THE UNIVERSITY OF CHICAGO

PALLADIUM NORBORNENE COOPERATIVE CATALYSIS

A DISSERTATION SUBMITTED TO

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BY

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Dedication

This thesis is dedicated to the memory of my grandfather Mr. Hui Ji, commemorating the fourteenth year of his death.

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ABSTRACTS

Chapter 1 introduce the historical background and discovery of Palladium/Norbornene cooperative catalysis. Catellani and coworkers did systematic organometallic study and catalytic system study to prove the concept and mechanism of palladium/norbornene cooperative catalysis. Detailed organometallic study and correct mechanism proposal provide were discussed. Electrophile constraint, aryl iodide constraint, *ortho* constraint are three major limitations for the Palladium/Norbornene cooperative catalysis.

Chapter 2 describe a palladium/norbornene-catalyzed *ortho*-arene amination to introduce amine at *ortho* position of aryl iodide and hydrogen atom at the *ipso* position. *O*-benzoyloxyamines and *iso*-propanol are employed as the amine source (oxidant) and reductant respectively. This transformation gives complementary site-selectivity at the *ortho* instead of the *ipso*-position of aryl halides with high functional group tolerance.

Chapter 3 describe a palladium/norbornene-catalyzed *ortho*-arene acylation of aryl iodides via Catellani-type C–H functionalization. This transformation is enabled by isopropyl carbonate anhydrides as a dual functional reagent serving as both an acyl cation equivalent and a hydride source.

Chapter 4 describe the development of general approaches for aryl bromide-mediated Pd/NBE cooperative catalysis. *Ortho* amination, acylation and alkylation of aryl bromides have all been realized in good efficiency. Importantly, various heteroarene substrates also work well and a wide range of functional groups are tolerated. Sequential cross coupling/*ortho* functionalization reactions and consecutive palladium/norbornene-catalyzed difunctionalization to construct penta-substituted aromatics and two-step meta-functionalization reactions are achieved.

Chapter 5 describe a highly *meta*-selective C−H arylation using simple tertiary amines as the directing group. This method takes advantages of Pd/norbornene catalysis offering a distinct strategy to control the site-selectivity. The reaction was promoted by commercially available $AsPh_3$ ligand and unique "acetate cocktail". Aryl iodides with an *ortho*-electron withdrawing group were employed as the coupling partner. A wide range of functional groups, including some heteroarenes, can be tolerated under the reaction conditions. The amine directing group can be easily installed and trans-formed to other common versatile functional groups.

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: Palladium and Norbornene Cooperative Catalysis: form the Organometallic Study to the Winning Catalysis

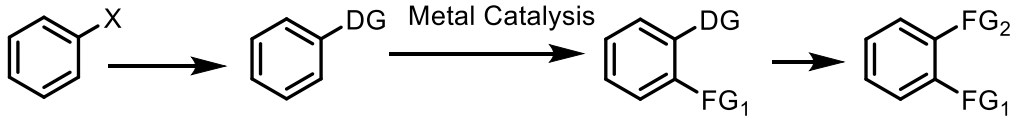
1.1 Introduction

Transition metals catalyzed aromatic carbon hydrogen bond functionalization (C-H functionalization) represents one of the most efficient way to prepare functionalize arenes.[1-3] In particularly, many novel transformations using palladium catalysis have been achieved.[4-6] To achieve the high site-selectivity, directing groups (DGs) was introduced and applied as a strategy to give complete control of regio-selectivity.[7-9] Among various DGs, the most common one is covalently directing group such as pyridine, amide, or carbonyl group. These DGs need one or more synthetic steps to install, and need one or more synthetic steps to remove.[10] Although, C-H activation steps may have a high efficiency, but the installation and remove of DGs greatly decrease the overall synthetic efficiency and limited their application. Second one is through the dynamic-covalent bonding.[11] The directing group was installed and removed under the same reaction conditions, thus enable people to use catalytic amount of directing group. This approach heavily replied on the nature of dynamic-covalent bonding, which greatly limited the substrate scope. Palladium/Norbornene Cooperative catalysis offer a distinct way to install directing group in one catalytic cycle and enable us to install two functional group onto arenes at the same time.[12-17]

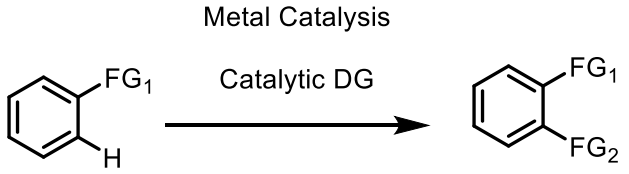
This chapter review the discovery and development of palladium/norbornene cooperative catalysis.

Scheme 1.1 Different directing group strategy**.**

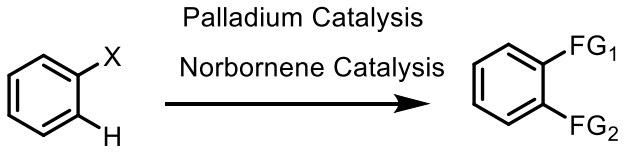
Covalent DG:



Dynamic-Covalent DG:



Pd/Norbornene DG:

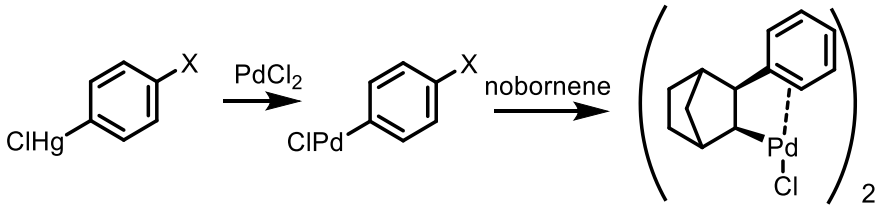


1.2 Organometallic Study in the Palladium/Norbornene Catalyzed C-H Activation.

Migratory insertion and β-hydride elimination were most common elemental steps in the organometallic chemistry. To gain a better understanding of these two steps, Inoue group report an interesting example: palladium phenyl chloride could reactive with norbornene at room temperate to form sp3-Pd bond species.[18] (Scheme 1.2) They observed phenyl-norbornene-palladium dimer product (PNP dimer) instead of common Heck Reaction product. They proposed that Pd-phenyl bond undergo a syn-migratory insertion with norbornene to form the

PNP dimer. Pd center in the product don't have β-hydrogen is syn to the Pd center so that β-hydride elimination couldn't happen at this stage. This work build the cornerstone for all the Pd/NBE catalysis

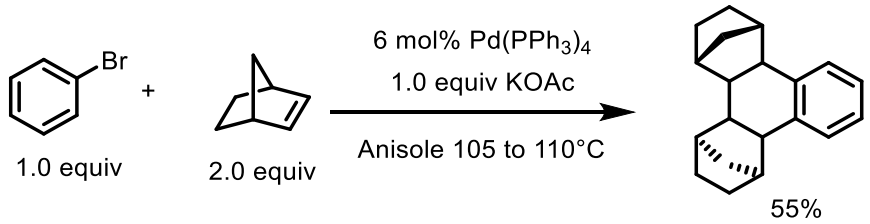
Scheme 1.2. Migratory insertion between Pd-phenyl bond and norbornene.



PNPdimer

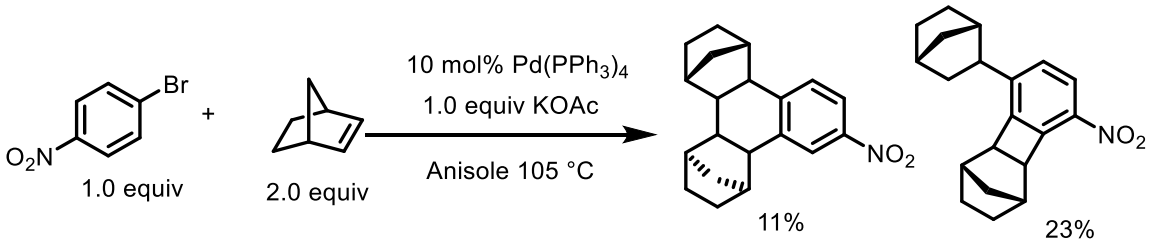
This unique system didn't catch much attention until Prof. Marta Catellani revisit the system in the 1980s. In 1982, Catellani and coworkers reported the first catalytic C-H activation of aromatic C-H bond involving the palladium and norbornene.[19] (Scheme 1.3) When bromobenzene was treated with norbornene, potassium acetate and 6 mol% $Pd(PPh_3)_4$ catalyst, a double-insertion product involving ortho C-H bond activation was isolated in 55% yield. This proved that norbornene can work as a intramolecular directing group for the aromatic *ortho* C-H activation. However, whether C-H activation happen after one norbornene to form 5-membered metallocycle or happen after double insertion to form 7-membered metallocycle was still not clear at this stage.

Scheme 1.3 First catalytic C-H activation involving Pd/NBE.



In 1984, Catellani group reported another interesting results that under similar condition, 4-nitrobromobenzene gave a cyclobutene containing product together with cyclohexane product.[20] (Scheme 1.4) The formation of cyclobutene product strongly imply that C-H activation involve 5-membered metallocycle.

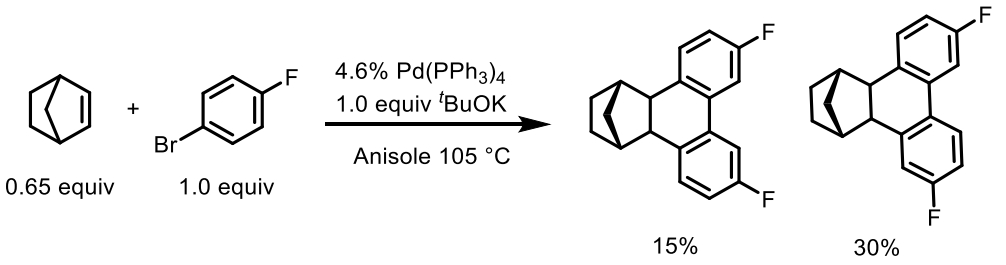
Scheme 1.4 First cyclobutane formation involving Pd/NBE catalysis.



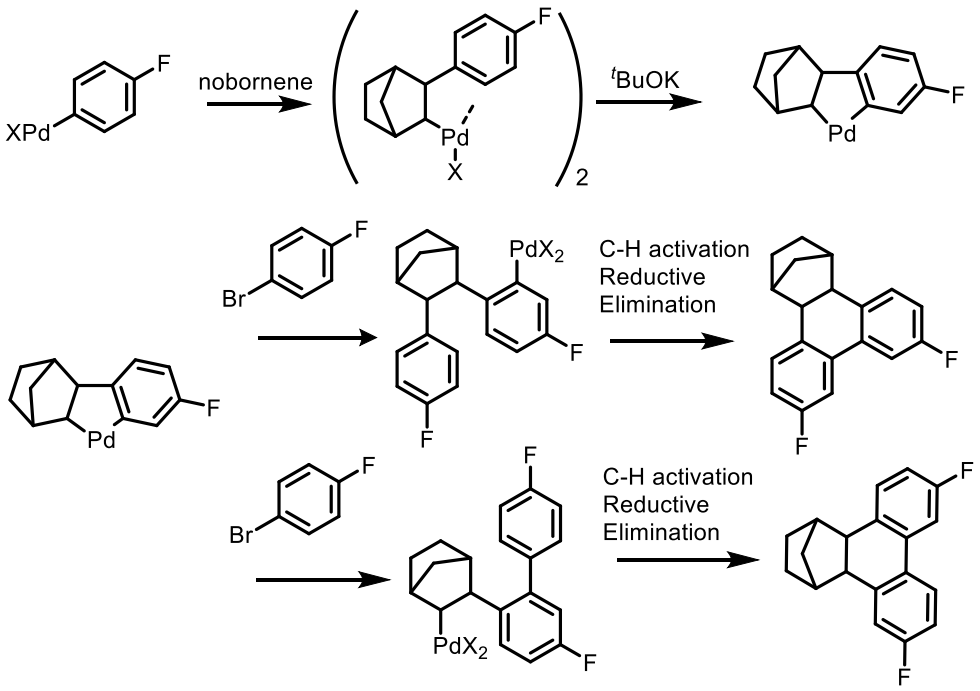
In 1985, Catellani group reported a complex tandem C-C bond formation involving the Pd/NBE catalyzed C-H activation. When bromombenzene was treated with potassium tert-butloxide, a biaryl containing cyclohexane product was isolated.[21] Interestingly, when *para*-substituted bromide was used, the product was a mixture of two regio-isomer.(Scheme 1.5) The proposed mechanism was shown in the Scheme 1.6; Pd(0) oxidative addition into the aryl bromide bond, then syn-migratory insertion into the norbornene. Intramolecular C-H activation to form key 5-membered metallocycle. This aryl-norbornyl palladium(II) species (ANP) could further react with aryl bromide with form C-C bond at both aryl site and norbornyl site. The

resulting Pd(II) species could undergo further C-H activation to form another C-C bond to give the final product.

Scheme 1.5 Pd/Nobornene co-cataylzed aryl-aryl bond formation.



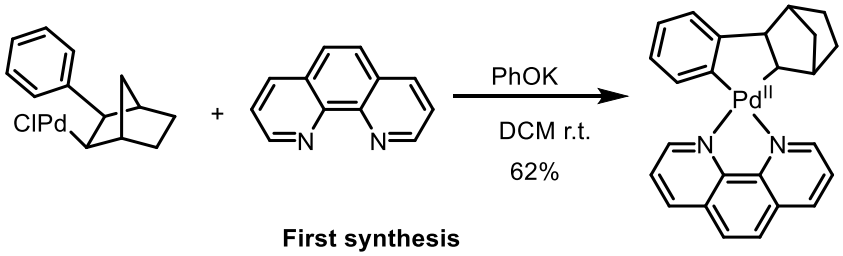
Scheme 1.6 Proposed mechanism for Pd/Nobornene co-cataylzed aryl-aryl bond formation.



One important breakthrough is that Prof. Catellani group isolated the first intramolecular C-H activation intermediate with Pd/NBE in 1988.[22] (Scheme 1.7) They found that when treating

the PNP dimer with potassium phenolate and 1,10- phenanthroline, a five-membered cyclometalled compound was isolated. The aryl-norbornyl palladium(II) species (ANP) has one sp2 carbon and one sp3 carbon as the X type ligand, which didn't undergo reductive elimination or β-hydride elimination at room temperature. This C-H activation occurred on mild basic condition at room temperature.

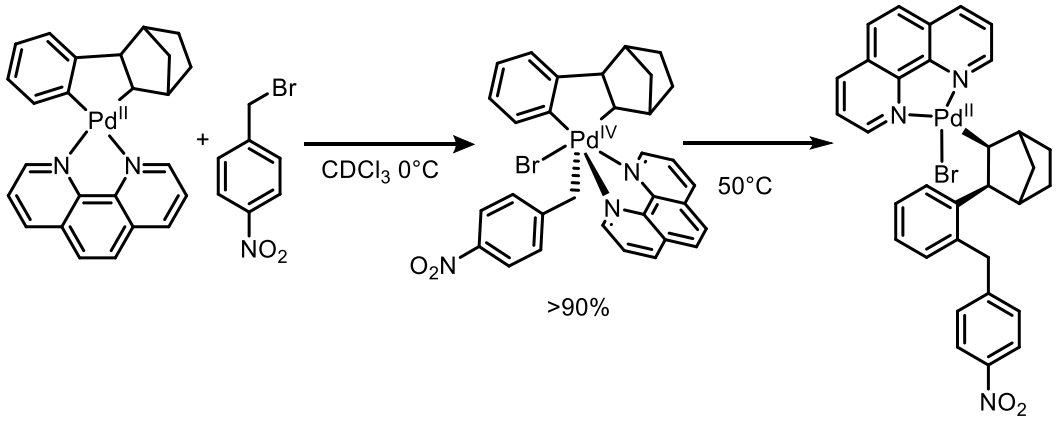
Scheme 1.7 Intramolecular Pd/NBE mediated C-H Activation.



First synthesis and isolation of ANP

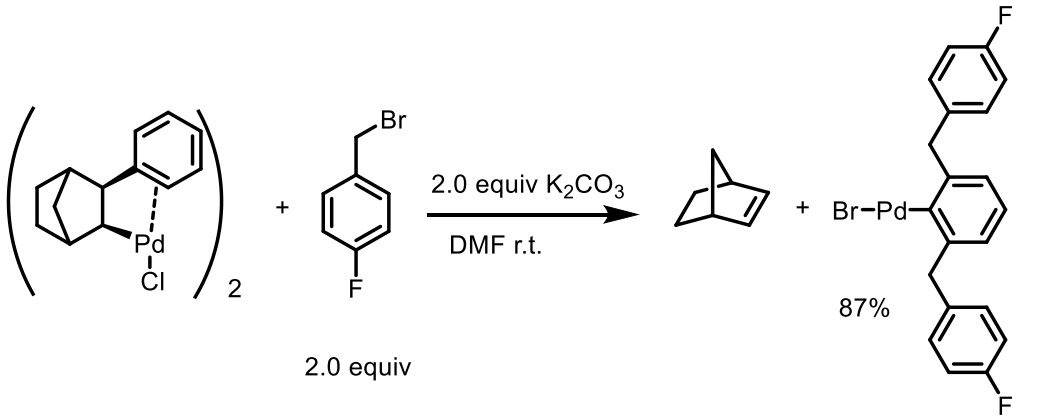
The further studies by Catellani group demonstrated that cyclometallted intermediated could react with benzyl halide at 0℃ to form stable palladium(IV) intermediate.[23-24] (Scheme 1.8) Interestingly, warm up to 50℃, the palladium (IV) metal center undergo selective sp2-sp3 reductive elimination to form benzylated arene product.[24] This provide us several key information: 1. ANP intermediate was highly electron rich, it can be oxidized to Pd(IV) by weak oxidant such as benzyl halide at 0℃. 2. Reductive elimination from the palladium center was highly selective, predominantly happen on sp2 carbon site. 3. Aryl-Pd bond in the ANP was nucleophilic instead of common Ary-Pd-X (X≠C) which was electrophilic in most cross-coupling reaction.

Scheme 1.8 Palladium(IV) intermediate and its reductive elimination



All previous results always had a norbornene attached to the product, which make the whole transformation muss less attractive to the synthetic chemist. In 1994, Catellani and coworker reported an elegant work to demonstrate that the norbornene can be removed from the arene product in the presence of palladium metal. [25] (Scheme 1.9)

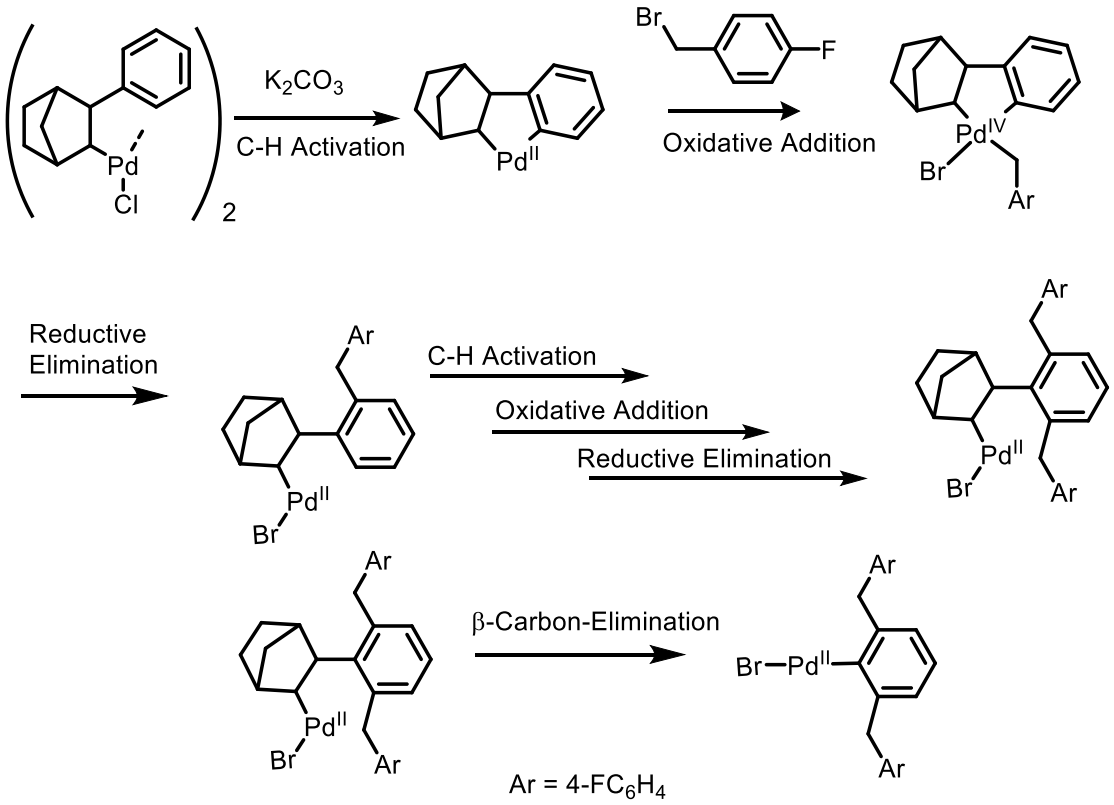
Scheme 1.9 First norbornene exclusion through β-carbon elimination.



The proposed mechanism was shown in the scheme 1.10. The PNP dimer could undergo C-H activation under basic condition, and then newly formed metallocycle would react with the benzyl bromide to form the Pd(IV) intermediate. Selective sp3-sp2 carbon-carbon bond reductive

elimination would give ortho benzylated arene. The same sequence could happen again to give 2,6-disubstituted arene with norbornene attached the middle carbon. Interestingly, due to the steric-repulsion between 2,6-disubstituted arene and palladium(II) center, a β-carbon elimination would happen to release the norbornene and palladium(II) would go back to the middle of the arene.

Scheme 1.10 First norbornene exclusion through β-carbon elimination.

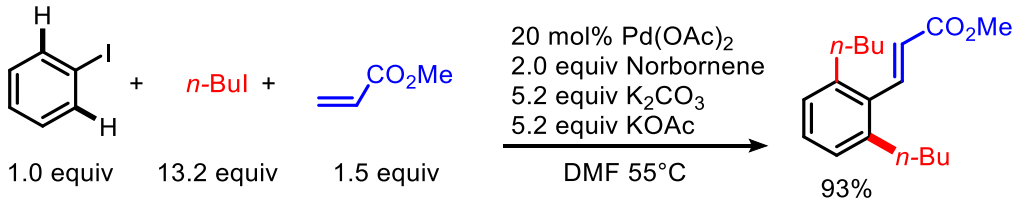


These systematic studies already prove that it is possible to use catalytic amount of palladium and norbornene to functionalize the arene's both *ipso* and *ortho* position to introduce two different functional groups.

1.3 Catalytic Palladium/Norbornene Catalyzed C-H Activation.

In 1997, Catellani group reported an elegant work of palladium catalyzed the ortho alkylation/ipso alkenylation of aryl iodide.[26] (Scheme 1.11) They found that alkyl chain can be introduced at the ortho position, and Heck-type alkenylation could happen at the ipso position. More interestingly, when aryl iodide without ortho substitution was used, the alkylation could happen at the both ortho position. Although, they used 2.0 equiv of norbornene in the system, however they were able to recycle majority of norbornene after the reaction. This imply that norbornene actually could be a catalyst for this transformation.

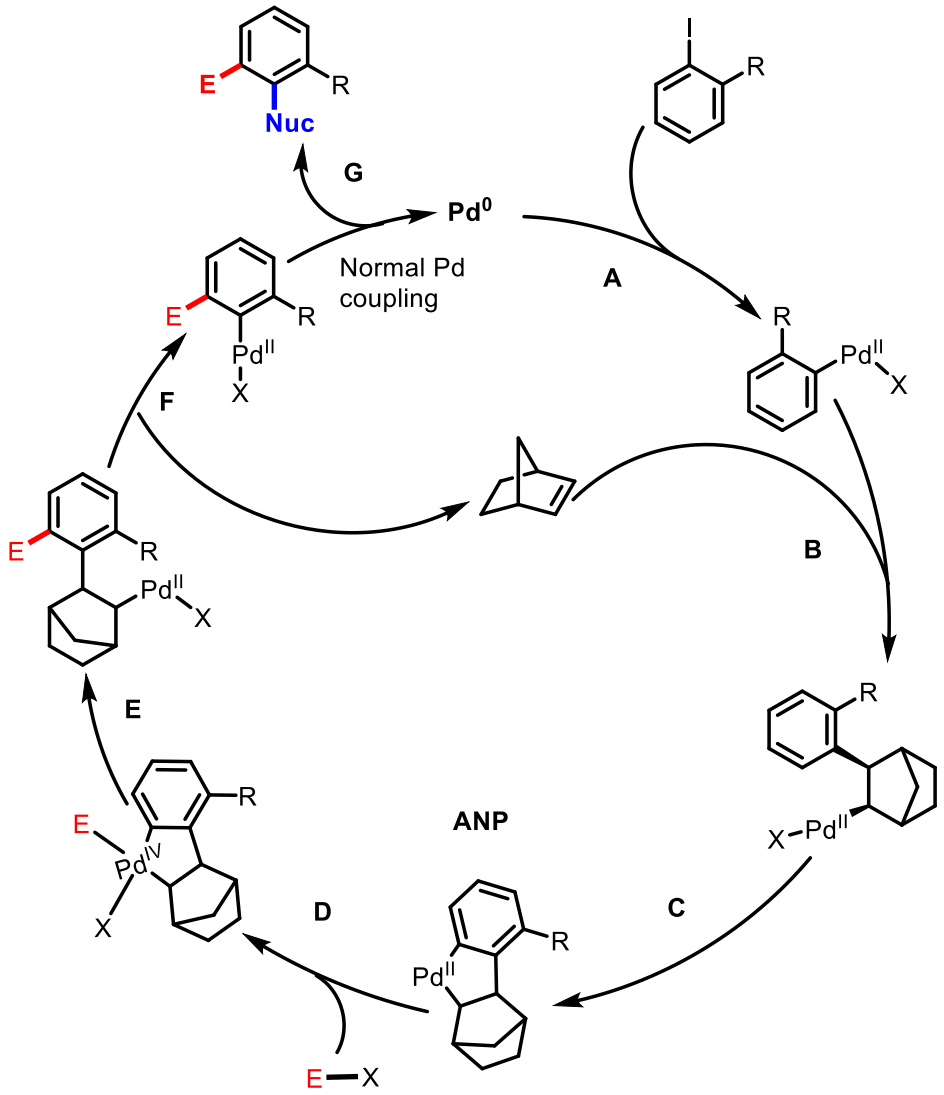
Scheme 1.11 First palladium catalyzed ortho/ipso difunctionalization of aryl iodide.



Based on previous study, Catellani group proposed the mechanism was shown in the Scheme 1.12. Reaction initiated with palladium(0) catalyst oxidative addition into the aryl-iodide bond, to form aryl-Pd(II) species. Then followed syn-migratory insertion of norbornene into the aryl-Pd bond to generate sp3-Pd(II) species. The migration was highly stereoselective, exclusively happen on the exo face of norbornene due to exo face was the less hindered than endo face. Then intramolecular cyclopalladation would happen to activate the ortho C-H bond of aromatic ring to form the key ANP intermediate. Then external electrophile such as alkyl iodide could oxidize the ANP to the Pd(IV). Then selective reductive elimination happen on the sp2 carbon site to introduce the electrophile at the ortho functional group. When arene's both ortho position was occupied, the sp3-Pd(II) center prefer to β-carbon elimination to form aryl-Pd(II).

Newly formed aryl-Pd(II) could undergo normal cross-coupling to introduce the nucleophile at the ipso position of the arene and regenerate Pd(0) catalyst.

Scheme 1.12 Proposed mechanism for Catellani type Pd/NBE cooperative catalysis.



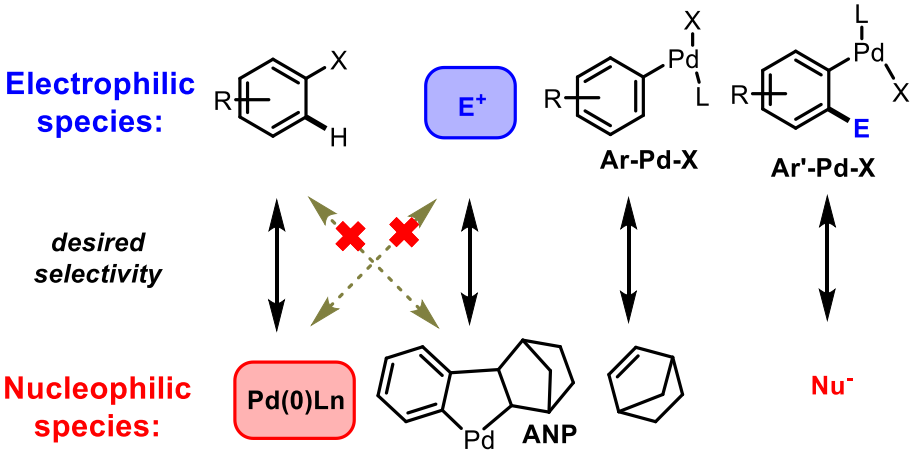
This complex catalytic cycle contains almost all the elemental steps in the organometallic chemistry, palladium catalyst's oxidative state change among Pd(0)/Pd(II)/Pd(IV) cycle. This catalytic cycle was further examined by Lautens[27] and other groups[28-29] both experimentally and computationally. Up to now all studies were consistent with Catellani group's original proposed

mechanism. This correct mechanism provide us plenty of information to further explore this wonderful and unique catalytic system.

Overall palladium/norbornene cooperative could introduce the electrophile at the *ortho* position and the nucleophile at the *ipso* position. Compared with other arene C-H activation methods, it has several advantages: 1. Substrates do not additional steps to install and remove directing group, simple aryl halides were widely available. 2. One step could introduce two different functional groups on the vicinal positions with 100% regio-selectivity. 3. Reaction usually happened under mild basic condition and mild oxidant, thus excellent functional group tolerance and board scope can be excepted. 4. The C-H activation only happens at the *ortho* position of aryl halide, this enable people to override the substrate's electronic and steric bias.

Based on the proposed mechanism, only catalytic amount of norbornene is required for this transformation,[30] although stoichiometric amount was often used to achieve a satisfactory yield.[15,17] Norbornene is not only the directing group for the *ortho* position, but also the protecting group for the *ipso* position. Norbornene insertion only need a activation energy of 17 kcal/mmol,[27] which is significant lower than the palladium catalyzed common cross-coupling reaction. This provide the high regio-selectivity for the difunctionalization. More importantly, the rigid backbond of norbornene make Pd(II) center quite close to the arene's *ortho* C-H bond, which significantly decrease the activation energy of key C-H activation.[31] After the migration insertion and C-H activation, norbornene actually become a catalytic directing chiral auxiliary. It can be expected that enantioselective catalytic C-H functionalization can be achieved using chiral norbornene or desymmetrization of simple norbornene.

Scheme 1.13 Selectivity issues for Pd/NBE cooperative catalysis.



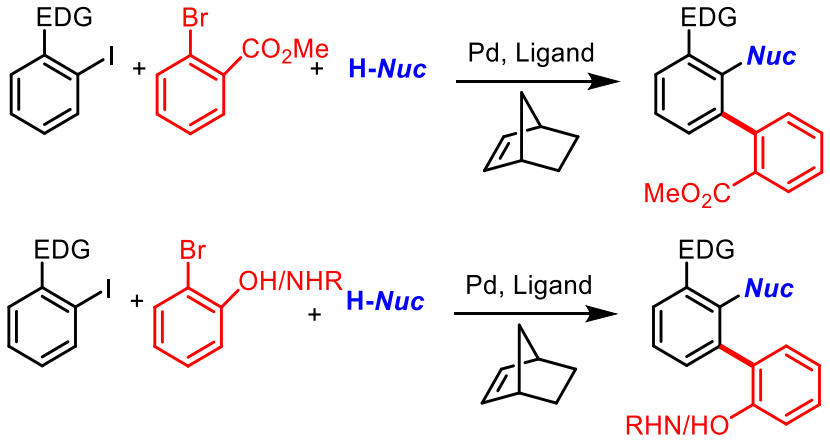
The major disadvantage of this complex catalysis system is the complex reaction, cause several selectivity issue and chemical compatibility issue. To further understand the key feature of Palladium/Norbornene Catalysis, we will next focus on the selectivity issues in the catalytic cycle. (Scheme 1.13) For redox-chemistry, there were two different oxidants: Aryl halides and external electrophile; and two different Pd(II) species need to be oxidized : Pd(0) and ANP intermediate. Aryl halide must oxidize the Pd(0) faster than external electrophile, external electrophile must oxidize the ANP to the Pd(IV) faster than the aryl halide. This is the most important rule for the success of the Pd/NBE cooperative catalysis. However, the oxidants can oxidize Pd(II) to Pd(IV) usually can also oxidize Pd(0) to Pd(II) very fast. This results in the very limited electrophile scope, so called **electrophile constraint**. Prior to our group's study, the electrophile scope was limited to the alkyl halide and electron-deficient aryl bromide.

On the other hand, to ensure rapid oxidation of Pd(0) to aryl-Pd(II) a strong aryl halide was required. Prior to our group's work, majority of Pd/NBE cooperative catalysis have to use aryl iodide as the aryl source. There is only one elegant work from Lautens and coworkers that

describing aryl triflate as the aryl source for the Pd/NBE cooperative catalysis. This is considered as the **aryl iodide constraint**.

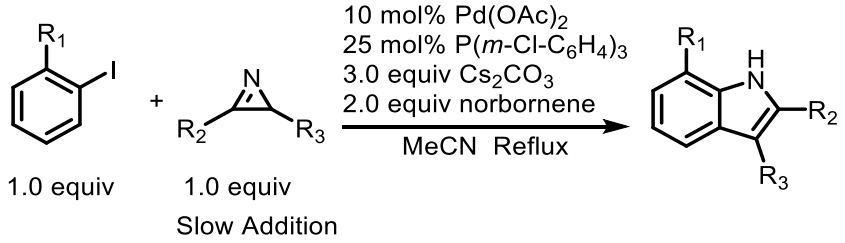
For non-redox-chemistry, there were two aryl-Pd(II) species, one is before ortho-activation **Ar-Pd-X**, another is after *ortho* C-H activation **Ar'-Pd-X**. In the ideal catalytic system, aryl-Pd(II) before the C-H activation should chemo-selectively react with norbornene to introduce *ortho* functional group. Aryl-Pd(II) after the C-H activation should only react with the nucleophile to regenerate the Pd(0) catalyst. In the reality, the nucleophile will not be introduced until the both *ortho* position was blocked. This was due to the face that β-carbon elimination was favored only with 2,6-disubstited arene. For catalysis, it means that aryl iodide has to have a *ortho* substitution, otherwise the C-H activation would happen twice. It was considered as the ortho constraint, which greatly limited the scope and application of Pd/NBE cooperative catalysis.

Scheme 1.14 *Ortho* arylation of aryl iodide using aryl bromide .



In 2004, Catellani and co-workers reported an elegant work demonstrated that *ortho* arylation of aryl iodide can be achieved using aryl bromide.[32] (Scheme 1.14) It is not surprising that aryl iodide react with Pd(0) faster than the aryl bromide. But really unique to observe that aryl bromide with ANP faster than the aryl iodide. The authors found that the key success reply on the aryl bromide's *ortho* substitution.[33-35] A weak coordinating group such as the ester or hydroxyl group could significantly improve the efficiency and selectivity for the aryl-aryl coupling reaction. It is proposed that weak coordinating group have a much better binding affinity with a Palladium intermediate (ANP) than simple Pd(0). The coordination lower activation energy for the aryl bromide to oxidize the ANP to the Pd(IV). It gave us some inspiration for developing other external electrophiles to selectively oxidize the ANP to the palladium(IV) intermediate.

Scheme 1.15 Indole synthesis of aryl iodide using 2H-Azirines using Pd/NBE cooperative catalysis.



In 2010, Lautens and coworker reported using 2H-Azirines as the alkylating reagents to form C-C bond at the *ortho* position of aryl iodide and C-N reductive elimination at the *ipso* carbon.[36] (Scheme 1.15) The imine product could quickly isomerize to indole product. The authors proposed the strain ring could directly oxidize the ANP intermediate to Pd(IV), then followed by the selective C-C bond reductive elimination. This prove strained ring could work a proper external electrophile for Pd/NBE cooperative catalysis.

1.4 Conclusion

The directing group strategy is still the most selective strategy for the C-H functionalization. Among them, Palladium/Norbornene cooperative catalysis show lots of unique features. Since Inoue group's original discovery, Catellani and coworkers did systematic organometallic study and catalytic system study to prove the concept and mechanism of palladium/norbornene cooperative catalysis. Detailed organometallic study and correct mechanism proposal provide people enough mechanism insight for further development. Electrophile constraint, aryl iodide constraint, *ortho* constraint are three major limitations for the

Palladium/Norbornene cooperative catalysis. My PHD work focus on solving these three constraints. Preliminary success on electrophile constraint, aryl iodide constraint was achieved.

1.5 References

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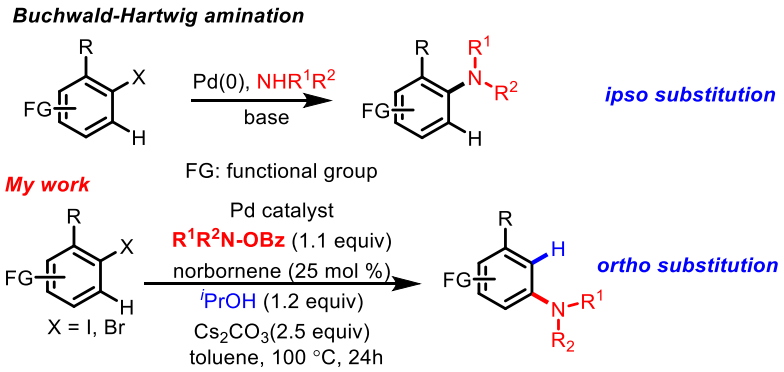
Chapter 2: Palladium and Norbornene Catalyzed *ortho*-Amination of Aryl Iodide

2.1 Introduction

Aromatic amines are widely found in agrochemical, materials pharmaceutical sciences,[1-2] arene amination holds a pivotal position in organic synthesis. Due to anilines' important applications, numerous arene amination approaches have been developed;[3-8] whereas the Buchwald–Hartwig amination[9-13] (a Pd-catalyzed direct substitution of aryl halides with amine groups) represents one of the most widely utilized methods to synthesize aromatic amines. Readily available aryl halides, broad functional group tolerance and controlled site-selectivity (comparing to the aryne-mediated amination[6]) make this transformation attractive to both industry and academic society. It is well known that Buchwald–Hartwig amination forms C–N bonds at the *ipso*-carbon of aryl halides,[14-15] thus the type of amine products is controlled by the position of the halide on the arene. Hence, highly regio-selective arene amination at different (other than *ipso*) positions of aryl halides would be significant and complementary to the Buchwald–Hartwig amination and nucleophilic aromatic substitution. Undoubtedly, direct amination of aryl C–H bonds would be an ideal alternative solution; however, control of the site-selectivity is non-trivial and largely relies on use of sterically/electronically biased substrates[16-20] or employing directing groups.[21-29]

Scheme 2.1. Amination with aryl halides.



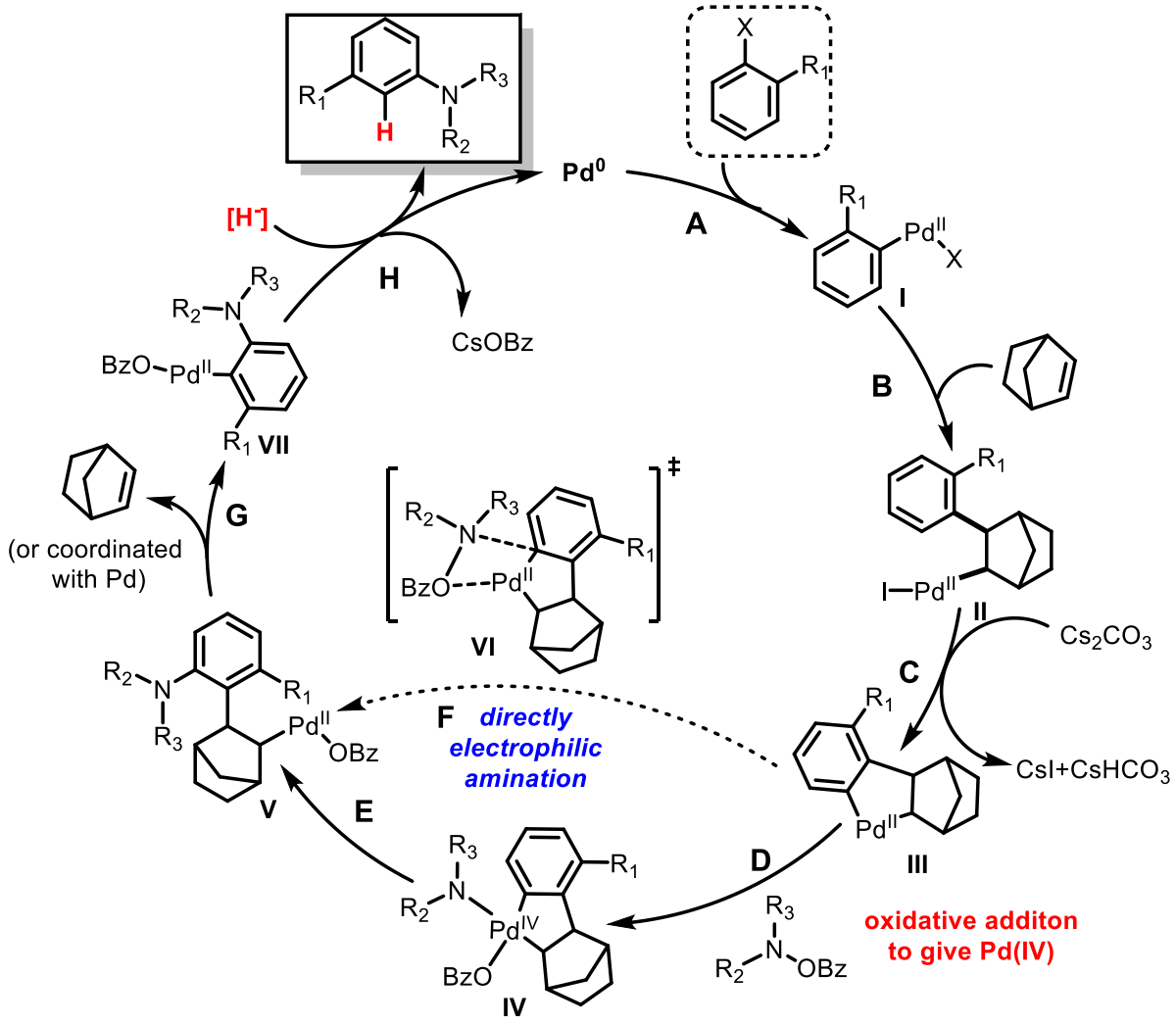
2.2 BACKGROUND

Catellani reaction[30-33] offers an unusual approach to activate the *ortho* C–H bonds of aryl iodides and to provide vicinal dual functionalizations at both the *ipso*- and *ortho*-positions.[34-44] A key for this transformation is capture of the aryl-Pd intermediate (**I**, Scheme 2.2) with NBE via a *syn* migratory insertion (step B) followed by an intramolecular palladation at the *ortho*-position (step C).[45-48] Seminal work by Catellani and Lautens show that a large different types of functional groups, including hydrogen atoms,[49-54] can be introduced at the *ipso*-carbon using different nucleophiles.[37-38,55-59] However, to our knowledge, functionalization at the *ortho*-position via this approach has only been restricted to carbon substituents (using alkyl or aryl halides) to date.[7,8]

Our proposed strategy for the *ortho*-amination, depicted in Scheme 2.2, is focused on developing a new *ortho* carbon nitrogen bond forming transformation. We proposed that if a electrophilic amination reagents can be employed through either a Pd(IV) intermediate (**IV**) or direct electrophilic substitution of the palladacycle (**III**),[60-66] C–N bond formation at the *ortho*-position would be achieved. In addition, if a proper reductant can be employed to quench the aryl-

Pd intermediate **VII** (after β-carbon elimination of NBE), the desired *ortho*-amination product would be afforded and the Pd(0) catalyst would be regenerated (step H). Nevertheless, two challenges must be met: 1) the oxidant not only needs to provide the amine group, but also has to be reactive enough to avoid the reductive elimination of palladacycle **III** to generate the undesired cyclobutane byproduct. However, it cannot be too strong to destroy the electron-rich norbornene or the Pd(0) catalyst. 2) a reductant needs to be orthogonal to the oxidant and capable of introducing a hydrogen at the *ipso*-position, but not too strong to reduce the aryl Pd **I** (direct arene reduction) or the alkyl Pd **II** intermediate (reductive Heck reaction).[67-69]

Scheme 2.2. Proposed reaction design

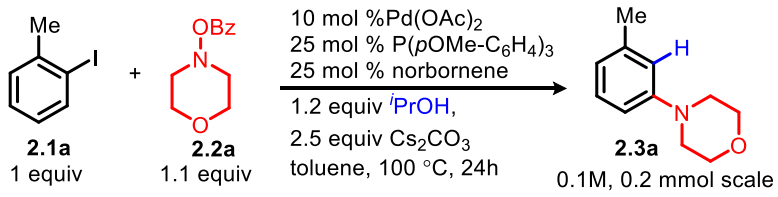


2.3 Reaction Development and Scope

2-iodotoluene (**1a**) was used as the model substrate, and a number of Pd pre-catalysts, ligands, oxidants, reductants, additives and solvents were extensively examined. Ultimately, *O*-benzoyloxyamine (**2**)[70-73] and *iso*-propanol[74] were found to be the optimal oxidant and reductant combination. For example, use of *N*-chloro-morpholine[75-78] gave a complex mixture of products; use of benzyl alcohol or ethyl formate gave significant over-reduction.[79] To our delight, when 10

mol % $Pd(OAc)_2$ with 25 mol % tris(4-methoxyphenyl)phosphine and 25 mol % NBE were employed as the catalysts, the *ortho*-C–H amination product was obtained in 89% yield in the presence of only 1.1 equiv of 4-(benzoyloxy)morpholine (**2a**), 1.2 equiv of *iso*-propanol and 2.5 equiv of cesium carbonate (Table 2.1, entry 1). It is worthy to note that previous Catellani reaction conditions often used stoichiometric to super-stoichiometric NBE,[7] while here only 25 mol % NBE is needed. In addition, the oxidant (*O*-benzoyloxyamine) and the reductant (*iso*-propanol) are well compatible, as no large excess of either reagent or slow addition is required for this transformation.

Table 2.1 Control experiments for the Pd- and NBE-catalyzed *ortho*-amination



2.1a 1 equiv + **2.2a** 1.1 equiv → **2.3a** 0.1M, 0.2 mmol scale

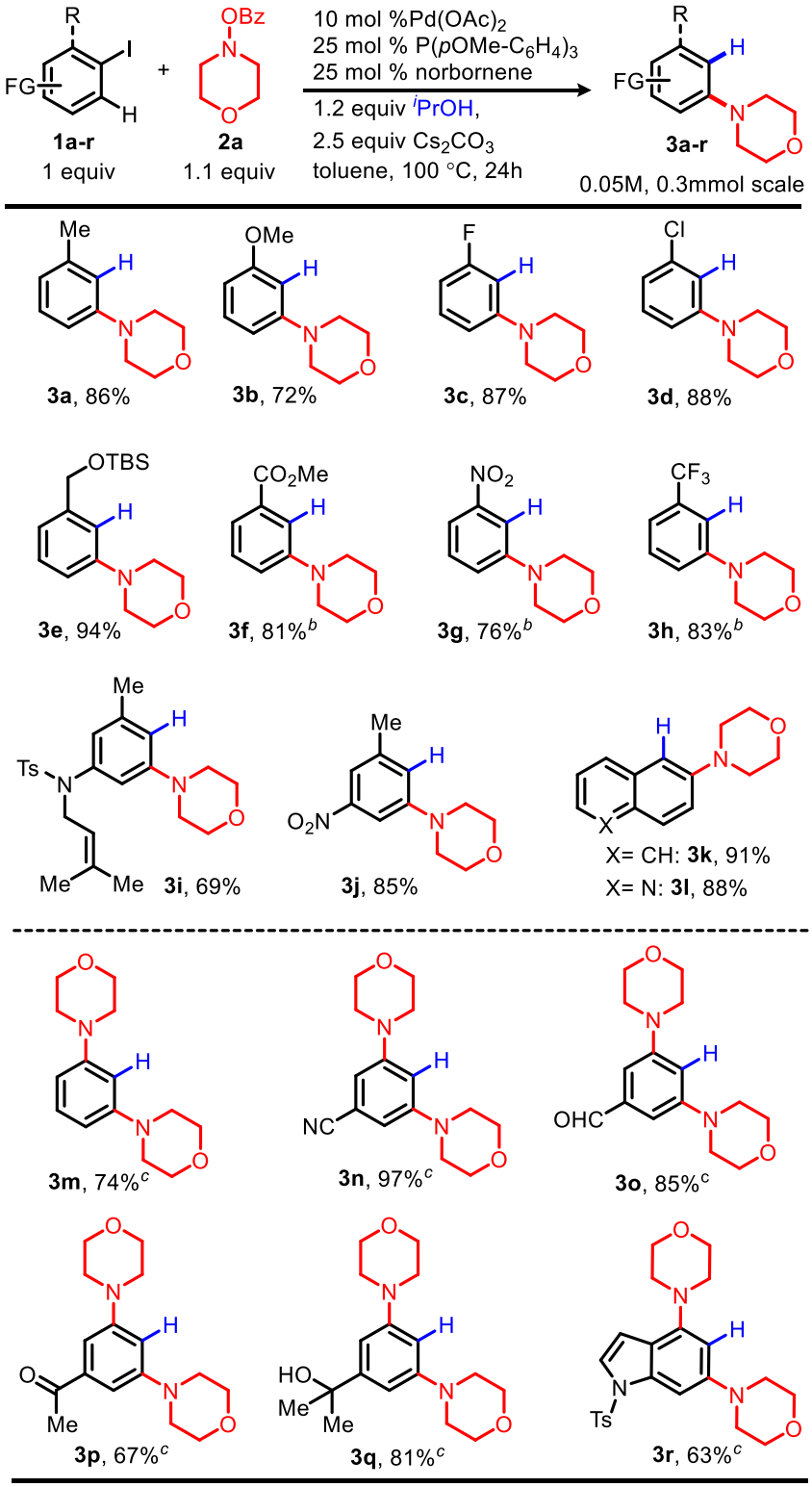
entry	change from standard conditions	yield[a]
1	None	89%
2	No $Pd(OAc)_2$	0%
3	No $P(p\text{OMe-}C_6H_4)_3$	0%
4	No norbornene	0%
5	No *i*PrOH	29%
6	No Cs_2CO_3	0%
7	$Pd_2(dba)_3$ instead of $Pd(OAc)_2$	65%
8	PPh_3 instead of $P(p\text{OMe-}C_6H_4)_3$	85%(81%)
9	$P(2\text{-furyl})_3$ instead of $P(p\text{OMe-}C_6H_4)_3$	60%
10	dppb instead of $P(p\text{OMe-}C_6H_4)_3$	75%
11	BINAP instead of $P(p\text{OMe-}C_6H_4)_3$	67%
12	K_2CO_3 instead of Cs_2CO_3	23%
13	Norborndiene instead of norbornene	23%
14	1,4-Dioxane instead of toluene	86%
15	DMF instead of Toluene	43%
16	***0.05M*** instead of 0.1M	***91%(86%)***
17	5 mol % $Pd(OAc)_2$ and 12 mol % $P(p\text{OMe-}C_6H_4)_3$	80%

[a] Determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard; values in the parentheses are isolated yields.

A series of control experiments were subsequently conducted to understand the role of each reactant (Table 2.1). In the absence of either Pd precatalyst, phosphine ligand, NBE or the base, no desired product was observed (entries 2-4 and 6). Interestingly, without *iso*-propanol the desired amination product was still obtained in 29% yield (entry 5).[80] Using of a Pd(0) precatalyst instead of $Pd(OAc)_2$ resulted in a lower yield (entry 7). Having examined a number of mono- and bidentate phosphine ligands (entries 8-11), tris(4-methoxyphenyl)phosphine was found most efficient. Weaker bases such as potassium carbonate dramatically decreased the yield (entry 12). Use of

norbornadiene (NBD) instead of NBE still gave the desired product, albeit in 23% yield (entry 13). Increasing the polarity of solvents from toluene to 1,4-dioxane to DMF led to decreased yields (entries 14 and 15), likely due to more polar solvents enhancing the background reactions between the base and the *O*-benzoyloxyamine.[81-82] Finally, when the reaction was diluted from 0.1 M to 0.05 M, a slightly higher yield (91%) was observed (entry16). Decrease the catalyst loading to 5% resulted in acceptable lower yield (entry17).

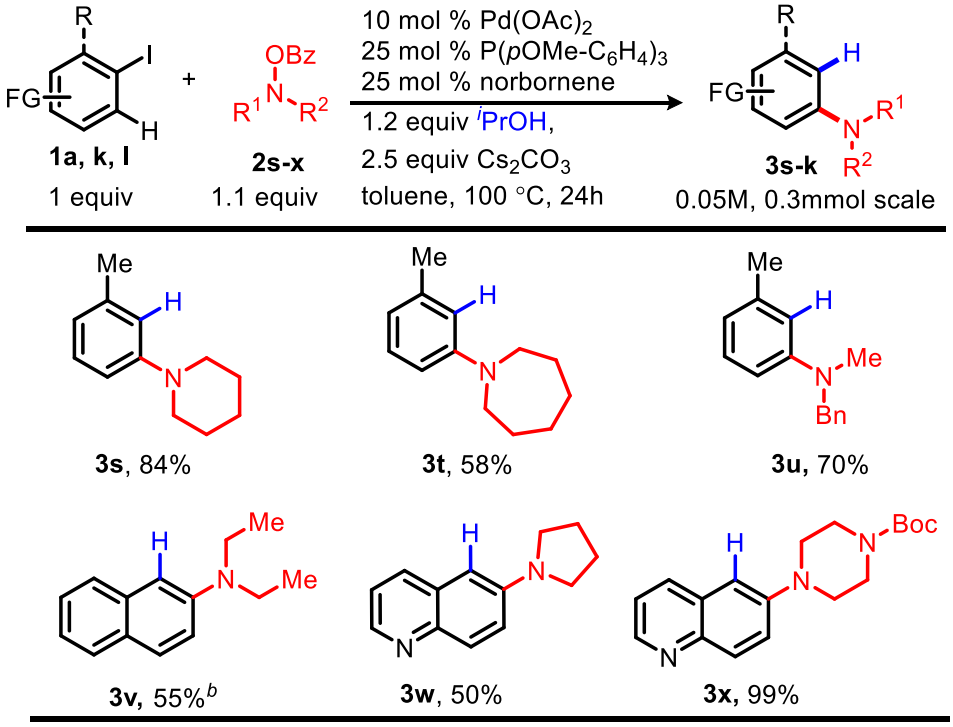
Table 2.2 Substrate scope with different aryl iodides[a]



[a]All yields are isolated yields. [b]25 mol % tri(2-furyl)phosphine and 2.0 equiv **2a** and 3.0 equiv Cs_2CO_3 were used. [c]50 mol % norbornene and 2.5 equiv **2a** and 4.0 equiv Cs_2CO_3 were used.

The substrates scope is illustrated in the Table 2.2. First, we examined different substitution at the *ortho*-position of the aryl halides using 4-(benzoyloxy)morpholine **2a** as the amine partner. Substrates containing both electron-donating and withdrawing groups worked well providing *meta-substituted aromatic amines* in good to excellent yields. When electron-deficient arenes were used, the more electron-poor tri(2-furyl)phosphine was found to be a better ligand to prevent homo-dimerization of the arene.[38,49,53,83] One important feature of this method is that a number of functional groups, including methoxy ethers, fluorides, chlorides, TBS protected benzyl alcohols, methyl esters, sulfonamides, nitro and trifluoromethyl groups are all compatible. Amination of the *ortho*, *para*-disubstituted aryl iodides also proceeded smoothly affording 1,3,5-trisubstituted arenes (**3i**, **3j**). Note that electron-rich trisubstituted olefins, which are generally sensitive to oxidants, were tolerated under the reaction conditions (**3i**). Moreover, high yields were obtained with naphthalene- and quinoline-derived substrates (**3k** and **3l**). Next, aryl iodides without an *ortho*-substituent were tested. Although selectively forming the mono-aminated products is difficult,[84] the 1,3-di-aminated arenes can be obtained in good to excellent yields. It is encouraging to note that sensitive functional groups, such as nitriles, aldehydes, methyl ketones, free tertiary alcohols and protected indoles, are all compatible.

