THE UNIVERSITY OF CHICAGO

DIRECT β-FUNCTIONALIZATION OF KETONES VIA PALLADIUM-CATALYZED REDOX CASCADE

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To my family

TABLE OF CONTENTS

LIST OF SCHEMES

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
Ar	aryl
ATRP	atom transfer radical polymerization
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bpin	4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl
bpy	2,2'-bipyridine
Bz	benzoyl
cat.	catalyst
Cbz	benzyloxycarbonyl
cod	1,5-cyclooctadiene
COSY	correlation spectroscopy
Cy	cyclohexyl
cyp	cyclopentyl
d.r.	diastereomeric ratio
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane

DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DG	directing group
DIBAL	diisobutylaluminum
DIPEA	diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMG	dimethylglyoxime
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DNP	2,4-dinitrophenylhydrazine
DPPA	diphenyl phosphoryl azide
dppp	1,3-bis(diphenylphosphino)propane
DTBMPP	tris(3,5-di-*tert*-butyl-4-methoxyphenyl) phosphine
dtbpy	4,4'-di-*tert*-butyl-2,2'-bipyridine
EDG	electron-donating group
ee	enantiomeric excess
equiv.	equivalent
Et	ethyl
EWG	electron-withdrawing group
FG	functional group

HFIP	hexafluoroisopropanol
HMPA	hexamethylphosphoramide
IBX	2-iodoxybenzoic acid
i-Pr	isopropyl
LA	Lewis acid
LED	light-emitting diode
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Mes	mesityl
MOM	methoxymethyl
NBE	norbornene
n-Bu	butyl
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
OAc	acetate
Opiv	pivalate
OTf	trifluoromethanesulfonate
PG	protecting group

Ph	phenyl
Phth	phthalate
ppy	2-phenylpyridine
PTFE	polytetrafluoroethylene
r.r.	regioisomeric ratio
r.t.	room temperature
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TC	2-thiophenecarboxylate
TEMPO	(2,2,6,6-tetramethyl-1-piperidinyl)oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetate / trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
Ts	4-toluenesulfonyl

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PREFACE

Each chapter of this dissertation is numbered independently. A given compound may have a different number in different chapters. All experimental details, references and notes for individual chapters are included at the end of each chapter.

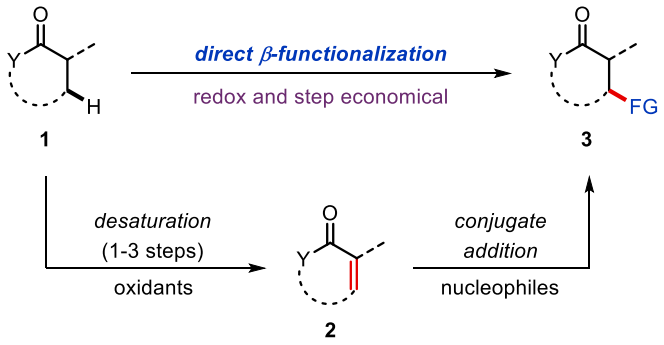
CHAPTER 1

Catalytic β-Functionalization of Carbonyl Compounds Enabled by α,β-Desaturation

1.1 Introduction

Preparation and derivatization of carbonyl compounds are cornerstones in organic synthesis. To date, rich chemistry has been developed to functionalize the *ipso* and α positions of carbonyl compounds via nucleophilic addition to carbonyl carbons and enolate couplings with electrophiles.[1] In contrast, direct functionalization at the β position has undoubtedly been a more challenging task, as the β-C−H bonds are significantly less acidic. To access β-functionalized carbonyl compounds, conventional methods mainly rely on conjugate addition of a nucleophile to an α,β-unsaturated carbonyl compound.[2] In many cases, the α,β-unsaturated carbonyl compounds need to be synthesized in one or a few steps from the corresponding saturated ones via an oxidation process.[3] Hence, efficient approaches that directly introduce functional groups at β positions of saturated carbonyl compounds would be attractive, from the redox- and step-economical viewpoints, to streamline complex molecule synthesis (Scheme 1.1).[4]

Scheme 1.1 Direct β-Functionalization of Carbonyl Compounds via α,β-Desaturation



Methods for direct and catalytic β-functionalization of carbonyl compounds have been extensively explored over the past two decades.[5] Firstly, directing group-based strategies have been popular, and typically operate through forming a five-membered metallocycle through C−H activation at the β positions.[6] In addition, enamine/photoredox cooperative catalysis provides a creative way to achieve β-functionalization, normally via selective homolytic C−H cleavage to generate a radical species at the β position.[7] While effective and broadly useful, there are intrinsic requirements associated with these methods, such as the capability of substrates to form five-membered metallocycles or to form enamines. As a complementary approach, the transition-metal-catalyzed desaturation reactions allow for directly forming a reactive center at the β position of carbonyl compounds,[8] which provides a new platform for β-functionalization given the versatile reactivity of α,β-unsaturated carbonyls. This chapter offers a brief overview of transition-metal-catalyzed α,β-desaturation processes and detailed discussion of β-functionalization methods enabled by these processes. In particular, it aims to highlight merits, pitfalls and potentials of each strategy.

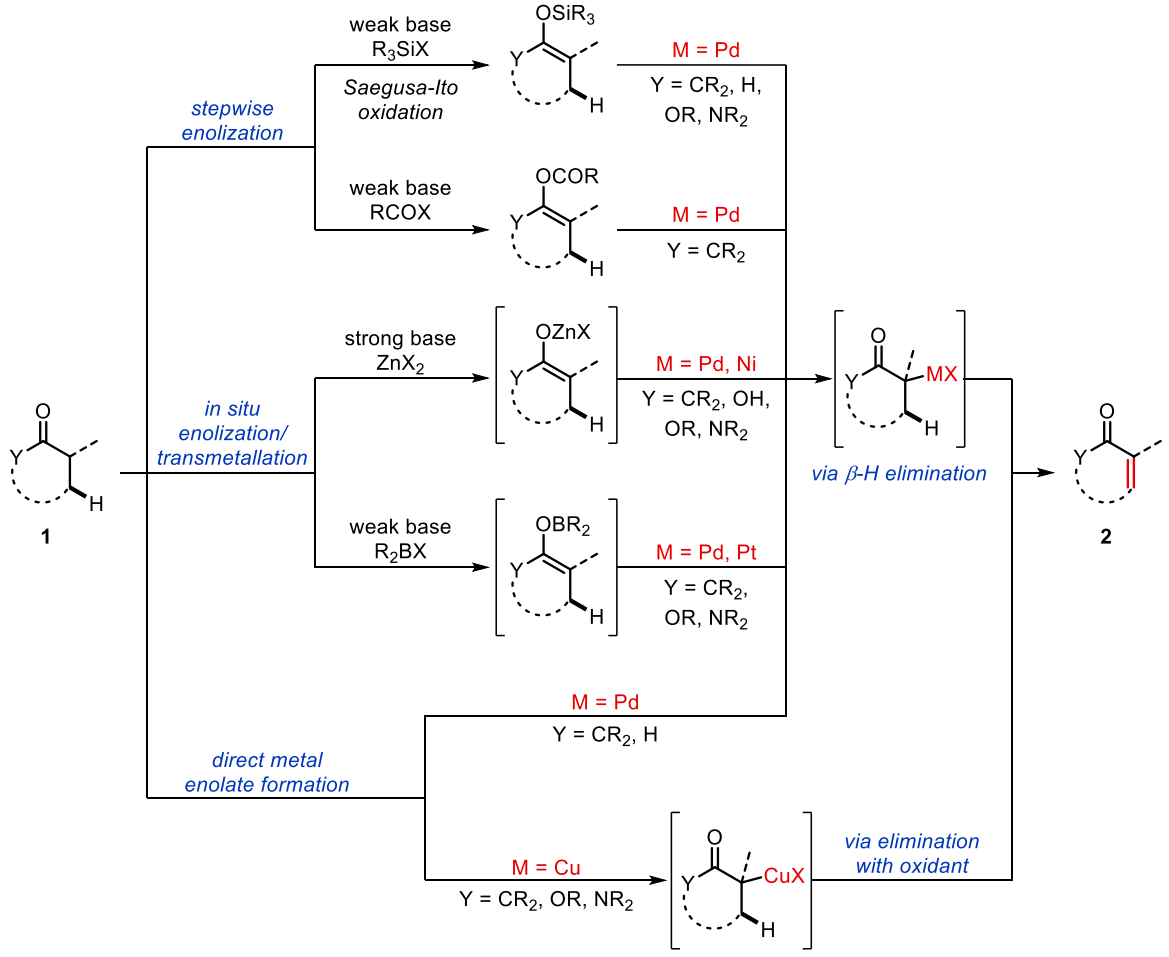
1.2 General Considerations

Till now, numerous strategies have been developed for α,β-desaturation of carbonyl compounds.[3,8] Conventionally, this transformation was often achieved through multiple steps by introducing heteroatoms, such as halide[9], sulfur[10] and selenium[11], to the α position of carbonyl compounds followed by an elimination process. Direct oxidation methods using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[12] or 2-iodoxybenzoic acid (IBX)[13] have also been found broadly useful.[14]

On the other hand, α,β-desaturation strategies based on transition metal catalysis have been explored since 1970s,[15] which renders the use of milder oxidants and less toxic reagents. Generally, almost all transition-metal-catalyzed α,β-desaturation reactions start with forming the corresponding metal enolate; thus, according to how enolates are generated, these reactions can be classified into three categories (Scheme 1.2). The first category involves stepwise enolization, in which a separate step is used to generate an isolatable enolate precursor. For example, the palladium-catalyzed oxidation of silyl enol ethers, known as Saegusa-Ito oxidation, is a well-established approach for carbonyl desaturation and has been widely employed in total synthesis of natural products.[16] Other enolate precursors, such as enol allyl carbonates or enol acetates, could also undergo desaturation via palladium catalysis.[17] The second category involves *in situ* enolization followed by transmetallation, which saves one step of operation and sometimes gives a broader substrate scope. Hard enolization via complete deprotonation by a strong base followed by forming a zinc enolate renders efficient α,β-desaturation of ketones, amides, esters, carboxylic

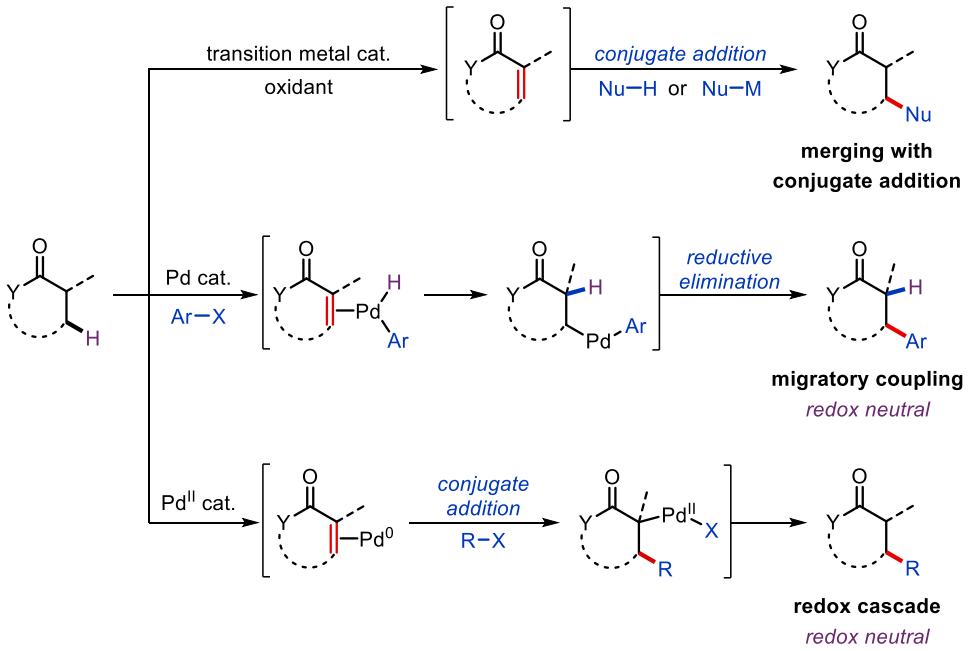
acids and nitriles using palladium or nickel catalysts.[18,19] Soft enolization using boron Lewis acids and weak bases has been found effective for desaturation of ketones, lactams, imides, lactones and esters catalyzed by palladium or platinum.[20,21] The third category involves direct formation of the reactive metal enolate. Palladium enolates could be directly generated from saturated ketones and aldehydes via α-palladation, which leads to a series of practical desaturation methods including those using air as the terminal oxidant.[22,23] Copper was recently found to be capable of catalyzing α,β-desaturation of diverse carbonyl compounds through a distinct radical-mediated pathway, with either TEMPO[24] or peroxides[25] as the oxidant.[26]

Scheme 1.2 Transition-Metal-Catalyzed α,β-Desaturation of Carbonyl Compounds



The versatility of the α,β-desaturation tactics provides rich inspiration and foundation for developing direct β-functionalization of carbonyl compounds through merging α,β-desaturation with various coupling approaches. The following content is divided into three sections, and each section is focused on a unique strategy about how functional groups are introduced at the carbonyl β position (Scheme 1.3).

Scheme 1.3 Strategies for Desaturation-Enabled β-Functionalization of Carbonyl Compounds

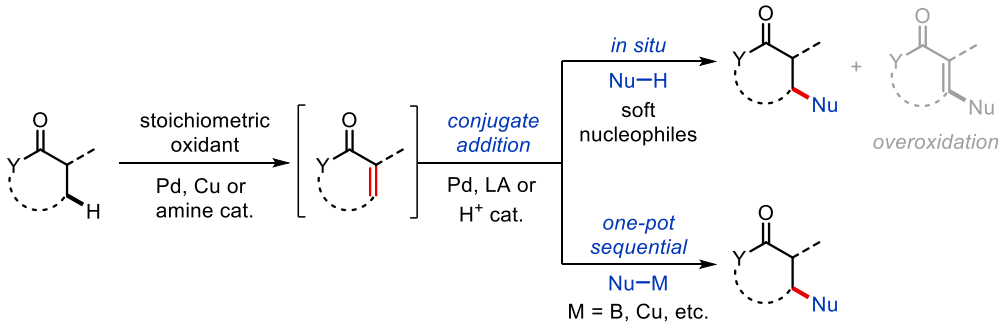


1.3 Merge with Conjugate Addition

Perhaps, the most straightforward strategy to access β-functionalized carbonyl compounds is to directly combine α,β-desaturation with conjugate addition of a nucleophile (Scheme 1.4). Compared with the conventional stepwise approaches, merging these two processes can save at least one step. The conjugate addition could be coupled with desaturation through either an *in situ* transformation or a one-pot sequential manner. In general, if nucleophiles used are compatible with

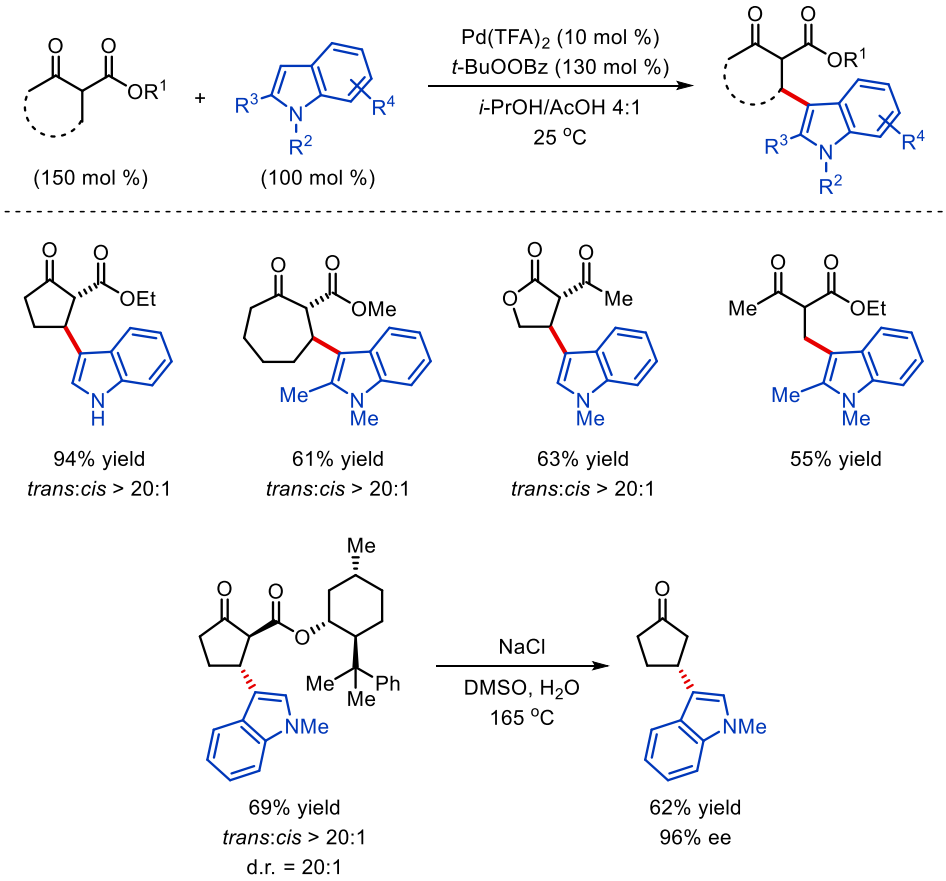
the desaturation processes, *in situ* conjugate addition would be feasible and more desirable. One potential pitfall of this approach is that the resulting products could undergo desaturation again leading to overoxidation. If nucleophiles used are incompatible with the desaturation processes, a sequential desaturation/conjugate addition has to be adopted, which, however, typically avoids the overoxidation problem. This section summarizes reactions of these two types, and methods that preferentially give overoxidation products, such as β-functionalized conjugated enones, are not included.[27]

Scheme 1.4 Merging α,β-Desaturation with Conjugate Addition



The first Pd-catalyzed β-functionalization of carbonyl compounds using an *in situ* addition strategy was developed by Pihko and coworkers. In 2012, they reported a Pd-catalyzed β'-arylation of β-keto esters using indoles as nucleophiles (Scheme 1.5).[28] The higher acidity of the α-proton in 1,3-dicarbonyl compounds allows facile formation of palladium enolates, thus this reaction took place in the absence of bases. *t*-BuOOBz was found to be the optimal oxidant. Both cyclic and linear β-keto esters are viable substrates, and the products predominantly possess *trans* configuration. It is impressive that free indole can be directly use as a C-nucleophile. An 8-phenylmenthyl-derived β-keto ester was also found an effective chiral auxiliary, and high enantiomeric excess was achieved after decarboxylation of the arylated product.[29]

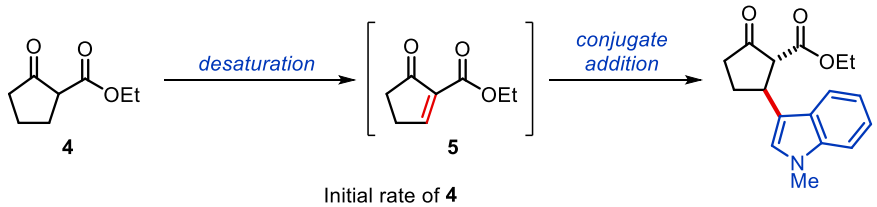
Scheme 1.5 β'-Arylation of β-Keto Esters Using Indoles



In order to gain deeper understanding of the reaction mechanism, mechanistic studies were performed using β-keto ester **4** and *N*-methylindole as the model substrates (Scheme 1.6). First, kinetic studies supported intermediacy of the α,β'-unsaturated β-keto ester **5**. During the initial stage, the concentration of **5** built up and then decayed, and a sigmoidal curve was found for product formation, indicating that α,β'-desaturation and indole conjugate addition could be separate processes. Interestingly, the rate of α,β'-desaturation was highly dependent on the concentration of *N*-methylindole, as *N*-methylindole accelerated the desaturation process (Scheme 1.6a).[28] Furthermore, an inverse kinetic isotope effect was detected for the C2-deuterated *N*-methylindole (Scheme 1.6b). Combining the results from their computational studies, the authors

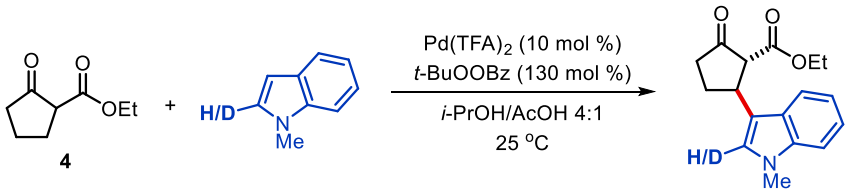
Scheme 1.6 Indole-Assisted α,β'-Desaturation of β-Keto Esters

(a) Rate dependence of α,β'-desaturation of 4 on *N*-methylindole



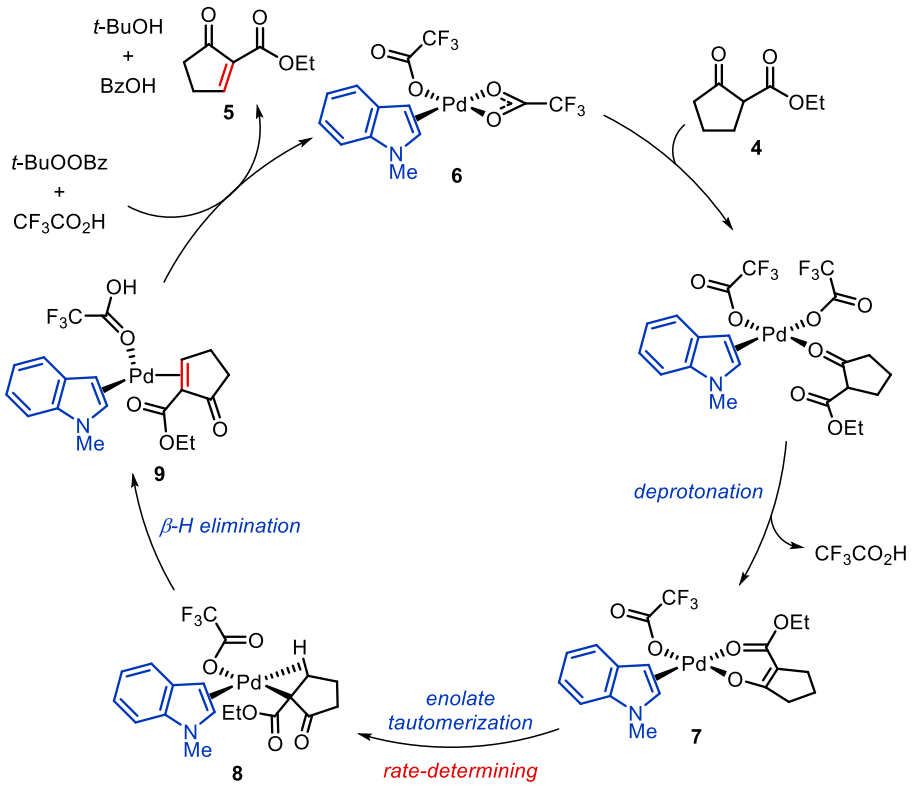
	Initial rate of **4**
without *N*-methylindole:	-0.25 mM·min^{-1}
0.318 M *N*-methylindole:	-5.7 mM·min^{-1}

(b) Inverse kinetic isotope effect for 2-deuterated *N*-methylindole



k_H / k_D = 0.82

(c) Proposed α,β'-desaturation cycle

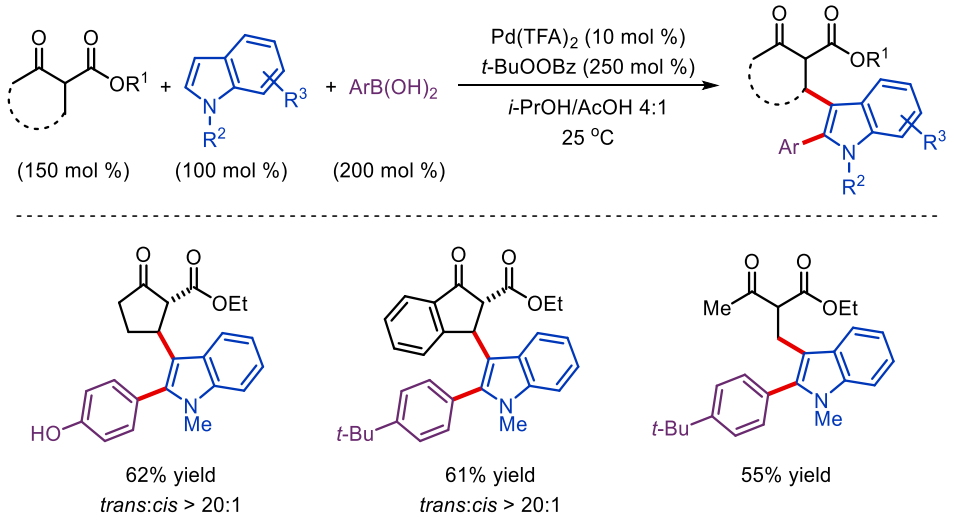


proposed an indole-assisted desaturation mechanism, in which indole serves as an electron-rich ligand (via 2,3-π-bond) and accelerates the desaturation process (Scheme 1.6c).[29] Starting from *N*-methylindole-coordinated $Pd(TFA)_2$ (**6**), substrate coordination and deprotonation delivers an *O*-bound Pd-enolate **7**. Likely due to the stronger bidentate coordination of enolate **7**, the subsequent enolate tautomerization to *C*-bound Pd-enolate **8** was calculated to be the rate-determining step. Subsequent β-hydrogen elimination generates a Pd(0) complex **9**, which could be oxidized by *t*-BuOOBz to regenerate complex **6** and release α,β'-unsaturated β-keto ester **5**. During the rate-determining step, tautomerization of the Pd-enolate leads to reduction of electron density at the Pd center in the transition state, which is alleviated by the tightly coordinated electron-rich indole ligand. This also results in a partial $C(sp^2)$ to $C(sp^3)$ rehybridization at the indole's C2 position, which is consistent with the inverse kinetic isotope effect. After the α,β'-desaturation process, the accumulated α,β'-unsaturated β-keto ester was proposed to undergo a Pd-catalyzed conjugate addition of indole to form the product. Though it was found that acids alone could also catalyze the conjugate addition, faster reaction rate was detected using the Pd catalyst.

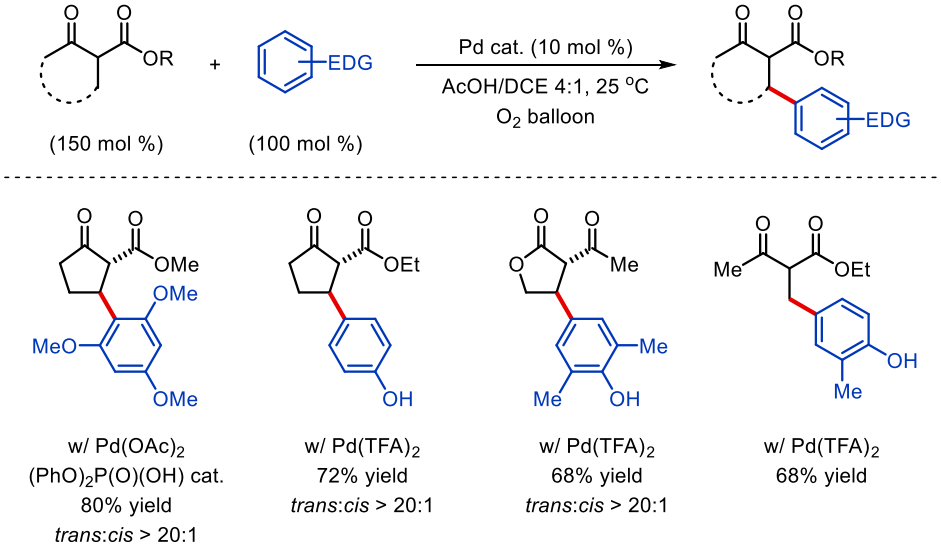
As an interesting extension of this transformation, the same group reported a three-component coupling reaction with β-keto esters, indoles and arylboronic acids (Scheme 1.7).[30] Kinetic studies showed that indoles first underwent fast coupling with arylboronic acids, which accumulated C2-arylated indoles during the initial stage. In addition, β'-arylation of β-keto esters with arylboronic acids was found slower than their reactions with indoles or C2-arylated indoles, which became the key for the high chemoselectivity in this three-component coupling reaction. Pihko and coworkers further explored the β'-arylation of β-keto esters using other electron-rich

arenes as the nucleophiles, such as 1,3,5-trimethoxybenzene and phenols (Scheme 1.8).[31] In this case, oxygen gas was employed as the terminal oxidant. The addition of electron-rich arenes was also found to accelerate the α,β'-desaturation process, which is consistent with the prior observation in the indole-mediated reactions.[28,29]

Scheme 1.7 Three-Component Coupling of β-Keto Esters, Indoles and Arylboronic Acids

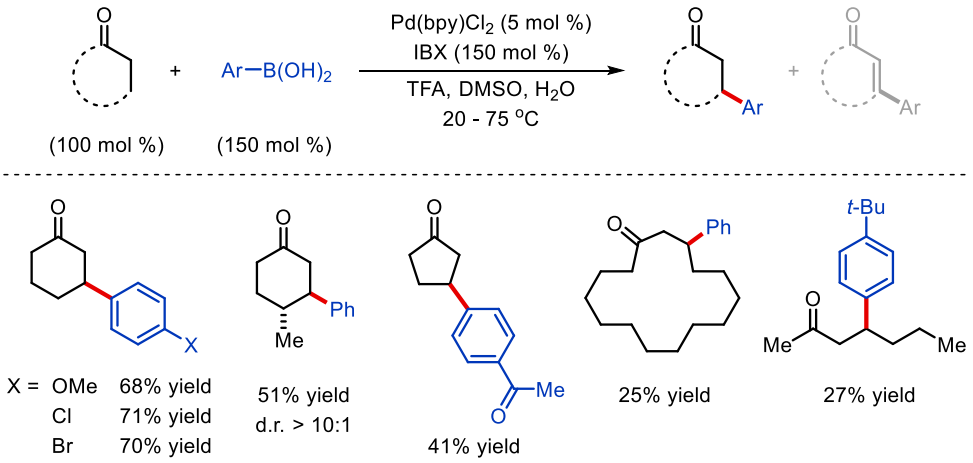


Scheme 1.8 β'-Arylation of β-Keto Esters Using Electron-Rich Arenes



Besides electron-rich arenes, arylboronic acids were later found to be a compatible nucleophile for β-functionalization. In 2017, Li and coworkers reported a Pd-catalyzed β-arylation of simple ketones using IBX as the oxidant (Scheme 1.9).[32] Control experiments showed that the ketone desaturation was solely mediated by IBX, while the Pd complex only catalyzed the conjugate addition of arylboronic acids to the enone intermediates. Generation of the overoxidation side products, i.e. arylated enones, was minimized by adding trifluoroacetic acid as the proton source, which promoted protonation of the β-arylated Pd-enolate thus minimizing the competing β-hydrogen elimination. Cyclohexanones worked the best in this reaction, and a wide range of functional groups on the aryl ring were tolerated. Other cyclic and linear ketones were also viable substrates albeit in diminished yields.

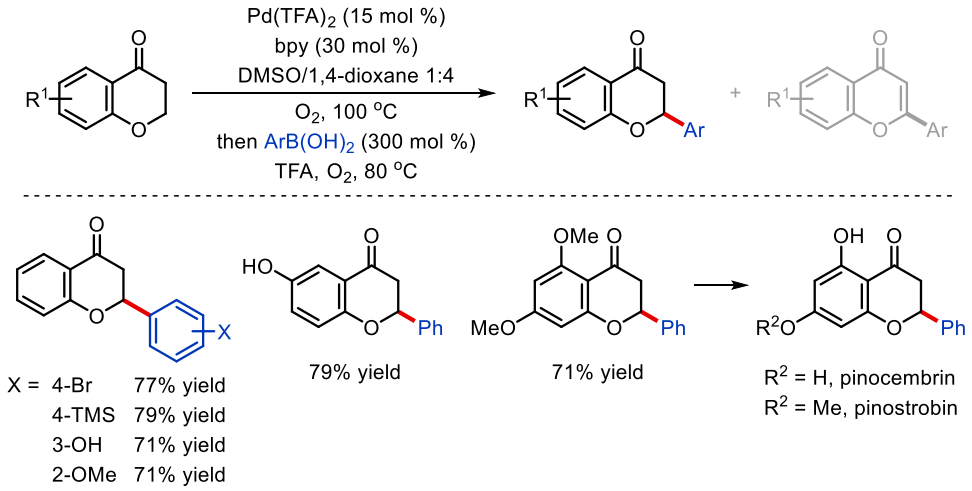
Scheme 1.9 Pd-Catalyzed β-Arylation of Ketones Using Arylboronic Acids



In 2019, Kim and coworkers reported the synthesis of flavanones from the Pd-catalyzed β-arylation of chromanones with arylboronic acids (Scheme 1.10).[33] While both α,β-desaturation and conjugate addition steps were catalyzed by Pd, addition of arylboronic acids in a sequential fashion after completion of the α,β-desaturation process was crucial for better yields and minimal

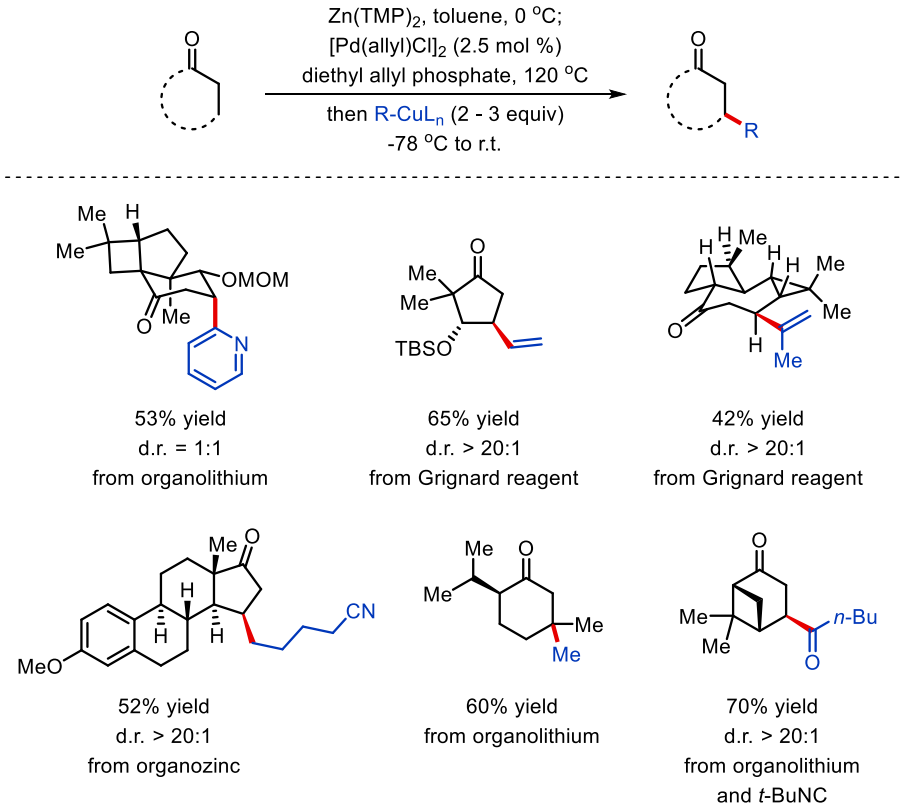
overoxidation (generating flavone). Trifluoroacetic acid was also found beneficial for suppressing overoxidation. Some sensitive functional groups were tolerated, including aryl bromides, silanes and free phenols. Natural flavanones such as pinocembrin and pinostrobin were accessed after deprotection of the β-arylated products.

Scheme 1.10 Pd-Catalyzed β-Arylation of Chromanones Using Arylboronic Acids



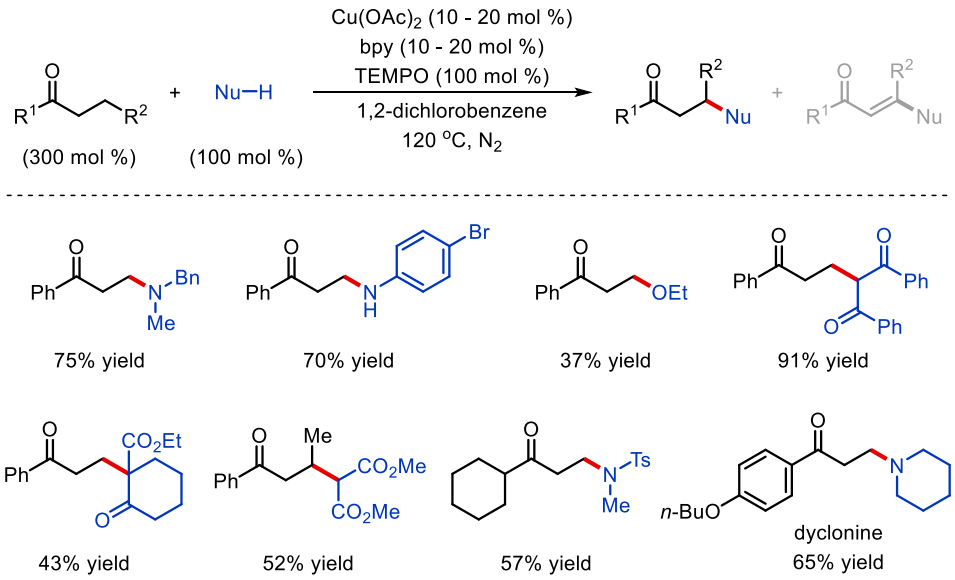
In addition to using soft nucleophiles, Newhouse and coworkers in 2017 disclosed a general and practical β-functionalization method that allows for a broadened scope of nucleophiles to be coupled (Scheme 1.11).[34] The new protocol was capitalized on the allyl-Pd-catalyzed ketone desaturation followed by the addition of organocuprate reagents, which enabled β-arylation, alkenylation, alkylation and acylation of ketones. Benefited from the robustness of their α,β-desaturation methods,[18] various cyclic ketones with complex fused- and bridged-ring structures were successfully coupled, and decent diastereoselectivity was observed in most cases. It is noteworthy that α,β-vicinal difunctionalization of ketones could also be achieved when electrophiles other than proton were used to quench the enolate generated after the organocuprate conjugate addition.

Scheme 1.11 Telescoped Ketone Desaturation and Conjugate Addition with Organocuprates



Besides palladium, copper catalysis has also been found effective to merge conjugate addition and α,β-desaturation of ketones. In 2016, Su and coworkers developed an efficient Cu/TEMPO system that allows for direct β-functionalization of linear ketones via merging α,β-desaturation with addition of soft nucleophiles (Scheme 1.12).[24a] In this reaction, copper catalyzed both the ketone desaturation and the conjugate addition steps. One merit of this catalytic system is that overoxidation side products were only observed in a trace amount. A wide range of nucleophiles, including amines, amides, alcohols and 1,3-dicarbonyl compounds, could be employed. Beyond propiophenone, other linear ketones with β-substituents and dialkyl ketones were also viable substrates.

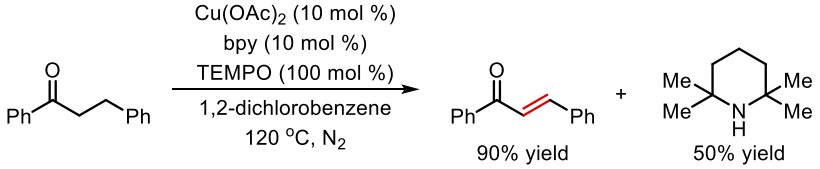
Scheme 1.12 Cu-Catalyzed β-Functionalization of Ketones



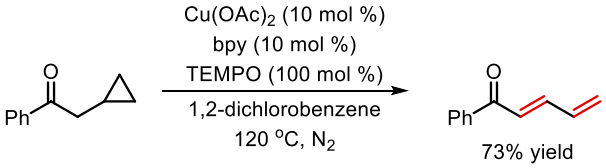
Given that the Cu-catalyzed α,β-desaturation of ketones using TEMPO as the oxidant was unprecedented, the authors performed detailed mechanistic studies to understand the reaction mechanism.[35] 3-Phenylpropiophenone was found to be a superior substrate that undergoes α,β-desaturation under the standard conditions (without a nucleophile) in an excellent yield, giving 2,2,6,6-tetramethylpiperidine as a byproduct (Scheme 1.13a). In addition, the involvement of ketone α-radical species was supported by a radical clock experiment (Scheme 1.13b). Inspired by the radical intermediacy, the authors proposed that TEMPO could likely combine with the ketone α-radical species. Indeed, the prepared TEMPO-bound ketone **10** was found to smoothly undergo elimination to generate the corresponding enone under the same conditions (Scheme 1.13c). Moreover, **10** was also observed as a reaction intermediate using 3-phenylpropiophenone with a higher catalyst loading.

Scheme 1.13 Cu-Catalyzed α,β-Desaturation of Ketones Using TEMPO Oxidant

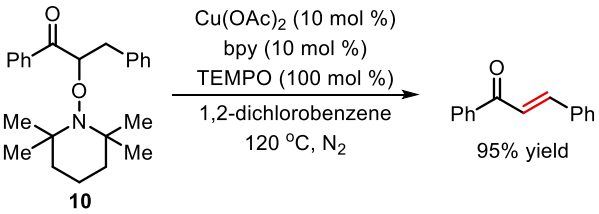
(a) Direct Cu-catalyzed desaturation of 3-phenylpropiophenone with TEMPO oxidant



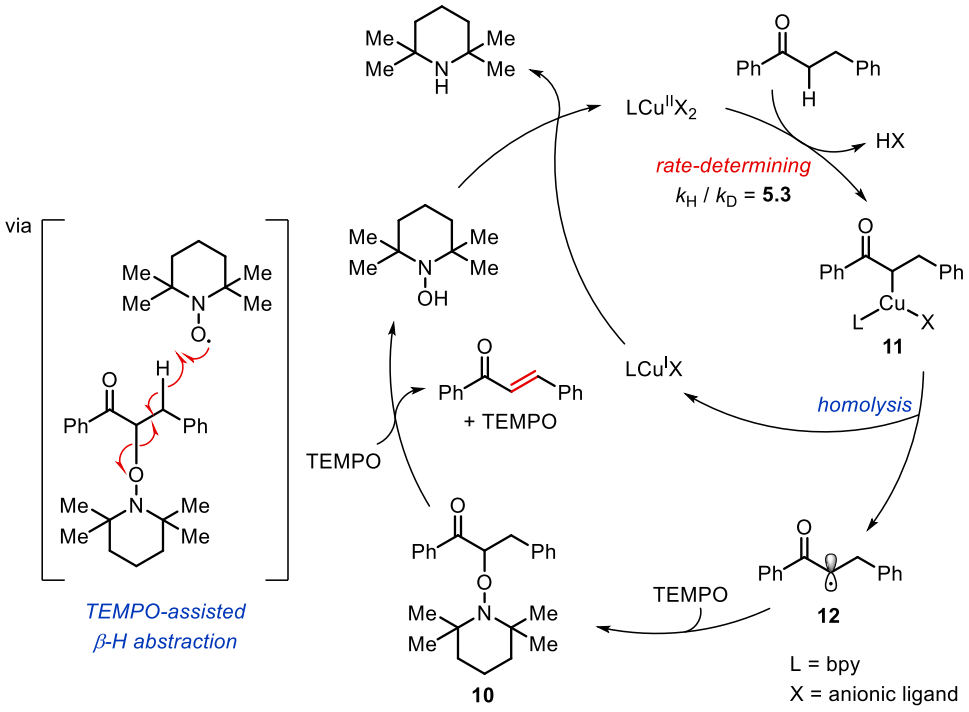
(b) Involvement of ketone α-radical intermediate



(c) Intermediacy of α-TEMPO-bound ketone

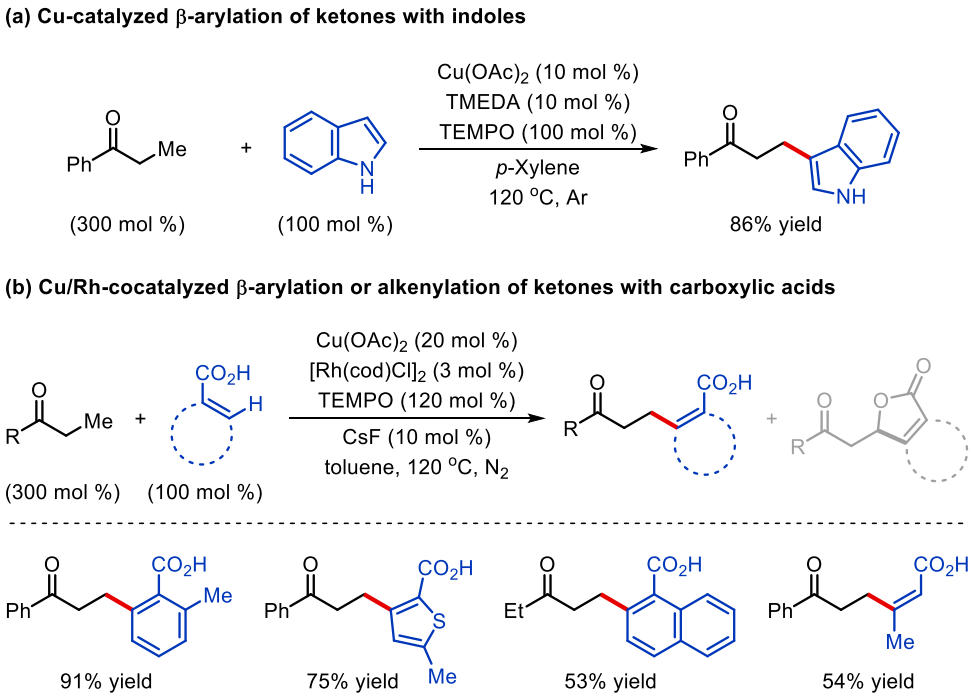


(d) Proposed α,β-desaturation cycle



Consequently, a novel catalytic cycle was proposed (Scheme 1.13d). The reaction starts with forming Cu(II)-enolate **11** from the Cu(II) salt and ketone, which is likely the rate-determining step due to the first order kinetic dependence on both the ketone substrate and the copper catalyst but zero order on TEMPO. In addition, a significant primary kinetic isotope effect was observed for the α-deuterated ketone, but not for the β-deuterated one. The subsequent step involves homolytic cleavage of the C−Cu bond to deliver the Cu(I) salt and an α-radical species **12**, which further recombines with TEMPO to deliver intermediate **10**. It was proposed that the following β-elimination step is assisted by another molecule of TEMPO, which delivers enone and TEMPOH that can further oxidize Cu(I) to Cu(II).

Scheme 1.14 Cu-Catalyzed β-Arylation and Alkenylation of Ketones

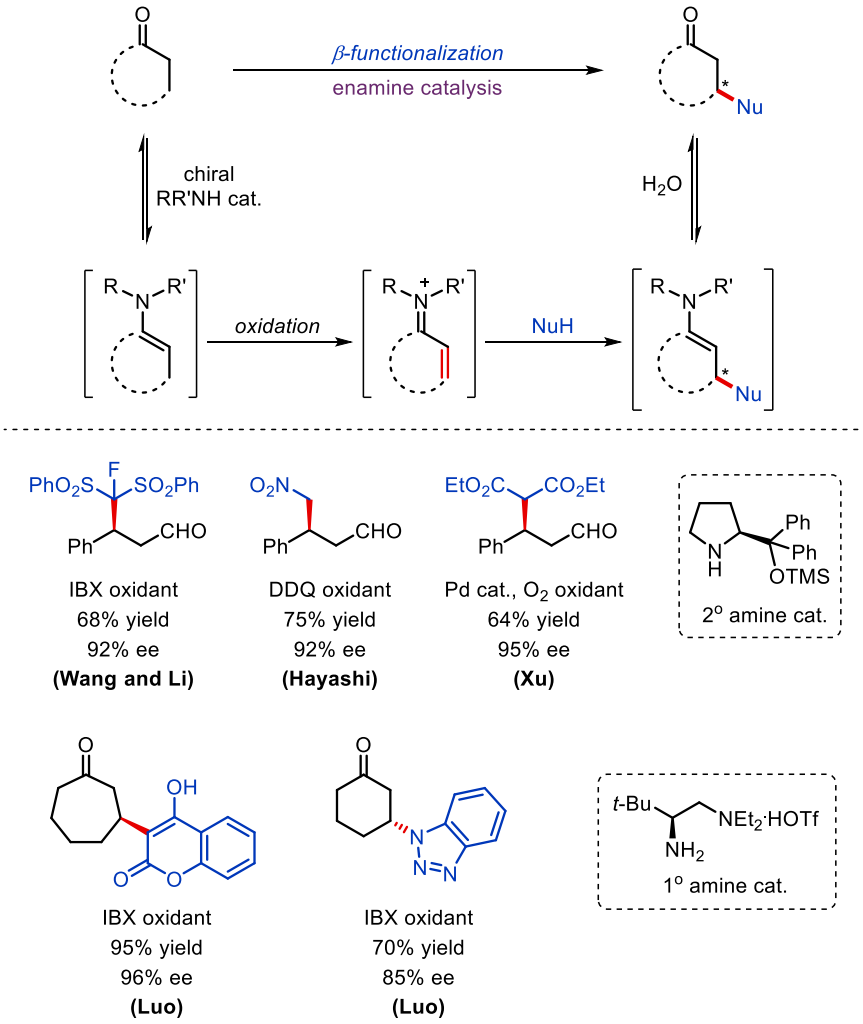


In the same year, Guo, Fang and coworkers reported a similar Cu/TEMPO system that catalyzed α,β-desaturation of propiophenones followed by conjugate addition of indoles (Scheme

1.14a).[36] Later, Su and Goossen developed a β-arylation and alkenylation of ketones through Cu/Rh cooperative catalysis (Scheme 1.14b).[37] While the Cu/TEMPO system was still responsible for the α,β-desaturation, the aryl nucleophile in the conjugate addition step was generated via a Rh-catalyzed carboxyl-directed C(sp^2)−H activation. Notably, while the C(sp^2)−H activation process can also be catalyzed by palladium or other rhodium complexes instead of $[Rh(cod)Cl]_2$, these catalyst systems predominantly gave an interesting oxa-Michael addition product due to overoxidation of the ketone.

Besides transition metals, amines can also be efficient catalysts for direct β-functionalization of aldehydes and ketones with soft nucleophiles. Through condensation of amines with aldehydes and ketones, the electron-rich enamine intermediates can undergo subsequent oxidation to realize α,β-desaturation.[13c,23] Moreover, the resulting iminium ion is also an activated electrophile, which could directly react with various soft electrophiles to enable β-functionalization, and the enantioselectivity could be controlled by using chiral amine catalysts (Scheme 1.15). Based on this idea, several innovative methods on asymmetric β-alkylation of aldehydes were developed by Wang and Li,[38] Hayashi[39] and Xu[40] using an *L*-proline-derived chiral amine catalyst. Later, Luo and coworkers employed a powerful chiral primary amine catalyst to achieve asymmetric β-C−C and C−N forming reactions of ketone substrates.[41] Among these works, IBX was used as the oxidant in Wang/Li and Luo's works and DDQ was employed as the oxidant in Hayashi's study; Xu's β-functionalization features the use of a Pd catalyst and O_2 as the terminal oxidant.

Scheme 1.15 Enamine Catalysis for Asymmetric β-Functionalization of Aldehydes and Ketones

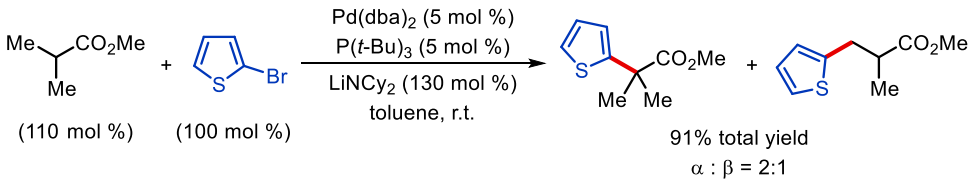


1.4 Migratory Coupling

The migratory coupling strategy renders a redox-neutral coupling between aryl halides and linear esters at their β positions. Interestingly, such reactivity arose from an accidental discovery. In 2002, during the study of the Pd-catalyzed α-arylation of esters using aryl bromides Hartwig and coworkers observed the formation of a β-arylated ester as a side product in one example (Scheme 1.16).[42] When methyl isobutyrate reacted with 2-bromothiophene, the α- and β-arylation

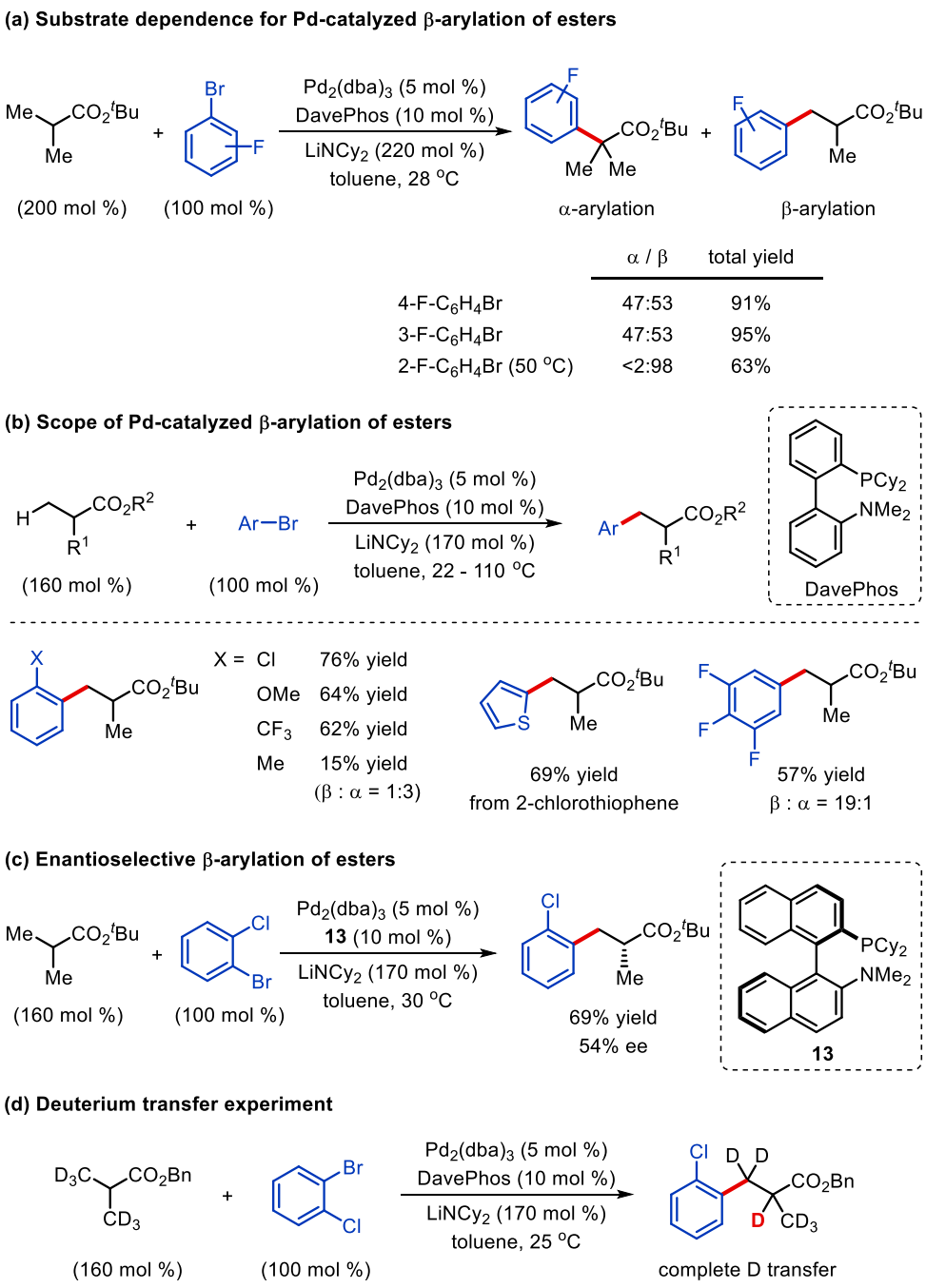
products were obtained in 2:1 ratio. The authors reasoned that the unforeseen β-arylation product was formed through isomerization of the hindered Pd enolate to the less hindered homoenolate via a sequence of β-hydrogen elimination, reinsertion and reductive elimination.

Scheme 1.16 Initial Discovery of Pd-Catalyzed β-Arylation of Esters



Later, this new pathway towards β functionalization was systematically studied and ultimately promoted to a practical level by Baudoin, Clot and coworkers. In 2010, they developed a selective β-arylation of esters through careful optimization of the catalytic conditions.[43] Both the ligand and the structure of the aryl halide were found to have profound influence on the β/α selectivity, as DavePhos was superior for β selectivity, and among the three fluorinated phenyl bromides, only the *ortho*-substituted one led to exclusive β-arylation (Scheme 1.17a). This structural dependence was further supported during the following substrate scope study (Scheme 1.17b).[44] Satisfactory β selectivity was mostly obtained with aryl bromides containing an electro-negative group at the *ortho* position. While the *ortho* methyl substituent gave poor reactivity and selectivity, 3,4,5-trifluorophenyl bromide still offered high β selectivity. Moderate enantio-selectivity was achieved using chiral ligand **13**, which is structurally similar to DavePhos (Scheme 1.17c). The deuterium labeling experiment showed that, when the ester with fully deuterated β positions was subjected to the reaction conditions, complete deuterium transfer to the α position of the product was detected (Scheme 1.17d).

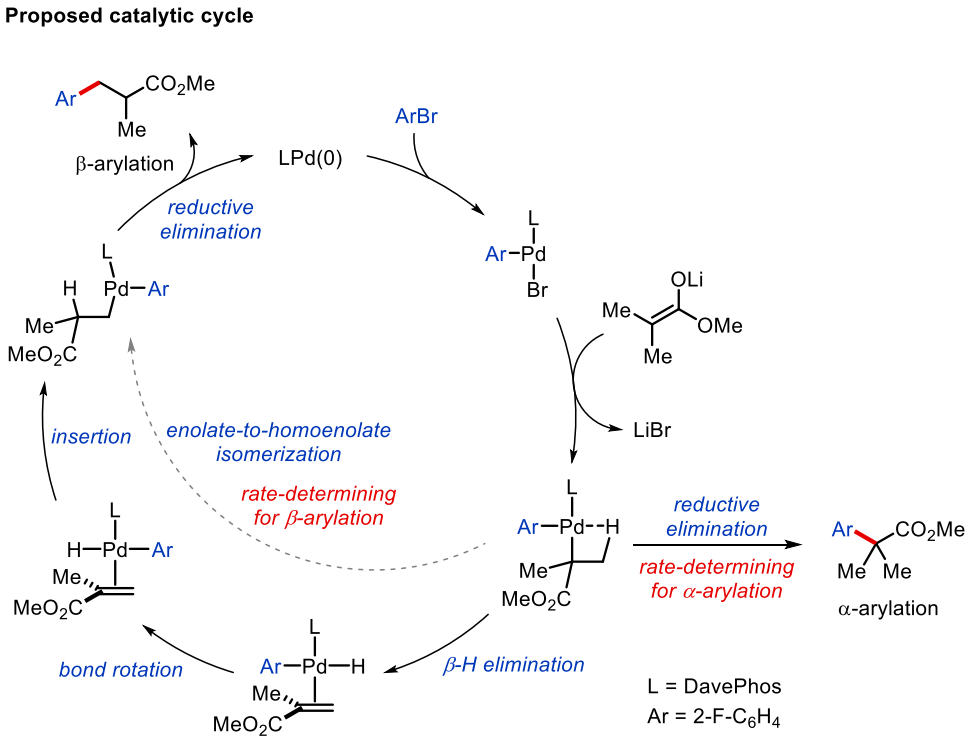
Scheme 1.17 Pd-Catalyzed β-Arylation of Esters via Migratory Coupling



To gain deeper understanding of the reaction mechanism and how the selectivity was affected by different factors, the same team further performed the DFT studies.[43,44] Consistent with the deuterium-labeling and computational results, the proposed catalytic cycle starts with oxidative

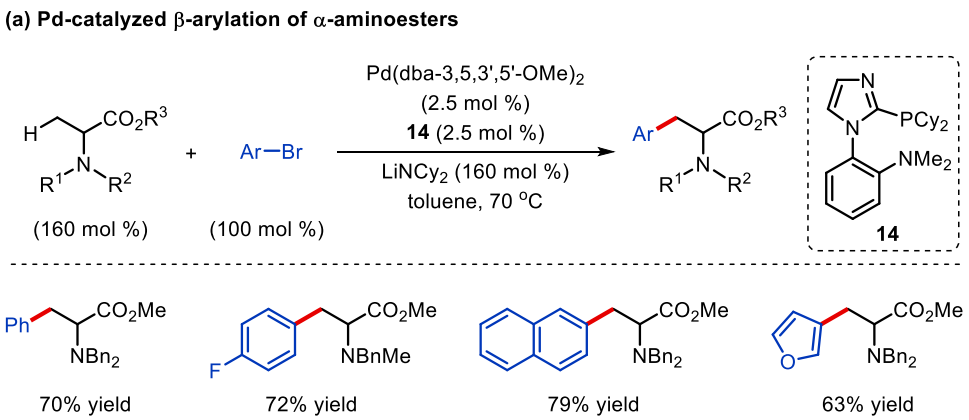
addition of Pd(0) with the aryl bromide, followed by transmetallation to give an aryl Pd-enolate (Scheme 1.18). The direct reductive elimination of the aryl and enolate groups would lead to α-arylation; however, if a competing β-hydrogen elimination takes place, after olefin π-bond rotation and Pd−H re-insertion into the resulting unsaturated ester, a Pd-homoenolate species would be generated, which delivers the β-arylated product upon reductive elimination. The possible olefin dissociation was calculated to possess a higher activation barrier than olefin rotation, which was in agreement with the experimental observation that the α,β-unsaturated ester was seldom found as a side product. Alternatively, olefin insertion into the Pd−Ar bond could be another potential pathway, but was found kinetically less favorable than Pd−H migration. The rate-determining step was the Pd-enolate-to-homoenolate isomerization process. Compared with β-arylation, the competing α-arylation pathway was both kinetically and thermodynamically unfavorable using α-disubstituted esters and DavePhos, with reductive elimination being the rate-determining step. Therefore, any factors that strengthens the Pd−Ar bond (e.g. a more electron-deficient aryl group) would disfavor the α-arylation pathway by increasing the energy barrier for the reductive elimination from the Pd-enolate, but the β-arylation pathway is less affected by the strength of the Pd−Ar bond. Finally, the higher reactivity of the DavePhos ligand could be attributed to its proper steric bulkiness and the stabilizing interaction between its biaryl backbone and palladium, which rendered easier generation of an active vacant site during transfer of the enolate ligand as well as a lower overall energy barrier for the β-arylation pathway.

Scheme 1.18 Mechanism of the β-Arylation of Esters via Migratory Coupling

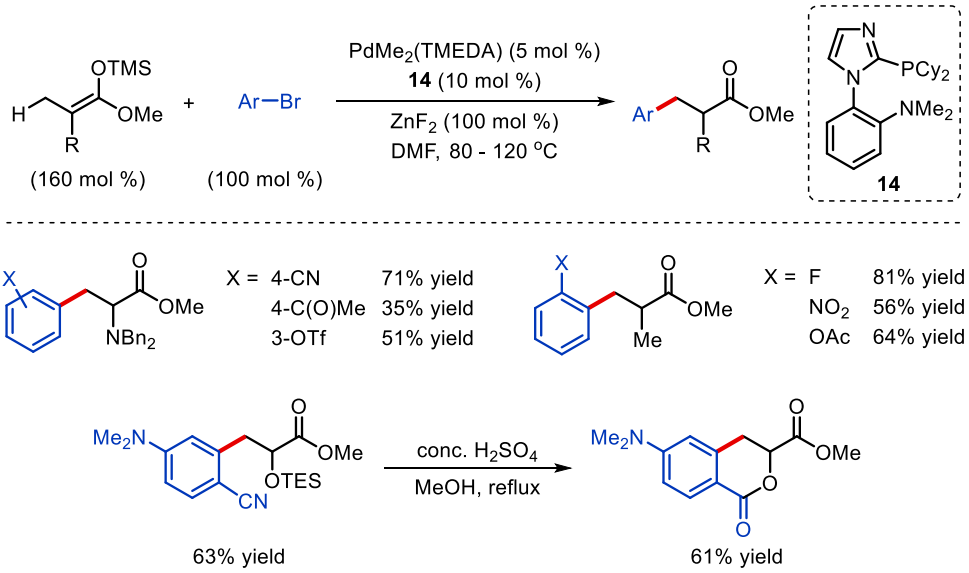


Notably, the β/α selectivity was not always affected by the electronic property of the aryl halides. Baudoin and coworkers later discovered that α-aminoesters were superior substrates for the highly β-selective arylation reaction (Scheme 1.19a).[45] In this case, the β selectivity was not sensitive to the structure and electronic properties of the aryl group, as a wide range of aryl bromides could be coupled, including electron-rich ones. The benzyl protecting group on the amine can be removed under hydrogenation conditions (Scheme 1.19b), giving free β-arylated α-aminoesters that are widely found in natural products and drug molecules. It is noteworthy that a long-range (γ to ζ) arylation of α-aminoesters was also reported using substrates bearing longer chains. The arylation preferentially occurred at the terminal carbon after multiple Pd migrations, though the yield usually dropped after each migration.

Scheme 1.19 Pd-Catalyzed β-Arylation of α-Aminoesters



Scheme 1.20 Pd-Catalyzed β-Arylation of Silyl Ketene Acetals



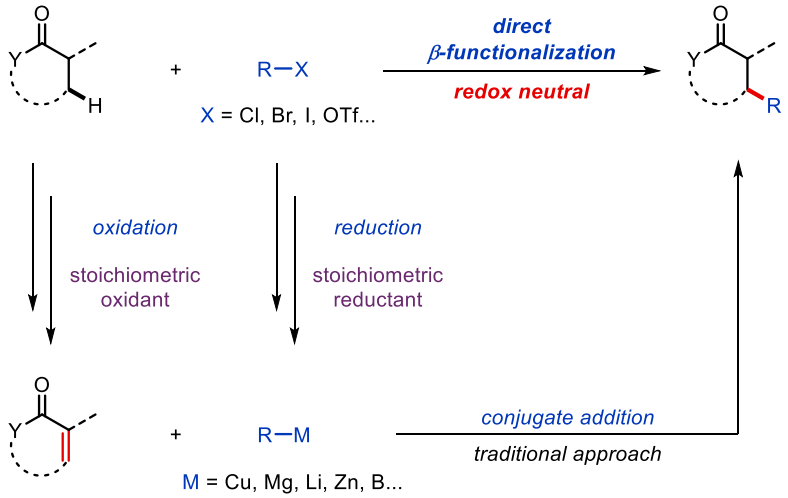
The same team further managed to expand the functional group tolerance by avoiding strong bases. To tackle this issue, they employed silyl ketene acetals as the substrate, which renders Pd-enolate formation simply using zinc fluoride as the activator (Scheme 1.20).[46] Indeed, more

sensitive substituents on the aryl ring were tolerated, including cyano, nitro and acetoxy groups, as well as methyl ketones and aryl triflates. This protocol is applicable not only to α-amino and α-methyl esters, but also to α-siloxy esters, which further enables the synthesis of benzo-fused δ-lactones through coupling a 2-cyanoaryl group.

1.5 Redox Cascade

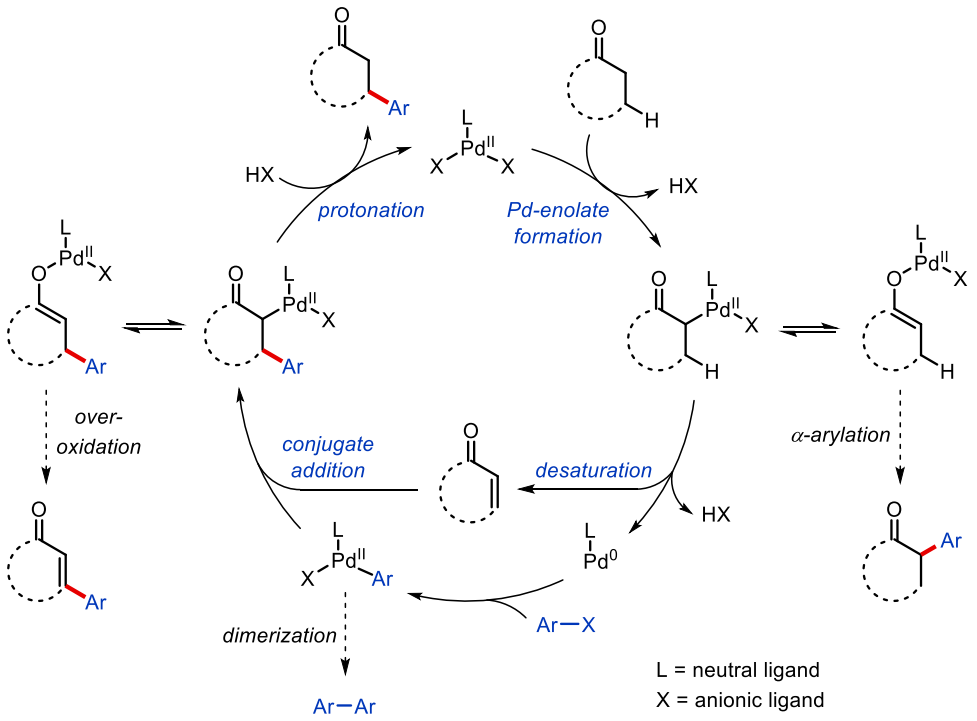
In many C−C forming conjugate addition reactions, the organometallic nucleophiles employed, such as organoboron reagents and organocuprate reagents, are typically generated via reduction of the corresponding organohalides in one or two steps. Given that α,β-desaturation is an oxidation process, it would be attractive to merge the generation of organometallic nucleophiles and α,β-desaturation through a catalytic redox cascade (Scheme 1.21). Consequently, the direct coupling of saturated carbonyl compounds with organohalides would provide a redox-neutral approach for the desaturation-promoted β-functionalization.

Scheme 1.21 Redox-Neutral Direct β-Functionalization of Carbonyl Compounds



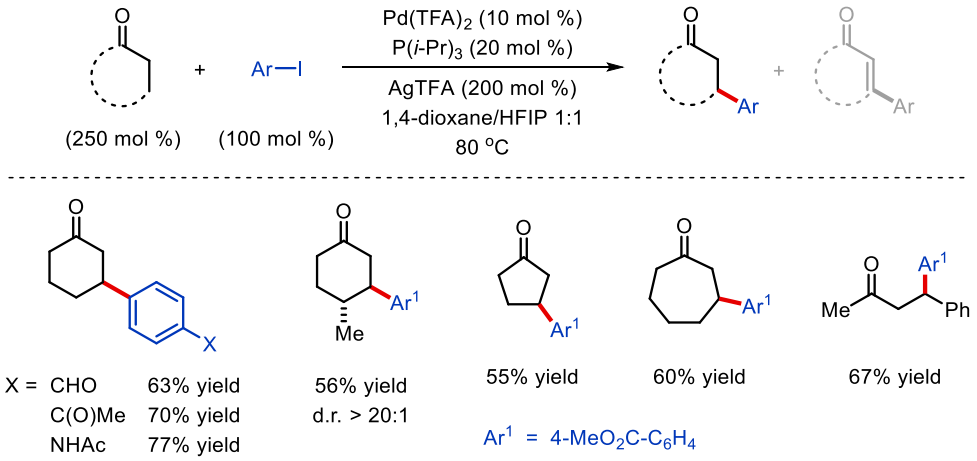
Based on this hypothesis, in 2013, Huang and Dong proposed a Pd-catalyzed redox cascade strategy for the direct β-arylation of ketones with aryl halides (Scheme 1.22).[47] It starts with a Pd-mediated ketone desaturation via formation of the Pd-enolate, β-hydrogen elimination and Pd(0) formation. The subsequent oxidative addition with aryl halides, followed by conjugate addition (or migratory insertion) of the resulting aryl-Pd species to the enone intermediate, introduces the β-aryl substituent. Finally, protonation of the new Pd-enolate delivers the product and regenerates the Pd(II) catalyst. In this catalytic cycle, the aryl halide serves not only as the carbon source for the C−C bond forming event, but also as the oxidant for the α,β-desaturation, thus the overall transformation is redox-neutral. Since several side reactions are possible, such as overoxidation, α-arylation and aryl dimerization, it is crucial to balance the reaction rates of all the steps involved.

Scheme 1.22 Pd-Catalyzed Redox Cascade Strategy for β-Arylation of Ketones



The Pd-catalyzed β-arylation of simple ketones with aryl iodides was found to be general (Scheme 1.23).[47,48] Triisopropylphosphine was found to be a superior ligand for this transformation, and a weakly acidic environment using HFIP was essential to suppress overoxidation and disfavor α-arylation. The Pd-enolate formation step was benefited from a relatively electrophilic Pd center bearing trifluoroacetate (TFA) ligands, and silver trifluoroacetate served as an iodide scavenger to help regenerate the active Pd catalyst. Attributed to the mild reaction conditions, a variety of functional groups, especially base-sensitive ones, were well tolerated. Other cyclic and linear ketones beyond cyclohexanones could also be smoothly arylated. It should be noted that, during one control experiment of the aforementioned β'-arylation of β-keto esters with electron-rich arene nucleophiles, Pihko and coworkers also observed the β-arylation product using iodobenzene.[31]

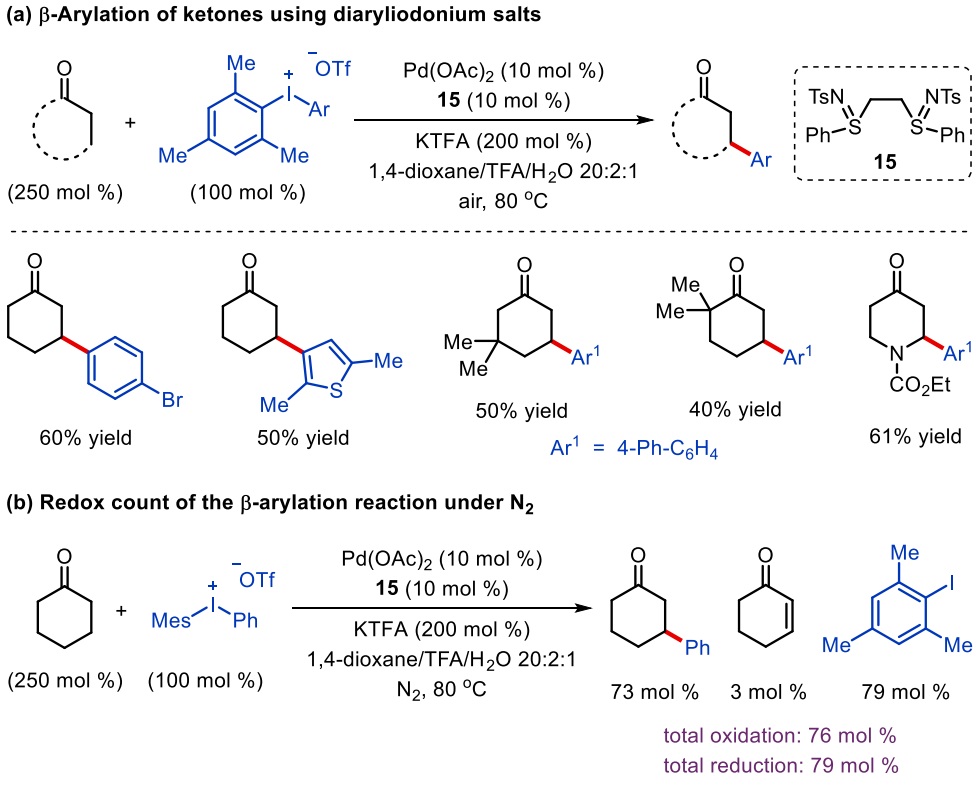
Scheme 1.23 β-Arylation of Ketones via the Pd-Catalyzed Redox Cascade



While the reaction was effective, the use of stoichiometric silver salt under the original reaction conditions not only was less economical, but also complicated the reaction mechanism since silver(I) is known to be capable of oxidizing Pd(0) to Pd(II). To enable a β-arylation method free of stoichiometric heavy metals, the Dong group developed a new catalytic system using diaryl-

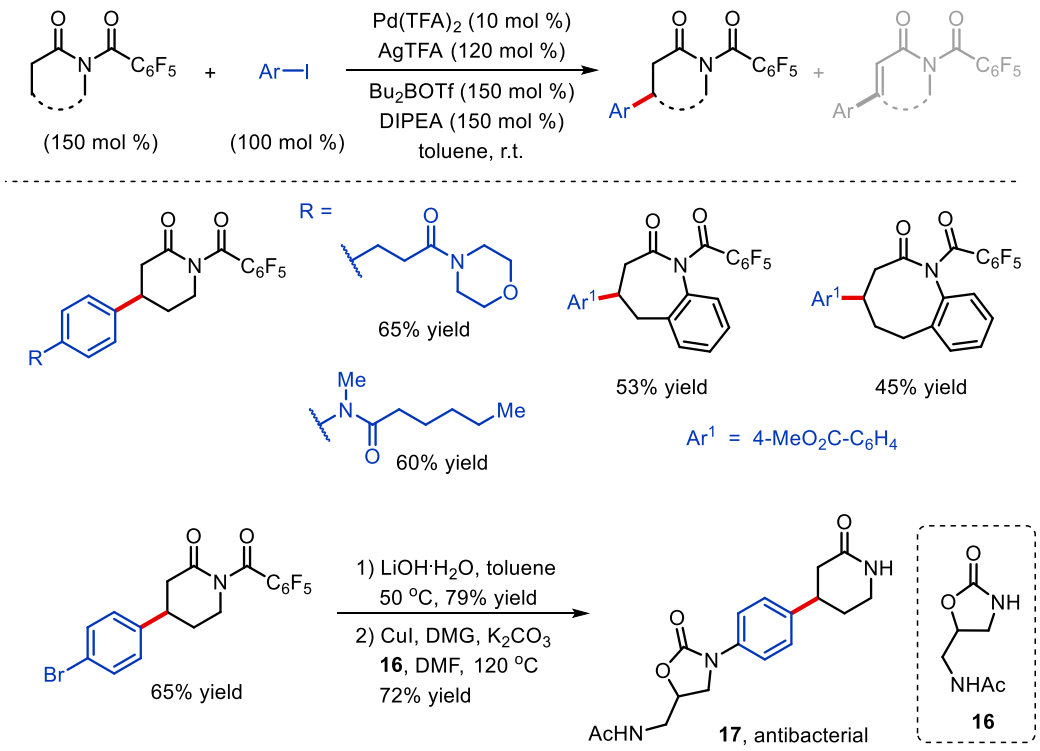
iodonium salts as the coupling partner in 2015 (Scheme 1.24a).[49] The use of mesitylaryliodonium salts as the aryl source was beneficial since they generate an inert byproduct, iodomesitylene, that is sufficiently bulky to avoid interfering with the main reaction. A trifluoroacetic acid/potassium trifluoroacetate buffer was used to balance the acidity. Interestingly, a new bis-sulfilimine ligand **15** was found advantageous in this transformation, likely due to its ability to stabilize the Pd nanoparticle that was proved to be the active catalyst in this reaction. Good functional group tolerance was also observed. In addition, a redox count based on the reaction operated under N_2 atmosphere showed that the total amount of ketone being oxidized (the β-arylation product plus the enone intermediate) was consistent with the total amount of the diaryliodonium salt being reduced, which supports the redox-neutral nature of this strategy (Scheme 1.24b).

Scheme 1.24 Pd-Catalyzed β-Arylation of Ketones Using Diaryliodonium Salts



The same team further expanded the carbonyl scope to less reactive lactams by employing a soft-enolization strategy (Scheme 1.25).[50] A combination of dibutylboron triflate and diisopropylethylamine (DIPEA) enabled enolization of lactams under mild reaction conditions, which promoted the α,β-desaturation process.[20b,21] The reaction selectively occurred at lactams with an acyl protecting group instead of linear amides. The substrate scope could be expanded to seven- and eight-membered lactams. Notably, aryl bromides were well tolerated, which facilitated the synthesis of an antibacterial compound **17** after removal of the protecting group and a Cu-catalyzed chemoselective C−N coupling.

Scheme 1.25 β-Arylation of Lactams via Pd-Catalyzed Redox Cascade



1.6 Conclusion and Outlook

In summary, taking advantage of the α,β-desaturation process, three distinct strategies for direct β-functionalization of carbonyl compounds have been developed. These strategies are classified based on how the β substituent is installed. Firstly, the conjugate addition strategy directly combines α,β-desaturation and nucleophilic 1,4-addition. Compared with the conventional stepwise processes, this one-pot strategy not only is step-economical, but also avoids handling reactive or sensitive α,β-unsaturated intermediates. One drawback is that stoichiometric oxidants are indispensable as stoichiometric α,β-desaturated intermediates need to be formed with this strategy. On the other hand, the migratory coupling strategy permits a redox-neutral β-arylation of esters using aryl halides as the reagent. It holds a novel mechanistic pathway through migrating the Pd from the α to the more remote β position, thus it has potential to realize enantioconvergent transformations from α-substituted racemic esters. The current development of this strategy is still in its early stage. It would be more attractive if the substrate scope could be expanded beyond α-branched esters and if the reaction scope could be extended beyond arylation. Finally, the redox cascade strategy is capitalized on reusing the Pd(0) species generated after α,β-desaturation in a subsequent carbon−halogen bond activation, in which the electrophile serves as both the oxidant and the source for the β substituents. Thus, the overall process is redox-neutral. The carbonyl scope has also been expanded beyond more acidic ketones and aldehydes. Further extension of the reaction scope beyond arylation would be expected using this strategy. The current limitation of

the redox cascade approach is the requirement of excess carbonyl compounds to avoid over-oxidation of the β-functionalized product.

As an outlook of the α,β-desaturation-based β-functionalization, there is still plenty of room to extend the scope of carbonyl substrates, which could likely be enabled through creating more efficient and mild α,β-desaturation methods. In addition, it would certainly be appealing if more and diverse enantioselective versions of these reactions could be developed to allow controlling the absolute stereochemistry at the β position. Careful catalyst and ligand design would probably be the key to address this challenge. Moreover, from the green chemical process and atom economy viewpoints, it could be highly attractive to realize a byproduct-free β-functionalization through direct coupling with olefins, alkynes or other unsaturated 2π units. This is likely going to require a new mode of activation or a new C−C bond-forming strategy. Overall, the α,β-desaturation-promoted carbonyl functionalization is a relatively young field with many potentials. The future development is expected to enrich the carbonyl chemistry and enable more general and efficient methods for streamlined synthesis.

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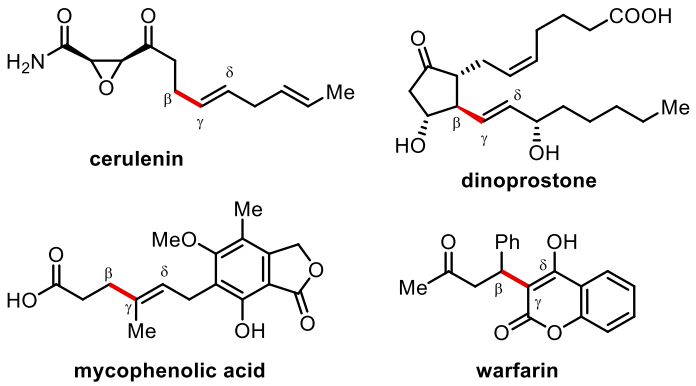
CHAPTER 2

Direct β-Alkenylation of Ketones

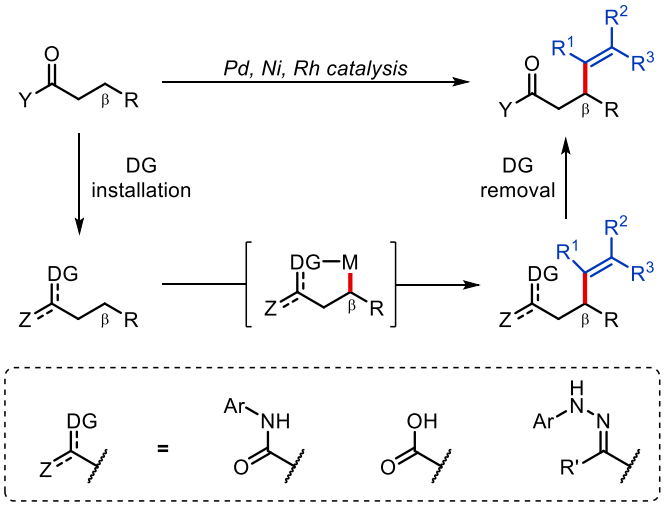
2.1 Introduction

Preparation and derivatization of carbonyl compounds are cornerstones in organic synthesis. While classical methods mainly focus on functionalizing the electrophilic carbonyl carbon and the acidic α-C−H bond, direct C−C bond forming reactions at the more inert β positions have been substantially developed over the past decade.[1] Among these transformations, β-alkenylation of carbonyl compounds is of particular interest, not only because γ,δ-unsaturated carbonyl structures are commonly found in pharmaceuticals and natural products (Figure 2.1), but also due to the fact that olefin moieties can serve as a versatile precursor to access various other functional groups.[2] In the past decade, the directing group (DG)-based strategy has emerged as a powerful approach to achieve the direct β-alkenylation of carbonyl compounds (Scheme 2.1). Amides and carboxylic acids have been extensively used as DGs in the Pd-catalyzed C−H alkenylation,[3,4] in which alkenyl halides and Michael acceptors can both serve as the alkenylation reagents. In addition, the Ni-catalyzed alkenylation using alkynes as the coupling partner has also

Figure 2.1 Selected Bioactive Compounds with β-Alkenyl Carbonyl Moieties



Scheme 2.1 β-Alkenylation of Carbonyl Compounds Using Directing Group Strategy

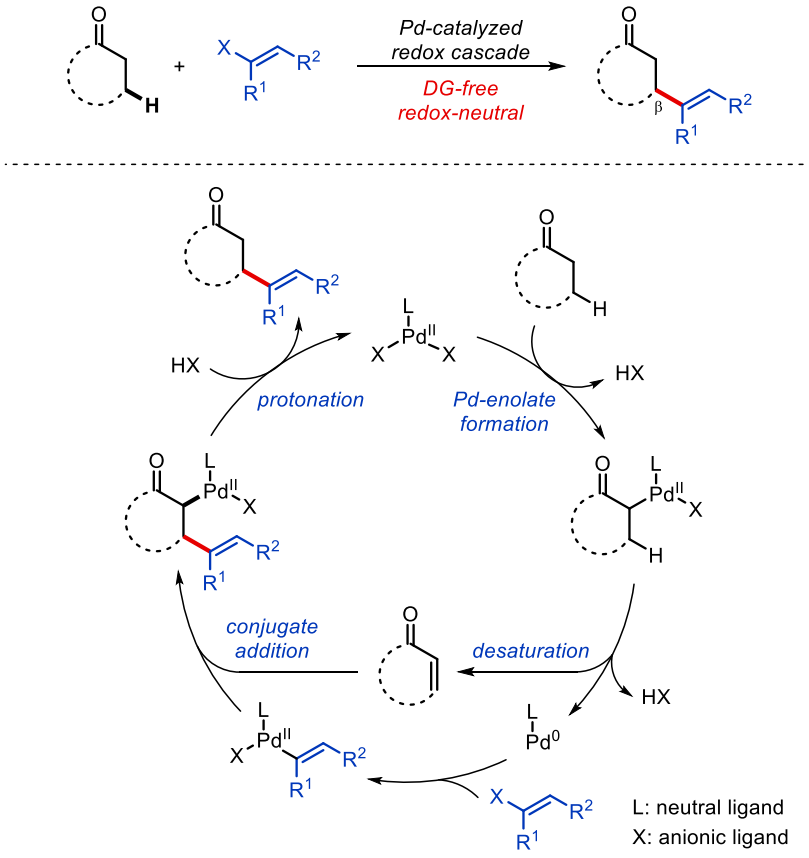


been demonstrated.[5] In contrast, the direct β-alkenylation of simple ketones remains challenging. Dong and coworkers recently reported a directed Rh-catalyzed β-alkenylation of ketones with alkynes through a hydrazone intermediate.[6] Newhouse and coworkers disclosed an efficient one-pot β-alkenylation strategy through a Pd-catalyzed ketone desaturation with allyl oxidants followed by subsequent conjugate addition with organocuprates.[7] However, These approaches require either stoichiometric redox manipulations or directing group installation and removal. Our laboratory has been engaged in systematic development of a Pd-catalyzed redox cascade strategy

for direct β-arylation of carbonyl compounds.[8] Therefore, we aimed to extend the electrophile scope to alkenyl halides employing the redox cascade strategy so that a direct, DG-free and redox-neutral β-alkenylation of ketones could be achieved.

As described in the proposed catalytic cycle (Scheme 2.2), the approach starts with a Pd(II)-mediated ketone desaturation to deliver an α,β-unsaturated ketone intermediate.[9] The generated Pd(0) then undergoes oxidative addition with alkenyl halide to form an alkenyl-palladium(II) species, which subsequently constructs the β-C−C bond through conjugate addition. Finally, protonation of the resulting Pd(II)-enolate provides the product and regenerates the Pd(II) catalyst.[10] The organohalide serves as both the oxidant for the ketone desaturation and the carbon

Scheme 2.2 β-Alkenylation of Ketones Using Pd-Catalyzed Redox Cascade Strategy



source for the β-C−C forming event. Distinct from the DG strategy, the Pd-catalyzed redox cascade avoids additional operations for DG installation and removal, and enables the functionalization at the β positions of cyclic ketones that are hard to reach through the DG approach.

However, compared with aryl halides, employment of alkenyl halides in the redox cascade strategy would introduce two new challenges: (a) alkenyl halides are generally less stable and prone to decompose in the reaction system; and (b) the alkenyl moiety could possibly undergo further Pd-catalyzed reactions under the reaction conditions. Thus, the key would be to balance the reaction rates among ketone desaturation, alkenyl conjugate addition and protonation of the alkenylated Pd(II)-enolate. In addition, we anticipated that a weakly acidic environment could be crucial for both minimizing the alkenyl halide decomposition and promoting the final protonation step.

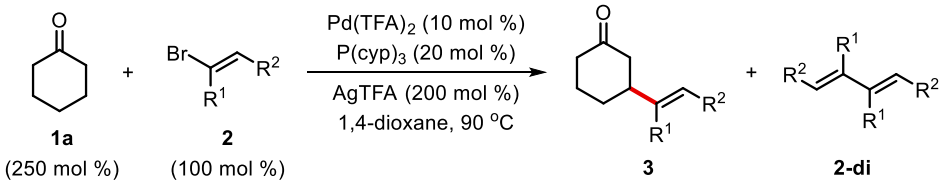
2.2 Results and Discussion

2.2.1 Optimization of the reaction conditions

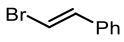
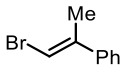
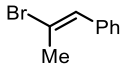
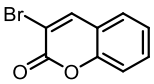
To explore this proposal, we first started with the catalytic system involving $Pd(TFA)_2$ and tricyclopentylphosphine as the precatalyst and AgTFA as the halide scavenger (Table 2.1). When cyclohexanone (**1a**) was chosen as the model ketone substrate, (*E*)-β-bromostyrene successfully delivered the desired β-alkenylation product in 17% yield (entry 1). However, full conversion of the alkenyl bromide substrate indicated significant decomposition. While most side products were hard to identify, the dimer of the alkenyl moiety (**2-di**) was observed in comparable yield. We

reasoned that the dimerization could be inhibited by increasing steric hindrance of the alkenyl moiety, so we next tested (*E*)-β-bromo-α-methylstyrene, but the results were inferior (entry 2). Instead, (*E*)-β-bromo-β-methylstyrene showed enhanced yield, decreased ratio of dimerization and an overall better mass balance (entry 3). Though the issue was not completely solved, the result indicated that the increased steric hindrance close to the bromo atom played an important role in suppressing the dimerization and stabilizing the alkenyl bromide. Indeed, when a more stabilized alkenyl bromide, 3-bromocoumarin, was tested under the same conditions, the dimerization was greatly inhibited (entry 4).

Table 2.1 Initial Development of the β-Alkenylation of Cyclohexanone[a]



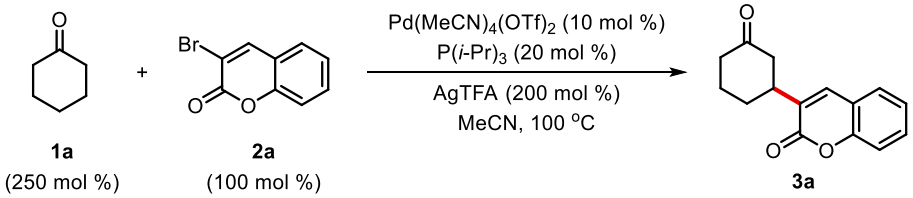
1a (250 mol %) + **2** (100 mol %) → **3** + **2-di**

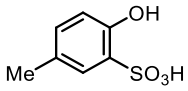
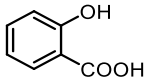
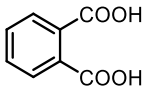
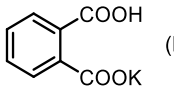
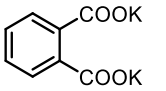
entry	structure of **2**	yield of **3** (%)[b]	yield of **2-di** (%)[b]	unreacted **2** (%)[b]
1		17	18	0
2		9	28	0
3		29	11	29
4		13	1	52

[a]All the reactions were run with **1a** (0.25 mmol) and **2** (0.1 mmol) in 1,4-dioxane (0.5 mL) for 18 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard.

Further condition optimization was conducted with 3-bromocoumarin (**2a**) as the alkenyl bromide substrate (Table 2.2). By switching the precatalyst to a more cationic $Pd(MeCN)_4(OTf)_2$ and triisopropylphosphine and running the reaction in acetonitrile at an elevated temperature, the yield could be improved to 49% along with negligible dimerization and reductive debromination

Table 2.2 Additive Screening for β-Alkenylation of Cyclohexanone[a]

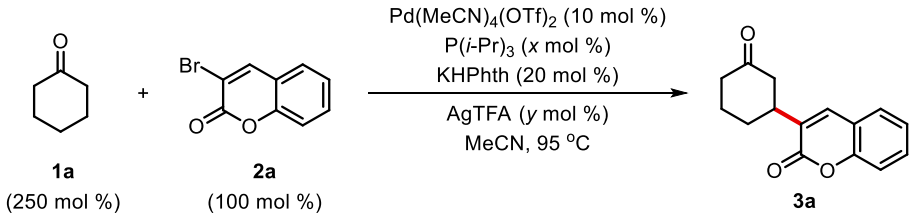


entry	additive (20 mol %)	yield of **3a** (%)[b]	unreacted **2a** (%)[b]
1	none	49	34
2		51	17
3		43	42
4		27	62
5	 (H_2Phth)	50	21
6	 (KHPhth)	56	21
7	 (K_2Phth)	51	23

[a]All the reactions were run with **1a** (0.25 mmol) and **2a** (0.1 mmol) in MeCN (0.5 mL) for 18 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard.

(entry 1). Considering that a weakly acidic environment would benefit protonation and substrate stability, we then screened acid additives, but none of them gave substantial improvement (entries 2−5). Interestingly, the monobasic salt of phthalic acid (KHPhth) turned out to enhance the yield to 56% (entry 6), while the dibasic salt (K_2Phth) provided similar results as phthalic acid (H_2Phth) (entry 7). Given that KHPhth is a weakly acidic buffering reagent, we reasoned that a balanced acidity could be important for the overall efficiency of this transformation (*vide infra*).

Table 2.3 Final Optimization for β-Alkenylation of Cyclohexanone[a]



1a (250 mol %) + **2a** (100 mol %) → **3a**

entry	*x*	*y*	yield of **3a** (%)[b]	unreacted **2a** (%)[b]
1	20	200	62	21
2	10	200	64	5
3	14	200	69	13
4	14	250	73	11
5	14	300	74	12

[a]All the reactions were run with **1a** (0.25 mmol) and **2a** (0.1 mmol) in MeCN (0.4 mL) for 18 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard.

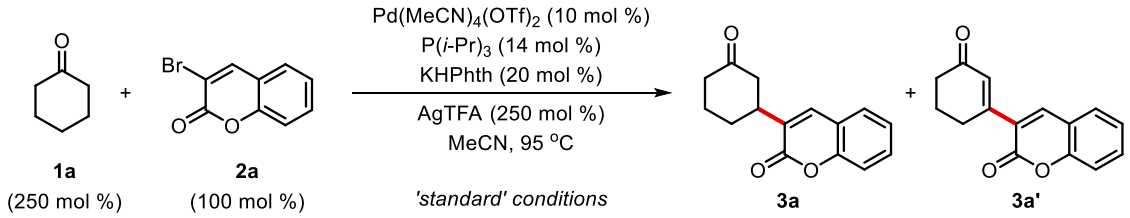
Using KHPhth as an effective additive, we further tuned some of the parameters to optimize the reaction conditions (Table 2.3). First, a slightly lower temperature (95 °C) and a higher concentration (0.25 M) enhanced the yield to 62% (entry 1). A 1:1 ratio of palladium and ligand was also effective despite worse mass balance (entry 2). Interestingly, a 1:1.4 ratio was found

optimal likely attributed to the balanced stability and electrophilicity of the palladium center (entry 3). Finally, higher loading of AgTFA was beneficial, and 2.5 equivalents were sufficient (entries 4 and 5).

After gaining the optimal reaction conditions, further investigation into the side products revealed that, besides the desired β-alkenylation product (**3a**), the overoxidation side product (**3a'**) was also formed in 5% yield which is generated from the undesired β-hydrogen elimination of the alkenylated Pd-enolate instead of protonation (Table 2.4, entry 1). Other side products of **2a**, i.e. reductive debromination and dimerization products, were observed in 2% and 4% yields, respectively. In order to understand the role of each component in the reaction, a series of control experiments were conducted (Table 2.4). No reaction occurred in the absence of the Pd precatalyst (entry 2). $Pd(TFA)_2$ was also a viable precatalyst though the yield was inferior than the cationic $Pd(MeCN)_4(OTf)_2$ (entry 3). The $P(i\text{-}Pr)_3$ ligand was indispensable for this transformation (entry 4), and replacing $P(i\text{-}Pr)_3$ with PPh_3 gave a worse catalytic performance and more overoxidation (entry 5). Potassium hydrogen phthalate (KHPhth) was still an effective additive to promote the reaction conversion under the 'standard' conditions (entry 6). While a combination of benzoic acid and potassium benzoate gave a comparable result to KHPhth (entry 7), more acidic phthalic acid (H_2Phth) led to diminished yields (entries 8) and more basic potassium phthalate (K_2Phth) caused slightly more overoxidation (entry 9). Based on these observations, we postulated that the role of KhPhth could be two-fold. The carboxylate moiety in this additive can serve as an X ligand on palladium (more basic than trifluoroacetate), which could facilitate the Pd-enolate formation by accelerating the cleavage of the ketone α-C−H bond, thus promoting ketone desaturation step.[9d]

On the other hand, such a buffered system may also benefit the protonation of the alkenylated Pd-enolate. In terms of halide scavenger, CsTFA and $Cu(TFA)_2$ were not as effective as AgTFA (entries 10 and 11). MeCN was the optimal solvent as it could help stabilizing the Pd catalyst and dissolving the inorganic salts. Finally, decreasing the amount of ketone **1a** to 1.5 equivalents still afforded the desired product in 58% yield (entry 12).

Table 2.4 Variations from the 'Standard' Conditions for β-Alkenylation of Cyclohexanone[a]

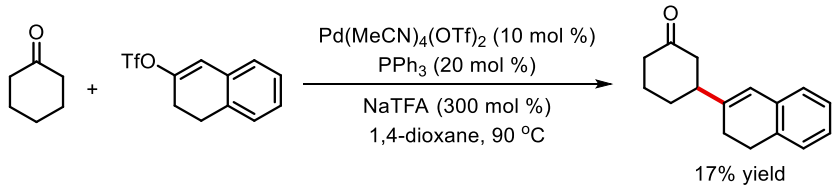


entry	variations from the 'standard' conditions	yield of **3a** (%)[b]	yield of **3a'** (%)[b]	unreacted **2a** (%)[b]
1	none	73 (77)[c]	5	11
2	without $Pd(MeCN)_4(OTf)_2$	0	0	99
3	$Pd(TFA)_2$ instead of $Pd(MeCN)_4(OTf)_2$	58	4	30
4	without P(*i*-Pr)$_3$	1	2	96
5	PPh_3 instead of P(*i*-Pr)$_3$	23	13	44
6	Without KHPhth	58	3	32
7	PhCOOH + PhCOOK instead of KHPhth	72	5	15
8	H_2Phth instead of KHPhth	69	5	13
9	K_2Phth instead of KHPhth	67	8	12
10	CsTFA instead of AgTFA	1	0	85
11	$Cu(TFA)_2$ instead of AgTFA	16	2	48
12	**1a** 150 mol % instead of 250 mol %	58	6	25

[a]Unless otherwise noted, all the reactions were run with **1a** (0.25 mmol) and **2a** (0.1 mmol) in MeCN (0.4 mL) for 18 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard. [c]Yield in the parenthesis refers to the isolation yield.

It is worth mentioning that, in addition to alkenyl bromides, alkenyl triflates were also tried as the alkenylation reagents, in which case halide scavengers were not necessary as promoters. Unfortunately, alkenyl triflates were found less stable in this reaction system, thereby giving poor mass balance and low efficiency. Nevertheless, they could still be coupled with cyclohexanone, leading to 17% yield of the β-alkenylation product in the absence of any silver salt (Scheme 2.3)

Scheme 2.3 β-Alkenylation of Cyclohexanone Using Alkenyl Triflate

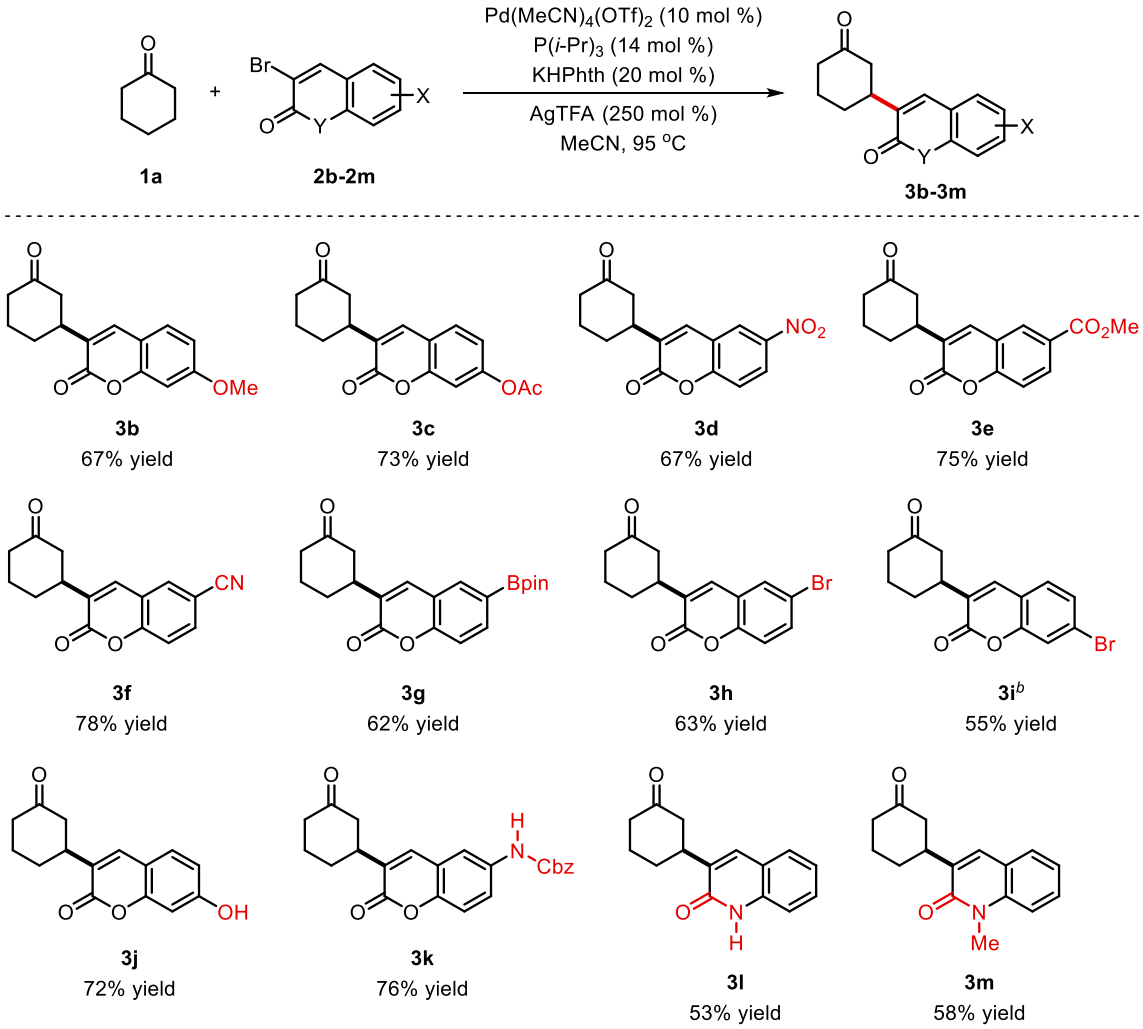


2.2.2 Substrate scope for the β-alkenylation of ketones

The substrate scope of the alkenyl bromides was then investigated under the 'standard' conditions (Scheme 2.4). Considering that coumarin moieties are often found in biologically important compounds,[11] a number of substituted 3-bromocoumarins were first tested and found to proceed smoothly in good yields (**3b**−**3k**). 2-Quinolone-derived alkenyl bromides were also viable substrates (**3l**, **3m**). Notably, a large variety of functional groups were tolerated, including methoxy (**3b**), acetoxy (**3c**), nitro (**3d**), methoxycarbonyl (**3e**) and cyano (**3f**) groups. The tolerance of acidic hydrogens, such as free phenols (**3j**), carbamates (**3k**) and lactams (**3l**) makes this method complementary to the conventional conjugate addition approach, which often uses alkenyl organo-metallic species. Encouragingly, aryl boronic esters (**3g**) and aryl bromides (**3h**, **3i**), which are typically reactive functional groups in the Pd-catalyzed reactions, largely remained intact. This

allows for further transformations of these functional groups, which would increase molecular complexity.

Scheme 2.4 Substrate Scope of Coumarin-Type Alkenyl Bromides[a]

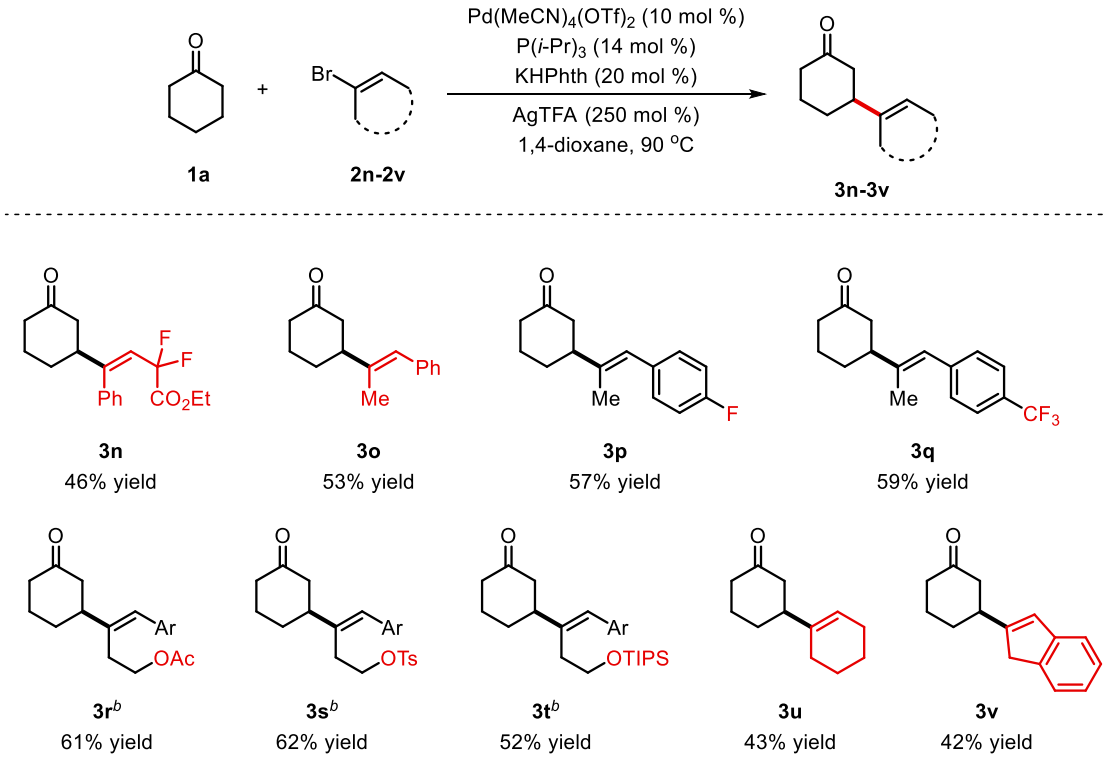


[a]All the reactions were run with **1a** (0.5 mmol) and **2** (0.2 mmol) in MeCN (0.8 mL) at 95 °C for 18 h. All yields refer to the isolation yields. [b]The β-arylation side product was obtained in 11% yield.

As mentioned before, non-stabilized alkenyl bromides are challenging substrates in this transformation due to severe dimerization and other decomposition pathways. Fortunately, with slightly modified conditions, a range of alkenyl bromides without conjugated carbonyls can also

be used for this transformation (Scheme 2.5), including both linear (**3n**–**3t**) and cyclic (**3u**, **3v**) ones. Again, a variety of functional groups are well tolerated, such as alkyl and aryl fluorides (**3n**, **3p**–**3t**), acetyl and silyl-protected alcohols (**3r**, **3t**) as well as alkyl tosylates (**3s**) that allows further derivatizations. While the yields are moderate due to more decomposition of these substrates, it nevertheless shows that the alkenyl bromide scope could be generalized.

Scheme 2.5 Substrate Scope of Non-Stabilized Alkenyl Bromides[a]

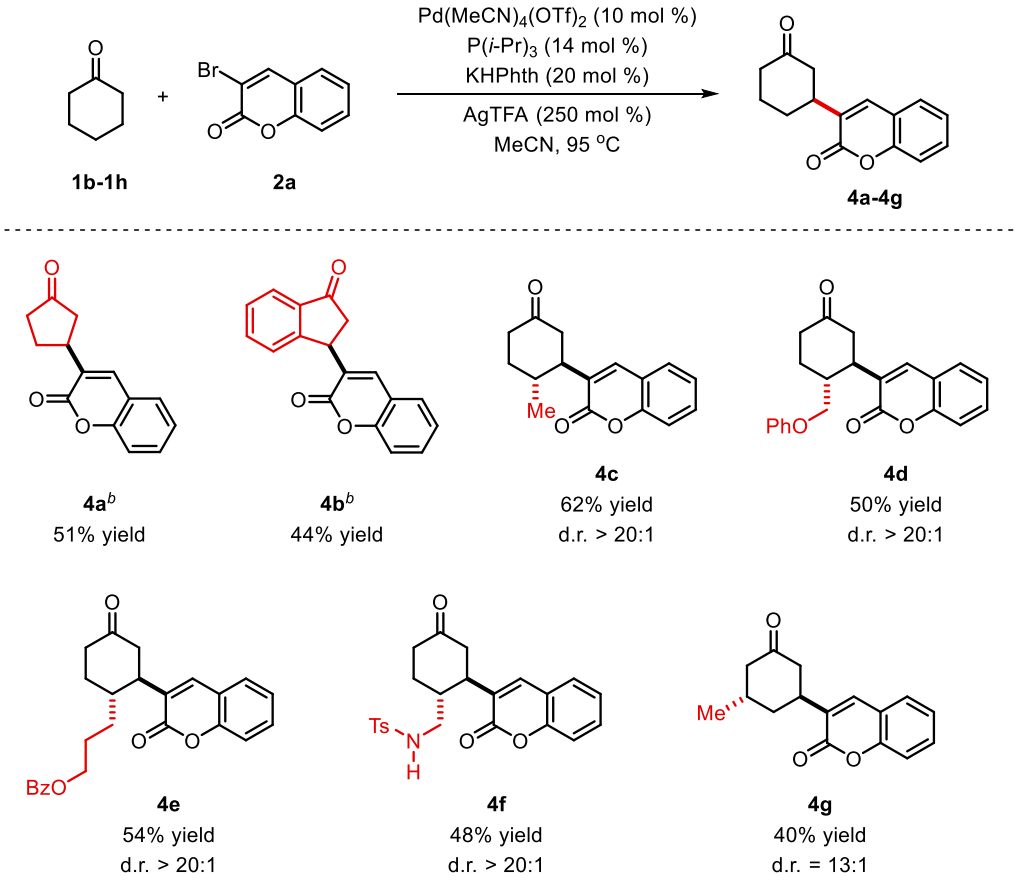


[a]All the reactions were run with **1a** (0.5 mmol) and **2** (0.2 mmol) in 1,4-dioxane (0.8 mL) at 90 °C for 18 h. All yields refer to the isolation yields. [b]Ar = 4-trifluoromethyl-phenyl.

Regarding the ketone scope, besides cyclohexanone, a range of cyclic ketones are also viable substrates (Scheme 2.6). For example, cyclopentanones and 1-indanones (**4a**, **4b**) could be successfully alkenylated at their β positions. Cyclohexanones with substitutions at the C4-position

exhibited satisfactory reactivity, and the products obtained (**4c**–**4f**) were single diastereomers possessing *trans* configuration. Moreover, 3-methylcyclohexanone also predominantly delivered the *trans*-alkenylation product in a moderate yield (**4g**).

Scheme 2.6 Substrate Scope of Cyclic Ketones[a]

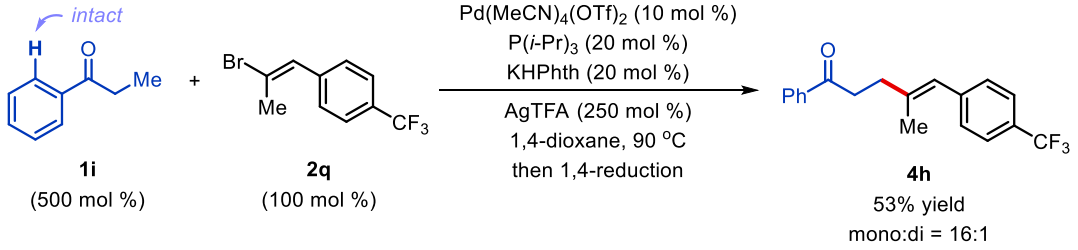


[a]Unless otherwise noted, all the reactions were run with **1** (0.5 mmol) and **2a** (0.2 mmol) in MeCN (0.8 mL) at 95 °C for 18 h. All yields refer to the isolation yields. [b]$Pd(MeCN)_4(OTf)_2$ (15 mol %) and $P(i\text{-}Pr)_3$ (21 mol %) were used.

Compared with cyclic ketones, linear ketones were even more challenging substrates. Due to the increased flexibility of the carbon skeleton, after conjugate addition to generate the alkenylated Pd-enolate, the undesired β-hydrogen elimination would be very facile which may lead to a higher ratio of overoxidation. Nonetheless, propiophenone was found a competent

substrate in terms of the overall reactivity with slightly modified conditions, though overoxidation product was predominantly observed along with small amount of di-alkenylation. However, a selective 1,4-reduction can be employed subsequently to transfer the overoxidation product to the desired β-alkenylation product, which unified the products and gave a decent overall yield and mono selectivity (Scheme 2.7).[12] It is noteworthy that, distinct from the DG approach, the *ortho* C(sp^2)–H bond on the phenyl ring was untouched during the reaction.[13]

Scheme 2.7 β-Alkenylation of Propiophenone[a]

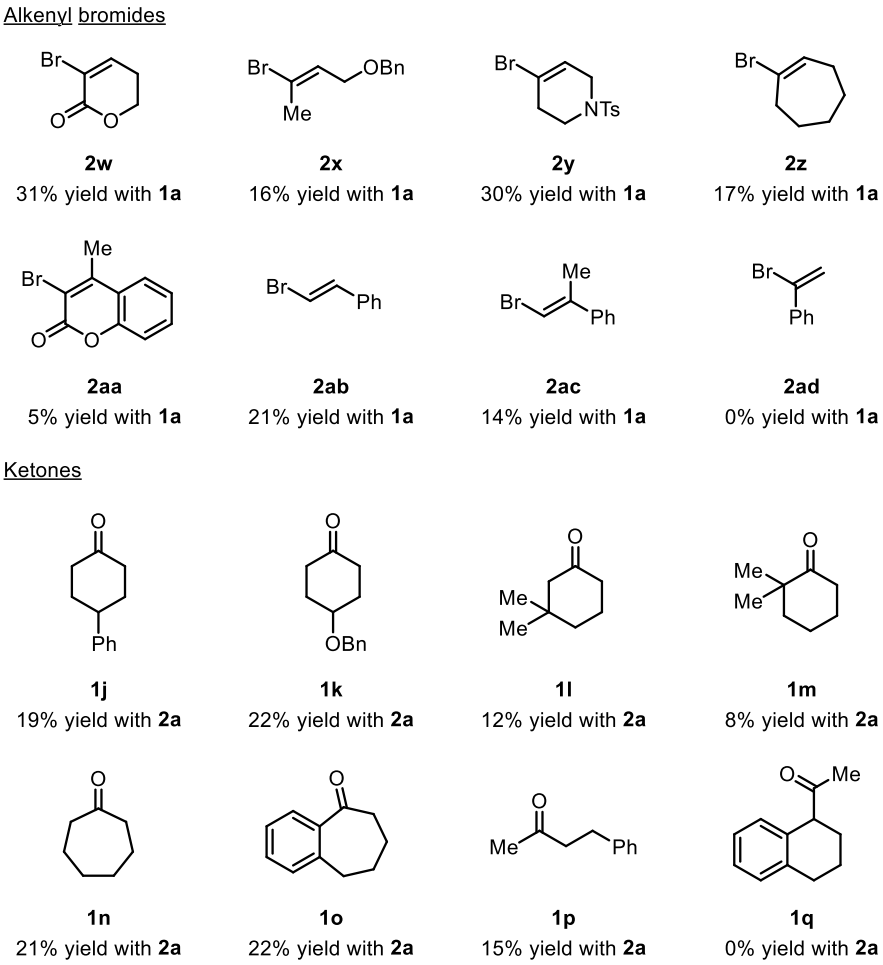


[a]The reaction was run with **1i** (1.0 mmol) and **2q** (0.2 mmol) in 1,4-dioxane (0.8 mL) at 90 °C for 18 h. The overoxidation product was converted to **4h** via reduction with $HSiCl_3$ (200 mol %) and HMPA (20 mol %) in DCM at 0 °C for 90 min.

In addition to these viable substrates, limitations were also found for many other alkenyl bromides and ketones (Scheme 2.8). The arene conjugation in the 3-bromocoumarin type substrate was found important, as the unconjugated α,β-unsaturated lactone moiety could also serve as an electrophile to compete with enones during the conjugate addition, thus leading to side reactions (**2w**). Linear alkenyl bromides with both alkyl substituents were less effective (**2x**), and cyclic alkenyl bromides bearing heteroatoms or large ring sizes gave diminished yields (**2y**, **2z**). Currently, only trisubstituted alkenyl bromides are well tolerated, as more substituted ones suffered from increased steric hindrance (**2aa**), while less substituted ones underwent more dimerization and

other decompositions (**2ab**−**2ad**). In terms of the ketone scope, aryl and alkoxy substituents on the C4-position of the cyclohexanone were not tolerated (**1j**, **1k**), and *gem*-dimethyl cyclohexanones underwent sluggish desaturation (**1l**, **1m**). Seven-membered ring ketones led to decreased efficiency (**1n**, **1o**), and linear ketones possessing β-substituents were also ineffective (**1p**, **1q**).

Scheme 2.8 Selected Challenging Substrates for β-Alkenylation of Ketones

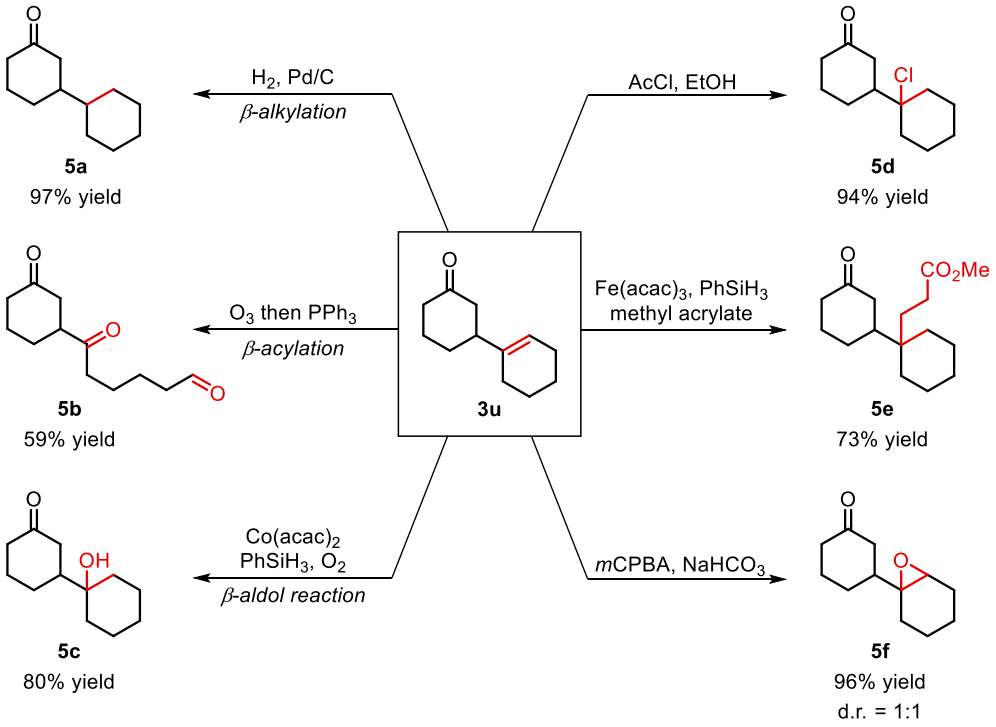


2.2.3 Derivatization of the β-alkenyl ketones

Derivatizations of the β-alkenylation product are illustrated using **3u** as the representative substrate (Scheme 2.9). Since alkenes are highly versatile functional groups that can readily

undergo diverse transformations,[2] this direct β-alkenylation method opens the door to access various other β-functionalized products. For example, formal β-alkylation, acylation and aldol products can be afforded through hydrogenation, ozonolysis and Mukaiyama hydration[14] of the alkene moiety, respectively (**5a**–**5c**). In addition, an electrophilic hydrochlorination (**5d**)[15] and an iron-mediated quaternary carbon-center formation (**5e**)[16] were successfully demonstrated in high efficiency. Moreover, difunctionalization of the alkene was also possible through epoxidation (**5f**).

Scheme 2.9 Derivatization of the β-Alkenylation Product



2.3 Conclusion

In summary, a direct method for β-alkenylation of simple ketones with alkenyl bromides has been developed using the Pd-catalyzed redox cascade strategy. Different from the existing β-alkenylation methods, this approach avoids the use of directing groups, tolerates both cyclic and

acyclic ketones, and is redox-neutral. The resulting β-alkenyl ketones are readily derivatized through diverse alkene functionalization. The high functional group compatibility could make this method attractive for complex molecule synthesis.

Future development could focus on enhancing the reaction efficiency and suppressing side reactions, particularly for non-stabilized alkenyl bromides, which would potentially expand the alkenyl bromide scope beyond trisubstituted ones. The use of alkenyl triflates as the alkenylation reagents would be highly appealing, since it permits silver-free conditions, and the preparation of alkenyl triflates from carbonyl compounds is facile. Finally, development of the enantioselective transformation using chiral ligands would be synthetically desirable.

2.4 Experimental Section

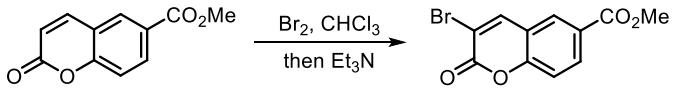
2.4.1 General information

Unless otherwise noted, all reactions were carried out in 8-mL culture tubes sealed with PTFE lined caps. Acetonitrile was distilled over calcium hydride and freeze-pump-thawed three times before use. 1,4-Dioxane was distilled over sodium and freeze-pump-thawed three times before use. $Pd(MeCN)_4(OTf)_2$ and P(*i*-Pr)$_3$ were synthesized based on literature procedures. Silver trifluoroacetate was purchased from Acros Organics. Potassium hydrogen phthalate was purchased from Sigma Aldrich. All commercially available substrates were used without further purification. Thin layer chromatography (TLC) analysis was run on silica gel plates purchased from EMD Chemical (silica gel 60, F254). 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, ^{13}C NMR and ^{19}F NMR) were recorded with a Bruker Model DMX 400 (400 MHz, ^{1}H at 400 MHz, ^{13}C at 101 MHz, ^{19}F at 376 MHz). For $CDCl_3$ solutions, the chemical shifts were 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 (77.00 ppm). Coupling constants were reported in Hertz (Hz). Data for ^{1}H NMR spectra were reported as following: chemical shift (δ, ppm), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet), coupling constant (Hz), and integration.

2.4.2 Synthesis and characterization of the substrates

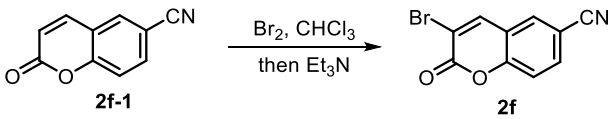
Compounds **2a**,[17] **2b**,[17] **2c**,[18] **2d**,[19] **2h**,[17] **2i**,[17] **2j**,[18] **2l**,[20] **2m**,[20] **2n**,[21] **2o**,[22] **2u**[23] and **1e**[24] were synthesized according to the literature procedures. Compounds **2v**, **1a**, **1b**, **1c**, **1d**, **1h** and **1i** were commercially available and used without further purification. Compounds **2e**, **2f**, **2g**, **2k**, **2p**, **2q**, **2r**, **2s**, **2t**, **1f** and **1g** were prepared according to the following procedures.



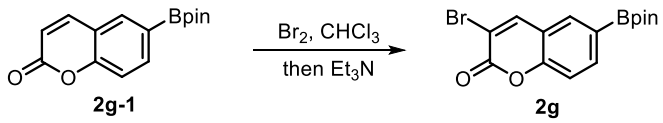
2e-1 **2e**

Methyl 3-bromo-2-oxo-2*H*-chromene-6-carboxylate (2e): A round bottom flask was charged with **2e-1**[25] (1 equiv., 5 mmol, 1.04 g) and chloroform (10 mL), and the mixture was cooled in an ice bath. Br_2 (1 equiv., 5 mmol, 258 μL) was added dropwise, and the mixture was

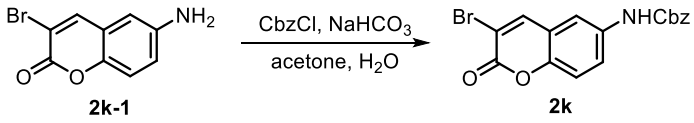
stirred at 50 °C for 6 h. Et_3N (2 equiv., 10 mmol, 1.39 mL) was then added slowly, and the mixture was further stirred for 30 min. The mixture was concentrated, and the residue was purified by column chromatography to give **2e** as a white solid in 67% yield (949 mg). Melting point: 198 − 200 °C. R_f = 0.5 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 8.7, 2.0 Hz, 1H), 8.19 (d, *J* = 2.0 Hz, 1H), 8.15 (s, 1H), 7.40 (d, *J* = 8.7 Hz, 1H), 3.97 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.33, 156.35, 155.83, 143.92, 132.93, 129.11, 127.13, 119.09, 117.08, 112.89, 52.59. **IR** (KBr, cm^{-1}) 3055, 1742, 1710, 1616, 1337, 767. **HRMS** calcd $C_{11}H_8BrO_4$ $[M+H]^+$: 282.9600. Found: 282.9595.



3-Bromo-2-oxo-2*H*-chromene-6-carbonitrile (2f): A round bottom flask was charged with **2f-1**[26] (1 equiv., 1.33 mmol, 228 mg) and chloroform (2.67 mL), and the mixture was cooled in an ice bath. Br_2 (1 equiv., 1.33 mmol, 68.6 μL) was added dropwise, and the mixture was stirred at 50 °C for 6 h. Et_3N (2 equiv., 2.67 mmol, 370 μL) was then added slowly, and the mixture was further stirred for 30 min. The mixture was concentrated, and the residue was purified by column chromatography to give **2f** as a white solid in 61% yield (202 mg). Melting point: 233 − 236 °C. R_f = 0.5 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.87 – 7.77 (m, 2H), 7.46 (dt, *J* = 8.3, 0.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.56, 155.26, 142.51, 134.79, 131.38, 119.88, 118.29, 117.15, 114.48, 109.30. **IR** (KBr, cm^{-1}) 3036, 2238, 1727, 1613, 1345, 848. **HRMS** calcd $C_{10}H_5BrNO_2$ $[M+H]^+$: 249.9498. Found: 249.9494.

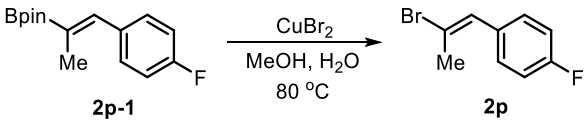


3-Bromo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-chromen-2-one (2g): A round bottom flask was charged with **2g-1**[27] (1 equiv., 1.0 mmol, 272 mg) and chloroform (2 mL), and the mixture was cooled in an ice bath. Br_2 (1 equiv., 1.0 mmol, 51.6 μL) was added dropwise, and the mixture was stirred at room temperature overnight. Et_3N (2 equiv., 2.0 mmol, 278 μL) was then added slowly, and the mixture was further stirred for 30 min. The mixture was concentrated, and the residue was purified by column chromatography to give **2g** as a white solid in 44% yield (153 mg). Melting point: 179 − 181 °C. R_f = 0.6 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.98 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.91 (d, *J* = 1.5 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 1.36 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.98, 155.18, 144.51, 138.31, 134.23, 118.85, 116.16, 111.63, 84.39, 24.86. **IR** (KBr, cm^{-1}) 2975, 1747, 1613, 1364, 1143, 965. **HRMS** calcd $C_{15}H_{17}BBrO_4$ $[M+H]^+$: 351.0398. Found: 351.0403.

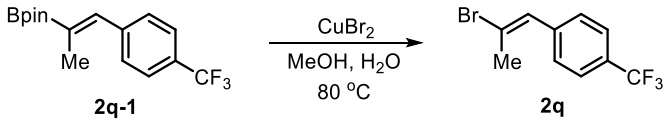


Benzyl (3-bromo-2-oxo-2*H*-chromen-6-yl)carbamate (2k): A round bottom flask was charged with **2k-1**[19] (1 equiv., 1.17 mmol, 281 mg), $NaHCO_3$ (2 equiv., 2.34 mmol, 197 mg), water (2.5 mL) and acetone (2.5 mL). CbzCl (1.1 equiv., 1.29 mmol, 184 μL) was then added dropwise, and the mixture was stirred at room temperature for 1 h. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried and concentrated, and the residue was purified by column chromatography to give **2k** as a pale-yellow solid in 86% yield (377 mg).

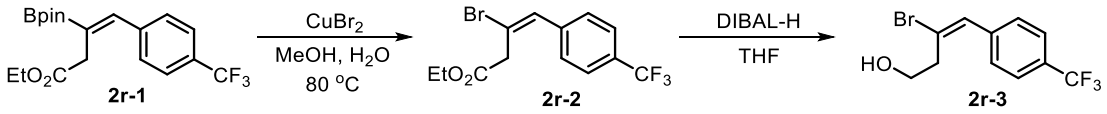
Melting point: 175 − 177 ºC. R_f = 0.3 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.05 (br, 1H), 8.64 (s, 1H), 7.87 (d, *J* = 2.6 Hz, 1H), 7.60 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.47 – 7.30 (m, 6H), 5.17 (s, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 156.55, 153.43, 148.23, 145.24, 136.45, 135.94, 128.48, 128.17, 128.12, 122.69, 119.44, 116.72, 115.75, 111.34, 65.98. **IR** (KBr, cm^{-1}) 3336, 2923, 1720, 1700, 1567, 1217, 735. **HRMS** calcd $C_{17}H_{13}BrNO_4$ $[M+H]^+$: 374.0022. Found: 374.0025.



(*E*)-1-(2-Bromoprop-1-en-1-yl)-4-fluorobenzene (2p): A round bottom flask was equipped with a reflux condenser and charged with $CuBr_2$ (3 equiv., 21 mmol, 4.69 g), water (35 mL), methanol (35 mL) and **2p-1**[28] (1 equiv., 7 mmol, 1.84 g). The mixture was heated at 80 ºC for 4h. After cooling to room temperature, the mixture was extracted with Et_2O four times. The combined organic layers were washed with water and brine, dried and concentrated. The residue was purified by column chromatography to give **2p** as a colorless oil in 72% yield (1.08 g). *E*/*Z* > 20:1. R_f = 0.6 (hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 – 7.13 (m, 2H), 7.07 – 6.98 (m, 2H), 6.92 (s, 1H), 2.43 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.74 (d, *J* = 247.3 Hz), 132.51 (d, *J* = 3.5 Hz), 131.20, 129.97 (d, *J* = 8.1 Hz), 123.52 (d, *J* = 1.7 Hz), 115.39 (d, *J* = 21.5 Hz), 24.79. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -114.33 (tt, *J* = 8.6, 5.4 Hz). **IR** (KBr, cm^{-1}) 2955, 1601, 1508, 1226, 1072, 865. **HRMS** calcd C_9H_8BrF $[M]^+$: 213.9788. Found: 213.9789.



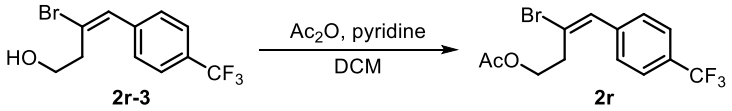
(*E*)-1-(2-Bromoprop-1-en-1-yl)-4-(trifluoromethyl)benzene (2q): A round bottom flask was equipped with a reflux condenser and charged with $CuBr_2$ (3 equiv., 26.1 mmol, 5.83 g), water (43.5 mL), methanol (43.5 mL) and **2q-1**[29] (1 equiv., 8.7 mmol, 2.71 g). The mixture was heated at 80 ºC for 4h. After cooling to room temperature, the mixture was extracted with Et_2O four times. The combined organic layers were washed with water and brine, dried and concentrated. The residue was purified by column chromatography to give **2q** as a colorless oil in 63% yield. *E*/*Z* > 20:1. R_f = 0.5 (hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.99 (s, 1H), 2.46 (d, *J* = 1.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.92, 131.07, 129.18 (q, *J* = 32.5 Hz), 128.58, 125.73, 125.41 (q, *J* = 3.8 Hz), 124.05 (q, *J* = 272.0 Hz), 24.99. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.61. **IR** (KBr, cm^{-1}) 2921, 1635, 1616, 1324, 1127, 1069, 869. **HRMS** calcd $C_{10}H_8BrF_3$ $[M]^+$: 263.9756. Found: 263.9750.



Ethyl (*E*)-3-bromo-4-(4-(trifluoromethyl)phenyl)but-3-enoate (2r-2): A round bottom flask was equipped with a reflux condenser and charged with $CuBr_2$ (3 equiv., 11.7 mmol, 2.61 g), water (20 mL), methanol (20 mL) and **2r-1**[30] (1 equiv., 3.9 mmol, 1.50 g). The mixture was heated at 80 ºC for 4h. After cooling to room temperature, the mixture was extracted with Et_2O four times. The combined organic layers were washed with water and brine, dried and concentrated. The residue was purified by column chromatography to give **2r-2** as a colorless oil in 70% yield (920

mg). *E*/*Z* > 20:1. R_f = 0.4 (hexane/EtOAc = 10:1).

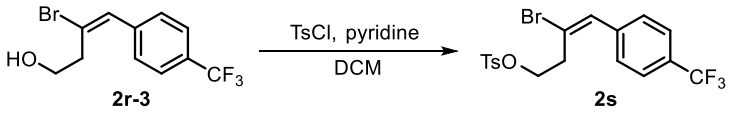
(*E*)-3-Bromo-4-(4-(trifluoromethyl)phenyl)but-3-en-1-ol (2r-3): A Schlenk flask was flame-dried and refilled with N_2. **2r-2** (1 equiv., 2.73 mmol, 920 mg) was dissolved in THF (16 mL), and the solution was added to the flask via syringe. The mixture was cooled to -78 °C, and DIBAL-H (1 M in hexane, 2.4 equiv., 6.55 mmol, 6.55 mL) was added dropwise via syringe. The mixture was slowly warmed to 0 °C and stirred for 2 h. Saturated sodium potassium tartrate solution was added, and the mixture was further stirred for 1 h. The mixture was then extracted with EtOAc, and the combined organic layers were washed with water and brine, dried and concentrated. The residue was purified by column chromatography to give **2r-3** as a colorless oil in 96% yield (773 mg). R_f = 0.8 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.18 (s, 1H), 3.96 (q, *J* = 5.9 Hz, 2H), 2.87 (td, *J* = 6.0, 0.8 Hz, 2H), 1.63 (t, *J* = 5.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.49, 133.92, 129.55 (q, *J* = 32.6 Hz), 128.71, 128.19, 125.49 (q, *J* = 3.8 Hz), 124.06 (q, *J* = 272.0 Hz), 60.49, 39.11. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.64. **IR** (KBr, cm^{-1}) 3343, 2958, 1617, 1325, 1126, 1068, 873. **HRMS** calcd $C_{11}H_{11}BrF_3O$ $[M+H]^+$: 294.9940. Found: 294.9944.



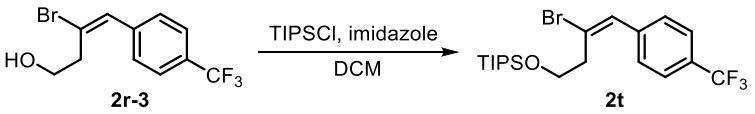
2r-3 **2r**

(*E*)-3-Bromo-4-(4-(trifluoromethyl)phenyl)but-3-en-1-yl acetate (2r): An 8-mL vial was charged with **2r-3** (1 equiv., 0.5 mmol, 147.5 mg), DCM (2.5 mL), pyridine (2.5 equiv., 1.25 mmol, 100.6 μL) and Ac_2O (1.5 equiv., 0.75 mmol, 70.7 μL), and the mixture was stirred at room temperature for 24 h. The mixture was washed with 1 M HCl twice, $NaHCO_3$ and brine, dried and

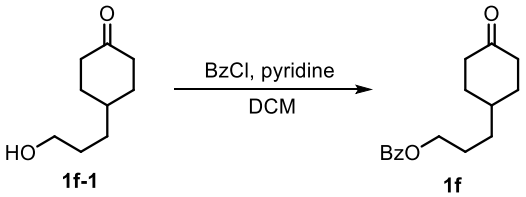
concentrated. The residue was purified by column chromatography to give **2r** as a colorless oil in 91% yield (154 mg). R_f = 0.7 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.43 – 7.35 (m, 2H), 7.14 (s, 1H), 4.35 (t, *J* = 6.5 Hz, 2H), 2.94 (td, *J* = 6.6, 0.8 Hz, 2H), 2.03 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.70, 139.39 (q, *J* = 1.5 Hz), 133.69, 129.62 (q, *J* = 32.7 Hz), 128.44, 126.69, 125.56 (q, *J* = 3.8 Hz), 123.97 (q, *J* = 272.0 Hz), 61.89, 35.64, 20.80. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.66. **IR** (KBr, cm^{-1}) 2960, 1744, 1616, 1325, 1127, 874. **HRMS** calcd $C_{13}H_{13}BrF_3O_2$ $[M+H]^+$: 337.0046. Found: 337.0044.



(*E*)-3-Bromo-4-(4-(trifluoromethyl)phenyl)but-3-en-1-yl 4-methylbenzenesulfonate (2s): A 4-mL vial was charged with **2r-3** (1 equiv., 0.5 mmol, 147.5 mg), DCM (1 mL), pyridine (2.2 equiv., 1.1 mmol, 88.5 μL) and TsCl (1.1 equiv., 0.55 mmol, 105 mg), and the mixture was stirred at room temperature overnight. The mixture was washed with 1 M HCl twice, $NaHCO_3$ and brine, dried and concentrated. The residue was purified by column chromatography to give **2s** as a colorless oil in 75% yield (168 mg). R_f = 0.5 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 – 7.72 (m, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.40 – 7.28 (m, 4H), 7.11 (s, 1H), 4.29 (t, *J* = 6.3 Hz, 2H), 2.90 (td, *J* = 6.2, 0.9 Hz, 2H), 2.45 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.04, 139.03 (q, *J* = 1.5 Hz), 134.54, 132.66, 129.87, 129.71 (q, *J* = 32.6 Hz), 128.49, 127.93, 125.56 (q, *J* = 3.8 Hz), 124.95, 123.95 (q, *J* = 272.0 Hz), 67.11, 35.83, 21.61. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.64. **IR** (KBr, cm^{-1}) 2924, 1364, 1324, 1177, 1068, 901. **HRMS** calcd $C_{18}H_{17}BrF_3O_3S$ $[M+H]^+$: 449.0028. Found: 449.0023.

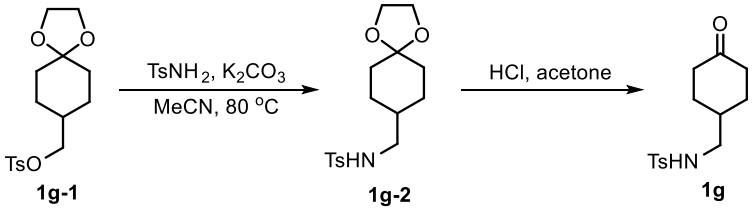


(*E*)-((3-Bromo-4-(4-(trifluoromethyl)phenyl)but-3-en-1-yl)oxy)triisopropylsilane (2t): A 4-mL vial was charged with **2r-3** (1 equiv., 0.5 mmol, 147.5 mg), DCM (1 mL), imidazole (2 equiv., 1 mmol, 68 mg) and TIPSCl (1 equiv., 0.5 mmol, 107 μL), and the mixture was stirred at room temperature overnight. The mixture was washed with 1 M HCl twice, $NaHCO_3$ and brine, dried and concentrated. The residue was purified by column chromatography to give **2t** as a colorless oil in 94% yield (212 mg). R_f = 0.8 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 – 7.53 (m, 4H), 7.12 (s, 1H), 4.03 (t, *J* = 5.9 Hz, 2H), 2.85 (td, *J* = 5.9, 0.7 Hz, 2H), 1.22 – 0.97 (m, 21H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.68, 133.14, 129.46, 129.29 (q, *J* = 32.5 Hz), 128.79, 125.20 (q, *J* = 3.8 Hz), 124.14 (q, *J* = 272.0 Hz), 61.08, 39.75, 17.96, 11.95. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.56. **IR** (KBr, cm^{-1}) 2944, 2867, 1464, 1325, 1129, 882. **HRMS** calcd $C_{20}H_{31}BrF_3OSi$ $[M+H]^+$: 451.1274. Found: 451.1279.



3-(4-Oxocyclohexyl)propyl benzoate (1f): A round bottom flask was charged with **1f-1**[31] (1 equiv., 1.41 mmol, 220 mg), DCM (7 mL), pyridine (2.2 equiv., 3.10 mmol, 250 μL) and BzCl (1.2 equiv., 1.69 mmol, 196 μL), and the mixture was stirred at room temperature overnight. The mixture was washed with 1 M HCl twice, $NaHCO_3$ and brine, dried and concentrated. The residue was purified by column chromatography to give **1f** as a white solid in 78% yield (286 mg). Melting

point: 62 − 64 ºC. R_f = 0.5 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 – 7.97 (m, 2H), 7.63 – 7.54 (m, 1H), 7.51 – 7.38 (m, 2H), 4.35 (t, *J* = 6.6 Hz, 2H), 2.49 – 2.26 (m, 4H), 2.16 – 1.99 (m, 2H), 1.93 – 1.73 (m, 3H), 1.54 – 1.36 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.99, 166.58, 132.90, 130.28, 129.47, 128.34, 64.94, 40.70, 35.70, 32.58, 31.89, 26.50. **IR** (KBr, cm^{-1}) 2937, 1711, 1449, 1283, 1170, 716. **HRMS** calcd $C_{16}H_{21}O_3$ $[M+H]^+$: 261.1485. Found: 261.1483.



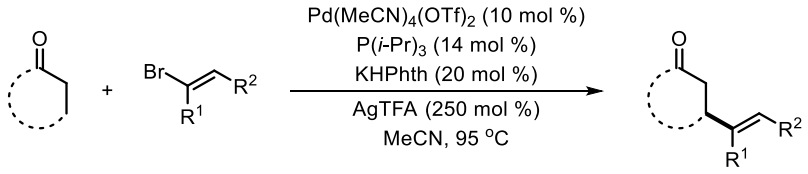
***N*-((1,4-Dioxaspiro[4.5]decan-8-yl)methyl)-4-methylbenzenesulfonamide (1g-2):** A round bottom flask was equipped with a reflux condenser and charged with **1g-1**[32] (1 equiv., 10 mmol, 3.26 g), $TsNH_2$ (2 equiv., 20 mmol, 3.42 g), K_2CO_3 (2 equiv., 20 mmol, 2.76 g) and MeCN (80 mL). The mixture was heated at 80 ºC for 48 h. The mixture was filtered, and the filtrate was concentrated. The residue was distributed between DCM and water, and the mixture was extracted with DCM. The combined organic layers were dried and concentrated, and the residue was purified by column chromatography to give **1g-2** as a colorless oil in 88% yield (2.86 g). R_f = 0.5 (hexane/EtOAc = 1:1).

4-Methyl-*N*-((4-oxocyclohexyl)methyl)benzenesulfonamide (1g): A round bottom flask was charged with **1g-2** (1 equiv., 8.8 mmol, 2.86 g), acetone (13.2 mL) and 3 M HCl (13.2 mL), and the mixture was stirred overnight. The acetone was removed *in vacuo*, and the residue was neutralized with $NaHCO_3$ till pH = 8. The mixture was then extracted with DCM, dried and

concentrated. The residue was purified by column chromatography to give **1g** as a white solid in 86% yield (2.13 g). Melting point: 109 − 111 °C. R_f = 0.3 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 – 7.67 (m, 2H), 7.40 – 7.31 (m, 2H), 5.01 (t, *J* = 6.6 Hz, 1H), 2.88 (t, *J* = 6.7 Hz, 2H), 2.44 (s, 3H), 2.42 – 2.31 (m, 2H), 2.34 – 2.21 (m, 2H), 2.12 – 1.99 (m, 2H), 2.00 – 1.84 (m, 1H), 1.45 – 1.26 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.00, 143.60, 136.77, 129.77, 126.99, 47.74, 40.06, 36.27, 29.87, 21.51. **IR** (KBr, cm^{-1}) 3278, 2929, 1712, 1322, 1159, 1093, 816. **HRMS** calcd $C_{14}H_{20}NO_3S$ $[M+H]^+$: 282.1158. Found: 282.1155.

2.4.3 Experimental procedure for the β-alkenylation of ketones

General procedure:

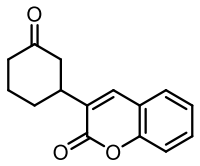


An 8-mL culture tube was flame-dried and charged with KHPhth (20 mol %, 0.04 mmol, 8.2 mg) and AgTFA (2.5 equiv., 0.5 mmol, 110.5 mg). The tube was then transferred into the glovebox. Inside the glovebox, $Pd(MeCN)_4(OTf)_2$ (10 mol %, 0.02 mmol, 11.4 mg), P(*i*-Pr)$_3$ (14 mol %, 0.028 mmol, 5.3 μL), MeCN (distilled over CaH_2 and freeze-pump-thawed, 0.8 mL), ketone (2.5 equiv., 0.5 mmol) and alkenyl bromide (1 equiv., 0.20 mmol) were added sequentially. The tube was sealed with a PTFE lined cap, transferred out of the glovebox and heated in an oil bath at 95 °C (oil temperature). After 18 h, the mixture was allowed to cool to room temperature. The mixture was diluted with EtOAc, passed through a small plug of silica gel and eluted with

EtOAc. The solvent was removed *in vacuo*, and the residue was purified by column chromatography to give the desired product.

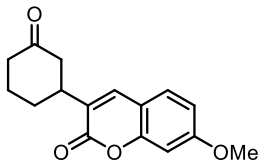
Note: If the ketone or alkenyl bromide is a solid, it is weighed and added into the reaction tube before transferring into the glovebox.

2.4.4 Characterization of the products for the β-alkenylation of ketones



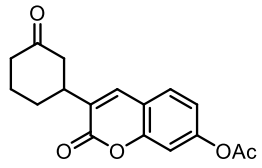
3a

3-(3-Oxocyclohexyl)-2*H*-chromen-2-one (3a): Synthesized from **1a** and **2a** according to the general procedure. 77% Yield (37.2 mg). White solid. Melting point: 120 − 122 ºC. R_f = 0.6 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.43 (m, 3H), 7.33 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.30 – 7.25 (m, 1H), 3.31 – 3.15 (m, 1H), 2.75 – 2.59 (m, 2H), 2.54 – 2.46 (m, 1H), 2.45 – 2.32 (m, 1H), 2.25 – 2.05 (m, 2H), 2.00 – 1.74 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.08, 160.70, 152.97, 137.82, 131.26, 131.16, 127.57, 124.44, 119.07, 116.40, 45.53, 41.19, 39.64, 29.73, 24.79. **IR** (KBr, cm^{-1}) 2951, 1711, 1610, 1456, 1176, 756. **HRMS** calcd $C_{15}H_{14}NaO_3$ $[M+Na]^+$: 265.0835. Found: 265.0838.



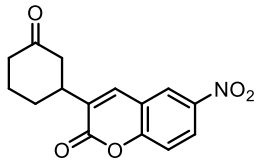
3b

7-Methoxy-3-(3-oxocyclohexyl)-2*H*-chromen-2-one (3b): Synthesized from **1a** and **2b** according to the general procedure. 67% Yield (36.3 mg). Colorless oil. R_f = 0.5 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.36 (d, *J* = 8.6 Hz, 1H), 6.85 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 3.87 (s, 3H), 3.45 – 3.06 (m, 1H), 2.69 – 2.56 (m, 2H), 2.53 – 2.44 (m, 1H), 2.45 – 2.32 (m, 1H), 2.18 – 2.03 (m, 2H), 1.98 – 1.74 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.33, 162.29, 161.04, 154.69, 137.92, 128.46, 127.57, 112.67, 112.58, 100.38, 55.73, 45.65, 41.19, 39.57, 29.78, 24.79. **IR** (KBr, cm^{-1}) 2939, 1712, 1616, 1508, 1241, 1154, 778. **HRMS** calcd $C_{16}H_{16}NaO_4$ $[M+Na]^+$: 295.0941. Found: 295.0944.



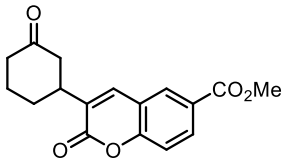
3c

2-Oxo-3-(3-oxocyclohexyl)-2*H*-chromen-7-yl acetate (3c): Synthesized from **1a** and **2c** according to the general procedure. 73% Yield (43.6 mg). White solid. Melting point: 191 − 193 °C. R_f = 0.5 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 – 7.44 (m, 2H), 7.11 (d, *J* = 2.2 Hz, 1H), 7.05 (dd, *J* = 8.5, 2.2 Hz, 1H), 3.32 – 3.16 (m, 1H), 2.74 – 2.59 (m, 2H), 2.54 – 2.45 (m, 1H), 2.44 – 2.31 (m, 4H), 2.19 – 2.04 (m, 2H), 1.99 – 1.73 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.01, 168.74, 160.34, 153.50, 152.58, 137.28, 130.71, 128.27, 118.44, 116.91, 109.99, 45.49, 41.19, 39.65, 29.69, 24.75, 21.10. **IR** (KBr, cm^{-1}) 2929, 1759, 1707, 1429, 1208, 776. **HRMS** calcd $C_{17}H_{16}NaO_5$ $[M+Na]^+$: 323.0890. Found: 323.0897.



3d

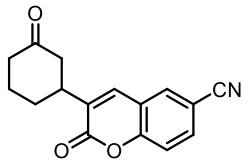
6-Nitro-3-(3-oxocyclohexyl)-2*H*-chromen-2-one (3d): Synthesized from **1a** and **2d** according to the general procedure. 67% Yield (38.5 mg). Colorless oil. R_f = 0.6 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 2.6 Hz, 1H), 8.37 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.60 (s, 1H), 7.46 (d, *J* = 9.0 Hz, 1H), 3.49 – 3.17 (m, 1H), 2.75 – 2.58 (m, 2H), 2.56 – 2.48 (m, 1H), 2.48 – 2.35 (m, 1H), 2.26 – 2.07 (m, 2H), 2.01 – 1.76 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.29, 159.12, 156.38, 144.06, 136.54, 133.80, 125.92, 123.45, 119.13, 117.58, 45.26, 41.08, 39.69, 29.56, 24.72. **IR** (KBr, cm^{-1}) 2955, 1732, 1711, 1618, 1529, 1346, 764. **HRMS** calcd $C_{15}H_{13}NNaO_5$ $[M+Na]^+$: 310.0686. Found: 310.0687.



3e

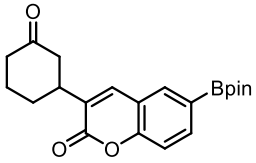
Methyl 2-oxo-3-(3-oxocyclohexyl)-2*H*-chromene-6-carboxylate (3e): Synthesized from **1a** and **2e** according to the general procedure. 75% Yield (44.9 mg). White solid. Melting point: 195 − 197 °C. R_f = 0.5 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 2.0 Hz, 1H), 8.17 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.54 (s, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 3.96 (s, 3H), 3.49 – 3.08 (m, 1H), 2.69 – 2.62 (m, 2H), 2.58 – 2.45 (m, 1H), 2.47 – 2.33 (m, 1H), 2.23 – 2.05 (m, 2H), 2.01 – 1.74 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.75, 165.66, 160.01, 155.75, 137.44, 132.23,

132.15, 129.68, 126.58, 118.82, 116.65, 52.47, 45.43, 41.16, 39.70, 29.67, 24.77. **IR** (KBr, cm^{-1}) 2951, 1710, 1614, 1490, 1248, 766. **HRMS** calcd $C_{17}H_{16}NaO_5$ $[M+Na]^+$: 323.0890. Found: 323.0892.



3f

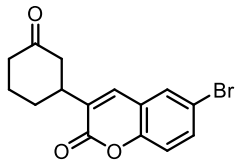
2-Oxo-3-(3-oxocyclohexyl)-2*H*-chromene-6-carbonitrile (3f): Synthesized from **1a** and **2f** according to the general procedure. 78% Yield (41.6 mg). White solid. Melting point: 231 − 233 ºC. R_f = 0.5 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 1.9 Hz, 1H), 7.76 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.49 (s, 1H), 7.43 (d, *J* = 8.6 Hz, 1H), 3.34 – 3.13 (m, 1H), 2.70 – 2.57 (m, 2H), 2.55 – 2.47 (m, 1H), 2.47 – 2.33 (m, 1H), 2.22 – 2.06 (m, 2H), 1.99 – 1.76 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.35, 159.19, 155.17, 136.10, 134.06, 133.68, 132.01, 119.72, 117.82, 117.54, 108.60, 45.27, 41.09, 39.71, 29.57, 24.72. **IR** (KBr, cm^{-1}) 2933, 2228, 1729, 1706, 1489, 1052, 748. **HRMS** calcd $C_{16}H_{13}NNaO_3$ $[M+Na]^+$: 290.0788. Found: 290.0786.



3g

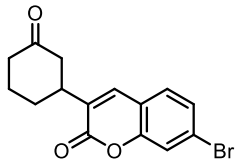
3-(3-Oxocyclohexyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-chromen-2-one (3g): Synthesized from **1a** and **2g** according to the general procedure. 62% Yield (45.7 mg). Colorless oil. R_f = 0.6 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.5 Hz, 1H), 7.91 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.50 (s, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 3.36 – 3.11 (m, 1H),

2.72 – 2.58 (m, 2H), 2.55 – 2.31 (m, 2H), 2.23 – 2.05 (m, 2H), 1.97 – 1.73 (m, 2H), 1.36 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.12, 160.62, 155.03, 137.97, 137.41, 134.83, 131.10, 118.55, 115.76, 84.23, 45.52, 41.19, 39.61, 29.68, 24.85, 24.74. **IR** (KBr, cm^{-1}) 2978, 1717, 1606, 1365, 1145, 733. **HRMS** calcd $C_{21}H_{26}BO_5$ $[M+H]^+$: 369.1868. Found: 369.1872.



3h

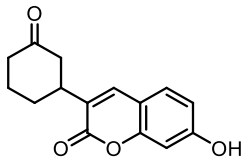
6-Bromo-3-(3-oxocyclohexyl)-2*H*-chromen-2-one (3h): Synthesized from **1a** and **2h** according to the general procedure. 63% Yield (40.7 mg). White solid. Melting point: 174 − 176 °C. R_f = 0.7 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 2.3 Hz, 1H), 7.59 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.41 (s, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 3.33 – 3.10 (m, 1H), 2.67 – 2.56 (m, 2H), 2.54 – 2.45 (m, 1H), 2.46 – 2.29 (m, 1H), 2.21 – 2.04 (m, 2H), 1.98 – 1.75 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.74, 160.02, 151.81, 136.49, 133.92, 132.58, 129.89, 120.61, 118.15, 116.99, 45.41, 41.15, 39.69, 29.66, 24.75. **IR** (KBr, cm^{-1}) 2925, 1713, 1478, 1246, 1177, 823. **HRMS** calcd $C_{15}H_{14}BrO_3$ $[M+H]^+$: 321.0121. Found: 321.0126.



3i

7-Bromo-3-(3-oxocyclohexyl)-2*H*-chromen-2-one (3i): Synthesized from **1a** and **2i** according to the general procedure. 55% Yield (41.8 mg). The arylation side product **3i'** was isolated in 11% yield as an inseparable mixture with **3i** (**3i**:**3i'** = 1:0.19). Colorless oil. R_f = 0.6

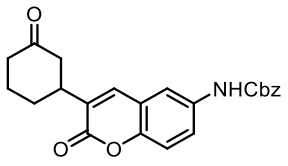
(hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (s, 0.19H), 7.50 (d, *J* = 1.8 Hz, 1H), 7.45 (s, 1H), 7.44 – 7.40 (m, 1.19H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.23 – 7.20 (m, 0.19H), 7.20 – 7.16 (m, 0.19H), 3.29 – 3.18 (m, 1H), 3.17 – 3.05 (m, 0.19H), 2.72 – 2.58 (m, 2.19H), 2.54 – 2.44 (m, 1.38H), 2.46 – 2.32 (m, 1.19H), 2.26 – 2.06 (m, 2.38H), 1.99 – 1.74 (m, 2.38H). **^{13}C NMR** (101 MHz, $CDCl_3$) carbon signals are found at δ 209.85, 209.60, 159.93, 157.06, 153.53, 153.17, 149.34, 144.03, 137.14, 131.59, 128.51, 127.88, 127.35, 124.93, 123.68, 119.69, 117.99, 114.67, 111.34, 48.28, 45.40, 44.55, 41.17, 40.99, 39.70, 32.28, 29.61, 25.27, 24.73. **IR** (KBr, cm^{-1}) 2942, 1737, 1714, 1599, 1055, 731. **HRMS** calcd $C_{15}H_{14}BrO_3$ $[M+H]^+$: 321.0121. Found: 321.0130.



3j

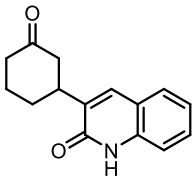
7-Hydroxy-3-(3-oxocyclohexyl)-2*H*-chromen-2-one (3j): Synthesized from **1a** and **2j** according to the general procedure. 72% Yield (37.3 mg). White solid. Melting point: 180 − 181 °C. R_f = 0.4 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, Acetone-d_6) δ 9.37 (br, 1H), 7.73 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 6.84 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.75 (d, *J* = 2.3 Hz, 1H), 3.08 (ddddd, *J* = 12.3, 11.2, 4.3, 3.3, 0.9 Hz, 1H), 2.62 (ddd, *J* = 13.5, 12.4, 1.0 Hz, 1H), 2.50 (ddt, *J* = 13.7, 4.1, 2.0 Hz, 1H), 2.42 (dddd, *J* = 13.9, 12.7, 6.1, 1.0 Hz, 1H), 2.31 (dddt, *J* = 14.3, 4.7, 3.3, 1.7 Hz, 1H), 2.18 – 2.07 (m, 2H), 1.99 – 1.84 (m, 1H), 1.83 – 1.67 (m, 1H). **^{13}C NMR** (101 MHz, Acetone-d_6) δ 209.42, 161.41, 161.29, 155.66, 138.79, 130.11, 128.05, 113.77, 113.19, 102.83, 46.47, 41.51, 40.10, 30.56, 25.83. **IR** (KBr, cm^{-1}) 3228, 2950, 1701, 1612, 1579, 1258, 1152, 849. **HRMS** calcd

$C_{15}H_{15}O_4$ $[M+H]^+$: 259.0965. Found: 259.0970.



