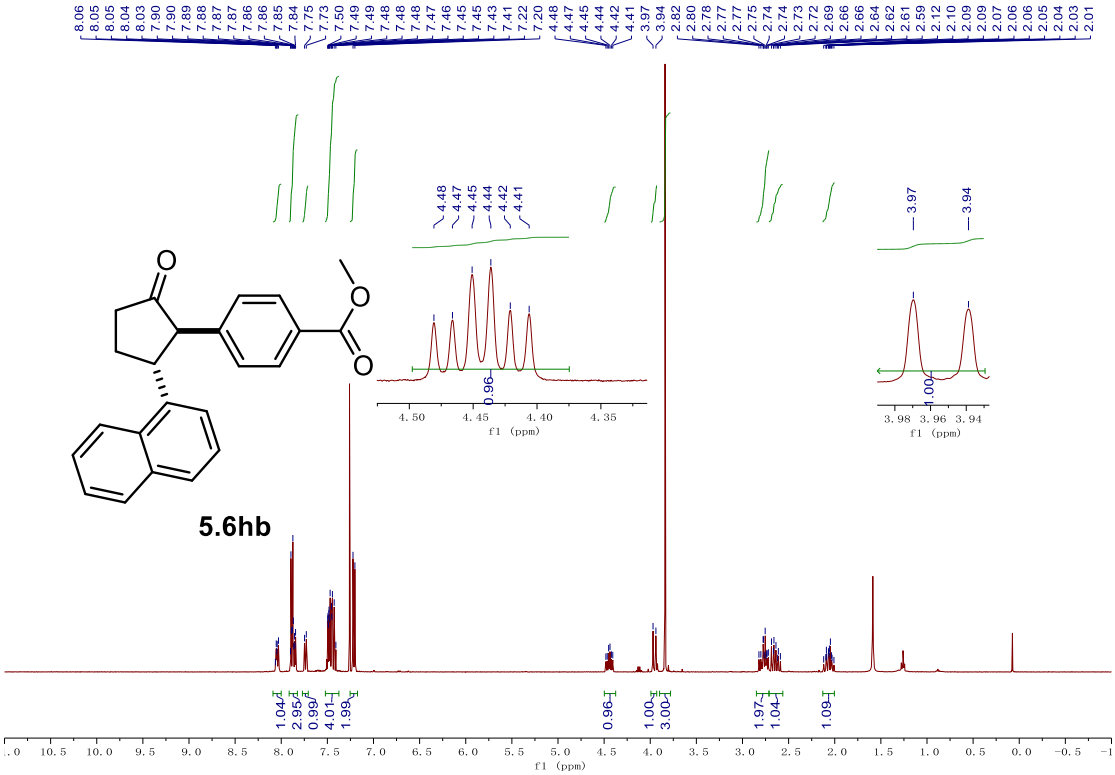


Figure 5.94 ^{13}C-NMR Spectrum of **5.6hb**

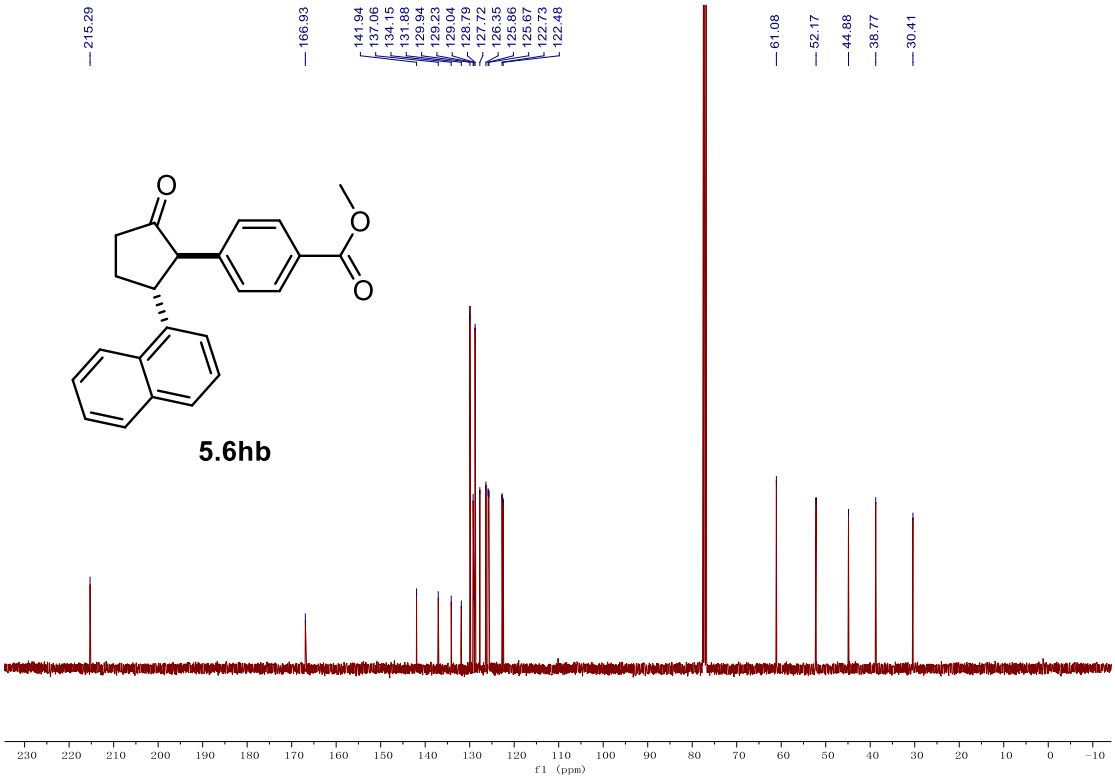


Figure 5.95 ^{1}H-NMR Spectrum of **5.ia-major**

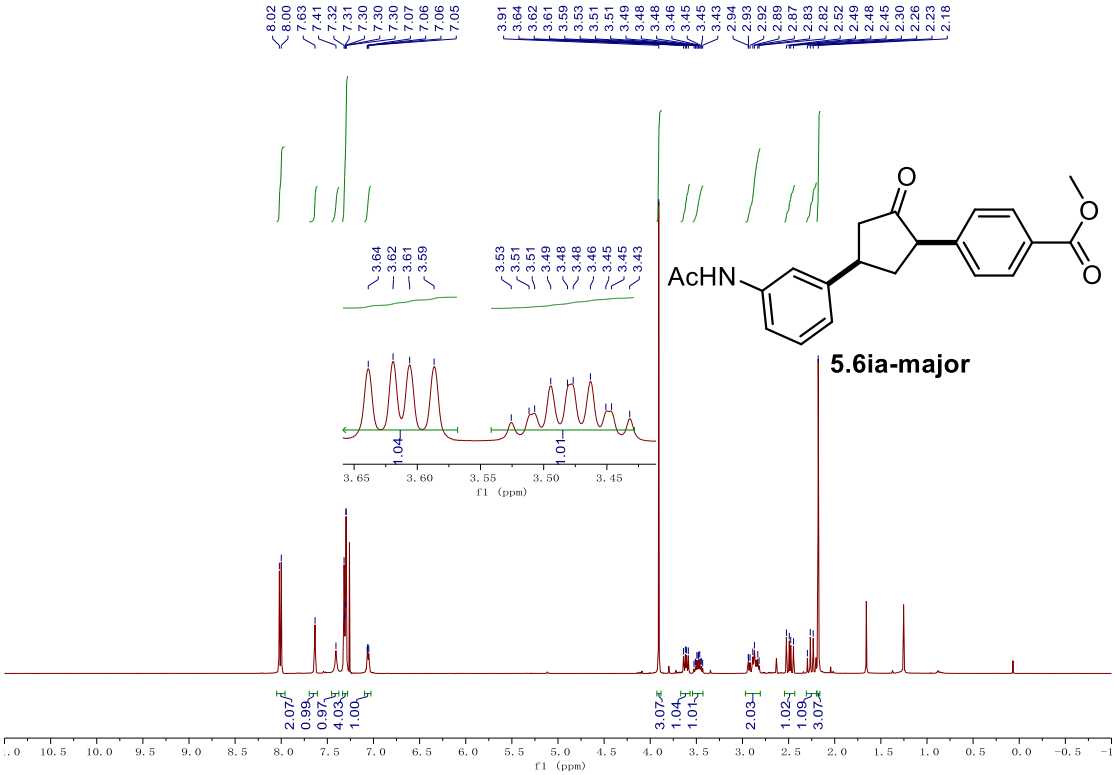


Figure 5.96 ^{13}C-NMR Spectrum of **5.ia-major**

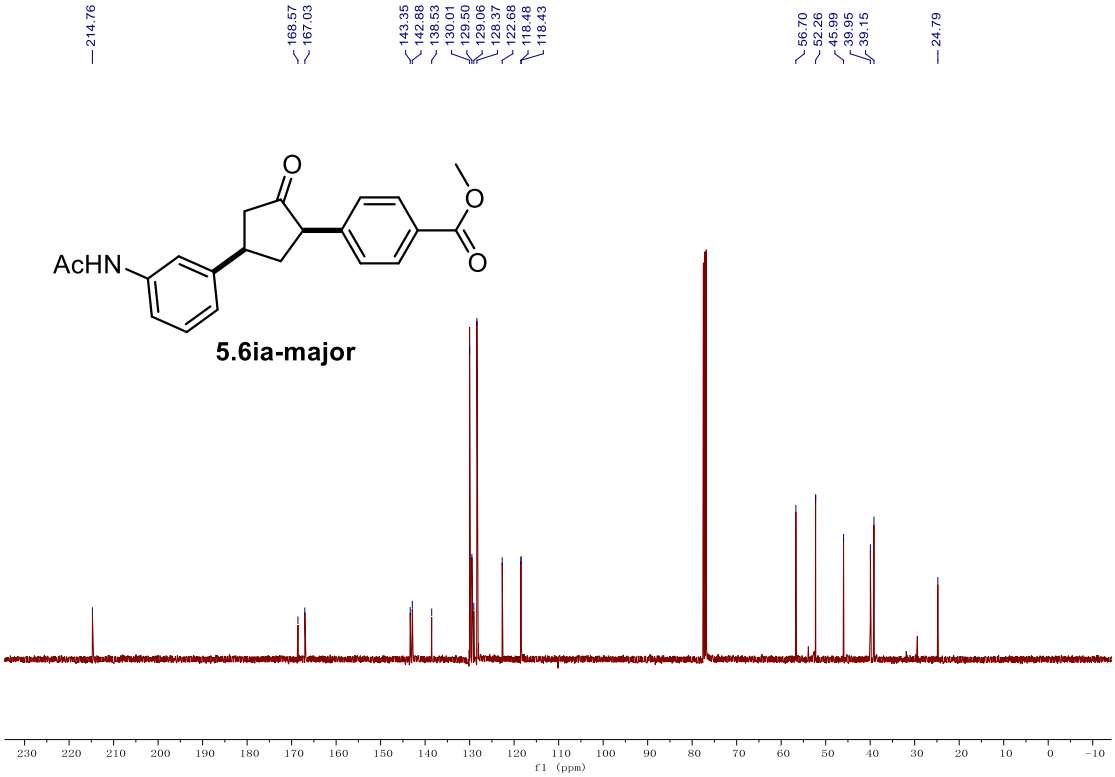


Figure 5.97 ^{1}H-NMR Spectrum of **5.6ib**

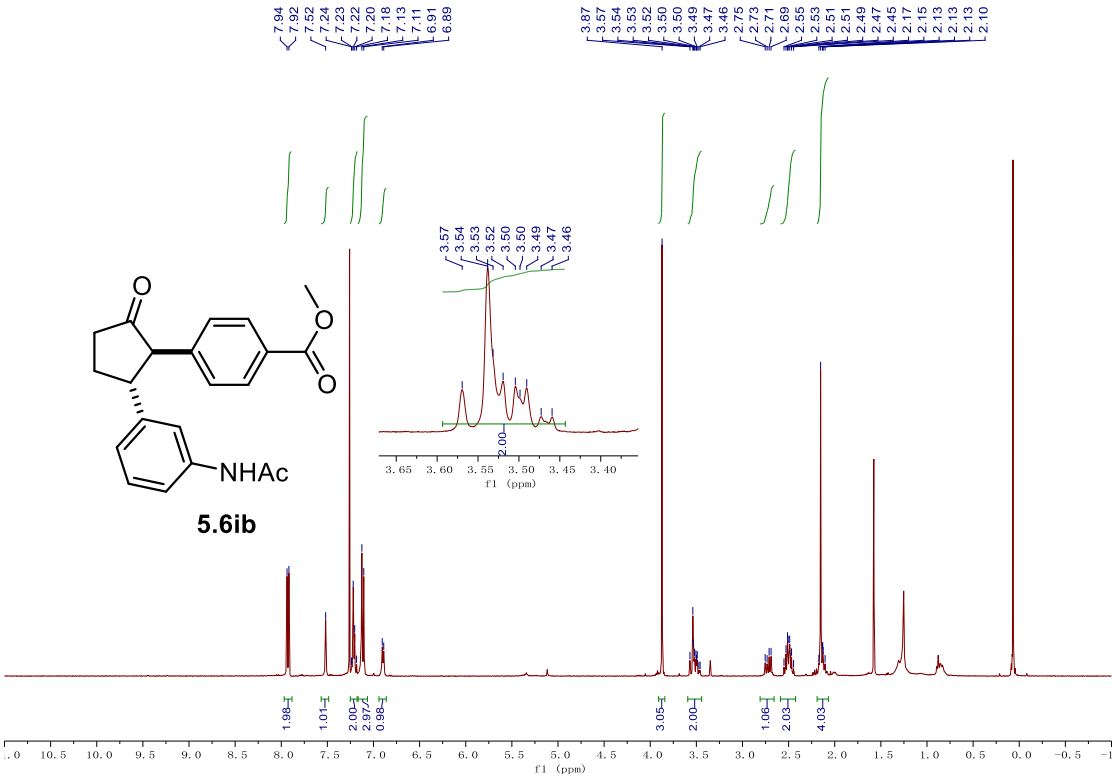


Figure 5.98 ^{13}C-NMR Spectrum of **5.6ib**

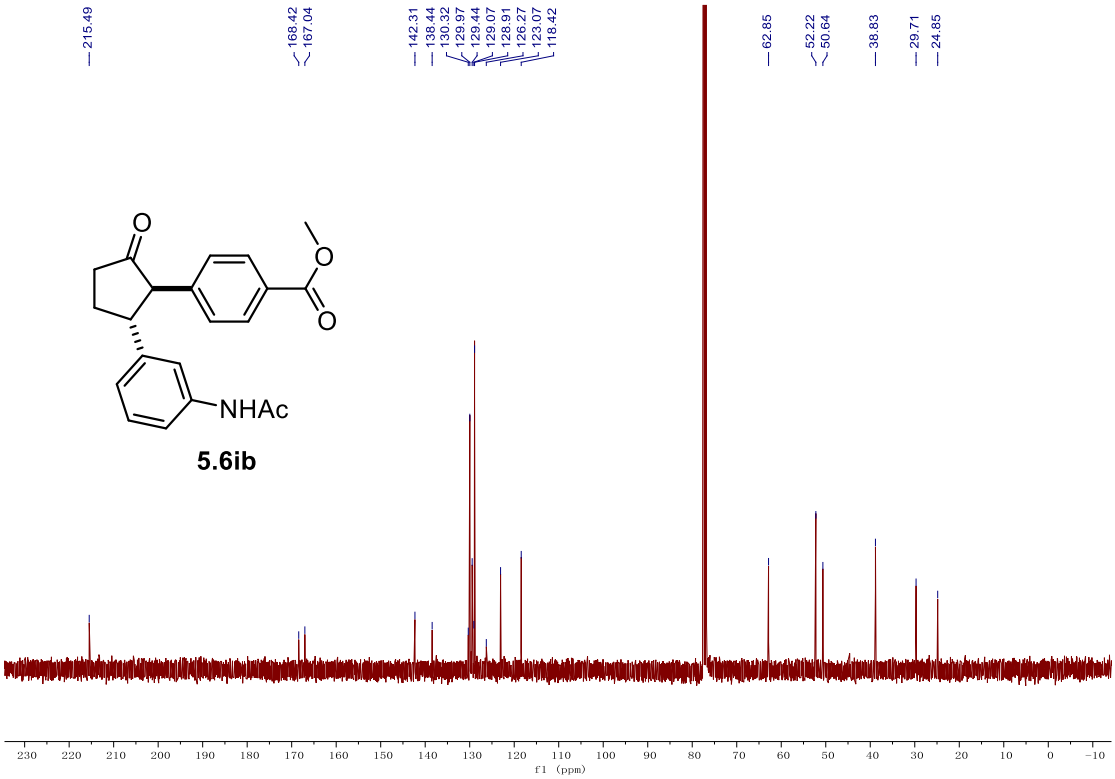


Figure 5.99 ^{1}H-NMR Spectrum of **5.8**

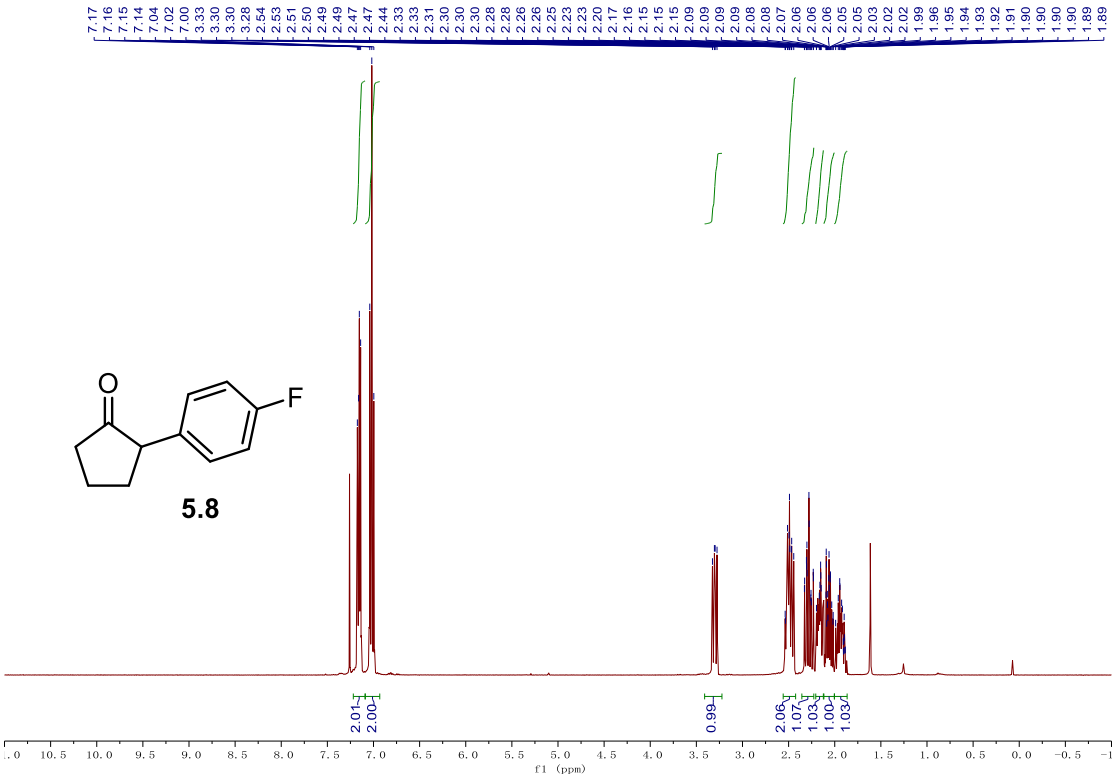


Figure 5.100 ^{13}C-NMR Spectrum of **5.8**

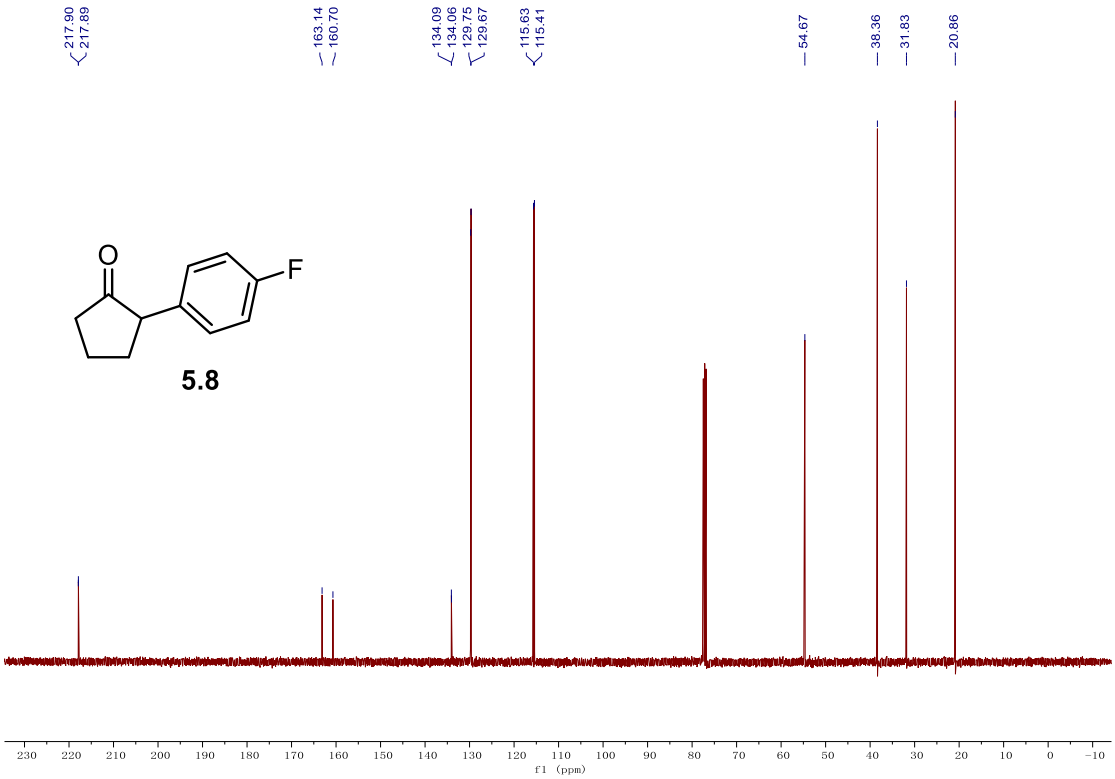


Figure 5.101 ^{19}F-NMR Spectrum of **5.8**

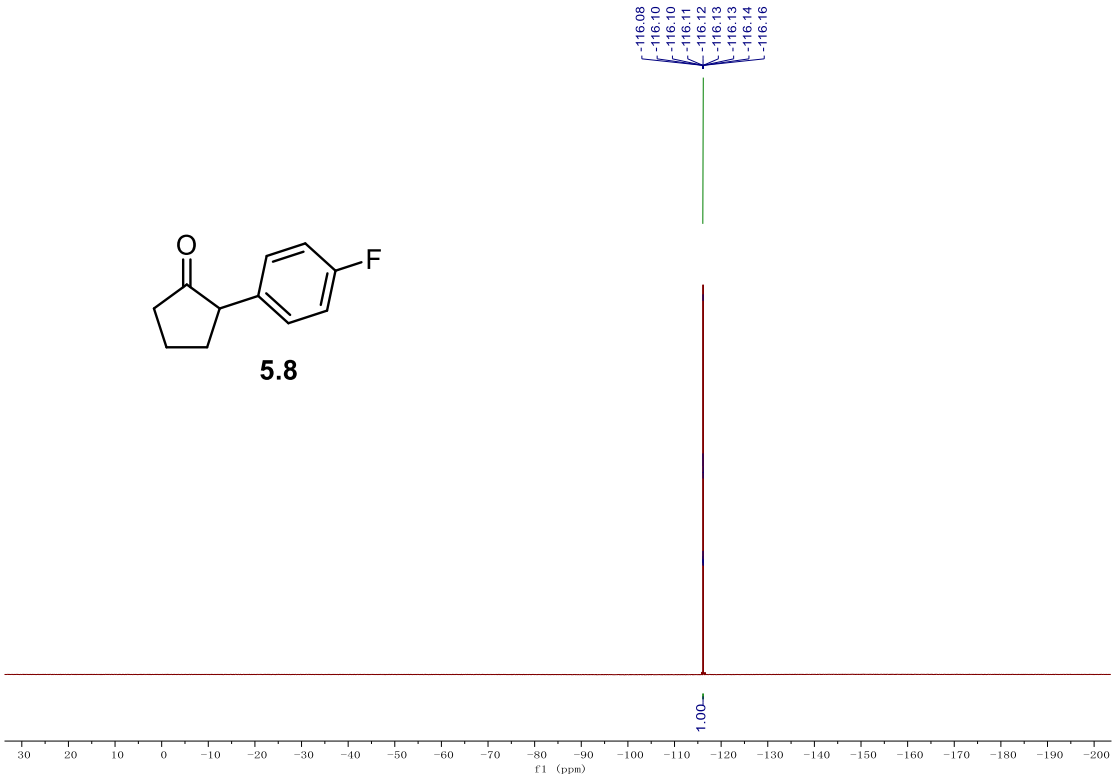


Figure 5.102 ^{1}H-NMR Spectrum of **5.9**

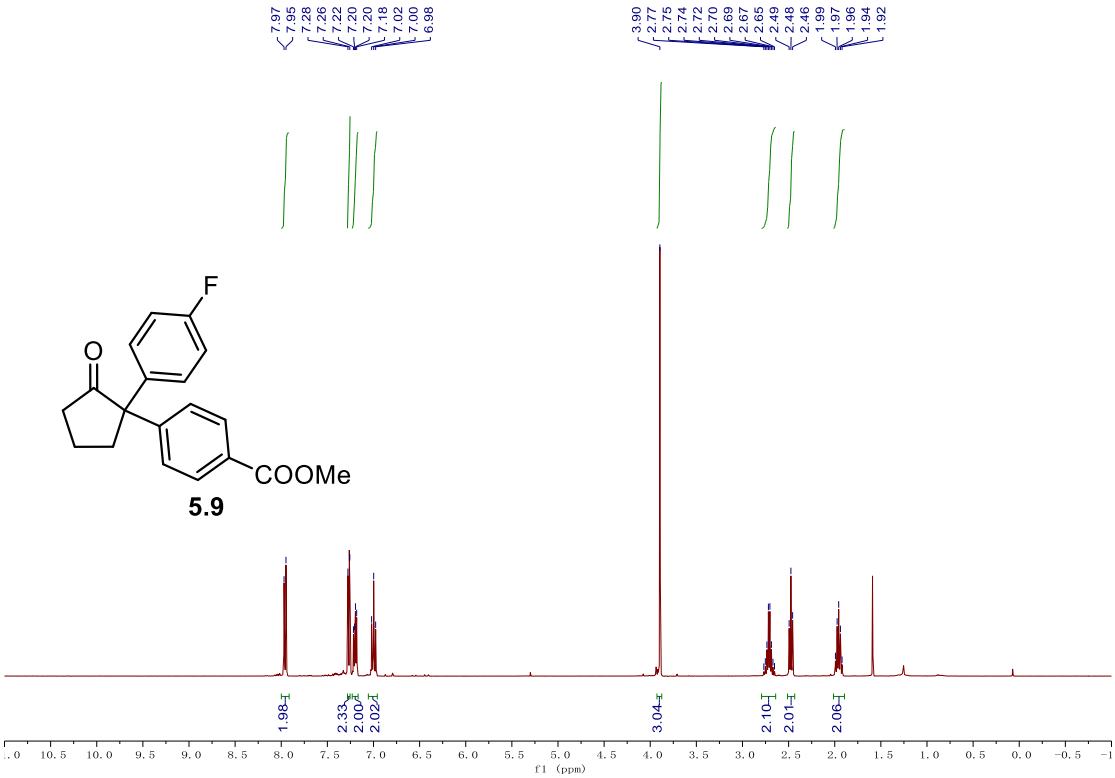


Figure 5.103 ^{13}C-NMR Spectrum of **5.9**

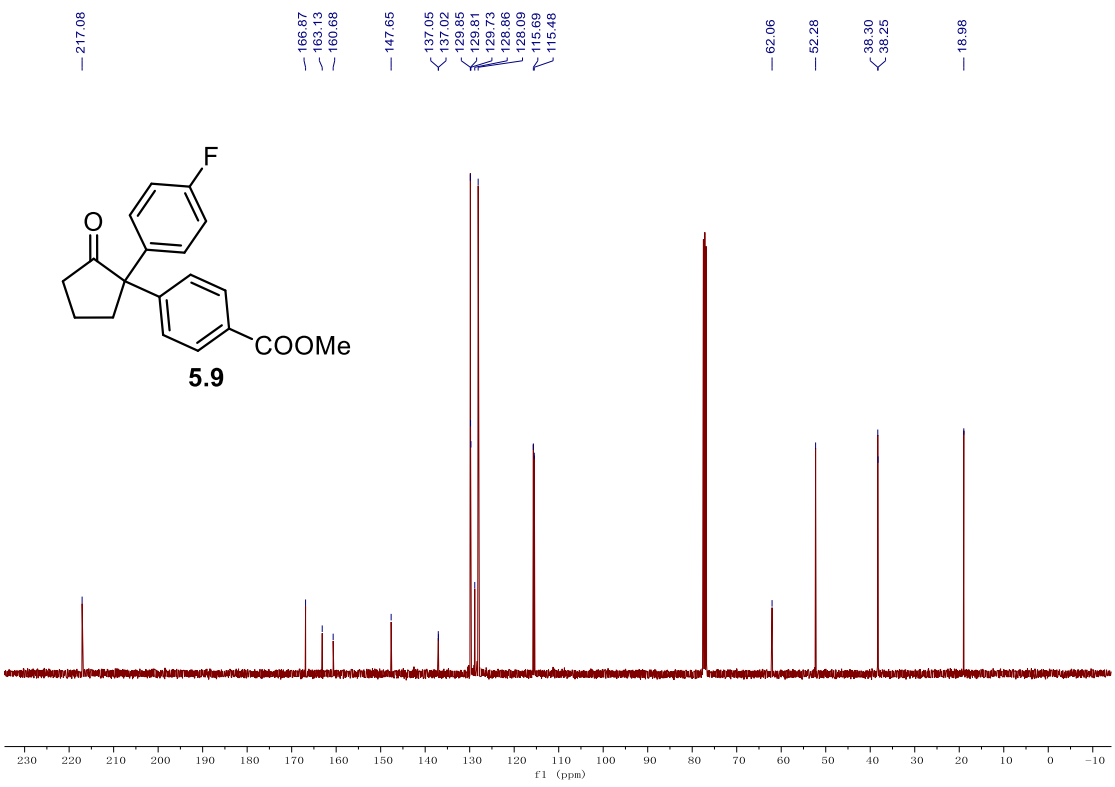


Figure 5.104 ^{1}H-NMR Spectrum of **5.11-major**

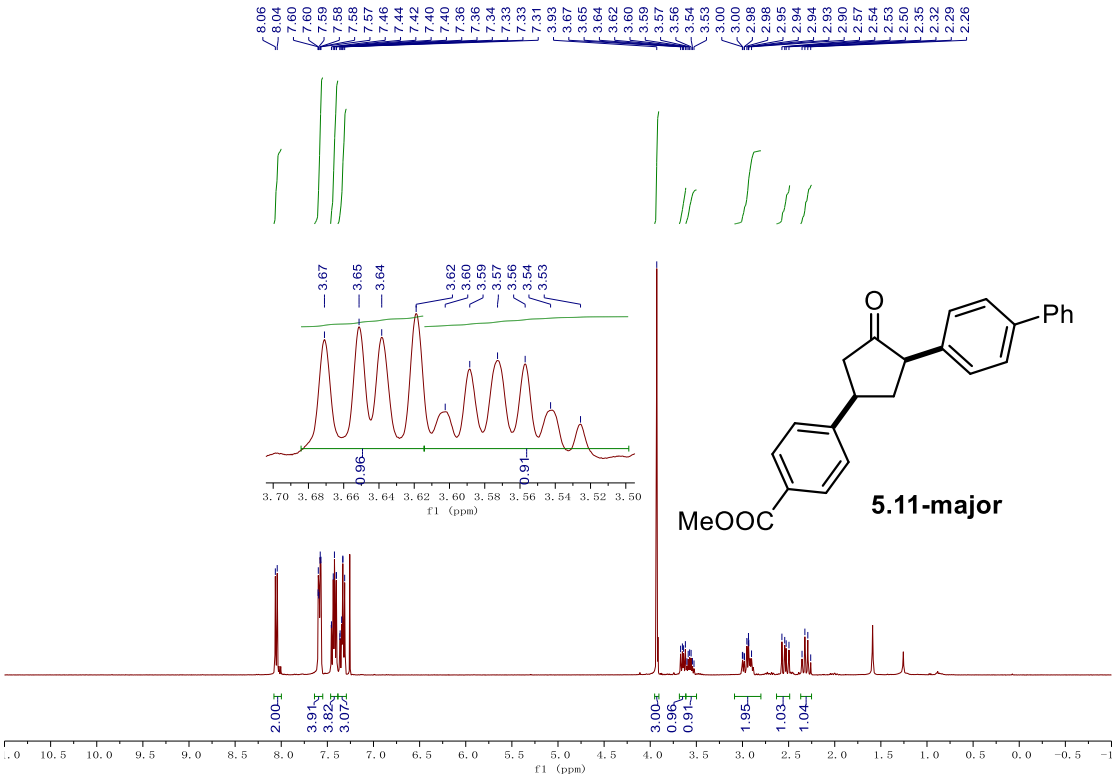


Figure 5.105 ^{13}C-NMR Spectrum of **5.11-major**

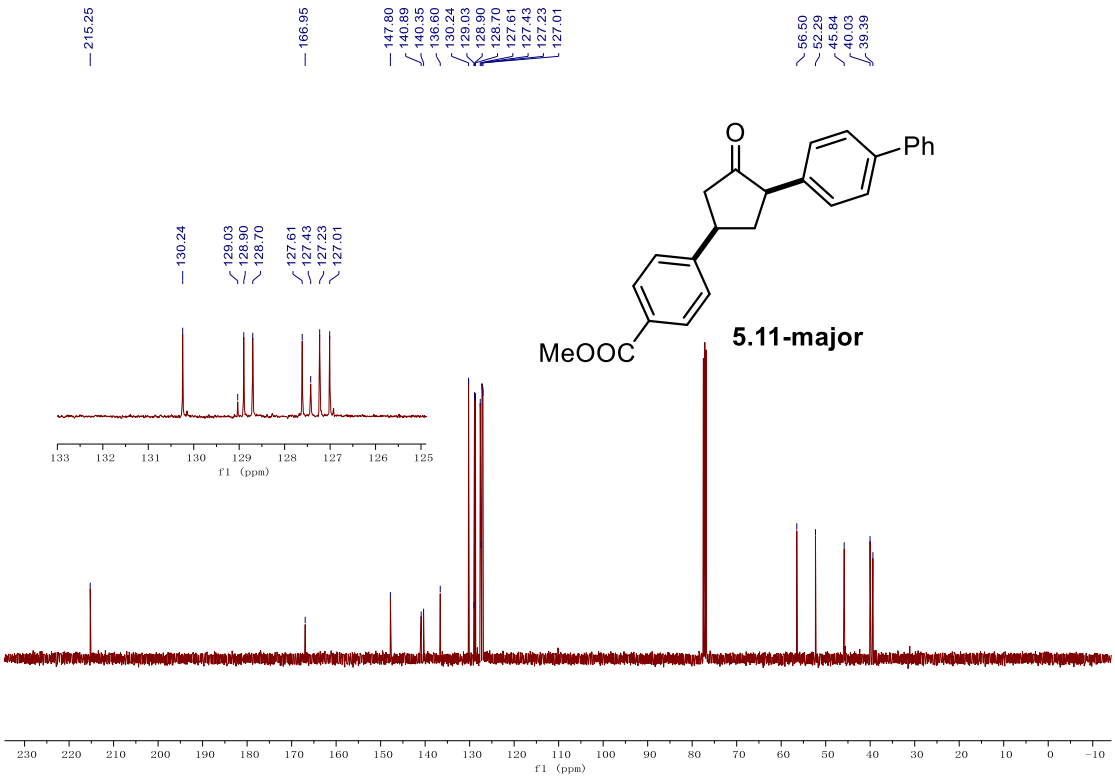


Figure 5.106 ^{1}H-NMR Spectrum of **5.11-minor**

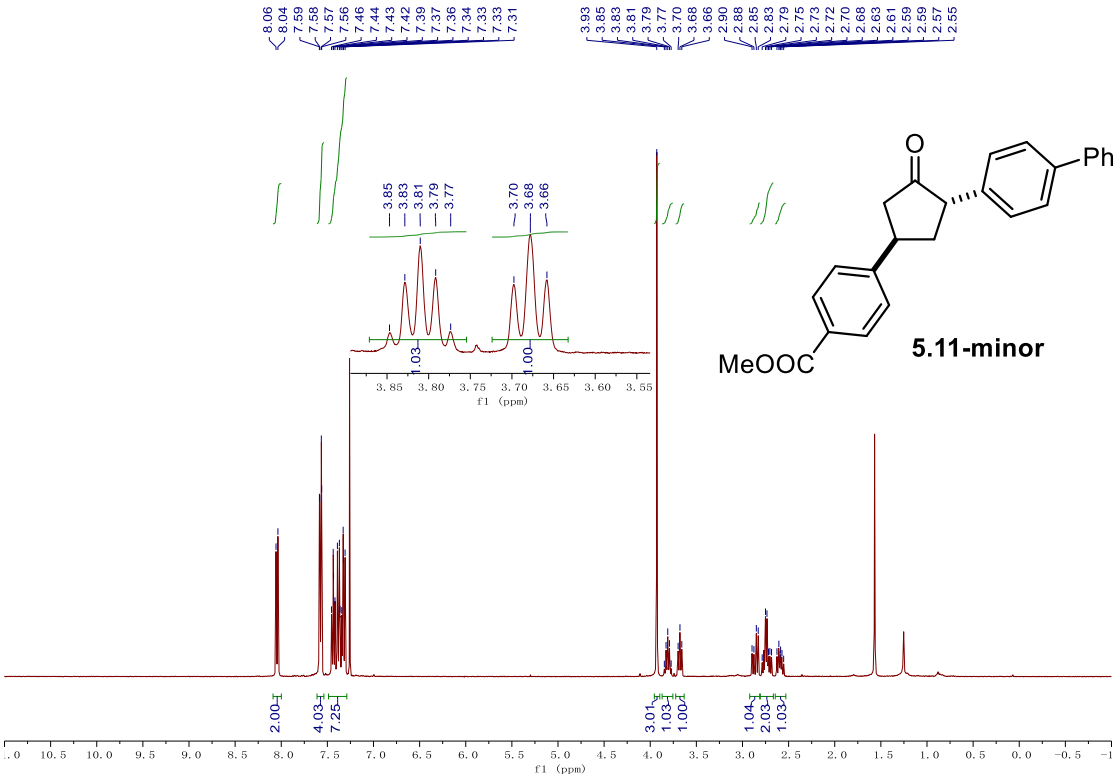


Figure 5.107 ^{13}C-NMR Spectrum of **5.11-minor**

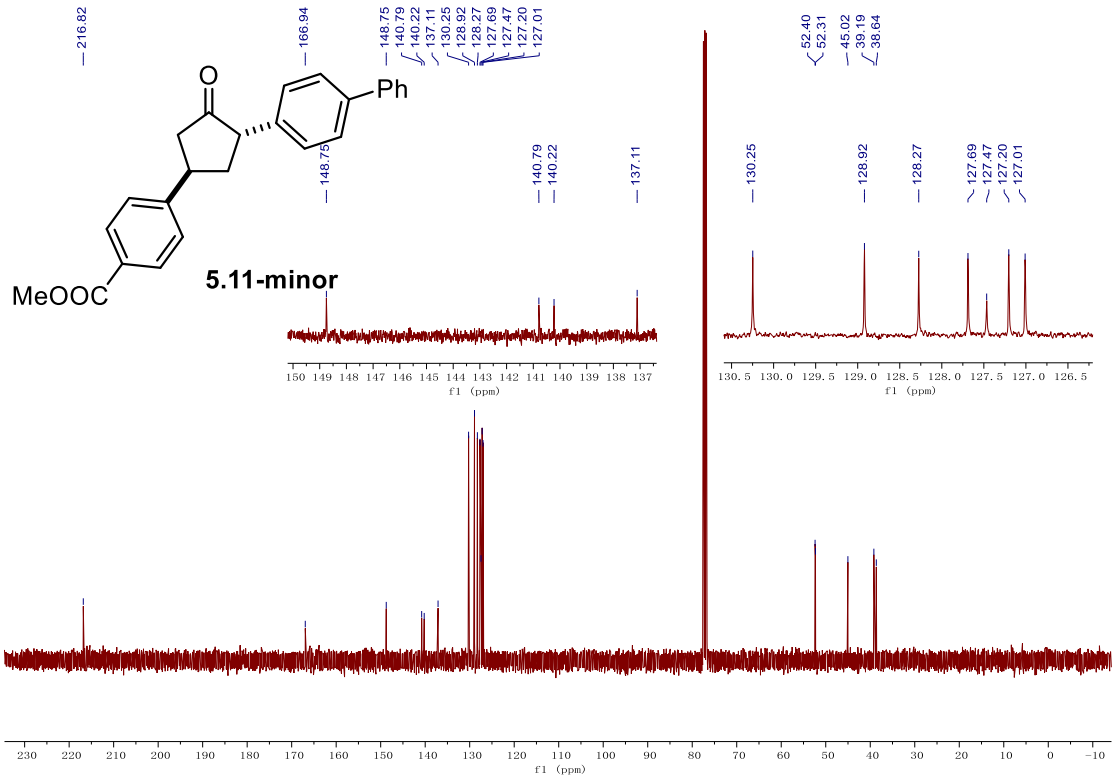


Figure 5.108 ^{1}H-NMR Spectrum of **5.12**

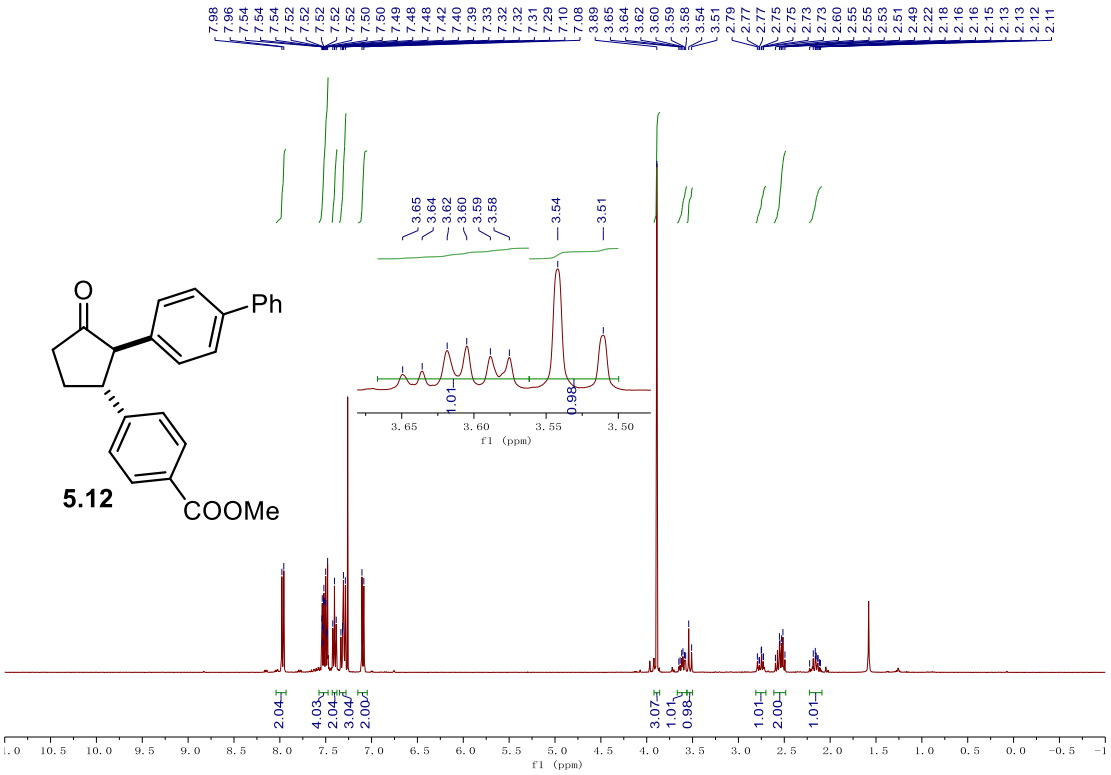
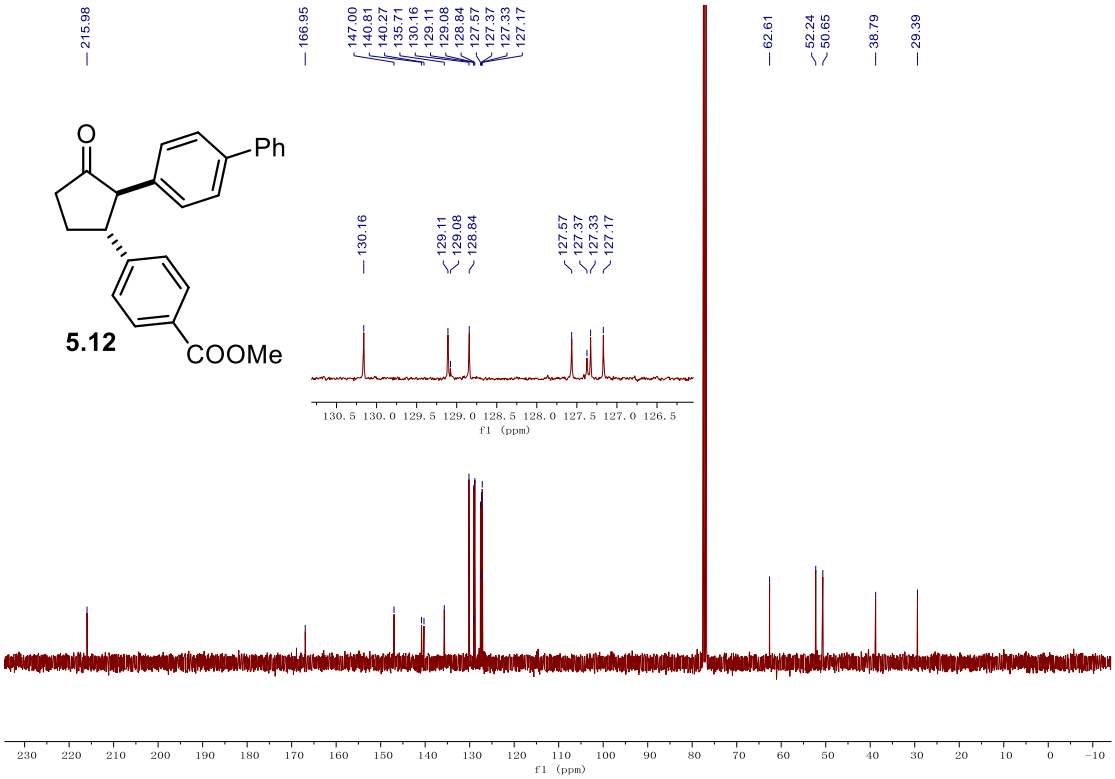


Figure 5.109 ^{13}C-NMR Spectrum of **5.12**



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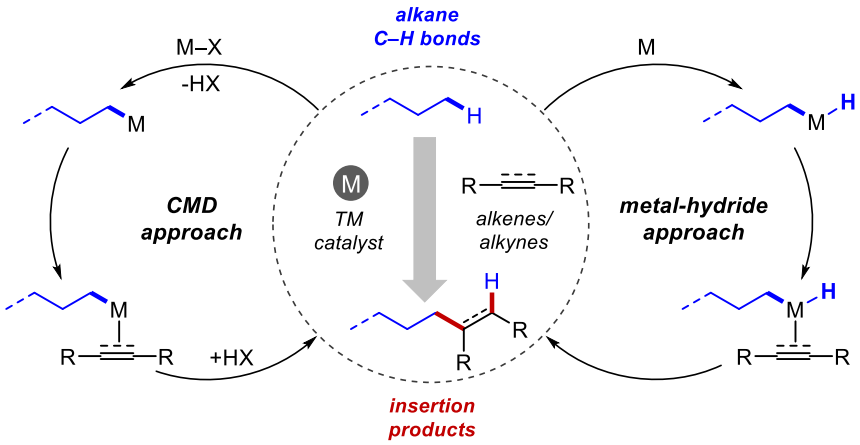
CHAPTER 6

Rh-Catalyzed Alkyne Insertion into Ketones β C(sp^3)–H Bonds

6.1 Introduction

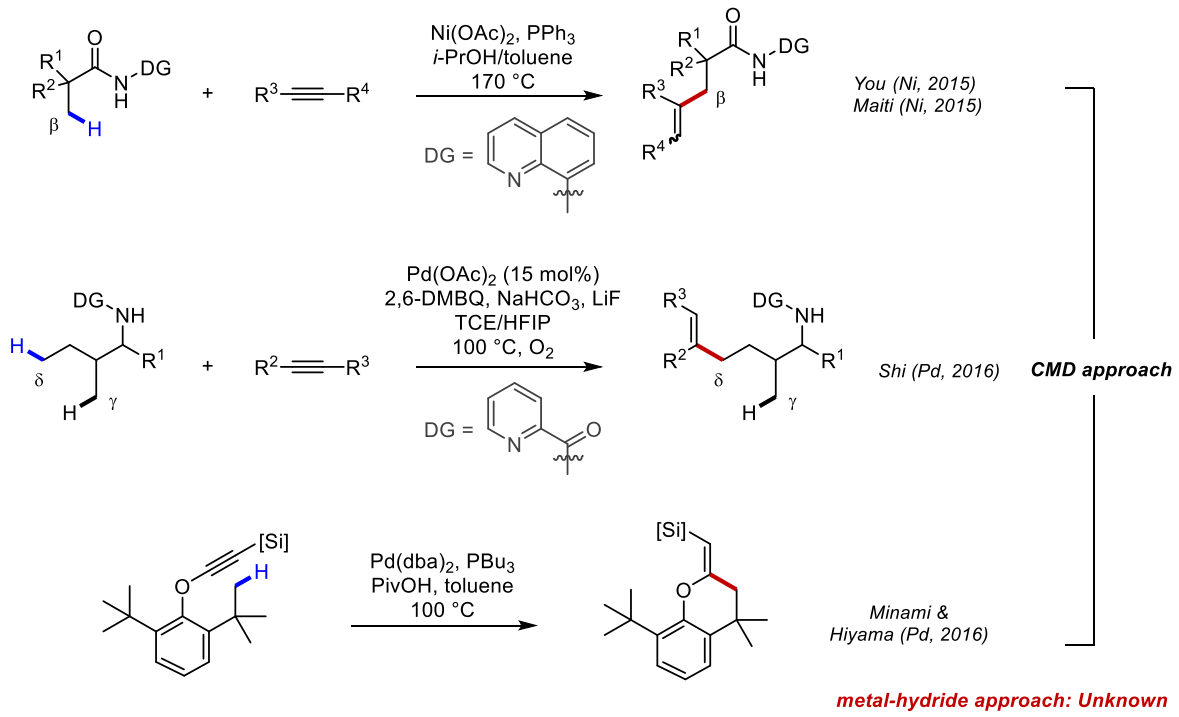
Direct addition of unactivated C−H bonds across unsaturated hydrocarbons, e.g. alkenes and alkynes, offers a *byproduct-free* and *redox-neutral* method to form carbon−carbon bonds.[1] This transformation can be possibly realized by two approaches (Scheme 6.1).[2] In the first case, the C–H bond is cleaved through a concerted metallation-deprotonation (CMD) pathway,[3] which is followed by migratory insertion of the alkene or alkyne and then protodemetallation to afford the coupling product (left cycle). Alternatively, a metal−hydride species can be formed through oxidative addition of a low-valent metal catalyst into a C–H bond.[4] Upon coordination of an unsaturate, the product is formed via a sequence involving migratory insertion and reductive elimination (right cycle).

Scheme 6.1 Addition of C−H bonds across Unsaturated Hydrocarbons



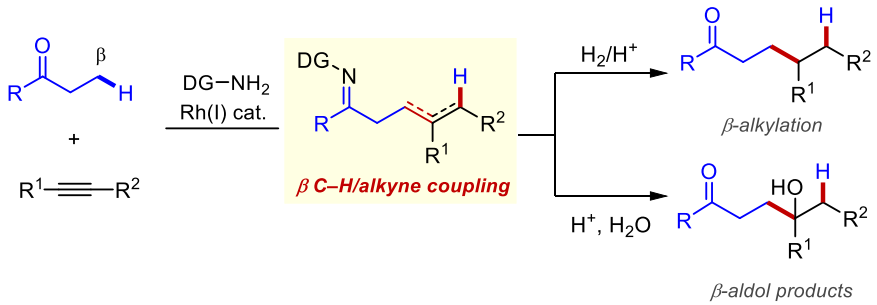
To date, addition of sp^2 C–H bonds across alkenes or alkynes has been extensively developed with both approaches,[5] often resulting in complementary regioselectivity. In contrast, much fewer examples are known for sp^3 C–H bonds,[6,7] of which the majority are at activated positions (benzylic,[7a-c] allylic,[7d] α-to-heteroatom[7e-h] or at activated methylene C−H bonds[7i]). For example, it was not until recently that alkenylations of unactivated aliphatic C–H bonds with alkynes were achieved with amide,[8] amine[9,10] and 2,6-(tBu)$_2$phenyl ether substrates,[11] exclusively *via* a *CMD pathway* (Scheme 2). The direct coupling of unactivated aliphatic C–H bonds with unsaturated hydrocarbons *via* a *metal−hydride approach* remains unknown.[12]

Scheme 6.2 Transition Metal-catalyzed Addition of Unactivated sp^3 C−H Bonds across Alkynes



In this chapter, a Rh-catalyzed alkyne insertion into ketones β C(sp^3)–H bonds was realized using an *in-situ*-installed directing group (DG) (Scheme 6.3). Our mechanistic study demonstrated that this C−H/alkyne coupling reaction proceeds through a metal−hydride reaction pathway. Upon further derivatization, β-alkylation and β-aldol products could be obtained.

Scheme 6.3 Rh-Catalyzed Alkyne Insertion into Ketones β C(sp^3)–H Bonds

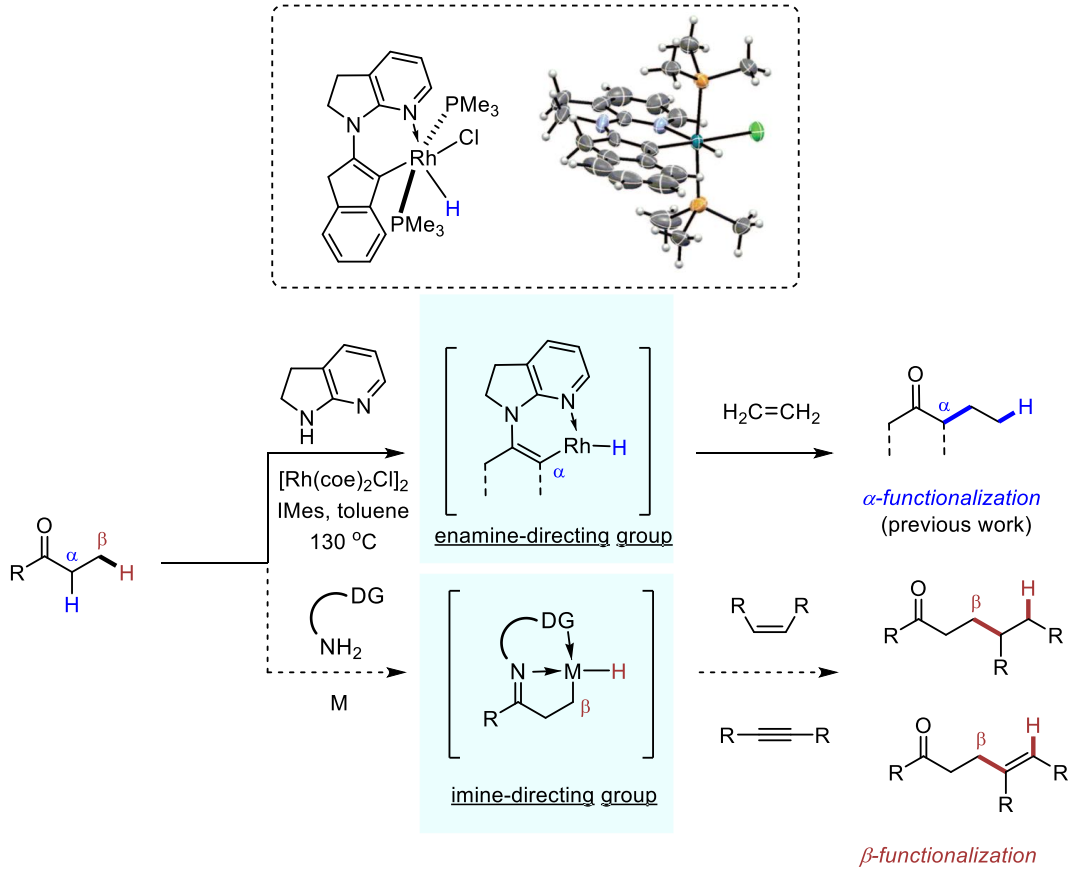


6.2 Results and Discussion

To realize such a transformation following a metal−hydride pathway, the challenge is three-fold: 1) oxidative addition into unactivated sp^3 C–H bonds is often significantly slower than sp^2 C–H bonds;[13] 2) reductive elimination involving an alkyl moiety is generally difficult;[14] and 3) low-valent metals often catalyze oligomerization of unsaturated hydrocarbons as a competitive reaction pathway.[15]

Our group previously discovered that the 7-azaindoline could serve as an effective amine catalyst to promote ketone α-functionalization.[16,17] A ketone first condenses with the 7-azaindoline to form an enamine. Through pyridine-directed oxidative addition of the enamine α C−H bond, a metal−hydride species would be generated at the ketone α positions, which leads to α−alkylation or alkenylation with olefins or alkynes.[16a-e] In order to form a metal−hydride species at the ketone β positions, we hypothesized that a properly selected *imine-type* DG would promote C−H oxidative addition through forming a five-membered metallocycle.[18,19] The coupling with an unsaturated hydrocarbons would lead to the formation of either the β−alkylation or alkenylation products (Scheme 6.4).

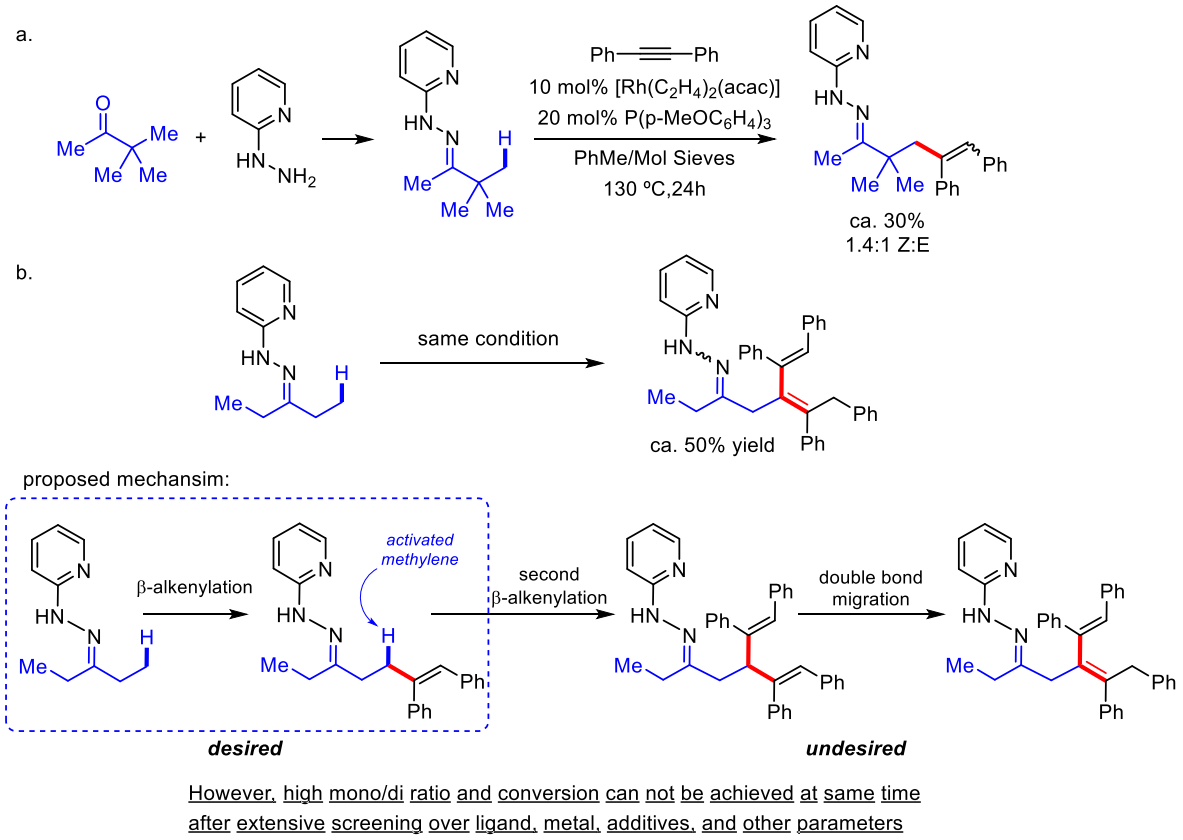
Scheme 6.4 Strategies to Promote C−H Oxidative addition



According to Dr. Michael Young's initial discovery, 2-pyridyl hydrazine was found to be an effective directing group that can be easily installed on to a ketone through condensation to form a hydrazone. After a brief screening over the metal catalysts and the ligands, the $Rh(C_2H_4)_2(acac)/(p\text{-}MeOC_6H_4)_3P$ was found to be an effective combination. When 3,3-dimethylbutan-2-one-derived hydrazone was used as the substrate, the β-alkenylation product was obtained in ca. 30% yield as a mixture of *Z/E* isomers using diphenylacetylene as the alkyne coupling partner (Scheme 6.5a). However, when a more general substrate, e.g. the 3-pentanone, was treated with the same reaction condition, *di*-β-alkenylation took place dominantly. Only small amount of *mono*-alkenylation product was observed (Scheme 6.5b). Extensive screening over metal, ligand, and additives was

conducted. Unfortunately, we were not able to achieve high mono/di ratio and high conversion at same time.

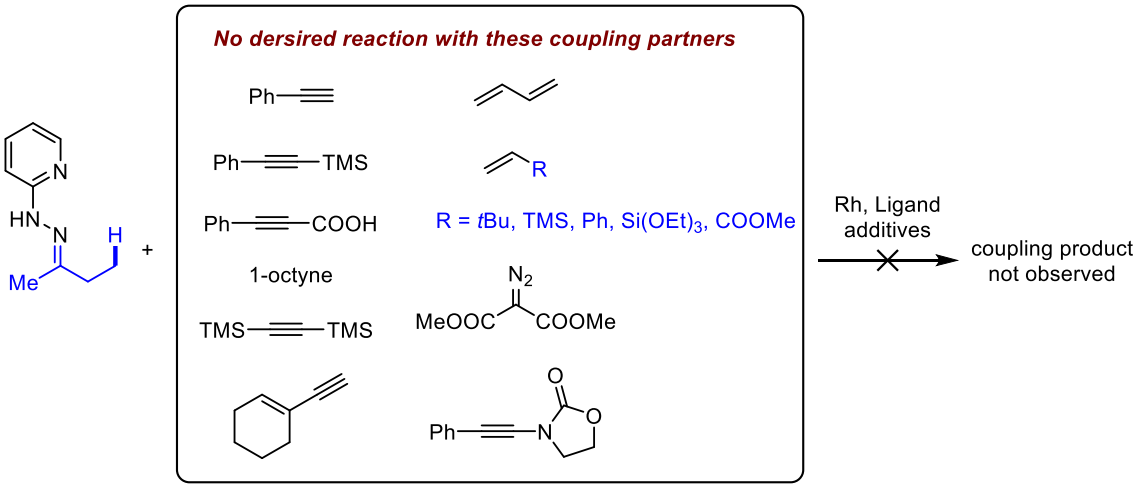
Scheme 6.5 β C−H Coupling of Ketones with Diphenylacetylene



However, high mono/di ratio and conversion can not be achieved at same time after extensive screening over ligand, metal, additives, and other parameters

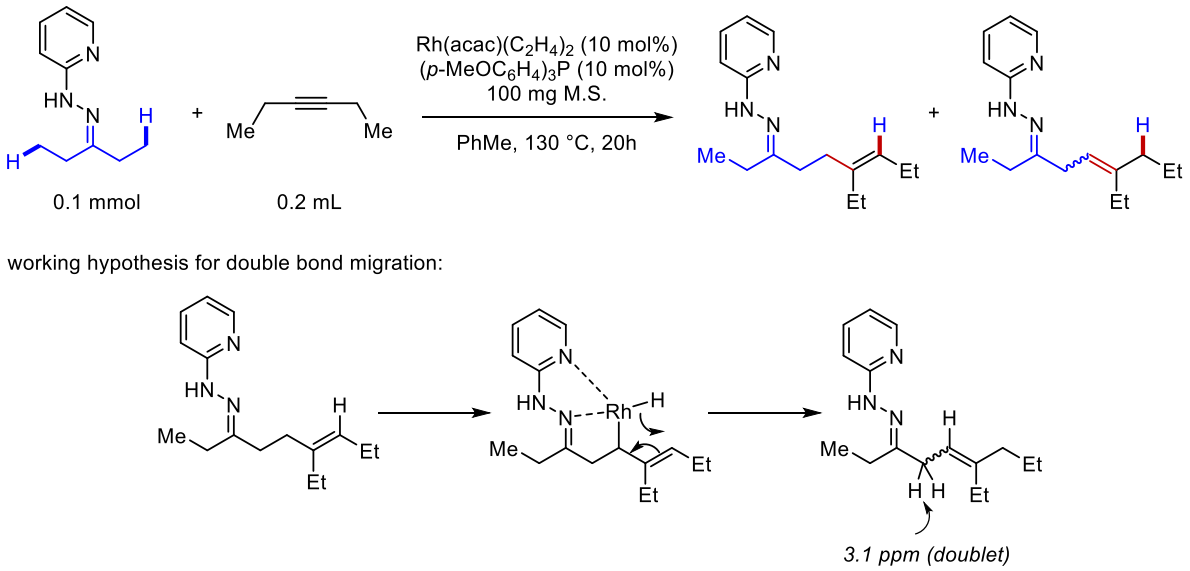
We then turned our attention to alternative coupling partners. A variety of alkenes, alkynes, dienes and enynes with different substituents and electronic properties were tested. However, no desired product was observed with any of the coupling partners listed in Scheme 6.6. While various alkenes and terminal alkynes were found incompatible, it is worth noting that phenylacetylene and trimethyl(phenylethynyl)silane showed no reactivity under the current catalytic system. A diazo compound was also tested, only leading to the decomposition products of itself.

Scheme 6.6 Screening of Coupling Partners for the β C−H Coupling of Ketones



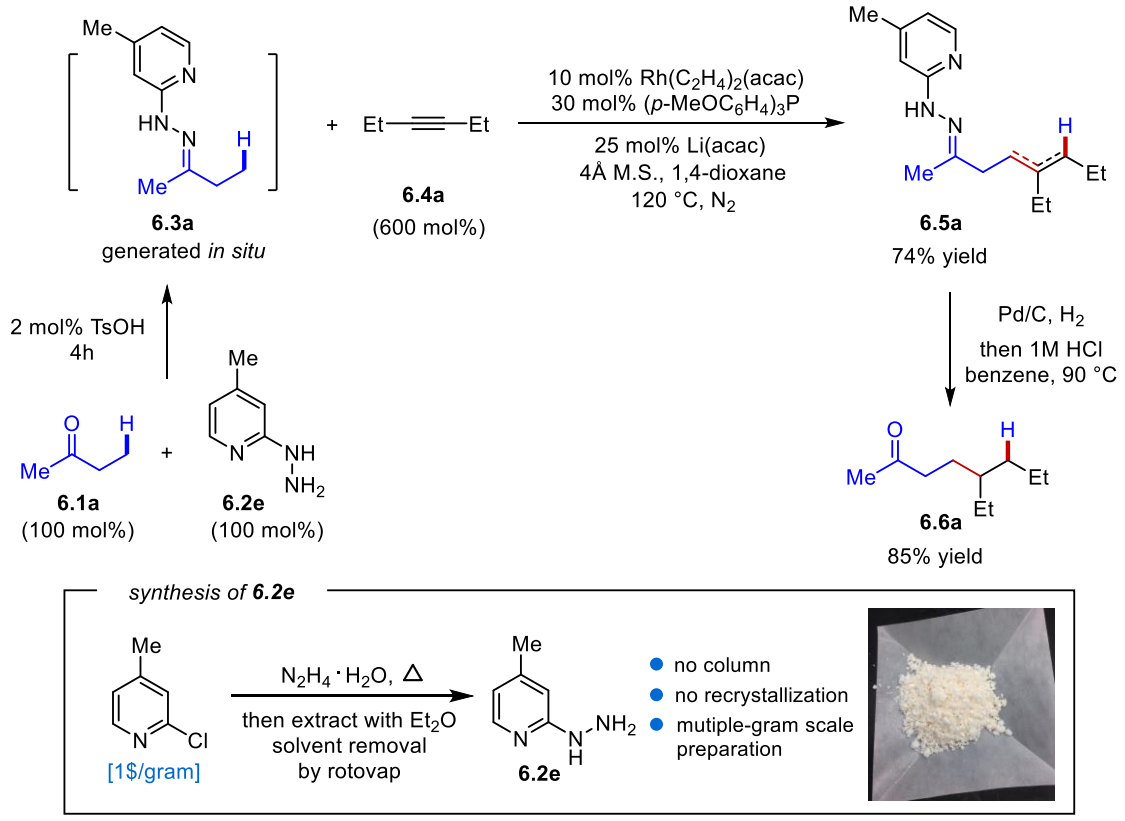
To our great delight, when a dialkyl alkyne, e.g. 3-hexyne, was used as the coupling partner under otherwise same reaction condition, the mono-alkenylation products were obtained selectively. Interestingly, along with the expected β-alkenylation product, a double bond migration derivative was observed as an inseparable mixture. Tentatively, we assumed that the double bond migration product was generated through allylic C−H oxidative addition to form an allyl-Rh-hydride spices, followed by hydride re-insertion form the other terminus of the allyl group (Scheme 6.7).

Scheme 6.7 Initial Results of the Rh-Catalyzed β C−H Alkenylation with 3-Hexynes



Our further optimization employed 2-butanone as a model substrate to couple with 3-hexyne. The hydrazone DG[20] could be generated *in situ* by pre-mix the ketone and the hydrazine precursor for 4 hours. After a thorough survey of various DGs, metal precatalysts, ligands and other reaction parameters, ultimately the desired product (**6.5a**) can be isolated in 74% yield using $Rh(C_2H_4)_2(acac)/(p\text{-}MeOC_6H_4)_3P$ as the metal/ligand combination, hydrazine **6.2e** to form the optimal DG, and Li(acac) as the additive at 120 °C. Noting that **6.5a** was a mixture of γ,δ- and β,γ-unsaturated products[21], simple treatment of **6.5a** with Pd/C and H_2, followed by addition of aqueous HCl in one pot afforded the corresponding β-alkylated ketone **6.6a** in 85% yield. Besides, it is worth noting that hydrazine **6.2e** could be easily synthesized in one step from inexpensive 2-chloro-4-methylpyridine on a multi-gram scale without recrystallization or chromatography purification (Scheme 6.8).

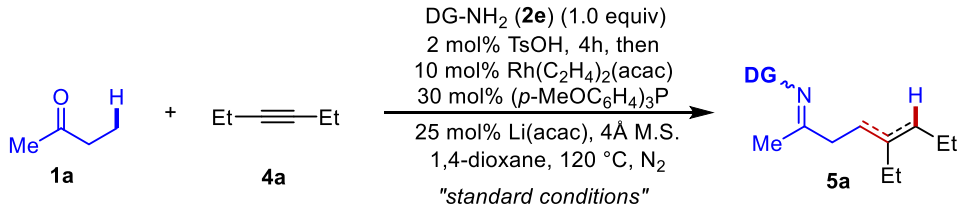
Scheme 6.8 Optimal Condition for the Rh-Catalyzed β C−H Alkenylation of Ketones



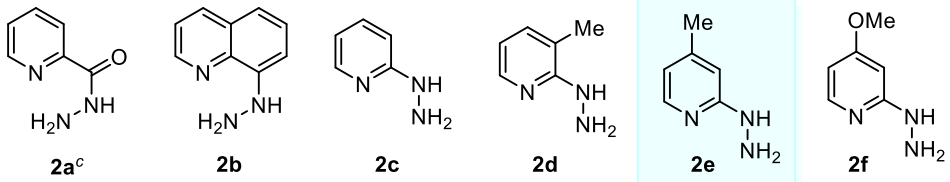
A set of control experiments were conducted from the optimal condition (Table 6.1). In general, the pyridine-derived hydrazone DGs are more effective than the corresponding hydrazide or quinoline-derived DG (entries 2 and 3). While use of the less electron-rich hydrazine **2c** gave a lower yield (entry 4), further increase of the electron density of the pyridyl group did not enhance the reactivity (**2f**, entry 6). No product was observed in the absence of either the DG or the Rh pre-catalyst (entries 7-8). The counter anion of Rh appears to be important, as replacing the $Rh(C_2H_4)_2(acac)$ with $[Rh(C_2H_4)_2Cl]_2$ (without Li(acac)) provided the desired product in a much lower yield (entry 9). (p-$MeOC_6H_4)_3P$ proved to be an optimal ligand for this transformation, while using bidentate ligands generally gave no conversion of the starting material, and other mono-dentate phosphines were less effective.[22] A diminished yield was observed when less phosphine was used (entry 11). The excess phosphine ligand is likely beneficial for the catalyst dissociation from the product. The use of

a lower catalyst loading, e.g. 5 mol% Rh, still afforded 70% yield (entry 12). Finally, the addition of Li(acac) improved the yield to some extent (entry 13), while the addition of water diminished the reaction efficiency (entry 14).

Table 6.1 Control Experiments for the Rh-Catalyzed Alkenylation of Ketone **6.1a** [a]



entry	deviation from above	yield (%)[b]	entry	deviation from above	yield (%)[b]
1	no change	83 (74[c])	8	no [Rh]	0
2	**2a**	<10	9	[Rh] = $[Rh(C_2H_4)_2Cl]_2$, no Li(acac)	24
3	**2b**	trace	10	no phosphine	<10
4	**2c**	74	11	10 mol% phosphine	60
5	**2d**	<10	12	5 mol% [Rh], 15 mol% phosphine	70
6	**2f**	71	13	no Li(acac)[d]	77
7	no DG	0	14	no M.S., + 1 equiv H_2O	30

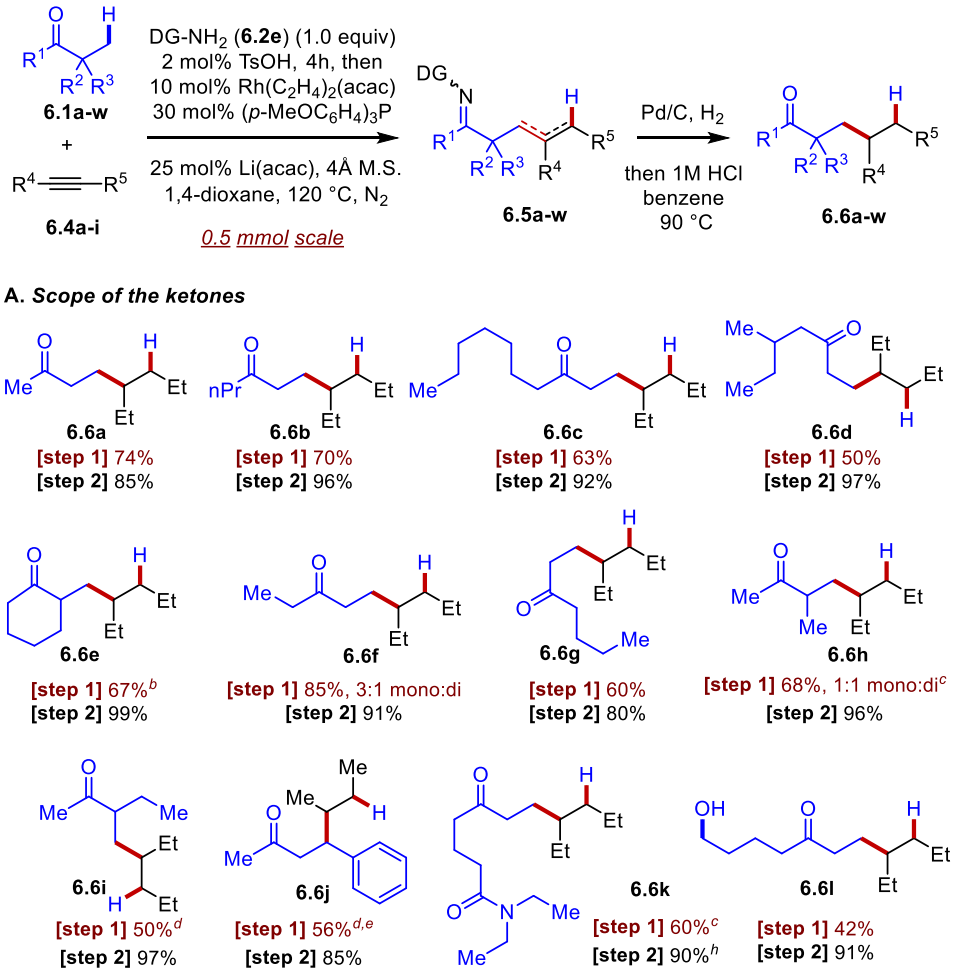


[a] The reactions were run with 0.1 mmol **1a** and 0.6 mmol **4a** in 1 ml 1,4-dioxane for 48h. Due to the volatility of **4a**, 6 equiv was used. [b] Determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard. [c] Isolated yield. [d] The pre-condensed hydrazone substrate was used.

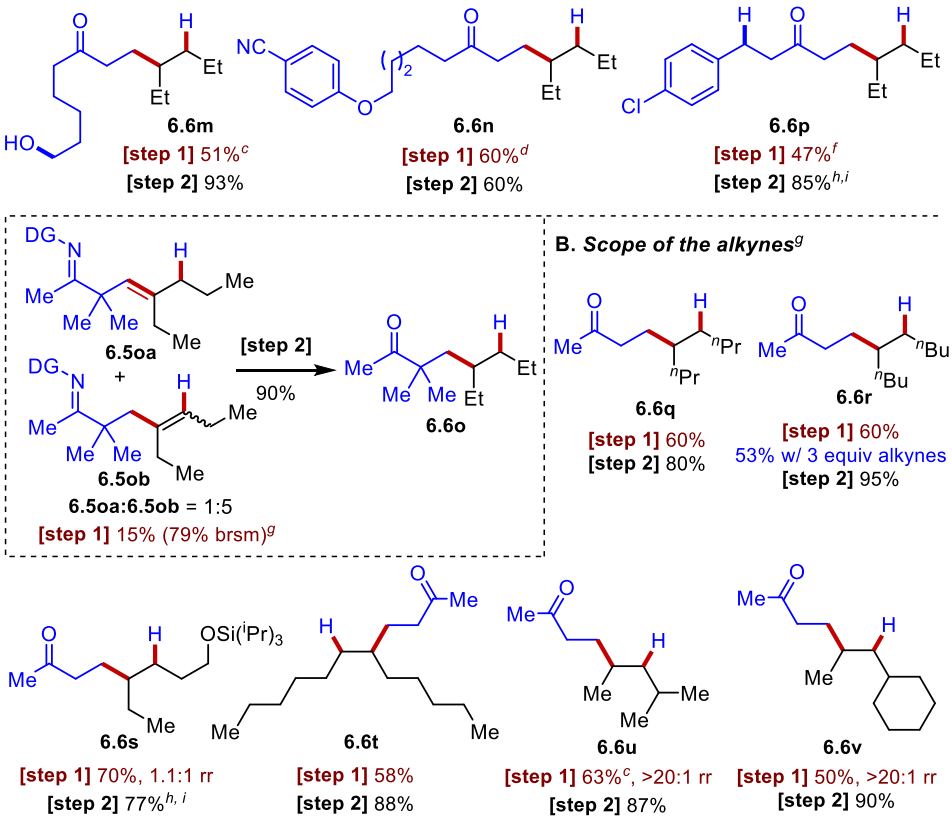
The scope of the ketone-alkyne coupling was then explored (Scheme 6.9). Both linear and cyclic ketones can couple with aliphatic internal alkynes efficiently.[23] When unsymmetrical ketones were employed as the substrates, alkenylation occurred predominately at the primary C–H bonds. However, in the absence of β methyl groups, the benzylic methylenes can also be activated (**6.6j**). A range of functional groups were compatible under the reaction conditions, including aryl chlorides (**6.6p**), free alcohols (**6.6l**, **6.6m**), ethers

(**6.6n**), amides (**6.6k**) and nitriles (**6.6n**). While the bulky pinacolone substrate gave low conversion (**6.6o**),[24] α-branches (**6.6e**, **6.6h**, **6.6i**) were well tolerated. In addition, various symmetrical and unsymmetrical aliphatic alkynes can be used as coupling partners (**6.6q-v**), including a protected homopropargyl alcohol moiety (**6.6s**) that are often used as synthetic handles. Note that when a heavier alkyne (e.g. 5-decyne) was employed, the alkyne loading can be reduced to 3 equiv without significantly affecting the yield (**6.6r**). Excellent regioselectivity was achieved when the two substitutes of alkynes are differentiated by size (**6.6u**, **6.6v**), favoring C–C formation at the less hindered side of the alkynes.

Scheme 6.9 Substrate Scope with Various Ketones and Alkynes[a]



Scheme 6.9 Substrate Scope with Various Ketones and Alkynes[a] (continued)

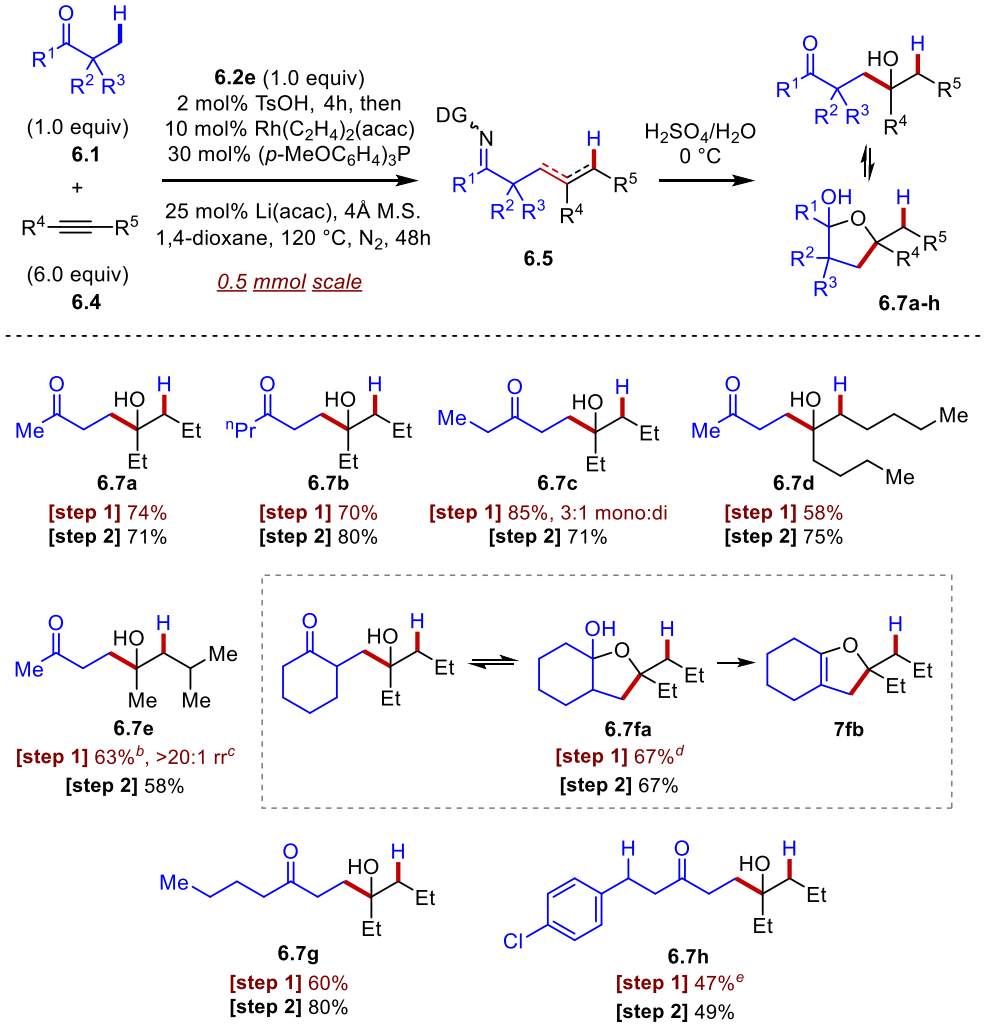


[a] Run with 0.5 mmol **6.1a** and 3.0 mmol **6.4a**. All yields are isolated yields. [b] 15 mol% [Rh]. [c] 72h. [d] 72h, 130 °C. [e] 2.5 ml 1,4-dioxane, 20 equiv alkyne. [f] The benzylic alkenylated product and the di-alkenylated product were observed in <5% yield. [g] Use the pre-condensed substrate. [h] no HCl was added in the hydrogenation step. [i] In step 2, the hydrolysis was conducted before the hydrogenation. brsm = based on recovered starting material. rr: regioisomer ratio.

While the initial alkenylation products contain olefin isomers, the olefins generally share the same tertiary carbon at the γ-position. Thus, a Markovnikov hydration is expected to yield a γ-ketol, formally a *β-aldol adduct*, as a unified product. Indeed, after simply treating the alkenylation products in aqueous H_2SO_4 at 0 ^oC for 1h, the hydration products (in equilibrium between γ-ketol and hemiketal forms) were readily obtained in moderate to good yields, and gratifyingly, the DG was removed at the same time (Scheme 6.10). Interestingly,

when 2-methylcyclohexanone was used as the substrate, the final hydration product underwent simultaneous cyclization and dehydration to afford dihydrofuran **6.7fb**.

Scheme 6.10 Synthesis of β-Aldol Adducts through C–H Alkenylation/Hydration Sequence[a]

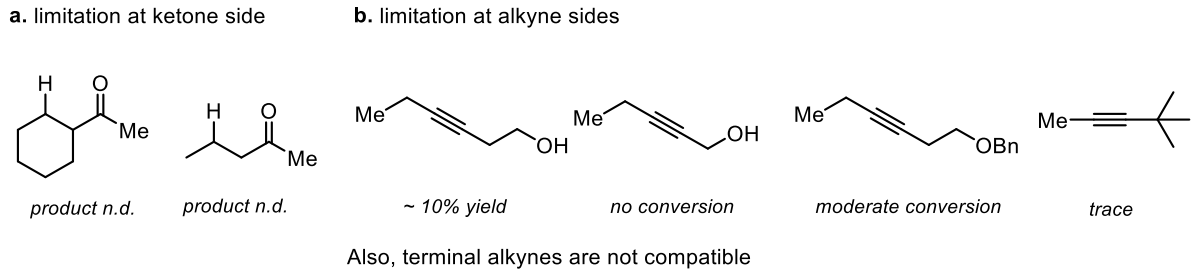


[a] All yields are isolated yields. [b] 72h. [c] from > 20:1 rr. [d] 15 mol% [Rh]. [e] The benzylic alkenylated product and the di-alkenylated product were observed in <5% yield.

Several types of substrates were found incompatible in this transformation. At ketone sides, C–H bonds at unactivated methylene positions (e.g. not benzylic) were generally not reactive. For instance, when methyl cyclohexyl ketone or 2-pentanone was subjected to the optimal condition, no desired product was observed. Regarding the alkyne scope, terminal

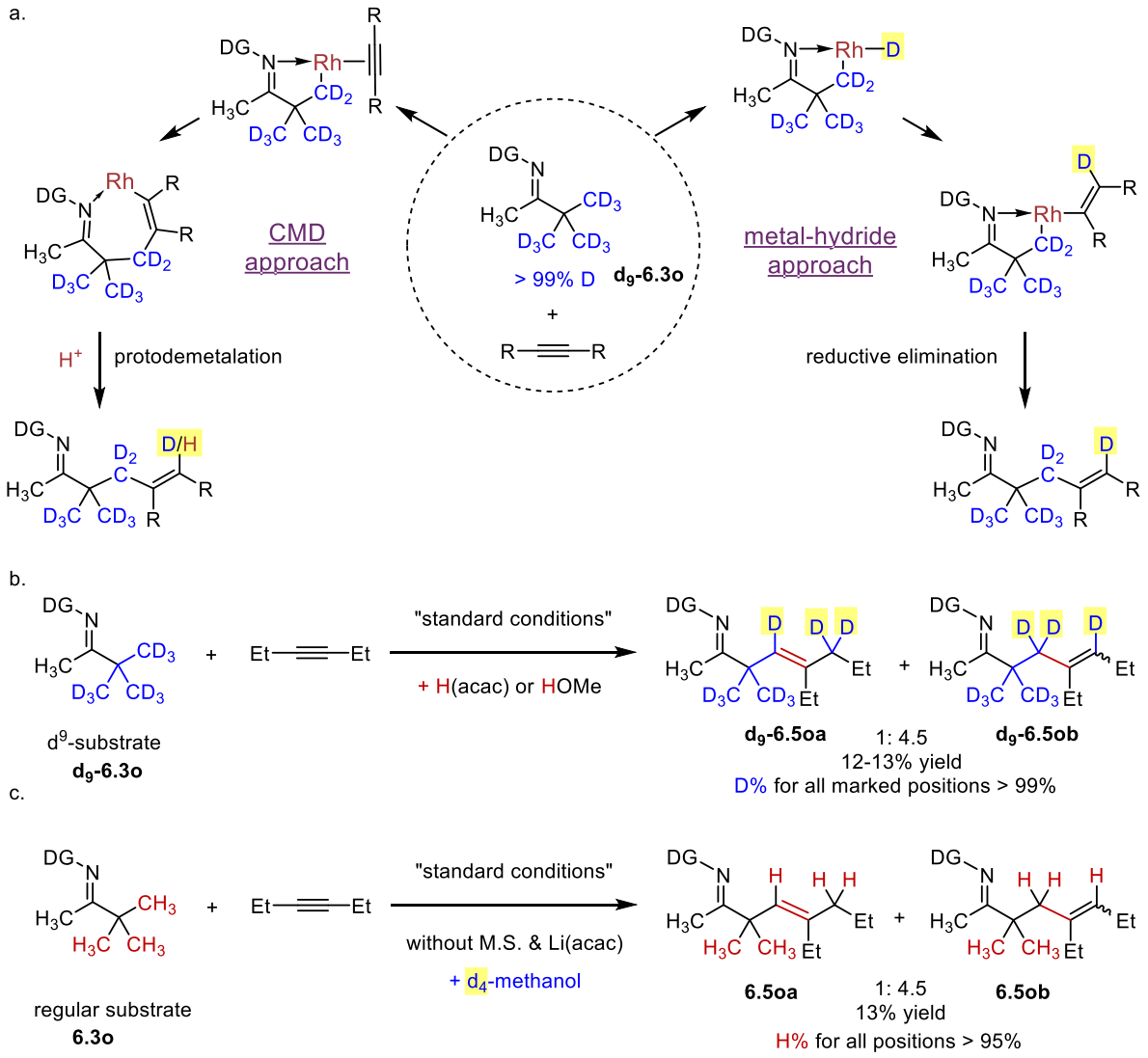
alkynes were not compatible. Internal alkynes with one alkyl/one phenyl or two phenyl substituents usually yielded a mixture of the mono- and di-alkenylation products. Homopropargyl alcohols were also found incompatible, resulting in no conversion of the hydrazone starting material, while moderate conversion could still be obtained with benzyl-protected homo-propargyl alcohols (Scheme 6.11).

Scheme 6.11 Selected examples of Failed Substrates



Regarding the mechanistic features of the β-C−H/alkyne coupling reaction, the key question is whether the C−H activation occurs through a metal−hydride pathway or a CMD pathway. To address this question, the following experiments were conducted. First, deuterium-labeling experiments were carried out with a β-d_9-pinacolone derivative in the presence of H(acac) or excess MeOH (Scheme 6.12b). A tertiary alkyl ketone substrate was specifically chosen to avoid potential H/D scrambling between the α and β positions through a β-H elimination and re-insertion pathway. If the reaction follows a metal−hydride pathway, the deuterium at the original β position should be transferred to the δ position of the product (the vinyl hydrogen in major product **6.5ob**).[7g] However, in the case of a CMD pathway, the reaction should end with a protodemetalation step, thus it is expected that significant deuterium erosion at the δ position would occur in the presence of external proton sources (Scheme 6.12a).[9]

Scheme 6.12 Preliminary Mechanistic Studies using Deuterium-labeled **6.3o**

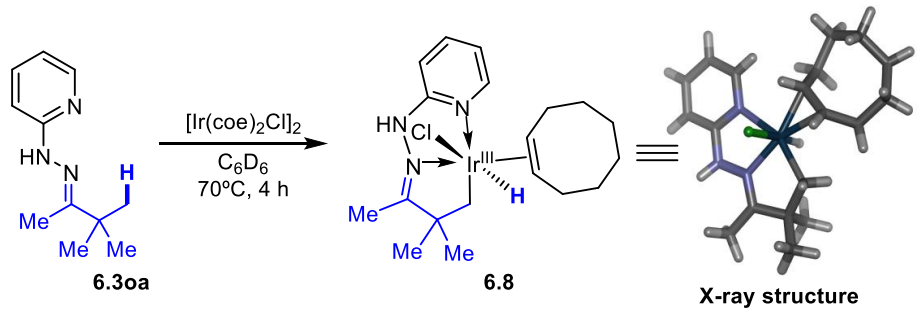


Our experiments showed that more than 99% deuterium incorporation was found at the vinyl position of product **d_9-6.5ob** with either acetylacetone (100 mol%) or MeOH (800 mol%) (Scheme 6.12b). Almost no deuterium loss was found at either the unreacted methyl groups or the recycled starting material. All of these observations support a metal−hydride pathway and disfavor a CMD pathway.[25] Second, as a control experiment, when non-deuterated substrate **3o** was subjected to the reaction with excess d_4-methanol, nearly no

deuterium incorporation was observed at either the β or vinyl position of the products or the recycled starting material. This result further ruled out a CMD pathway (Scheme 6.12c).

Attempts to capture the Rh–H intermediate via NMR experiments were unfruitful; however, a related Ir–H complex was successfully isolated and characterized by Dr. Michael Young, which is likely driven by forming a stronger Ir–H bond (Scheme 6.13). While this specific Ir complex was found catalytically inactive, this result nevertheless demonstrates the feasibility of oxidative addition of a low-valent group-9 metal into unactivated β C–H bonds with the hydrazone DG. Finally, the observed regioselectivity for insertion of unsymmetrical alkynes (**6.6v**, **6.6w** and **6.7e**) is consistent with a hydride-migratory insertion pathway instead of alkyl-migratory insertion pathway.[26] Altogether, our mechanistic investigations strongly support a metal−hydride reaction pathway.

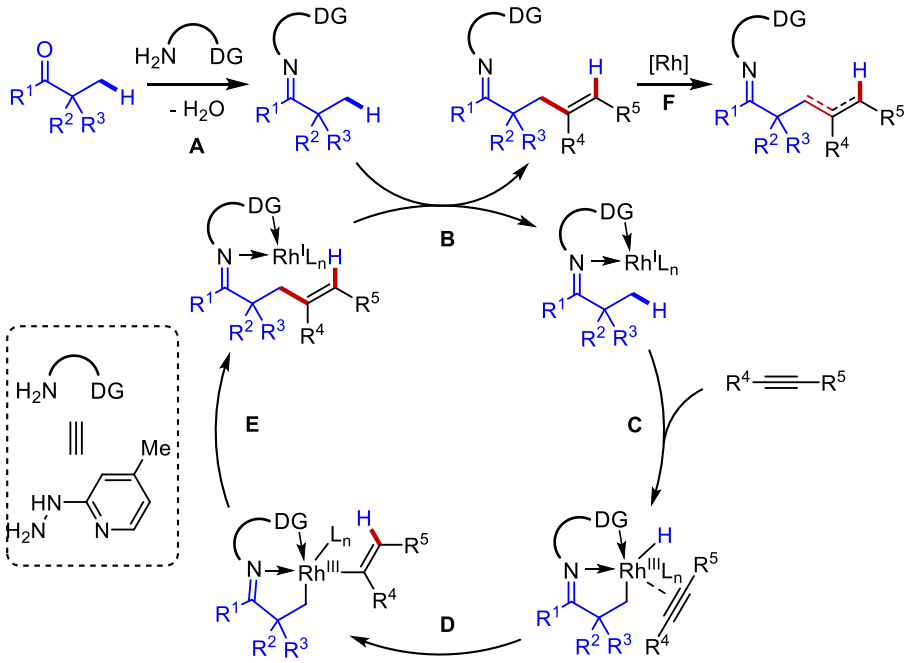
Scheme 6.13 Synthesis of a Mechanistically related Metal-hydride Complex



Accordingly, a plausible catalytic cycle is proposed (Scheme 6.14). First, upon hydrazone formation (step A), coordination with Rh(I) through chelation with the DG facilitates oxidative addition into the β-C(sp^3)–H bond to generate a Rh(III)−hydride species (step C). The hydride intermediate then undergoes alkyne migratory insertion (step D), sp^2-sp^3 reductive elimination (step E), and ligand exchange with a new substrate (step B) to yield

the alkenylation product and resume the catalytic cycle. Further olefin migration of the product may take place, which can also be catalyzed by Rh (step F).[27]

Scheme 6.14 Proposed Catalytic Cycle



6.3 Conclusions

In this chapter, a Rh(I)-catalyzed site-selective coupling between ketone β C(sp^3)−H bonds and aliphatic alkynes was developed using an *in-situ* installed hydrazine DG. Mechanistic investigations supported the involvement of a Rh−H intermediate through oxidative addition of Rh into the β C−H bonds, which indicated the first example of catalytic addition of unactivated aliphatic C−H bonds across unsaturated hydrocarbons through a metal−hydride pathway. Upon hydrogenation or hydration, various β-alkylation or β-aldol products of the ketones could be further obtained.

(Some contents of this chapter has been published in *J. Am. Chem. Soc.* **2017**, *139*, 5716)

6.4 Experimental

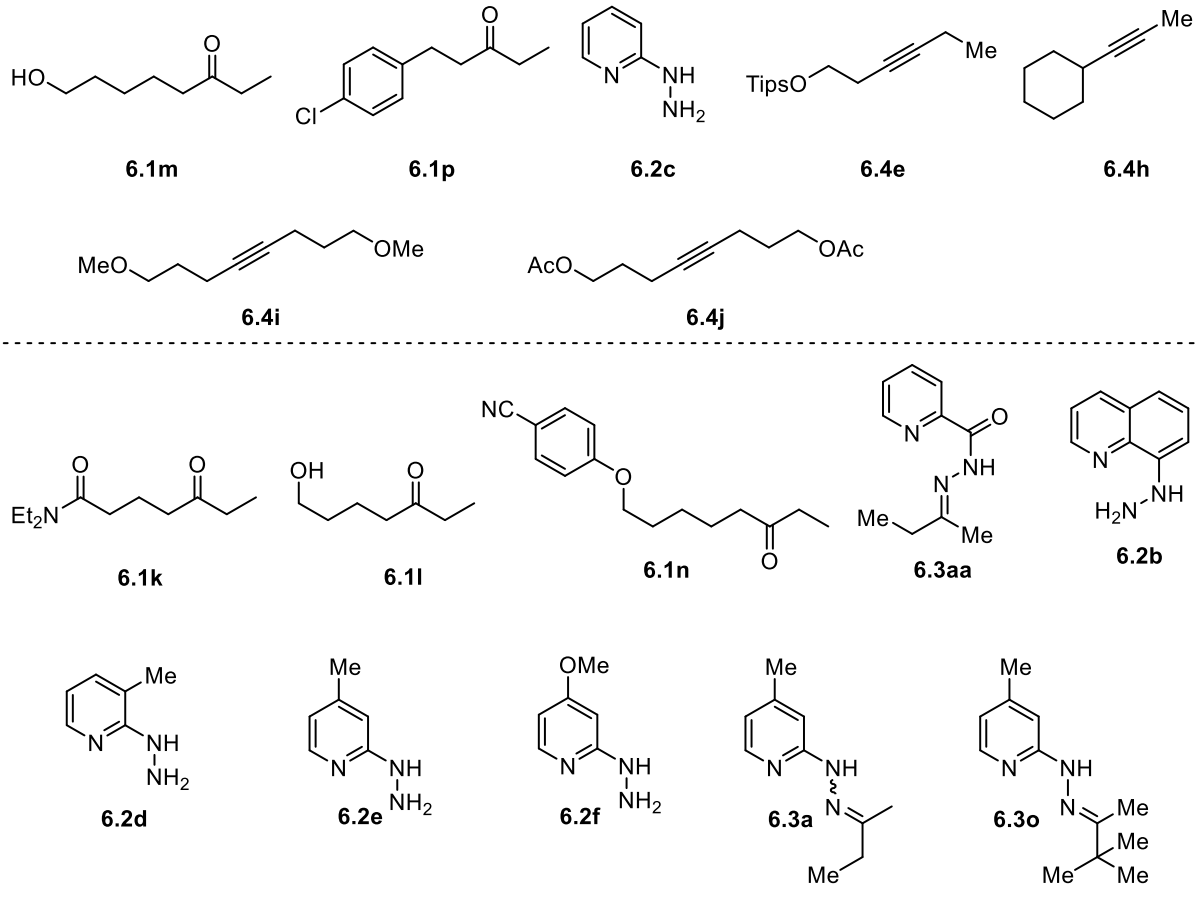
Unless otherwise noted, all experiments were carried out under air atmosphere. 1,4-dioxane was distilled over Na. The 4Å molecule sieves were pre-dried overnight at 110 °C in an oven, and then flame-dried under *vacuo* for 30 minutes. Other reagents and solvents were directly used from the supplier without further purification unless noted. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plate (silica gel 60, F254, EMD chemical). The vials (1 dram, 15×45 mm with PTFE lined cap attached) were purchased from Qorpak and used directly. Infrared spectra were recorded on a Nicolet iS5 FT-IR Spectrometer using neat thin film technique. High-resolution mass spectra (HRMS) were obtained on an Agilent 6224 Tof-MS spectrometer and are reported as m/z. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded with a Bruker Avance 500 instrument (500 MHz, ^{1}H at 500 MHz, ^{13}C at 126 MHz) unless noted. For $CDCl_3$ solutions, the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; $CHCl_3$ δ H (7.26 ppm) and $CDCl_3$ δ C (77.16 ppm). For C_6D_6 solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; C_6D_5H δ H (7.16 ppm) and C_6D_6 δ C (128.06 ppm). For CD_3OD solutions, the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; CD_2HOD δ H (3.31 ppm) and CD_3OD δ C (49.00 ppm). Coupling constants are reported in Hertz (Hz). Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm, referenced to protium: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet (quintet), dd = doublet of doublets, td = triplet of

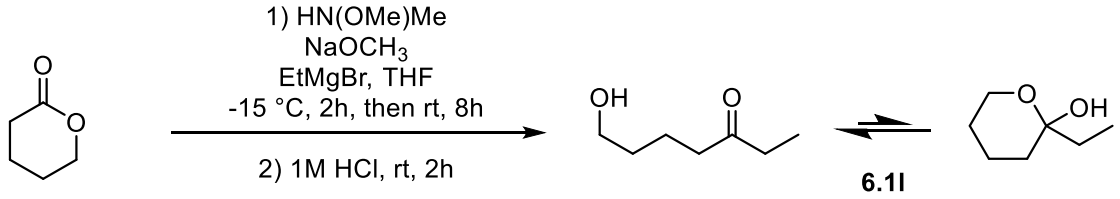
doublets, ddd = doublet of doublet of doublets, m = multiplet, coupling constant (Hz), and integration).

Substrate synthesis and characterization

Compounds **6.1m**[27], **6.1p**[28], **6.2c**[29], **6.4e**[30], **6.4h**[31], **6.4i**[32], and **6.4j**[33] were synthesized according to the previously reported literatures. Compounds **6.1k**, **6.1l**, **6.1n**, **6.3aa**, **6.2b**, **6.2d**, **6.2e**, **6.2f**, **6.3a**, and **6.3o** were prepared according to the following procedures. The others were commercially available and were used as received.

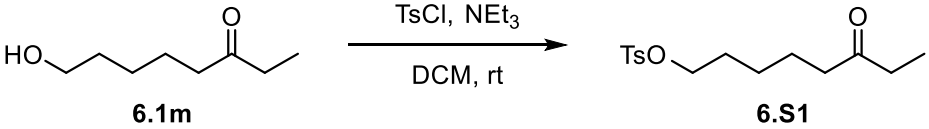
Scheme 6.15 Structures of the Substrates Synthesized for this Study





6.1l

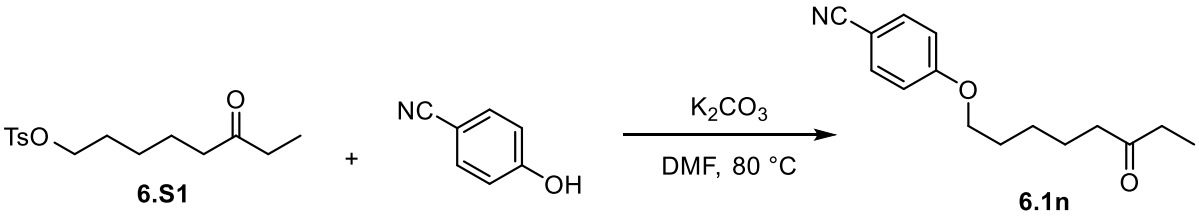
6.1l[32]: Following a modified procedure of literature[27], a THF (160 mL) solution of tetrahydro-2*H*-pyran-2-one (1.0 g, 10 mmol, 1 equiv), *N*,*O*-dimethylhydroxylamine hydrochloride (1.16g, 12 mmol, 1.2 equiv) and sodium methoxide (140 mg, 2.5 mmol, 0.25 equiv) was cooled to -15 °C using ethylene glycol/dry ice as the cooling bath. A THF (100 mL) solution of EtMgBr (25mL, 3.0 M in Et_2O) was then added slowly over 20 mins. The reaction mixture was stirred at -15 °C for 2 hours, and then at room temperature for 8 hours. 1M HCl (100 mL) was added, and the stirring was continued for another 2 hours. The reaction mixture was treated with H_2O (100 mL), extracted with DCM, and dried over $MgSO_4$. The filtrate was concentrated under *vacuo* and further purified by flash column chromatography (hexane/ethyl acetate, from 10:1 to 4:1) to give product **6.1l** as a colorless oil (520 mg, 40% yield). R_f = 0.25 (Hex/EA = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (td, *J* = 11.0, 4.5 Hz, 0.13H), 3.70 – 2.50 (m, 1.87H), 2.50 – 2.35 (m, 3.48H), 1.90 (br, 1H), 1.81 – 1.40 (m, 4.52H), 1.04 (t, *J* = 7.3 Hz, 2.6H), 0.92 (t, *J* = 7.6 Hz, 0.4H).



6.1m **6.S1**

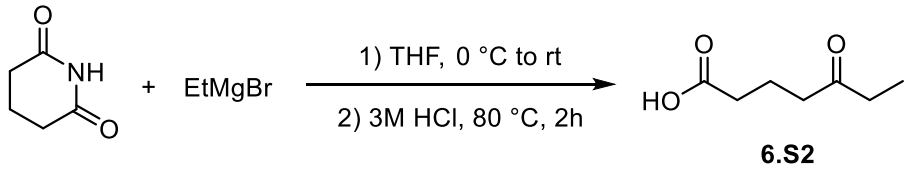
6.S1: To a DCM (6 mL) solution of **6.1m** (380 mg, 2.6 mmol, 1 equiv), triethylamine (530 mg, 5.2 mmol, 2 equiv) was added TsCl (545 mg, 2.86 mmol, 1.1 equiv) at room

temperature. The mixture was stirred at room temperature for 12 hours. The reaction was then concentrated under *vacuo* and further purified by flash column chromatography (hexane/ethyl acetate, from 20:1 to 5:1) to give product **6.S1** as a colorless oil (660 mg, 85% yield). R_f = 0.3 (Hex/EA = 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.00 (t, *J* = 6.4 Hz, 2H), 2.44 (s, 3H), 2.37 (dt, *J* = 17.4, 7.3 Hz, 4H), 1.69 – 1.59 (m, 2H), 1.51 (p, *J* = 7.4 Hz, 2H), 1.33 – 1.25 (m, 2H), 1.02 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.35, 144.83, 133.22, 129.94, 127.98, 70.45, 42.03, 36.04, 28.81, 25.13, 23.17, 21.75, 7.93. IR (KBr) 3067, 2974, 2941, 2873, 1710, 1597, 1462, 1462, 1412, 1361, 1178, 1103 cm^{-1}. HRMS: Ref. Mass 298.1239 Obs. mass: 298.1245.



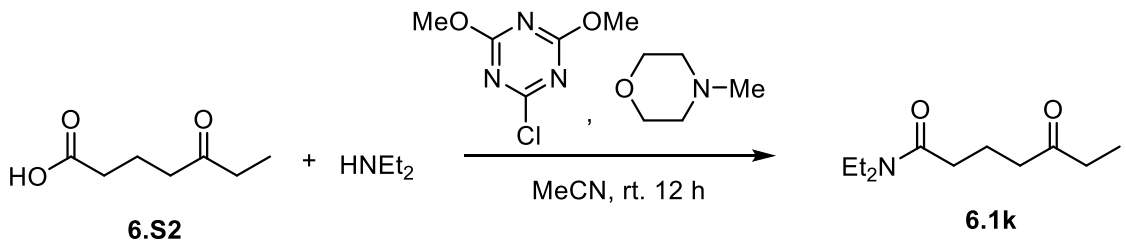
6.1n: To a DMF (10 mL) solution of **6.S1** (450 mg, 1.5 mmol, 1 equiv) and 4-hydroxybenzonitrile (220 mg, 1.8 mmol, 1.2 equiv) was added K_2CO_3 (310 mg, 2.25 mmol, 1.5 equiv) at room temperature. The mixture was then heated to 80 °C for 4 hours. The reaction was filtered, concentrated under *vacuo*, and further purified by flash column chromatography (hexane/ethyl acetate, from 20:1 to 5:1) to give product **6.1n** as a white solid (300 mg, 82% yield). R_f = 0.35 (Hex/Acetone = 3:1). M. p. = 58-60 °C. IR (KBr) 3050, 2980, 2949, 2901, 2224, 1715, 1659, 1606, 1513, 1406, 1381, 1311, 1263, 1178, 1117 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.99 (t, *J* = 6.4

Hz, 2H), 2.43 (dt, *J* = 14.4, 7.2 Hz, 4H), 1.81 (dt, *J* = 14.3, 6.5 Hz, 2H), 1.65 (ddd, *J* = 15.1, 8.2, 6.3 Hz, 2H), 1.51 – 1.38 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.46, 162.48, 134.09, 119.38, 115.30, 103.93, 68.22, 42.22, 36.11, 28.98, 25.78, 23.58, 7.98. HRMS: Ref. mass 245.1416 Obs. mass: 245.1424.



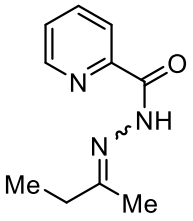
6.S2

6.S2[35]**:** To a THF (50 mL) solution of piperidine-2,6-dione (1.13 g, 10 mmol, 1 equiv) was added EtMgBr (3.0 M in diethyl ether, 10 mL, 3 equiv) slowly at 0 °C. The mixture was stirred at 0 °C for 1 hour, and then at room temperature overnight. HCl (3 M, 200 mL) was added, and the mixture was stirred at 80 °C for 2 hours. Solid KOH was added to the solution to adjust the pH to >13, and the mixture was extracted by Et_2O twice. The aqueous phase was separated and acidified to pH < 2 by using HCl (conc.), and further extracted by Et_2O for three times. The organic phase was dried over $MgSO_4$, and concentrated under *vacuo* to give product **6.S2** as a white solid (1.22 g, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.22 (br, 1H), 2.49 (t, *J* = 7.2 Hz, 2H), 2.45 – 2.35 (m, 4H), 1.89 (p, *J* = 7.2 Hz, 2H), 1.04 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.98, 179.57, 41.02, 36.08, 33.16, 18.72, 7.89.



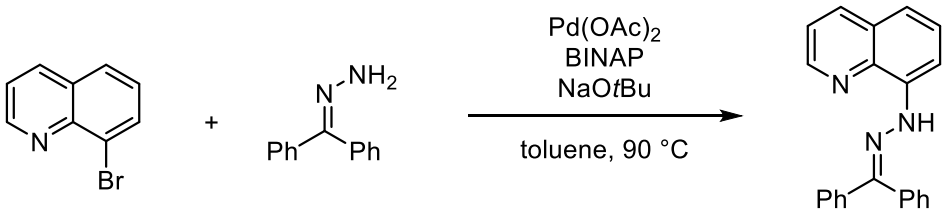
6.S2 **6.1k**

6.1k: 6.1k was synthesized following a modified procedure of literature[36]. To a mixture of **6.S2** (360 mg, 2.5 mmol) and 2-chloro-4,6-dimethoxy-l,3,5-triazine (1 g, 5.7 mmol) in anhydrous CH_3CN (10.0 mL) under inert atmosphere was added *N*-methyl morpholine (1.25 g, 12.4 mmol) and diethylamine (365 mg, 5.0 mmol). The mixture was stirred at room temperature for 12 h. DCM (60 mL) was added. The mixture was washed with HCl (2.0 M) for three times, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was further purified by flash column chromatography (hexane/acetone, from 6:1 to 4:1) to give product **6.1k** as a colorless oil (400 mg, 80% yield). R_f = 0.25 (Hex/Acetone = 3:1). IR (KBr) 2977, 2937, 1712, 1645, 1462, 1431, 1266, 1229 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 3.35 (q, *J* = 7.1 Hz, 2H), 3.29 (q, *J* = 7.2 Hz, 2H), 2.51 (t, *J* = 7.0 Hz, 2H), 2.42 (q, *J* = 7.3 Hz, 2H), 2.31 (t, *J* = 7.2 Hz, 2H), 1.91 (p, *J* = 7.1 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.61, 171.62, 42.03, 41.61, 40.17, 35.99, 32.20, 19.68, 14.48, 13.25, 7.97. HRMS: Ref. mass 199.1572 Obs. mass: 199.1579.



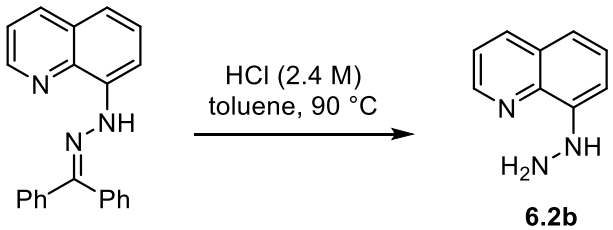
6.3aa

6.3aa: A MeOH solution of picolinohydrazide (550 mg, 4 mmol, 1 equiv) and 2-butanone (640 mg, 8.8 mmol, 2.2 equiv) was stirred at 70 °C for 5 hours. The reaction was concentrated under *vacuo*, and further purified by recrystallization in toluene (1 mL) to give product **6.3aa** as a white solid (670 mg, 88%). R_f = 0.25 (Hex/EA = 1:1). M. p. = 97-99 °C. IR (KBr) 3331, 2985, 2943, 2898, 1692, 1572, 1521, 1434, 1282 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 10.79 (s, 0.12H), 10.65 (s, 0.88H), 8.52 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.26 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.43 (ddd, *J* = 7.6, 4.8, 1.3 Hz, 1H), 2.49 – 2.36 (m, 2H), 2.12 (s, 0.36H), 2.00 (s, 2.64H), 1.24 – 1.10 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) carbon signals were found at δ 160.46, 159.95, 159.75, 149.65, 148.07, 148.04, 148.03, 137.49, 137.47, 126.51, 126.48, 122.69, 122.68, 32.38, 23.59, 22.95, 14.84, 11.09, 9.69. HRMS: Ref. mass 191.1059 Obs. mass: 191.1072.



6.S3
(mixed with benzophenone)

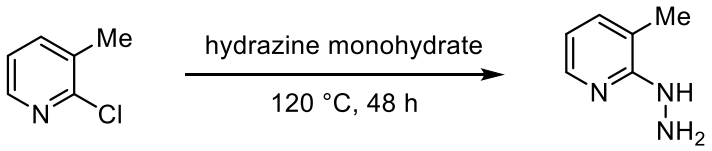
6.S3: Following a slightly modified procedure of literature[37], a toluene (20 mL) solution of 8-bromoquinoline (1.04 g, 5 mmol, 1 equiv), (diphenylmethylene)hydrazine (1.2g, 6 mmol, 1.2 equiv), $Pd(OAc)_2$ (92 mg, 0.4 mmol, 0.08 equiv), BINAP (311 mg, 0.5 mmol, 0.1 equiv) and sodium *tert*-butoxide (1.2 g, 12.5 mmol, 2.5 equiv) was stirred at 90 °C under N_2 atmosphere for 6 hours. The reaction was filtered, concentrated under *vacuo*, and further purified by flash column chromatography (hexane/ethyl acetate, from 20:1 to 8:1) to give the crude product **6.S3** (700 mg, mixed with inseparable benzophenone). R_f = 0.75 (Hex/EA = 3:1). The crude **6.S3** was directly used for the next step without further purification.



6.S3 **6.2b**

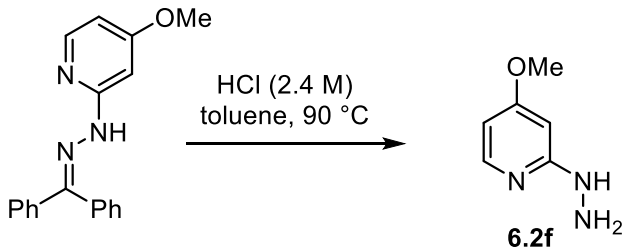
6.2b: A HCl (2.4 M, 7.5 mL)/toluene (3 mL) solution of **6.S3** (600 mg) was stirred at 90 °C under N_2 atmosphere for 19 hours. The reaction mixture was then cooled to room temperature. The aqueous phase was separated and washed by toluene. NaOH (10 M, 3 mL) was added, and the aqueous phase was further extracted with Et_2O, and dried over Na_2SO_4. The filtrate was then concentrated under *vacuo* to give the product **6.2b** as a yellow solid (210 mg, 71% yield). M. p. = 63-65 °C. IR (KBr) 3325, 3193, 3039, 1622, 1577, 1510, 1473, 1378, 1333 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.72 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.08 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.28 (s, 1H), 7.16 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.08 (dd, *J* = 7.6, 1.2 Hz, 1H), 3.68 (s, 2H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ 147.46, 147.32, 137.73, 135.99, 128.44, 127.60, 121.63, 116.02, 105.88. HRMS: Ref. mass 159.0796 Obs. mass: 159.0801.



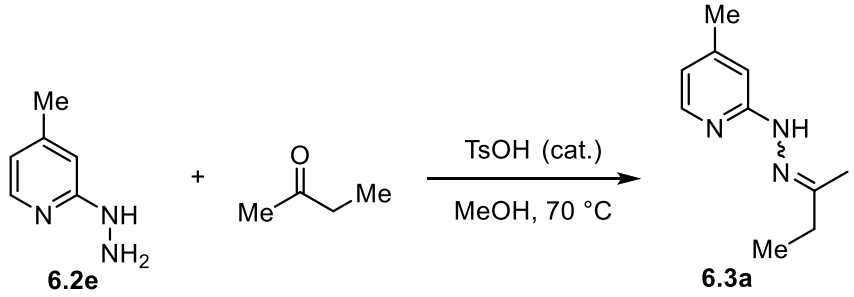
6.2d

6.2d: Following a modified procedure of literature[29], a mixture of 2-chloro-3-methylpyridine (0. mL) and hydrazine monohydrate (3.5 mL) was stirred under N_2 atmosphere at 120 °C in a sealed 20 mL vials for 48 hours. After cooled to room temperature, the reaction mixture was extracted with Et_2O (40 mL * 3) and dried over Mg_2SO_4. The filtrate was then concentrated under *vacuo* to yield 2-hydrazinyl-3-methylpyridine **6.2d** as a white solid (0.4 g, 49%). M. p. = 117-119 °C. IR (KBr) 3314, 3280, 3199, 2943, 2912, 1692, 1630, 1608, 1510, 1470, 1381 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 5.2 Hz, 1H), 7.23 (d, *J* = 7.1 Hz, 1H), 6.62 (t, *J* = 6.0 Hz, 1H), 5.61 (s, 1H), 4.00 (s, 2H), 2.06 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.51, 145.06, 137.13, 117.01, 114.44, 16.36. HRMS: Ref. mass 123.0796 Obs. mass: 123.0800.



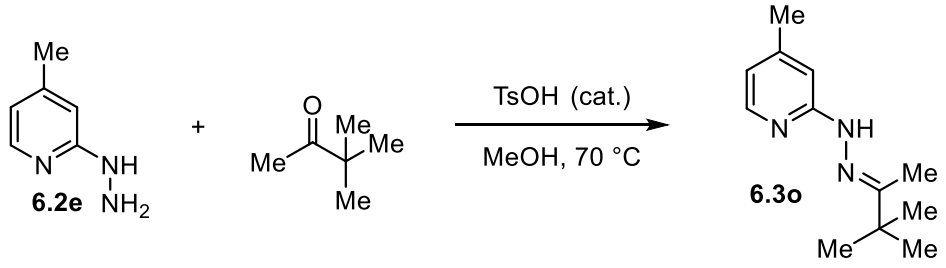
6.S4 **6.2f**

6.2f: **6.S4** was synthesized according to the previously reported literatures.[37] A HCl (2.4 M, 2.5 mL)/toluene (1 mL) solution of **6.S4** (150 mg) was stirred at 90 °C under N_2 atmosphere for 15 hours. The reaction mixture was then cooled to room temperature. The aqueous phase was separated and washed by toluene. NaOH (10 M, 1 mL) was added, and the aqueous phase was further extracted with Et_2O, and dried over Na_2SO_4. The filtrate was then concentrated under *vacuo* to give the product **6.2b** as a yellow solid (60 mg, 87% yield). M. p. = 100-101 °C. IR (KBr) 3297, 3255, 3171, 3025, 2971, 1625, 1583, 1529, 1223 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 5.9 Hz, 1H), 6.39 – 6.10 (m, 2H), 5.82 (s, 1H), 4.00 – 3.63 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.42, 163.55, 148.98, 103.35, 90.55, 55.13. HRMS: Ref. mass 139.0746 Obs. mass: 139.0752.

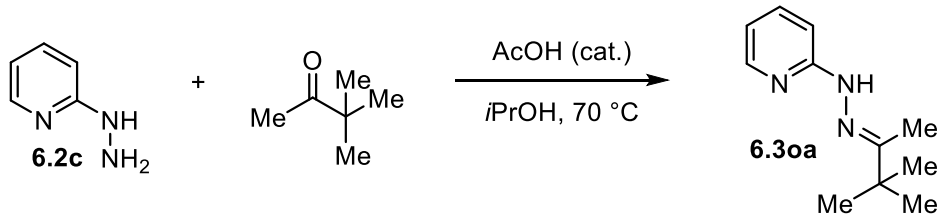


6.3a: A MeOH (5 mL) solution of **6.2e** (246 mg, 2 mmol, 1 equiv), 2-butanone (152 mg, 2.1 mmol, 1.05 equiv), and *p*-TsOH (2 mg) was stirred at 70 °C under N_2 atmosphere for 5 hours. The reaction was then concentrated under *vacuo*, and further purified by flash column chromatography (hexane/ethyl acetate, from 10:1 to 5:1) to give product **6.3a** as a colorless oil (330 mg, 93% yield). R_f = 0.3 (Hex/EA = 3:1). IR (KBr) 3353, 3204, 2968, 2938, 2879, 1611, 1569, 1440, 1142, 1063 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* =

5.2 Hz, 1H), 7.70 (s, 0.21H), 7.60 (s, 0.79H), 7.05 (s, 1H), 6.55 (dd, *J* = 5.2, 1.6 Hz, 1H), 2.38 – 2.25 (m, 5H), 2.02 (s, 0.63H), 1.86 (s, 2.37H), 1.20 – 1.10 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) carbon signals were found at δ 157.82, 149.31, 149.27, 147.42, 147.41, 116.85, 107.61, 107.46, 32.19, 22.77, 22.72, 21.45, 21.42, 14.47, 11.16, 9.64. HRMS: Ref. mass 177.1266 Obs. mass: 177.1278.

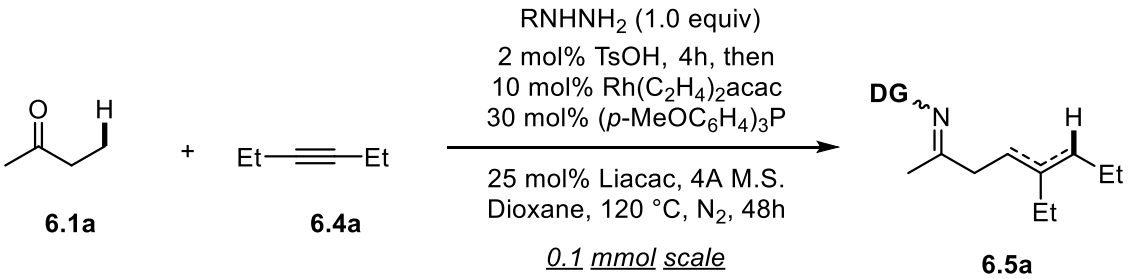


6.3o: A MeOH (5 mL) solution of **6.2e** (246 mg, 2 mmol, 1 equiv), 2-butanone (210 mg, 2.1 mmol, 1.1 equiv), and *p*-TsOH (2 mg) was stirred at 70 °C under N_2 atmosphere for 5 hours. The reaction was then concentrated under *vacuo*, and further purified by flash column chromatography (hexane/ethyl acetate, from 10:1 to 5:1) to give the product **6.3o** as a yellowish solid (390 mg, 95% yield). R_f = 0.35 (Hex/EA = 3:1). M. p. = 49-51 °C. IR (KBr) 3356, 3215, 3058, 2968, 2935, 2873, 1614, 1569, 1442, 1291, 1156, 1094, 990 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 5.0 Hz, 0.05H), 7.99 – 7.87 (m, 0.95H), 7.62 (br, 1H), 7.24 – 7.16 (m, 0.1H), 7.05 (t, *J* = 0.8 Hz, 0.95H), 6.54 (dd, *J* = 5.2, 1.5 Hz, 0.95H), 2.40 (s, 0.15H), 2.30 (s, 2.85H), 1.82 (s, 2.85H), 1.67 (s, 0.15H), 1.16 (s, 8.55H), 1.09 (s, 0.45H). ^{13}C NMR (126 MHz, $CDCl_3$) carbon signals were found at δ 158.09, 153.55, 153.50, 150.09, 149.23, 149.08, 147.36, 126.38, 116.76, 113.94, 108.24, 107.74, 39.07, 38.55, 27.91, 25.83, 21.53, 21.27, 15.07, 10.87. HRMS: Ref. mass 205.1579 Obs. mass: 205.1590.



6.3oa: 2-Hydrazinopyridine[3] (500 mg, 4.58 mmol, 1 equiv) was combined with pinacolone (600 μL, 4.79 mmol, 1.05 equiv) in *i*PrOH (10 mL) with catalytic AcOH (10 μL) followed by heating at 70 ºC. After 24 h the reaction was cooled and evaporated in *vacuo* to give product **6.3oa** as a light orange solid (820 mg, 93% yield). R_f = 0.66 (Hex/EA = 2:1). M. p. (*i*PrOH): 72-75 ºC. IR (KBr): 3360, 3221, 3087, 3052, 2966, 2906, 2868, 1599, 1576, 1508 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (ddd, *J* = 4.9, 1.9, 0.8 Hz, 1H), 7.74 (br, 1H), 7.56 (ddd, *J* = 8.7, 7.2, 1.8 Hz, 1H), 7.24 (dt, *J* = 8.4, 0.8 Hz, 1H), 6.71 (ddd, *J* = 7.1, 5.0, 1.0 Hz, 1H), 1.84 (s, 3H), 1.17 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.96, 153.71, 147.49, 138.01, 115.15, 107.54, 38.49, 27.80, 10.87. HRMS: $[M+H]^+$ Ref. mass 192.14930 Obs. mass: 192.14950.

Typical procedure for the control experiments in Table 6.1



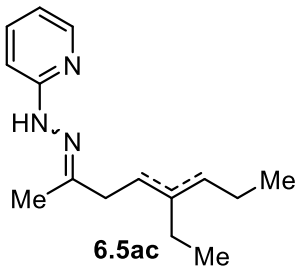
The reaction was conducted on a 0.1 mmol scale. A 4 mL vial was charged with $RNHNH_2$ (0.1 mmol, 1.0 equiv) and *p*-toluenesulfonic acid monohydrate (0.4 mg, 0.002

mmol, 0.02 equiv). The vial was sealed with a PTFE lined cap and transferred into a glove box. After purged under N_2 atmosphere for 5 min, the vial was charged with 1,4-dioxane (1 mL) and 2-butanone (**6.1a**) (7.2 mg, 0.1 mmol, 1.0 equiv). The vial was then sealed again and taken out of the glove box, and heated in a pie-block at 90 °C under stirring for 4 hours. After cooled to room temperature, (p-$MeOC_6H_4)_3P$ (10.5 mg, 0.03 mmol, 0.30 equiv) and Liacac (2.7 mg, 0.025 mmol, 0.25 equiv) was added into the reaction mixture. The vial was sealed again and transferred into a glove box. After purged under N_2 atmosphere for 5 min, 4Å molecular sieve (150 mg), $Rh(C_2H_4)_2$acac (2.6 mg, 0.01 mmol, 0.10 equiv) and 3-hexyne (50 mg, 0.6 mmol, 6.0 equiv) was added into the reaction mixture. The vial was then sealed again and taken out of the glove box, and heated in a pie-block at 120 °C under stirring for 48 hours (unless otherwise noted).

For ^{1}H-NMR analysis: After cooled to room temperature, the reaction mixture was filtered through a short plug of Celite and eluted with DCM to remove the 4Å molecular sieve. The filtrate was then concentrated under *vacuo*. $CDCl_3$ (1 mL) and 1,1,2,2-tetrachloroethane (as the internal standard, about 25 mg) was added to the residue and the resulting mixture was directly used for ^{1}H-NMR analysis.

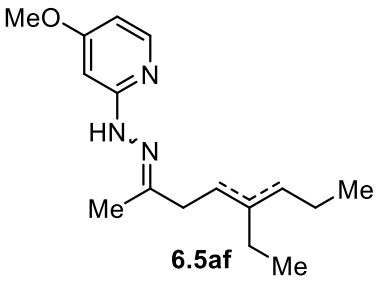
For analysis through isolation: After cooled to room temperature, the reaction mixture was filtered through a short plug of Celite and eluted with DCM to remove the 4Å molecular sieve. The filtrate was then concentrated under *vacuo* and further purified by flash column chromatography (toluene/ethyl acetate) to give the alkenylation product as an

inseparable mixture of the γ,δ- and β,γ-unsaturated hydrazones with both E and Z configurational stereoisomers of the vinyl and hydrazonoyl groups.



6.5ac

6.5ac: The reaction was conducted on a 0.1 mmol scale. Yellowish oil (16.2 mg, 66% yield). R_f = 0.6 (Hex/EA = 1:1). IR (KBr) 3359, 3207, 3087, 2963, 2932, 2873, 1600, 1578, 1510, 1445, 1322, 1128 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.22 – 8.00 (m, 1H), 7.92 – 7.44 (m, 2H), 7.25 – 7.15 (m, 1H), 6.80 – 6.57 (m, 1H), 5.45 – 5.01 (m, 1H), 3.06 – 2.96 (m, 0.6H), 2.44 – 2.23 (m, 2.5H), 2.14 – 1.99 (m, 4.1H), 1.91 – 1.83 (m, 2.6H), 1.71 – 1.39 (m, 1.2H), 1.07 – 0.81 (m, 6H). HRMS: Ref. mass 245.1892 Obs. mass: 245.1899.



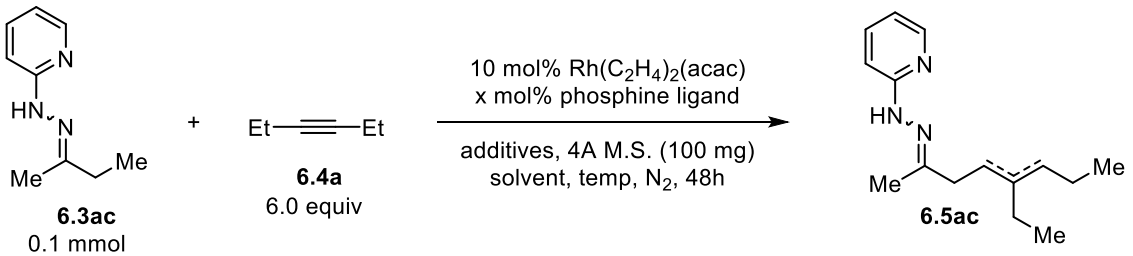
6.5af

6.5af: The reaction was conducted on a 0.1 mmol scale. Yellowish oil (17.3 mg, 63% yield). R_f = 0.5 (Hex/EA = 1:2). IR (KBr) 3356, 3199, 2969, 2932, 2873, 1603, 1578, 1510, 1479, 1445, 1209, 1170 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.84 (m, 1H), 7.84 – 7.51

(m, 1H), 6.90 – 6.66 (m, 1H), 6.50 – 6.24 (m, 1H), 5.43 – 4.98 (m, 1H), 4.04 – 3.72 (m, 3H), 3.06 – 2.96 (m, 0.6H), 2.45 – 2.18 (m, 2.4H), 2.15 – 1.95 (m, 4.2H), 1.90 – 1.82 (m, 2.5H), 1.74 – 1.39 (m, 1.3H), 1.08 – 0.81 (m, 6H). HRMS: Ref. mass 275.1998 Obs. mass: 275.2015.

Additional control experiments for the Rh-catalyzed alkenylation

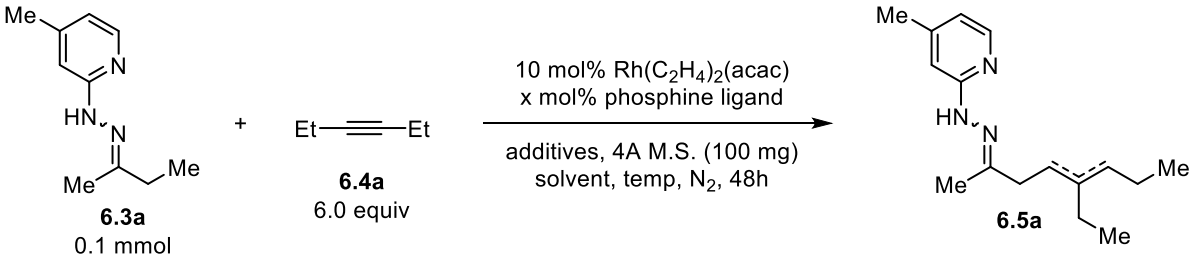
Table 6.2 Control Experiments for the Rh-Catalyzed Alkenylation using **6.2c** as the DG



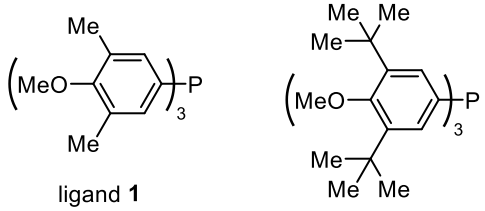
entry	phosphine ligand (mol%)	solvent	temp	additive	yield[a]	recovered starting material[a]
1	(p-$MeOC_6H_4)_3P$ (10)	toluene	130 °C	--	48	34
2	(p-$MeC_6H_4)_3P$ (10)	toluene	130 °C	--	37	50
3	(o-$MeOC_6H_4)_3P$ (10)	toluene	130 °C	--	n.d.	78
4	(2,4,6-tri-$MeOC_6H_2)_3P$ (10)	toluene	130 °C	--	n.d.	76
5	(p-$MeOC_6H_4)_3P$ (30)	toluene	110 °C	--	66	25
6	PMe_3 (30)	toluene	110 °C	--	n.d	n.a.
7	PMe_2Ph (20)	toluene	110 °C	--	3	84
8	$PMePh_2$ (20)	toluene	110 °C	--	29	54
9	$PCyPh_2$ (20)	toluene	110 °C	--	21	62

[a] All yields are determined through crude ^{1}H-NMR analysis using 1,1,2,2-tetrachloroethane as the internal standard.

Table 6.3 Control Experiments for the Rh-Catalyzed Alkenylation using **6.2e** as DG

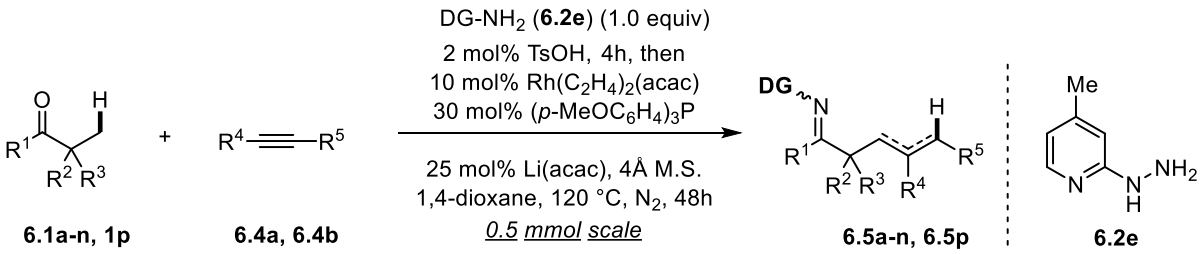


entry	phosphine ligand (mol%)	solvent	temp	additive	yield[a]	recovered starting material[a]
1	(*p*-MeOC$_6$H$_4$)$_3$P (30)	1,4-dioxane	120 °C	Li(acac) (25 mol%)	84	17
2	ligand **1** (30)	1,4-dioxane	120 °C	Li(acac) (25 mol%)	82	24
3	ligand **2** (30)	1,4-dioxane	120 °C	Li(acac) (25 mol%)	82	23



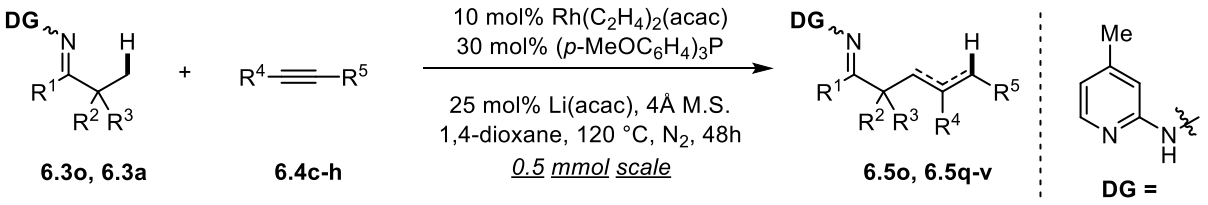
[a] All yields are determined through crude ^{1}H-NMR analysis using 1,1,2,2-tetrachloroethane as the internal standard.

Typical procedure for the substrate scope study in Schemes 6.9 and 6.10



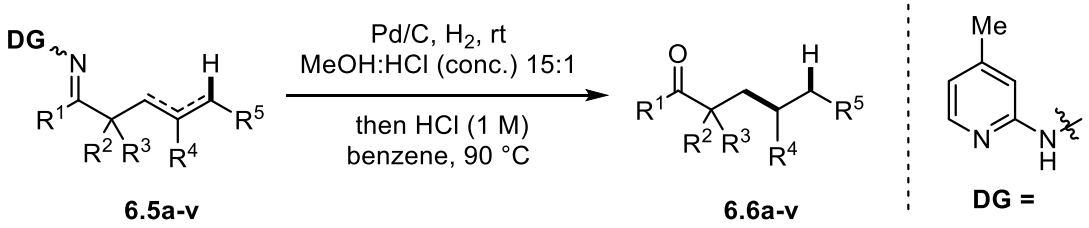
General procedure A: An 8 mL vial was charged with **6.2e** (61.5 mg, 0.5 mmol, 1.0 equiv) and *p*-toluenesulfonic acid monohydrate (1.9 mg, 0.01 mmol, 0.02 equiv). The vial was sealed with a PTFE lined cap and transferred into a glove box. After purged under N_2 atmosphere for 5 min, the vial was charged with 1,4-dioxane (5 mL) and the ketone substrate (0.5 mmol, 1.0 equiv). The vial was then sealed again and taken out of the glove box, and

heated in a pie-block at 90 °C under stirring for 4 hours. After cooled to room temperature, (*p*-$MeOC_6H_4)_3P$ (52.5 mg, 0.15 mmol, 0.30 equiv) and Li(acac) (13.5 mg, 0.125 mmol, 0.25 equiv) were added into the reaction mixture. The vial was sealed again and transferred into a glove box. After purged under N_2 atmosphere for 5 min, 4Å molecular sieve (750 mg), $Rh(C_2H_4)_2(acac)$ (12.9 mg, 0.05 mmol, 0.10 equiv) and the alkyne substrate (3 mmol, 6.0 equiv) were added into the reaction mixture. The vial was then sealed again and taken out of the glove box, and heated in a pie-block at 120 °C under stirring for 48 hours (unless otherwise noted). After cooled to room temperature, the reaction mixture was filtered through a short plug of Celite and eluted with DCM to remove the molecular sieves. The filtrate was then concentrated under *vacuo* and further purified by flash column chromatography (toluene/ethyl acetate) to give the alkenylation product as an inseparable mixture of the γ,δ- and β,γ-unsaturated hydrazones with both E and Z configurational stereoisomers of vinyl and hydrazonoyl groups.



General procedure B: An 8 mL vial was charged with the hydrazone substrates (0.5 mmol, 1.0 equiv), (*p*-$MeOC_6H_4)_3P$ (52.5 mg, 0.15 mmol, 0.30 equiv) and Li(acac) (13.5 mg, 0.125 mmol, 0.25 equiv). The vial was sealed with a PTFE lined cap and transferred into a

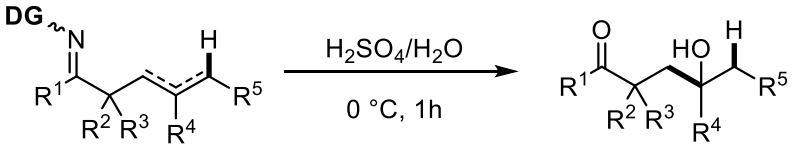
glove box. After purged under N_2 atmosphere for 5 min, the vial was charged with 1,4-dioxane (5 mL), 4Å molecular sieve (500 mg), $Rh(C_2H_4)_2(acac)$ (12.9 mg, 0.05 mmol, 0.10 equiv) and the alkyne substrate (3 mmol, 6.0 equiv). The vial was then sealed again and taken out of the glove box, and heated in a pie-block at 120 °C under stirring for 48 hours (unless otherwise noted). After cooled to room temperature, the reaction mixture was filtered through a short plug of Celite and eluted with DCM to remove the molecular sieves. The filtrate was then concentrated under *vacuo* and further purified by flash column chromatography (toluene/ethyl acetate) to give the alkenylation product as an inseparable mixture of the γ,δ- and β,γ-unsaturated hydrazones with both E and Z configurational stereoisomers of vinyl and hydrazonoyl groups. *Procedure for the condensation between* **6.*2e*** *and the ketone substrates*: A MeOH solution of **6.2e** (1 equiv) and the ketone substrate (1.05 equiv) was stirred under N_2 atmosphere at 70 °C. Very small amount of *p*-TsOH (ca. 1 mol%) was added as the catalyst, and the condensation reaction was usually completed within 4 hours. The reaction mixture was then concentrated under *vacuo* and purified by flash column chromatography (hexane/ethyl acetate) to give the hydrazone product typically in > 90% yield.



6.5a-v **6.6a-v**

General procedure C: To an 8 mL vial charged with the alkenylation product (ca. 0.1 mmol, 1.0 equiv) and the Pd/C (10% w/w, 40 mg) under a hydrogen atmosphere, a 15:1

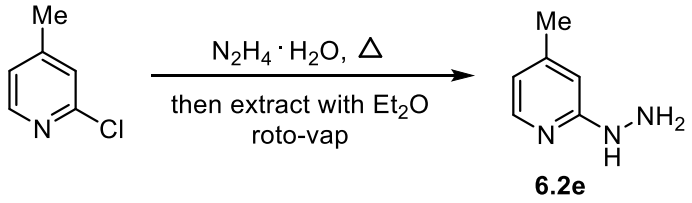
MeOH/HCl(conc.) solution (0.6 mL) was added through a syringe. The reaction mixture was stirred overnight at room temperature. Benzene (1.5 mL) and HCl (aq.) (1.0M, 2 mL) was then added, and the vial was sealed with a PTFE lined cap and transferred into a glove box. After purged under an N_2 atmosphere for 5 min, the vial was then sealed again and taken out of the glove box, and stirred overnight at 90 °C. The reaction mixture was extracted with Et_2O, and dried over Na_2SO_4. The filtrate was concentrated under *vacuo* and further purified by flash column chromatography (hexane/ethyl acetate) to give the β-alkylated ketone product.



6.5 **6.7a-e**

General procedure D: To a 4 mL vial charged with the alkenylation product (ca. 0.1 mmol, 1.0 equiv), a 1:1 H_2SO_4/H_2O (v/v, 1.2 mL) was added at 0 °C. The reaction was stirred at 0 °C for 1-2 hours and monitored by TLC. Upon done, the reaction was rapidly extracted with Et_2O, washed with $NaHCO_3$ (sat.), and dried over Na_2SO_4. The filtrate was then concentrated under *vacuo* and further purified by flash column chromatography (hexane/ethyl acetate) to give the β-aldol product.

Synthesis of DG–NH_2

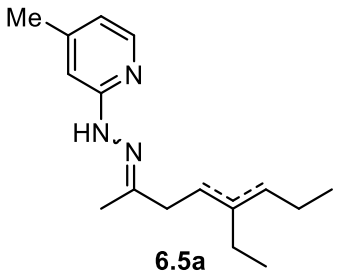


6.2e

Following a modified procedure from literature,[29] a mixture of 2-chloro-4-methylpyridine (2 mL) and hydrazine monohydrate (10 mL) was stirred under an N_2 atmosphere at 120 °C in a sealed 20 mL vials for 32 hours. After cooled to room temperature, the reaction mixture was extracted with Et_2O (40 mL×3) and dried over Mg_2SO_4. The filtrate was then concentrated under *vacuo* to yield the 2-hydrazinyl-4-methylpyridine (**6.2e**) as a white solid (1.77 g, 80%), which is stable during storage at –20 °C for at least 4 weeks. IR (KBr) 3303, 3075, 3019, 2921, 1625, 1569, 1448, 1288, 1190, 987 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 5.2 Hz, 1H), 6.50 (s, 2H), 5.85 (br, 1H), 3.79 (br, 2H), 2.25 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.64, 148.70, 147.47, 116.21, 107.26, 21.25. HRMS: Ref. mass 123.0796 Obs. mass: 123.0798.

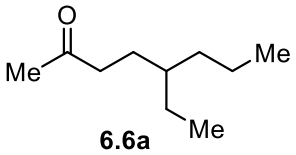
** In some batches, the synthesized* ***6.2e*** *was slightly contaminated by ca. 5% of unknown impurities. In such cases, slightly excess* ***6.2e*** *(0.51 mmol, 1.05 equiv) was used in the C–H alkenylation reaction.*

Characterization data for the products



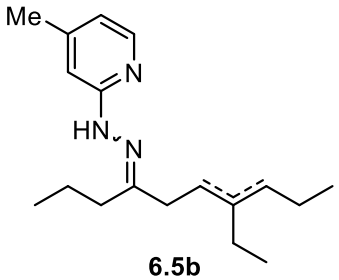
6.5a

6.5a: The reaction was conducted on a 0.5 mmol scale. Yellowish oil (100 mg, 77% yield). R_f = 0.3 (Hex/EA = 3:1). IR (KBr) 3204, 2960, 2926, 2871, 1612, 1569, 1506, 1440 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 – 7.98 (m, *J* = 39.4 Hz, 1H), 7.98 – 7.63 (m, 1H), 7.22 – 6.91 (m, 1H), 6.75 – 6.36 (m, 1H), 5.33 – 5.05 (m, 1H), 3.10 – 2.95 (m, 0.6H), 2.47 – 2.20 (m, 5.6H), 2.14 – 1.98 (m, 4.4H), 1.93 – 1.85 (m, 2.4H), 1.62 – 1.40 (m, 1H), 1.05 – 0.85 (m, 6H). HRMS: Ref. mass 259.2048 Obs. mass: 259.2053.



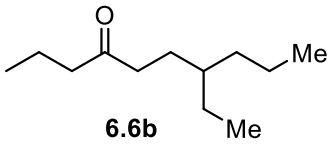
6.6a

6.6a: The reaction was conducted on a 0.1 mmol scale using 25.9 mg **6.5a**. Colorless oil (13.2 mg, 85% yield). R_f = 0.7 (Hex/EA = 5:1). IR (KBr) 2958, 2926, 2875, 1722, 1462, 1358, 1165 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.45 – 2.32 (m, 2H), 2.14 (s, 3H), 1.53 (ddd, *J* = 9.4, 7.9, 5.5 Hz, 2H), 1.32 – 1.13 (m, 7H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.84 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.66, 41.42, 38.40, 35.48, 29.96, 27.25, 25.83, 19.92, 14.58, 10.91.HRMS: Ref. mass 156.1514 Obs. mass: 156.1504.



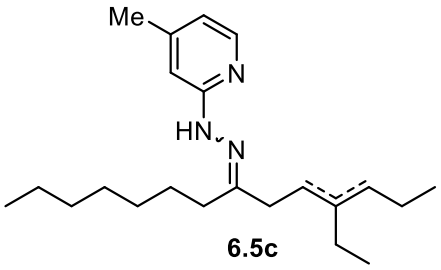
6.5b

6.5b: The reaction was conducted on a 0.5 mmol scale. Yellowish oil (99.8 mg, 70% yield). R_f = 0.35 (Hex/EA = 3:1). IR (KBr) 2956, 2926, 2873, 1716, 1612, 1568, 1462 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 – 7.92 (m, 1H), 7.92 – 7.64 (m, 1H), 7.17 – 6.90 (m, 1H), 6.72 – 6.43 (m, 1H), 5.31 – 4.97 (m, 1H), 3.02 (dd, *J* = 19.6, 7.1 Hz, 0.7H), 2.41 – 2.00 (m, 11.3H), 1.67 – 1.54 (m, 2H), 1.48 – 1.36 (m, 1H), 1.04 – 0.85 (m, 9H). HRMS: Ref. mass 287.2361 Obs. mass: 287.2367.



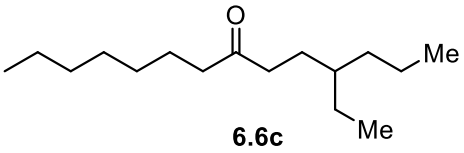
6.6b

6.6b: The reaction was conducted with 24.8 mg **6.5b**. Colorless oil (15.2 mg, 96% yield). R_f = 0.7 (Hex/EA = 5:1). IR (KBr) 2962, 2932, 2873, 1716, 1462, 1383, 1127 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.39 (dt, *J* = 13.7, 7.7 Hz, 4H), 1.62 (h, *J* = 7.4 Hz, 2H), 1.54 (ddd, *J* = 9.3, 7.8, 5.4 Hz, 2H), 1.34 – 1.18 (m, 7H), 0.97 – 0.82 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.87, 44.85, 40.40, 38.44, 35.49, 27.23, 25.84, 19.91, 17.50, 14.58, 13.93, 10.90. HRMS: Ref. mass 184.1827 Obs. mass: 184.1822.



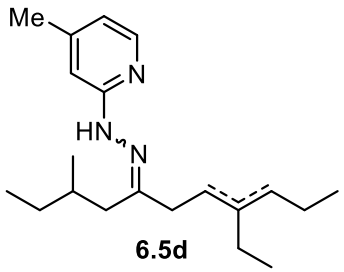
6.5c

6.5c: The reaction was conducted on a 0.5 mmol scale. Yellowish oil (107.6 mg, 63% yield). R_f = 0.45-0.5 (Hex/EA = 3:1). IR (KBr) 3194, 2962, 2928, 2857, 1610, 1570, 1458, 1429 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 – 7.95 (m, 1H), 7.94 – 7.61 (m, 1H), 7.26 – 6.99 (m, 1H), 6.62 – 6.50 (m, 1H), 5.39 – 4.94 (m, 1H), 3.01 (dd, *J* = 19.2, 7.1 Hz, 0.6H), 2.39 – 1.98 (m, 10H), 1.66 – 1.23 (m, 12.4H), 1.06 – 0.84 (m, 9H). HRMS: Ref. mass 343.2987 Obs. mass: 343.2988.



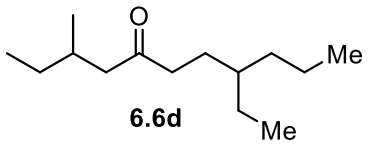
6.6c

6.6c: The reaction was conducted with 28.4 mg **6.5c**. Colorless oil (18.3 mg, 92% yield). R_f = 0.8 (Hex/EA = 5:1). IR (KBr) 2958, 2926, 2873, 2859, 1718, 1462, 1379, 1072 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.45 – 2.35 (m, 4H), 1.65 – 1.49 (m, 4H), 1.34 – 1.21 (m, 15H), 0.92 – 0.84 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.01, 42.96, 40.37, 38.45, 35.50, 31.83, 29.40, 29.22, 27.26, 25.85, 24.10, 22.75, 19.92, 14.58, 14.18, 10.91. HRMS: Ref. mass 240.2453 Obs. mass: 240.2465.



6.5d

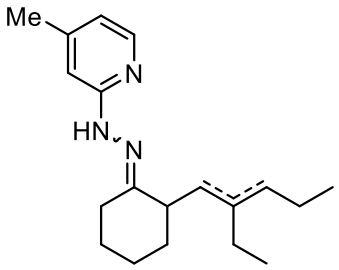
6.5d: The reaction was conducted on a 0.5 mmol scale. Yellowish oil (78 mg, 50% yield). R_f = 0.6 (Hex/EA = 3:1). IR (KBr) 3053, 2963, 2926, 2870, 1614, 1569, 1507, 1457 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 – 7.90 (m, 1H), 7.90 – 7.63 (m, 1H), 7.15 – 7.00 (m, 1H), 6.66 – 6.49 (m, 1H), 5.33 – 4.96 (m, 1H), 3.01 (dd, *J* = 26.7, 7.1 Hz, 0.7H), 2.36 – 2.01 (m, 10.3H), 1.82 – 1.58 (m, 2H), 1.48 – 1.37 (m, 2H), 1.25 – 1.18 (m, 1H), 1.06 – 0.86 (m, 12H). HRMS: Ref. mass 315.2674 Obs. mass: 315.2681.



6.6d

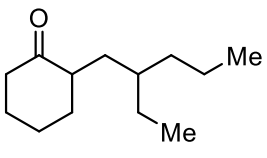
6.6d: The reaction was conducted with 25.9 mg **6.5d**. The product is obtained as colorless oil (16.8 mg, 97% yield) as an inseparable mixture of diastereomers. The dr is not available through either ^1H-NMR or GC analysis. R_f = 0.7 (Hex/EA = 5:1). IR (KBr) 2965, 2928, 2873, 1713, 1460, 1378, 1141 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.47 – 2.24 (m, 3H), 2.19 (dd, *J* = 15.8, 8.1 Hz, 1H), 1.97 – 1.86 (m, *J* = 6.7 Hz, 1H), 1.51 (td, *J* = 7.8, 5.1 Hz, 2H), 1.34 – 1.14 (m, 9H), 0.92 – 0.80 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) carbon signals were found at δ 211.82, 211.79, 50.08, 40.95, 38.42, 35.49, 31.01, 29.71, 27.19,

25.85, 25.84, 19.92, 19.58, 14.58, 11.47, 10.91, 10.90. HRMS: Ref. mass 212.2140 Obs. mass: 212.2140.



6.5e

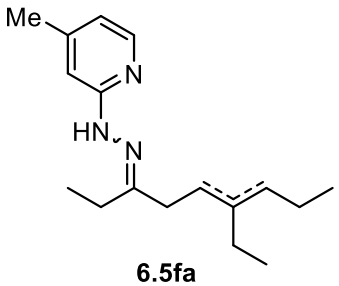
6.5e: The reaction was conducted on a 0.5 mmol scale with 15 mol% of $Rh(C_2H_4)_2(acac)$ and 45 mol% of phosphine. Yellowish oil (99.5 mg, 67% yield). R_f = 0.5 (Hex/EA = 3:1). IR (KBr) 3188, 2956, 2928, 2857, 1610, 1570, 1452, 1145 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 – 7.89 (m, 1H), 7.89 – 7.55 (m, 1H), 7.16 – 6.95 (m, 1H), 6.56 (t, *J* = 6.0 Hz, 1H), 5.51 – 5.10 (m, 1H), 3.33 – 3.20 (m, 0.2H), 3.15 – 3.04 (m, 0.1H), 2.73 – 2.40 (m, 2.5H), 2.36 – 2.28 (m, 3H), 2.20 – 1.77 (m, 9H), 1.65 – 1.51 (m, 2.5H), 1.38 – 1.28 (m, 1H), 1.09 – 0.91 (m, 6H). HRMS: Ref. mass 299.2361 Obs. mass: 299.2363.



6.6e

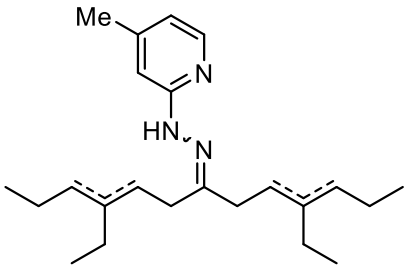
6.6e: The reaction was conducted with 20.0 mg **6.5e**. The product is obtained as colorless oil (13.1 mg, 99% yield) as an inseparable mixture of diastereomers. The dr is not available through either ^1H-NMR or GC analysis. R_f = 0.7 (Hex/EA = 5:1). IR (KBr) 2965,

2932, 2870, 1715, 1462, 1449, 1379, 1123 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 – 2.25 (m, 3H), 2.12 – 1.98 (m, 2H), 1.89 – 1.81 (m, 1H), 1.81 – 1.61 (m, 3H), 1.41 – 1.15 (m, 8H), 1.13 – 1.02 (m, 1H), 0.91 – 0.80 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) carbon signals were found at δ 213.88, 48.58, 42.12, 36.16, 35.95, 35.90, 35.57, 34.47, 34.36, 33.48, 33.37, 30.49, 29.85, 28.27, 28.26, 26.29, 25.76, 24.95, 24.93, 19.93, 19.66, 14.66, 14.60, 10.91, 10.54. HRMS: Ref. mass 196.1827 Obs. mass: 196.1819.



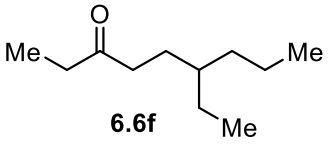
6.5fa

6.5fa: The reaction was conducted on a 0.5 mmol scale. Yellowish oil (88 mg, 64% yield). R_f = 0.35 (Hex/EA = 3:1). IR (KBr) 3348, 3058, 2967, 2930, 2872, 1616, 1569, 1508, 1455 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.91 (m, 1H), 7.89 – 7.59 (m, 1H), 7.10 – 7.01 (m, 1H), 6.59 – 6.50 (m, 1H), 5.36 – 4.96 (m, 1H), 3.12 – 2.96 (m, 0.7H), 2.39 – 1.99 (m, 11.3H), 1.63 – 1.42 (m, 1H), 1.19 – 1.08 (m, 3H), 1.04 – 0.87 (m, 6H). HRMS: Ref. mass 273.2205 Obs. mass: 273.2215.



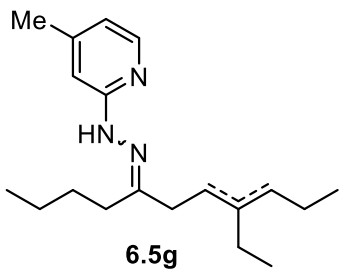
6.5fb

6.5fb: The reaction was conducted on a 0.5 mmol scale. Yellowish oil (38 mg, 21% yield). R_f = 0.55 (Hex/EA = 3:1). IR (KBr) 3342, 3058, 2963, 2930, 2874, 1611, 1569, 1504, 1451, 1167, 1131, 1091 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 – 7.68 (m, 2H), 7.13 – 6.94 (m, 1H), 6.61 – 6.48 (m, 1H), 5.37 – 4.93 (m, 2H), 3.13 – 2.96 (m, 1.5H), 2.41 – 1.97 (m, 15.5H), 1.49 – 1.36 (m, 2H), 1.05 – 0.86 (m, 12H). HRMS: Ref. mass 355.2987 Obs. mass: 355.2994.



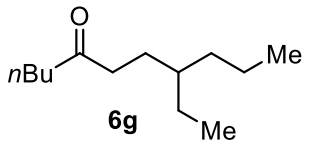
6.6f

6.6f: The reaction was conducted with 22.5 mg **6.5fa**. Colorless oil (12.7 mg, 91% yield). R_f = 0.7 (Hex/EA = 5:1). IR (KBr) 2963, 2921, 2876, 1698, 1634, 1412, 1372, 1013 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.58 – 2.30 (m, 4H), 1.60 – 1.49 (m, 2H), 1.35 – 1.21 (m, 7H), 1.07 (t, *J* = 7.4 Hz, 3H), 0.94 – 0.84 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.28, 40.00, 38.45, 35.96, 35.48, 27.32, 25.83, 19.91, 14.58, 10.90, 8.04. HRMS: Ref. mass 170.1671 Obs. mass: 170.1673.



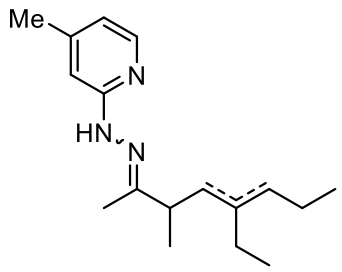
6.5g

6.5g: The reaction was conducted on a 0.5 mmol scale. Yellowish oil (90 mg, 60% yield). R_f = 0.6 (Hex/EA = 3:1). IR (KBr) 3345, 3060, 2957, 2934, 2872, 1609, 1567, 1510, 1457, 1164, 1133, 1072 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 – 7.90 (m, 1H), 7.89 – 7.59 (m, 1H), 7.15 – 6.94 (m, 1H), 6.60 – 6.48 (m, 1H), 5.40 – 4.92 (m, 1H), 3.02 (dd, *J* = 18.6, 7.1 Hz, 0.7H), 2.42 – 1.95 (m, 11.3H), 1.60 – 1.35 (m, 5H), 1.04 – 0.85 (m, 9H). HRMS: Ref. mass 301.2518 Obs. mass: 301.2519.



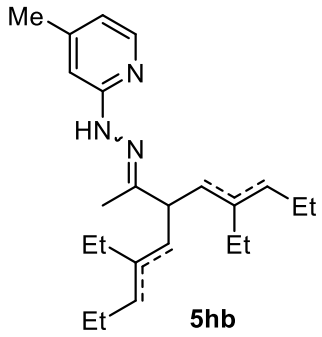
6g

6.6g: The reaction was conducted with 23.2 mg **6.5g**. Colorless oil (13.1 mg, 86% yield). IR (KBr) 2959, 2934, 2876, 1715, 1466, 1413, 1379, 1260 cm^{-1}. R_f = 0.8 (Hex/EA = 5:1). ^1H NMR (500 MHz, $CDCl_3$) δ 2.46 – 2.32 (m, 4H), 1.61 – 1.48 (m, 4H), 1.35 – 1.14 (m, 9H), 0.96 – 0.81 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.98, 42.66, 40.38, 38.45, 35.50, 27.27, 26.19, 25.85, 22.55, 19.92, 14.58, 13.99, 10.91. HRMS: Ref. mass 196.1827 Obs. mass: 196.1833.



5ha

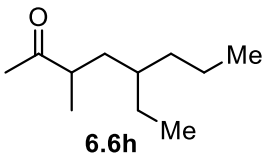
6.5ha: The reaction was conducted on a 0.5 mmol scale. Yellowish oil (46.0 mg, 34% yield). R_f = 0.2 – 0.3 (Hex/EA = 3:1). IR (KBr) 3205, 3056, 2966, 2932, 2873, 1611, 1572, 1510, 1445, 1372, 1170, 1094 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 – 7.92 (m, 1H), 7.75 – 7.50 (m, 1H), 7.13 – 7.01 (m, 1H), 6.64 – 7.50 (m, 1H), 5.37 – 4.99 (m, 1H), 3.39 (dq, *J* = 9.5, 6.8 Hz, 0.2H), 2.70 -2.60 (m, 0.7H), 2.36 – 2.00 (m, 8.6H), 1.84 (d, *J* = 15.8 Hz, 3H), 1.47 – 1.41 (m, 0.5H), 1.23 – 0.90 (m, 9H). HRMS: Ref. mass 273.2205 Obs. mass: 273.2213.



5hb

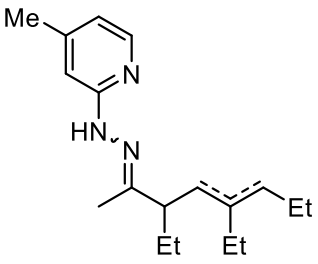
6.5hb: The reaction was conducted on a 0.5 mmol scale. Yellowish oil (59.5 mg, 34% yield). R_f = 0.3 – 0.35 (Hex/EA = 3:1). IR (KBr) 3191, 2960, 2932, 2876, 1611, 1572, 1510, 1445, 1263, 1131, 1094 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 – 7.82 (m, 1H), 7.77 – 7.38 (m, 1H), 7.16 – 6.97 (m, 1H), 6.65 – 6.45 (m, 1H), 5.27 – 4.90 (m, 2H), 4.17 (t, *J* = 9.0 Hz,

0.1H), 3.48 – 3.37 (m, 0.6H), 2.80 – 2.67 (m, 0.25H), 2.45 – 1.95 (m, 13.3H), 1.81 – 1.71 (m, 3H), 1.45 – 1.35 (m, 1.75H), 1.01 – 0.84 (m, 12H). HRMS: Ref. mass 355.2987 Obs. mass: 355.2993.



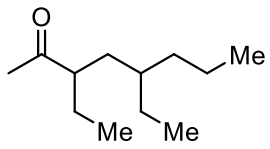
6.6h

6.6h: The reaction was conducted with 18.8 mg **6.5h**. The product was isolated as colorless oil (11.2 mg, 96% yield) as a 1:1 mixture of diastereomers determined by ^{1}H NMR analysis. R_f = 0.7 (Hex/EA = 5:1). IR (KBr) 2966, 2929, 2873, 1715, 1462, 1381, 1356 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.58 (hd, *J* = 7.0, 1.9 Hz, 1H), 2.13 (s, 3H), 1.57 (ddt, *J* = 13.2, 8.1, 6.2 Hz, 1H), 1.32 – 1.18 (m, 8H), 1.06 (dd, *J* = 6.9, 1.3 Hz, 3H), 0.91 – 0.79 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) carbon signals were found at δ 213.18, 45.12, 37.16, 37.07, 36.60, 36.46, 35.72, 35.48, 27.95, 26.11, 25.72, 19.79, 19.65, 16.85, 16.73, 14.61, 14.56, 10.74, 10.52. HRMS: Ref. mass 170.1671 Obs. mass: 170.1673.



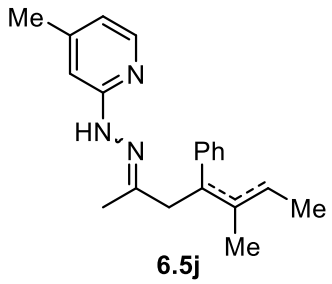
6.5i

6.5i: The reaction was conducted on a 0.5 mmol scale at 130 °C for 72 h. Yellowish oil (71 mg, 50% yield). R_f = 0.3 – 0.4 (Hex/EA = 3:1). IR (KBr) 3199, 2966, 2929, 2876, 1617, 1575, 1448, 1372, 1263, 1136, 1083 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 5.1 Hz, 1H), 7.87 – 7.44 (m, 1H), 7.16 – 6.91 (m, 1H), 6.64 – 6.46 (m, 1H), 5.28 – 4.90 (m, 1H), 3.14 (ddd, *J* = 9.6, 8.2, 6.4 Hz, 0.4H), 2.53 – 2.40 (m, 0.6H), 2.31 (s, 3H), 2.23 – 1.95 (m, 5H), 1.81 – 1.73 (m, 3H), 1.72 – 1.66 (m, 0.5H), 1.53 – 1.39 (m, 2.5H), 1.01 – 0.83 (m, 9H). HRMS: Ref. mass 287.2361 Obs. mass: 287.2369.



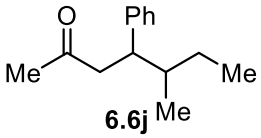
6.6i

6.6i: The reaction was conducted with 22.6 mg **6.5i**. The product was obtained as a colorless oil (14.0 mg, 97% yield) as an inseparable mixture of diastereomers. The dr cannot be determined through either ^1H-NMR or GC analysis. R_f = 0.7 (Hex/EA = 5:1). IR (KBr) 2969, 2935, 2879, 1712, 1462, 1381, 1355, 1167 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.57 – 2.34 (m, 1H), 2.10 (s, 3H), 1.62 – 1.42 (m, 3H), 1.34 – 1.15 (m, 8H), 0.92 – 0.76 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) carbon signals were found at δ 213.16, 213.13, 52.76, 36.88, 36.77, 35.87, 35.51, 35.49, 35.46, 28.58, 28.55, 26.22, 25.68, 25.41, 25.30, 19.80, 19.64, 14.59, 14.56, 11.96, 10.73, 10.49. HRMS: Ref. mass 184.1827 Obs. mass: 184.1840.



6.5j

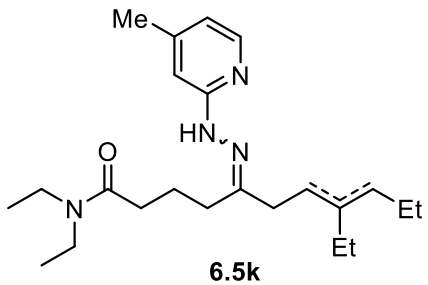
6.5j: The reaction was conducted on a 0.5 mmol scale at 130 °C for 72 h with 20 equiv of 3-hexyne in 2.5 mL 1,4-dioxane. Yellowish oil (85.4 mg, 56% yield). R_f = 0.3 (Toluene/Acetone = 5:1). R_f for hydrazone of the starting material: 0.2 (Toluene/Acetone = 5:1). IR (KBr) 3193, 3059, 3028, 2921, 2859, 1617, 1566, 1445, 1271, 1136 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.71 (m, 1H), 7.70 – 7.50 (m, 1H), 7.28 – 7.16 (m, 5H), 7.05 – 6.83 (m, 1H), 6.62 – 6.44 (m, 1H), 5.47 (q, *J* = 6.7 Hz, 0.9H), 3.81 – 3.55 (m, 0.9H), 3.55 – 3.32 (m, 0.2H), 2.95 – 2.80 (m, 0.9H), 2.78 – 2.58 (m, 0.9H), 2.36 – 2.24 (m, 3.2H), 1.82 – 1.71 (m, 3H), 1.66 – 1.58 (m, 2.7H), 1.50 (s, 3H), 1.03 – 0.90 (m, 0.3H). HRMS: Ref. mass 307.2048 Obs. mass: 307.2061.



6.6j

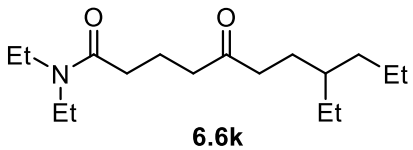
6.6j: The reaction was conducted with 17.3 mg **6.5j**. The product was obtained as colorless oil (9.8 mg, 85% yield) containing a 1.1:1 inseparable mixture of diastereomers determined by ^1H-NMR analysis. R_f = 0.75 (Hex/EA = 5:1). IR (KBr) 3087, 3067, 3033, 2969, 2921, 2882, 1712, 1701, 1561, 1459, 1327, 1105, 1058 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 2H), 7.22 – 7.09 (m, 3H), 3.15 – 3.01 (m, 1H), 2.85 – 2.71 (m, 2H),

1.99 (s, 1.6H), 1.97 (s, 1.4H), 1.65 – 1.56 (m, 1H), 1.5 – 1.42 (m, 0.53H), 1.34 – 1.28 (m, 0.47H), 1.12 – 1.03 (m, 0.53H), 1.03 – 0.92 (m, 0.47H), 0.92 – 0.88 (m, 3H), 0.82 (t, *J* = 7.4 Hz, 1.4H), 0.73 (d, *J* = 6.8 Hz, 1.6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.50, 208.34, 143.83, 142.97, 128.64, 128.37, 128.34, 128.25, 126.40, 126.36, 47.85, 47.11, 46.67, 46.10, 40.18, 39.74, 30.73, 30.69, 27.21, 26.96, 16.55, 16.29, 11.63, 11.61. HRMS: Ref. mass 204.1514 Obs. mass: 204.1508.



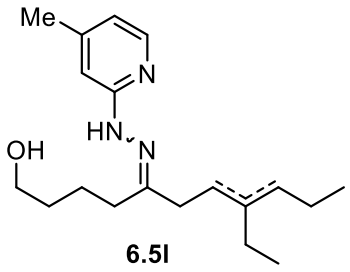
6.5k

6.5k: The reaction was conducted on a 0.5 mmol scale for 72h. The product was isolated by flash column chromatography (toluene/acetone, from 20:1 to 5:1). Yellowish oil (115 mg, 60% yield). R_f = 0.3 – 0.5 (Toluene/Acetone = 2:1). R_f for hydrazone of the starting material: 0.2 (toluene/acetone = 2:1). IR (KBr) 3244, 2971, 2932, 2876, 1639, 1608, 1569, 1457, 1429, 1263, 1136, 1091 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 – 7.65 (m, 2H), 7.08 – 6.95 (m, 1H), 6.62 – 6.43 (m, 1H), 5.35 – 4.94 (m, 1H), 3.56 – 3.34 (m, 2H), 3.33 – 3.25 (m, 2H), 3.12 – 2.97 (m, 0.6H), 2.45 – 2.25 (m, 9H), 2.16 – 1.80 (m, 6.4H), 1.48 – 1.35 (m, 1H), 1.19 – 1.09 (m, 6H), 1.03 – 0.84 (m, 6H). HRMS: Ref. mass 386.3046 Obs. mass: 386.3053.



6.6k

6.6k: The reaction was conducted with 21.5 mg **6.5k**. MeOH was used as solvent for the hydrogenation instead of a MeOH/HCl solution. The product was obtained as a colorless oil (14.2 mg, 90% yield). R_f = 0.3 (Hex/acetone = 3:1). IR (KBr) 2969, 2932, 2873, 1718, 1648, 1462, 1431, 1381, 1266, 1226, 1100 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 3.35 (q, *J* = 7.1 Hz, 2H), 3.29 (q, *J* = 7.2 Hz, 2H), 2.51 (t, *J* = 7.0 Hz, 2H), 2.41 – 2.33 (m, 2H), 2.31 (t, *J* = 7.2 Hz, 2H), 1.90 (p, *J* = 7.1 Hz, 2H), 1.50 (ddd, *J* = 9.5, 7.9, 5.5 Hz, 2H), 1.29 – 1.18 (m, 7H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H), 0.82 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.67, 171.63, 42.01, 41.96, 40.35, 40.15, 38.37, 35.40, 32.18, 27.16, 25.77, 19.87, 19.65, 14.58, 14.47, 13.24, 10.88. HRMS: Ref. mass 283.2511 Obs. mass: 283.2510.



6.5l

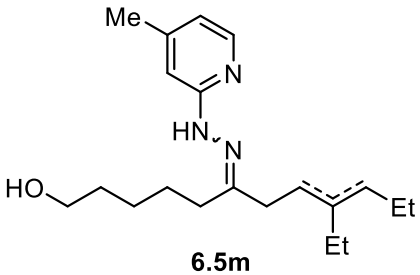
6.5l: The reaction was conducted on a 0.5 mmol scale. Yellowish oil (66 mg, 42% yield). R_f = 0.3-0.4 (Hex/Acetone = 2:1). IR (KBr) 3336, 3068, 2963, 2934, 2870, 1616, 1569, 1508, 1453, 1301, 1166, 1064 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.59 – 7.42 (m, 2H), 7.26 – 6.94 (m, 1H), 6.74 – 6.47 (m, 1H), 5.42 – 4.87 (m, 1H), 3.78 – 3.55 (m, 2H), 3.30

– 2.69 (m, 1.5H), 2.57 – 1.88 (m, 11.5H), 1.70 – 1.39 (m, 5H), 1.06 – 0.83 (m, 6H). HRMS: 317.2467 Ref. mass Obs. mass: 317.2478.



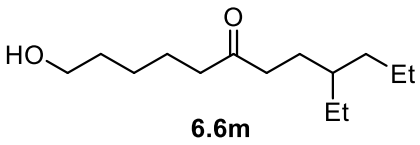
6.6l

6.6l: The reaction was conducted with 20.8 mg **6.5l**. After the reaction was finished, the reaction mixture was cooled to room temperature, and extracted with Et_2O (5 mL × 3). The combined organic phase was filtered through a short plug of silica gel (1 cm)/ Na_2SO_4 (3 cm)/ Na_2CO_3 (0.5 cm), and then concentrated under reduced pressure to afford product **6l** as a ~1:1 mixture of the δ-ketol and the hemiketal (colorless oil, 12.8 mg, 91% yield). R_f = 0.7 (Hex/EA = 3:1) and 0.35 (Hex/EA = 3:1) (two spots on TLC). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 – 3.52 (m, 4H)(H_a), 3.16 (s, 2H) (H_b), 2.45 (t, J = 7.1 Hz, 2H) (H_c), 2.41 – 2.33 (m, 2H), 1.78 – 1.47 (m, 13H), 1.37 – 1.19 (m, 17H), 0.91 – 0.80 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) carbon signals were found at δ 211.66, 99.23, 62.31, 61.27, 47.25, 42.23, 40.26, 38.91, 38.87, 38.28, 35.55, 35.46, 35.32, 33.49, 33.46, 32.83, 32.20, 30.32, 29.68, 27.11, 26.12, 26.09, 25.89, 25.85, 25.67, 25.34, 19.89, 19.84, 19.75, 18.66, 14.44, 14.42, 10.91, 10.84, 10.74. IR (KBr) 3435, 2960, 2938, 2870, 1718, 1462, 1378, 1103, 1063 cm^{-1}. HRMS: Ref. mass 214.1933 Obs. mass: 214.1936.



6.5m

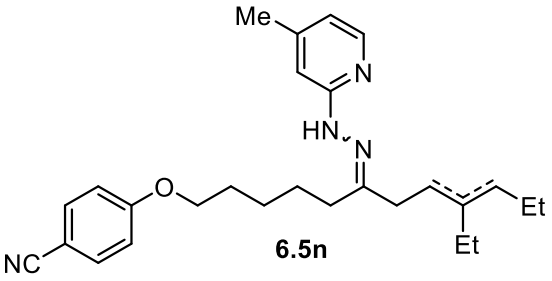
6.5m: The reaction was conducted on a 0.5 mmol scale for 72h. The product was isolated by flash column chromatography with the use of toluene/acetone (from 20:1 to 10:1) to remove impurities and then toluene/acetone (from 5:1 to 4:1) to obtain the pure product. Yellowish oil (84 mg, 51% yield). R_f = 0.4 (Hex/Acetone = 1:1). R_f for hydrazone of the starting material: 0.2 (Hex/Acetone = 1:1). IR (KBr) 3323, 2963, 2929, 2870, 1617, 1566, 1454, 1260, 1072 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 – 7.55 (m, 2H), 7.12 – 6.94 (m, 1H), 6.70 – 6.47 (m, 1H), 5.32 – 4.91 (m, 1H), 3.71 – 3.60 (m, 2H), 3.14 – 2.98 (m, 0.6H), 2.52 – 1.91 (m, 12H), 1.66 – 1.56 (m, 4.4H), 1.51 – 1.37 (m, 3H), 1.07 – 0.86 (m, 6H). HRMS: Ref. mass 331.2624 Obs. mass: 331.2631.



6.6m

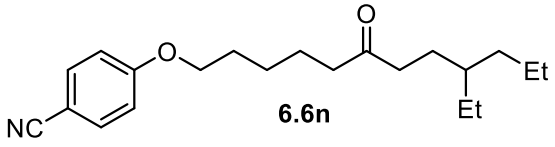
6.6m: The reaction was conducted with 17.0 mg **6.5m**. The product was obtained as colorless oil (10.9 mg, 93% yield). R_f = 0.4 (Hex/EA = 2:1). IR (KBr) 3404, 2960, 2932, 2867, 1710, 1561, 1459, 1412, 1378, 1327, 1060 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 3.64 (t, *J* = 6.5 Hz, 2H), 2.42 (t, *J* = 7.4 Hz, 2H), 2.40 – 2.31 (m, 2H), 1.63 – 1.50 (m, 6H), 1.39 – 1.32 (m, 2H), 1.31 – 1.14 (m, 8H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.83 (t, *J* = 7.3 Hz, 3H). ^{13}C

NMR (126 MHz, $CDCl_3$) δ 211.78, 62.82, 42.74, 40.45, 38.44, 35.48, 32.61, 27.26, 25.83, 25.53, 23.62, 19.91, 14.58, 10.91. HRMS: Ref. mass 283.2511 Obs. mass: 283.2510.



6.5n

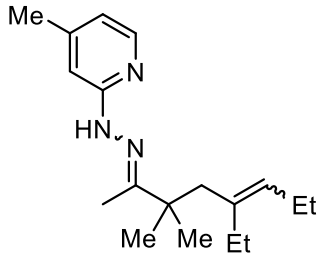
6.5n: The reaction was conducted on a 0.5 mmol scale at 130 °C for 72h. Yellowish oil (129 mg, 60% yield). R_f = 0.65 (Hex/Acetone = 1:1). R_f for hydrazone of the starting material: 0.4 (Hex/Acetone = 1:1). IR (KBr) 3059, 2960, 2929, 2873, 2227, 1698, 1653, 1611, 1569, 1510, 1426, 1263, 1170, 1010 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.40 – 7.65 (m, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.20 – 6.99 (m, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.64 – 6.46 (m, 1H), 5.43 – 4.96 (m, 1H), 4.05 – 3.96 (m, 2H), 3.11 – 2.99 (m, 0.7H), 2.40 – 1.98 (m, 11.3H), 1.89 – 1.80 (m, 2H), 1.70 – 1.51 (m, 4H), 1.45 – 1.38 (m, 1H), 1.05 – 0.87 (m, 6H). HRMS: Ref. mass 432.2889 Obs. mass: 432.2893.



6.6n

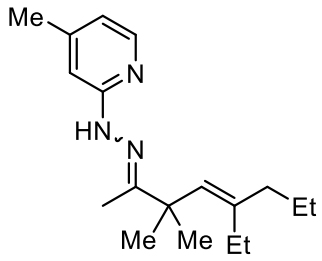
6.6n: The reaction was conducted with 27 mg **6.5n** following a modified *General Procedure C*. To a 4 mL vial charged with **5n** was added benzene (1.5 mL) and HCl (aq.) (1.0M, 3 mL). The vial was sealed with a PTFE lined cap and transferred into a glove box.

After purged under N_2 atmosphere for 5 min, the vial was then sealed again and taken out of the glove box, and stirred at 90 °C for 3 hours. The reaction mixture was extracted with Et_2O, and dried over Na_2SO_4. The filtrate was concentrated under *vacuo.* Pd/C (10% w/w, 40 mg) and EtOAc (2 mL) were then added, and the reaction was degassed with hydrogen gas. After stirred at room temperature for 3 hours, the reaction mixture was filtered through a short plug of Celite. The filtrate was concentrated under *vacuo,* and further purified by flash column chromatography (hexane/ethyl acetate 10:1) to give **6n** as a colorless oil (12.3 mg, 60% yield). R_f = 0.6 (Hex/EA = 3:1). IR (KBr) 2960, 2935, 2918, 2876, 2227, 1701, 1659, 1634, 1608, 1561, 1510, 1406, 1372, 1260, 1170, 1010 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.99 (t, *J* = 6.4 Hz, 2H), 2.45 (t, *J* = 7.3 Hz, 2H), 2.41 – 2.28 (m, 2H), 1.81 (dq, *J* = 7.9, 6.4 Hz, 2H), 1.64 (p, *J* = 7.3 Hz, 2H), 1.56 – 1.42 (m, 4H), 1.32 – 1.14 (m, 7H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.84 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.57, 162.48, 134.11, 119.44, 115.28, 103.88, 68.21, 42.61, 40.47, 38.37, 35.43, 28.99, 27.18, 25.79, 25.78, 23.55, 19.89, 14.61, 10.91. HRMS: Ref. mass 329.2355 Obs. mass: 329.2356.



6.5ob

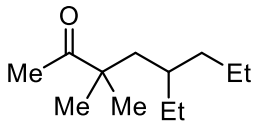
6.5ob: The reaction was conducted on a 0.5 mmol scale using the pre-condensed hydrazone **6.3o** as the starting material. Product **6.5ob** was obtained as a yellowish oil (17.4 mg, 12.5% yield) as an inseparable 1.4:1 mixture of *E*/*Z* isomers of the double bond determined by ^{1}H-NMR. Besides, product **6.5oa** was obtained as yellowish oil (3.5 mg, 2.5% yield). The starting material was recovered as yellowish oil (83 mg, 81%). R_f = 0.3 (Hex/EA = 3:1). IR (KBr) 3199, 3059, 2971, 2932, 2870, 1617, 1569, 1445, 1299, 1159, 1094 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 5.2 Hz, 1H), 7.63 (br, 1H), 7.03 (s, 1H), 6.55 (d, *J* = 5.2 Hz, 1H), 5.25 – 5.00 (m, 1H), 2.30 (s, 3H), 2.28 – 2.14 (m, 2H), 2.05 – 1.80 (m, 7H), 1.20 – 1.10 (m, 6H), 0.97 – 0.86 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) carbon signals were found at δ 158.11, 158.06, 152.94, 152.86, 149.28, 149.25, 147.33, 137.92, 137.73, 130.40, 128.98, 116.83, 116.77, 107.87, 107.84, 46.46, 42.64, 42.29, 39.94, 30.56, 29.85, 26.53, 26.47, 24.16, 21.92, 21.57, 21.16, 14.84, 14.59, 13.65, 13.38, 11.68. HRMS: Ref. mass 287.2361 Obs. mass: 287.2376.



6.5oa

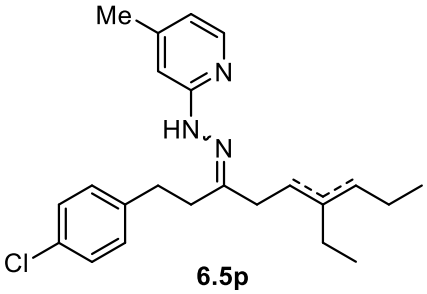
6.5oa: Product **5oa** was obtained as a yellowish oil (3.5 mg, 2.5% yield) as a single *E* isomer determined by ^{1}H NMR and 1D NOE analysis. R_f = 0.35 (Hex/EA = 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 5.1 Hz, 1H), 7.64 (s, 1H), 7.08 (s, 1H), 6.56 (dd, *J* = 5.3, 1.5

Hz, 1H), 5.16 (s, 1H), 2.32 (s, 3H), 1.98 – 1.89 (m, 4H), 1.80 (s, 3H), 1.39 (h, *J* = 7.4 Hz, 2H), 1.28 (s, 6H), 0.87 (td, *J* = 7.4, 4.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.14, 153.76, 149.30, 147.34, 143.43, 131.33, 116.74, 107.82, 43.14, 38.47, 28.45, 22.04, 21.60, 21.48, 13.93, 12.93, 12.50. HRMS: Ref. mass 287.2361 Obs. mass: 287.2372.



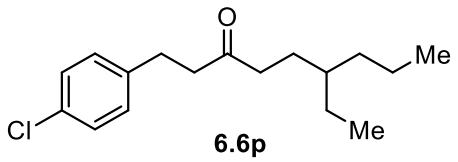
6.6o

6.6o: The reaction was conducted with 11.0 mg **6.5ob**/**6.5oa** (**6.5ob**: **6.5oa** = 5:1). The product was obtained as a colorless oil (6.4 mg, 90% yield). R_f = 0.6 (Hex/EA = 10:1). IR (KBr) 2966, 2929, 2873, 1707, 1563, 1462, 1356, 1330, 1105 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13 (s, 3H), 1.53 – 1.43 (m, 2H), 1.29 – 1.09 (m, 13H), 0.86 (t, *J* = 7.1 Hz, 3H), 0.81 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.56, 48.06, 44.18, 36.74, 35.33, 27.08, 25.50, 25.20, 25.08, 19.74, 14.54, 10.75. HRMS: Ref. mass 184.1827 Obs. mass: 184.1828.



6.5p

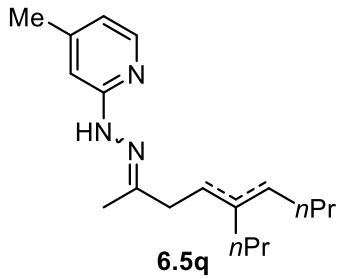
6.5p: The reaction was conducted on a 0.5 mmol scale. Yellowish oil (78 mg, 41% yield). The benzylic alkenylated product and the di-alkenylated product were observed in <5% yield. R_f = 0.4 (Hex/EA = 3:1). IR (KBr) 3348, 3028, 2963, 2926, 2873, 1611, 1572, 1493, 1448, 1091 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 – 7.92 (m, 1H), 7.92 – 7.63 (m, 1H), 7.29 – 7.24 (m, 2H), 7.20 – 7.09 (m, 2H), 7.09 – 6.95 (m, 1H), 6.66 – 6.51 (m, 1H), 5.35 – 4.93 (m, 1H), 3.03 – 2.79 (m, 2.5H), 2.70 – 2.45 (m, 2H), 2.35 – 1.94 (m, 9.5H), 1.58 – 1.36 (m, 1H), 1.06 – 0.85 (m, 6H). HRMS: Ref. mass 383.2128 Obs. mass: 383.2128.



6.6p

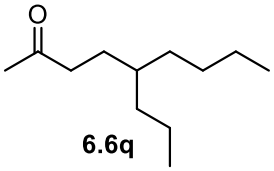
6.6p: The reaction was conducted with 13.5 mg **6.5p** following a modified *General Procedure C*. To an 8 mL vial charged with **5p** was added benzene (1.5 mL) and HCl (aq.) (1.0M, 2 mL). The vial was sealed with a PTFE lined cap and transferred into a glove box. After purged under N_2 atmosphere for 5 min, the vial was then sealed again and taken out of the glove box, and stirred overnight at 90 °C. The reaction mixture was extracted with Et_2O, and dried over Na_2SO_4. The filtrate was concentrated under *vacuo.* Pd/C (10% w/w, 15 mg) and EtOAc (2 mL) were then added, and the reaction was degassed with hydrogen gas. After stirred at room temperature for 7 hours, the reaction mixture was filtered through a short plug of Celite. The filtrate was concentrated under *vacuo,* and further purified by flash column chromatography (hexane/ethyl acetate 30:1) to give **6.6p** as a colorless oil (8.4 mg, 85% yield). R_f = 0.6 (Hex/EA = 10:1). IR (KBr) 2957, 2926, 2873, 1721, 1493, 1468, 1412, 1378,

1094, 1015 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 2.38 – 2.29 (m, 2H), 1.53 – 1.45 (m, 2H), 1.31 – 1.13 (m, 7H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.82 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.29, 139.83, 131.99, 129.87, 128.70, 44.12, 40.68, 38.37, 35.44, 29.28, 27.14, 25.81, 19.89, 14.58, 10.89. HRMS: Ref. mass 280.1594 Obs. mass: 280.1582.



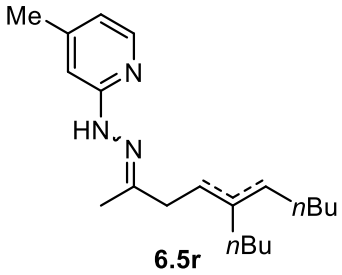
6.5q

6.5q: The reaction was conducted on a 0.5 mmol scale using the pre-condensed hydrazone **6.3a** as the starting material. Yellowish oil (85.4 mg, 60% yield). R_f = 0.35 (Hex/EA = 3:1). IR (KBr) 3359, 3205, 3059, 2960, 2924, 2867, 1614, 1575, 1510, 1451, 1375, 1280, 1167, 1131, 1094, 1038 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 – 7.86 (m, 1H), 7.86 – 7.42 (m, 1H), 7.14 – 6.95 (m, 1H), 6.64 – 6.46 (m, 1H), 5.40 – 5.02 (m, 1H), 3.07 – 2.97 (m, 0.4H), 2.43 – 2.24 (m, 6H), 2.15 – 1.95 (m, 4.6H), 1.92 – 1.77 (m, 3H), 1.44 – 1.29 (m, 4H), 0.95 – 0.85 (m, 6H). HRMS: Ref. mass 287.2361 Obs. mass: 287.2370.



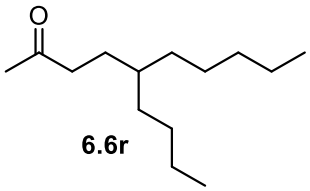
6.6q

6.6q: The reaction was conducted with 18.8 mg **6.5q**. Colorless oil (9.7 mg, 80% yield). R_f = 0.7 (Hex/EA = 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 – 2.34 (m, 2H), 2.14 (s, 3H), 1.52 (ddd, *J* = 9.7, 7.9, 6.1 Hz, 2H), 1.30 – 1.18 (m, 11H), 0.91 – 0.85 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.67, 41.38, 36.92, 35.95, 33.25, 29.97, 28.97, 27.70, 23.23, 19.89, 14.59, 14.25. IR (KBr) 2957, 2926, 2870, 1721, 1622, 1403, 1364, 1254 cm^{-1}. HRMS: Ref. mass 184.1827 Obs. mass: 184.1832.



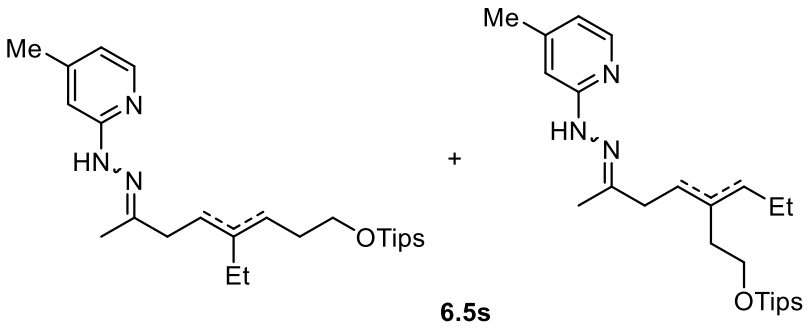
6.5r

6.5r: The reaction was conducted on a 0.5 mmol scale using the pre-condensed hydrazone **6.3a** as the starting material. Yellowish oil (94 mg, 60% yield). The reaction could also be performed on a 0.5 mmol scale with 3 equiv of 5-decyne to yield **6.5r** as yellowish oil (83 mg, 53% yield). R_f = 0.4 – 0.45 (Hex/EA = 3:1). IR (KBr) 3351, 3216, 3059, 2960, 2929, 2859, 1608, 1575, 1510, 1443, 1375, 1277, 1131, 1091 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 – 7.85 (m, 1H), 7.72 – 7.51 (m, 1H), 7.05 (d, *J* = 6.4 Hz, 1H), 6.55 (d, *J* = 4.8 Hz, 1H), 5.37 – 5.10 (m, 1H), 3.09 – 2.98 (m, 0.4H), 2.43 – 2.25 (m, 5.6H), 2.12 – 1.97 (m, 4H), 1.97 – 1.78 (m, 3H), 1.44 – 1.16 (m, 9H), 0.97 – 0.82 (m, 6H). HRMS: Ref. mass 315.2674 Obs. mass: 315.2676.