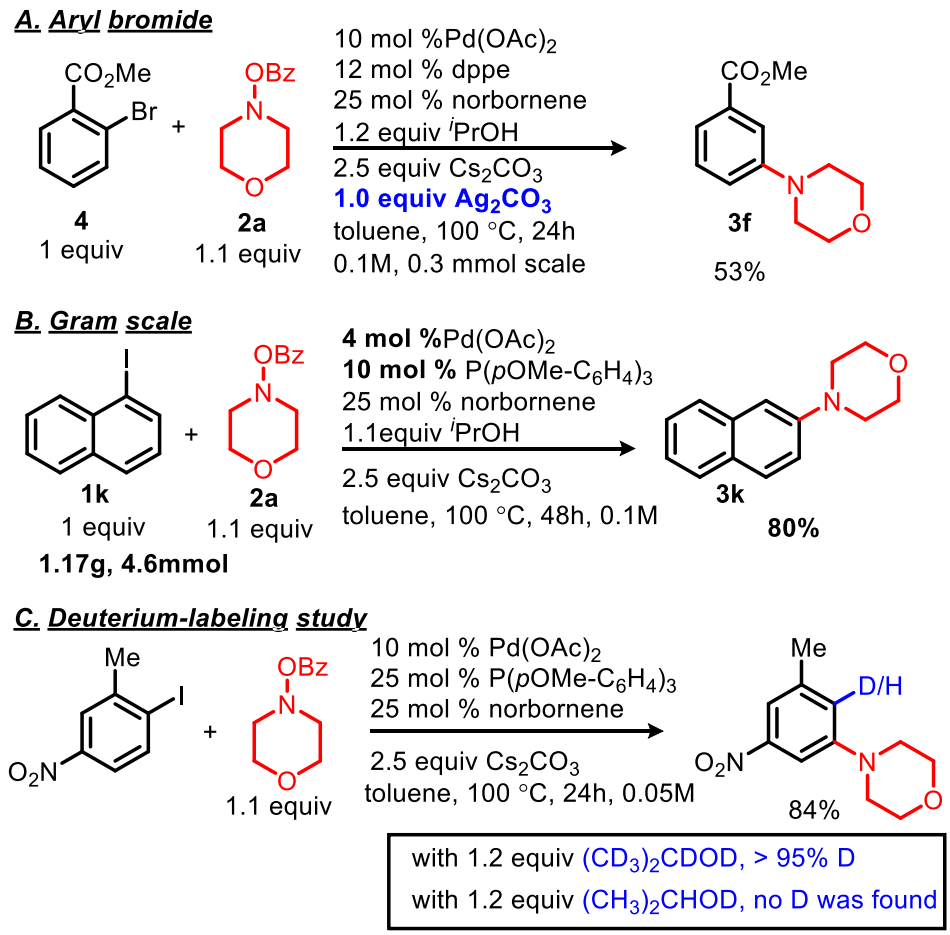
Table 2.3 Substrate scope with different amines[a]



[a]All yields are isolated yields. [b]2.0 equiv BzO-NEt_2 and 4.0 equiv Cs_2CO_3 was used.

The scope of the amine coupling partner was investigated next (Table 2.3). Piperidine, azepane, diethylamine, pyrrolidine and Boc-protected piperazine all provided the desired amination products in moderate to excellent yields. Primary amine derivatives (*e.g.* ^{n}BuNHOBz) do not couple under these conditions; however, the benzyl-protected *O*-benzoyloxyamines reacted uneventfully (**3u**), which may serve as an alternative way to access the secondary aryl amine products.[85-86]

Scheme 2.3 Aryl bromide and brief mechanism study



Comparing to aryl iodides, aryl bromides are known to the more challenging substrates for Catellani reaction because they are weaker oxidants and often less competitive towards Pd(0) oxidative addition than other oxidants.[38-39] Our preliminary study shows that, simply by adding a silver salt (Ag_2CO_3) and using dppe as the ligand, aryl bromide **4** can be coupled and provided the desired *ortho*-amination product (Scheme 2.3 A). In addition, this method is also readily scalable, and when operated on a gram scale, the Pd loading can be lowered to 4 mol % (Scheme 2.3 B). Furthermore, to gain mechanistic insights of this reaction, a deuterium-labeling study was performed (Scheme 2.3 C). When d_8-isopropanol was used as the reductant, more than 95%

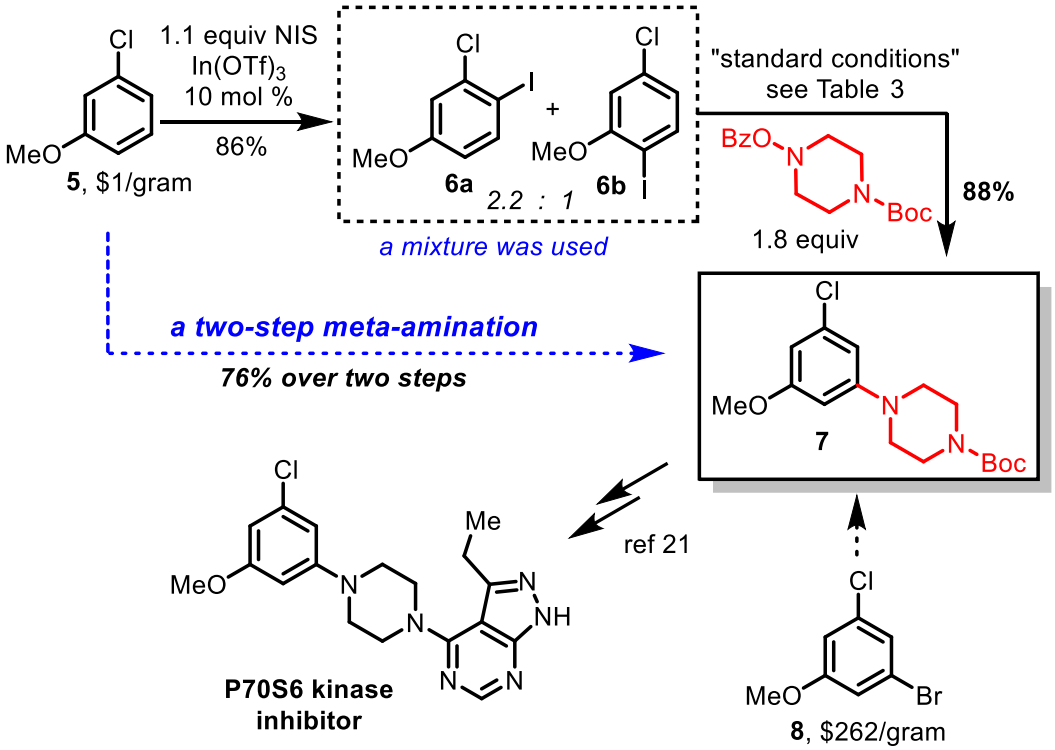
deuterium was incorporated at the *ipso*-position. In contrast, when d_1-$(CH_3)_2CHOD$ was employed, no deuterium incorporation was observed (confirmed by both HRMS and ^1H NMR). This study supports our proposed hydride-transfer mechanism (step H, Scheme 2.2) instead of a proton-transfer mechanism.

Finally, we demonstrated the usage of this methodology in preparing a key aryl amine intermediate (**7**) used in a synthesis of a P70S6 kinase inhibitor (Scheme 2.4).[87] Our strategy employed inexpensive 3-chloroanisole (**5**) ($1.0/gram) as the starting material. Iodination gave an inseparable mixture of regioisomers (**6a**/**6b**);[88] nevertheless, this mixture can be directly subjected to the *ortho*-amination reaction offering a *single regioisomer* of amine **7** in 88% yield. It is worthy to note that this approach provided a unique *net meta-amination of arenes* (from **5**). In contrast, the corresponding 3-chloro-5-bromoanisole (**8**), a potential precursor for the direct amination, costs $262/gram due to the difficulty for its preparation.[89] Therefore, this Pd and NBE co-catalyzed *ortho*-amination reaction is synthetically useful and complementary to the existing amination methods.

Table 2.4 listed selective failed examples for ortho amination of aryl iodides. 2-iodoaniline derivatives gave the indoline product in the presence of norbornene. When the ortho position have electrophilic functional groups such as ketone or cyano group, no desired product was observed. Heterocycle substrates such as 4-iodoindole, 2-iodothiophene, a complex mixture was observed. This reaction is quite sensitive to the steric effect of the meta position of the aryl iodide. Simply replays the hydrogen atoms with the fluoride, the desired reaction pathway was dramatically shut down. For some di-iodide case, norbornene attached product was observed as the byproduct. For the electrophilic amination reagent part, the primary amine directives are not tolerated, may due to the high acidity of the proton. The O-benzoylhydroxylamine part proved to be very sensitive for the steric effect. The ortho position for the N atom must be two methylene, more steric bulky

substrates all didn't work under the optimized condition, no desired product was observed. More powerful catalyst overcome these limitation need to be developed.

Scheme 2.4. Synthetic application

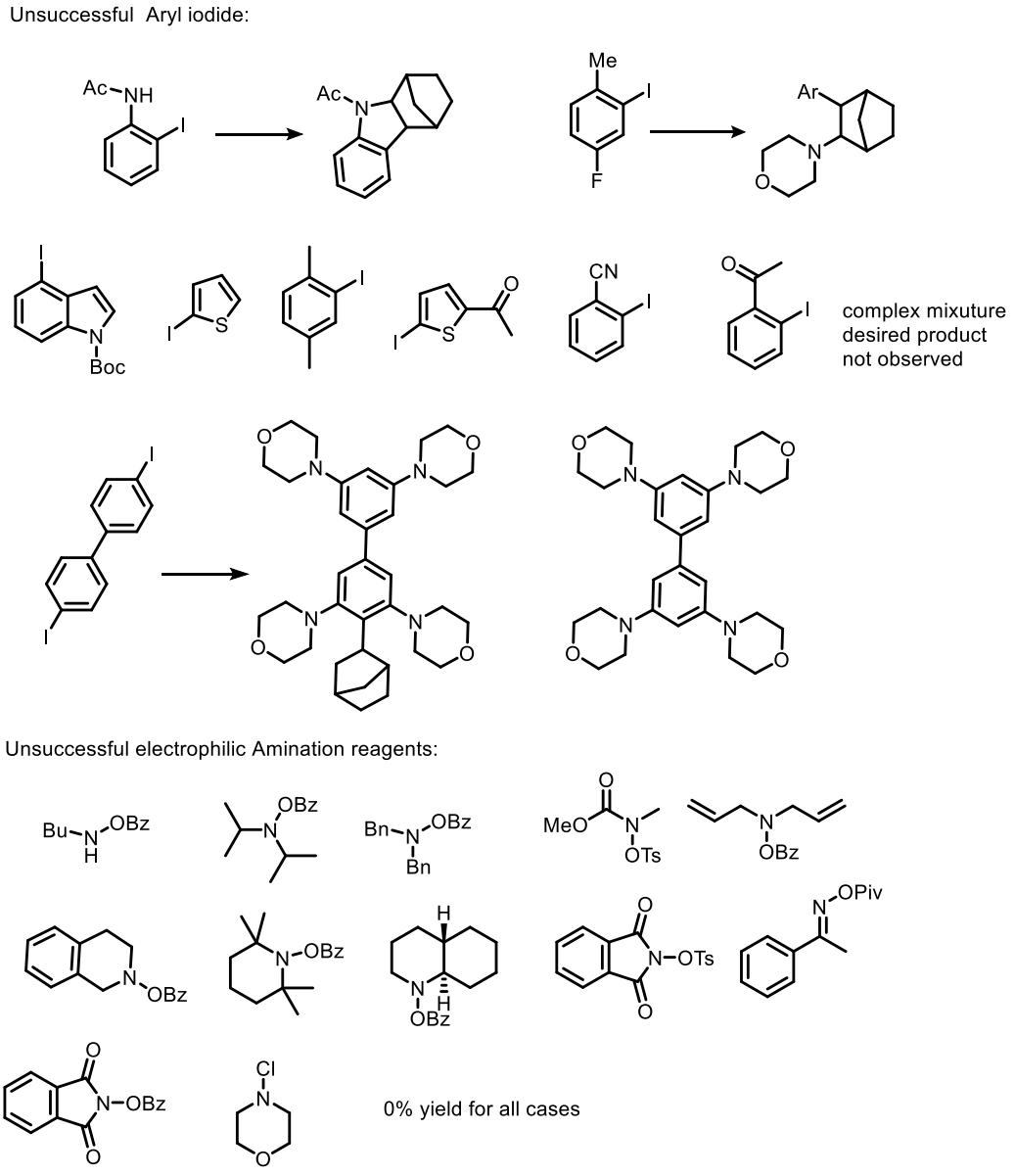


2.4 Conclusion

In summary, we have developed a novel arene-amination strategy with aryl halides using Pd and NBE as the co-catalysts. Comparing to the Buchwald–Hartwig reaction, this approach provides arene amination at the *ortho*-position instead of *ipso* with 100% regioselectivity. In addition, this method represents the first example of forming C–N bonds at the *ortho*-carbon via palladium/nobornene cooperative catalysis, which should provide broad implications for

developing various other dual functionalizations of arenes that involve different *ipso* functionalization with *ortho*-C–N bond formation at the *ortho* position. Furthermore, this method is scalable and chemo-selective with excellent functional group tolerance.

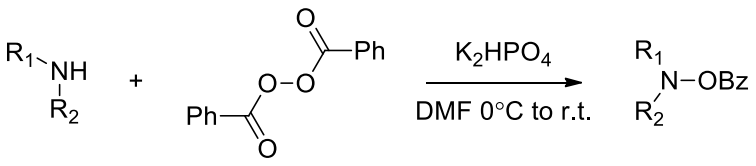
Table 2.4 Representative failed examples for *ortho*-amination reaction.



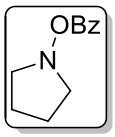
2.5 EXPERIMENTAL RESULTS

2.5.1 Experimental Procedure and Characterization Data

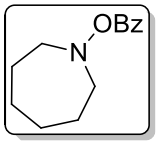
Scheme 2.5 General preparation of O-Benzoyl Hydroxylamines



O-benzoyl hydroxylamines was synthesized using a modified procedure[90]: To a 50 mL flask equipped with stir bar and a rubber septum was charged with benzoyl peroxide (3.46 g, 70% purity 10 mmol, 1 equiv), dipotassium hydrogen phosphate (3.50 g, 20 mmol, 2 equiv), and *N*,*N*-dimethylformamide (25 mL). A solution of pyrrolidine (1.1 g, 1.5 mmol, 1.5 equiv) was added dropwise at zero degree. Upon completion, the reaction was further stirred at room temperature overnight. After monitored by TLC to see the full conversion of benzoyl peroxide, water (100 mL) was added, and the products were extracted with ether (4 × 30 mL). The combined organic extract was washed with brine (60 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate=10:1) to give 1.021 g of *O*-benzoyl hydroxylamine as a white solid in 54% yield. The corresponding *O*-Benzoyl hydroxylamines of morpholine,[90] *N*-methylbenzyl amine,[91] diethylamine,[90] piperidine[90] and tert-butyl piperazine-1- carboxylate[64] were all literature known compound.

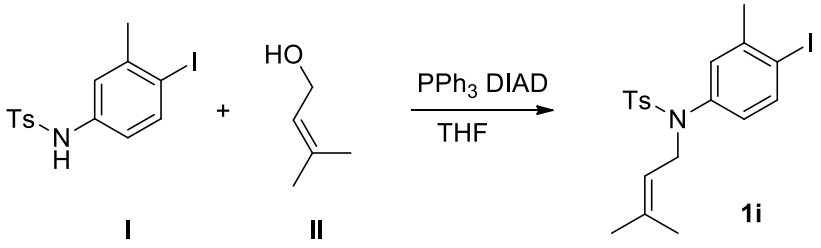


A white solid, (1.021 g, 54% yield) mp=35℃, Rf=0.24 (hexane/ethyl acetate=5:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 − 7.88 (m, 2H), 7.51 (dd, *J* = 6.9, 1.1 Hz, 1H), 7.43−7.34 (m, 2H), 3.37−3.19 (m, 4H), 1.93 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) 165.03, 132.80, 129.36, 129.21, 128.22, 57.60, 22.06. IR (KBr): *v* 2993, 2977, 2875, 1717, 1598, 1451, 1258, 1071, 1021, 717 cm^{-1}. HRMS (ESI): Calcd for $C_{11}H_{13}NO_2Na$ ($M+Na^+$):214.0838*;* found: 214.0842.



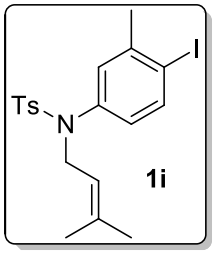
A white solid mp=45-48℃ (1.62 g, 74% yield) Rf=0.48 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 –7.91 (m, 2H), 7.56 – 7.47 (m, 1H), 7.44 – 7.35 (m, 2H), 3.29 (dd, J = 10.6, 5.1 Hz, 4H), 1.78 (d, J = 4.2 Hz, 4H), 1.70 – 1.57 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.61, 132.72, 129.54, 129.19, 128.19, 59.35, 26.24, 23.97. IR (KBr): *v* 2931, 2856, 1737, 1450, 1249, 1086, 1065, 1023, 708 cm^{-1}; HRMS (ESI): Calcd for $C_{13}H_{17}NO_2Na$ ($M+Na^+$):242.1151*;* found: 242.1158.

Scheme 2.6 Preparation of aryl-iodide substrates **1i**:



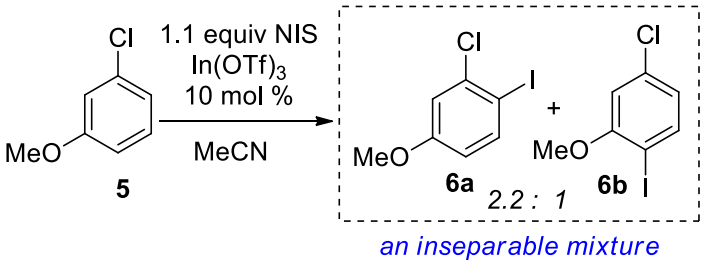
To a 50 mL flask equipped with stir bar and a rubber septum was charged with compound **I**[92] (500 mg, 1.3 mmol, 1 equiv), commercial available compound **II** (224 mg, 2.6 mmol, 2 equiv),

triphenylphospine (409 mg, 1.56 mmol, 1.2 equiv) and THF (20 ml). The pure diisopropyl azodicarboxylate (289 mg, 1.43 mol, 1.1 equiv) was added dropwise at zero degree. When the addition is finished, the solution was warmed to room temperature and stirred overnight. After monitored by TLC till the full conversion, the solution was concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 50:1 to 30:1) to give the **1i** as a pale yellow solid (560 mg) in 89% yield.

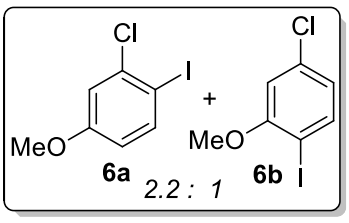


A pale yellow solid mp=80-82℃ Rf=0.44 (hexane/ethyl acetate=10:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 6.98 (d, J = 2.4 Hz, 1H), 6.45 (dd, J = 8.4, 2.3 Hz, 1H), 5.02 (td, J = 6.9, 1.1 Hz, 1H), 4.07 (d, J = 6.9 Hz, 2H), 2.41 (s, 3H), 2.35 (s, 3H), 1.57 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.40, 142.10, 139.59, 138.97, 137.14, 135.37, 130.46, 129.38, 127.68, 126.89, 118.47, 99.91, 48.36, 28.06, 25.64, 21.55, 17.83; IR (KBr): *v* 2973, 2918, 2359, 1597, 1470, 1348, 1163, 1091, 1016, 813 cm^{-1}; HRMS (ESI): Calcd for C19H22INO2SNa ($M+Na^{+}$):478.0308*;* found: 478.0304.

Scheme 2.7 Preparation of aryl-iodide substrates **6a/6b**:



The same reaction conditions as the literature reported were employed for the synthesis of **6a/6b** from the exactly same substrate.[88] A mixture of 3-chloroanisole (730 mg, 5.14 mmol), NIS (1.26 g, 5.6 mmol) and $In(OTf)_3$ (330 mg, 0.58 mmol) in CH_3CN (15 mL) was stirred in a sealed 20 ml vial at 35℃ in the dark (wrapped in foil) for 20 h. The reaction progress was monitored by GC. After completion of the reaction, the mixture was diluted with water (40 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic solutions were washed with saturated sodium thiosulfate solution and brine. The organic layer was dried over magnesium sulfate and concentrated under vacuum. The residue was purified carefully by flash chromatography on silica gel (100% hexane) to give an inseparable mixture of **6a** and **6b** (1.18 g, 4.4 mmol) in 86% yield as a colorless oil. The mixture sometimes still contains a di-iodination product, bubble to bubble distillation can easily remove the impurity. (Distillation conditions: 0.25 Torr, 110℃ by oil bath).



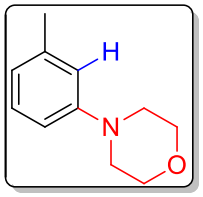
Aryl iodide **6a** and **6b** are both known compounds.[88] For **6a**: ^{1}H NMR (400 MHz, CDCl3) δ 7.68

(d, J = 8.8 Hz, 1H), 7.02 (d, J = 2.9 Hz, 1H), 6.56 (dd, J = 8.8, 2.9 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz,$CDCl_3$) δ 160.4, 140.1, 138.9, 115.1, 111.6, 86.4, 55.6; Data for **6b**: ^{1}H NMR (400 MHz, CDCl3) δ 7.66 (d, J = 8.3 Hz, 1H), 6.80 (d, J = 2.2 Hz, 1H), 6.73 (dd, J = 8.3, 2.2 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz,$CDCl_3$) δ 158.7, 139.8, 135.2, 122.5, 114.8, 83.2, 56.5.

General procedure of Palladium and Nobornene catalyzed C-N bond formation reaction：

An oven-dried 8 mL (one dram) vial was charged with aryl iodide (1.0 equiv), *O*-Benzoyl hydroxylamines (1.1 equiv), Cs_2CO_3 (2.5 equiv), isopropanol (1.2 equiv), norbornene (0.25 equiv), $Pd(OAc)_2$ (0.10 equiv) and tris(4-methoxyphenyl)phosphine (0.25 equiv), which was sealed outside and transferred in a nitrogen-filled glovebox. Toluene was added into the vial, and the vial was then sealed with PTFE lined cap in the glovebox. The resulting mixture was stirred at RT for 10 minutes until the $Pd(OAc)_2$ was fully dissolved (the solution took on a light yellow color). The vial was subsequently transferred out of glovebox and stirred on a pie-block preheated to 100℃ for 24 hours. After completion of the reaction, the mixture was filtered through a thin pad of celite. The filter cake was washed with diethyl ether or ethyl acetate, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography on silica gel to yield the desired product.

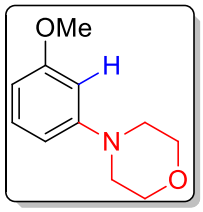
An oven-dried 8 mL (one dram) vial was charged with aryl iodide 2-iodotoluene (66.4 mg, 0.3 mmol 1.0 equiv), *O*-Benzoyl hydroxylamines **2a** (68.4 mg, 0.33 mmol, 1.1 equiv), Cs_2CO_3 (245 mg, 0.75 mmol, 2.5 equiv), isopropanol (21.4 mg, 0.36 mmol, 1.2 equiv), norbornene (7.0 mg, 0.075 mmol, 0.25 equiv), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 equiv) and tris(4-methoxyphenyl)phosphine (26.4 mg, 0.075 mmol, 0.25 equiv), which was sealed outside and transferred in a nitrogen-filled glovebox. Toluene (6 ml) was added into the vial, then the vial was sealed with PTFE lined cap in the glovebox again and stirred at RT for 10 minutes until the $Pd(OAc)_2$ was fully dissolved (the solution takes on a light yellow color). The vial was subsequently transferred out of glovebox and stirred on a pie-block preheated to 100℃ for 24 hours. The mixture was then filtered through a thin pad of celite. The filter cake was washed with diethyl ether, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography (from hexane:dichloromethane = 2:1 to hexane : ethyl acetate = 25 : 1) on silica gel to give the desired product **3a** 46. 3mg (86% yield) as a colorless oil.



CAS: 7025-91-4

***3a*:** a colorless oil. Rf=0.52 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, J = 7.6 Hz, 1H), 6.80 – 6.71 (m, 3H), 3.91 – 3.85 (m, 4H), 3.21 – 3.12 (m, 4H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.23, 138.78, 128.94, 120.90, 116.47, 112.79, 66.87, 49.39, 21.71. Both the proton and carbon NMR match the literature reported data.[93]

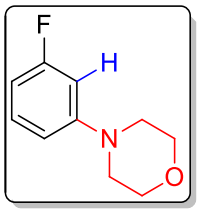
Following the general procedure, 2-iodo-anisole (68.2 mg, 0.3 mmol, 1.0 eq) was used. Flash column chromatography (from hexane:ethyl acetate = 10:1 to hexane : ethyl acetate = 5 : 1) on silica gel to give the desired product **3b** 40.5 mg (72% yield) as a pale yellow oil.



CAS:32040-09-8

3b： a pale yellow oil. Rf=0.24 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-.7.15 (m, 1H), 6.55 – 6.49 (m, 1H), 6.47 – 6.40 (m, 2H), 3.86 – 3.81 (m, 4H), 3.78 (s, 3H), 3.17 – 3.10 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.56, 152.63, 129.81, 108.42, 104.67, 102.17, 66.83, 55.14, 49.24. Both the proton and carbon NMR match the literature reported data.[94]

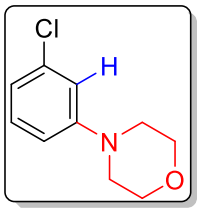
Following the general procedure, 2-fluoro-iodobenzene (66.2 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography ((from hexane : dichloromethane = 2 : 1 to hexane : ethyl acetate = 10 : 1) on silica gel to give the desired product **3c** 46.9 mg (87% yield) as a colorless oil



3c： a colorless oil. Rf=0.47 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, J = 15.1, 8.1 Hz, 1H), 6.69 – 6.64 (m, 1H), 6.61 – 6.52 (m, 2H), 3.88 – 3.83 (m, 4H), 3.18 – 3.13 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.83 (d, J = 243.4 Hz), 152.89 (d, J = 9.5 Hz), 130.17

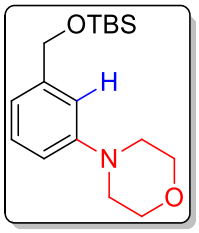
(d, J = 9.9 Hz), 110.79 (d, J = 2.4 Hz), 106.26 (d, J = 21.2 Hz), 102.42 (d, J=25.1 Hz), 66.69, 48.82. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.18 (dt, J = 12.2, 7.7 Hz). Both the proton and carbon NMR match the literature reported data.[95]

Following the general procedure, 2-chloro-iodobenzene (69.0 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography ((from hexane : dichloromethane = 2 : 1 to hexane : ethyl acetate = 10 : 1) on silica gel to give the desired product **3d** 50.2 mg (88% yield) as a colorless oil.



***3d*:** a colorless oil. Rf=0.46 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, J = 8.1 Hz, 1H), 6.87 (t, J = 2.2 Hz, 1H), 6.84 (ddd, J = 7.8, 1.9, 0.8 Hz, 1H), 6.77 (ddd, J = 8.4, 2.4, 0.7 Hz, 1H), 3.87 – 3.82 (m, 4H), 3.17 – 3.13 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.27, 134.96, 130.03, 119.61, 115.42, 113.52, 66.67, 48.79. Both the proton and carbon NMR match the literature reported data.[65]

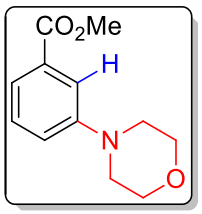
Following the general procedure, aryl iodide **1e** (104.0 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane : ethyl acetate = 50 : 1 to hexane : ethyl acetate = 25 : 1) on silica gel to give the desired product **3e** 86.5 mg (94% yield) as a colorless oil.



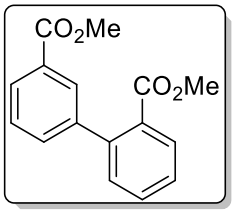
3e: a colorless oil. Rf=0.43 (hexane/ethyl acetate=10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 1H), 6.94 (s, 1H), 6.87 – 6.78 (m, 2H), 4.73 (s, 2H), 3.91–3.85 (m, 4H), 3.21 – 3.12 (m, 4H), 0.96 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.26, 142.46, 128.93, 117.72, 114.30, 113.23, 66.90, 65.02, 49.39, 25.93, 18.39, -5.25; IR (KBr): *v* 2955, 2928, 2855, 1604, 1448, 1243, 1123, 1080, 960, 838 cm^{-1}. HRMS (ESI): Calcd for $C_{17}H_{30}NO_2Si$ ($M+H^+$):308.2040*;* found: 308.2045.

An oven-dried 8 mL vial was charged with aryl iodide **1f** (78.5 mg, 0.3 mmol 1.0 equiv), *O*-Benzoyl hydroxylamines **2a** (127.2 mg, 0.61 mmol, 2.0 equiv), Cs_2CO_3 (308 mg, 0.92 mmol, 3.0 equiv), isopropanol (21.5 mg, 0.36 mmol, 1.2 equiv), norbornene (7.0 mg, 0.075 mmol, 0.25 equiv), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 equiv) and tris(2-furyl)phosphine (17.4 mg, 0.075 mmol, 0.25 equiv), which was sealed outside and transferred in a nitrogen-filled glovebox. Toluene (6 ml) was added into the vial. The vial was sealed with PTFE lined cap in the glovebox and stirred at RT for 10 minutes until the $Pd(OAc)_2$ was fully dissolved. After that the vial was transferred out of glovebox and stirred on a pie-block preheated to 100℃ for 24 hours. The mixture was then filtered through a thin pad of celite. The filter cake was washed with diethyl ether, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography (from hexane : ethyl acetate = 15 : 1 to hexane : ethyl acetate = 6 : 1) on silica gel to give the homo-

coupling product **3f'** 6.7 mg (17% yield) and the desired product **4f** 53.4 mg (81% yield) as a colorless oil.



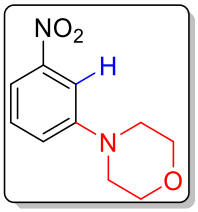
***3f*:** a colorless oil. Rf=0.20 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 2.5, 1.5 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.08 (ddd, J = 8.3, 2.6, 0.8 Hz, 1H), 3.89 (s, 3H), 3.87 – 3.83 (m, 4H), 3.22 – 3.16 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.22, 151.14, 130.90, 129.07, 120.88, 119.91, 116.25, 66.70, 52.04, 49.00. Both the proton and carbon NMR match the literature reported data.[96]



3f': a colorless oil. Rf=0.72 (hexane/ethyl acetate=5:1) ^{1}H NMR (400 MHz, CDCl3) δ 8.06 – 8.02 (m, 1H), 8.01 (td, J = 1.7, 0.8 Hz, 1H), 7.89 (ddd, J = 7.7, 1.4, 0.4 Hz, 1H), 7.56 (td, J = 7.6, 1.5 Hz, 1H), 7.52 – 7.42 (m, 3H), 7.37 (ddd, J = 7.6, 1.3, 0.5 Hz, 1H), 3.92 (s, 3H), 3.64 (s, 3H); The proton NMR match the literature reported data.[53]

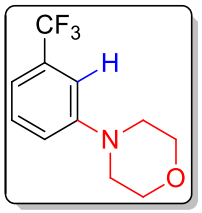
Using the similar conditions as **3f**, 1-iodo-2-nitrobenzene (76.4 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane : ethyl acetate = 8 : 1 to hexane : ethyl acetate = 5 :

1) on silica gel to give the desired product **3g** 48.3 mg (76% yield) as a yellow solid.



3g: a yellow solid. Rf=0.18 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 2H), 7.38 (t, J = 8.2 Hz, 1H), 7.17 (ddd, J = 8.3, 2.5, 0.7 Hz, 1H), 3.90 – 3.85 (m, 4H), 3.27 – 3.21 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.76, 149.18, 129.70, 120.77, 114.03, 109.33, 66.49, 48.41. Both the proton and carbon NMR match the literature reported data.[97]

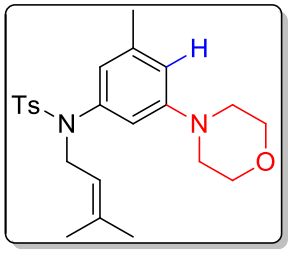
Using the similar conditions as **3f**, 1-iodo-2-(trifluoromethyl)benzene (80.3 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (hexane : ethyl acetate = 5 : 1) on silica gel to give the desired product **3h** 56.8 mg (83% yield) as a colorless oil.



3h: a colorless oil. Rf=0.39 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (td, J = 8.3, 0.7 Hz, 1H), 7.14 – 7.08 (m, 2H), 7.06 (dd, J = 8.3, 2.3 Hz, 1H), 3.92 – 3.82 (m, 4H), 3.24 – 3.15 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.35 (s), 131.44 (q, J = 31.7 Hz), 129.57 (s), 124.25 (q, J = 272.4 Hz), 118.39 (d, J = 1.2 Hz), 116.16 (q, J = 3.9 Hz), 111.80 (q, J = 4.0 Hz), 66.67, 48.78 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.76 (s). Both the proton and carbon NMR

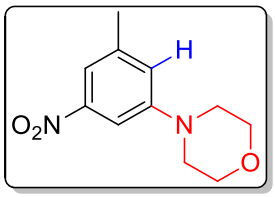
match the literature reported data.[98]

Following the general procedure, aryl iodide **1i** (135.2 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane : ethyl acetate = 10 : 1 to hexane : ethyl acetate = 5 : 1) on silica gel to give the desired product **3i** 84.4 mg (69% yield) as a yellow oil.



3i: a yellow oil. Rf=0.17 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 6.61 (s, 1H), 6.37 (t, J = 1.8 Hz, 1H), 6.32 (s, 1H), 5.12 – 5.07 (m, 1H), 4.09 (d, J = 6.9 Hz, 2H), 3.84 – 3.75 (m, 4H), 3.06 – 2.99 (m, 4H), 2.41 (s, 3H), 2.21 (s, 3H), 1.59 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.32, 143.01, 140.10, 138.90, 136.36, 135.90, 129.11, 127.74, 120.62, 118.98, 115.68, 113.73, 66.70, 49.11, 48.67, 25.59, 21.59, 21.44, 17.76; IR (KBr): *v* 2963, 2918, 2854, 1599, 1450, 1345, 1254, 1162, 1122, 1092 cm^{-1}. HRMS (ESI): Calcd for $C_{23}H_{31}N_2O_3S$ $(M+H^+)$:415.2050*;* found: 415.2060.

Following the general procedure, aryl iodide **1j** (78.1 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane : ethyl acetate = 10 : 1 to hexane : ethyl acetate = 8 : 1) on silica gel to give the desired product **3j** 56.1 mg (85% yield) as a yellow solid.

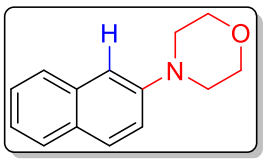


3j: a yellow solid. mp=86-88℃. Rf=0.24 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 2.2 Hz, 2H), 6.99 (s, 1H), 3.93 – 3.81 (m, 4H), 3.27 – 3.16 (m, 4H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.66, 149.15, 140.12, 121.55, 114.85, 106.95, 66.53, 48.57, 21.65; IR (KBr): *v* 2843, 1526, 1357, 1304, 1254, 1118, 871, 743 cm^{-1}; HRMS (CI): Calcd for $C_{11}H_{14}N_2O_3$ (M^+) :222.1004*;* found: 222.1006.

Following the general procedure, 1-iodonaphthalene (68.0 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane : ethyl acetate = 20 : 1 to hexane : ethyl acetate = 10 : 1) on silica gel to give the desired product **3k** 56.7 mg (91% yield) as a pale yellow solid.

Gram scale procedure:

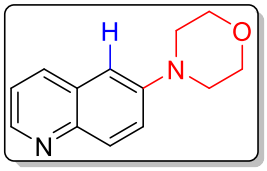
An oven-dried 40 mL vial was charged with 1-iodonaphthalene (1168 mg, 4.6 mmol 1.0 equiv), O-Benzoyl hydroxylamines **2a** (1037 mg, 5.0 mmol, 1.1 equiv), Cs_2CO_3 (3.26 g, 10.0 mmol, 2.5 equiv), isopropanol (304 mg, 5.1 mmol, 1.1 equiv), norbornene (124 mg, 1.2 mmol, 0.25 equiv), $Pd(OAc)_2$ (41.2 mg, 0.18 mmol, 0.04 equiv) and tris(4-methoxyphenyl)phosphine (162 mg, 0.46 mmol, 0.10 equiv), which was sealed outside and transferred in a nitrogen-filled glovebox. Toluene (35 ml) was added into the vial. The vial was sealed with PTFE lined cap in the glovebox and stirred at RT for 10 minutes until the $Pd(OAc)_2$ was



fully dissolved. The vial was then transferred out of glovebox and stirred on a pie-block preheated to 100℃ for 48 hours. After that, the mixture was filtered through a thin pad of celite. The filter cake was washed with diethyl ether, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography (from hexane : ethyl acetate = 20 : 1 to hexane : ethyl acetate = 10 : 1) on silica gel to give the desired product **3k** 785 mg (80% yield) as a pale yellow solid.

3k: a pale yellow solid. Rf=0.22 (hexane/ethyl acetate=10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.68 (m, 3H), 7.44 (t, J = 7.5 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.27 (dd, J = 8.8, 2.7 Hz, 1H), 7.13 (d, J = 2.3 Hz, 1H), 3.97 – 3.89 (m, 4H), 3.30 – 3.25 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.04, 134.46, 128.77, 128.61, 127.40, 126.72, 126.30, 123.49, 118.85, 110.02, 66.89, 49.74. Both the proton and carbon NMR match the literature reported data.[99]

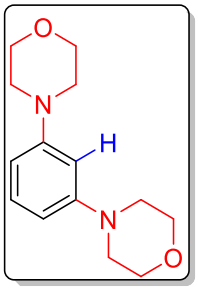
Following the general procedure, 5-iodoquinoline (75.7 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane : ethyl acetate = 2 : 1 to hexane : ethyl acetate = 1 : 1) on silica gel to give the desired product **3l** 56.2 mg (88% yield) as a white solid.



3l: a white solid. Rf=0.18 (hexane/ethyl acetate=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, J = 4.2, 1.7 Hz, 1H), 7.98 (s, 1H), 7.96 (s, 1H), 7.45 (dd, J = 9.3, 2.7 Hz, 1H), 7.29 (dd, J = 8.2, 4.2 Hz, 1H), 6.99 (d, J = 2.8 Hz, 1H), 3.91 – 3.87 (m, 4H), 3.29 – 3.21 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.16, 147.69, 143.93, 134.58, 130.09, 129.24, 121.93, 121.34, 108.86, 66.72, 49.29. Both the proton and carbon NMR match the literature reported data.[100]

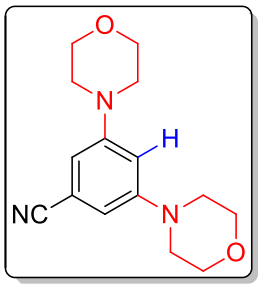
Diamination Procedure:

An oven-dried 8 mL vial was charged with 1-iodobenzene (60.2 mg, 0.3 mmol 1.0 equiv), *O*-benzoyl hydroxylamines **2a** (156.3 mg, 0.75 mmol, 2.5 equiv), Cs_2CO_3 (391mg, 1.2 mmol, 4.0 equiv), isopropanol (21.4 mg, 0.36 mmol, 1.2 equiv), norbornene (14.5 mg, 0.15 mmol, 0.5 equiv), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 equiv) and tris(4-methoxyphenyl)phosphine (26.5 mg, 0.075 mmol, 0.25 equiv), which was sealed outside and transferred in a nitrogen-filled glovebox. Toluene (6 ml) was added into the vial. The vial was sealed with PTFE lined cap in the glovebox again and stirred at RT for 10 minutes until the $Pd(OAc)_2$ was fully dissolved. The vial was then transferred out of glovebox and stirred on a pie-block preheated to 100℃ for 48 hours. The mixture was filtered through a thin pad of celite. The filter cake was washed with ethyl acetate, and the combined filtrate was concentrated. The residue directly was purified by flash column chromatography (from hexane : ethyl acetate = 5 : 1 to hexane : ethyl acetate = 3 : 1) on silica gel to give desired product **3m** 54.0 mg (74% yield) as a white solid.



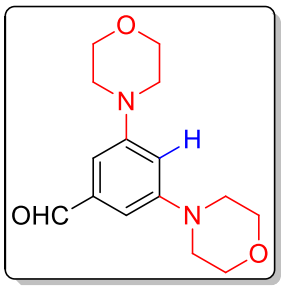
3m: a white solid. Rf=0.12 (hexane/ethyl acetate=3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.15 (m, 1H), 6.51 – 6.42 (m, 3H), 3.91 – 3.81 (m, 8H), 3.21 – 3.09 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.36, 129.67, 108.09, 103.82, 66.88, 49.58. Both the proton and carbon NMR match the literature reported data.[101]

Using the similar conditions as **3m**, 4-iodobenzonitrile (63.3 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane : ethyl acetate = 2 : 1 to hexane : ethyl acetate = 1 : 1) on silica gel to give the desired product **3n** 73.4 mg (97% yield) as a white solid.



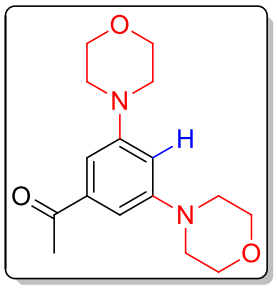
3n: a white solid. Rf=0.18 (hexane/ethyl acetate=1:1); ^{1}H NMR (400 MHz, CDCl3) δ 6.64 (d, J = 2.2 Hz, 2H), 6.56 (t, J = 2.2 Hz, 1H), 3.86-3.80 (m, 8H), 3.18-3.10 (m, 8H); ^{13}C NMR (100 MHz, CDCl3) δ 152.44, 119.52, 113.39, 110.40, 106.65, 66.54, 48.76. The proton NMR match the literature reported data.[102]

Using the similar conditions as **3m**, 4-iodobenzaldehyde (70.4 mg, 0.3 mmol, 1.0 eq) was used. Flash column chromatography (from hexane : ethyl acetate = 3 : 1 to hexane : ethyl acetate = 1 : 1) on silica gel to give the desired product **3o** 72.1 mg (86% yield) as a white solid.



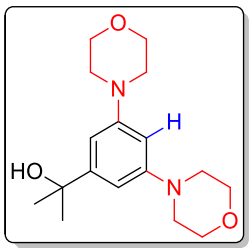
3o: a white solid. mp=121-123℃. Rf=0.21 (hexane/ethyl acetate=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 6.91 (d, J = 2.2 Hz, 2H), 6.66 (t, J = 2.1 Hz, 1H), 3.87 – 3.80 (m, 8H), 3.22 – 3.15 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.76, 152.68, 137.86, 108.62, 108.57, 66.63, 49.09; IR (KBr): *v* 2959, 2855, 2820, 1692, 1596, 1481, 1449, 1268, 1255, 1214, 1121, 1003cm^{-1}; HRMS(ESI): Calcd for $C_{15}H_{21}N_2O_3$ ($M+H^+$):277.1547*;* found: 277.1555.

Using the similar conditions as **3m**, 4′-iodoacetophenone (72.0 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane : ethyl acetate = 3 : 1 to hexane : ethyl acetate = 1 : 1) on silica gel to give the desired product **3p** 57.9 mg (68% yield) as a white solid.



3p: a white solid. mp=113-117℃. Rf=0.21 (hexane/ethyl acetate=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 2.2 Hz, 2H), 6.63 (t, J = 2.1 Hz, 1H), 3.89 – 3.80 (m, 8H), 3.24 – 3.11 (m, 8H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.48, 152.43, 138.64, 107.91, 107.80, 66.75, 49.46, 26.74; IR (KBr): *v* 2958, 2851, 1680, 1590 1448, 1374, 1262, 1204, 1006, 937cm^{-1}; HRMS (ESI): Calcd for $C_{16}H_{23}N_2O_3$ ($M+H^+$) : 291.1703*;* found: 291.1708.

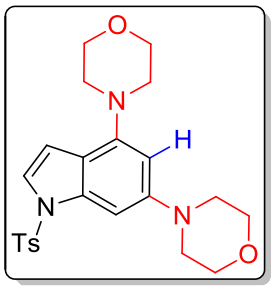
Using the similar conditions as **3m**, 2-(4-iodophenyl)propan-2-ol (81.0 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane : ethyl acetate = 1 : 1 to hexane : ethyl acetate = 1 : 2) on silica gel to give the desired product **3q** 77.0 mg (81% yield) as a white solid.



3q: a white solid. mp=125-128℃. Rf=0.54 (100% ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, J = 1.8 Hz, 2H), 6.33 (s, 1H), 3.93 – 3.76 (m, 8H), 3.23 – 3.07 (m, 8H), 2.22 (br, 1H), 1.53 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.16, 151.10, 104.76, 102.10, 72.59, 66.82, 49.71, 31.67; IR (KBr): *v* 3999(br), 2955, 2923, 2855, 1721, 1591, 1445, 1375, 1264, 1194, 1109, 1065, 996 cm^{-}

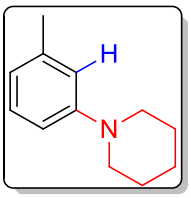
[1]; HRMS (ESI): Calcd for C17H27N2O3 ($M+H^+$) : 307.2016; found: 307.2017.

Using the similar conditions as **3m**, 5-iodo-1-tosyl-1H-indole (118.2 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane : ethyl acetate = 2 : 1 to hexane : ethyl acetate = 1 : 1) on silica gel to give the desired product **3r** 82.6 mg (63% yield) as a white solid.



3r: a white solid. mp=218-223(decompose)℃. Rf=0.25 (hexane/ethyl acetate=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 3.7 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 1.4 Hz, 1H), 6.55 (dd, J = 3.7, 0.5 Hz, 1H), 6.39 (d, J = 1.9 Hz, 1H), 3.95 – 3.82 (m, 8H), 3.22 – 3.05 (m, 8H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.42, 146.12, 144.80, 137.04, 135.20, 129.76, 126.72, 123.59, 117.86, 106.98, 102.17, 94.93, 67.05, 66.91, 51.87, 50.57, 21.52; IR (KBr):*v* 2968, 2853, 1581, 1446, 1361, 1184, 1169, 1114, 1067 1036, 996 cm^{-1}; HRMS (ESI): Calcd for C21H28N3O4S ($M+H^+$) :442.1795; found: 442.1795.

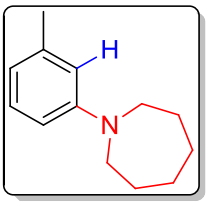
Following the general procedure, 2-iodotoluene (64.0 mg, 0.3 mmol, 1.0 eq) was used. Flash column chromatography (from hexane : ethyl acetate = 50 : 1 to hexane : ethyl acetate = 30 : 1) on silica gel to give the desired product **3s** 43.1 mg (84% yield) as a colorless oil.



CAS: 71982-24-6

3s: a colorless oil. Rf=0.72 (hexane/ethyl acetate=10:1); ^{1}H NMR (400 MHz, CDCl3) δ 7.17 (t, J = 7.8 Hz, 1H), 6.83–6.76 (m, 2H), 6.71–6.65 (m, 1H), 3.21–3.11 (m, 4H), 2.34 (s, 3H), 1.78-1.70 (m,4H), 1.64-1.56 (m, 2H); ^{13}C NMR (100 MHz, CDCl3) δ 152.26, 138.55, 128.78, 120.15, 117.43, 113.67, 50.80, 25.87, 24.30, 21.75. The proton NMR match the literature reported data.[103]

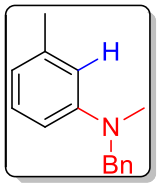
Following the general procedure, 2-iodotoluene (65.0 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane : ethyl acetate = 50 : 1 to hexane : ethyl acetate = 30 : 1) on silica gel to give the desired product **3t** 32.9 mg (58% yield) as a colorless oil.



3t: a colorless oil. Rf=0.77 (hexane/ethyl acetate=10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.11 (m, 1H), 6.59 – 6.53 (m, 2H), 6.50 (d, J = 7.3 Hz, 1H), 3.52 – 3.42 (m, 4H), 2.35 (s, 3H), 1.88 – 1.75 (m, 4H), 1.66 – 1.54 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.95, 138.75, 129.05, 116.06, 111.78, 108.33, 48.98, 27.86, 27.18, 21.99; IR (KBr): *v* 2924, 2852, 1600, 1497, 1390, 1368, 1270, 1184, 1158, 762cm^{-1}; HRMS (ESI): Calcd for C17H27N2O3 ($M+H^+$) : 307.2016*;* found: 307.2017.

Following the general procedure, 2-iodotoluene (65.0 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane : ethyl acetate = 50 : 1 to hexane : ethyl acetate = 30 : 1) on

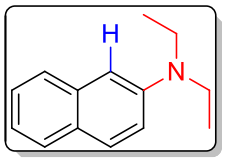
silica gel to give the desired product **3u** 44.0 mg (70% yield) as a colorless oil.



CAS: 101663-45-0

3u: a colorless oil. Rf=0.78 (hexane/ethyl acetate=10:1); ^{1}H NMR (400 MHz, CDCl3) δ 7.36 (ddd, J = 7.0, 6.1, 2.8 Hz, 2H), 7.33 – 7.24 (m, 3H), 7.16 (t, J = 7.7 Hz, 1H), 6.69 – 6.55 (m, 3H), 4.56 (s, 2H), 3.04 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 149.83, 139.09, 138.81, 129.00, 128.48, 126.77, 126.72, 117.50, 113.03, 109.60, 56.58, 38.40, 21.89. Both the proton and carbon NMR match the literature reported data.[104]

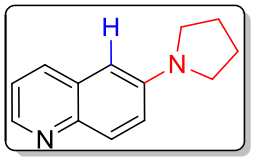
Following the general procedure, 1-iodonaphthalene (74.0 mg, 0.3 mmol, 1.0 eq) was used. Flash column chromatography (from hexane : ethyl acetate = 100 : 1 to hexane : ethyl acetate = 50 : 1) on silica gel to give desired product **3v** 32.1 mg (55% yield) as a pale yellow oil.



CAS: 13672-17-8

3v: a pale yellow oil. Rf=0.62 (hexane/ethyl acetate=10:1); ^{1}H NMR (400 MHz, CDCl3) δ 7.77 – 7.62 (m, 3H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.21 (t, *J* = 7.0 Hz, 1H), 7.15 (d, *J* = 9.1 Hz, 1H), 6.93 (s, 1H), 3.50 (q, *J* = 7.0 Hz, 4H), 1.26 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, CDCl3) δ 145.73, 135.23, 128.79, 127.33, 126.23, 126.05, 125.84, 121.45, 115.94, 105.45, 44.48, 12.62. Both the proton NMR and ^{13}C NMR match the literature reported data.[99]

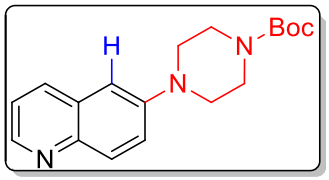
Following the general procedure, 5-iodoquinoline (77.3 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane : ethyl acetate = 5 : 1 to hexane : ethyl acetate = 3 : 1) on silica gel to give the desired product **3w** 30.2 mg (50% yield) as a pale yellow oil.



CAS: 343954-65-4

3w: a white solid. Rf=0.38 (hexane/ethyl acetate=1:1); ^{1}H NMR (400 MHz, CDCl3) δ 8.57 (dd, J = 4.2, 1.7 Hz, 1H), 7.96 – 7.86 (m, 2H), 7.22 (q, J = 4.2 Hz, 1H), 7.18 (dd, J = 9.2, 2.7 Hz, 1H), 6.60 (d, J = 2.7 Hz, 1H), 3.43 – 3.34 (m, 4H), 2.08 – 2.00 (m, 4H);^{13}C NMR (100 MHz, CDCl3) δ 145.81, 145.45, 141.93, 133.51, 130.05, 129.98, 121.19, 118.86, 103.29, 47.74, 25.49. Both the proton and carbon NMR match the literature reported data.[100]

Following the general procedure, 5-iodoquinoline (73.0 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane : ethyl acetate = 2 : 1 to hexane : ethyl acetate = 1 : 1) on silica gel to give desired product **3x** 89.0 mg (99% yield) as a pale yellow oil.

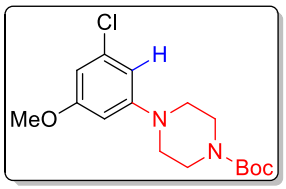


CAS: 683243-00-7

3x: a pale yellow oil. Rf=0.14 (hexane/ethyl acetate=1:1); ^{1}H NMR (400 MHz, CDCl3) δ 8.71 – 8.66 (m, 1H), 7.95 (dd, J = 8.6, 1.2 Hz, 2H), 7.47 – 7.40 (m, 1H), 7.30 – 7.24 (m, 1H), 6.98 (d, J = 1.2 Hz, 1H), 3.60 (s, 4H), 3.21 (s, 4H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, CDCl3) δ 154.55, 149.08, 147.69, 143.91, 134.60, 130.03, 129.19, 122.77, 121.31, 109.55, 79.89, 49.22, 43(br),

28.32. Both the proton and carbon NMR match the literature reported data.[100]

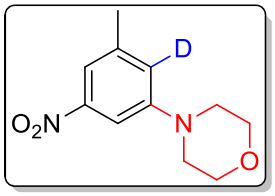
An oven-dried 8 mL vial was charged with the mixture of **6a** and **6b** (80.5 mg, 0.3 mmol 1.0 equiv), *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate (165 mg, 0.54 mmol, 1.8 equiv), Cs_2CO_3 (246 mg, 0.75 mmol, 2.5 equiv), isopropanol (19.8 mg, 0.33 mmol, 1.1 equiv), norbornene (7.0 mg, 0.075 mmol, 0.25 equiv), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 equiv) and tris(4-methoxyphenyl) phosphine (26.4 mg, 0.075 mmol, 0.25 equiv), which was sealed outside and transferred in a nitrogen-filled glovebox. Toluene (6 ml) was added into the vial. The vial was sealed with PTFE lined cap in the glovebox and stirred at RT for 10 minutes until the $Pd(OAc)_2$ fully dissolved. The vial was then transferred out of glovebox and stirred on a pie-block preheated to 100℃ for 48 hours. The mixture was then filtered through a thin pad of celite. The filter cake was washed with diethyl ether, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography (from to hexane : ethyl acetate = 20 : 1 to hexane : ethyl acetate = 5 : 1) on silica gel to give the desired product **7** 86.2 mg (88% yield) as a colorless oil.



7: a colorless oil. Rf=0.32 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.50 (t, J = 1.9 Hz, 1H), 6.41 (t, J = 1.9 Hz, 1H), 6.31 (t, J = 2.2 Hz, 1H), 3.76 (s, 3H), 3.58 – 3.49 (m, 4H), 3.16 – 3.07 (m, 4H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.98, 154.60, 152.79, 135.43,

109.27, 105.27, 101.06, 79.99, 55.40, 48.82, 43(br), 28.37; IR (KBr): *v* 2975, 2930, 1697, 1599, 1573, 1454, 1423, 1365, 1202, 1172, 1048, 991, 879cm^{-1}; HRMS (ESI): Calcd for C16H23ClN2O3Na (M+Na^{+}) : 349.1289*;* found: 349.1299.

Following the general procedure, aryl iodide **1j** (78.6 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane : ethyl acetate = 10 : 1 to hexane : ethyl acetate = 8 : 1) on silica gel to give the desired product D-**3j** 56.0 mg (84% yield) as a yellow solid.



D-3j: a yellow solid. Rf=0.24 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 – 7.48 (m, 2H), 3.89 – 3.82 (m, 4H), 3.27 – 3.15 (m, 4H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.58, 149.13, 140.03, 121.44(C-D), 121.20(C-D), 120.96(C-D), 114.83, 106.92, 66.51, 48.54, 21.57; HRMS (ESI): Calcd for C11H14DN2O3 (M+H^{+}) : 224.1140*;* found: 224.1142.