3k

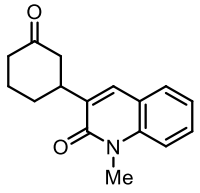
Benzyl (2-oxo-3-(3-oxocyclohexyl)-2*H*-chromen-6-yl)carbamate (3k): Synthesized from **1a** and **2k** according to the general procedure. 76% Yield (59.6 mg). Pale-yellow oil. R_f = 0.5 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (br, 1H), 7.44 (s, 1H), 7.42 – 7.32 (m, 6H), 7.23 (d, *J* = 8.9 Hz, 1H), 7.08 (br, 1H), 5.21 (s, 2H), 3.31 – 3.09 (m, 1H), 2.70 – 2.53 (m, 2H), 2.52 – 2.43 (m, 1H), 2.44 – 2.31 (m, 1H), 2.18 – 2.02 (m, 2H), 1.96 – 1.75 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.20, 160.68, 153.38, 148.92, 137.64, 135.72, 134.43, 131.78, 128.61, 128.45, 128.31, 121.93, 119.33, 116.81, 116.59, 67.24, 45.50, 41.11, 39.57, 29.71, 24.80. **IR** (KBr, cm^{-1}) 3313, 2952, 1708, 1551, 1221, 1057, 733. **HRMS** calcd $C_{23}H_{21}NNaO_5$ $[M+Na]^+$: 414.1312. Found: 414.1310.



3l

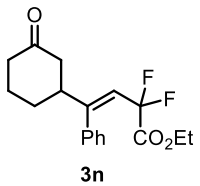
3-(3-Oxocyclohexyl)quinolin-2(1*H*)-one (3l): Synthesized from **1a** and **2l** according to the general procedure. 53% Yield (25.7 mg). White solid. Melting point: 254 − 257 °C. R_f = 0.2 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.57 (s, 1H), 7.61 (s, 1H), 7.55 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.49 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1H), 7.34 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.22 (ddd, *J*

= 8.1, 7.3, 1.1 Hz, 1H), 3.58 – 3.39 (m, 1H), 2.77 – 2.63 (m, 2H), 2.58 – 2.38 (m, 2H), 2.24 – 2.08 (m, 2H), 2.01 – 1.82 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.99, 163.15, 137.28, 135.55, 135.52, 130.04, 127.51, 122.66, 119.90, 115.38, 46.17, 41.37, 38.70, 30.20, 25.05. **IR** (KBr, cm^{-1}) 3157, 2948, 1709, 1652, 1568, 1436, 668. **HRMS** calcd $C_{15}H_{16}NO_2$ $[M+H]^+$: 242.1176. Found: 242.1177.



3m

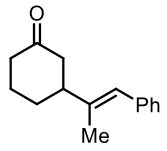
1-Methyl-3-(3-oxocyclohexyl)quinolin-2(1*H*)-one (3m): Synthesized from **1a** and **2m** according to the general procedure. 58% Yield (29.7 mg). White solid. Melting point: 138 − 140 °C. R_f = 0.4 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 – 7.50 (m, 2H), 7.50 (s, 1H), 7.39 – 7.32 (m, 1H), 7.29 – 7.20 (m, 1H), 3.75 (s, 3H), 3.49 – 3.33 (m, 1H), 2.77 – 2.58 (m, 2H), 2.54 – 2.33 (m, 2H), 2.22 – 2.03 (m, 2H), 1.97 – 1.77 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.01, 161.56, 138.93, 135.32, 133.92, 129.96, 128.43, 122.15, 120.27, 113.86, 46.00, 41.34, 39.43, 30.21, 29.72, 24.99. **IR** (KBr, cm^{-1}) 2927, 1705, 1641, 1593, 1459, 1224, 783. **HRMS** calcd $C_{16}H_{18}NO_2$ $[M+H]^+$: 256.1332. Found: 256.1341.



3n

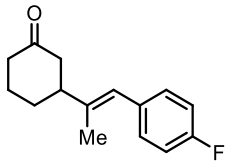
Ethyl (*Z*)-2,2-difluoro-4-(3-oxocyclohexyl)-4-phenylbut-3-enoate (3n): Synthesized from **1a** and **2n** according to the general procedure except for using 1,4-dioxane (0.8 mL) as the

solvent at 90 °C. 46% Yield (29.6 mg). Light-yellow oil. R_f = 0.3 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 3H), 7.09 – 7.01 (m, 2H), 5.78 (td, *J* = 11.3, 1.2 Hz, 1H), 3.89 (q, *J* = 7.2 Hz, 2H), 2.86 – 2.65 (m, 1H), 2.47 (ddt, *J* = 13.8, 4.0, 2.0 Hz, 1H), 2.43 – 2.32 (m, 1H), 2.30 – 2.19 (m, 2H), 2.16 – 2.03 (m, 1H), 2.02 – 1.91 (m, 1H), 1.79 – 1.47 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.86, 163.37 (t, *J* = 33.8 Hz), 154.13 (t, *J* = 9.0 Hz), 136.21, 128.38 (t, *J* = 1.9 Hz), 128.26, 127.96, 119.52 (t, *J* = 28.3 Hz), 112.28 (t, *J* = 246.1 Hz), 62.69, 47.04, 46.03, 40.98, 29.62, 24.78, 13.63. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -92.28 (dd, *J* = 277.3, 10.8 Hz), -92.50 (dd, *J* = 277.3, 11.2 Hz). **IR** (KBr, cm^{-1}) 2942, 1771, 1713, 1306, 1195, 1097, 704. **HRMS** calcd $C_{18}H_{21}F_2O_3$ $[M+H]^+$: 323.1453. Found: 323.1461.



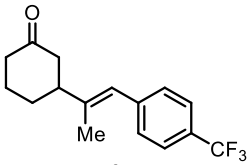
3o

(*E*)-3-(1-Phenylprop-1-en-2-yl)cyclohexan-1-one (3o)[33]: Synthesized from **1a** and **2o** according to the general procedure except for using 1,4-dioxane (0.8 mL) as the solvent at 90 °C. 53% Yield (22.6 mg). Colorless oil. R_f = 0.4 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 2H), 7.25 – 7.16 (m, 3H), 6.31 (s, 1H), 2.64 – 2.38 (m, 4H), 2.37 – 2.24 (m, 1H), 2.18 – 2.07 (m, 1H), 2.05 – 1.95 (m, 1H), 1.86 (d, *J* = 1.3 Hz, 3H), 1.81 – 1.66 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.41, 140.30, 137.91, 128.88, 128.03, 126.19, 124.79, 48.28, 46.74, 41.25, 30.08, 25.25, 15.71.



3p

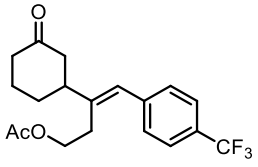
(*E*)-3-(1-(4-Fluorophenyl)prop-1-en-2-yl)cyclohexan-1-one (3p): Synthesized from **1a** and **2p** according to the general procedure except for using 1,4-dioxane (0.8 mL) as the solvent at 90 °C. 57% Yield (26.4 mg). Colorless oil. R_f = 0.4 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 – 7.12 (m, 2H), 7.07 – 6.96 (m, 2H), 6.26 (s, 1H), 2.61 – 2.38 (m, 4H), 2.36 – 2.25 (m, 1H), 2.22 – 2.06 (m, 1H), 2.03 – 1.91 (m, 1H), 1.83 (d, *J* = 1.3 Hz, 3H), 1.78 – 1.64 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.21, 161.17 (d, *J* = 245.5 Hz), 140.27 (d, *J* = 1.3 Hz), 133.85 (d, *J* = 3.3 Hz), 130.36 (d, *J* = 7.8 Hz), 123.69, 114.83 (d, *J* = 21.3 Hz), 48.13, 46.64, 41.18, 29.99, 25.16, 15.56. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -116.10 (tt, *J* = 8.5, 5.5 Hz). **IR** (KBr, cm^{-1}) 2940, 1714, 1600, 1508, 1225, 866. **HRMS** calcd $C_{15}H_{18}FO$ $[M+H]^+$: 233.1336. Found: 233.1344.



3q

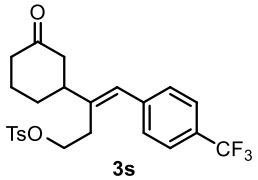
(*E*)-3-(1-(4-(trifluoromethyl)phenyl)prop-1-en-2-yl)cyclohexan-1-one (3q): Synthesized from **1a** and **2q** according to the general procedure except for using 1,4-dioxane (0.8 mL) as the solvent at 90 °C. 59% Yield (33.4 mg). Colorless oil. R_f = 0.3 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 6.33 (s, 1H), 2.62 – 2.48 (m, 2H), 2.47 – 2.40 (m, 2H), 2.38 – 2.25 (m, 1H), 2.21 – 2.09 (m, 1H), 2.04 – 1.95 (m, 1H), 1.86 (d, *J* = 1.3 Hz, 3H), 1.80 – 1.67 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.08,

142.70, 141.62, 129.14, 128.25 (q, J = 32.4 Hz), 125.01 (q, J = 3.8 Hz), 124.28 (q, J = 271.9 Hz), 123.79, 48.25, 46.63, 41.26, 30.04, 25.22, 15.86. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.40. **IR** (KBr, cm^{-1}) 2941, 1713, 1614, 1325, 1122, 868. **HRMS** calcd $C_{16}H_{18}F_3O$ $[M+H]^+$: 283.1304. Found: 283.1310.



3r

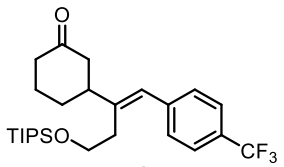
(*E*)-3-(3-Oxocyclohexyl)-4-(4-(trifluoromethyl)phenyl)but-3-en-1-yl acetate (3r): Synthesized from **1a** and **2r** according to the general procedure except for using 1,4-dioxane (0.8 mL) as the solvent at 90 °C. 61% Yield (42.9 mg). Colorless oil. R_f = 0.6 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 6.47 (s, 1H), 4.17 – 4.04 (m, 2H), 2.64 – 2.51 (m, 4H), 2.49 – 2.28 (m, 3H), 2.20 – 2.11 (m, 1H), 2.11 – 2.03 (m, 1H), 2.01 (s, 3H), 1.80 – 1.65 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.59, 170.79, 142.65, 140.99 (q, J = 1.6 Hz), 128.78, 128.76 (q, J = 32.5 Hz), 126.46, 125.27 (q, J = 3.7 Hz), 124.13 (q, J = 271.9 Hz), 62.29, 47.18, 44.90, 41.17, 30.74, 29.46, 25.15, 20.83. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.48. **IR** (KBr, cm^{-1}) 2956, 1740, 1712, 1326, 1232, 1122, 867. **HRMS** calcd $C_{19}H_{22}F_3O_3$ $[M+H]^+$: 355.1516. Found: 355.1519.



3s

(*E*)-3-(3-Oxocyclohexyl)-4-(4-(trifluoromethyl)phenyl)but-3-en-1-yl 4-methyl-

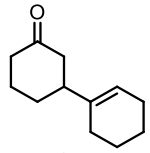
benzenesulfonate (3s): Synthesized from **1a** and **2s** according to the general procedure except for using 1,4-dioxane (0.8 mL) as the solvent at 90 ºC. 62% Yield (57.7 mg). Colorless oil. R_f = 0.5 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.44 (s, 1H), 4.19 – 3.87 (m, 2H), 2.59 (t, *J* = 7.2 Hz, 2H), 2.49 – 2.25 (m, 8H), 2.17 – 2.06 (m, 1H), 2.01 – 1.91 (m, 1H), 1.76 – 1.57 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.22, 145.03, 141.12, 140.66, 132.68, 129.87, 128.84 (q, *J* = 32.5 Hz), 128.70, 127.77, 127.18, 125.26 (q, *J* = 3.8 Hz), 124.07 (q, *J* = 272.0 Hz), 67.56, 46.84, 44.59, 41.09, 30.46, 29.54, 24.96, 21.55. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.48. **IR** (KBr, cm^{-1}) 2955, 1711, 1325, 1176, 1122, 962. **HRMS** calcd $C_{24}H_{26}F_3O_4S$ $[M+H]^+$: 467.1498. Found: 467.1505.



3t

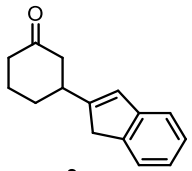
(*E*)-3-(1-(4-(Trifluoromethyl)phenyl)-4-((triisopropylsilyl)oxy)but-1-en-2-yl)cyclo-hexan-1-one (3t): Synthesized from **1a** and **2t** according to the general procedure except for using 1,4-dioxane (0.8 mL) as the solvent at 90 ºC. 52% Yield (48.3 mg). Colorless oil. R_f = 0.5 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 6.42 (s, 1H), 3.80 – 3.66 (m, 2H), 2.69 – 2.28 (m, 7H), 2.20 – 2.01 (m, 2H), 1.79 – 1.64 (m, 2H), 1.09 – 0.92 (m, 21H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.03, 144.55, 141.55 (q, *J* = 1.6 Hz), 128.96, 128.44 (q, *J* = 32.3 Hz), 125.33, 125.02 (q, *J* = 3.8 Hz), 124.24 (q, *J* = 271.8 Hz), 61.84, 47.28, 44.90, 41.27, 33.56, 30.84, 25.24, 17.92, 11.83. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -

62.42. **IR** (KBr, cm^{-1}) 2944, 2867, 1714, 1325, 1125, 882. **HRMS** calcd $C_{26}H_{40}F_3O_2Si$ $[M+H]^+$: 469.2744. Found: 469.2751.



3u

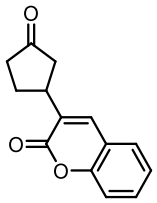
[1,1'-Bi(cyclohexan)]-1'-en-3-one (3u)[34]**:** Synthesized from **1a** and **2u** according to the general procedure except for using 1,4-dioxane (0.8 mL) as the solvent at 90 °C. 43% Yield (15.4 mg). Colorless oil. R_f = 0.5 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.44 (tdd, *J* = 3.7, 2.4, 1.5 Hz, 1H), 2.43 – 2.20 (m, 5H), 2.11 – 1.82 (m, 6H), 1.72 – 1.48 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 212.16, 139.61, 120.92, 46.75, 46.07, 41.36, 29.98, 26.41, 25.20, 25.14, 22.93, 22.51.



3v

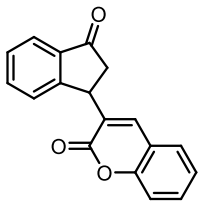
3-(1*H*-Inden-2-yl)cyclohexan-1-one (3v): Synthesized from **1a** and **2v** according to the general procedure except for using 1,4-dioxane (0.8 mL) as the solvent at 90 °C. 42% Yield (18.0 mg). White solid. Melting point: 76 − 77 °C. R_f = 0.4 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.4, 1.0 Hz, 1H), 7.30 (dt, *J* = 7.4, 1.0 Hz, 1H), 7.23 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.14 (td, *J* = 7.4, 1.3 Hz, 1H), 6.57 (dq, *J* = 2.1, 1.3 Hz, 1H), 3.46 – 3.27 (m, 2H), 3.21 – 2.89 (m, 1H), 2.75 – 2.60 (m, 1H), 2.57 – 2.29 (m, 3H), 2.21 – 1.98 (m, 2H), 1.89 – 1.70 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.90, 151.90, 144.81, 142.60, 126.44, 126.14, 124.19, 123.54,

120.45, 47.35, 41.32, 40.29, 39.25, 31.28, 24.91. **IR** (KBr, cm^{-1}) 3065, 2947, 1709, 1460, 1226, 756. **HRMS** calcd $C_{15}H_{17}O$ $[M+H]^+$: 213.1274. Found: 213.1273.



4a

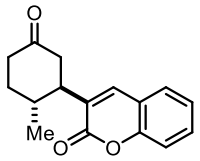
3-(3-Oxocyclopentyl)-2*H*-chromen-2-one (4a): Synthesized from **1b** and **2a** according to the general procedure except for using 15 mol % $Pd(MeCN)_4(OTf)_2$ and 21 mol % P(*i*-Pr)$_3$. 51% Yield (23.3 mg). Colorless oil. R_f = 0.5 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 – 7.43 (m, 3H), 7.38 – 7.23 (m, 2H), 3.52 (tddd, *J* = 9.8, 7.2, 5.8, 1.0 Hz, 1H), 2.69 (ddt, *J* = 19.0, 7.4, 1.3 Hz, 1H), 2.55 – 2.27 (m, 4H), 2.14 – 1.96 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 217.17, 160.98, 152.99, 137.31, 131.19, 130.31, 127.52, 124.50, 118.98, 116.45, 43.11, 38.20, 38.00, 27.98. **IR** (KBr, cm^{-1}) 2960, 1741, 1717, 1608, 1457, 1057, 757. **HRMS** calcd $C_{14}H_{13}O_3$ $[M+H]^+$: 229.0859. Found: 229.0865.



4b

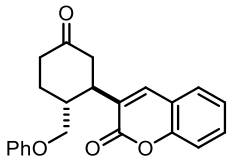
3-(3-Oxo-2,3-dihydro-1*H*-inden-1-yl)-2*H*-chromen-2-one (4b): Synthesized from **1c** and **2a** according to the general procedure except for using 15 mol % $Pd(MeCN)_4(OTf)_2$ and 21 mol % P(*i*-Pr)$_3$. 44% Yield (24.3 mg). Light-yellow oil. R_f = 0.6 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.7 Hz, 1H), 7.66 (td, *J* = 7.5, 1.3 Hz, 1H), 7.54 – 7.42 (m, 3H),

7.40 – 7.30 (m, 3H), 7.29 – 7.21 (m, 1H), 4.81 (dd, *J* = 8.3, 3.5 Hz, 1H), 3.25 (dd, *J* = 19.1, 8.3 Hz, 1H), 2.68 (dd, *J* = 19.2, 3.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.69, 161.10, 154.45, 153.13, 138.50, 137.37, 135.09, 131.42, 131.21, 128.49, 127.66, 126.44, 124.53, 124.02, 118.91, 116.53, 43.93, 39.35. **IR** (KBr, cm^{-1}) 2925, 1712, 1607, 1457, 1176, 757. **HRMS** calcd $C_{18}H_{12}NaO_3$ $[M+Na]^+$: 299.0679. Found: 299.0678.



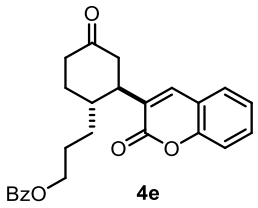
4c

***trans*-3-(2-Methyl-5-oxocyclohexyl)-2*H*-chromen-2-one (4c):** Synthesized from **1d** and **2a** according to the general procedure. 62% Yield (31.9 mg). d.r. > 20:1 based on crude NMR of the reaction mixture. The stereochemistry is assigned to be *trans* as determined by the coupling constant analysis, and the proton signal assignment is based on COSY analysis (*vide infra*). Colorless oil. R_f = 0.6 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 – 7.45 (m, 3H), 7.36 – 7.23 (m, 2H), 2.94 (t, *J* = 13.4 Hz, 1H), 2.76 (ddd, *J* = 12.7, 10.5, 4.0 Hz, 1H), 2.61 – 2.42 (m, 4H), 2.13 (ddt, *J* = 12.7, 6.3, 3.3 Hz, 1H), 1.53 (tdd, *J* = 13.3, 11.4, 4.8 Hz, 1H), 0.94 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.20, 160.46, 153.16, 139.77, 131.23, 130.03, 127.50, 124.43, 119.05, 116.39, 48.51, 45.10, 41.02, 33.95, 33.48, 19.30. **IR** (KBr, cm^{-1}) 2957, 1715, 1609, 1281, 1058, 757. **HRMS** calcd $C_{16}H_{17}O_3$ $[M+H]^+$: 257.1172. Found: 257.1180.



4d

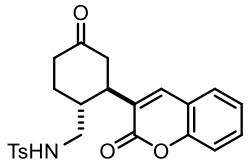
***trans*-3-(5-Oxo-2-(phenoxymethyl)cyclohexyl)-2*H*-chromen-2-one (4d):** Synthesized from **1e** and **2a** according to the general procedure. 50% Yield (34.9 mg). d.r. > 20:1 based on crude NMR of the reaction mixture. Colorless oil. R_f = 0.6 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 2H), 7.36 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.27 – 7.15 (m, 3H), 6.88 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.81 – 6.68 (m, 2H), 3.91 (dd, *J* = 9.5, 4.2 Hz, 1H), 3.86 (dd, *J* = 9.5, 5.1 Hz, 1H), 3.23 – 3.07 (m, 2H), 2.94 (dp, *J* = 15.2, 4.6 Hz, 1H), 2.66 – 2.45 (m, 3H), 2.29 (ddt, *J* = 13.2, 6.0, 3.5 Hz, 1H), 1.96 – 1.79 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.67, 160.46, 158.54, 153.24, 140.21, 131.34, 129.39, 128.94, 127.61, 124.46, 120.88, 118.98, 116.35, 114.27, 69.51, 44.70, 44.49, 40.49, 38.29, 28.65. **IR** (KBr, cm^{-1}) 2929, 1716, 1608, 1497, 1244, 755. **HRMS** calcd $C_{22}H_{21}O_4$ $[M+H]^+$: 349.1434. Found: 349.1436.



4e

***trans*-3-(4-Oxo-2-(2-oxo-2*H*-chromen-3-yl)cyclohexyl)propyl benzoate (4e):** Synthesized from **1f** and **2a** according to the general procedure. 54% Yield (43.5 mg). d.r. > 20:1 based on crude NMR of the reaction mixture. Colorless oil. R_f = 0.5 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 – 7.76 (m, 2H), 7.56 – 7.47 (m, 3H), 7.43 (dd, *J* = 7.8, 1.6 Hz,

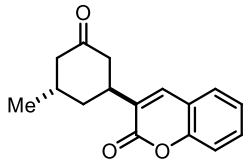
1H), 7.35 – 7.19 (m, 4H), 4.37 – 4.19 (m, 2H), 3.04 – 2.86 (m, 2H), 2.60 – 2.39 (m, 4H), 2.34 – 2.19 (m, 1H), 1.99 – 1.83 (m, 1H), 1.78 – 1.67 (m, 1H), 1.64 – 1.45 (m, 2H), 1.37 – 1.21 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.93, 166.42, 160.38, 153.13, 140.07, 132.79, 131.30, 130.08, 129.71, 129.32, 128.23, 127.57, 124.48, 118.91, 116.39, 64.53, 47.03, 45.11, 40.57, 37.40, 30.27, 29.36, 25.78. **IR** (KBr, cm^{-1}) 2953, 1716, 1609, 1446, 1276, 713. **HRMS** calcd $C_{25}H_{24}NaO_5$ $[M+Na]^+$: 427.1516. Found: 427.1518.



4f

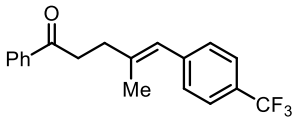
***trans*-4-Methyl-*N*-((4-oxo-2-(2-oxo-2*H*-chromen-3-yl)cyclohexyl)methyl)benzene-sulfonamide (4f):** Synthesized from **1g** and **2a** according to the general procedure. 48% Yield (44.9 mg). d.r. > 20:1 based on crude NMR of the reaction mixture. The overoxidation side product **4f'** was isolated in 5% yield as an inseparable mixture with **4f** (**4f**:**4f'** = 1:0.10). Colorless oil. R_f = 0.2 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (s, 0.1H), 7.65 – 7.60 (m, 3.2H), 7.58 – 7.48 (m, 2.2H), 7.37 – 7.29 (m, 2.2H), 7.22 – 7.15 (m, 2.2H), 6.41 (d, *J* = 1.1 Hz, 0.1H), 5.09 – 4.95 (m, 1.1H), 3.48 – 3.40 (m, 0.1H), 3.15 – 2.93 (m, 2.2H), 2.90 – 2.66 (m, 2H), 2.54 – 2.40 (m, 4.2H), 2.35 (s, 3.3H), 2.22 – 2.11 (m, 1.2H), 1.82 – 1.66 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) carbon signals of **4f** are found at δ 209.00, 161.14, 153.03, 143.50, 140.67, 136.47, 131.63, 129.68, 128.75, 127.84, 126.91, 124.73, 118.94, 116.39, 45.51, 44.78, 42.42, 40.06, 39.13, 28.59, 21.46. **IR** (KBr, cm^{-1}) 3272, 2925, 1714, 1608, 1327, 1160, 732. **HRMS** calcd $C_{23}H_{24}NO_5S$

$[M+H]^+$: 426.1370. Found: 426.1377.



4g

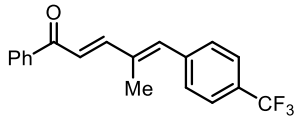
***trans*-3-(3-Methyl-5-oxocyclohexyl)-2*H*-chromen-2-one (4g):** Synthesized from **1h** and **2a** according to the general procedure. 40% Yield (20.6 mg). d.r. = 13:1 based on crude NMR of the reaction mixture. The stereochemistry is assigned to be *trans* as determined by NOESY analysis (*vide infra*). Colorless oil. R_f = 0.6 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 – 7.41 (m, 3H), 7.35 – 7.19 (m, 2H), 3.61 (qdd, *J* = 6.1, 4.6, 1.1 Hz, 0.93H), 3.23 – 3.11 (m, 0.07H), 2.72 – 2.55 (m, 2H), 2.56 – 2.43 (m, 1H), 2.29 – 1.99 (m, 3H), 1.83 (ddd, *J* = 13.6, 8.5, 4.8 Hz, 0.93H), 1.59 (td, *J* = 12.7, 11.3 Hz, 0.07H), 1.09 (d, *J* = 6.1 Hz, 0.21H), 1.03 (d, *J* = 6.5 Hz, 2.79H). **^{13}C NMR** (101 MHz, $CDCl_3$) carbon signals of the major diastereomer are found at δ 211.22, 160.76, 152.92, 138.53, 131.45, 131.10, 127.68, 124.43, 118.99, 116.33, 49.09, 44.55, 35.62, 35.48, 29.22, 20.71. **IR** (KBr, cm^{-1}) 2956, 1714, 1609, 1457, 1176, 757. **HRMS** calcd $C_{16}H_{16}NaO_3$ $[M+Na]^+$: 279.0992. Found: 279.0992.



4h

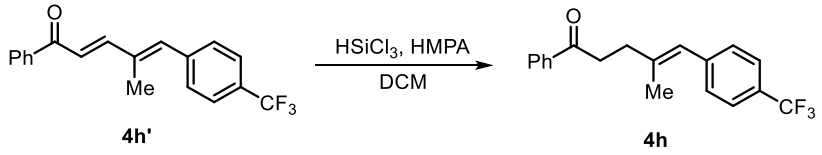
(*E*)-4-Methyl-1-phenyl-5-(4-(trifluoromethyl)phenyl)pent-4-en-1-one (4h): Synthesized from **1i** and **2q** according to the general procedure except for using 5 equiv. of **1i**, 20 mol % P(*i*-Pr)$_3$ and 1,4-dioxane (0.8 mL) as the solvent at 90 °C. The product **4h**, the overoxidation

product **4h'** and the di-alkenylation product were isolated in 7.6% (4.8 mg), 42% (26.5 mg) and 3.1% yields (3.1 mg), respectively. The overoxidation product **4h'** can be quantitatively transferred to **4h** (*vide infra*). 53% Total yield (mono:di = 16:1). Colorless oil. R_f = 0.4 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 7.90 (m, 2H), 7.63 – 7.53 (m, 3H), 7.48 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.34 (s, 1H), 3.38 – 3.05 (m, 2H), 2.64 (td, *J* = 7.6, 1.2 Hz, 2H), 1.92 (d, *J* = 1.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.41, 141.80, 140.06, 136.86, 133.11, 128.97, 128.64, 128.03, 127.96 (q, *J* = 32.5 Hz), 124.94 (q, *J* = 3.8 Hz), 124.38, 124.29 (q, *J* = 271.8 Hz), 37.04, 34.78, 18.03. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.33. **IR** (KBr, cm^{-1}) 3061, 2914, 1686, 1326, 1121, 1068, 867. **HRMS** calcd $C_{19}H_{18}F_3O$ $[M+H]^+$: 319.1304. Found: 319.1303.



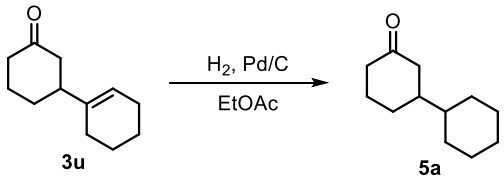
4h'

(2*E*,4*E*)-4-Methyl-1-phenyl-5-(4-(trifluoromethyl)phenyl)penta-2,4-dien-1-one (4h'): Isolated as the side product from the synthesis of **4h** in 42% yield (26.5 mg). Light-yellow solid. Melting point: 153 − 155 °C. R_f = 0.3 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 – 7.91 (m, 2H), 7.70 – 7.55 (m, 4H), 7.54 – 7.44 (m, 4H), 7.11 (d, *J* = 15.4 Hz, 1H), 6.97 (s, 1H), 2.16 (d, *J* = 1.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.57, 149.14, 140.20, 138.28, 138.19, 136.52, 132.74, 129.60, 129.47 (q, *J* = 32.5 Hz), 128.59, 128.42, 125.24 (q, *J* = 3.8 Hz), 124.02 (q, *J* = 272.0 Hz), 122.52, 13.93. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.58. **IR** (KBr, cm^{-1}) 3062, 1655, 1587, 1330, 1111, 861. **HRMS** calcd $C_{19}H_{16}F_3O$ $[M+H]^+$: 317.1148. Found: 317.1153.



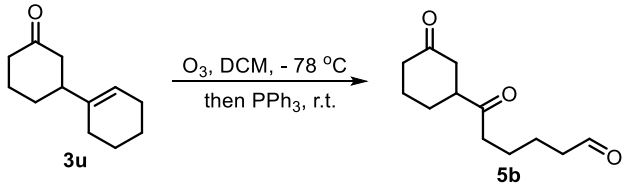
The selective 1,4-reduction was performed based on a literature procedure.[12] A 4-mL vial was flame-dried and charged with **4h'** (1 equiv., 0.084 mmol, 26.5 mg), DCM (0.4 mL) and HMPA (20 mol %, 0.017 mmol, 3.0 μL). $HSiCl_3$ (2 equiv., 0.168 mmol, 17.0 μL) was dissolved in DCM (0.1 mL), and the solution was added to the reaction vial dropwise at 0 °C. The mixture was stirred at 0 °C until the yellow color faded (90 min). The mixture was quenched with $NaHCO_3$ and extracted with Et_2O. The combined organic layers were filtered through Celite, and the filtrate was concentrated. The residue was purified by column chromatography to give **4h** as a colorless oil in a quantitative yield (26.7 mg).

2.4.5 Procedures for the derivatization of the β-alkenylated ketone

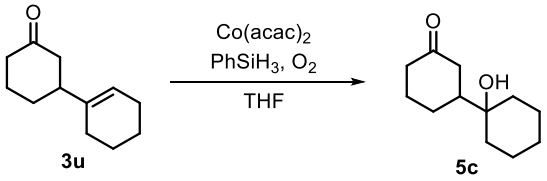


[1,1'-Bi(cyclohexan)]-3-one (5a)[35]**:** An 8-mL culture tube was charged with Pd/C (10 wt.%, 5 mol %, 0.005 mmol, 5.3 mg) and replaced with N_2. **3u** (1 equiv., 0.1 mmol, 17.8 mg) was dissolved in EtOAc (1.5 mL), and the solution was added via syringe. The atmosphere was replaced with H_2 using a balloon, and the mixture was stirred under H_2 overnight. The mixture was filtered through Celite, eluting with EtOAc. The filtrate was concentrated, and the residue was purified by column chromatography to give **5a** as a colorless oil in 97% yield (17.5 mg). R_f = 0.5

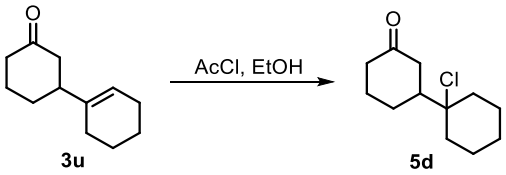
(hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.51 – 2.32 (m, 2H), 2.24 (dddd, *J* = 14.1, 12.9, 6.2, 1.3 Hz, 1H), 2.15 – 2.02 (m, 2H), 1.93 – 1.82 (m, 1H), 1.79 – 1.50 (m, 7H), 1.38 (tdd, *J* = 12.8, 11.5, 3.6 Hz, 1H), 1.29 – 1.06 (m, 4H), 1.05 – 0.87 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 212.87, 45.54, 44.64, 42.63, 41.59, 29.92, 29.82, 28.39, 26.55, 26.53, 26.49, 25.60.



6-Oxo-6-(3-oxocyclohexyl)hexanal (5b): An 8-mL culture tube was charged with **3u** (1 equiv., 0.1 mmol, 17.8 mg) and DCM (2 mL), and the solution was cooled to -78 °C. PPh_3 (10 equiv., 1 mmol, 262 mg) was dissolved in minimum amount of DCM. The **3u** solution was treated with an O_3 flow until the solution stayed blue. The O_3 flow was then stopped, and the PPh_3 solution was added to the tube immediately. The mixture was warmed to room temperature and stirred overnight. The mixture was concentrated, and the residue was purified by column chromatography to give **5b** as a colorless oil in 59% yield (12.4 mg). R_f = 0.4 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.5 Hz, 1H), 2.96 – 2.79 (m, 1H), 2.67 – 2.21 (m, 8H), 2.15 – 1.98 (m, 2H), 1.82 – 1.55 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.10, 209.96, 202.02, 50.21, 43.66, 42.53, 40.91, 40.71, 27.38, 24.92, 22.93, 21.47. **IR** (KBr, cm^{-1}) 2941, 1712, 1450, 1226, 1118, 976. **HRMS** calcd $C_{12}H_{19}O_3$ $[M+H]^+$: 211.1329. Found: 211.1332.

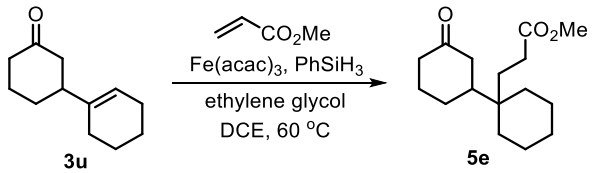


1'-Hydroxy-[1,1'-bi(cyclohexan)]-3-one (5c): The reaction was performed based on a literature procedure.[14] An 8-mL culture tube was charged with $Co(acac)_2$ (20 mol %, 0.02 mmol, 5.1 mg), THF (0.5 mL), **3u** (1 equiv., 0.1 mmol, 17.8 mg) and $PhSiH_3$ (2 equiv., 0.2 mmol, 24.6 μL). The atmosphere was replaced with O_2 using a balloon, and the mixture was stirred under O_2 overnight. The mixture was concentrated, and the residue was purified by column chromatography to give **5c** as a colorless oil in 80% yield (15.7 mg). R_f = 0.5 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.49 (ddt, *J* = 13.8, 4.2, 2.1 Hz, 1H), 2.37 (dddd, *J* = 14.2, 6.4, 2.6, 1.6 Hz, 1H), 2.32 – 2.20 (m, 2H), 2.13 (ddq, *J* = 11.9, 5.6, 3.0 Hz, 1H), 1.99 (dddd, *J* = 12.7, 5.3, 3.6, 1.8 Hz, 1H), 1.75 (ddt, *J* = 12.8, 11.5, 3.7 Hz, 1H), 1.68 – 1.51 (m, 8H), 1.50 – 1.31 (m, 3H), 1.29 – 1.14 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 212.90, 72.33, 48.32, 42.17, 41.33, 34.95, 34.61, 25.65, 25.24, 24.72, 21.87, 21.78. **IR** (KBr, cm^{-1}) 3463, 2932, 1702, 1449, 1150, 960. **HRMS** calcd $C_{12}H_{21}O_2$ $[M+H]^+$: 197.1536. Found: 197.1533.

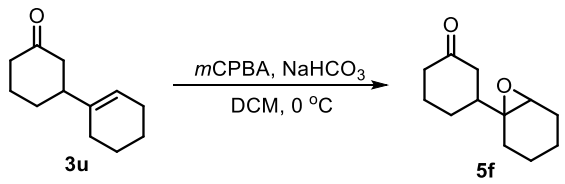


1'-Chloro-[1,1'-bi(cyclohexan)]-3-one (5d): The reaction was performed based on a literature procedure.[15] A 2-mL vial was flame-dried and charged with **3u** (1 equiv., 0.1 mmol, 17.8 mg) and EtOH (8 equiv., 0.8 mmol, 46.7 μL). The mixture was cooled to 0 °C, and AcCl (8 equiv., 0.8 mmol, 56.9 μL) was added dropwise. The mixture was heated at 30 °C for 1 h. The mixture was concentrated, and the residue was purified by column chromatography to give **5d** as an colorless oil in 94% yield (20.2 mg). R_f = 0.4 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$)

δ 2.59 (ddt, J = 14.1, 4.2, 2.1 Hz, 1H), 2.50 – 2.35 (m, 2H), 2.29 (tdd, J = 14.3, 6.2, 1.1 Hz, 1H), 2.20 – 2.05 (m, 3H), 2.01 – 1.87 (m, 2H), 1.82 – 1.39 (m, 9H), 1.24 – 1.09 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.76, 77.86, 49.99, 42.69, 41.19, 37.88, 37.45, 25.23, 24.53, 22.19, 21.99. **IR** (KBr, cm^{-1}) 2932, 2863, 1713, 1448, 1261, 890. **HRMS** calcd $C_{12}H_{20}ClO$ $[M+H]^+$: 215.1197. Found: 215.1204.



Methyl 3-(3'-oxo-[1,1'-bi(cyclohexan)]-1-yl)propanoate (5e): The reaction was performed based on a literature procedure.[16] An 8-mL culture tube was charged with $Fe(acac)_3$ (1 equiv., 0.1 mmol, 35.3 mg) and refilled with N_2. DCE (0.8 mL), ethylene glycol (0.16 mL), **3u** (1 equiv., 0.1 mmol, 17.8 mg), methyl acrylate (3 equiv., 0.3 mmol, 27.2 μL) and $PhSiH_3$ (1.5 equiv., 0.15 mmol, 18.5 μL) were added via syringe. The mixture was heated at 60 °C for 1 h. After cooling to room temperature, the mixture was diluted with water and brine, and extracted with Et_2O. The combined organic layers were dried and concentrated, and the residue was purified by column chromatography to give **5e** as a colorless oil in 73% yield (19.4 mg). R_f = 0.5 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.43 – 2.31 (m, 2H), 2.30 – 2.17 (m, 3H), 2.16 – 2.06 (m, 2H), 1.93 – 1.82 (m, 1H), 1.82 – 1.63 (m, 3H), 1.61 – 1.18 (m, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 212.77, 174.60, 51.64, 43.57, 42.42, 41.44, 36.68, 31.31, 31.29, 28.26, 27.73, 26.02, 25.75, 25.06, 21.13, 21.07. **IR** (KBr, cm^{-1}) 2932, 1738, 1712, 1435, 1173, 760. **HRMS** calcd $C_{16}H_{27}O_3$ $[M+H]^+$: 267.1955. Found: 267.1962.



3-(7-Oxabicyclo[4.1.0]heptan-1-yl)cyclohexan-1-one (5f): A 4-mL vial was charged with **3u** (1 equiv., 0.1 mmol, 17.8 mg), DCM (1 mL) and $NaHCO_3$ (1.5 equiv., 0.15 mmol, 12.6 mg). The mixture was cooled to 0 ºC before *m*CPBA (1.1 equiv., 0.11 mmol, 24.6 mg) was added. After being stirred at 0 ºC for 2 h, the mixture was then diluted with DCM and quenched with Na_2SO_3. The mixture was further stirred for 10 min and then extracted with DCM. The combined organic layers were washed with brine, dried and concentrated. The residue was purified by column chromatography to give **5f** as a colorless oil in 96% yield (18.6 mg). d.r. was not identifiable in ^{1}H NMR; it was estimated to be 1:1 based on ^{13}C NMR of the isolated product. R_f = 0.4 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.00 (t, *J* = 3.1 Hz, 1H), 2.49 – 2.33 (m, 2H), 2.30 – 2.05 (m, 3H), 2.01 – 1.89 (m, 2H), 1.88 – 1.36 (m, 8H), 1.30 – 1.15 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) carbon signals are found at δ 210.93, 210.91, 61.55, 61.39, 57.82, 57.12, 46.10, 45.38, 43.71, 42.72, 41.34, 41.22, 26.68, 25.98, 25.60, 25.09, 24.98, 24.97, 24.85, 24.84, 20.32, 20.26, 19.48. **IR** (KBr, cm^{-1}) 2937, 1712, 1448, 1317, 1218, 968. **HRMS** calcd $C_{12}H_{19}O_2$ $[M+H]^+$: 195.1380. Found: 195.1376.