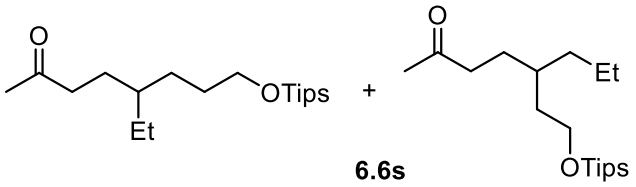
6.6r

6.6r: The reaction was conducted with 19.7 mg **6.5r**. Colorless oil (12.6 mg, 95% yield). R_f = 0.75 (Hex/EA = 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 – 2.35 (m, 2H), 2.14 (s, 3H), 1.57 – 1.48 (m, 2H), 1.35 – 1.15 (m, 15H), 0.97 – 0.79 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.68, 41.40, 37.15, 33.54, 33.25, 32.43, 29.97, 28.98, 27.71, 26.42, 23.23, 22.82, 14.25, 14.24. IR (KBr) 2960, 2924, 2859, 1715, 1457, 1361, 1263, 1164 cm^{-1}. HRMS: Ref. mass 212.2140 Obs. mass: 212.2136.



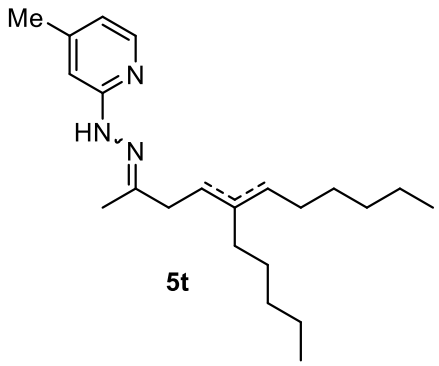
6.5s

6.5s: The reaction was conducted at 0.4 mmol scale using the pre-condensed hydrazone **6.3a** as the starting material. Yellowish oil (120.5 mg, 70% yield). R_f = 0.25 – 0.3 (Hex/EA = 3:1). IR (KBr) 3362, 3210, 3059, 2957, 2898, 2870, 1608, 1572, 1510, 1451, 1277, 1094 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 – 7.83 (m, 1H), 7.80 – 7.41 (m, 1H), 7.16 – 7.01 (m, 1H), 6.56 (d, *J* = 5.2 Hz, 1H), 5.41 – 5.08 (m, 1H), 3.79 – 3.60 (m, 2H), 3.10 – 2.95 (m, 0.5H), 2.46 – 2.05 (m, 9.3H), 2.01 – 1.79 (m, 3H), 1.72 – 1.61 (m, 0.6H), 1.50 – 1.41 (m, 0.6H), 1.10 – 0.91 (m, 24H). HRMS: Ref. mass 433.3488 Obs. mass: 433.3452.



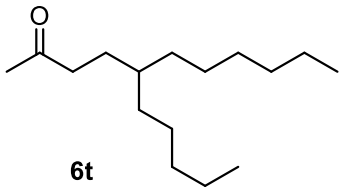
6.6s

6.6s: The reaction was conducted with 19.9 mg **6.5s** following a modified *General Procedure C*. To an 8 mL vial charged with **6.5s** was added benzene (1.5 mL) and HCl (aq.) (1.0M, 2 mL). The vial was sealed with a PTFE lined cap and transferred into a glove box. After purged under N_2 atmosphere for 5 min, the vial was then sealed again and taken out of the glove box, and stirred overnight at 90 °C. The reaction mixture was extracted with Et_2O, and dried over Na_2SO_4. The filtrate was concentrated under *vacuo.* Pd/C (10% w/w, 15 mg), MeOH (0.6 mL) and several drops of DCM were then added, and the reaction was degassed with hydrogen gas. After stirred overnight at room temperature, the reaction mixture was filtered through a short plug of Celite. The filtrate was concentrated under *vacuo,* and further purified by flash column chromatography (hexane/ethyl acetate 30:1) to give **6.6s** as a 1.1:1 mixture of regioisomers determined by ^{1}H NMR (colorless oil, 11.6 mg, 77% yield). R_f = 0.6 (Hex/EA = 10:1). IR (KBr) 2961, 2928, 2867, 1717, 1464, 1378, 1109, 882 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 – 3.63 (m, 2H), 2.45 – 2.36 (m, 2H), 2.14 (s, 3H), 1.54 – 1.19 (m, 9H), 1.12 – 0.95 (m, 21H), 0.9 – 0.82 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) carbon signals were found at δ 209.53, 209.46, 63.85, 61.64, 41.38, 41.37, 38.45, 36.99, 36.15, 33.89, 30.50, 30.15, 29.99, 29.97, 29.01, 27.83, 27.26, 25.88, 19.85, 18.20, 14.52, 12.21, 12.19, 10.91. HRMS: Ref. mass 328.2798 Obs. mass: 328.2805.



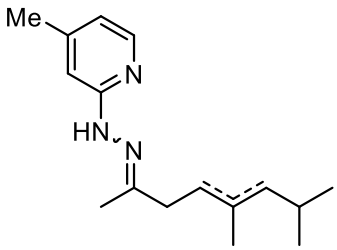
5t

6.5t: The reaction was conducted on a 0.5 mmol scale using the pre-condensed hydrazone **6.3a** as the starting material. Yellowish oil (99 mg, 58% yield). R_f = 0.3 (Hex/EA = 3:1). IR (KBr) 3362, 3213, 3059, 2960, 2926, 2851, 1608, 1571, 1510, 1445, 1280, 1133, 1094 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 – 7.82 (m, 1H), 7.82 – 7.45 (m, 1H), 7.13 – 6.97 (m, 1H), 6.68 – 6.46 (m, 1H), 5.42 – 4.99 (m, 1H), 3.10 – 2.96 (m, 0.5H), 2.46 – 2.18 (m, 6H), 2.10 – 1.96 (m, 4H), 1.94 – 1.79 (m, 3H), 1.41 – 1.24 (m, 12.5H), 0.92 – 0.84 (m, 6H). HRMS: Ref. mass 343.2987 Obs. mass: 343.2992.



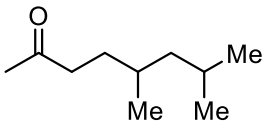
6t

6.6t: The reaction was conducted with 22.8 mg **6.5t**. Colorless oil (14.0 mg, 88% yield). R_f = 0.75 (Hex/EA = 5:1). ^1H NMR (500 MHz, $CDCl_3$) δ 2.38 (t, *J* = 7.9 Hz, 2H), 2.14 (s, 3H), 1.55 – 1.48 (m, 2H), 1.35 – 1.15 (m, 19H), 0.94 – 0.82 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.66, 41.41, 37.20, 33.60, 33.55, 32.44, 32.05, 29.97, 29.88, 27.73, 26.73, 26.43, 22.83, 14.24. IR (KBr) 2966, 2926, 2859, 1721, 1457, 1361, 1162, 1007 cm^{-1}. HRMS: Ref. mass 240.2453 Obs. mass: 240.2451.



6.5u

6.5u: The reaction was conducted on a 0.5 mmol scale for 72h using the pre-condensed hydrazone **6.3a** as the starting material. Yellowish oil (81 mg, 63% yield). R_f = 0.2 – 0.35 (Hex/EA = 3:1). IR (KBr) 3205, 3064, 2963, 2921, 2870, 1614, 1569, 1437, 1372, 1167, 1131, 1091 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 – 7.85 (m, 1H), 7.86 – 7.46 (m, 1H), 7.16 – 6.93 (m, 1H), 6.73 – 6.33 (m, 1H), 5.35 – 4.68 (m, 1H), 3.10 – 2.95 (m, 1H), 2.56 – 2.20 (m, 5H), 2.06 – 1.50 (m, 8H), 0.96 – 0.81 (m, 6H). HRMS: Ref. mass 259.2048 Obs. mass: 259.2056.

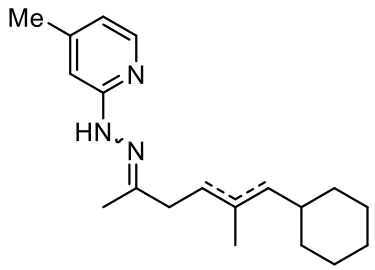


6u

6.6u: The reaction was conducted with 21.0 mg **6.5u**. Colorless oil (11.0 mg, 87% yield). R_f = 0.7 (Hex/EA = 5:1). The crude material* was determined to contain a > 20:1 mixture of regioisomers by GC-MS analysis and was isolated as a > 20:1 mixture of regioisomers as determined by GC-MS analysis. ^1H NMR (500 MHz, $CDCl_3$) δ 2.53 – 2.33 (m, 2H), 2.14 (s, 3H), 1.67 – 1.55 (m, 2H), 1.5 – 1.4 (m, 1H), 1.4 – 1.3 (m, 1H), 1.09 (ddd, *J* = 13.8, 8.2, 5.8 Hz, 1H), 1.00 (ddd, *J* = 13.8, 8.3, 6.1 Hz, 1H), 0.91 – 0.79 (m, 9H). ^{13}C NMR

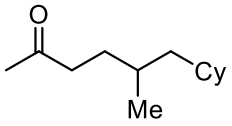
(126 MHz, $CDCl_3$) δ 209.54, 46.63, 41.62, 31.27, 30.15, 29.97, 25.36, 23.48, 22.41, 19.68. IR (KBr) 2960, 2932, 2879, 1721, 1465, 1364, 1167 cm^{-1}. HRMS: Ref. mass 156.1514 Obs. mass: 156.1511.

* For the measurement of crude rr, no isolation was performed for either *step 1* (the C–H activation) or *step 2* (the hydrogenation/hydolysis). When *step 1* was done, the reaction mixture was filtered through a short plug of Celite before concentrated under reduced pressure. The residue was then directly used in *step 2* without any further purification. When the *step 2* is done, the reaction mixture was extracted with Et_2O, and dried over Na_2SO_4. The filtrate was directly used for GC-MS analysis without any further purification.



5v

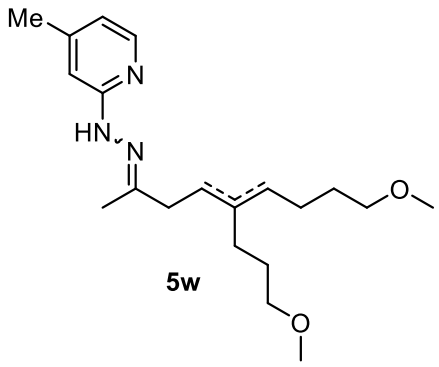
6.5v: The reaction was conducted at 0.4 mmol scale using the pre-condensed hydrazone **6.3a** as the starting material. Yellowish oil (74 mg, 50% yield). R_f = 0.3 (Hex/EA = 3:1). IR (KBr) 3359, 3205, 3059, 2918, 2853, 1732, 1611, 1572, 1507, 1451, 1274, 1136, 1094 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 – 7.89 (m, 1H), 7.89 – 7.52 (m, 1H), 7.16 – 6.94 (m, 1H), 6.66 – 6.45 (m, 1H), 5.33 – 4.98 (m, 1H), 3.10 – 2.95 (m, 0.9H), 2.46 – 2.12 (m, 6.1H), 1.93 – 1.56 (m, 12H), 1.29 – 0.79 (m, 6H). HRMS: Ref. mass 299.2361 Obs. mass: 299.2369.



6.6v

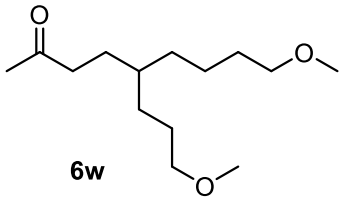
6.6v: The reaction was conducted with 18.8 mg **6.5v**. Colorless oil (11.1 mg, 90% yield). R_f = 0.7 (Hex/EA = 5:1). The crude material* was determined to contain a >20:1 mixture of regioisomers by GC-MS analysis and was isolated as a > 20:1 mixture of regioisomers as determined by GC-MS analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.56 – 2.28 (m, 2H), 2.14 (s, 3H), 1.72 – 1.46 (m, 7H), 1.39 – 1.08 (m, 6H), 0.98 (ddd, *J* = 13.8, 8.2, 6.0 Hz, 1H), 0.94 – 0.67 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.60, 45.09, 41.66, 35.01, 34.29, 33.36, 31.30, 29.98, 29.35, 26.90, 26.59, 26.52, 19.84. IR (KBr) 2955, 2926, 2856, 1721, 1625, 1448, 1361, 1263 cm^{-1}. HRMS: Ref. mass 196.1827 Obs. mass: 196.1827.

* For the measurement of crude rr, no isolation was performed for either *step 1* (the C–H activation) or *step 2* (the hydrogenation/hydolysis). When *step 1* was done, the reaction mixture was filtered through a short plug of Celite before concentrated under reduced pressure. The residue was then directly used in *step 2* without any further purification. When the *step 2* is done, the reaction mixture was extracted with Et_2O, and dried over Na_2SO_4. The filtrate was directly used for GC-MS analysis without any further purification.



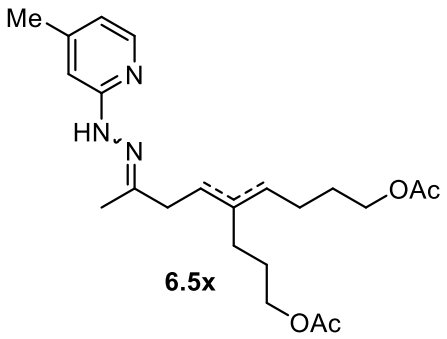
5w

6.5w: The reaction was conducted on a 0.5 mmol scale using the pre-condensed hydrazone **3a** as the starting material. Yellowish oil (93 mg, 54% yield). R_f = 0.15 (Hex/EA = 1:1). IR (KBr) 3062, 2926, 2866, 2827, 2807, 1658, 1609, 1573, 1429, 1374, 1119 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 – 7.92 (m, 1H), 7.92 – 7.49 (m, 1H), 7.14 – 6.93 (m, 1H), 6.55 (d, *J* = 5.0 Hz, 1H), 5.39 – 5.06 (m, 1H), 3.47 – 3.23 (m, 10H), 3.09 – 2.96 (m, 0.6H), 2.44 – 2.01 (m, 10.5H), 1.90 – 1.80 (m, 2.5H), 1.75 – 1.47 (m, 4.4H). HRMS: Ref. mass 347.2573 Obs. mass: 347.2579.



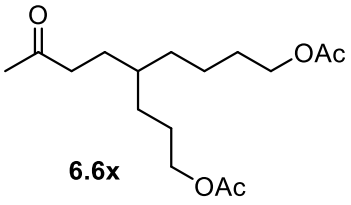
6w

6.6w: The reaction was conducted with 20 mg **6.5w**. Colorless oil (11.9 mg, 85% yield). R_f = 0.3 (Hex/EA = 3:1). ^1H NMR (400 MHz, $CDCl_3$) δ 3.39 – 3.22 (m, 10H), 2.45 – 2.32 (m, 2H), 2.13 (s, 3H), 1.62 – 1.47 (m, 6H), 1.35 – 1.20 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.47, 73.28, 72.97, 58.72, 58.71, 41.22, 36.98, 33.32, 30.17, 30.04, 29.82, 27.43, 26.85, 23.30. IR (KBr) 2934, 2859, 2829, 2809, 1715, 1656, 1634, 1409, 1370, 1119 cm^{-1}. HRMS: Ref. mass 244.2038 Obs. mass: 244.2046.



6.5x

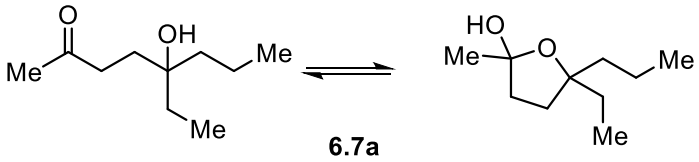
6.5x: The reaction was conducted on a 0.2 mmol scale using the pre-condensed hydrazone **6.3a** as the starting material. Yellowish oil (36.5 mg, 45% yield). R_f = 0.15 (Hex/EA = 1:1). IR (KBr) 3321, 3056, 2953, 2861, 1737, 1609, 1569, 1433, 1364, 1247, 1038 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.78 (m, 1H), 7.61 (s, 1H), 7.05 – 6.87 (m, 1H), 6.57 – 6.41 (m, 1H), 5.43 – 5.03 (m, 1H), 4.06 – 3.90 (m, 4H), 3.00 – 2.92 (m, 0.5H), 2.39 – 1.94 (m, 16.5H), 1.84 – 1.76 (m, 2.5H), 1.70 – 1.40 (m, 4.5H). HRMS: Ref. mass 403.2471 Obs. mass: 403.2477.



6.6x

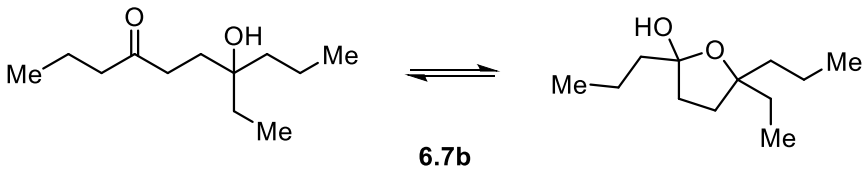
6.6x: The reaction was conducted with 29 mg **6.5x** following a modified *General Procedure C*. To an 8 mL vial charged with **6.5x** was added benzene (1.5 mL) and HCl (aq.) (1.0M, 2 mL). The vial was sealed with a PTFE lined cap and transferred into a glove box. After purged under N_2 atmosphere for 5 min, the vial was then sealed again, taken out of the glove box, and stirred for 1 hour at 90 °C. The reaction mixture was extracted with Et_2O, and dried over Na_2SO_4. The filtrate was concentrated under *vacuo*. Pd/C (10% w/w, 30 mg) and

EtOAc (1 mL) were then added, and the reaction was degassed with hydrogen gas. After stirred overnight at room temperature, the reaction mixture was filtered through a short plug of Celite. The filtrate was concentrated under *vacuo,* and further purified by flash column chromatography (hexane/ethyl acetate 3:1) to give **6.6x** as a colorless oil (18.3 mg, 85% yield). R_f = 0.3 (Hex/EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (q, *J* = 6.8 Hz, 4H), 2.49 – 2.31 (m, 2H), 2.14 (s, 3H), 2.04 (s, 6H), 1.64 – 1.49 (m, 6H), 1.37 – 1.23 (m, 7H).^{13}C NMR (101 MHz, $CDCl_3$) δ 209.11, 171.32, 171.28, 64.83, 64.51, 41.05, 36.71, 32.97, 30.08, 29.52, 29.03, 27.19, 25.78, 23.02, 21.14, 21.13. IR (KBr) 2936, 2866, 1739, 1719, 1654, 1415, 1391, 1368, 1245, 1038 cm^{-1}. HRMS: Ref. mass 300.1937 Obs. mass: 300.1951.



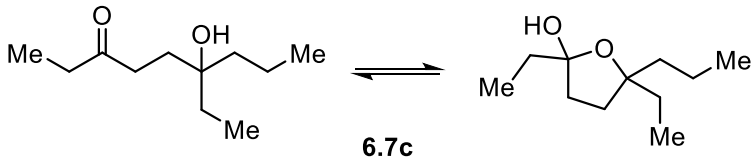
6.7a

6.7a: The reaction was conducted with 21.1 mg **6.5a**. Upon isolation, the product was obtained as a mixture of the γ-ketol and the hemiketal (colorless oil, 9.9 mg, 71% yield). For convenience of the characterization, the NMR spectra were recorded in a 2:1 CD_3OD:$CDCl_3$ solution, in which the product existed fully in its hemiketal form. R_f = 0.2 (Hex/EA = 5:1). IR (KBr) 3419, 2959, 2926, 2872, 2853, 1464, 1376 cm^{-1}. ^{1}H NMR (500 MHz, 2:1 CD_3OD:$CDCl_3$) δ 1.63 – 0.82 (m, 13H), 0.61 – 0.27 (m, 6H). ^{13}C NMR (126 MHz, 2:1 CD_3OD:$CDCl_3$) carbon signals were observed at δ 108.54, 108.51, 88.93, 88.89, 43.56, 40.99, 39.11, 34.66, 33.92, 31.42, 22.38, 22.35, 18.47, 18.07, 15.00, 14.92, 9.15, 8.77. HRMS: Ref. mass 172.1463 Obs. mass: 172.1469.



6.7b

6.7b: The reaction was conducted with 14.3 mg **6.5b**. Upon isolation, the product was obtained as a colorless oil (8.0 mg, 80% yield) as a mixture of the γ-ketol and the hemiketal. For convenience of the characterization, the NMR spectra were recorded in a 2:1 CD_3OD:$CDCl_3$ solution, in which the product existed fully in its hemiketal form. R_f = 0.3 (Hex/EA = 5:1). IR (KBr) 3396, 2963, 2928, 2876, 2857, 1462, 1381 cm^{-1}. ^1H NMR (500 MHz, 2:1 CD_3OD:$CDCl_3$) δ 2.02 – 1.22 (m, 14H), 1.07 – 0.70 (m, 9H). ^{13}C NMR (126 MHz, 2:1 CD_3OD:$CDCl_3$) carbon signals were observed at δ 110.34, 110.32, 88.35, 88.28, 43.29, 40.72, 37.67, 37.65, 36.59, 34.27, 33.69, 31.14, 30.16, 18.51, 18.33, 17.92, 14.85, 14.78, 14.42, 9.04, 8.66. HRMS: Ref. mass 200.1776 Obs. mass: 200.1785.

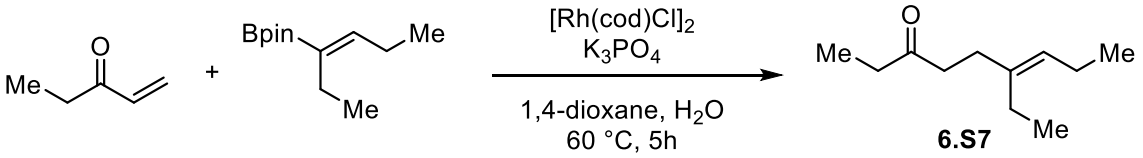


6.7c

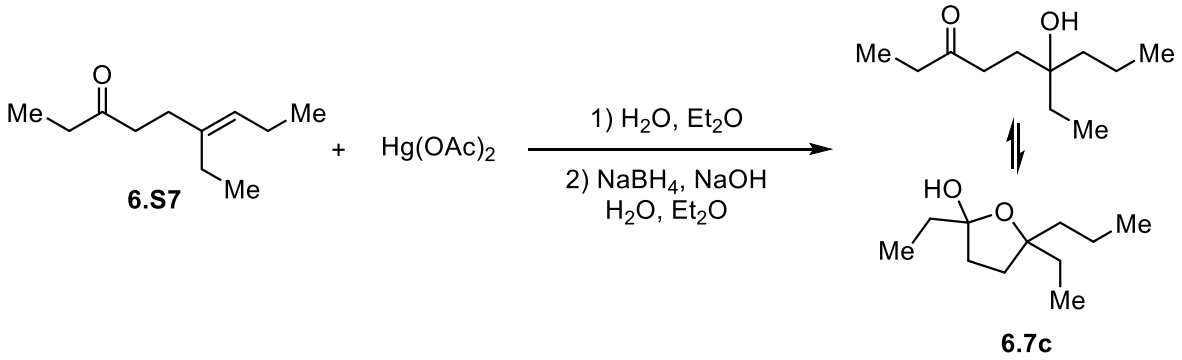
6.7c: The reaction was conducted with 31.0 mg **6.5fa**. Upon isolation, the product was obtained as a colorless oil (14.9 mg, 71% yield) as a mixture of the γ-ketol and the hemiketal. For convenience of the characterization, the NMR spectra were recorded in a 2:1 CD_3OD:$CDCl_3$ solution, in which the product existed fully in its hemiketal form. R_f = 0.35 (Hex/EA = 5:1). IR (KBr) 3419, 2967, 2942, 2876, 1667, 1464, 1332, 1119, 1036 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) (*ketol*:*hemiketal* = ca. 3:4) δ 2.5 – 2.42 (m, 1.68H, *from ketol*), 2.02

– 1.23 (m, 11.32H), 1.16 – 0.72 (m, 9H). ^{1}H NMR (500 MHz, 2:1 CD_3OD:$CDCl_3$) (as *hemiketal*) δ 1.96 – 1.24 (m, 12H), 1.05 – 0.68 (m, 9H). ^{13}C NMR (126 MHz, 2:1 CD_3OD:$CDCl_3$) (as *hemiketal*) carbon signals were observed at δ 111.08, 111.06, 88.70, 88.63, 43.44, 40.91, 36.20, 36.18, 34.40, 34.39, 33.82, 31.32, 28.24, 28.20, 18.53, 18.11, 15.03, 14.95, 9.20, 9.18, 8.82. HRMS: Ref. mass 186.1620 Obs. mass: 186.1619. The identity of the product **7c** was established by comparing its ^{1}H NMR spectrum with the authentic sample of the same compound synthesized independently (*see spectra section*)

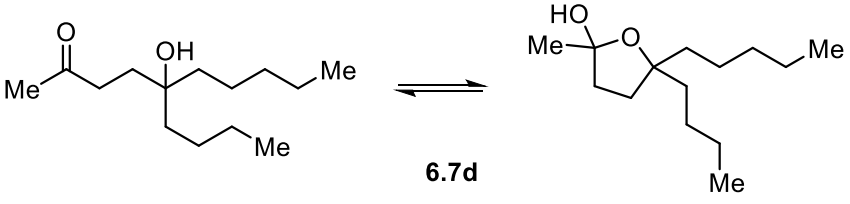
Procedure for the independent synthesis of compound **6.7c**:



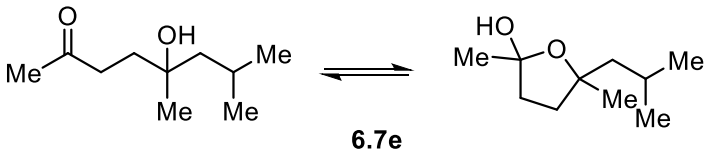
6.S7[38]: Following a modified procedure of literature[39], a 1,4-dioxane (6 mL) solution of pent-1-en-3-one (250 mg, 3 mmol, 1.5 equiv), (*Z*)-2-(hex-3-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[14] (420 mg, 2 mmol, 1 equiv), $[Rh(cod)Cl]_2$ (30 mg, 0.06 mmol, 0.03 equiv), and K_3PO_4 (aq) (3M, 1mL) was stirred at 60 °C for 5 hours. The reaction was extracted with ethyl acetate, and dried over Na_2SO_4. The filtrate was concentrated under *vacuo* and further purified by flash column chromatography (hexane/ethyl acetate, from 20:1 to 10:1) to give the product as a colorless oil (200 mg, 60% yield). R_f = 0.5 (Hex/EA = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (t, *J* = 7.1 Hz, 1H), 2.56 – 2.46 (m, 2H), 2.43 (q, *J* = 7.3 Hz, 2H), 2.34 – 2.18 (m, 2H), 2.06 – 1.93 (m, 4H), 1.05 (t, *J* = 7.4 Hz, 3H), 0.94 (dt, *J* = 14.1, 7.5 Hz, 6H).



6.7c: Following a modified procedure of literature[15], The $Hg(OAc)_2$ was dissolved in H_2O (0.25 mL), followed by the addition of Et_2O (0.5 mL). Under vigorous stirring, **6.S7** was added into the $Hg(OAc)_2$ solution. The reaction mixture was then stirred at room temperature for 30 minutes before cooled to 0 °C with an ice bath. NaOH (aq) (3M, 0.25 mL) was added, followed by a $NaBH_4$/NaOH solution (1mL, 0.5 M for $NaBH_4$, 3 M for NaOH). The mixture was further stirred at room temperature for 2 hours, and allowed to stand for another two hours after stirring was stopped. The Et_2O phase was separated, and the aqueous phase was extracted twice with Et_2O. The combined organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated under *vacuo* and further purified by flash column chromatography (hexane/ethyl acetate, from 20:1 to 10:1) to give the product as a colorless oil (200 mg, 60% yield). R_f = 0.35 (Hex/EA = 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) (*ketol*:*hemiketal* = ca. 3:4) δ 2.5 – 2.42 (m, 1.68H, *from ketol*), 2.02 – 1.23 (m, 11.32H), 1.16 – 0.72 (m, 9H).



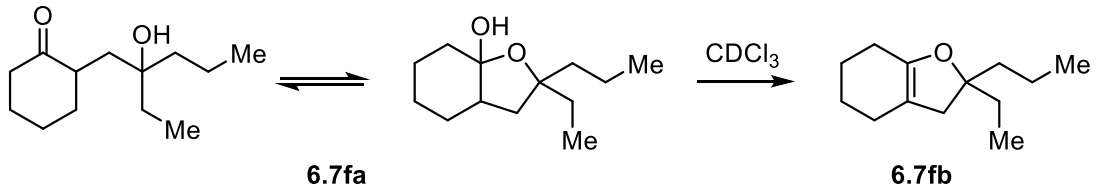
6.7d: The reaction was conducted with 29.5 mg **6.5r**. Upon isolation, the product was obtained as a colorless oil (16.8 mg, 75% yield) as a mixture of the γ-ketol and the hemiketal. For convenience of the characterization, the NMR spectra were recorded in a 2:1 CD_3OD:$CDCl_3$ solution, in which the product existed fully in its hemiketal form. R_f = 0.45 (Hex/EA = 5:1). IR (KBr) 3424, 2960, 2932, 2867, 1642, 1460, 1378, 1327, 1103 cm^{-1}. ^1H NMR (500 MHz, 2:1 CD_3OD:$CDCl_3$) δ 2.06 – 1.94 (m, 1H), 1.94 – 1.73 (m, 3H), 1.67 – 1.57 (m, 1H), 1.55 – 1.21 (m, 16H), 0.91 (q, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, 2:1 CD_3OD:$CDCl_3$) carbon signals were found at δ 108.76, 88.83, 41.72, 41.45, 39.32, 39.27, 39.09, 35.50, 35.48, 33.53, 33.44, 27.81, 27.46, 25.21, 24.83, 24.26, 24.20, 23.54, 22.49, 14.44, 14.38. HRMS: Ref. mass 228.2089 Obs. mass: 228.2097.



6.7e

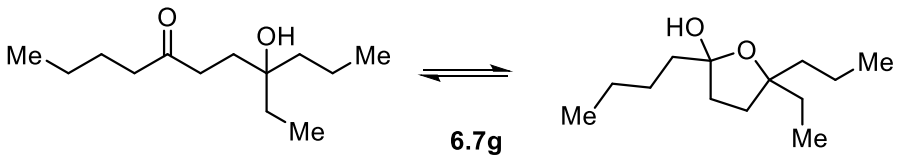
6.7e: The reaction was conducted with 27.0 mg **6.5v**. Upon isolation, the product was obtained as a colorless oil (10.3 mg, 58% yield) as a mixture of the γ-ketol and the hemiketal. For convenience of the characterization, the NMR spectra were recorded in a 2:1 CD_3OD:$CDCl_3$ solution, in which the product existed fully in its hemiketal form. R_f = 0.35 (Hex/EA = 5:1). IR (KBr) 3399, 2963, 2924, 2856, 1665, 1642, 1459, 1333, 1105, 1074 cm^{-1}. ^1H NMR (500 MHz, 2:1 CD_3OD:$CDCl_3$) δ 2.04 – 1.63 (m, 4.4H), 1.55 (dd, *J* = 13.9, 6.3 Hz, 0.6H), 1.47 (dd, *J* = 13.9, 6.4 Hz, 0.6H), 1.43 – 1.32 (m, 3.2H), 1.28 (s, 2H), 1.24 – 1.10 (s, 2.2H), 0.99 – 0.89 (m, 6H). ^{13}C NMR (126 MHz, 2:1 CD_3OD:$CDCl_3$) carbon signals were

found at δ 108.57, 108.28, 86.61, 86.37, 52.46, 51.28, 39.09, 38.64, 38.10, 37.39, 28.11, 26.29, 25.60, 25.45, 25.00, 24.94, 24.62, 24.59, 22.96, 22.77. HRMS: Ref. mass 172.1463 Obs. mass: 172.1469.



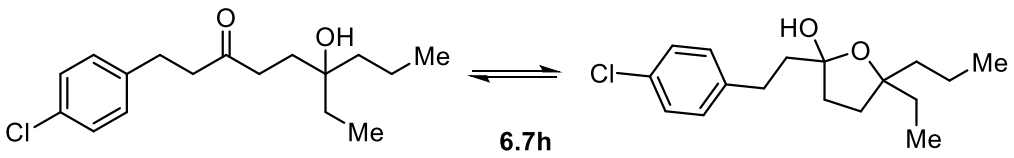
6.7fa **6.7fb**

6.7fa & 6.7fb: The reaction was conducted with 20.0 mg **5e**. Upon isolation, the product **6.7fa** was obtained as a colorless oil (9.5 mg, 67% yield) as a mixture of the γ-ketol and the hemiketal (R_f = 0.3 in Hex/EA = 5:1). Upon treated with $CDCl_3$, **6.7fa** was fully transformed into compound **6.7fb** through dehydration within 5 minutes (R_f = 0.75 in Hex/EA = 5:1). The NMR, IR, and mass spectra of **6.7fb** were recorded. IR (KBr) 3432, 2966, 2935, 2870, 1735, 1462, 1271, 1150 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.38 – 2.17 (m, 2H), 2.00 (tt, *J* = 6.1, 2.7 Hz, 2H), 1.97 – 1.89 (m, 2H), 1.69 – 1.64 (m, 2H), 1.62 – 1.52 (m, 6H), 1.37 – 1.28 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.75, 103.98, 87.75, 42.35, 41.98, 32.50, 23.89, 23.31, 23.21, 16.93, 14.82, 8.00. HRMS: Ref. mass 194.1671 Obs. mass: 194.1674.



6.7g

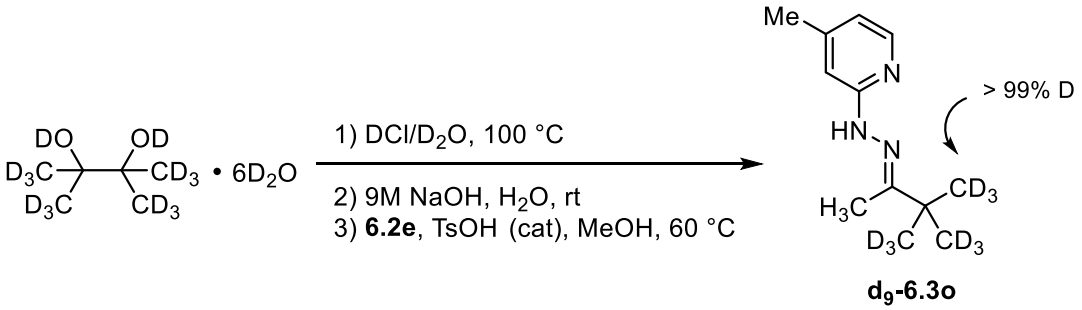
6.7g: The reaction was conducted with 17.3 mg **6.5g**. Upon isolation, the product was obtained as a colorless oil (9.9 mg, 80% yield) as a mixture of the γ-ketol and the hemiketal. For convenience of the characterization, the NMR spectra were recorded in a 2:1 CD_3OD:$CDCl_3$ solution, in which the product existed fully in its hemiketal form. R_f = 0.3 (Hex/EA = 5:1). IR (KBr) 3444, 2960, 2932, 2873, 1462, 1333, 1114, 1035 cm^{-1}. ^1H NMR (500 MHz, 2:1 CD_3OD:$CDCl_3$) δ 1.94 – 1.22 (m, 16H), 0.99 – 0.74 (m, 9H). ^{13}C NMR (126 MHz, 2:1 CD_3OD:$CDCl_3$) carbon signals were found at δ 110.62, 110.59, 88.55, 88.48, 43.48, 40.91, 36.81, 36.79, 35.29, 35.26, 34.46, 34.46, 33.87, 31.34, 27.60, 23.58, 18.52, 18.11, 15.03, 14.95, 14.29, 9.21, 8.84. HRMS: Ref. mass 214.1933 Obs. mass: 214.1936.



6.7h: The reaction was conducted with 20.0 mg **6.5p**. Upon isolation, the product was obtained as a colorless oil (7.5 mg, 80% yield) as a mixture of the γ-ketol and the hemiketal. For convenience of the characterization, the NMR spectra were recorded in a 2:1 CD_3OD:$CDCl_3$ solution, in which the product existed fully in its hemiketal form. R_f = 0.3 (Hex/EA = 5:1). IR (KBr) 3407, 2963, 2938, 2876, 1493, 1465, 1330, 1271, 1100, 1018 cm^{-1}. ^1H NMR (500 MHz, 2:1 CD_3OD:$CDCl_3$) δ 7.22 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 2.57 (q, *J* = 6.6 Hz, 2H), 2.31 – 2.01 (m, 1H), 1.99 – 1.28 (m, 11H), 0.87 (d, *J* = 30.0 Hz, 6H). ^{13}C NMR (126 MHz, 2:1 CD_3OD:$CDCl_3$) carbon signals were found at δ 141.37, 132.26, 130.38, 129.08, 109.90, 88.67, 43.27, 40.86, 37.54, 36.74, 34.54, 34.44, 34.35, 33.71,

31.17, 31.07, 30.98, 30.32, 18.51, 18.11, 14.97, 9.20, 8.85. HRMS: Ref. mass 296.1543 Obs. mass: 296.1568.

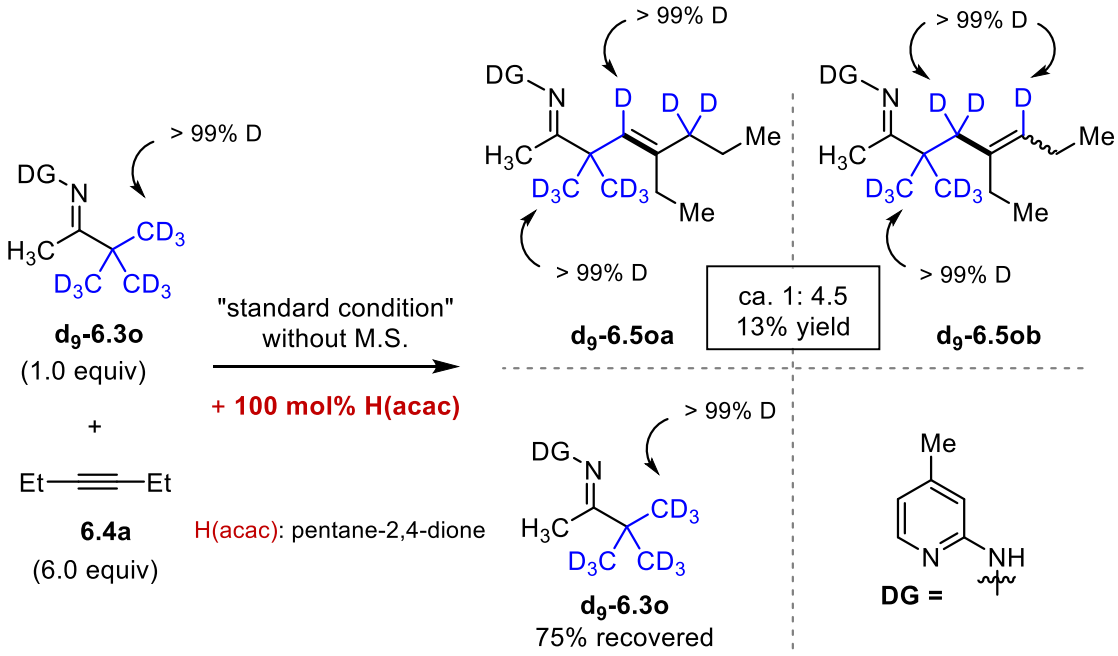
Synthesis of the deuterium labeled substrate



d_9-6.3o: d_{26}-Pinacol hexahydrate[42] (1.5 g, 6 mmol, 2 equiv) was dissolved in 8 mL DCl (35% w/w in D_2O) and stirred at 100 °C for 4 hours. After cooled to room temperature, NaOH (aq) (9M) was added to adjust the pH to >9. The resulting solution was extracted with Et_2O (5 mL × 3). The combined organic phase was treated with H_2O (25 mL) and NaOH (aq) (9M, 5 mL), and stirred vigorously for 16 hours at room temperature. The aqueous phase was removed, and the organic phase was treated again with H_2O (25 mL) and NaOH (aq) (9M, 5 mL), and stirred vigorously for another 8 hours at room temperature. The organic phase was transferred to a MeOH (25 mL) solution of **6.2e** (360 mg, 3 mmol, 1 equiv) and *p*-TsOH (ca. 5 mg), and further stirred overnight at 60 °C. The reaction was then concentrated under *vacuo* and purified by flash column chromatography (hexane/ethyl acetate, from 20:1 to 5:1) to give the product **d_9-6.3o** as a yellowish solid (420 mg, 66% yield). R_f = 0.3 (Hex/EA = 3:1). M. p. = 52-54 °C. IR (KBr) 3207, 3059, 2918, 2851, 2221, 1614, 1569, 1440, 1370, 1280, 1136, 1094 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 5.1 Hz, 1H), 7.60 (br, 1H), 7.05 (s,

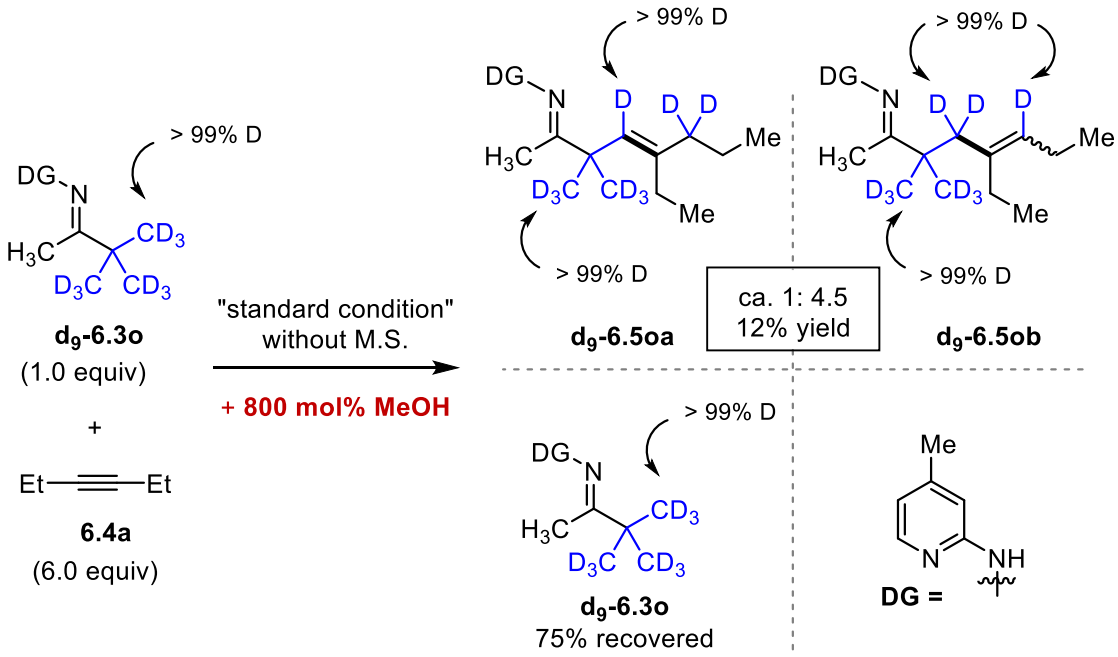
1H), 6.55 (d, J = 5.9 Hz, 1H), 2.31 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.13, 153.54, 149.20, 147.39, 116.76, 107.74, 37.91, 26.84 (septet, J_{CD} = 19.1 Hz), 21.52, 10.84. HRMS: Ref. mass 214.2144 Obs. mass: 214.2151.

Deuterium labeling experiments



A 4 mL vial was charged with **d_9-6.3o** (43 mg, 0.2 mmol, 1.0 equiv), (p-$MeOC_6H_4)_3P$ (21.0 mg, 0.06 mmol, 0.30 equiv), Li(acac) (5.4 mg, 0.05 mmol, 0.25 equiv), and pentane-2,4-dione (20 mg, 0.2 mmol, 1.0 equiv). The vial was sealed with a PTFE lined cap and transferred into a glove box. After purged under N_2 atmosphere for 5 min, the vial was charged with 1,4-dioxane (2 mL), $Rh(C_2H_4)_2(acac)$ (5.2 mg, 0.02 mmol, 0.10 equiv) and the alkyne substrate **6.4a** (138 μL, 1.2 mmol, 6.0 equiv). The vial was then sealed again and taken out of the glove box, and heated in a pie-block at 120 °C under stirring for 48 hours. After cooled to room temperature, the reaction mixture was filtered through a short plug of

Celite and eluted with DCM. The filtrate was then concentrated under *vacuo* and further purified by flash column chromatography (toluene/ethyl acetate) to give **d_9-6.5oa** as a yellowish oil (1.4 mg, 2.4% yield) and **d_9-6.5ob** as a yellowish oil (6.2 mg, 10.5% yield).

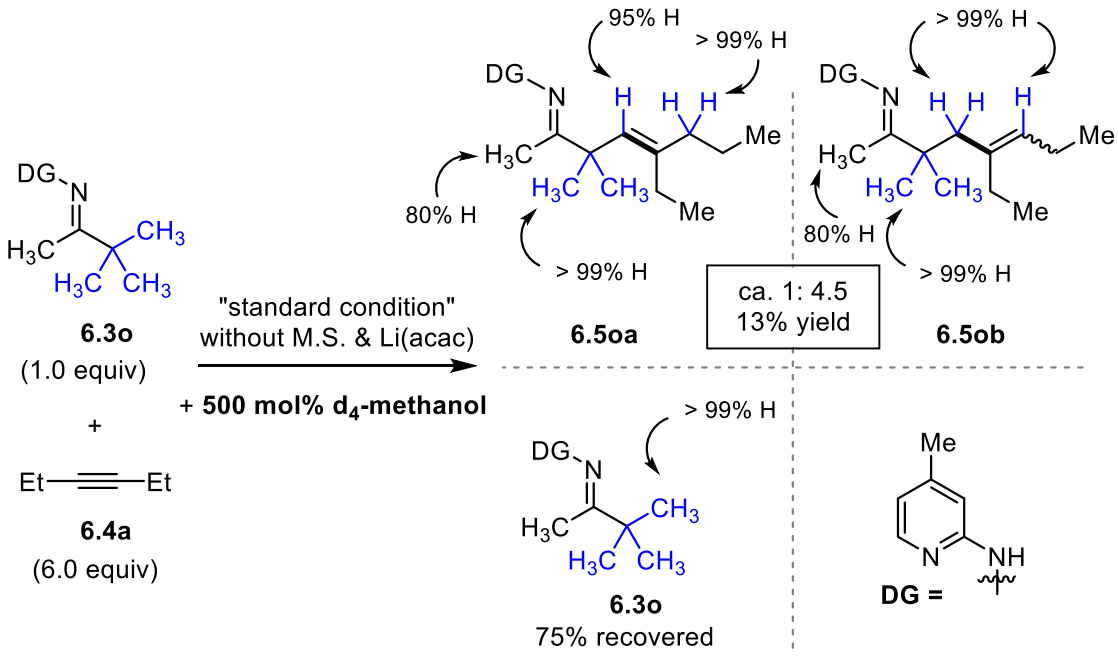


A 4 mL vial was charged with **d_9-6.3o** (107 mg, 0.5 mmol, 1.0 equiv), (p-$MeOC_6H_4)_3P$ (52.5 mg, 1.5 mmol, 0.30 equiv), Li(acac) (13.5 mg, 0.125 mmol, 0.25 equiv), and MeOH (160 μL, 4 mmol, 8.0 equiv). The vial was sealed with a PTFE lined cap and transferred into a glove box. After purged under N_2 atmosphere for 5 min, the vial was charged with 1,4-dioxane (5 mL), $Rh(C_2H_4)_2(acac)$ (12.9 mg, 0.05 mmol, 0.10 equiv) and the alkyne substrate **6.4a** (345 μL, 3 mmol, 6.0 equiv). The vial was then sealed again and taken out of the glove box, and heated in a pie-block at 120 °C under stirring for 48 hours. After cooled to room temperature, the reaction mixture was filtered through a short plug of Celite and eluted with DCM. The filtrate was then concentrated under *vacuo* and further purified by

flash column chromatography (toluene/ethyl acetate) to give **d_9-6.5oa** as a yellowish oil (3.1 mg, 2.1% yield) and **d_9-6.5ob** as a yellowish oil (14.1 mg, 9.6% yield).

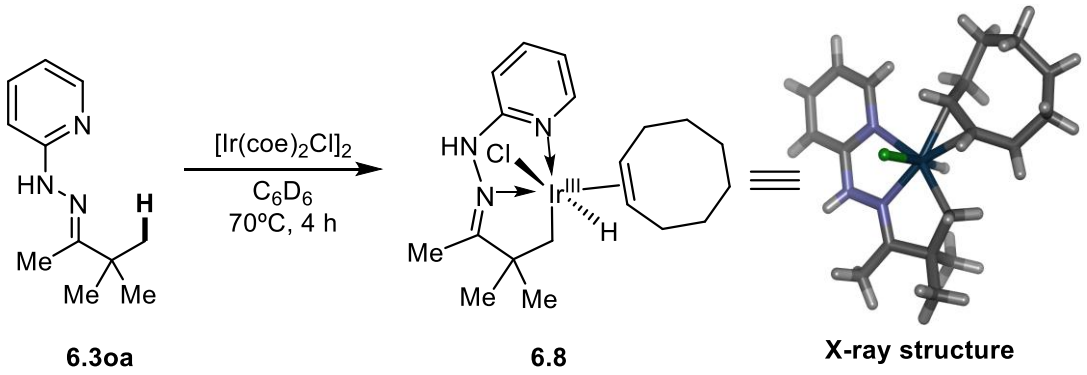
d_9-6.5oa: IR (KBr) 3059, 2960, 2935, 2918, 2853, 1656, 1628, 1561, 1403, 1372, 1010, 982 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 5.2 Hz, 2H), 7.11 (s, 1H), 6.56 (ddd, *J* = 5.3, 1.6, 0.6 Hz, 1H), 2.33 (s, 3H), 1.93 (q, *J* = 7.6 Hz, 2H), 1.82 (s, 3H), 1.37 (q, *J* = 7.3 Hz, 2H), 0.90 – 0.84 (m, 6H). HRMS: Ref. mass 296.2926 Obs. mass: 296.2930.

d_9-6.5ob: IR (KBr) 3059, 2966, 2929, 2915, 2870, 2851, 2221, 1656, 1611, 1566, 1429, 1406, 1372, 1282, 1136, 1007 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 5.1 Hz, 1H), 7.65 (br, 1H), 7.04 (s, 1H), 6.55 (dd, *J* = 5.1, 1.9 Hz, 1H), 2.31 (s, 3H), 2.05 – 1.95 (m, 2H), 1.93 – 1.80 (m, 5H), 1.02 – 0.82 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) carbon signals were found at δ 158.11, 158.07, 153.16, 153.09, 149.40, 149.36, 147.26, 137.78, 137.60, 129.98 (t, J_{CD} = 22.1 Hz), 116.82, 116.76, 107.92, 107.89, 45.50 (br), 41.75 (br), 30.49, 29.86, 25.44 (br), 24.12, 21.82, 21.59, 21.05. HRMS: Ref. mass 296.2926 Obs. mass: 296.2933.



A 4 mL vial was charged with **6.3o** (20.5 mg, 0.1 mmol, 1.0 equiv), (p-$MeOC_6H_4)_3P$ (10.5 mg, 0.03 mmol, 0.30 equiv), and d_4-methanol (20 μL, 0.5 mmol, 5.0 equiv). The vial was sealed with a PTFE lined cap and transferred into a glove box. After purged under N_2 atmosphere for 5 min, the vial was charged with 1,4-dioxane (1 mL), $Rh(C_2H_4)_2(acac)$ (2.6 mg, 0.01 mmol, 0.10 equiv) and the alkyne substrate **6.4a** (69 μL, 0.6 mmol, 6.0 equiv). The vial was then sealed again and taken out of the glove box, and heated in a pie-block at 120 °C under stirring for 48 hours. After cooled to room temperature, the reaction mixture was filtered through a short plug of Celite and eluted with DCM. The filtrate was then concentrated under *vacuo* and further purified by flash column chromatography (toluene/ethyl acetate) to give **6.5oa** as a yellowish oil (0.7 mg, 2.4% yield) and **6.5ob** as a yellowish oil (3.0 mg, 10.5% yield).

Synthesis of Ir–H complex 6.8



Substrate **6.3oa** (19.1 mg, 0.1 mmol, 1 equiv) and $[Ir(coe)_2Cl]_2$ (44.8 mg, 0.05 mmol, 1 equiv) were combined in an NMR tube under an inert atmosphere (N_2), followed by addition of d_6-benzene (600 μL). The NMR tube was capped, sealed with parafilm, and then heated to 70°C for 4 hours. After cooling, the NMR spectrum showed complete conversion of the starting material and a faint presence of a single metal–hydride peak. The Ir–H Complex **6.8** was observed at the bottom of the NMR tube as small yellow crystals (8 mg, 15% yield), and was decanted and immediately immersed in mineral oil prior to X-ray crystallographic analysis. Attempts to purify or isolate additional materials from the mother solution were unsuccessful.

X-Ray structure of complex 6.8

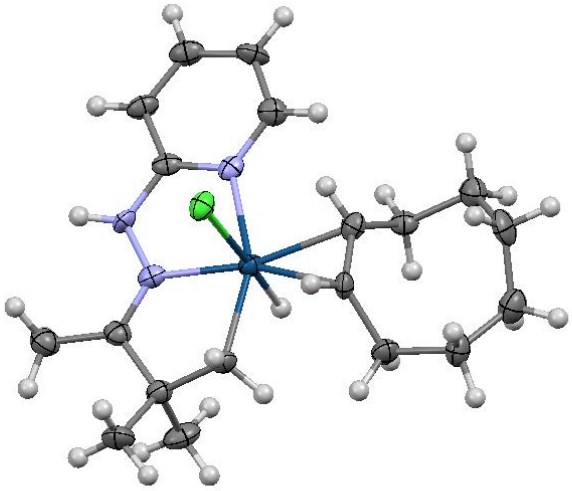


Table 6.4 Crystal Data and Structure Refinement for **6.8**

Identification code	MY-119-12b	
Empirical formula	C9.50 H15.50 Cl0.50 Ir0.50 N1.50	
Formula weight	264.56	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 13.242(6) Å	α = 90°.
	b = 11.996(6) Å	β = 98.032(9)°.
	c = 12.795(6) Å	γ = 90°.
Volume	2012.6(17) $Å^3$	
Z	8	
Density (calculated)	1.746 Mg/m^3	
Absorption coefficient	6.772 mm^{-1}	
F(000)	1040	
Crystal size	0.150 x 0.100 x 0.040 mm^3	
Theta range for data collection	2.301 to 27.500°.	
Index ranges	-17<=h<=17, -15<=k<=15, -11<=l<=16	
Reflections collected	12773	

Independent reflections	4605 [R(int) = 0.0518]
Completeness to theta = 25.242°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.7021
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4605 / 0 / 228
Goodness-of-fit on F^2	1.030
Final R indices [I>2sigma(I)]	R1 = 0.0382, wR2 = 0.0827
R indices (all data)	R1 = 0.0500, wR2 = 0.0908
Extinction coefficient	n/a
Largest diff. peak and hole	2.102 and -1.684 e.$Å^{-3}$