2.6 NMR Spectra

Figure 2.1 ^{1}H and ^{13}C NMR spectrum of compound **2w.**

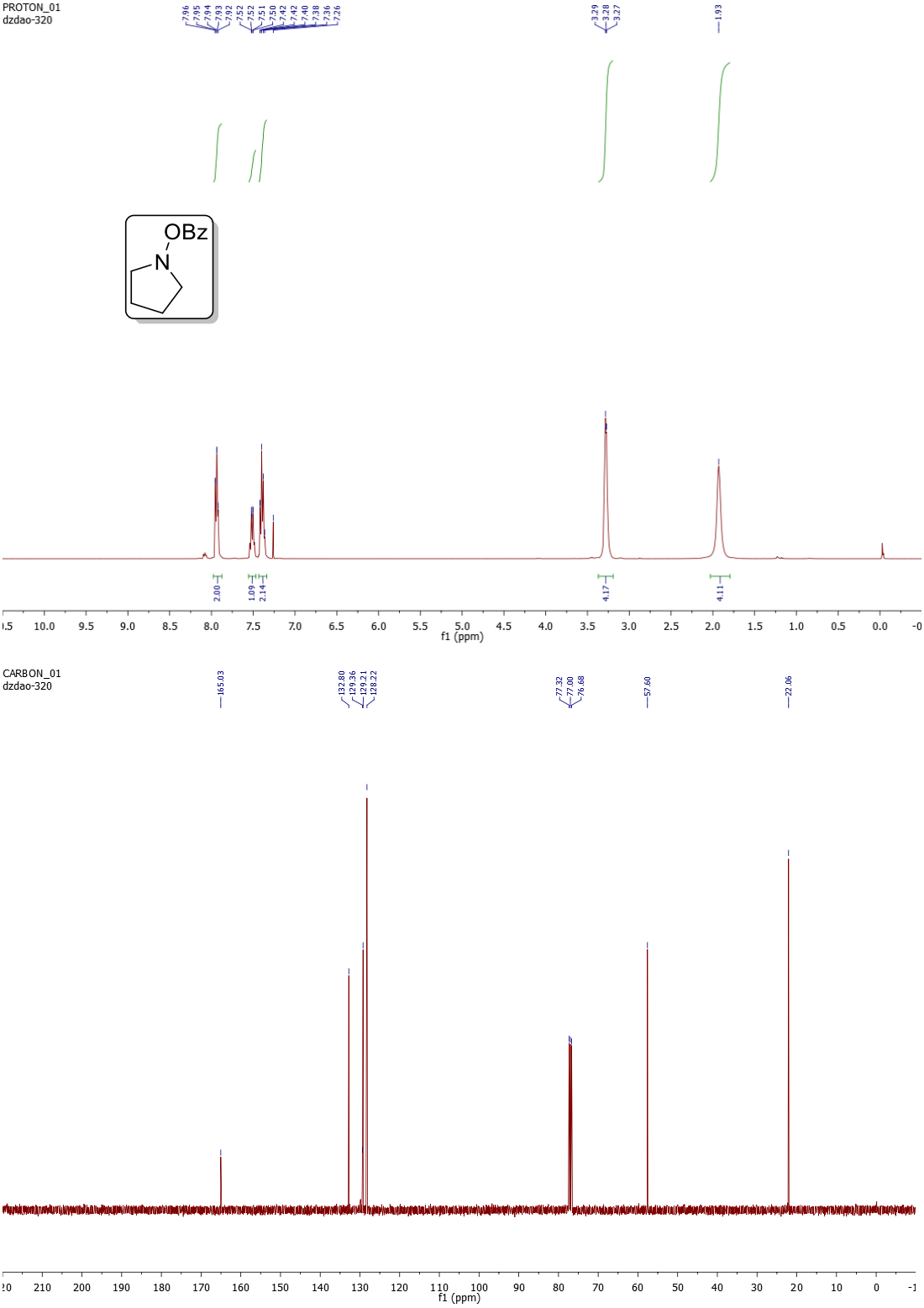


Figure 2.2 ^{1}H and ^{13}C NMR spectrum of compound **2t.**

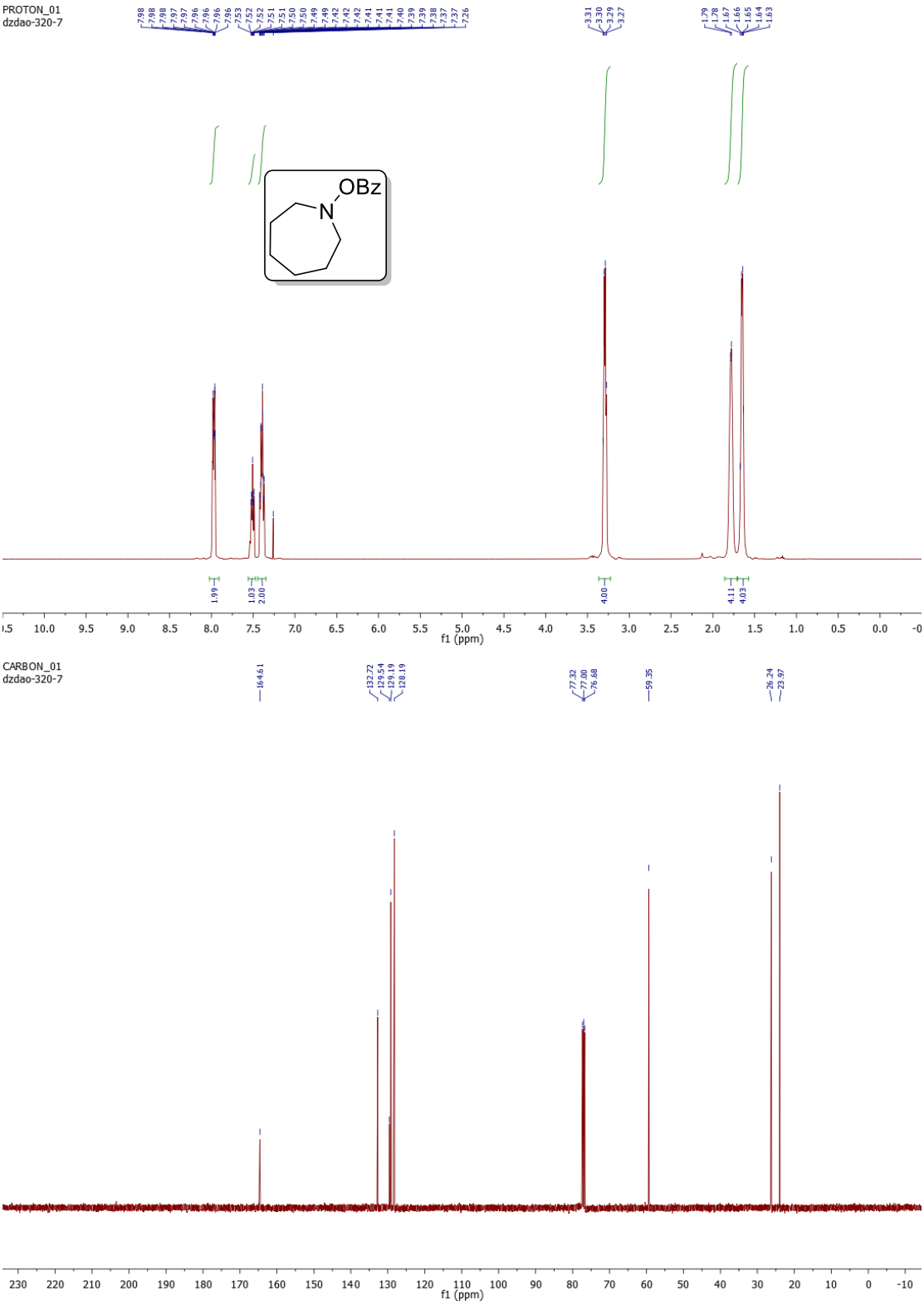


Figure 2.3 ^{1}H and ^{13}C NMR spectrum of compound **1i.**

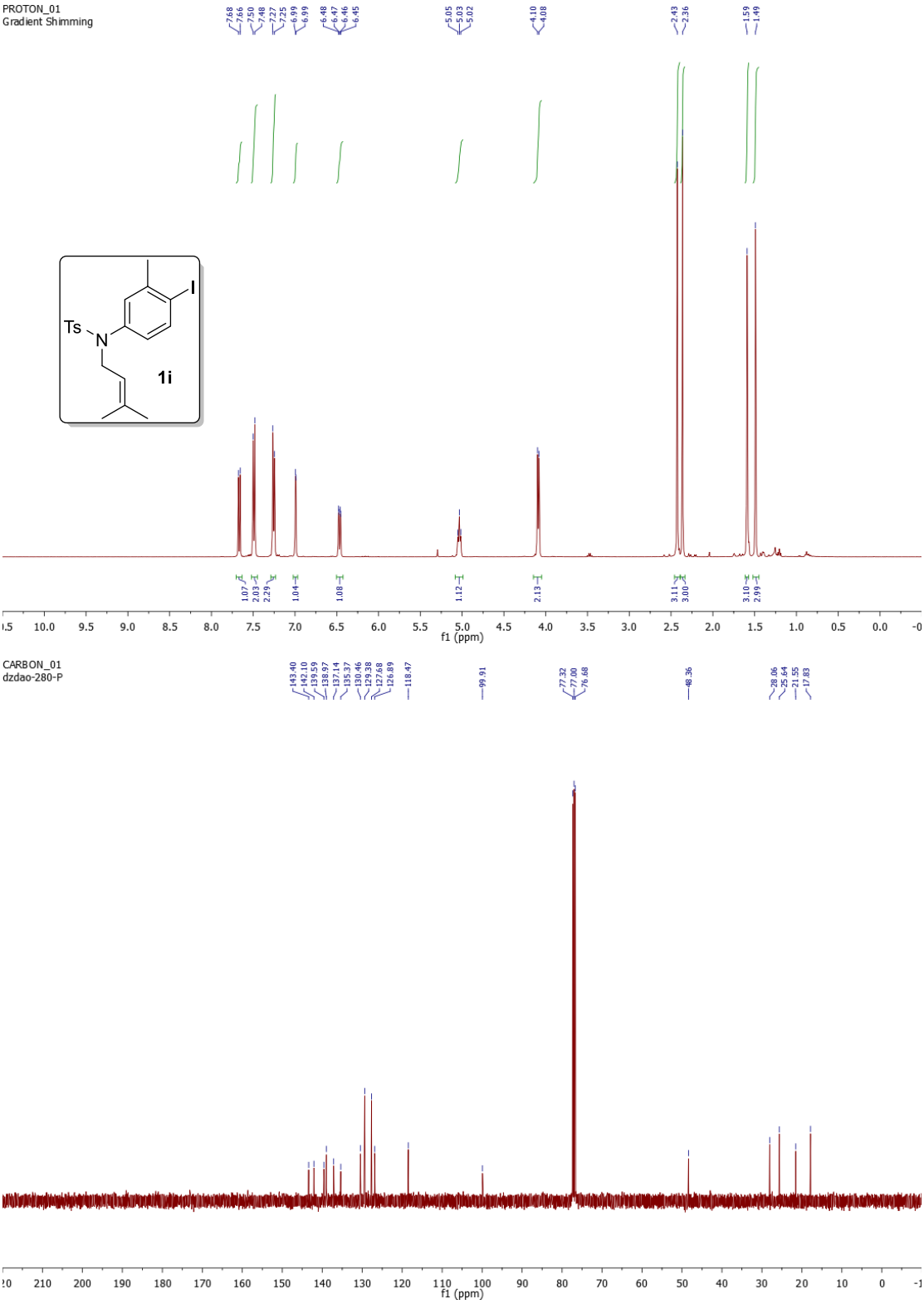


Figure 2.4[1]H and [13]C NMR spectrum of compound **6a/6b.**

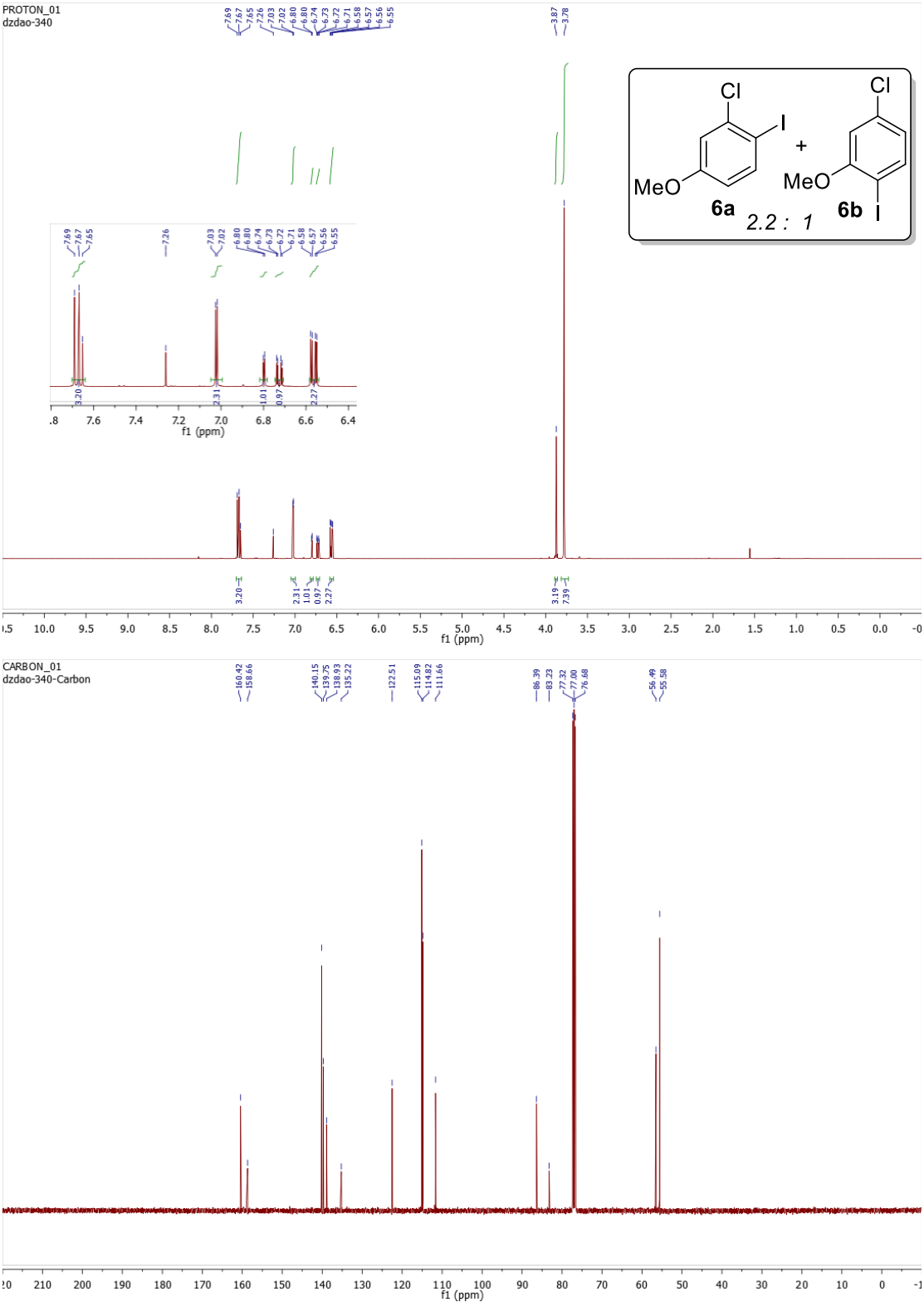


Figure 2.5 ^{1}H and ^{13}C NMR spectrum of compound **3a**.

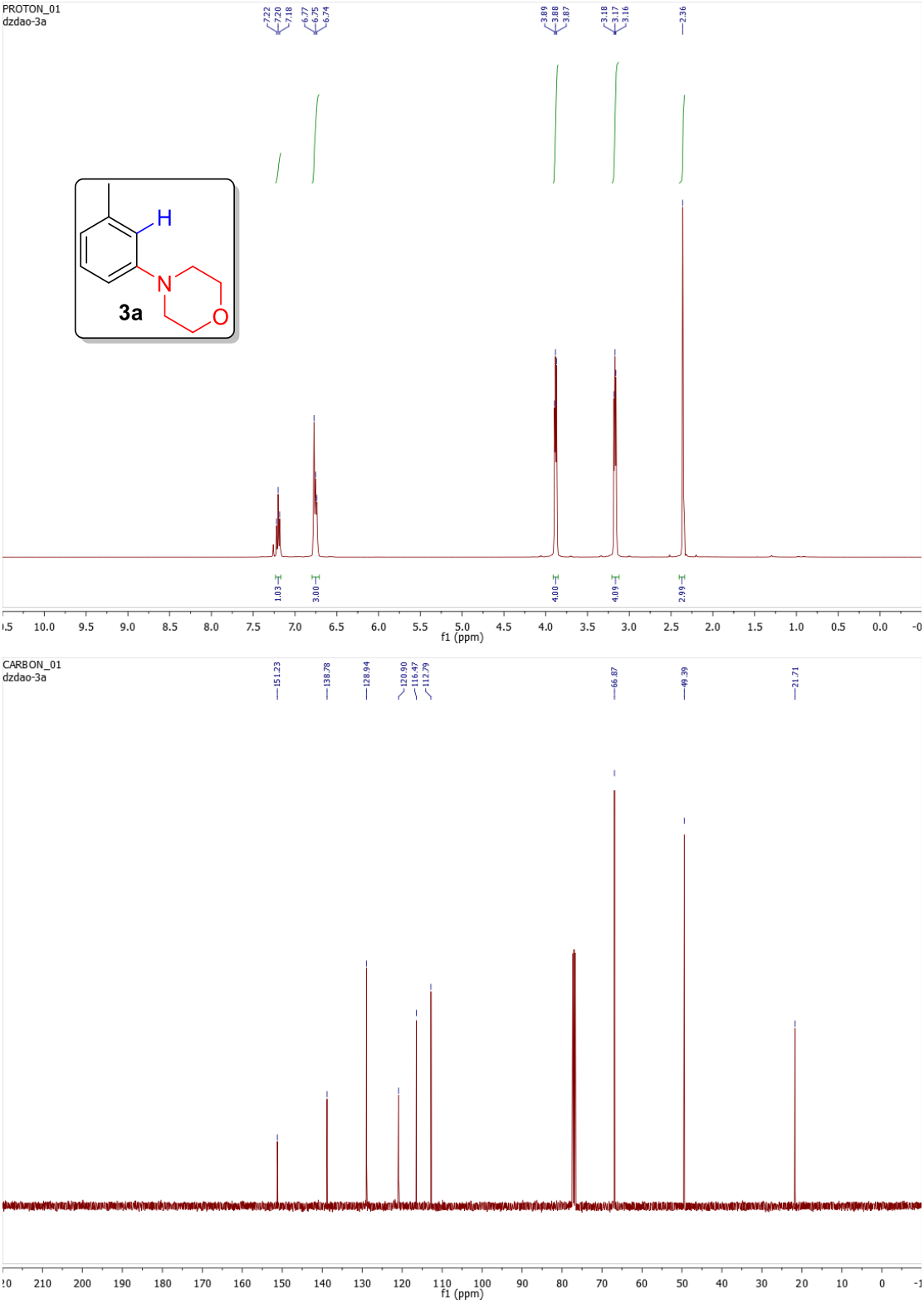


Figure 2.6 ^{1}H and ^{13}C NMR spectrum of compound **3b**.

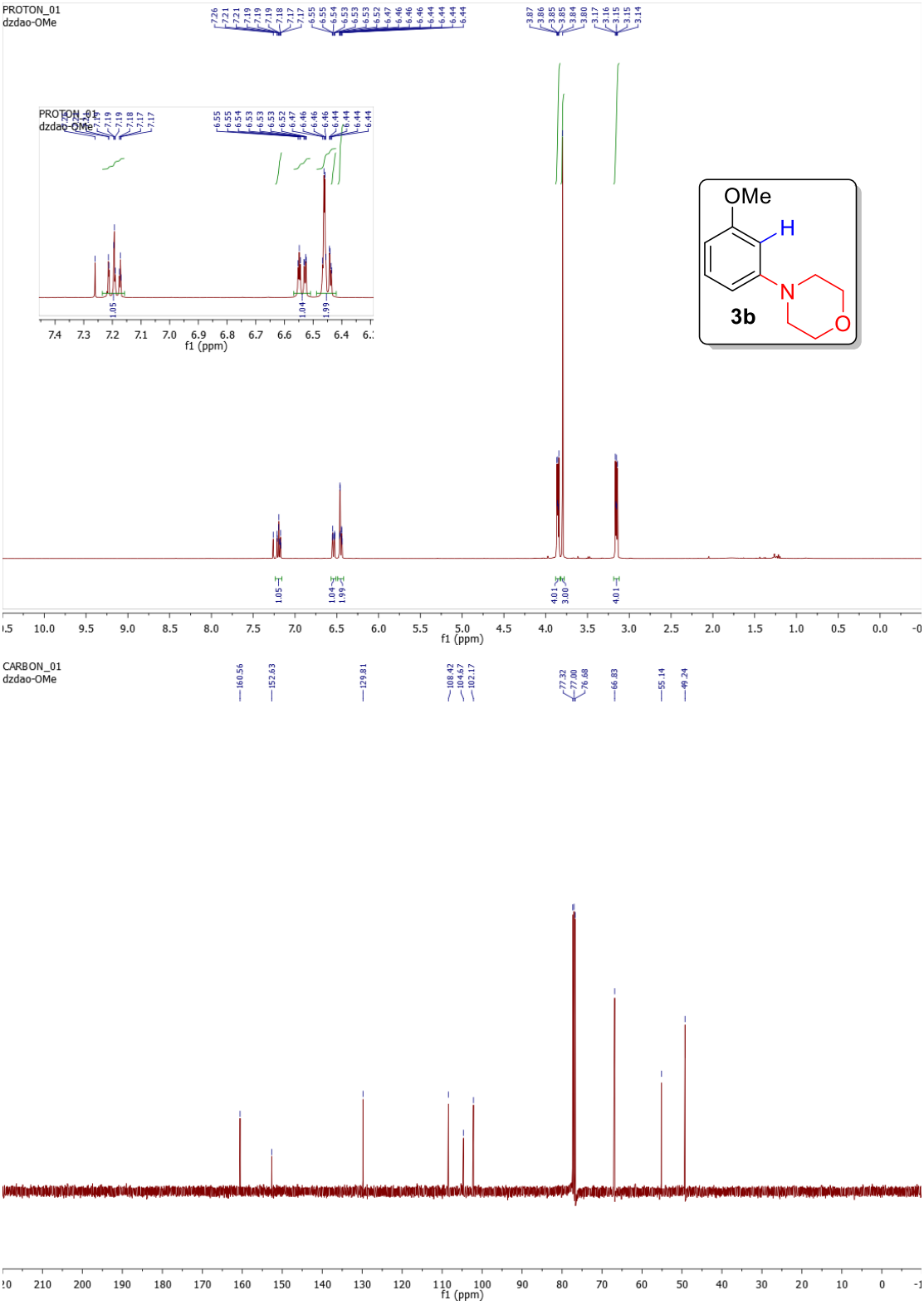


Figure 2.7 ^{1}H and ^{13}C NMR spectrum of compound **3c**.

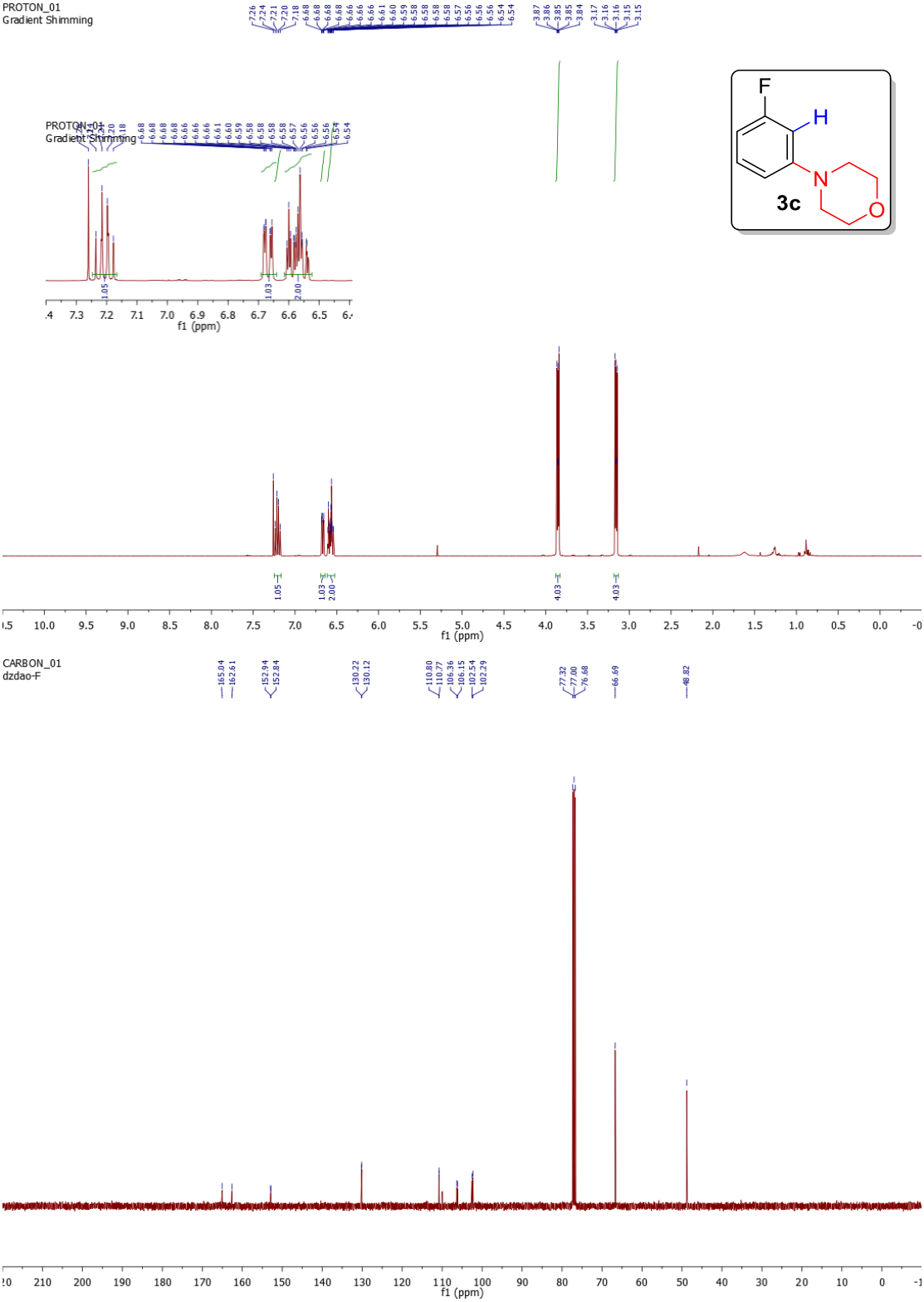


Figure 2.8 ^{19}F NMR spectrum of compound **3c**.

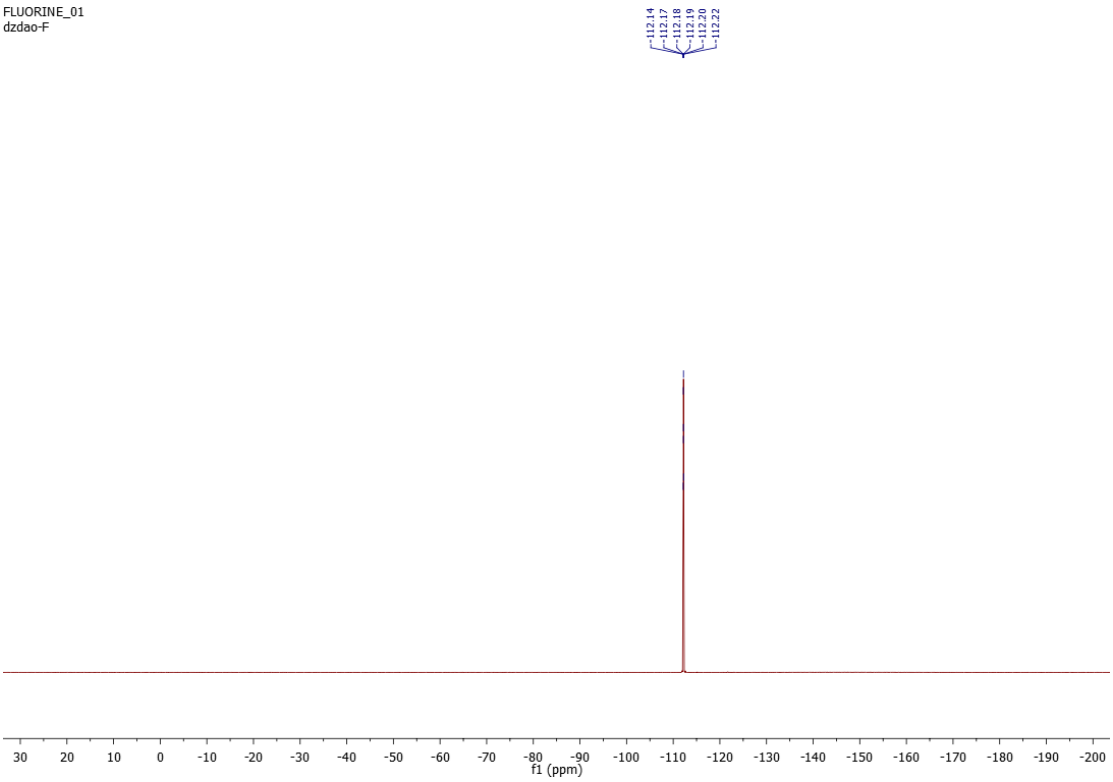


Figure 2.9 ^{1}H and ^{13}C NMR spectrum of compound **3d**.

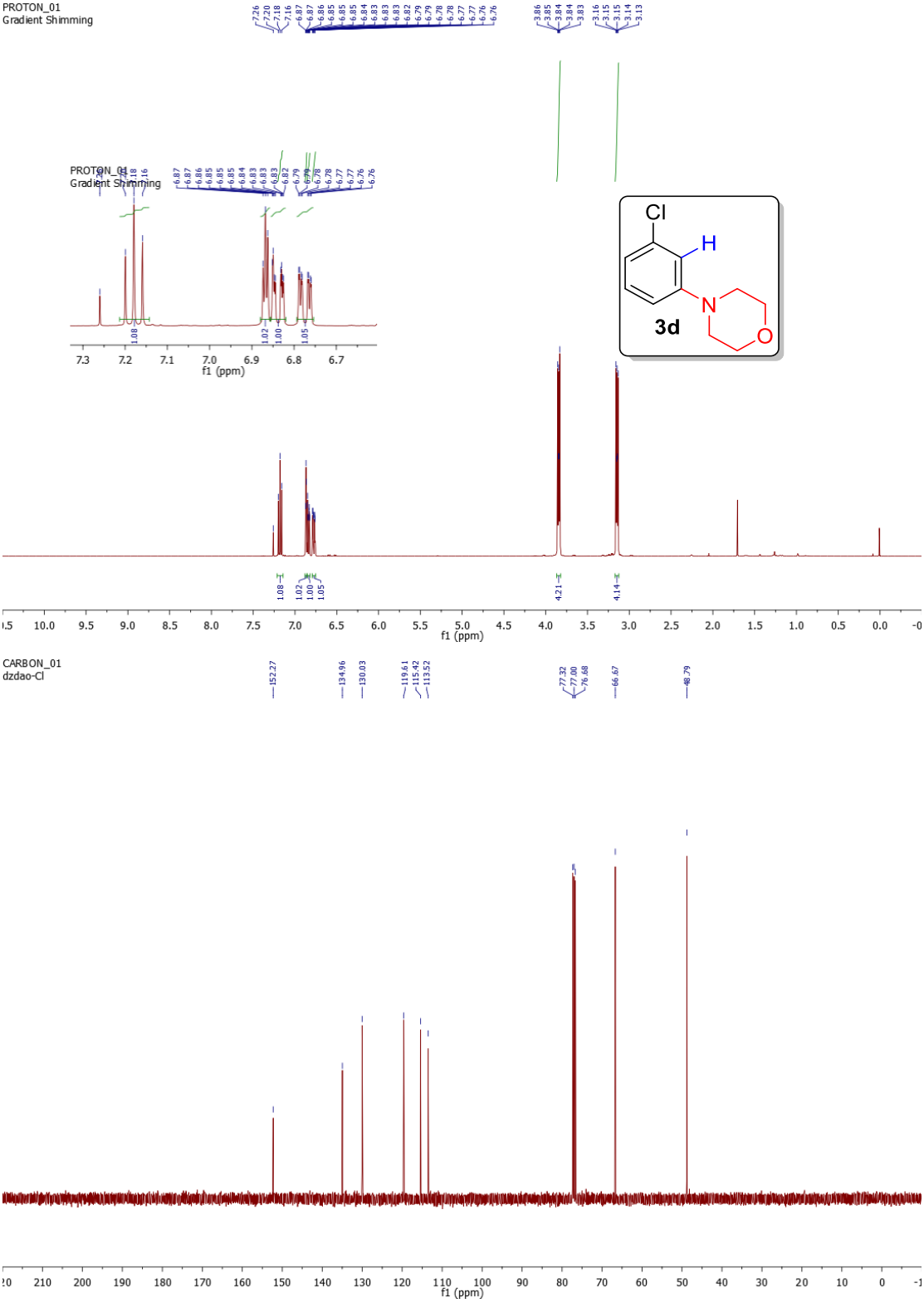


Figure 2.10 ^{1}H and ^{13}C NMR spectrum of compound **3e**.

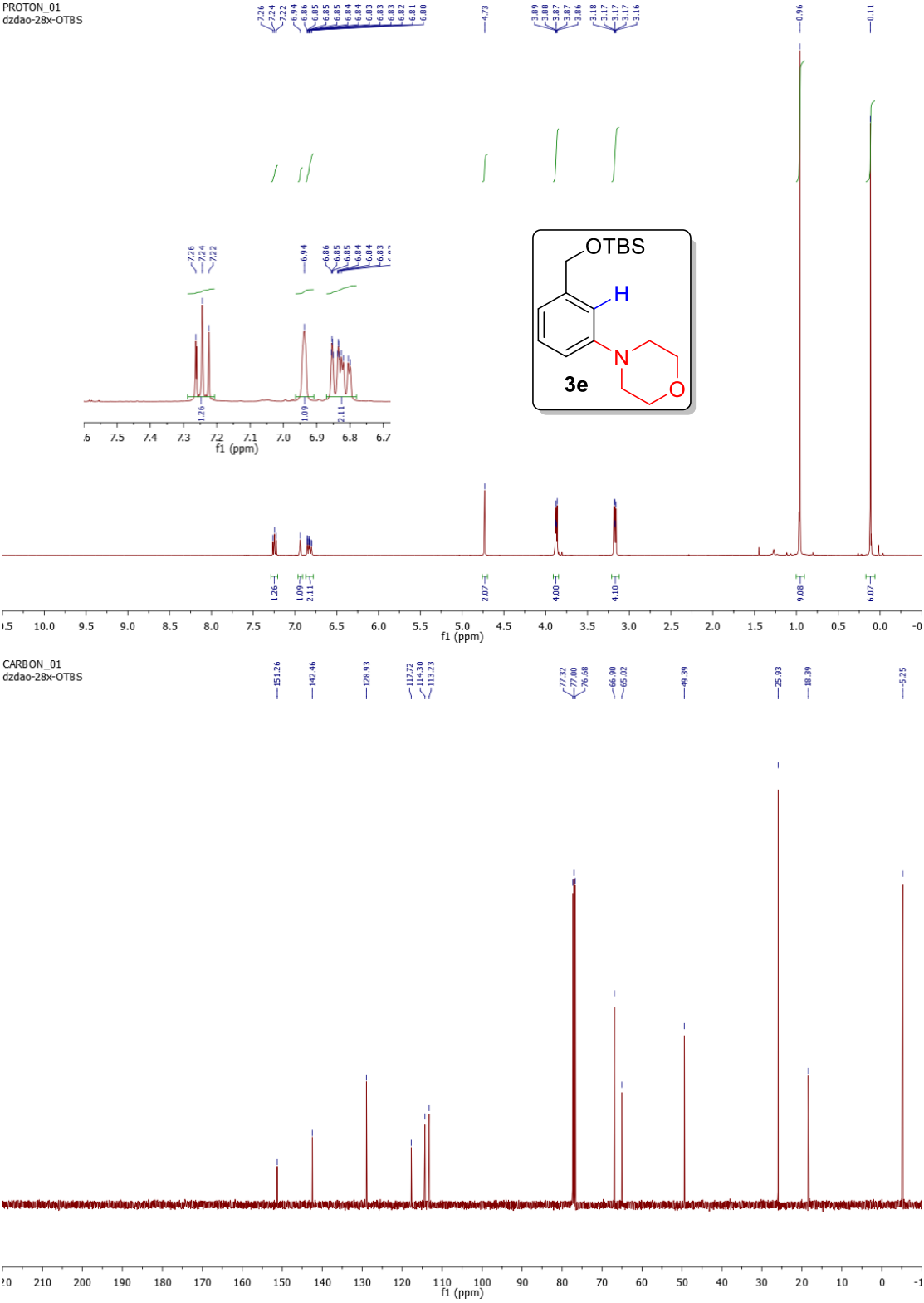


Figure 2.11 ^{1}H and ^{13}C NMR spectrum of compound **3f**.

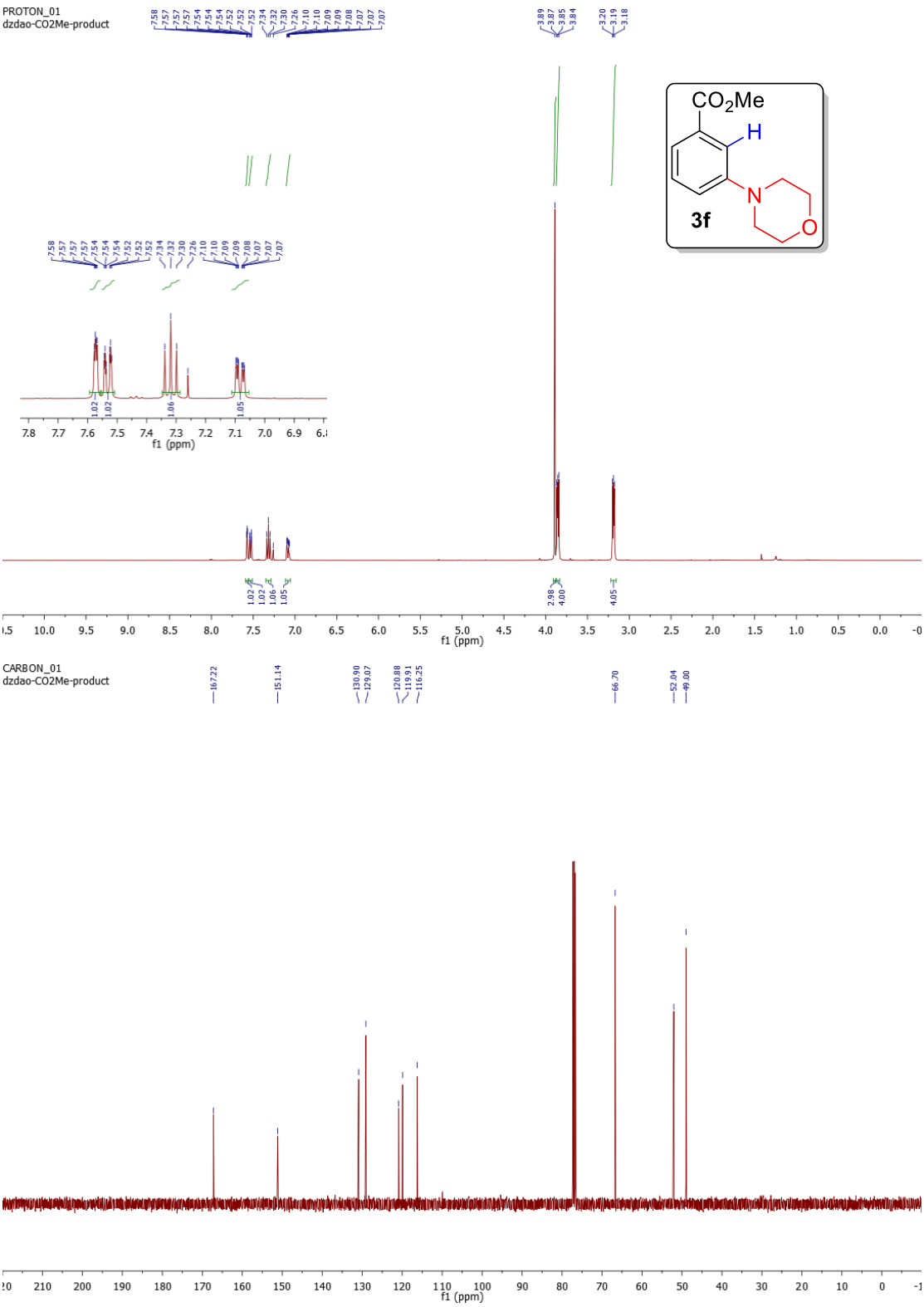


Figure 2.12 ^{1}H and ^{13}C NMR spectrum of compound **3g**.

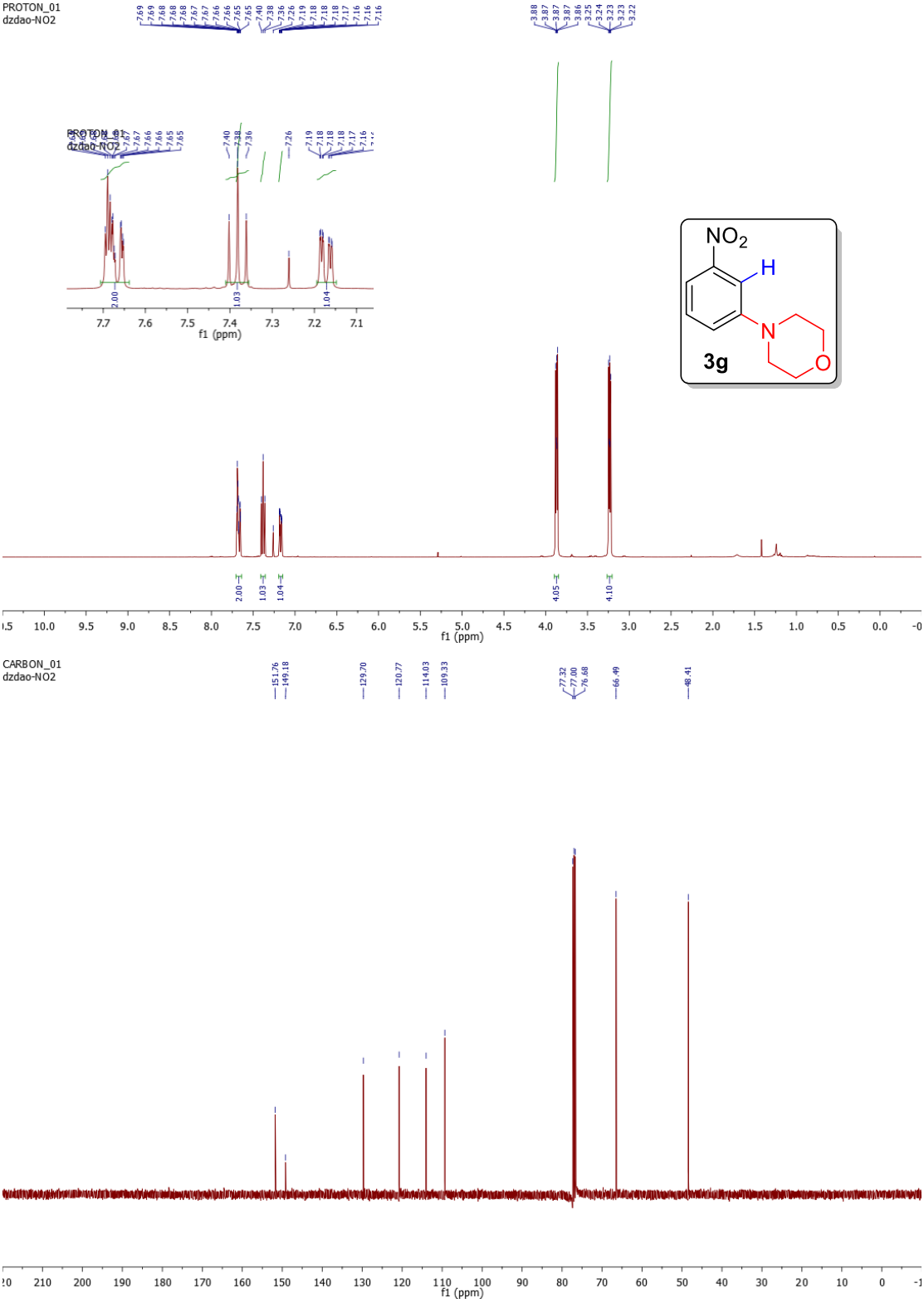


Figure 2.13 ^{1}H and ^{13}C NMR spectrum of compound **3h**.

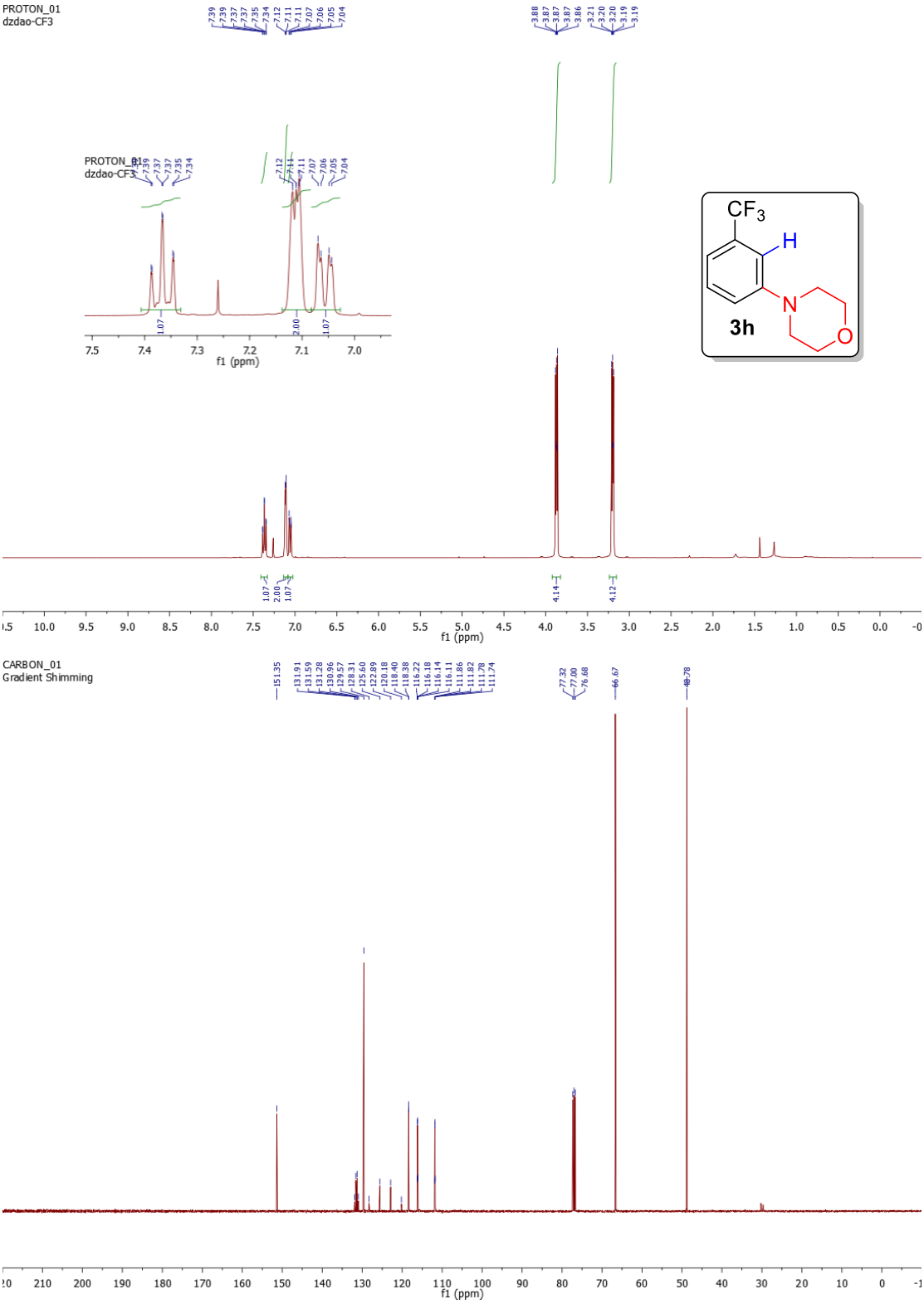


Figure 2.14 ^{1}H and ^{13}C NMR spectrum of compound **3f**.

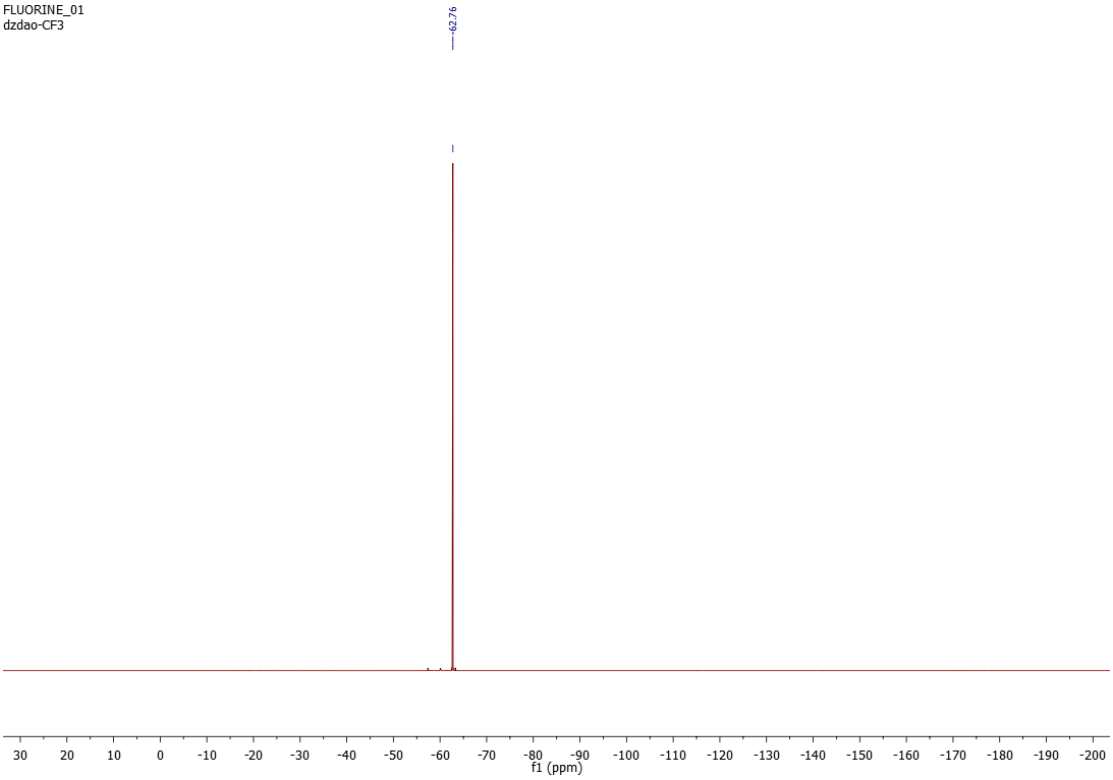


Figure 2.15 ^{1}H and ^{13}C NMR spectrum of compound **3i**.

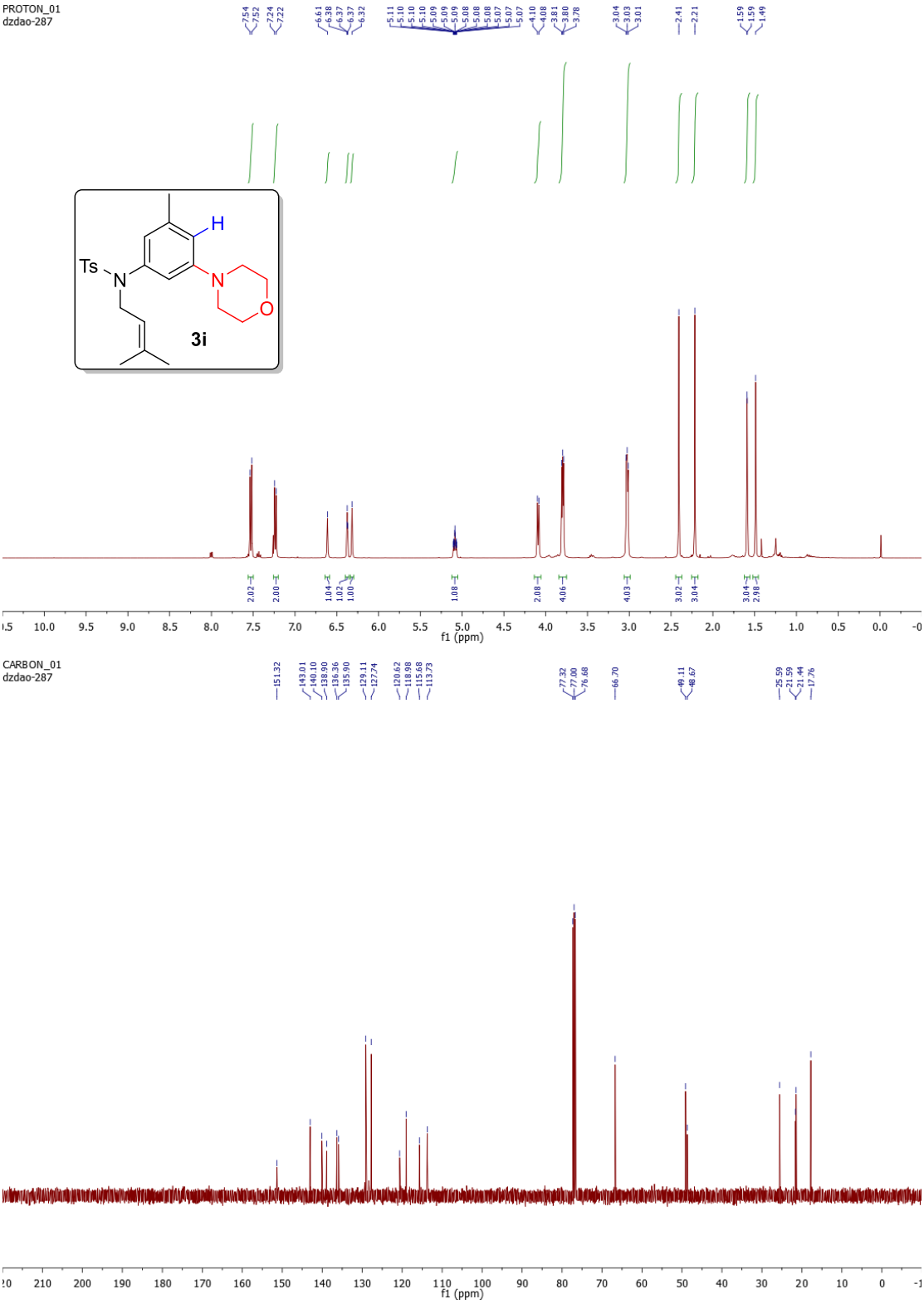


Figure 2.16 ^{1}H and ^{13}C NMR spectrum of compound **3j**.