2.5 References

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2.6 NMR Spectra

Figure 2.2 ^{1}H-NMR and ^{13}C-NMR Spectra of **2e**

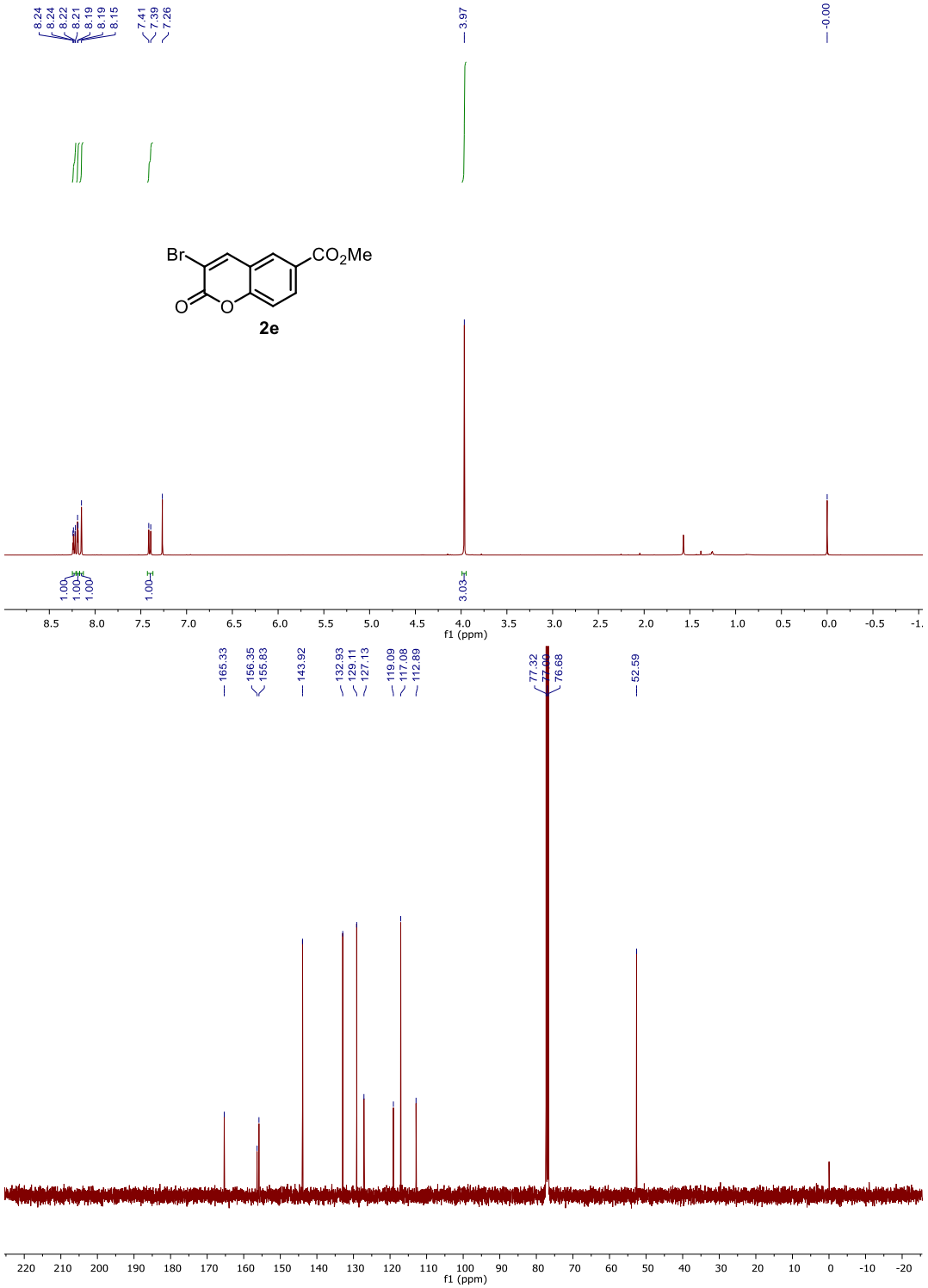


Figure 2.3 ^{1}H-NMR and ^{13}C-NMR Spectra of **2f**

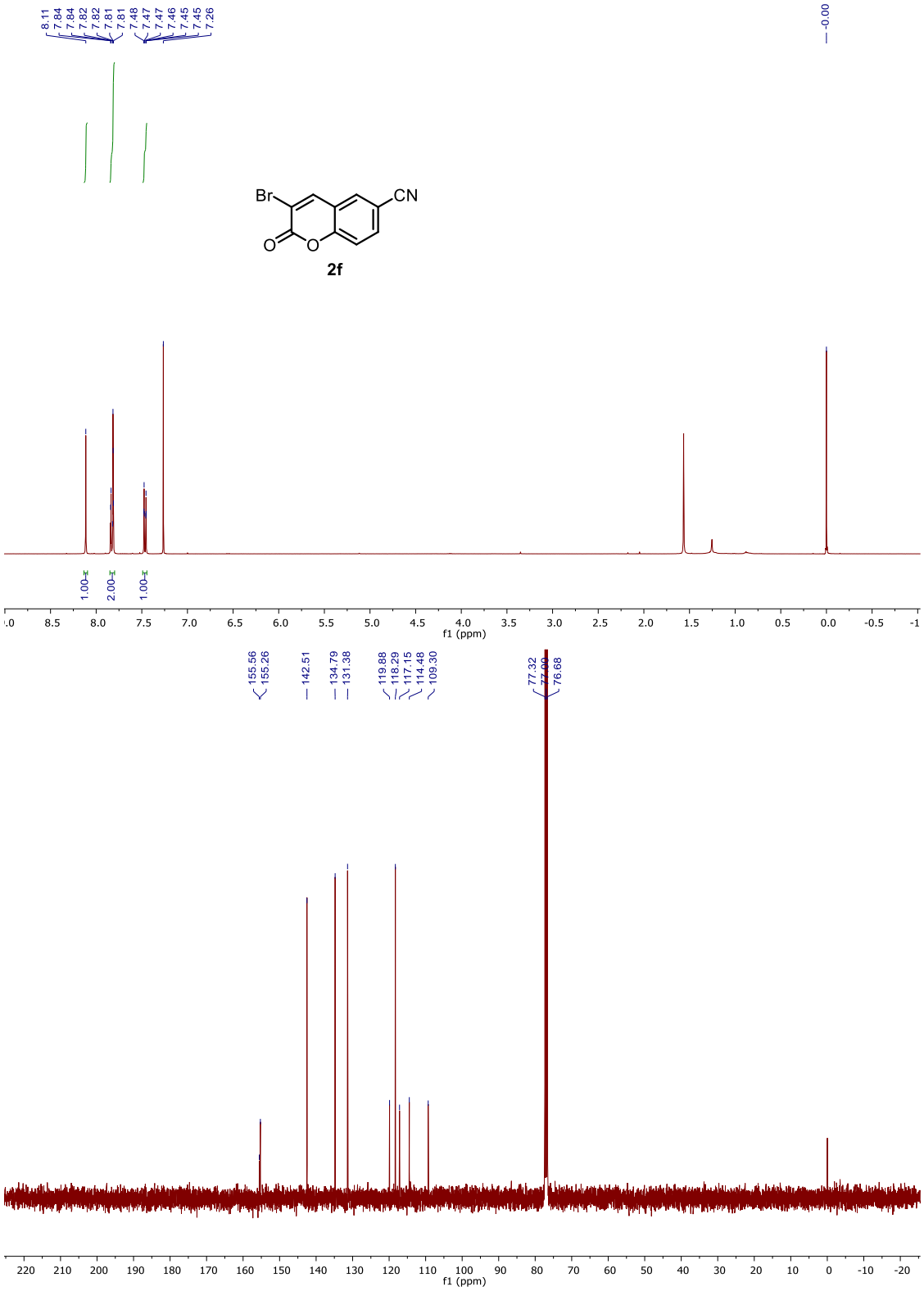


Figure 2.4 ^{1}H-NMR and ^{13}C-NMR Spectra of **2g**

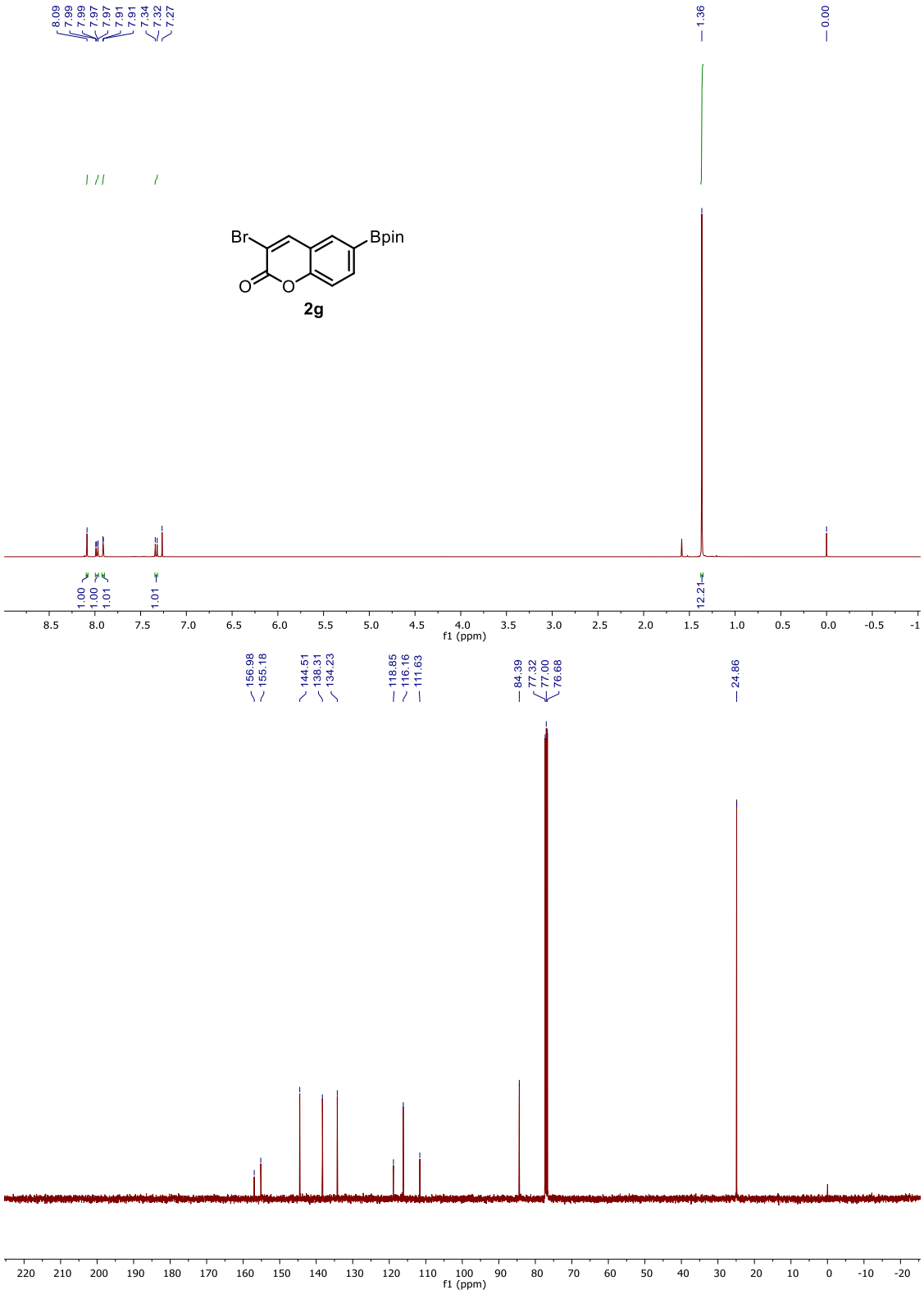


Figure 2.5 ^{1}H-NMR and ^{13}C-NMR Spectra of **2k**

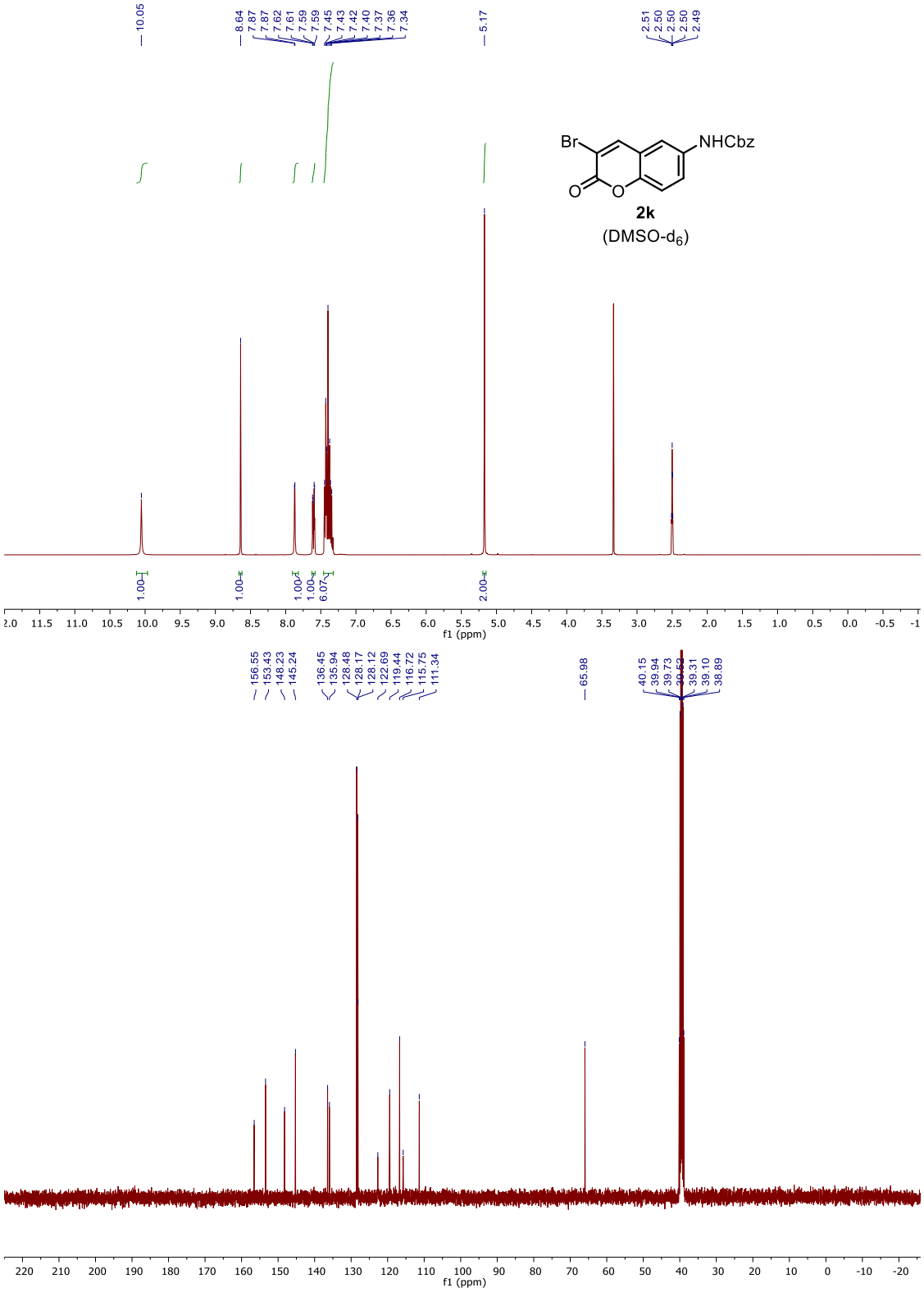


Figure 2.6 ^{1}H-NMR and ^{13}C-NMR Spectra of **2p**

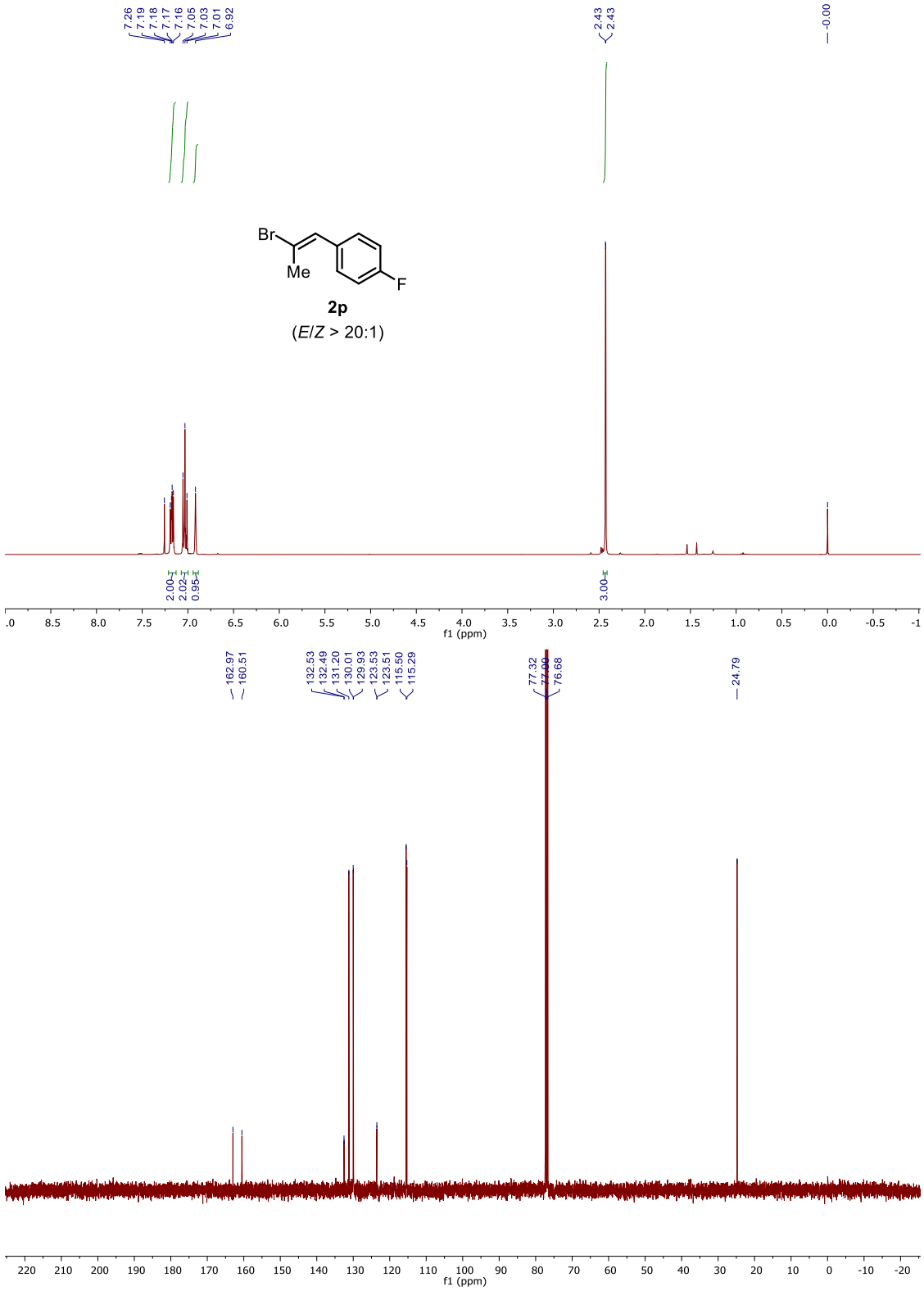


Figure 2.7 ^{19}F-NMR Spectrum of **2p**

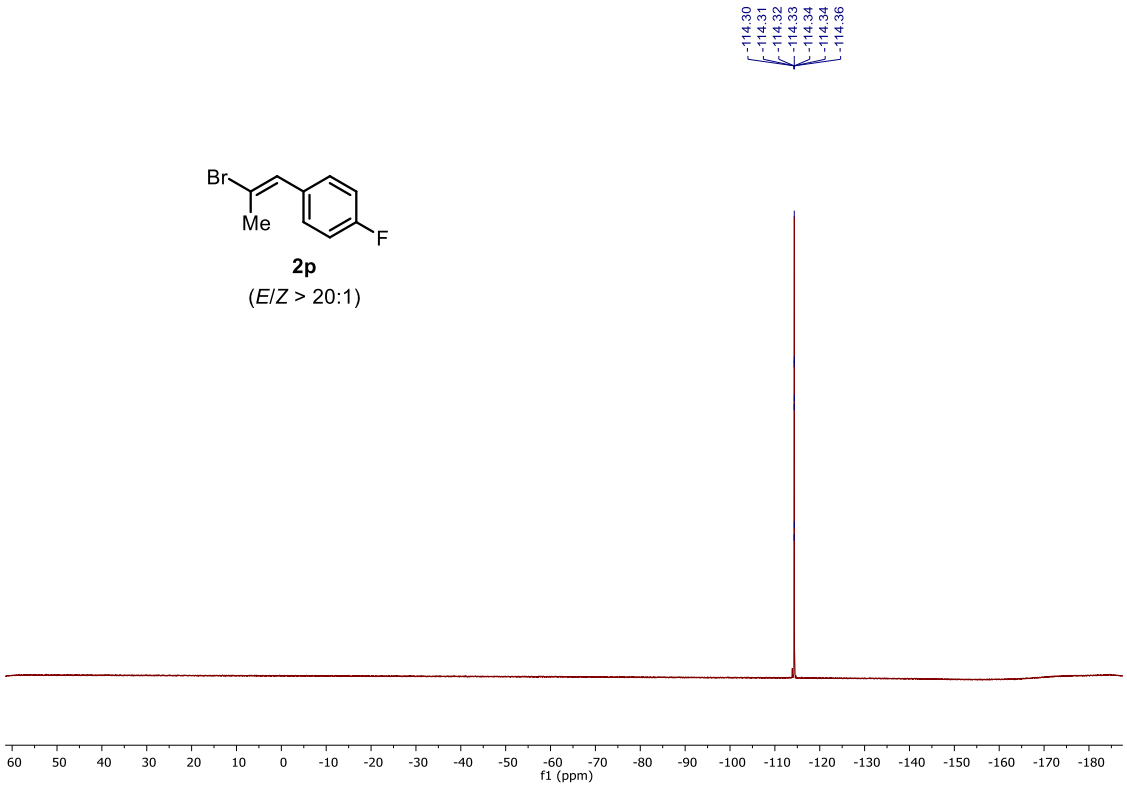


Figure 2.8 ^{1}H-NMR and ^{13}C-NMR Spectra of **2q**

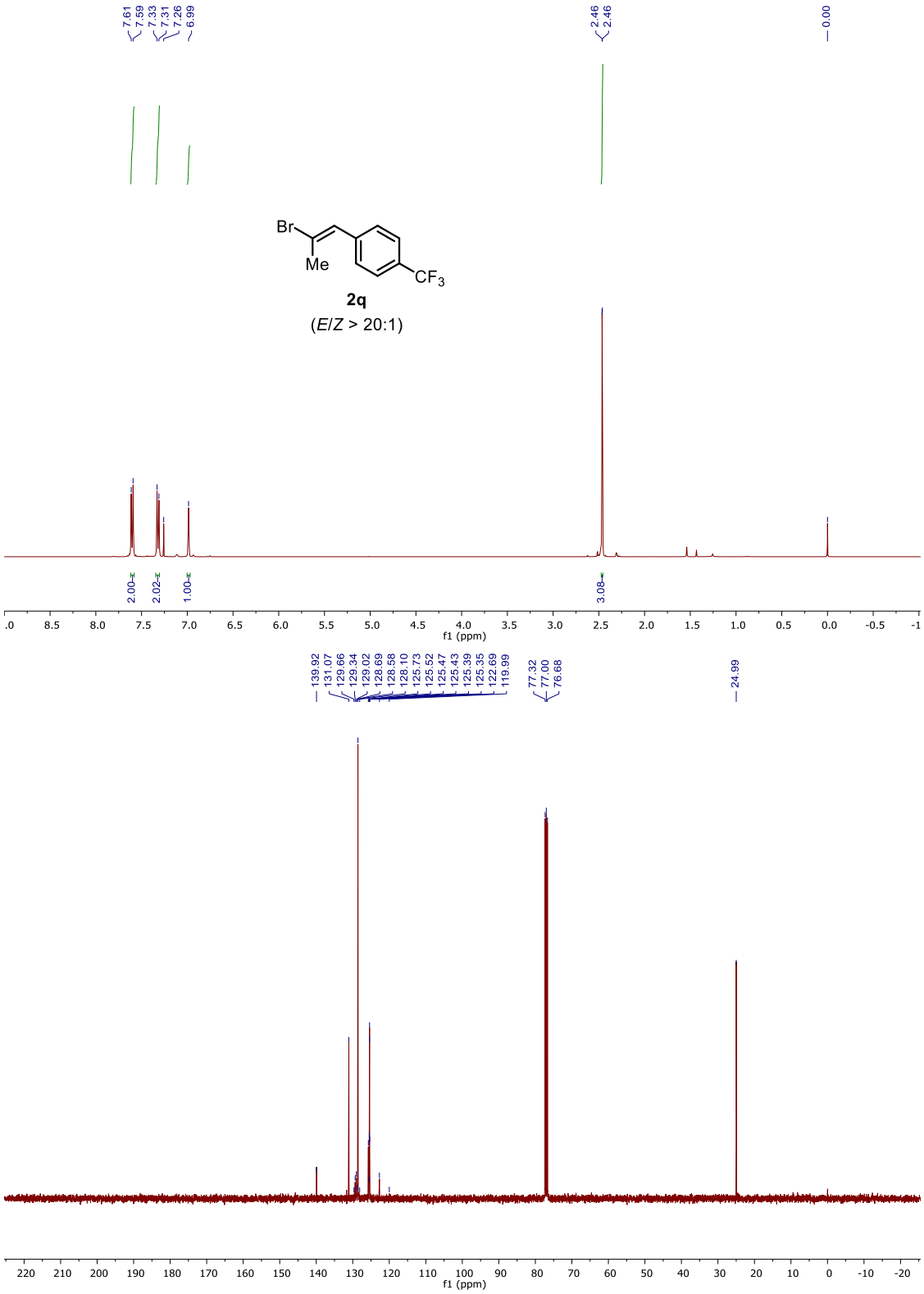


Figure 2.9 ^{19}F-NMR Spectrum of **2q**

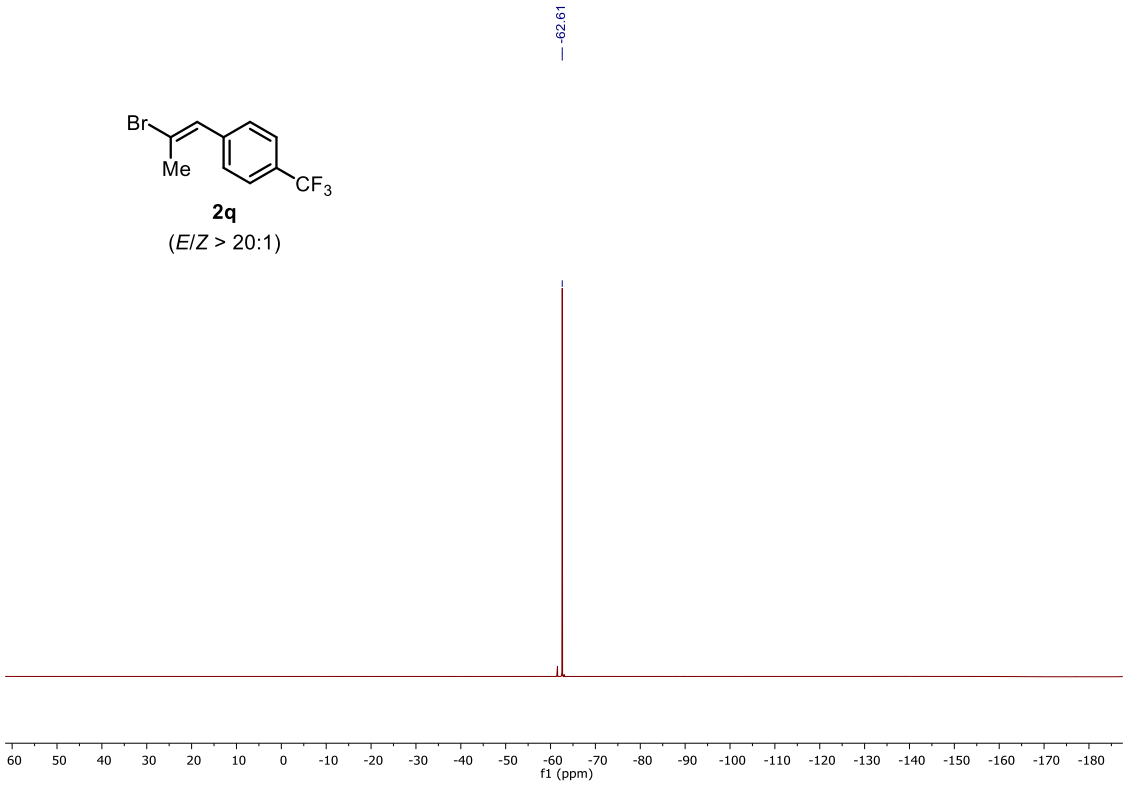


Figure 2.10 ^{1}H-NMR and ^{13}C-NMR Spectra of **2r-3**

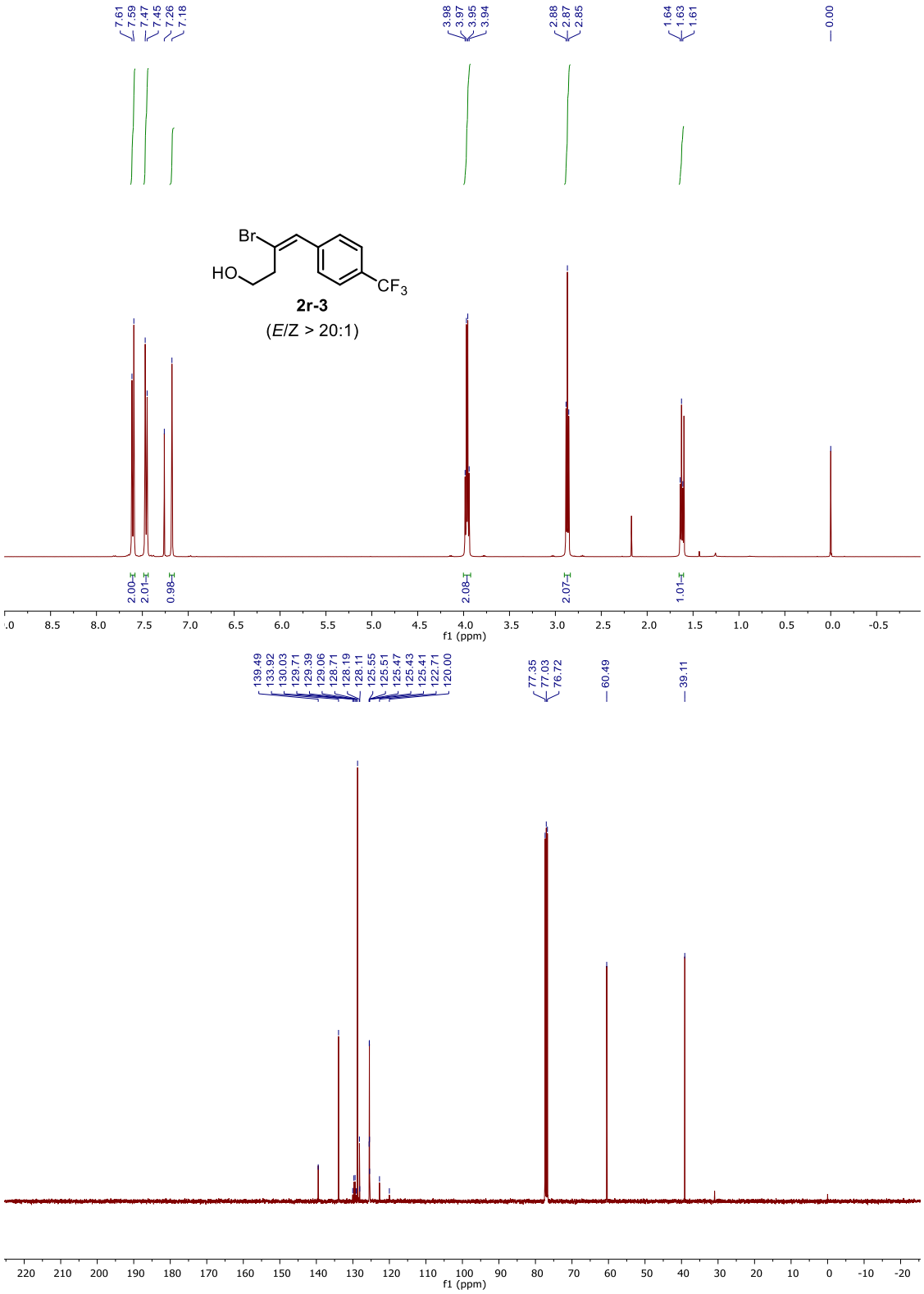


Figure 2.11 ^{19}F-NMR Spectrum of **2r-3**

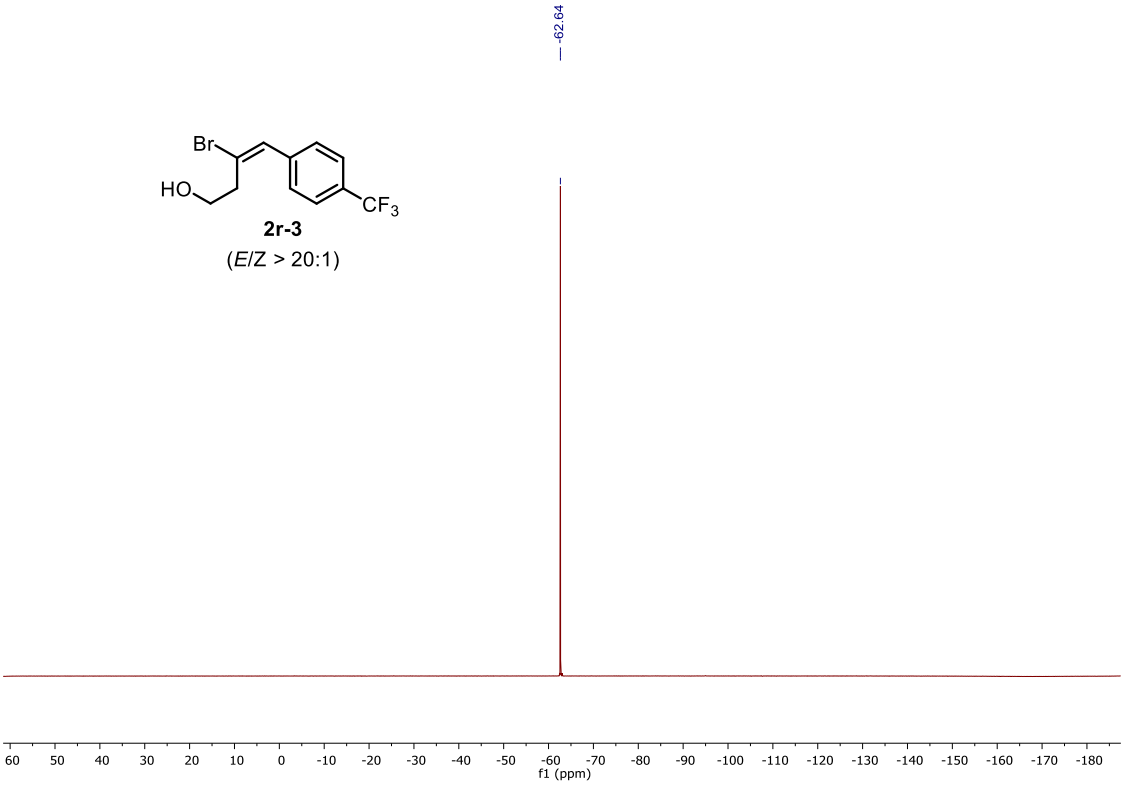


Figure 2.12 ^{1}H-NMR and ^{13}C-NMR Spectra of **2r**

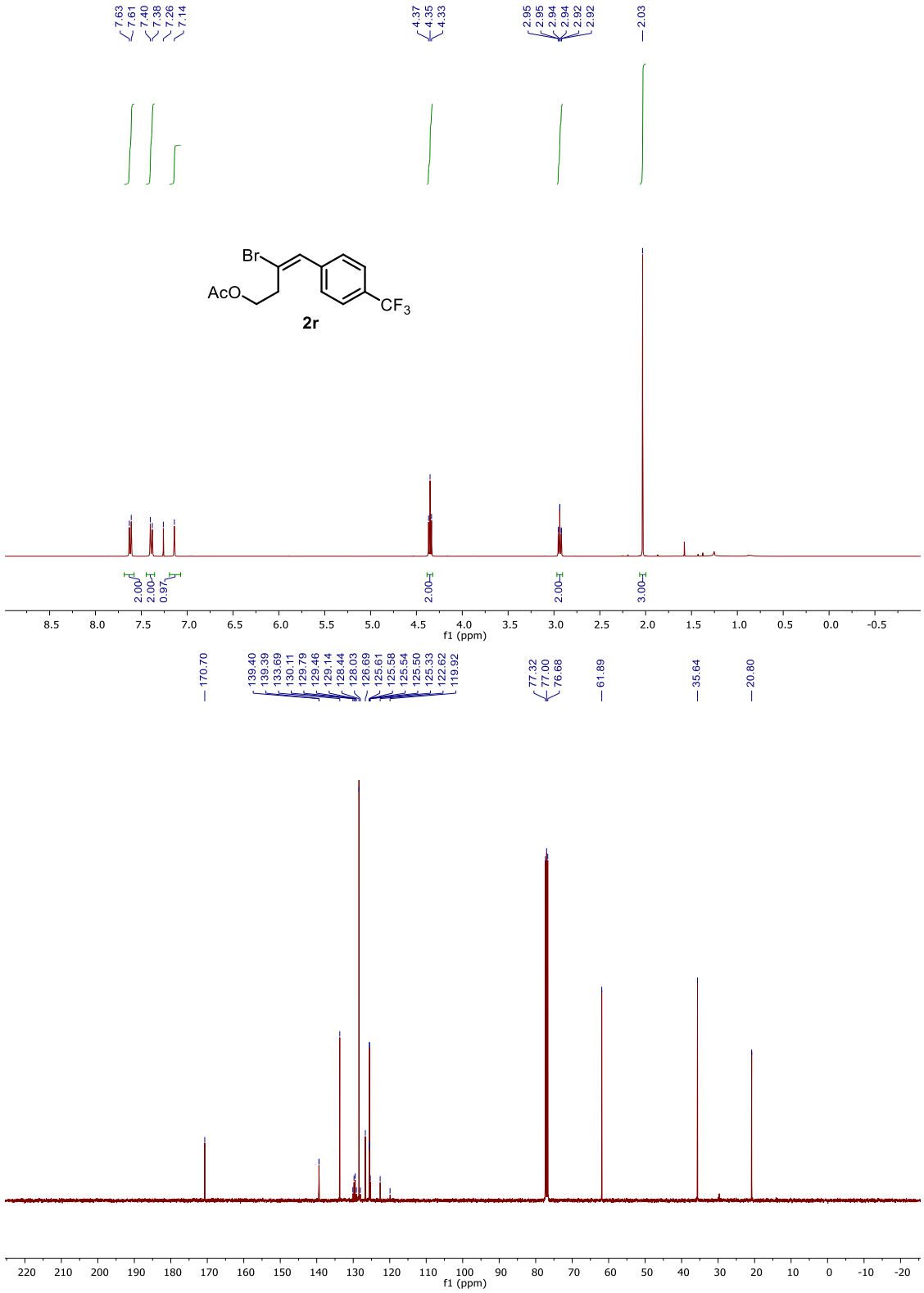


Figure 2.13 ^{19}F-NMR Spectrum of **2r**

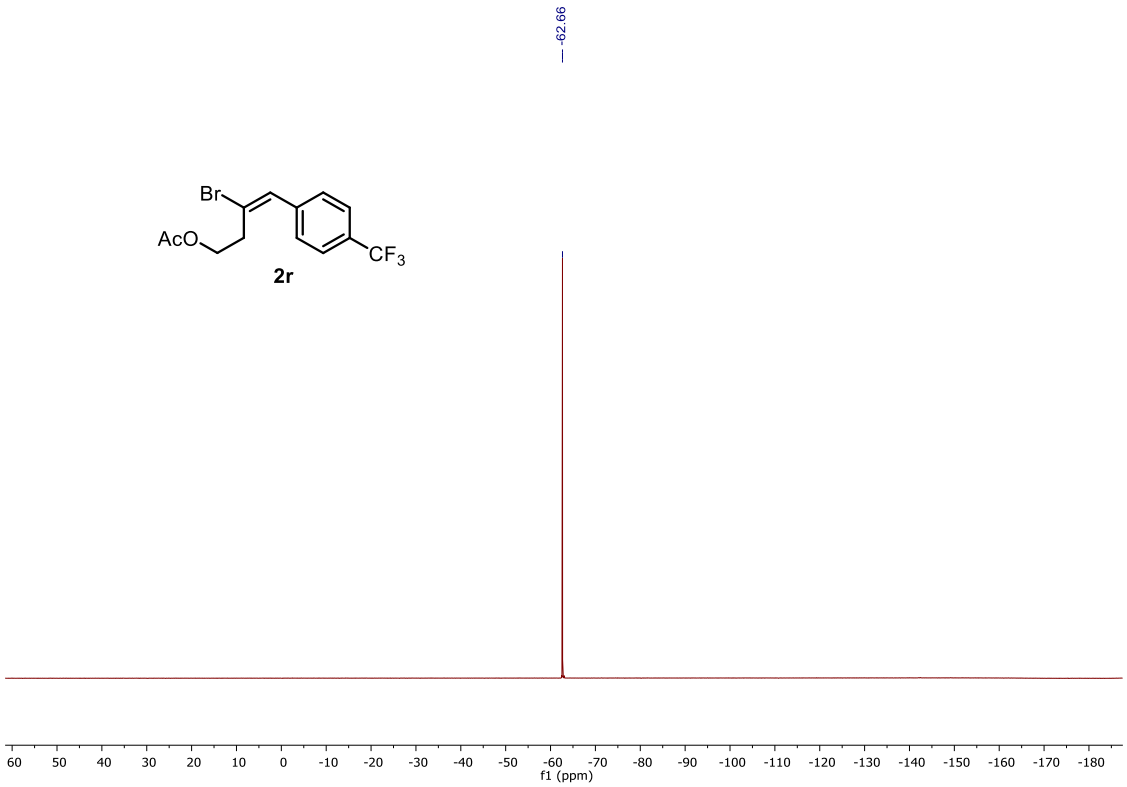


Figure 2.14 ^{1}H-NMR and ^{13}C-NMR Spectra of **2s**

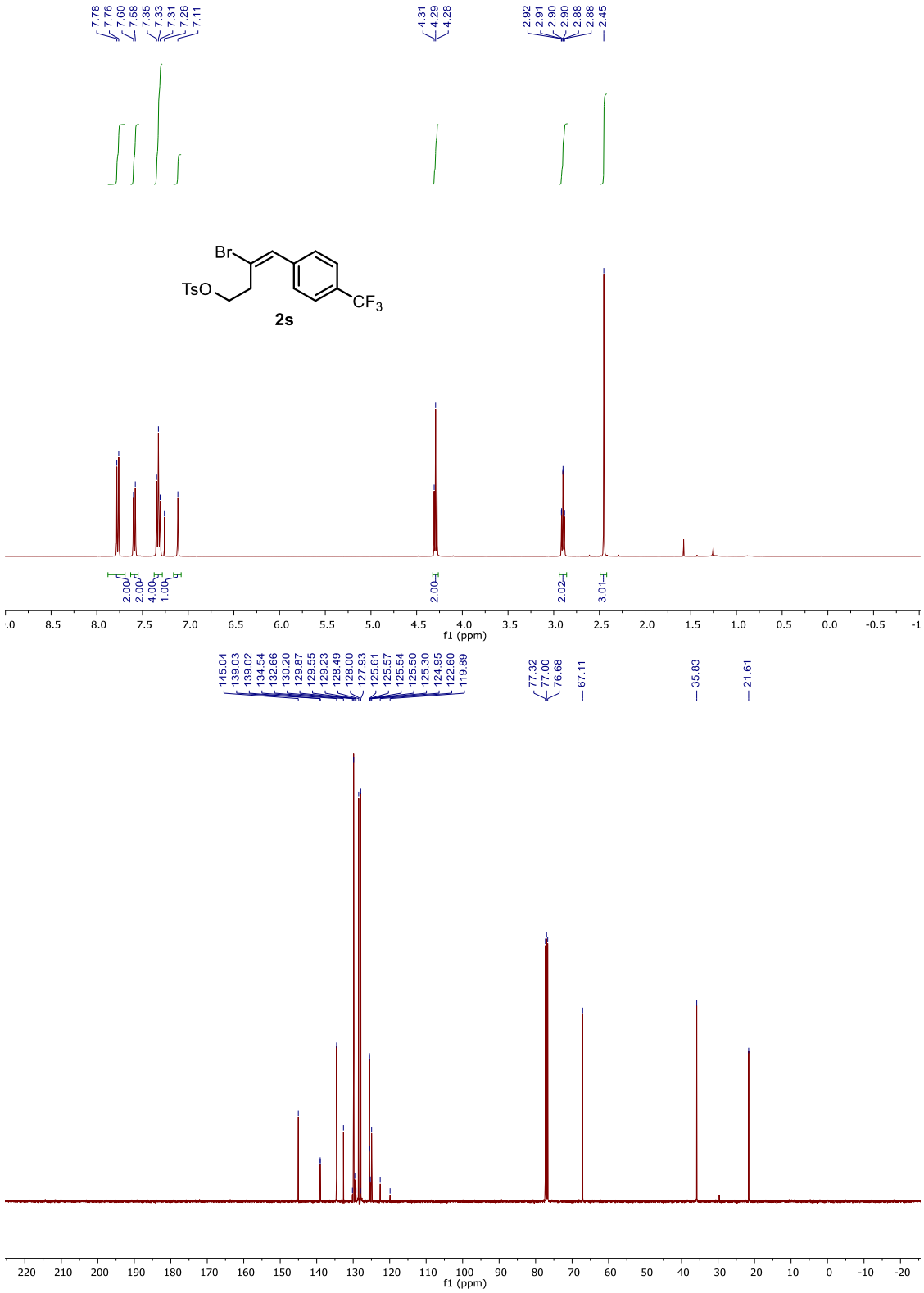


Figure 2.15 ^{1}H-NMR and ^{13}C-NMR Spectra of **2s**

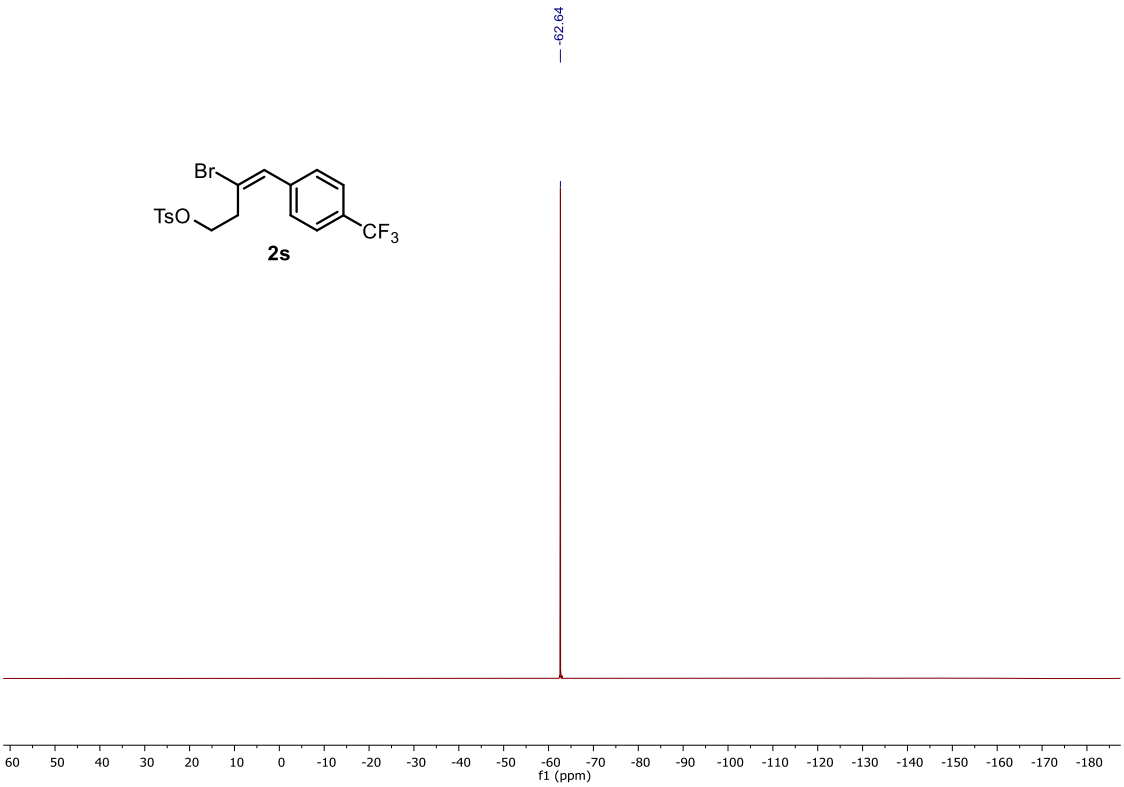


Figure 2.16 ^{1}H-NMR and ^{13}C-NMR Spectra of **2t**

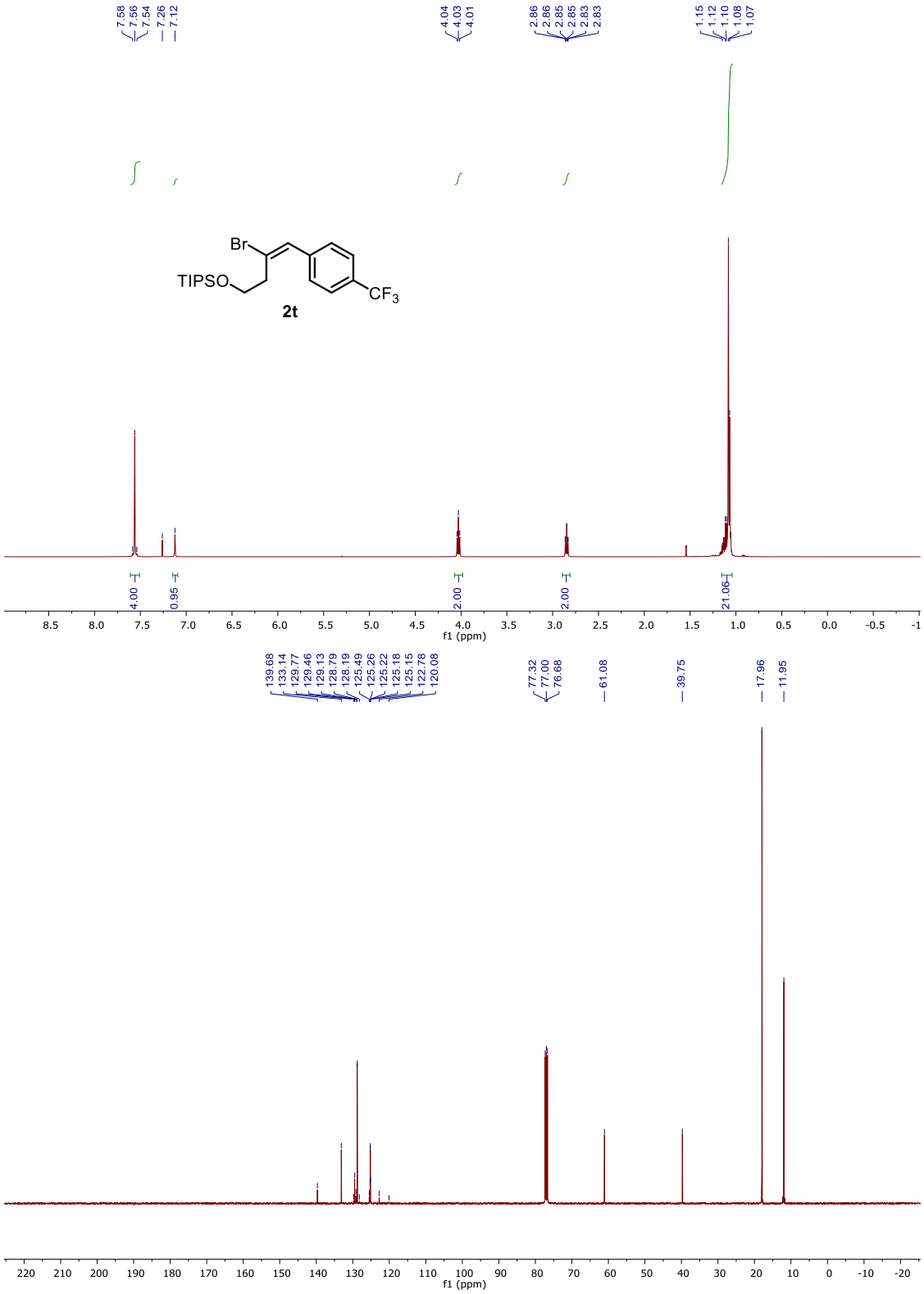


Figure 2.17 ^{19}F-NMR Spectrum of **2t**

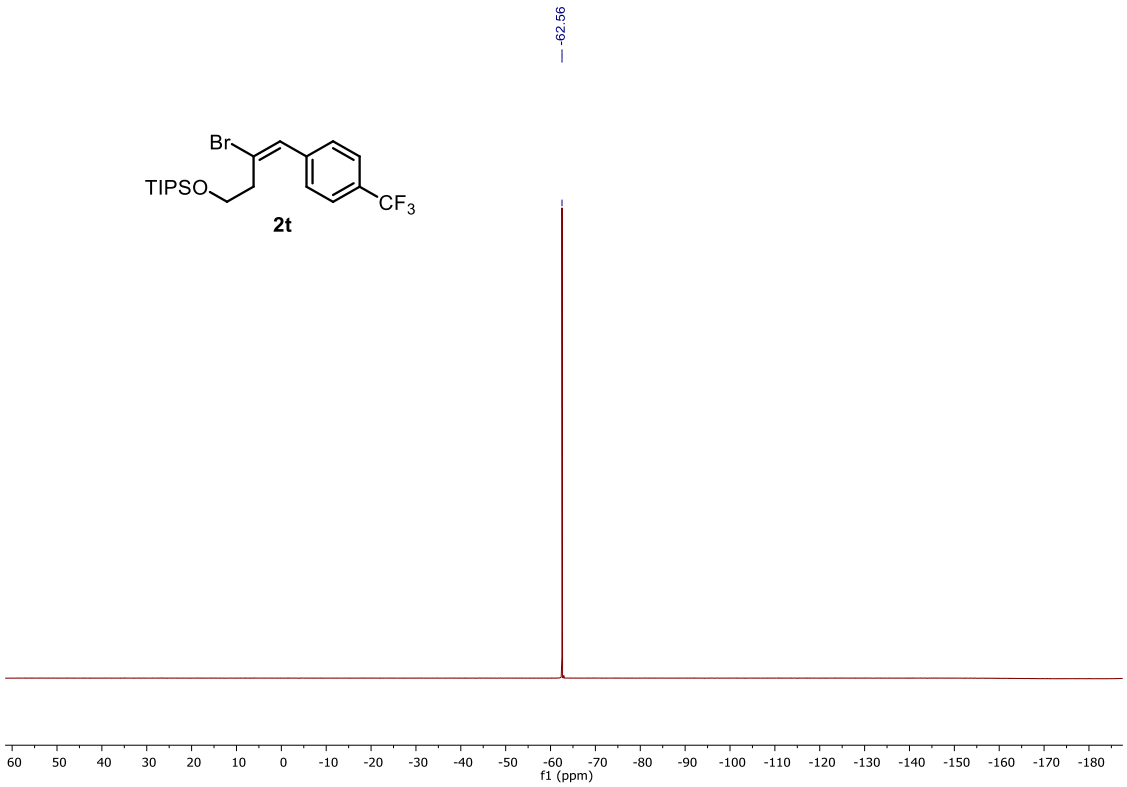


Figure 2.18 ^{1}H-NMR and ^{13}C-NMR Spectra of **1f**

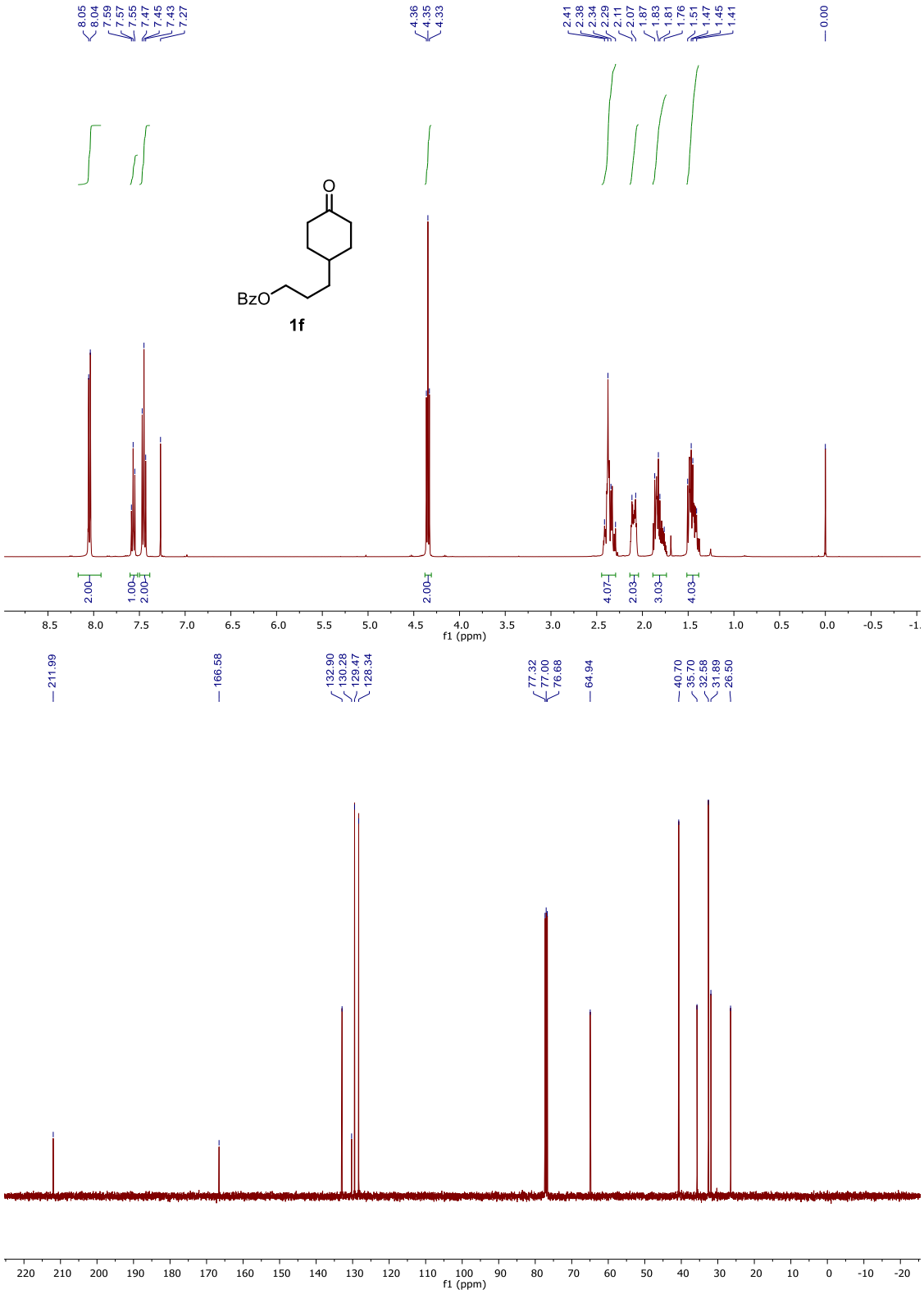


Figure 2.19 ^{1}H-NMR and ^{13}C-NMR Spectra of **1g**

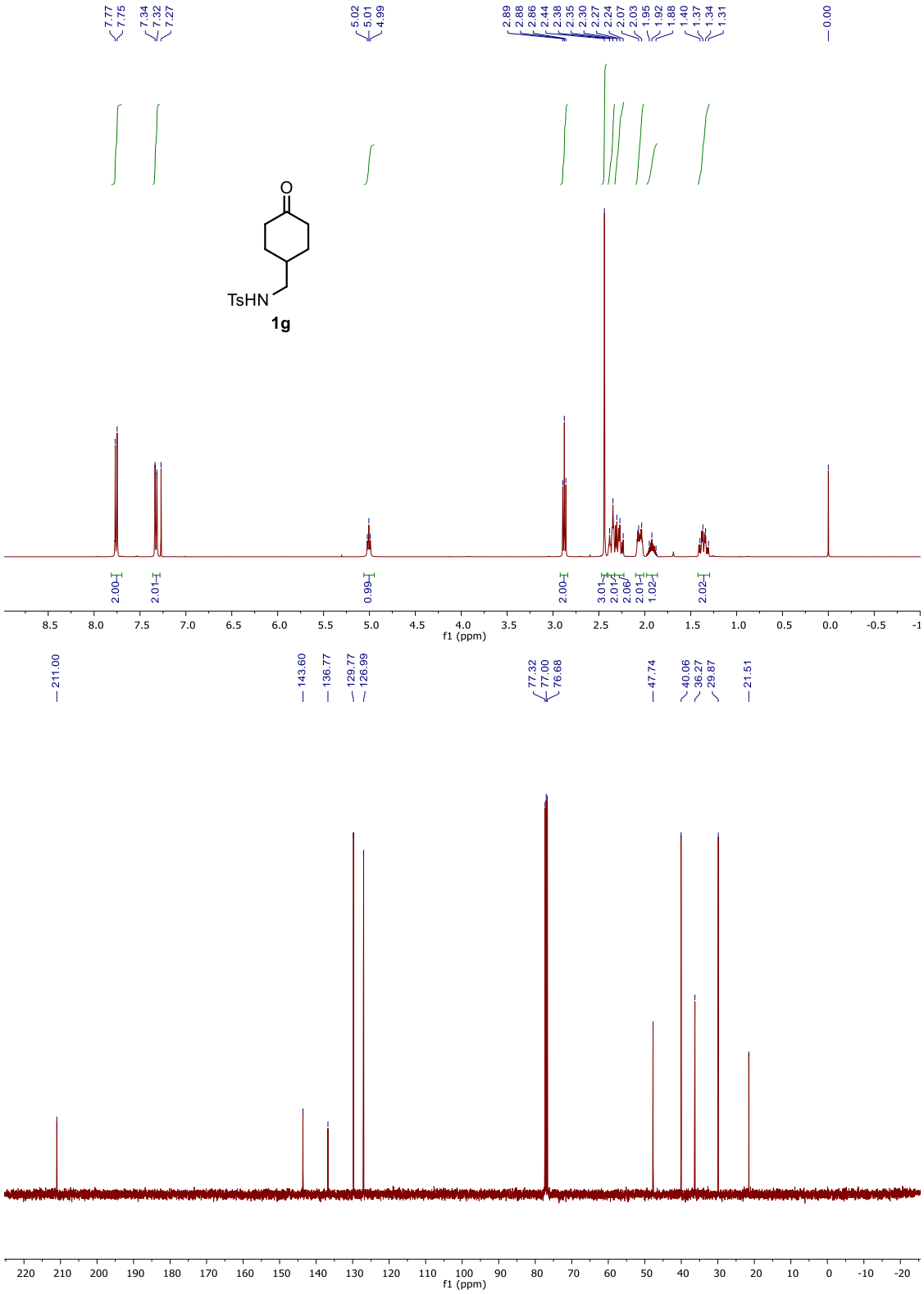


Figure 2.20 ^{1}H-NMR and ^{13}C-NMR Spectra of **3a**

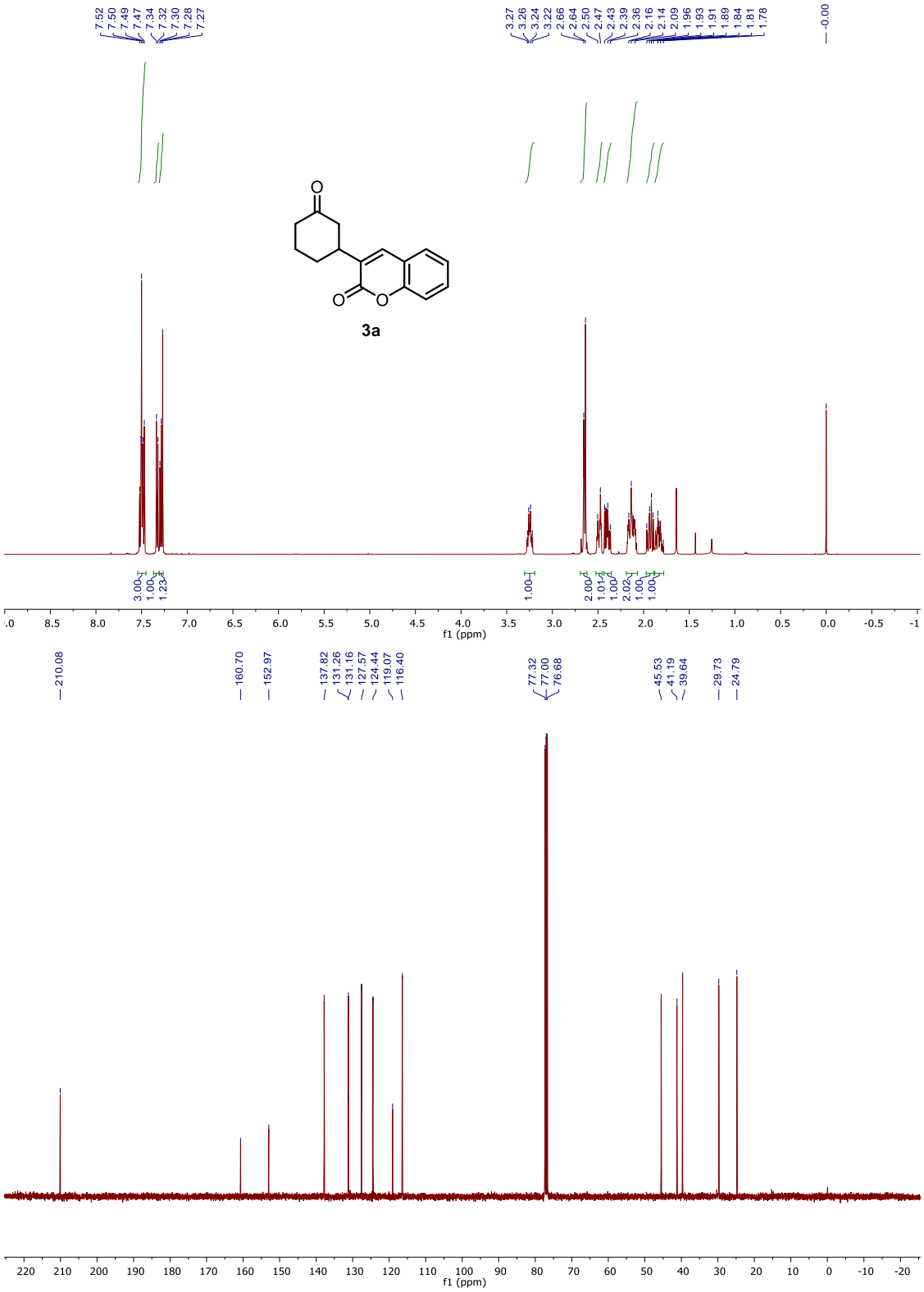


Figure 2.21 ^{1}H-NMR and ^{13}C-NMR Spectra of **3b**

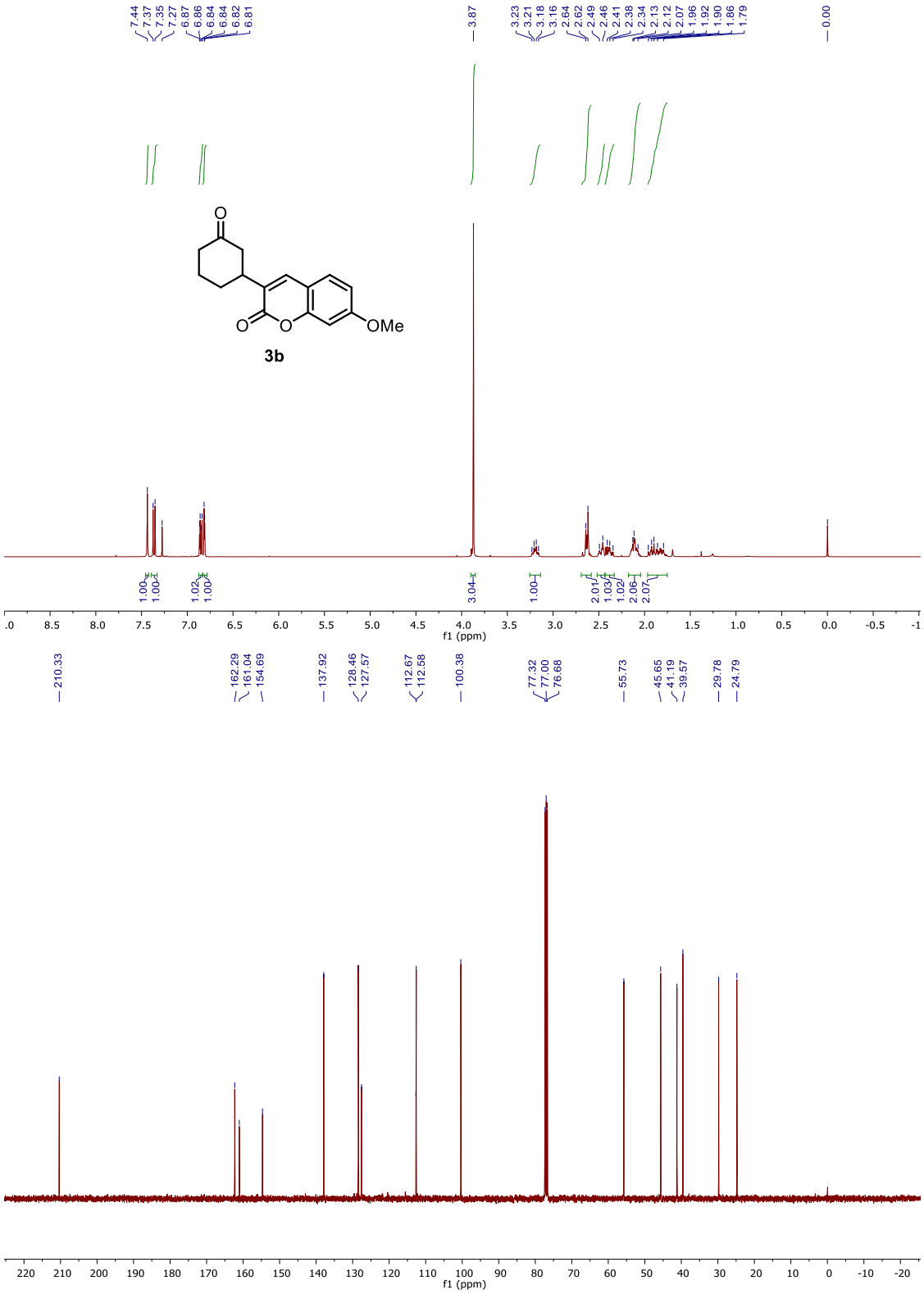


Figure 2.22 ^{1}H-NMR and ^{13}C-NMR Spectra of **3c**

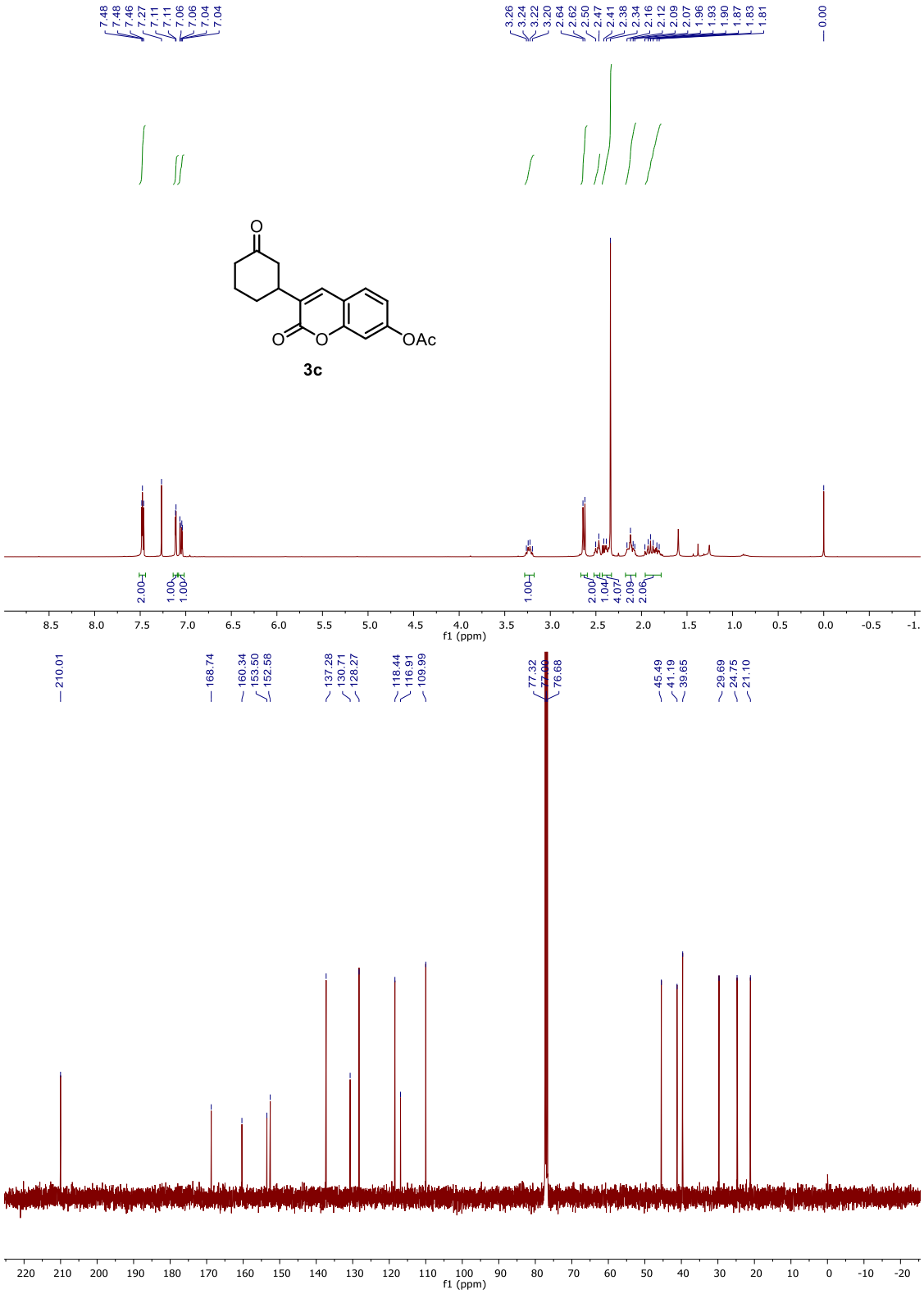


Figure 2.23 ^{1}H-NMR and ^{13}C-NMR Spectra of **3d**

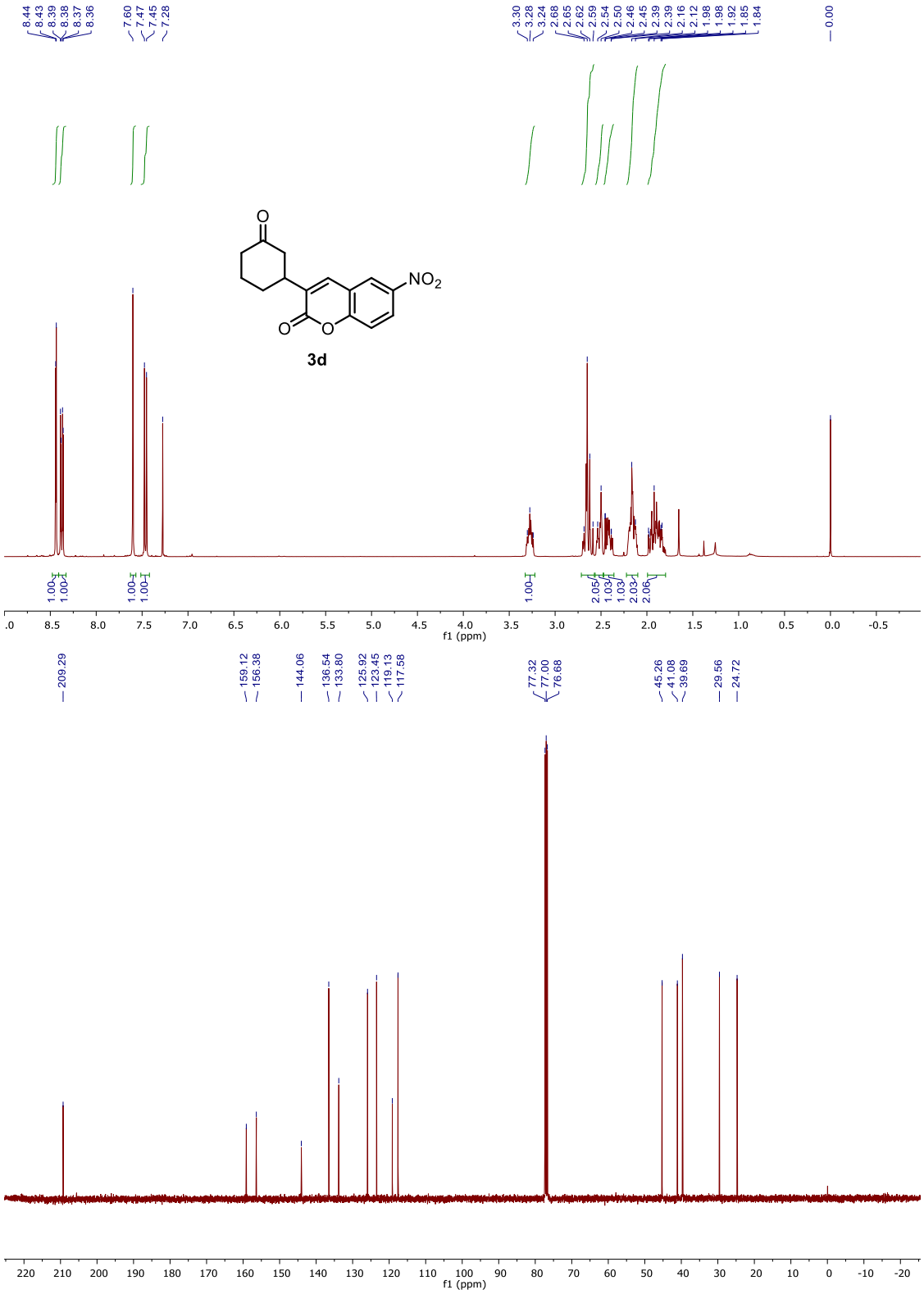


Figure 2.24 ^{1}H-NMR and ^{13}C-NMR Spectra of **3e**

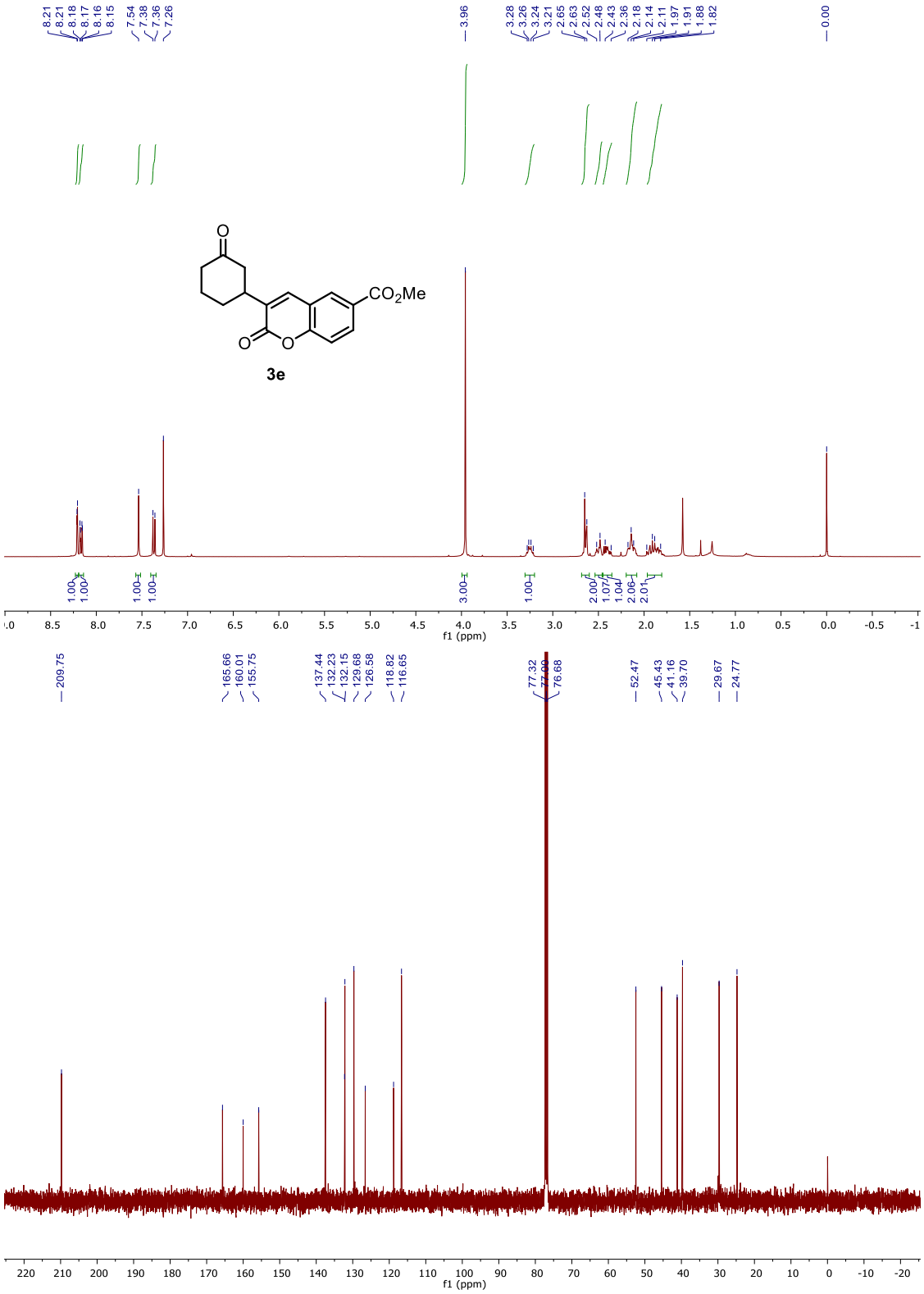


Figure 2.25 ^{1}H-NMR and ^{13}C-NMR Spectra of **3f**

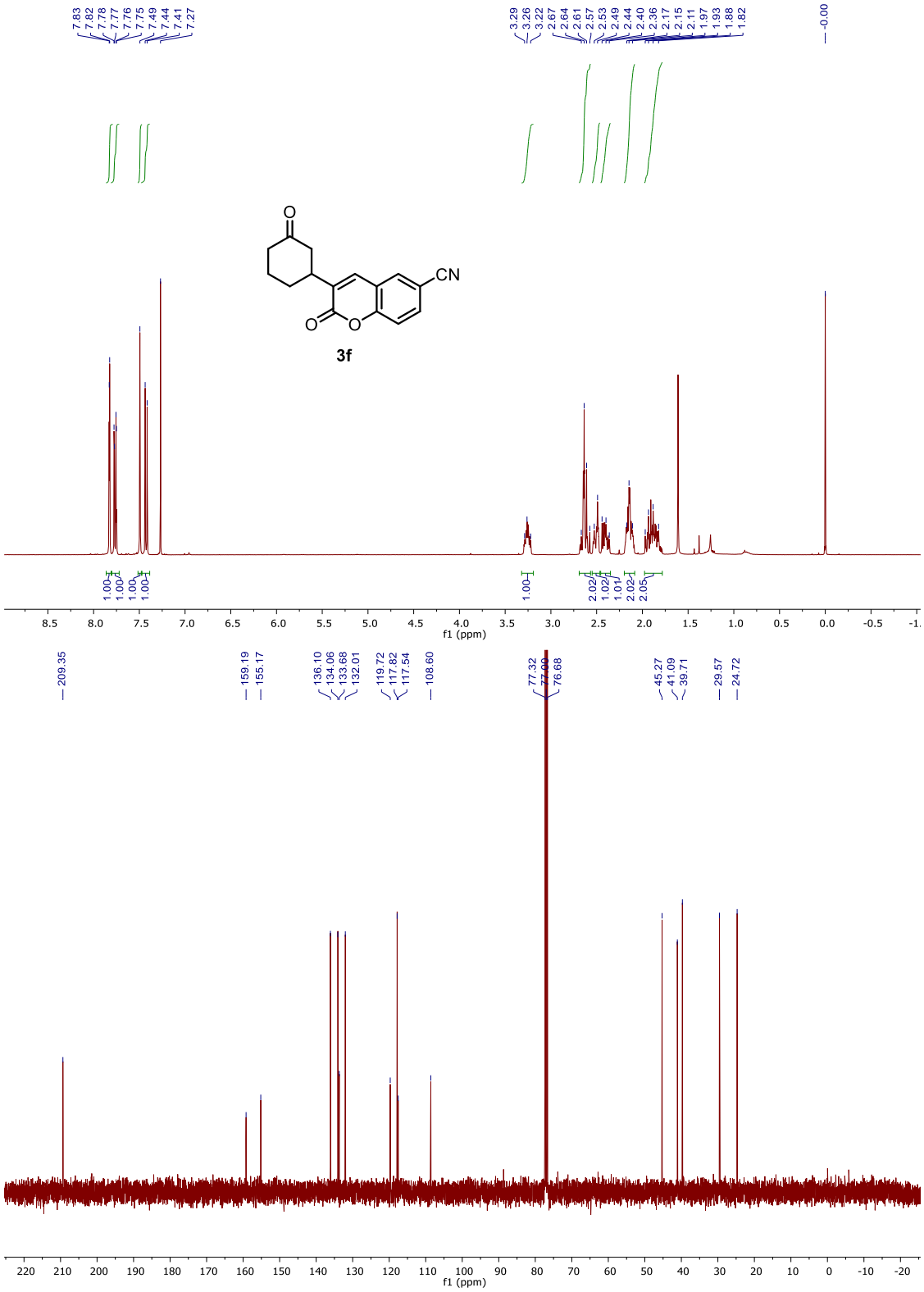


Figure 2.26 ^{1}H-NMR and ^{13}C-NMR Spectra of **3g**

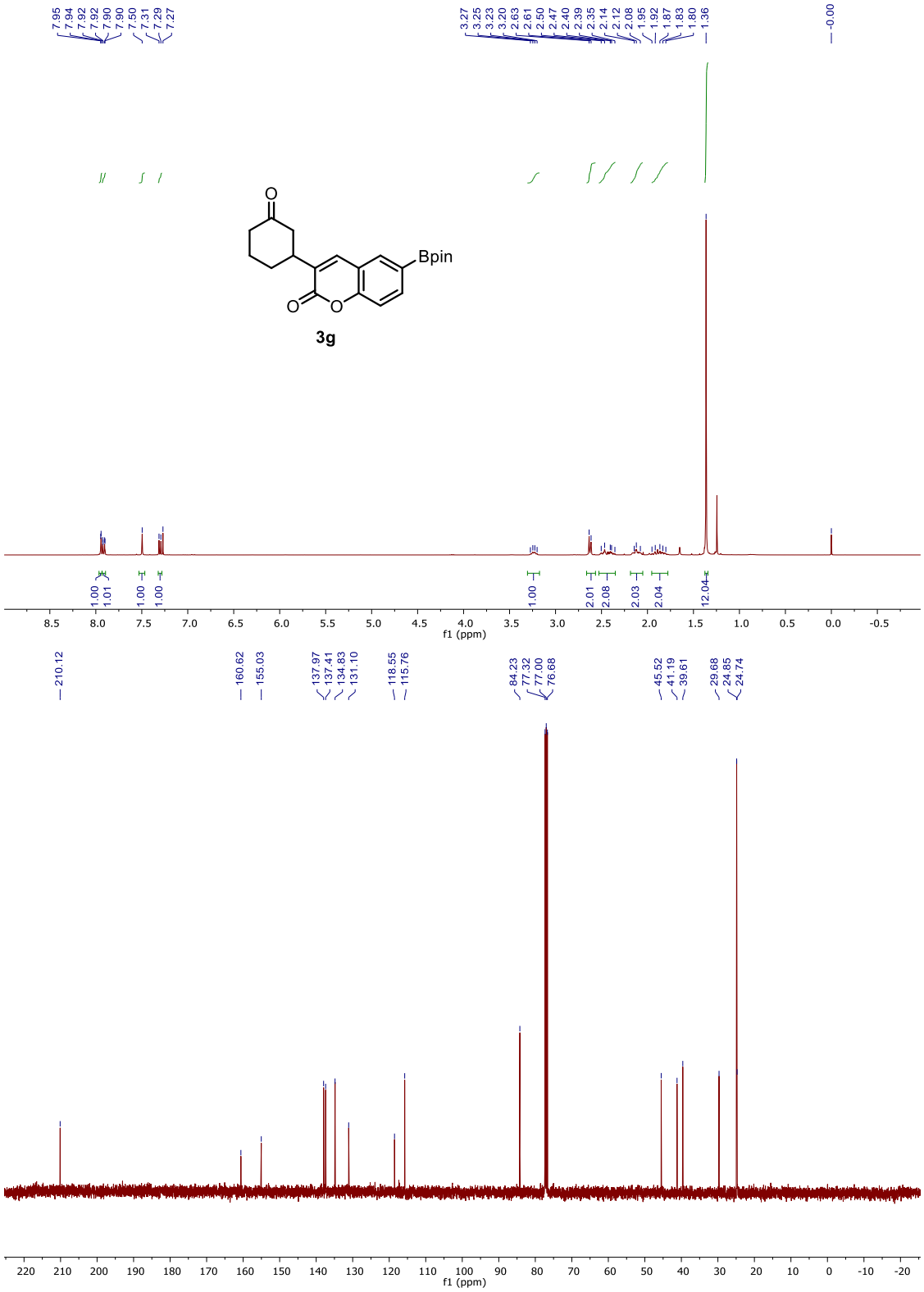


Figure 2.27 ^{1}H-NMR and ^{13}C-NMR Spectra of **3h**

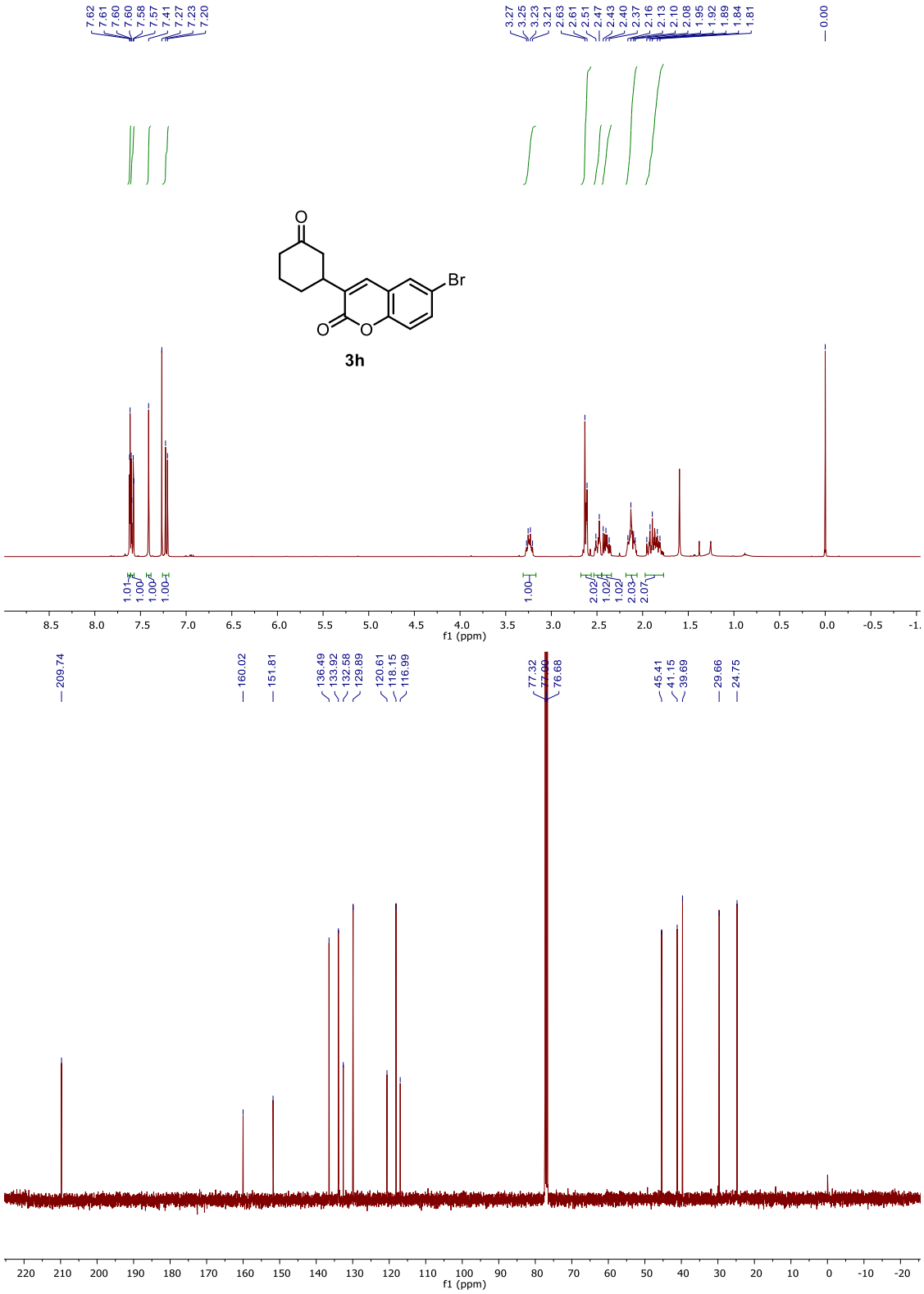


Figure 2.28 ^{1}H-NMR and ^{13}C-NMR Spectra of **3i**

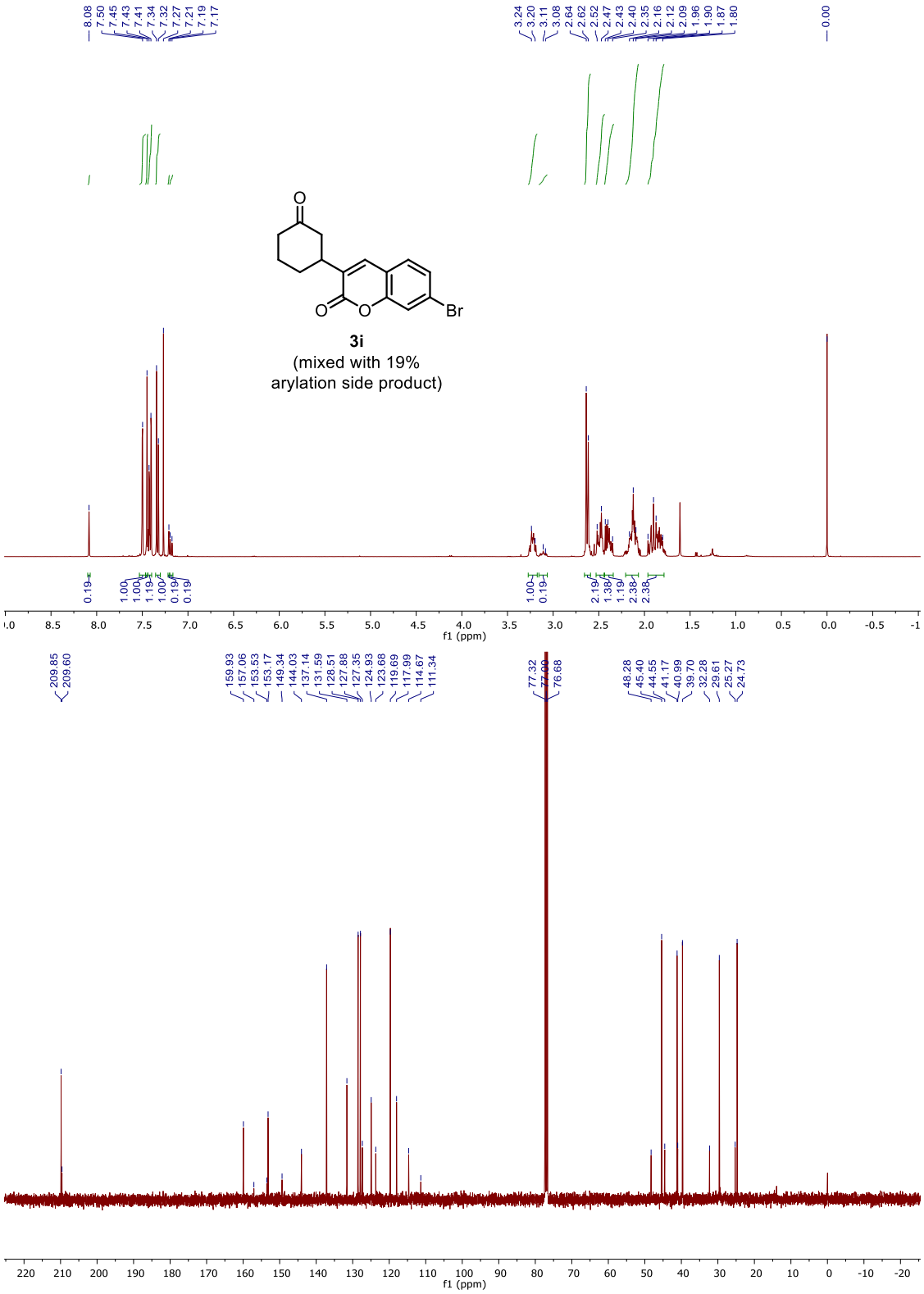


Figure 2.29 ^{1}H-NMR and ^{13}C-NMR Spectra of **3j**

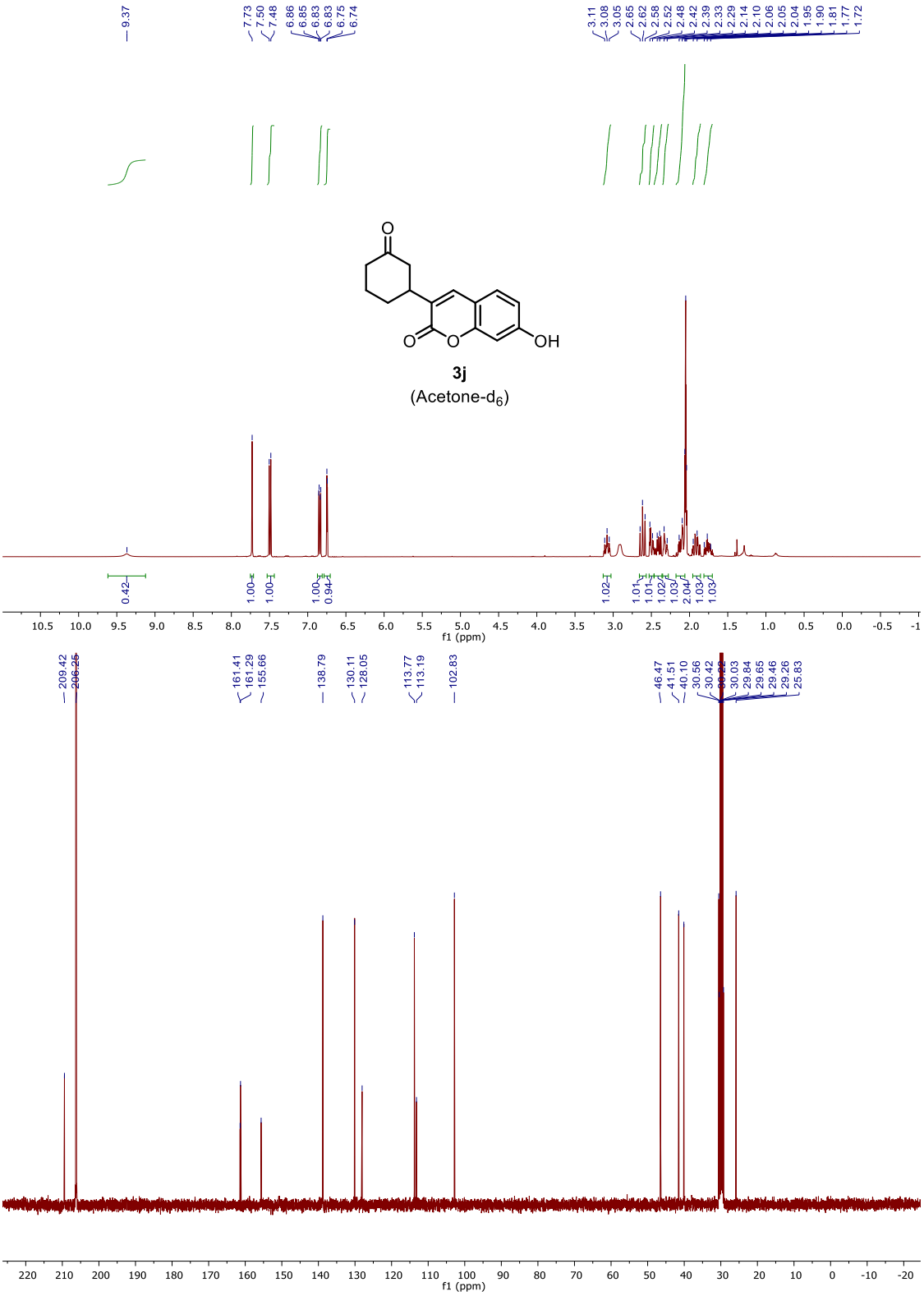


Figure 2.30 ^{1}H-NMR and ^{13}C-NMR Spectra of **3k**

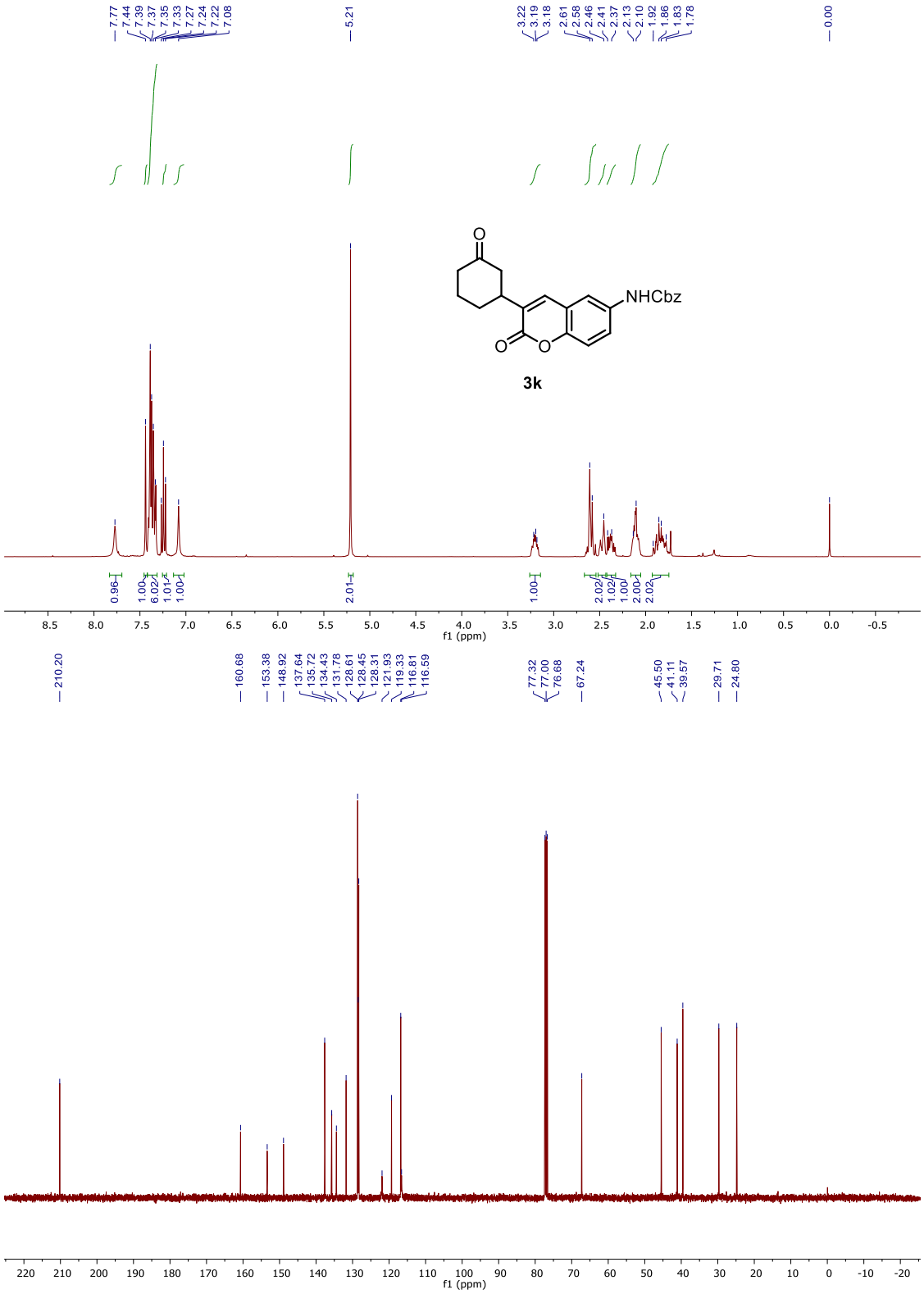


Figure 2.31 ^{1}H-NMR and ^{13}C-NMR Spectra of **3l**

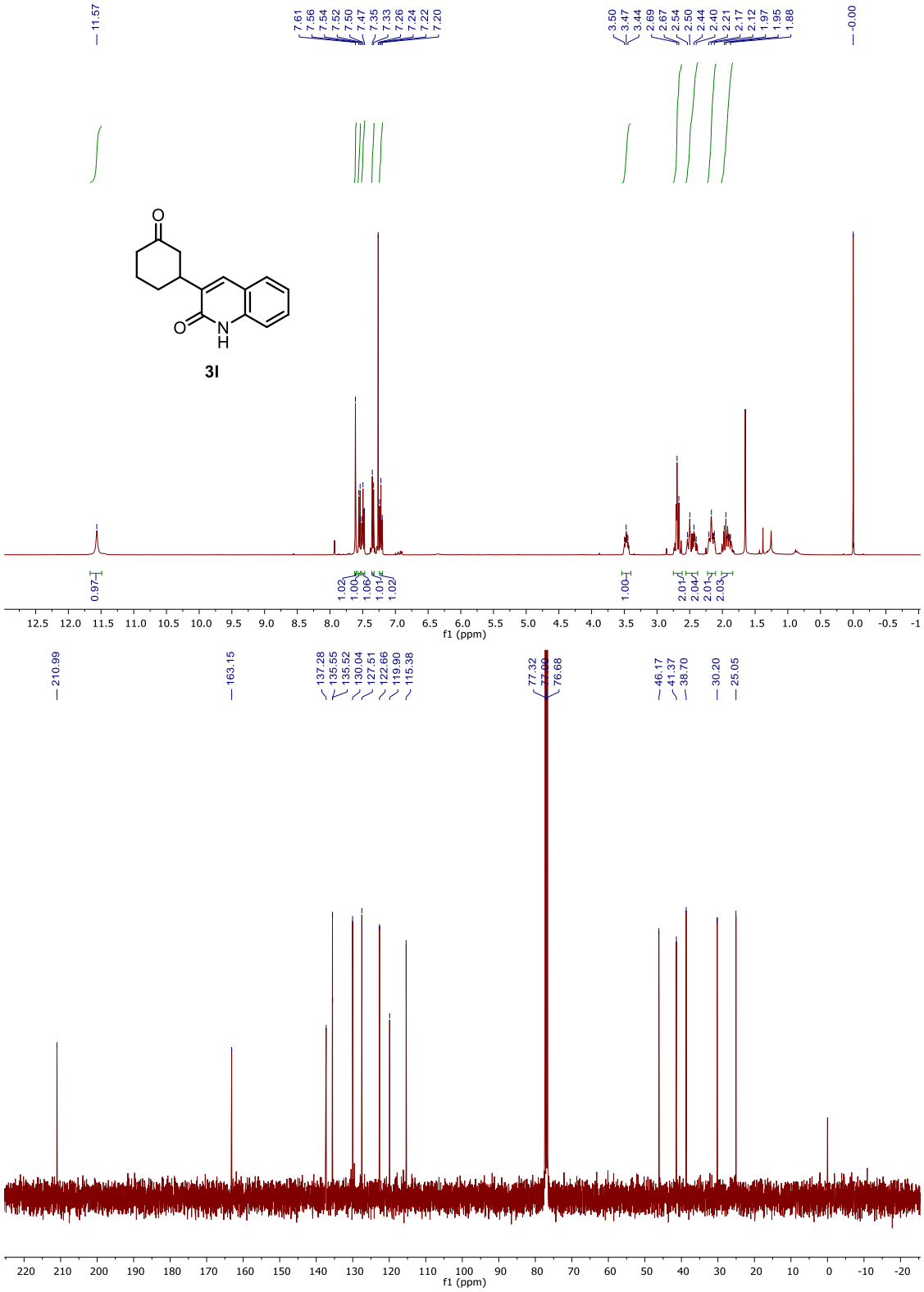


Figure 2.32 ^{1}H-NMR and ^{13}C-NMR Spectra of **3m**

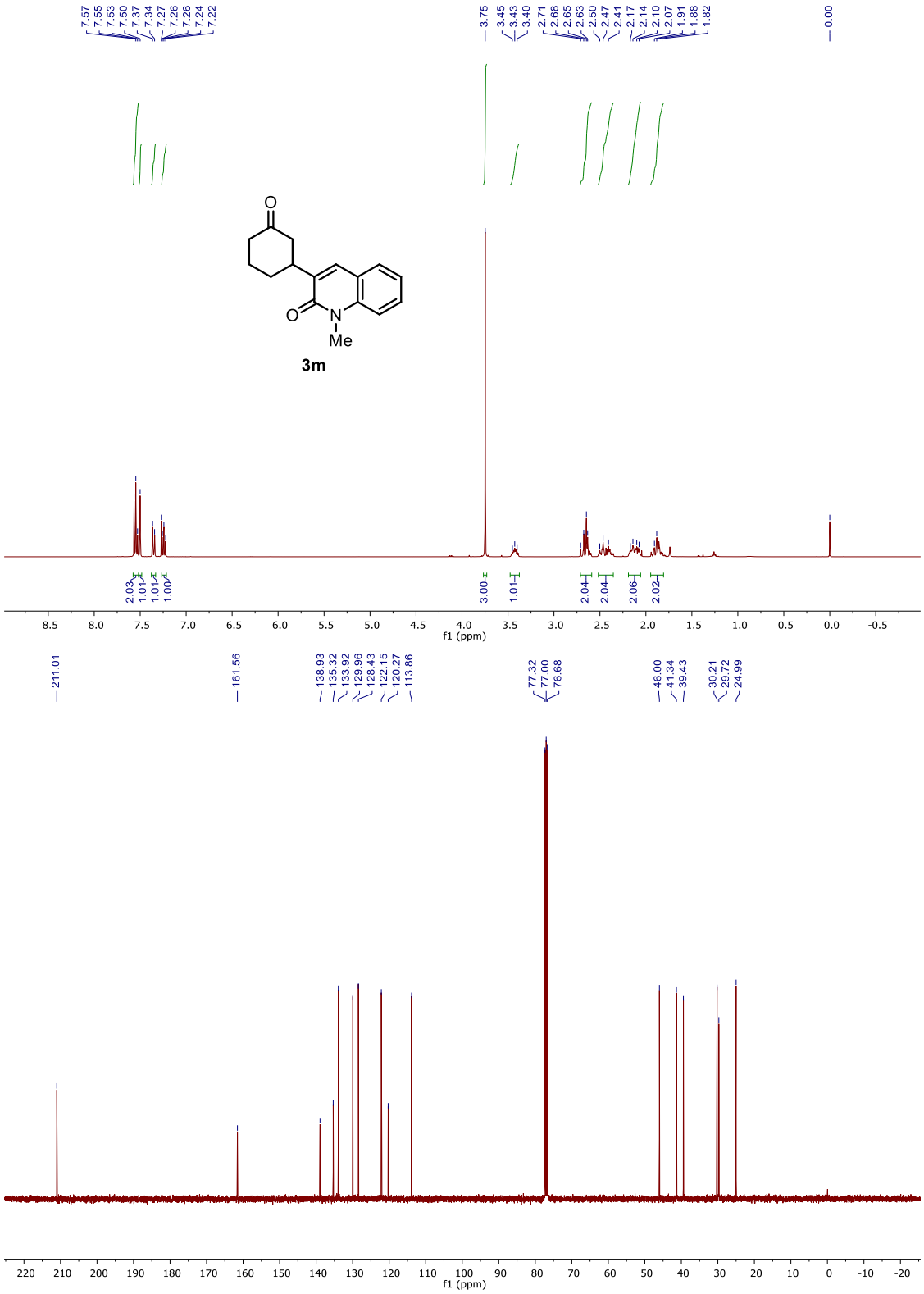


Figure 2.33 ^{1}H-NMR and ^{13}C-NMR Spectra of **3n**

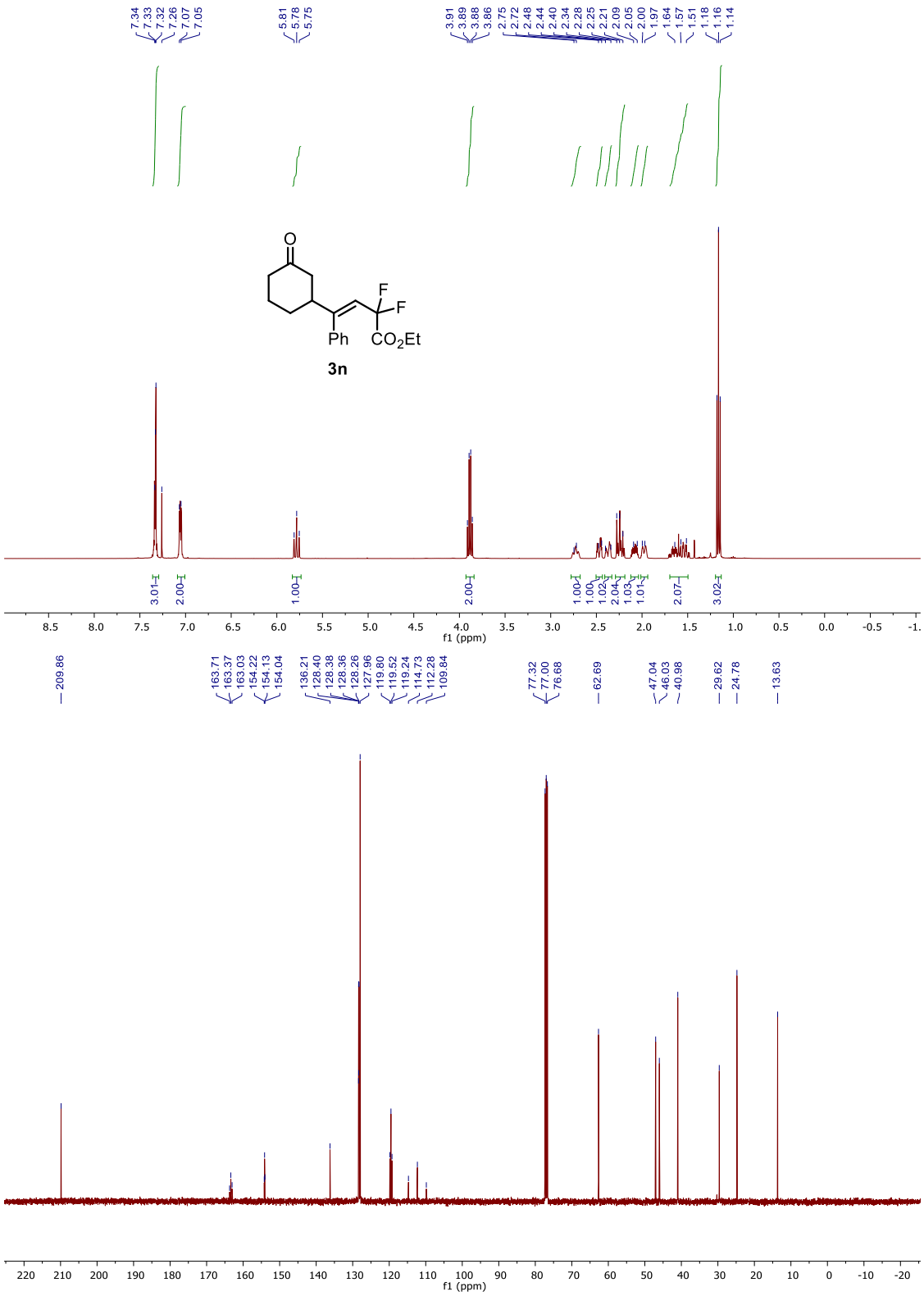


Figure 2.34 ^{19}F-NMR Spectrum of **3n**

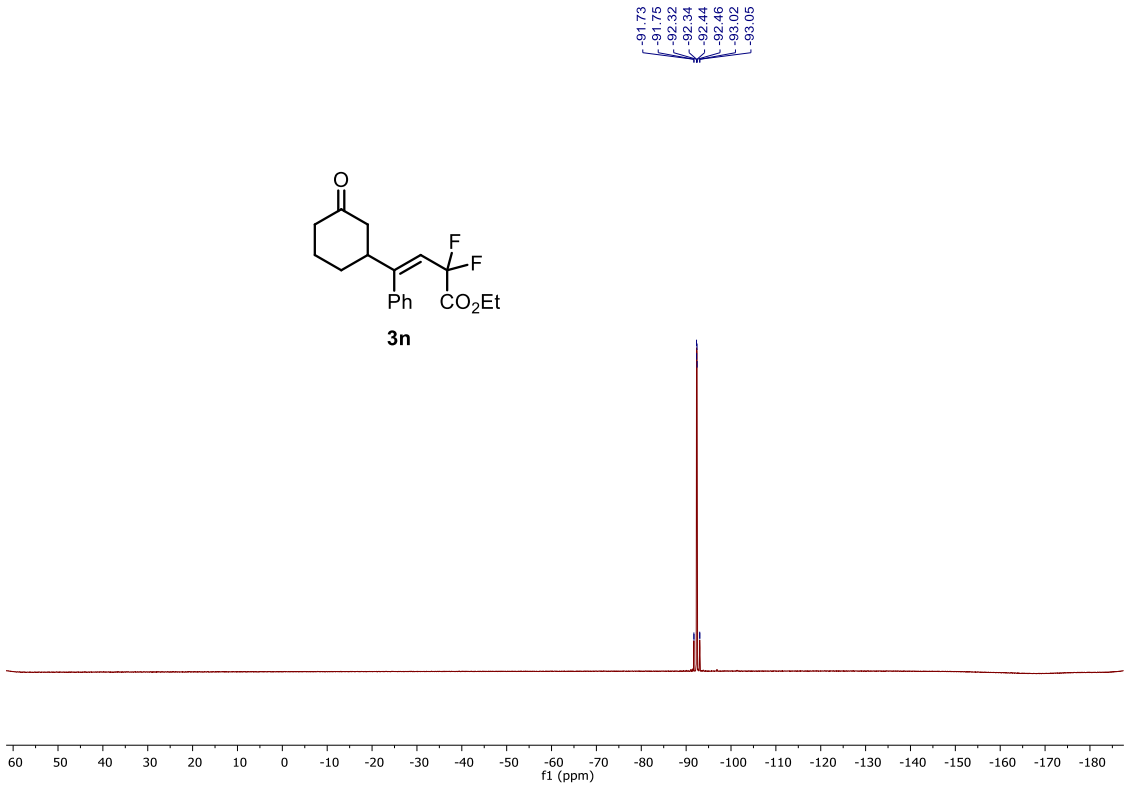


Figure 2.35 ^{1}H-NMR and ^{13}C-NMR Spectra of **3o**

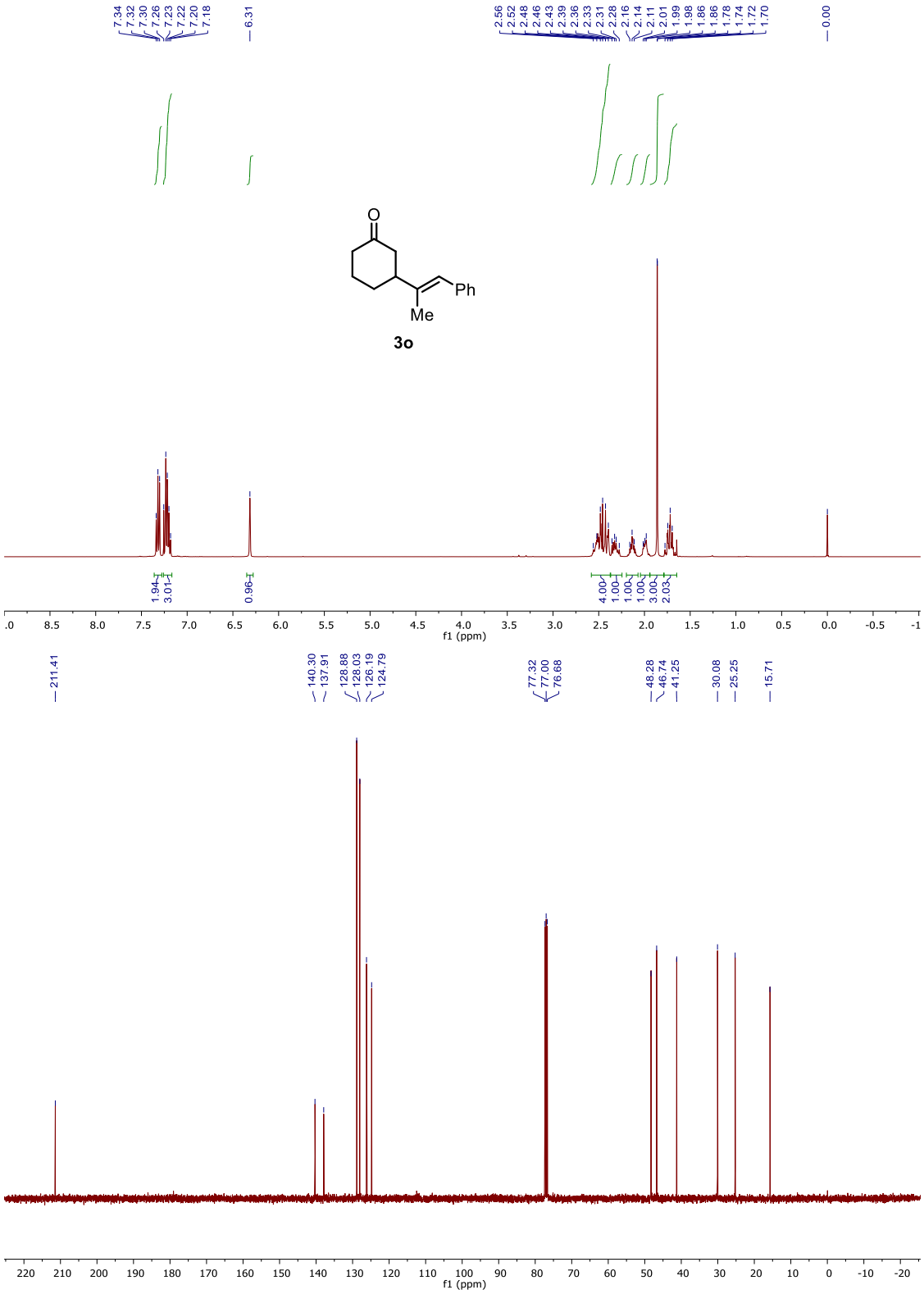


Figure 2.36 ^{1}H-NMR and ^{13}C-NMR Spectra of **3p**

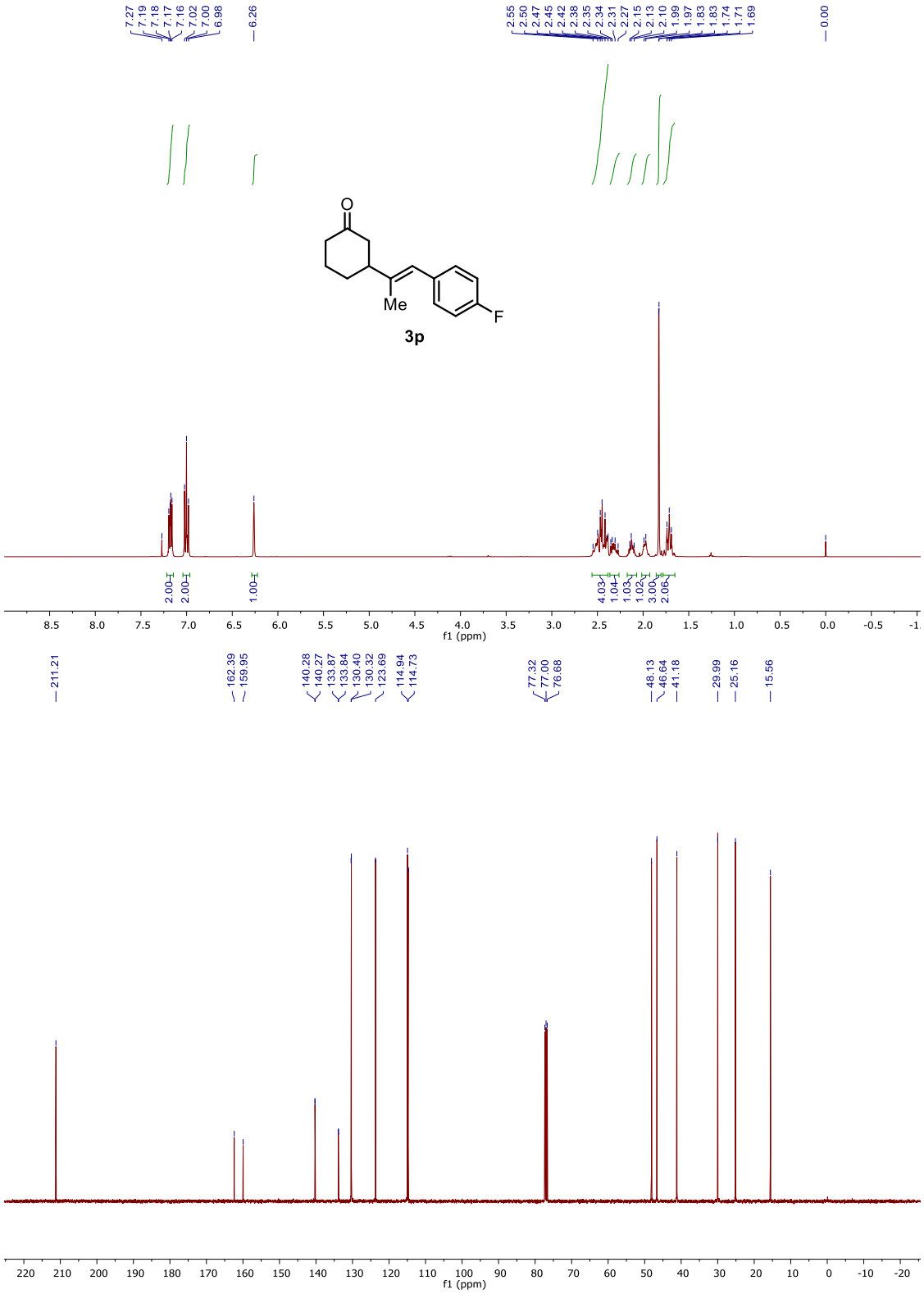


Figure 2.37 ^{19}F-NMR Spectrum of **3p**

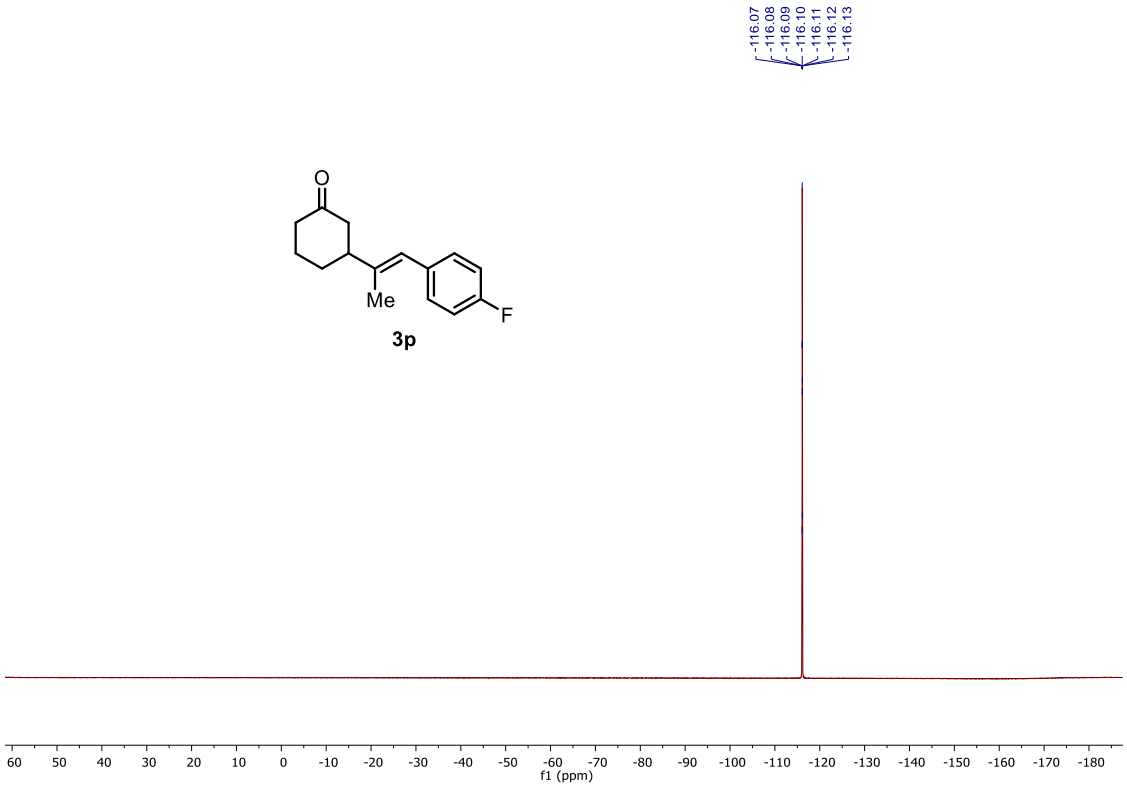


Figure 2.38 ^{1}H-NMR and ^{13}C-NMR Spectra of **3q**

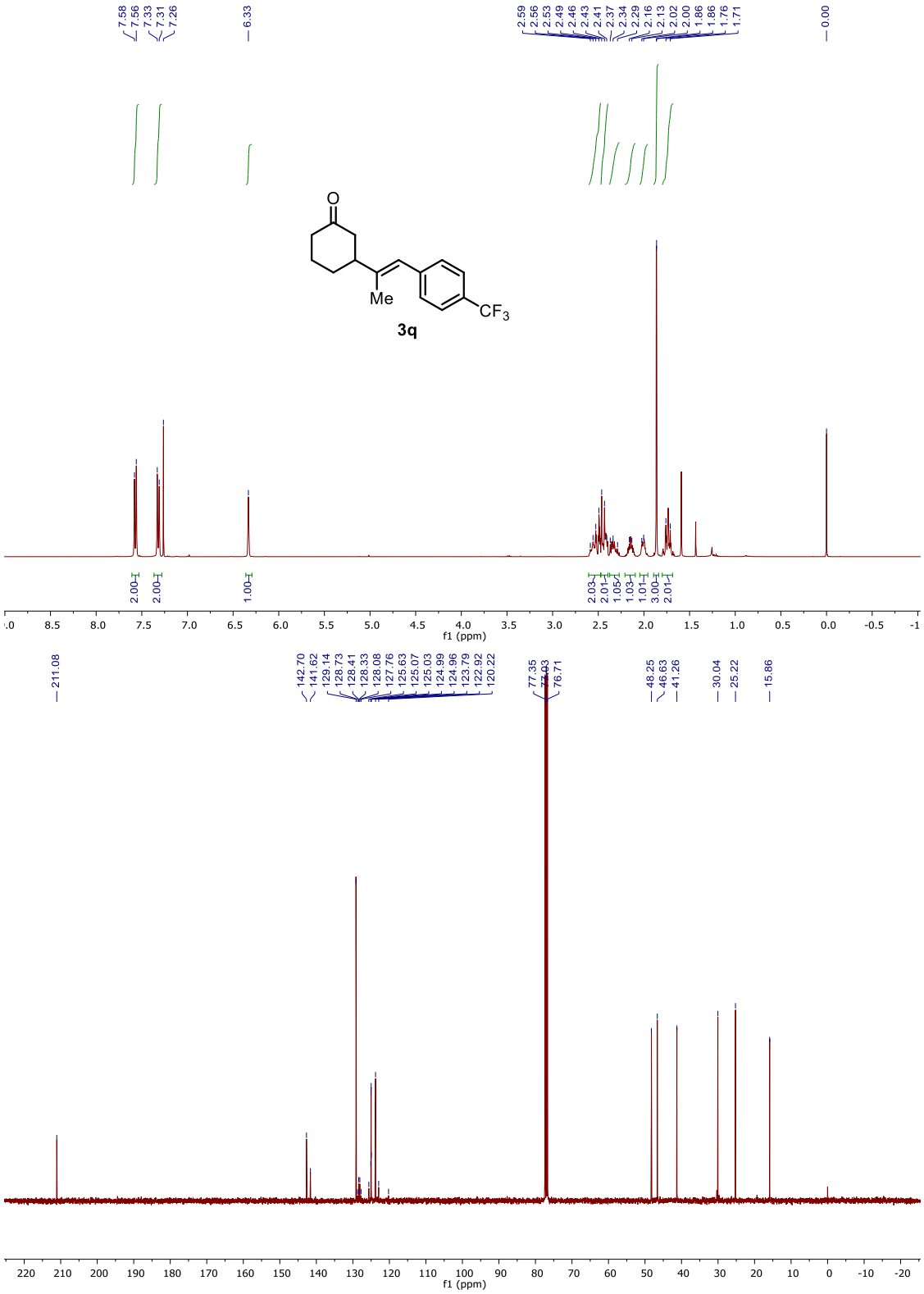


Figure 2.39 ^{1}F-NMR Spectrum of **3q**

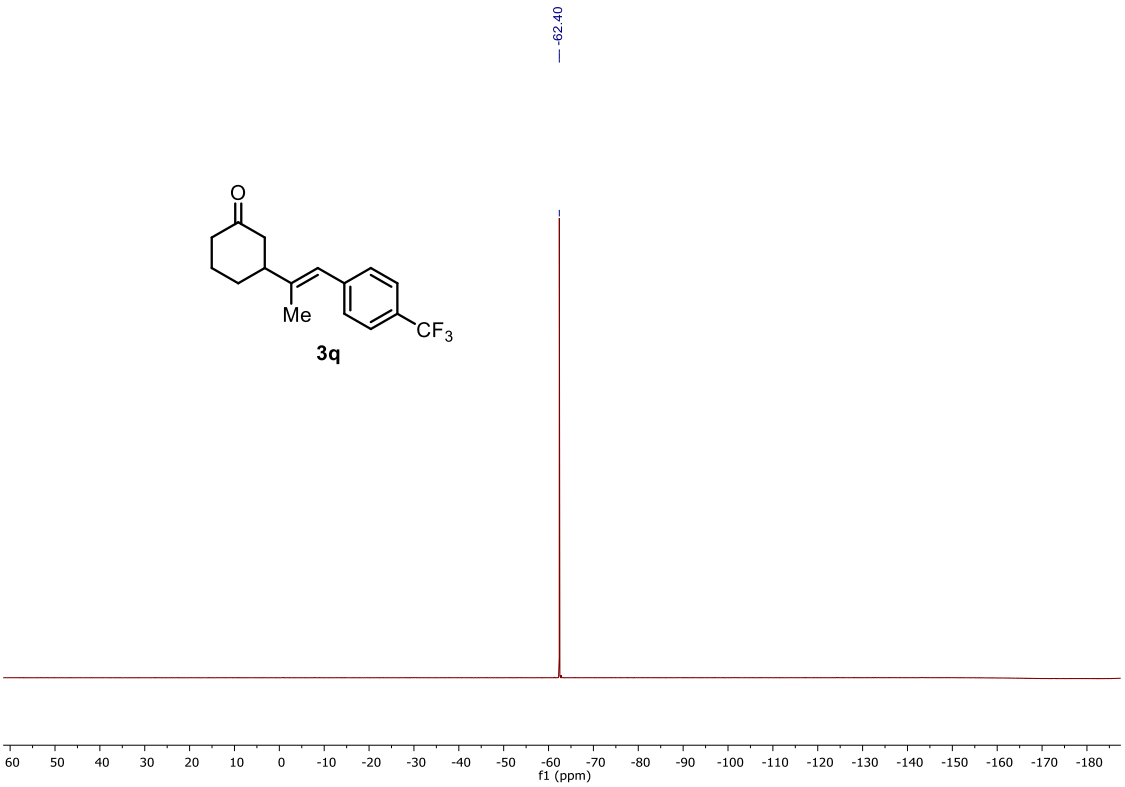


Figure 2.40 ^{1}H-NMR and ^{13}C-NMR Spectra of **3r**

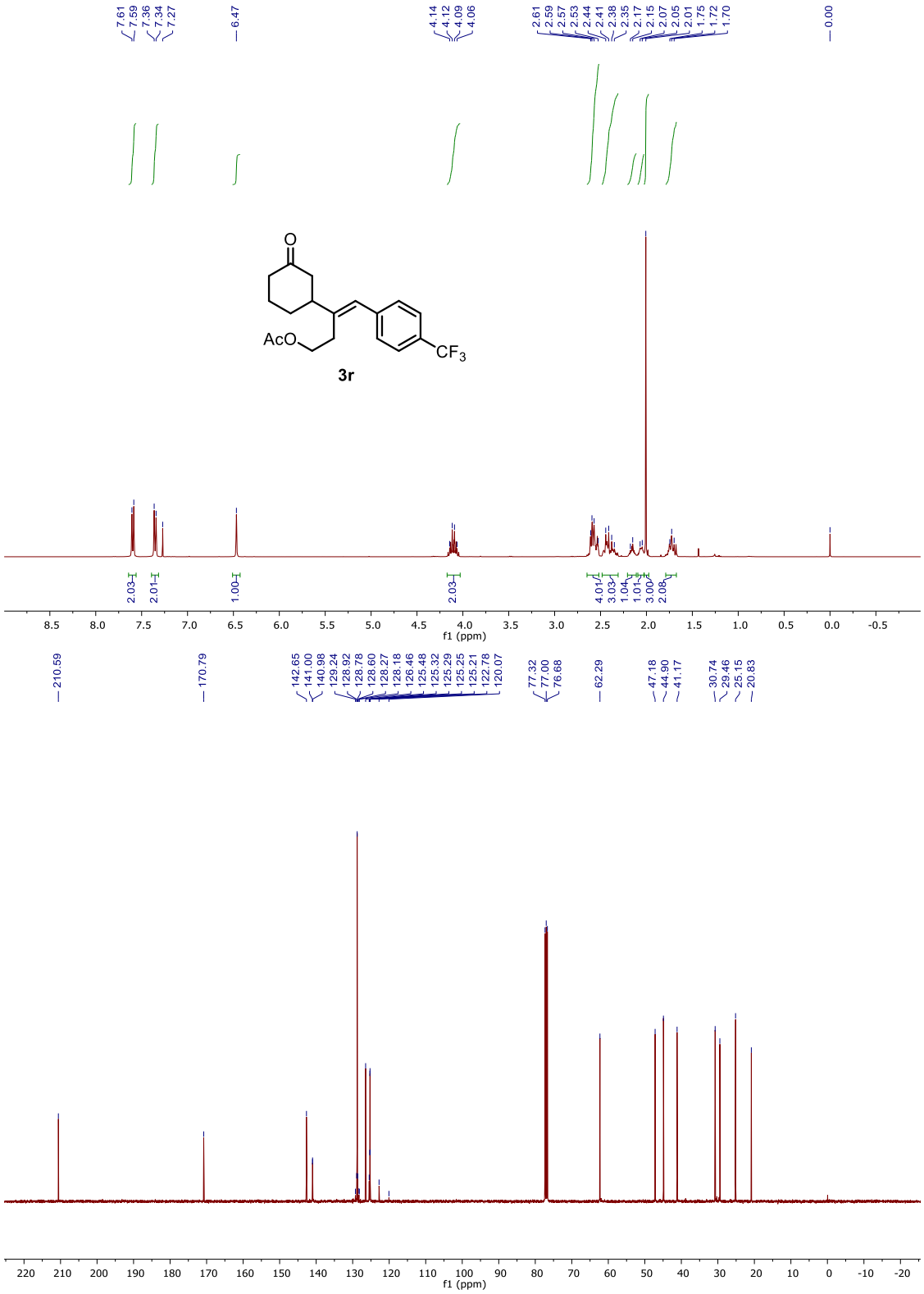


Figure 2.41 ^{19}F-NMR Spectrum of **3r**

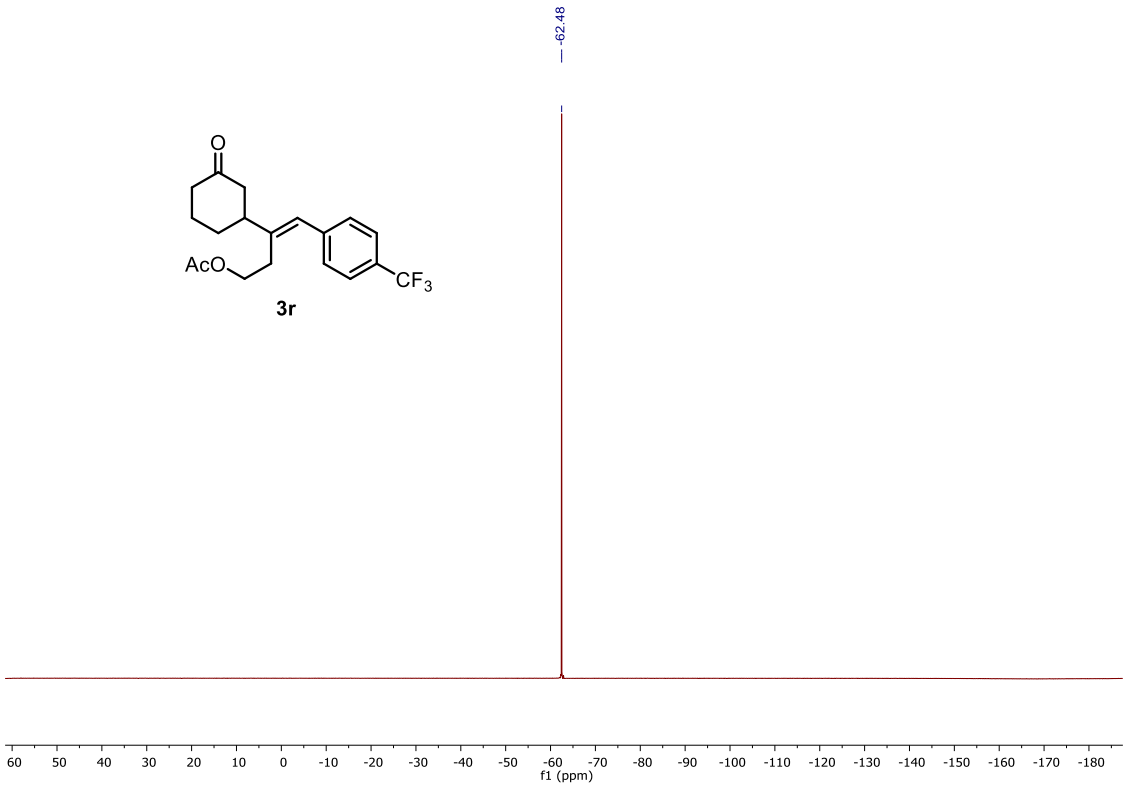


Figure 2.42 ^{1}H-NMR and ^{13}C-NMR Spectra of **3s**

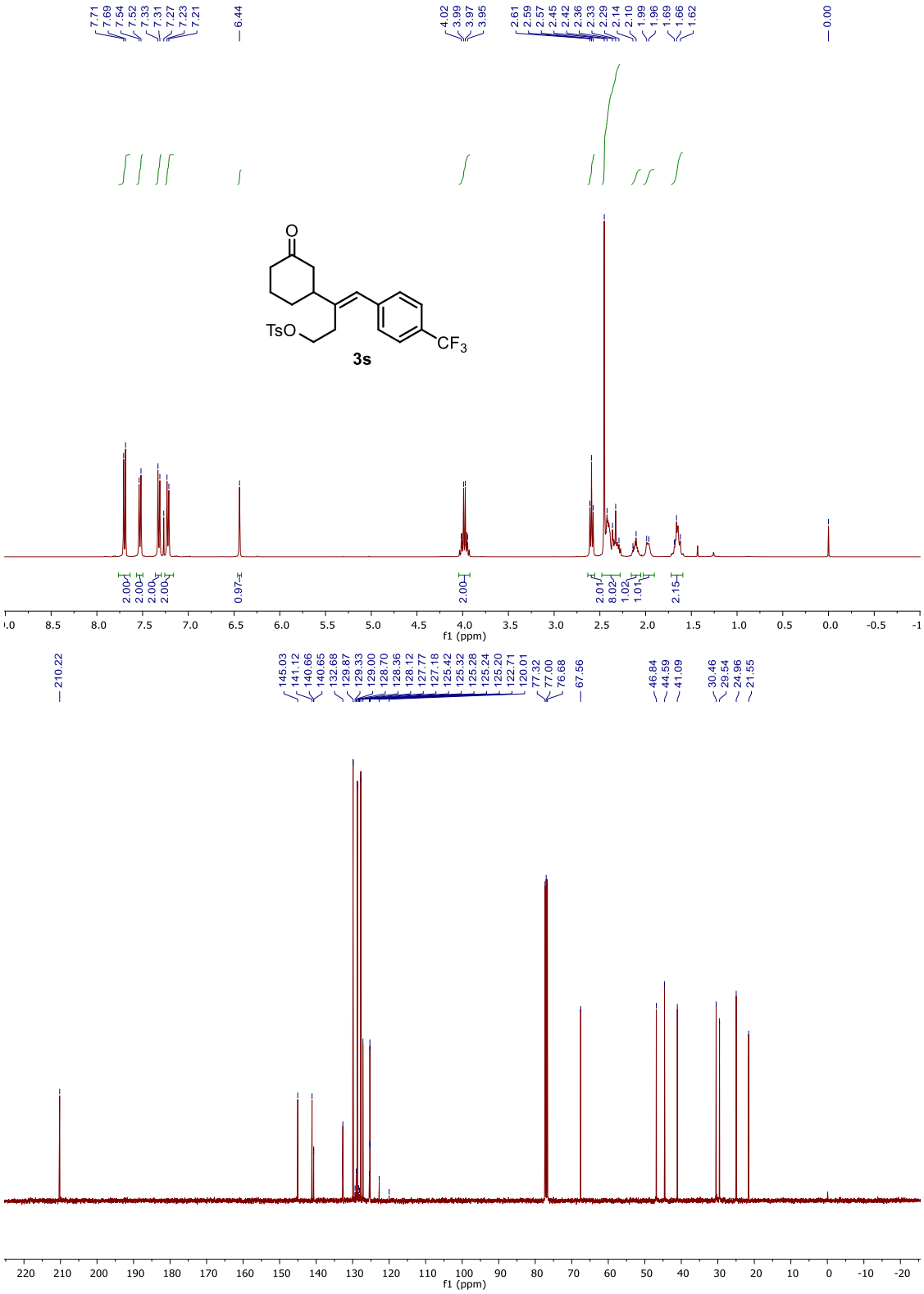


Figure 2.43 ^{19}F-NMR Spectrum of **3s**

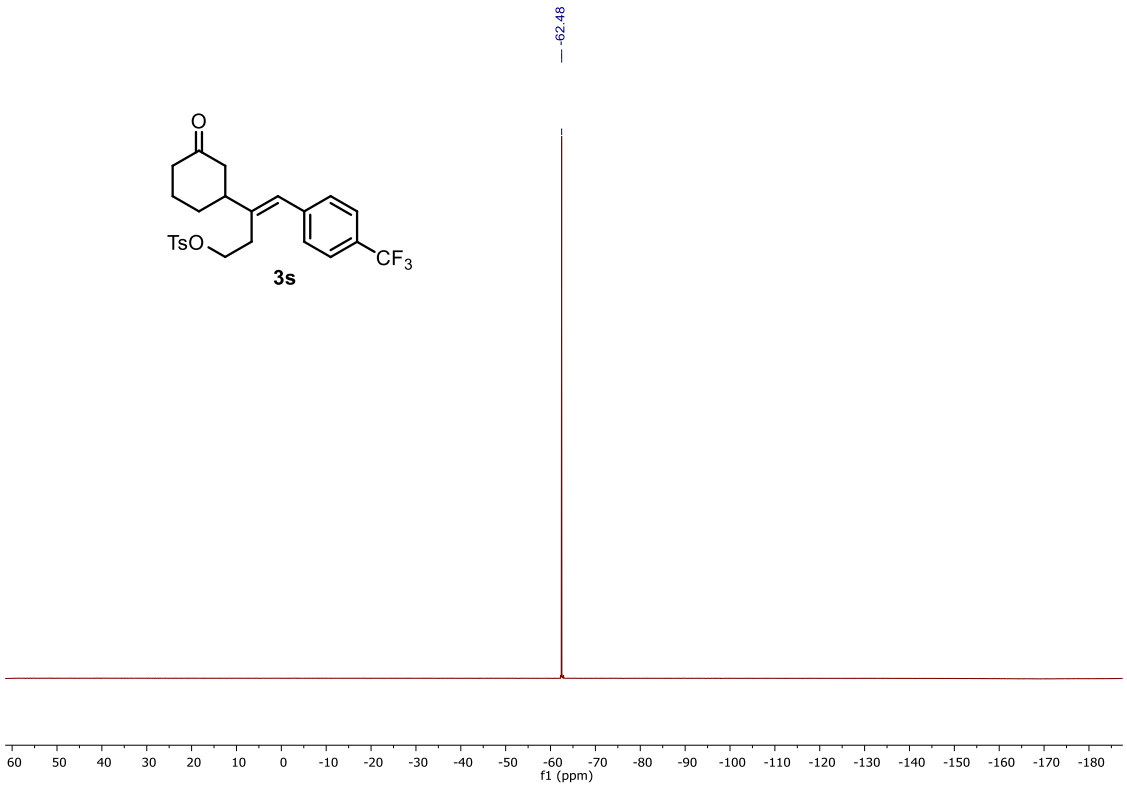


Figure 2.44 ^{1}H-NMR and ^{13}C-NMR Spectra of **3t**

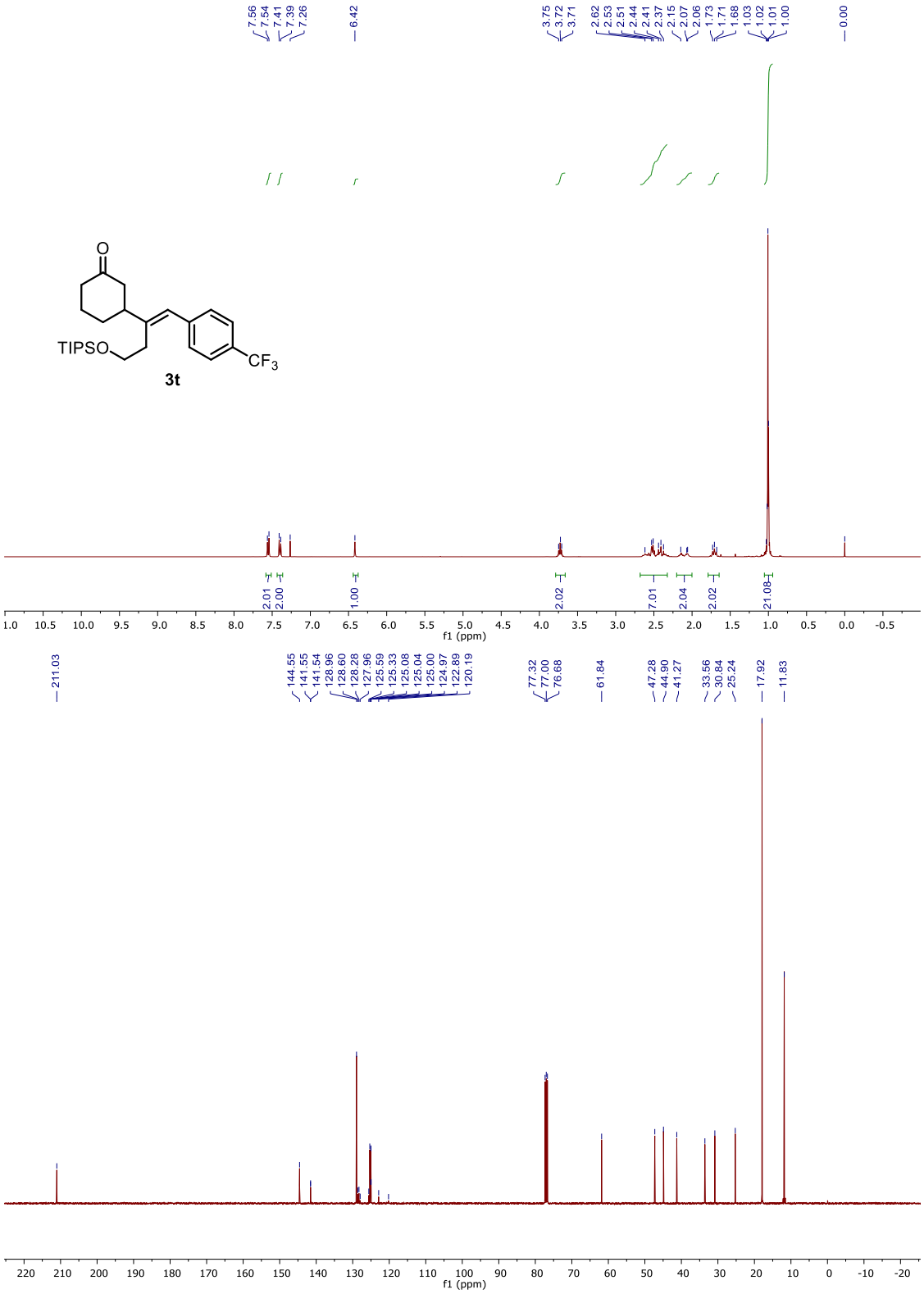


Figure 2.45 ^{19}F-NMR Spectrum of **3t**

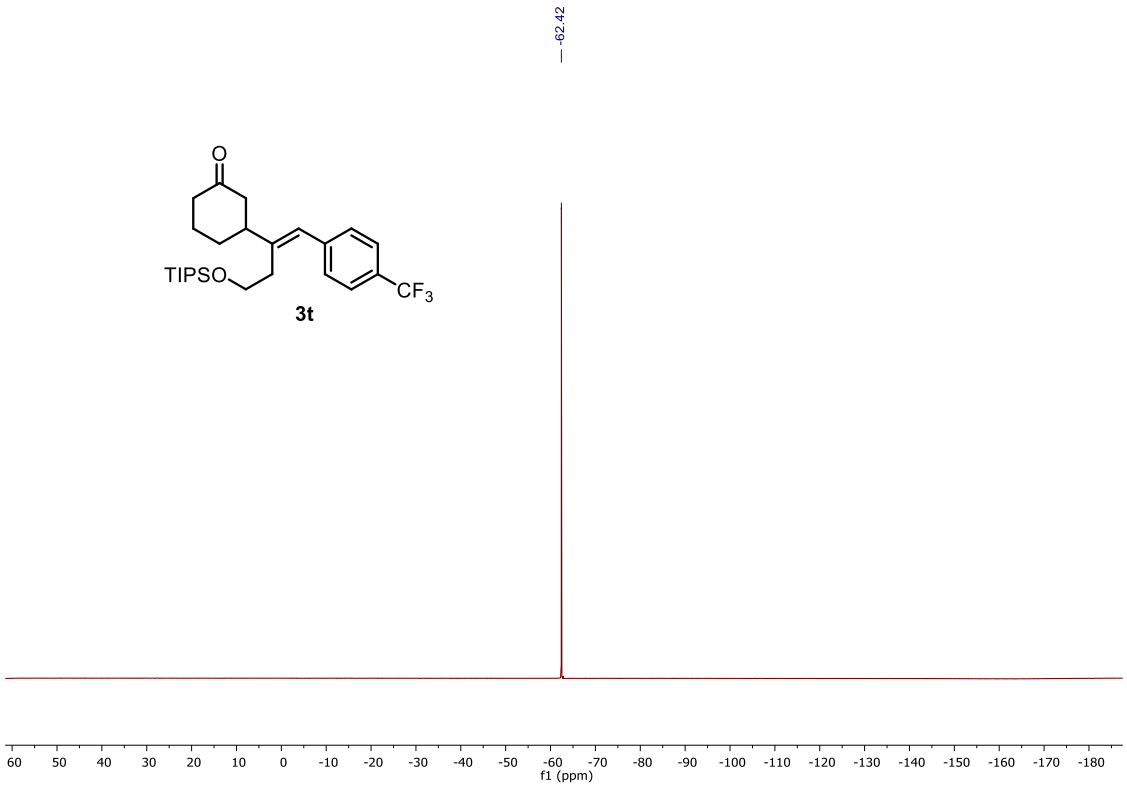


Figure 2.46 ^{1}H-NMR and ^{13}C-NMR Spectra of **3u**

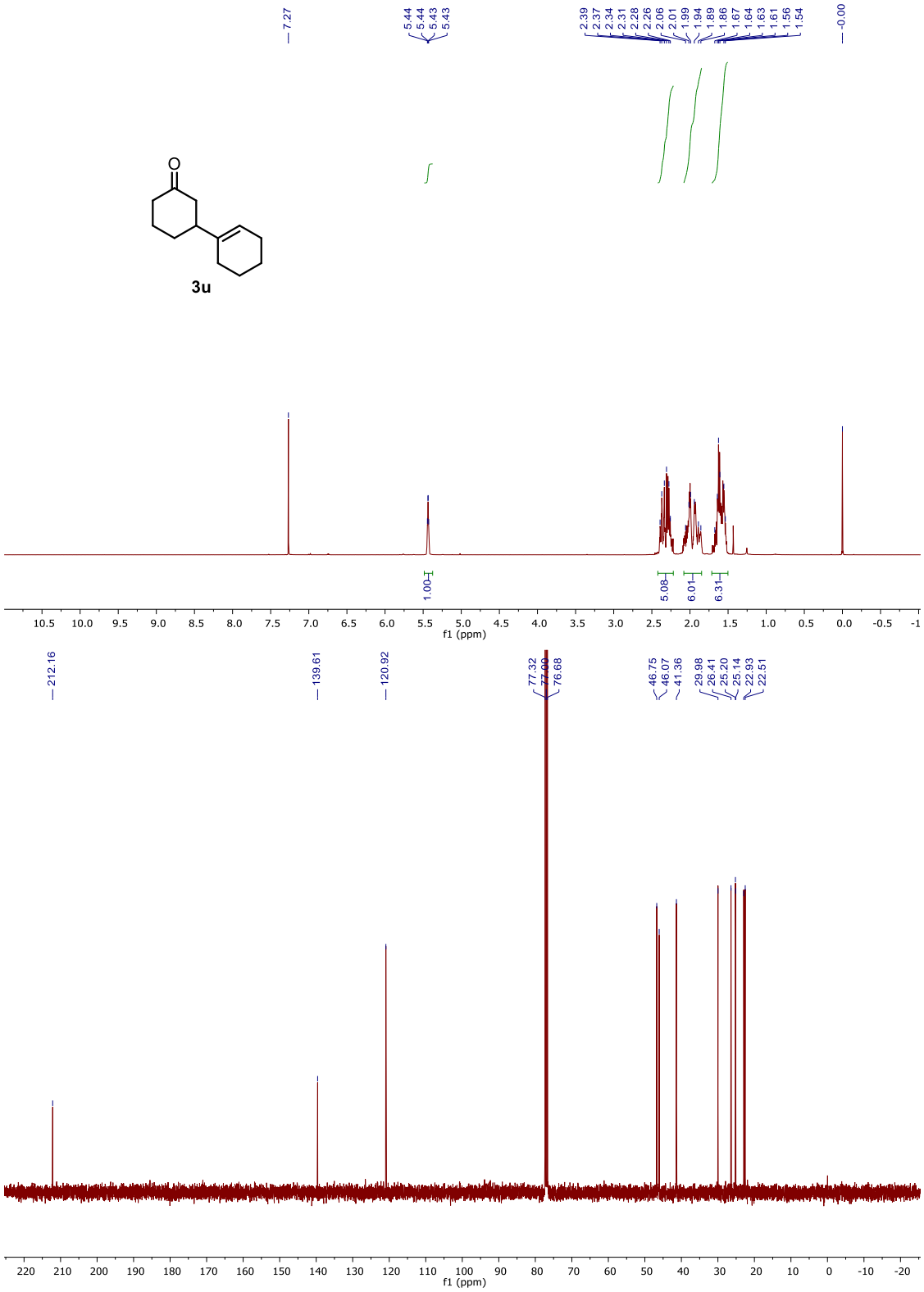


Figure 2.47 ^{1}H-NMR and ^{13}C-NMR Spectra of **3v**

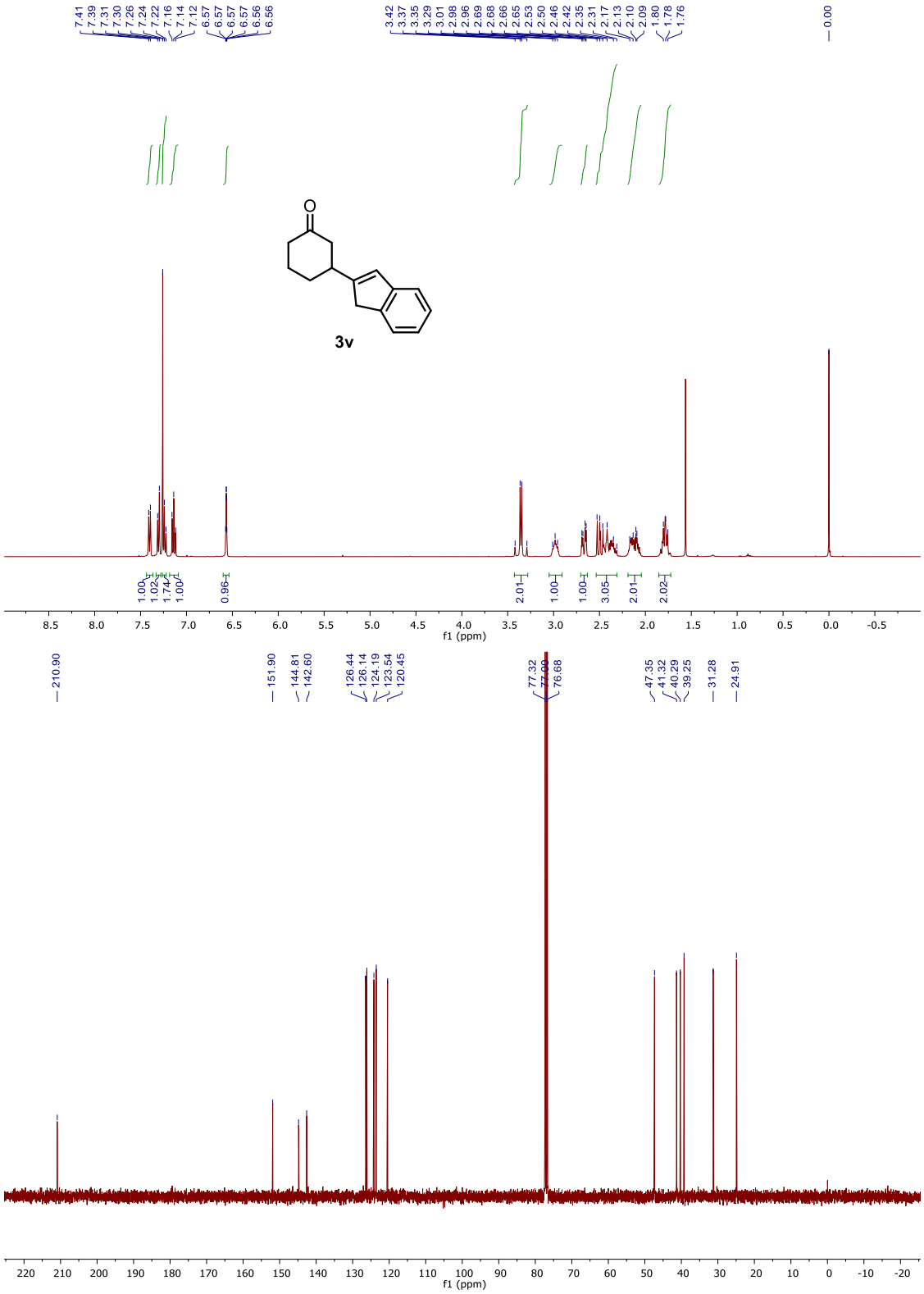


Figure 2.48 ^{1}H-NMR and ^{13}C-NMR Spectra of **4a**

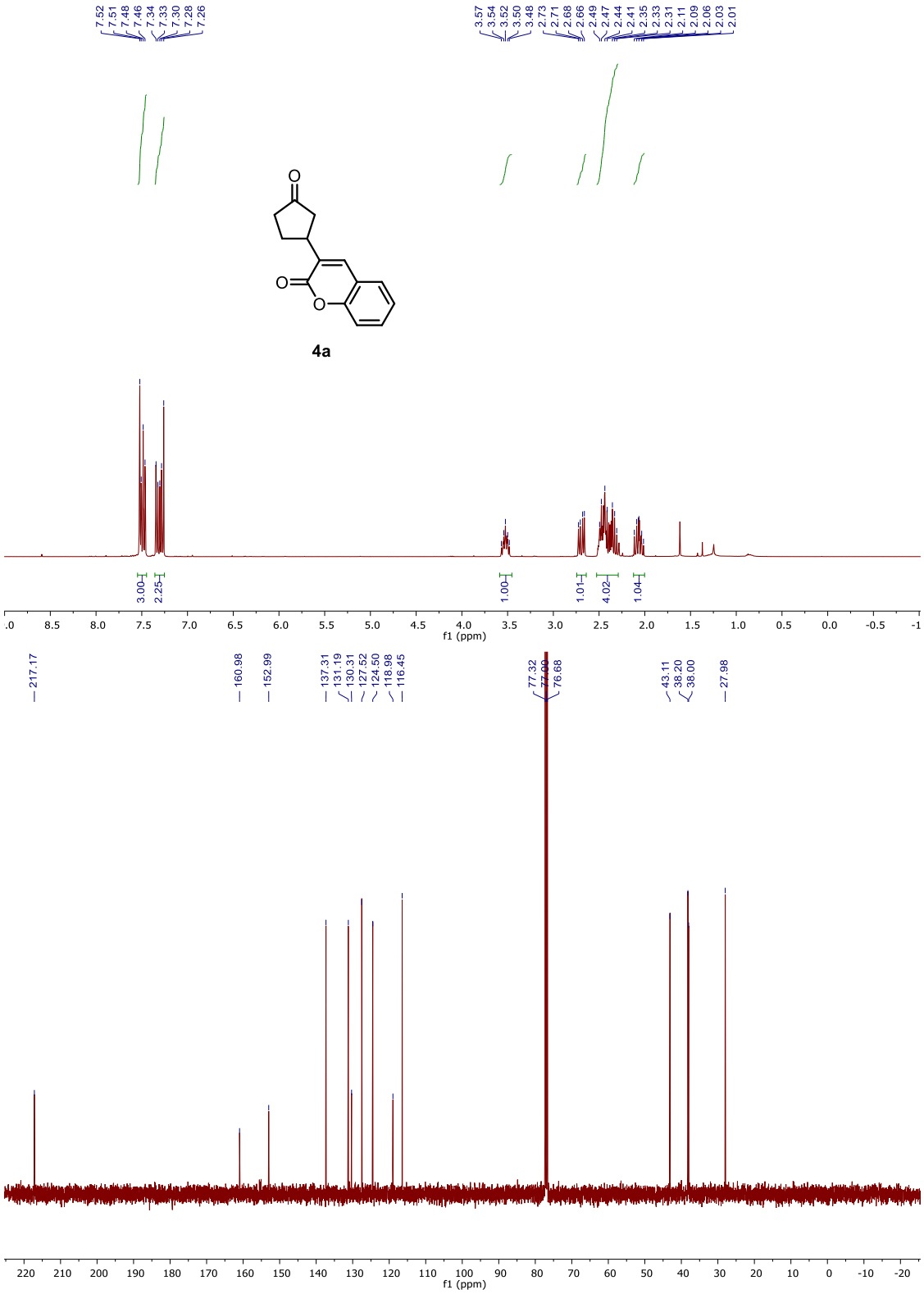


Figure 2.49 ^{1}H-NMR and ^{13}C-NMR Spectra of **4b**

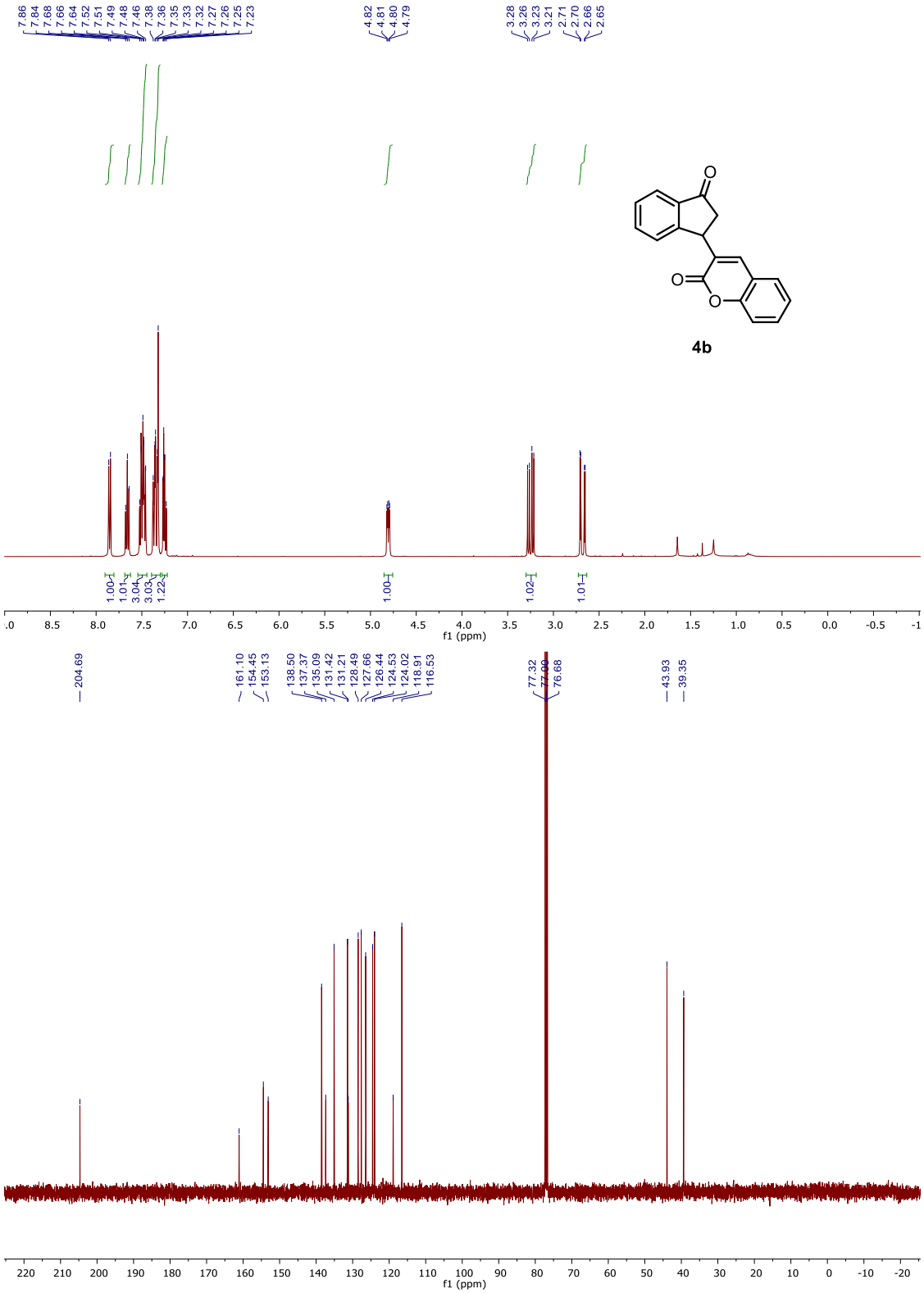


Figure 2.50 ^{1}H-NMR and ^{13}C-NMR Spectra of **4c**

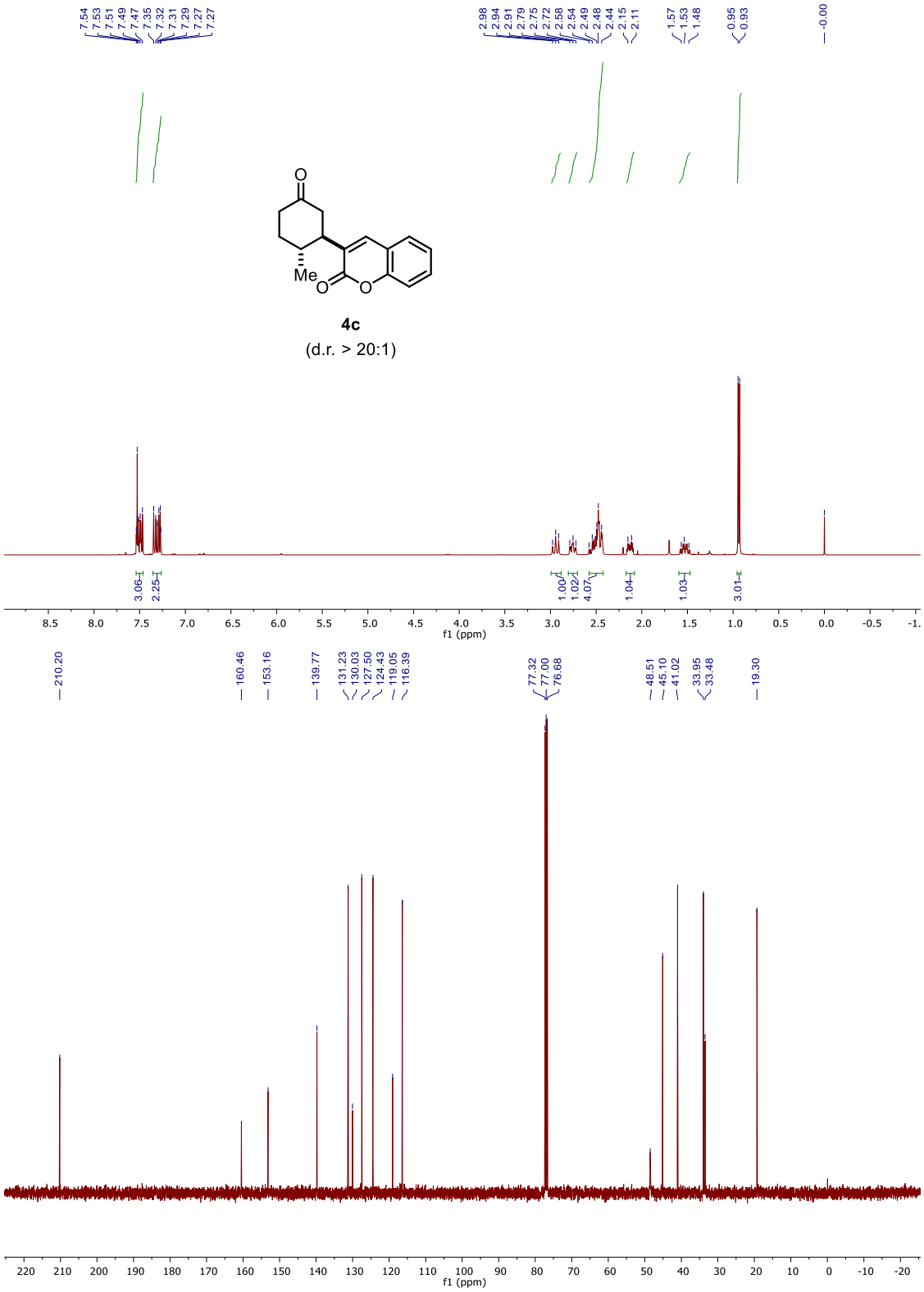


Figure 2.51 COSY Spectrum of **4c**

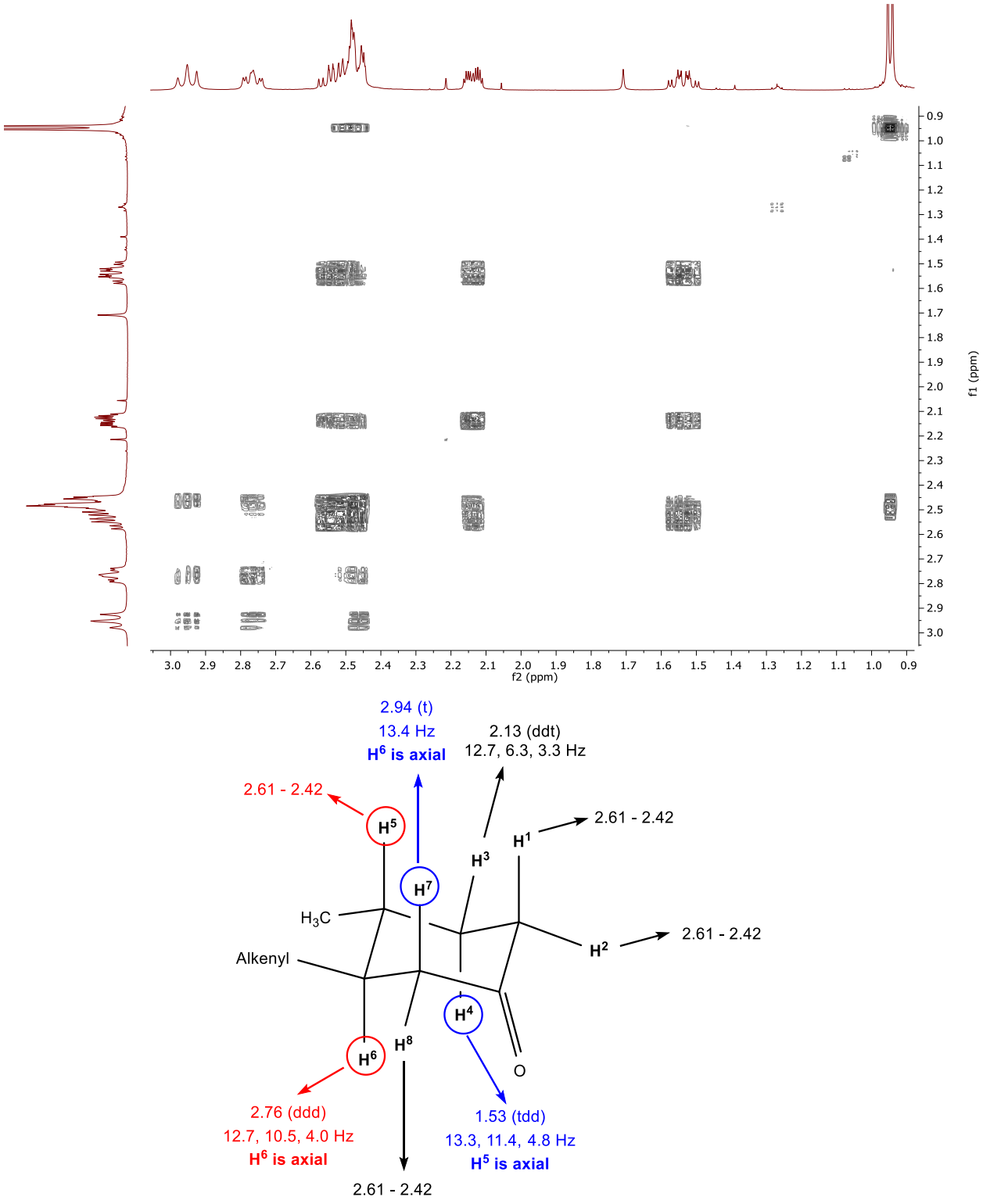


Figure 2.52 ^{1}H-NMR and ^{13}C-NMR Spectra of **4d**

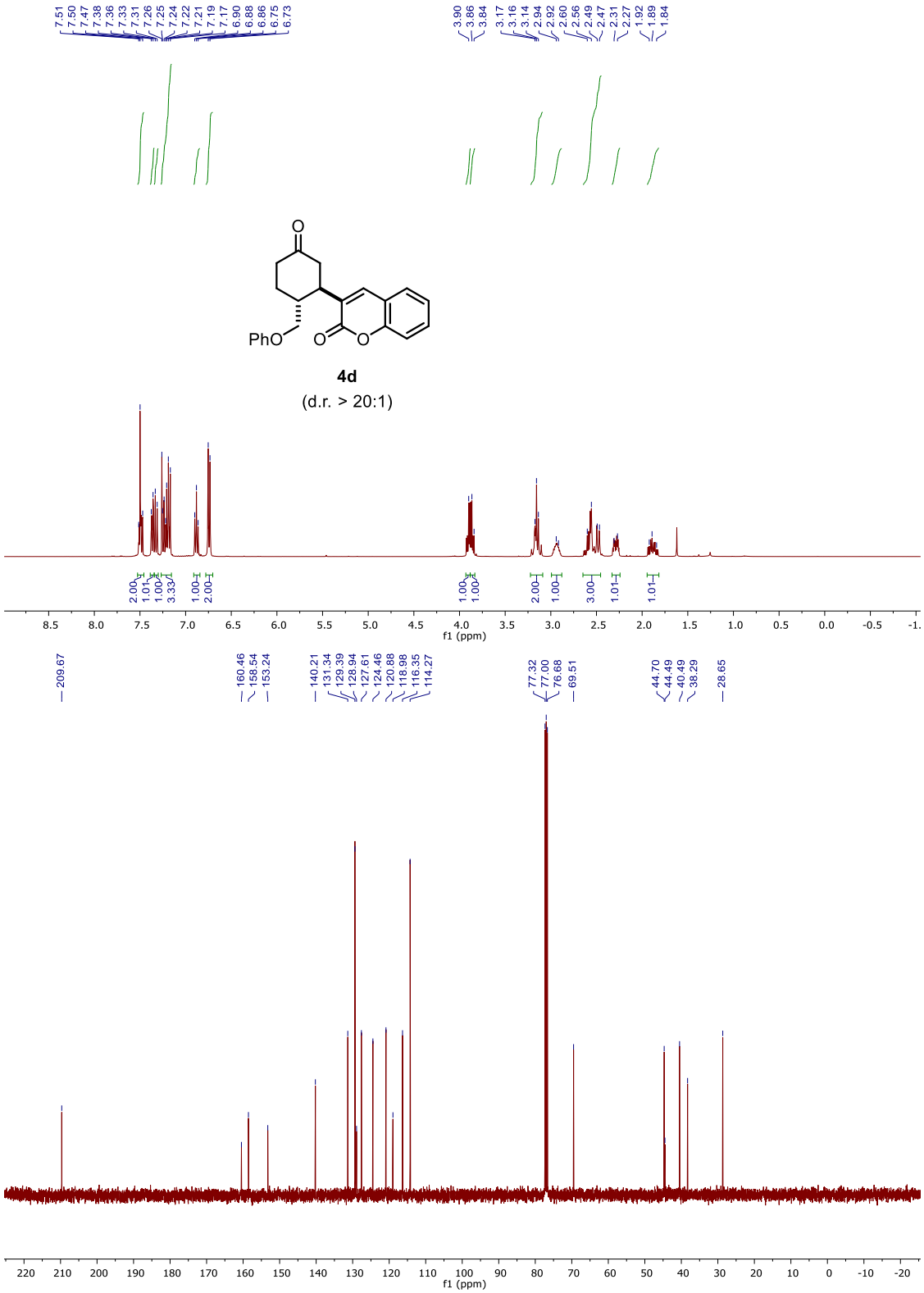


Figure 2.53 ^{1}H-NMR and ^{13}C-NMR Spectra of **4e**

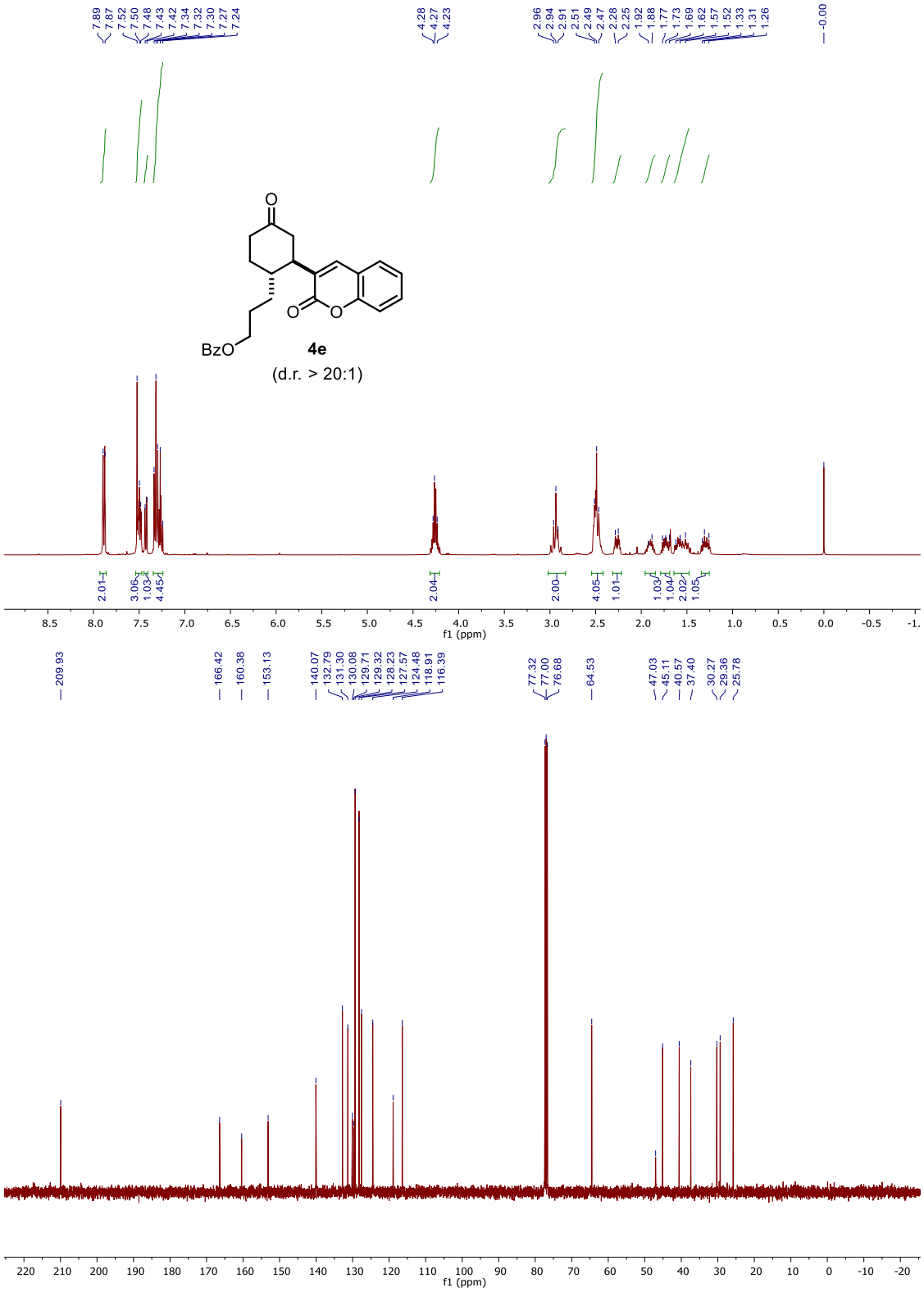


Figure 2.54 ^{1}H-NMR and ^{13}C-NMR Spectra of **4f**

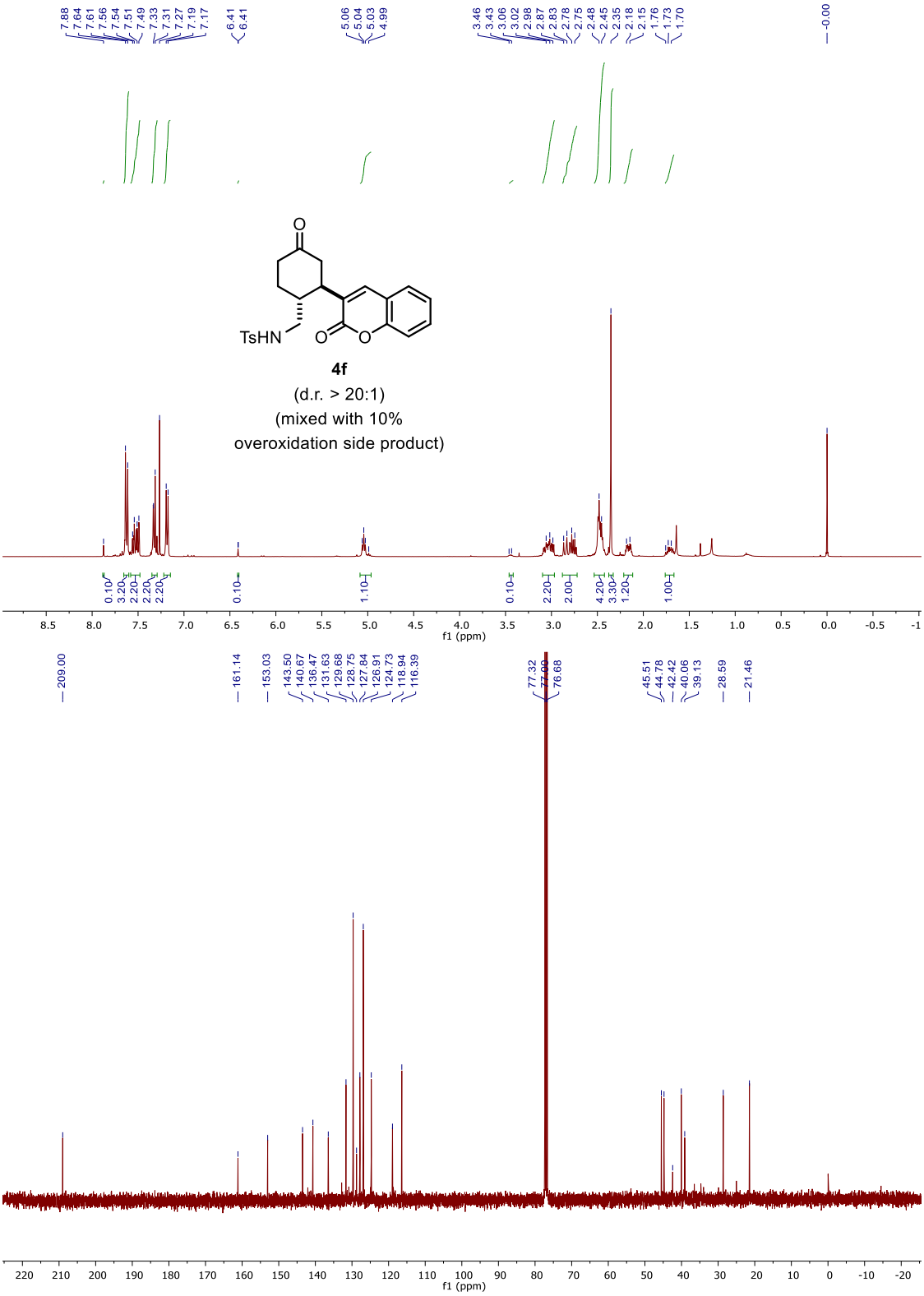


Figure 2.55 ^{1}H-NMR and ^{13}C-NMR Spectra of **4g**

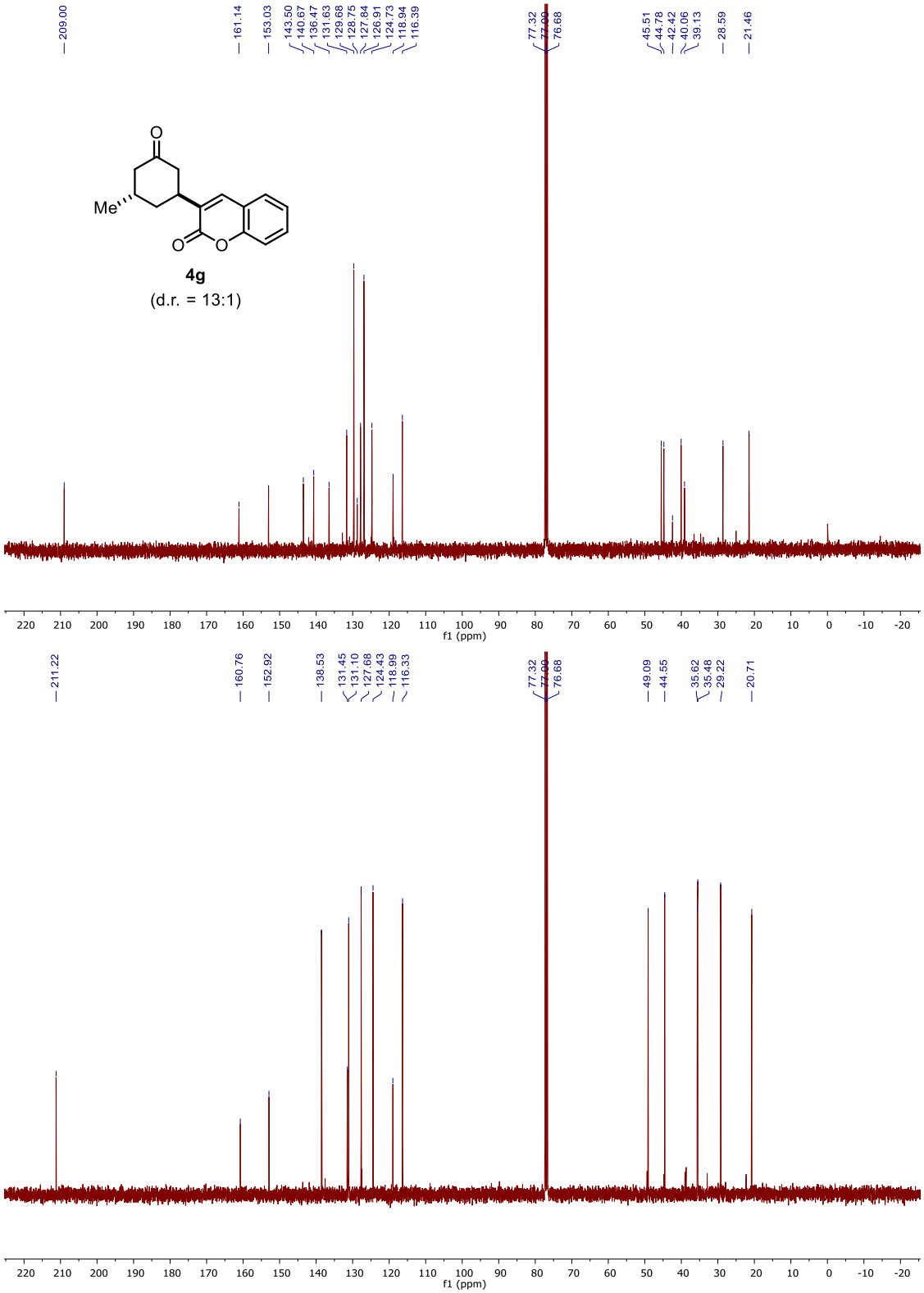


Figure 2.56 COSY Spectrum of **4g**

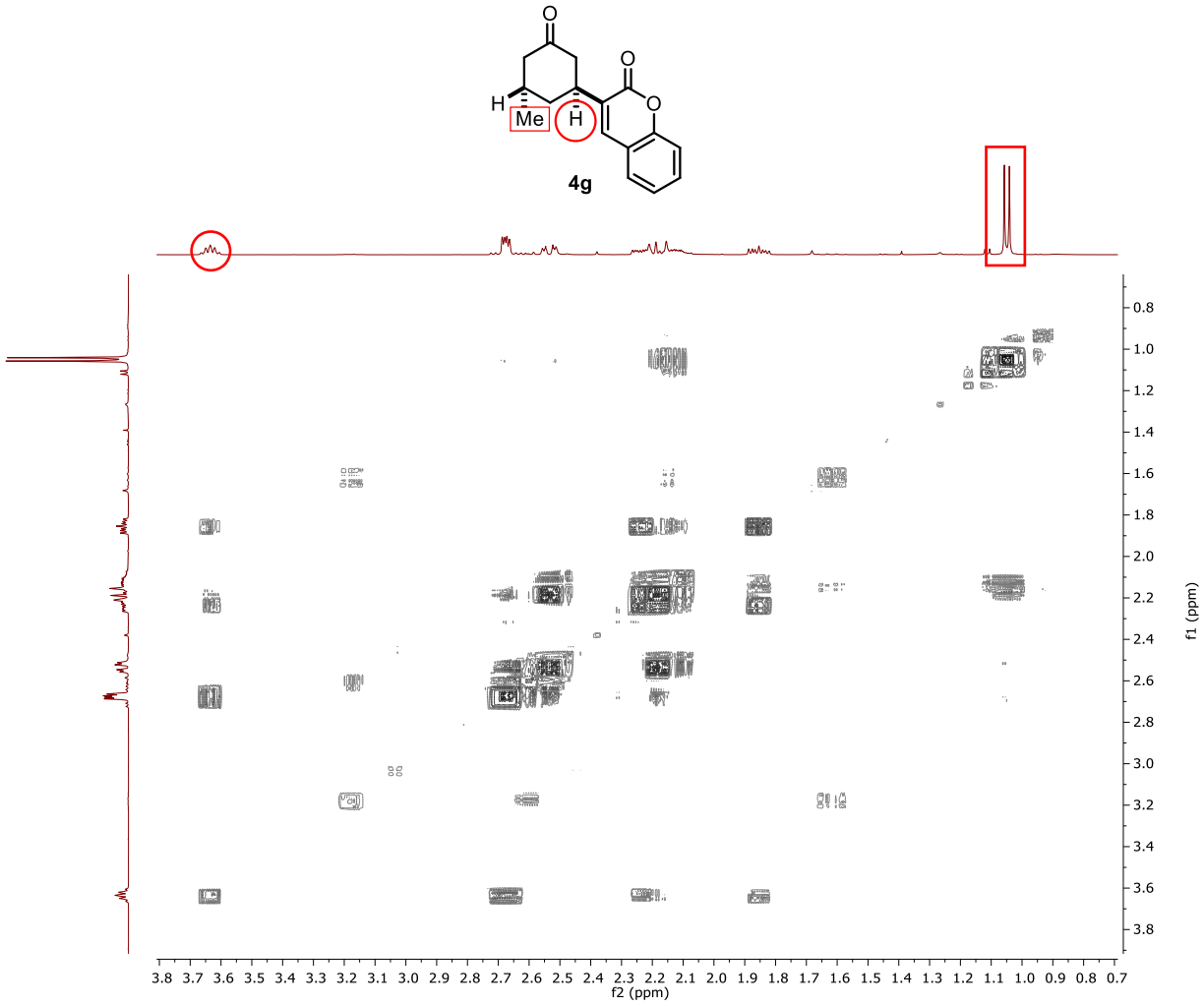


Figure 2.57 NOESY Spectrum of **4g**

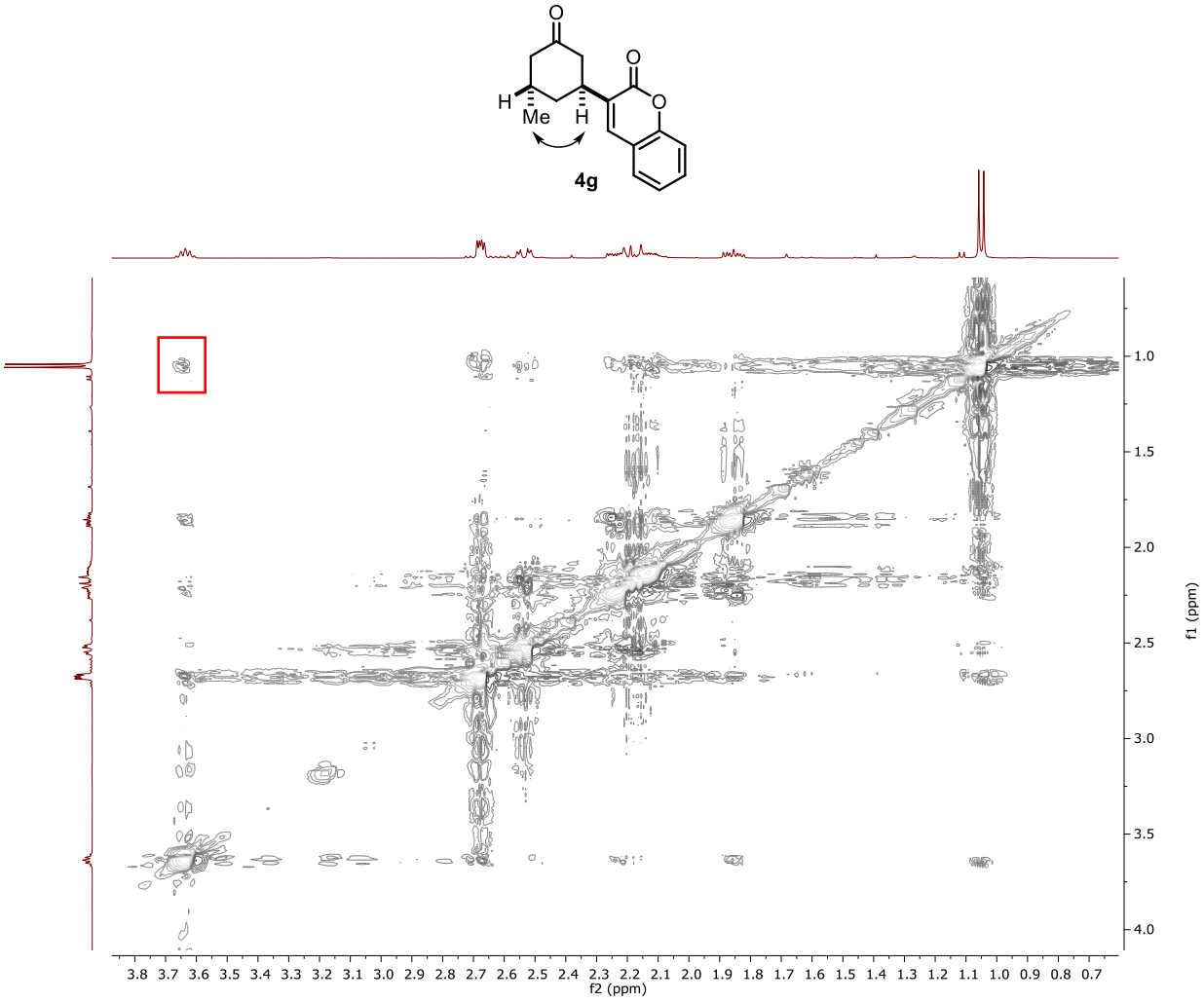


Figure 2.58 ^{1}H-NMR and ^{13}C-NMR Spectra of **4h**

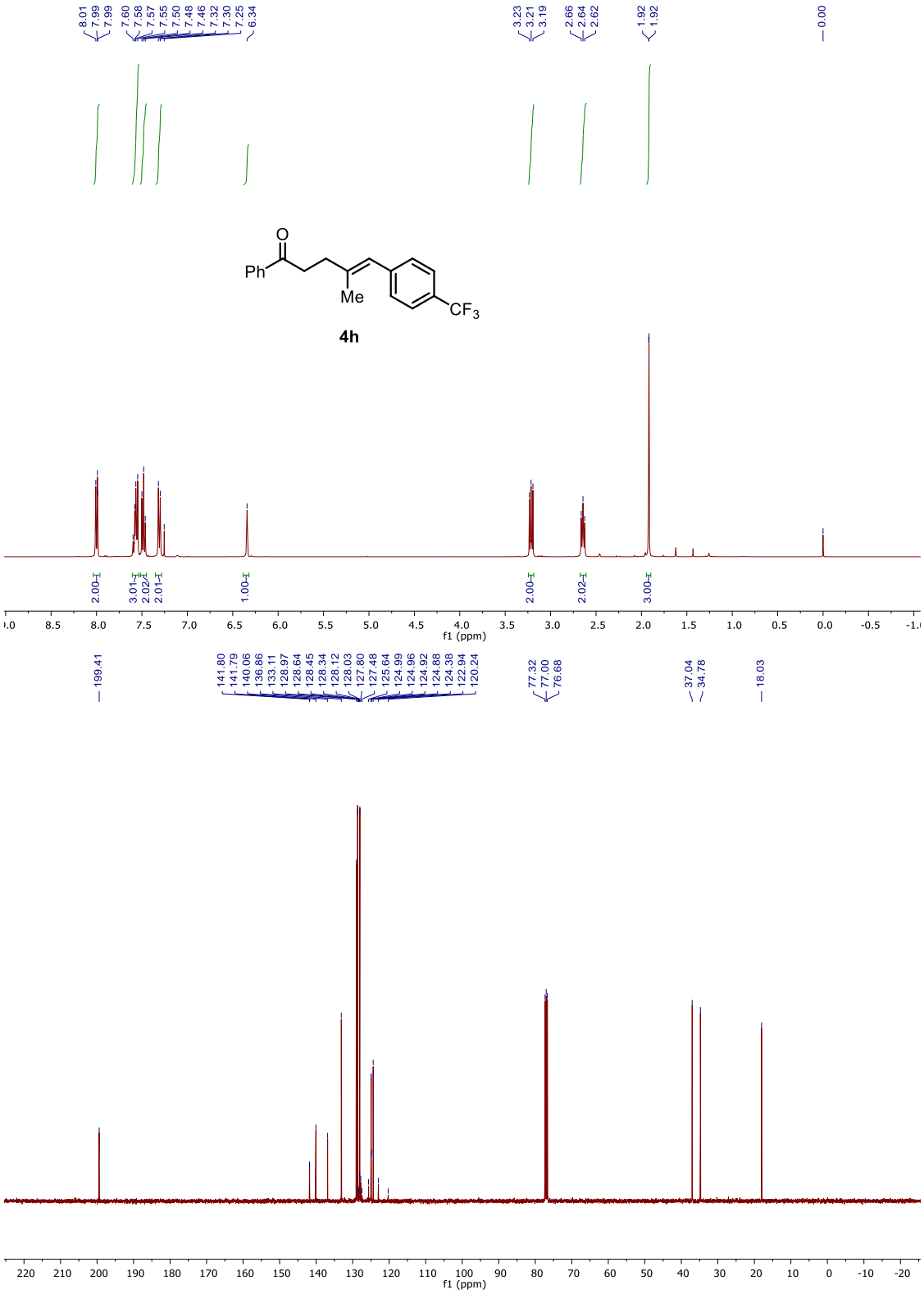


Figure 2.59 ^{19}F-NMR Spectrum of **4h**

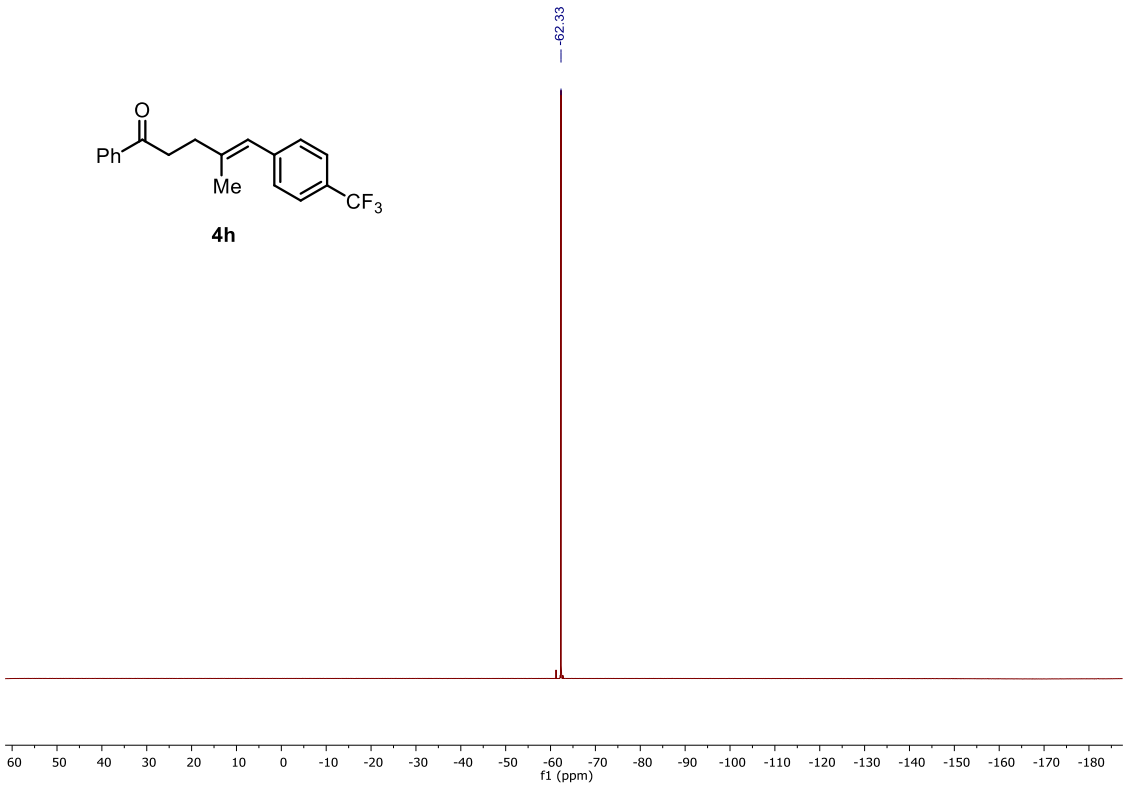


Figure 2.60 ^{1}H-NMR and ^{13}C-NMR Spectra of **4h'**

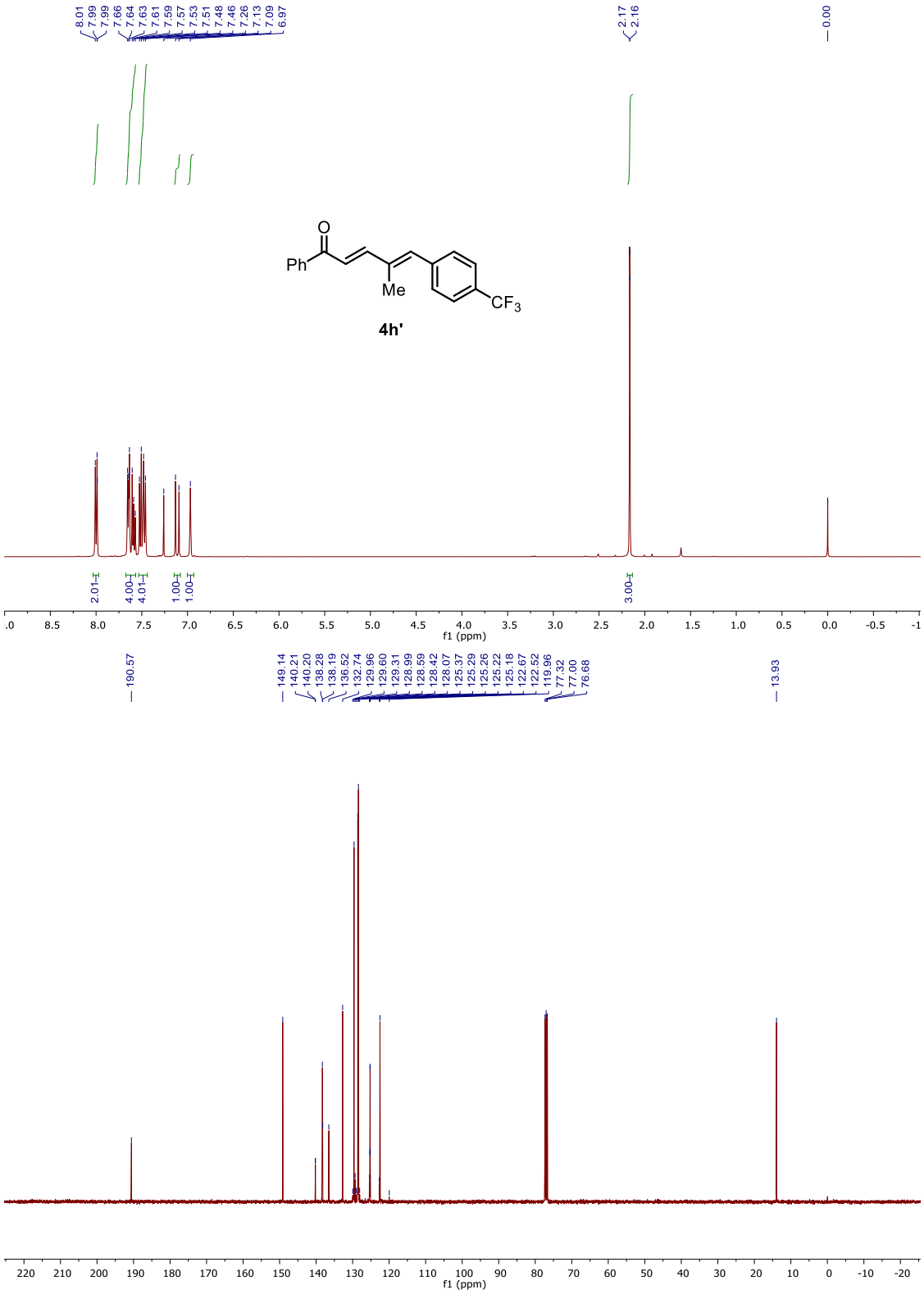


Figure 2.61 ^{19}F-NMR Spectrum of **4h'**

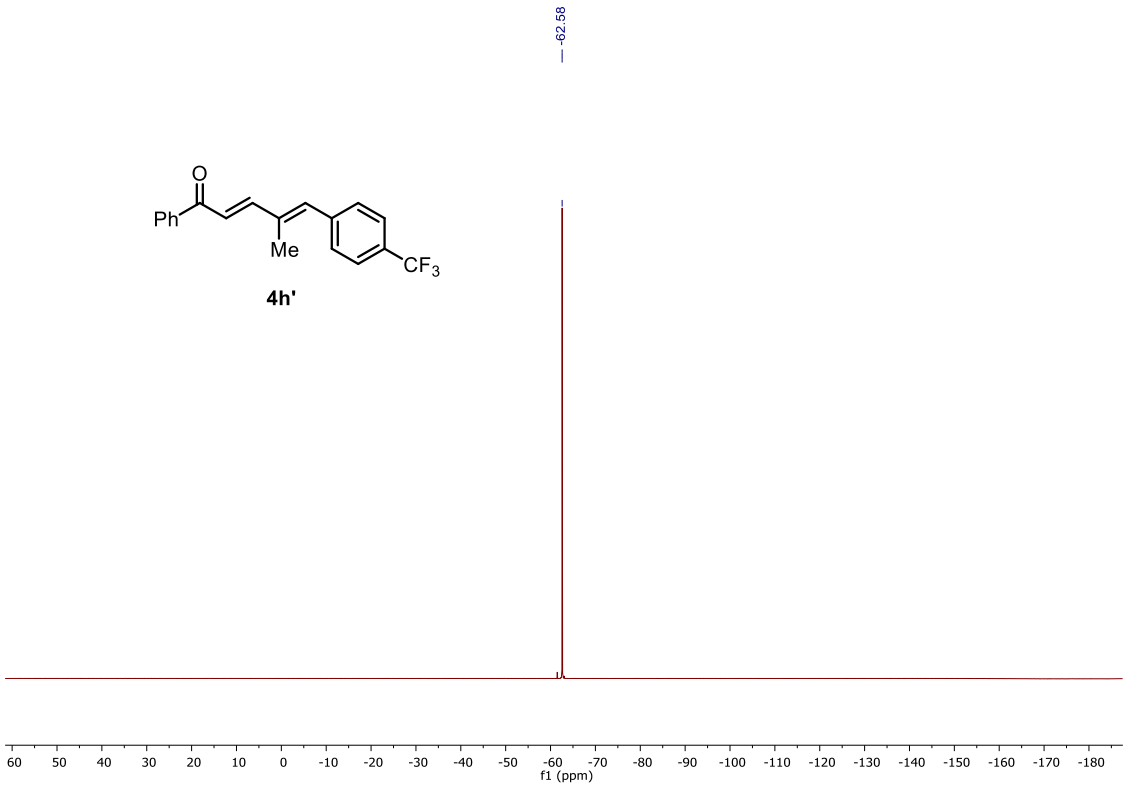


Figure 2.62 ^{1}H-NMR and ^{13}C-NMR Spectra of **5a**

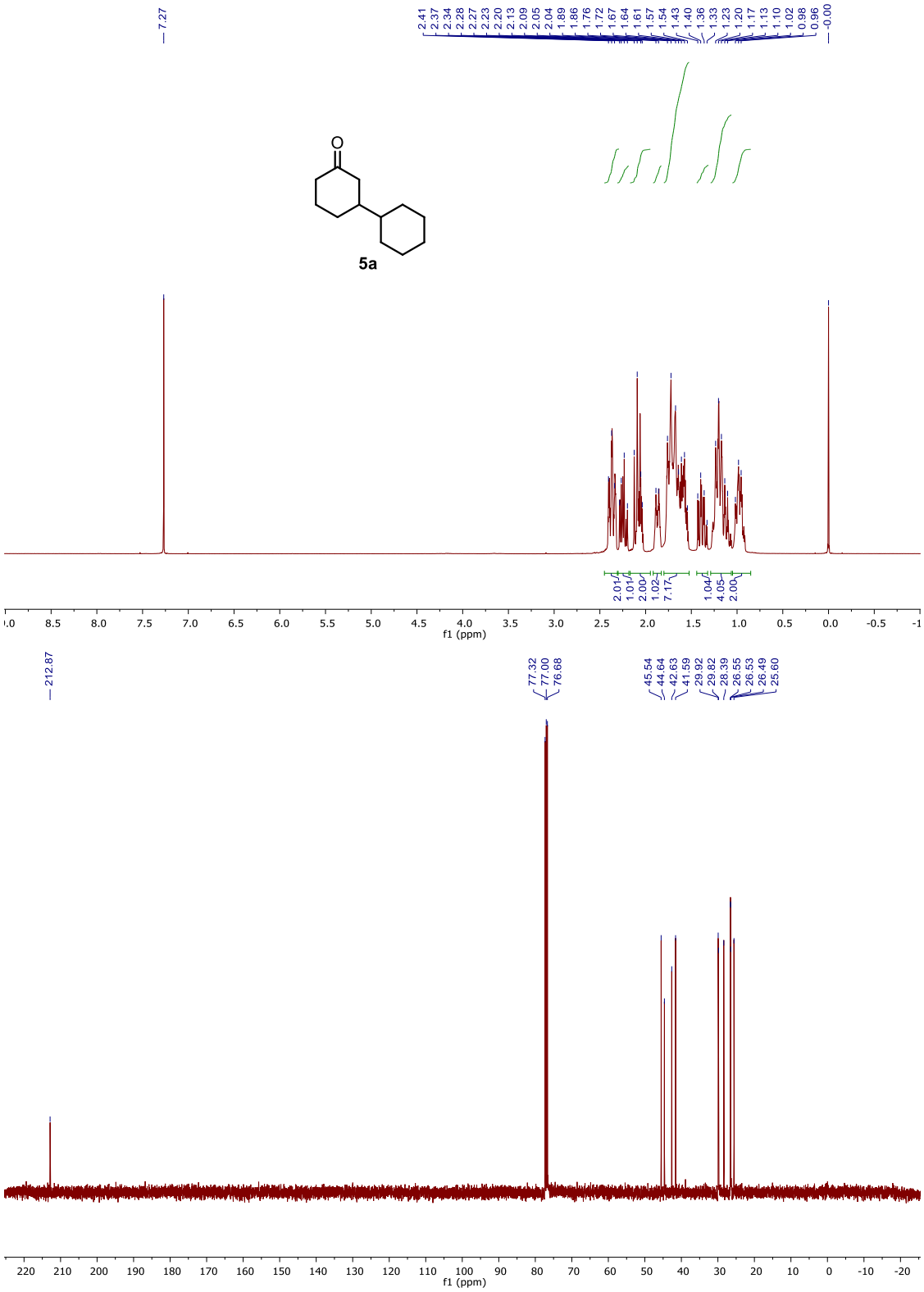


Figure 2.63 ^{1}H-NMR and ^{13}C-NMR Spectra of **5b**

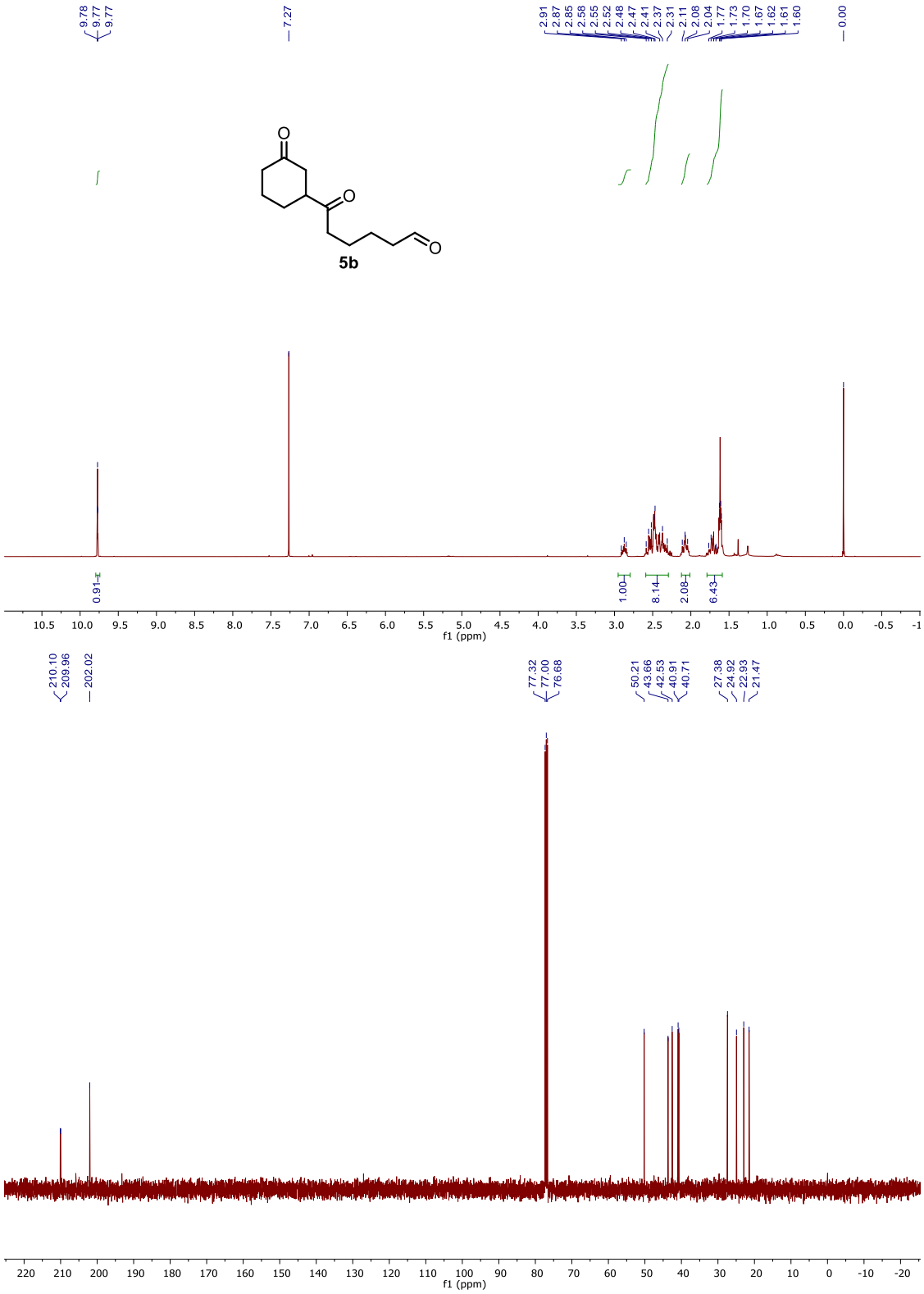


Figure 2.64 ^{1}H-NMR and ^{13}C-NMR Spectra of **5c**

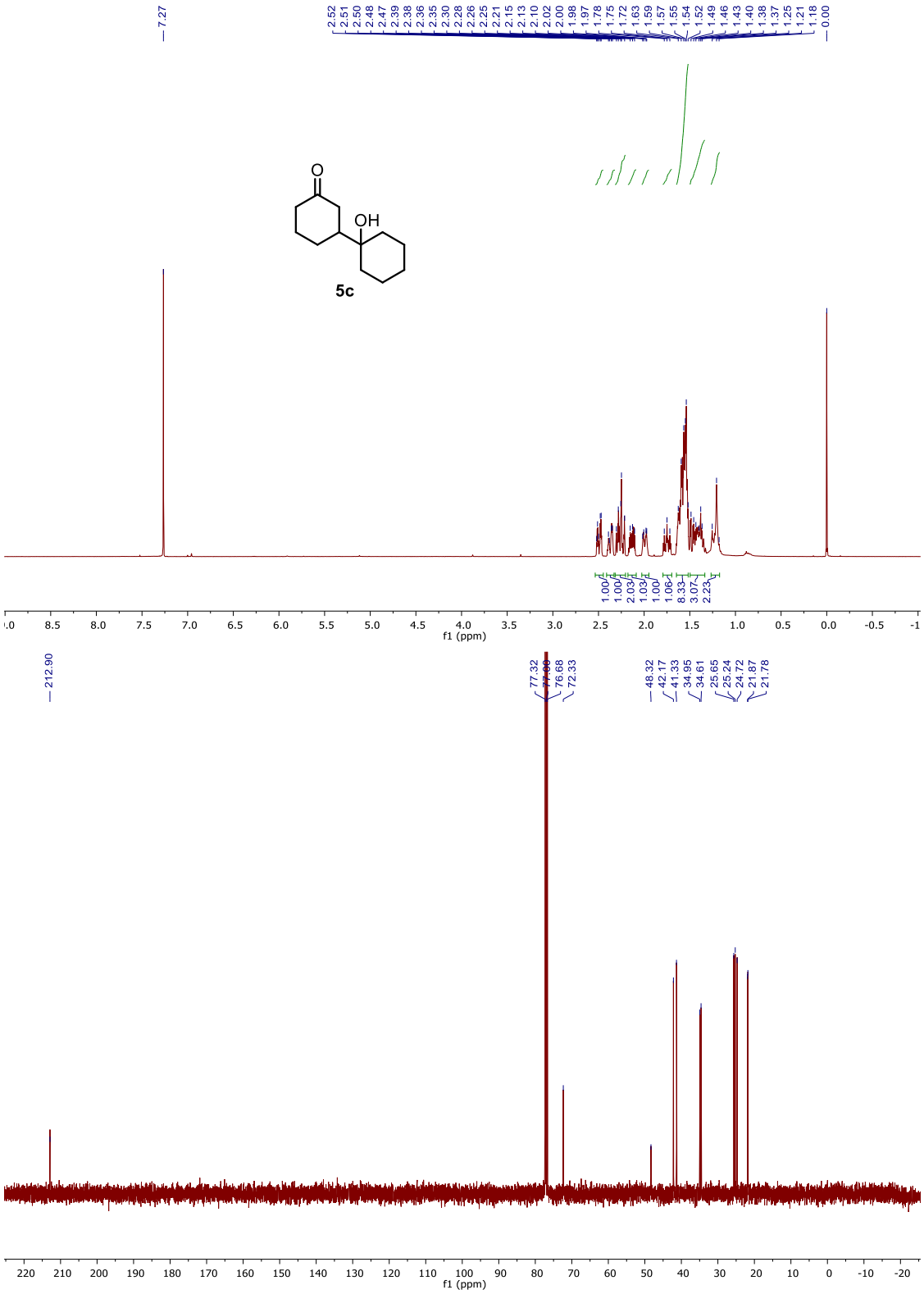


Figure 2.65 ^{1}H-NMR and ^{13}C-NMR Spectra of **5d**

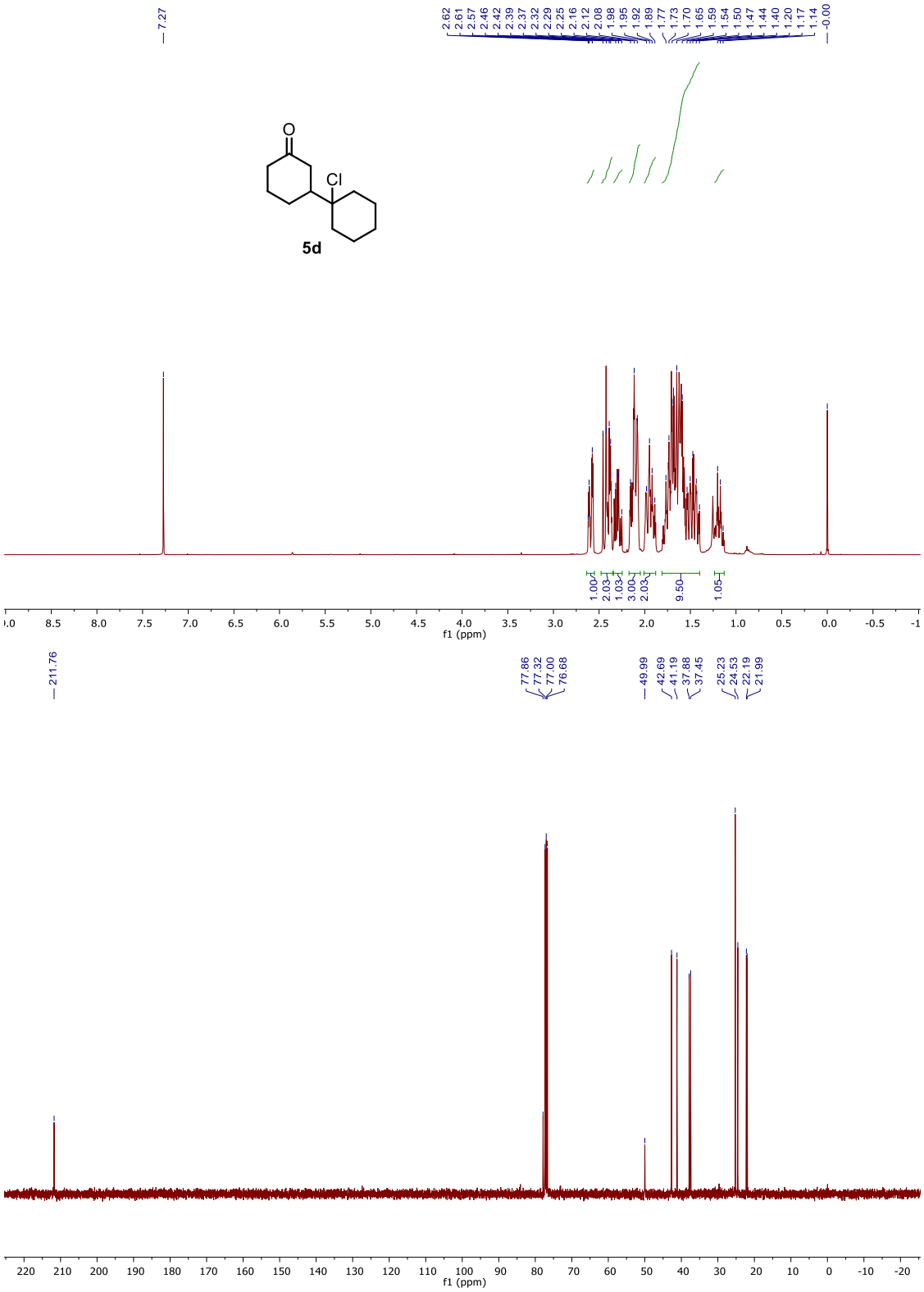


Figure 2.66 ^{1}H-NMR and ^{13}C-NMR Spectra of **5e**

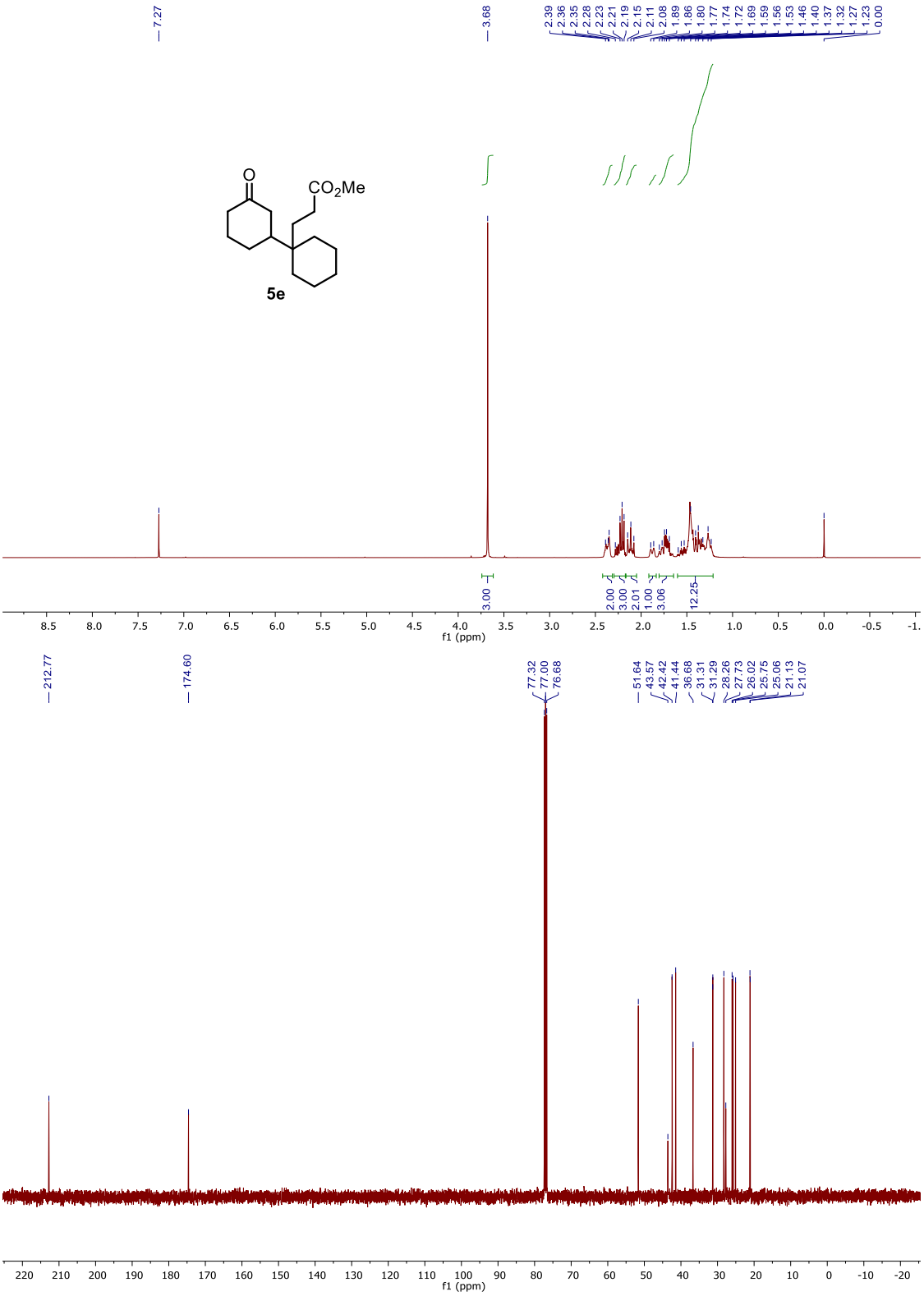
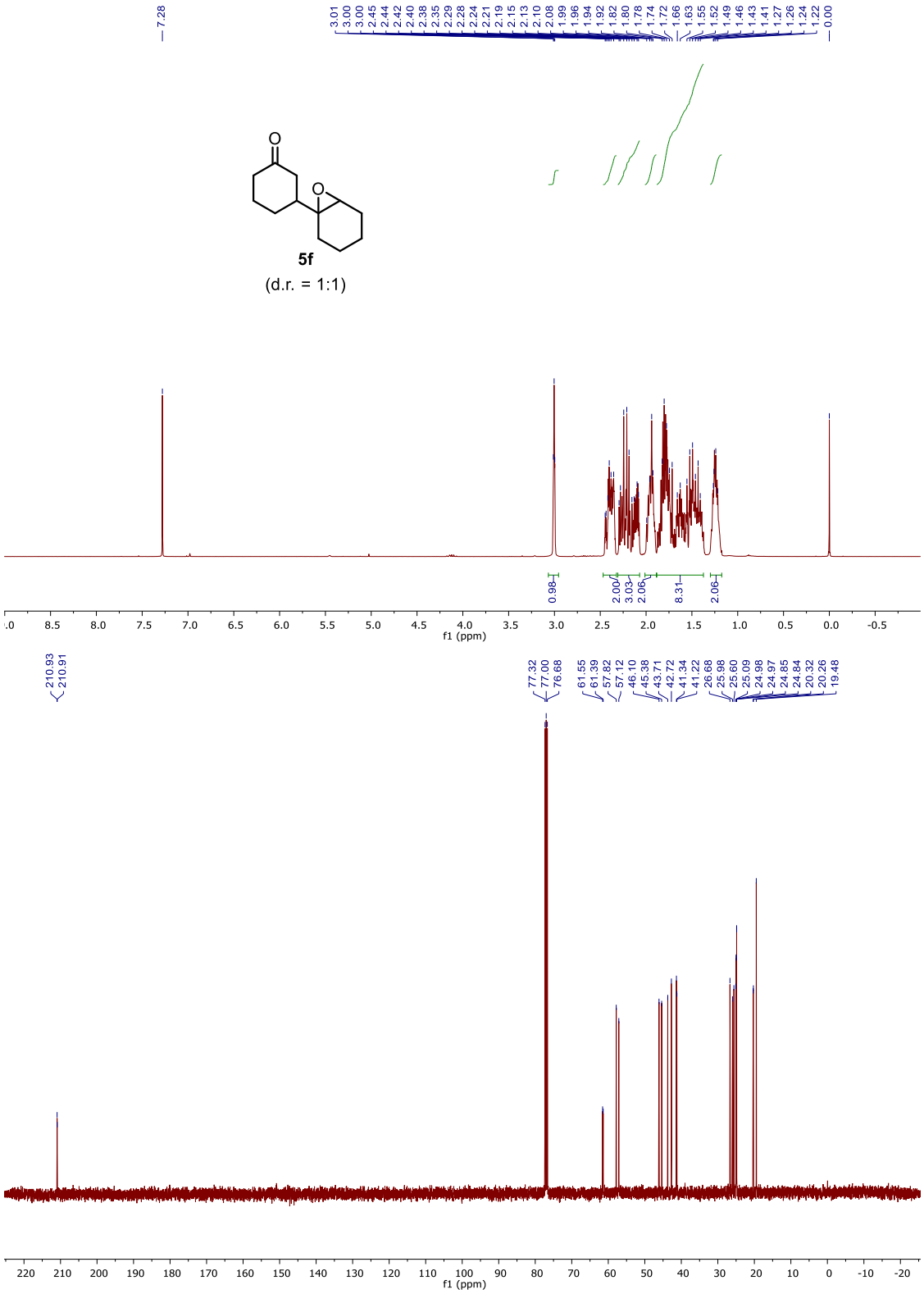


Figure 2.67 ^{1}H-NMR and ^{13}C-NMR Spectra of **5f**



CHAPTER 3

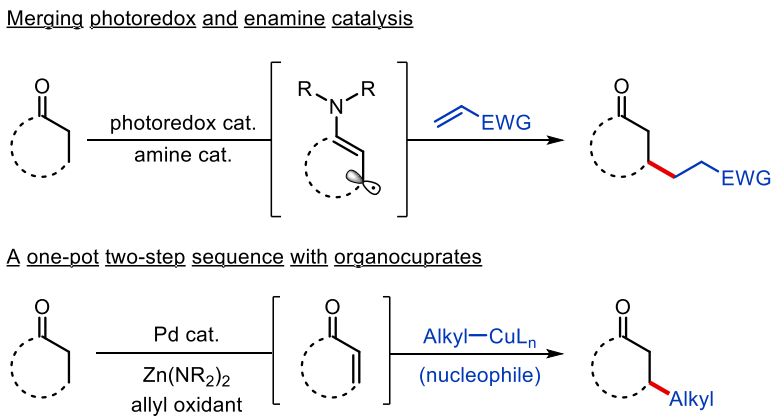
Direct β-Alkylation of Ketones and Aldehydes

3.1 Introduction

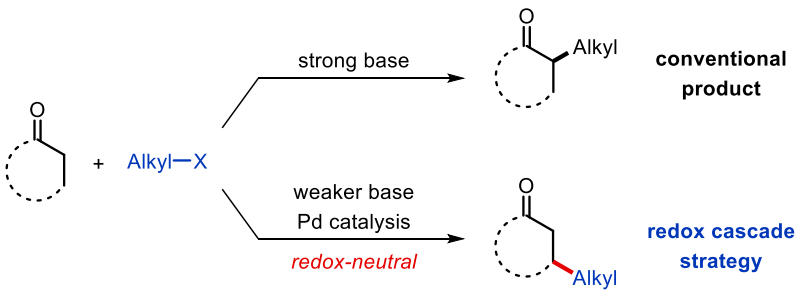
Alkylation of carbonyl compounds has been one of the most important and fundamental approaches to form carbon−carbon bonds in organic syntheses.[1] Conventionally, treatment of ketones with strong bases followed by addition of alkyl halides provides α-alkylated products. On the other hand, β-alkylation of ketones would provide a distinct and equally effective bond disconnection strategy for synthesis design. Furthermore, a broader impact would be expected from this approach as an $C(sp^3)-C(sp^3)$ bond formation strategy from the alkylation of unactivated $C(sp^3)-H$ bonds.[2] However, direct alkylation at the unactivated β positions of ketones is much more challenging.[3] While the powerful directing group (DG) approach enables β-C−H functionalization of various carbonyl compounds,[4,5] β-alkylation of ketones and aldehydes using DG strategy remains elusive; in addition, the β positions of cyclic ketones are generally inaccessible via a directing mode. Recently, MacMillan and coworkers disclosed an elegant approach for β-alkylation via merging enamine and photoredox catalysis, in which Michael

acceptors, or aryl ketones/imines were employed as the alkyl source.[6,7] More recently, an efficient one-pot β-alkylation protocol was developed by Newhouse and coworkers through a sequence of Pd-catalyzed ketone desaturation followed by conjugate addition of an organocuprate nucleophile (Scheme 3.1).[8,9] Nevertheless, a more general and redox-neutral approach for direct β-alkylation of ketones remains to be developed. We were motivated by the convenience of using readily available simple alkyl halides as the alkyl source, which could possibly enable a direct β-alkylation of saturated carbonyl compounds in the absence of stoichiometric oxidants or reductants. Therefore, we aimed to develop a redox-neutral β-alkylation of ketones employing our Pd-catalyzed redox cascade strategy (Scheme 3.2).

Scheme 3.1 Reported β-Alkenylation of Ketones and Aldehydes



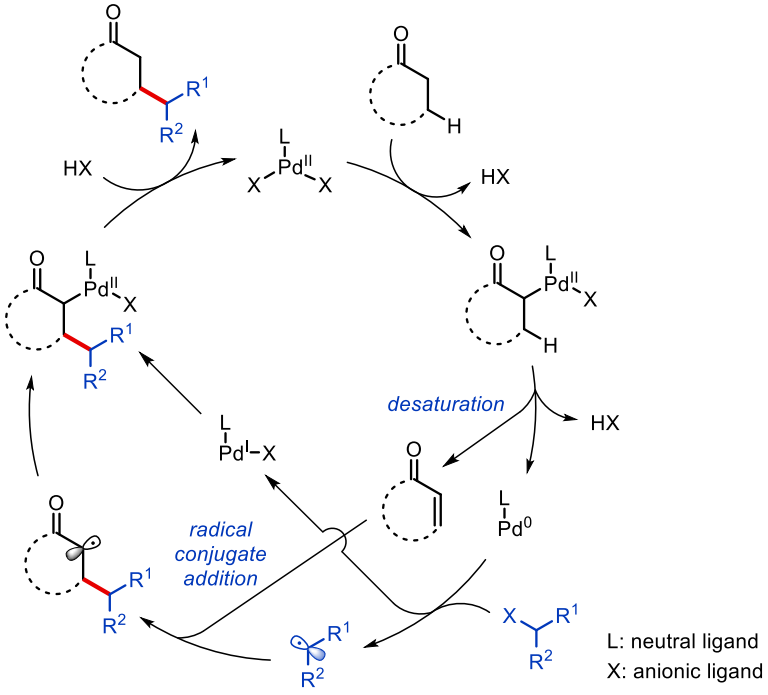
Scheme 3.2 Redox-Neutral α- and β-Alkylation of Ketones with Alkyl Halides



Our laboratory has been engaged in systematic development of a Pd-catalyzed redox cascade approach for β-functionalization of carbonyl compounds.[10] This strategy starts with Pd(II)-enolate formation between a Pd(II) precatalyst and the carbonyl substrate, followed by β-hydrogen elimination to give an unsaturated carbonyl intermediate.[11] The resulting Pd(0) species then undergoes oxidative addition with the electrophile, e.g. an aryl halide, to give an aryl-Pd(II) intermediate, which upon migratory insertion and protonation of the new Pd(II)-enolate provides the β-product and regenerates the Pd(II) catalyst.[12] As a result, the electrophile serves as both the oxidant for carbonyl desaturation and the carbon source for β-functionalization. However, to extend this Pd-catalyzed redox cascade strategy to β-alkylation, the use of alkyl halides as the electrophile constitutes significant difficulties. First, oxidative addition of Pd(0) to alkyl halides is generally more difficult than to aryl halides.[13] Second, the resulting alkyl-Pd(II) species are prone to β-hydrogen elimination rather than migratory insertion.[14] The seminal work by Firmansjah and Fu shows that such an issue could be addressed using a bulky NHC ligand, but it remains challenging to use secondary or tertiary alkyl halides.[15] Alternatively, besides a two-electron oxidative addition, electron-rich Pd(0) is also known to undergo a one-electron pathway, in which Pd(0) can abstract the halogen atom from an alkyl halide to give a Pd(I)−X species and an alkyl radical.[16] This process has appeared in several Pd-catalyzed atom-transfer, cross coupling, and carbonylative reactions using alkyl halides as the substrate.[17] For example, Alexanian,[18] Zhou,[19] Gevorgyan,[20] Fu and Shang[21] recently demonstrated this concept in elegant alkyl-Heck reactions with attractive scopes and synthetic applications.

For the proposed β-alkylation pathway (Scheme 3.3), it is possible to trigger the same radical formation from an alkyl halide with the electron-rich Pd(0) species, which could be followed by a radical relay with the enone intermediate and then recombination of the α-radical with the Pd(I)−X to generate the β-alkylated Pd(II)-enolate. However, several challenges could be envisioned from this radical redox cascade strategy. First, alkyl halides could be vulnerable to bases and nucleophiles, which may suffer from elimination and substitution side reactions at elevated temperature. In addition, radical conjugate addition may not be efficient with catalytically generated enones, so various side reactions would be expected from radical intermediates, e.g. C−H abstraction and dimerization. Moreover, whether the Pd-catalyzed two-electron desaturation process would be compatible in the presence of reactive radical species could be another concern.

Scheme 3.3 Proposed Radical Redox Cascade Strategy for β-Alkylation of Ketones

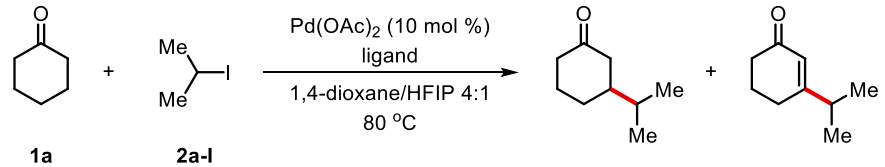


3.2 Results and Discussion

3.2.1 Optimization of the reaction conditions

Considering that radical generation would be facile from secondary alkyl iodides, we started testing our hypothesis with cyclohexanone (**1a**) and 2-iodopropane (**2a-I**) as the model substrates (Table 3.1). Fortunately, when $Pd(OAc)_2$/P(*i*-Pr)$_3$ was used as the precatalyst and hexafluoroisopropanol (HFIP) was used as an acidic cosolvent, the desired β-alkylation product (**3a**) could be observed in 0.5% yield along with 0.5% overoxidation product (**3a'**) (entry 1). Based on this encouraging result, we further identified 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) as an effective ligand that gave 1.7% yield of the product (entry 2). It is known that photoirradiation could accelerate Pd(0)-mediated alkyl radical generation processes,[17] so we tested the reactivity in the presence of blue LED light, but the results were the same (entry 3). Interestingly, when $Ir(ppy)_3$,

Table 3.1 Initial Discovery of the β-Alkylation of Cyclohexanone[a]



1a (250 mol %) **2a-I** (100 mol %) **3a** **3a'**

entry	ligand	variations	yield of **3a** (%)[b]	yield of **3a'** (%)[b]
1	P(*i*-Pr)$_3$ (20 mol %)	none	0.5	0.5
2	dtbpy (10 mol %)	none	1.7	0.7
3	dtbpy (10 mol %)	with blue LED light	1.7	0.7
4	dtbpy (10 mol %)	with $Ir(ppy)_3$ (1 mol %), blue LED light	2.7	0.5

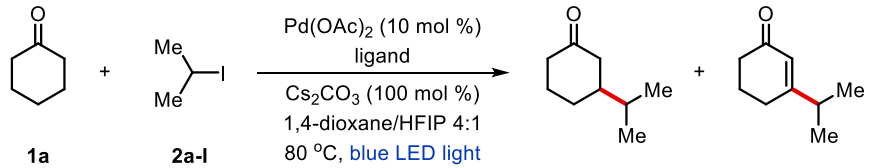
[a]All the reactions were run with **1a** (0.25 mmol) and **2a-I** (0.1 mmol) in 1,4-dioxane (0.4 mL) and HFIP (0.1 mL) for 18 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard.

a photoredox catalyst, was used as the cocatalyst with blue LED light, the yield was slightly enhanced (entry 4).

Based on our previous experience on β-arylation reactions, the palladium catalyst would be poisoned by iodide anions, which would lose catalytic activity for ketone desaturation step. Indeed, we were able to isolate a stable species, *trans*-Pd[P(*i*-Pr)$_3$]$_2$I$_2$, from the reaction system when P(*i*-Pr)$_3$ was used as the ligand. Therefore, suitable halide scavenger would be necessary to regenerate the active catalyst. However, alkyl iodides were found incompatible with silver salts which might directly trigger carbocation generation with silver iodide precipitation.

Notably, this problem was later solved by using cesium salts as the halide scavenger, among which cesium carbonate was the optimal additive (Table 3.2). It is worth mentioning that cesium carbonate alone did not lead to any boost in yield when dtbpy served as the ligand (entry 1), but its cooperation with photoredox cocatalyst provided 18% yield of the desired product using Ir(ppy)$_3$ and blue LED light (entry 2). In addition, Ru(bpy)$_3$(PF$_6$)$_2$ could also promote this reaction as a photocatalyst (entry 3). On the other hand, when electron-rich P(*i*-Pr)$_3$ was used as the ligand, photoredox cocatalyst was no longer necessary to enhance the reactivity (entries 4 and 5). The difference between the two ligands indicates that the alkyl radical generation could only be effectively triggered by electron-rich palladium species, while merging photoredox catalysis could also assist the single-electron processes, though the exact role of the photocatalyst remained unclear and its enhancement was marginal for P(*i*-Pr)$_3$.

Table 3.2 Photoredox Catalyst Screening for the β-Alkylation of Cyclohexanone[a]



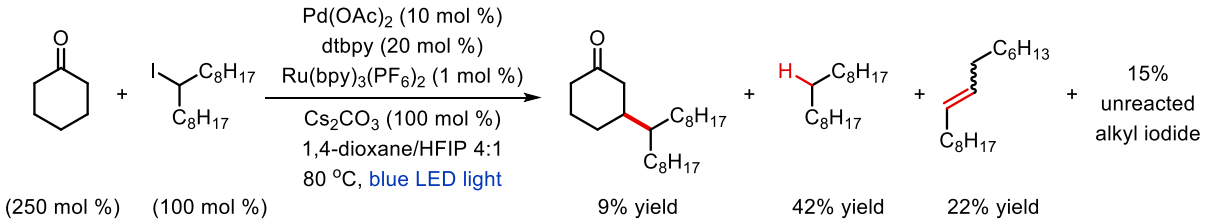
1a (250 mol %) + **2a-I** (100 mol %) → **3a** + **3a'**

entry	ligand	photocatalyst	yield of **3a** (%)[b]	yield of **3a'** (%)[b]
1	dtbpy (10 mol %)	none	1	0.2
2	dtbpy (10 mol %)	$Ir(ppy)_3$ (1 mol %)	18	5
3	dtbpy (10 mol %)	$Ru(bpy)_3(PF_6)_2$ (1 mol %)	22	1
4	P(*i*-Pr)$_3$ (20 mol %)	none	18	3
5	P(*i*-Pr)$_3$ (20 mol %)	$Ir(ppy)_3$ (1 mol %)	20	3

[a]All the reactions were run with **1a** (0.25 mmol) and **2a-I** (0.1 mmol) in 1,4-dioxane (0.4 mL) and HFIP (0.1 mL) for 18 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard.

However, further attempts to improve the efficiency of this transformation was not fruitful. In order to identify the major problem of this transformation, we synthesized a heavier secondary alkyl iodide to track the possible side products and the substrate recovery (Scheme 3.4). Though the yield was lower with this substrate, it still clearly showed that the major issue came from two side reactions: reductive deiodination to give the alkane (42% yield), and elimination of HI to give the alkenes (22% yield). We reasoned that the elimination of HI may directly arise from alkyl iodide in the presence of base. However, the reductive deiodination should come from C−H abstraction of the alkyl radical species, indicating that the radical generation process is not a problem, but the radical conjugate addition step is much less efficient. Notably, such an observation is consistent with other previously mentioned reaction conditions.

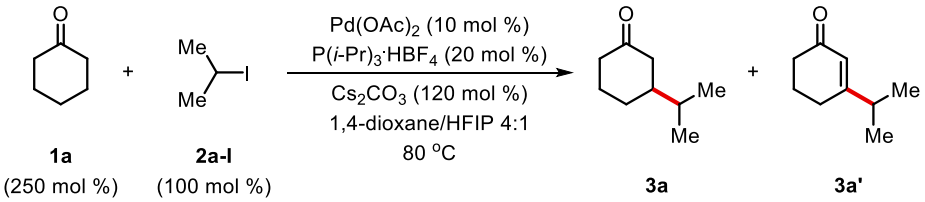
Scheme 3.4 Mass Balance for the β-Alkylation of Cyclohexanone



Actually, such a high ratio of the reductive deiodination side product revealed a key challenge of this strategy: different from the reported Pd(I)-mediated alkyl-Heck reactions, in this transformation, the enone is generated *in situ* from desaturation of the saturated ketone with the Pd(II) catalyst. Therefore, at any given time, only a catalytic amount of enone exists in this system. As a consequence, if the generated unstabilized alkyl radical species cannot react with the enone in a timely fashion, side reactions would occur, among which C−H abstraction is the predominant pathway. Given the high reactivity of radical species, we anticipated that a radical stabilizer would be the key to extend the lifetime of the alkyl radical species, thereby improving the selectivity towards conjugate addition.

Our inspiration came from the copper-catalyzed atom transfer radical polymerization (ATRP) reactions, where the copper catalyst could reversibly generate the radical species from an alkyl halide, thus stabilizing the reactive radical intermediate.[22] Considering the excellent redox properties of the copper salt, we started testing copper cocatalysts in the reaction system (Table 3.3). Fortunately, the reactivity was indeed improved, and among all the Cu(I) salts tested, copper(I) acetate was found optimal (entry 7). Interestingly, copper(II) acetate was also found effective, likely indicating that Cu(I) and Cu(II) species are interconvertible in the reaction system (entry 8).

Table 3.3 Copper Cocatalyst Screening for the β-Alkylation of Cyclohexanone[a]



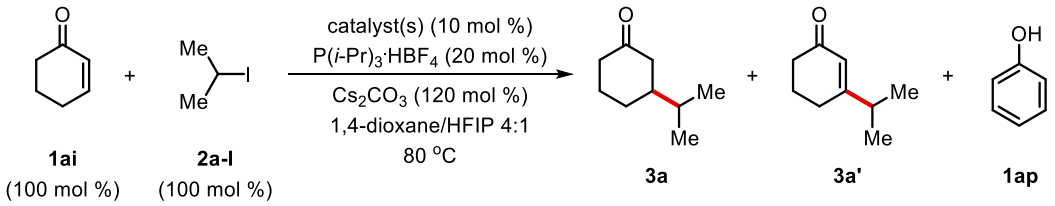
1a (250 mol %) + **2a-I** (100 mol %) → **3a** + **3a'**

entry	Cu cocatalyst (10 mol %)	yield of **3a** (%)[b]	yield of **3a'** (%)[b]
1	CuCl	22	0.5
2	CuBr	17	1
3	CuI	24	1
4	CuCN	0	0
5	$Cu(MeCN)_4PF_6$	14	0.3
6	CuTC	25	1
7	CuOAc	27	1
8	$Cu(OAc)_2$	24	0.3

[a]All the reactions were run with **1a** (0.25 mmol) and **2a-I** (0.1 mmol) in 1,4-dioxane (0.4 mL) and HFIP (0.1 mL) for 18 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard.

As the copper cocatalyst is clearly playing a role in the reaction, we further examined whether copper alone was effective in the radical generation process. In order to exclude the influence from the ketone desaturation step, we directly used enone (**1ai**) as the substrate instead of ketone (Table 3.4). Obviously, palladium alone could catalyze the conjugate addition step along with the formation of phenol (**1ap**) for Pd(0) generation (entry 1). When palladium and copper(I) were both used, the overall efficiency stayed similar, but the overoxidation ratio was significantly lower (entry 2). Copper alone, however, did not lead to any reactivity (entry 3), demonstrating that palladium is still responsible for radical generation from alkyl halides, while copper plays a role after radicals are formed, which is different from the role of copper catalyst in ATRP reactions.[22]

Table 3.4 Reaction of 2-Iodopropane with 2-Cyclohexen-1-one[a]



entry	catalyst(s)	yield of **3a** (%)[b]	yield of **3a'** (%)[b]	yield of **1ap** (%)[b]
1	$Pd(OAc)_2$	36	10	22
2	$Pd(OAc)_2$ + CuOAc	39	2	27
3	CuOAc	0	0	0

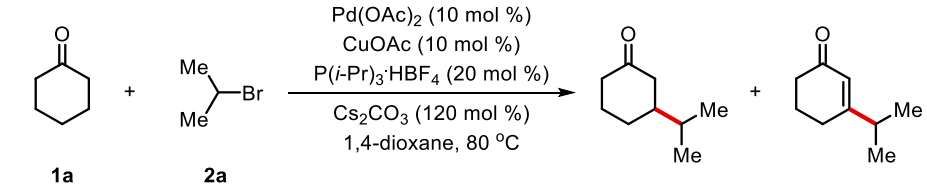
[a]All the reactions were run with **1a** (0.25 mmol) and **2a-I** (0.1 mmol) in 1,4-dioxane (0.4 mL) and HFIP (0.1 mL) for 18 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard.

One observation drawing our attention was that the overoxidation seemed to be suppressed by the copper cocatalyst (Table 3.4, entries 1 and 2). Therefore, it is likely that the copper cocatalyst plays multiple roles in enhancing the reactivity and selectivity. Though the exact function of copper was obscure at that stage, these results were sufficient to support the positive effects of copper in the radical processes, thus leading us to move forward with the Pd/Cu dual catalytic system.

As discussed earlier, the elimination of HI from alkyl iodides is another major side reaction (Scheme 3.4). Replacing alkyl iodides with less vulnerable alkyl bromides may help solve this issue, but it would also be more challenging for radical generation processes. Fortunately, with the help of acetic acid additive in lieu of HFIP cosolvent, 2-bromopropane (**2a**) successfully coupled with cyclohexanone (Table 3.5, entry 1), giving comparable yield as 2-iodopropane. The acid additive might help adjust the acidity of the reaction system, thus rendering optimal catalytic

behavior. A catalytic amount of acetic acid was found sufficient (entry 2), while the efficiency dropped significantly in the absence of any acid (entry 3).

Table 3.5 β-Alkylation of Cyclohexanone Using Alkyl Bromide[a]



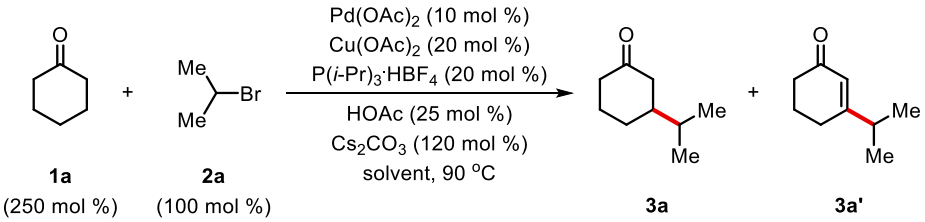
1a (250 mol %) + **2a** (100 mol %) → **3a** + **3a'**

entry	additive	yield of **3a** (%)[b]	yield of **3a'** (%)[b]
1	HOAc (100 mol %)	27	1
2	HOAc (25 mol %)	31	2
3	none	7	1

[a]All the reactions were run with **1a** (0.25 mmol) and **2a** (0.1 mmol) in 1,4-dioxane (0.5 mL) for 18 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard.

Based on these results, the yield could be further improved to 49% by using $Cu(OAc)_2$ (20 mol %) cocatalyst with increased concentration (1.0 M) at slightly elevated temperature (Table 3.6, entry 1). At this stage, benzene was found superior to 1,4-dioxane likely because of its innocence in radical involved reactions (entry 2). However, the solubility of the copper salt was not ideal in benzene, so a mixed solvent using benzene and another polar solvent (methyl acetate) was found effective (entry 3), and a 10:1 ratio was optimal (entry 4). Finally, the solubility concern was further addressed by using copper(II) pivalate as the cocatalyst, delivering the desired β-alkylation product in 65% yield, and the selectivity versus overoxidation was greater than 20:1 (entry 5). Notably, the potential α-alkylation of ketone was not observed under the optimal reaction conditions.

Table 3.6 Final Optimization for β-Alkylation of Cyclohexanone[a]



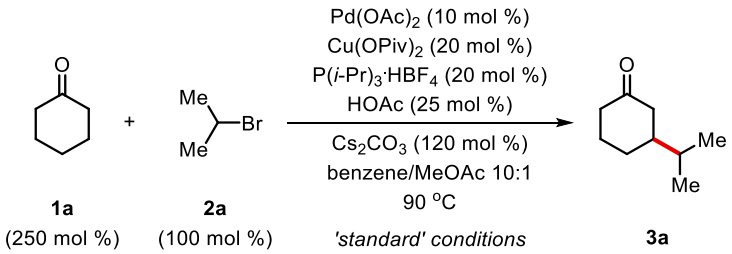
1a (250 mol %) + **2a** (100 mol %) → **3a** + **3a'**

entry	solvent	variation	yield of **3a** (%)[b]	yield of **3a'** (%)[b]
1	1,4-dioxane	none	49	3
2	benzene	none	53	3
3	benzene/MeOAc 3:1	none	59	3
4	benzene/MeOAc 10:1	none	61	3
5	benzene/MeOAc 10:1	$Cu(OPiv)_2$ instead of $Cu(OAc)_2$	65	3

[a]All the reactions were run with **1a** (1.0 mmol) and **2a** (0.4 mmol) in indicated solvent (0.4 mL) for 18 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard.

A number of control experiments were then conducted to understand the role of each component (Table 3.7). First, a high concentration of the ketone substrate appeared to be necessary to maintain fast desaturation, since lower efficiency was observed when the ketone and alkyl bromide were used in 1:1 ratio (entry 2). A comparable yield was obtained when the reaction was performed in the dark (entry 3), suggesting that light is indeed not needed for the radical generation in this reaction. Alkyl iodide was again less effective (entry 4), and alkyl chloride was not reactive for this transformation (entry 5). Unsurprisingly, no product was detected without palladium (entry 6), and the ligand played a pivotal role (entries 7−9). P(*i*-Pr)$_3$ was optimal due to its electronic richness and proper steric bulkiness, as bulkier P(*t*-Bu)$_3$ or less electron-rich PPh_3 gave much lower yields. Though 20% yield could still be obtained in the absence of copper cocatalyst, it nevertheless

Table 3.7 Variations from the 'Standard' Conditions for β-Alkylation of Cyclohexanone[a]



1a (250 mol %) + **2a** (100 mol %) — *'standard' conditions* → **3a**

entry	variations from the 'standard' conditions	yield of **3a** (%)[b]
1	none	65 (63)[c]
2	**1a** : **2a** = 1:1	34
3	performed in the dark	63
4	2-iodopropane instead of **2a**	40
5	2-chloropropane instead of **2a**	1
6	without $Pd(OAc)_2$	0
7	without $P(i\text{-}Pr)_3{\cdot}HBF_4$	2
8	$P(t\text{-}Bu)_3{\cdot}HBF_4$ instead of $P(i\text{-}Pr)_3{\cdot}HBF_4$	1
9	PPh_3 instead of $P(i\text{-}Pr)_3{\cdot}HBF_4$	5
10	without $Cu(OPiv)_2$	20
11	$Cu(OPiv)_2$ 10 mol % instead of 20 mol %	61
12	CuOAc instead of $Cu(OPiv)_2$	59
13	benzene as solvent (without MeOAc)	63
14	MeOAc as solvent	54
15	K_2CO_3 instead of Cs_2CO_3	1
16	$CsHCO_3$ instead of Cs_2CO_3	34
17	CsOAc instead of Cs_2CO_3	21
18	without HOAc	38

[a]Unless otherwise noted, all the reactions were run with **1a** (1.0 mmol) and **2a** (0.4 mmol) in benzene (0.4 mL) and MeOAc (0.04 mL) for 18 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard. [c]Yield in the parenthesis refers to the isolation yield.

demonstrated that copper is crucial for improved efficiency (entry 10) (for detailed discussion on the role of copper cocatalyst, see section 3.2.4).[23] Meanwhile, lowering the Cu loading to 10 mol %

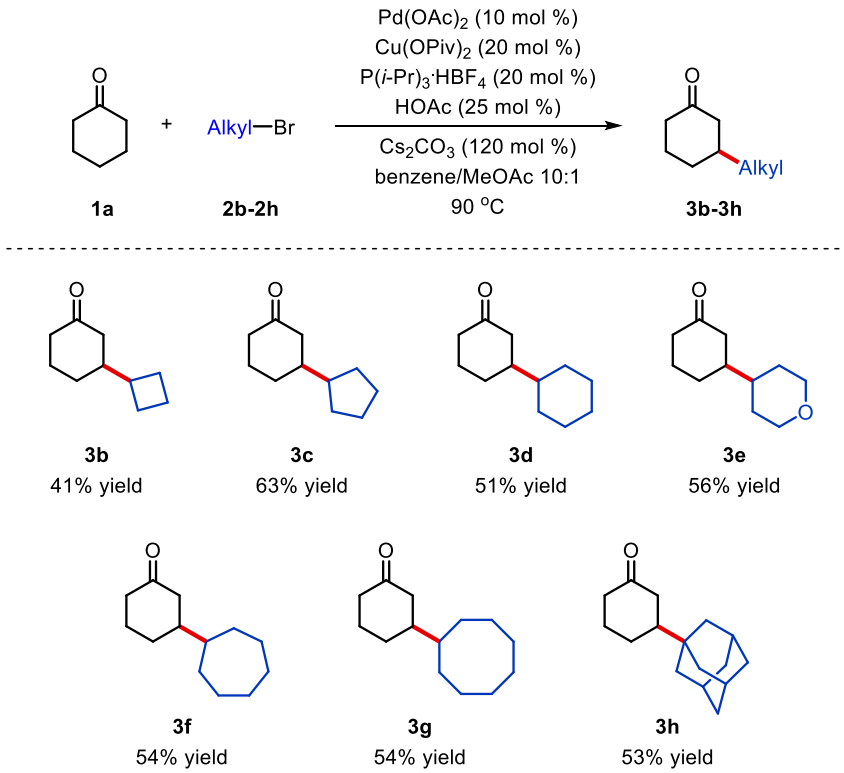
maintained its catalytic activity (entry 11), and switching to Cu(I) precatalyst only slightly reduced the yield (entry 12). With the highly soluble $Cu(OPiv)_2$ salt, though a mixed solvent was still optimal, benzene alone as the solvent also gave a comparable yield (entry 13) while methyl acetate alone gave worse results (entry 14). The role of Cs_2CO_3 was proposed to first neutralize the HBr generated in the reaction and second serve as a halide scavenger due to the low solubility of CsBr, given lower efficiency using potassium carbonate or other cesium bases (entries 15−17). A catalytic amount of acetic acid was still beneficial under the optimal conditions for tuning the acidity of the reaction mixture (entry 18).

3.2.2 Substrate scope for the β-alkylation of ketones

The substrate scope of the alkyl bromides was then investigated under the 'standard' conditions with cyclohexanone (Scheme 3.5). Besides isopropyl bromide, cyclic alkyl bromides, ranging from 4- to 8-membered rings, smoothly delivered the desired products in moderate to good yields (**3b**−**3g**). Attributed to the radical pathway, tertiary alkyl bromides were also found viable substrates in this transformation such as 1-bromoadamantane (**3h**).

Unfortunately, alkyl bromides with increased steric hindrance were found less reactive for β-alkylation of cyclohexanone, likely because the conjugate addition step is sensitive to steric repulsion. In order to further expand the substrate scope of alkyl bromides, we managed to use propiophenone (**1b**) as the substrate, which would generate a less hindered terminal enone (Table 3.8). Though the yield was moderate under the 'standard' reaction conditions, the undesired over-

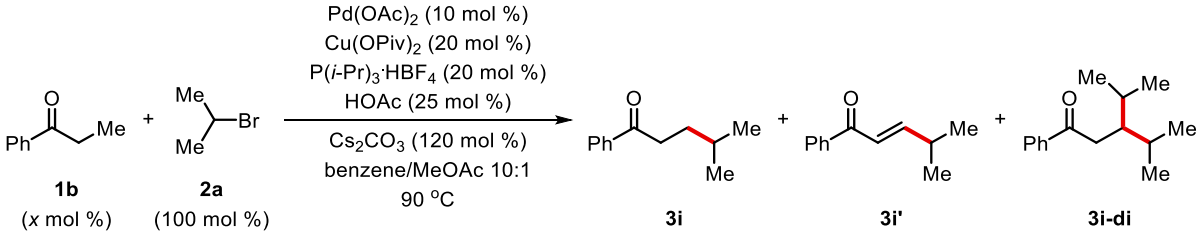
Scheme 3.5 Substrate Scope of Alkyl Bromides with Cyclohexanone[a]



[a]All the reactions were run with **1a** (1.0 mmol) and **2** (0.4 mmol) in benzene (0.4 mL) and MeOAc (0.04 mL) for 18 h. All yields refer to the isolation yields.

oxidation and di-alkylation products were both observed in relatively small amount (entry 1). In fact, the overoxidation has been an unsolved problem for linear ketones during the previous β-functionalization studies, because the increased flexibility of the ketone skeleton leads to a higher propensity of the alkylated Pd-enolate to undergo further β-hydrogen elimination. However, as we realized that copper cocatalyst helps suppress overoxidation, it becomes a tolerable issue in this case. A higher efficiency for coupling propiophenone was achieved by increasing its loading to 5 equivalents, giving 51% yield of the mono-alkylation product along with overoxidation and di-alkylation in 10:1 and >20:1 ratio, respectively (entry 2).

Table 3.8 Condition Variation for β-Alkylation of Propiophenone

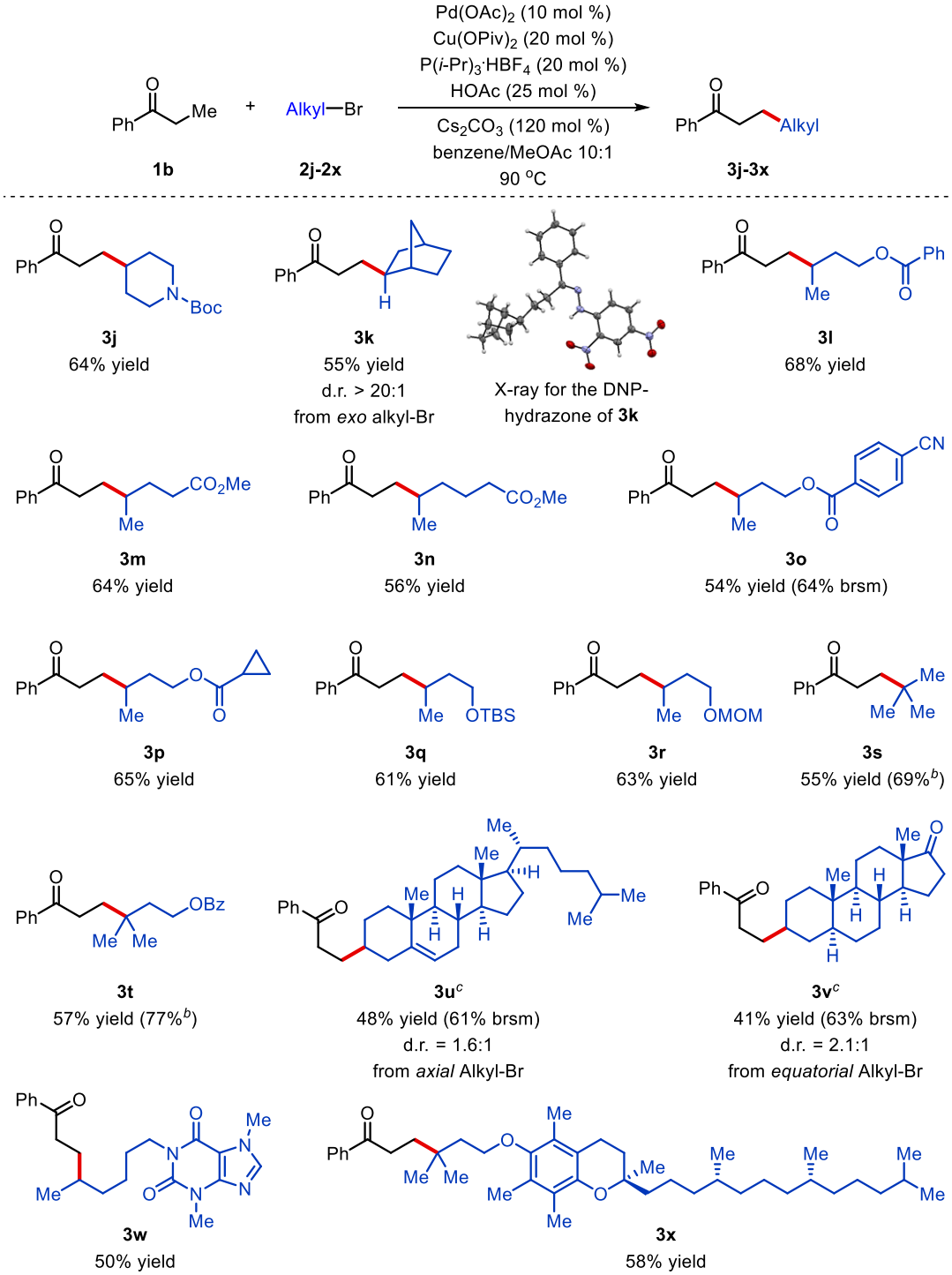


entry	*x*	yield of **3i** (%)[c]	yield of **3i'** (%)[c]	yield of **3i-di** (%)[c]
1[a]	250	43	5	5
2[b]	500	51 (51)[d]	5	2

[a]The reaction was run with **1b** (1.0 mmol) and **2a** (0.4 mmol) in benzene (0.4 mL) and MeOAc (0.04 mL) for 18 h. [b]The reaction was run with **1b** (1.0 mmol) and **2a** (0.2 mmol) in benzene (0.4 mL) and MeOAc (0.04 mL) for 18 h. [c]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard. [d]Yield in the parenthesis refers to the isolation yield.

Next, we explored a wider range of alkyl bromides using propiophenone as the ketone substrate (Scheme 3.6). Interestingly, alkyl bromides bearing a heteroatom substituent typically gave higher yields (e.g. 68% for **3l**). Though the exact reason was not clear, we postulated that the weak coordination of these heteroatoms with palladium might facilitate its interaction with the alkyl bromide moiety. Attributed to the near-neutral reaction conditions, acid- and base-reactive functional groups were well tolerated, including Boc-protected amines (**3j**), esters (**3l**–**3p**), nitriles (**3o**), cyclopropane moieties (**3p**), benzoyl-, TBS- and MOM-protected alcohols (**3l**, **3q**, **3r**), amides (**3w**), electron-rich olefins (**3u**) and cyclic ketones (**3v**). 2-Bromonorbornane gave the alkylation at the *exo* face of norbornane (**3k**), which was confirmed by X-ray crystallography. Tertiary alkyl bromides also worked well for linear ketones (**3s**, **3t**), but the overoxidation became

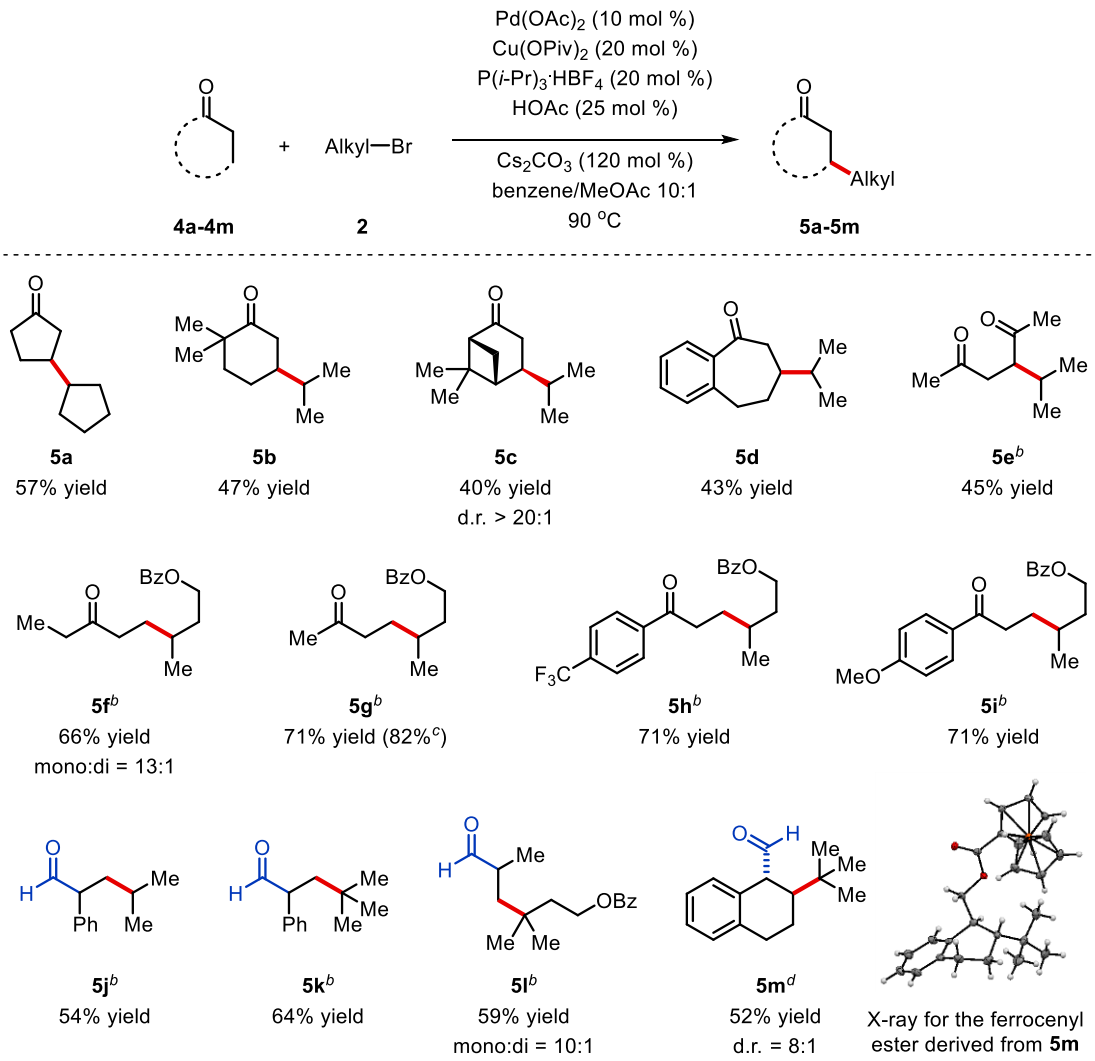
Scheme 3.6 Substrate Scope of Alkyl Bromides with Propiophenone[a]



[a]All the reactions were run with **1b** (1.0 mmol) and **2** (0.2 mmol) in benzene (0.4 mL) and MeOAc (0.04 mL) for 18 h. All yields refer to the isolation yields. [b]Yield in the parentheses was obtained when a one-pot hydrogenation was conducted after the reaction. [c]15 mol % $Pd(OAc)_2$, 30 mol % P(*i*-Pr)$_3$·HBF_4 and 30 mol % $Cu(OPiv)_2$ were used.

somewhat competitive. A one-pot hydrogenation protocol could be adopted to unify the product and ease the isolation. Alkyl bromides derived from bioactive natural products, such as cholesterol (**3u**), androsterone (**3v**), pentoxyphylline (**3w**), and α-tocopherol (**3x**), also smoothly afforded the desired coupling products.

Scheme 3.7 Substrate Scope of Ketones and Aldehydes[a]



[a]Unless otherwise noted, all the reactions were run with **1** (1.0 mmol) and **2** (0.4 mmol) in benzene (0.4 mL) and MeOAc (0.04 mL) for 18 h. All yields refer to the isolation yields. [b]The reactions were run with **1** (1.0 mmol) and **2** (0.2 mmol) in benzene (0.4 mL) and MeOAc (0.04 mL) for 18 h. [c]Yield in the parentheses was obtained when a one-pot hydrogenation was conducted after the reaction. [d]The product was isolated as an alcohol after $NaBH_4$ reduction.

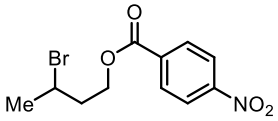
The scope of the carbonyl substrates was further explored (Scheme 3.7). Cyclic ketones, such as cyclopentanone (**5a**), poly-substituted cyclohexanones (**5b**, **5c**) and benzocycloheptanone (**5d**), were competent substrates. The 1,4-diketone also yielded the desired product (**5e**). Simple linear ketones, e.g. 3-pentanone (**5f**) and 2-butanone (**5g**), exhibited higher reactivity. In addition, propiophenones with trifluoromethyl or methoxy substituents at the *para* position afforded the desired β-alkylation products in good yields (**5h**, **5i**). Intriguingly, aldehydes with α-branches were also feasible substrates under the identical reaction conditions (**5j**–**5m**). The α-substituents were important to prevent self-aldol condensation reactions. Nevertheless, both secondary and tertiary alkyl bromides could effectively couple with α-aryl- or alkyl-substituted aldehydes. In particular, the aldehyde containing a cyclic structure gave predominately the *trans*-product (**5m**).

In addition to these viable substrates, limitations were also found for many other alkyl bromides and carbonyl compounds (Scheme 3.8). First, some sensitive functional groups were found incompatible with the reaction system: nitro group might interfere with the radical processes (**2y**); aryl bromide would preferably undergo oxidative addition with Pd(0) catalyst (**2z**); thiophene might have strong coordination with palladium, thus diminishing its catalytic activity (**2aa**); free alcohol was also vulnerable in this reaction (**2ab**). Moreover, β-bromoester easily decomposed via elimination of HBr (**2ac**). Unexpectedly, (1-bromoethyl)benzene (**2ad**) seemed like a viable substrate due to easier radical generation, but the resulting secondary benzylic radicals might be too stable, which was reluctant to undergo conjugate addition. Instead, the radical dimerization product was detected for **2ad**, which was seldom observed for other alkyl bromides. Lastly, primary alkyl bromides are potentially viable substrates, but they suffer from low reaction rates

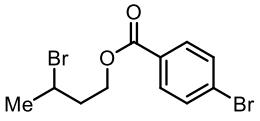
and undesired S_N2 reactions with acetate or pivalate salts. In fact, neopentyl bromide delivered the desired product in 12% yield (**2ae**).