6.5 ^{1}H-NMR and ^{13}C-NMR spectra

Figure 6.1 ^{1}H-NMR Spectrum of **6.1l**

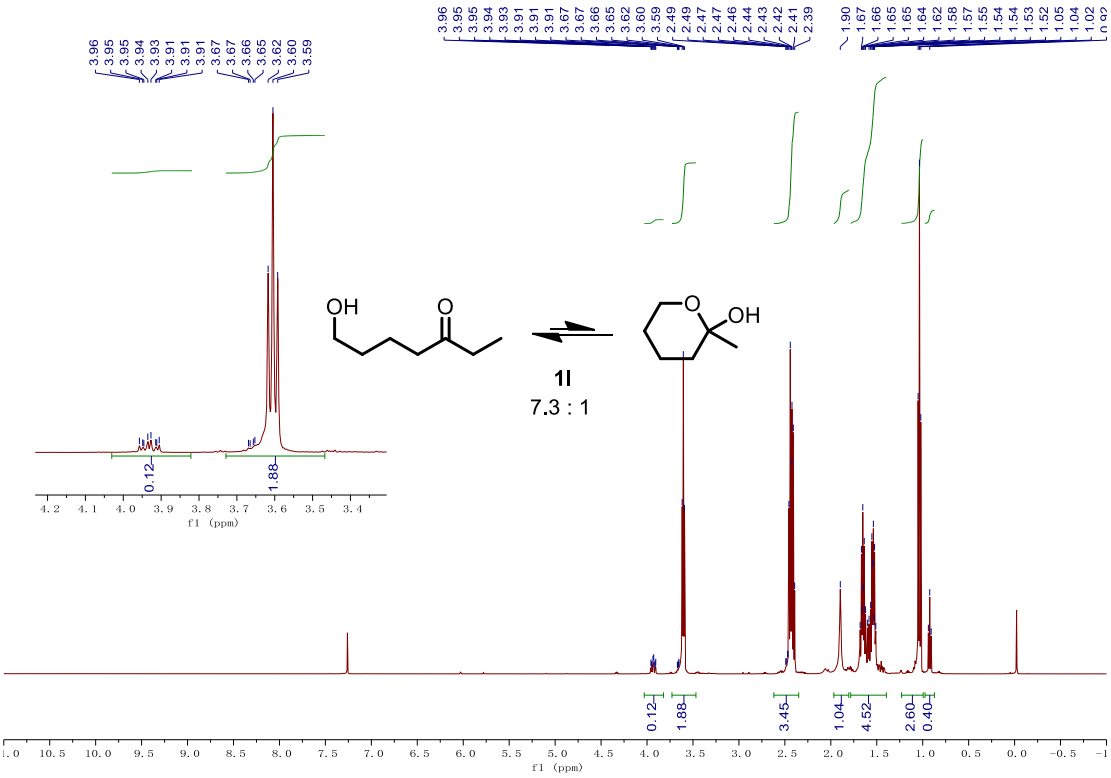


Figure 6.2 ^{1}H-NMR Spectrum of **6.S1**

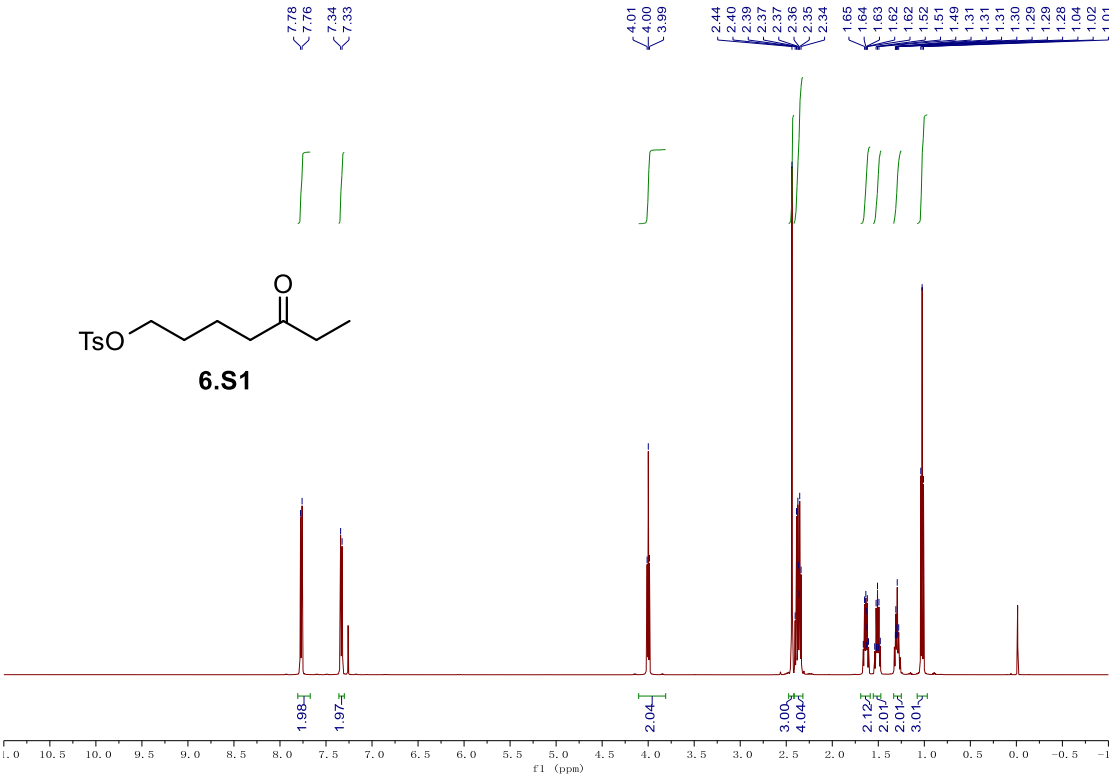


Figure 6.3 ^{13}C-NMR Spectrum of **6.S1**

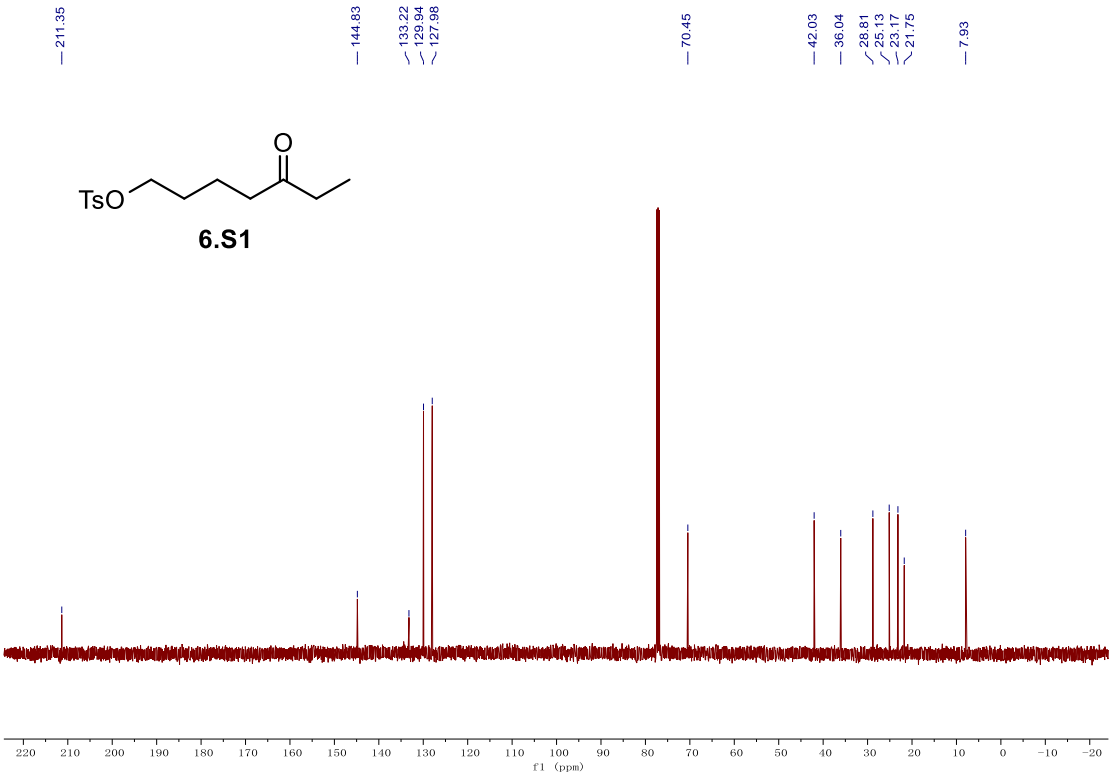


Figure 6.4 ^{1}H-NMR Spectrum of **6.1n**

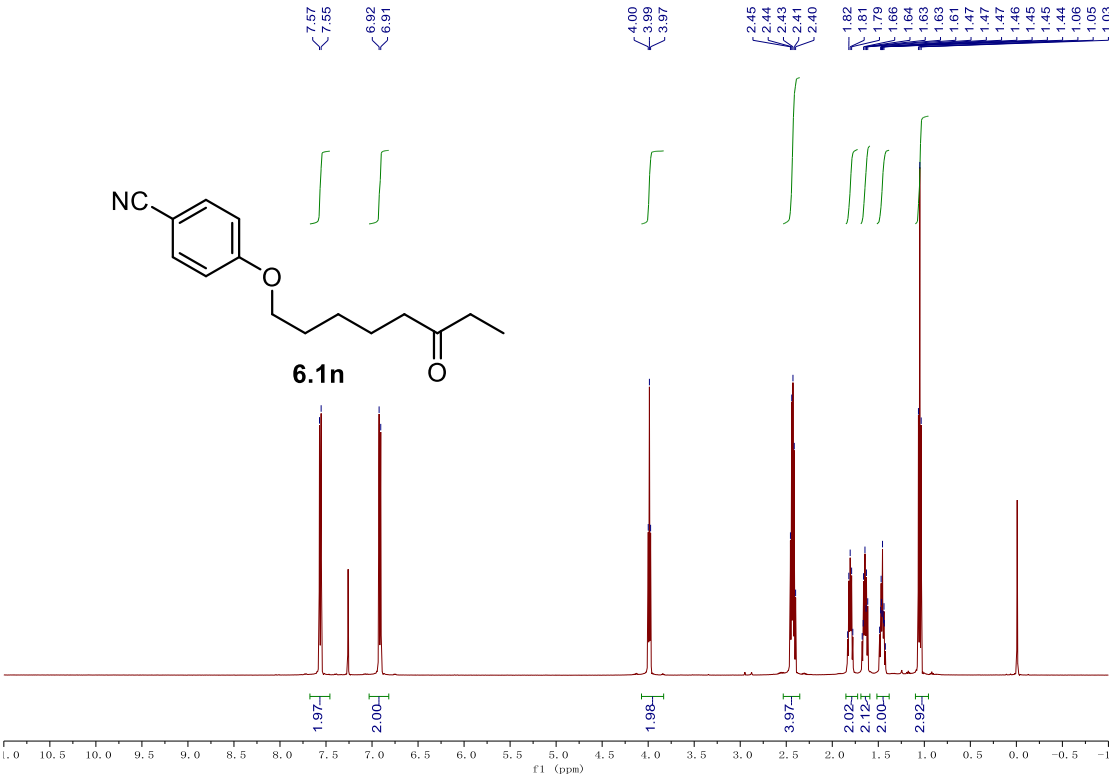


Figure 6.5 ^{13}C-NMR Spectrum of **6.1n**

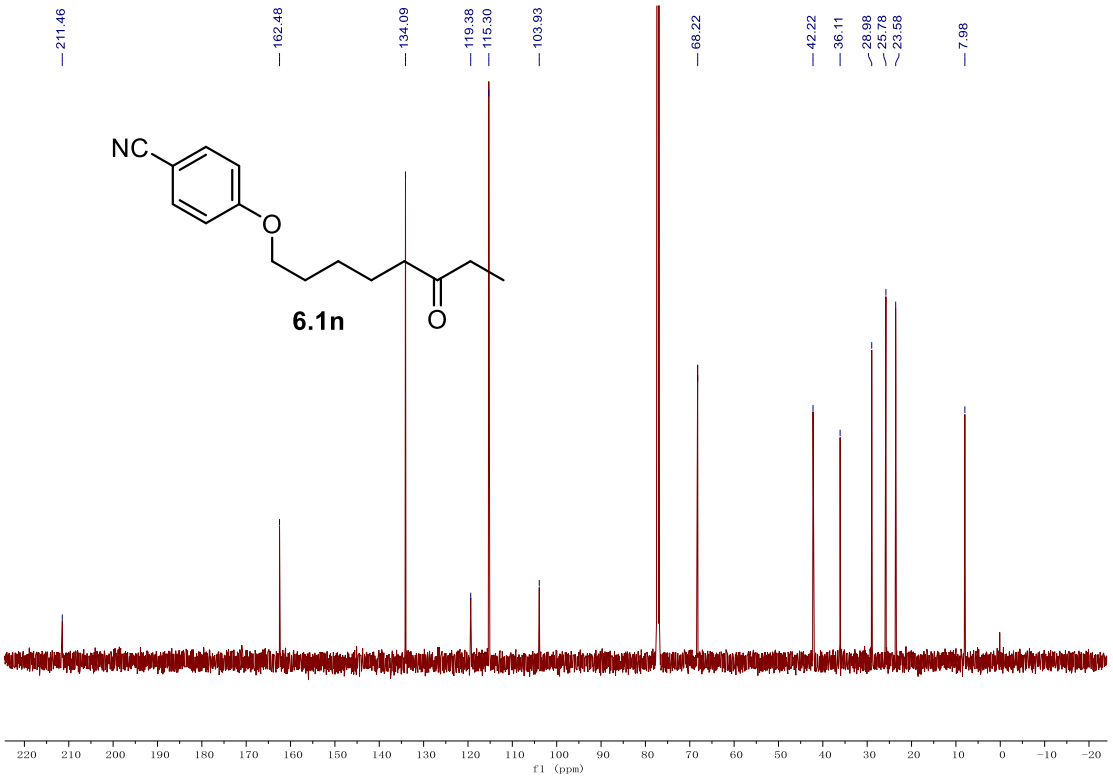


Figure 6.6 [1]H-NMR Spectrum of **6.S2**

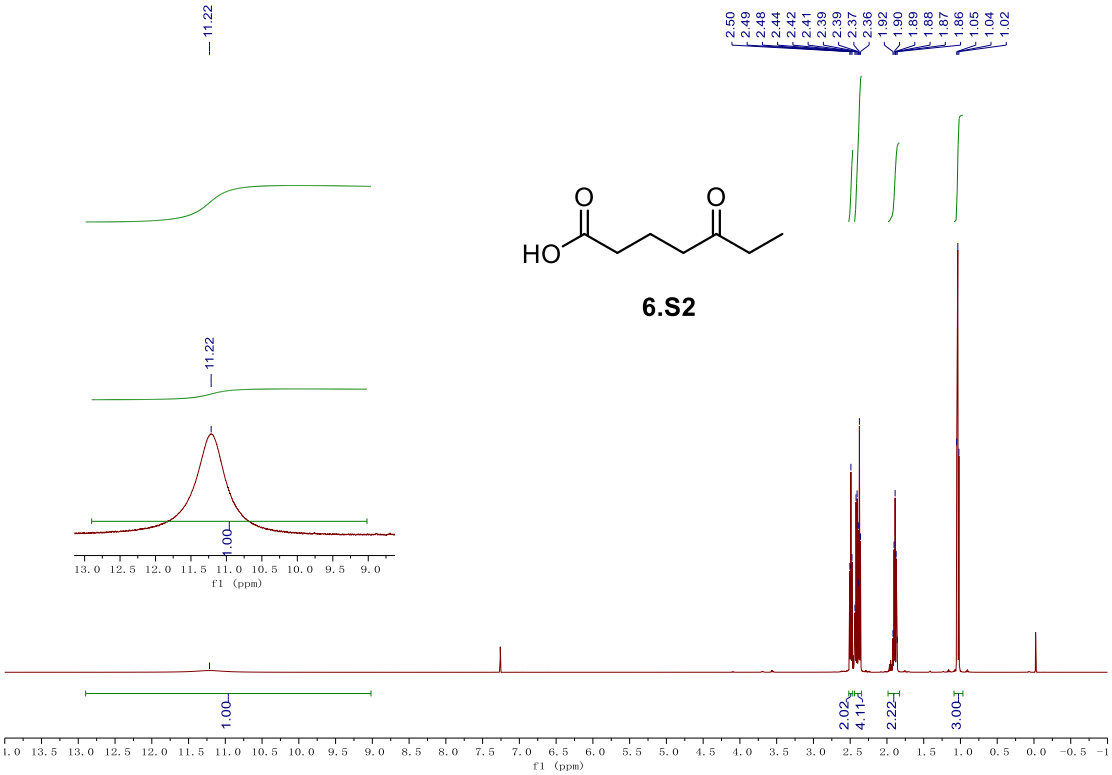


Figure 6.7 [13]C-NMR Spectrum of **6.S2**

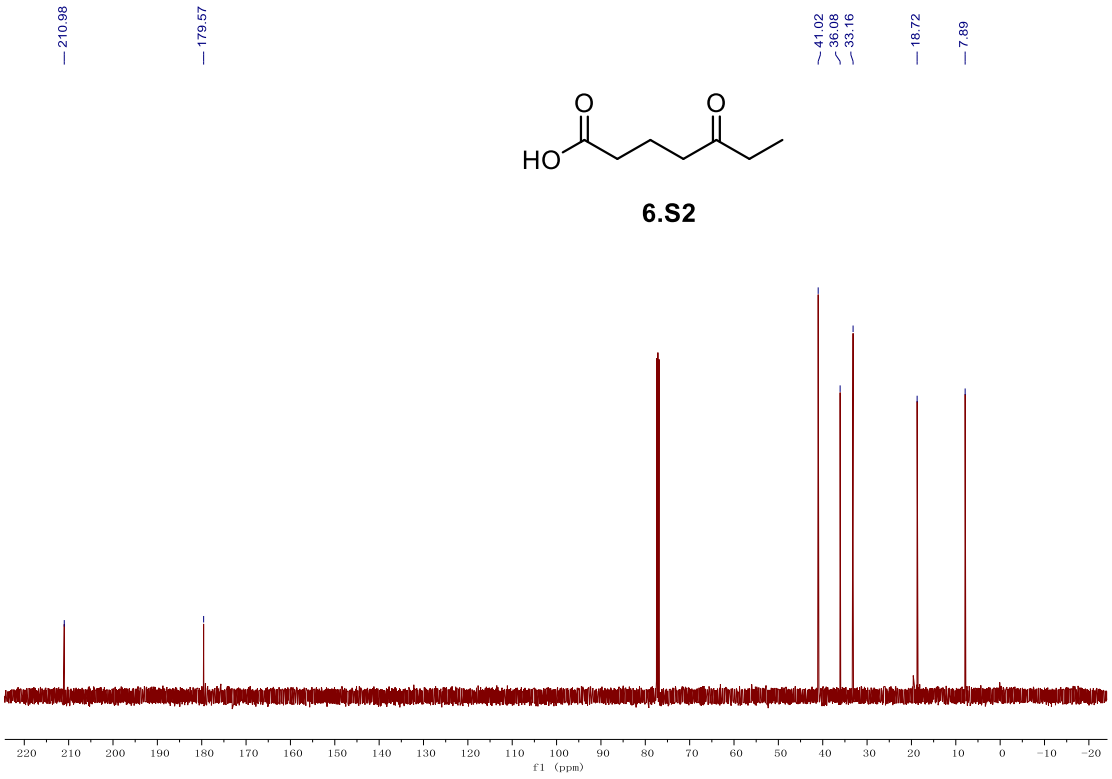


Figure 6.8 ^{1}H-NMR Spectrum of **6.1k**

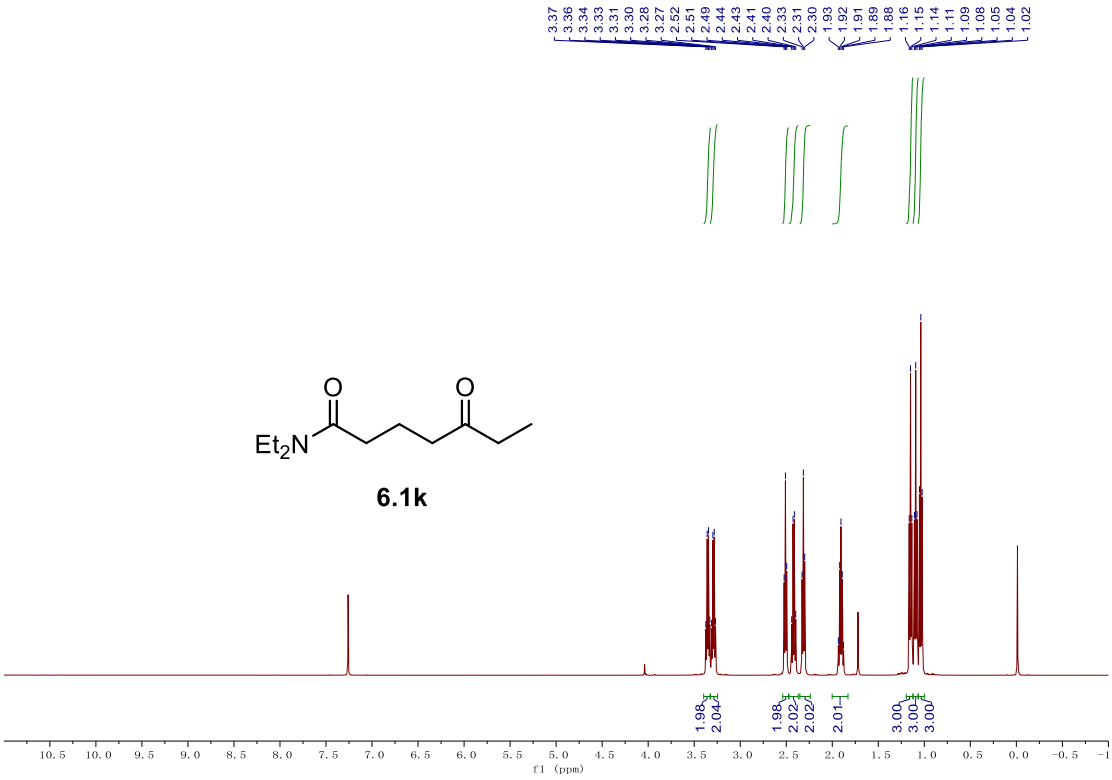


Figure 6.9 ^{13}C-NMR Spectrum of **6.1k**

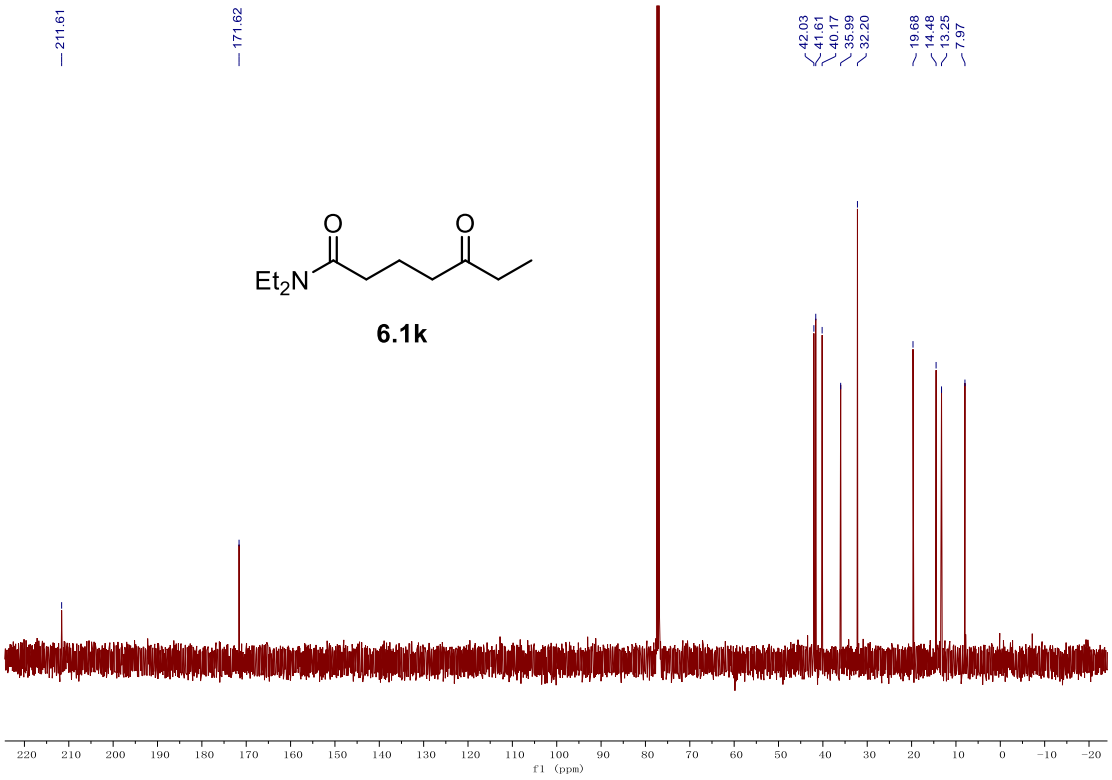


Figure 6.10 ^{1}H-NMR Spectrum of **6.2b**

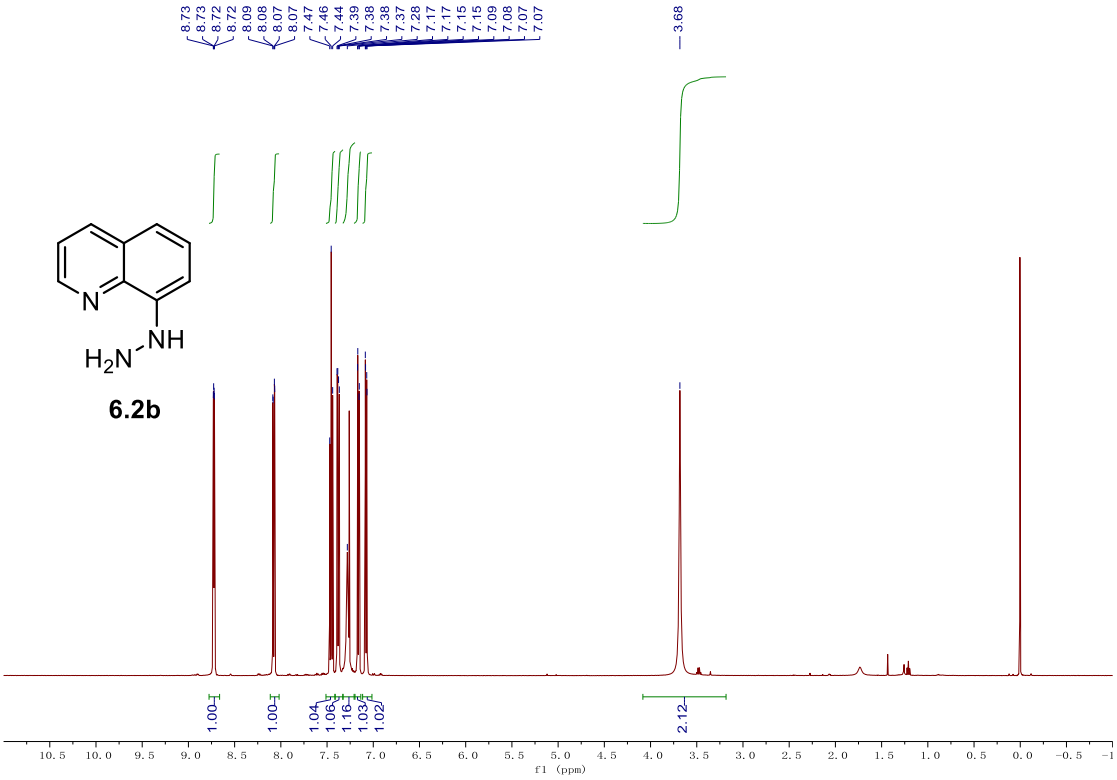


Figure 6.11 ^{13}C-NMR Spectrum of **6.2b**

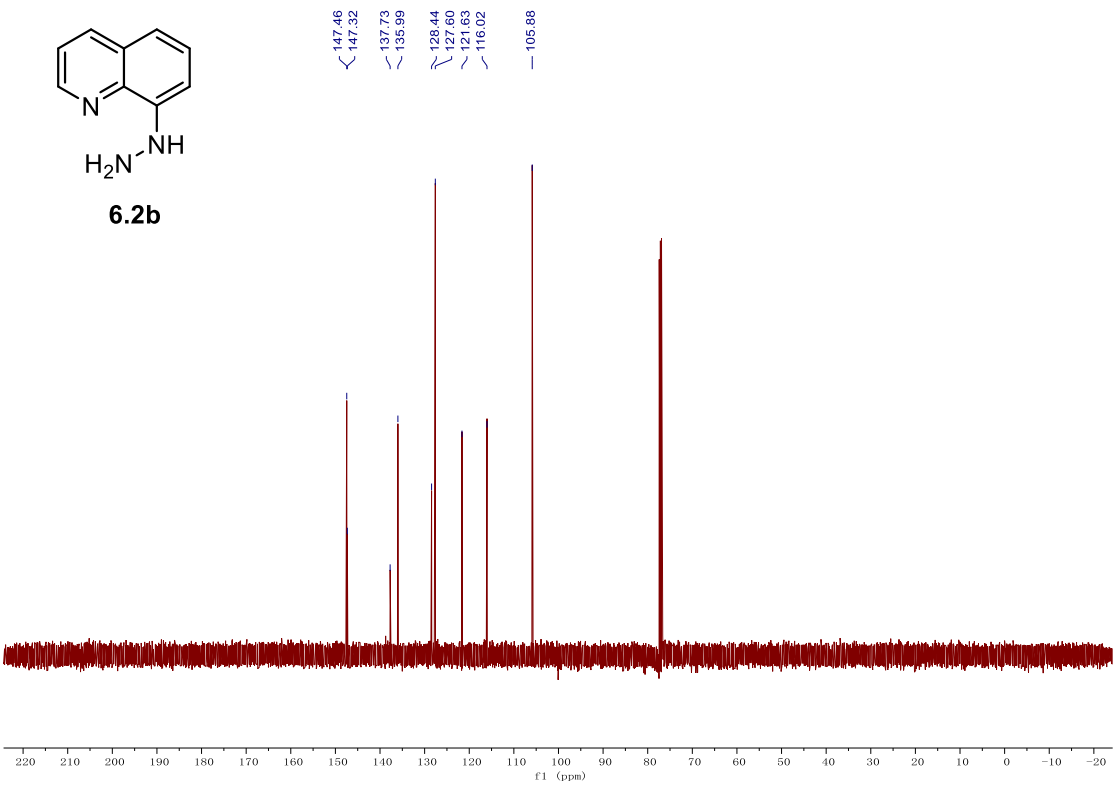


Figure 6.12 ^{1}H-NMR Spectrum of **6.2d**

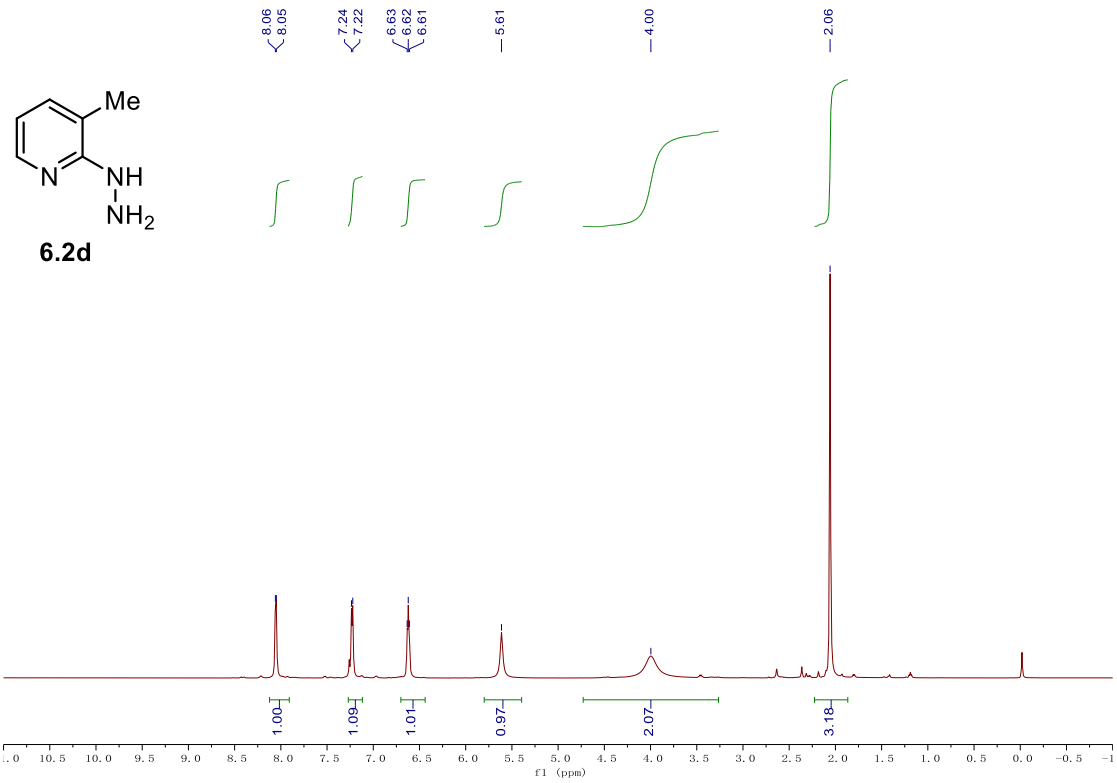


Figure 6.13 ^{13}C-NMR Spectrum of **6.2d**

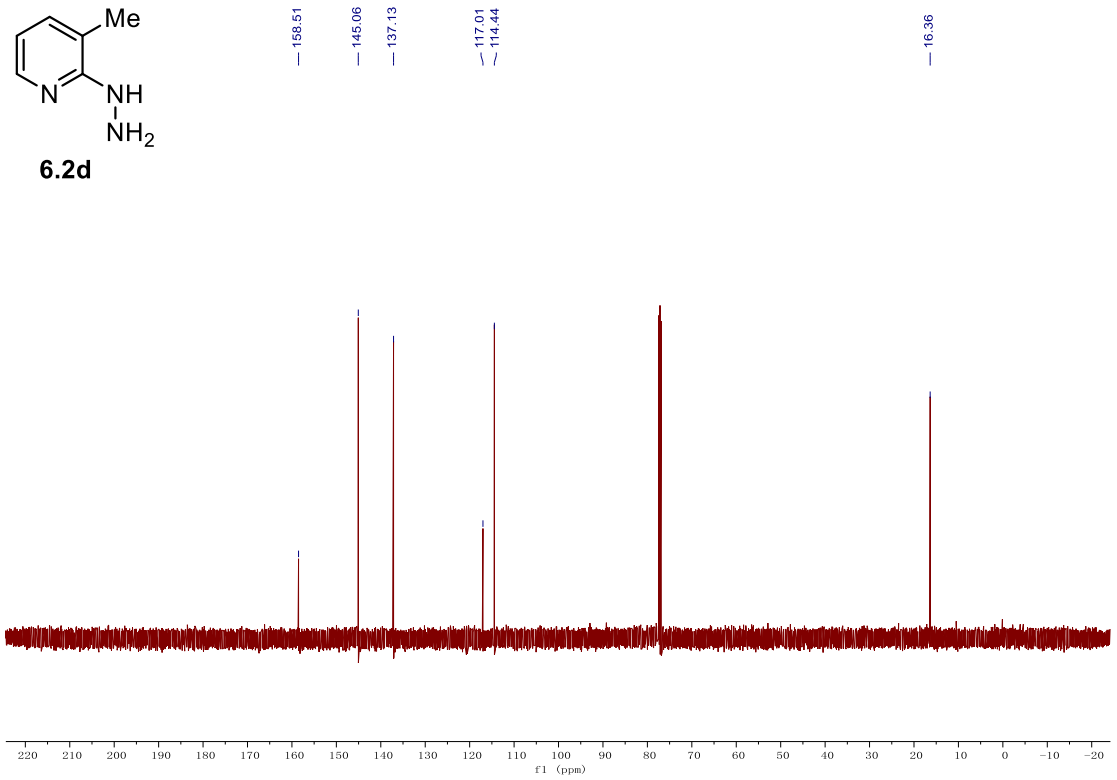


Figure 6.14 ^{1}H-NMR Spectrum of **6.2f**

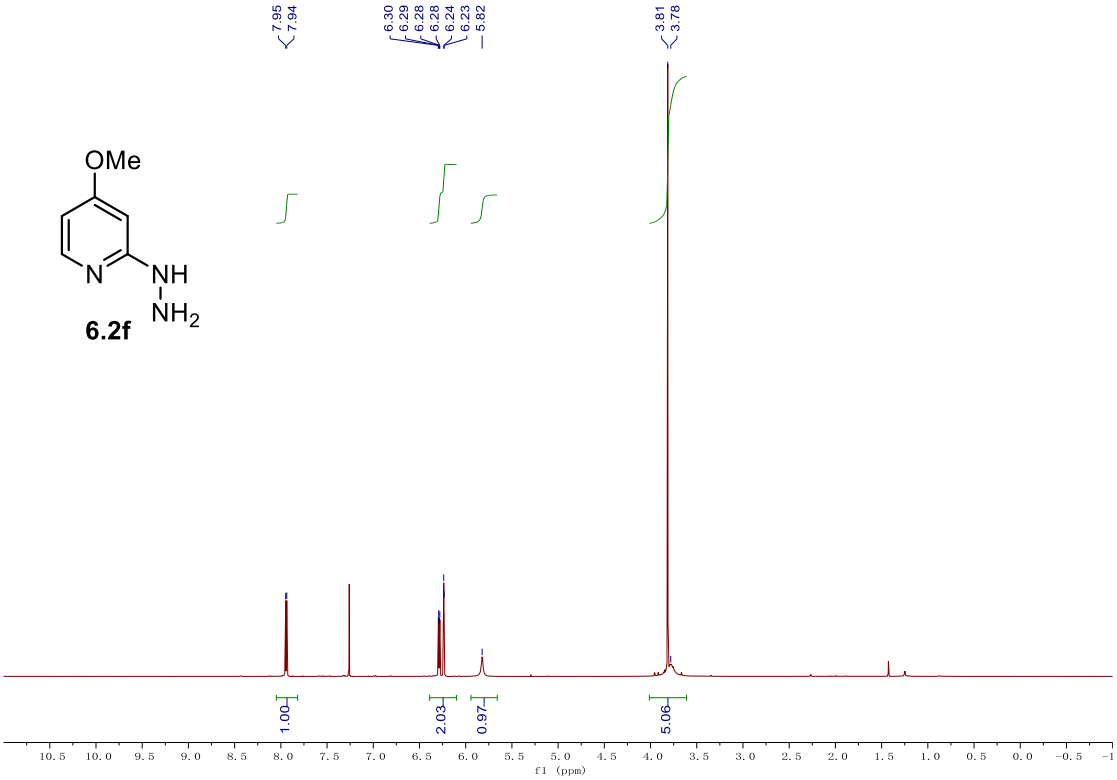


Figure 6.15 ^{13}C-NMR Spectrum of **6.2f**

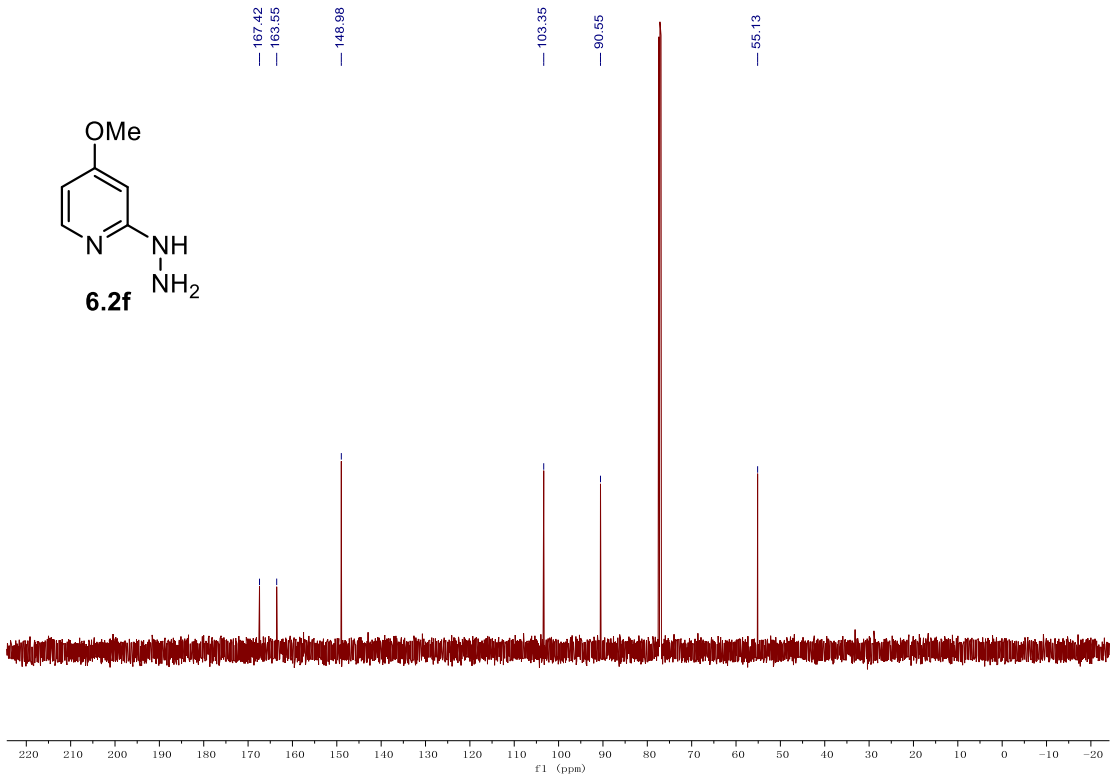


Figure 6.16 ^{1}H-NMR Spectrum of **6.3aa**

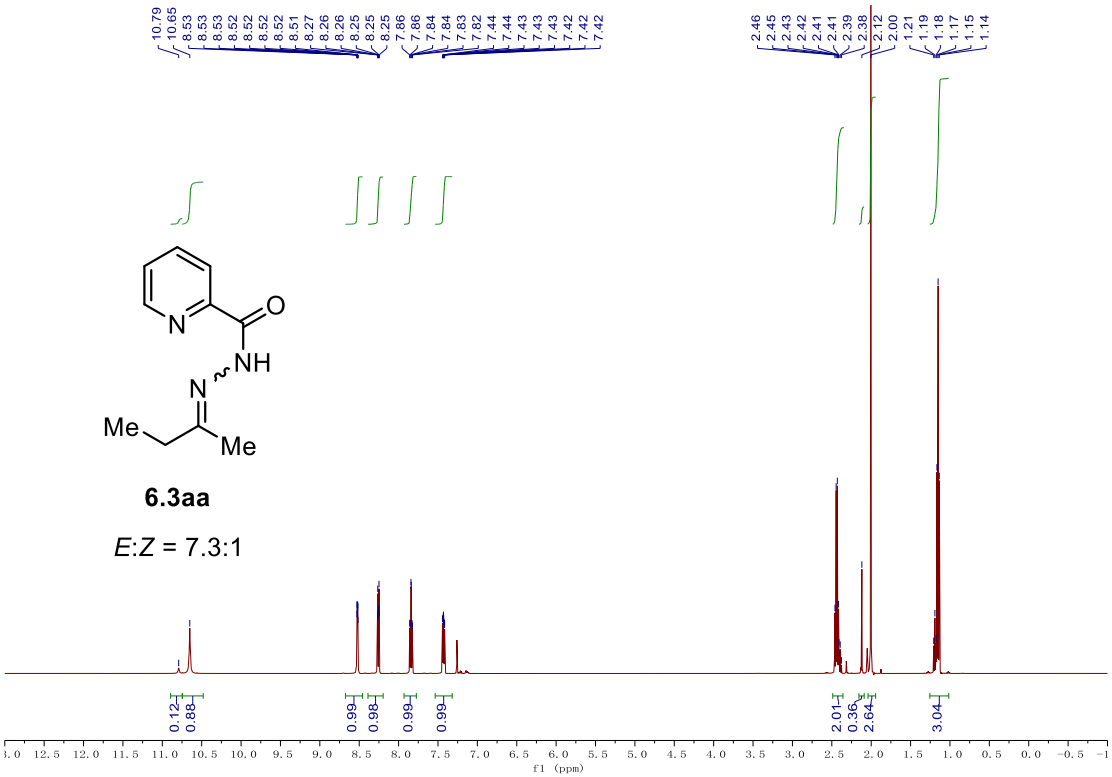


Figure 6.17 ^{13}C-NMR Spectrum of **6.3aa**

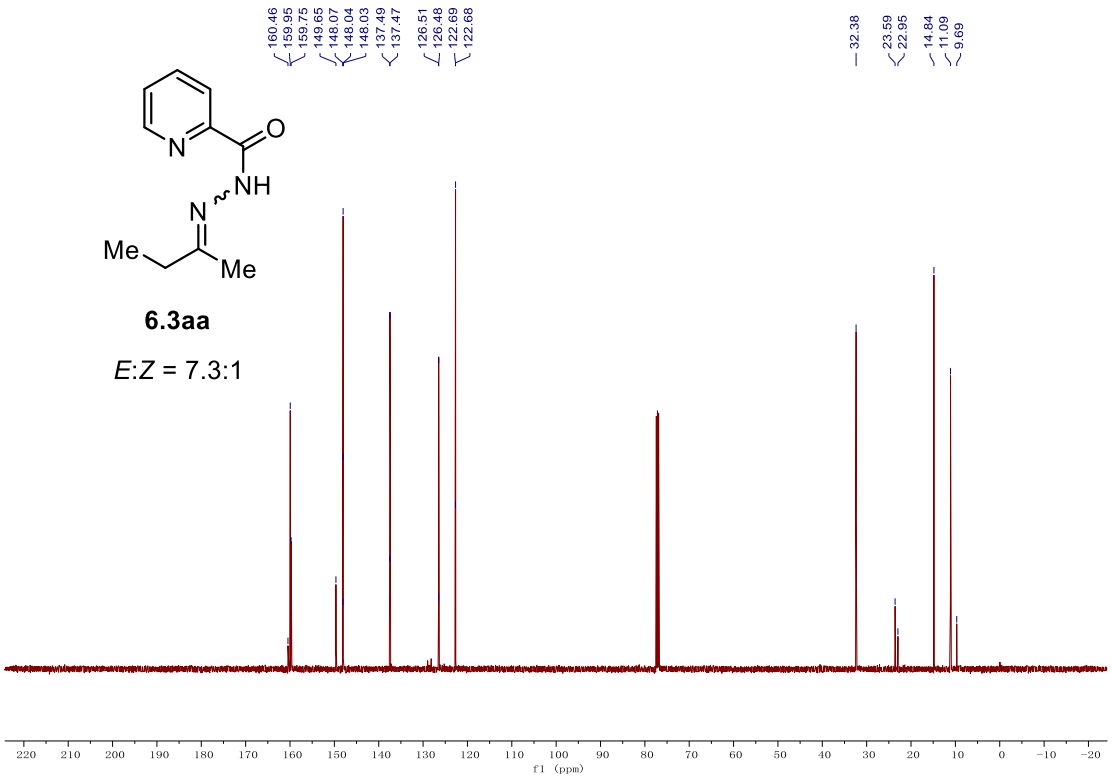


Figure 6.18 ^{1}H-NMR Spectrum of **6.3a**

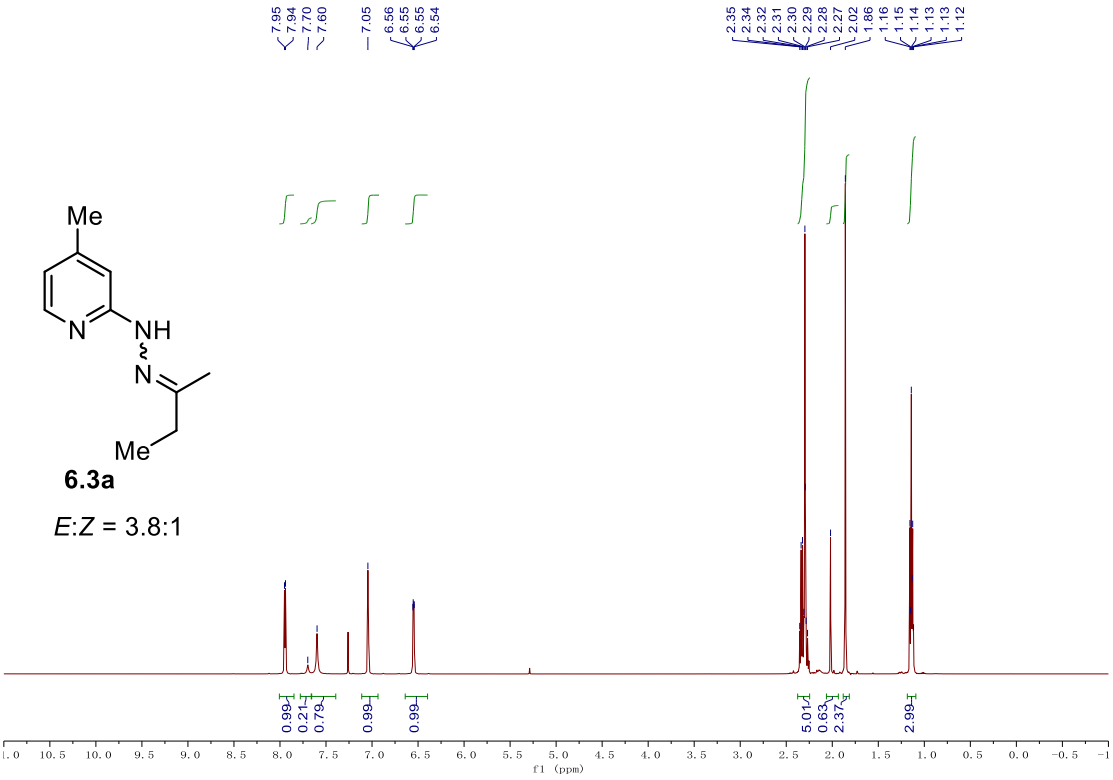


Figure 6.19 ^{13}C-NMR Spectrum of **6.3a**

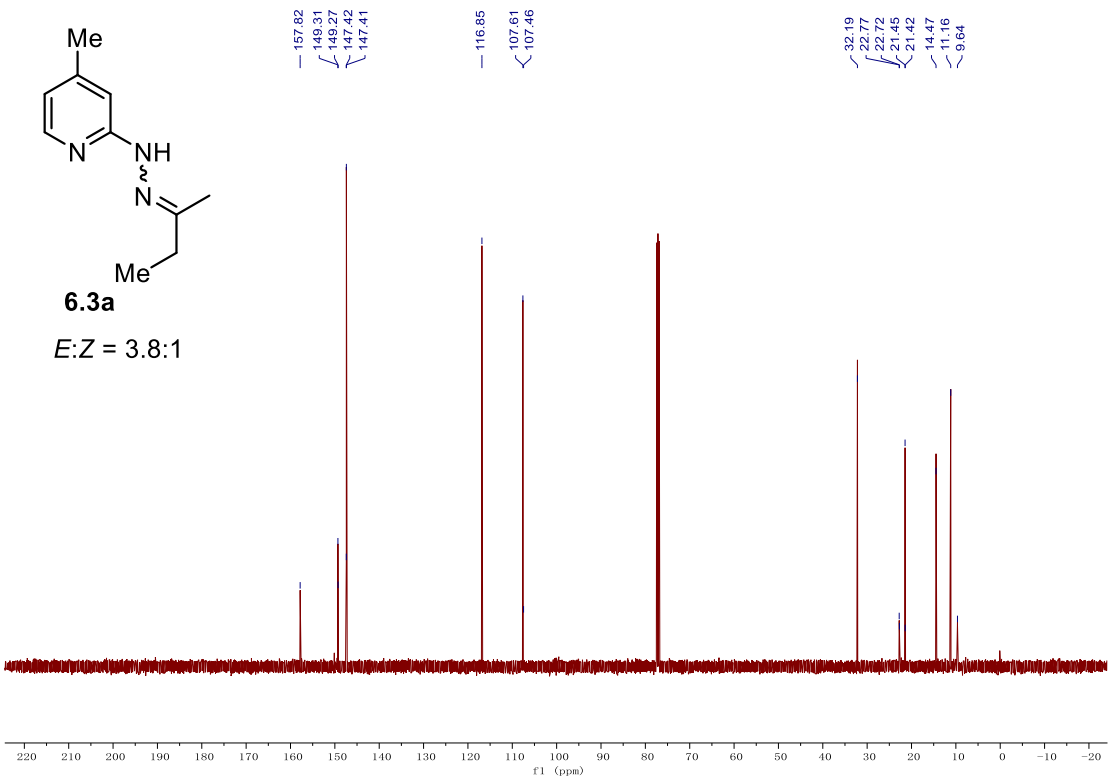


Figure 6.20 ^{1}H-NMR Spectrum of **6.3o**

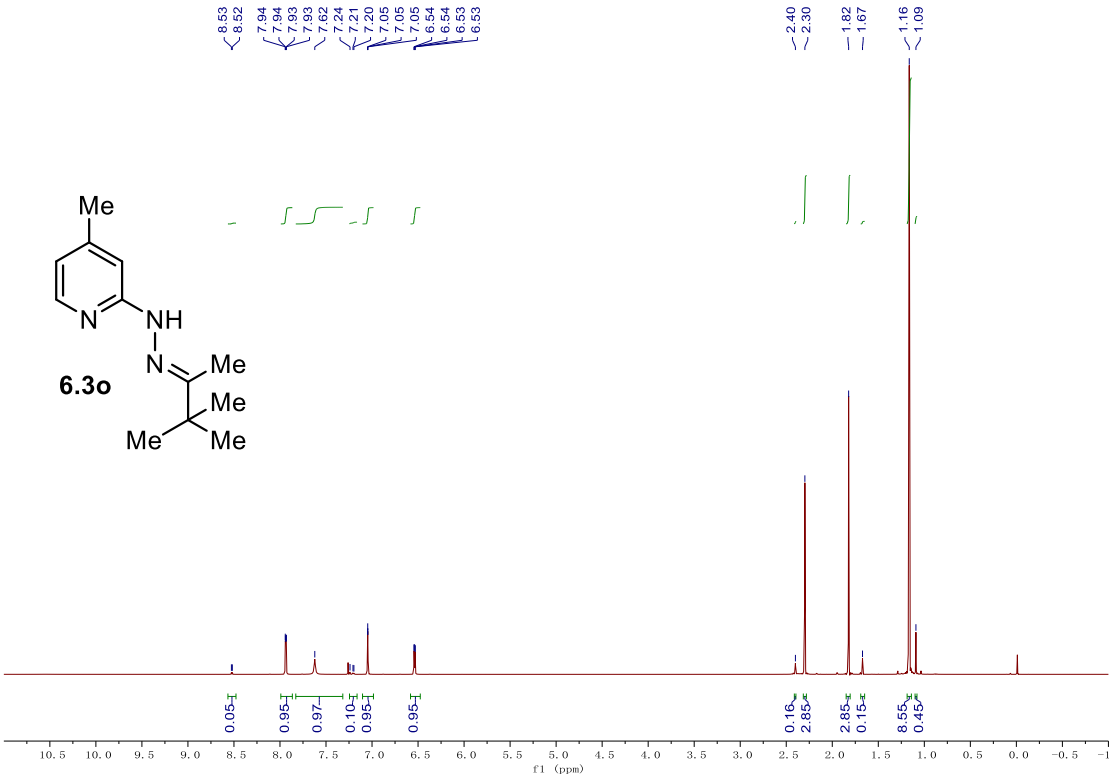


Figure 6.21 ^{13}C-NMR Spectrum of **6.3o**

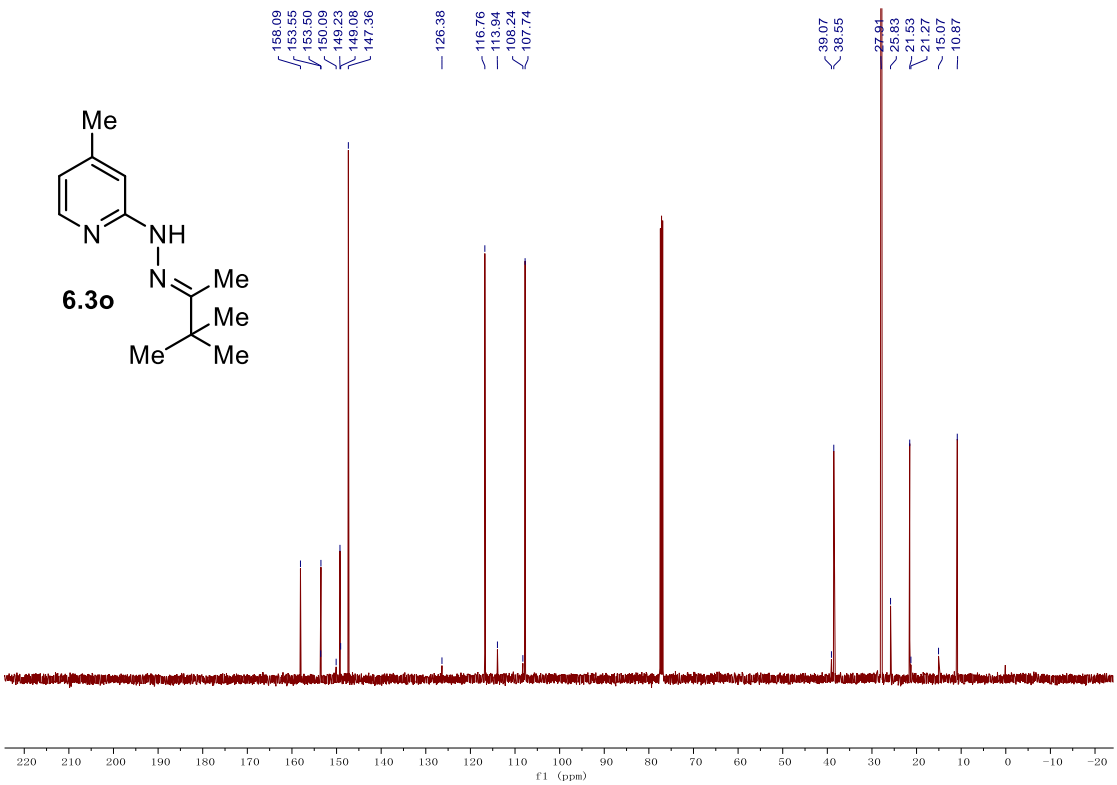


Figure 6.22 ^{1}H-NMR Spectrum of **6.3oa**

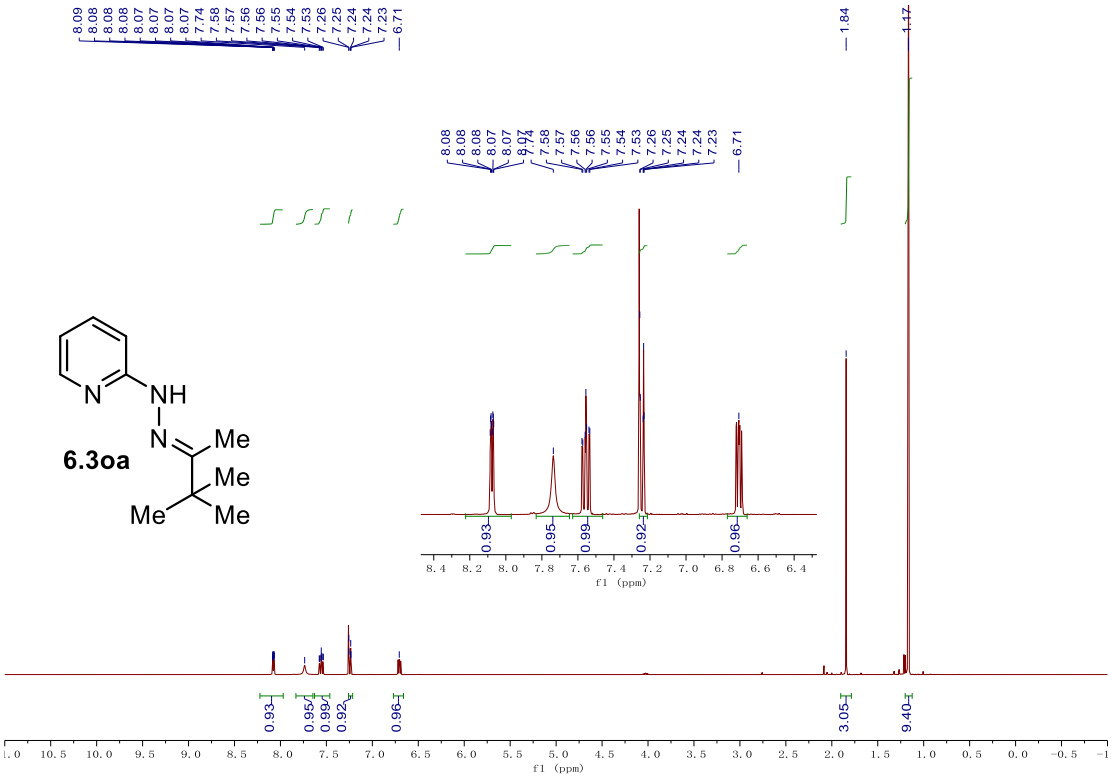


Figure 6.23 ^{13}C-NMR Spectrum of **6.3oa**

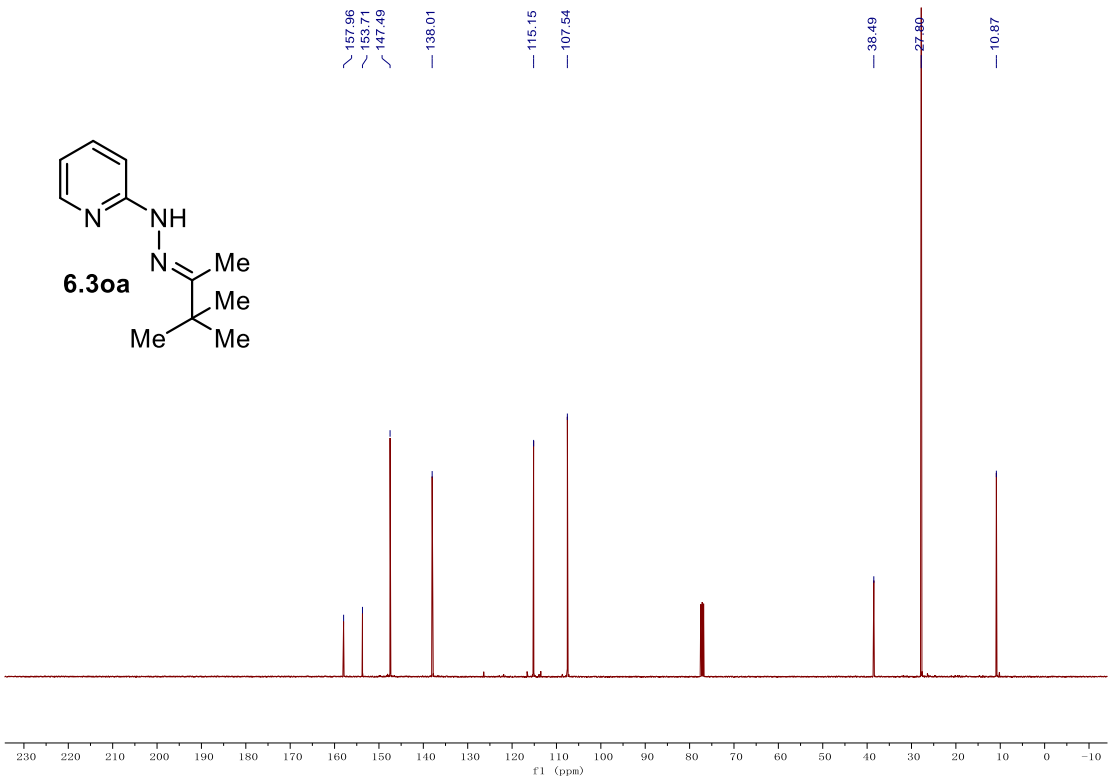


Figure 6.24 ^{1}H-NMR Spectrum of **6.5ac**

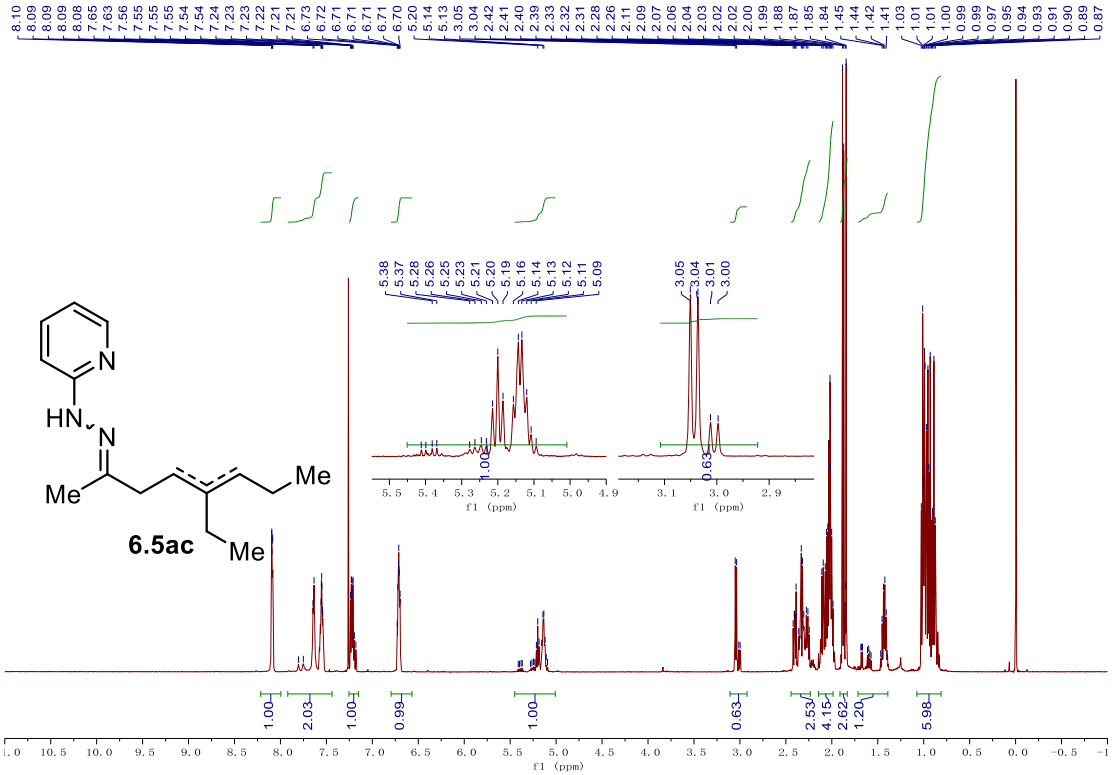


Figure 6.25 ^{1}H-NMR Spectrum of **6.5af**

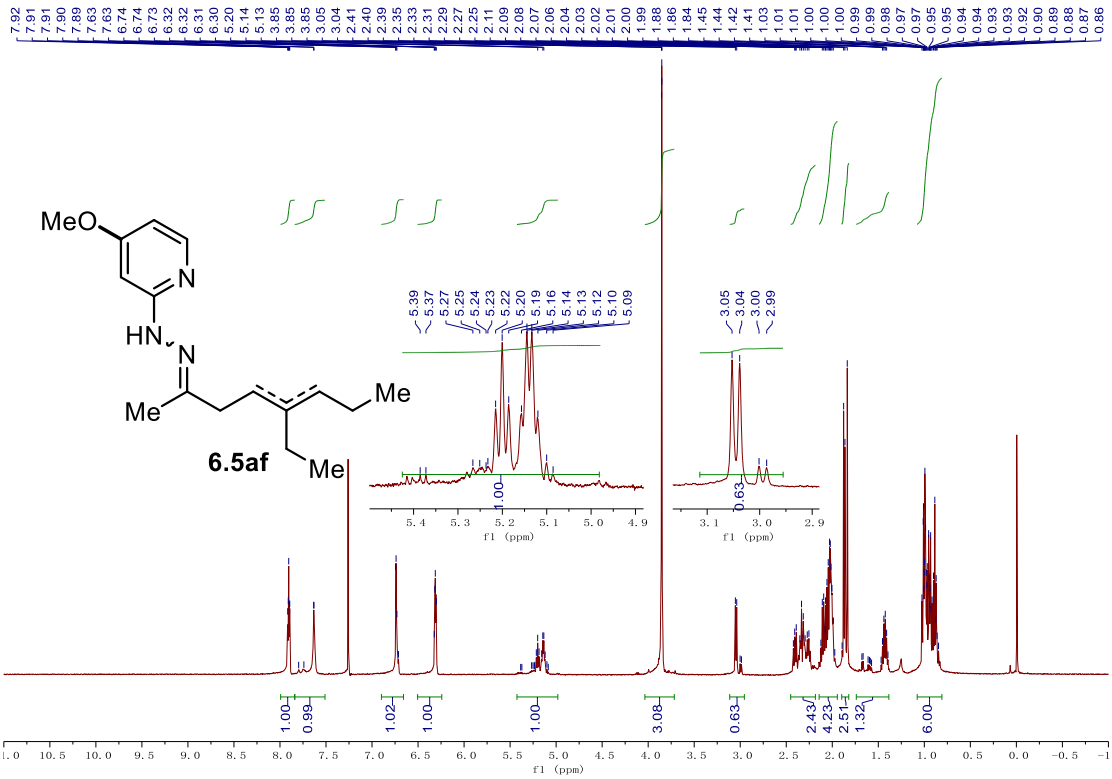


Figure 6.26 ^{1}H-NMR Spectrum of **6.2e**

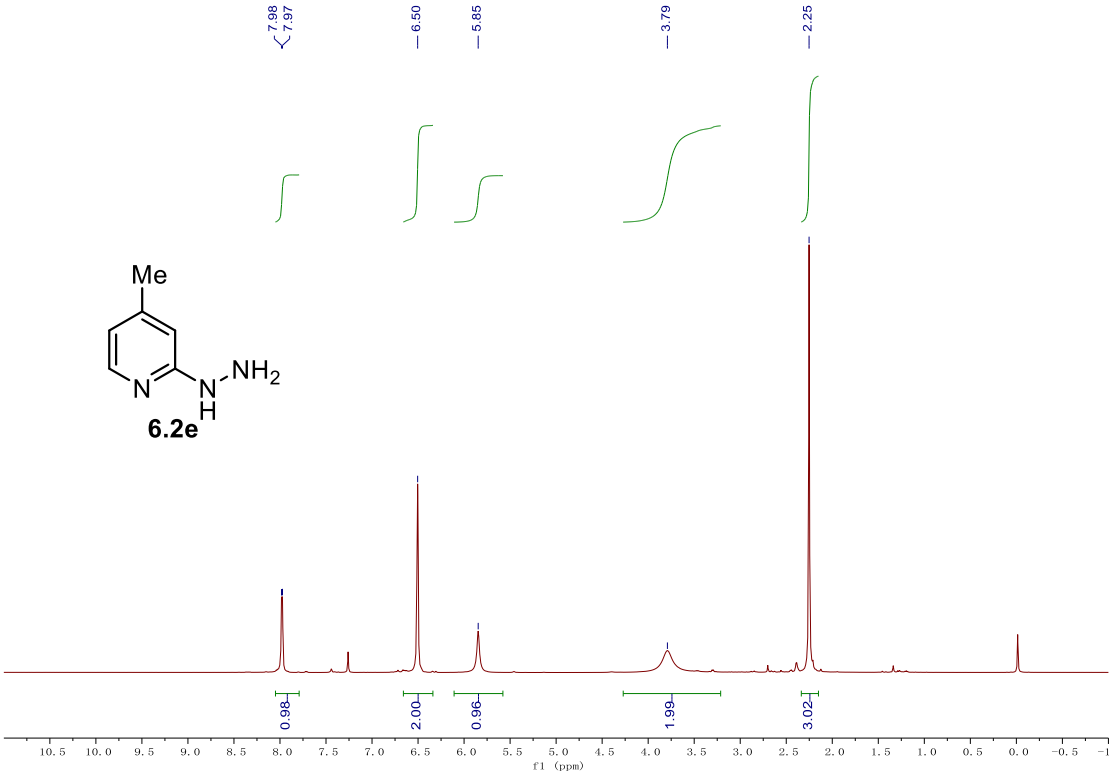


Figure 6.27 ^{13}C-NMR Spectrum of **6.2e**

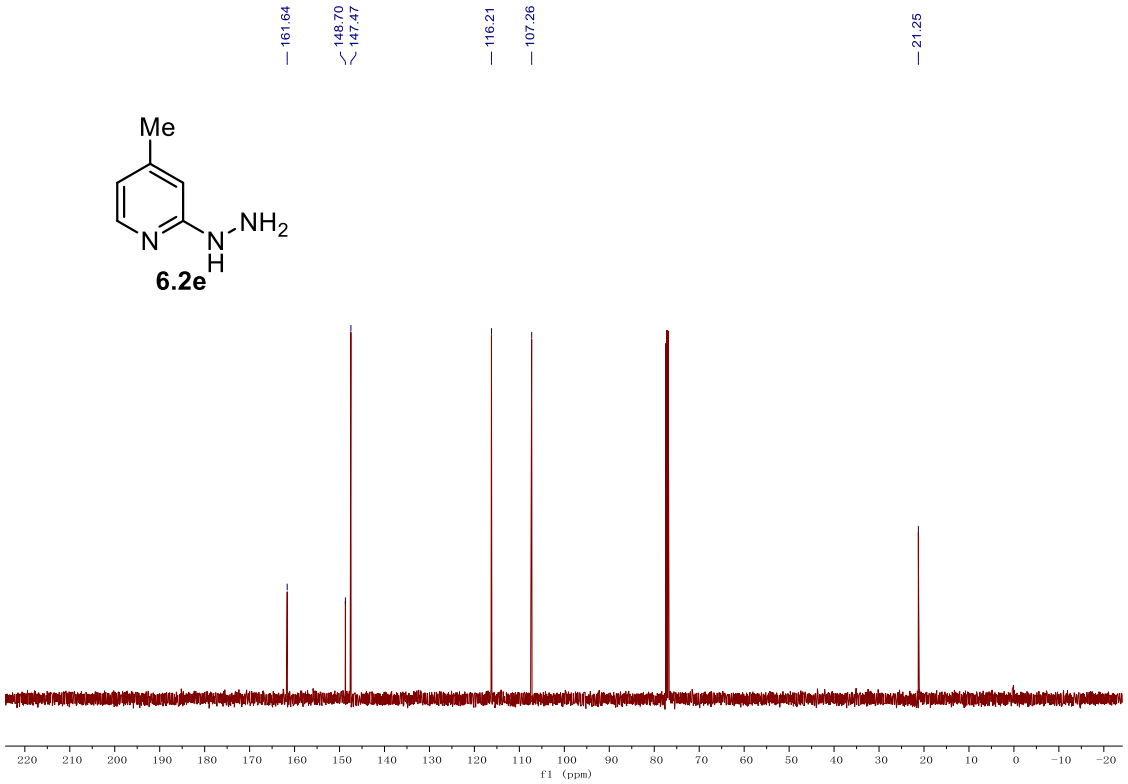


Figure 6.28 ^{1}H-NMR Spectrum of **6.5a**

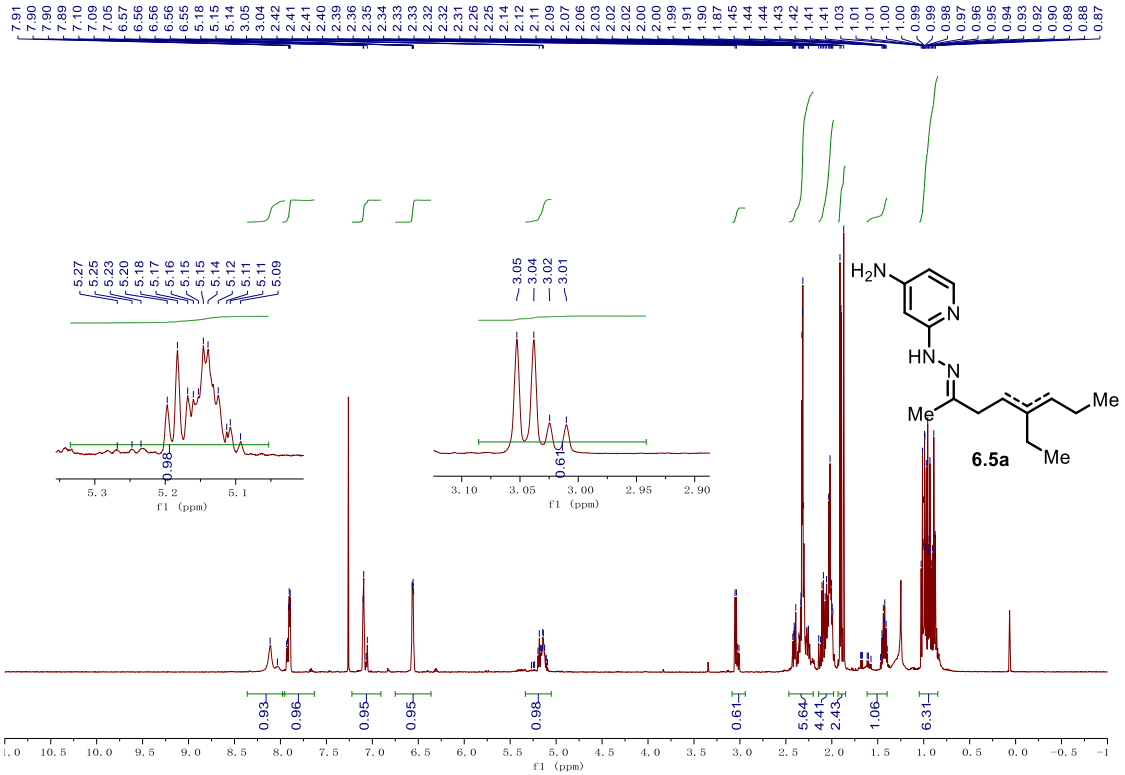


Figure 6.29 ^{1}H-NMR Spectrum of **6.6a**

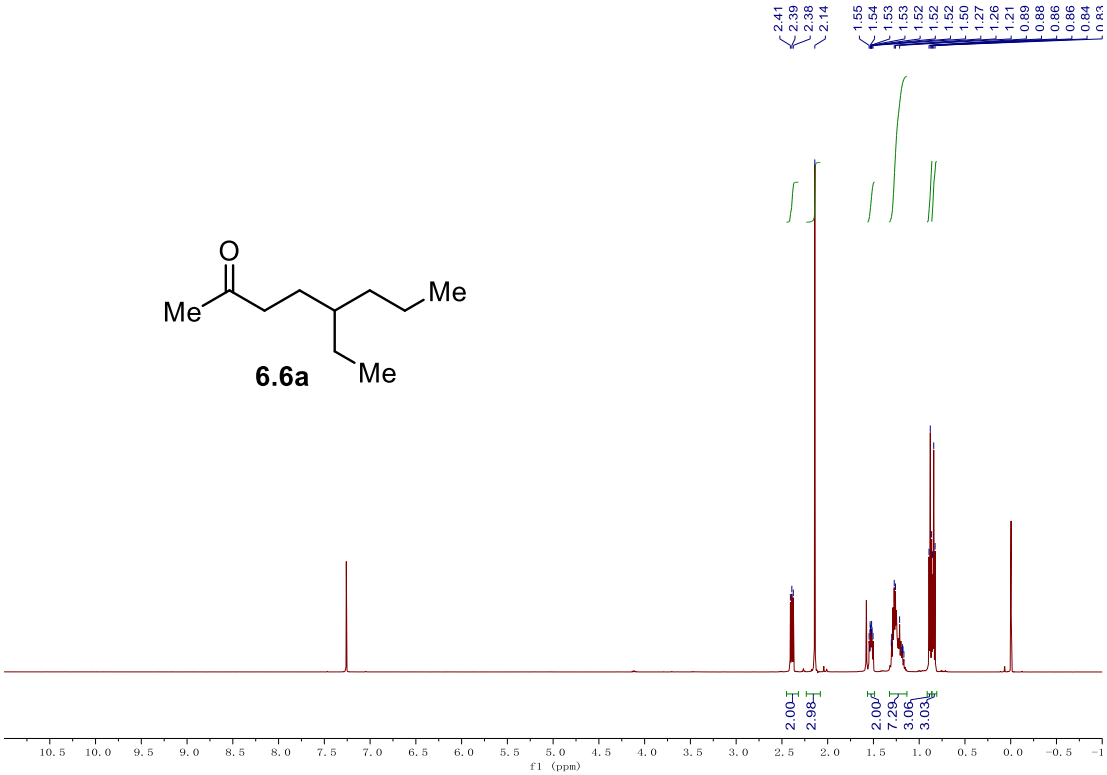


Figure 6.30 ^{13}C-NMR Spectrum of **6.6a**

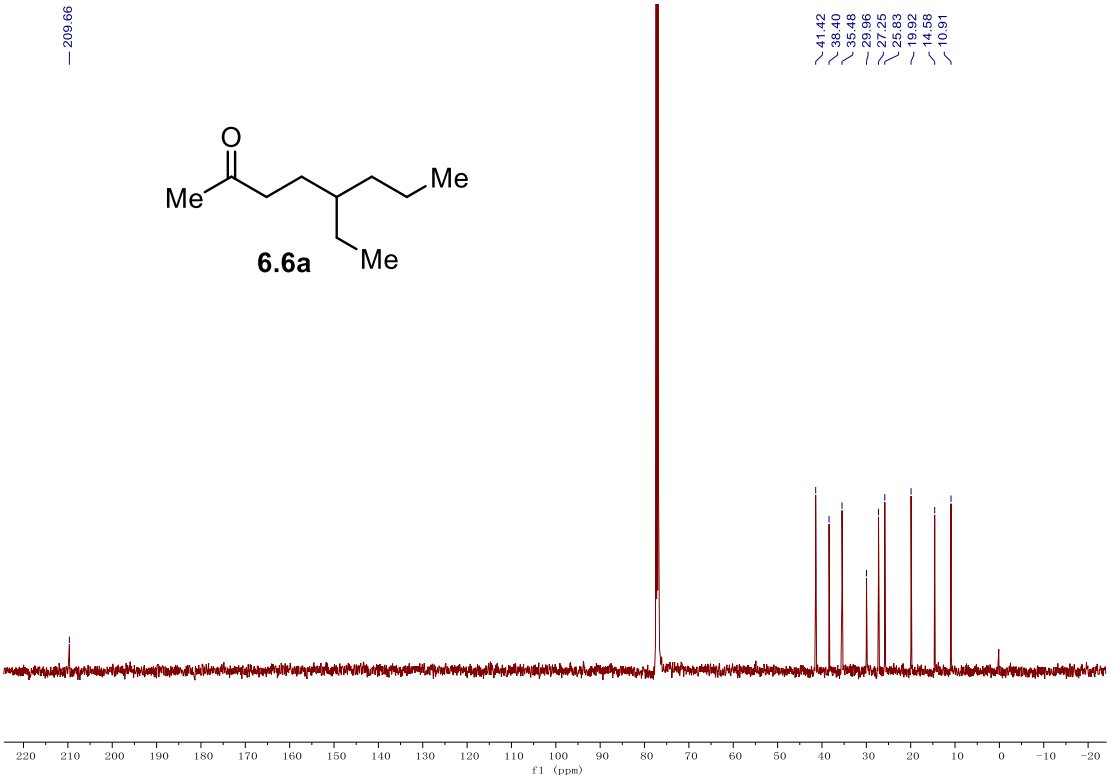


Figure 6.31 ^{1}H-NMR Spectrum of **6.5b**

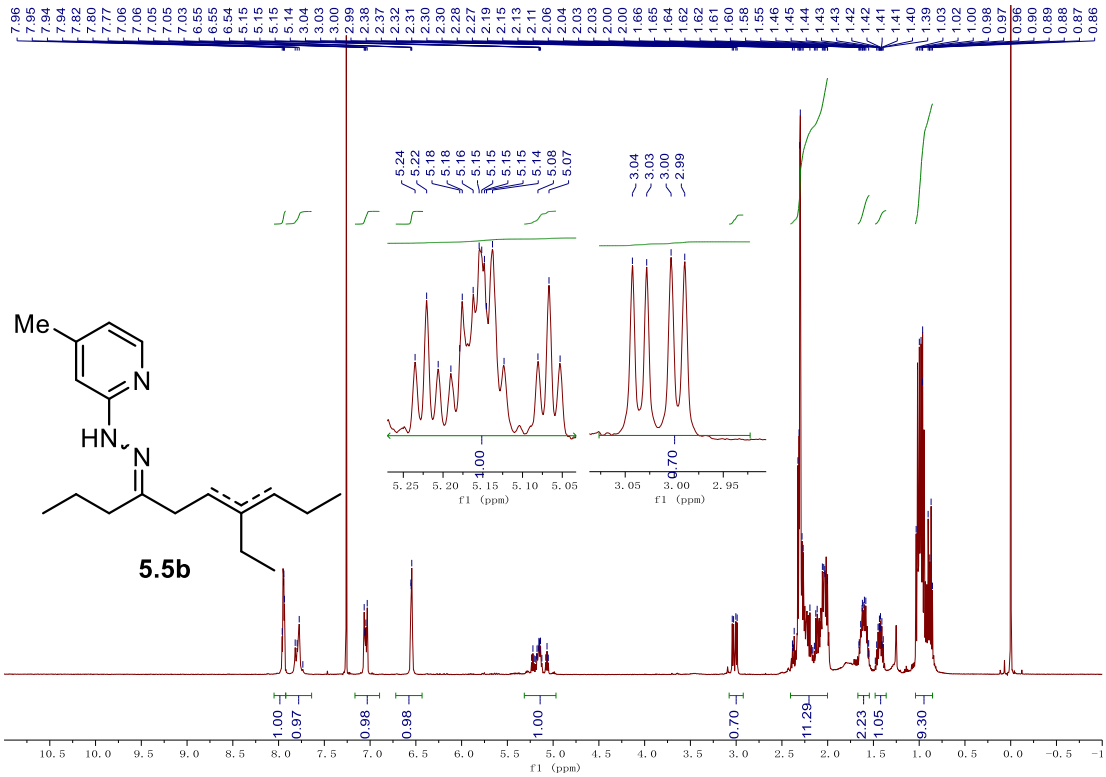


Figure 6.32 ^{1}H-NMR Spectrum of **6.6b**

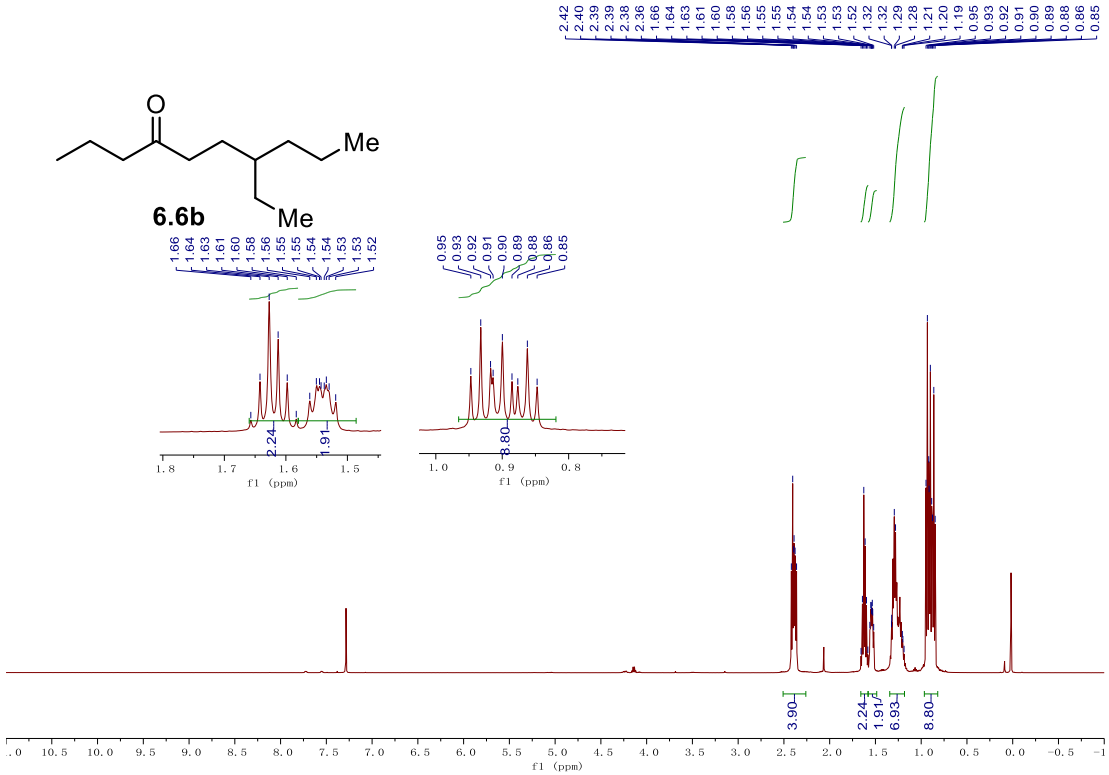


Figure 6.33 ^{13}C-NMR Spectrum of **6.6b**

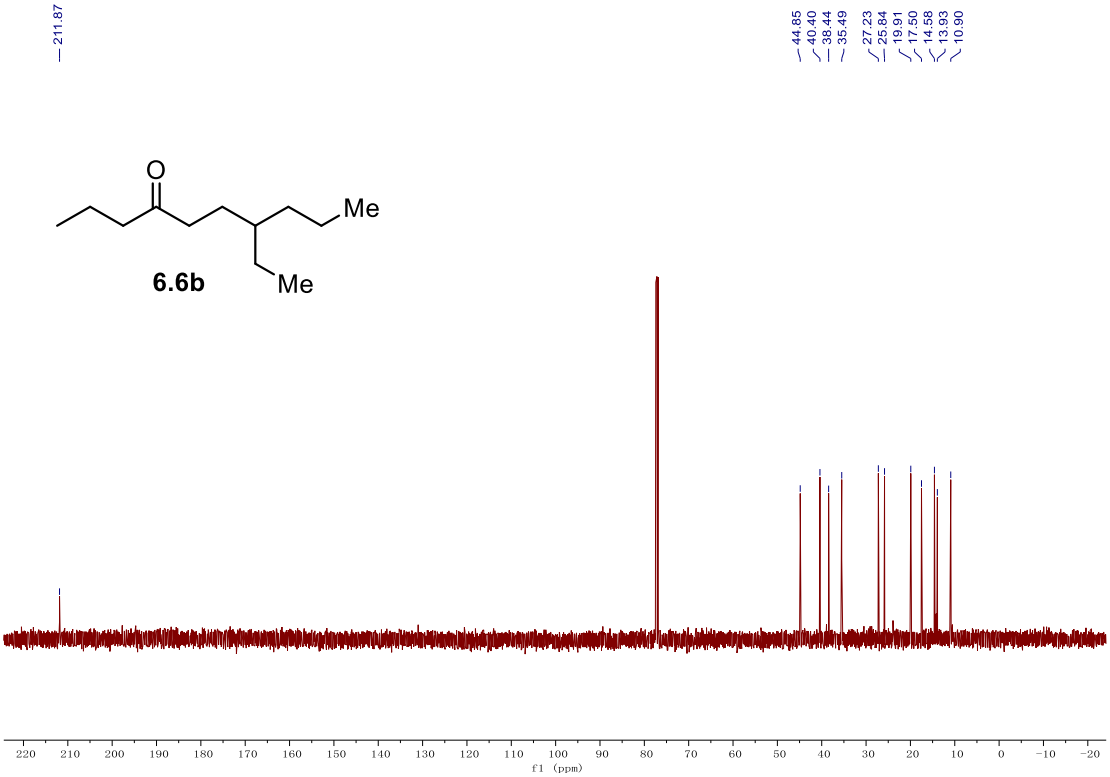


Figure 6.34 ^{1}H-NMR Spectrum of **6.5c**

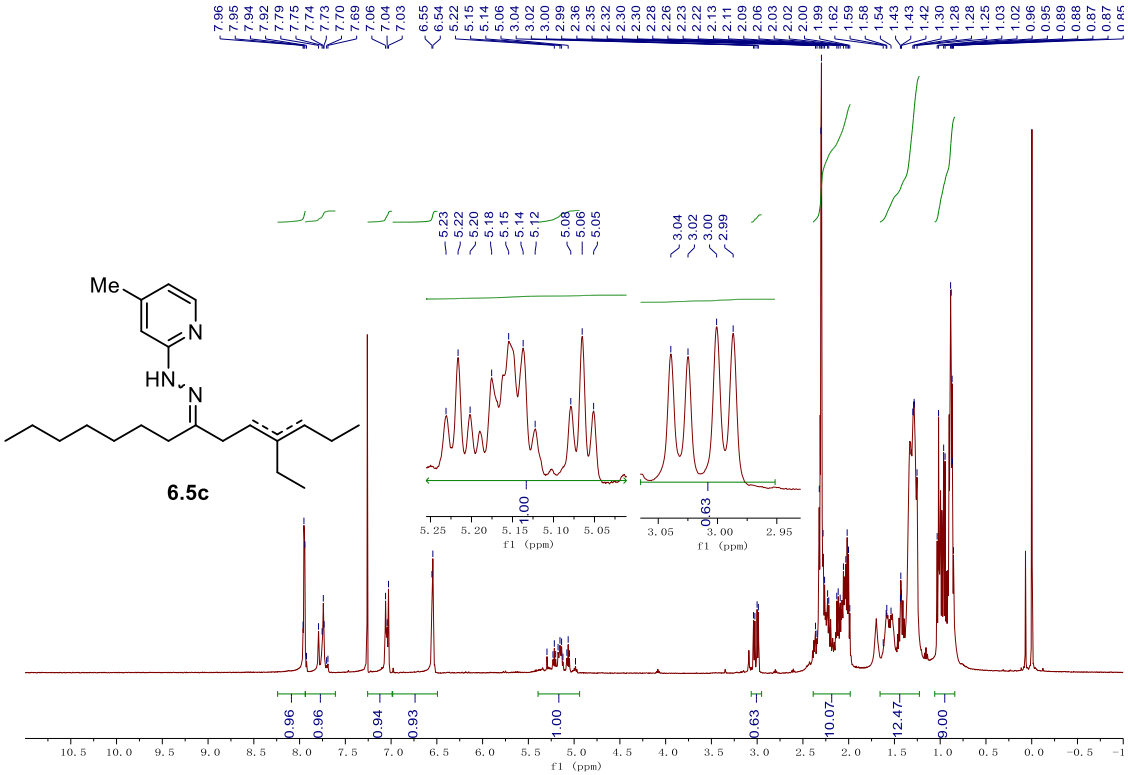


Figure 6.35 ^{1}H-NMR Spectrum of **6.6c**

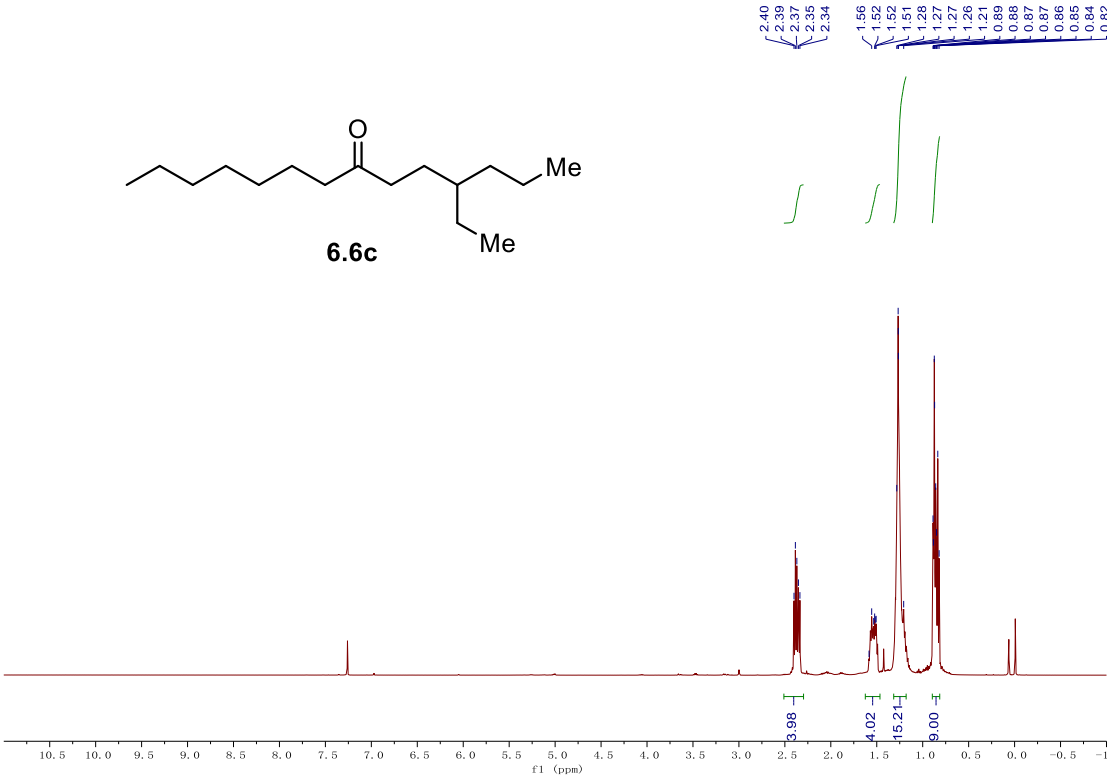


Figure 6.36 ^{13}C-NMR Spectrum of **6.6c**

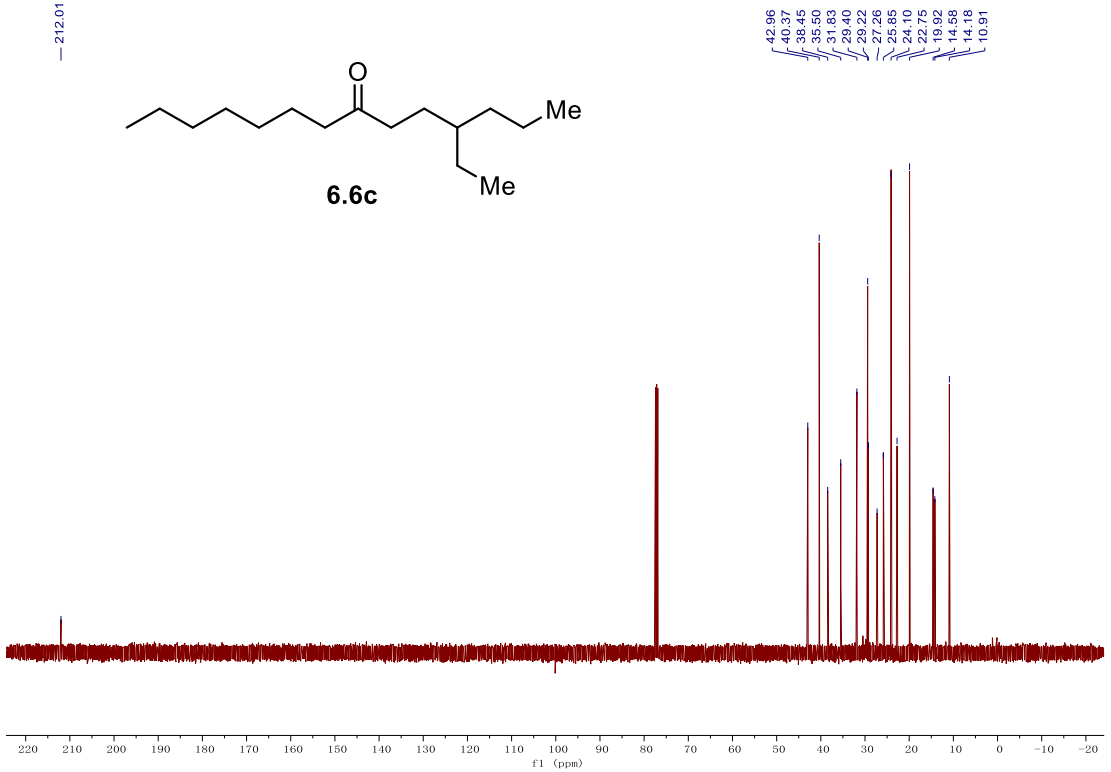


Figure 6.37 ^{1}H-NMR Spectrum of **6.5d**

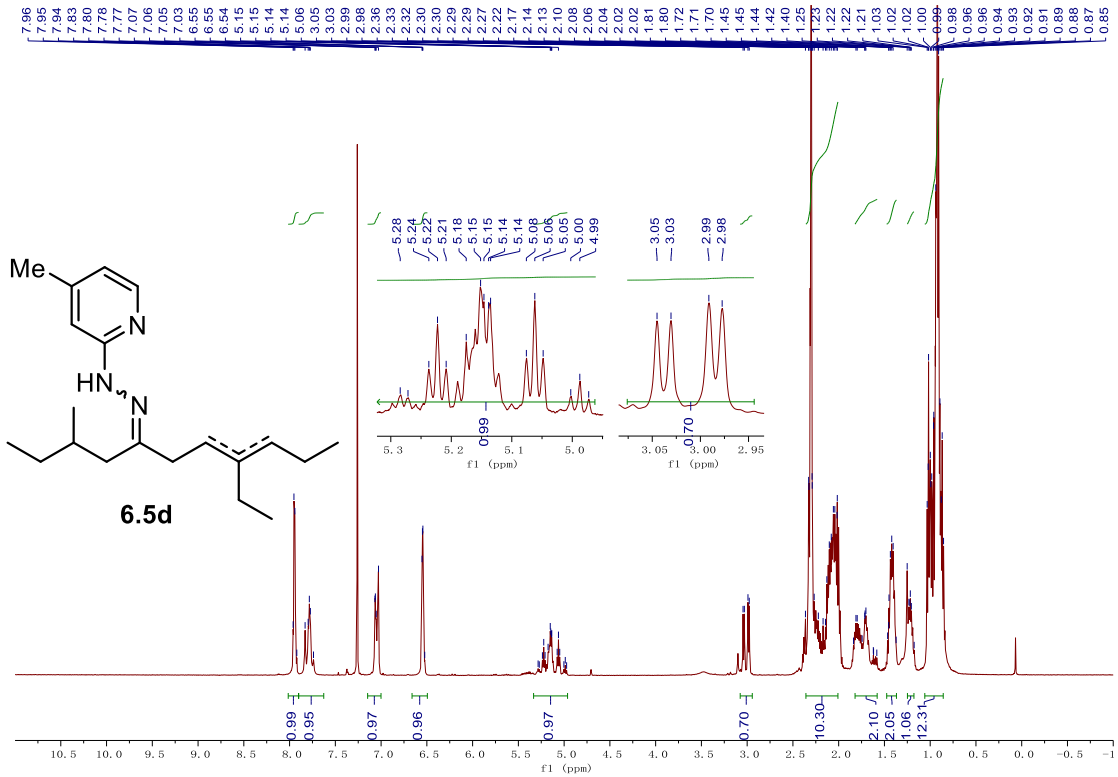


Figure 6.38 ^{1}H-NMR Spectrum of **6.6d**

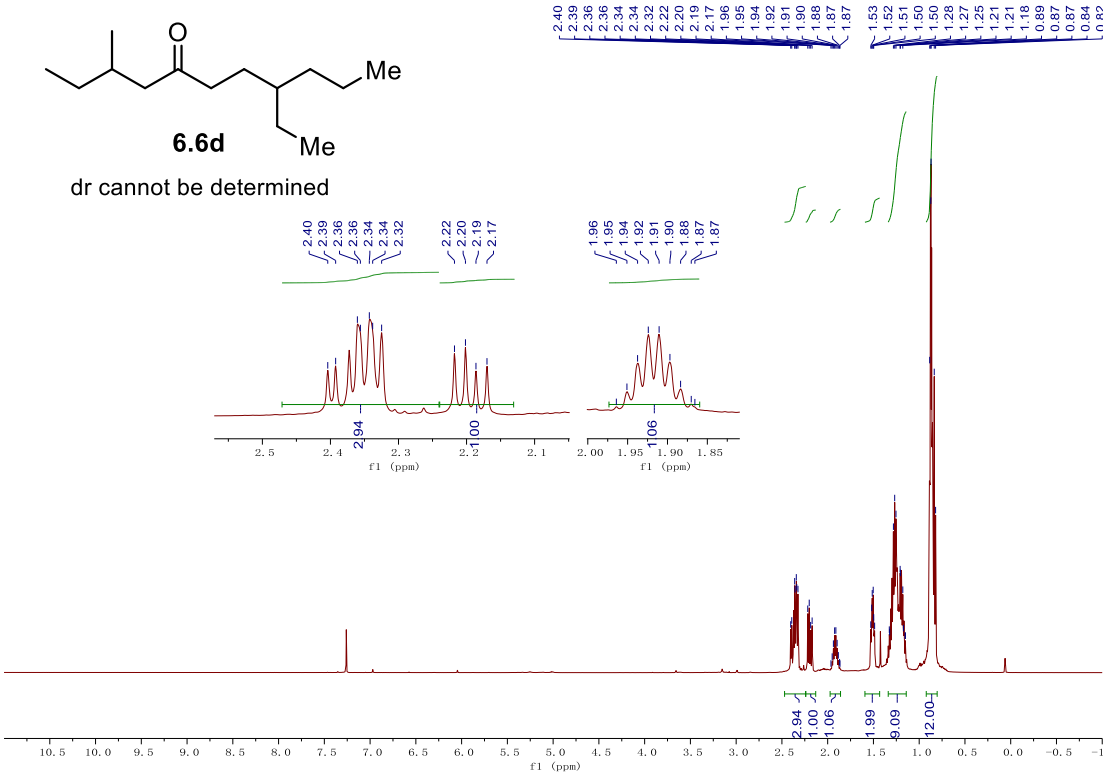


Figure 6.39 ^{13}C-NMR Spectrum of **6.6d**

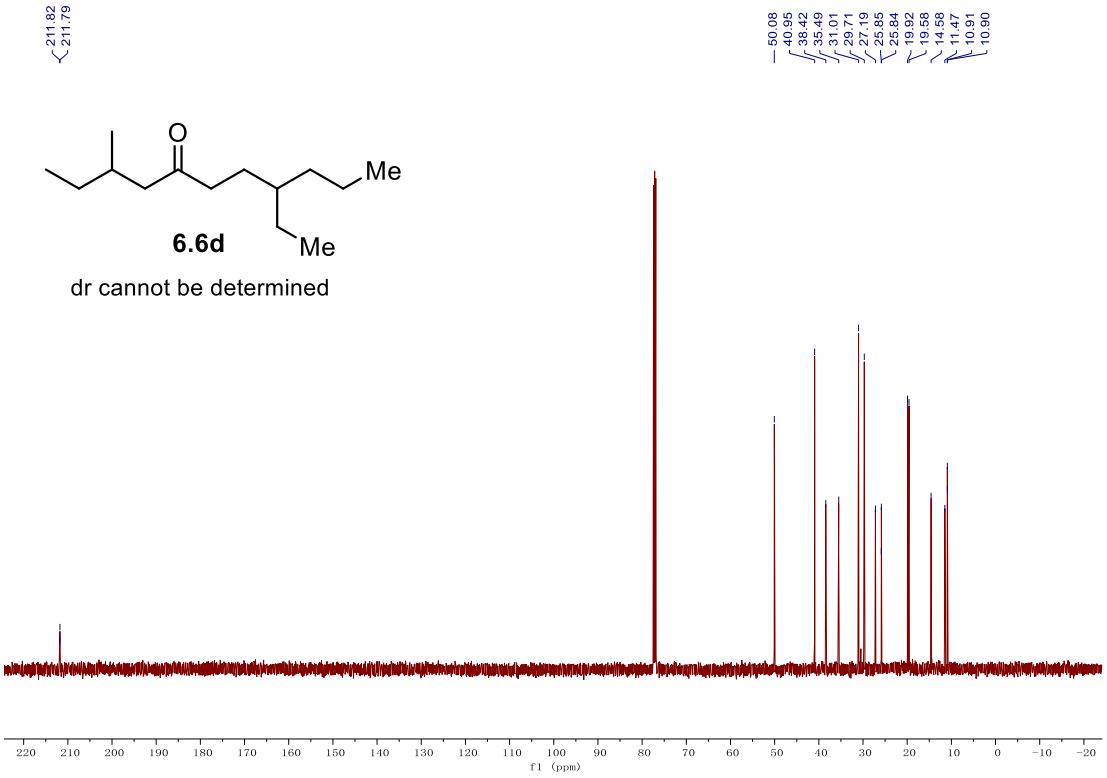


Figure 6.40 ^{1}H-NMR Spectrum of **6.5e**

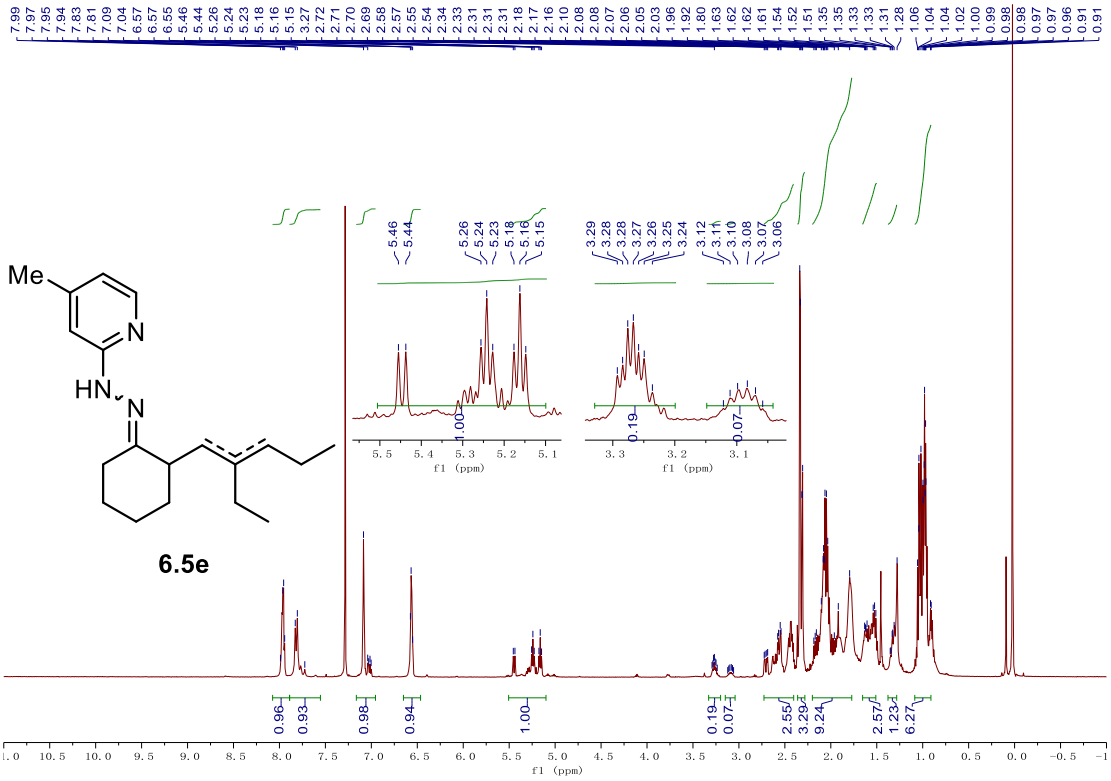


Figure 6.41 ^{1}H-NMR Spectrum of **6.6e**

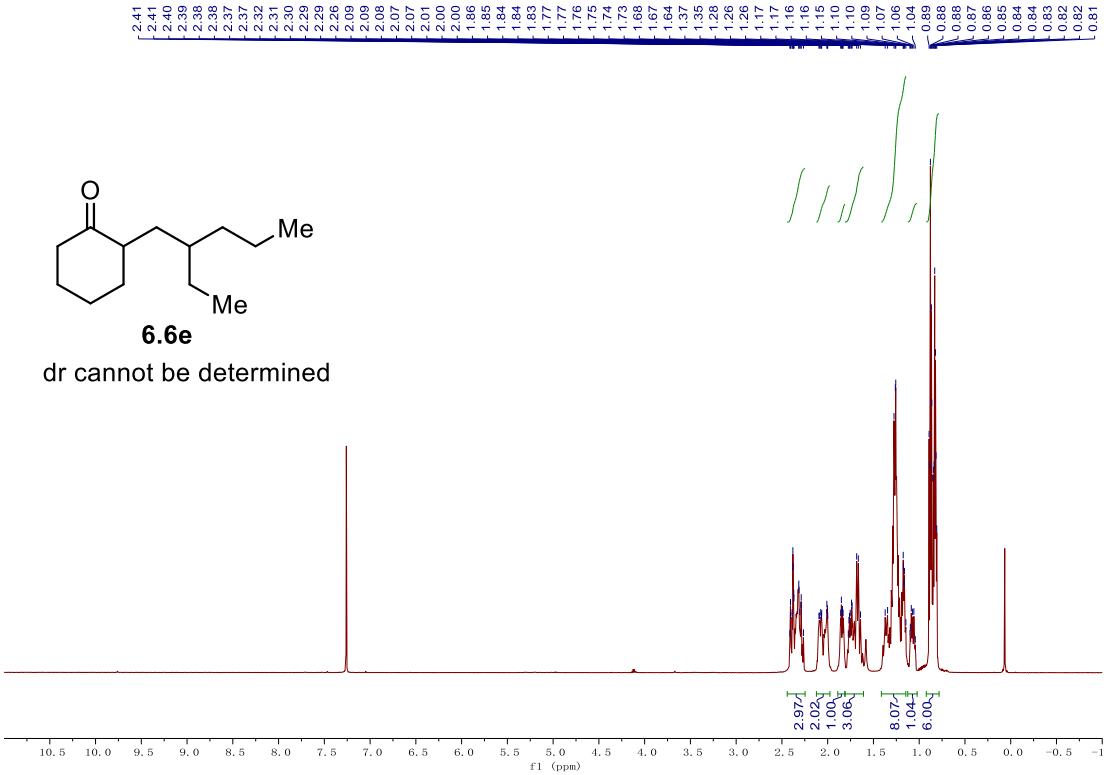


Figure 6.42 ^{13}C-NMR Spectrum of **6.6e**

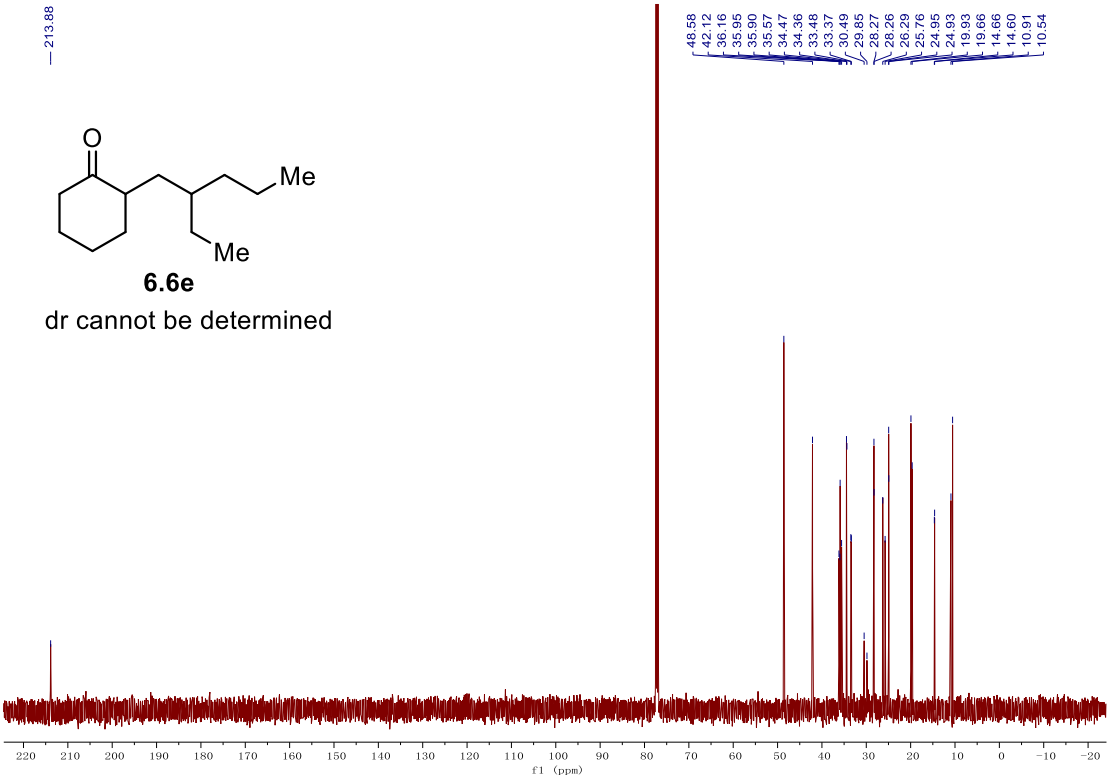


Figure 6.43 [1]H-NMR Spectrum of **6.5fa**

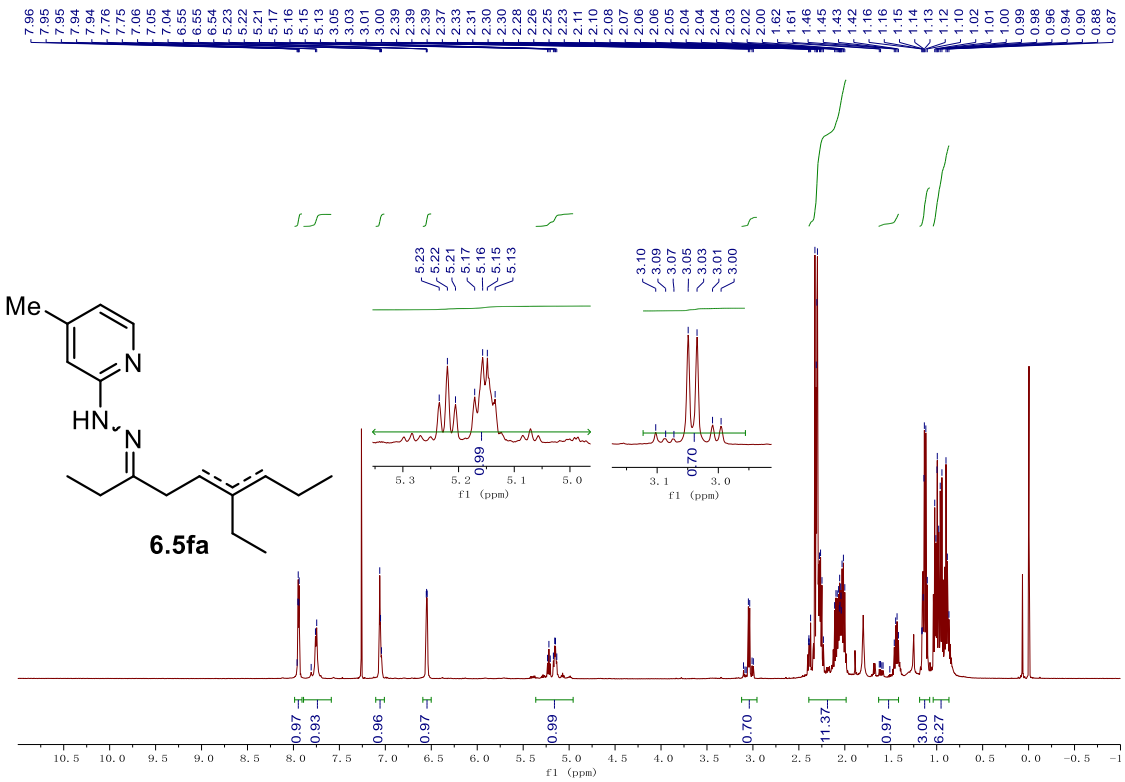


Figure 6.44 [1]H-NMR Spectrum of **6.5fb**

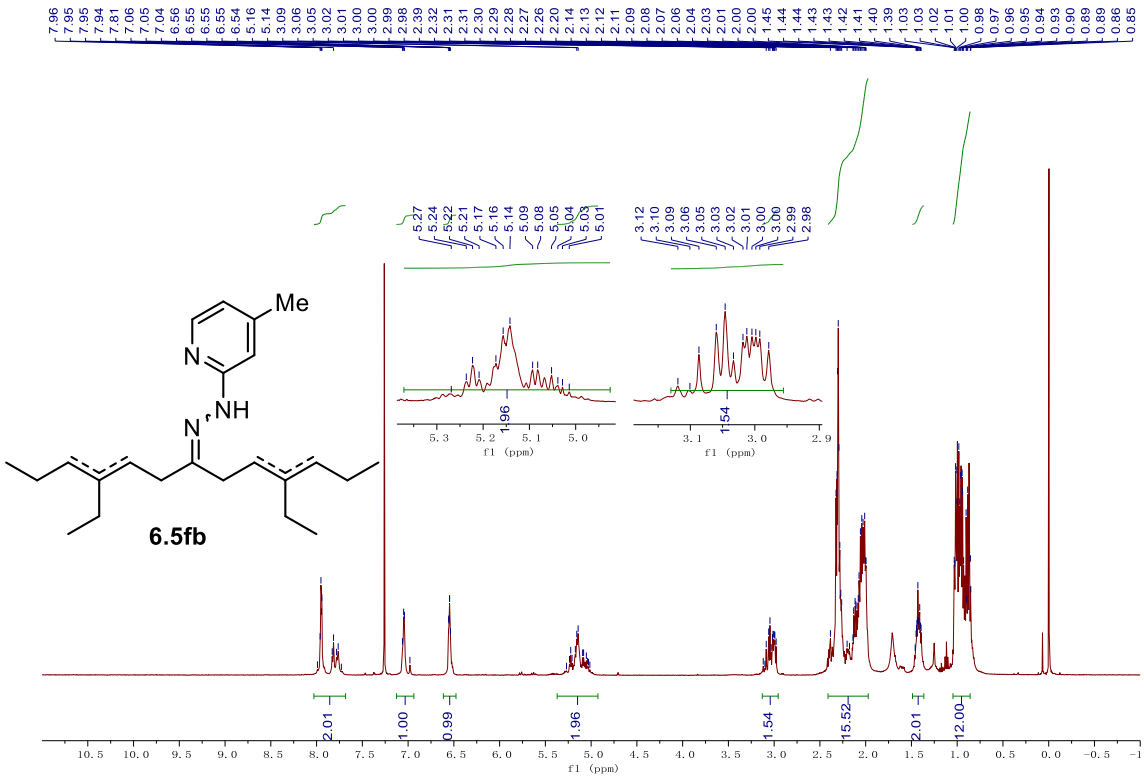


Figure 6.45 ^{1}H-NMR Spectrum of **6.6f**

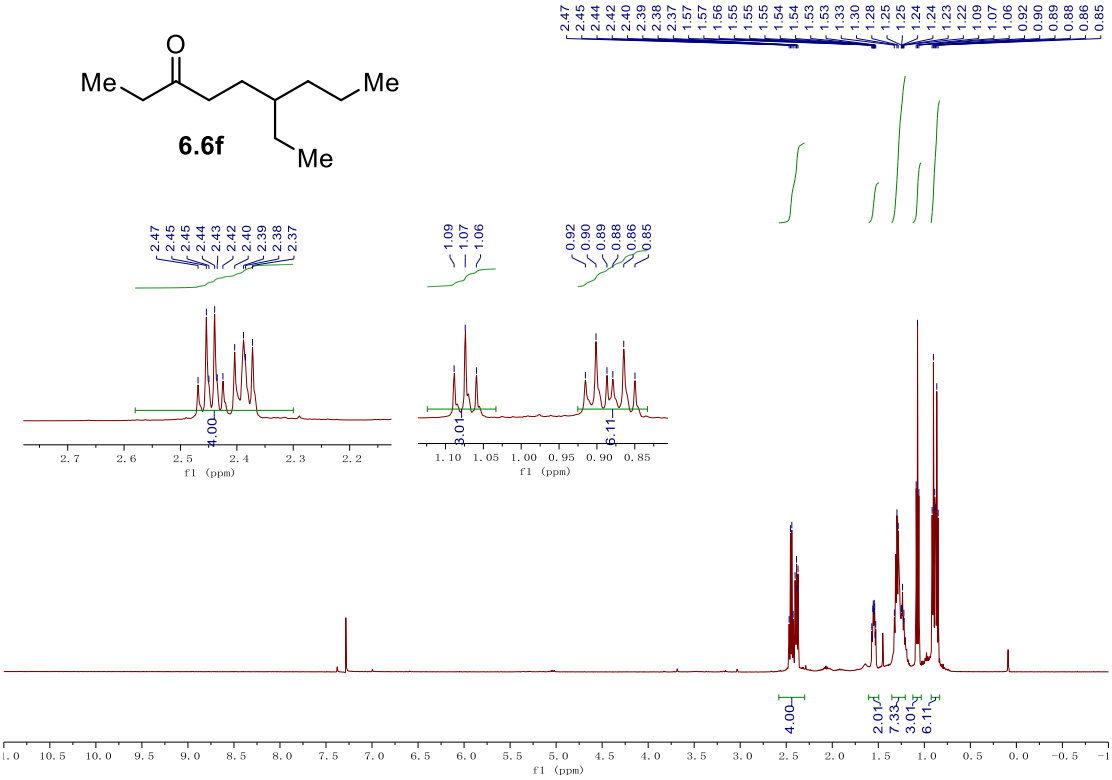


Figure 6.46 ^{13}C-NMR Spectrum of **6.6f**

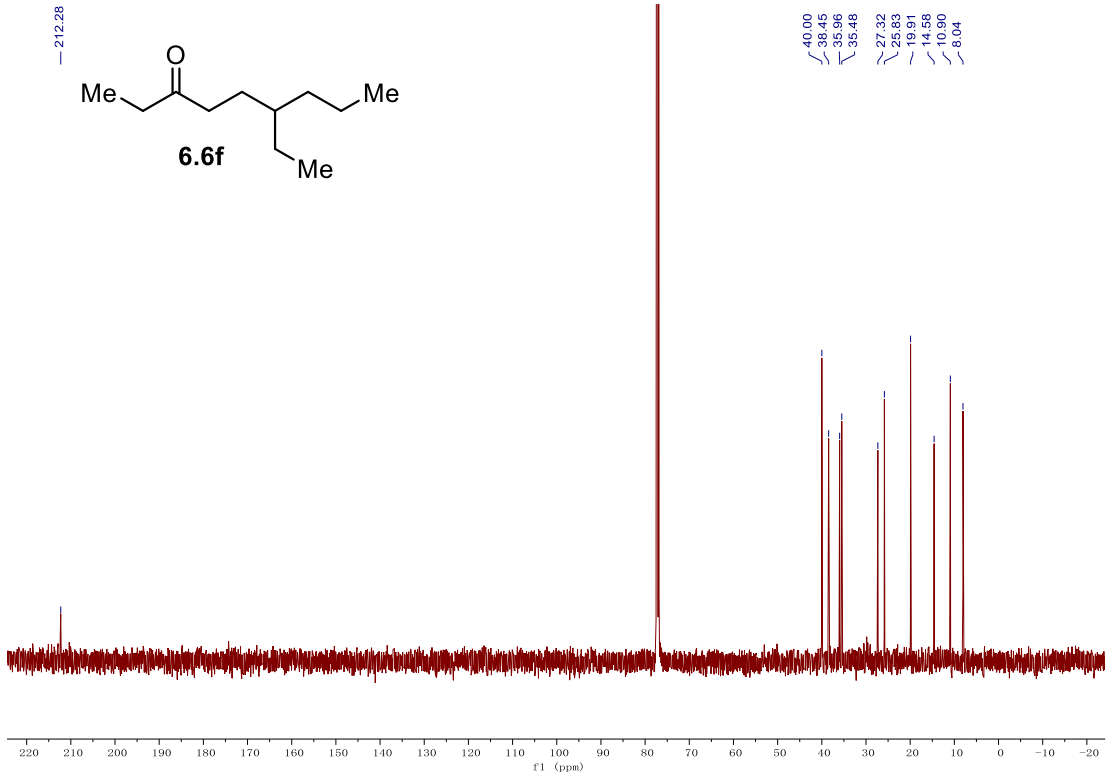


Figure 6.47 ^{1}H-NMR Spectrum of **6.5g**

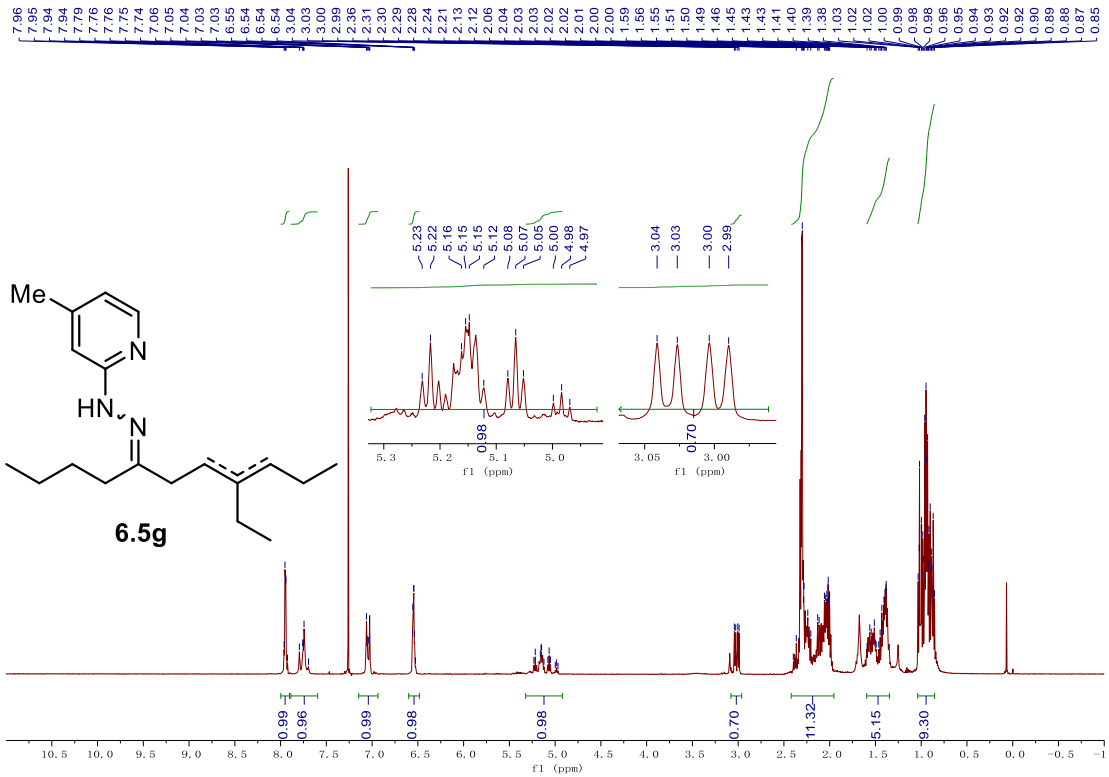


Figure 6.48 ^{1}H-NMR Spectrum of **6.6g**

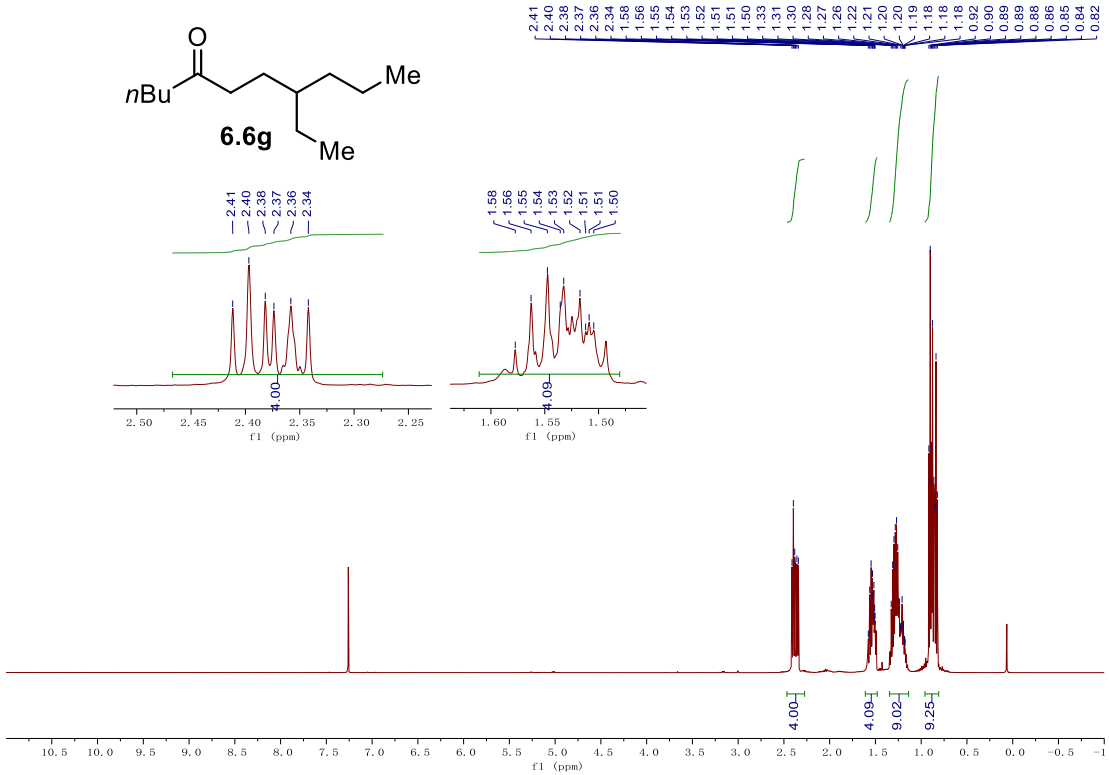


Figure 6.49 ^{13}C-NMR Spectrum of **6.6g**

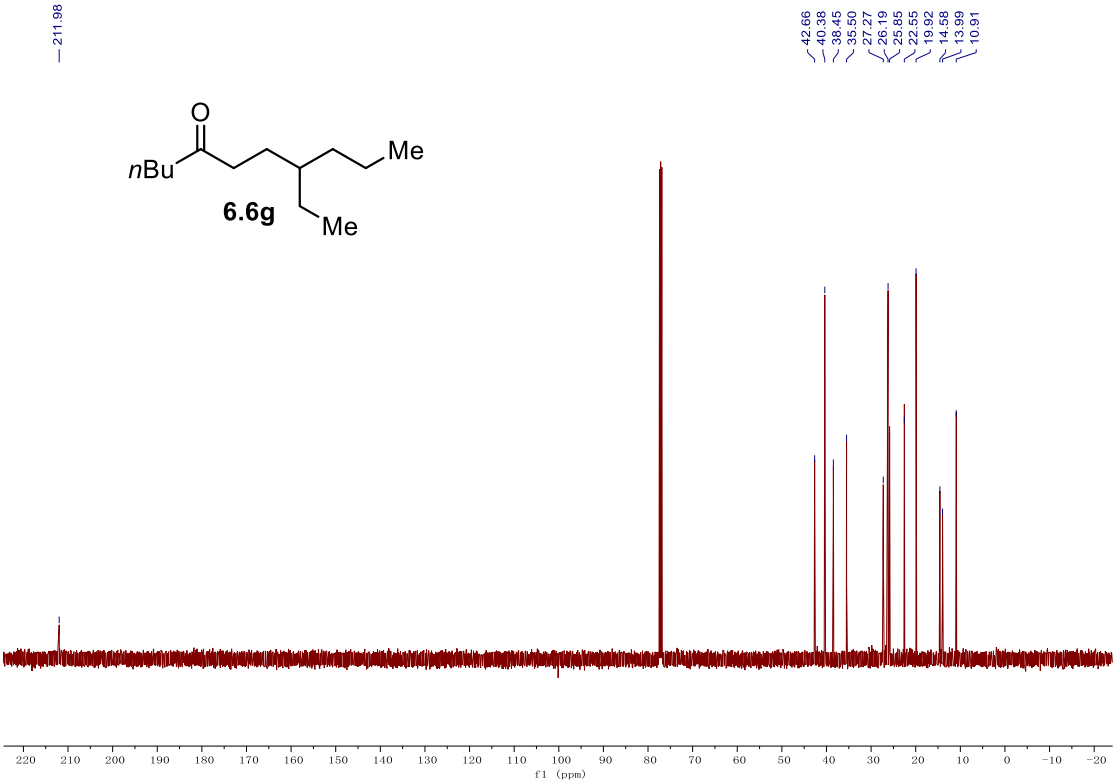


Figure 6.50 ^{1}H-NMR Spectrum of **6.5ha**

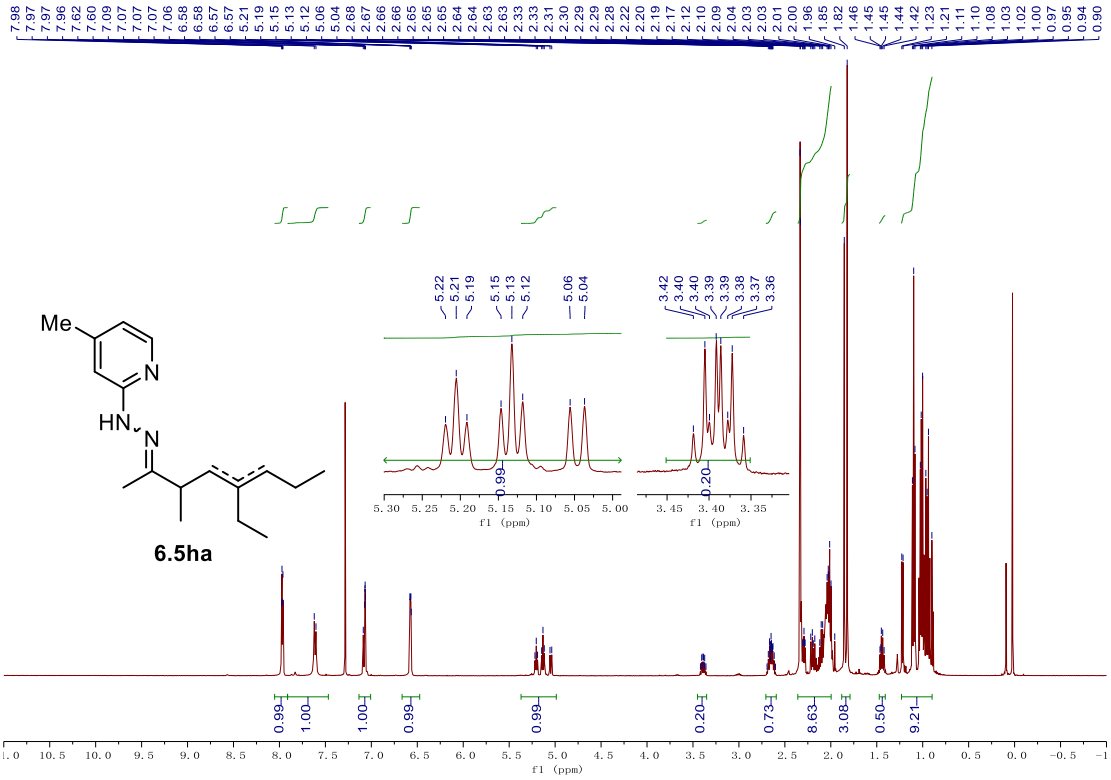


Figure 6.51 ^{1}H-NMR Spectrum of **6.5hb**

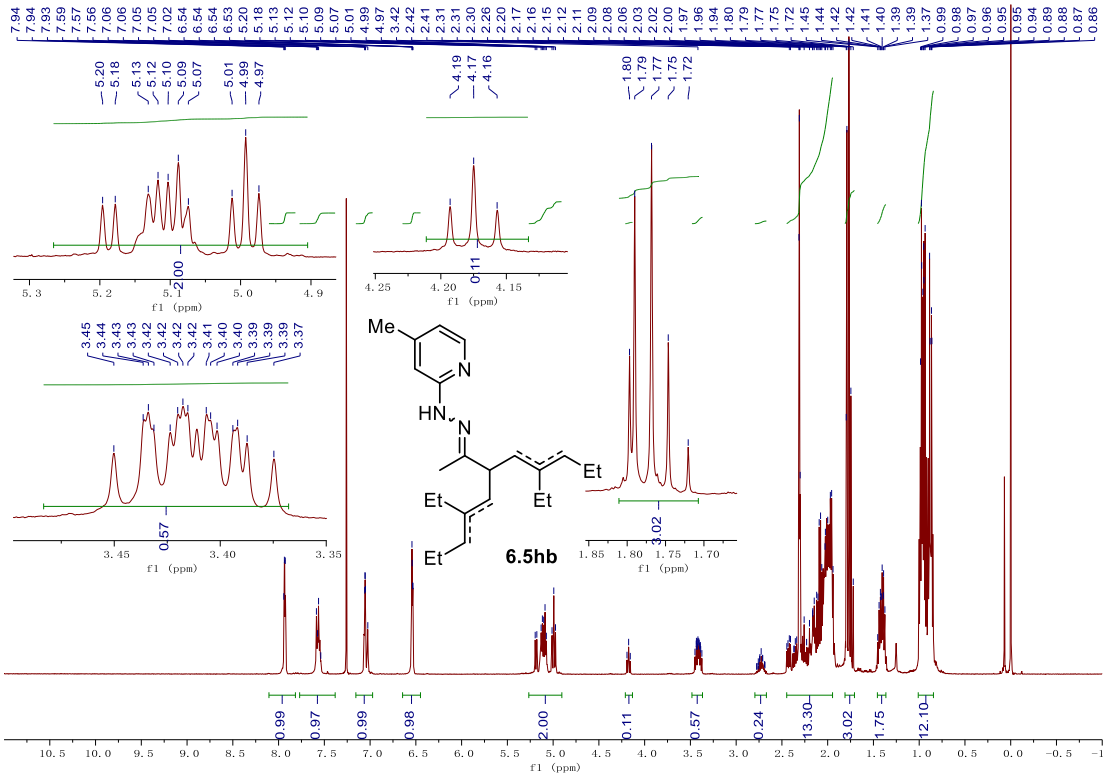


Figure 6.52 ^{1}H-NMR Spectrum of **6.6h**

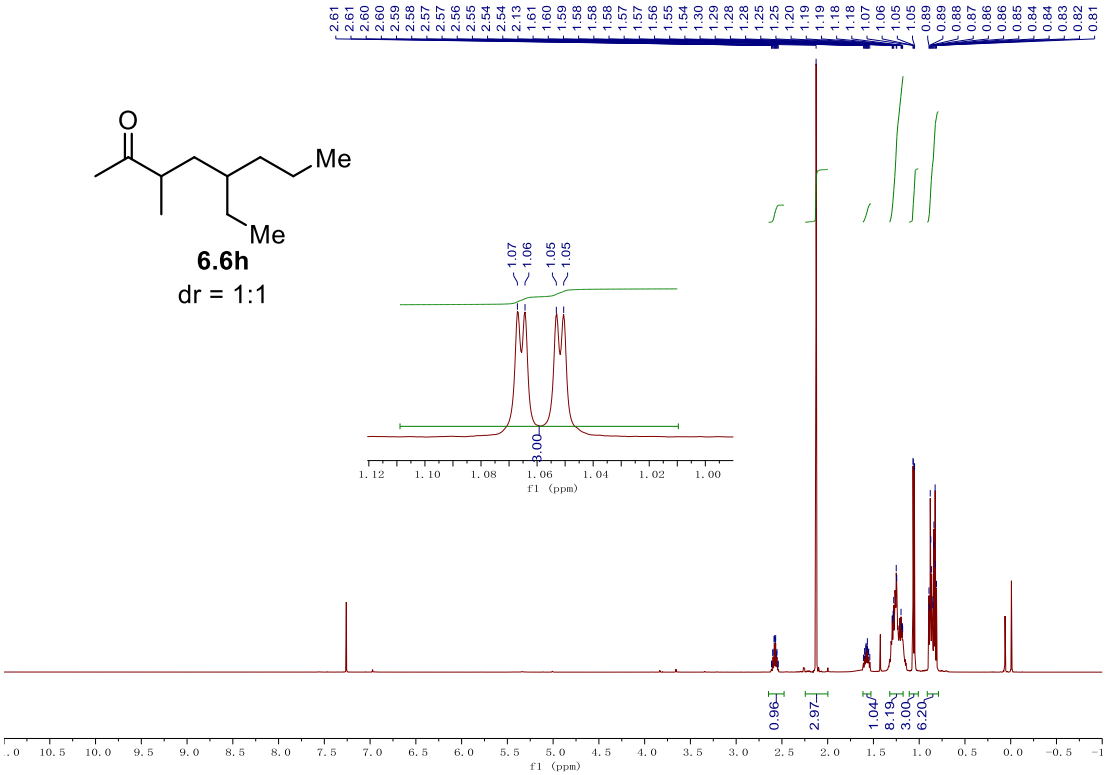


Figure 6.53 ^{13}C-NMR Spectrum of **6.6h**

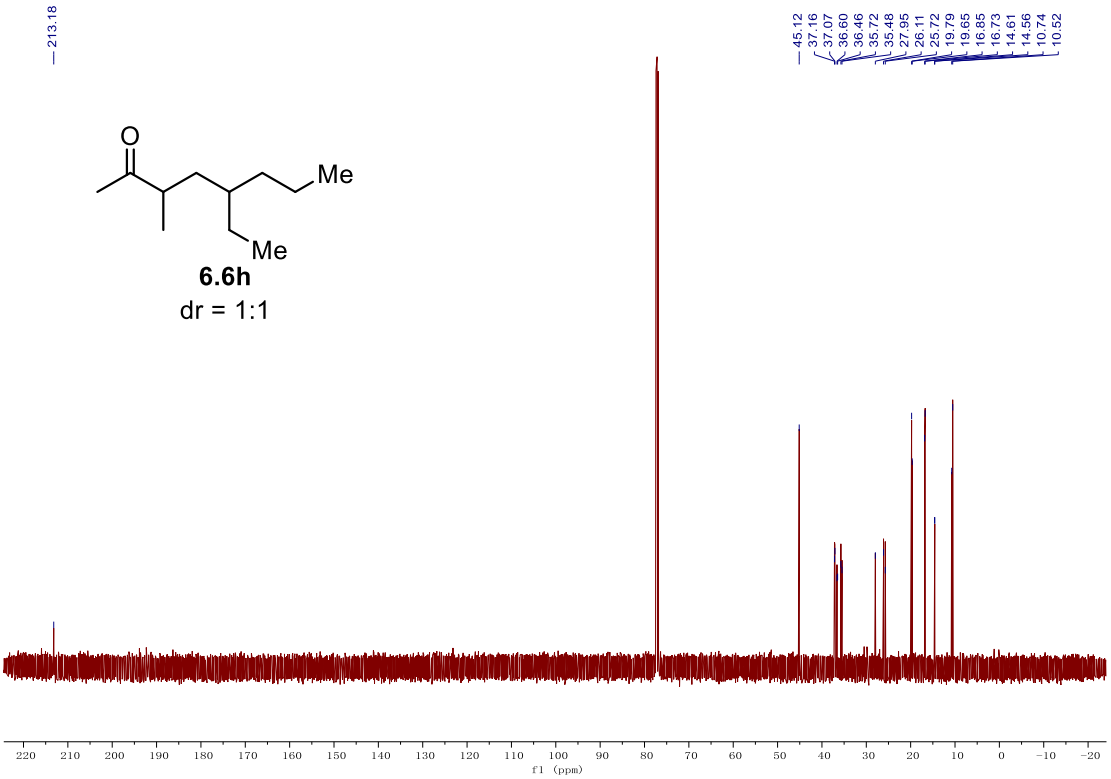


Figure 6.54 ^{1}H-NMR Spectrum of **6.5i**

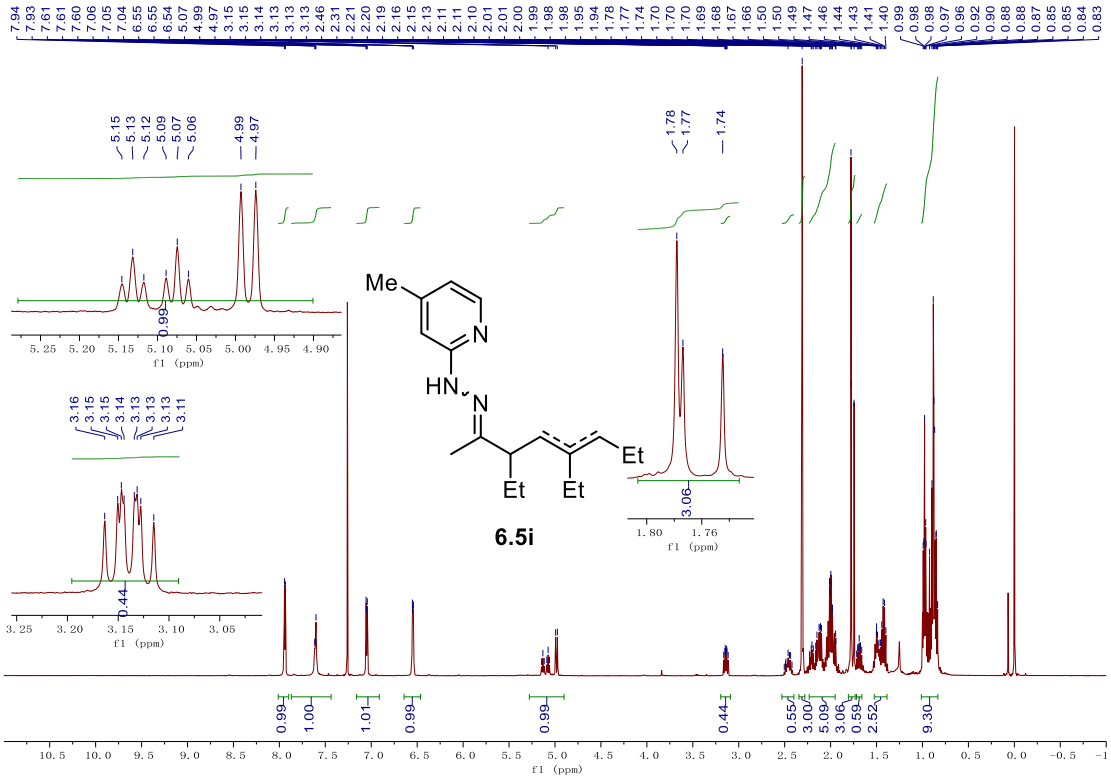


Figure 6.55 ^{1}H-NMR Spectrum of **6.6i**

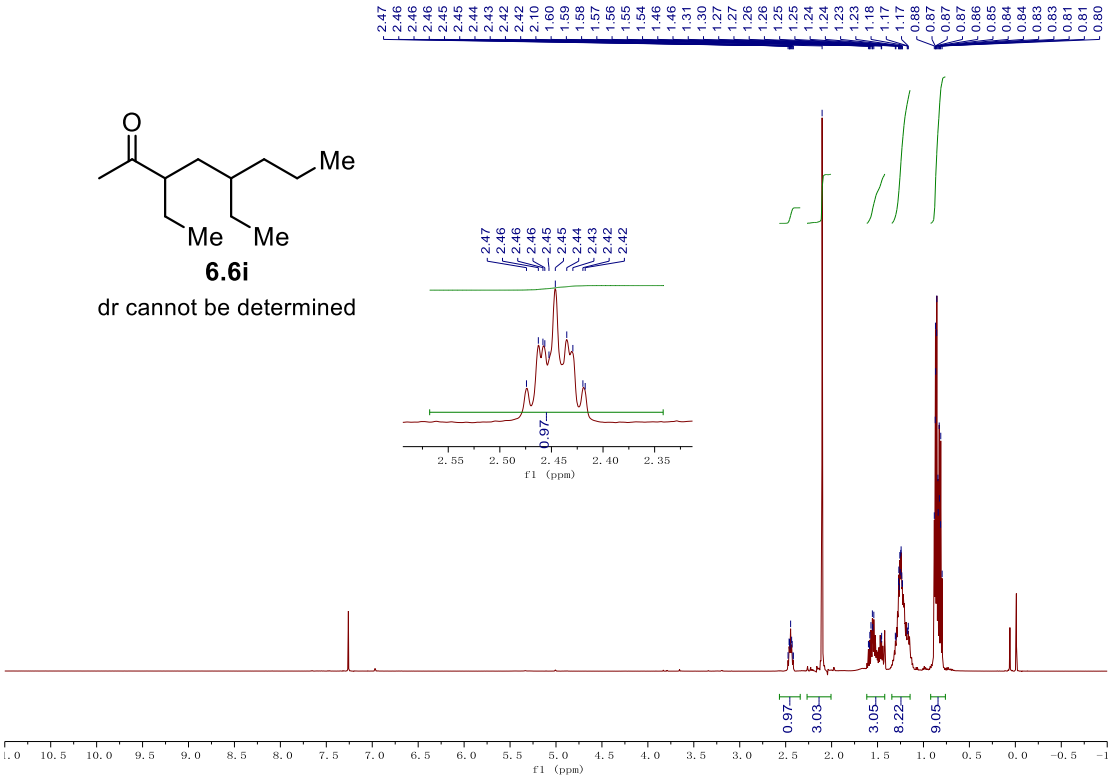


Figure 6.56 ^{13}C-NMR Spectrum of **6.6i**

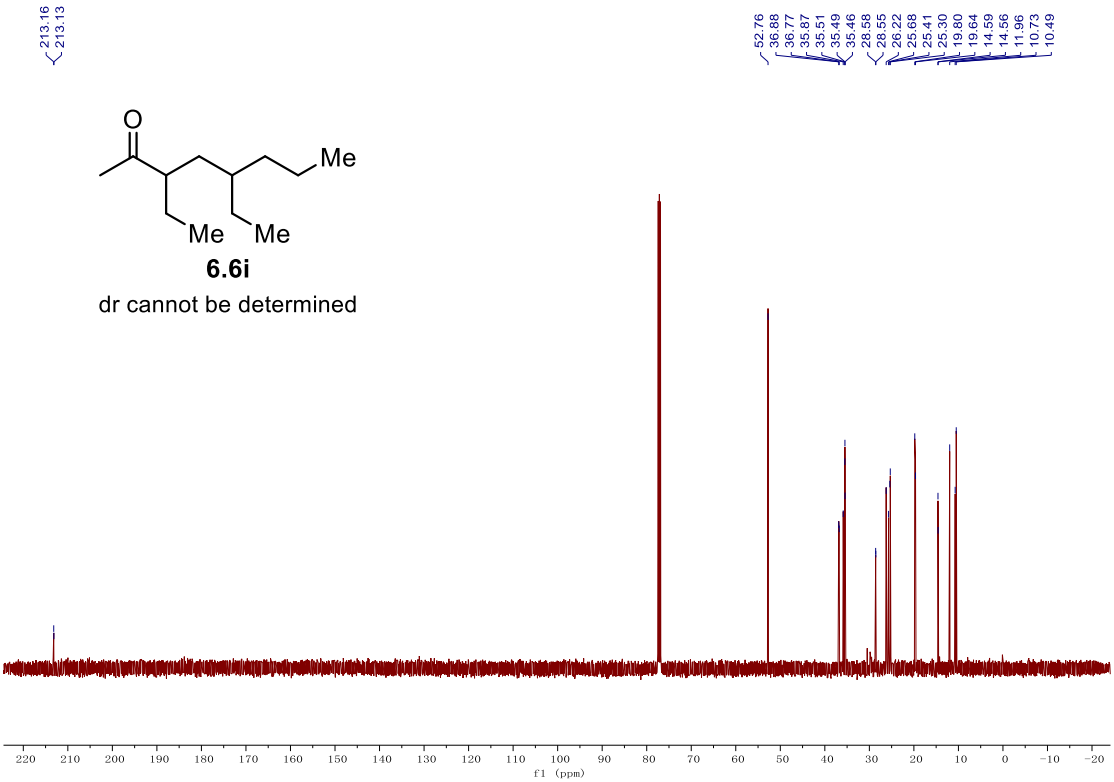


Figure 6.57 ^{1}H-NMR Spectrum of **6.5j**

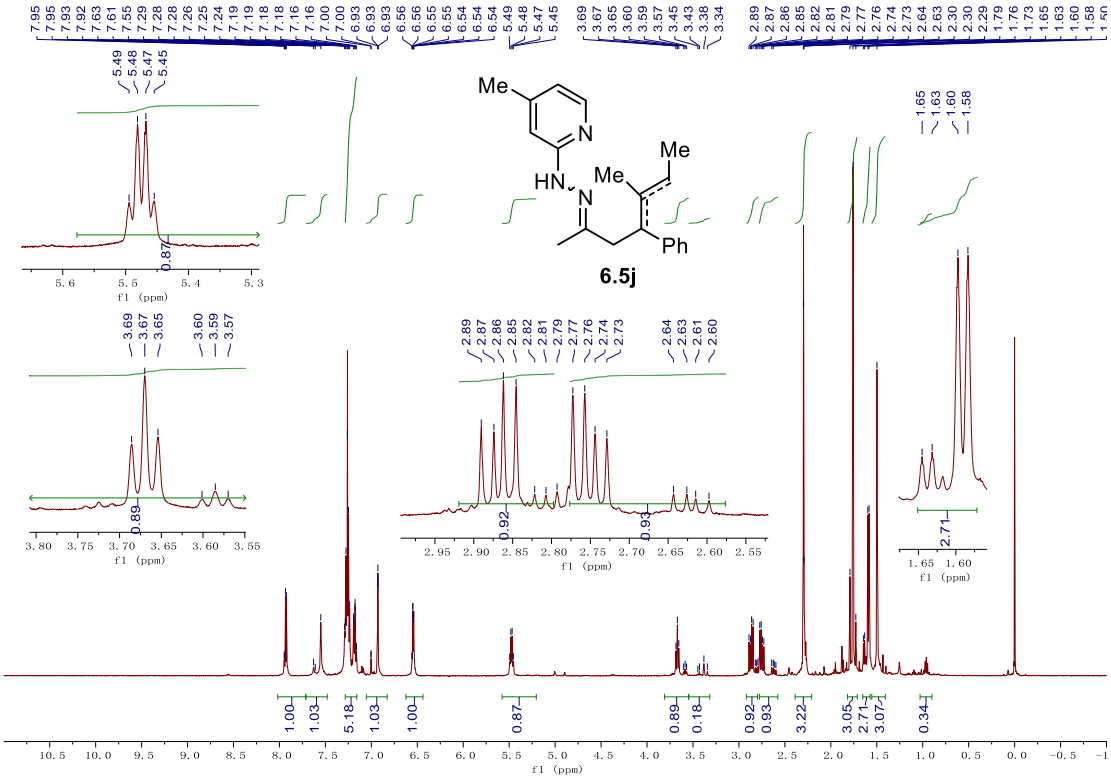


Figure 6.58 ^{1}H-NMR Spectrum of **6.6j**

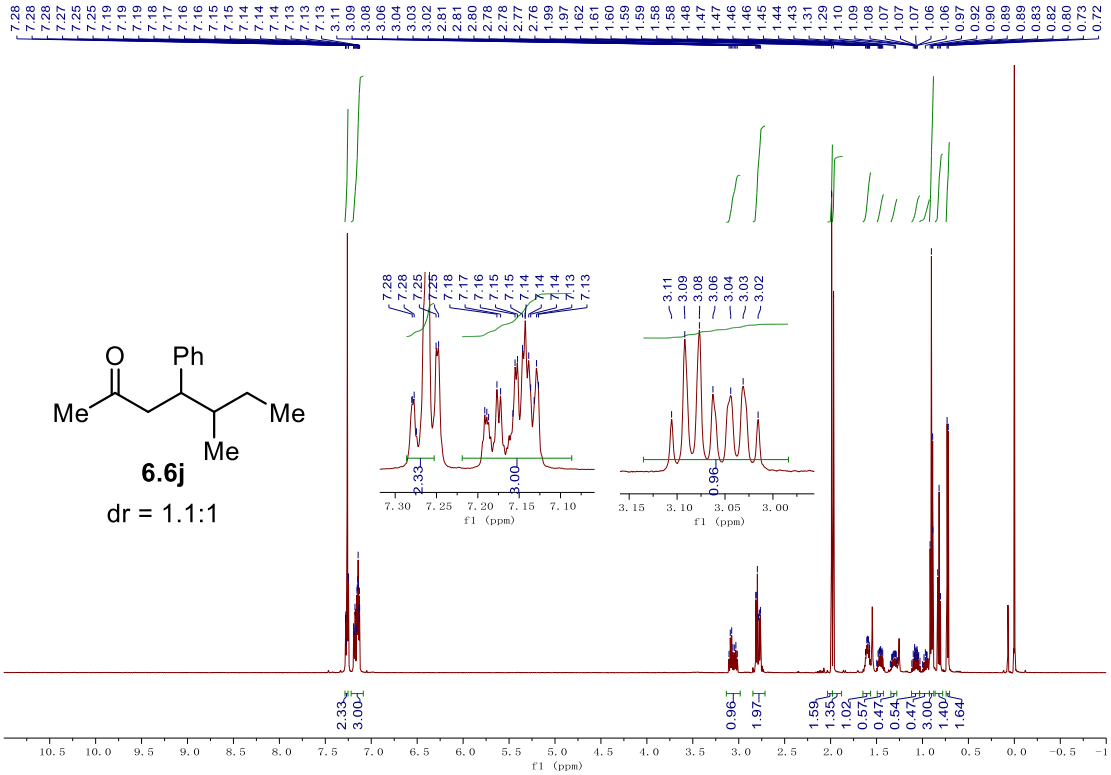


Figure 6.59 ^{13}C-NMR Spectrum of **6.6j**

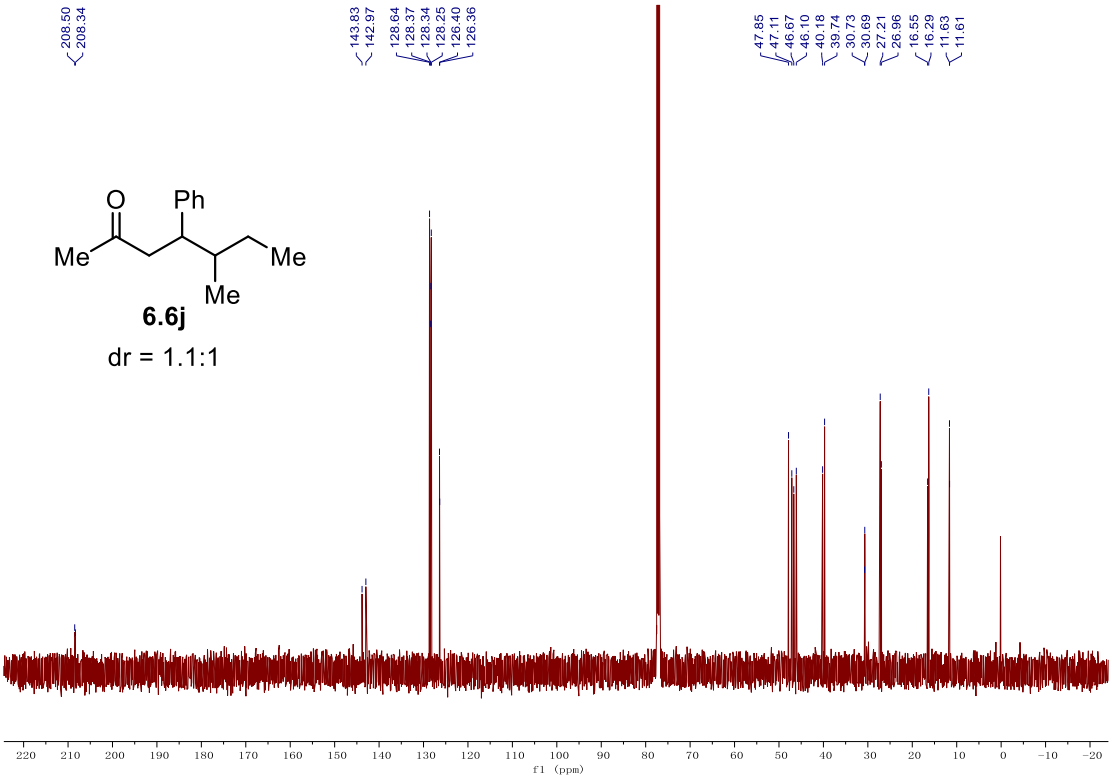


Figure 6.60 ^{1}H-NMR Spectrum of **6.5k**

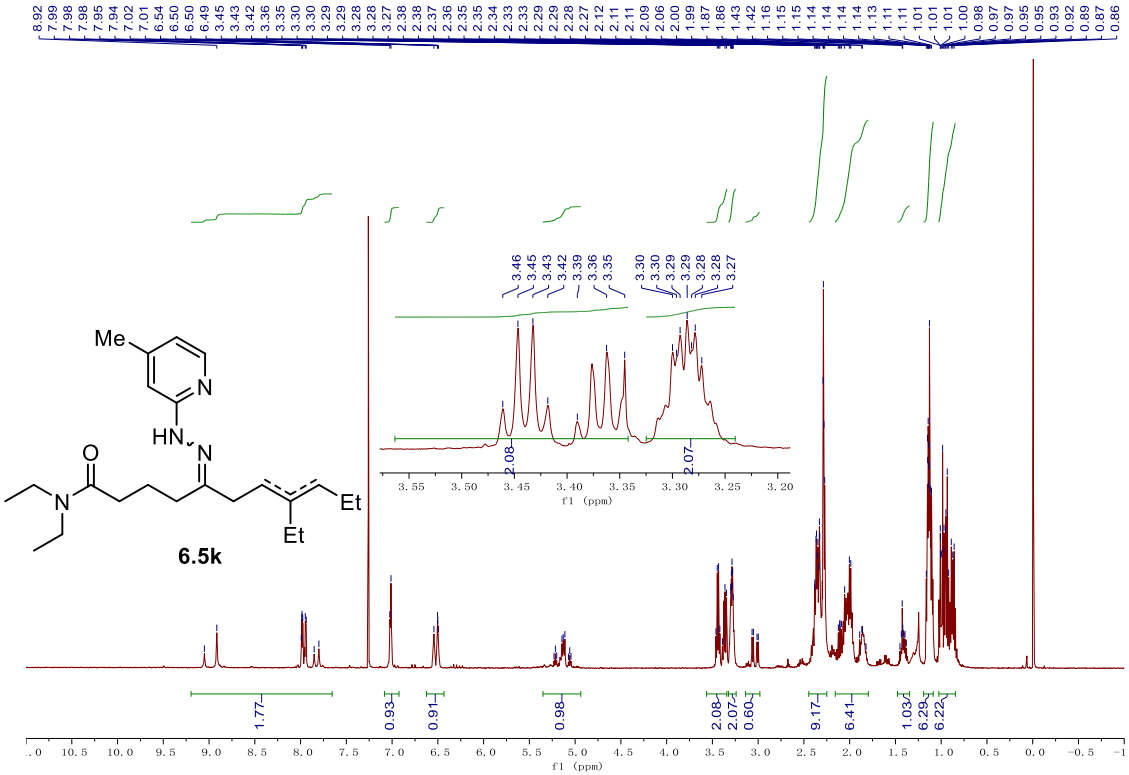


Figure 6.61 ^{1}H-NMR Spectrum of **6.6k**

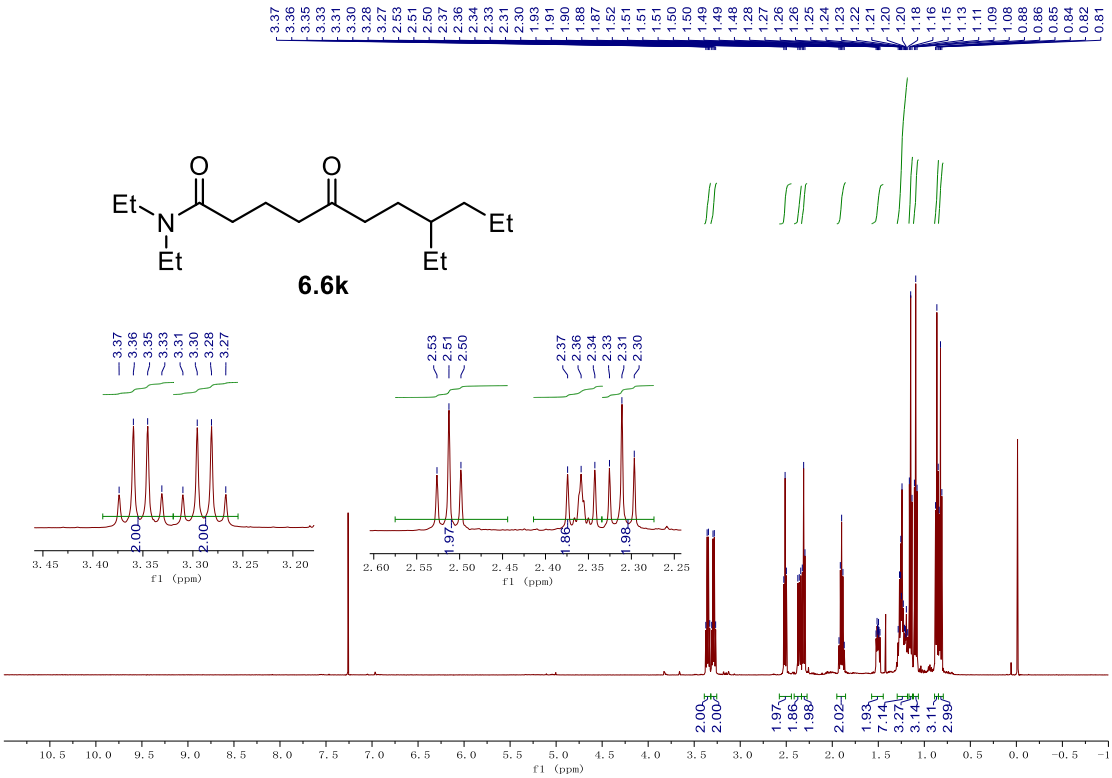


Figure 6.62 ^{13}C-NMR Spectrum of **6.6k**

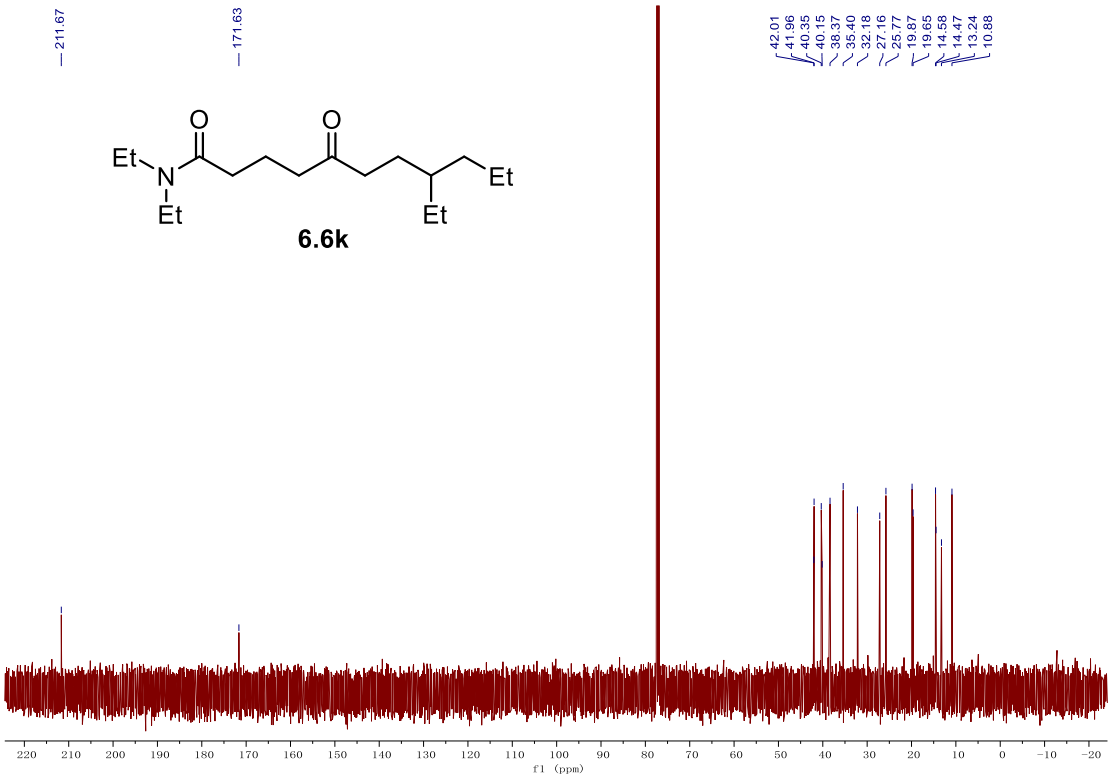


Figure 6.63 ^{1}H-NMR Spectrum of **6.5l**

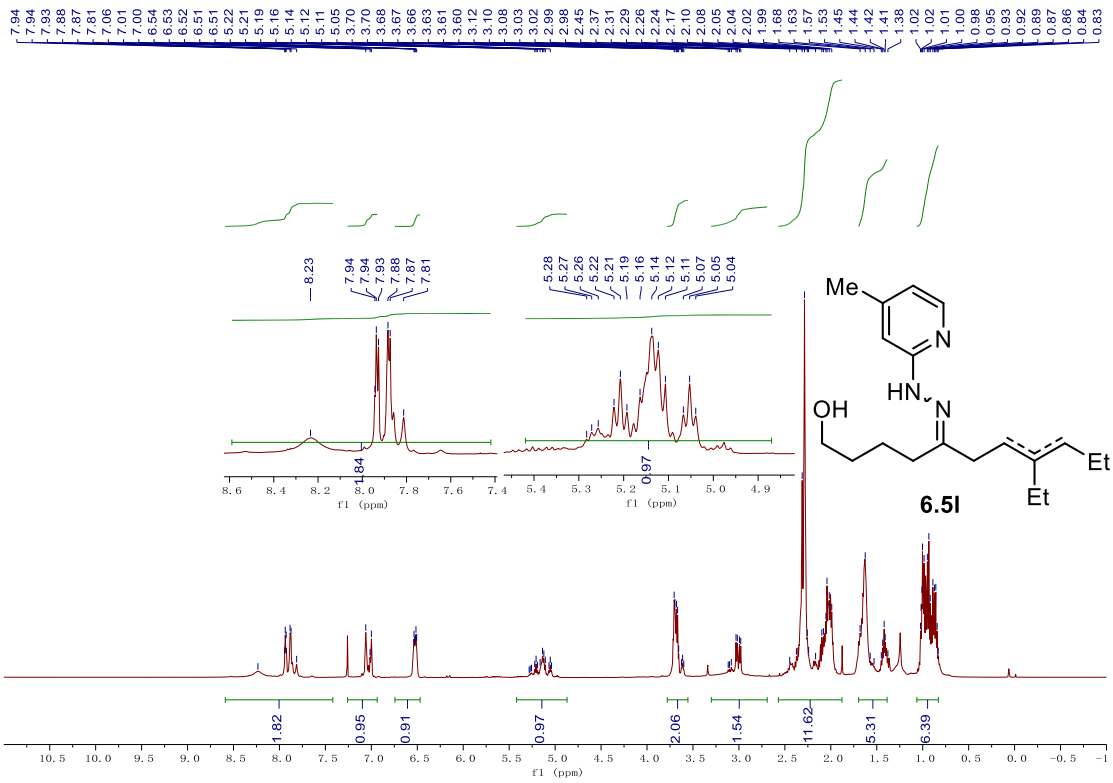


Figure 6.64 ^{1}H-NMR Spectrum of **6.6l**

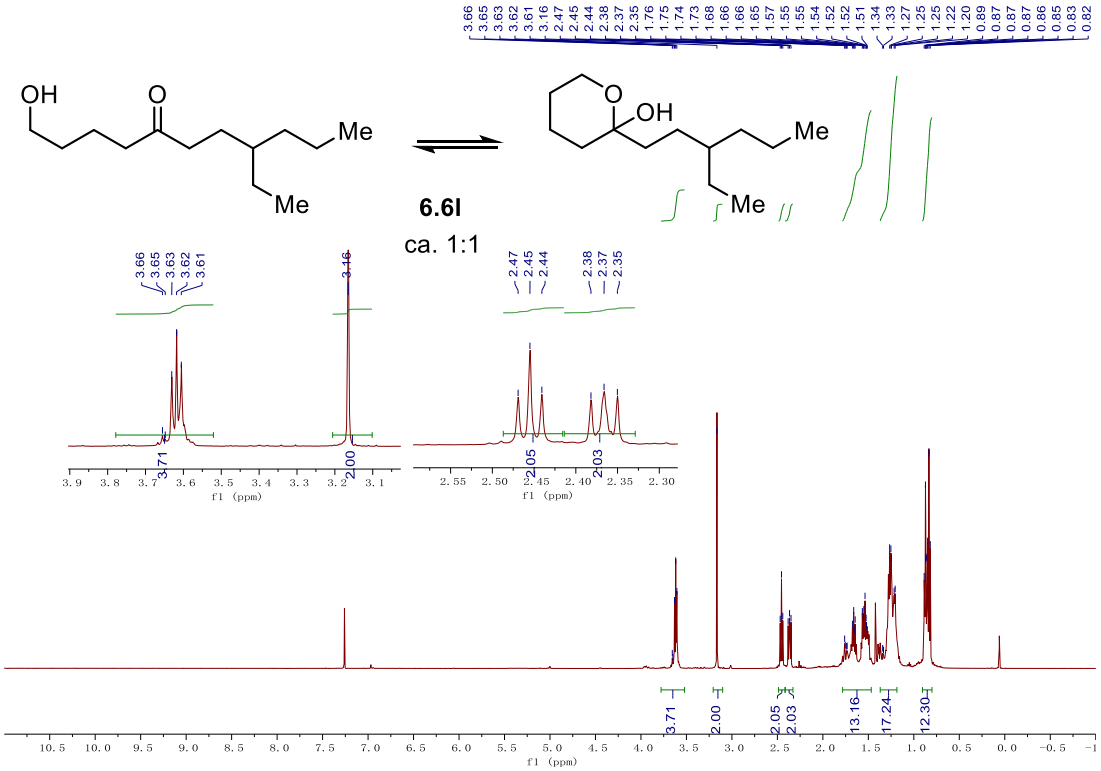


Figure 6.65 ^{13}C-NMR Spectrum of **6.6l**

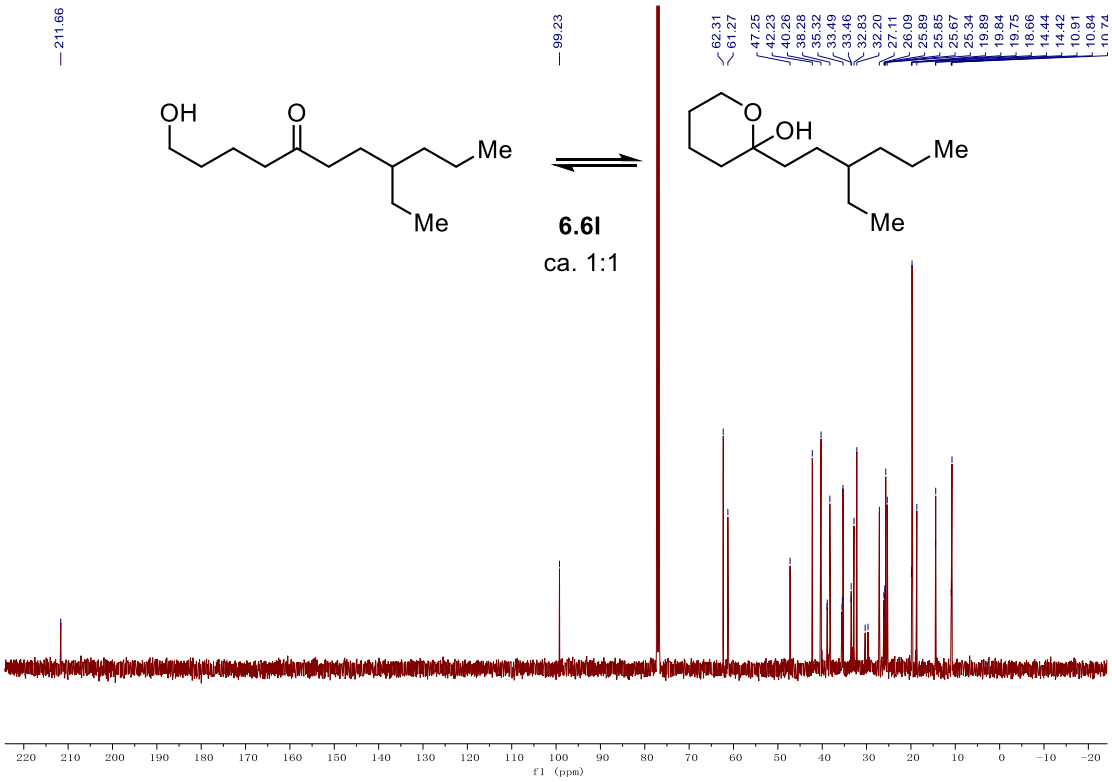


Figure 6.66 ^{1}H-NMR Spectrum of **6.5m**

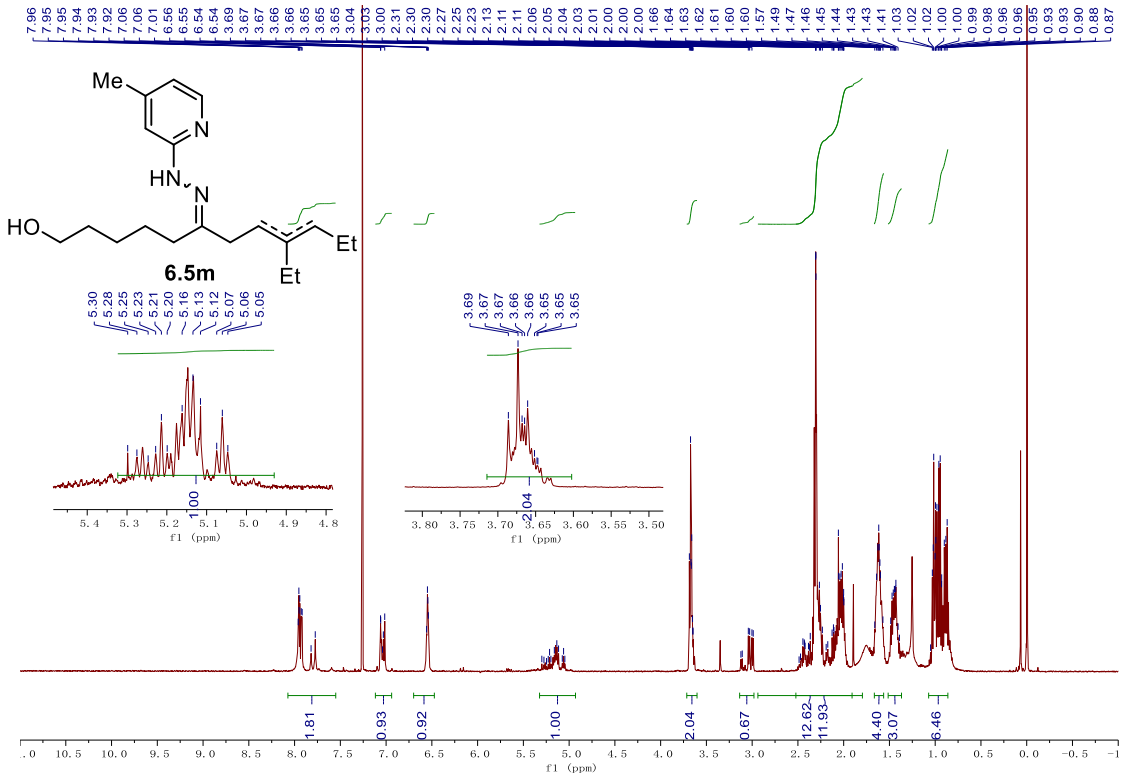


Figure 6.67 ^{1}H-NMR Spectrum of **6.6m**

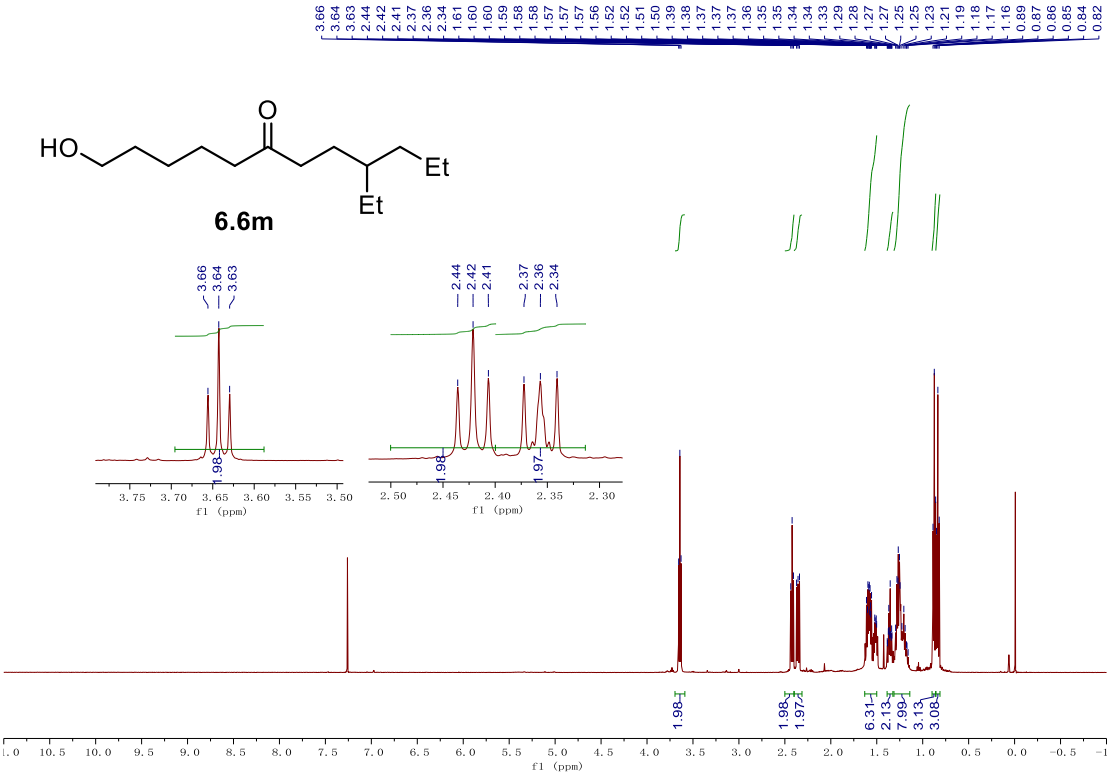


Figure 6.68 ^{13}C-NMR Spectrum of **6.6m**

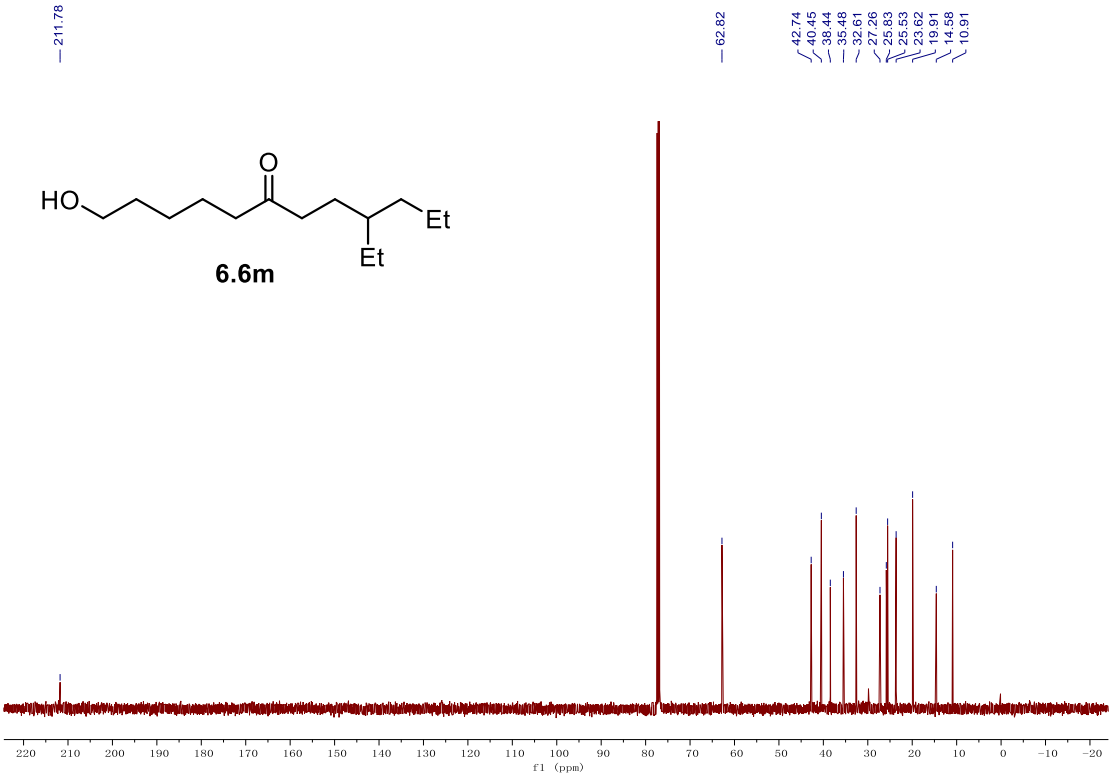


Figure 6.69 ^{1}H-NMR Spectrum of **6.5n**

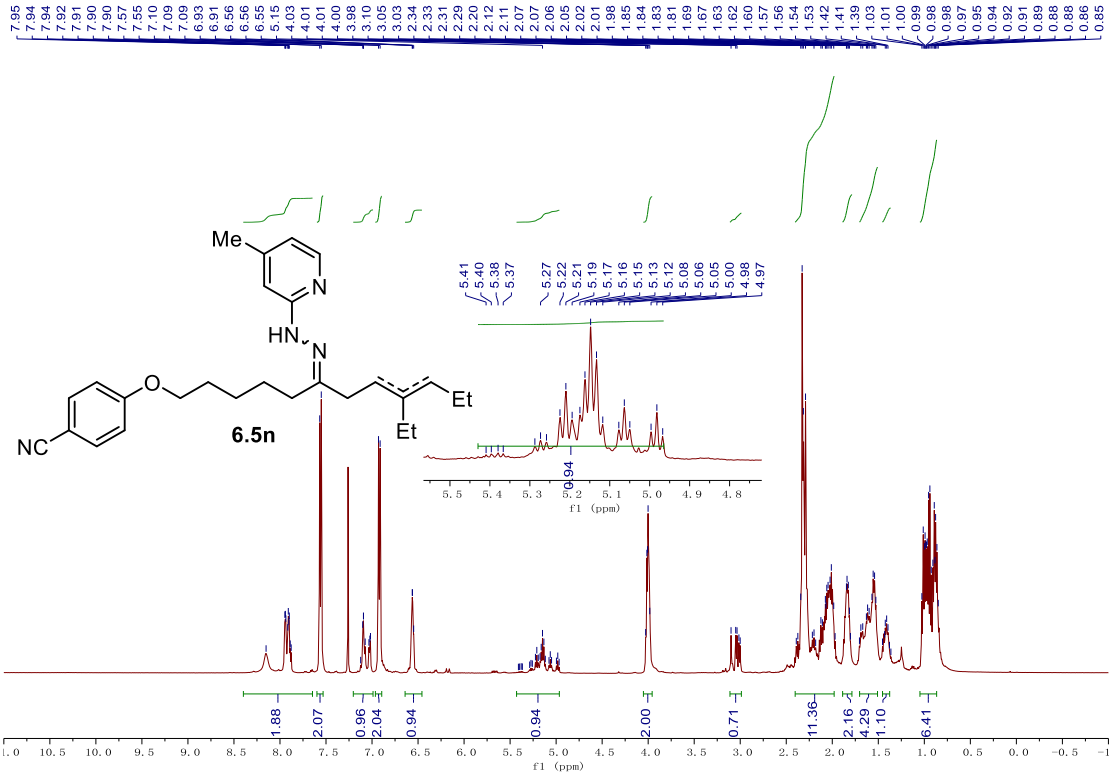


Figure 6.70 ^{1}H-NMR Spectrum of **6.n**

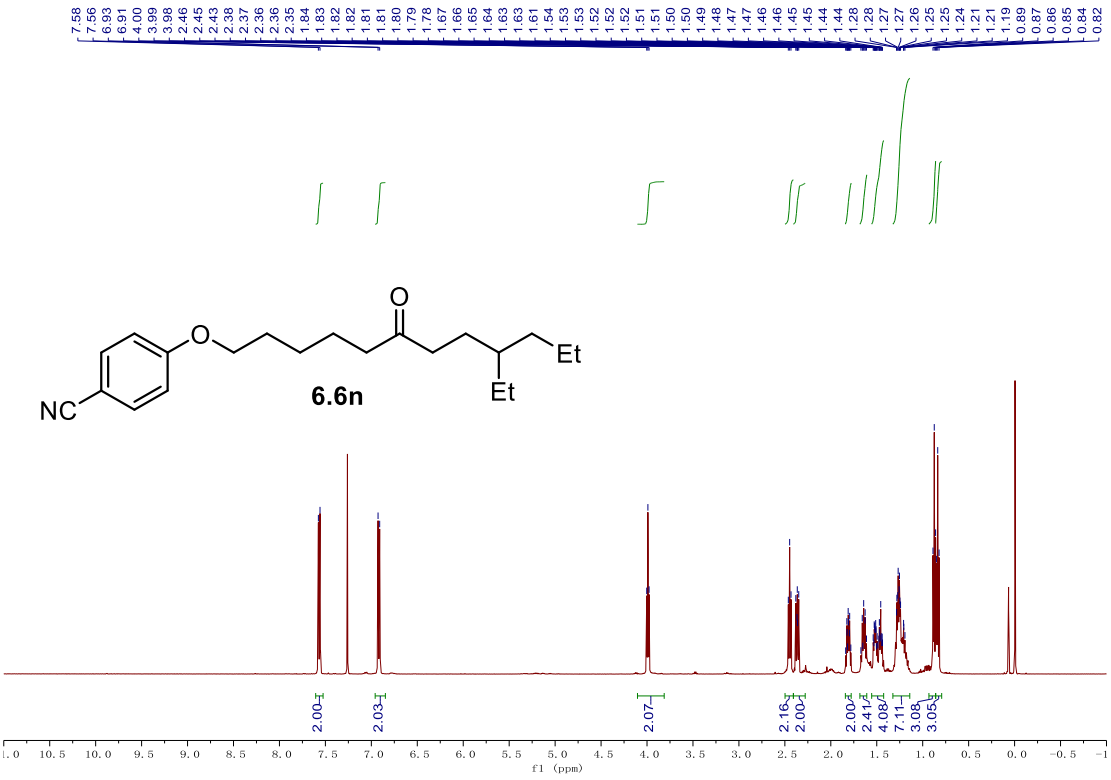


Figure 6.71 ^{13}C-NMR Spectrum of **6.n**

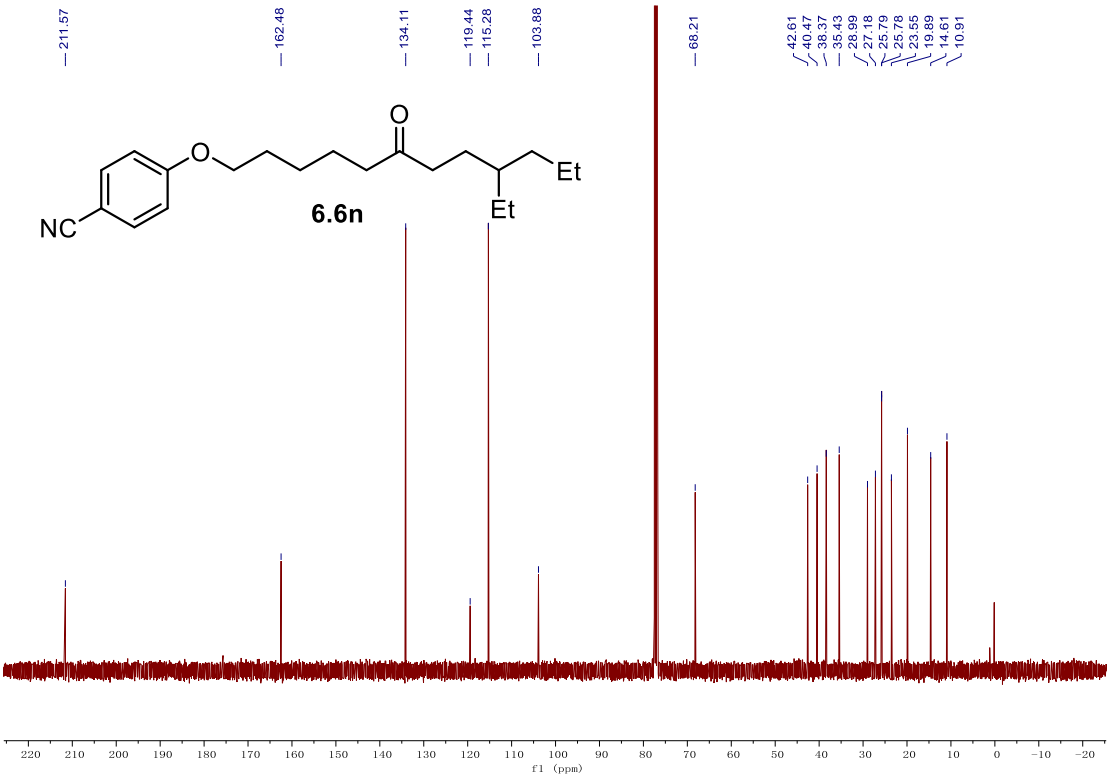


Figure 6.72 ^{1}H-NMR Spectrum of **6.ob**

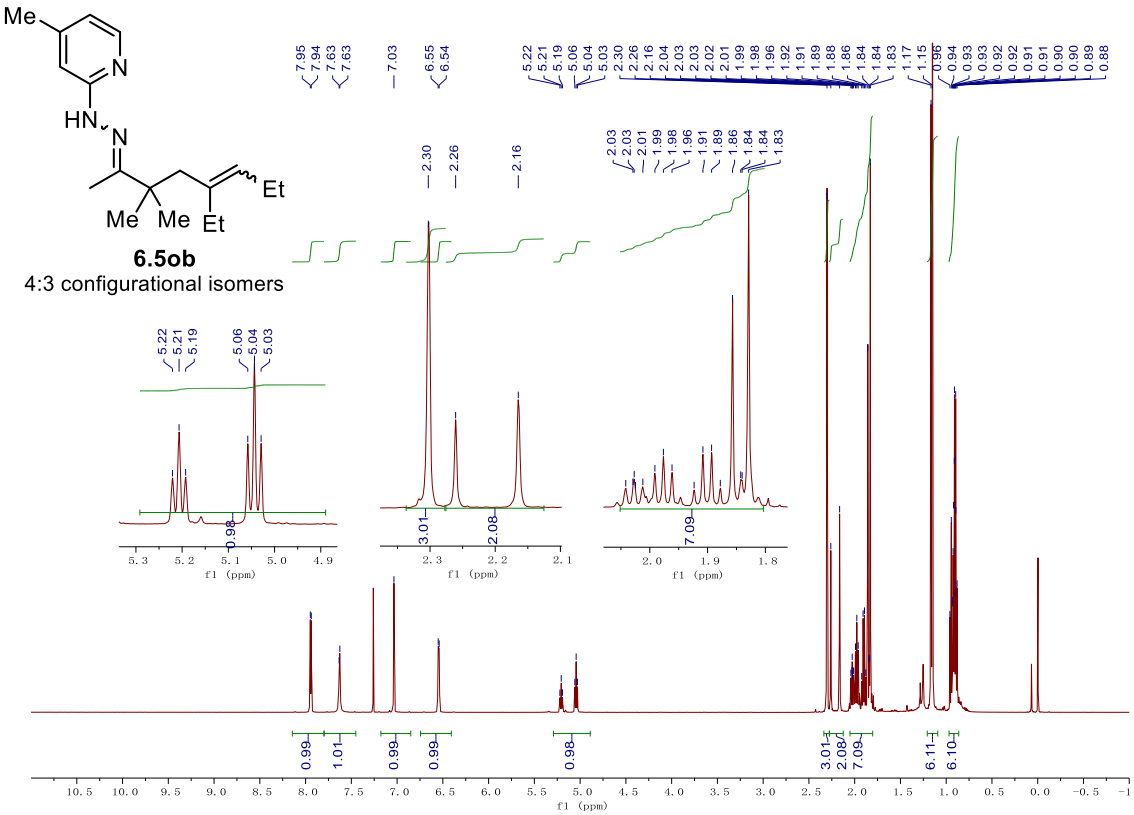


Figure 6.73 ^{13}C-NMR Spectrum of **6.ob**

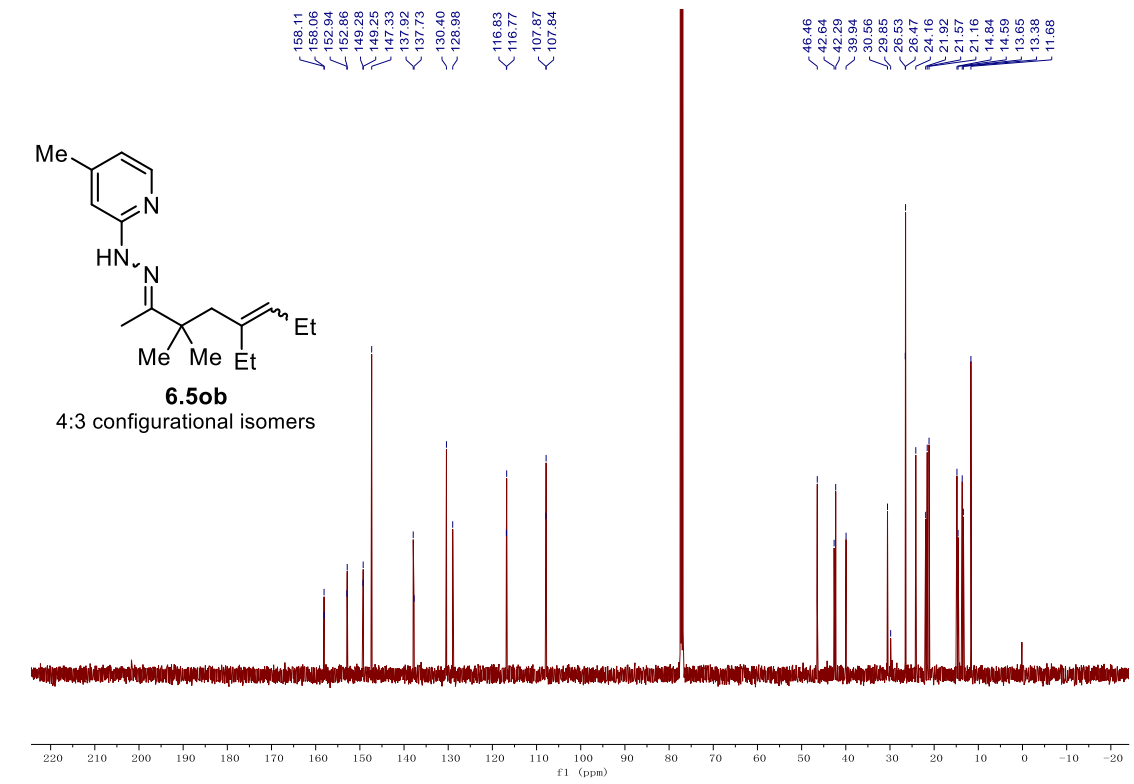


Figure 6.74 ^{1}H-NMR Spectrum of **6.oa**

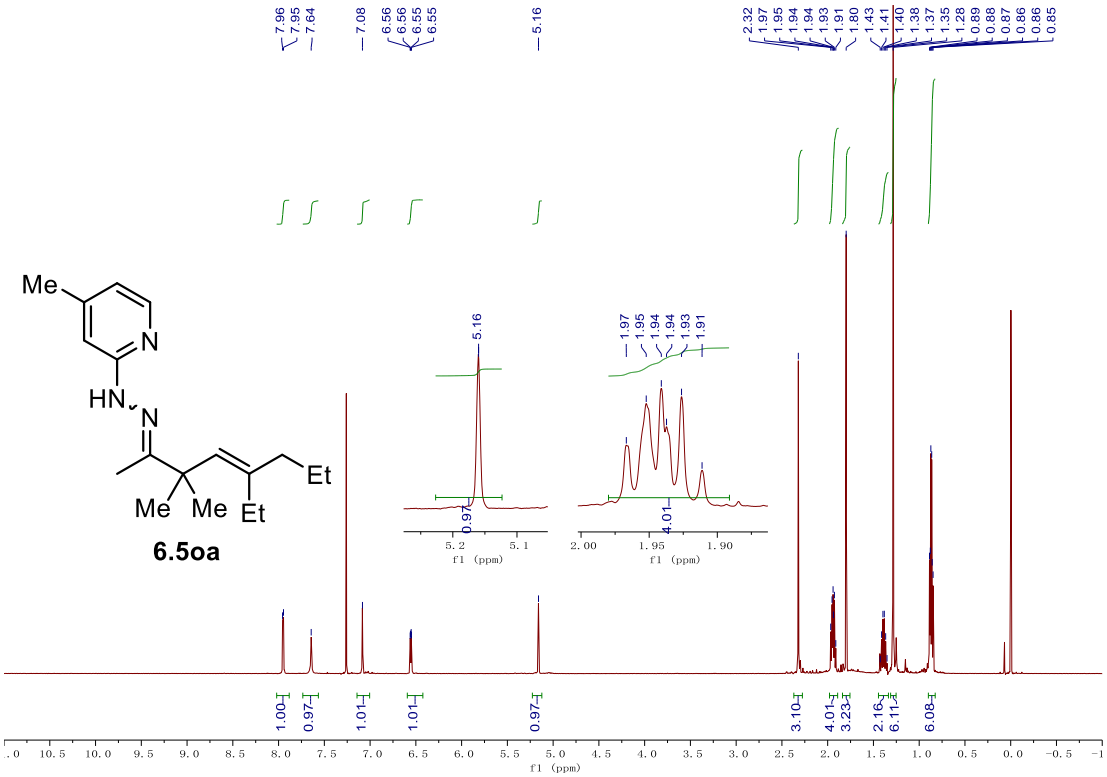


Figure 6.75 ^{13}C-NMR Spectrum of **6.5oa**

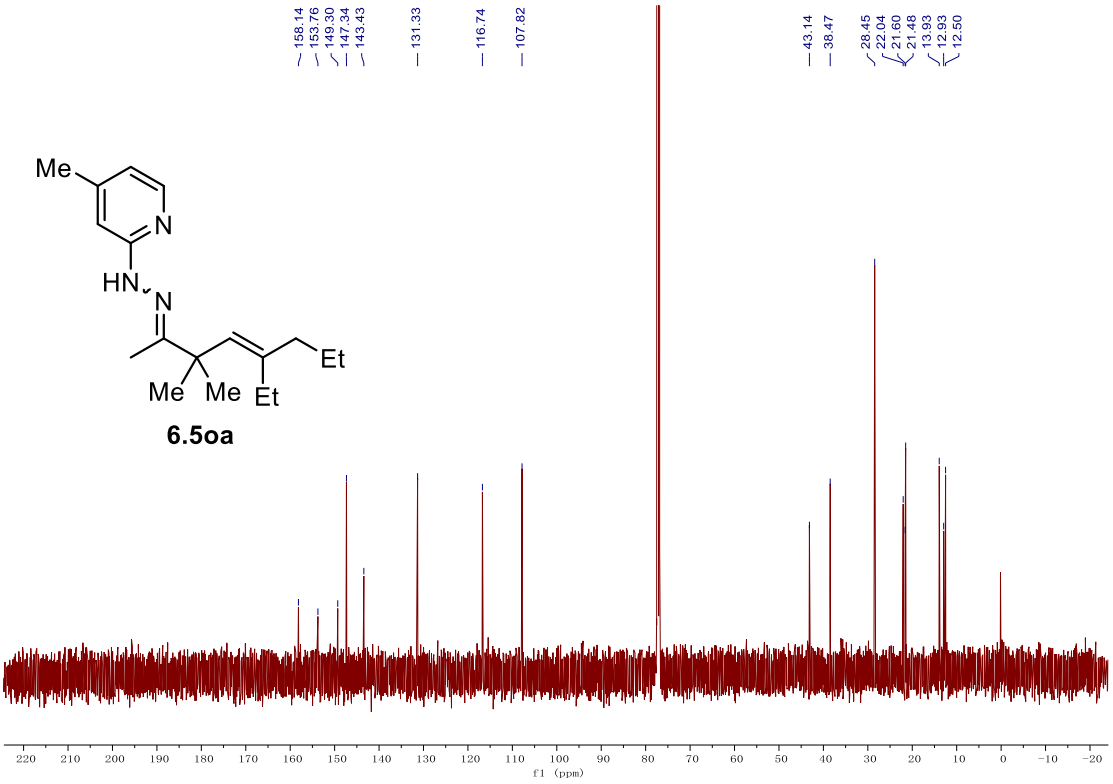


Figure 6.76 ^{1}H-NMR Spectrum of **6.6o**

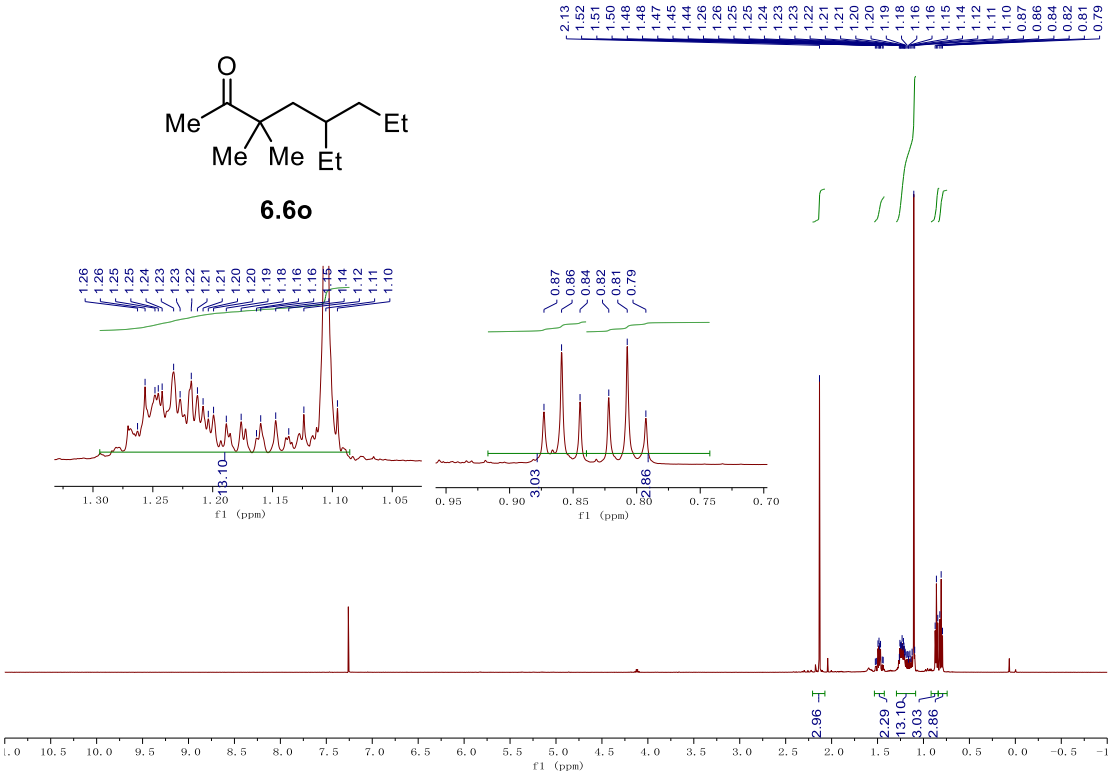


Figure 6.77 ^{13}C-NMR Spectrum of **6.6o**

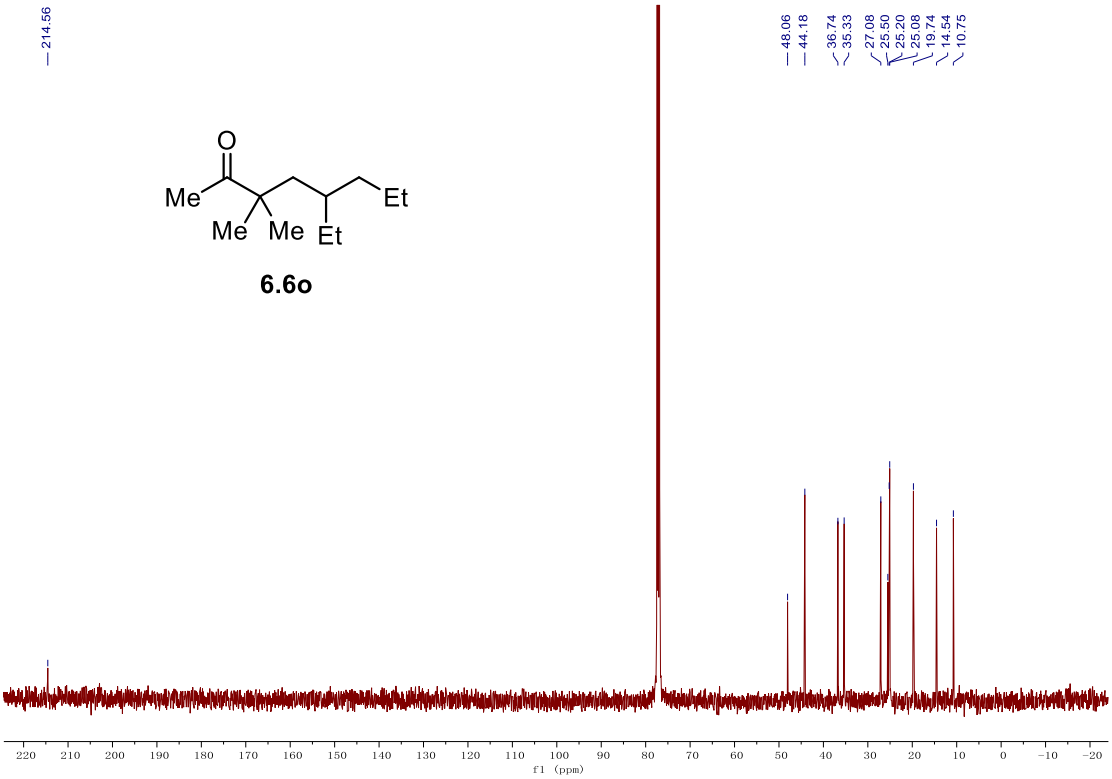


Figure 6.78 ^{1}H-NMR Spectrum of **6.5p**

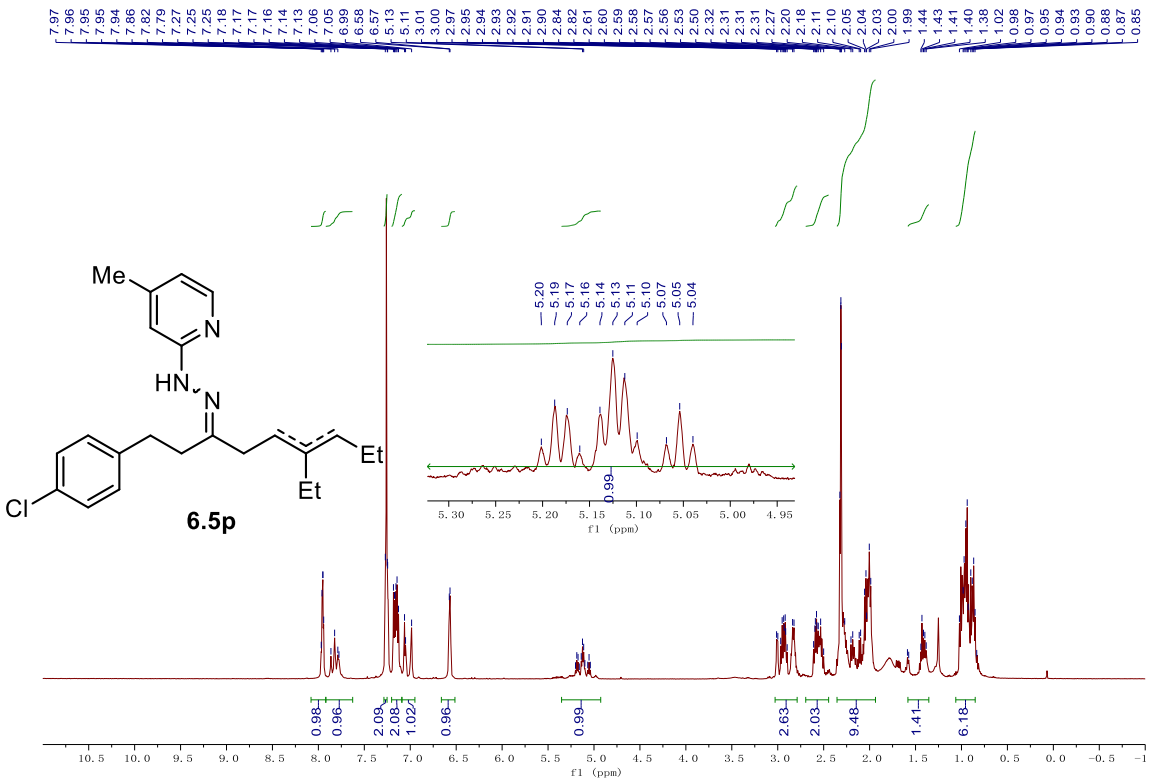


Figure 6.79 ^{1}H-NMR Spectrum of **6.6p**

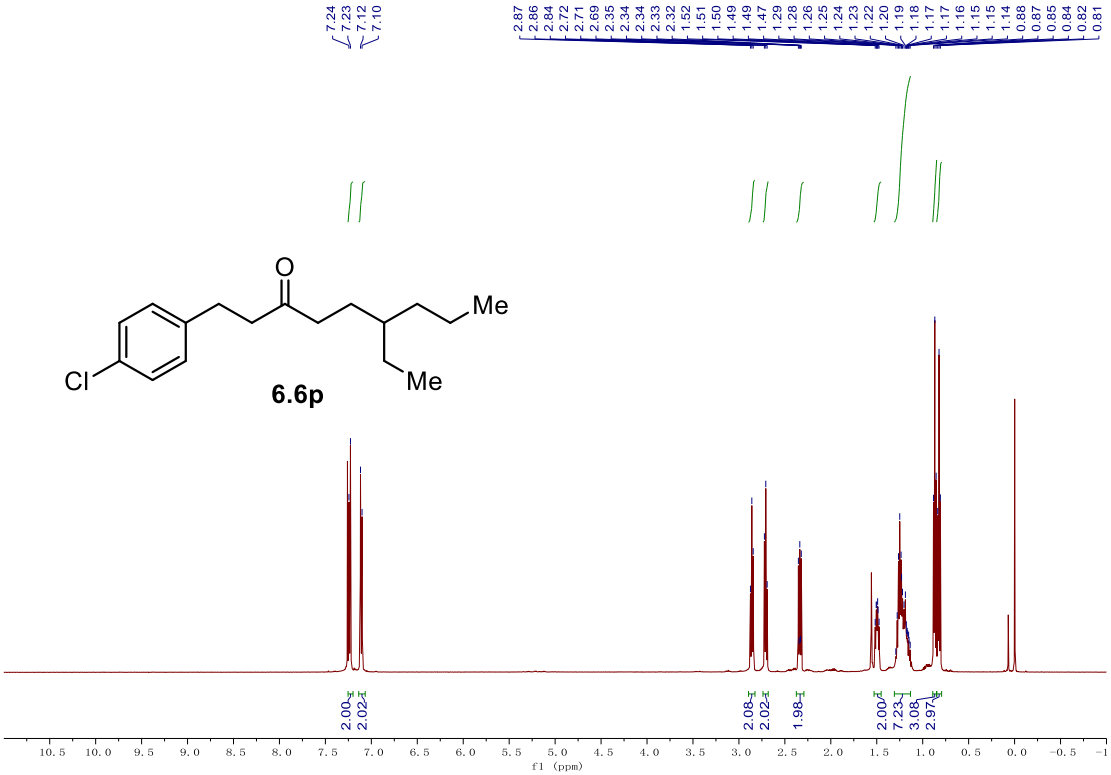


Figure 6.80 ^{13}C-NMR Spectrum of **6.6p**

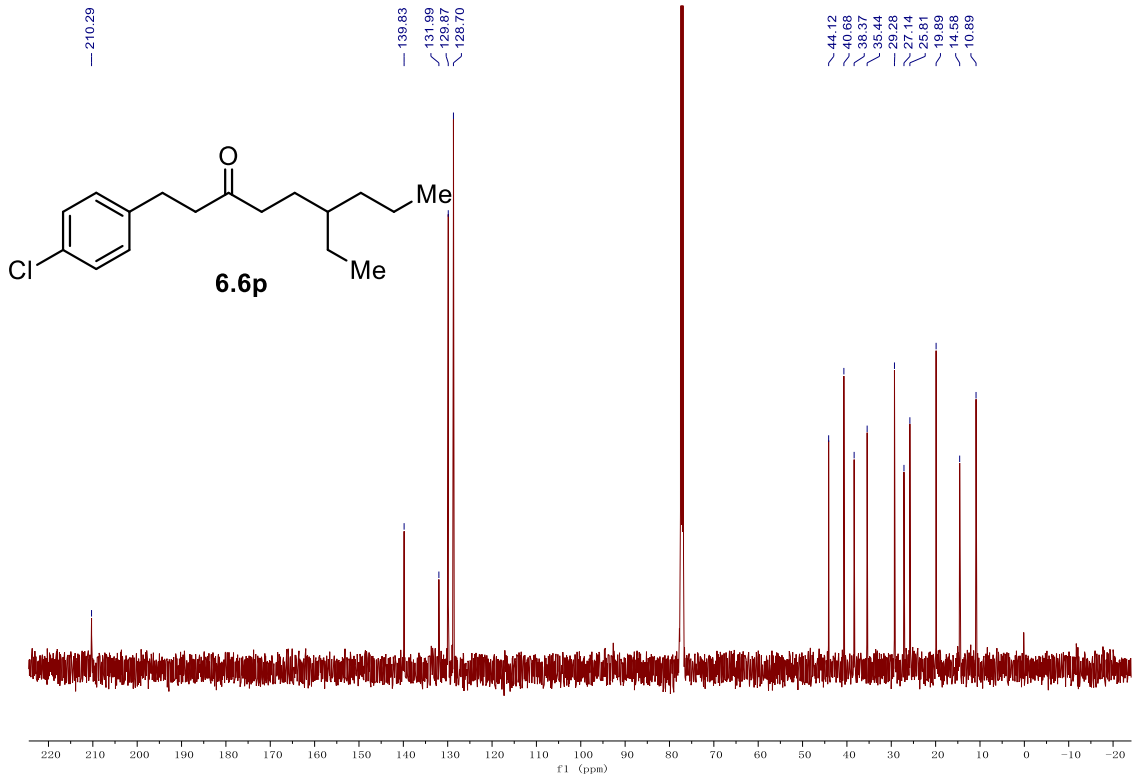


Figure 6.81 ^{1}H-NMR Spectrum of **6.5q**

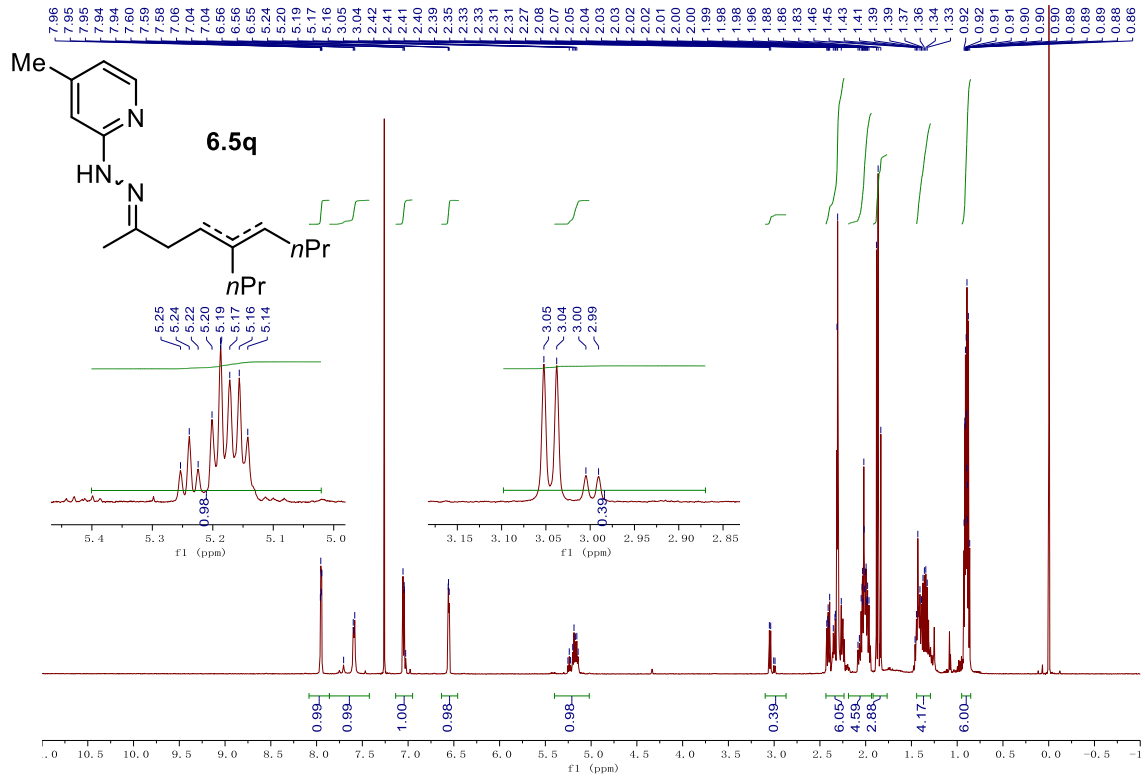


Figure 6.82 ^{1}H-NMR Spectrum of **6.6q**

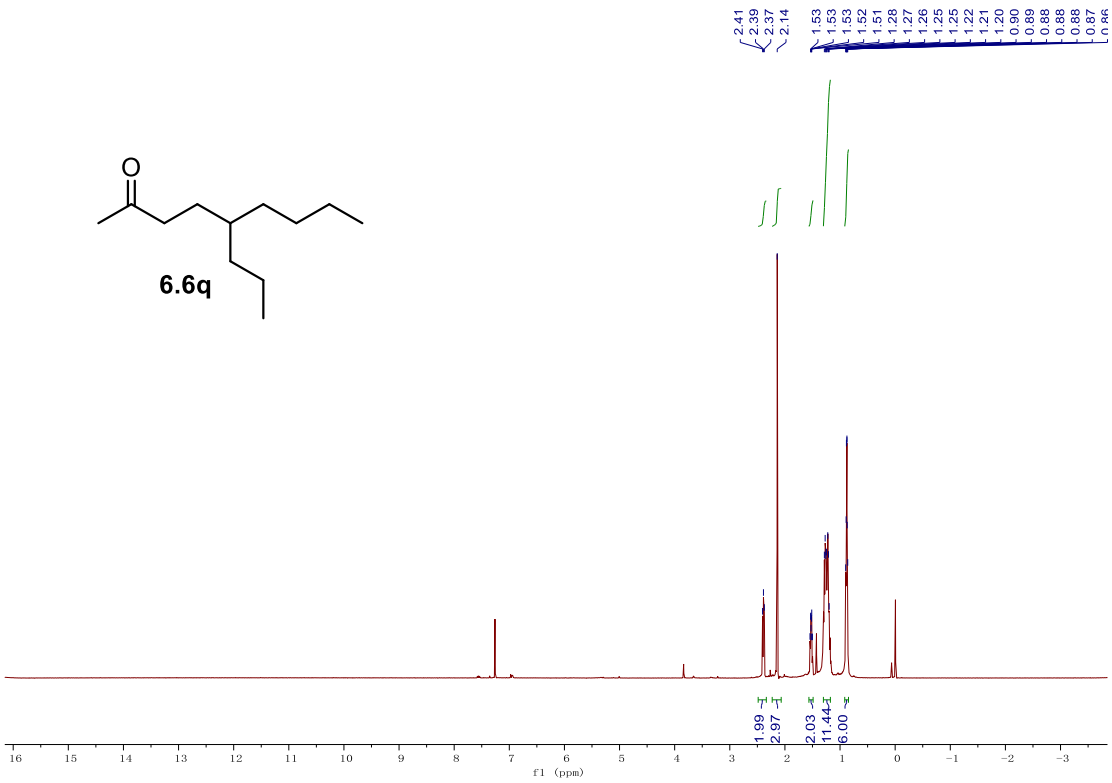


Figure 6.83 ^{13}C-NMR Spectrum of **6.6q**

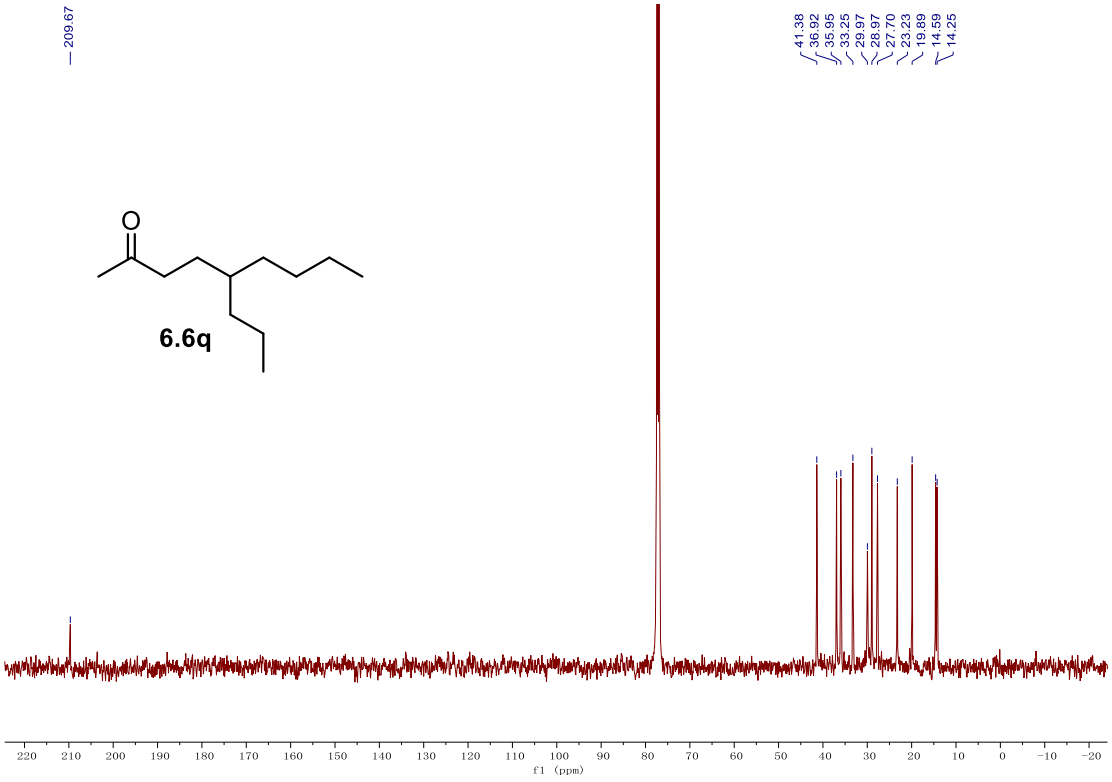


Figure 6.84 ^{1}H-NMR Spectrum of **6.5r**

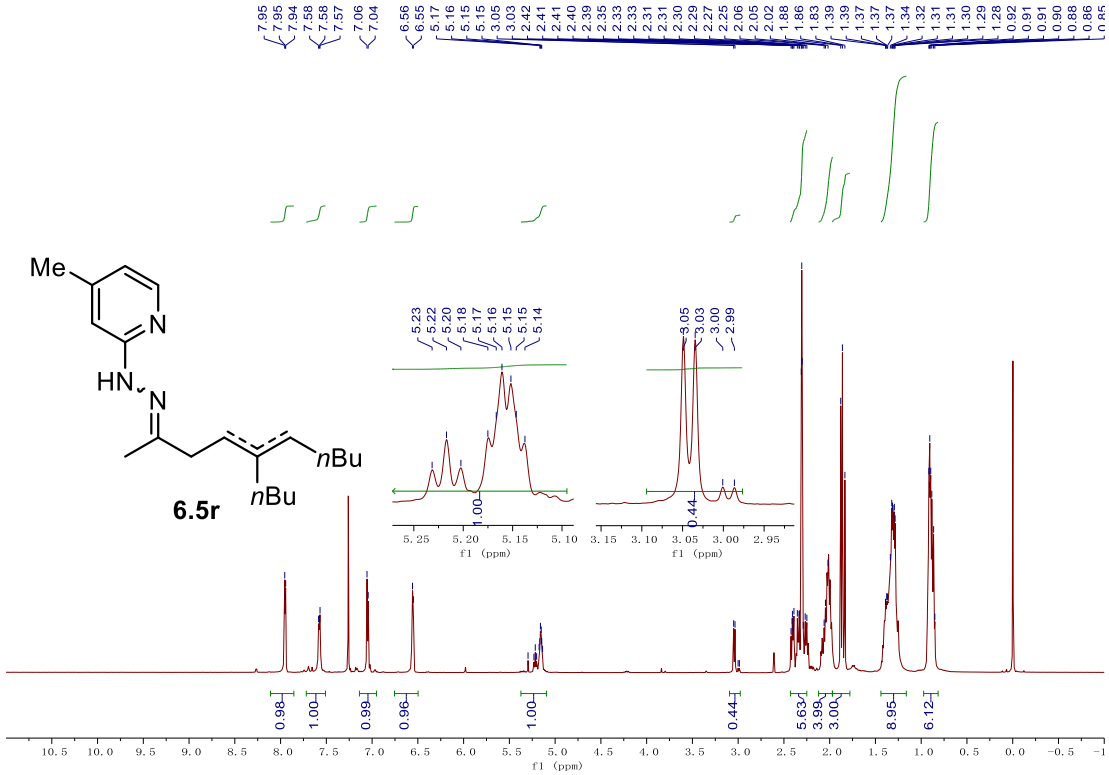


Figure 6.85 ^{1}H-NMR Spectrum of **6.6r**

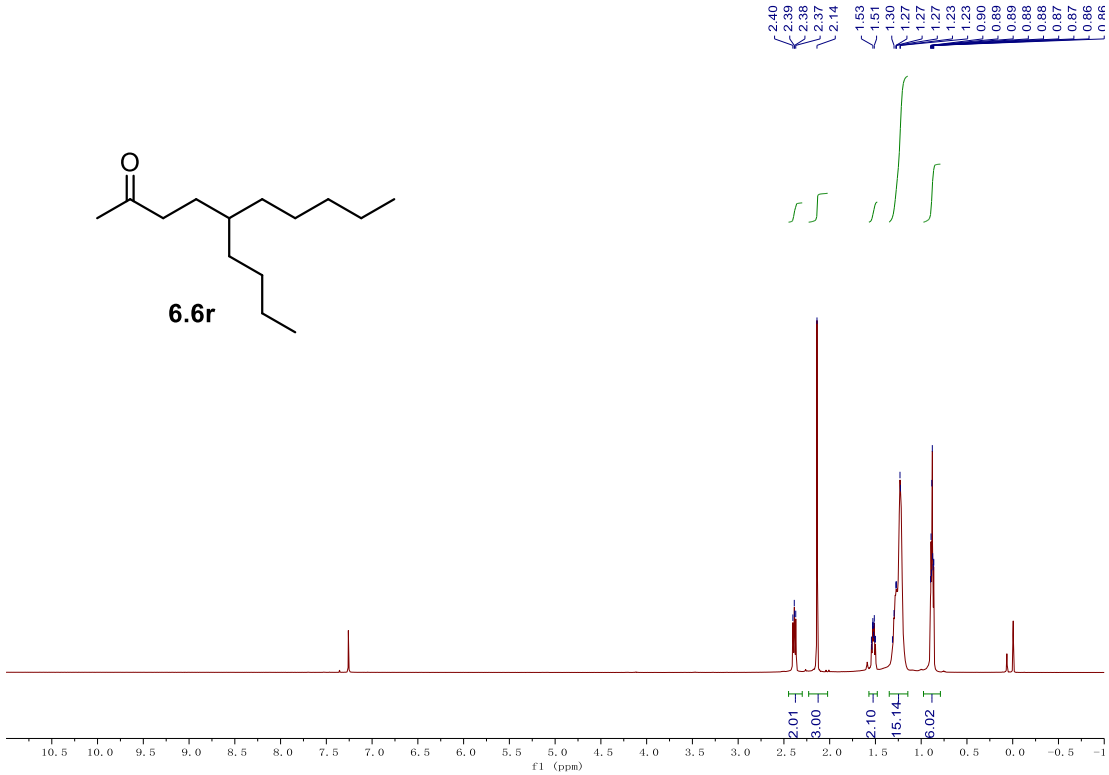


Figure 6.86 ^{13}C-NMR Spectrum of **6.6r**

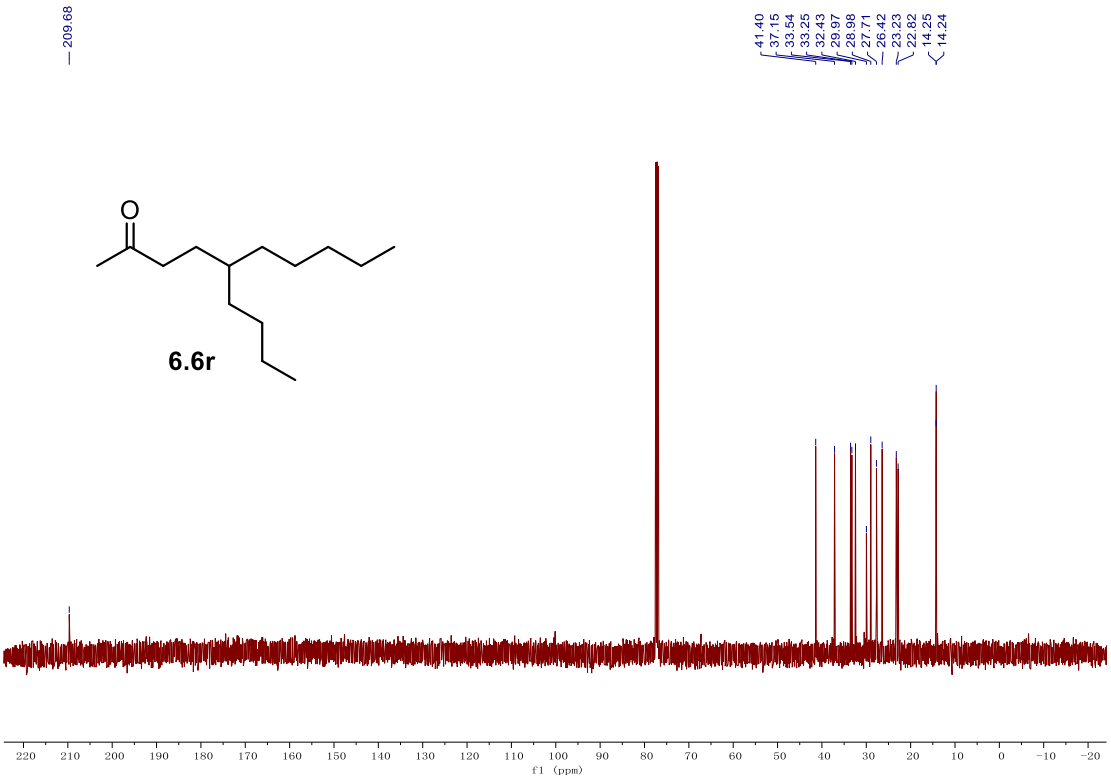


Figure 6.87 ^{1}H-NMR Spectrum of **6.5s**

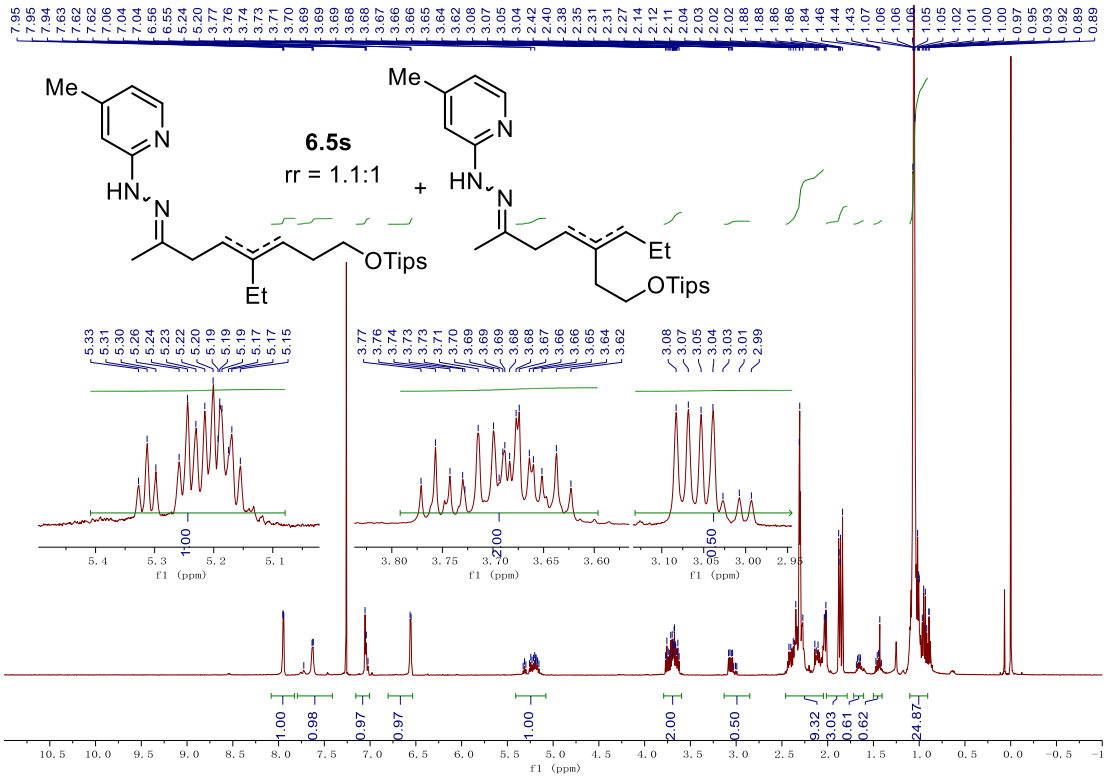


Figure 6.88 ^{1}H-NMR Spectrum of **6.6s**

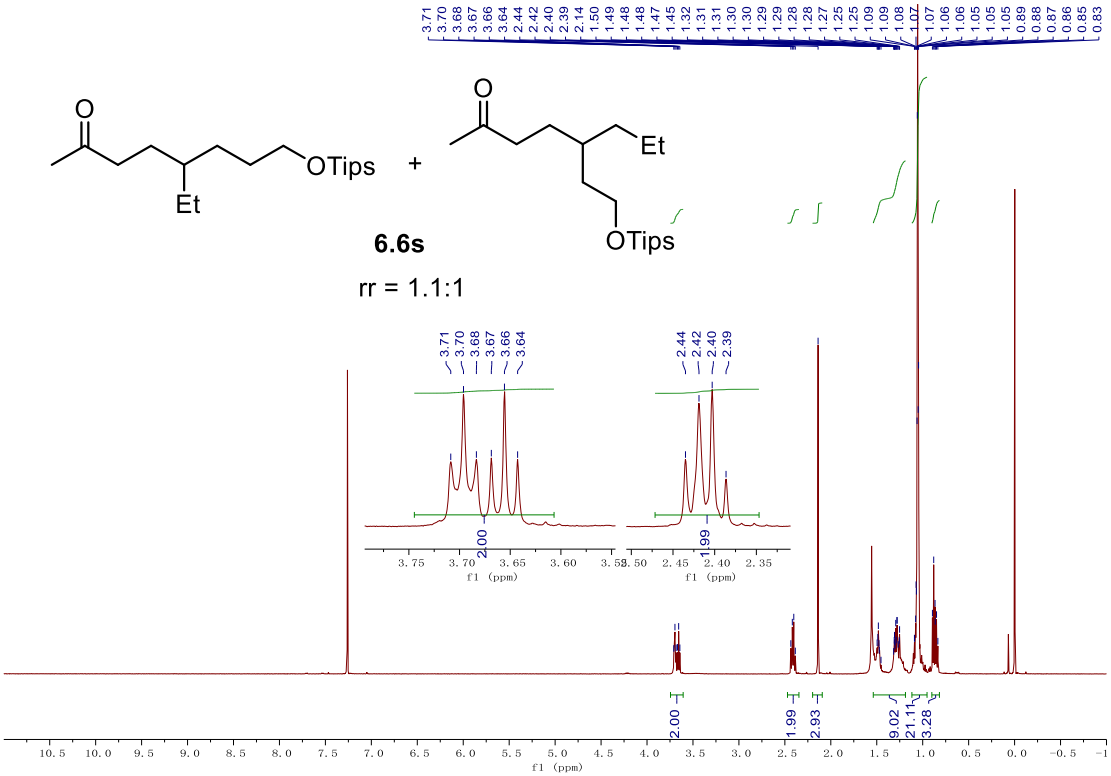


Figure 6.89 ^{13}C-NMR Spectrum of **6.6s**

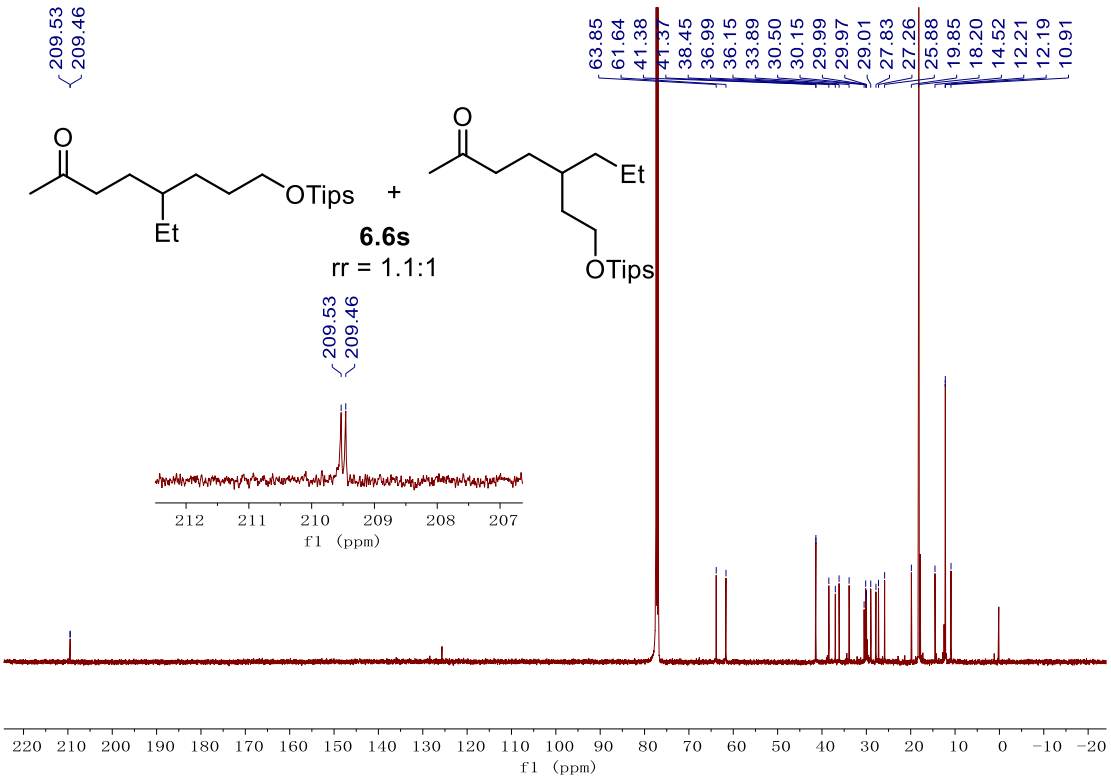


Figure 6.90 ^{1}H-NMR Spectrum of **6.5t**

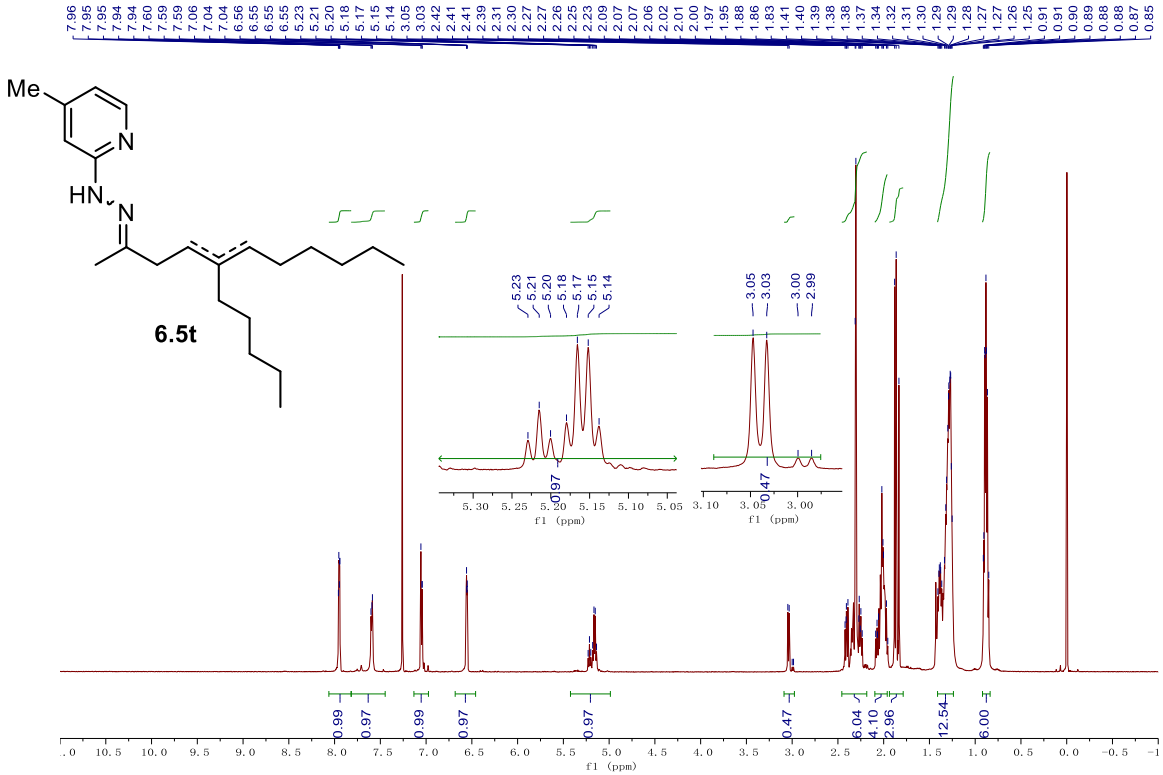


Figure 6.91 ^{1}H-NMR Spectrum of **6.6t**

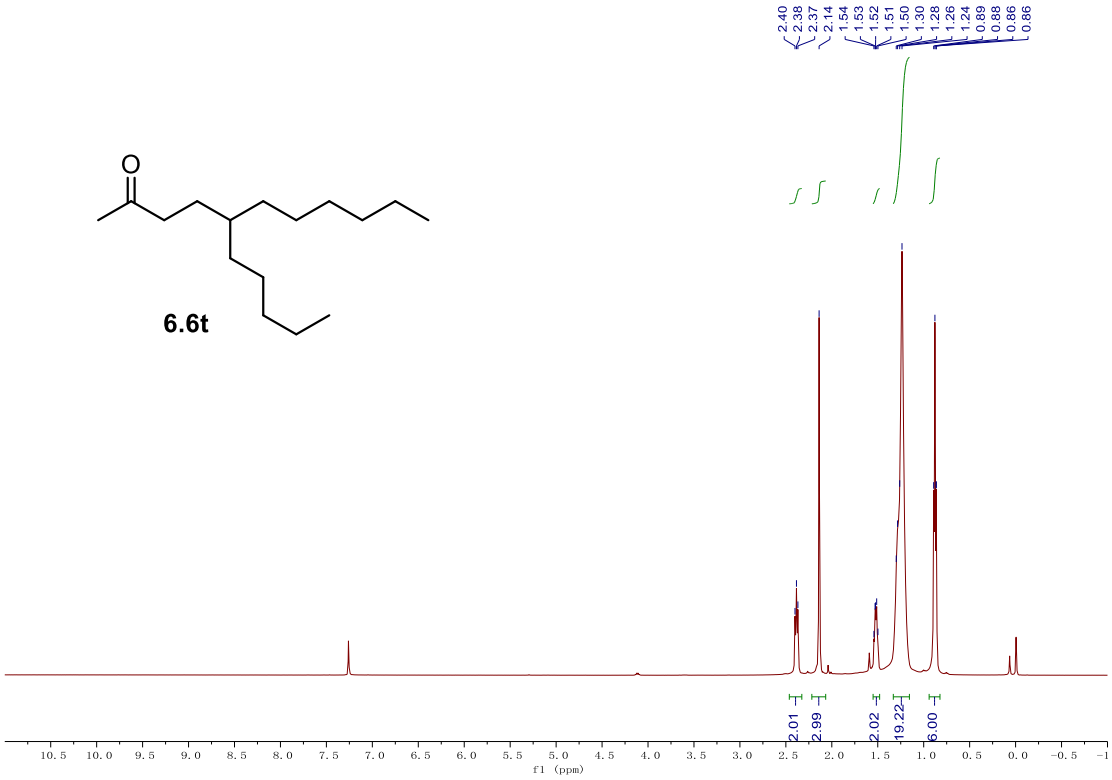


Figure 6.92 ^{13}C-NMR Spectrum of **6.6t**

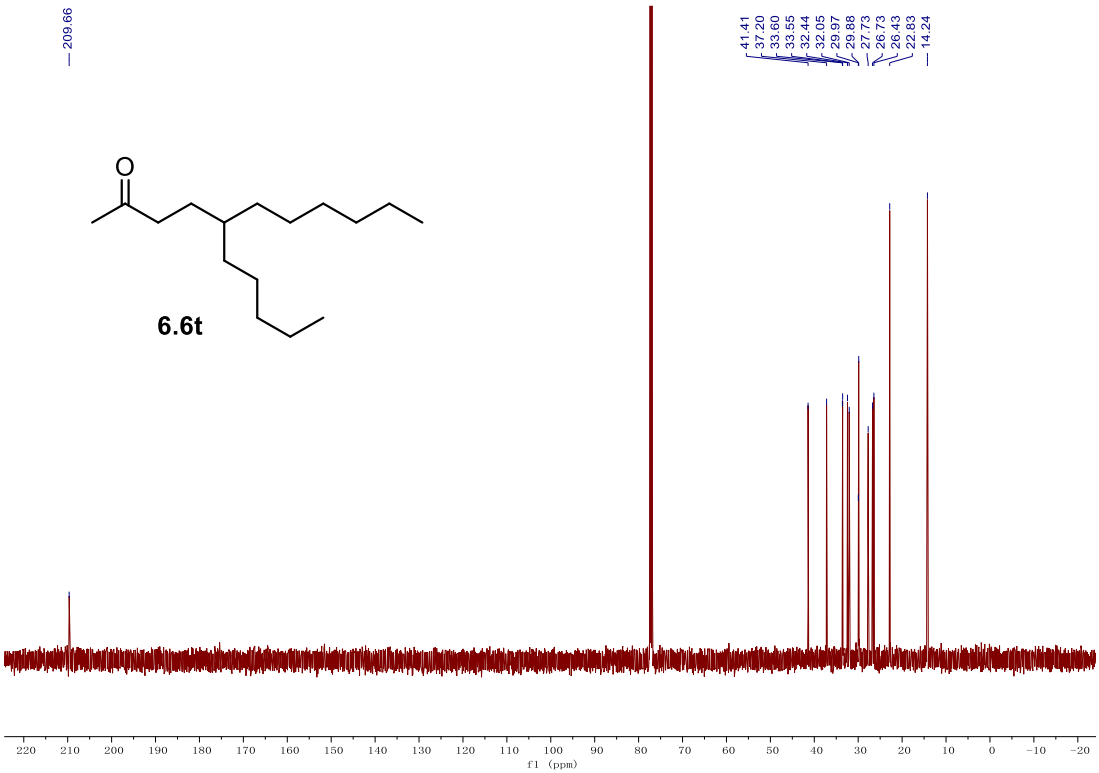


Figure 6.93 ^{1}H-NMR Spectrum of **6.5u**

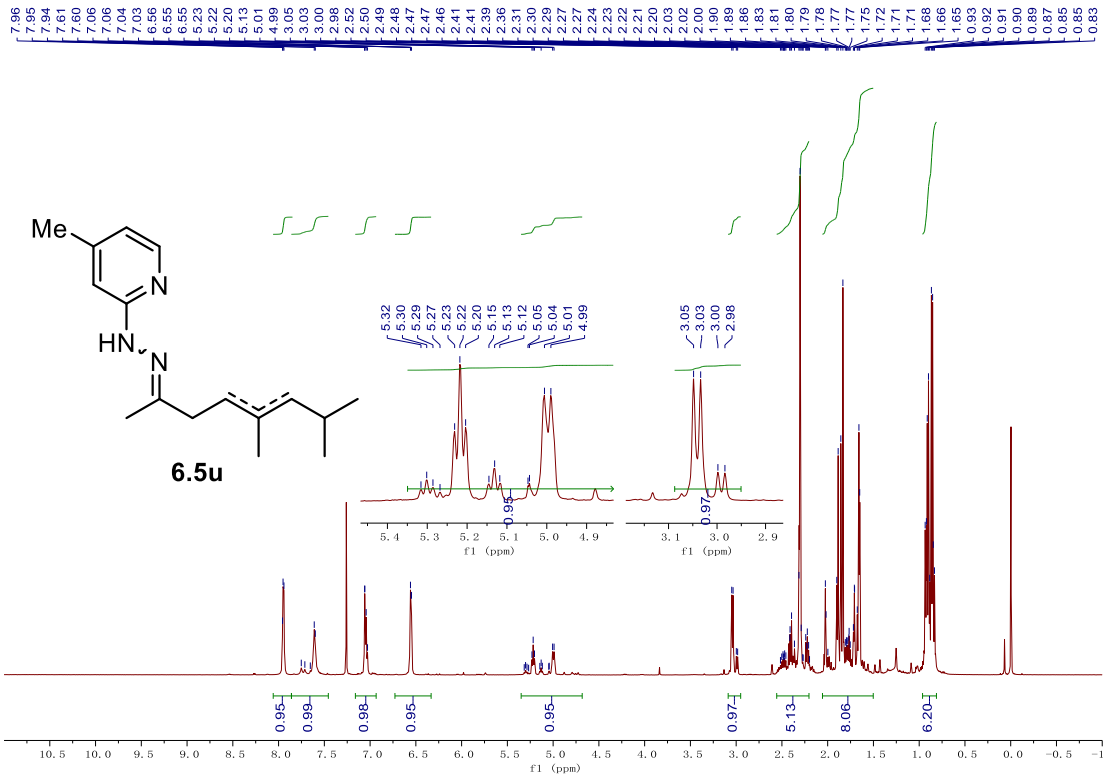


Figure 6.94 ^{1}H-NMR Spectrum of **6.6u**

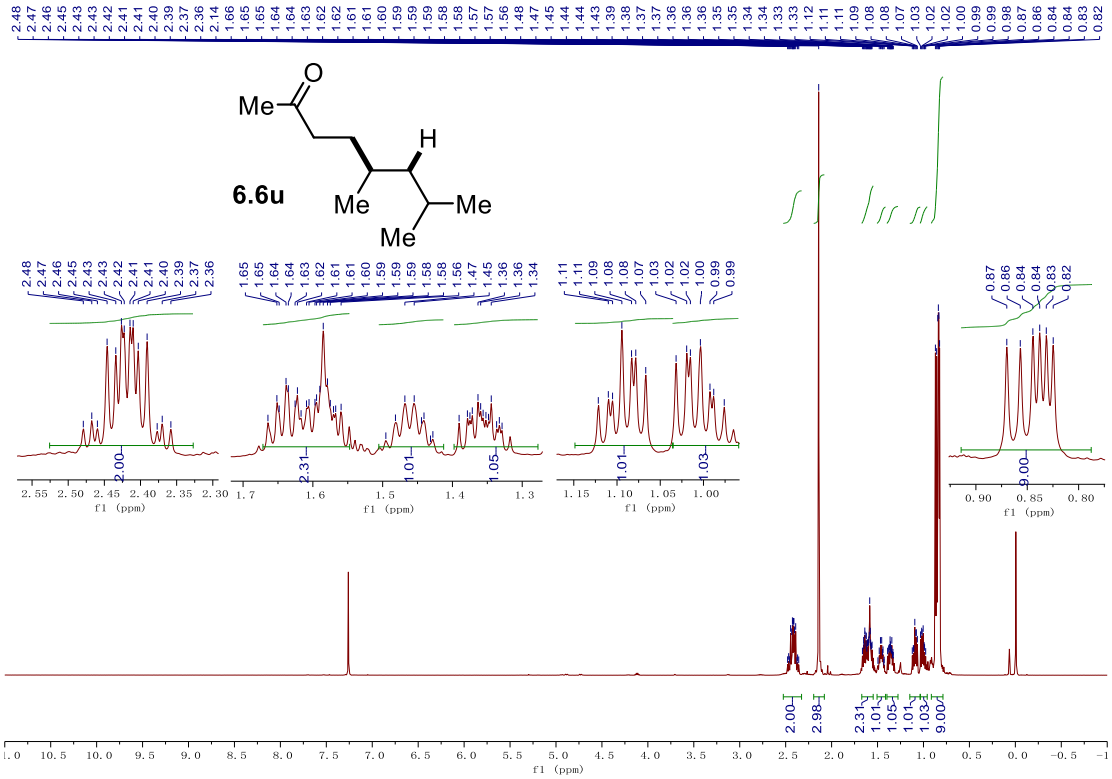


Figure 6.95 ^{13}C-NMR Spectrum of **6.6u**

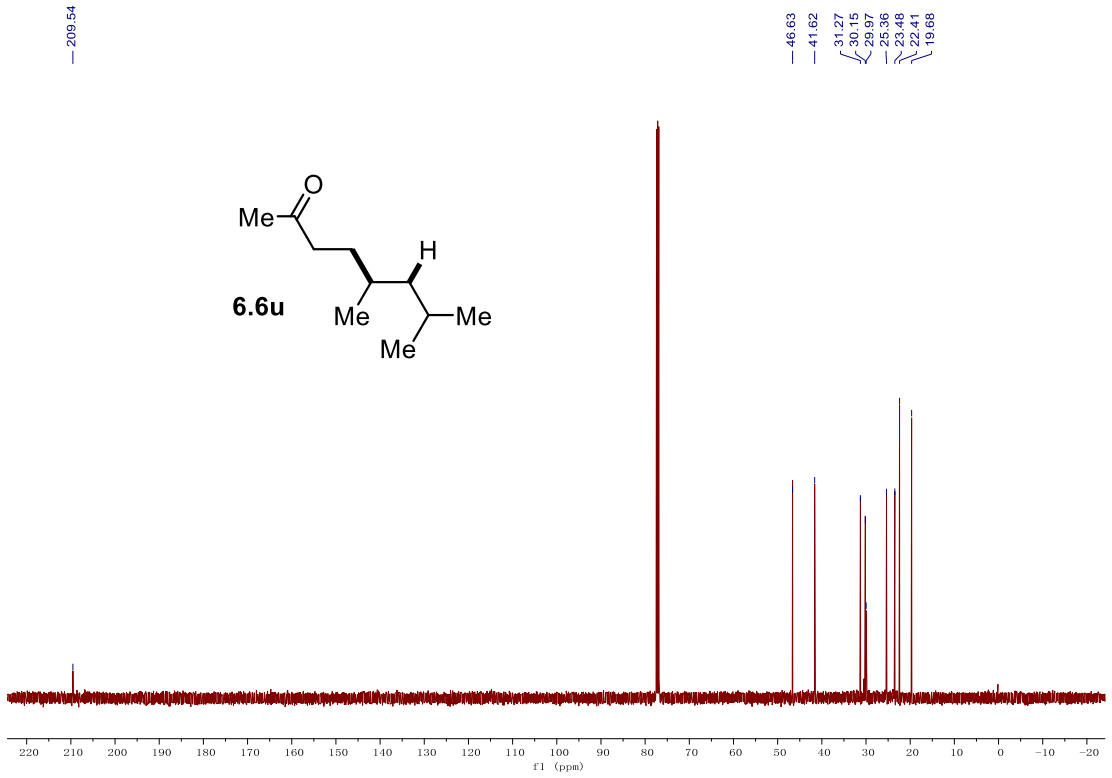


Figure 6.96 ^{1}H-NMR Spectrum of **6.5v**

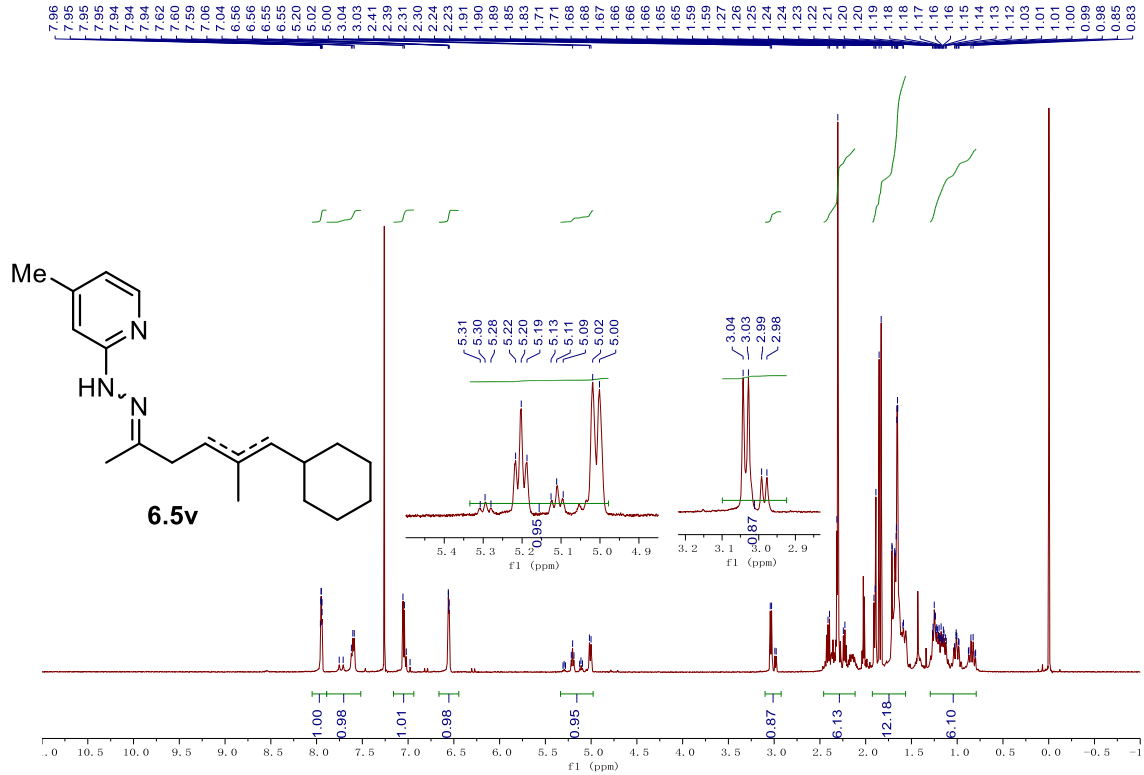


Figure 6.97 ^{1}H-NMR Spectrum of **6.6v**

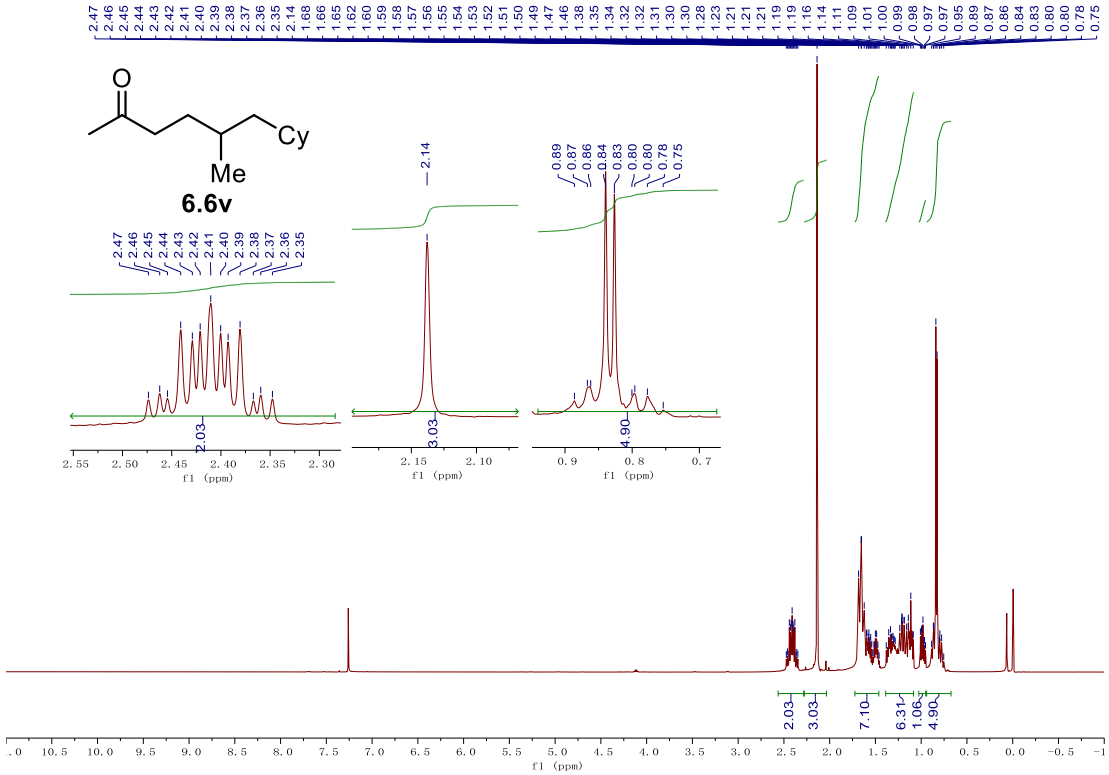


Figure 6.98 ^{13}C-NMR Spectrum of **6.6v**

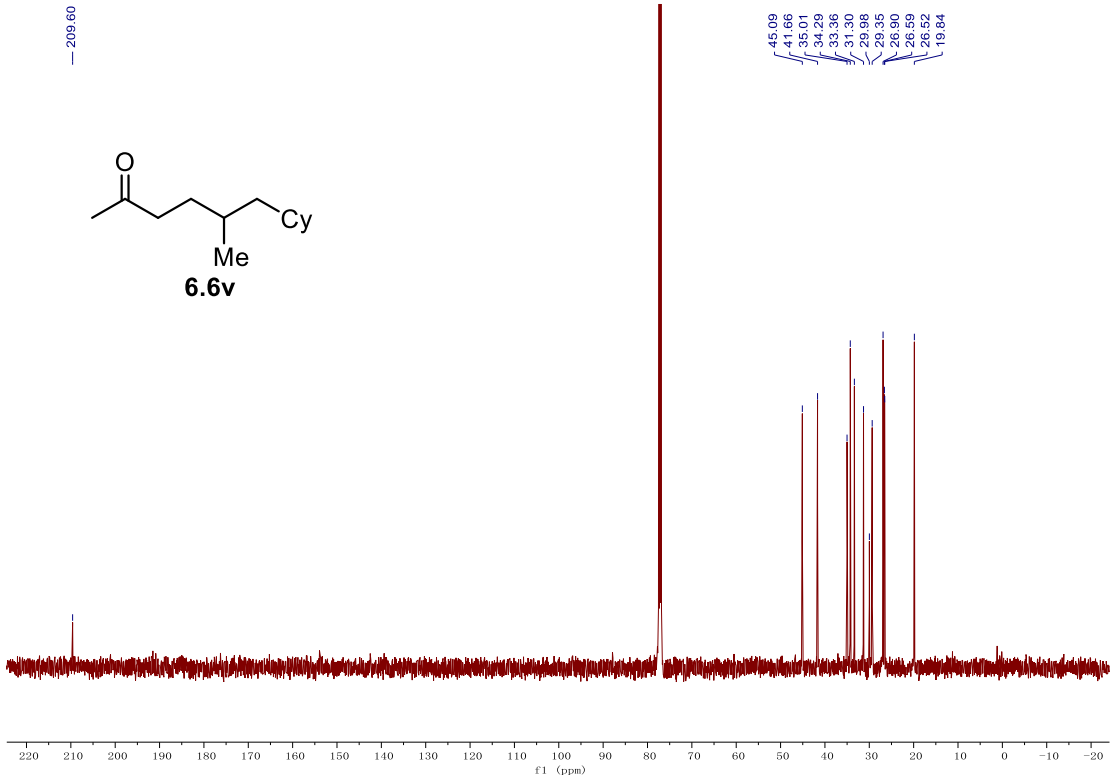


Figure 6.99 ^{1}H-NMR Spectrum of **6.5w**

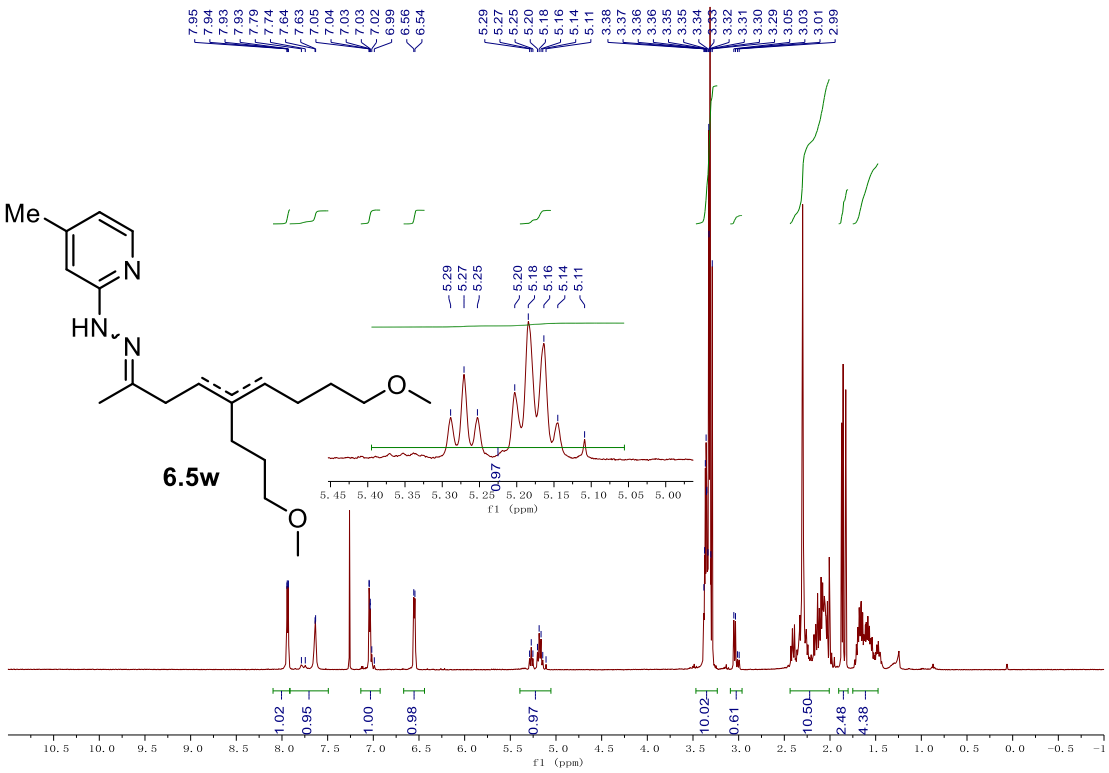


Figure 6.100 ^{1}H-NMR Spectrum of **6.6w**

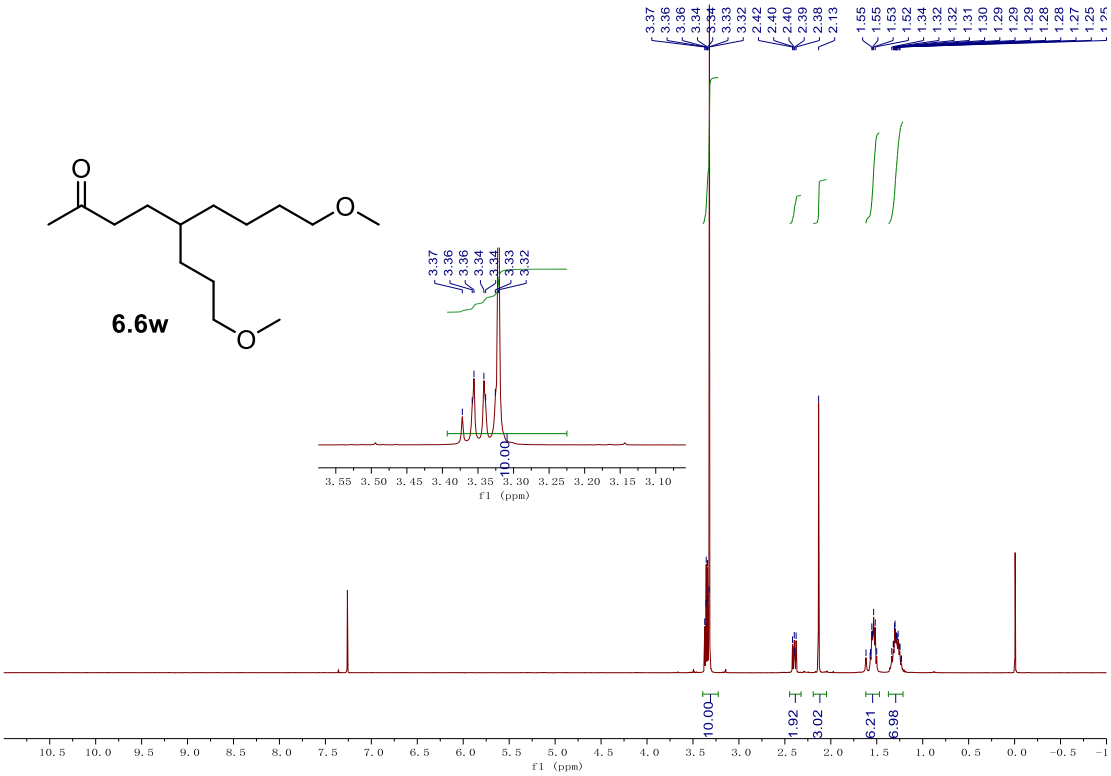


Figure 6.101 ^{13}C-NMR Spectrum of **6.6w**

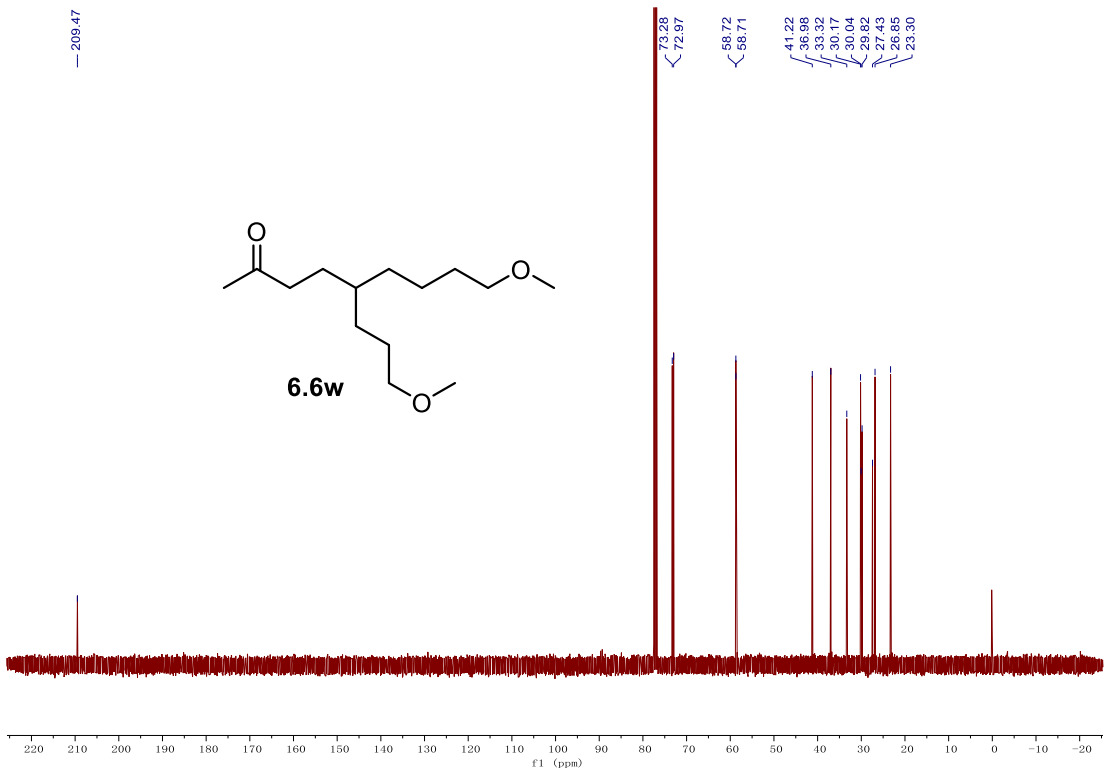


Figure 6.102 ^{1}H-NMR Spectrum of **6.5x**

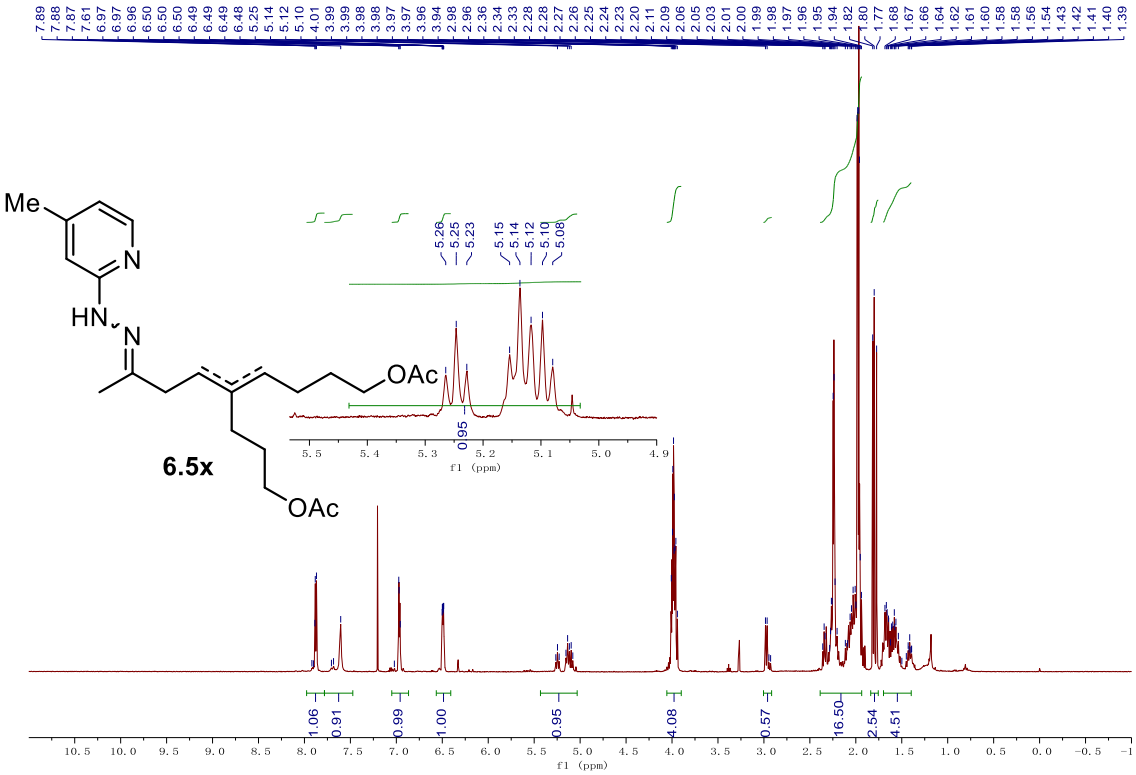


Figure 6.103 ^{1}H-NMR Spectrum of **6.6x**

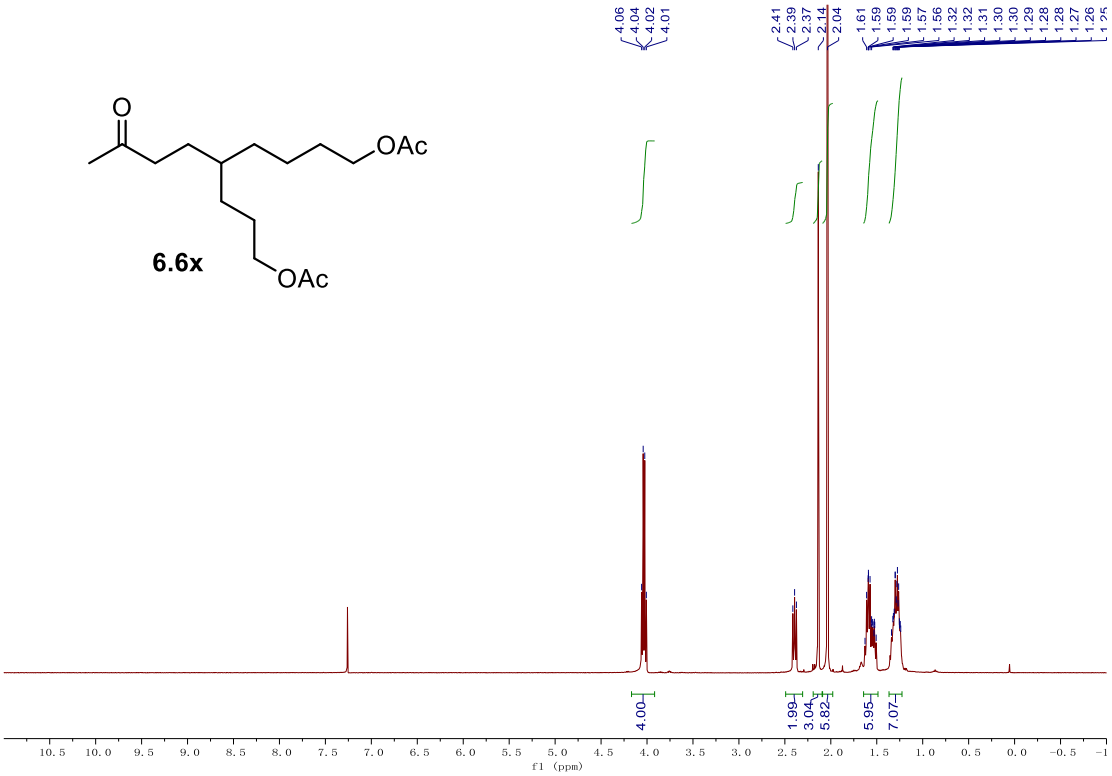


Figure 6.104 ^{13}C-NMR Spectrum of **6.6x**

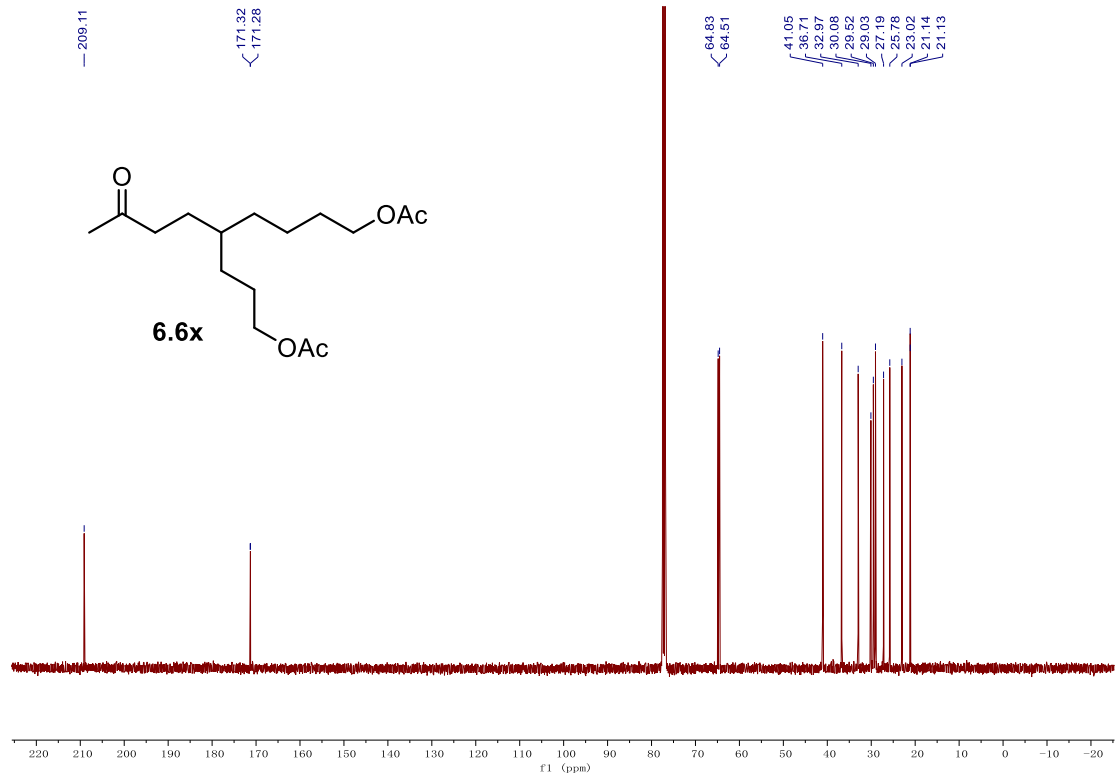


Figure 6.105 ^{1}H-NMR Spectrum of **6.7a**

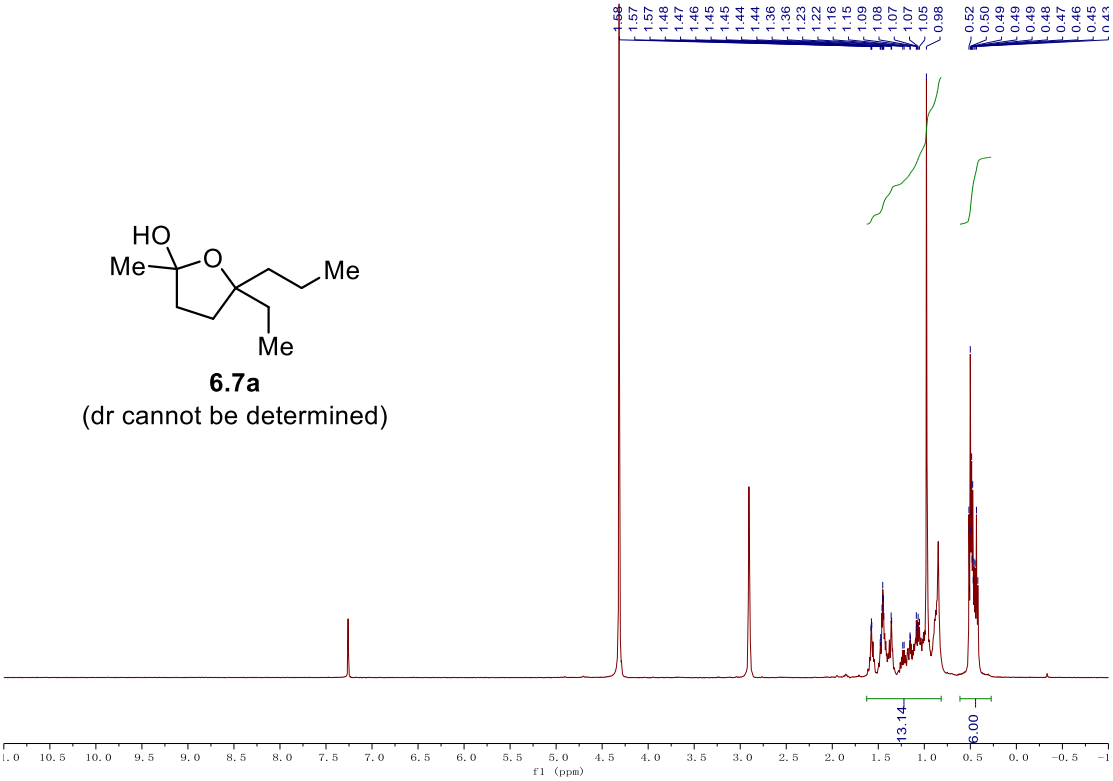


Figure 6.106 ^{13}C-NMR Spectrum of **6.7a**

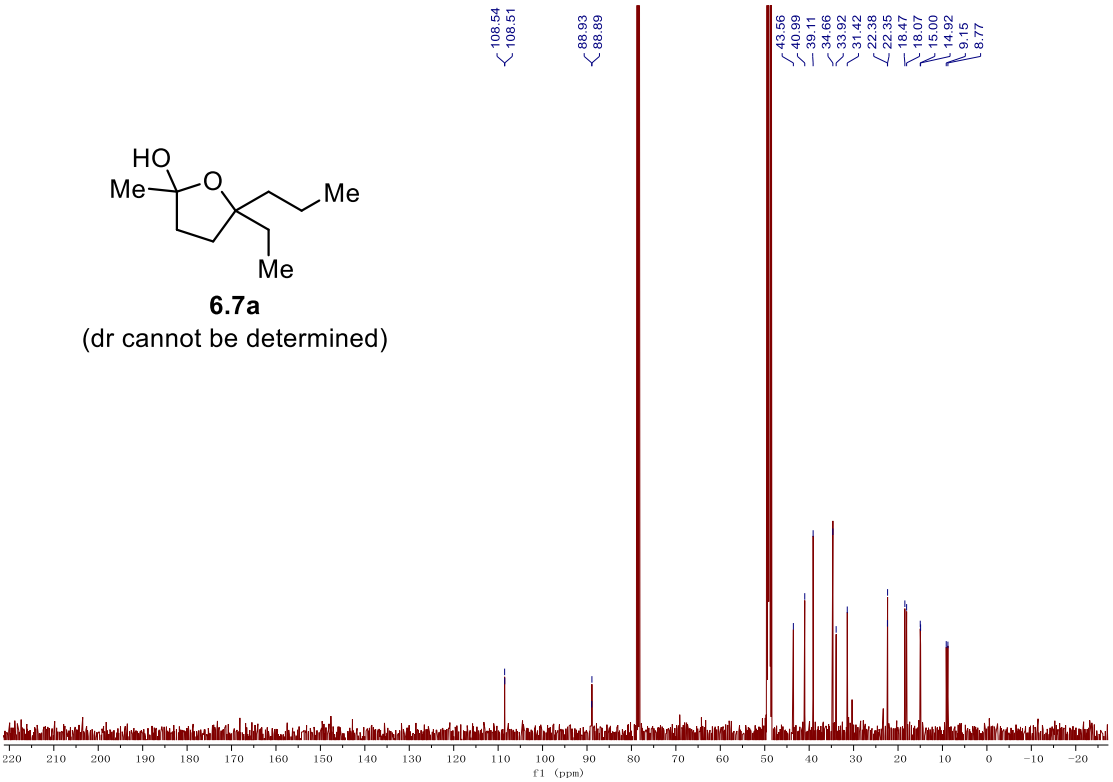


Figure 6.107 ^{1}H-NMR Spectrum of **6.7b**

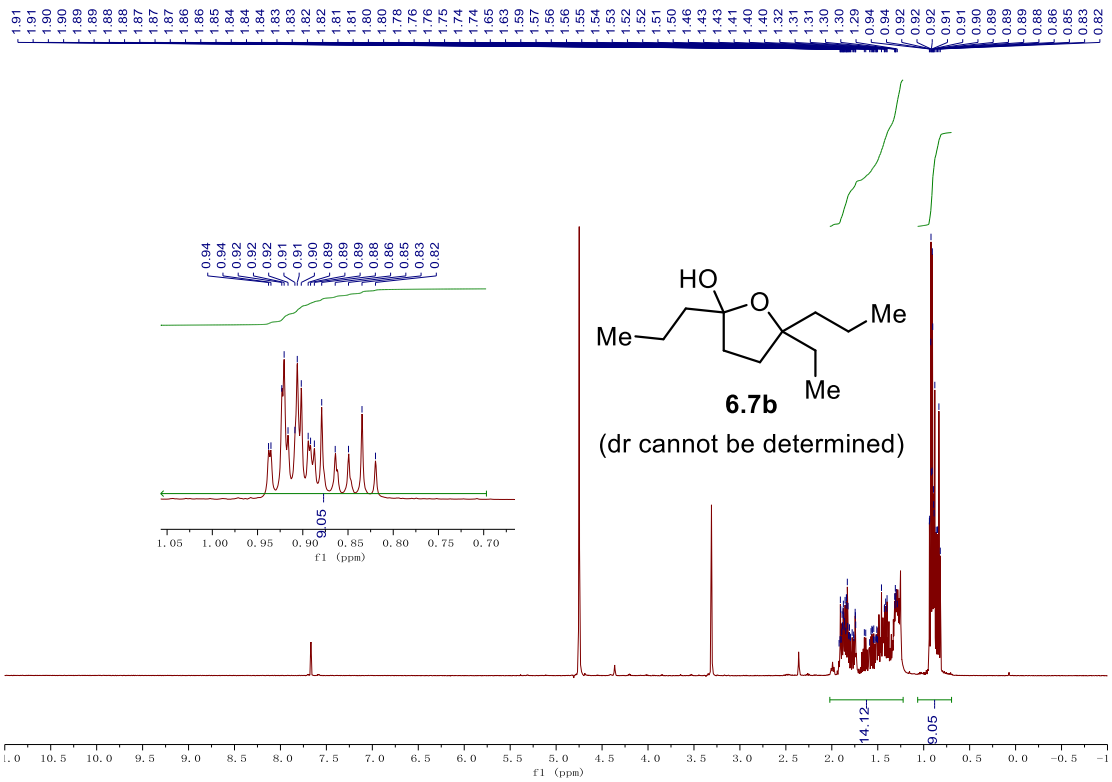


Figure 6.108 ^{13}C-NMR Spectrum of **6.7b**

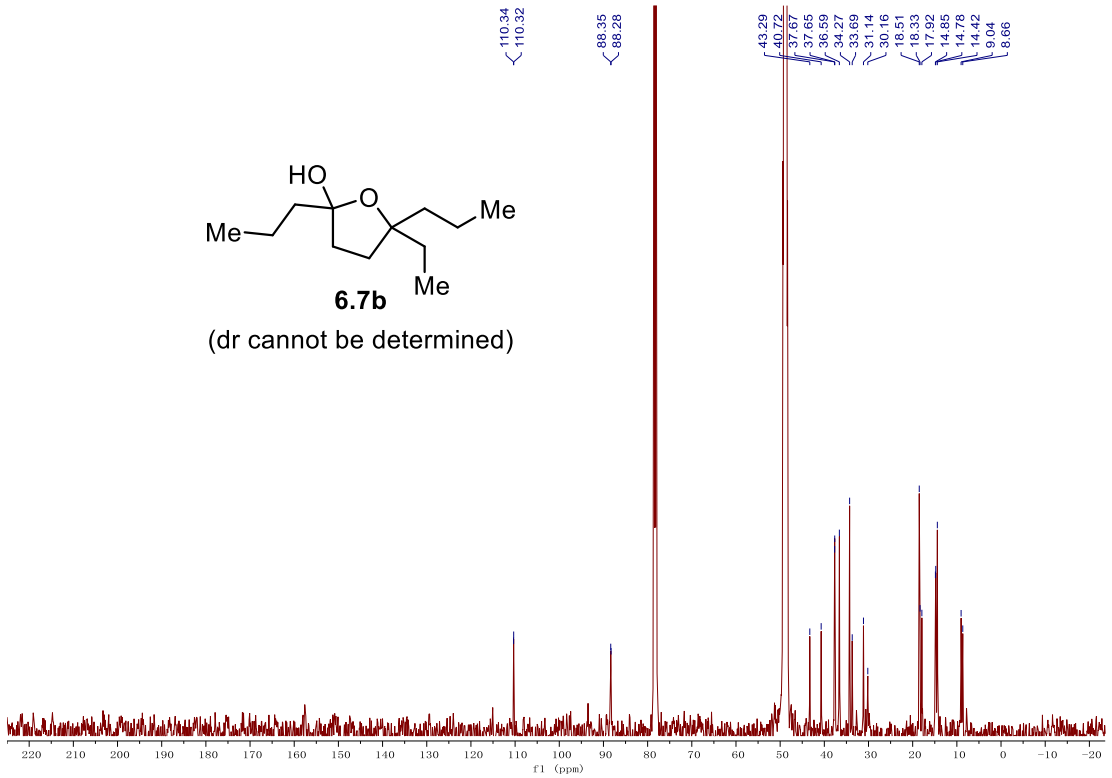


Figure 6.109 ^{1}H-NMR Spectrum of **6.7c** (in $CDCl_3$)

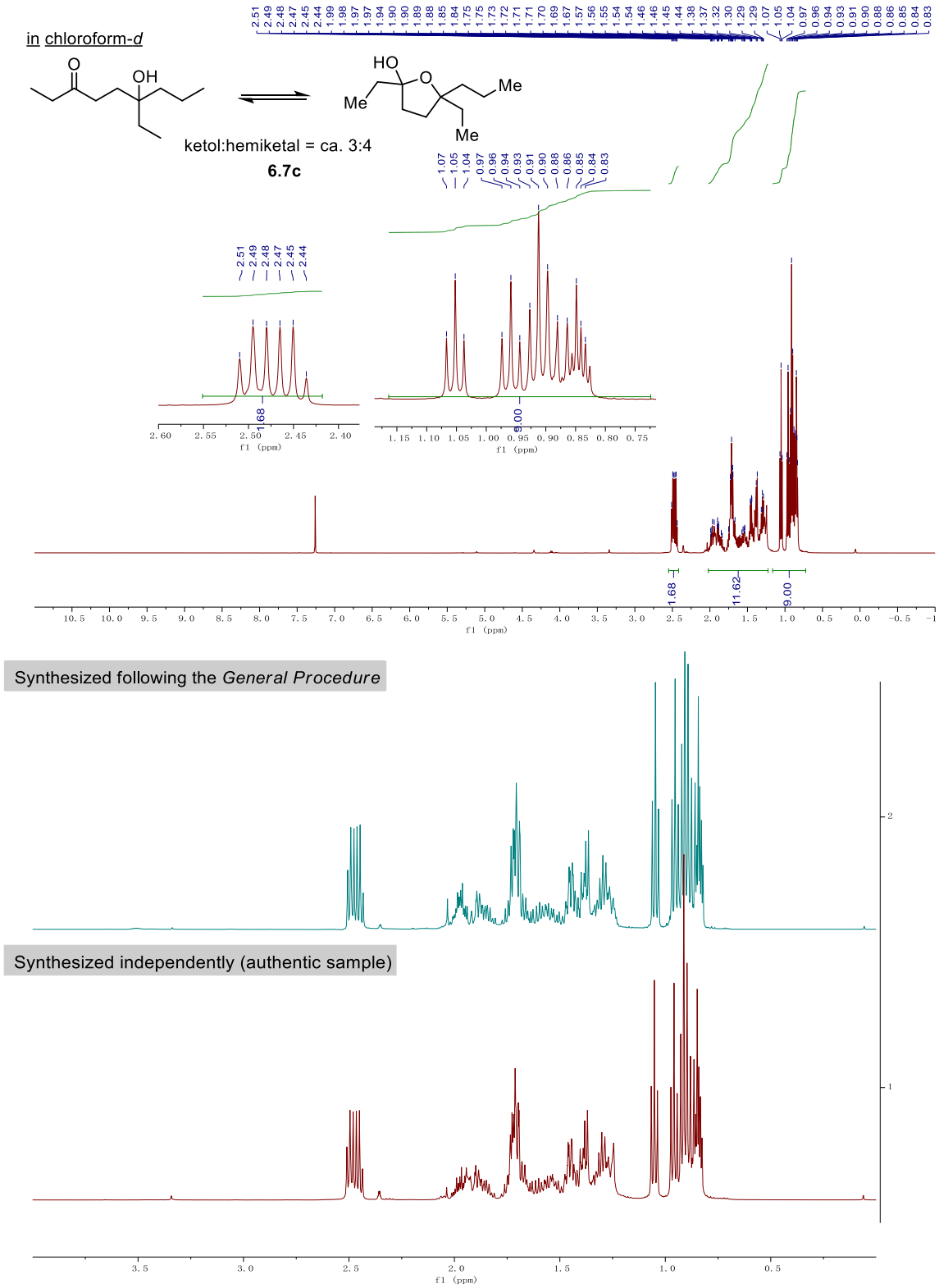


Figure 6.110 ^{1}H-NMR Spectrum of **6.7c** (in $CD_3OD/CDCl_3$)

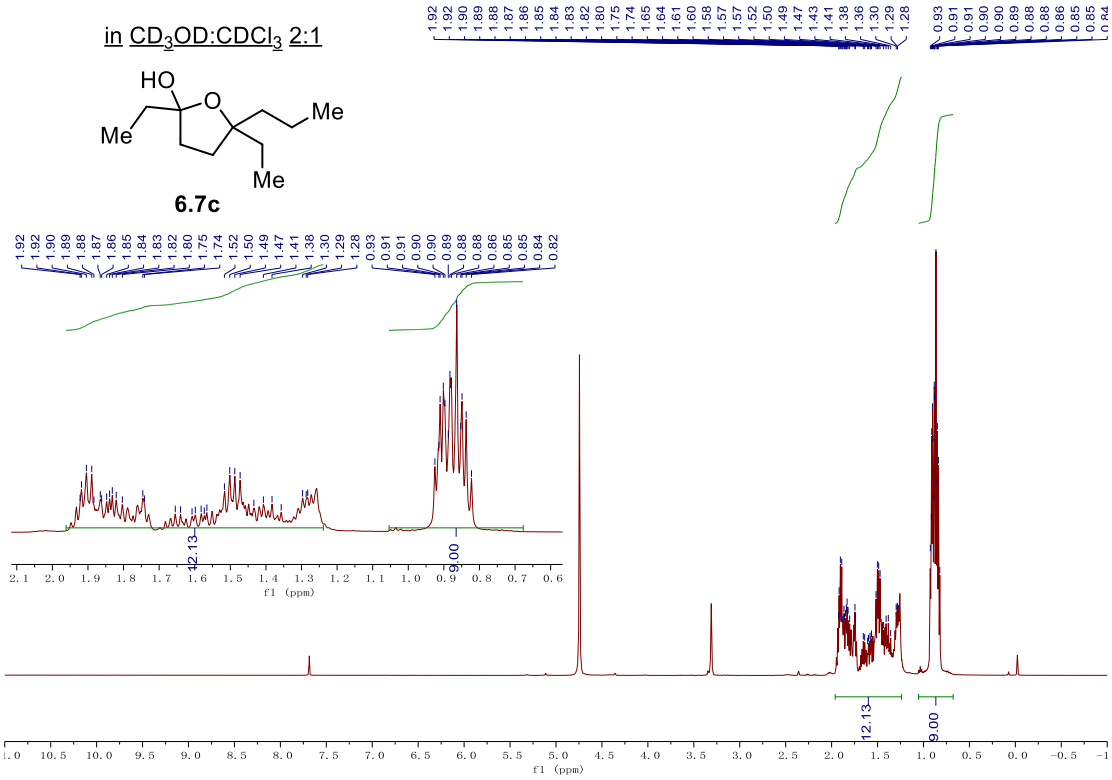


Figure 6.111 ^{13}C-NMR Spectrum of **6.7c**

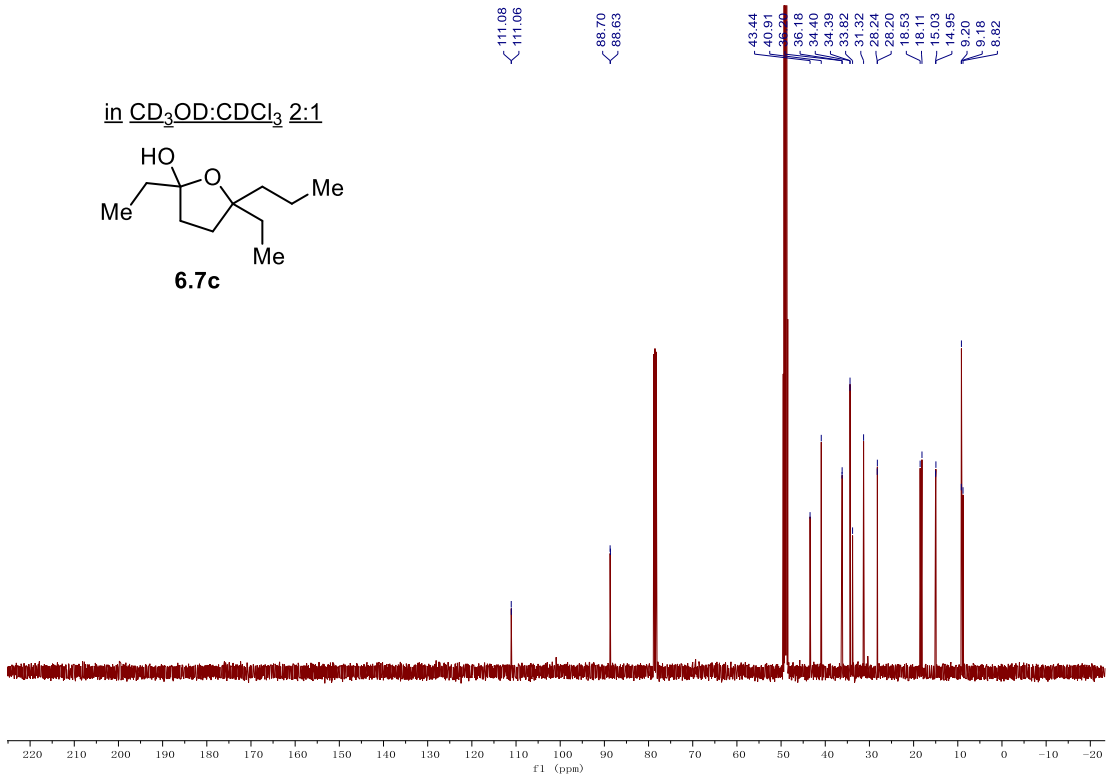


Figure 6.112 ^{1}H-NMR Spectrum of **6.7d**

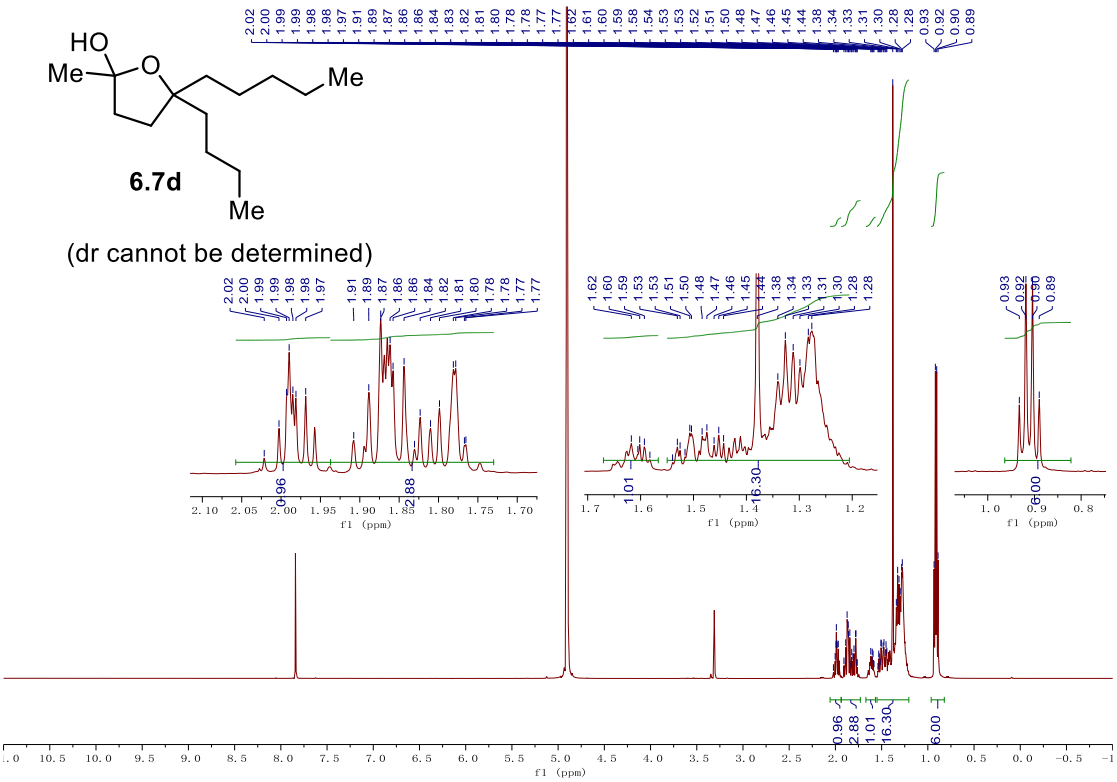


Figure 6.113 ^{13}C-NMR Spectrum of **6.7d**

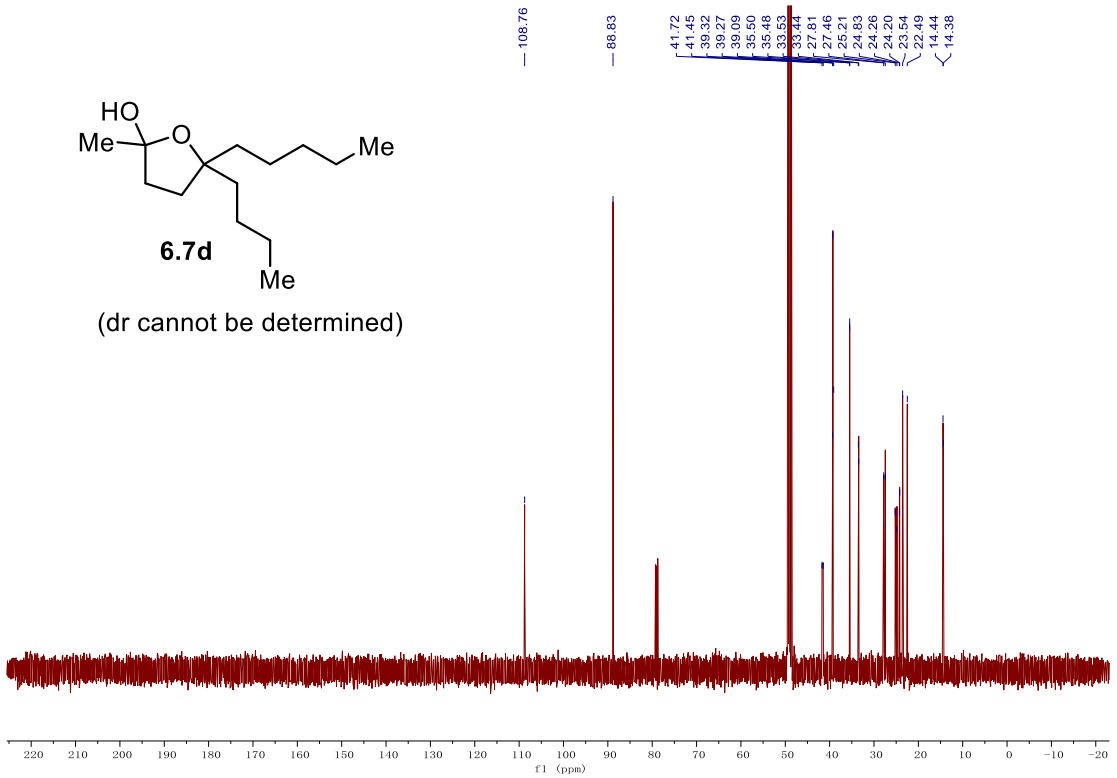


Figure 6.114 ^{1}H-NMR Spectrum of **6.7e**

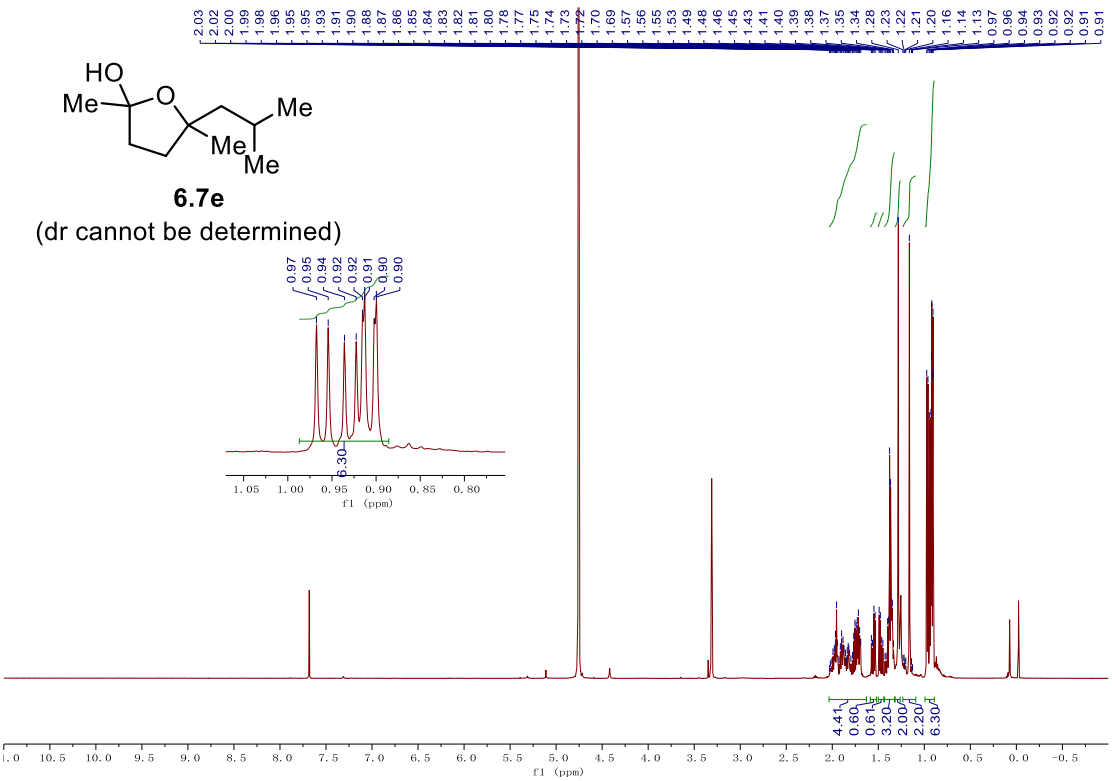


Figure 6.115 ^{13}C-NMR Spectrum of **6.7e**

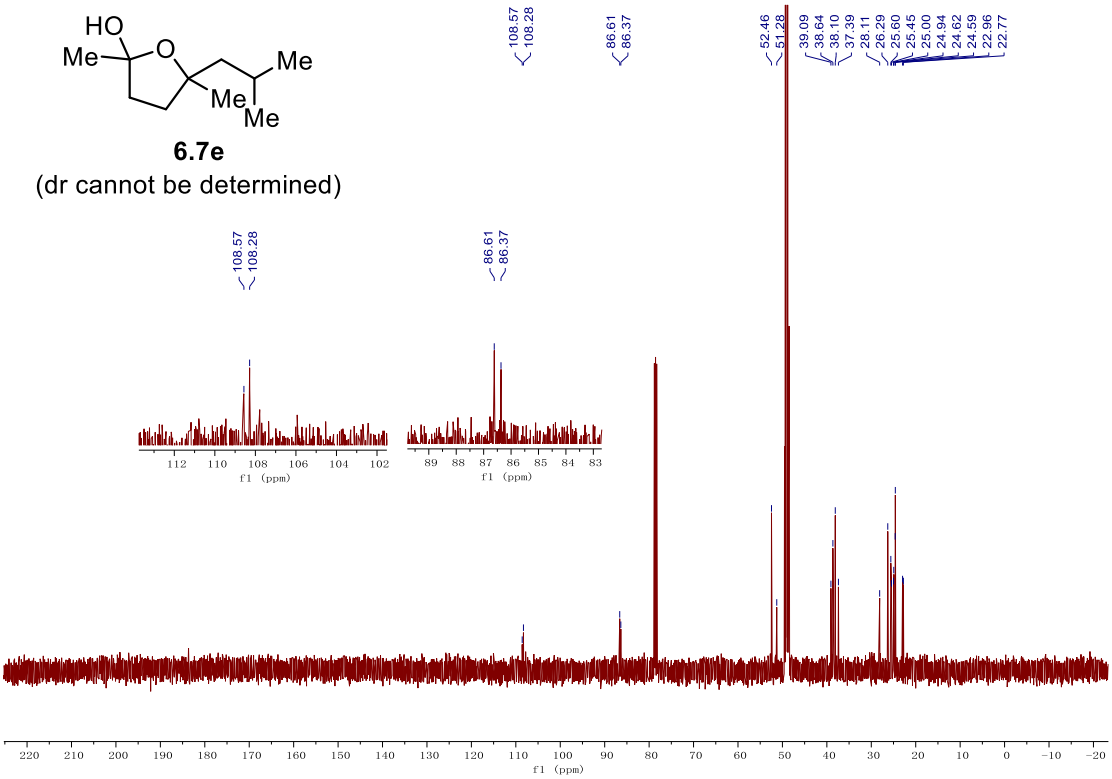


Figure 6.116 ^{1}H-NMR Spectrum of **6.7fb**

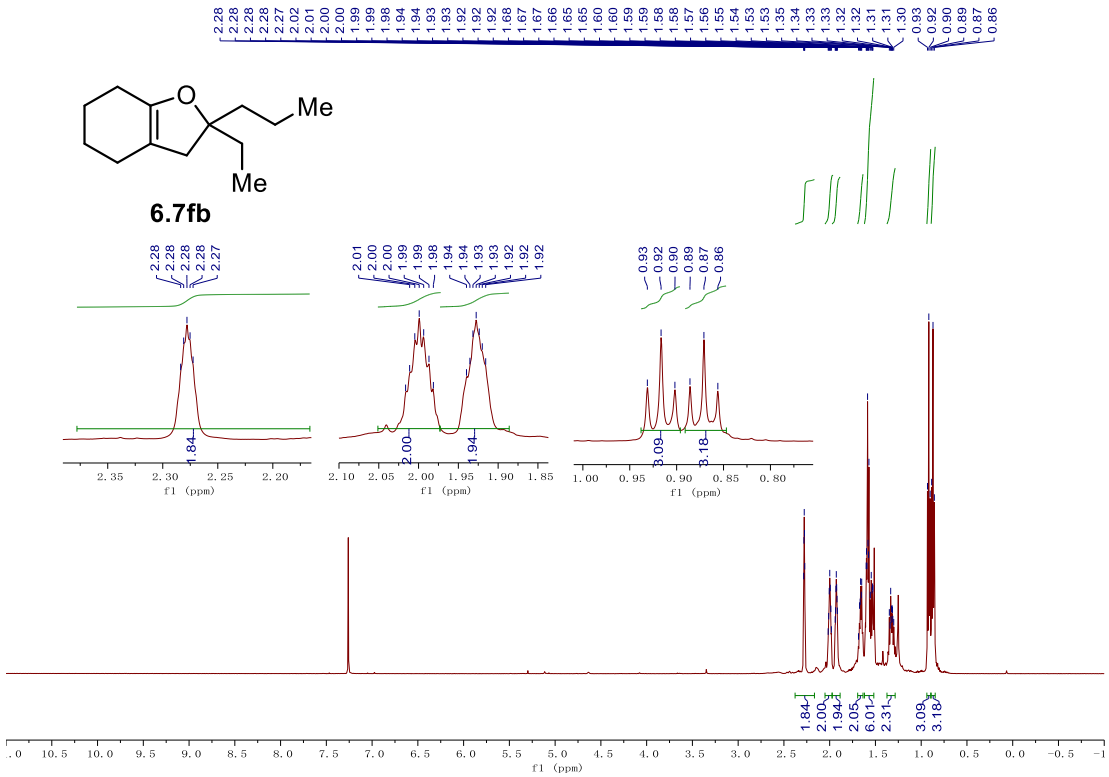


Figure 6.117 ^{13}C-NMR Spectrum of **6.7fb**

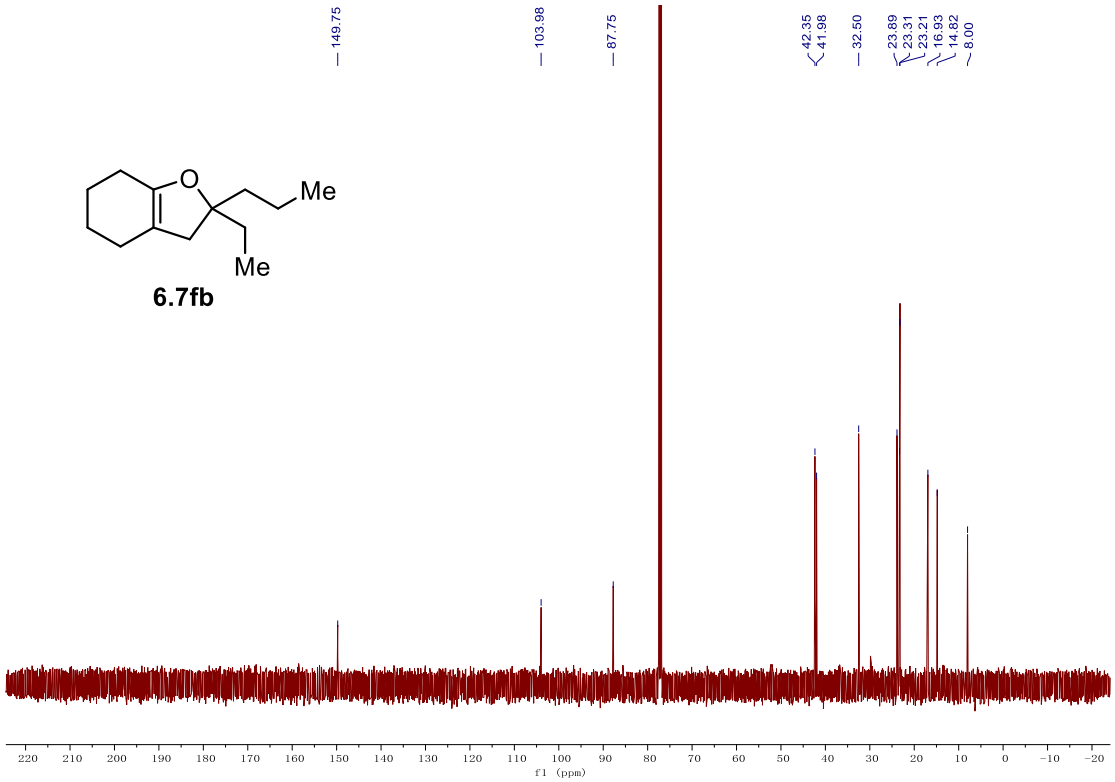


Figure 6.118 ^{1}H-NMR Spectrum of **6.7g**

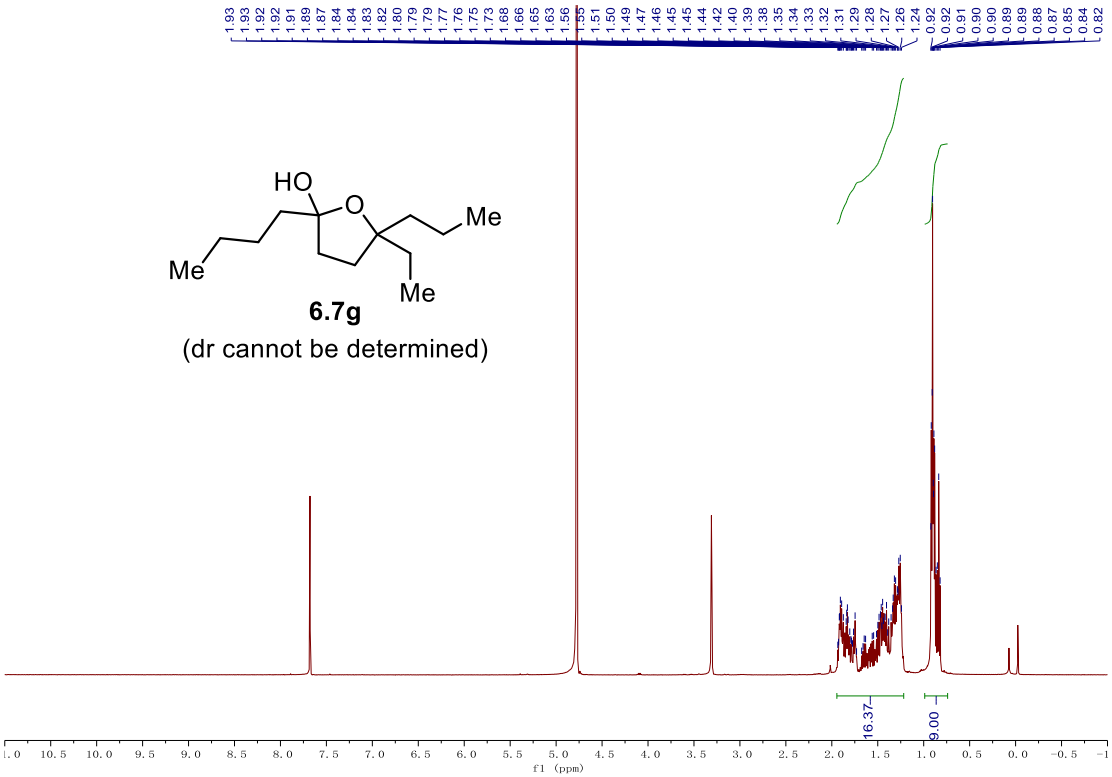


Figure 6.119 ^{13}C-NMR Spectrum of **6.7g**

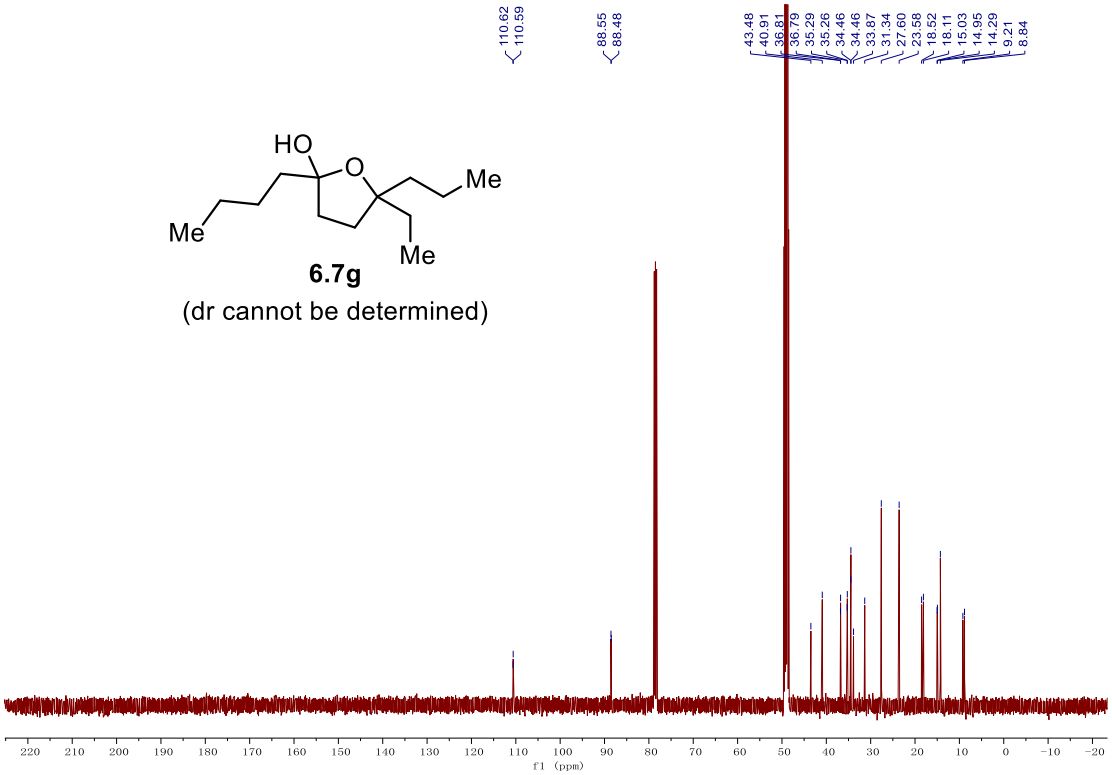


Figure 6.120 ^{1}H-NMR Spectrum of **6.7h**

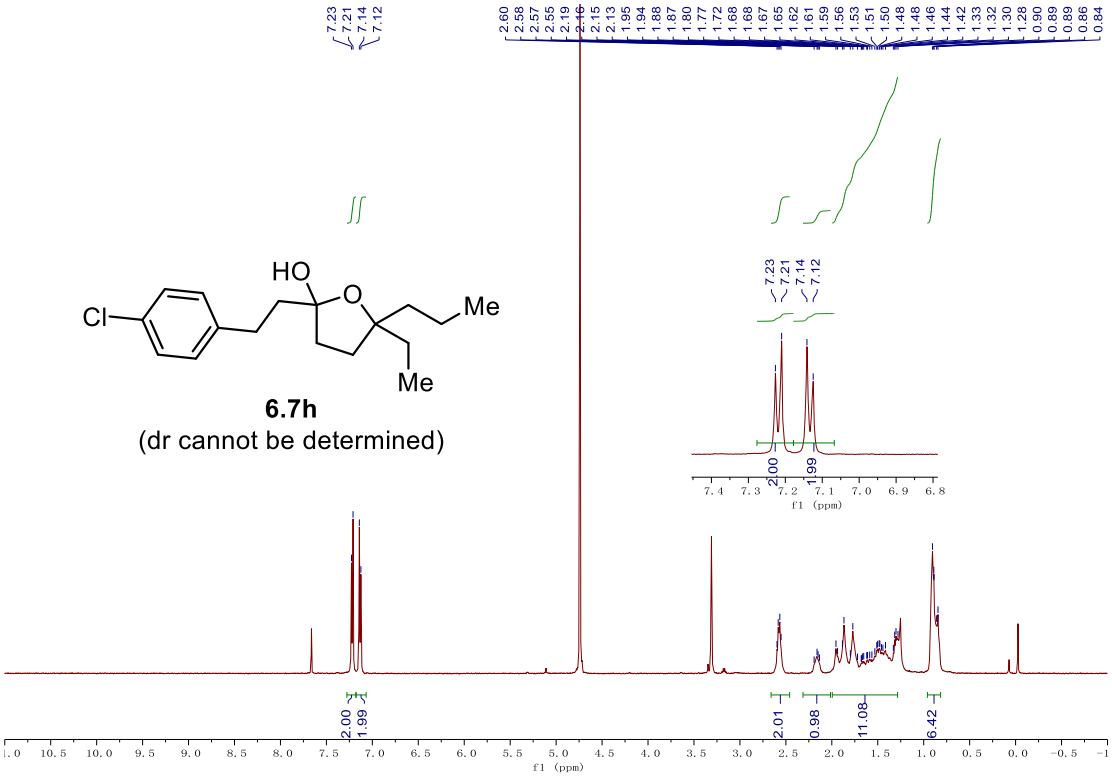


Figure 6.121 ^{13}C-NMR Spectrum of **6.7h**

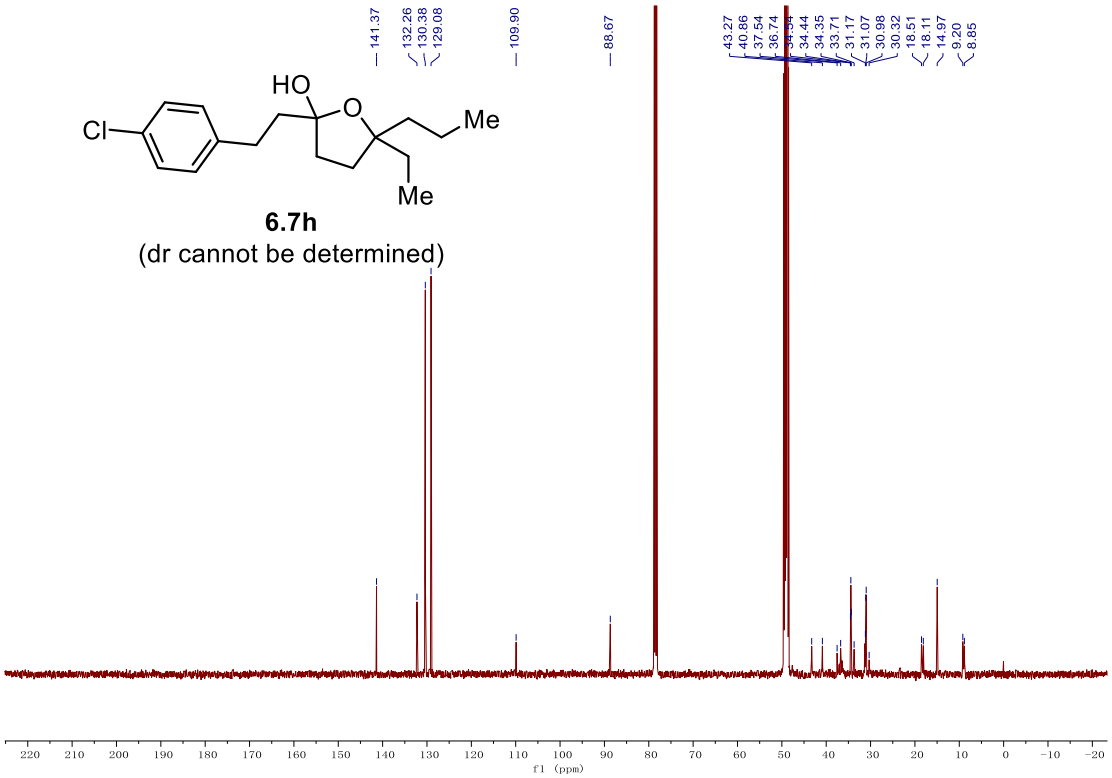


Figure 6.122 ^{1}H-NMR Spectrum of **d_9-6.3o**

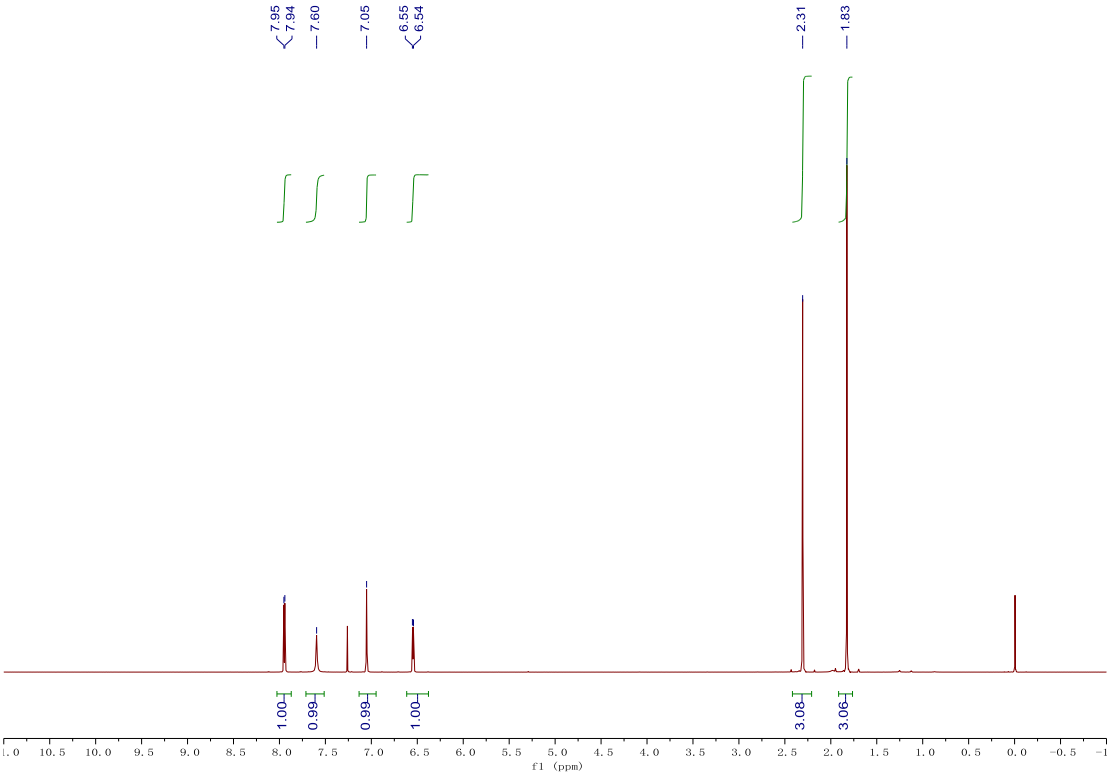


Figure 6.123 ^{13}C-NMR Spectrum of **d_9-6.3o**

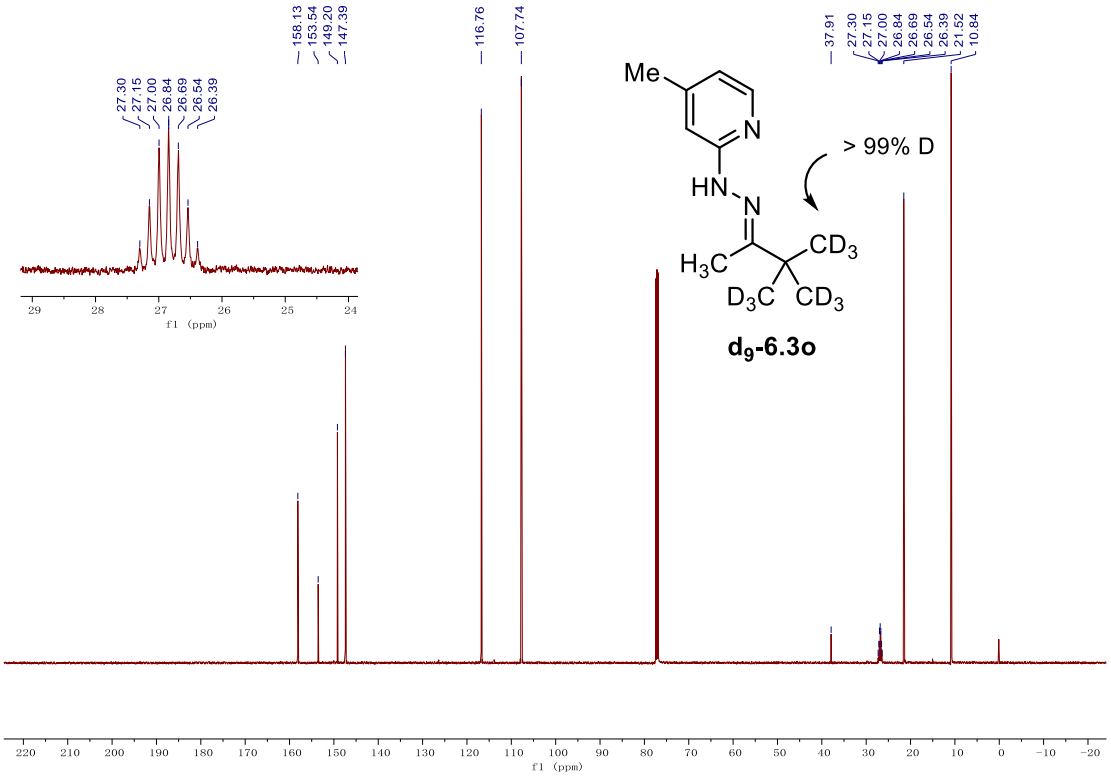


Figure 6.124 ^{1}H-NMR Spectrum of **d_9-6.5oa**

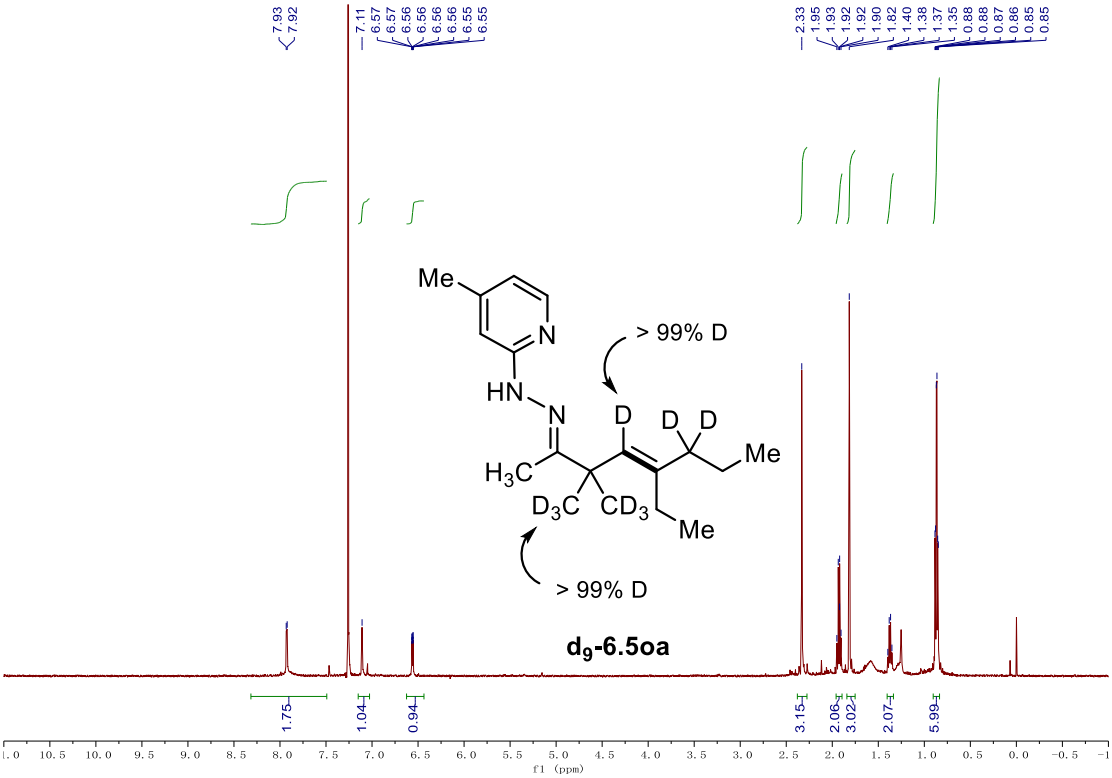


Figure 6.125 ^{1}H-NMR Spectrum of **d_9-6.5ob**

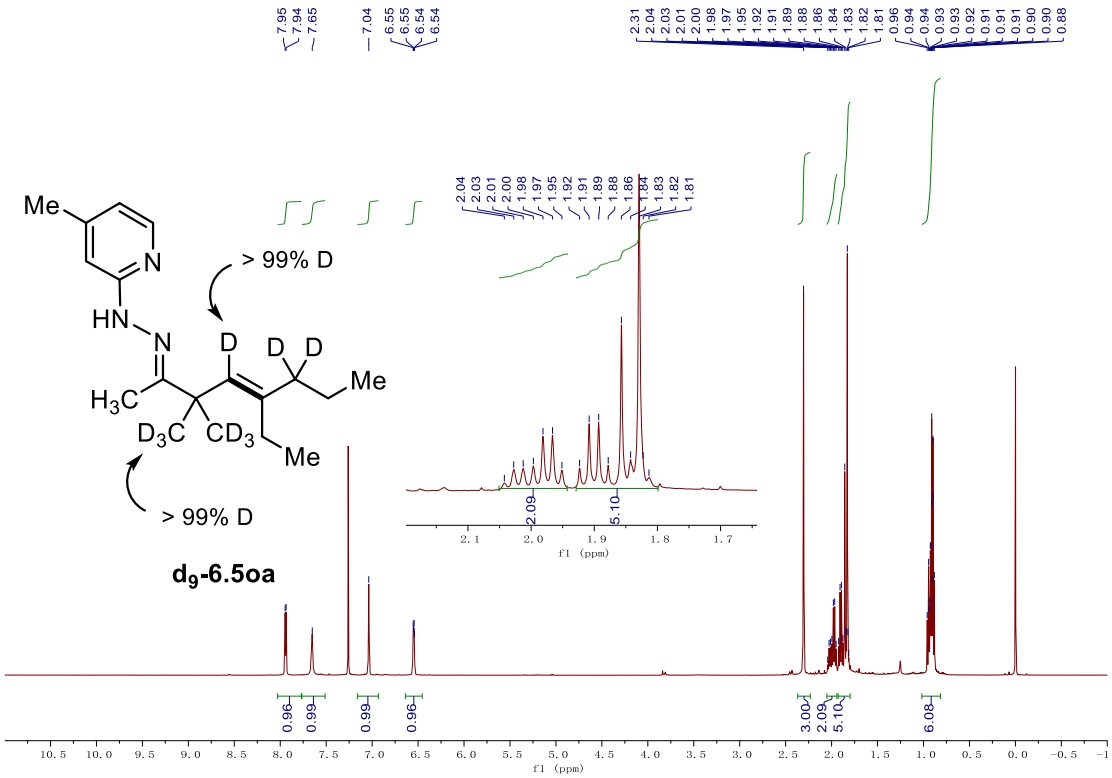
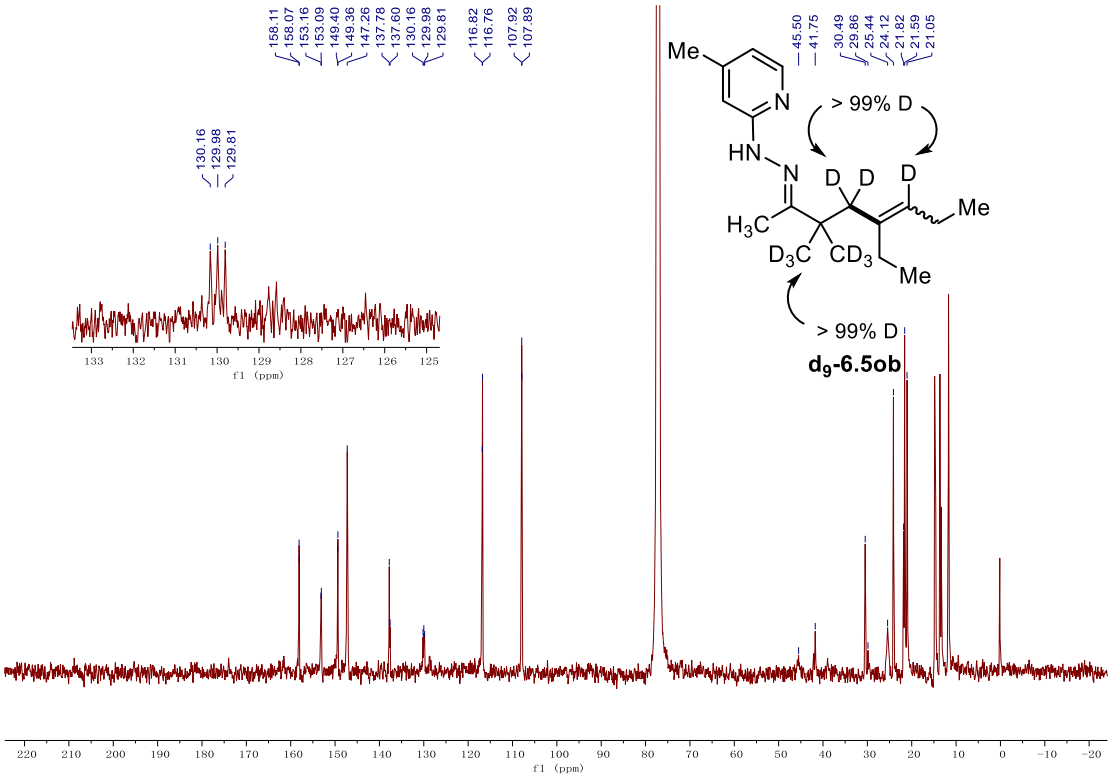


Figure 6.126 ^{13}C-NMR Spectrum of **d_9-6.5ob**



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CHAPTER 7

Aromatization-Promoted C−C Bond Activation of Unstrained Ketones

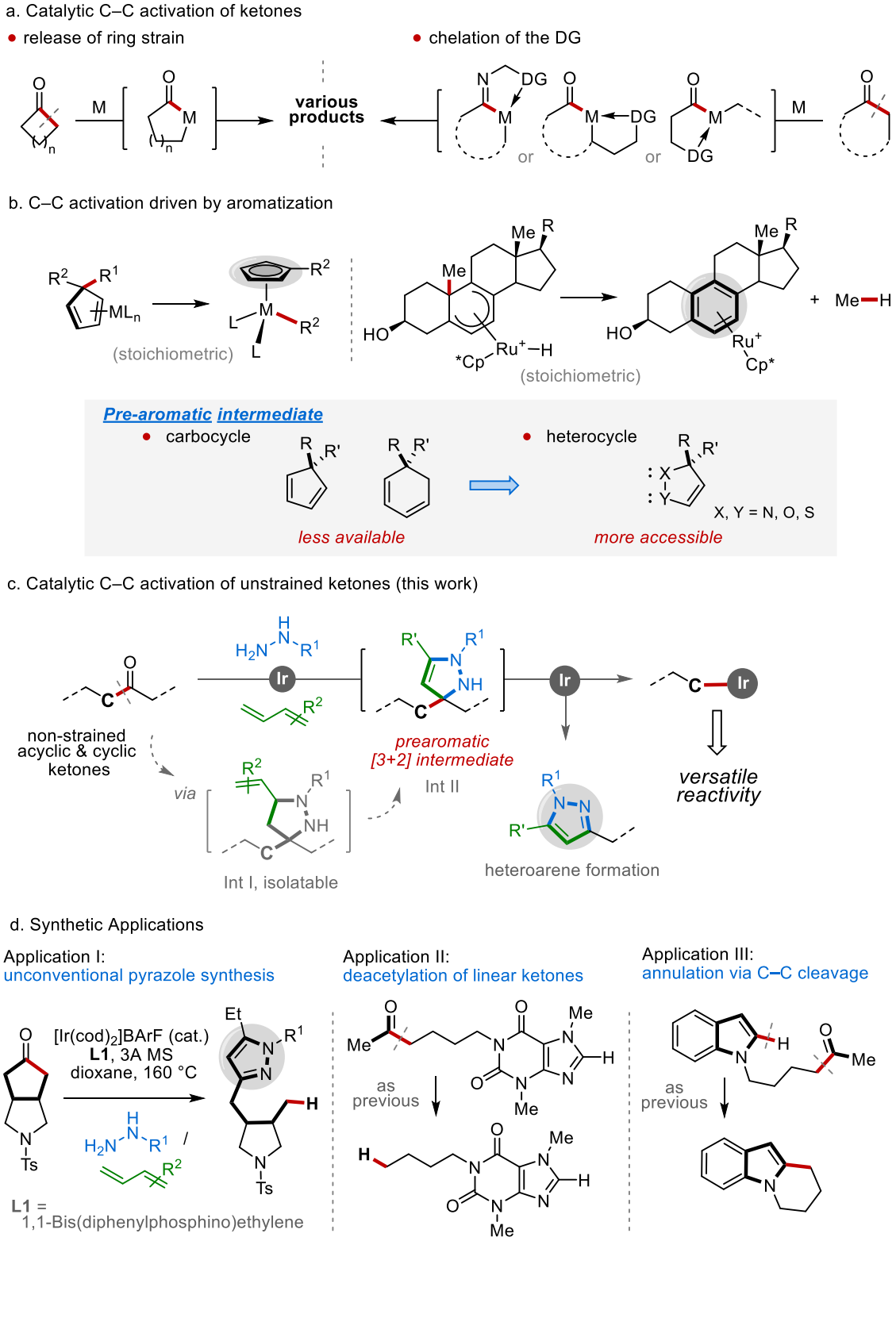
7.1 Introduction

The catalytic cleavages of carbon−hydrogen (C−H) and carbon−carbon (C−C) bonds have received drastically increased attention in recent decades, as they are generally the most abundant bonds in organic compounds, regardless for simple feedstock chemicals or complex drugs/natural products. The recent advancement of C−H functionalization technology has vastly expanded our tool box for efficient and selective manipulations of C−H bonds on molecular surfaces;[1-9] in contrast, widely applicable C−C activation methods that allow for selectively editing embedded molecular skeletons remain limited.[10-16] One attractive approach is to transform a relatively inert C−C single bond to a more versatile C−TM (TM: transition metal) bond that can be subsequently converted to other functional groups (FGs). To date, a number of methods have appeared for catalytic C−C activation, particularly for ketone substrates, which are typically promoted either by ring-strain release as a thermodynamic

driving force or by using auxiliary[17-19] or temporary directing groups[15] (DGs) to gain kinetic benefits (Scheme 7.1a). While they have effectively led to novel synthetic applications, these strategies require employment of ketone substrates that are highly strained, or contain a preinstalled DG, or can easily condense with 2-aminopyridines (e.g. *cyclopentanones*). To extend the synthetic utility of C−C activation, methods that activate a broad range of unstrained substrates would be very desirable.