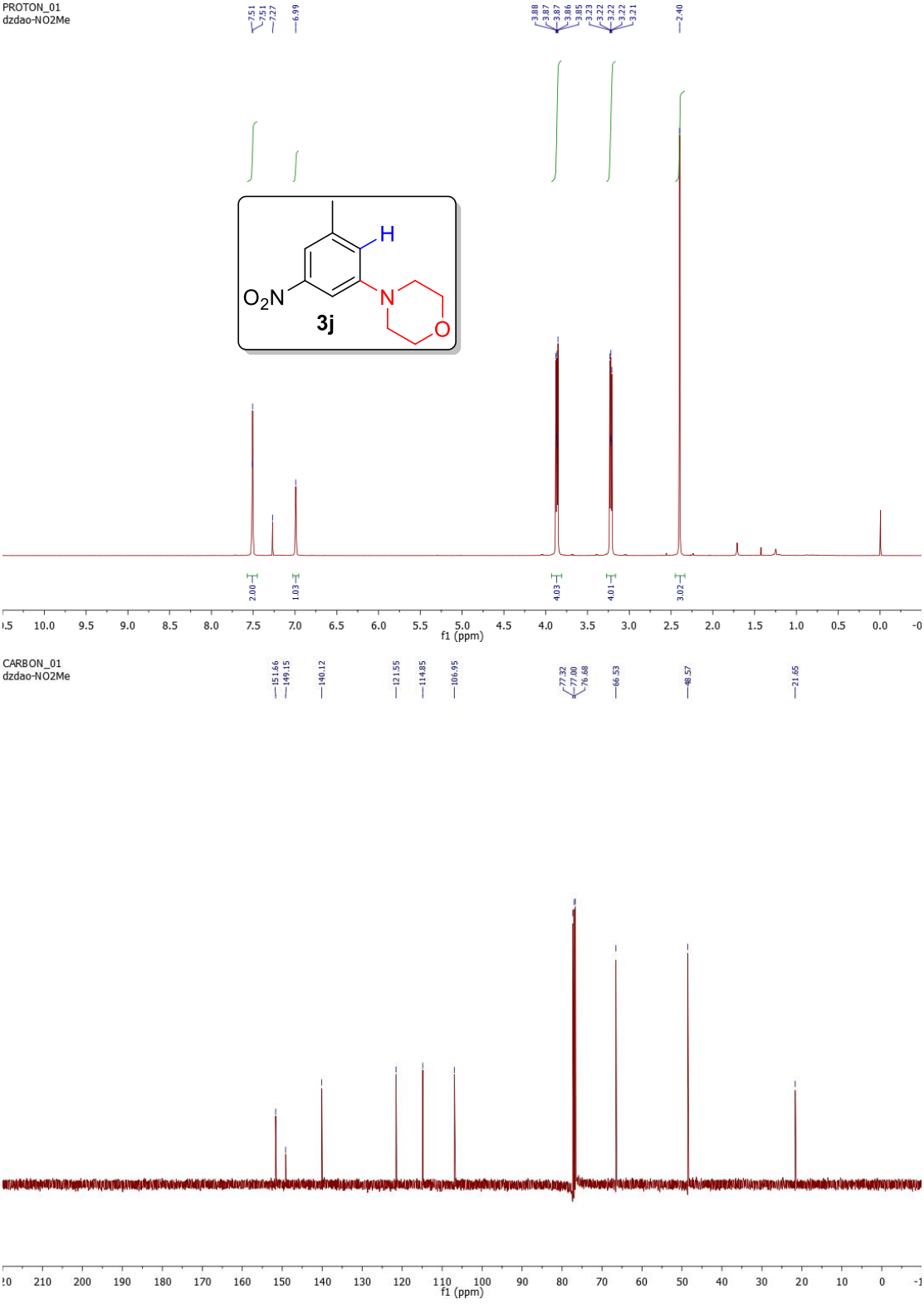


Figure 2.17 ^{1}H and ^{13}C NMR spectrum of compound **3k**.

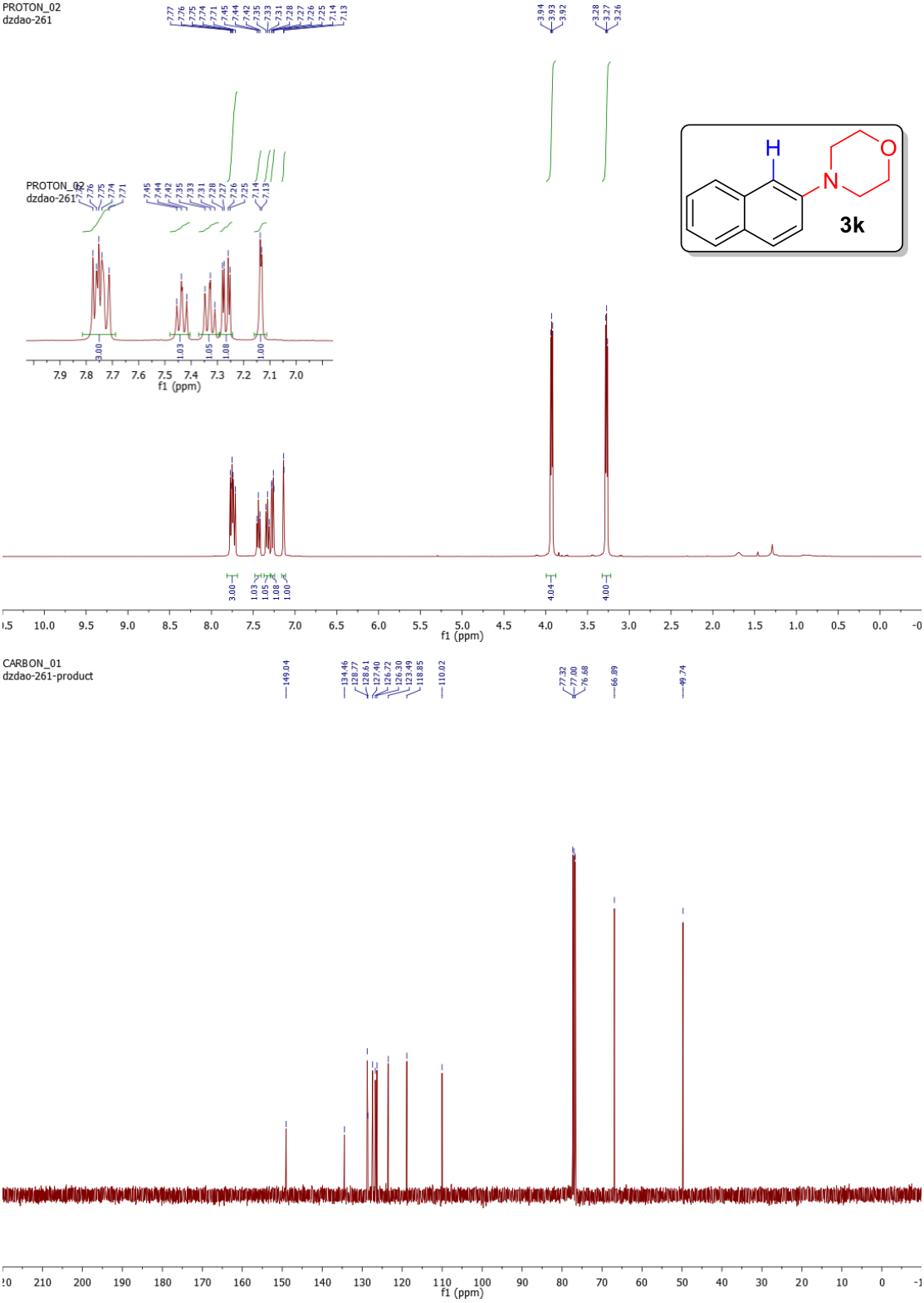


Figure 2.18 ^{1}H and ^{13}C NMR spectrum of compound **3l**.

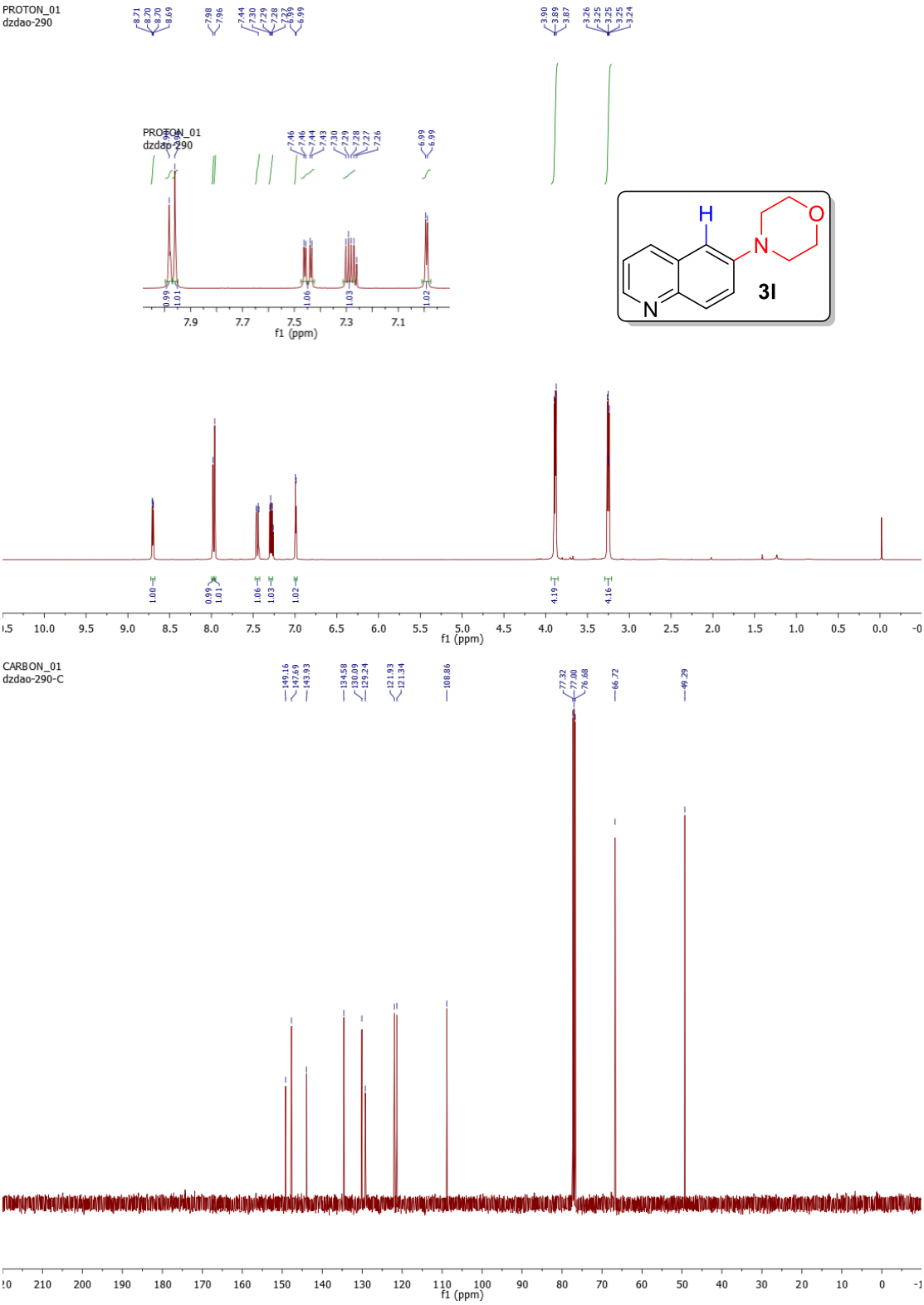


Figure 2.19 ^{1}H and ^{13}C NMR spectrum of compound **3m**.

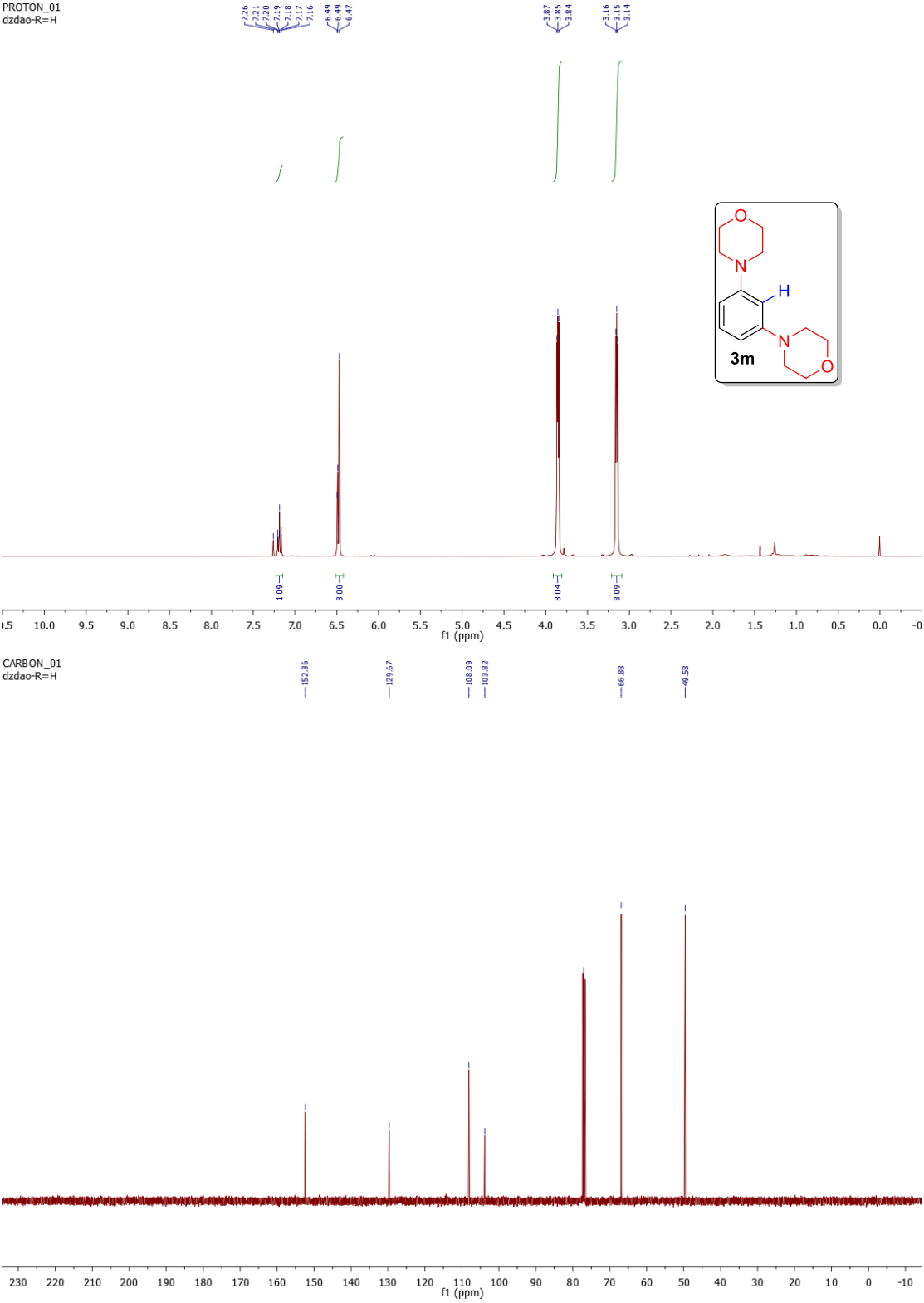


Figure 2.20 ^{1}H and ^{13}C NMR spectrum of compound **3n**.

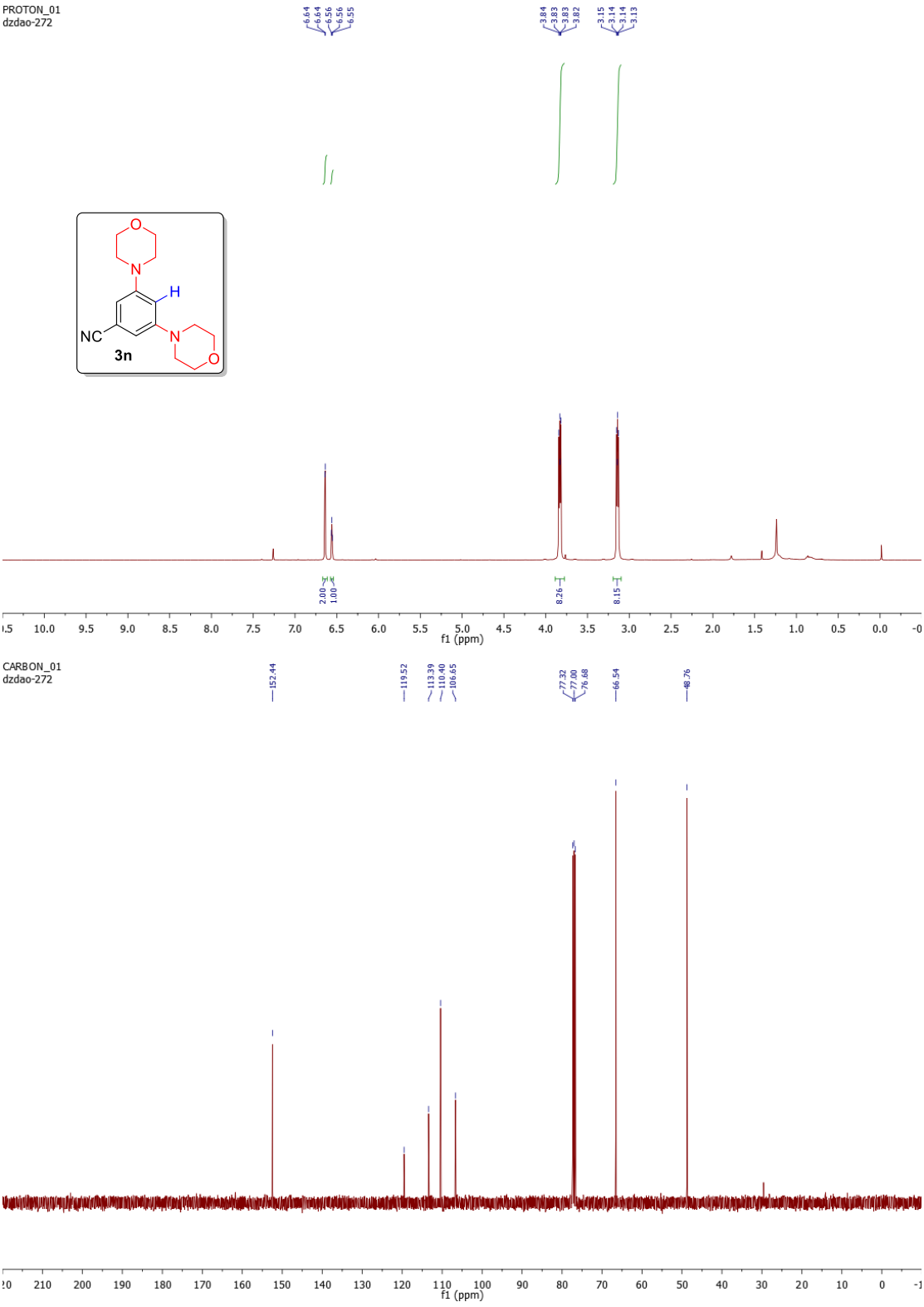


Figure 2.21 ^{1}H and ^{13}C NMR spectrum of compound **3o**.

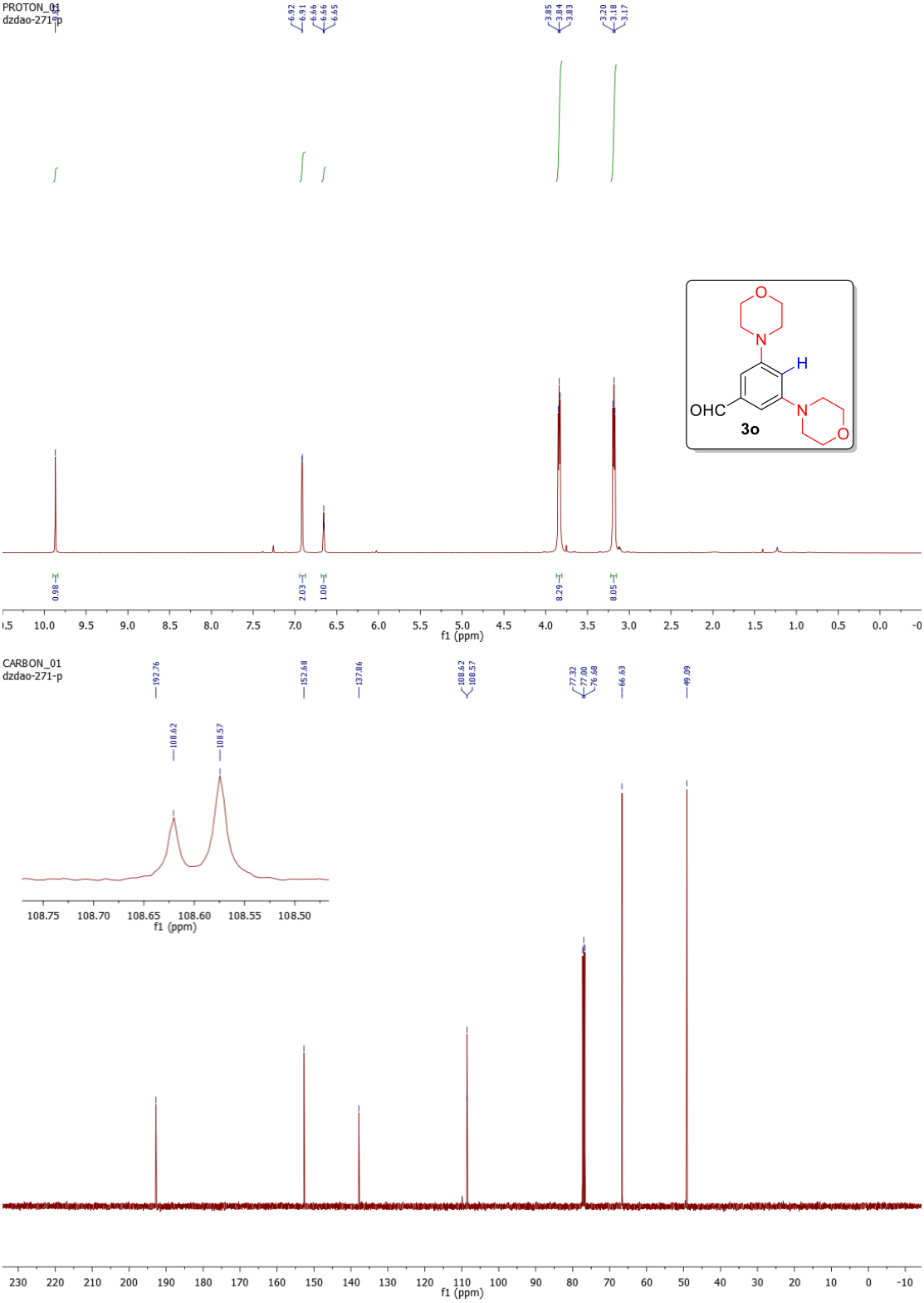


Figure 2.22 ^{1}H and ^{13}C NMR spectrum of compound **3p**.

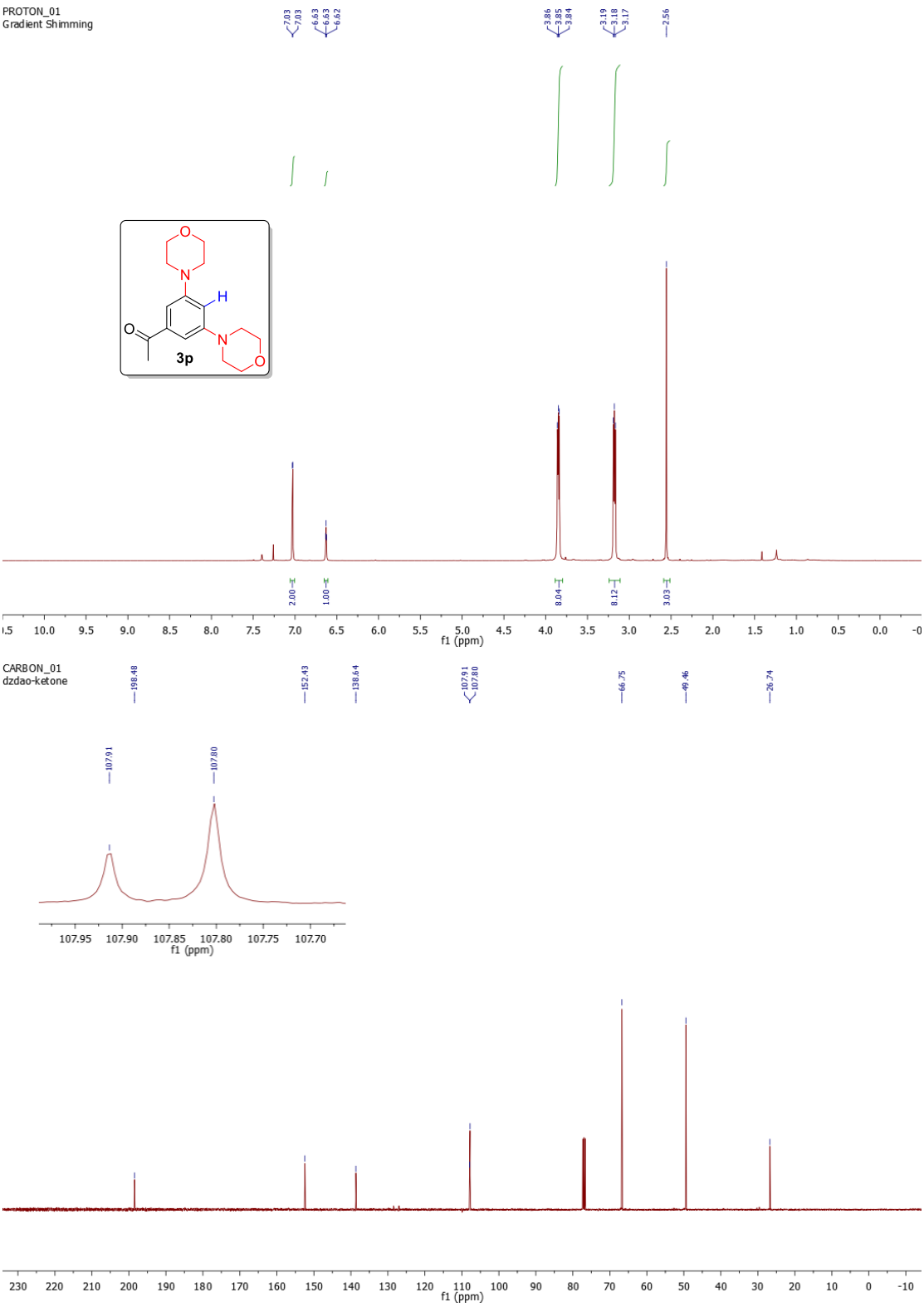


Figure 2.23 ^{1}H and ^{13}C NMR spectrum of compound **3q**.

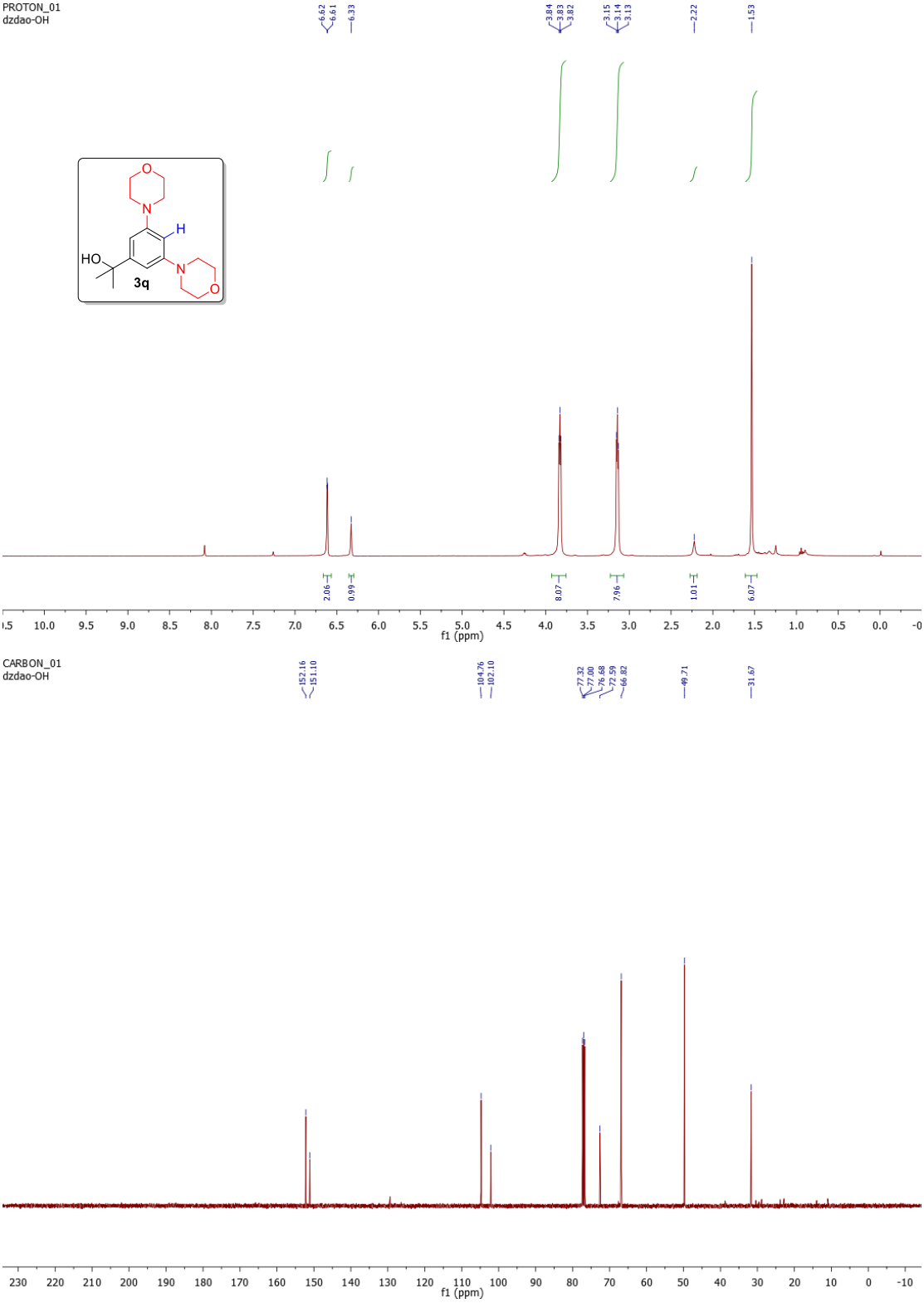


Figure 2.24 ^{1}H and ^{13}C NMR spectrum of compound **3r**.

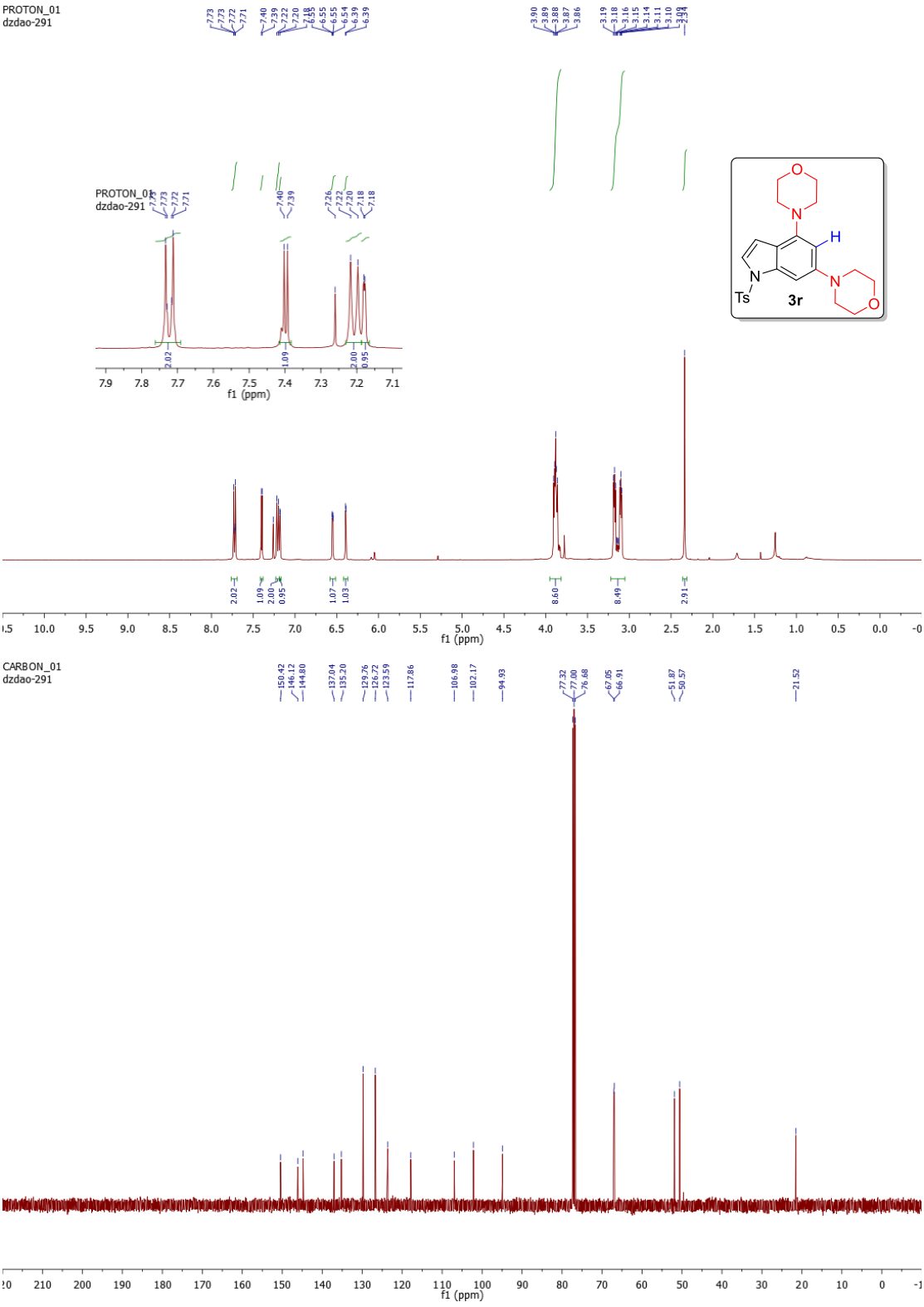


Figure 2.25 ^{1}H and ^{13}C NMR spectrum of compound **3s**.

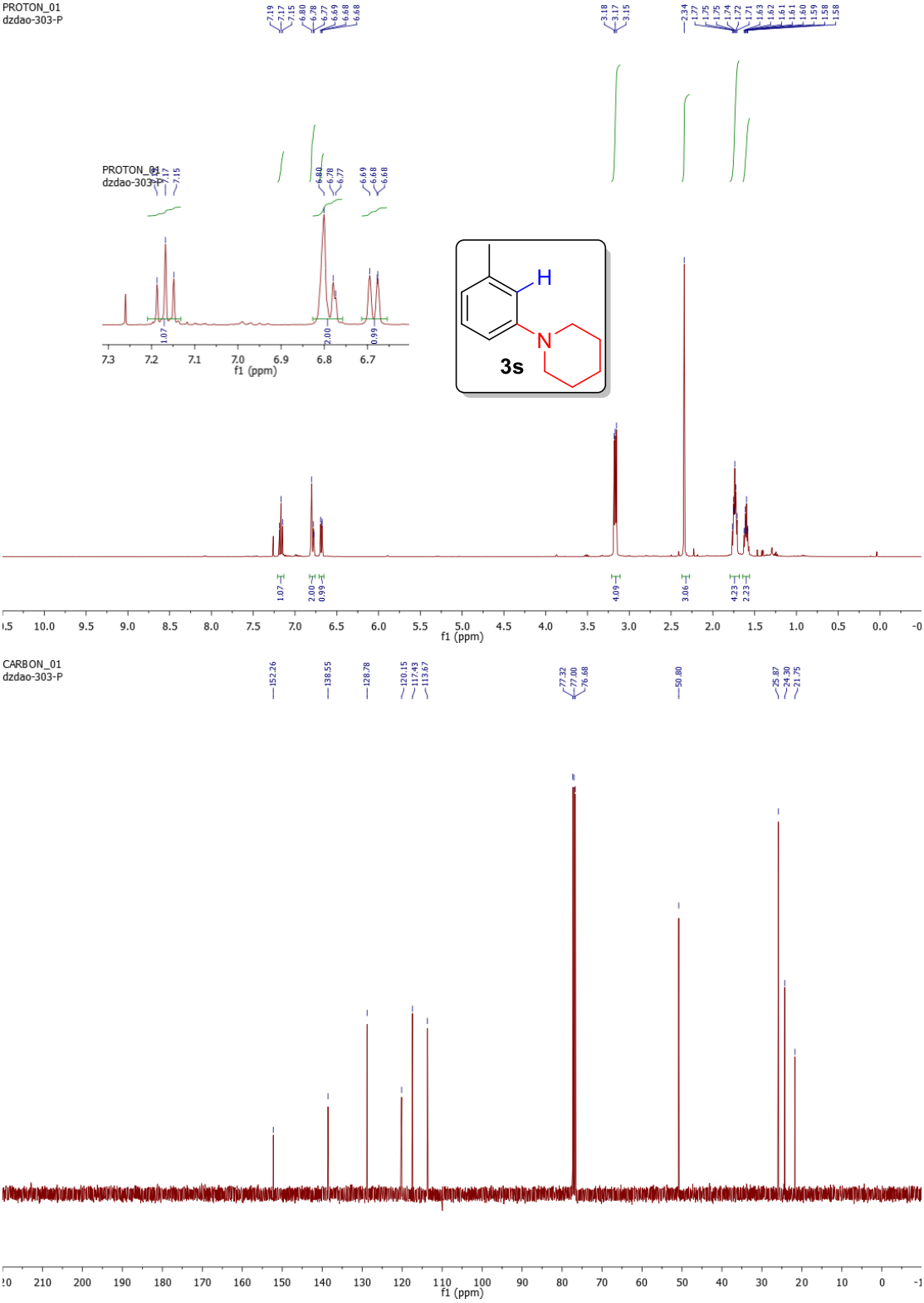


Figure 2.26 ^{1}H and ^{13}C NMR spectrum of compound **3t**.

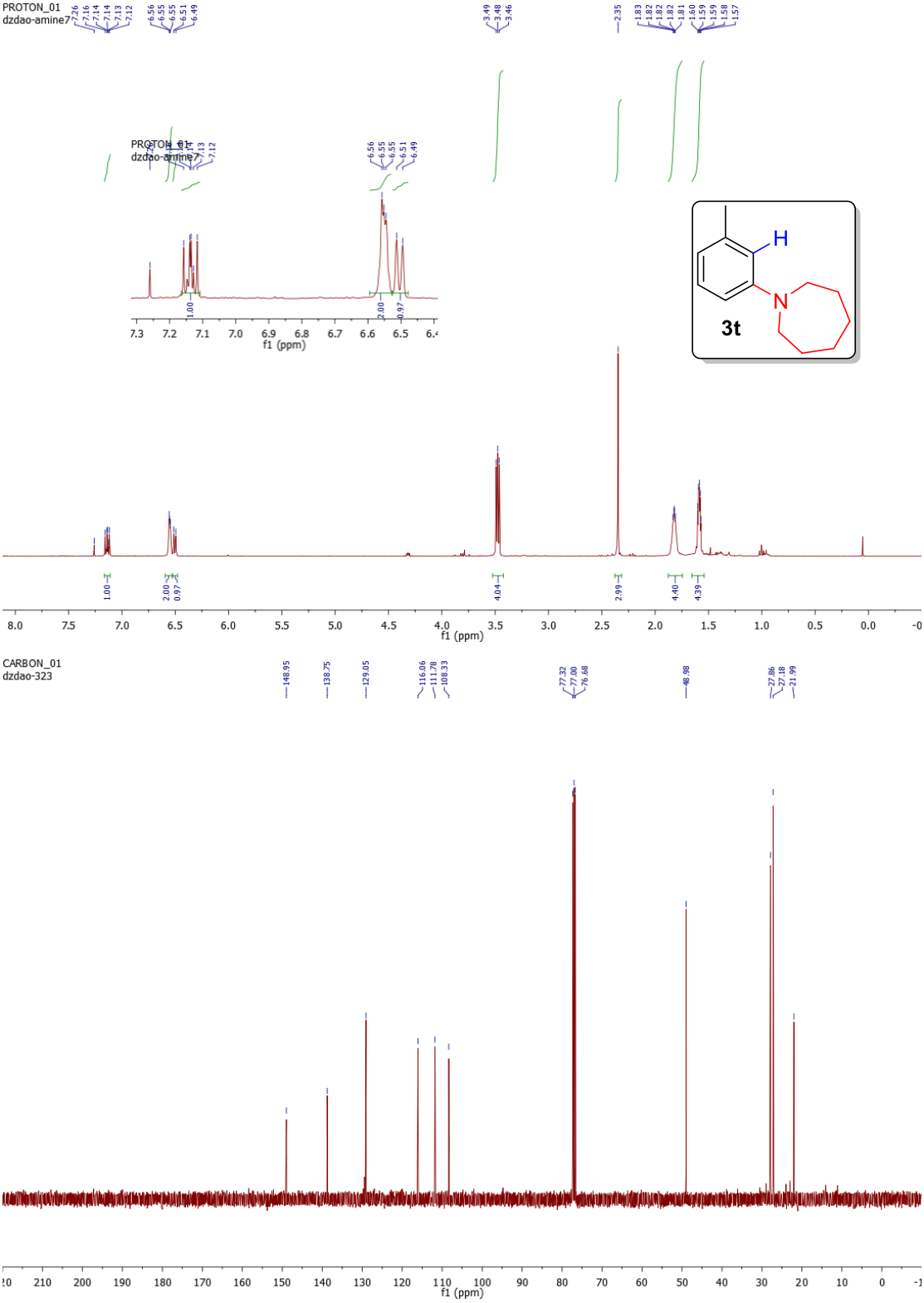


Figure 2.27 ^{1}H and ^{13}C NMR spectrum of compound **3u**.

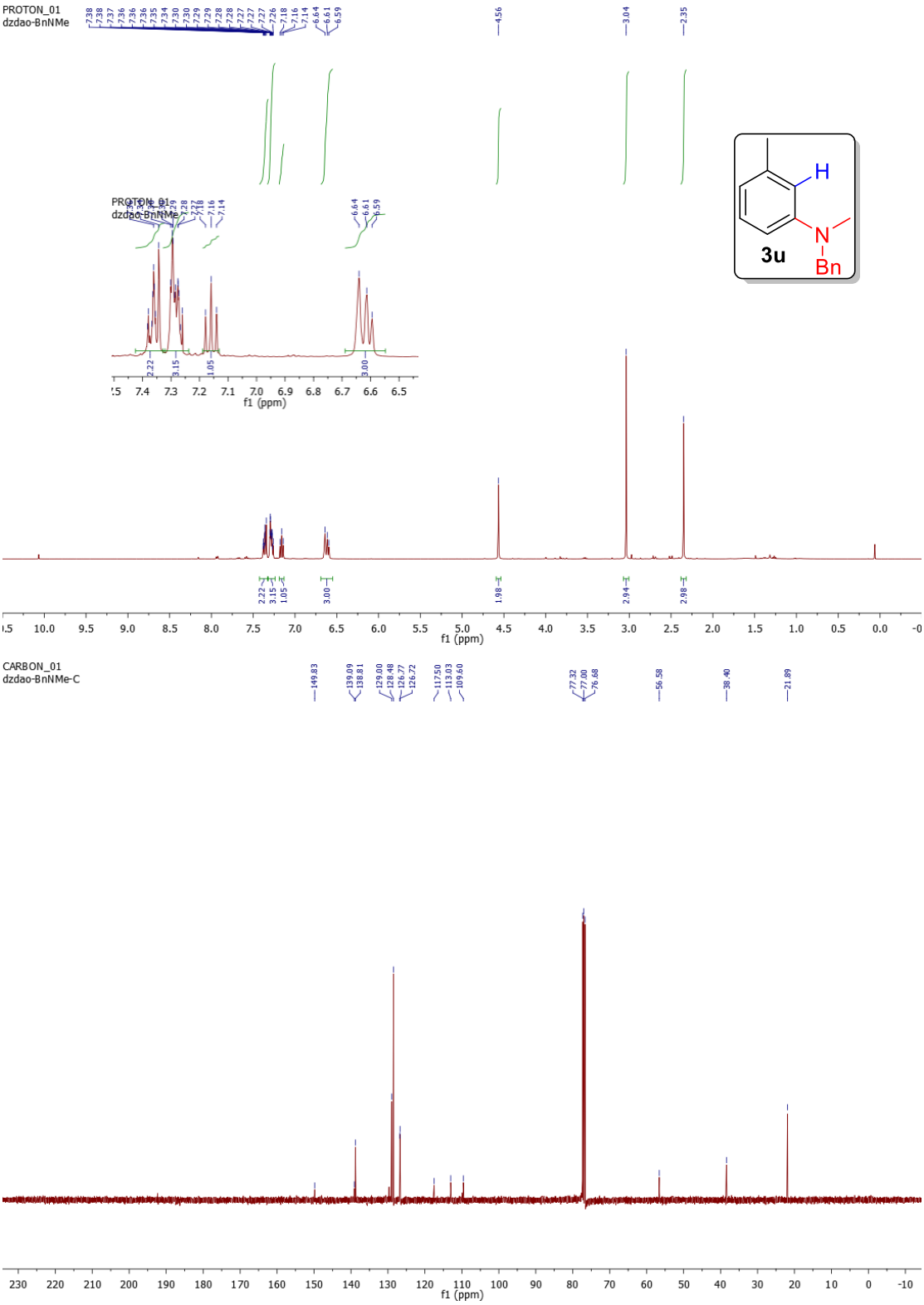


Figure 2.28 ^{1}H and ^{13}C NMR spectrum of compound **3v**.

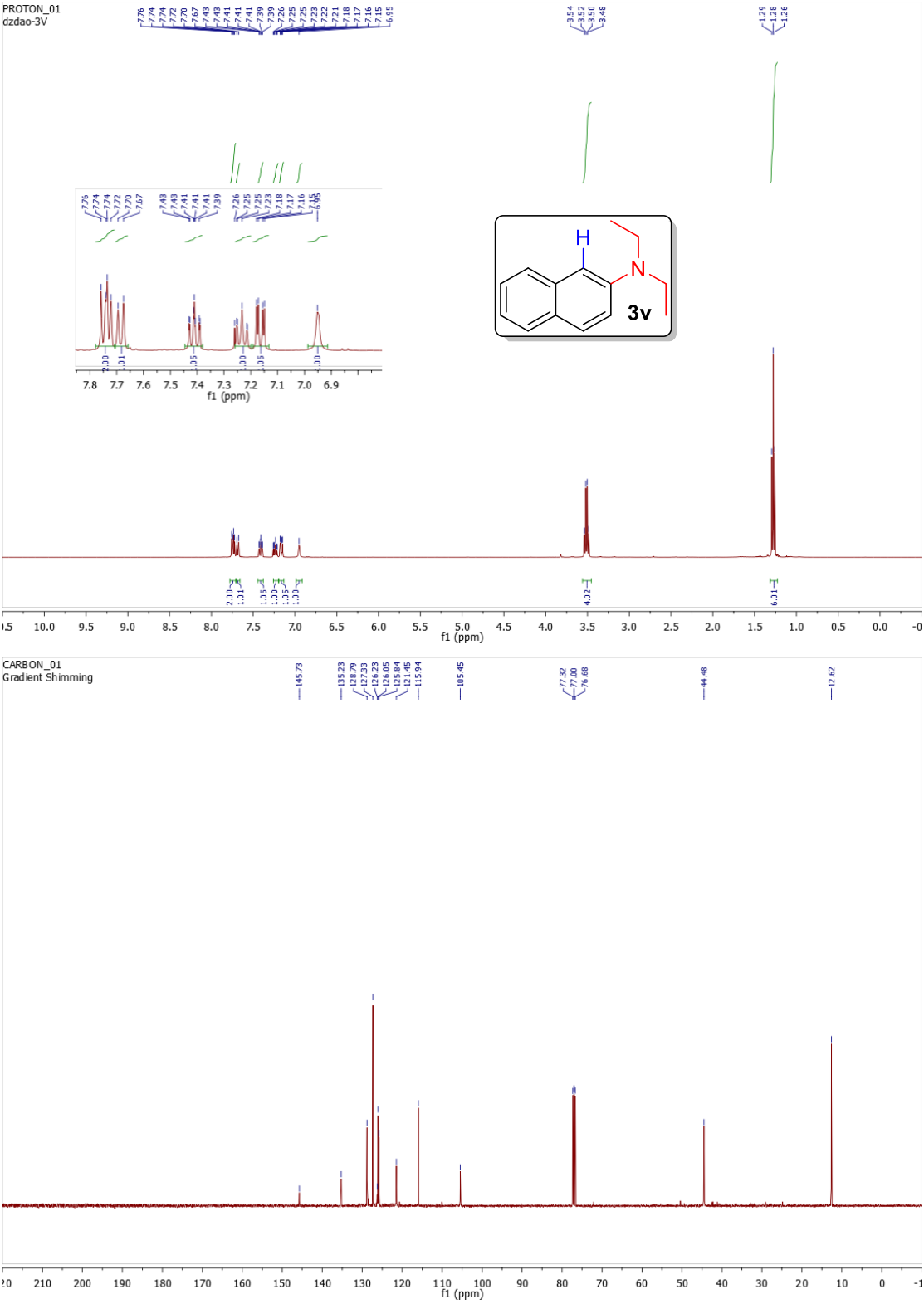


Figure 2.29 ^{1}H and ^{13}C NMR spectrum of compound **3w**.

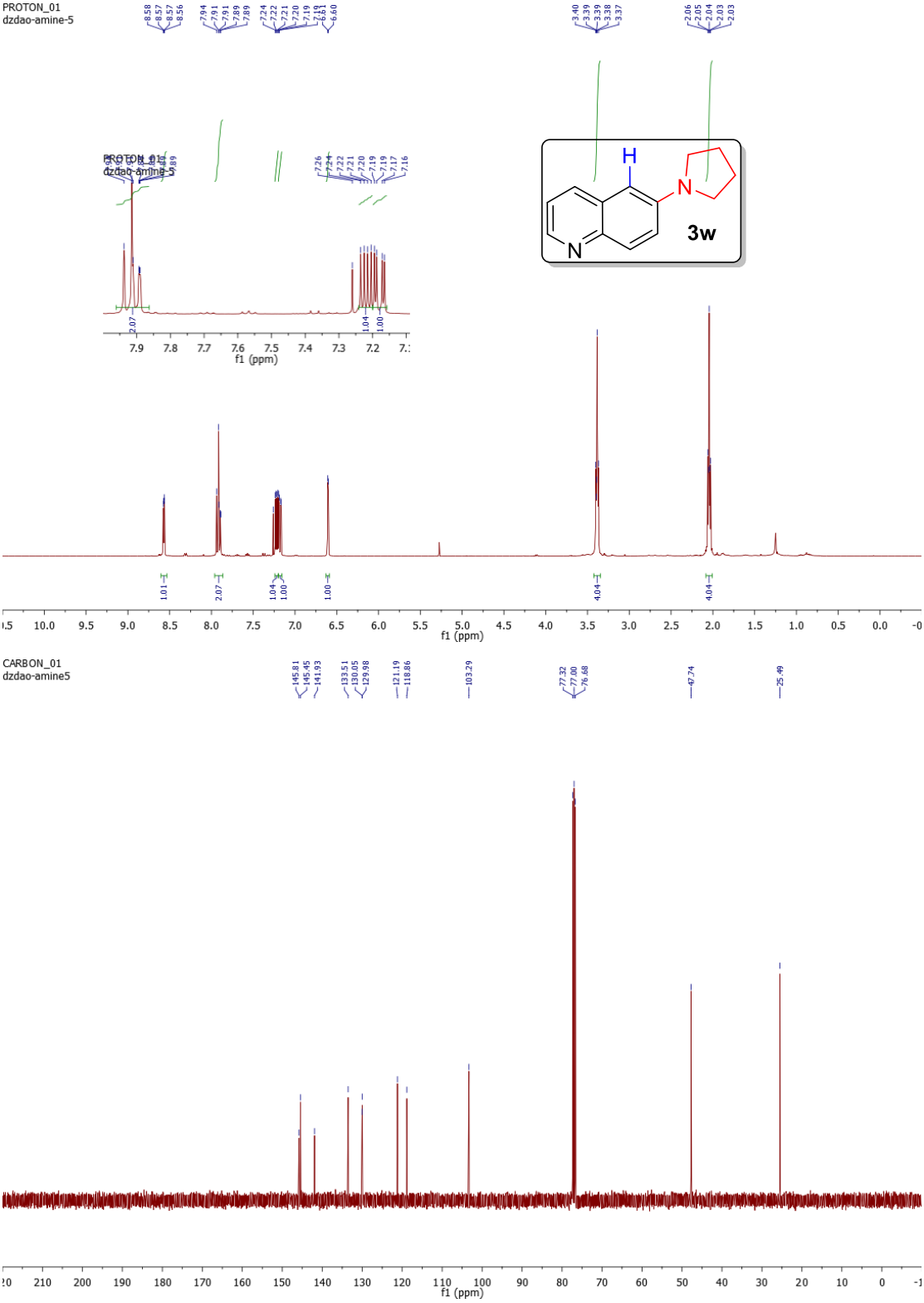


Figure 2.30 ^{1}H and ^{13}C NMR spectrum of compound **3x**.

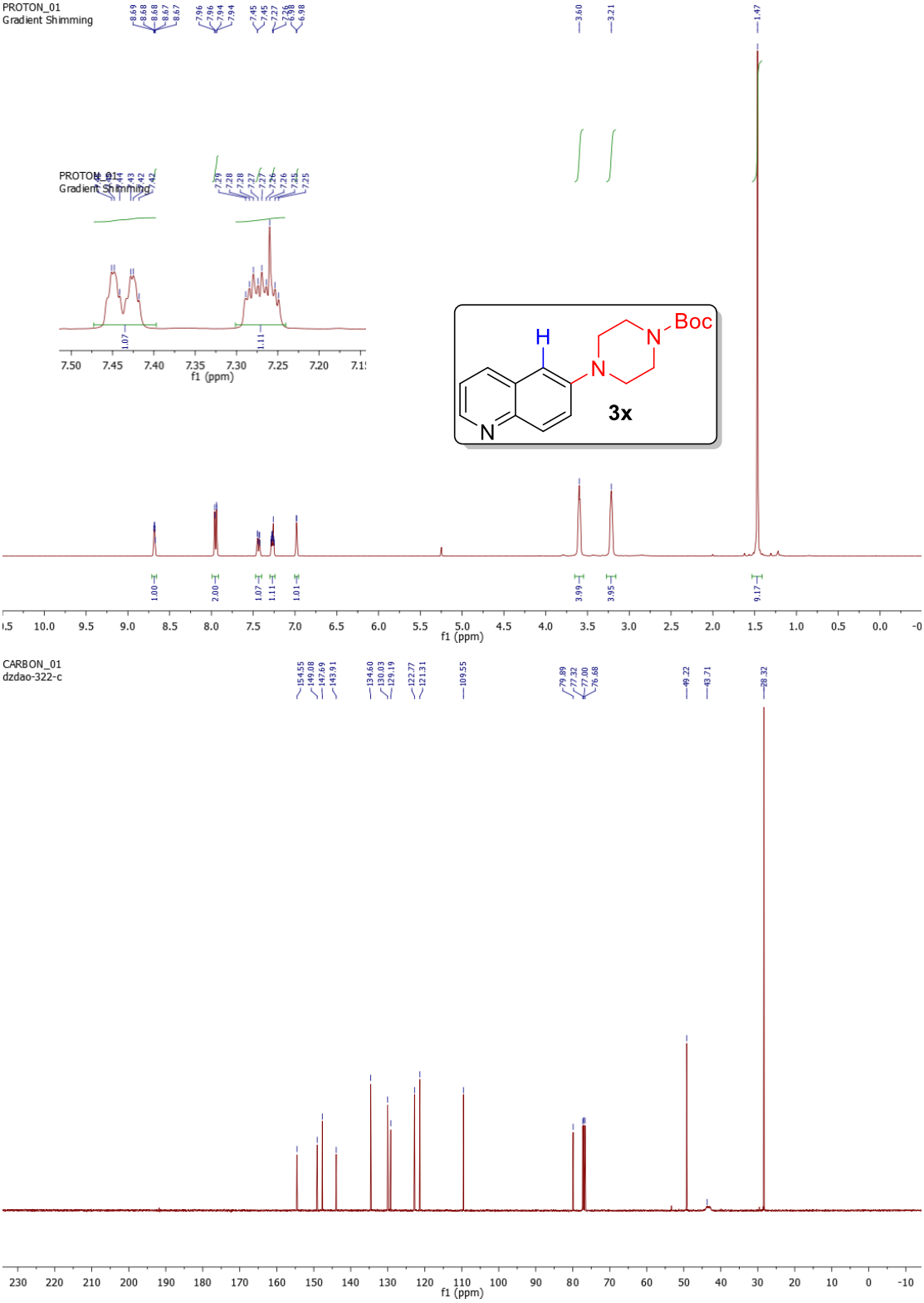


Figure 2.31 ^{1}H and ^{13}C NMR spectrum of compound **7**.