Scheme 3.8 Selected Challenging Substrates for β-Alkylation of Ketones

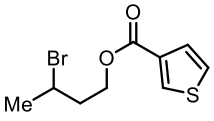
Alkyl bromides



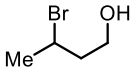
2y
0% yield with **1b**



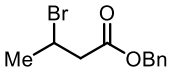
2z
0% yield with **1b**



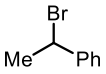
2aa
28% yield with **1b**



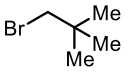
2ab
0% yield with **1b**



2ac
0% yield with **1b**

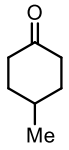


2ad
<5% yield with **1b**

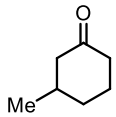


2ae
12% yield with **1b**
mono:di = 10:1

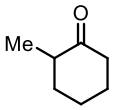
Ketones and aldehydes



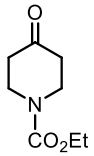
4n
33% yield with **2a**



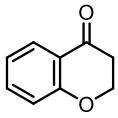
4o
39% yield with **2a**



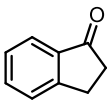
4p
30% yield with **2a**



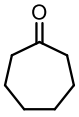
4q
26% yield with **2a**



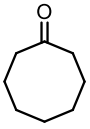
4r
37% yield with **2a**



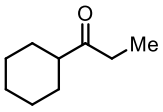
4s
18% yield with **2a**



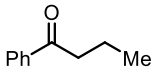
4t
20% yield with **2a**



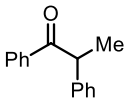
4u
29% yield with **2a**



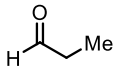
4v
36% yield with **2a**



4w
28% yield with **2a**



4x
33% yield with **2a**



4y
0% yield with **2t**

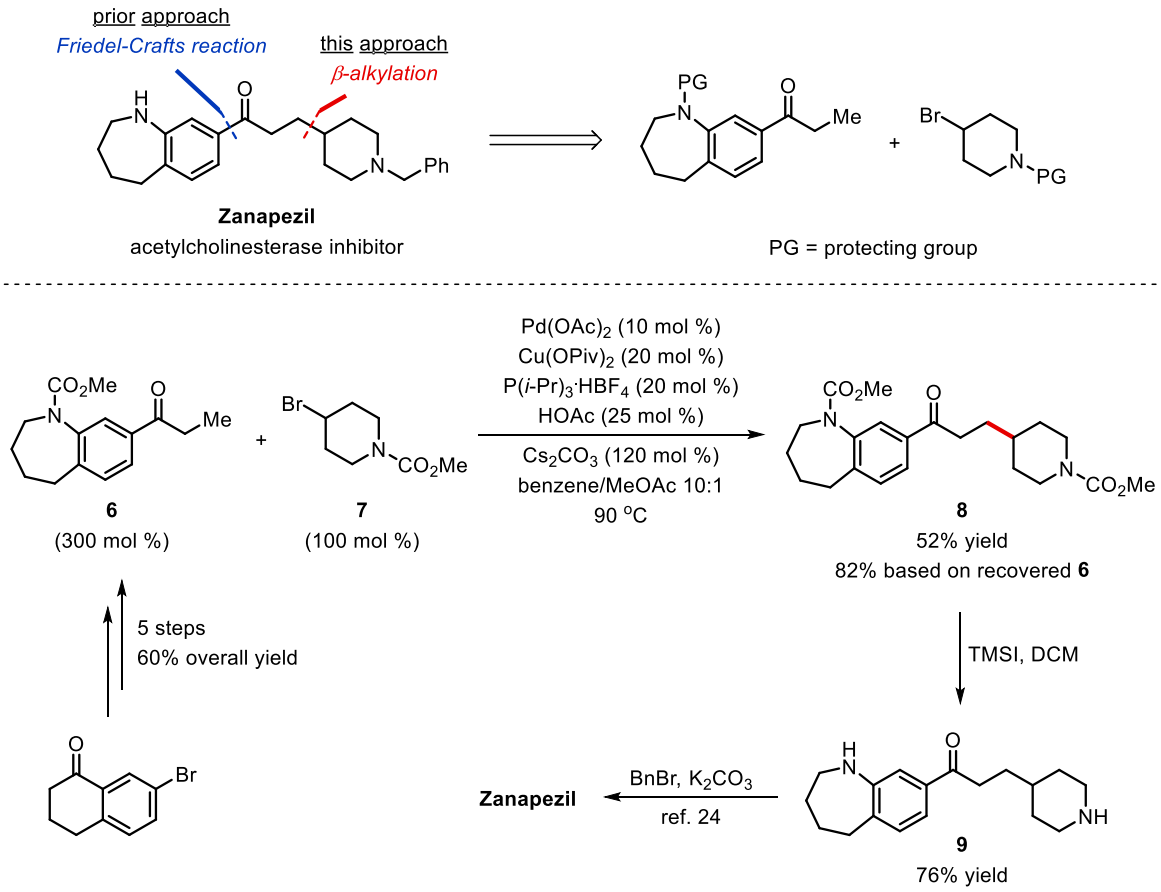
In terms of the carbonyl scope, unfortunately, sensitivity to the steric effect of the ketone moiety was observed, as C4-, C3- and C2-monosubstituted cyclohexanones all gave moderate

yields (**4n**−**4p**). Electronic effect was another concern, since protected 4-piperidinone and 4-chromanone suffered from low efficiency of the conjugate addition step arising from diminished electrophilicity of the enone intermediates (**4q**, **4r**). In addition, 1-indanone, unsubstituted cycloheptanone and cyclooctanone all gave unsatisfactory yields (**4s**−**4u**). For linear ketones, again, increased steric hindrance leads to decreased efficiency, including the carbonyl, β and α positions of the ketone (**4v**−**4x**). Finally, aldehydes without α-branches were ineffective substrates due to facile self-aldol condensation reactions.

3.2.3 Synthesis of Zanapezil

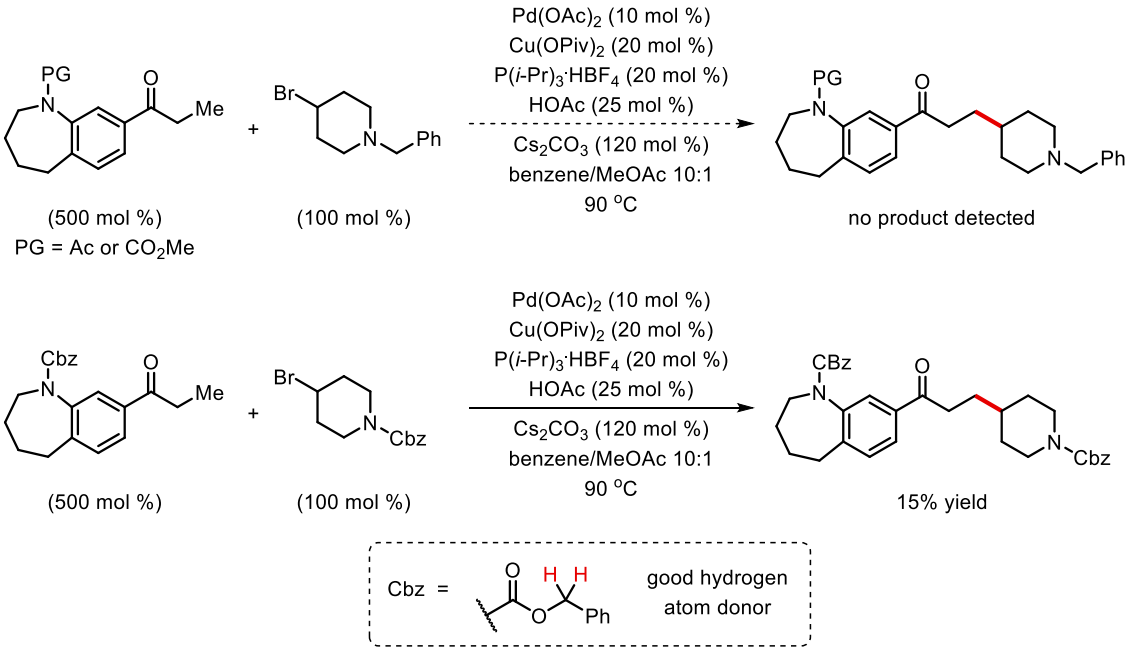
The synthetic utility of this method is illustrated in a concise formal synthesis of Zanapezil, a selective acetylcholinesterase inhibitor (Scheme 3.9).[24] Previously it has been synthesized using Friedel-Crafts acylation in the late stage, which suffered from unsatisfactory regioselectivity. Our β-alkylation strategy provides an alternative bond disconnection strategy, which could trace back to a ketone precursor and a simple secondary alkyl bromide. Among all the protecting groups tested, methoxycarbonyl group was found optimal. Therefore, we adopted ketone **6** as the ketone substrate, which could be synthesized from readily available 7-bromo-1-tetralone in 5 steps with great overall efficiency. Ketone **6** could smoothly undergo β-alkylation with alkyl bromide **7** under the 'standard' reaction conditions. Notably, the loading of **6** could be lowered to 3 equivalents while maintaining the reactivity (compared with 5 equivalents for most linear ketone substrates), and most unreacted ketone could be easily recovered, giving 82% yield of the product based on recovered **6**. Finally, global deprotection and selective benzylation could deliver Zanapezil as the target.

Scheme 3.9 Formal Synthesis of Zanapezil



Before we moved forward with substrates **6** and **7**, attempts on other potential substrates had been made, especially with protecting groups that were easier to remove (Scheme 3.10). Directly using 1-benzyl-4-bromopiperidine as the substrate would be desirable for saving one subsequent step, but the reaction was found sluggish. Even if we used Cbz protecting group instead of methoxycarbonyl, the reaction only delivered 15% yield of the product, which might be caused by the undesired interaction between radical species and the highly reactive benzylic C−H bonds. In addition, Boc protection group was also examined, but unfortunately, the ketone substrate bearing a Boc-protected amine moiety was not sufficiently stable.

Scheme 3.10 Unsuccessful Trials towards the Synthesis of Zanapezil



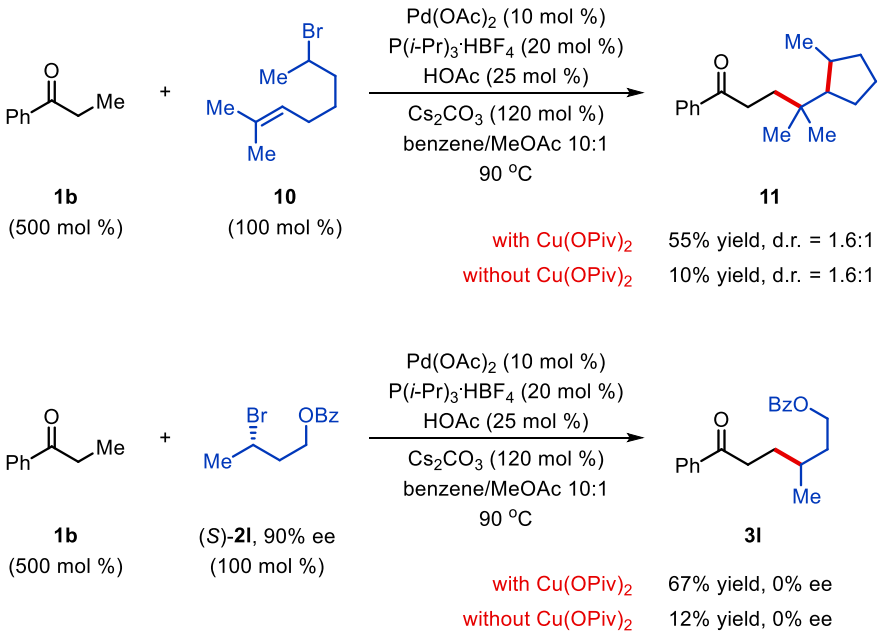
3.2.4 Mechanistic studies

The involvement of alkyl radical species in this transformation has been particularly intriguing to us. Merging the two-electron ketone desaturation process with the single-electron chemistry brought us indispensable opportunities to achieve the β-alkylation of ketones and aldehydes, but also came with unprecedented challenges. Till now, three major concerns remained about the mechanism of this transformation, which are (a) whether free radical intermediates truly exist in this transformation, (b) what exactly the role of the copper cocatalyst is, and (c) concerning the main side reaction, radical C−H abstraction, what serves as the hydrogen atom donor.

First, to probe the radical participation in this reaction (Scheme 3.11), a radical clock experiment was conducted. When alkyl bromide **10** with a tethered trisubstituted olefin was subjected to the reaction conditions, ketone **11** was obtained as the only product in which the 5-

exo-trig cyclization proceeded prior to the conjugate addition.[25] This observation is consistent with the proposed radical-involved mechanism, as the cyclization would be sluggish for the alternative oxidative addition/migratory insertion pathway due to the steric hindrance of the olefin. Additionally, an enantioenriched alkyl bromide (*S*)-**2l** with 90% enantiomeric excess delivered the racemic alkylation product, which also indicates alkyl radicals to be reasonable intermediates. Notably, both results are consistent in the absence of copper and the only difference is the lower yields, which further suggested that the radical generation process is only associated with palladium, while copper started to play a role after radicals are generated.

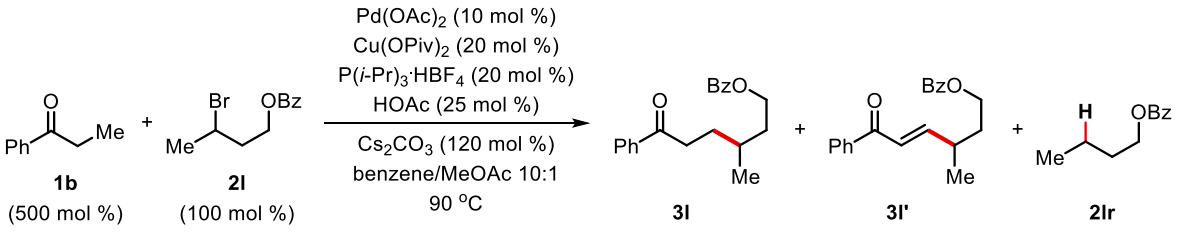
Scheme 3.11 Experiments for Probing the Radical Involvement



Unfortunately, due to the high complexity of the reaction system, the role of copper cocatalyst would be hard to clearly illustrate. Nonetheless, we could gain some insight through the detailed analysis of the reaction between **1b** and **3l** by tracking the mass balance of the reaction

(Table 3.9). Under the 'standard' conditions (entry 1), the β-alkylation product (**3l**) and overoxidation product (**3l'**) were observed in 68% and 7% yield, respectively. While all the alkyl bromide substrate was fully consumed, the reductive debromination product (**2lr**), generated via radical C−H abstraction, was almost the exclusive side product, as the mass balance could reach 98% by counting these three observable products. Though the radical C−H abstraction is not completely inhibited, it is nonetheless significantly suppressed by adding copper. In contrast, in the absence of copper (entry 2), the yield of **3l** dropped dramatically along with a lower conversion. Importantly, both overoxidation and reductive debromination side products were observed in a much higher ratio.

Table 3.9 Mass Balance of the β-Alkylation of Propiophenone[a]



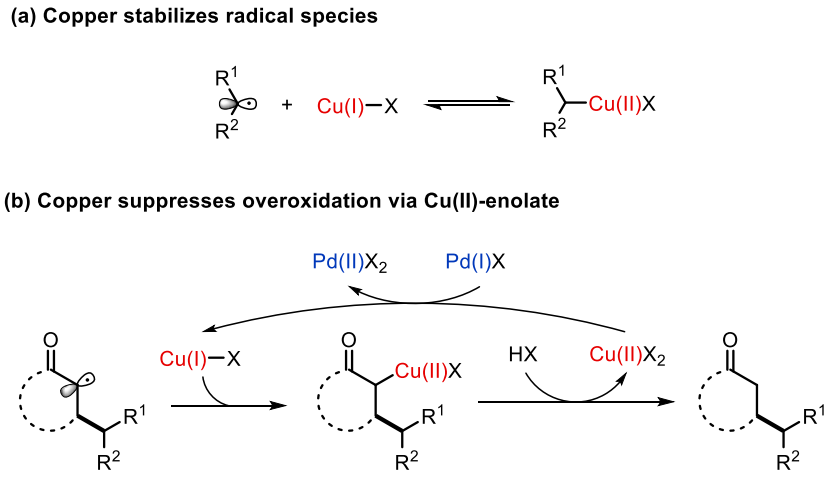
entry	variation	yield of **3l** (%)[b]	yield of **3l'** (%)[b]	yield of **2lr** (%)[b]	unreacted **2l** (%)[b]	total (%)	**3l** : **3l'**	**3l** : **2lr**
1	none	68	7	23	0	98	10:1	3:1
2	without $Cu(OPiv)_2$	12	6	42	25	85	2:1	1:4

[a]All the reaction was run with **1b** (1.0 mmol) and **2l** (0.2 mmol) in benzene (0.4 mL) and MeOAc (0.04 mL) for 18 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard.

By comparing the ratio of the two side products between the above two entries, we hypothesized that the role of copper cocatalyst in this reaction is at least two-fold (Scheme 3.12). First, copper successfully enhances the selectivity of the radical intermediate to undergo conjugate

addition rather than C−H abstraction, indicating that copper stabilizes the radical species, likely through a reversible combination mode, which elongates the lifetime of the radical and improves its chance to find less concentrated but more reactive enones. Second, overoxidation ratio is greatly improved by copper, suggesting that after radical conjugate addition, the generated ketone α-radical species could recombine with Cu(I) to give the Cu(II)-enolate instead of Pd(I),[9c,26] which avoids the potential β-hydrogen elimination of the β-alkylated Pd(II)-enolate that delivers undesired overoxidation product. The resulting Cu(II) could oxidize Pd(I) intermediate back to Pd(II) with itself being reduced to Cu(I) for the next cycle.

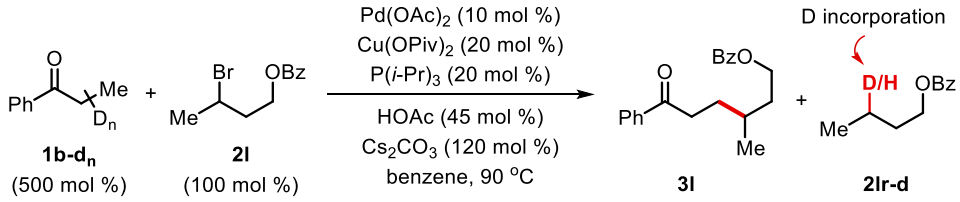
Scheme 3.12 Possible Roles of Copper Cocatalyst

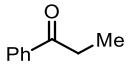
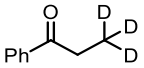
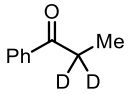
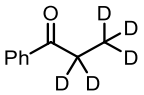
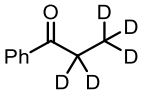


Though the radical C−H abstraction process could not be fully eliminated, it would be intriguing to know where the hydrogen atoms actually come from. In order to avoid potential influences, we simplified the reaction conditions by using P(*i*-Pr)$_3$ instead of its HBF_4 salt, so that acetic acid was the only external proton source. Moreover, methyl acetate was removed (Table 3.10). Not surprisingly, benzene is not an effective hydrogen atom donor (entry 1). In addition, β-

deuterated propiophenone led to marginal deuterium incorporation (entry 2), while α-deuterated one gave 22% incorporation ratio (entry 3, deuterated acetic acid was used in this case to prevent α-deuterium loss due to proton exchange). This is consistent with the bond dissociation energy data, as α-C−H bonds of ketones are generally weaker than β-C−H bonds.[27] However, when α,β-perdeuterated propiophenone was used, the incorporation ratio was further enhanced to 49% (entry 4). Obviously, β-C−H bonds serve as more effective hydrogen atom donors when α-C−H bonds are deuterated. We attribute this phenomenon to the kinetic isotope effect, because C−D bonds are

Table 3.10 Deuterium-Labeling Experiments for the Study of Radical C−H Abstraction[a]



entry	**1b-d_n**	condition variations	D incorporation ratio (%)[b]
1		benzene-d_6 instead of benzene	0
2		none	<5%
3		HOAc-d_4 instead of HOAc	22%
4		HOAc-d_4 instead of HOAc	49%
5		HOAc-d_4 instead of HOAc P(*i*-Pr)$_3$-d_{21} instead of P(*i*-Pr)$_3$	51%

[a]Unless otherwise noted, all the reactions were run with **1b-d_n** (1.0 mmol) and **2l** (0.2 mmol) in benzene (0.4 mL) for 18 h. [b]NMR ratio determined from the isolated reductive debromination product.

kinetically harder to break than C−H bonds. Therefore, stronger C−H bonds are more likely abstracted when weaker C−H bonds are replaced by C−D bonds. This also explains why the deuterium incorporation ratio is still only ca. 50% when all the highly concentrated ketones are deuterated, because other C−H bonds present in the system, e.g. alkyl bromide, ligand or α-deuterium loss by trace amount of water, become kinetically competent (entry 5). Overall, there is no single hydrogen atom donor in the reaction system, since C−H bonds are abundant, any C−H bond could be abstracted though weaker C−H bonds have higher chances.

3.3 Conclusion

In summary, we have developed a new method for direct β-alkylation of simple ketones and α-branched aldehydes via Pd-catalyzed redox cascade. Different from existing β-functionalization methods, this strategy permits the use of simple and readily available alkyl bromides as the alkylation source. The success of the radical redox cascade is highlighted by the use of a copper cocatalyst that enhances the efficiency by suppressing both radical C−H abstraction and overoxidation. In addition, merging a radical process with Pd-catalyzed desaturation should also have implications beyond this work. Considering the relatively broad substrate scope, the redox-neutral feature, and high functional group tolerance, this approach should find use in complex molecule synthesis.

In the future, efforts could be made to further enhance the reaction efficiency and suppress side reactions, which would improve the yields of current examples and potentially expand the

scope, especially for carbonyl compounds. Such a radical redox cascade strategy might also be extended to enrich the β-functionalization methods, such as β-acylation of ketones from acyl radical precursors or carbonylation of alkyl radicals. Finally, though development of the asymmetric version would be challenging, there could be chances for using chiral ligands on the copper cocatalyst, chiral amine cocatalyst for carbonyl activation or chiral Lewis acid cocatalyst for controlling the conjugate addition step.

3.4 Experimental Section

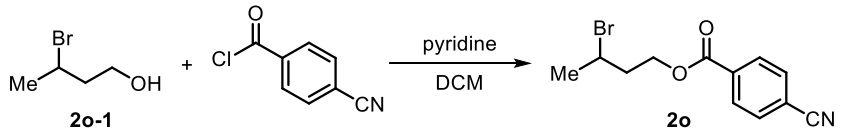
3.4.1 General information

Unless otherwise noted, all reactions were carried out in 8-mL culture tubes sealed with PTFE lined caps. Benzene was distilled over sodium and freeze-pump-thawed three times before use. Methyl acetate was distilled over phosphorus pentoxide and freeze-pump-thawed three times before use. $Pd(OAc)_2$ was purchased from Sigma-Aldrich. $Cu(OPiv)_2$ and $P(i\text{-}Pr)_3{\cdot}HBF_4$ were synthesized based on literature procedures. Cs_2CO_3 was purchased from Strem and stored in the glovebox. All commercially available substrates were used without further purification. Thin layer chromatography (TLC) analysis was run on silica gel plates purchased from EMD Chemical (silica gel 60, F254). 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 Model DMX 400 (400 MHz, ^{1}H at 400 MHz, ^{13}C at 101 MHz). For

$CDCl_3$ solutions, the chemical shifts were 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 (77.00 ppm). Coupling constants were reported in Hertz (Hz). Data for ^{1}H NMR spectra were reported as following: chemical shift (δ, ppm), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet), coupling constant (Hz), and integration.

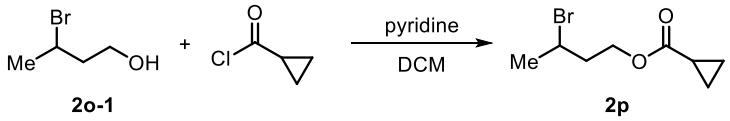
3.4.2 Synthesis and characterization of the substrates

Compounds **2l**,[28] **2m**,[29] **2n**,[29] **2q**,[30] **2t**,[31] **2u**,[21] **2v**,[32] **4c**[33] and **4m**[34] were synthesized according to the literature procedures. Compounds **2o**, **2p**, **2r**, **2w**, **2x**, **6**, **7**, **10**, (*S*)-**2l**, **1b-α-d$_2$**, **1b-β-d$_3$** and **1b-d$_5$** were prepared according to the following procedures. The others were commercially available and used without further purification.

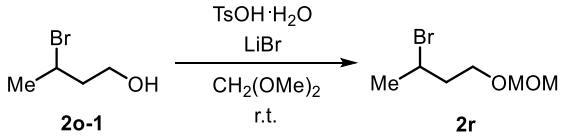


3-Bromobutyl 4-cyanobenzoate (2o): A round bottom flask was charged with **2o-1**[35] (1 equiv., 2.0 mmol, 306 mg), DCM (10 mL) and pyridine (2.2 equiv., 4.4 mmol, 354 μL). The solution was cooled to 0 ^{o}C, and 4-cyanobenzoyl chloride (1.2 equiv., 2.4 mmol, 397 mg) was added slowly. The mixture was warmed to room temperature and stirred overnight. The mixture was washed with 1 M HCl twice and $NaHCO_3$, dried and concentrated. The residue was purified by column chromatography to give **2o** as a pale-yellow oil in 81% yield (457 mg). R_f = 0.5

(hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.25 – 8.04 (m, 2H), 7.80 – 7.60 (m, 2H), 4.61 – 4.54 (m, 1H), 4.49 (ddd, *J* = 11.2, 7.8, 5.7 Hz, 1H), 4.27 (dqd, *J* = 8.9, 6.7, 4.5 Hz, 1H), 2.40 – 2.09 (m, 2H), 1.80 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.71, 133.82, 132.23, 130.07, 117.89, 116.51, 63.87, 46.47, 39.56, 26.53. **IR** (KBr, cm^{-1}) 2971, 2231, 1725, 1277, 1107, 766. **HRMS** calcd $C_{12}H_{13}BrNO_2$ $[M+H]^+$: 282.0124. Found: 282.0128.

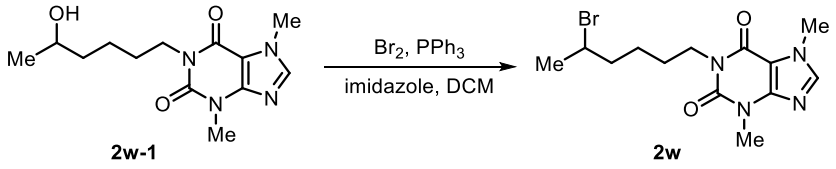


3-Bromobutyl cyclopropanecarboxylate (2p): A round bottom flask was charged with **2o-1**[35] (1 equiv., 2.0 mmol, 306 mg), DCM (10 mL) and pyridine (2.2 equiv., 4.4 mmol, 354 μL). The solution was cooled to 0 ºC, and cyclopropanecarbonyl chloride (1.2 equiv., 2.4 mmol, 251 mg) was added slowly. The mixture was warmed to room temperature and stirred overnight. The mixture was concentrated, and the residue was purified by column chromatography to give **2p** as a colorless liquid in 91% yield (402 mg). R_f = 0.5 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.33 – 4.13 (m, 3H), 2.19 – 2.02 (m, 2H), 1.75 (d, *J* = 6.7 Hz, 3H), 1.68 – 1.52 (m, 1H), 1.04 – 0.95 (m, 2H), 0.89 – 0.81 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.70, 62.49, 46.92, 39.79, 26.48, 12.78, 8.48. **IR** (KBr, cm^{-1}) 2965, 1728, 1405, 1267, 1174, 824. **HRMS** calcd $C_8H_{14}BrO_2$ $[M+H]^+$: 221.0172. Found: 221.0164.



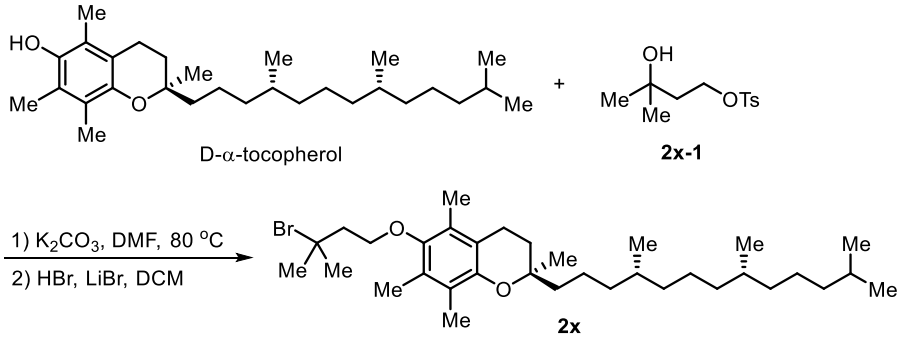
3-Bromo-1-(methoxymethoxy)butane (2r): A round bottom flask was charged with LiBr

(1.5 equiv., 3.0 mmol, 261 mg), $TsOH{\cdot}H_2O$ (10 mol %, 0.2 mmol, 38 mg), dimethoxymethane (4 mL) and **2o-1**[35] (1 equiv., 2.0 mmol, 306 mg), and the mixture was stirred at room temperature for 1 h. Brine was added, and the mixture was extracted with diethyl ether. The combined organic layers were washed with brine, dried and concentrated. The residue was purified by column chromatography to give **2r** as a colorless liquid in 67% yield (264 mg). R_f = 0.4 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.62 (s, 2H), 4.39 – 4.22 (m, 1H), 3.74 – 3.60 (m, 2H), 3.37 (s, 3H), 2.10 – 1.98 (m, 2H), 1.75 (d, J = 6.7 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 96.53, 65.56, 55.26, 47.98, 40.96, 26.59. **IR** (KBr, cm^{-1}) 2926, 2884, 1443, 1153, 1041, 808. **HRMS** calcd $C_6H_{13}BrNaO_2$ $[M+Na]^+$: 218.9991. Found: 218.9985.



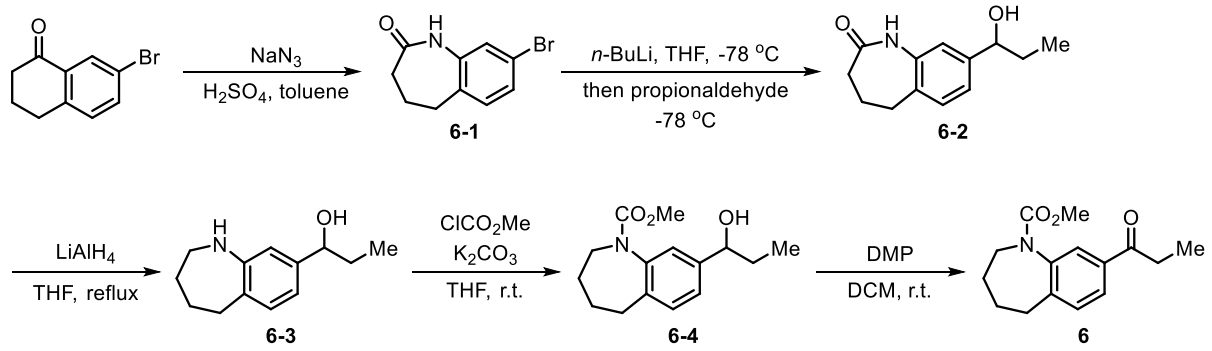
1-(5-Bromohexyl)-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (2w): A round bottom flask was charged with PPh_3 (1.2 equiv., 6 mmol, 1.57 g) and DCM (16 mL). Br_2 (1.2 equiv., 6 mmol, 309 μL) was added dropwise, and the resulting mixture was stirred for 10 min before imidazole (1.2 equiv., 6 mmol, 408 mg) was added. **2w-1**[36] (1 equiv., 5 mmol, 1.40 g) was dissolved in DCM (8 mL), and the solution was added slowly to the reaction mixture. The mixture was stirred at room temperature overnight, filtered through Celite and eluted with DCM. The filtrate was concentrated, and the residue was purified by column chromatography to give **2w** as a colorless oil in 75% yield (1.29 g). R_f = 0.15 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 4.20 – 4.07 (m, 1H), 4.04 – 3.96 (m, 5H), 3.57 (s, 3H), 1.96 – 1.75 (m, 2H), 1.76 –

1.41 (m, 7H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.27, 151.46, 148.78, 141.38, 107.67, 51.41, 41.05, 40.65, 33.56, 29.67, 27.30, 26.43, 25.09. **IR** (KBr, cm^{-1}) 2946, 1701, 1654, 1551, 1457, 1235, 668. **HRMS** calcd $C_{13}H_{20}BrN_4O_2$ $[M+H]^+$: 343.0764. Found: 343.0761.



(*R*)-6-(3-Bromo-3-methylbutoxy)-2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyl-tridecyl)chromane (2x): A round bottom flask was charged with K_2CO_3 (1.1 equiv., 8.0 mmol, 1.11 g), D-α-Tocopherol (1 equiv., 7.3 mmol, 3.14 g), DMF (50 mL) and **2x-1**[37] (1.05 equiv., 7.7 mmol, 2.0 g), and the mixture was heated at 80 °C for 24 h. After cooling to room temperature, the mixture was poured into water and extracted with diethyl ether. The combined organic layers were washed with brine, dried and concentrated. The residue was filtered through a short plug of silica gel and eluted with a solution containing hexane/EtOAc (1:1). The filtrate was concentrated, and the residue (ca. 2.5 mmol crude product) was dissolved in DCM (3 mL). To this solution were added LiBr (2 equiv., 5.0 mmol, 435 mg) and HBr (48 wt% aqueous solution, 3 mL), and the mixture was stirred at room temperature for 48 h. The mixture was diluted with diethyl ether, washed with water, $NaHCO_3$ and brine, dried and concentrated. The residue was purified by column chromatography to give **2x** as a colorless oil in 13% yield over 2 steps (590 mg). Olefin side product (from elimination of alkyl bromide or alcohol, ca. 10%) was inseparable from the

alkyl bromide. The mixture was directly used for the key reaction with the amount adjusted based on the ratio. R_f = 0.5 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.94 – 3.85 (m, 2H), 2.58 (t, *J* = 6.8 Hz, 2H), 2.37 (t, *J* = 7.2 Hz, 2H), 2.19 (s, 3H), 2.15 (s, 3H), 2.09 (s, 3H), 1.85 (s, 6H), 1.83 – 1.70 (m, 3H), 1.60 – 1.46 (m, 3H), 1.45 – 1.34 (m, 4H), 1.32 – 1.20 (m, 10H), 1.18 – 1.00 (m, 6H), 0.93 – 0.72 (m, 12H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.39, 147.82, 127.73, 125.74, 122.89, 117.54, 74.78, 71.00, 65.07, 46.87, 39.99, 39.36, 37.45, 37.41, 37.28, 34.90, 32.79, 32.69, 31.28, 27.97, 24.80, 24.43, 23.88, 22.72, 22.62, 21.02, 20.67, 19.74, 19.65, 12.88, 12.02, 11.79. **IR** (KBr, cm^{-1}) 2926, 2868, 1459, 1378, 1259, 668. **HRMS** calcd $C_{34}H_{60}BrO_2$ $[M+H]^+$: 579.3771. Found: 579.3769.



8-Bromo-1,3,4,5-tetrahydro-2*H*-benzo[*b*]azepin-2-one (6-1)[38]**:** A three-neck flask was equipped with a mechanical stirrer. 7-Bromo-1-tetralone (1 equiv., 50 mmol, 11.3 g), sodium azide (4 equiv., 200 mmol, 13.0 g) and toluene (100 mL) were added, and the mixture was cooled to 0 °C. While slowly stirring, concentrated H_2SO_4 (12 mL) was added dropwise over 1 h. The mixture was warmed to room temperature and stirred overnight. The mixture was quenched with $NaHCO_3$ and extracted with ethyl acetate three times. The combined organic layers were washed with $NaHCO_3$, dried and concentrated. The residue was filtered, washed with diethyl ether and dried *in*

vacuo, giving **6-1** as an off-white solid in 84% yield (10.1 g). R_f = 0.3 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (br, 1H), 7.26 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.15 (d, *J* = 2.0 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 2.77 (t, *J* = 7.2 Hz, 2H), 2.49 – 2.31 (m, 2H), 2.29 – 2.16 (m, 2H).

8-(1-Hydroxypropyl)-1,3,4,5-tetrahydro-2*H*-benzo[*b*]azepin-2-one (6-2): A Schlenk flask was flame-dried and refilled with N_2. *n*-BuLi (1.6 M in hexane, 2.5 equiv., 76.8 mmol, 48 mL) was added via syringe, and the mixture was cooled to -78 ºC. **6-1** (1 equiv., 30.7 mmol, 7.37 g) was dissolved in THF (distilled over Na, 150 mL), and the solution was added dropwise into the flask via syringe over 30 min. The mixture was stirred at -78 ºC for additional 10 min. Propionaldehyde (distilled before use, 2.5 equiv., 76.8 mmol, 5.50 mL) was then added dropwise via syringe over 10 min. The mixture was further stirred at -78 ºC for 1 h before quenching with water at this temperature. After warming to room temperature, the mixture was extracted with ethyl acetate four times. The combined organic layers were dried and concentrated. The residue was purified by column chromatography to give **6-2** as a white solid in 76% yield (5.10 g). Melting point: 152 – 155 ºC. R_f = 0.4 (EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (br, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.10 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.96 (d, *J* = 1.7 Hz, 1H), 4.59 (td, *J* = 6.5, 3.4 Hz, 1H), 2.78 (t, *J* = 7.2 Hz, 2H), 2.34 (t, *J* = 7.6 Hz, 2H), 2.22 (p, *J* = 7.3 Hz, 2H), 2.05 (d, *J* = 3.6 Hz, 1H), 1.90 – 1.68 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.92, 144.37, 137.76, 133.39, 129.88, 123.32, 119.28, 75.32, 32.72, 31.95, 30.04, 28.35, 10.09. **IR** (KBr, cm^{-1}) 3220, 2936, 2872, 1663, 1387, 668. **HRMS** calcd $C_{13}H_{18}NO_2$ $[M+H]^+$: 220.1332. Found: 220.1333.

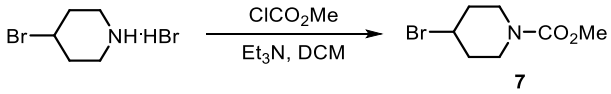
1-(2,3,4,5-Tetrahydro-1*H*-benzo[*b*]azepin-8-yl)propan-1-ol (6-3): A round bottom flask was charged with **6-2** (1 equiv., 23.3 mmol, 5.10 g) and THF (distilled over Na, 230 mL). $LiAlH_4$

(3 equiv., 69.9 mmol, 2.66 g) was added portionwise, and the mixture was heated to reflux for 3 h. After cooling to room temperature, the mixture was cooled to 0 °C and quenched with water (7 mL), 20% NaOH (14 mL) and water (21 mL). The mixture was diluted with ethyl acetate, filtered through Celite, eluted with ethyl acetate and concentrated to give **6-3** as a white solid which was directly used in the next step without further purification. R_f = 0.5 (hexane/EtOAc = 1:1).

Methyl 8-(1-hydroxypropyl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxylate (6-4): A round bottom flask was charged with all the **6-3** obtained (1 equiv., ca. 23 mmol), THF (50 mL) and K_2CO_3 (2 equiv., 46 mmol, 6.35 g). The mixture was cooled to 0 °C and methyl chloroformate (1.2 equiv., 27.6 mmol, 2.13 mL) was added slowly. The mixture was stirred at room temperature until full conversion of the starting material indicated by TLC analysis. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 1 M NaOH, dried and concentrated to give **6-4** as a colorless oil which was directly used in the next step without further purification. R_f = 0.55 (hexane/EtOAc = 1:1).

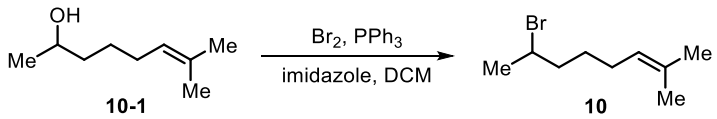
Methyl 8-propionyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxylate (6): A round bottom flask was charged with all the **6-4** obtained (1 equiv., ca. 22 mmol) and DCM (230 mL). Dess-Martin periodinane (1.1 equiv., 24.2 mmol, 10.3 g) was added, and the mixture was stirred at room temperature for 1 h. The mixture was filtered through Celite, eluted with DCM, washed with $NaHCO_3$, dried and concentrated. The residue was purified by column chromatography to give **6** as a white solid in 93% yield over 3 steps (5.64 g). Melting point: 88 – 91 °C. R_f = 0.5 (hexane/EtOAc = 2:1). Two rotamers are observed in 64:36 ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 – 7.69 (m, 2H), 7.36 – 7.15 (m, 1H), 4.45 (br, 0.64H), 3.88 – 3.51 (m, 3.36H),

3.20 – 2.52 (m, 5H), 2.19 – 1.10 (m, 7H). **^{13}C NMR** (100 MHz, $CDCl_3$) carbon signals are found at δ 199.80, 155.14, 145.17, 142.84, 142.46, 135.96, 130.27, 130.04, 128.12, 127.84, 126.73, 126.62, 52.92, 48.89, 34.62, 31.79, 29.89, 29.27, 25.91, 8.21. **IR** (KBr, cm^{-1}) 2939, 1700, 1689, 1454, 1264, 765. **HRMS** calcd $C_{15}H_{20}NO_3$ $[M+H]^+$: 262.1438. Found: 262.1441.



7

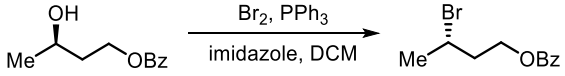
Methyl 4-bromopiperidine-1-carboxylate (7): A round bottom flask was charged with 4-bromopiperidine hydrobromide (1 equiv., 10 mmol, 2.45 g), DCM (30 mL) and Et_3N (4 equiv., 40 mmol, 5.57 mL). The mixture was cooled to 0 ºC, and methyl chloroformate (1.3 equiv., 13 mmol, 1.00 mL) was added dropwise. The mixture was stirred at room temperature overnight. The mixture was quenched with water and extracted with DCM. The combined organic layers were dried and concentrated. The residue was purified by column chromatography to give **7** as a colorless liquid in 96% yield (2.14 g). R_f = 0.4 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.35 (tt, J = 7.5, 3.7 Hz, 1H), 3.76 – 3.63 (m, 5H), 3.45 – 3.30 (m, 2H), 2.15 – 2.02 (m, 2H), 2.00 – 1.83 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.78, 52.66, 49.09, 42.11, 35.40. **IR** (KBr, cm^{-1}) 2956, 2869, 1699, 1449, 1240, 767. **HRMS** calcd $C_7H_{13}BrNO_2$ $[M+H]^+$: 222.0124. Found: 222.0124.



10-1 **10**

7-Bromo-2-methyloct-2-ene (10): A round bottom flask was charged with PPh_3 (1.2 equiv., 4.56 mmol, 1.19 g) and DCM (12 mL). Br_2 (1.2 equiv., 4.56 mmol, 235 μL) was added

dropwise, and the resulting mixture was stirred for 10 min before imidazole (1.2 equiv., 4.56 mmol, 310 mg) was added. **10-1**[39] (1 equiv., 3.8 mmol, 587 mg) was dissolved in DCM (8 mL), and the solution was added slowly to the reaction mixture. The mixture was stirred at room temperature overnight and then diluted with pentane. The resulting mixture was filtered through a short plug of silica gel and eluted with pentane. The filtrate was concentrated, and the residue was purified by column chromatography to give **10** as a colorless liquid in 77% yield (600 mg). R_f = 0.5 (hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.10 (t, *J* = 7.3 Hz, 1H), 4.29 – 4.01 (m, 1H), 2.09 – 1.90 (m, 2H), 1.89 – 1.74 (m, 2H), 1.74 – 1.66 (m, 6H), 1.60 (s, 3H), 1.57 – 1.38 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.96, 124.01, 51.82, 40.73, 27.98, 27.30, 26.45, 25.69, 17.68. **IR** (KBr, cm^{-1}) 2968, 2927, 2859, 1450, 1378, 654. **HRMS** calcd $C_9H_{18}Br$ $[M+H]^+$: 205.0586. Found: 205.0588.



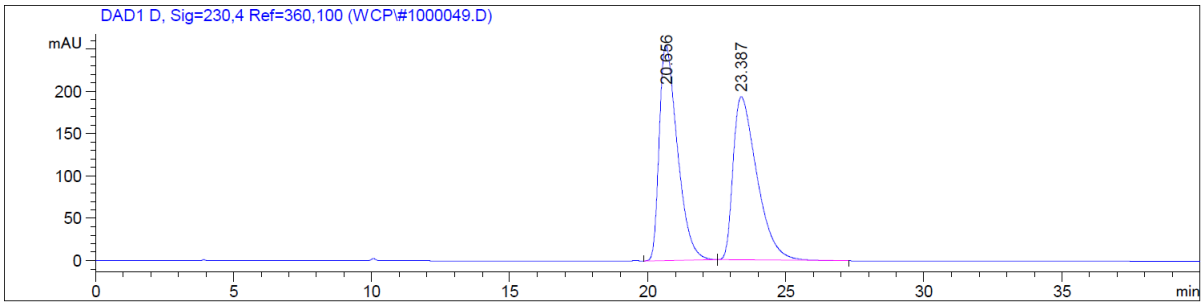
(*R*)-**2l-1** (*S*)-**2l**

(*S*)-3-Bromobutyl benzoate ((*S*)-2l): A round bottom flask was charged with PPh_3 (1.2 equiv., 12.8 mmol, 3.35 g) and DCM (35 mL). Br_2 (1.2 equiv., 12.8 mmol, 660 μL) was added dropwise, and the resulting mixture was stirred for 10 min before imidazole (1.2 equiv., 12.8 mmol, 870 mg) was added. (*R*)-**2l-1**[40] (1 equiv., 10.65 mmol, 2.10 g) was dissolved in DCM (18 mL), and the solution was added slowly to the reaction mixture. The mixture was stirred at room temperature overnight, filtered through Celite and eluted with DCM. The filtrate was concentrated, and the residue was purified by column chromatography to give (*S*)-**2l** as a colorless oil in 95% yield (2.60 g). R_f = 0.5 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 – 7.98 (m, 2H), 7.63 –

7.52 (m, 1H), 7.50 – 7.38 (m, 2H), 4.54 (dt, J = 11.3, 5.6 Hz, 1H), 4.45 (ddd, J = 11.2, 7.7, 5.8 Hz, 1H), 4.38 – 4.22 (m, 1H), 2.36 – 2.16 (m, 2H), 1.80 (d, J = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.37, 133.03, 130.08, 129.57, 128.39, 63.00, 46.86, 39.85, 26.53. **IR** (KBr, cm^{-1}) 2971, 1719, 1451, 1275, 1113, 711. **HRMS** calcd $C_{11}H_{14}BrO_2$ $[M+H]^+$: 257.0172. Found: 257.0170.

Chiral HPLC (Chiralpak ID, hexane:isopropanol = 99.5:0.5, 1 mL/min, 230 nm): ee = 90%. Note: due to the extremely low ratio of isopropanol (0.5%), the solvent ratio was unstable during the HPLC analysis, so the retention time for sample **2l** between different runs was inconsistent.

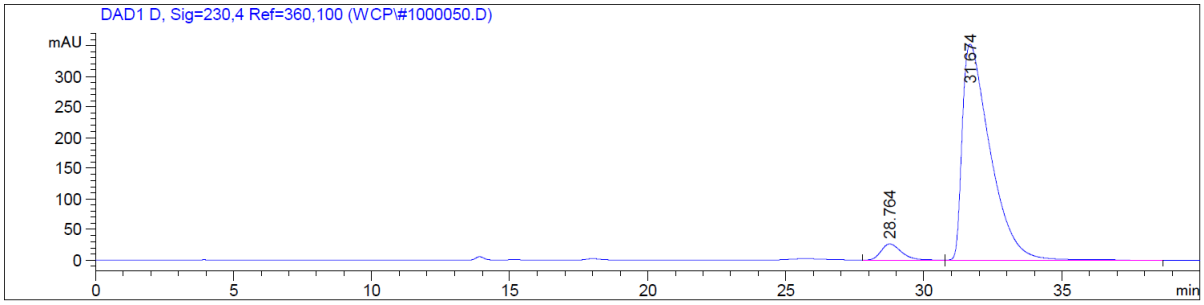
Sample of racemic **2l**:



Signal 4: DAD1 D, Sig=230,4 Ref=360,100

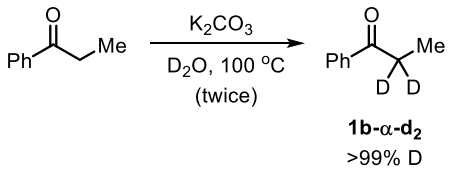
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.656	BB	0.6961	1.16024e4	254.37726	50.0792
2	23.387	BB	0.9163	1.15657e4	192.67609	49.9208

Sample of enantioenriched (*S*)-**2l**:



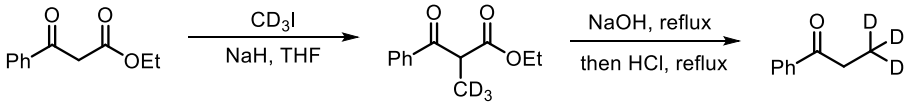
Signal 4: DAD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.764	BB	0.7750	1319.55872	26.13894	5.0810
2	31.674	BB	1.0422	2.46508e4	352.35190	94.9190



1b-α-d$_2$
>99% D

Propiophenone-2,2-d$_2$ (1b-α-d$_2$): A 20-mL vial was charged with propiophenone (1 equiv., 10 mmol, 1.33 mL), K_2CO_3 (1 equiv., 10 mmol, 1.38 g) and D_2O (10 mL). The vial was sealed and heated at 100 °C for 12 h. After cooling to room temperature, the mixture was extracted with diethyl ether, dried and concentrated to give a pale-yellow liquid. The above procedure was repeated again, and the residue was purified by column chromatography to give **1b-α-d$_2$** as a colorless liquid in 97% yield (1.32 g). >99% D. R_f = 0.5 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 – 7.89 (m, 2H), 7.64 – 7.53 (m, 1H), 7.50 – 7.40 (m, 2H), 1.22 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.94, 136.94, 132.86, 128.55, 127.98, 8.13. **IR** (KBr, cm^{-1}) 2978, 2939, 1684, 1449, 1280, 701. **HRMS** calcd $C_9H_9D_2O$ $[M+H]^+$: 137.0930. Found: 137.0927.



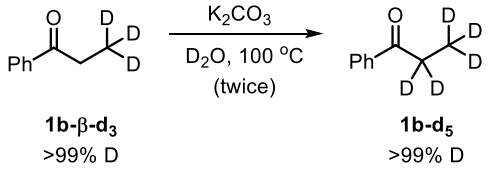
1b-1
>99% D

1b-β-d$_3$
>99% D

Ethyl 2-benzoylpropanoate-3,3,3-d$_3$ (1b-1): A Schlenk flask was flame-dried and charged with NaH (60% in oil, 1 equiv., 20 mmol, 800 mg). The flask was refilled with N_2, and anhydrous THF (30 mL) was added via syringe. Ethyl 3-oxo-3-phenylpropanoate (1 equiv., 20

mmol, 3.46 mL) was added dropwise, and the mixture was kept stirring until no gas was generated. CD_3I (>99% D, 1 equiv., 20 mmol, 1.25 mL) was then added slowly, and the mixture was stirred at room temperature for 20 h. The mixture was quenched with NH_4Cl solution, extracted with diethyl ether, dried and concentrated. The residue was purified by column chromatography to give **1b-1** as a colorless oil in 75% yield (3.13 g). >99% D. R_f = 0.4 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 – 7.90 (m, 2H), 7.64 – 7.55 (m, 1H), 7.53 – 7.43 (m, 2H), 4.35 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.88, 170.88, 135.95, 133.40, 128.70, 128.57, 61.33, 48.22, 13.94. **IR** (KBr, cm^{-1}) 2983, 1739, 1685, 1449, 1185, 693. **HRMS** calcd $C_{12}H_{12}D_3O_3$ $[M+H]^+$: 210.1204. Found: 210.1207.

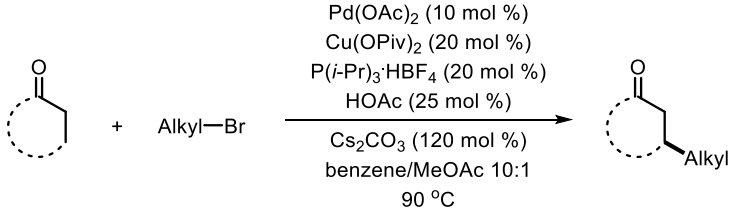
Propiophenone-3,3,3-d_3 (1b-β-d_3): A round bottom flask was charged with **1b-1** (1 equiv., 11.9 mmol, 2.60 g), NaOH (4 equiv., 47.6 mmol, 1.90 g), MeOH (80 mL) and H_2O (40 mL), and the mixture was refluxed at 80 ºC for 2 h. After cooling to temperature, the mixture was acidified with 6 M HCl till pH = 1. The mixture was further refluxed at 80 ºC for 2 h. The mixture was concentrated to remove most methanol. The residue was extracted with ether. The combined organic layers were washed with $NaHCO_3$ solution, dried and concentrated. The residue was purified by column chromatography to give **1b-β-d_3** as a colorless liquid in 80% yield (1.30 g). >99% D. R_f = 0.5 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 – 7.89 (m, 2H), 7.62 – 7.52 (m, 1H), 7.51 – 7.41 (m, 2H), 2.99 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.85, 136.97, 132.84, 128.54, 127.97, 31.54. **IR** (KBr, cm^{-1}) 2903, 1685, 1449, 1354, 1218, 692. **HRMS** calcd $C_9H_8D_3O$ $[M+H]^+$: 138.0993. Found: 138.0995.



Propiophenone-2,2,3,3,3-d$_5$ (1b-d$_5$): A 20-mL vial was charged with **1b-β-d$_3$** (1 equiv., 5.4 mmol, 760 mg), K_2CO_3 (1 equiv., 5.4 mmol, 745 mg) and D_2O (8 mL). The vial was sealed and heated at 100 °C for 12 h. After cooling to room temperature, the mixture was extracted with diethyl ether, dried and concentrated to give a pale-yellow liquid. The above procedure was repeated again, and the residue was purified by column chromatography to give **1b-d$_5$** as a colorless liquid in 91% yield (695 mg). >99% D. R_f = 0.5 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 – 7.83 (m, 2H), 7.60 – 7.52 (m, 1H), 7.51 – 7.41 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.01, 136.90, 132.87, 128.54, 127.97. **IR** (KBr, cm^{-1}) 3064, 1684, 1449, 1281, 1168, 690. **HRMS** calcd $C_9H_6D_5O$ $[M+H]^+$: 140.1118. Found: 140.1114.

3.4.3 Experimental procedure for the β-alkylation of ketones and aldehydes

General procedure A: β-alkylation of cyclic ketones

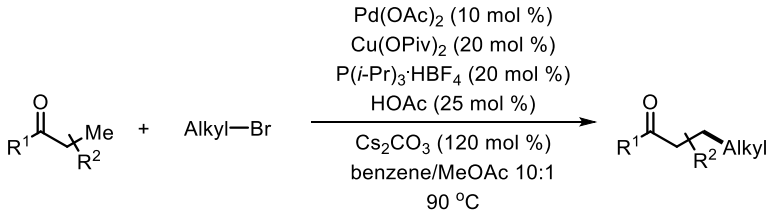


An 8-mL culture tube was flame-dried and charged with P(*i*-Pr)$_3$·HBF$_4$ (20 mol %, 0.08 mmol, 19.8 mg), $Pd(OAc)_2$ (10 mol %, 0.04 mmol, 9.0 mg) and $Cu(OPiv)_2$ (20 mol %, 0.08 mmol, 21.2 mg). The tube was then transferred into the glovebox. Inside the glovebox, Cs_2CO_3 (1.2 equiv.,

0.48 mmol, 156.5 mg), benzene (distilled over Na and freeze-pump-thawed, 0.4 mL), MeOAc (distilled over P_2O_5 and freeze-pump-thawed, 0.04 mL), ketone (2.5 equiv., 1.0 mmol), alkyl bromide (1 equiv., 0.40 mmol) and HOAc (25 mol %, 0.10 mmol, 5.7 μL) were added sequentially. The tube was sealed with a PTFE lined cap, transferred out of the glovebox and heated in an oil bath at 90 °C (oil temperature). After 18 h, the mixture was allowed to cool to room temperature. The mixture was diluted with EtOAc, passed through a small plug of silica gel and eluted with EtOAc. The solvent was removed *in vacuo*, and the residue was purified by column chromatography to give the desired product.

Note: If the ketone or alkenyl bromide is a solid, it is weighed and added into the reaction tube before transferring into the glovebox.

General procedure B: β-alkylation of linear ketones and aldehydes



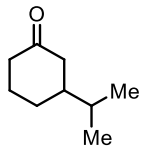
An 8-mL culture tube was flame-dried and charged with P(*i*-Pr)$_3$·HBF$_4$ (20 mol %, 0.04 mmol, 9.9 mg), Pd(OAc)$_2$ (10 mol %, 0.02 mmol, 4.5 mg) and Cu(OPiv)$_2$ (20 mol %, 0.04 mmol, 10.6 mg). The tube was then transferred into the glovebox. Inside the glovebox, Cs_2CO_3 (1.2 equiv., 0.24 mmol, 78.2 mg), benzene (distilled over Na and freeze-pump-thawed, 0.4 mL), MeOAc (distilled over P_2O_5 and freeze-pump-thawed, 0.04 mL), ketone/aldehyde (5.0 equiv., 1.0 mmol), alkyl bromide (1 equiv., 0.20 mmol) and HOAc (25 mol %, 0.05 mmol, 2.85 μL) were added

sequentially. The tube was sealed with a PTFE lined cap, transferred out of the glovebox and heated in an oil bath at 90 °C (oil temperature). After 18 h, the mixture was allowed to cool to room temperature. The mixture was diluted with EtOAc, passed through a small plug of silica gel and eluted with EtOAc. The solvent was removed *in vacuo*, and the residue was purified by column chromatography to give the desired product.

Note: If the ketone or alkenyl bromide is a solid, it is weighed and added into the reaction tube before transferring into the glovebox.

One-pot hydrogenation procedure: After the β-alkylation reaction finished, the mixture was cooled to room temperature. Pd/C (10 wt %, 20 mg) and EtOAc (1.5 mL) were then added to the mixture. The mixture was then stirred under H_2 atmosphere using a H_2 balloon at room temperature for another 3 h. The mixture was diluted with EtOAc, passed through a small plug of silica gel and eluted with EtOAc. The solvent was removed *in vacuo*, and the residue was purified by column chromatography to give the desired product.

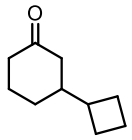
3.4.4 Characterization of the products for the β-alkylation of ketones and aldehydes



3a

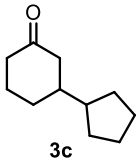
3-Isopropylcyclohexan-1-one (3a)[41]: Synthesized from **1a** and **2a** according to general procedure A. 63% Yield. Colorless oil. R_f = 0.7 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.40 – 2.31 (m, 2H), 2.30 – 2.16 (m, 1H), 2.11 – 2.02 (m, 2H), 1.91 – 1.79 (m, 1H), 1.66 – 1.51

(m, 3H), 1.43 – 1.30 (m, 1H), 0.90 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 212.62, 45.39, 45.31, 41.48, 32.47, 28.31, 25.51, 19.53, 19.29.



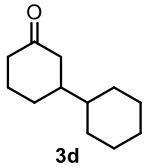
3b

3-Cyclobutylcyclohexan-1-one (3b): Synthesized from **1a** and **2b** according to general procedure A. 41% Yield. Colorless oil. R_f = 0.7 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.40 – 2.29 (m, 2H), 2.30 – 2.17 (m, 1H), 2.18 – 1.93 (m, 4H), 1.92 – 1.79 (m, 3H), 1.78 – 1.55 (m, 5H), 1.26 – 1.13 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 212.06, 45.71, 45.27, 41.48, 41.31, 28.17, 26.62, 26.33, 25.28, 17.79. **IR** (KBr, cm^{-1}) 2935, 2863, 1713, 1313, 1223, 913. **HRMS** calcd $C_{10}H_{17}O$ $[M+H]^+$: 153.1274. Found: 153.1270.



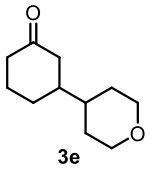
3c

3-Cyclopentylcyclohexan-1-one (3c)[41]: Synthesized from **1a** and **2c** according to general procedure A. 63% Yield. Colorless oil. R_f = 0.7 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.46 (ddt, J = 13.7, 3.9, 2.0 Hz, 1H), 2.40 – 2.28 (m, 1H), 2.32 – 2.18 (m, 1H), 2.09 – 1.99 (m, 2H), 1.99 – 1.87 (m, 1H), 1.83 – 1.70 (m, 2H), 1.68 – 1.45 (m, 7H), 1.43 – 1.30 (m, 1H), 1.18 – 1.02 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 212.28, 47.43, 46.18, 44.91, 41.50, 30.62, 30.39, 30.30, 25.38, 25.12, 25.11.



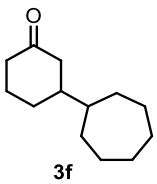
3d

[1,1'-Bi(cyclohexan)]-3-one (3d)[41]: Synthesized from **1a** and **2d** according to general procedure A. 51% Yield. Colorless oil. R_f = 0.6 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.43 – 2.30 (m, 2H), 2.30 – 2.16 (m, 1H), 2.15 – 1.97 (m, 2H), 1.92 – 1.81 (m, 1H), 1.78 – 1.50 (m, 7H), 1.45 – 1.29 (m, 1H), 1.29 – 1.05 (m, 4H), 1.03 – 0.89 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 212.77, 45.54, 44.63, 42.64, 41.58, 29.93, 29.83, 28.40, 26.56, 26.54, 26.50, 25.59.



3e

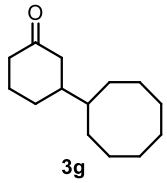
3-(Tetrahydro-2*H*-pyran-4-yl)cyclohexan-1-one (3e): Synthesized from **1a** and **2e** according to general procedure A. 56% Yield. Colorless oil. R_f = 0.3 (hexane/EtOAc = 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.00 – 3.96 (m, 2H), 3.40 – 3.26 (m, 2H), 2.49 – 2.32 (m, 2H), 2.31 – 2.18 (m, 1H), 2.13 – 2.00 (m, 2H), 1.96 – 1.86 (m, 1H), 1.69 – 1.53 (m, 4H), 1.48 – 1.26 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 211.82, 68.08, 68.07, 45.19, 44.02, 41.46, 40.01, 30.07, 29.96, 28.04, 25.22. **IR** (KBr, cm^{-1}) 2937, 2844, 1712, 1136, 1094, 880. **HRMS** calcd $C_{11}H_{19}O_2$ $[M+H]^+$: 183.1380. Found: 183.1372.



3f

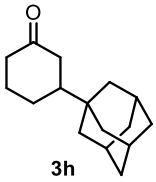
3-Cycloheptylcyclohexan-1-one (3f)[42]: Synthesized from **1a** and **2f** according to general

procedure A. 54% Yield. Colorless oil. R_f = 0.7 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.39 – 2.25 (m, 2H), 2.28 – 2.15 (m, 1H), 2.16 – 2.00 (m, 2H), 1.83 – 1.73 (m, 1H), 1.74 – 1.34 (m, 14H), 1.32 – 1.21 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 212.71, 45.66, 45.30, 43.72, 41.55, 31.03, 31.01, 28.20, 28.16, 27.06, 26.99, 25.66.



3g

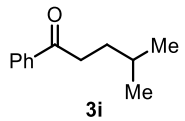
3-Cyclooctylcyclohexan-1-one (3g): Synthesized from **1a** and **2g** according to general procedure A. 54% Yield. Colorless oil. R_f = 0.6 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.38 – 2.28 (m, 2H), 2.29 – 2.15 (m, 1H), 2.15 – 1.98 (m, 2H), 1.87 – 1.76 (m, 1H), 1.73 – 1.22 (m, 18H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 212.71, 46.04, 45.40, 41.56, 41.50, 29.96, 29.82, 28.27, 26.74, 26.62, 26.14, 26.10, 25.56. **IR** (KBr, cm^{-1}) 2921, 2857, 1711, 1447, 1225, 647. **HRMS** calcd $C_{14}H_{25}O$ $[M+H]^+$: 209.1900. Found: 209.1898.



3h

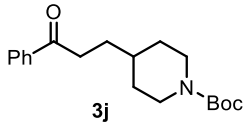
3-(Adamantan-1-yl)cyclohexan-1-one (3h)[43]: Synthesized from **1a** and **2h** according to general procedure A. 53% Yield. White solid. R_f = 0.7 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.43 (ddt, *J* = 13.6, 3.3, 2.2 Hz, 1H), 2.40 – 2.29 (m, 1H), 2.29 – 2.15 (m, 1H), 2.13 – 2.01 (m, 2H), 2.01 – 1.90 (m, 4H), 1.74-1.68 (m, 3H), 1.65 – 1.46 (m, 10H), 1.39 – 1.25 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 213.52, 49.69, 42.13, 41.59, 39.44, 37.22, 34.47, 28.65, 25.71,

24.61.



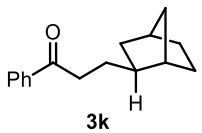
3i

4-Methyl-1-phenylpentan-1-one (3i)[44]: Synthesized from **1b** and **2a** according to general procedure B. 51% Yield. Colorless oil. R_f = 0.7 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 – 7.94 (m, 2H), 7.58 – 7.53 (m, 1H), 7.49 – 7.43 (m, 2H), 3.00 – 2.92 (m, 2H), 1.75 – 1.59 (m, 3H), 0.95 (d, *J* = 6.4 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.75, 137.09, 132.84, 128.54, 128.05, 36.62, 33.24, 27.85, 22.43.



3j

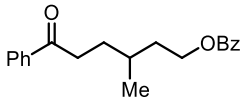
***tert*-Butyl 4-(3-oxo-3-phenylpropyl)piperidine-1-carboxylate (3j)**: Synthesized from **1b** and **2j** according to general procedure B. 64% Yield. Colorless oil. R_f = 0.5 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 – 7.86 (m, 2H), 7.59 – 7.52 (m, 1H), 7.50 – 7.41 (m, 2H), 4.09 (br, 2H), 2.99 (t, *J* = 7.6 Hz, 2H), 2.78 – 2.54 (m, 2H), 1.76 – 1.60 (m, 4H), 1.52 – 1.40 (m, 10H), 1.14 (qd, *J* = 13.0, 4.7 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.12, 154.84, 136.92, 132.98, 128.59, 127.99, 79.22, 43.92, 35.61, 35.59, 32.01, 30.68, 28.45. **IR** (KBr, cm^{-1}) 2977, 2931, 2853, 1684, 1426, 1163, 964. **HRMS** calcd $C_{19}H_{27}NNaO_3$ $[M+Na]^+$: 340.1883. Found: 340.1890.



3k

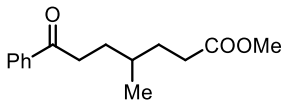
***exo*-3-(Bicyclo[2.2.1]heptan-2-yl)-1-phenylpropan-1-one (3k)**: Synthesized from **1b** and

2k (*exo*) according to general procedure B. 55% Yield. d.r. > 20:1 based on crude NMR of the reaction mixture. The stereochemistry (*exo*) is determined by X-ray structure of the crystal from its 2,4-dinitrophenylhydrazone form (*vide infra*). Colorless oil. R_f = 0.5 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 – 7.93 (m, 2H), 7.61 – 7.51 (m, 1H), 7.51 – 7.39 (m, 2H), 2.99 – 2.89 (m, 2H), 2.21 (br, 1H), 2.00 (br, 1H), 1.78 – 1.64 (m, 1H), 1.59 – 1.39 (m, 5H), 1.38 – 1.29 (m, 1H), 1.20 – 1.02 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.75, 137.09, 132.84, 128.53, 128.06, 41.99, 41.06, 38.10, 37.16, 36.57, 35.25, 31.31, 30.05, 28.75. **IR** (KBr, cm^{-1}) 2947, 2868, 1686, 1448, 1215, 972. **HRMS** calcd $C_{16}H_{21}O$ $[M+H]^+$: 229.1587. Found: 229.1585.



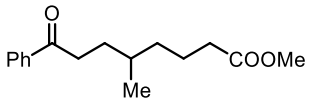
3l

3-Methyl-6-oxo-6-phenylhexyl benzoate (3l): Synthesized from **1b** and **2l** according to general procedure B. 68% Yield. Colorless oil. R_f = 0.7 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 – 7.99 (m, 2H), 8.00 – 7.92 (m, 2H), 7.61 – 7.51 (m, 2H), 7.48 – 7.40 (m, 4H), 4.47 – 4.33 (m, 2H), 3.11 – 2.92 (m, 2H), 1.94 – 1.83 (m, 2H), 1.82 – 1.72 (m, 1H), 1.70 – 1.60 (m, 2H), 1.04 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.25, 166.58, 136.95, 132.92, 132.80, 130.37, 129.50, 128.55, 128.30, 127.99, 63.22, 36.09, 35.45, 31.16, 29.80, 19.38. **IR** (KBr, cm^{-1}) 3063, 2959, 1717, 1685, 1275, 712. **HRMS** calcd $C_{20}H_{23}O_3$ $[M+H]^+$: 311.1642. Found: 311.1644.



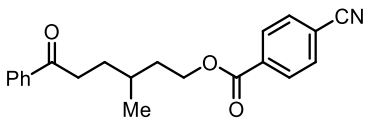
3m

Methyl 4-methyl-7-oxo-7-phenylheptanoate (3m): Synthesized from **1b** and **2m** according to general procedure B. 64% Yield. Colorless oil. R_f = 0.5 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 – 7.90 (m, 2H), 7.59 – 7.51 (m, 1H), 7.50 – 7.40 (m, 2H), 3.66 (s, 3H), 3.04 – 2.90 (m, 2H), 2.45 – 2.22 (m, 2H), 1.85 – 1.67 (m, 2H), 1.65 – 1.44 (m, 3H), 0.94 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.30, 174.26, 137.00, 132.89, 128.54, 127.99, 51.47, 36.04, 32.15, 31.70, 31.61, 30.79, 19.14. **IR** (KBr, cm^{-1}) 2954, 2873, 1737, 1685, 1449, 1207, 691. **HRMS** calcd $C_{15}H_{21}O_3$ $[M+H]^+$: 249.1485. Found: 249.1485.



3n

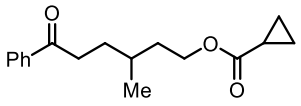
Methyl 5-methyl-8-oxo-8-phenyloctanoate (3n): Synthesized from **1b** and **2n** according to general procedure B. 56% Yield. Colorless oil. R_f = 0.5 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 – 7.92 (m, 2H), 7.59 – 7.51 (m, 1H), 7.51 – 7.41 (m, 2H), 3.66 (s, 3H), 3.04 – 2.88 (m, 2H), 2.30 (t, *J* = 7.8 Hz, 2H), 1.85 – 1.47 (m, 5H), 1.43 – 1.32 (m, 1H), 1.28 – 1.13 (m, 1H), 0.94 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.56, 174.11, 137.02, 132.86, 128.53, 128.01, 51.42, 36.19, 36.16, 34.23, 32.32, 31.09, 22.38, 19.32. **IR** (KBr, cm^{-1}) 2953, 2872, 1737, 1686, 1449, 1207, 691. **HRMS** calcd $C_{16}H_{23}O_3$ $[M+H]^+$: 263.1642. Found: 263.1643.



3o

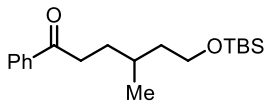
3-Methyl-6-oxo-6-phenylhexyl 4-cyanobenzoate (3o): Synthesized from **1b** and **2o** according to general procedure B. 54% Yield. 64% Yield based on recovered starting material **2o**

(15%). Light yellow solid. Melting point: 67 – 69 °C. R_f = 0.3 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 – 8.05 (m, 2H), 8.00 – 7.87 (m, 2H), 7.78 – 7.67 (m, 2H), 7.63 – 7.53 (m, 1H), 7.50 – 7.41 (m, 2H), 4.56 – 4.33 (m, 2H), 3.12 – 2.92 (m, 2H), 1.97 – 1.81 (m, 2H), 1.80 – 1.58 (m, 3H), 1.03 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.07, 164.92, 136.91, 134.16, 133.00, 132.17, 130.03, 128.58, 127.96, 117.97, 116.27, 64.07, 35.94, 35.36, 30.99, 29.71, 19.36. **IR** (KBr, cm^{-1}) 2959, 2231, 1722, 1684, 1276, 1106, 691. **HRMS** calcd $C_{21}H_{22}NO_3$ $[M+H]^+$: 336.1594. Found: 336.1597.



3p

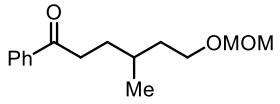
3-Methyl-6-oxo-6-phenylhexyl cyclopropanecarboxylate (3p): Synthesized from **1b** and **2p** according to general procedure B. 65% Yield. Colorless oil. R_f = 0.5 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 – 7.89 (m, 2H), 7.62 – 7.52 (m, 1H), 7.50 – 7.41 (m, 2H), 4.31 – 4.00 (m, 2H), 3.12 – 2.84 (m, 2H), 1.93 – 1.44 (m, 6H), 1.02 – 0.94 (m, 5H), 0.87 – 0.78 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.27, 174.89, 136.97, 132.91, 128.55, 127.99, 62.71, 36.06, 35.39, 31.13, 29.67, 19.32, 12.86, 8.28. **IR** (KBr, cm^{-1}) 2959, 1724, 1686, 1405, 1177, 691. **HRMS** calcd $C_{17}H_{23}O_3$ $[M+H]^+$: 275.1642. Found: 275.1643.



3q

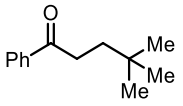
6-((*tert*-Butyldimethylsilyl)oxy)-4-methyl-1-phenylhexan-1-one (3q): Synthesized from **1b** and **2q** according to general procedure B. 61% Yield. Colorless oil. R_f = 0.5 (hexane/EtOAc =

10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 – 7.89 (m, 2H), 7.60 – 7.52 (m, 1H), 7.49 – 7.41 (m, 2H), 3.81 – 3.54 (m, 2H), 3.13 – 2.87 (m, 2H), 1.83 – 1.72 (m, 1H), 1.71 – 1.53 (m, 3H), 1.45 – 1.35 (m, 1H), 0.95 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.64, 137.06, 132.85, 128.53, 128.03, 61.20, 39.70, 36.29, 31.39, 29.38, 25.95, 19.55, 18.30, -5.30, -5.32. **IR** (KBr, cm^{-1}) 2955, 2929, 2857, 1688, 1256, 1093, 836. **HRMS** calcd $C_{19}H_{33}O_2Si$ $[M+H]^+$: 321.2244. Found: 321.2237.



3r

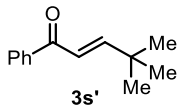
6-(Methoxymethoxy)-4-methyl-1-phenylhexan-1-one (3r): Synthesized from **1b** and **2r** according to general procedure B. 63% Yield. Colorless oil. R_f = 0.4 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 – 7.90 (m, 2H), 7.59 – 7.51 (m, 1H), 7.50 – 7.40 (m, 2H), 4.61 (s, 2H), 3.65 – 3.51 (m, 2H), 3.35 (s, 3H), 3.05 – 2.88 (m, 2H), 1.87 – 1.55 (m, 4H), 1.53 – 1.40 (m, 1H), 0.97 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.45, 137.03, 132.86, 128.53, 128.01, 96.45, 65.84, 55.13, 36.54, 36.18, 31.31, 29.72, 19.40. **IR** (KBr, cm^{-1}) 2930, 2881, 1684, 1449, 1109, 1037, 691. **HRMS** calcd $C_{15}H_{22}NaO_3$ $[M+Na]^+$: 273.1461. Found: 273.1468.



3s

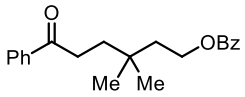
4,4-Dimethyl-1-phenylpentan-1-one (3s)[45]: Synthesized from **1b** and **2s** according to general procedure B. 55% Yield. 69% Yield after hydrogenation following the one-pot hydrogenation procedure. The α,β-unsaturated ketone **3s'** was isolated in 17% yield (see below).

Colorless oil. R_f = 0.5 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 – 7.95 (m, 2H), 7.58 – 7.52 (m, 1H), 7.50 – 7.42 (m, 2H), 2.99 – 2.90 (m, 2H), 1.70 – 1.56 (m, 2H), 0.96 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.04, 137.09, 132.83, 128.54, 128.06, 38.13, 34.29, 30.20, 29.21.



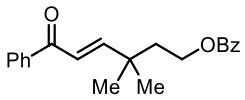
3s'

(*E*)-4,4-Dimethyl-1-phenylpent-2-en-1-one (3s')[46]: Isolated as the side product from the synthesis of **3s** in 17% yield. Colorless oil. R_f = 0.45 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 – 7.89 (m, 2H), 7.63 – 7.52 (m, 1H), 7.52 – 7.42 (m, 2H), 7.06 (d, *J* = 15.7 Hz, 1H), 6.78 (d, *J* = 15.7 Hz, 1H), 1.16 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 191.63, 159.64, 138.25, 132.53, 128.53, 128.48, 121.00, 34.18, 28.76.



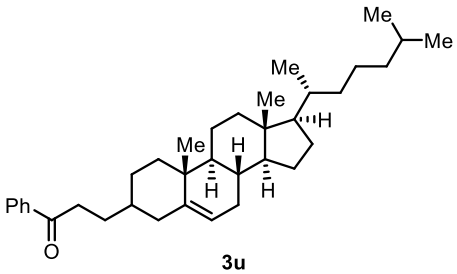
3t

3,3-Dimethyl-6-oxo-6-phenylhexyl benzoate (3t): Synthesized from **1b** and **2t** according to general procedure B. 57% Yield. 77% Yield after hydrogenation following the one-pot hydrogenation procedure. The α,β-unsaturated ketone **3t'** was isolated in 21% yield (see below). Colorless oil. R_f = 0.7 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 – 8.00 (m, 2H), 7.98 – 7.94 (m, 2H), 7.59 – 7.50 (m, 2H), 7.50 – 7.43 (m, 2H), 7.42 – 7.36 (m, 2H), 4.41 (t, *J* = 7.3 Hz, 2H), 3.07 – 2.88 (m, 2H), 1.84 – 1.68 (m, 4H), 1.05 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.44, 166.62, 136.98, 132.91, 132.81, 130.33, 129.47, 128.56, 128.30, 128.01, 62.15, 39.71, 36.29, 33.58, 32.09, 27.14. **IR** (KBr, cm^{-1}) 3063, 2959, 1717, 1684, 1275, 1114, 712. **HRMS** calcd $C_{21}H_{25}O_3$ $[M+H]^+$: 325.1798. Found: 325.1795.



3t'

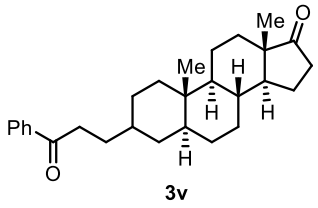
(*E*)-3,3-Dimethyl-6-oxo-6-phenylhex-4-en-1-yl benzoate (3t'): Isolated as the side product from the synthesis of **3t** in 21% yield. Colorless oil. R_f = 0.6 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 – 7.95 (m, 2H), 7.94 – 7.86 (m, 2H), 7.58 – 7.49 (m, 2H), 7.48 – 7.43 (m, 2H), 7.43 – 7.34 (m, 2H), 7.10 (d, *J* = 15.7 Hz, 1H), 6.85 (d, *J* = 15.7 Hz, 1H), 4.37 (t, *J* = 6.9 Hz, 2H), 1.97 (t, *J* = 6.9 Hz, 2H), 1.25 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.84, 166.52, 157.34, 138.01, 132.87, 132.64, 130.08, 129.55, 128.49, 128.31, 122.17, 61.89, 40.47, 36.29, 26.78. **IR** (KBr, cm^{-1}) 3062, 2963, 1717, 1669, 1616, 1274, 712. **HRMS** calcd $C_{21}H_{23}O_3$ $[M+H]^+$: 323.1642. Found: 323.1642.



3u

3-((8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)-1-phenylpropan-1-one (3u): Synthesized from **1b** and **2u** (*axial*-Br) according to general procedure B except for using 15 mol % $Pd(OAc)_2$, 30 mol % P(*i*-Pr)$_3$·HBF_4 and 30 mol % $Cu(OPiv)_2$. 48% Yield. 61% Yield based on recovered starting material **2u** (21%). d.r. = 1.6:1 based on crude NMR of the reaction mixture. White solid. Melting point: 140 – 145 ºC. R_f = 0.5 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 – 7.91 (m, 2H), 7.61 – 7.52 (m, 1H), 7.49 – 7.40 (m, 2H), 5.40 –

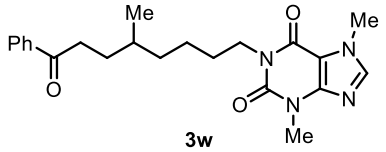
5.18 (m, 1H), 3.04 – 2.92 (m, 1.39H), 2.85 (ddd, J = 15.8, 9.3, 5.8 Hz, 0.61H), 2.57 – 2.43 (m, 0.61H), 2.12 – 2.02 (m, 0.39H), 2.03 – 0.94 (m, 33H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.69 – 0.66 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) carbon signals are found at δ 200.89, 200.63, 142.97, 140.26, 137.01, 132.86, 132.84, 128.54, 128.53, 128.11, 128.05, 121.48, 119.59, 56.82, 56.80, 56.14, 56.11, 50.44, 50.38, 42.29, 39.82, 39.79, 39.51, 39.49, 39.46, 39.19, 37.42, 37.20, 36.92, 36.71, 36.18, 36.13, 35.80, 35.78, 34.20, 33.96, 31.90, 31.88, 31.53, 29.03, 28.24, 28.00, 26.31, 25.64, 24.27, 23.82, 22.82, 22.56, 20.91, 20.73, 19.49, 19.45, 18.70, 11.86, 11.84. **IR** (KBr, cm^{-1}) 2932, 2867, 1683, 1448, 1364, 688. **HRMS** calcd $C_{36}H_{54}NaO$ $[M+Na]^+$: 525.4067. Found: 525.4067.



3v

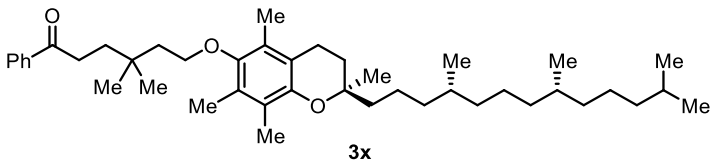
(5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-10,13-Dimethyl-3-(3-oxo-3-phenylpropyl)hexadecahydro-17*H*-cyclopenta[*a*]phenan-thren-17-one (3v): Synthesized from **1b** and **2v** (*equatorial*-Br) according to general procedure B except for using 15 mol % $Pd(OAc)_2$, 30 mol % $P(i\text{-}Pr)_3{\cdot}HBF_4$ and 30 mol % $Cu(OPiv)_2$. 41% Yield. 63% Yield based on recovered starting material **2v** (35%). d.r. = 2.1:1 based on crude NMR of the reaction mixture. Colorless oil. R_f = 0.3 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 – 7.87 (m, 2H), 7.59 – 7.52 (m, 1H), 7.50 – 7.41 (m, 2H), 3.04 – 2.87 (m, 2H), 2.48 – 2.37 (m, 1H), 2.14 – 1.98 (m, 1H), 1.98 – 1.40 (m, 12H), 1.39 – 1.06 (m, 8H), 1.07 – 0.88 (m, 2H), 0.87 – 0.83 (m, 3H), 0.82 (s, 2.04H), 0.78 (s, 0.96H), 0.77 – 0.65

(m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) carbon signals are found at δ 221.48, 200.77, 200.73, 137.05, 137.00, 132.87, 132.85, 128.53, 128.03, 128.01, 54.72, 54.70, 51.51, 51.48, 47.80, 46.55, 40.28, 38.44, 37.72, 37.38, 36.61, 36.24, 36.15, 35.83, 35.46, 35.07, 35.04, 33.10, 32.89, 32.84, 31.62, 31.57, 31.55, 30.93, 30.87, 28.70, 28.64, 28.60, 26.46, 25.34, 21.74, 21.72, 20.25, 20.01, 13.81, 13.80, 12.29, 11.72. **IR** (KBr, cm^{-1}) 2919, 2855, 1738, 1685, 1448, 691. **HRMS** calcd $C_{28}H_{39}O_2$ $[M+H]^+$: 407.2945. Found: 407.2942.



3w

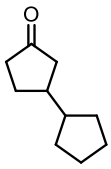
3,7-Dimethyl-1-(5-methyl-8-oxo-8-phenyloctyl)-3,7-dihydro-1*H*-purine-2,6-dione (3w): Synthesized from **1b** and **2w** according to general procedure B. 50% Yield. Colorless oil. R_f = 0.4 (hexane/acetone = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 – 7.92 (m, 2H), 7.59 – 7.52 (m, 1H), 7.50 – 7.41 (m, 3H), 4.04 – 3.95 (m, 5H), 3.57 (s, 3H), 3.03 – 2.88 (m, 2H), 1.80 – 1.70 (m, 1H), 1.69 – 1.33 (m, 7H), 1.29 – 1.16 (m, 1H), 0.93 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.75, 155.31, 151.48, 148.73, 141.31, 137.10, 132.81, 128.53, 128.05, 107.69, 41.36, 36.39, 36.33, 33.54, 32.56, 31.28, 29.64, 28.29, 24.37, 19.51. **IR** (KBr, cm^{-1}) 2936, 1702, 1685, 1655, 1551, 1234, 692. **HRMS** calcd $C_{22}H_{28}N_4NaO_3$ $[M+Na]^+$: 419.2054. Found: 419.2052.



3x

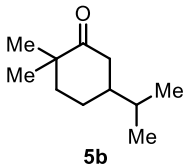
4,4-Dimethyl-1-phenyl-6-(((*R*)-2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)hexan-1-one (3x): Synthesized from **1b** and **2x** according to general

procedure B. 58% Yield. Colorless oil. R_f = 0.4 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 – 7.94 (m, 2H), 7.61 – 7.52 (m, 1H), 7.50 – 7.41 (m, 2H), 3.72 (t, *J* = 7.6 Hz, 2H), 3.12 – 2.86 (m, 2H), 2.58 (t, *J* = 6.8 Hz, 2H), 2.18 (s, 3H), 2.14 (s, 3H), 2.09 (s, 3H), 1.93 – 1.68 (m, 6H), 1.62 – 1.04 (m, 24H), 1.02 (s, 6H), 0.91 – 0.82 (m, 12H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.72, 148.63, 147.70, 137.04, 132.87, 128.55, 128.07, 127.72, 125.70, 122.81, 117.48, 74.74, 69.96, 41.18, 40.06, 39.37, 37.48, 37.45, 37.41, 37.28, 36.60, 33.77, 32.78, 32.70, 31.96, 31.30, 27.96, 27.34, 24.78, 24.43, 23.87, 22.70, 22.61, 21.02, 20.66, 19.74, 19.65, 12.84, 11.98, 11.78. **IR** (KBr, cm^{-1}) 2952, 2927, 2868, 1688, 1458, 1089, 691. **HRMS** calcd $C_{43}H_{69}O_3$ $[M+H]^+$: 633.5241. Found: 633.5246.



5a

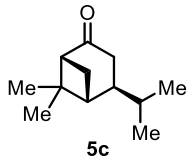
[1,1'-Bi(cyclopentan)]-3-one (5a)[47]: Synthesized from **4a** and **2c** according to general procedure A. 57% Yield. Colorless oil. R_f = 0.6 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.42 – 2.23 (m, 2H), 2.20 – 2.05 (m, 2H), 2.02 – 1.46 (m, 10H), 1.27 – 1.05 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 220.06, 45.92, 44.63, 42.99, 38.73, 31.47, 30.76, 28.77, 25.18, 25.15.



5b

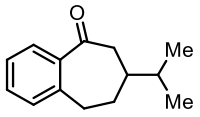
5-Isopropyl-2,2-dimethylcyclohexan-1-one (5b)[48]: Synthesized from **4b** and **2a** according to general procedure A. 47% Yield. Colorless oil. R_f = 0.6 (hexane/EtOAc = 10:1). **^{1}H**

NMR (400 MHz, $CDCl_3$) δ 2.38 – 2.15 (m, 2H), 1.84 – 1.72 (m, 1H), 1.72 – 1.65 (m, 1H), 1.64 – 1.45 (m, 4H), 1.14 (s, 3H), 1.05 (s, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 216.63, 46.07, 44.58, 41.70, 39.91, 32.52, 25.14, 25.01, 24.76, 19.60, 19.41.



5c

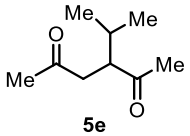
(1*R*,4*S*,5*R*)-4-Isopropyl-6,6-dimethylbicyclo[3.1.1]heptan-2-one (5c): Synthesized from **4c** and **2a** according to general procedure A. 40% Yield. d.r. > 20:1 based on crude NMR of the reaction mixture. The stereochemistry is determined by NOESY analysis (*vide infra*). Colorless oil. R_f = 0.6 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.53 – 2.34 (m, 3H), 2.28 – 2.15 (m, 2H), 1.77 – 1.66 (m, 1H), 1.63 – 1.50 (m, 2H), 1.34 (s, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.82 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 214.67, 57.68, 43.22, 41.31, 39.27, 39.05, 31.73, 26.20, 22.43, 21.86, 20.85, 20.55. **IR** (KBr, cm^{-1}) 2957, 2872, 1713, 1473, 1387, 971. **HRMS** calcd $C_{12}H_{21}O$ $[M+H]^+$: 181.1587. Found: 181.1588.



5d

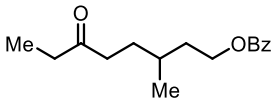
3-Isopropyl-1-benzosuberone (5d): Synthesized from **4d** and **2a** according to general procedure A. 43% Yield. Colorless oil. R_f = 0.6 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.41 (td, *J* = 7.5, 1.5 Hz, 1H), 7.30 (td, *J* = 7.6, 1.3 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 3.00 (ddd, *J* = 15.2, 11.4, 4.1 Hz, 1H), 2.87 (dt, *J* = 15.0, 4.4 Hz, 1H), 2.73

(dd, J = 15.6, 2.4 Hz, 1H), 2.68 – 2.59 (m, 1H), 1.96 – 1.81 (m, 1H), 1.75 – 1.59 (m, 3H), 0.92 (d, J = 6.2 Hz, 3H), 0.90 (d, J = 6.3 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 205.23, 141.83, 138.44, 132.18, 129.61, 128.50, 126.60, 44.86, 38.72, 32.25, 32.20, 28.87, 19.77, 19.48. **IR** (KBr, cm^{-1}) 2957, 2872, 1675, 1599, 1449, 1290, 760. **HRMS** calcd $C_{14}H_{19}O$ $[M+H]^+$: 203.1430. Found: 203.1433.



5e

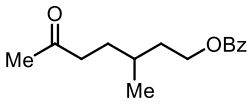
3-Isopropylhexane-2,5-dione (5e): Synthesized from **4e** and **2a** according to general procedure B. 45% Yield. Colorless oil. R_f = 0.3 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.06 – 2.85 (m, 2H), 2.46 – 2.31 (m, 1H), 2.24 (s, 3H), 2.14 (s, 3H), 2.06 – 1.90 (m, 1H), 0.96 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 211.27, 207.79, 52.90, 41.07, 30.51, 30.00, 28.89, 21.03, 18.77. **IR** (KBr, cm^{-1}) 2964, 2876, 1709, 1359, 1163, 668. **HRMS** calcd $C_9H_{17}O_2$ $[M+H]^+$: 157.1223. Found: 157.1221.



5f

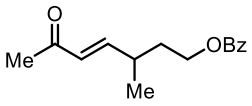
3-Methyl-6-oxooctyl benzoate (5f): Synthesized from **4f** and **2l** according to general procedure B. 66% Yield. The di-alkylation product was observed in 5% yield. Colorless oil. R_f = 0.5 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 – 7.93 (m, 2H), 7.67 – 7.51 (m, 1H), 7.47 – 7.36 (m, 2H), 4.51 – 4.26 (m, 2H), 2.59 – 2.32 (m, 4H), 1.90 – 1.75 (m, 1H), 1.74 – 1.44 (m, 4H), 1.04 (t, J = 7.3 Hz, 3H), 0.96 (d, J = 6.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ

211.52, 166.58, 132.82, 130.36, 129.48, 128.30, 63.18, 39.86, 35.86, 35.35, 30.65, 29.66, 19.26, 7.82. **IR** (KBr, cm^{-1}) 2960, 2936, 1716, 1275, 1111, 712. **HRMS** calcd $C_{16}H_{23}O_3$ $[M+H]^+$: 263.1642. Found: 263.1643.



5g

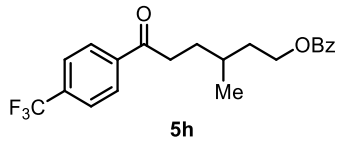
3-Methyl-6-oxoheptyl benzoate (5g): Synthesized from **4g** and **2l** according to general procedure B. 71% Yield. 82% Yield after hydrogenation following the one-pot hydrogenation procedure. The α,β-unsaturated ketone **5g'** was isolated in 16% yield (see below). Colorless oil. R_f = 0.3 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.99 (m, 2H), 7.59 – 7.51 (m, 1H), 7.47 – 7.39 (m, 2H), 4.50 – 4.26 (m, 2H), 2.61 – 2.37 (m, 2H), 2.14 (s, 3H), 1.86 – 1.76 (m, 1H), 1.75 – 1.45 (m, 4H), 0.96 (d, J = 6.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 208.85, 166.57, 132.83, 130.35, 129.48, 128.31, 63.16, 41.24, 35.35, 30.54, 29.87, 29.59, 19.24. **IR** (KBr, cm^{-1}) 2959, 2930, 1714, 1275, 1111, 712. **HRMS** calcd $C_{15}H_{21}O_3$ $[M+H]^+$: 249.1485. Found: 249.1487.



5g'

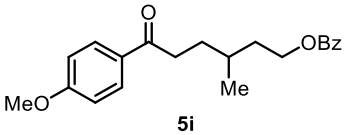
(*E*)-3-Methyl-6-oxohept-4-en-1-yl benzoate (5g'): Isolated as the side product from the synthesis of **5g** in 16% yield. Colorless oil. R_f = 0.25 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 – 7.90 (m, 2H), 7.64 – 7.52 (m, 1H), 7.49 – 7.37 (m, 2H), 6.73 (dd, J = 16.0, 7.9 Hz, 1H), 6.09 (dd, J = 16.0, 1.2 Hz, 1H), 4.45 – 4.25 (m, 2H), 2.67 – 2.51 (m, 1H), 2.21 (s, 3H), 1.95 – 1.84 (m, 2H), 1.16 (d, J = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.56, 166.45,

151.85, 133.01, 130.12, 129.97, 129.53, 128.39, 62.74, 34.81, 33.93, 27.08, 19.49. **IR** (KBr, cm^{-1}) 2963, 1718, 1675, 1275, 1112, 712. **HRMS** calcd $C_{15}H_{19}O_3$ $[M+H]^+$: 247.1329. Found: 247.1327.



5h

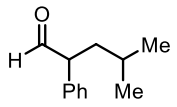
3-Methyl-6-oxo-6-(4-(trifluoromethyl)phenyl)hexyl benzoate (5h): Synthesized from **4h** and **2l** according to general procedure B. 71% Yield. Colorless oil. R_f = 0.5 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 – 7.99 (m, 4H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.60 – 7.51 (m, 1H), 7.47 – 7.38 (m, 2H), 4.47 – 4.33 (m, 2H), 3.13 – 2.95 (m, 2H), 2.10 – 1.57 (m, 5H), 1.04 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.15, 166.58, 139.58, 134.25 (q, *J* = 32.6 Hz), 132.86, 130.33, 129.49, 128.32, 125.65 (q, *J* = 3.8 Hz), 123.58 (q, *J* = 272.7 Hz), 63.13, 36.40, 35.44, 30.88, 29.74, 19.39. **IR** (KBr, cm^{-1}) 2961, 1717, 1693, 1325, 1275, 1130, 712. **HRMS** calcd $C_{21}H_{22}F_3O_3$ $[M+H]^+$: 379.1516. Found: 379.1519.



5i

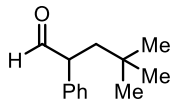
6-(4-Methoxyphenyl)-3-methyl-6-oxohexyl benzoate (5i): Synthesized from **4i** and **2l** according to general procedure B. 56% Yield. Colorless oil. R_f = 0.4 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 7.99 (m, 2H), 7.97 – 7.90 (m, 2H), 7.58 – 7.50 (m, 1H), 7.47 – 7.38 (m, 2H), 7.07 – 6.72 (m, 2H), 4.49 – 4.29 (m, 2H), 3.86 (s, 3H), 3.15 – 2.84 (m, 2H), 1.96 – 1.56 (m, 5H), 1.03 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.87, 166.59, 163.33, 132.79, 130.39, 130.26, 130.04, 129.50, 128.29, 113.67, 63.25, 55.41, 35.76, 35.45, 31.43, 29.85,

19.40. **IR** (KBr, cm^{-1}) 2958, 1715, 1676, 1275, 1112, 712. **HRMS** calcd $C_{21}H_{25}O_4$ $[M+H]^+$: 341.1747. Found: 341.1751.



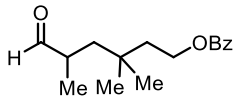
5j

4-Methyl-2-phenylpentanal (5j)[49]: Synthesized from **4j** and **2a** according to general procedure B. 54% Yield. Colorless oil. R_f = 0.5 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.66 (d, *J* = 2.1 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.33 – 7.27 (m, 1H), 7.24 – 7.19 (m, 2H), 3.60 (ddd, *J* = 8.7, 6.5, 2.2 Hz, 1H), 1.91 (ddd, *J* = 14.2, 8.3, 6.5 Hz, 1H), 1.69 (ddd, *J* = 14.0, 8.7, 5.8 Hz, 1H), 1.57 – 1.43 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.06, 136.51, 129.03, 128.78, 127.49, 57.23, 38.51, 25.30, 23.00, 21.94.



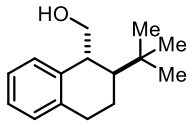
5k

4,4-Dimethyl-2-phenylpentanal (5k): Synthesized from **4j** and **2s** according to general procedure B. 64% Yield. Colorless oil. R_f = 0.5 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.63 (d, *J* = 2.5 Hz, 1H), 7.39 – 7.33 (m, 2H), 7.30 – 7.25 (m, 1H), 7.24 – 7.19 (m, 2H), 3.62 (ddd, *J* = 6.6, 5.5, 2.5 Hz, 1H), 2.25 (dd, *J* = 14.2, 6.8 Hz, 1H), 1.62 (dd, *J* = 14.1, 5.6 Hz, 1H), 0.89 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.68, 137.91, 129.06, 128.82, 127.38, 56.04, 43.14, 30.99, 29.80. **IR** (KBr, cm^{-1}) 2956, 2867, 1726, 1366, 1074, 759. **HRMS** calcd $C_{13}H_{19}O$ $[M+H]^+$: 191.1430. Found: 191.1439.



5l

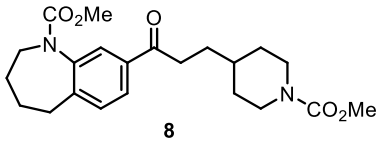
3,3,5-Trimethyl-6-oxohexyl benzoate (5l): Synthesized from **4l** and **2t** according to general procedure B. 59% Yield. The di-alkylation product was observed in 6% yield. Colorless oil. R_f = 0.5 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.58 (d, *J* = 2.8 Hz, 1H), 8.07 – 7.92 (m, 2H), 7.58 – 7.52 (m, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 4.38 (t, *J* = 7.1 Hz, 2H), 2.55 – 2.41 (m, 1H), 1.94 (dd, *J* = 14.5, 7.6 Hz, 1H), 1.81 – 1.67 (m, 2H), 1.24 (dd, *J* = 14.4, 3.6 Hz, 1H), 1.12 (d, *J* = 7.1 Hz, 3H), 0.99 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.95, 166.64, 132.89, 130.33, 129.52, 128.35, 62.00, 43.20, 42.73, 40.39, 32.82, 27.47, 27.37, 16.52. **IR** (KBr, cm^{-1}) 2962, 2873, 1720, 1452, 1275, 1114, 712. **HRMS** calcd $C_{16}H_{23}O_3$ $[M+H]^+$: 263.1642. Found: 263.1638.



5m'

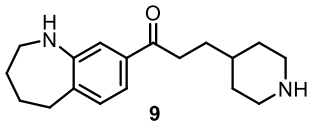
((1*S*,2*R*)-2-(*tert*-Butyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (5m'): Synthesized from **4m** and **2s** according to general procedure A. Due to the instability of the aldehyde product during the purification, the aldehyde was reduced to alcohol for characterization. After the reaction was finished, MeOH (2 mL) and $NaBH_4$ (5 equiv., 2.0 mmol, 76 mg) was added, and the mixture was further stirred at room temperature for 1 h. The alcohol was then isolated according to the general procedure. 52% Yield. d.r. = 8:1 based on crude NMR of the reaction mixture. The stereochemistry of the major diastereomer (*trans*) is determined by X-ray structure of the crystal from its ferrocenyl ester form (*vide infra*). Colorless oil. R_f = 0.5 (hexane/EtOAc =

3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 – 7.08 (m, 4H), 3.65 – 3.54 (m, 1H), 3.46 – 3.33 (m, 1H), 2.89 (ddd, *J* = 8.7, 5.5, 3.0 Hz, 1H), 2.66 (dt, *J* = 15.0, 3.9 Hz, 1H), 2.55 (ddd, *J* = 15.1, 12.5, 3.6 Hz, 1H), 2.01 (ddt, *J* = 12.6, 6.6, 3.8 Hz, 1H), 1.50 (ddd, *J* = 11.3, 6.7, 3.0 Hz, 1H), 1.36 – 1.15 (m, 2H), 0.91 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.56, 138.33, 129.45, 127.78, 126.17, 126.12, 68.63, 46.09, 43.87, 34.12, 29.20, 27.41, 25.22. **IR** (KBr, cm^{-1}) 3352, 2950, 2867, 1457, 1366, 1043, 602. **HRMS** calcd $C_{15}H_{22}NaO$ $[M+Na]^+$: 241.1563. Found: 241.1556.



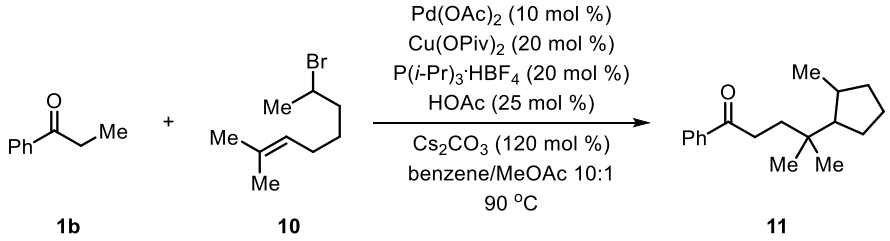
8

Methyl 8-(3-(1-(methoxycarbonyl)piperidin-4-yl)propanoyl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxylate (8): Synthesized from **6** and **7** according to general procedure B except for using 3 equivalents (0.6 mmol) of ketone **6**. 52% Yield. 82% Yield based on recovered starting material **6** (0.473 mmol, 123.5 mg). Colorless oil. R_f = 0.4 (hexane/EtOAc = 1:1). Two rotamers are observed in 64:36 ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 – 7.64 (m, 2H), 7.31 – 7.21 (m, 1H), 4.44 (br, 0.64H), 4.11 (br, 2H), 3.84 – 3.56 (m, 6.36H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.86 – 2.64 (m, 4.64H), 2.04 – 1.30 (m, 9.36H), 1.21 – 1.05 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) carbon signals are found at δ 199.02, 155.88, 155.06, 145.41, 145.23, 142.85, 142.48, 135.84, 130.35, 130.09, 128.13, 127.84, 126.75, 126.59, 52.95, 52.42, 49.00, 48.86, 44.01, 35.52, 35.40, 34.61, 31.88, 30.55, 30.39, 29.84, 29.23, 25.86. **IR** (KBr, cm^{-1}) 2933, 2855, 1700, 1451, 1276, 1192, 768. **HRMS** calcd $C_{22}H_{31}N_2O_5$ $[M+H]^+$: 403.2227. Found: 403.2230.



9

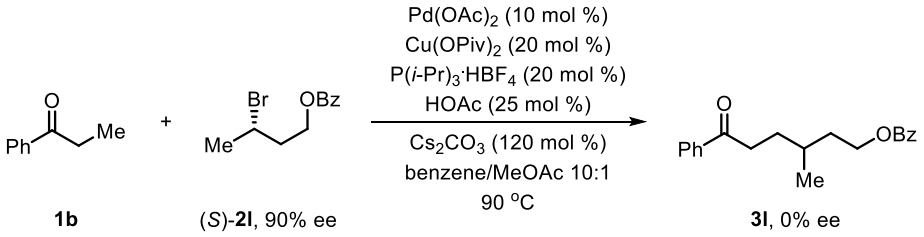
3-(Piperidin-4-yl)-1-(2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-8-yl)propan-1-one (9)[24]: A 10-mL Schlenk flask was flame-dried and refilled with N_2. Compound **8** (1 equiv., 0.2 mmol, 80.4 mg) was dissolved in DCM (4 mL), and the solution was added into the flask via syringe. The mixture was cooled to 0 °C, and TMSI (5 equiv., 1.0 mmol, 142 μL) was added dropwise via syringe. The mixture was stirred at room temperature overnight. The mixture was diluted with DCM and added slowly to a stirred solution of $NaHCO_3$ and $Na_2S_2O_3$. The mixture was extracted with DCM four times. The combined organic layers were extracted with 1 M HCl twice, and the combined aqueous layers were washed with DCM once. The aqueous layer was collected, basified with 10% NaOH and extracted with DCM four times. The combined organic layers were dried and concentrated to give **9** as a pale-yellow oil in 76% yield (43.6 mg). R_f < 0.05 (EtOAc/MeOH = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.33 (d, *J* = 1.7 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 3.92 (br, 1H), 3.16 – 3.00 (m, 4H), 2.97 – 2.89 (m, 2H), 2.87 – 2.74 (m, 2H), 2.59 (td, *J* = 12.2, 2.6 Hz, 2H), 2.54 (br, 1H), 1.85 – 1.77 (m, 2H), 1.77 – 1.59 (m, 6H), 1.52 – 1.36 (m, 1H), 1.23 – 1.11 (m, 2H).



1b **10** **11**

4-Methyl-4-(2-methylcyclopentyl)-1-phenylpentan-1-one (11): Following the general

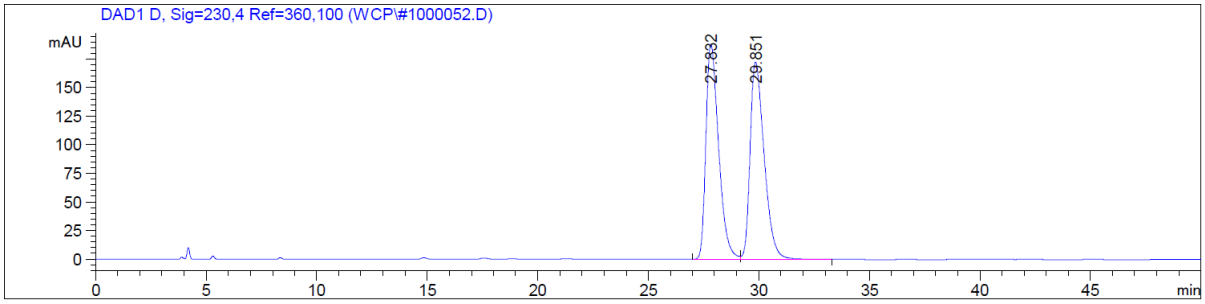
procedure B, substrate **10** underwent 5-*exo*-trig cyclization to give cyclized product **11** in 55% yield. d.r. = 1.6:1 based on crude NMR of the reaction mixture. Following the general procedure B except for running the reaction without $Cu(OPiv)_2$, substrate **10** underwent cyclization to give the same product **11** in 10% yield. d.r. = 1.6:1 based on crude NMR of the reaction mixture. The uncyclized product was not observed in both cases. Colorless oil. R_f = 0.5 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 – 7.91 (m, 2H), 7.59 – 7.52 (m, 1H), 7.51 – 7.41 (m, 2H), 3.03 – 2.83 (m, 2H), 2.24 – 2.10 (m, 0.62H), 1.94 – 1.84 (m, 0.38H), 1.80 – 1.46 (m, 7H), 1.45 – 1.19 (m, 2H), 1.02 – 0.95 (m, 4.86H), 0.92 – 0.84 (m, 4.14H). **^{13}C NMR** (100 MHz, $CDCl_3$) carbon signals are found at δ 201.22, 201.17, 137.16, 132.81, 128.54, 128.06, 56.14, 53.02, 36.85, 36.15, 35.36, 35.11, 34.69, 34.35, 34.01, 33.80, 33.71, 28.98, 26.31, 25.42, 24.86, 23.99, 23.84, 22.60, 21.02, 17.12. **IR** (KBr, cm^{-1}) 2955, 2869, 1685, 1448, 1282, 691. **HRMS** calcd $C_{18}H_{27}O$ $[M+H]^+$: 259.2056. Found: 259.2059.



Following the general procedure B, enantioenriched substrate (*S*)-**2l** delivered racemic product **3l** in 67% yield. Following the general procedure B except for running the reaction without $Cu(OPiv)_2$, enantioenriched substrate (*S*)-**2l** delivered racemic product **3l** in 12% yield.

Chiral HPLC (Chiralpak ID, hexane:isopropanol = 97:3, 1 mL/min, 230 nm): ee = 0%.

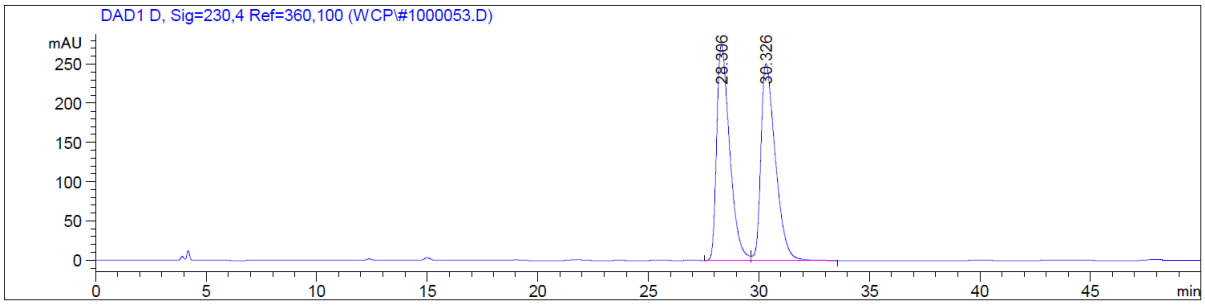
Sample of **3l** from racemic substrate **2l**:



Signal 4: DAD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.832	BV	0.6132	7512.10889	188.40303	49.6586
2	29.851	VB	0.6769	7615.38770	172.56502	50.3414

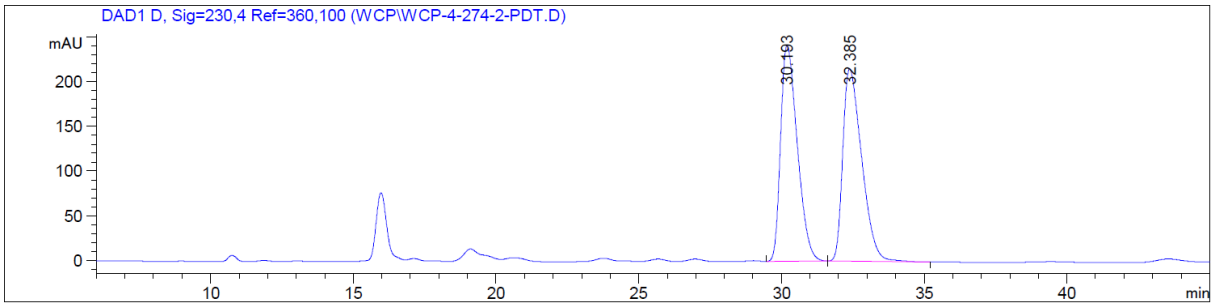
Sample of **3l** from enantioenriched substrate (*S*)-**2l** in the presence of $Cu(OPiv)_2$:



Signal 4: DAD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.306	BV	0.6228	1.12255e4	274.69901	49.6165
2	30.326	VB	0.6900	1.13990e4	250.92159	50.3835

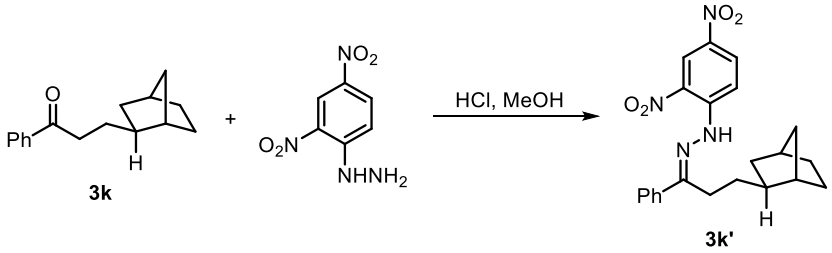
Sample of **3l** from enantioenriched substrate (*S*)-**2l** in the absence of $Cu(OPiv)_2$:



Signal 4: DAD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.193	BB	0.6270	9796.21191	241.63495	49.6732
2	32.385	BB	0.7060	9925.11035	215.23398	50.3268

3.4.5 X-ray crystallography data



A 4-mL vial was charged with **3k** (1 equiv., 0.046 mmol, 10.6 mg), DNP (1 equiv., 0.046 mmol, 9.1 mg), methanol (0.5 mL) and concentrated HCl (2 μL), and the mixture was stirred at room temperature for 2 days. The precipitate was collected through filtration and washed with methanol. The solid was then eluted with DCM, and the filtrate was concentrated to give **3k'** as an orange solid. The solid was dissolved in DCM/hexane mixed solvent for crystal growth by slow evaporation.

Figure 3.1 Crystal Structure of **3k'**

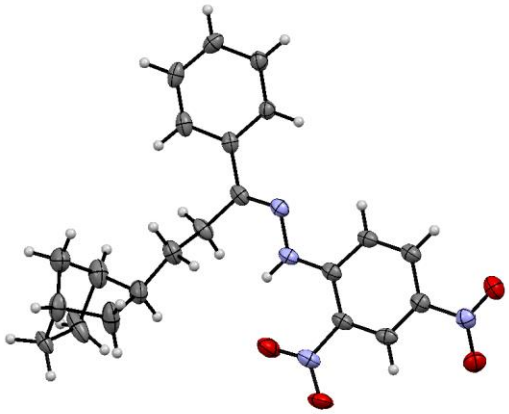
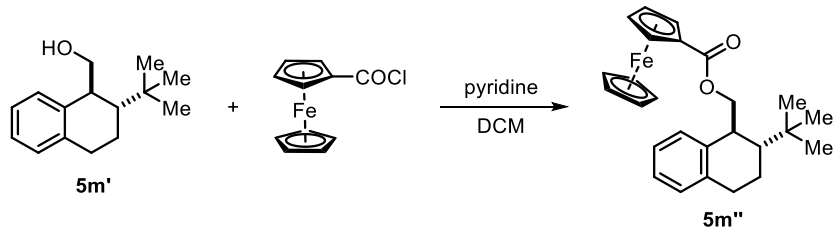


Table 3.11 X-Ray Crystallography Data of **3k'**

Empirical formula	$C_{22}H_{24}N_4O_4$
Formula weight	408.45
Temperature/K	100(2)
Wavelength/Å	0.71073
Crystal system	triclinic
Space group	P-1
a/Å	8.7271(16)
b/Å	13.977(3)
c/Å	16.680(3)
α/°	92.757(5)
β/°	98.833(5)
γ/°	91.076(5)
Volume/Å^3	2007.4(7)
Z	4
Density (calculated) g/cm^3	1.351
Absorption coefficient/mm^{-1}	0.095
F(000)	864
Crystal size/mm^3	0.340 x 0.170 x 0.090
2Θ range for data collection/°	3.111 to 27.524
Index ranges	$-11 \leq h \leq 11$, $-18 \leq k \leq 18$, $-21 \leq l \leq 21$
Reflections collected	37490
Independent reflections	9179 [R(int) = 0.0549]
Completeness to theta = 25.242°	99.8%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00 and 0.840
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	9179/1116/707
Goodness-of-fit on F^2	1.049
Final R indexes [I>=2σ (I)]	R1 = 0.0885, wR2 = 0.2132
Final R indexes [all data]	R1 = 0.1255, wR2 = 0.2371
Largest diff. peak and hole/e Å^{-3}	1.248 and -0.796



A 4-mL vial was charged with **5m'** (1 equiv., 0.062 mmol, 13.5 mg), ferrocenyl chloride (1.5 equiv., 0.093 mmol, 23.1 mg), DCM (0.5 mL) and pyridine (2.5 equiv., 0.155 mmol, 12.5 µL). The mixture was stirred at room temperature overnight. The mixture was concentrated and the residue was purified by column chromatography to give **5m''** as an orange solid. The solid was dissolved in pentane for crystal growth by slow evaporation.

Figure 3.2 Crystal Structure of **5m''**

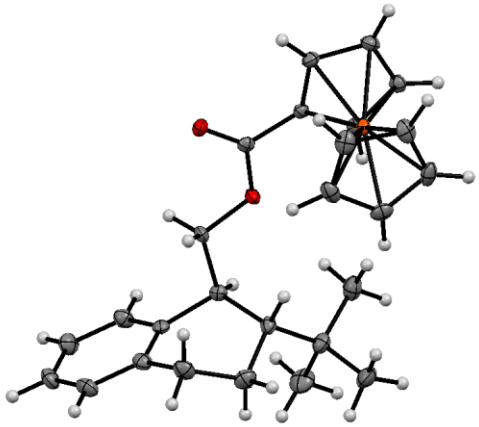


Table 3.12 X-Ray Crystallography Data of **5m"**

Empirical formula	$C_{26}H_{30}FeO_2$
Formula weight	430.35
Temperature/K	100(2)
Wavelength/Å	0.71073
Crystal system	triclinic
Space group	P-1
a/Å	13.6378(8)
b/Å	13.6481(8)
c/Å	19.0182(11)
α/°	93.601(2)
β/°	102.190(2)
γ/°	111.741(2)
Volume/Å^3	3174.9(3)
Z	6
Density (calculated) g/cm^3	1.350
Absorption coefficient/mm^{-1}	0.732
F(000)	1368.0
Crystal size/mm^3	0.1 × 0.02 × 0.02
2Θ range for data collection/°	4.212 to 55.146
Index ranges	-17 ≤ h ≤ 17, -17 ≤ k ≤ 17, -24 ≤ l ≤ 24
Reflections collected	108888
Independent reflections	14670 [R_{int} = 0.0493, R_{sigma} = 0.0384]
Data/restraints/parameters	14670/0/793
Goodness-of-fit on F^2	1.011
Final R indexes [I>=2σ (I)]	R_1 = 0.0382, wR_2 = 0.0770
Final R indexes [all data]	R_1 = 0.0606, wR_2 = 0.0844
Largest diff. peak and hole/e Å^{-3}	0.61 and -0.35