On the other hand, the strategy of C−C activation driven by forming aromatic compounds, which has been known since 1972,[20] is largely underappreciated with scattered examples[21-25] (Scheme 7.1b). The approach usually uses a pre-aromatic substrate to complex with a low-valent TM, and subsequent C−C cleavage leads to stable arene-metal species, such as Cp-TM complexs (Cp: cyclopentadienyl).[20-23,25] However, to utilize such a strategy for catalytic synthetic applications,[26] *a number of challenges exist*. First, special high-energy pre-aromatic substrates, e.g. cyclopentadienes, are generally needed; thus, it is concerned that whether readily available compounds can be used as substrates with this approach. In addition, the aromatic products generated in this reaction typically coordinate strongly with TMs; thus, enabling catalyst turnover could be another issue.[20-23] Moreover, given the narrow reaction scope, developing attractive and synthetically valuable transformations with aromatization-driven C−C activation represent further difficulty.

Scheme 7.1 Catalytic C–C Activation of Ketones



In contrast to the less accessible carbocyclic pre-aromatics, a number of heterocycles, prepared from readily available chemicals through 1,3-dipolar addition,[27] can potentially serve as precursors to form heteroarenes. Thus, if heterocyclic pre-aromatics could be employed as key intermediates for aromatization-driven C−C activation, a distinct and synthetically impactful reaction mode can be imagined. In this chapter, we describes a new approach to activate α-C−C bonds of unstrained ketones,[15,28,29] which is promoted by forming aromatic heterocycles (Scheme 7.1c). The reaction involves an *in situ* three-component coupling among a ketone, a 1,3-diene and a substituted hydrazine to generate a dihydropyrazole intermediate that can subsequently undergo metal-mediated C−C cleavage to form a pyrazole and potentially an alky-TM species. Given the versatility of the alkyl-TM species, various products can be formed under different reaction conditions or with different substrates, leading to several interesting transformations, including (i) an unconventional three-component pyrazole synthesis, (ii) deacetylation of linear ketones, and (iii) C−H annulation through C−C cleavage (Scheme 7.1d).

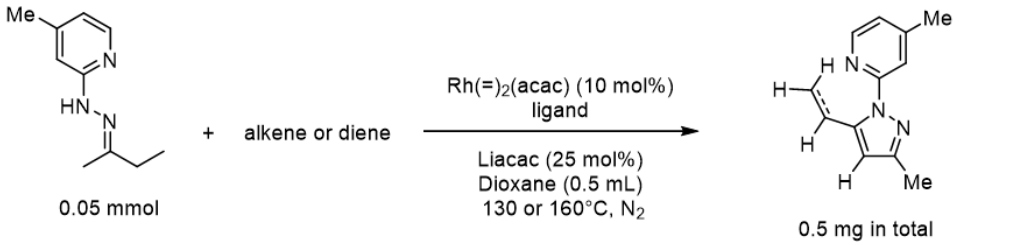
7.2 Results and Discussion

The initial reaction mode was discovered during our exploration of the Rh-catalyzed β-C−H functionalization of ketones with 1,3-butadiene using an *in situ* generated DG, in which a small amount of pyrazoles (ca. 5%) were surprisingly yielded as a side product.

The initial reaction mode was discovered during the development of ketone β C−H alkylation reactions by coupling ketone derivatives with alkenes and dienes (Scheme 7.2).[30] A

2-butanone derivative was used as the model substrate, and same as the Chapter 6, the $Rh(C_2H_4)_2(acac)$ was selected as the TM pre-catalyst. A variety of different alkenes and dienes, as well as several different types of representative ligands were screened orthogonally at 130 °C and 160 °C. While the desired C−H alkylation reaction was never observed, we were surprised to find that a small amount of pyrazoles (ca. 5%) was generated by using 1,3-butadiene as the coupling partner and Ruphos as the ligand (condition 53). After careful isolation, the structure was assigned. Similar reaction was also observed with some other Buchwald type ligands, such as in conditions 51, 52 and 54.

Scheme 7.2 Initial Hits of the Reactivity



	Ligand	IMes (10%)	XPhos (15%)	RuPhos (15%)	BrettPhos (15%)	JohnPhos (15%)	Me_2PPh (20%)	$CyPPh_2$ (20%)	PCy_3 (15%)
Alkene	Temp	Reaction							
*t*Bu 150 μL	130 °C	1	3	5	7	9	11	13	15
	160 °C	2	4	6	8	10	12	14	16
$Si(OMe)_3$ 150 μL	130 °C	17	19	21	23	25	27	29	31
	160 °C	18	20	22	24	26	28	30	32
Ph 150 μL	130 °C	33	35	37	39	41	43	45	47
	160 °C	34	36	38	40	42	44	46	48

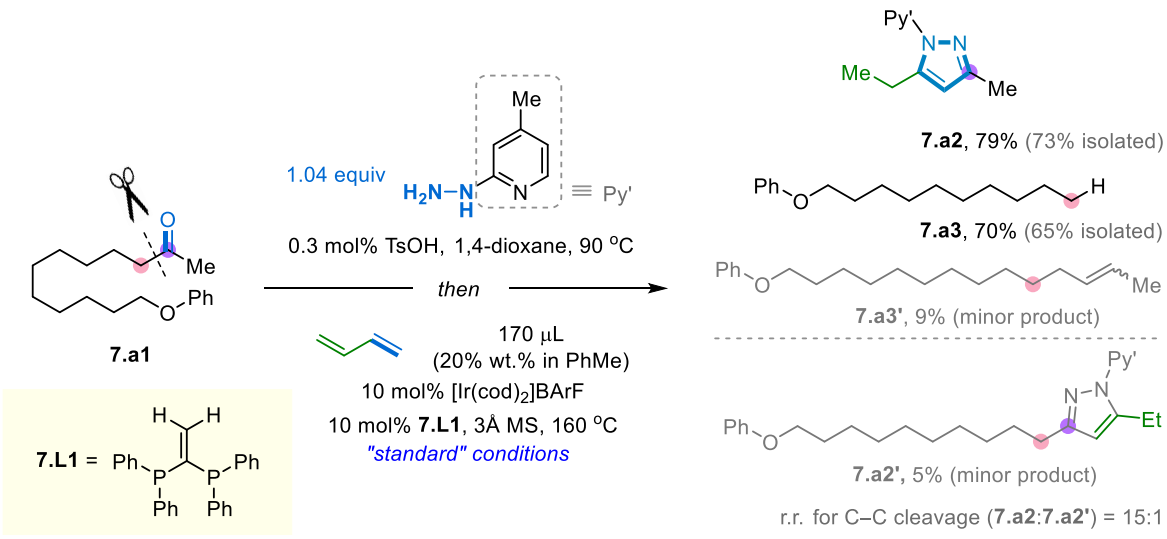
We propose that in this reaction 1,3-butadiene first undergoes [3+2] cycloaddition

with the hydrazone intermediate[31] to give pyrazolidine **Int I** (Scheme 7.1c),[32,33] and then the *exocyclic* double bond migrates to generate dihydropyrazole **Int II**, which is one unsaturation degree shy of an aromatic pyrazole structure. At this stage, a TM-mediated C−C cleavage occurs at the *tetra*-substituted carbon center to furnish the pyrazole product and a C−TM species that can undergo further diverse transformations, e.g. C−H and C−C bond formations.

To investigate and optimize this reaction, 12-phenoxydodecan-2-one (**7.a1**) was selected as the model substrate, and iridium was then found to offer a more efficient catalytic system than rhodium. After a systematic survey of reaction parameters, the ketone substrate, upon treatment with 4-methyl-2-pyridyl hydrazine and 1,3-butadiene in toluene, underwent efficient α-C−C bond cleavage using cationic $[Ir(cod)_2]BArF$ and *1,1-bis(diphenylphosphino)ethylene* as the optimal metal/ligand combination (Table 7.1). Pyrazole product **7.a2** was formed in 79% yield, along with deacetylation product **7.a3** in 70% yield, as the two major products. A minor deacylative crotylation product (**7.a3'**) was also observed in 9% yield. Resulted from cleavage at the alternative methyl side, compound **7.a2'** was isolated in 5% yield, which indicated >15:1 site-selectivity in the key C−C cleavage step favoring cleavage at the bulkier side (*vide infra*, Scheme 7.4 for more examples).[34] A number of control experiments were then carried out to probe the role of each reactant (Table 7.1). Unsurprisingly, the cationic Ir catalyst was indispensable (entry 1); in contrast, a neutral Ir complex gave no conversion of the hydrazone (entry 2), and the cationic Rh was much less efficient (entry 3). Omitting or replacing **7.L1** with either monodentate PPh_3 or bidentate dppe ligands resulted in dramatically decreased reactivity (entries 4-6). The pyridyl moiety in hydrazine was also found to be critical for this transformation, as replacing

the pyridyl group with a phenyl group led to no conversion of the hydrazone intermediate. It is likely that the pyridyl moiety chelates with the cationic Ir catalyst thereby promoting the [3+2] cycloaddition with 1,3-diene.[32] High reaction conversion can be obtained at 130 °C albeit with diminished selectivity due to the formation of more C–C coupling product **7.a3'** (entry 7). Finally, use of the pre-formed hydrazone directly as the substrate gave comparable yields and similar product distribution (entry 8), supporting hydrazone to be an intermediate for this reaction.

Table 7.1 Reaction Optimization[a]

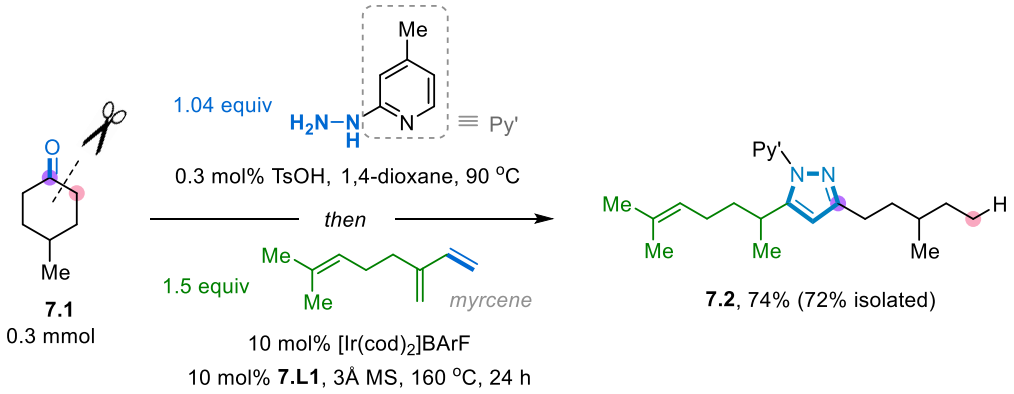


entry	deviation from above	yield **7.a2** (%)[b]	**7.a3** (%)[b]	entry	deviation from above	yield **7.a2** (%)[b]	**7.a3** (%)[b]
1	without Ir	0	0[c]	5	with PPh_3	3	3[c]
2	with $[Ir(cod)Cl]_2$	0	0[c]	6	with dppe	20	16[d]
3	with $[Rh(cod)_2]BF_4$	14	13[d]	7	130 °C	83	56[e]
4	without **7.L1**	12	11[d]	8	using pre-formed hydrazone	79	72

[a] The reactions were conducted with 0.05 mmol **1**, 0.05 mmol of 4-methyl-2-pyridyl hydrazine, and 0.5 mmol 1,3-butadiene. Due to the volatility of 1,3-butadiene, 10 equiv was used. [b] Determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard. [c] The hydrazone of **1** was recovered in > 90% yield. [d] The hydrazone of **1** was recovered in > 70% yield. [e] 26% of **3'** was generated. r.r., regioselectivity ratio. cod, 1,5-cyclooctadiene. dppe, 1,2-bis(diphenylphosphino)ethane; Py', 4-methyl-2-pyridyl.

Noting that a large excess of 1,3-butadiene (ca. 12 equivalent) was used in the reaction, possibly due to it volatility, we were wondering whether a smaller diene loading could be used when heavier 1,3-diene was employed. Indeed, by increasing the reaction concentration, the α C−C bond of ketone **7.1** could be readily cleaved, furnishing pyrazole **7.2** in 74% yield by only using 1.5 equivalent of *myrcene* as the 1,3-diene coupling partner.

Scheme 7.3 Optimal Condition When Using Non-volatile 1,3-Dienes

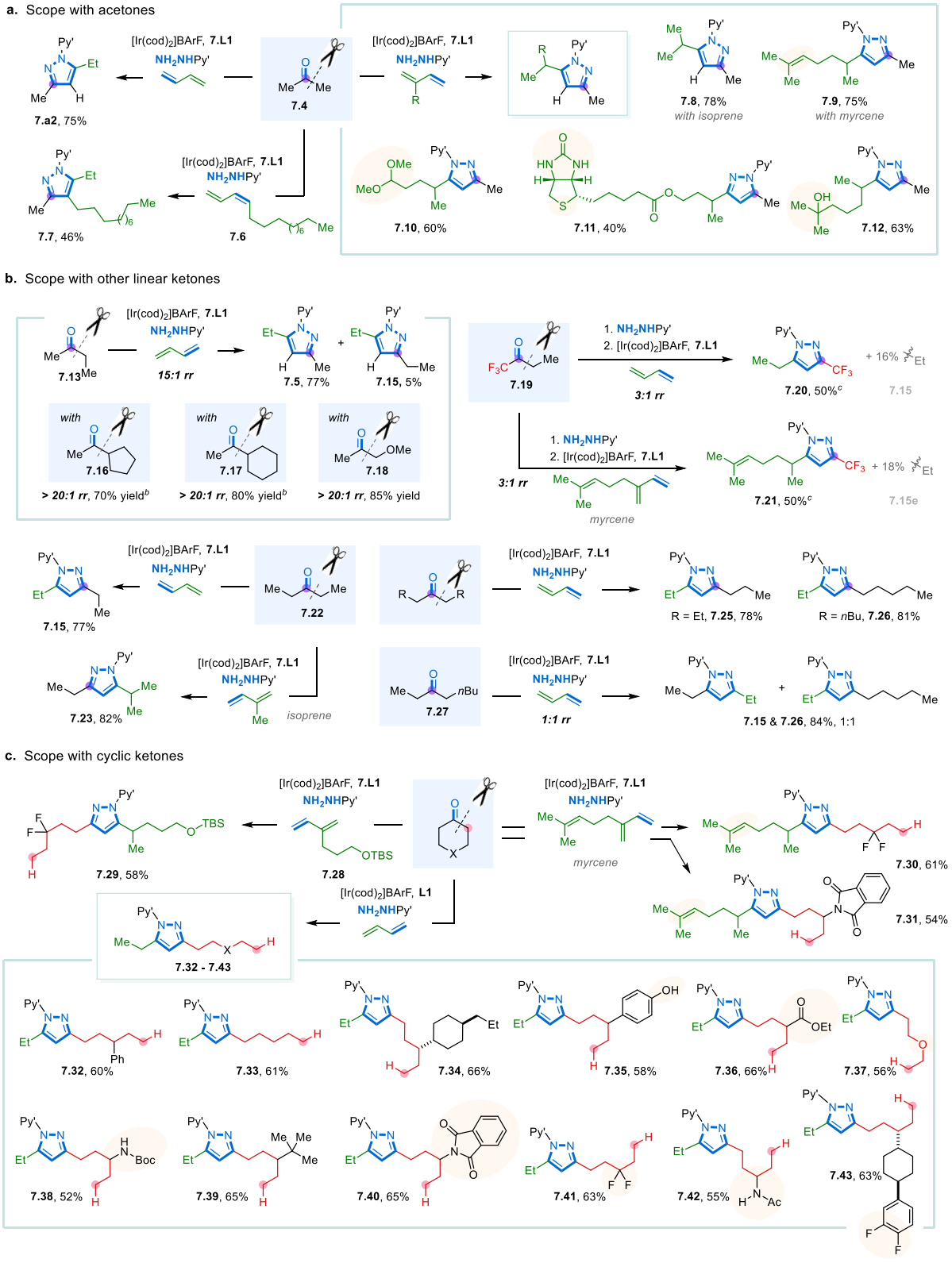


The scope of the reaction was next examined under the optimized C−C cleavage conditions (Scheme 7.4). Gratifyingly, both *linear* (Schemes 7.4a/b) and *cyclic* ketones (Scheme 7.4c) with different substitutions delivered the desired pyrazoles as the C−C cleavage products. The *site-selectivity* for the C−C cleavage is rather intriguing. For unsymmetrical ketones, the cleavage tends to occur at more substituted carbons.[33] For instance, the scission with methyl ketones generally favors at the non-methyl side, furnishing pyrazole **7.5** in good yields and >15:1 selectivity; from the prospect of the cleaved non-methyl fragments that generally got protonated during the reaction, the reaction can be considered as a de-acetylation process (*vide infra*). The similar trend on site-selectivity was also observed with cyclic ketones, such as 3,3-dimethylcyclohexanone **7.48.** If one of the two

C−C bonds to be cleaved is at a benzylic position or α to a heteroatom (**7.52**), breaking of these weaker bonds took place dominantly. For example, β-tetralones are excellent substrates giving complete site-selectivity at the benzylic C1−C2 position (**7.56-59**). In addition, removal of an ethyl group is favored over a CF_3 group (**7.19**). Unsurprisingly, no selectivity was observed between an ethyl and an *n*-butyl group (**7.27**).

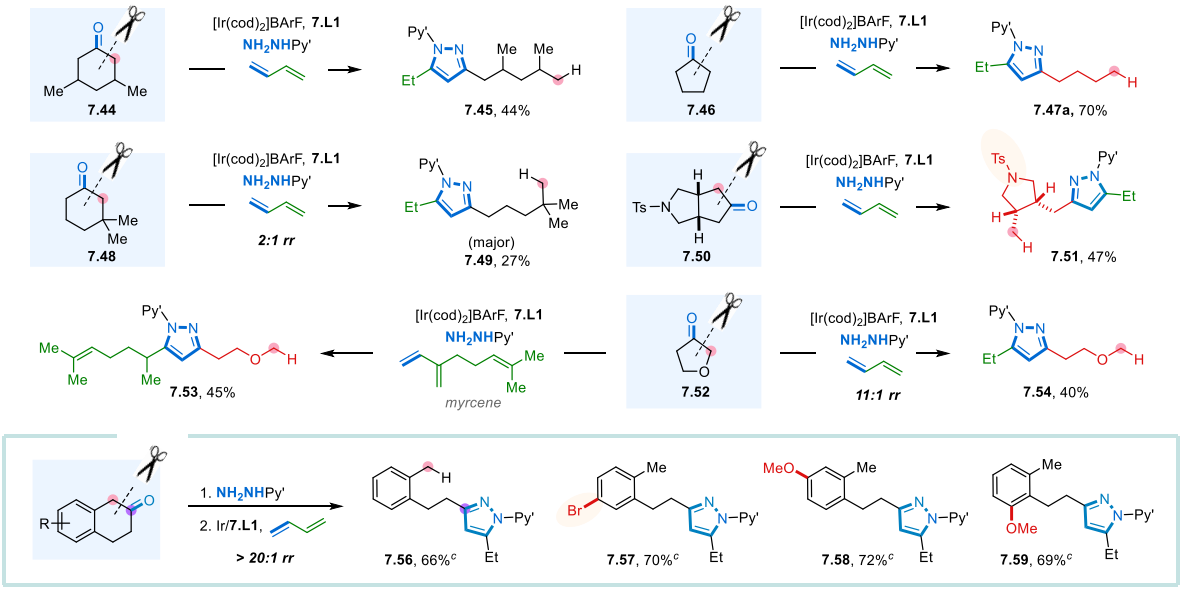
On the other hand, symmetrical ketones, including acyclic ketones, substituted cyclopentanones and cyclohexanones, are all competent substrates, forging various structurally complex pyrazoles in good efficiency. Ketones featuring oxygen heterocycles, such as dihydrofuran-3(2*H*)-one (**7.52**) and tetrahydro-4*H*-pyran-4-one (**7.37**), reacted as well. A variety of different dienes, such as 1,3-butadiene, *isoprene*, *myrcene*, and other functionalized 1,3-dienes, could be readily coupled to introduce different substitution patterns. While the terminal 1-substituted 1,3-dienes (e.g. **7.6**) led to 3,4,5-trisubstituted pyrazoles (**7.7**), simple and 2-substituted 1,3-dienes furnished 3,5-disubstitued pyrazoles in high efficiency (Scheme 7.4a). Given that the reaction conditions are redox-neutral and strong acid/base-free, many functional groups were well tolerated, including trisubstituted olefins (**7.9**), aryl bromides (**7.57**), free and protected alcohols (**7.12** and **7.29**), free phenols (**7.35**), thioethers (**7.11**), dimethyl acetals (**7.10**), Ac- and Boc-protected amines (**7.42** and **7.38**), phthalimides (**7.40**), sulfonamides (**7.50**), esters (**7.36**), ethers (**7.37** and **7.58**), aliphatic and aromatic fluorides (**7.20**, **7.30** and **7.43**), and ureas (**7.11**).

Scheme 7.4 Application I: Pyrazole Synthesis through Aromatization-driven C−C Cleavage



Scheme 7.4 Application I**:** Pyrazole Synthesis through Aromatization-driven C−C Cleavage

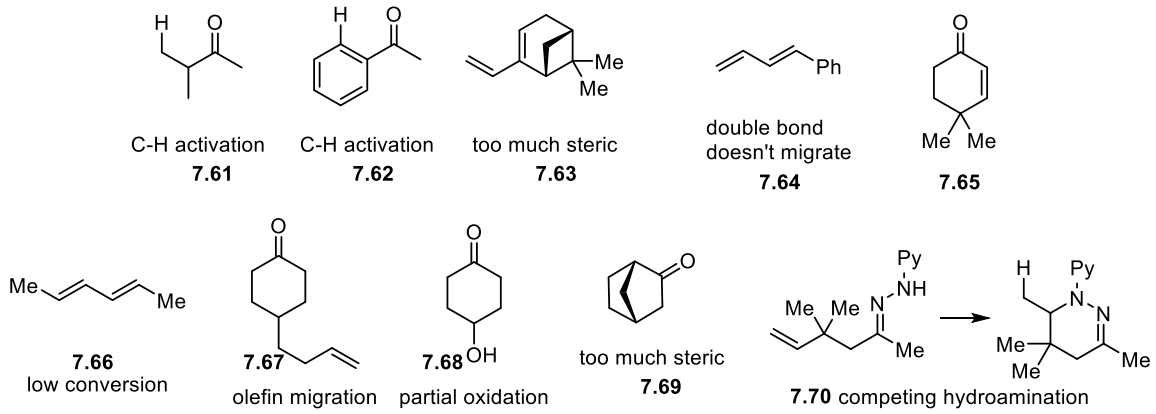
(continued)



[a] All yields are isolated yields. [b] The reaction was conducted using (2-(4-methoxyphenyl)ethene-1,1-diyl)bis(diphenylphosphane) instead of **7.L1** as the ligand. [c] Yields refer to the key C−C activation reaction using pre-formed hydrazone as the substrate.

Some failed examples were listed in Scheme 7.5. When *ortho* sp^2 or β methyl sp^3 C−H bonds are available, dramatically decreased reactivity was observed, possibly due to the formation of a tridentate Ir-complex through competing C−H activation. With diene **64**, as the double bond in the [3+2] intermediate tends not to migrate due to the nearby phenyl group, no desired product was observed. Enone substrates were not compatible (**65**), as well as internal 1,4-dienes (**66**). FGs that are sensitive to Ir-catalyzed side reactions, such as olefin migration or transfer hydrogenation, were not tolerate, such as terminal olefins (**67**) and alcohols with α-hydrogen (**68**). A sluggish reaction was observed with norcamphor (**69**) possibly due to the steric. Finally, a competing hydroamination reaction took place dominantly with alkenyl ketone **70.**

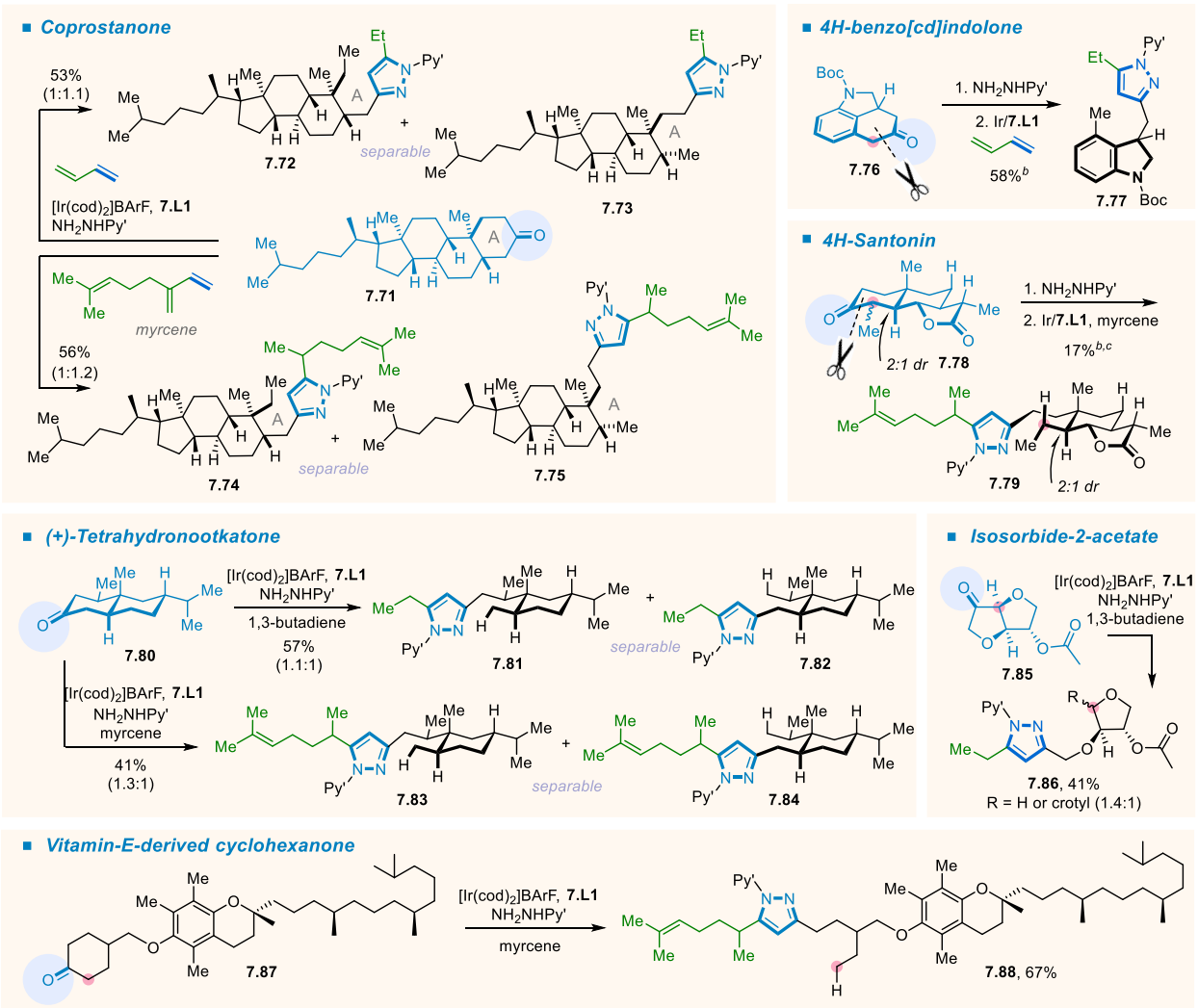
Scheme 7.5 Selected Examples of Failed Substrates



As a highly important class of pharmacophores, pyrazoles are commonly found in bioactive compounds and approved drugs[34], e.g. *Celecoxib*, *Rimonabant*, *Fomepizole* and *Sildenafi.* While a number of methods have been developed for pyrazole synthesis, two general approaches include (a) condensation between hydrazine and 1,3-dicarbonyl or ynone compounds (Knorr pyrazole synthesis) and (b) cycloaddition between diazo compounds and Michael accepters.[35] Compared with the conventional pyrazole synthesis methods,[34,35] this approach only requires a mono-ketone FG to be used as a handle. Thus, it could provide a straightforward and distinct strategy to introduce pyrazole moieties into complex natural products or biologically interesting scaffolds. As a proof of concept, a variety of ketone-containing natural products and advanced synthetic intermediates were subjected to the optimized reaction conditions (Scheme 7.6). To our delight, in all the cases, the pyrazole derivatives were rapidly constructed via cleaving the ketone-containing rings in the presence of different FGs and chemical environments. In addition, simply by switching the 1,3-diene coupling partners, several structurally related, separable pyrazole-derived analogues were rapidly made available in a single step from *(+)-tetrahydronootkatone* and *coprostanone.*

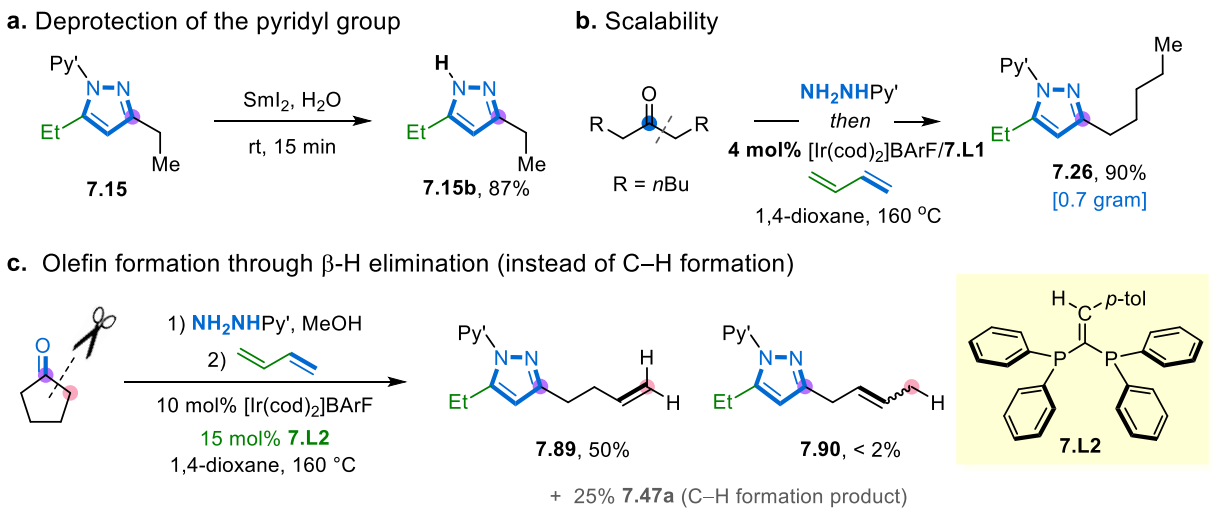
Thus, it offers a diverse, late-stage "pyrazolization" from complex ketones. Given that pyrazole derivatives are known to exhibit a broad spectrum of biological activity and mono-ketone moieties are prevalent in complex molecules or readily accessible from other FGs, this C−C activation method might become a useful tool of preparing novel pyrazole-containing analogues for pharmaceutical or agrochemical research.

Scheme 7.6 Conversion of Complex Ketones into Pyrazoles



The 2-pyridyl moiety on the pyrazoles could be readily removed using SmI_2 and water, furnishing free pyrazole products in a high yield (Scheme 7.7a). Also, the catalyst loading for this transformation could be reduced to *4 mol% on larger scales,* where 0.7 gram of product **7.26** was isolated in an even higher yield (90% *vs* 81% on a smaller scale, Scheme 7.7b). Finally, using a new bisphosphine ligand **7.L2** that was recently prepared in our laboratory, olefin **7.89** was found to be the major product isolated from the reaction (Scheme 7.7c), which indicates that β-hydrogen elimination was favored instead of the protonation of the resulting putative alkyl−Ir species. While the yield and selectivity of this preliminary result remain to be further improved, it nevertheless shows promise for enabling diverse transformations of the alkyl fragment after C−C cleavage.

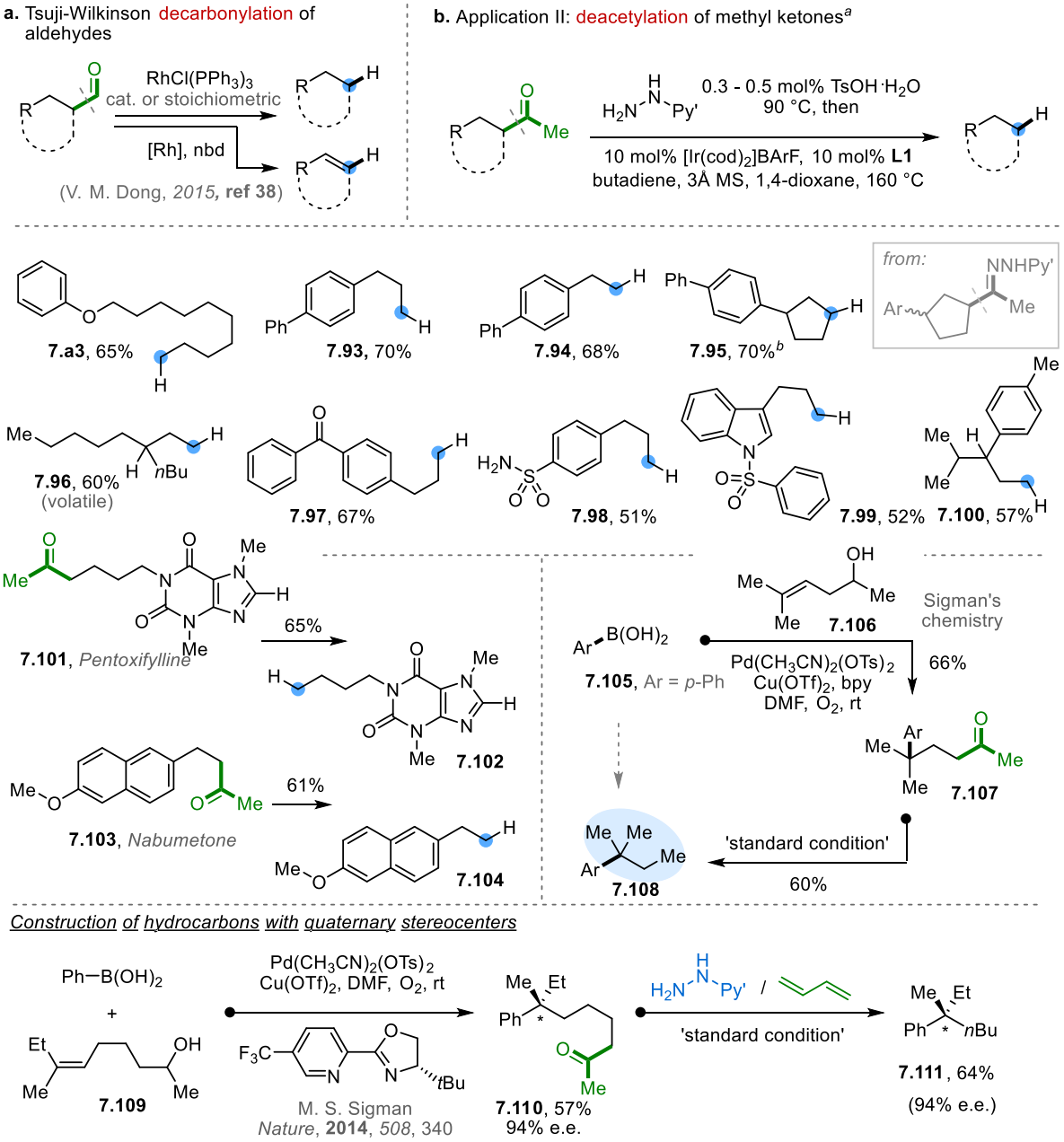
Scheme 7.7 Further Investigation of the Pyrazoles Synthesis



Another synthetic utility of this method involves deacetylation of linear ketones. In term of a brief introduction of the background, the Tsuji−Wilkinson decarbonylation of

aldehydes has been frequently employed in complex molecule synthesis,[36, 37] and recently a transfer hydroformylation approach to access unsaturated products was reported by Dong and coworkers[38] (Scheme 7.8a). The related deacetylation, namely the removal of an acetyl group from the substrate, will be synthetically valuable from a strategic viewpoint, which, however, remains an elusive transformation. Encouraged by excellent site-selectivity for the aromatization-promoted C−C activation of methyl ketones, we foresaw an opportunity of exploiting this method to realize a general deacetylation strategy (Scheme 7.8b). Indeed, when various structurally diverse methyl ketones were subjected to the optimized C−C cleavage conditions, the deacetylation took place smoothly with C−H formation at primary or cyclic secondary positions. Notably, when two ketone carbonyl groups are present in the substrate, the C−C cleavage occurred selectively at the methyl ketone moiety while the benzophenone moiety remained untouched (**7.97**). In addition, more FGs, such as primary sulfonamides (**7.98**), and heteroarenes, such as indole (**7.99**) and purine (**7.102**), were found compatible. This approach holds promise for post-modification of bioactive compounds. For example, anti-inflammatory drugs with methyl ketone motifs, such as *Pentoxifylline* (**7.101**) and *Nabumetone* (**7.103**), underwent facile C−C cleavage to generate deacetylated analogues. Furthermore, *tert*-amylation of arenes is nontrivial *via* direct cross coupling approaches,[39] but it can be realized through first coupling of aryl boronic acid **7.105** with 5-methylhex-4-en-2-ol using Sigman's redox-relay oxidative-Heck reaction[40] followed by this deacetylation reaction. Finally, enantioselective construction of hydrocarbon quaternary stereocenters that lack nearby polar FGs[41] (**7.111**) was also achieved using a similar strategy.[40]

Scheme 7.8 Application II: Deacetylation of Methyl Ketones

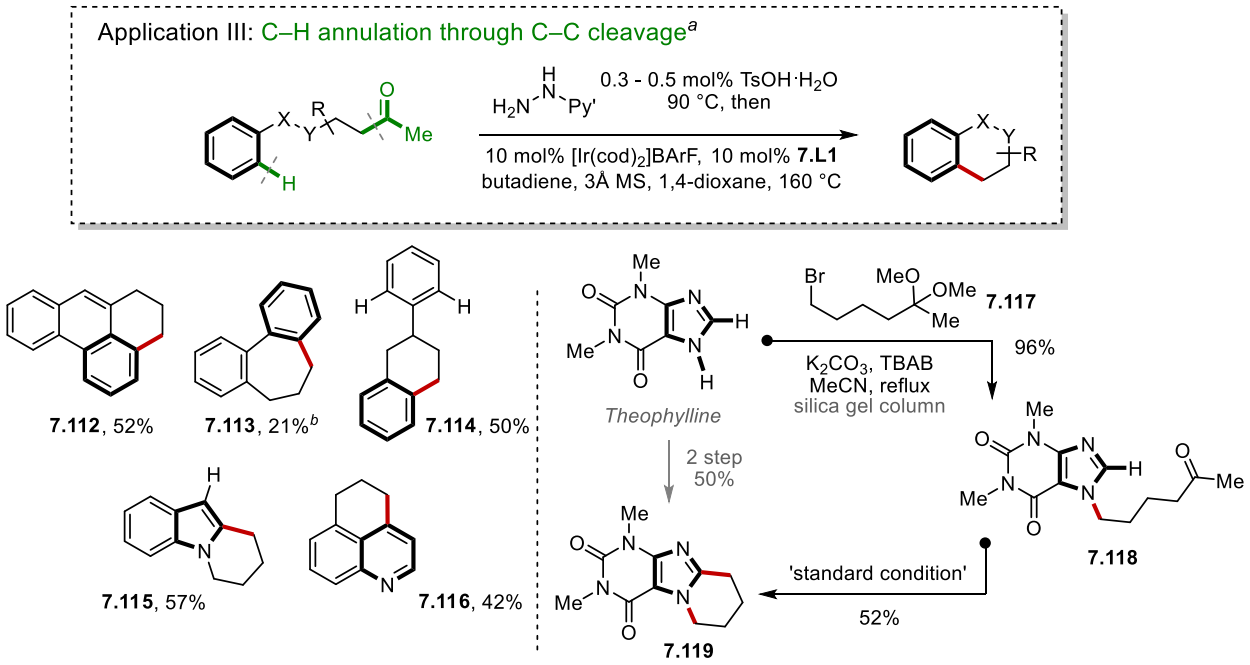


[a] All yields are isolated yields based on average of 2 runs. [b] The reaction was conducted using dppm instead of **7.L1** as the ligand and the pre-formed hydrazone as the substrate. nbd, norbornadiene.

Furthermore, an intriguing deacetylative C−H annulation reaction[33,42,43] was observed when arenes were placed in a proper distance from the ketone moieties (Scheme 7.9). Various arene-fused cyclohexane skeletons were forged through C−C bond formation

between arene *ortho*-positions and ketone α-terminus, which serves as a distinct approach to construct fused ring systems. Strong preference in forming six- over five-membered rings was observed (**7.114**), though the exact reason is unclear yet. When it was impossible to form six-membered rings, seven-membered rings (**7.113**) was also formed albeit in a lower yield. In addition to simple benzenes, polyarenes (**7.112**), as well as electron-rich and -poor heteroarenes (e.g. indole **7.115** and pyridine **7.116**), are all competent substrates. To further highlight the utility of this method, a rapid installation of a four-carbon linkage between the 9- and 8-positions of *Theophylline* was smoothly realized (**7.119**), which represents a distinct, rapid and redox neutral approach to derivatize bio-interesting molecules.[44]

Scheme 7.9 Application III: The Deacetylative C−H Annulation through C−C Cleavage

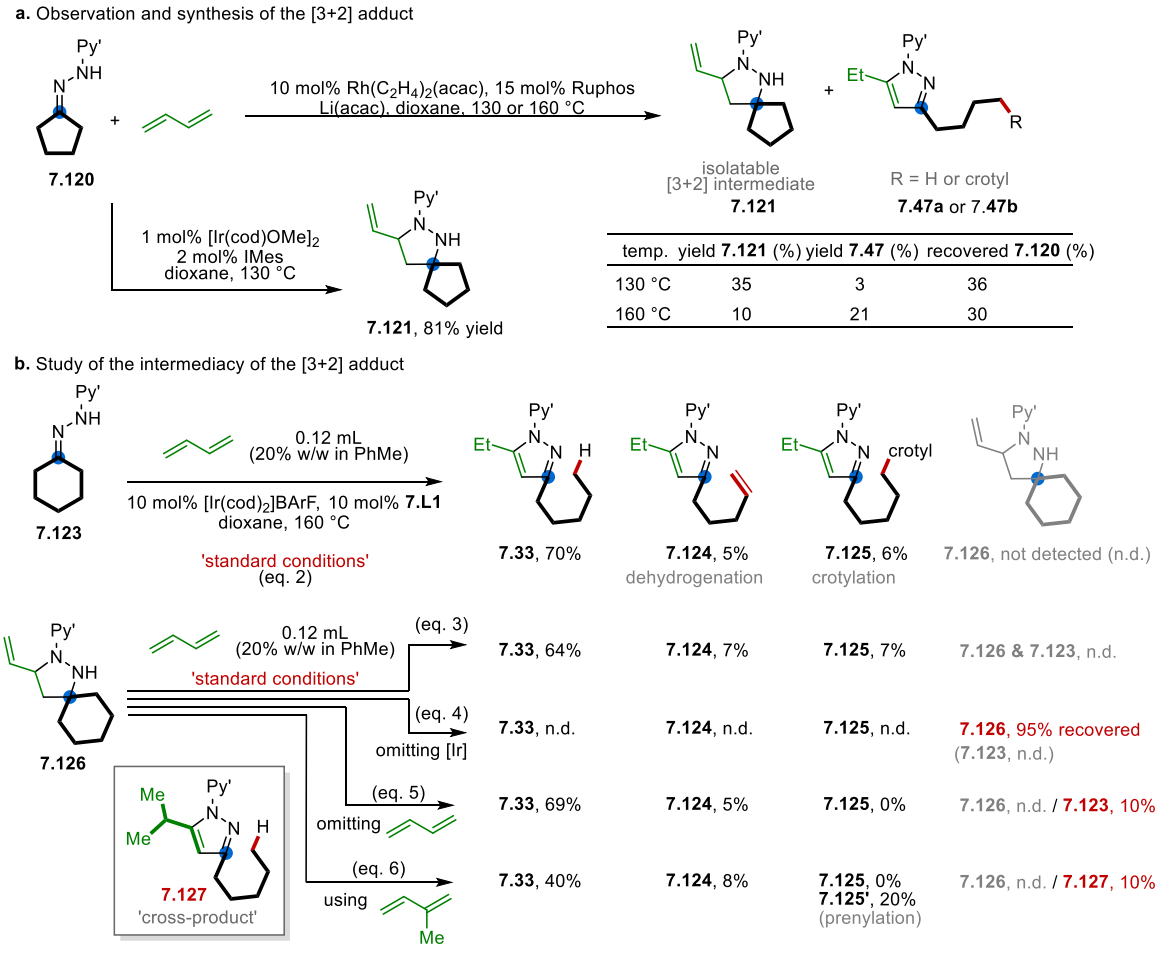


[a] All yields are isolated yields based on average of 2 runs. [b] 2-Propyl-1,1'-biphenyl (the regular deacetylation product) was also obtained in 45% yield.

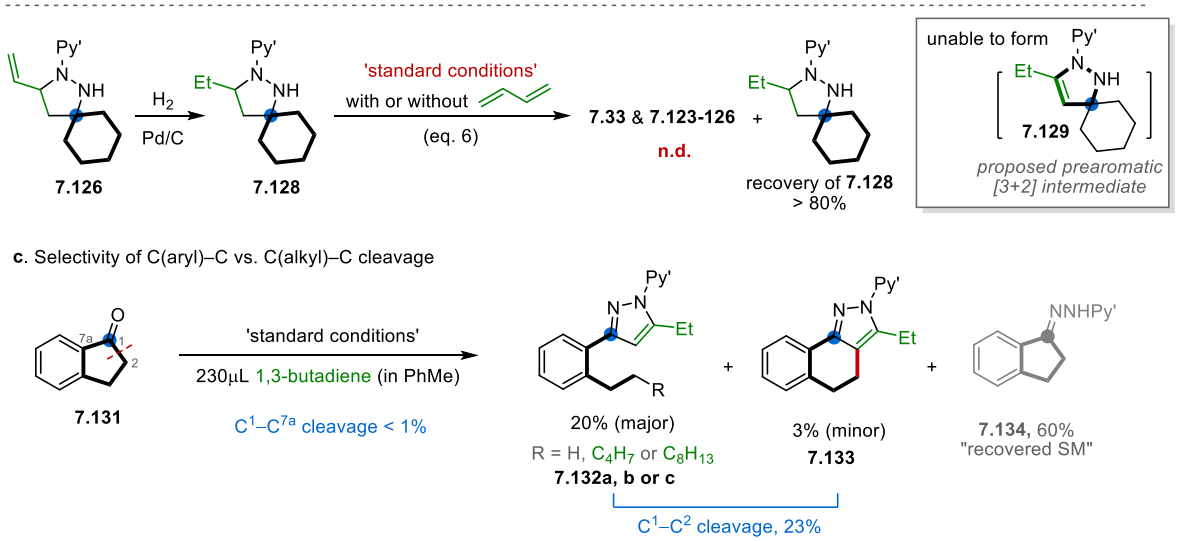
Preliminary mechanistic studies were carried out to elucidate the primary pathway of this C−C activation reaction (Scheme 7.10). First, the [3+2] pyrazolidine adducts between hydrazones and 1,3-dienes were frequently observed during the condition optimizations with various Rh and Ir catalysts (Scheme 7.10a). For instance, using $Rh(C_2H_4)_2(acac)$ and Ruphos, pyrazolidine **7.121** was observed in 35% yield along with a trace amount of C−C cleavage products (**47**) at 130 °C, while at 160 °C pyrazole **47** became the major product with pyrazolidine **7.121** being observed in 10% yield. **7.121** could also be isolated in a high yield by using $[Ir(cod)OMe]_2$/IMes as a catalyst. A set of control experiments were then conducted to elucidate the intermediacy of the [3+2] adduct (Scheme 7.10b). Cyclohexanone-derived substrate was chosen due to the convenience of identifying the series of products generated in this reaction. Under the "standard" conditions, using either hydrazone **7.123** or pyrazolidine **7.126**, the C−C cleavage reaction occurred to give similar yields and distributions of products (eqs. 2 and 3). In the absence of the Ir catalyst, no reaction was observed with the [3+2] adduct, suggesting that Ir is indispensible in the C−C cleavage step (eq. 4). As the diene fragment has already been incorporated into the [3+2] adduct, omitting 1,3-butadiene from the standard condition still furnished pyrazole product **7.33** in high efficiency; interestingly, under such conditions hydrazone **7.123** was formed in 10% yield, indicating that *the [3+2] cycloaddition is reversible* (eq. 5). The reversibility was further confirmed by the observation of the "*cross-product*" **7.127** by treating the 1,3-butadiene-derived **7.126** with isoprene under otherwise identical conditions (eq. 6). No C−C cleavage was observed when the hydrogenated pyrazolidine (**7.128**) was used as the substrate (eq. 7); in the absence of the olefin moiety, the proposed pre-aromatic intermediate cannot be formed through olefin

migration, therefore supporting that *the C−C cleavage is driven by aromatization*. Finally, the C−C cleavage step also seems to be distinct from a typical TM-mediated β-carbon elimination process.[45,46] When using 1-indanone as the ketone substrate, no C−aryl cleavage was observed, indicating that the C−alkyl bond is preferred to be cleaved than the C−aryl bond from the key pre-aromatic intermediate (Scheme 7.10c); in contrast, β-carbon elimination normally favors cleavage of a C−aryl bond in less strained systems.[47] Altogether, the reaction pathway is consistent with the proposal depicted in Scheme 7.1c, which involves a reversible [3+2] cycloaddition, followed by olefin migration to generate a dihydropyrazole intermediate, and C−C cleavage to give aromatic products.

Scheme 7.10 Preliminary Mechanistic Investigation

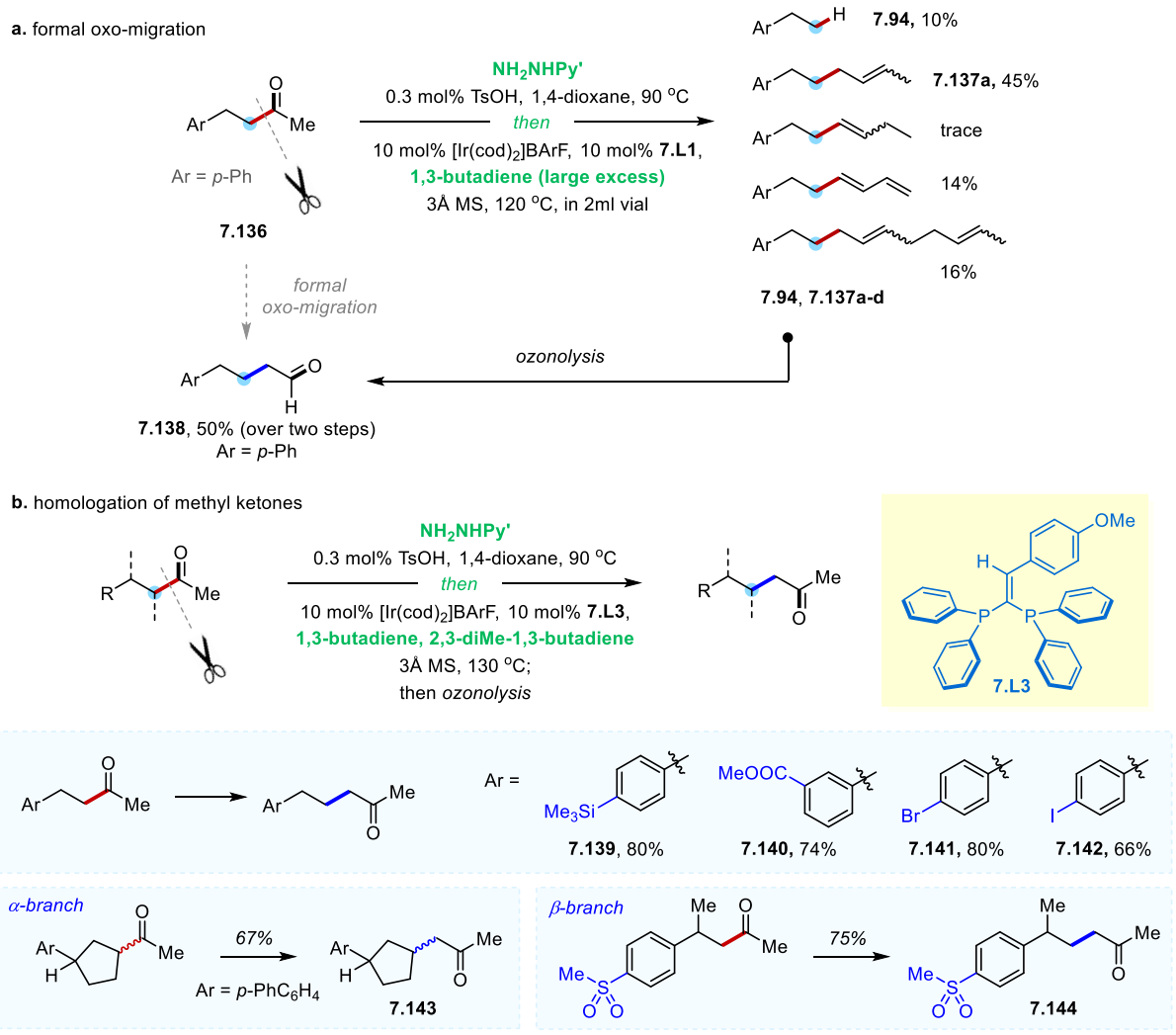


Scheme 7.10 Preliminary Mechanistic Investigation (continued)



Lastly, in this aromatization-driven C−C activation, a C−C single bond is hypothetically transformed into a C−Ir bond; thus, unsurprisingly, in the presence of large excess of 1,3-dienes at a lower reaction temperature (*vide supra*, Table 7.1, entry 7), the deacetylative crotylation instead of protonation became the dominant pathway. Using ketone **7.136** as the substrate, a formal "*oxo*-migration", relocating the carbonyl moiety from the internal to the terminal position, was realized through the deacetylative C−C coupling followed by ozonolysis (Scheme 7.11a). Besides, we recently found that by using a combination of 1,3-butadiene and 2,3-dimethyl-1,3-butadiene as a "diene combination" and **7.L3** as the optimal ligand, followed by ozonolysis, a two-step homologation of methyl ketones could be realized in high yield. Preliminary study of the substrate scope demonstrated the tolerance of aryl bromides **(7.141)**, iodides **(7.142)** and silanes **(7.139)**, as well as α- **(7.143)** and β-branch **(7.144)** of the ketones (Scheme 7.11b). Further investigation into this transformation is currently on the way.

Scheme 7.11 Preliminary Study for "Oxo-migration" and Homologation of Methyl Ketones



7.3 Conclusions

In this chapter, a new mode for the C−C cleavage of unstrained ketones was achieved with Ir catalysis driven by the aromatization of a [3+2] cycloaddition intermediate derived *via* a three-component reaction from ketones, 1,3-dienes and a special hydrazine. This new reaction mode found applications in (1) the three-component pyrazole synthesis; (2) the deacetylation of methyl ketones; and (3) the cyclization reaction through tandem C−C/C−H

cleavage. The development of more applications of this new C−C cleavage mode is currently on the way.

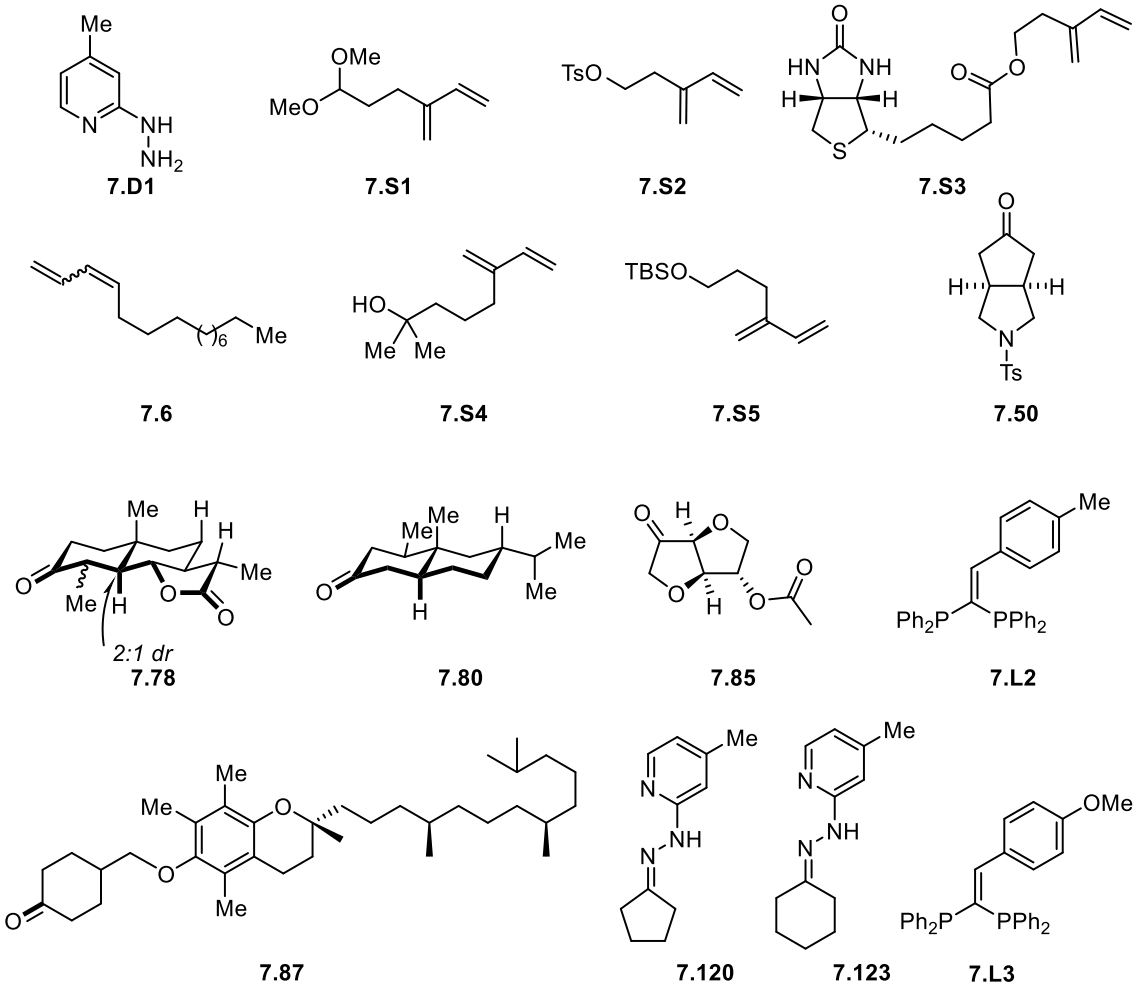
7.4 Experimental

Unless otherwise noted, all experiments were carried out under air atmosphere. 1,4-dioxane was distilled over Na. The 3Å and 4Å molecule sieves were pre-dried overnight at 110 °C in an oven, and then flame-dried under *vacuo* for 30 minutes. Other reagents and solvents were directly used from the supplier without further purification unless noted. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plate (silica gel 60, F254, EMD chemical). The vials (1 dram, 15×45 mm or 2 dram, 17×60 mm, with PTFE lined cap attached) were purchased from Qorpak and used directly. Infrared spectra were recorded on a Nicolet iS5 FT-IR Spectrometer using neat thin film technique. High-resolution mass spectra (HRMS) were obtained on an Agilent 6224 Tof-MS spectrometer and are reported as m/z. Accurate masses are reported for the molecular ion $[M+H]^+$ or $[M]^+$. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded with a Bruker Avance 400 instrument (500 MHz, ^{1}H at 400 MHz, ^{13}C at 101 MHz) unless noted. For $CDCl_3$ solutions, the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; $CHCl_3$ δ H (7.26 ppm) and $CDCl_3$ δ C (77.16 ppm). For C_6D_6 solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; C_6D_5H δ H (7.16 ppm) and C_6D_6 δ C (128.06 ppm). Coupling constants are reported in Hertz (Hz). Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm, referenced to protium: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet (quintet), dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet, coupling constant (Hz), and integration).

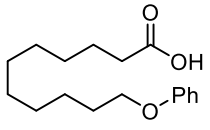
Substrate preparation

Compounds **7.D1**[30], **7.S1**[48], **7.S2**[49], **7.S5**[50], **7.50**[51], **7.85**[52], **7.L3**[53] **7.S6**[60], **7.S12b**[62], **S11**[30], **7.109**[63], **7.CL1**[63], **7.110**[63], **7.B18**[64], **7.S19a**[65], **7.S19c**[66], and **7.S20**[67] were synthesized according to the previously reported literatures. Compounds **7.a1**, **7.S3**, **7.S4**, **7.S7**, **7.S8**, **7.S10**, **7.S12**, **7.S13**, **7.S14**, **7.S15**, **7.S16**, **7.S17**, **7.S18**, **7.S18b**, **7.S19**, **7.S19b**, **7.6**, **7.78**, **7.80**, **7.L2**, **7.87**, **7.106**, **7.107**, **7.117**, **7.118**, **7.120**, and **7.123** were prepared according to the following procedures (see Scheme 7.12). The others were commercially available and were used as received.

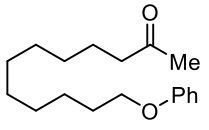
Scheme 7.12 Structures of the Substrates Synthesized for this Study



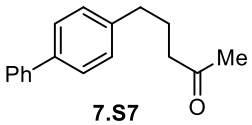
Scheme 7.12 Structures of the Substrates Synthesized for this Study (continued)



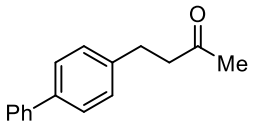
7.S6



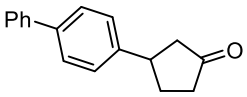
7.a1



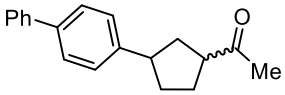
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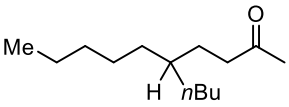
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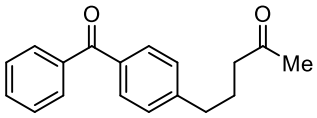
7.S12b



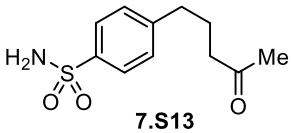
7.S10



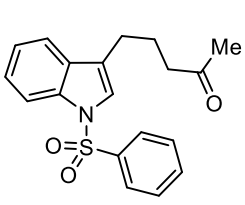
7.S11



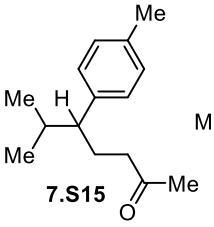
7.S12



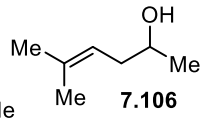
7.S13



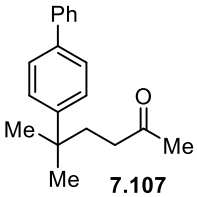
7.S14



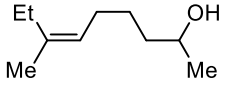
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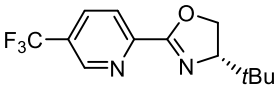
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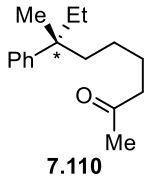
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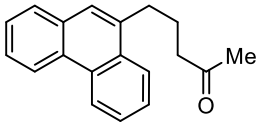
7.109



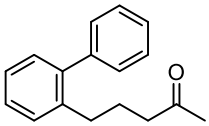
7.CL1



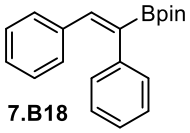
7.110
(94% e.e.)



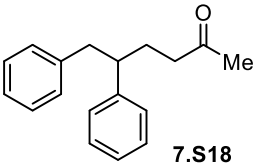
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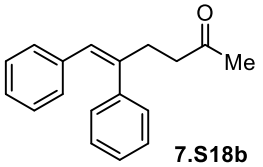
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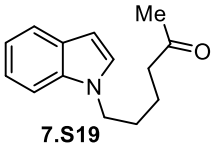
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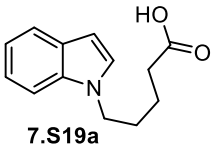
7.S18



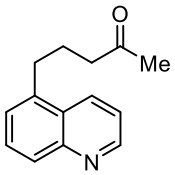
7.S18b



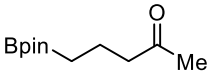
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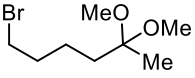
7.S19a



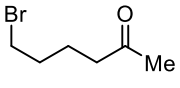
7.S19b



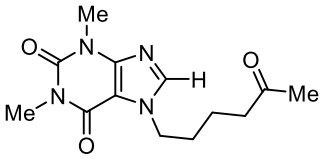
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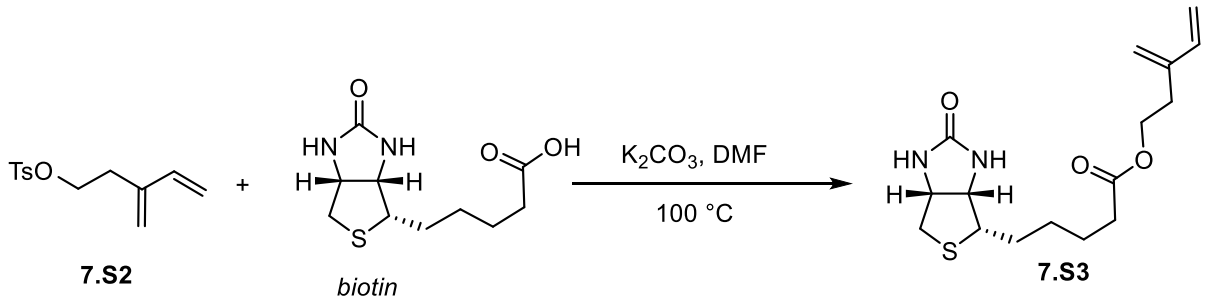
7.117



7.S20

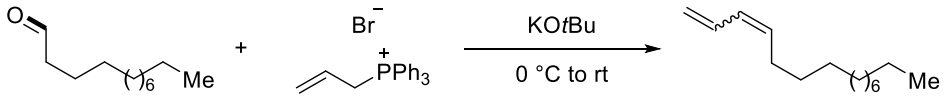


7.118



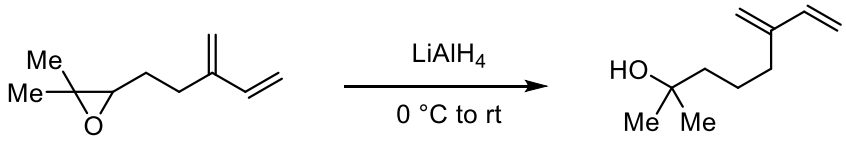
7.S2 biotin 7.S3

7.S3: A DMF (16 mL) suspension of **7.S2**[49] (150 mg, 0.6 mmol, 1.0 equiv), biotin (800 mg, 3.2 mmol, 5.3 equiv), and K_2CO_3 (870mg, 6.4 mmol, 10.7 equiv) was heated at 100 °C for 4 hours in a 40 mL vial under N_2 atmosphere. After cooled to room temperature, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The organic phase was combined, washed with brine, and dried over $MgSO_4$. The filtrate was concentrated *in vacuo* and purified by flash column chromatography over silica (DCM/MeOH, 30:1) to give **7.S3** as a white solid (110 mg, 57% yield, ca. 90~95% purity). R_f = 0.35 (DCM/MeOH = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.43 (s, 1H), 5.27 (d, *J* = 17.6 Hz, 1H), 5.13 – 5.08 (m, 2H), 5.05 (s, 2H), 4.51 (dd, *J* = 7.7, 4.9 Hz, 1H), 4.37 – 4.30 (m, 1H), 4.22 (t, *J* = 7.1 Hz, 2H), 3.16 (q, *J* = 7.0 Hz, 1H), 2.92 (dd, *J* = 12.8, 5.0 Hz, 1H), 2.73 (d, *J* = 12.8 Hz, 1H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.33 (t, *J* = 7.4 Hz, 2H), 1.76 – 1.64 (m, 5H), 1.51 – 1.37 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.71, 163.38, 142.26, 138.46, 117.79, 113.96, 63.07, 62.05, 60.22, 55.48, 40.70, 34.03, 30.75, 28.47, 28.41, 24.91. IR (KBr) 3228, 2926, 2857, 1739, 1699, 1468, 1267, 1174 cm^{-1}. HRMS: calcd. 325.1581 $[M+H]^+$ Found: 325.1591.



6

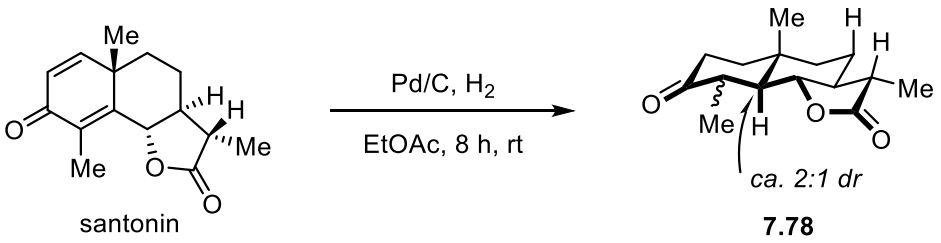
7.6: To a flame dried 250 mL round bottom flask, anhydrous THF (50 mL), allyl triphenylphosphonium bromide (3.52 g, 9.2 mmol, 1.6 equiv) and potassium tert-butoxide (1.03 g, 9.2 mmol, 1.6 equiv) were added and cooled to 0 °C. Dodecanal (1.06 g, 5.75 mmol, 1 equiv) was added dropwise, and the reaction was stirred for 16 hours while warming to room temperature. The reaction mixture was diluted with hexane and filtered. The filtrate was concentrated *in vacuo* and purified by flash column chromatography over silica (hexane/ethyl acetate, 40:1) to give **7.6** as a colorless oil (1.01 g, 83% yield, ca 1:1.2 *Z*/*E*). R_f = 0.8 (hexane/ethyl acetate = 30:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (dt, *J* = 16.8, 10.6 Hz, 0.46H), 6.31 (dt, *J* = 17.0, 10.3 Hz, 0.54H), 6.11 – 5.92 (m, 1H), 5.71 (dt, *J* = 14.7, 7.0 Hz, 0.54H), 5.46 (dt, *J* = 10.9, 7.8 Hz, 0.46H), 5.18 (dd, *J* = 16.9, 1.9 Hz, 0.46H), 5.12 – 5.05 (m, 1H), 4.95 (dd, *J* = 10.2, 1.7 Hz, 0.54H), 2.18 (qd, *J* = 7.6, 1.5 Hz, 0.92H), 2.08 (q, *J* = 7.2 Hz, 1.08H), 1.46 – 1.35 (m, 2H), 1.35 – 1.23 (m, 16H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) carbon signals were found at δ 137.51, 135.60, 133.06, 132.48, 131.08, 129.33, 116.71, 114.62, 32.78, 32.15, 29.91, 29.90, 29.88, 29.87, 29.85, 29.85, 29.84, 29.75, 29.74, 29.59, 29.59, 29.47, 29.46, 29.44, 27.93, 22.91, 14.27. The spectra match the reported literature.[54]



7.S12 **7.S4**

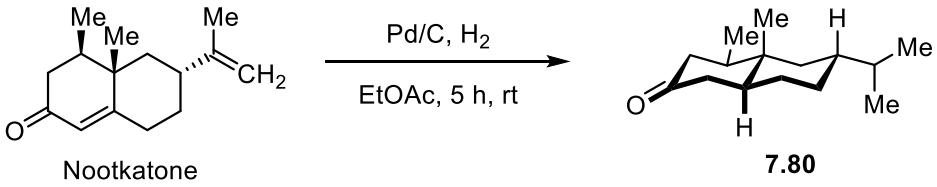
7.S4: Myrcene oxide **7.S12** was prepared according to a literature.[55] To a flame dried

100 mL round bottom flask, myrcene oxide (2.66 g, 17.5 mmol, 1 equiv) and 50 mL anhydrous THF were added and cooled to 0 °C. Lithium aluminum hydride (0.750 mg, 19.7 mmol, 1.12 equiv) was added portion-wise and the mixture was stirred at room temperature for 18 hours. The reaction was slowly quenched with sat. aqueous Rochelle's Salt (25 mL), diluted with H_2O (25 mL), and extracted with diethyl ether (3x30 mL). Organic extracts were dried over Na_2SO_4, filtered, and concentrated. Crude product was purified by flash column chromatography over silica (hexane/diethyl ether, 1:1) to give **7.S4** as a colorless oil (1.89 g, 70% yield). R_f = 0.40 (hexane/ether = 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.23 (d, *J* = 17.6 Hz, 1H), 5.04 (dd, *J* = 24.1, 10.3 Hz, 3H), 2.26 – 2.20 (m, 2H), 1.61 – 1.55 (m, 2H), 1.53 – 1.47 (m, 2H), 1.22 (s, 6H). The spectrum matches the reported literature.[56]



7.78: An ethyl acetate (10 mL) suspension of Santonin (600 mg, 1.0 equiv) and Pd/C (5 wt.%, 150 mg) was stirred at room temperature for 8 hours under H_2 atmosphere (balloon pressure). The mixture was then filtered through Celite. The filtrate was concentrated *in vacuo* and purified by flash column chromatography over silica (hexane/ethyl acetate, 3:1) to give **7.78** as a white solid (450 mg, 75% yield, mixture of diastereomers). R_f = 0.5 (hexane/ethyl acetate = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (dd, *J* = 11.3, 4.5 Hz, 0.35H), 3.98 (dd, *J* = 11.4, 9.8 Hz, 0.42H), 3.89 (t, *J* = 10.3 Hz, 0.23H), 2.85 – 2.21 (m, 4H),

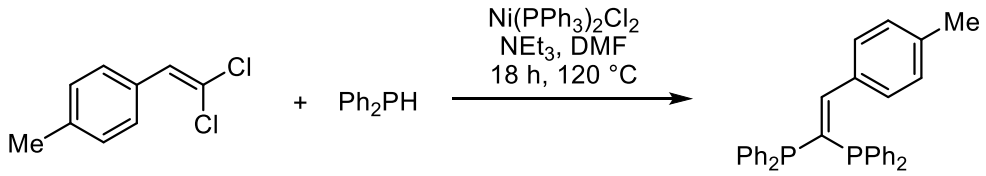
2.12 – 1.53 (m, 7H), 1.34 – 1.13 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were found at δ 213.86, 212.98, 211.55, 179.31, 179.14, 178.59, 83.23, 82.11, 79.69, 53.64, 53.01, 50.90, 49.21, 45.10, 44.31, 43.95, 42.30, 41.85, 41.62, 41.55, 40.82, 40.76, 40.33, 40.11, 37.44, 36.73, 36.59, 35.84, 35.81, 35.20, 30.70, 27.95, 24.29, 23.45, 23.22, 20.24, 18.52, 15.13, 14.01, 13.85, 12.70, 12.64, 12.59. IR (KBr) 2977, 2936, 2878, 1774, 1709, 1458, 1148, 1008cm^{-1}. HRMS: calcd. 251.1642 $[M+H]^+$ Found: 251.1649.



Nootkatone **7.80**

7.80: : An ethyl acetate (10 mL) suspension of Nootkatone (400 mg, 1.0 equiv) and Pd/C (5 wt.%, 80 mg) was stirred at room temperature for 5 hours under H_2 atmosphere (balloon pressure). The mixture was then filtered through Celite. The filtrate was concentrated *in vacuo* and purified by flash column chromatography over silica (hexane/ethyl acetate, 20:1) to give 7.**80** as a white solid (310 mg, 78% yield). R_f = 0.6 (hexane/ethyl acetate = 5:1). ^{1}H NMR (400 MHz, Toluene-d_8) δ 2.09 – 2.04 (m, 1H), 1.96 (ddd, J = 14.5, 3.6, 2.2 Hz, 1H), 1.84 – 1.69 (m, 2H), 1.57 – 1.45 (m, 2H), 1.30 – 0.87 (m, 6H), 0.82 (dd, J = 6.8, 5.4 Hz, 6H), 0.76 – 0.65 (m, 1H), 0.60 (d, J = 6.7 Hz, 3H), 0.51 (s, 3H), 0.37 (t, J = 12.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.41, 46.73, 46.05, 45.27, 44.17, 41.84, 38.84, 36.18, 33.05, 29.63, 29.16, 20.15, 19.71, 15.15, 10.77. IR (KBr) 2961, 2920, 2872, 1715, 1468, 1445, 1389, 1291, 1245 cm^{-1}. HRMS: calcd. 223.2057 $[M+H]^+$ Found: 223.2054. The

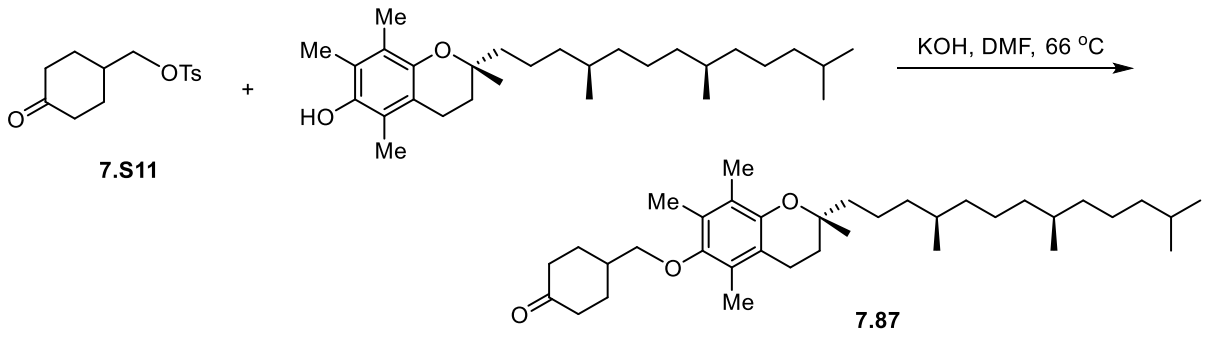
spectra match the reported literature.[57]



7.L2

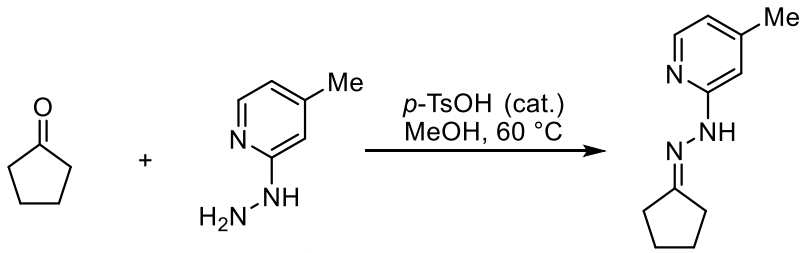
7.L2 was prepared following a modified procedure from literature.[53] A Schlenk flask was charged with 1-(2,2-dichlorovinyl)-4-methylbenzene[59] (260 mg, 1.39 mmol, 2.4 equiv), Et_3N (642 µL, 4.64 mmol, 8.0 equiv), diphenylphosphine (202 µL, 1.16 mmol, 1.0 equiv), DMF (1.5 mL), and $Ni(PPh_3)_2Cl_2$ (23 mg, 0.0348 mmol, 0.06 equiv) in a glove box. The reaction mixture was stirred for 18 h under N_2 atmosphere at 120 °C. After cooling, to the solution were added 10 mL of H_2O and 10 mL of toluene. The toluene phase was separated, washed with 10 mL of H_2O and dried over $MgSO_4$. To this mixture, 10 mg of dimethylglyoxime was added, and the resulting mixture was sit at room temperature for 1 hour. The mixture was then passed through a short plug of silica gel. The filtrate was concentrated *in vacuo* and purified by flash column chromatography over Al_2O_3 (hexane/ethyl acetate, from hexane to hexane/ethyl acetate = 50:1) to give the product **7.L2** as a white solid (200 mg, 71% yield). R_f = 0.5 (hexane/ethyl acetate = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.1 Hz, 4H), 7.21 – 7.02 (m, 19H), 6.99 (d, *J* = 7.9 Hz, 2H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were observed at δ 153.70, 153.46, 138.35, 136.69, 136.54, 136.25, 136.19, 136.15, 136.09, 134.78, 134.75, 134.73, 134.64, 134.62, 134.45, 134.43, 134.21, 134.01, 129.87, 129.79, 128.79, 128.78, 128.67, 128.58,

128.33, 128.27, 127.95, 127.88, 21.41. IR (KBr) 3070, 3056, 3002, 1507, 1482, 1440, 1187, 1027 cm^{-1}. HRMS: calcd. 487.1739 $[M+H]^+$ Found: 487.1753.



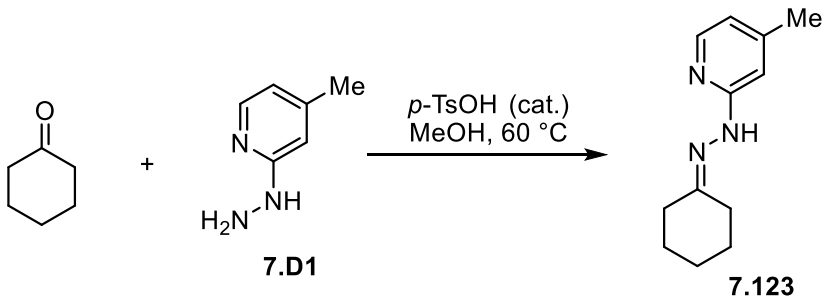
7.87: A 20 mL vial was charged with **7.S11**[58] (282 mg, 1 mmol, 1 equiv), KOH (48 mg, 1.2 equiv), Vitamin E (430 mg, 1 equiv) and DMF **(**6 mL). The reaction was stirred at room temperature for 1 hour before heated to 66 °C for 6 hours under N_2 atmosphere. After cooled to room temperature, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The organic phase was combined, washed with brine, and dried over $MgSO_4$. The filtrate was concentrated *in vacuo* and purified by flash column chromatography over silica (hexane/ethyl acetate, 30:1) to give **7.87** as a colorless oil (350 mg, 65% yield, mixture of diastereomers). R_f = 0.75 (hexane/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (d, *J* = 5.9 Hz, 2H), 2.57 (t, *J* = 6.8 Hz, 2H), 2.52 – 2.37 (m, 4H), 2.29 (td, *J* = 12.5, 11.9, 3.0 Hz, 3H), 2.16 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 1.78 (ddq, *J* = 20.1, 13.4, 6.9 Hz, 2H), 1.65 (ddt, *J* = 12.1, 6.0, 3.2 Hz, 2H), 1.57 – 1.48 (m, 3H), 1.46 – 1.03 (m, 21H), 0.87 (s, 3H), 0.87 – 0.82 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were observed at δ 211.89,

147.98, 147.94, 127.78, 125.78, 123.11, 117.76, 76.44, 74.94, 40.68, 40.13, 39.51, 37.60, 37.59, 37.55, 37.42, 37.26, 32.94, 32.83, 31.42, 29.74, 28.13, 24.95, 24.59, 24.03, 22.87, 22.78, 21.16, 20.80, 19.90, 19.81, 12.81, 11.95, 11.93. IR (KBr) 2951, 2930, 2866, 1717, 1461, 1381, 1261, 1089 cm^{-1}. HRMS: calcd. 541.4615 $[M+H]^+$ Found: 541.4621.

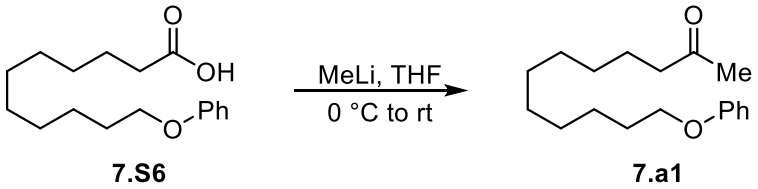


7.D1 **7.120**

7.120: A MeOH solution (1 M) of the cyclopentanone (840 mg, 10 mmol, 1 equiv) and 2-hydrazineyl-4-methylpyridine **7.D1** (1.23 g, 10 mmol, 1 equiv) was heated at 60 °C for 4 hours (monitored by TLC). After cooled to room temperature, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography over silica (hexane/ethyl acetate, 10:1) to give the hydrazone product **7.120** as a white solid (1.77 g, 94% yield). R_f = 0.15 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 5.1 Hz, 1H), 7.40 (s, 1H), 7.00 (s, 1H), 6.53 (d, *J* = 5.1 Hz, 1H), 2.46 (t, *J* = 7.2 Hz, 2H), 2.27 (d, *J* = 8.5 Hz, 5H), 1.87 (p, *J* = 6.9 Hz, 2H), 1.75 (p, *J* = 6.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.11, 157.58, 149.35, 147.46, 116.81, 107.33, 33.28, 26.86, 25.09, 25.05, 21.37. IR (KBr) 3185, 3064, 2960, 2884, 1608, 1577, 1431, 1288, 1167, 1086 cm^{-1}. HRMS: calcd. 190.1339 $[M+H]^+$ Found: 190.1346.

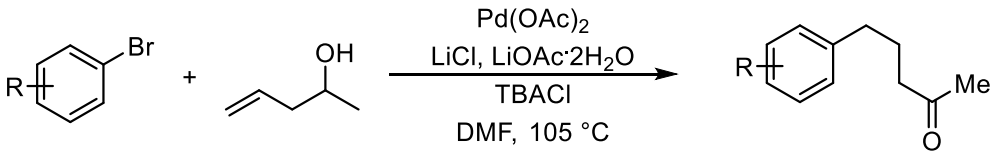


7.123: A MeOH solution (1 M) of the cyclopentanone (980 mg, 10 mmol, 1 equiv) and 2-hydrazineyl-4-methylpyridine **7.D1** (1.23 g, 10 mmol, 1 equiv) was heated at 60 °C for 4 hours (monitored by TLC). After cooled to room temperature, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography over silica (hexane/ethyl acetate, 10:1) to give the hydrazone product **7.123** as a white solid (1.88 g, 93% yield). R_f = 0.15 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 5.1 Hz, 1H), 7.80 (s, 1H), 7.02 (s, 1H), 6.52 (d, *J* = 5.1 Hz, 1H), 2.35 (t, *J* = 6.3 Hz, 2H), 2.32 – 2.23 (m, 5H), 1.77 – 1.47 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.87, 151.77, 149.24, 147.40, 116.69, 107.37, 35.47, 27.13, 25.83, 25.77, 25.72, 21.38. IR (KBr) 3199, 3064, 3022, 2935, 2862, 2862, 1575, 1513, 1459, 1131, 1083 cm^{-1}. HRMS: calcd. 204.1495 $[M+H]^+$ Found: 204.1504.



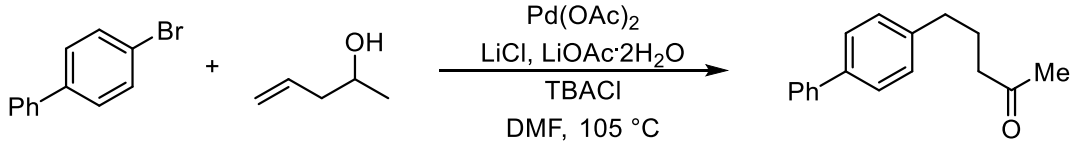
7.S6 was prepared according to a known procedure[60]. A THF solution of MeLi (18 mmol, 1.6M, 11.25 mL, 2.5 equiv) was added to a flame-dried 50 mL round bottom flask

charged with THF (15 mL). To this, a THF (15 mL) solution of **7.S6** (2 gram, 7.2 mmol) was added slowly at 0 °C over 5 mins. The reaction mixture was stirred at 0 °C for 3 hours, and then at room temperature for 2 hours. The reaction mixture was treated with aqueous NH_4Cl (sat.) (50 mL), extracted with DCM, and dried over $MgSO_4$. The filtrate was concentrated under *vacuo* and further purified by flash column chromatography over silica (hexane/ethyl acetate, from 100:1 to 20:1) to give product **l** as a colorless oil (900 mg, 45% yield). R_f = 0.6 (Hex/EA= 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 2H), 7.00 – 6.80 (m, 3H), 3.95 (t, *J* = 6.5 Hz, 2H), 2.42 (t, *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 1.78 (p, *J* = 6.8 Hz, 2H), 1.63 – 1.51 (m, 2H), 1.45 (p, *J* = 6.7 Hz, 2H), 1.40 – 1.19 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.48, 159.25, 129.53, 120.57, 114.62, 67.99, 43.96, 30.00, 29.64, 29.52, 29.52, 29.51, 29.43, 29.31, 26.19, 24.00. IR (KBr) 3066, 3040, 3030, 2930, 2853, 1721, 1601, 1585, 1502, 1472, 1358, 1247, 1172 cm^{-1}. HRMS: calcd. 277.2162 $[M+H]^+$ Found: 277.2168.



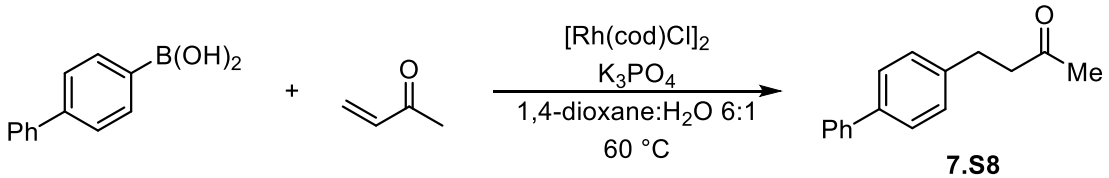
General procedure S-1 for the synthesis of 5-arylpentan-2-one through Pd-catalyzed cross-coupling reactions (*at 2 mmol scale*): Following a modified procedure from literature[68], a 20 ml vial was charged with aryl bromide starting material (2 mmol, 1.0 equiv), $Pd(OAc)_2$ (200 mg, 0.9 mmol, 0.45 equiv), TBACl (1.12 g, 4 mmol, 2.0 equiv), LiCl (80 mg, 2 mmol, 1.0 equiv), $LiOAc{\cdot}2H_2O$ (520 mg, 5 mmol, 2.5 equiv), DMF (4 mL), and pent-4-en-2-ol (260 mg, 3 mmol, 1.5 equiv). The reaction mixture was heated at 105 °C for 24-48 hours

(monitored by TLC). After cooled to room temperature, the reaction mixture was poured into 100 mL brine, extracted with Et_2O (100mL × 2), and dried over Na_2SO_4. The filtrate was concentrated under *vacuo* and further purified by flash column chromatography to give the coupling products.



7.B7 **7.S7**

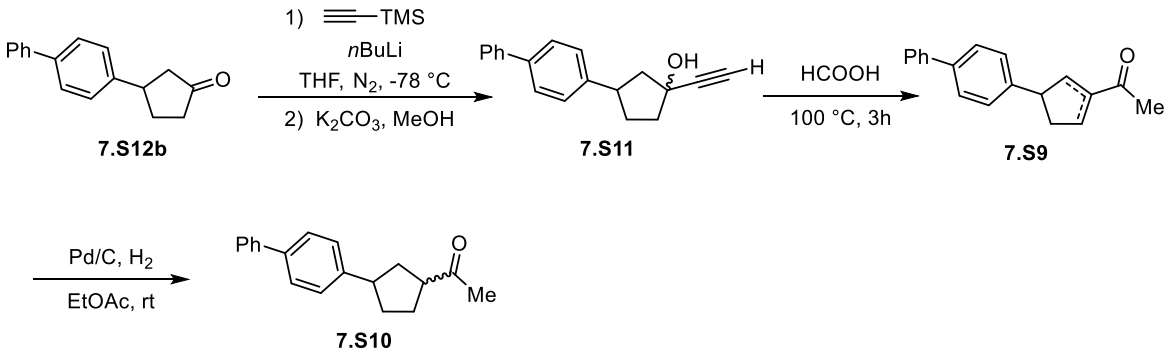
7.S7: Following **General procedure S-1,** the reaction was conducted with 300 mg 7.**B7** as the aryl bromide starting material at 1.3 mmol scale. The titled compound was obtained as a white solid (155 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.55 (m, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.25 (d, *J* = 8.6 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.48 (t, *J* = 7.4 Hz, 2H), 2.14 (s, 3H), 1.95 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.87, 141.16, 140.83, 139.09, 129.03, 128.87, 127.27, 127.20, 127.13, 43.01, 34.80, 30.14, 25.32. IR (KBr) 3028, 2942, 2890, 1707, 1492, 1409, 1356, 1158, 838, 763 cm^{-1}. HRMS: calcd. 239.1430 $[M+H]^+$ Found: 239.1424.



7.S8

7.S8: A 20 mL vial was charged with [1,1'-biphenyl]-4-ylboronic acid (900 mg, 4.5

mmol, 1.5 equiv), $[Rh(cod)Cl]_2$ (45 mg, 0.09 mmol, 0.03 equiv), aqueous K_3PO_4 (3M,1.5 mL, 4.5 mmol, 1.5 equiv), 1,4-dioxane (9 mL), and methy vinyl ketone (250 mg, 3 mmol, 1.0 equiv). The mixture was heated overnight at 60 °C. After cooled to room temperature, the reaction mixture was extracted with EA and dried over Na_2SO_4. The filtrate was concentrated under *vacuo* and further purified by flash column chromatography over silica (hexane/ethyl acetate, from 50:1 to 20:1) to give product as a white solid (610 mg, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.3 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 2H), 2.95 (t, *J* = 7.6 Hz, 2H), 2.81 (t, *J* = 7.5 Hz, 2H), 2.17 (s, 3H). The spectrum matches the reported literature.[69]



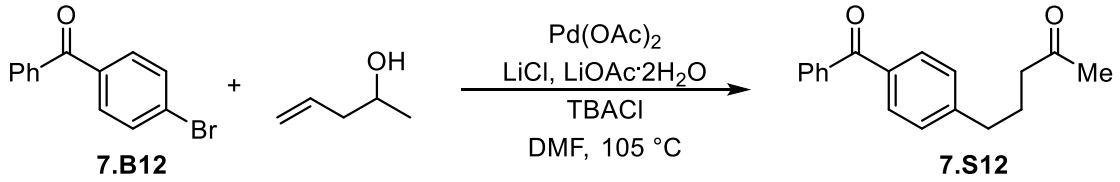
7.S12b was prepared according to a known procedure[62]. To an ethynyltrimethylsilane (882 mg, 9 mmol, 1.5 equiv) solution in THF (10 mL) was added *n*BuLi (2.5 M, 2.9 mL, 7.2 mmol, 1.2 equiv) dropwise at -78 °C under N_2. The mixture was further stirred at this temperature for 30 mins. A solution of **7.S12b** (1.4 g, 6 mmol, 1.0 equiv) in THF (3 mL) was then added, and the mixture was allowed to warm to room temperature and stirred for 4 hours. The reaction mixture was quenched with aqueous NH_4Cl (sat.), extracted with DCM,

and dried over Na_2SO_4. The filtrate was concentrated under *vacuo*. The residue was treated with K_2CO_3 (828 mg, 6 mmol, 1.0 equiv) and MeOH (12 mL) at room temperature overnight. The reaction mixture was filtered and concentrated under *vacuo* to yield the crude **7.S11** (ca. 1.3 g), which was used directly for the next step without further purification.

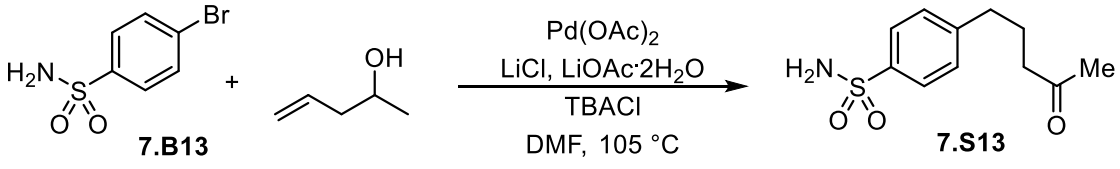
A formic acid solution (8 mL) of the crude **7.S11** (1.04 g) was stirred at 100 °C for 3 hours. After cooled to room temperature, the reaction mixture was diluted with brine and Et_2O (1:1) and neutralized by KOH (solid) at 0 °C. The resulting mixture was extracted with Et_2O, and dried over Na_2SO_4. The filtrate was concentrated under *vacuo* and further purified by flash column chromatography over silica (hexane/ethyl acetate, 15:1) to give compound **7.S9** as a pair of inseparable isomers (colorless oil, 810 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.51 (m, 5H), 7.47 – 7.41 (m, 2H), 7.36 – 7.30 (m, 2H), 6.85 – 6.79 (m, 0.65H), 6.74 (q, *J* = 2.0 Hz, 0.35H), 3.62 (p, *J* = 8.2 Hz, 0.65H), 3.09 (ddd, *J* = 17.6, 9.0, 2.9 Hz, 1.35H), 2.85 – 2.48 (m, 3H), 2.38 (d, *J* = 2.9 Hz, 3H).

The compound **7.S9** (800 mg) was treated with EA (12 mL) and Pd/C (10% wt.%, 300 mg), and stirred at room temperature under H_2 atmosphere for 8 hours. The reaction mixture was filtered, concentrated in *vacuo*, and then purified by flash column chromatography over silica (hexane/ethyl acetate, 20:1) to give the product **7.S10** as a pair of diastereomers (colorless oil, 690 mg, 86% yield). R_f = 0.6 (Hex/EA = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.2 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.34 (dd, *J* = 8.4, 4.9 Hz, 3H), 3.25 – 3.04 (m, 2H), 2.45 – 2.30 (m, 1H), 2.22 (s, 3H), 2.19 – 2.06 (m, 2H), 2.05 – 1.82 (m, 2H), 1.82 – 1.69 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.67, 210.51, 144.14,

143.65, 141.14, 141.12, 139.30, 139.17, 128.84, 127.61, 127.55, 127.24, 127.22, 127.19, 127.13, 52.08, 51.46, 46.17, 44.71, 37.35, 36.19, 34.81, 33.94, 29.09, 28.98, 28.88, 27.87. IR (KBr) 3058, 3034, 2951, 2870, 1709, 1488, 1449, 1360, 1180, 1008 cm^{-1}. HRMS: calcd. 265.1587 $[M+H]^+$ Found: 265.1590.

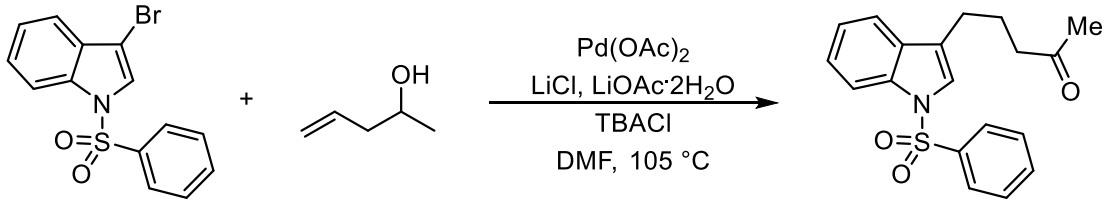


7.S12: Following **General procedure S-1,** the reaction was conducted with 522 mg **7.B12** as the aryl bromide starting material at 2 mmol scale. The titled compound was obtained as a yellow solid (280 mg, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.73 (m, 4H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 2.73 (t, *J* = 7.6 Hz, 2H), 2.50 (t, *J* = 7.2 Hz, 2H), 2.16 (s, 3H), 1.97 (p, *J* = 7.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.50, 196.56, 146.90, 137.96, 135.59, 132.37, 130.55, 130.08, 128.52, 128.37, 42.81, 35.16, 30.16, 24.96. The spectra match the reported literature.[70]



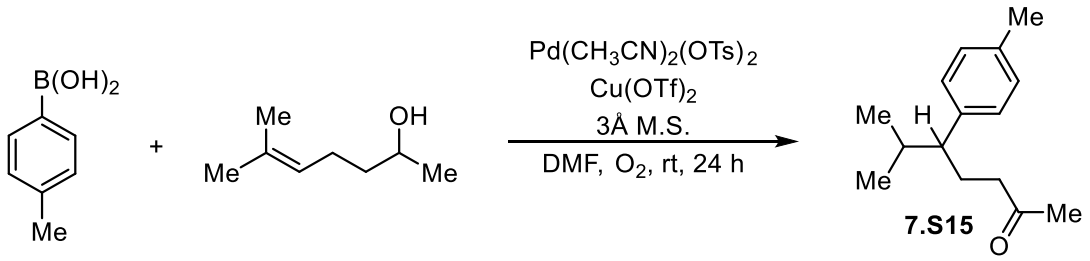
7.S13: Following **General procedure S-1,** the reaction was conducted with 472 mg **7.B13** as the aryl bromide starting material at 2 mmol scale. After purified by the flash

column chromatography over silica, the crude product (290 mg) was further recrystallized from refluxed methanol to furnish **7.B13** as a white solid (120 mg, 25% yield). M.p. = 110-112 °C (Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 4.93 (br, 2H), 2.78 – 2.62 (m, 2H), 2.45 (t, *J* = 7.2 Hz, 2H), 2.13 (s, 3H), 1.91 (p, *J* = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.42, 147.39, 139.79, 129.30, 126.77, 42.65, 34.98, 30.18, 24.88. IR (KBr) 3338, 3240, 3113, 2957, 2938, 2865, 1709, 1573, 1409, 1318, 1158 cm^{-1}. HRMS: calcd. 242.0845 $[M+H]^+$ Found: 242.085.

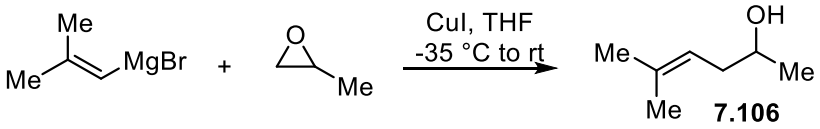


7.B14 **7.S14**

7.S14: Following **General procedure S-1,** the reaction was conducted with 670 mg **B9** as the aryl bromide starting material at 2 mmol scale. The titled compound was obtained as a yellow solid (300 mg, 44% yield). M.p. = 110-112 °C (Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 7.9 Hz, 2H), 7.55 – 7.46 (m, 2H), 7.46 – 7.37 (m, 2H), 7.38 – 7.28 (m, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.47 (t, *J* = 7.2 Hz, 2H), 2.12 (s, 3H), 1.95 (p, *J* = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.48, 138.37, 135.52, 133.79, 131.03, 129.31, 126.80, 124.91, 123.28, 122.87, 122.85, 119.68, 113.88, 42.92, 30.15, 24.27, 22.93. IR (KBr) 3408, 3109, 3066, 2942, 2861, 1713, 1611, 1447, 1368, 1178, 1119 cm^{-1}. HRMS: calcd. 342.1158 $[M+H]^+$ Found: 342.1158.

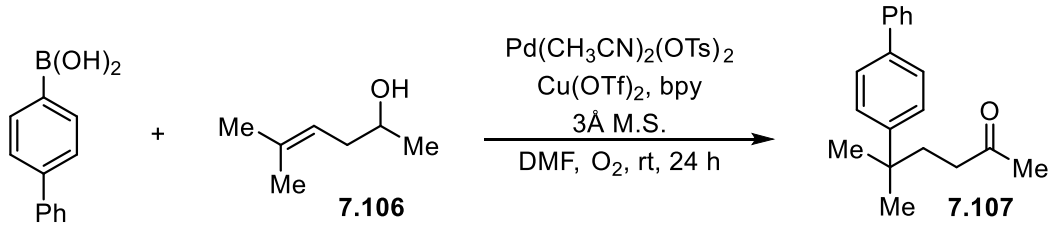


7.S15: A suspension of $Pd(CH_3CN)_2(OTs)_2$ (15.9 mg, 0.03 mmol, 0.06 equiv), $Cu(OTf)_2$ (5.4 mg, 0.015 mmol, 0.03 equiv) and 3Å M.S. (75 mg) in DMF (8 mL) was stirred at room temperature for 10 mins. To this, a DMF (2 mL) solution of *p*-tolylboronic acid (228 mg, 1.5 mmol, 3.0 equiv) and 6-methylhept-5-en-2-ol (64 mg, 0.5 mmol, 1.0 equiv) was added through syringe, and the resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was then filtered through Celite, concentrated under *vacuo,* and further purified by flash column chromatography over silica (hexane/ethyl acetate, from 40:1 to 20:1) to give product **7.S15** as a colorless oil (43 mg, 39% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 7.7 Hz, 2H), 6.97 (d, J = 7.7 Hz, 2H), 2.32 (s, 3H), 2.23 – 2.05 (m, 4H), 2.00 (s, 3H), 1.88 – 1.69 (m, 2H), 0.95 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 6.7 Hz, 3H). The spectrum matches the reported literature.[71]



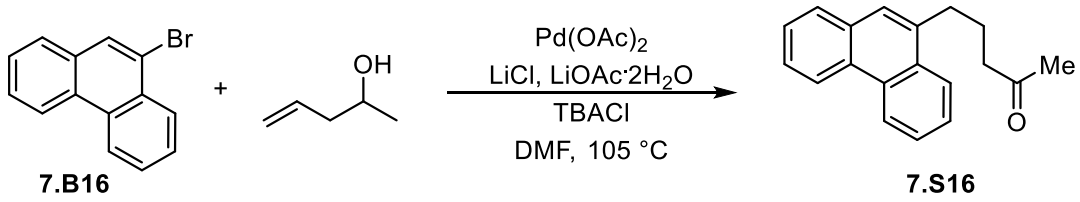
7.106: To a 2-methyl-1-propenylmagnesium bromide solution (0.5 M in THF, 10 mmol, 20 mL, 1.1 equiv) was added CuI (95 mg, 0.5 mmol, 0.056 equiv) at -35 °C. The reaction mixture was stirred at this temperature for 15 mins. To this, a propylene oxide (522

mg, 9 mmol, 1.0 equiv) solution in THF (5 mL) was then added dropwise over 20 mins at -35 °C. The reaction mixture was stirred at this temperature for 30 min, at then allowed to warm to room temperature for another 1.5 hour. The reaction mixture was then treated with small amount of aqueous NH_4Cl (sat.), extracted with Et_2O, and dried over Na_2SO_4. The filtrate was carefully concentrated under *vacuo.* The residue was further purified by fractional distillation under reduced pressure (b.p. = 50-52 °C, at 10 torr) to yield the product **7.106** as a colorless oil (710 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (t, *J* = 6.9 Hz, 1H), 3.79 (h, *J* = 6.3 Hz, 1H), 2.23 – 2.06 (m, 2H), 1.73 (s, 3H), 1.64 (s, 3H), 1.61 (br, 1H), 1.19 (d, *J* = 6.3 Hz, 3H). The spectrum matches the reported literature.[72]



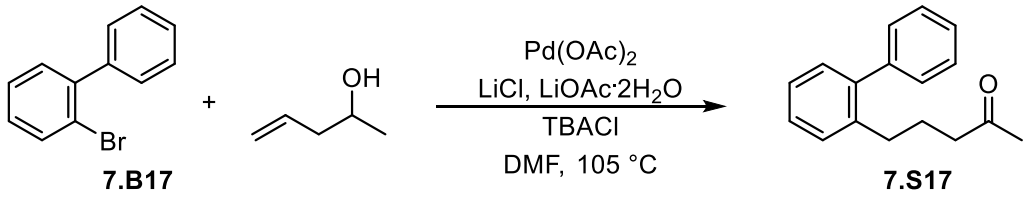
7.107: Following a modified procedure of literature,[63] a suspension of $Pd(CH_3CN)_2(OTs)_2$ (32 mg, 0.06 mmol, 0.06 equiv), $Cu(OTf)_2$ (10.8 mg, 0.03 mmol, 0.03 equiv), 2,2'-bipyridine (14 mg, 0.09 mmol, 0.09 equiv) and 3Å M.S. (150 mg) in DMF (16 mL) was stirred at room temperature for 10 mins. To this, a DMF (4 mL) solution of 4-biphenylylboronic acid (600 mg, 3 mmol, 3.0 equiv) and **7.106** (114 mg, 1.0 mmol, 1.0 equiv) was added through syringe, and the resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was then filtered through Celite, concentrated under *vacuo,* and further purified by flash column chromatography over silica (hexane/ethyl acetate,

from 40:1 to 20:1) to give product **7.107** as a colorless oil (175 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.58 (m, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.37 – 7.30 (m, 1H), 2.26 – 2.19 (m, 2H), 2.05 (s, 3H), 2.01 – 1.92 (m, 2H), 1.36 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.17, 147.54, 140.95, 138.68, 128.87, 127.24, 127.09, 127.05, 126.37, 39.78, 37.68, 37.17, 30.09, 29.09. IR (KBr) 3030, 2966, 2876, 1721, 1488, 1367, 1164 cm^{-1}. HRMS: calcd. 267.1743 $[M+H]^+$ Found: 267.1741.

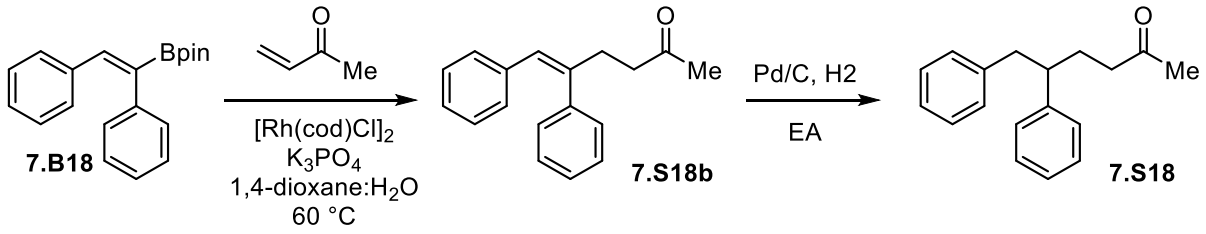


7.B16 **7.S16**

7.S16: Following **General procedure S-1,** the reaction was conducted with 514 mg **7.B16** as the aryl bromide starting material at 2 mmol scale. The titled compound was obtained as a yellowish oil (320 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 – 8.70 (m, 1H), 8.66 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.22 – 8.07 (m, 1H), 7.83 (dd, *J* = 7.1, 2.2 Hz, 1H), 7.73 – 7.51 (m, 8H), 3.13 (t, *J* = 7.6 Hz, 2H), 2.56 (t, *J* = 7.2 Hz, 2H), 2.20 – 1.99 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.82, 135.96, 131.92, 131.27, 130.86, 129.87, 128.18, 128.16, 126.78, 126.76, 126.47, 126.38, 126.37, 126.20, 126.18, 124.62, 124.60, 123.36, 123.35, 122.60, 122.58, 43.25, 32.73, 30.19, 24.10. IR (KBr) 3075, 2943, 2876, 1718, 1499, 1454, 1372, 1162 cm^{-1}. HRMS: calcd. 263.1430 $[M+Na-H_2O]^+$ Found: 263.1432.



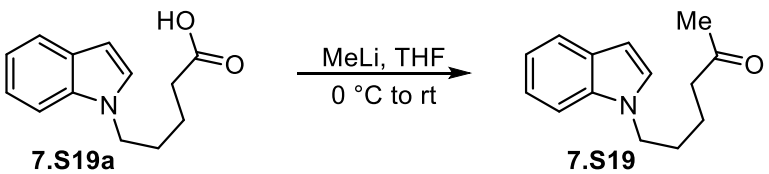
7.S17: Following **General procedure S-1,** the reaction was conducted with 466 mg **7.B17** as the aryl bromide starting material at 2 mmol scale. The titled compound was obtained as a yellowish oil (120 mg, 25% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.15 (m, 10H), 2.60 (dd, J = 8.7, 6.9 Hz, 2H), 2.29 (t, J = 7.4 Hz, 2H), 2.00 (s, 3H), 1.79 – 1.68 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.81, 142.06, 141.92, 139.18, 130.26, 129.41, 129.34, 128.24, 127.59, 126.99, 126.05, 43.33, 32.36, 29.80, 25.30. IR (KBr) 3061, 3025, 2938, 1710, 1479, 1434, 1361, 1162 cm^{-1}. HRMS: calcd. 239.1430 $[M]^+$ Found: 239.1433.



7.S18b: Compound **7.B18** was prepared according to the previously reported literatures.[64] A 20 mL vial was charged with **7.B18** (688 mg, 2.25 mmol, 1.5 equiv), $[Rh(cod)Cl]_2$ (23 mg, 0.045 mmol, 0.03 equiv), aqueous K_3PO_4 (3M, 0.75 mL, 2.25 mmol, 1.5 equiv), 1,4-dioxane (4.5 mL), and methy vinyl ketone (125 mg, 1.5 mmol, 1.0 equiv). The mixture was heated overnight at 60 °C. After cooled to room temperature, the reaction mixture was extracted with EA and dried over Na_2SO_4. The filtrate was concentrated under *vacuo* and further purified by flash column chromatography over silica (hexane/ethyl acetate,

from 50:1 to 20:1) to give product **7.S18b** as a colorless oil (270 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 3H), 7.15 (d, *J* = 6.5 Hz, 2H), 7.12 – 7.01 (m, 3H), 6.96 – 6.86 (m, 2H), 6.48 (s, 1H), 2.79 (t, *J* = 7.7 Hz, 2H), 2.52 (t, *J* = 7.7 Hz, 2H), 2.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.19, 141.62, 140.52, 137.19, 129.16, 128.81, 128.77, 127.97, 127.32, 127.12, 126.48, 42.26, 34.69, 30.17. The spectrum matches the reported literature.[73]

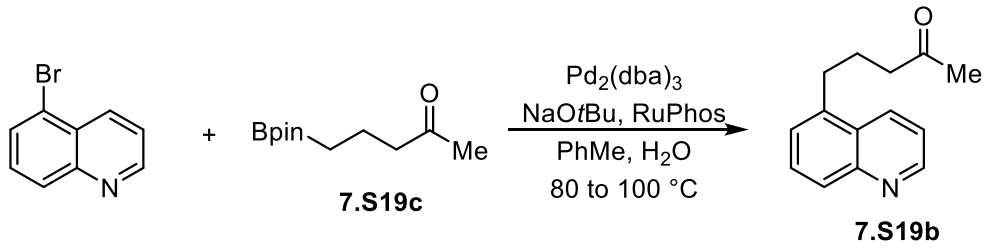
7.S18: Compound **7.S18b** (250 mg) was treated with EA (8 mL) and Pd/C (10% wt.%, 50 mg), and stirred at room temperature under H_2 atmosphere for 10 hours. The reaction mixture was filtered, concentrated in *vacuo*, and then purified by flash column chromatography over silica (hexane/ethyl acetate, 20:1) to give the product **7.S18** as a colorless oil (235 mg, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 2H), 7.27 – 7.20 (m, 3H), 7.17 (d, *J* = 7.1 Hz, 1H), 7.16 – 7.10 (m, 2H), 7.10 – 7.01 (m, 2H), 2.99 – 2.88 (m, 2H), 2.88 – 2.78 (m, 1H), 2.31 – 2.21 (m, 2H), 2.11 – 1.97 (m, 4H), 1.95 – 1.83 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.88, 144.17, 140.37, 129.25, 128.56, 128.23, 127.86, 126.52, 126.03, 47.46, 44.06, 41.86, 30.05, 29.31. The spectrum matches the reported literature.[74]



7.S19a **7.S19**

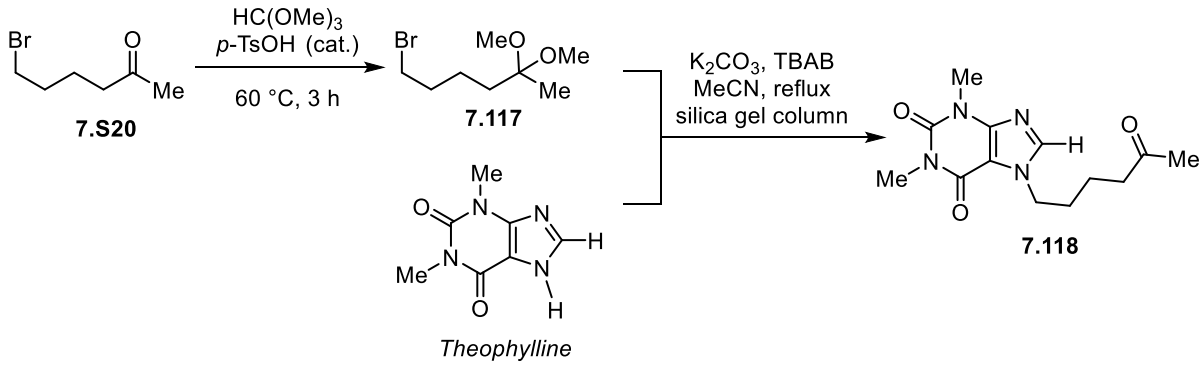
7.S19a was prepared according to a known procedure[65]. A THF solution of MeLi (18

mmol, 1.6M, 11.25 mL, 2.5 equiv) was added to a flame-dried 50 mL round bottom flask charged with THF (15 mL). To this, a THF (15 mL) solution of **7.S19a** (1.56 gram, 7.2 mmol) was added slowly at 0 °C over 10 mins. The reaction mixture was stirred at 0 °C for 3 hours, and then at room temperature for 4 hours. The reaction mixture was treated with aqueous NH_4Cl (sat.) (50 mL), extracted with DCM, and dried over $MgSO_4$. The filtrate was concentrated under *vacuo* and further purified by flash column chromatography over silica (hexane/ethyl acetate, 20:1) to give product **7.S19** as a colorless oil (770 mg, 50% yield). R_f = 0.5 (Hex/EA= 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.16 – 7.07 (m, 2H), 6.50 (t, *J* = 2.3 Hz, 1H), 4.14 (t, *J* = 7.0 Hz, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 2.09 (s, 3H), 1.84 (p, *J* = 7.1 Hz, 2H), 1.60 (p, *J* = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.32, 136.00, 128.75, 127.85, 121.52, 121.10, 119.37, 109.41, 101.20, 46.34, 43.06, 30.00, 29.75, 21.25. IR (KBr) 3101, 3053, 2946, 2870, 1718, 1516, 1465, 1358, 1316, 1162, 1013 cm^{-1}. HRMS: calcd. 216.1383 $[M+H]^+$ Found: 216.1401.



7.S19c was prepared according to a known procedure.[66] An 8 mL vial was charged with 5-bromoquinoline (125 mg, 0.6 mmol, 1.0 equiv), **7.S19c** (126 mg, 0.6 mmol, 1.0

equiv), $Pd_2(dba)_3$ (6 mg), NaO*t*Bu (100 mg, 1.04 mmol, 1.75 equiv), RuPhos (10 mg), PhMe (1 mL) and H_2O (0.1 mL). The vial was sealed, transferred in to a glove box, and then purged under N_2 atmosphere for 5 mins. The vial was sealed again and transferred out from the glove box. The reaction mixture was stirred at 80 °C for 4 hours, and then at 100 °C overnight. After cooled to room temperature, the reaction mixture was filtered through Celite. The filtrate was concentrated under *vacuo* and further purified by flash column chromatography over silica (hexane/ethyl acetate, from 5:1 to 2:1) to give product **7.S19b** as a colorless oil (36 mg, 28% yield). R_f = 0.2 (Hex/EA= 3:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 – 8.78 (m, 1H), 8.47 (d, *J* = 8.6 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.63 (ddd, *J* = 8.9, 7.3, 2.0 Hz, 1H), 7.44 (dd, *J* = 8.4, 4.1 Hz, 1H), 7.36 (d, *J* = 6.9 Hz, 1H), 3.07 (t, *J* = 7.7 Hz, 2H), 2.54 (t, *J* = 6.9 Hz, 2H), 2.15 (s, 3H), 2.00 (p, *J* = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.56, 150.15, 148.94, 138.51, 132.50, 129.20, 128.31, 127.11, 126.64, 121.00, 42.98, 31.76, 30.25, 24.92. IR (KBr) 3064, 3033, 2941, 2879, 1715, 1597, 1502, 1370, 1159 cm^{-1}. HRMS: calcd. 214.1226 $[M+H]^+$ Found: 214.1231.

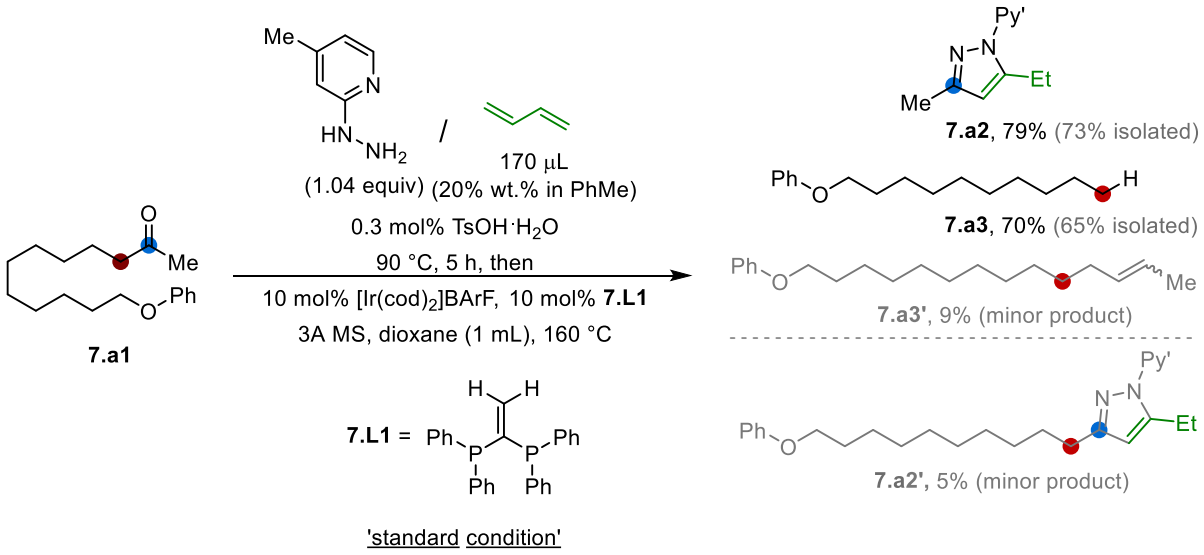


7.S20 was prepared according to a known procedure.[67] To a methyl orthoformate (4

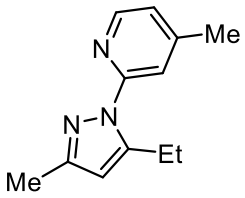
mL) solution of **7.S20** (540 mg, 3 mmol, 1.0 equiv) was added *p*-TsOH (10 mg). The resulting mixture was heated at 60 °C for 3 hours, and then was concentrated under *vacuo.* The residue (crude compound **7.117**) was directed used for the next step without further purification.

A MeCN (10 mL) solution of *Theophylline* (360 mg, 2 mmol, 1.0 equiv), **7.117** (563 mg, 2.5 mmol, 1.25 equiv), K_2CO_3 (280 mg, 2 mmol, 1.0 equiv) and TBAB (20 mg) was heated at 80 °C for 20 hours. After cooled to room temperature, the reaction mixture was concentrated under *vacuo*. The residue was dissolved in $CHCl_3$ (50 mL), washed with H_2O (20 mL × 3), and dried over Na_2SO_4. The filtrate was concentrated under *vacuo* and further purified by flash column chromatography over silica (hexane/ethyl acetate, 1:1) to give product **7.118** as a white solid (532 mg, 96% yield) (*the deprotection of the ketal took place spontaneously over silica gel*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 4.26 (t, J = 7.1 Hz, 2H), 3.56 (s, 3H), 3.38 (s, 3H), 2.48 (t, J = 7.1 Hz, 2H), 2.11 (s, 3H), 1.86 (p, J = 7.5 Hz, 2H), 1.57 (p, J = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.98, 155.23, 151.77, 149.11, 140.98, 107.03, 47.12, 42.69, 30.42, 30.10, 29.86, 28.08, 20.32. The spectra match the reported literature.[68]

Condition optimization

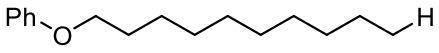


"Standard condition": An 8 mL vial was charged with **7.a1** (13.8 mg, 0.05 mmol, 1.0 equiv) and 2-hydrazineyl-4-methylpyridine **7.D1** (6.4 mg, 0.052 mmol, 1.04 equiv), and transferred into a glove box. 1,4-Dioxane (1 mL) and a stock solution of $TsOH{\cdot}H_2O$ in 1,4-dioxane (0.05 M, 3.0 µL, 0.003 equiv) were then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 90 °C for 5 hours. After cooled to room temperature, the vial was opened, and charged with $[Ir(cod)_2]BArF$ (6.4 mg, 0.005 mmol, 0.1 equiv) and **7.L1** (2.0 mg, 0.005 mmol, 0.1 equiv). The vial was sealed and transferred into the glove box, and then opened and purged under N_2 atmosphere for 3 mins. Pre-dried 3Å molecular sieve (100 mg) and 1,3-butadiene (20% wt.% in PhMe, 170 µL, ca. 10 equiv) were then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 160 °C under stirring for 72 hours. After cooled to room temperature, the reaction mixture was filtered through a short plug of Celite, concentrated *in vacuo*, and further purified by flash column chromatography over silica (from hexane to hexane/ethyl acetate, 15:1) to give products **7.a2**, **7.a3**, **7.a2'** and **7.a3'**. *The reported yields were based on average of 3 runs.*



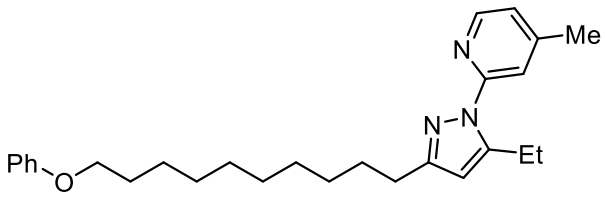
7.a2

7.a2: The reaction was conducted with 41.4 mg **7.a1** in 3 parallel vessels (0.05 mmol for each, 0.15 mmol combined). The titled compound was obtained as a colorless oil (22.1 mg, 73% yield). R_f = 0.65 (Hex/EA= 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 5.1 Hz, 1H), 7.63 (t, *J* = 0.8 Hz, 1H), 6.96 (ddd, *J* = 5.0, 1.5, 0.7 Hz, 1H), 6.02 (s, 1H), 3.09 (qd, *J* = 7.5, 0.9 Hz, 2H), 2.38 (t, *J* = 0.7 Hz, 3H), 2.30 (s, 3H), 1.23 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.78, 149.76, 149.73, 148.00, 147.35, 122.18, 116.88, 106.87, 21.43, 21.26, 13.83, 13.27. IR (KBr) 3066, 3026, 2977, 2930, 2874, 1614, 1575, 1480, 1443, 1419, 1358, 1024 cm^{-1}. HRMS: calcd. 202.1339 $[M+H]^+$ Found: 202.1344.



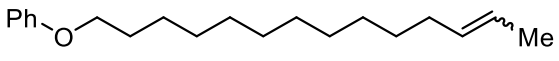
7.a3

7.a3: The reaction was conducted with 41.4 mg **7.a1** in 3 parallel vessels (0.05 mmol for each, 0.15 mmol combined). The titled compound was obtained as a colorless oil (22.8 mg, 65% yield). R_f = 0.3(Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, *J* = 8.0 Hz, 2H), 7.09 – 6.77 (m, 3H), 3.96 (t, *J* = 6.6 Hz, 2H), 1.79 (p, *J* = 6.8 Hz, 2H), 1.53 – 1.44 (m, 2H), 1.38 – 1.24 (m, 12H), 0.89 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.27, 129.53, 120.57, 114.64, 68.03, 32.06, 29.74, 29.72, 29.57, 29.48, 29.46, 26.23, 22.84, 14.27. The spectra match the reported literature.[76]



7.a2'

7.a2': The reaction was conducted with 41.4 mg **7.a1** in 3 parallel vessels (0.05 mmol for each, 0.15 mmol combined). The titled compound was obtained as a colorless oil (3 mg, 5% yield). R_f = 0.7 (Hex/EA= 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.0 Hz, 1H), 7.64 (s, 1H), 7.31 – 7.26 (m, 2H), 7.01 – 6.83 (m, 4H), 6.04 (s, 1H), 3.95 (t, *J* = 6.6 Hz, 2H), 3.10 (q, *J* = 7.5 Hz, 2H), 2.70 – 2.57 (m, 2H), 2.40 (s, 3H), 1.78 (p, *J* = 6.7 Hz, 2H), 1.68 (p, *J* = 8.0, 7.5 Hz, 2H), 1.47 – 1.29 (m, 12H), 1.24 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.28, 154.61, 153.90, 149.72, 147.82, 147.36, 129.53, 122.17, 120.57, 117.06, 114.65, 105.72, 68.04, 29.78, 29.71, 29.65, 29.65, 29.61, 29.55, 29.46, 28.63, 26.22, 21.52, 21.29, 13.28. IR (KBr) 3028, 2932, 2856, 1608, 1569, 1474, 1423, 1252, 1041 cm^{-1}. HRMS: calcd. 420.3009 $[M+H]^+$ Found: 420.3005.



7.a3'

7.a3': The reaction was conducted with 41.4 mg **7.a1** in 3 parallel vessels (0.05 mmol for each, 0.15 mmol combined). The titled compound was obtained as a colorless oil (4.1 mg, 9% yield). R_f = 0.2 (Hex). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.25 (m, 3H), 6.96 – 6.87 (m, 3H), 5.41 (dt, *J* = 9.4, 4.7 Hz, 2H), 3.95 (t, *J* = 6.6 Hz, 2H), 2.07 – 1.90 (m, 2H), 1.78 (p, *J* = 6.7 Hz, 2H), 1.69 – 1.57 (m, 3H), 1.46 (dt, *J* = 14.7, 6.8 Hz, 2H), 1.28 (s, 14H).

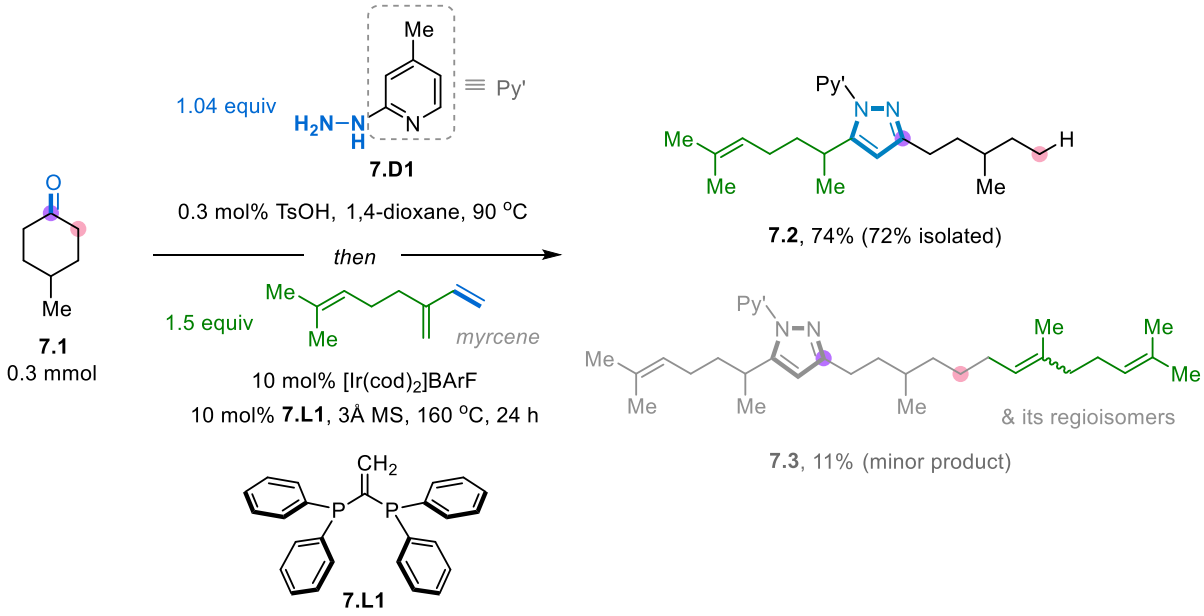
^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were found at δ 159.28, 131.84, 131.06, 129.53, 124.67, 123.74, 120.58, 114.64, 68.04, 32.77, 31.75, 29.78, 29.76, 29.74, 29.73, 29.71, 29.68, 29.56, 29.46, 29.36, 27.00, 26.22, 22.81, 18.08, 15.44, 14.31, 14.28, 12.90. IR (KBr) 3025, 2932, 2859, 1606, 1496, 1471, 1246, 1041 cm^{-1}. HRMS: calcd. 289.2526 $[M+H]^+$ Found: 289.2526.

Typical procedure for control experiments

An 8 mL vial was charged with **7.a1** (13.8 mg, 0.05 mmol, 1.0 equiv) and 2-hydrazineyl-4-methylpyridine **7.D1** (6.4 mg, 0.052 mmol, 1.04 equiv), and transferred into a glove box. 1,4-Dioxane (1 mL) and a stock solution of $TsOH{\cdot}H_2O$ in 1,4-dioxane (0.05 M, 3.0 μL, 0.003 equiv) were then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 90 °C for 5 hours. After cooled to room temperature, the vial was opened, and charged with the transition metal catalyst (0.005 mmol, 0.1 equiv) and the ligand (0.005 mmol, 0.1 equiv). The vial was sealed and transferred into the glove box, and then opened and purged under N_2 atmosphere for 3 mins. Pre-dried 3Å molecular sieve (100 mg) and 1,3-butadiene (20% wt.% in PhMe, 170 μL, ca. 10 equiv) were then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 130 or 160 °C under stirring for 72 hours. After cooled to room temperature, the reaction mixture was filtered through a short plug of Celite and concentrated *in vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yields of the products were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard. All control experiments were conducted at

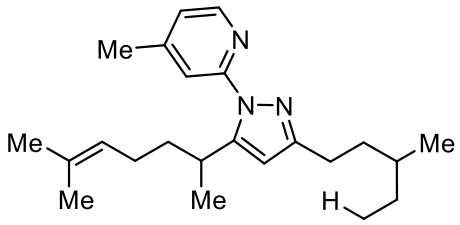
0.05 mmol scale, and changes were made on the "*standard conditions*" described above according to **Table 7.1**.

Optimal condition when using non-volatile 1,3-dienes



A 1,4-dioxane (0.15 mL) solution of **7.1** (33.6 mg, 0.3 mmol, 1.0 equiv), **7.D1** (38.4 mg, 0.312 mmol, 1.04 equiv), and *p*-TsOH·H_2O (*stock solution in 1,4-dioxane*, 0.05 M, 18 µL, 0.003 equiv) was heated at 90 °C for 5 hours in a 4 mL vial. After cooled to room temperature, the vial was charged first with [Ir(cod)$_2$]BArF (38 mg, 0.03 mmol, 0.1 equiv) and **7.L1** (12 mg, 0.03 mmol, 0.1 equiv) under air atmosphere, and then with 3Å molecular sieve (*pre-dried*, 220 mg) and myrcene (78 µL, 0.45 mmol, 1.5 equiv) in a glovebox. The vial was sealed and heated at 160 °C under stirring for 24 hours. The reaction mixture was filtered through a short plug of Celite and concentrated *in vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yields of the products were determined by ^{1}H NMR using

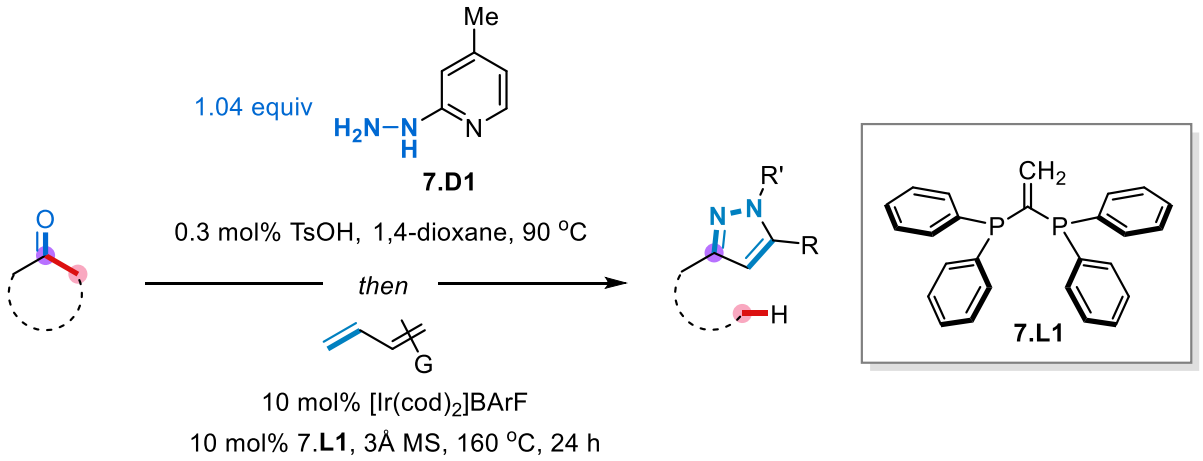
1,1,2,2-tetrachloroethane as the internal standard. Product **7.2** could also be isolated by flash column chromatography over silica (hexane/ethyl acetate, 20:1).



7.2

7.2: The titled compound was isolated as a colorless oil (75.8 mg, 72% yield, inseparable mixture of diastereomers). R_f = 0.7 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.1 Hz, 1H), 7.58 (d, *J* = 1.5 Hz, 1H), 6.97 (dd, *J* = 5.1, 1.4 Hz, 1H), 6.04 (s, 1H), 5.07 – 4.98 (m, 1H), 3.82 (h, *J* = 6.9 Hz, 1H), 2.74 – 2.55 (m, 2H), 2.39 (s, 3H), 1.94 (q, *J* = 7.6 Hz, 2H), 1.77 – 1.65 (m, 2H), 1.62 (s, 3H), 1.54 – 1.37 (m, 7H), 1.24 (d, *J* = 6.9 Hz, 3H), 1.23 – 1.14 (m, 1H), 0.93 (d, *J* = 6.3 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were observed at δ 154.68, 153.92, 151.79, 149.65, 147.35, 131.50, 124.40, 122.35, 117.87, 103.96, 103.95, 37.36, 36.44, 34.47, 30.68, 29.46, 29.44, 26.26, 25.88, 25.79, 21.22, 20.58, 19.19, 19.17, 17.62, 11.48. IR (KBr) 3019, 2963, 2930, 2853, 1607, 1567, 1472, 1377, 1012 cm^{-1}. HRMS: calcd. 354.2904 $[M+H]^+$ Found: 354.2913.

Application I: Pyrazole synthesis through aromatization-driven C-C cleavage



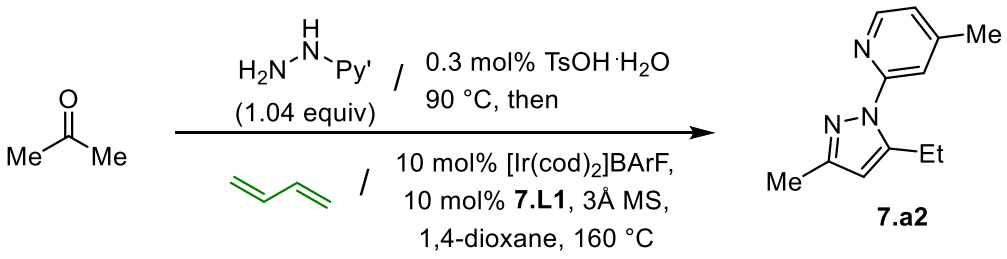
General procedure A *(with non-volatile dienes, e.g. >9 carbons)*: For a 0.3 mmol scale reaction, a 1,4-dioxane (0.15 mL) solution of the ketone substrate (0.3 mmol, 1.0 equiv), **7.D1** (38.4 mg, 0.312 mmol, 1.04 equiv), and *p*-TsOH·H_2O (*stock solution in 1,4-dioxane*, 0.05 M, 18 μL, 0.003 equiv) was heated at 90 °C for 5 hours in a 4 mL vial. After cooled to room temperature, the vial was charged first with $[Ir(cod)_2]BArF$ (38 mg, 0.03 mmol, 0.1 equiv) and **7.L1** (12 mg, 0.03 mmol, 0.1 equiv) under air atmosphere, and then with 3Å molecular sieve (pre-dried, 220 mg) and 1,3-diene (0.45-0.60 mmol, 1.5-2.0 equiv) in a glovebox. The vial was sealed and heated at 160 °C under stirring for 24-36 hours monitored by TLC. After cooled to room temperature, the reaction mixture was filtered through a short plug of Celite, concentrated *in vacuo*, and further purified by flash column chromatography over silica (hexane/ethyl acetate) to give the products**.**

General procedure B *(with volatile dienes, such as 1,3-butadiene and isoprene)*: 1 mL 1,4-dioxane and 100 mg 3Å molecular sieve was used for a 0.1 mmol scale reaction. Due to the volatility, 0.7-1.2 mmol 1,3-diene (7-12 equiv) was used as coupling partner. The rest is

the same as **General procedure A**.

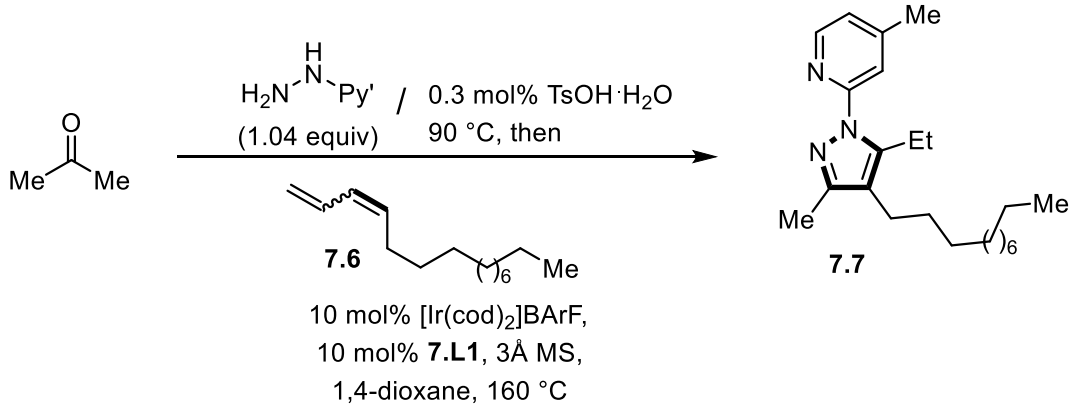
Note 1 When 1,3-butadiene was used as the 1,3-diene coupling partner, its solution in PhMe was used (purchased from *Sigma-Aldrich*, 20% wt.%). For a 0.1 mmol scale reaction, 240-400 μL was used (0.7-1.2 mmol, 7-12 equiv, *see infra*).

Note 2 When *cyclohexanones* was used as the ketone substrates, a slightly modified procedure was used. After the addition of $[Ir(cod)_2]BArF$ and **7.L1,** the resulting mixture was stirred at room temperature for 2-3 mins before adding other reaction components. The rest is the same as the general procedure.

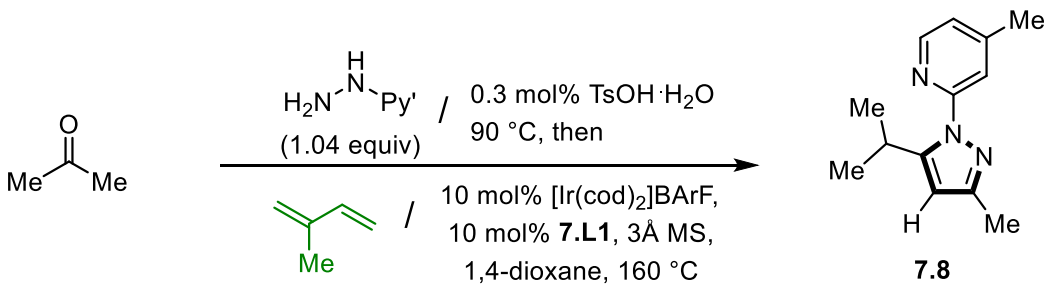


Following **General procedure B,** the reaction was conducted at 0.1 mmol scale with 5.8 mg acetone as the ketone substrates and 400 μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions were conducted (0.1 mmol for each, 0.2 mmol in total) and combined, giving compound **7.a2** as a colorless oil (30.2 mg, 75% yield). R_f = 0.6 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 5.1 Hz, 1H), 7.63 (t, *J* = 0.8 Hz, 1H), 6.96 (ddd, *J* = 5.0, 1.5, 0.7 Hz, 1H), 6.02 (s, 1H), 3.09 (qd, *J* = 7.5, 0.9 Hz, 2H), 2.38 (t, *J* = 0.7 Hz, 3H), 2.30 (s, 3H), 1.23 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.78, 149.76, 149.73, 148.00, 147.35, 122.18, 116.88, 106.87, 21.43, 21.26, 13.83, 13.27. IR (KBr)

3066, 3026, 2977, 2930, 2874, 1614, 1575, 1480, 1443, 1419, 1358, 1024 cm^{-1}. HRMS: calcd. 202.1339 $[M+H]^+$ Found: 202.1344.



Following modified **General Procedure A**, the reaction was conducted at 0.05 mmol scale using 10 equiv of diene **7.6** (104 mg, 1.0 mmol) in 0.4 mL 1,4-dioxane for 48 h. Two parallel reactions were conducted (0.05 mmol for each, 0.1 mmol in total) and combined, giving compound **7.7** as a colorless oil (15.8 mg, 45% yield). R_f = 0.7 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, C_6D_6) δ 8.06 (d, *J* = 5.0 Hz, 1H), 8.00 (s, 1H), 6.32 (dd, *J* = 5.0, 1.5 Hz, 1H), 3.26 (q, *J* = 7.3 Hz, 2H), 2.32 (t, *J* = 7.6 Hz, 2H), 2.29 (s, 3H), 1.76 (s, 3H), 1.46 (p, *J* = 7.2 Hz, 2H), 1.36 – 1.20 (m, 19H), 0.91 – 0.81 (m, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ 155.01, 149.17, 148.88, 147.26, 143.69, 121.31, 119.79, 116.36, 32.36, 31.58, 30.18, 30.14, 30.14, 30.08, 30.02, 29.84, 23.76, 23.15, 20.79, 19.91, 14.95, 14.41, 12.65. IR (KBr) 2926, 2853, 1608, 1583, 1445, 1412 cm^{-1}. HRMS: calcd. 466.3060 $[M+H]^+$ Found: 466.307.

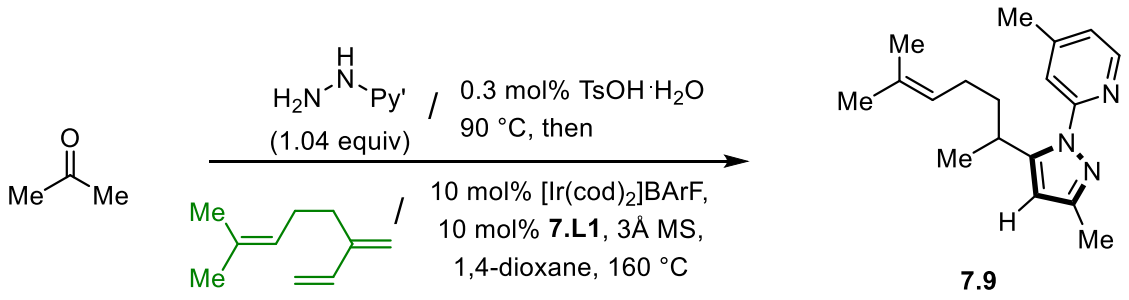


7.8

7.8: Following **General procedure B,** the reaction was conducted at 0.1 mmol scale with 5.8 mg acetone as the ketone substrates and 120 μL isoprene. Two parallel reactions were conducted (0.1 mmol for each, 0.2 mmol in total) and combined, giving the titled compound as a colorless oil (33.4 mg, 78% yield). R_f = 0.65 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 5.1, 0.7 Hz, 1H), 7.68 – 7.47 (m, 1H), 6.98 (ddd, *J* = 5.0, 1.6, 0.8 Hz, 1H), 6.04 (s, 1H), 3.93 (pd, *J* = 6.9, 0.7 Hz, 1H), 2.39 (s, 3H), 2.30 (s, 3H), 1.21 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.90, 152.95, 149.79, 149.65, 147.43, 122.43, 117.64, 104.92, 26.16, 22.86, 21.25, 13.83. IR (KBr) 3064, 3023, 2971, 2928, 2874, 1609, 1571, 1461, 1381, 1358, 1299, 1095, 1018 cm^{-1}. HRMS: calcd. 216.1495 $[M+H]^+$ Found: 216.1503.

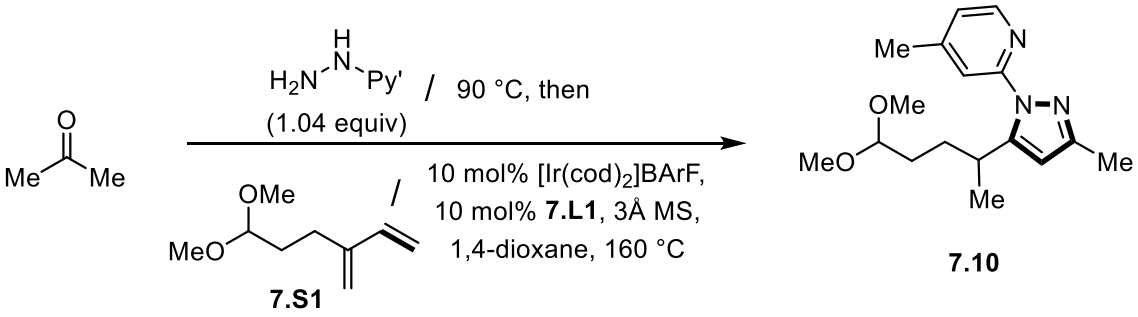
7.8 could also be synthesized following slightly modified **General procedure B** *with the use of less diene coupling partner*: A 2 mL vial was charged with acetone (5.8 mg, 0.1 mmol, 1.0 equiv) and 2-hydrazineyl-4-methylpyridine **7.D1** (12.8 mg, 0.104 mmol, 1.04 equiv), and transferred into a glove box. 1,4-Dioxane (0.5 mL) and a stock solution of $TsOH·H_2O$ in 1,4-dioxane (0.05 M, 6.0-10.0 μL, 0.003-0.005 equiv) was added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 90 °C for 5 hours. After cooled to room temperature, the vial was charged with $[Ir(cod)_2]BArF$ (12.8 mg, 0.01 mmol,

0.1 equiv) and **7.L1** (4.0 mg, 0.01 mmol, 0.1 equiv), transferred into the glove box, and purged under N_2 atmosphere for 3 mins. Pre-dried 3Å molecular sieve (100 mg) and isoprene (60 µL, 6 equiv) were then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 160 °C under stirring for 72 hours. After cooled to room temperature, the reaction mixture was filtered through a short plug of Celite, concentrated *in vacuo*, and further purified by flash column chromatography over silica (hexane/ethyl acetate, from 40:1 to 20:1). Combining 2 parallel reactions furnished **7.8** in 77% yield (33.0 mg) as a colorless oil.

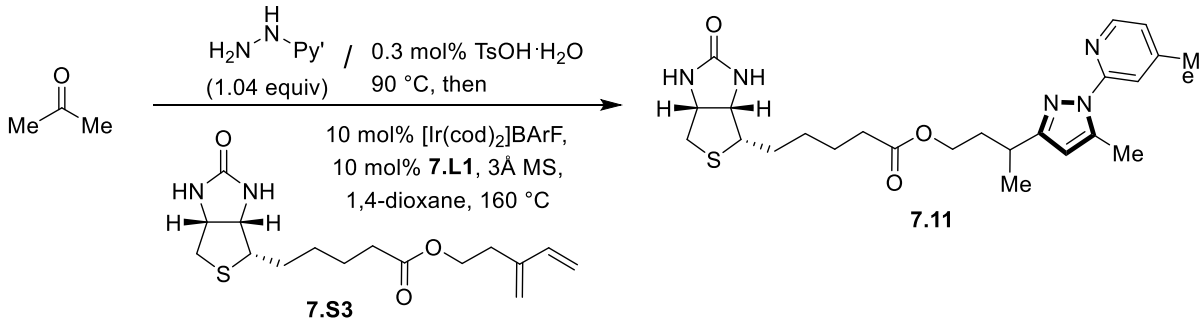


7.9: Following **General procedure A,** the reaction was conducted at 0.2 mmol scale with 5.8 mg acetone and 69 µL myrcene (2 equiv) in 0.07 ml 1,4-dioxane. **7.9** was isolated as a colorless oil (42.3 mg, 75% yield). R_f = 0.3 (hexane/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 5.0 Hz, 1H), 7.67 – 7.39 (m, 1H), 7.11 – 6.84 (m, 1H), 6.03 (s, 1H), 5.02 (ddq, *J* = 7.2, 5.7, 1.5 Hz, 1H), 3.82 (h, *J* = 6.9 Hz, 1H), 2.40 (s, 3H), 2.31 (s, 3H), 1.95 (q, *J* = 7.7 Hz, 2H), 1.72 – 1.61 (m, 4H), 1.51 – 1.41 (m, 4H), 1.24 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.89, 152.08, 149.73, 149.71, 147.41, 131.59, 124.41, 122.44, 117.80, 105.22, 37.39, 30.68, 25.91, 25.81, 21.25, 20.61, 17.68, 13.86. IR (KBr)

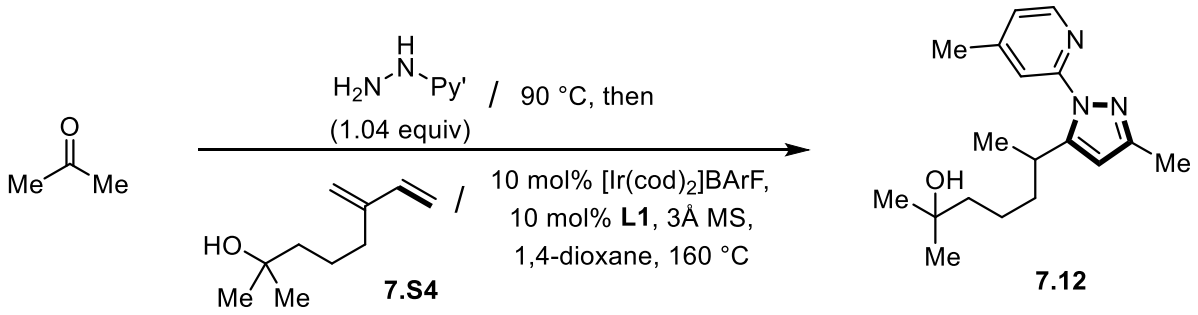
3064, 3024, 2969, 2918, 2861, 1605, 1573, 1455, 1415, 1381, 1018 cm^{-1}. HRMS: calcd. 284.2121 $[M+H]^+$ Found: 284.2132.



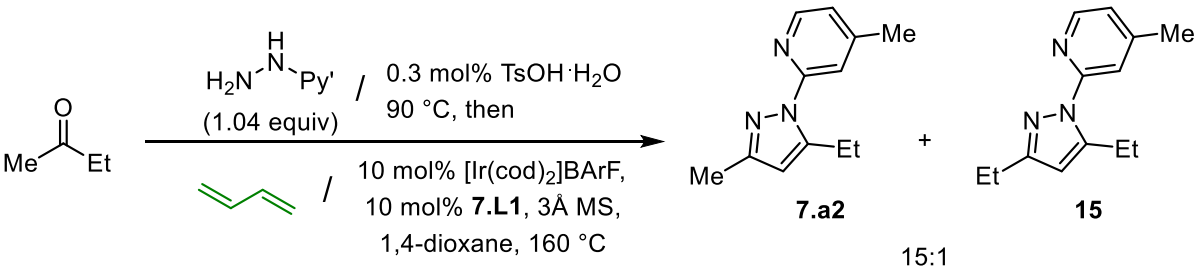
7.10: Following **General procedure A,** the reaction was conducted at 0.2 mmol scale with 5.8 mg acetone and 63 mg **7.S1** (2 equiv) in 0.07 ml 1,4-dioxane. No *p*-TsOH was used for the condensation step. **7.10** was isolated as a colorless oil (36.2 mg, 60% yield). R_f = 0.4 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 5.0, 0.7 Hz, 1H), 7.59 (s, 1H), 6.98 (dd, *J* = 5.0, 0.8 Hz, 1H), 6.03 (s, 1H), 4.28 (t, *J* = 5.4 Hz, 1H), 3.87 (p, *J* = 6.7 Hz, 1H), 3.23 (d, *J* = 3.2 Hz, 6H), 2.39 (s, 3H), 2.29 (s, 3H), 1.73 – 1.64 (m, 1H), 1.62 – 1.47 (m, 3H), 1.23 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.83, 151.56, 149.81, 149.74, 147.37, 122.45, 117.71, 105.37, 104.57, 52.82, 52.43, 32.09, 30.81, 30.23, 21.24, 20.81, 13.84. IR (KBr) 2957, 2932, 2828, 1608, 1572, 1457, 1136, 1060 cm^{-1}. HRMS: calcd. 304.2020 $[M+H]^+$ Found: 304.2023.



7.11: Following **General procedure A,** the reaction was conducted at 0.1 mmol scale with 5.8 mg acetone and 87 mg **7.S3** (2.7 equiv) in 0.05 ml 1,4-dioxane for 48 h. **7.11** was isolated as a colorless oil (18.7 mg, 40% yield, inseparable mixture of diastereomers). R_f = 0.35 (DCM/MeOH = 10:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.0 Hz, 1H), 7.61 (s, 1H), 7.00 (d, *J* = 4.8 Hz, 1H), 6.05 (s, 1H), 5.76 (d, *J* = 16.8 Hz, 1H), 5.32 (s, 1H), 4.48 (dd, *J* = 7.8, 5.0 Hz, 1H), 4.27 (dd, *J* = 7.5, 4.8 Hz, 1H), 4.14 – 3.95 (m, 3H), 3.17 – 3.06 (m, 1H), 2.88 (dd, *J* = 12.9, 4.5 Hz, 1H), 2.71 (d, *J* = 12.8 Hz, 1H), 2.40 (s, 3H), 2.30 (s, 3H), 2.24 – 2.17 (m, 2H), 2.01 (dqd, *J* = 13.8, 6.9, 2.7 Hz, 1H), 1.83 (ddd, *J* = 12.1, 7.5, 5.9 Hz, 1H), 1.71 – 1.57 (m, 4H), 1.45 – 1.36 (m, 2H), 1.27 (dd, *J* = 6.9, 1.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.69, 163.62, 153.72, 150.84, 150.82, 149.99, 149.97, 149.83, 147.36, 122.57, 117.63, 117.61, 105.53, 62.87, 62.05, 60.22, 55.48, 40.67, 35.92, 35.88, 33.95, 28.45, 28.34, 24.84, 24.82, 21.29, 20.92, 13.84. IR (KBr) 3252, 2934, 2863, 1709, 1609, 1458, 1413, 1267, 1182 cm^{-1}. HRMS: calcd. 472.2377 $[M+H]^+$ Found: 472.2387.



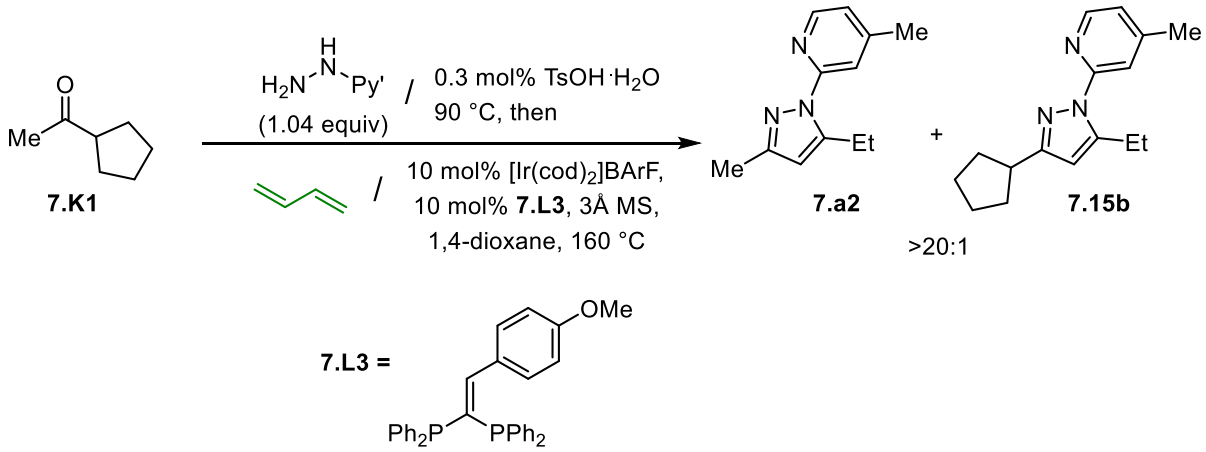
7.12: Following **General procedure A,** the reaction was conducted at 0.2 mmol scale with 5.8 mg acetone and 62 mg **7.S4** (2 equiv) in 0.07 ml 1,4-dioxane. No *p*-TsOH was used for the condensation step. **7.12** was isolated as a colorless oil (37.8 mg, 63% yield). R_f = 0.35 (hexane/ethyl acetate = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 0.7 Hz, 1H), 7.58 (s, 1H), 6.99 (dd, *J* = 5.1, 0.8 Hz, 1H), 6.02 (s, 1H), 3.82 (h, *J* = 6.9 Hz, 1H), 2.39 (s, 3H), 2.30 (s, 3H), 1.65 (dq, *J* = 13.9, 7.0 Hz, 1H), 1.49 – 1.42 (m, 1H), 1.40 – 1.27 (m, 4H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 3.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.84, 152.08, 149.87, 149.76, 147.39, 122.54, 117.95, 105.15, 71.02, 43.84, 37.83, 30.86, 29.46, 29.19, 22.07, 21.24, 20.79, 13.86. IR (KBr) 3407, 2969, 2935, 2867, 1614, 1563, 1457, 1415, 1367 cm^{-1}. HRMS: calcd. 302.2227 $[M+H]^+$ Found: 302.2236.



Following **General procedure B,** the reaction was conducted at 0.1 mmol scale with 7.2 mg 2-butanone and 400 μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions

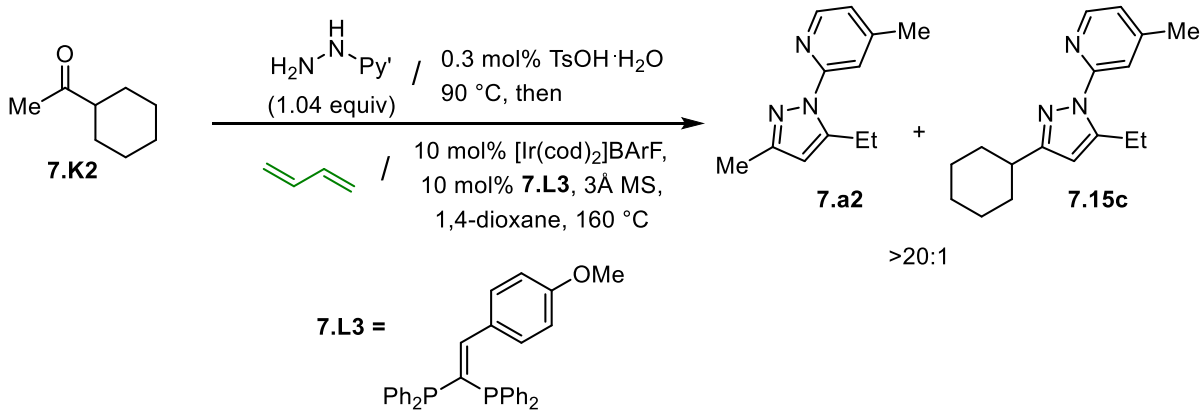
were conducted (0.1 mmol for each, 0.2 mmol in total) and combined, yielding pyrazoles **7.a2** and **7.15** in 15:1 ratio as determined by ^{1}H NMR analysis of the crude mixture. The compound **7.a2** was isolated as a colorless oil (31.1 mg, 78% yield). The compound **7.15** was isolated as a colorless oil (1.9 mg, 4% yield). The characterization data for compound **7.a2** has been reported *vide supra*.

7.15: R_f = 0.7 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 5.0, 0.8 Hz, 1H), 7.73 – 7.57 (m, 1H), 6.96 (ddd, *J* = 5.1, 1.5, 0.7 Hz, 1H), 6.06 (s, 1H), 3.10 (qd, *J* = 7.5, 0.9 Hz, 2H), 2.68 (q, *J* = 7.6 Hz, 2H), 2.39 (s, 3H), 1.26 (dt, *J* = 14.8, 7.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.71, 153.85, 149.71, 147.87, 147.34, 122.17, 116.98, 105.24, 21.77, 21.50, 21.26, 13.95, 13.25. IR (KBr) 3064, 3021, 2971, 2930, 2873, 1613, 1571, 1478, 1421, 1358, 1304, 1050, 1010 cm^{-1}. HRMS: calcd. 216.1495 $[M+H]^+$ Found: 216.1500.

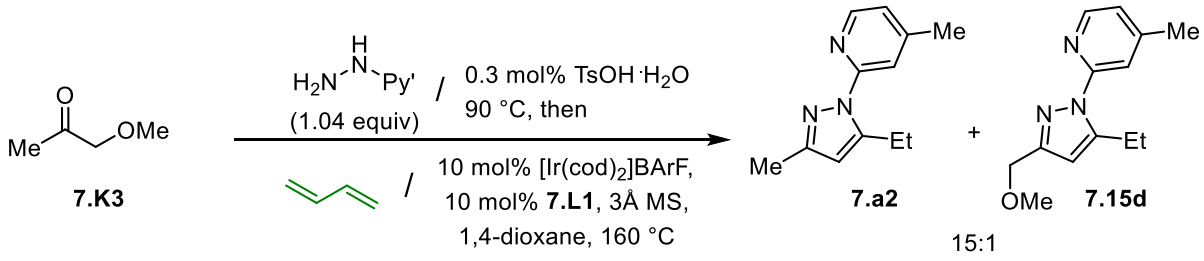


Following slightly modified **General procedure B,** the reaction was conducted at 0.1 mmol scale with 11.2 mg **7.K1** as the ketone substrates, **7.L3** as the ligand (5.0 mg), and 400

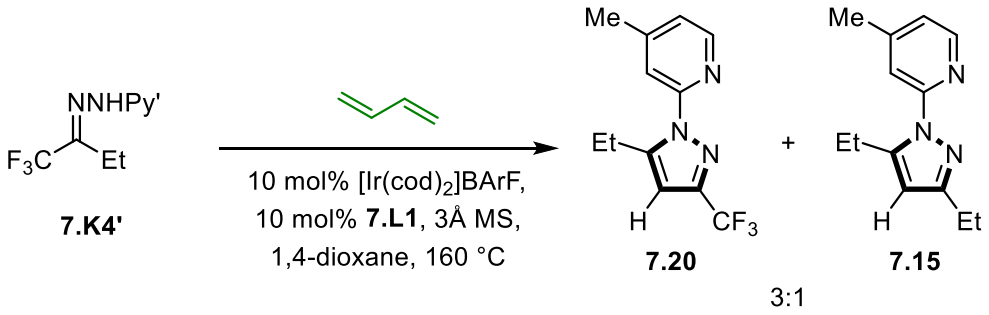
μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions were conducted (0.1 mmol for each, 0.2 mmol in total) and combined, giving compound **7.a2** as a colorless oil (28 mg, 78% yield). The ratio between compounds **7.a2** and **7.15b** was determined to be >20:1 according to the ^{1}H NMR analysis of the crude mixture. The characterization data for compound **7.a2** has been reported *vide supra*.



Following slightly modified **General procedure B,** the reaction was conducted at 0.1 mmol scale with 12.6 mg **7.K2** as the ketone substrates, **7.L3** as the ligand (5.0 mg), and 400 μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions were conducted (0.1 mmol for each, 0.2 mmol in total) and combined, giving compound **7.a2** as a colorless oil (32 mg, 80% yield). The ratio between compounds **7.a2** and **7.15c** was determined to be >20:1 according to the ^{1}H NMR analysis of the crude mixture. The characterization data for compound **7.a2** has been reported *vide supra*.



Following **General procedure B,** the reaction was conducted at 0.1 mmol scale with 8.8 mg **7.K3** as the ketone substrates and 400 μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions were conducted (0.1 mmol for each, 0.2 mmol in total) and combined, giving compound **7.a2** as a colorless oil (34 mg, 85% yield). The ratio between compounds **7.a2** and **7.15d** was determined to be >20:1 according to the ^{1}H NMR analysis of the crude mixture. The characterization data for compound **7.a2** has been reported *vide supra*.

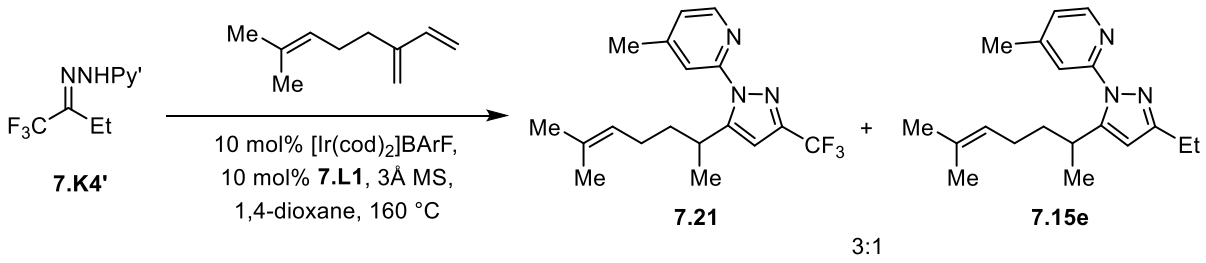


The reaction was conducted following modified **General procedure B**: A 4 mL vial was charged with the hydrazone **7.K4'** (21.7 mg, 0.1 mmol, 1.0 equiv) which was derived from its corresponding ketone, [Ir(cod)$_2$]BArF (12.8 mg, 0.01 mmol, 0.1 equiv), **7.L1** (4.0 mg, 0.01 mmol, 0.1 equiv) and 1,4-dioxane (1 mL). The vial was transferred into the glove box, and was charged with 1,3-butadiene (20% wt.% in PhMe, 200 μL, ca. 12 equiv). The vial was sealed, transferred out of the glove box, and heated at 160 °C under stirring for 24

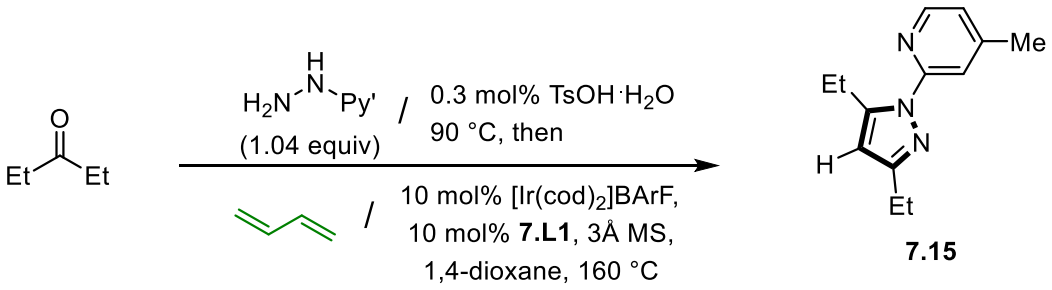
hours. After cooled to room temperature, the reaction mixture was filtered through a short plug of Celite, concentrated *in vacuo*, and further purified by flash column chromatography over silica (hexane/ethyl acetate, from 30:1 to 20:1). Combining 2 parallel reactions furnished **7.20** in 50% yield (25.3 mg) as a colorless oil, and **7.15** in 16% yield (6.9 mg). The characterization data for compound **7.15** has been reported *vide supra*.

7.20: R_f = 0.5 (hexane /ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 5.0, 0.7 Hz, 1H), 7.75 – 7.61 (m, 1H), 7.10 (ddd, *J* = 5.1, 1.5, 0.7 Hz, 1H), 6.48 (s, 1H), 3.23 – 3.07 (m, 2H), 2.44 (s, 3H), 1.28 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.04, 150.48, 148.95, 147.53, 143.08 (q, *J* = 38.1 Hz), 123.81, 121.49 (q, *J* = 268.8 Hz), 117.99, 104.46 (q, *J* = 2.0 Hz), 21.32, 21.30, 13.01. IR (KBr) 3068, 2975, 2932, 2880, 1611, 1573, 1490, 1419, 1247, 1137, 1052, 973 cm^{-1}. HRMS: calcd. 256.1056 $[M+H]^+$ Found: 256.1061.

*General procedure for hydrazones formation from the corresponding ketones and 2-hydrazineyl-4-methylpyridine **7.D1***: A MeOH solution (1 M) of the ketone substrate (1 equiv) and 2-hydrazineyl-4-methylpyridine **7.D1** (1 equiv) was heated at 60 °C for 2-4 hours (monitored by TLC). After cooled to room temperature, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography over silica (hexane/ethyl acetate, typically from 10:1 to 3:1) to give the hydrazone product in generally >90% yield.

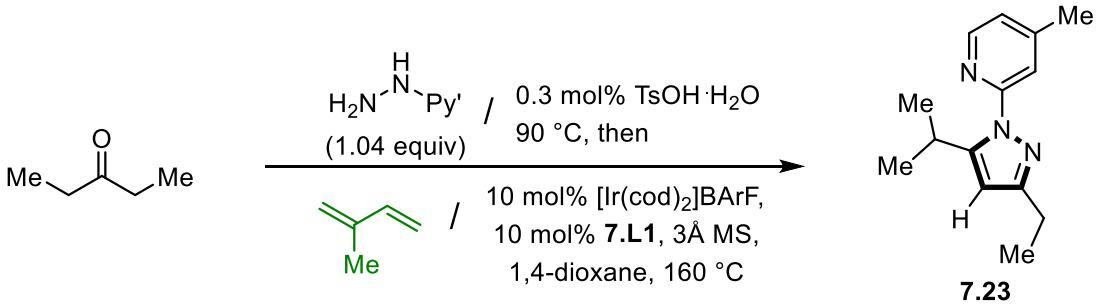


The reaction was conducted following modified **General procedure A**: A 4 mL vial was charged with the hydrazone **7.K4'** (69.3 mg, 0.3 mmol, 1.0 equiv), $[Ir(cod)_2]BArF$ (12.8 mg, 0.01 mmol, 0.1 equiv), **7.L1** (4.0 mg, 0.01 mmol, 0.1 equiv) and 1,4-dioxane (0.2 mL). The vial was transferred into the glove box, and was charged with myrcene (104 μL, 2.0 equiv). The vial was sealed and heated at 160 °C under stirring for 48 hours. After cooled to room temperature, the reaction mixture was filtered through a short plug of Celite, concentrated *in vacuo*, and further purified by flash column chromatography over silica (hexane/ethyl acetate, from 30:1 to 20:1). **7.21** was isolated in 50% yield (50.5 mg) as a colorless oil, and **7.15e** was isolated in 18% yield (16 mg). **7.21**: R_f = 0.75 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 5.0, 0.7 Hz, 1H), 7.68 – 7.53 (m, 1H), 7.12 (ddd, *J* = 5.0, 1.5, 0.8 Hz, 1H), 6.48 (s, 1H), 4.99 (ddq, *J* = 8.6, 5.7, 1.4 Hz, 1H), 3.81 (h, *J* = 6.9 Hz, 1H), 2.44 (s, 3H), 1.95 (q, *J* = 7.4 Hz, 2H), 1.75 – 1.65 (m, 1H), 1.62 (t, *J* = 1.3 Hz, 3H), 1.55 – 1.43 (m, 4H), 1.27 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.07, 153.03, 150.49, 147.60, 143.13 (q, *J* = 38.0 Hz), 131.98, 124.03, 123.89, 121.53 (q, *J* = 268.9 Hz), 118.85, 102.96 (q, *J* = 1.9 Hz), 37.12, 30.69, 25.78, 25.74, 21.25, 20.42, 17.64. IR (KBr) 2973, 2926, 2857, 1607, 1571, 1484, 1419, 1249, 1137 cm^{-1}. HRMS: calcd. 338.1839 $[M+H]^+$ Found: 338.1843.



7.15

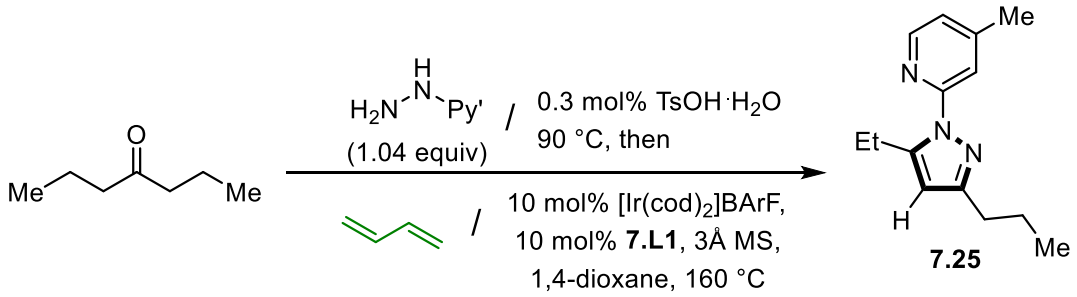
Following **General procedure B,** the reaction was conducted at 0.1 mmol scale with 8.6 mg 3-pentanone and 400 μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions were conducted (0.1 mmol for each, 0.2 mmol in total) and combined, giving compound **7.15** as a colorless oil (33.2 mg, 77% yield). The characterization data for compound **7.15** has been reported *vide supra*.