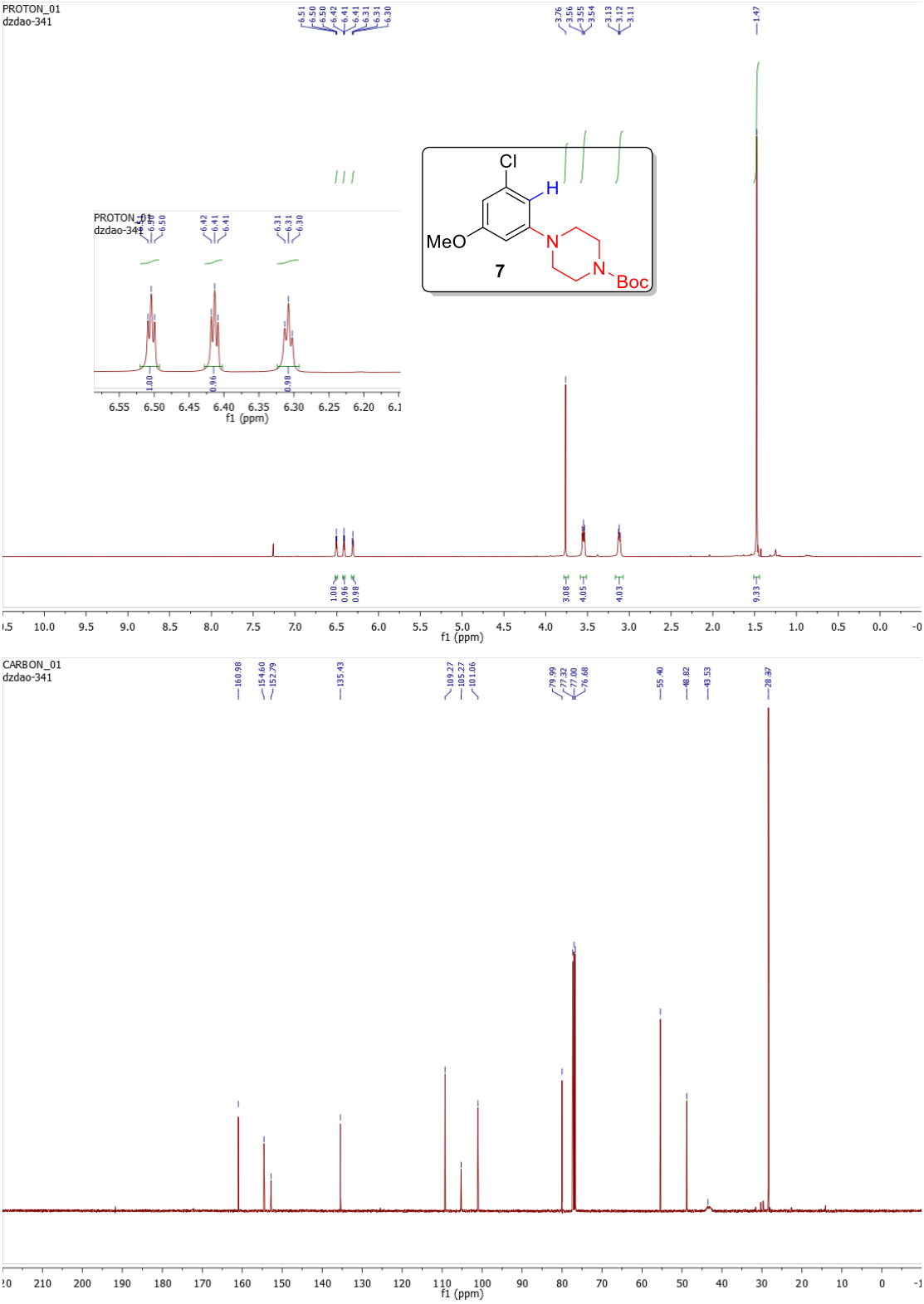


Figure 2.32 ^{1}H NMR spectrum of compound **3f'**.

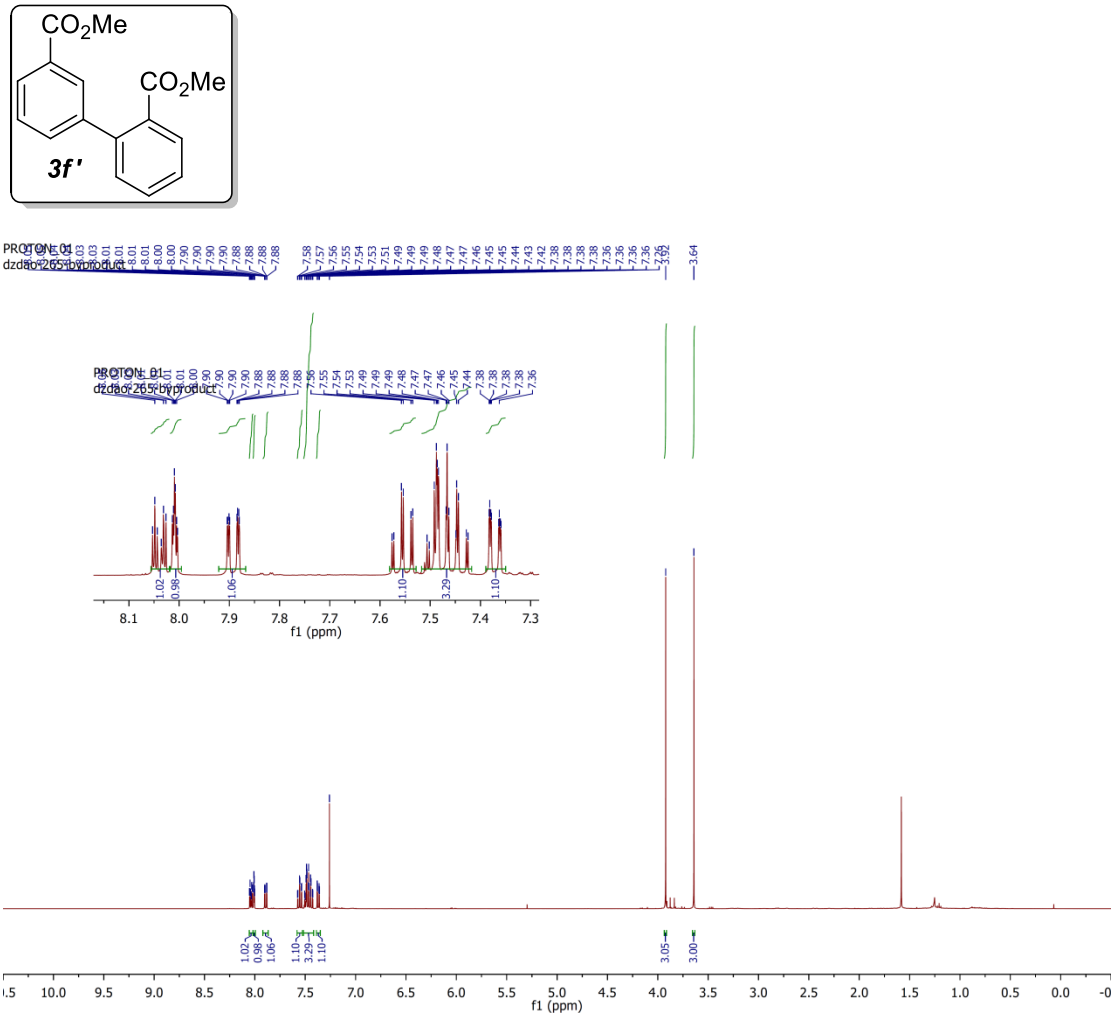


Figure 2.33 ^{1}H and ^{13}C NMR spectrum of compound **D-3j**.

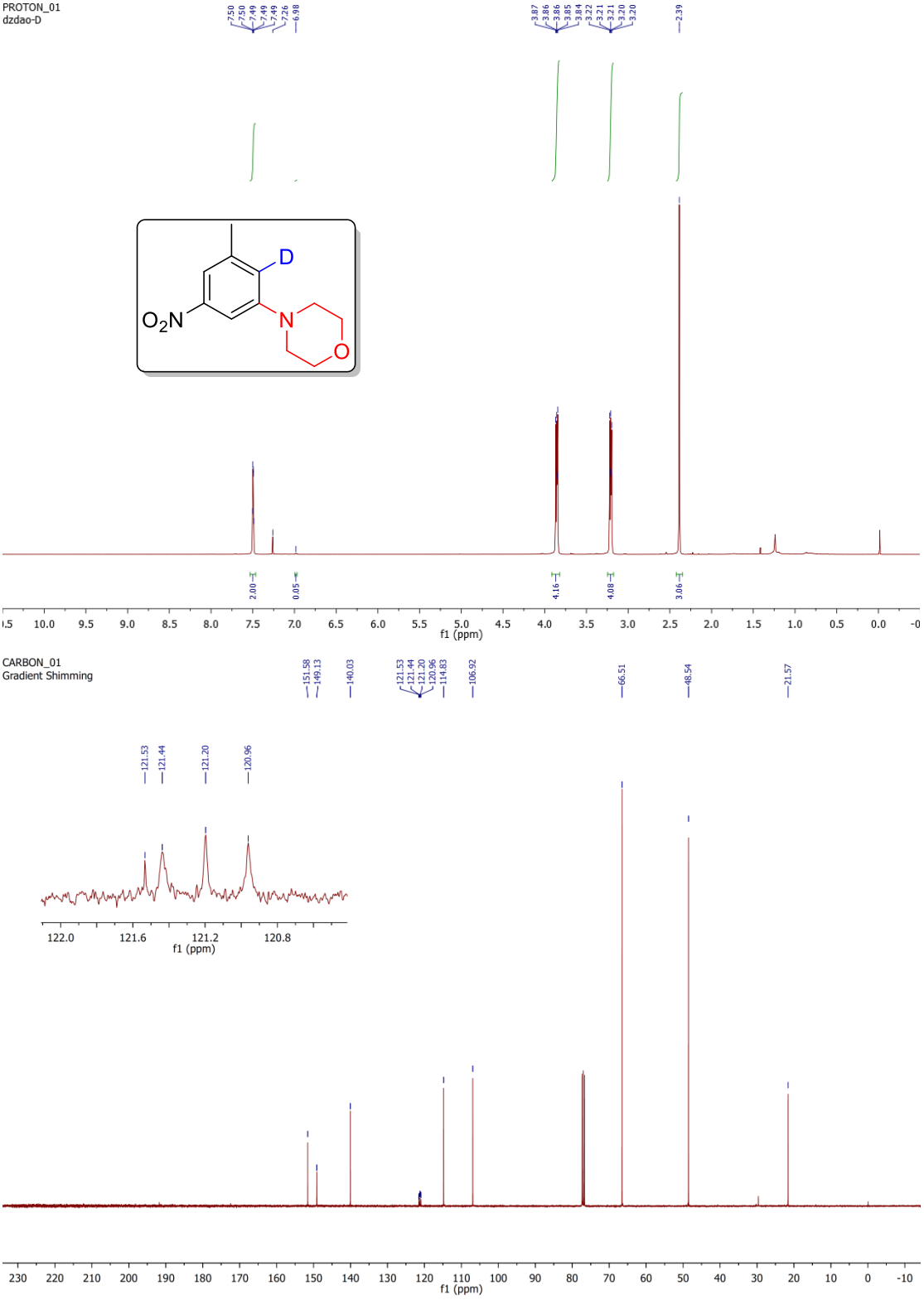
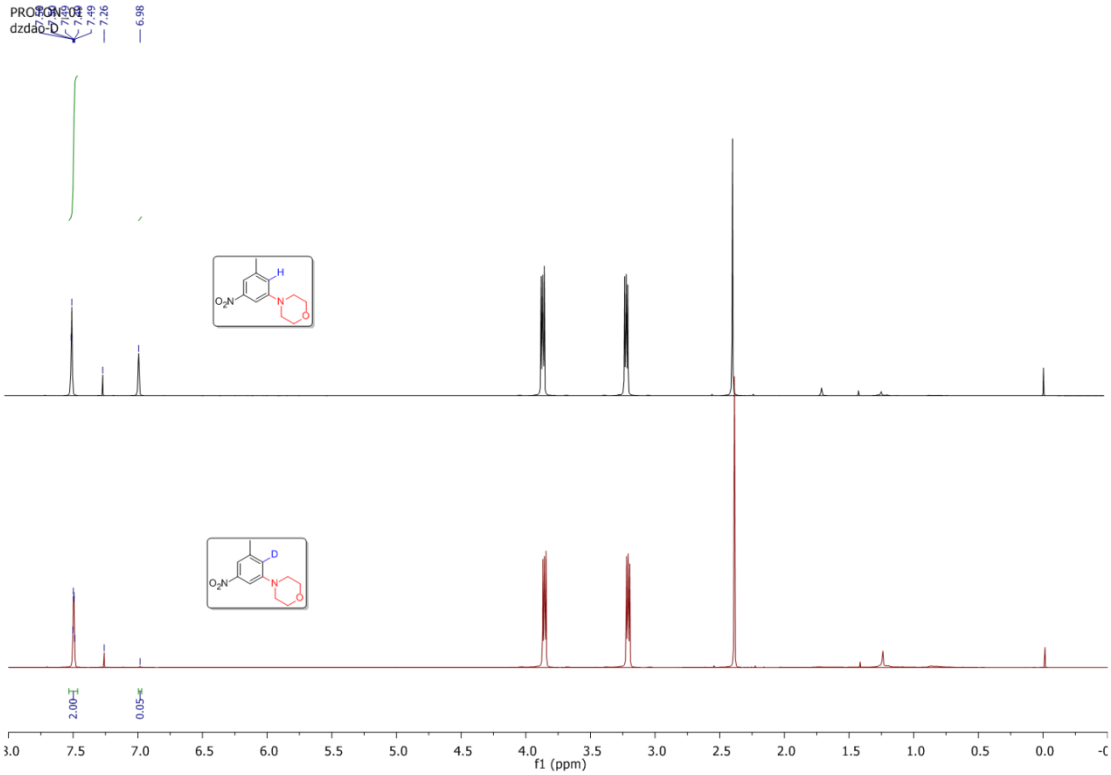


Figure 2.34 ^{1}H NMR spectrum comparison of compound **D-3j** and **3j**.



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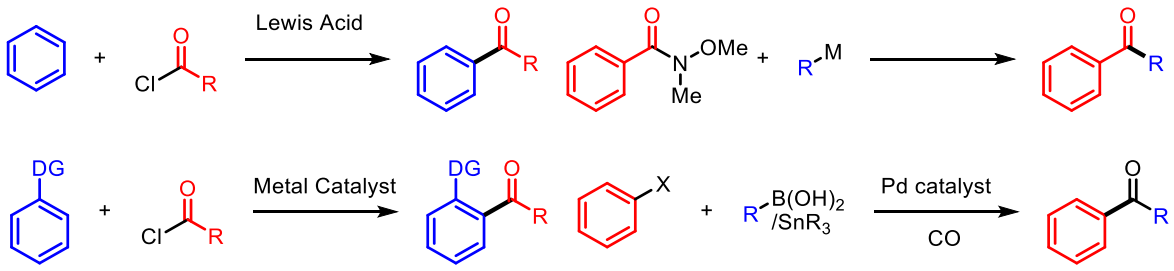
Chapter 3: Palladium and Norbornene Catalyzed *ortho*-Acylation of Aryl Iodide

3.1 Introduction

Aromatic ketones are widely found in pharmaceuticals,[1-2] agrochemicals,[3] organic electrons[4-5] and polymers.[6-8] They have also played a critical role as dyes,[9] photo-labels[10-11] and photo-sensitizers.[6,12-13] The aromactic carbonyl group work as a generic synthon for those compounds containing benzylic functionality. Conventionally, aryl ketones are synthesized via Friedel−Crafts acylation[14-16] of arenes with strong Lewis acids. Generally, its site-selectivity is dominated by the electronic-preference of the substrates. Addition of aryl nucleophiles to carbonyl compounds[17-30] and carbonylative cross-couplings[31-33] represent two effective methods to prepare aryl ketones from pre-functionalized arenes (e.g. aryl halides) to give *ipso*-substituted products (Scheme 3.1). Transition-metal-catalyzed arene C−H activation-acylation offers a distinct approach, but use of a directing group[34-47] is usually critical. Directing group strategy usually only gave the *ortho*-acylation product. (Scheme 3.1).

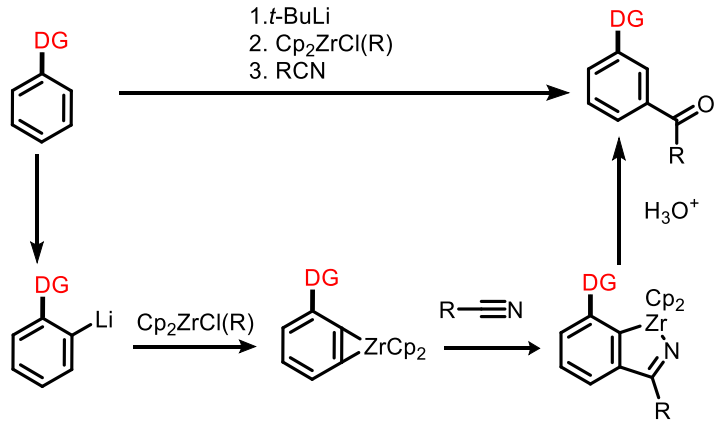
Scheme 3.1. Different directing modes in aromatic palladation.



3.2 BACKGROUND

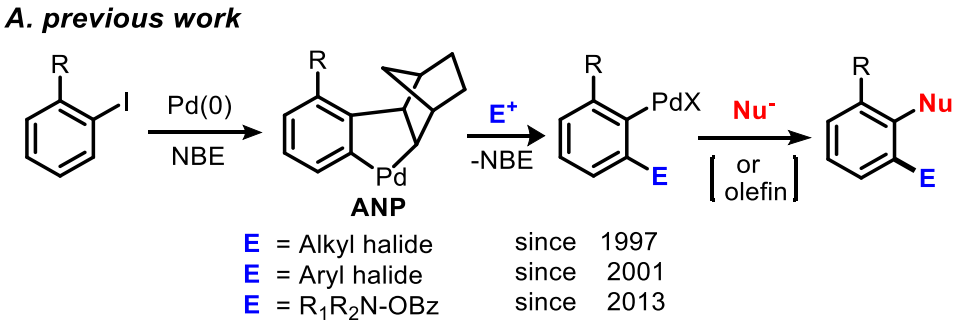
The pioneering work by Buchwald and co-workers demonstrate that the *meta*-substituted aryl ketone can be synthesized through the zirconium mediated 1,2-addition to the nitriles.[48] Although the reaction had an excellent regio-selectivity; but harsh reaction condition limited its synthetic application. (Scheme 3.2)

Scheme 3.2 Zirconium mediated *meta*-selective arene C-H acylation.



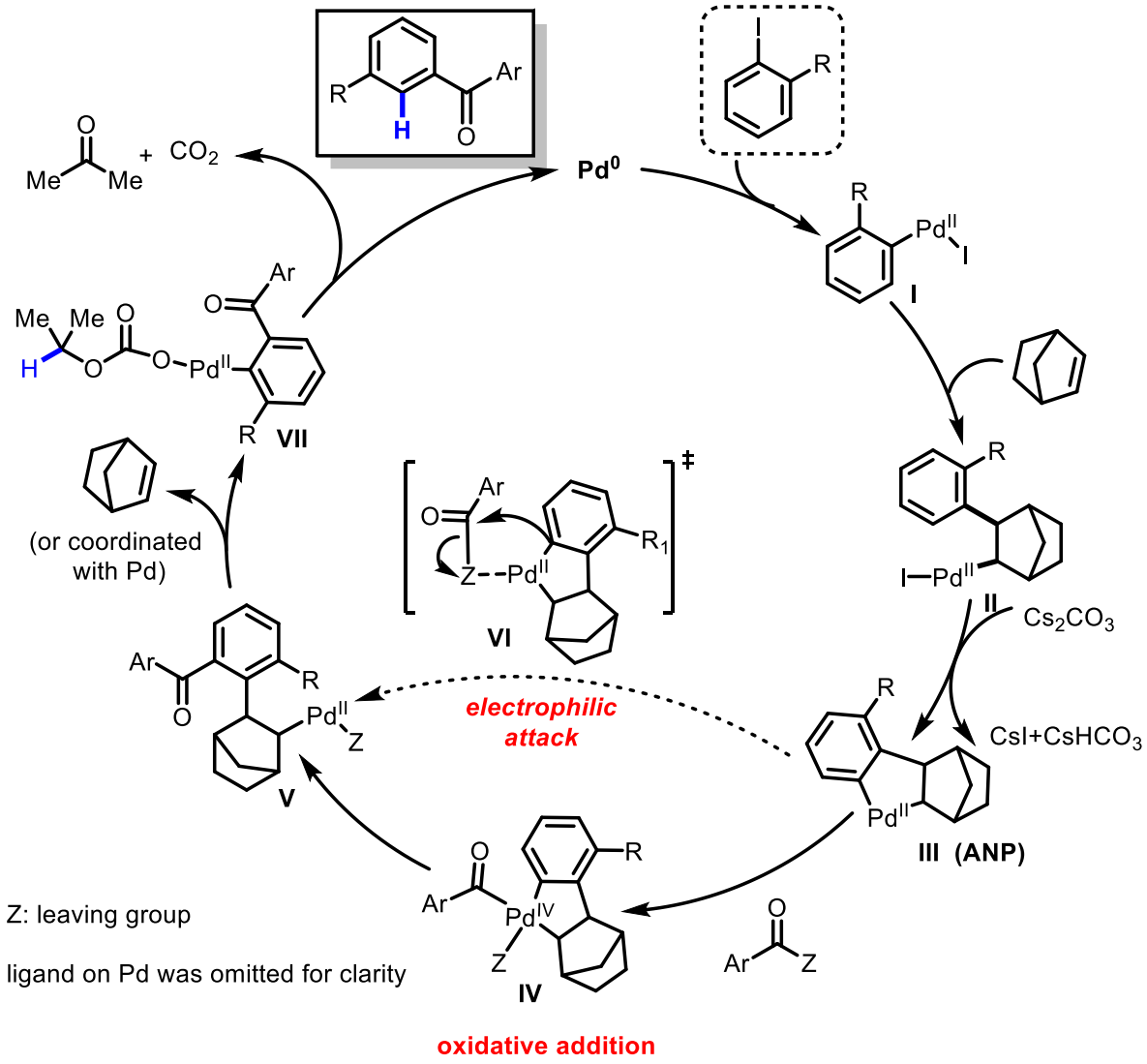
Due to the wide availability of aryl halides, here, a complementary strategy for aryl-ketone synthesis was sought through introducing an acyl group to the *ortho* position of iodoarenes with palladium/norbornene (NBE) catalysis. Up to this method was developed, palladium/norbornene (NBE) catalysis could only introduce alkyl group, aryl group and amine group at the *ortho* position. (Scheme 3.3)

Scheme 3.3 Palladium/norbornene catalysis.



The Pd/NBE chemistry, originally discovered by Catellani,[49-53] allows functionalization of both *ipso* and *ortho* positions of aryl halides in one catalytic circle. The proposed mechanism is shown in the Scheme 3.4.[51-54] This reaction is initiated by Pd(0) oxidative addition into the Ar−X bond,[55-58] followed by a NBE-mediated vicinal C−H metalation to generate a unique electron-rich aryl-NBE-palladacycle (**ANP**),[59] which can react with an electrophile to introduce a functional group (FG) at the *ortho* position.[60] Subsequent de-insertion of NBE through β-carbon elimination gives back an aryl-palladium (Ar−Pd−X) species, which can then be trapped by a nucleophile (or an olefin) to furnish the *ipso* functionalization and meanwhile regenerate the Pd(0) catalyst.[49] Seminal work by Catellani and Lautens,[49-50,61-70] showed a variety of FGs can be installed at the *ipso*-carbon by choosing different nucleophiles; however, functionalization at the *ortho* position was previously restricted to alkylation and arylation.[49,71-72] Recently, *ortho* amination was realized by using *N*-benzoyl-oxyamines as the reagent.[73-78] Nevertheless, introduction of other FGs at the *ortho* position remains challenging, mainly due to the difficulty of selective oxidation of the **ANP** intermediate versus the initial Pd(0) catalyst. The key to achieve the ortho acylation of the aryl iodide is found the right electrophilic acylating reagent.

Scheme 3.4 Proposed catalytic cycle for palladium/norbornene catalysis.

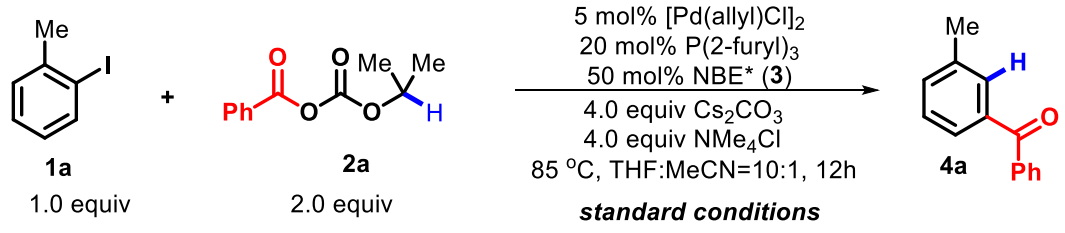


3.3 Reaction Development and Scope

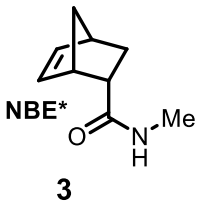
We hypothesized that a properly masked "acyl cation" could selectively react with the electron-rich **ANP** intermediate to form the *ortho* aryl−acyl bond through either a Pd(IV) intermediate or direct electrophilic substitution (Scheme 3.4). In the presence of a suitable hydride source, hydrogen would be introduced at the *ipso* position to complete the *ortho* acylation; meanwhile, Pd(0) would be regenerated. To examine this hypothesis, benzoyl chloride and

anhydride were employed as the initial acyl source; isopropanol was used as the hydride source due to our previous success with this reductant.[73] Not surprisingly, this combination in the presence of a base led to severe esterification without producing any desired *ortho* acylation product.[79] Survey of other common hydride sources, such as formate salts,[65] alky boronic acids[80-81] and tributyltin hydride, was unfruitful. Thus, in contrast to the previous reductive *ortho* amination reaction,[73] the compatibility between the acyl electrophile and the reductant became a new challenge. The key is how to produce the hydride for palladium in the absence of massive alcohol nucleophiles. To address the aforementioned challenge, a unique isopropyl carbonate anhydride (**2a**), available in one step from the corresponding carboxylic acid,[82-83] was sought as a bifunctional reagent. The expected benefits are two-fold: 1) the isopropoxide was masked in the form of a carbonate, thus minimizing the esterification side reaction; 2) the reagent contains both the acyl electrophile and hydride source in a single molecule, thus the operation is simplified. Indeed, using **2a** as the coupling partner, the desired *ortho* acylation product (**2a**) can be obtained in up to 76% yield when using $[Pd(allyl)Cl]_2$ and tri(2-furyl)phosphine as the metal/ligand combination (entry 1, Table 3.1). A series of control experiments indicated palladium, phosphine ligand,[62] NBE and base were all essential for this transformation (entries 2-4 and 6). While simple NBE can promote the desired transformation (entry 5), use of an amide-substituted NBE (**3**, NBE*) was found to give enhanced yield and importantly ease isolation of the desired product from NBE-containing byproducts.[84] The use of NMe_4Cl as an additive is not critical (entry 7), but was found beneficial to reduce side reactions involving reduction of the **ANP** intermediate.[85]

Table 3.1 Control experiments for *ortho* acylation



entry	change from the standard condition	yield (%)[a]
1	none	76
2	no $[Pd(allyl)Cl]_2$	0
3	no $P(2\text{-furyl})_3$	0
4	no **3**	0
5	norbornene instead of **3**	73
6	no Cs_2CO_3	0
7	no NMe_4Cl	60
8	$Pd(OAc)_2$ instead of $[Pd(allylCl)]_2$	69
9	PPh_3 instead of $P(2\text{-furyl})_3$	28
10	K_2CO_3 instead of Cs_2CO_3	12
11	pure THF as solvent	63
12	60 °C[b]	56

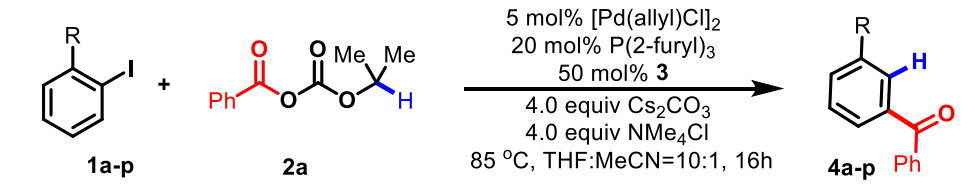


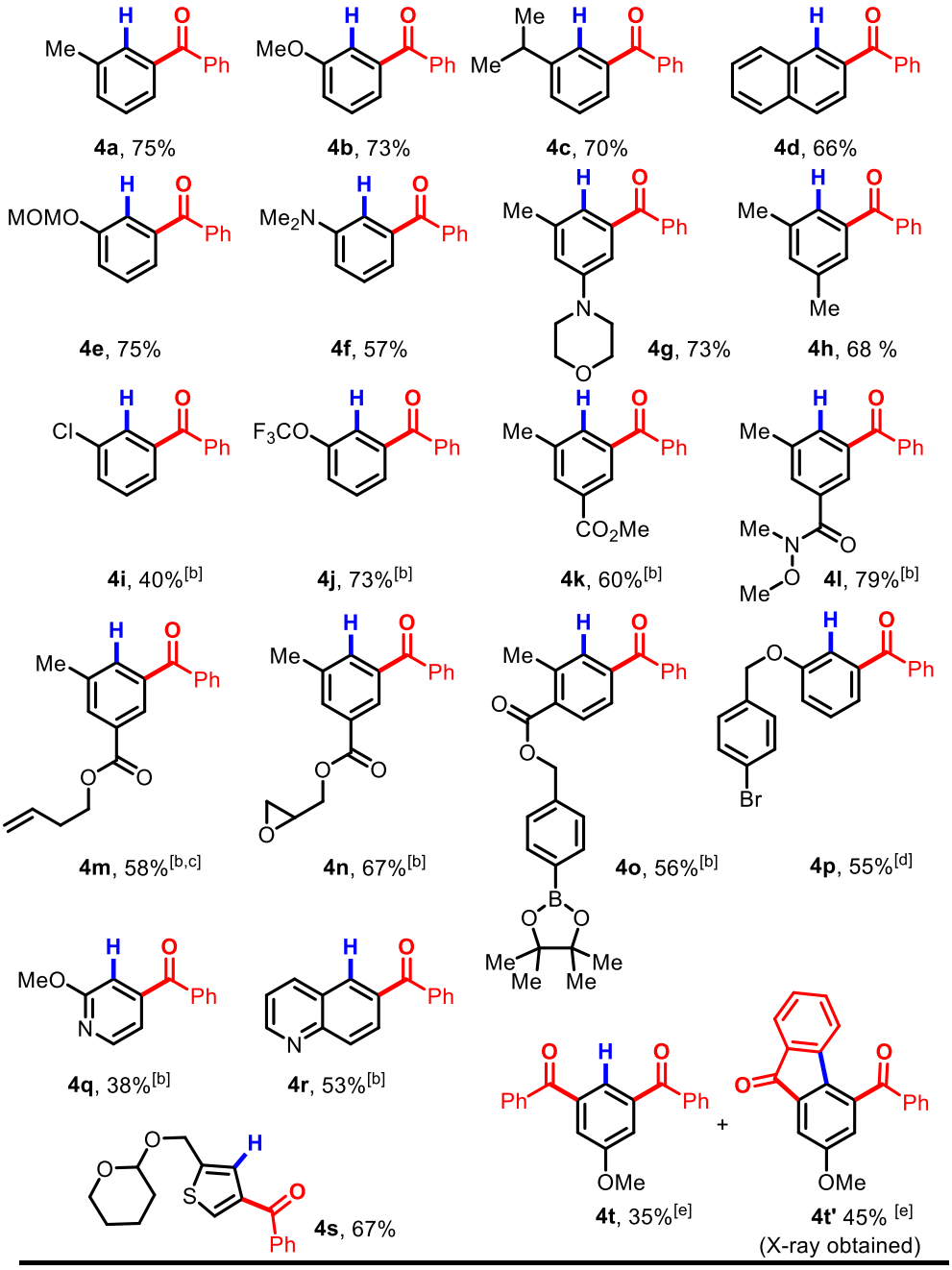
3

[a] Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard. [b] Run for 40 hours.

Among all the phosphine ligands tested, the more electron-deficient tri(2-furyl)phosphine gave the optimal results (entry 9).[62] Use of potassium carbonate as base dramatically decreased the yield (entry 10). Addition of acetonitrile as a minor co-solvent is expected to assist de-chelation of the ketone carbonyl from the palladium intermediate; in pure THF the yield was lower[86] (entry 11). Finally, the reaction can still proceed at 60°C albeit requiring a longer time (entry 12).

Table 3.2 Substrate scope with different aryl iodides[a]





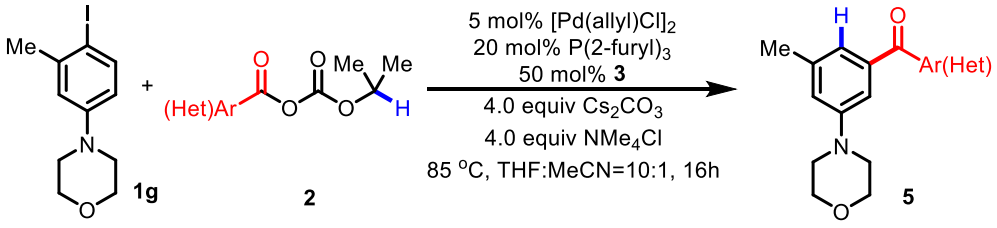
[a] All yields are isolated yields. [b] 70°C for 20h without CH_3CN and NMe_4Cl; 1.5 equiv of **3.2a** and 2.0 equiv of Bz_2O were used. [c] 1.0 equiv of NBE* **3.3** was used. [d] 2.0 equiv of Bz_2O and 1.05 equiv of $ClCO_2{}^iPr$ were used instead of **3.2a** and NMe_4Cl. [e] 1.5 equiv of **3.2a** and 2.0 equiv of Bz_2O were used.

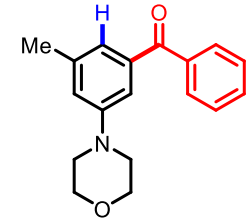
The scope of aryl iodides was examined first (Table 3.2). Gratifyingly, aryl iodides with various electron properties reacted well to afford the *meta*-substituted aryl ketones.[48] When electron-deficient aryl iodides were used, additional benzoyl anhydride and lower reaction temperature were required to prevent homo-dimerization.[12b] Moreover, reactions with these substrates gave higher yields in the absence of acetonitrile. *Excellent functional group tolerance* was observed: methyl (**4a**), benzyl (**4p**) and trifluoromethyl ethers (**4j**), MOM-protected phenols (**4e**), tertiary amines (**4f**), THP-protected alcohols (**4s**), ester (**4k**), aryl chlorides (**4i**) and *bromides* (**4p**), *Weinreb amides* (**4l**), *terminal olefins* (**4m**), *epoxides* (**4n**) and *arylboronic acid pinacol esters* (**4o**) were all tolerated. Furthermore, heteroaryl iodides such as pyridine, thiophene and quinoline derivatives (**4q**-**4s**), are also suitable substrates, implying a good potential for pharmaceutical applications. The low yield of nitrogen containing heteroarene may be due to the undesired decomposion of reagent **2a** which was cataylzed by iodo-pyiridine/quinoline itself.

For non-*ortho*-substituted aryl iodides (e.g **4t**), double *ortho* acylation was predominant giving 1,3-diacylated arenes; Interestingly, a tandem cyclilaztion product (**4t'**) was also isolated in this case, giving a 9-fluorenone derivative. The detailed reason for this further cyclization was clear at

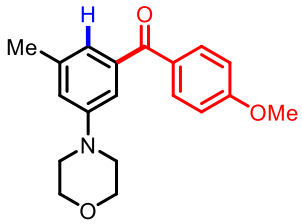
this stage. We proposed this futher C-H activation was promoted by the neighbouring ketone group.

Table 3.3 Substrate scope with carbonate anhydrides[a]

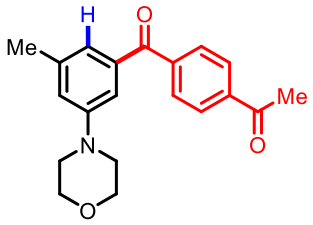




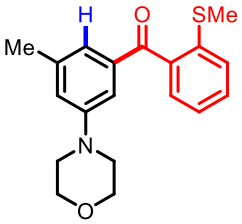
4g, 73%



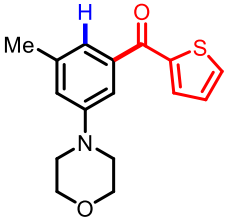
5b, 68%



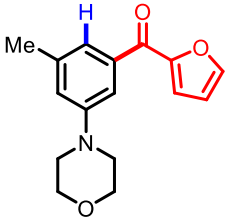
5c, 40%



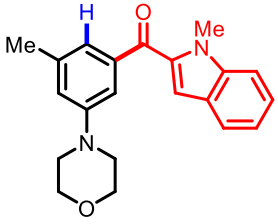
5d, 67%



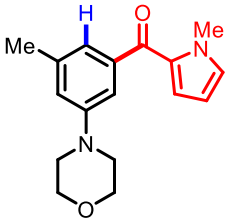
5e, 71%



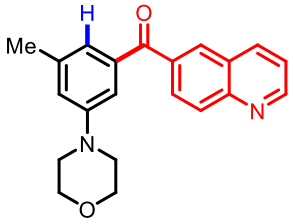
5f, 40%



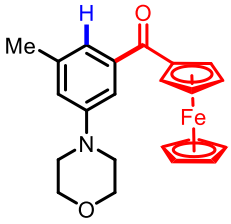
5g, 63%



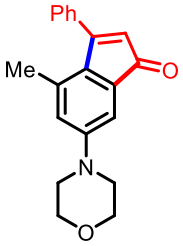
5h, 53%



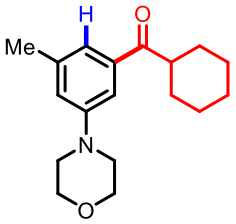
5i, 56%



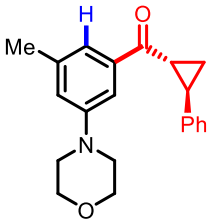
5j, 86%



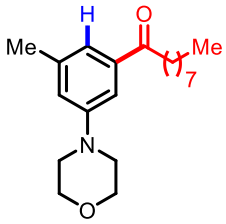
5k, 85%



5l, 66%



5m, 69%

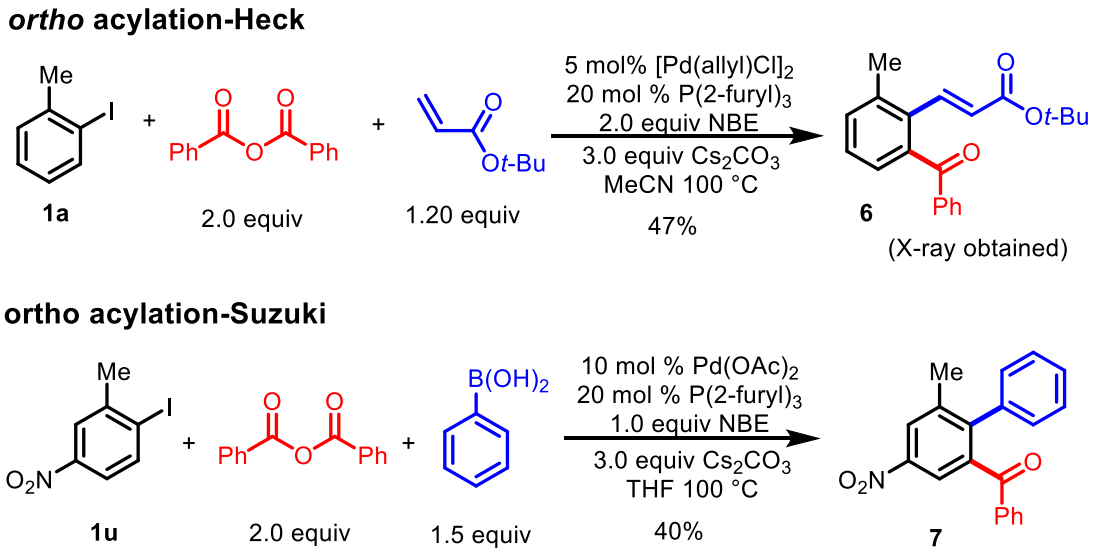


5n, 19%

[a] All yields are isolated yields.

Next, the scope of anhydrides was explored (Table 3.3). A variety of isopropyl carbonate anhydrides were prepared rapidly in a single step from the corresponding carboxylic acids and commercially available isopropyl chloroformate. Both electron-rich and deficient aryl anhydrides worked under the standard conditions (**5b** and **5c**). Enolizable methyl ketone and *ortho* thioether (**5d**), are compatible. Anhydrides derived from heteroarenes, such as thiophene (**5e**), furan (**5f**), *N*-methyl indole (**5g**), pyrrole (**5h**), quinoline (**5i**), and ferrocene (**5j**), all successfully coupled in moderate to good yields. Surprisingly, the alkenyl anhydride preferred to give a cyclized product (**5k**), although the reason is unclear. The alkyl carboxylic acid derivatives also afforded the desired acylation products **5l-5n**. We proposed that low yield of primary carboxylic acid regeant was due to the quick elimination to form the ketene under basic reaction condition.

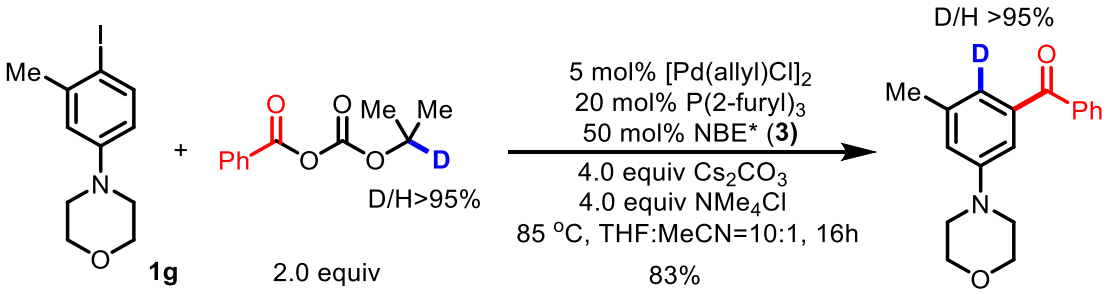
Scheme 3.5 Coupling with ipso functionalization



To further explore the reaction scope, we found other functional groups beside hydrogen can also be introduced at the *ipso* position, which is paralleled with standard Pd/NBE catalysis (Scheme 3.5). Preliminary study indicated that the *ortho* acylation reaction can be coupled with Heck or Suzuki reactions to install a vinyl or aryl group respectively vicinal to the acyl group.[87] Note that, while the aryl-B(pin) moiety is intact under the reaction conditions (*vide supra*, Table 3.1, **4o**), aryl bornic acids can be effectively coupled.[61,88]

To gain mechanistic insights of this reaction, a deuterium-labeling study was performed (Scheme 3.6). When mono-deuterated **2a** was synthesized and tested under the standard reaction conditions, more than 95% deuterium was incorporated at the *ipso* position, which strongly supports the proposed hydride-transfer pathway (Scheme 3.4).

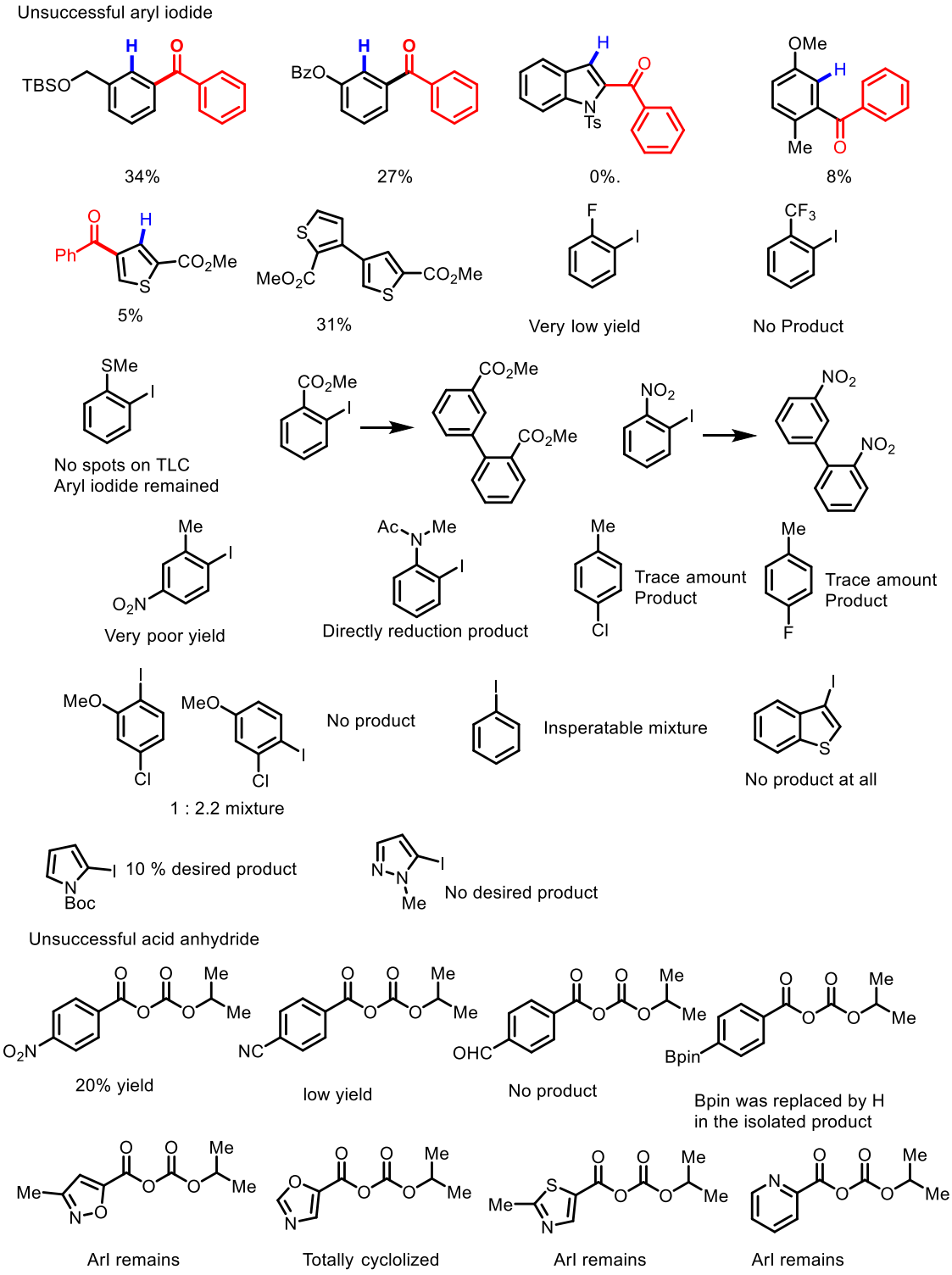
Scheme 3.6 Deuterium labeling at the *ipso* position.



Tables 3 listed the unsuccessful aryl iodide substrate, for hetero-cycle one, the most case the fast directly reduction to arene or reductive heck was the major by-product observed. The electron deficient iodide generally gave cyclobutane or homodimer as byproduct, poor yield was observed for all cases. For the mix-anyhydride part, the electron deficient aromatic anhydride gave low yield. The alkynyl carboxylic acid was not stable once treated with Pd(0) catalyst at room temperature,

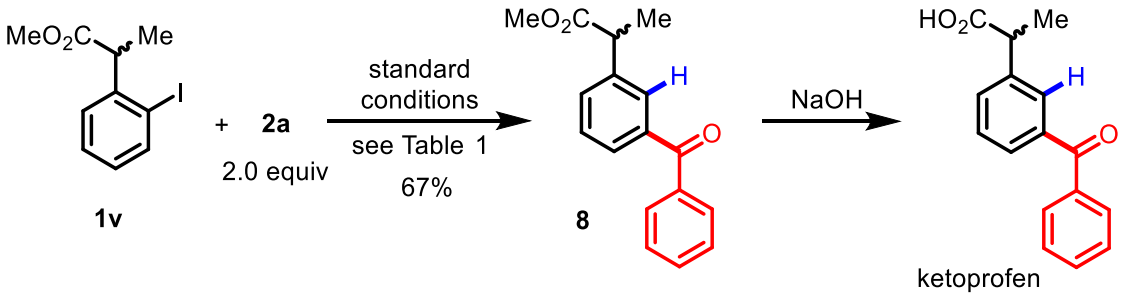
no desired product was observed.

Scheme 3.7 Representative failed examples for *ortho*-acylation reaction.



Finally, the synthetic utility of this method is demonstrated in the concise synthesis of ketoprofen (sold in a racemic form),[89] which is a nonsteroidal anti-inflammatory drug for relieving arthritis-related inflammatory pains or severe toothaches. Starting with readily available iodoarene **1v**,[90-91] reductive *ortho* acylation followed by hydrolysis[92-93] offered a distinct and efficient strategy to access ketoprofen (Scheme 3.8).

Scheme 3.8. Short synthesis of racemic drug ketoprofen.



3.4. CONCLUSION

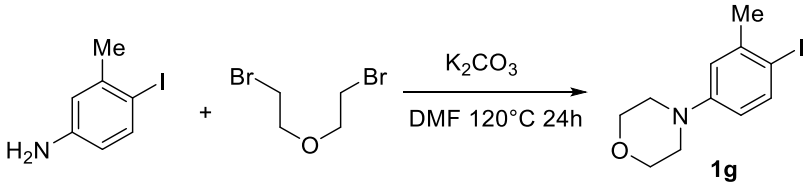
In conclusion, we have developed a reductive ortho acylation method with a wide range of aryl iodides using Pd/NBE catalysis. This transformation introduces an acyl group and a hydrogen atom at the ortho and ipso positions respectively, which is enabled by a bifunctional carbonate anhydride. Broad functional group tolerance was observed; particularly, various heterocycles were found suitable. We expect this mode of reactivity could potentially be generalized allowing for other related ortho functionalization or ortho/ipso difunctionalization.

3.5. Experimental Procedure and Characterization of New Compound

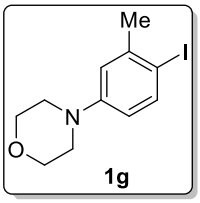
Preparation of aryl-iodide substrates

Aryl iodides **1a**, **1b**, **1c**, **1d**, **1h**, **1i**, **1j**, **1k**, **1q**, and **1t** are all commercially available from Combi-blocks. For those commercial available aryl iodides, they were directly used in the C–H acylation reaction without further purification. Aryl iodide **1e**[94], **1f**[95], **1r**[96], were literature known compounds. These compounds were synthesized via literature reported procedures.

Scheme 3.9 Preparation of compound **1g**.

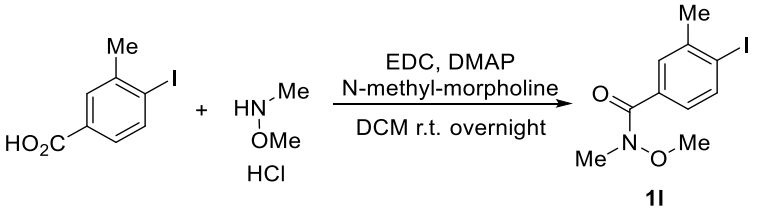


1g was synthesized using a modified procedure: A 250 mL round bottomed flask was charged with 80 mL of *N*,*N*-dimethylformamide, 4-iodo-3-methylaniline (4.66 g, 20.0 mmol, 1.0 equiv) and anhydrous potassium carbonate (8.29 g, 60.0 mmol, 3.0 equiv) under nitrogen atmosphere. To the rapidly stirred mixture was then added 1-bromo-2-(2-bromoethoxy) ethane (5.57 g, 24.0 mmol, 1.2 equiv). The mixture was stirred for 24 hours at 120 ^{o}C. When most of the solvent was evaporated under vacuum, 100 mL water was added to the residue. The aqueous phase were extracted with ethyl acetate (100 mL×3), the combined organic phase were wash with 100 mL brine and dried over $MgSO_4$. The crude product was purified on silica gel (15:1 hexanes/ethyl acetate) to afford **1g** as a pale pink solid (2.43 g, 40%).

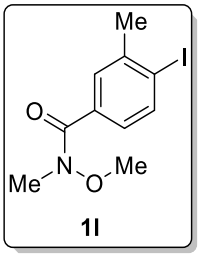


1g : a pink solid; mp=87-88 ºC (1.62 g, 74% yield); R*f*=0.32 (hexane/ethyl acetate=5:1);^{1}H NMR (400 MHz, Chloroform-d) δ 7.63 (dd, *J* = 8.7, 1.4 Hz, 1H), 6.81 (d, *J* = 2.9 Hz, 1H), 6.47 (dd, *J* = 8.7, 2.9 Hz, 1H), 3.84 (m, 4H), 3.16 – 3.08 (m, 4H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 151.43, 141.74, 139.09 , 117.18 , 115.13 , 88.89 , 66.74 , 49.02 , 28.36. IR (KBr): *v* 2961, 2891, 2854, 1588, 1560, 1480, 1449, 1260, 1240, 1189, 1122 cm^{-1}; HRMS (ESI): Calcd for $C_{11}H_{15}INO_2$ ($M+H^+$): 304.0193*;* found: 304.0194.

Scheme 3.10 Preparation of compound **1l**.

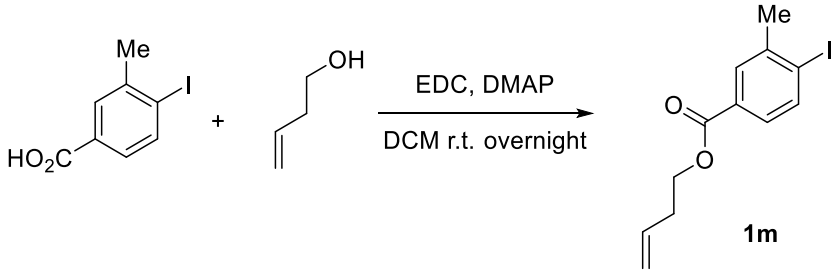


4-iodo-3-methylbenzoic acid (4.0 g, 15.3 mmol) was dissolved in dichloromethane (80 mL). To this solution, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (3.53 g, 18.4 mmol) and *N*-methyl morpholine (1.55 g, 15.3 mmol) followed by *N*,*O*-dimethylhydroxylamine hydrochloride (1.64 g, 16.8 mmol) were added. The reaction mixture was stirred at room temperature for 12 hours. It was diluted with diethyl ether, washed with water and brine, dried over $MgSO_4$, concentrated *in vacuo* and purified on silica gel (hexanes/ ethyl acetate= 10 : 1) to afford **1l** as a colorless oil (3.71 g, 71%).

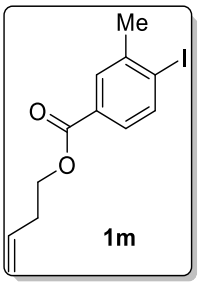


1l : a colorless oil; R*f*=0.28 (hexane/ethyl acetate=1:1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.84 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 1.6 Hz, 1H), 7.18 (dd, *J* = 8.1, 2.1 Hz, 1H), 3.55 (s, 3H), 3.35 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.10, 141.41, 138.57, 134.03, 129.28, 126.85, 104.06, 61.13, 28.07; IR (KBr): *v* 2985, 1799, 1740, 1644, 1592, 1275, 1261, 1201, 1171, 1054, 1014 cm^{-1}; HRMS (ESI): Calcd for $C_{10}H_{12}INO_2Na$ (M+Na^{+}): 327.9805; found: 327.9804.

Scheme 3.11 Preparation of compound **1m**.

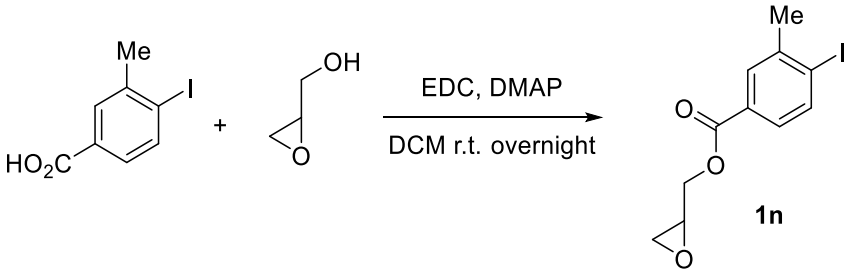


To a solution of 4-iodo-3-methylbenzoic acid (1.50 g, 5.7 mmol, 1.0 equiv) in dichloromethane (40 mL) was added the prop-2-en-1-ol (0.82 g, 11.4 mmol, 2.0 equiv), DMAP (0.07 g, 0.57 mmol, 0.1 equiv), and EDC (1.43 g, 7.44 mmol, 1.3 equiv). After stirring overnight, the reaction mixture was quenched with water, the organic phase was washed with brine, and dried over $MgSO_4$. After the filtration, the solution was concentrated under vacuum, and purified by chromatography on silica gel (20:1 hexanes/ethyl acetate) to afford **1m** (1.48 g, 82%) as a pale pink oil.