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3.6 NMR Spectra

Figure 3.3 ^{1}H-NMR and ^{13}C-NMR Spectra of **2o**

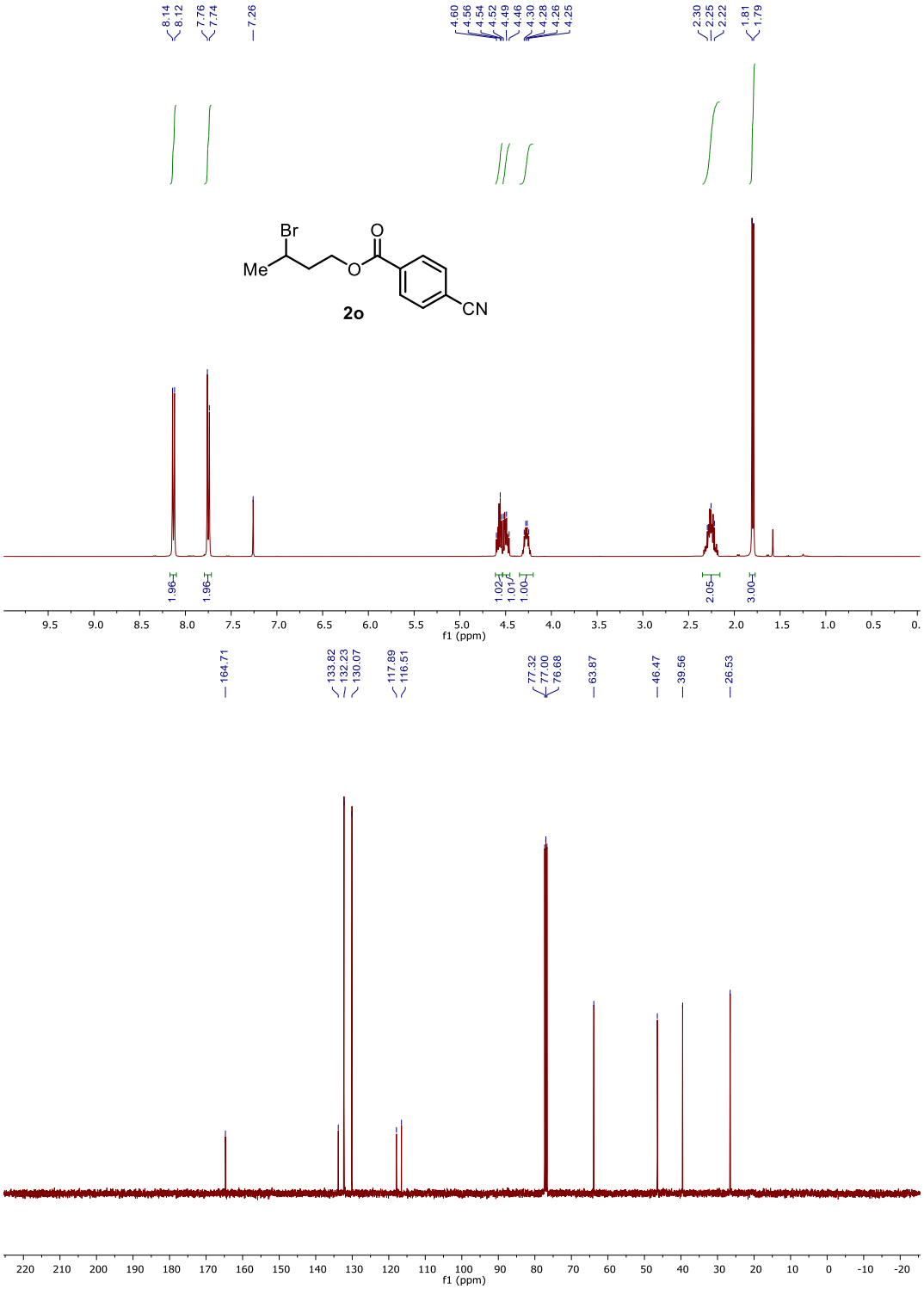


Figure 3.4 ^{1}H-NMR and ^{13}C-NMR Spectra of **2p**

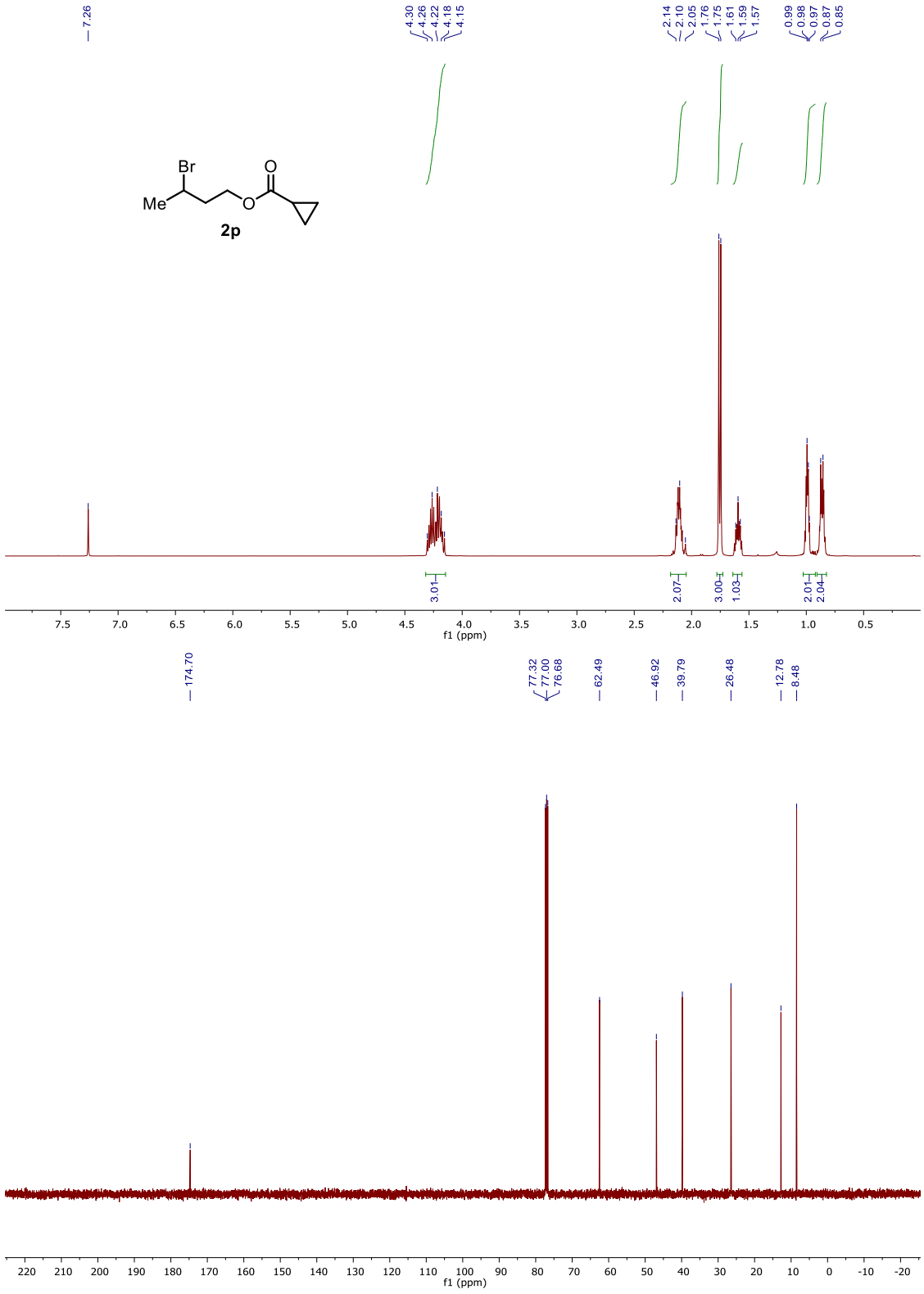


Figure 3.5 ^{1}H-NMR and ^{13}C-NMR Spectra of **2r**

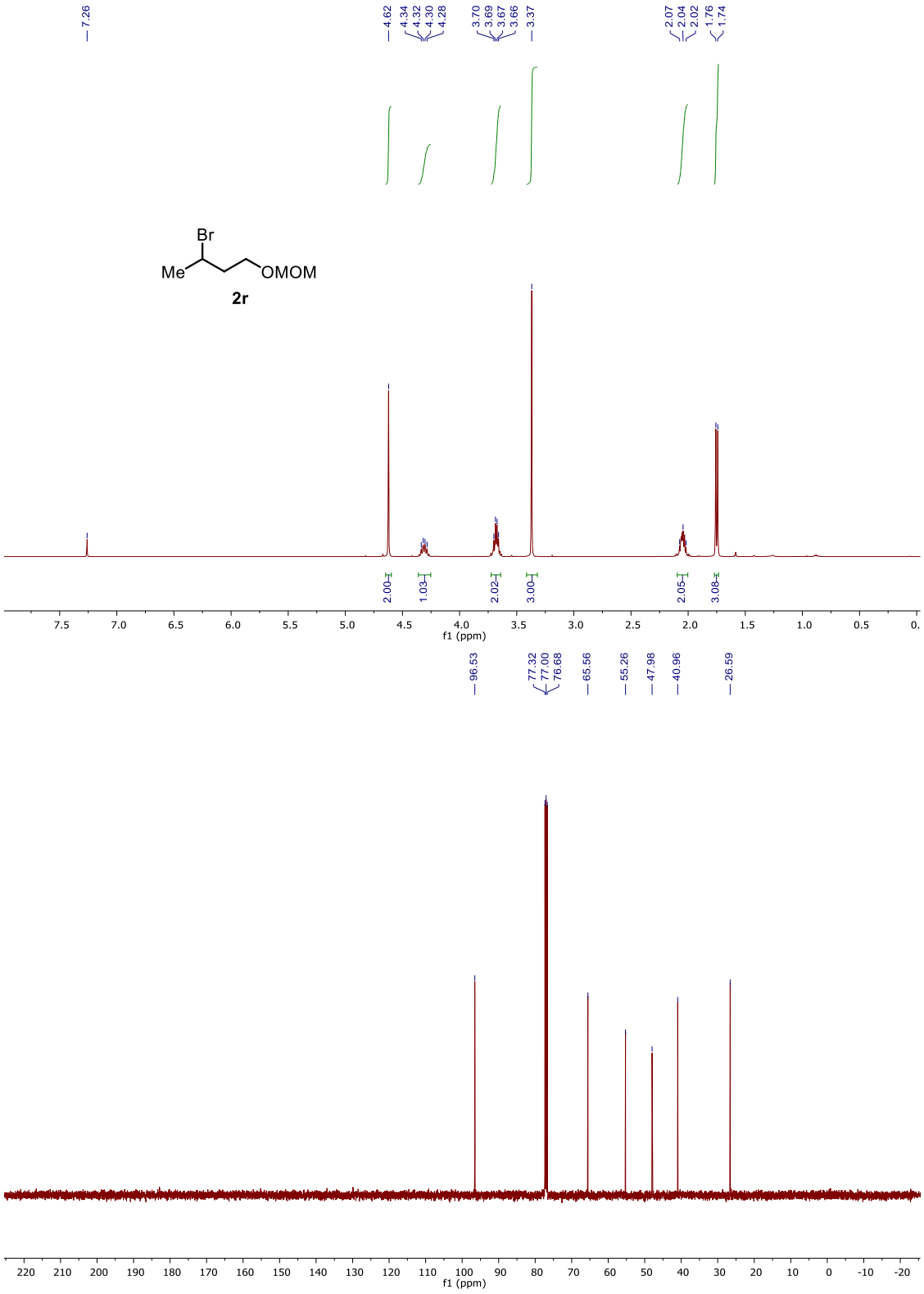


Figure 3.6 ^{1}H-NMR and ^{13}C-NMR Spectra of **2w**

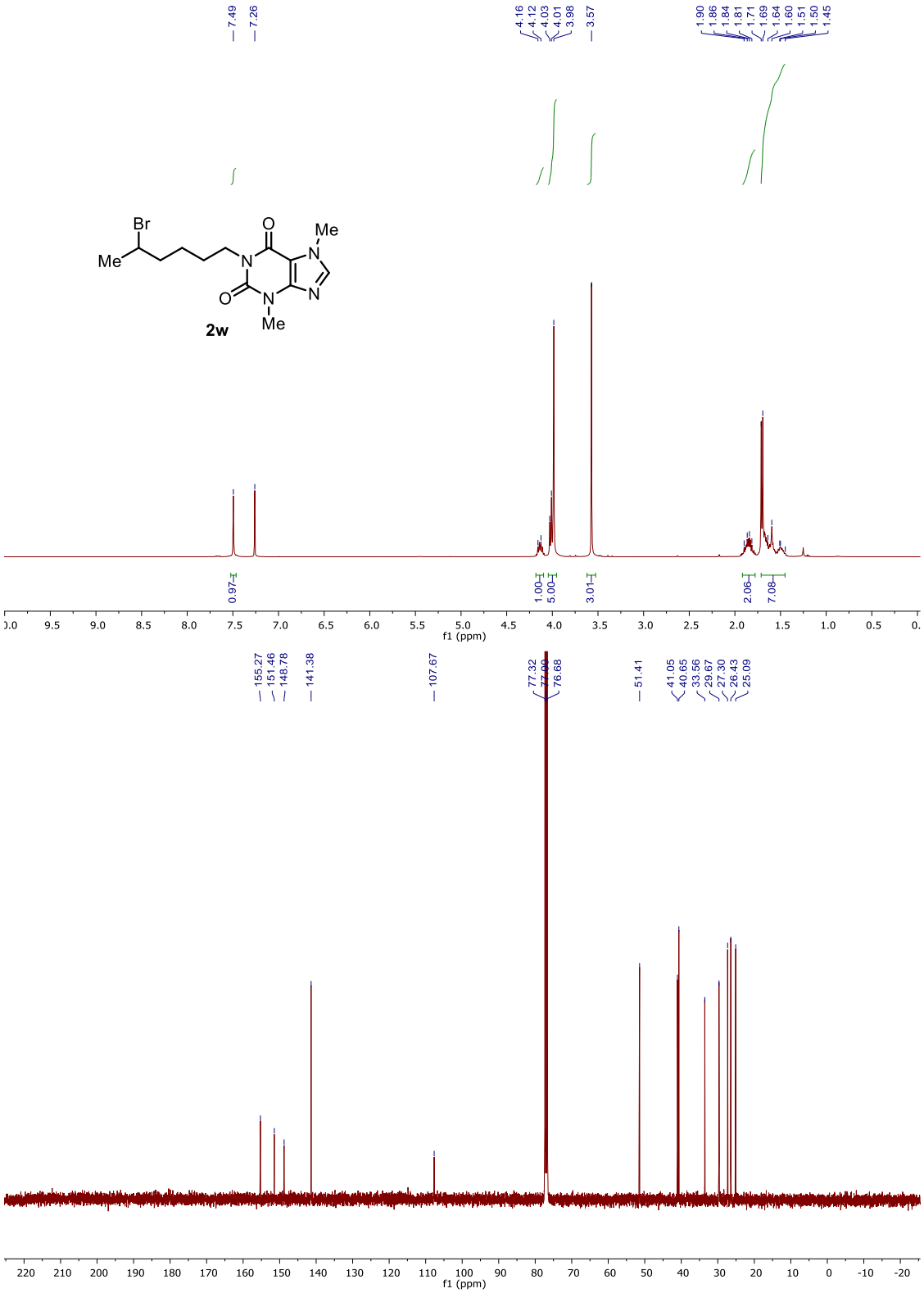


Figure 3.7 ^{1}H-NMR and ^{13}C-NMR Spectra of **2x**

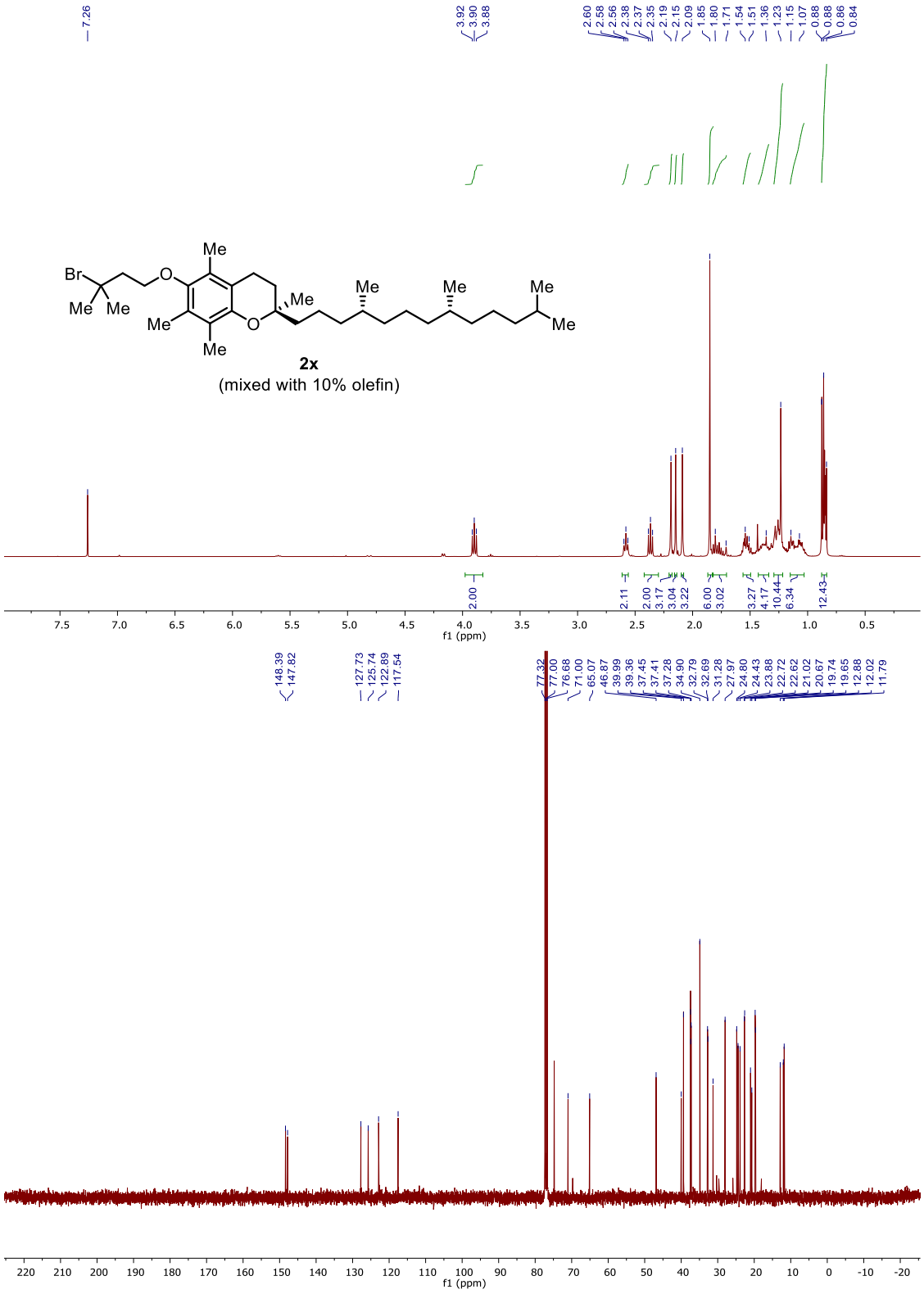


Figure 3.8 ^{1}H-NMR Spectrum of **6-1**

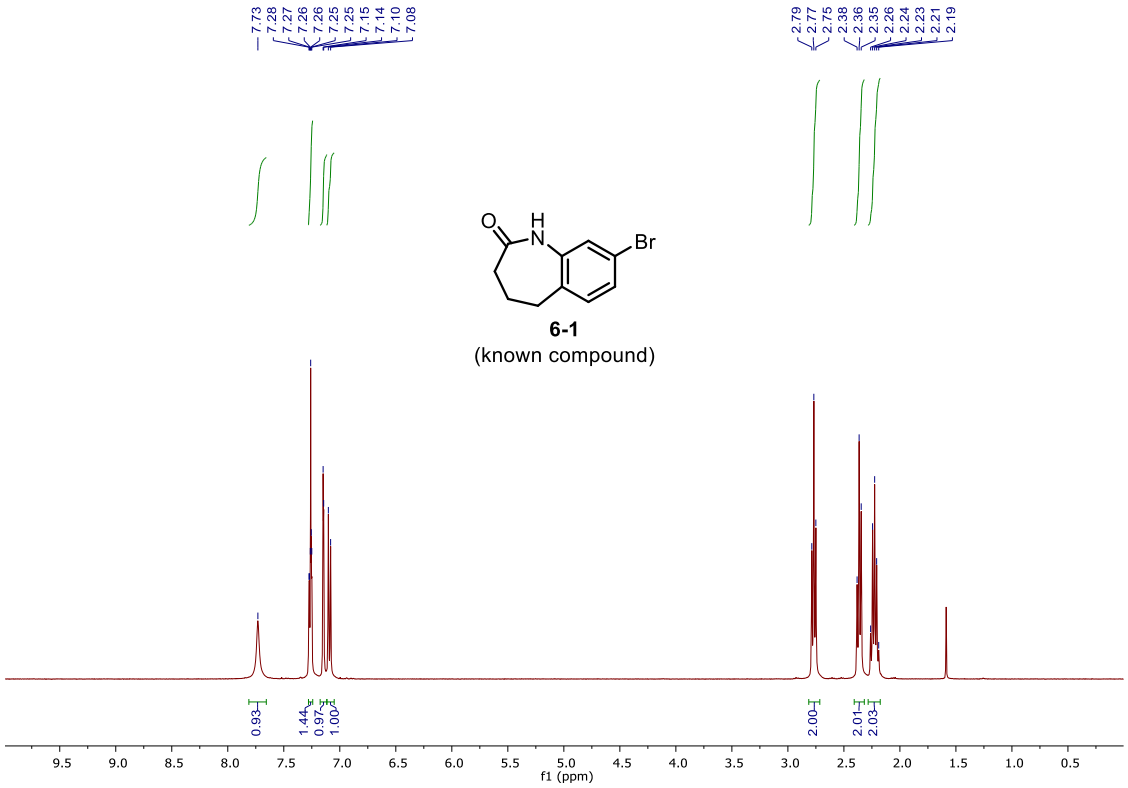


Figure 3.9 ^{1}H-NMR and ^{13}C-NMR Spectra of **6-2**

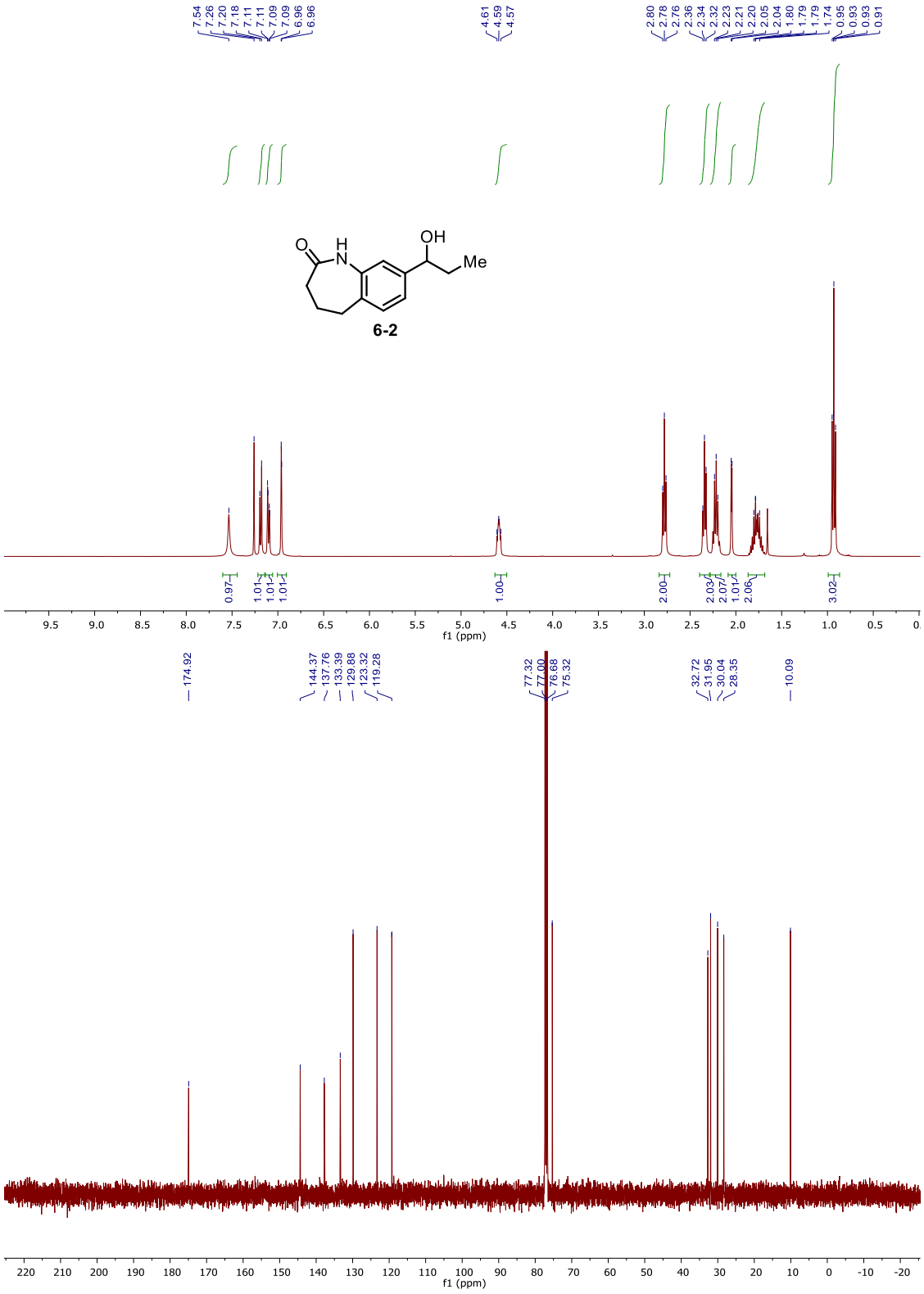


Figure 3.10 ^{1}H-NMR and ^{13}C-NMR Spectra of **6**

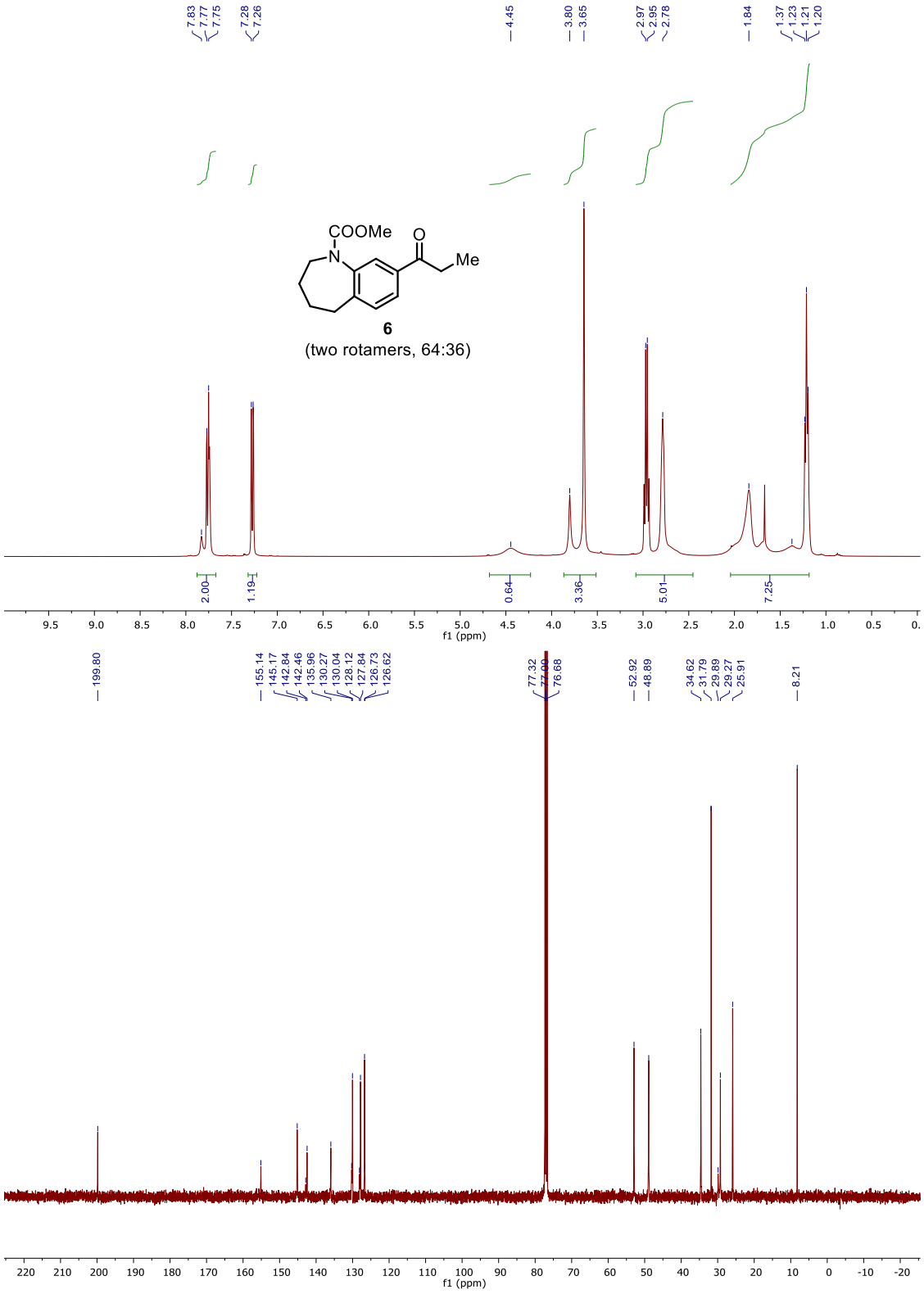


Figure 3.11 ^{1}H-NMR and ^{13}C-NMR Spectra of **7**

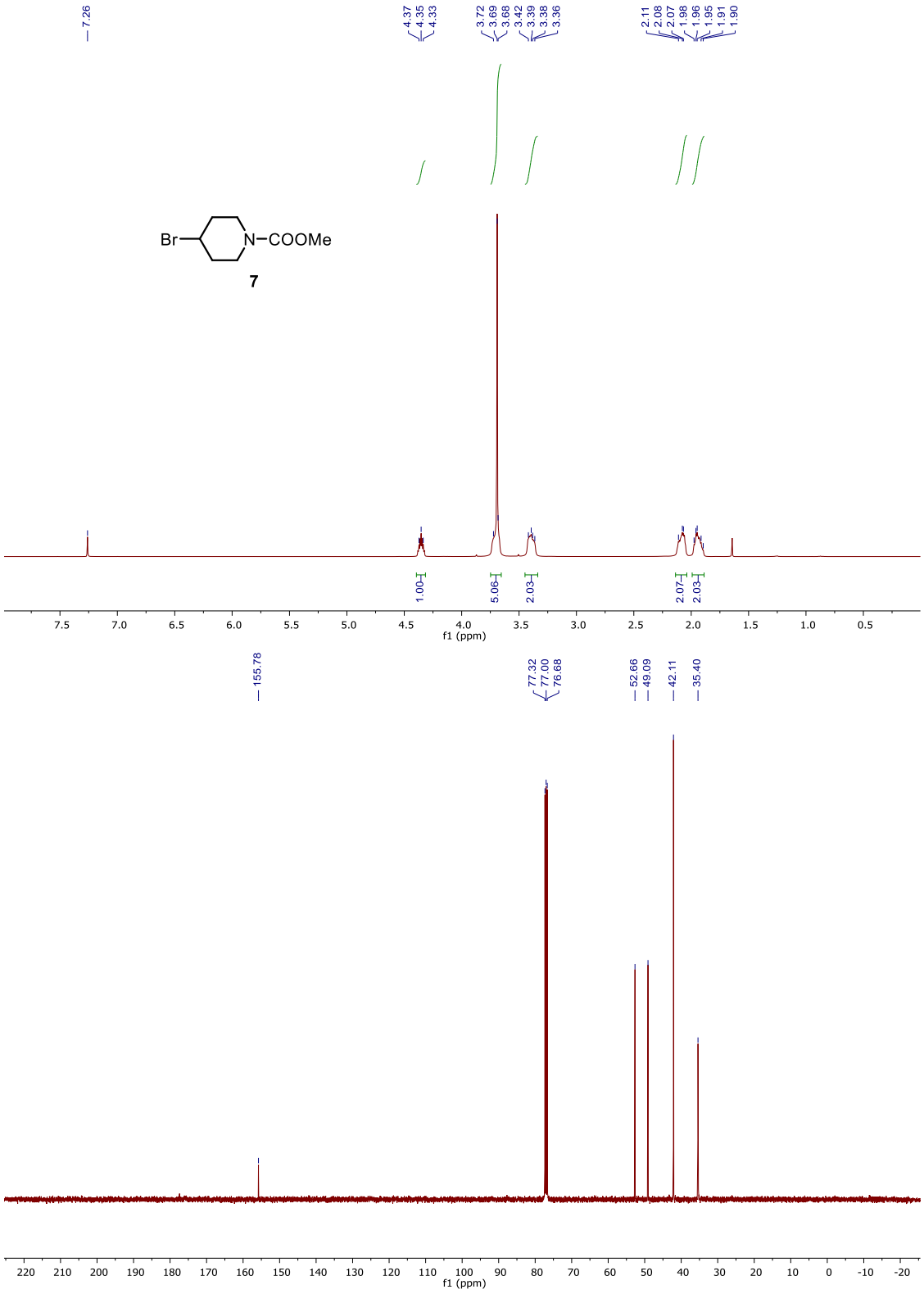


Figure 3.12 ^{1}H-NMR and ^{13}C-NMR Spectra of **10**

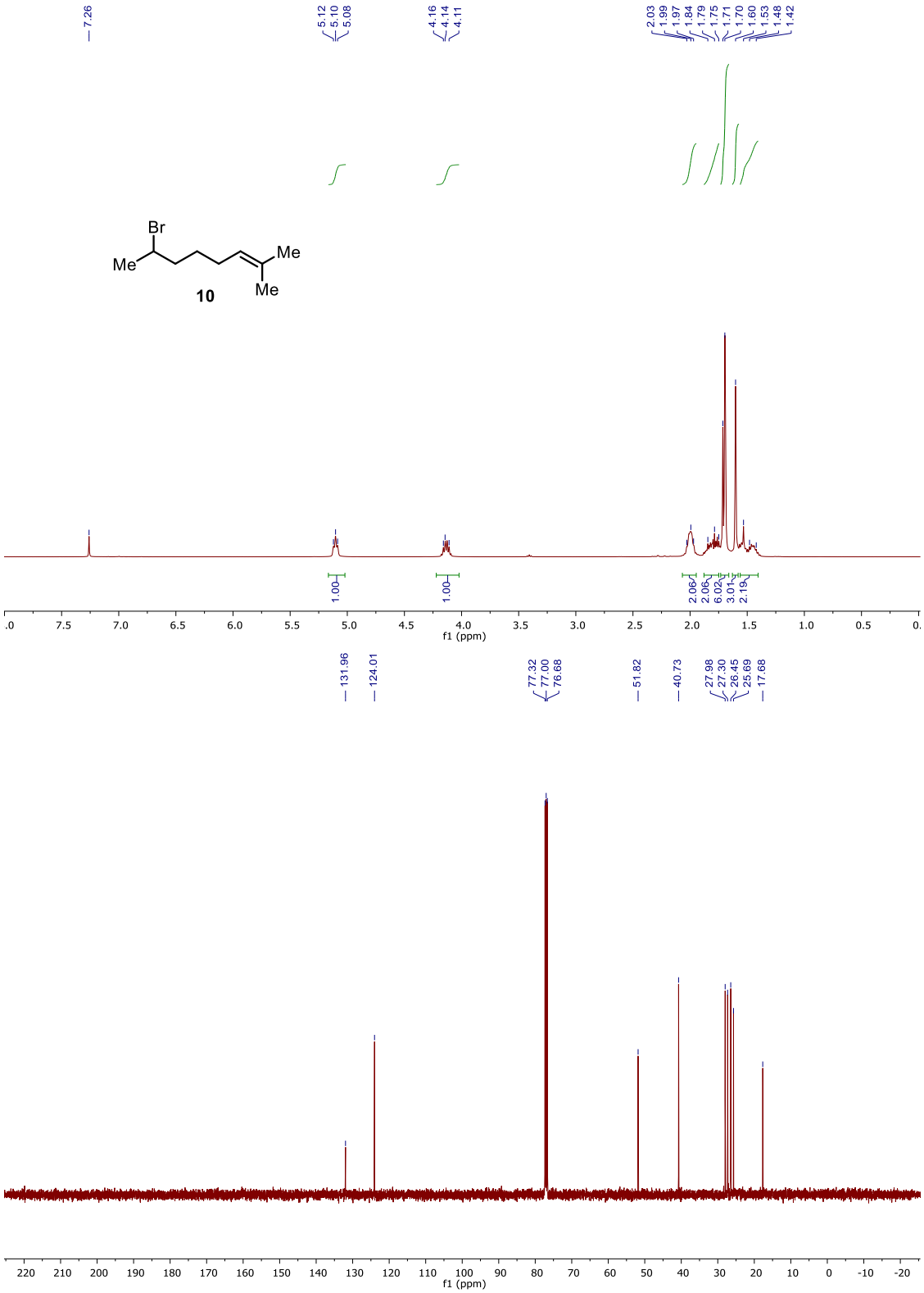


Figure 3.13 ^{1}H-NMR and ^{13}C-NMR Spectra of (*S*)-**2l**

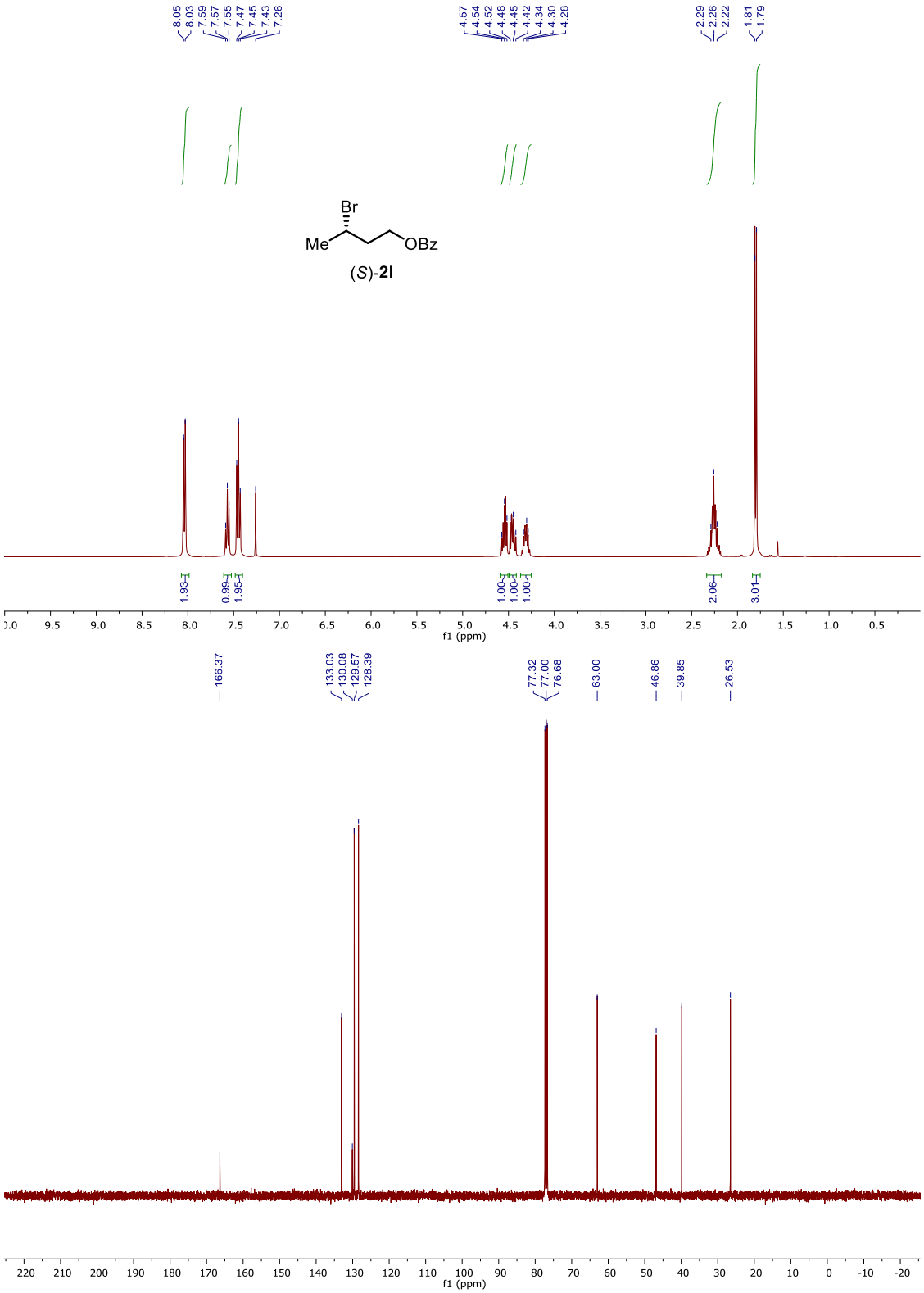


Figure 3.14 ^{1}H-NMR and ^{13}C-NMR Spectra of **1b-α-d$_2$**

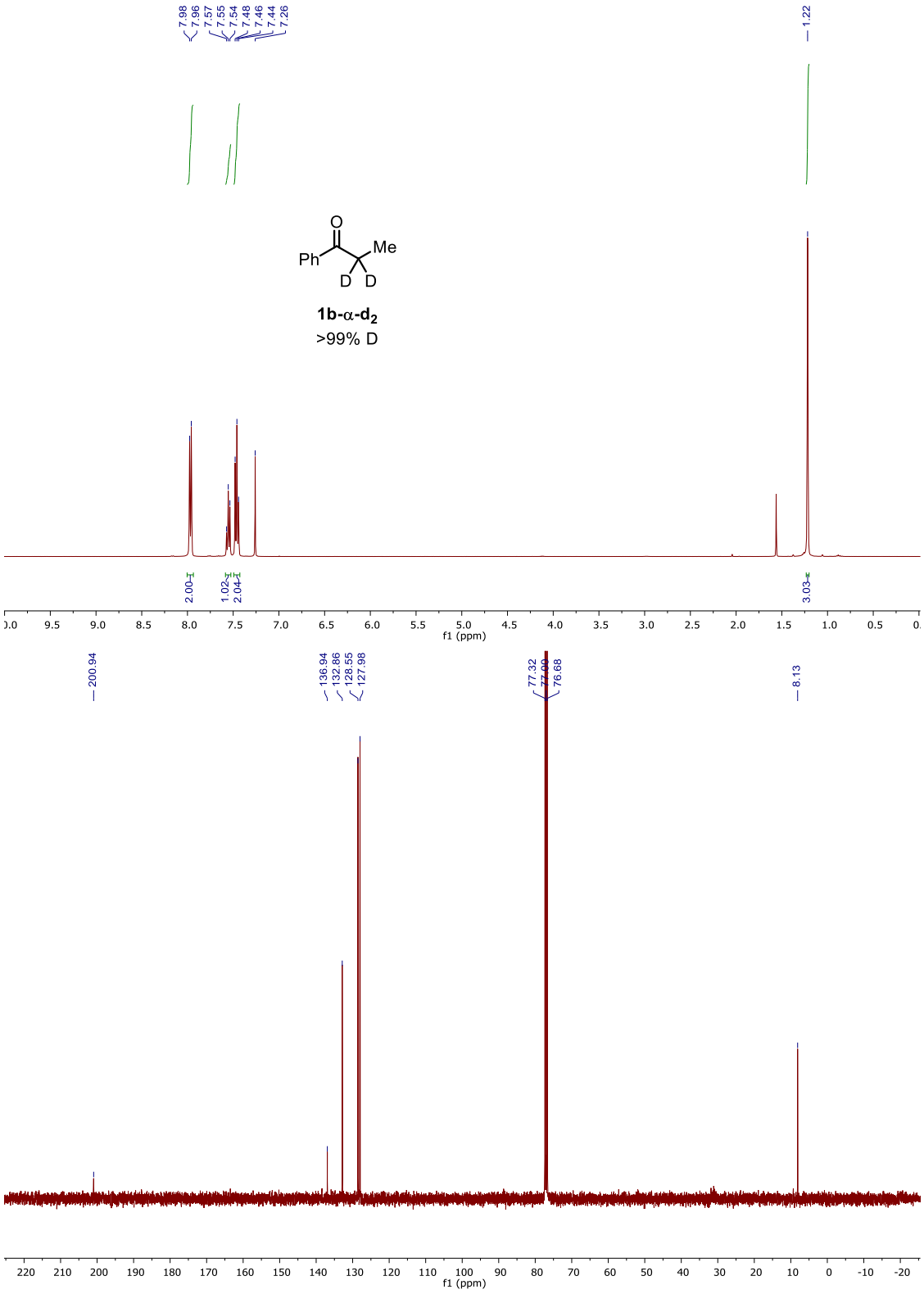


Figure 3.15 ^{1}H-NMR and ^{13}C-NMR Spectra of **1b-1**

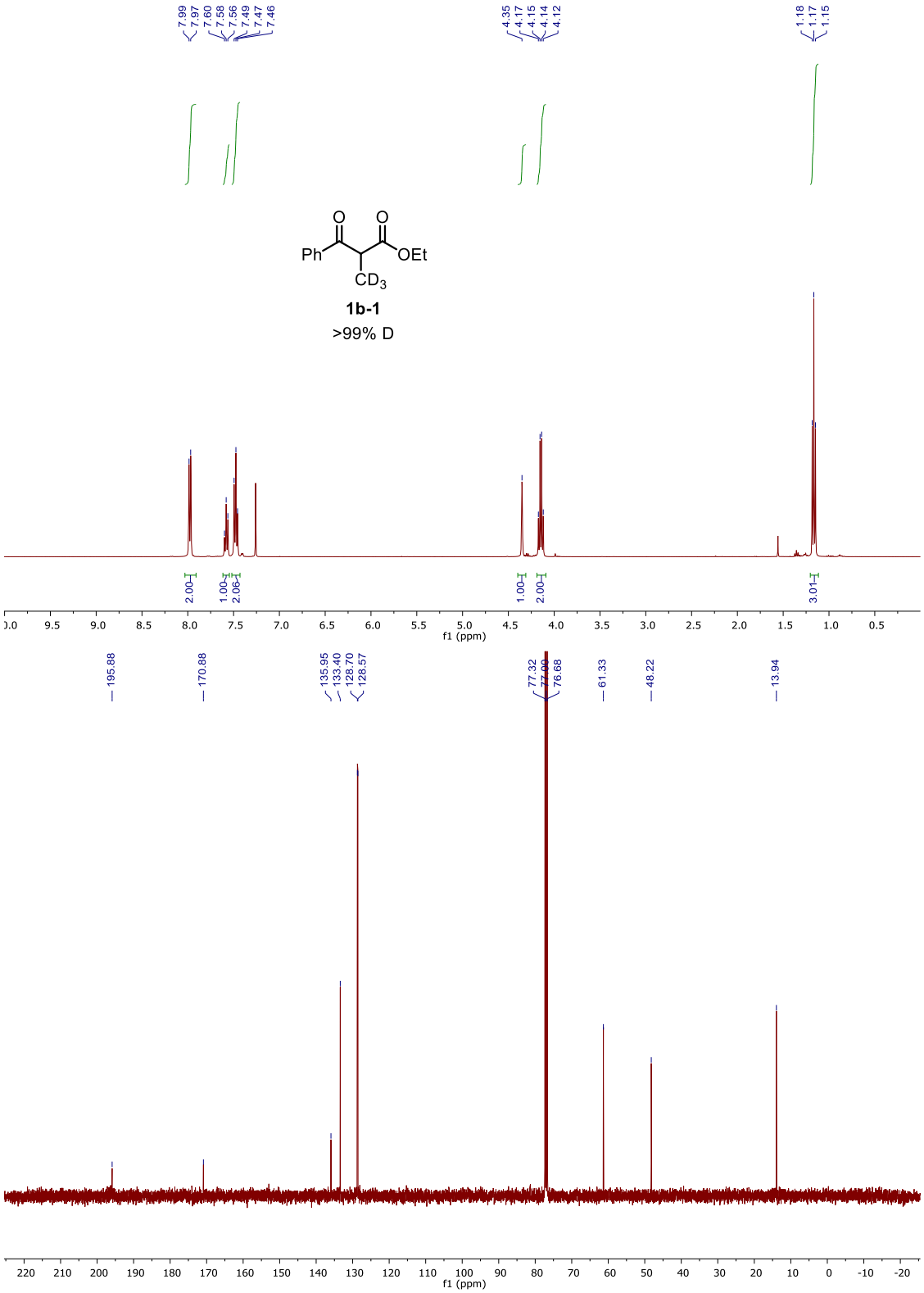


Figure 3.16 ^{1}H-NMR and ^{13}C-NMR Spectra of **1b-β-d$_3$**

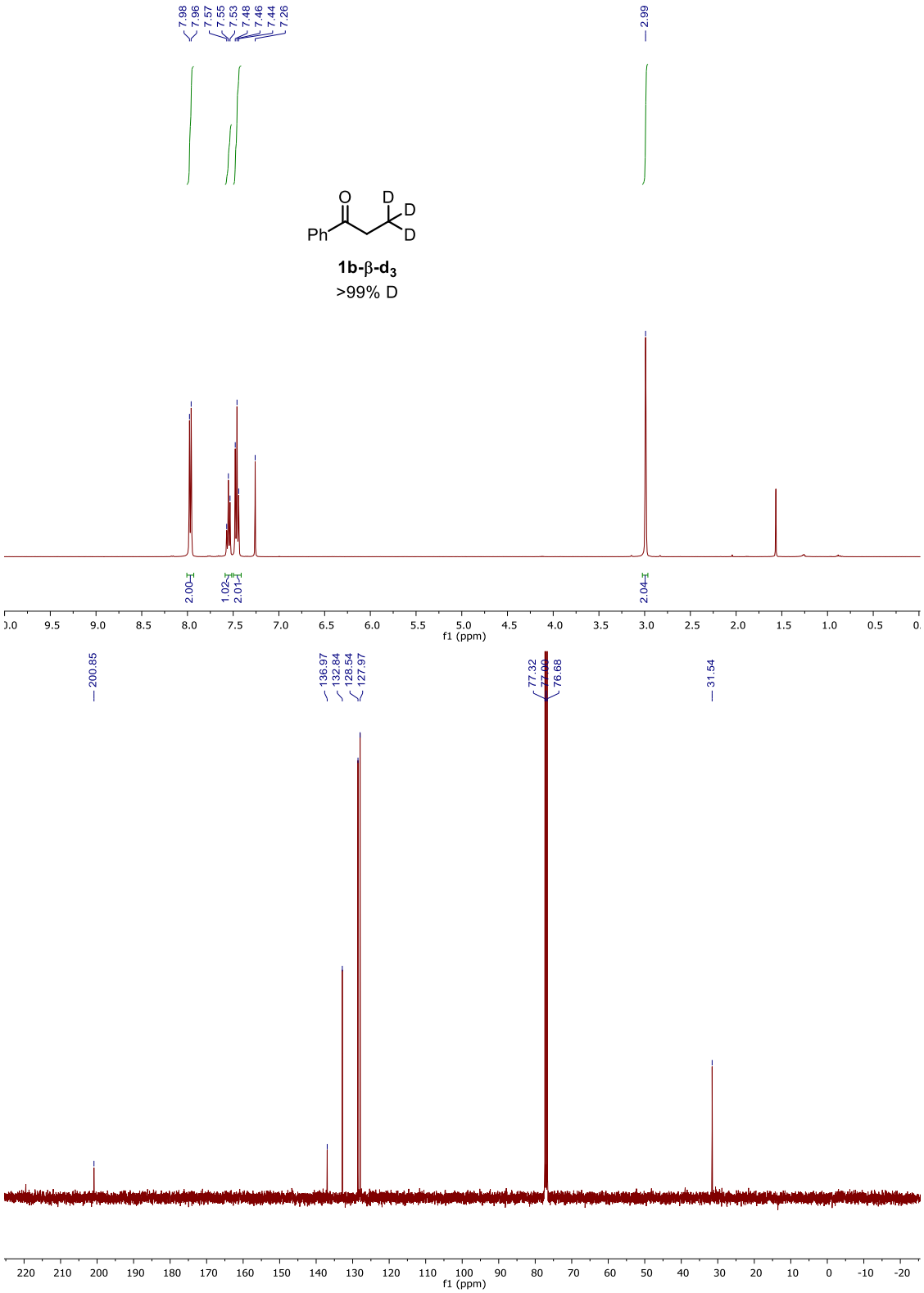


Figure 3.17 ^{1}H-NMR and ^{13}C-NMR Spectra of **1b-d$_5$**

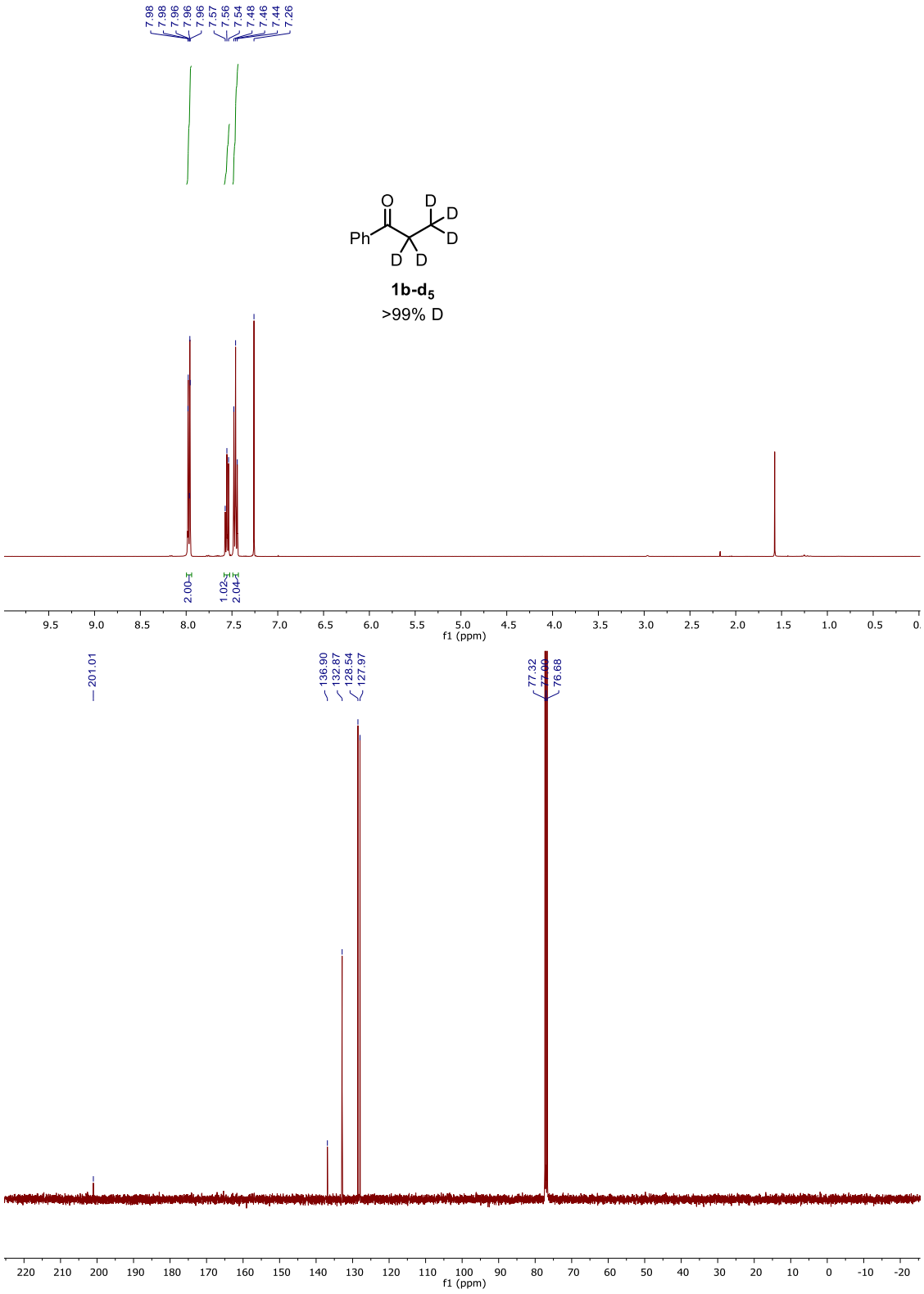


Figure 3.18 ^{1}H-NMR and ^{13}C-NMR Spectra of **3a**

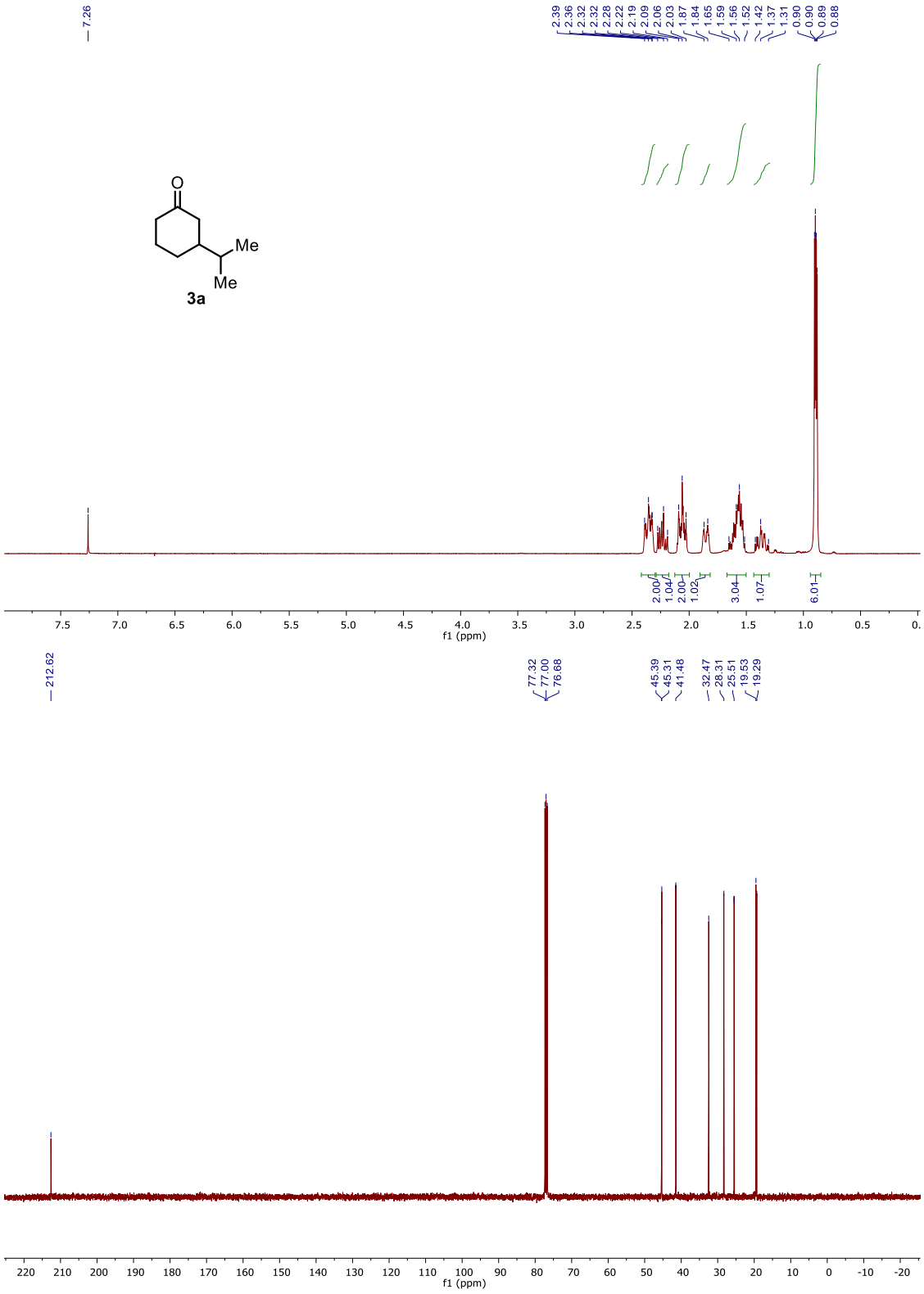


Figure 3.19 ^{1}H-NMR and ^{13}C-NMR Spectra of **3b**

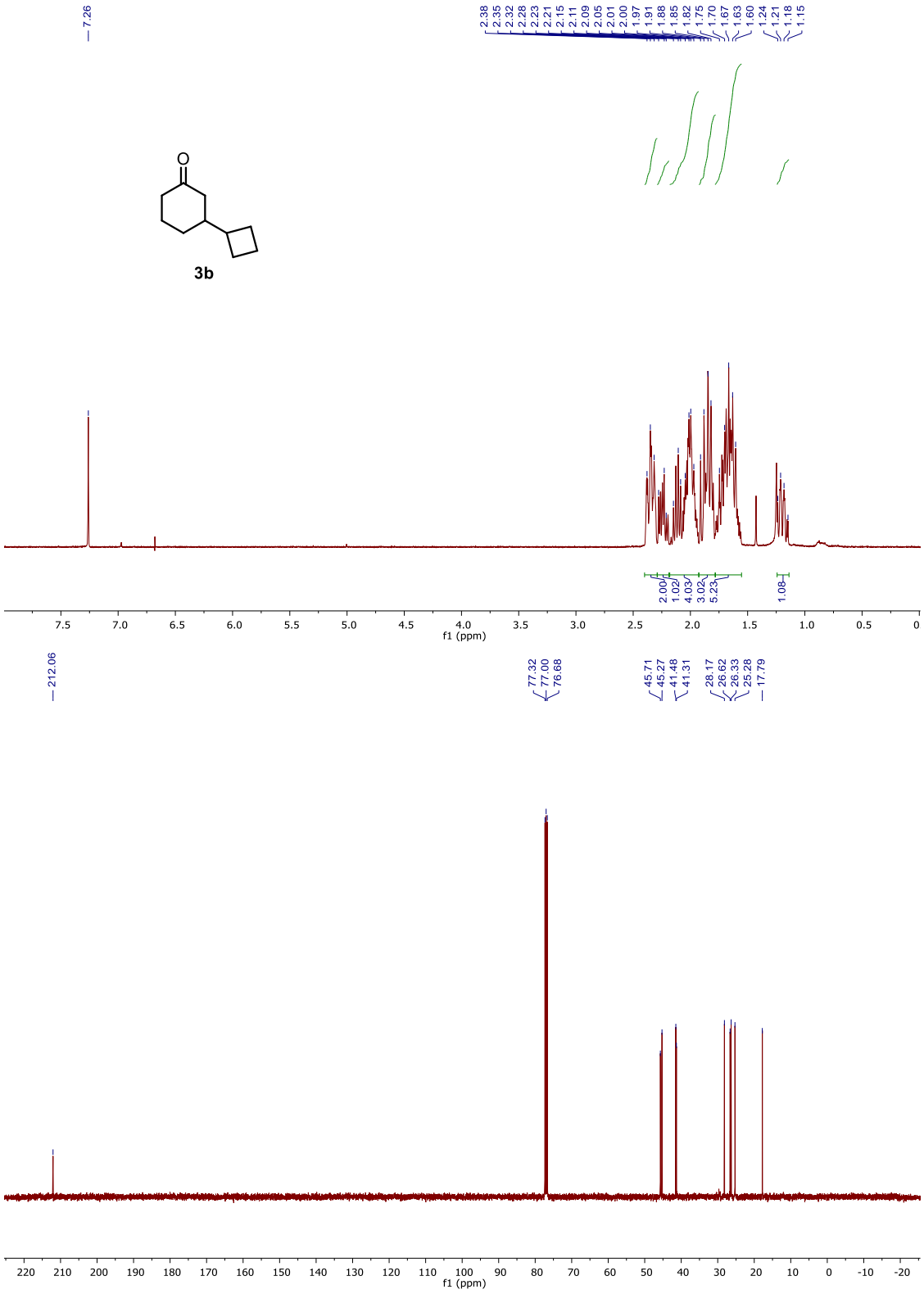


Figure 3.20 ^{1}H-NMR and ^{13}C-NMR Spectra of **3c**

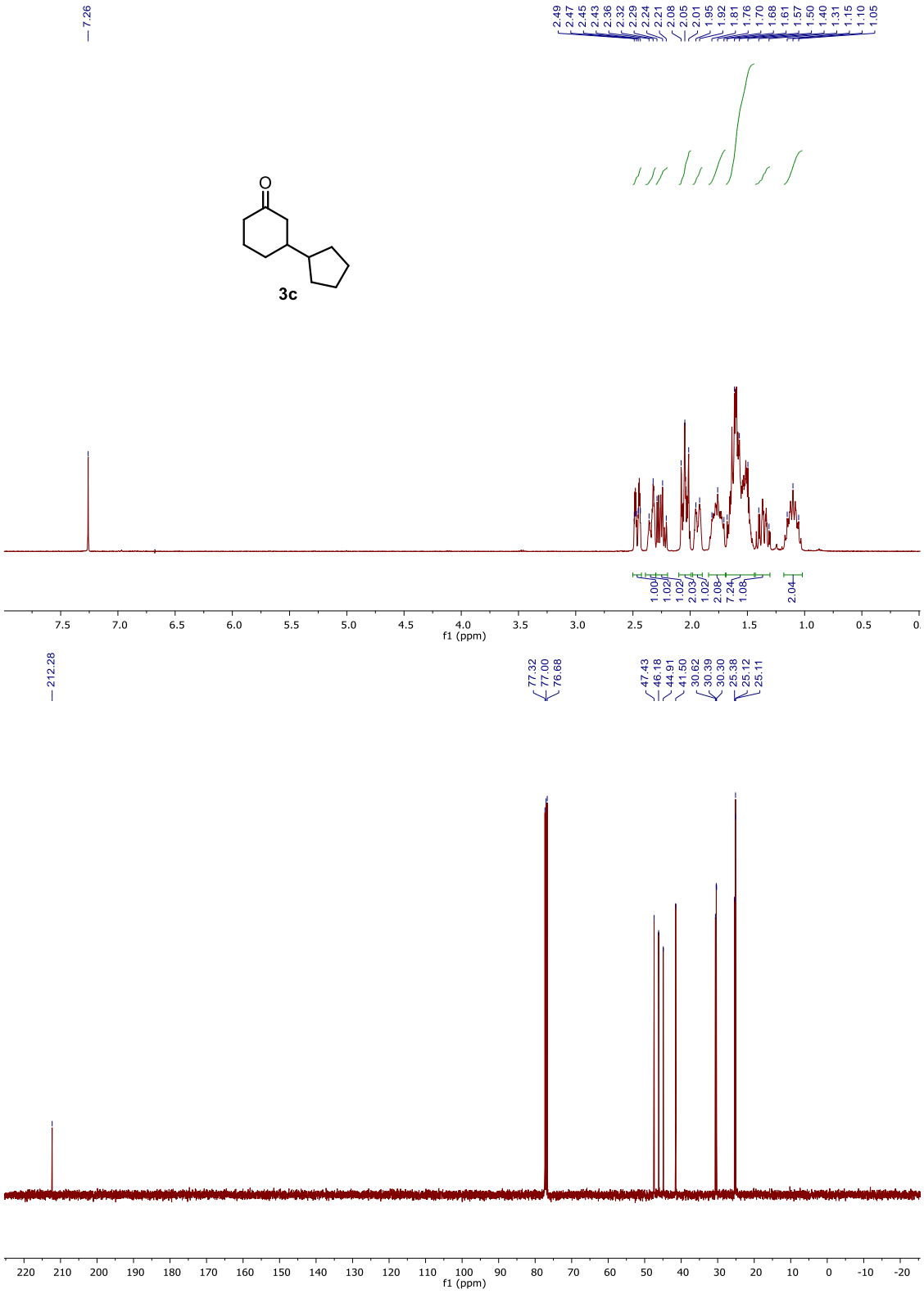


Figure 3.21 ^{1}H-NMR and ^{13}C-NMR Spectra of **3d**

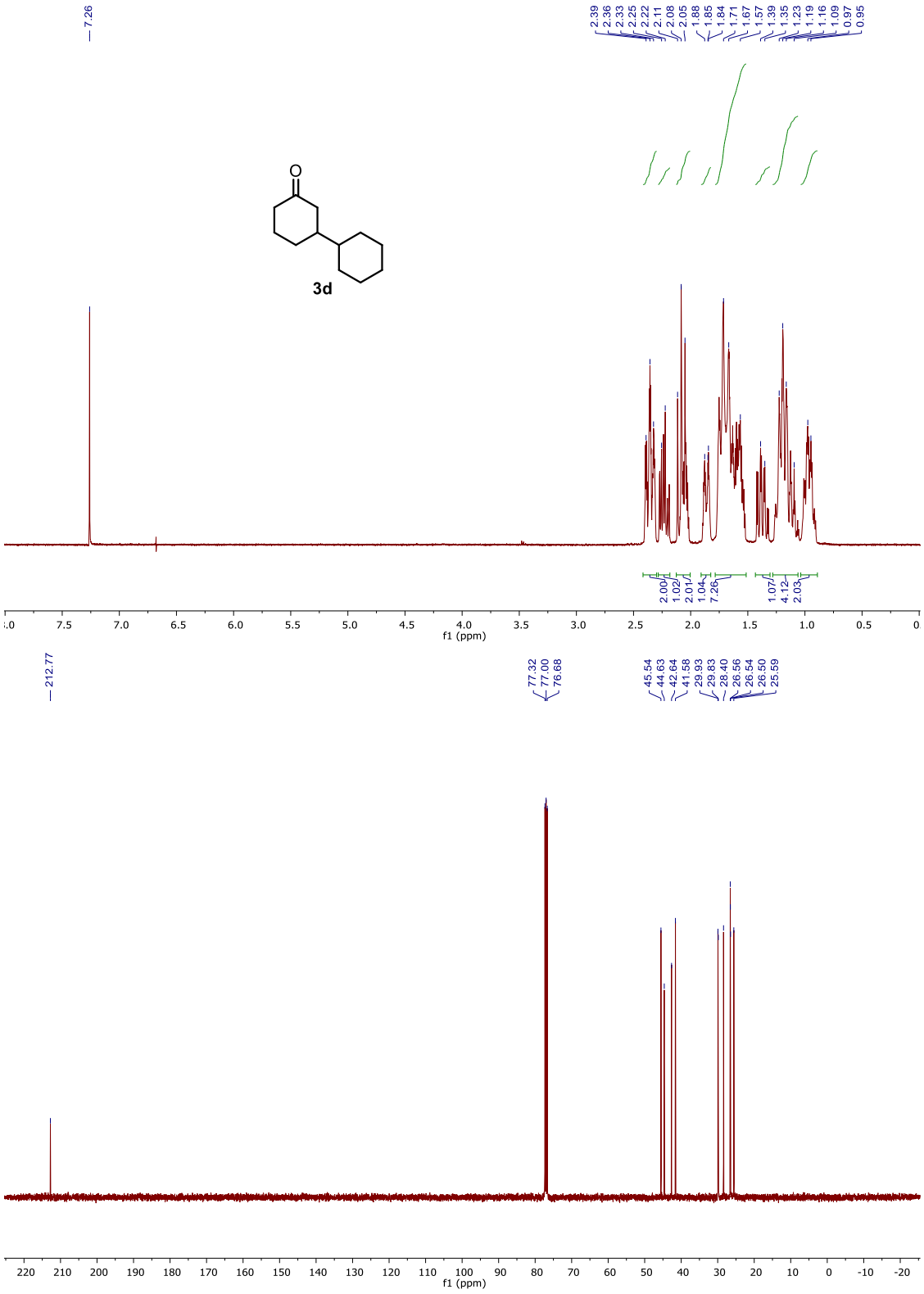


Figure 3.22 ^{1}H-NMR and ^{13}C-NMR Spectra of **3e**

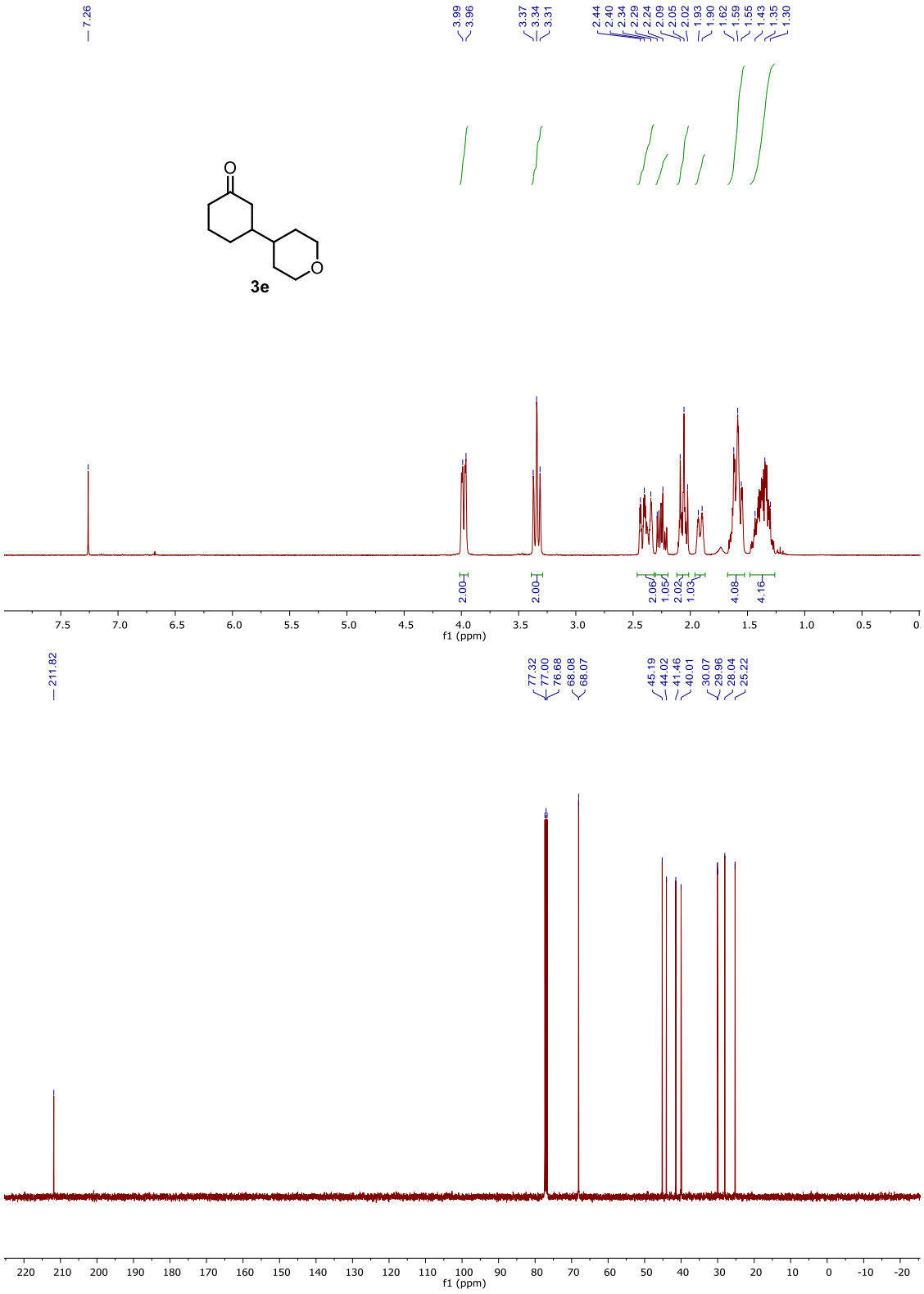


Figure 3.23 ^{1}H-NMR and ^{13}C-NMR Spectra of **3f**

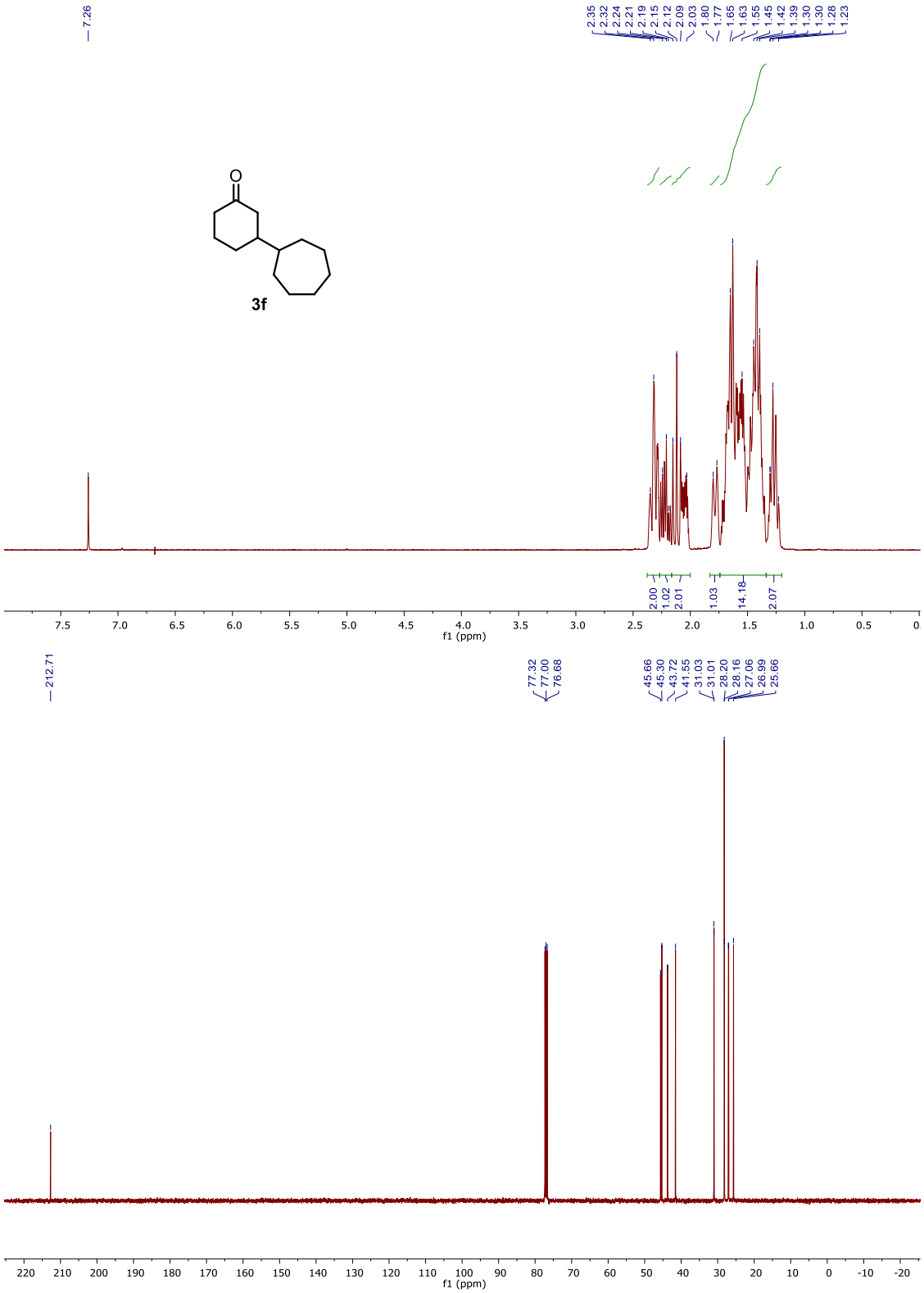


Figure 3.24 ^{1}H-NMR and ^{13}C-NMR Spectra of **3g**

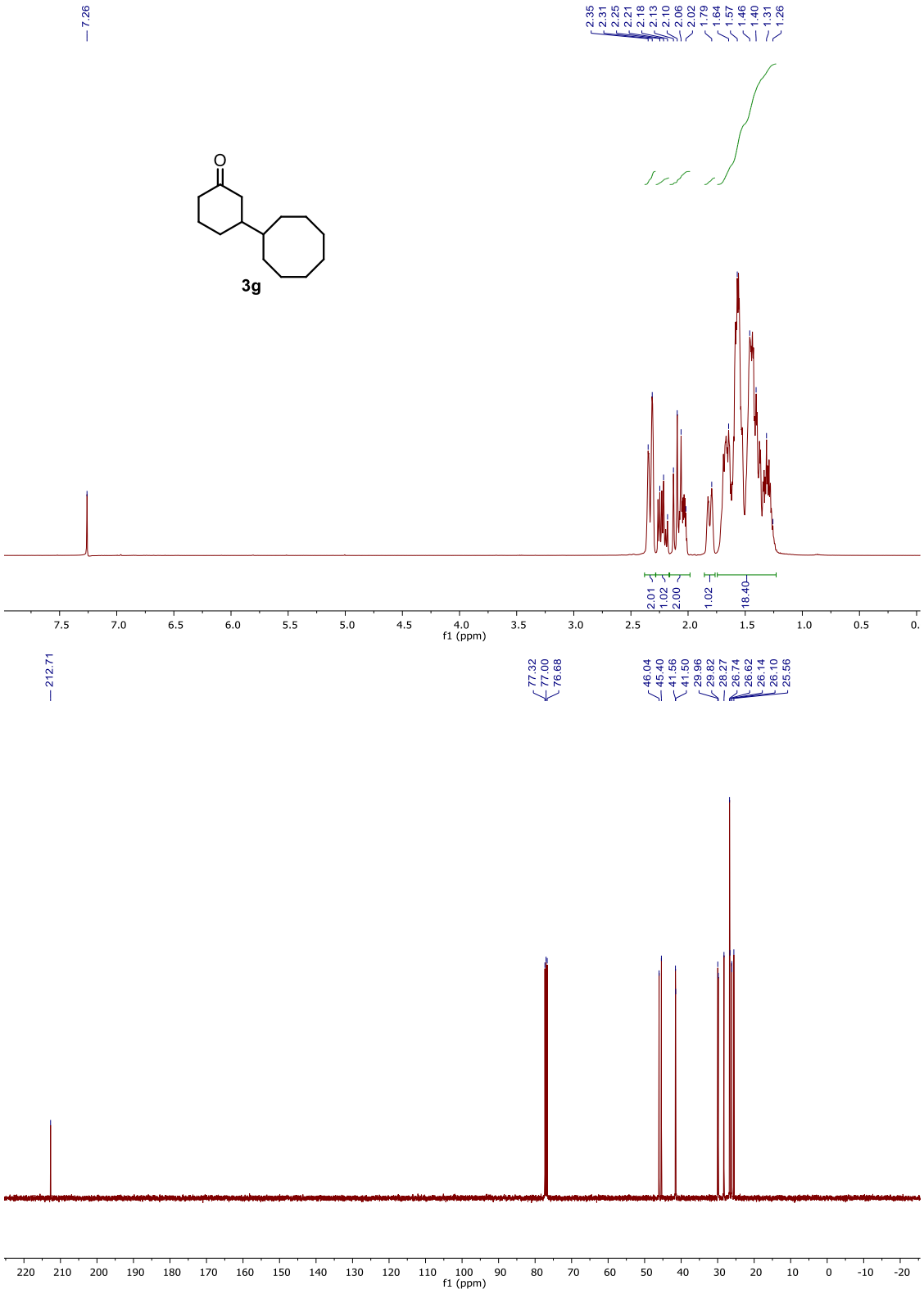


Figure 3.25 ^{1}H-NMR and ^{13}C-NMR Spectra of **3h**

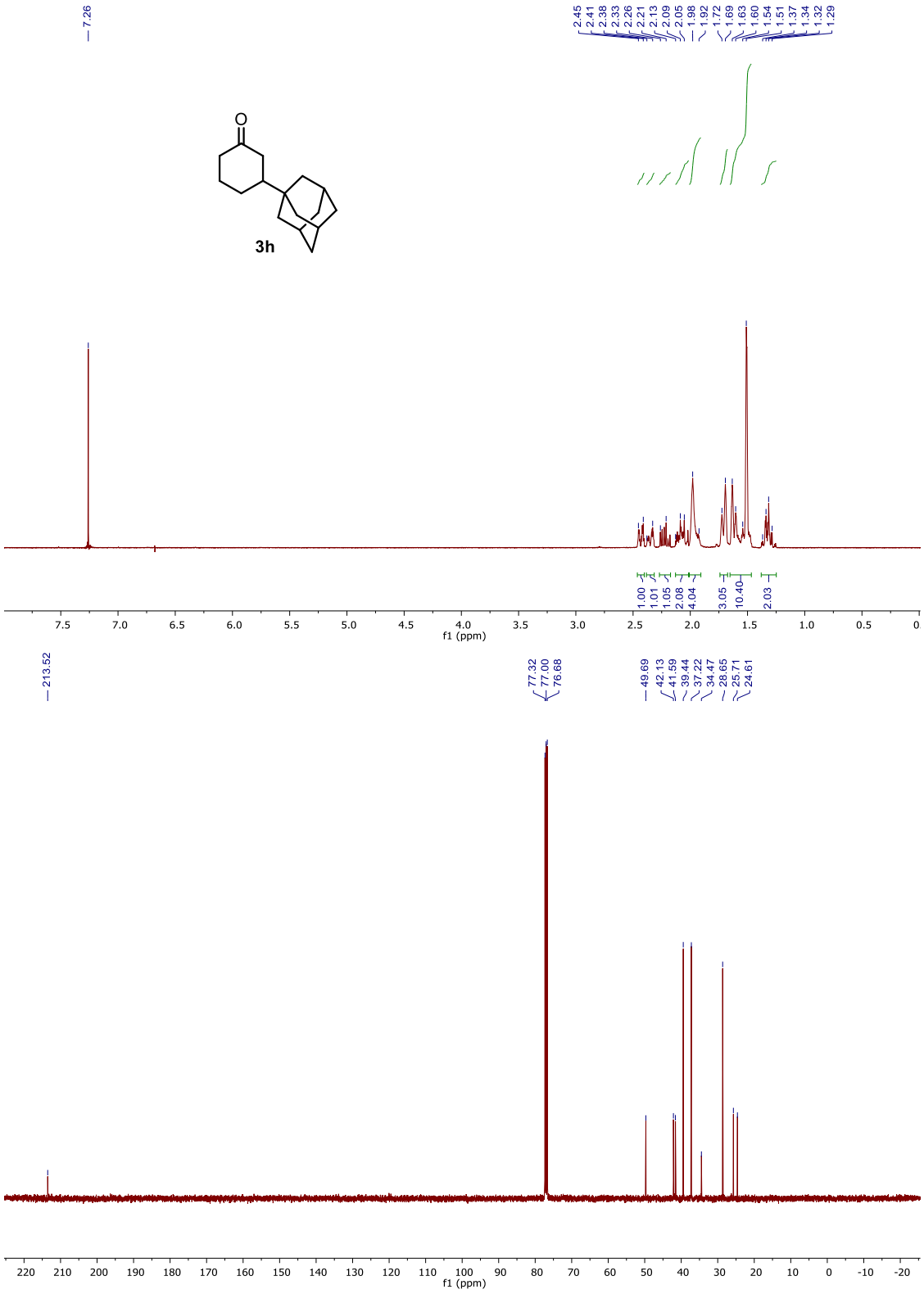


Figure 3.26 ^{1}H-NMR and ^{13}C-NMR Spectra of **3i**

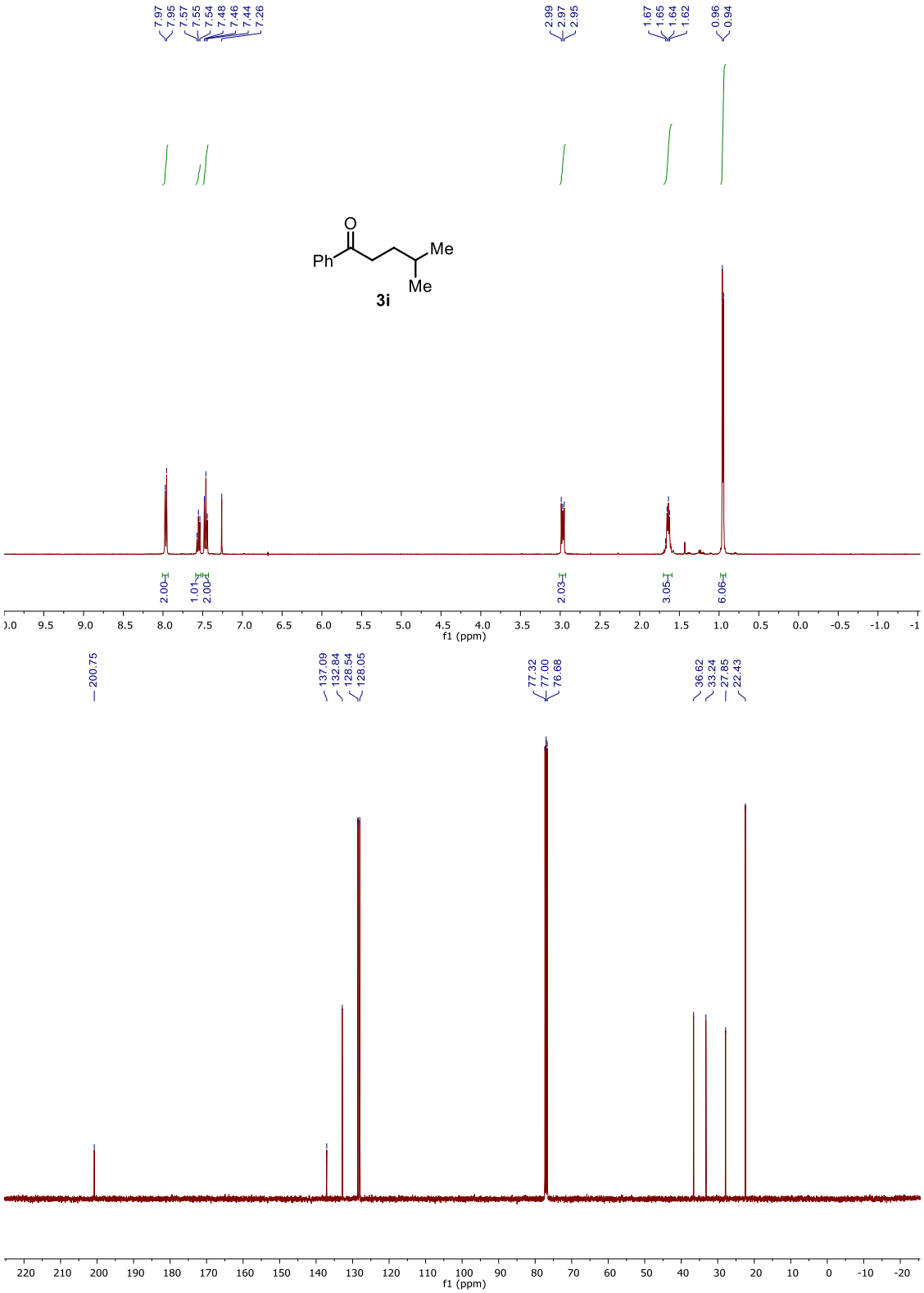


Figure 3.27 ^{1}H-NMR and ^{13}C-NMR Spectra of **3j**

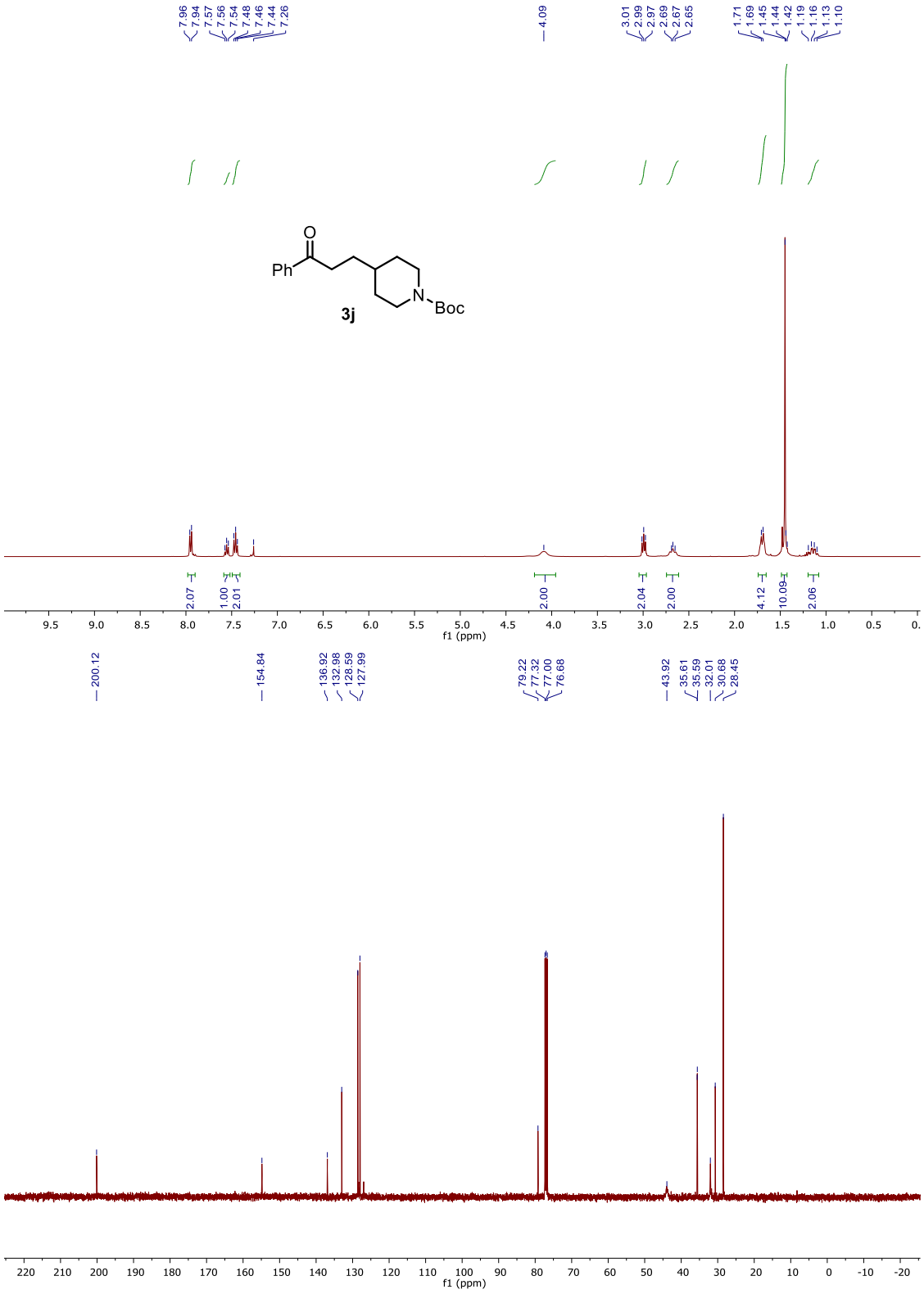


Figure 3.28 ^{1}H-NMR and ^{13}C-NMR Spectra of **3k**

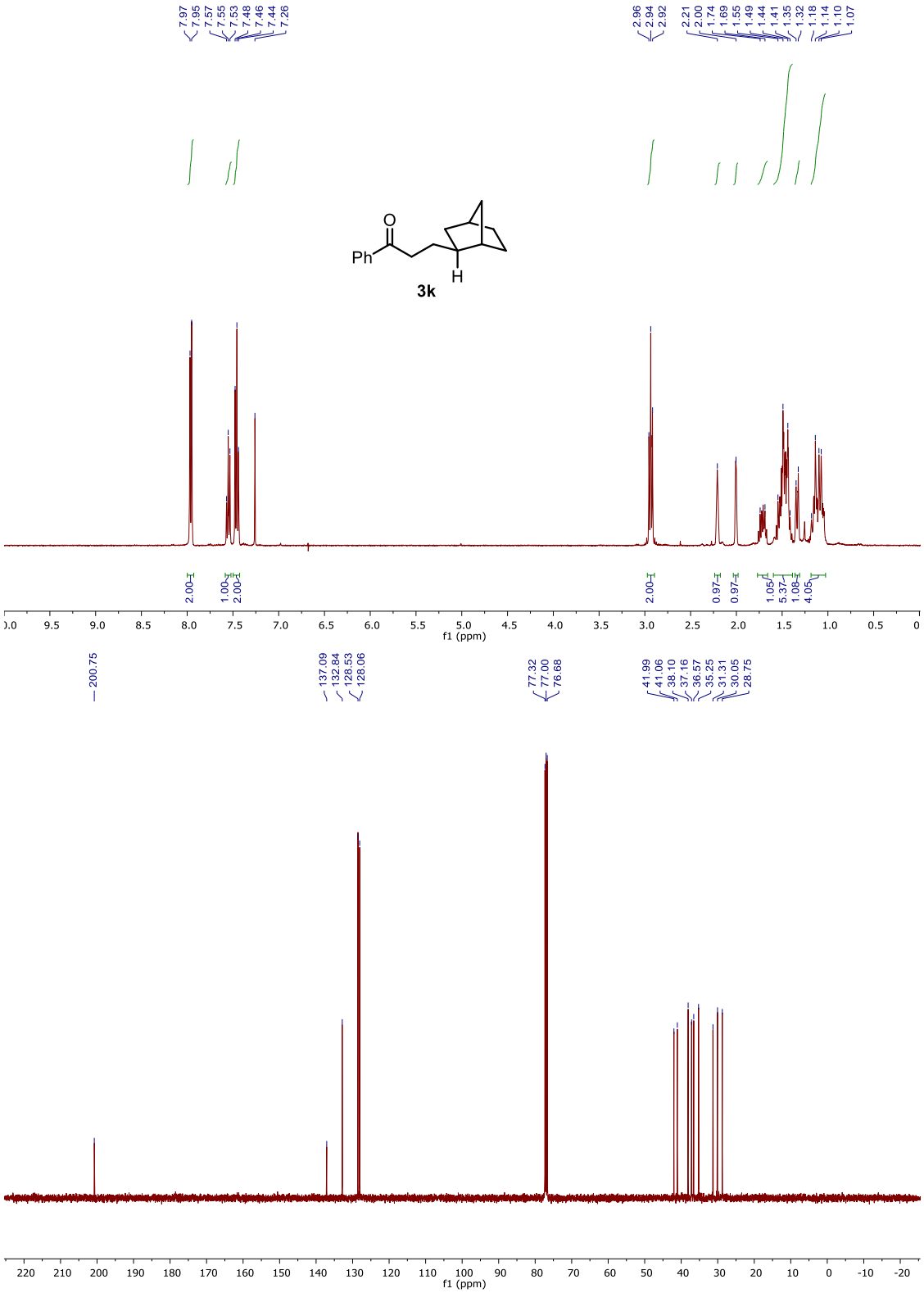


Figure 3.29 ^{1}H-NMR and ^{13}C-NMR Spectra of **3l**

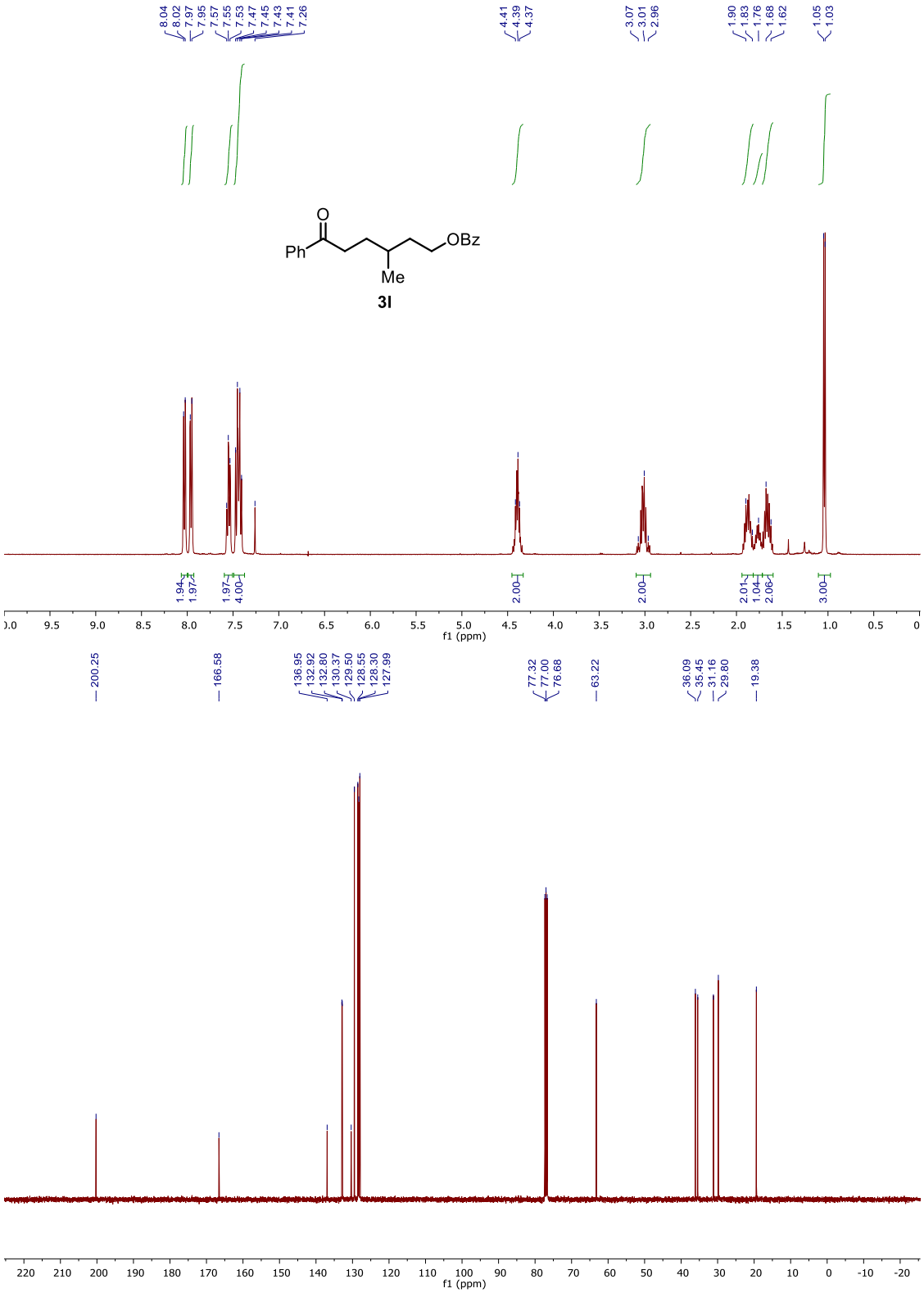


Figure 3.30 ^{1}H-NMR and ^{13}C-NMR Spectra of **3m**

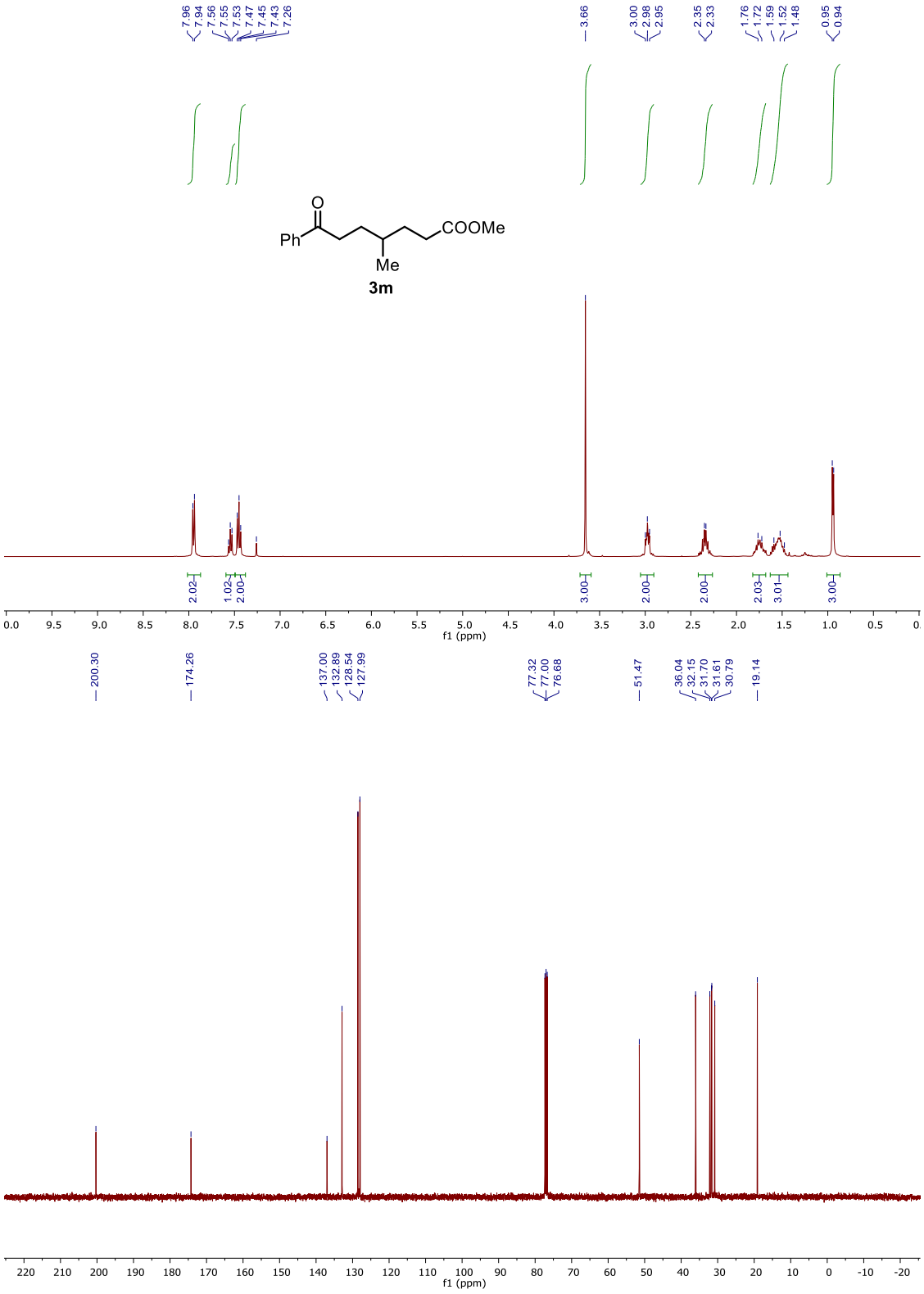


Figure 3.31 ^{1}H-NMR and ^{13}C-NMR Spectra of **3n**

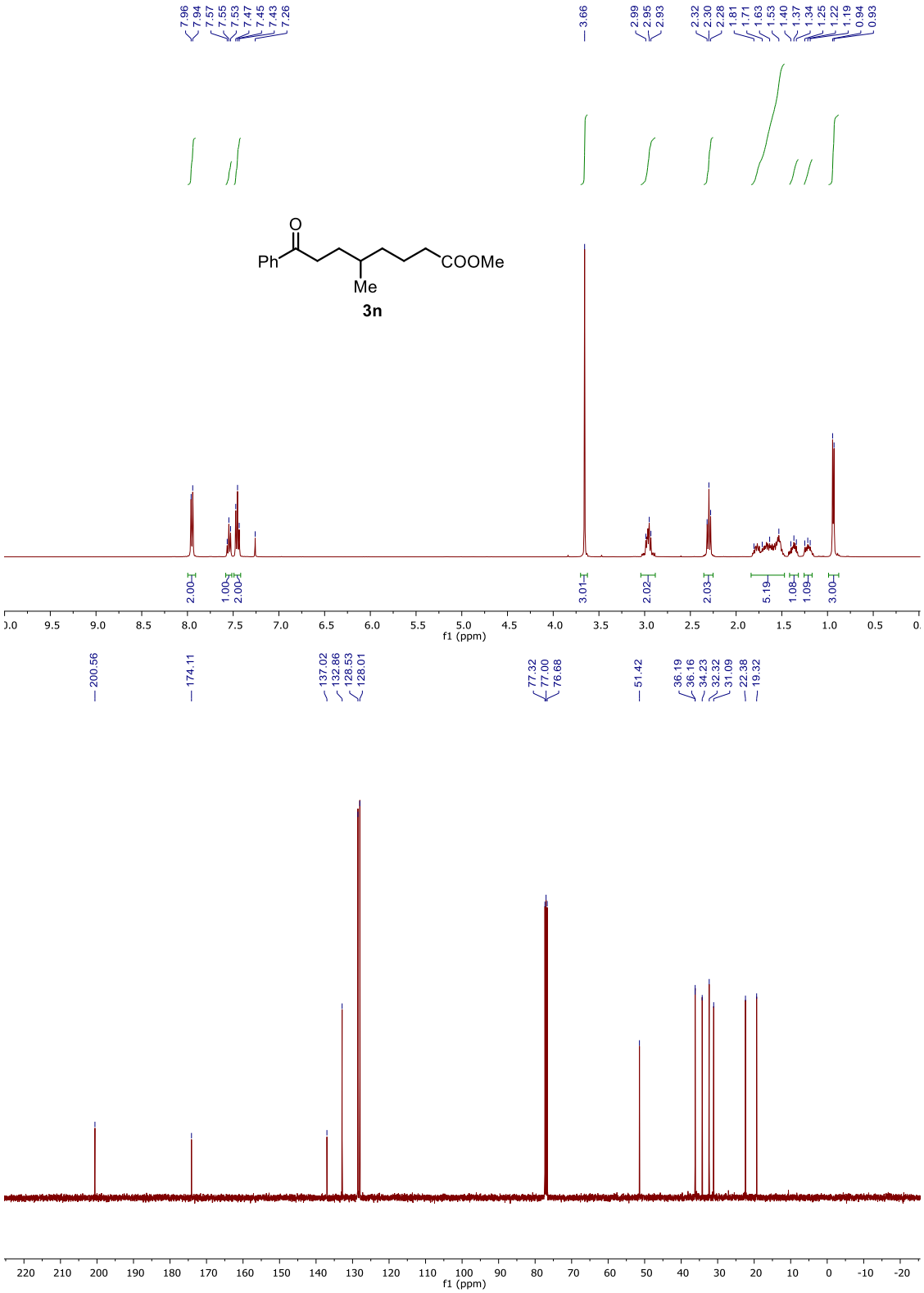


Figure 3.32 ^{1}H-NMR and ^{13}C-NMR Spectra of **3o**

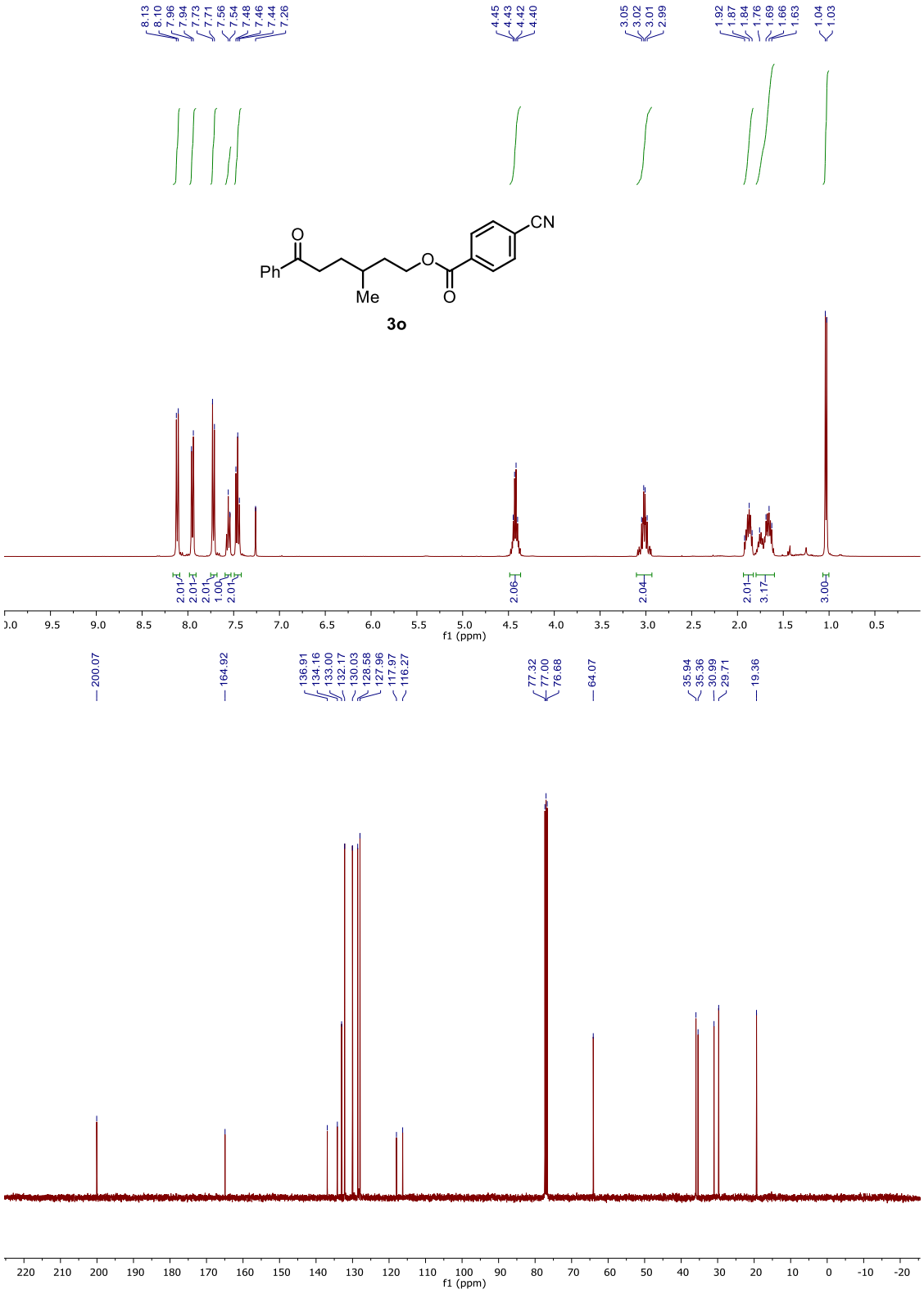


Figure 3.33 ^{1}H-NMR and ^{13}C-NMR Spectra of **3p**

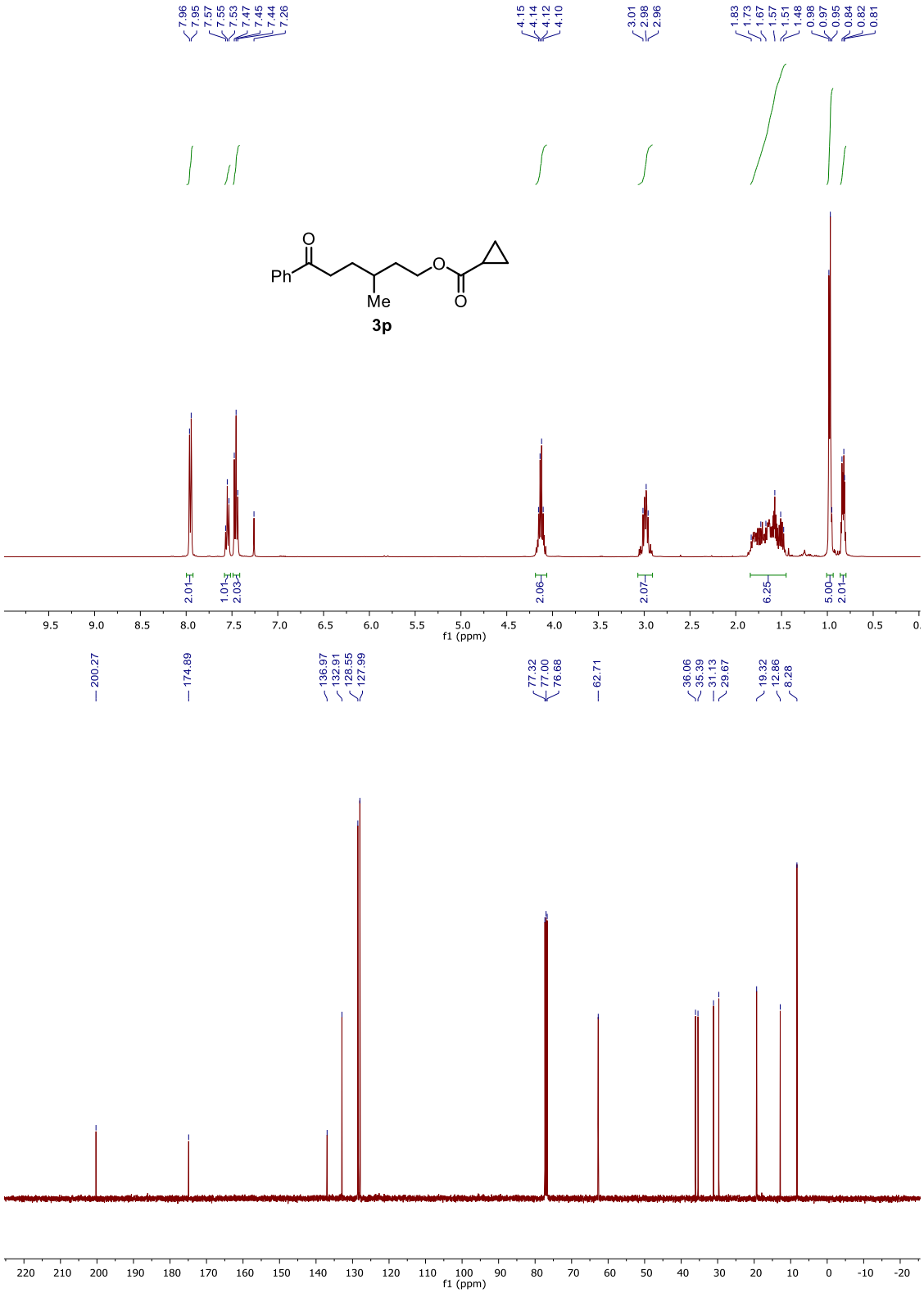


Figure 3.34 ^{1}H-NMR and ^{13}C-NMR Spectra of **3q**

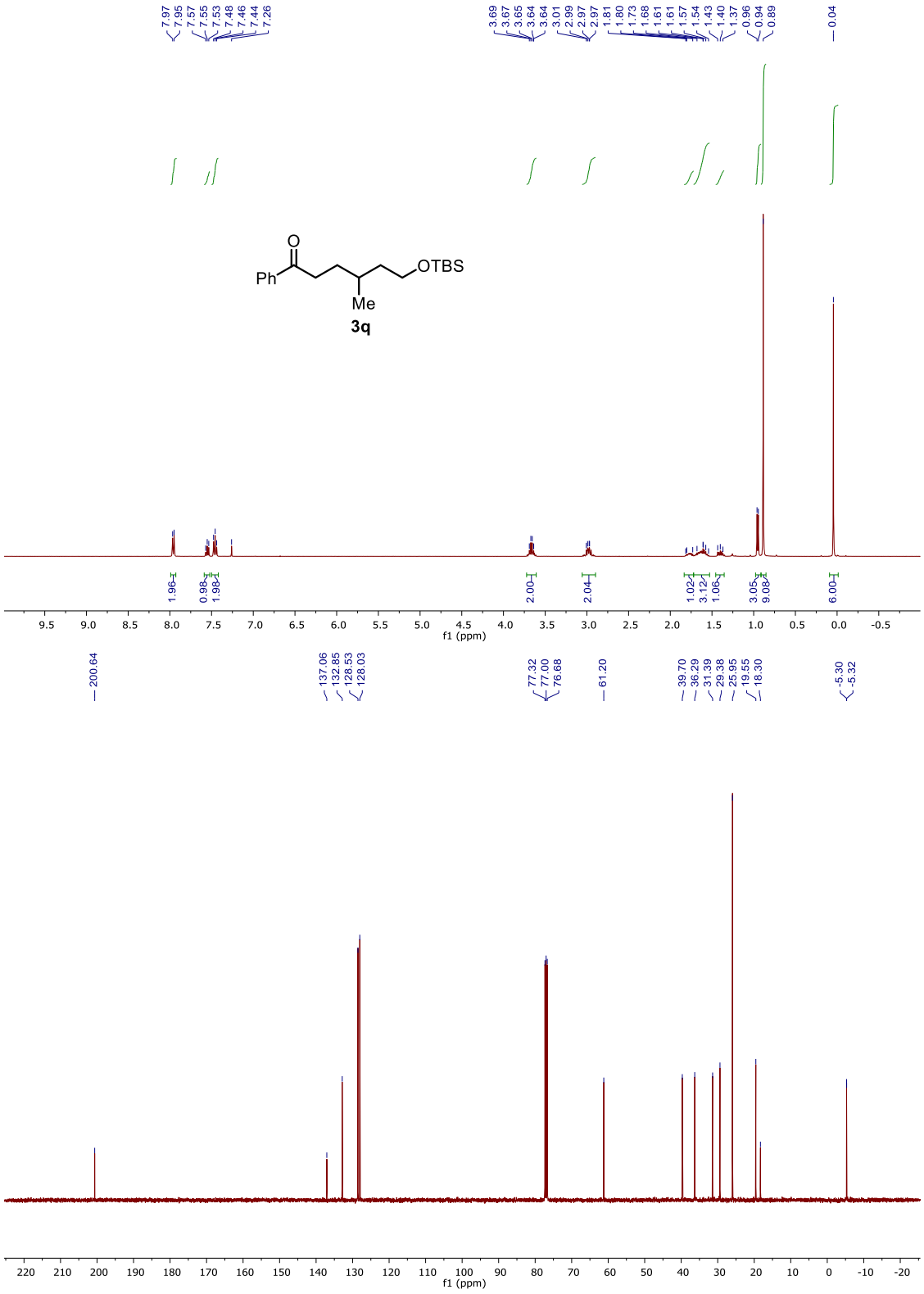


Figure 3.35 ^{1}H-NMR and ^{13}C-NMR Spectra of **3r**

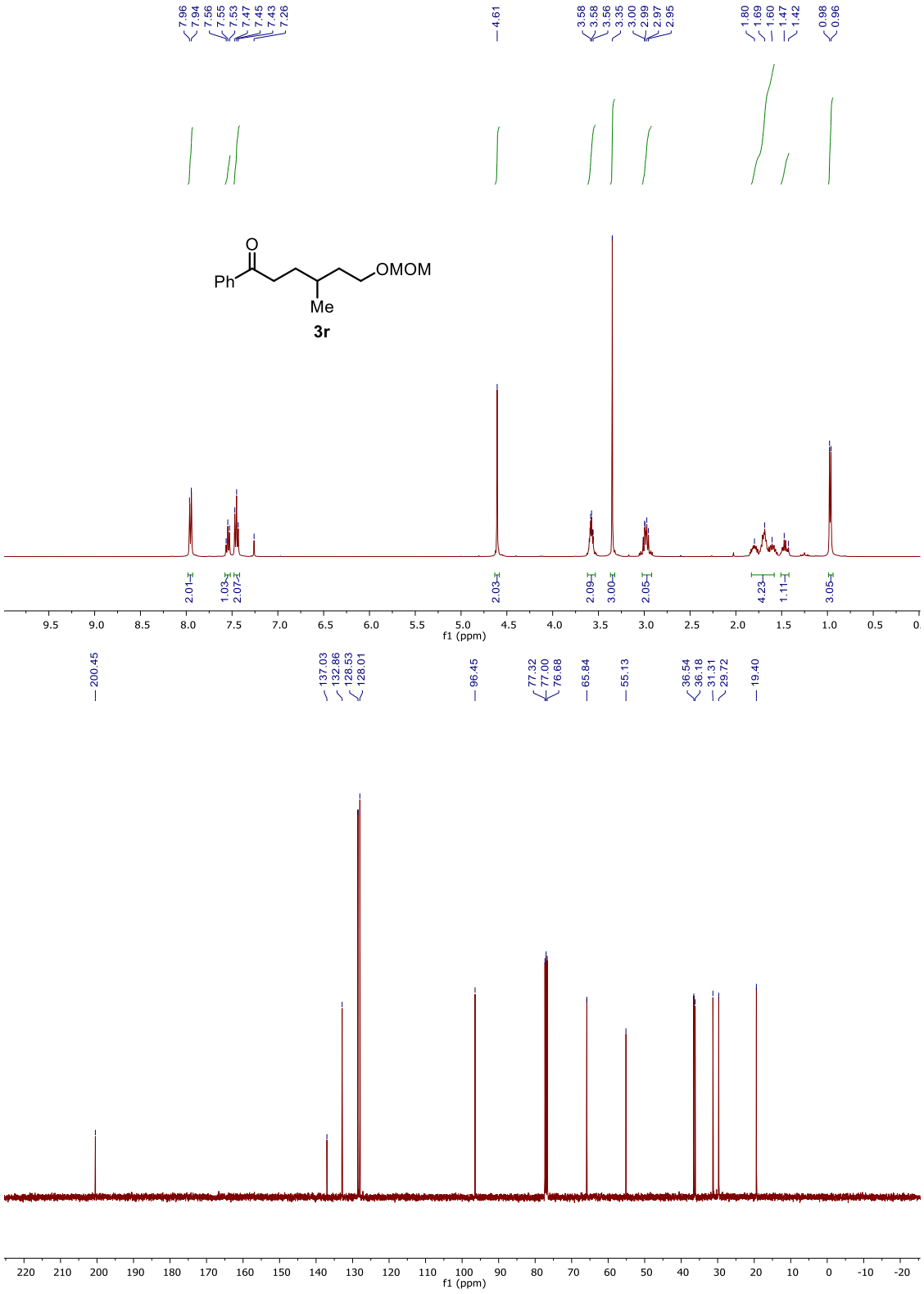


Figure 3.36 ^{1}H-NMR and ^{13}C-NMR Spectra of **3s**

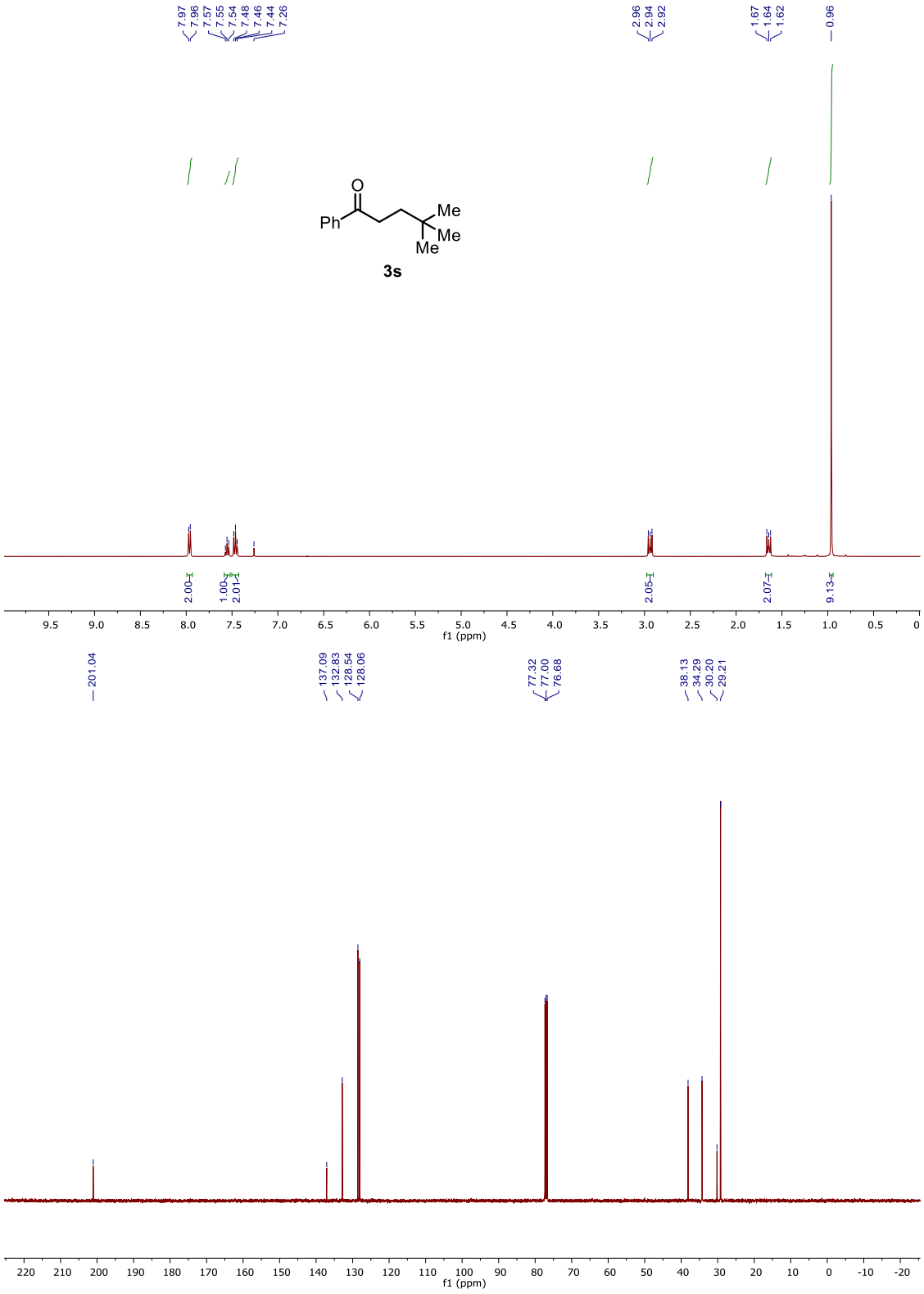


Figure 3.37 ^{1}H-NMR and ^{13}C-NMR Spectra of **3s'**

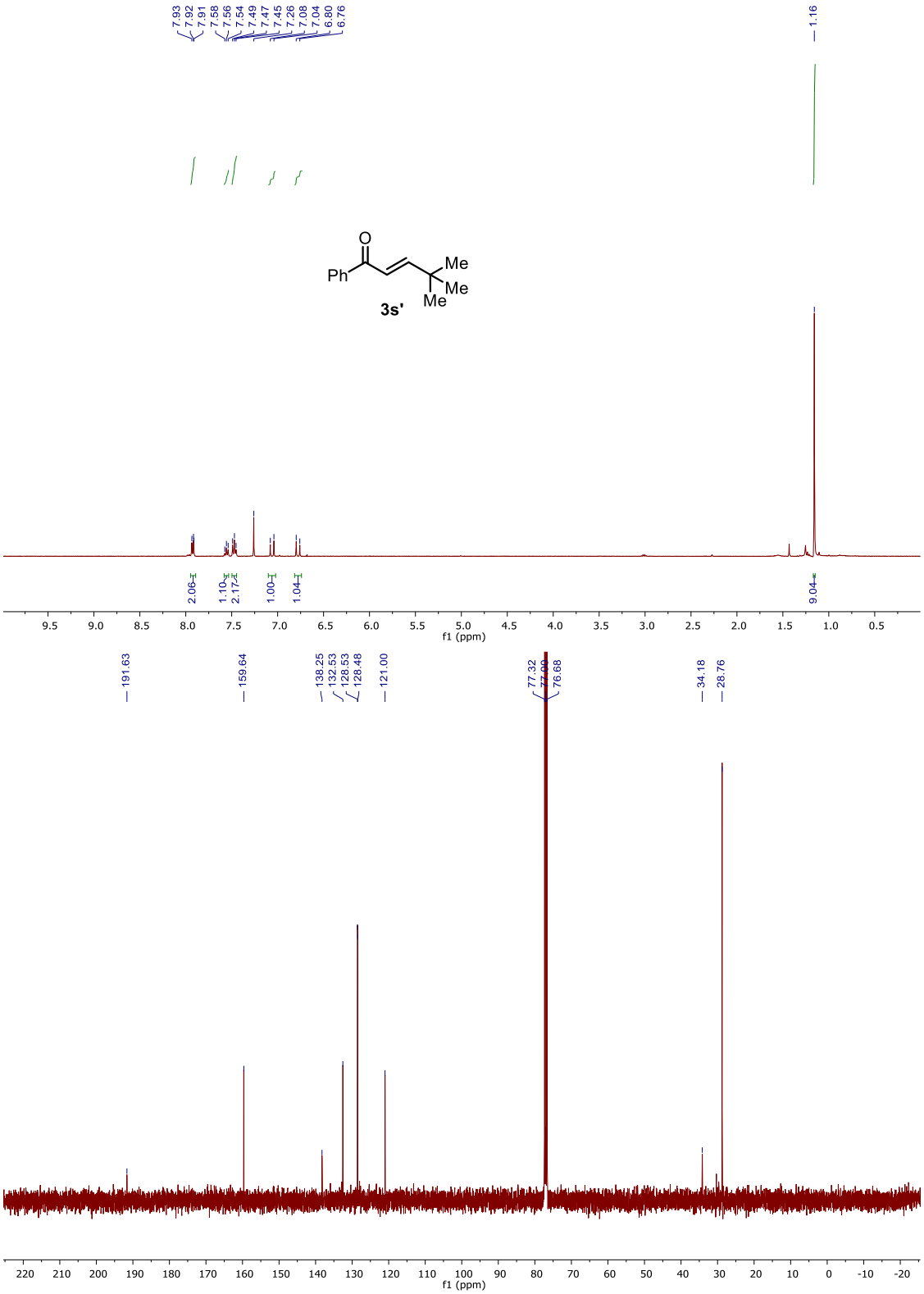


Figure 3.38 ^{1}H-NMR and ^{13}C-NMR Spectra of **3t**

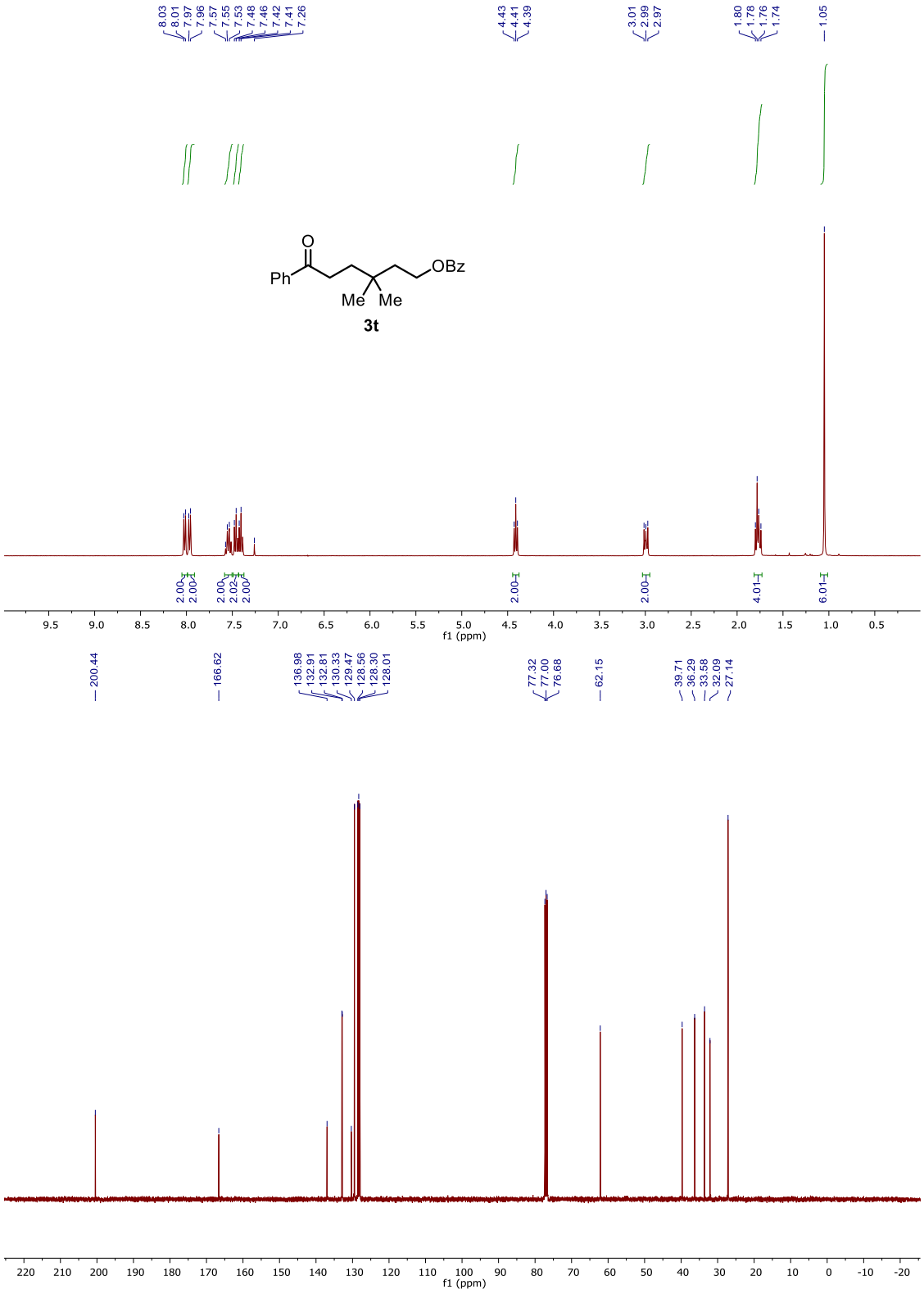


Figure 3.39 ^{1}H-NMR and ^{13}C-NMR Spectra of **3t'**

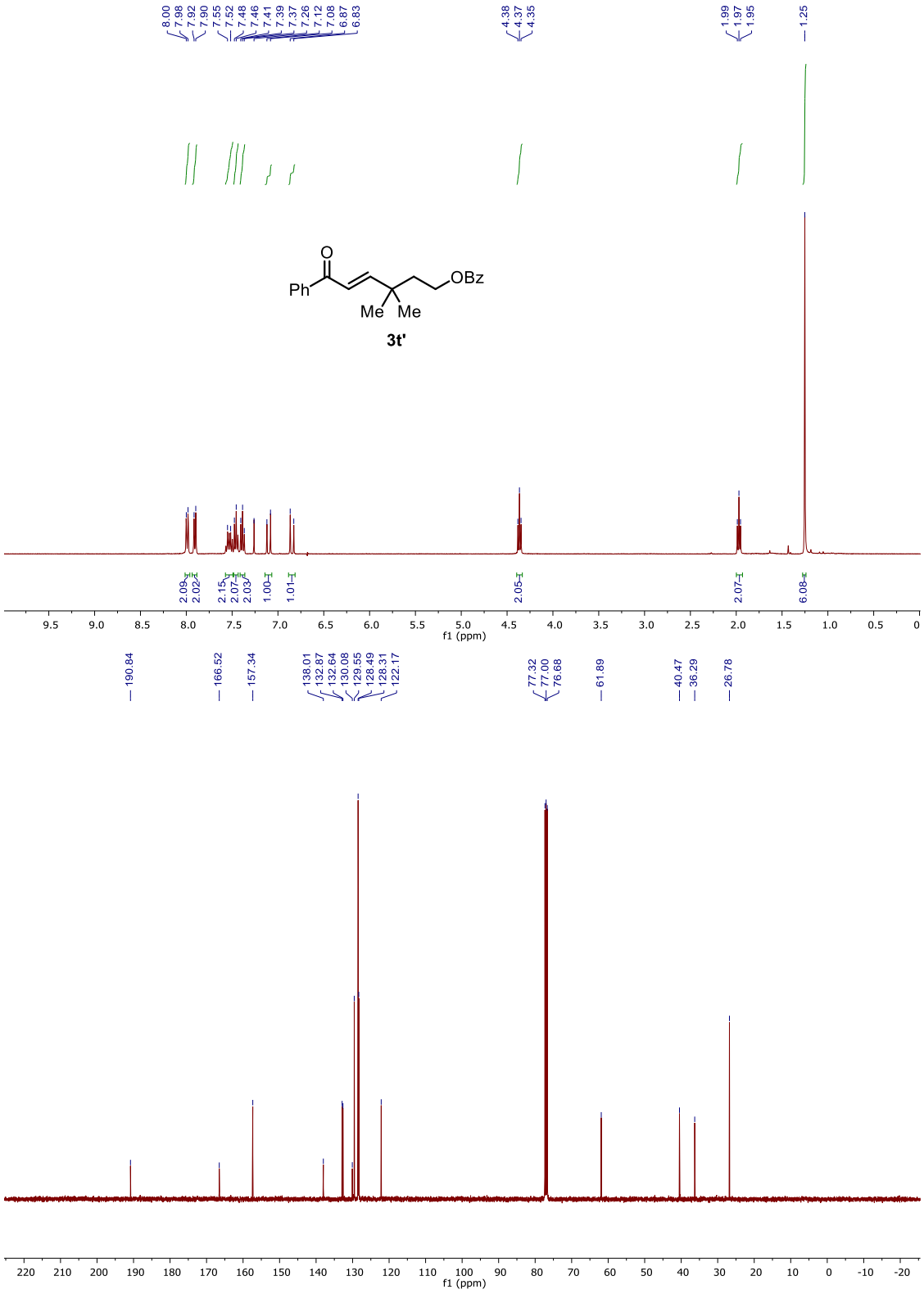


Figure 3.40 ^{1}H-NMR and ^{13}C-NMR Spectra of **3u**

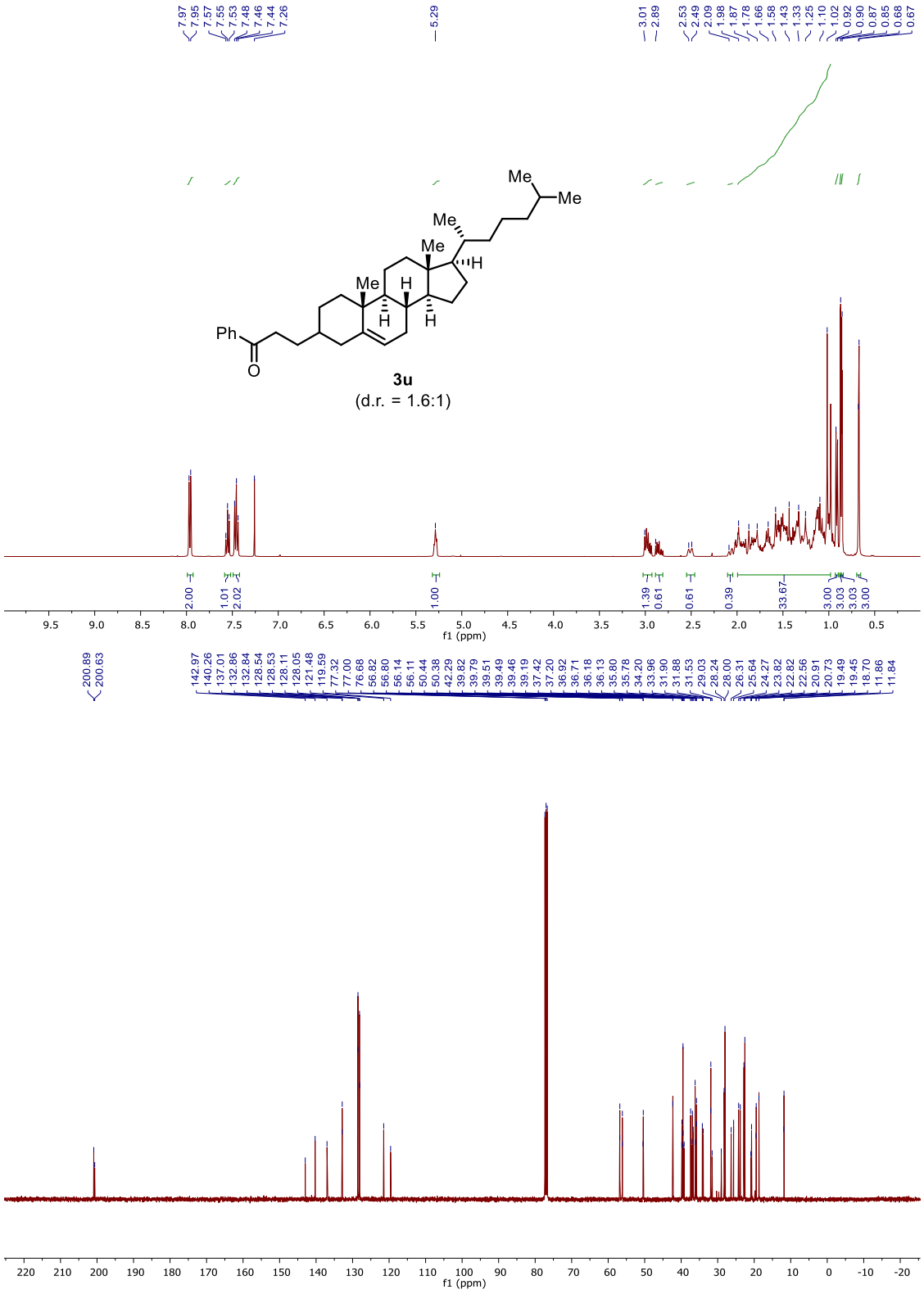


Figure 3.41 ^{1}H-NMR and ^{13}C-NMR Spectra of **3v**

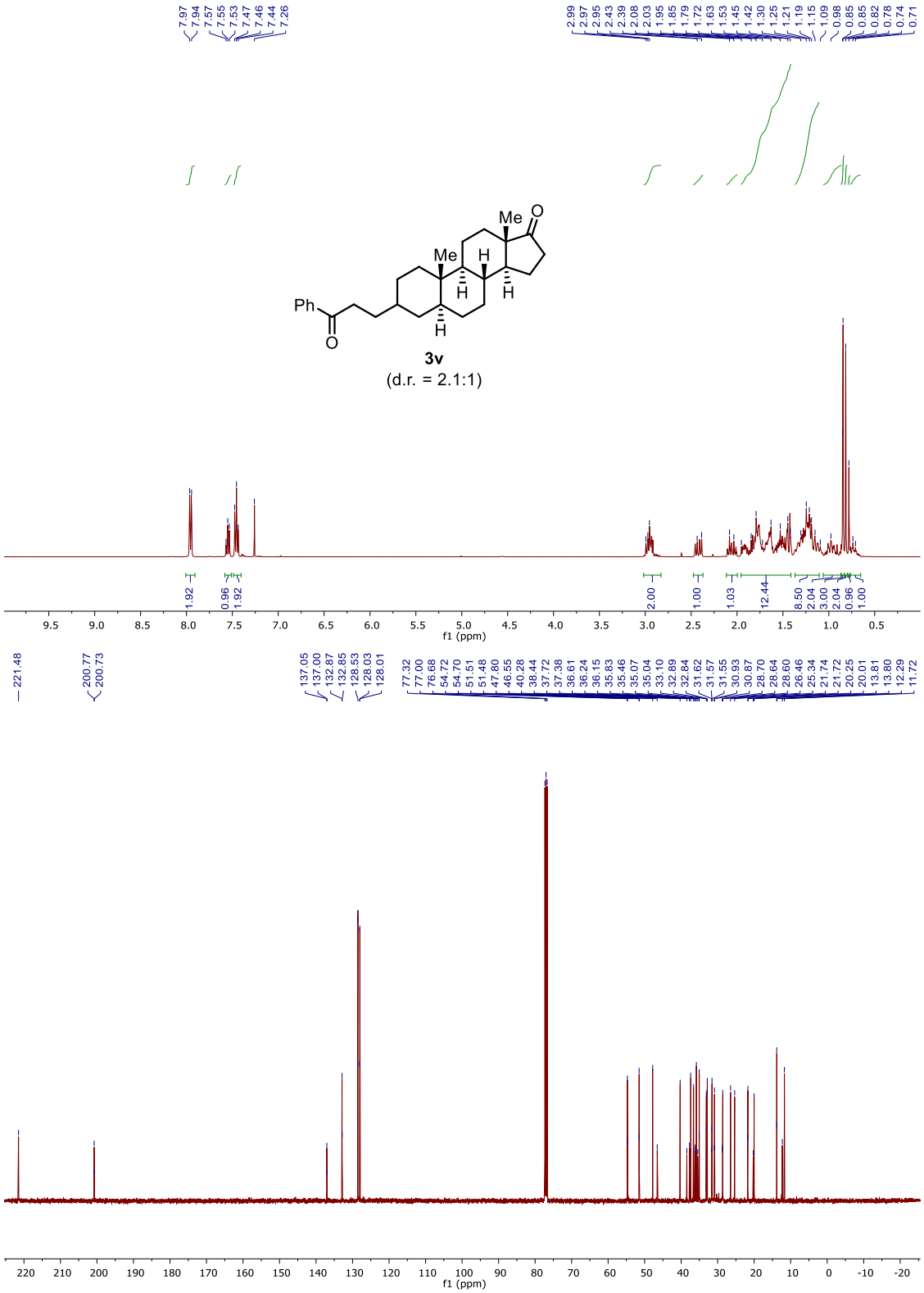


Figure 3.42 ^{1}H-NMR and ^{13}C-NMR Spectra of **3w**

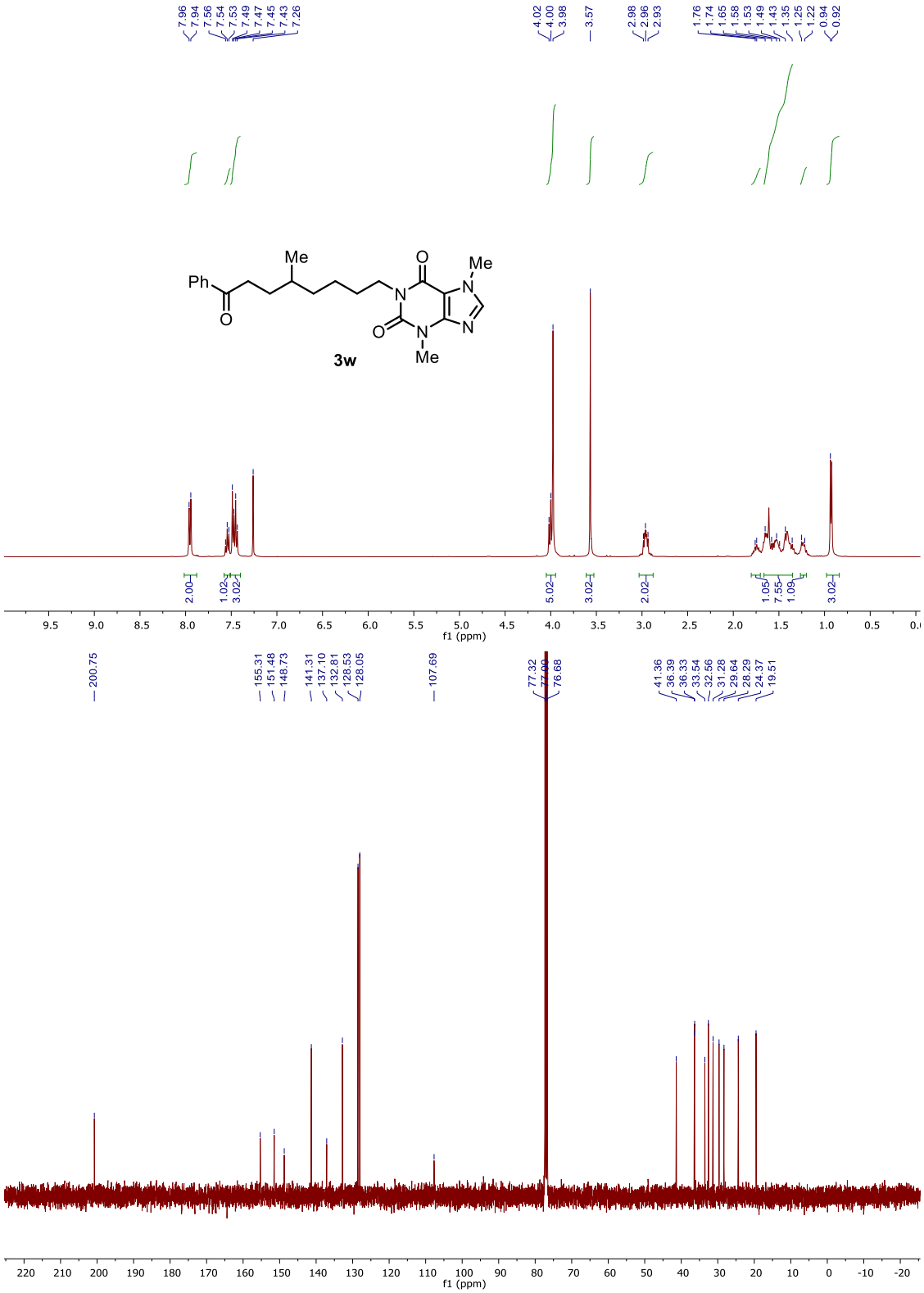


Figure 3.43 ^{1}H-NMR and ^{13}C-NMR Spectra of **3x**

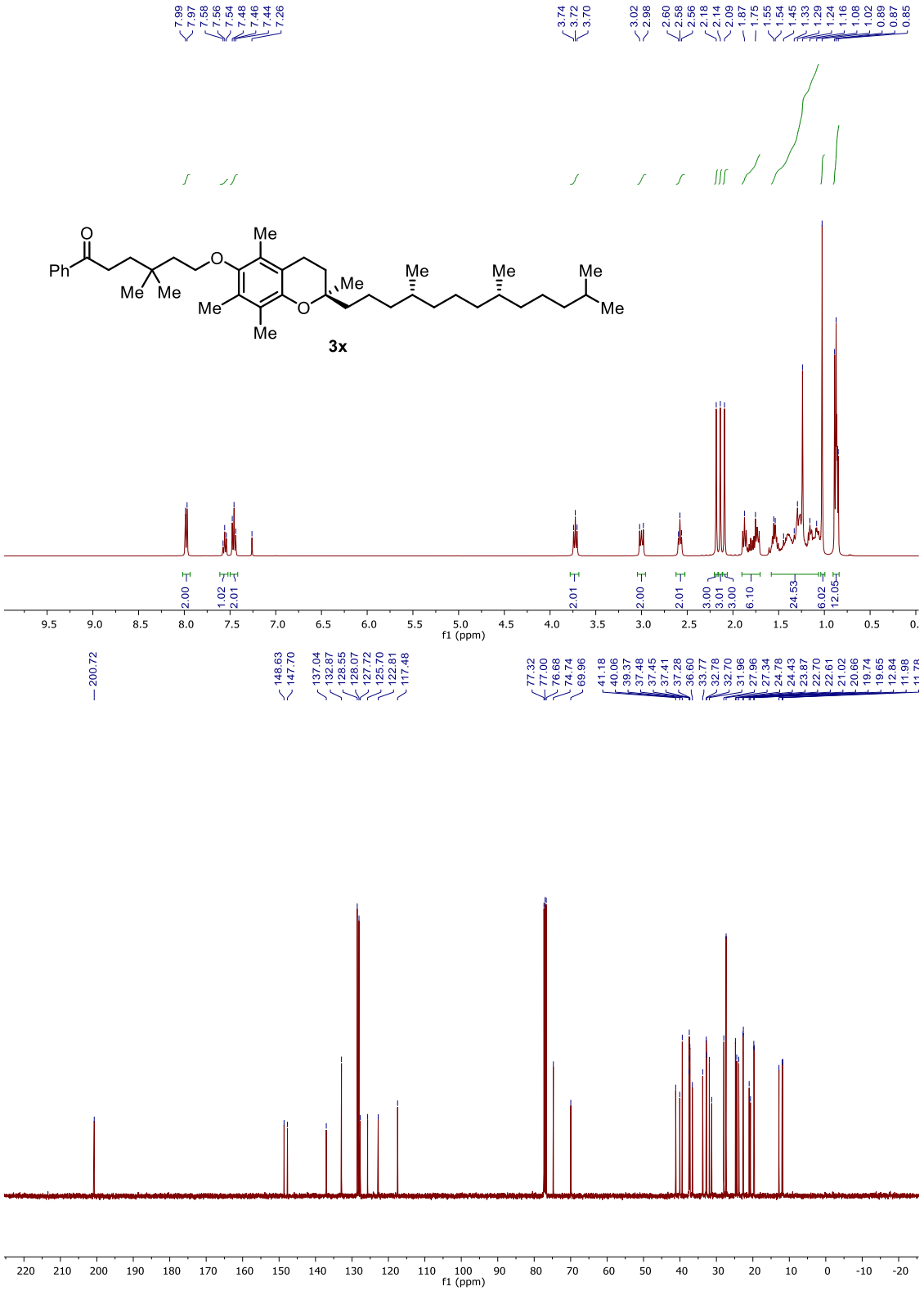


Figure 3.44 ^{1}H-NMR and ^{13}C-NMR Spectra of **5a**

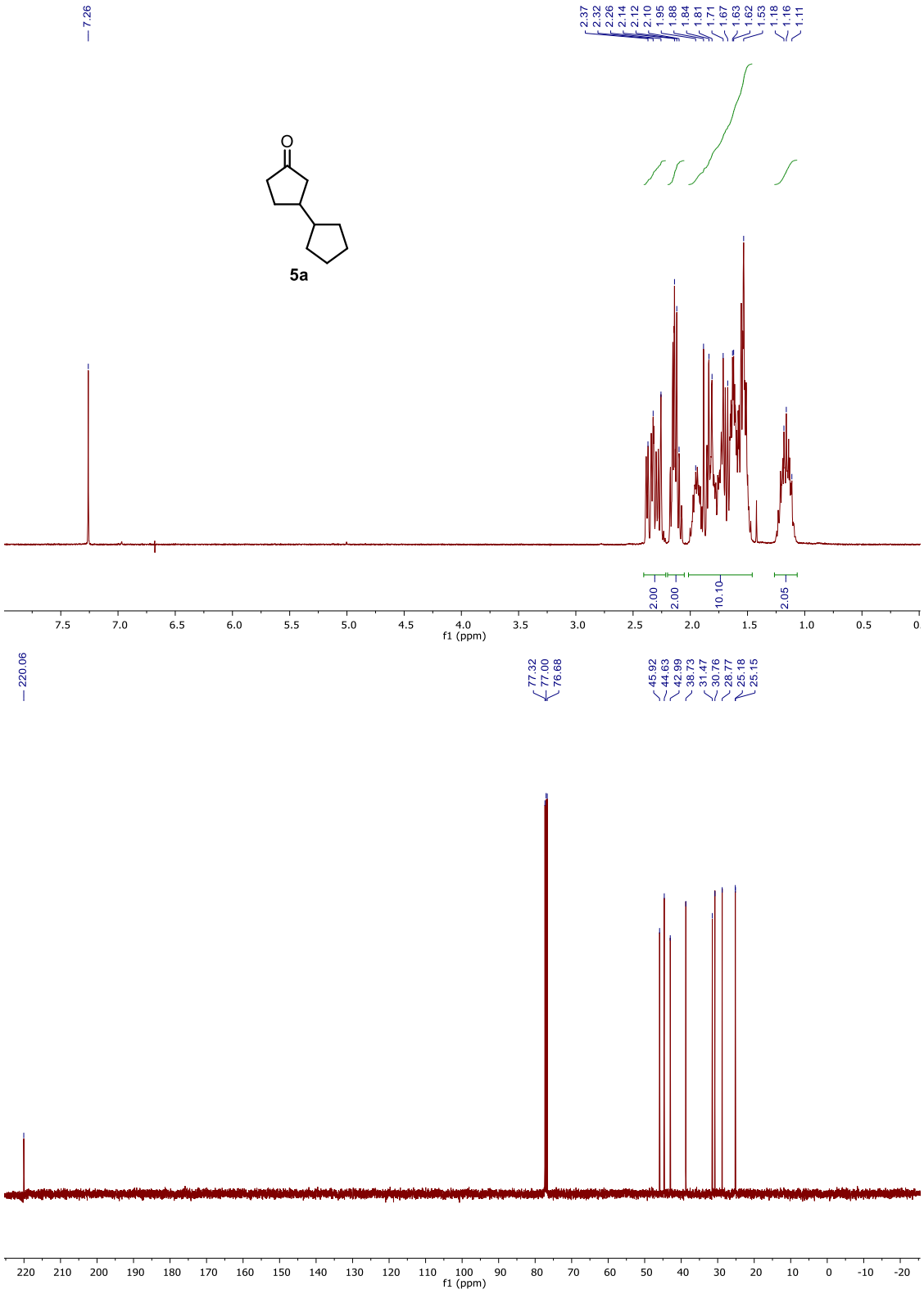


Figure 3.45 ^{1}H-NMR and ^{13}C-NMR Spectra of **5b**

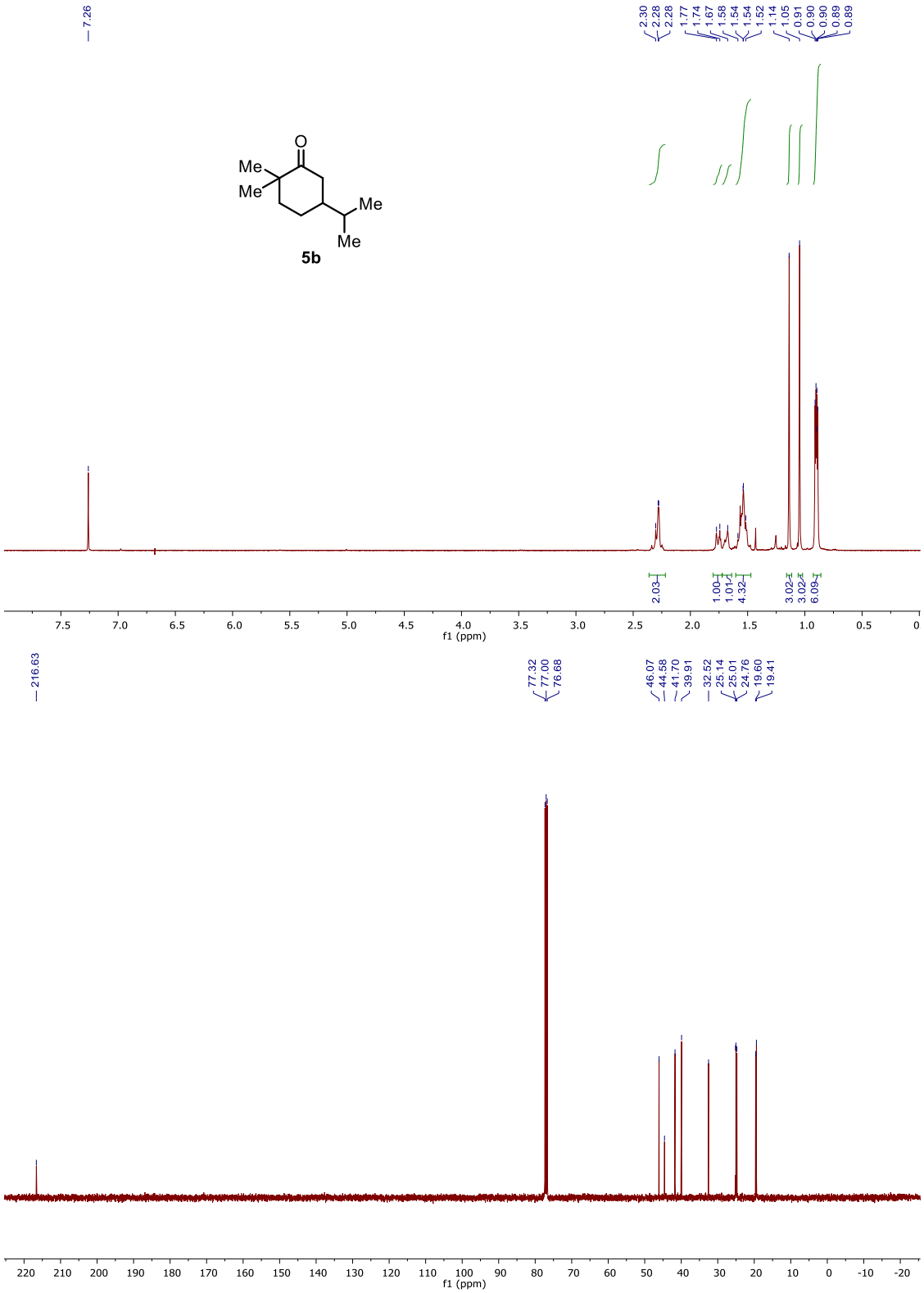


Figure 3.46 ^{1}H-NMR and ^{13}C-NMR Spectra of **5c**

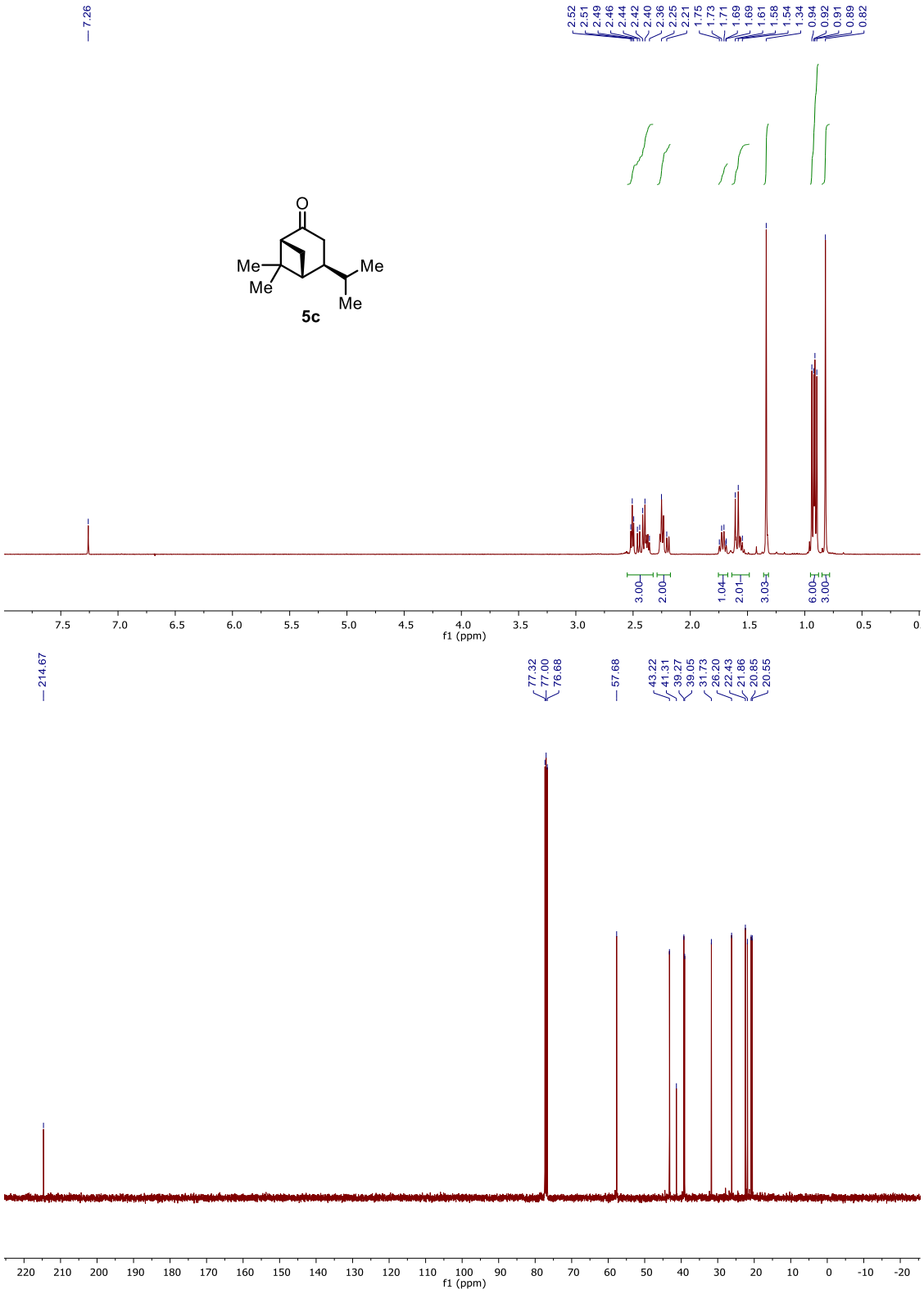


Figure 3.47 COSY Spectrum of **5c**

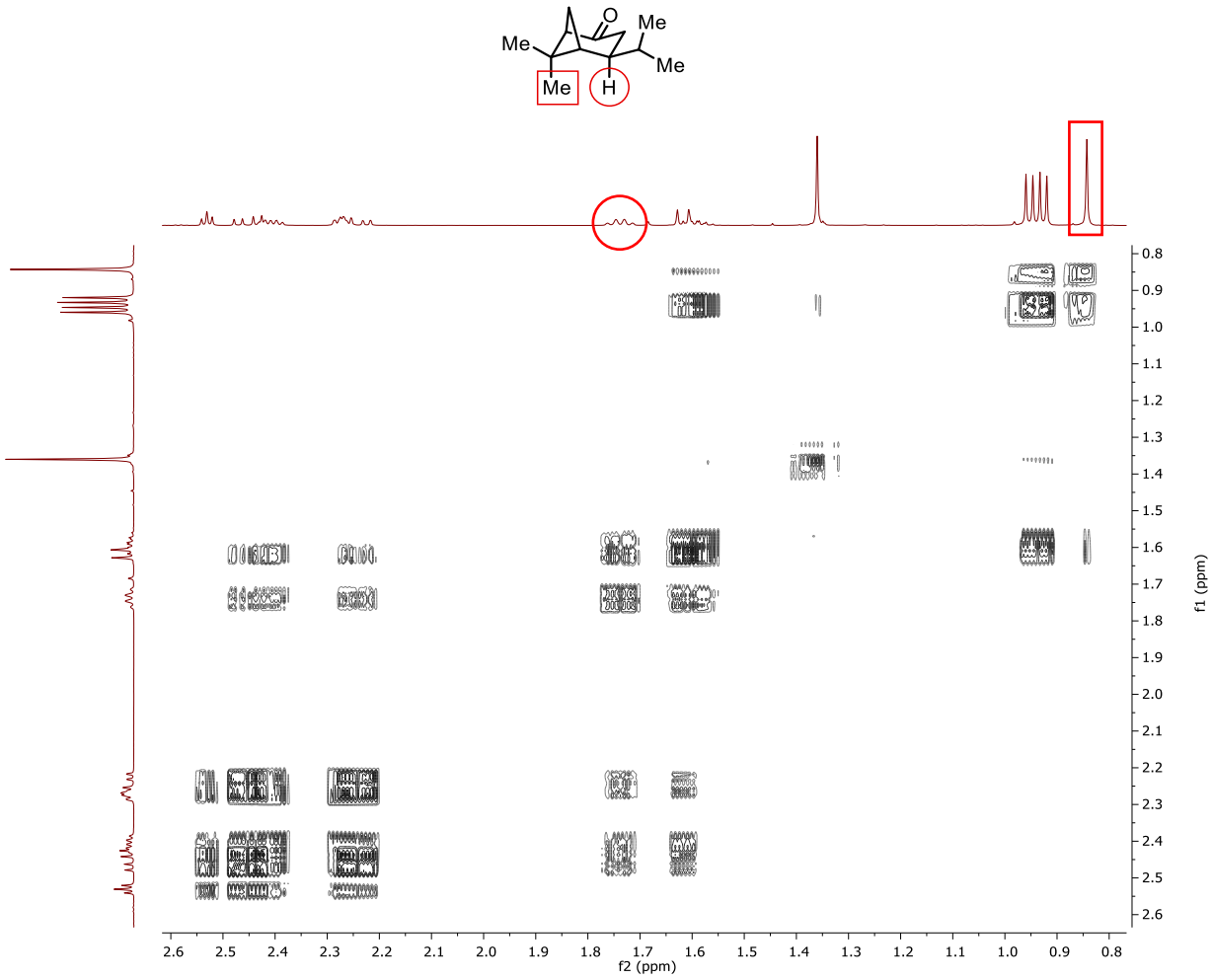


Figure 3.48 NOESY Spectrum of **5c**

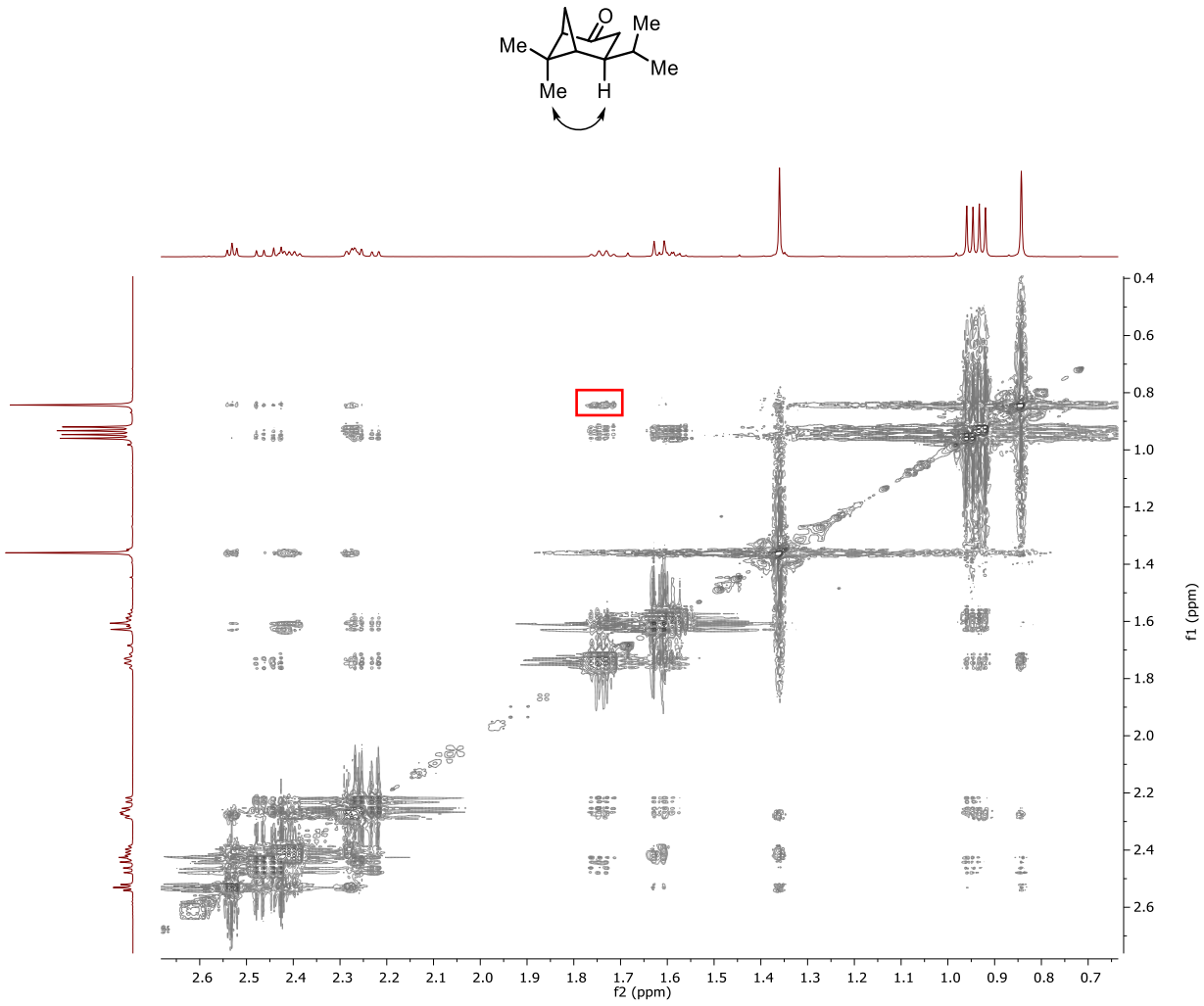


Figure 3.49 ^{1}H-NMR and ^{13}C-NMR Spectra of **5d**

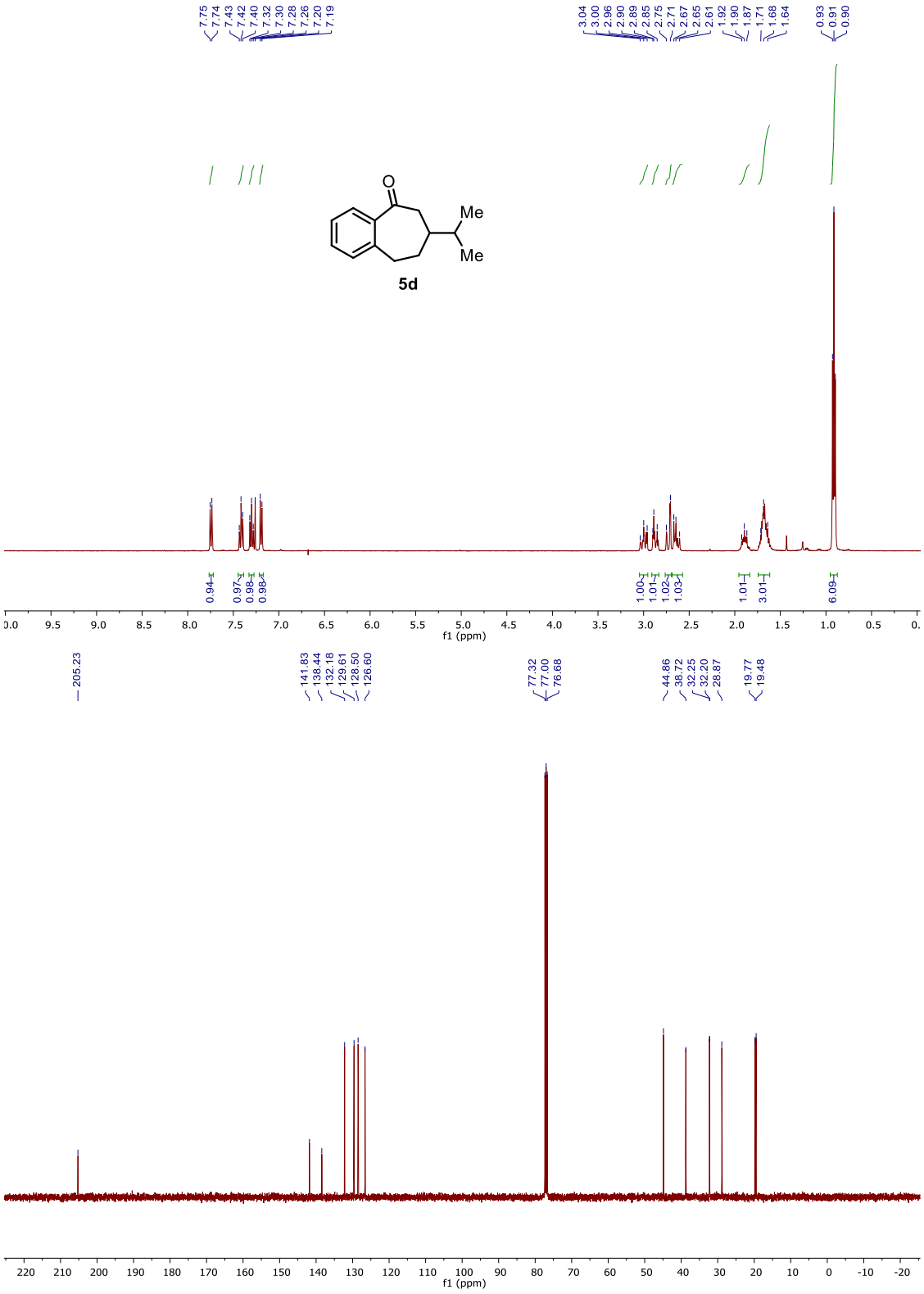


Figure 3.50 ^{1}H-NMR and ^{13}C-NMR Spectra of **5e**

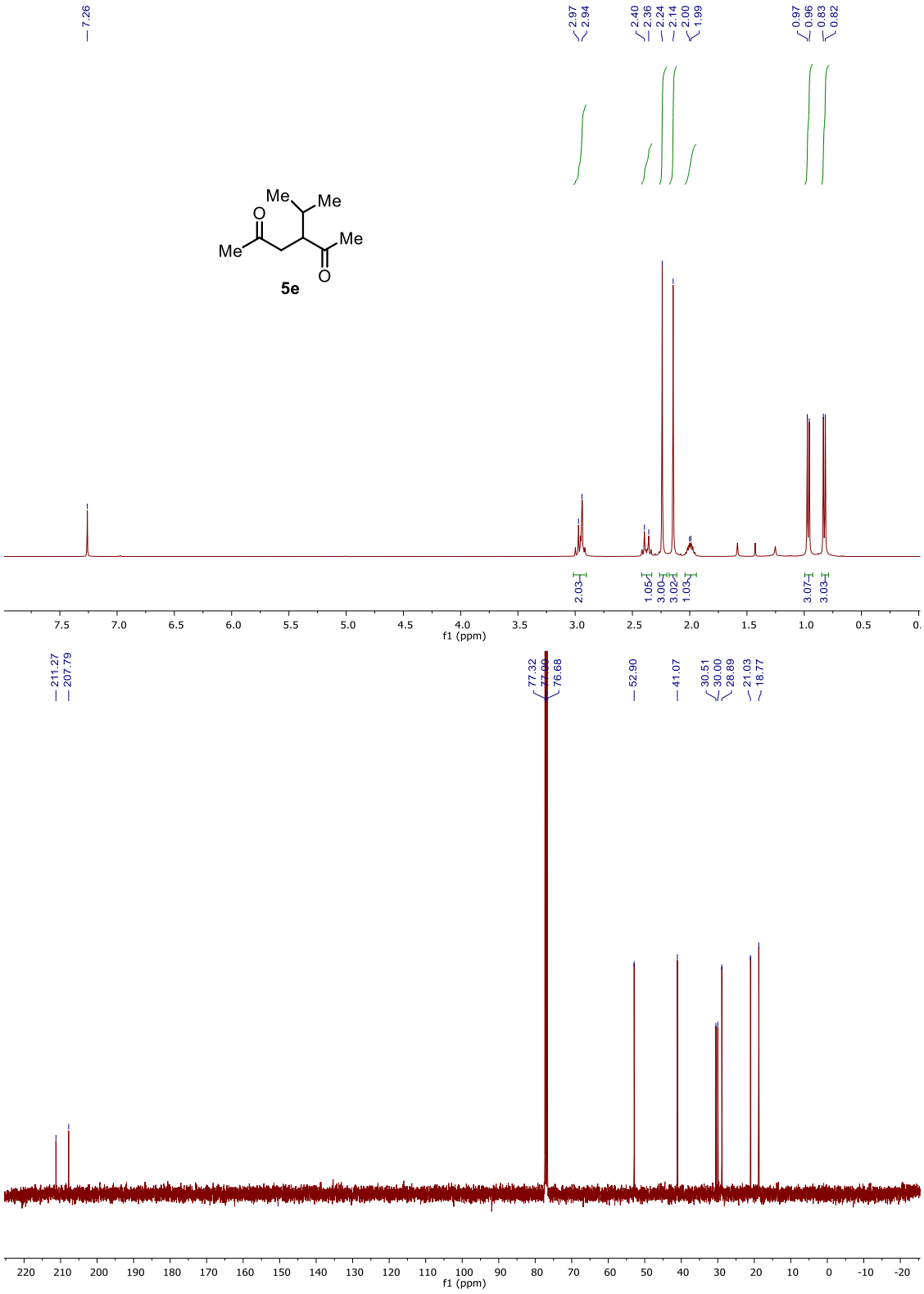


Figure 3.51 ^{1}H-NMR and ^{13}C-NMR Spectra of **5f**

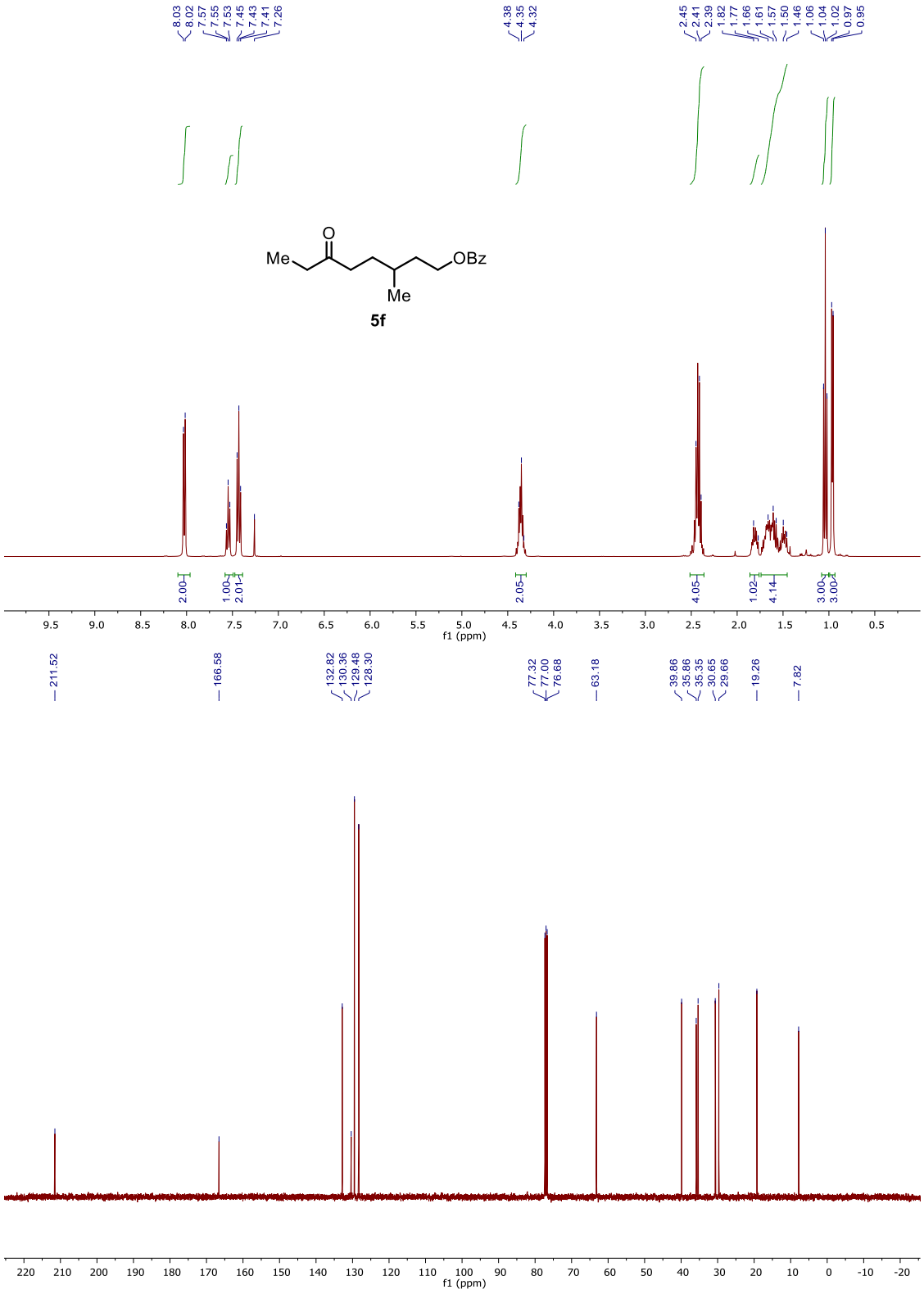


Figure 3.52 ^{1}H-NMR and ^{13}C-NMR Spectra of **5g**

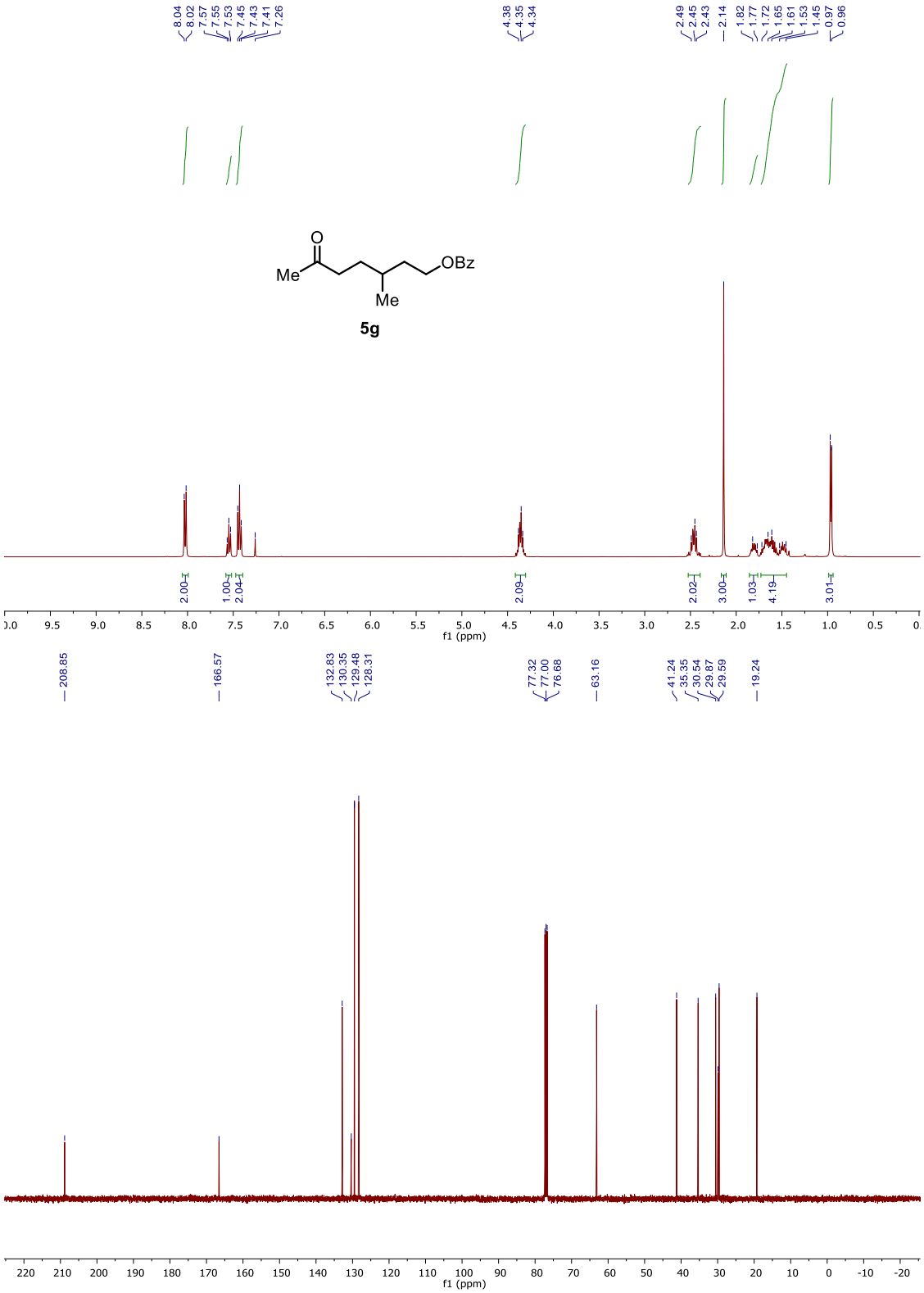


Figure 3.53 ^{1}H-NMR and ^{13}C-NMR Spectra of **5g'**

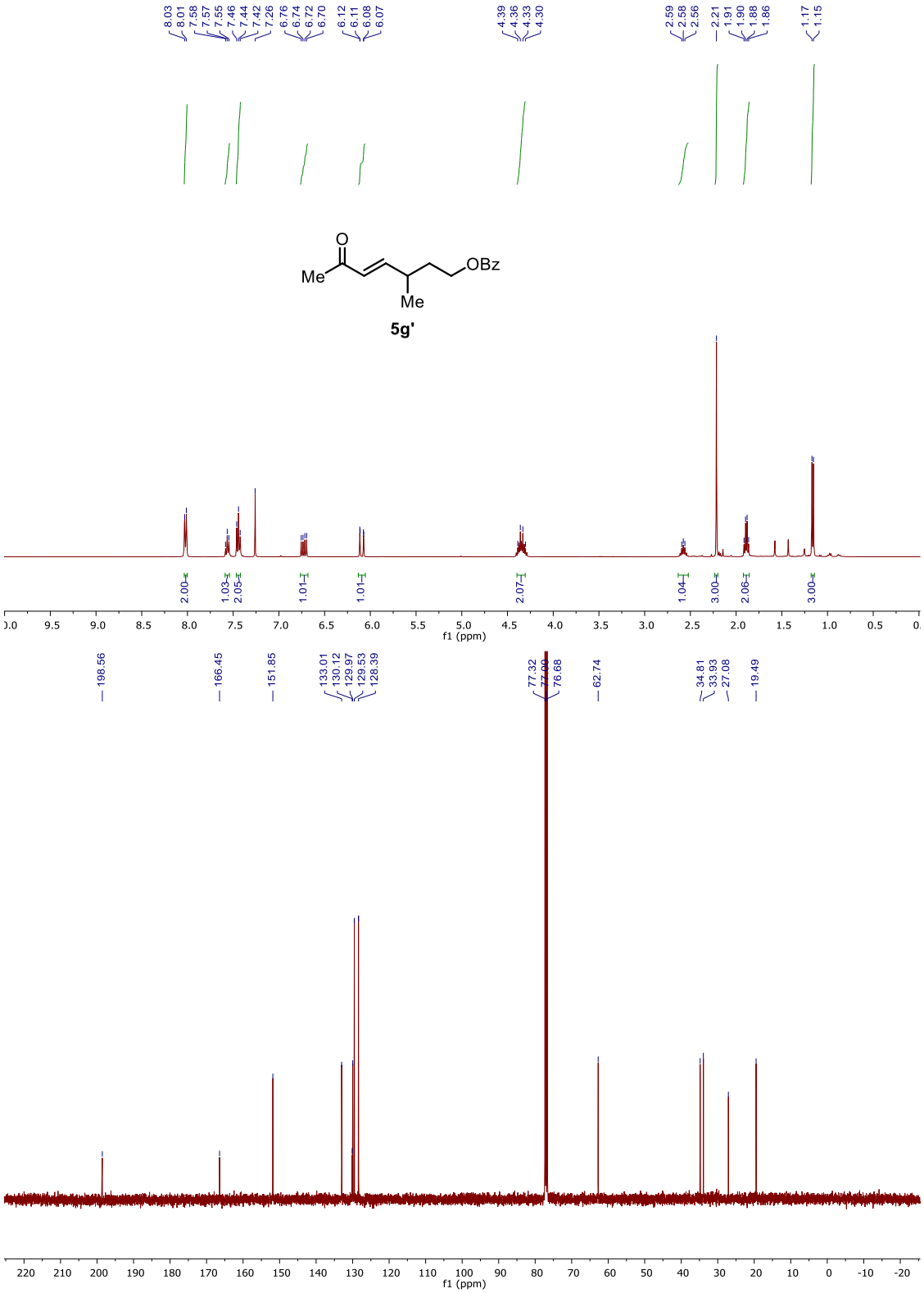


Figure 3.54 ^{1}H-NMR and ^{13}C-NMR Spectra of **5h**

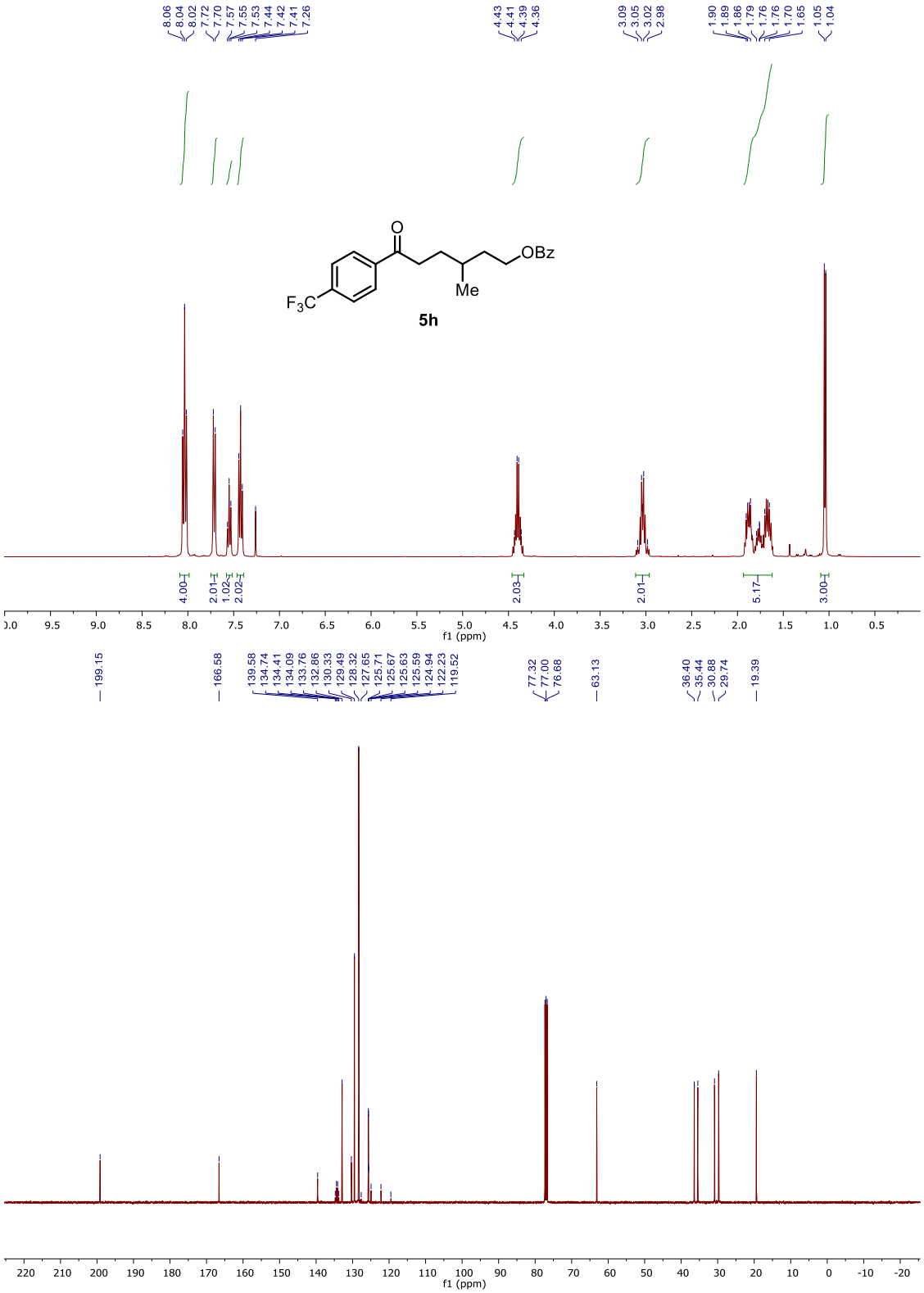


Figure 3.55 ^{1}H-NMR and ^{13}C-NMR Spectra of **5i**

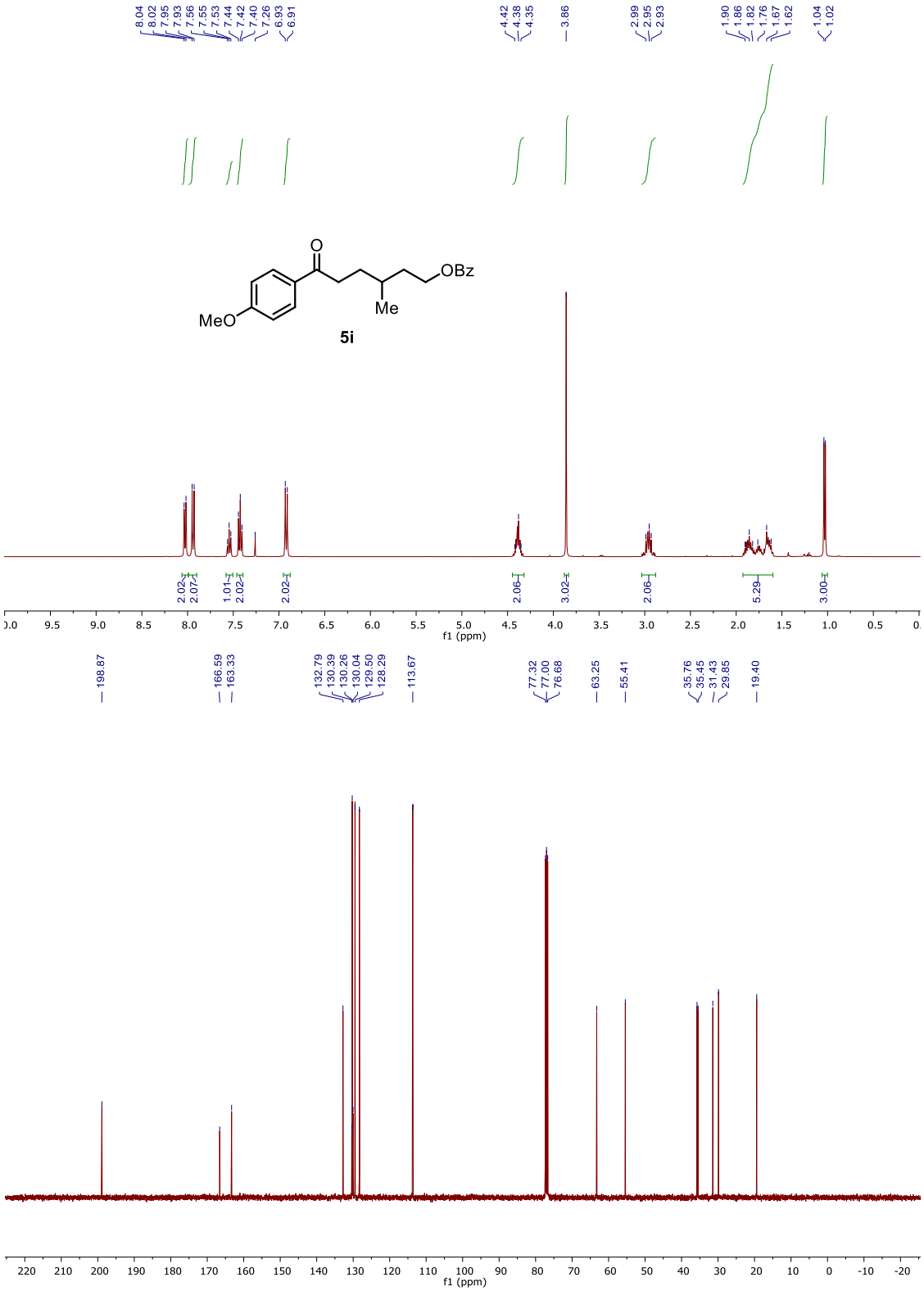


Figure 3.56 ^{1}H-NMR and ^{13}C-NMR Spectra of **5j**

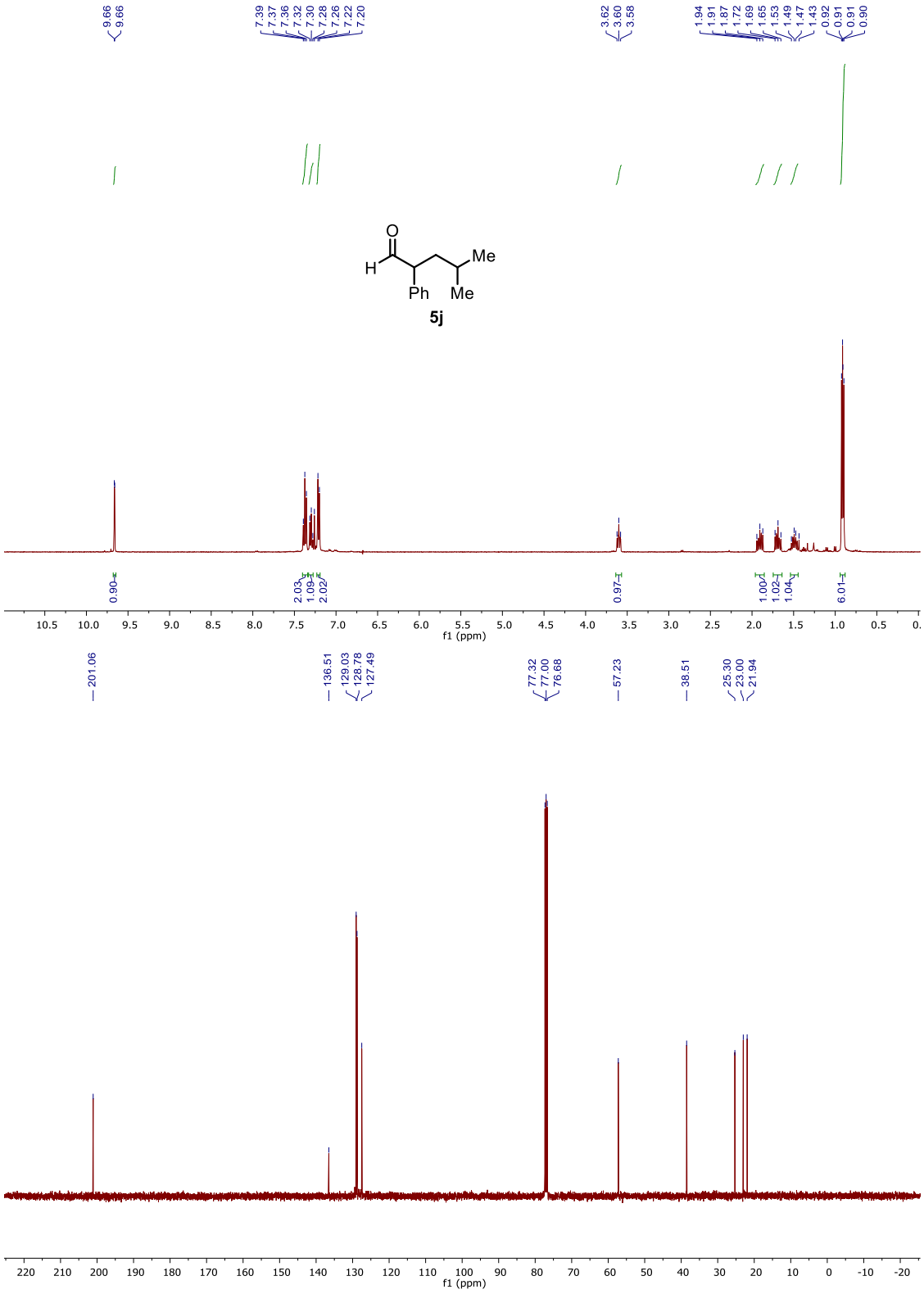


Figure 3.57 ^{1}H-NMR and ^{13}C-NMR Spectra of **5k**

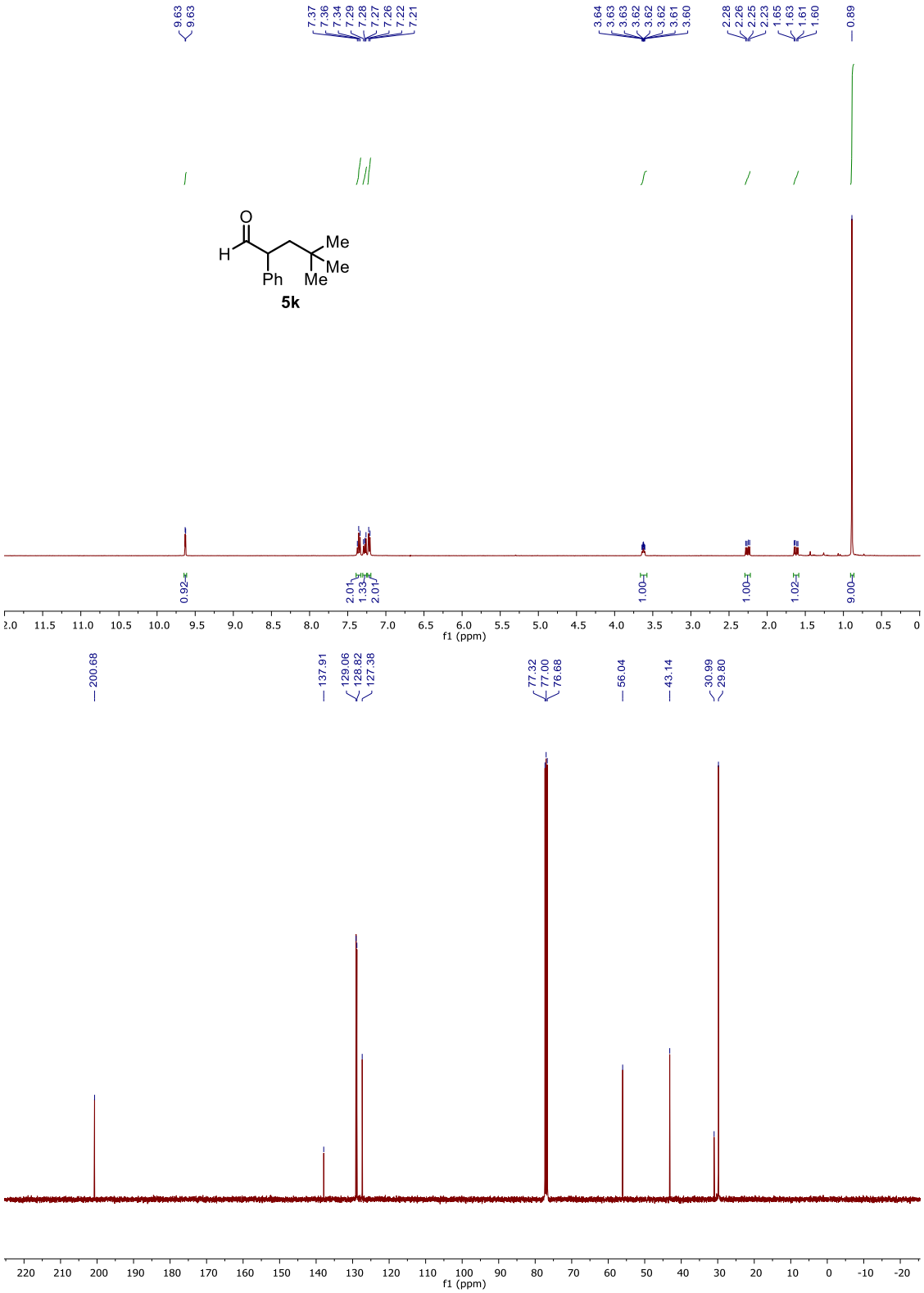


Figure 3.58 ^{1}H-NMR and ^{13}C-NMR Spectra of **5l**

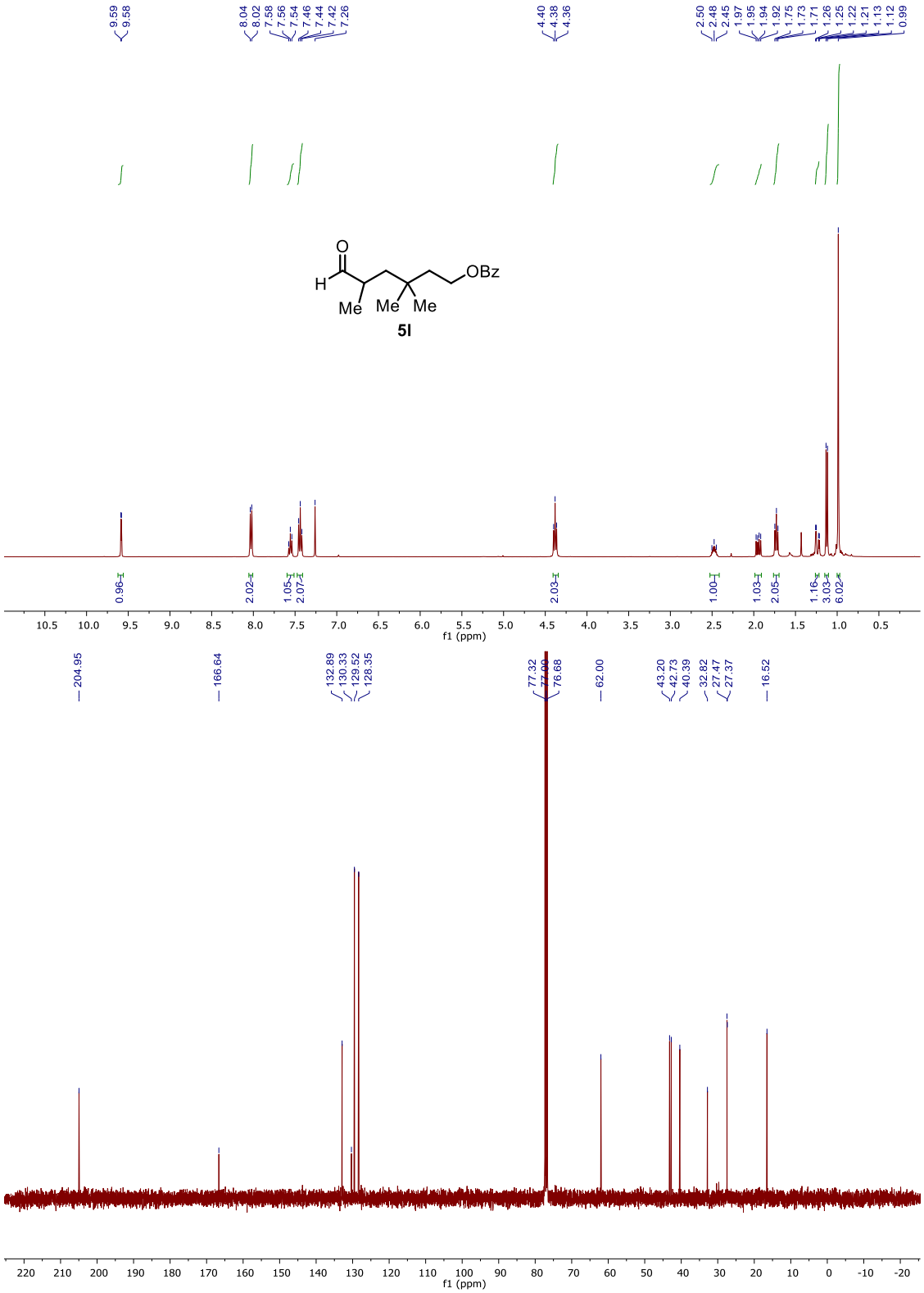


Figure 3.59 ^{1}H-NMR and ^{13}C-NMR Spectra of **5m'**

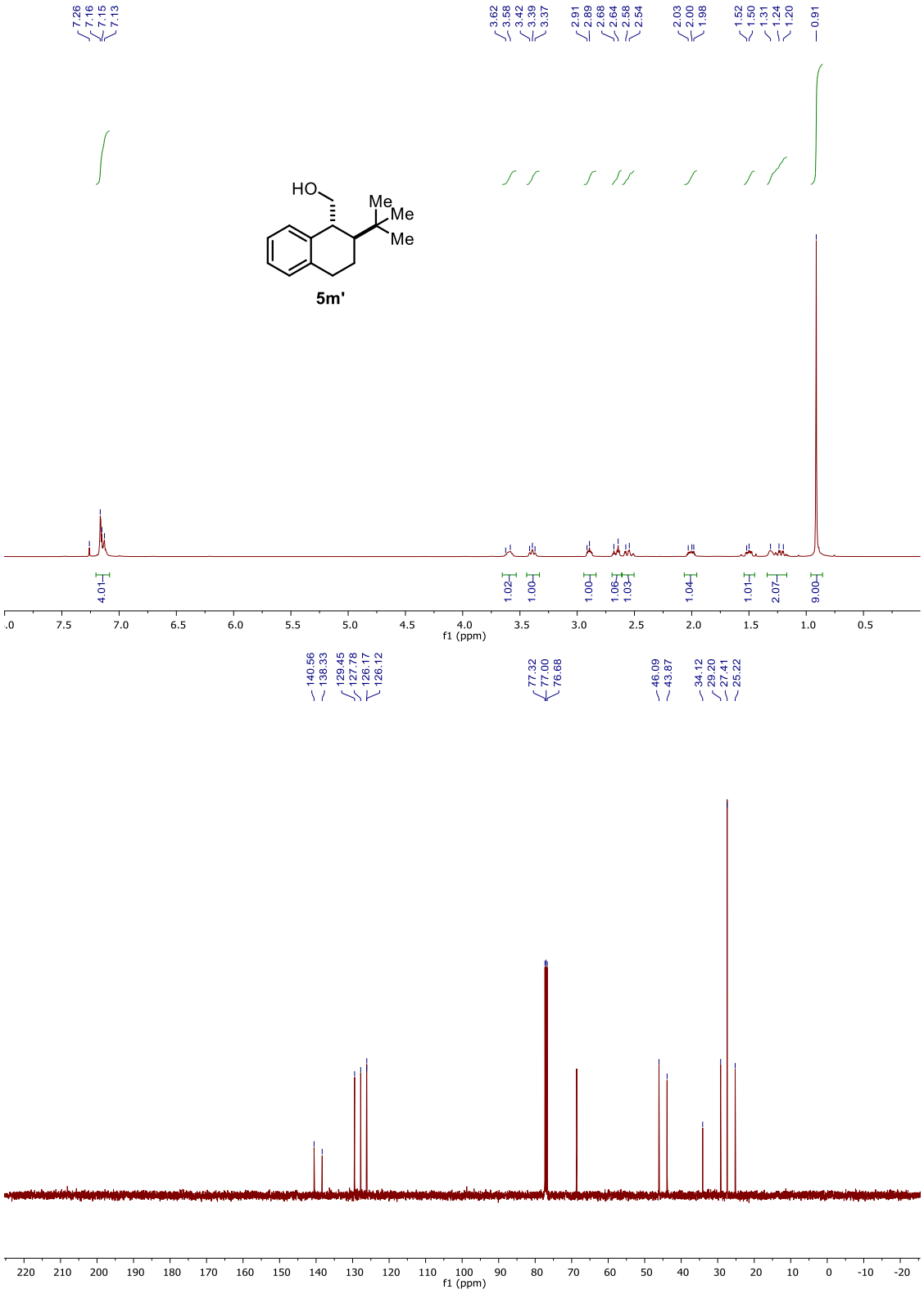


Figure 3.60 ^{1}H-NMR and ^{13}C-NMR Spectra of **8**

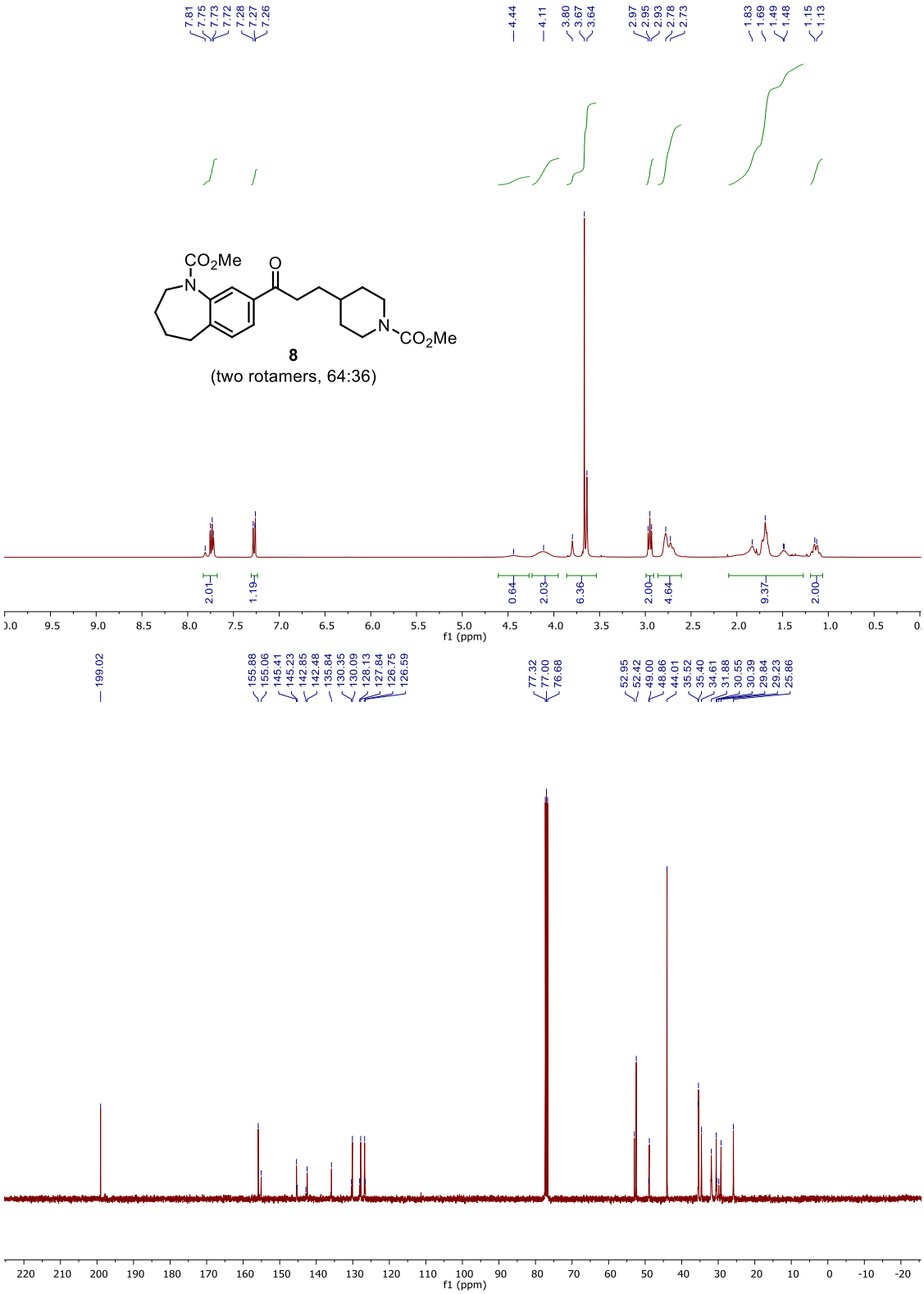


Figure 3.61 ^{1}H-NMR Spectrum of **9**

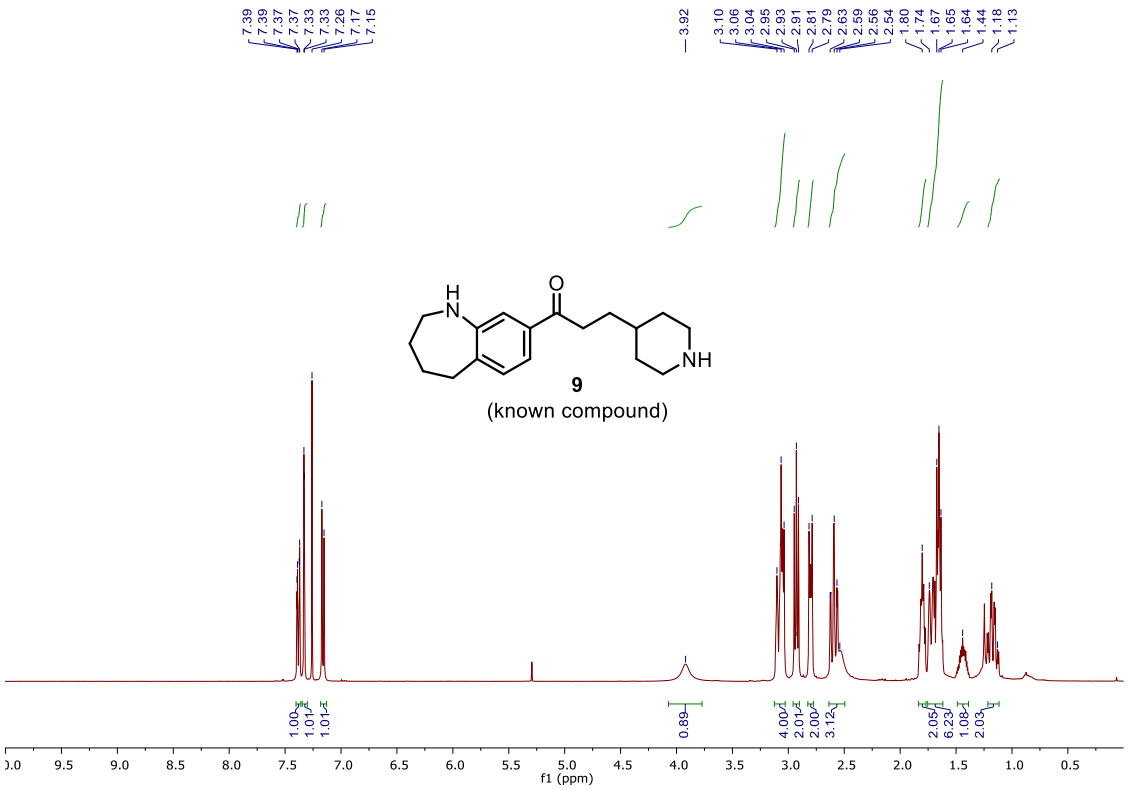
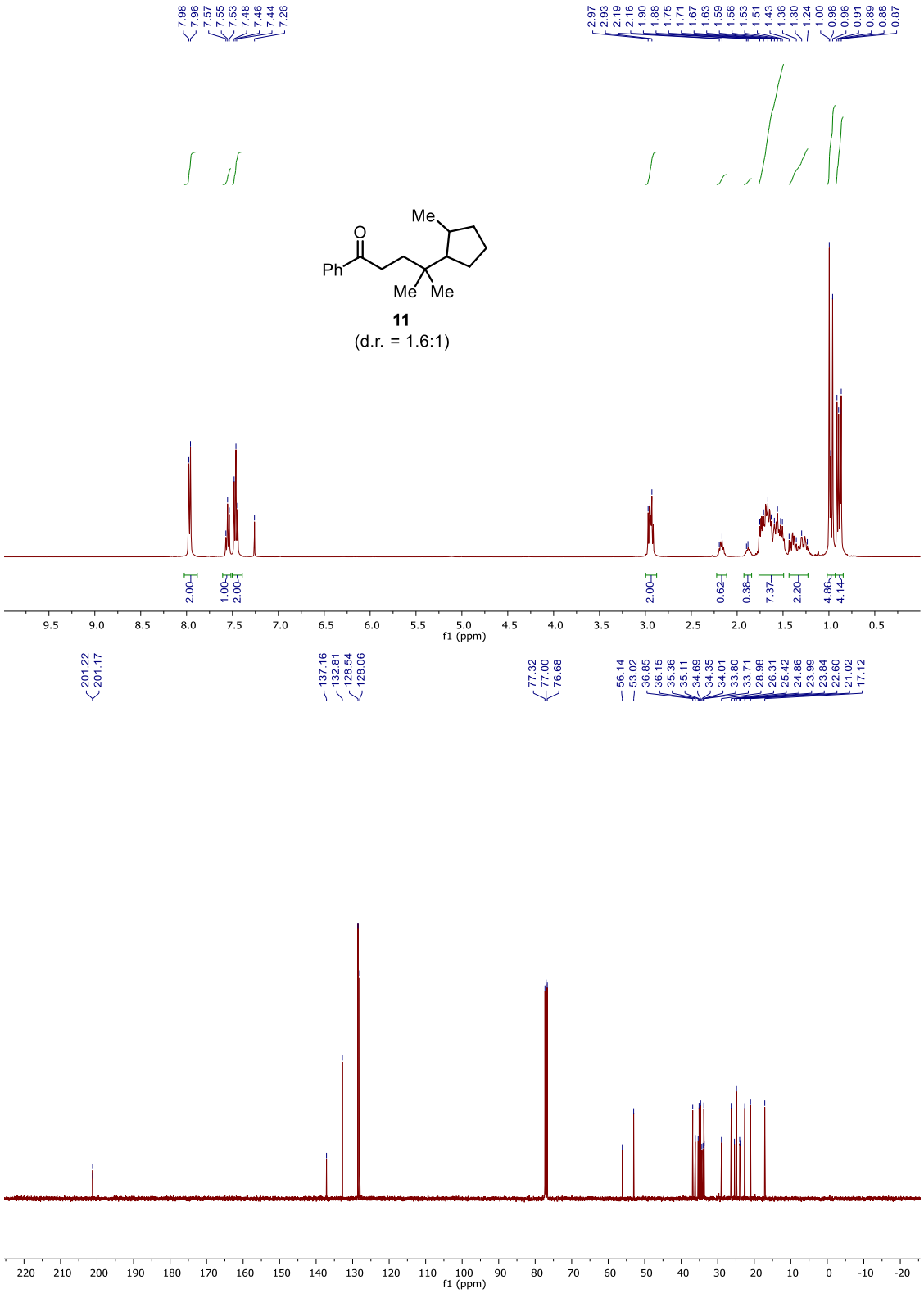