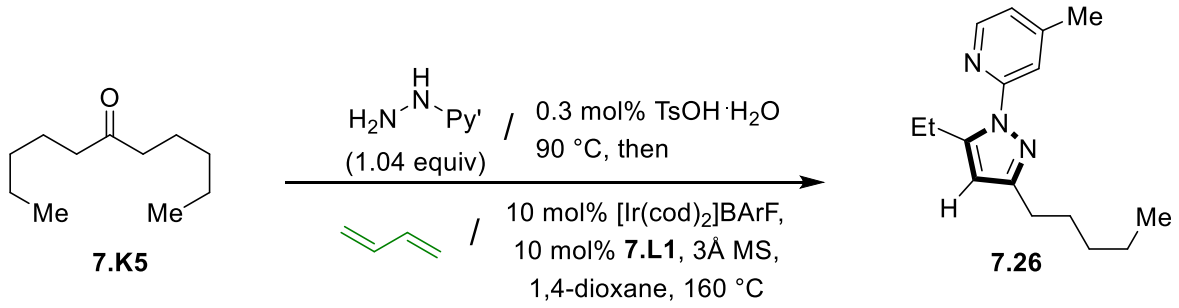
7.23

7.23: Following **General procedure B,** the reaction was conducted at 0.1 mmol scale with 8.6 mg 3-pentanone and 120 μL isoprene. Two parallel reactions were conducted (0.1 mmol for each, 0.2 mmol in total) and combined, giving the titled compound as a colorless oil (37.4 mg, 82% yield). R_f = 0.7 (Hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 5.0 Hz, 1H), 7.73 – 7.54 (m, 1H), 7.05 – 6.92 (m, 1H), 6.07 (s, 1H), 3.93 (pd, *J* = 6.8, 0.7 Hz, 1H), 2.68 (q, *J* = 7.6 Hz, 2H), 2.39 (s, 3H), 1.28 (t, *J* = 7.6 Hz, 3H), 1.22 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.58, 153.97, 152.80, 149.77, 147.42, 122.41,

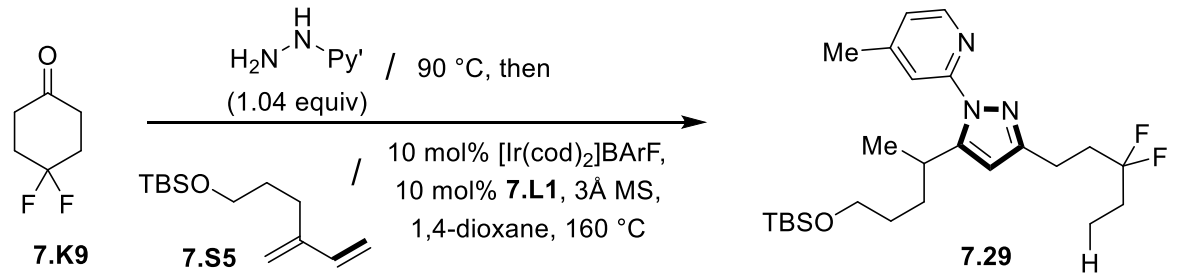
117.74, 103.28, 26.20, 22.86, 21.78, 21.25, 13.89. IR (KBr) 3066, 3019, 2969, 2932, 2874, 1605, 1571, 1462, 1415, 1383, 1299, 1010 cm^{-1}. HRMS: calcd. 230.1652 $[M+H]^+$ Found: 230.1661.



7.25: Following **General procedure B,** the reaction was conducted at 0.1 mmol scale with 11.4 mg 4-heptanone and 400 μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions were conducted (0.1 mmol for each, 0.2 mmol in total) and combined, giving the titled compound as a colorless oil (35.6 mg, 78% yield). R_f = 0.7 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 5.1, 0.7 Hz, 1H), 7.64 (dt, *J* = 1.6, 0.8 Hz, 1H), 6.96 (ddd, *J* = 5.1, 1.6, 0.7 Hz, 1H), 6.04 (s, 1H), 3.10 (qd, *J* = 7.4, 0.9 Hz, 2H), 2.71 – 2.56 (m, 2H), 2.39 (s, 3H), 1.70 (h, *J* = 7.4 Hz, 2H), 1.24 (t, *J* = 7.5 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.39, 153.86, 149.71, 147.78, 147.33, 122.16, 117.04, 105.73, 30.60, 22.99, 21.49, 21.26, 14.17, 13.24. IR (KBr) 3062, 3022, 2963, 2932, 2872, 1605, 1571, 1476, 1419, 1364, 1141, 1052, 1006 cm^{-1}. HRMS: calcd. 230.1652 $[M+H]^+$ Found: 230.1658.

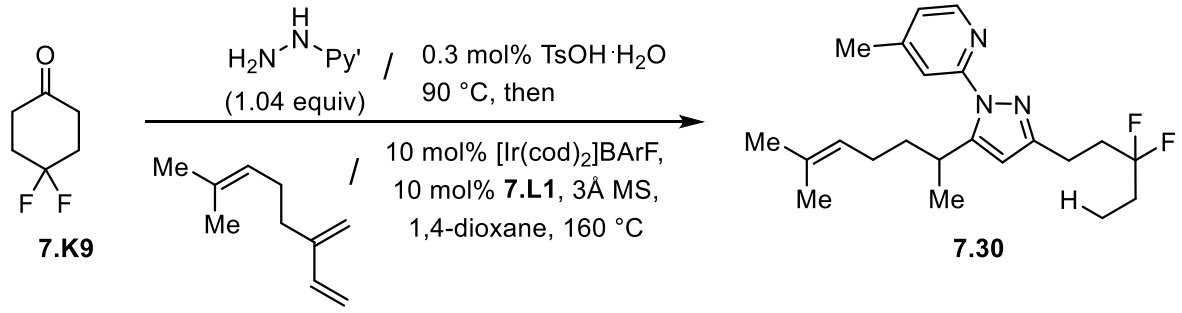


7.26: Following **General procedure B,** the reaction was conducted at 0.1 mmol scale with 17 mg **7.K5** and 400 μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions were conducted (0.1 mmol for each, 0.2 mmol in total) and combined, giving the titled compound as a colorless oil (41.8 mg, 81% yield). R_f = 0.75 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 5.1, 0.7 Hz, 1H), 7.64 (dt, *J* = 1.5, 0.8 Hz, 1H), 7.03 – 6.86 (m, 1H), 6.04 (s, 1H), 3.10 (qd, *J* = 7.5, 0.9 Hz, 2H), 2.69 – 2.59 (m, 2H), 2.39 (s, 3H), 1.77 – 1.60 (m, 2H), 1.42 – 1.33 (m, 4H), 1.24 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.61, 153.87, 149.71, 147.78, 147.33, 122.16, 117.04, 105.70, 31.88, 29.47, 28.58, 22.67, 21.50, 21.27, 14.20, 13.25. IR (KBr) 3060, 3023, 2959, 2924, 2861, 1607, 1569, 1480, 1423, 1362, 1006 cm^{-1}. HRMS: calcd. 258.1965 $[M+H]^+$ Found: 258.1970.



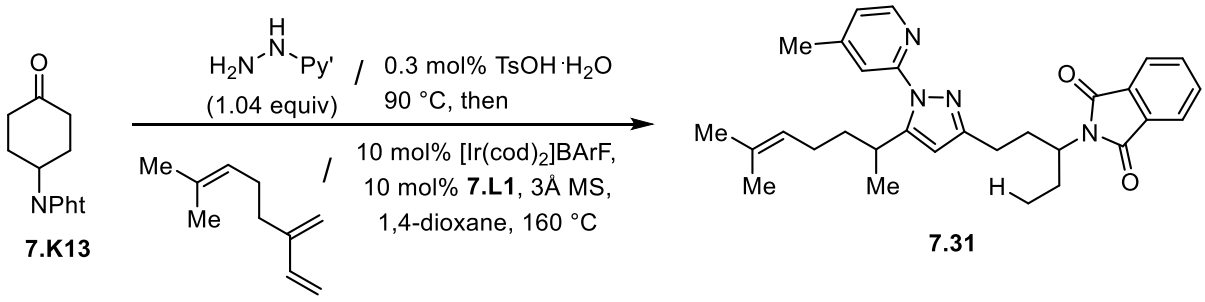
7.29: Following **General procedure A,** the reaction was conducted at 0.2 mmol scale

with 26.8 mg **7.K9** and 59 mg **7.S5** in 0.07 mL 1,4-dioxane. No *p*-TsOH was used for the condensation step. The titled compound was isolated as a colorless oil (53.5 mg, 58% yield). R_f = 0.65 (hexane/ethyl acetate = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.20 (m, 1H), 7.57 (s, 1H), 7.00 (dd, *J* = 5.0, 0.8 Hz, 1H), 6.06 (s, 1H), 3.82 (h, *J* = 6.7 Hz, 1H), 3.52 (t, *J* = 6.2 Hz, 2H), 2.89 – 2.77 (m, 2H), 2.40 (s, 3H), 2.35 – 2.17 (m, 2H), 1.89 (tt, *J* = 16.5, 7.5 Hz, 2H), 1.69 – 1.59 (m, 1H), 1.55 – 1.44 (m, 3H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.03 (t, *J* = 7.5 Hz, 3H), 0.85 (s, 9H), -0.01 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.82, 152.43, 152.02, 149.88, 147.47, 125.17 (t, *J* = 240.6 Hz), 122.67, 117.98, 104.08, 63.29, 35.73 (t, *J* = 25.7 Hz), 33.44, 30.80, 30.61, 29.76 (t, *J* = 26.2 Hz), 26.07, 21.52 (t, *J* = 5.5 Hz), 21.27, 20.82, 18.45, 6.79 (t, *J* = 5.7 Hz), -5.18. IR (KBr) 3064, 2955, 2930, 2857, 1609, 1569, 1474, 1417, 1255, 1200, 1097 cm^{-1}. HRMS: calcd. 466.3060 $[M+H]^+$ Found: 466.3070.



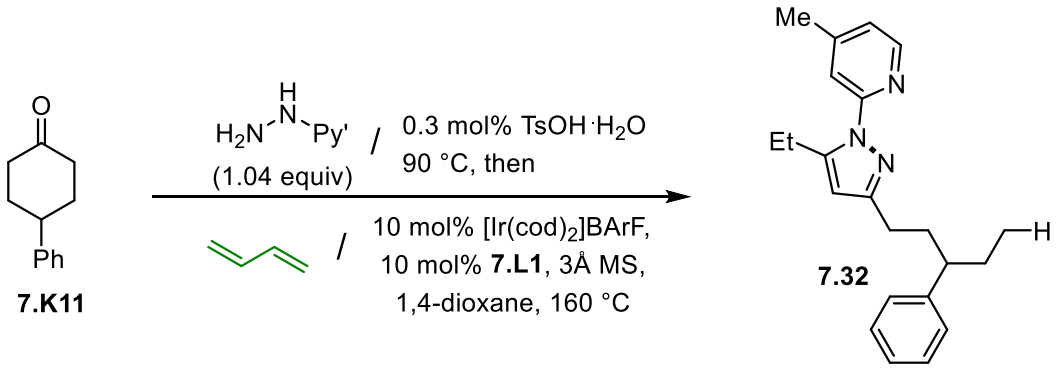
7.30: Following **General procedure A,** the reaction was conducted at 0.3 mmol scale with 40.2 mg **7.K9** and 78 μL myrcene. The titled compound was isolated as a colorless oil (68.3 mg, 61% yield). R_f = 0.65 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 5.1 Hz, 1H), 7.56 (dd, *J* = 1.7, 0.9 Hz, 1H), 7.00 (dd, *J* = 5.1, 1.4 Hz, 1H), 6.06 (s, 1H), 5.01 (dddd, *J* = 7.2, 5.7, 2.9, 1.4 Hz, 1H), 3.79 (h, *J* = 6.9 Hz, 1H), 2.92 – 2.79 (m,

2H), 2.40 (s, 3H), 2.32 – 2.17 (m, 2H), 1.97 – 1.82 (m, 4H), 1.74 – 1.56 (m, 4H), 1.52 – 1.36 (m, 4H), 1.24 (d, J = 6.9 Hz, 3H), 1.03 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.78, 152.45, 152.15, 149.84, 147.48, 131.63, 125.18 (t, J = 240.7 Hz), 124.32, 122.66, 118.03, 104.00, 37.36, 35.75 (t, J = 25.7 Hz), 30.67, 29.76 (t, J = 26.1 Hz), 25.88, 25.80, 21.53 (t, J = 5.5 Hz), 21.27, 20.58, 17.66, 6.79 (t, J = 5.7 Hz). IR (KBr) 3064, 2973, 2926, 2861, 1605, 1575, 1478, 1419, 1372, 1198 cm^{-1}. HRMS: calcd. 376.2559 $[M+H]^+$ Found: 376.2555.



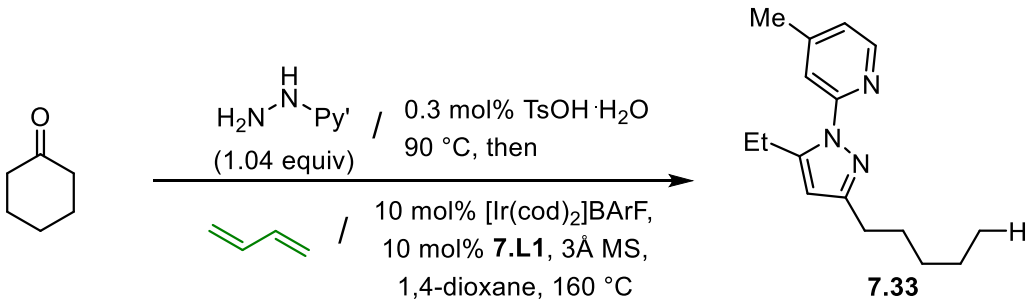
7.31: Following **General procedure A,** the reaction was conducted at 0.3 mmol scale with 73 mg **7.K13** and 78 μL myrcene. The titled compound was isolated as a colorless oil (78.3 mg, 54% yield, inseparable mixture of diastereomers). R_f = 0.4 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 5.0 Hz, 1H), 7.78 – 7.72 (m, 2H), 7.63 (ddd, J = 5.2, 3.1, 1.9 Hz, 2H), 7.51 (s, 1H), 6.95 (dd, J = 5.1, 1.4 Hz, 1H), 6.00 (s, 1H), 5.01 (q, J = 7.2, 6.0 Hz, 1H), 4.23 (ttd, J = 9.9, 5.1, 3.6 Hz, 1H), 3.74 (h, J = 6.9 Hz, 1H), 2.72 – 2.45 (m, 3H), 2.37 (s, 3H), 2.18 – 2.05 (m, 2H), 1.99 – 1.76 (m, 3H), 1.68 – 1.54 (m, 4H), 1.48 (d, J = 3.7 Hz, 3H), 1.43 – 1.34 (m, 1H), 1.17 (dd, J = 8.6, 6.9 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were found at δ 168.82, 153.79, 152.91, 152.89,

151.94, 151.93, 149.57, 147.22, 147.20, 133.76, 133.75, 131.92, 131.47, 124.42, 124.39, 123.07, 123.05, 122.31, 117.73, 117.71, 104.09, 104.06, 53.95, 53.89, 37.28, 37.22, 31.74, 31.67, 30.65, 26.03, 26.01, 25.87, 25.85, 25.79, 25.78, 25.72, 25.70, 21.23, 20.41, 20.39, 17.65, 17.63, 11.20, 11.19. IR (KBr) 3062, 2965, 2934, 2878, 1770, 1715, 1609, 1567, 1474, 1366, 1050 cm^{-1}. HRMS: calcd. 485.2911 $[M+H]^+$ Found: 485.2921.

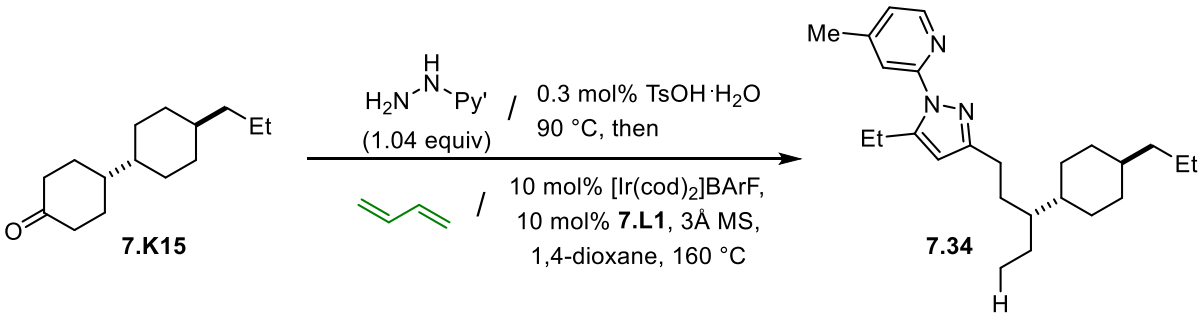


7.32: Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 8.7 mg **7.K11** and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Three parallel reactions were conducted (0.05 mmol for each, 0.15 mmol in total) and combined, giving the titled compound as a colorless oil (30.0 mg, 60% yield). R_f = 0.3 (hexane/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.0 Hz, 1H), 7.62 (s, 1H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.24 – 7.14 (m, 3H), 6.96 (d, *J* = 4.9 Hz, 1H), 5.98 (s, 1H), 3.08 (q, *J* = 7.4 Hz, 2H), 2.53 (dq, *J* = 15.0, 9.3, 8.9 Hz, 3H), 2.39 (s, 3H), 2.07 (tt, *J* = 11.3, 5.8 Hz, 1H), 2.01 – 1.89 (m, 1H), 1.76 (dp, *J* = 14.0, 7.2 Hz, 1H), 1.63 (dq, *J* = 13.3, 6.7, 5.8 Hz, 1H), 1.23 (t, *J* = 7.5 Hz, 3H), 0.79 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.30, 153.84, 149.72, 147.75, 147.34, 145.53, 128.39, 128.00, 126.06, 122.18, 117.04, 105.74, 47.88, 36.37, 29.69,

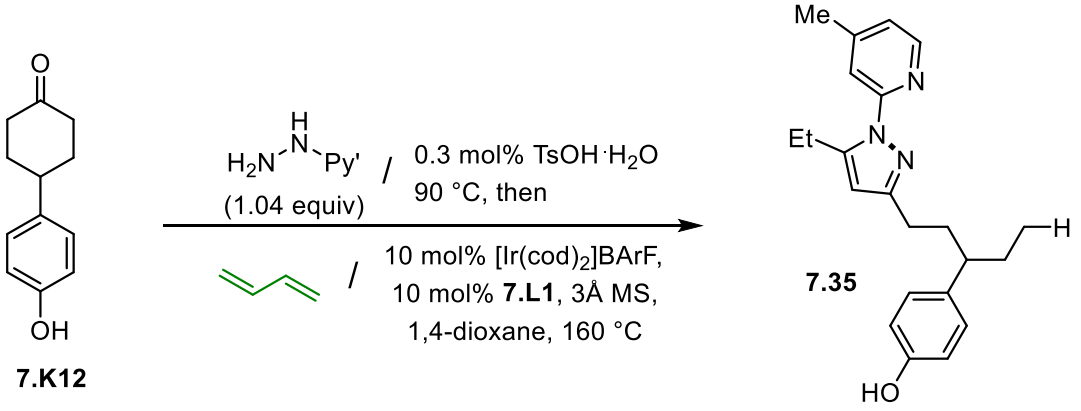
26.76, 21.48, 21.29, 13.24, 12.34. IR (KBr) 3026, 2967, 2928, 2876, 1607, 1571, 1476, 1419, 1014 cm^{-1}. HRMS: calcd. 334.2278 $[M+H]^+$ Found: 334.2278.



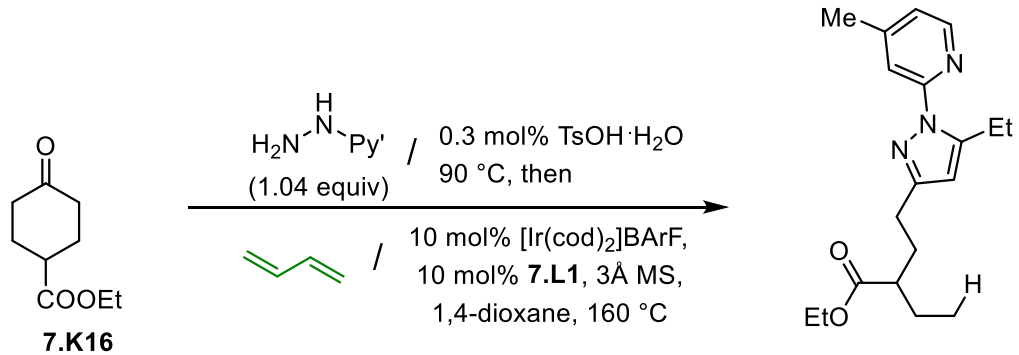
7.33: Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 4.9 mg cyclohexanone and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Three parallel reactions were conducted (0.05 mmol for each, 0.15 mmol in total) and combined, giving the titled compound as a colorless oil (23.4 mg, 61% yield). R_f = 0. 4 (hexane/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.0 Hz, 1H), 7.64 (s, 1H), 6.96 (d, *J* = 5.0 Hz, 1H), 6.04 (s, 1H), 3.10 (q, *J* = 7.5 Hz, 2H), 2.70 – 2.58 (m, 2H), 2.39 (s, 3H), 1.68 (p, *J* = 7.4 Hz, 2H), 1.42 – 1.32 (m, 4H), 1.24 (t, *J* = 7.5 Hz, 3H), 0.91 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.62, 153.89, 149.71, 147.80, 147.35, 122.16, 117.05, 105.71, 31.89, 29.47, 28.60, 22.68, 21.51, 21.28, 14.20, 13.26. IR (KBr) 2961, 2932, 2863, 1614, 1575, 1476, 1476, 1417, 1362, 1006, 913 cm^{-1}. HRMS: calcd. 258.1965 $[M+H]^+$ Found: 258.1971.



7.34: Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 11.1 mg **7.K15** and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Three parallel reactions were conducted (0.05 mmol for each, 0.15 mmol in total) and combined, giving the titled compound as a colorless oil (37.5 mg, 66% yield). R_f = 0.35 (hexane/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 4.9 Hz, 1H), 7.64 (s, 1H), 6.96 (d, *J* = 5.0 Hz, 1H), 6.05 (s, 1H), 3.10 (q, *J* = 7.4 Hz, 2H), 2.62 (tp, *J* = 15.7, 7.9, 7.1 Hz, 2H), 2.39 (s, 3H), 1.81 – 1.03 (m, 22H), 0.92 – 0.85 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.91, 153.86, 149.67, 147.78, 147.33, 122.13, 117.03, 105.62, 44.86, 39.94, 37.84, 33.81, 30.41, 29.84, 29.66, 26.86, 23.19, 21.50, 21.27, 20.18, 14.56, 13.27, 12.25. IR (KBr) 3062, 2961, 2926, 2853, 1609, 1571, 1478, 1421, 1360, 1006 cm^{-1}. HRMS: calcd. 382.3217 $[M+H]^+$ Found: 382.3229.

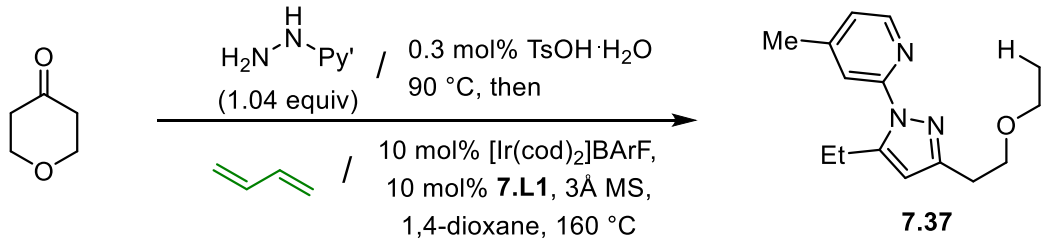


7.35: Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 9.5 mg **7.K12** and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Three parallel reactions were conducted (0.05 mmol for each, 0.15 mmol in total) and combined, giving the titled compound as a colorless oil (30.3 mg, 58% yield). R_f = 0. 35 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.0 Hz, 1H), 7.57 (s, 1H), 6.97 (d, *J* = 8.6 Hz, 3H), 6.91 – 6.60 (m, 3H), 6.00 (s, 1H), 3.05 (q, *J* = 7.5 Hz, 2H), 2.50 (t, *J* = 7.7 Hz, 2H), 2.40 (tt, *J* = 9.8, 5.0 Hz, 1H), 2.32 (s, 3H), 2.06 – 1.95 (m, 1H), 1.95 – 1.83 (m, 1H), 1.75 – 1.62 (m, 1H), 1.58 – 1.46 (m, 1H), 1.22 (t, *J* = 7.4 Hz, 3H), 0.76 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.66, 154.37, 153.41, 150.02, 147.86, 147.34, 136.80, 128.79, 122.51, 117.61, 115.33, 105.70, 46.99, 36.51, 29.90, 26.61, 21.24, 21.19, 13.17, 12.29. IR (KBr) 3169, 2967, 2926, 2874, 1611, 1567, 1516, 1474, 1421, 1362, 1237 cm^{-1}. HRMS: calcd. 350.2227 $[M+H]^+$ Found: 350.2234.



7.36: Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 8.5 mg **7.K16** and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Three parallel reactions were conducted (0.05 mmol for each, 0.15 mmol in total) and combined, giving the

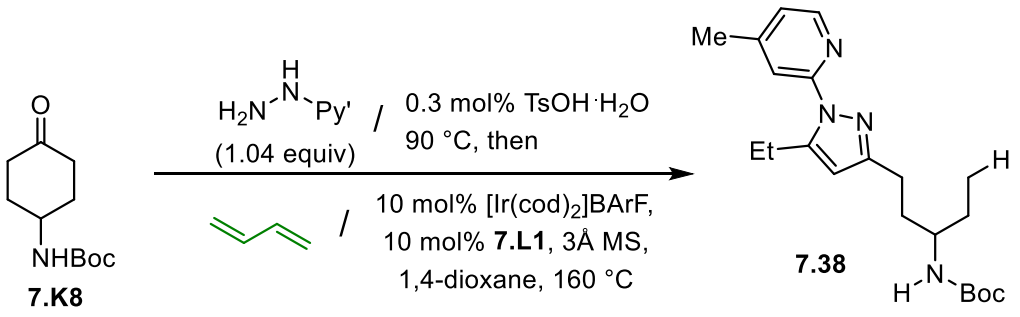
titled compound as a colorless oil (32.4 mg, 66% yield). R_f = 0.5 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.0 Hz, 1H), 7.62 (s, 1H), 6.96 (d, *J* = 4.8 Hz, 1H), 6.04 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.17 – 3.03 (m, 2H), 2.64 (t, *J* = 8.1 Hz, 2H), 2.39 (s, 4H), 2.01 (dq, *J* = 15.7, 8.8, 7.3 Hz, 1H), 1.92 – 1.79 (m, 1H), 1.68 (dt, *J* = 15.4, 7.7 Hz, 1H), 1.63 – 1.53 (m, 1H), 1.29 – 1.21 (m, 6H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.84, 153.50, 153.15, 149.40, 147.55, 147.03, 121.91, 116.72, 105.46, 59.89, 46.72, 31.45, 26.15, 25.19, 21.15, 20.95, 14.18, 12.91, 11.53. IR (KBr) 3062, 2965, 2938, 2878, 1731, 1607, 1571, 1474, 1421, 1158 cm^{-1}. HRMS: calcd. 330.2176 $[M+H]^+$ Found: 330.2184.



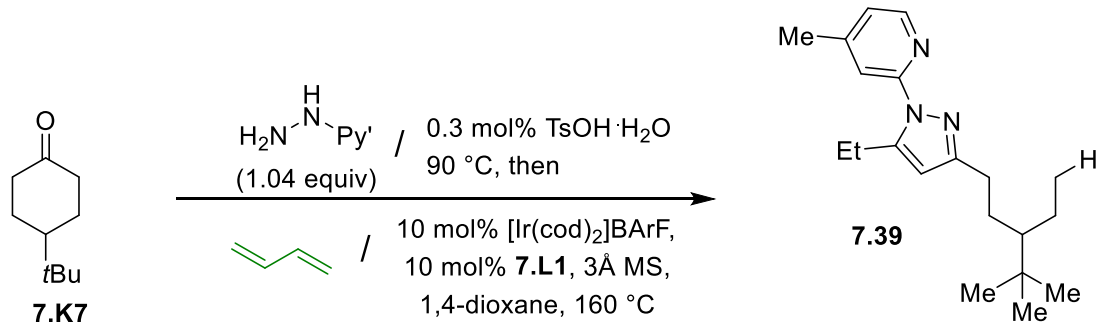
7.37

7.37: Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 5.0 mg tetrahydro-4*H*-pyran-4-one and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Three parallel reactions were conducted (0.05 mmol for each, 0.15 mmol in total) and combined, giving the titled compound as a colorless oil (21.6 mg, 56% yield). R_f = 0.4 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.1 Hz, 1H), 7.63 (s, 1H), 6.97 (d, *J* = 5.0 Hz, 1H), 6.10 (s, 1H), 3.73 (t, *J* = 7.3 Hz, 2H), 3.54 (q, *J* = 7.0 Hz, 2H), 3.08 (q, *J* = 7.5 Hz, 2H), 2.95 (t, *J* = 7.3 Hz, 2H), 2.39 (s, 3H), 1.27 – 1.15 (m, 6H). ^{13}C NMR

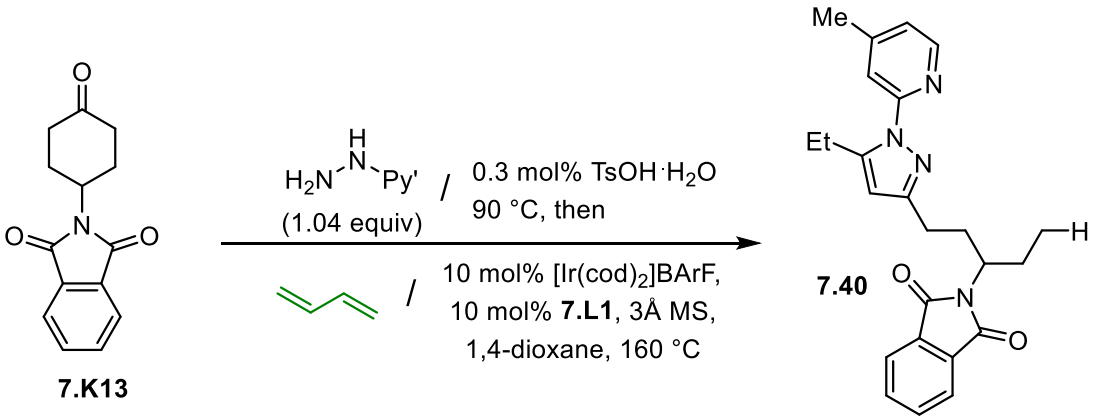
(101 MHz, $CDCl_3$) δ 153.76, 151.13, 149.75, 147.85, 147.37, 122.31, 117.10, 106.27, 70.03, 66.30, 29.27, 21.43, 21.26, 15.35, 13.20. IR (KBr) 2977, 2930, 2870, 1607, 1571, 1478, 1421, 1360, 1109, 1006 cm^{-1}. HRMS: calcd. 260.1757 $[M+H]^+$ Found: 260.1764.



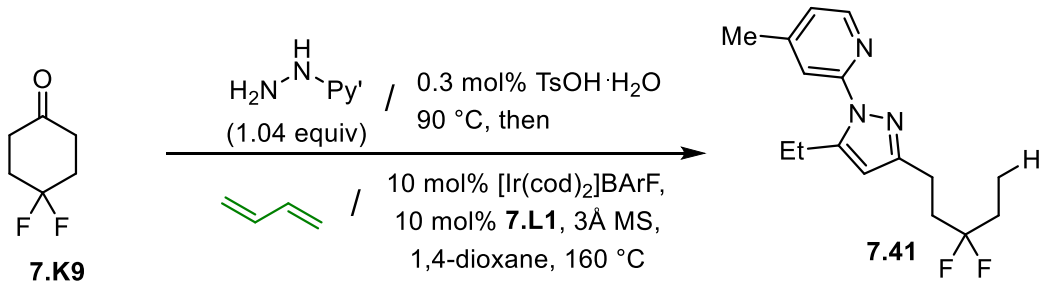
7.38: Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 10.7 mg **7.K8** and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions were conducted (0.05 mmol for each, 0.1 mmol in total) and combined, giving the titled compound as a colorless oil (19.2 mg, 52% yield). R_f = 0. 4 (hexane/ethyl acetate = 3:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.0 Hz, 1H), 7.62 (s, 1H), 6.97 (d, *J* = 5.0 Hz, 1H), 6.05 (s, 1H), 4.39 (d, *J* = 9.1 Hz, 1H), 3.60 (br, 1H), 3.09 (q, *J* = 7.4 Hz, 2H), 2.70 (qdd, *J* = 14.9, 10.1, 5.9 Hz, 2H), 2.40 (s, 3H), 1.89 (s, 1H), 1.72 (s, 1H), 1.44 (s, 11H), 1.24 (t, *J* = 7.4 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.93, 153.82, 149.75, 147.93, 147.39, 122.27, 117.09, 105.86, 78.97, 52.21, 34.85, 28.59, 25.21, 21.46, 21.29, 13.26, 10.36. IR (KBr) 3340, 2969, 2935, 2881, 1701, 1611, 1479, 1420, 1364, 1249, 1170 cm^{-1}. HRMS: calcd. 373.2598 $[M+H]^+$ Found: 373.2611.



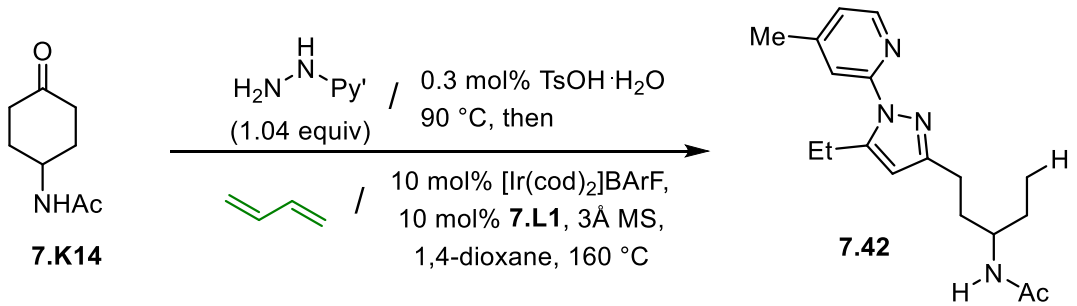
7.39: Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 7.7 mg **7.K7** and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Three parallel reactions were conducted (0.05 mmol for each, 0.15 mmol in total) and combined, giving the titled compound as a colorless oil (30.5 mg, 65% yield). R_f = 0. 4 (hexane/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.0 Hz, 1H), 7.70 – 7.61 (m, 1H), 6.96 (d, *J* = 5.0 Hz, 1H), 6.06 (s, 1H), 3.10 (q, *J* = 7.5 Hz, 2H), 2.74 (ddd, *J* = 14.6, 11.4, 5.2 Hz, 1H), 2.61 (ddd, *J* = 14.5, 11.3, 5.9 Hz, 1H), 2.39 (s, 3H), 1.90 – 1.81 (m, 1H), 1.57 (dtd, *J* = 14.0, 7.5, 3.6 Hz, 1H), 1.51 – 1.37 (m, 1H), 1.25 (t, *J* = 7.5 Hz, 3H), 1.18 (dt, *J* = 14.2, 7.3 Hz, 1H), 1.02 – 0.93 (m, 4H), 0.89 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.88, 153.87, 149.71, 147.79, 147.34, 122.16, 117.07, 105.63, 50.61, 34.17, 31.11, 28.89, 28.00, 23.85, 21.50, 21.28, 14.70, 13.27. IR (KBr) 3062, 2967, 2876, 1611, 1571, 1482, 1417, 1366, 1008 cm^{-1}. HRMS: calcd. 314.2591 $[M+H]^+$ Found: 314.2598.



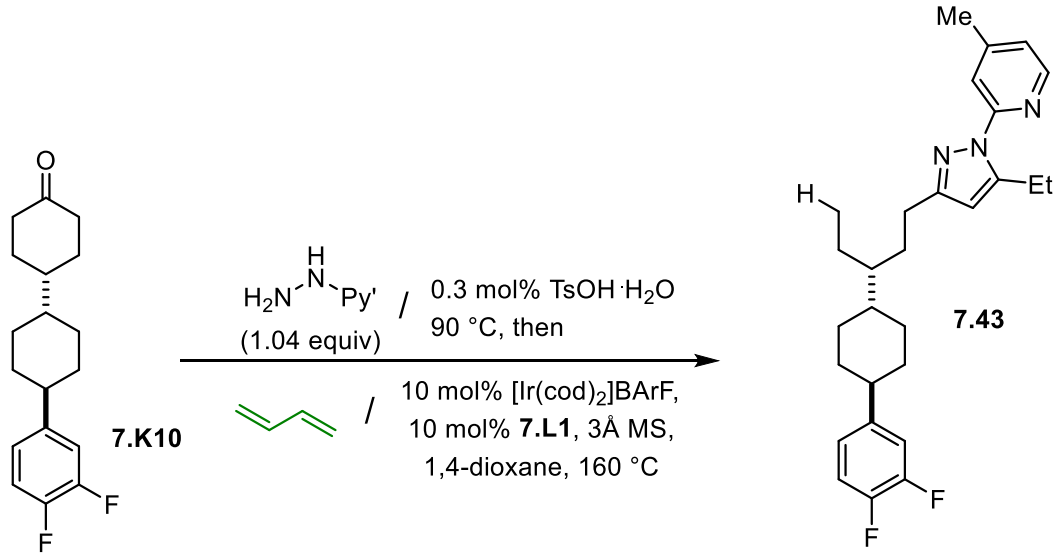
7.40: Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 12.2 mg **7.K13** as the ketone substrates and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Three parallel reactions were conducted (0.05 mmol for each, 0.15 mmol in total) and combined, giving the titled compound as a colorless oil (39.3 mg, 65% yield). R_f = 0.3 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 5.0 Hz, 1H), 7.72 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.61 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.57 (s, 1H), 6.93 (d, *J* = 5.0 Hz, 1H), 5.98 (s, 1H), 4.23 (tt, *J* = 10.1, 5.0 Hz, 1H), 2.94 (q, *J* = 7.4 Hz, 2H), 2.76 – 2.50 (m, 3H), 2.38 (s, 3H), 2.20 – 2.03 (m, 2H), 1.82 (dt, *J* = 13.5, 6.8 Hz, 1H), 1.17 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.83, 153.66, 152.92, 149.56, 147.79, 147.13, 133.69, 131.86, 122.95, 122.05, 116.83, 105.77, 53.95, 31.51, 26.07, 25.80, 21.45, 21.26, 13.08, 11.18. IR (KBr) 3062, 2973, 2928, 2878, 1769, 1711, 1607, 1571, 1476, 1370, 1048 cm^{-1}. HRMS: calcd. 403.2129 $[M+H]^+$ Found: 403.2118.



7.41: Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 6.7 mg **7.K9** as the ketone substrates and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Three parallel reactions were conducted (0.05 mmol for each, 0.15 mmol in total) and combined, giving the titled compound as a colorless oil (27.5 mg, 63% yield). R_f = 0. 25 (hexane/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 5.1 Hz, 1H), 7.62 (s, 1H), 6.98 (d, *J* = 5.2 Hz, 1H), 6.06 (s, 1H), 3.09 (q, *J* = 7.5 Hz, 2H), 2.93 – 2.78 (m, 2H), 2.40 (s, 3H), 2.34 – 2.16 (m, 2H), 2.02 – 1.80 (m, 2H), 1.24 (t, *J* = 7.4 Hz, 3H), 1.04 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.71, 152.50, 149.84, 148.08, 147.42, 125.17 (t, *J* = 240.6 Hz), 122.41, 117.11, 105.67, 35.75 (t, *J* = 25.7 Hz), 29.78 (t, *J* = 26.1 Hz), 21.50 (t, *J* = 5.6 Hz), 21.42, 21.29, 13.22, 6.79 (t, *J* = 5.7 Hz). IR (KBr) 3064, 2973, 2942, 2890, 1607, 1571, 1478, 1421, 1362, 1202, 1137, 1050, 1018 cm^{-1}. HRMS: calcd. 294.1776 $[M+H]^+$ Found: 294.1788.

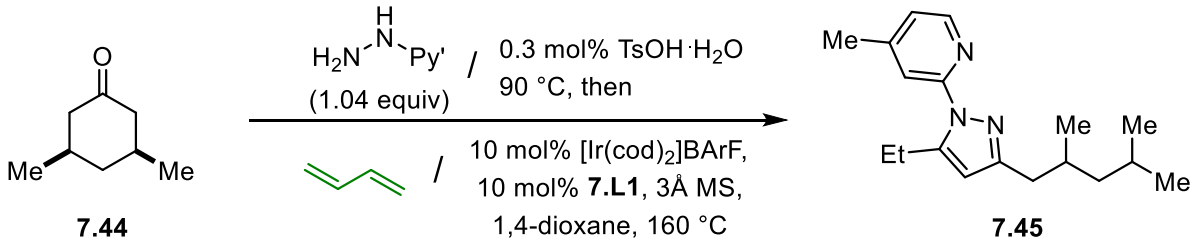


7.42: Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 7.8 mg **7.K14** as the ketone substrates and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Three parallel reactions were conducted (0.05 mmol for each, 0.15 mmol in total) and combined, giving the titled compound as a white solid (25.7 mg, 55% yield). R_f = 0.4 (hexane/acetone = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.1 Hz, 1H), 7.59 (s, 1H), 6.97 (d, *J* = 5.1 Hz, 1H), 6.05 (s, 1H), 5.47 (d, *J* = 9.0 Hz, 1H), 3.95 (dtd, *J* = 13.8, 8.7, 5.2 Hz, 1H), 3.06 (q, *J* = 7.5 Hz, 2H), 2.68 (t, *J* = 7.8 Hz, 2H), 2.39 (s, 3H), 1.96 – 1.89 (m, 4H), 1.75 (dt, *J* = 13.6, 7.5 Hz, 1H), 1.57 (dq, *J* = 13.7, 6.9 Hz, 1H), 1.46 (td, *J* = 13.4, 12.1, 6.3 Hz, 1H), 1.22 (t, *J* = 7.5 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.86, 153.75, 153.67, 149.79, 147.98, 147.43, 122.36, 117.09, 105.88, 50.92, 34.05, 28.00, 25.06, 23.64, 21.37, 21.28, 13.22, 10.34. IR (KBr) 3283, 3072, 2969, 2932, 2876, 1644, 1611, 1569, 1474, 1421, 1372, 1302, 1014 cm^{-1}. HRMS: calcd. 315.2179 $[M+H]^+$ Found: 315.2190.



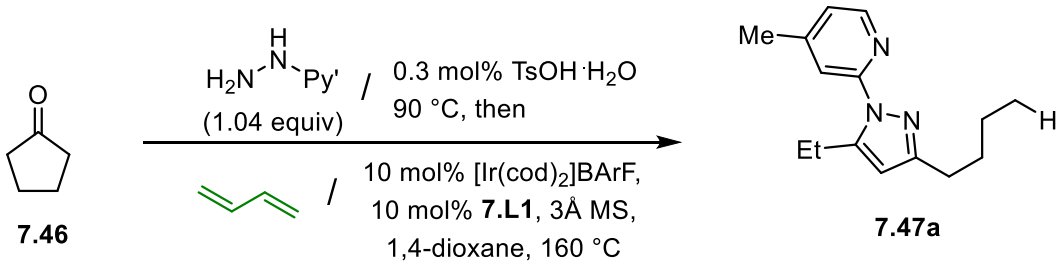
7.43: Following **General procedure B,** the reaction was conducted at 0.05 mmol

scale with 14.6 mg **7.K10** as the ketone substrates and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Three parallel reactions were conducted (0.05 mmol for each, 0.15 mmol in total) and combined, giving the titled compound as a colorless oil (42.5 mg, 63% yield). R_f = 0. 3 (hexane/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 5.0 Hz, 1H), 7.65 (s, 1H), 7.10 – 6.94 (m, 3H), 6.89 (dd, *J* = 6.9, 3.5 Hz, 1H), 6.06 (s, 1H), 3.11 (q, *J* = 7.5 Hz, 2H), 2.65 (pt, *J* = 10.4, 5.5 Hz, 2H), 2.40 (s, 4H), 1.90 (d, *J* = 12.8 Hz, 2H), 1.85 – 1.69 (m, 3H), 1.67 – 1.57 (m, 1H), 1.51 – 1.33 (m, 5H), 1.32 – 1.20 (m, 6H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.72, 153.86, 149.72, 147.85, 147.38, 122.20, 117.06, 105.62, 44.69, 44.08, 39.26, 34.76, 30.38, 29.91, 29.74, 26.86, 23.19, 21.50, 21.28, 13.28, 12.22. IR (KBr) 3060, 2928, 2857, 1605, 1573, 1518, 1423, 1360, 1275, 1208, 1008 cm^{-1}. HRMS: calcd. 452.2872 $[M+H]^+$ Found: 452.2892.



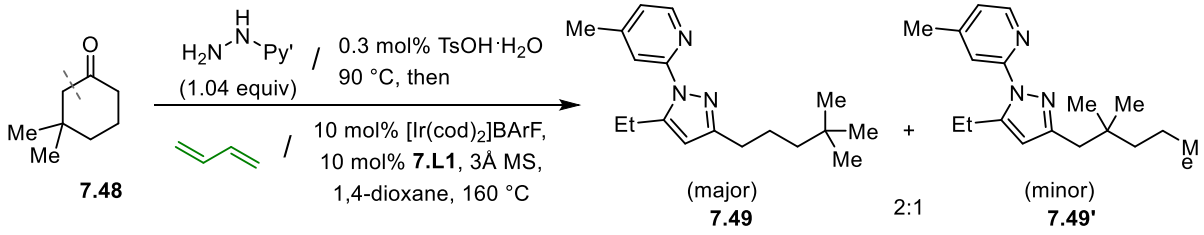
7.45: Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 6.3 mg **7.44** as the ketone substrates and 110 μL 1,3-butadiene (in PhMe, 20% wt.%). Three parallel reactions were conducted (0.05 mmol for each, 0.15 mmol in total) and combined, giving the titled compound as a colorless oil (19.0 mg, 44% yield). R_f = 0.4 (hexane/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.1 Hz, 1H), 7.64

(s, 1H), 6.96 (d, J = 4.7 Hz, 1H), 6.02 (s, 1H), 3.10 (q, J = 7.5 Hz, 2H), 2.63 (dd, J = 14.1, 5.8 Hz, 1H), 2.47 – 2.34 (m, 4H), 1.97 – 1.83 (m, 1H), 1.71 (dp, J = 13.0, 6.6 Hz, 1H), 1.28 – 1.19 (m, 5H), 1.10 (ddd, J = 13.9, 8.7, 5.8 Hz, 1H), 0.95 – 0.83 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.93, 153.48, 149.71, 147.68, 147.32, 122.16, 117.18, 106.36, 46.69, 36.46, 31.21, 25.45, 23.68, 22.26, 21.48, 21.29, 19.86, 13.28. IR (KBr) 3060, 2957, 2926, 2872, 1607, 1569, 1480, 1423, 1362, 1004 cm^{-1}. HRMS: calcd. 286.2278 $[M+H]^+$ Found: 286.2279.



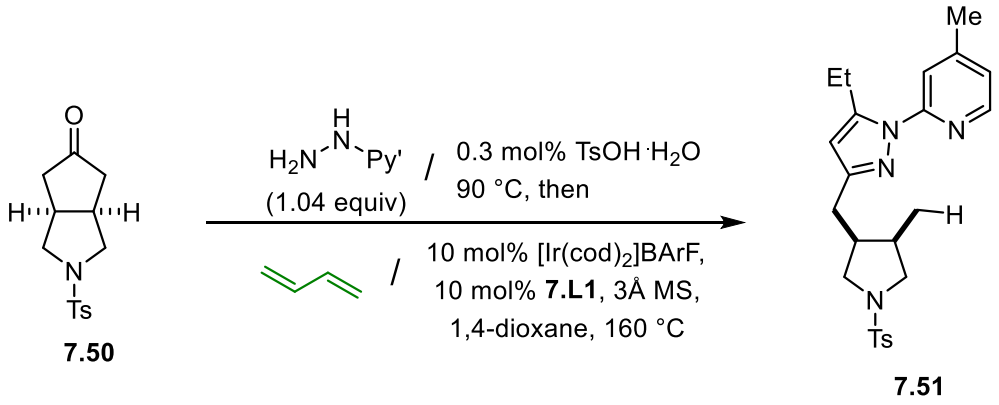
Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 4.2 mg cyclopentanone as the ketone substrates and 170 μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions were conducted accordingly (0.05 mmol for each, 0.1 mmol in total). When the key reaction was finished, the reaction mixture from the two parallel reactions was combined, filtered through a short plug of Celite, and concentrated in *vacuo*. The residue was further treated with ethyl acetate (1 mL) and Pd/C (5% wt.%, 30 mg), and stirred at room temperature under H_2 atmosphere for 10 hours. The reaction mixture was filtered, concentrated in *vacuo*, and then purified by flash column chromatography over silica (hexane/ethyl acetate, 20:1) to give the product **7.47a** as a colorless oil (16.9 mg, 70% yield).

R_f = 0.3 (hexane/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.0 Hz, 1H), 7.64 (s, 1H), 6.96 (dd, *J* = 5.0, 1.5 Hz, 1H), 6.04 (s, 1H), 3.10 (q, *J* = 7.5 Hz, 2H), 2.84 – 2.56 (m, 2H), 2.39 (s, 3H), 1.67 (p, *J* = 7.6 Hz, 2H), 1.47 – 1.39 (m, 2H), 1.24 (t, *J* = 7.5 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.57, 153.87, 149.71, 147.79, 147.34, 122.16, 117.04, 105.71, 31.91, 28.30, 22.74, 21.49, 21.27, 14.09, 13.25. IR (KBr) 3062, 2959, 2932, 2874, 1607, 1569, 1476, 1423, 1364, 994 cm^{-1}. HRMS: calcd. 244.1808 $[M+H]^+$ Found: 244.1814.



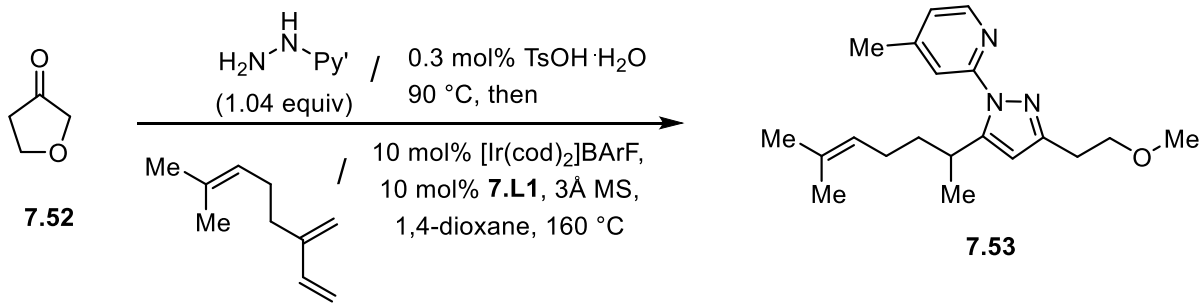
Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 6.3 mg **7.48** as the ketone substrates and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions were conducted (0.05 mmol for each, 0.1 mmol in total) and combined after the key reaction was finished. A hydrogenation reaction with Pd/C (5% wt.%, 30 mg) in ethyl acetate (1 mL) under H_2 atmosphere was conducted to hydrogenate a small amount of the crotylation by-product (ca. 5%) in order to achieve better separation *via* flash column chromatography over silica. The pyrazoles **7.49** and **7.49'** were then isolated in 2:1 ratio with a combined yield of 27% (colorless oil, 7.7 mg). The pure sample for compound **7.49** was obtained by preparative thin layer chromatography for characterization. **7.49**: R_f = 0.45

(hexane/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 5.1 Hz, 1H), 7.64 (d, *J* = 0.8 Hz, 1H), 6.97 (d, *J* = 5.0 Hz, 1H), 6.05 (s, 1H), 3.11 (q, *J* = 7.5 Hz, 2H), 2.61 (t, *J* = 7.8 Hz, 2H), 2.40 (s, 3H), 1.65 (tdd, *J* = 11.7, 7.9, 6.2 Hz, 2H), 1.30 – 1.20 (m, 5H), 0.89 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.66, 153.90, 149.74, 147.86, 147.36, 122.18, 117.06, 105.69, 44.26, 30.50, 29.58, 29.48, 25.04, 21.53, 21.29, 13.27. IR (KBr) 3064, 2955, 2868, 1607, 1571, 1476, 1417, 1364, 819 cm^{-1}. HRMS: calcd. 286.2278 $[M+H]^+$ Found: 286.2284.

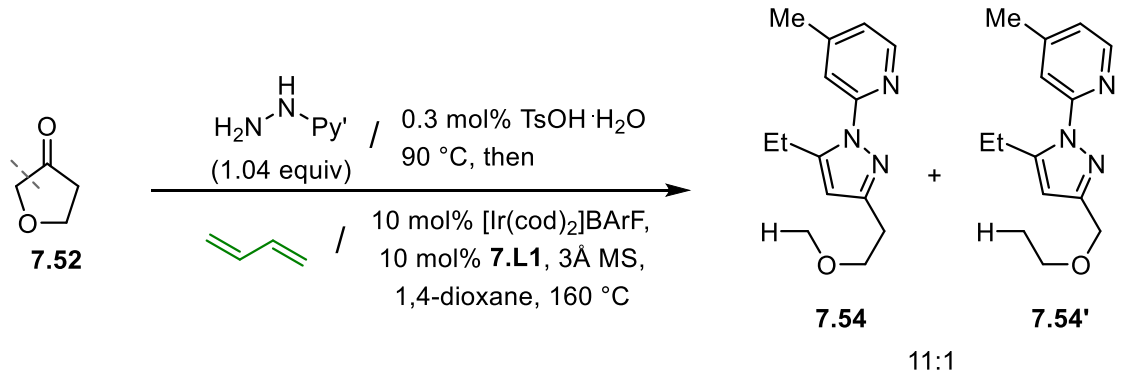


7.51: Compound **7.50** was prepared according to a known procedure[51]. Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 14.0 mg **7.50** as the ketone substrates and 170 μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions were conducted (0.05 mmol for each, 0.1 mmol in total) and combined, giving the titled compound as a colorless oil (20.5 mg, 47% yield). R_f = 0.3 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 5.1 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.56 (s, 1H), 7.30 (d, *J* = 7.9 Hz, 2H), 6.99 (d, *J* = 5.1 Hz, 1H), 5.93 (s, 1H), 3.41 (td, *J* = 9.8, 6.5 Hz, 2H), 3.17 – 2.99 (m, 4H), 2.64 (dd, *J* = 13.1, 4.9 Hz, 1H), 2.53 – 2.30 (m, 8H), 2.29 – 2.20 (m, 1H), 1.22 (t, *J* = 7.5 Hz, 3H), 0.82 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ

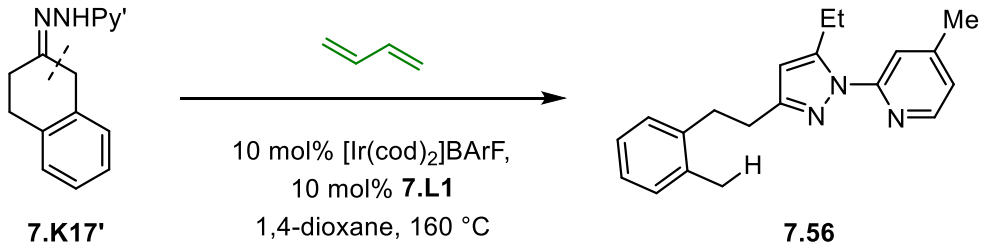
153.63, 151.69, 149.82, 147.99, 147.41, 143.30, 134.31, 129.70, 127.58, 122.46, 117.11, 105.86, 54.93, 51.37, 41.96, 35.45, 26.91, 21.65, 21.38, 21.31, 13.40, 13.21. IR (KBr) 3060, 2967, 2926, 2876, 1607, 1573, 1476, 1417, 1344, 1160, 1093, 1050 cm^{-1}. HRMS: calcd. 439.2162 $[M+H]^+$ Found: 439.2175.



7.53: Following **General procedure A,** the reaction was conducted at 0.3 mmol scale with 26 mg **7.52** and 104 μL myrcene (2.0 equiv) in 0.1 mL 1,4-dioxane. The titled compound was isolated as a colorless oil (43.8 mg, 45% yield). The other C–C cleavage regioisomer was not observed from the reaction mixture. **7.53**: R_f = 0.6 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 5.0, 0.7 Hz, 1H), 7.58 (s, 1H), 6.99 (dd, *J* = 5.1, 0.8 Hz, 1H), 6.09 (s, 1H), 5.02 (ddt, *J* = 8.7, 5.8, 1.4 Hz, 1H), 3.81 (p, *J* = 6.9 Hz, 1H), 3.69 (t, *J* = 7.2 Hz, 2H), 3.39 (s, 3H), 2.94 (t, *J* = 7.2 Hz, 2H), 2.39 (s, 3H), 1.94 (q, *J* = 7.5 Hz, 2H), 1.72 – 1.64 (m, 1H), 1.61 (s, 3H), 1.49 (s, 3H), 1.48 – 1.38 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.84, 151.96, 150.94, 149.75, 147.42, 131.57, 124.37, 122.56, 118.00, 104.55, 72.19, 58.77, 37.33, 30.69, 29.14, 25.90, 25.80, 21.25, 20.53, 17.65. IR (KBr) 2965, 2926, 2870, 1609, 1567, 1474, 1421, 1119 cm^{-1}. HRMS: calcd. 328.2384 $[M+H]^+$ Found: 328.2394.

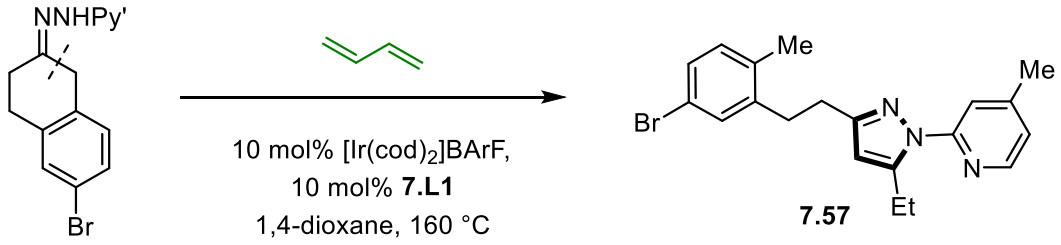


Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 4.3 mg **7.52** as the ketone substrates and 170 μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions were conducted (0.05 mmol for each, 0.10 mmol in total) and combined, yielding pyrazoles **7.54** and **7.54'** in 11:1 ratio as determined by ^{1}H NMR analysis of the crude mixture. The compound **7.54** was isolated as a colorless oil (9.7 mg, 40% yield). **7.54**: R_f = 0.5 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 5.0 Hz, 1H), 7.64 (s, 1H), 6.98 (d, *J* = 4.6 Hz, 1H), 6.10 (s, 1H), 3.71 (t, *J* = 7.0 Hz, 2H), 3.40 (s, 3H), 3.10 (q, *J* = 7.5 Hz, 2H), 2.95 (t, *J* = 7.0 Hz, 2H), 2.40 (s, 3H), 1.25 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.81, 151.07, 149.76, 147.96, 147.39, 122.33, 117.13, 106.21, 72.17, 58.81, 29.13, 21.48, 21.29, 13.21. IR (KBr) 2973, 2928, 2874, 2825, 1607, 1569, 1476, 1417, 1362, 1119 cm^{-1}. HRMS: calcd. 246.1601 $[M+H]^+$ Found: 246.1604.



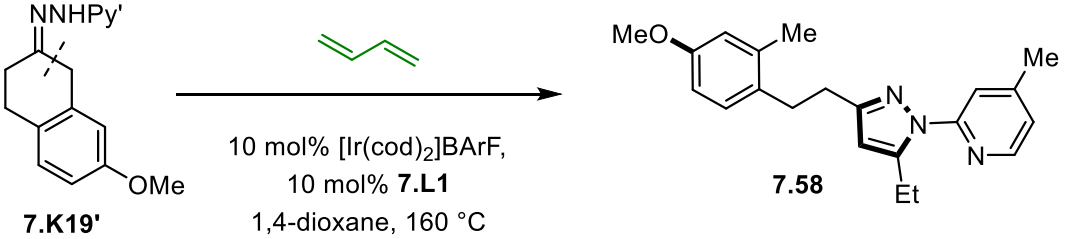
7.K17' **7.56**

7.56: The reaction was conducted following modified **General procedure B** using the pre-formed hydrazone as the substrate: An 4 mL vial was charged with the hydrazone **7.K17'** (12.5 mg, 0.05 mmol, 1.0 equiv) which was derived from its corresponding ketone following *General procedure for hydrazones formation (vide supra)*, $[Ir(cod)_2]BArF$ (6.4 mg, 0.005 mmol, 0.1 equiv), **7.L1** (2.0 mg, 0.005 mmol, 0.1 equiv) and 1,4-dioxane (0.5 mL). The vial was transferred into the glove box, and was charged with 1,3-butadiene (20% wt.% in PhMe, 120 μL, ca. 7 equiv). The vial was sealed, transferred out of the glove box, and heated at 160 °C under stirring for 24 hours. After cooled to room temperature, the reaction mixture was filtered through a short plug of Celite, concentrated *in vacuo*, and further purified by flash column chromatography over silica (hexane/ethyl acetate, from 30:1 to 20:1). Combining 2 parallel reactions furnished **7.56** in 66% yield (20.0 mg) as a colorless oil**.** R_f = 0.7 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 5.0 Hz, 1H), 7.66 (s, 1H), 7.26 – 7.20 (m, 1H), 7.20 – 7.10 (m, 3H), 6.99 (d, *J* = 4.4 Hz, 1H), 6.05 (s, 1H), 3.11 (q, *J* = 7.5 Hz, 2H), 3.06 – 2.97 (m, 2H), 2.97 – 2.89 (m, 2H), 2.42 (s, 3H), 2.37 (s, 3H), 1.25 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.85, 153.67, 149.79, 147.90, 147.41, 140.21, 136.17, 130.27, 128.92, 126.19, 126.13, 122.31, 117.17, 105.84, 33.34, 29.27, 21.46, 21.31, 19.50, 13.29. IR (KBr) 3064, 3022, 2973, 2932, 2874, 1609, 1571, 1474, 1417, 1364, 1016 cm^{-1}. HRMS: calcd. 306.1965 $[M+H]^+$ Found: 306.1973.



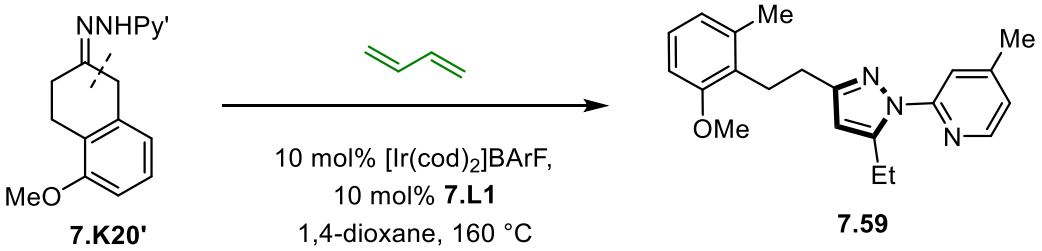
7.K18' **7.57**

7.57: the compound **7.57** was synthesized using the same protocol as described for **7.56** with 16.5 mg pre-formed hydrazone **7.K18'** and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions were conducted (0.05 mmol for each, 0.1 mmol in total) and combined, giving the titled compound as a colorless oil (26.7 mg, 70% yield). R_f = 0.6 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 – 8.24 (m, 1H), 7.68 – 7.58 (m, 1H), 7.36 (d, *J* = 2.1 Hz, 1H), 7.24 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.05 – 7.00 (m, 1H), 7.00 – 6.97 (m, 1H), 6.01 (s, 1H), 3.10 (qd, *J* = 7.5, 0.9 Hz, 2H), 3.00 – 2.83 (m, 4H), 2.42 (s, 3H), 2.28 (s, 3H), 1.24 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.78, 153.07, 149.84, 147.97, 147.42, 142.45, 135.13, 131.84, 131.82, 129.08, 122.39, 119.53, 117.22, 105.82, 33.11, 28.98, 21.42, 21.32, 19.03, 13.29. IR (KBr) 3019, 2971, 2928, 2872, 1607, 1573, 1478, 1419, 1362, 1018 cm^{-1}. HRMS: calcd. 384.1070 $[M+H]^+$ Found: 384.1065.



7.K19' **7.58**

7.58: the compound **7.58** was synthesized using the same protocol as described for **7.56** with 14.1 mg pre-formed hydrazone **7.K19'** and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions were conducted (0.05 mmol for each, 0.1 mmol in total) and combined, giving the titled compound as a colorless oil (24.0 mg, 72% yield). R_f = 0.5 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 5.0 Hz, 1H), 7.64 (s, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 6.99 (d, *J* = 5.1 Hz, 1H), 6.77 – 6.67 (m, 2H), 6.04 (s, 1H), 3.79 (s, 3H), 3.10 (q, *J* = 7.5 Hz, 2H), 2.99 – 2.81 (m, 4H), 2.41 (s, 3H), 2.33 (s, 3H), 1.25 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.91, 153.83, 153.75, 149.80, 147.87, 147.42, 137.45, 132.45, 129.85, 122.32, 117.18, 115.94, 111.14, 105.85, 55.34, 32.58, 29.59, 21.45, 21.32, 19.79, 13.30. IR (KBr) 3019, 2967, 2940, 1609, 1569, 1506, 1476, 1421, 1253 cm^{-1}. HRMS: calcd. 336.2071 $[M+H]^+$ Found: 336.2080.

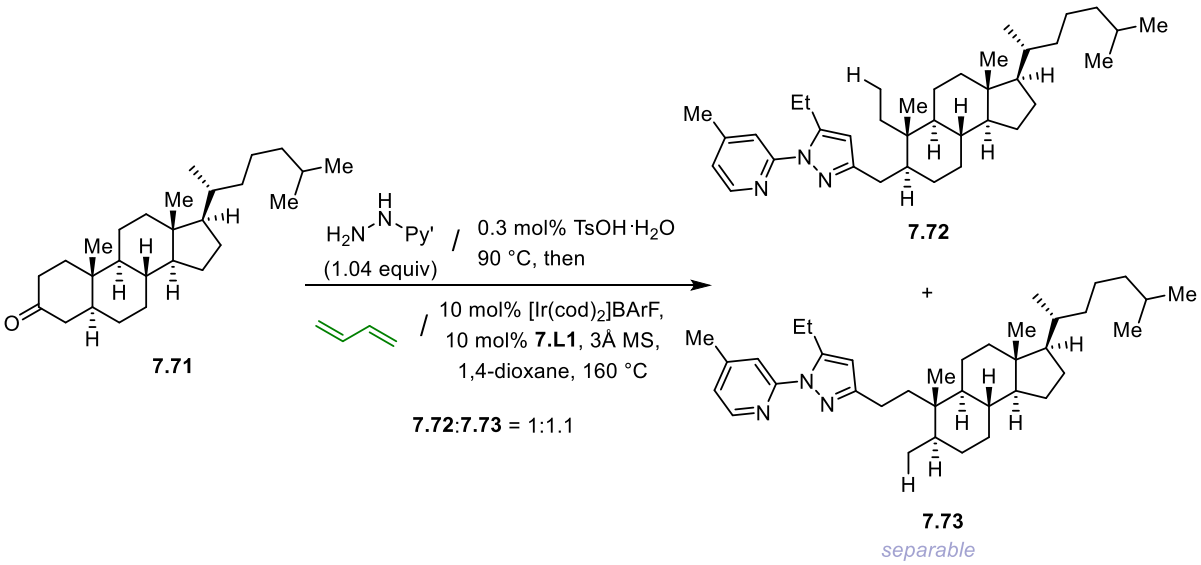


7.K20' **7.59**

7.59: the compound **7.59** was synthesized using the same protocol as described for **7.56** with 14.1 mg pre-formed hydrazone **7.K20'** and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions were conducted (0.05 mmol for each, 0.1 mmol in total) and combined, giving the titled compound as a colorless oil (23.0 mg, 69% yield). R_f = 0.55 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.18 (m, 1H), 7.66 (dd, *J* =

1.6, 0.8 Hz, 1H), 7.10 (t, *J* = 7.9 Hz, 1H), 6.98 (ddd, *J* = 5.0, 1.5, 0.8 Hz, 1H), 6.77 (dd, *J* = 15.3, 7.9 Hz, 2H), 6.05 (s, 1H), 3.83 (s, 3H), 3.11 (qd, *J* = 7.5, 0.8 Hz, 2H), 3.07 – 2.98 (m, 2H), 2.87 – 2.74 (m, 2H), 2.41 (s, 3H), 2.32 (s, 3H), 1.25 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.81, 154.34, 153.90, 149.74, 147.74, 147.38, 137.72, 128.93, 126.52, 122.64, 122.22, 117.19, 108.08, 105.90, 55.56, 27.89, 26.63, 21.46, 21.31, 19.66, 13.32. IR (KBr) 3017, 2971, 2928, 1608, 1573, 1417, 1263, 1085 cm^{-1}. HRMS: calcd. 336.2071 $[M+H]^+$ Found: 336.2078.

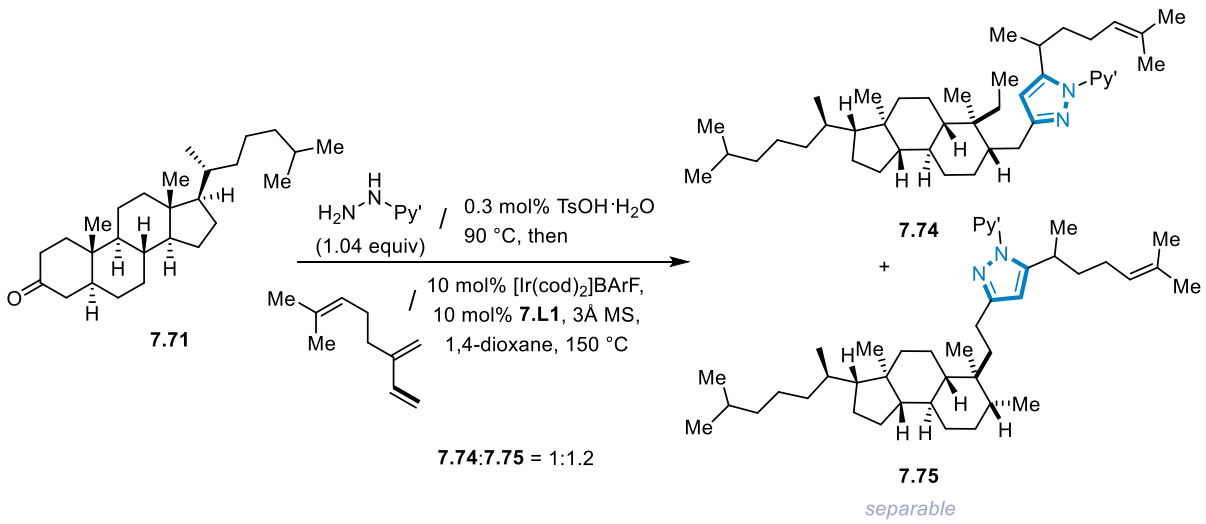
Conversion of complex ketones into pyrazoles



Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 19.3 mg **7.71** and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Three parallel reactions were conducted (0.05 mmol for each, 0.15 mmol in total) and combined, yielding pyrazoles **7.72** and **7.73** in 1:1.1 ratio after isolation. The characterization data for **7.72** and **7.73** are listed as follows:

7.72: colorless oil (20.5 mg, 25.5% yield). R_f = 0.35 (hexane/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.0 Hz, 1H), 7.64 (s, 1H), 6.96 (d, *J* = 5.1 Hz, 1H), 5.99 (s, 1H), 3.10 (q, *J* = 7.4 Hz, 2H), 2.79 (dd, *J* = 14.0, 2.5 Hz, 1H), 2.39 (s, 3H), 2.21 (dd, *J* = 14.0, 11.2 Hz, 1H), 1.98 (dt, *J* = 12.6, 3.4 Hz, 1H), 1.79 (ddd, *J* = 14.6, 9.4, 5.3 Hz, 1H), 1.72 – 1.41 (m, 8H), 1.36 – 0.95 (m, 19H), 0.93 – 0.70 (m, 16H), 0.65 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were observed at δ 154.49, 153.92, 149.67, 147.85, 147.30, 122.09, 117.10, 105.87, 57.00, 56.47, 47.00, 42.51, 42.05, 40.34, 39.67, 38.44, 36.33, 35.95, 35.46, 32.08, 29.03, 28.54, 28.43, 28.17, 26.92, 24.42, 23.99, 22.97, 22.71, 21.54, 21.43, 21.29, 18.82, 16.64, 13.28, 12.12, 6.72. IR (KBr) 3060, 2963, 2870, 2851, 1609, 1571, 1476, 1423, 1379, 1010 cm^{-1}. HRMS: calcd. 546.4781 $[M+H]^+$ Found: 546.4798.

7.73: colorless oil (22.5 mg, 27.5% yield). R_f = 0.4 (hexane/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.0 Hz, 1H), 7.64 (s, 1H), 6.96 (d, *J* = 5.1 Hz, 1H), 6.03 (s, 1H), 3.09 (q, *J* = 7.5 Hz, 2H), 2.51 (tt, *J* = 13.3, 6.3 Hz, 2H), 2.40 (s, 3H), 1.98 (dd, *J* = 12.6, 3.4 Hz, 1H), 1.88 – 1.77 (m, 1H), 1.74 – 1.50 (m, 7H), 1.47 – 1.22 (m, 11H), 1.21 – 0.98 (m, 9H), 0.93 – 0.81 (m, 13H), 0.77 (s, 3H), 0.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were observed at δ 155.07, 153.89, 149.69, 147.83, 147.35, 122.15, 117.09, 105.47, 56.98, 56.48, 47.67, 42.52, 40.30, 39.68, 38.47, 36.89, 36.33, 36.30, 35.96, 35.52, 32.37, 30.68, 28.45, 28.17, 24.45, 24.00, 22.98, 22.72, 21.52, 21.49, 21.30, 21.16, 18.82, 16.15, 15.80, 13.29, 12.14. IR (KBr) 3060, 2959, 2934, 2874, 1611, 1571, 1478, 1419, 1381, 1362, 1014 cm^{-1}. HRMS: calcd. 546.4781 $[M+H]^+$ Found: 546.4789.

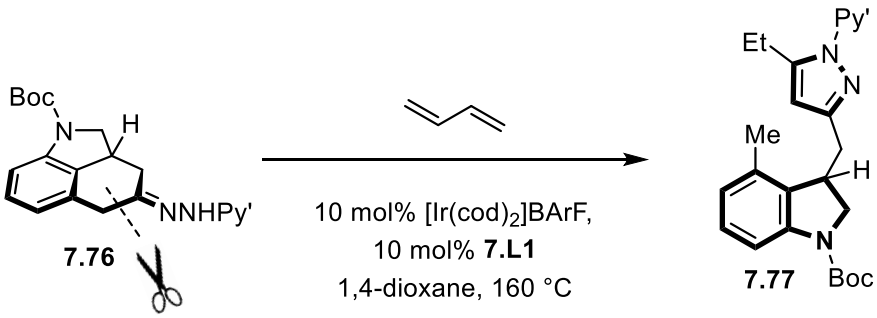


Following **General procedure A,** the reaction was conducted at 0.3 mmol scale with 116 mg **7.71** and 70 µL myrcene (1.35 equiv) in 0.1 ml 1,4-dioxane at 150 °C. Pyrazoles **7.74** and **7.75** were isolated in 1:1.2 ratio. The characterization data for **7.74** and **7.75** are listed as follows:

7.74: colorless oil (47 mg, 25% yield, inseparable mixture of diastereomers). R_f = 0.7 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.0 Hz, 1H), 7.57 (s, 1H), 6.98 (d, *J* = 1.5 Hz, 1H), 5.99 (s, 1H), 5.20 – 4.96 (m, 1H), 3.82 (h, *J* = 6.8 Hz, 1H), 2.78 (dd, *J* = 14.1, 2.6 Hz, 1H), 2.39 (s, 3H), 2.30 – 2.14 (m, 1H), 1.96 (dd, *J* = 18.0, 5.6 Hz, 3H), 1.86 – 1.74 (m, 1H), 1.70 – 1.51 (m, 10H), 1.49 – 1.40 (m, 5H), 1.39 – 0.94 (m, 20H), 0.93 – 0.79 (m, 15H), 0.76 – 0.69 (m, 1H), 0.65 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were found at δ 154.43, 153.99, 151.91, 151.86, 149.69, 147.36, 131.57, 131.56, 124.48, 124.45, 122.36, 118.05, 118.01, 104.26, 104.08, 57.01, 56.46, 47.00, 42.51, 42.06, 42.04, 40.34, 39.67, 38.44, 37.46, 37.34, 36.33, 35.95, 35.43, 32.09, 30.78, 30.71, 29.07, 29.02, 28.55, 28.44, 28.17, 26.92, 26.88, 25.98, 25.91, 25.84, 25.83, 24.42, 23.99, 22.98, 22.72, 21.41, 21.29, 20.74, 20.50, 18.82, 17.66, 17.64, 16.65, 16.64, 12.12, 6.75, 6.74. IR

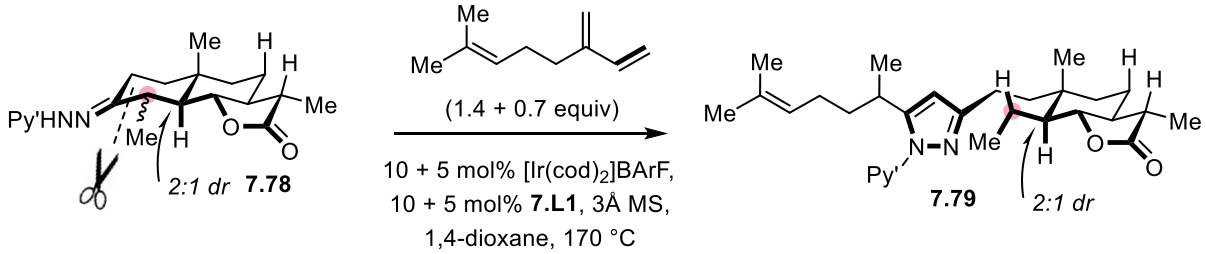
(KBr) 3062, 2961, 2932, 2872, 1609, 1470, 1417, 1376, 1012 cm^{-1}. HRMS: calcd. 628.5564 $[M+H]^+$ Found: 628.5549.

7.75: colorless oil (57.5 mg, 31% yield, inseparable mixture of diastereomers). R_f = 0.8 (hexane/ethyl acetate = 3:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 5.1, 0.6 Hz, 1H), 7.65 – 7.54 (m, 1H), 6.98 (dd, *J* = 5.0, 0.8 Hz, 1H), 6.02 (s, 1H), 5.03 (ddt, *J* = 8.7, 5.7, 1.4 Hz, 1H), 3.81 (h, *J* = 6.9 Hz, 1H), 2.60 – 2.43 (m, 2H), 2.40 (s, 3H), 1.95 (q, *J* = 8.3 Hz, 3H), 1.80 (ddd, *J* = 14.6, 9.1, 5.3 Hz, 1H), 1.73 – 1.50 (m, 14H), 1.49 – 1.40 (m, 2H), 1.29 (dd, *J* = 38.4, 7.2 Hz, 10H), 1.19 – 0.94 (m, 9H), 0.93 – 0.82 (m, 13H), 0.77 (s, 3H), 0.65 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were found at δ 155.00, 153.96, 151.89, 149.69, 147.40, 131.56, 124.46, 122.39, 117.99, 103.78, 56.96, 56.46, 47.64, 42.50, 40.30, 39.67, 38.47, 37.41, 36.87, 36.32, 36.23, 35.96, 35.50, 32.36, 30.75, 30.67, 28.44, 28.16, 25.97, 25.84, 24.44, 24.00, 22.98, 22.72, 21.48, 21.29, 21.17, 20.58, 18.80, 17.68, 16.16, 15.80, 12.13. IR (KBr) 2961, 2930, 2868, 1605, 1565, 1472, 1415, 1379, 1016 cm^{-1}. HRMS: calcd. 628.5564 $[M+H]^+$ Found: 628.5576.

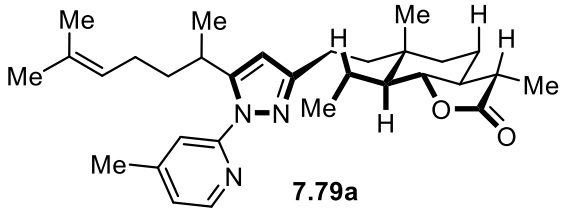


7.77: The reaction was conducted following modified **General procedure B** using the pre-formed hydrazone as the substrate: An 4 mL vial was charged with the hydrazone **7.76**

(12.5 mg, 0.05 mmol, 1.0 equiv) that was derived from its corresponding ketone following *General procedure for hydrazones formation (vide supra, 94% yield)*, $[Ir(cod)_2]BArF$ (6.4 mg, 0.005 mmol, 0.1 equiv), **7.L1** (2.0 mg, 0.005 mmol, 0.1 equiv) and 1,4-dioxane (0.5 mL). The vial was transferred into the glove box and charged with 1,3-butadiene (20% wt.% in PhMe, 170 μL, ca. 10 equiv). The vial was sealed and heated at 160 °C under stirring for 24 hours. 2 Parallel reactions were conducted. After cooled to room temperature, the reactions were combined, filtered through a short plug of Celite, concentrated *in vacuo*, and further purified by flash column chromatography over silica (hexane/ethyl acetate, 10:1) to furnished **7.77** as a colorless oil (25 mg, 58% yield). R_f = 0.55 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 5.1 Hz, 1H), 7.68 – 7.61 (m, 1H), 7.11 (t, *J* = 7.9 Hz, 1H), 7.00 (dt, *J* = 5.2, 1.1 Hz, 1H), 6.80 (dt, *J* = 7.6, 0.9 Hz, 1H), 5.92 (s, 1H), 4.11 – 3.95 (m, 1H), 3.95 – 3.80 (m, 1H), 3.65 (t, *J* = 9.6 Hz, 1H), 3.08 (q, *J* = 7.4 Hz, 2H), 3.00 (dd, *J* = 14.7, 3.6 Hz, 1H), 2.72 (dd, *J* = 14.7, 10.1 Hz, 1H), 2.42 (s, 3H), 2.36 (s, 3H), 1.52 (s, 9H), 1.22 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were found at δ 153.79, 151.29, 149.83, 148.00, 147.39, 128.09, 124.01, 122.43, 117.30, 112.49, 106.39, 53.18, 32.83, 28.61, 21.41, 21.34, 18.54, 13.26. IR (KBr) 2973, 2932, 1701, 1607, 1474, 1466, 1387, 1170, 1144 cm^{-1}. HRMS: calcd. 433.2598 $[M+H]^+$ Found: 433.2603.



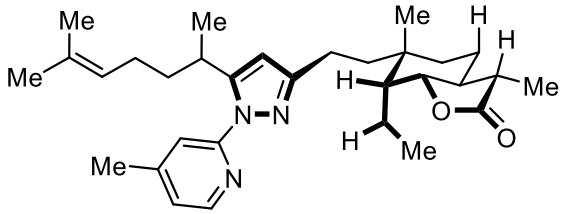
An 4 mL vial was charged with the hydrazone **7.78** (107 mg, 0.3 mmol, 1.0 equiv) that was derived from its corresponding ketone following *General procedure for hydrazones formation (vide supra, 95% yield)*, $[Ir(cod)_2]BArF$ (38 mg, 0.03 mmol, 0.1 equiv), **7.L1** (12.0 mg, 0.03 mmol, 0.1 equiv) and 1,4-dioxane (0.1 mL). The vial was transferred into the glove box and charged with myrcene (72 μL, 1.4 equiv). The vial was sealed and heated at 170 °C under stirring for 48 hours. Additional 5 mol% of $[Ir(cod)_2]BArF$ (19 mg) and **7.L1** (6 mg), together with 0.7 equiv of myrcene (36 μL) and 3Å MS (50 mg), was added to the reaction in a glovebox. The resulting mixture was further heated at 170 °C for 12 hours. The reaction was then filtered through a short plug of Celite, concentrated *in vacuo*, and purified by flash column chromatography over silica (hexane/ethyl acetate) to furnished **7.79a** and **7.79b** (24.5 mg combined, 17% yield).



7.79a

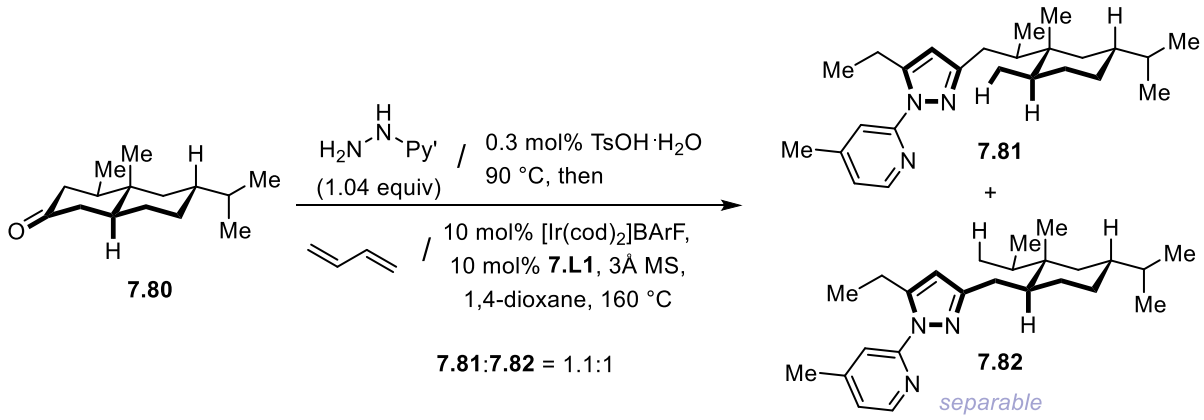
7.79a: colorless oil (16.5 mg, 11.5% yield). R_f = 0.3 (hexane/ethyl acetate = 3:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 5.1 Hz, 1H), 7.56 (d, *J* = 1.4 Hz, 1H), 7.00 (dd, *J* = 5.0, 1.4 Hz, 1H), 6.04 (s, 1H), 5.02 (t, *J* = 6.2 Hz, 1H), 3.83 (t, *J* = 10.5 Hz, 1H), 3.80 – 3.72 (m, 1H), 2.74 – 2.53 (m, 2H), 2.41 (s, 3H), 2.34 – 2.18 (m, 1H), 1.94 (q, *J* = 7.4 Hz, 2H), 1.84 (dq, *J* = 12.3, 3.1 Hz, 1H), 1.75 (p, *J* = 7.9 Hz, 2H), 1.71 – 1.55 (m, 8H), 1.51 – 1.32 (m, 7H), 1.27 – 1.20 (m, 6H), 1.07 (t, *J* = 7.4 Hz, 3H), 0.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$)

carbon signals were found at δ 180.01, 154.16, 153.80, 152.06, 149.82, 147.51, 131.64, 124.36, 122.62, 118.06, 103.82, 86.44, 52.36, 49.43, 41.47, 41.44, 39.10, 37.40, 37.38, 37.33, 30.70, 25.92, 25.82, 23.80, 22.60, 21.56, 21.29, 20.59, 20.58, 20.11, 17.68, 14.69, 12.66. IR (KBr) 3056, 2965, 2932, 2878, 1778, 1607, 1569, 1472, 1458, 1417, 1379, 1121, 1073 cm^{-1}. HRMS: calcd. 492.3585 $[M+H]^+$ Found: 492.3594.



7.79b

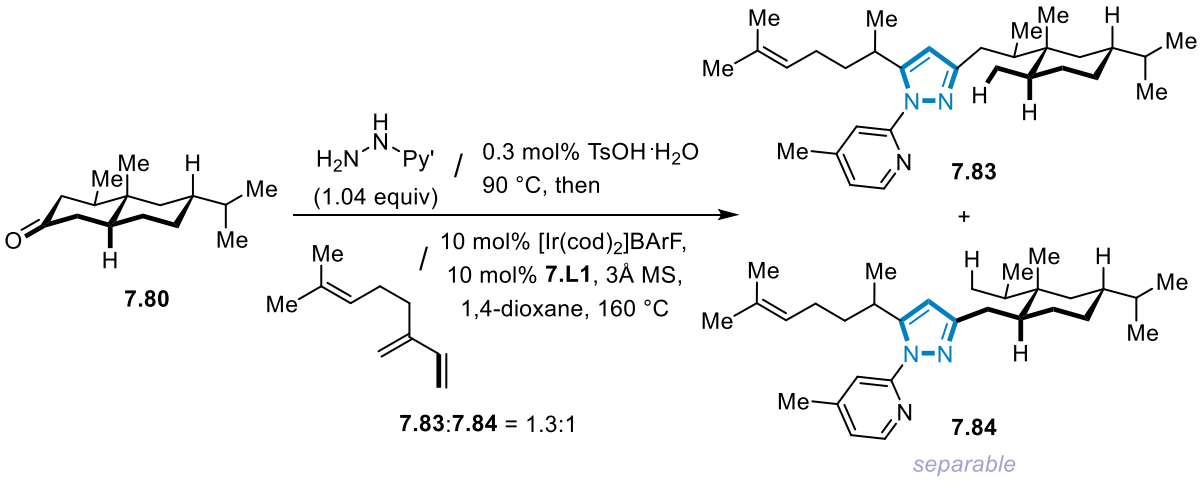
7.79b: colorless oil (8 mg, 5.5% yield). R_f = 0.27 (hexane/ethyl acetate = 3:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 5.1 Hz, 1H), 7.56 (s, 1H), 7.06 – 6.94 (m, 1H), 6.04 (s, 1H), 5.03 (dddd, *J* = 8.7, 7.2, 3.7, 2.3 Hz, 1H), 4.29 (dd, *J* = 11.1, 4.6 Hz, 1H), 3.79 (h, *J* = 6.9 Hz, 1H), 2.74 – 2.59 (m, 2H), 2.41 (s, 3H), 2.25 (dq, *J* = 11.9, 6.9 Hz, 1H), 1.98 – 1.86 (m, 3H), 1.86 – 1.61 (m, 8H), 1.53 – 1.37 (m, 9H), 1.27 – 1.21 (m, 6H), 1.15 (s, 3H), 1.03 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.73, 154.12, 153.85, 152.03, 149.82, 147.50, 131.65, 124.38, 122.61, 118.06, 103.76, 83.38, 45.88, 45.18, 41.83, 41.28, 38.50, 37.38, 33.74, 30.72, 25.93, 25.83, 24.14, 24.10, 22.41, 21.30, 20.59, 17.68, 17.26, 15.58, 12.68. IR (KBr) 2963, 2936, 2878, 1780, 1609, 1567, 1474, 1462, 1415, 1381, 1239, 1170, 1008 cm^{-1}. HRMS: calcd. 492.3585 $[M+H]^+$ Found: 492.3590.



Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 11.1 mg **7.80** and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions were conducted (0.05 mmol for each, 0.1 mmol in total) and combined, yielding pyrazoles **7.81** and **7.82** in 1.1:1 ratio after isolation. The characterization data for **7.81** and **7.82** are listed as follows:

7.81 was isolated as a colorless oil (11.2 mg, 30% yield). R_f = 0.3 (hexane/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 5.1, 0.7 Hz, 1H), 7.65 (t, *J* = 0.8 Hz, 1H), 6.96 (ddd, *J* = 5.1, 1.6, 0.8 Hz, 1H), 6.03 (s, 1H), 3.11 (qd, *J* = 7.5, 0.8 Hz, 2H), 2.80 (dd, *J* = 13.9, 2.5 Hz, 1H), 2.40 (s, 3H), 2.32 (dd, *J* = 13.9, 11.7 Hz, 1H), 1.86 (dqd, *J* = 11.6, 6.8, 2.5 Hz, 1H), 1.65 (dp, *J* = 12.4, 3.2 Hz, 1H), 1.55 – 1.43 (m, 2H), 1.39 – 1.19 (m, 7H), 1.01 – 0.87 (m, 5H), 0.87 – 0.80 (m, 9H), 0.77 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.05, 153.91, 149.71, 147.88, 147.32, 122.13, 117.13, 105.84, 41.54, 38.88, 38.28, 36.05, 34.78, 33.37, 31.46, 30.28, 29.89, 21.56, 21.29, 20.15, 19.80, 18.76, 15.40, 13.26, 12.75. IR (KBr) 2969, 2934, 2876, 1607, 1573, 1472, 1423, 1362, 1004 cm^{-1}. HRMS: calcd. 382.3217 $[M+H]^+$ Found: 382.3217.

7.82 was isolated as a colorless oil (10.4 mg, 27% yield). The titled compound was isolated as a colorless oil (10.4 mg, 27% yield). R_f = 0.26 (hexane/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 – 8.19 (m, 1H), 7.66 – 7.55 (m, 1H), 6.96 (ddd, *J* = 5.1, 1.6, 0.8 Hz, 1H), 6.00 (s, 1H), 3.10 (qd, *J* = 7.5, 0.9 Hz, 2H), 2.81 (dd, *J* = 14.1, 2.5 Hz, 1H), 2.39 (s, 3H), 2.13 (dd, *J* = 14.1, 11.4 Hz, 1H), 1.90 (p, *J* = 6.9 Hz, 1H), 1.69 (tt, *J* = 11.7, 3.0 Hz, 1H), 1.64 – 1.58 (m, 2H), 1.39 – 1.16 (m, 7H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.93 – 0.87 (m, 6H), 0.87 – 0.72 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.39, 153.90, 149.69, 147.86, 147.30, 122.12, 117.12, 105.77, 41.89, 38.75, 37.97, 34.71, 34.04, 33.35, 29.55, 28.32, 27.62, 21.54, 21.30, 20.21, 19.72, 19.08, 17.42, 16.56, 13.27. IR (KBr) 2957, 2930, 2872, 1609, 1567, 1476, 1419, 1362 cm^{-1}. HRMS: calcd. 382.3217 $[M+H]^+$ Found: 382.3227.

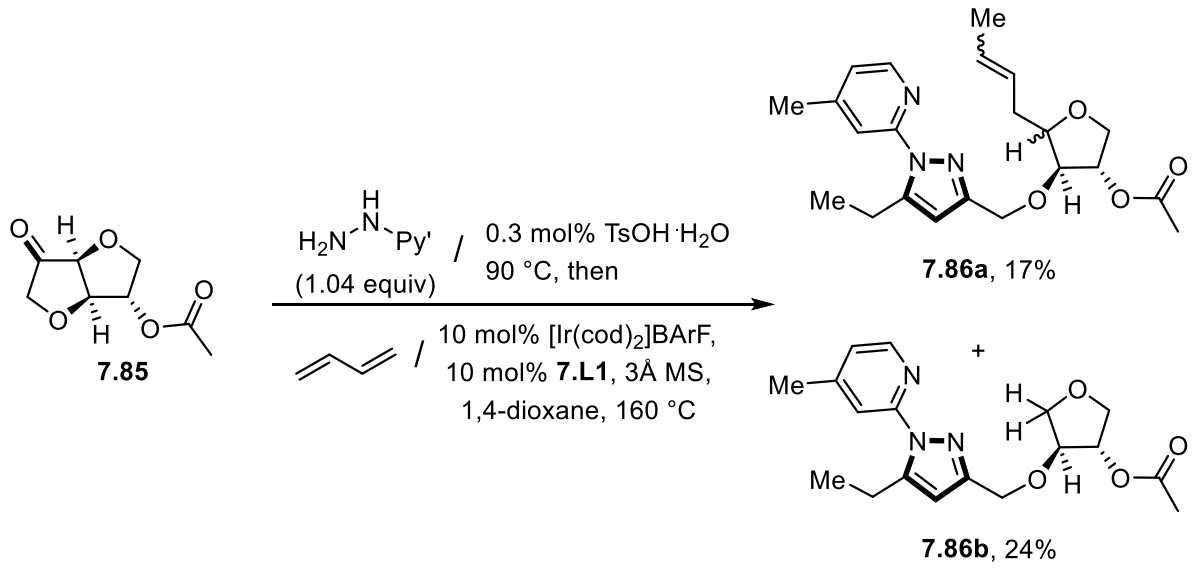


Following **General procedure A,** the reaction was conducted at 0.3 mmol scale with 67 mg **7.80** and 78 μL myrcene (1.5 equiv) in 0.1 ml 1,4-dioxane. Pyrazoles **7.83** and **7.84** were isolated in 1.3:1 ratio. The characterization data for **7.83** and **7.84** are listed as follows:

7.83: colorless oil (32 mg, 23% yield, inseparable mixture of diastereomers). R_f = 0.8

(hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 5.1 Hz, 1H), 7.59 (s, 1H), 6.98 (dd, *J* = 5.2, 1.4 Hz, 1H), 6.03 (d, *J* = 1.9 Hz, 1H), 5.03 (ddddd, *J* = 14.5, 7.1, 5.7, 2.9, 1.5 Hz, 1H), 3.83 (h, *J* = 6.9 Hz, 1H), 2.80 (d, *J* = 14.0 Hz, 1H), 2.40 (s, 3H), 2.38 – 2.27 (m, 1H), 2.01 – 1.82 (m, 3H), 1.72 – 1.55 (m, 6H), 1.56 – 1.45 (m, 5H), 1.39 – 1.16 (m, 7H), 0.99 – 0.88 (m, 5H), 0.87 – 0.73 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were found at δ 154.97, 154.94, 153.99, 151.93, 151.86, 149.70, 149.68, 147.35, 131.55, 124.47, 124.44, 122.37, 122.35, 118.03, 117.99, 104.28, 104.10, 41.50, 38.86, 38.26, 37.45, 37.37, 36.04, 34.77, 33.36, 31.45, 30.78, 30.71, 30.29, 30.24, 29.88, 25.98, 25.88, 25.83, 25.82, 21.27, 20.72, 20.53, 20.14, 19.79, 18.75, 17.66, 17.62, 15.41, 15.39, 12.75, 12.69. IR (KBr) 3062, 2963, 2924, 2872, 1607, 1573, 1470, 1419, 1376, 1010 cm^{-1}. HRMS: calcd. 464.3999 $[M+H]^+$ Found: 464.3994.

7.84: colorless oil (24.5 mg, 18% yield). R_f = 0.7 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 5.1, 0.7 Hz, 1H), 7.64 – 7.51 (m, 1H), 6.98 (ddd, *J* = 5.1, 1.6, 0.8 Hz, 1H), 5.99 (s, 1H), 5.05 (ddt, *J* = 8.6, 5.8, 1.4 Hz, 1H), 3.82 (h, *J* = 6.9 Hz, 1H), 2.80 (dd, *J* = 14.2, 2.6 Hz, 1H), 2.40 (s, 3H), 2.14 (dd, *J* = 14.1, 11.5 Hz, 1H), 2.03 – 1.85 (m, 3H), 1.74 – 1.54 (m, 8H), 1.50 – 1.42 (m, 3H), 1.38 – 1.17 (m, 7H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.93 – 0.86 (m, 7H), 0.86 – 0.71 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.32, 153.98, 151.93, 149.69, 147.35, 131.57, 124.48, 122.36, 118.01, 103.99, 41.89, 38.74, 37.97, 37.34, 34.71, 34.06, 33.35, 30.78, 29.57, 28.32, 27.59, 25.99, 25.84, 21.29, 20.73, 20.21, 19.71, 19.10, 17.63, 17.41, 16.57. IR (KBr) 3062, 2967, 2932, 2873, 1607, 1569, 1470, 1415, 1376, 1013 cm^{-1}. HRMS: calcd. 464.3999 $[M+H]^+$ Found: 464.4004.

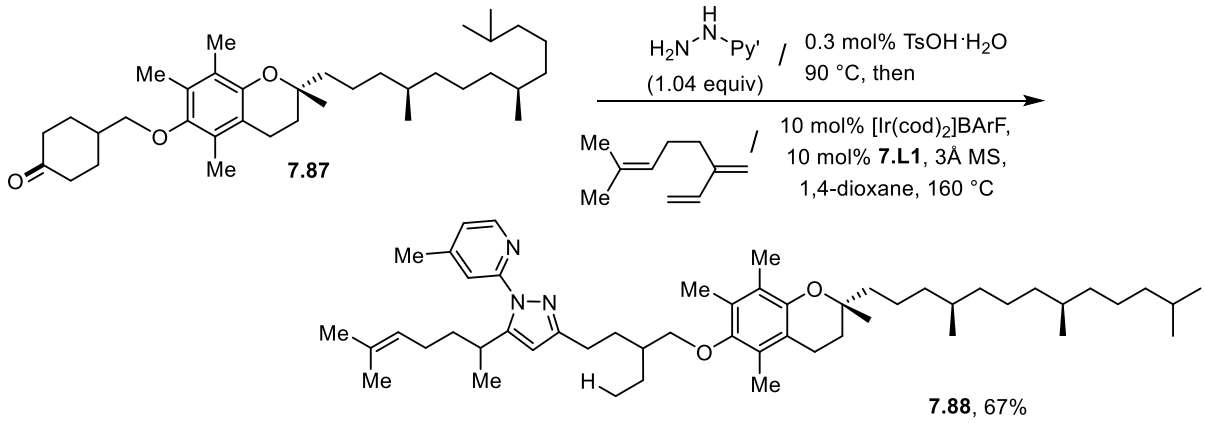


Following **General procedure B,** the reaction was conducted at 0.05 mmol scale with 9.3 mg **7.85** and 120 μL 1,3-butadiene (in PhMe, 20% wt.%). Two parallel reactions were conducted (0.05 mmol for each, 0.1 mmol in total) and combined, yielding pyrazoles **7.86a** and **7.86b** in 41% yield combined. The characterization data for **7.86a** and **7.86b** are listed as follows:

7.86a: colorless oil (6.8 mg, 17% yield, inseparable mixture of diasteroermers). R_f = 0.25 (hexane/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 5.0 Hz, 1H), 7.64 (s, 1H), 7.01 (d, *J* = 4.9 Hz, 1H), 6.25 (s, 1H), 5.90 – 5.30 (m, 2H), 5.25 – 5.15 (m, 1H), 4.77 – 4.66 (m, 1H), 4.66 – 4.54 (m, 1H), 4.05 – 3.97 (m, 1H), 3.97 – 3.89 (m, 1H), 3.89 – 3.72 (m, 2H), 3.11 (q, *J* = 7.5 Hz, 2H), 2.50 – 2.28 (m, 5H), 2.12 – 2.02 (m, 3H), 1.70 – 1.60 (m, 3H), 1.26 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were observed at δ 170.55, 153.66, 150.00, 149.91, 148.48, 147.45, 128.13, 126.70, 125.52, 122.73, 117.33, 106.22, 87.03, 86.93, 83.84, 78.86, 71.93, 66.39, 36.59, 21.48, 21.31, 21.21, 18.20, 13.16,

13.12. R (KBr) 2973, 2926, 2874, 1741, 1609, 1569, 1421, 1372, 1241, 1099 cm^{-1}. HRMS: calcd. 400.2231 $[M+H]^+$ Found: 400.2238.

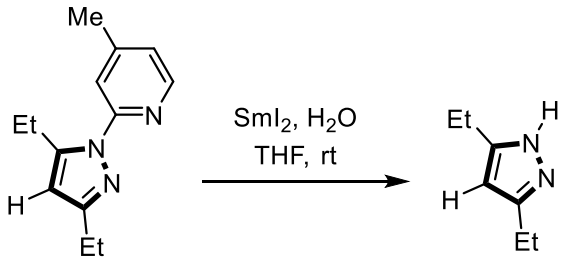
7.86b: The titled compound was isolated as a colorless oil (8.2 mg, 24% yield). R_f = 0.15 (hexane/ethyl acetate = 3:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 5.1 Hz, 1H), 7.63 (s, 1H), 7.11 – 6.92 (m, 1H), 6.26 (s, 1H), 5.25 (d, *J* = 4.3 Hz, 1H), 4.71 (d, *J* = 11.9 Hz, 1H), 4.61 (d, *J* = 11.9 Hz, 1H), 4.16 (dd, *J* = 4.8, 2.3 Hz, 1H), 4.06 (ddd, *J* = 14.1, 10.3, 4.7 Hz, 2H), 3.87 – 3.77 (m, 2H), 3.10 (qd, *J* = 7.5, 0.9 Hz, 2H), 2.41 (s, 3H), 2.07 (s, 3H), 1.25 (t, *J* = 7.5 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.28, 153.48, 149.82, 149.78, 148.38, 147.33, 122.65, 117.28, 106.11, 82.59, 77.55, 72.00, 71.77, 65.78, 21.30, 21.17, 21.05, 13.02. R (KBr) 2977, 2936, 2874, 1739, 1609, 1423, 1239, 1090 cm^{-1}.



Following **General procedure A,** the reaction was conducted at 0.3 mmol scale with 162.3 mg **7.87** and 78 μL myrcene (1.5 equiv). **7.88** was isolated as a colorless oil (156.1 mg, 67% yield, inseparable mixture of diastereomers). R_f = 0.7 (hexane/ethyl acetate = 5:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 5.0 Hz, 1H), 7.60 (s, 1H), 7.05 – 6.93 (m, 1H), 6.09

(d, J = 1.6 Hz, 1H), 5.03 (t, J = 6.7 Hz, 1H), 3.84 (h, J = 7.5, 7.0 Hz, 1H), 3.60 (d, J = 4.4 Hz, 2H), 2.76 (td, J = 8.0, 1.8 Hz, 2H), 2.57 (t, J = 6.8 Hz, 2H), 2.40 (s, 3H), 2.19 (s, 3H), 2.14 (s, 3H), 2.09 (s, 3H), 2.00 – 1.51 (m, 17H), 1.48 – 0.95 (m, 30H), 0.90 – 0.82 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) carbon signals were found at δ 154.35, 153.99, 151.91, 149.70, 148.47, 147.74, 147.39, 131.56, 128.00, 125.96, 124.45, 122.93, 122.41, 117.92, 117.63, 104.06, 75.52, 75.50, 74.85, 40.60, 40.58, 40.16, 39.52, 37.63, 37.60, 37.57, 37.43, 37.39, 32.95, 32.85, 31.50, 30.74, 30.67, 30.64, 28.13, 26.22, 25.92, 25.83, 24.95, 24.59, 24.03, 23.85, 22.88, 22.78, 21.28, 21.18, 20.83, 20.61, 19.91, 19.81, 17.68, 12.91, 12.05, 11.94, 11.37. IR (KBr) 2953, 2922, 2868, 1607, 1569, 1466, 1415, 1374, 1259, 1089 cm^{-1}. HRMS: calcd. 782.6558 $[M+H]^+$ Found: 782.6578.

Deprotection of the pyridyl group

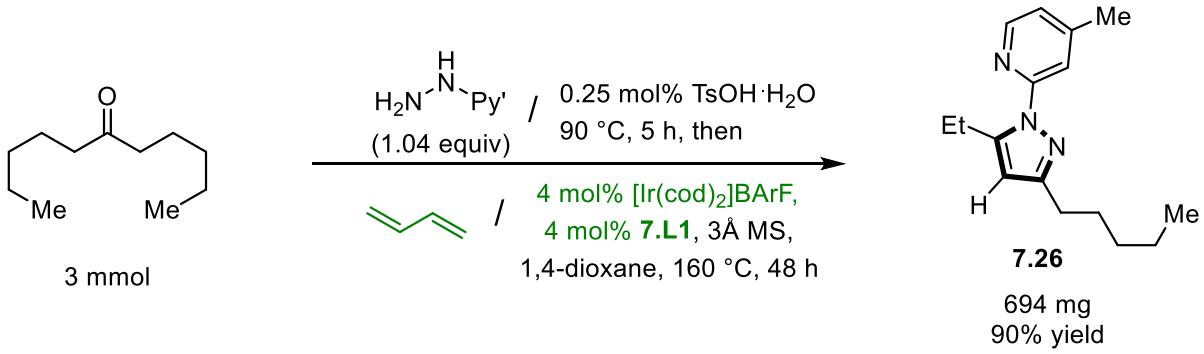


7.15 **7.15b**

A THF solution of SmI_2 (0.1M, 10.5 mL, 1.05 mmol, 7 equiv) was added to a 25 mL round-bottom flask charged with **7.15** (32 mg, 0.15 mmol, 1.0 equiv) under N_2 atmosphere using a syringe. Degassed H_2O (81 μL, 4.5 mmol, 30 equiv) was then added using a syringe. The reaction mixture was stirred at room temperature for 15 mins and then concentrated under *vacuo*. The residue was treated with aqueous NH_4Cl (sat.) (5 mL), H_2O (5 mL), and

DCM (10 mL), and was stirred vigorously at room temperature for 45 mins. The reaction mixture was then extracted with DCM and dried over Na_2SO_4. The filtrate was concentrated under *vacuo* and purified by flash column chromatography over silica (DCM/MeOH, from 30:1 to 15:1) to give product **7.15b** as a colorless oil (16.1 mg, 87% yield). R_f = 0. 35 (DCM/MeOH = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (br, 1H), 5.88 (s, 1H), 2.65 (q, *J* = 7.6 Hz, 4H), 1.25 (t, *J* = 7.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.73, 101.08, 20.44, 13.70. The spectra match the reported literature.[69]

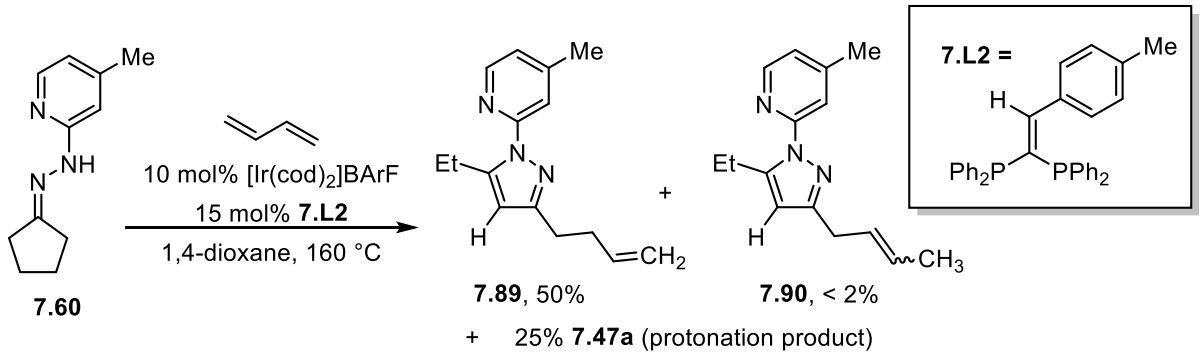
Semi-gram-scale preparation of 7.26 with 4% catalyst:



A 40 mL vial was charged with the ketone substrate undecan-6-one (510 mg, 3 mmol, 1.0 equiv) and 2-hydrazineyl-4-methylpyridine **7.D1** (384 mg, 3.12 mmol, 1.04 equiv), and transferred into a glove box. 1,4-Dioxane (2.5 mL) and a stock solution of $TsOH{\cdot}H_2O$ in 1,4-dioxane (0.05 M, 150 μL, 0.0025 equiv) was added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 90 °C for 5 hours. After cooled to room temperature, the vial was charged with $[Ir(cod)_2]BArF$ (153 mg, 0.12 mmol, 0.04 equiv) and **7.L1** (48 mg, 0.12 mmol, 0.04 equiv), transferred into the glove box, and then purged under

N_2 atmosphere for 6 mins. Pre-dried 3Å molecular sieve (2.5 g) and the 1,3-butadiene (20% wt.% in PhMe, 12 mL) were then added. The vial was sealed and heated at 160 °C under stirring for 48 hours. After cooled to room temperature, the reaction mixture was filtered through a short plug of Celite, concentrated *in vacuo*, and further purified by flash column chromatography over silica (hexane/ethyl acetate, from 40:1 to 20:1) to give the pyrazole product **7.26** as a colorless oil (694 mg, 90% yield).

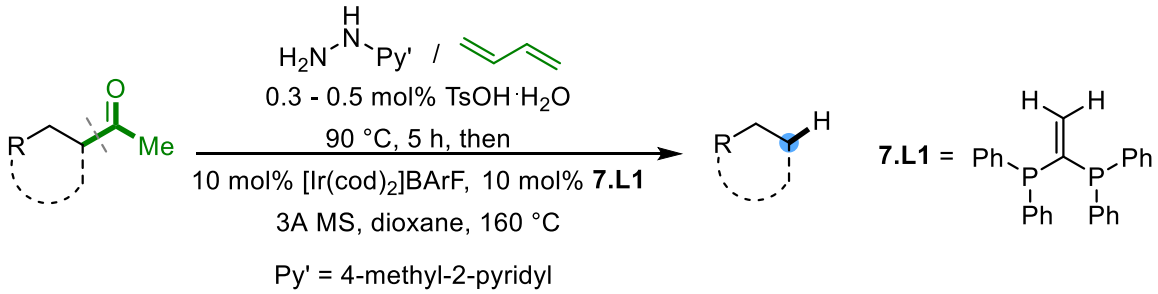
Olefin formation through β-H elimination



A 4 mL vial was charged with hydrazone **7.60** (9.5 mg, 0.05 mmol, 1.0 equiv), $[Ir(cod)_2]BArF$ (6.4 mg, 0.005 mmol, 0.1 equiv) and **7.L2** (3.6 mg, 0.0075 mmol, 0.15 equiv). The vial was transferred into the glove box. 1,4-Dioxane (0.5 mL) and 1,3-butadiene (20% wt.% in PhMe, 160 μL, ca. 12 equiv) were then added. The vial was sealed, transferred out of the glove box, and heated at 160 °C under stirring for 18 hours. Two parallel reactions were set up. After cooled to room temperature, the reactions were combined, concentrated *in vacuo*, and further purified by flash column chromatography over silica (hexane/ethyl acetate,

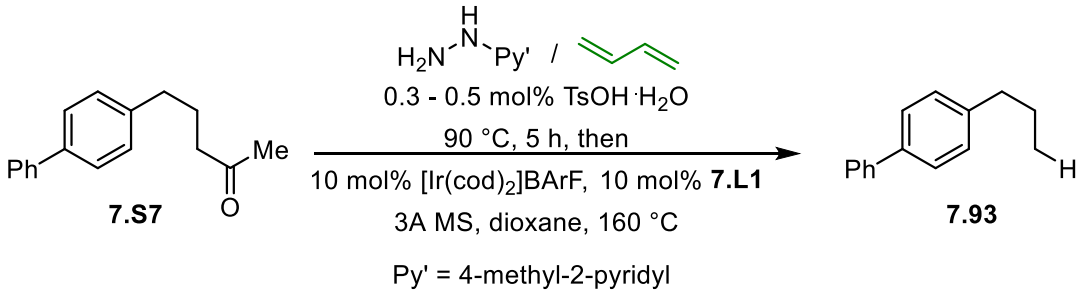
from 40:1 to 20:1) to give the pyrazole products**.** The protonation product **7.47a** was obtained as a colorless oil (6.0 mg, 25% yield), whose spectra have been reported *vide supra*. Compound **7.89** was obtained as a colorless oil (12.0 mg, 50% yield). R_f = 0.29 (hexane/ethyl acetate = 10:1) (slightly more polar than compound **7.47a**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 5.1 Hz, 1H), 7.64 (s, 1H), 6.97 (d, *J* = 4.4 Hz, 1H), 6.06 (s, 1H), 5.92 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.09 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.00 (dd, *J* = 10.2, 1.2 Hz, 1H), 3.10 (q, *J* = 7.4 Hz, 2H), 2.86 – 2.68 (m, 2H), 2.45 (q, *J* = 7.6, 7.1 Hz, 2H), 2.40 (s, 3H), 1.24 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.90, 153.65, 149.75, 147.90, 147.37, 138.31, 122.24, 117.07, 115.02, 105.80, 33.71, 28.09, 21.51, 21.29, 13.28. IR (KBr) 3059, 2977, 2929, 1611, 1569, 1479, 1420, 1001 cm^{-1}. HRMS: calcd. 242.1652 $[M+H]^+$ Found: 242.1661.

Application II: Deacetylation of methyl ketones



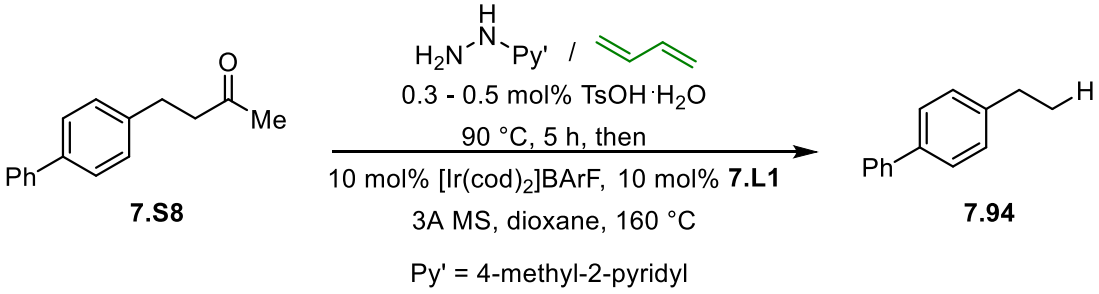
General procedure C: An 8 mL vial was charged with the ketone substrate (0.05 mmol, 1.0 equiv) and 2-hydrazineyl-4-methylpyridine **7.D1** (6.4 mg, 0.052 mmol, 1.04 equiv), and was transferred into a glove box. 1,4-Dioxane (1 mL) and a stock solution of $TsOH{\cdot}H_2O$ in 1,4-dioxane (0.05 M, 3.0–5.0 μL, 0.003-0.005 equiv) were then added. The vial

was sealed, transferred out of the glove box, and heated in a pie-block at 90 °C for 5 hours. After cooled to room temperature, the vial was opened, and charged with [Ir(cod)$_2$]BArF (6.4 mg, 0.005 mmol, 0.1 equiv) and **7.L1** (2.0 mg, 0.005 mmol, 0.1 equiv). The vial was sealed and transferred into the glove box, and then opened and purged under N_2 atmosphere for 3 mins. Pre-dried 3Å molecular sieve (100 mg) and 1,3-butadiene (20% wt.% in PhMe, 170 μL, ca. 10 equiv) were then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 160 °C under stirring for 72 hours. After cooled to room temperature, the reaction mixture was filtered through a short plug of Celite, concentrated *in vacuo*, and further purified by flash column chromatography over silica (hexane/ethyl acetate or hexane/acetone) to give the deacetylation products. The reported yields were based on average of 2 runs.

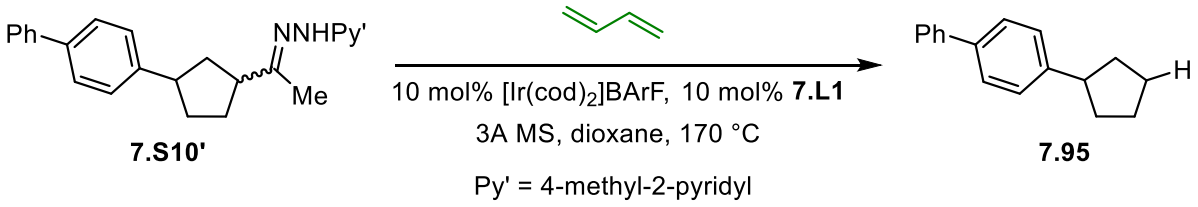


7.93: Following modified **General procedure C** *in which slightly more amount of 1,3-butadiene was used* (20% wt.% in PhMe, 190 μL per 0.05 mmol-scale reaction), the reaction was conducted with 23.8 mg **7.S7** as the ketone starting material in 2 parallel vessels (0.05 mmol for each, 0.1 mmol combined). The titled compound was obtained as a colorless oil (13.6 mg, 70% yield). R_f = 0.4 (Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.2 Hz,

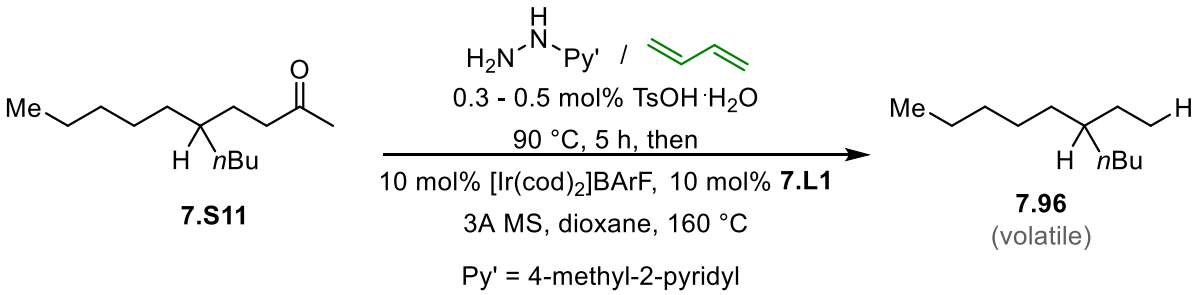
2H), 7.51 (d, J = 8.0 Hz, 2H), 7.42 (t, J = 7.7 Hz, 2H), 7.32 (t, J = 7.1 Hz, 1H), 7.27 – 7.22 (m, 2H), 2.72 – 2.55 (m, 2H), 1.68 (h, J = 7.4 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.99, 141.32, 138.71, 129.02, 128.83, 127.13, 127.10, 127.08, 37.85, 24.72, 14.05. The spectra match the reported literature.[70]



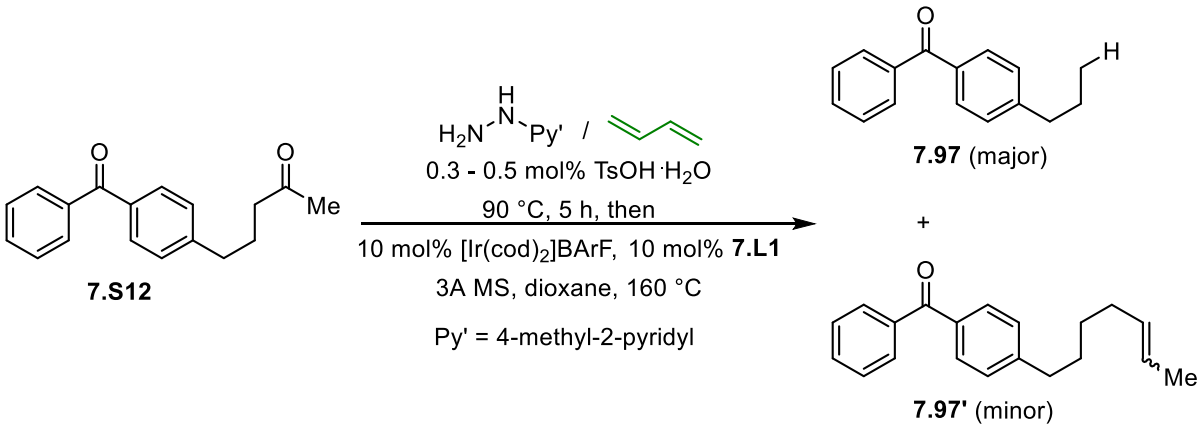
7.94: Following modified **General procedure C** *in which slightly less amount of 1,3-butadiene was used* (20% wt.% in PhMe, 160 μL per 0.05 mmol-scale reaction), the reaction was conducted with 22.4 mg **7.S8** as the ketone starting material in 2 parallel vessels (0.05 mmol for each, 0.1 mmol combined). The titled compound was obtained as a colorless oil (12.3 mg, 68% yield). R_f = 0.4 (Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 8.2, 1.3 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.37 – 7.31 (m, 1H), 7.29 (d, J = 8.4 Hz, 2H), 2.72 (q, J = 7.6 Hz, 2H), 1.30 (t, J = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.53, 141.34, 138.76, 128.84, 128.42, 127.22, 127.15, 127.10, 28.67, 15.73. The spectra match the reported literature.[71]



7.95: The reaction was conducted following modified **General procedure C**: An 8 mL vial was charged with the hydrazone **7.S10'** (17.8 mg, 0.05 mmol, 1.0 equiv) which was derived from its corresponding ketone **7.S9** following *General procedure for hydrazones formation (vide supra)*, $[Ir(cod)_2]BArF$ (6.4 mg, 0.005 mmol, 0.1 equiv), dppm (1.9 mg, 0.005 mmol, 0.1 equiv) and 1,4-dioxane (1 mL) . The vial was transferred into the glove box, and was charged with 1,3-butadiene (20% wt.% in PhMe, 140 μL, ca. 12 equiv). The vial was sealed, transferred out of the glove box, and heated in a pie-block at 170 °C under stirring for 72 hours. After cooled to room temperature, the reaction mixture was filtered through a short plug of Celite, concentrated *in vacuo*, and further purified by flash column chromatography over silica (hexane). Combining 2 parallel reactions furnished **7.95** in 70% yield (15.5 mg) as a white solid. R_f = 0.4 (Hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.6 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.41 – 7.29 (m, 3H), 3.05 (ddd, *J* = 16.9, 9.6, 7.5 Hz, 1H), 2.18 – 2.00 (m, 2H), 1.90 – 1.79 (m, 2H), 1.78 – 1.60 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.83, 141.33, 138.80, 128.83, 127.66, 127.15, 127.13, 127.08, 45.79, 34.80, 25.70. The spectra match the reported literature.[72]

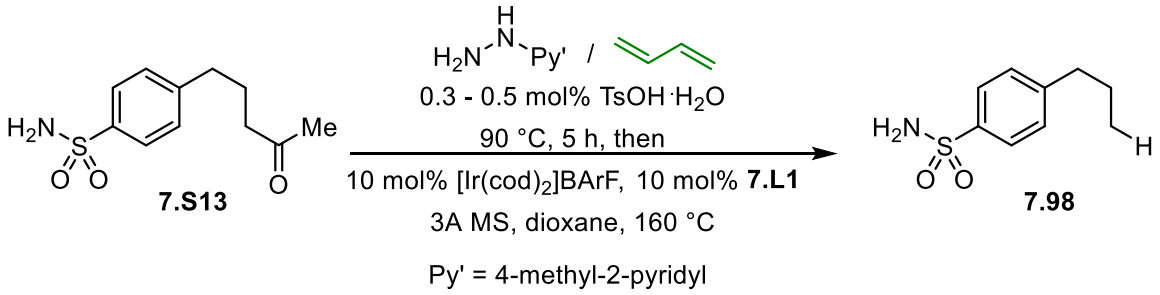


7.96: Following **General procedure C**, the reaction was conducted with 21.2 mg **7.S11** as the ketone starting material in 2 parallel vessels (0.05 mmol for each, 0.1 mmol combined). The titled compound was obtained as a colorless oil (10.1 mg, 60% yield) (*cautious: the product is volatile!*). R_f = 0.8 (Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 – 1.20 (m, 17H), 1.05 – 0.69 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 39.01, 33.35, 33.06, 32.55, 29.17, 26.58, 26.07, 23.33, 22.89, 14.33, 14.29, 11.04. The spectra match the reported literature.[73]



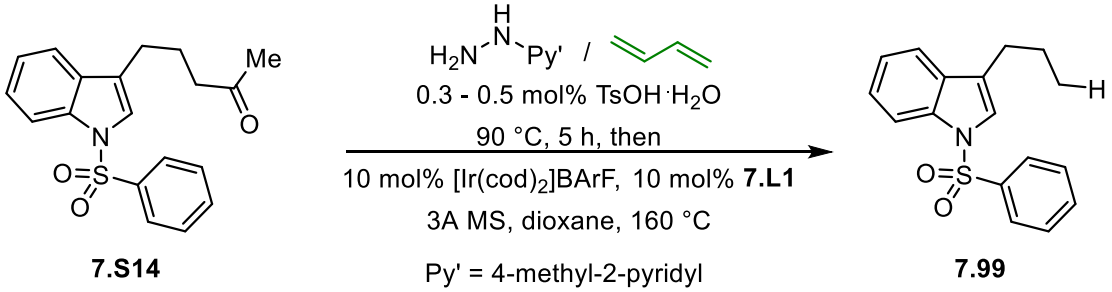
7.97: Following **General procedure C**, the reaction was conducted with 26.6 mg **7.S7** as the ketone starting material in 2 parallel vessels (0.05 mmol for each, 0.1 mmol combined). The compound **7.97** was isolated as a colorless oil along with a minor inseparable

deacetylative crotylation by-product (ca. 17%). Based on ^{1}H-NMR analysis of the isolated products, the desired product **7.97** was obtained in 67% yield (14.9 mg). R_f = 0.3 (Hex/EA = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.74 (m, 2H, **7.97** & **7.97'**), 7.71 (d, *J* = 7.9 Hz, 2H, **7.97** & **7.97'**), 7.57 – 7.51 (m, 1H, **7.97** & **7.97'**), 7.44 (t, *J* = 7.6 Hz, 2H, **7.97** & **7.97'**), 7.25 (d, *J* = 7.9 Hz, 2H, **7.97** & **7.97'**), 5.54 – 5.06 (m, 0.35H, **7.97'**), 2.64 (t, *J* = 7.6 Hz, 2H, **7.97** & **7.97'**), 2.08 – 1.93 (m, 0.35H, **7.97'**), 1.75 – 1.55 (m, 2.5H, **7.97** & **7.97'**), 1.45 – 1.35 (m, 0.35H, **7.97'**), 0.94 (t, *J* = 7.3 Hz, 2.5H, **7.97**). ^{13}C NMR (101 MHz, $CDCl_3$) major signals (for compound **7.97**): δ 196.62, 148.04, 138.13, 135.28, 132.26, 130.43, 130.07, 128.52, 128.33, 38.21, 24.40, 13.93; minor signals (from compound **7.97'**) was also observed at δ 131.24, 130.46, 128.47, 125.17, 36.03, 32.51, 30.77, 29.31, 18.05. The spectra match the reported literature.[74]



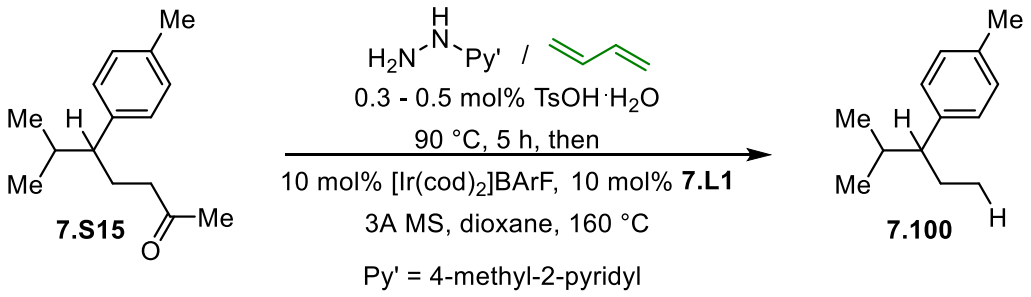
7.98: Following modified **General procedure C** *in which slightly more amount of 1,3-butadiene was used* (20% wt.% in PhMe, 180 μL per 0.05 mmol-scale reaction), the reaction was conducted with 24.1 mg **7.S13** as the ketone starting material in 2 parallel vessels (0.05 mmol for each, 0.1 mmol combined) for 96 hours. The titled compound was obtained as a colorless oil (10.1 mg, 51% yield). R_f = 0.75 (Hex/acetone = 1:1). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 4.87 (s, 2H), 2.66 (t, *J* = 7.6 Hz, 2H), 1.66 (h, *J* = 7.4 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.45, 139.36, 129.32, 126.61, 38.00, 24.37, 13.83. The spectra match the reported literature.[75]

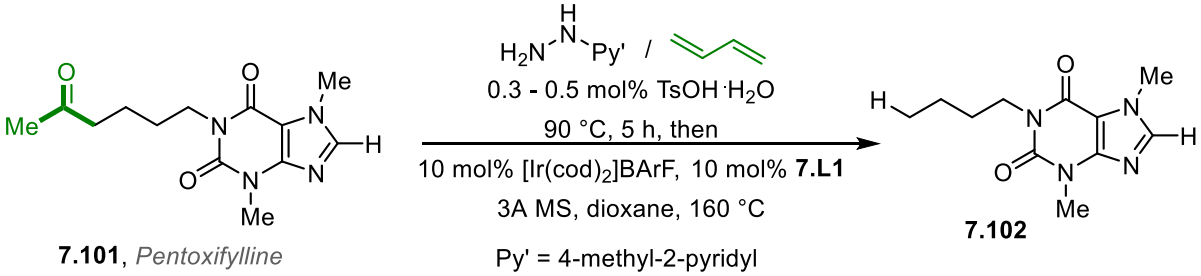


7.S14 **7.99**

7.99: Following modified **General procedure C** *in which slightly more amount of 1,3-butadiene was used* (20% wt.% in PhMe, 180 μL per 0.05 mmol-scale reaction), the reaction was conducted with 34.1 mg **7.S14** as the ketone starting material in 2 parallel vessels (0.05 mmol for each, 0.1 mmol combined). The titled compound was obtained as a colorless oil (15.4 mg, 52% yield). R_f = 0.65 (Hex/EA = 3:1). M.p. = 90-92 °C (Et_2O). ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.85 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.54 – 7.45 (m, 2H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.34 – 7.28 (m, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 2.63 (t, *J* = 7.5 Hz, 2H), 1.71 (h, *J* = 7.5 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.45, 135.58, 133.70, 131.40, 129.27, 126.80, 124.74, 123.79, 123.16, 122.76, 119.70, 113.91, 27.06, 22.23, 14.06. The spectra match the reported literature.[76]

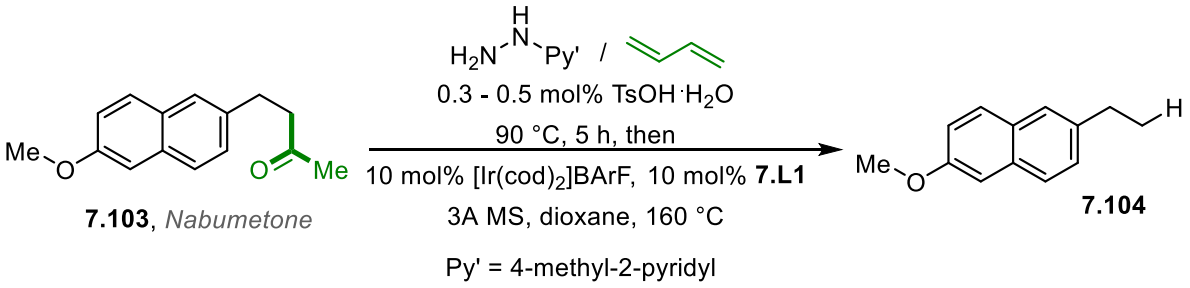


7.100: Following **General procedure C**, the reaction was conducted with 21.8 mg **7.S15** as the ketone starting material in 2 parallel vessels (0.05 mmol for each, 0.1 mmol combined). The titled compound was obtained as a colorless oil (10.0 mg, 57% yield). R_f = 0.65 (Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J = 7.7 Hz, 2H), 6.99 (d, J = 7.8 Hz, 2H), 2.32 (s, 3H), 2.12 (ddd, J = 11.1, 7.5, 4.2 Hz, 1H), 1.79 (dqd, J = 14.0, 7.2, 4.2 Hz, 2H), 1.62 – 1.48 (m, 1H), 0.93 (d, J = 6.7 Hz, 3H), 0.78 – 0.65 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.47, 135.13, 128.71, 128.62, 54.69, 33.26, 25.82, 21.17, 21.16, 20.83, 12.61. IR (KBr) 3024, 2963, 2932, 2876, 1512, 1464, 1385 cm^{-1}. HRMS: calcd. 177.1638 $[M+H]^+$ Found: 177.1631.



7.102: Following modified **General procedure C** *in which slightly more amount of 1,3-butadiene was used* (20% wt.% in PhMe, 180 μL per 0.05 mmol-scale reaction), the reaction was conducted with 27.8 mg **7.101** as the ketone starting material in 2 parallel

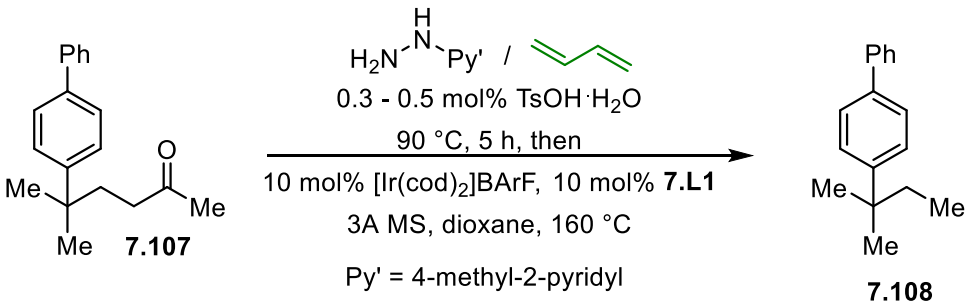
vessels (0.05 mmol for each, 0.1 mmol combined). The reaction mixture was purified by flash column chromatography over silica (hexane/acetone, from 10:1 to 2.5:1) to give product **7.102** as a colorless oil (15.3 mg, 65% yield). R_f = 0.5 (Hex/acetone = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 4.05 – 3.92 (m, 5H), 3.56 (s, 3H), 1.68 – 1.58 (m, 2H), 1.44 – 1.34 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.48, 151.64, 148.86, 141.45, 107.83, 41.39, 33.70, 30.29, 29.80, 20.39, 13.94. The spectra match the reported literature.[77]



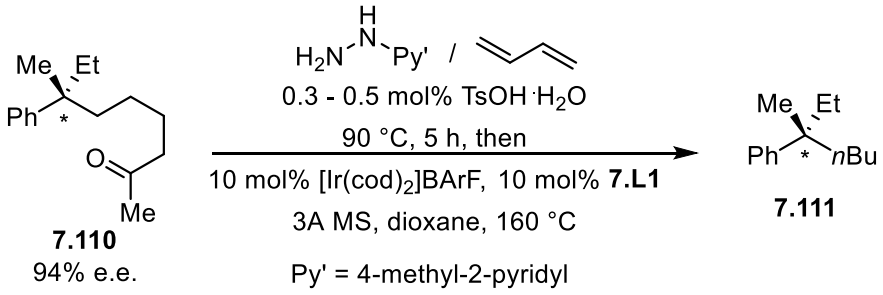
7.103, *Nabumetone* **7.104**

7.104: Following **General procedure C**, the reaction was conducted with 22.8 mg **7.103** as the ketone starting material in 2 parallel vessels (0.05 mmol for each, 0.1 mmol combined). When the key reaction was finished, a hydrogenation reaction with Pd/C (10% wt.%, 20 mg) and EA (1 mL) under H_2 atmosphere (monitored by TLC) was conducted to hydrogenate a small amount of the deacetylative crotylation by-product (ca. 15%) in order to achieve better separation *via* flash column chromatography over silica. The compound **7.104** was obtained as a colorless oil (11.3 mg, 61% yield). R_f = 0.5 (Hex/EA = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 9.4, 3.0 Hz, 2H), 7.56 (s, 1H), 7.32 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.17 – 7.07 (m, 2H), 3.92 (s, 3H), 2.79 (q, *J* = 7.6 Hz, 2H), 1.32 (t, *J* = 7.6 Hz, 3H). ^{13}C

NMR (101 MHz, $CDCl_3$) δ 157.24, 139.59, 133.05, 129.33, 129.03, 127.68, 126.82, 125.56, 118.72, 105.85, 55.43, 28.98, 15.75. The spectra match the reported literature.[78]



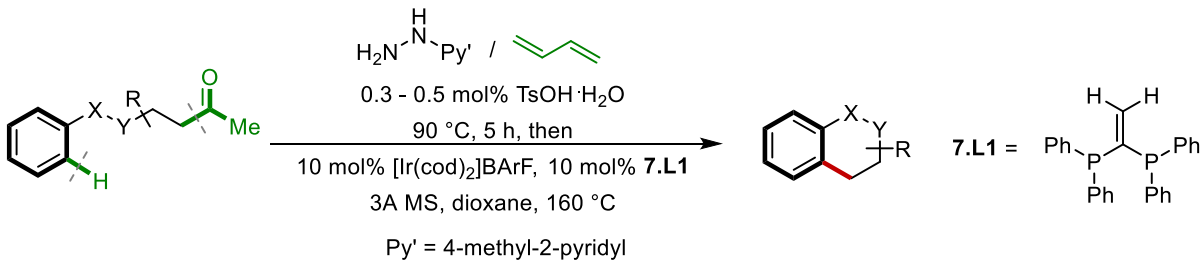
7.108: Following **General procedure C**, the reaction was conducted with 26.6 mg **7.107** as the ketone starting material in 2 parallel vessels (0.05 mmol for each, 0.1 mmol combined). The compound **7.108** was obtained as a colorless oil (13.4 mg, 60% yield). R_f = 0.4 (Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.58 (m, 2H), 7.58 – 7.52 (m, 2H), 7.47 – 7.38 (m, 4H), 7.37 – 7.30 (m, 1H), 1.69 (q, J = 7.4 Hz, 2H), 1.33 (s, 6H), 0.74 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.79, 141.21, 138.25, 128.82, 127.13, 127.08, 126.80, 126.52, 37.91, 37.00, 28.61, 9.33. The spectra match the reported literature.[79]



Compound **7.110** was prepared according to the previously reported literatures.[63] The

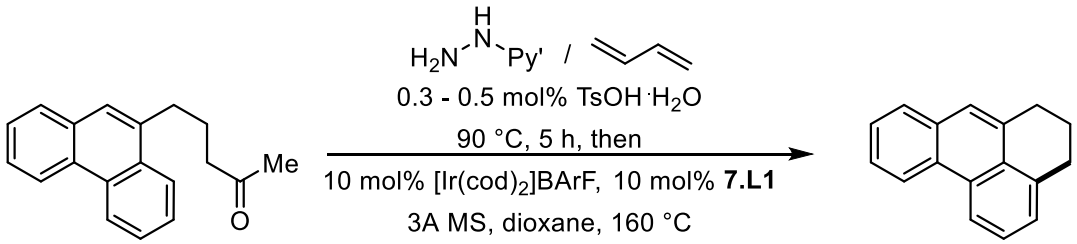
racemic sample was prepared by replacing the chiral ligand **7.CL1**[63] with 2,2'-bipyridine under the otherwise identical reaction condition. The enantiomeric excess (ee) value was measure to be 94% as determined by HPLC analysis on a chiral stationary phase (hexane:*i*PrOH = 99:1, 0.4 mL/min, chiral IF). Following **General procedure C**, the deacetylation reaction was conducted with 23.2 mg **7.110** as the ketone starting material in 2 parallel vessels (0.05 mmol for each, 0.1 mmol combined). The chiral compound **7.111** was obtained as a colorless oil (12.1 mg, 64% yield). R_f = 0.7 (Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 4H), 7.20 – 7.12 (m, 1H), 1.80 – 1.63 (m, 2H), 1.60 – 1.46 (m, 2H), 1.31 – 1.17 (m, 5H), 1.16 – 1.06 (m, 1H), 0.99 – 0.88 (m, 1H), 0.83 (t, *J* = 7.3 Hz, 3H), 0.67 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.17, 128.00, 126.63, 125.26, 42.87, 41.10, 35.75, 26.61, 23.62, 23.57, 14.21, 8.80. IR (KBr) 3064, 3030, 2966, 2929, 2879, 1499, 1465, 1381 cm^{-1}. LRMS (EI): 190.2 (M^+, 8), 161.2 (28), 133.2 (53), 105.1 (69), 91.1 (100). $[\alpha]_D^{20}$ = 6.1 (1.15 c, $CDCl_3$).

Application III: **Deacetylative C−H annulation through C−C cleavage**



General procedure D: An 8 mL vial was charged with the ketone substrate (0.05 mmol, 1.0 equiv) and 2-hydrazineyl-4-methylpyridine **7.D1** (6.4 mg, 0.052 mmol, 1.04

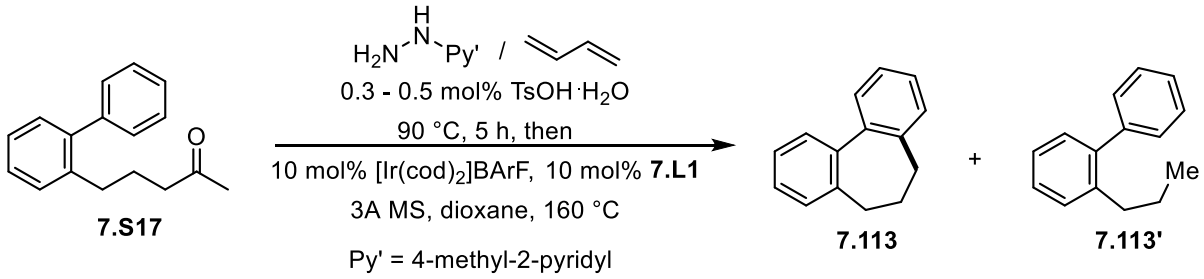
equiv), and was transferred into a glove box. 1,4-Dioxane (1 mL) and a stock solution of $TsOH{\cdot}H_2O$ in 1,4-dioxane (0.05 M, 3.0–5.0 μL, 0.003-0.005 equiv) were then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 90 °C for 5 hours. After cooled to room temperature, the vial was opened, and charged with $[Ir(cod)_2]BArF$ (6.4 mg, 0.005 mmol, 0.1 equiv) and **7.L1** (2.0 mg, 0.005 mmol, 0.1 equiv). The vial was sealed and transferred into the glove box, and then opened and purged under N_2 atmosphere for 3 mins. Pre-dried 3Å molecular sieve (100 mg) and 1,3-butadiene (20% wt.% in PhMe, 170 μL, ca. 10 equiv) were then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 160 °C under stirring for 72 hours. After cooled to room temperature, the reaction mixture was filtered through a short plug of Celite, concentrated *in vacuo*, and further purified by flash column chromatography over silica (hexane/ethyl acetate or hexane/acetone) to give the deacetylation products. *The reported yields were based on average of 2 runs.*



7.S16 Py' = 4-methyl-2-pyridyl **7.112**

Following modified **General procedure D**, *in which slightly more amount of 1,3-butadiene was used* (20% wt.% in PhMe, 180 μL per 0.05 mmol-scale reaction), the reaction was conducted with 26.2 mg **7.S16** as the ketone starting material in 2 parallel vessels (0.05

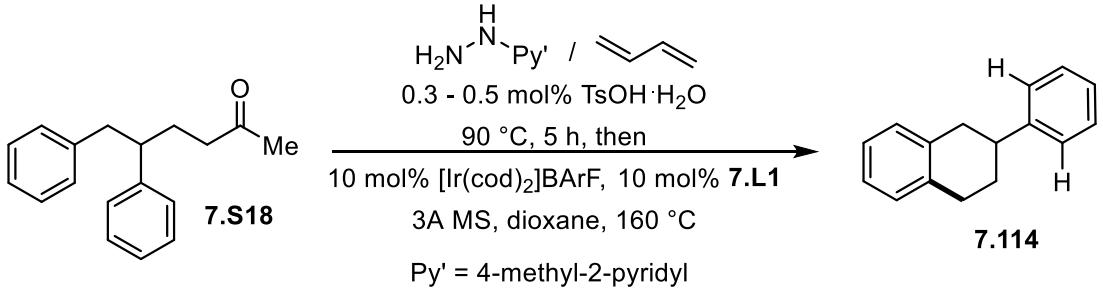
mmol for each, 0.1 mmol combined). The compound **7.112** was obtained as a white solid (11.3 mg, 52% yield). R_f = 0.2 (Hex). M.p. = 78-80 °C (Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 8.3 Hz, 1H), 8.56 (d, *J* = 8.3 Hz, 1H), 7.88 – 7.76 (m, 1H), 7.56 (dt, *J* = 9.4, 4.2 Hz, 3H), 7.49 (s, 1H), 7.39 (d, *J* = 7.1 Hz, 1H), 3.18 (q, *J* = 5.5 Hz, 4H), 2.12 (p, *J* = 6.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.97, 134.33, 131.84, 130.57, 129.60, 129.02, 127.72, 126.49, 125.92, 125.79, 125.48, 123.70, 122.74, 120.69, 31.95, 31.72, 23.12. The spectra match the reported literature.[80]



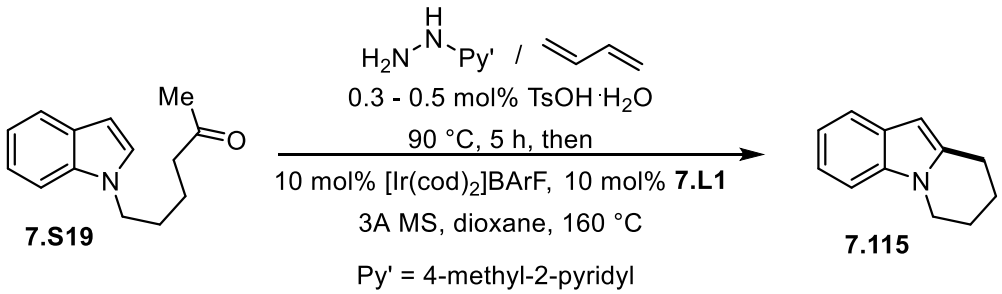
Following modified **General procedure D**, *in which slightly more amount of 1,3-butadiene was used* (20% wt.% in PhMe, 180 μL per 0.05 mmol-scale reaction), the reaction was conducted with 23.8 mg **7.S17** as the ketone starting material in 2 parallel vessels (0.05 mmol for each, 0.1 mmol combined). Compound **7.113** was obtained as a colorless oil (4.0 mg, 21% yield). R_f = 0.35 (Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.20 (m, 10H), 2.50 (t, *J* = 7.1 Hz, 4H), 2.19 (p, *J* = 7.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.21, 139.75, 128.54, 128.40, 127.57, 126.75, 33.57, 31.50. The spectra of **7.113** match the reported literature.[81]

Compound **7.113'** was also obtained as a colorless oil (8.8 mg, 45% yield). R_f = 0.4

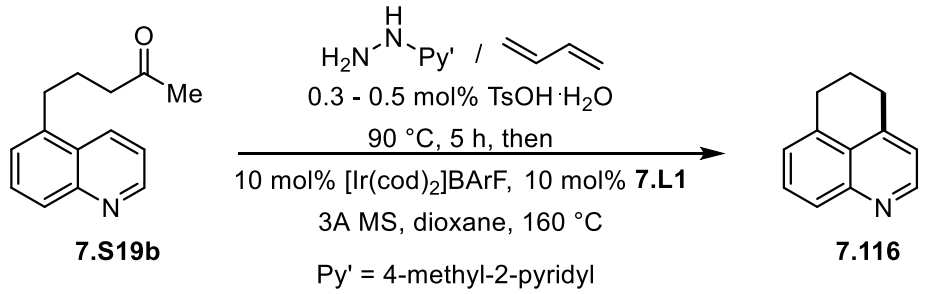
(Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 7H), 7.25 – 7.18 (m, 2H), 2.62 – 2.46 (m, 2H), 1.54 – 1.42 (m, 2H), 0.81 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.22, 142.02, 140.24, 130.15, 129.39, 129.36, 128.10, 127.41, 126.82, 125.67, 35.27, 24.59, 14.18. The spectra of **7.113'** match the reported literature.[82]



7.114: Following modified **General procedure D**, *in which slightly more amount of 1,3-butadiene was used* (20% wt.% in PhMe, 180 μL per 0.05 mmol-scale reaction), the reaction was conducted with 10.3 mg **7.S18** as the ketone starting material in 2 parallel vessels (0.05 mmol for each, 0.1 mmol combined). The compound **7.114** was obtained as a colorless oil (10.3 mg, 50% yield). R_f = 0.2 (Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 5H), 7.19 – 7.06 (m, 4H), 3.16 – 2.84 (m, 5H), 2.23 – 2.08 (m, 1H), 1.96 (p, *J* = 11.7, 10.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.80, 136.81, 136.44, 129.17, 129.08, 128.63, 127.02, 126.35, 125.88, 125.77, 40.89, 37.89, 30.50, 29.91. The spectra match the reported literature.[83]

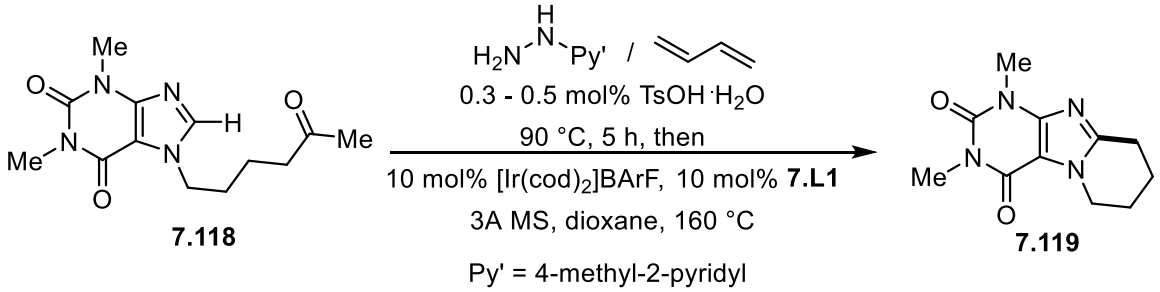


7.115: Following **General procedure D**, the reaction was conducted with 21.5 mg **7.S19** as the ketone starting material in 2 parallel vessels (0.05 mmol for each, 0.1 mmol combined). The titled compound was obtained as a white solid (9.8 mg, 57% yield). R_f = 0.4 (Hex/EA = 20:1). M.p. = 54-56 °C (Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.11 (dtd, *J* = 21.1, 7.1, 1.3 Hz, 2H), 6.20 (s, 1H), 4.05 (t, *J* = 6.2 Hz, 2H), 2.98 (t, *J* = 6.3 Hz, 2H), 2.13 – 2.03 (m, 2H), 1.94 – 1.85 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.30, 136.39, 128.34, 120.23, 119.71, 119.69, 108.66, 97.62, 42.47, 24.42, 23.61, 21.43. The spectra match the reported literature.[84]



7.116: Following modified **General procedure D**, *in which slightly more amount of 1,3-butadiene was used* (20% wt.% in PhMe, 180 μL per 0.05 mmol-scale reaction), the reaction was conducted with 21.3 mg **7.S19b** as the ketone starting material in 2 parallel vessels (0.05 mmol for each, 0.1 mmol combined). The titled compound was obtained as a

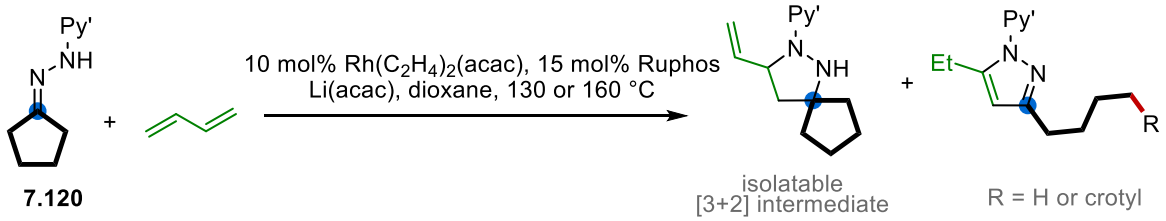
colorless oil (7.1 mg, 42% yield). R_f = 0.3 (Hex/EA = 3:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 4.4 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.60 (dd, *J* = 8.4, 7.1 Hz, 1H), 7.28 (dd, *J* = 7.1, 1.3 Hz, 1H), 7.13 (d, *J* = 4.4 Hz, 2H), 3.20 – 3.02 (m, 4H), 2.10 (p, *J* = 6.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.03, 148.47, 146.35, 136.73, 129.08, 127.28, 125.83, 124.28, 119.12, 30.68, 30.53, 22.85. IR (KBr) 3062, 3030, 2932, 2868, 2835, 1599, 1573, 1510, 1441, 1293 cm^{-1}. HRMS: calcd. 170.0964 $[M+H]^+$ Found: 170.0972.



7.119: Following modified **General procedure D**, *in which slightly more amount of 1,3-butadiene was used* (20% wt.% in PhMe, 180 μL per 0.05 mmol-scale reaction), the reaction was conducted with 27.8 mg **7.118** as the ketone starting material in 2 parallel vessels (0.05 mmol for each, 0.1 mmol combined). The titled compound was isolated through flash column chromatography over silica (DCM/MeOH, from 30:1 to 10:1), and further purified by preparative thin layer chromatography as a white solid (12.1 mg, 52% yield). R_f = 0.45 (DCM/MeOH = 10:1). M.p. = 225-227 °C ($CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (t, *J* = 5.9 Hz, 2H), 3.56 (s, 3H), 3.39 (s, 3H), 2.93 (t, *J* = 6.4 Hz, 2H), 2.04 (tt, *J* = 7.6, 3.7 Hz, 2H), 2.01 – 1.93 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.20, 151.94, 150.52, 148.52, 106.78, 44.96, 29.86, 27.98, 24.96, 22.28, 19.97. The spectra match the reported

literature.[85]

Preliminary mechanistic investigation



7.120

isolatable [3+2] intermediate **7.121**

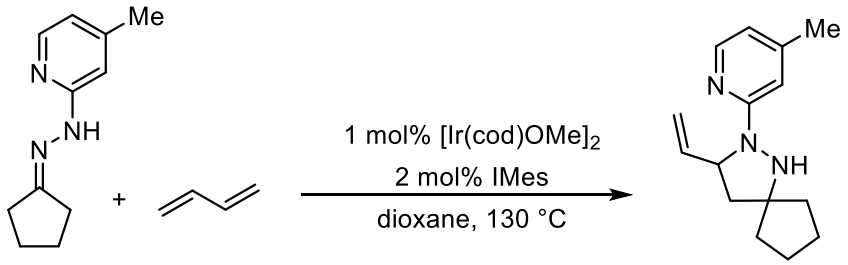
R = H or crotyl **7.47a** or 7.**47b**

temp.	yield **7.121** (%)	yield **7.47** (%)	recovered **7.120** (%)
130 °C	35	3	36
160 °C	10	21	30

A 4 mL vial was charged with the **7.120** (18.9 mg, 0.1 mmol, 1.0 equiv), $Rh(C_2H_4)_2(acac)$ (2.6 mg, 0.01 mmol, 0.1 equiv), RuPhos (7 mg, 0.015 mmol, 0.15 equiv), Li(acac) (2.7 mg, 0.025 mmol, 0.25 equiv) and 1,4-dioxane (1 mL). The vial was sealed and transferred into the glove box, and then opened and purged under N_2 atmosphere for 5 mins. 1,3-Butadiene (20% wt.% in PhMe, 400 μL, ca. 12 equiv) was then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 160 or 130 °C under stirring for 60 hours. After cooled to room temperature, the reaction mixture was concentrated *in vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yields of the products were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard.

An additional reaction at 130 °C was further set up in order to isolate the compound **7.121** for characterization**.** After cooled to room temperature, the reaction mixture was

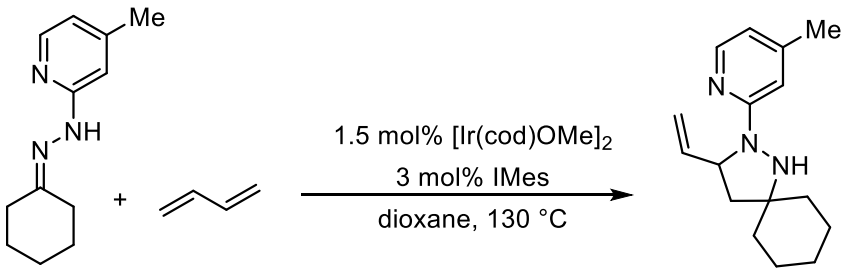
concentrated *in vacuo*. The residue was further purified by flash column chromatography over neutral Al_2O_3 (hexane/ethyl acetate, 40:1) to give compound **7.121** as a colorless oil (7 mg, 29% yield). R_f = 0.4 (Hex/EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 5.1, 0.8 Hz, 1H), 7.02 (dt, *J* = 1.6, 0.8 Hz, 1H), 6.44 (ddd, *J* = 5.1, 1.6, 0.6 Hz, 1H), 6.04 (ddd, *J* = 17.1, 10.3, 5.0 Hz, 1H), 5.26 (dt, *J* = 17.1, 1.6 Hz, 1H), 5.08 (dt, *J* = 10.3, 1.6 Hz, 1H), 4.81 (dddt, *J* = 9.3, 7.9, 5.0, 1.5 Hz, 1H), 2.34 (dd, *J* = 12.1, 7.8 Hz, 1H), 2.25 (s, 3H), 1.86 (dd, *J* = 12.1, 9.2 Hz, 1H), 1.82 – 1.71 (m, 3H), 1.69 – 1.59 (m, 3H), 1.44 (ddd, *J* = 10.6, 6.6, 3.7 Hz, 1H), 1.21 – 1.12 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.65, 147.59, 147.24, 139.94, 115.14, 113.27, 109.33, 71.35, 62.87, 47.30, 36.66, 35.05, 25.08, 24.50, 21.49. IR (KBr) 3086, 3052, 2955, 2869, 1642, 1597, 1479, 1350, 1294, 1204, 1148 cm^{-1}.



7.120 **7.121**

A 4 mL vial was charged with the **7.120** (18.9 mg, 0.1 mmol, 1.0 equiv), $[Ir(cod)OMe]_2$ (0.7 mg, 0.001 mmol, 0.01 equiv), IMes (0.6 mg, 0.002 mmol, 0.02 equiv) and 1,4-dioxane (1 mL). The vial was sealed and transferred into the glove box, and then opened and purged under N_2 atmosphere for 5 mins. 1,3-Butadiene (20% wt.% in PhMe, 400 μL, ca. 12 equiv) was then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 130 °C under stirring for 80 hours. After cooled to room temperature, the

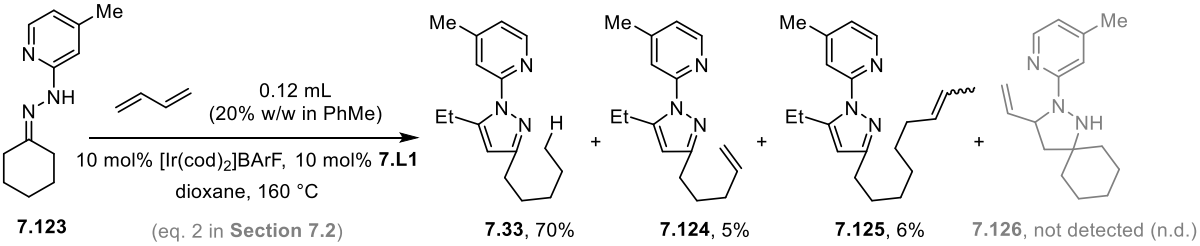
reaction mixture was concentrated *in vacuo.* The residue was further purified by flash column chromatography over neutral Al_2O_3 (hexane/ethyl acetate, 40:1) to give compound **7.121** as a colorless oil (19.6 mg, 81% yield). The characterization data for compound **7.121** has been reported *vide supra*.



7.123 **7.126**

A 4 mL vial was charged with the **7.123** (20.3 mg, 0.1 mmol, 1.0 equiv), $[Ir(cod)OMe]_2$ (1 mg, 0.0015 mmol, 0.015 equiv), IMes (0.9 mg, 0.003 mmol, 0.03 equiv) and 1,4-dioxane (1 mL). The vial was sealed and transferred into the glove box, and then opened and purged under N_2 atmosphere for 5 mins. 1,3-Butadiene (20% wt.% in PhMe, 400 μL, ca. 12 equiv) was then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 130 °C under stirring for 60 hours. After cooled to room temperature, the reaction mixture was concentrated *in vacuo.* The residue was further purified by flash column chromatography over neutral Al_2O_3 (hexane/ethyl acetate, 40:1) to give compound **7.126** as a colorless oil (22 mg, 86% yield). R_f = 0.4 (Hex/EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 5.1 Hz, 1H), 7.08 (s, 1H), 6.43 (d, *J* = 4.8 Hz, 1H), 6.01 (ddd, *J* = 16.7, 10.2, 4.8 Hz, 1H), 5.25 (dd, *J* = 17.0, 1.7 Hz, 1H), 5.06 (dd, *J* = 10.3, 1.6 Hz, 1H), 4.91 (dddt, *J* = 8.4, 6.6, 4.9, 1.5 Hz, 1H), 3.76 (s, 1H), 2.36 (dd, *J* = 12.2, 8.2 Hz, 1H), 2.26 (s, 3H), 1.80

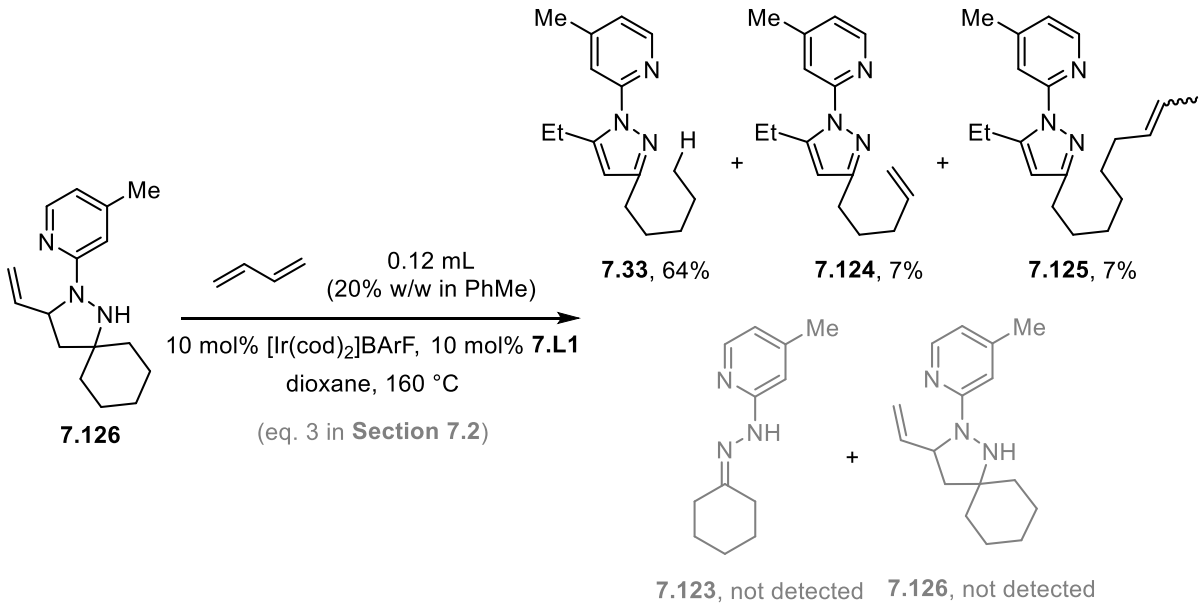
– 1.40 (m, 8H), 1.33 – 1.11 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.71, 147.54, 147.23, 139.99, 115.05, 113.02, 109.34, 63.47, 61.88, 46.56, 36.02, 33.86, 26.15, 23.99, 23.03, 21.47. IR (KBr) 3244, 3014, 2935, 2861, 1611, 1558, 1479, 1451, 1409, 1291 cm^{-1}. HRMS: calcd. 258.1965 $[M+H]^+$ Found: 258.1941.



A 4 mL vial was charged with **7.123** (10.2 mg, 0.05 mmol, 1.0 equiv), $[Ir(cod)_2]BArF$ (6.4 mg, 0.005 mmol, 0.1 equiv), **7.L1** (2.0 mg, 0.005 mmol, 0.1 equiv) and 1,4-dioxane (0.5 mL), and was stirred at room temperature for 5 mins. The vial was transferred into the glove box. 1,3-Butadiene (20% wt.% in PhMe, 120 µL, ca. 7.2 equiv) was then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 160 °C under stirring for 24 hours. After cooled to room temperature, the reaction mixture was concentrated *in vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yields of the products were determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard.

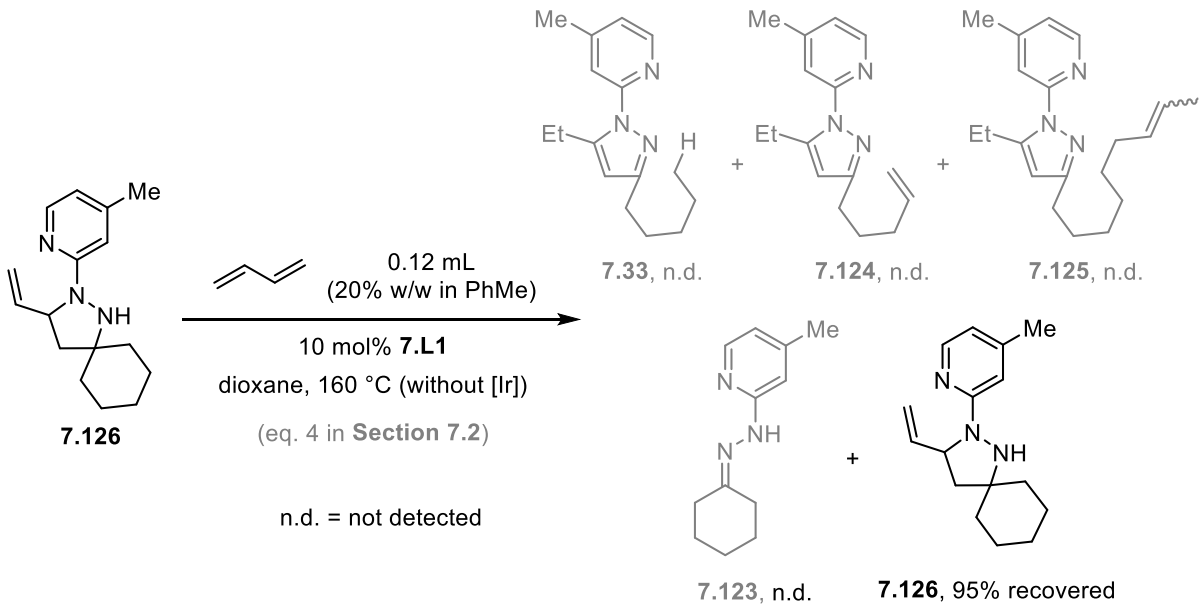
Five parallel reactions at 0.05 mmol scale were set up in order to isolate and characterize compound **7.124.** After cooled to room temperature, the reactions were combined and concentrated *in vacuo.* The residue was purified by flash column chromatography over silica (hexane/ethyl acetate, 20:1) to give compound **7.124** as a colorless oil (3.2 mg, 5% yield). R_f = 0. 39 (Hex/EA= 10:1) (slightly more polar than

compound **15**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.1 Hz, 1H), 7.64 (s, 1H), 6.97 (d, *J* = 4.5 Hz, 1H), 6.04 (s, 1H), 5.86 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 5.05 (dd, *J* = 17.1, 1.8 Hz, 1H), 4.98 (dd, *J* = 10.2, 1.1 Hz, 1H), 3.10 (q, *J* = 7.5 Hz, 2H), 2.74 – 2.59 (m, 2H), 2.40 (s, 3H), 2.16 (q, *J* = 7.2 Hz, 2H), 1.79 (p, *J* = 7.7 Hz, 2H), 1.25 (td, *J* = 7.5, 1.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.15, 153.91, 149.72, 147.87, 147.36, 138.74, 122.20, 117.06, 114.82, 105.77, 33.69, 28.96, 28.05, 21.51, 21.28, 13.27. IR (KBr) 3067, 2971, 2932, 1614, 1569, 1474, 1420, 1361 cm^{-1}. HRMS: calcd. 256.1808 $[M+H]^+$ Found: 256.1813.



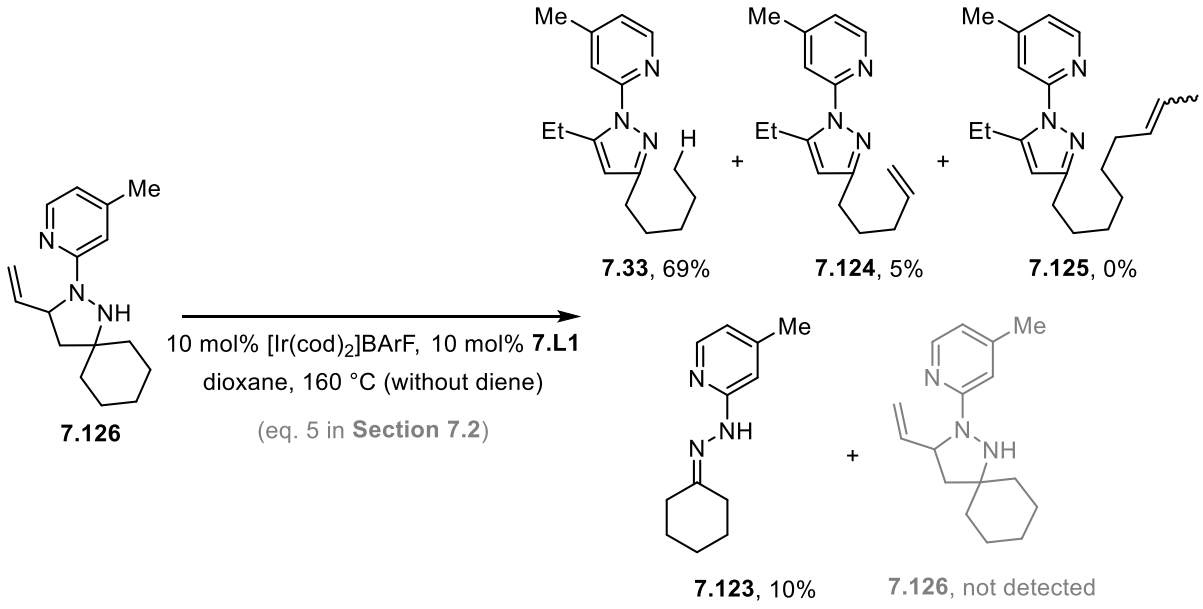
A 4 mL vial was charged with **7.126** (12.9 mg, 0.05 mmol, 1.0 equiv), $[Ir(cod)_2]BArF$ (6.4 mg, 0.005 mmol, 0.1 equiv), **7.L1** (2.0 mg, 0.005 mmol, 0.1 equiv) and 1,4-dioxane (0.5 mL), and was stirred at room temperature for 5 mins. The vial was transferred into the glove box. 1,3-Butadiene (20% wt.% in PhMe, 120 μL, ca. 7.2 equiv) was then added. The vial was

sealed, transferred out of the glove box, and heated in a pie-block at 160 °C under stirring for 24 hours. After cooled to room temperature, the reaction mixture was concentrated *in vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yields of the products were determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard.

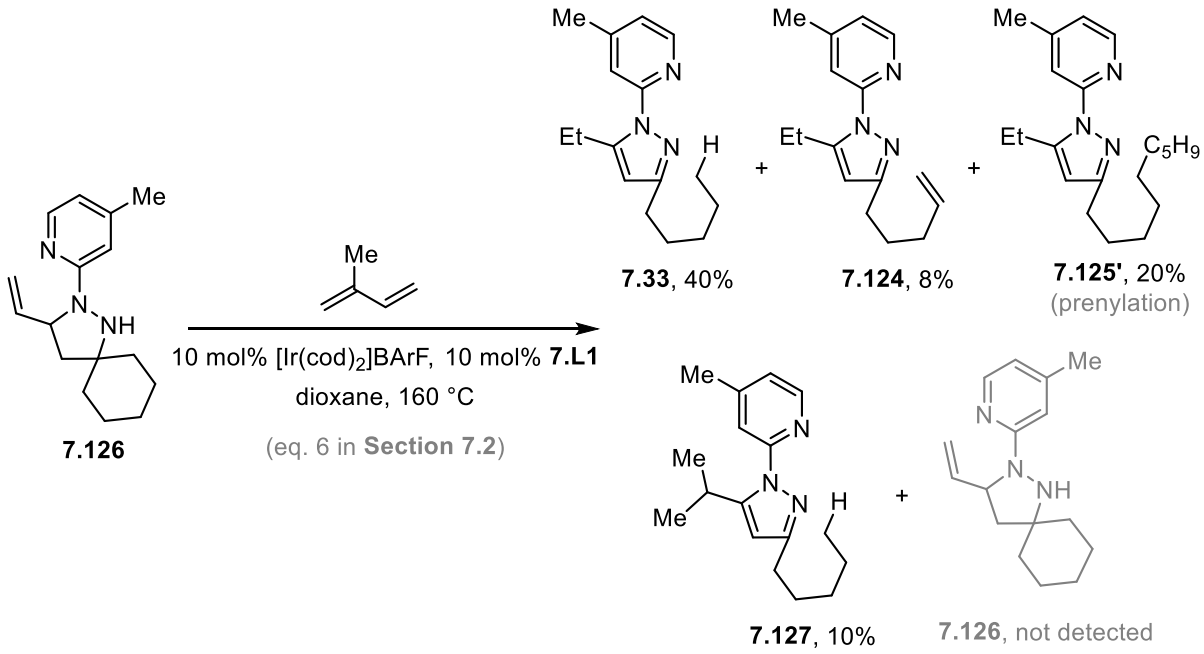


A 4 mL vial was charged with **7.126** (12.9 mg, 0.05 mmol, 1.0 equiv), **7.L1** (2.0 mg, 0.005 mmol, 0.1 equiv) and 1,4-dioxane (0.5 mL), and was stirred at room temperature for 5 mins. The vial was transferred into the glove box. 1,3-Butadiene (20% wt.% in PhMe, 120 μL, ca. 7.2 equiv) was then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 160 °C under stirring for 24 hours. After cooled to room temperature, the reaction mixture was concentrated *in vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yields of the products were determined by ^{1}H NMR using 1,1,2,2-

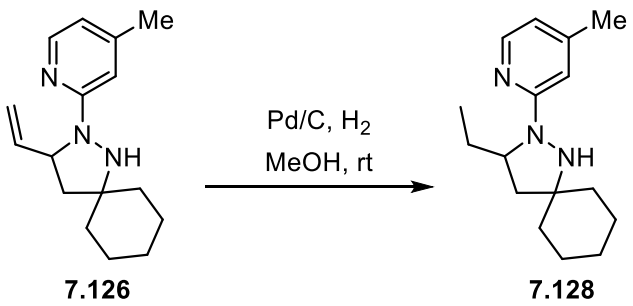
tetrachloroethane as the internal standard.



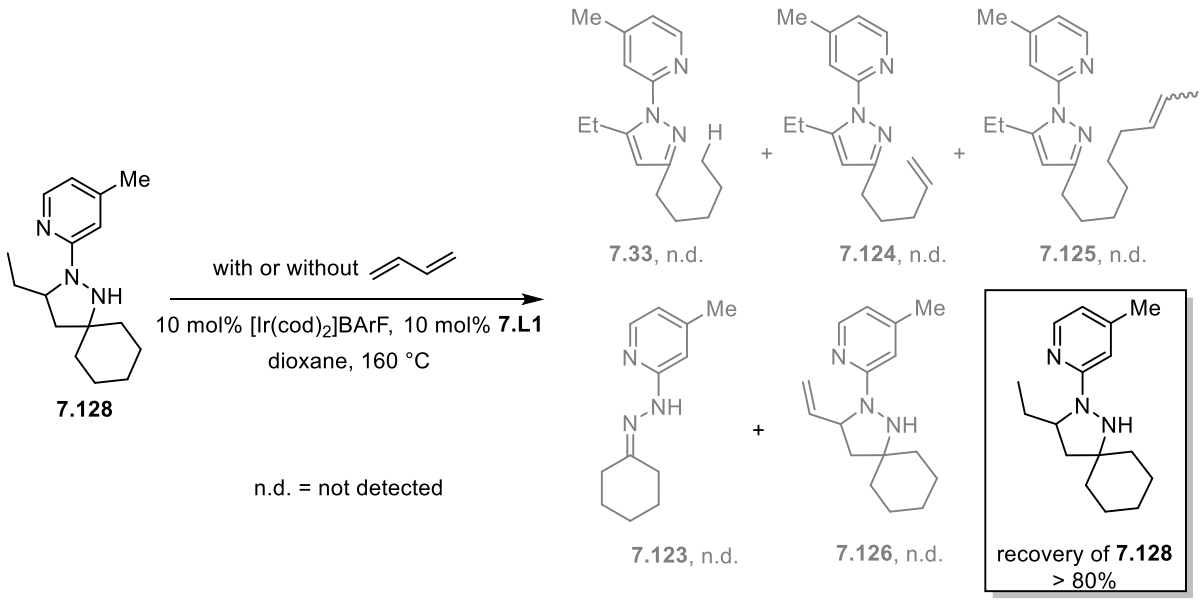
A 4 mL vial was charged with **7.126** (12.9 mg, 0.05 mmol, 1.0 equiv), $[Ir(cod)_2]BArF$ (6.4 mg, 0.005 mmol, 0.1 equiv), **7.L1** (2.0 mg, 0.005 mmol, 0.1 equiv) and 1,4-dioxane (0.5 mL), and was stirred at room temperature for 5 mins. The vial was transferred into the glove box. 1,3-Butadiene (20% wt.% in PhMe, 120 μL, ca. 7.2 equiv) was then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 160 °C under stirring for 24 hours. After cooled to room temperature, the reaction mixture was concentrated *in vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yields of the products were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard.



A 4 mL vial was charged with **7.126** (12.9 mg, 0.05 mmol, 1.0 equiv), $[Ir(cod)_2]BArF$ (6.4 mg, 0.005 mmol, 0.1 equiv), **7.L1** (2.0 mg, 0.005 mmol, 0.1 equiv) and 1,4-dioxane (0.5 mL), and was stirred at room temperature for 5 mins. The vial was transferred into the glove box. Isoprene (36 μL, 7.2 equiv) was then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 160 °C under stirring for 24 hours. After cooled to room temperature, the reaction mixture was concentrated *in vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yields of the products were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard.

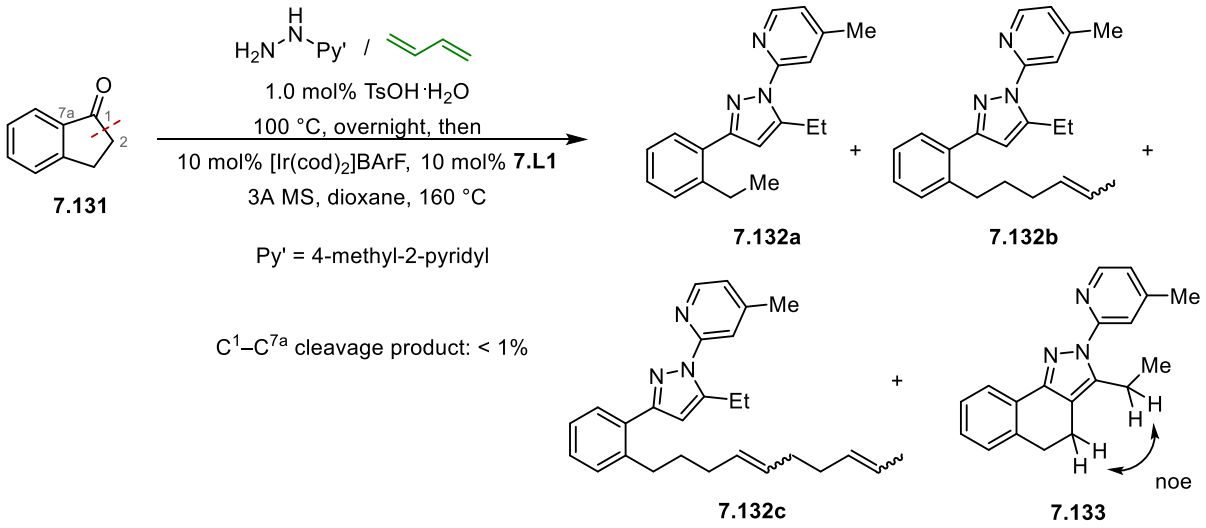


The compound **7.126** (48 mg) was treated with MeOH (2.5 mL) and Pd/C (10% wt.%, 30 mg), and stirred at room temperature under H_2 atmosphere for 1.5 hours. The reaction mixture was filtered through Celite and concentrated in *vacuo*, yielding **7.128** as a colorless oil without any further purification (46 mg, 96% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 5.1 Hz, 1H), 7.05 (s, 1H), 6.39 (d, *J* = 4.6 Hz, 1H), 4.35 (qd, *J* = 8.1, 4.6 Hz, 1H), 3.66 (s, 1H), 2.25 (d, *J* = 7.1 Hz, 4H), 2.01 – 1.87 (m, 1H), 1.76 – 1.34 (m, 9H), 1.30 – 1.05 (m, 3H), 0.94 (t, *J* = 7.4 Hz, 3H). IR (KBr) 3056, 2932, 2857, 1609, 1555, 1484, 1411, 1289 cm^{-1}. HRMS: calcd. 260.2121 $[M+H]^+$ Found: 260.2128.



A 4 mL vial was charged with **7.128** (13.0 mg, 0.05 mmol, 1.0 equiv), $[Ir(cod)_2]BArF$ (6.4 mg, 0.005 mmol, 0.1 equiv), **7.L1** (2.0 mg, 0.005 mmol, 0.1 equiv). The vial was transferred into the glove box. 1,4-Dioxane (0.5 mL) and 1,3-butadiene (20% wt.% in PhMe,

120 μL, ca. 7.2 equiv) *(or without the addition of diene)* was then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 160 °C under stirring for 24 hours. After cooled to room temperature, the reaction mixture was concentrated *in vacuo* before 1,1,2,2-tetrachloroethane (0.1 mmol, 16.7 mg) was added. The yields of the products were determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard. The recovery of **7.128** was further confirmed through isolation by preparative thin layer chromatography.



The reaction was conducted following modified **General procedure B:** A 4 mL vial was charged with the ketone substrate **7.131** (6.6 mg, 0.05 mmol, 1.0 equiv) and 2-hydrazineyl-4-methylpyridine **7.D1** (6.4 mg, 0.052 mmol, 1.04 equiv), and transferred into a glove box. 1,4-Dioxane (0.5 mL) and a stock solution of TsOH·H_2O in 1,4-dioxane (0.05 M, 10 μL, 0.01 equiv) was then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 100 °C overnight. After cooled to room temperature, the vial was

opened, and charged with $[Ir(cod)_2]BArF$ (6.4 mg, 0.005 mmol, 0.1 equiv) and **7.L1** (2.0 mg, 0.005 mmol, 0.1 equiv). The vial was sealed and transferred into the glove box, and then opened and purged under N_2 atmosphere for 3 mins. Pre-dried 3Å molecular sieve (50 mg) and the 1,3-butadiene (20% wt.% in PhMe, 230 μL) were then added. The vial was sealed, transferred out of the glove box, and heated in a pie-block at 160 °C under stirring for 72 hours. 10 parallel reactions were set up accordingly. After cooled to room temperature, the reactions were combined and filtered through a short plug of Celite. The filtrate was concentrated *in vacuo* and further purified by flash column chromatography over silica (hexane/ethyl acetate, from 80:1 to 30:1) to give the pyrazole products.

7.132a was obtained as a colorless oil (11.3 mg, 8% yield). R_f = 0.5 (Hex/EA= 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 5.1 Hz, 1H), 7.78 (s, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.31 (d, *J* = 4.3 Hz, 2H), 7.25 – 7.21 (m, 1H), 7.00 (d, *J* = 5.0 Hz, 1H), 6.36 (s, 1H), 3.23 (q, *J* = 7.5 Hz, 2H), 2.91 (q, *J* = 7.5 Hz, 2H), 2.41 (s, 3H), 1.32 (t, *J* = 7.5 Hz, 3H), 1.24 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.12, 152.55, 149.77, 147.71, 147.27, 142.82, 132.97, 129.92, 129.22, 128.24, 125.82, 122.36, 117.10, 107.36, 27.00, 21.71, 21.36, 15.93, 13.35. IR (KBr) 3061, 2969, 2929, 2870, 1611, 1575, 1448, 1400, 1355, 1052 cm^{-1}. HRMS: calcd. 292.1808 $[M+H]^+$ Found: 292.1816.

7.132b and **7.132c** were obtained as an inseparable mixture (colorless oil, 21.6 mg, 12% yield combined). R_f = 0.55 (Hex/EA= 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 5.0 Hz, 1H), 7.79 (s, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.25 – 7.20 (m, 1H), 7.03 – 6.96 (m, 1H), 6.36 (s, 1H), 5.53 – 5.22 (m, 2.6H), 5.03 – 4.83 (m, 0.4H), 3.23 (q, *J* =

7.4 Hz, 2H), 3.02 – 2.80 (m, 2H), 2.41 (s, 3H), 2.19 – 1.87 (m, 4H), 1.70 (dt, *J* = 15.3, 7.7 Hz, 2H), 1.65 – 1.55 (m, 3H), 1.32 (t, *J* = 7.4 Hz, 3H). IR (KBr) 3022, 2969, 2926, 2856, 1611, 1572, 1445, 1445, 1046 cm^{-1}. HRMS: calcd. 346.2277 [**7.132b**, $M+H]^+$; 400.2747 [**7.132c**, $M+H]^+$ Found: 346.2267; 400.2737.

7.133 was obtained as a colorless oil (4.8 mg, 3% yield). R_f = 0.4 (Hex/EA= 5:1). ^1H NMR (400 MHz, DCM-d_2) δ 8.29 (d, *J* = 5.1 Hz, 1H), 7.88 (d, *J* = 7.3 Hz, 1H), 7.79 (s, 1H), 7.34 – 7.18 (m, 3H), 7.03 (d, *J* = 5.0 Hz, 1H), 3.15 (q, *J* = 7.4 Hz, 2H), 2.98 (t, *J* = 7.2 Hz, 2H), 2.76 (t, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 1.20 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.17, 149.76, 149.05, 147.47, 142.33, 137.46, 129.82, 128.45, 127.92, 126.92, 122.79, 122.30, 117.21, 116.86, 29.80, 21.37, 19.63, 19.02, 13.93. IR (KBr) 3070, 2926, 2851, 1606, 1569, 1485, 1462, 1412, 1350, 1086 cm^{-1}. HRMS: calcd. 290.1652 $[M+H]^+$ Found: 290.1659.