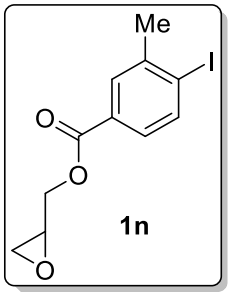
1m: a pink oil, R*f*=0.60 (hexane/ethyl acetate=10:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.2 Hz, 1H), 7.87 – 7.85 (m, 1H), 7.52 – 7.47 (m, 1H), 5.86 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H), 5.17 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.13 – 5.07 (m, 1H), 4.36 (t, *J* = 6.7 Hz, 2H), 2.52 (qt, *J* = 6.7, 1.4 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.14, 141.75, 139.09, 133.85, 130.27, 130.24, 128.02, 117.39, 107.39, 64.08, 33.08, 28.03. IR (KBr): *v* 2985, 1801, 1720, 1293, 1276, 1259, 1198, 1054, 1014 cm^{-1}; HRMS (ESI): Calcd for $C_{12}H_{13}IO_2Na$ (M+Na^{+}):338.9852*;* found: 338.9848.

Scheme 3.12 Preparation of compound **1n**.



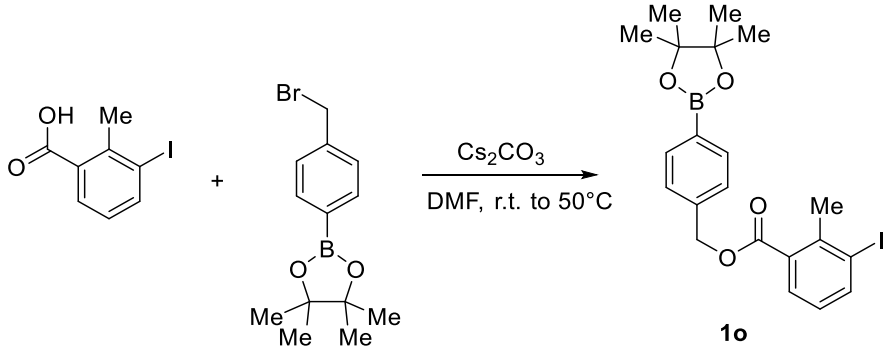
To a solution of the 4-iodo-3-methylbenzoic acid (1.50 g, 5.7 mmol, 1.0 equiv) in dichloromethane (40 mL) was added the oxiran-2-ylmethanol (1.27 g, 17.1 mmol), DMAP (0.07 g, 0.57 mmol), and DCC (1.77 g, 8.6 mmol). After stirring overnight, the reaction mixture was quenched with water, the organic phase was washed with brine, and dried over $MgSO_4$. After the filtration, the solution was concentrated under vacuum, and purified by chromatography on silica

gel using (20:1 hexanes/EtOAc) the eluent to afford **1n** (1.42 g, 87%) as a colorless oil.



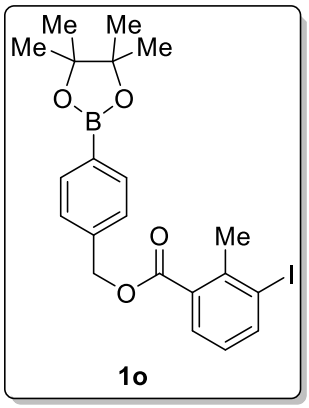
1n: Colorless oil; Rf=0.30 (hexane/ethyl acetate=10:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 – 7.87 (m, 2H), 7.55 – 7.49 (m, 1H), 4.65 (dd, *J* = 12.3, 3.0 Hz, 1H), 4.13 (dd, *J* = 12.3, 6.4 Hz, 1H), 3.34 (ddt, *J* = 6.7, 4.1, 2.8 Hz, 1H), 2.90 (dd, *J* = 4.8, 4.1 Hz, 1H), 2.72 (dd, *J* = 4.9, 2.6 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.93, 141.94, 139.22, 130.38, 129.59, 128.18, 107.87, 65.65, 49.39, 44.68, 28.03; IR (KBr): *v* 2941, 1796, 1723, 1593, 1259, 1198, 1171, 1111, 1053, 1013 cm^{-1}; HRMS (ESI): Calcd for $C_{11}H_{11}IO_3Na$ (M+Na^{+}): 340.9645; found: 340.9644.

Scheme 3.13 Preparation of compound **1o**.



To a flask charged with 3-iodo-2-methylbenzoic acid (1.00 g, 3.8 mmol, 1.1 equiv), 4-bromomethyl-phenylboronic acid pinacol ester (1.00 g, 3.4 mmol, 1.0 equiv) and cesium carbonate

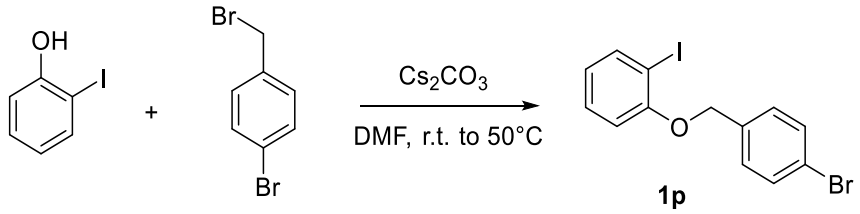
(1.66 g, 5.1 mmol), 16 mL DMF was added at room temperature. The reaction was heated to 50 ^{o}C overnight, and was monitored by TLC. The mixture was diluted with ethyl acetate and then sequentially washed with water and brine. The organic layer was dried over $MgSO_4$, the solvents were removed under reduced pressure. The desired aryl iodide was purified by flash column chromatography (10:1 hexanes/ethyl acetate) on silica gel to give desired product **1o** (0.88 g, 55%) as a white solid.



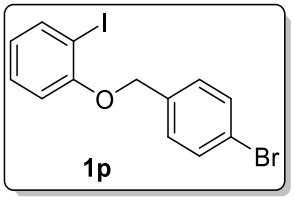
1o

1o : a white solid, mp=110-112 ^{o}C; R*f*= 0.48 (hexane/ethyl acetate=5:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.98 (ddd, *J* = 7.9, 1.4, 0.4, 1H), 7.86 – 7.81 (m, 2H), 7.76 (ddd, *J* = 7.8, 1.4, 0.5, 1H), 7.43 (dd, *J*=7.7, 0.6, 2H), 6.92 (td, *J* = 7.8, 0.6, 1H), 5.35 (s, 2H), 2.66 (d, *J* = 0.5, 3H), 1.35 (s, 12H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 167.29, 142.77, 141.76, 138.77, 135.22, 131.87, 130.18, 127.56, 127.25, 104.24, 84.03, 67.10, 26.69, 25.00. IR (KBr): *v* 2982, 1795, 1724, 1594, 1292, 1277, 1258, 1199, 1053 cm^{-1}; HRMS (ESI): Calcd for $C_{21}H_{24}BIO_4Na$ ($M+Na^{+}$): 501.0708; found: 501.0708.

Scheme 3.14 Preparation of compound **1p**.

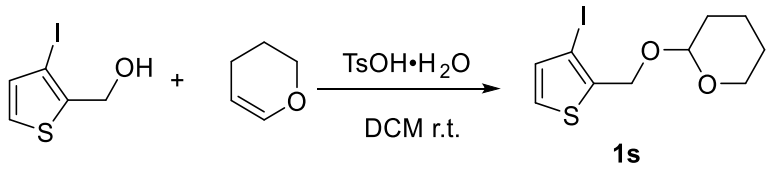


To a flask charged with 2-iodophenol (2.60 g, 12 mmol, 1.0 equiv), 4-Bromobenzyl Bromide (4.50 g, 18 mmol, 1.5 equiv) and potassium carbonate (3.31 g, 24 mmol, 2 equiv), 30 ml DMF was added at room temperature. The reaction was heated to 50^{o}C overnight, the reaction monitored by TLC. The mixture was diluted with ethyl acetate and then sequentially washed with water, brine. The organic layers was dried over $MgSO_4$, the solvents was removed under reduced pressure. The desired product was purified by flash column chromatography (hexane/ethyl acetate=40:1) on silica gel to give **1p** (4.06 g, 87%) as a white solid.

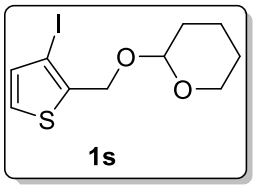


1p : a white solid; mp=74-77 ℃; R*f*= 0.43 (hexane/ethyl acetate=10:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.38 (dd, *J* = 7.9, 1.3 Hz, 2H), 7.32 – 7.26 (m, 1H), 6.83 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.74 (td, *J* = 7.6, 1.3 Hz, 1H), 5.09 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.86, 139.58, 135.47, 131.67, 129.42, 128.65, 123.00, 121.76, 112.62, 86.74, 70.06. IR (KBr): *v* 2986, 1793, 1723, 1469, 1276, 1261, 1199, 1053, 1013 cm^{-1}; HRMS (ESI): Calcd for $C_{13}H_{10}BrIONa$ ($M+Na^{+}$): 410.8852; found: 410.8888.

Scheme 3.15 Preparation of compound **1s**.

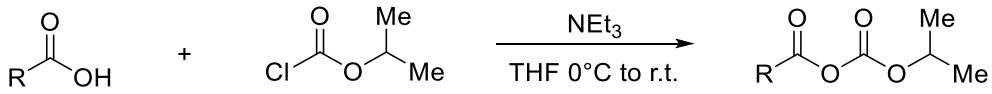


To a foil covered vial, (3-iodo-thiophen-2-yl)-methanol[97] (1.00 g, 4.2 mmol, 1 equiv) and dihydrogenpyran (0.57 mL, 6.3 mmol, 1.5 equiv) in 10 mL DCM was added p-toluenesulfonic acid monohydrate (0.16 g, 0.84mmol, 0.2 equiv). The reaction was stirred at room temperature and monitored by TLC. The reaction was filtered through a short pad of celite and the solvent was then removed under reduced pressure. The desired aryl iodide was purified by flash column chromatography (from hexcane/dichloromethane= 5:1 to hexcane/dichloromethane = 2:1) on silica gel to give **1s** (0.65 g, 48%) as a colorless oil.



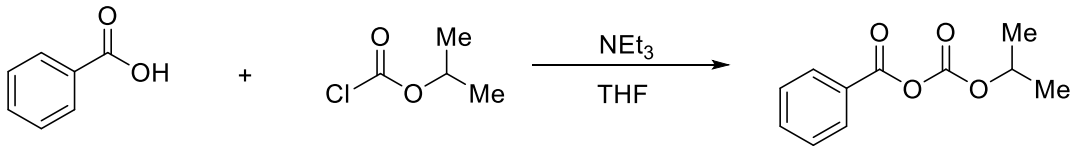
1s : A colorless oil; R*f*= 0.52 (hexane/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.26 (d, *J*=5.2, 1H), 7.04 (d, *J*=5.2, 1H), 4.84 (d, *J*=13.0, 1H), 4.77 (t, *J*=3.5, 1H), 4.64 (d, *J*=12.9, 1H), 3.94 (dddd, *J*=9.0, 8.4, 3.3, 2.6, 1H), 3.59 (dtd, *J*=11.3, 4.2, 1.4, 1H), 1.93 – 1.50 (m, 6H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 140.10, 134.91, 126.93, 97.90, 79.74, 65.47, 62.26, 30.47, 25.54, 19.25. IR (KBr): *v* 2941, 1800, 1455, 1275, 1261, 1201, 1118 cm^{-1}; HRMS (ESI): Calcd for $C_{10}H_{13}IO_2$ NaS (M+Na^{+}): 346.9573; found: 346.9572.

Scheme 3.16 General procedure for the preparation of isopropyl carbonate ***2***[82-83]***:***

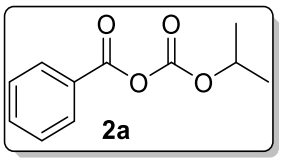


In a round-bottom flask, carboxylic acid (10.0 mmol, 1.0 equiv) and trimethylamine (1.40 mL, 10.0 mmol, 1.0 equiv) were dissolved in 50 mL anhydrous THF. The mixture was stirred for 10 min at room temperature. In another round-bottom flask, 1 M isopropyl choloroformate toluene solution (12.0 mL, 12.0 mmol, 1.2 equiv) was diluted with 50 mL anhydrous THF. At 0 ^{o}C, the mixture of carboxylic acid and triethylamine was added dropwise to the diluted isopropyl choloroformate solution via addition funnel over 40 min. Then the reaction mixture was stirred at room temperature for additional 1 hour monitored by TLC. When TLC shows full conversion, 10% critic acid (30 mL) was added to the reaction mixture until the system became clear. After extraction with ethyl ether (40 mL×2), the organic layer was washed with saturated sodium bicarbonate solution (40 mL) and brine (40 mL), dried over $MgSO_4$. The solvent were evaporated under vacuum. The crude products can be directly used in the C–H acylation reaction. The analytical pure sample was obtained through distillation or recrystallization. (Note: some of isopropyl carbonatse are not stable for flash column chromatography. All of them were not thermostable at high temperature (>110°C). For long term storage, -20°C is required. Even so in some cases positive pressure was still build in the vial after several months, implying decarboxylation still happened.) The anhydride **2k** was known compound, synthesized by a similar procedure.[98]

Scheme 3.17 Large Scale preparation of compound **1s**.

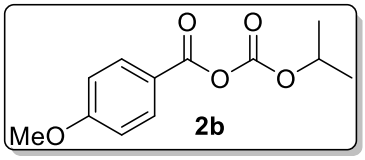


In a round-bottom flask, benzoic acid (20.0 g, 164 mmol, 1.0 equiv) and trimethylamine (22.9 mL, 164 mmol, 1.0 equiv) were dissolved in 300 mL anhydrous THF. Then the mixture was stirred for 10 min. In another round-bottom flask, 1 M isopropyl choloroformate toluene solution (196.8 mL, 196.8 mmol, 1.2 equiv) was diluted with 200 mL anhydrous THF. At 0 ºC, the acid and amine mixture was added dropwise to the diluted isopropyl choloroformate solution via addition funnel over 40 min. The reaction mixture was stirred at room temperature for additional 2 hours. Then 150 mL 10% critic acid and 450 mL water were added to the reaction mixture. After extraction with ethyl acetate (200 mL×3), the combined organic layer was washed with saturated sodium bicarbonate solution (700 mL), water (1000 mL×2), and brine (700 mL), and dried over $MgSO_4$. The solvent were evaporated *in vacuo*. The crude products were then subjected to reduced pressure distillation to give **2a** (29.2 g, 86%) as a colorless oil. (boiling point: 67-68 ºC at 15 mTorr). ***2a*** *was stable at the bench top for more than eight months.*

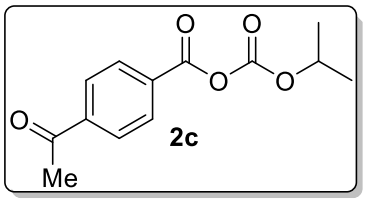


2a : a colorless oil; 29.20 g, 164 mmol scale, 86% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 – 8.03 (m, 2H), 7.67 – 7.59 (m, 1H), 7.51 – 7.44 (m, 2H), 5.07 (hept, *J* = 6.3 Hz, 1H), 1.39

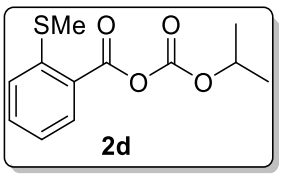
(d, *J* = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.31, 148.67, 134.37, 130.38, 128.62, 127.68, 74.48, 21.37; IR (KBr): *v* 3066, 2987, 2941, 1802, 1743, 1453, 1287, 1201, 1175, 1050 cm^{-1}; HRMS (ESI): Calcd for $C_{11}H_{12}O_4Na$ (M+Na$^+$): 231.0628; found: 231.0631.



2b: a colorless oil; 2.09 g, 10 mmol scale, 88% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 – 7.97 (d, *J* = 9.1, 2H), 6.94 (d, *J* = 9.1, 2H), 5.07 (hept, *J* = 6.3, 1H), 3.83 (s, 3H), 1.39 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.56, 160.99, 149.00, 132.79, 119.93, 114.00, 74.29, 55.53, 21.48; IR (KBr): *v* 2986, 2940, 1798, 1739, 1606, 1512, 1264, 1206, 1164 cm^{-1}; HRMS (ESI): Calcd for $C_{12}H_{14}O_5Na$ (M+Na$^+$): 261.0733; found: 261.0735.

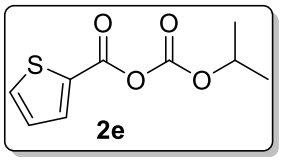


2c: a white solid; 1.35 g, 10 mmol scale, 54% yield; mp=64-66 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 8.3 Hz, 2H), 8.04 (d, *J* = 8.2 Hz, 2H), 5.10 (hept, *J* = 6.4 Hz, 1H), 2.66 (s, 3H), 1.42 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 197.17, 160.60, 148.30, 141.22, 131.44, 130.69, 128.38, 74.99, 26.90, 21.44; IR (KBr): *v* 2985, 1804, 1743, 1692, 1275, 1261, 1202, 1053, 1014 cm^{-1}; HRMS (ESI): Calcd for $C_{13}H_{14}O_5Na$ (M+Na$^+$): 273.0733; found: 273.0732.



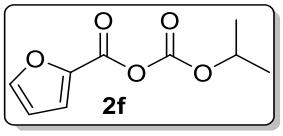
2d

2d: a white solid; 2.27 g, 10 mmol scale, 89% yield; mp=73-75 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (ddd, *J* = 7.9, 1.6, 0.4 Hz, 1H), 7.55 (ddd, *J* = 8.2, 7.3, 1.6 Hz, 1H), 7.31 (ddd, *J* = 8.2, 1.1, 0.5 Hz, 1H), 7.18 (ddd, *J* = 7.9, 7.3, 1.1 Hz, 1H), 5.07 (hept, *J* = 6.3 Hz, 1H), 2.48 (s, 3H), 1.40 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.47, 148.67, 145.98, 133.89, 132.39, 124.38, 123.58, 123.39, 74.57, 21.45, 15.37; IR (KBr): *v* 2986, 1799, 1738, 1469, 1196, 1083 cm^{-1}; HRMS (ESI): Calcd for $C_{12}H_{14}O_4SNa$ ($M+Na^+$): 277.0505; found: 277.0503.



2e

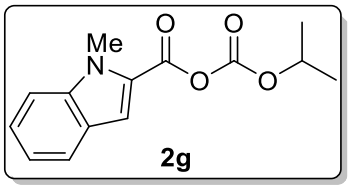
2e: a colorless oil; 2.11 g, 10 mmol scale, 98% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 (dd, *J* = 3.8, 1.3, 1H), 7.70 (dd, *J* = 5.0, 1.3, 1H), 7.15 (dd, *J* = 5.0, 3.8 Hz, 1H), 5.06 (hept, *J* = 6.3 Hz, 1H), 1.40 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.40, 148.17, 136.00, 135.19, 131.04, 128.27, 74.66, 21.46; IR (KBr): *v* 2987, 1798, 1735, 1414, 1229, 1197, 1056 cm^{-1}; HRMS (ESI): Calcd for $C_9H_{10}O_4SNa$ ($M+Na^+$): 237.0192; found: 237.0203.



2f

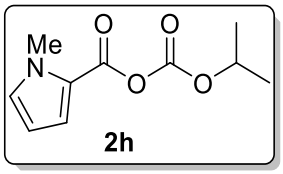
2f: a colorless oil; 2.01 g, 10 mmol scale, 99% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67

(dd, *J* = 1.7, 0.8 Hz, 1H), 7.35 (dd, *J* = 3.5, 0.7 Hz, 1H), 6.57 (dd, *J* = 3.6, 1.7 Hz, 1H), 5.05 (hept, *J* = 6.3, 1H), 1.38 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.36, 148.38, 147.99, 142.35, 121.44, 112.51, 74.73, 21.43; IR (KBr): *v* 2988, 1803, 1743, 1470, 1391, 1222, 1167, 1061 cm^{-1}; HRMS (ESI): Calcd for $C_9H_{10}O_5Na$ (M+Na$^+$): 221.0420; found: 221.0422.



2g

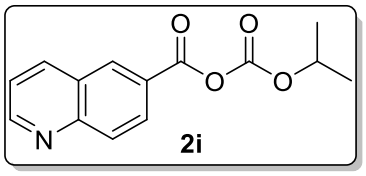
2g: a white solid; 1.07 g, 5 mmol scale, 82% yield; mp=69-72 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.46 (s, 1H), 7.45 – 7.36 (m, 2H), 7.18 (m, 1H), 5.09 (hept, *J* = 6.3 Hz, 1H), 4.08 (s, 3H), 1.43 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.11, 148.69, 140.72, 126.41, 125.56, 124.89, 123.16, 121.06, 113.64, 110.38, 74.29, 31.60, 21.52; IR (KBr): *v* 2985, 2939, 1796, 1734, 1262, 1204, 1170, 1104, 1057 cm^{-1}; HRMS (ESI): Calcd for $C_{14}H_{15}NO_4Na$ (M+Na$^+$): 284.0893; found: 284.0894.



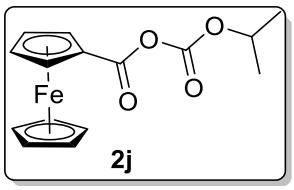
2h

2h: a colorless oil; 1.96 g, 10 mmol scale, 93% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.06 (dd, *J* = 4.2, 1.8 Hz, 1H), 6.92 (dd, *J* = 2.4, 1.8 Hz, 1H), 6.15 (dd, *J* = 4.1, 2.5 Hz, 1H), 5.03 (hept, *J* = 6.3 Hz, 1H), 3.94 (s, 3H), 1.38 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.76, 149.18, 132.42, 121.28, 119.97, 108.83, 73.81, 36.84, 21.52; IR (KBr): *v* 2986, 1790, 1727, 1408, 1261, 1236, 1198, 1052 cm^{-1}; HRMS (ESI): Calcd for $C_{10}H_{13}NO_4Na$ (M+Na$^+$):

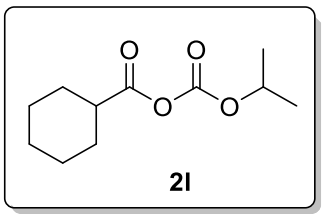
234.0737; found: 234.0734.



2i: a brown oil; 1.95 g, 10 mmol scale, 75% yield, DMF instead of THF was used as the solvent; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.99 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.59 (d, *J* = 2.0 Hz, 1H), 8.29 – 8.18 (m, 2H), 8.12 (dt, *J* = 8.8, 0.7 Hz, 1H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.09 (hept, *J* = 6.3 Hz, 1H), 1.40 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.82, 153.18, 150.39, 148.42, 137.36, 132.46, 130.22, 128.84, 127.19, 125.61, 122.11, 74.77, 21.40; IR (KBr): *v* 2985, 1801, 1740, 1212, 1162, 1104, 1055 cm^{-1}; HRMS (ESI): Calcd for $C_{14}H_{13}NO_4Na$ ($M+Na^+$): 282.0737; found: 282.0742.

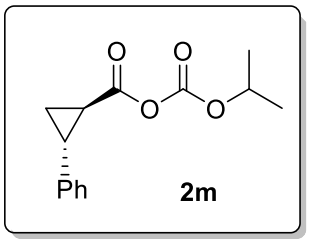


2j: an orange solid; 3.00 g, 10 mmol scale, 95% yield; mp=63-64 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.06 (hept, *J* = 6.3 Hz, 1H), 4.89 – 4.82 (m, 2H), 4.55 – 4.51 (m, 2H), 4.32 (s, 5H), 1.40 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.64, 149.13, 74.09, 74.06, 72.80, 70.91, 70.87, 70.28, 67.75, 21.56; IR (KBr): *v* 2986, 1791, 1736, 1288, 1217, 1070, 1028 cm^{-1}; HRMS (ESI): Calcd for $C_{15}H_{16}FeO_4Na$ ($M+Na^+$): 339.0290; found: 339.0297.



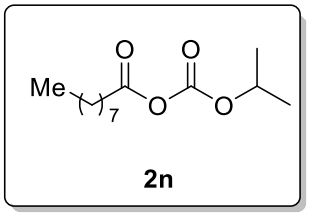
2l

2l: a colorless liquid; 1.92 g, 10 mmol scale, 90% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.99 (hept, *J* = 6.3 Hz, 1H), 2.47 – 2.36 (m, 1H), 2.02 – 1.93 (m, 2H), 1.83 – 1.72 (m, 2H), 1.68 – 1.60 (m, 1H), 1.50 (ddd, *J* = 12.3, 4.1, 1.6 Hz, 2H), 1.34 (d, *J* = 6.3 Hz, 6H), 1.32 – 1.15 (m, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.32, 148.84, 74.05, 43.00, 28.32, 25.46, 25.04, 21.39; IR (KBr): *v* 2986, 2937, 2859, 2261, 1815, 1755, 1453, 1262, 1232, 1143, 1072, 1029 cm^{-1}; HRMS (ESI): Calcd for $C_{11}H_{18}O_4Na$ (M+Na$^+$): 237.1097; found: 237.1100.



2m

2m: a colorless liquid; 2.46 g, 10 mmol scale, 99% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.27 (m, 2H), 7.26 – 7.20 (m, 1H), 7.14 – 7.09 (m, 2H), 5.01 (hept, *J* = 6.3 Hz, 1H), 2.70 (ddd, *J* = 9.3, 6.9, 4.1 Hz, 1H), 1.95 (ddd, *J* = 8.3, 5.2, 4.1 Hz, 1H), 1.76 (ddd, *J* = 9.4, 5.2, 4.8 Hz, 1H), 1.51 (ddd, *J* = 8.3, 6.9, 4.8 Hz, 1H), 1.37 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.99, 148.28, 138.71, 128.54, 126.92, 126.26, 74.34, 27.96, 23.80, 21.42, 17.96; IR (KBr): *v* 2987, 2939, 1807, 1749, 1246, 1174, 1123, 1072, 1050 cm^{-1}; HRMS (ESI): Calcd for $C_{14}H_{16}O_4Na$ (M+Na$^+$): 271.0941; found: 271.0944.



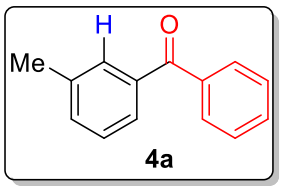
2n

2n: a colorless liquid; 2.20 g, 10 mmol scale, 90% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.99 (hept, *J* = 6.3 Hz, 1H), 2.44 (t, *J* = 7.5 Hz, 2H), 1.72 – 1.59 (m, 2H), 1.35 (d, *J* = 6.2 Hz, 6H), 1.33 – 1.22 (m, 10H), 0.91 – 0.81 (m, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.21, 148.58, 74.18, 34.19, 31.73, 29.08, 29.01, 28.79, 24.18, 22.60, 21.43, 14.05; IR (KBr): *v* 2929, 2857, 1820, 1767, 1468, 1378, 1245, 1068 cm^{-1}; HRMS (ESI): Calcd for $C_{13}H_{24}O_4Na$ ($M+Na^+$): 267.1567; found: 267.1570.

General procedure of palladium and nobornene catalyzed C-H acylation reaction：

An oven-dried 7.5 mL vial was charged with aryl iodide (0.3 mmol, 1.0 equiv), isopropanyl carbonate (0.6 mmol, 2.0 equiv), Cs_2CO_3 (392.4 mg, 1.20 mmol, 4.0 equiv), NMe_4Cl (130.4 mg, 1.20 mmol, 4.0 equiv) and another oven-dried 2 mL vial was charged endo-*N*-methyl-5-norbornene-2- carboxamide (NBE*, **3**) (22.7 mg, 0.15 mmol, 0.5 equiv), allylpalladium(II) chloride dimer (5.1 mg, 0.015mmol, 0.05 equiv) and tris(2-furyl)phosphine (13.9 mg, 0.06 mmol, 0.20 equiv). They were directly transferred in a nitrogen-filled glovebox without caps. Then 1 mL of degassed THF was added into the 2 mL vial containing the palladium/norbornene catalyst, and the resulting mixture was stirred at room temperature for 10 minutes until fully dissolved (the homogeneous solution resulted in a bright yellow color). Degassed acetonitrile (0.54 mL) and degassed THF (4.5 mL) were added to the 7.5 ml vial containing substrates, then the 1mL palladium/norbornene THF solution was transferred to that 7.5mL vial. Then the 7.5mL vial was tightly sealed, transferred out of glovebox and stirred on a pie-block preheated to 85 ^{o}C for 16 hours. After completion of the reaction, the mixture was filtered through a thin pad of celite. The filter cake was washed with ethyl acetate, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography on silica gel to give the desired product. (Note: a significant amount of white/black precipitates were formed during the course of the reaction. The reaction was quite sensitive to moisture, carefully dried reagent, freshly distilled anhydrous solvent and vigorous stirring were critical to achieve reproducible yields.)

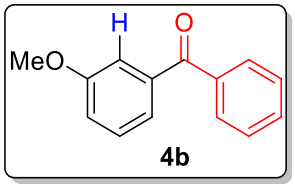
Following the general procedure, 2-iodo-toluene (65.5 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (toluene: hexane=1:1 to 100% toluene) on silica gel to give the desired product **4a** (44.0 mg, 75% yield) as a colorless oil.



4a

4a: a colorless oil. R*f*=0.45 (hexane/ethyl acetate=20:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (ddd, *J* = 8.6, 2.1, 1.3 Hz, 2H), 7.65 – 7.61 (m, 1H), 7.61 – 7.53 (m, 2H), 7.48 (ddd, *J* = 9.1, 6.9, 1.5 Hz, 2H), 7.42 – 7.31 (m, 2H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.96, 138.12, 137.70, 137.57, 133.16, 132.30, 130.42, 130.01, 128.20, 128.05, 127.33, 21.34. Both the ^{1}H and ^{13}C NMR spectra match the literature reported data.[99]

Following the general procedure, 2-iodo-anisole (70.0 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane: diethyl ether = 30:1 to hexane: diethyl ether= 25 : 1) on silica gel to give the desired product **4b** (46.3 mg, 73% yield) as a colorless oil.

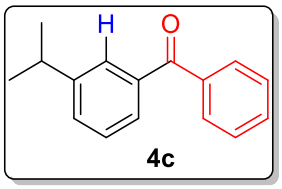


4b

4b: a colorless oil. Rf=0.20 (hexane/ethyl acetate=20:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83 – 7.78 (m, 2H), 7.62 – 7.55 (m, 1H), 7.51 – 7.44 (m, 2H), 7.40 – 7.31 (m, 3H), 7.13 (ddd, *J* = 8.1, 2.6, 1.4 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.44, 159.49, 138.81,

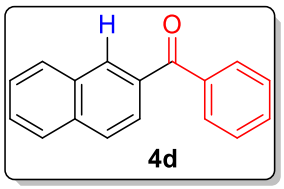
137.53, 132.37, 129.97, 129.15, 128.19, 122.80, 118.78, 114.25, 55.40. Both the ^{1}H and ^{13}C NMR spectra match the literature reported data.[99]

Following the general procedure, 2-iodo-isopropylbenzene (73.9 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (toluene: hexane=1:1 to 100% toluene) on silica gel to give the desired product **4c** (47.3 mg, 73% yield) as a colorless oil.



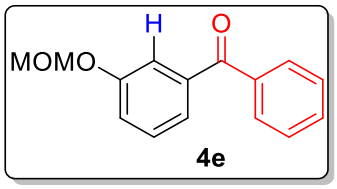
4c： a colorless oil. R*f*=0.45 (hexane/ethyl acetate=20:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 – 7.79 (m, 2H), 7.71 (td, *J* = 1.8, 0.9 Hz, 1H), 7.58 (ddt, *J* = 6.8, 5.3, 1.5 Hz, 2H), 7.52 – 7.44 (m, 3H), 7.39 (td, *J* = 7.6, 0.5 Hz, 1H), 2.99 (hept, *J* = 6.9 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.96, 149.07, 137.74, 137.55, 132.25, 130.61, 130.00, 128.17, 128.08, 127.94, 127.80, 34.02, 23.85; IR (KBr): *v* 3060, 2961, 2927, 1660, 1597, 1579, 1447, 1317, 1286, 1270, 1211 cm^{-1}; HRMS (ESI): Calcd for $C_{16}H_{16}ONa$ ($M+Na^{+}$): 247.1093; found: 247.1095. The ^{1}H NMR and IR match the literature reported data.[100]

Following the general procedure, 1-iodonaphathelene (73.8 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (toluene: hexane=1:1 to 100% toluene) on silica gel to give the desired product **4d** (44.5 mg, 66% yield) as a colorless oil.



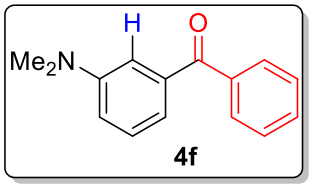
4d: a colorless oil. R*f*=0.45 (hexane/ethyl acetate=20:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 (dt, *J* = 1.5, 0.8 Hz, 1H), 7.97 – 7.90 (m, 4H), 7.89 – 7.85 (m, 2H), 7.66 – 7.59 (m, 2H), 7.58 – 7.49 (m, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.70, 137.84, 135.21, 134.75, 132.33, 132.19, 131.83, 130.05, 129.36, 128.29, 128.28, 128.25, 127.77, 126.75, 125.73. Both the ^{1}H and ^{13}C NMR spectra match the literature reported data.[99]

Following the general procedure, 1-iodo-2-(methoxymethoxy)benzene (79.0 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane: diethyl ether = 30:1 to hexane: diethyl ether= 15 : 1) on silica gel to give the desired product **4e** (54.3 mg, 75% yield) as a colorless oil.



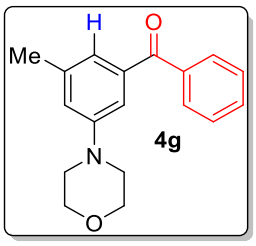
4e: a colorless oil. R*f*=0.18 (hexane/ethyl acetate=20:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83 – 7.77 (m, 2H), 7.61 – 7.55 (m, 1H), 7.50 – 7.44 (m, 3H), 7.42 – 7.35 (m, 2H), 7.29 – 7.24 (m, 1H), 5.21 (s, 2H), 3.48 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.19, 157.05, 138.89, 137.41, 132.40, 129.98, 129.24, 128.19, 123.71, 120.33, 117.36, 94.36, 56.06. Both the ^{1}H and ^{13}C NMR spectra match the literature reported data.[48]

Following the general procedure, 2-iodo-*N*,*N*-dimethylaniline (75.8 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane: diethyl ether = 30:1 to hexane: diethyl ether= 10 : 1) on silica gel to give the desired product **4f** (39.7 mg, 57% yield) as a yellow oil.



4f : a yellow oil. R*f*= 0.26 (hexane/ethyl acetate=20:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 – 7.79 (m, 2H), 7.61 – 7.53 (m, 1H), 7.51 – 7.44 (m, 2H), 7.31 (dd, *J* = 8.3, 7.5 Hz, 1H), 7.19 (dd, *J* = 2.8, 1.5 Hz, 1H), 7.06 (ddd, *J* = 7.5, 1.6, 0.9 Hz, 1H), 6.94 (ddd, *J* = 8.3, 2.8, 0.9 Hz, 1H), 3.00 (s, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 197.43, 150.37, 138.25, 137.95, 132.12, 130.01, 128.63, 128.05, 118.62, 116.26, 113.15, 40.46; IR (KBr): *v* 3061, 2922, 2807, 1655, 1598, 1572, 1497, 1447, 1356, 1272 cm^{-1}; HRMS (ESI):): Calcd for $C_{15}H_{15}NONa$ ($M+Na^{+}$): 248.1046; found: 248.1050.

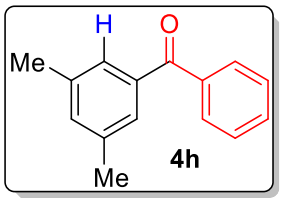
Following the general procedure, **1g** (91.3mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane: ethyl acetate= 10:1) on silica gel to give the desired product **4g** (61.7 mg, 73% yield) as a yellow oil.



4g : a yellow oil. R*f*=0.19 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83

– 7.76 (m, 2H), 7.62 – 7.53 (m, 1H), 7.47 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.16 (s, 1H), 7.06 (s, 1H), 6.95 (s, 1H), 3.90 – 3.81 (m, 4H), 3.23 – 3.13 (m, 4H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 197.10, 151.16, 138.73, 138.41, 137.78, 132.21, 129.93, 128.11, 122.61, 120.22, 113.91, 66.73, 49.08, 21.64; IR (KBr): *v* 3058, 2961, 2917, 2854, 2363, 1655, 1594, 1448, 1352, 1275, 1237, 1122 cm^{-1}; HRMS (ESI): Calcd for $C_{18}H_{19}NO_2Na$ (M+Na$^+$): 304.1308; found: 304.1312.

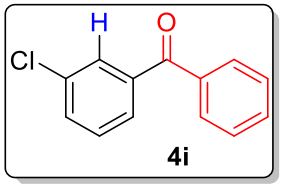
Following the general procedure, 1-iodo-2,4-dimethylbenzene (70.1 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (toluene: hexane=1:1 to 100% toluene) on silica gel to give the desired product **4h** (43.2 mg, 68% yield) as a colorless oil.



4h： a colorless oil. R*f*=0.45 (hexane/ethyl acetate=20:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 – 7.77 (m, 2H), 7.62 – 7.55 (m, 1H), 7.51 – 7.44 (m, 2H), 7.42 – 7.40 (m, 2H), 7.23 – 7.21 (m, 1H), 2.38 (q, *J* = 0.7 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 197.12, 137.87, 137.84, 137.62, 134.03, 132.20, 129.96, 128.15, 127.75, 21.19. The proton and carbon NMR match the literature reported data.[101]

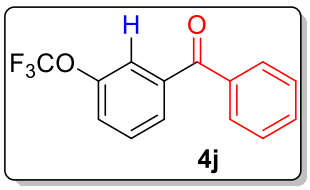
Following the general procedure, 2-chloro-iodobenzene (73.0 mg, 0.3 mmol, 1.0 equiv) was used. 2.0 equiv BzOBz and 1.50 equiv of **2a** were used instead of 2.0 equiv **2a.** The reaction run at 70°C for 20 hours in the absence of acetonitrile and NMe_4Cl. Flash column chromatography (toluene: hexane=1:1 to 100% toluene) on silica gel to give the desired product **4i** (26.8 mg, 40%

yield) as a colorless oil.



***4i*:** a colorless oil. R*f*=0.45 (hexane/ethyl acetate=20:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 – 7.76 (m, 3H), 7.67 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.64 – 7.59 (m, 1H), 7.56 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.43 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.23, 139.20, 136.89, 134.52, 132.81, 132.32, 129.99, 129.86, 129.60, 128.42, 128.08. The proton and carbon NMR match the literature reported data.[102]

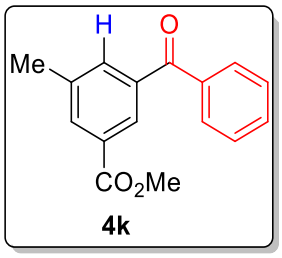
Following the general procedure, 1-iodo-2-(trifluoromethoxy)benzene (89.0 mg, 0.3 mmol, 1.0 equiv) was used. 2.0 equiv BzOBz and 1.50 equiv of **2a** were used instead of 2.0 equiv **2a.** The reaction run at 70°C for 20 hours in the absence of acetonitrile and NMe_4Cl. Flash column chromatography (toluene: hexane=1:1 to 100% toluene) on silica gel to give the desired product **4j** (60.1 mg, 73% yield) as a colorless oil.



***4j*:** a colorless oil. R*f*=0.45 (hexane/ethyl acetate=20:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83 – 7.78 (m, 2H), 7.73 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.67 (dd, *J* = 2.4, 1.2 Hz, 1H), 7.65 – 7.59 (m, 1H), 7.57 – 7.48 (m, 3H), 7.45 (ddt, *J* = 8.2, 2.3, 1.1 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-

d) δ 194.97 , 149.09 (q, *J* = 1.9 Hz), 139.41 , 136.77 , 132.90 , 129.99 , 129.82 , 128.46 , 128.32 , 124.70 (d, *J* = 1.1 Hz), 122.32 (d, *J* = 1.1 Hz), 120.39 (q, *J* = 258.0 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -57.93. The proton and carbon NMR match the literature reported data.[103]

Following the general procedure, **1k** (82.5 mg, 0.3 mmol, 1.0 equiv) was used. 2.0 equiv BzOBz and 1.50 equiv of **2a** were used instead of 2.0 equiv **2a.** The reaction run at 70°C for 20 hours in the absence of acetonitrile and NMe_4Cl. Flash column chromatography (hexane: ethyl acetate =50:1) on silica gel to give the desired product **4k** (45.7 mg, 60% yield) as a pink oil.

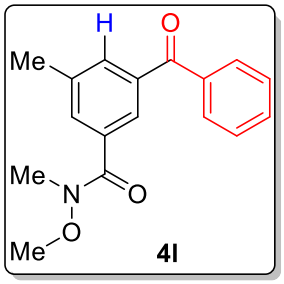


4k

4k： a pink oil. R*f*=0.25 (hexane/ethyl acetate=20:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (s, 1H), 8.08 (s, 1H), 7.84 – 7.77 (m, 3H), 7.65 – 7.58 (m, 1H), 7.55 – 7.47 (m, 2H), 3.92 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.02, 166.47, 138.77, 137.96, 137.17, 134.56, 133.85, 132.72, 130.18, 130.03, 128.43, 128.34, 52.33, 21.22; IR (KBr): *v* 2951, 1724, 1663, 1597, 1438, 1330, 1270, 1246 cm^{-1}; HRMS (ESI): Calcd for $C_{16}H_{14}O_3Na$ ($M+Na^+$): 277.0835; found: 277.0841.

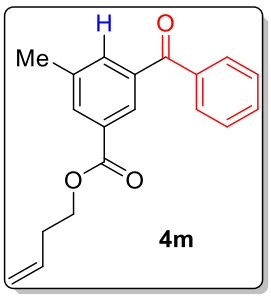
Following the general procedure, **1l** (91.4 mg, 0.3 mmol, 1.0 equiv) was used. 2.0 equiv BzOBz and 1.50 equiv of **2a** were used instead of 2.0 equiv **2a.** The reaction run at 70°C for 20 hours in the absence of acetonitrile and NMe_4Cl. Flash column chromatography (hexane: ethyl acetate =

4:1) on silica gel to give the desired product **4l** (67.4mg, 79% yield) as a colorless oil.



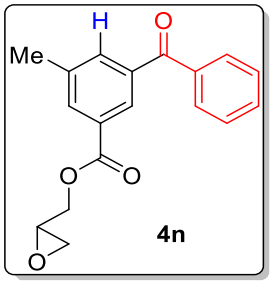
***4l*:** a colorless oil. R*f*=0.29 (hexane/ethyl acetate=2:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.82 (m, 1H), 7.81 – 7.76 (m, 2H), 7.73 – 7.68 (m, 2H), 7.60 – 7.55 (m, 1H), 7.50 – 7.43 (m, 2H), 3.53 (s, 3H), 3.33 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.10, 169.02, 138.30, 137.28, 137.17, 134.02, 132.59, 132.54, 132.25, 129.92, 128.27, 126.83, 61.07, 21.20; IR (KBr): *v* 2934, 1659, 1596, 1447, 1382, 1318, 1297, 1229, 1180 cm^{-1}; HRMS (ESI): Calcd for $C_{17}H_{17}NO_3Na$ ($M+Na^+$): 306.1101; found: 306.1100.

Following the general procedure, **1m** (96.6 mg, 0.3 mmol, 1.0 equiv) was used. 2.0 equiv BzOBz and 1.50 equiv of **2a** were used instead of 2.0 equiv **2a.** 1.5 equiv of **3** instead of 0.5 equiv were used for this substrate. The reaction run at 70°C for 20 hours in the absence of acetonitrile and NMe_4Cl. Flash column chromatography (hexane: ethyl acetate = 40:1) on silica gel to give the desired product **4m** (52.8 mg, 59% yield) as a colorless oil.



4m： a colorless oil. R*f*=0.25 (hexane/ethyl acetate=20:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (td, *J* = 1.6, 0.6 Hz, 1H), 8.06 (td, *J* = 1.7, 0.8 Hz, 1H), 7.84 – 7.77 (m, 3H), 7.64 – 7.58 (m, 1H), 7.53 – 7.46 (m, 2H), 5.84 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.19 – 5.06 (m, 2H), 4.37 (t, *J* = 6.7 Hz, 2H), 2.55 – 2.48 (m, 2H), 2.47 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.98, 165.87, 138.69, 137.89, 137.13, 134.50, 133.80, 133.77, 132.68, 130.38, 130.00, 128.37, 128.35, 117.44, 64.20, 33.08, 21.20; IR (KBr): *v* 2922, 2365, 23451721, 1663m 1598, 1328, 1243, 1203 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{18}O_3Na$ ($M+Na^+$): 317.1148; found: 317.1154.

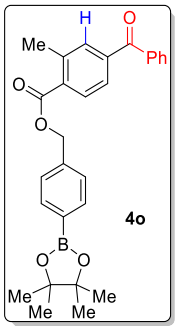
Following the general procedure, **1n** (95.1 mg, 0.3 mmol, 1.0 equiv) was used. 2.0 equiv BzOBz and 1.50 equiv of **2a** were used instead of 2.0 equiv **2a.** The reaction run at 70°C for 20 hours in the absence of acetonitrile and NMe_4Cl. Flash column chromatography (hexane: ethyl acetate = 10:1) on silica gel to give the desired product **4n** (59.8 mg, 67% yield) as a colorless oil.



4n： a colorless oil. R*f*=0.15 (hexane/ethyl acetate=10:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 (td, *J* = 1.6, 0.7 Hz, 1H), 8.09 (td, *J* = 1.7, 0.8 Hz, 1H), 7.85 – 7.74 (m, 3H), 7.64 – 7.55 (m, 1H), 7.54 – 7.46 (m, 2H), 4.66 (dd, *J* = 12.3, 3.1 Hz, 1H), 4.16 (dd, *J* = 12.3, 6.3 Hz, 1H), 3.33 (ddt, *J* = 6.5, 4.1, 2.8 Hz, 1H), 2.89 (dd, *J* = 4.9, 4.1 Hz, 1H), 2.71 (dd, *J* = 4.8, 2.6 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.87, 165.61, 138.79, 138.01, 137.04, 134.81,

133.88, 132.74, 129.98, 129.70, 128.40, 65.75, 49.32, 44.68, 21.17; IR (KBr): *v* 3060, 3001, 2925, 1724, 11662, 1598, 1446, 1325, 1270, 1243, 1204 cm^{-1}; HRMS (ESI): Calcd for $C_{18}H_{16}O_4Na$ ($M+Na^+$): 319.0941; found: 319.0949.

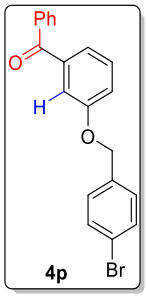
Following the general procedure, **1o** (143.9 mg, 0.3 mmol, 1.0 equiv) was used. 2.0 equiv BzOBz and 1.50 equiv of **2a** were used instead of 2.0 equiv **2a.** The reaction run at 70°C for 20 hours in the absence of acetonitrile and NMe_4Cl. Flash column chromatography (hexane: ethyl acetate = 30:1) on silica gel to give the desired product **4o** (76.5 mg, 56% yield) as a colorless oil.



***4o*:** a colorless oil. R*f*=0.13 (hexane/ethyl acetate=20:1); ^1H NMR (400 MHz, Chloroform-*d*) δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.88 – 7.83 (m, 2H), 7.83 – 7.76 (m, 2H), 7.68 – 7.64 (m, 1H), 7.64 – 7.57 (m, 2H), 7.53 – 7.42 (m, 4H), 5.39 (s, 2H), 2.65 (s, 3H), 1.35 (s, 12H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.07, 166.64, 140.33, 140.32, 138.67, 136.97, 135.05, 132.81, 132.68, 130.44, 130.05, 128.36, 127.40, 127.02, 83.85, 66.81, 24.82, 21.69; IR (KBr): *v* 2978, 2927, 1724, 1662, 1361, 1275, 1257, 1143, 1088 cm^{-1}; HRMS (ESI): Calcd for $C_{28}H_{29}BO_5Na$ ($M+Na^+$): 479.2005; found: 479.2003.

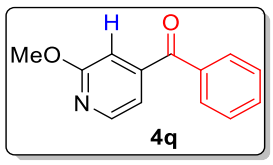
Following the general procedure, **1p** (115.5mg, 0.3 mmol, 1.0 equiv) was used. 2.0 equiv BzOBz and 1.50 equiv of isopropyl chloroformate were used instead of 2.0 equiv **2a.** The reaction

run at 85°C for 16 hours in the absence of NMe_4Cl. Flash column chromatography (hexane: ether = 30:1) on silica gel to give the desired product **4p** (58.9 mg, 55% yield) as a colorless oil.



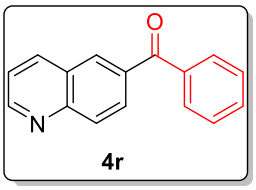
4p: a colorless oil. R*f*=0.32 (hexane/ethyl acetate=20:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 – 7.75 (m, 2H), 7.58 (d, *J* = 7.4 Hz, 1H), 7.54 – 7.43 (m, 4H), 7.42 – 7.36 (m, 3H), 7.34 – 7.27 (m, 2H), 7.22 – 7.15 (m, 1H), 5.06 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.26, 158.30, 138.86, 137.40, 135.50, 132.42, 131.72, 129.96, 129.34, 129.06, 128.23, 123.21, 121.97, 119.61, 115.30, 69.32; IR (KBr): *v* 3063, 2925, 2363, 2345, 1655, 1596, 1578, 1489, 1459, 1438, 1318, 1279, 1221 cm^{-1}; HRMS (ESI): Calcd for $C_{20}H_{15}BrO_2Na$ ($M+Na^+$): 389.0148; found: 389.0152.

Following the general procedure, **1q** (72.4 mg, 0.3 mmol, 1.0 equiv) was used. 2.0 equiv BzOBz and 1.50 equiv of **2a** were used instead of 2.0 equiv **2a.** The reaction run at 70°C for 20 hours in the absence of acetonitrile and NMe_4Cl. Flash column chromatography (hexane: ethyl acetate = 30:1) on silica gel to give the desired product **4q** (25.0 mg, 38% yield) as a colorless oil.



4q： a colorless oil; R*f*=0.31 (hexane/ethyl acetate=20:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (dt, *J* = 5.2, 1.0 Hz, 1H), 7.86 – 7.77 (m, 2H), 7.62 (ddt, *J* = 8.0, 6.9, 1.3 Hz, 1H), 7.53 – 7.42 (m, 2H), 7.15 (dd, *J* = 5.2, 1.4 Hz, 1H), 6.99 (dd, *J* = 1.4, 0.8 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.00, 164.37, 147.50, 147.32, 135.94, 133.40, 130.09, 128.52, 115.83, 111.02, 53.81; IR (KBr): *v* 2950, 2855, 1669, 1597, 1552, 1449, 1387, 1321, 1266, 1219 cm^{-1}; HRMS (ESI): Calcd for $C_{13}H_{12}NO_2$ ($M+H^+$): 214.0863; found: 214.0860.

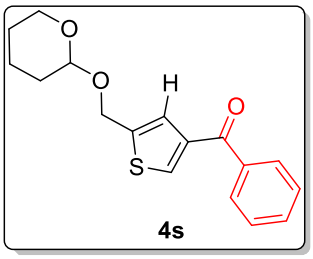
Following the general procedure, **1r** (76.0 mg, 0.3 mmol, 1.0 equiv) was used. 2.0 equiv BzOBz and 1.50 equiv of **2a** were used instead of 2.0 equiv **2a.** The reaction run at 70°C for 20 hours in the absence of acetonitrile and NMe_4Cl. Flash column chromatography (hexane: ethyl acetate = 3:1) on silica gel to give the desired product **4r** (37.1 mg, 53% yield) as a yellow oil.



4r： a colorless oil; R*f*=0.52 (hexane/ethyl acetate=1:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.02 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.27 – 8.11 (m, 4H), 7.90 – 7.81 (m, 2H), 7.66 – 7.58 (m, 1H), 7.54 – 7.44 (m, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.98, 152.40, 149.65, 137.36, 137.33, 135.39, 132.65, 131.31, 130.03, 129.73, 129.47, 128.40, 127.21, 121.94. The proton and carbon NMR match the literature reported data.[104]

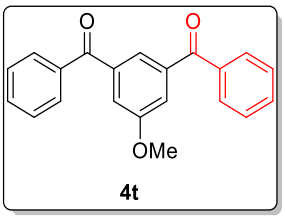
Following the general procedure, **1s** (99.8 mg, 0.3 mmol, 1.0 equiv) was used. Flash column

chromatography (hexane: ethyl acetate = 20:1) on silica gel to give the desired product **4s** (62.2 mg, 67% yield) as a colorless oil.



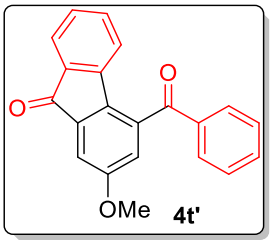
4s： a colorless oil; R*f*=0.10 (hexane/ethyl acetate=20:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 – 7.78 (m, 3H), 7.62 – 7.52 (m, 1H), 4.89 (dd, *J* = 12.7, 1.0 Hz, 1H), 4.75 (t, *J* = 3.5 Hz, 1H), 4.71 (dd, *J* = 12.7, 0.8 Hz, 1H), 3.98 – 3.84 (m, 1H), 3.62 – 3.48 (m, 1H), 1.90 – 1.69 (m, 2H), 1.68 – 1.49 (m, 4H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 189.80, 142.32, 140.73, 138.37, 134.26, 132.18, 129.24, 128.28, 127.01, 97.35, 63.02, 62.08, 30.28, 25.29, 19.08; IR (KBr): *v* 2943, 2869, 1648, 1453, 1260, 1118, 1026 cm^{-1}; HRMS (ESI): Calcd for $C_{17}H_{18}O_3SNa$ (M+Na^{+}): 325.0869; found: 325.0869.

Following the general procedure, **1t** (71.3 mg, 0.3 mmol, 1.0 equiv) was used. 2.0 equiv BzOBz and 1.50 equiv of **2a** were used instead of 2.0 equiv **2a.** Flash column chromatography (toluene 100%) on silica gel to give the desired product **4t** (33.0 mg, 35% yield) as a colorless oil.



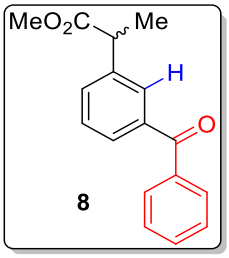
4t： a colorless oil; R*f*=0.15 (hexane/ethyl acetate=20:1); ^{1}H NMR (400 MHz, Chloroform-*d*)

δ 7.85 – 7.80 (m, 4H), 7.71 (t, *J* = 1.4 Hz, 1H), 7.63 – 7.57 (m, 2H), 7.56 (d, *J* = 1.4 Hz, 2H), 7.52 – 7.45 (m, 4H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.58, 159.63, 138.97, 136.96, 132.84, 130.03, 128.42, 123.90, 118.81, 55.84; IR (KBr): *v* 3060, 2941, 2869, 1660, 1596, 1450, 1338, 1121, 1027 cm^{-1}; HRMS (ESI): Calcd for $C_{21}H_{17}O_3$ ($M+H^+$): 317.1172; found: 317.1168.



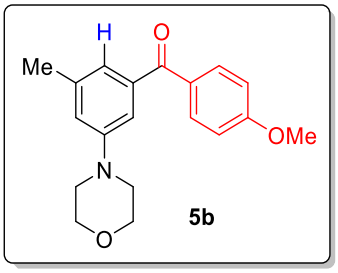
***4t'*:** a yellow solid; mp=173-174℃; R*f*=0.15 (hexane/ethyl acetate=20:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 – 7.93 (m, 2H), 7.68 – 7.61 (m, 2H), 7.54 – 7.48 (m, 2H), 7.36 (d, *J* = 2.5 Hz, 1H), 7.25 (td, *J* = 7.6, 1.3 Hz, 1H), 7.17 (td, *J* = 7.5, 1.1 Hz, 1H), 7.13 – 7.08 (m, 1H), 6.93 (d, *J* = 2.5 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.29, 192.85, 160.02, 143.32, 136.99, 136.12, 135.29, 135.03, 134.37, 134.21, 134.16, 130.33, 128.87, 128.26, 124.33, 122.97, 119.08, 111.25, 55.94. IR (KBr): *v* 2926, 1719, 1668, 1597, 1275, 1260 cm^{-1}; HRMS (ESI): Calcd for $C_{21}H_{15}O_3$ ($M+H^+$): 315.1016; found: 315.1013.