Figure 3.62 ^{1}H-NMR and ^{13}C-NMR Spectra of **11**



CHAPTER 4

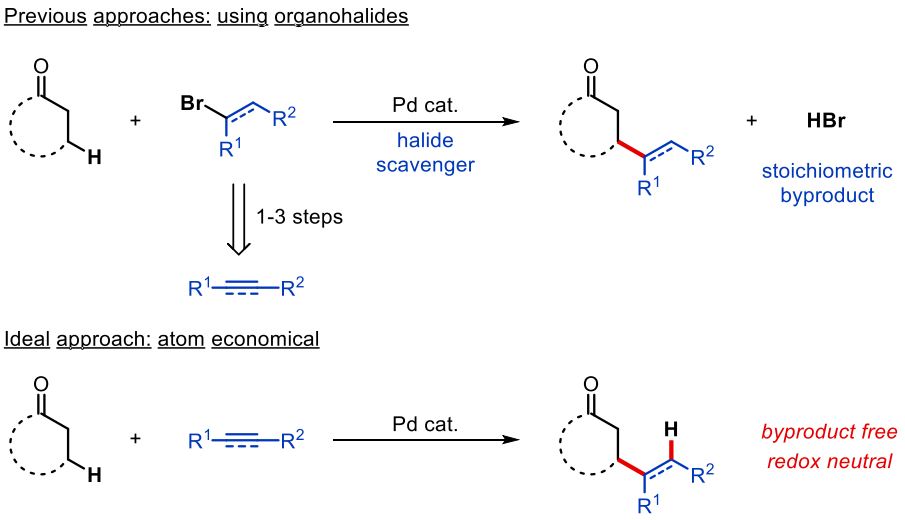
Intramolecular β-Alkenylation of Ketones via C(sp^3)−H Alkyne Coupling

4.1 Introduction

In our previous studies, we have demonstrated the effectiveness of the palladium-catalyzed redox cascade strategy that enables direct alkenylation and alkylation of ketones at their less reactive β positions. Mediated by ketone desaturation processes, organohalides (RXs) have been employed as both the oxidant and the source for the β-C−C bond forming event, which realized efficient and redox-neutral transformations. From the green chemical process and atom economy viewpoints,[1] however, there is still plenty of room for improvement. While it is attractive to use readily available organohalides as the functionalization reagents, stoichiometric HX is generated as a byproduct from the net reaction outcome. Meanwhile, the resulting HX is deleterious to the Pd-catalyzed ketone desaturation step, and, therefore, stoichiometric halide scavengers, such as silver salts, were required in these reactions.[2] On the other hand, many alkyl and alkenyl halides are ultimately prepared from unsaturated hydrocarbons, such as alkenes and alkynes.[3] Thus, it would be strategically appealing if unsaturated hydrocarbons could be directly coupled at the β

position of ketones, which not only avoids any byproduct formation and the need for halide scavengers, but also saves steps and additional materials for organohalide preparation from these unsaturated hydrocarbons (Scheme 4.1). Distinct from previous methods using organohalide, such an approach features both redox economy[4] and atom economy.[5]

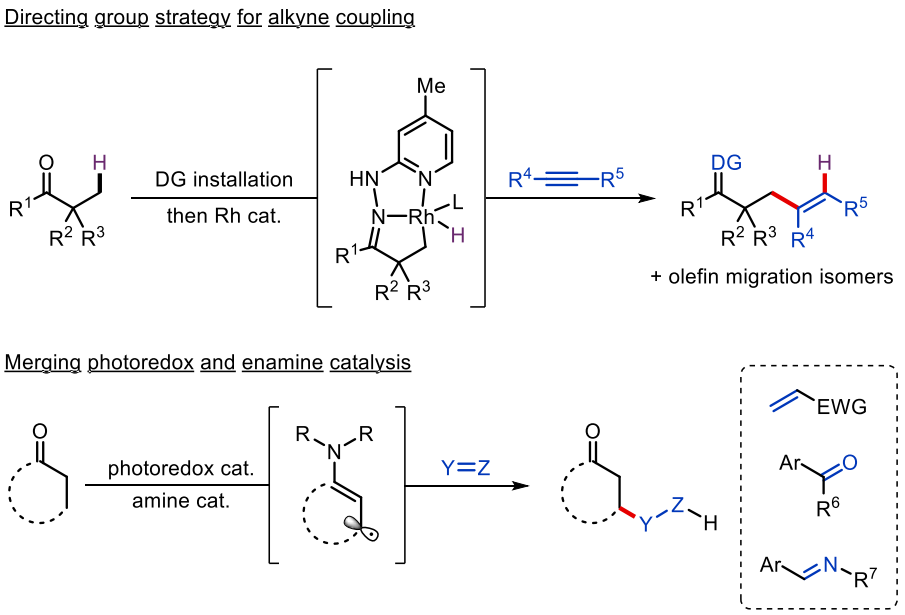
Scheme 4.1 Atom Economical Approach for β-Functionalization of Ketones



Generally, reactivity of unsaturated hydrocarbons is lower compared with organohalides. Therefore, direct coupling of unsaturated hydrocarbons with unactivated β-C(sp^3)–H bonds of ketones remains underdeveloped. While the majority of β-functionalization approaches utilize a directing group (DG) to enable reactivity and site-selectivity via proximity effect,[6] amide-based strong bidentate DGs had been necessary to facilitate the coupling with alkynes.[7] Recently, our group developed a Rh-catalyzed β-alkenylation of ketones with alkynes via a Rh−hydride pathway, in which a hydrazone-based DG was employed through *in situ* installation.[8] While effective and versatile, the DG approach is generally not suitable for cyclic carbonyl compounds. MacMillan and coworkers pioneered a unique photoredox-enamine catalysis strategy via generating β-radicals

of ketones and aldehydes, which are then trapped by different unsaturated 2π units.[9,10] Nevertheless, the reported scope was restricted to good radical accepters such as acrylates, arylketones and imines (Scheme 4.2).

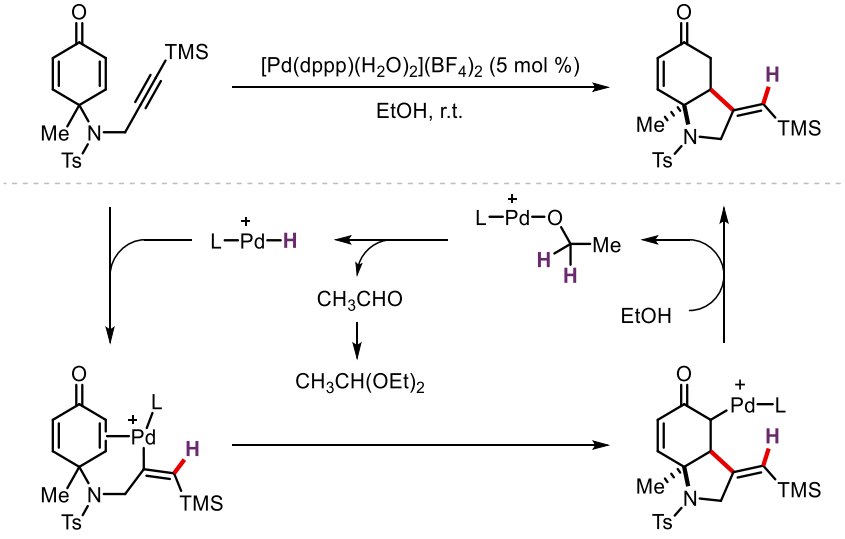
Scheme 4.2 Reported β-Functionalization of Ketones and Aldehydes Using Unsaturated 2π Units



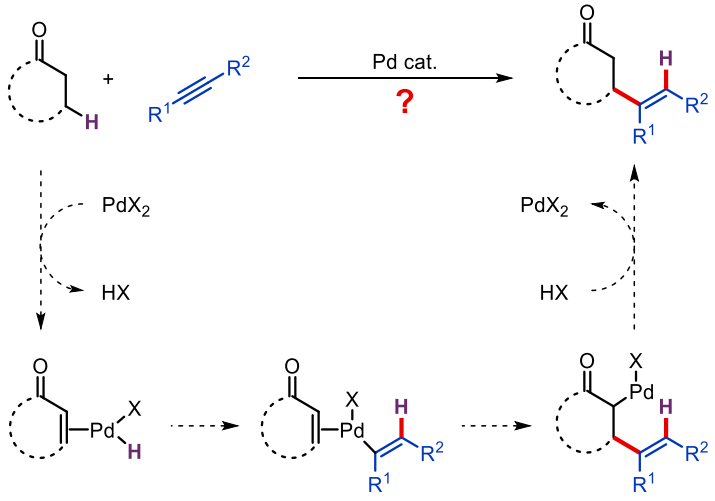
On the other hand, though Pd-catalyzed ketone desaturation has been well studied,[11,12] the 'Pd−hydride' species generated via β-hydrogen elimination in this reaction, to the best of our knowledge, has not been utilized to allow for C−C couplings. Hence, our originally proposed strategy was to trap the 'Pd−hydride' species with an unsaturated 2π unit, i.e. alkyne, and then add the resulting alkenyl-Pd species to the conjugated enone intermediate, which could install the β functional group and regenerate the Pd(II) catalyst. Actually, when external reductants are present such as ethanol, reductive couplings between alkyne and enone have been realized, which was proposed to be mediated by a 'Pd−hydride' species (Scheme 4.3).[13] In our proposed strategy, however, ketone substrate serves as the hydride source, so the overall transformation would be

redox-neutral and byproduct-free. Such a hydride-transfer strategy is expected to furnish ketone β-alkenylation directly via a formal C(sp^3)−H/alkyne coupling without the aid of DGs (Scheme 4.4).

Scheme 4.3 Pd−Hydride-Mediated Reductive Enyne Cyclization in Ethanol



Scheme 4.4 Originally Proposed Strategy for β-Alkenylation of Ketones via Hydride-Transfer[a]



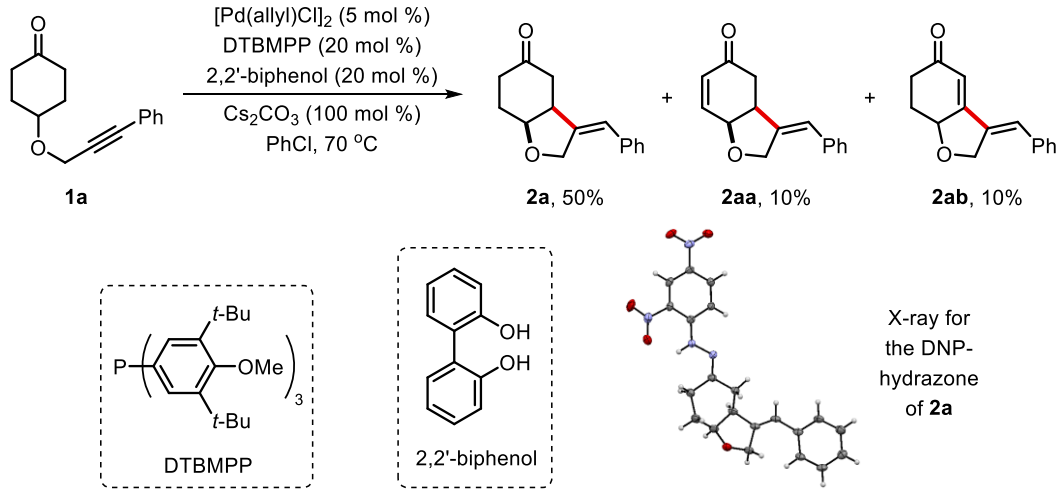
[a]Note: for detailed mechanistic studies and a revised reaction mechanism, see section 4.2.2.

4.2 Results and Discussion

4.2.1 Optimization of the reaction conditions

Before I got involved in this project, Mr. Pengfei Zheng had achieved significant progress in uncovering a class of effective substrate and obtaining key improvements in the efficiency of the transformation (Scheme 4.5). In his optimal reaction conditions, several features are worth mentioning. (a) The product (**2a**) was obtained as a single diastereomer, and its relative configuration was unambiguously confirmed by X-ray crystallography. (b) Overoxidation side products, **2aa** and **2ab**, were obtained in relatively high ratios. (c) Tris(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine (DTBMPP) was identified as a superior ligand for this transformation. (d) An acidic additive, 2,2'-biphenol, helped improve the efficiency. (e) Cesium carbonate was an irreplaceable base, as no product could ever been obtained in the absence of cesium carbonate or with other bases. (f) Chlorobenzene was crucial for a high conversion while other common solvents gave dramatically lower yields.

Scheme 4.5 Previously Developed Optimal Conditions for β-Ketone/Alkyne Coupling

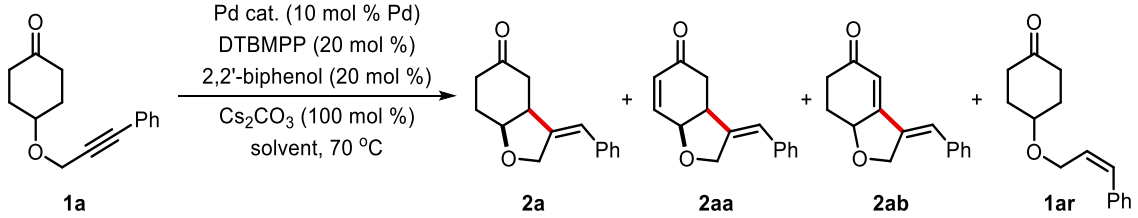


Despite the satisfactory overall efficiency, overoxidation is a major concern since it consumes the β-alkenylation product formed. However, we realize that the relatively high ratio of overoxidation seems inevitable in this case, because the ketone moiety is used in one equivalent and the product is also a ketone, thus the concentration of the product will gradually exceed the substrate as the conversion gets higher. To tackle this issue, an ideal way would be to enhance the selectivity towards desaturation of the substrate over product, though it could be very difficult at high conversion. Alternatively, we could find an effective way to convert the overoxidized products to the saturated ketones via selective 1,4-reduction. Considering the good overall efficiency, we decided to move forward based on this set of conditions.

One interesting feature of this set of conditions is the use of chlorobenzene as the solvent (Table 4.1, entry 1). Since it was almost the only solvent among common ones that led to high overall efficiency, we reasoned that it served as an external weak oxidant that helped restore the Pd(II) catalyst from accumulated Pd(0). Indeed, when we switched the solvent to 1,4-dioxane using $[Pd(allyl)Cl]_2$ (a Pd(0) precatalyst), no conversion was observed (entry 2), while $Pd(OAc)_2$ (a Pd(II) precatalyst) delivered 31% overall yield at 80 °C in 1,4-dioxane (entry 3). These results suggested that the reaction was initiated from Pd(II)-catalyzed ketone desaturation, and chlorobenzene was responsible for oxidizing dead Pd(0) to Pd(II) but likely at a moderate rate that did not interfere with the main reaction pathway. Another interesting observation was that an alkyne reduction side product (**1ar**), adopting *Z*-configuration, could be obtained only in the absence of chlorobenzene (entry 3), likely indicating that such an alkyne reduction was triggered by Pd(0) (*vide infra*). Moreover, a mixed solvent using 1,4-dioxane and chlorobenzene was found

effective (entry 4), and fluorinated ones were superior, with 1-chloro-3-fluorobenzene being the optimal cosolvent (entries 5−7).

Table 4.1 Solvent and Catalyst Screening for the β-Ketone/Alkyne Coupling[a]



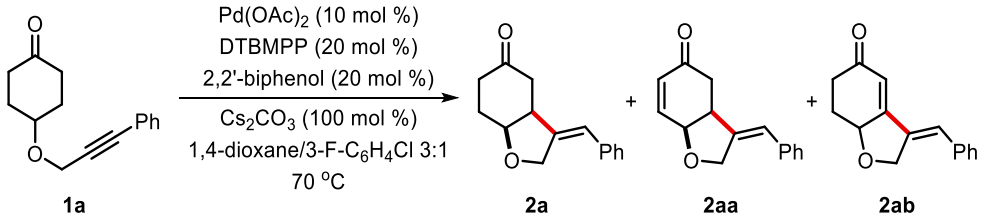
entry	precatalyst	solvent	β-alkenylation yield (%)[b]	**2a**/**2aa**/**2ab**[c]	unreacted **1a** (%)[c]	yield of **1ar** (%)[c]
1	$[Pd(allyl)Cl]_2$	PhCl	70	50/10/10	0	0
2[d]	$[Pd(allyl)Cl]_2$	1,4-dioxane	0	0/0/0	100	0
3[d]	$Pd(OAc)_2$	1,4-dioxane	31	28/2/1	60	10
4	$Pd(OAc)_2$	1,4-dioxane/PhCl 3:1	63	35/15/13	5	0
5	$Pd(OAc)_2$	1,4-dioxane/2-F-C_6H_4Cl 3:1	72	38/17/17	9	0
6	$Pd(OAc)_2$	1,4-dioxane/3-F-C_6H_4Cl 3:1	74	46/15/13	9	0
7	$Pd(OAc)_2$	1,4-dioxane/4-F-C_6H_4Cl 3:1	71	45/14/12	12	0

[a]All the reactions were run with **1a** (0.1 mmol) in indicated solvent (1.0 mL) for 48 h. [b]β-Alkenylation yield refers to the total yield of **2a**, **2aa** and **2ab**. [c]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard. [d]The reaction was run at 80 °C.

Adopting the mixed solvent system, we further managed to improve the efficiency (Table 4.2). An elevated temperature led to more decomposition (entry 2). Interestingly, cesium carbonate was required in certain amount, as 75 mol % still afforded the same efficiency (entry 3), but 50 mol % caused significant decomposition (entry 4). It is worth mentioning that, when the reactions were not well-stirred, the results would also be sluggish, and the mass balance was similar to the ones observed with less cesium carbonate. We postulated that a basic environment might be essential to prevent decomposition of the substrate or reaction intermediate (*vide infra*). Finally,

when we used the precoordinated complex, $Pd(DTBMPP)_2(OAc)_2$, as the catalyst, the yield was further enhanced to 79% (entry 5).

Table 4.2 Further Condition Optimization Based on Mixed Solvent System[a]

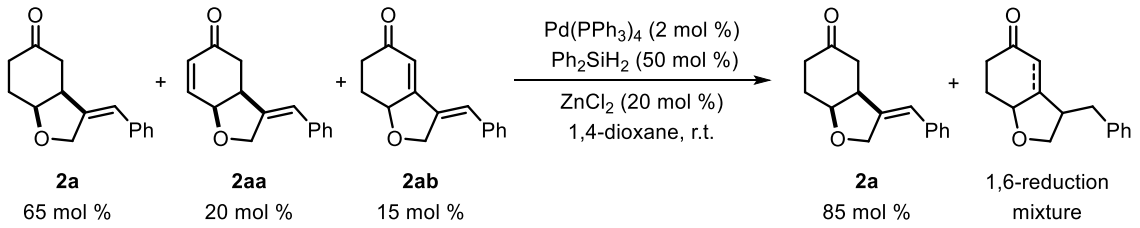


entry	variations	β-alkenylation yield (%)[b]	**2a**/**2aa**/**2ab**[c]	unreacted **1a** (%)[c]
1	none	74	46/15/13	9
2	80 °C	69	40/16/13	0
3	Cs_2CO_3 (75 mol %)	72	47/14/11	10
4	Cs_2CO_3 (50 mol %)	38	23/8/7	8
5	$Pd(DTBMPP)_2(OAc)_2$ as the catalyst	79	49/16/14	3

[a]All the reactions were run with **1a** (0.1 mmol) in the mixed solvent (1.0 mL) for 48 h. [b]β-Alkenylation yield refers to the total yield of **2a**, **2aa** and **2ab**. [c]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard.

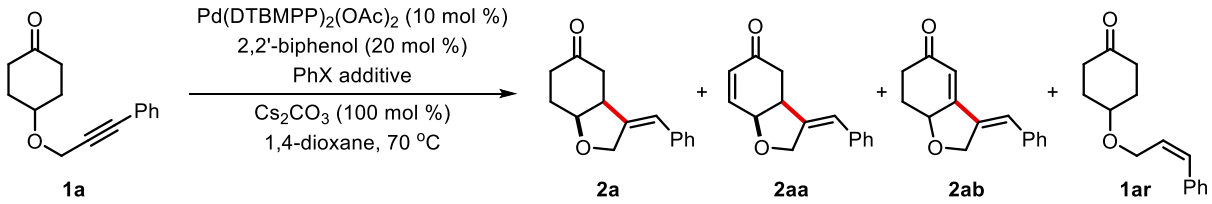
Since the overall efficiency was satisfactory, we then managed to explore selective 1,4-reduction protocols to unify the products isolated from the reaction. Though a Pd-catalyzed silane reduction condition[14] could quantitively convert **2aa** to **2a**, unfortunately, selective 1,4-reduction of **2ab** was not successful as the competing 1,6-addition was more accessible (Scheme 4.6). Other reduction methods have also been tested, but the 1,4-reduction of **2ab** remained challenging. Moreover, it was found extremely difficult to purify **2a** in the presence of **2ab** or its 1,6-reduction products. Therefore, it became imperative to explore new reaction conditions that give lower ratios of overoxidation (especially **2ab**).

Scheme 4.6 Reduction of the β-Alkenylation Products



In fact, high conversion and good selectivity seem to be contradictory in this transformation, particularly in terms of the use of chlorobenzene cosolvent. On one hand, chlorobenzene helps constantly regenerate active Pd(II) from accumulated Pd(0). On the other hand, excess chlorobenzene serves as external oxidant that leads to more severe overoxidation. To overcome this drawback, it might be feasible to switch to a stronger oxidant but in a catalytic amount, which could possibly reach a balance between the enhanced reactivity and controllable selectivity. Based on this idea, we tested bromobenzene which has a higher tendency to undergo oxidative addition with Pd(0) (Table 4.3). To our delight, 30 mol % bromobenzene additive afforded moderate efficiency, and more importantly, diminished overoxidation ratio (entry 1). Notably, the yield of **2ab** was particularly low, which met our goal. While iodobenzene was too reactive (entry 2), phenyl triflate showed a better performance, giving slightly higher yield and better selectivity (entry 3). Moreover, increasing the additive loading to 50 mol % lead to marginal improvement in the yield, but the overoxidation became more serious (entries 4 and 5). Interesting, possible side reactions caused by the aryl halides, such as α-arylation of ketones and aryl conjugate addition to enones, were not detected. However, in these cases where excess oxidant was not present, the alkyne reduction side product (**1ar**) appeared again though in a low yield.

Table 4.3 Aryl Halide Additive for the β-Ketone/Alkyne Coupling[a]



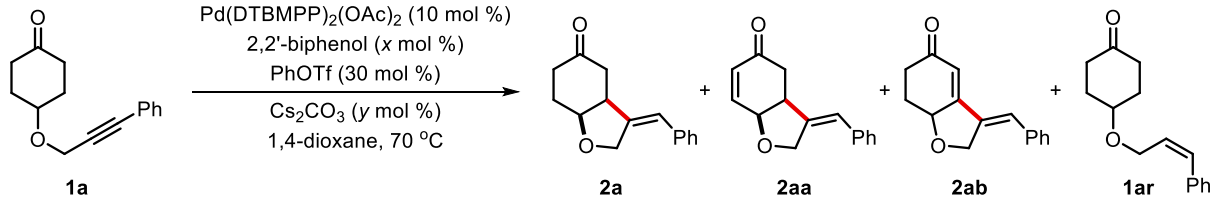
entry	PhX	β-alkenylation yield (%)[b]	**2a**/**2aa**/**2ab**[c]	unreacted **1a** (%)[c]	yield of **1ar** (%)[c]
1	PhBr (30 mol %)	57	47/8/2	19	8
2	PhI (30 mol %)	14	11/3/0	48	0
3	PhOTf (30 mol %)	58	51/6/1	23	6
4	PhBr (50 mol %)	60	44/10/6	12	3
5	PhOTf (50 mol %)	62	49/9/4	15	4

[a]All the reactions were run with **1a** (0.1 mmol) in 1,4-dioxane (1.0 mL) for 48 h. [b]β-Alkenylation yield refers to the total yield of **2a**, **2aa** and **2ab**. [c]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard.

In addition to unsubstituted aryl halides, we also performed systematic screening of substituted aryl bromides and triflates, as well as aryl tosylates and nosylates. Unfortunately, none of them was found superior than simple phenyl triflate. Thus, we moved on with phenyl triflate as the additive, and further attempted to increase the efficiency (Table 4.4). Interestingly, when the loading of 2,2'-biphenol was increased to 30 mol %, the overall yield rose though overoxidation ratio was also higher (entry 1). Further increasing the loading to 40 mol % caused significant overoxidation (entry 2). We then tried to add more cesium carbonate to balance the raised acidity due to higher loading of 2,2'-biphenol, and indeed, a combination of 30 mol % 2,2'-biphenol and 120 mol % Cs_2CO_3 provided the optimal yield and selectivity (entry 3). Further increasing the loading of these additives (entries 4 and 5) or changing to a more acidic 6,6'-difluoro-2,2'-biphenol

(entry 6) did not give any improvement.

Table 4.4 Final Optimization for the β-Ketone/Alkyne Coupling[a]



entry	*x*	*y*	β-alkenylation yield (%)[b]	**2a**/**2aa**/**2ab**[c]	unreacted **1a** (%)[c]	yield of **1ar** (%)[c]
1	30	100	66	54/9/3	21	7
2	40	100	69	51/10/8	14	6
3	30	120	64	55/8/1	23	5
4	40	120	65	54/8/3	21	5
5	40	140	62	55/6/1	26	4
6[d]	30	120	62	55/6/1	24	7

[a]All the reactions were run with **1a** (0.1 mmol) in 1,4-dioxane (1.0 mL) for 48 h. [b]β-Alkenylation yield refers to the total yield of **2a**, **2aa** and **2ab**. [c]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard. [d]6,6'-Difluoro-2,2'-biphenol was used instead of unsubstituted 2,2'-biphenol.

With the most balanced reaction conditions in hand, we managed to perform the selective 1,4-reduction using the Pd-catalyzed silane reduction conditions.[14] Gratifyingly, reduction of the isolated mixture of **2a**, **2aa** and **2ab** worked perfectly, which eased isolation. Furthermore, a desirable one-pot reduction protocol led to the same isolation yield, which circumvents the necessity for work-up or solvent switch (Scheme 4.7). Therefore, simpler operations in the same reaction vessel would deliver the unified product. It is worth mentioning that, in such a one-pot protocol, the alkyne moiety in the unreacted substrate would also be reduced by silane, likely through a hydrosilylation pathway.

Scheme 4.7 One-Pot β-Alkenylation and Reduction Protocol

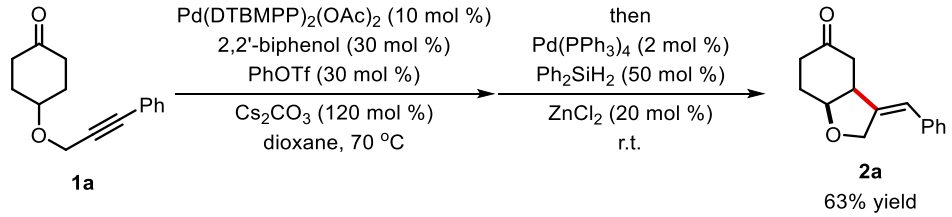
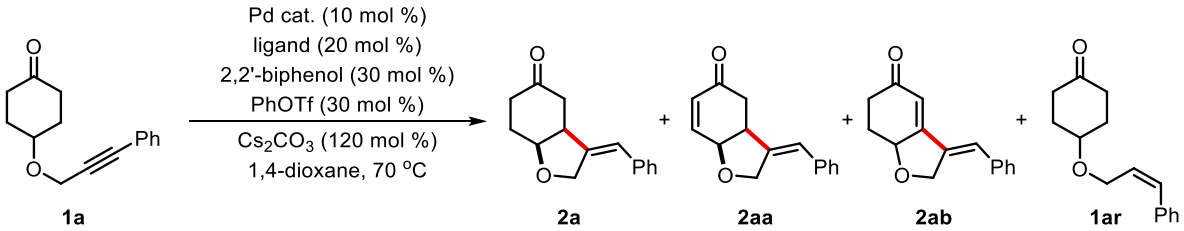
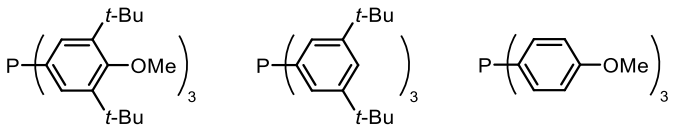


Table 4.5 Catalyst and Ligand Variations for the β-Ketone/Alkyne Coupling[a]



entry	Pd	ligand	β-alkenylation yield (%)[b]	**2a**/**2aa**/**2ab**[c]	unreacted **1a** (%)[c]	yield of **1ar** (%)[c]
1	$Pd(DTBMPP)_2(OAc)_2$		64	55/8/1	23	5
2	none	DTBMPP	0	0/0/0	100	0
3	$Pd(OAc)_2$	none	0	0/0/0	78	1
4	$Pd(OAc)_2$	DTBMPP	61	53/7/1	22	4
5	$Pd(MeCN)_4(OTf)_2$	DTBMPP	59	51/6/2	26	1
6	$Pd(OAc)_2$	**L1**	47	40/5/2	28	3
7	$Pd(OAc)_2$	**L2**	21	20/1/0	56	2
8	$Pd(OAc)_2$	$P(i\text{-}Pr)_3$	45	32/5/8	29	10



[a]All the reactions were run with **1a** (0.1 mmol) in 1,4-dioxane (1.0 mL) for 48 h. [b]β-Alkenylation yield refers to the total yield of **2a**, **2aa** and **2ab**. [c]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard.

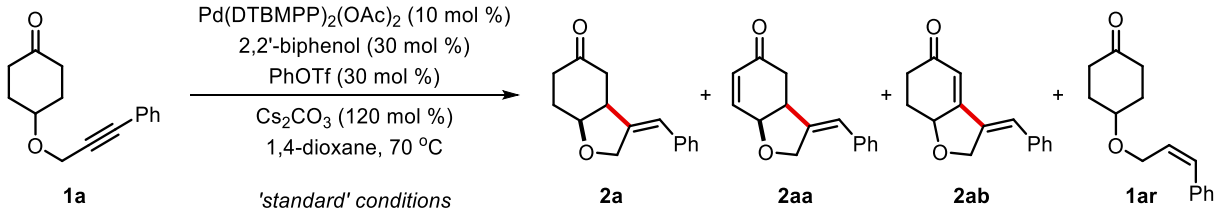
A series of control experiments were then conducted to understand the role of each component, starting with the effects of the catalyst and ligand (Table 4.5). Both the palladium

complex and the ligand were essential (entries 2 and 3). Separate addition of $Pd(OAc)_2$ and DTBMPP instead of the precoordinated complex gave comparable results (entry 4), and cationic Pd complexes such as $Pd(MeCN)_4(OTf)_2$ were also suitable catalysts (entry 5). Both the electron-richness and bulkiness of the DTBMPP ligand were necessary for the success of this transformation, as similar ligands without methoxy (**L1**) or *tert*-butyl groups (**L2**) led to diminished yields (entries 6 and 7). In addition, triisopropylphosphine, a superior ligand for the previously developed β-functionalization reactions, only gave a moderate yield (entry 8).

Variations of other additives were then examined (Table 4.6). Phenyl triflate was found again the most effective promoter for this transformation, as the reaction efficiency still dropped significantly in the absence of PhOTf (entry 2), and both catalytic bromobenzene and solvent amount of chlorobenzene gave lower efficiency or selectivity (entries 3 and 4). A catalytic amount of 2,2'-biphenol also benefited the reactivity (entry 5). For comparison, the use of simple phenol did not work; however, more acidic carboxylic acid additives were also effective albeit with lower selectivity (entries 6−8). Though the exact role of 2,2'-biphenol is unclear at this stage, the observed higher reactivity, compared with the use of mono phenol, might be attributed to its enhanced acidity (pK_a = 8.0)[15] that could promote protonation of the Pd-enolate intermediate. Finally, cesium carbonate was found indispensable for this transformation, as substrate decomposition and various undesired side reactions occurred in the absence of Cs_2CO_3 (entry 9) or with weaker bases (entries 10 and 11). The role of the base was proposed to suppress side reactions and decomposition of the substrate or intermediate. Though numerous side reactions may have occurred in the absence of base, the observed major ones included intramolecular ketone α-

allylation[16] and C−O bond cleavage of the substrate to deliver cinnamaldehyde which likely arose from alkyne to allene isomerization[17] (for more detailed discussions on the roles of these additives, see section 4.2.2).

Table 4.6 Variations from the 'Standard' Conditions for the β-Ketone/Alkyne Coupling[a]



entry	variations from the 'standard' conditions	β-alkenylation yield (%)[b]	**2a**/**2aa**/**2ab**[c]	unreacted **1a** (%)[c]	yield of **1ar** (%)[c]
1	none	64	55/8/1	23	5
2	without PhOTf	16	16/0/0	71	6
3	PhBr instead of PhOTf	54	48/5/1	25	5
4	PhCl instead of 1,4-dioxane, without PhOTf	59	43/8/8	28	0
5	without 2,2'-biphenol	42	39/3/0	34	3
6[d]	phenol instead of 2,2'-biphenol	18	17/1/0	47	9
7	phthalic acid instead of 2,2'-biphenol	62	45/10/7	13	3
8[d]	benzoic acid instead of 2,2'-biphenol	56	41/9/6	24	10
9	without Cs_2CO_3	0	0/0/0	0	3
10	K_2CO_3 instead of Cs_2CO_3	0	0/0/0	0	0
11	$CsHCO_3$ instead of Cs_2CO_3	0	0/0/0	0	0

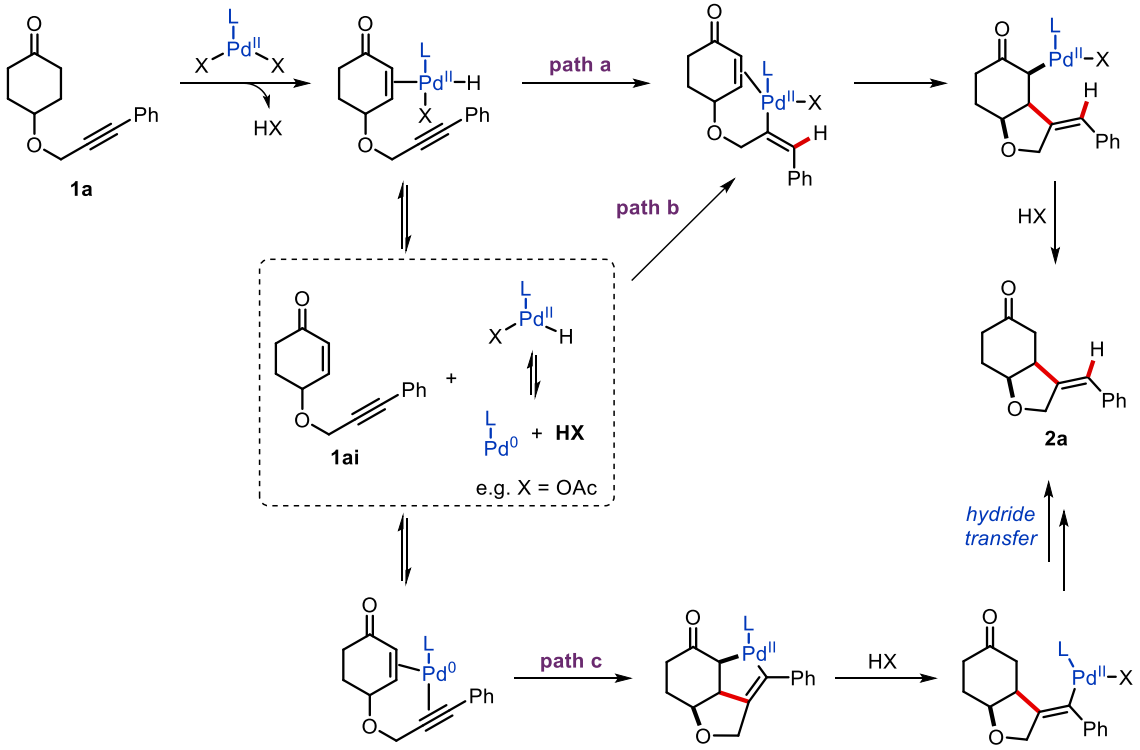
[a]All the reactions were run with **1a** (0.1 mmol) in 1,4-dioxane (1.0 mL) for 48 h. [b]β-Alkenylation yield refers to the total yield of **2a**, **2aa** and **2ab**. [c]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard. [d]For these additives, 60 mol % was used.

4.2.2 Mechanistic studies

The unique transformation discovered here motivated us to gain more insights into the reaction mechanism. Particularly, the originally proposed Pd−hydride pathway may not be true

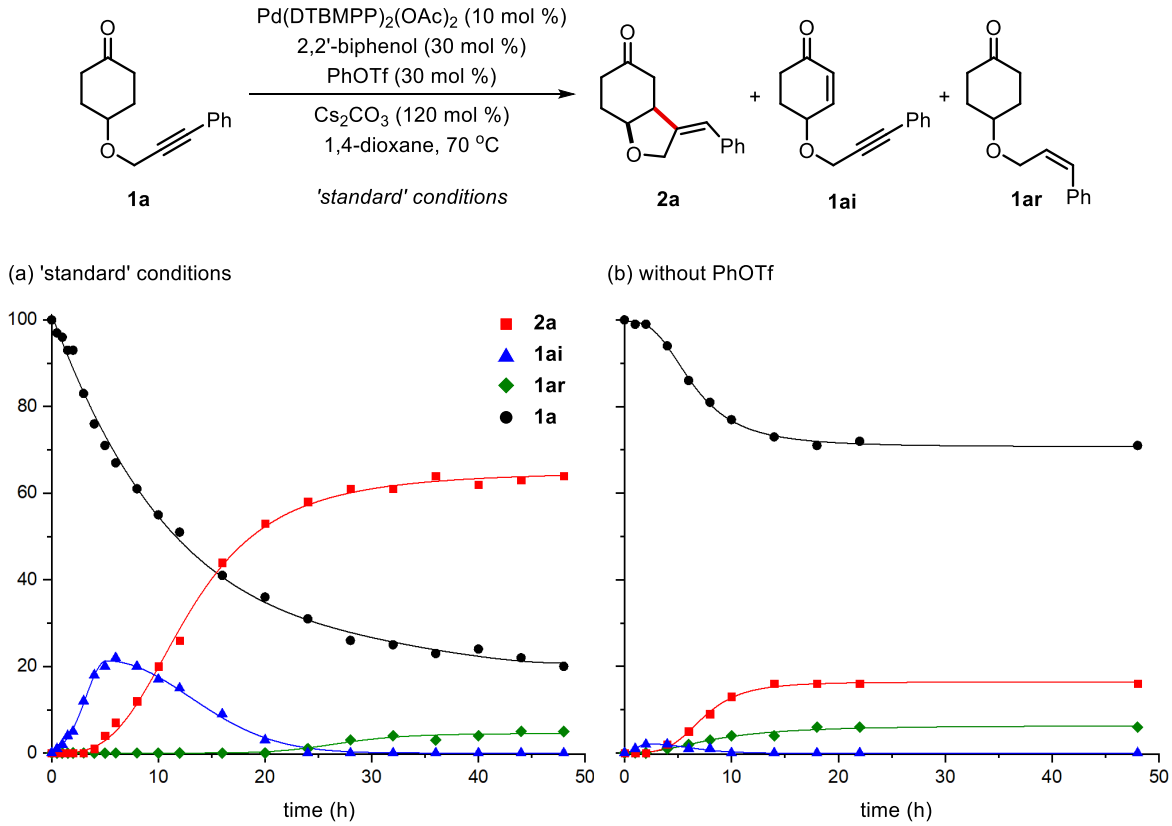
since it would have been suppressed by adding stoichiometric base. Based on the *Z*-olefin geometry of **2a** and the catalytic conditions employed, we proposed three plausible pathways (Scheme 4.8). All pathways are expected to start with ketone desaturation by a Pd(II) species to deliver enyne intermediate **1ai** and a Pd−hydride (Pd−H) species. **Path a**, as the originally proposed strategy, involves an intramolecular Pd−H addition to the alkyne moiety followed by conjugate addition to forge the β-C−C bond.[18] Alternatively, the Pd−H species could dissociate from the enyne intermediate and react with the alkyne moiety of another substrate (**path b**). Trost and coworkers demonstrated that X−Pd−H (e.g. X = OAc) could be a transient species, which is in equilibrium with Pd(0) and the acid (HX).[19] Thus, **path b** involves a proton-mediated Pd−H addition mechanism.[20] Moreover, one can imagine that the β-C−C bond could be formed via cyclo-

Scheme 4.8 Three Plausible Mechanisms



metallation between Pd(0) and the enyne intermediate (**path c**).[21,22] The resulting palladacycle could then undergo protonation at the enolate carbon and hydride transfer to the alkenyl position in the subsequent steps (*vide infra*).

Figure 4.1 Kinetic Profiles with and without Phenyl Triflate[a]



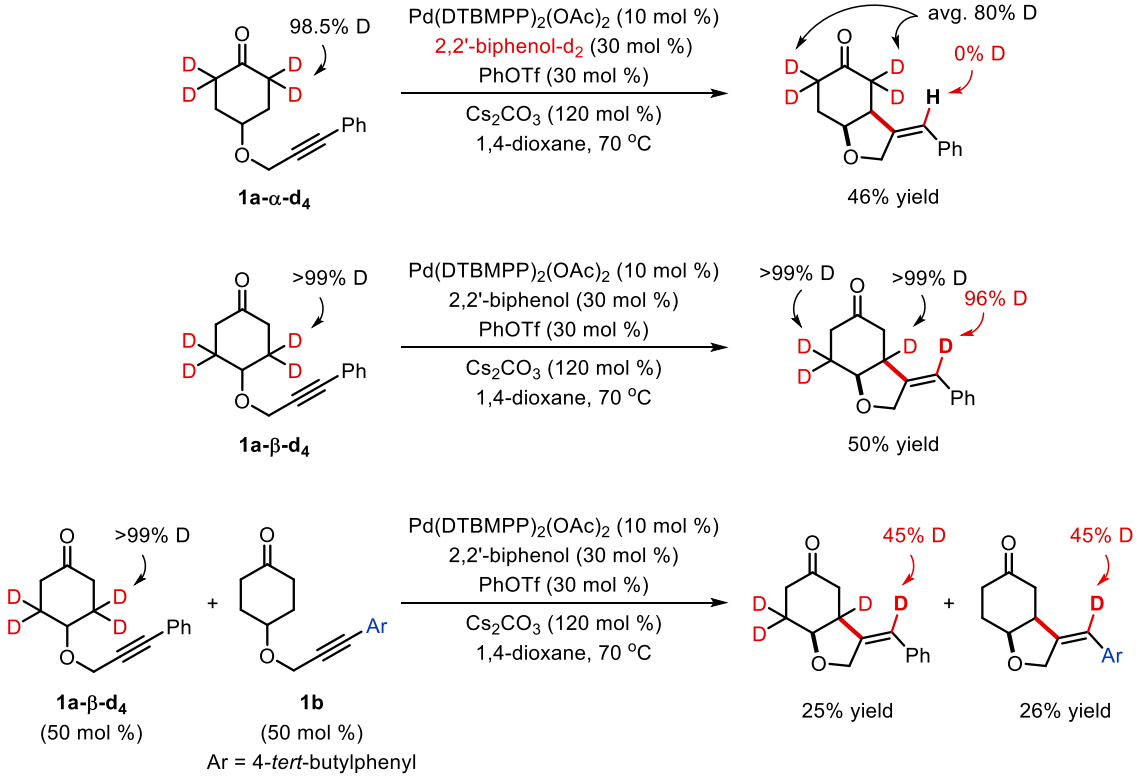
[a]All the reactions were run with **1a** (0.1 mmol) in 1,4-dioxane (1.0 mL) for given reaction time. Yields were determined via NMR using 1,1,2,2-tetrachloroethane as the internal standard. The yield of **2a** refers to all β-alkenylation products. The trendlines were obtained through nonlinear curve fit.

First, the kinetic profiles of the reaction were obtained with and without PhOTf (Figure 4.1). Under the standard conditions (with PhOTf additive), a 4-hour induction period was observed before product **2a** started to form, during which period fast accumulation of enyne intermediate **1ai** occurred. The product formation was accompanied with consumption of enyne **1ai** in the next

24 hours. Note that the alkyne reduction side product (**1ar**) only appeared after enyne **1ai** was mostly consumed (after 24 h). In contrast, in the absence of PhOTf, only a maximum of 2% enyne accumulation was observed during the induction period, which led to a low overall yield of **2a** and early formation of alkyne reduction product **1ar**. Considering the facts that **path a** involves an intramolecular Pd−H addition mechanism and the enyne intermediate was formed almost immediately, the unusually long induction period for **2a** formation is inconsistent with **path a**.

Next, to understand the source of the alkenyl hydrogen in **2a**, a series of deuterium labeling experiments were conducted (Scheme 4.9). Interestingly, the α-deuterated ketone substrate with 2,2'-biphenol-d_2 led to no deuterium incorporation at the alkenyl position, while the β-deuterated substrate surprisingly gave nearly complete deuterium transfer to the alkenyl position. These results suggest that the alkenyl hydrogen does not arise from proton sources; instead, it should come from the ketone β position. In addition, a deuterium crossover experiment shows that the β-deuterium equally distributes to both products, which demonstrates that an intermolecular hydrogen transfer mechanism is involved in the alkenyl C−H bond formation and further excludes **path a**. On the other hand, while the intermolecular Pd−H addition mechanism (**path b**) cannot be fully excluded, it is unlikely to represent the main reaction pathway. This is because, when X is an electronegative element, e.g. OAc, the X−Pd−D species is known to undergo reversible reductive elimination to give DX that would have fast proton exchange with existing proton sources.[19] Thus, given the presence of various proton sources in the reaction conditions, e.g. 2,2'-biphenol and ketone α-protons, the lack of deuterium loss at the alkenyl position is not consistent with an intermolecular X−Pd−H addition mechanism (**path b**).

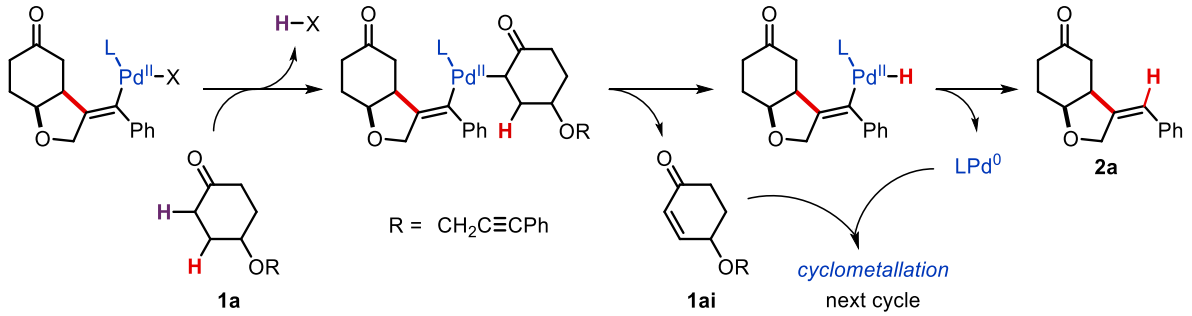
Scheme 4.9 Deuterium Labeling Experiments



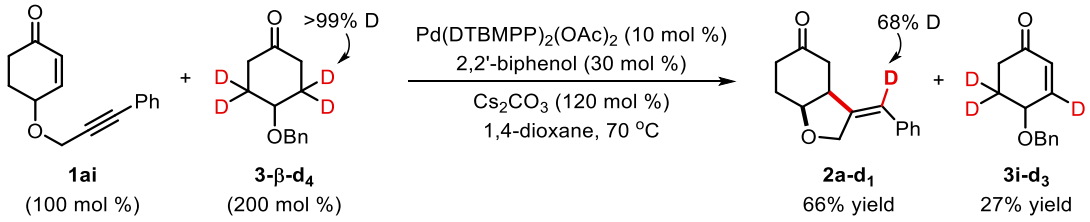
At this stage, the remaining questions are: 1) whether **path c** could be a possible reaction pathway; 2) what the role of PhOTf is and 3) how to explain the formation of the alkyne reduction side product. To address the first question, one can imagine that, in **path c** after enyne cyclopalladation and protonation of the enolate, the resulting alkenyl-Pd species could react with another ketone substrate (Scheme 4.10). The strong *trans effect* of the alkenyl group is expected to enhance the basicity of the X ligand on Pd.[23] After deprotonation of the ketone α-hydrogen, a sequence of β-hydrogen elimination and alkenyl C−H reductive elimination should furnish the desired product (**2a**) and reinitiate the catalytic cycle by giving Pd(0) and enyne **1ai** (a chain-like mechanism). This pathway is the most consistent with the deuterium labeling and crossover experiments (Scheme 4.9). In addition, a reductive cyclization of enyne **1ai** using β-deuterated

ketone **3-β-d$_4$** as the hydrogen source worked smoothly under similar conditions, which supports the intermediacy of the enyne species and an intermolecular hydrogen transfer mechanism (Scheme 4.11). The reduced deuterium incorporation in product **2a-d$_1$** was likely caused by some hydrogen transfer from substrate **1ai**.

Scheme 4.10 Proposed Intermolecular Hydrogen Transfer Mechanism

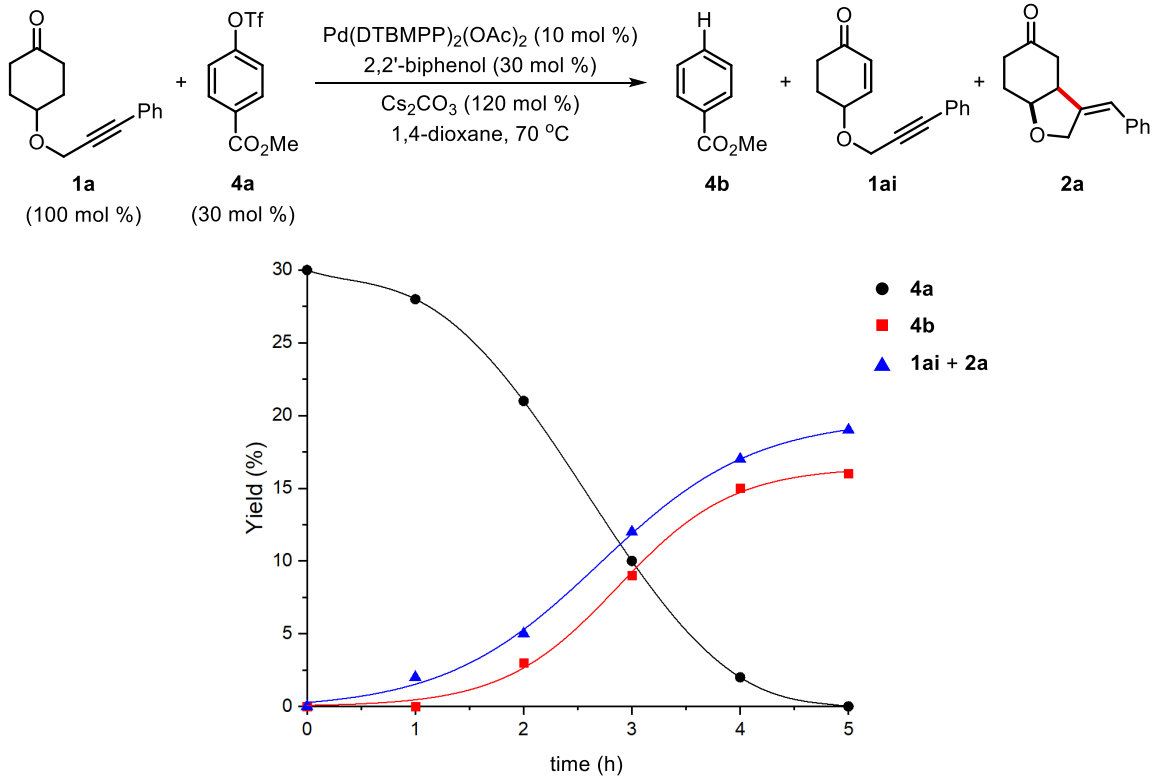


Scheme 4.11 Intermolecular Deuterium Transfer Experiment



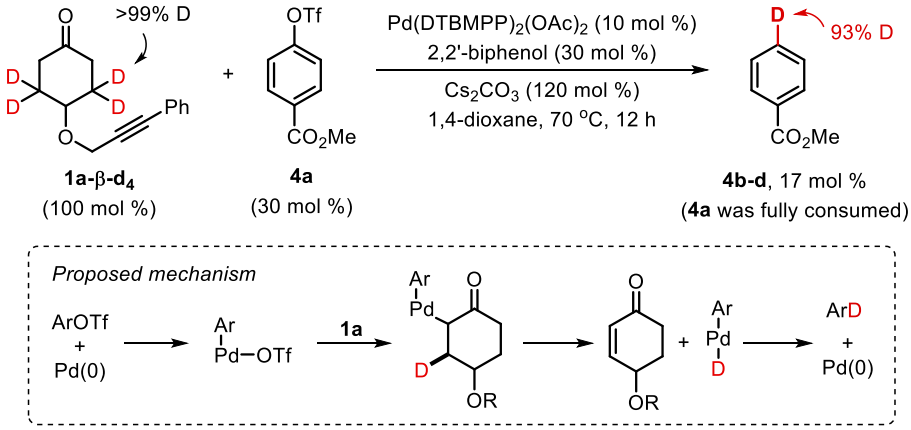
Next, to understand the role of PhOTf (See Table 4.6, entries 2−4 and Figure 4.1 for more data), 4-methoxycarbonylphenyl triflate (**4a**) was used as the additive instead for easy monitoring of the reaction. It was observed that **4a** was fully consumed in the first 5 hours of the reaction, which corresponds to the initial enyne accumulation period (Figure 4.2). The reduction product of **4a**, methyl benzoate (**4b**), was detected, and its generation rate correlates with the rate of ketone desaturation during this period. The source of the hydrogen was further confirmed to be from the β position of the ketone substrate (Scheme 4.12).

Figure 4.2 Kinetic Profile Using 4-Methoxycarbonylphenyl Triflate[a]



[a]All the reactions were run with **1a** (0.1 mmol) in 1,4-dioxane (1.0 mL) for given reaction time. Yields were determined via NMR using 1,1,2,2-tetrachloroethane as the internal standard. All yields were based on **1a**. The trendlines were obtained through nonlinear curve fit.

Scheme 4.12 Deuterium Transfer from Ketone β Position to the Arene

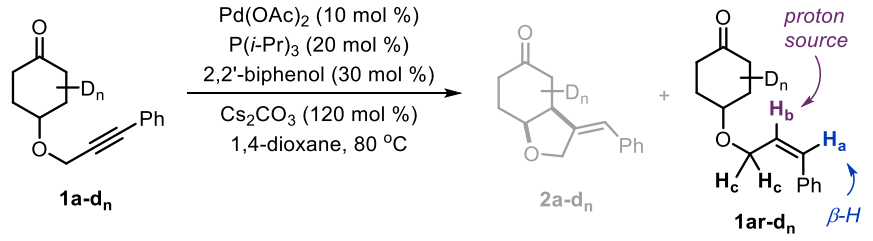


These results indicate that at the initial stage the aryl triflate serves as the oxidant to initiate

the reaction via a similar mechanism shown in Scheme 4.10 to generate the initial amount of enyne **1ai**. This could explain the existence of the induction period. One can imagine that Pd(0) would prefer to react with PhOTf (a stronger oxidant) rather than enyne **1ai** during the induction period, which leads to accumulation of the enyne intermediate. It also implies that (a) Pd(0) exists in the catalytic system and (b) aryl triflates could be employed as an effective oxidant for ketone desaturation. These observations are consistent with the Pd(0)-initiated catalytic cycle (**path c**).

Lastly, one remaining question is to understand the formation of the alkyne reduction side product (**1ar**). Deuterium track experiments were conducted using a slightly different set of conditions that gave higher yields of **1ar** (Table 4.7, entry 1). Interestingly, $\mathbf{H_a}$ in the reduction product arose almost only from the β position of ketone (entry 2), while $\mathbf{H_b}$ clearly came from proton sources (entry 3). In addition, no deuterium was found incorporated into the allylic position.

Table 4.7 Deuterium Labeling Studies on the Alkyne Reduction[a]



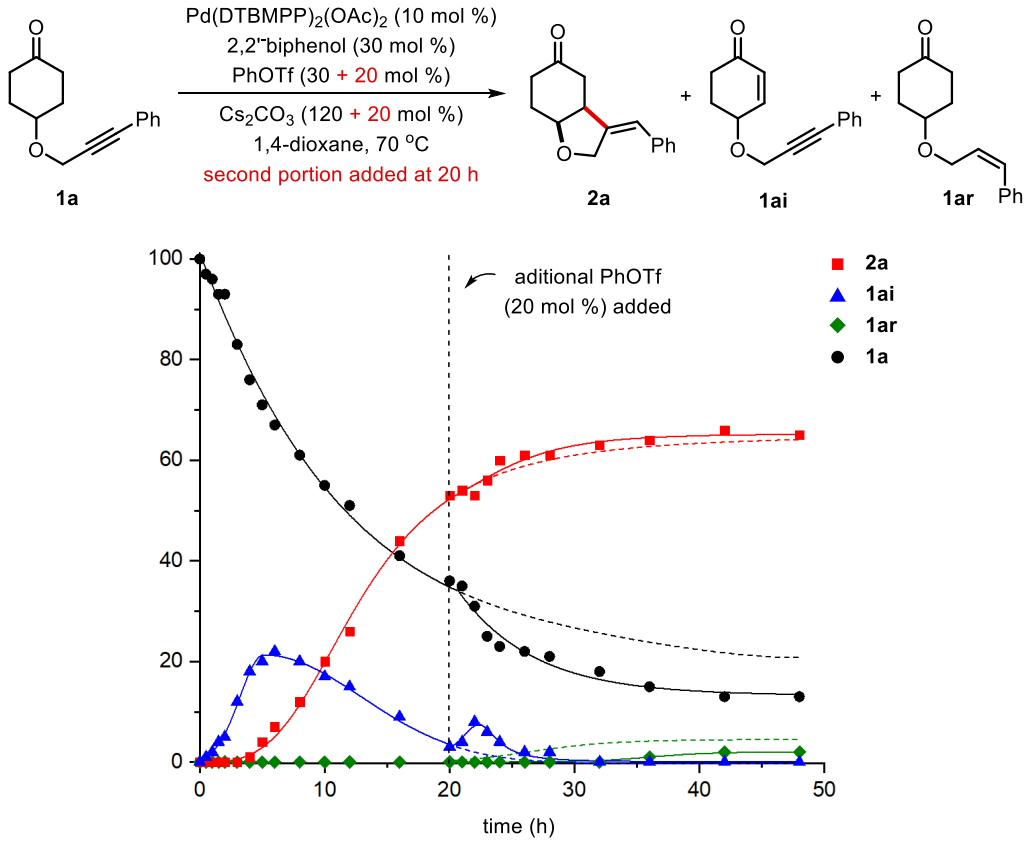
entry	substrate	yield of **2a-dₙ** (%)[b]	yield of **1ar-dₙ** (%)[b]	D incorporation ratio (%)[c] $\mathbf{H_a}$	$\mathbf{H_b}$	$\mathbf{H_c}$
1	**1a**	23	16	0	0	0
2	**1a-β-d₄**	19	10	88	0	0
3[d]	**1a-α-d₄**	10	5	0	58	0

[a]All the reactions were run with **1a** (0.1 mmol) in 1,4-dioxane (1.0 mL) for 48 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard. [c]NMR ratio determined from isolated product. [d]2,2'-Biphenol-d_2 was used instead of 2,2'-biphenol.

According to the kinetic study (Figure 4.1), **1ar** started to form when the enyne concentration was low, indicating a kinetic competition between enyne cyclometallation and alkyne reduction. Thus, we hypothesized that the alkyne reduction starts with addition of a Pd−H species (in equilibrium with Pd(0) and a proton)[20] to the alkyne, and the resulting alkenylpalladium species then undergoes a similar β-hydrogen transfer process (as in Scheme 4.10) to deliver the *cis*-alkene. The observed regioselectivity is consistent with this hypothesis, where during the Pd−H addition step Pd stays at the more stable benzylic position.[24]

It is noticeable that the alkyne reduction only started to occur when the enone concentration was sufficiently low, which was also the time when the product formation became very slow. Based on the proposed mechanism, we postulated that the reaction died with Pd(0) accumulation. We were then wondering if the reaction could be reinitiated by adding additional phenyl triflate at certain point. As the reduction was not observed in the first 20 h, the second portion of PhOTf (20 mol %) and Cs_2CO_3 (20 mol %, for neutralizing the additional acid) was added at 20 h. Indeed, the kinetic profile showed that the reaction system was activated again, leading to a drop of the substrate concentration, a new peak of enyne generation and a postponed alkyne reduction (Figure 4.3). These results further supported our proposed mechanism, where Pd(0) interacted with enyne to forge the β-C−C bond but accumulated when enyne was nearly consumed, while PhOTf helped regenerate enyne via Pd(II)-mediated ketone desaturation. Unfortunately, the second portion of PhOTf did not lead to the further improvement in the yield of the product, as more decomposition also occurred along with the product formation and overoxidation.

Figure 4.3 Kinetic Profile with Additional Portion of PhOTf[a]

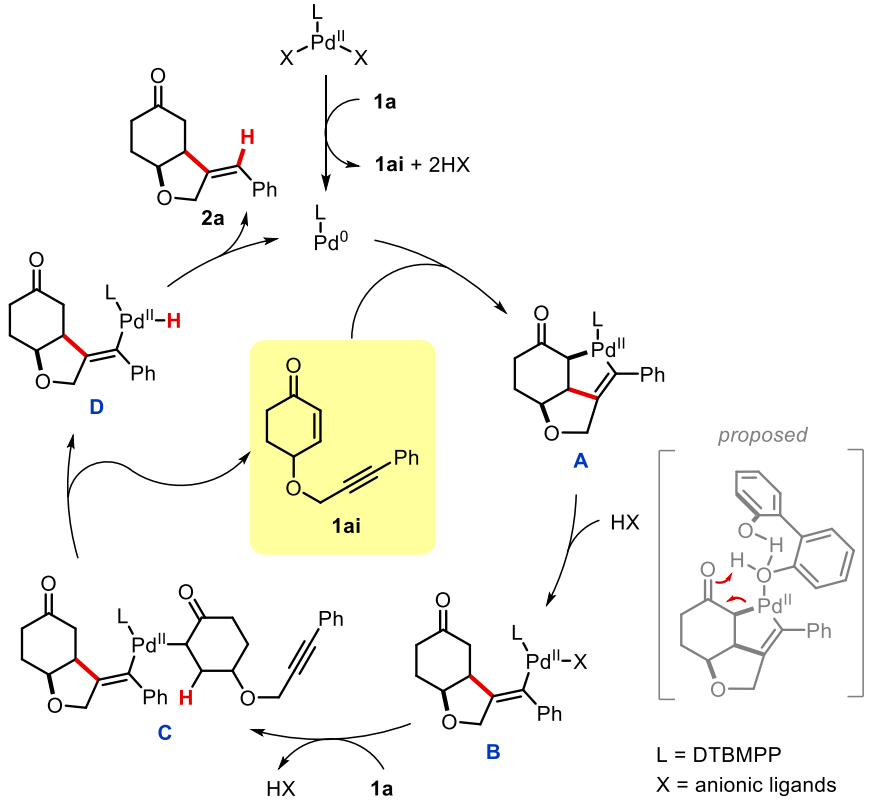


[a]All the reactions were run with **1a** (0.1 mmol) in 1,4-dioxane (1.0 mL) for given reaction time. Second portion of PhOTf (20 mol %) and Cs_2CO_3 (20 mol %) was added at 20 h. Yields were determined via NMR using 1,1,2,2-tetrachloroethane as the internal standard. The trendlines were obtained through nonlinear curve fit. Dotted lines represent the original kinetic profile without additional PhOTf.

While some mechanistic details of this reaction remain unclear, the data above allow us to propose a hypothesis for the main catalytic cycle (Scheme 4.13). The reaction is initiated by generation of active Pd(0) catalyst and enyne **1ai** via ketone desaturation. Cyclometallation followed by protonation of the enolate ligand gives an alkenylpalladium species **B** that can deprotonate another ketone substrate (**1a**). The subsequent β-hydrogen elimination regenerates enyne **1ai** and forms an alkenylpalladium hydride species **D**. Finally, C−H reductive elimination

gives the β-alkenylation product and regenerates the Pd(0) catalyst that can re-enter the cycle with enyne **1ai** as a chain-like mechanism. The alkenyl hydrogen in **2a** is ultimately transferred from the β-hydrogen of ketone, consistent with the proposed 'hydride-transfer' strategy. The role of 2,2'-biphenol is possibly to promote protonation from **A** to **B**.

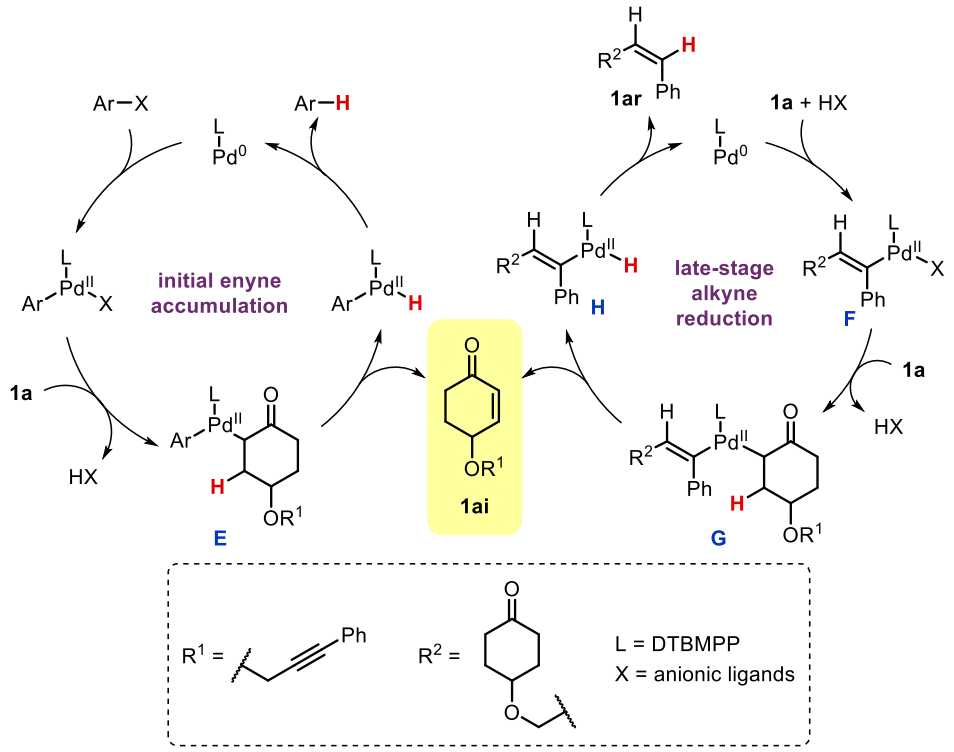
Scheme 4.13 Summary of the Proposed Mechanism for the Main Catalytic Cycle



In addition, two off-cycle pathways are responsible for the initial enyne accumulation and alkyne reduction (Scheme 4.14). During the induction period, Pd(0) would preferably undergo oxidative addition with aryl triflate (ArX) to give an arylpalladium species that effectively desaturates the ketone substrate. Subsequently, the normal catalytic cycle starts to convert enyne **1ai** and substrate **1a** to the β-alkenylation products. While in principle the enyne concentration should maintain constant, side reactions, such as over-desaturation of product **2a** to give **2aa** and

2ab or decomposition of **1ai** to phenol via elimination, would reduce the enyne concentration during the reaction. When the enyne concentration becomes very low, the alkyne reduction pathway would be triggered due to the equilibrium between Pd(0)/HX and X−Pd−H. This involves addition of Pd−H to the alkyne moiety and the resulting alkenylpalladium intermediate **F** can participate in another desaturation process. In this case, the alkyne moiety serves as a 'hydrogen acceptor' or an oxidant, leading to more enyne (and eventually product **2a**) formation at the late stage before the death of the catalyst.

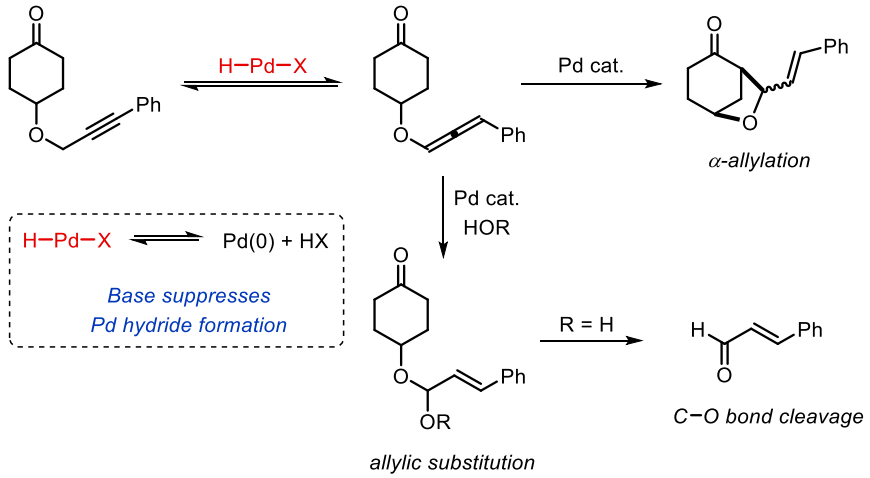
Scheme 4.14 Summary of the Proposed Mechanism for Two Off-Cycle Pathways



We postulated that the role of the base additive (Cs_2CO_3) could be to neutralize HOTf generated in the reaction and to balance the reaction acidity (Scheme 4.15). Major side reactions observed in the absence of base, e.g. ketone α-allylation[16] and C−O bond cleavage,[17] arise from

the undesired alkyne to allene isomerization, which is promoted by Pd−hydride species that stays in equilibrium with acid. Therefore, a basic environment is crucial to suppress the Pd−hydride formation, thus avoiding these side reactions.

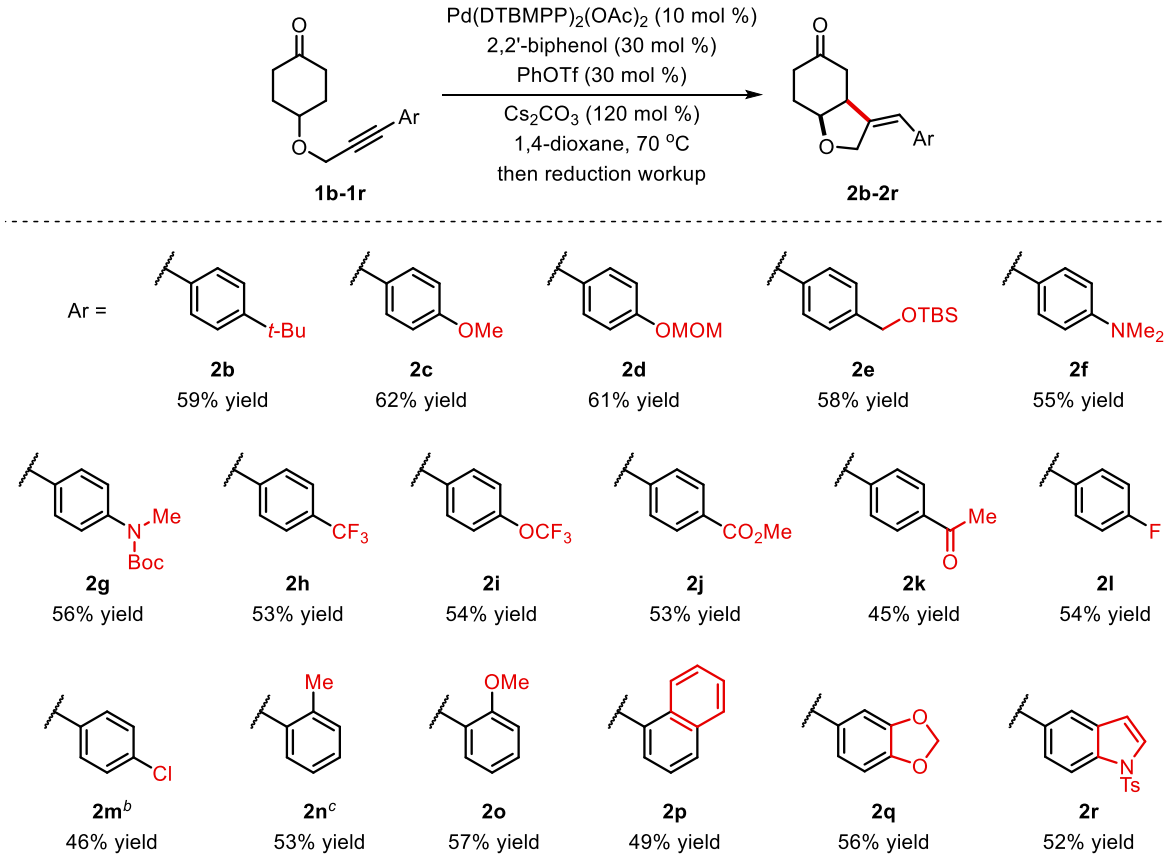
Scheme 4.15 Possible Pd−Hydride-Mediated Pathways for Side Reactions



4.2.3 Substrate scope for the β-ketone/alkyne coupling

The substrate scope of this transformation was then examined, starting with the functional group tolerance (Scheme 4.16). Substrates bearing either electron-rich (**2b**−**2g**) or electron-deficient (**2h**−**2m**) arenes are suitable for this reaction. Attributed to the relatively mild reaction conditions, a wide range of functional groups were tolerated, including methyl ether (**2c**), MOM (**2d**), TBS ether (**2e**), tertiary amine (**2f**), carbamate (**2g**), ester (**2j**), ketone (**2k**) and aryl halides (**2l**, **2m**). The reaction is not sensitive to steric hindrance on the arene, as both *ortho*-substituted phenyl (**2n**, **2o**) and 1-naphthyl (**2p**) groups delivered the β-alkenylation product in satisfactory yields. Heterocyclic moieties are also compatible, such as 1,3-benzodioxole (**2q**) and Ts-protected indole (**2r**).

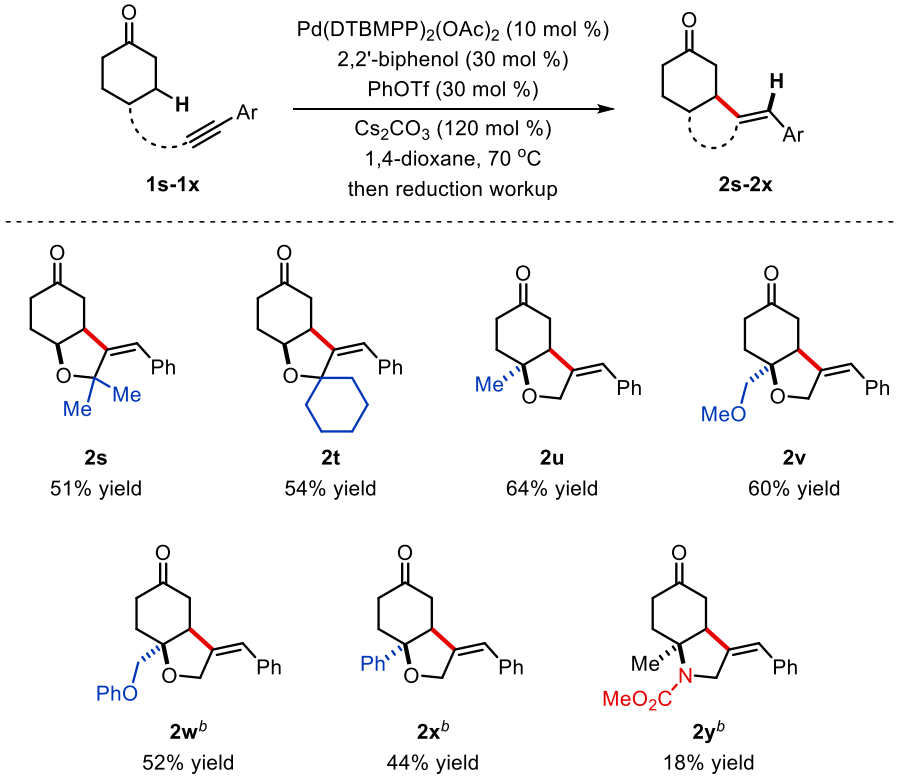
Scheme 4.16 Functional Group Tolerance of the β-Ketone/Alkyne Coupling[a]



[a]Unless otherwise noted, all the reactions were run with **1** (1.0 mmol) in 1,4-dioxane (1.0 mL) for 48 h. All yields refer to the isolation yields. [b]Dechlorination product (**2a**) was observed in 5% yield. [c]Reaction was run for 72 h.

In addition, substrates bearing other linkages and substitution patterns could also undergo the transformation (Scheme 4.17). Interestingly, substituents on the propargylic position does not significantly influence the reactivity (**2s**, **2t**), which also excludes the involvement of alkyne to allene isomerization in the productive pathway.[16] Furthermore, C4-alkyl and aryl substituted cyclohexanones (**2u**−**2x**) were also suitable substrates. Besides oxygen linkers, a nitrogen-tethered substrate also delivered the desired bicyclic product, albeit in a lower yield (**2y**).

Scheme 4.17 Structural Variation of the Substrates for the β-Ketone/Alkyne Coupling[a]

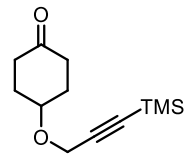


[a]Unless otherwise noted, all the reactions were run with **1** (1.0 mmol) in 1,4-dioxane (1.0 mL) for 48 h. All yields refer to the isolation yields. [b]Reactions were run for 60 h.

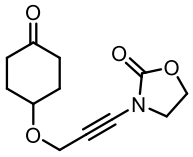
Unfortunately, the current reaction conditions were relatively restricted to these types of substrate structures. Other types of linkers or ketone substrates exhibit low reactivity likely due to the difficulties of the desaturation or enyne cyclometallation step (Scheme 4.18). Replacing the phenyl substituent with silyl, acylamino or alkyl groups led to poor results (**1z**–**1ab**). Interestingly, enyne generation was observed for **1z** but no cyclization product was formed, indicating that the cyclometallation step was inhibited by the silyl protecting group. Introduced steric hindrance on the β position of ketone caused low reactivity (**1ac**). Nitrogen linkage without a C4-substutient on cyclohexanone gave further lower yield (**1ad**). Substrates with all-carbon linkages turned out to

be sluggish as well. The simple ethylene linkage suffered from isomerization to diene, likely via allene intermediacy (**1ae**). This indicated that alkyne/allene isomerization actually exists in the reaction system, but alkyne is still favored if diene formation is prohibited. Therefore, substrates

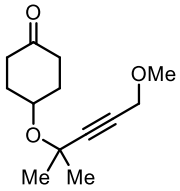
Scheme 4.18 Selected Challenging Substrates for the β-Ketone/Alkyne Coupling



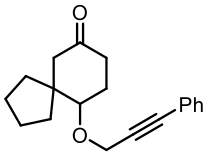
1z
0% yield
78% unreacted **1z**
15% enyne formation



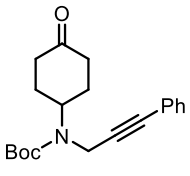
1aa
0% yield
15% unreacted **1aa**



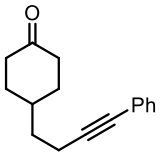
1ab
7% yield
42% unreacted **1ab**



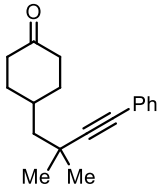
1ac
5% yield
73% unreacted **1ac**



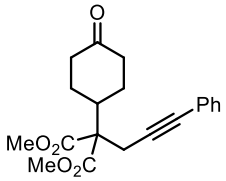
1ad
9% yield
64% unreacted **1ad**



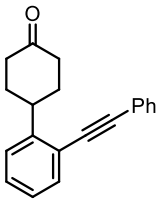
1ae
0% yield
isomerized to diene



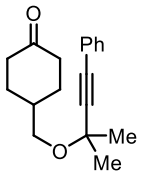
1af
4% yield
94% unreacted **1af**



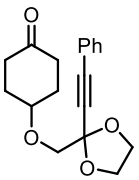
1ag
0% yield
41% unreacted **1ag**



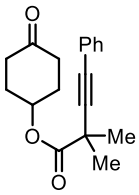
1ah
0% yield
79% unreacted **1ah**



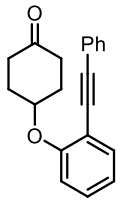
1aj
0% yield
89% unreacted **1aj**



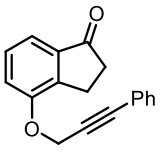
1ak
0% yield
84% unreacted **1ak**
14% enyne formation



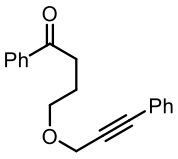
1al
0% yield
87% unreacted **1al**
5% enyne formation



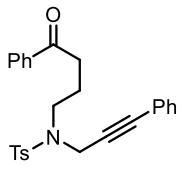
1am
0% yield
97% unreacted **1am**



1an
0% yield
39% unreacted **1an**



1ao
0% yield
59% unreacted **1ao**

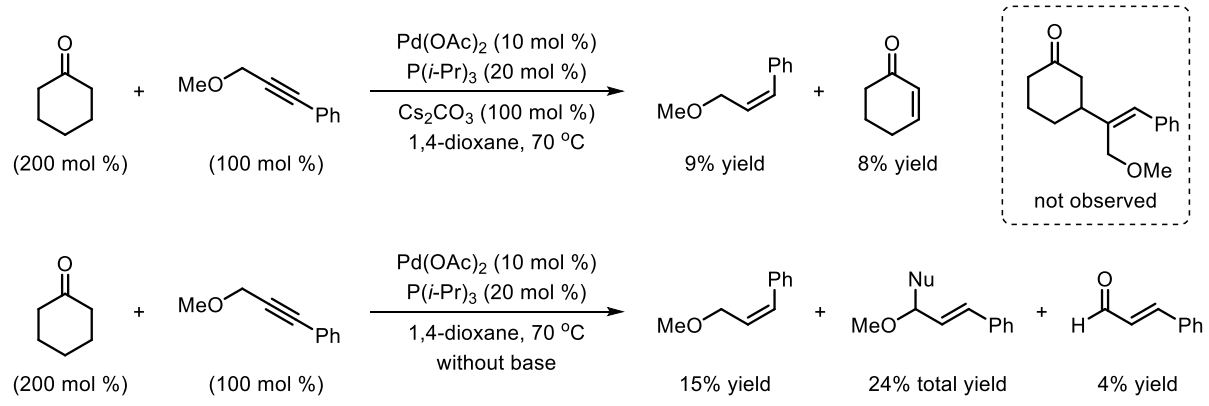


1ap
0% yield
100% unreacted **1ap**

with propargylic *gem*-dimethyl (**1af**), homopropargylic *gem*-diester (**1ag**) and benzene linkage (**1ah**) were synthesized, but unfortunately none of them exhibited good reactivity. Substrates with three-atom linkage would potentially cyclize to form a six-membered ring, but the corresponding cyclometallation step seemed challenging given the observed enyne formation for some substrates (**1aj**−**1am**). Five-membered ring ketones (**1an**) and linear ketones (**1ao**, **1ap**) likely suffered from sluggish ketone desaturation.

Moreover, attempts to realize intermolecular β-alkenylation of ketones using alkynes have been made, though it has been even more challenging (Scheme 4.19). In a representative example, the C−C bond formation product was not observed, while ketone desaturation and alkyne reduction both occurred, suggesting that the intermolecular cyclometallation step was sluggish without a proximity effect. In addition, decomposition of the alkyne substrate was detected in the absence of base, including allylic substitution and C−O cleavage, which was consistent with the results obtained using alkyne-tethered ketones.

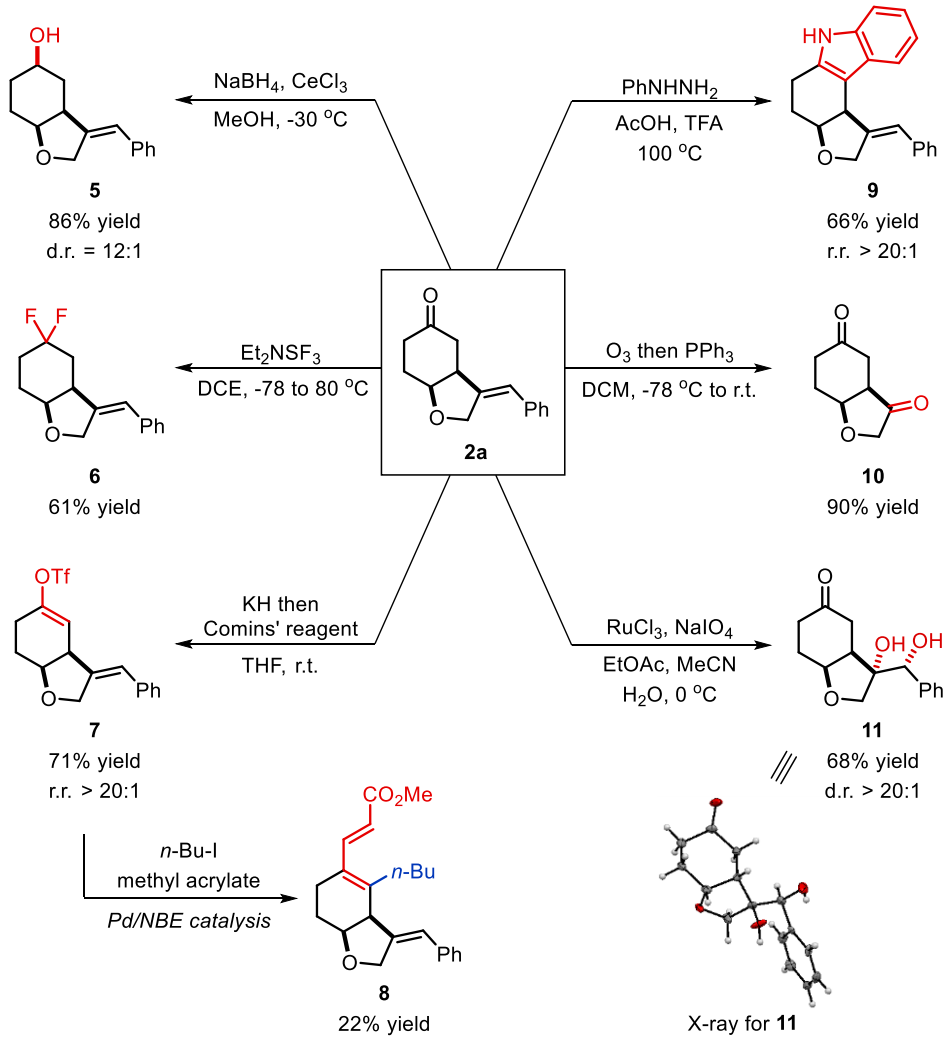
Scheme 4.19 Attempts for the Intermolecular β-Ketone/Alkyne Coupling



4.2.4 Derivatization of the bicyclic product

Containing both the ketone and alkene moieties, the β-alkenylation product could undergo various transformations, leading to synthetically valuable products (Scheme 4.20). For example, the carbonyl group could be selectively converted to the corresponding alcohol (**5**) or *gem*-difluoro group (**6**). Notably, enolization took place selectively at the more sterically hindered site, likely due to the *cis*-5,6-fused bicyclic structure.[25] This led to the synthesis of an indole-derived tetracycle

Scheme 4.20 Transformations of Bicyclic Product **2a**



(**9**) and alkenyl triflate (**7**) with complete regioselectivity. In addition, alkenyl triflate **7** could be converted to an all-carbon tetrasubstituted olefin (**8**) in one step via Pd/norbornene (NBE) catalysis.[26] Furthermore, the olefin could undergo ozonolysis to give diketone **10** or dihydroxylation to provide vicinal diol **11** exclusively from the convex face, and the relative configuration of diol **11** has been elucidated by X-ray crystallography.

4.3 Conclusion

In summary, a new reaction mode for direct β-alkenylation of ketones via a formal C(sp^3)−H/alkyne coupling has been discovered. The method is capitalized on a Pd-catalyzed hydride-transfer strategy, which is distinct from other β-functionalization approaches. The reaction operates at relatively mild conditions and avoids the use of strong acids or bases; it is also overall redox-neutral without the need of stoichiometric oxidants or reductants, thus showing excellent functional group tolerance. Mechanistic studies reveal several interesting features of this reaction, which include an ArOTf-mediated ketone desaturation during the induction period and a chain-like enyne cyclization via transfer hydrogenation. While the yields and scope of the reaction remain to be further improved, the concept of merging ketone desaturation with a constructive C−C-forming event using readily available 2π units should have broad implications.

Further development could focus on revised strategies to enable more efficient couplings of carbonyl compounds with various unsaturated 2π units. For example, nickel could be a more effective catalyst for this transformation with opportunities to realize intermolecular β-

ketone/alkyne couplings, since nickel has shown higher catalytic reactivity in reductive enyne cyclometallation reactions, including intermolecular ones;[21] meanwhile, Ni-enolate formation under mild reaction conditions[27] and Ni-catalyzed carbonyl desaturation via β-hydrogen elimination[28] have both been proved feasible. In addition, the originally proposed metal−hydride addition pathway could also be achievable, which might be benefited by more stable metal−hydride species such as platinum or iridium, or facilitated by more efficient ketone desaturation via enamine catalysis that also brings chances for enantioselective transformations.[29]

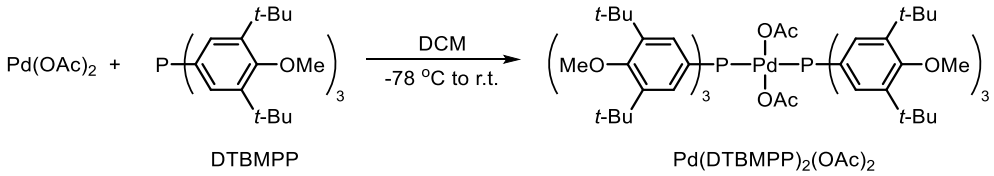
4.4 Experimental Section

4.4.1 General information

Unless otherwise noted, all reactions were carried out in 8-mL culture tubes sealed with PTFE lined caps. 1,4-Dioxane was distilled over sodium and freeze-pump-thawed three times before use. $Pd(DTBMPP)_2(OAc)_2$ was prepared according to the following procedure. 2,2'-Biphenol and phenyl triflate were purchased from Sigma-Aldrich. Cs_2CO_3 was purchased from Strem and stored in the glovebox. All commercially available substrates were used without further purification. Thin layer chromatography (TLC) analysis was run on silica gel plates purchased from EMD Chemical (silica gel 60, F254). 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 Model DMX 400 (400 MHz, ^{1}H at

400 MHz, ^{13}C at 101 MHz). For $CDCl_3$ solutions, the chemical shifts were 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 (77.00 ppm). Coupling constants were reported in Hertz (Hz). Data for ^1H NMR spectra were reported as following: chemical shift (δ, ppm), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet), coupling constant (Hz), and integration.

4.4.2 Synthesis and characterization of the catalyst

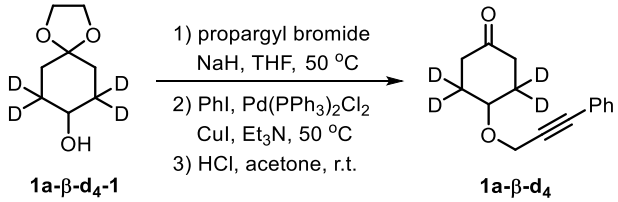


Bis(tris(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphane)palladium diacetate: A Schlenk flask was flame-dried and charged with $Pd(OAc)_2$ (1 equiv., 10 mmol, 2.25 g). The flask was refilled with N_2, and DCM (20 mL) was added via syringe. The mixture was cooled to -78 °C. DTBMPP[16] (2 equiv., 20 mmol, 13.8 g) was dissolved in DCM (20 mL), and the solution was added dropwise to the flask via syringe over 15 min. The mixture was stirred at -78 °C for 1 h and slowly returned to room temperature. The mixture was further stirred at room temperature for 1 h before concentrated *in vacuo*. MeOH was added to the residue, and the mixture was vigorously stirred to allow the precipitation of a light-yellow solid. The mixture was filtered and washed with MeOH. The solid was dried *in vacuo* to give the catalyst as a light-yellow solid in 93% yield. The catalyst is stable to air and moisture. **^1H NMR** (400 MHz, $CDCl_3$) δ 7.37 (t, J = 5.6 Hz, 12H), 3.65

(s, 18H), 1.29 (s, 108H), 1.06 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.24, 160.95, 143.12 (t, J = 5.1 Hz), 132.95 (t, J = 7.0 Hz), 125.06 (t, J = 23.8 Hz), 64.25, 35.84, 31.96, 23.00. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 11.37. **HRMS** calcd $C_{94}H_{144}NaO_{10}P_2Pd$ $[M+Na]^+$: 1623.9162. Found: 1623.9160.

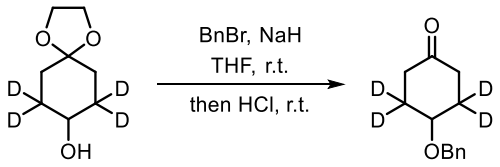
4.4.3 Synthesis and characterization of the substrates

Compounds **1a**, **1a-α-d$_4$**, **1b**, **1c**, **1h**, **1i**, **1j**, **1k**, **1l**, **1m**, **1n**, **1o**, **1p**, **1q** and **1r** were synthesized according to the literature procedures, and the characterization data are included therein.[16] Compounds **1a-β-d$_4$**, **3-β-d$_4$**, **1ai**, **1d**, **1e**, **1f**, **1g**, **1s**, **1t**, **1u**, **1v**, **1w**, **1x** and **1y** were prepared according to the following procedures.



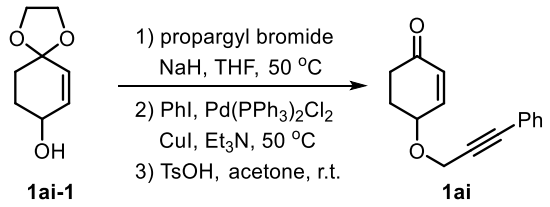
4-((3-Phenylprop-2-yn-1-yl)oxy)cyclohexan-1-one-3,3,5,5-*d*$_4$ (1a-β-d$_4$): A Schlenk flask was flame-dried and charged with NaH (60% in oil, 1.5 equiv., 15 mmol, 600 mg). The flask was refilled with N_2, and THF (40 mL) was added via syringe. The mixture was then cooled to 0 °C. **1a-β-d$_4$-1**[30] (1 equiv., 10 mmol, 1.62 g) was dissolved in THF (10 mL), and the solution was added to the flask via syringe dropwise at 0 °C. The resulting mixture was stirred at room temperature for 30 min and then cooled to 0 °C. Propargyl bromide (80% in toluene, 1.25 equiv., 12.5 mmol, 1.86 g) was added dropwise via syringe, and the mixture was heated to 50 °C overnight. After cooling to room temperature, the mixture was quenched with saturated NH_4Cl solution and

extracted with diethyl ether. The combined organic layers were washed with brine, dried and concentrated. The residue was filtered through a short plug of silica gel and eluted with a solution containing hexane/EtOAc (1:1). The filtrate was concentrated, and the residue was directly used in the next step without further purification (ca. 5 mmol crude product). A Schlenk flask was flame-dried and charged with $Pd(PPh_3)_2Cl_2$ (2 mol %, 0.1 mmol, 70 mg) and CuI (1 mol %, 0.05 mmol, 9.5 mg). The flask was refilled with N_2. The crude product from the previous step (1 equiv., ca. 5 mmol) and iodobenzene (1.1 equiv., 5.5 mmol, 615 μL) were dissolved in triethylamine (20 mL), and the solution was added via syringe. The mixture was heated at 50 °C overnight. After cooling to room temperature, the mixture was diluted with diethyl ether and filtered. The filtrate was concentrated, and the residue was dissolved in acetone (12.5 mL) and 3 M HCl (12.5 mL). The mixture was stirred at room temperature for 6 h. The mixture was basified with saturated $NaHCO_3$ solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried and concentrated. The residue was purified by column chromatography to give **1a-β-d_4** as a colorless oil in 36% yield (836 mg) over 3 steps. >99% D. R_f = 0.4 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.41 (m, 2H), 7.36 – 7.29 (m, 3H), 4.48 (s, 2H), 4.03 (s, 1H), 2.62 (d, *J* = 14.8 Hz, 2H), 2.29 (d, *J* = 14.8 Hz, 2H). **^{2}H NMR** (77 MHz, $CHCl_3$) δ 2.16 (2D), 1.99 (2D). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.16, 131.71, 128.54, 128.31, 122.45, 86.04, 85.16, 71.82, 56.47, 36.96, 29.67 (p, *J* = 19.5 Hz). **IR** (KBr, cm^{-1}) 2960, 2208, 1715, 1490, 1280, 1091, 759. **HRMS** calcd $C_{15}H_{13}D_4O_2$ $[M+H]^+$: 233.1474. Found: 233.1479.



1a-β-d_4-1 **3-β-d_4**

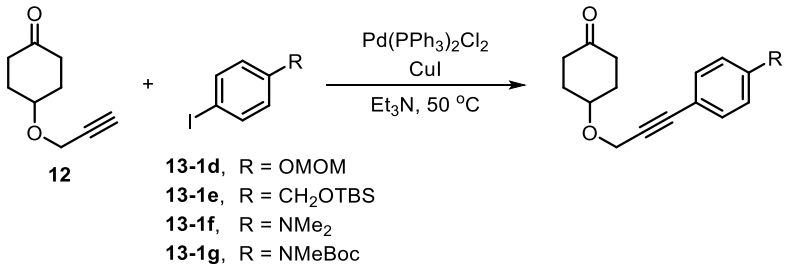
8-(Benzyloxy)-1,4-dioxaspiro[4.5]decane-7,7,9,9-*d*$_4$ (3-β-d$_4$): A Schlenk flask was flame-dried and charged with NaH (60% in oil, 2 equiv., 12 mmol, 480 mg). The flask was refilled with N_2, and THF (12 mL) was added via syringe. The mixture was then cooled to 0 °C. **1a-β-d$_4$-1**[30] (1 equiv., 6 mmol, 972 mg) was dissolved in THF (4 mL), and the solution was added to the flask via syringe dropwise at 0 °C. The resulting mixture was stirred at room temperature for 1 h and then cooled to 0 °C. Benzyl bromide (1.2 equiv., 7.2 mmol, 856 μL) was added dropwise via syringe, and the mixture was stirred at room temperature for 24 h. The mixture was quenched with saturated NH_4Cl solution, and then 3 M HCl (12 mL) was added to the flask. The mixture was further stirred at room temperature for 6 h. The mixture was basified with saturated $NaHCO_3$ solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried and concentrated. The residue was purified by column chromatography to give **1a-β-d$_4$** as a colorless oil in 75% yield (939 mg). >99% D. R_f = 0.4 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 4.60 (s, 2H), 3.81 (s, 1H), 2.61 (d, *J* = 14.7 Hz, 2H), 2.26 (d, *J* = 14.8 Hz, 2H). **^{2}H NMR** (77 MHz, $CHCl_3$) δ 2.15 (2D), 1.96 (2D). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.32, 138.45, 128.41, 127.61, 127.39, 71.94, 70.22, 36.99, 29.75 (p, *J* = 20.1 Hz). **IR** (KBr, cm^{-1}) 2863, 2208, 1714, 1280, 1095, 738. **HRMS** calcd $C_{13}H_{13}D_4O_2$ $[M+H]^+$: 209.1474. Found: 209.1471.



4-((3-Phenylprop-2-yn-1-yl)oxy)cyclohex-2-en-1-one (1ai): A Schlenk flask was flame-dried and charged with NaH (60% in oil, 1.5 equiv., 7.5 mmol, 300 mg). The flask was refilled with N_2, and THF (20 mL) was added via syringe. The mixture was then cooled to 0 °C. **1ai-1**[31] (1 equiv., 5 mmol, 780 mg) was dissolved in THF (5 mL), and the solution was added to the flask via syringe dropwise at 0 °C. The resulting mixture was stirred at room temperature for 30 min and then cooled to 0 °C. Propargyl bromide (80% in toluene, 1.25 equiv., 6.25 mmol, 930 mg) was added dropwise via syringe, and the mixture was heated to 50 °C overnight. After cooling to room temperature, the mixture was quenched with saturated NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried and concentrated. The residue was filtered through a short plug of silica gel and eluted with a solution containing hexane/EtOAc (1:1). The filtrate was concentrated, and the residue was directly used in the next step without further purification (ca. 4.6 mmol crude product). A Schlenk flask was flame-dried and charged with $Pd(PPh_3)_2Cl_2$ (2 mol %, 0.092 mmol, 64 mg) and CuI (1 mol %, 0.046 mmol, 8.8 mg). The flask was refilled with N_2. The crude product from the previous step (1 equiv., ca. 4.6 mmol) and iodobenzene (1.1 equiv., 5.1 mmol, 572 μL) were dissolved in triethylamine (18 mL), and the solution was added via syringe. The mixture was heated at 50 °C overnight. After cooling to room temperature, the mixture was diluted with diethyl ether and filtered. The filtrate was concentrated, and the residue was dissolved in acetone (37.5 mL) and water (2.5 mL). $TsOH{\cdot}H_2O$ (10 mol %,

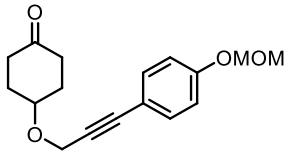
0.46 mmol, 88 mg) was added, and the mixture was stirred at room temperature for 3 h. The mixture was basified with saturated $NaHCO_3$ solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried and concentrated. The residue was purified by column chromatography to give **1ai** as a light-yellow solid in 75% yield (844 mg) over 3 steps. Melting point = 51 – 53 °C. R_f = 0.4 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.41 (m, 2H), 7.38 – 7.29 (m, 3H), 7.03 (ddd, *J* = 10.3, 2.6, 1.5 Hz, 1H), 6.02 (ddd, *J* = 10.3, 2.0, 0.9 Hz, 1H), 4.64 – 4.39 (m, 3H), 2.78 – 2.54 (m, 1H), 2.52 – 2.31 (m, 2H), 2.15 – 1.91 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.58, 150.04, 131.75, 129.90, 128.71, 128.36, 122.23, 86.80, 84.48, 72.04, 57.02, 35.19, 28.94. **IR** (KBr, cm^{-1}) 2955, 2236, 1687, 1490, 1250, 1088, 865. **HRMS** calcd $C_{15}H_{15}O_2$ $[M+H]^+$: 227.1067. Found: 227.1070.

Compounds **1d**, **1e**, **1f** and **1g** were synthesized according to the following general procedure:



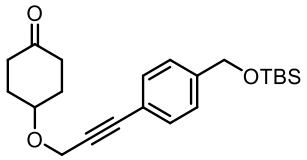
A Schlenk flask was flame-dried and charged with $Pd(PPh_3)_2Cl_2$ (2 mol %, 0.02 mmol, 14.0 mg), CuI (1 mol %, 0.01 mmol, 1.9 mg), **12**[16] (1 equiv., 1 mmol, 152 mg) and **13** (1.1 equiv., 1.1 mmol). The flask was refilled with N_2, and triethylamine (4 mL) was added via syringe. The mixture was heated at 50 °C overnight. After cooling to room temperature, the mixture was diluted

with diethyl ether and filtered. The filtrate was concentrated, and the residue was purified by column chromatography to give the product.



1d

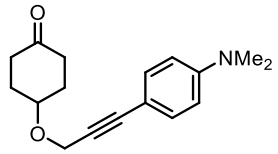
4-((3-(4-(Methoxymethoxy)phenyl)prop-2-yn-1-yl)oxy)cyclohexan-1-one (1d): Synthesized from **12**[16] and **13-1d**[32]. 72% Yield (208 mg). Light-yellow solid. Melting point = 52 – 54 ºC. R_f = 0.4 (hexane/EtOAc = 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.33 (m, 2H), 7.04 – 6.93 (m, 2H), 5.18 (s, 2H), 4.46 (s, 2H), 4.03 (tt, *J* = 5.8, 3.0 Hz, 1H), 3.47 (s, 3H), 2.72 – 2.52 (m, 2H), 2.38 – 2.26 (m, 2H), 2.23 – 2.10 (m, 2H), 2.06 – 1.93 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.08, 157.39, 133.18, 116.12, 115.74, 94.22, 85.86, 84.00, 71.97, 56.53, 56.09, 37.17, 30.42. **IR** (KBr, cm^{-1}) 2952, 2235, 1712, 1605, 1508, 1237, 1081, 995. **HRMS** calcd $C_{17}H_{21}O_4$ $[M+H]^+$: 289.1434. Found: 289.1435.



1e

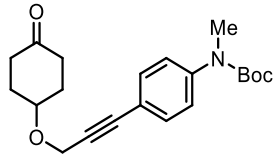
4-((3-(4-(((*tert*-Butyldimethylsilyl)oxy)methyl)phenyl)prop-2-yn-1-yl)oxy)cyclohexan-1-one (1e): Synthesized from **12**[16] and **13-1e**[33]. 79% Yield (294 mg). Yellow oil. R_f = 0.7 (hexane/EtOAc = 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 – 7.38 (m, 2H), 7.35 – 7.15 (m, 2H), 4.73 (s, 2H), 4.47 (s, 2H), 4.04 (tt, *J* = 5.7, 3.0 Hz, 1H), 2.63 (ddd, *J* = 15.5, 10.5, 5.7 Hz, 2H), 2.40 – 2.22 (m, 2H), 2.26 – 2.10 (m, 2H), 2.07 – 1.94 (m, 2H), 0.94 (s, 9H), 0.10 (s, 6H). **^{13}C NMR**

(101 MHz, $CDCl_3$) δ 211.08, 142.11, 131.63, 125.87, 120.86, 86.16, 84.73, 72.03, 64.57, 56.53, 37.17, 30.43, 25.90, 18.38, -5.29. **IR** (KBr, cm^{-1}) 2954, 2856, 2244, 1714, 1259, 1091, 839. **HRMS** calcd $C_{22}H_{33}O_3Si$ $[M+H]^+$: 373.2193. Found: 373.2190.



1f

4-((3-(4-(Dimethylamino)phenyl)prop-2-yn-1-yl)oxy)cyclohexan-1-one (1f): Synthesized from **12**[16] and **13-1f** (commercially available). The reaction was conducted with $Pd(PPh_3)_2Cl_2$ (10 mol %, 0.1 mmol, 70.1 mg) and CuI (5 mol %, 0.05 mmol, 9.5 mg) at room temperature for 24 h. 50% Yield (136 mg). Off-white solid. Melting point = 77 – 79 °C. R_f = 0.5 (hexane/EtOAc = 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 6.73 – 6.56 (m, 2H), 4.46 (s, 2H), 4.04 (tt, *J* = 5.8, 3.0 Hz, 1H), 2.97 (s, 6H), 2.63 (ddd, *J* = 14.8, 10.3, 5.7 Hz, 2H), 2.42 – 2.25 (m, 2H), 2.21 – 2.10 (m, 2H), 2.05 – 1.92 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.27, 150.23, 132.88, 111.68, 109.13, 87.10, 82.80, 71.72, 56.70, 40.16, 37.22, 30.45. **IR** (KBr, cm^{-1}) 2937, 2207, 1712, 1608, 1522, 1356, 1061, 819. **HRMS** calcd $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1645. Found: 272.1646.

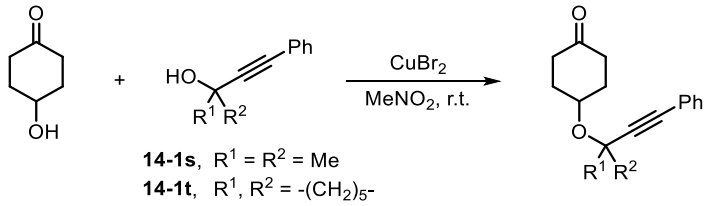


1g

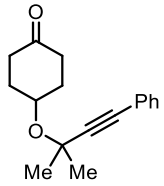
***tert*-Butyl methyl(4-(3-((4-oxocyclohexyl)oxy)prop-1-yn-1-yl)phenyl)carbamate (1g)**: Synthesized from **12**[16] and **13-1g**[34]. 74% Yield (265 mg). Yellow oil. R_f = 0.5 (hexane/EtOAc =

2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.35 (m, 2H), 7.24 – 7.16 (m, 2H), 4.47 (s, 2H), 4.03 (tt, *J* = 5.7, 3.0 Hz, 1H), 3.26 (s, 3H), 2.63 (ddd, *J* = 14.9, 10.5, 5.7 Hz, 2H), 2.37 – 2.24 (m, 2H), 2.22 – 2.12 (m, 2H), 2.06 – 1.94 (m, 2H), 1.46 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.02, 154.34, 143.97, 131.96, 124.97, 119.00, 85.71, 85.01, 80.71, 72.07, 56.50, 37.14, 36.98, 30.40, 28.27. **IR** (KBr, cm^{-1}) 2974, 2244, 1702, 1510, 1347, 1152, 842. **HRMS** calcd $C_{21}H_{27}NNaO_4$ $[M+Na]^+$: 380.1832. Found: 380.1831.

Compounds **1s** and **1t** were synthesized according to the following general procedure:

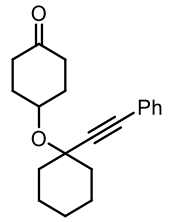


A Schlenk flask was flame-dried and charged with $CuBr_2$ (5 mol %, 0.05 mmol, 11.2 mg). The flask was refilled with N_2. 4-Hydroxycyclohexanone (3 equiv., 3 mmol, 342 mg) and **14** (1 equiv., 1 mmol, 160 mg) were dissolved in nitromethane (4 mL), and the solution was added to the flask via syringe. The mixture was stirred at room temperature overnight. The mixture was then diluted with diethyl ether and filtered. The filtrate was concentrated, and the residue was purified by column chromatography to give the product.



1s

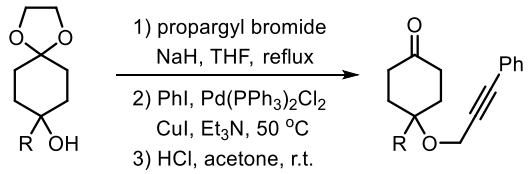
4-((2-Methyl-4-phenylbut-3-yn-2-yl)oxy)cyclohexan-1-one (1s): Synthesized from **14-1s** (commercially available). 51% Yield (131 mg). White solid. Melting point = 40 – 41 °C. R_f = 0.6 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2H), 7.34 – 7.29 (m, 3H), 4.25 (tt, *J* = 6.2, 3.3 Hz, 1H), 2.85 – 2.52 (m, 2H), 2.30 (dtd, *J* = 14.7, 5.7, 1.3 Hz, 2H), 2.16 – 1.96 (m, 4H), 1.58 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.83, 131.50, 128.32, 128.28, 122.73, 92.02, 83.40, 70.71, 68.43, 37.71, 33.10, 29.79. **IR** (KBr, cm^{-1}) 2982, 2249, 1716, 1276, 1154, 692. **HRMS** calcd $C_{17}H_{20}NaO_2$ $[M+Na]^+$: 279.1356. Found: 279.1353.



1t

4-((1-(Phenylethynyl)cyclohexyl)oxy)cyclohexan-1-one (1t): Synthesized from **14-1t** (commercially available). 35% Yield (105 mg). Colorless oil. R_f = 0.6 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 2H), 7.35 – 7.29 (m, 3H), 4.33 (tt, *J* = 6.1, 3.2 Hz, 1H), 2.82 – 2.56 (m, 2H), 2.30 (dtd, *J* = 14.6, 5.6, 1.3 Hz, 2H), 2.11 (dq, *J* = 12.2, 6.1 Hz, 2H), 2.06 – 1.95 (m, 4H), 1.79 – 1.48 (m, 7H), 1.42 – 1.27 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 212.03, 131.52, 128.33, 128.23, 122.91, 91.27, 85.53, 74.32, 67.69, 38.32, 37.75, 33.24, 25.44, 23.06. **IR** (KBr, cm^{-1}) 2935, 2857, 1715, 1443, 1069, 757. **HRMS** calcd $C_{20}H_{25}O_2$ $[M+H]^+$: 297.1849. Found: 297.1851.

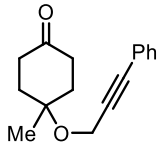
Compounds **1u**, **1v**, **1w** and **1x** were synthesized according to the following general procedure:



15-1u, R = Me
15-1v, R = CH_2OMe
15-1w, R = CH_2OPh
15-1x, R = Ph

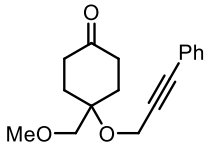
A Schlenk flask was flame-dried and charged with NaH (60% in oil, 2 equiv.). The flask was refilled with N_2, and THF (0.2 mL/mmol) was added via syringe. The mixture was then cooled to 0 °C. **15** (1 equiv.) was dissolved in THF (0.8 mL/mmol), and the solution was added to the flask via syringe dropwise at 0 °C. The resulting mixture was stirred at room temperature for 30 min and then cooled to 0 °C. Propargyl bromide (80% in toluene, 2 equiv.) was added dropwise via syringe, and the mixture was heated to reflux overnight. After cooling to room temperature, the mixture was quenched with saturated NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried and concentrated. The residue was filtered through a short plug of silica gel and eluted with a solution containing hexane/EtOAc (1:1). The filtrate was concentrated, and the residue was directly used in the next step without further purification. A Schlenk flask was flame-dried and charged with $Pd(PPh_3)_2Cl_2$ (2 mol %) and CuI (1 mol %). The flask was refilled with N_2. The crude product from the previous step (1 equiv.) and iodobenzene (1.1 equiv.) were dissolved in triethylamine (4 mL/mmol), and the solution was added via syringe. The mixture was heated at 50 °C overnight. After cooling to room temperature, the mixture was diluted with diethyl ether and filtered. The filtrate was concentrated, and the residue

was dissolved in acetone (2.5 mL/mmol) and 3 M HCl (2.5 mL/mmol). The mixture was stirred at room temperature for 6 h. The mixture was basified with saturated $NaHCO_3$ solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried and concentrated. The residue was purified by column chromatography to give the product.



1u

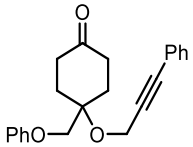
4-Methyl-4-((3-phenylprop-2-yn-1-yl)oxy)cyclohexan-1-one (1u): Synthesized from **15-1u**[35] (10 mmol scale). 13% Yield (312 mg) over 3 steps. Colorless oil. R_f = 0.4 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 2H), 7.35 – 7.28 (m, 3H), 4.41 (s, 2H), 3.01 – 2.67 (m, 2H), 2.38 – 1.99 (m, 4H), 1.85 – 1.68 (m, 2H), 1.36 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.82, 131.64, 128.43, 128.27, 122.59, 86.27, 85.19, 73.60, 51.00, 36.94, 36.05, 24.16. **IR** (KBr, cm^{-1}) 2967, 1712, 1490, 1381, 1124, 1058, 758. **HRMS** calcd $C_{16}H_{19}O_2$ $[M+H]^+$: 243.1380. Found: 243.1380.



1v

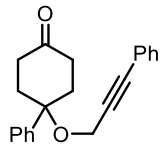
4-(Methoxymethyl)-4-((3-phenylprop-2-yn-1-yl)oxy)cyclohexan-1-one (1v): Synthesized from **15-1v**[36] (6.2 mmol scale). 22% Yield (373 mg) over 3 steps. Light-yellow solid. Melting point = 61 – 63 °C. R_f = 0.4 (hexane/EtOAc = 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.39 (m, 2H), 7.35 – 7.26 (m, 3H), 4.53 (s, 2H), 3.49 (s, 2H), 3.40 (s, 3H), 2.94 – 2.68 (m, 2H),

2.43 – 2.19 (m, 4H), 1.75 (td, *J* = 14.8, 14.3, 5.3 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.66, 131.64, 128.40, 128.27, 122.63, 86.28, 85.17, 77.22, 75.09, 59.35, 52.04, 36.48, 31.38. **IR** (KBr, cm^{-1}) 2928, 1713, 1490, 1103, 1057, 759. **HRMS** calcd $C_{17}H_{21}O_3$ $[M+H]^+$: 273.1485. Found: 273.1491.



1w

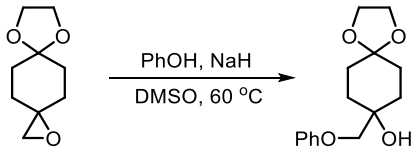
4-(Phenoxymethyl)-4-((3-phenylprop-2-yn-1-yl)oxy)cyclohexan-1-one (1w): Synthesized from **15-1w** (synthesized from **15-1w-1**, see below, 4.6 mmol scale). 36% Yield (556 mg) over 3 steps. Light-yellow solid. Melting point = 94 – 96 °C. R_f = 0.5 (hexane/EtOAc = 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.19 (m, 7H), 7.04 – 6.87 (m, 3H), 4.60 (s, 2H), 4.08 (s, 2H), 3.09 – 2.67 (m, 2H), 2.46 (ddt, *J* = 15.0, 6.3, 3.4 Hz, 2H), 2.33 (ddt, *J* = 15.0, 4.6, 2.0 Hz, 2H), 1.91 (td, *J* = 13.9, 4.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.22, 158.33, 131.66, 129.55, 128.44, 128.22, 122.42, 121.27, 114.48, 85.94, 85.49, 74.84, 72.03, 52.27, 36.40, 31.38. **IR** (KBr, cm^{-1}) 2931, 1713, 1599, 1491, 1243, 1057, 756. **HRMS** calcd $C_{22}H_{23}O_3$ $[M+H]^+$: 335.1642. Found: 335.1642.



1x

4-Phenyl-4-((3-phenylprop-2-yn-1-yl)oxy)cyclohexan-1-one (1x): Synthesized from **15-1x**[37] (5.2 mmol scale). 27% Yield (427 mg) over 3 steps. Light-yellow solid. Melting point = 90 –

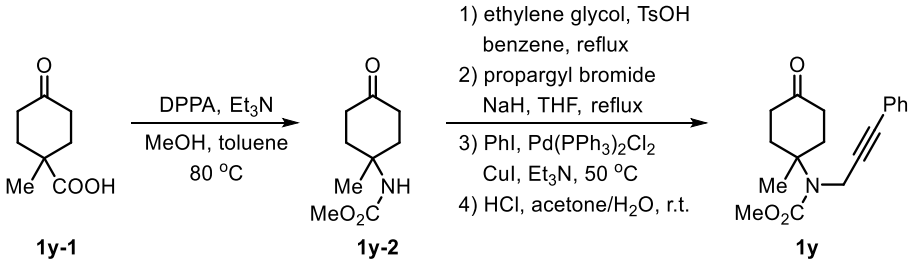
92 °C. R_f = 0.5 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 2H), 7.46 – 7.36 (m, 4H), 7.37 – 7.28 (m, 4H), 4.11 (s, 2H), 3.12 – 2.91 (m, 2H), 2.58 – 2.46 (m, 2H), 2.37 (ddt, *J* = 14.9, 4.5, 2.1 Hz, 2H), 2.19 (td, *J* = 13.9, 4.7 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.24, 142.74, 131.66, 128.72, 128.44, 128.27, 127.93, 125.99, 122.53, 85.85, 85.45, 77.63, 52.38, 37.22, 35.51. **IR** (KBr, cm^{-1}) 2951, 2245, 1714, 1490, 1051, 759. **HRMS** calcd $C_{21}H_{21}O_2$ $[M+H]^+$: 305.1536. Found: 305.1539.



15-1w-1 **15-1w**

8-(Phenoxymethyl)-1,4-dioxaspiro[4.5]decan-8-ol (15-1w): A Schlenk flask was flame-dried and charged with NaH (60% in oil, 1.5 equiv., 15 mmol, 600 mg). The flask was refilled with N_2. Phenol (2 equiv., 20 mmol, 1.88 g) was dissolved in DMSO (20 mL), and the solution was added to the flask slowly via syringe. The mixture was stirred at room temperature for 45 min. **15-1w-1**[38] (1 equiv., 10 mmol, 1.70 g) was dissolved in DMSO (10 mL), and the solution was added dropwise to the flask via syringe. The mixture was then heated to 60 °C and stirred overnight. After cooling to room temperature, the mixture was poured into water (200 mL) and extracted with diethyl ether. The combined organic layers were washed with 10% NaOH solution and brine, dried and concentrated. The residue was recrystallized from toluene to give **15-1w** as a white solid in 46% yield (1.21 g). Melting point = 106 – 107 °C. R_f = 0.4 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.02 – 6.94 (m, 1H), 6.94 – 6.89 (m, 2H), 4.09 – 3.90 (m, 4H), 3.82 (s, 2H), 2.15 (s, 1H), 2.00 (td, *J* = 12.8, 4.4 Hz, 2H), 1.88 (dt, *J* = 11.7, 3.3 Hz, 2H), 1.82

– 1.61 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.66, 129.50, 121.11, 114.56, 108.81, 75.38, 69.77, 64.34, 64.20, 31.79, 29.99. **IR** (KBr, cm^{-1}) 3461, 2931, 1601, 1497, 1246, 1094, 755. **HRMS** calcd $C_{15}H_{19}O_3$ $[M+H-H_2O]^+$: 247.1329. Found: 247.1327.



Methyl (1-methyl-4-oxocyclohexyl)carbamate (1y-2): A Schlenk flask was flame-dried and charged with **1y-1**[39] (1 equiv., 15 mmol, 2.34 g). The flask was refilled with N_2, and toluene (150 mL), Et_3N (1.2 equiv., 18 mmol, 2.50 mL), diphenyl phosphoryl azide (1.1 equiv., 16.5 mmol, 4.54 g) and methanol (2.4 equiv., 36 mmol, 1.45 mL) were added sequentially via syringe. The mixture was heated to 80 °C overnight. After cooling to room temperature, water (150 mL) was added, and the mixture was extracted with ethyl acetate. The combined organic layers were dried and concentrated, and the residue was purified by column chromatography to give **1y-2** as a white solid in 46% yield (1.27 g). Meliting point = 98 – 100 °C. R_f = 0.4 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.71 (br, 1H), 3.66 (s, 3H), 2.54 – 2.22 (m, 6H), 1.83 (ddd, J = 13.2, 11.4, 4.7 Hz, 2H), 1.45 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.44, 51.75, 51.43, 36.98, 36.37, 25.96. **IR** (KBr, cm^{-1}) 3338, 2966, 1711, 1537, 1280, 1095, 785. **HRMS** calcd $C_9H_{16}NO_3$ $[M+H]^+$: 186.1125. Found: 186.1131.

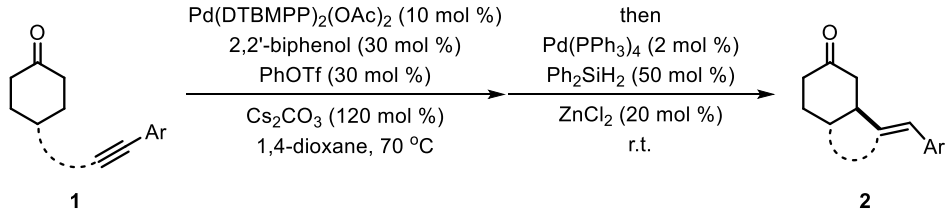
Methyl (1-methyl-4-oxocyclohexyl)(3-phenylprop-2-yn-1-yl)carbamate (1y): A round bottom flask was charged with **1y-1** (1 equiv., 6.9 mmol, 1.27 g), $TsOH{\cdot}H_2O$ (1 mol %, 0.07 mmol,

13.3 mg), ethylene glycol (3 equiv., 20.7 mmol, 1.28 g) and benzene (14 mL). The flask was equipped with a Dean-Stark apparatus, and the mixture was heated to reflux overnight. After cooling to room temperature, the mixture was basified with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were dried and concentrated, and the residue was directly used in the next step without further purification (ca. 6.8 mmol crude product). A Schlenk flask was flame-dried and charged with NaH (60% in oil, 2.5 equiv., 17 mmol, 680 mg). The flask was refilled with N_2, and DMF (20 mL) was added via syringe. The mixture was then cooled to 0 °C. The crude product from the last step (1 equiv., ca. 6.8 mmol) was dissolved in DMF (20 mL), and the solution was added to the flask via syringe dropwise at 0 °C. The resulting mixture was stirred at room temperature for 2 h and then cooled to 0 °C. Propargyl bromide (80% in toluene, 5 equiv., 34 mmol, 5.06 g) was added dropwise via syringe, and the mixture was stirred at room temperature overnight. The mixture was quenched with saturated NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried and concentrated. The residue was filtered through a short plug of silica gel and eluted with a solution containing hexane/EtOAc (1:1). The filtrate was concentrated, and the residue was directly used in the next step without further purification (ca. 1 mmol crude product). A Schlenk flask was flame-dried and charged with $Pd(PPh_3)_2Cl_2$ (4 mol %, 0.04 mmol, 28 mg) and CuI (2 mol %, 0.02 mmol, 3.8 mg). The flask was refilled with N_2. The crude product from the previous step (1 equiv., ca. 1 mmol) and iodobenzene (1.1 equiv., 1.1 mmol, 123 μL) were dissolved in triethylamine (4 mL), and the solution was added via syringe. The mixture was heated at 50 °C overnight. After cooling to room temperature, the mixture was diluted with diethyl ether and filtered. The filtrate was concentrated,

and the residue was dissolved in acetone (2.5 mL) and 3 M HCl (2.5 mL). The mixture was stirred at room temperature for 6 h. The mixture was basified with saturated $NaHCO_3$ solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried and concentrated. The residue was purified by column chromatography to give **1y** as an off-white solid in 10% yield (204 mg) over 4 steps. Melting point = 82 – 84 °C. R_f = 0.5 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 2H), 7.33 – 7.28 (m, 3H), 4.40 (s, 2H), 3.76 (s, 3H), 2.98 – 2.71 (m, 2H), 2.52 (ddd, *J* = 15.9, 10.7, 5.3 Hz, 2H), 2.43 – 2.31 (m, 2H), 2.04 – 1.95 (m, 2H), 1.59 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.74, 156.63, 131.49, 128.39, 128.31, 122.58, 86.38, 83.50, 58.04, 52.69, 37.61, 36.23, 34.92, 24.01. **IR** (KBr, cm^{-1}) 2955, 1712, 1444, 1367, 1231, 758. **HRMS** calcd $C_{18}H_{22}NO_3$ $[M+H]^+$: 300.1594. Found: 300.1601.

4.4.4 Experimental procedure for the β-ketone/alkyne coupling

General procedure:



An 8-mL culture tube was flame-dried and charged with $Pd(DTBMPP)_2(OAc)_2$ (10 mol %, 0.01 mmol, 16.0 mg) and 2,2'-biphenol (30 mol %, 0.03 mmol, 5.6 mg). The tube was then transferred into the glovebox. Inside the glovebox, Cs_2CO_3 (1.2 equiv., 0.12 mmol, 39.1 mg), 1,4-dioxane (distilled over Na and freeze-pump-thawed, 1 mL), substrate **1** (1 equiv., 0.1 mmol) and PhOTf (30 mol %, 0.03 mmol, 6.8 mg) were added sequentially to the tube. The tube was sealed

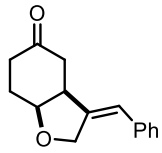
with a PTFE lined cap, transferred out of the glovebox and heated in an oil bath at 70 °C (oil temperature). After 48 h, the mixture was allowed to cool to room temperature.

(a) For NMR analysis of the crude mixture: The mixture was diluted with EtOAc, passed through a small plug of silica gel and eluted with EtOAc. The solvent was removed *in vacuo*, and the residue was dissolved in $CDCl_3$ for crude NMR analysis with 1,1,2,2-tetrachloroethane as the internal standard.

(b) For isolation of the product: The tube was transferred into the glovebox before the cap was opened. Inside the glovebox, $Pd(PPh_3)_4$ (2 mol %, 0.002 mmol, 2.3 mg), $ZnCl_2$ (20 mol %, 0.02 mmol, 2.7 mg) and diphenylsilane (50 mol %, 0.05 mmol, 9.2 mg) were added sequentially to the tube. The tube was sealed with a PTFE lined cap, transferred out of the glovebox and stirred at room temperature for 12 h. The mixture was diluted with EtOAc, passed through a small plug of silica gel and eluted with EtOAc. The solvent was removed *in vacuo*, and the residue was purified by column chromatography to give the product.

Note: If the ketone or alkenyl bromide is a solid, it is weighed and added into the reaction tube before transferring into the glovebox.

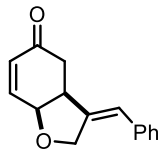
4.4.5 Characterization of the products for the β-ketone/alkyne coupling



2a

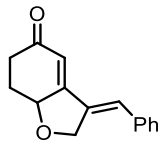
***cis*-3-((*Z*)-Benzylidene)hexahydrobenzofuran-5(4*H*)-one (2a)**: Synthesized from **1a**

according to the general procedure. The structure is determined by X-ray crystallography of the crystal from its 2,4-dinitrophenylhydrazone form (*vide infra*). 63% Yield (14.3 mg). White solid. Melting point = 71 – 73 °C. R_f = 0.3 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 2H), 7.28 – 7.18 (m, 1H), 7.16 – 7.08 (m, 2H), 6.35 (q, *J* = 2.3 Hz, 1H), 4.84 (dt, *J* = 14.0, 2.0 Hz, 1H), 4.63 (ddd, *J* = 14.1, 2.6, 1.2 Hz, 1H), 4.32 (dt, *J* = 6.4, 4.4 Hz, 1H), 3.25 (tdd, *J* = 7.5, 6.1, 1.5 Hz, 1H), 2.66 – 2.40 (m, 3H), 2.30 – 2.02 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.89, 143.81, 136.68, 128.54, 128.06, 127.00, 121.84, 75.14, 69.45, 44.72, 42.09, 35.03, 26.95. **IR** (KBr, cm^{-1}) 2928, 1715, 1448, 1275, 1060, 697. **HRMS** calcd $C_{15}H_{17}O_2$ $[M+H]^+$: 229.1223. Found: 229.1225.



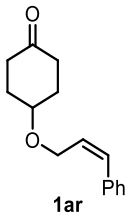
2aa

***cis*-3-((*Z*)-Benzylidene)-2,3,3a,7a-tetrahydrobenzofuran-5(4*H*)-one (2aa)**: Isolated from the synthesis of **2a** as a side product. Colorless oil. R_f = 0.5 (hexane/EtOAc/DCM = 2:1:6). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 2H), 7.25 – 7.19 (m, 1H), 7.16 – 7.05 (m, 2H), 6.69 (ddd, *J* = 10.3, 2.7, 1.2 Hz, 1H), 6.31 (q, *J* = 2.6 Hz, 1H), 6.02 (ddd, *J* = 10.3, 1.5, 0.9 Hz, 1H), 4.92 – 4.87 (m, 1H), 4.81 (ddd, *J* = 14.2, 2.7, 1.5 Hz, 1H), 4.61 (dt, *J* = 14.2, 2.4 Hz, 1H), 3.57 – 3.44 (m, 1H), 2.93 (ddd, *J* = 16.9, 3.8, 1.0 Hz, 1H), 2.83 (dd, *J* = 16.9, 5.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.75, 146.75, 140.73, 136.43, 131.34, 128.56, 128.12, 127.04, 121.90, 74.05, 69.56, 42.42, 37.49. **IR** (KBr, cm^{-1}) 2924, 1685, 1493, 1239, 1050, 695. **HRMS** calcd $C_{15}H_{15}O_2$ $[M+H]^+$: 227.1067. Found: 227.1067.



2ab

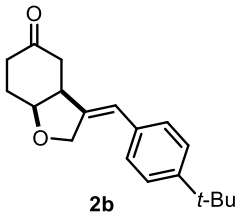
(*Z*)-3-Benzylidene-2,3,7,7a-tetrahydrobenzofuran-5(6*H*)-one (2ab): Isolated from the synthesis of **2a** as a side product. Light-yellow oil. R_f = 0.4 (hexane/EtOAc/DCM = 2:1:6). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.39 (m, 2H), 7.40 – 7.32 (m, 1H), 7.31 – 7.27 (m, 2H), 7.12 (t, *J* = 2.6 Hz, 1H), 6.25 (s, 1H), 5.00 (dd, *J* = 13.7, 2.3 Hz, 1H), 4.85 (dd, *J* = 13.6, 2.8 Hz, 1H), 4.62 (ddd, *J* = 11.1, 5.0, 2.0 Hz, 1H), 2.69 – 2.57 (m, 1H), 2.50 (dtd, *J* = 11.8, 4.8, 2.2 Hz, 1H), 2.40 (ddd, *J* = 17.4, 14.2, 4.7 Hz, 1H), 1.99 (dtd, *J* = 14.0, 11.3, 4.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.46, 162.64, 135.41, 135.39, 129.35, 129.01, 128.98, 127.31, 115.31, 78.03, 71.48, 34.87, 29.36. **IR** (KBr, cm^{-1}) 2935, 1654, 1610, 1448, 1093, 882. **HRMS** calcd $C_{15}H_{15}O_2$ $[M+H]^+$: 227.1067. Found: 227.1075.



1ar

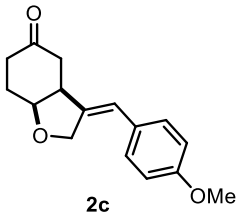
(*Z*)-4-((3-Phenylallyl)oxy)cyclohexan-1-one (1ar): Isolated from the synthesis of **2a** as a side product. Colorless oil. R_f = 0.45 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 2H), 7.32 – 7.25 (m, 1H), 7.25 – 7.18 (m, 2H), 6.63 (dt, *J* = 11.8, 1.8 Hz, 1H), 5.88 (dt, *J* = 12.1, 6.3 Hz, 1H), 4.34 (dd, *J* = 6.3, 1.8 Hz, 2H), 3.78 (tt, *J* = 5.9, 3.0 Hz, 1H), 2.59 (ddd, *J* = 15.3, 10.2, 5.7 Hz, 2H), 2.25 (dt, *J* = 14.8, 6.0 Hz, 2H), 2.07 (dq, *J* = 11.7, 5.7 Hz, 2H), 1.99 – 1.87 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.25, 136.59, 131.63, 129.12, 128.72, 128.26, 127.26,

72.61, 65.18, 37.22, 30.59. **IR** (KBr, cm^{-1}) 2935, 1714, 1447, 1104, 1070, 775. **HRMS** calcd $C_{15}H_{19}O_2$ $[M+H]^+$: 231.1380. Found: 231.1380.



2b

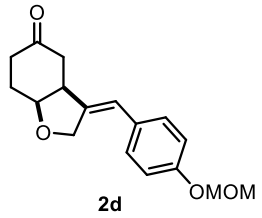
***cis*-3-((*Z*)-4-(*tert*-Butyl)benzylidene)hexahydrobenzofuran-5(4*H*)-one (2b)**: Synthesized from **1b** according to the general procedure. 59% Yield (16.7 mg). Colorless oil. R_f = 0.4 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.32 (m, 2H), 7.16 – 6.98 (m, 2H), 6.32 (q, *J* = 2.3 Hz, 1H), 4.85 (dt, *J* = 14.0, 2.0 Hz, 1H), 4.63 (ddd, *J* = 14.0, 2.6, 1.2 Hz, 1H), 4.31 (dt, *J* = 6.4, 4.4 Hz, 1H), 3.24 (dt, *J* = 9.0, 7.3 Hz, 1H), 2.63 – 2.41 (m, 3H), 2.29 – 2.07 (m, 3H), 1.32 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.96, 150.07, 142.90, 133.89, 127.83, 125.48, 121.51, 75.13, 69.51, 44.69, 42.10, 35.04, 34.54, 31.23, 26.99. **IR** (KBr, cm^{-1}) 2960, 2867, 1717, 1363, 1064, 870. **HRMS** calcd $C_{19}H_{25}O_2$ $[M+H]^+$: 285.1849. Found: 285.1848.



2c

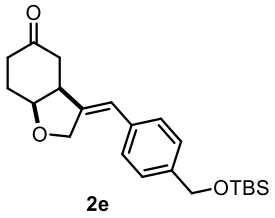
***cis*-3-((*Z*)-4-Methoxybenzylidene)hexahydrobenzofuran-5(4*H*)-one (2c)**: Synthesized from **1c** according to the general procedure. 62% Yield (15.9 mg). Light-yellow oil. R_f = 0.5 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.12 – 6.99 (m, 2H), 6.94 – 6.79 (m, 2H), 6.28 (q, *J* = 2.3 Hz, 1H), 4.82 (dt, *J* = 13.8, 2.0 Hz, 1H), 4.60 (ddd, *J* = 13.8, 2.6, 1.2 Hz, 1H), 4.31

(dt, J = 6.4, 4.4 Hz, 1H), 3.81 (s, 3H), 3.30 – 3.13 (m, 1H), 2.63 – 2.40 (m, 3H), 2.30 – 2.03 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.06, 158.54, 141.40, 129.50, 129.32, 121.22, 113.95, 75.14, 69.45, 55.27, 44.65, 42.14, 35.04, 26.98. **IR** (KBr, cm^{-1}) 2954, 1715, 1607, 1512, 1251, 1030, 824. **HRMS** calcd $C_{16}H_{19}O_3$ $[M+H]^+$: 259.1329. Found: 259.1323.



2d

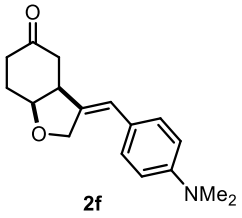
***cis*-3-((*Z*)-4-(Methoxymethoxy)benzylidene)hexahydrobenzofuran-5(4*H*)-one (2d)**: Synthesized from **1d** according to the general procedure. 61% Yield (17.5 mg). Colorless oil. R_f = 0.4 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.11 – 6.96 (m, 4H), 6.29 (q, J = 2.3 Hz, 1H), 5.18 (s, 2H), 4.81 (dt, J = 13.9, 2.0 Hz, 1H), 4.60 (ddd, J = 13.9, 2.6, 1.2 Hz, 1H), 4.31 (dt, J = 6.5, 4.4 Hz, 1H), 3.48 (s, 3H), 3.28 – 3.17 (m, 1H), 2.65 – 2.43 (m, 3H), 2.30 – 2.06 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.00, 156.14, 141.94, 130.64, 129.29, 121.17, 116.25, 94.33, 75.14, 69.43, 56.01, 44.64, 42.11, 35.03, 26.97. **IR** (KBr, cm^{-1}) 2953, 1715, 1606, 1510, 1238, 1152, 998. **HRMS** calcd $C_{17}H_{21}O_4$ $[M+H]^+$: 289.1434. Found: 289.1435.



2e

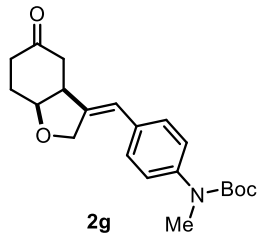
***cis*-3-((*Z*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)benzylidene)hexahydrobenzofuran-5(4*H*)-one (2e)**: Synthesized from **1e** according to the general procedure. 58% Yield (21.6 mg).