7.5 ^{1}H-NMR and ^{13}C-NMR spectra

Figure 7.1 ^{1}H-NMR Spectrum of **7.S3**

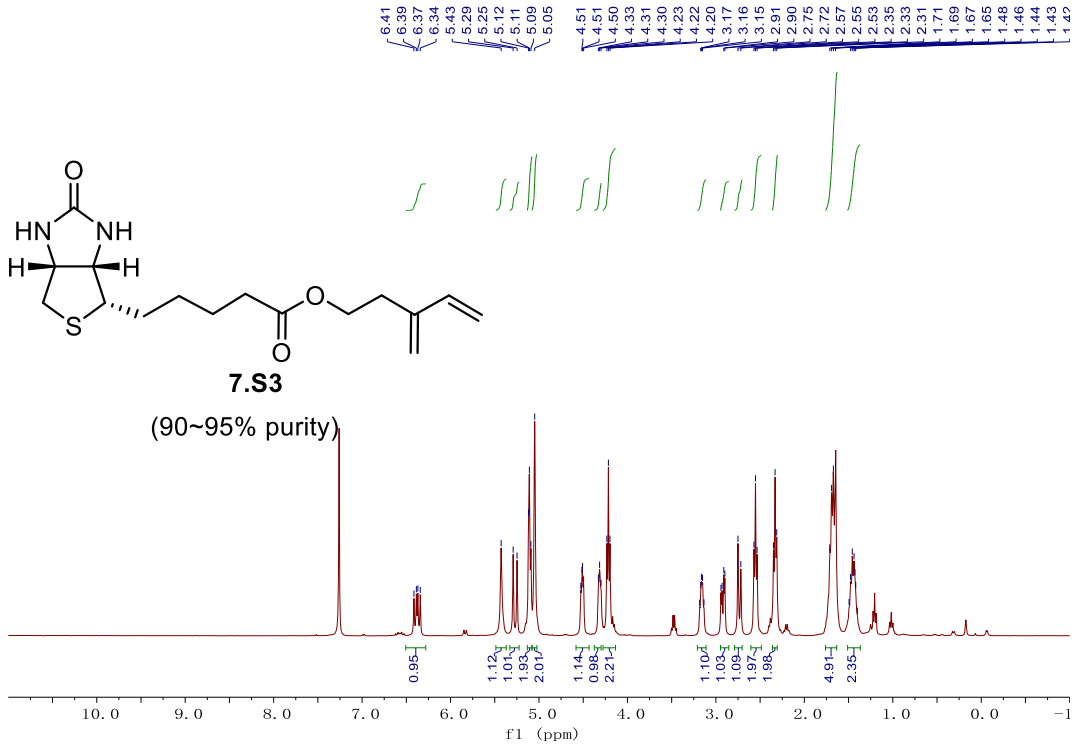


Figure 7.2 ^{13}C-NMR Spectrum of **7.S3**

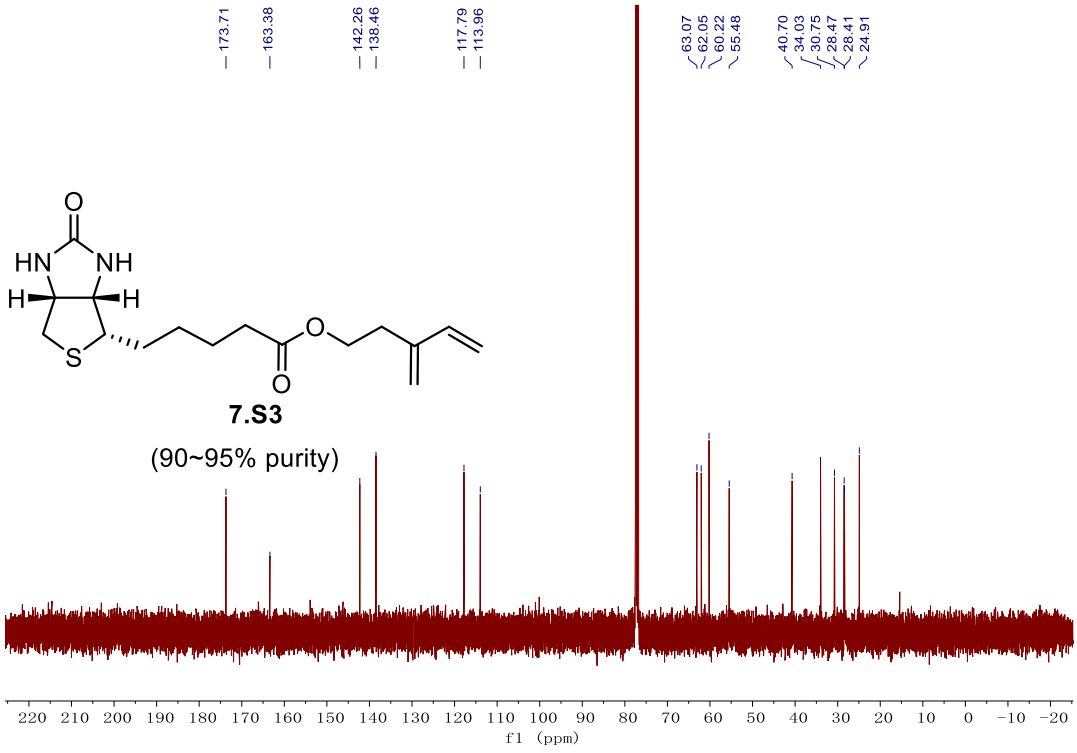


Figure 7.3 ^{1}H-NMR Spectrum of **7.6**

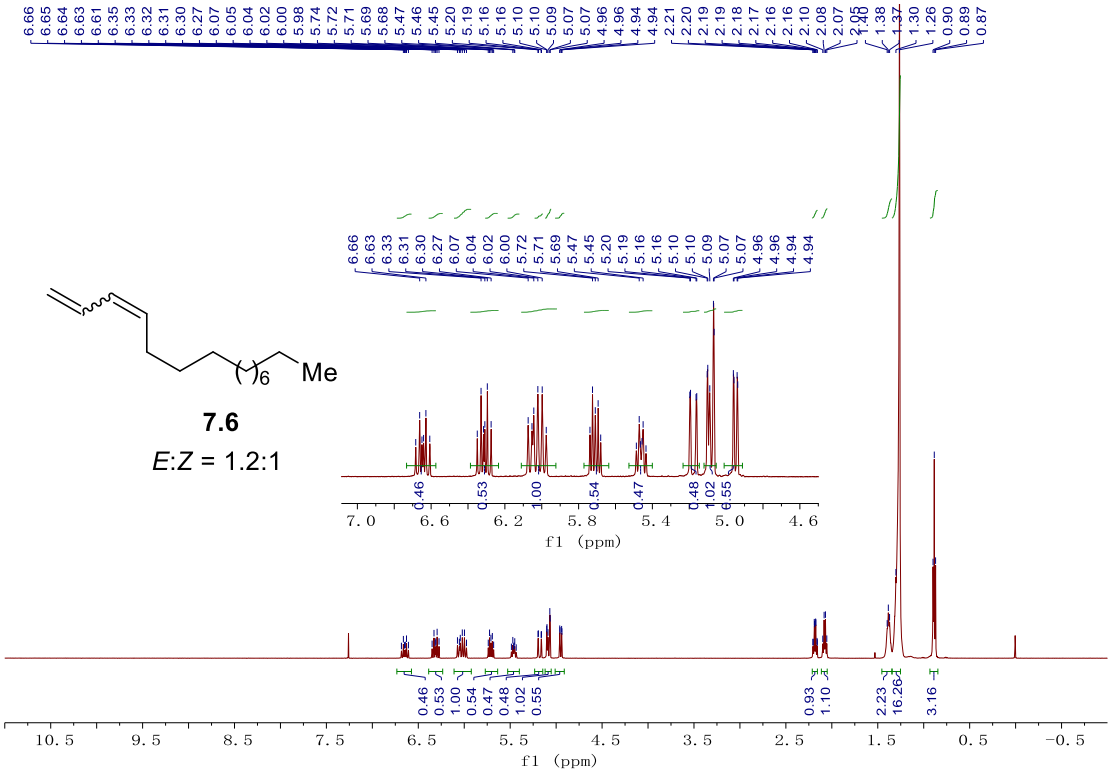


Figure 7.4 ^{13}C-NMR Spectrum of **7.6**

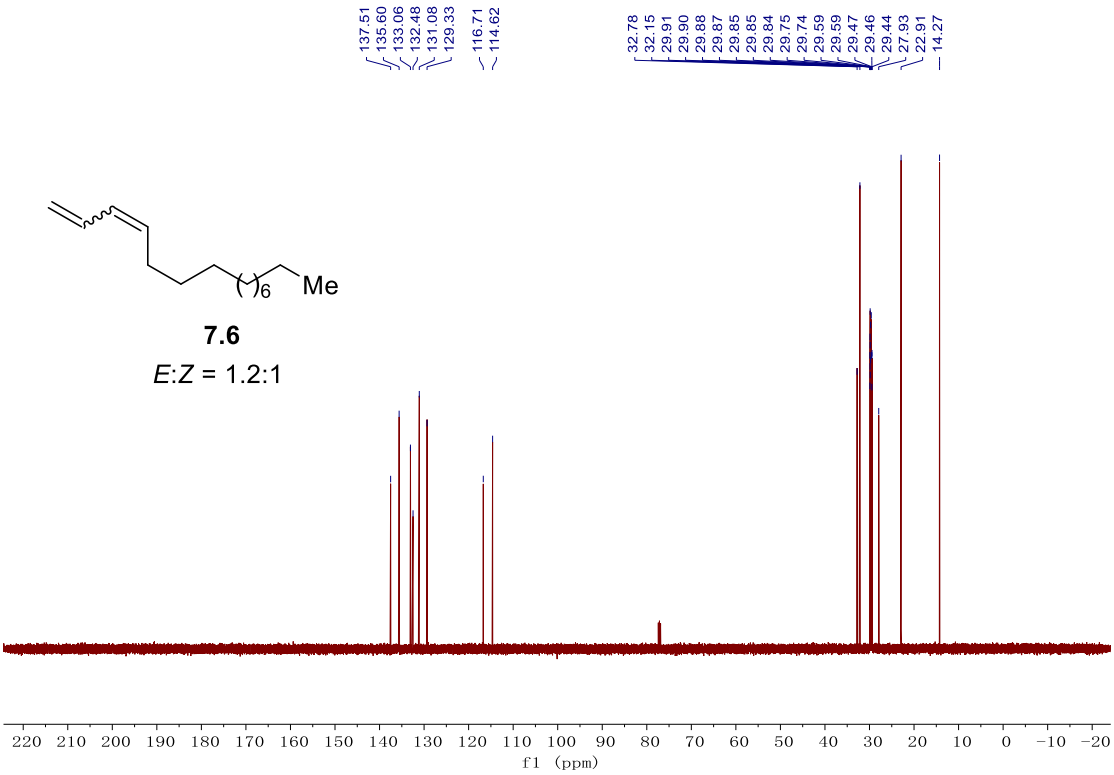


Figure 7.5 ^{1}H-NMR Spectrum of **7.S4**

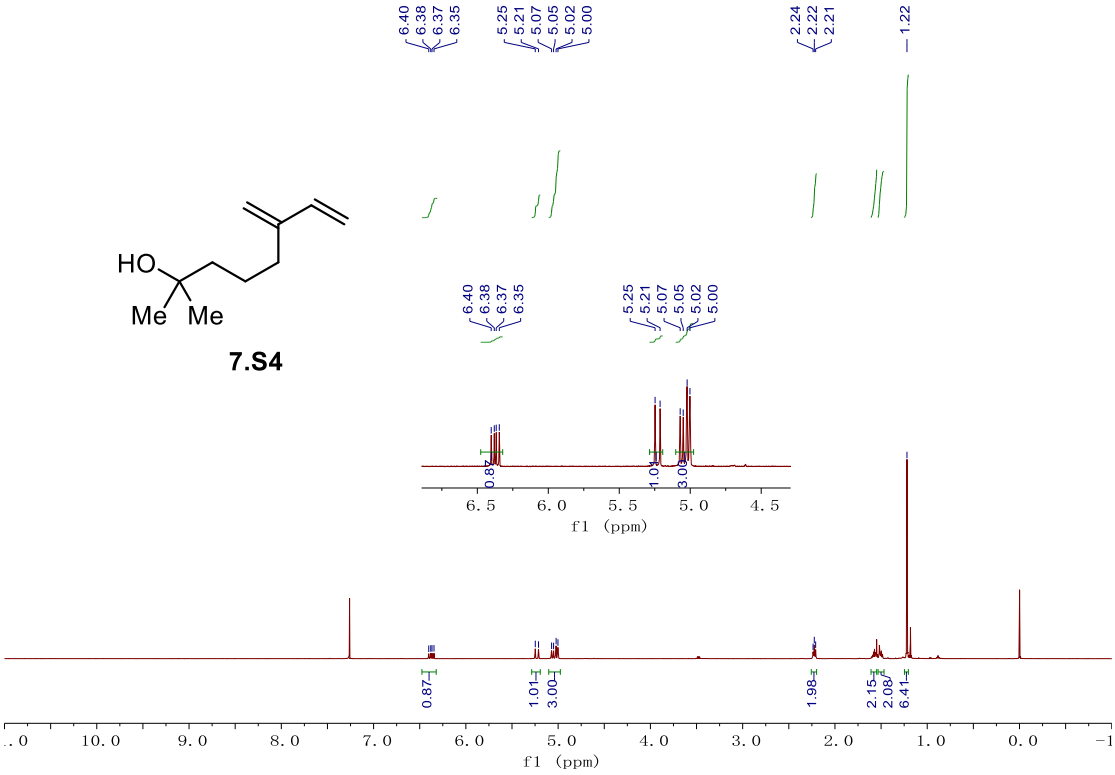


Figure 7.6 ^{1}H-NMR Spectrum of **7.a1**

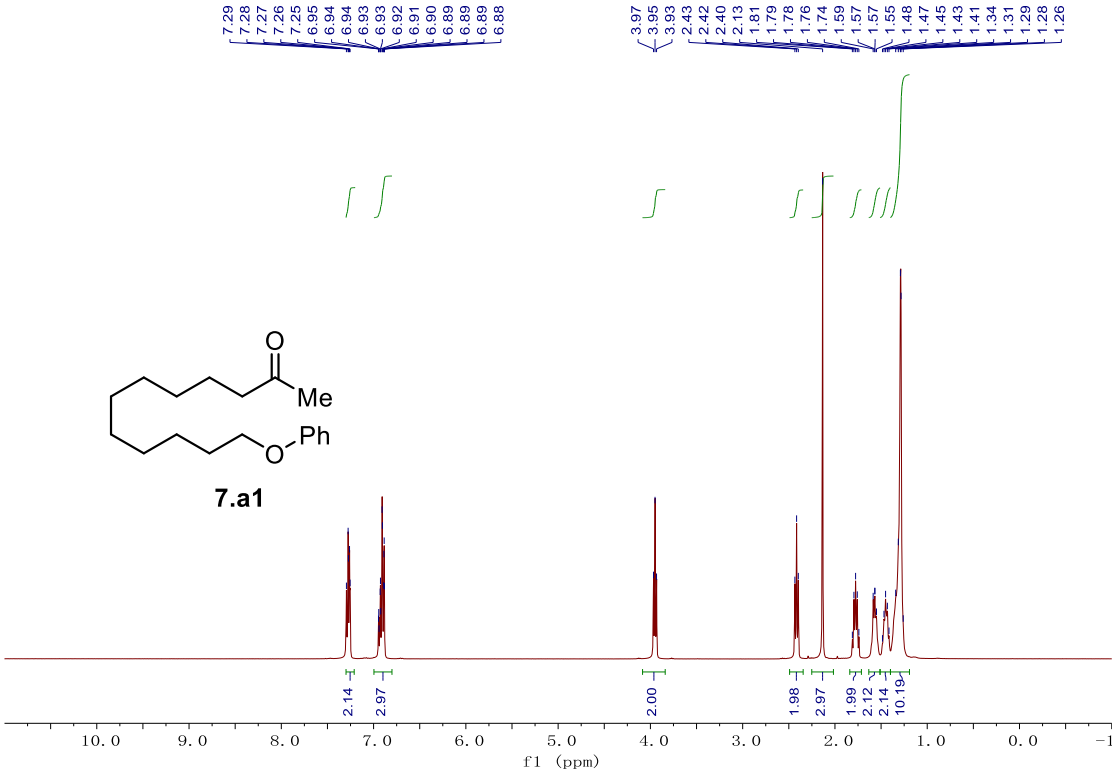


Figure 7.7 ^{13}C-NMR Spectrum of **7.a1**

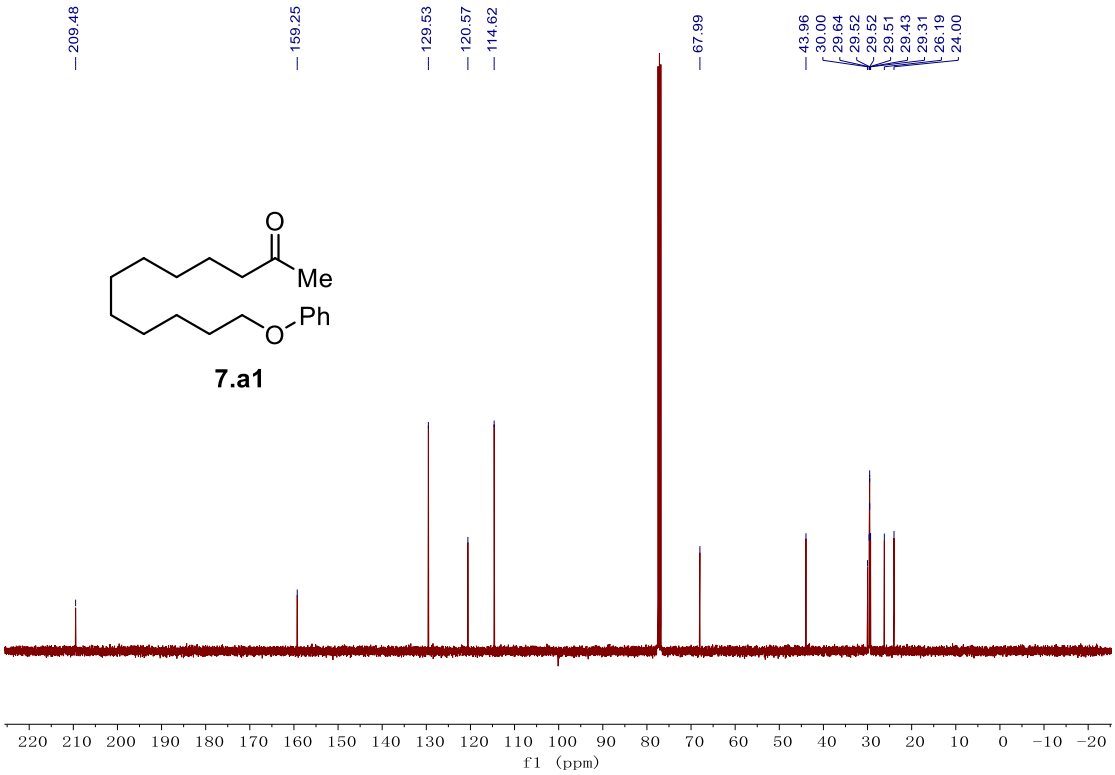


Figure 7.8 ^{1}H-NMR Spectrum of **7.S7**

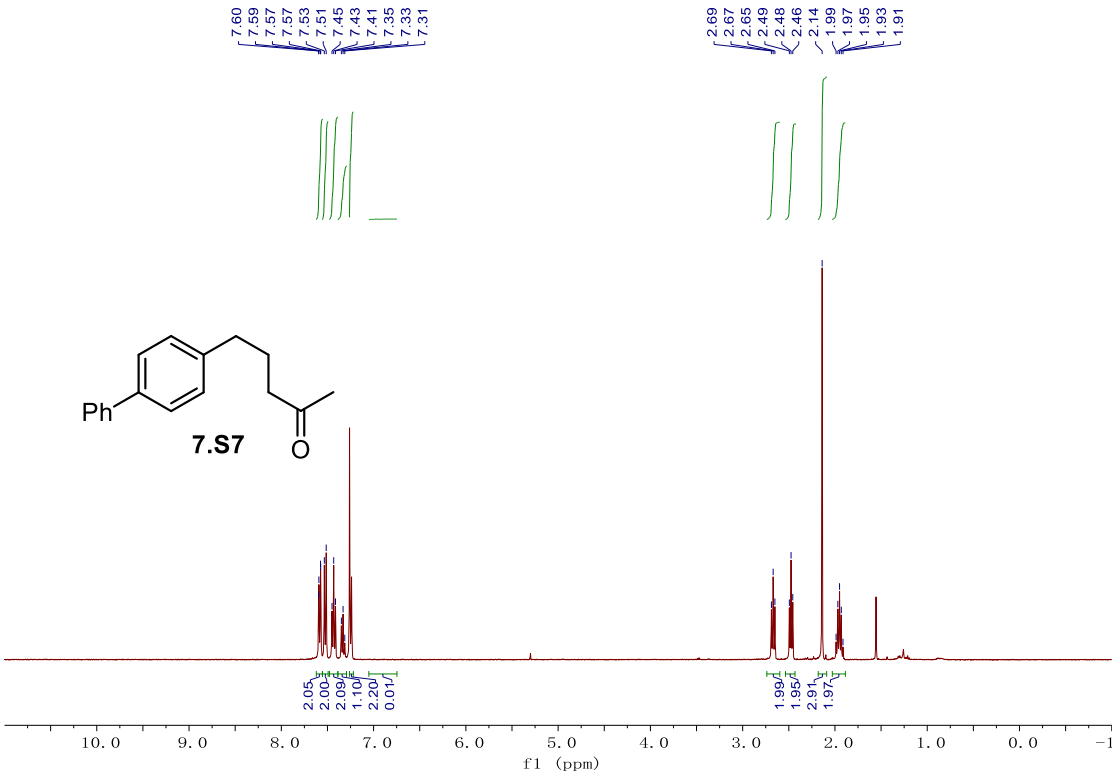


Figure 7.9 ^{13}C-NMR Spectrum of **7.S7**

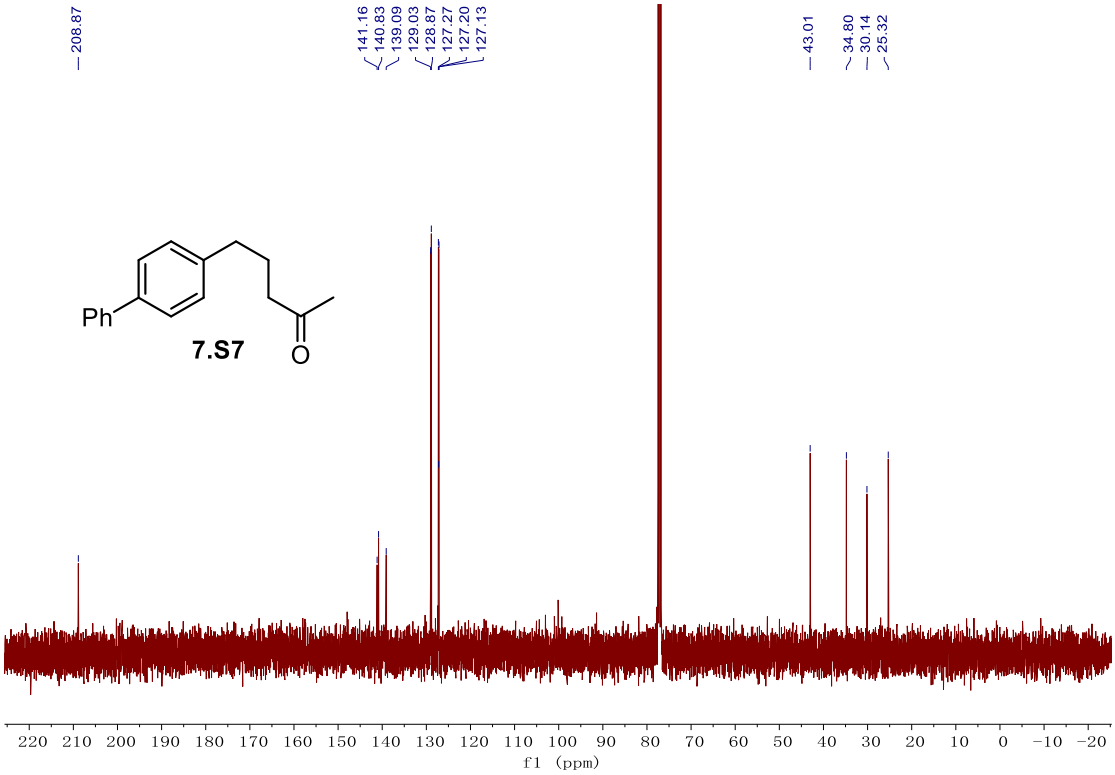


Figure 7.10 ^{1}H-NMR Spectrum of **7.S8**

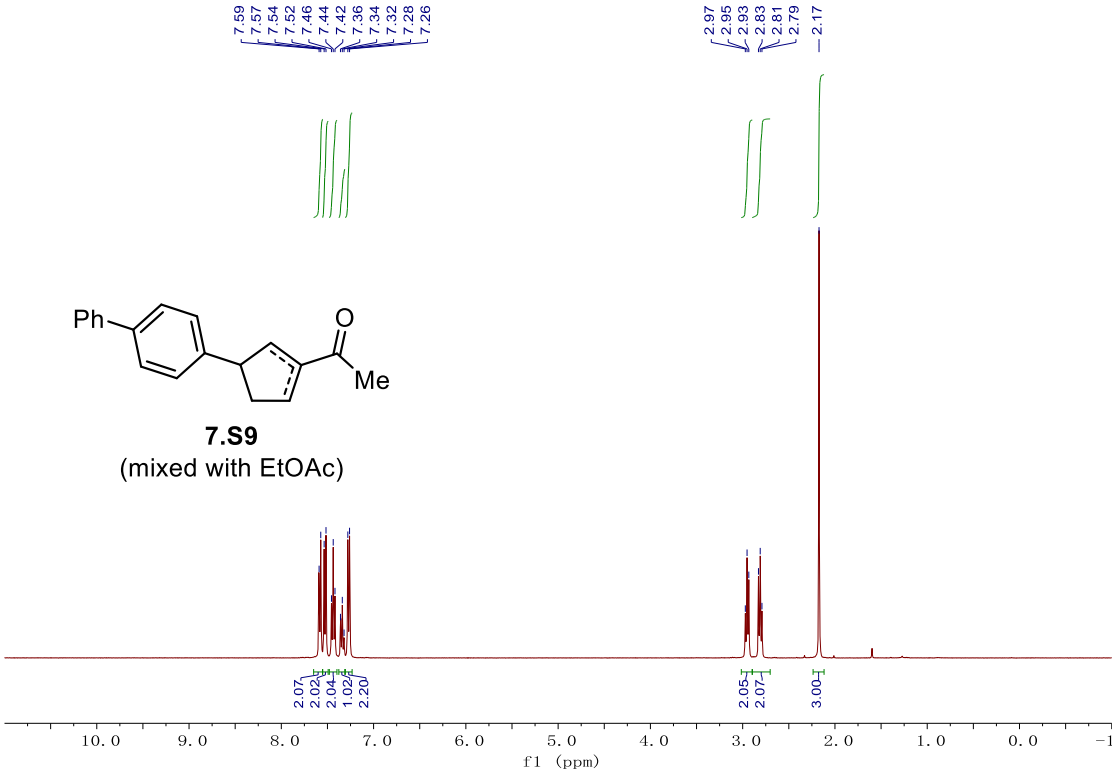


Figure 7.11 ^{1}H-NMR Spectrum of **7.S9**

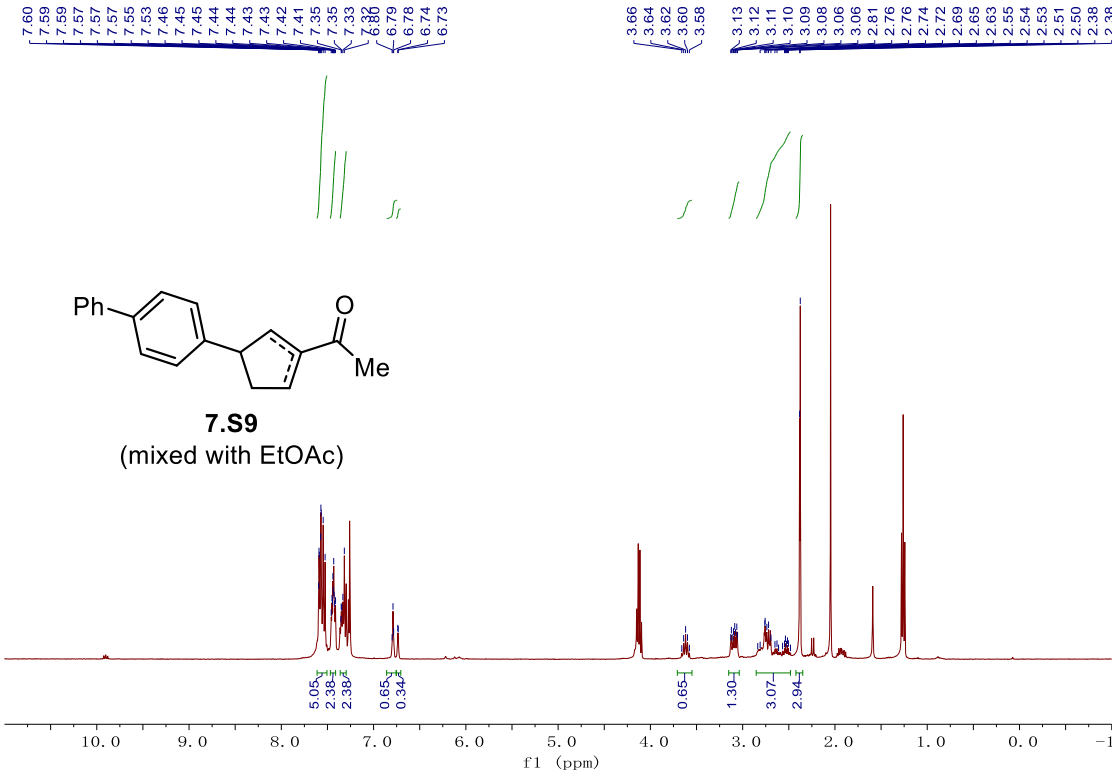


Figure 7.12 ^{1}H-NMR Spectrum of **7.S10**

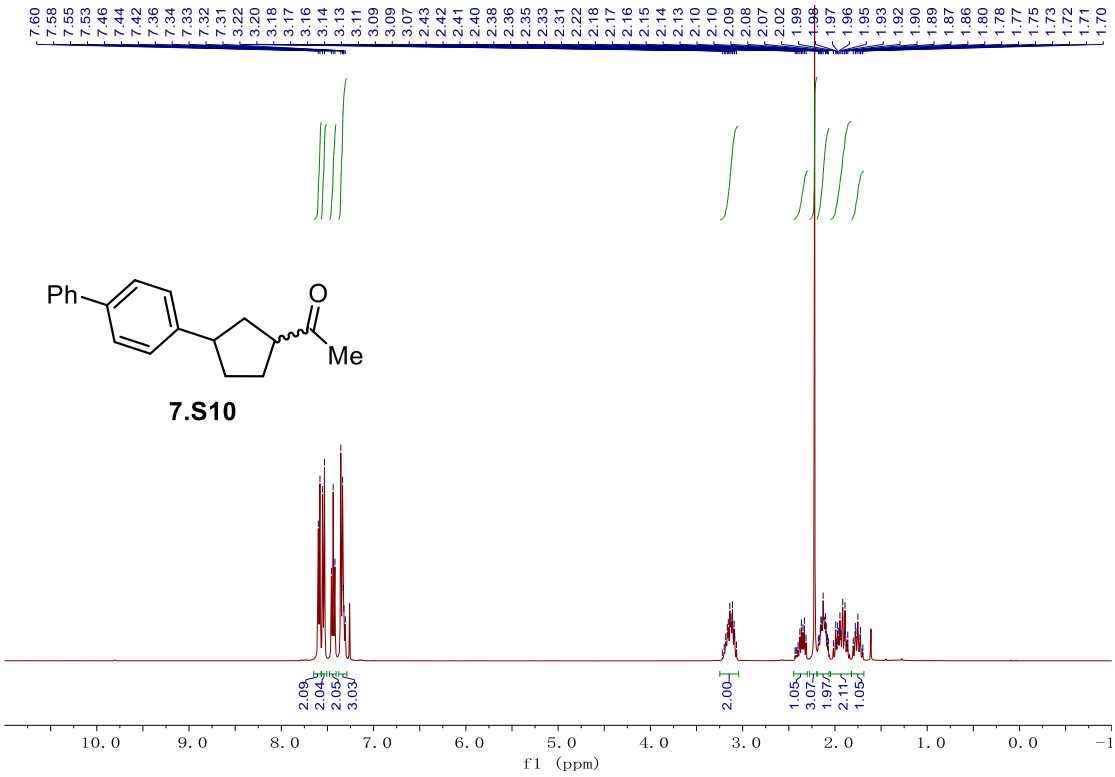


Figure 7.13 ^{13}C-NMR Spectrum of **7.S10**

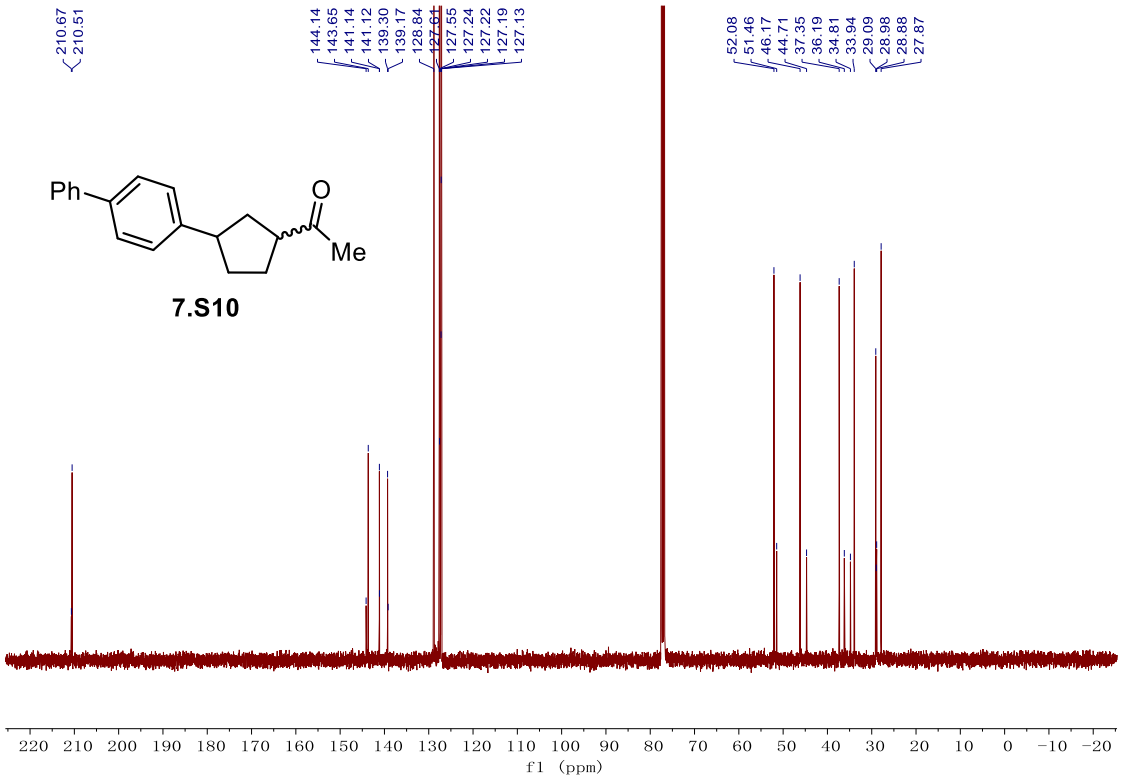


Figure 7.14 ^{1}H-NMR Spectrum of **7.S12**

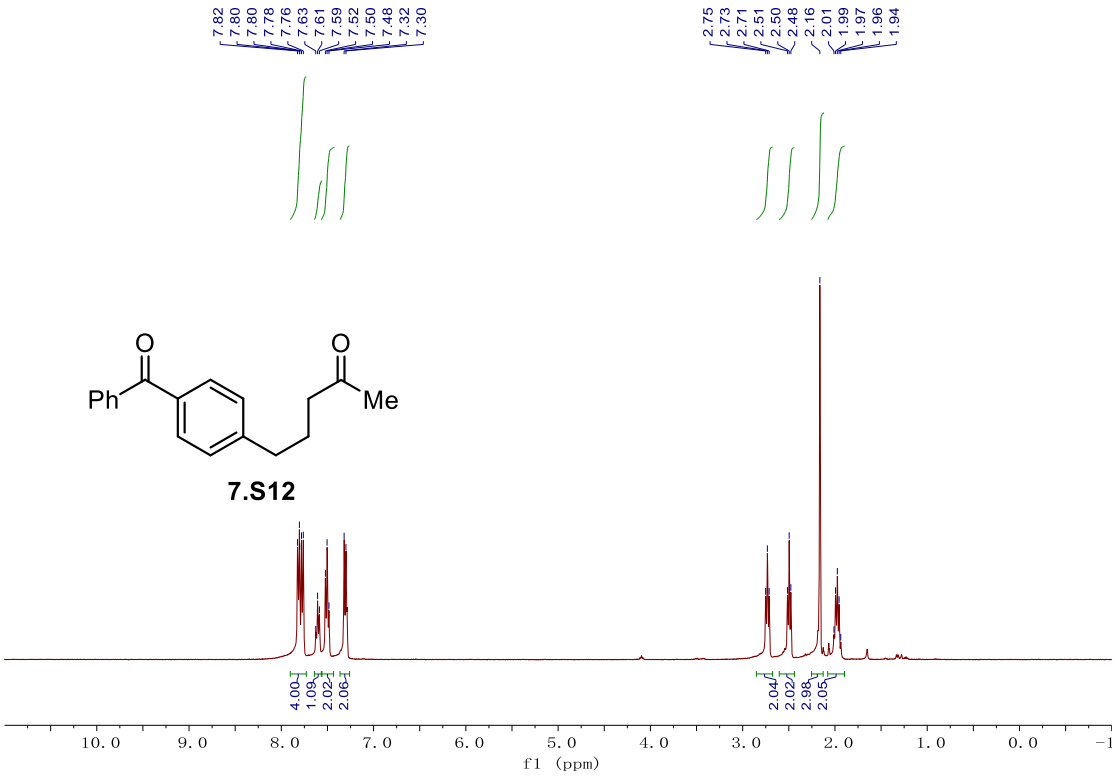


Figure 7.15 ^{13}C-NMR Spectrum of **7.S12**

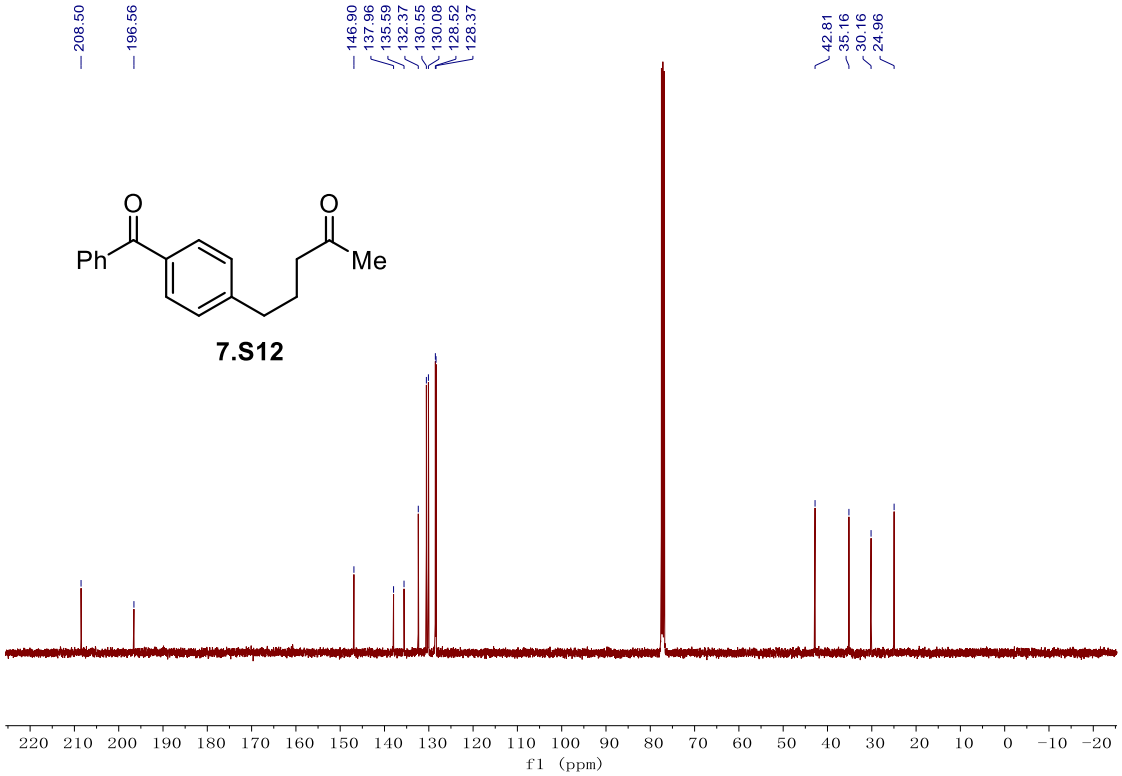


Figure 7.16 ^{1}H-NMR Spectrum of **7.S13**

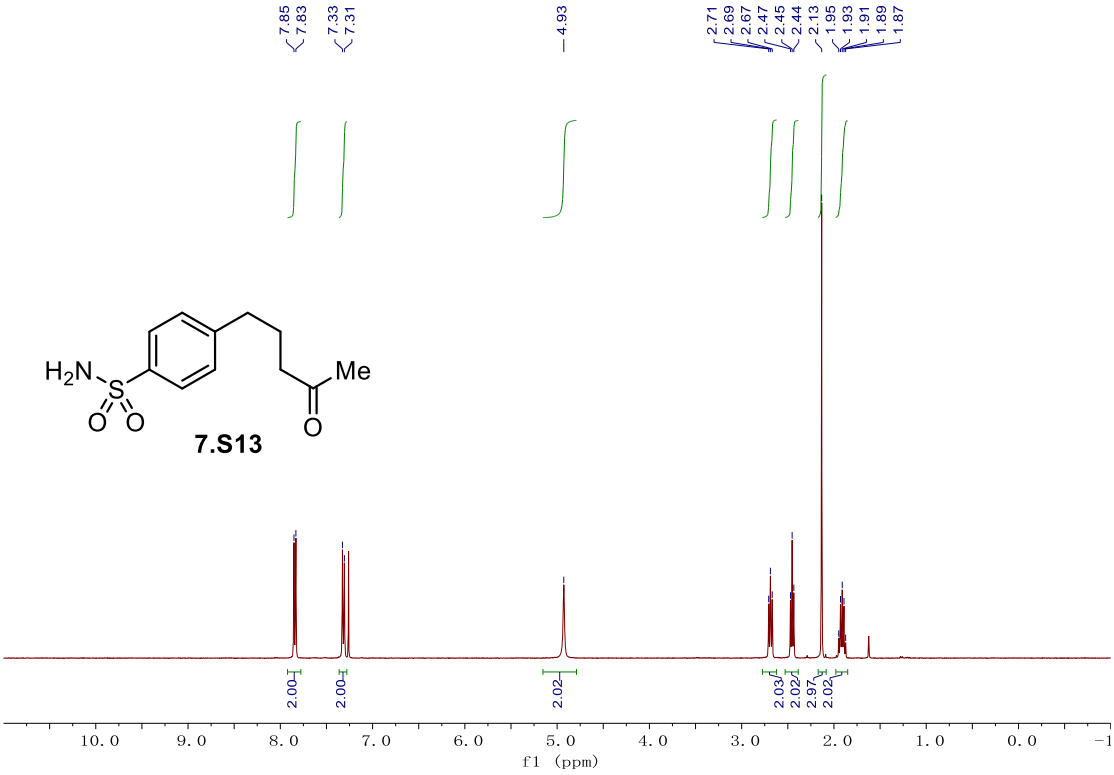


Figure 7.17 ^{13}C-NMR Spectrum of **7.S13**

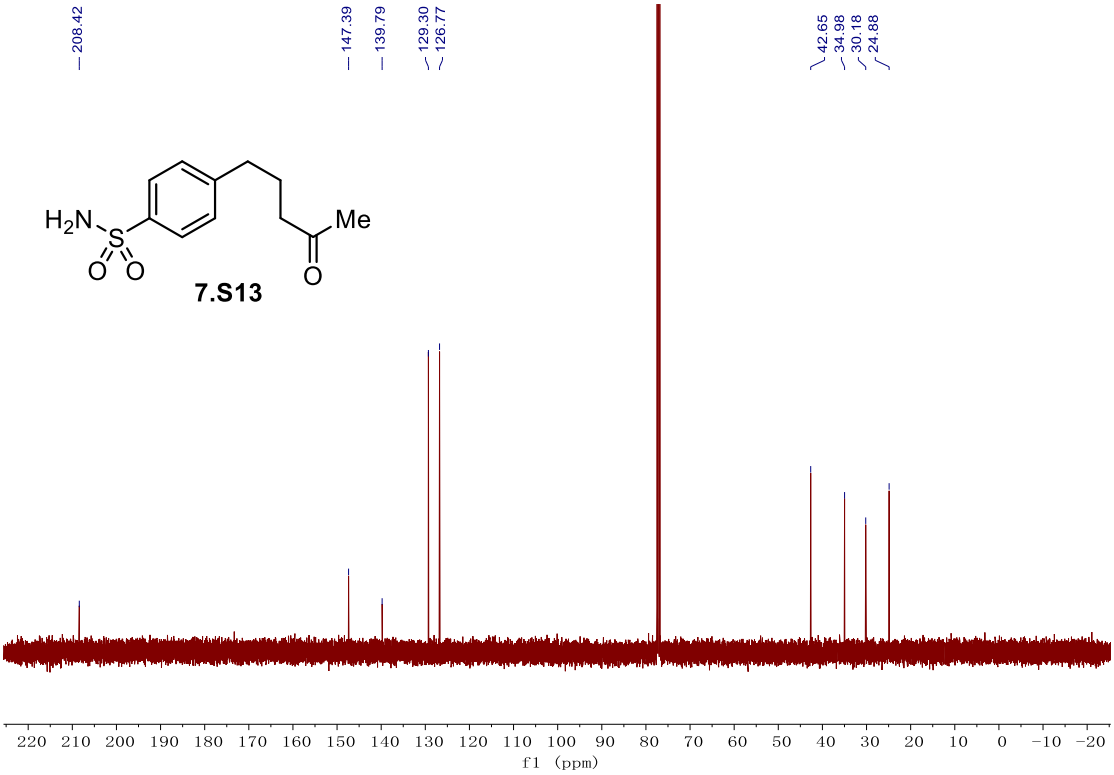


Figure 7.18 ^{1}H-NMR Spectrum of **7.S14**

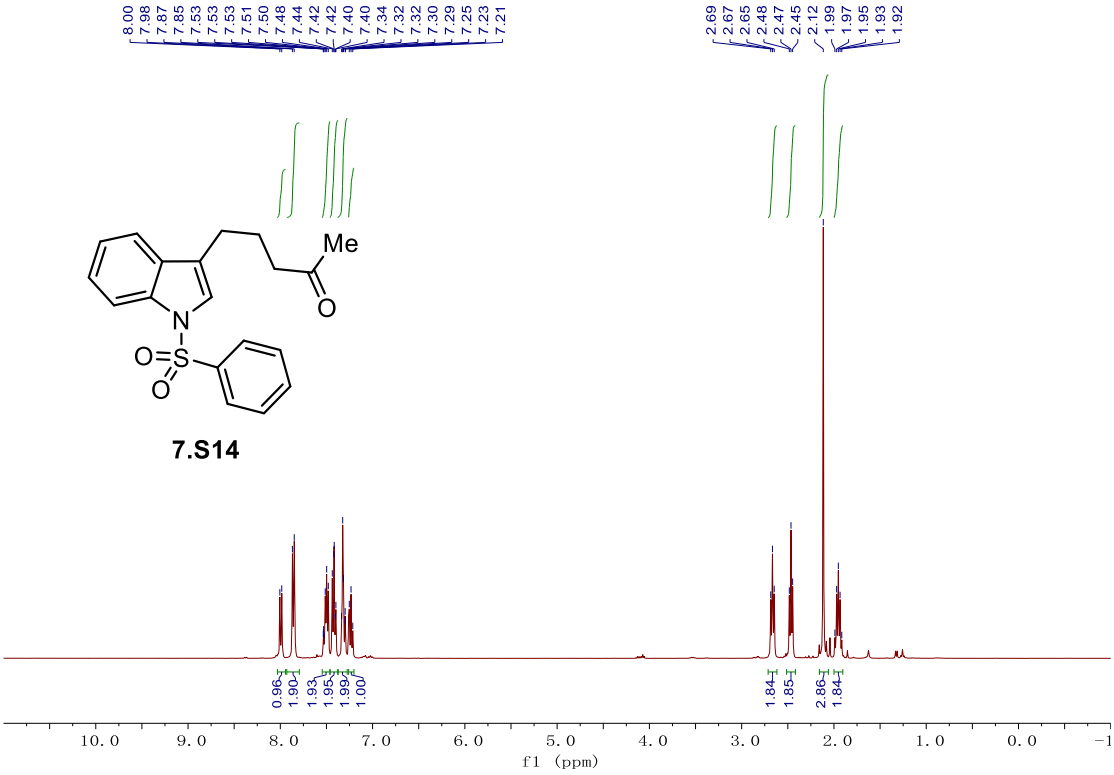


Figure 7.19 ^{13}C-NMR Spectrum of **7.S14**

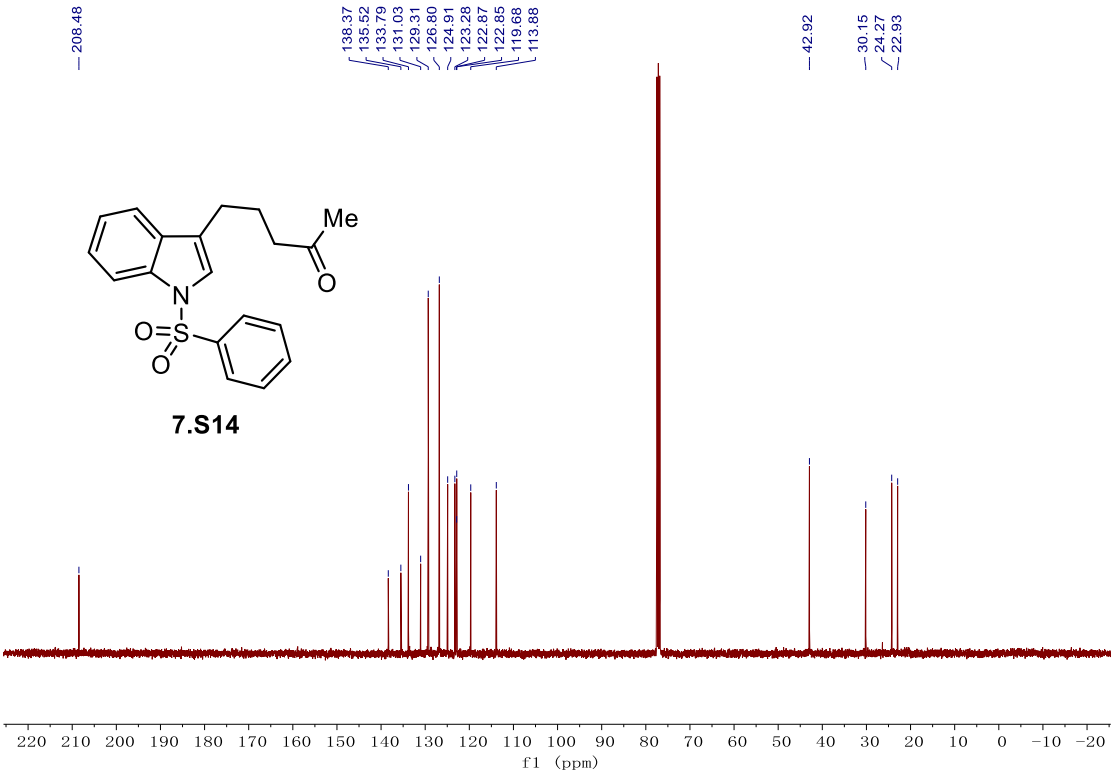


Figure 7.20 ^{1}H-NMR Spectrum of **7.S15**

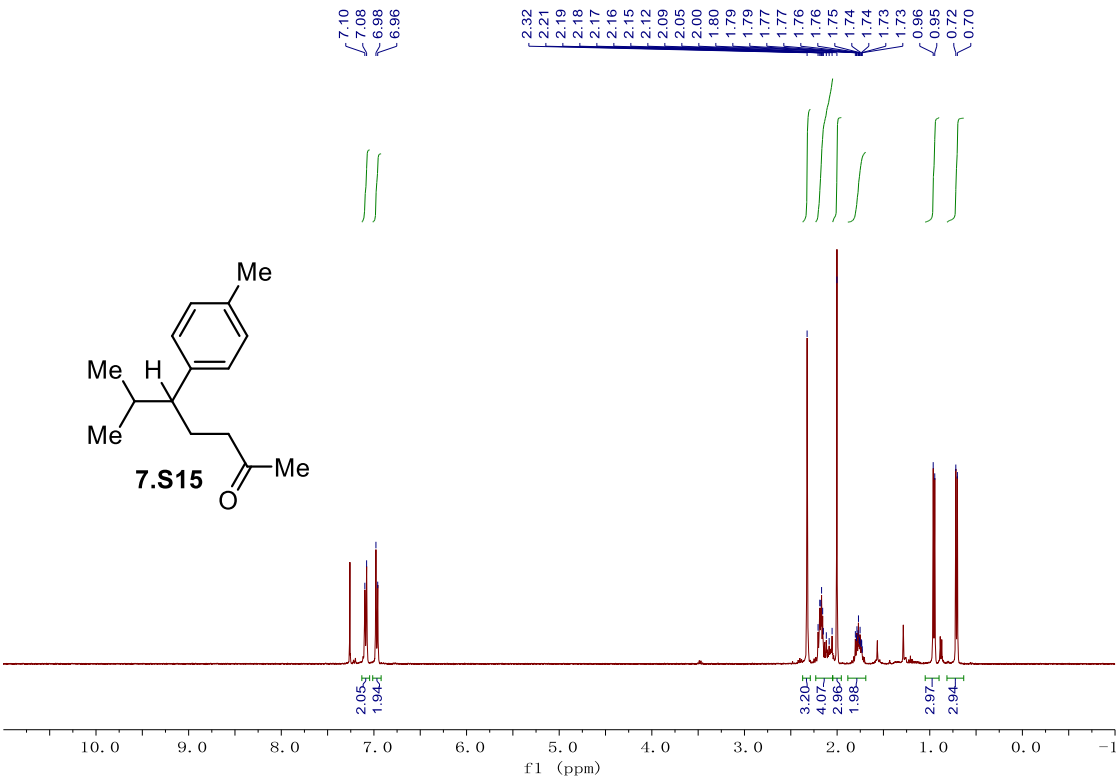


Figure 7.21 ^{1}H-NMR Spectrum of **7.S16**

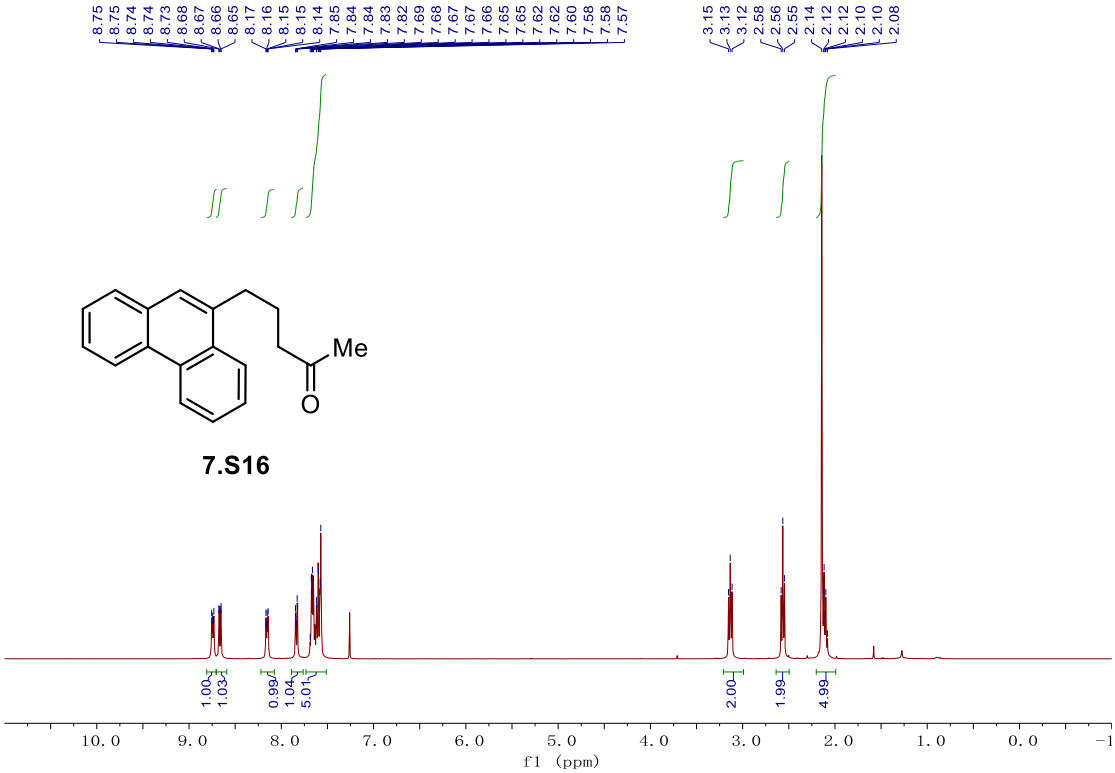


Figure 7.22 ^{13}C-NMR Spectrum of **7.S16**

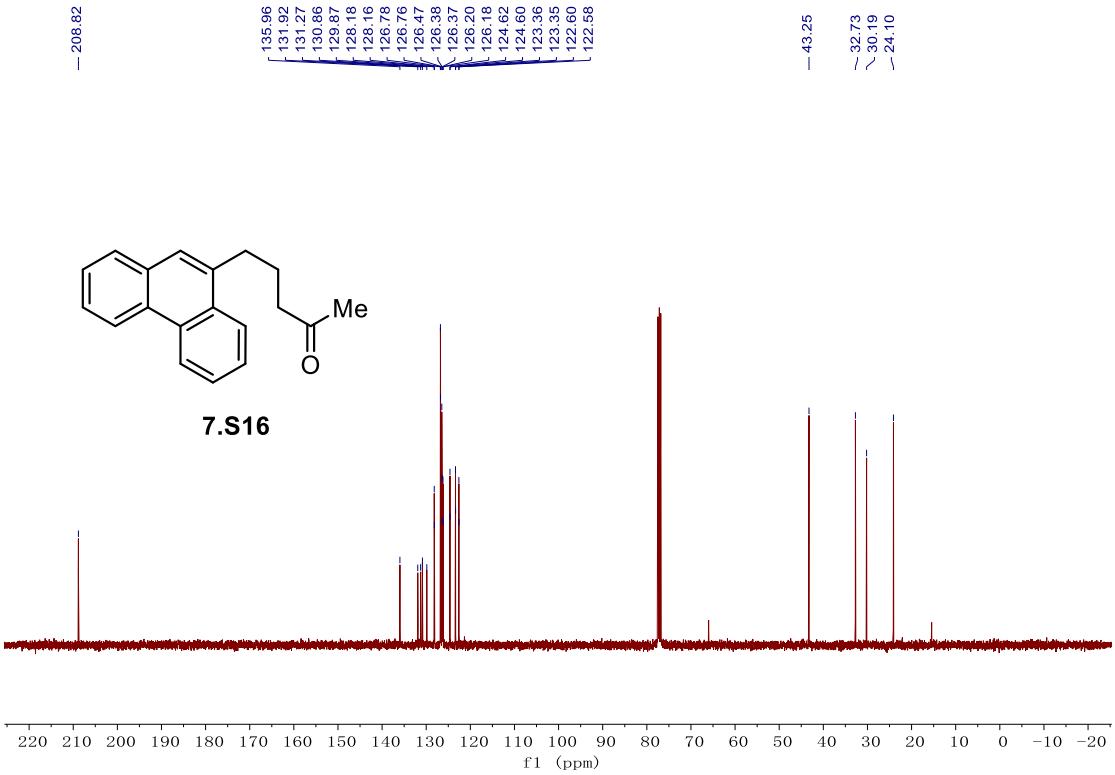


Figure 7.23 ^{1}H-NMR Spectrum of **7.S17**

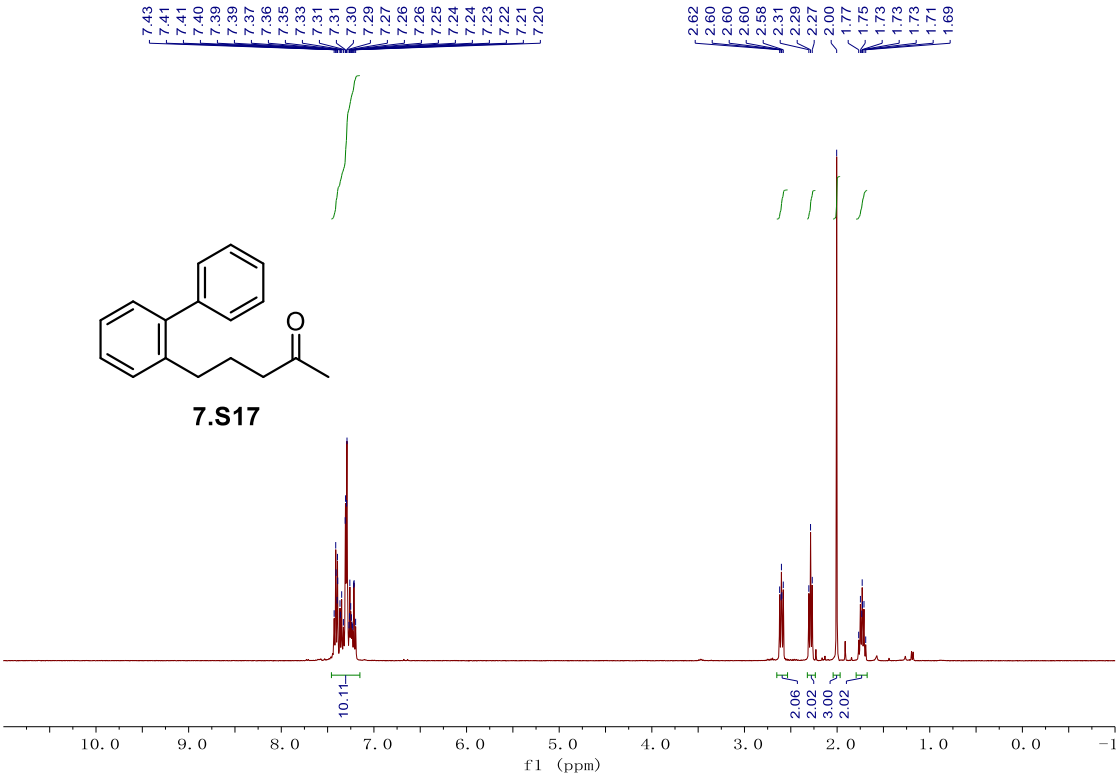


Figure 7.24 ^{13}C-NMR Spectrum of **7.S17**

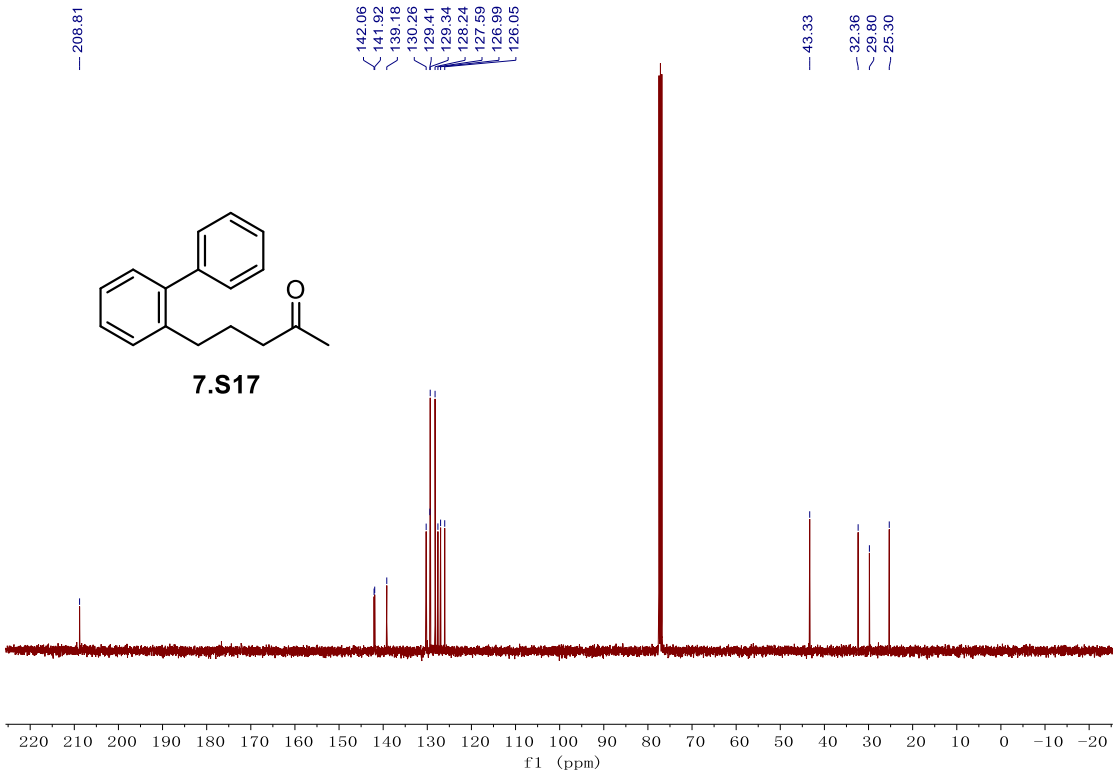


Figure 7.25 ^{1}H-NMR Spectrum of **7.S18b**

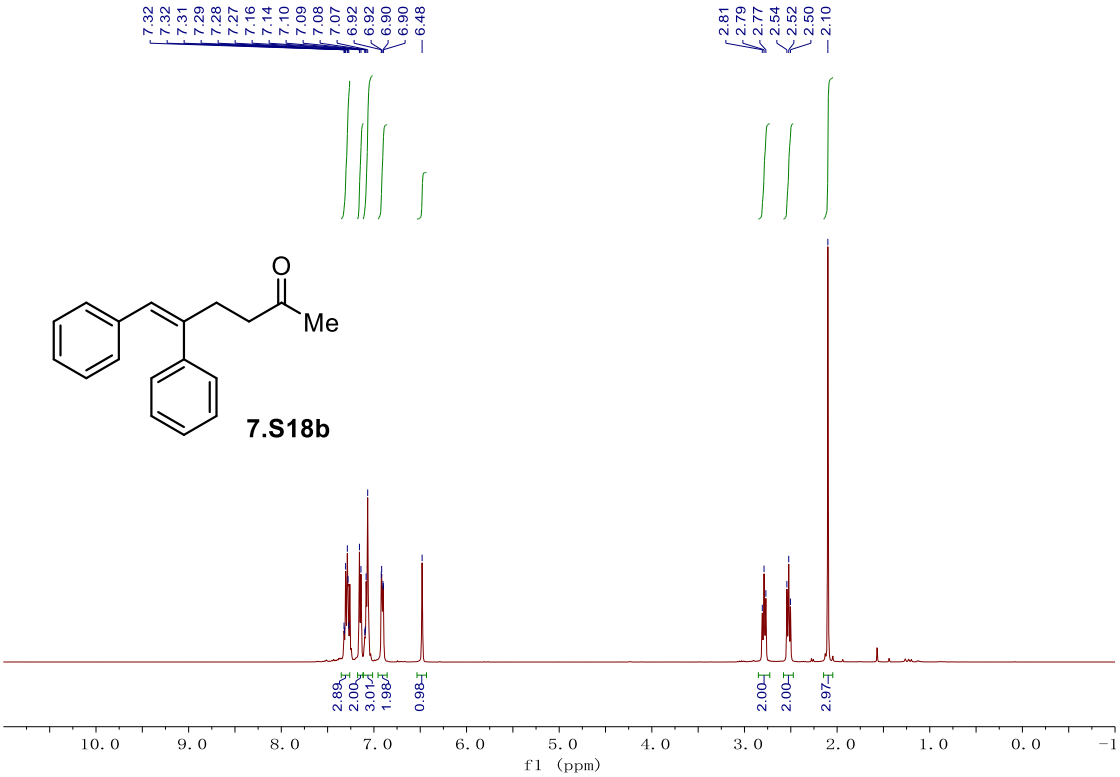


Figure 7.26 ^{13}C-NMR Spectrum of **7.S18b**

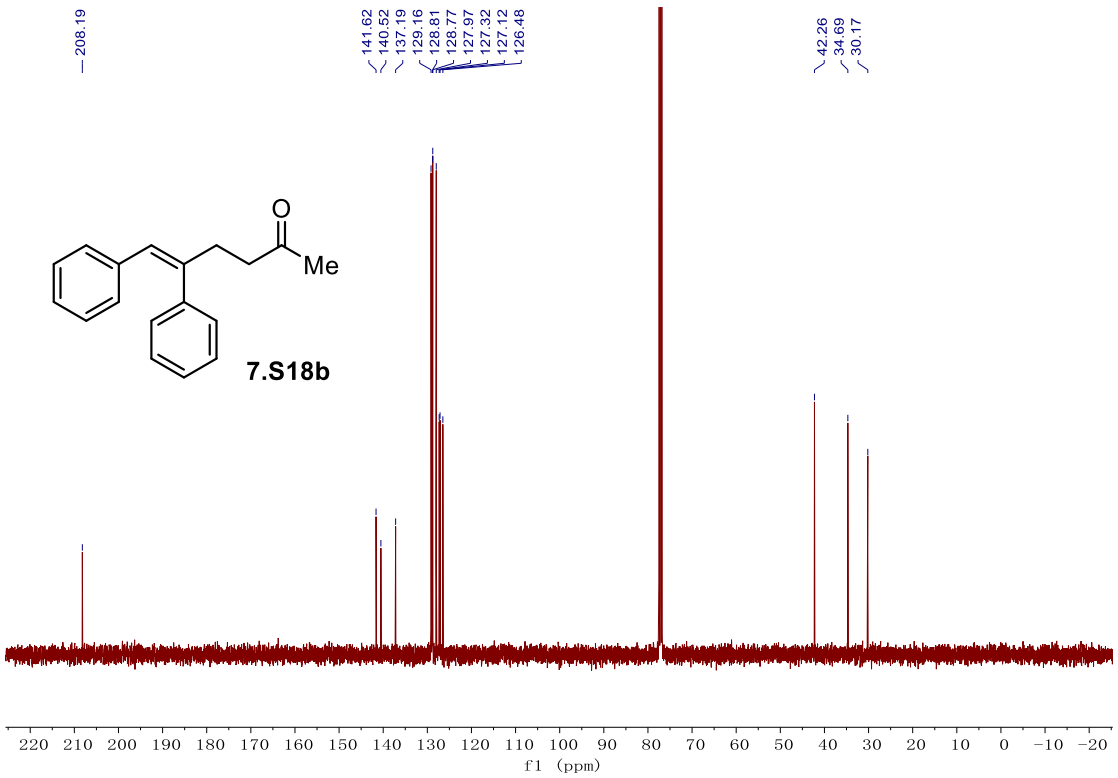


Figure 7.27 ^{1}H-NMR Spectrum of **7.S18**

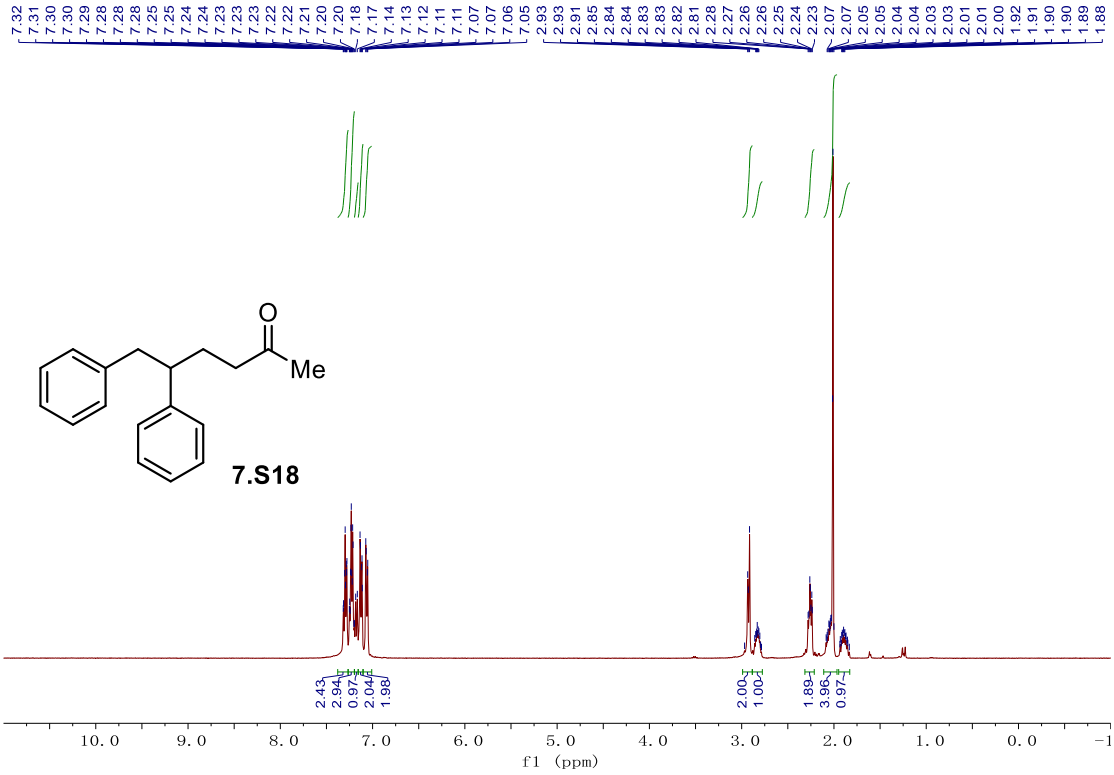


Figure 7.28 ^{13}C-NMR Spectrum of **7.S18**

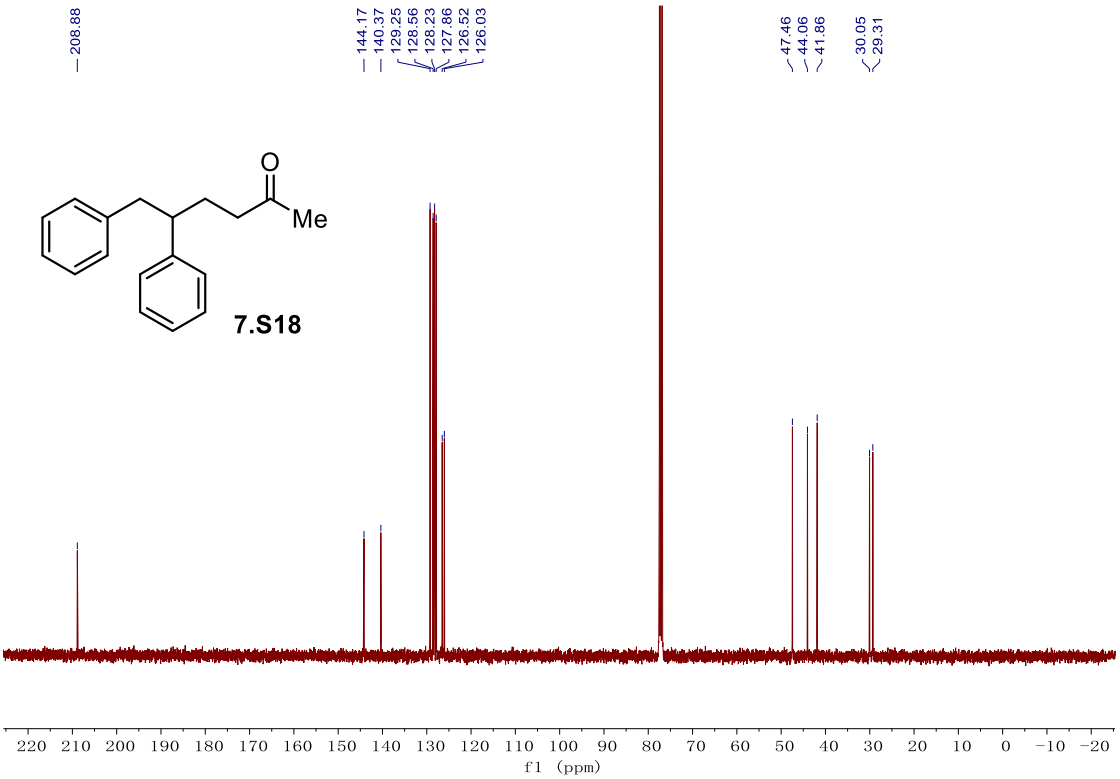


Figure 7.29 ^{1}H-NMR Spectrum of **7.S19**

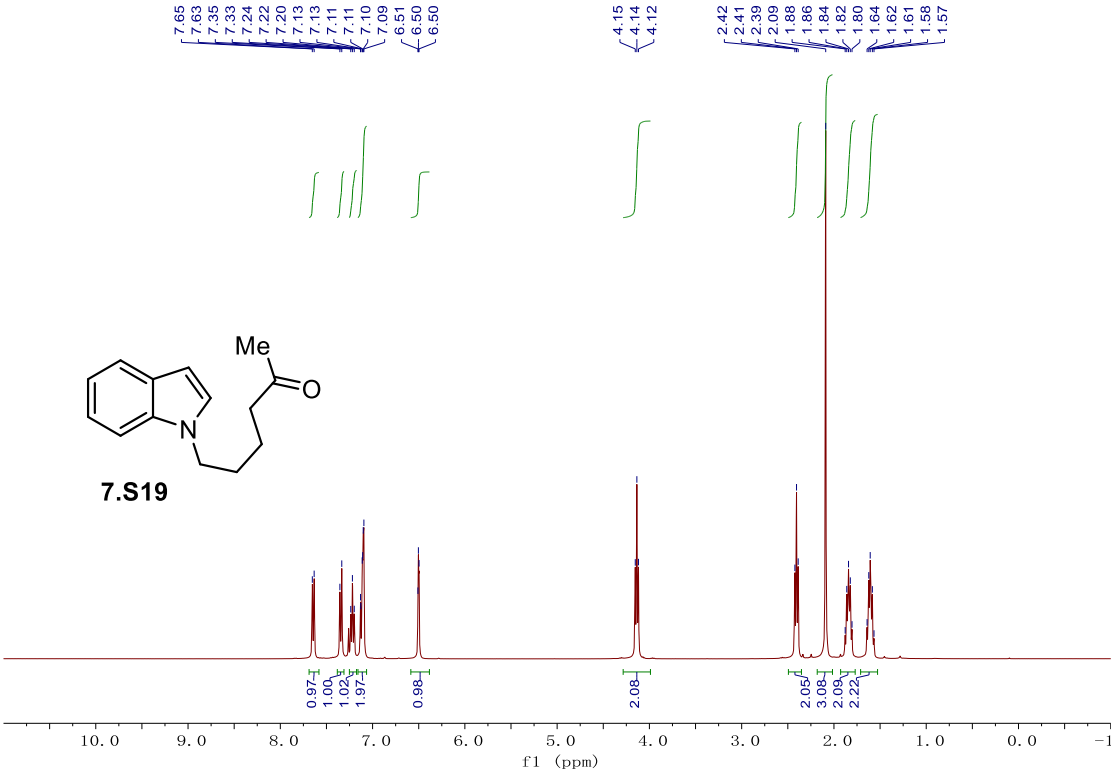


Figure 7.30 ^{13}C-NMR Spectrum of **7.S19**

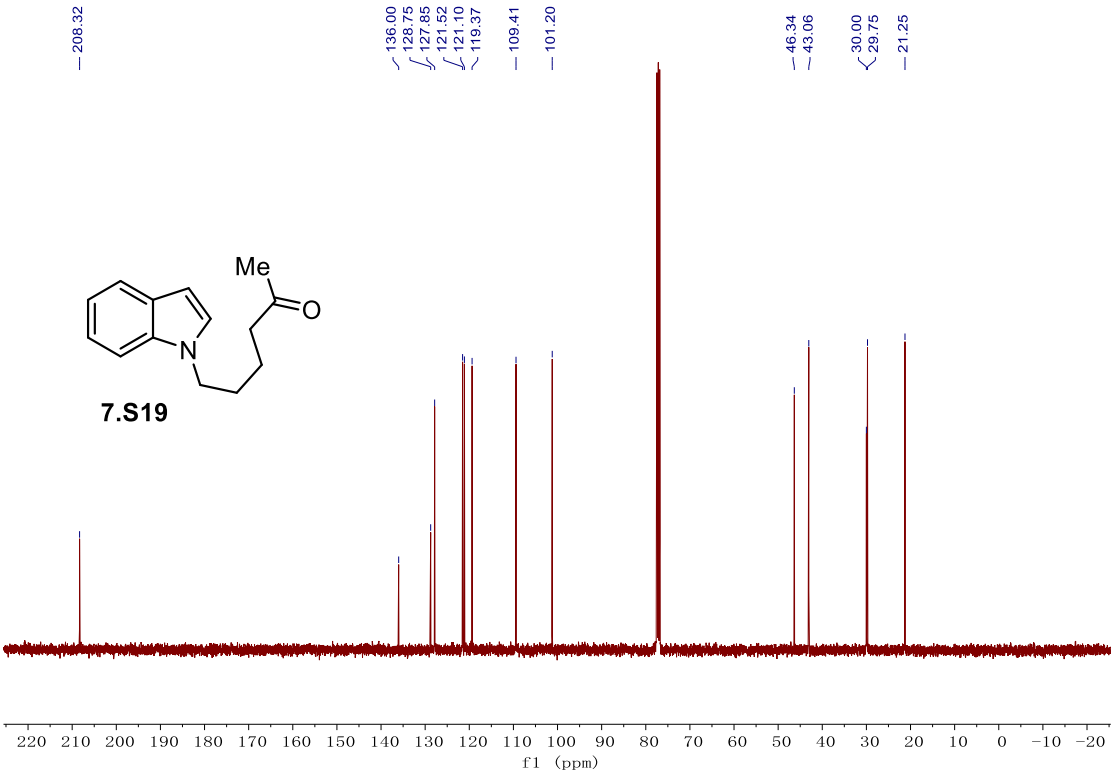


Figure 7.31 ^{1}H-NMR Spectrum of **7.S19b**

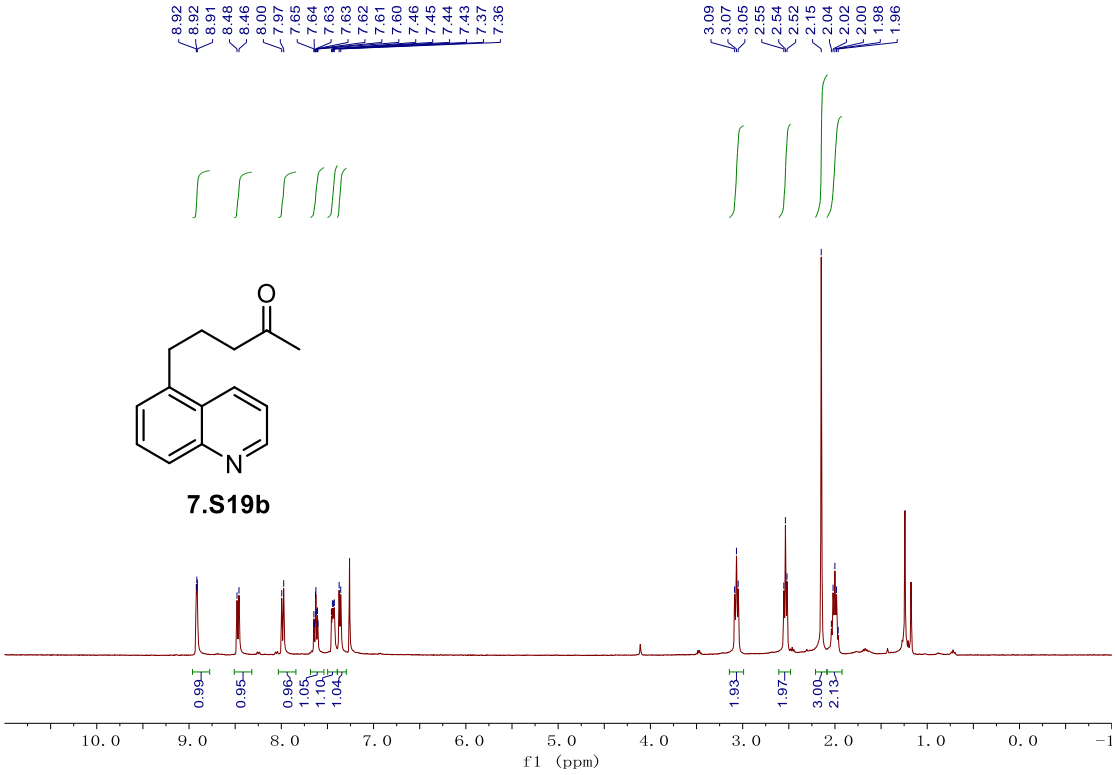


Figure 7.32 ^{13}C-NMR Spectrum of **7.S19b**

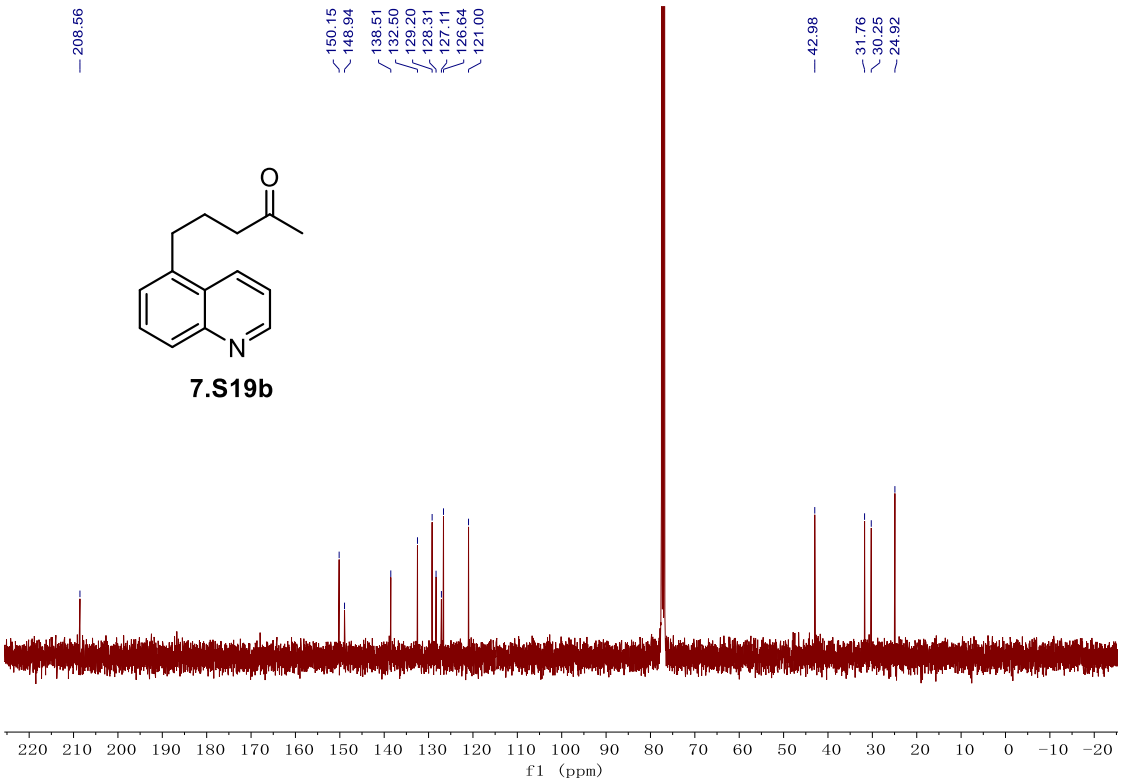


Figure 7.33 ^{1}H-NMR Spectrum of **7.78**

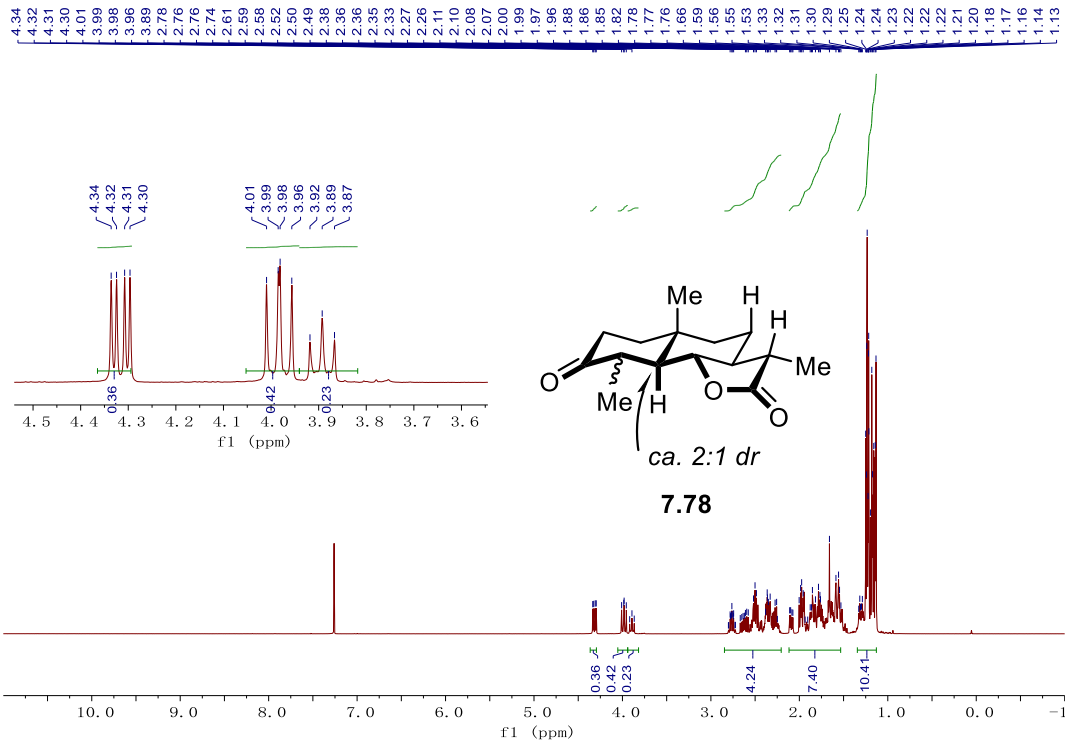


Figure 7.34 ^{13}C-NMR Spectrum of **7.78**

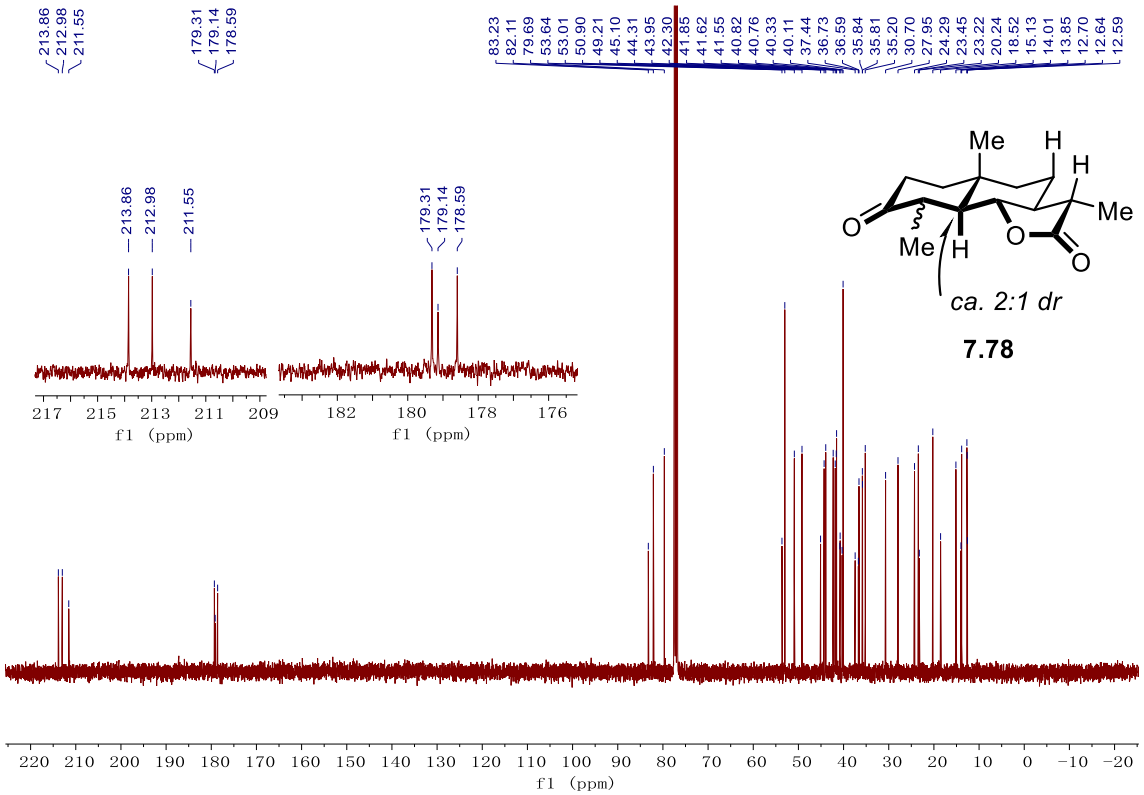


Figure 7.35 ^{1}H-NMR Spectrum of **7.80**

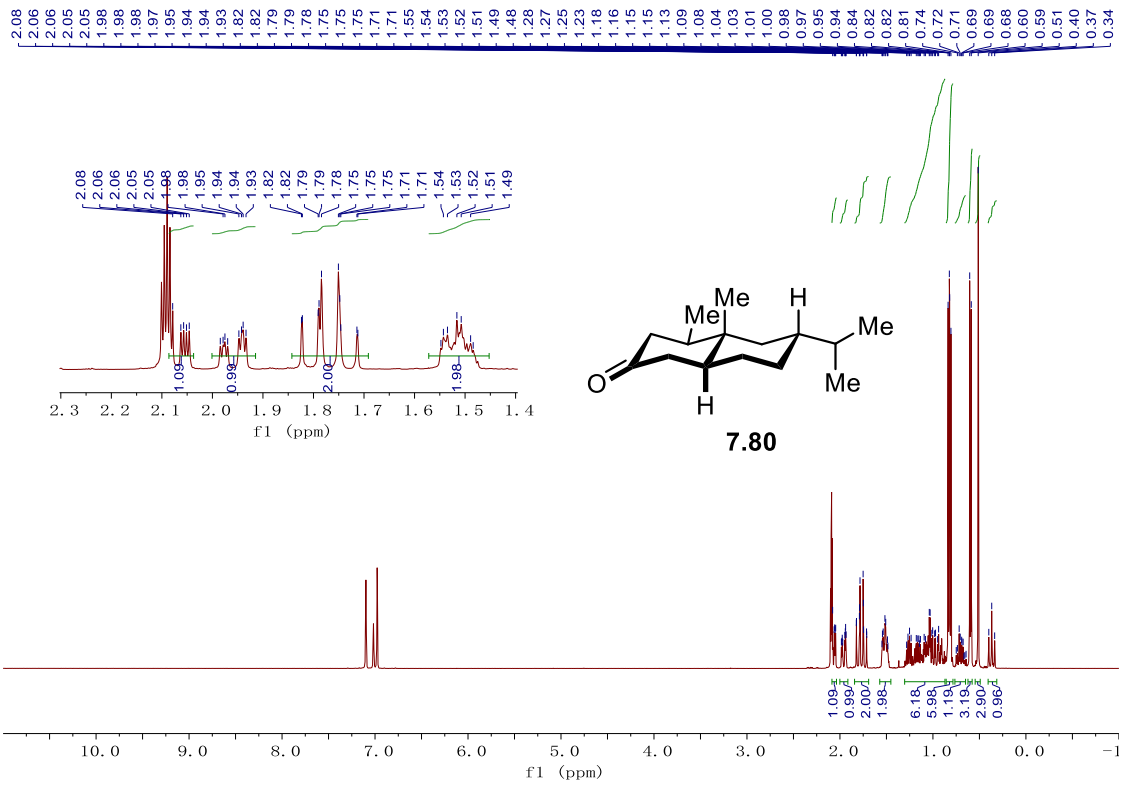


Figure 7.36 ^{13}C-NMR Spectrum of **7.80**

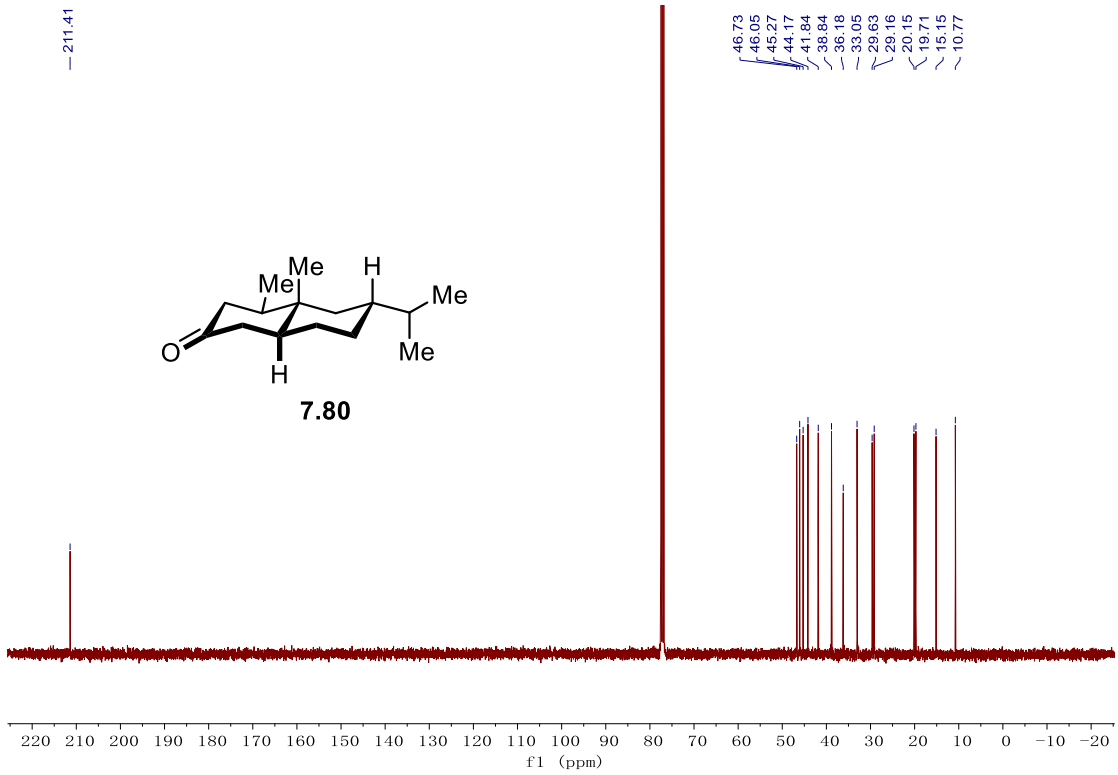


Figure 7.37 ^{1}H-NMR Spectrum of **7.87**

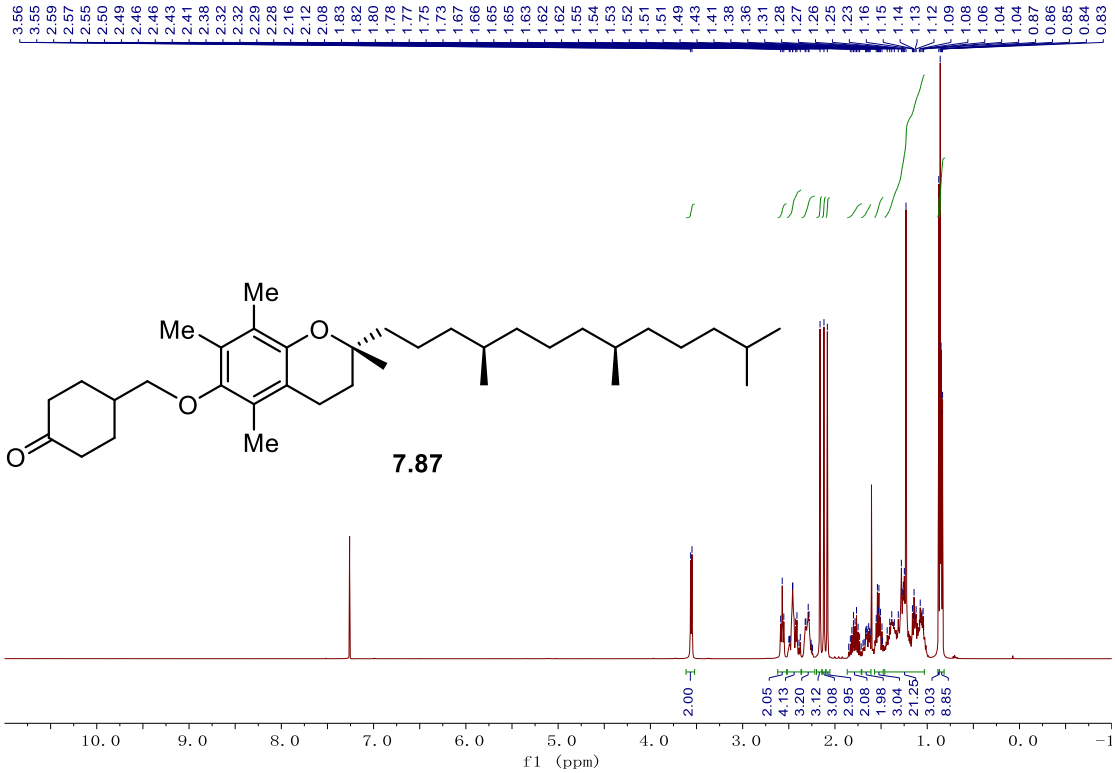


Figure 7.38 ^{13}C-NMR Spectrum of **7.87**

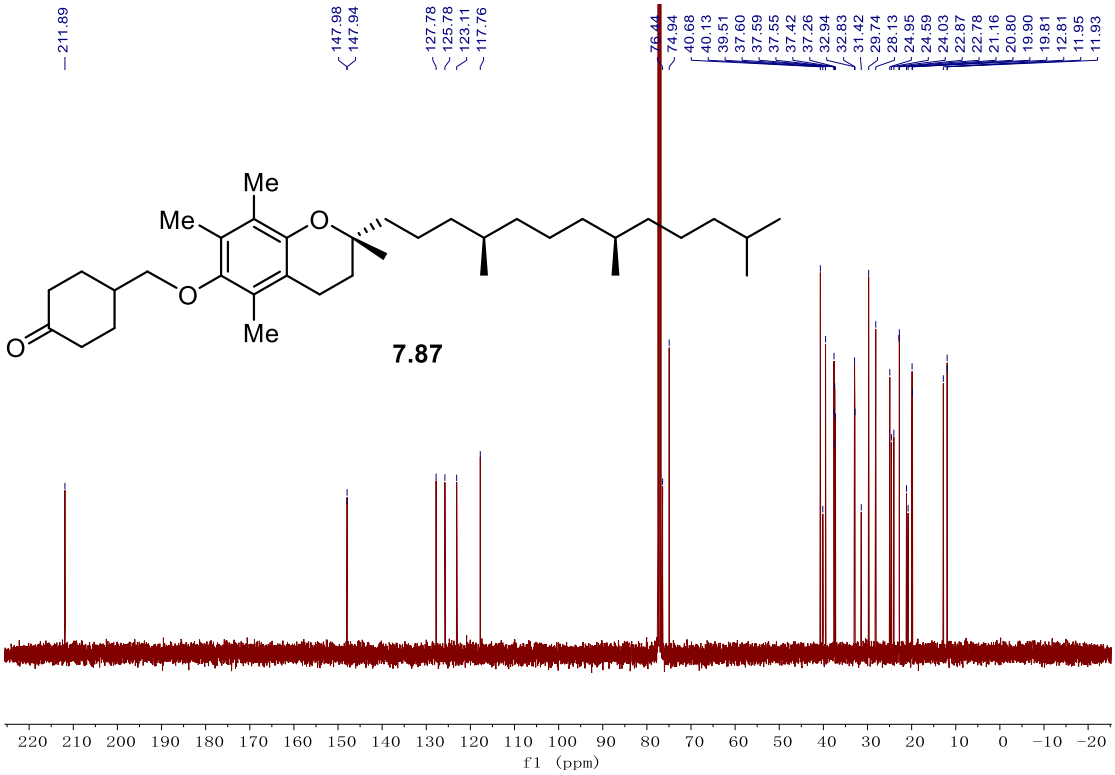


Figure 7.39 ^{1}H-NMR Spectrum of **7.106**

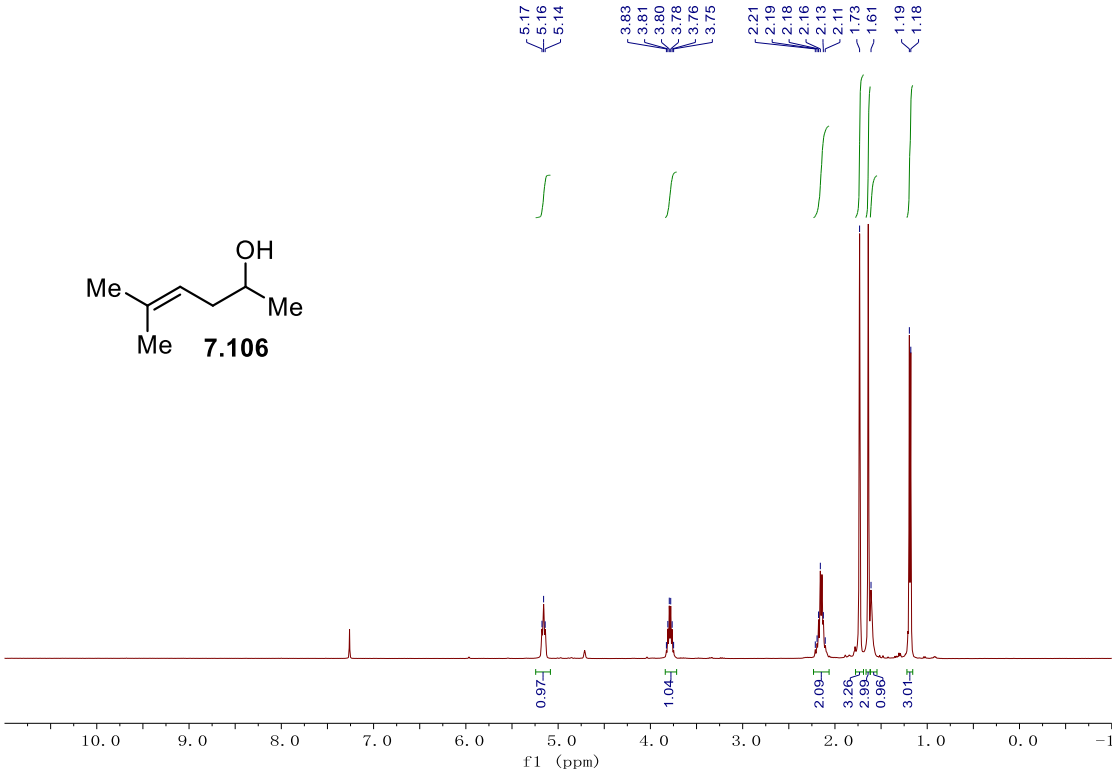


Figure 7.40 ^{1}H-NMR Spectrum of **7.107**

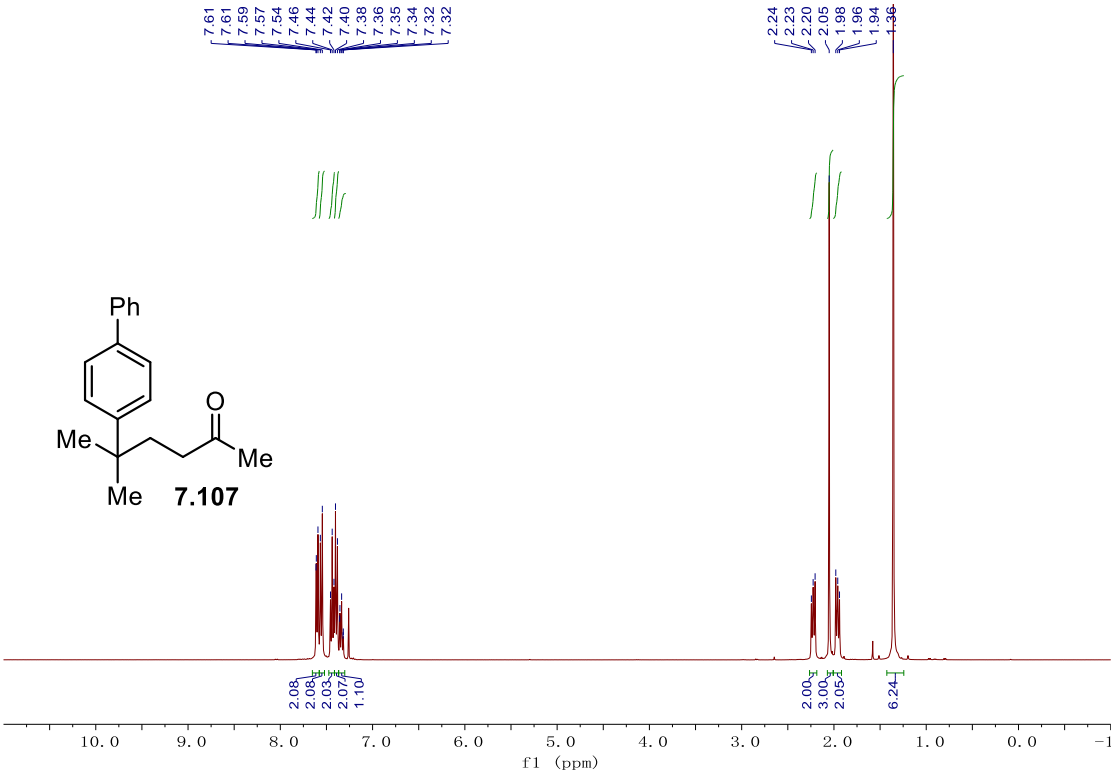


Figure 7.41 ^{13}C-NMR Spectrum of **7.107**

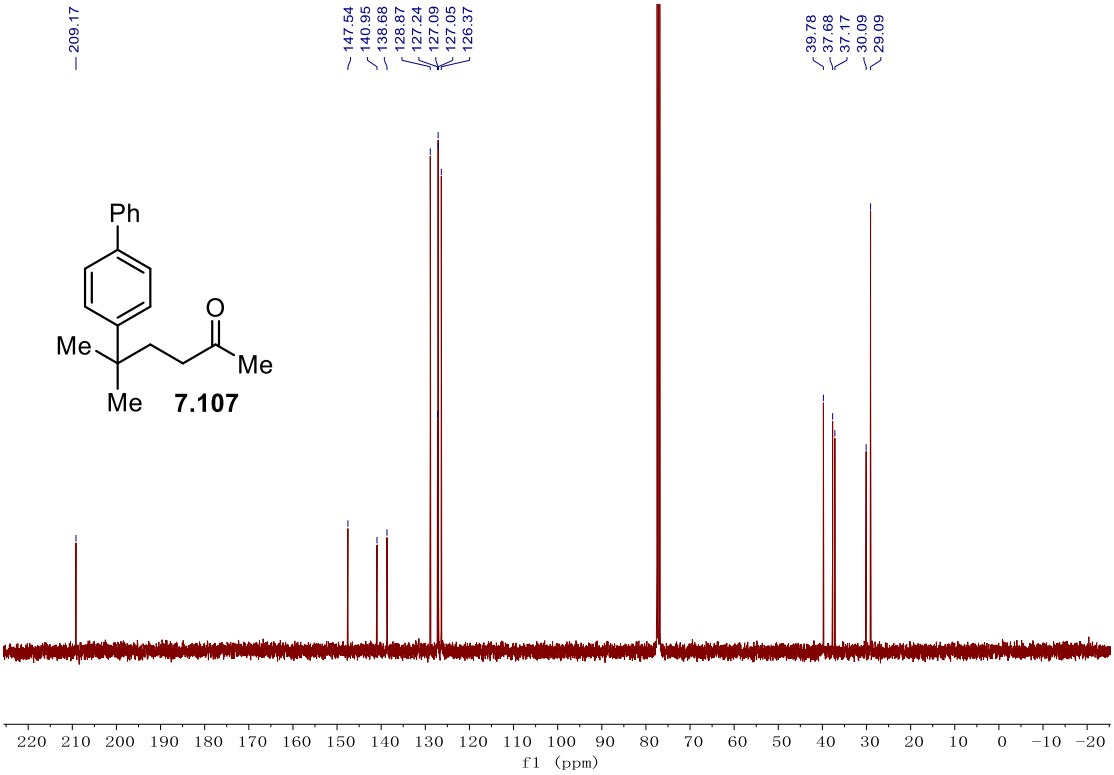


Figure 7.42 ^{1}H-NMR Spectrum of **7.118**

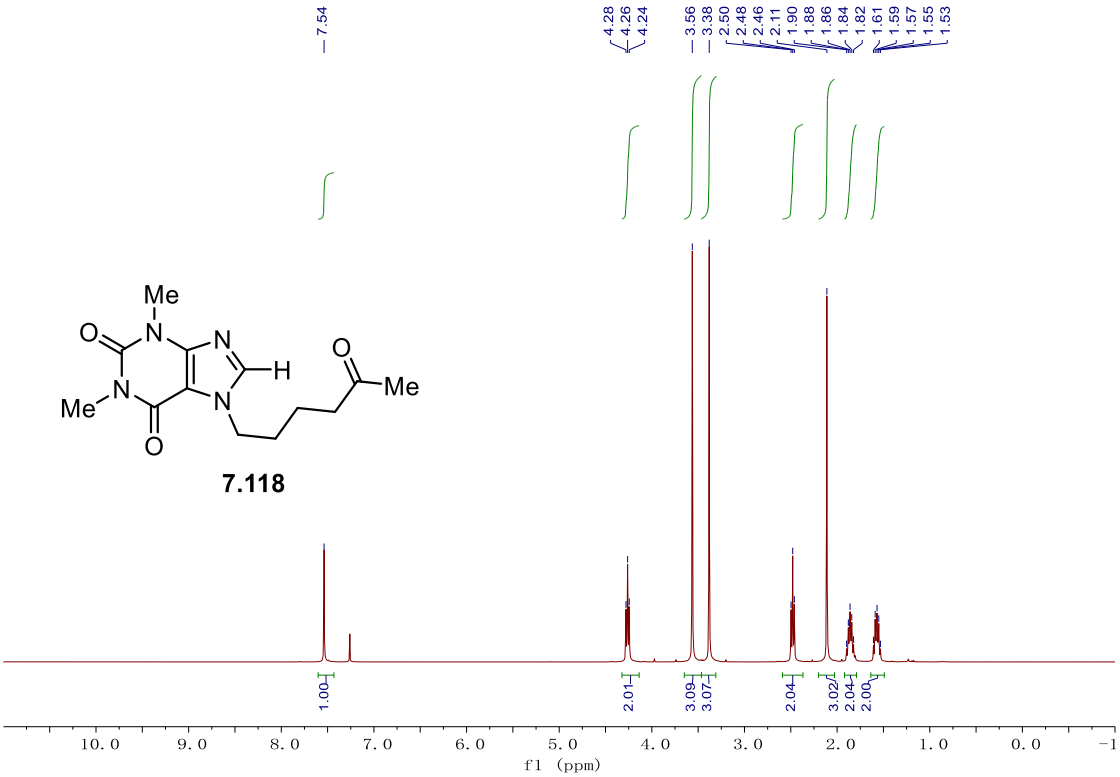


Figure 7.43 ^{13}C-NMR Spectrum of **7.118**

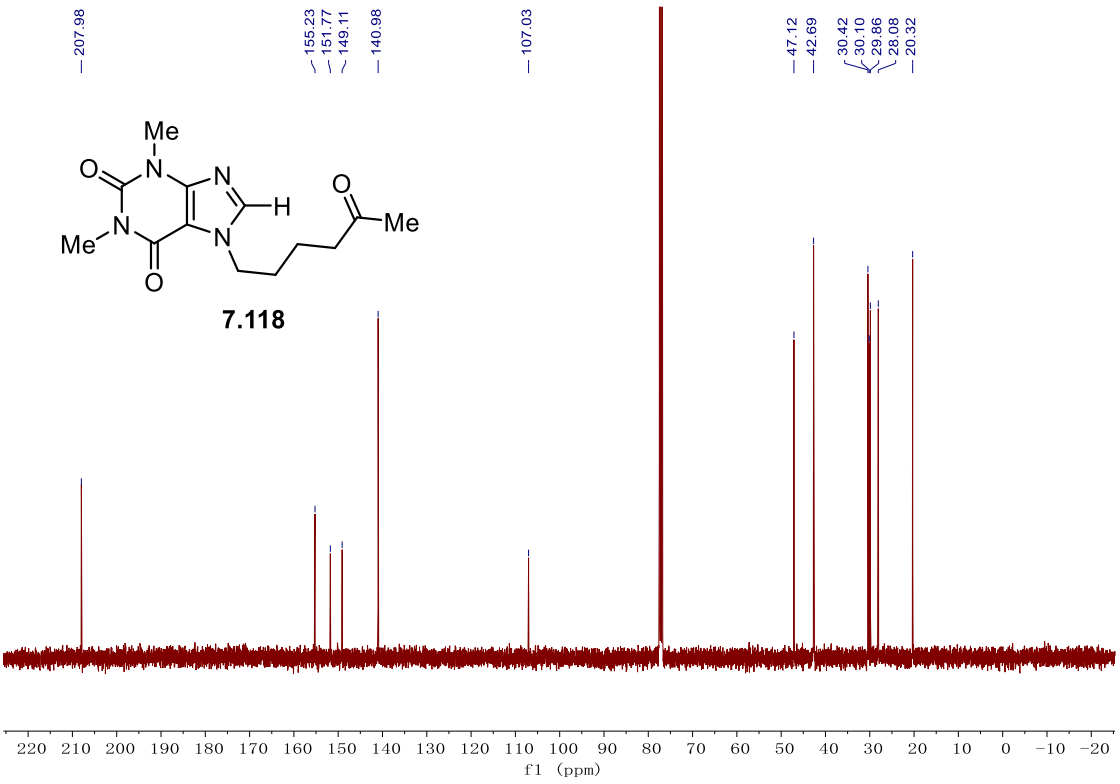


Figure 7.44 ^{1}H-NMR Spectrum of **7.120**

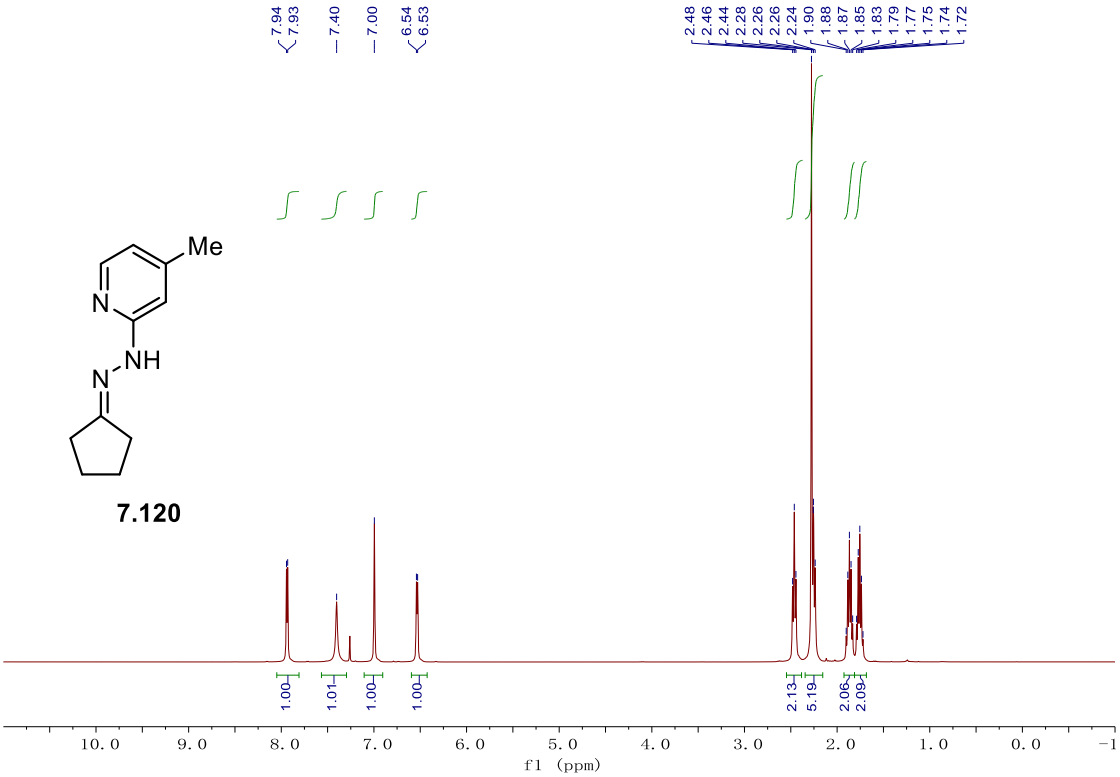


Figure 7.45 ^{13}C-NMR Spectrum of **7.120**

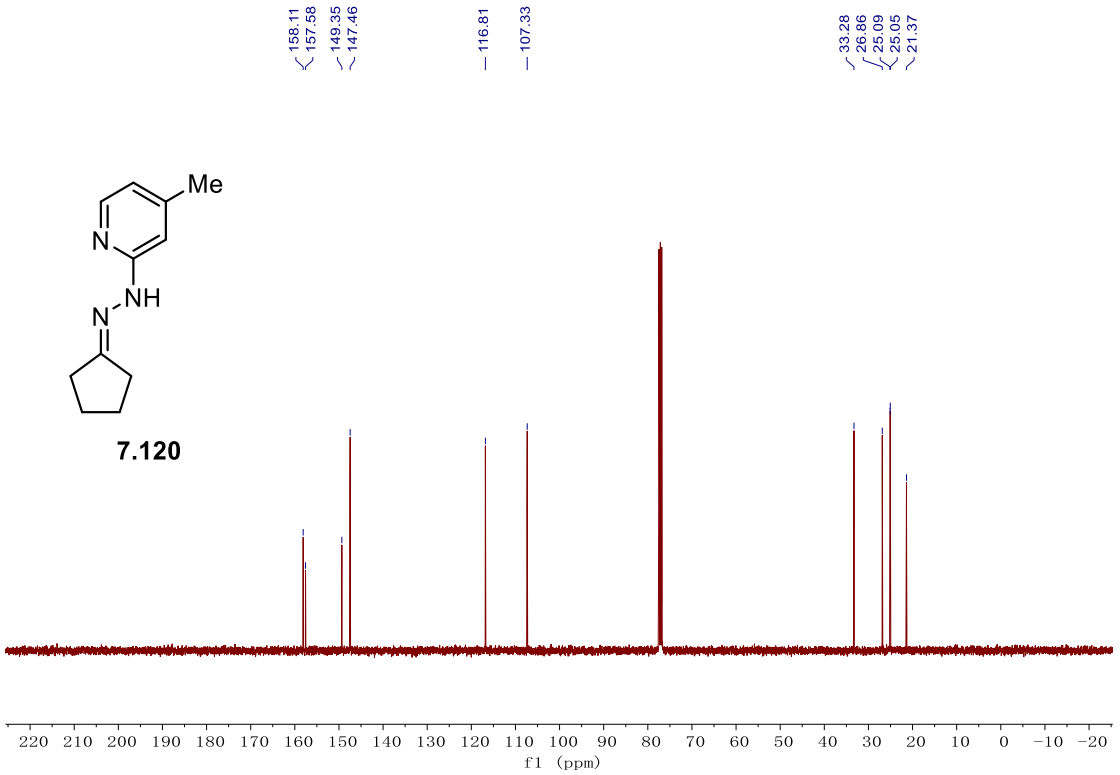


Figure 7.46 ^{1}H-NMR Spectrum of **7.123**

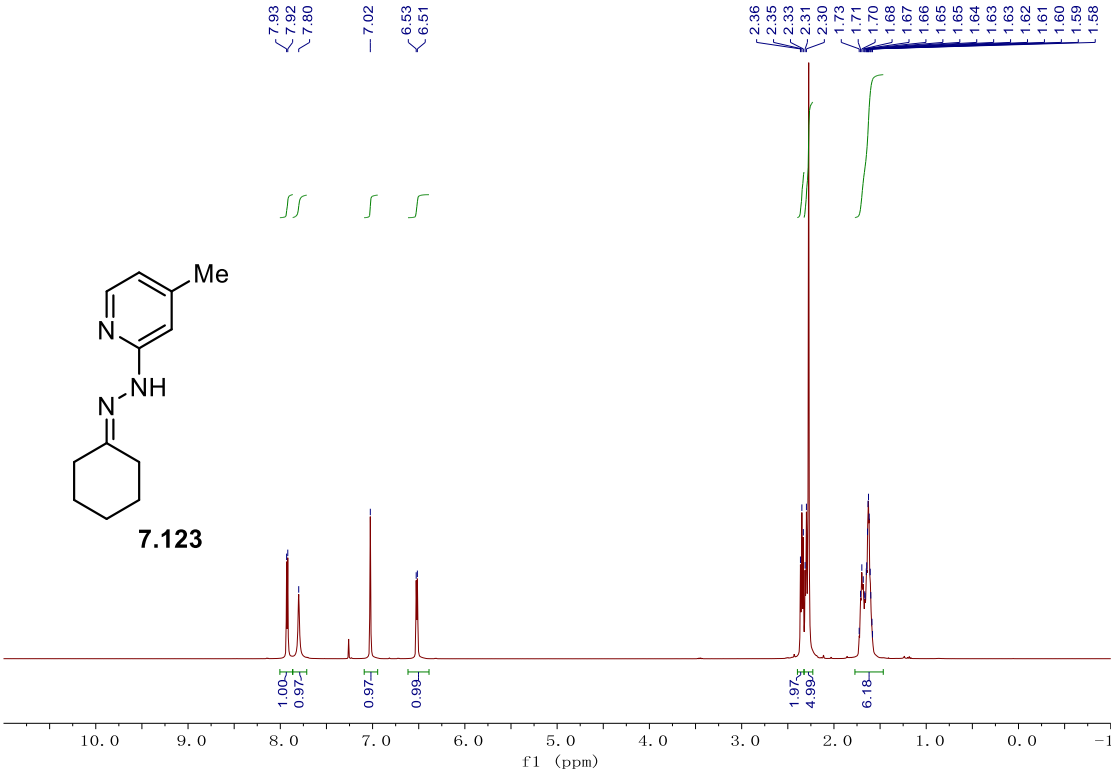


Figure 7.47 ^{13}C-NMR Spectrum of **7.123**

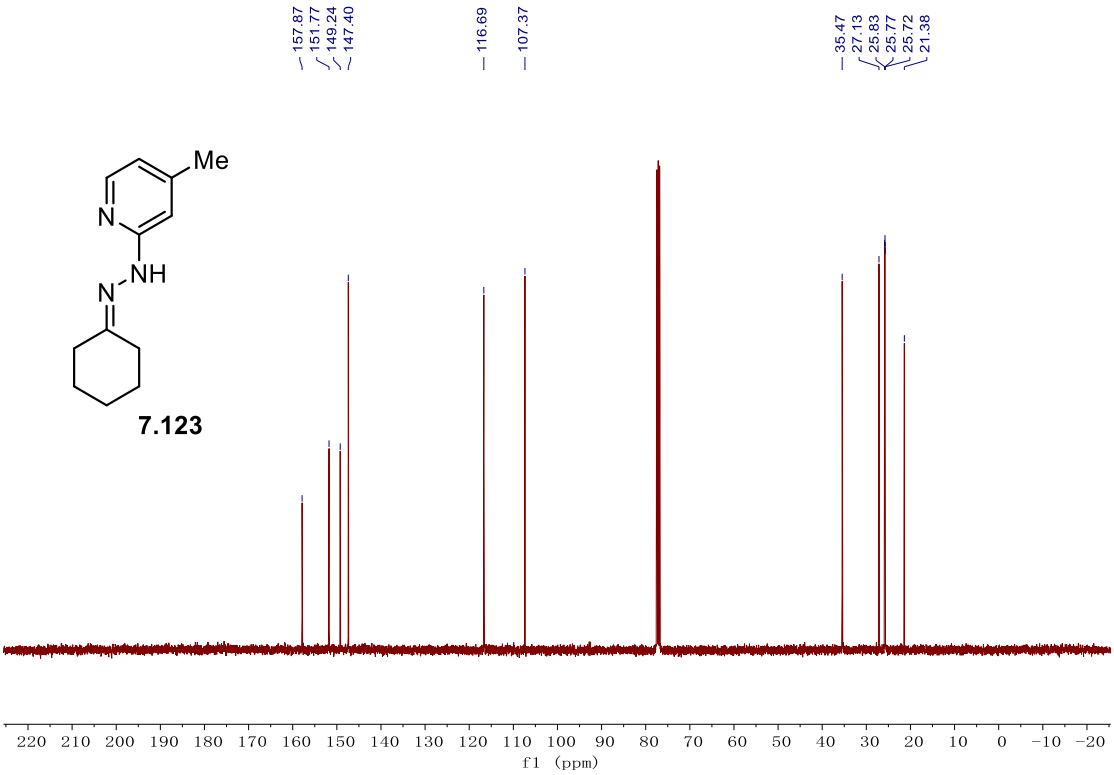


Figure 7.48 ^{1}H-NMR Spectrum of **7.L2**

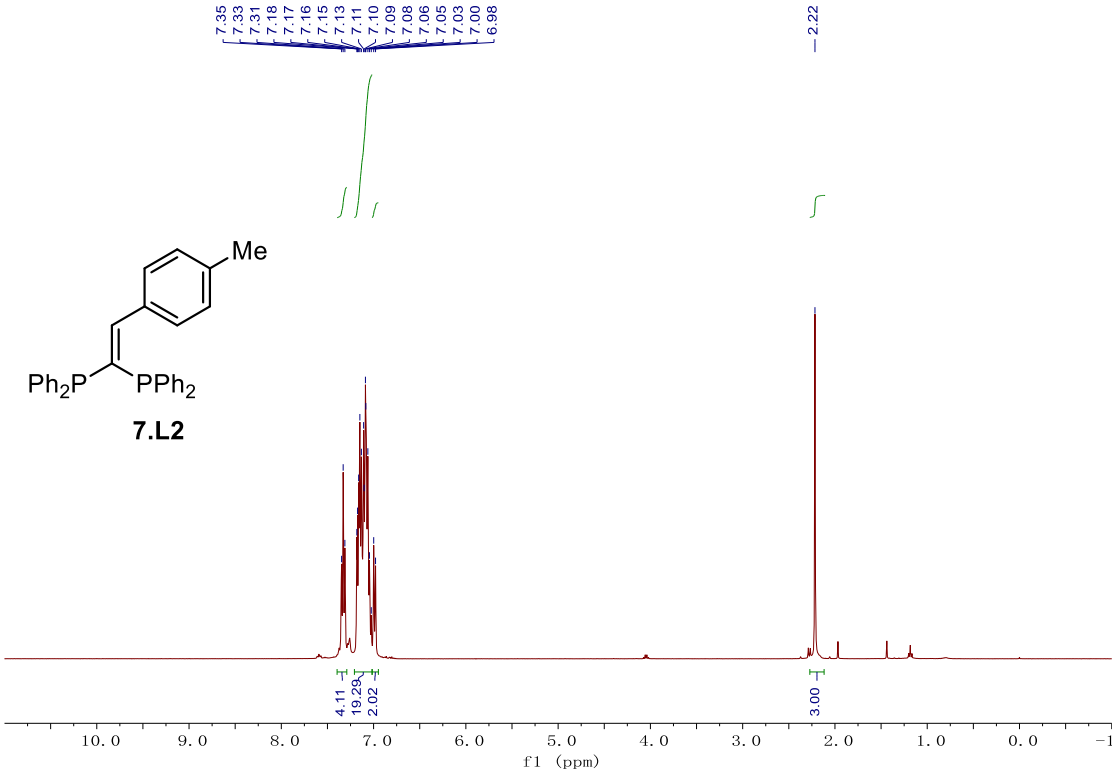


Figure 7.49 ^{13}C-NMR Spectrum of **7.L2**

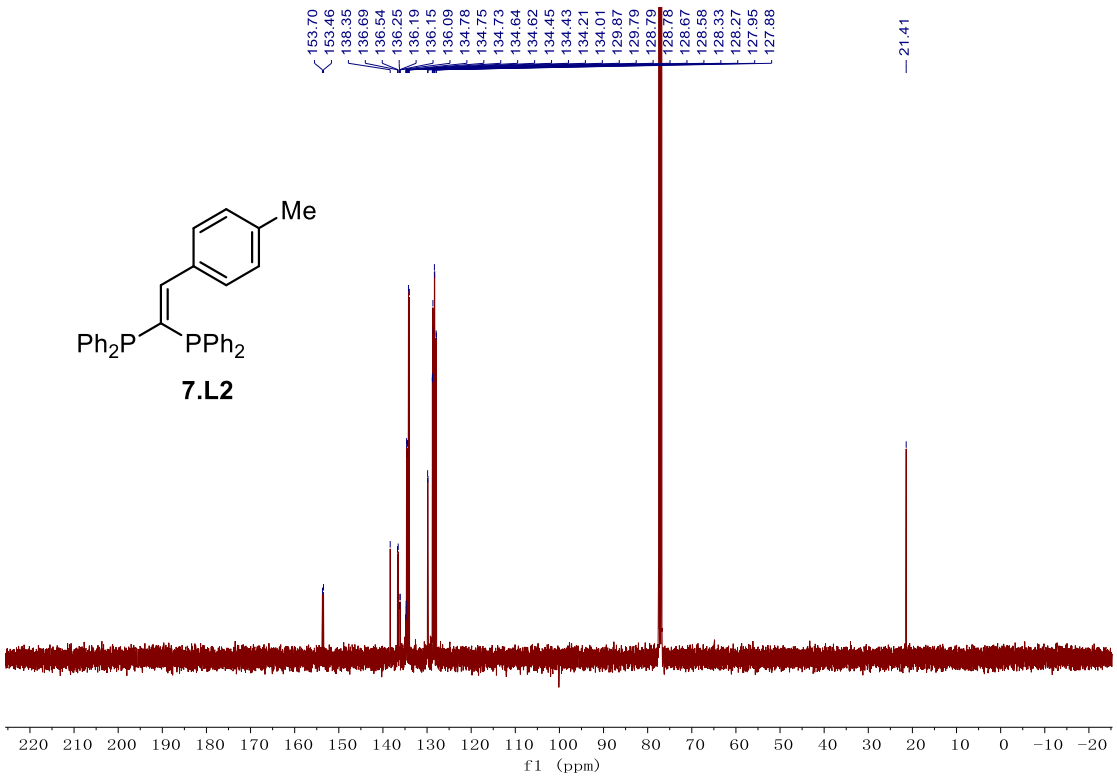


Figure 7.50 ^{1}H-NMR Spectrum of **7.2**

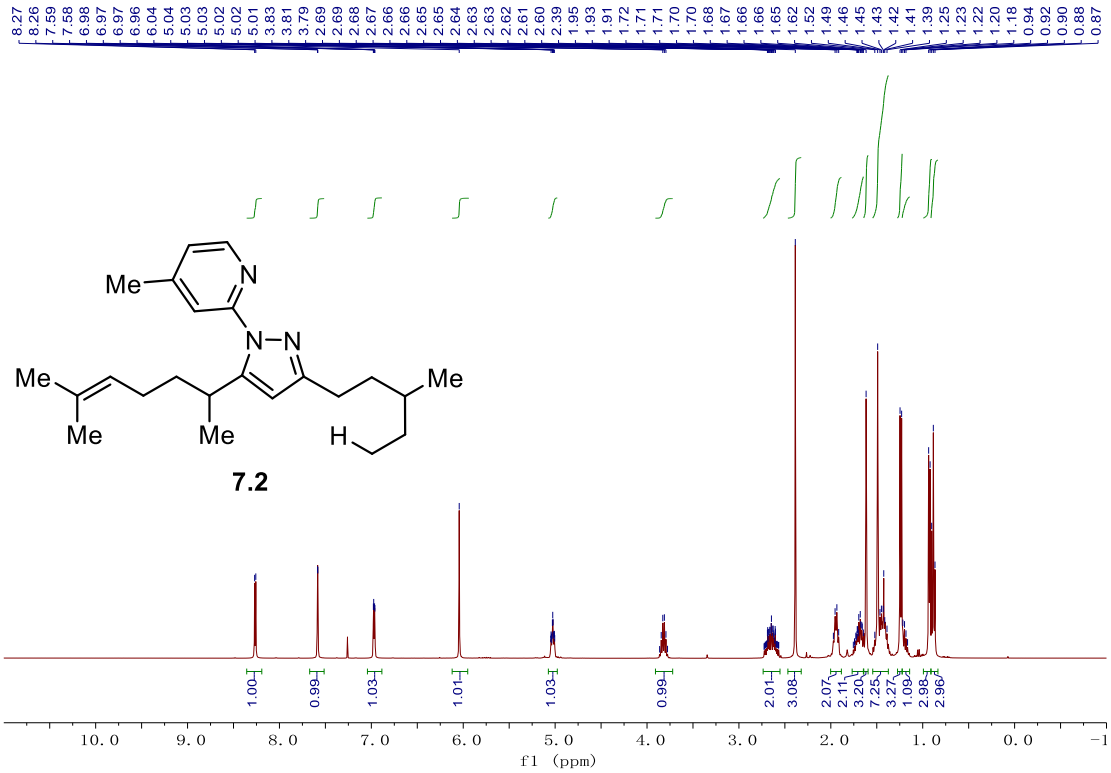


Figure 7.51 ^{13}C-NMR Spectrum of **7.2**

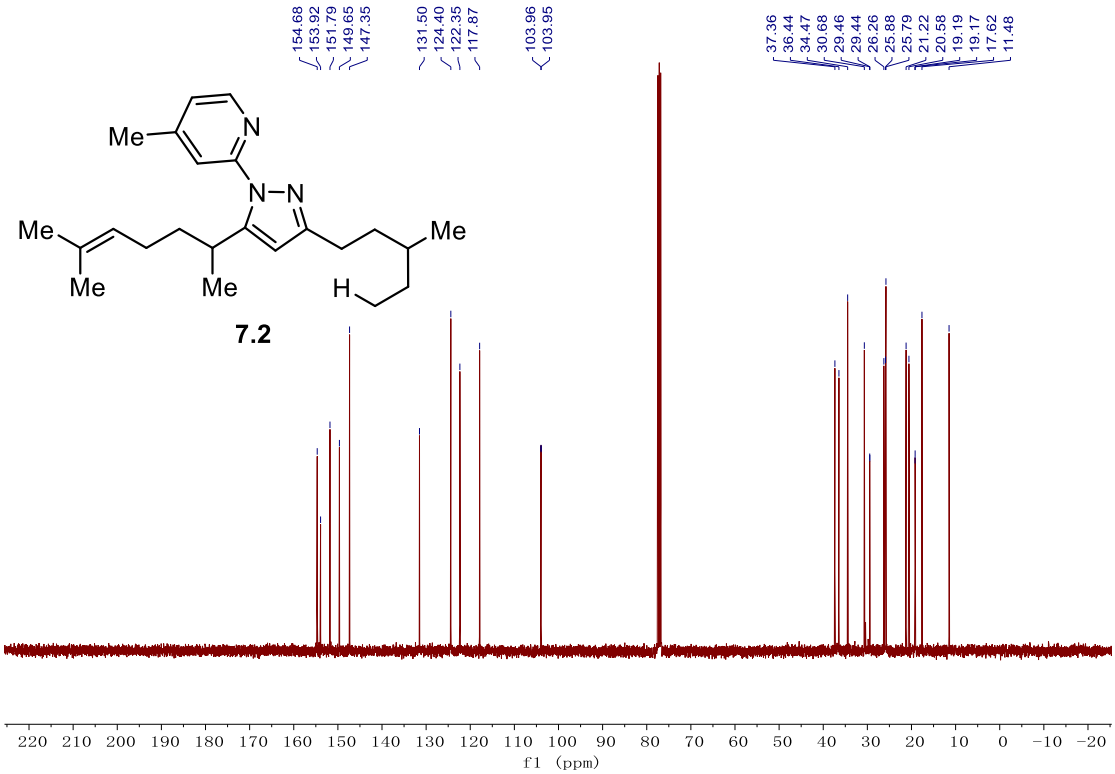


Figure 7.52 ^{1}H-NMR Spectrum of **7.5**

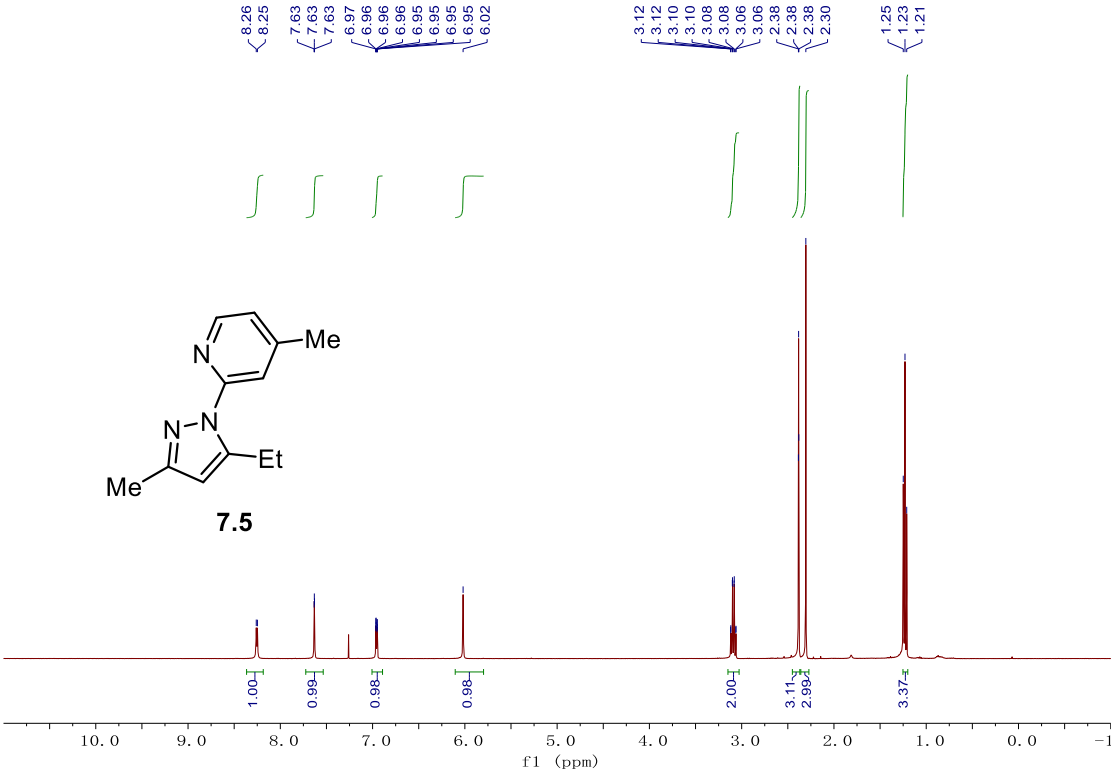


Figure 7.53 ^{13}C-NMR Spectrum of **7.5**

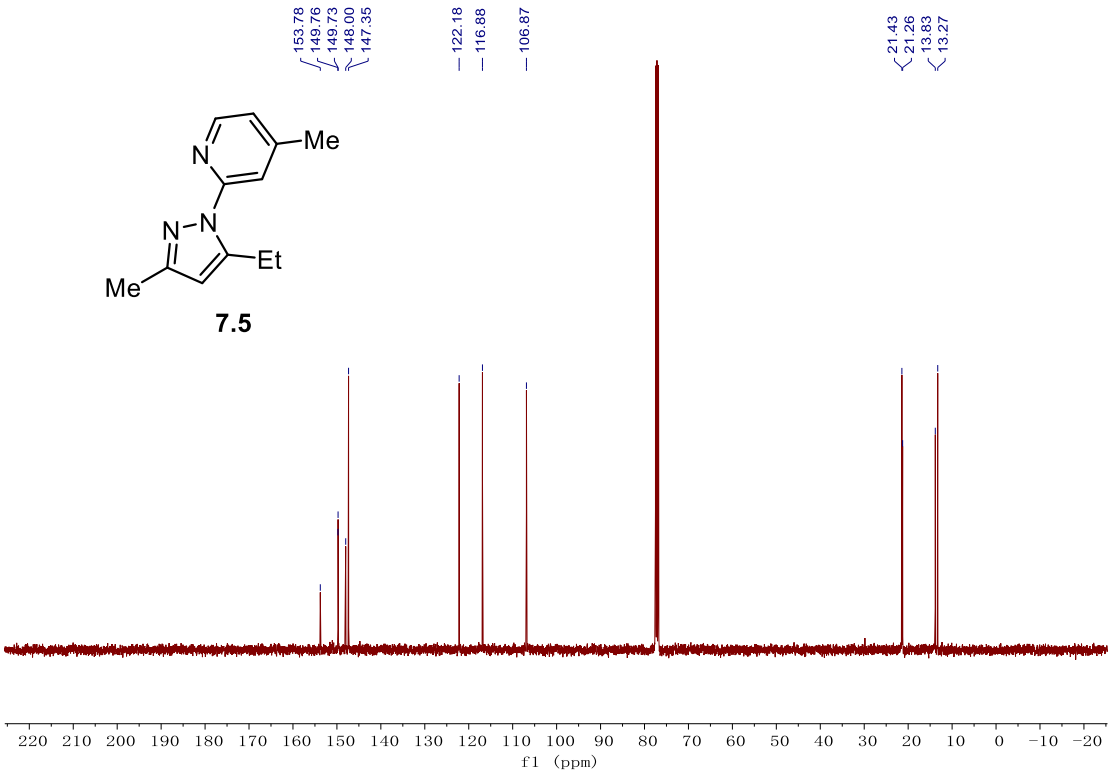


Figure 7.54 ^{1}H-NMR Spectrum of **7.7**

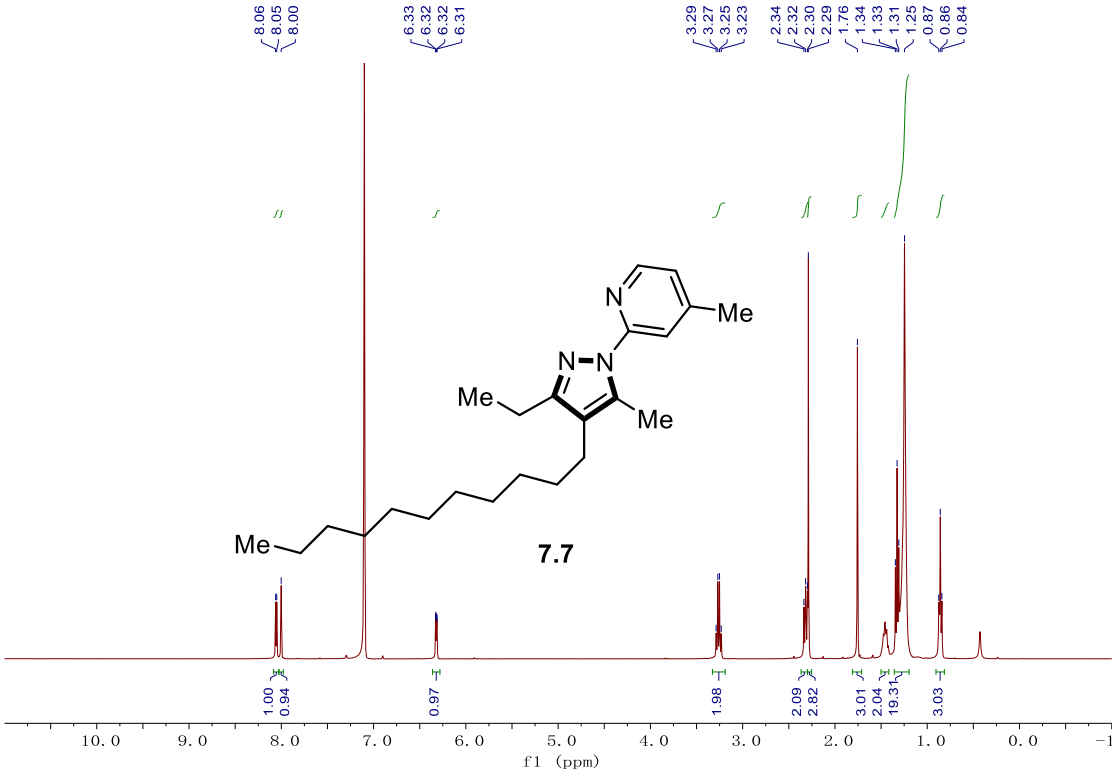


Figure 7.55 ^{13}C-NMR Spectrum of **7.7**

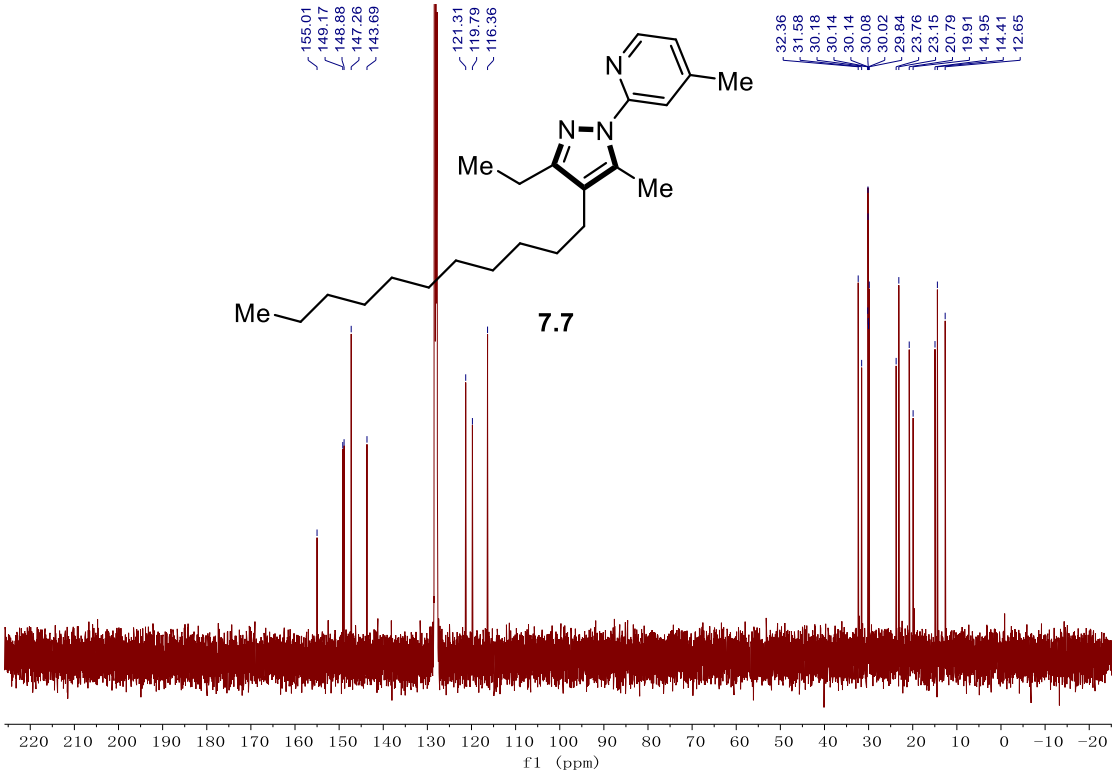


Figure 7.56 ^{1}H-NMR Spectrum of **7.8**

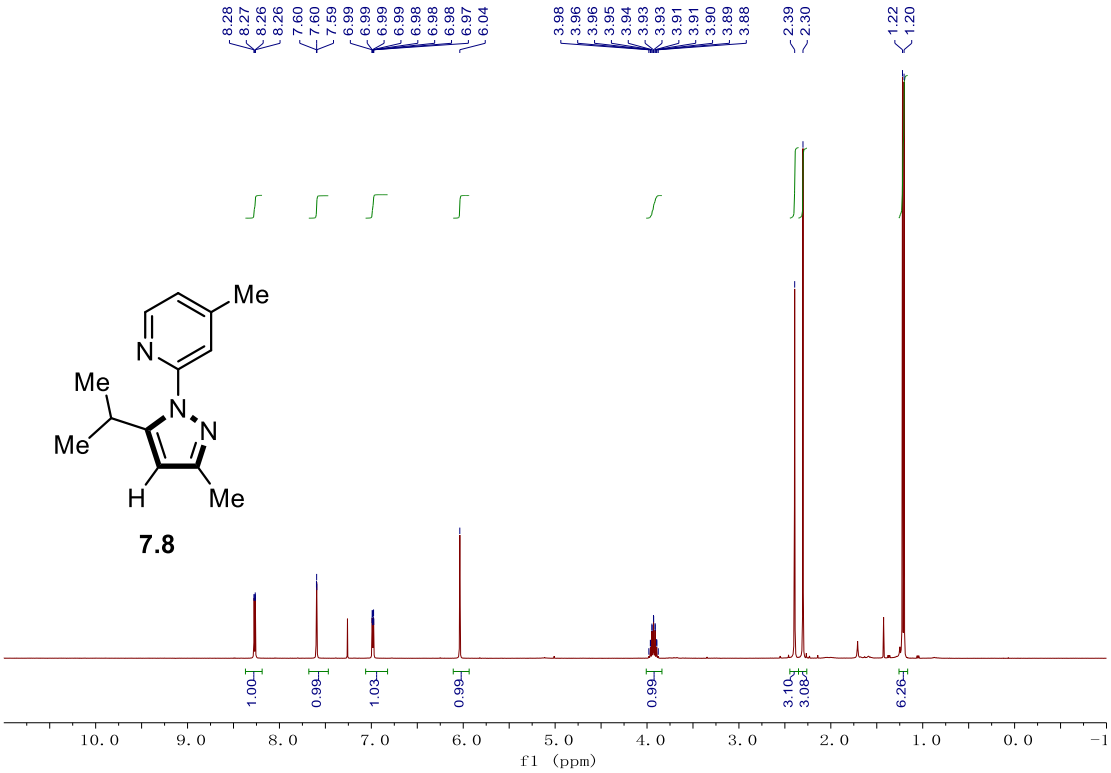


Figure 7.57 ^{13}C-NMR Spectrum of **7.8**

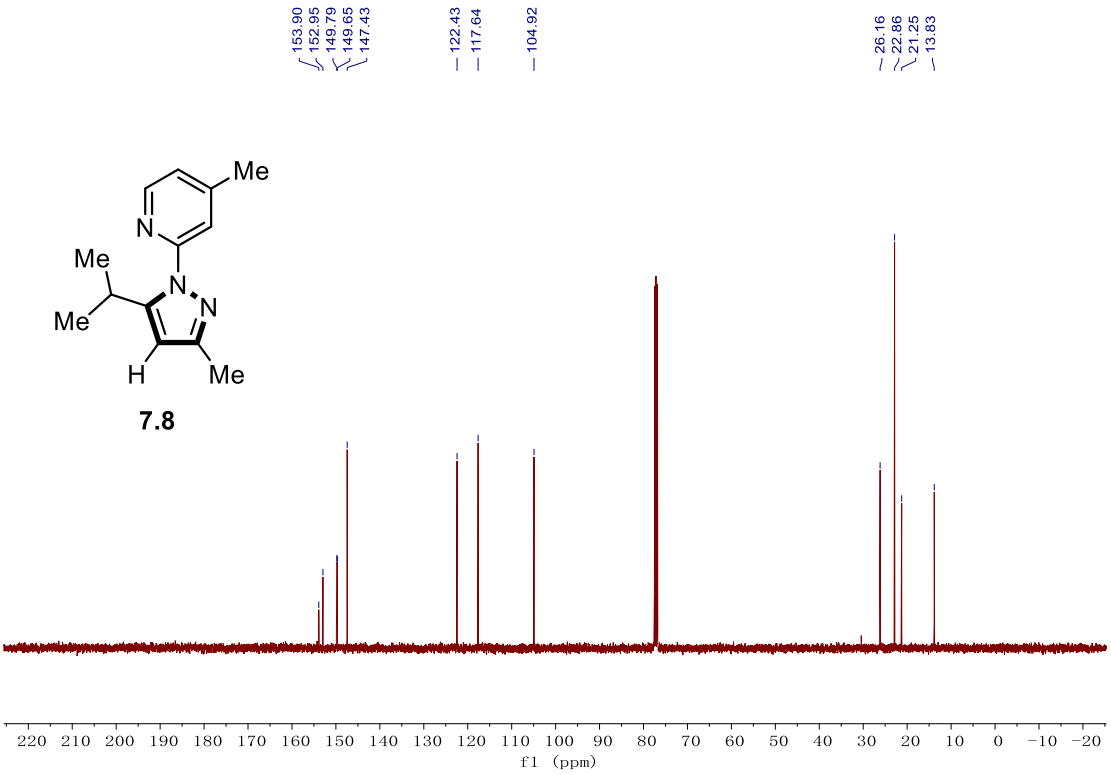


Figure 7.58 ^{1}H-NMR Spectrum of **7.9**

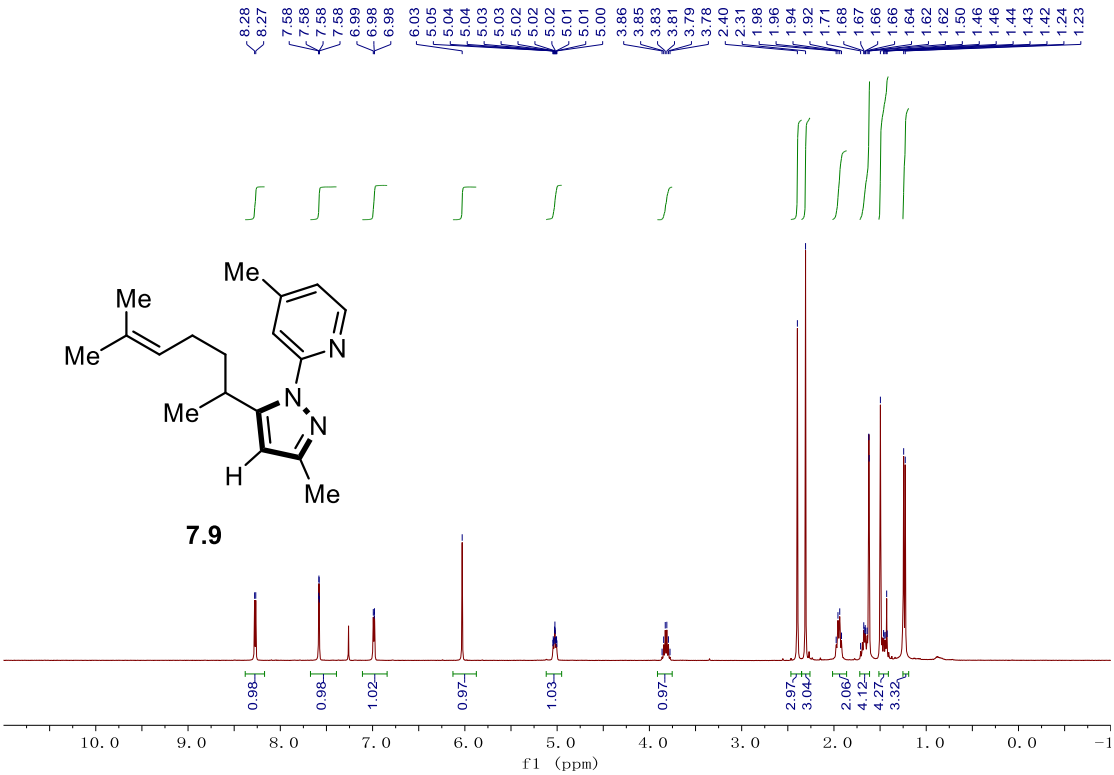


Figure 7.59 ^{13}C-NMR Spectrum of **7.9**

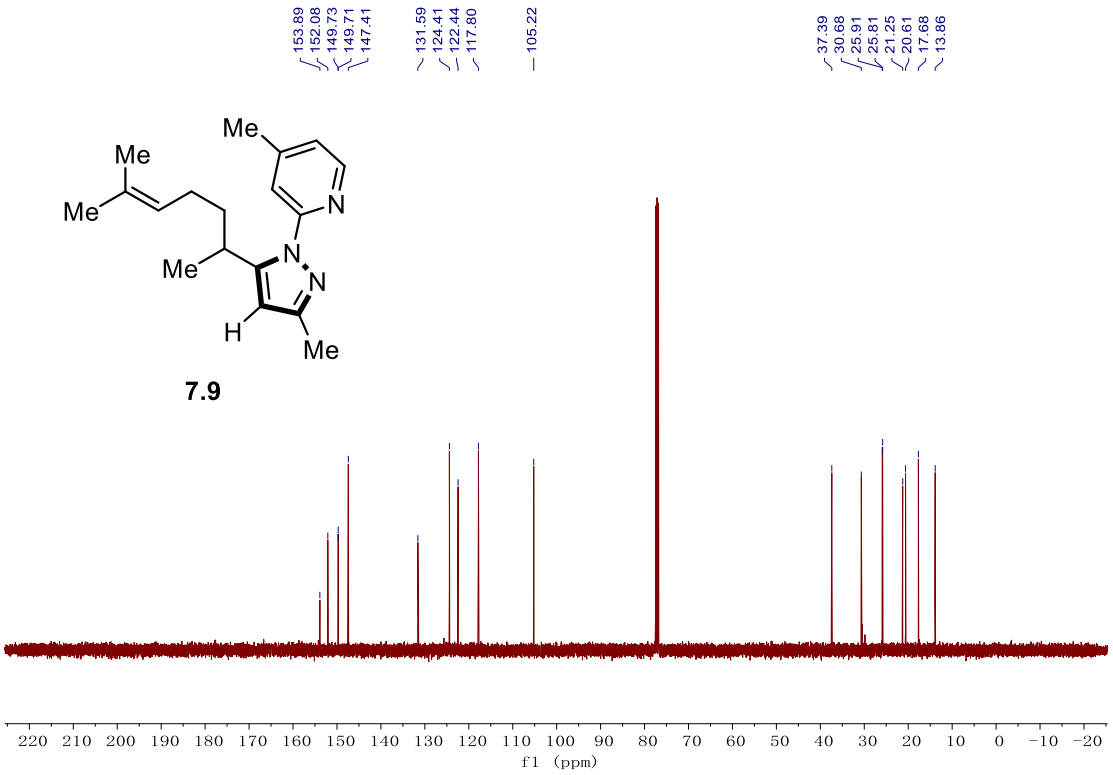


Figure 7.60 ^{1}H-NMR Spectrum of **7.10**

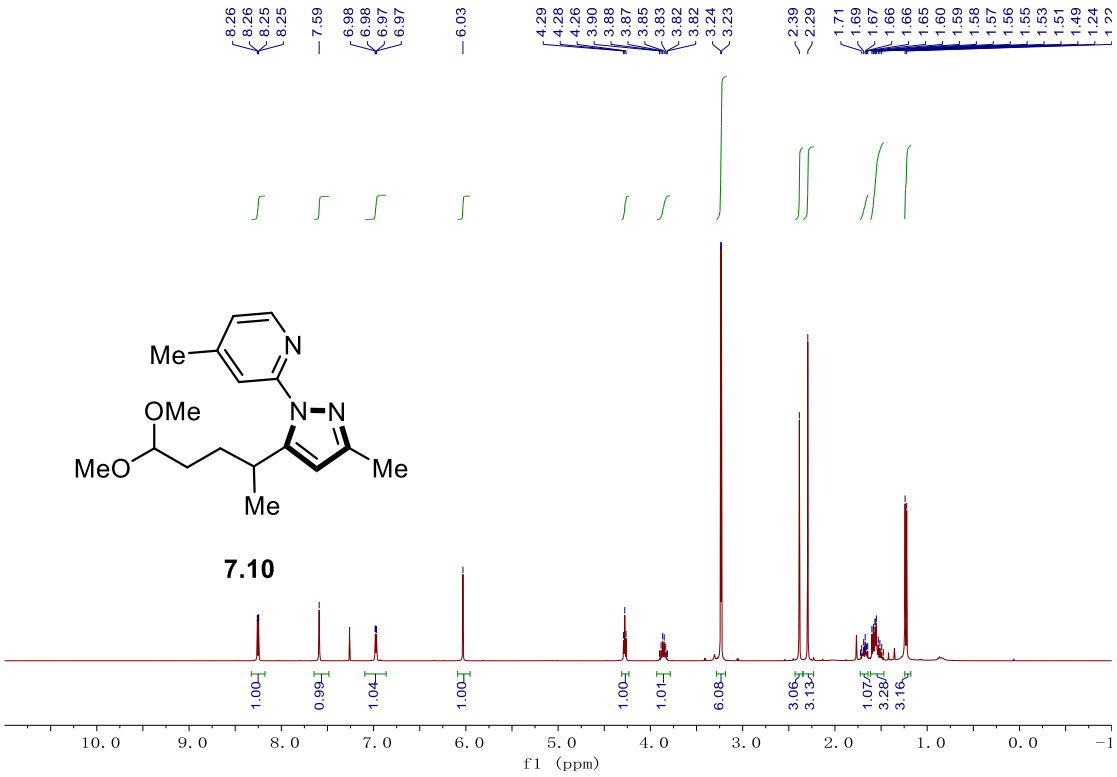


Figure 7.61 ^{13}C-NMR Spectrum of **7.10**

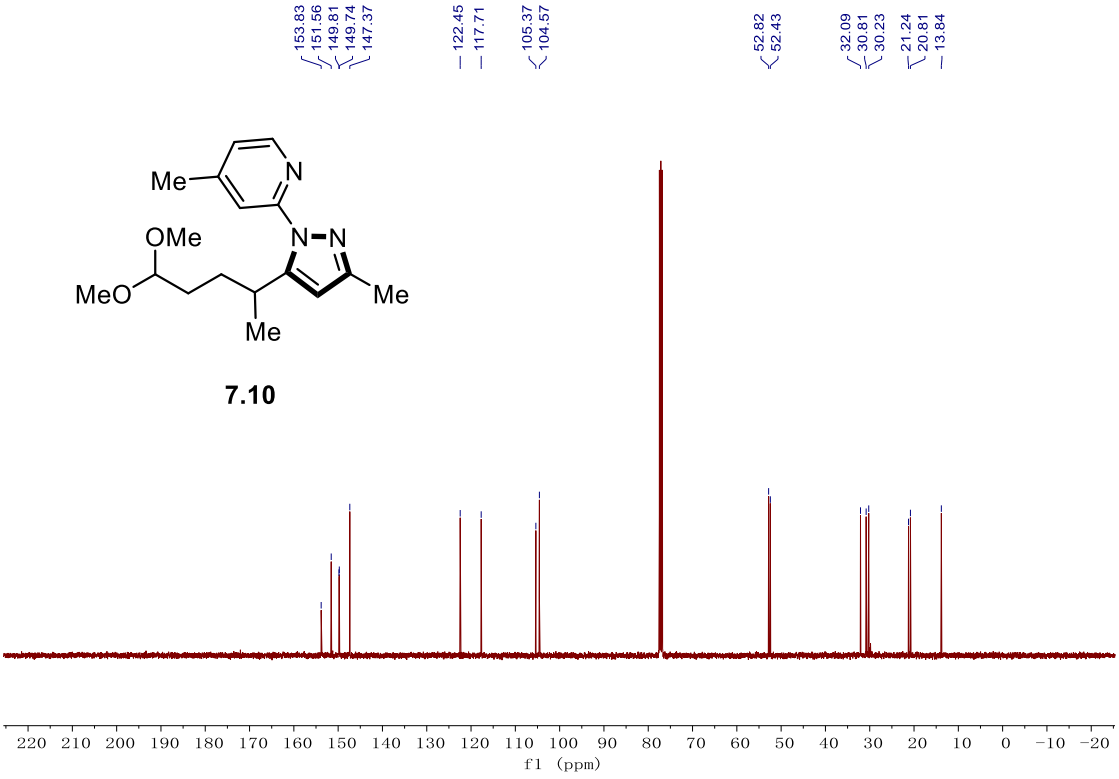


Figure 7.62 ^{1}H-NMR Spectrum of **7.11**

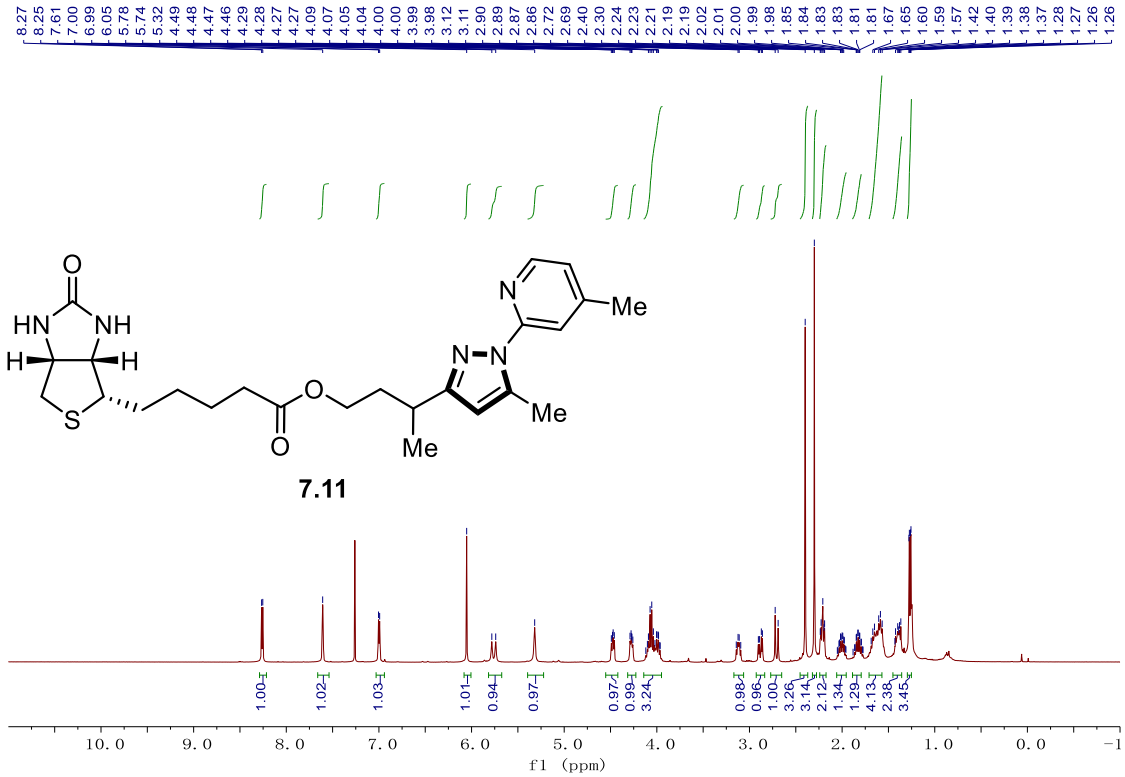


Figure 7.63 ^{13}C-NMR Spectrum of **7.11**

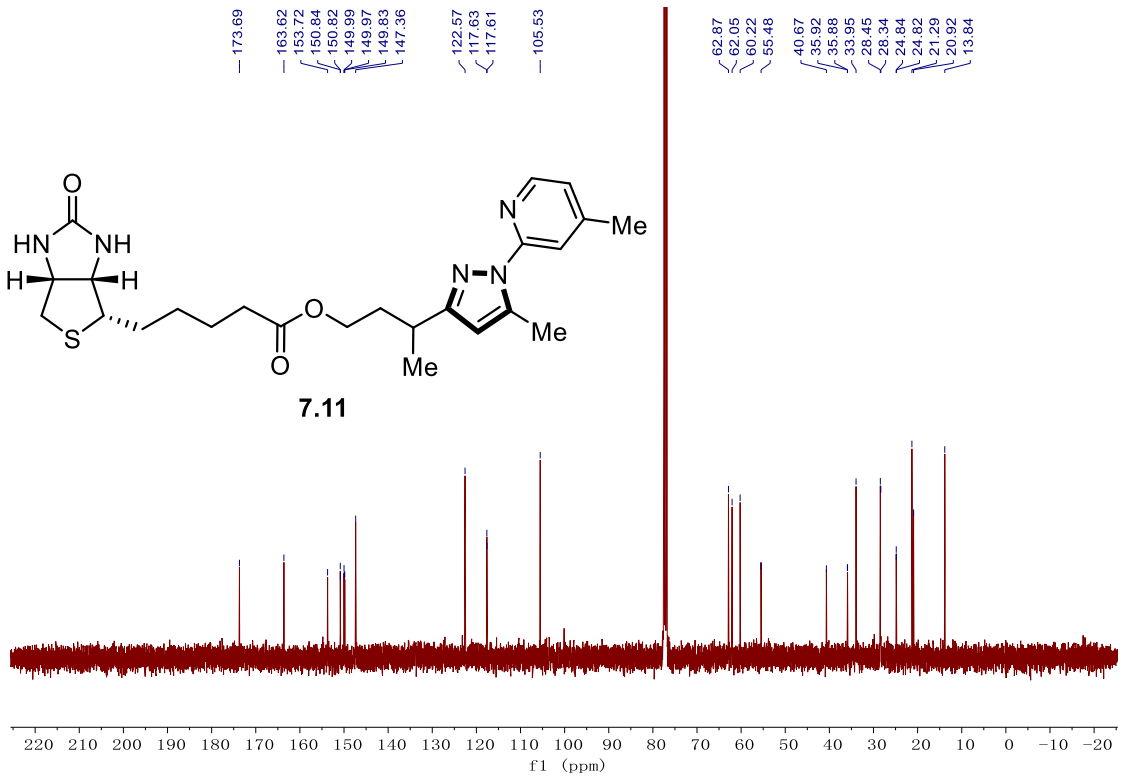


Figure 7.64 ^{1}H-NMR Spectrum of **7.12**

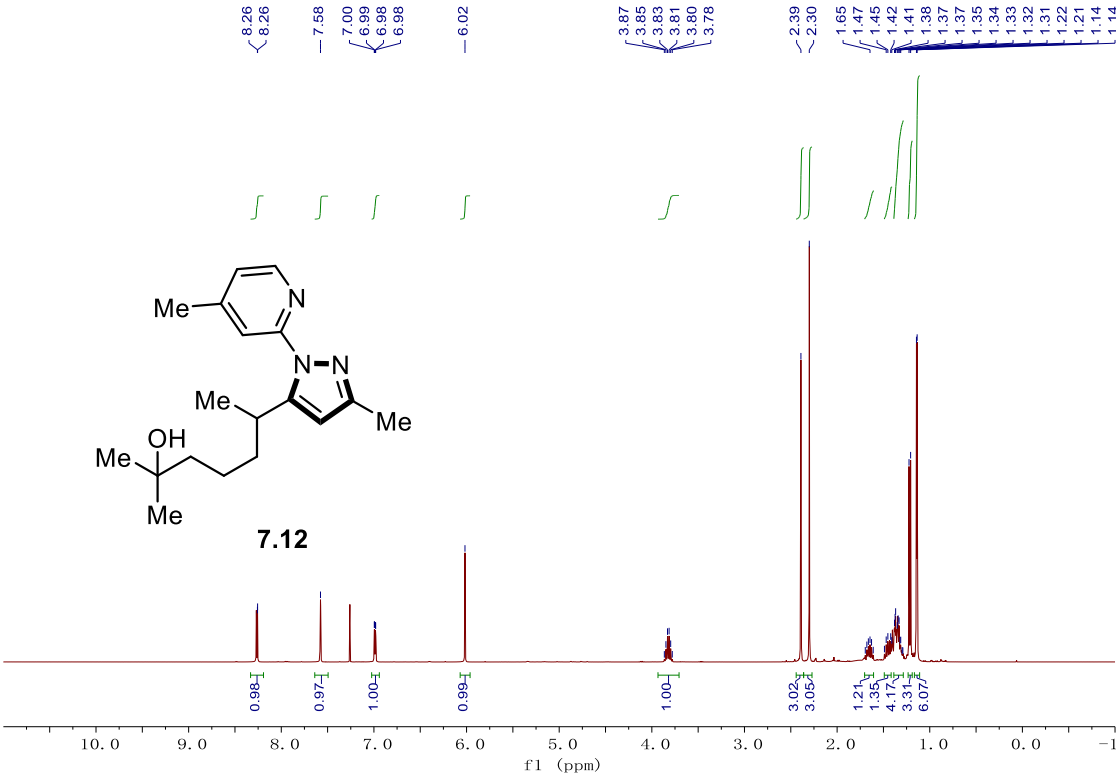


Figure 7.65 ^{13}C-NMR Spectrum of **7.12**

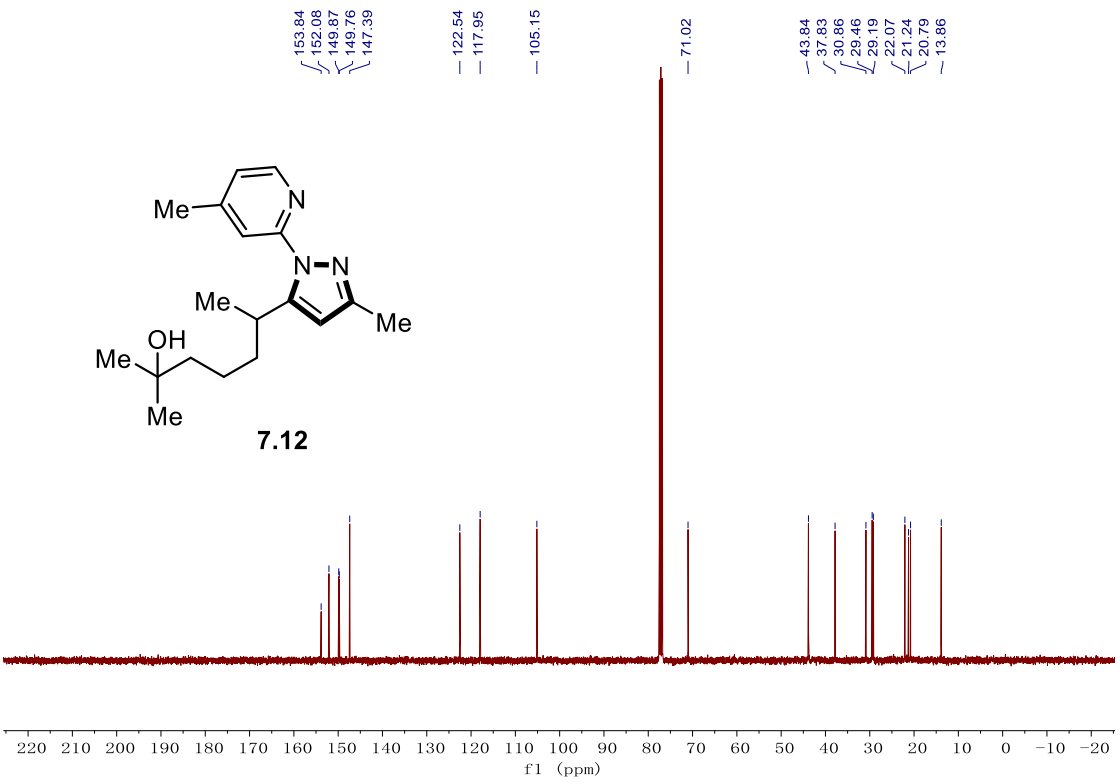


Figure 7.66 ^{1}H-NMR Spectrum of **7.15**

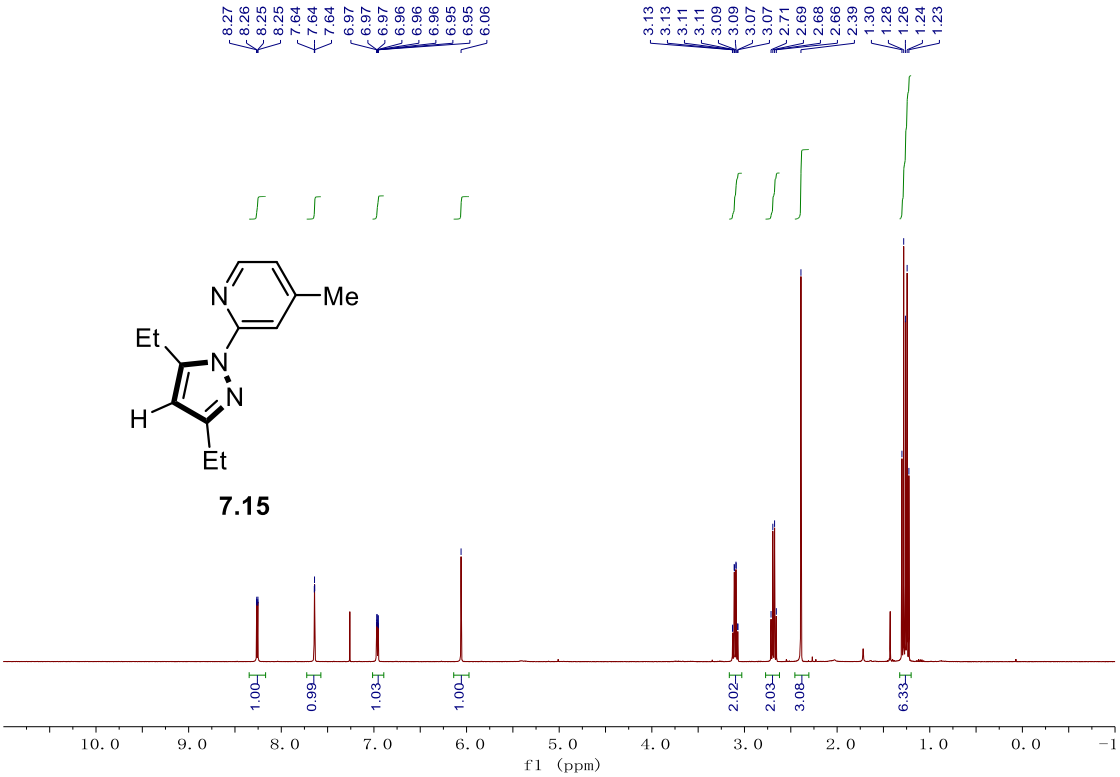


Figure 7.67 ^{13}C-NMR Spectrum of **7.15**

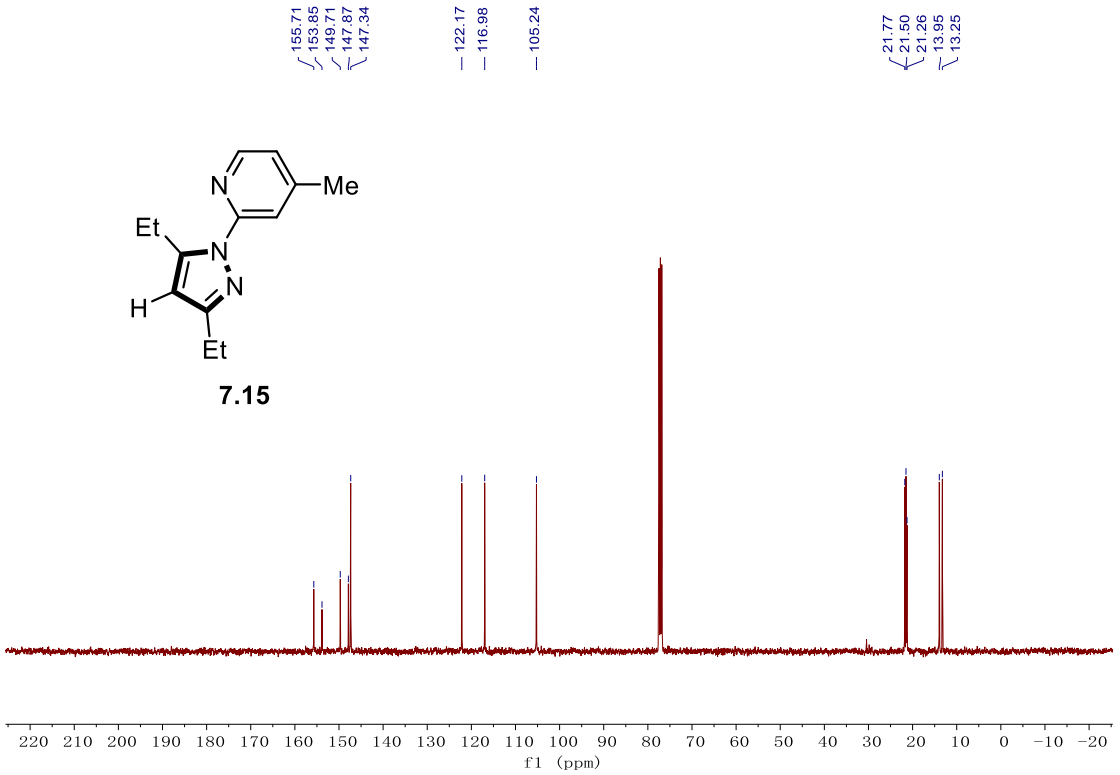


Figure 7.68 ^{1}H-NMR Spectrum of **7.20**

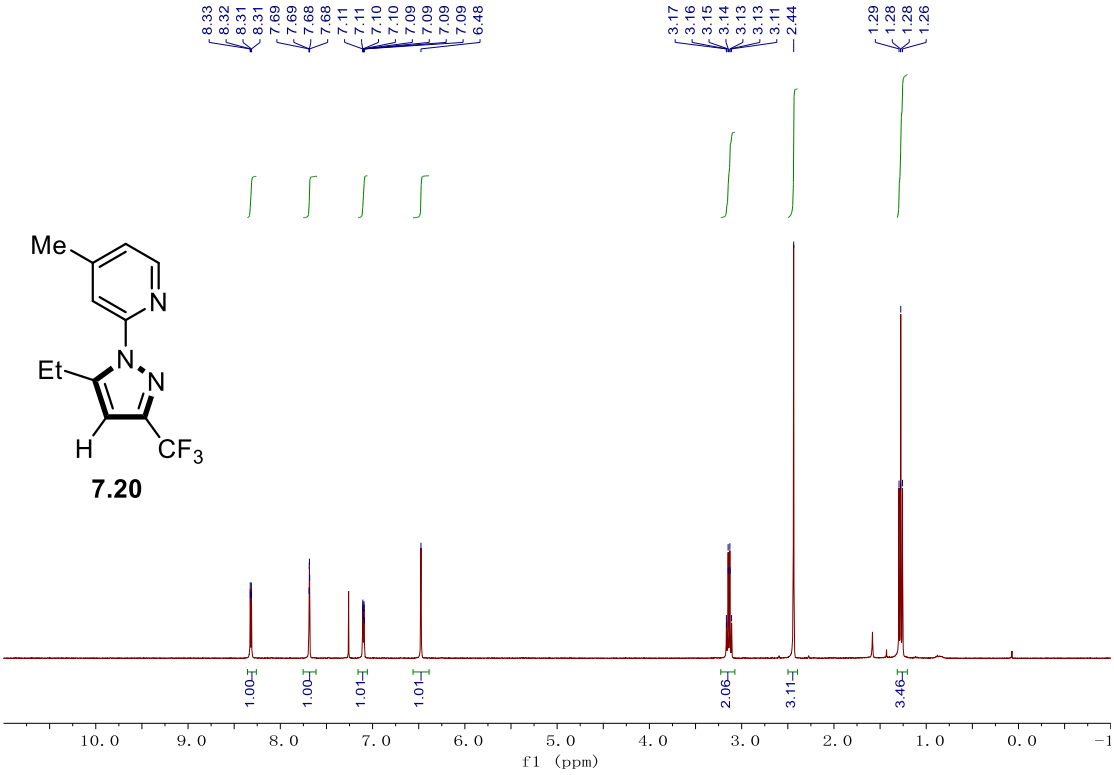


Figure 7.69 ^{13}C-NMR Spectrum of **7.20**

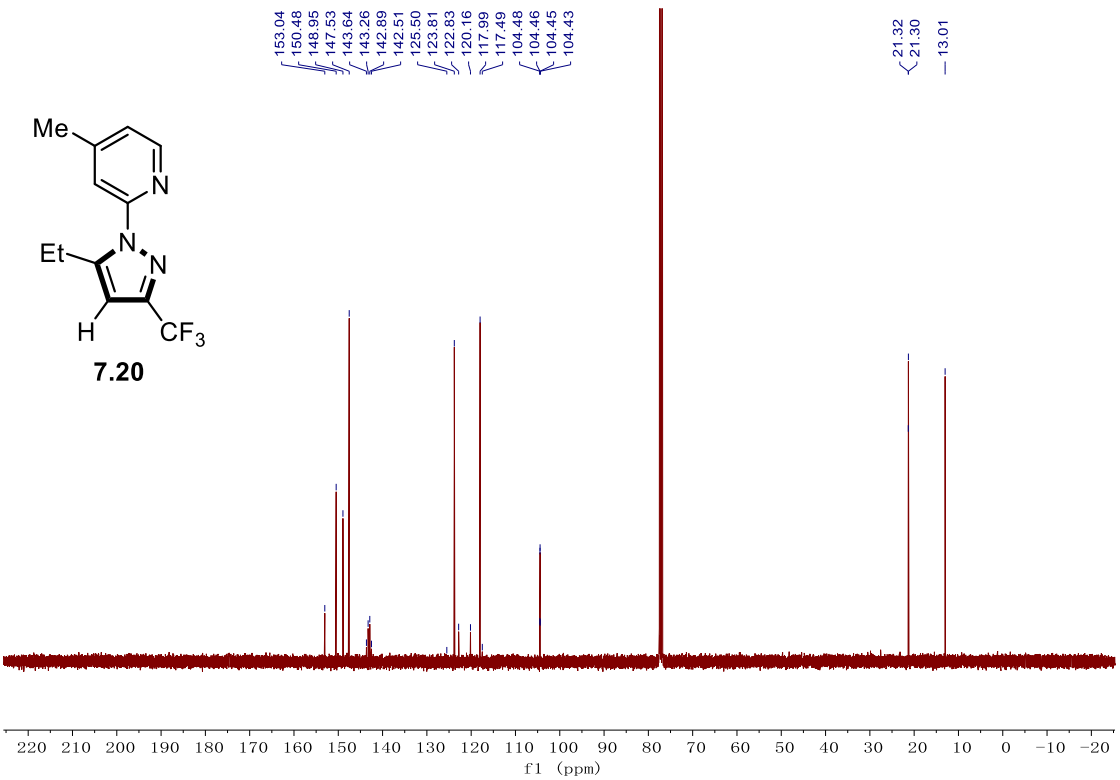


Figure 7.70 ^{1}H-NMR Spectrum of **7.21**

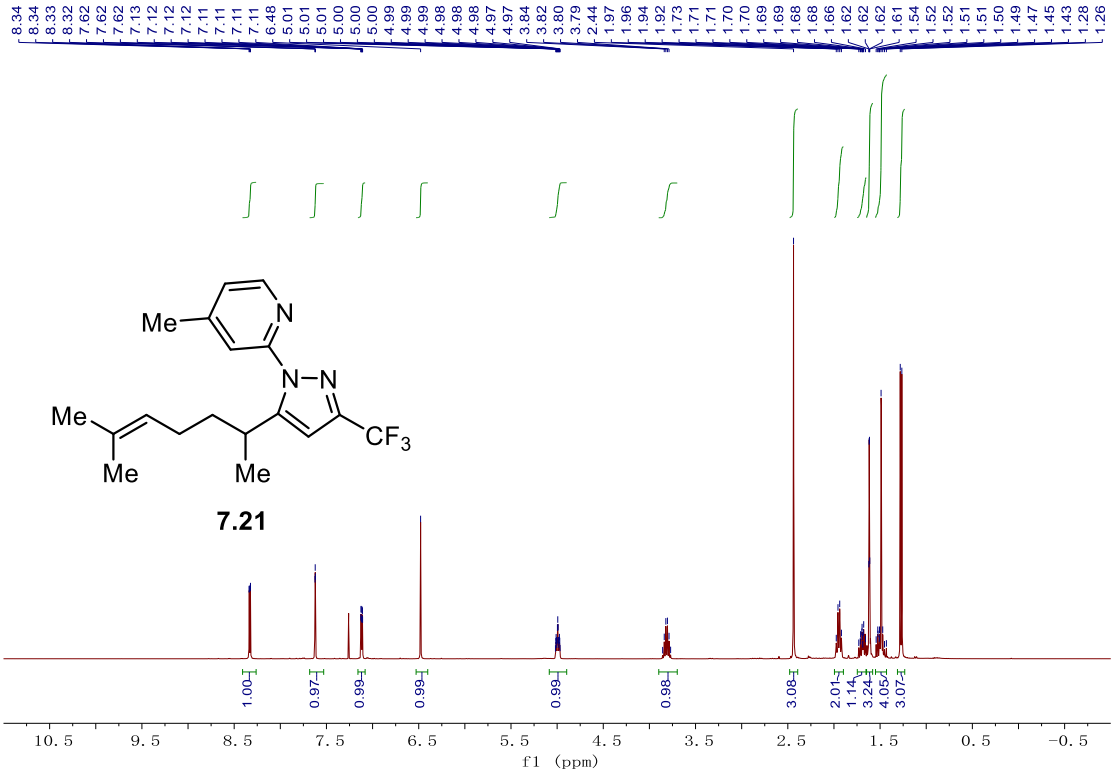


Figure 7.71 ^{13}C-NMR Spectrum of **7.21**

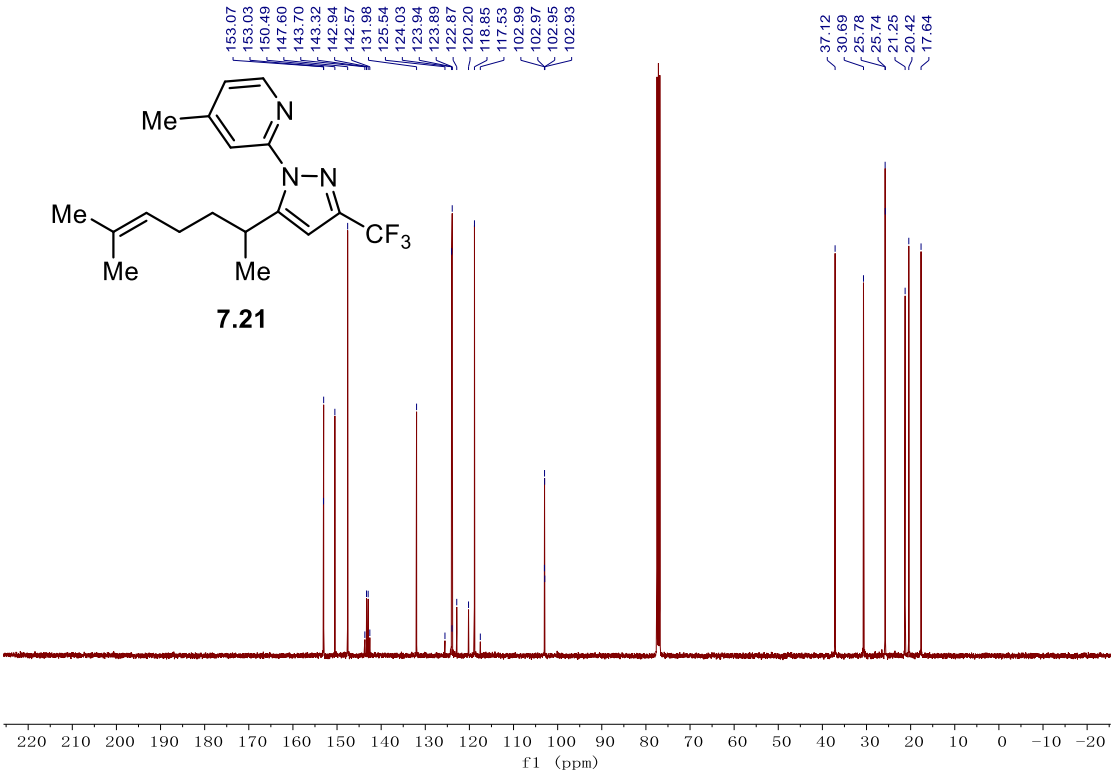


Figure 7.72 ^{1}H-NMR Spectrum of **7.23**

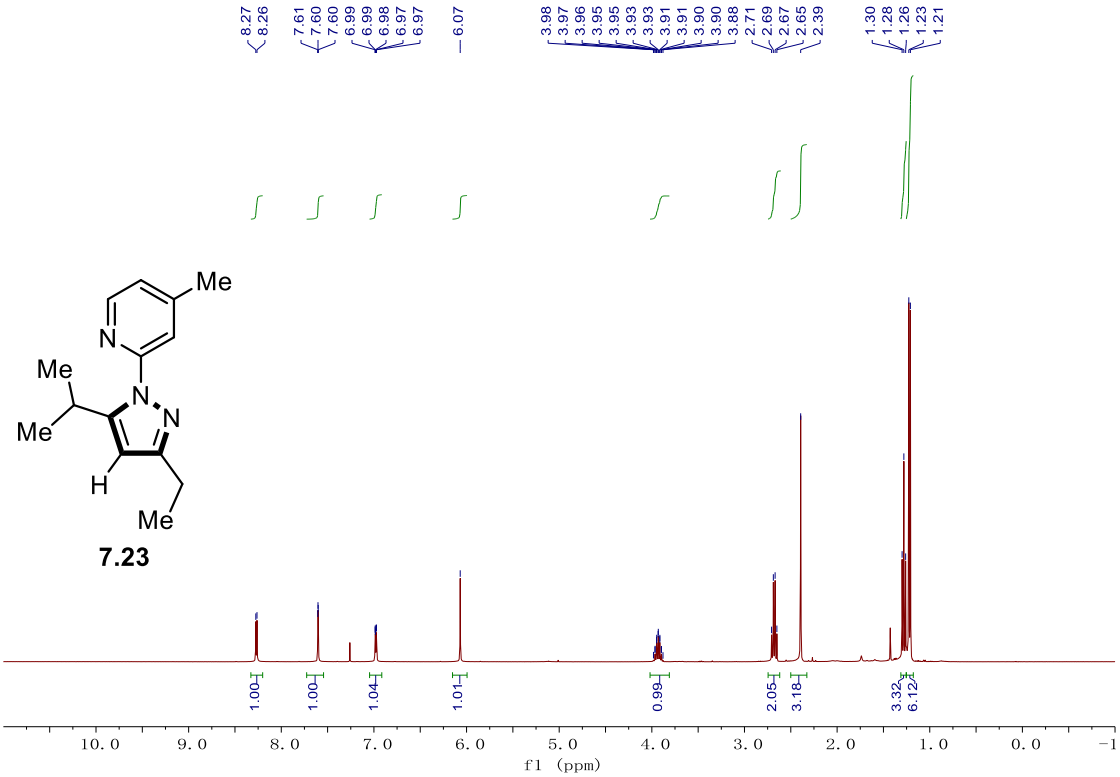


Figure 7.73 ^{13}C-NMR Spectrum of **7.23**