Following the general procedure, **1v** (88.7 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (hexane: ethyl acetate = 20:1) on silica gel to give the desired product **8** (54.9 mg, 67% yield) as a colorless oil.



8 : a colorless oil. R*f*=0.25, (hexane/ethyl acetate =10: 1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 – 7.78 (m, 2H), 7.76 – 7.73 (m, 1H), 7.70 – 7.65 (m, 1H), 7.62 – 7.56 (m, 1H), 7.56 – 7.52 (m, 1H), 7.51 – 7.41 (m, 3H), 3.81 (q, *J* = 7.2 Hz, 1H), 3.67 (s, 3H), 1.53 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 140.77, 137.85, 137.43, 132.46, 131.45, 130.03, 129.17, 128.99, 128.51, 128.25, 52.13, 45.23, 18.47. The proton and carbon NMR matches the literature's report.[105]

Following the general procedure, **1g** (91.2 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane: ethyl acetate=10:1) on silica gel to give the desired product **5b** (63.5 mg, 68% yield) as a yellow solid.

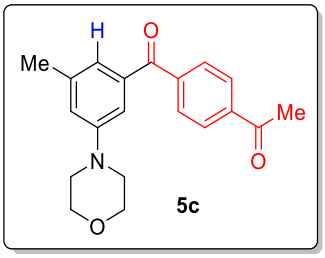


5b

5b：a yellow solid. R*f*=0.15 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 8.8 Hz, 2H), 7.09 (s, 1H), 7.04 – 7.00 (m, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.93 – 6.90 (m, 1H), 3.87 (s, 3H), 3.86 – 3.80 (m, 4H), 3.22 – 3.13 (m, 4H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.91, 163.02, 151.07, 139.11, 138.62, 132.40, 130.28, 122.17, 119.68, 113.73, 113.37, 66.74, 55.38, 49.09, 21.64; IR (KBr): *v* 2961, 2916, 2853, 1649, 1596, 1449, 1352, 1259, 1170, 1122 cm^{-1}; HRMS (ESI): Calcd for $C_{19}H_{21}NO_3Na$ ($M+Na^+$): 334.1414; found: 334.1419.

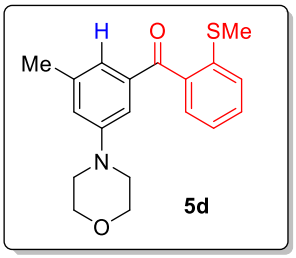
Following the general procedure, **1g** (90.9 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane: ethyl acetate=5:1) on silica gel to give the desired product **5c** (39.2

mg, 40% yield) as a colorless liquid.



5c：a colorless oil. *Rf*=0.11 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 8.3 Hz, 2H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.14 (s, 1H), 7.02 (s, 1H), 6.97 (s, 1H), 3.90 – 3.80 (m, 4H), 3.22 – 3.15 (m, 4H), 2.66 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 197.55, 196.36, 151.31, 141.62, 139.37, 139.00, 137.73, 129.91, 128.02, 122.65, 120.74, 113.81, 66.72, 49.00, 26.85, 21.67, 21.65; IR (KBr): *v* 2961, 2919, 2854, 1687, 1658, 1594, 1449, 1354, 1265, 1236, 1122 cm^{-1}; HRMS (ESI): Calcd for $C_{20}H_{21}NO_3Na$ ($M+Na^+$): 346.1414; found: 346.1420.

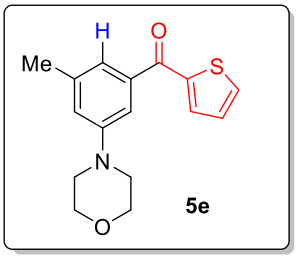
Following the general procedure, **1g** (90.9 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane: ethyl acetate=10:1 to 5:1) on silica gel to give the desired product **5d** (64.4 mg, 67% yield) as a yellow solid.



5d：a yellow solid; mp=126-127 ºC; R*f*=0.25 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz,

Chloroform-*d*) δ 7.45 (ddd, *J* = 8.6, 7.1, 1.5 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.24 – 7.16 (m, 2H), 6.99 (td, *J* = 1.5, 0.7 Hz, 1H), 6.94 (ddd, *J* = 2.4, 1.5, 0.8 Hz, 1H), 3.86 – 3.79 (m, 4H), 3.21 – 3.13 (m, 4H), 2.41 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.91, 151.23, 138.91, 138.81, 138.17, 137.91, 130.76, 129.57, 126.93, 124.15, 122.89, 120.90, 113.57, 66.68, 48.98, 21.57, 16.71; IR (KBr): *v* 3056, 2962, 1919, 2854, 2827, 1656, 1595, 1449, 1433, 1352, 1263, 1122 cm^{-1}; HRMS (ESI): Calcd for $C_{19}H_{21}NO_2SNa$ ($M+Na^+$): 350.1185; found: 350.1191.

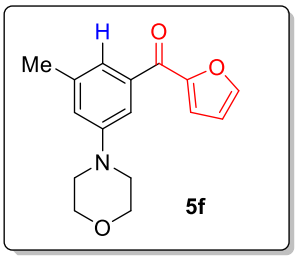
Following the general procedure, **1g** (90.7 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane: ethyl acetate=10:1 to 5:1) on silica gel to give the desired product **5e** (60.6 mg, 71% yield) as a yellow oil.



***5e*:** a yellow oil. R*f*=0.26 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.67 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.21 – 7.12 (m, 3H), 6.95 (s, 1H), 3.90 – 3.82 (m, 4H), 3.24 – 3.16 (m, 4H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.61, 151.25, 143.75, 139.03, 139.00, 134.68, 133.99, 127.87, 121.55, 120.08, 113.25, 66.79, 49.11, 21.74; IR (KBr): *v* 3088, 2960, 2918, 2853, 1636, 1592, 1448, 1412, 1355, 1281, 1241, 1122 cm^{-1}; HRMS (ESI): Calcd for $C_{16}H_{17}NO_2SNa$ ($M+Na^+$): 310.0872; found: 310.0878.

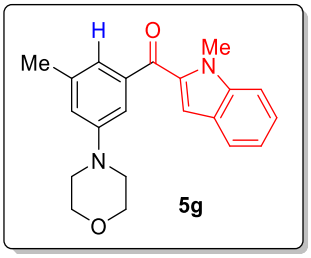
Following the general procedure, **1g** (90.5 mg, 0.3 mmol, 1.0 equiv) was used. Flash column

chromatography (from hexane: ethyl acetate=10:1 to 5:1) on silica gel to give the desired product **5e** (31.2 mg, 40% yield) as a yellow oil.



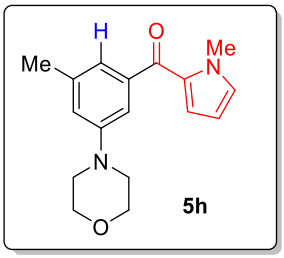
***5f*:** a yellow oil. R*f*=0.14 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.73 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.23 (dd, *J* = 1.9, 0.7 Hz, 2H), 7.20 (dd, *J* = 3.5, 0.8 Hz, 1H), 6.97 (dt, *J* = 2.1, 1.0 Hz, 1H), 6.61 (dd, *J* = 3.6, 1.7 Hz, 1H), 3.88 – 3.80 (m, 4H), 3.23 – 3.14 (m, 4H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, Methylene Chloride-d_2) δ 183.14, 152.72, 151.85, 147.49, 139.49, 138.61, 121.63, 120.75, 120.64, 113.47, 112.41, 67.12, 49.51, 21.84; IR (KBr): *v* 3128, 2960, 2918, 2854, 2363, 2345, 1647, 1594, 1466, 1390, 1251, 1122 cm^{-1}; HRMS (ESI): Calcd for $C_{16}H_{17}NO_3Na$ ($M+Na^+$): 294.1101; found: 294.1109.

Following the general procedure, **1g** (91.4 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane: diethyl ether=1:2) on silica gel to give the desired product **5e** (63.0 mg, 63% yield) as a colorless oil.



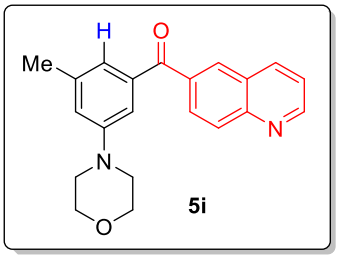
5g : a colorless oil. R*f*=0.13 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.48 – 7.36 (m, 2H), 7.29 – 7.23 (m, 2H), 7.18 (ddd, *J* = 8.0, 6.4, 1.4 Hz, 1H), 7.04 (d, *J* = 0.8 Hz, 1H), 6.98 (t, *J* = 2.0 Hz, 1H), 4.11 (s, 3H), 3.91 – 3.83 (m, 4H), 3.25 – 3.17 (m, 4H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.98, 151.08, 140.19, 140.17, 138.72, 135.20, 125.74, 122.92, 122.30, 120.63, 120.09, 114.37, 113.84, 110.28, 66.78, 49.17, 31.87, 21.71; IR (KBr): *v* 2959, 2854, 1636, 1592, 1510, 1464, 1449, 1390, 1267, 1122 cm^{-1}; HRMS (ESI): Calcd for $C_{21}H_{22}N_2O_2Na$ ($M+Na^+$): 357.1573; found: 357.1572.

Following the general procedure, **1g** (90.6 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane: ethyl acetate=10:1 to 5:1) on silica gel to give the desired product **5h** (44.8 mg, 53% yield) as a colorless oil.



5h : a colorless oil. R*f*=0.15 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.16 – 7.09 (m, 2H), 6.93 – 6.88 (m, 2H), 6.75 (dd, *J* = 4.0, 1.7 Hz, 1H), 6.14 (dd, *J* = 4.0, 2.5 Hz, 1H), 4.02 (s, 3H), 3.90 – 3.82 (m, 4H), 3.23 – 3.15 (m, 4H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 186.54, 150.97, 140.70, 138.51, 131.26, 130.58, 122.57, 121.77, 119.39, 113.47, 107.93, 66.81, 49.25, 37.29, 21.69; IR (KBr): *v* 2960, 2855, 1626, 1591, 1525, 1449, 1404, 1266, 1122, 1060 cm^{-1}; HRMS (ESI): Calcd for $C_{17}H_{20}N_2O_2Na$ ($M+Na^+$): 307.1417; found: 307.1415.

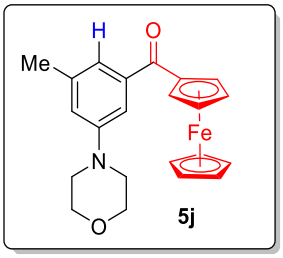
Following the general procedure, **1g** (91.6 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane: diethyl ether=1:2 to 1:5) on silica gel to give the desired product **5i** (56.3 mg, 56% yield) as a colorless oil.



5i

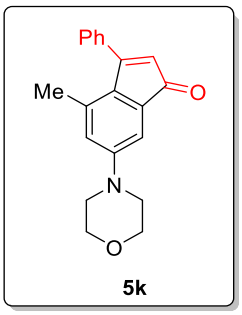
***5i*：** a colorless oil. R*f*=0.15 (hexane/ethyl acetate=1:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.01 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.29 – 8.09 (m, 4H), 7.47 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.18 (t, *J* = 1.7 Hz, 1H), 7.09 (td, *J* = 1.5, 0.7 Hz, 1H), 7.02 – 6.95 (m, 1H), 3.90 – 3.78 (m, 4H), 3.24 – 3.14 (m, 4H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.50, 152.34, 151.28, 151.27, 149.66, 138.96, 138.30, 137.29, 135.73, 131.12, 129.61, 129.49, 127.22, 122.55, 121.87, 120.42, 113.83, 66.71, 49.01, 21.69; IR (KBr): *v* 2961, 2855, 1656, 1593, 1459, 1449, 1360, 1274, 1177, 1122 cm^{-1}; HRMS (ESI): Calcd for $C_{21}H_{20}N_2O_2Na$ ($M+Na^+$): 355.1417; found: 355.1419.

Following the general procedure, **1g** (90.9 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane: ethyl acetate=10:1) on silica gel to give the desired product **5j** (100.7 mg, 86% yield) as a reddish oil.



5j：a reddish oil. R*f*=0.19 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.21 (m, 1H), 7.21 – 7.17 (m, 1H), 6.93 – 6.88 (m, 1H), 4.93 – 4.87 (m, 2H), 4.59 – 4.54 (m, 2H), 4.19 (s, 5H), 3.91 – 3.83 (m, 4H), 3.24 – 3.17 (m, 4H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 199.41, 151.08, 140.60, 138.62, 120.60, 119.41, 112.36, 78.22, 72.36, 71.48, 70.13, 66.76, 49.23, 21.74; IR (KBr): *v* 3096, 2960, 2917, 1855, 2245, 1637, 1592, 1449, 1378, 1353, 1286, 1248, 1122 cm^{-1}; HRMS (ESI): Calcd for $C_{22}H_{23}FeNO_2Na$ ($M+Na^+$): 412.0971; found: 412.0978.

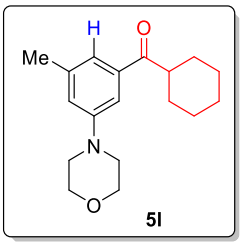
Following the general procedure, **1g** (90.4 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane: ethyl acetate=10:1) on silica gel to give the desired product **5k** (77.8 mg, 85% yield) as a reddish oil.



5k：a reddish oil. R*f*=0.31 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.37 (m, 5H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 5.63 (s, 1H), 3.88 – 3.78

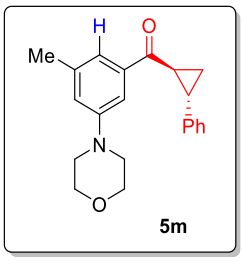
(m, 4H), 3.24 – 3.15 (m, 4H), 1.90 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 197.40, 167.57, 152.16, 136.15, 134.45, 133.95, 131.65, 129.03, 128.33, 126.74, 123.72, 119.48, 119.45, 109.74, 66.53, 48.52, 20.16; IR (KBr): *v* 2988, 1719, 1664, 1450, 1275, 1261 cm^{-1}; HRMS (ESI): Calcd for $C_{20}H_{20}NO_2$ ($M+H^+$): 306.1489; found: 306.1482.

Following the general procedure, **1g** (90.5 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane: ethyl acetate=10:1) on silica gel to give the desired product **5l** (56.8 mg, 66% yield) as a colorless oil.



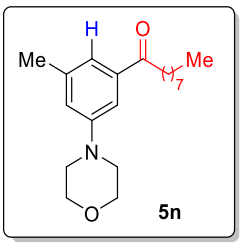
***5l*:** a colorless oil. R*f*=0.32 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 (s, 1H), 7.23 (s, 1H), 6.91 (s, 1H), 3.91 – 3.81 (m, 4H), 3.28 – 3.13 (m, 5H), 2.38 (s, 3H), 1.94 – 1.78 (m, 4H), 1.76 – 1.67 (m, 1H), 1.57 – 1.18 (m, 5H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 204.28, 151.49, 138.95, 137.31, 120.63, 112.19, 66.75, 49.15, 45.60, 29.41, 25.88, 25.77, 21.70; IR (KBr): *v* 2931, 2855, 1676, 1594, 1450, 1262, 1123 cm^{-1}; HRMS (ESI): Calcd for $C_{18}H_{26}NO_2$ ($M+H^+$): 288.1958; found: 288.1962.

Following the general procedure, **1g** (91.3 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane: ethyl acetate=10:1) on silica gel to give the desired product **5m** (66.8 mg, 69% yield) as a reddish oil.



5m： a colorless oil. R*f*=0.25 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.29 (m, 4H), 7.27 – 7.21 (m, 1H), 7.21 – 7.17 (m, 2H), 6.95 (t, *J* = 1.9 Hz, 1H), 3.90 – 3.82 (m, 4H), 3.22 – 3.16 (m, 4H), 2.88 (ddd, *J* = 8.0, 5.2, 4.0 Hz, 1H), 2.71 (ddd, *J* = 9.0, 6.6, 4.0 Hz, 1H), 2.38 (s, 3H), 1.90 (ddd, *J* = 9.2, 5.3, 4.1 Hz, 1H), 1.56 (ddd, *J* = 8.0, 6.6, 4.1 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 198.85, 151.39, 140.46, 139.01, 138.55, 128.42, 126.43, 126.16, 126.15, 120.79, 120.72, 111.86, 66.70, 49.09, 29.80, 29.35, 21.65, 19.29; IR (KBr): *v* 2960, 2919, 2854, 1663, 1594, 1450, 1396, 1353, 1260, 1122 cm^{-1}; HRMS (ESI): Calcd for $C_{21}H_{23}NO_2Na$ (M+Na^{+}): 344.1621; found: 344.1627.

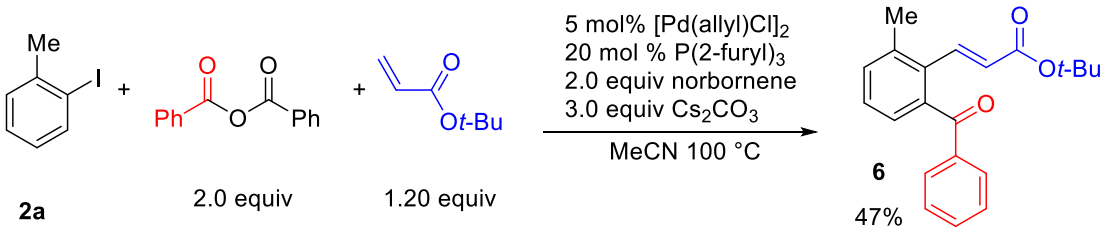
Following the general procedure, **1g** (90.9 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane: ethyl acetate=10:1) on silica gel to give the desired product **5n** (17.6 mg, 19 yield) as a colorless oil.



5n： a colorless oil. R*f*=0.34 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 (s, 1H), 7.26 (s, 1H), 6.92 (s, 1H), 3.90 – 3.82 (m, 4H), 3.24 – 3.13 (m, 4H), 2.92 (t, *J* = 7.4

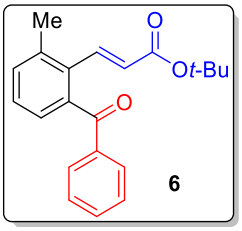
Hz, 2H), 2.38 (s, 3H), 1.78 – 1.65 (m, 2H), 1.45 – 1.17 (m, 10H), 0.97 – 0.78 (m, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 201.07, 151.49, 139.07, 138.05, 120.82, 120.75, 111.97, 66.84, 49.24, 38.76, 31.83, 29.43, 29.37, 29.17, 24.49, 22.65, 21.74, 14.10; IR (KBr): *v* 2955, 2925, 2854, 1663, 1594, 1450, 1396, 1353, 1260, 1122 cm^{-1}; HRMS (ESI): Calcd for $C_{20}H_{31}NO_2Na$ (M+Na$^+$): 340.2247; found: 340.2253.

Scheme 3.18 Preparation of compound **6**.



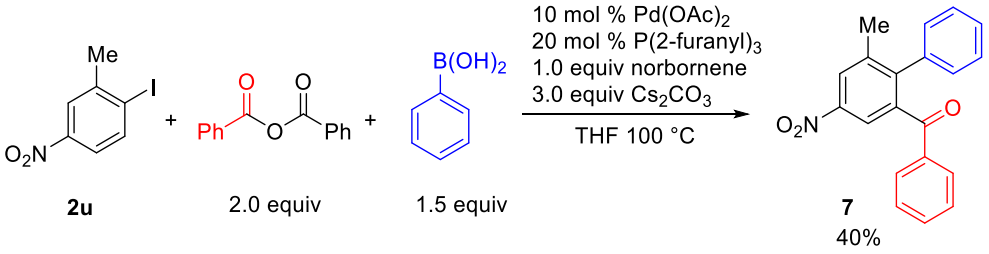
An oven-dried 7.5 mL vial was charged with 2-iodotoluene (89.0 mg; 0.4 mmol, 1.0 equiv), benzoyl anhydride (182.0 mg; 0.8 mmol, 2.0 equiv), Cs_2CO_3 (395.4 mg, 1.20 mmol, 3.0 equiv), *tert*-butyl acrylate (61.4 mg, 0.48 mmol, 1.20 equiv), norbornene (75.0 mg, 0.80 mmol, 2.0 equiv), allylpalladium(II) chloride dimer (6.7 mg, 0.02mmol, 0.05 equiv) and tris(2-furyl)phosphine (18.8 mg, 0.08 mmol, 0.20 equiv). They were sealed outside, then transferred in a nitrogen-filled glovebox. Degassed acetonitrile (6 mL) was added to the vial, and the resulting mixture was stirred at room temperature for 10 minutes until everything was fully dissolved. Then the vial was tightly sealed and subsequently transferred out of glovebox and stirred on a pie-block preheated to 100℃ for 24 hours. After completion of the reaction, the mixture was filtered through a thin pad of celite. The filter cake was washed with ethyl acetate, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography (hexane/ethyl acetate = 30: 1 to 20:

1) on silica gel to give the desired product **6** (61.3 mg, 47% yield) as a white solid. The X-ray crystal was obtained from hexane/ethyl acetate as the solvent.

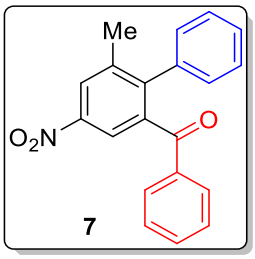


6：a white solid; mp=86-89 ºC. R*f*=0.19 (hexane/ethyl acetate=10:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 – 7.65 (m, 2H), 7.60 – 7.49 (m, 2H), 7.39 (ddd, *J* = 8.0, 6.7, 1.2 Hz, 2H), 7.36 – 7.26 (m, 3H), 5.78 (d, *J* = 16.1 Hz, 1H), 2.40 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 198.61, 165.07, 140.45, 139.62, 137.76, 137.42, 133.46, 133.03, 132.15, 129.67, 128.39, 128.36, 128.14, 127.01, 126.43, 80.45, 27.98, 20.44; IR (KBr): *v* 3062, 2977, 2931, 1711, 1668, 1449, 1317, 1283, 1151 cm^{-1}; HRMS (ESI): Calcd for $C_{21}H_{22}O_3Na$ ($M+Na^+$): 345.1461; found: 345.1464.

Scheme 3.19 Preparation of compound **7**.

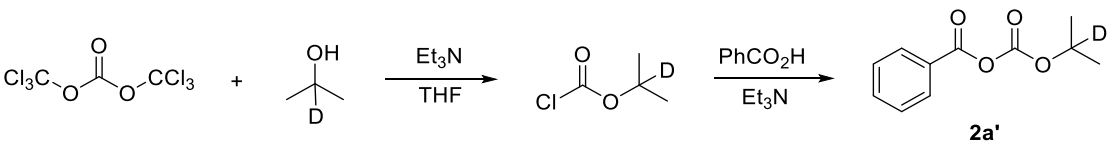


An oven-dried 7.5 mL vial was charged with **2u** (106.5 mg; 0.4 mmol, 1.0 equiv), benzoyl anhydride (182.0 mg; 0.8 mmol, 2.0 equiv), Cs_2CO_3 (395.9 mg, 1.20 mmol, 3.0 equiv), phenyl boronic acid (73.9 mg, 0.60 mmol, 1.50 equiv), norbornene (37.5 mg, 0.40 mmol, 1.0 equiv), palladium acetate (9.0 mg, 0.04mmol, 0.01 equiv) and tris(2-furyl)phosphine (18.6 mg, 0.08 mmol, 0.20 equiv). They were sealed outside, then transferred in a nitrogen-filled glovebox. Degassed THF (6mL) was added to the vial, the resulting mixture was stirred at room temperature for 10 minutes. Then the vial was tightly sealed and subsequently transferred out of glovebox and stirred on a pie-block preheated to 100 ℃ for 24 hours. After completion of the reaction, the mixture was filtered through a thin pad of celite. The filter cake was washed with ethyl acetate, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography (hexane: ethyl acetate = 30: 1) on silica gel to give the desired product 7 (51.2 mg, 40% yield) as a yellow oil.

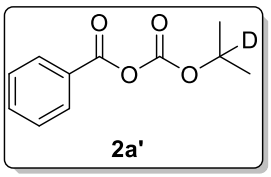


***6*:** a yellow oil. R*f*=0.32 (hexane/ethyl acetate=10:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 – 8.26 (m, 1H), 8.17 – 8.13 (m, 1H), 7.60 – 7.53 (m, 2H), 7.50 – 7.43 (m, 1H), 7.36 – 7.28 (m, 2H), 7.26 – 7.16 (m, 3H), 7.10 – 7.02 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.15, 146.39, 146.34, 141.33, 139.29, 136.59, 133.40, 129.64, 129.02, 128.26, 128.17, 128.04, 125.88, 120.13, 20.67; IR (KBr): *v* 3062, 2929, 1673, 1597, 1524, 1449, 1347, 1291 cm^{-1}; HRMS (ESI): Calcd for $C_{20}H_{16}NO_3$ ($M+H^+$): 318.1130; found: 318.1130.

Scheme 3.20 Preparation of Deuterated **2a'**.



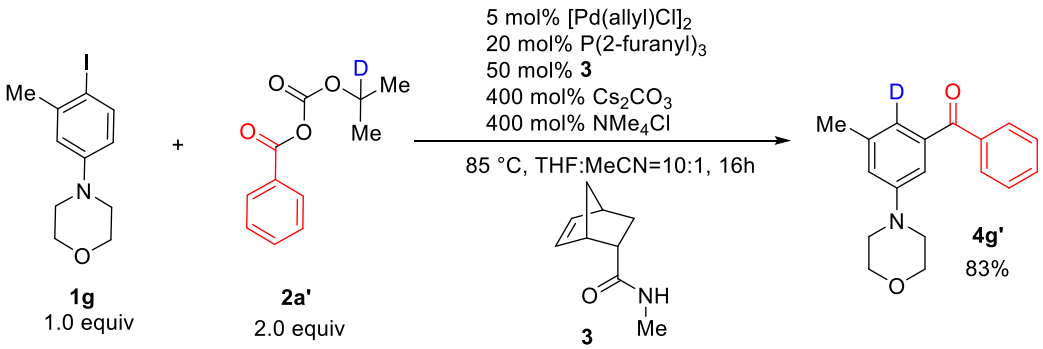
Under a nitrogen atmosphere, a solution of triethylamine (3.34 mL, 24.0 mmol, 1.2 equiv) and 2-D-isopropanol (1.83 mL, 24.0 mmol, 1.2 equiv) in 50 mL THF was cooled down to 0 °C. A solution of triphosgene (2.67 g, 9.0 mmol, 0.45 equiv) in 50 mL THF was then added dropwise. The mixture was slowly warmed to room temperature and stirred for additional 2 hours. At 0 °C, the THF solution of benzoic acid (2.44 g, 20.0 mmol, 1.0 equiv) and trimethylamine (2.78 mL, 20.0 mmol, 1.0 equiv) was added dropwise via addition funnel over 40 min. Then the reaction mixture was stirred at room temperature for additional 1 hour monitored by TLC. When TLC shows full conversion, 10% critic acid (50 mL) was added to the reaction mixture until the system became clear. After extraction with ethyl ether (50 mL×3), the organic layer was washed with saturated sodium bicarbonate solution (50 mL) and brine (50 mL×2), and dried over $MgSO_4$. The crude product was further purified by reduced pressure distillation (boiling point: 67-68 °C at 15 mTorr).



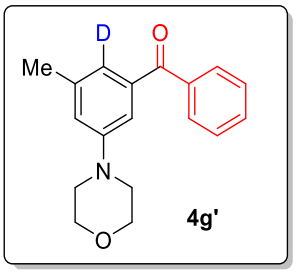
2a': a colorless oil. 1.93 g, 20 mmol scale, 46% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 – 8.03 (m, 2H), 7.68 – 7.59 (m, 1H), 7.51 – 7.44 (m, 2H), 1.40 (t, *J* = 0.8 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.37 , 148.74 , 134.41 , 130.46 , 128.67 , 127.77 , 74.20 (t, *J* = 22.7

Hz), 21.32; HRMS (ESI): Calcd for $C_{11}H_{11}DO_4Na$ ($M+Na^+$): 232.0691; found: 232.0694.

Scheme 3.21 Preparation of Deuterated **4g'**.



Following the general procedure, **1g** (90.7 mg, 0.3 mmol, 1.0 equiv) was used. Flash column chromatography (from hexane: ethyl acetate=10:1) on silica gel to give the desired product **4g'** (70.3 mg, 83% yield) as a yellow oil.



***4g'*:** a yellow oil. R*f*=0.19 (hexane/ethyl acetate=5:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.74 (m, 2H), 7.61 – 7.54 (m, 1H), 7.51 – 7.43 (m, 2H), 7.16 (d, *J* = 2.5 Hz, 1H), 6.95 (d, *J* = 2.5 Hz, 1H), 3.88 – 3.82 (m, 4H), 3.22 – 3.15 (m, 4H), 2.36 (s, 3H).^{13}C NMR (101 MHz, Chloroform-*d*) δ 197.07, 151.16, 138.64, 138.62, 138.31, 137.78, 132.20, 129.92, 128.34, 128.11, 122.60 (C-

D), 122.33 (C-D), 122.08 (C-D), 120.24, 120.22, 113.88, 66.73, 49.07, 29.61, 21.57; HRMS (ESI): Calcd for $C_{18}H_{18}DNO_2Na$ ($M+Na^+$): 305.1371; found: 305.1385.