Colorless oil. R_f = 0.3 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 2H), 7.15 – 7.01 (m, 2H), 6.34 (q, *J* = 2.3 Hz, 1H), 4.84 (dt, *J* = 14.0, 2.0 Hz, 1H), 4.73 (s, 2H), 4.62 (ddd, *J* = 14.0, 2.7, 1.1 Hz, 1H), 4.31 (dt, *J* = 6.3, 4.3 Hz, 1H), 3.41 – 3.15 (m, 1H), 2.75 – 2.42 (m, 3H), 2.33 – 2.07 (m, 3H), 0.94 (s, 9H), 0.10 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.94, 143.30, 140.32, 135.35, 127.96, 126.19, 121.67, 75.14, 69.50, 64.64, 44.74, 42.11, 35.04, 26.97, 25.93, 18.40, -5.26. **IR** (KBr, cm^{-1}) 2954, 2856, 1718, 1255, 1090, 839. **HRMS** calcd $C_{22}H_{32}NaO_3Si$ $[M+Na]^+$: 395.2013. Found: 395.2018.



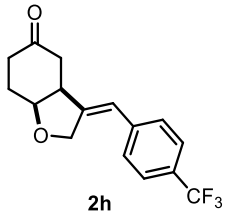
2f

***cis*-3-((*Z*)-4-(Dimethylamino)benzylidene)hexahydrobenzofuran-5(4*H*)-one (2f)**: Synthesized from **1f** according to the general procedure. 55% Yield (14.8 mg). Yellow oil. R_f = 0.5 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.10 – 6.93 (m, 2H), 6.78 – 6.62 (m, 2H), 6.24 (q, *J* = 2.3 Hz, 1H), 4.83 (dt, *J* = 13.7, 2.0 Hz, 1H), 4.62 (ddd, *J* = 13.7, 2.6, 1.2 Hz, 1H), 4.29 (dt, *J* = 6.3, 4.3 Hz, 1H), 3.21 (tdd, *J* = 7.4, 6.0, 1.6 Hz, 1H), 2.96 (s, 6H), 2.63 – 2.42 (m, 3H), 2.29 – 2.06 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.32, 149.33, 139.06, 129.12, 125.19, 121.56, 112.25, 75.12, 69.59, 44.71, 42.25, 40.39, 35.10, 27.07. **IR** (KBr, cm^{-1}) 2890, 1714, 1609, 1522, 1356, 1062, 811. **HRMS** calcd $C_{17}H_{21}NNaO_2$ $[M+Na]^+$: 294.1465. Found: 294.1459.



2g

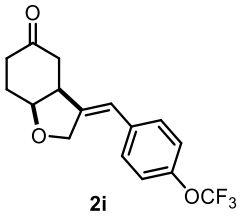
***tert*-Butyl methyl(*cis*-4-(((*Z*)-5-oxohexahydrobenzofuran-3(2*H*)-ylidene)methyl) phenyl)carbamate (2g)**: Synthesized from **1g** according to the general procedure. 56% Yield (20.0 mg). Colorless oil. R_f = 0.4 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 2H), 7.12 – 7.02 (m, 2H), 6.32 (q, *J* = 2.3 Hz, 1H), 4.83 (dt, *J* = 14.0, 2.0 Hz, 1H), 4.61 (ddd, *J* = 14.0, 2.6, 1.2 Hz, 1H), 4.32 (dt, *J* = 6.4, 4.4 Hz, 1H), 3.30 – 3.19 (m, 4H), 2.64 – 2.44 (m, 3H), 2.29 – 2.06 (m, 3H), 1.46 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.88, 154.60, 143.51, 142.53, 133.65, 128.21, 125.27, 121.19, 80.48, 75.15, 69.44, 44.71, 42.09, 37.12, 35.01, 28.31, 26.94. **IR** (KBr, cm^{-1}) 2973, 1699, 1513, 1366, 1153, 866. **HRMS** calcd $C_{21}H_{27}NNaO_4$ $[M+Na]^+$: 380.1832. Found: 380.1842.



2h

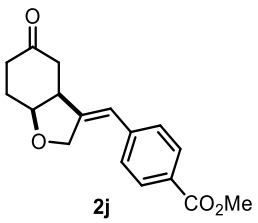
***cis*-3-((*Z*)-4-(Trifluoromethyl)benzylidene)hexahydrobenzofuran-5(4*H*)-one (2h)**: Synthesized from **1h** according to the general procedure. 53% Yield (15.8 mg). Colorless oil. R_f = 0.5 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.39 (q, *J* = 2.3 Hz, 1H), 4.83 (dt, *J* = 14.2, 2.0 Hz, 1H), 4.62 (ddd, *J* = 14.3, 2.7, 1.1 Hz, 1H), 4.34 (dt, *J* = 6.5, 4.4 Hz, 1H), 3.29 (q, *J* = 7.8 Hz, 1H), 2.71 – 2.39 (m, 3H), 2.32 – 1.98

(m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.48, 146.82, 140.06 (q, *J* = 1.1 Hz), 128.84 (q, *J* = 32.6 Hz), 128.18, 125.48 (q, *J* = 3.9 Hz), 124.05 (q, *J* = 273.0 Hz), 120.70, 75.20, 69.36, 44.81, 41.97, 34.95, 26.83. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.52. **IR** (KBr, cm^{-1}) 2935, 1717, 1616, 1326, 1122, 1068, 873. **HRMS** calcd $C_{16}H_{16}F_3O_2$ $[M+H]^+$: 297.1097. Found: 297.1098.



2i

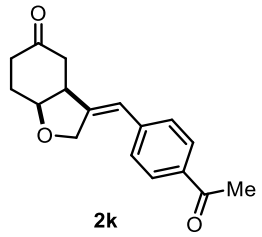
***cis*-3-((*Z*)-4-(Trifluoromethoxy)benzylidene)hexahydrobenzofuran-5(4*H*)-one (2i)**: Synthesized from **1i** according to the general procedure. 54% Yield (16.8 mg). Colorless oil. R_f = 0.4 (hexane/EtOAc = 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 – 7.16 (m, 2H), 7.16 – 7.10 (m, 2H), 6.33 (q, *J* = 2.3 Hz, 1H), 4.81 (dt, *J* = 14.1, 2.0 Hz, 1H), 4.60 (ddd, *J* = 14.0, 2.6, 1.2 Hz, 1H), 4.33 (dt, *J* = 6.5, 4.4 Hz, 1H), 3.30 – 3.17 (m, 1H), 2.66 – 2.43 (m, 3H), 2.29 – 2.06 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.65, 147.91 (q, *J* = 1.8 Hz), 144.92, 135.39, 129.33, 121.02, 120.50, 120.42 (q, *J* = 257.9 Hz), 75.20, 69.31, 44.68, 42.00, 34.96, 26.87. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -57.85. **IR** (KBr, cm^{-1}) 2933, 1717, 1509, 1261, 1222, 1163, 872. **HRMS** calcd $C_{16}H_{16}F_3O_3$ $[M+H]^+$: 313.1046. Found: 313.1041.



2j

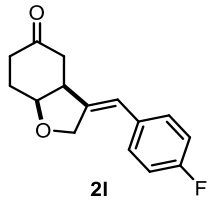
Methyl *cis*-4-(((*Z*)-5-oxohexahydrobenzofuran-3(2*H*)-ylidene)methyl)benzoate (2j):

Synthesized from **1j** according to the general procedure. 53% Yield (15.2 mg). Colorless oil. R_f = 0.4 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 – 7.89 (m, 2H), 7.21 – 7.06 (m, 2H), 6.39 (q, *J* = 2.3 Hz, 1H), 4.85 (dt, *J* = 14.3, 2.0 Hz, 1H), 4.74 – 4.52 (m, 1H), 4.33 (dt, *J* = 6.5, 4.4 Hz, 1H), 3.92 (s, 3H), 3.28 (q, *J* = 7.7 Hz, 1H), 2.64 – 2.41 (m, 3H), 2.39 – 2.04 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.54, 166.71, 146.82, 141.05, 129.83, 128.40, 127.91, 121.14, 75.17, 69.47, 52.12, 44.96, 42.00, 34.97, 26.84. **IR** (KBr, cm^{-1}) 2951, 1717, 1607, 1435, 1280, 1110, 769. **HRMS** calcd $C_{17}H_{18}NaO_4$ $[M+Na]^+$: 309.1097. Found: 309.1102.



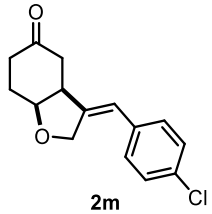
2k

***cis*-3-((*Z*)-4-Acetylbenzylidene)hexahydrobenzofuran-5(4*H*)-one (2k)**: Synthesized from **1k** according to the general procedure. 45% Yield (12.2 mg). Colorless oil. R_f = 0.3 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 – 7.89 (m, 2H), 7.23 – 7.15 (m, 2H), 6.40 (q, *J* = 2.3 Hz, 1H), 4.86 (dt, *J* = 14.3, 2.0 Hz, 1H), 4.64 (ddd, *J* = 14.2, 2.6, 1.1 Hz, 1H), 4.34 (dt, *J* = 6.5, 4.4 Hz, 1H), 3.43 – 3.20 (m, 1H), 2.70 – 2.45 (m, 6H), 2.34 – 1.99 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.52, 197.44, 147.11, 141.24, 135.33, 128.66, 128.12, 121.08, 75.18, 69.50, 44.99, 42.00, 34.97, 26.84, 26.59. **IR** (KBr, cm^{-1}) 2930, 1715, 1679, 1602, 1269, 1065, 959. **HRMS** calcd $C_{17}H_{19}O_3$ $[M+H]^+$: 271.1329. Found: 271.1335.



2l

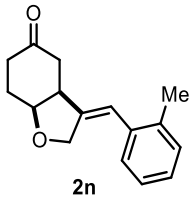
***cis*-3-((*Z*)-4-Fluorobenzylidene)hexahydrobenzofuran-5(4*H*)-one (2l)**: Synthesized from **1l** according to the general procedure. 54% Yield (13.3 mg). Colorless oil. R_f = 0.4 (hexane/EtOAc = 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 – 6.89 (m, 4H), 6.31 (q, *J* = 2.3 Hz, 1H), 4.80 (dt, *J* = 13.9, 2.0 Hz, 1H), 4.58 (dd, *J* = 13.9, 2.5 Hz, 1H), 4.32 (dt, *J* = 6.4, 4.4 Hz, 1H), 3.25 (q, *J* = 7.1 Hz, 1H), 2.66 – 2.42 (m, 3H), 2.31 – 2.03 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.81, 161.66 (d, *J* = 247.5 Hz), 143.46 (d, *J* = 2.3 Hz), 132.85 (d, *J* = 3.5 Hz), 129.63 (d, *J* = 7.9 Hz), 120.73, 115.48 (d, *J* = 21.5 Hz), 75.17, 69.31, 44.60, 42.04, 34.98, 26.89. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -114.59. **IR** (KBr, cm^{-1}) 2930, 1716, 1509, 1229, 1063, 826. **HRMS** calcd $C_{15}H_{16}FO_2$ $[M+H]^+$: 247.1129. Found: 247.1137.



2m

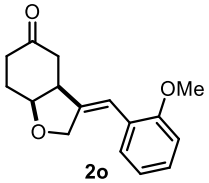
***cis*-3-((*Z*)-4-Chlorobenzylidene)hexahydrobenzofuran-5(4*H*)-one (2m)**: Synthesized from **1m** according to the general procedure. 46% Yield (12.1 mg). **2a** was isolated in 5% yield (1.2 mg) as a side product. Colorless oil. R_f = 0.4 (hexane/EtOAc = 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 2H), 7.10 – 6.97 (m, 2H), 6.30 (q, *J* = 2.3 Hz, 1H), 4.80 (dt, *J* = 14.0, 2.0 Hz, 1H), 4.58 (ddd, *J* = 14.1, 2.7, 1.1 Hz, 1H), 4.32 (dt, *J* = 6.6, 4.4 Hz, 1H), 3.36 – 3.16 (m, 1H), 2.68 – 2.42 (m, 3H), 2.30 – 2.07 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.71, 144.60, 135.12,

132.78, 129.26, 128.70, 120.73, 75.17, 69.35, 44.71, 42.01, 34.97, 26.87. **IR** (KBr, cm^{-1}) 2931, 1716, 1492, 1092, 1064, 869. **HRMS** calcd $C_{15}H_{16}ClO_2$ $[M+H]^+$: 263.0833. Found: 263.0841.



2n

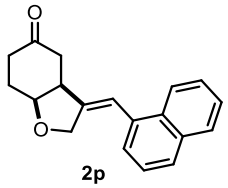
***cis*-3-((*Z*)-2-Methylbenzylidene)hexahydrobenzofuran-5(4*H*)-one (2n)**: Synthesized from **1n** according to the general procedure except for running the reaction for 60 h. 53% Yield (12.9 mg). Colorless oil. R_f = 0.5 (hexane/EtOAc = 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 – 7.10 (m, 3H), 7.06 – 6.91 (m, 1H), 6.43 (q, *J* = 2.3 Hz, 1H), 4.64 (dt, *J* = 13.7, 1.8 Hz, 1H), 4.50 (ddd, *J* = 13.8, 2.6, 1.3 Hz, 1H), 4.39 (dt, *J* = 7.2, 4.2 Hz, 1H), 3.30 (dddd, *J* = 8.6, 6.9, 5.2, 1.7 Hz, 1H), 2.64 (d, *J* = 6.7 Hz, 2H), 2.53 – 2.39 (m, 1H), 2.28 (s, 3H), 2.26 – 2.05 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.96, 143.69, 136.13, 135.59, 130.10, 127.63, 127.32, 125.78, 120.16, 75.26, 69.16, 43.36, 41.77, 34.83, 26.98, 19.85. **IR** (KBr, cm^{-1}) 2926, 1716, 1484, 1227, 1062, 884. **HRMS** calcd $C_{16}H_{19}O_2$ $[M+H]^+$: 243.1380. Found: 243.1382.



2o

***cis*-3-((*Z*)-2-Methoxybenzylidene)hexahydrobenzofuran-5(4*H*)-one (2o)**: Synthesized from **1o** according to the general procedure. 57% Yield (14.6 mg). Colorless oil. R_f = 0.5 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (ddd, *J* = 8.2, 7.2, 1.9 Hz, 1H), 6.99 (dd, *J* = 7.6, 1.9 Hz, 1H), 6.93 (td, *J* = 7.4, 1.1 Hz, 1H), 6.87 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.64 (q, *J*

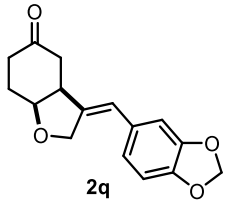
= 2.3 Hz, 1H), 4.78 (dt, *J* = 13.9, 1.9 Hz, 1H), 4.54 (ddd, *J* = 13.9, 2.6, 1.1 Hz, 1H), 4.31 (dt, *J* = 6.4, 4.4 Hz, 1H), 3.83 (s, 3H), 3.25 (dtt, *J* = 7.6, 6.2, 1.5 Hz, 1H), 2.63 – 2.45 (m, 3H), 2.28 – 2.07 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.16, 156.60, 143.48, 128.46, 128.44, 125.65, 120.34, 116.42, 110.59, 75.21, 69.40, 55.46, 44.54, 42.19, 35.01, 26.99. **IR** (KBr, cm^{-1}) 2937, 1715, 1488, 1245, 1025, 753. **HRMS** calcd $C_{16}H_{19}O_3$ $[M+H]^+$: 259.1329. Found: 259.1325.



2p

***cis*-(*Z*)-3-(Naphthalen-1-ylmethylene)hexahydrobenzofuran-5(4*H*)-one (2p)**:

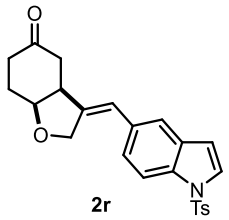
Synthesized from **1p** according to the general procedure. 49% Yield (13.7 mg). Colorless oil. R_f = 0.5 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 – 7.91 (m, 1H), 7.90 – 7.83 (m, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.59 – 7.46 (m, 2H), 7.43 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.18 (d, *J* = 7.0 Hz, 1H), 6.93 (q, *J* = 2.3 Hz, 1H), 4.62 (dt, *J* = 13.7, 1.8 Hz, 1H), 4.52 (ddd, *J* = 13.7, 2.5, 1.2 Hz, 1H), 4.46 (dt, *J* = 7.2, 4.3 Hz, 1H), 3.42 (qd, *J* = 6.7, 1.7 Hz, 1H), 2.81 – 2.70 (m, 2H), 2.48 (ddd, *J* = 16.0, 10.3, 5.4 Hz, 1H), 2.32 – 2.07 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.04, 145.33, 133.66, 133.47, 131.35, 128.46, 127.89, 126.33, 125.99, 125.60, 125.21, 124.22, 119.33, 75.41, 69.32, 43.20, 41.63, 34.86, 27.04. **IR** (KBr, cm^{-1}) 3057, 2948, 1715, 1397, 1060, 781. **HRMS** calcd $C_{19}H_{19}O_2$ $[M+H]^+$: 279.1380. Found: 279.1383.



2q

***cis*-(*Z*)-3-(Benzo[*d*][1,3]dioxol-5-ylmethylene)hexahydrobenzofuran-5(4*H*)-one (2q)**:

Synthesized from **1q** according to the general procedure. 56% Yield (15.3 mg). Colorless oil. R_f = 0.4 (hexane/EtOAc = 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.92 – 6.71 (m, 1H), 6.69 – 6.56 (m, 2H), 6.25 (q, *J* = 2.3 Hz, 1H), 5.97 (s, 2H), 4.80 (dt, *J* = 13.9, 2.0 Hz, 1H), 4.58 (ddd, *J* = 13.9, 2.6, 1.2 Hz, 1H), 4.30 (dt, *J* = 6.4, 4.4 Hz, 1H), 3.21 (q, *J* = 7.7 Hz, 1H), 2.68 – 2.42 (m, 3H), 2.30 – 2.08 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.95, 147.85, 146.54, 142.02, 131.05, 122.21, 121.48, 108.38, 108.02, 101.12, 75.13, 69.40, 44.68, 42.12, 35.01, 26.94. **IR** (KBr, cm^{-1}) 2897, 1715, 1503, 1490, 1257, 1037, 929. **HRMS** calcd $C_{16}H_{17}O_4$ $[M+H]^+$: 273.1121. Found: 273.1129.

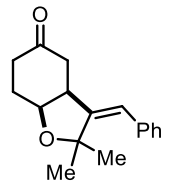


2r

***cis*-(*Z*)-3-((1-Tosyl-1*H*-indol-5-yl)methylene)hexahydrobenzofuran-5(4*H*)-one (2r)**:

Synthesized from **1r** according to the general procedure. 52% Yield (22.0 mg). Colorless oil. R_f = 0.3 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.6 Hz, 1H), 7.81 – 7.67 (m, 2H), 7.55 (d, *J* = 3.7 Hz, 1H), 7.25 – 7.19 (m, 3H), 7.08 (dd, *J* = 8.7, 1.8 Hz, 1H), 6.63 (dd, *J* = 3.7, 0.8 Hz, 1H), 6.39 (q, *J* = 2.3 Hz, 1H), 4.83 (dt, *J* = 13.8, 1.9 Hz, 1H), 4.62 (ddd, *J* = 13.9, 2.6, 1.2 Hz, 1H), 4.32 (dt, *J* = 6.5, 4.4 Hz, 1H), 3.25 (dt, *J* = 8.7, 6.4 Hz, 1H), 2.65 – 2.42 (m, 3H), 2.34 (s, 3H), 2.29 – 2.07 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.93, 145.02, 143.00, 135.12, 133.60, 132.18, 131.02, 129.89, 127.01, 126.75, 125.00, 121.74, 120.64, 113.50, 109.08, 75.14, 69.44, 44.61, 42.08, 34.98, 26.91, 21.55. **IR** (KBr, cm^{-1}) 2928, 1715, 1457, 1371, 1175, 1127, 730.

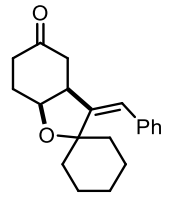
HRMS calcd $C_{24}H_{24}NO_4S$ $[M+H]^+$: 422.1421. Found: 422.1422.



2s

***cis*-3-((*Z*)-Benzylidene)-2,2-dimethylhexahydrobenzofuran-5(4*H*)-one (2s)**:

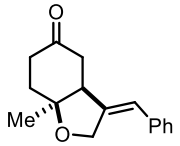
Synthesized from **1s** according to the general procedure. 51% Yield (13.1 mg). Colorless oil. R_f = 0.3 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.26 – 7.20 (m, 1H), 7.18 – 7.11 (m, 2H), 6.42 (br, 1H), 4.41 (dt, *J* = 6.8, 3.9 Hz, 1H), 3.30 (qd, *J* = 6.9, 1.9 Hz, 1H), 2.60 (d, *J* = 7.0 Hz, 2H), 2.58 – 2.42 (m, 1H), 2.26 – 2.02 (m, 3H), 1.34 (s, 3H), 1.18 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.56, 151.46, 136.89, 128.74, 127.94, 126.84, 122.10, 81.73, 71.42, 45.31, 42.88, 34.63, 27.99, 27.54, 26.82. **IR** (KBr, cm^{-1}) 2970, 1716, 1360, 1233, 1149, 703. **HRMS** calcd $C_{17}H_{21}O_2$ $[M+H]^+$: 257.1536. Found: 257.1535.



2t

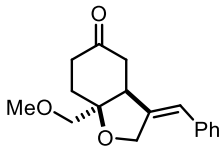
***cis*-3-((*Z*)-Benzylidene)tetrahydro-3*H*-spiro[benzofuran-2,1'-cyclohexan]-5(4*H*)-one (2t)**: Synthesized from **1t** according to the general procedure. 54% Yield (16.1 mg). Colorless oil. R_f = 0.5 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.20 (m, 3H), 7.19 – 7.12 (m, 2H), 6.42 (d, *J* = 1.6 Hz, 1H), 4.34 (dt, *J* = 6.5, 4.1 Hz, 1H), 3.23 (qd, *J* = 7.0, 1.8 Hz, 1H), 2.74 – 2.40 (m, 3H), 2.30 – 1.97 (m, 3H), 1.83 (dt, *J* = 12.7, 2.7 Hz, 1H), 1.70 – 1.29 (m, 8H), 1.00

– 0.72 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.96, 151.91, 137.04, 128.90, 127.83, 126.69, 122.08, 83.23, 71.01, 45.30, 43.21, 36.32, 34.78, 34.34, 26.93, 25.15, 22.38, 21.97. **IR** (KBr, cm^{-1}) 2927, 2858, 1717, 1446, 1072, 701. **HRMS** calcd $C_{20}H_{25}O_2$ $[M+H]^+$: 297.1849. Found: 297.1855.



2u

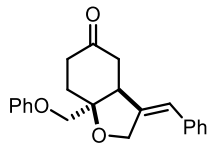
***cis*-3-((*Z*)-Benzylidene)-7a-methylhexahydrobenzofuran-5(4*H*)-one (2u)**: Synthesized from **1u** according to the general procedure. 64% Yield (15.4 mg). Colorless oil. R_f = 0.5 (hexane/EtOAc = 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 2H), 7.26 – 7.20 (m, 1H), 7.19 – 7.08 (m, 2H), 6.32 (q, *J* = 2.3 Hz, 1H), 4.77 (dt, *J* = 14.2, 2.1 Hz, 1H), 4.71 (ddd, *J* = 14.2, 2.6, 1.3 Hz, 1H), 3.18 – 2.92 (m, 1H), 2.70 – 2.57 (m, 2H), 2.50 – 2.37 (m, 1H), 2.23 (ddd, *J* = 16.8, 7.1, 5.1 Hz, 1H), 2.13 (ddd, *J* = 14.3, 7.1, 5.2 Hz, 1H), 1.96 (ddd, *J* = 14.4, 9.5, 5.1 Hz, 1H), 1.42 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.95, 143.80, 136.61, 128.52, 128.16, 126.98, 122.06, 79.80, 67.97, 50.00, 41.86, 35.88, 33.17, 25.47. **IR** (KBr, cm^{-1}) 2963, 1718, 1448, 1149, 1058, 757. **HRMS** calcd $C_{16}H_{19}O_2$ $[M+H]^+$: 243.1380. Found: 243.1380.



2v

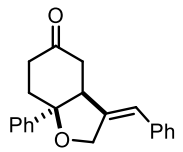
***cis*-3-((*Z*)-Benzylidene)-7a-(methoxymethyl)hexahydrobenzofuran-5(4*H*)-one (2v)**: Synthesized from **1v** according to the general procedure. 60% Yield (16.2 mg). Colorless oil. R_f =

0.4 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 2H), 7.26 – 7.19 (m, 1H), 7.14 – 7.02 (m, 2H), 6.30 (q, *J* = 2.4 Hz, 1H), 4.77 (dt, *J* = 13.7, 2.0 Hz, 1H), 4.70 (dt, *J* = 13.8, 1.9 Hz, 1H), 3.46 (s, 2H), 3.43 (s, 3H), 3.25 (td, *J* = 5.5, 5.1, 2.8 Hz, 1H), 2.77 – 2.60 (m, 2H), 2.36 (ddd, *J* = 17.9, 10.7, 5.4 Hz, 1H), 2.26 (dt, *J* = 17.9, 5.1 Hz, 1H), 2.15 – 1.88 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.33, 143.29, 136.58, 128.47, 128.21, 127.03, 121.99, 81.66, 77.38, 69.09, 59.62, 44.54, 41.55, 34.84, 29.09. **IR** (KBr, cm^{-1}) 2926, 1718, 1448, 1195, 1099, 759. **HRMS** calcd $C_{17}H_{21}O_3$ $[M+H]^+$: 273.1485. Found: 273.1485.



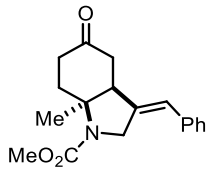
2w

***cis*-3-((*Z*)-Benzylidene)-7a-(phenoxymethyl)hexahydrobenzofuran-5(4*H*)-one (2w)**: Synthesized from **1w** according to the general procedure except for running the reaction for 60 h. 52% Yield (17.5 mg). Colorless oil. R_f = 0.45 (hexane/EtOAc = 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.19 (m, 5H), 7.15 – 7.07 (m, 2H), 7.02 – 6.95 (m, 1H), 6.95 – 6.90 (m, 2H), 6.34 (q, *J* = 2.3 Hz, 1H), 4.84 (dt, *J* = 13.8, 2.0 Hz, 1H), 4.76 (ddd, *J* = 13.8, 2.5, 1.4 Hz, 1H), 4.06 – 3.96 (m, 2H), 3.50 – 3.35 (m, 1H), 2.88 – 2.67 (m, 2H), 2.53 – 2.21 (m, 3H), 2.12 (dt, *J* = 14.3, 5.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.05, 158.53, 142.85, 136.46, 129.54, 128.50, 128.23, 127.14, 122.34, 121.25, 114.44, 81.34, 72.41, 69.32, 44.87, 41.75, 34.72, 29.38. **IR** (KBr, cm^{-1}) 2924, 1718, 1599, 1495, 1244, 1047, 756. **HRMS** calcd $C_{22}H_{23}O_3$ $[M+H]^+$: 335.1642. Found: 335.1644.



2x

***cis*-3-((*Z*)-Benzylidene)-7a-phenylhexahydrobenzofuran-5(4*H*)-one (2x)**: Synthesized from **1x** according to the general procedure except for running the reaction for 60 h. 44% Yield (13.4 mg). Colorless oil. R_f = 0.4 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 2H), 7.42 – 7.33 (m, 2H), 7.33 – 7.27 (m, 3H), 7.23 – 7.17 (m, 1H), 7.09 – 7.00 (m, 2H), 6.29 (q, *J* = 2.3 Hz, 1H), 4.86 (dt, *J* = 13.9, 2.0 Hz, 1H), 4.63 (ddd, *J* = 13.8, 2.6, 1.3 Hz, 1H), 3.62 (tt, *J* = 5.4, 1.7 Hz, 1H), 2.91 (dd, *J* = 15.2, 7.2 Hz, 1H), 2.74 (ddd, *J* = 15.2, 5.2, 0.8 Hz, 1H), 2.68 – 2.52 (m, 1H), 2.42 – 2.18 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.06, 145.53, 143.52, 136.54, 128.60, 128.44, 128.13, 127.27, 126.97, 124.64, 121.90, 83.73, 68.37, 50.37, 43.41, 35.86, 35.36. **IR** (KBr, cm^{-1}) 3056, 2954, 1717, 1446, 1059, 760. **HRMS** calcd $C_{21}H_{21}O_2$ $[M+H]^+$: 305.1536. Found: 305.1544.

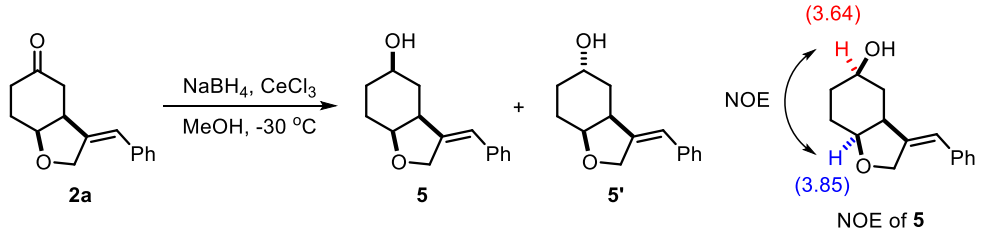


2y

Methyl *cis*-3-((*Z*)-benzylidene)-7a-methyl-5-oxooctahydro-1*H*-indole-1-carboxylate (2y): Synthesized from **1y** according to the general procedure except for running the reaction for 60 h. 18% Yield (5.5 mg). Colorless oil. R_f = 0.5 (hexane/EtOAc = 1:1). Two rotamers are observed in ca. 3:1 ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 2H), 7.30 – 7.21 (m, 1H), 7.23 – 7.14 (m, 2H), 6.35 (d, *J* = 2.4 Hz, 1H), 4.58 – 4.22 (m, 2H), 3.84 – 3.56 (m, 3H), 3.00 (t, *J* = 6.4

Hz, 1H), 2.79 – 1.98 (m, 6H), 1.58 – 1.46 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) carbon signals for the major rotamer are found at δ 211.08, 154.64, 138.26, 136.28, 128.51, 128.35, 127.22, 123.48, 61.13, 52.08, 51.84, 49.57, 41.52, 35.96, 31.19, 24.48. **IR** (KBr, cm^{-1}) 2956, 1705, 1445, 1363, 1190, 918. **HRMS** calcd $C_{18}H_{22}NO_3$ $[M+H]^+$: 300.1594. Found: 300.1589.

4.4.6 Procedures for the derivatization of the bicyclic product

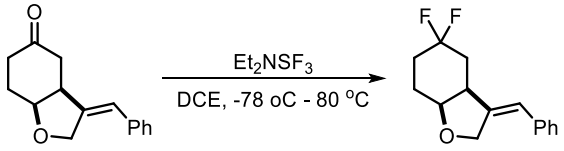


A Schlenk tube was flame-dried and charged with **2a** (1 equiv., 0.05 mmol, 11.4 mg) and $CeCl_3$ (15 mol %, 0.0075 mmol, 1.8 mg). The tube was refilled with N_2, and methanol (0.35 mL) was added via syringe. The mixture was stirred at room temperature for 20 min and then cooled to -30 °C. $NaBH_4$ (4 equiv., 0.2 mmol, 7.6 mg) was added in one portion, and the mixture was stirred at -30 °C for 2 h before warming up to room temperature. Methanol was removed *in vacuo*, and water was added to the residue. The mixture was extracted with ethyl acetate, dried and concentrated. The residue was purified by column chromatography to give **5** and **5'** as separable diastereomers. Diastereomeric ratio is 12:1 based on crude NMR of the reaction mixture.

***rac*-(*3*a*S*,*5R*,*7*a*S*)-3-((*Z*)-Benzylidene)octahydrobenzofuran-5-ol (5, major diastereomer)**: The stereochemistry of **5** was determined by COSY and NOESY analysis. 86% Yield (9.9 mg). Colorless oil. R_f = 0.2 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 2H), 7.24 – 7.18 (m, 1H), 7.16 – 7.03 (m, 2H), 6.58 – 6.21 (m, 1H), 4.86 (ddd, *J* = 14.3, 2.6, 1.3

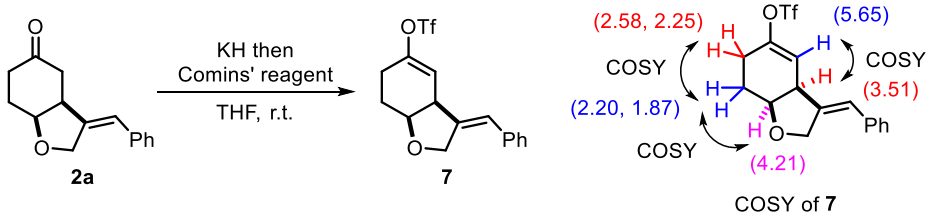
Hz, 1H), 4.55 (dd, *J* = 14.4, 2.6 Hz, 1H), 3.85 (q, *J* = 3.4 Hz, 1H), 3.64 (tt, *J* = 11.0, 3.8 Hz, 1H), 2.71 (ddd, *J* = 11.2, 6.1, 4.3 Hz, 1H), 2.27 – 2.08 (m, 1H), 1.95 (dddd, *J* = 12.6, 6.3, 3.8, 2.4 Hz, 1H), 1.84 – 1.64 (m, 2H), 1.61 – 1.49 (m, 2H), 1.41 (q, *J* = 11.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.29, 137.10, 128.53, 127.87, 126.56, 120.14, 75.03, 69.15, 69.02, 45.63, 37.61, 29.59, 26.09. **IR** (KBr, cm^{-1}) 3382, 2934, 1448, 1364, 1045, 956. **HRMS** calcd $C_{15}H_{19}O_2$ $[M+H]^+$: 231.1380. Found: 231.1381.

***rac*-(*3*a*S*,*5S*,*7*a*S*)-3-((*Z*)-Benzylidene)octahydrobenzofuran-5-ol (5', minor diastereomer)**: Colorless oil. 6% Yield (0.7 mg). R_f = 0.3 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 2H), 7.24 – 7.18 (m, 1H), 7.16 – 7.08 (m, 2H), 6.34 (q, *J* = 2.4 Hz, 1H), 4.78 (dt, *J* = 14.4, 2.2 Hz, 1H), 4.63 (ddd, *J* = 14.4, 2.7, 1.1 Hz, 1H), 4.21 – 3.88 (m, 2H), 3.13 – 2.92 (m, 1H), 2.05 – 1.75 (m, 4H), 1.69 (dddd, *J* = 14.0, 6.5, 5.6, 4.1 Hz, 1H), 1.48 (dtdd, *J* = 13.2, 6.5, 4.1, 1.2 Hz, 1H), 1.39 (br, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.06, 137.14, 128.54, 127.90, 126.52, 119.87, 76.13, 68.93, 65.80, 41.99, 33.92, 28.68, 22.67. **IR** (KBr, cm^{-1}) 3405, 2931, 1448, 1366, 1027, 754. **HRMS** calcd $C_{15}H_{19}O_2$ $[M+H]^+$: 231.1380. Found: 231.1375.



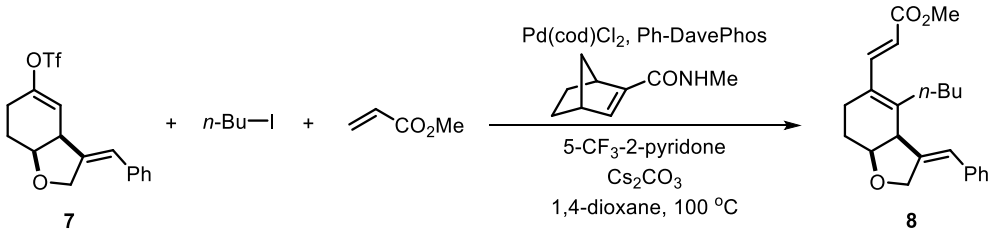
***cis*-3-((*Z*)-Benzylidene)-5,5-difluorooctahydrobenzofuran (6)**: A Schlenk tube was flame-dried and charged with **2a** (1 equiv., 0.05 mmol, 11.4 mg). The tube was refilled with N_2, and distilled DCE (0.5 mL) was added via syringe. The mixture was cooled to -78 °C, and diethylaminosulfur trifluoride (4 equiv., 0.2 mmol, 26.4 μL) was added dropwise via syringe. The

mixture was warmed to room temperature, and then heated to 80 °C for 2 h. The mixture was cooled to room temperature and quenched with saturated $NaHCO_3$ solution (1 mL). The mixture was extracted with DCM, dried and concentrated. The residue was purified by column chromatography to give **6** as a colorless oil in 61% yield (7.6 mg). R_f = 0.6 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.30 (m, 2H), 7.26 – 7.20 (m, 1H), 7.17 – 7.07 (m, 2H), 6.56 – 6.33 (m, 1H), 4.85 (ddd, *J* = 14.5, 2.7, 1.2 Hz, 1H), 4.58 (dd, *J* = 14.5, 2.6 Hz, 1H), 3.92 (p, *J* = 3.6 Hz, 1H), 2.91 (ddd, *J* = 11.3, 6.7, 4.0 Hz, 1H), 2.27 – 1.89 (m, 5H), 1.79 (dddd, *J* = 36.3, 14.3, 11.5, 3.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.37, 136.71, 128.60, 127.95, 126.88, 123.06 (dd, *J* = 244.1, 239.2 Hz), 121.23, 74.51 (d, *J* = 1.9 Hz), 69.07, 44.19 (d, *J* = 9.1 Hz), 35.02 (dd, *J* = 25.3, 22.0 Hz), 27.94 (dd, *J* = 24.8, 23.0 Hz), 24.36 (d, *J* = 9.2 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -90.27 (d, *J* = 237.4 Hz), -105.08 (d, *J* = 237.4 Hz). **IR** (KBr, cm^{-1}) 2942, 1449, 1371, 1124, 1030, 755. **HRMS** calcd $C_{15}H_{17}F_2O$ $[M+H]^+$: 251.1242. Found: 251.1246.



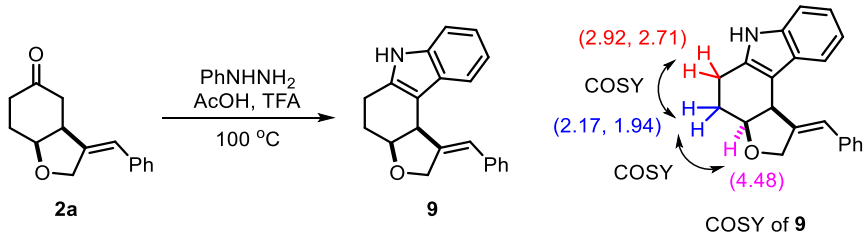
***cis*-3-((*Z*)-Benzylidene)-2,3,3a,6,7,7a-hexahydrobenzofuran-5-yl trifluoromethane-sulfonate (7)**: A 4-mL vial was flame-dried and transferred into the glovebox. Inside the glovebox, potassium hydride (washed with hexanes, 1.5 equiv., 0.075 mmol, 3.0 mg) and distilled THF (0.25 mL) were added to the vial, and the mixture was kept stirring. **2a** (1 equiv., 0.05 mmol, 11.4 mg) was dissolved in distilled THF (0.25 mL), and the solution was added to the vial dropwise. The

mixture was stirred at room temperature for 40 min. Comins' reagent (1.5 equiv., 0.075 mmol, 29.5 mg) was dissolved in distilled THF (0.25 mL), and the solution was added to the vial dropwise. The vial was sealed with a PTFE lined cap, transferred out of the glovebox and stirred at room temperature for 1 h. The mixture was quenched with saturated NH_4Cl solution and extracted with DCM. The combined organic layers were dried and concentrated, and the residue was purified by column chromatography to give **7** as a colorless oil in 71% yield (12.7 mg). Regioisomeric ratio is > 20:1 based on crude NMR of the reaction mixture. The structure of **7** was further characterized by COSY analysis. R_f = 0.5 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 2H), 7.29 – 7.19 (m, 1H), 7.17 – 7.07 (m, 2H), 6.47 (q, *J* = 2.2 Hz, 1H), 5.65 (dd, *J* = 3.8, 2.3 Hz, 1H), 4.76 (dt, *J* = 14.1, 2.1 Hz, 1H), 4.58 (ddd, *J* = 14.1, 2.6, 0.9 Hz, 1H), 4.21 (td, *J* = 4.7, 2.4 Hz, 1H), 3.61 – 3.39 (m, 1H), 2.58 (dddt, *J* = 17.3, 12.0, 6.0, 2.5 Hz, 1H), 2.41 – 2.16 (m, 2H), 1.97 – 1.77 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.75, 141.80, 136.58, 128.60, 128.03, 127.13, 123.19, 118.49 (q, *J* = 320.4 Hz), 117.43, 73.55, 69.03, 45.39, 25.26, 22.57. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.81. **IR** (KBr, cm^{-1}) 2929, 1417, 1211, 1142, 1045, 881. **HRMS** calcd $C_{16}H_{16}F_3O_4S$ $[M+H]^+$: 361.0716 . Found: 361.0725.



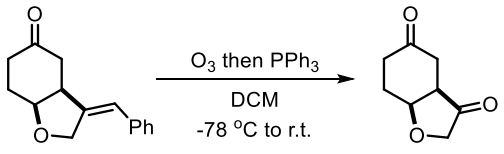
Methyl (*E*)-3-(*cis*-3-((*Z*)-benzylidene)-4-butyl-2,3,3a,6,7,7a-hexahydrobenzofuran-5-yl)acrylate (8): Following a literature procedure,[26] a 4-mL vial was flame-dried and charged with

$Pd(cod)Cl_2$ (10 mol %, 0.005 mmol, 1.4 mg), Ph-DavePhos (10 mol %, 0.005 mmol, 1.9 mg), *N*-methylnorbornene-2-carboxamide (50 mol %, 0.025 mmol, 3.8 mg) and 5-trifluoromethyl-2-pyridone (20 mol %, 0.01 mmol, 1.6 mg). The vial was transferred into the glovebox. Inside the glovebox, 1,4-dioxane (distilled over Na and freeze-pump-thawed, 1 mL) was added, and the mixture was stirred at room temperature for 5 min before Cs_2CO_3 (3 equiv., 0.15 mmol, 48.9 mg), **7** (1 equiv., 0.05 mmol, 18.0 mg), 1-iodobutane (3 equiv., 0.15 mmol, 17.1 μL) and methyl acrylate (1.5 equiv., 0.075 mmol, 6.8 μL) were added. The vial was sealed with a PTFE lined cap, transferred out of the glovebox and stirred at 100 °C for 16 h. After cooling to room temperature, the mixture was diluted with EtOAc, passed through a small plug of silica gel and eluted with EtOAc. The solvent was removed *in vacuo*, and the residue was purified by column chromatography to give **8** as a colorless oil in 22% yield (3.9 mg). R_f = 0.6 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 15.6 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.27 – 7.20 (m, 1H), 7.17 – 7.07 (m, 2H), 6.54 (q, *J* = 2.0 Hz, 1H), 5.92 (d, *J* = 15.6 Hz, 1H), 4.63 – 4.56 (m, 1H), 4.53 (dd, *J* = 13.5, 2.2 Hz, 1H), 4.24 (td, *J* = 5.2, 2.4 Hz, 1H), 3.77 (s, 3H), 3.40 (d, *J* = 5.3 Hz, 1H), 2.59 (ddd, *J* = 14.1, 9.9, 4.9 Hz, 1H), 2.51 – 2.27 (m, 2H), 2.21 (dt, *J* = 16.4, 4.9 Hz, 1H), 2.04 (dq, *J* = 14.2, 4.9 Hz, 1H), 1.64 (dddd, *J* = 13.5, 10.8, 5.7, 2.5 Hz, 1H), 1.55 – 1.46 (m, 1H), 1.44 – 1.29 (m, 3H), 0.91 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.22, 143.67, 142.79, 142.59, 136.76, 128.99, 128.47, 128.18, 126.99, 124.07, 116.38, 74.74, 68.49, 51.52, 50.29, 32.46, 30.21, 24.68, 22.81, 20.37, 13.92. **IR** (KBr, cm^{-1}) 2931, 1718, 1616, 1301, 1171, 855. **HRMS** calcd $C_{23}H_{29}O_3$ $[M+H]^+$: 353.2111. Found: 353.2120.



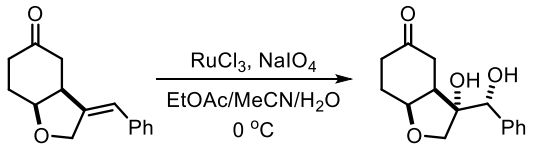
2a **9** COSY of **9**

***cis*-1-((*Z*)-Benzylidene)-1,3a,4,5,6,10c-hexahydro-2*H*-furo[2,3-c]carbazole (9)**: A 4-mL vial was charged with **2a** (1 equiv., 0.05 mmol, 11.4 mg), acetic acid (0.6 mL), trifluoroacetic acid (0.2 mL) and phenylhydrazine (2.6 equiv., 0.13 mmol, 12.8 μL). The vial was sealed with a PTFE lined cap and stirred at 100 °C for 16 h. After cooling to room temperature, the mixture was poured into ice water and extracted with DCM. The combined organic layers were washed with saturated $NaHCO_3$ solution, dried and concentrated. The residue was purified by column chromatography to give **9** as a light-yellow oil in 66% yield (9.9 mg). Regioisomeric ratio is > 20:1 based on crude NMR of the reaction mixture. The structure of **9** was further characterized by COSY analysis. R_f = 0.3 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (br, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 3H), 7.22 – 7.04 (m, 5H), 6.78 (q, *J* = 2.3 Hz, 1H), 4.81 – 4.61 (m, 2H), 4.48 (ddd, *J* = 7.1, 5.8, 2.9 Hz, 1H), 4.21 (d, *J* = 5.8 Hz, 1H), 3.03 – 2.84 (m, 1H), 2.71 (dt, *J* = 16.2, 5.8 Hz, 1H), 2.17 (dq, *J* = 12.9, 6.3 Hz, 1H), 1.94 (dddd, *J* = 13.6, 8.3, 5.6, 2.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.79, 137.16, 136.06, 133.74, 128.32, 128.20, 127.74, 126.56, 122.69, 121.24, 119.56, 118.82, 110.61, 107.62, 76.08, 68.89, 44.10, 25.70, 19.45. **IR** (KBr, cm^{-1}) 3289, 2925, 1463, 1233, 1055, 909. **HRMS** calcd $C_{21}H_{20}NO$ $[M+H]^+$: 302.1539. Found: 302.1537.



2a **10**

***cis*-Tetrahydrobenzofuran-3,5(2*H*,4*H*)-dione (10)**: An 8-mL culture tube was charged with **2a** (1 equiv., 0.05 mmol, 11.4 mg) and DCM (1 mL), and the solution was cooled to -78 °C. PPh_3 (10 equiv., 0.5 mmol, 131 mg) was dissolved in DCM (0.2 mL). The **2a** solution was treated with an O_3 flow until the solution stayed blue. The O_3 flow was then stopped, and the PPh_3 solution was added to the tube immediately. The mixture was warmed to room temperature and stirred overnight. The mixture was concentrated, and the residue was purified by column chromatography to give **10** as a colorless oil in 90% yield (6.9 mg). R_f = 0.3 (hexane/EtOAc = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.67 (dt, *J* = 7.2, 4.6 Hz, 1H), 4.18 (d, *J* = 17.2 Hz, 1H), 4.04 (d, *J* = 17.2 Hz, 1H), 2.88 (dt, *J* = 8.6, 7.0 Hz, 1H), 2.66 – 2.43 (m, 3H), 2.36 – 2.15 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 214.03, 208.09, 75.00, 70.54, 45.13, 36.42, 35.02, 27.04. **IR** (KBr, cm^{-1}) 2917, 1756, 1715, 1418, 1163, 1064, 908. **HRMS** calcd $C_8H_{11}O_3$ $[M+H]^+$: 155.0703. Found: 155.0699.



2a **11**

***rac*-(3*S*,3a*R*,7a*S*)-3-Hydroxy-3-((*R*)-hydroxy(phenyl)methyl)hexahydrobenzofuran-5(4*H*)-one (11)**: An 8-mL vial was charged with **2a** (1 equiv., 0.05 mmol, 11.4 mg), ethyl acetate (1.5 mL) and acetonitrile (1.5 mL), and the solution was kept vigorously stirring at 0 °C. $RuCl_3$ (10 mol %, 0.005 mmol, 1.0 mg) and $NaIO_4$ (2 equiv., 0.1 mmol, 21.4 mg) were dissolved in water (0.5 mL) before they were added to the reaction vial. The mixture was vigorously stirred at 0 °C for 3 min and quenched with saturated $Na_2S_2O_3$ solution (5 mL). The mixture was extracted with ethyl acetate, dried and concentrated. The residue was purified by column chromatography to give

11 as a white solid in 68% yield (8.9 mg). Diastereomeric ratio is > 20:1 based on crude NMR of the reaction mixture. The relative configuration of **11** was determined by X-ray crystallography (*vide infra*). Melting point = 138 – 140 ºC. R_f = 0.5 (EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.31 (m, 5H), 4.76 – 4.63 (m, 1H), 4.58 (q, *J* = 3.9 Hz, 1H), 3.90 (dd, *J* = 10.5, 0.9 Hz, 1H), 3.20 (d, *J* = 10.4 Hz, 1H), 2.72 – 2.49 (m, 5H), 2.43 – 2.24 (m, 2H), 2.19 (dtd, *J* = 14.8, 4.6, 1.5 Hz, 1H), 2.09 (dddd, *J* = 14.6, 11.9, 5.2, 3.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.40, 139.54, 128.65, 128.56, 126.99, 86.12, 75.73, 74.17, 73.20, 50.21, 39.08, 35.20, 27.56. **IR** (KBr, cm^{-1}) 3407, 2925, 1713, 1200, 1053, 732. **HRMS** calcd $C_{15}H_{18}NaO_4$ $[M+Na]^+$: 285.1097. Found: 285.1098.

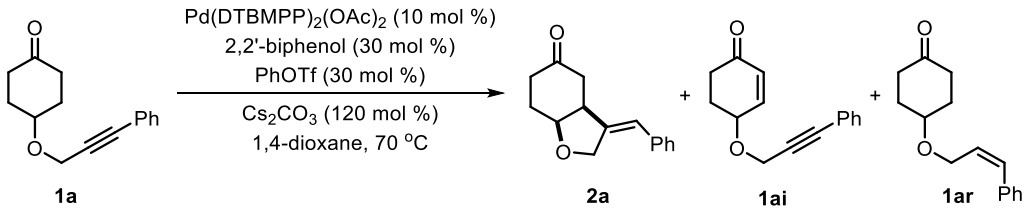
4.4.7 Procedures and data for the mechanistic studies

General procedure for mechanistic studies (without one-pot reduction workup):

An 8-mL culture tube was flame-dried and charged with $Pd(DTBMPP)_2(OAc)_2$ (10 mol %, 0.01 mmol, 16.0 mg) and 2,2'-biphenol (30 mol %, 0.03 mmol, 5.6 mg). The tube was then transferred into the glovebox. Inside the glovebox, Cs_2CO_3 (1.2 equiv., 0.12 mmol, 39.1 mg), 1,4-dioxane (distilled over Na and freeze-pump-thawed, 1 mL), substrate **1** (1 equiv., 0.1 mmol) and PhOTf (30 mol %, 0.03 mmol, 6.8 mg) were added sequentially to the tube. The tube was sealed with a PTFE lined cap, transferred out of the glovebox and heated in an oil bath at 70 ºC (oil temperature). After 48 h, the mixture was allowed to cool to room temperature. The mixture was diluted with EtOAc, passed through a small plug of silica gel and eluted with EtOAc. The solvent was removed *in vacuo*, and the residue was either purified by column chromatography (for

deuterium-labeling studies) or dissolved in $CDCl_3$ for crude NMR with 1,1,2,2-tetrachloroethane as the internal standard (for kinetic studies except for specified changes in the conditions and given reaction time).

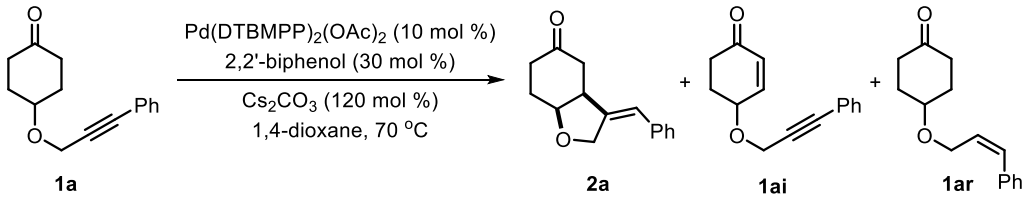
Table 4.8 Kinetic Data for Figure 4.1 with PhOTf



entry	time (h)	yield of **2a** (%)[a]	yield of **1ai** (%)	yield of **1ar** (%)	unreacted **1a** (%)
1	0	0	0	0	100
2	0.5	0	1	0	97
3	1	0	2	0	96
4	1.5	0	4	0	93
5	2	0	5	0	93
6	3	0	12	0	83
7	4	1	18	0	76
8	5	4	20	0	71
9	6	7	22	0	67
10	8	12	20	0	61
11	10	20	17	0	55
12	12	26	15	0	51
13	16	44	9	0	41
14	20	53	3	0	36
15	24	58	0	1	31
16	28	61	0	3	26
17	32	61	0	4	25
18	36	64	0	3	23
19	40	62	0	4	24
20	44	63	0	5	22
21	48	64	0	5	20

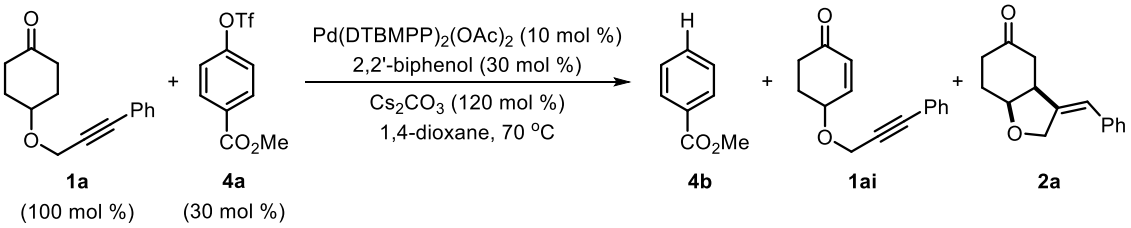
[a] **2a** refers to total β-alkenylation products.

Table 4.9 Kinetic Data for Figure 4.1 without PhOTf



entry	time (h)	yield of **2a** (%)	yield of **1ai** (%)	yield of **1ar** (%)	unreacted **1a** (%)
1	0	0	0	0	100
2	1	0	1	0	99
3	2	0	2	0	99
4	4	2	2	1	94
5	6	5	1	2	86
6	8	9	1	3	81
7	10	13	0	4	77
8	14	16	0	4	73
9	18	16	0	6	71
10	22	16	0	6	72
11	48	16	0	6	71

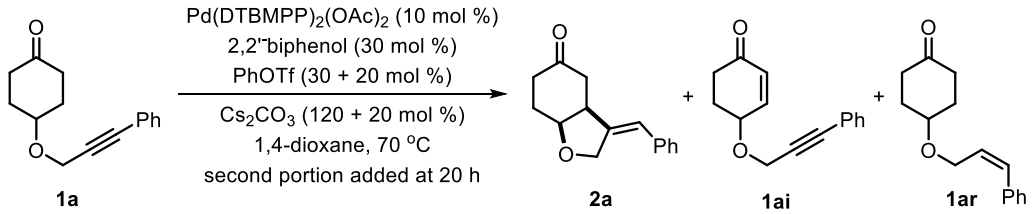
Table 4.10 Kinetic Data for Figure 4.2



entry	time (h)	unreacted **4a** (%)[a]	yield of **4b** (%)[a]	yield of **1ai** (%)[a]	yield of **2a** (%)[a]
1	0	30	0	0	0
2	1	28	0	2	0
3	2	21	3	5	0
4	3	10	9	12	0
5	4	2	15	16	1
6	5	0	16	16	3

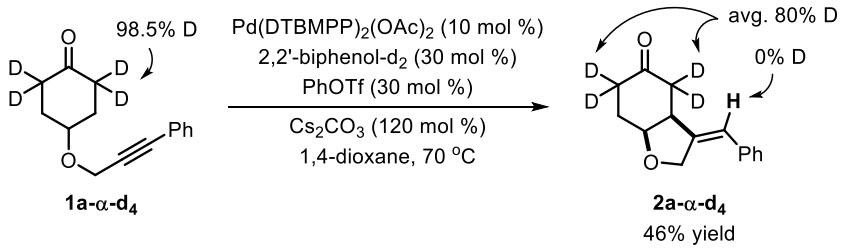
[a]All yields are based on **1a**.

Table 4.11 Kinetic Data for Figure 4.3 from 20 h[a]



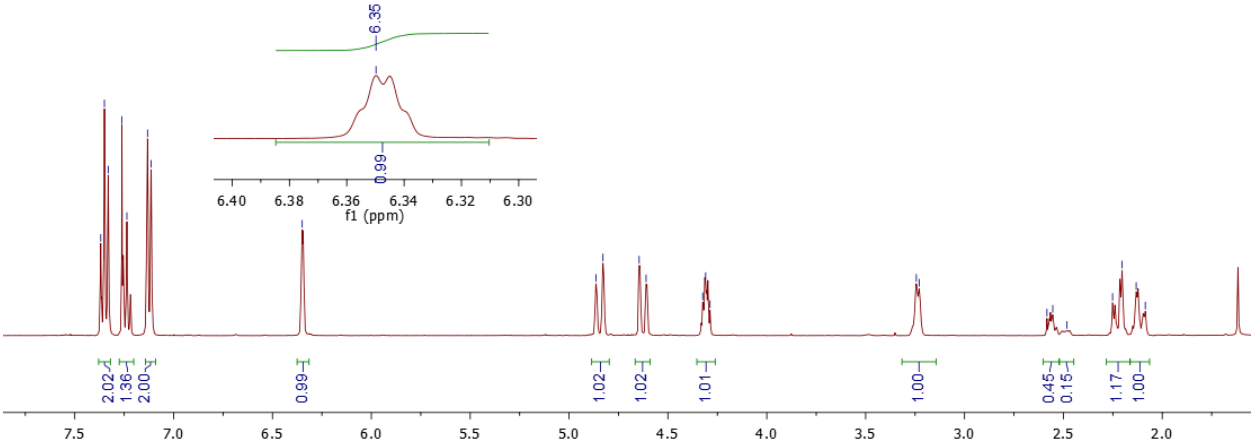
entry	time (h)	yield of **2a** (%)[b]	yield of **1ai** (%)	yield of **1ar** (%)	unreacted **1a** (%)
1	20	53	3	0	36
2	21	54	4	0	35
3	22	53	8	0	31
4	23	56	6	0	25
5	24	60	4	0	23
6	26	61	2	0	22
7	28	61	2	0	21
8	32	63	0	0	18
9	36	64	0	1	15
10	42	66	0	2	13
11	48	65	0	2	13

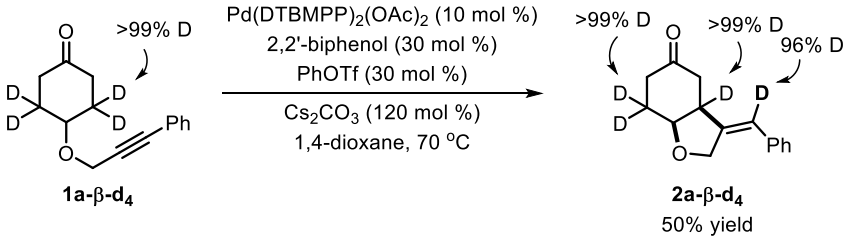
[a]Additional PhOTf (20 mol %) and Cs_2CO_3 (20 mol %) were added at 20 h. [b]**2a** refers to total β-alkenylation products.



Following the general procedure for mechanistic studies except for using 2,2'-biphenol-d_2 instead of 2,2'-biphenol, **1a-α-d4** was converted to **2a-α-d4** in 46% yield. The ^{1}H NMR spectrum shows nearly 100% hydrogen on the alkenyl position.

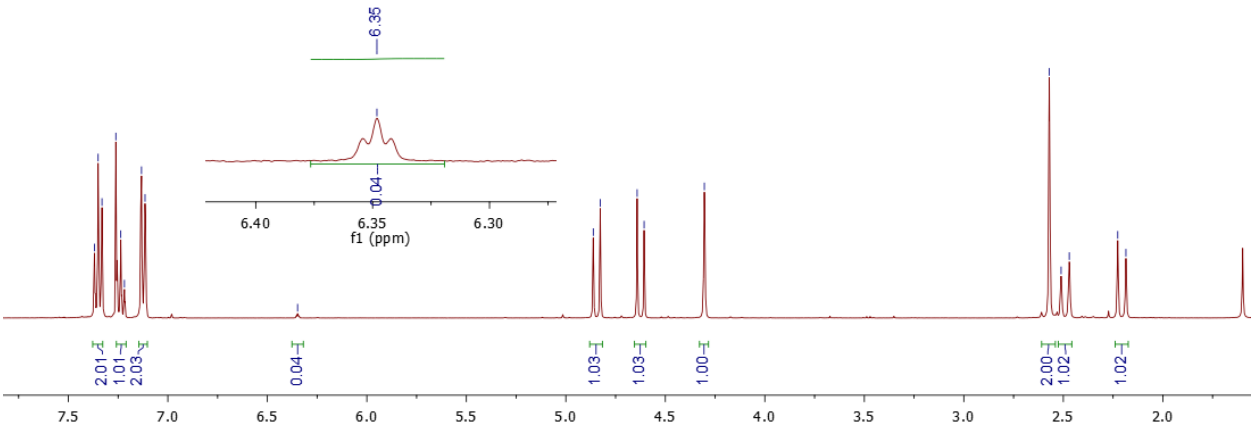
Figure 4.4 Partial ^{1}H-NMR Spectrum of **2a-α-d$_4$**





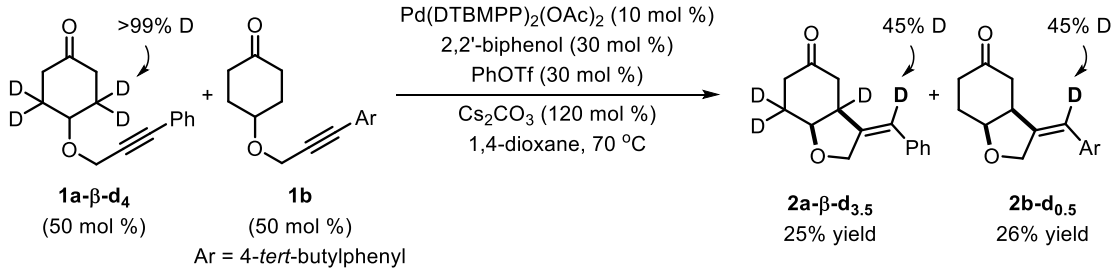
Following the general procedure for mechanistic studies, **1a-β-d$_4$** was converted to **2a-β-d$_4$** in 50% yield. The ^{1}H NMR spectrum shows 4% hydrogen on the alkenyl position.

Figure 4.5 Partial ^{1}H-NMR Spectrum of **2a-β-d$_4$**



Characterization data for **2a-β-d$_4$**:

***cis*-(*Z*)-3-(Phenylmethylene-d)hexahydrobenzofuran-5(4*H*)-one-3a,7,7-d$_3$ (2a-β-d$_4$)**: Colorless oil. R_f = 0.3 (hexane/EtOAc = 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 2H), 7.27 – 7.20 (m, 1H), 7.16 – 7.06 (m, 2H), 6.35 (t, *J* = 2.5 Hz, 0.04H), 4.84 (d, *J* = 14.0 Hz, 1H), 4.62 (d, *J* = 14.0 Hz, 1H), 4.30 (s, 1H), 2.57 (s, 2H), 2.49 (d, *J* = 16.4 Hz, 1H), 2.21 (d, *J* = 16.5 Hz, 1H). **^{2}H NMR** (77 MHz, $CHCl_3$) δ 6.39 (0.96D), 3.26 (1D), 2.21 (1D), 2.12 (1D). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.94, 143.66, 136.62, 128.54, 128.04, 127.00, 74.96, 69.45, 42.01, 34.85. **IR** (KBr, cm^{-1}) 2917, 2221, 1716, 1445, 1279, 1054, 698. **HRMS** calcd $C_{15}H_{13}D_4O_2$ $[M+H]^+$: 233.1474. Found: 233.1473.



Following the general procedure for mechanistic studies, **1a-β-d$_4$** (0.05 mmol) and **1b** (0.05 mmol) were converted to **2a-β-d$_{3.5}$** and **2b-d$_{0.5}$** in 25% and 26% yields, respectively. The ^{1}H NMR spectrum of **2a-β-d$_{3.5}$** (mixed with 7% **2aa-β-d$_{2.5}$**) shows 55% hydrogen on the alkenyl position. The ^{1}H NMR spectrum of **2b-d$_{0.5}$** (mixed with 14% **2ba-d$_{0.5}$**) shows 55% hydrogen on the alkenyl position.

Figure 4.6 Partial ^{1}H-NMR Spectrum of **2a-β-d$_{3.5}$**

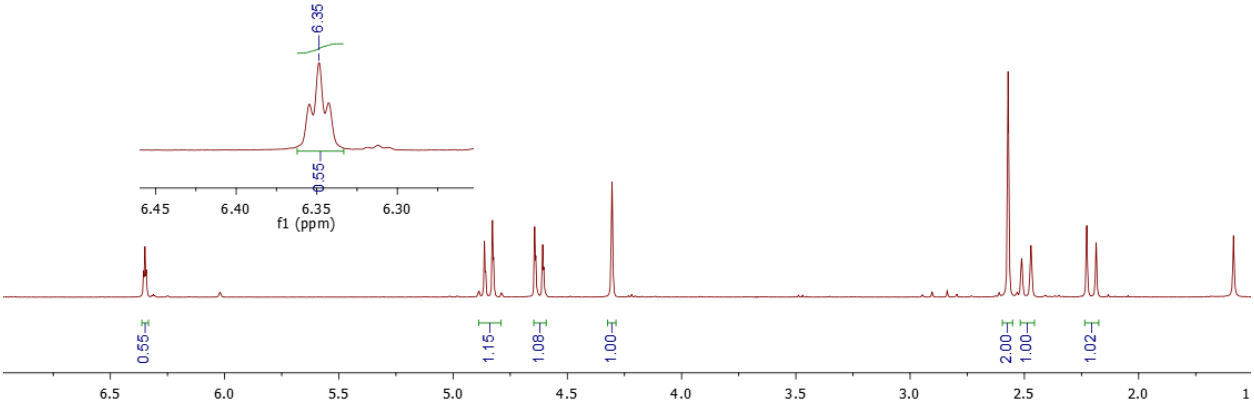
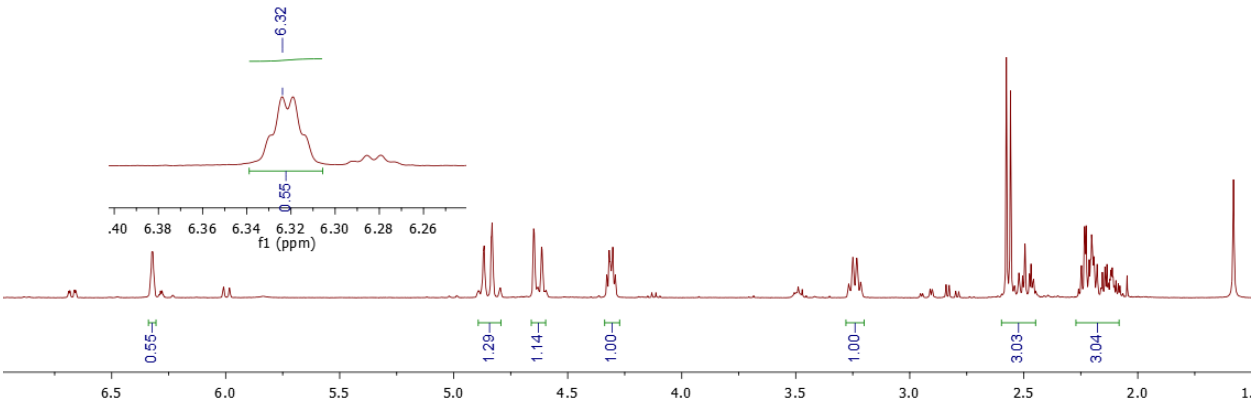
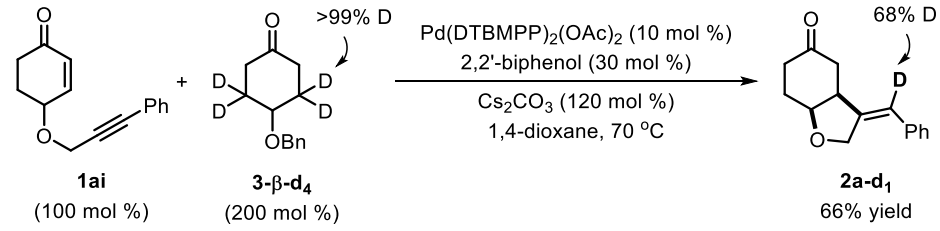


Figure 4.7 Partial ^{1}H-NMR Spectrum of **2b-d$_{0.5}$**

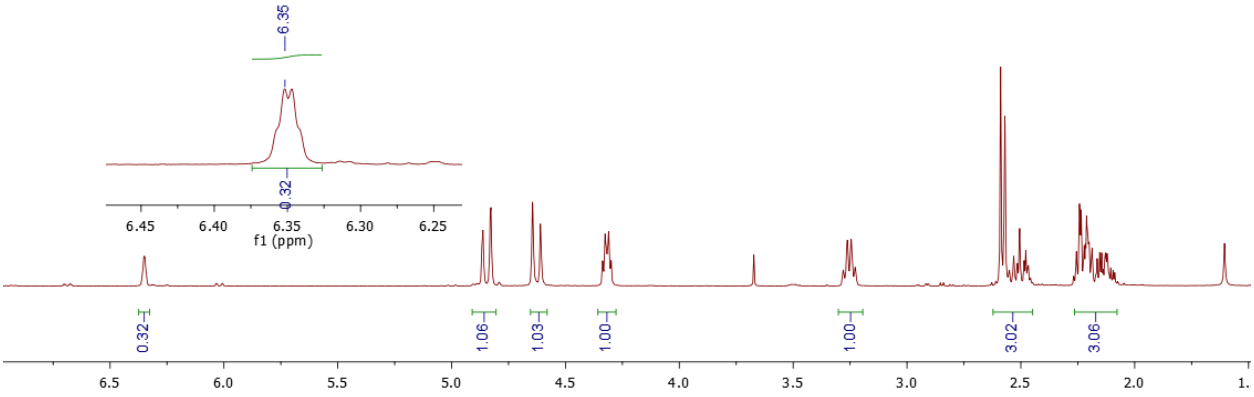


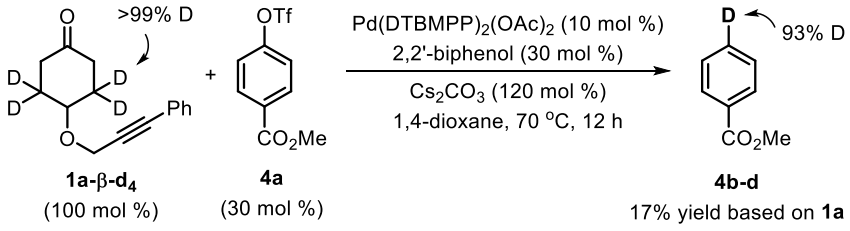


An 8-mL culture tube was flame-dried and charged with $Pd(DTBMPP)_2(OAc)_2$ (10 mol %, 0.01 mmol, 16.0 mg) and 2,2'-biphenol (30 mol %, 0.03 mmol, 5.6 mg). The tube was then transferred into the glovebox. Inside the glovebox, Cs_2CO_3 (1.2 equiv., 0.12 mmol, 39.1 mg), 1,4-dioxane (distilled over Na and freeze-pump-thawed, 1 mL), **1ai** (50 mol %, 0.05 mmol, 11.3 mg)

and **3-β-d$_4$** (1 equiv., 0.1 mmol, 20.8 mg) were added sequentially to the tube. The tube was sealed with a PTFE lined cap, transferred out of the glovebox and heated in an oil bath at 70 °C (oil temperature). After 24 h, the mixture was allowed to cool to room temperature. The mixture was diluted with EtOAc, passed through a small plug of silica gel and eluted with EtOAc. The solvent was removed *in vacuo*, and the residue was purified by column chromatography to give **2a-d$_1$** in 66% yield (based on **1ai**). The ^{1}H NMR spectrum (mixed with 3% **2aa-d$_1$**) shows 32% hydrogen on the alkenyl position.

Figure 4.8 Partial ^{1}H-NMR Spectrum of **2a-d$_1$**

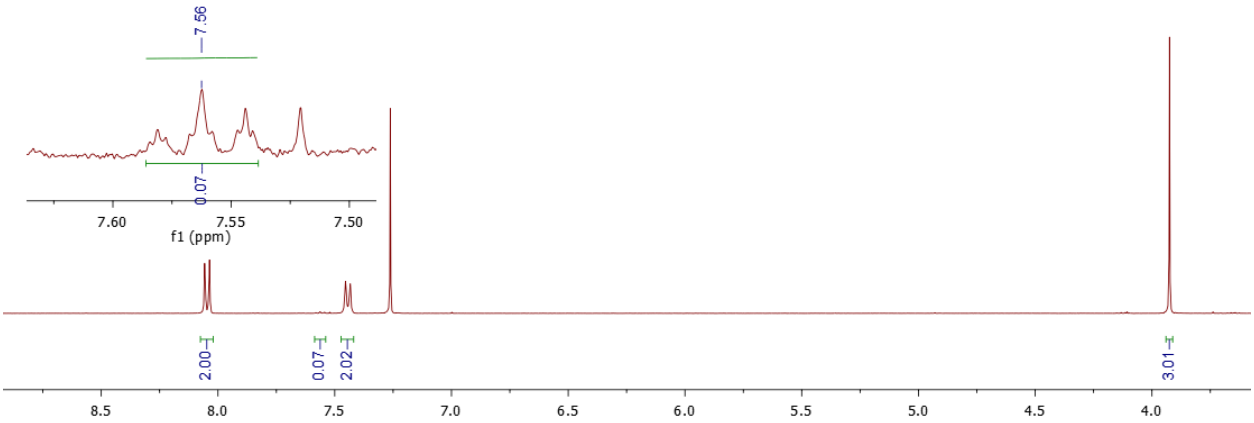


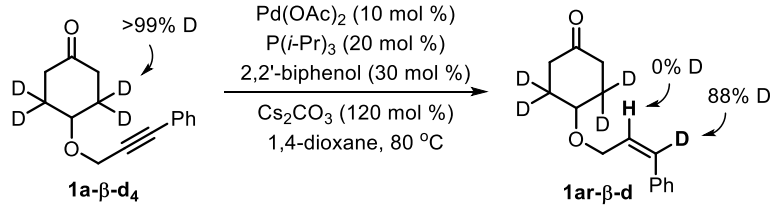


1a-β-d$_4$ (100 mol %) + **4a** (30 mol %) → **4b-d** 17% yield based on **1a**

Following the general procedure for mechanistic studies except for using **4a** instead of PhOTf and running for 12 h, **4a** was converted to **4b-d** in 17% yield based on **1a**. The ^{1}H NMR spectrum shows ca. 7% hydrogen at the *para* position.

Figure 4.9 Partial ^{1}H-NMR Spectrum of **4b-d**

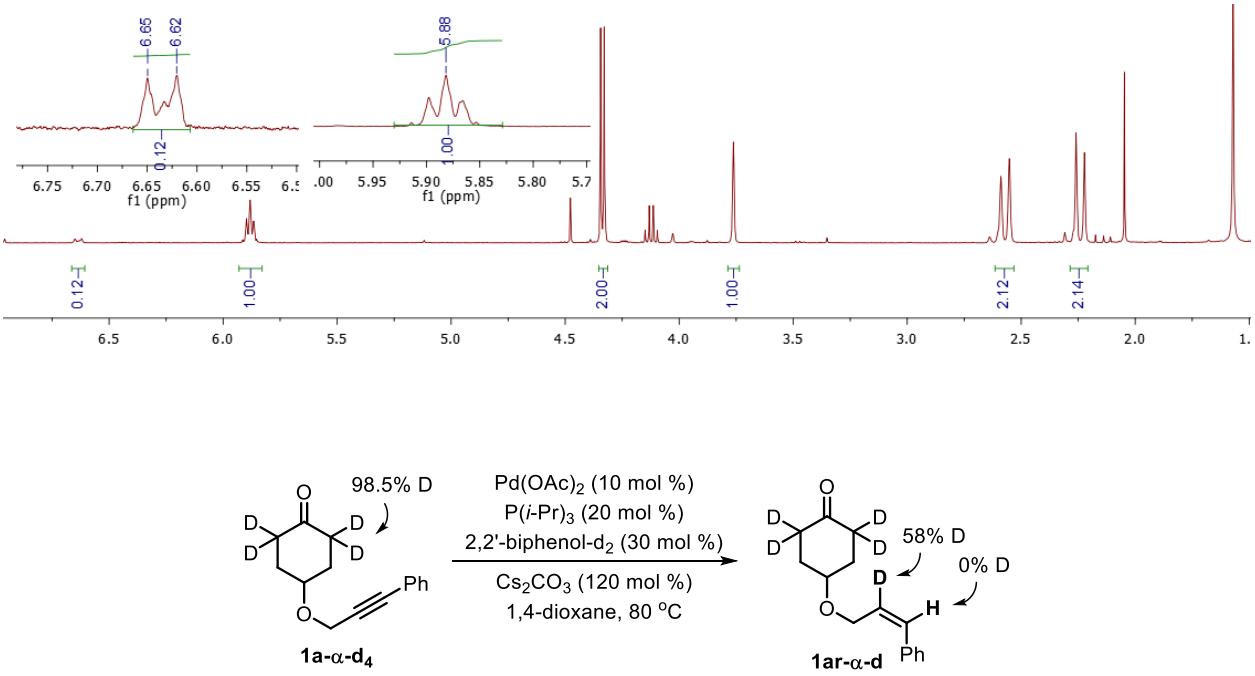




An 8-mL culture tube was flame-dried and charged with $Pd(OAc)_2$ (10 mol %, 0.01 mmol, 2.3 mg) and 2,2'-biphenol (30 mol %, 0.03 mmol, 5.6 mg). The tube was then transferred into the glovebox. Inside the glovebox, Cs_2CO_3 (1.2 equiv., 0.12 mmol, 39.1 mg), 1,4-dioxane (distilled over Na and freeze-pump-thawed, 1 mL), P(*i*-Pr)$_3$ (20 mol %, 0.02 mmol, 3.2 mg) and **1a-β-d$_4$** (1 equiv., 0.1 mmol, 23.2 mg) were added sequentially to the tube. The tube was sealed with a PTFE lined cap, transferred out of the glovebox and heated in an oil bath at 80 °C (oil temperature). After 36 h, the mixture was allowed to cool to room temperature. The mixture was diluted with EtOAc, passed through a small plug of silica gel and eluted with EtOAc. The solvent was removed *in vacuo*, and the residue was either purified by column chromatography to give **1ar-β-d** in 10% yield. The ^{1}H NMR spectrum (mixed with 10% **1a-β-d$_4$**) shows 12% hydrogen on the position adjacent

to phenyl, 100% hydrogen on the position adjacent to methylene, and 100% hydrogen on the allylic position.

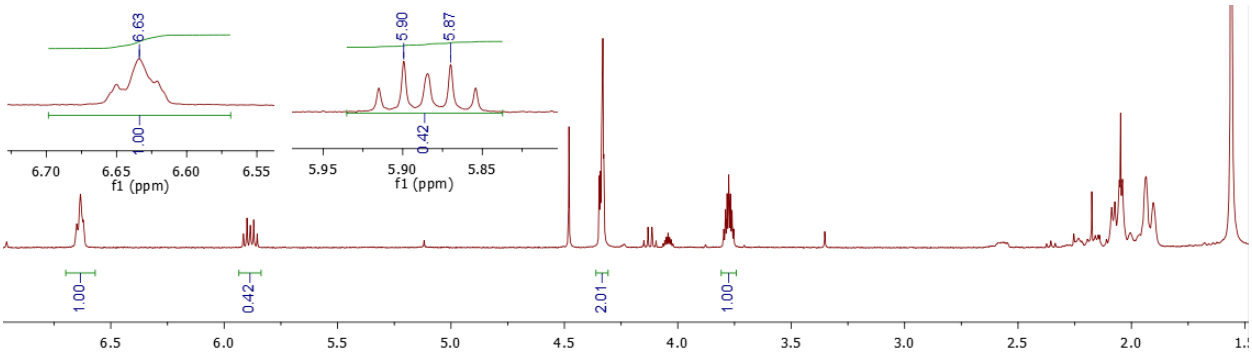
Figure 4.10 Partial ^{1}H-NMR Spectrum of **1ar-β-d**



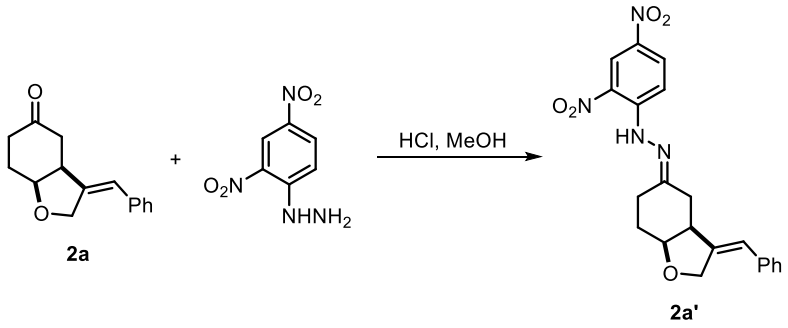
An 8-mL culture tube was flame-dried and charged with $Pd(OAc)_2$ (10 mol %, 0.01 mmol, 2.3 mg) and 2,2'-biphenol-d_2 (30 mol %, 0.03 mmol, 5.6 mg). The tube was then transferred into the glovebox. Inside the glovebox, Cs_2CO_3 (1.2 equiv., 0.12 mmol, 39.1 mg), 1,4-dioxane (distilled over Na and freeze-pump-thawed, 1 mL), P(*i*-Pr)$_3$ (20 mol %, 0.02 mmol, 3.2 mg) and **1a-α-d$_4$** (1 equiv., 0.1 mmol, 23.2 mg) were added sequentially to the tube. The tube was sealed with a PTFE lined cap, transferred out of the glovebox and heated in an oil bath at 80 °C (oil temperature). After 36 h, the mixture was allowed to cool to room temperature. The mixture was diluted with EtOAc, passed through a small plug of silica gel and eluted with EtOAc. The solvent was removed *in vacuo*, and the residue was either purified by column chromatography to give **1ar-α-d** in 5% yield.

The ^{1}H NMR spectrum (mixed with 20% **1a-α-d$_4$**) shows 100% hydrogen on the position adjacent to phenyl, 42% hydrogen on the position adjacent to methylene, and 100% hydrogen on the allylic position.

Figure 4.11 Partial ^{1}H-NMR Spectrum of **1ar-α-d**



4.4.8 X-ray crystallography data



A 4-mL vial was charged with **2a** (1 equiv., 0.05 mmol, 11.4 mg), DNP (1 equiv., 0.05 mmol, 9.9 mg), methanol (0.5 mL) and concentrated HCl (2 μL), and the mixture was stirred at room temperature for 2 days. The precipitate was collected through filtration and washed with methanol. The solid was then eluted with DCM, and the filtrate was concentrated to give **2a'** as an orange solid. The solid was dissolved in DCM/hexane mixed solvent for crystal growth by slow evaporation.

Figure 4.12 Crystal Structure of **2a'**

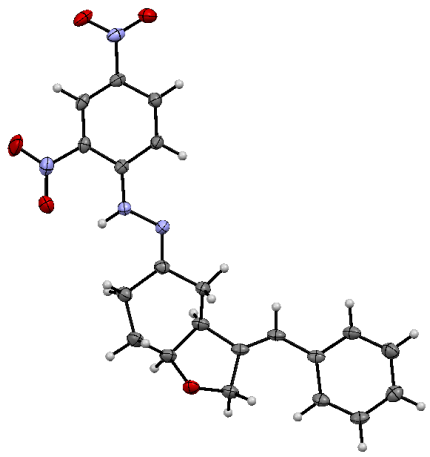
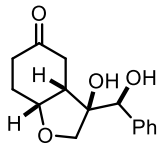


Table 4.12 X-Ray Crystallography Data of **2a'**

Empirical formula	$C_{21}H_{20}N_4O_5$
Formula weight	408.41
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	7.6040(4)
b/Å	20.0492(8)
c/Å	12.5383(6)
α/°	90
β/°	97.5110(10)
γ/°	90
Volume/Å^3	1895.11(15)
Z	4
Density (calculated) g/cm^3	1.431
Absorption coefficient/mm^{-1}	0.104
F(000)	856.0
Crystal size/mm^3	0.03 × 0.03 × 0.02
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.22 to 56.64
Index ranges	$-10 \leq h \leq 8$, $-25 \leq k \leq 26$, $-16 \leq l \leq 16$

Table 4.12 Continued X-Ray Crystallography Data of **2a'**

Reflections collected	33272
Independent reflections	4706 [R_{int} = 0.0378, R_{sigma} = 0.0321]
Data/restraints/parameters	4706/0/271
Goodness-of-fit on F^2	1.025
Final R indexes [I>=2σ (I)]	R_1 = 0.0485, wR_2 = 0.1082
Final R indexes [all data]	R_1 = 0.0782, wR_2 = 0.1197
Largest diff. peak and hole/e $Å^{-3}$	0.38/-0.31



11

The white solid **11** was dissolved in benzene for crystal growth by slow evaporation. Note: **11** might be a colorless oil if isolated from evaporation of polar solvents such as chloroform or EtOAc.

Figure 4.13 Crystal Structure of **11**

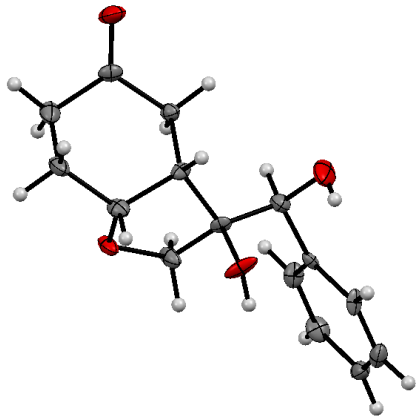


Table 4.13 X-Ray Crystallography Data of **11**

Empirical formula	$C_{15}H_{18}O_4$
Formula weight	262.29
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	$Pca2_1$
a/Å	19.8814(14)
b/Å	5.9438(4)
c/Å	21.4591(15)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2535.8(3)
Z	8
Density (calculated) g/cm^3	1.374
Absorption coefficient/mm^{-1}	0.099
F(000)	1120.0
Crystal size/mm^3	0.301 × 0.109 × 0.088
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.098 to 56.002
Index ranges	$-26 \leq h \leq 26$, $-7 \leq k \leq 7$, $-28 \leq l \leq 28$
Reflections collected	65551
Independent reflections	6099 [R_{int} = 0.1280, R_{sigma} = 0.0712]
Data/restraints/parameters	6099/1/347
Goodness-of-fit on F^2	1.164
Final R indexes [I>=2σ (I)]	R_1 = 0.0779, wR_2 = 0.1224
Final R indexes [all data]	R_1 = 0.1168, wR_2 = 0.1333
Largest diff. peak and hole/e Å^{-3}	0.36/-0.33
Flack parameter	-0.3(5)