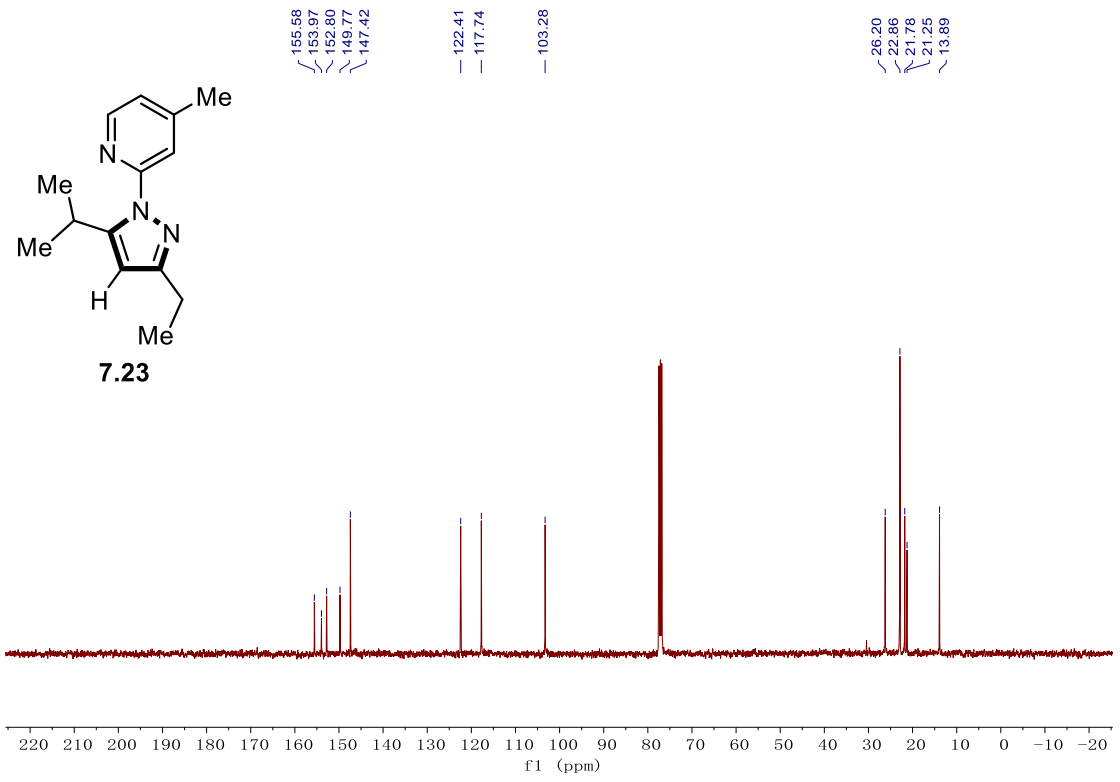


Figure 7.74 ^{1}H-NMR Spectrum of **7.25**

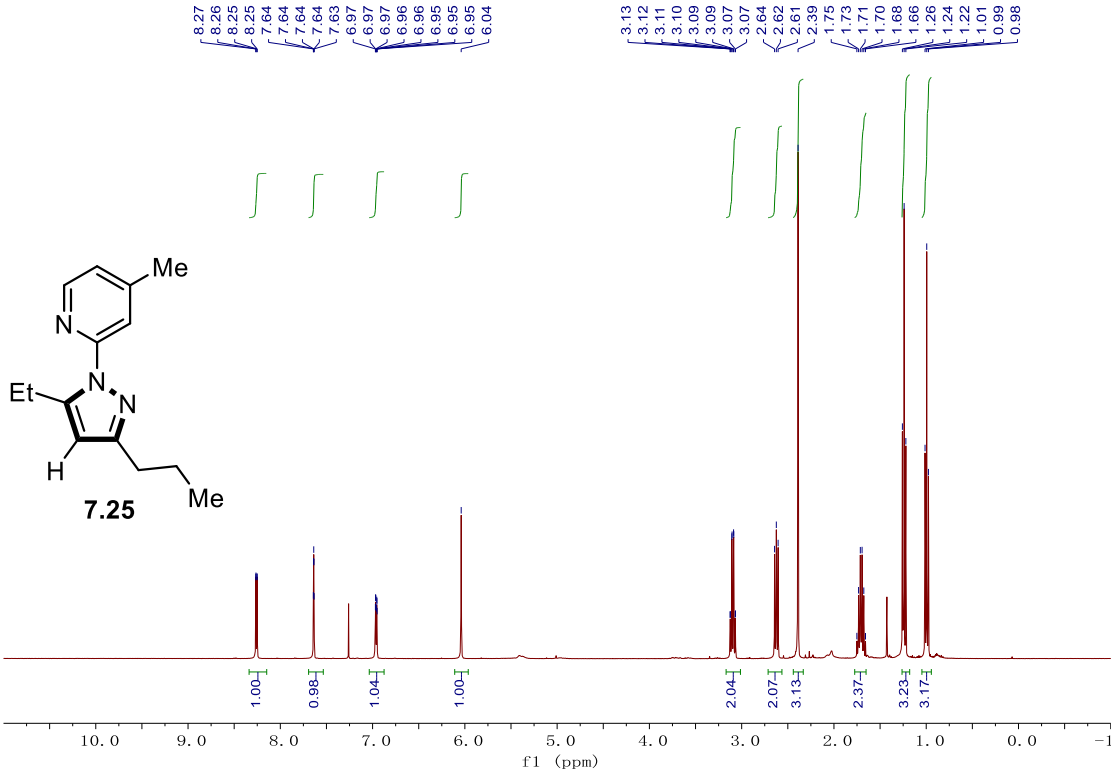


Figure 7.75 ^{13}C-NMR Spectrum of **7.25**

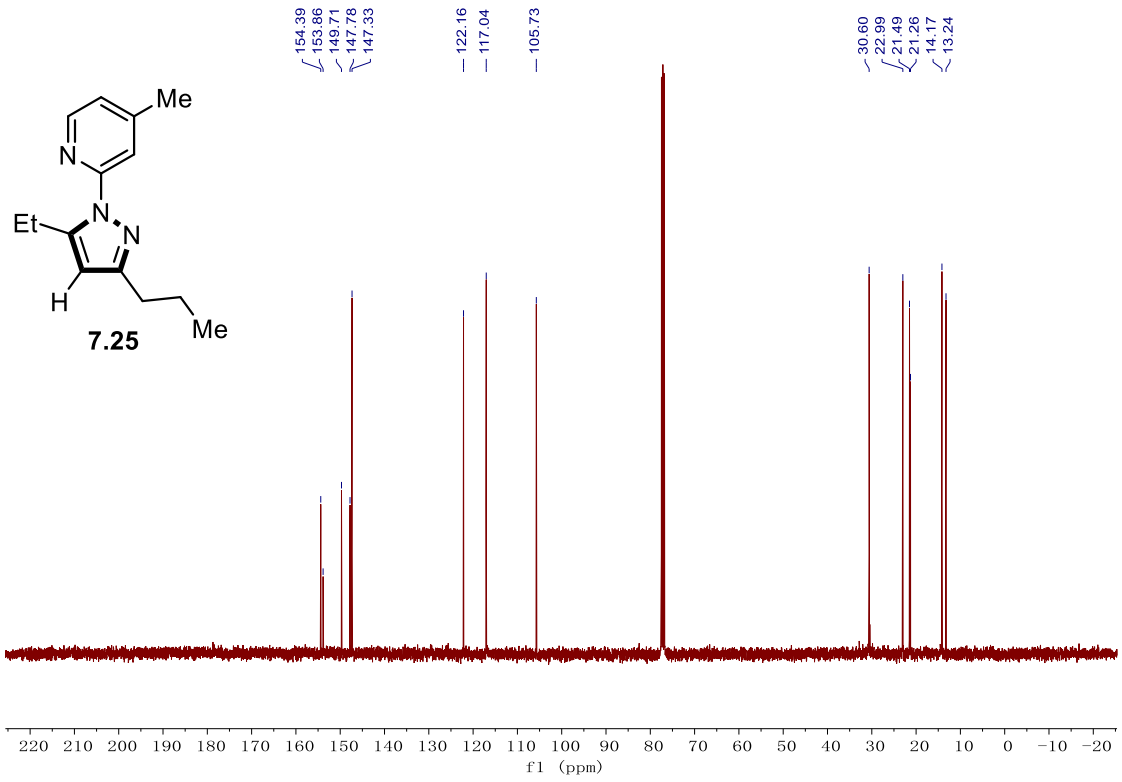


Figure 7.76 ^{1}H-NMR Spectrum of **7.26**

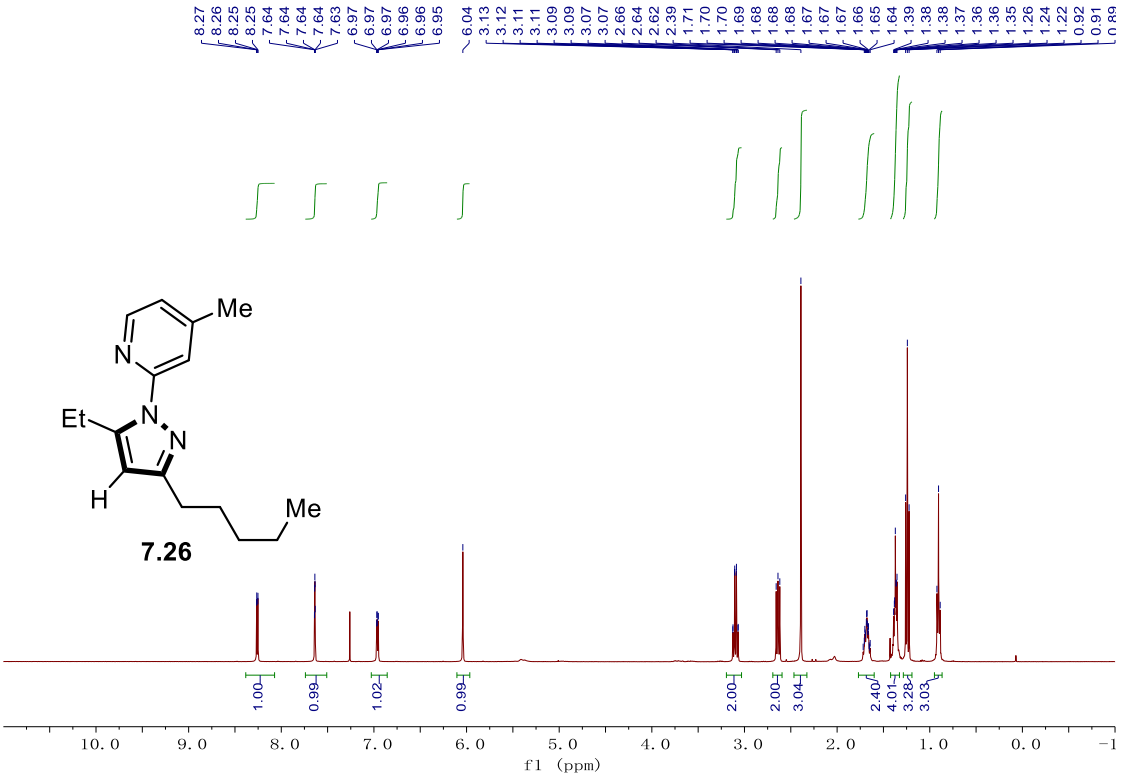


Figure 7.77 ^{13}C-NMR Spectrum of **7.26**

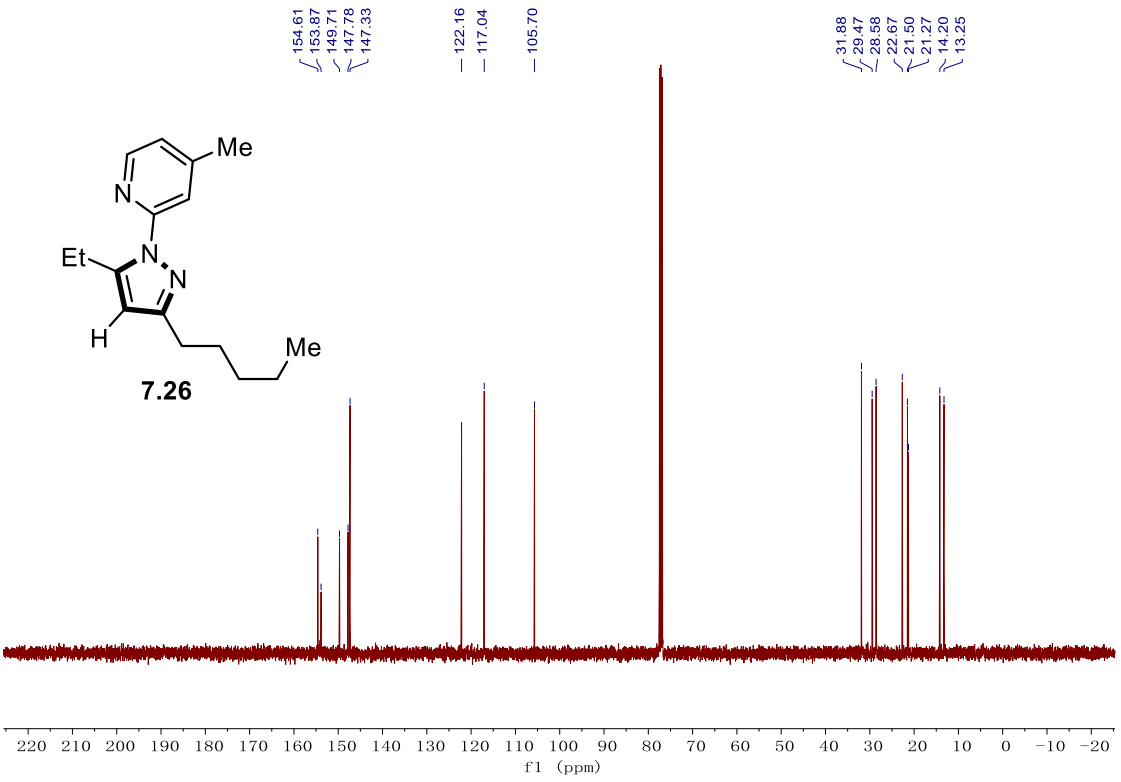


Figure 7.78 ^{1}H-NMR Spectrum of **7.29**

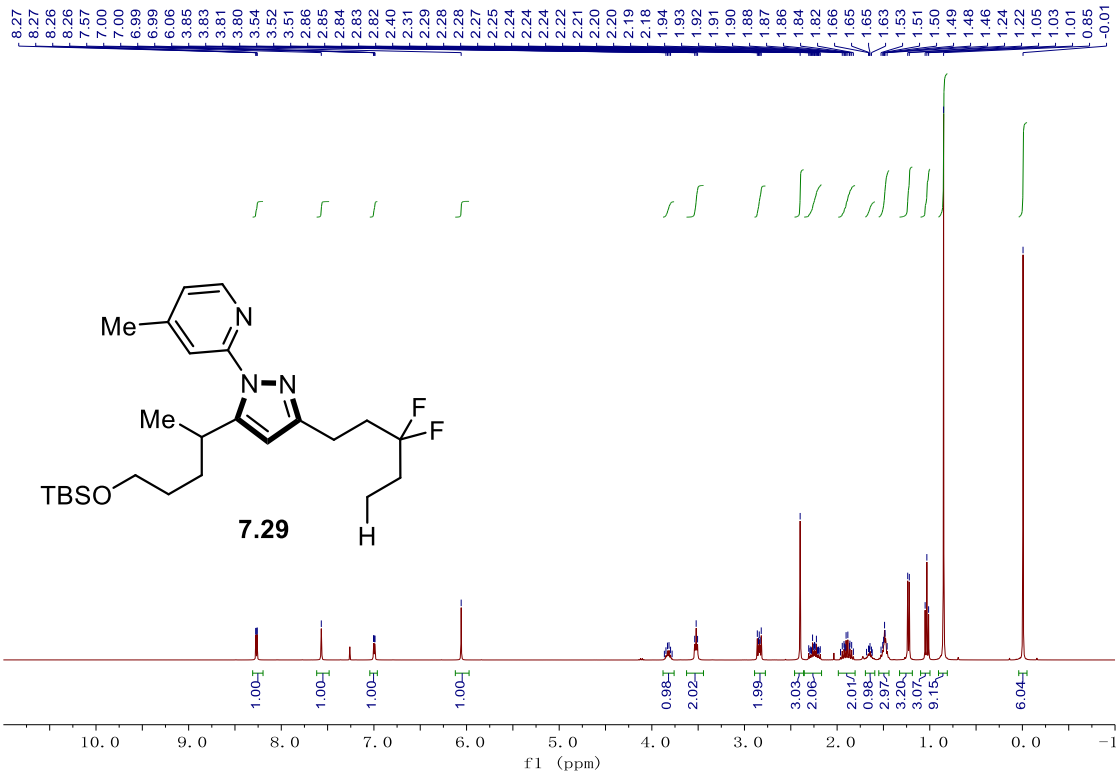


Figure 7.79 ^{13}C-NMR Spectrum of **7.29**

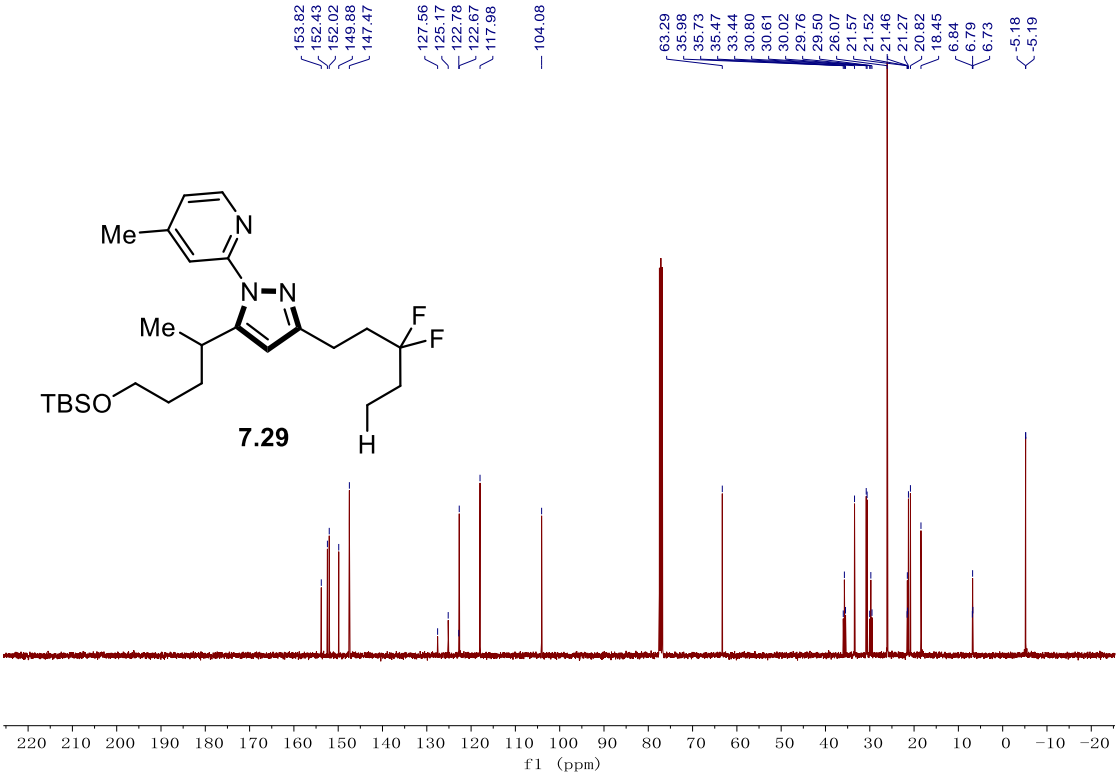


Figure 7.80 ^{1}H-NMR Spectrum of **7.30**

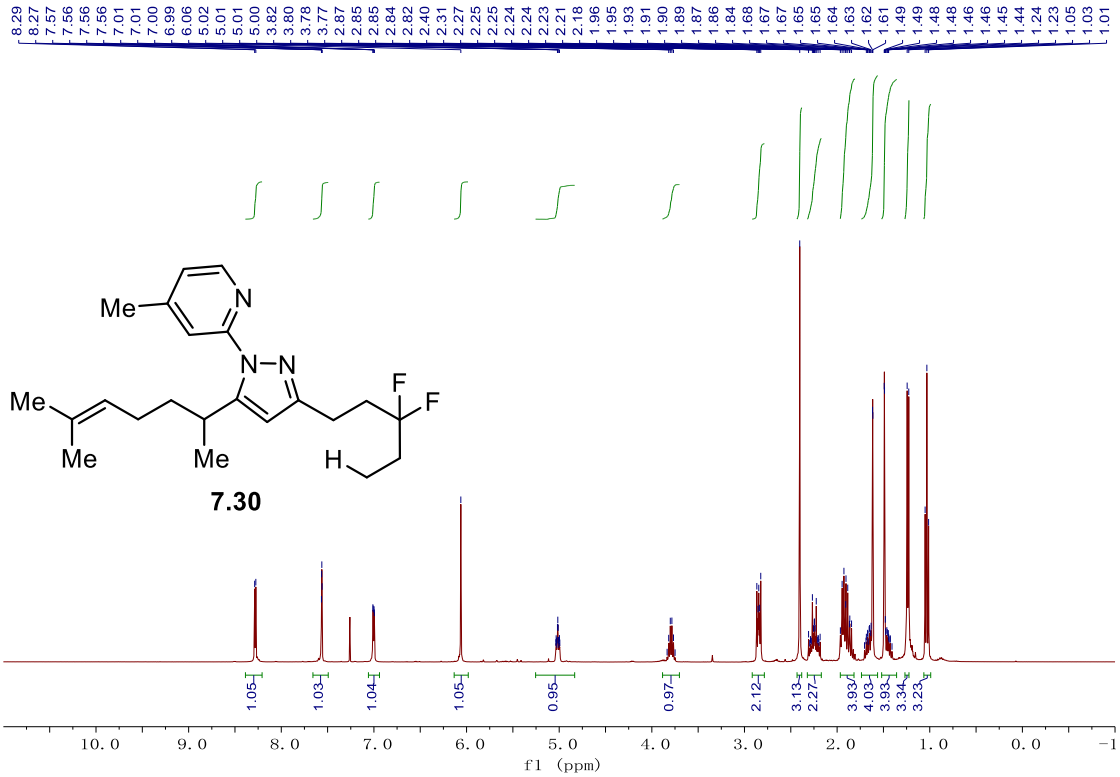


Figure 7.81 ^{13}C-NMR Spectrum of **7.30**

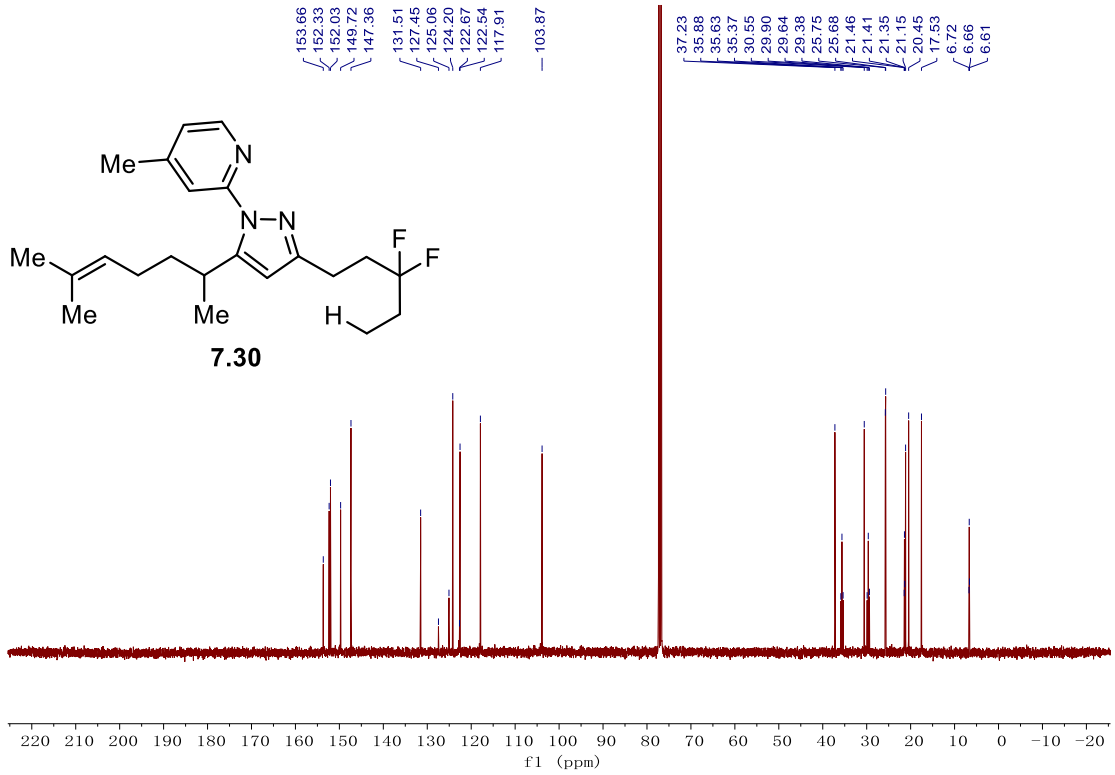


Figure 7.82 ^{1}H-NMR Spectrum of **7.31**

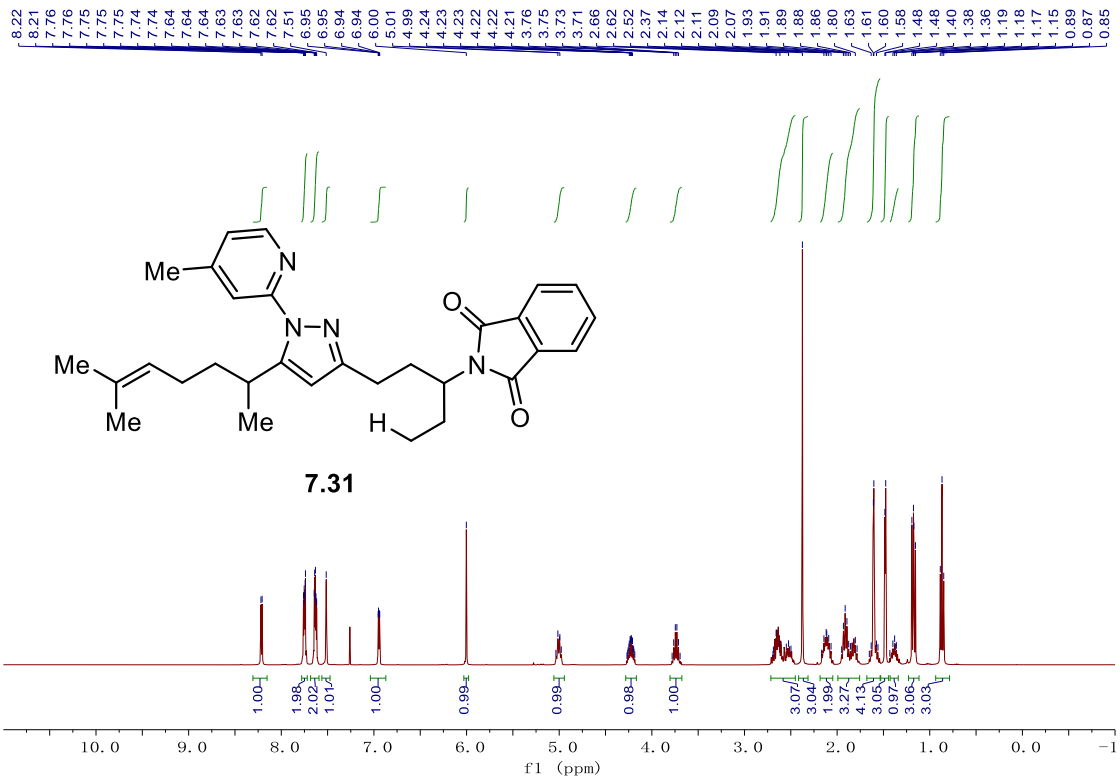


Figure 7.83 ^{13}C-NMR Spectrum of **7.31**

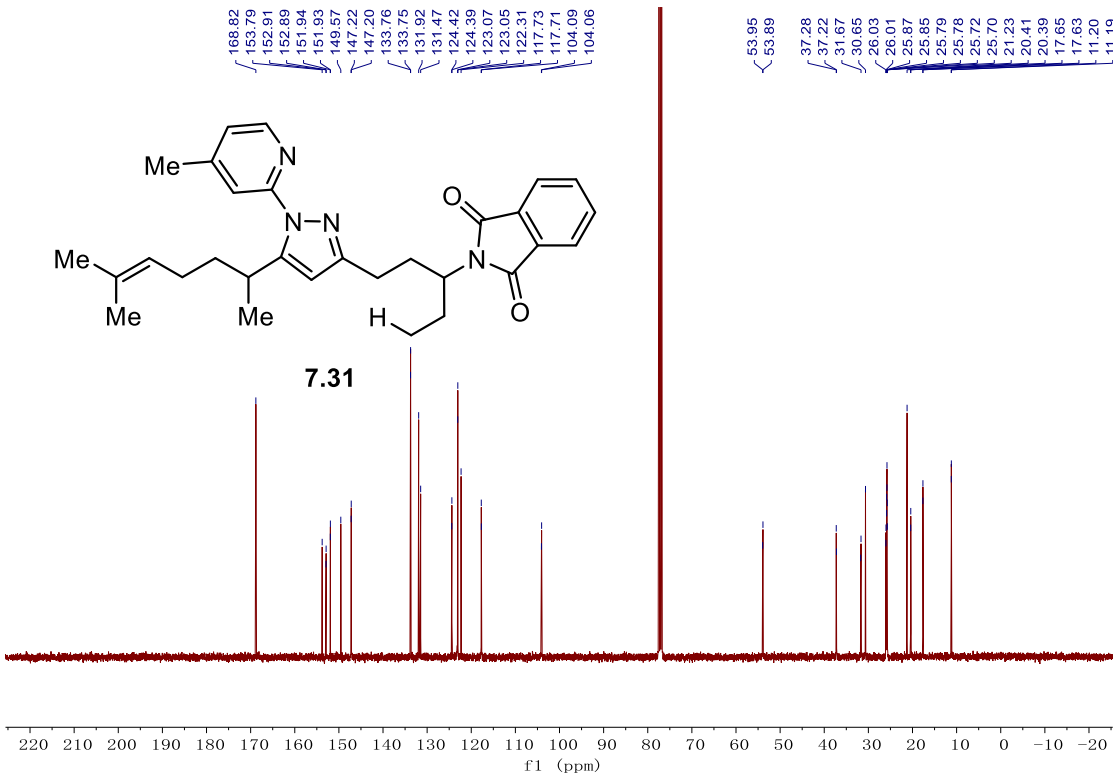


Figure 7.84 ^{1}H-NMR Spectrum of **7.32**

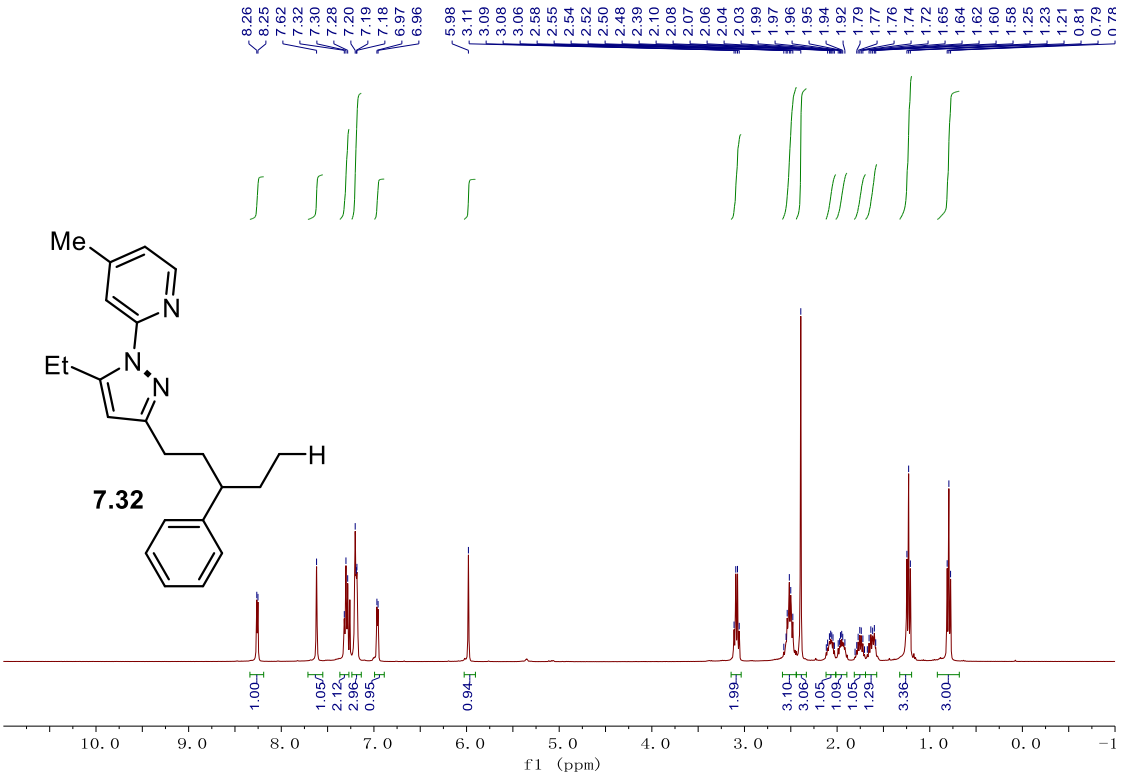


Figure 7.85 ^{13}C-NMR Spectrum of **7.32**

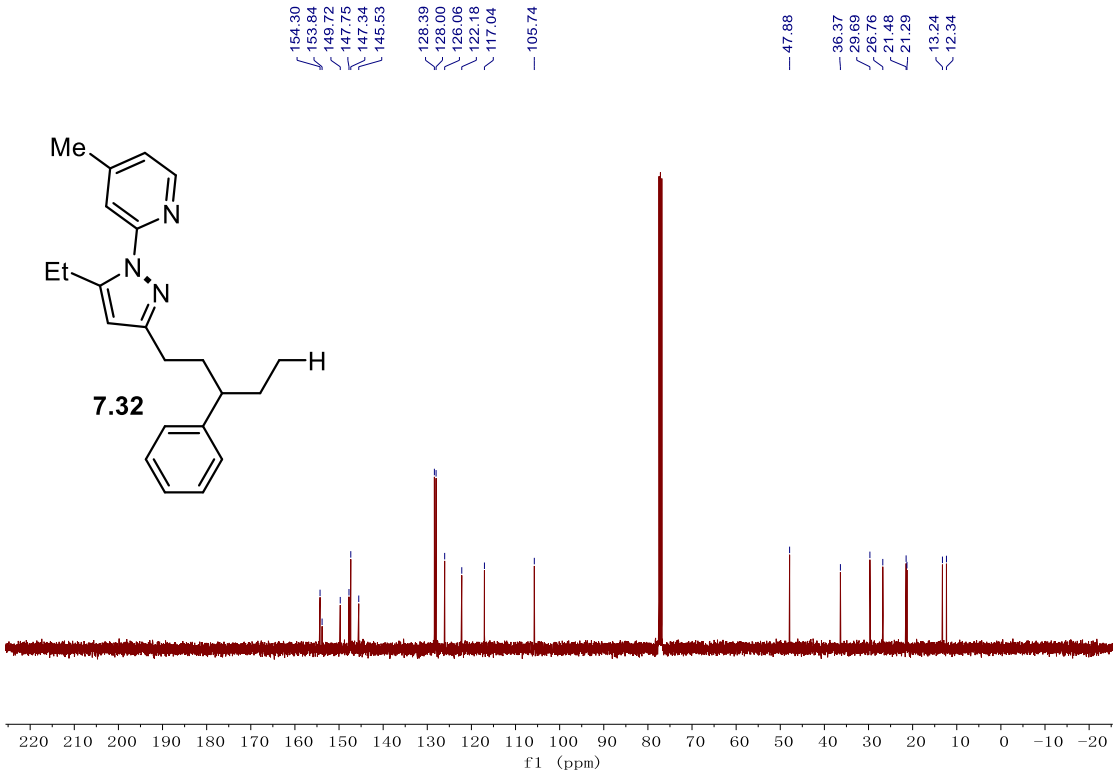


Figure 7.86 ^{1}H-NMR Spectrum of **7.33**

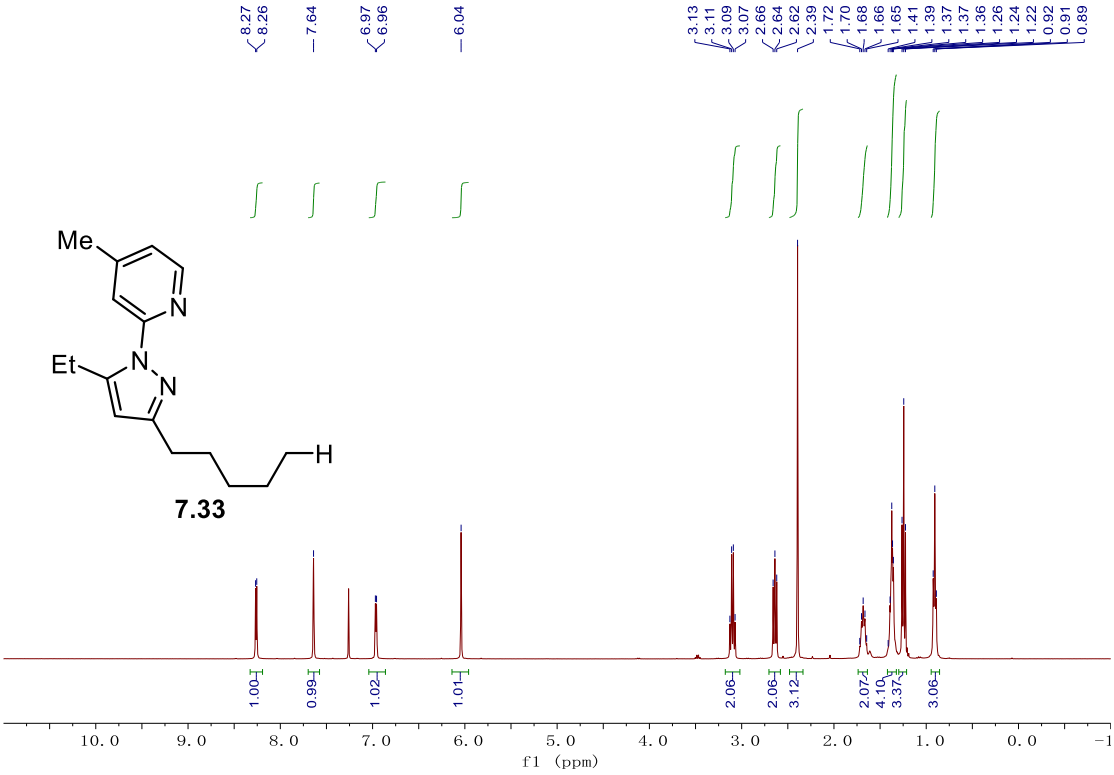


Figure 7.87 ^{13}C-NMR Spectrum **of 7.33**

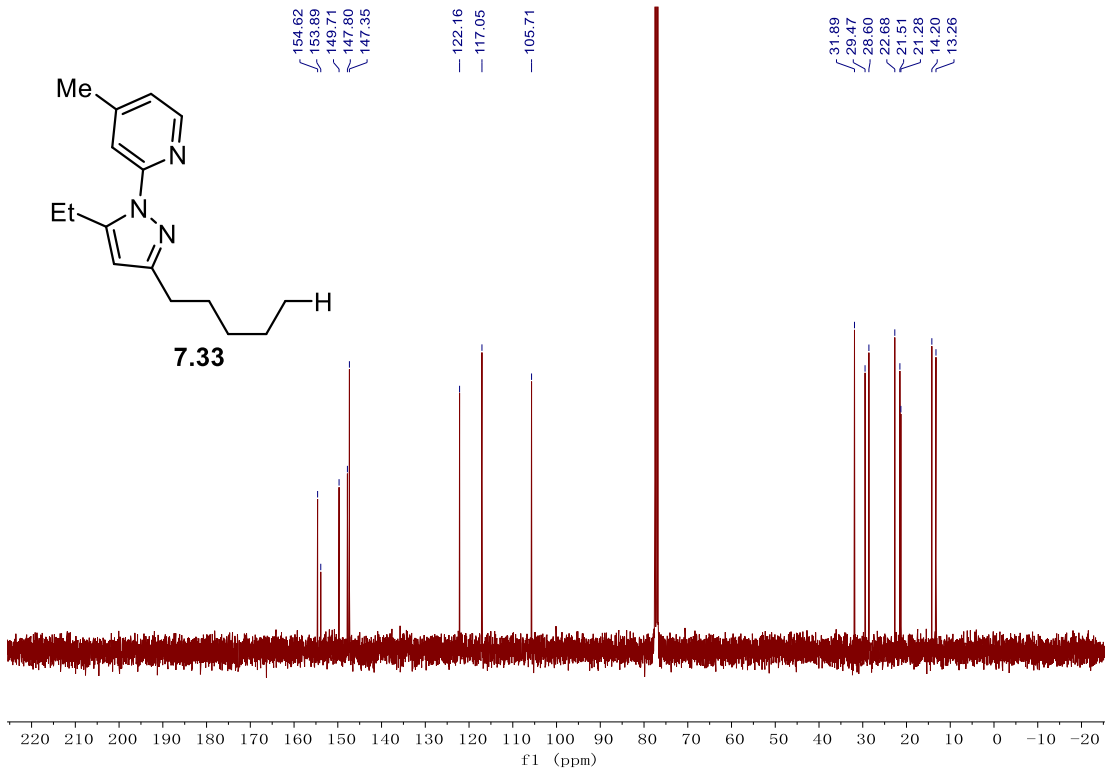


Figure 7.88 ^{1}H-NMR Spectrum of **7.34**

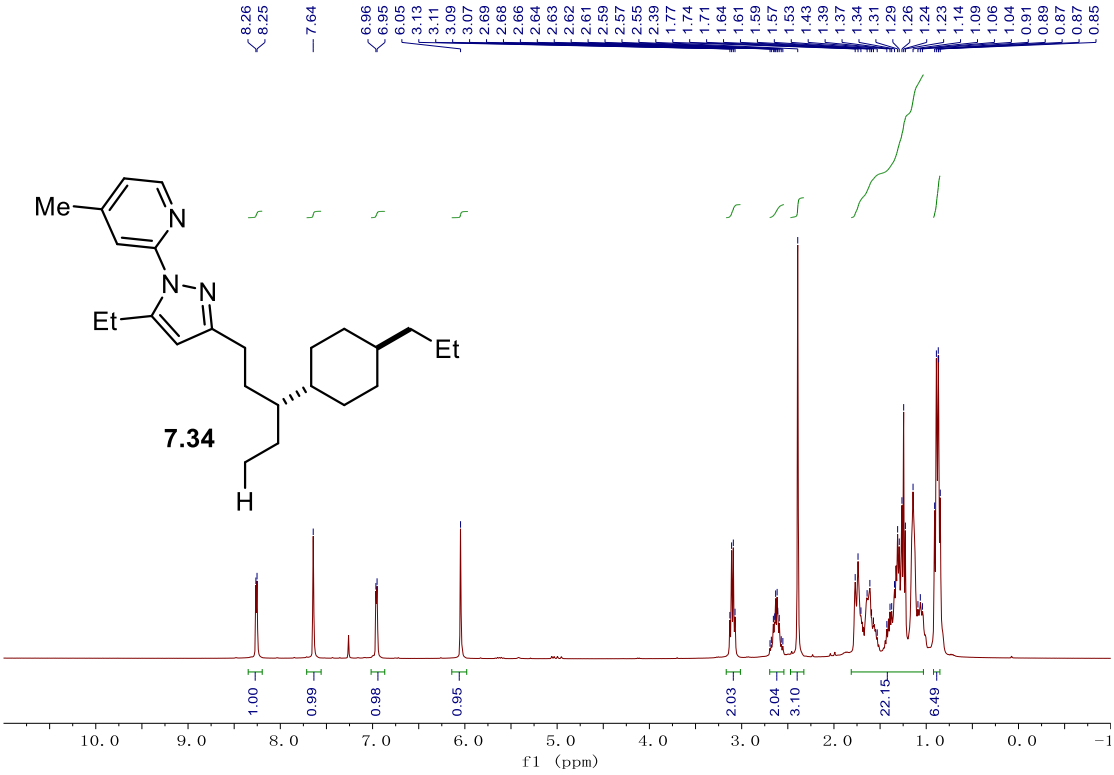


Figure 7.89 ^{13}C-NMR Spectrum of **7.34**

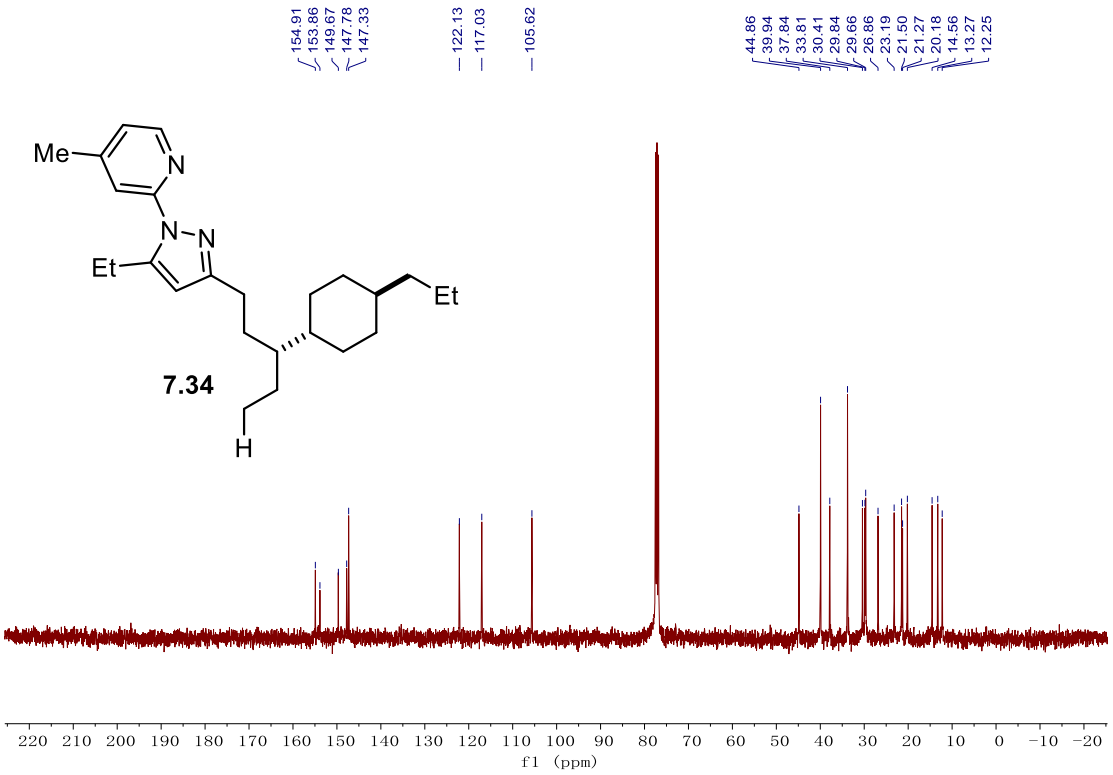


Figure 7.90 ^{1}H-NMR Spectrum of **7.35**

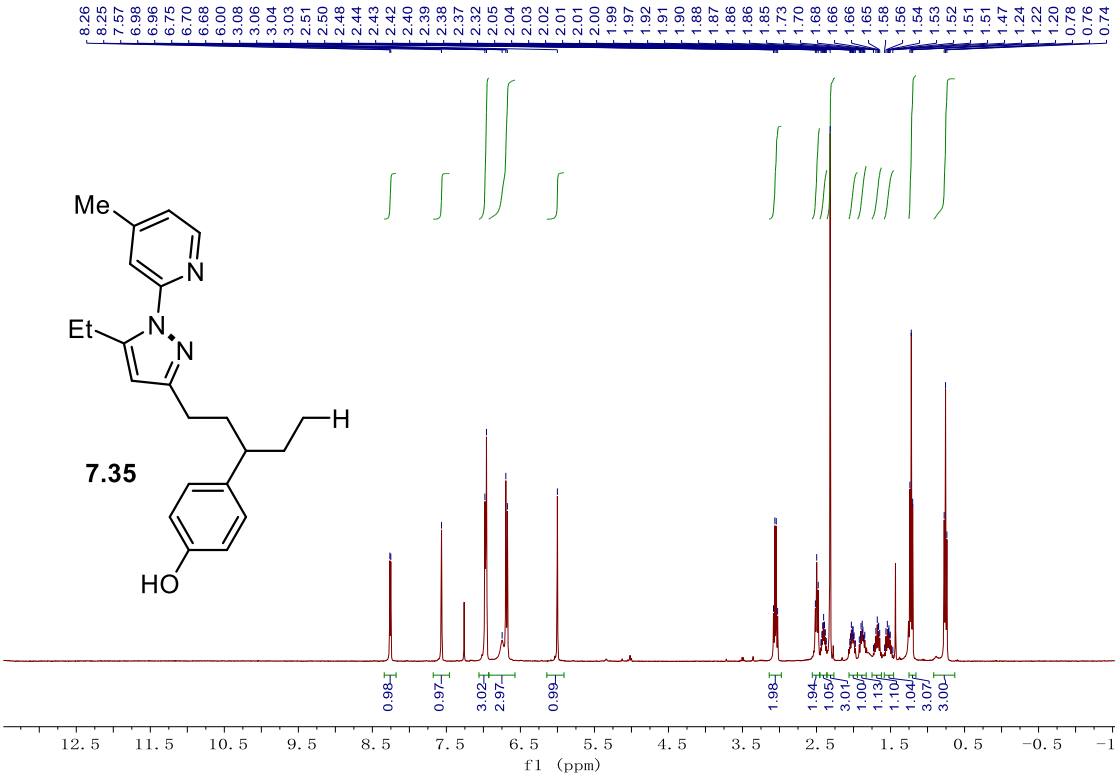


Figure 7.91 ^{13}C-NMR Spectrum of **7.35**

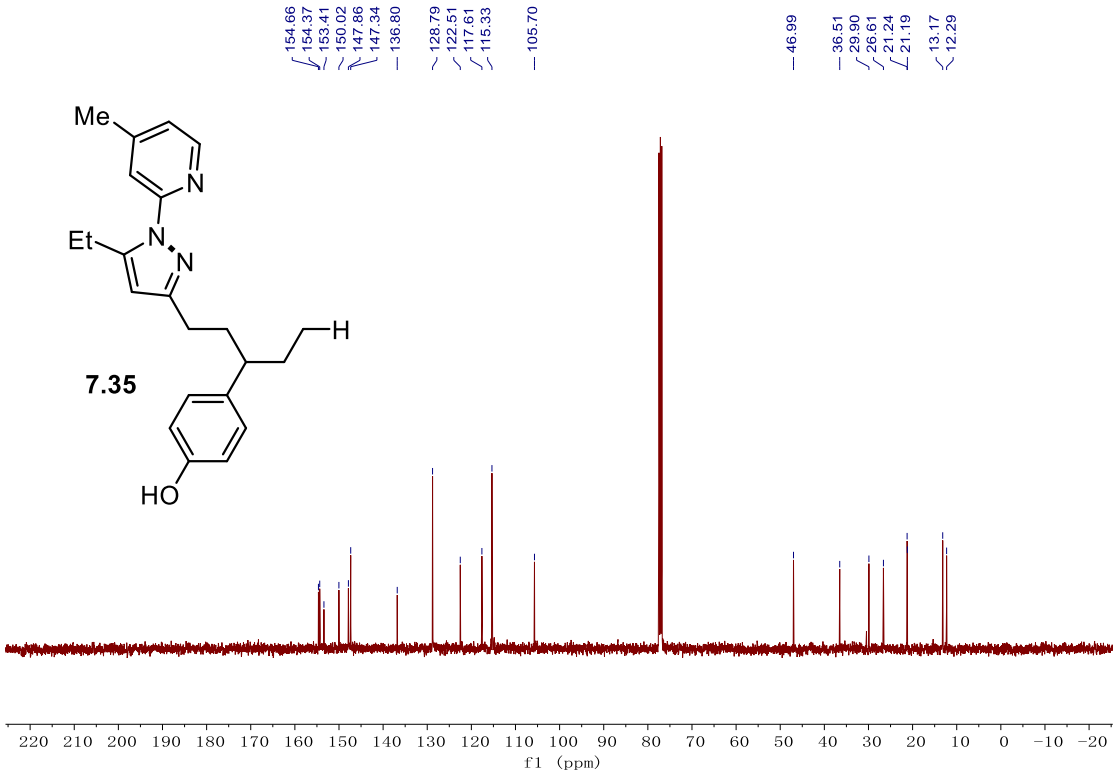


Figure 7.92 ^{1}H-NMR Spectrum of **7.36**

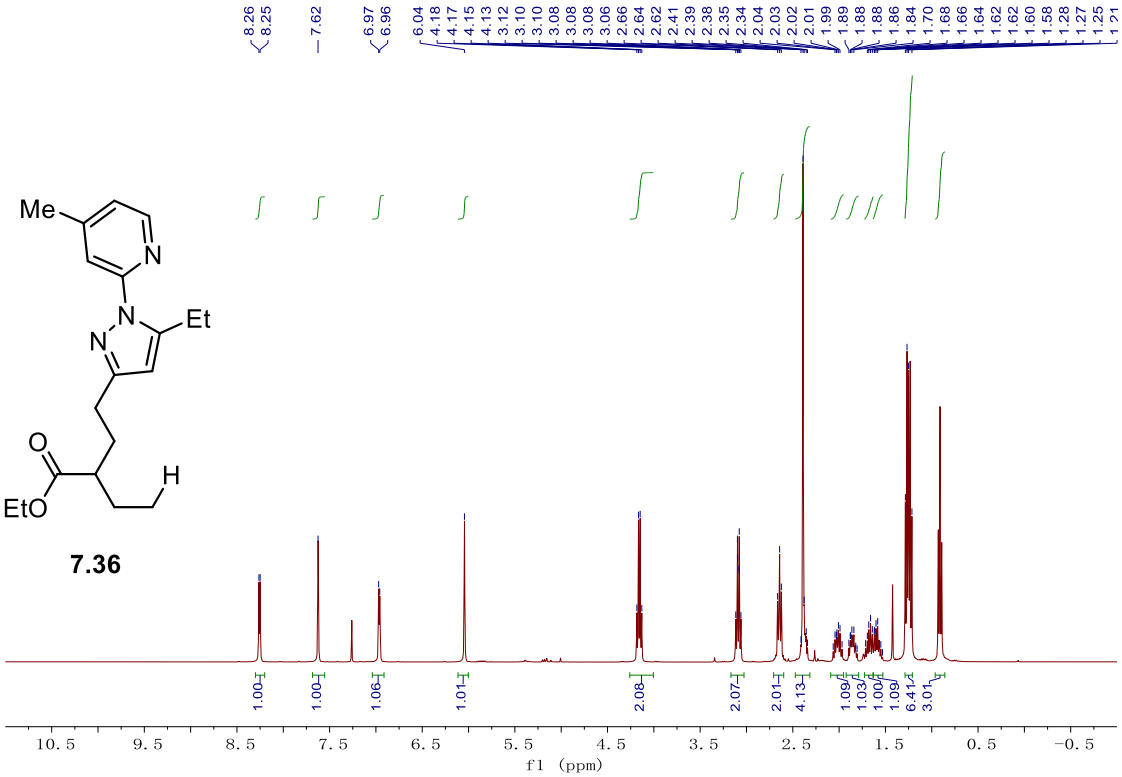


Figure 7.93 ^{13}C-NMR Spectrum of **7.36**

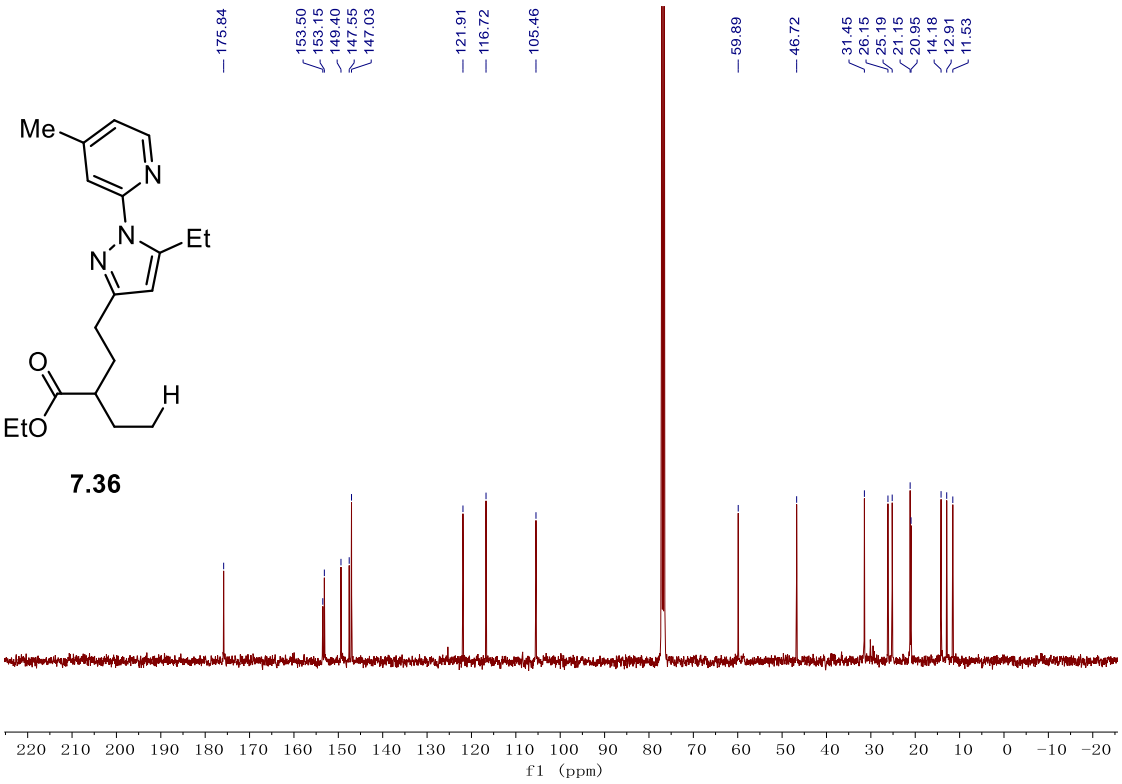


Figure 7.94 ^{1}H-NMR Spectrum of **7.37**

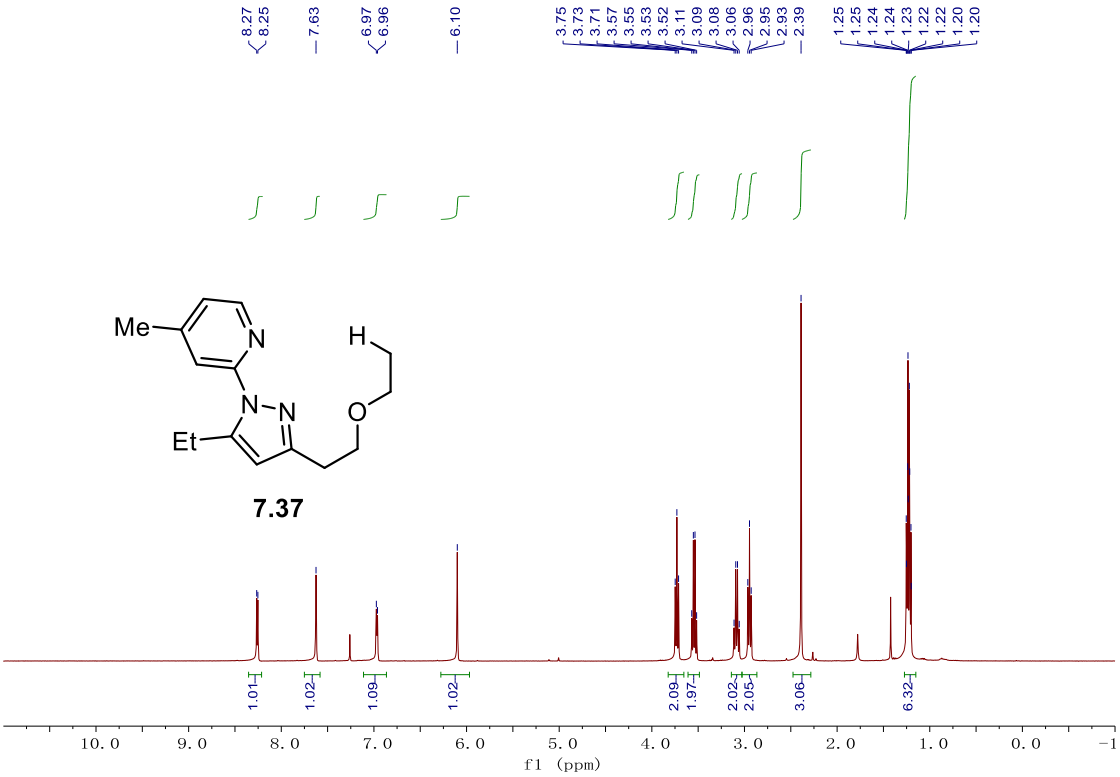


Figure 7.95 ^{13}C-NMR Spectrum of **7.37**

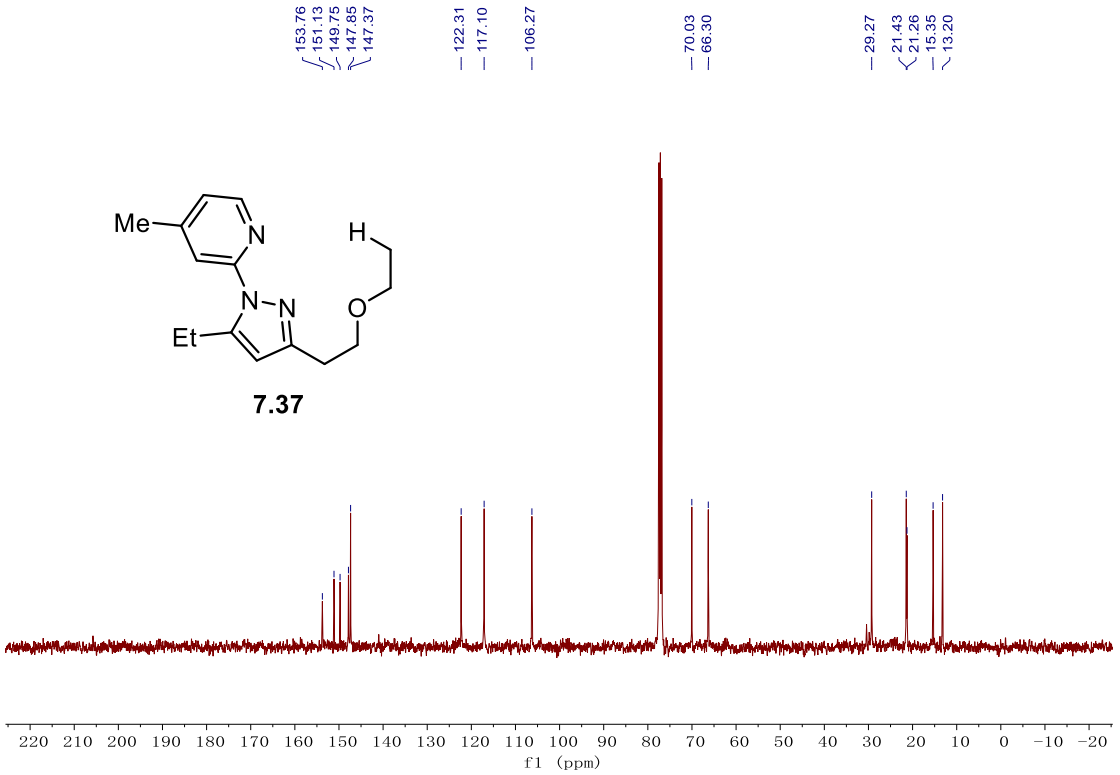


Figure 7.96 ^{1}H-NMR Spectrum of **7.38**

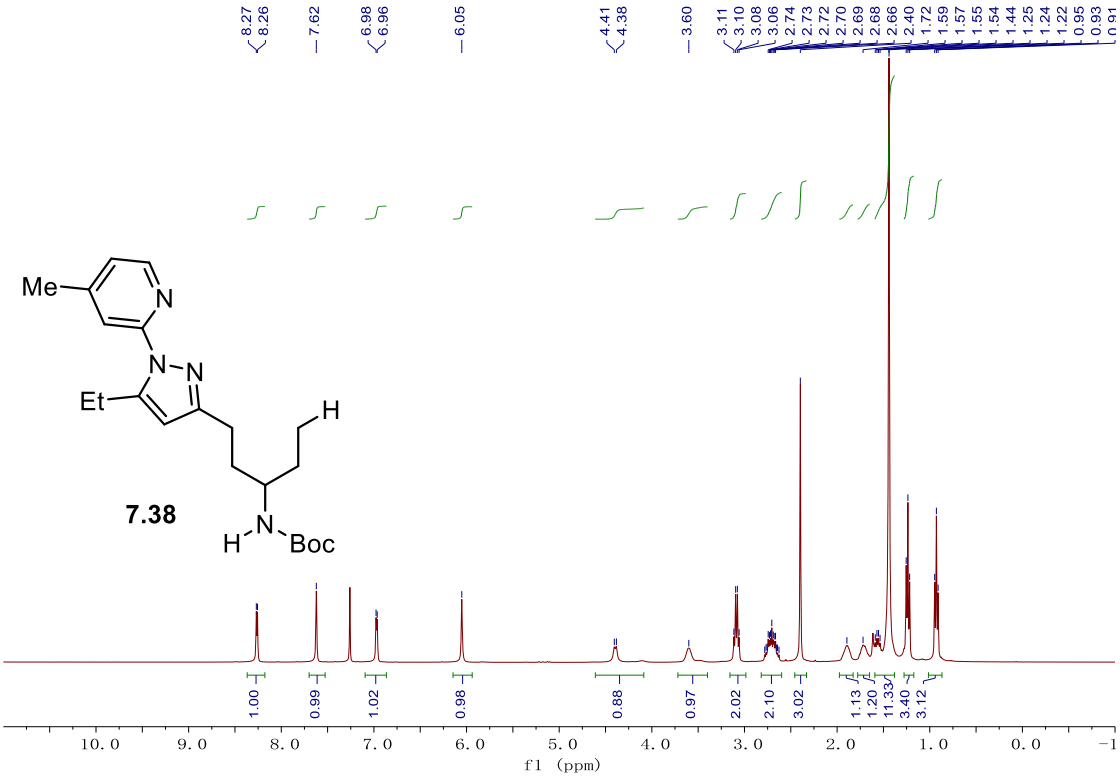


Figure 7.97 ^{13}C-NMR Spectrum of **7.38**

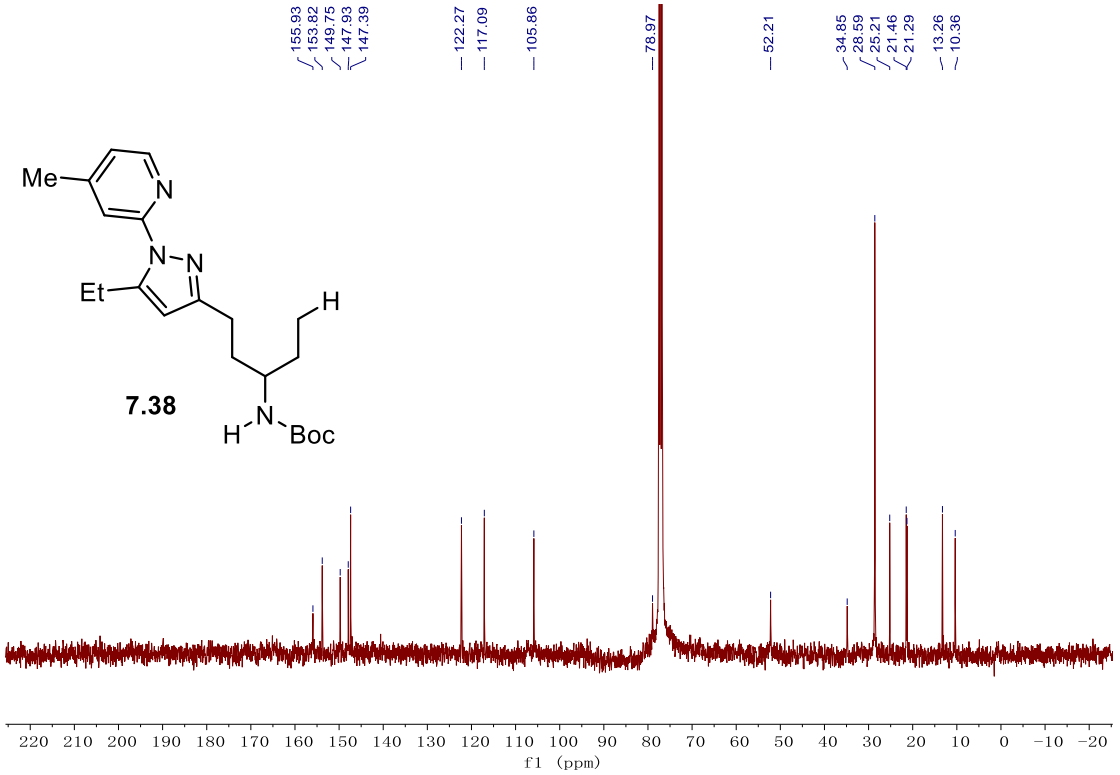


Figure 7.98 ^{1}H-NMR Spectrum of **7.39**

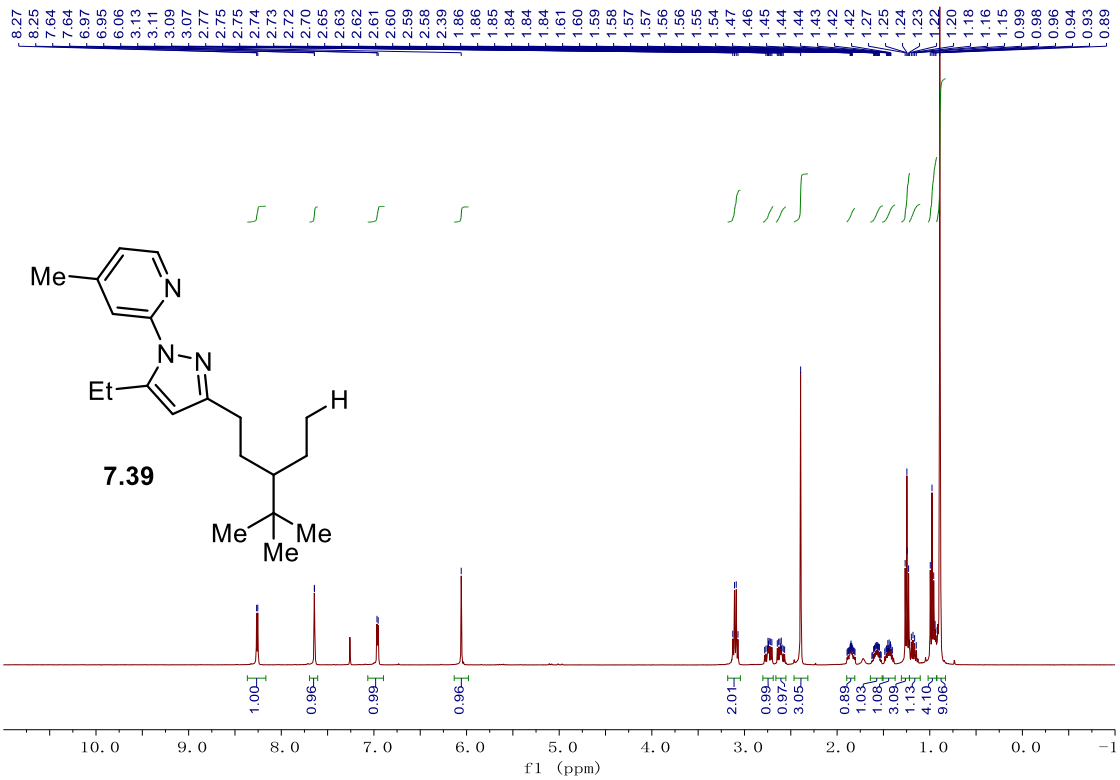


Figure 7.99 ^{13}C-NMR Spectrum of **7.39**

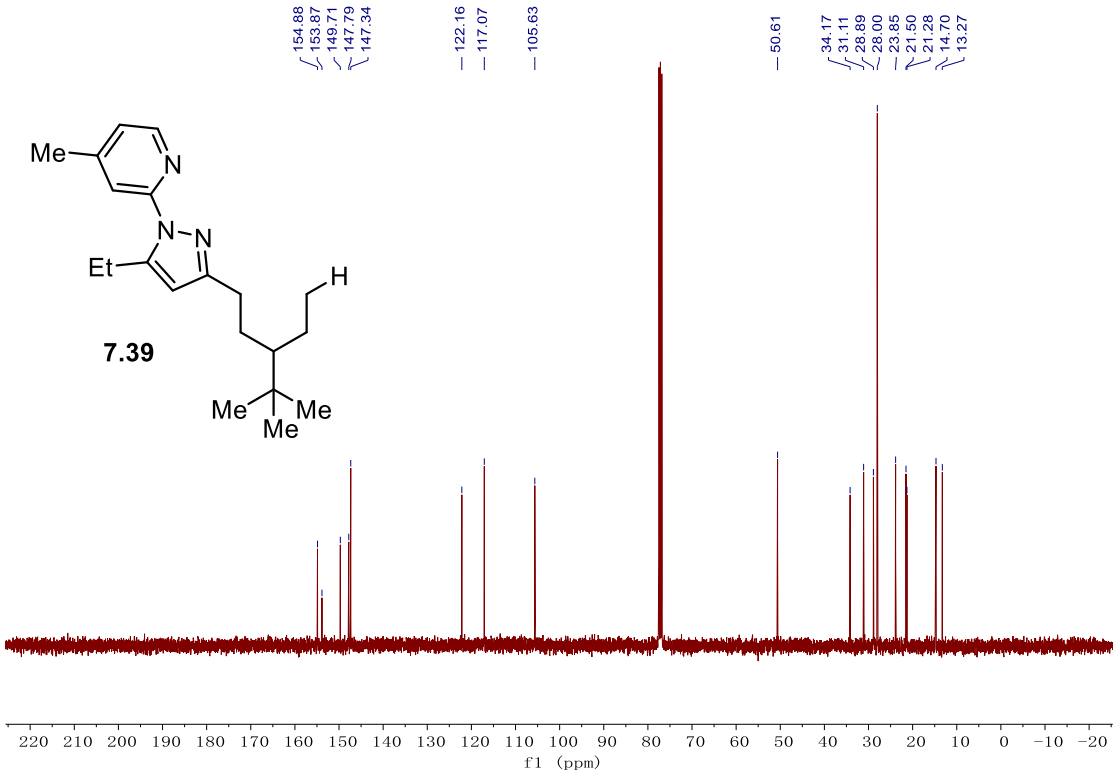


Figure 7.100 ^{1}H-NMR Spectrum of **7.40**

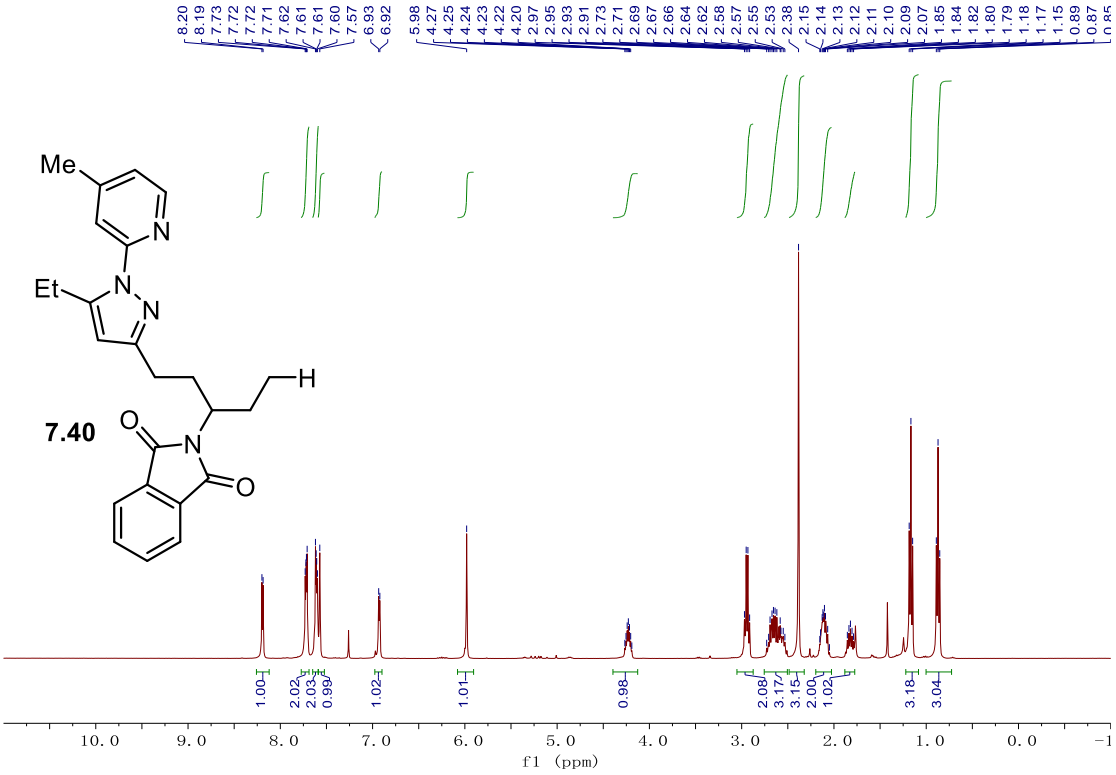


Figure 7.101 ^{13}C-NMR Spectrum of **7.40**

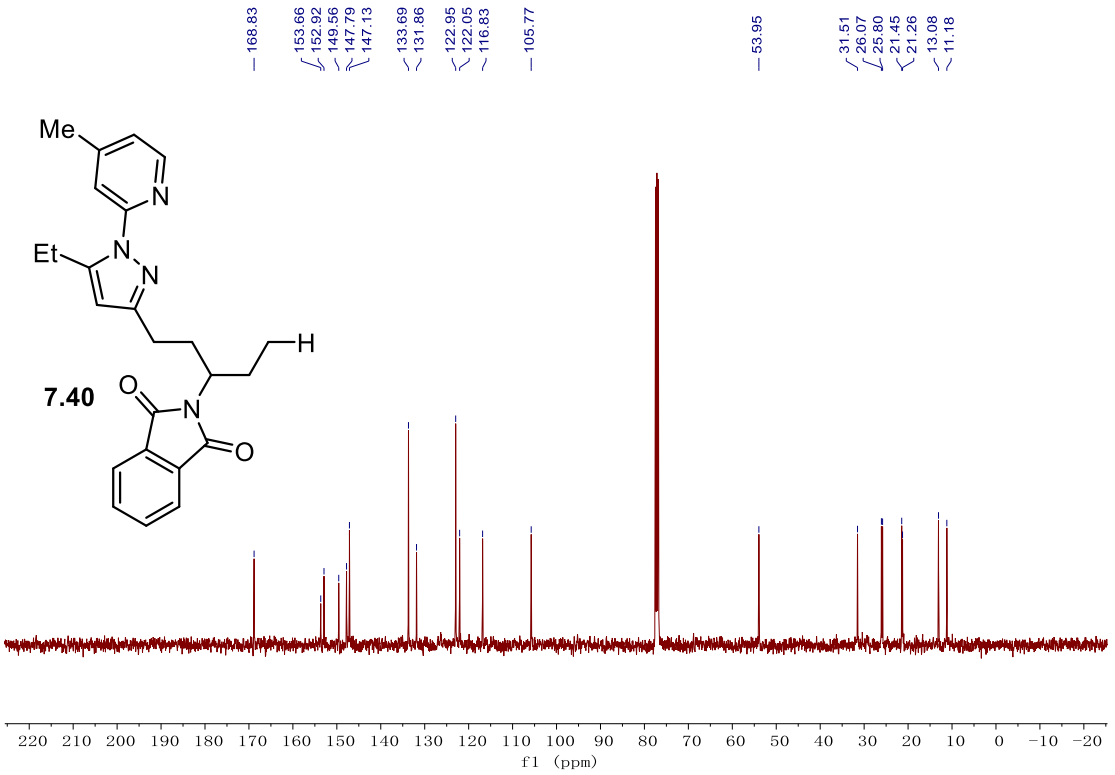


Figure 7.102 ^{1}H-NMR Spectrum of **7.41**

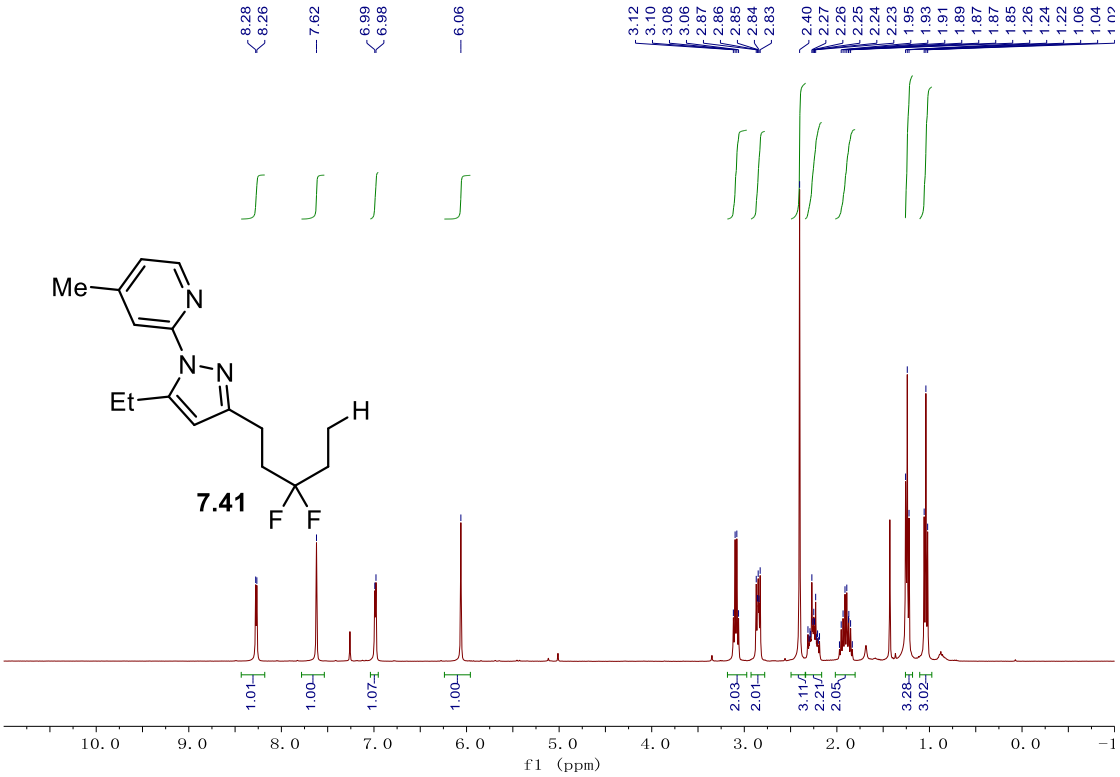


Figure 7.103 ^{13}C-NMR Spectrum of **7.41**

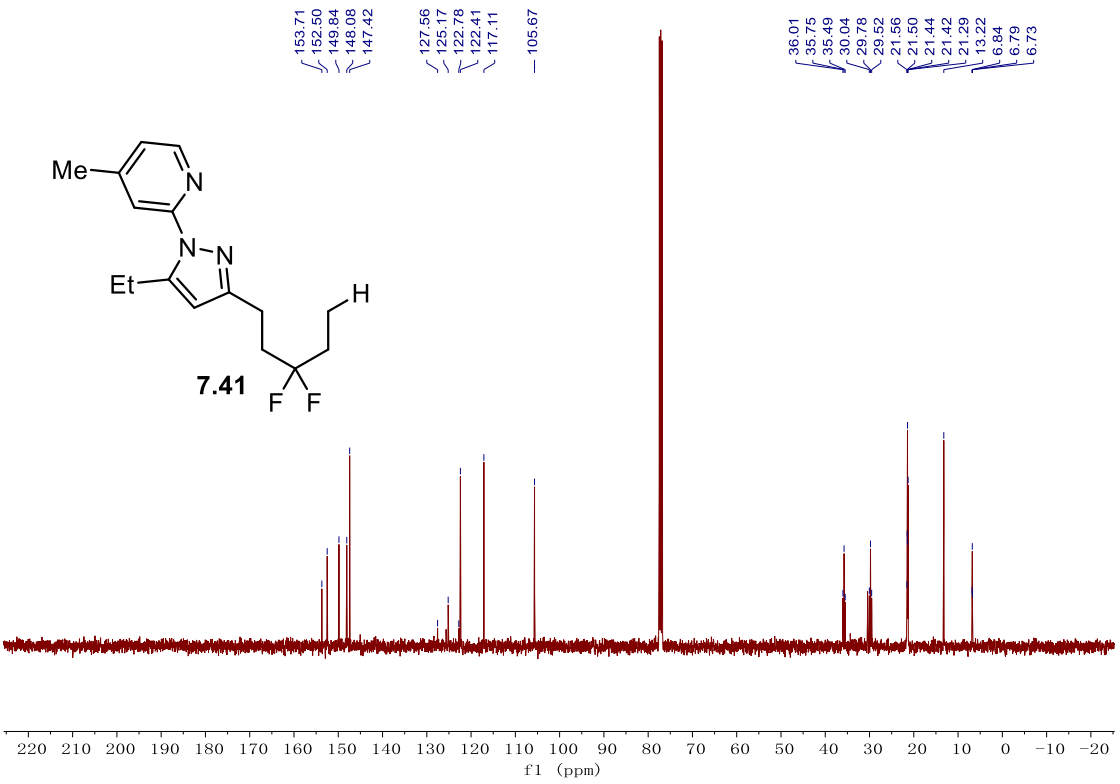


Figure 7.104 ^{1}H-NMR Spectrum of **7.42**

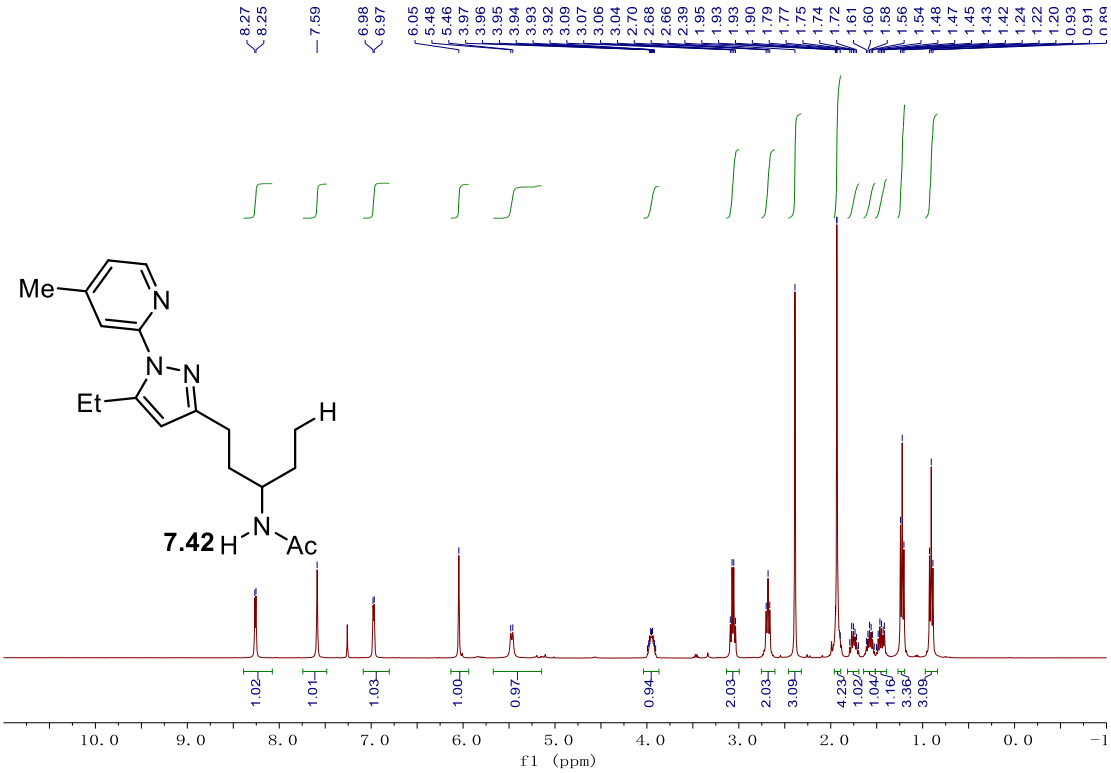


Figure 7.105 ^{13}C-NMR Spectrum of **7.42**

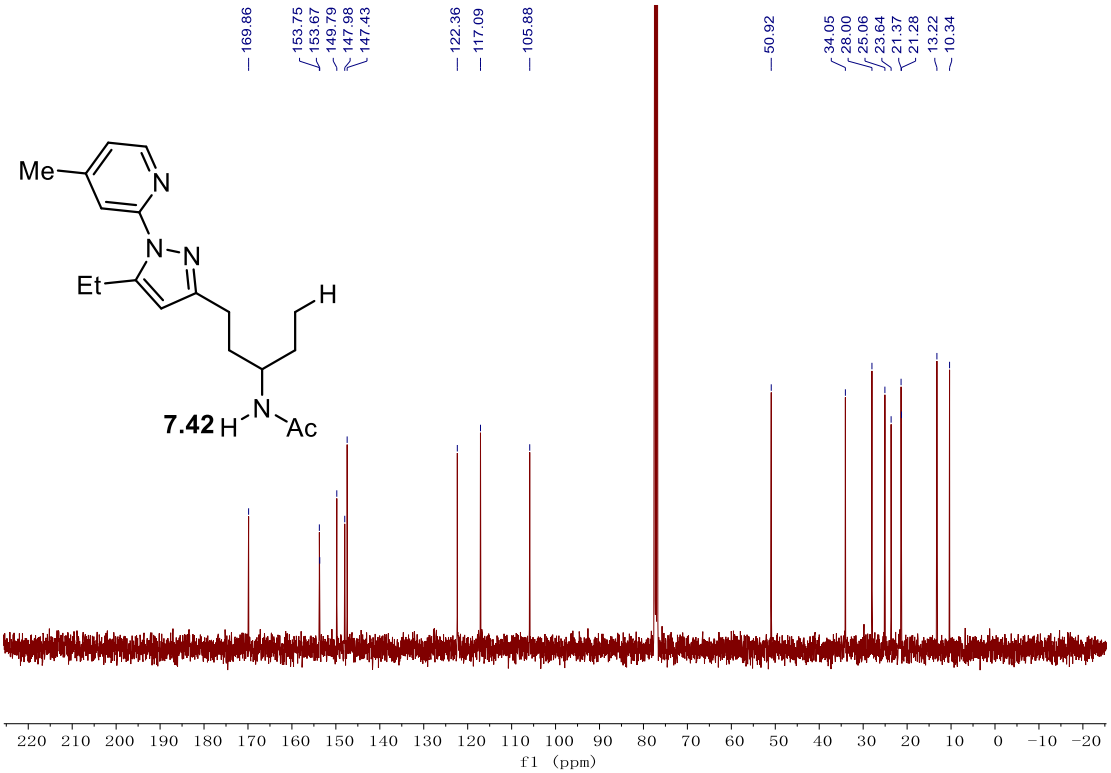


Figure 7.106 ^{1}H-NMR Spectrum of **7.43**

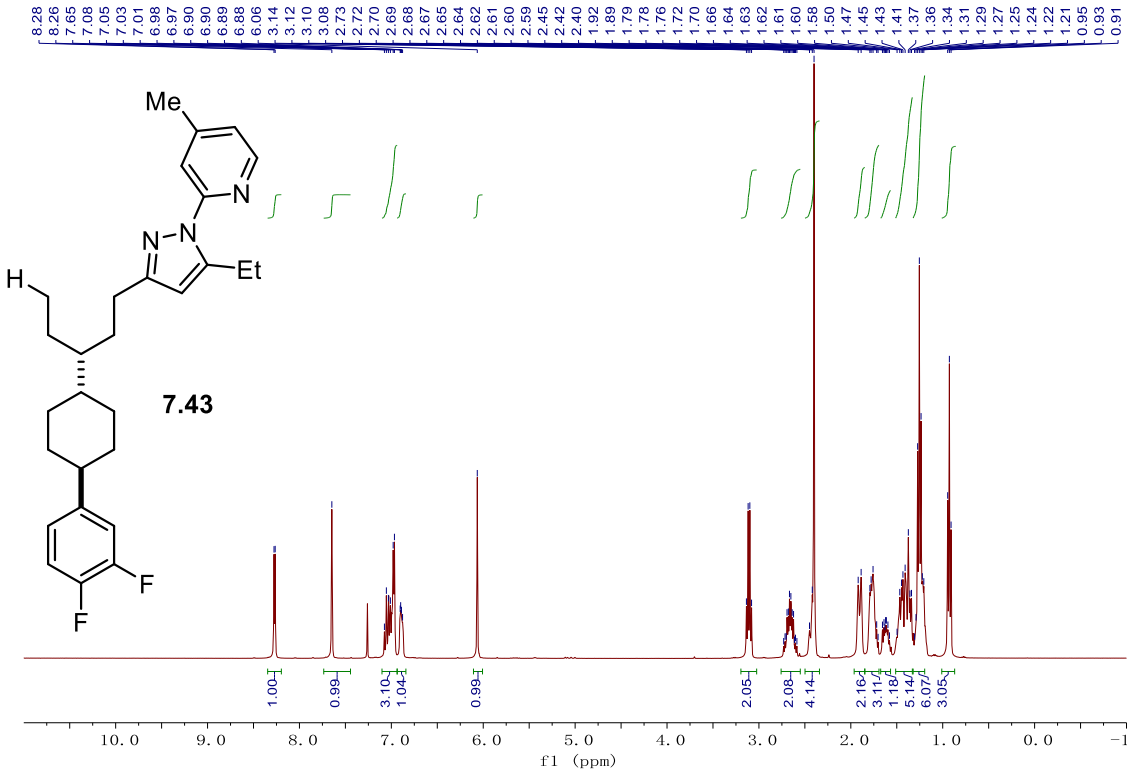


Figure 7.107 ^{13}C-NMR Spectrum of **7.43**

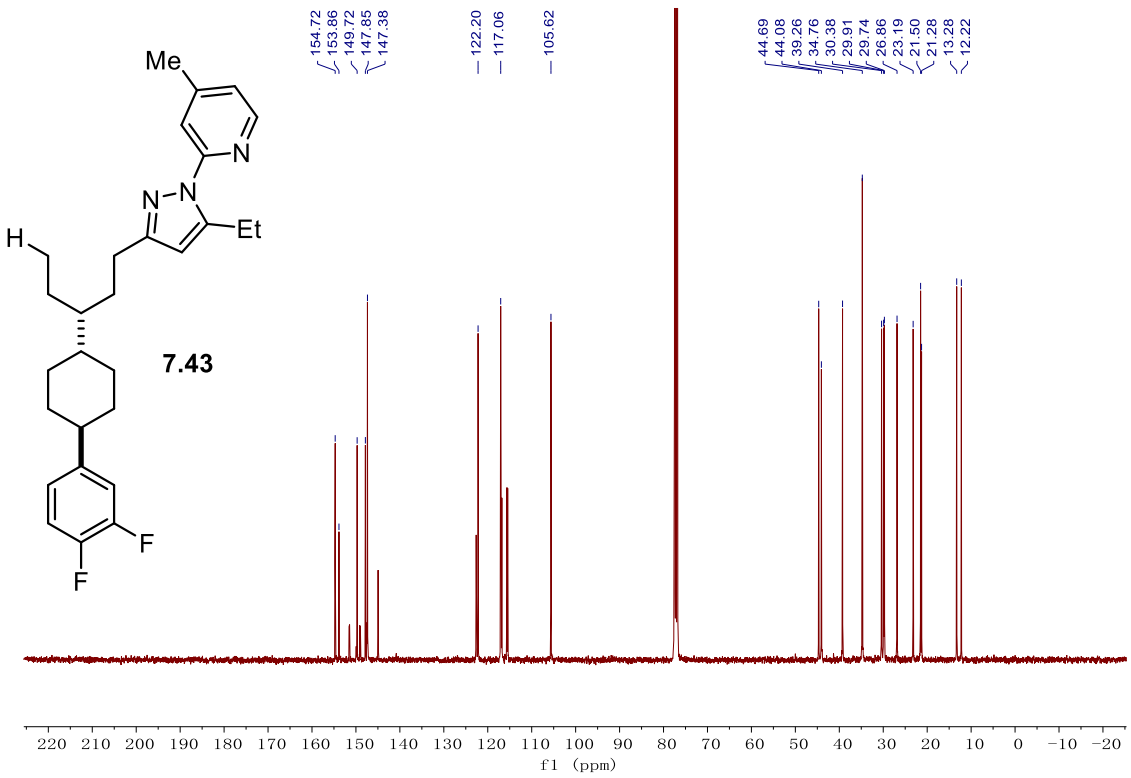


Figure 7.108 ^{1}H-NMR Spectrum of **7.45**

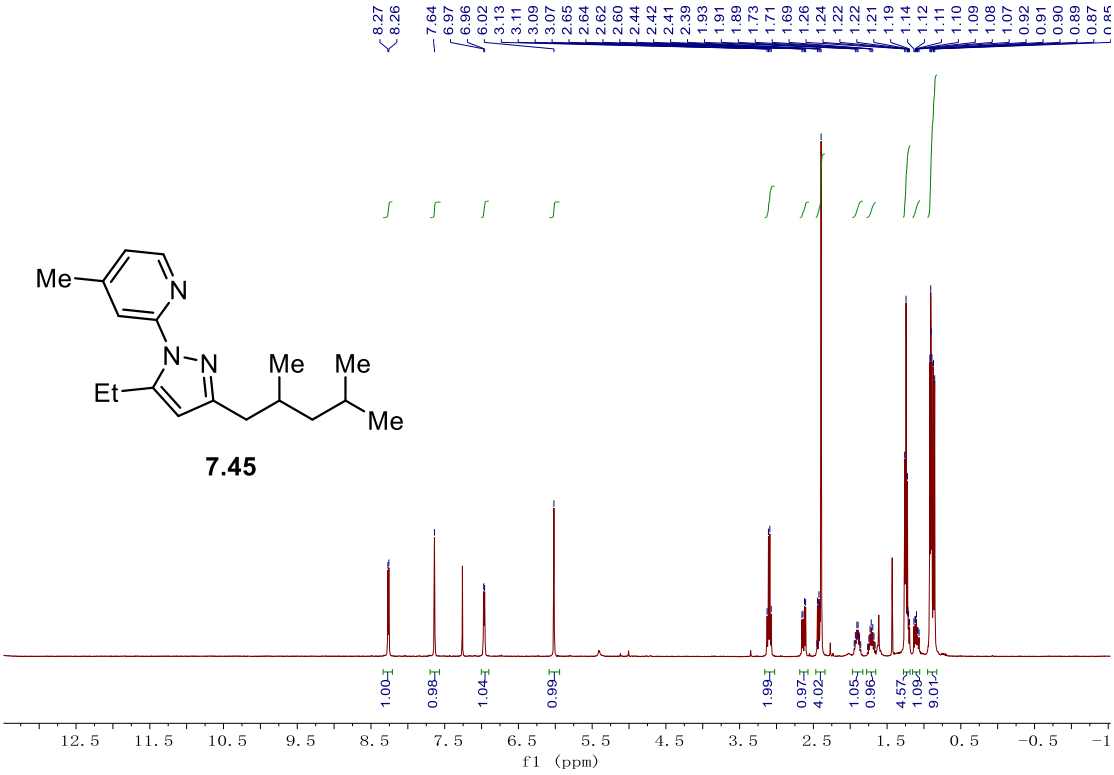


Figure 7.109 ^{13}C-NMR Spectrum of **7.45**

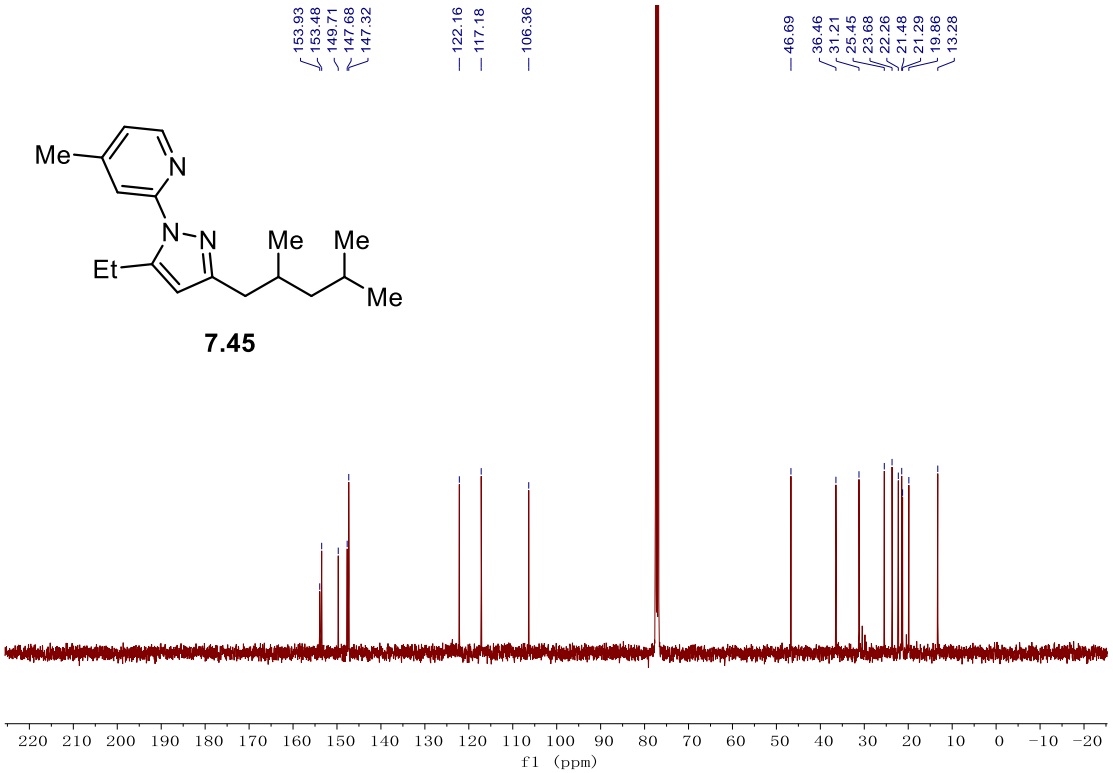


Figure 7.110 ^{1}H-NMR Spectrum of **7.47a**

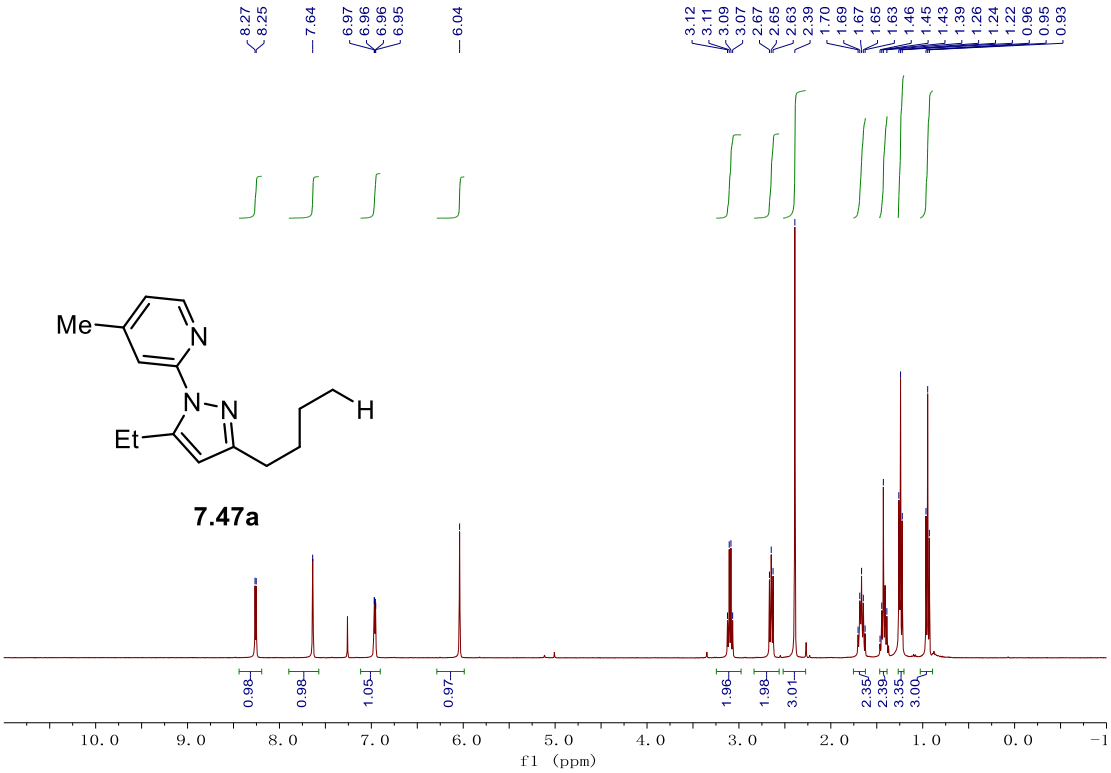


Figure 7.111 ^{13}C-NMR Spectrum of **7.47a**

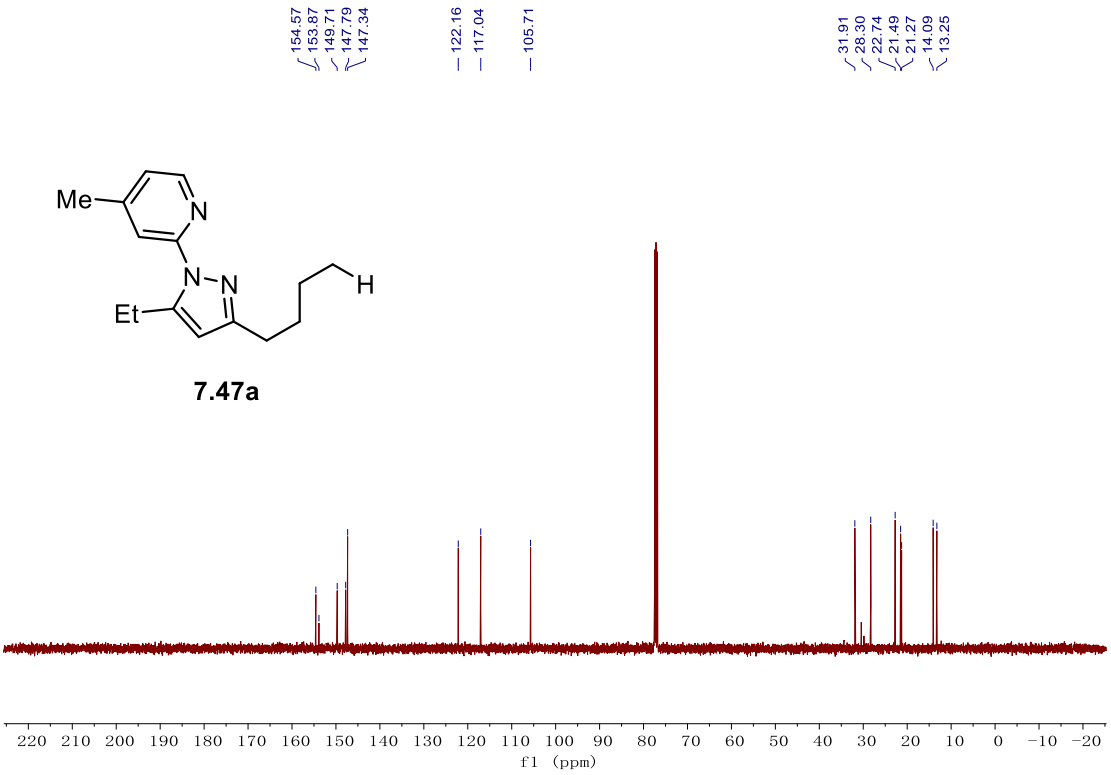


Figure 7.112 ^{1}H-NMR Spectrum of **7.49**

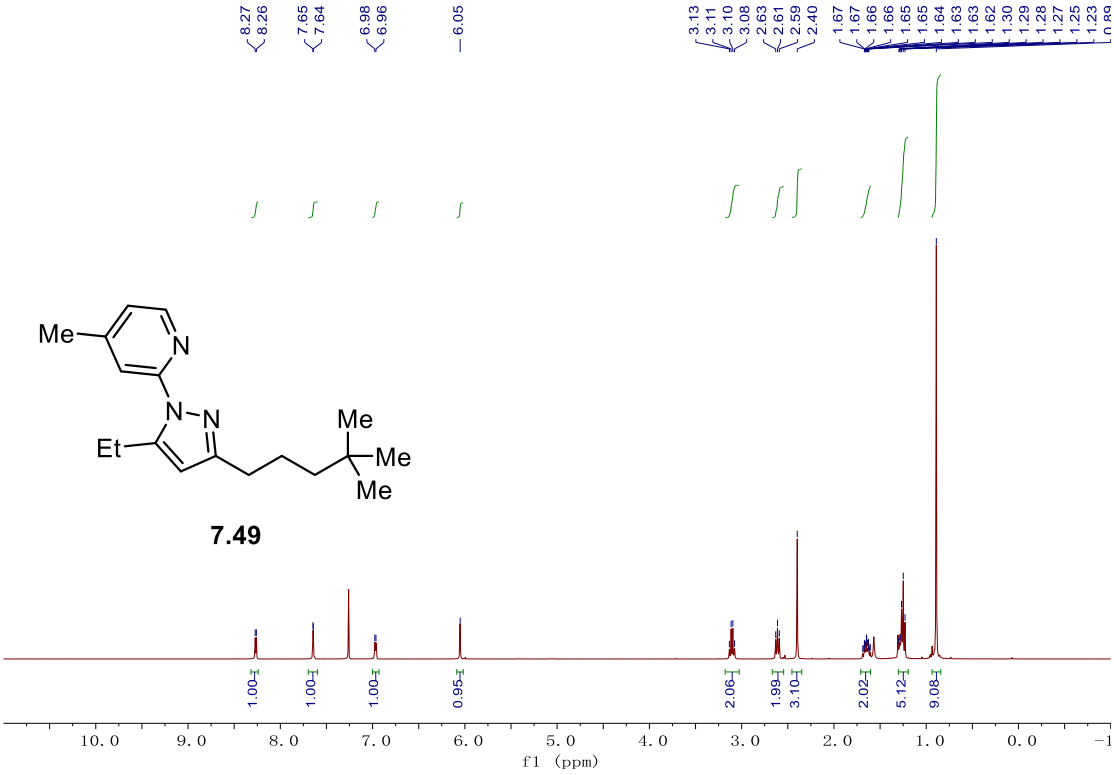


Figure 7.113 ^{13}C-NMR Spectrum of **7.49**

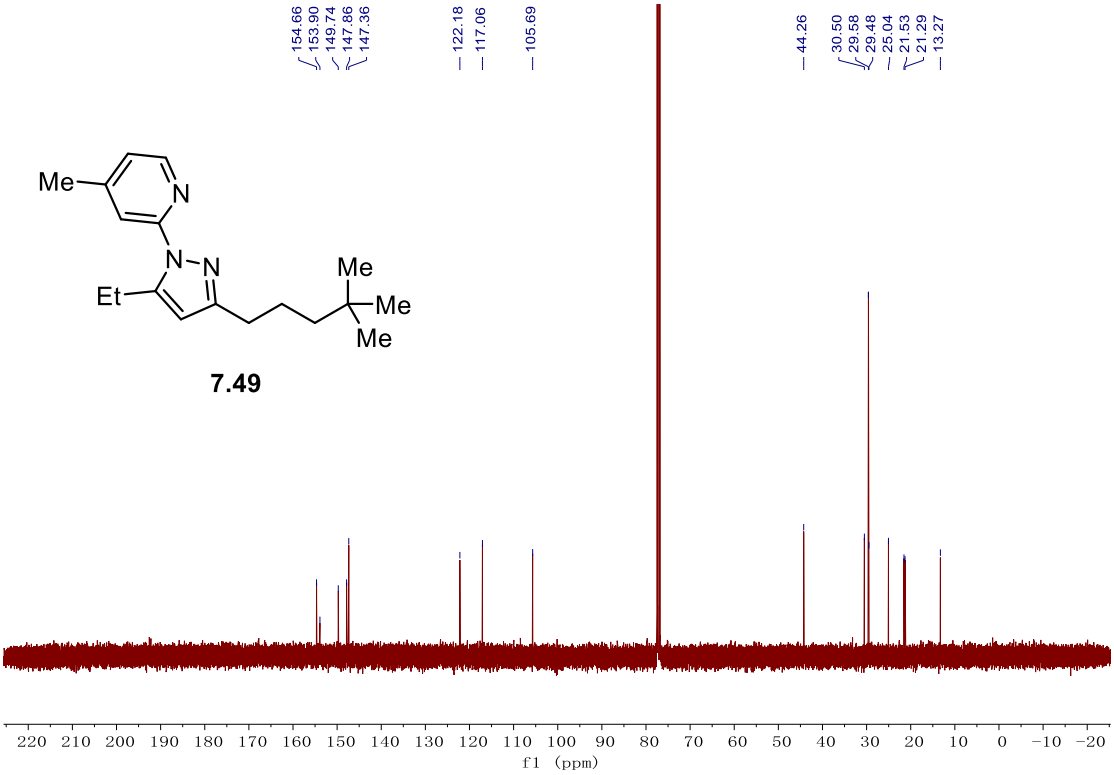


Figure 7.114 ^{1}H-NMR Spectrum of **7.51**

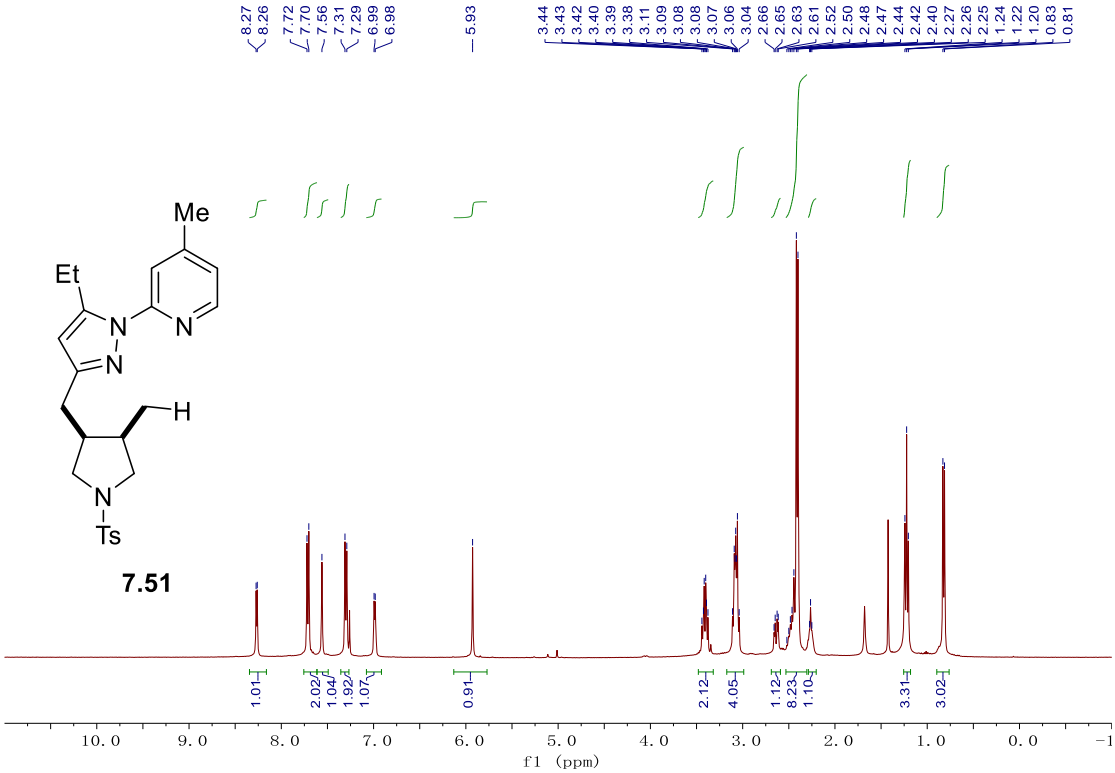


Figure 7.115 ^{13}C-NMR Spectrum of **7.51**

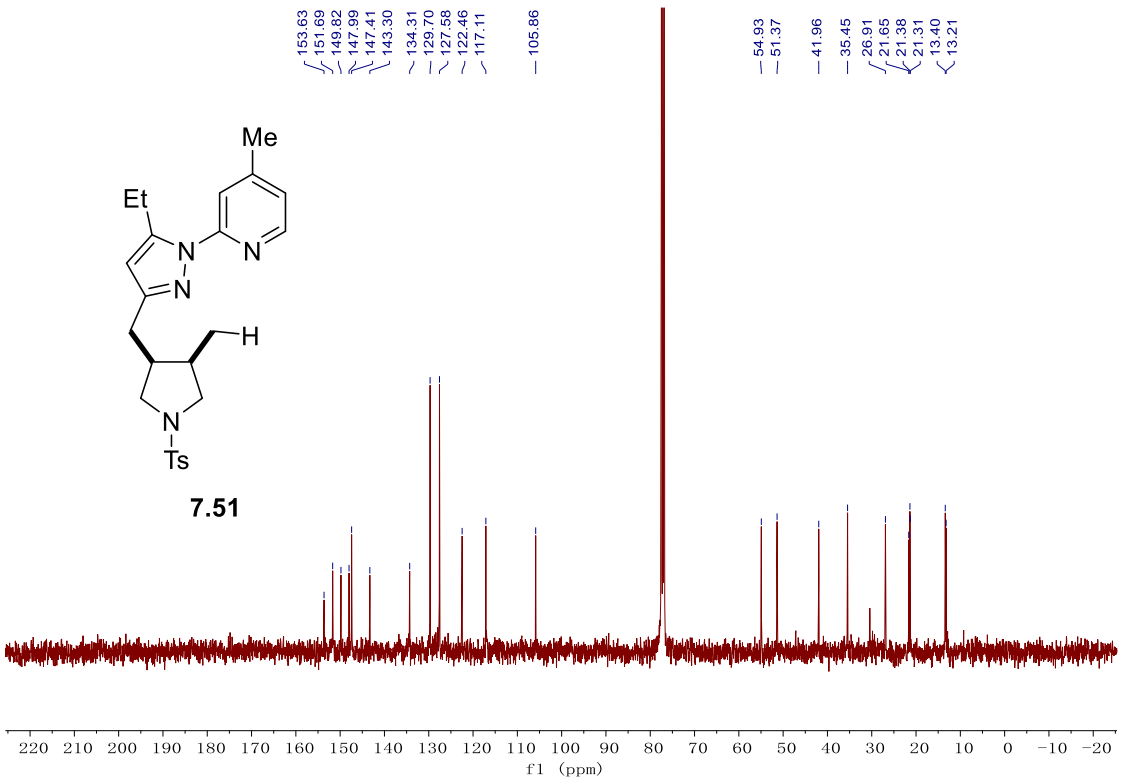


Figure 7.116 ^{1}H-NMR Spectrum of **7.53**

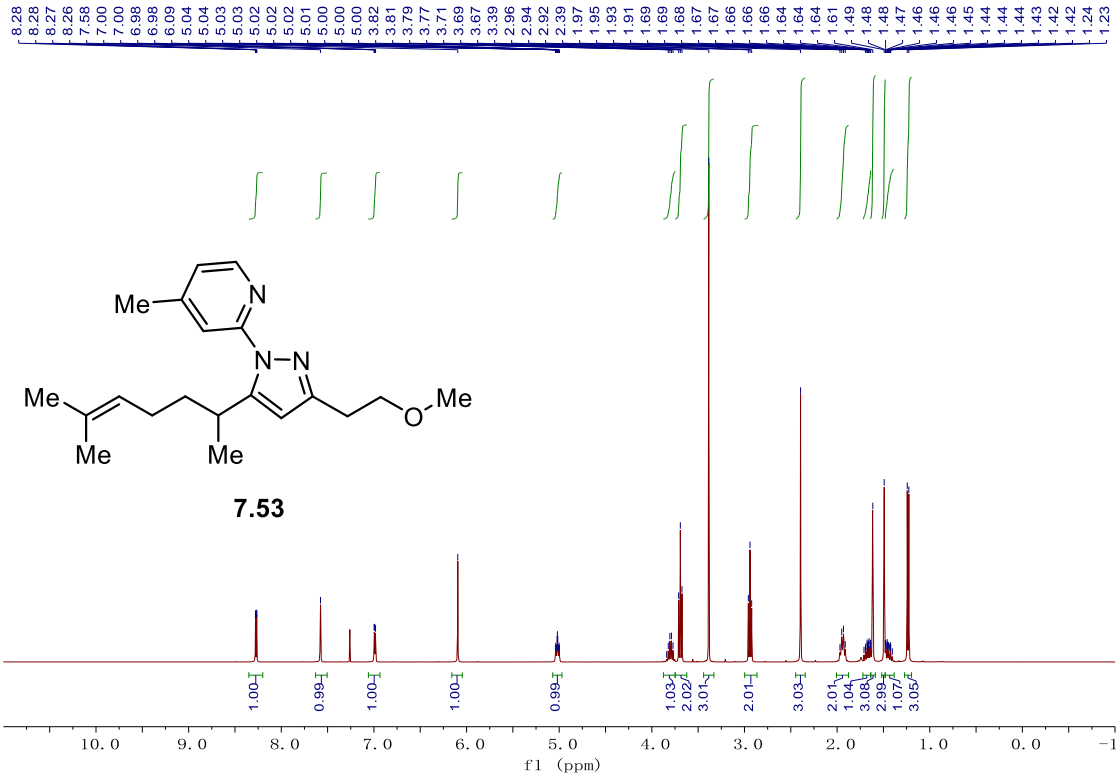


Figure 7.117 ^{13}C-NMR Spectrum of **7.53**

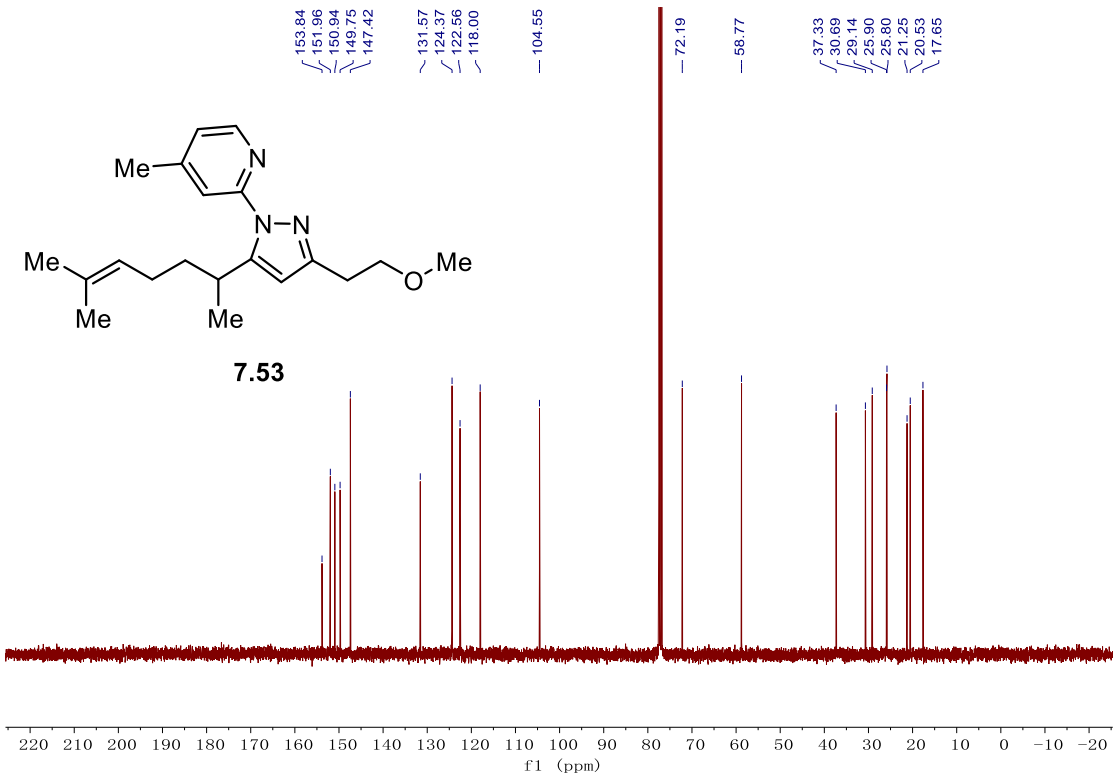


Figure 7.118 ^{1}H-NMR Spectrum of **7.54**

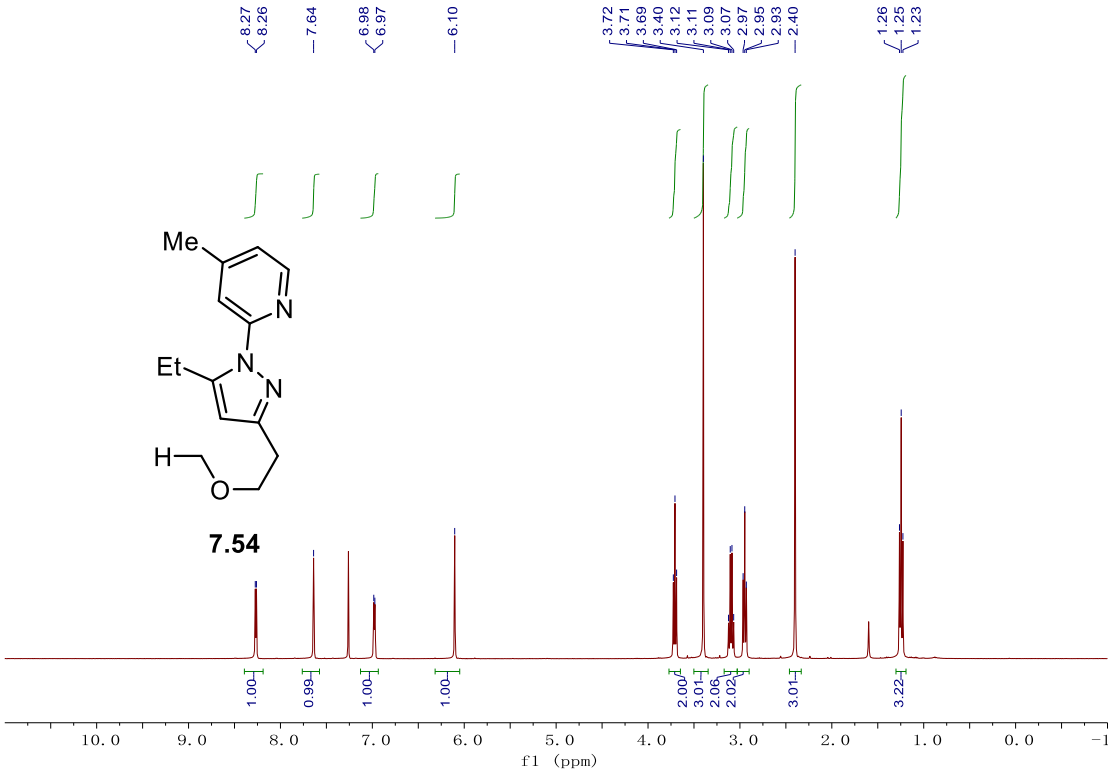


Figure 7.119 ^{13}C-NMR Spectrum of **7.54**

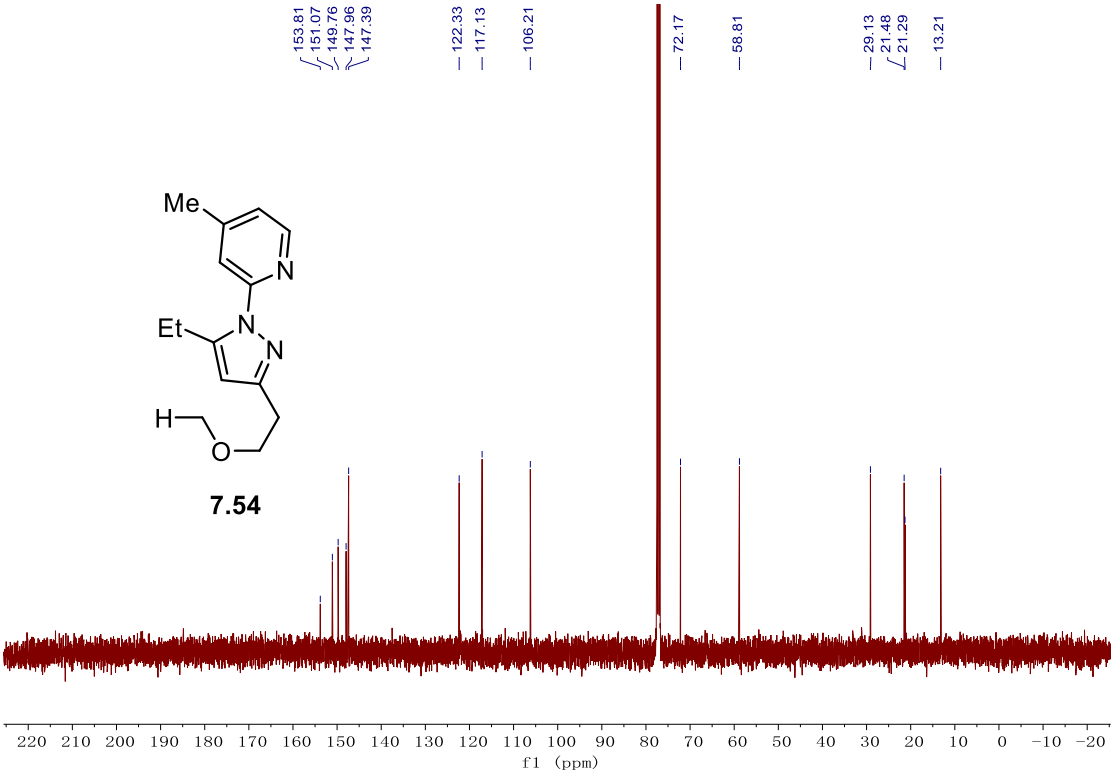


Figure 7.120 ^{1}H-NMR Spectrum of **7.56**

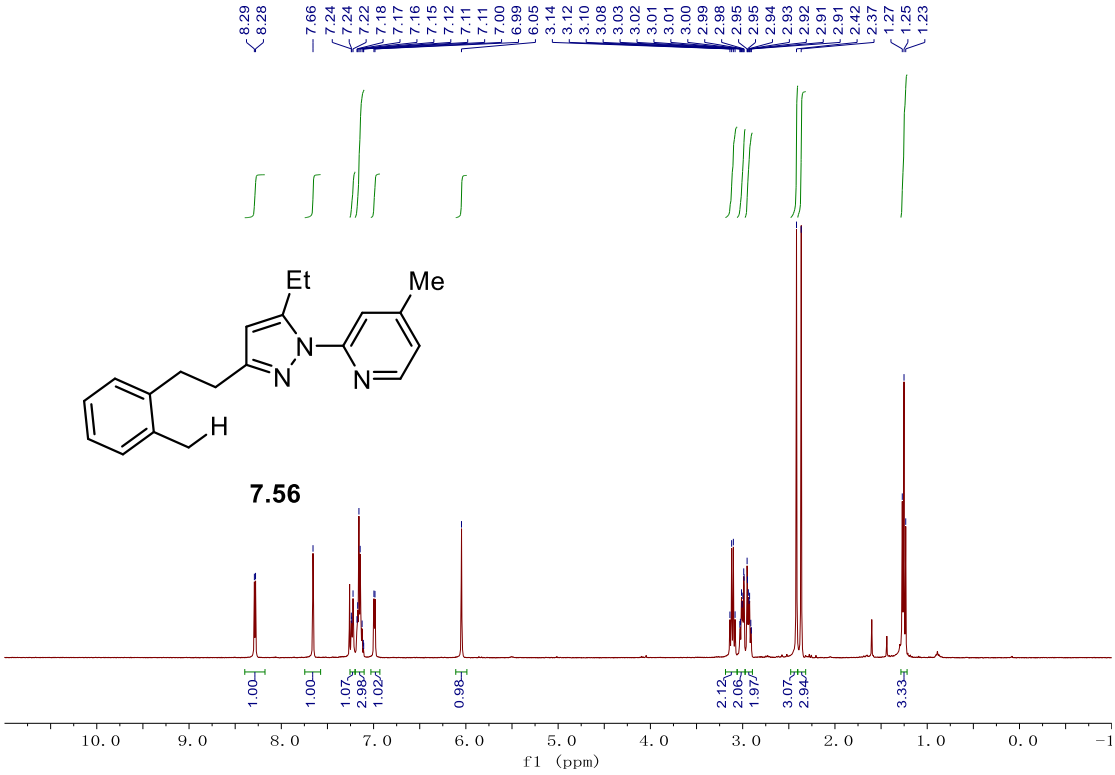


Figure 7.121 ^{13}C-NMR Spectrum of **7.56**

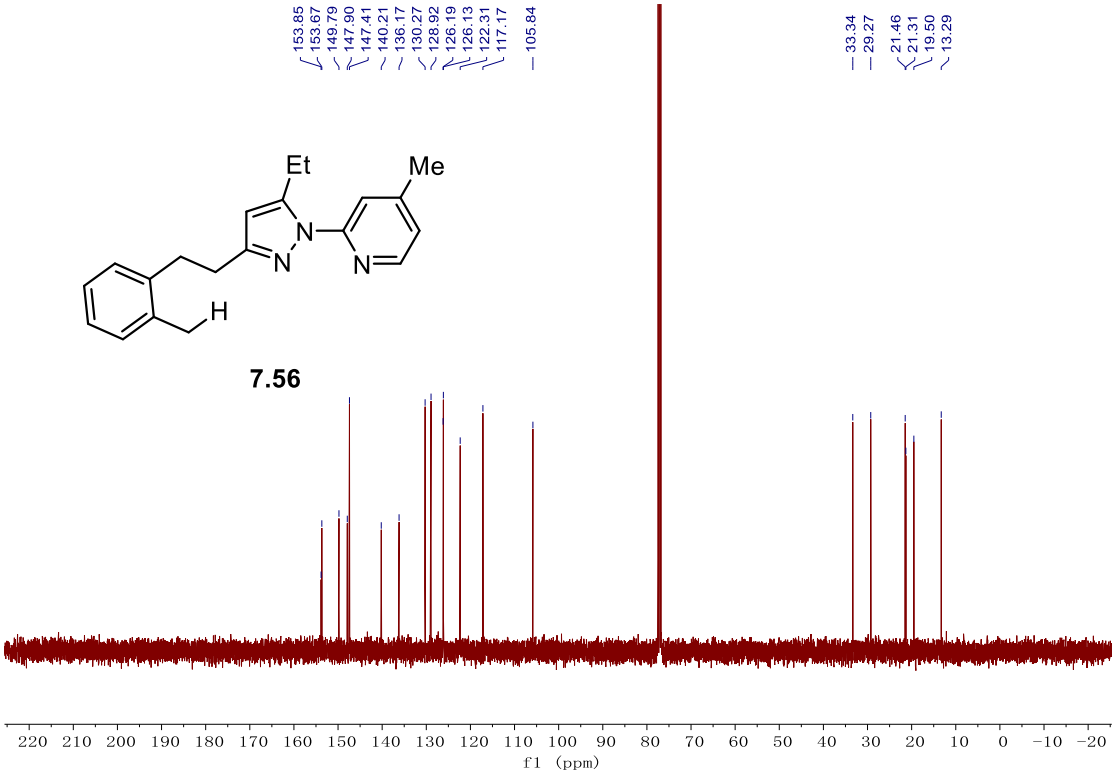


Figure 7.122 ^{1}H-NMR Spectrum of **7.57**

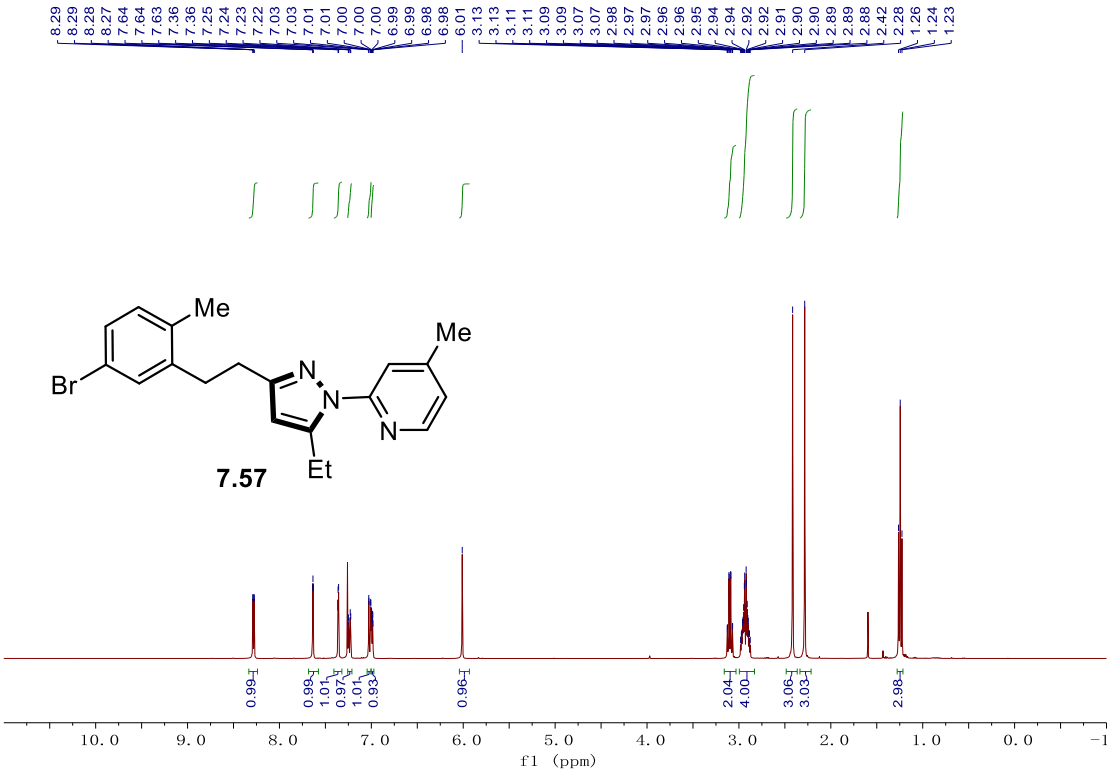


Figure 7.123 ^{13}C-NMR Spectrum of **7.57**

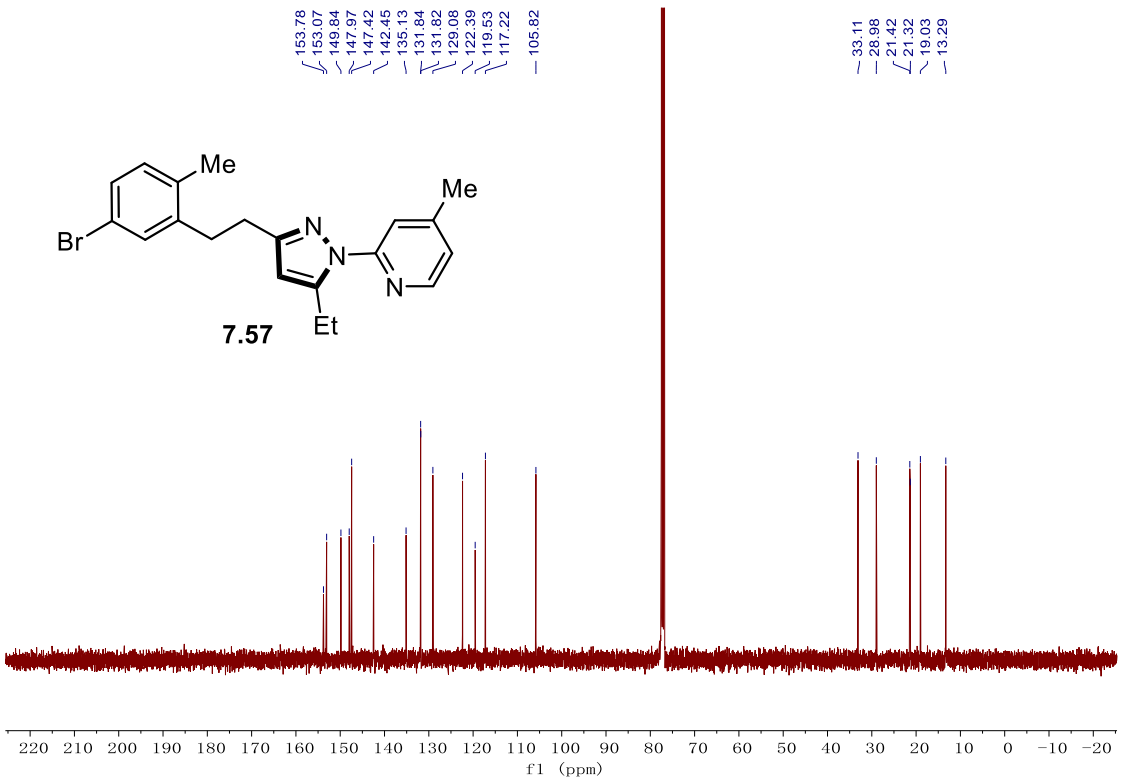


Figure 7.124 ^{1}H-NMR Spectrum of **7.58**

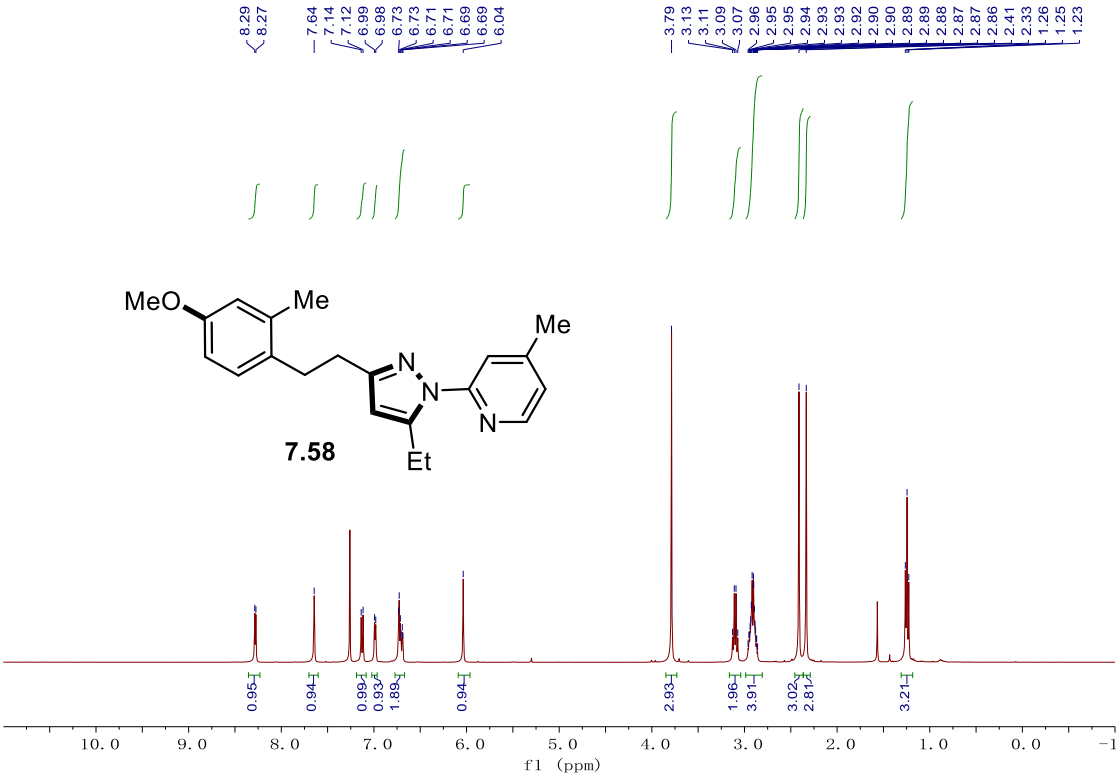


Figure 7.125 ^{13}C-NMR Spectrum of **7.58**

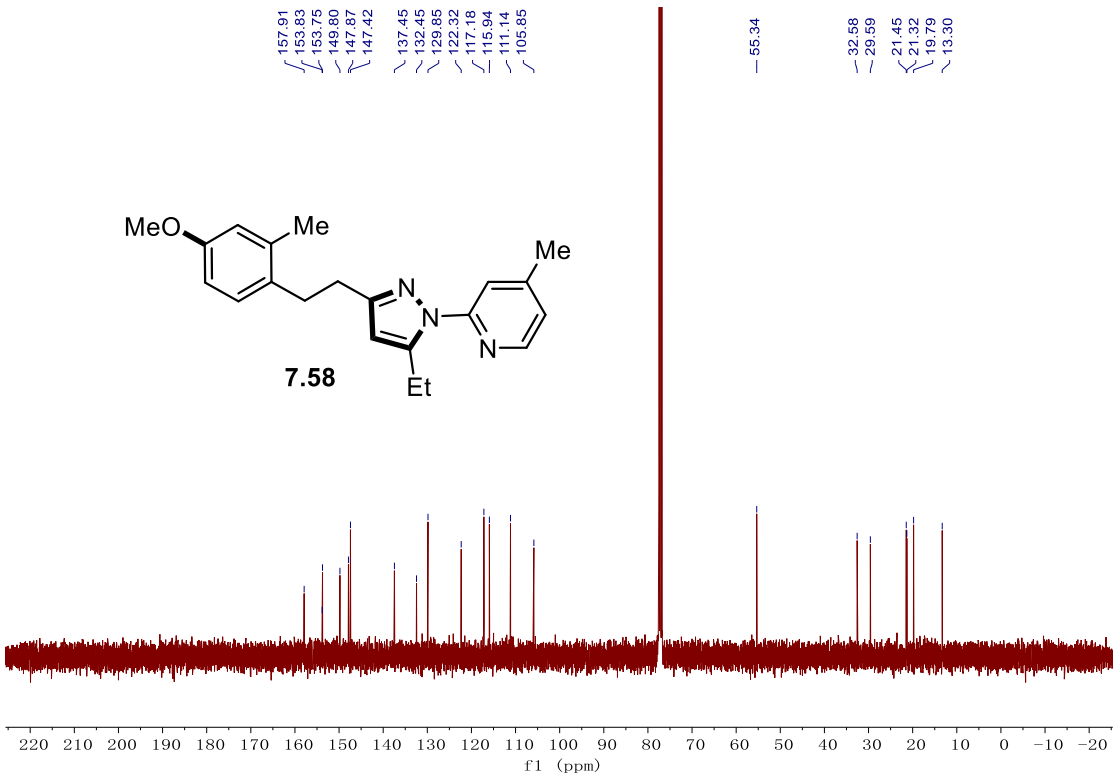


Figure 7.126 ^{1}H-NMR Spectrum of **7.59**

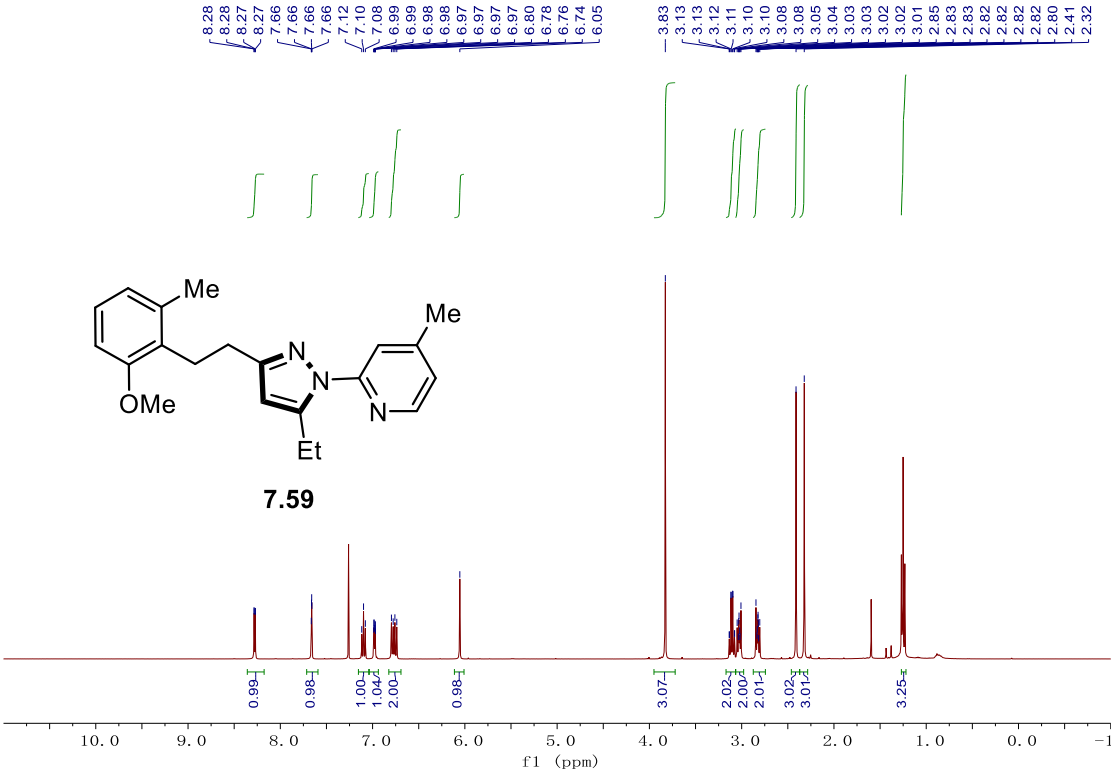


Figure 7.127 ^{13}C-NMR Spectrum of **7.59**

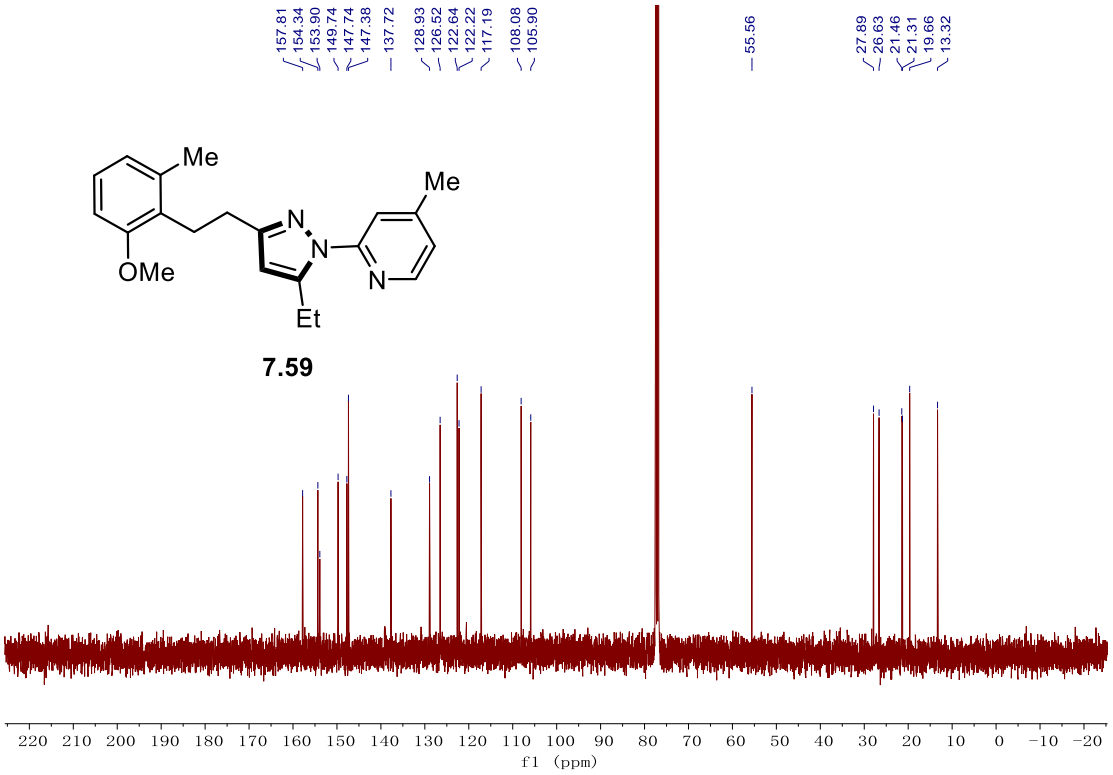


Figure 7.128 ^{1}H-NMR Spectrum of **7.72**

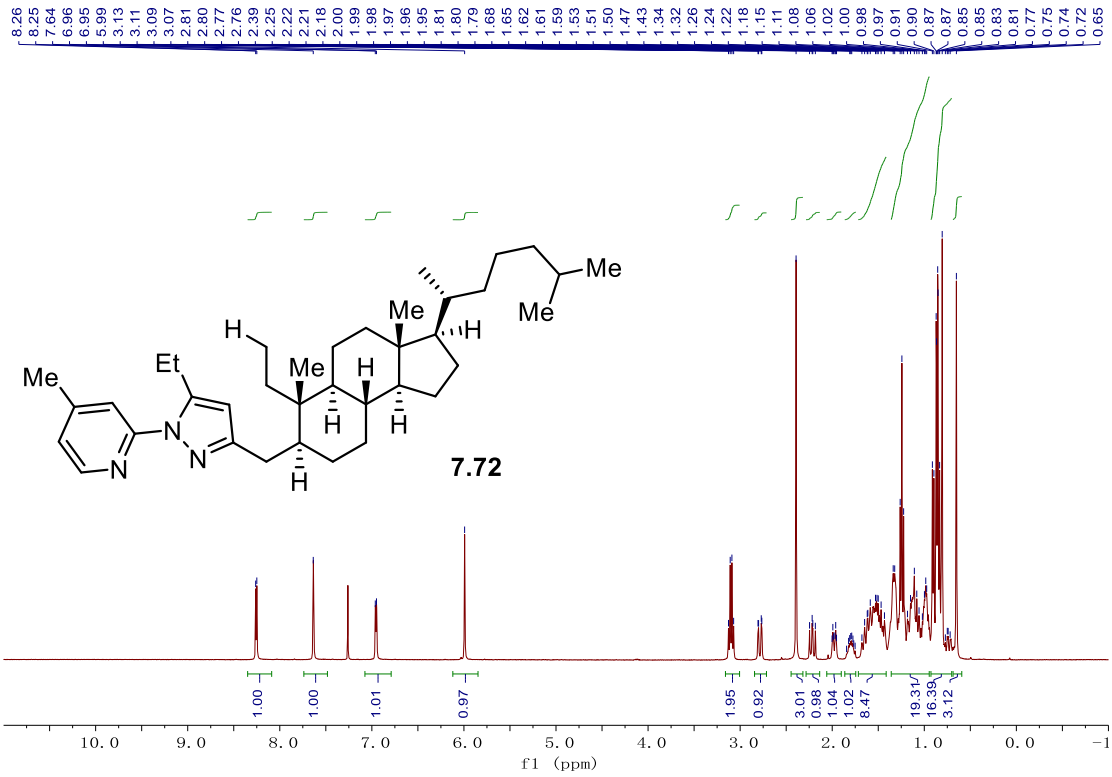


Figure 7.129 ^{13}C-NMR Spectrum of **7.72**

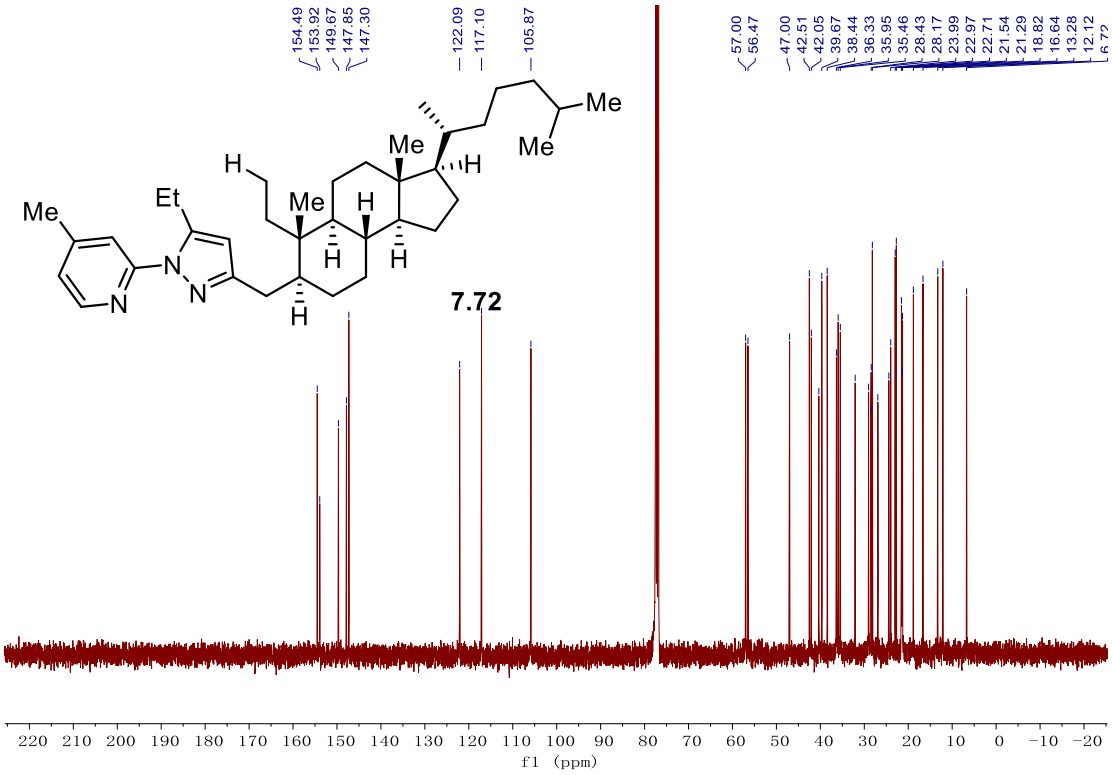


Figure 7.130 ^{1}H-NMR Spectrum of **7.73**

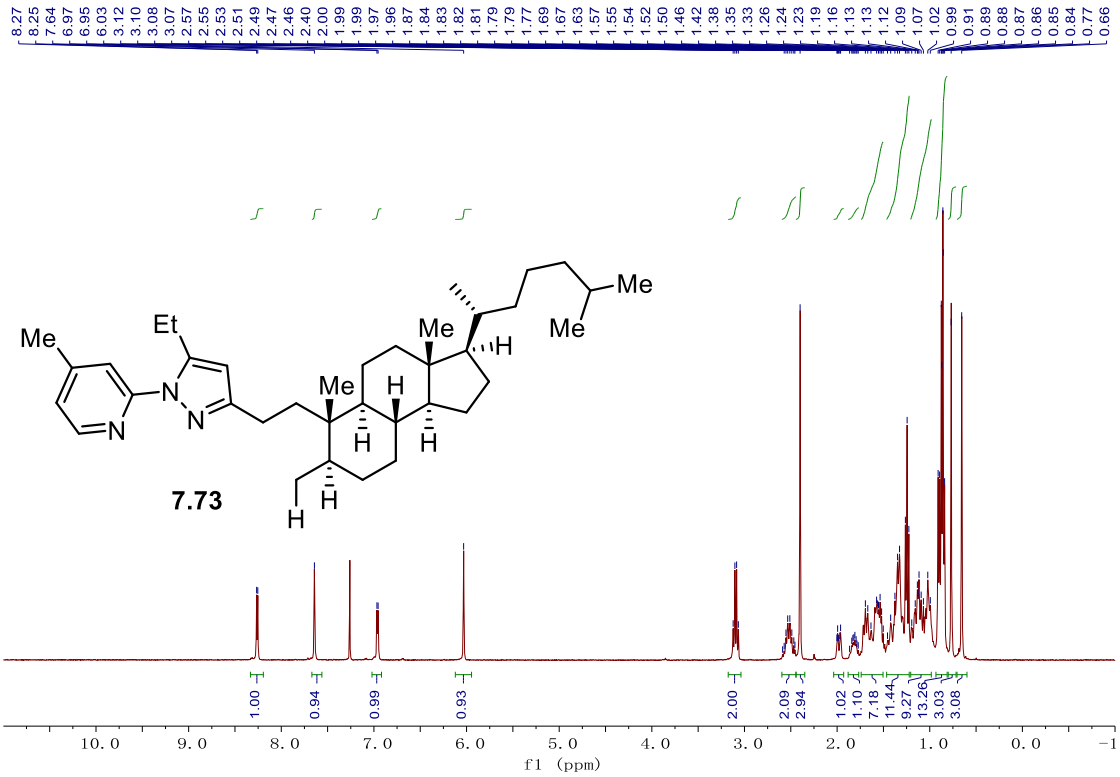


Figure 7.131 ^{13}C-NMR Spectrum of **7.73**

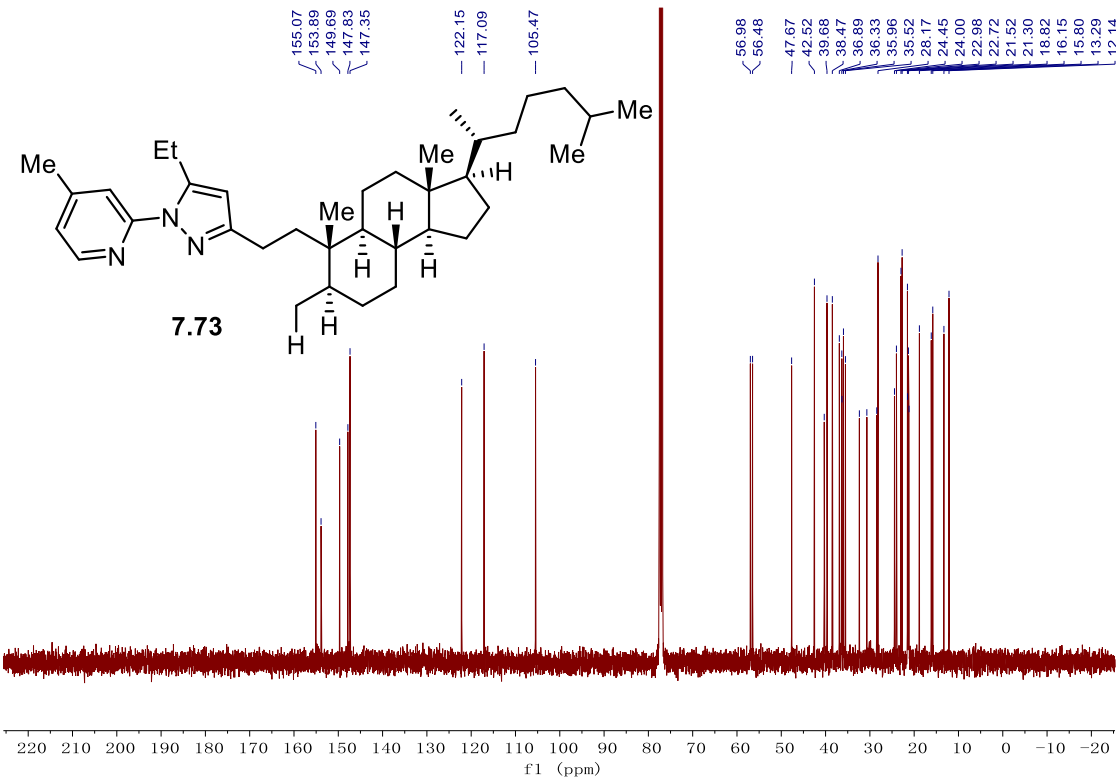


Figure 7.132 ^{1}H-NMR Spectrum of **7.74**

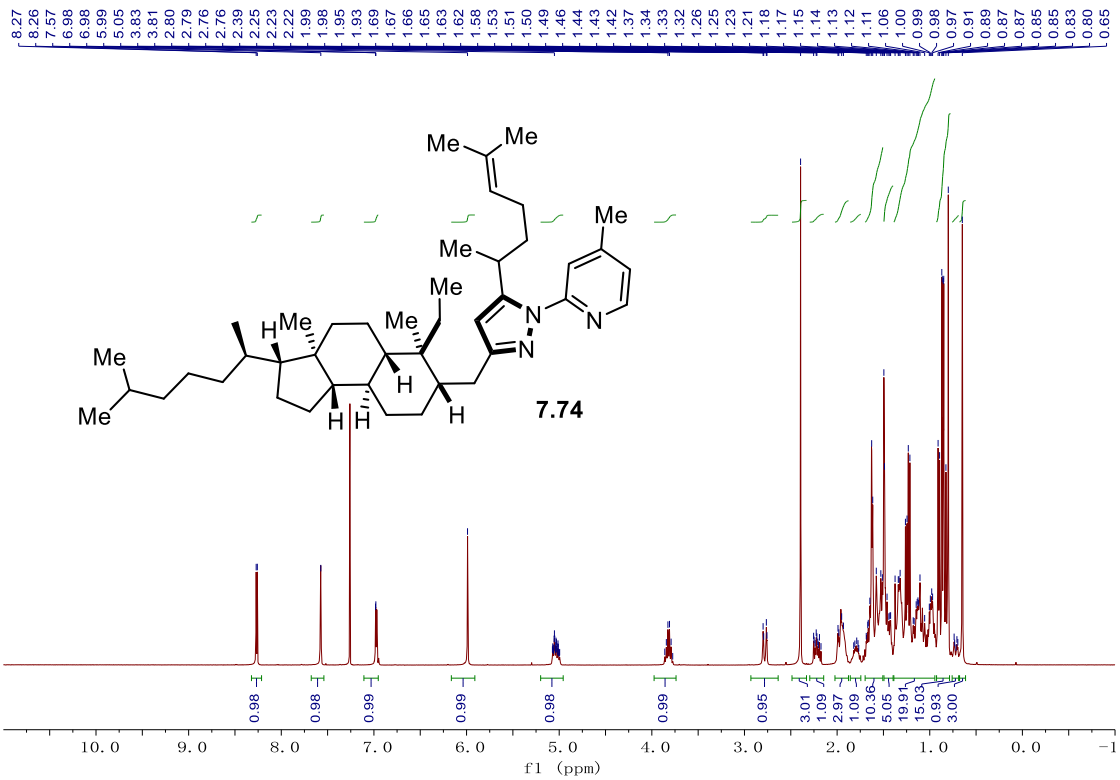


Figure 7.133 ^{13}C-NMR Spectrum of **7.74**

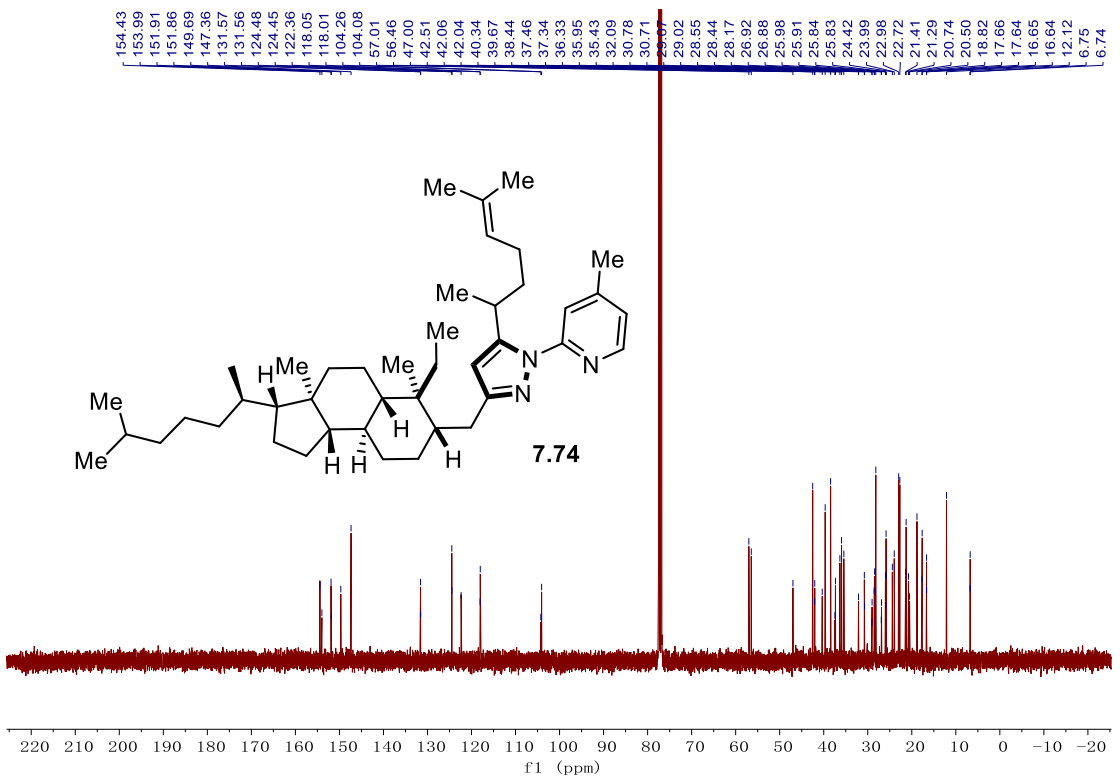


Figure 7.134 ^{1}H-NMR Spectrum of **7.75**

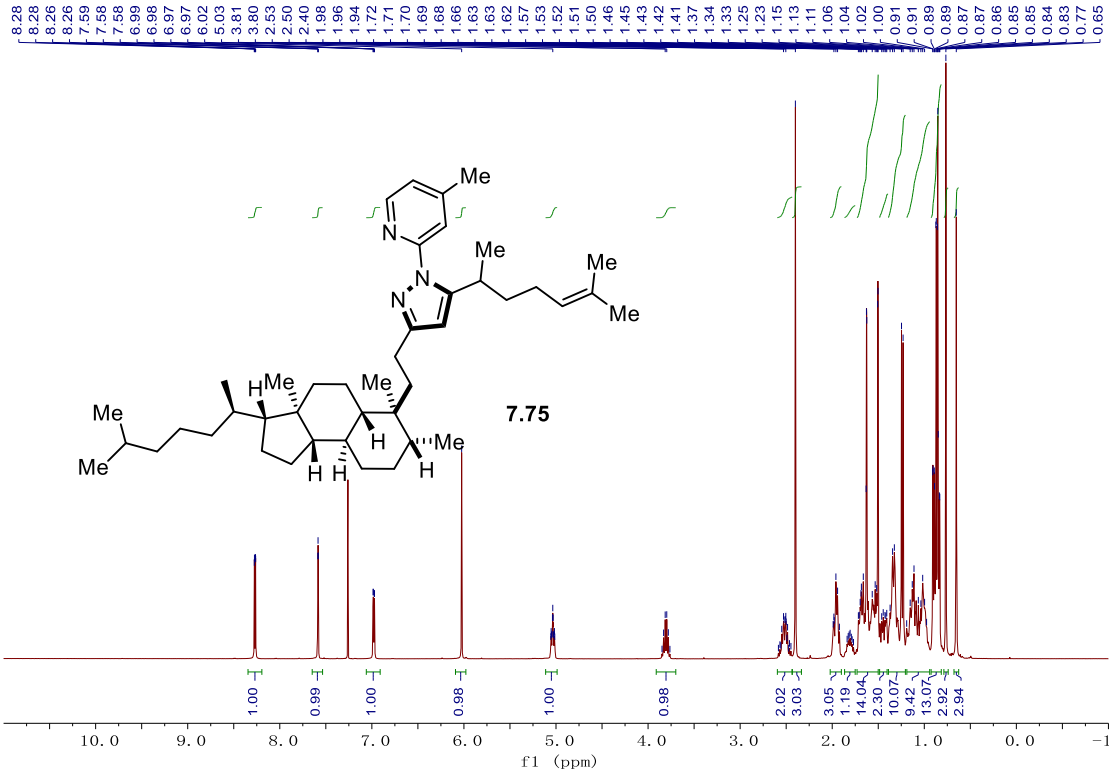


Figure 7.135 ^{13}C-NMR Spectrum of **7.75**

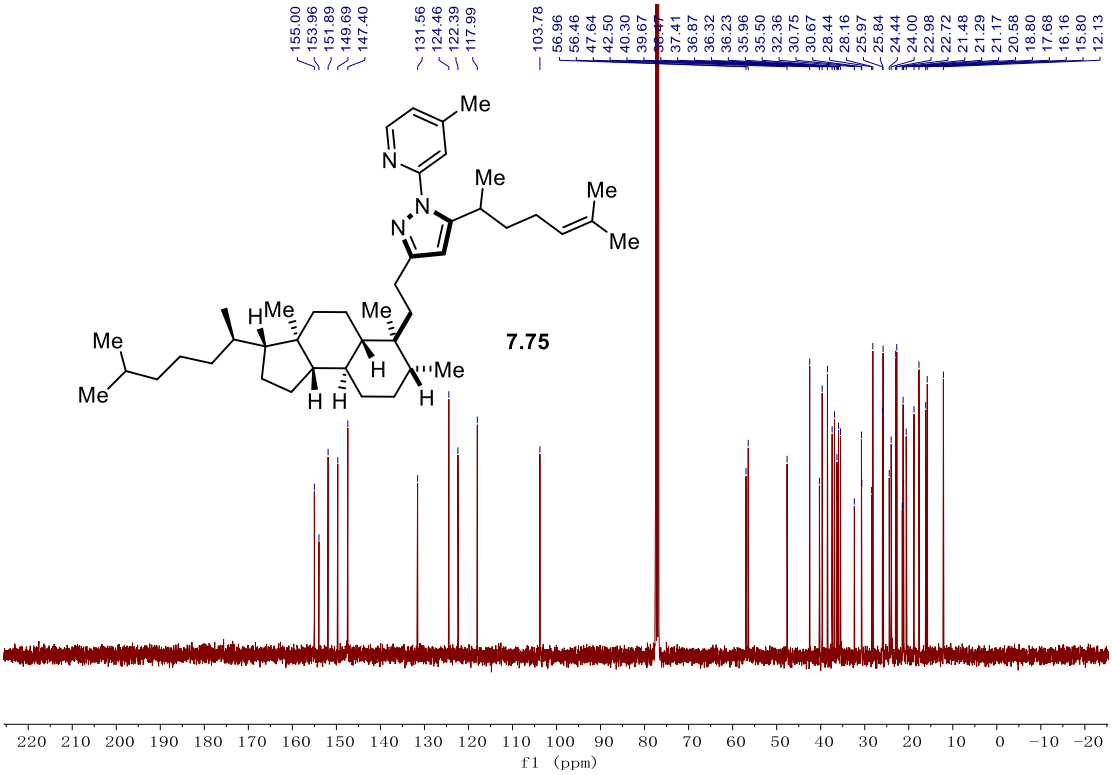


Figure 7.136 ^{1}H-NMR Spectrum of **7.77**

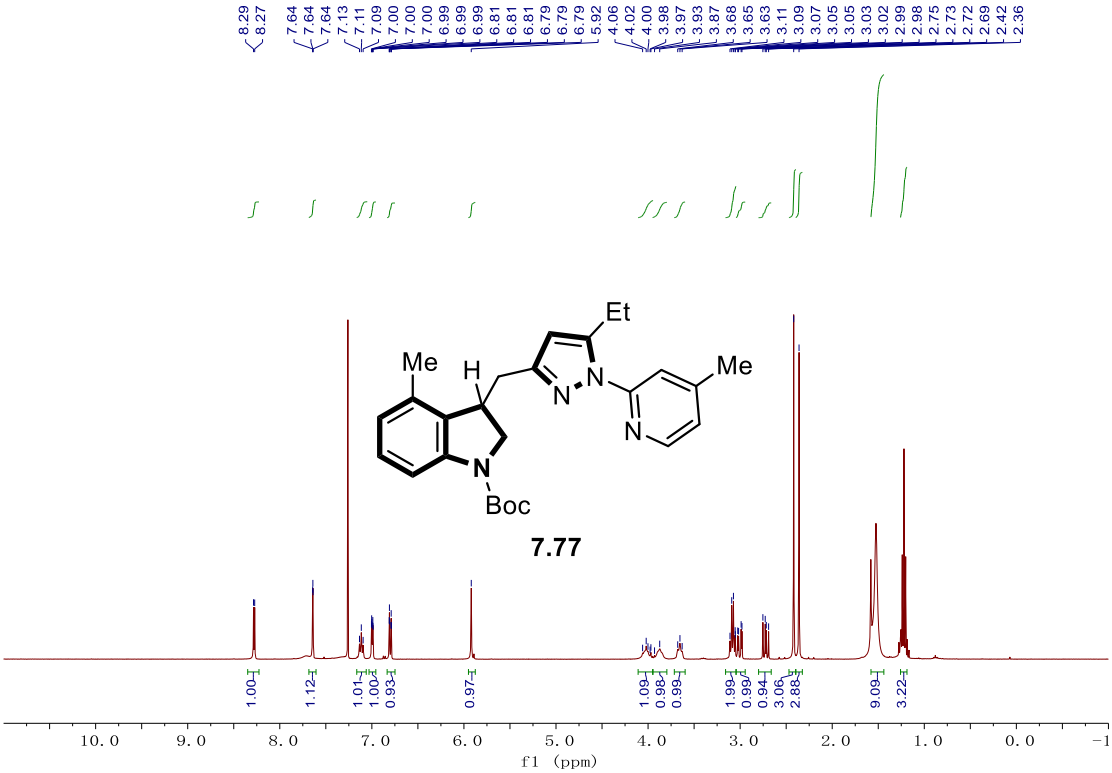


Figure 7.137 ^{13}C-NMR Spectrum of **7.77**

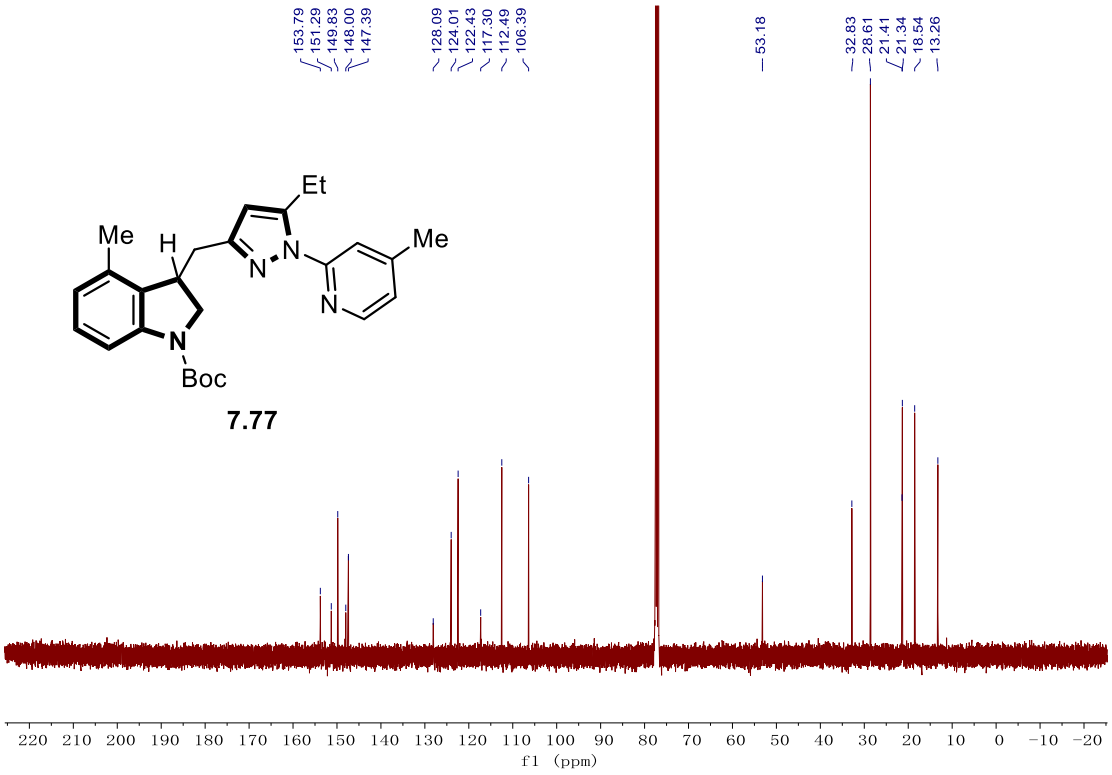


Figure 7.138 ^{1}H-NMR Spectrum of **7.79a**

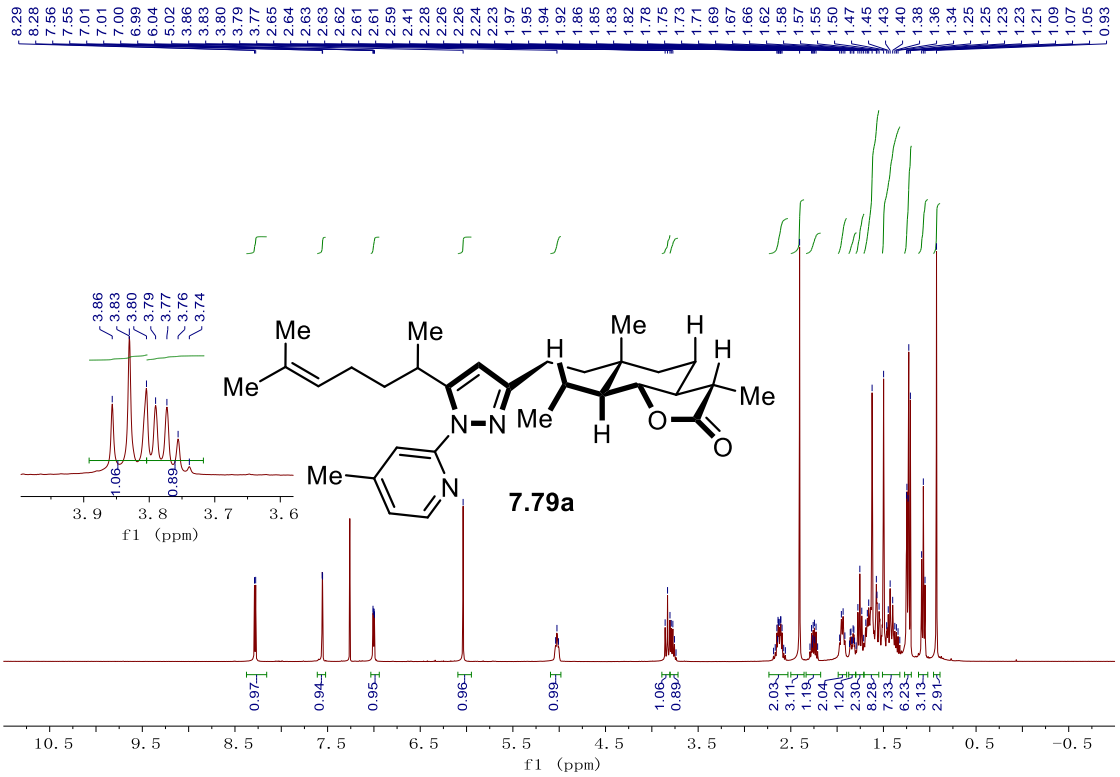


Figure 7.139 ^{13}C-NMR Spectrum of **7.79a**

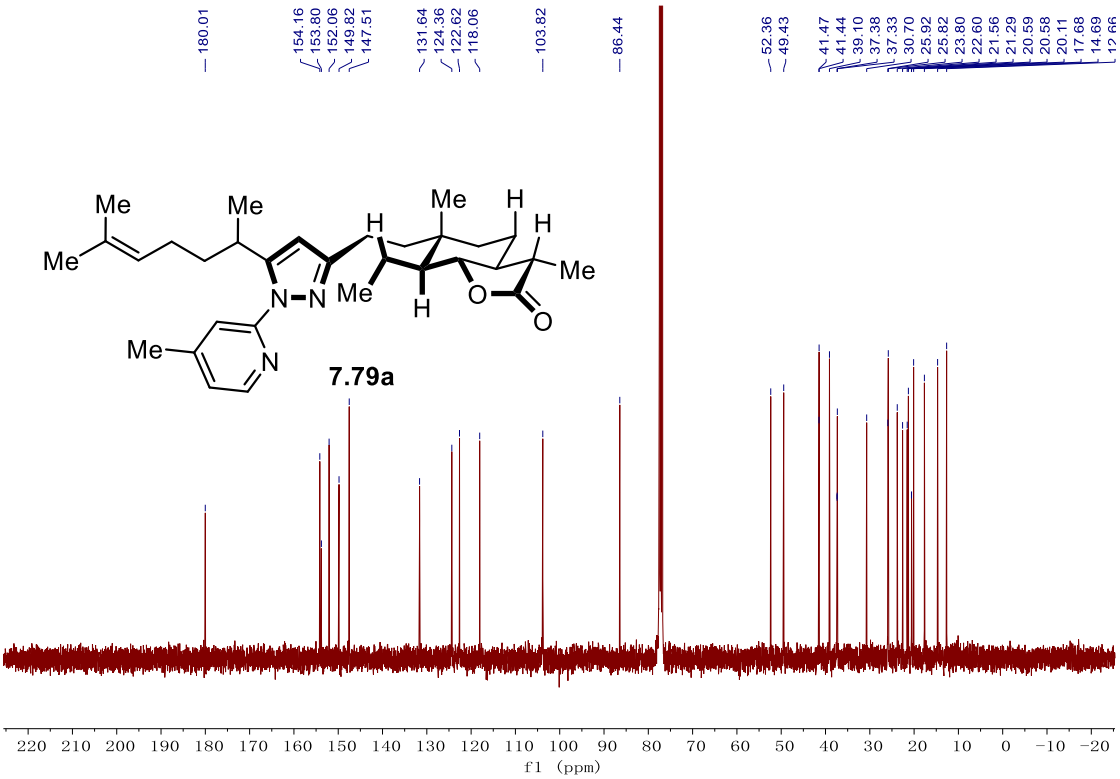


Figure 7.140 ^{1}H-NMR Spectrum of **7.79b**

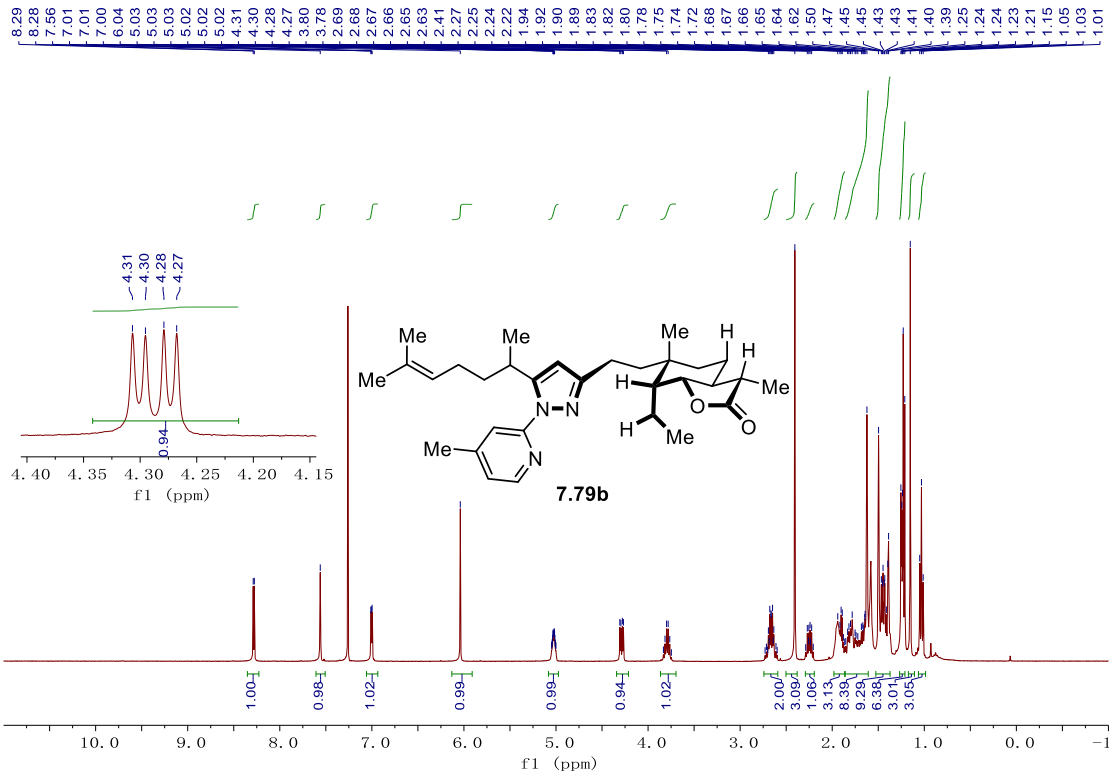


Figure 7.141 ^{13}C-NMR Spectrum of **7.79b**

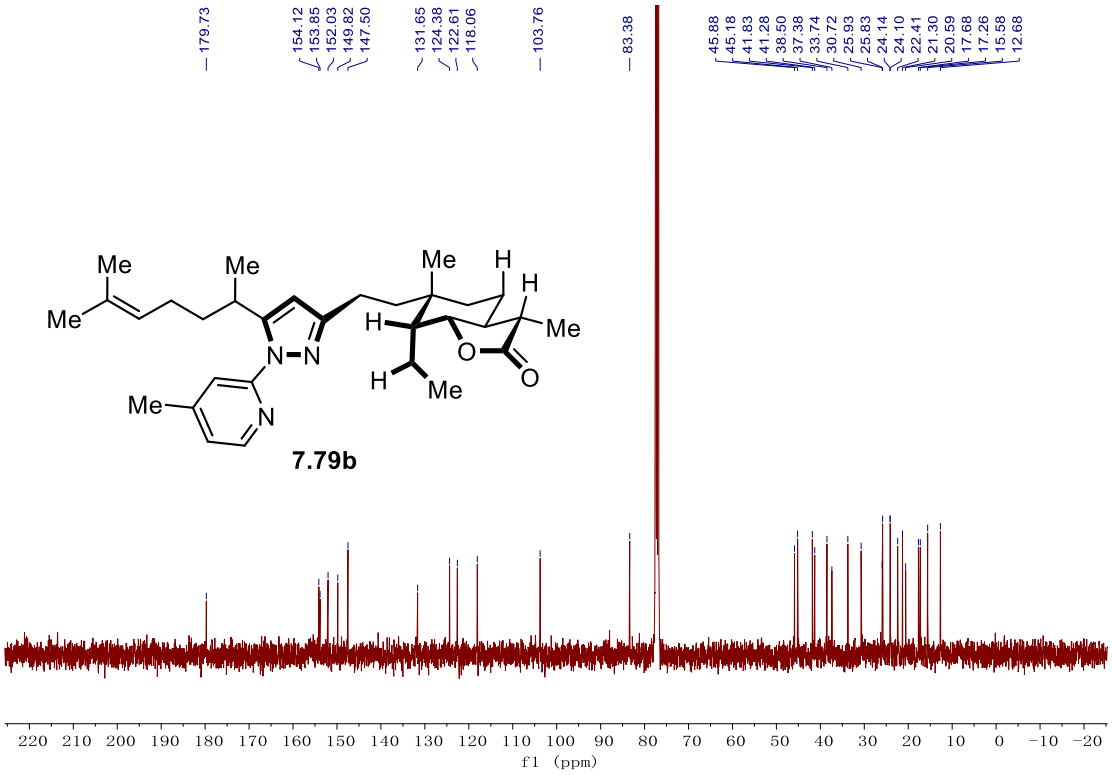


Figure 7.142 ^{1}H-NMR Spectrum of **7.81**

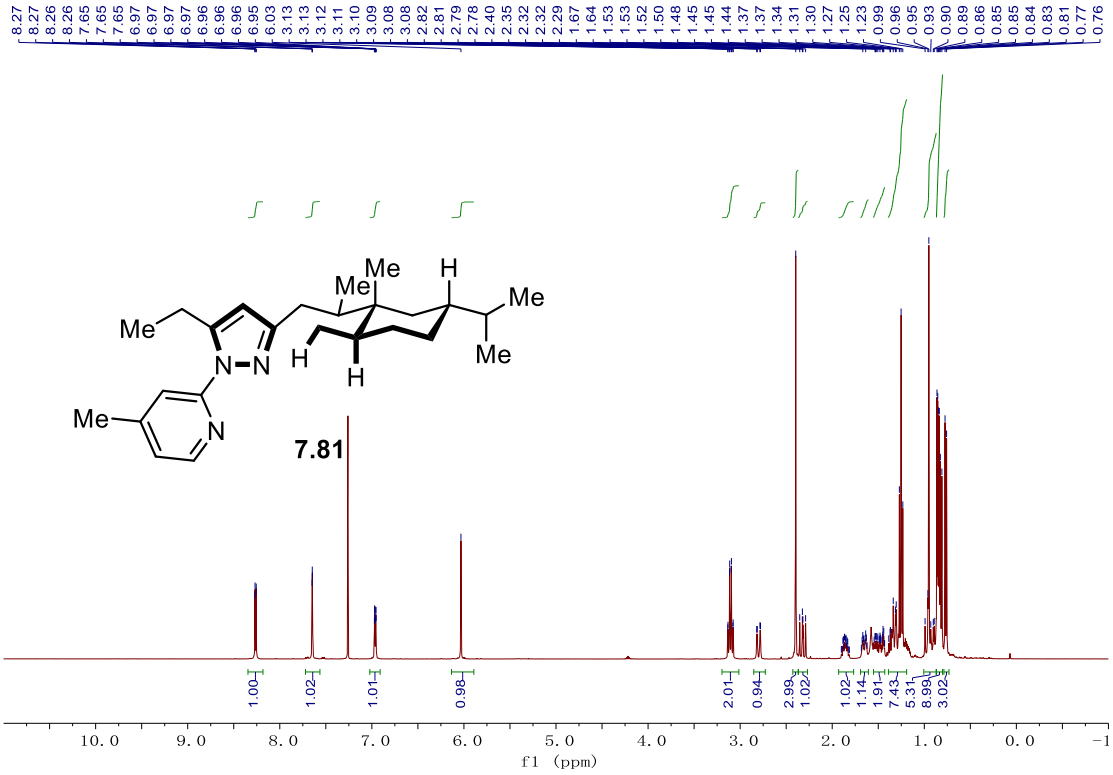


Figure 7.143 ^{13}C-NMR Spectrum of **7.81**

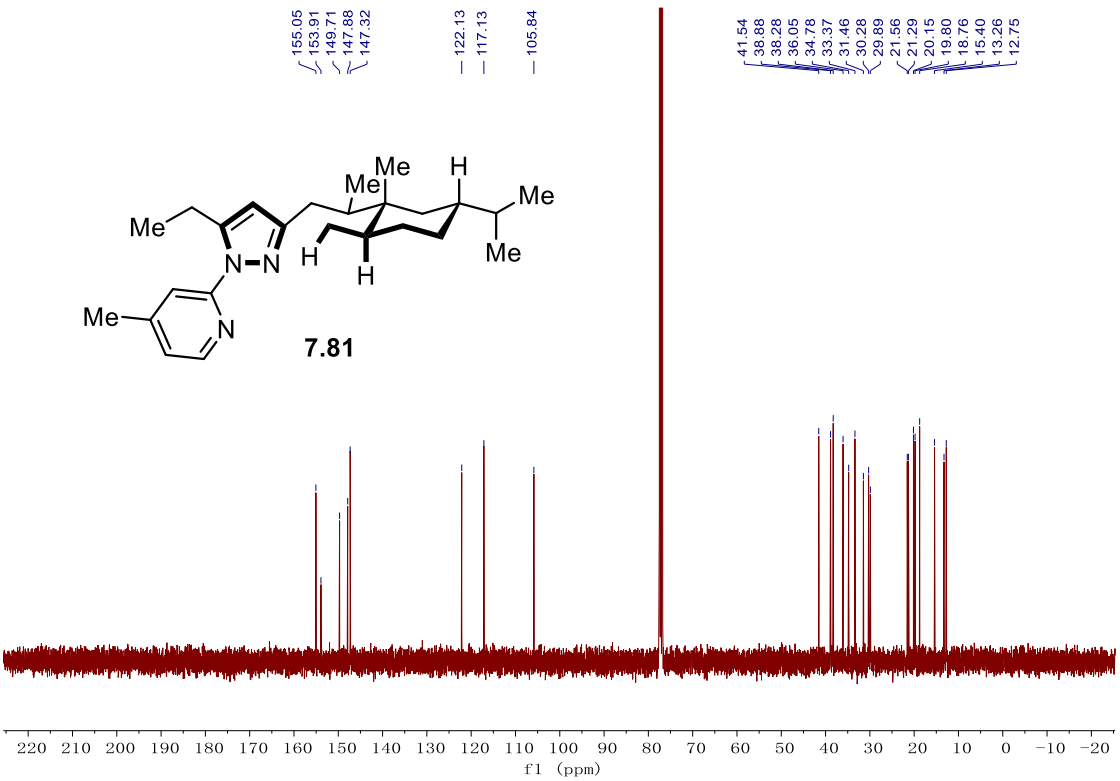


Figure 7.144 ^{1}H-NMR Spectrum of **7.82**

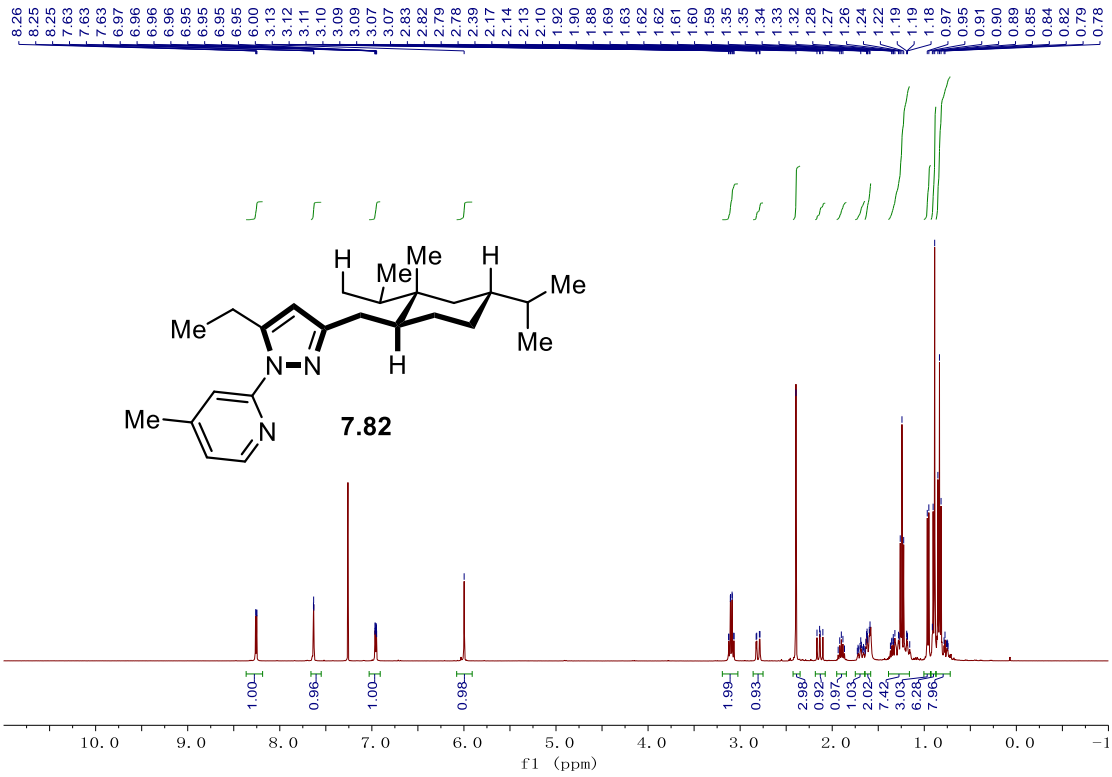


Figure 7.145 ^{13}C-NMR Spectrum of **7.82**

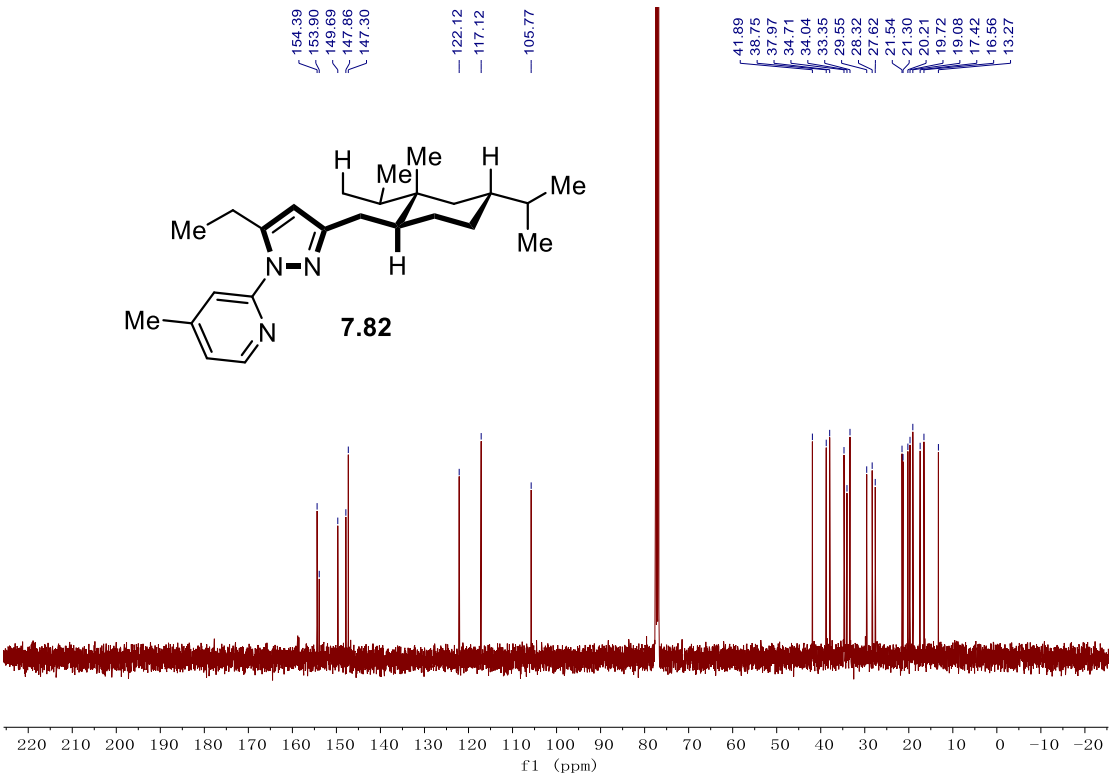


Figure 7.146 ^{1}H-NMR Spectrum of **7.83**

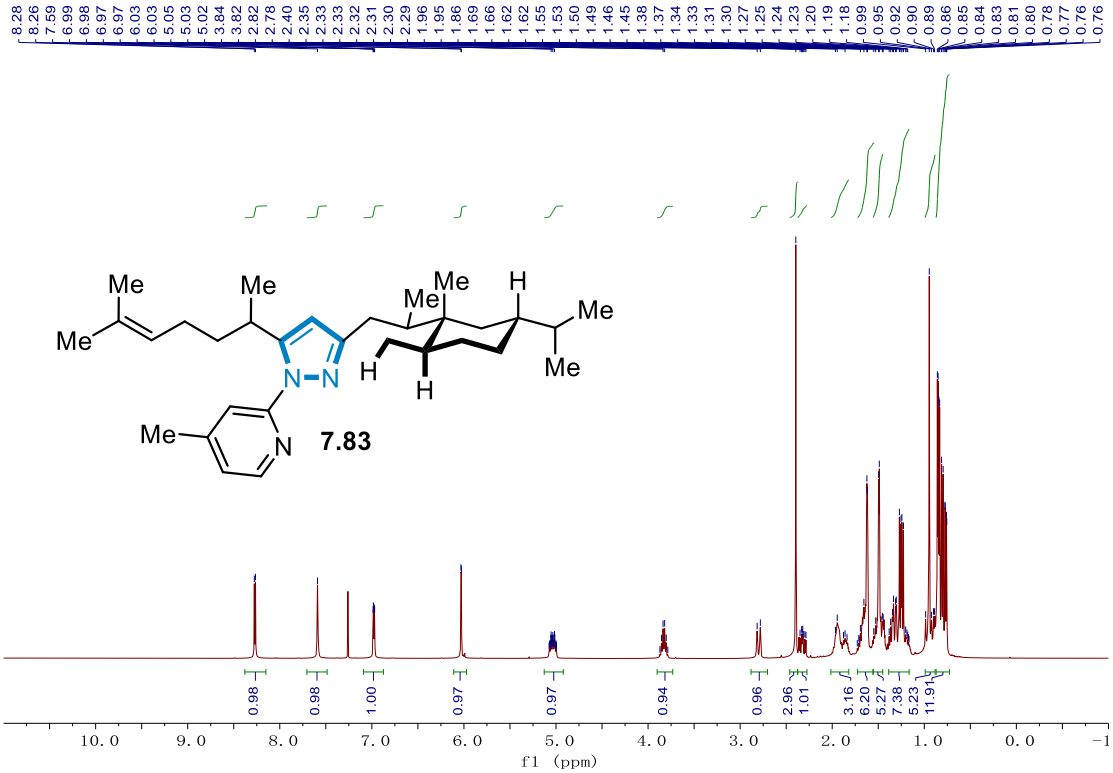


Figure 7.147 ^{13}C-NMR Spectrum of **7.83**

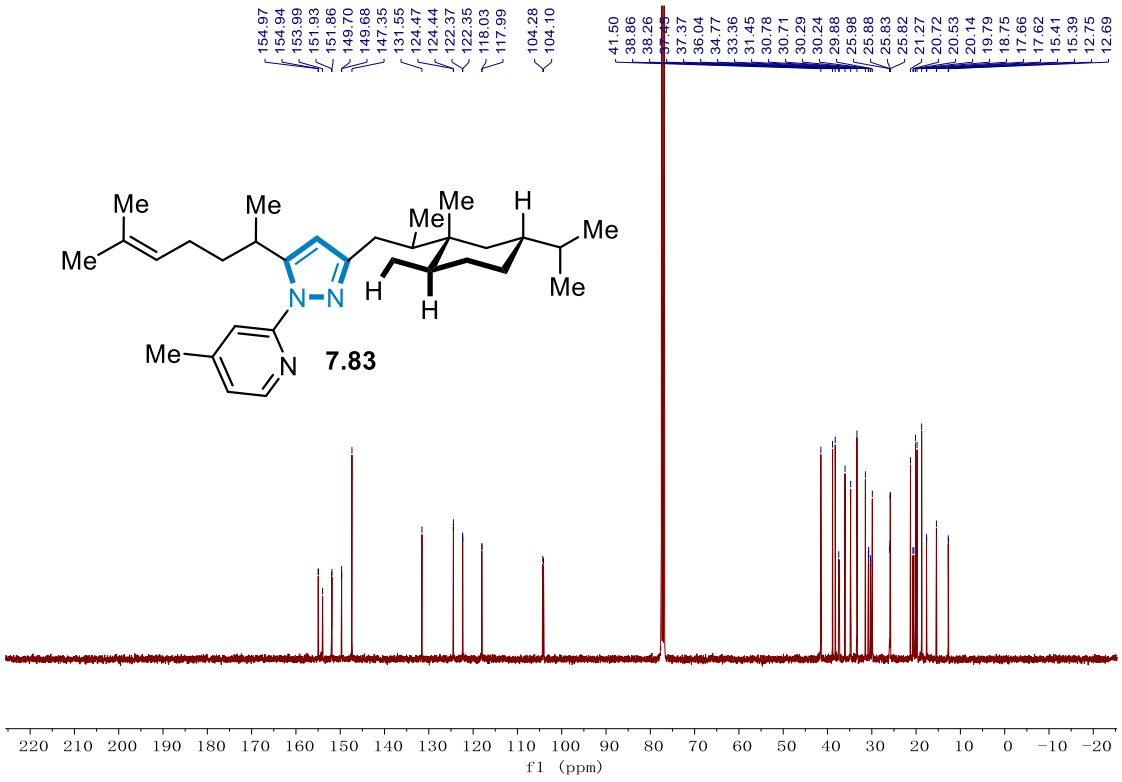


Figure 7.148 ^{1}H-NMR Spectrum of **7.84**

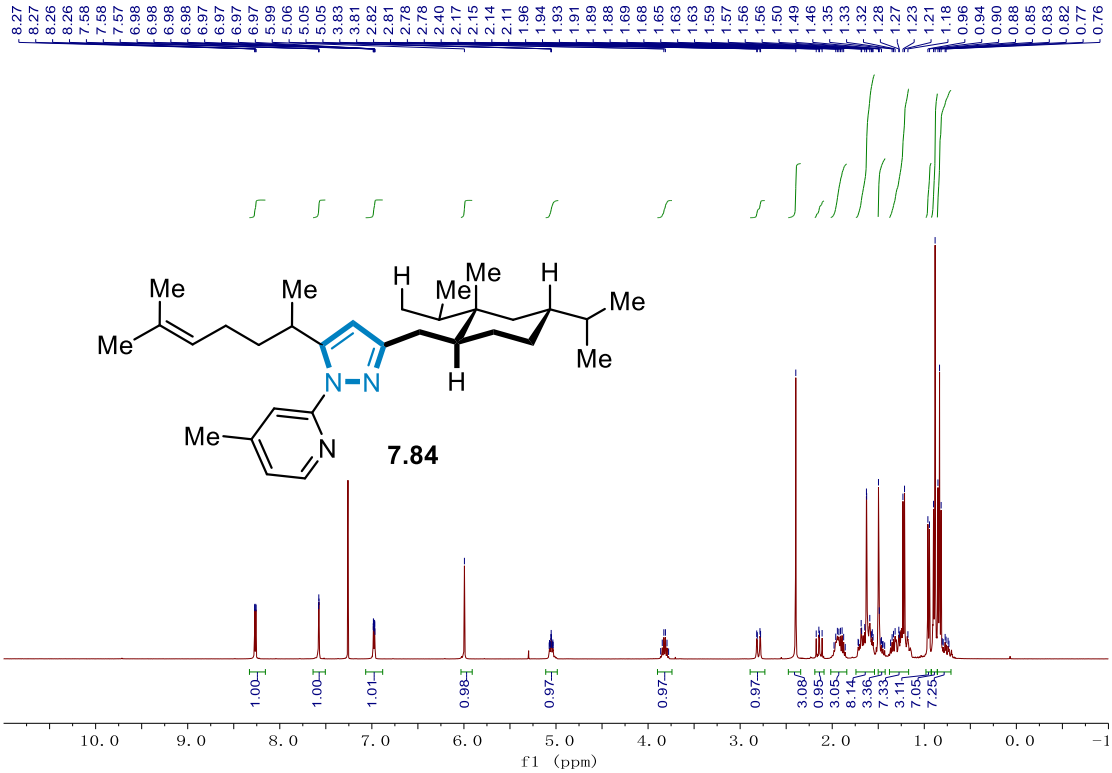


Figure 7.149 ^{13}C-NMR Spectrum of **7.84**

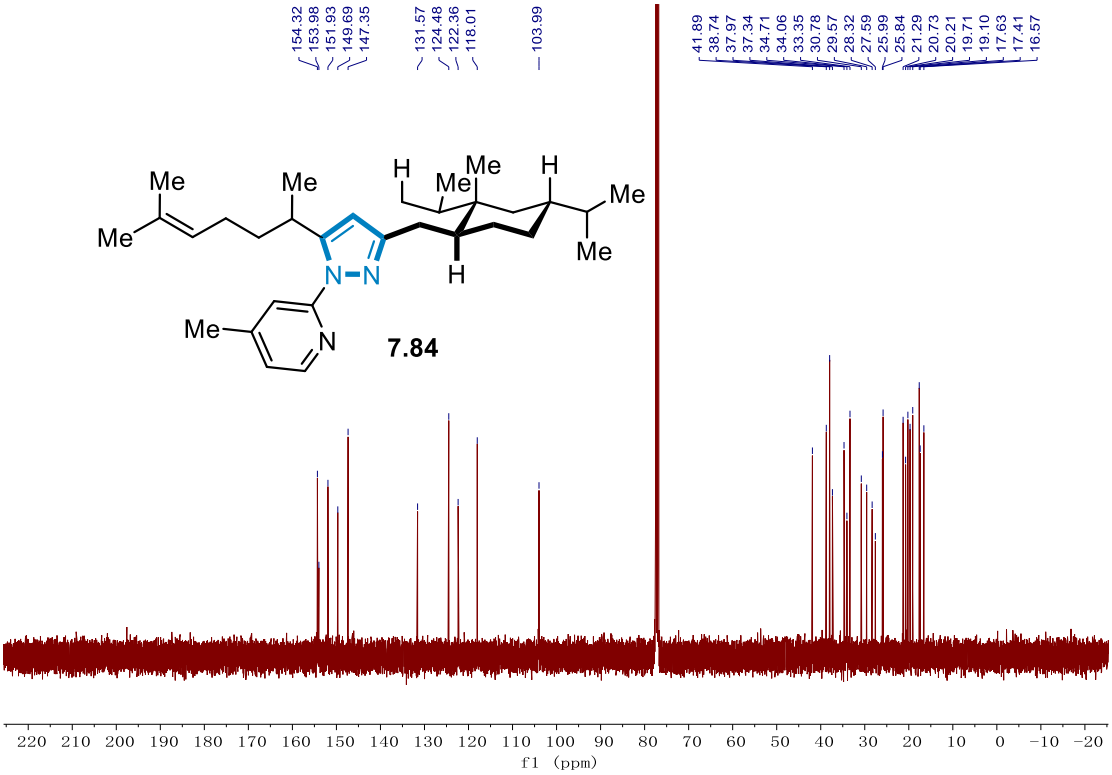


Figure 7.150 ^{1}H-NMR Spectrum of **7.86a**

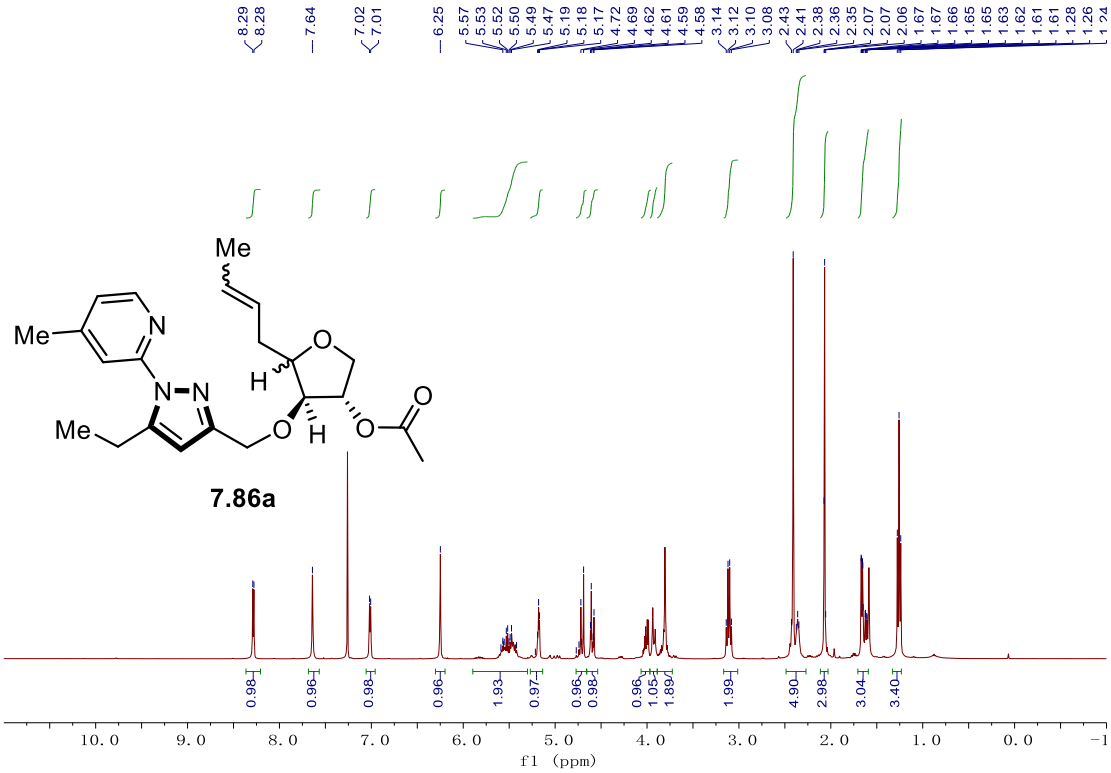


Figure 7.151 ^{13}C-NMR Spectrum of **7.86a**

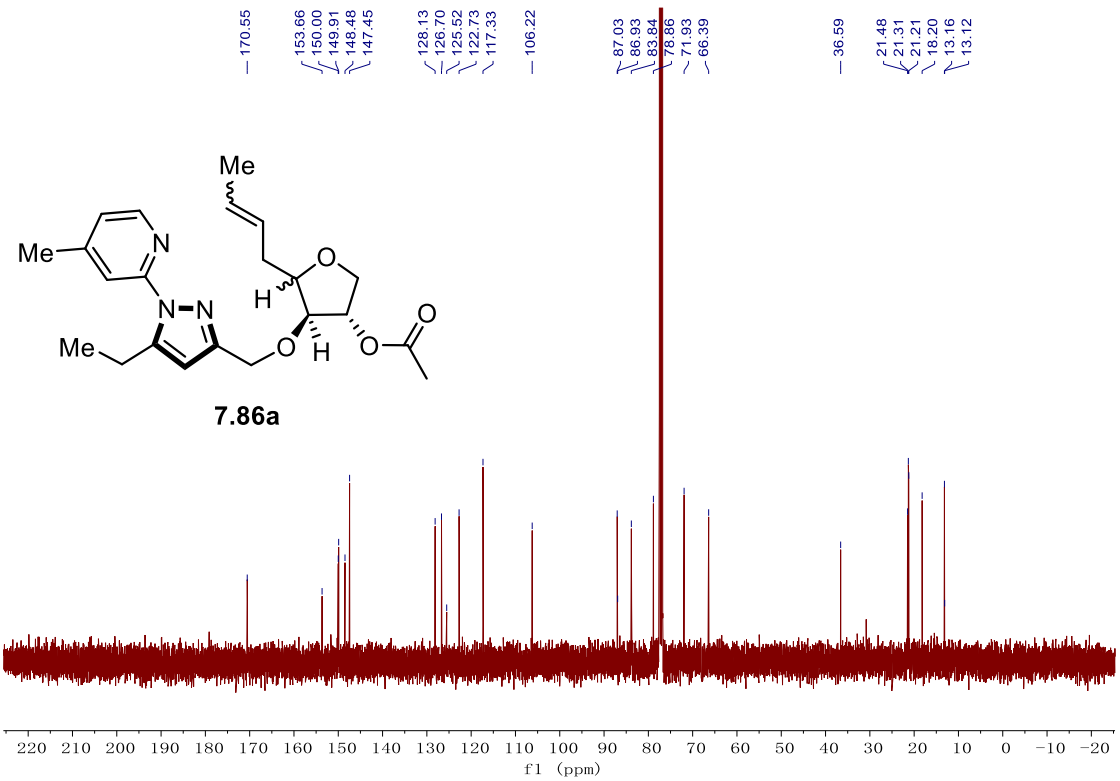


Figure 7.152 ^{1}H-NMR Spectrum of **7.86b**

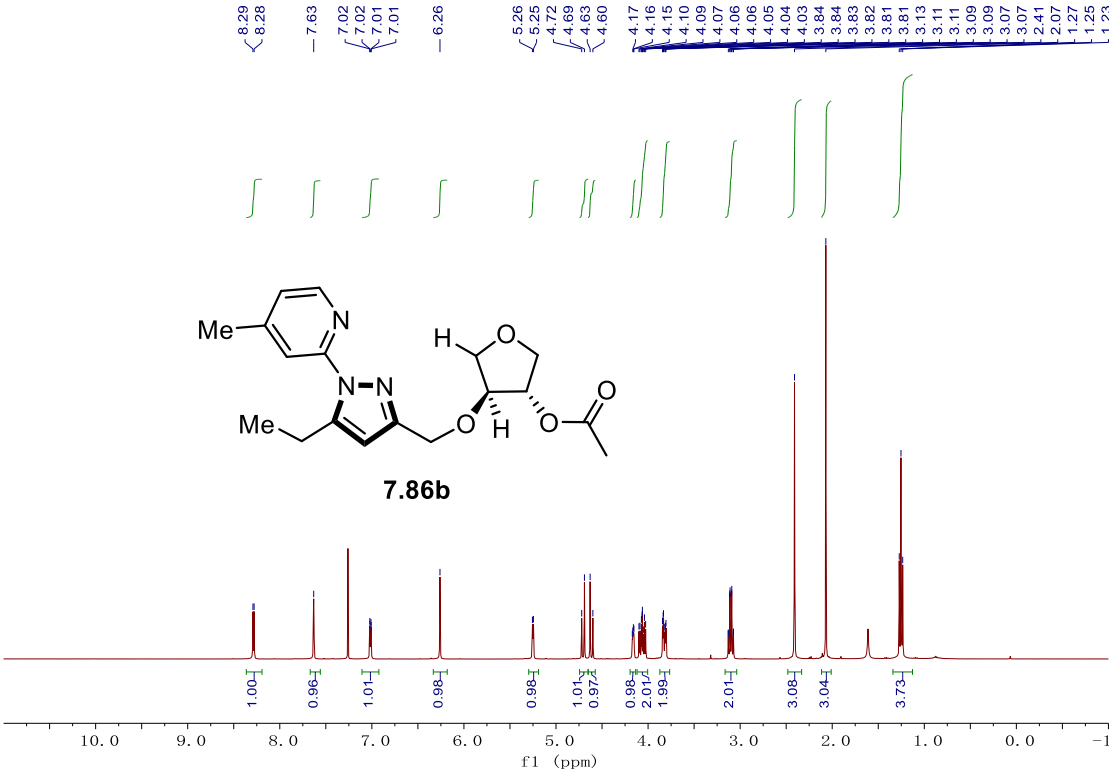


Figure 7.153 ^{13}C-NMR Spectrum of **7.86b**

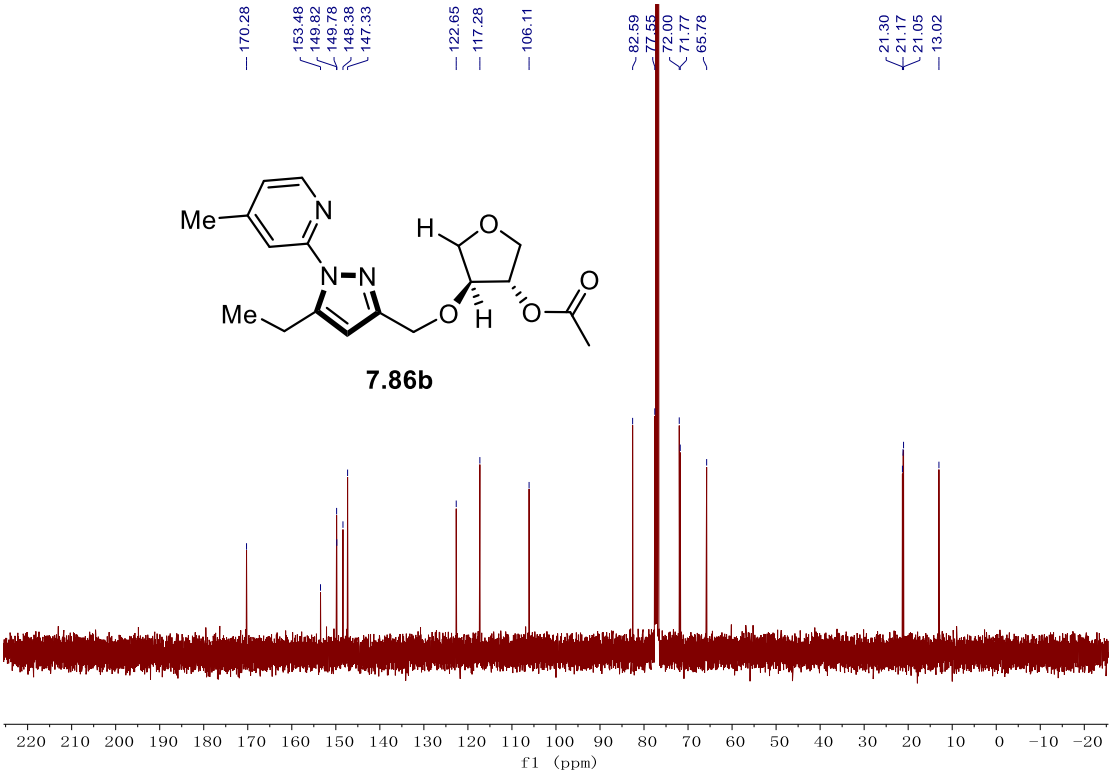


Figure 7.154 ^{1}H-NMR Spectrum of **7.88**

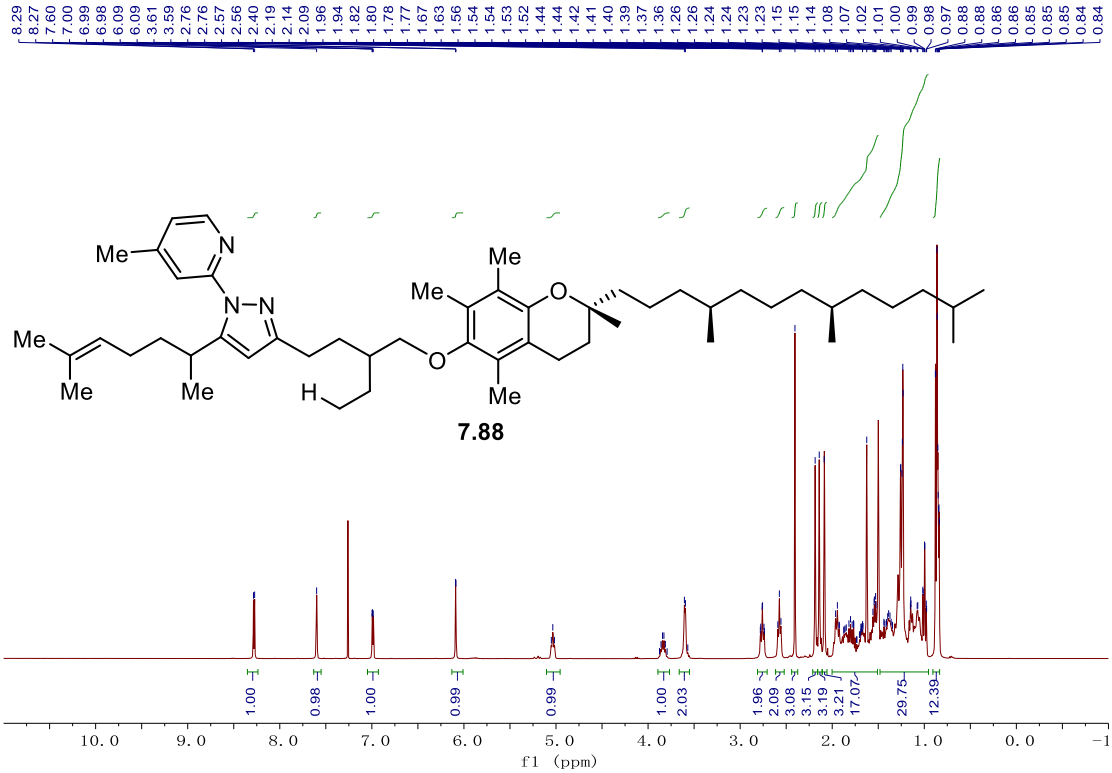


Figure 7.155 ^{13}C-NMR Spectrum of **7.88**

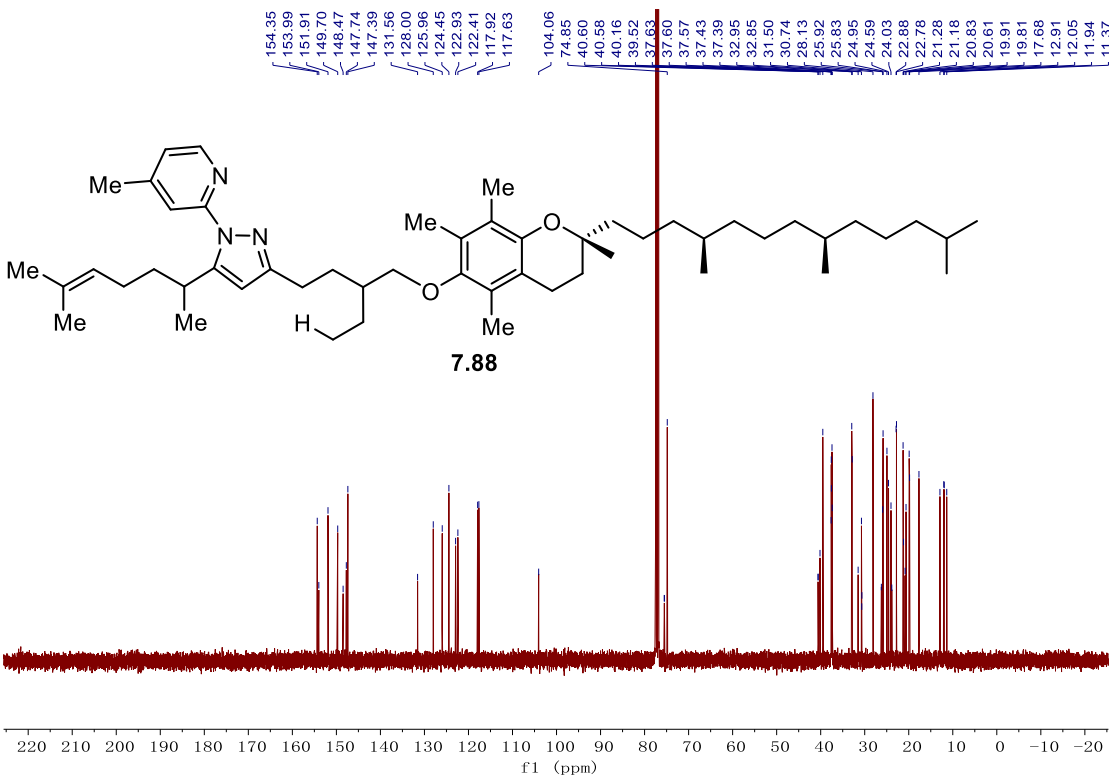


Figure 7.156 ^{1}H-NMR Spectrum of **7.15b**

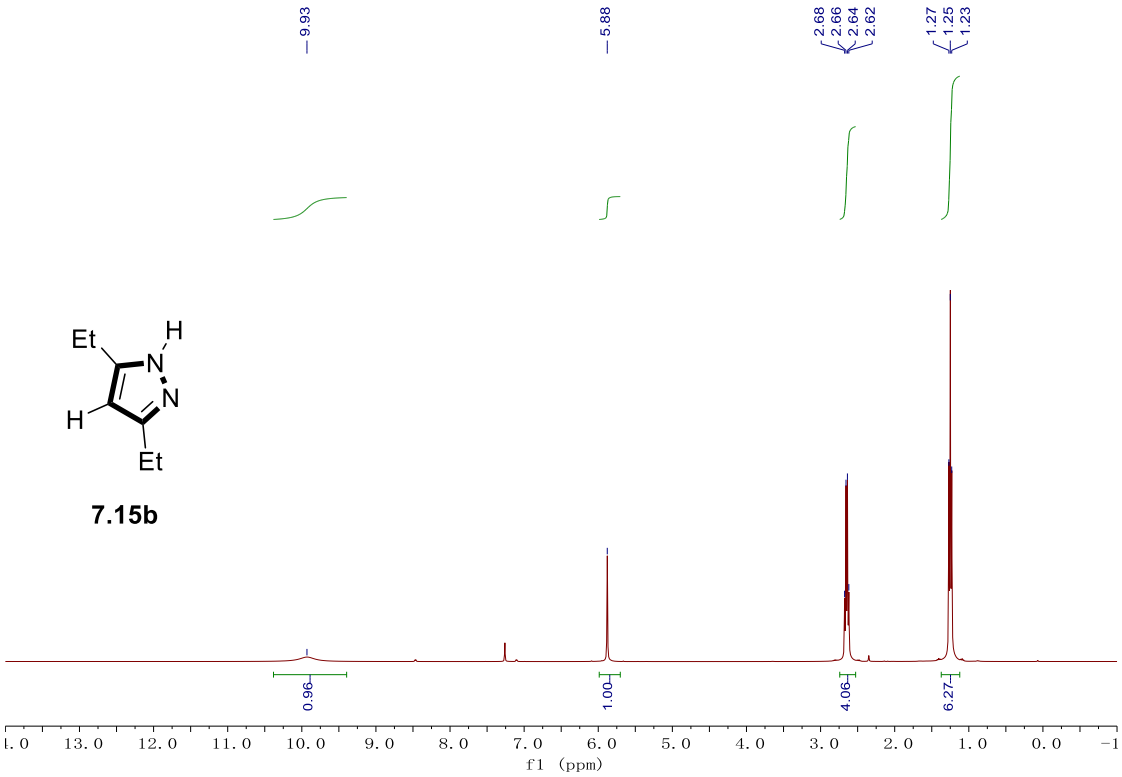


Figure 7.157 ^{13}C-NMR Spectrum of **7.15b**

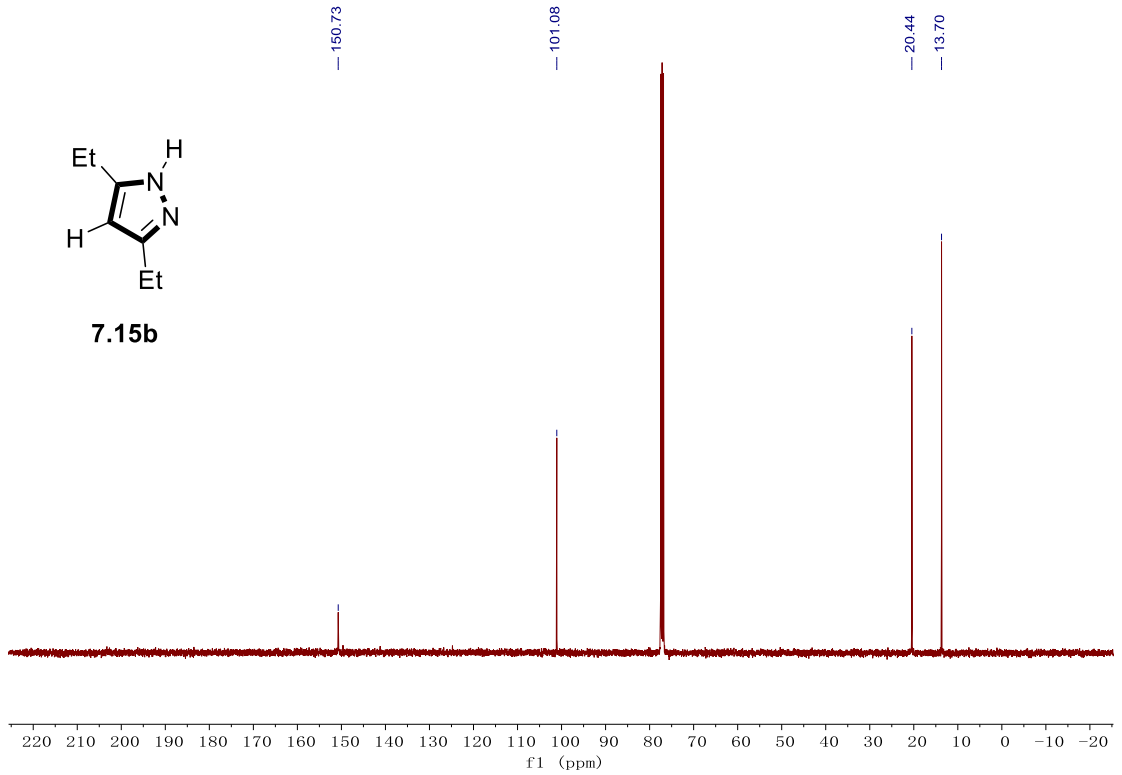


Figure 7.158 ^{1}H-NMR Spectrum of **7.89**

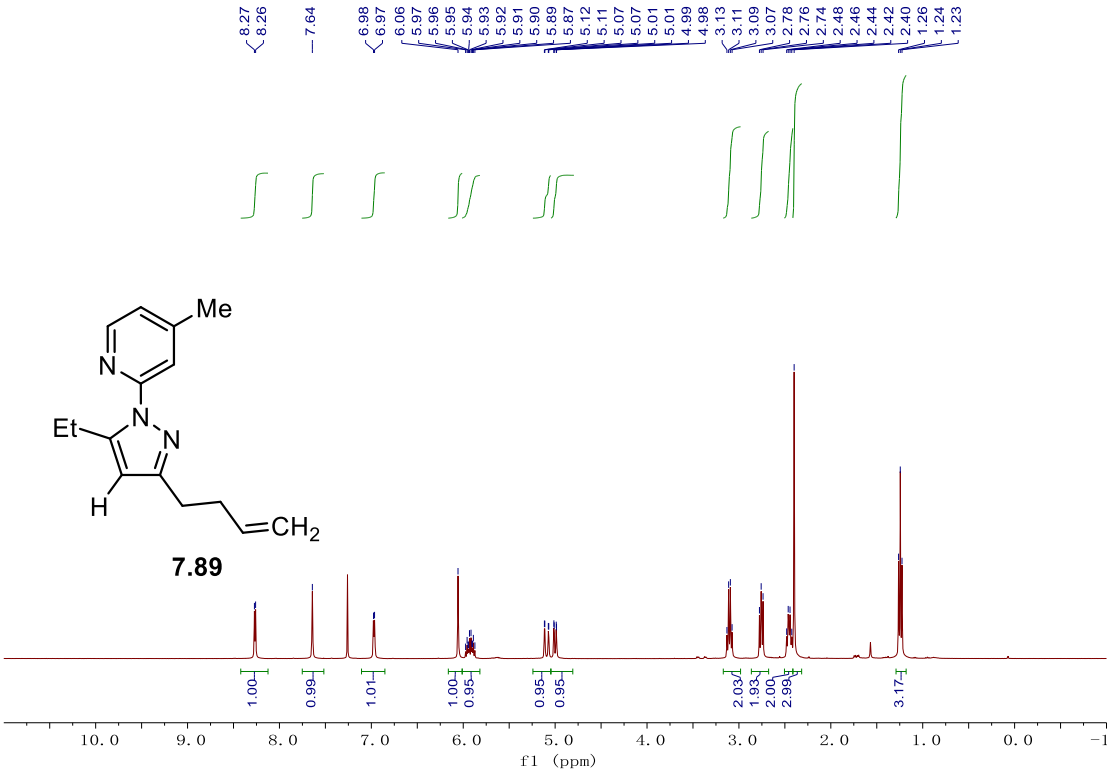


Figure 7.159 ^{13}C-NMR Spectrum of **7.89**

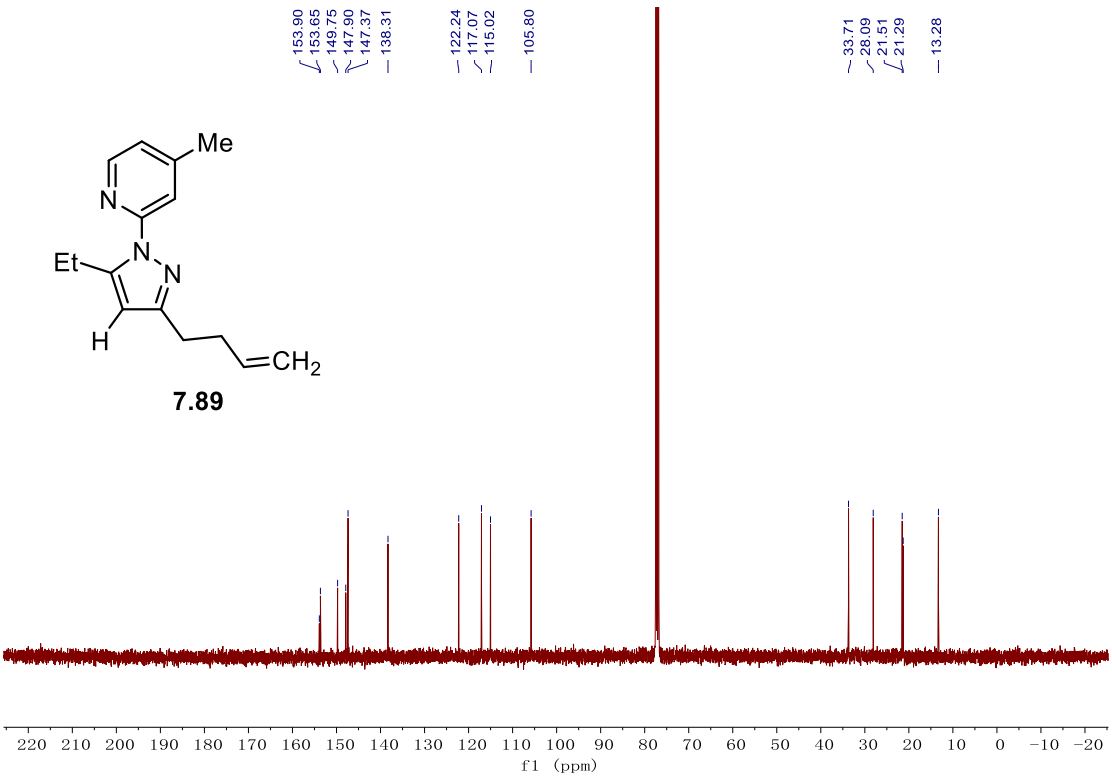


Figure 7.160 ^{1}H-NMR Spectrum of **7.93**

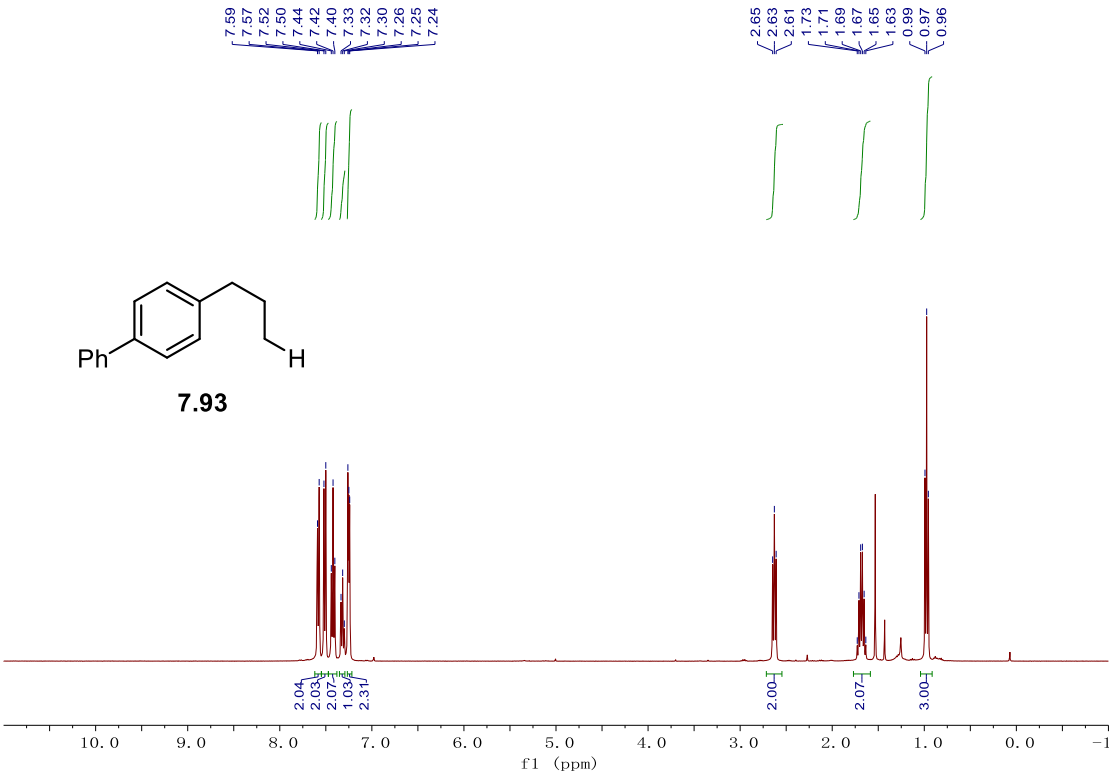


Figure 7.161 ^{13}C-NMR Spectrum of **7.93**

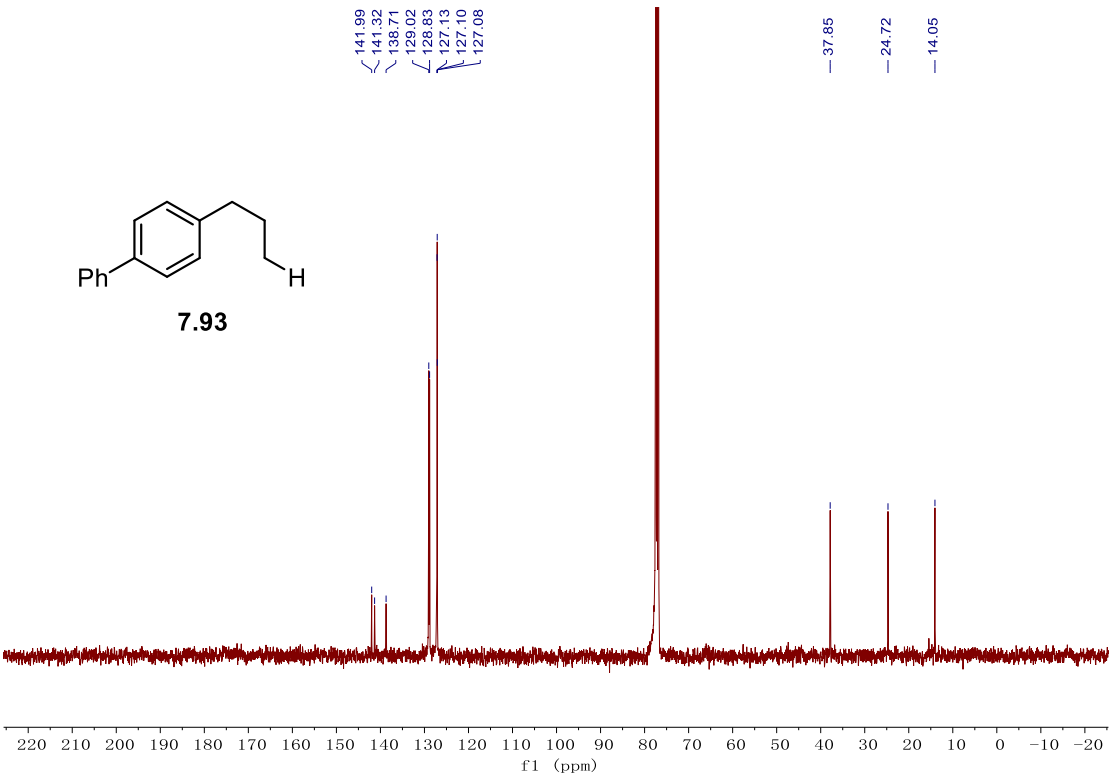


Figure 7.162 ^{1}H-NMR Spectrum of **7.94**

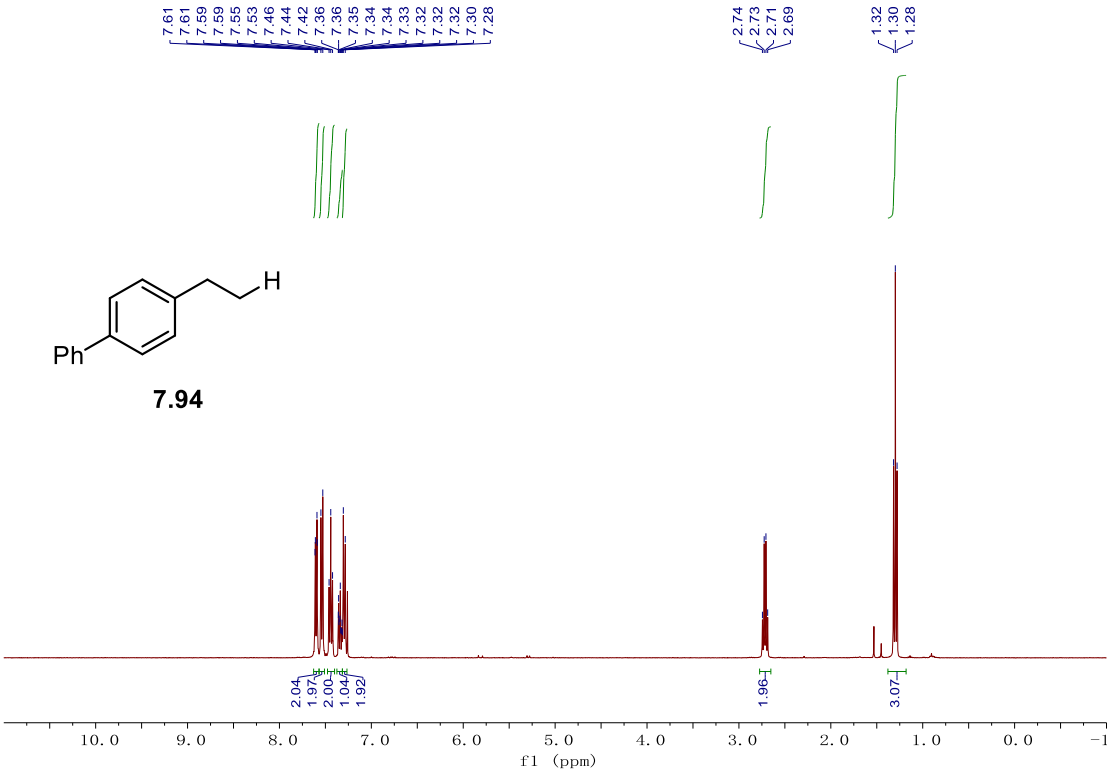


Figure 7.163 ^{13}C-NMR Spectrum of **7.94**

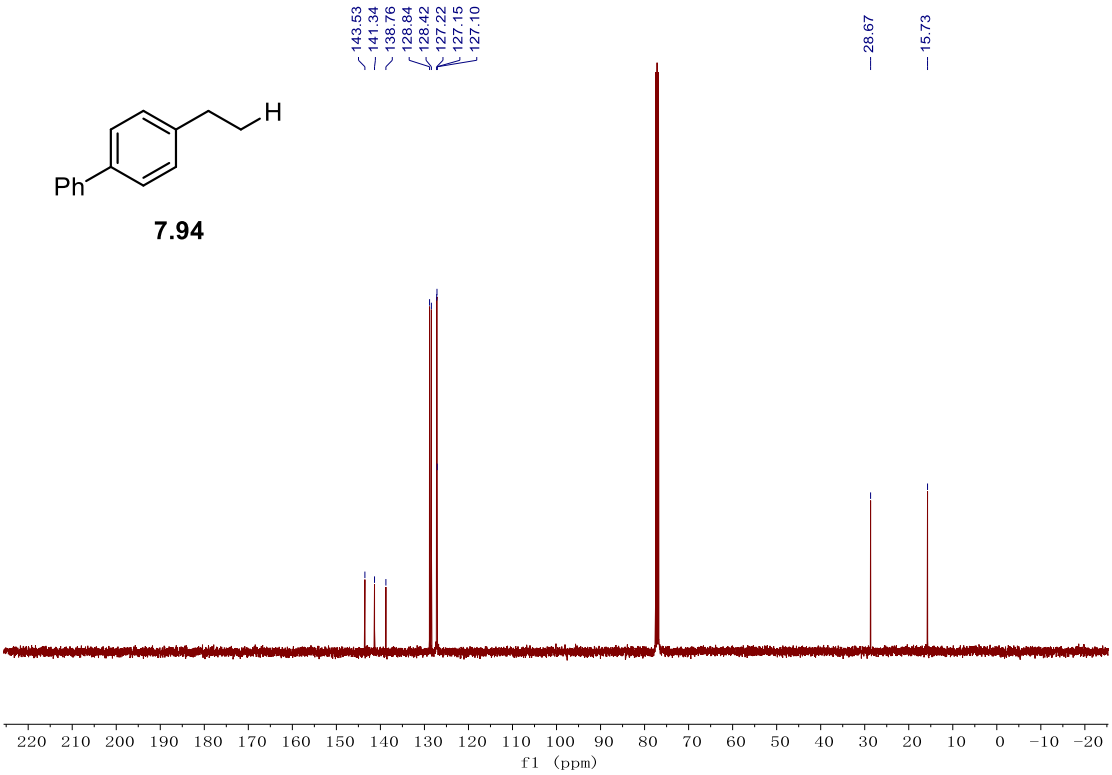


Figure 7.164 ^{1}H-NMR Spectrum of **7.95**

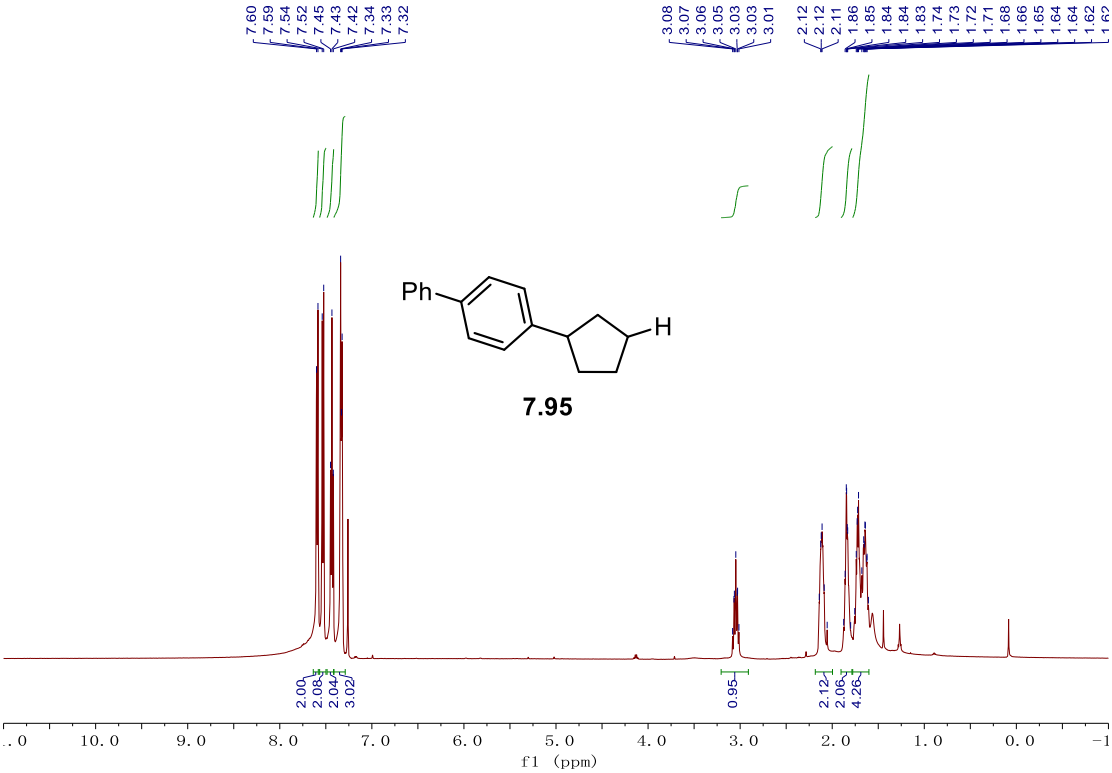


Figure 7.165 ^{13}C-NMR Spectrum of **7.95**

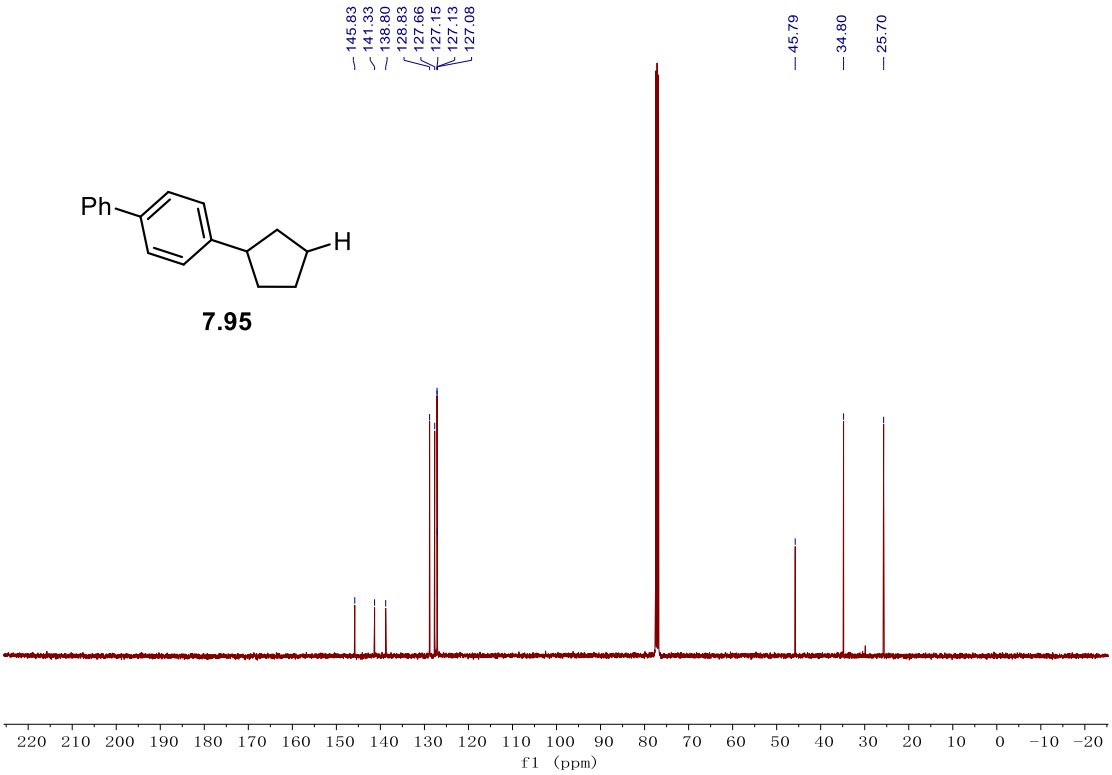
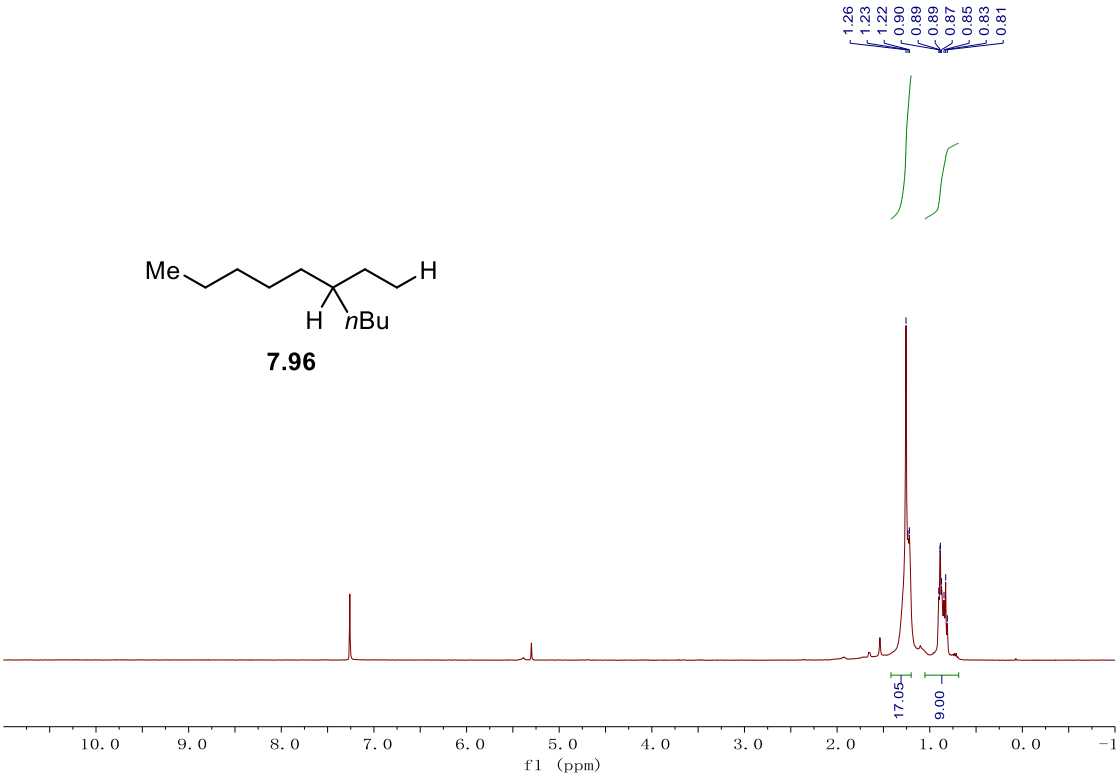
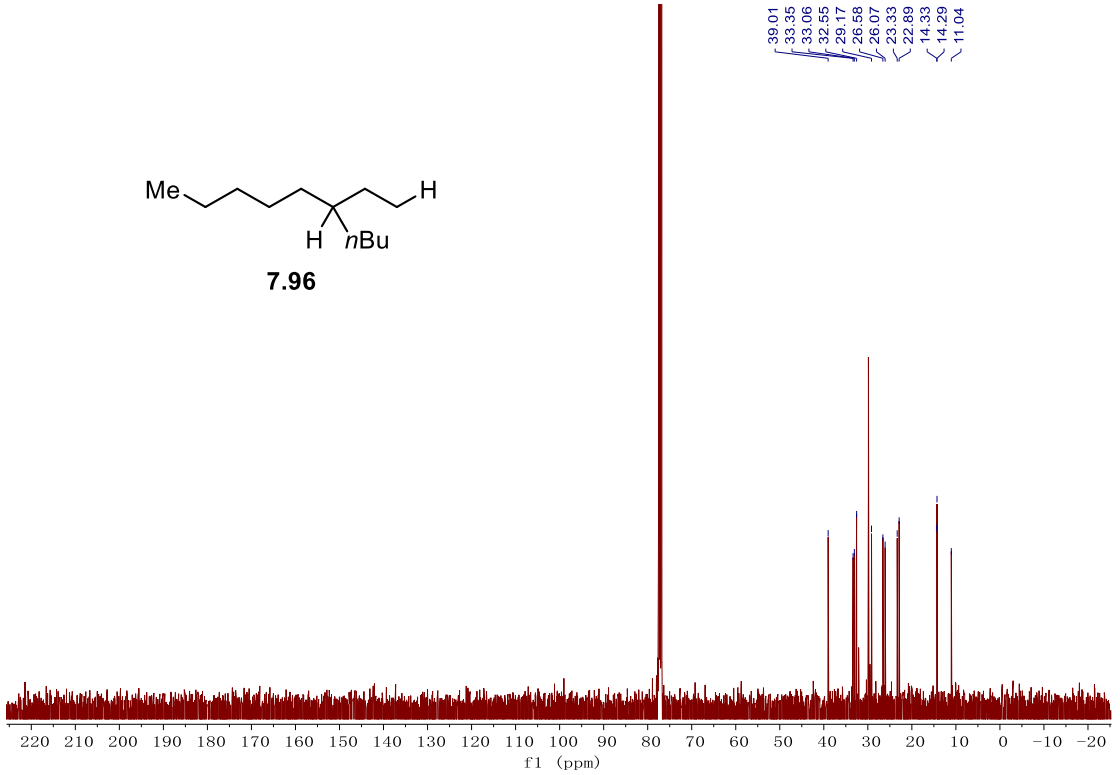


Figure 7.166 ^{1}H-NMR Spectrum of **7.96**



7.96

Figure 7.167 ^{13}C-NMR Spectrum of **7.96**



7.96

Figure 7.168 ^{1}H-NMR Spectrum of **7.97** and **7.97'**

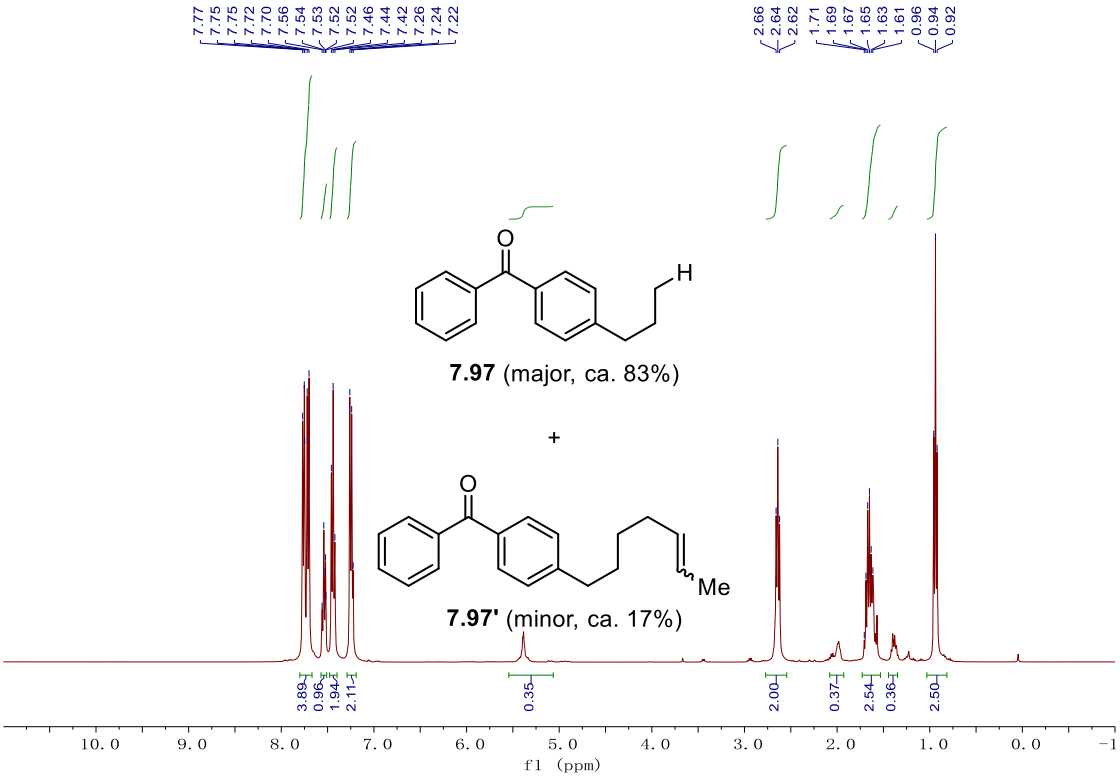


Figure 7.169 ^{13}C-NMR Spectrum of **7.97** and **7.97'**

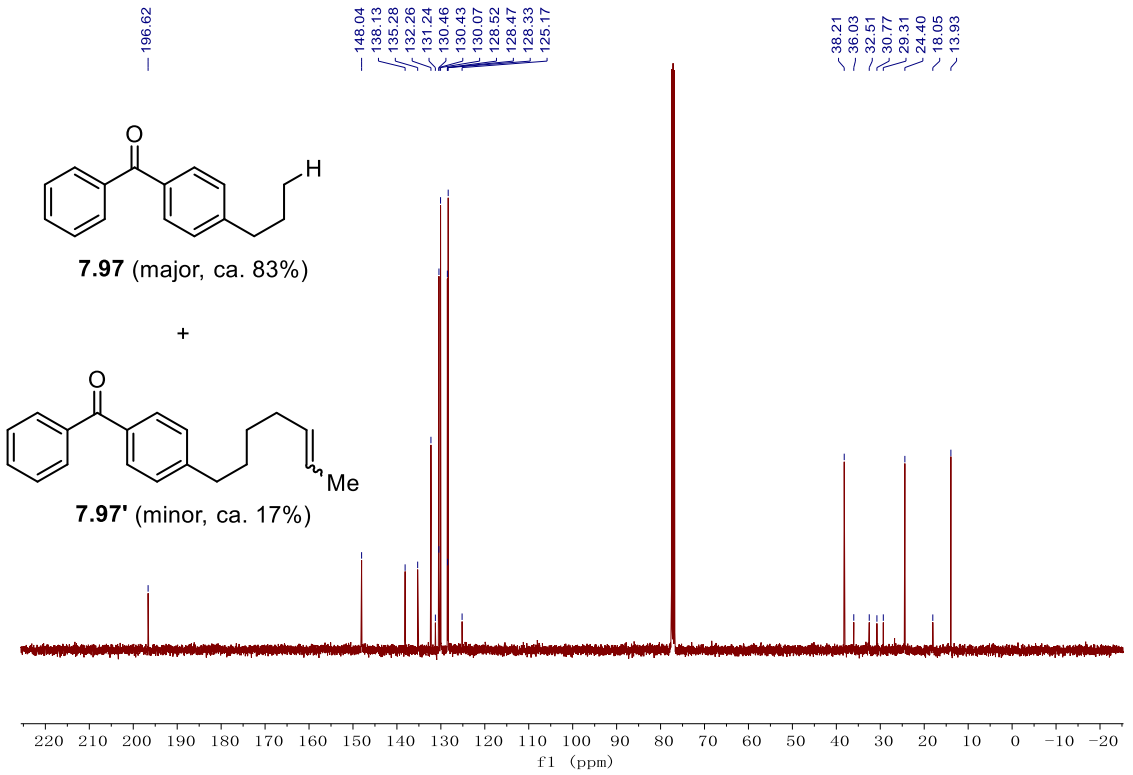


Figure 7.170 ^{1}H-NMR Spectrum of **7.98**

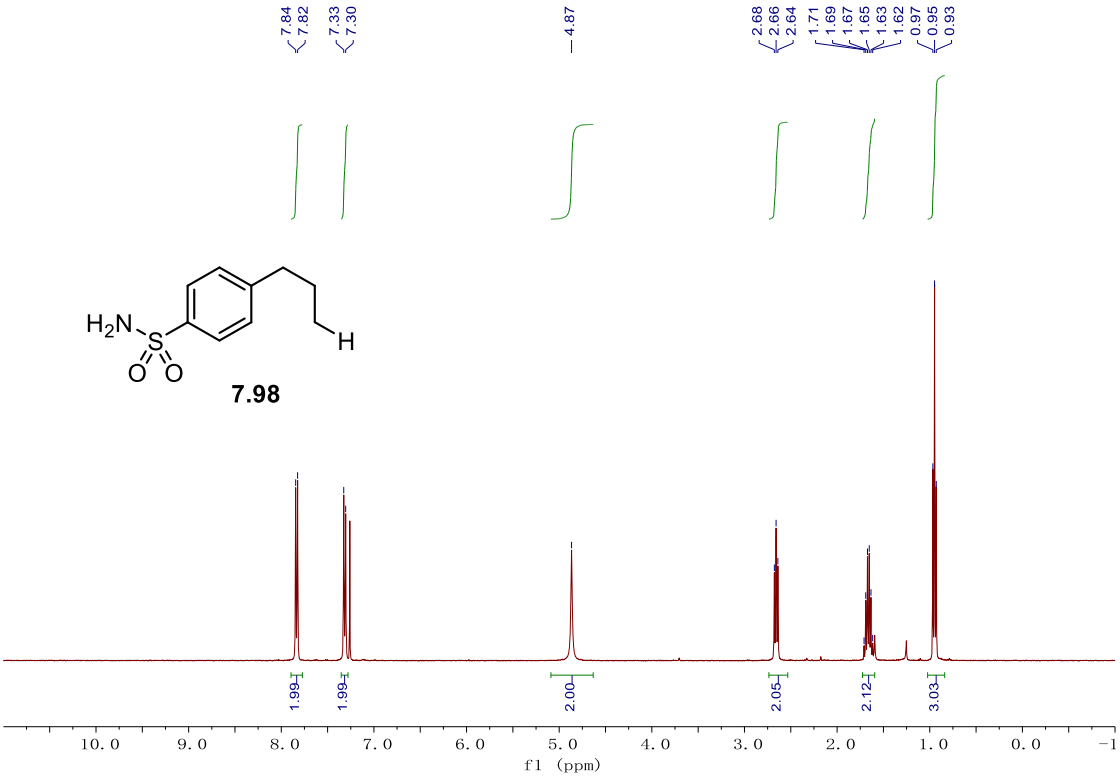


Figure 7.171 ^{13}C-NMR Spectrum of **7.98**

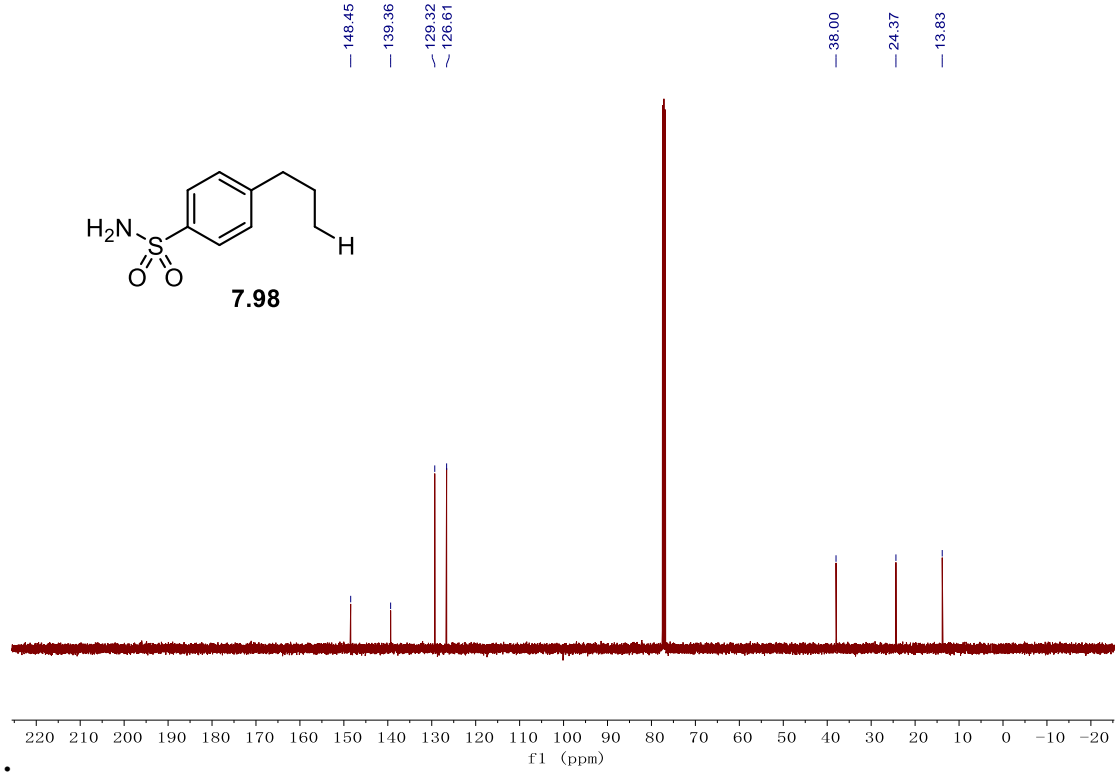


Figure 7.172 ^{1}H-NMR Spectrum of **7.99**

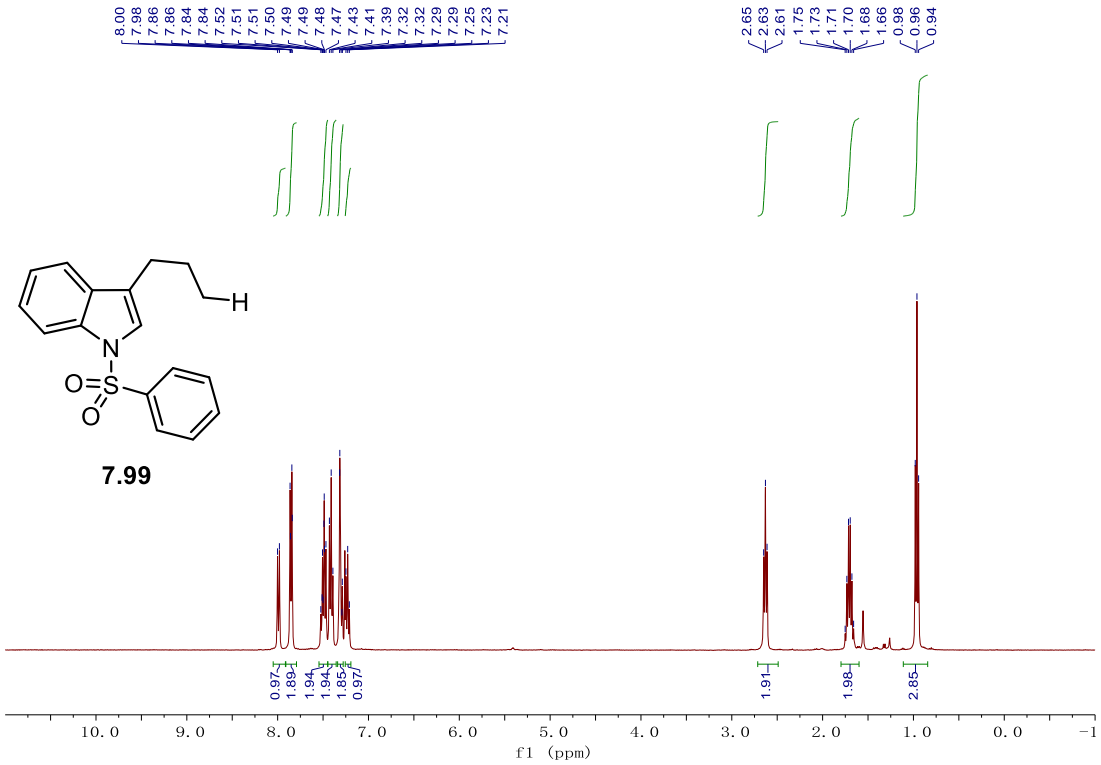


Figure 7.173 ^{13}C-NMR Spectrum of **7.99**

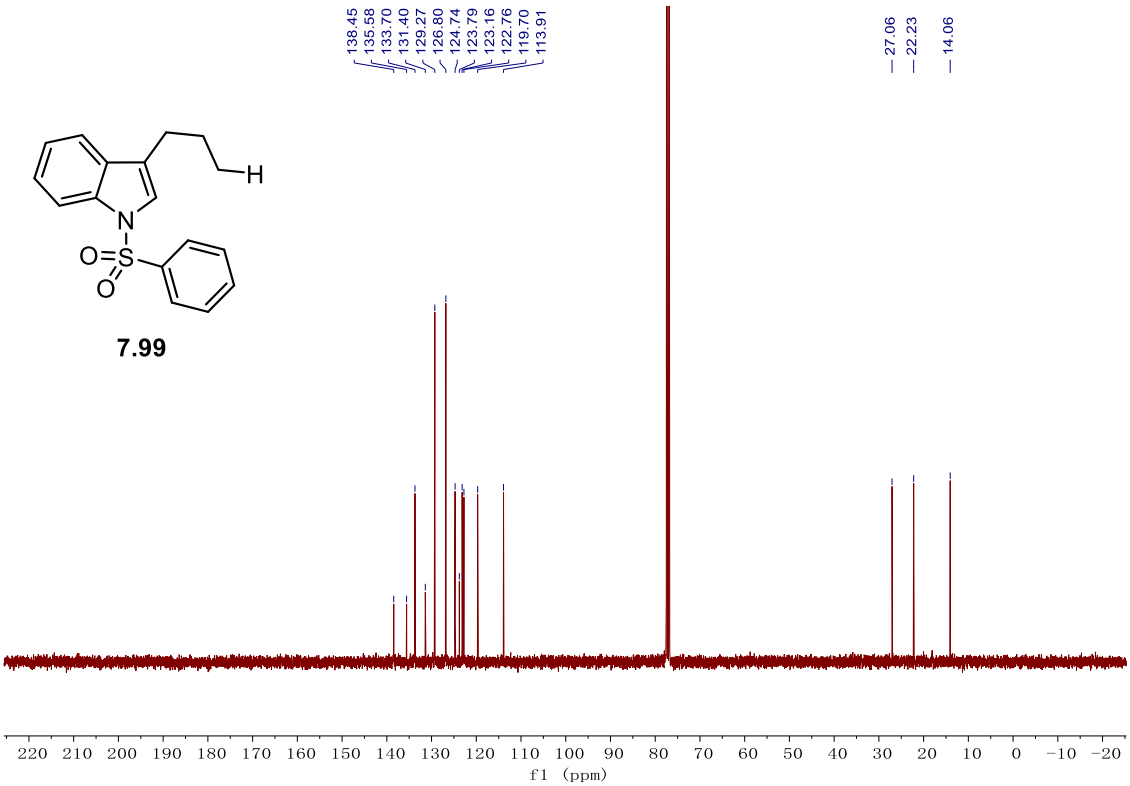


Figure 7.174 ^{1}H-NMR Spectrum of **7.100**

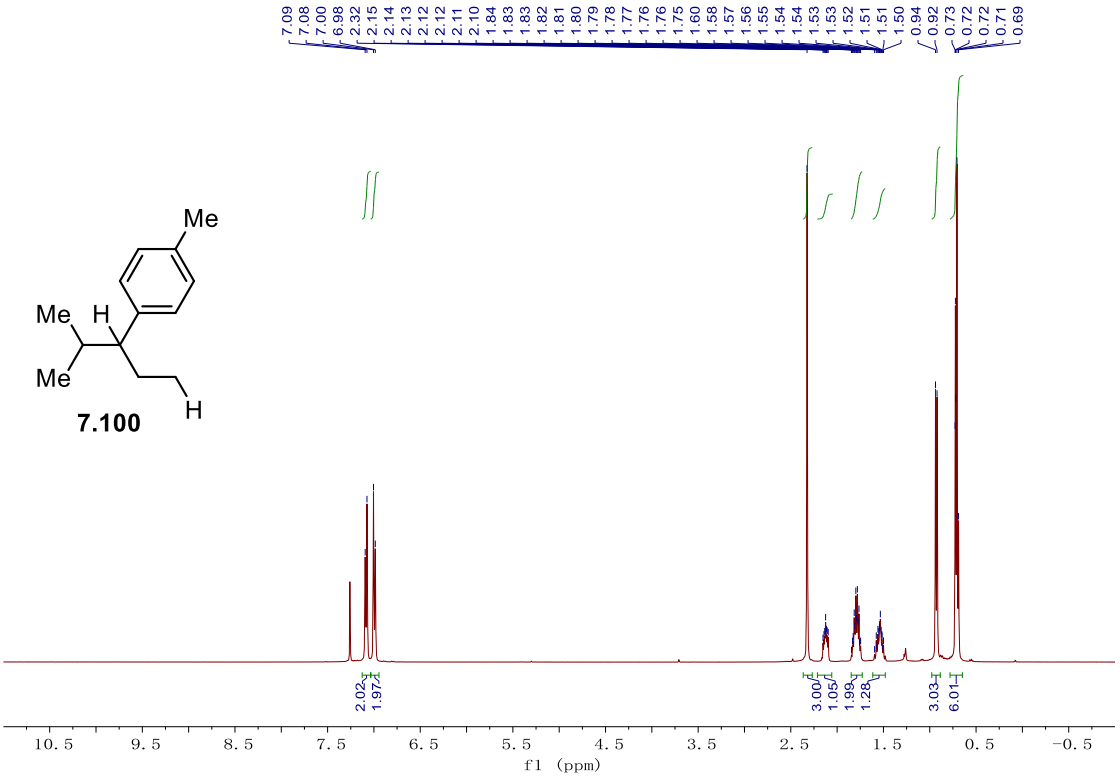


Figure 7.175 ^{13}C-NMR Spectrum of **7.100**

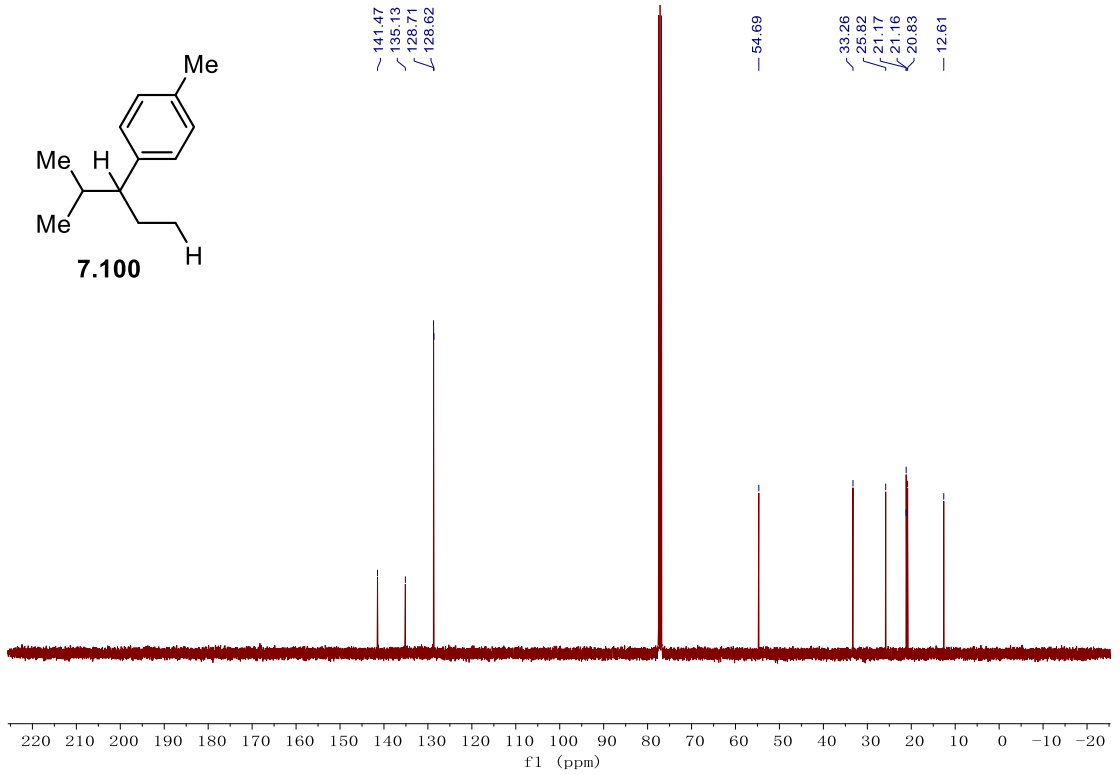


Figure 7.176 ^{1}H-NMR Spectrum of **7.102**

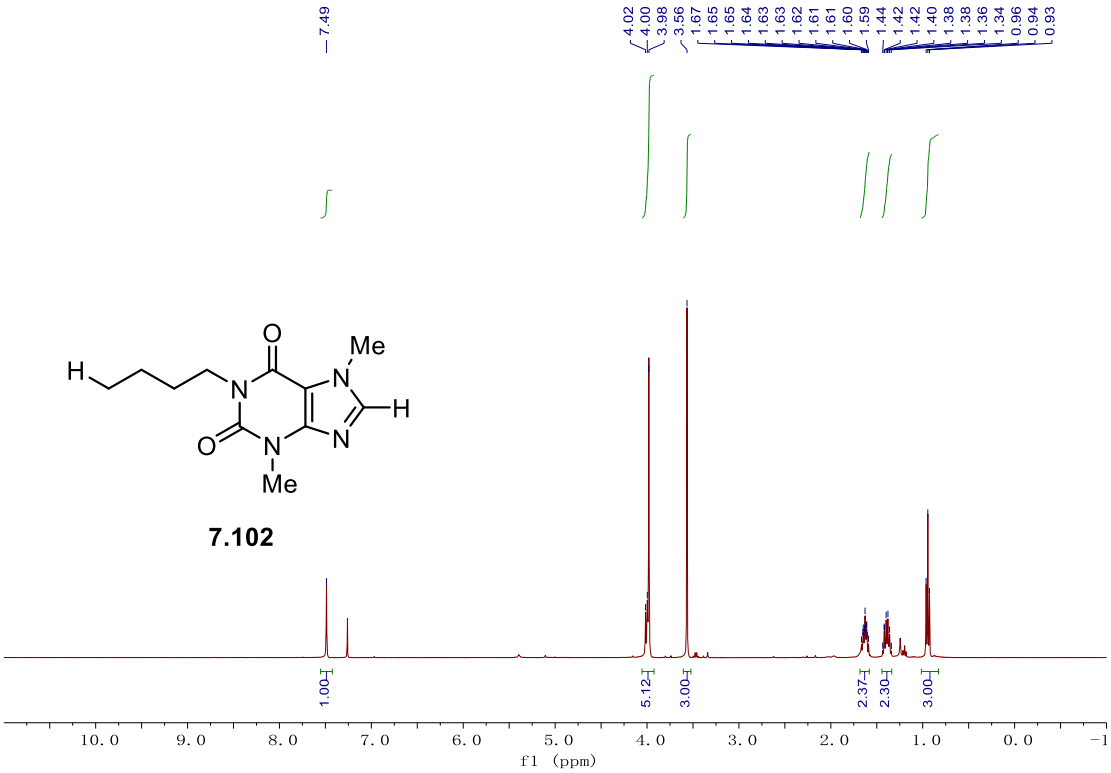


Figure 7.177 ^{13}C-NMR Spectrum of **7.102**

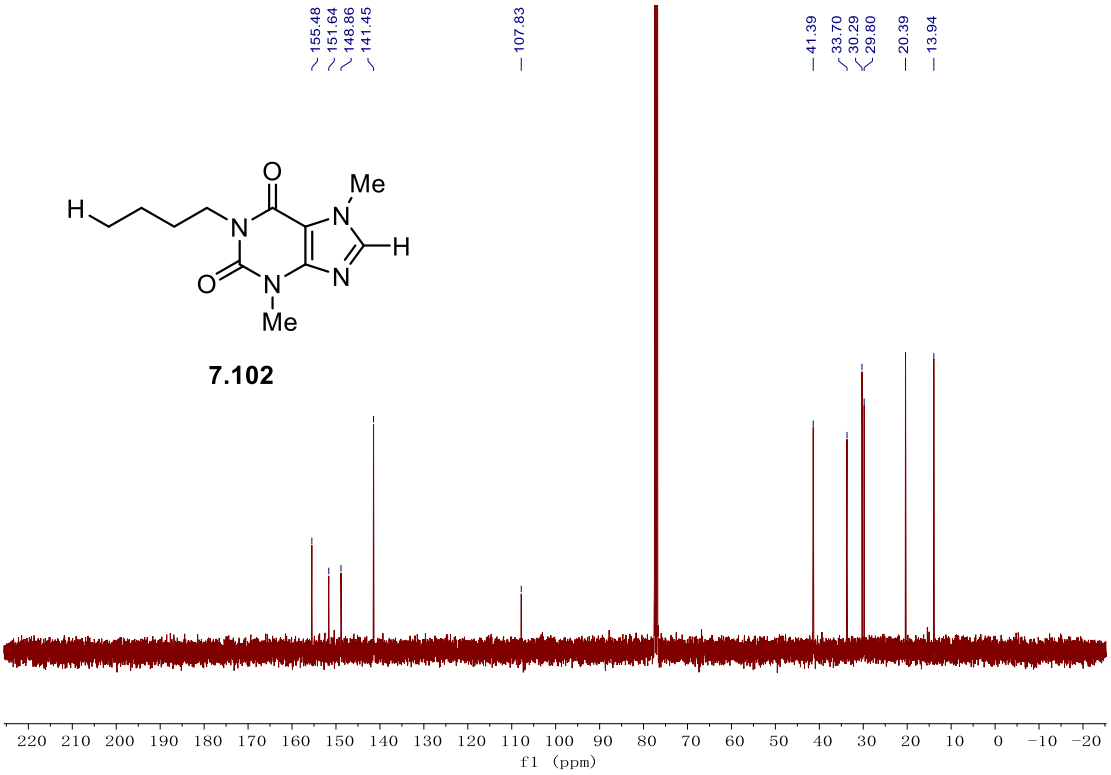


Figure 7.178 ^{1}H-NMR Spectrum of **7.104**

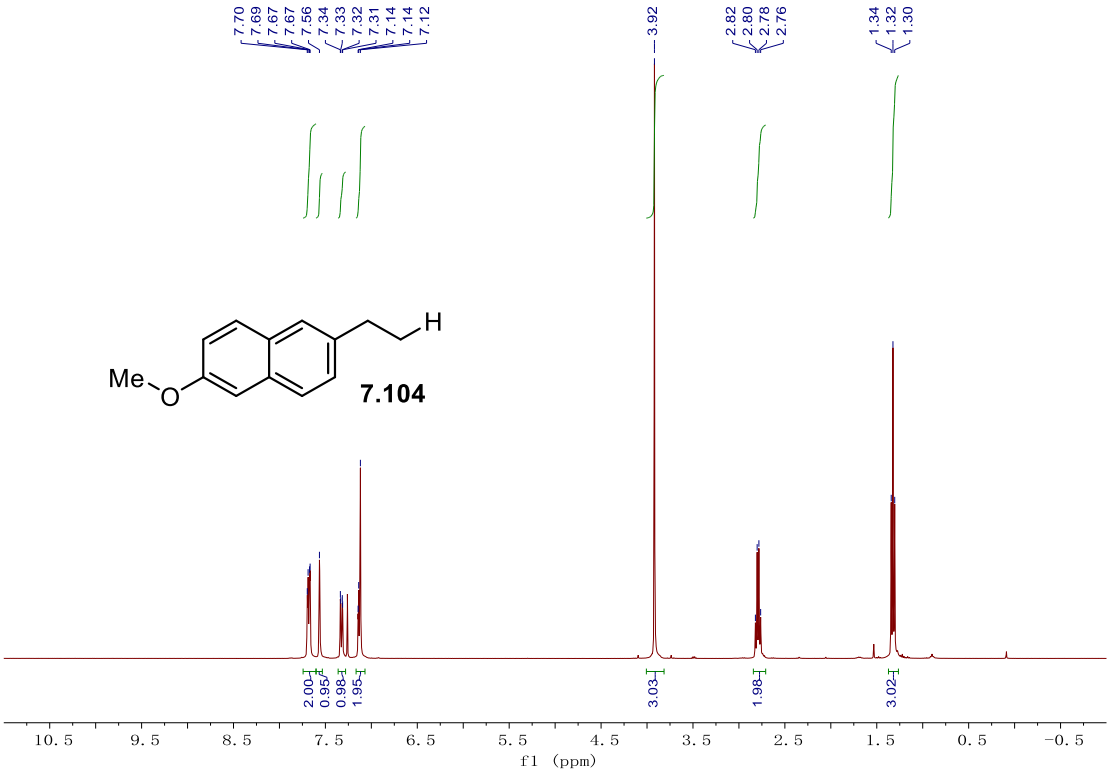


Figure 7.179 ^{13}C-NMR Spectrum of **7.104**

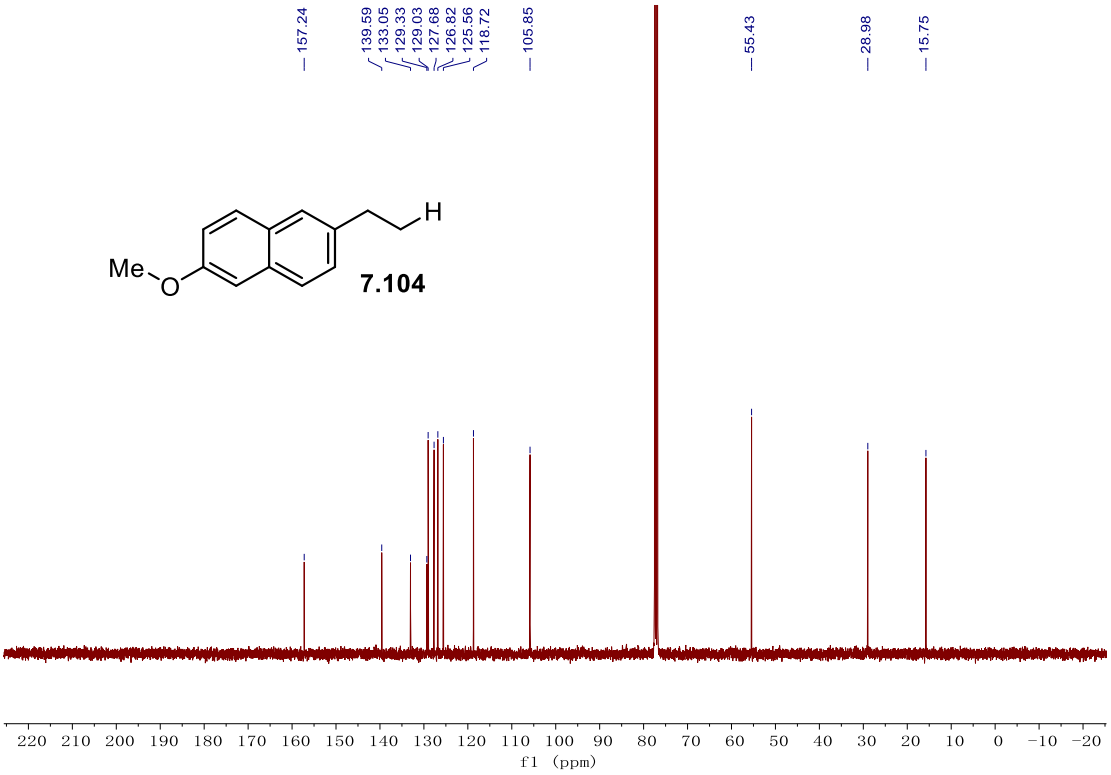


Figure 7.180 ^{1}H-NMR Spectrum of **7.108**

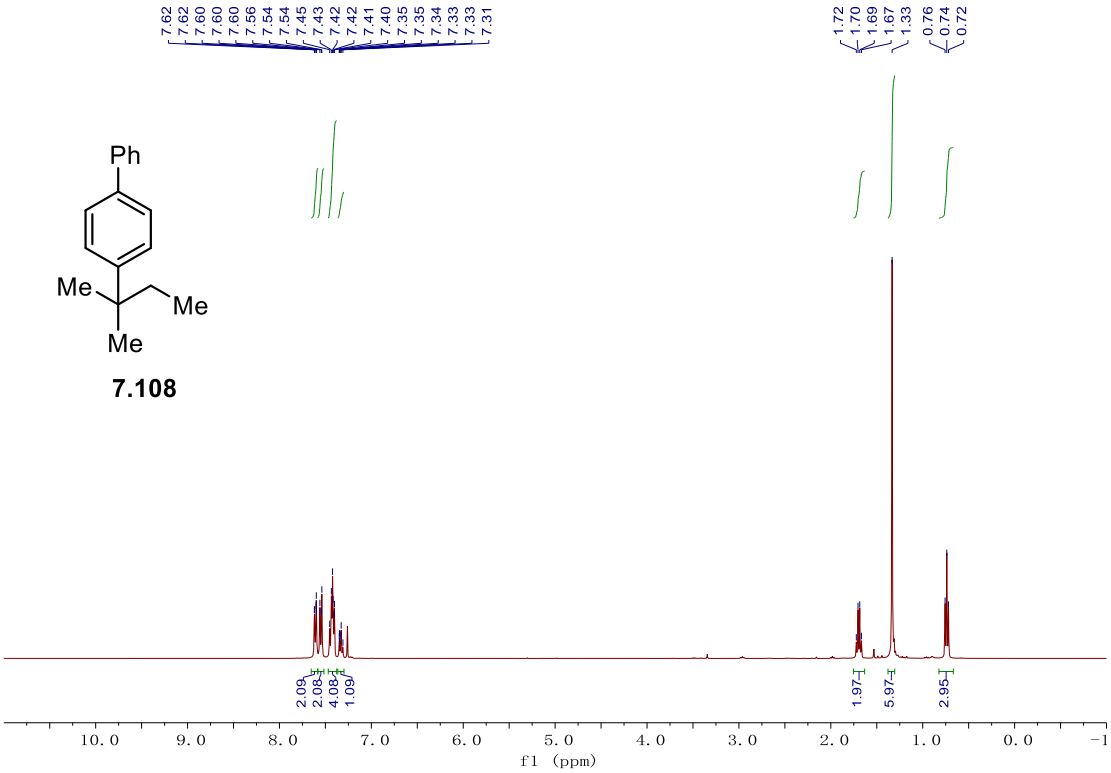


Figure 7.181 ^{13}C-NMR Spectrum of **7.108**

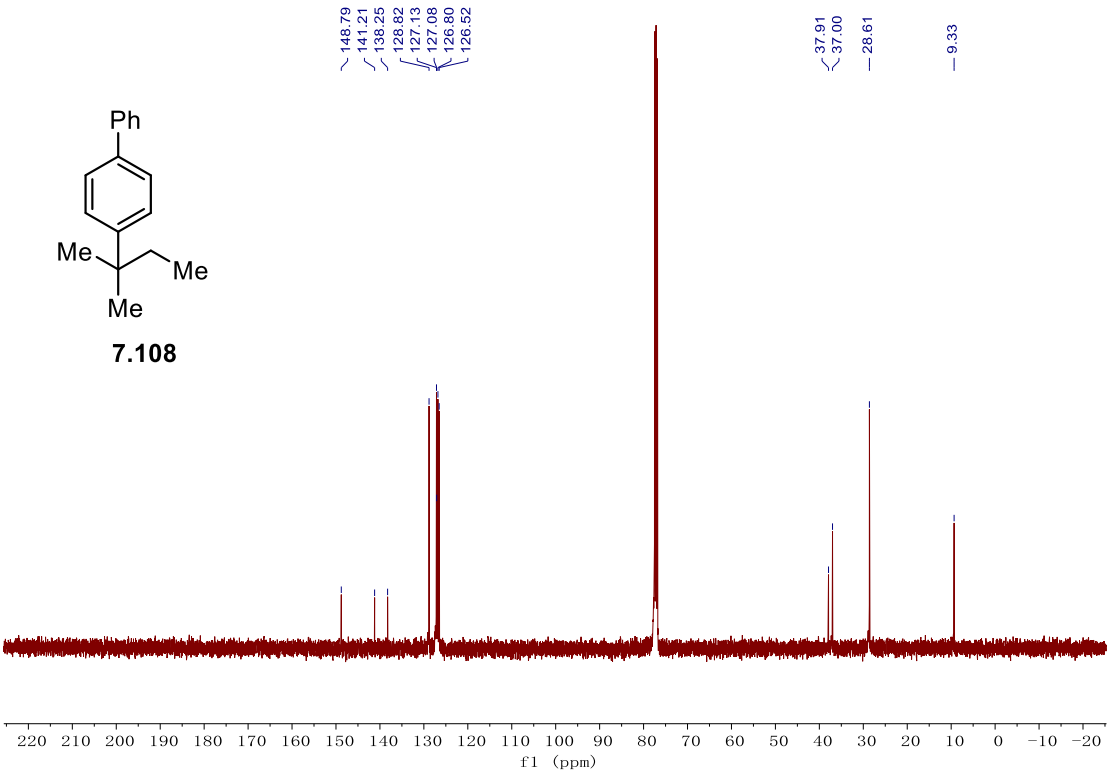


Figure 7.182 ^{1}H-NMR Spectrum of **7.111**

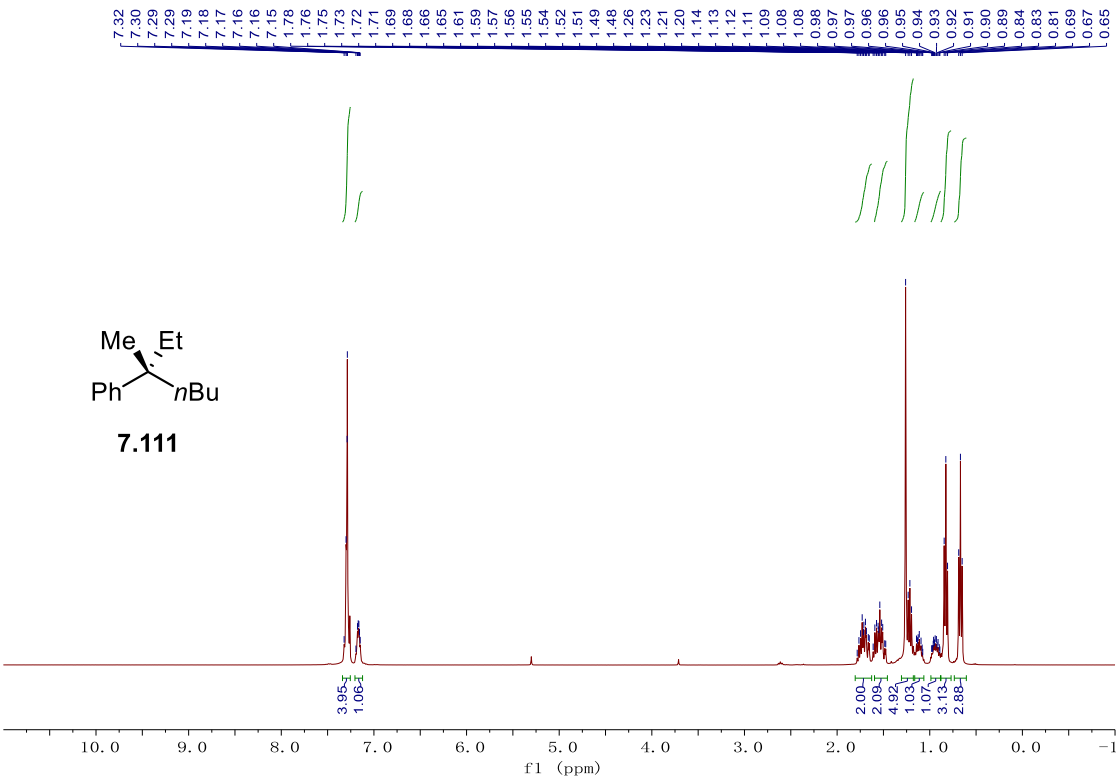


Figure 7.183 ^{13}C-NMR Spectrum of **7.111**

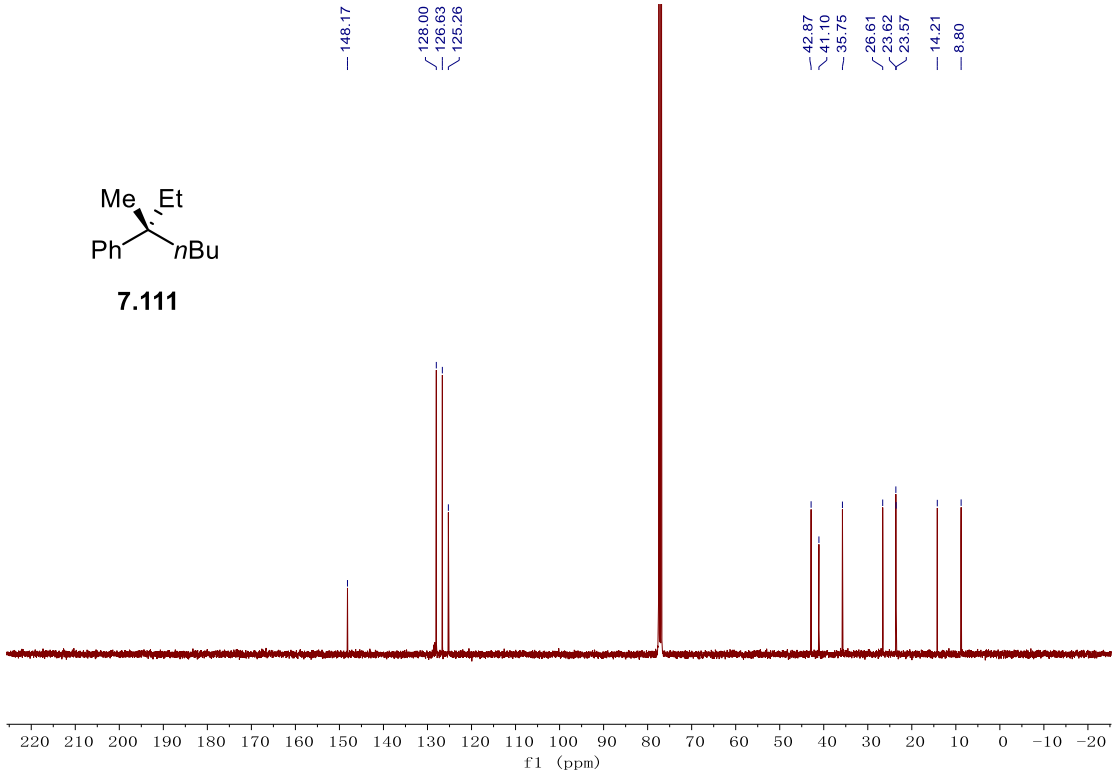


Figure 7.184 ^{1}H-NMR Spectrum of **7.112**

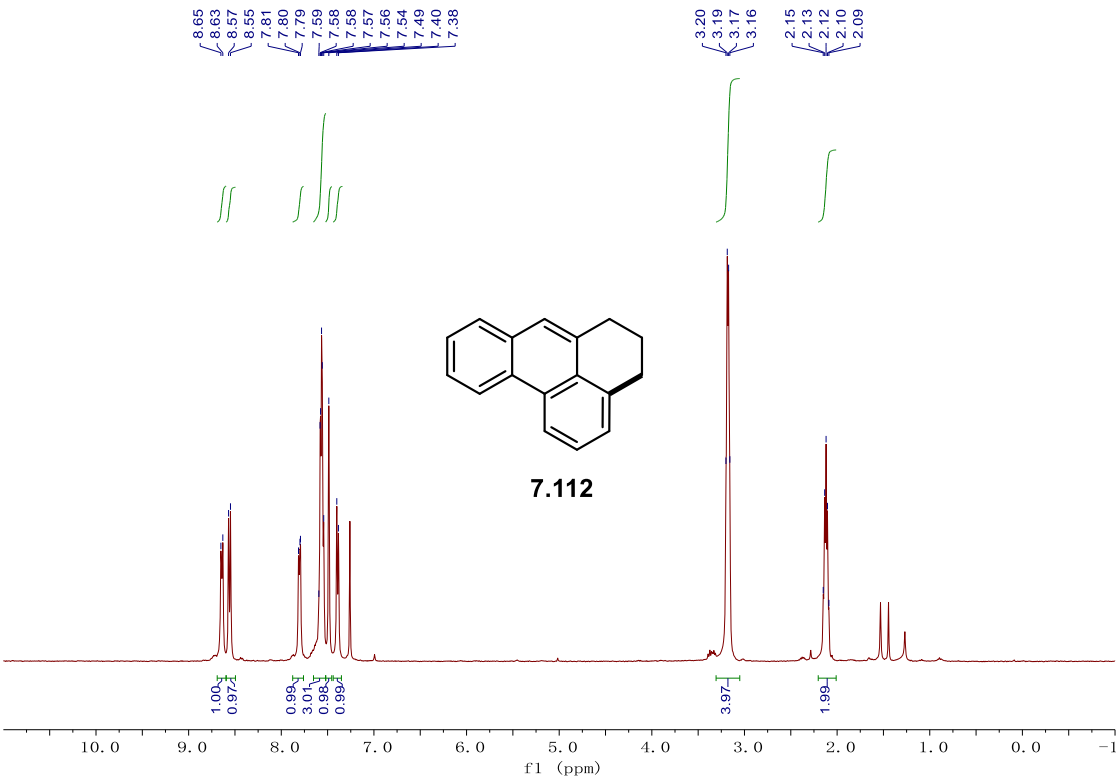


Figure 7.185 ^{13}C-NMR Spectrum of **7.112**

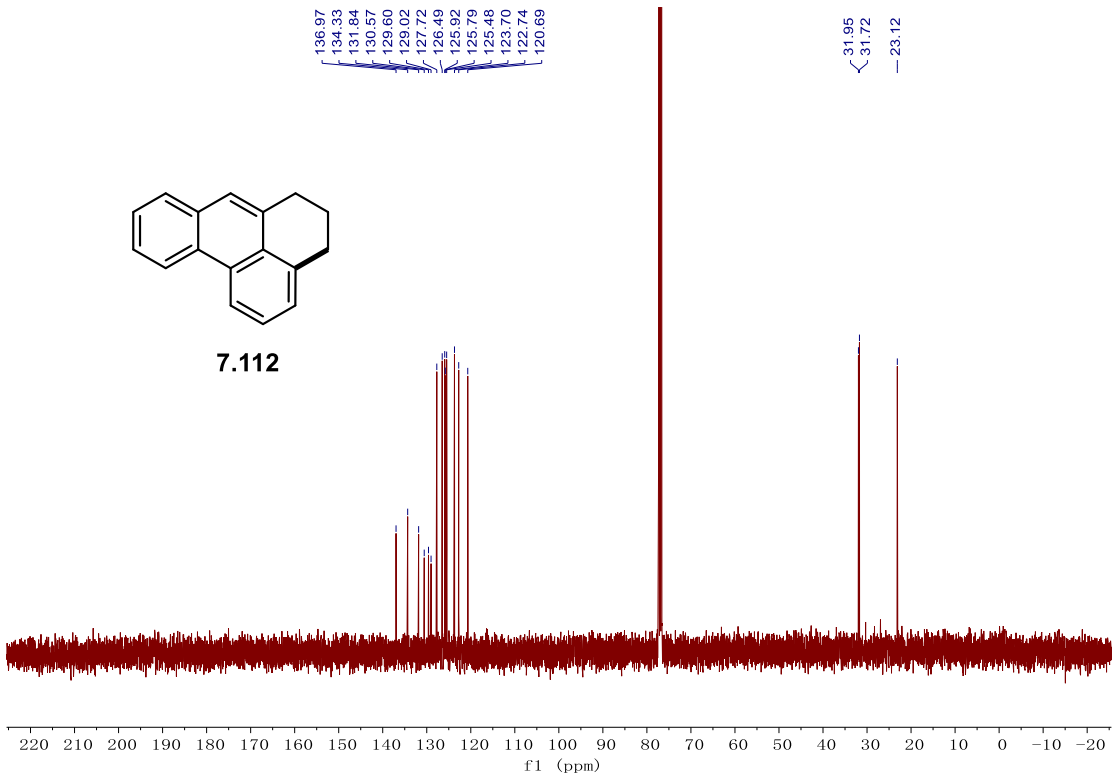


Figure 7.186 ^{1}H-NMR Spectrum of **7.113**

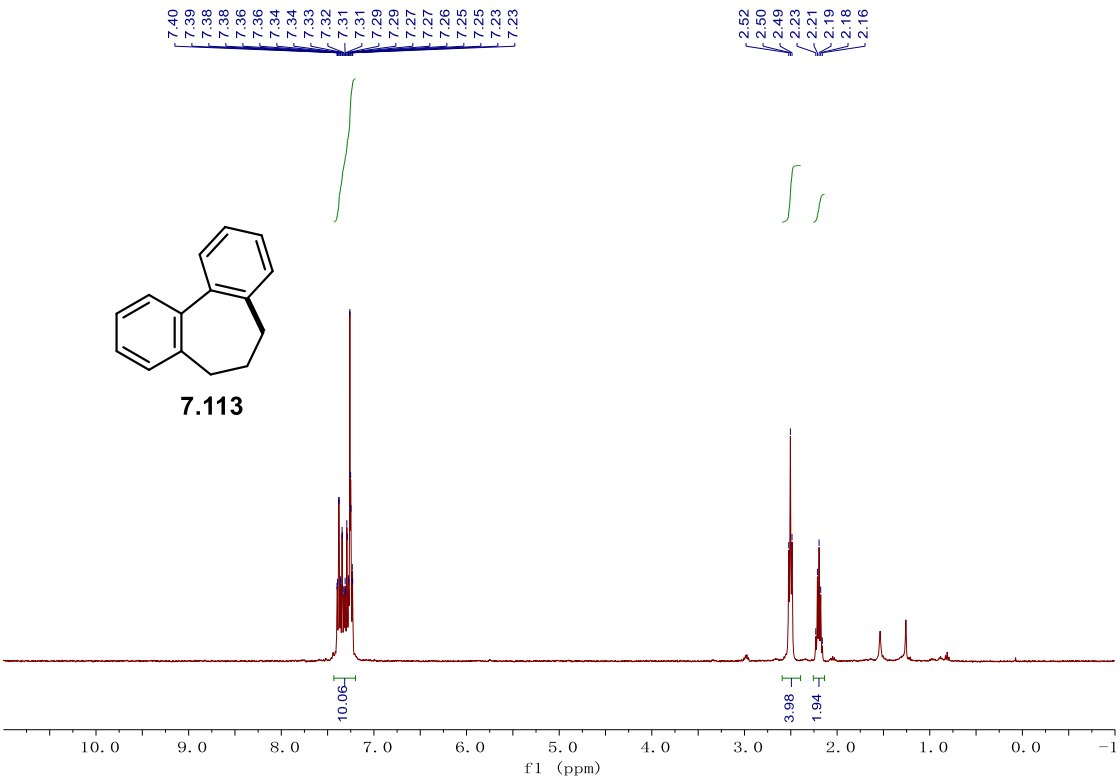


Figure 7.187 ^{13}C-NMR Spectrum of **7.113**

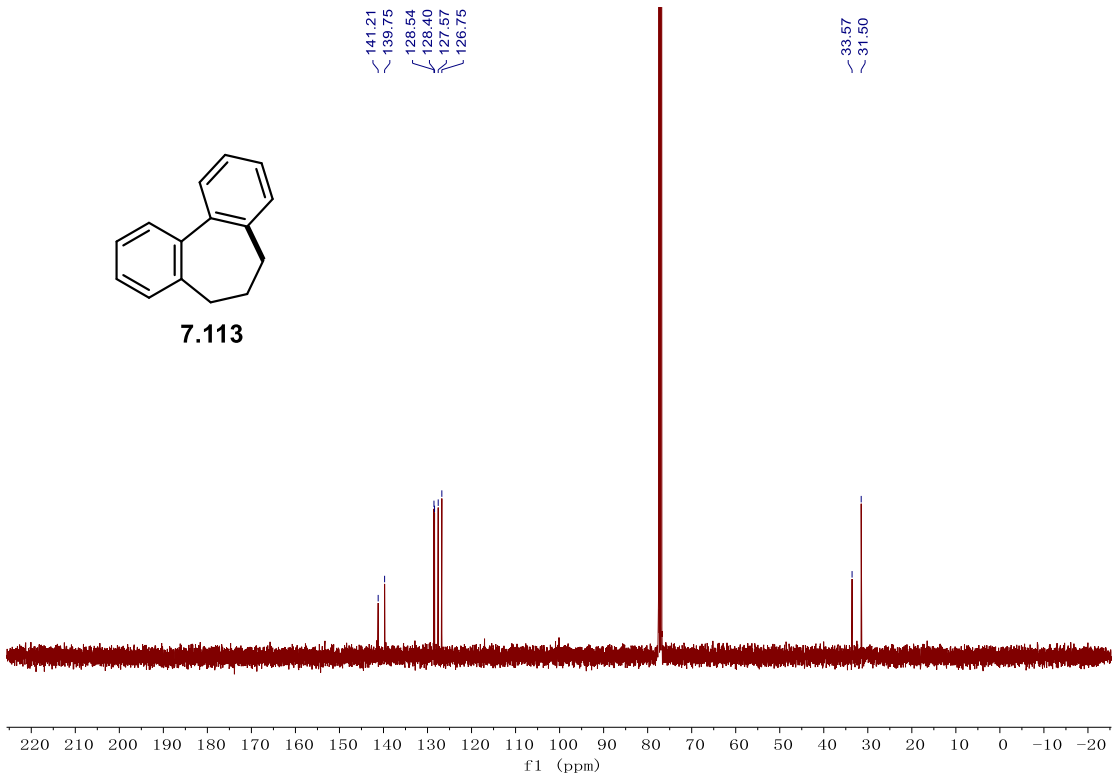


Figure 7.188 ^{1}H-NMR Spectrum of **7.113'**

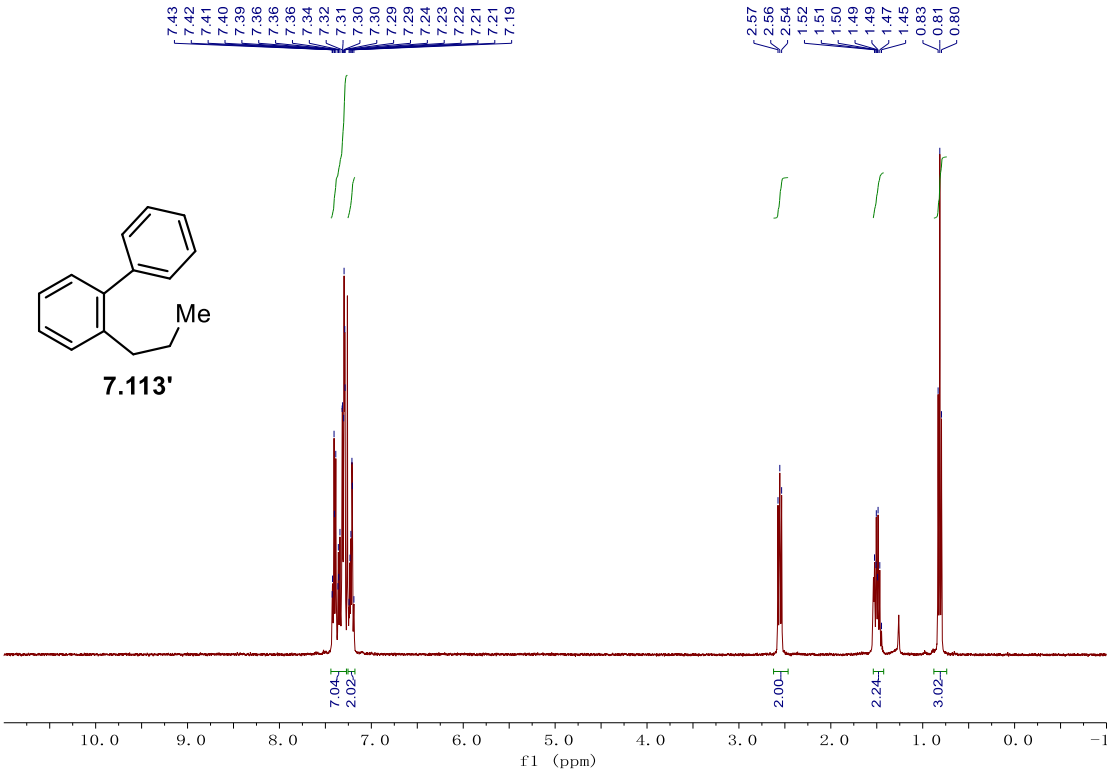


Figure 7.189 ^{13}C-NMR Spectrum of **7.113'**

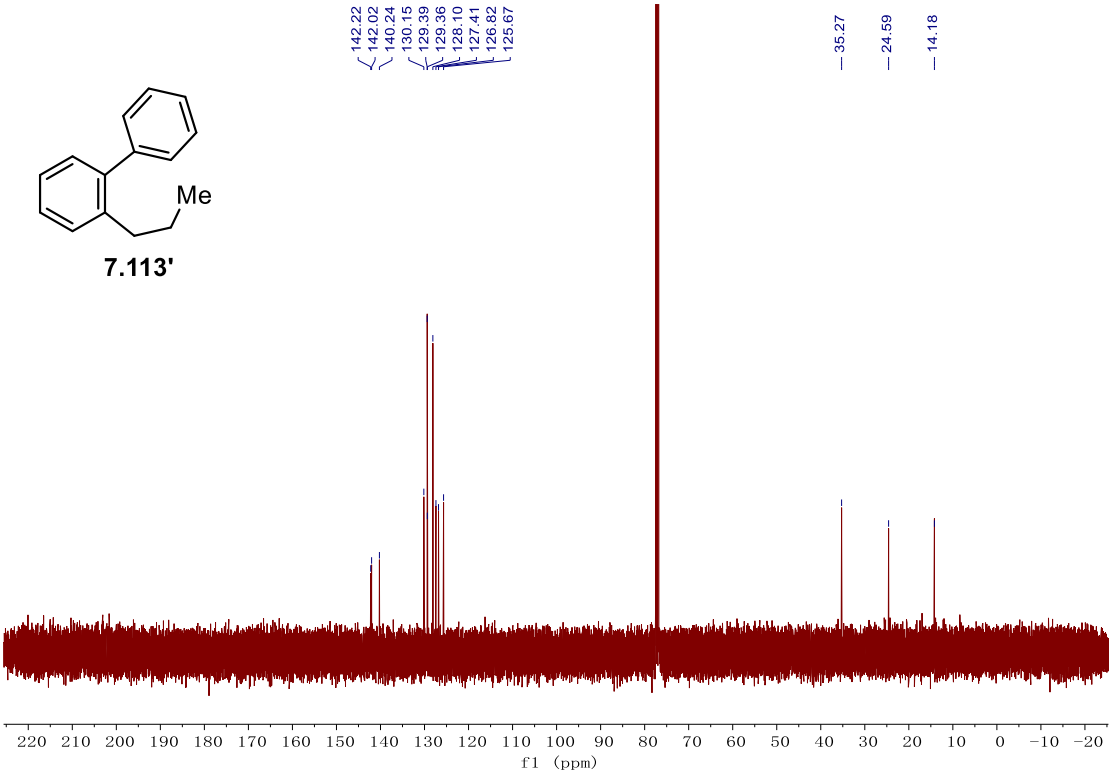


Figure 7.190 ^{1}H-NMR Spectrum of **7.114**

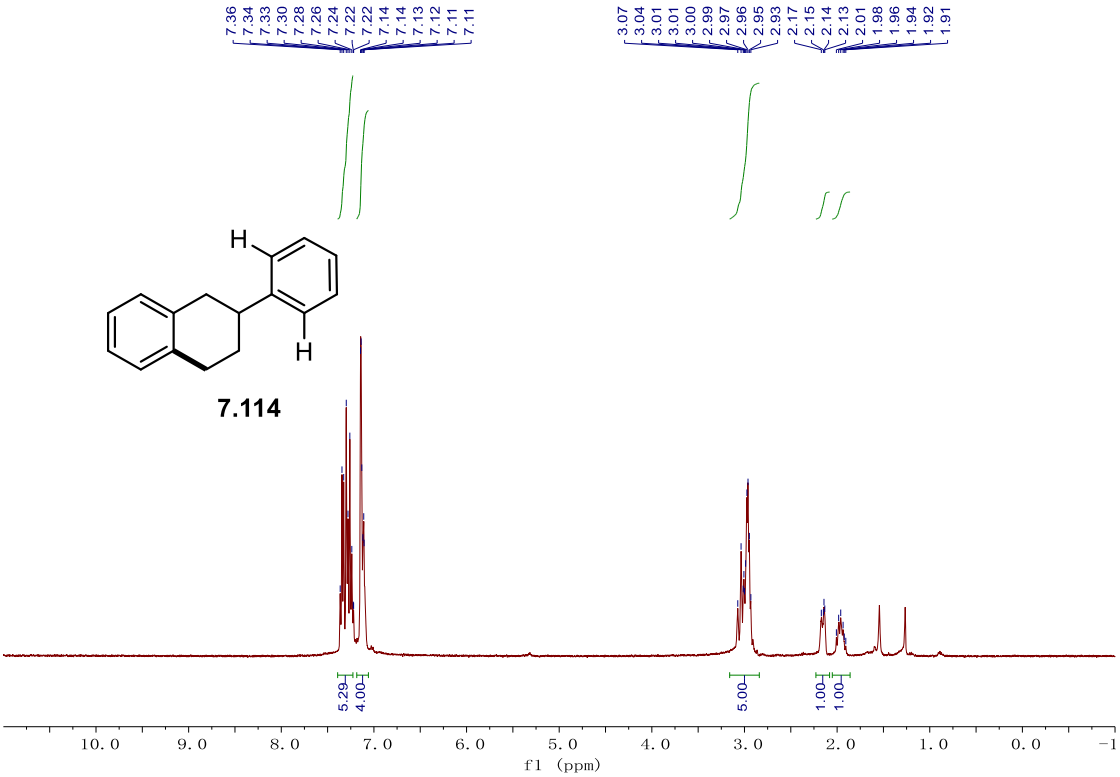


Figure 7.191 ^{13}C-NMR Spectrum of **7.114**

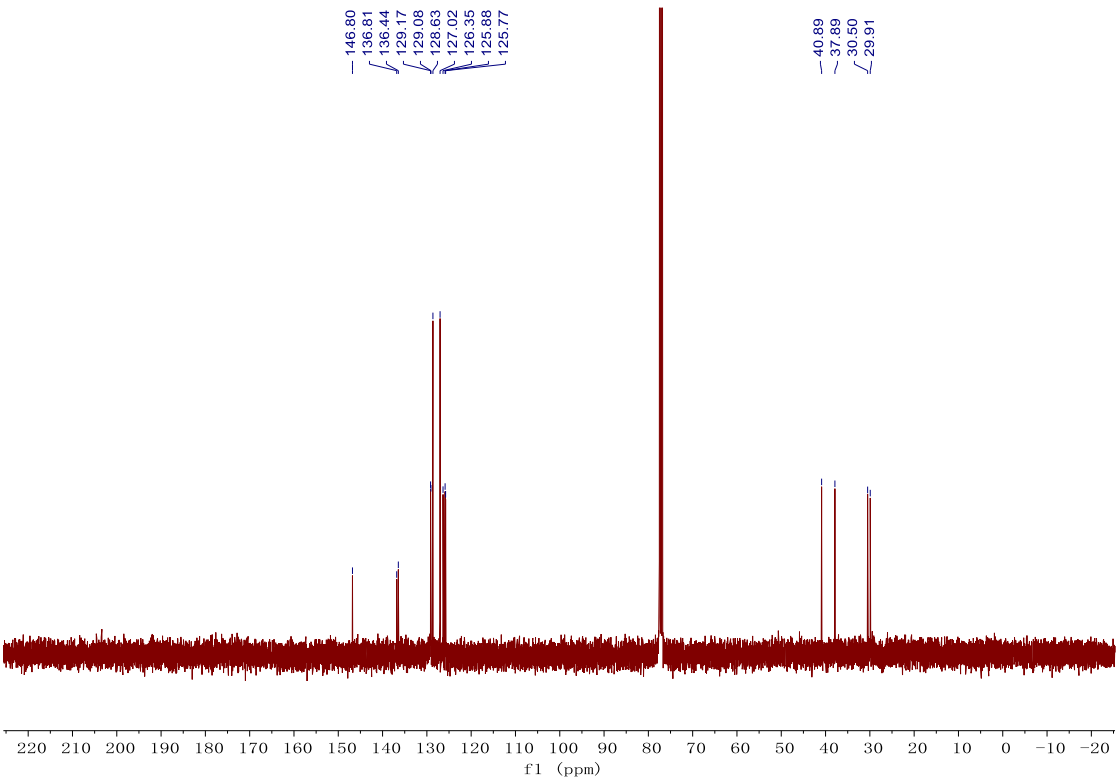


Figure 7.192 ^{1}H-NMR Spectrum of **7.115**

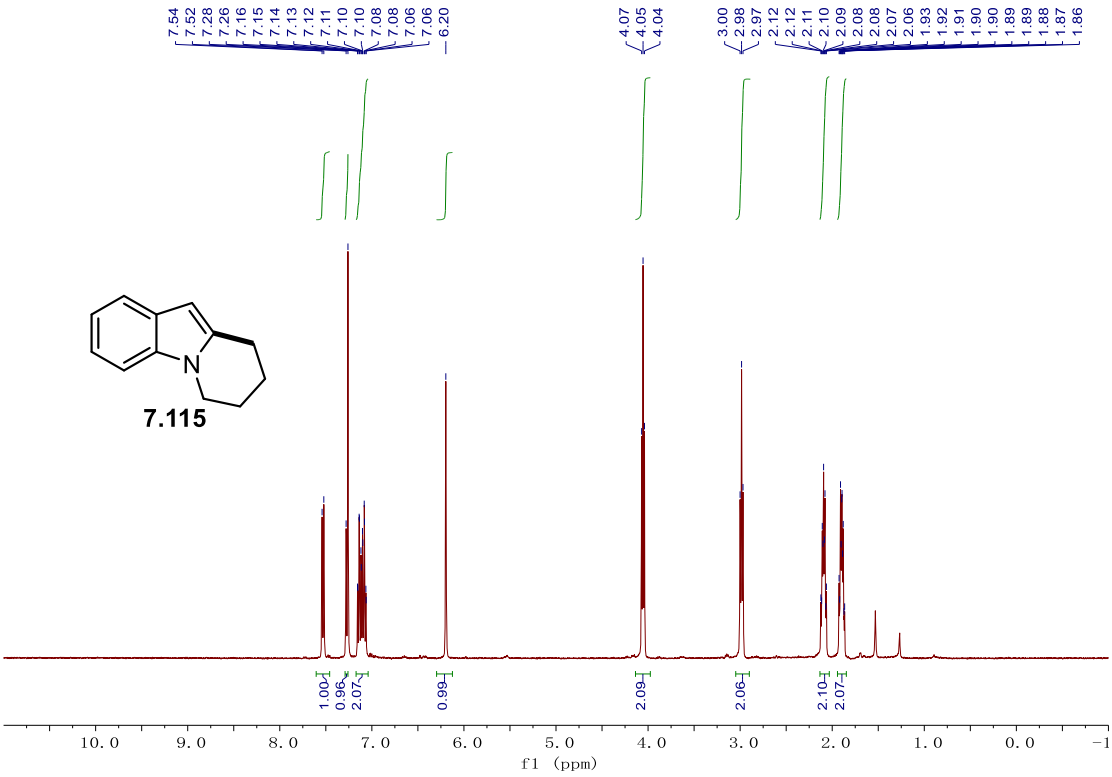


Figure 7.193 ^{13}C-NMR Spectrum of **7.115**

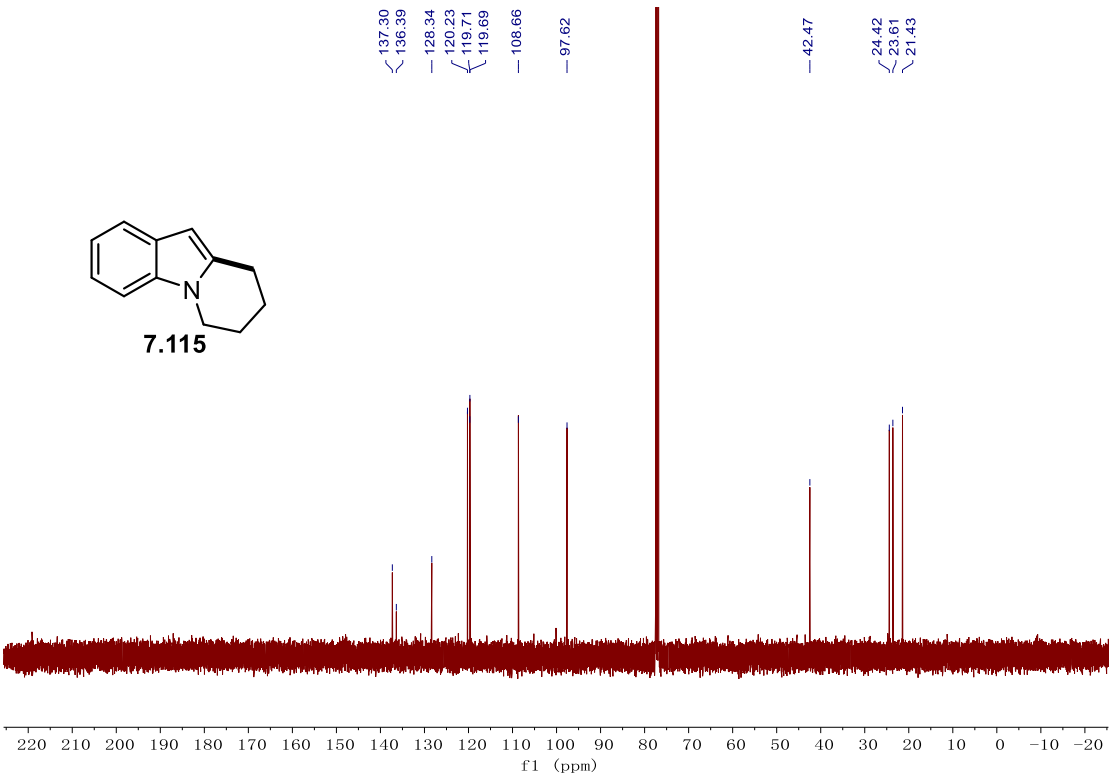


Figure 7.194 ^{1}H-NMR Spectrum of **7.116**

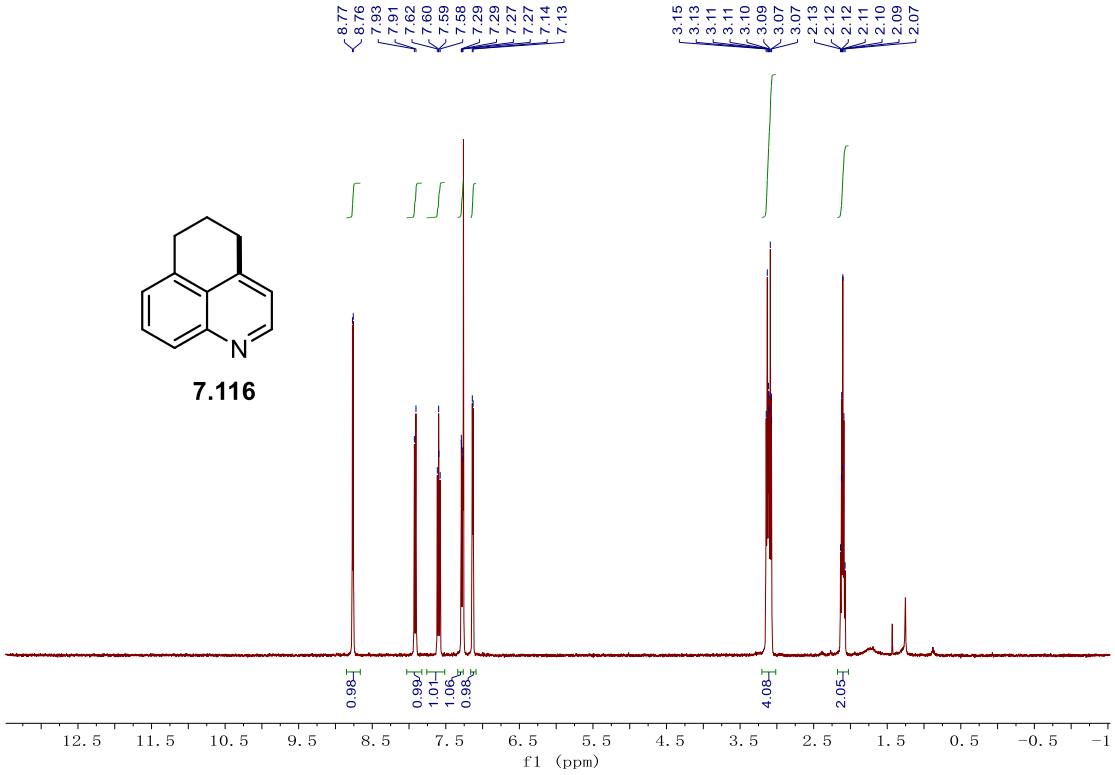


Figure 7.195 ^{13}C-NMR Spectrum of **7.116**

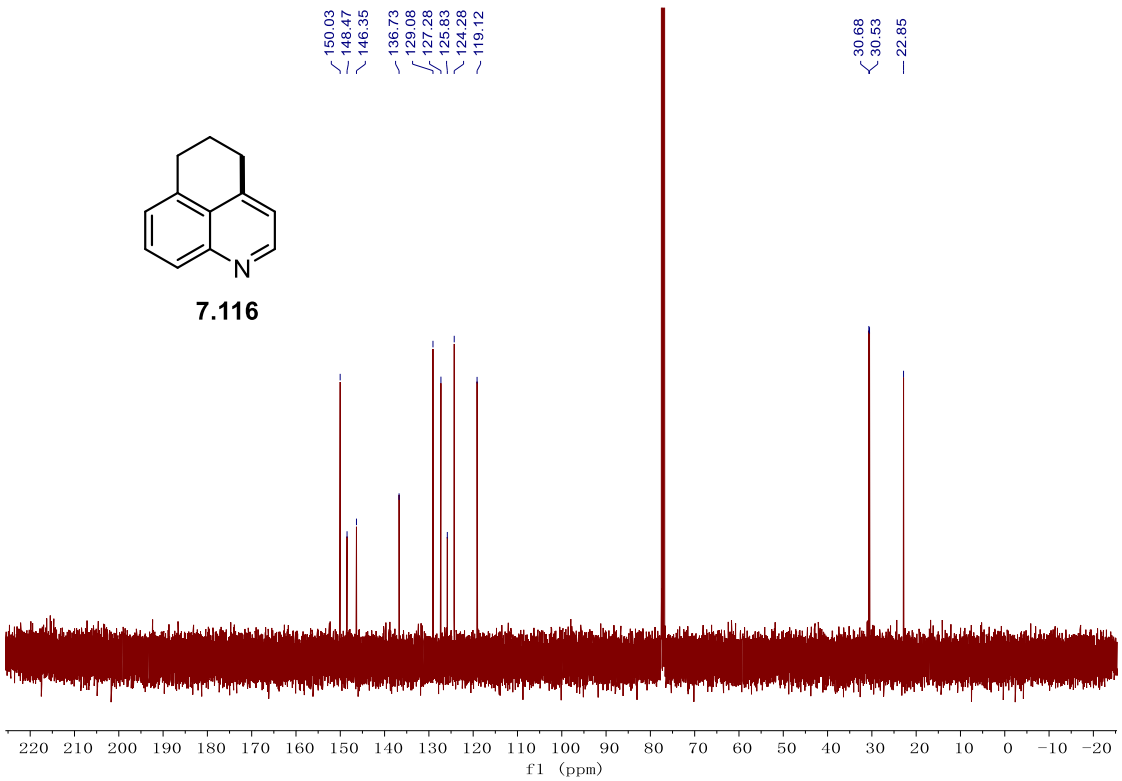


Figure 7.196 ^{1}H-NMR Spectrum of **7.119**

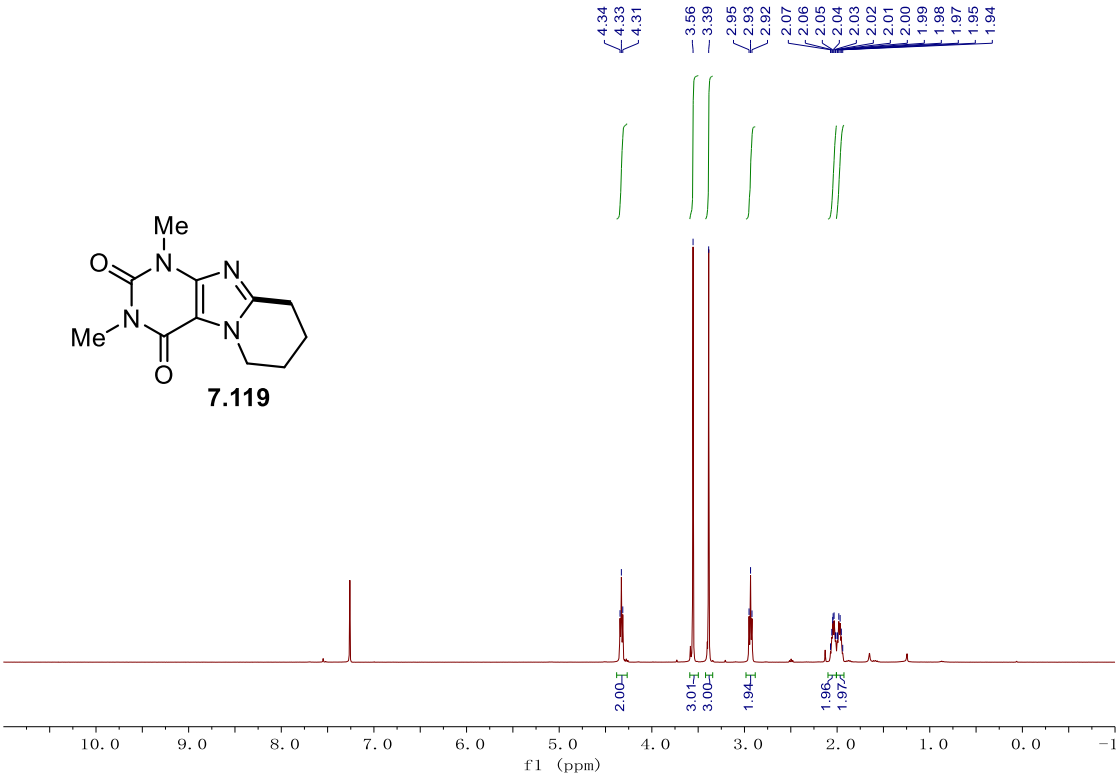


Figure 7.197 ^{13}C-NMR Spectrum of **7.119**

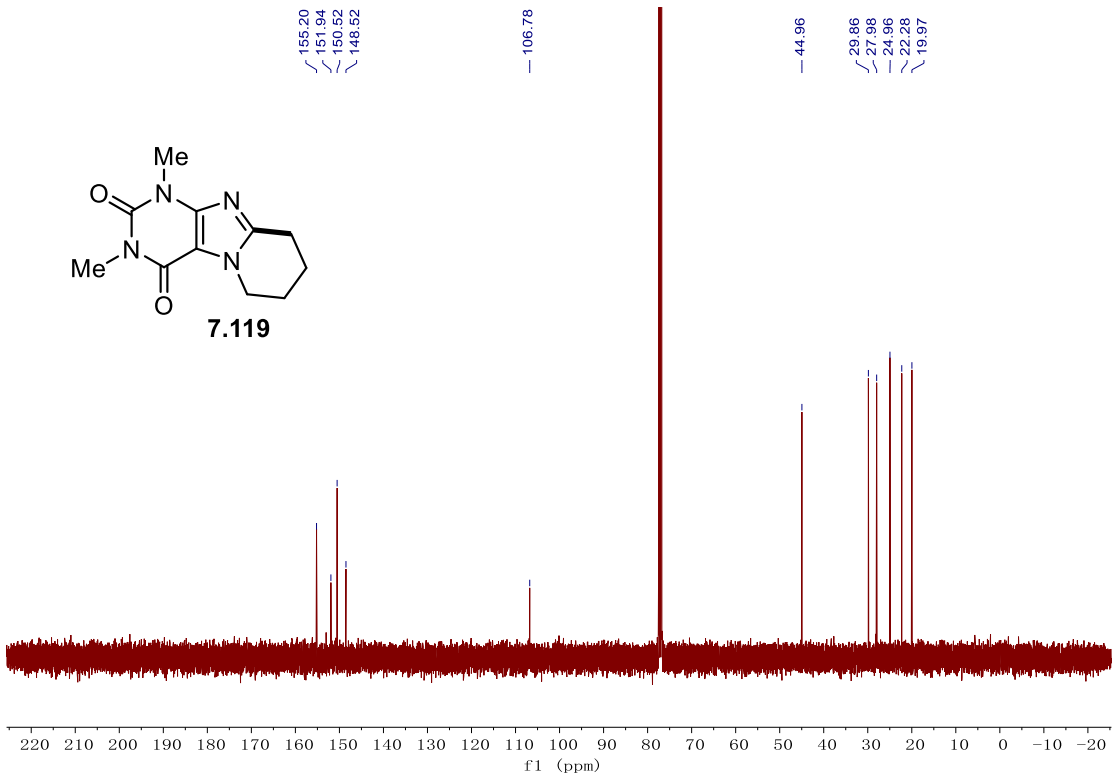


Figure 7.198 ^{1}H-NMR Spectrum of **7.121**

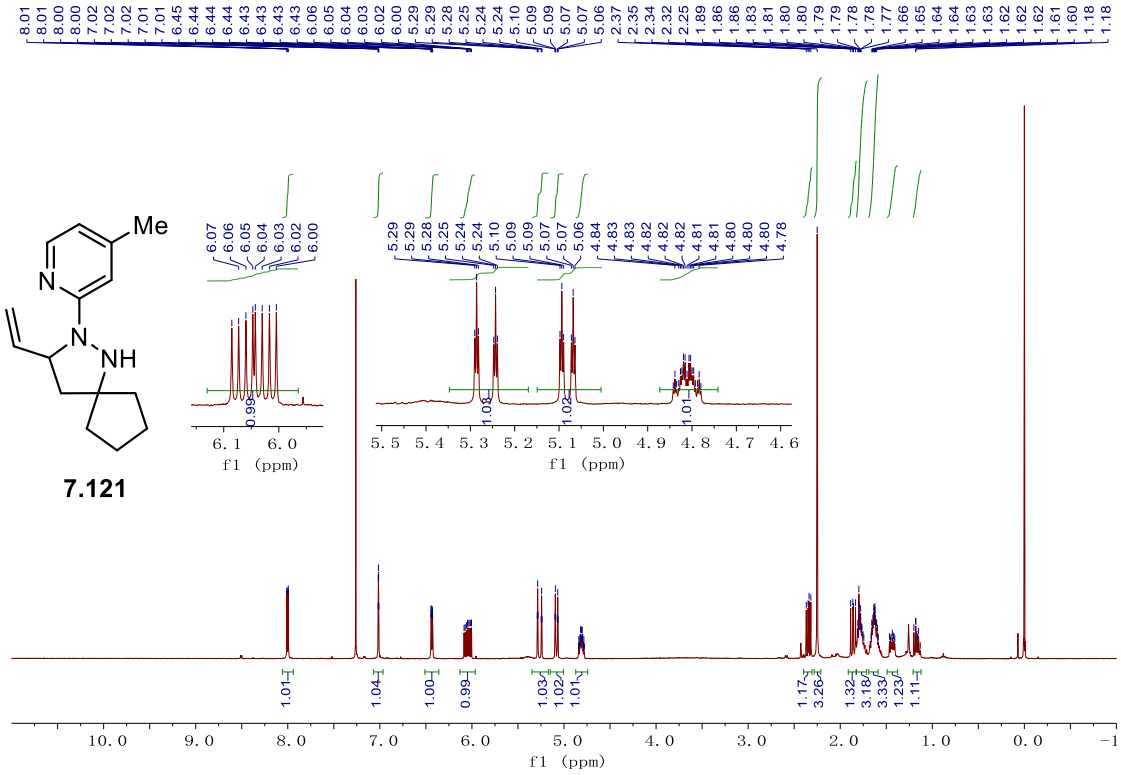


Figure 7.199 ^{13}C-NMR Spectrum of **7.121**

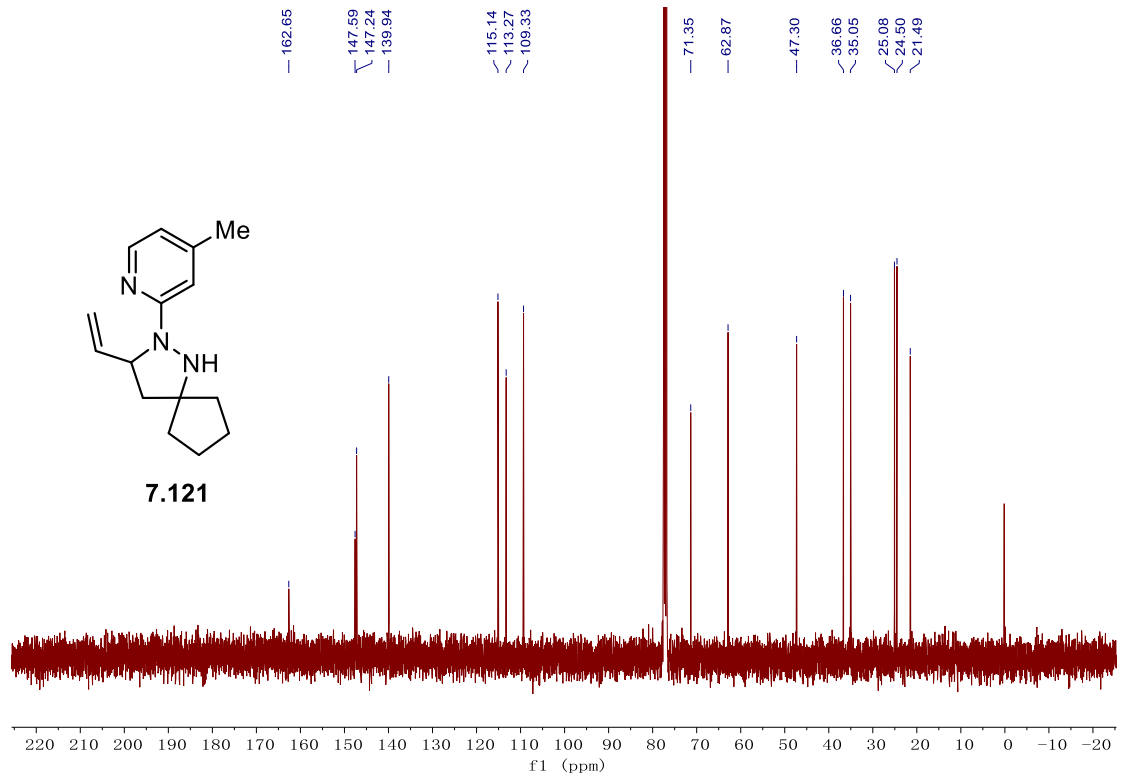


Figure 7.200 ^{1}H-NMR Spectrum of **7.126**

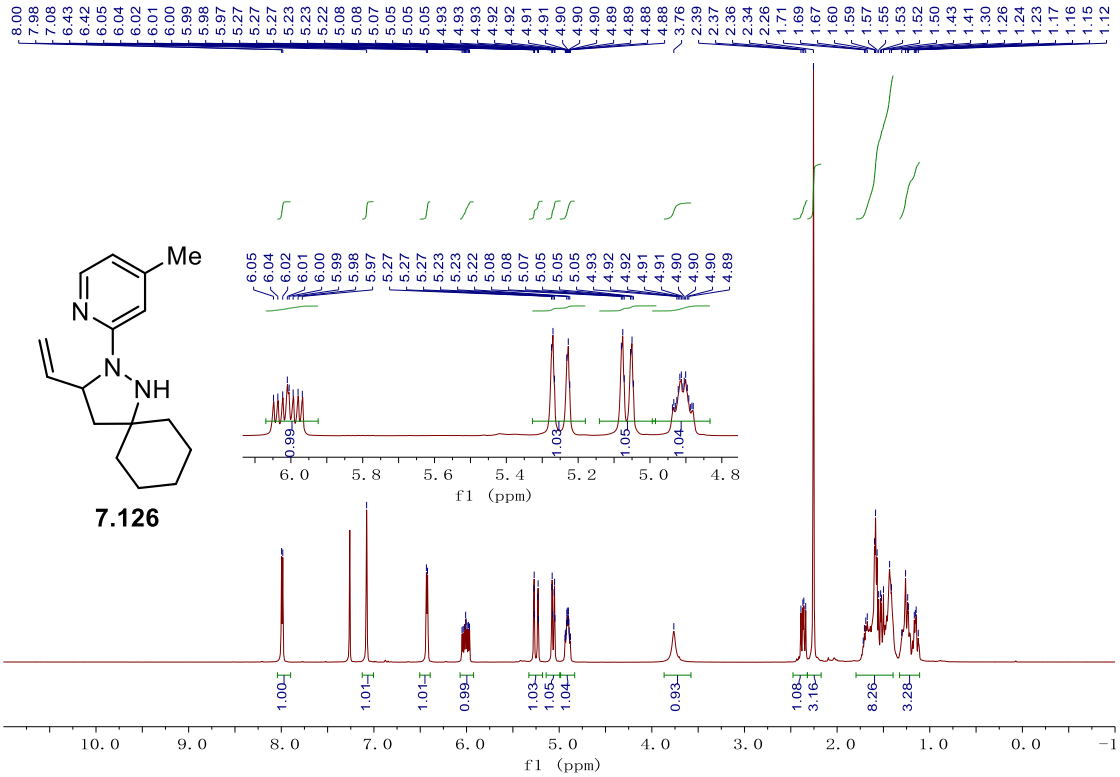


Figure 7.201 ^{13}C-NMR Spectrum of **7.126**

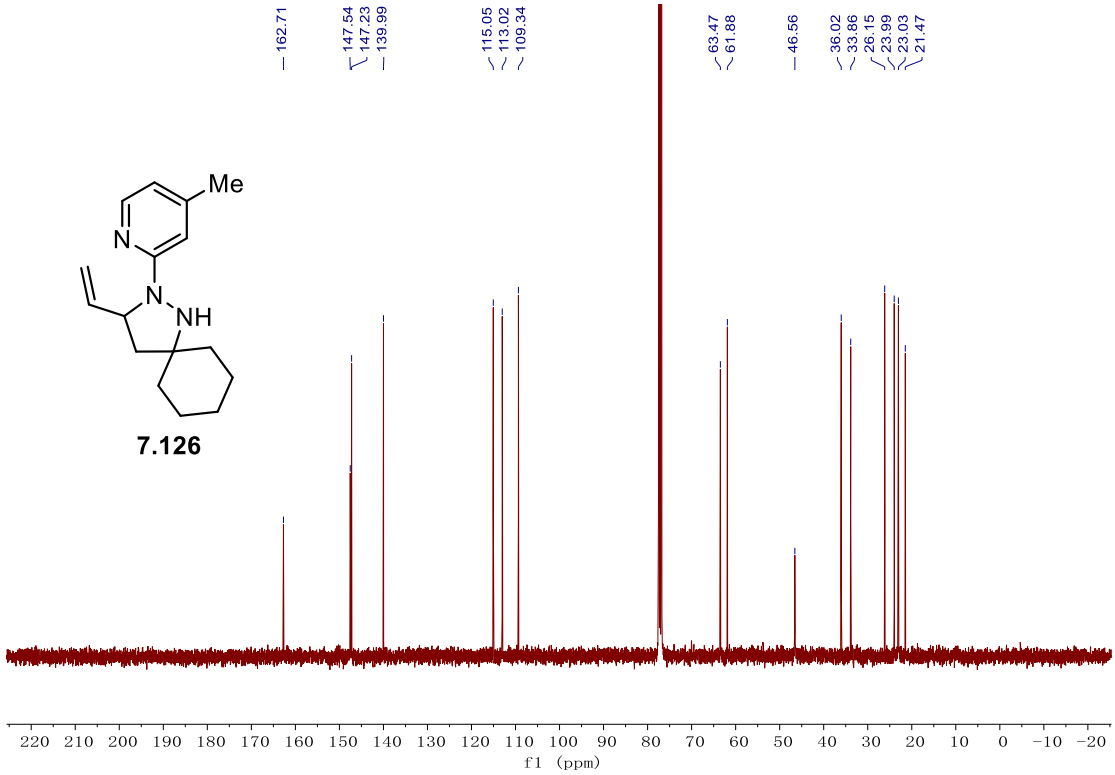


Figure 7.202 ^{1}H-NMR Spectrum of **7.124**

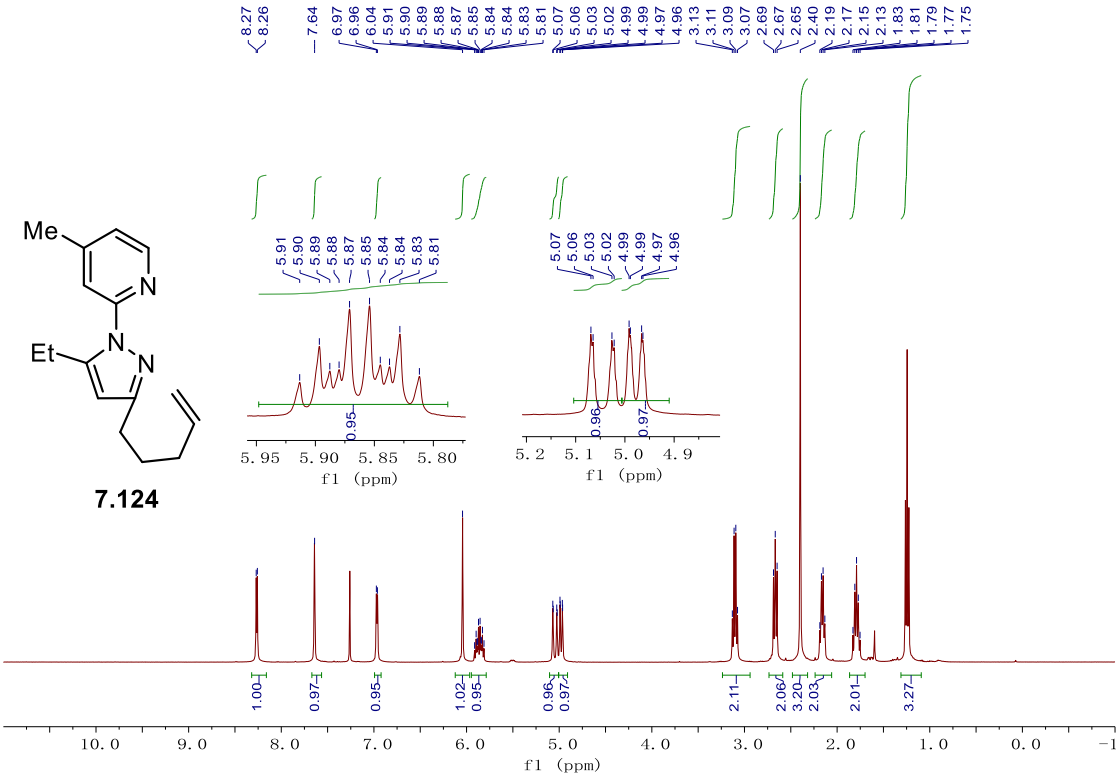


Figure 7.203 ^{13}C-NMR Spectrum of 7.124

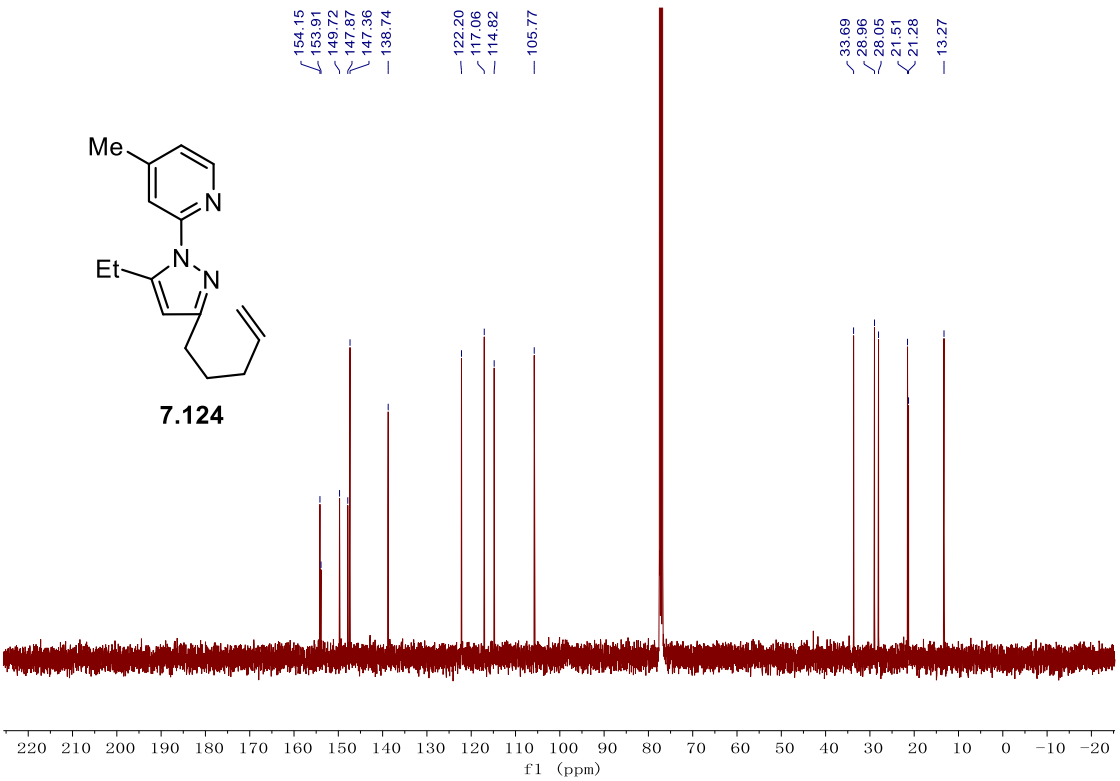


Figure 7.204 ^{1}H-NMR Spectrum of **7.128**

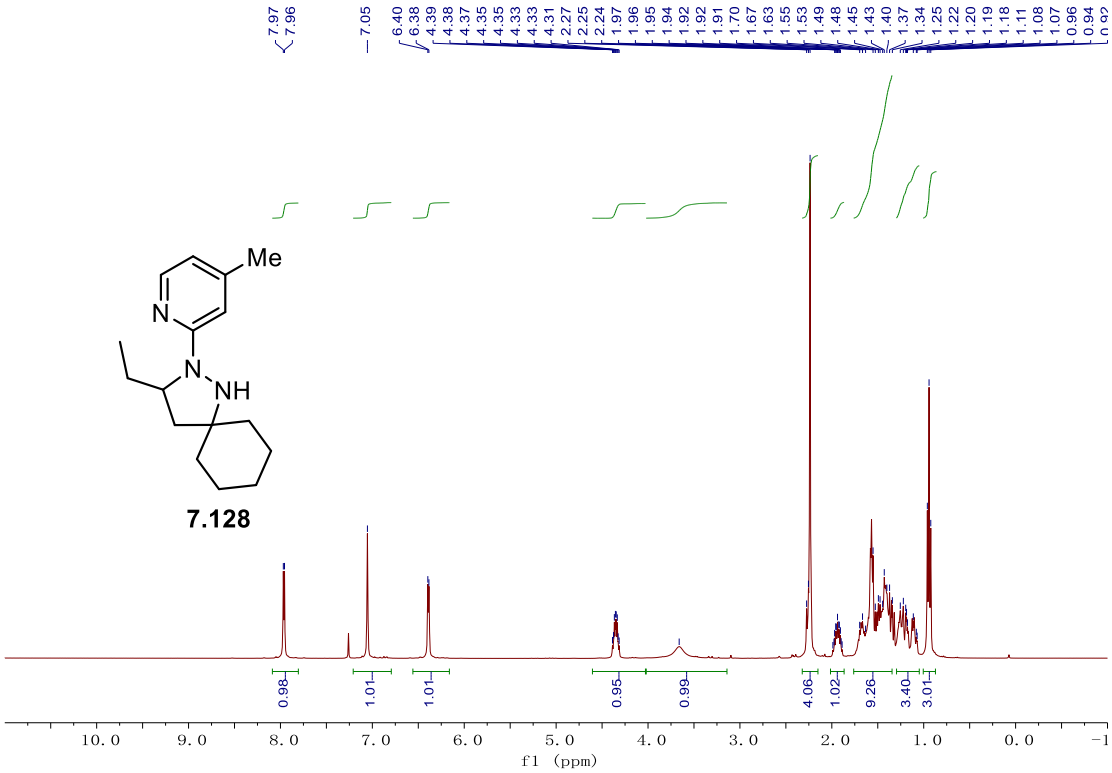


Figure 7.205 ^{13}C-NMR Spectrum of **7.128**

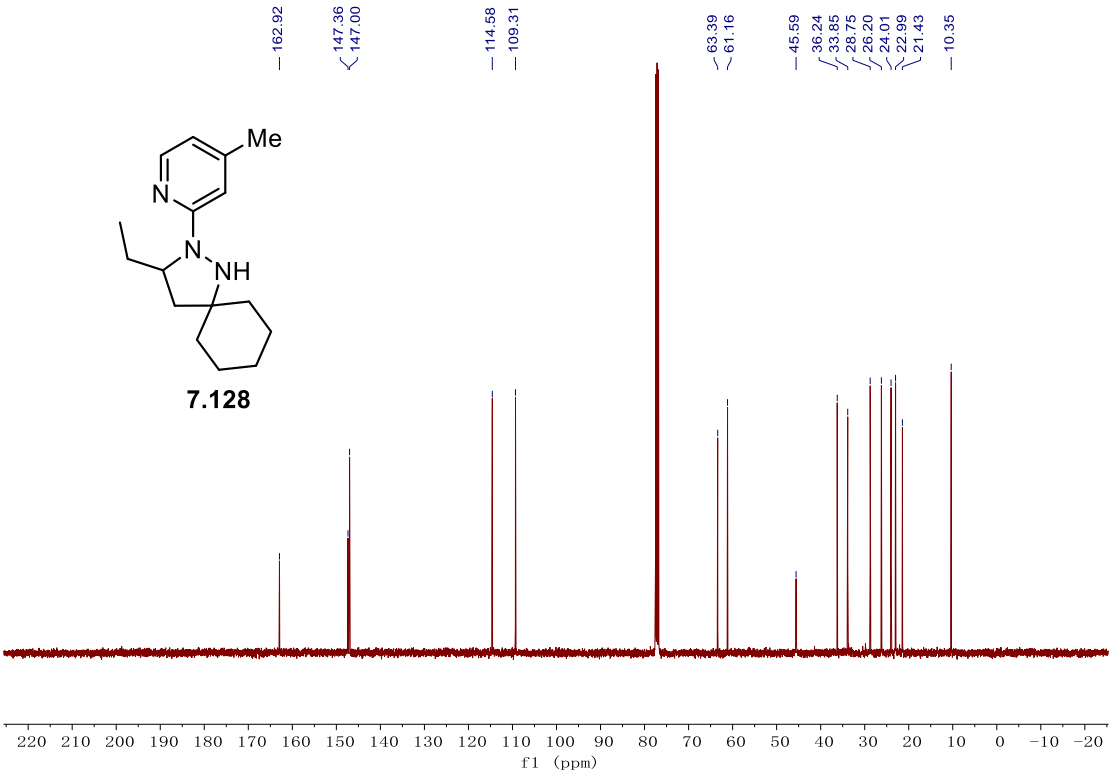


Figure 7.206 ^{1}H-NMR Spectrum of **7.132a**

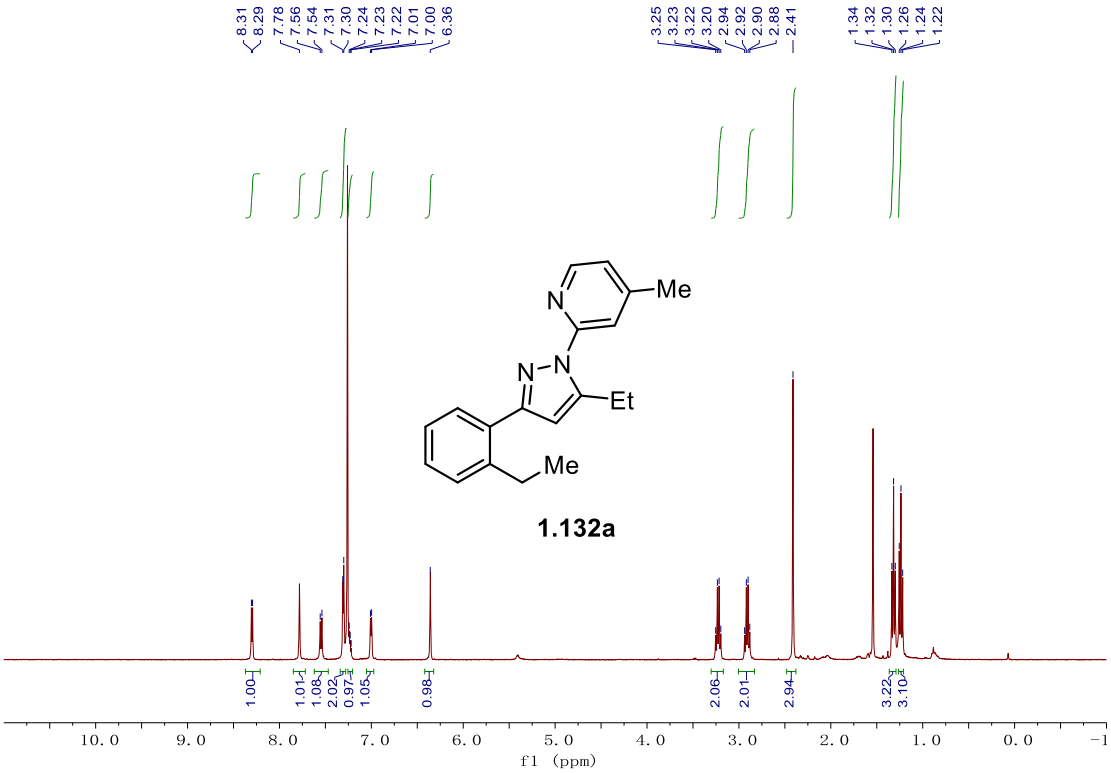


Figure 7.207 ^{13}C-NMR Spectrum of **7.132a**

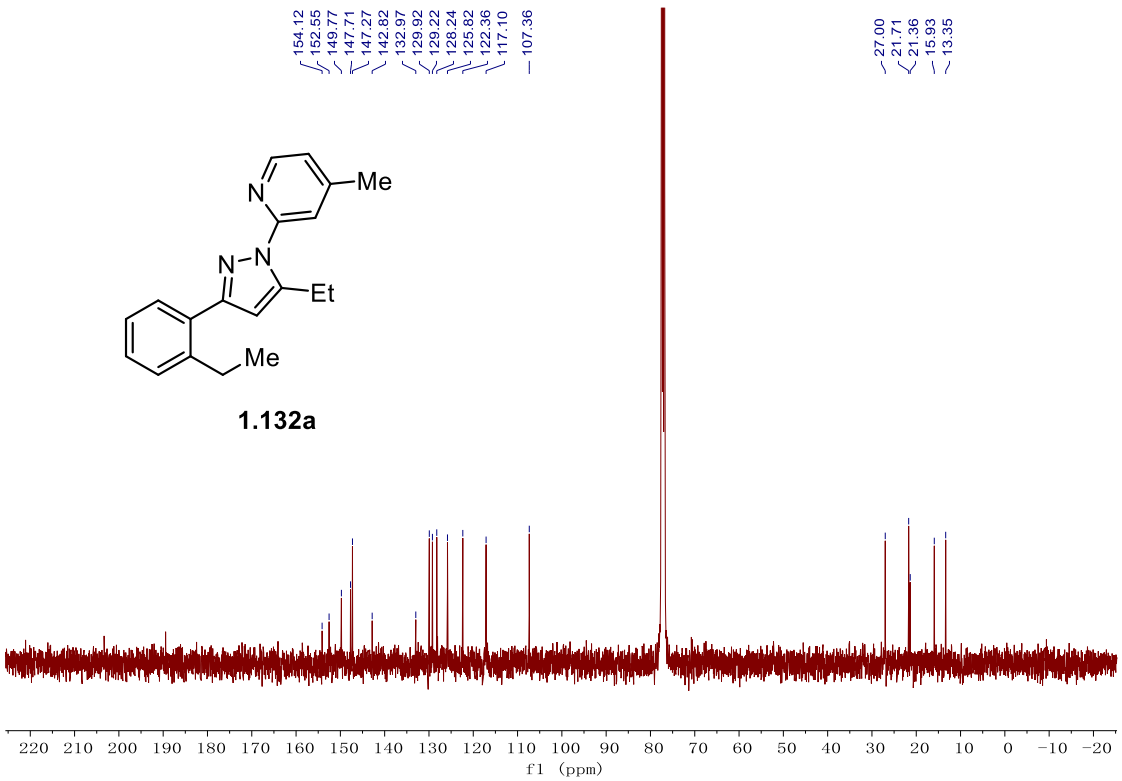


Figure 7.208 ^{1}H-NMR Spectrum of **7.132b** and **7.132c**

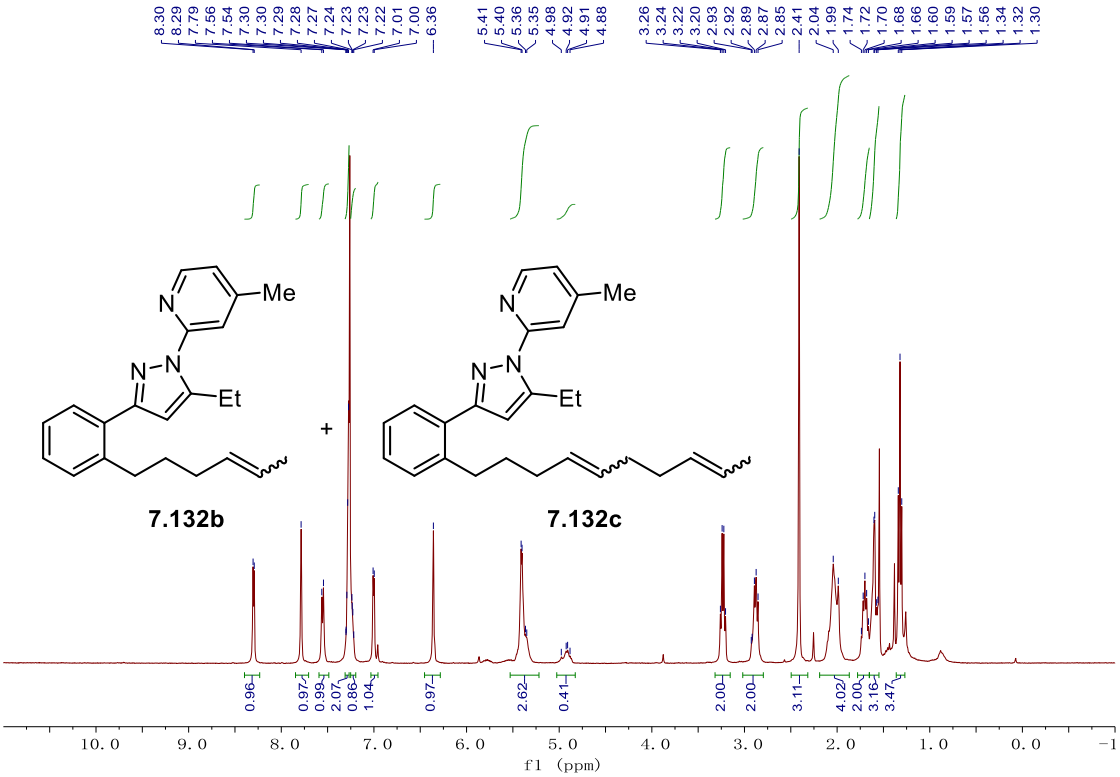


Figure 7.209 ^{1}H-NMR Spectrum of **7.133**

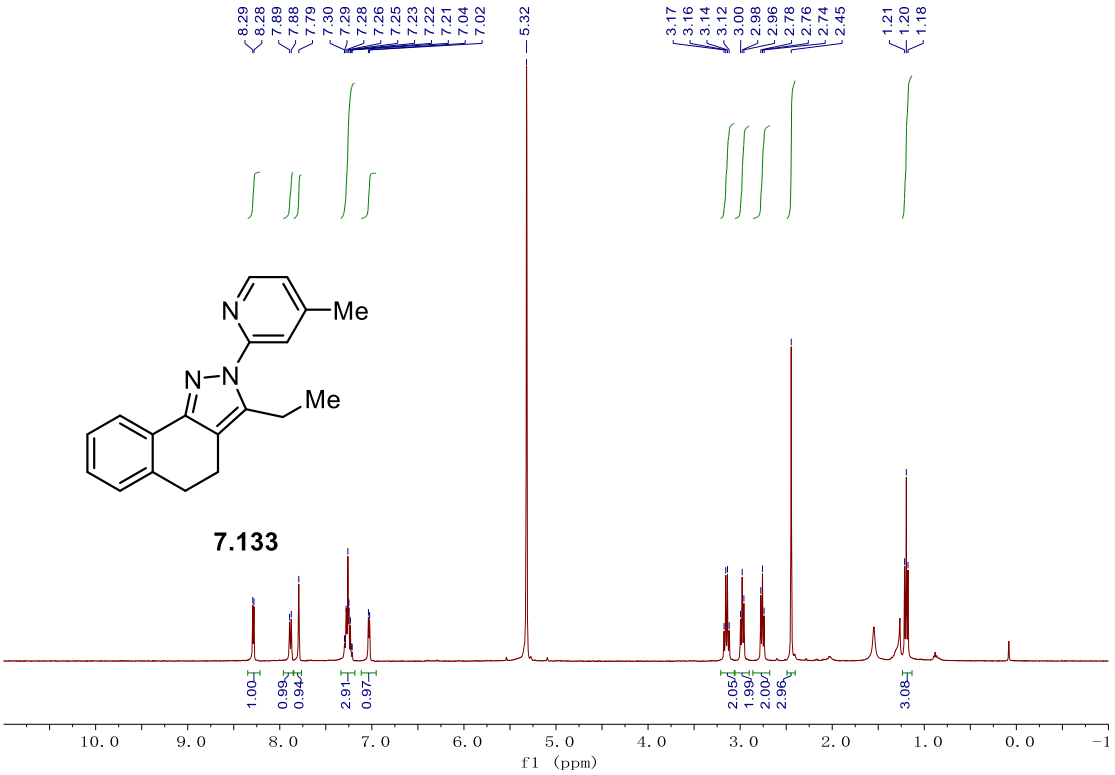


Figure 7.210 ^{13}C-NMR Spectrum of **7.133**

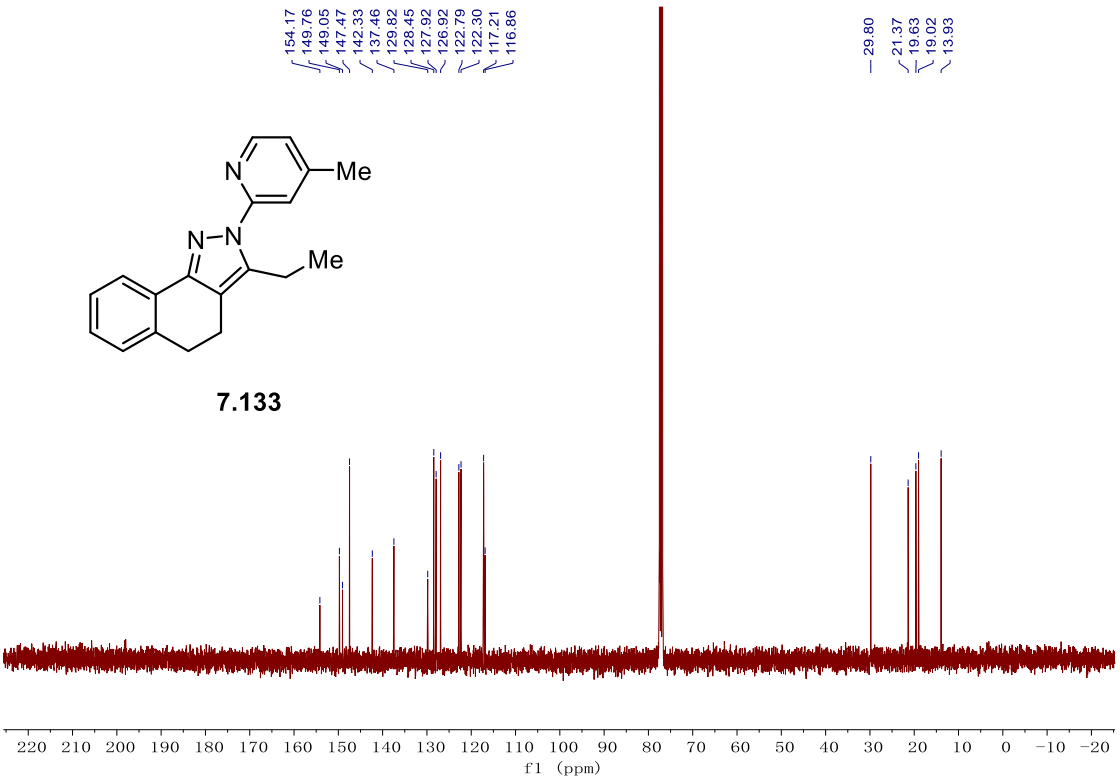


Figure 7.211 1D-NOE Spectrum of **7.133**

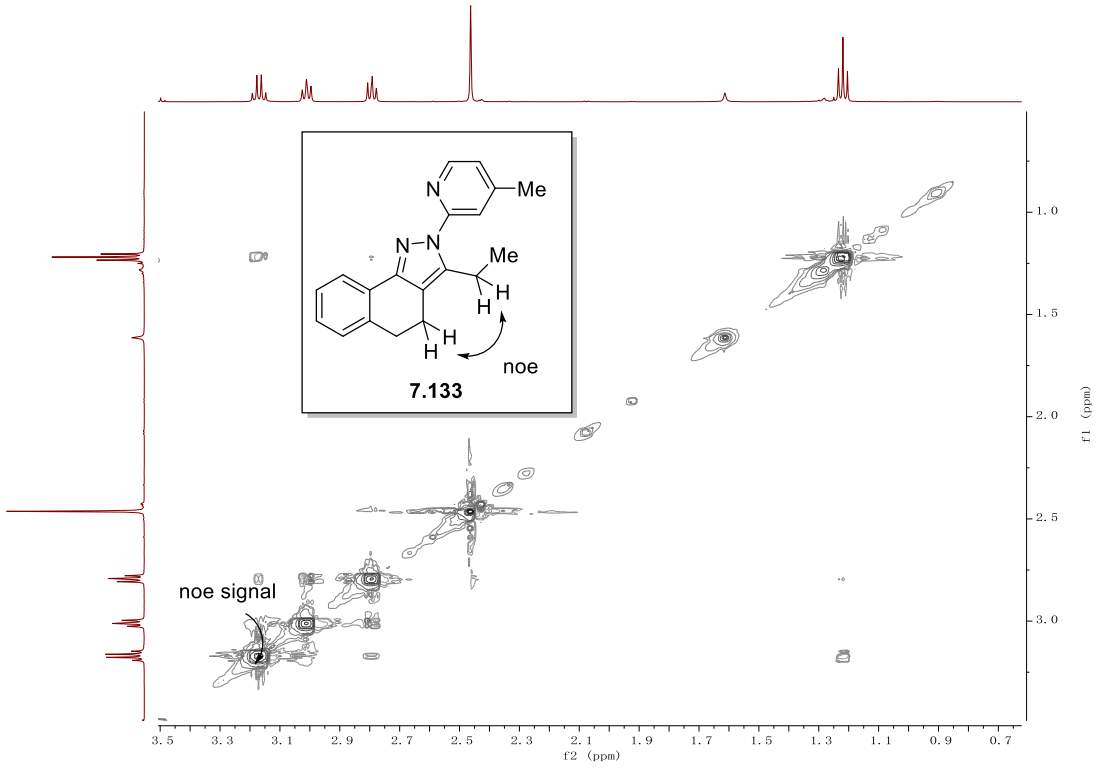


Figure 7.212 ^{1}H-NMR Spectrum of **7.138**

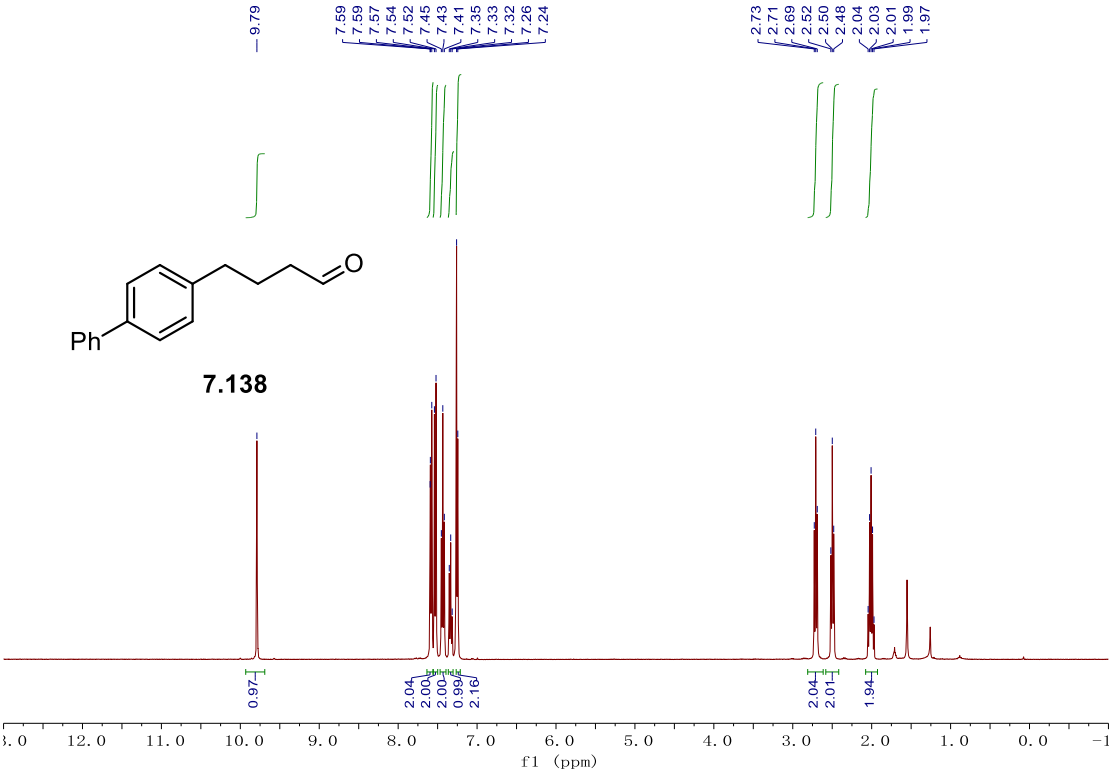


Figure 7.213 ^{13}C-NMR Spectrum of **7.138**

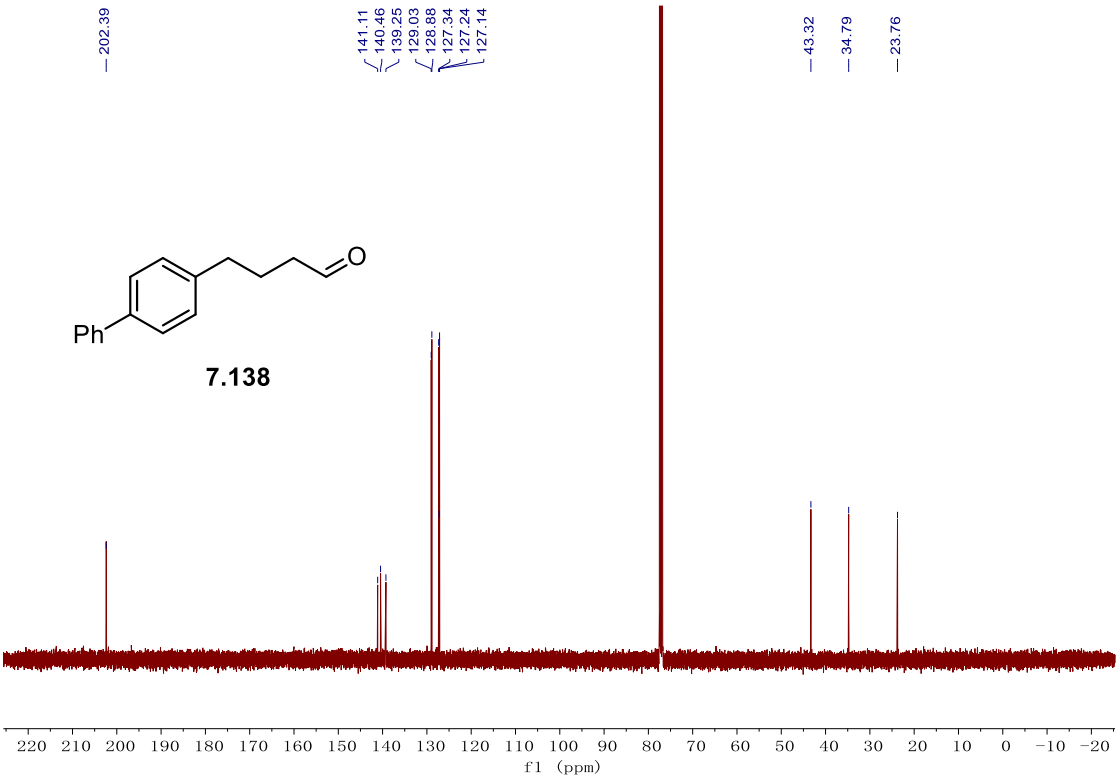


Figure 7.214 ^{1}H-NMR Spectrum of **7.137a**

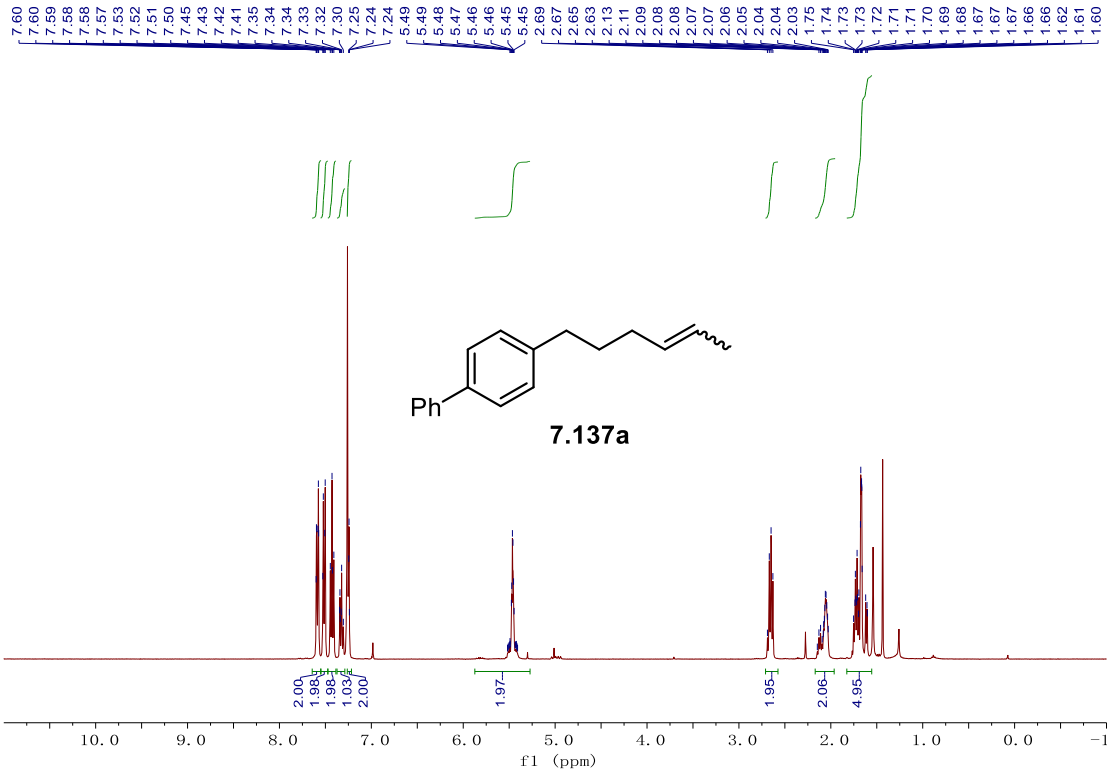
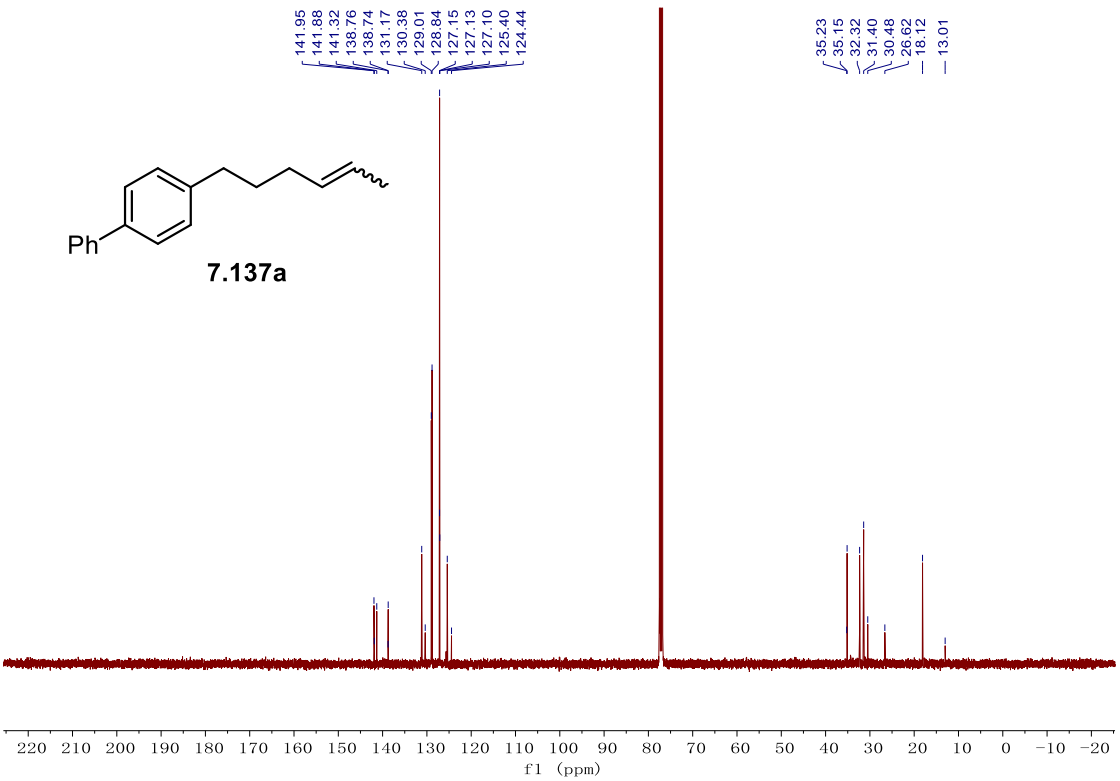


Figure 7.215 ^{13}C-NMR Spectrum of **7.137a**



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