4.5 References

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4.6 NMR Spectra

Figure 4.14 ^{1}H-NMR and ^{13}C-NMR Spectra of $Pd(DTBMPP)_2(OAc)_2$

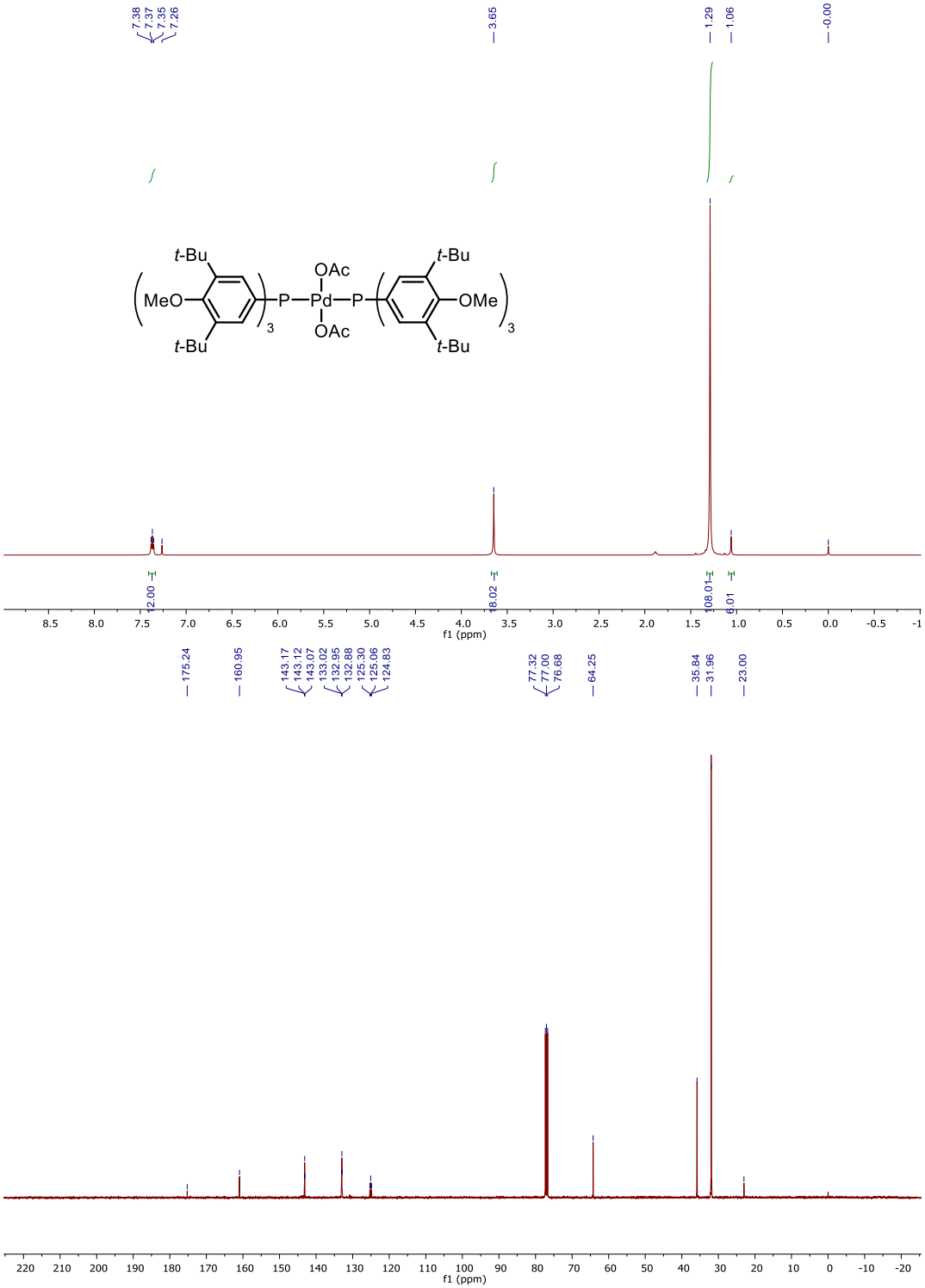


Figure 4.15 ^{31}P-NMR Spectrum of $Pd(DTBMPP)_2(OAc)_2$

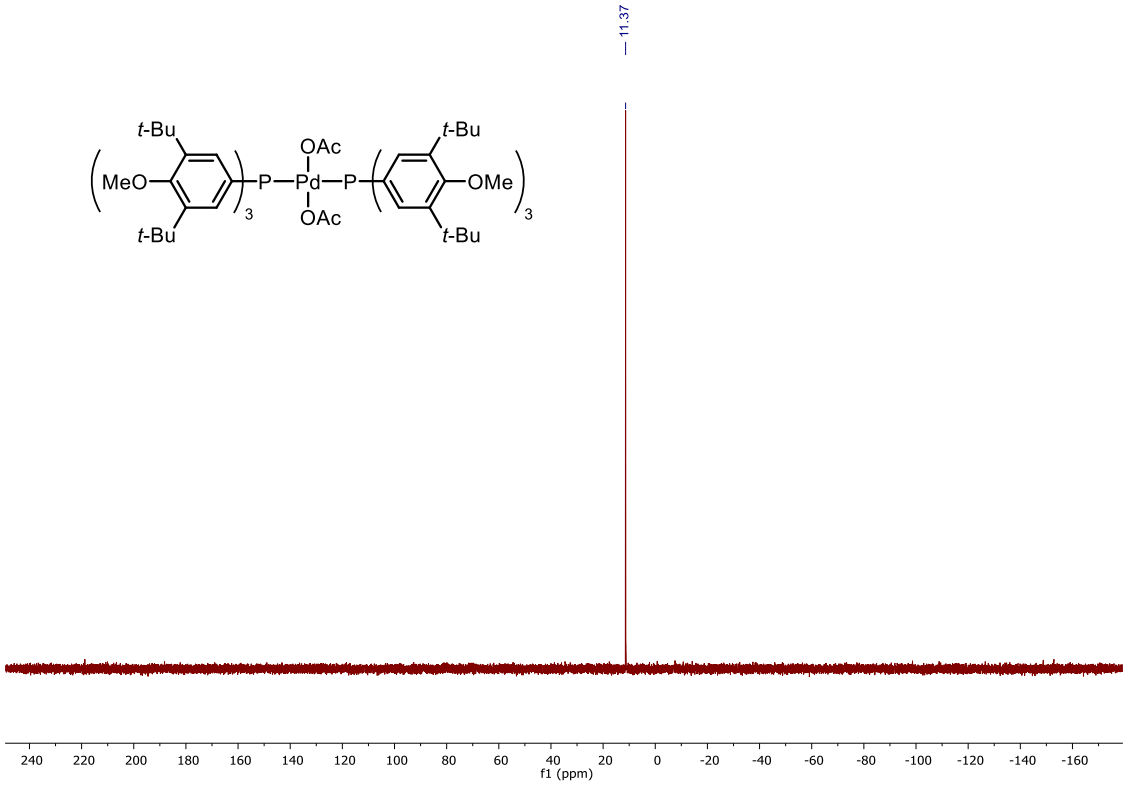


Figure 4.16 ^{1}H-NMR and ^{13}C-NMR Spectra of **1a-β-d$_4$**

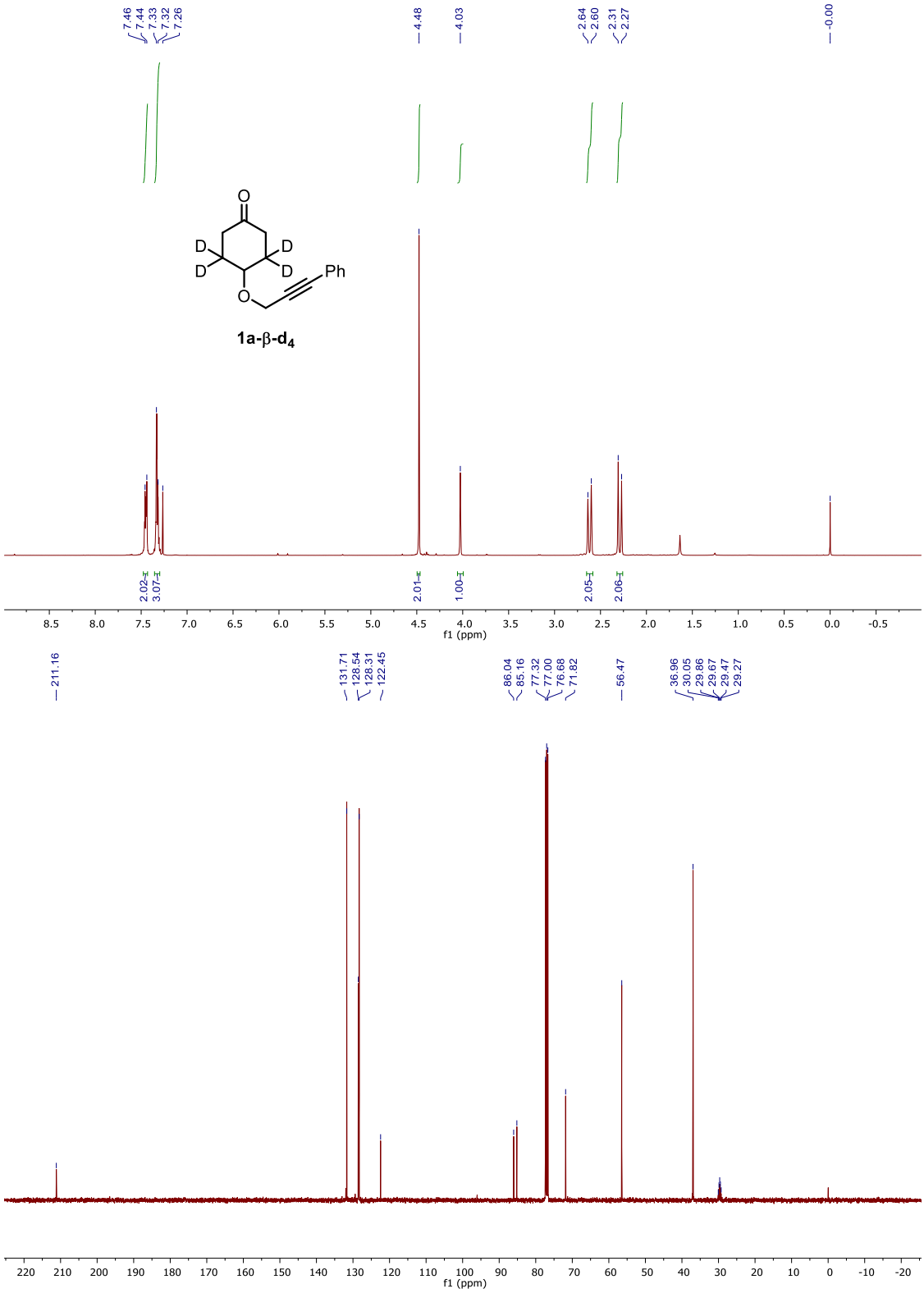


Figure 4.17 ^{2}H-NMR Spectrum of **1a-β-d$_4$**

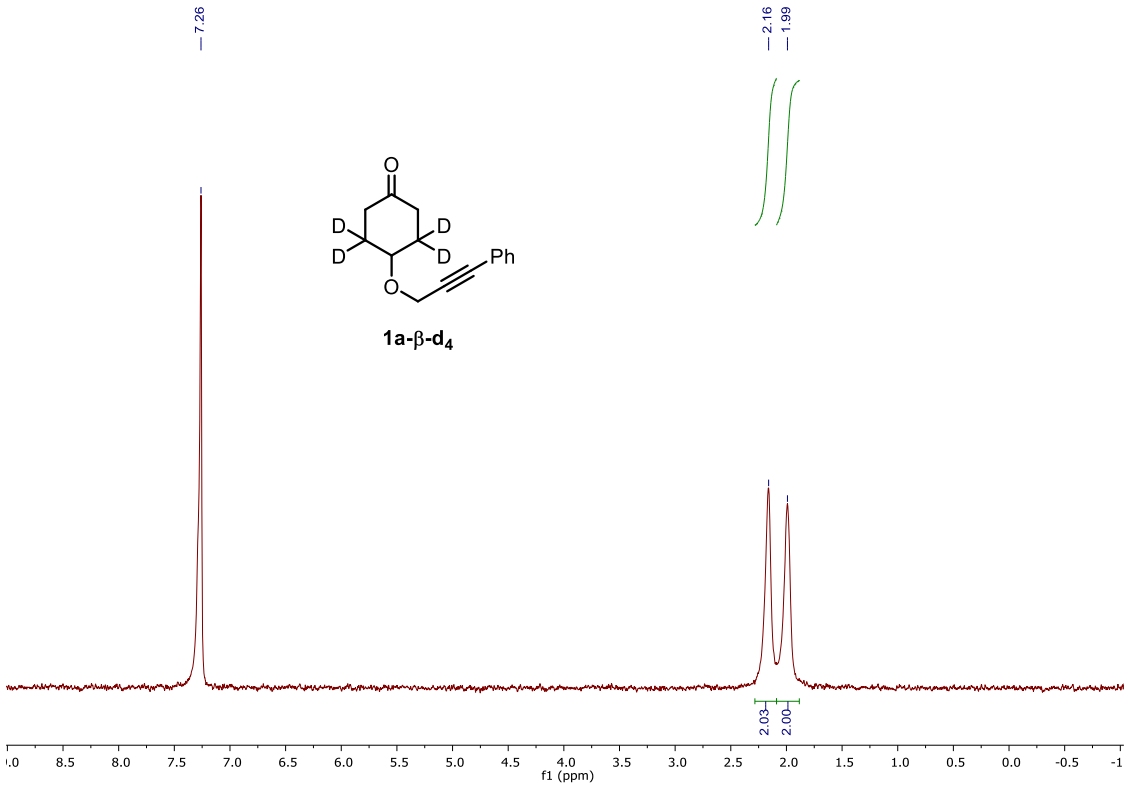


Figure 4.18 ^{1}H-NMR and ^{13}C-NMR Spectra of **3-β-d$_4$**

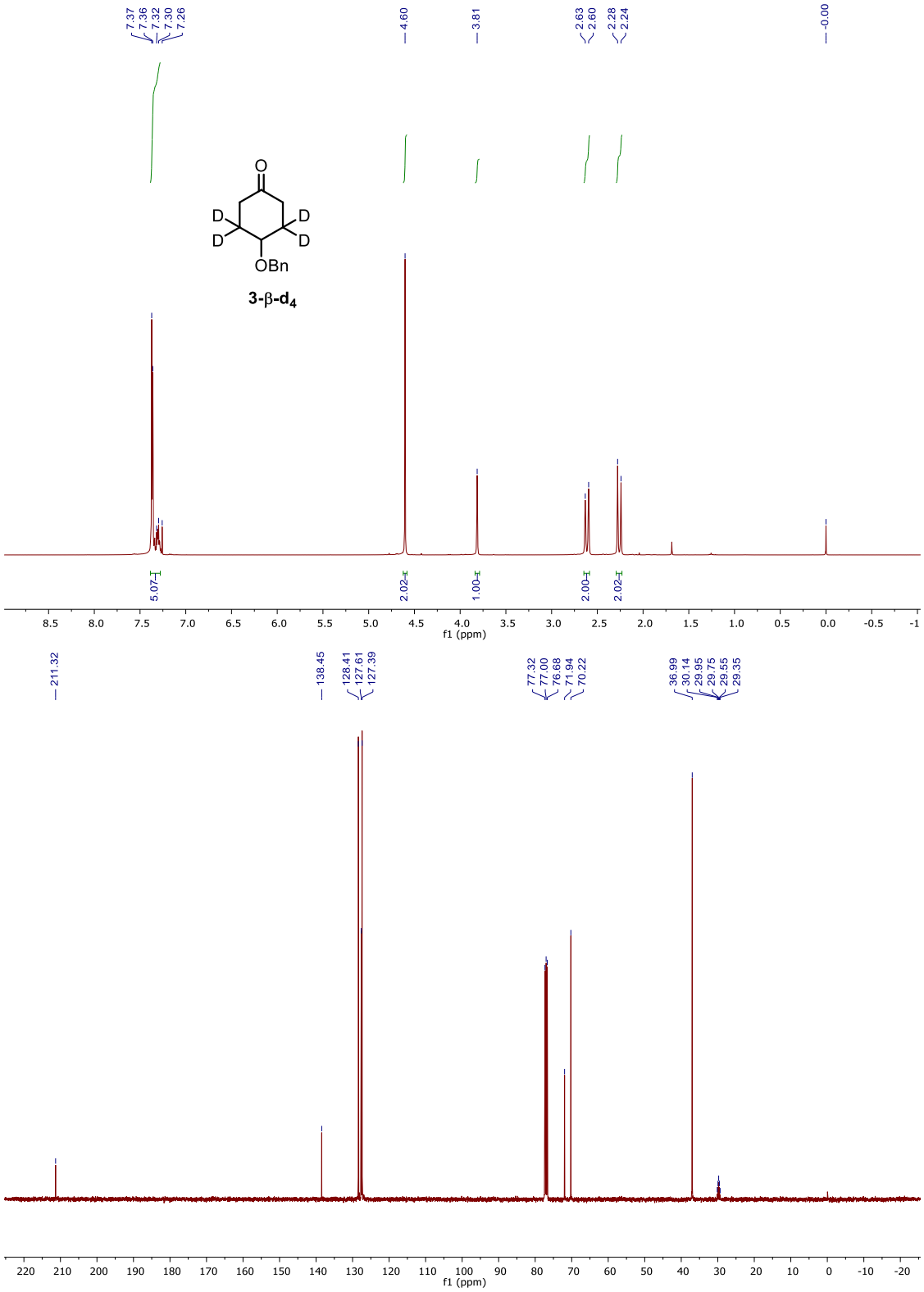


Figure 4.19 ^{2}H-NMR Spectrum of **3-β-d$_4$**

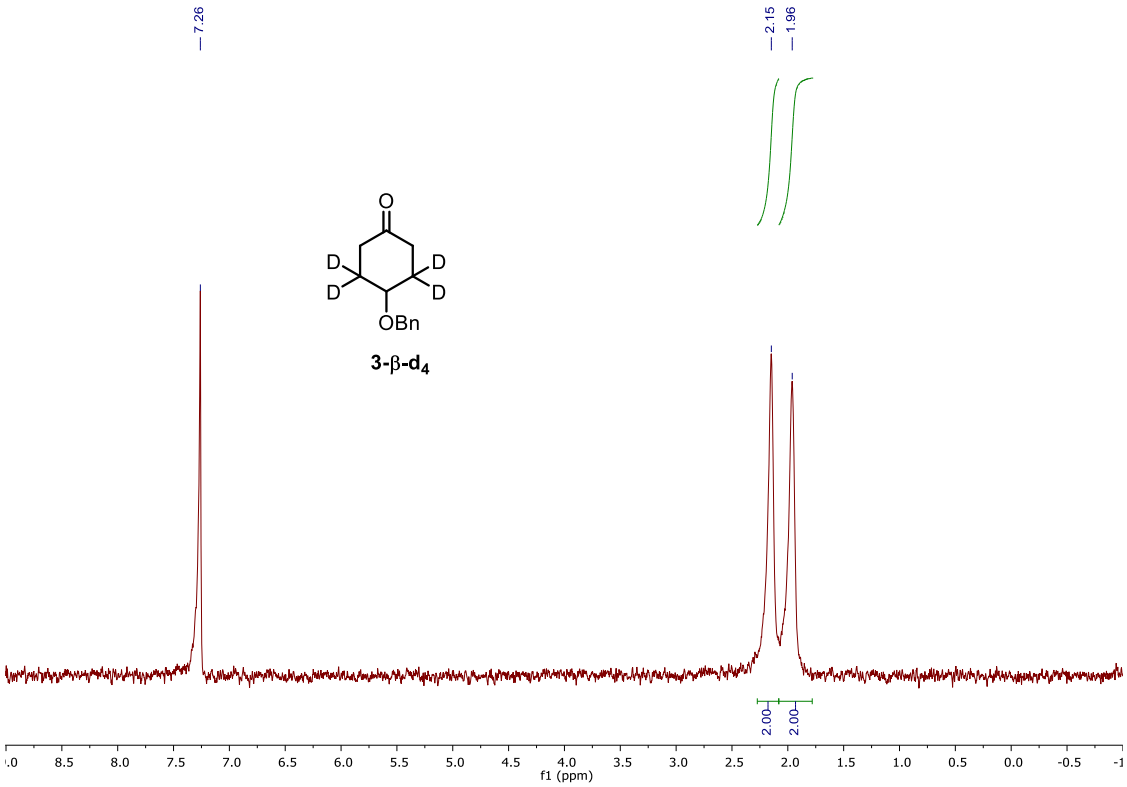


Figure 4.20 ^{1}H-NMR and ^{13}C-NMR Spectra of **1ai**

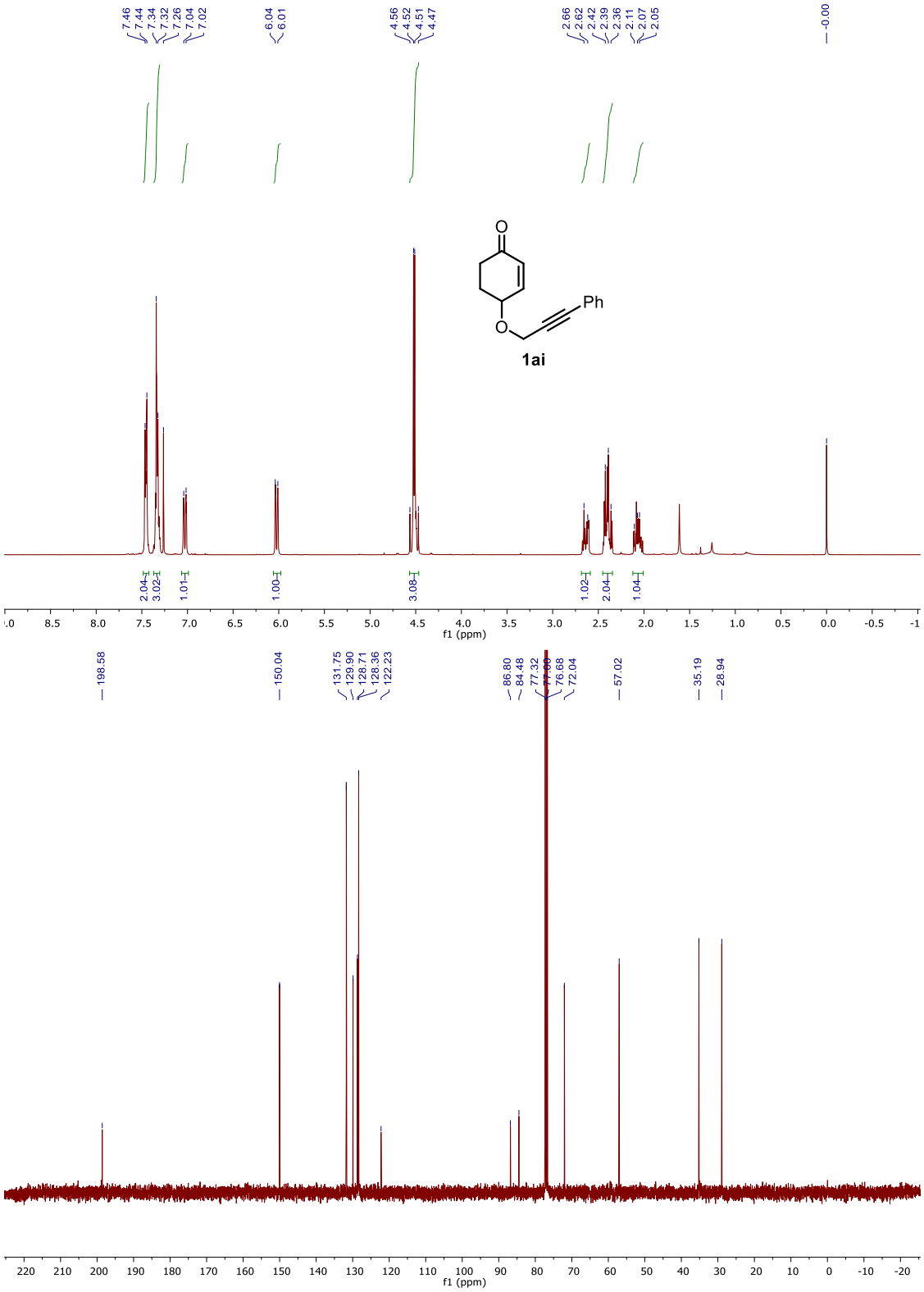


Figure 4.21 ^{1}H-NMR and ^{13}C-NMR Spectra of **1d**

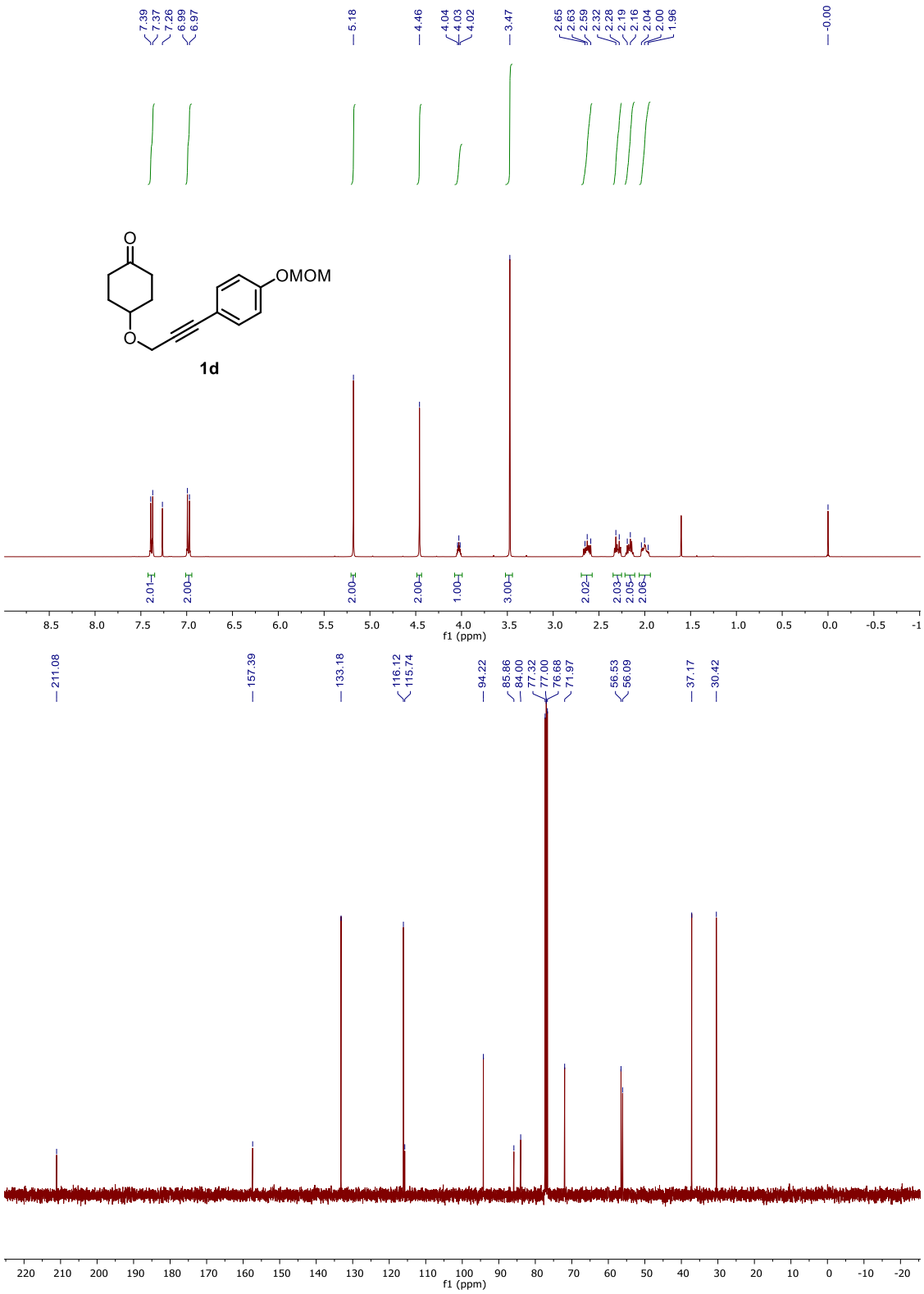


Figure 4.22 ^{1}H-NMR and ^{13}C-NMR Spectra of **1e**

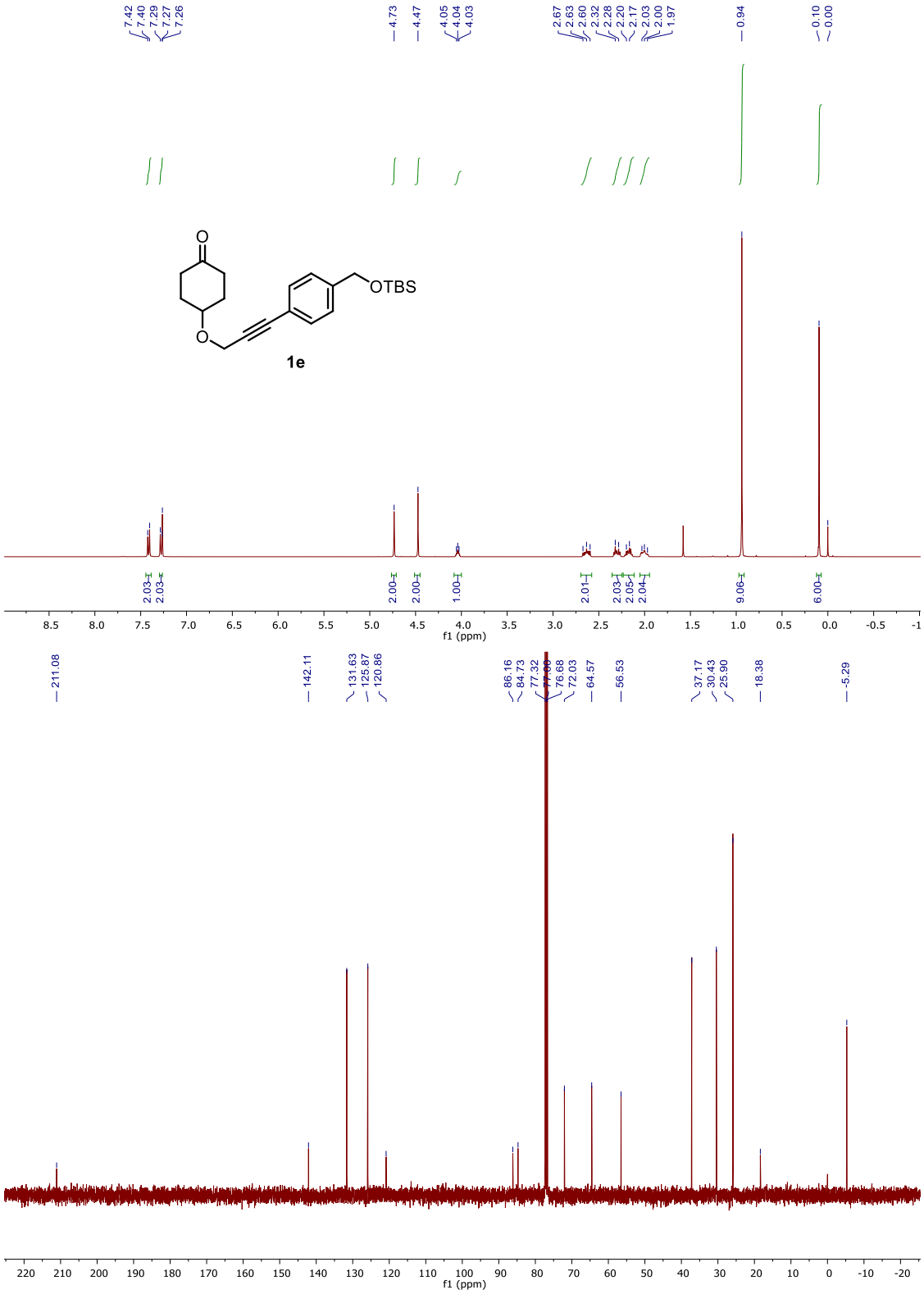


Figure 4.23 ^{1}H-NMR and ^{13}C-NMR Spectra of **1f**

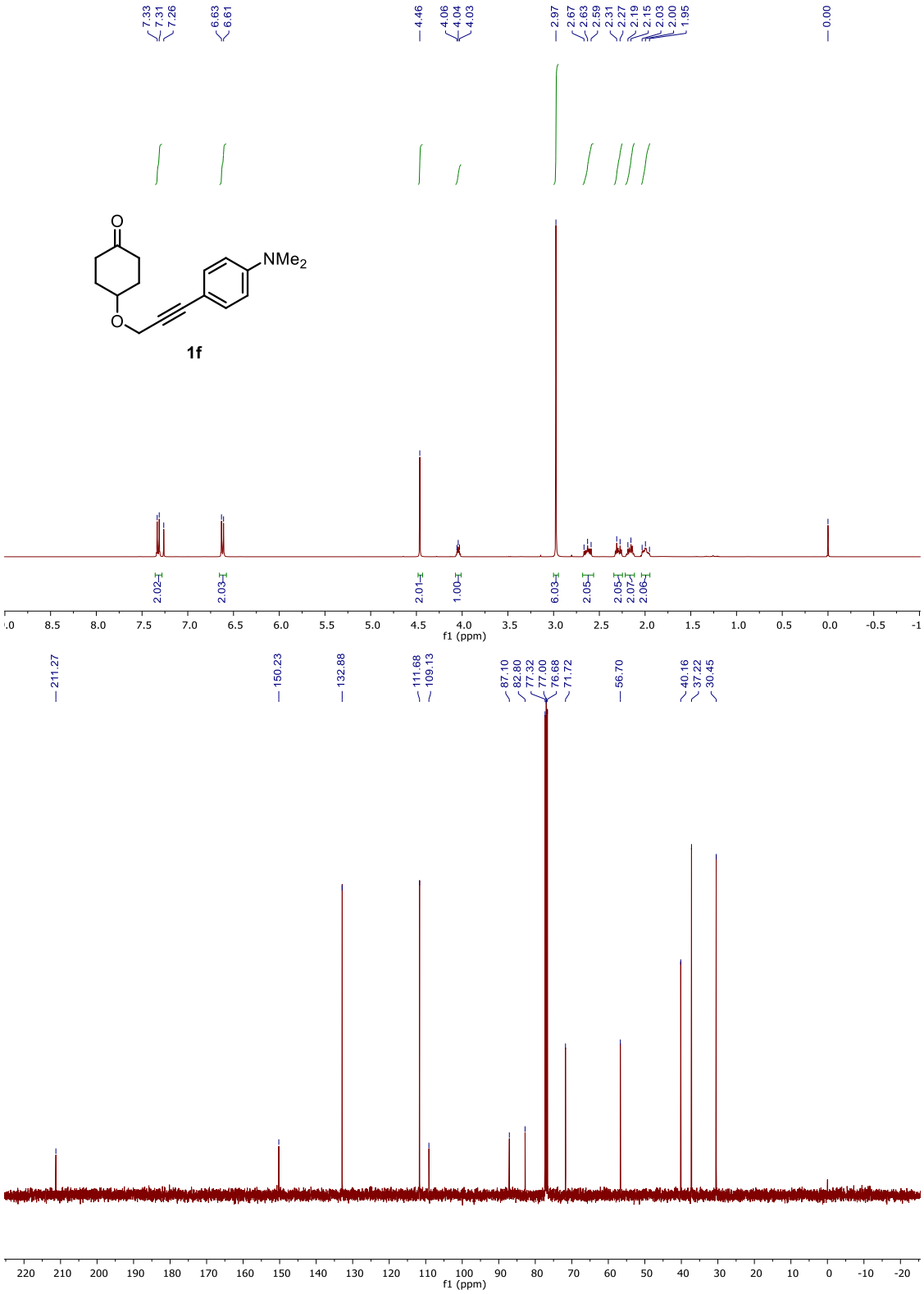


Figure 4.24 ^{1}H-NMR and ^{13}C-NMR Spectra of **1g**

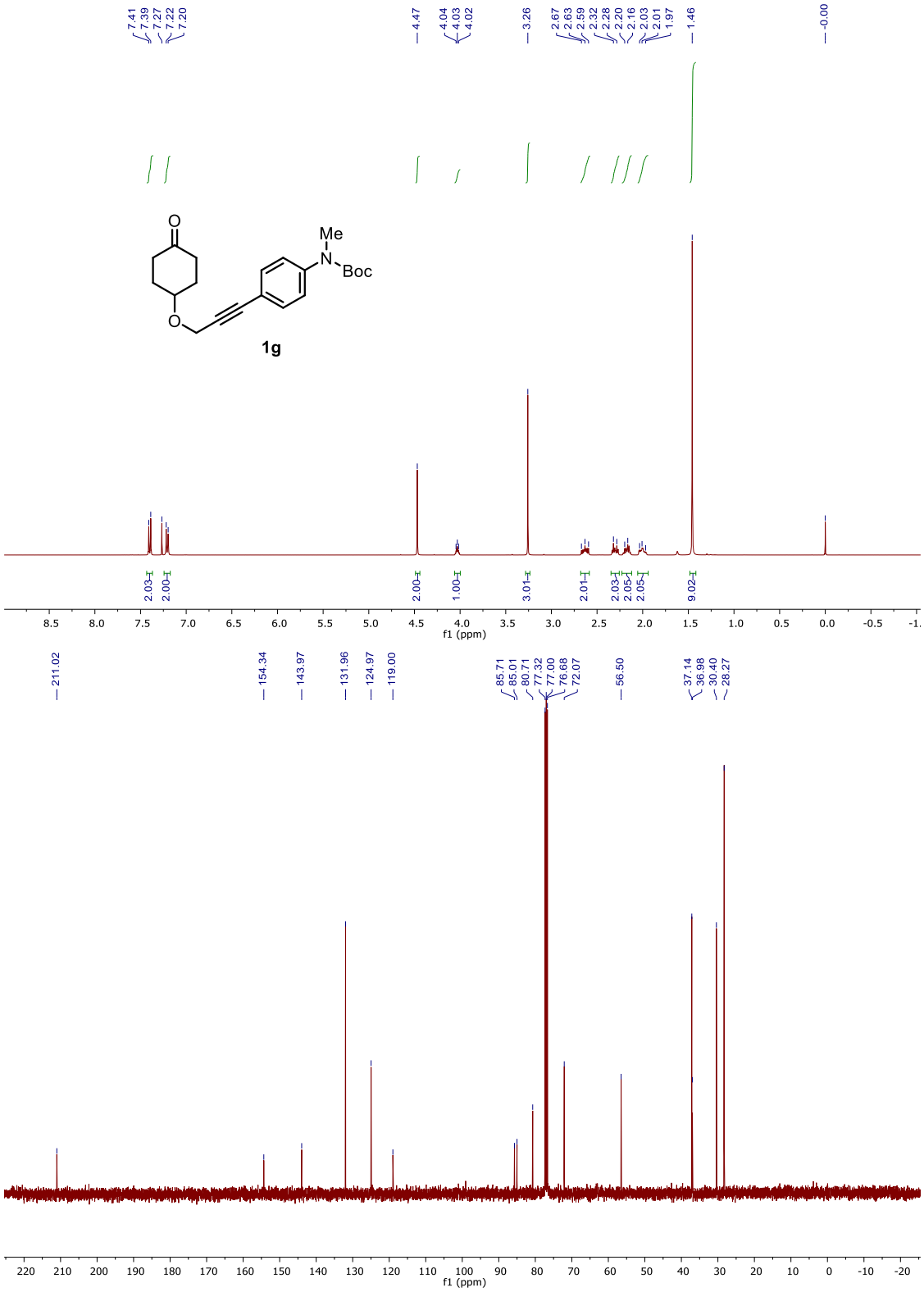


Figure 4.25 ^{1}H-NMR and ^{13}C-NMR Spectra of **1s**

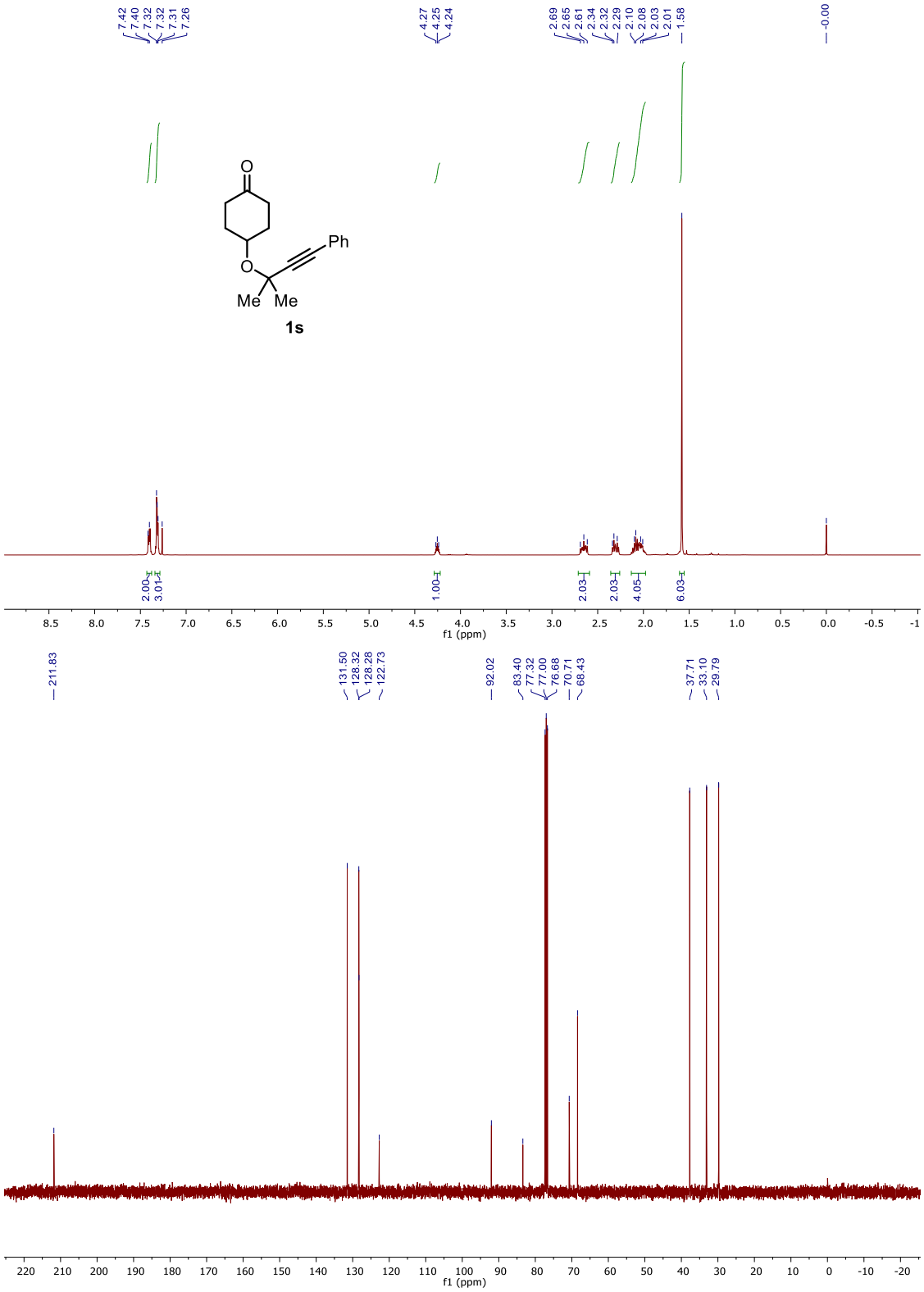


Figure 4.26 ^{1}H-NMR and ^{13}C-NMR Spectra of **1t**

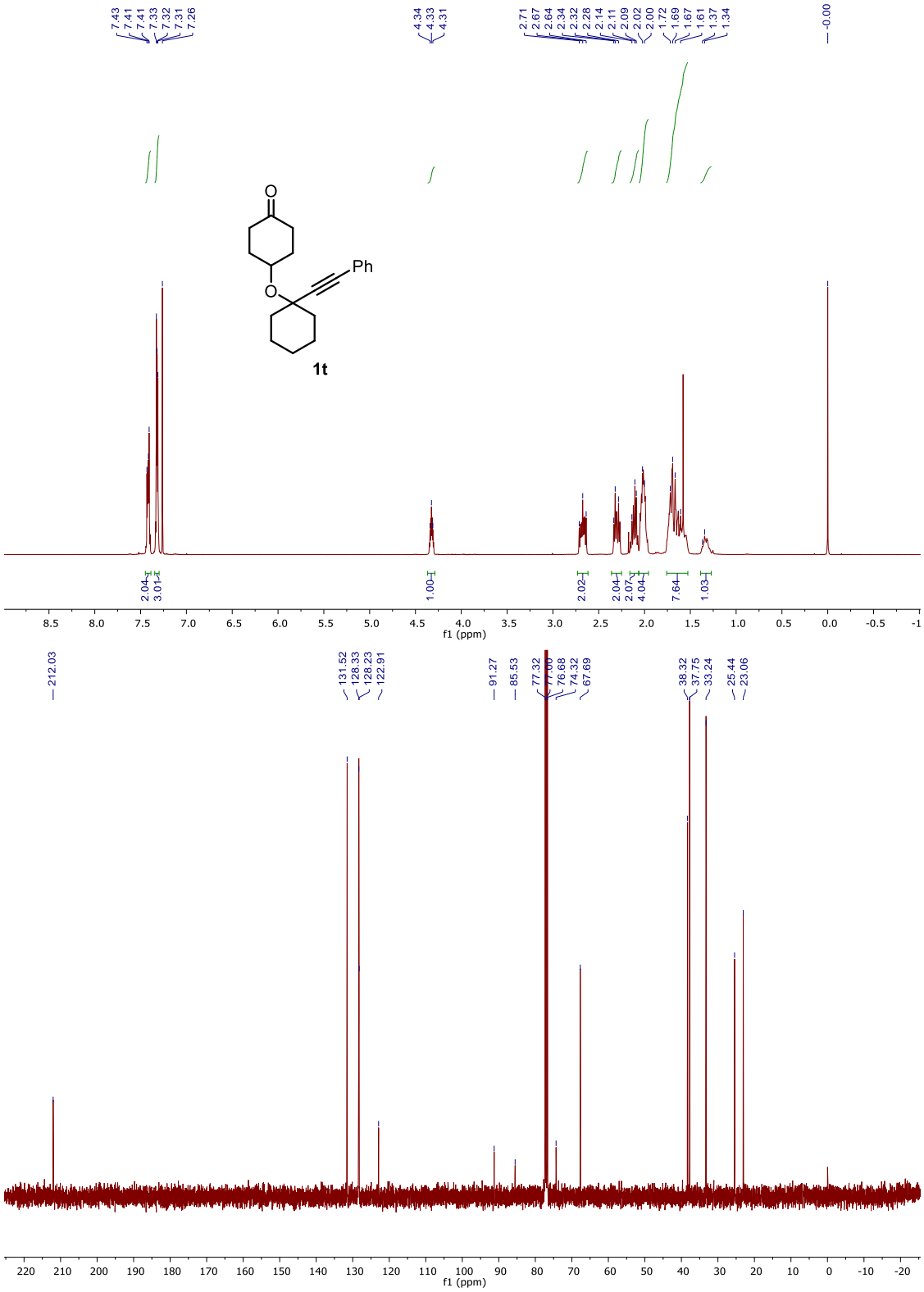


Figure 4.27 ^{1}H-NMR and ^{13}C-NMR Spectra of **1u**

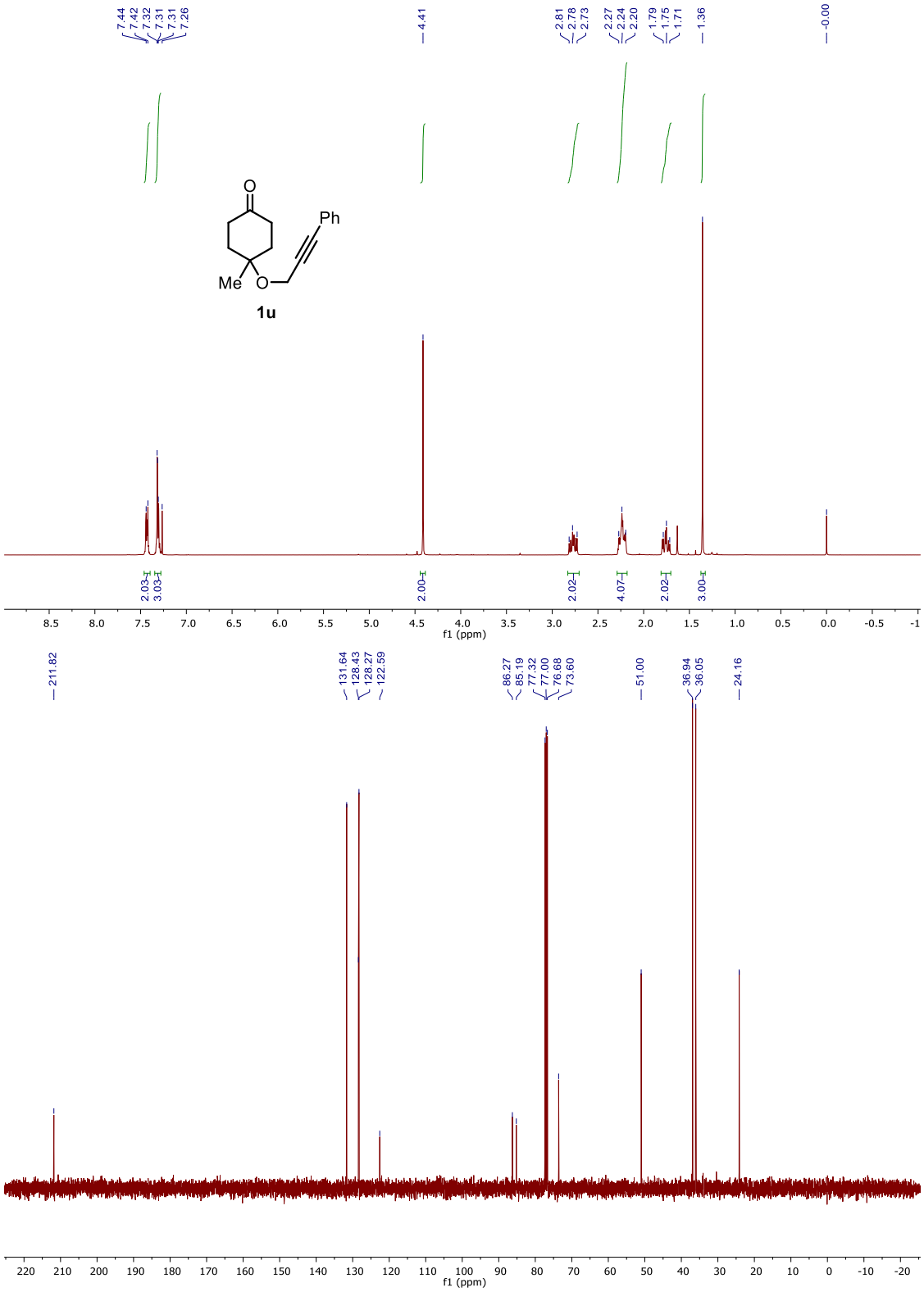


Figure 4.28 ^{1}H-NMR and ^{13}C-NMR Spectra of **1v**

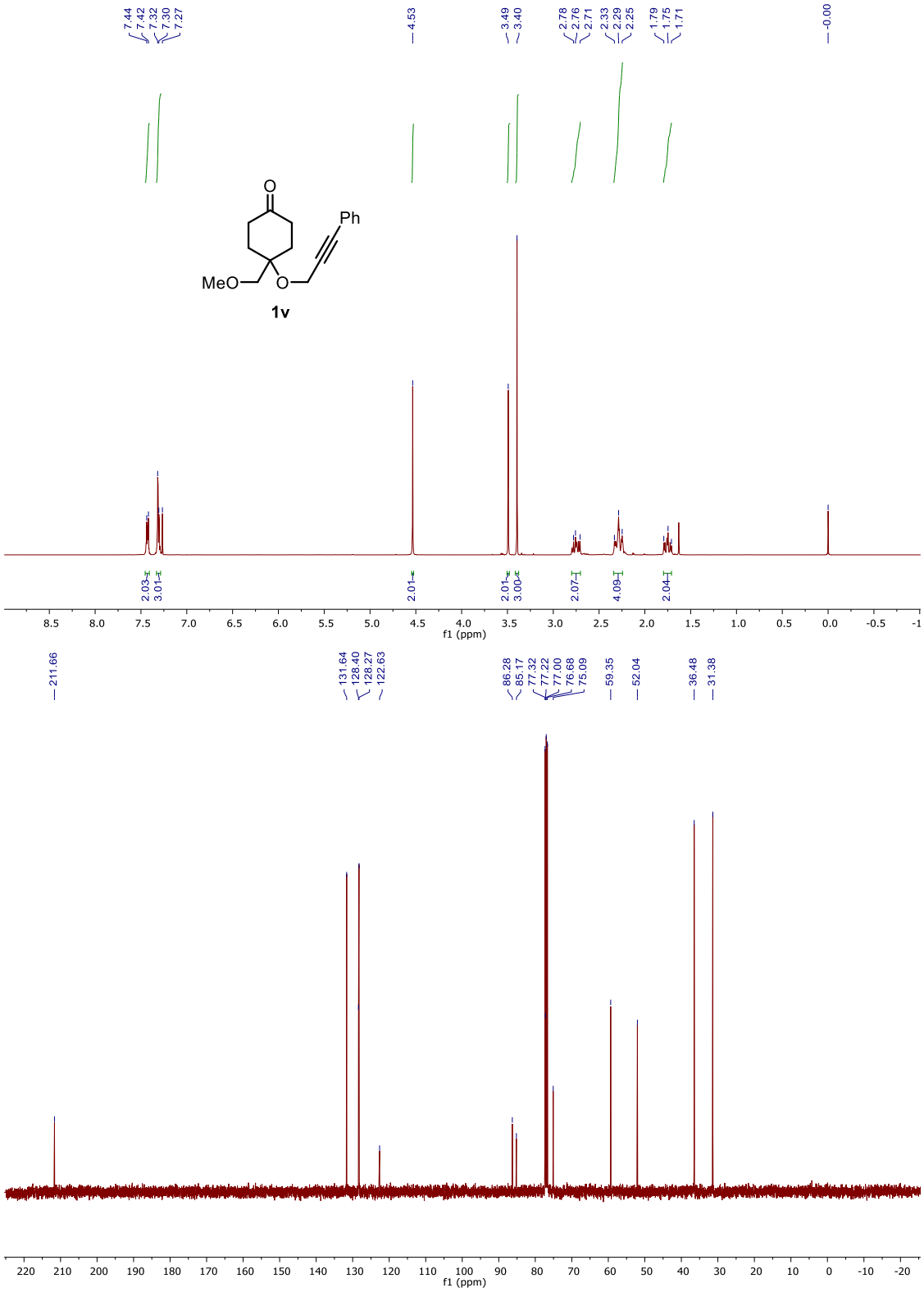


Figure 4.29 ^{1}H-NMR and ^{13}C-NMR Spectra of **1w**

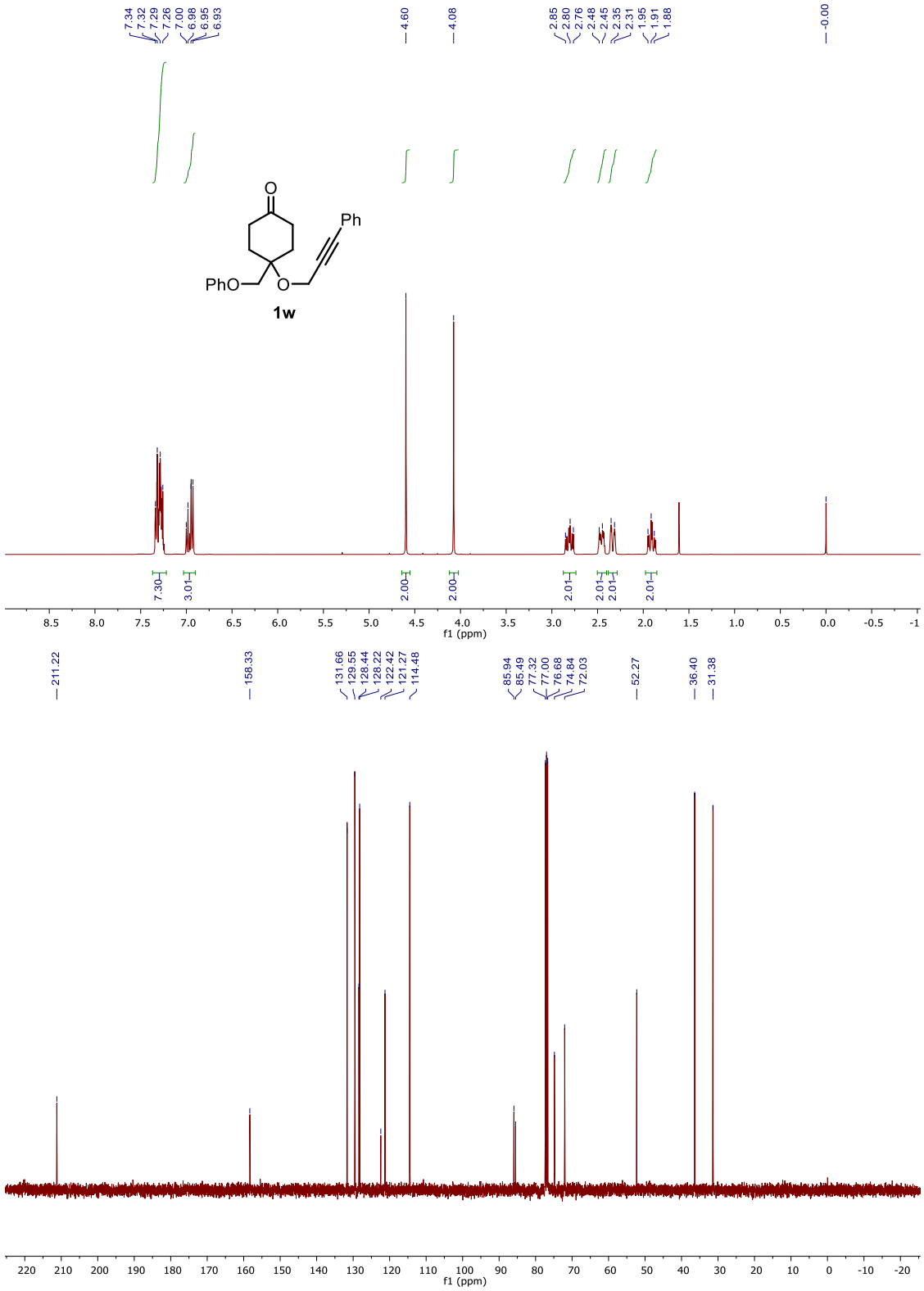


Figure 4.30 ^{1}H-NMR and ^{13}C-NMR Spectra of **1x**

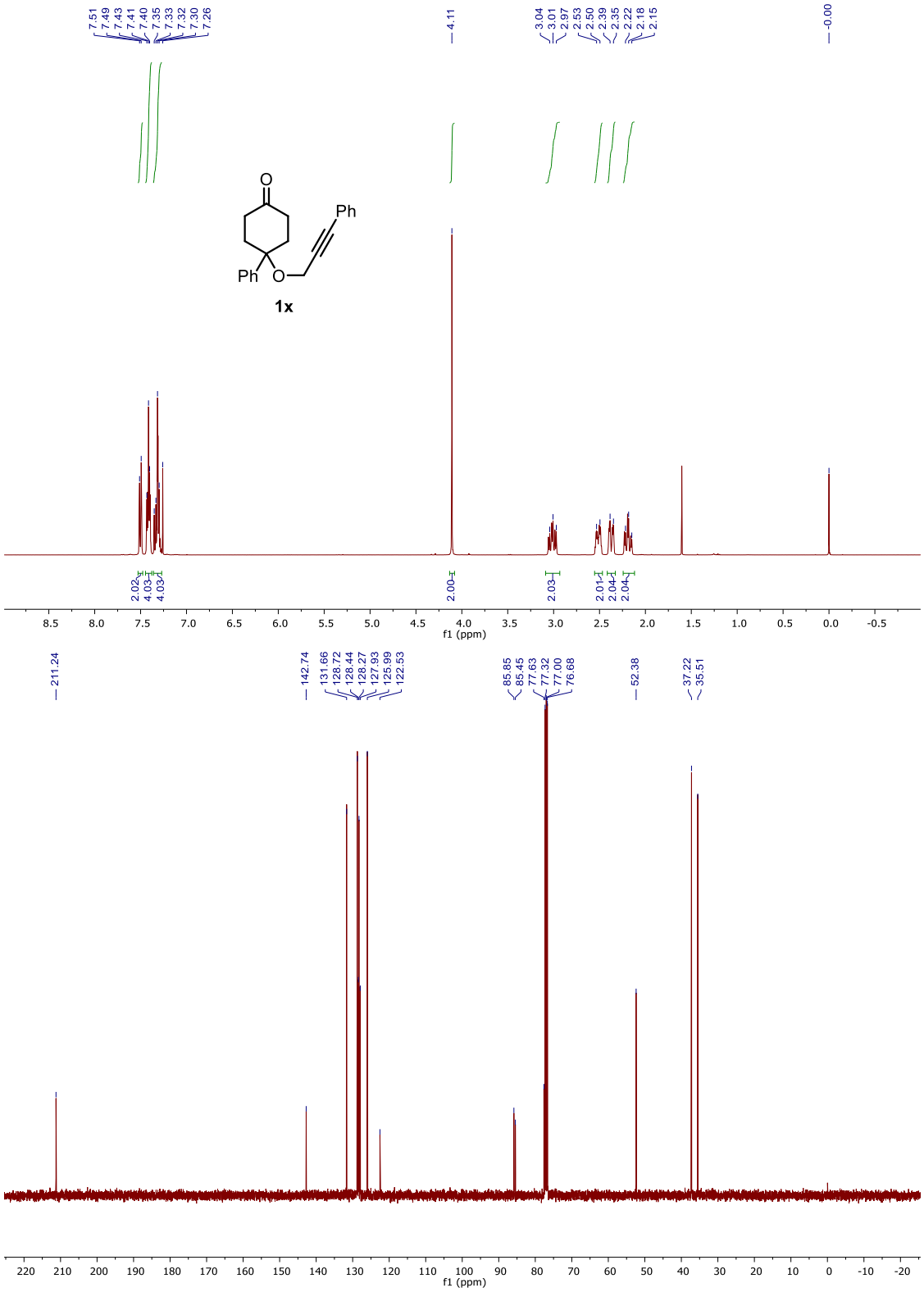


Figure 4.31 ^{1}H-NMR and ^{13}C-NMR Spectra of **15-1w**

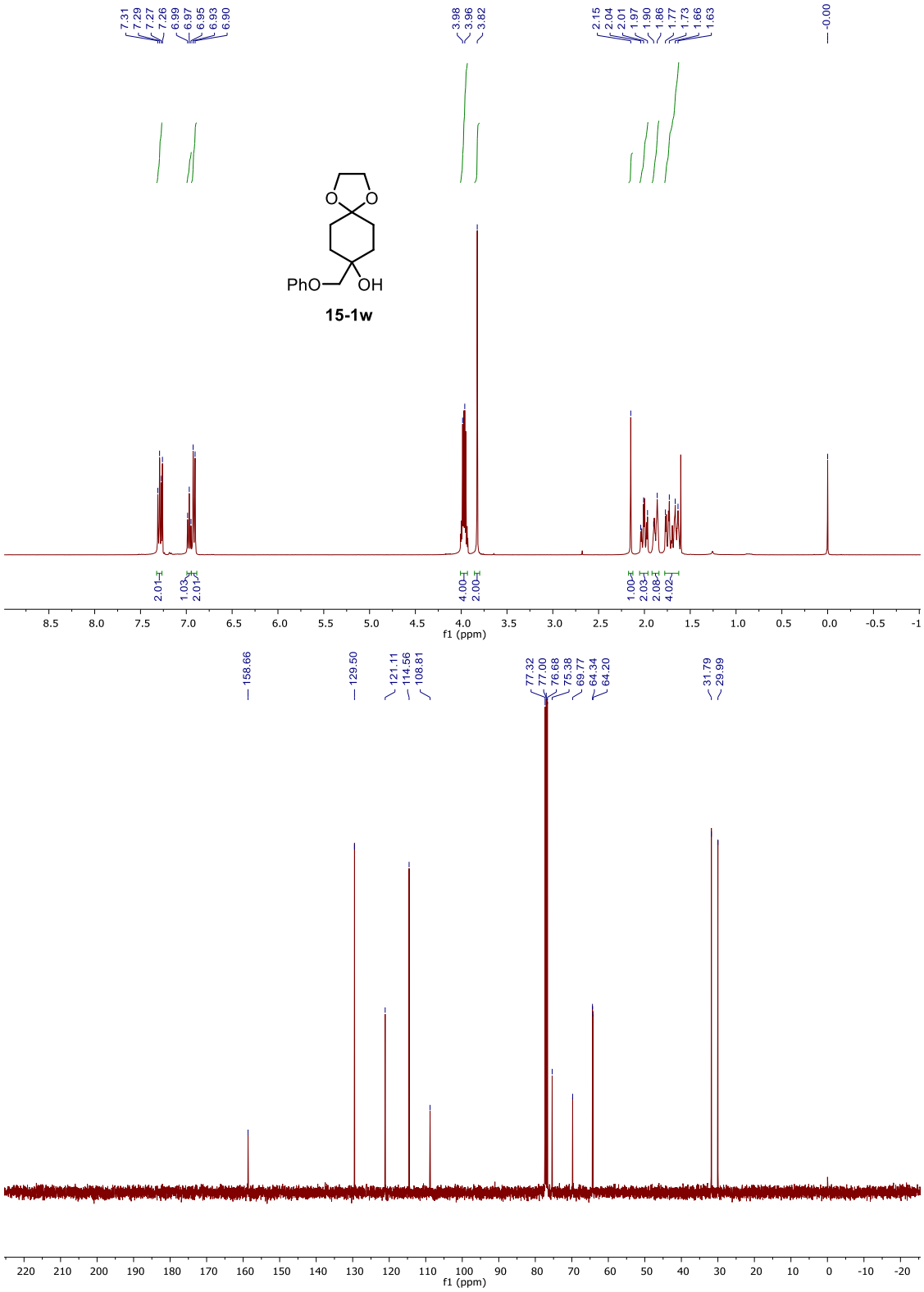


Figure 4.32 ^{1}H-NMR and ^{13}C-NMR Spectra of **1y-2**

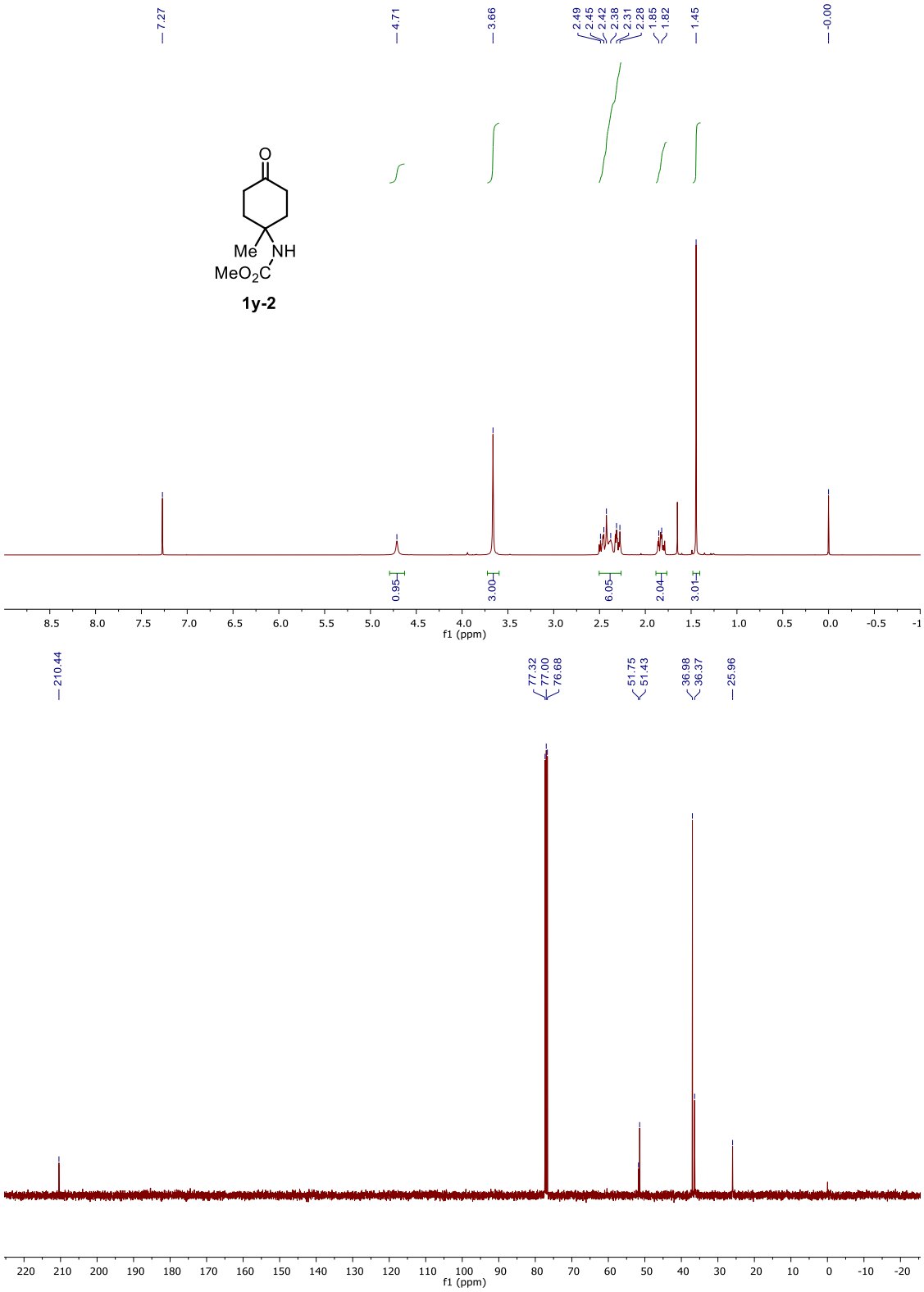


Figure 4.33 ^{1}H-NMR and ^{13}C-NMR Spectra of **1y**

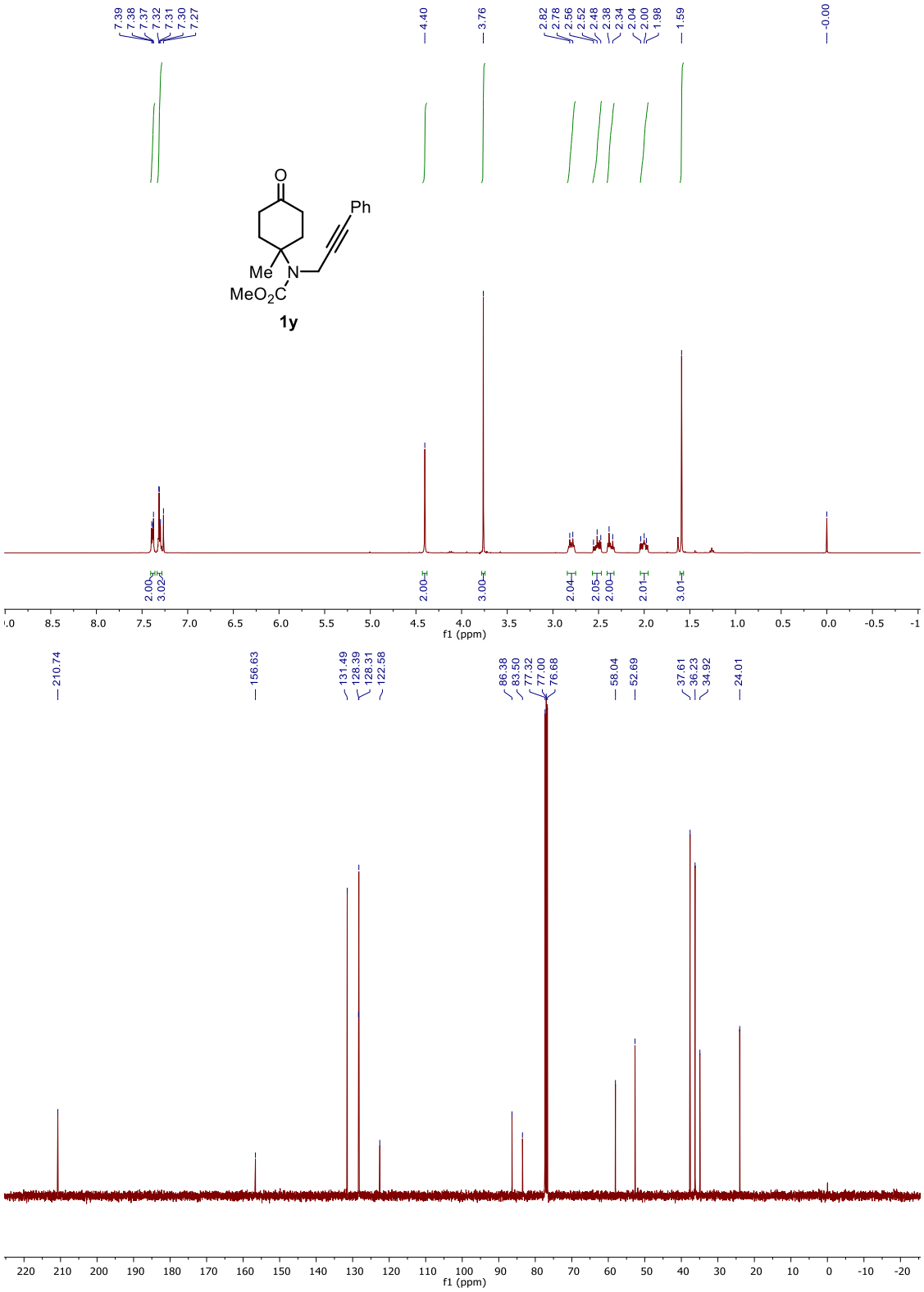


Figure 4.34 ^{1}H-NMR and ^{13}C-NMR Spectra of **2a**

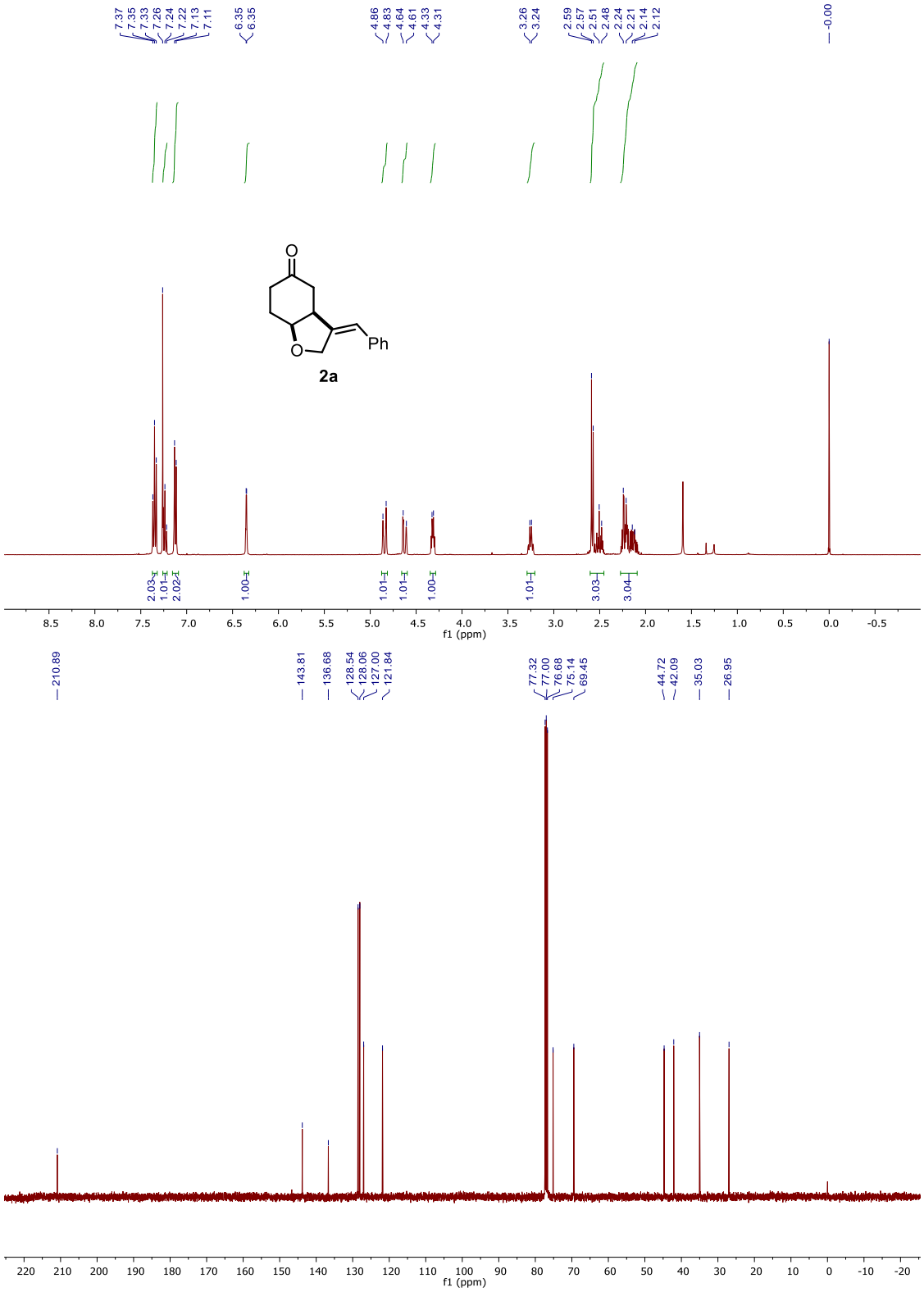


Figure 4.35 ^{1}H-NMR and ^{13}C-NMR Spectra of **2aa**

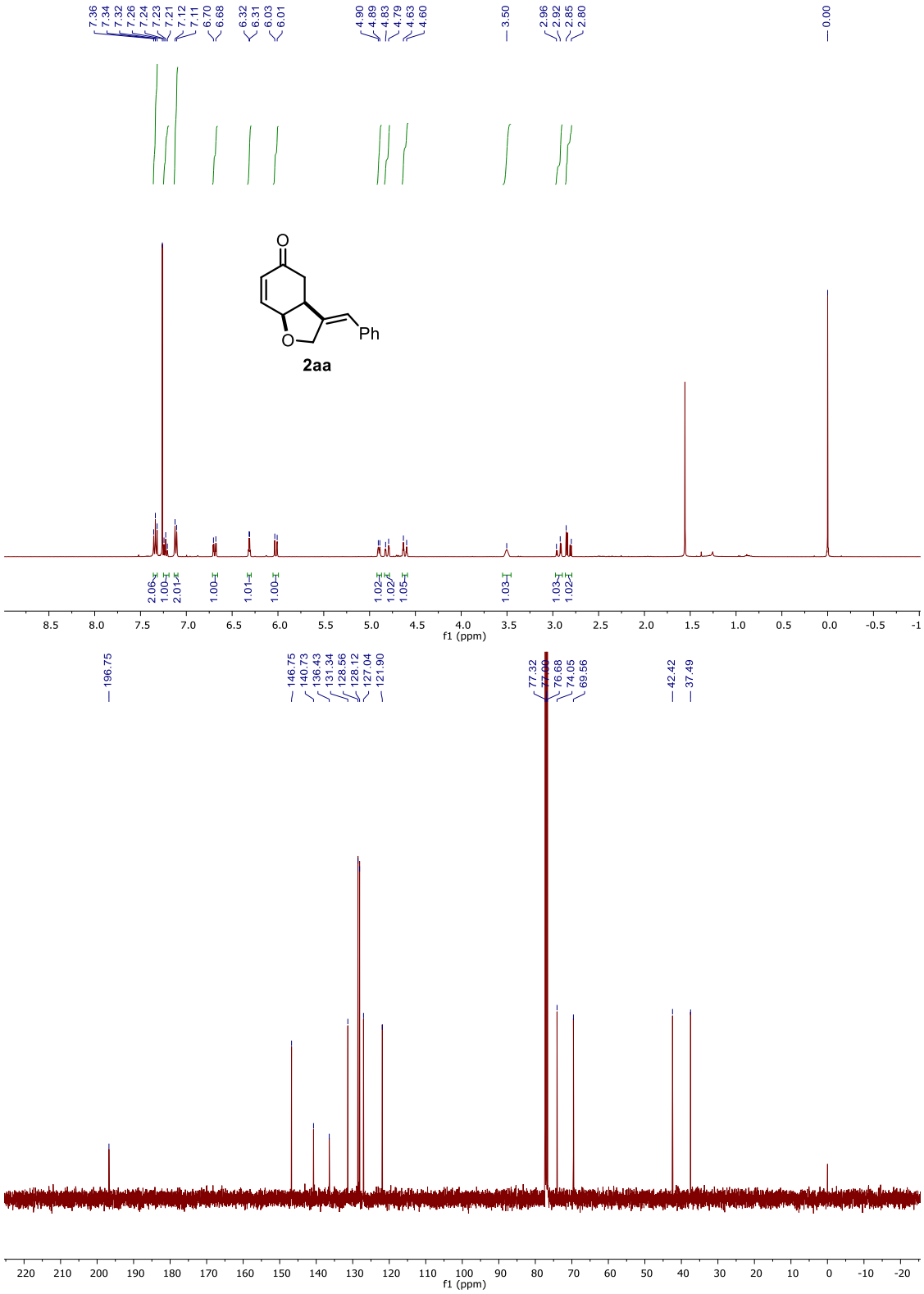


Figure 4.36 ^{1}H-NMR and ^{13}C-NMR Spectra of **2ab**

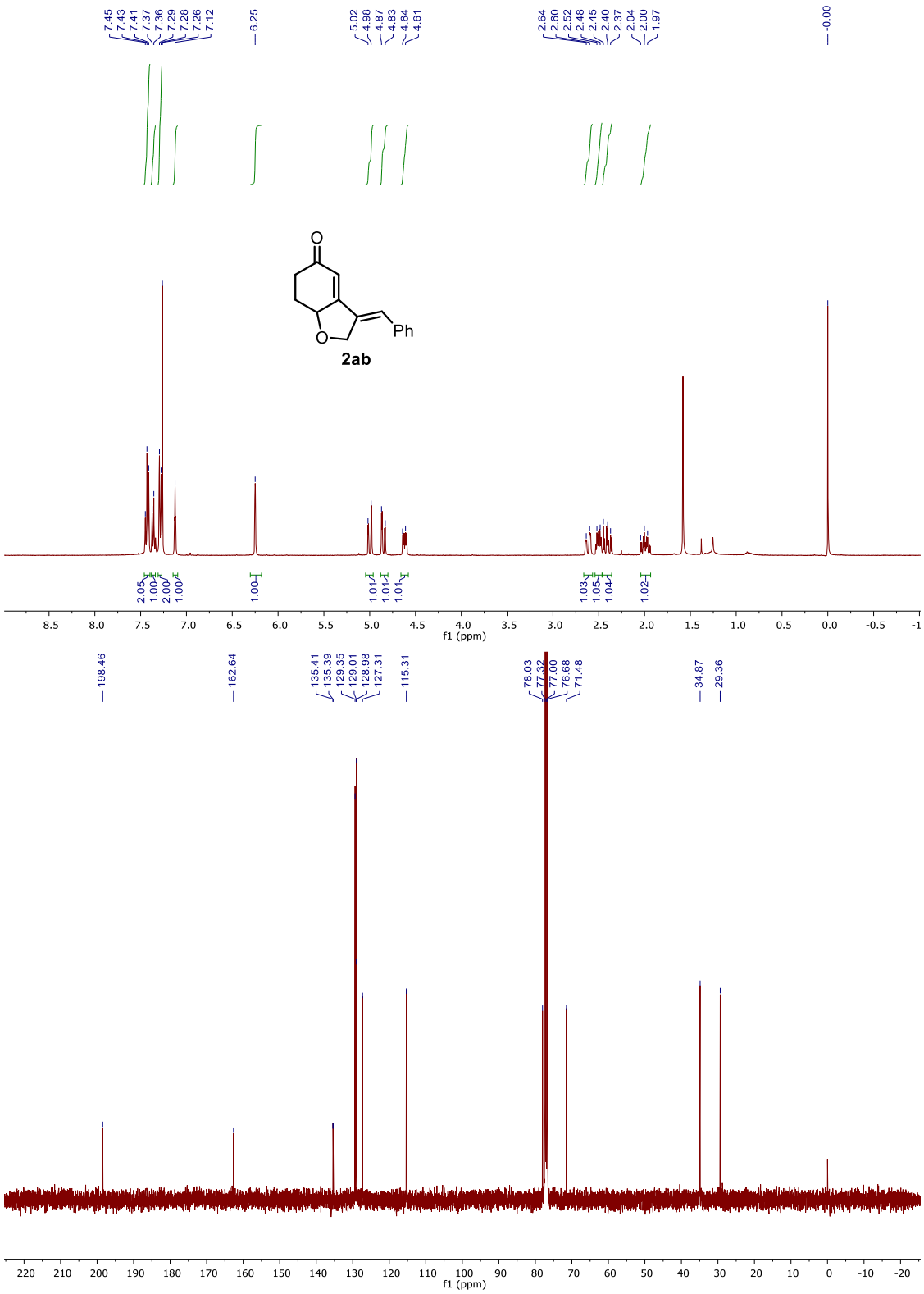


Figure 4.37 ^{1}H-NMR and ^{13}C-NMR Spectra of **1ar**

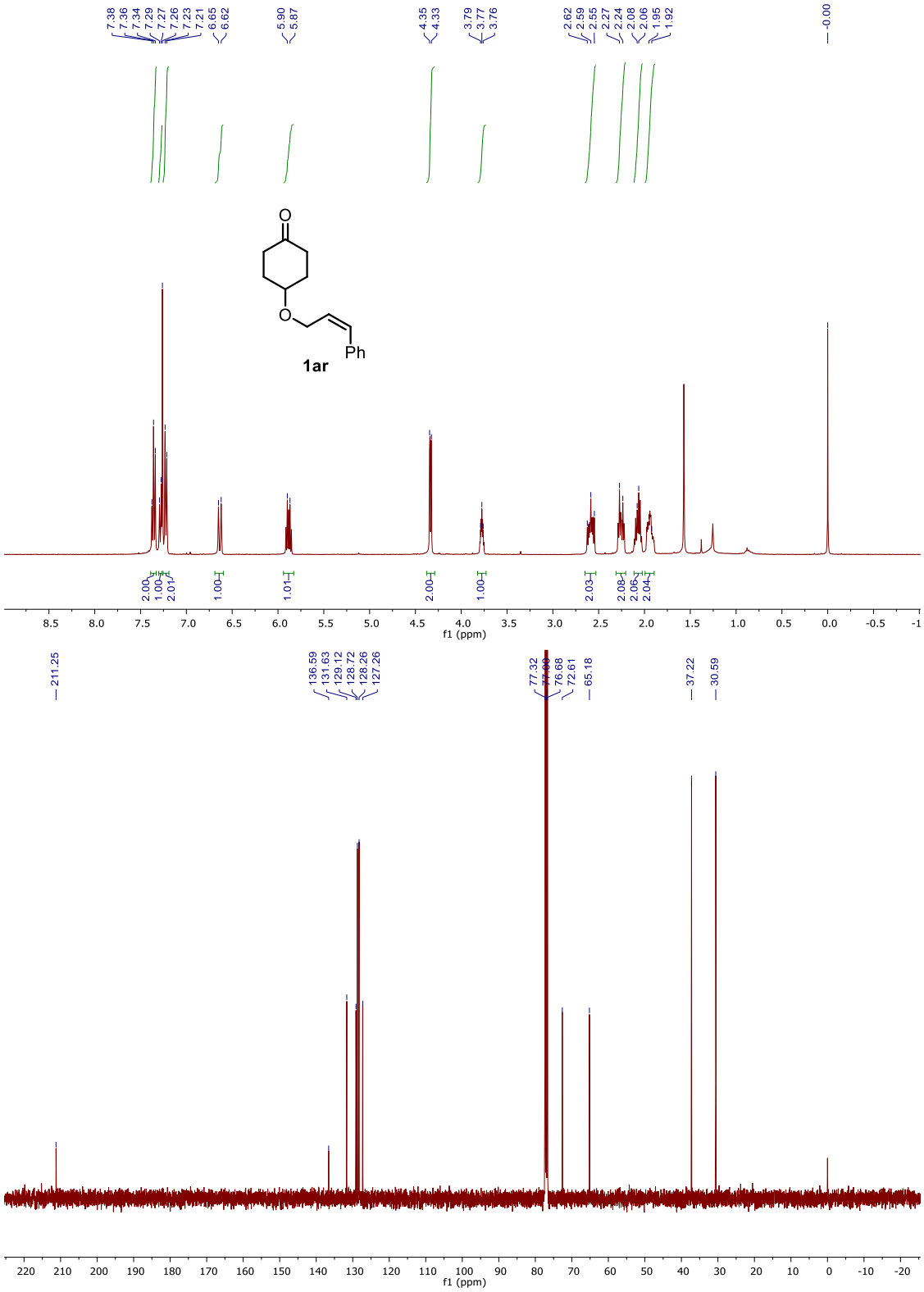


Figure 4.38 ^{1}H-NMR and ^{13}C-NMR Spectra of **2b**

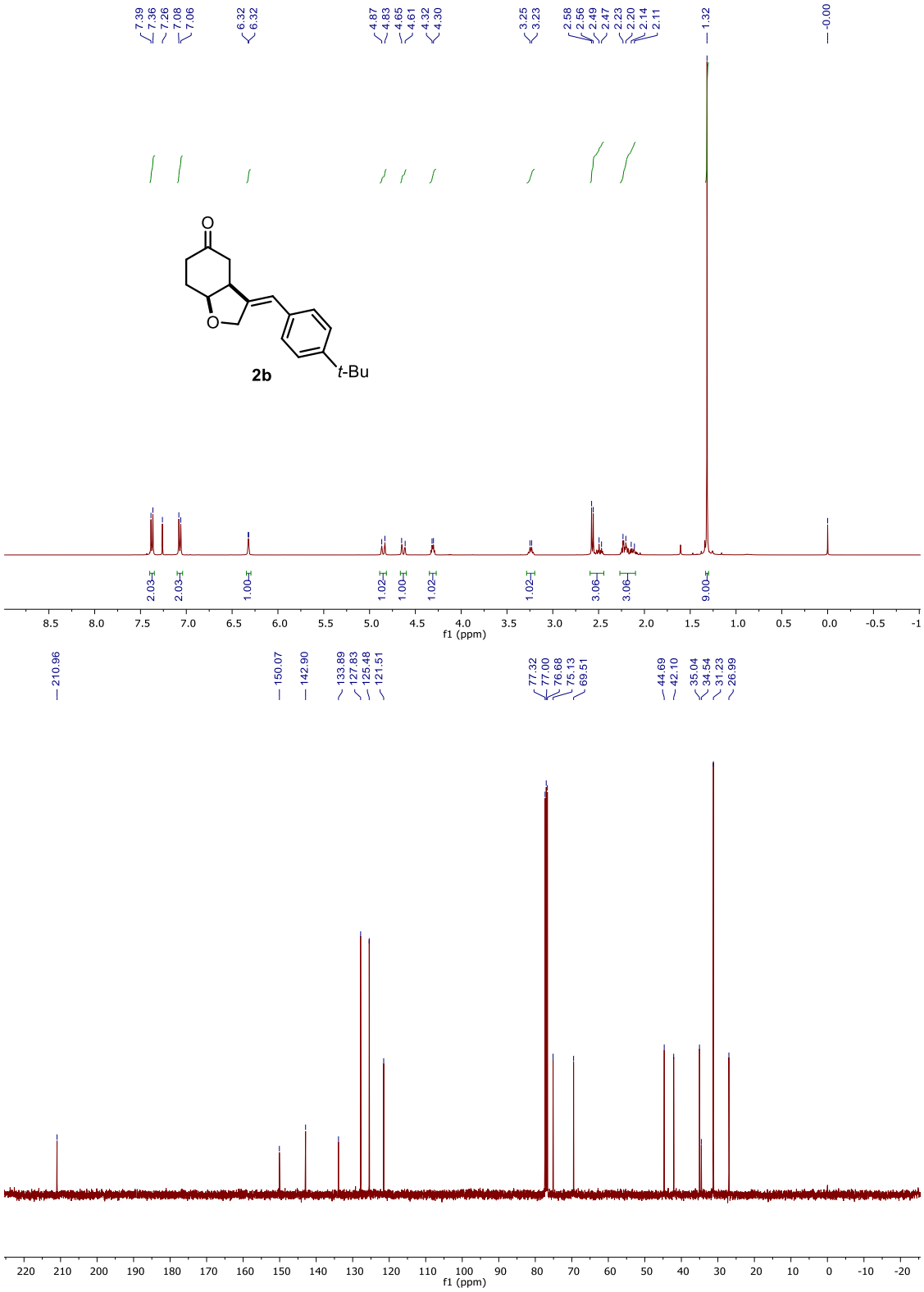


Figure 4.39 ^{1}H-NMR and ^{13}C-NMR Spectra of **2c**

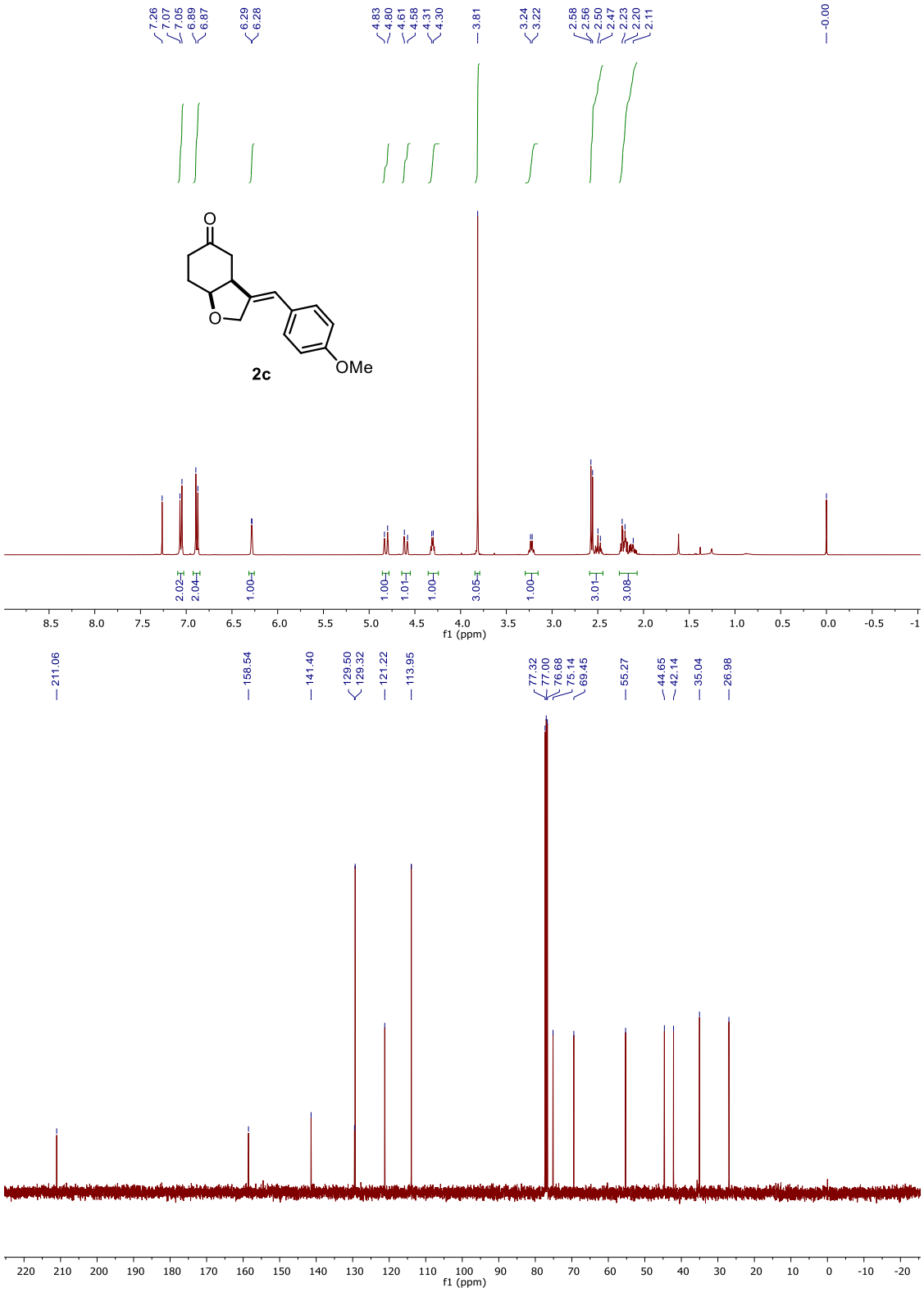


Figure 4.40 ^{1}H-NMR and ^{13}C-NMR Spectra of **2d**

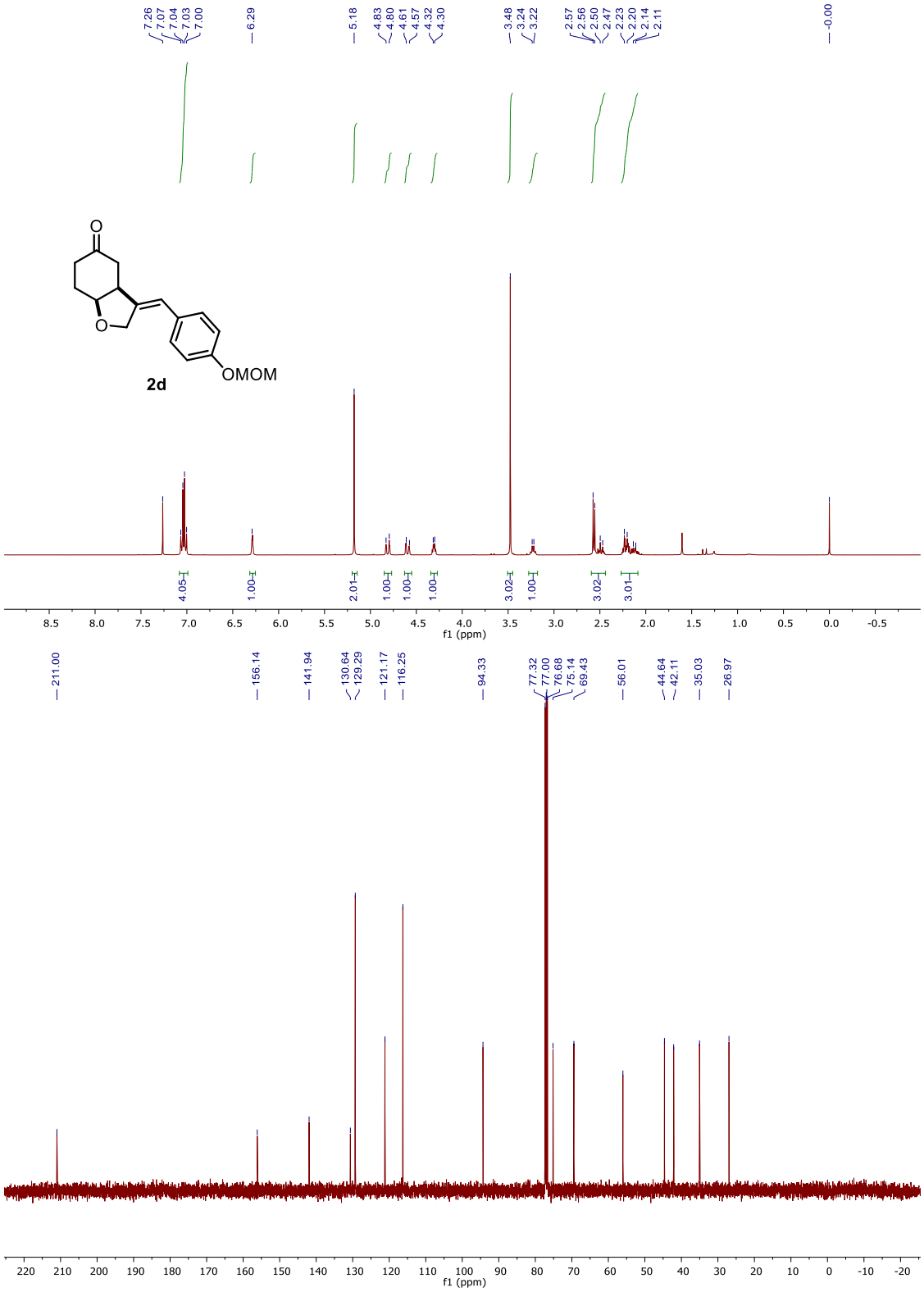


Figure 4.41 ^{1}H-NMR and ^{13}C-NMR Spectra of **2e**

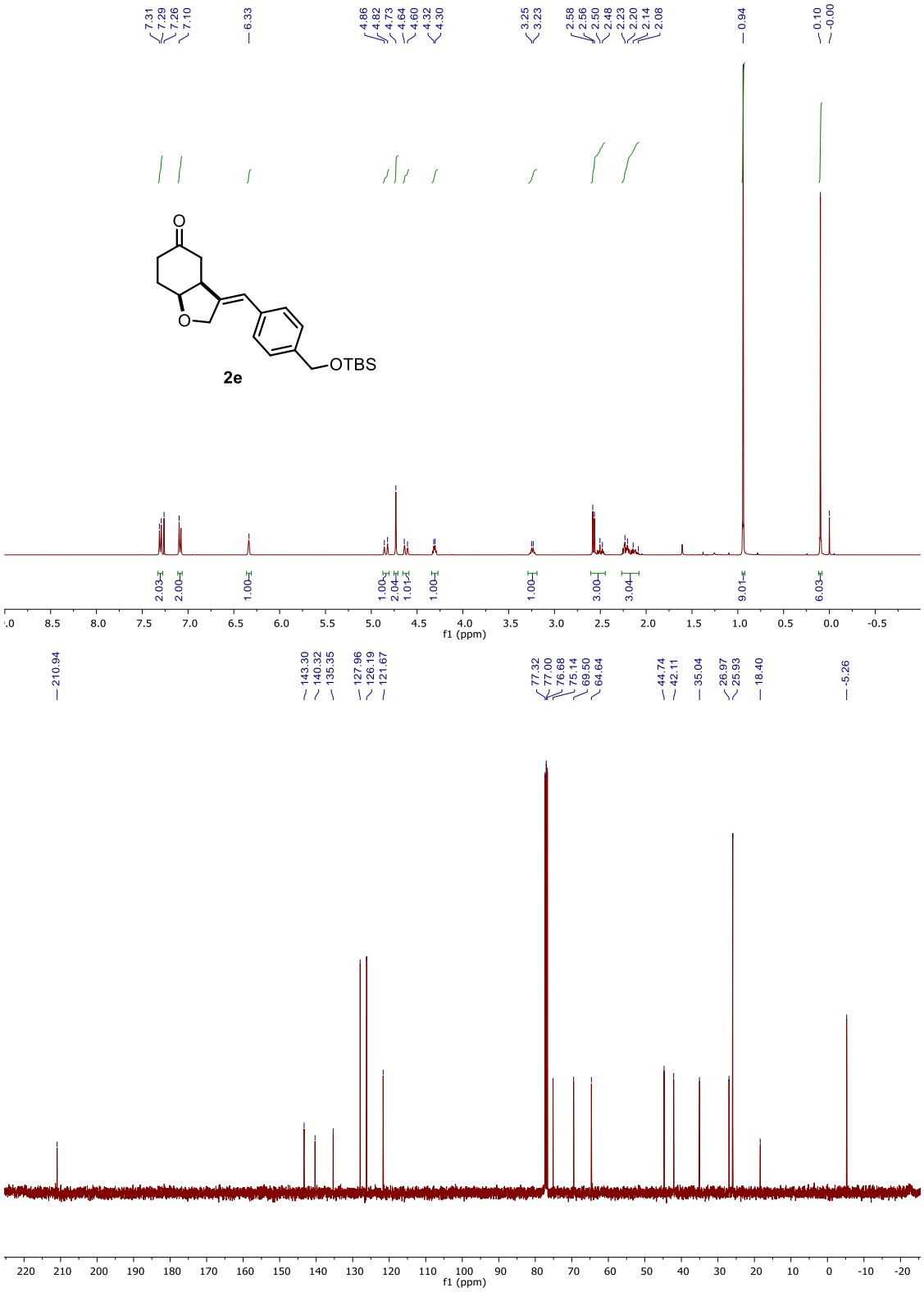


Figure 4.42 ^{1}H-NMR and ^{13}C-NMR Spectra of **2f**

Figure 4.43 ^{1}H-NMR and ^{13}C-NMR Spectra of **2g**

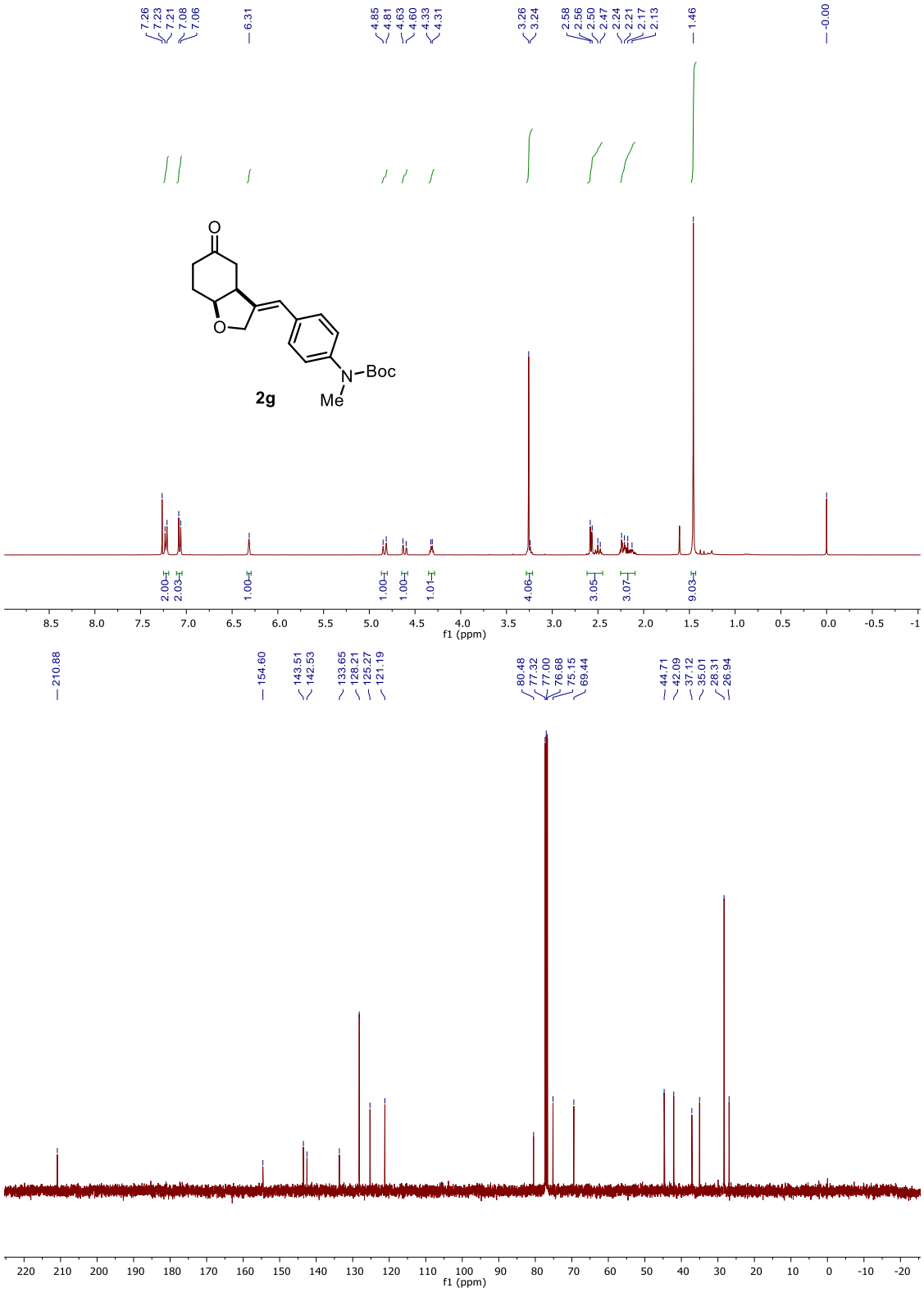


Figure 4.44 ^{1}H-NMR and ^{13}C-NMR Spectra of **2h**

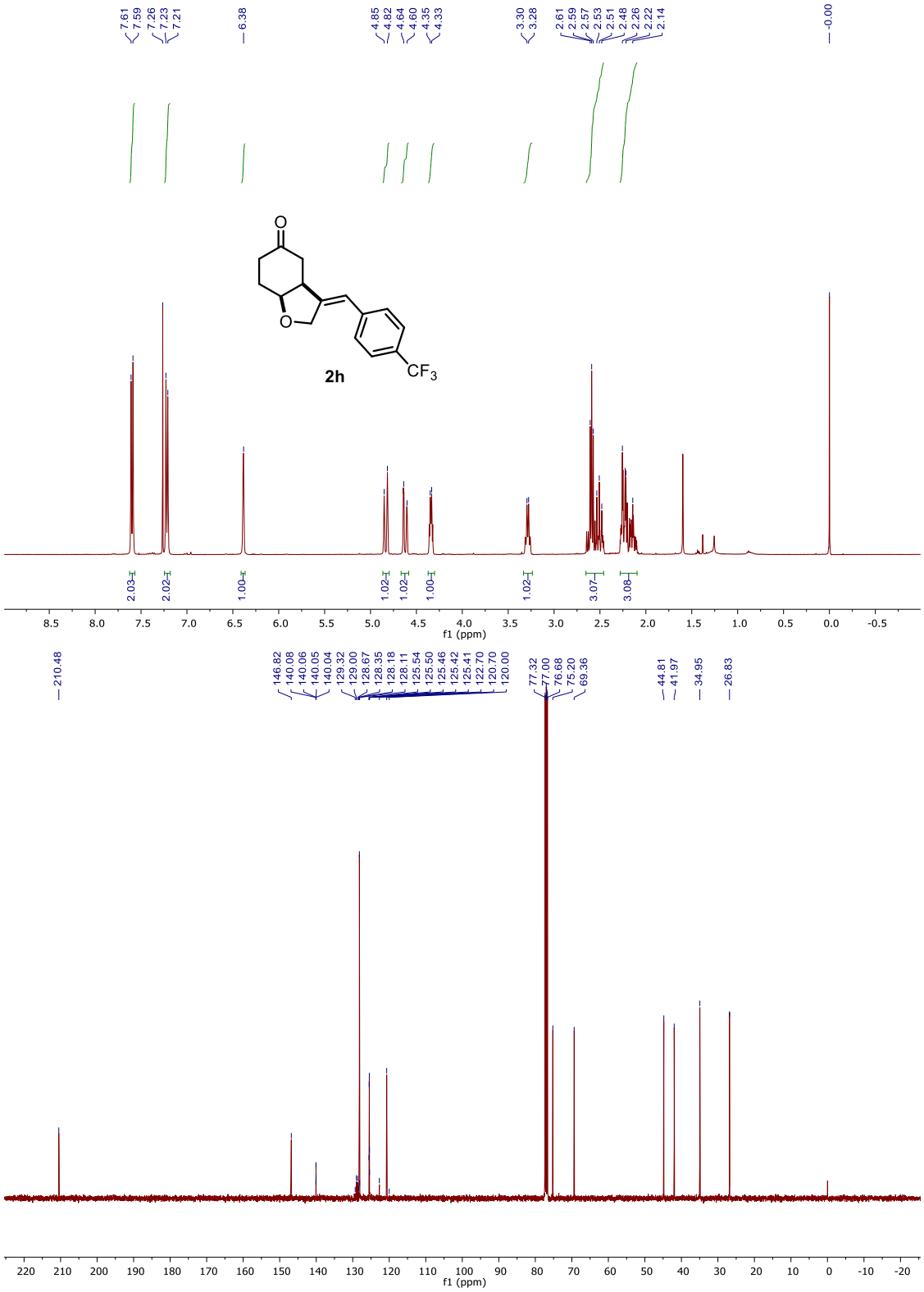


Figure 4.45 ^{19}F-NMR Spectrum of **2h**

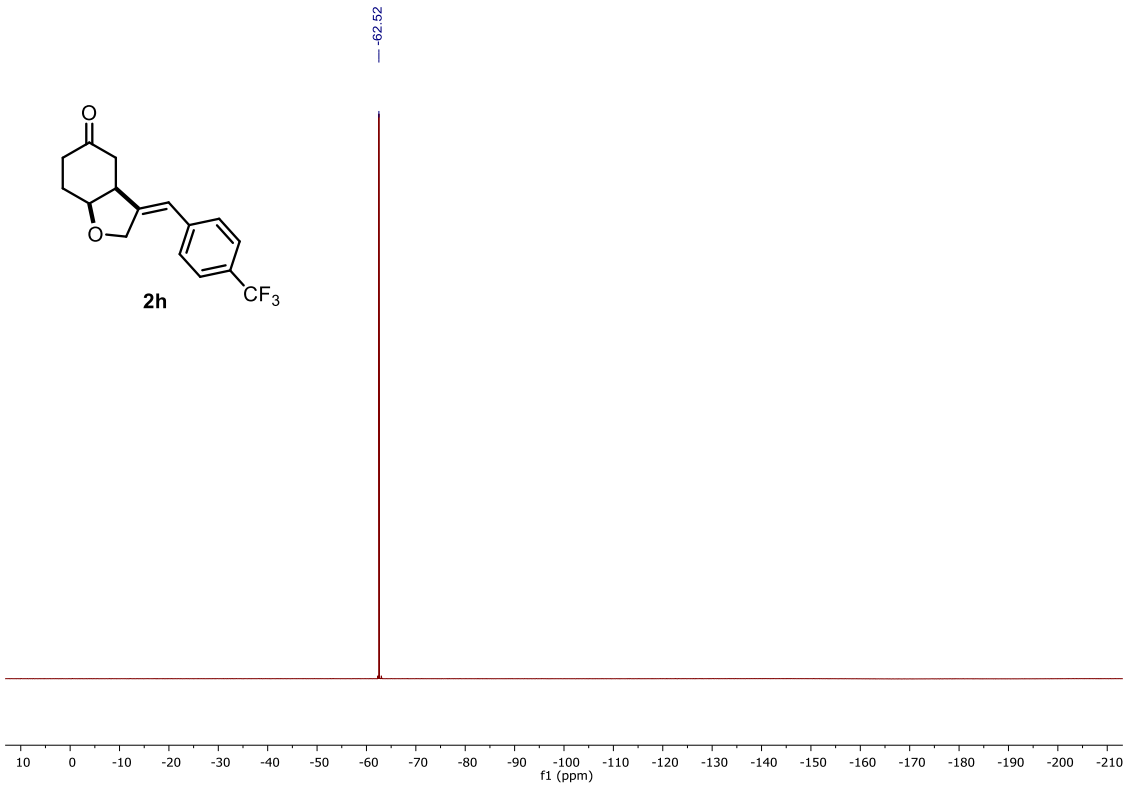


Figure 4.46 ^{1}H-NMR and ^{13}C-NMR Spectra of **2i**

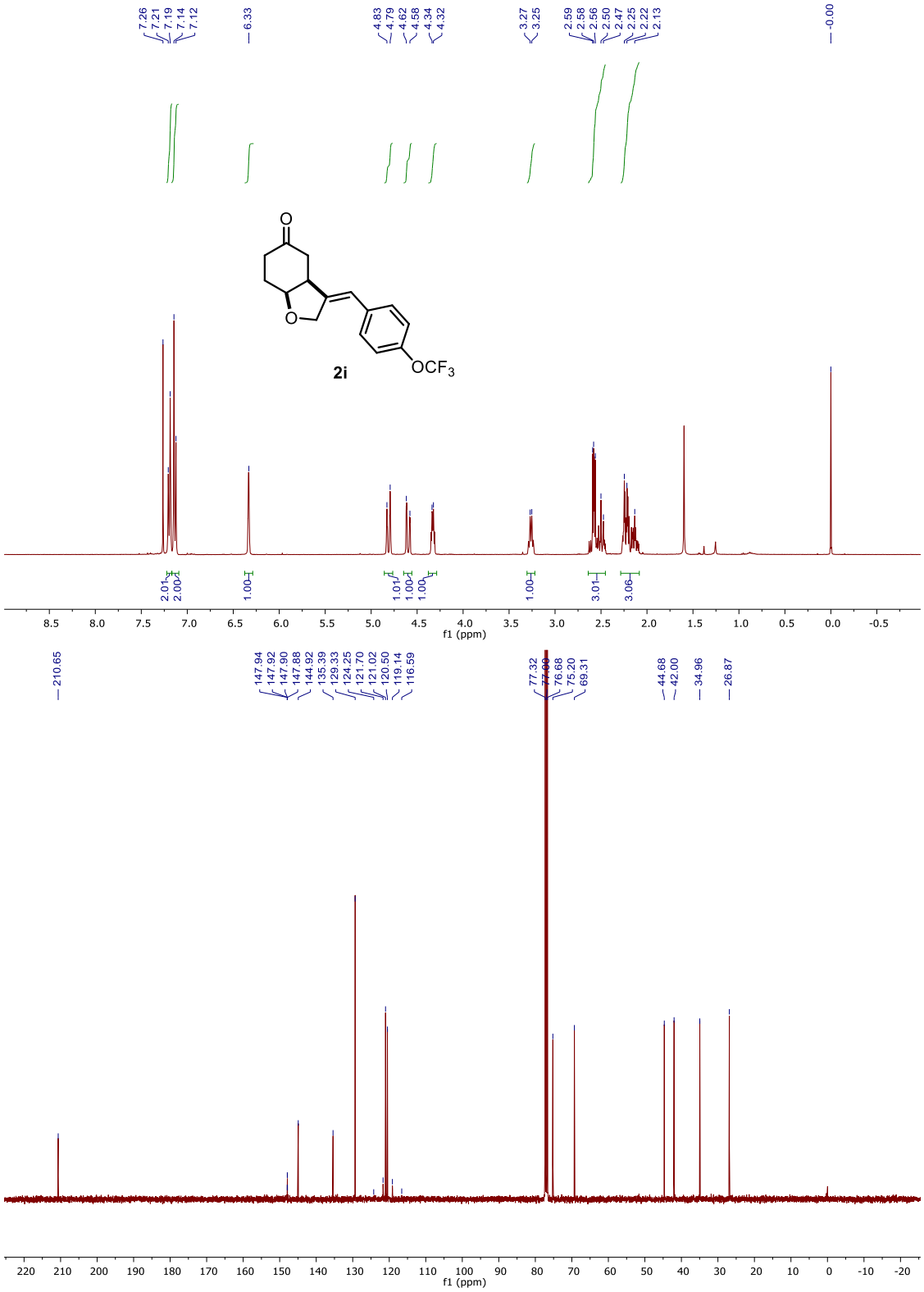


Figure 4.47 ^{19}F-NMR Spectrum of **2i**

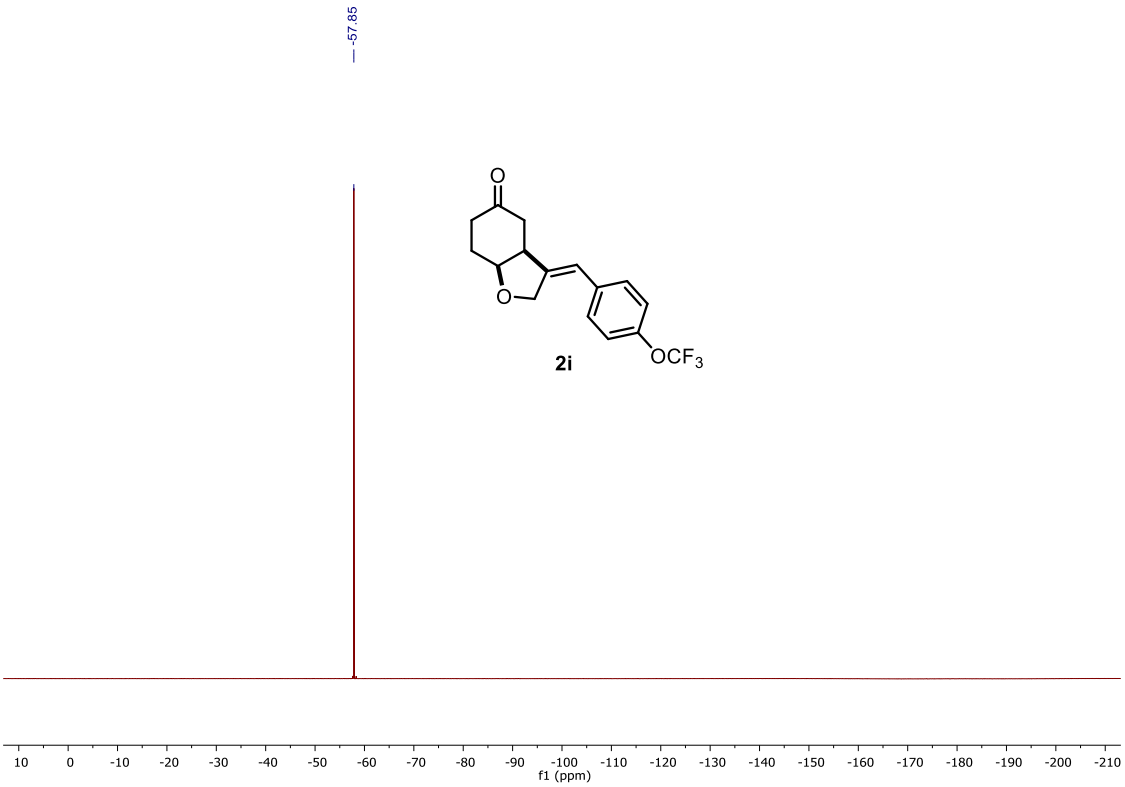


Figure 4.48 ^{1}H-NMR and ^{13}C-NMR Spectra of **2j**

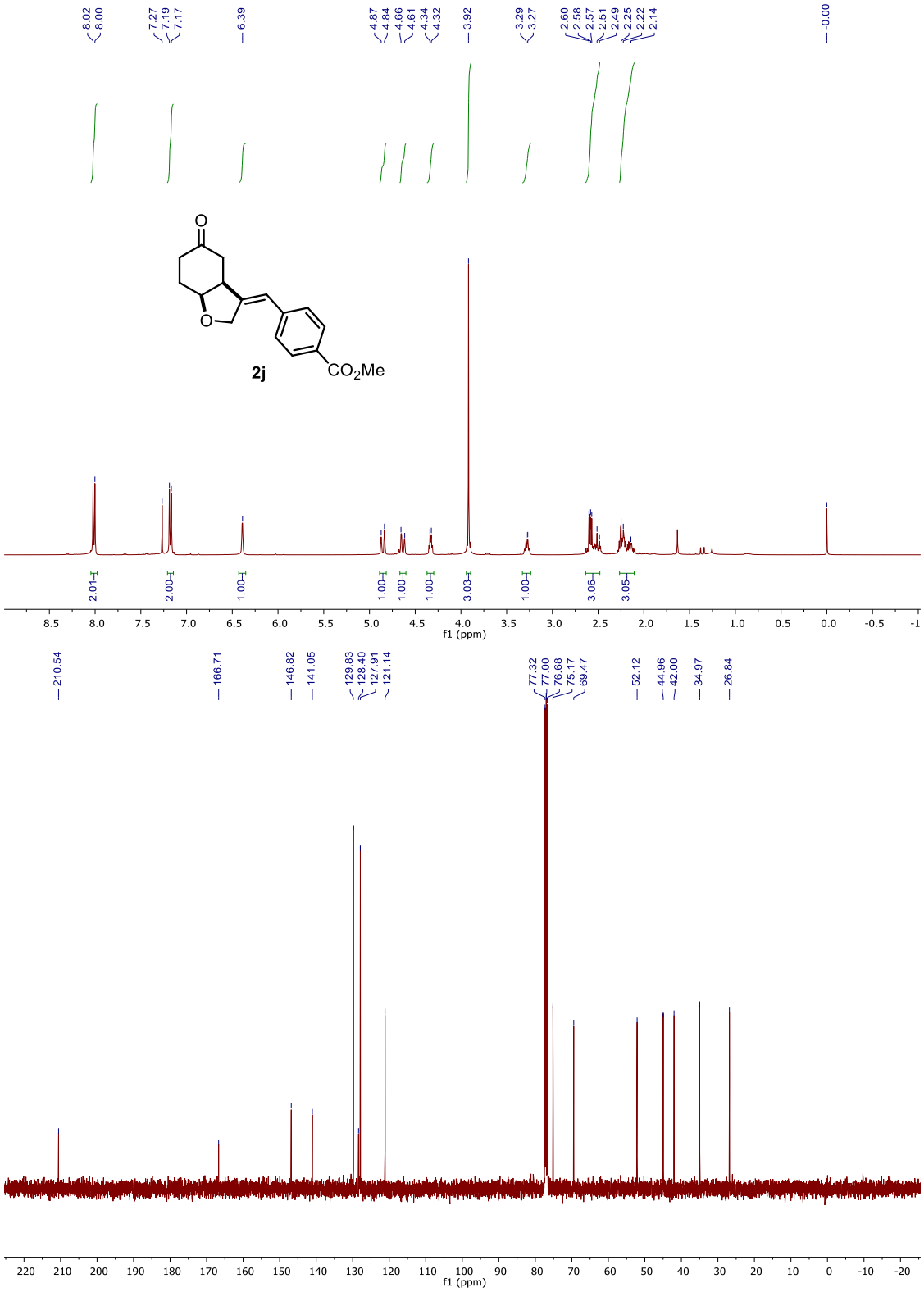


Figure 4.49 ^{1}H-NMR and ^{13}C-NMR Spectra of **2k**

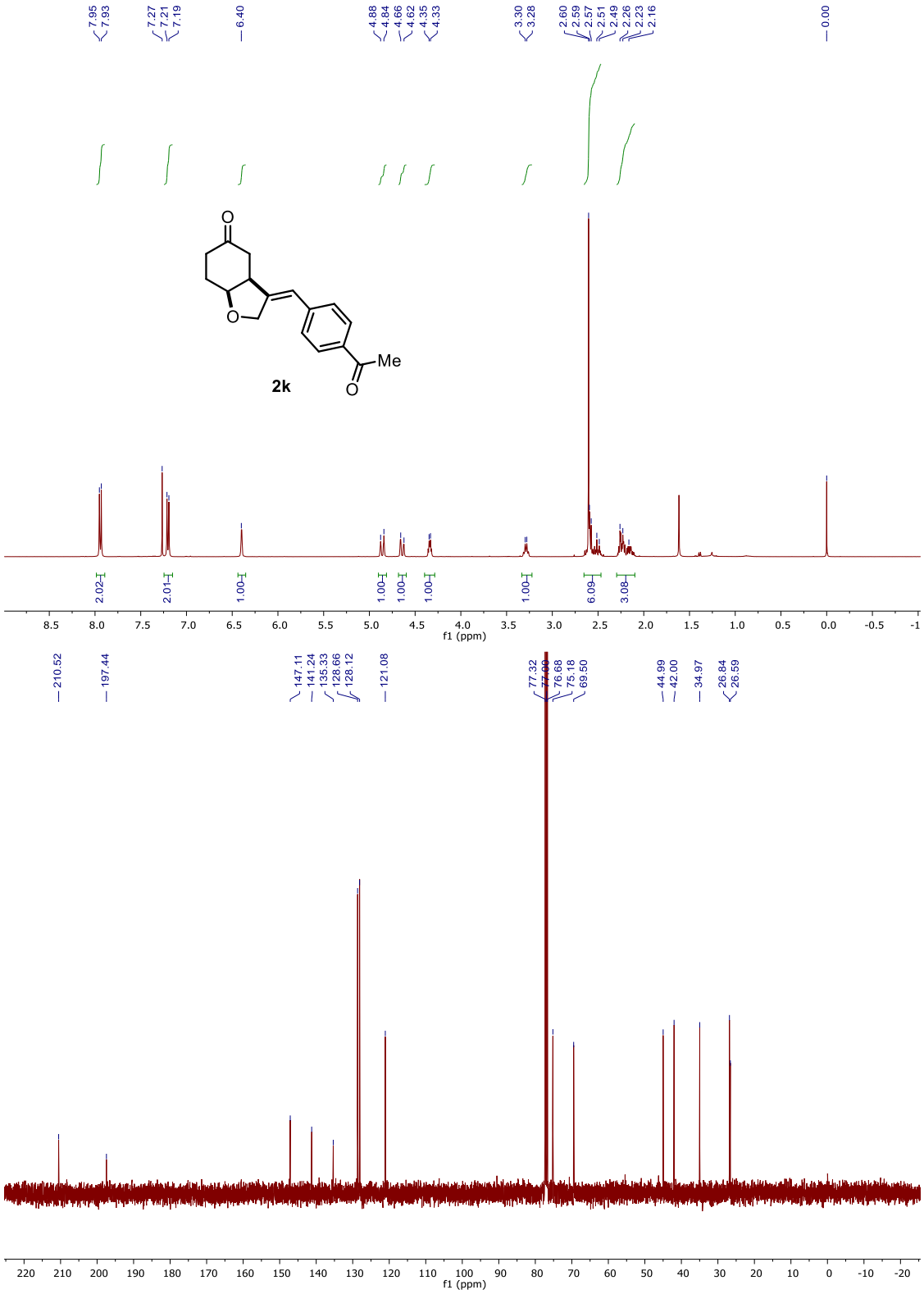


Figure 4.50 ^{1}H-NMR and ^{13}C-NMR Spectra of **2l**

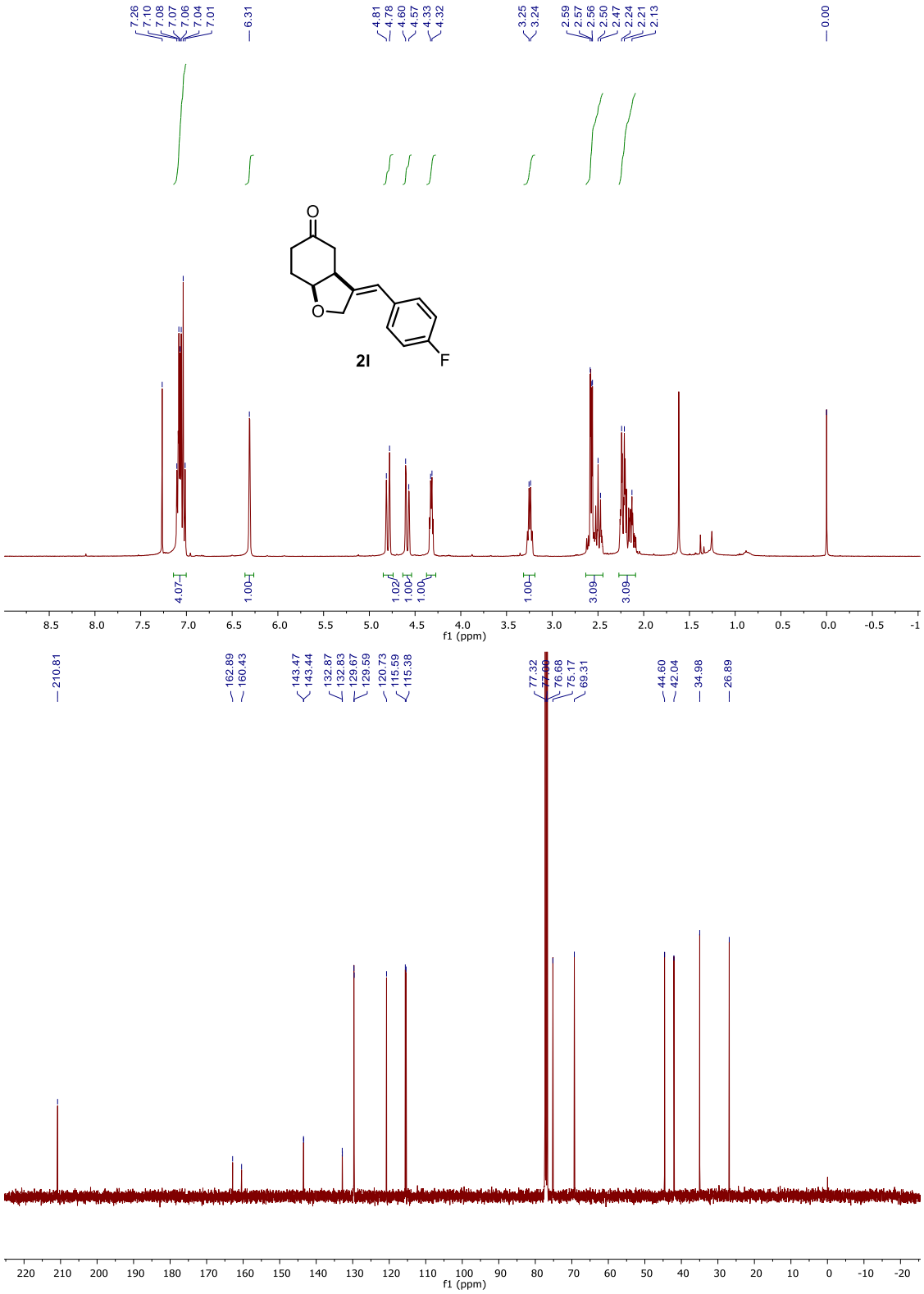


Figure 4.51 ^{19}F-NMR Spectrum of **2l**

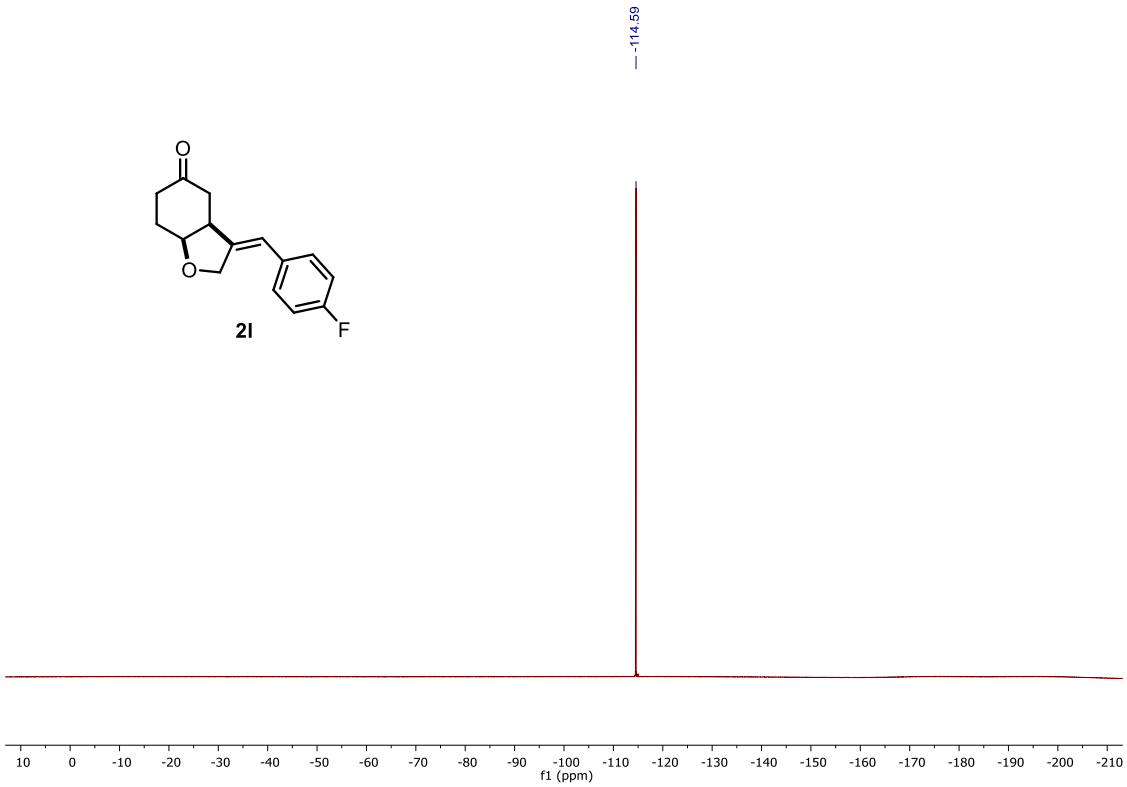


Figure 4.52 ^{1}H-NMR and ^{13}C-NMR Spectra of **2m**

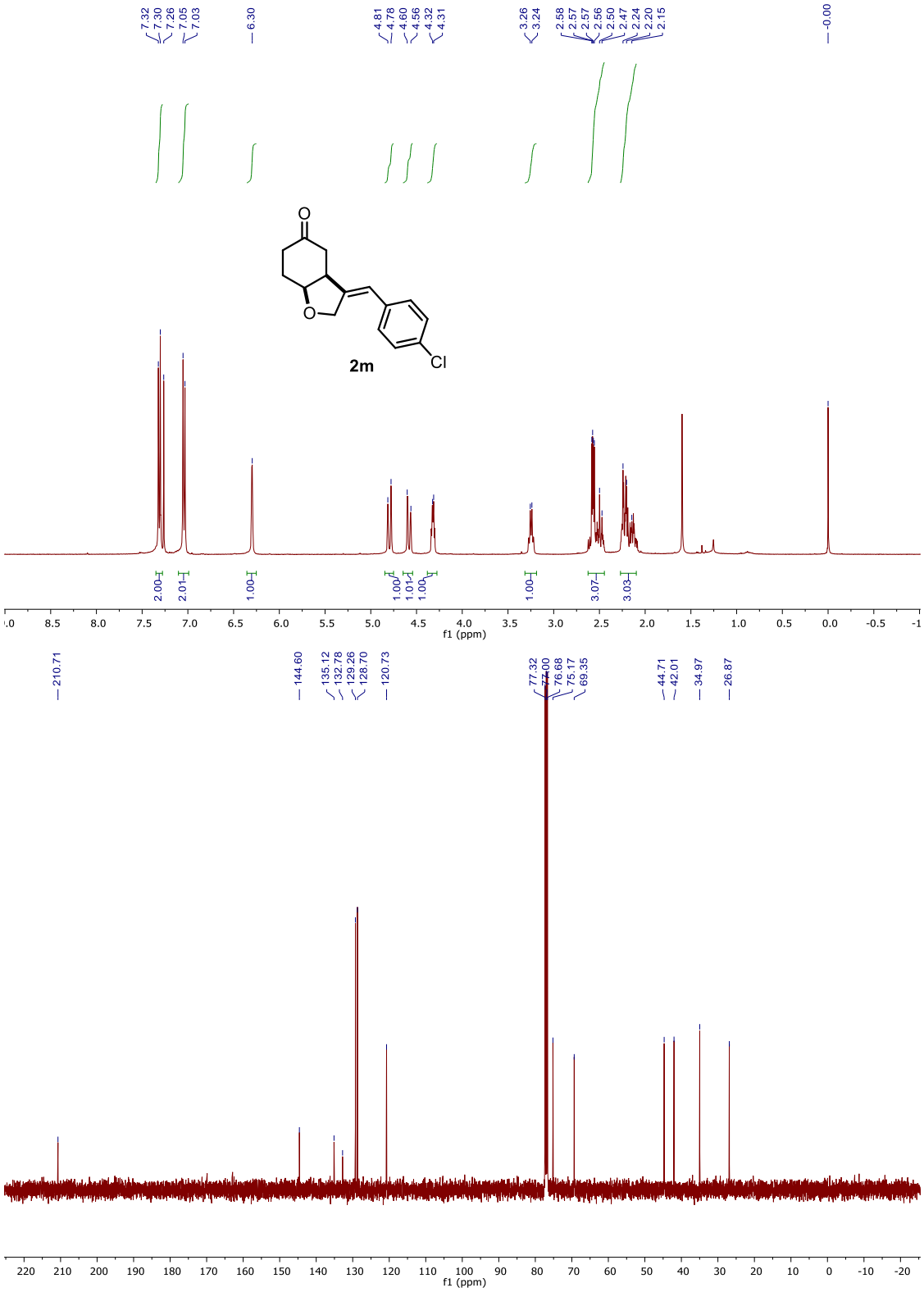


Figure 4.53 ^{1}H-NMR and ^{13}C-NMR Spectra of **2n**

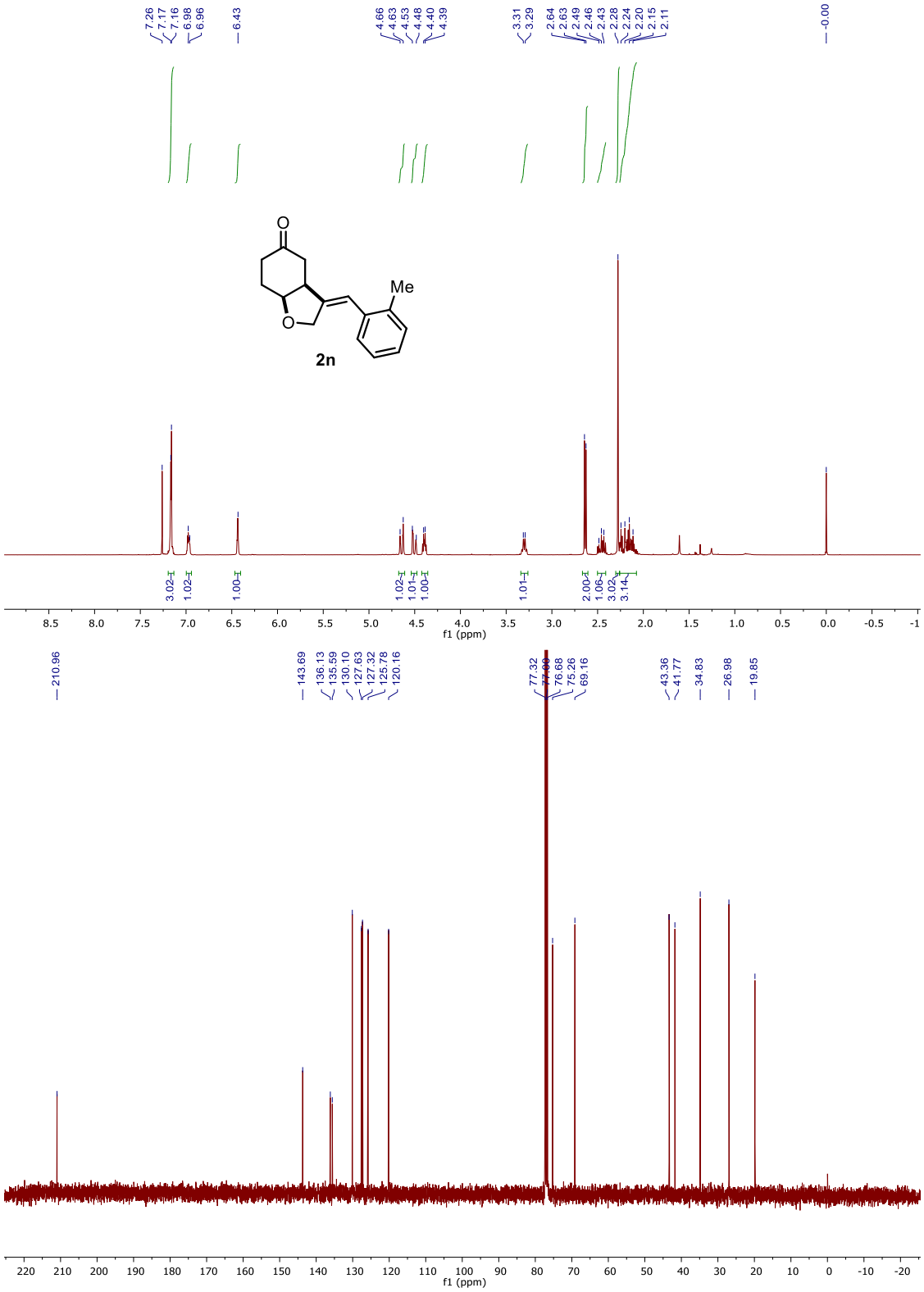


Figure 4.54 ^{1}H-NMR and ^{13}C-NMR Spectra of **2o**

Figure 4.55 ^{1}H-NMR and ^{13}C-NMR Spectra of **2p**

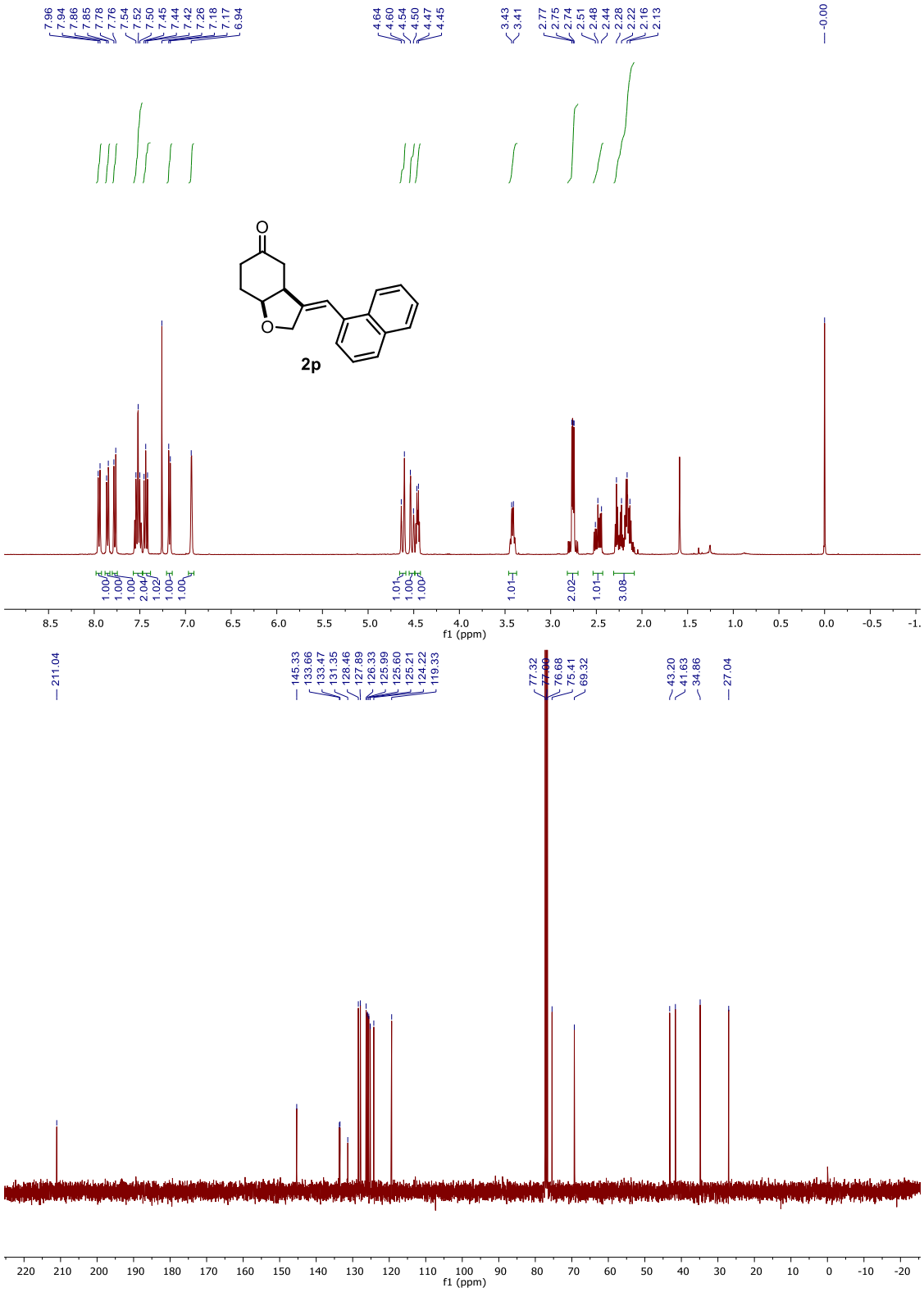


Figure 4.56 ^{1}H-NMR and ^{13}C-NMR Spectra of **2q**

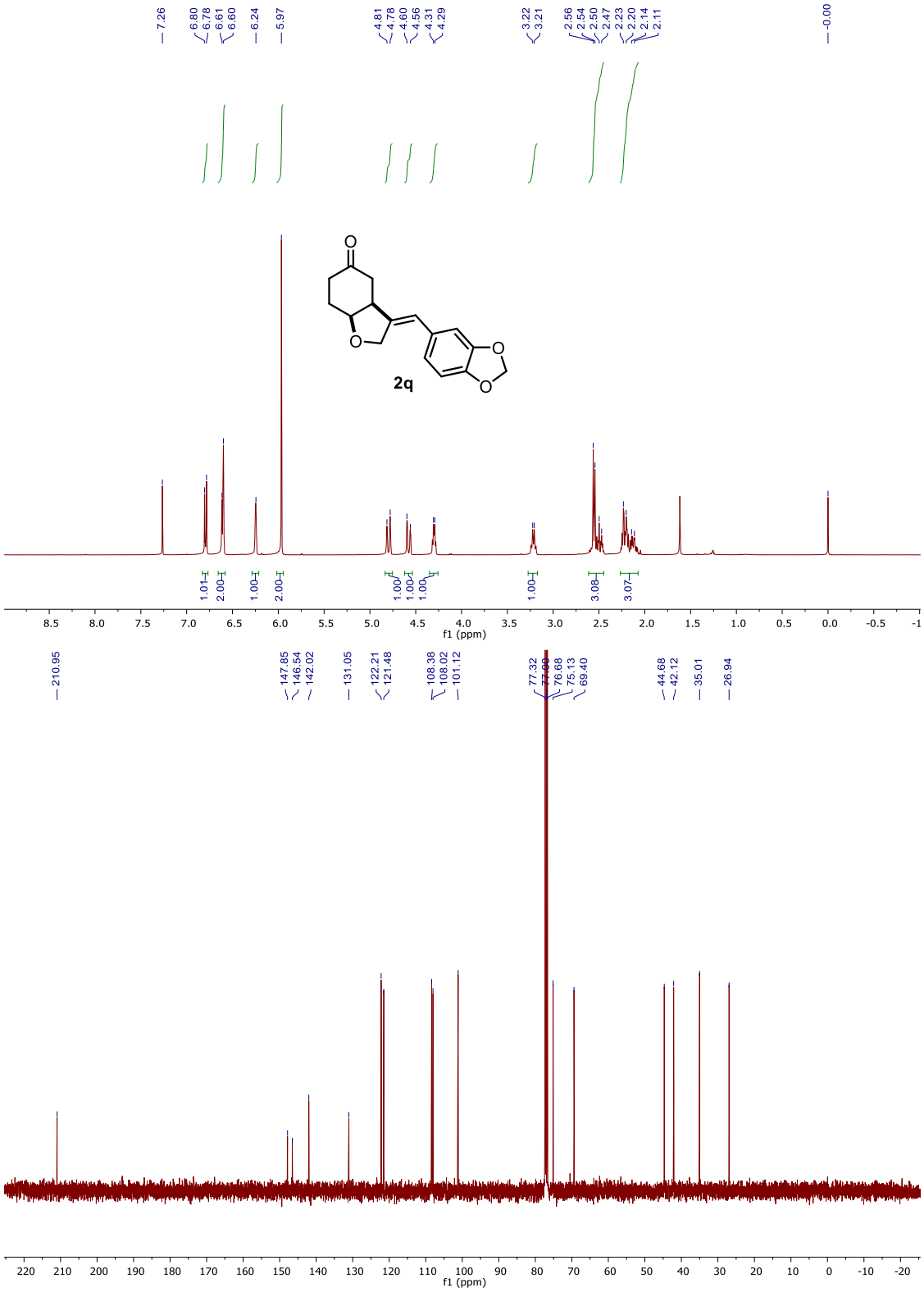


Figure 4.57 ^{1}H-NMR and ^{13}C-NMR Spectra of **2r**

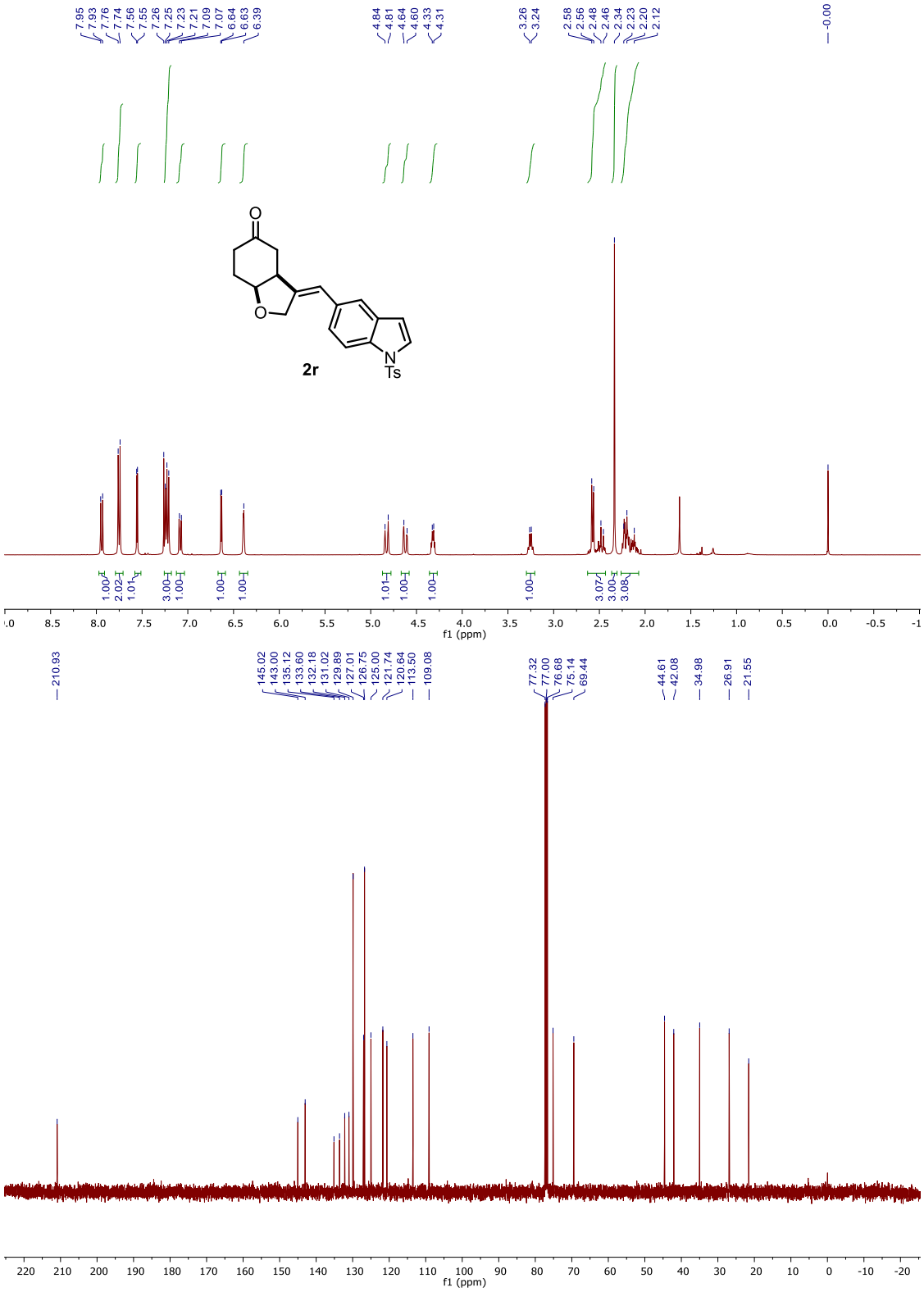


Figure 4.58 ^{1}H-NMR and ^{13}C-NMR Spectra of **2s**

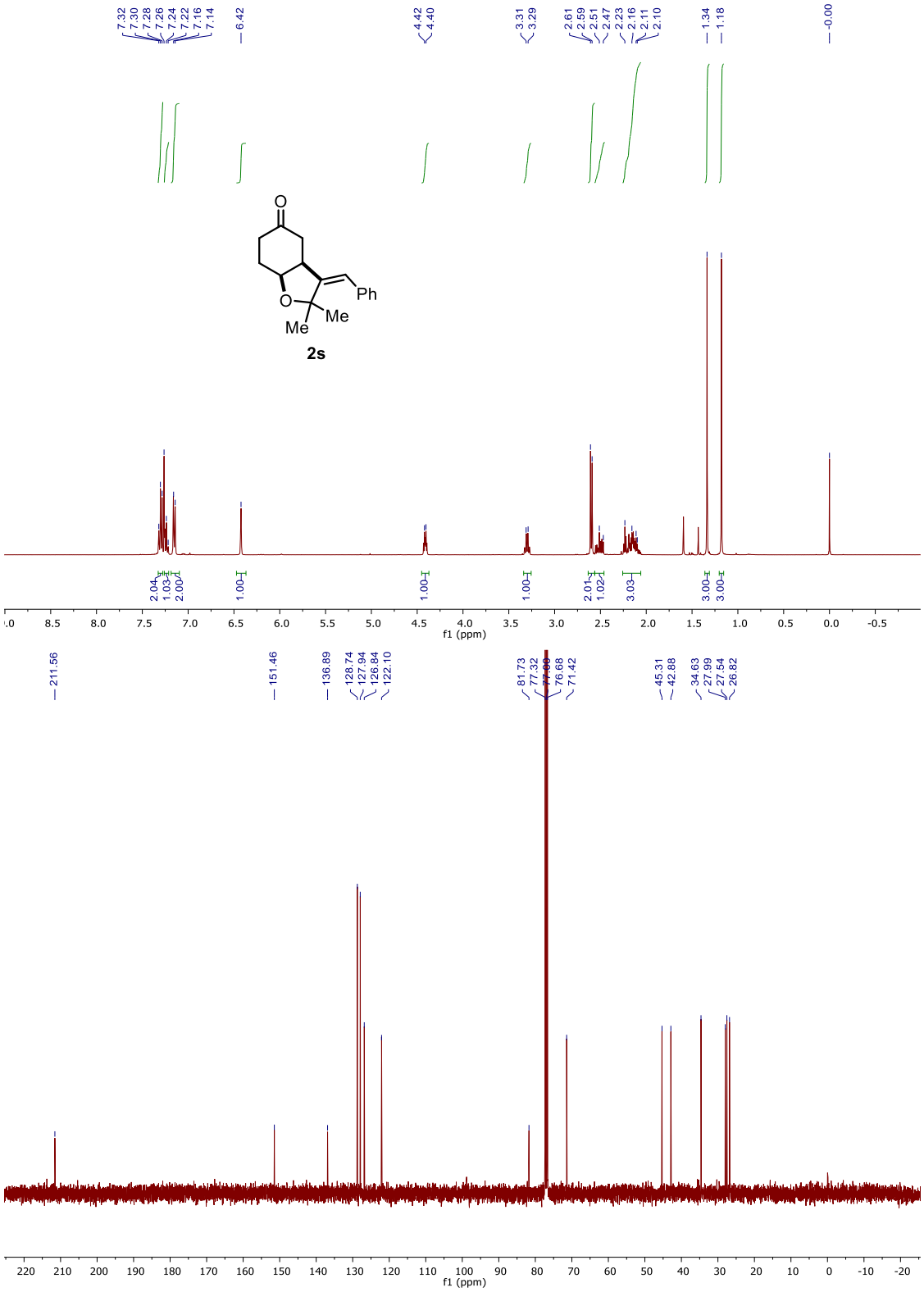


Figure 4.59 ^{1}H-NMR and ^{13}C-NMR Spectra of **2t**

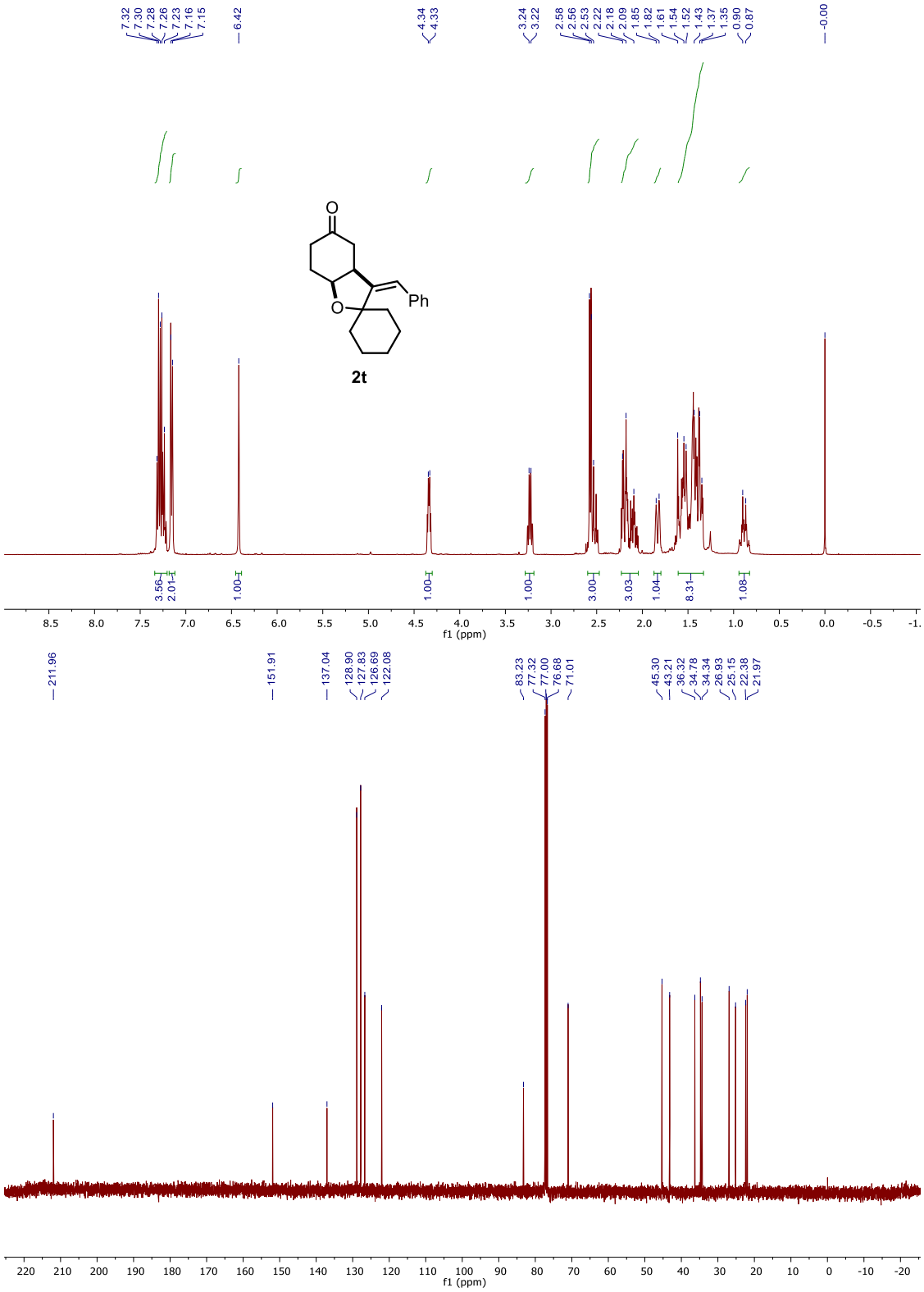


Figure 4.60 ^{1}H-NMR and ^{13}C-NMR Spectra of **2u**

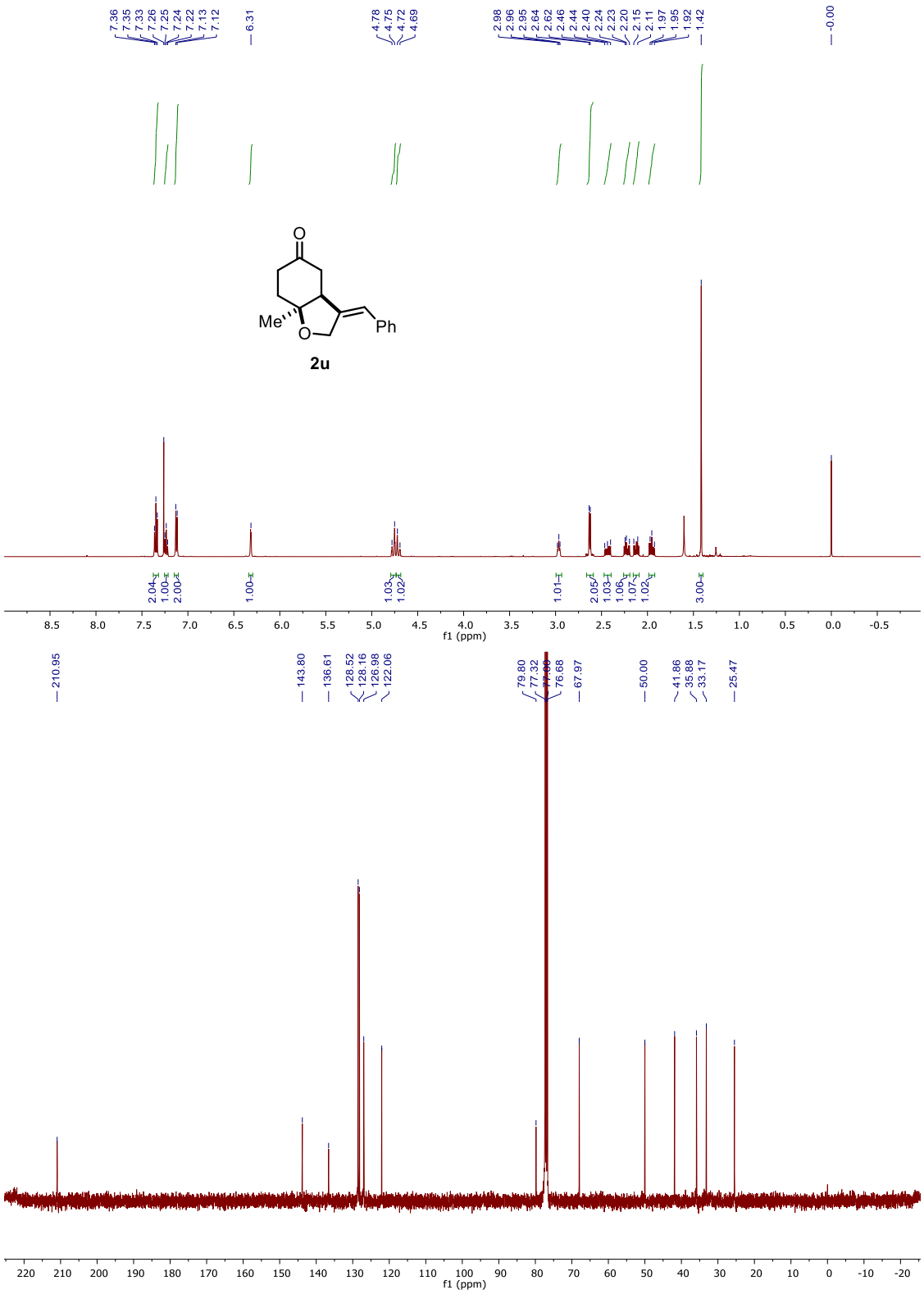


Figure 4.61 ^{1}H-NMR and ^{13}C-NMR Spectra of **2v**

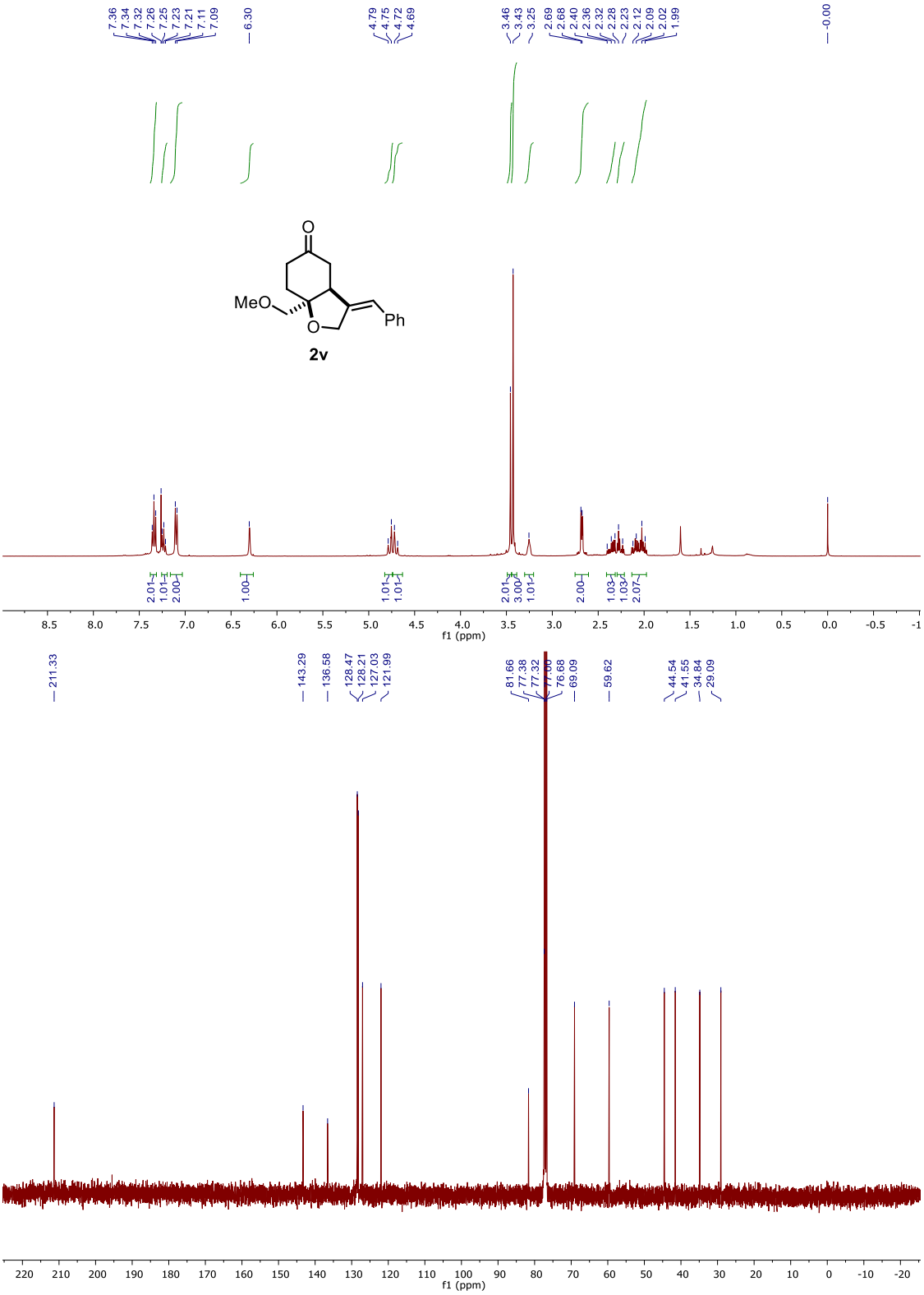


Figure 4.62 ^{1}H-NMR and ^{13}C-NMR Spectra of **2w**

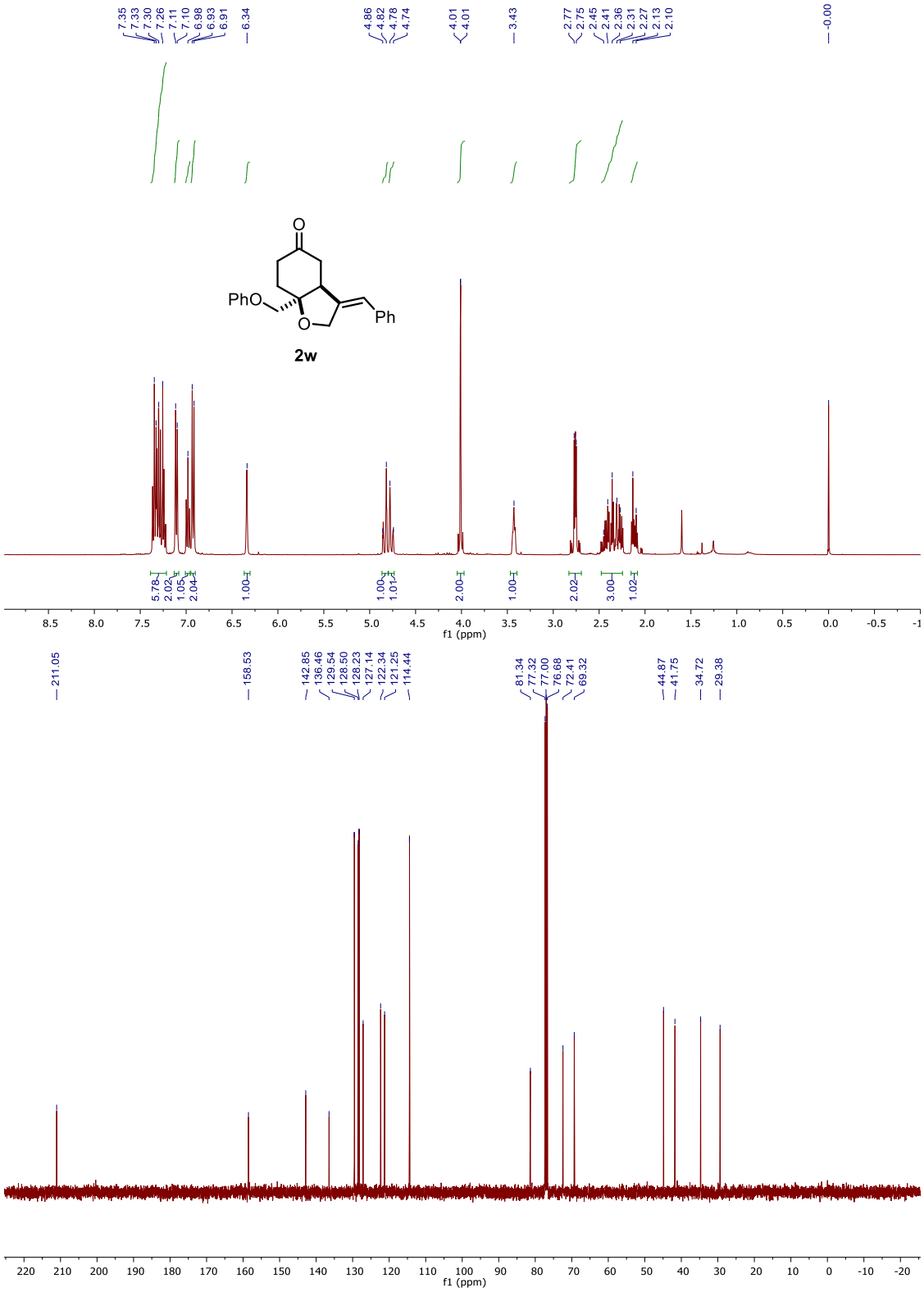


Figure 4.63 ^{1}H-NMR and ^{13}C-NMR Spectra of **2x**

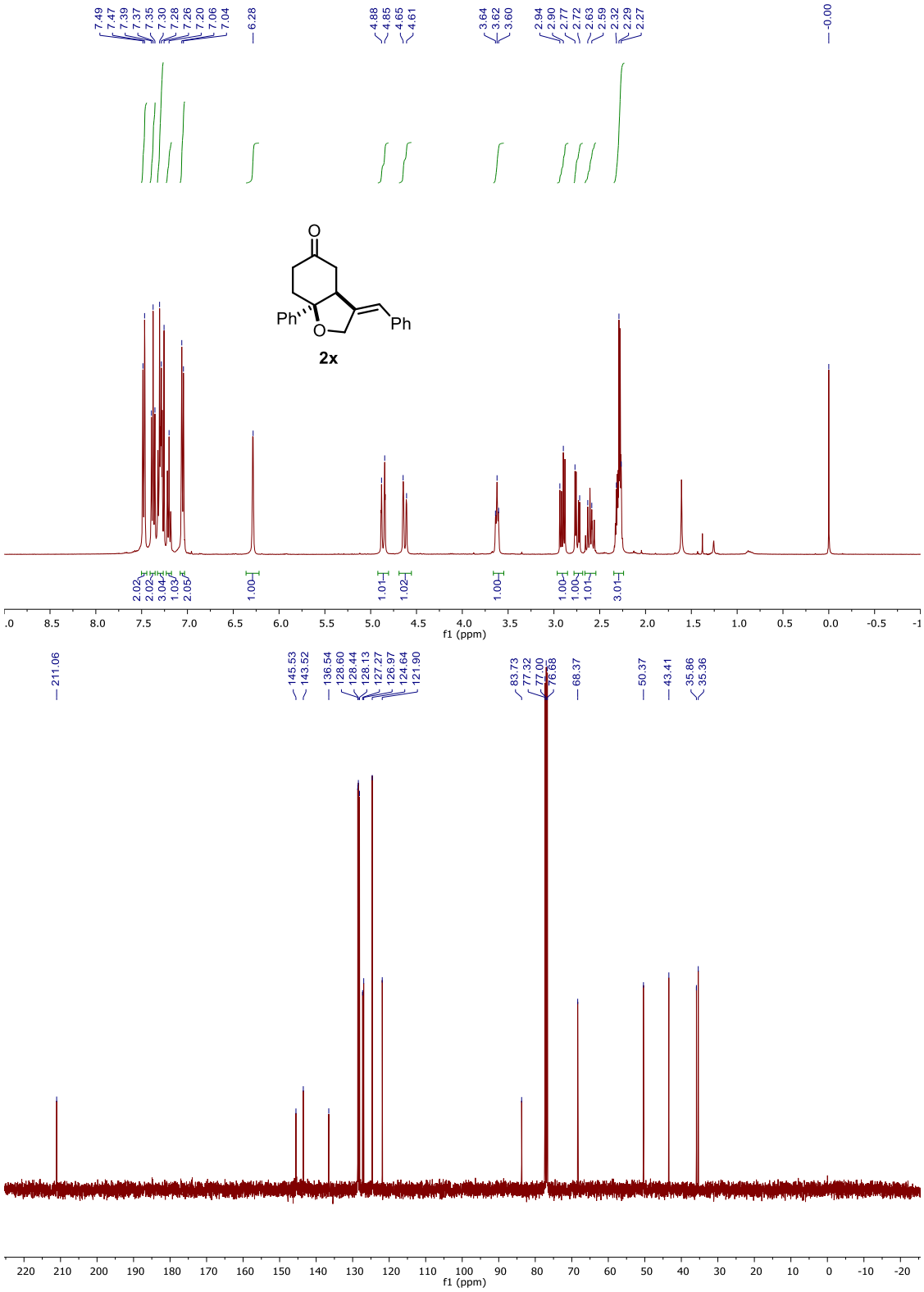


Figure 4.64 ^{1}H-NMR and ^{13}C-NMR Spectra of **2y**

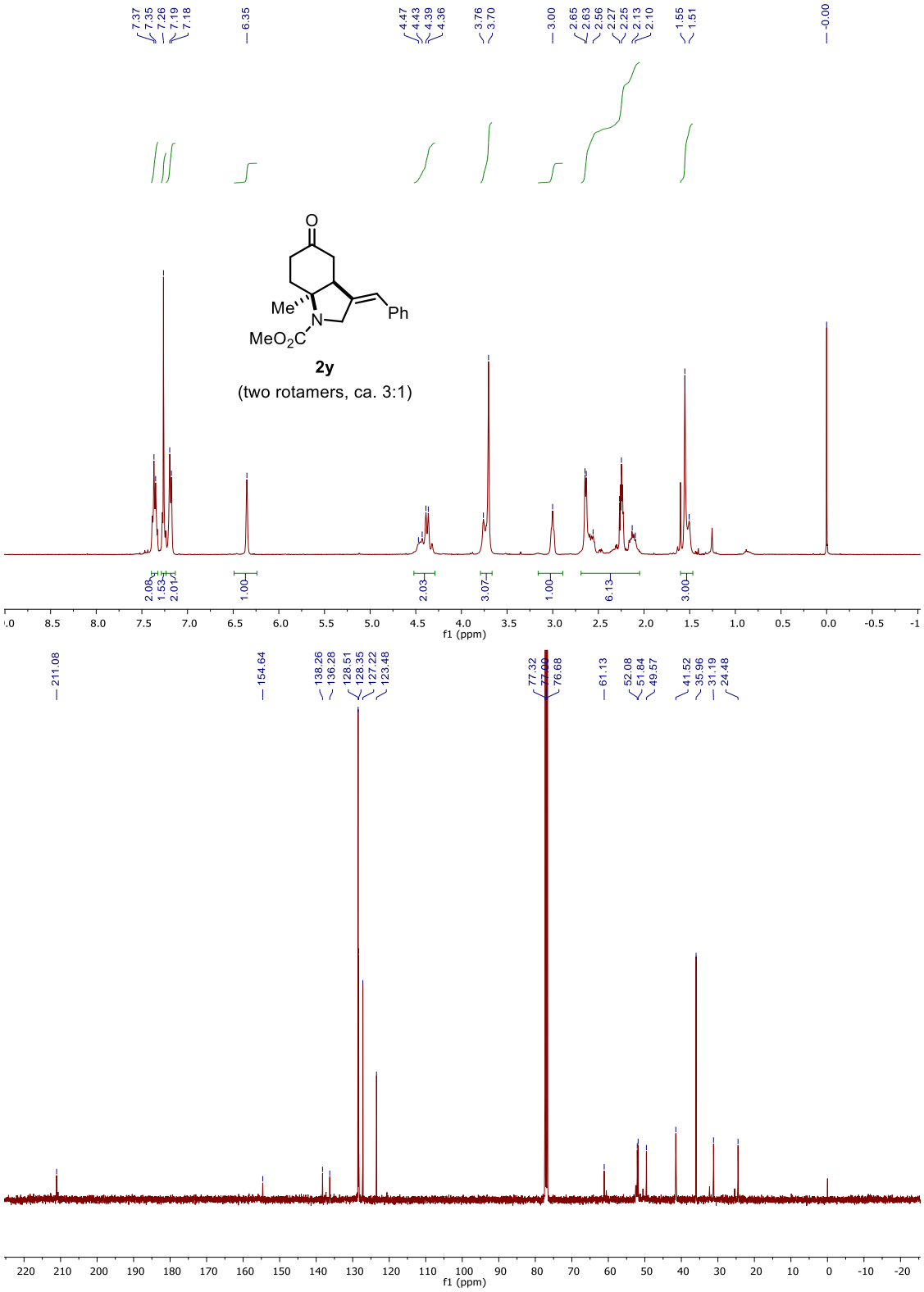


Figure 4.65 ^{1}H-NMR and ^{13}C-NMR Spectra of **5**

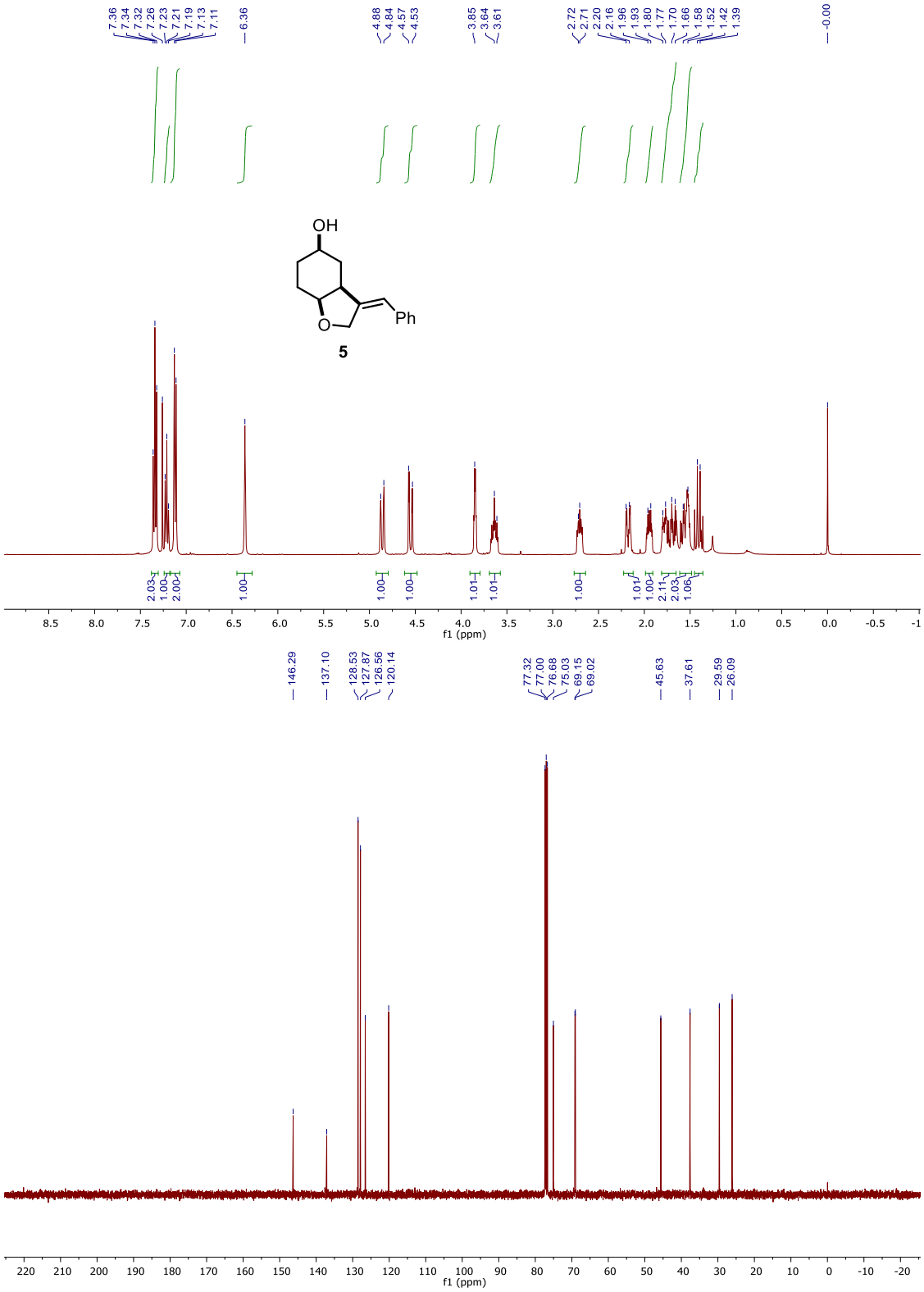


Figure 4.66 COSY Spectrum of **5**

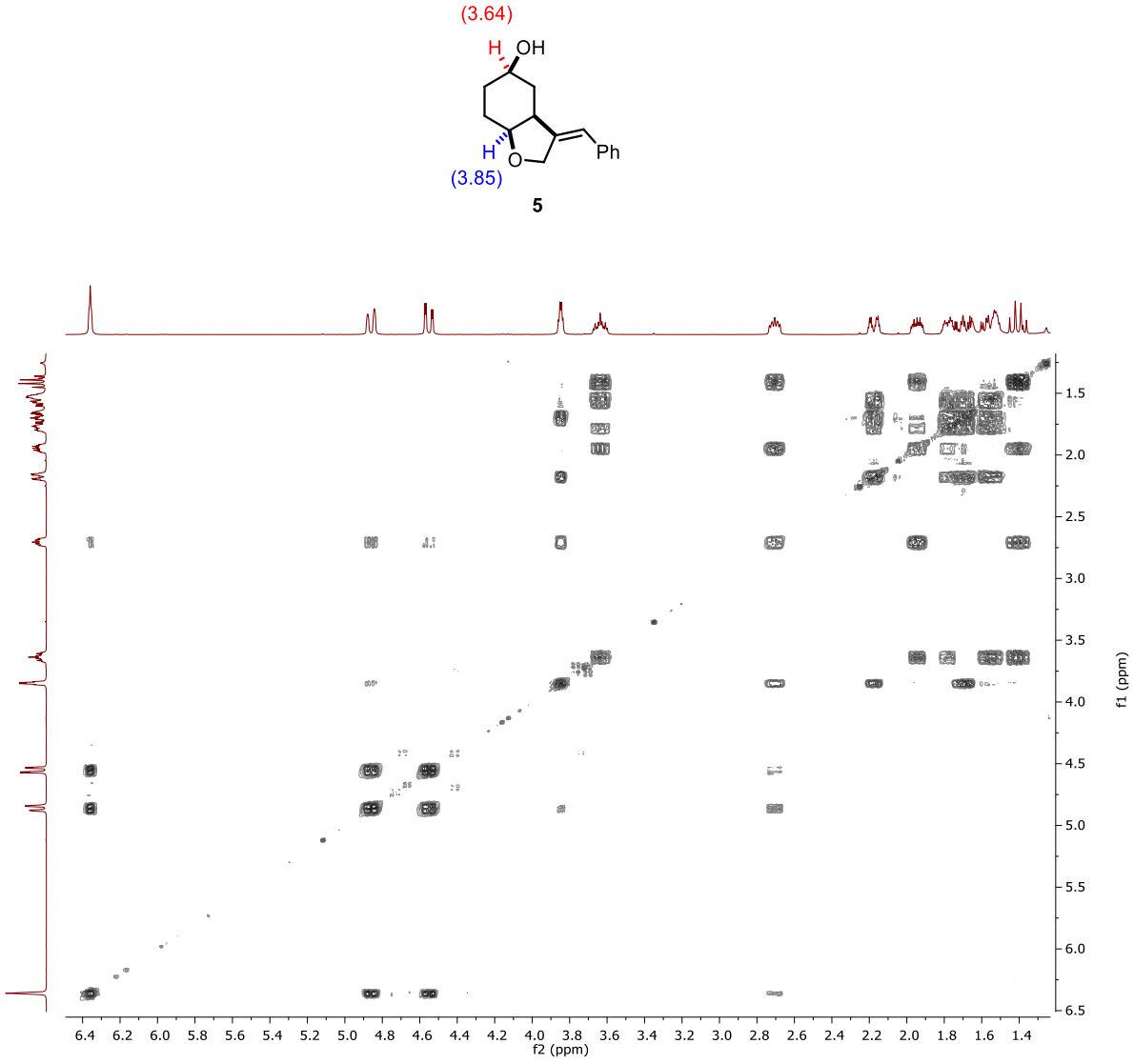


Figure 4.67 NOESY Spectrum of **5**

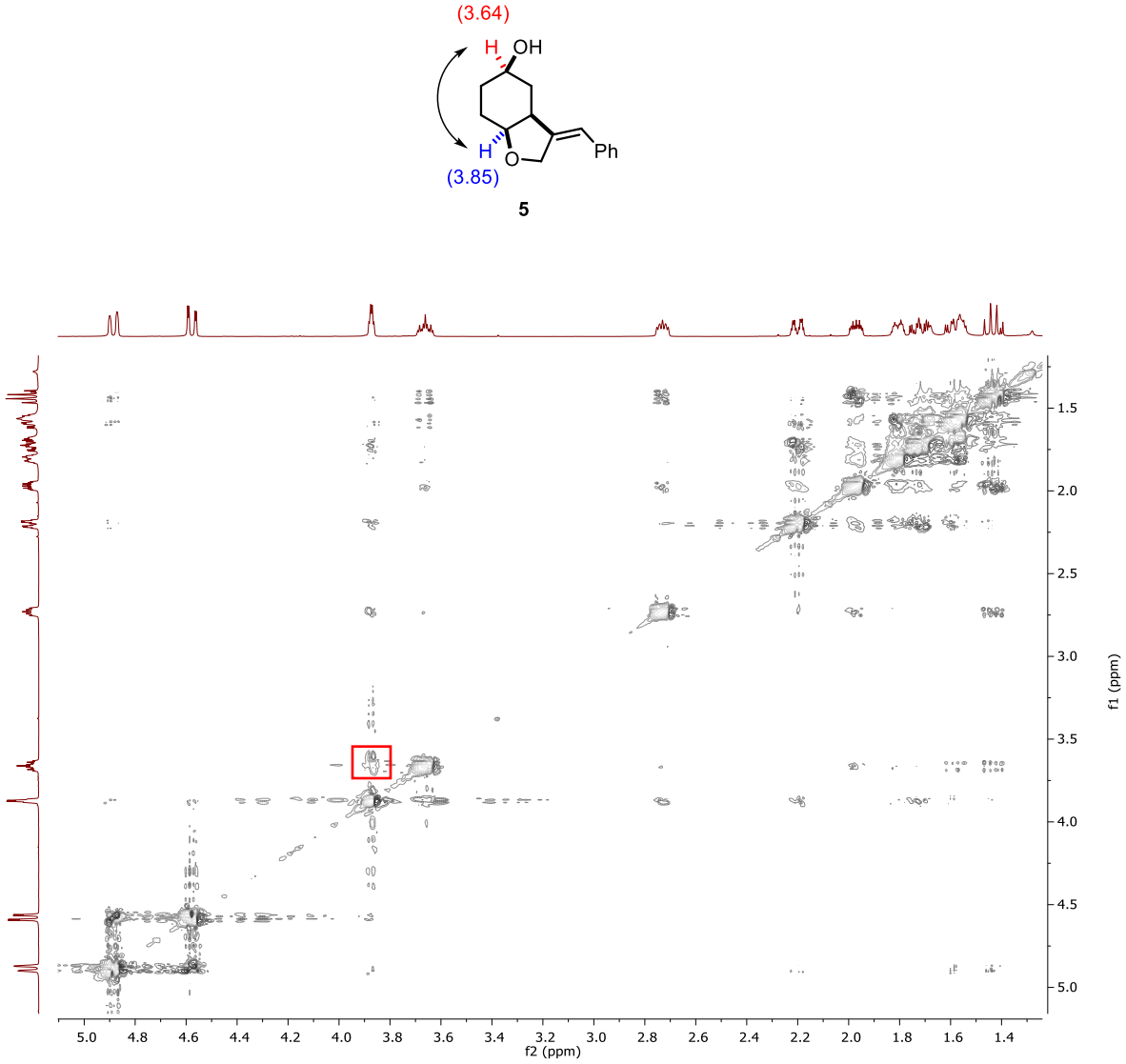


Figure 4.68 ^{1}H-NMR and ^{13}C-NMR Spectra of **5'**

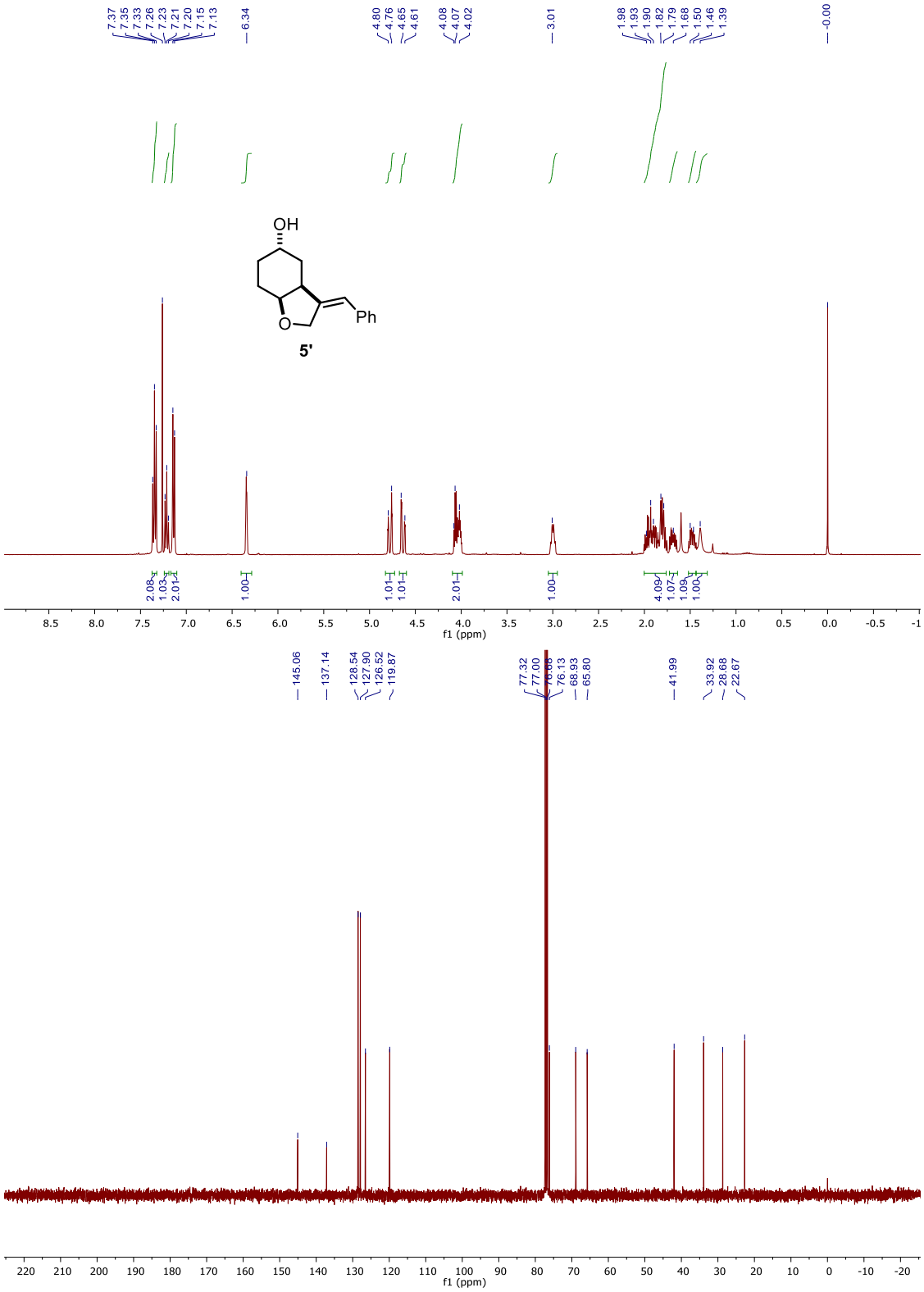


Figure 4.69 ^{1}H-NMR and ^{13}C-NMR Spectra of **6**

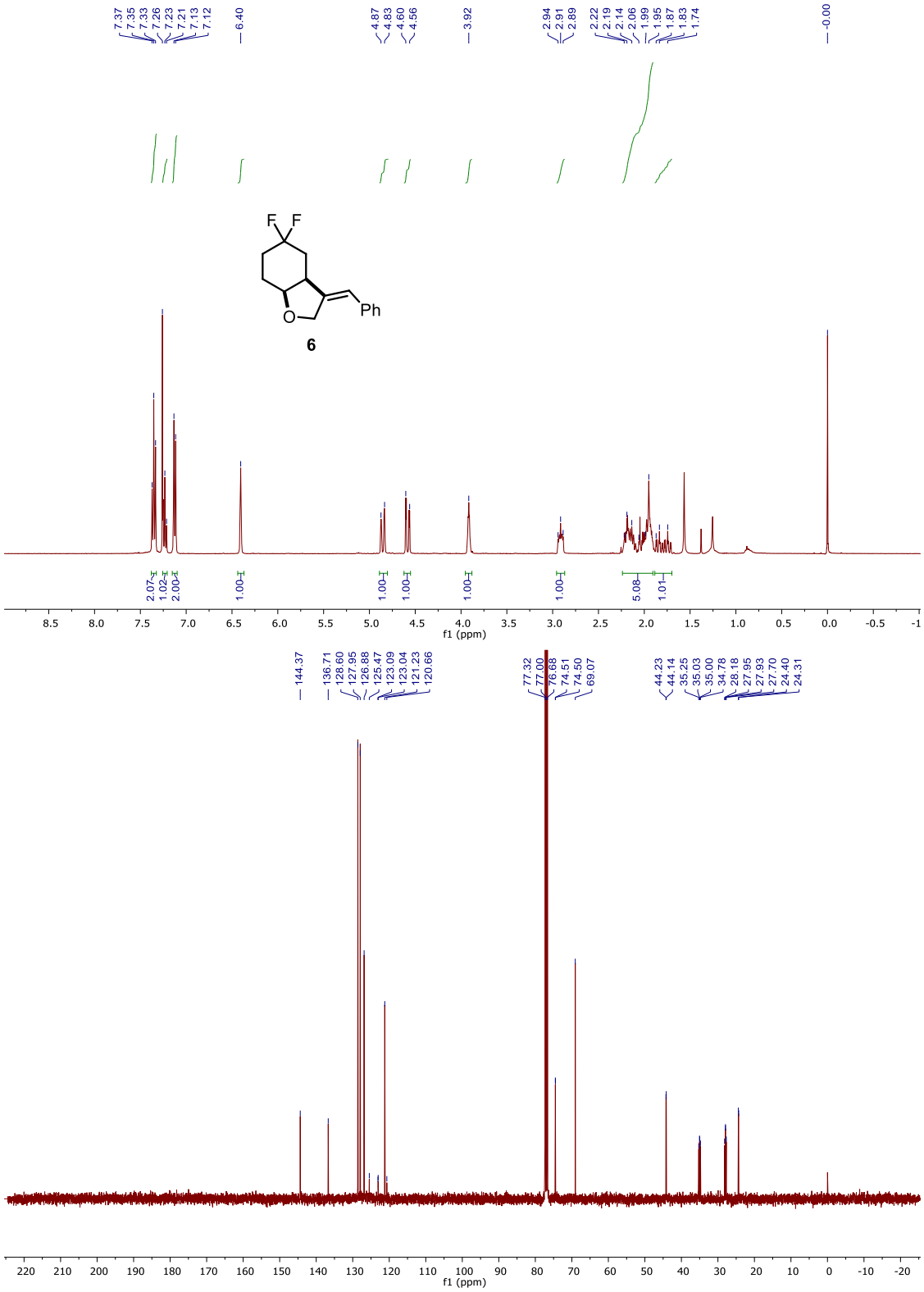


Figure 4.70 ^{19}F-NMR Spectrum of **6**

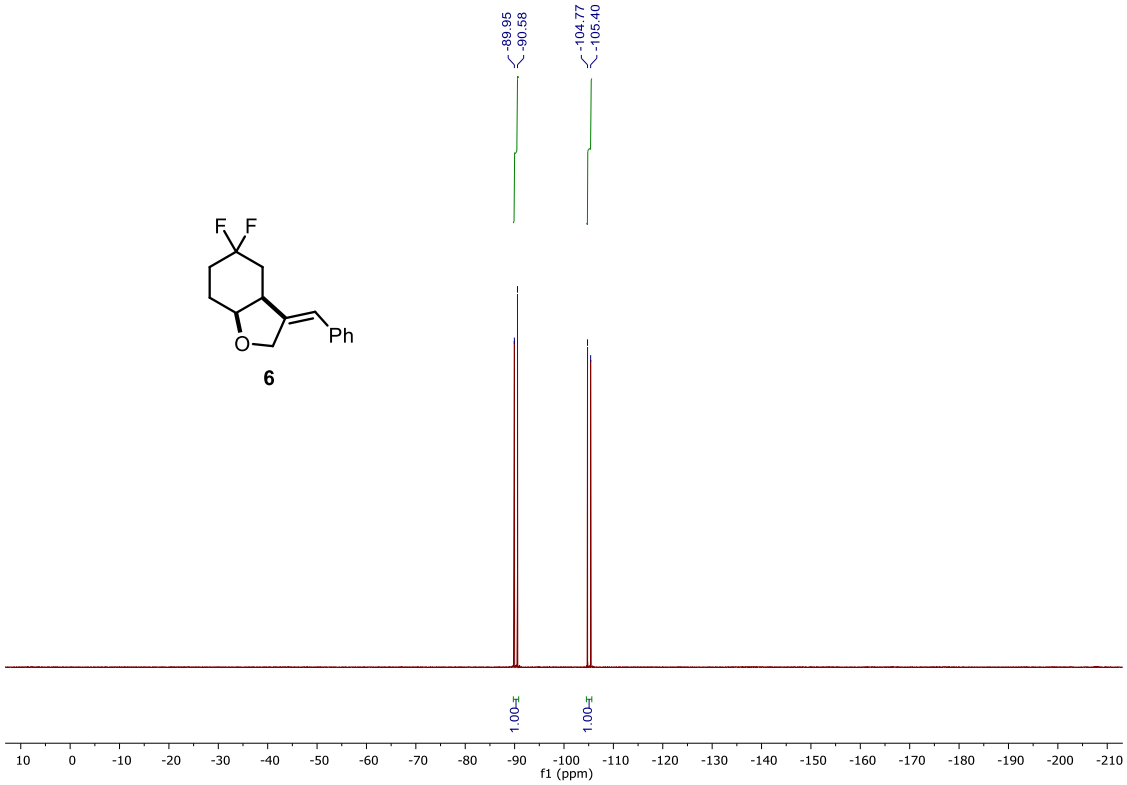


Figure 4.71 ^{1}H-NMR and ^{13}C-NMR Spectra of **7**

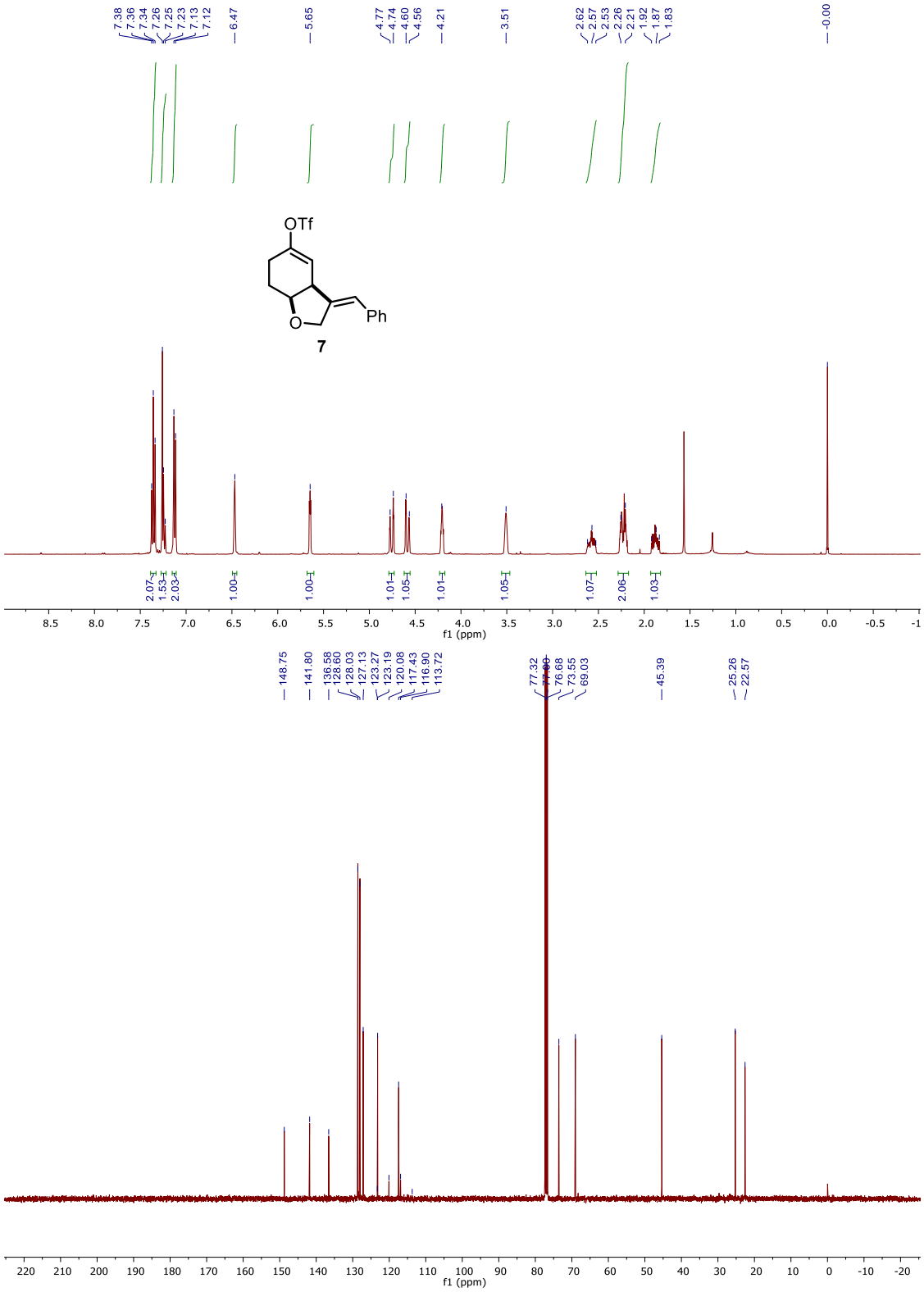


Figure 4.72 ^{19}F-NMR Spectrum of **7**

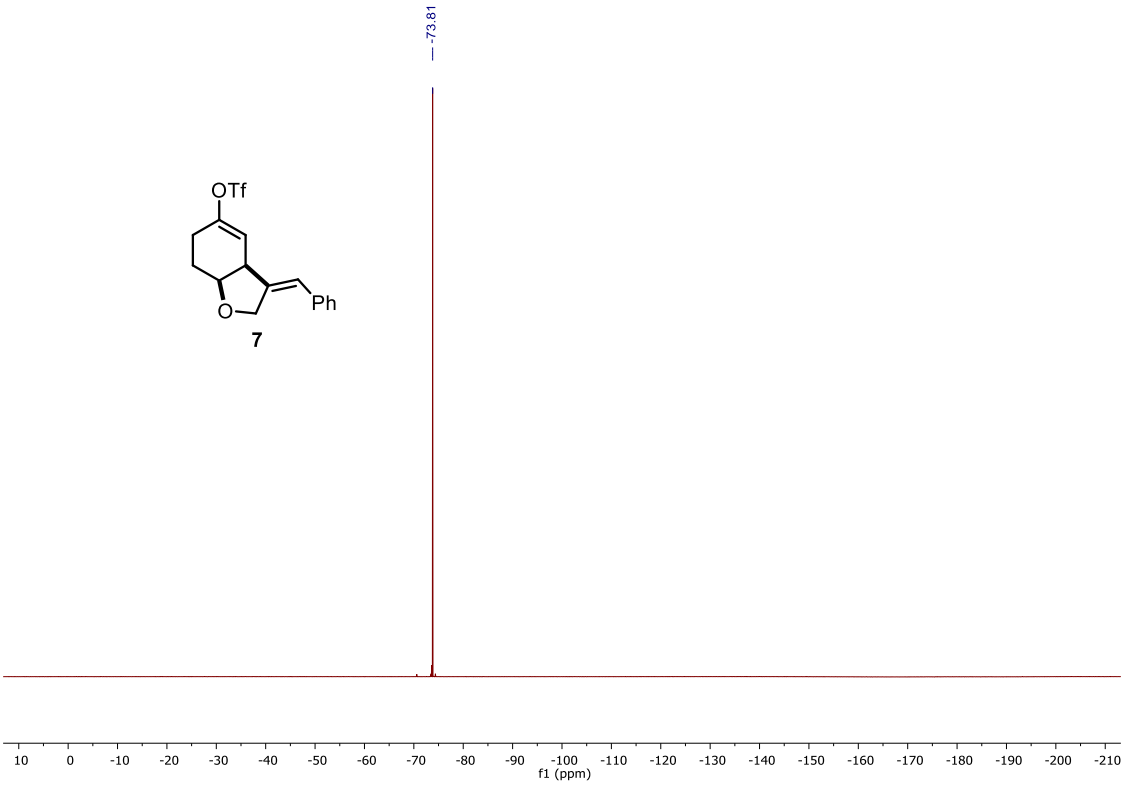
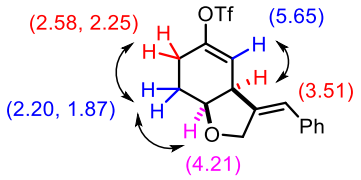


Figure 4.73 COSY Spectrum of **7**



7

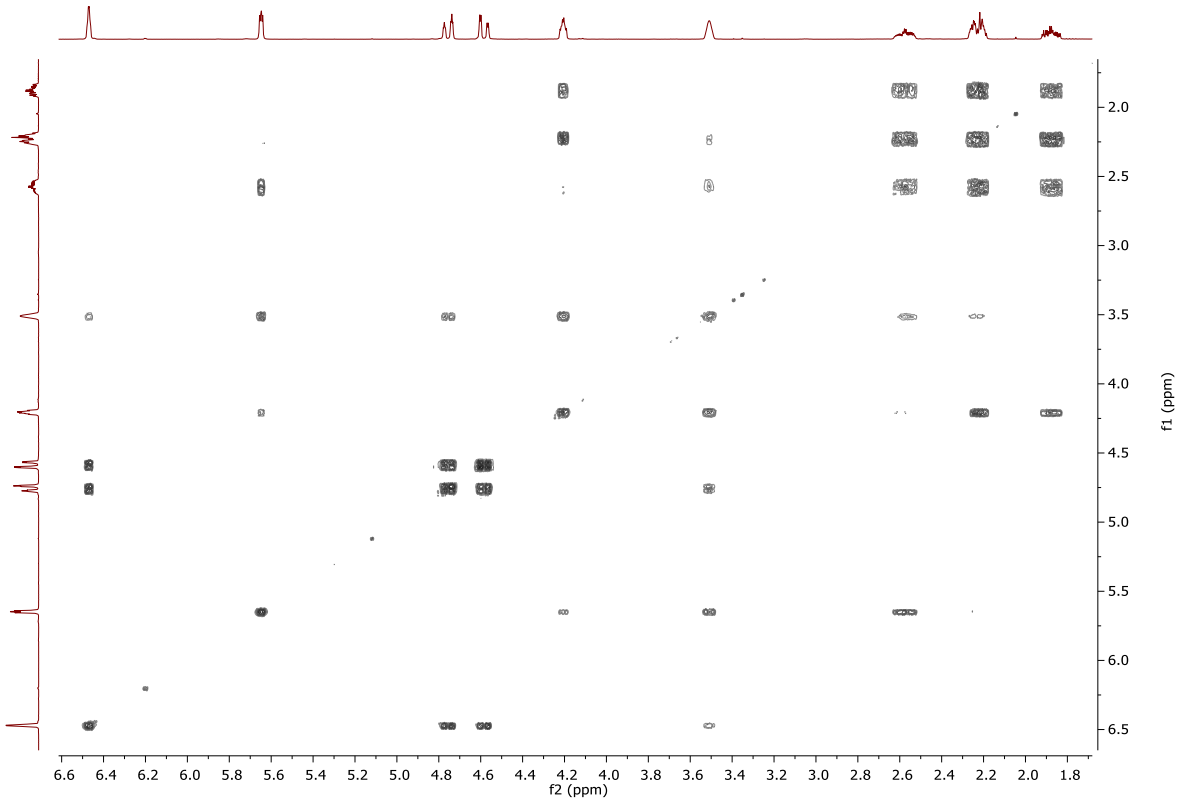


Figure 4.74 ^{1}H-NMR and ^{13}C-NMR Spectra of **8**

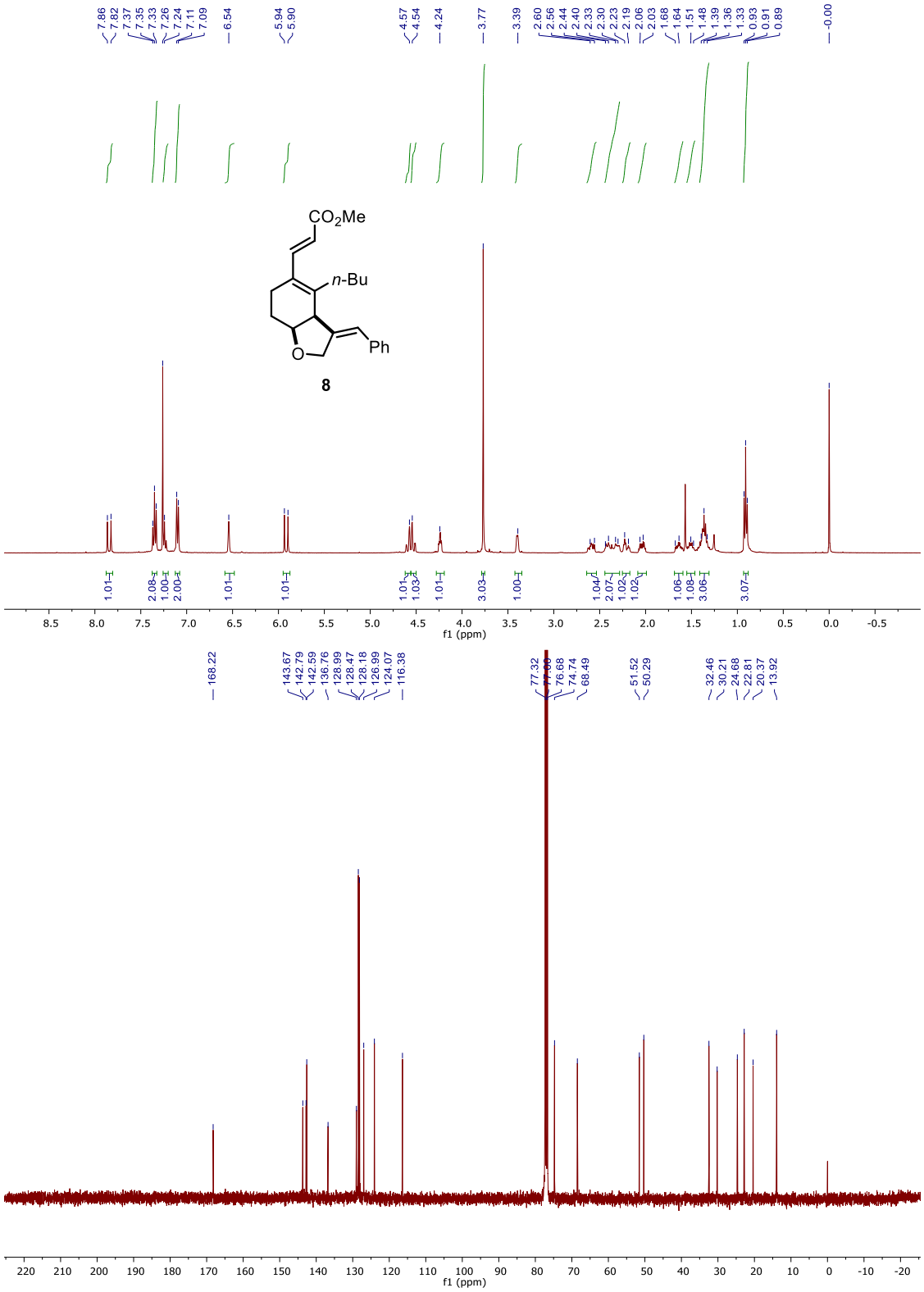


Figure 4.75 ^{1}H-NMR and ^{13}C-NMR Spectra of **9**

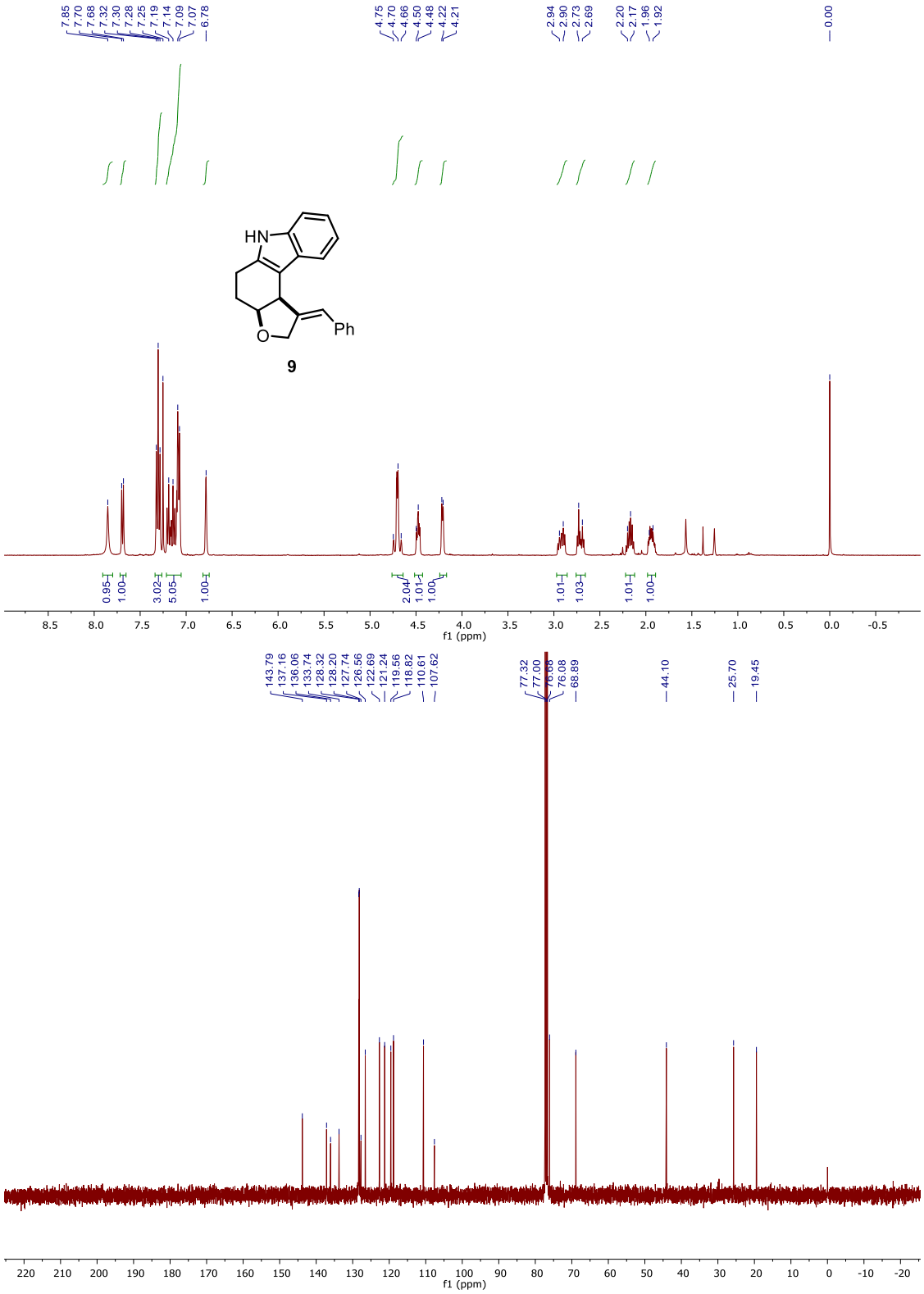
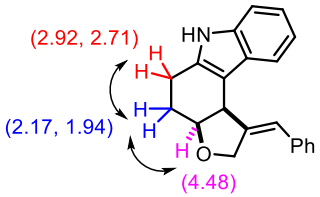


Figure 4.76 COSY Spectrum of **9**



9

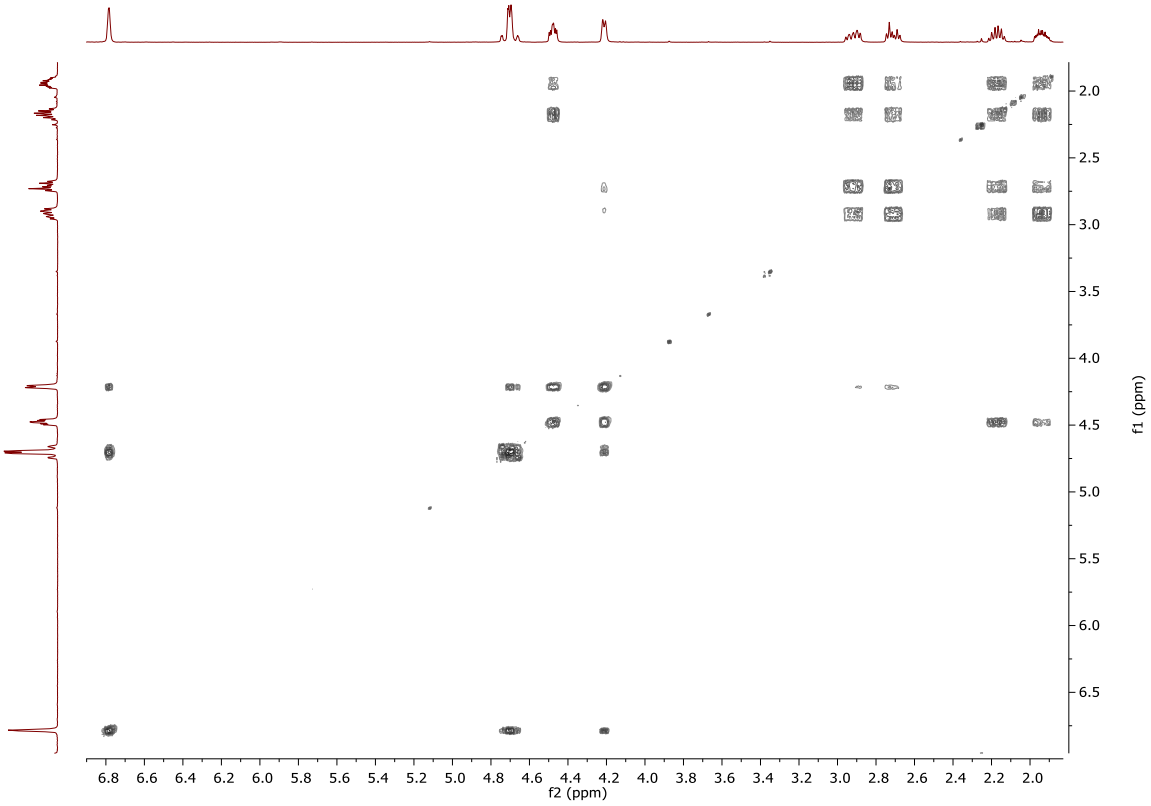


Figure 4.77 ^{1}H-NMR and ^{13}C-NMR Spectra of **10**

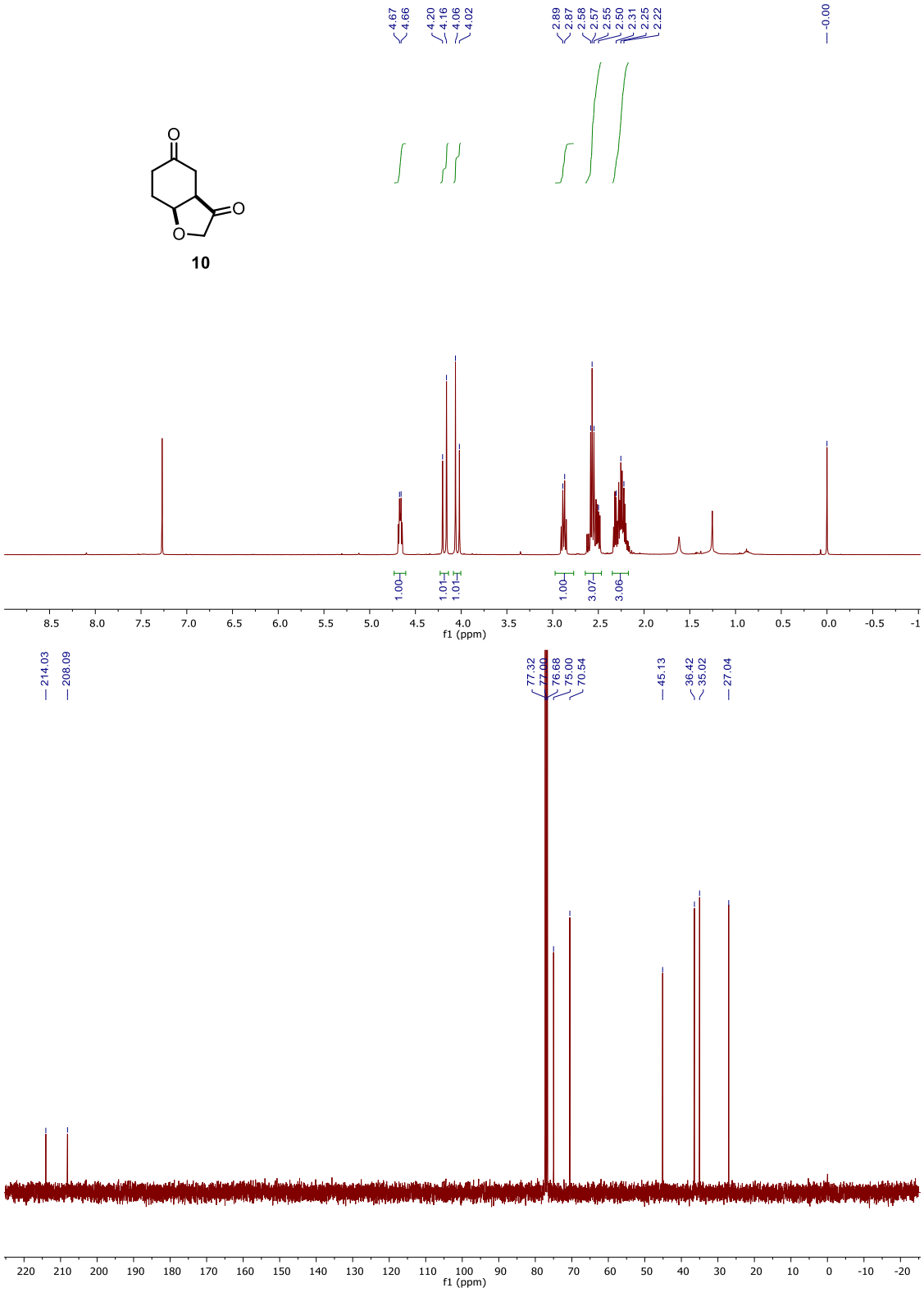


Figure 4.78 ^{1}H-NMR and ^{13}C-NMR Spectra of **11**

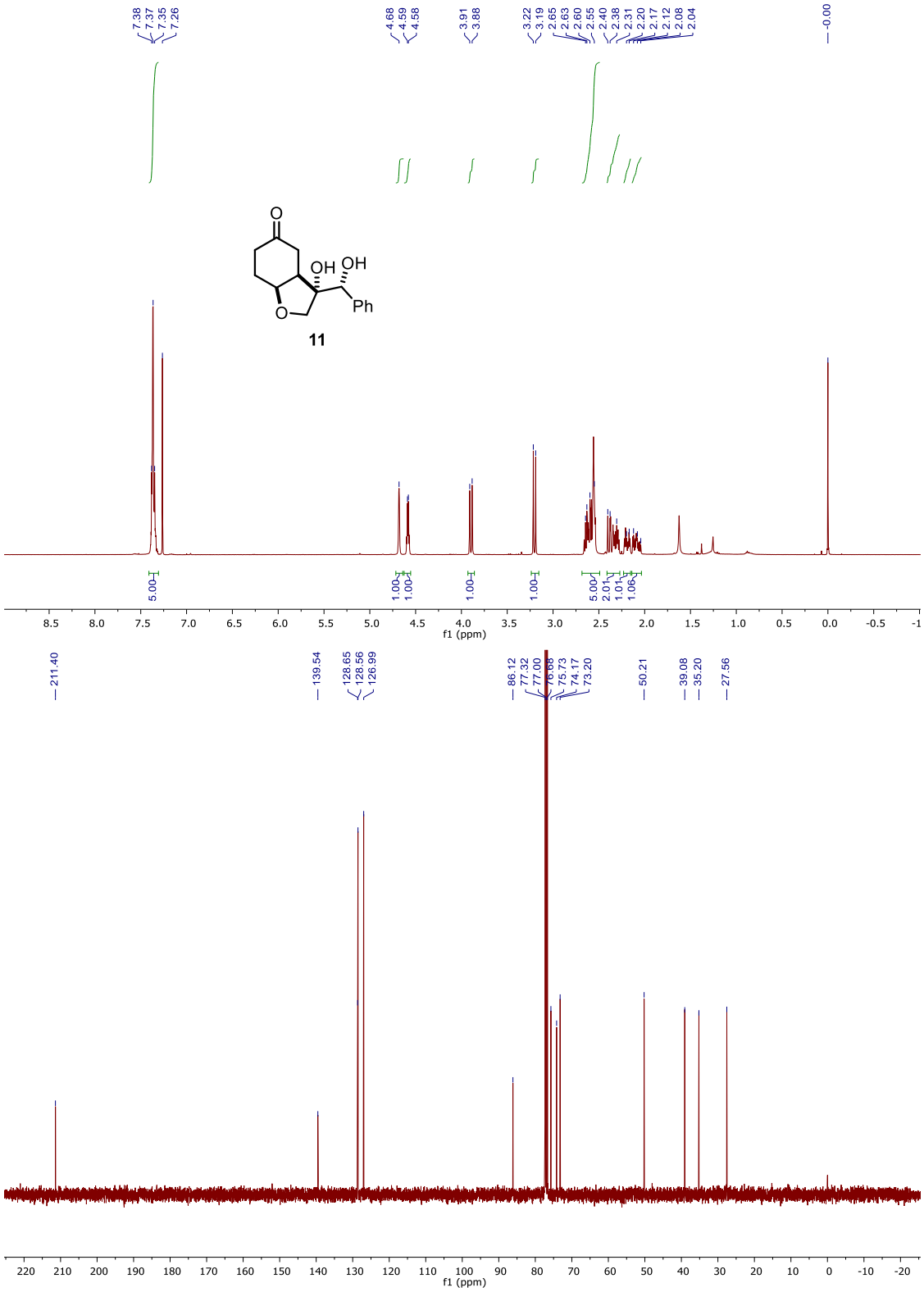


Figure 4.79 ^{1}H-NMR and ^{13}C-NMR Spectra of **2a-β-d$_4$**

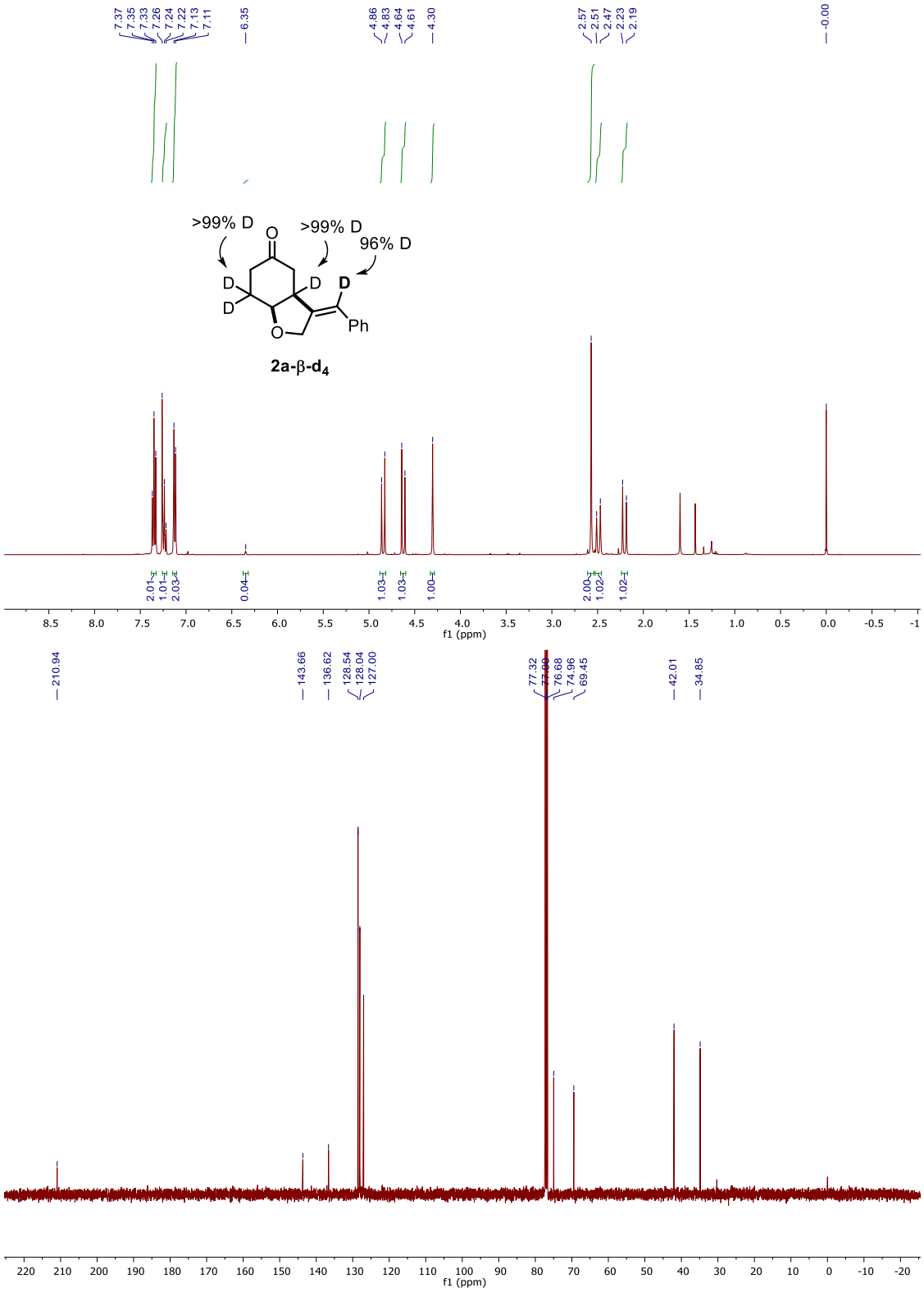


Figure 4.80 ^{2}H-NMR Spectrum of **2a-β-d$_4$**