3.6 NMR Spectra and X-ray

Figure 3.1 ^{1}H and ^{13}C NMR spectrum of compound **3.**

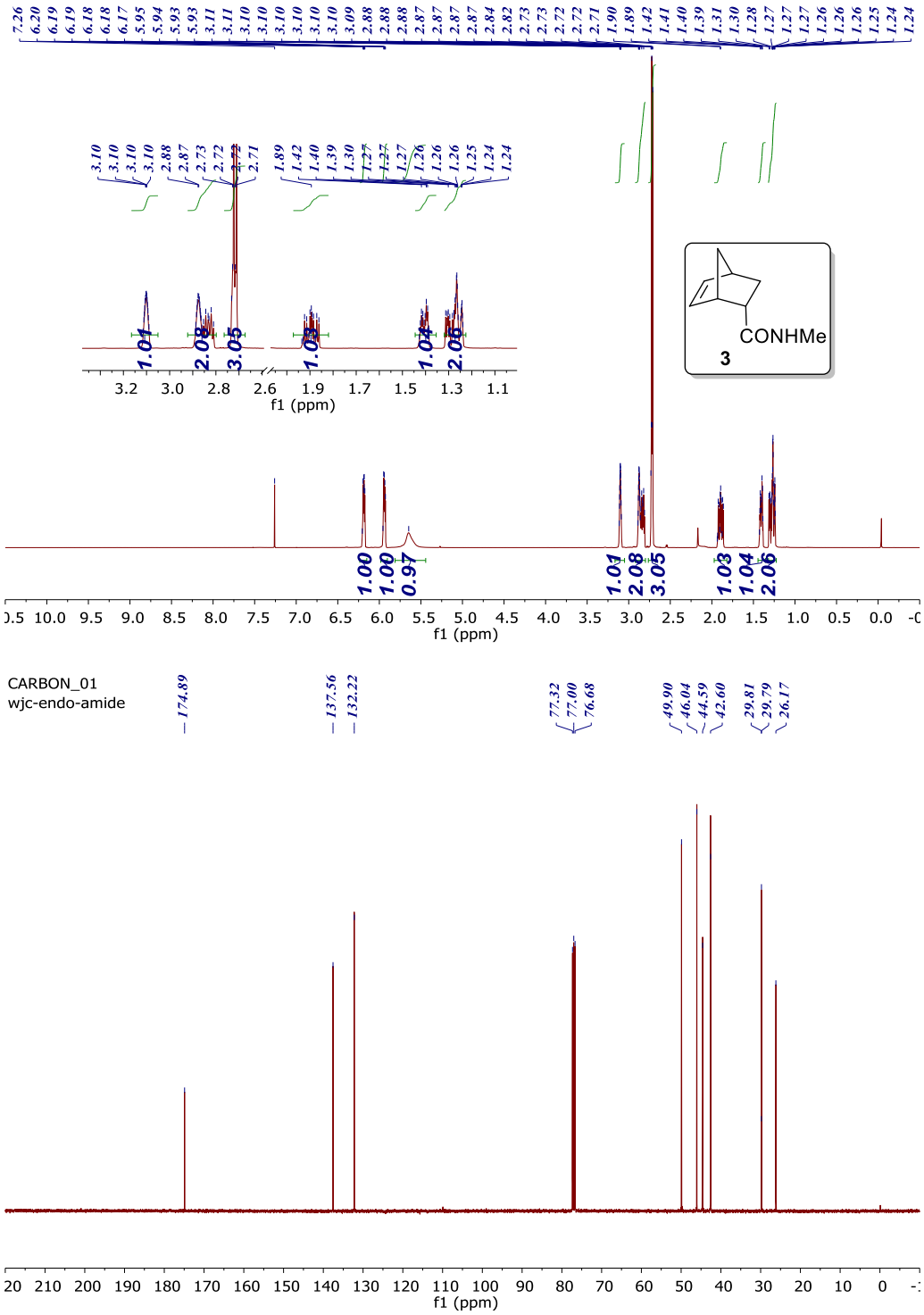


Figure 3.2 ^{1}H and ^{13}C NMR spectrum of compound **1g.**

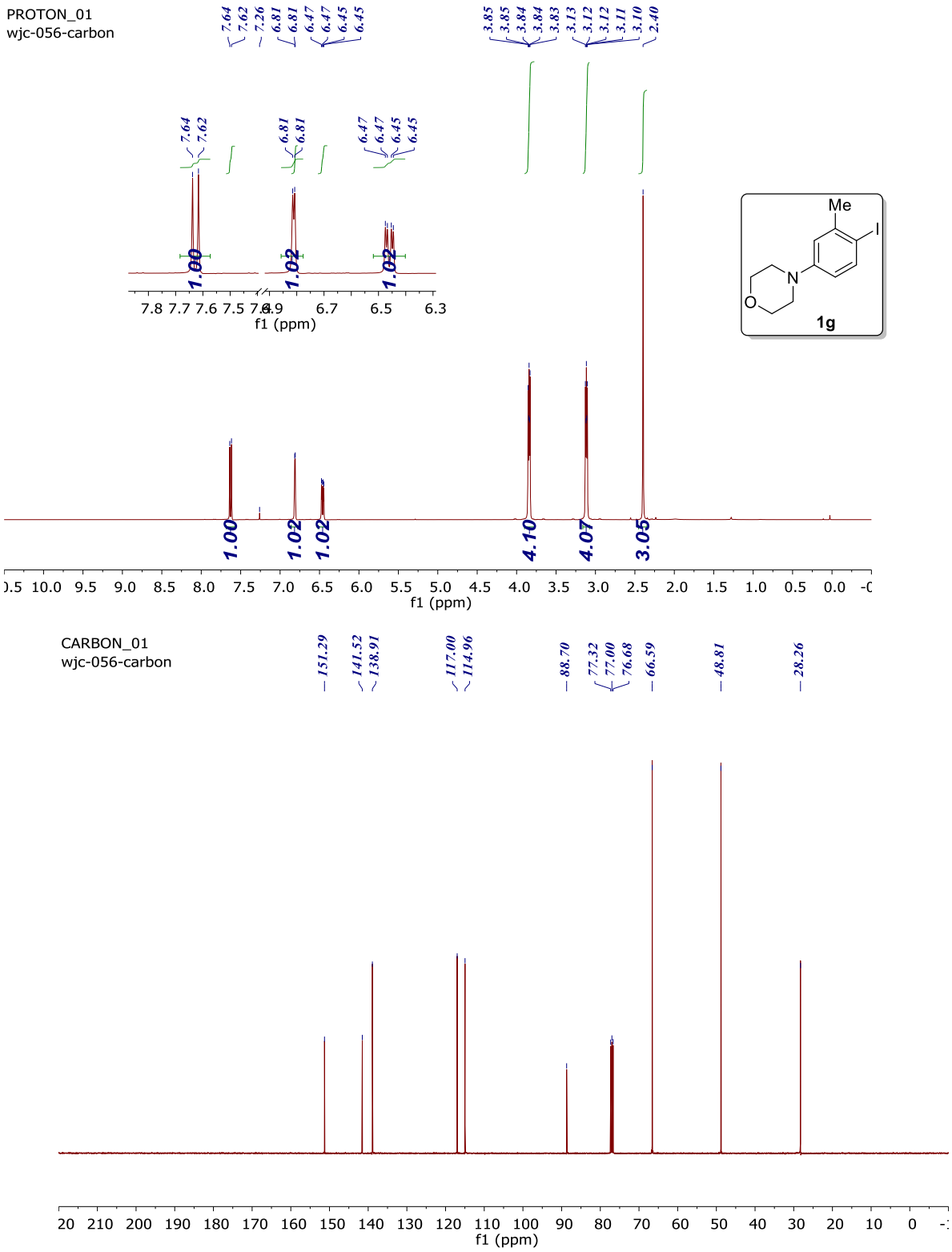


Figure 3.3 ^{1}H and ^{13}C NMR spectrum of compound **1l.**

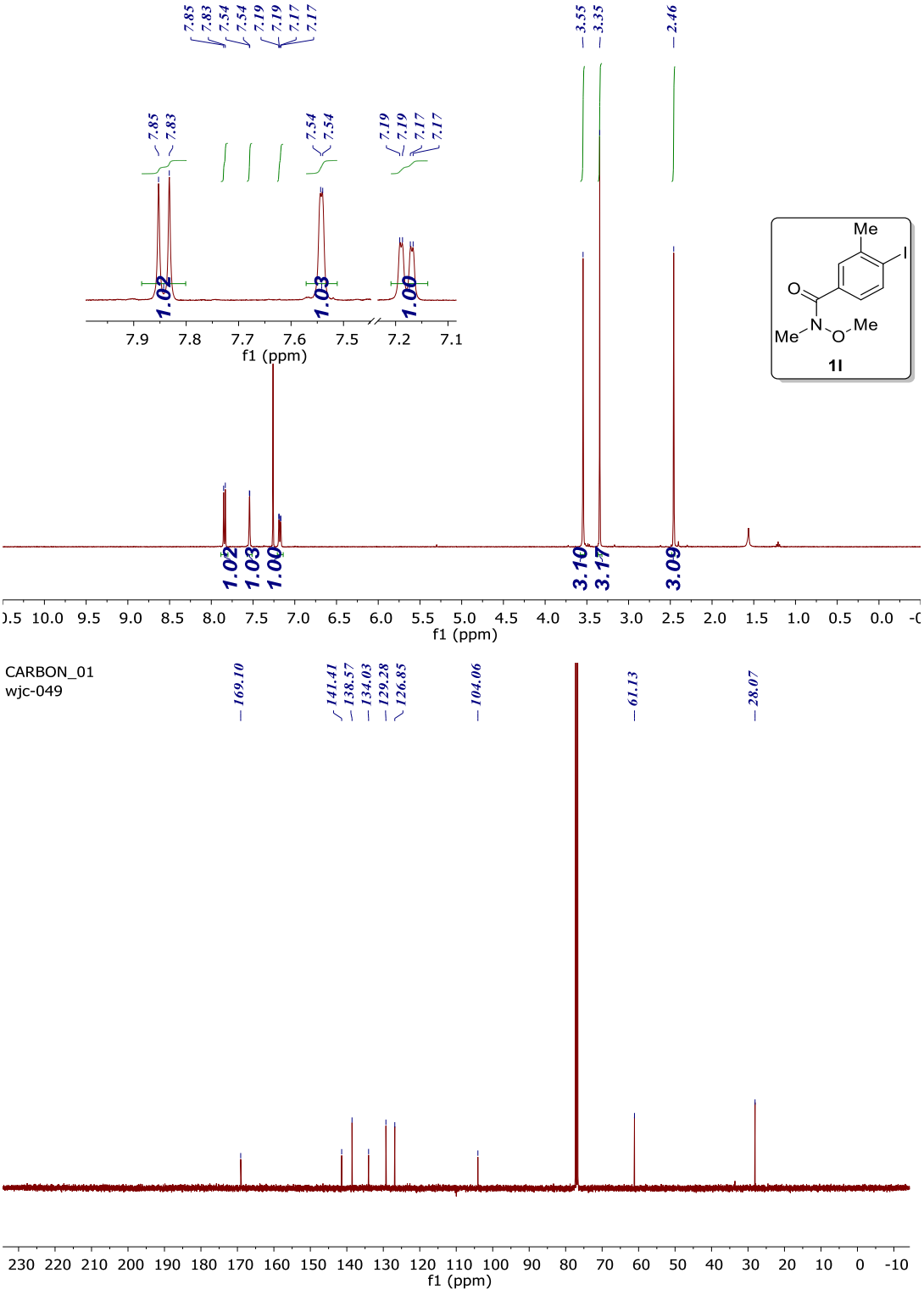


Figure 3.4 ^{1}H and ^{13}C NMR spectrum of compound **1m.**

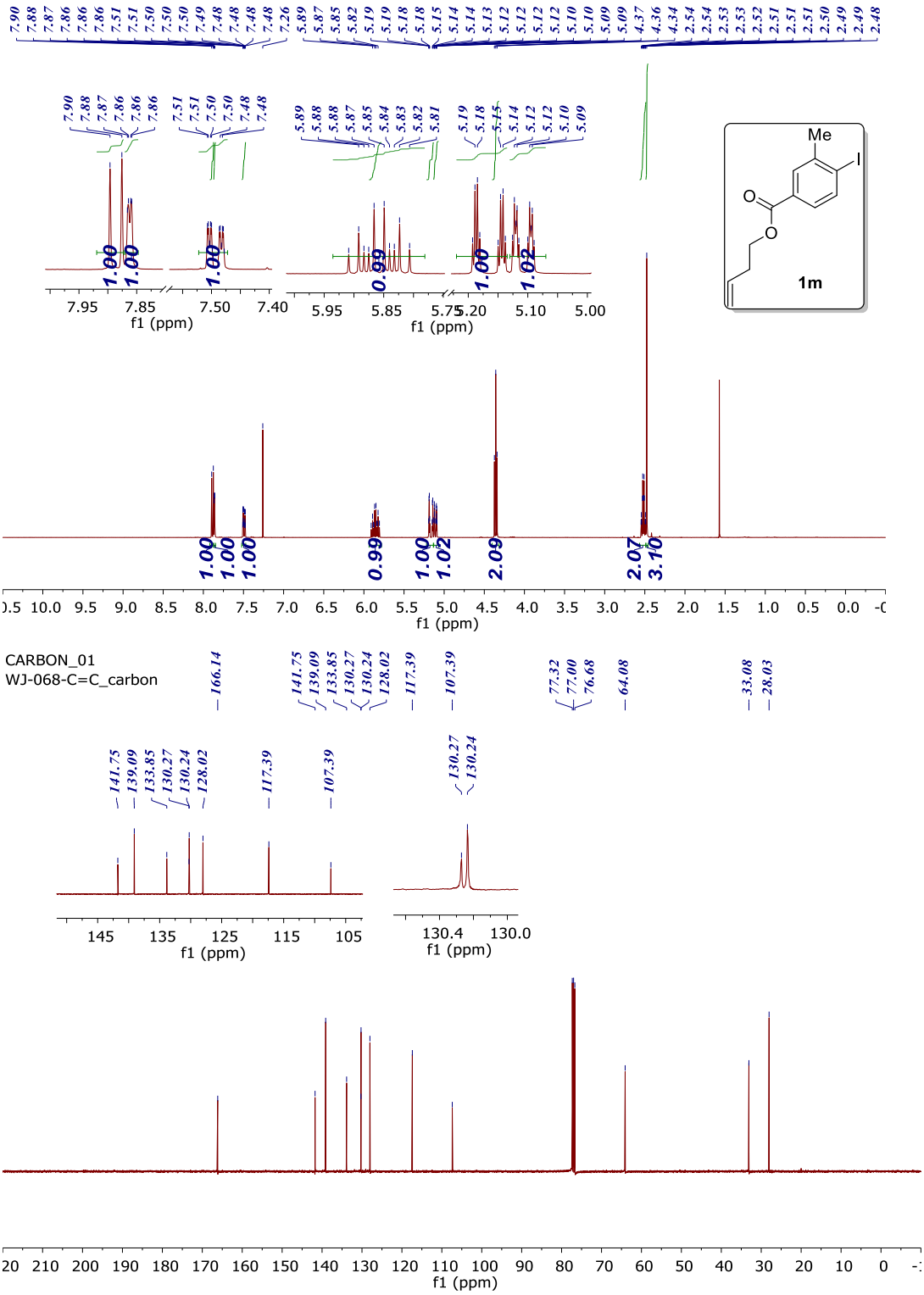


Figure 3.5 ^{1}H and ^{13}C NMR spectrum of compound **1n.**

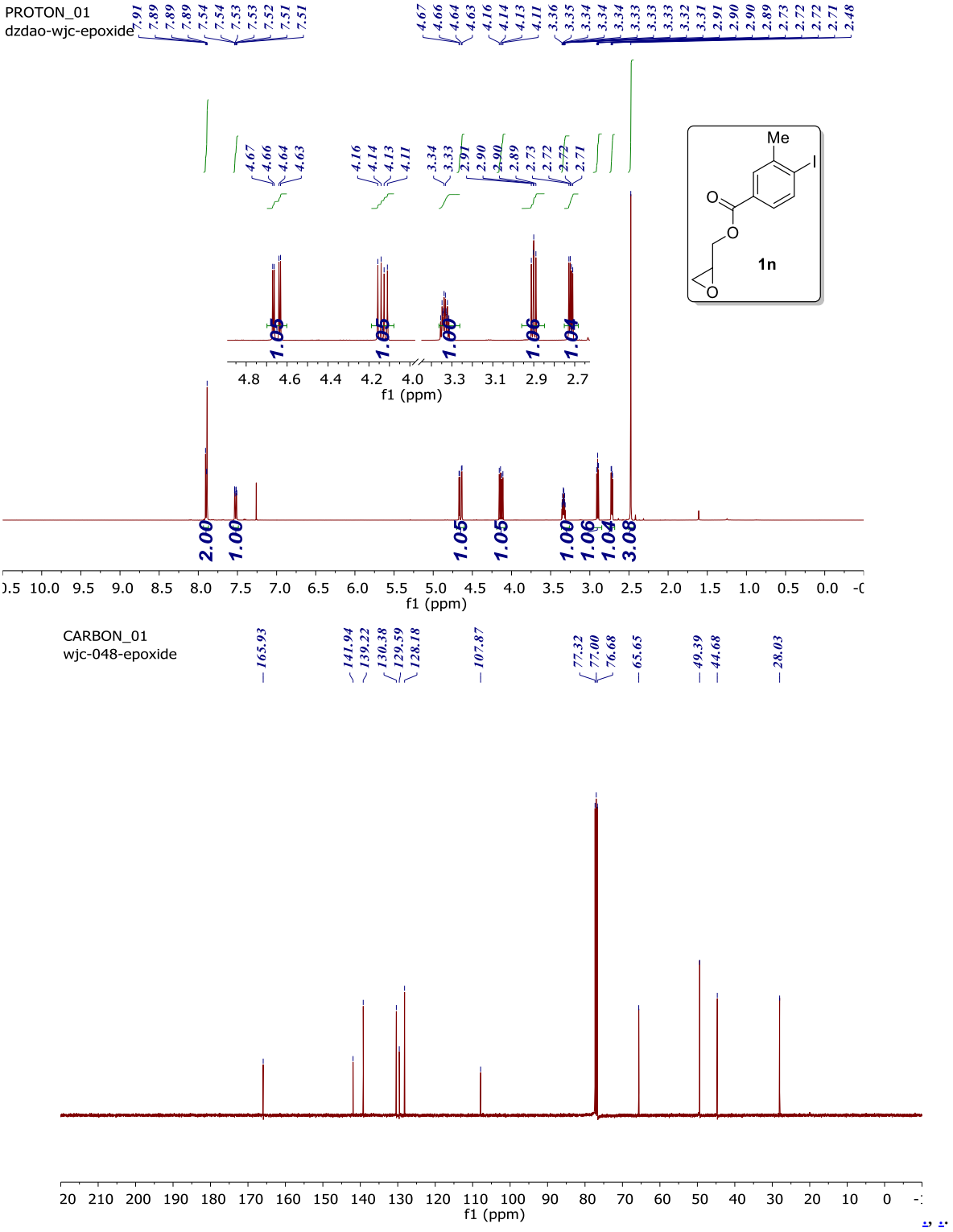


Figure 3.6 ^{1}H and ^{13}C NMR spectrum of compound **1o.**

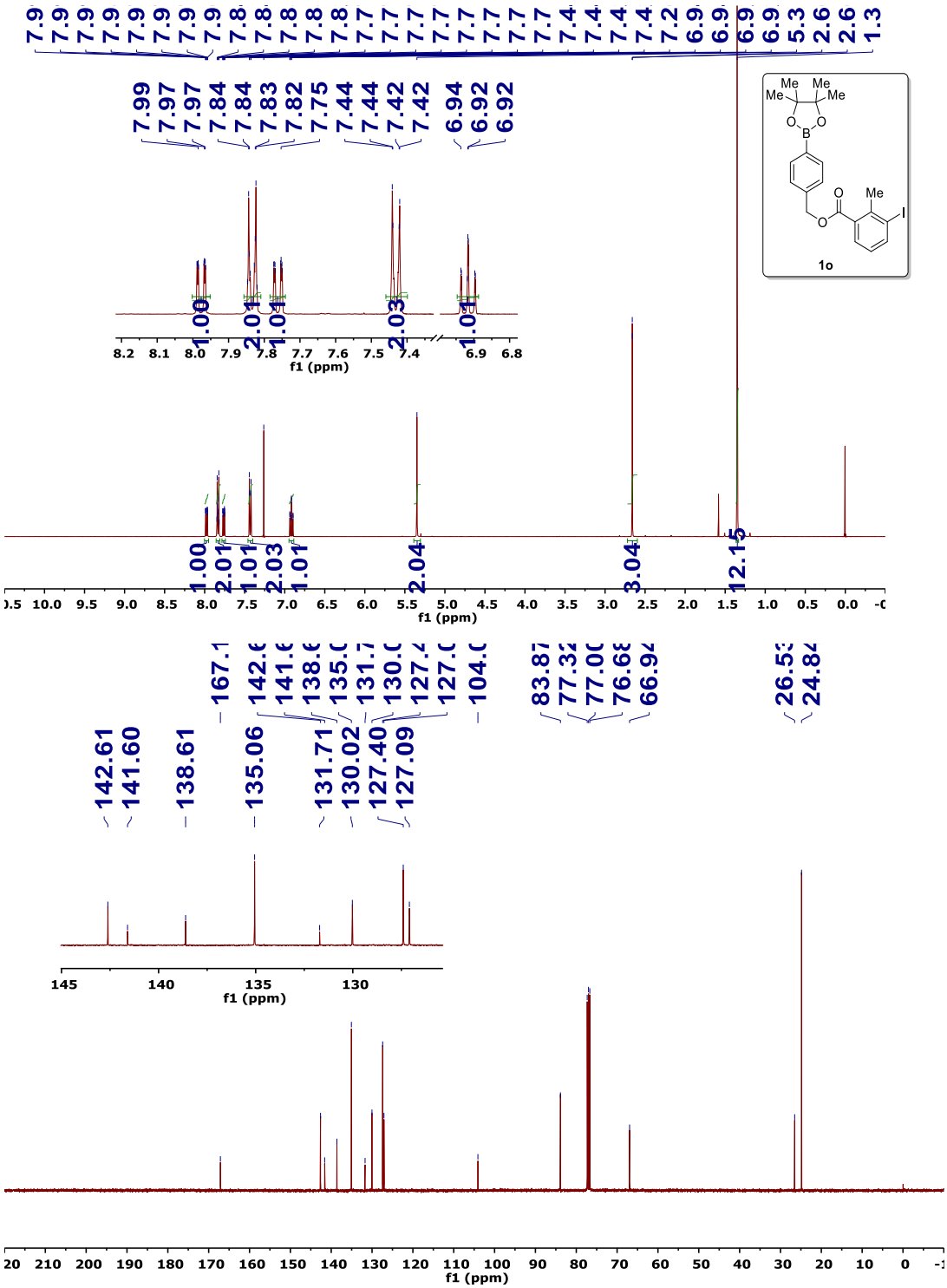


Figure 3.7 ^{1}H and ^{13}C NMR spectrum of compound **1p.**

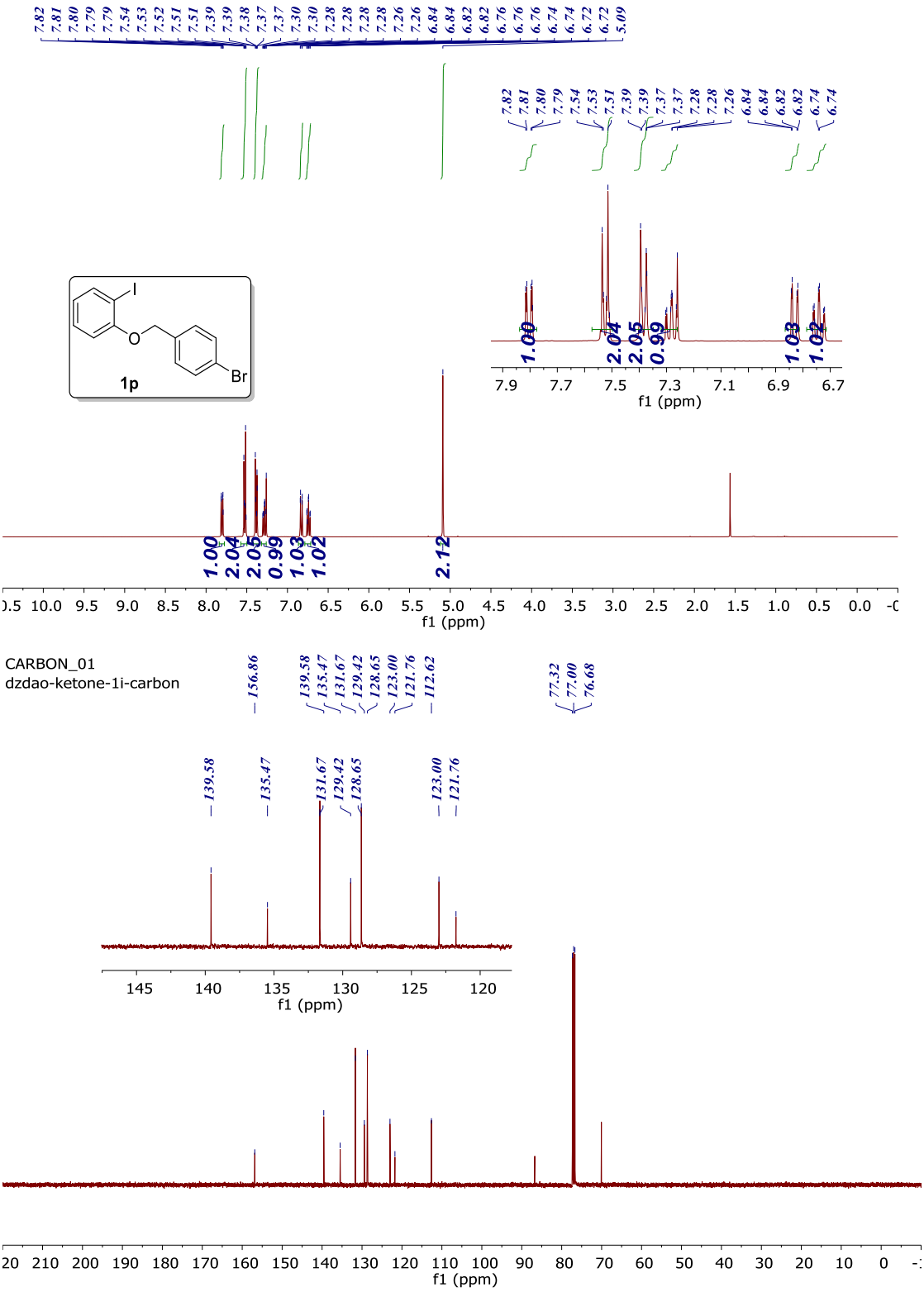


Figure 3.8 ^{1}H and ^{13}C NMR spectrum of compound **1s.**

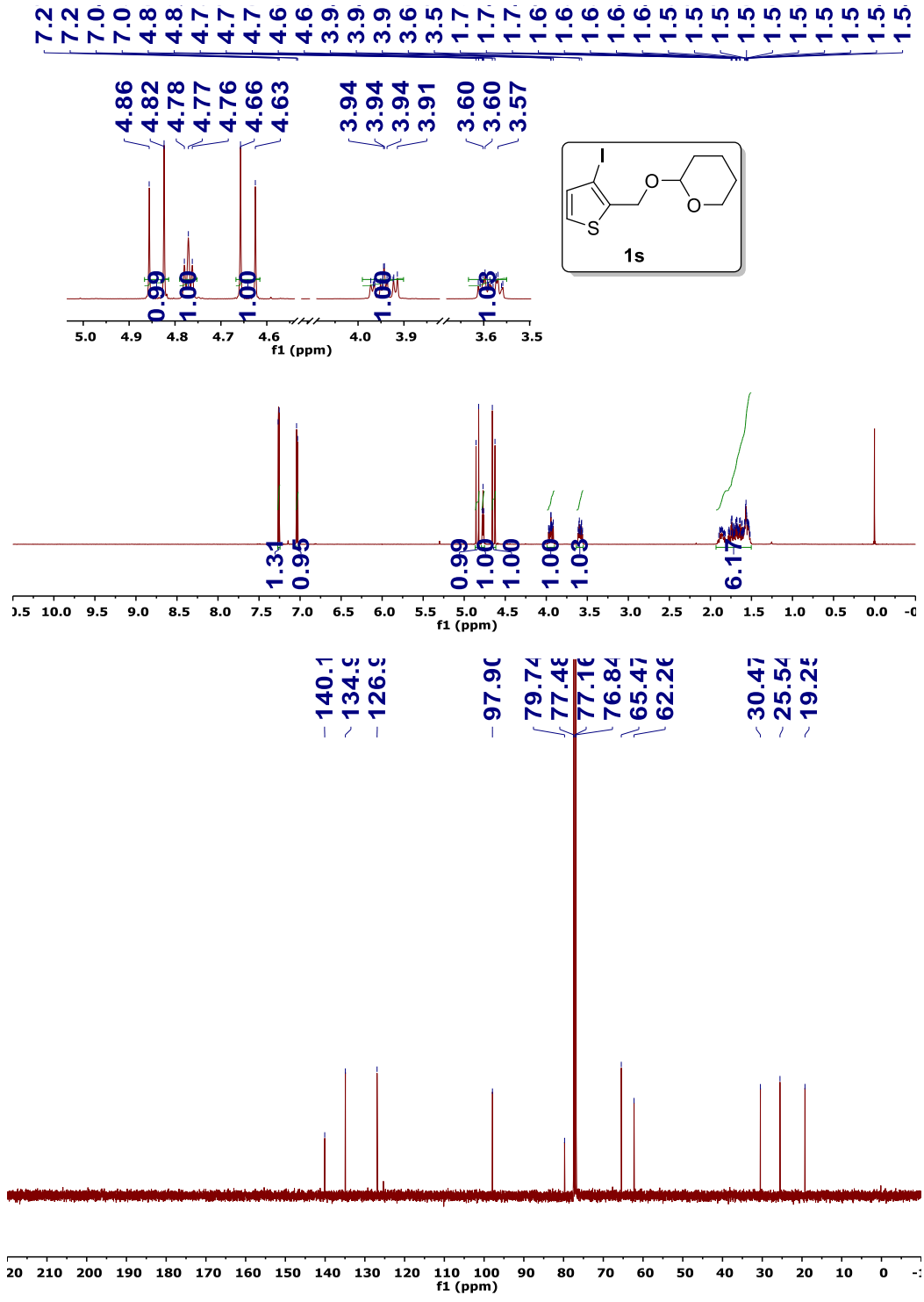


Figure 3.9 ^{1}H and ^{13}C NMR spectrum of compound **2a.**

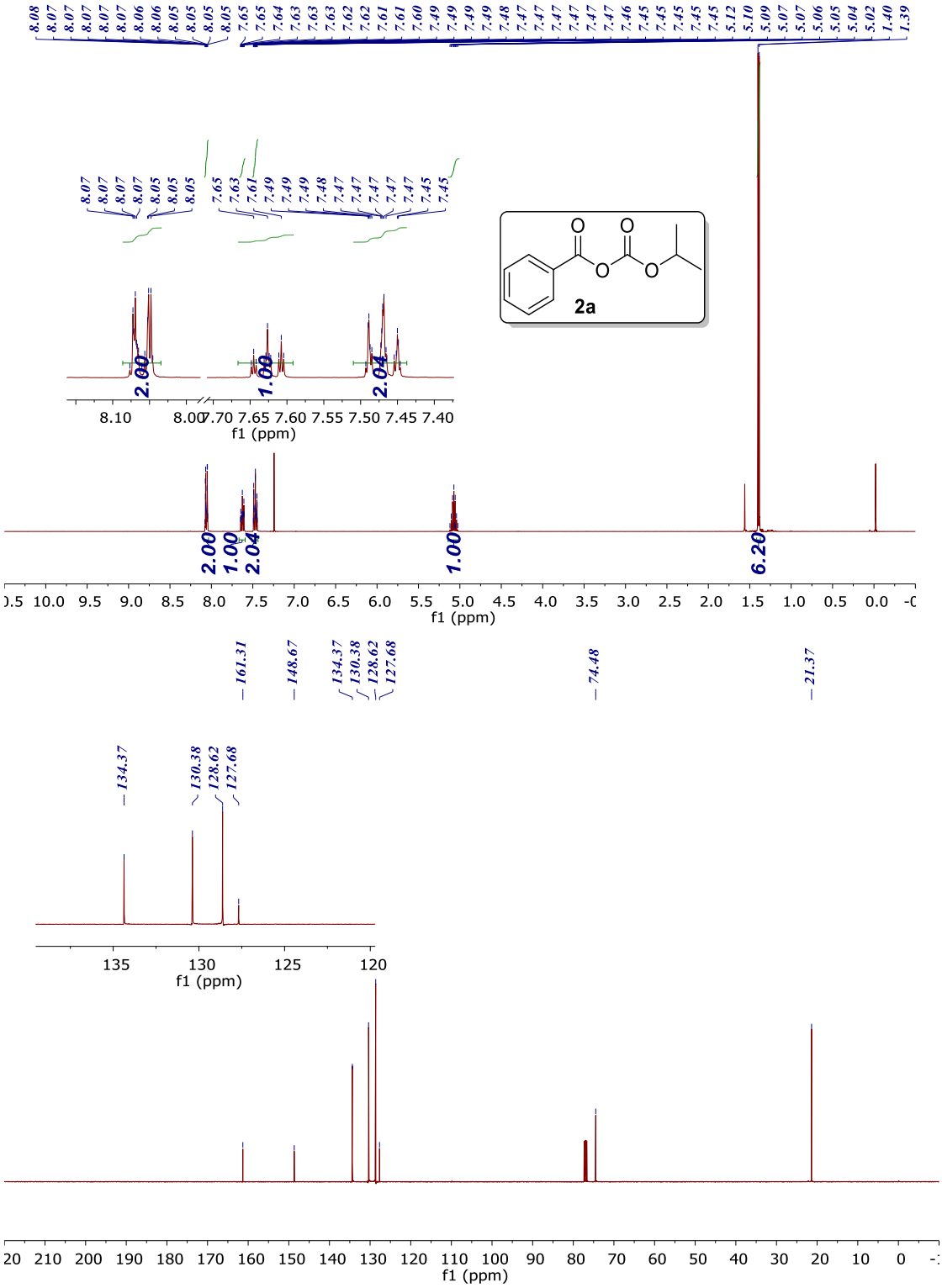


Figure 3.10 ^{1}H and ^{13}C NMR spectrum of compound **2b.**

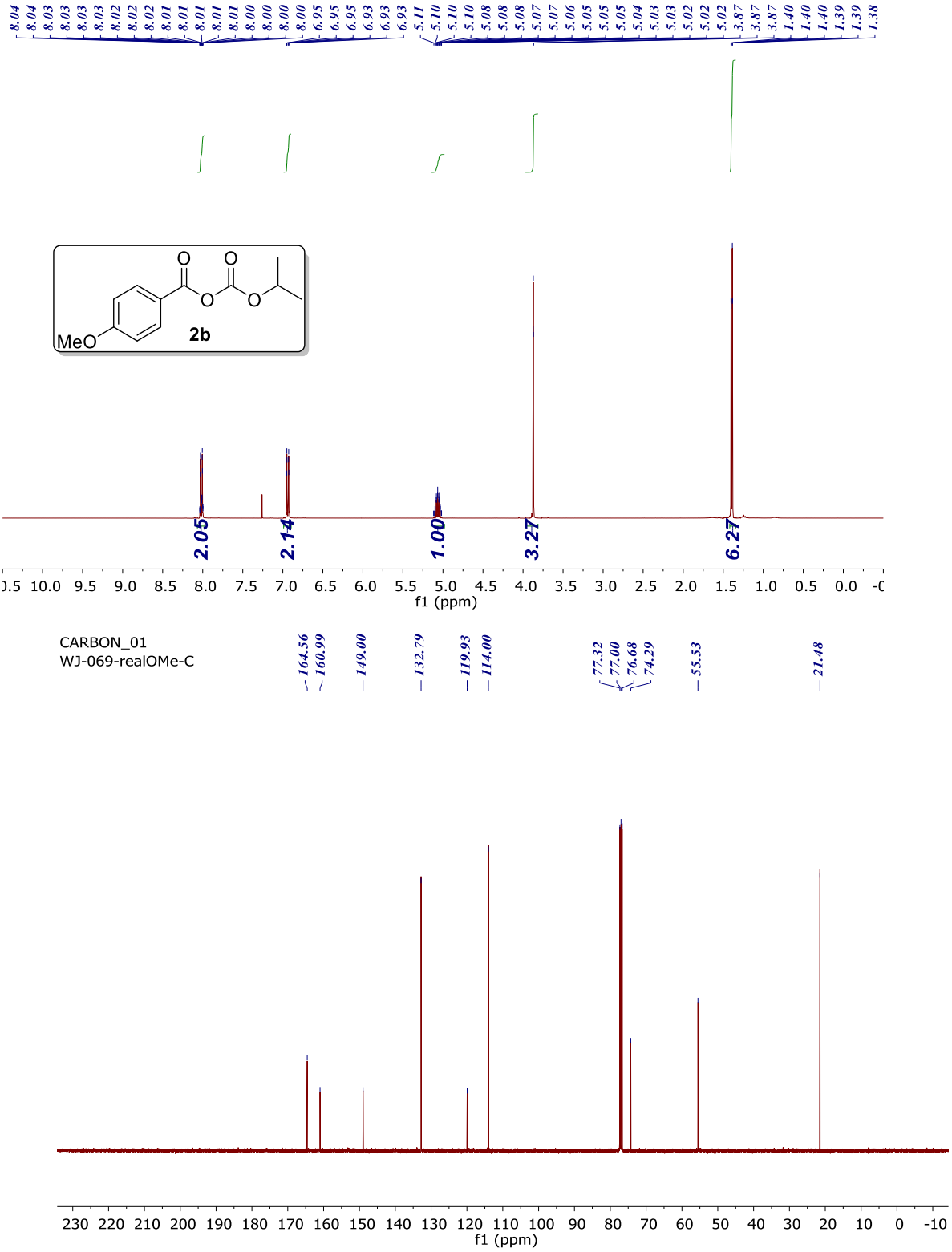


Figure 3.11 ^{1}H and ^{13}C NMR spectrum of compound **2c.**

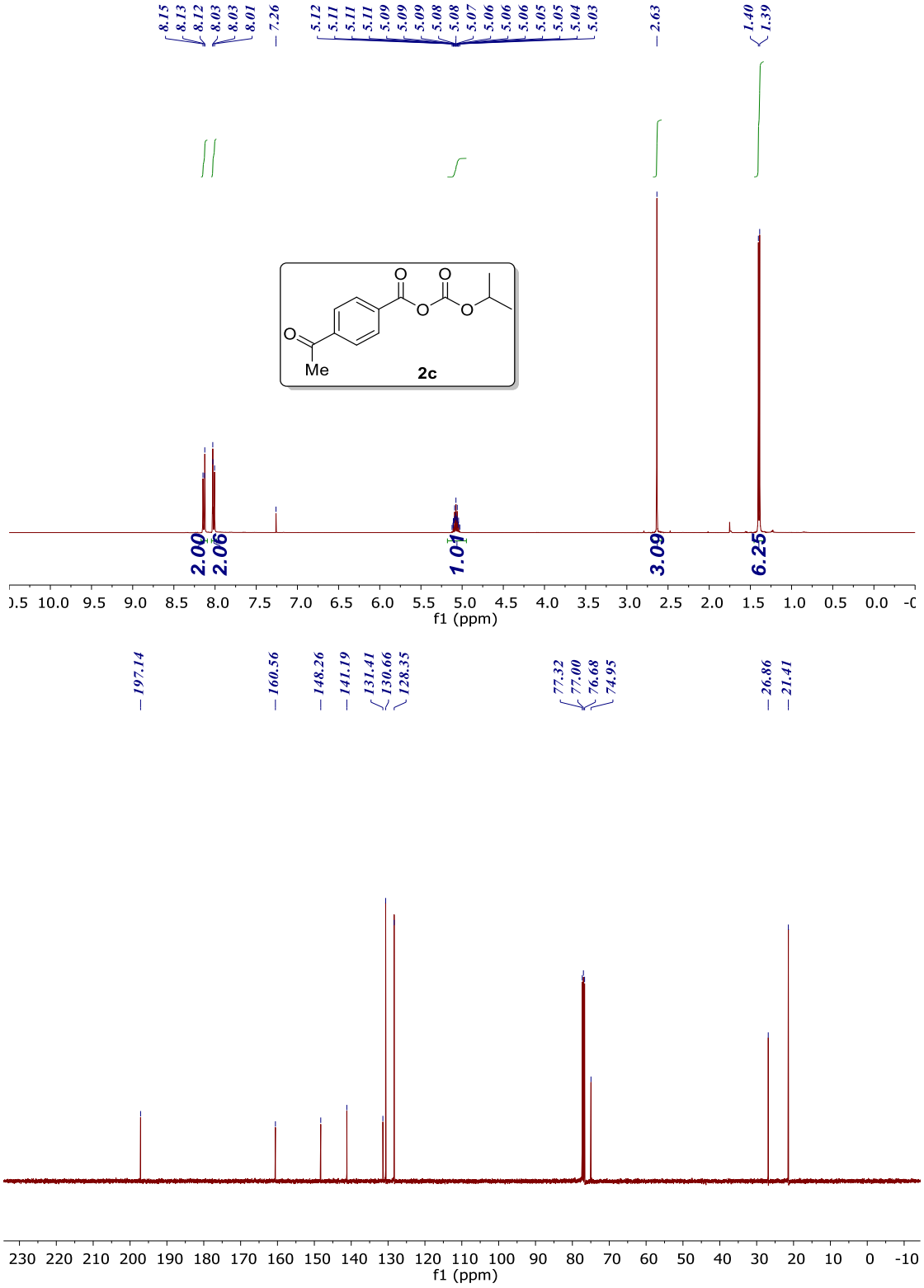


Figure 3.12 ^{1}H and ^{13}C NMR spectrum of compound **2d.**

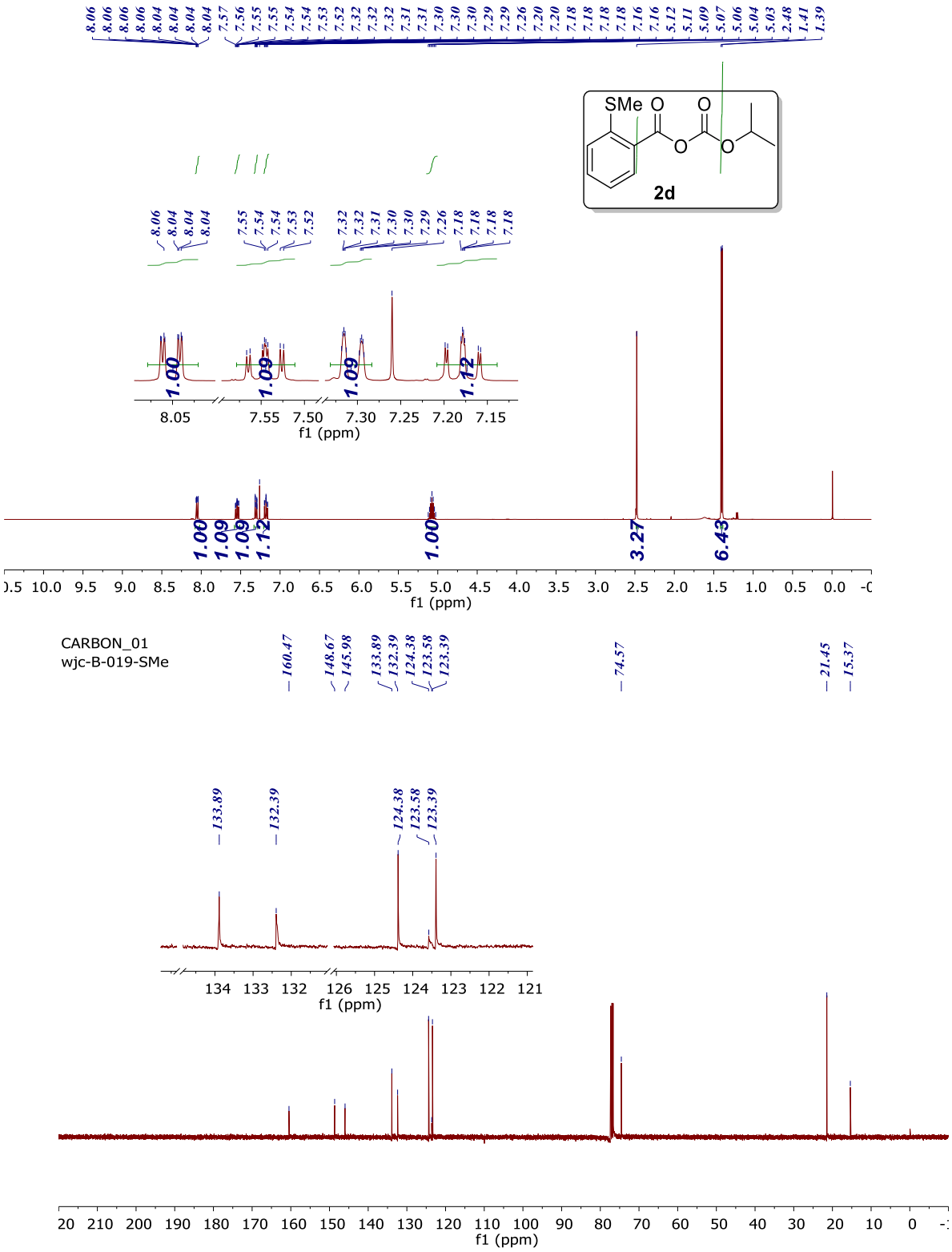


Figure 3.13 ^{1}H and ^{13}C NMR spectrum of compound **2e.**

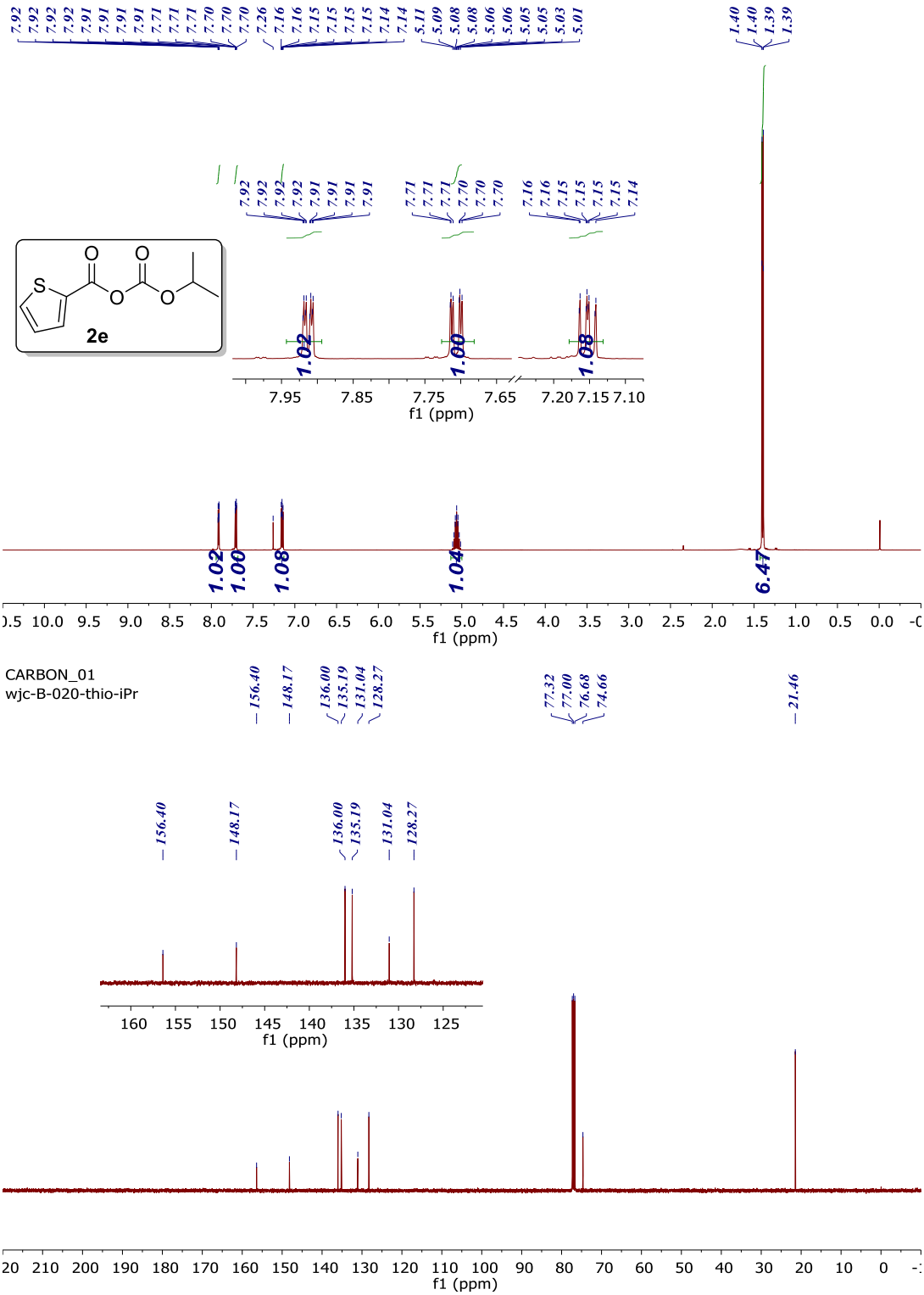


Figure 3.14 ^{1}H and ^{13}C NMR spectrum of compound **2f.**

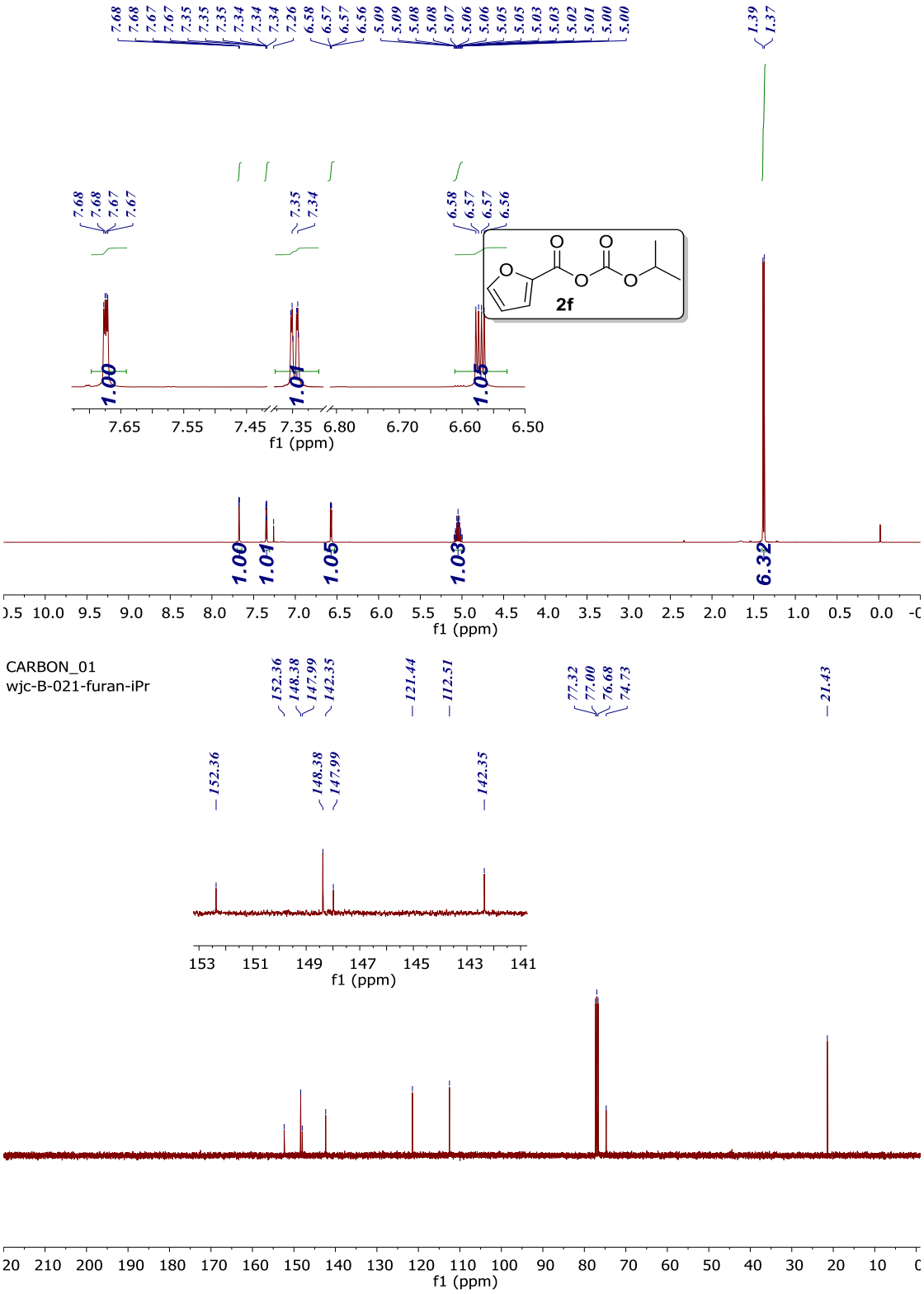


Figure 3.15 ^{1}H and ^{13}C NMR spectrum of compound **2g.**

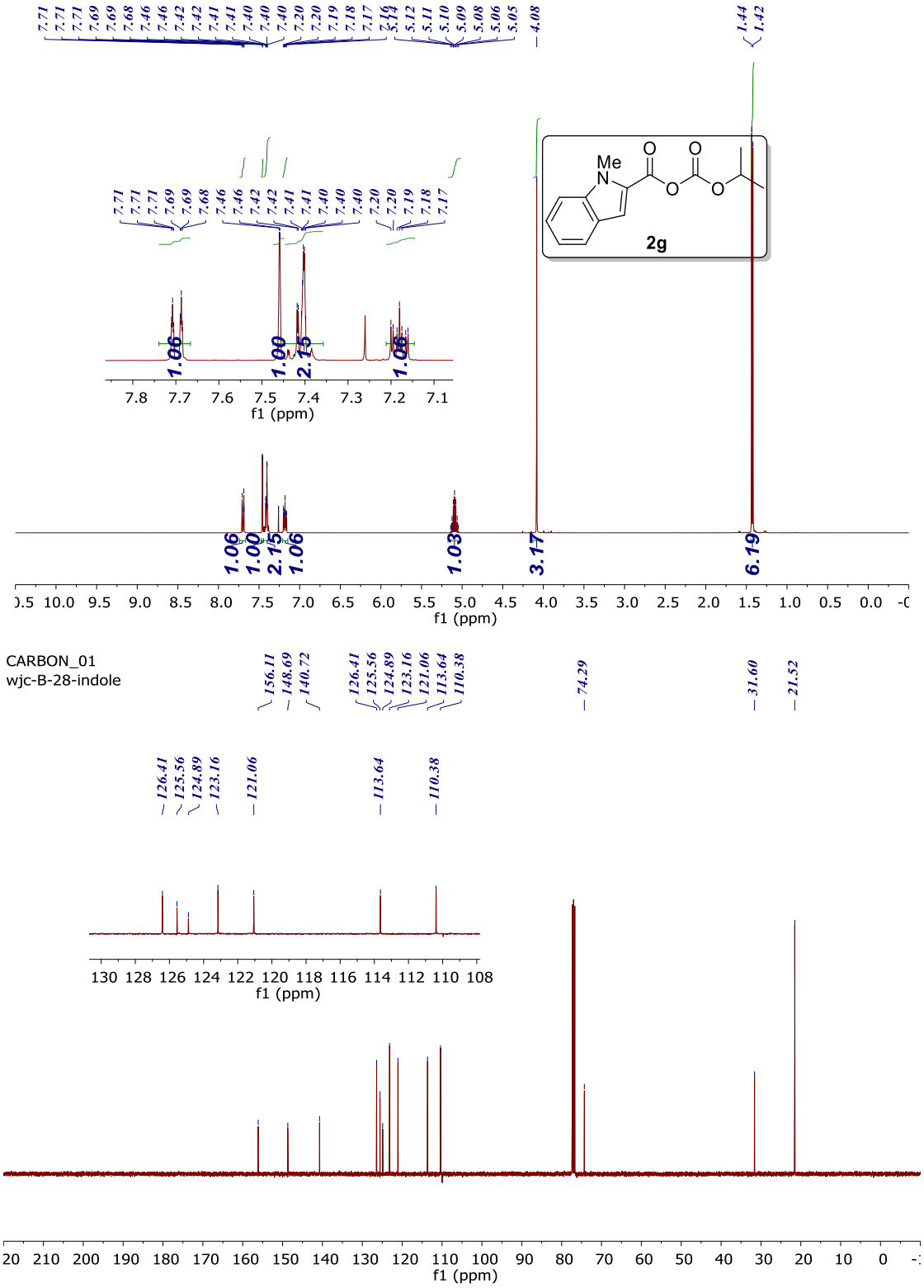


Figure 3.16 ^{1}H and ^{13}C NMR spectrum of compound **2h.**

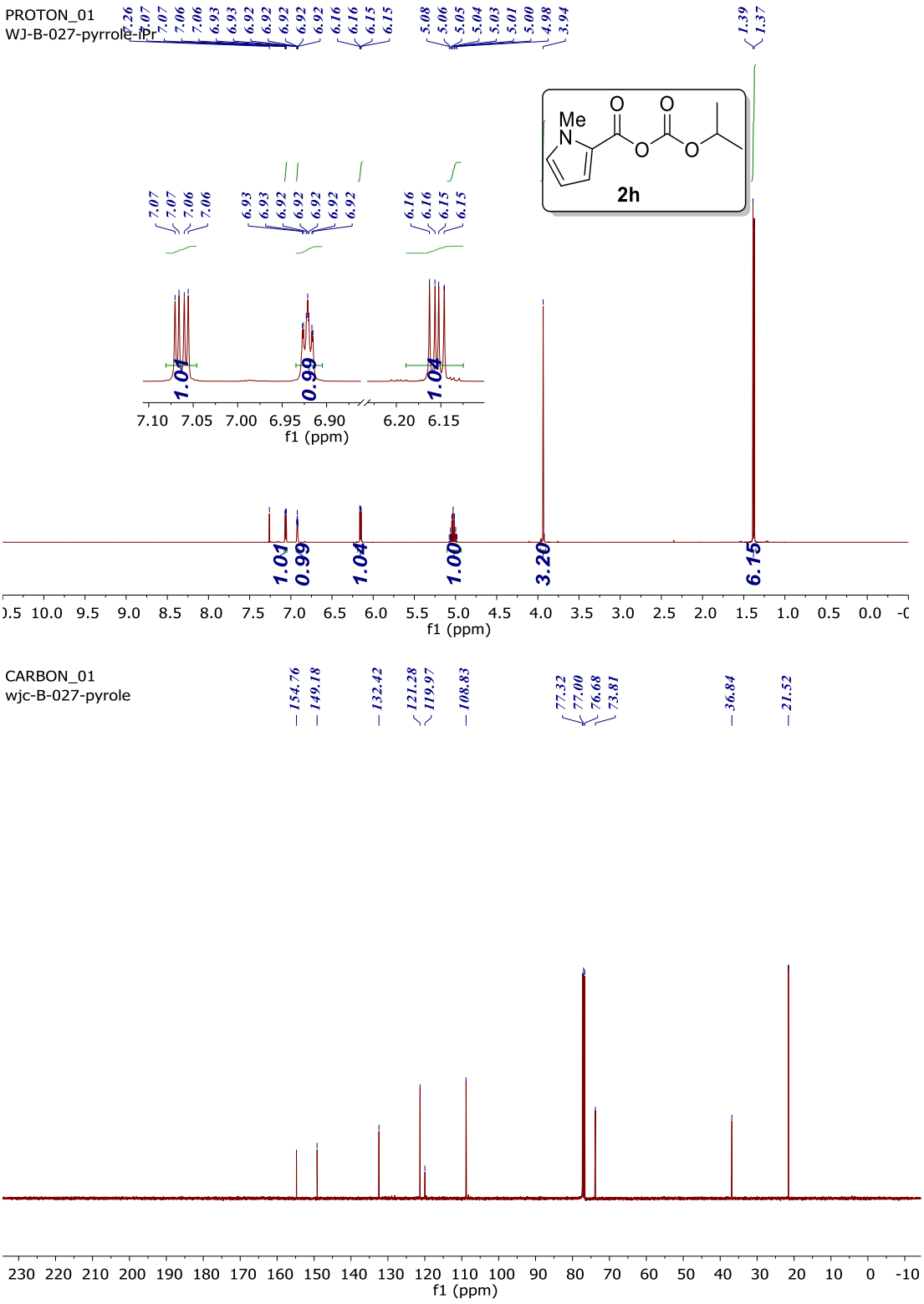


Figure 3.17 ^{1}H and ^{13}C NMR spectrum of compound **2i.**

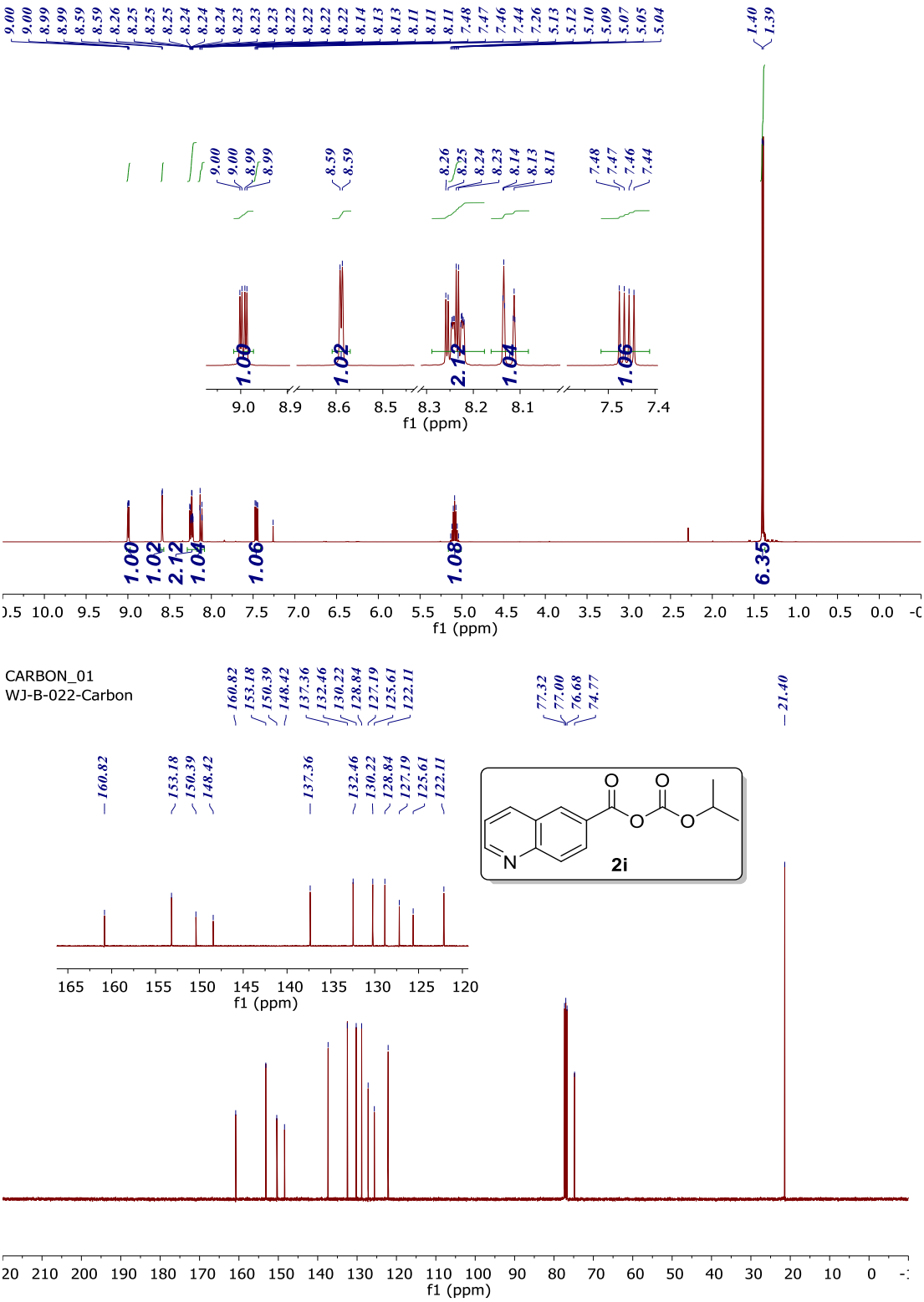


Figure 3.18 ^{1}H and ^{13}C NMR spectrum of compound **2j.**

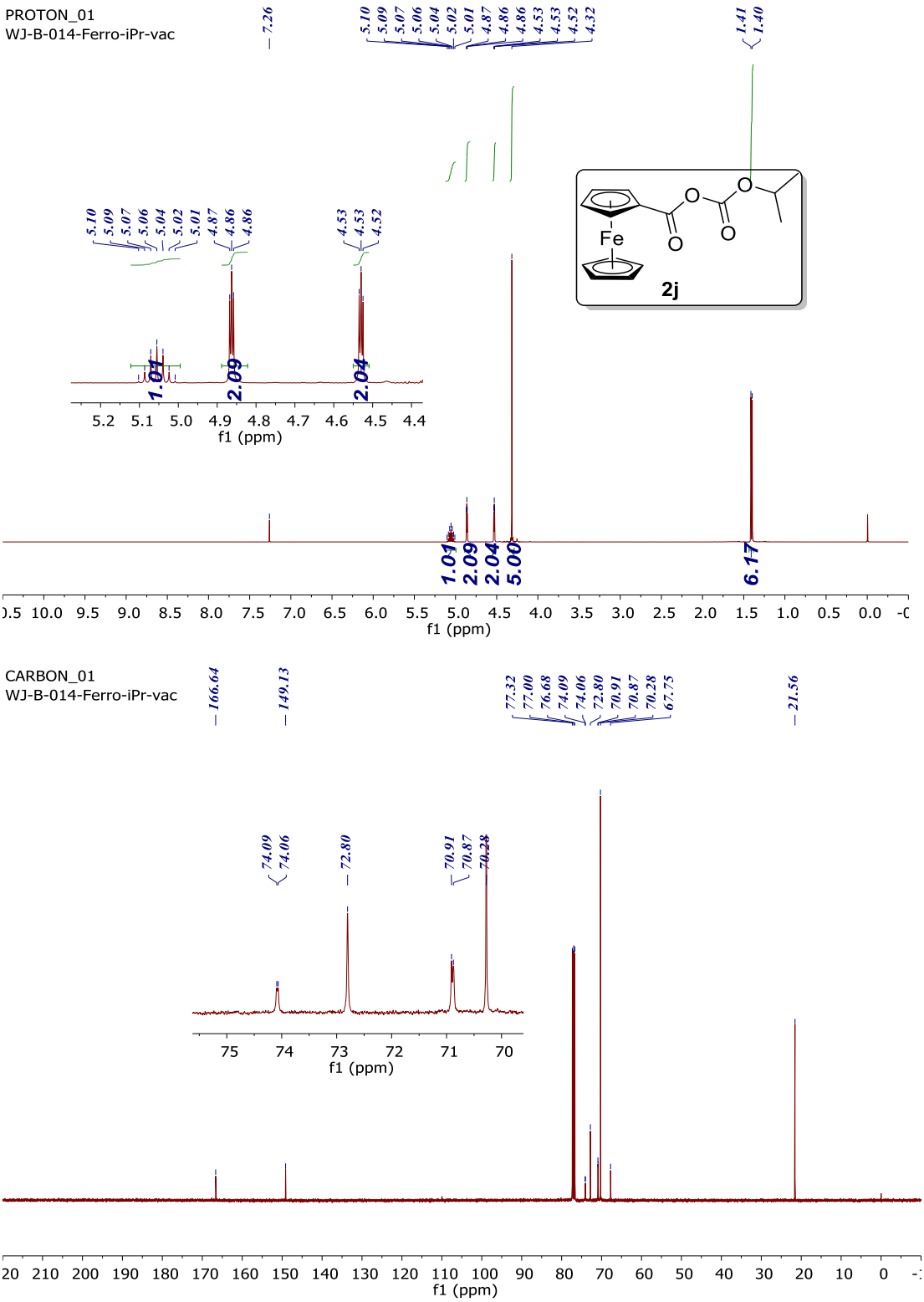


Figure 3.19 ^{1}H and ^{13}C NMR spectrum of compound **2l.**

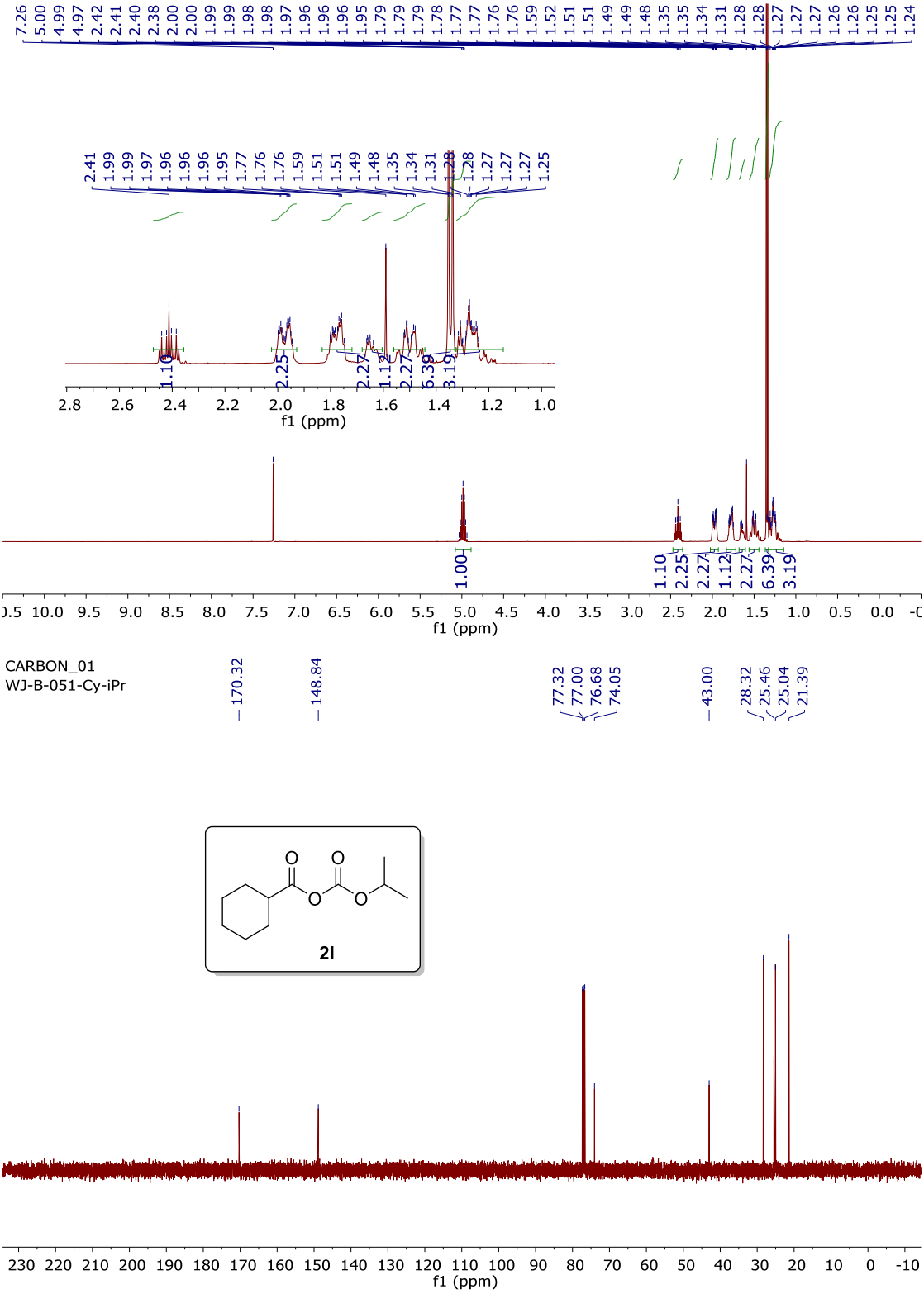


Figure 3.20 ^{1}H and ^{13}C NMR spectrum of compound **2m.**

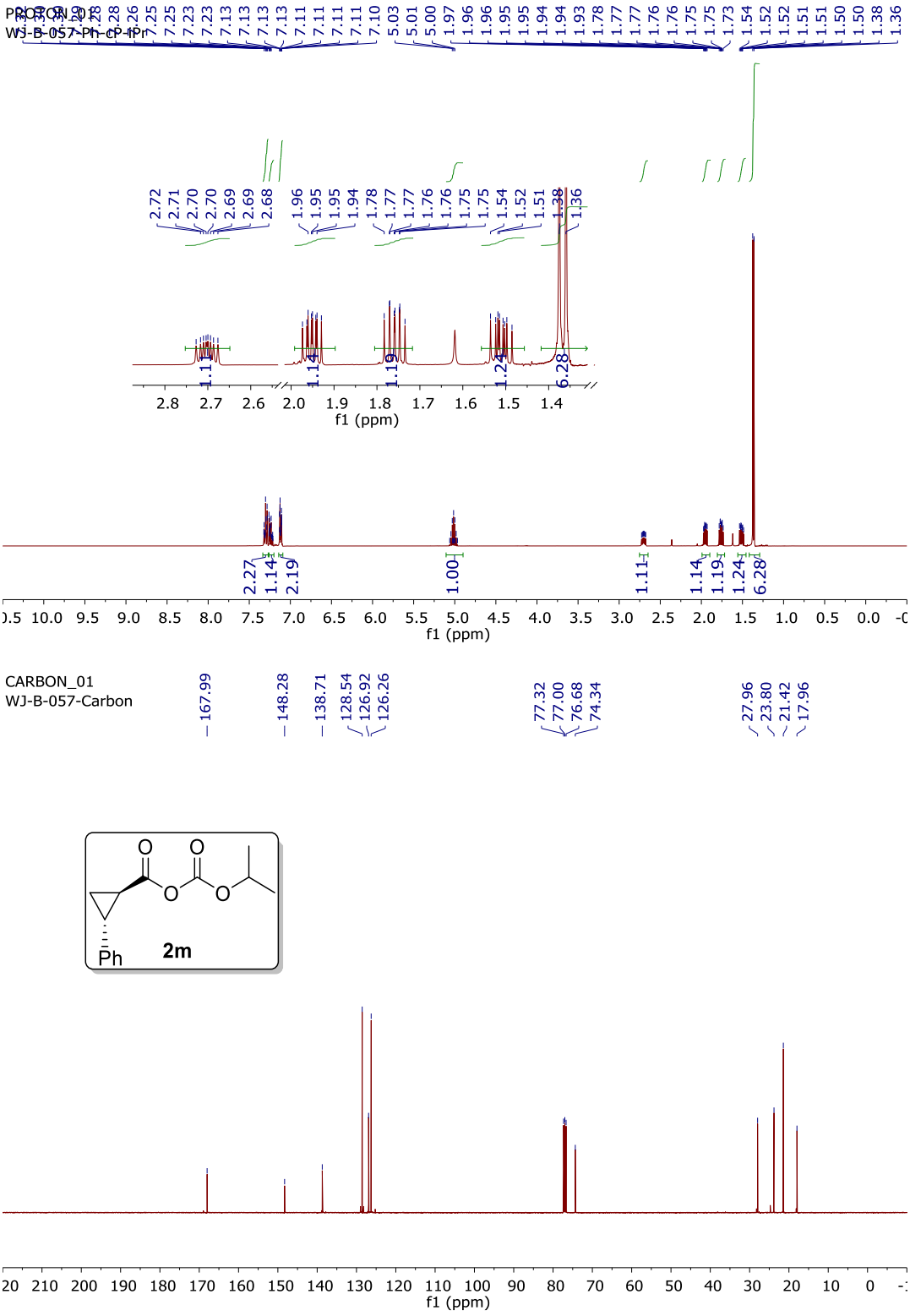


Figure 3.21 ^{1}H and ^{13}C NMR spectrum of compound **2n.**

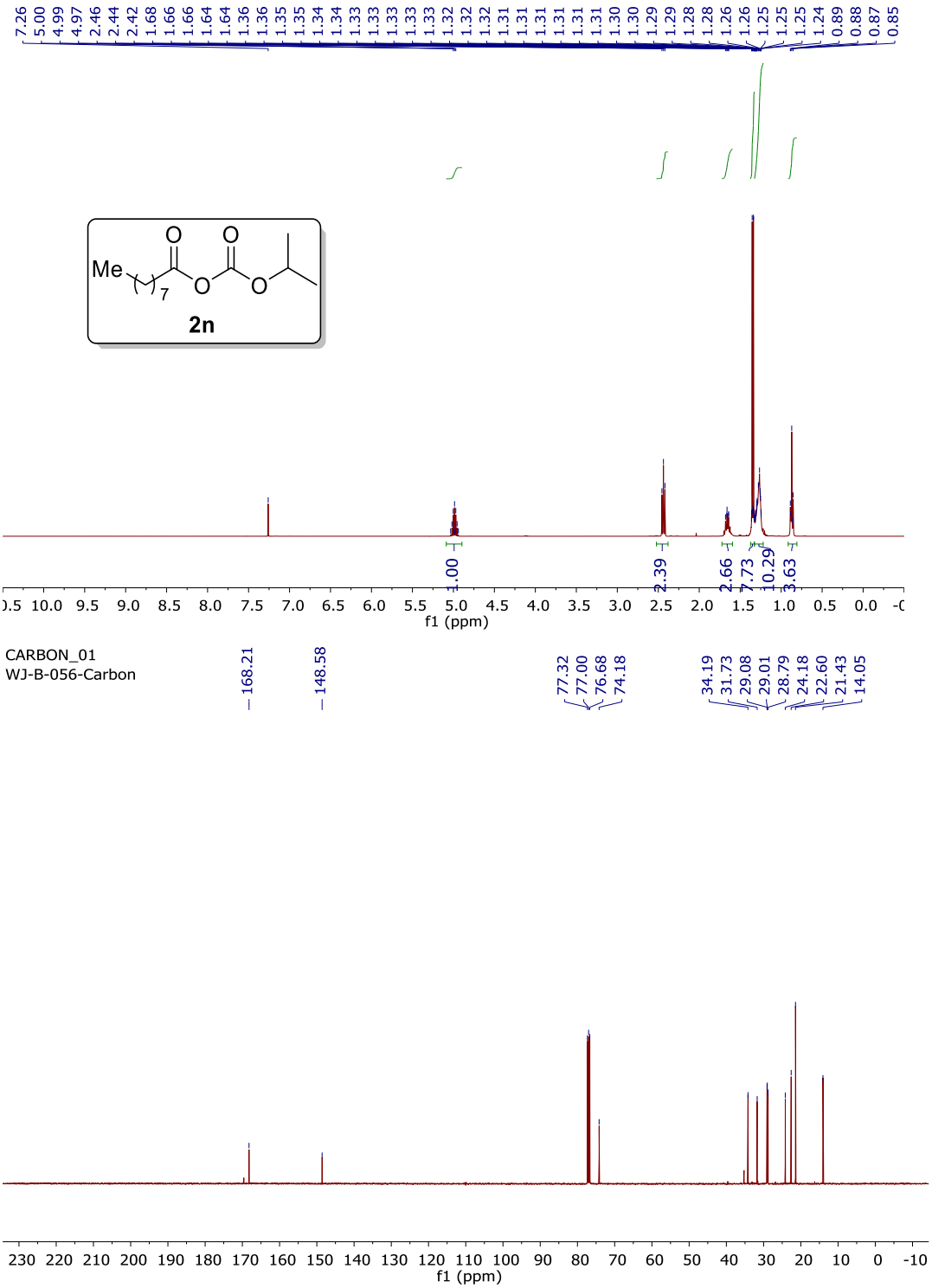


Figure 3.22 ^{1}H and ^{13}C NMR spectrum of compound **4a**.

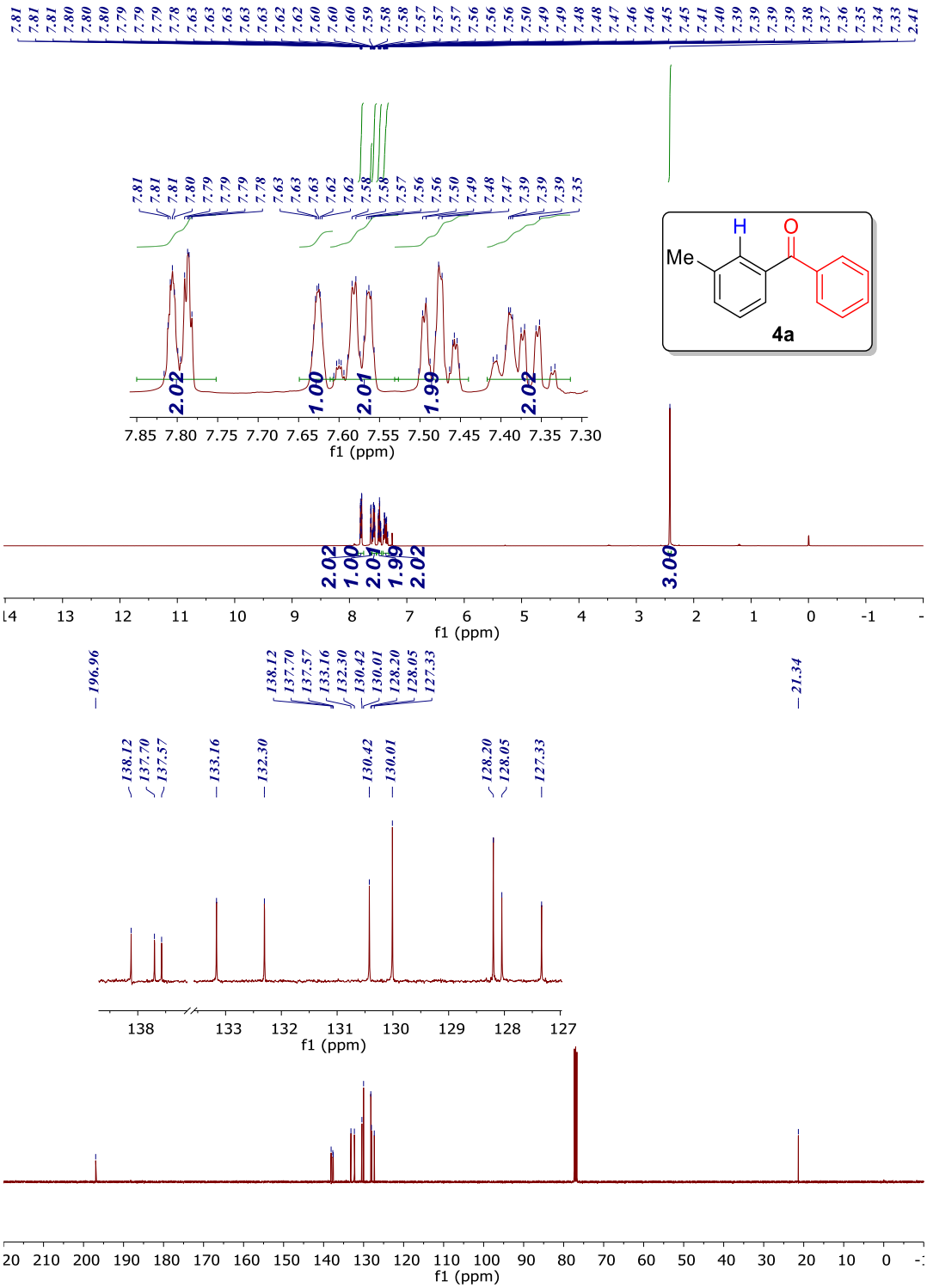


Figure 3.23 ^{1}H and ^{13}C NMR spectrum of compound **4b**.

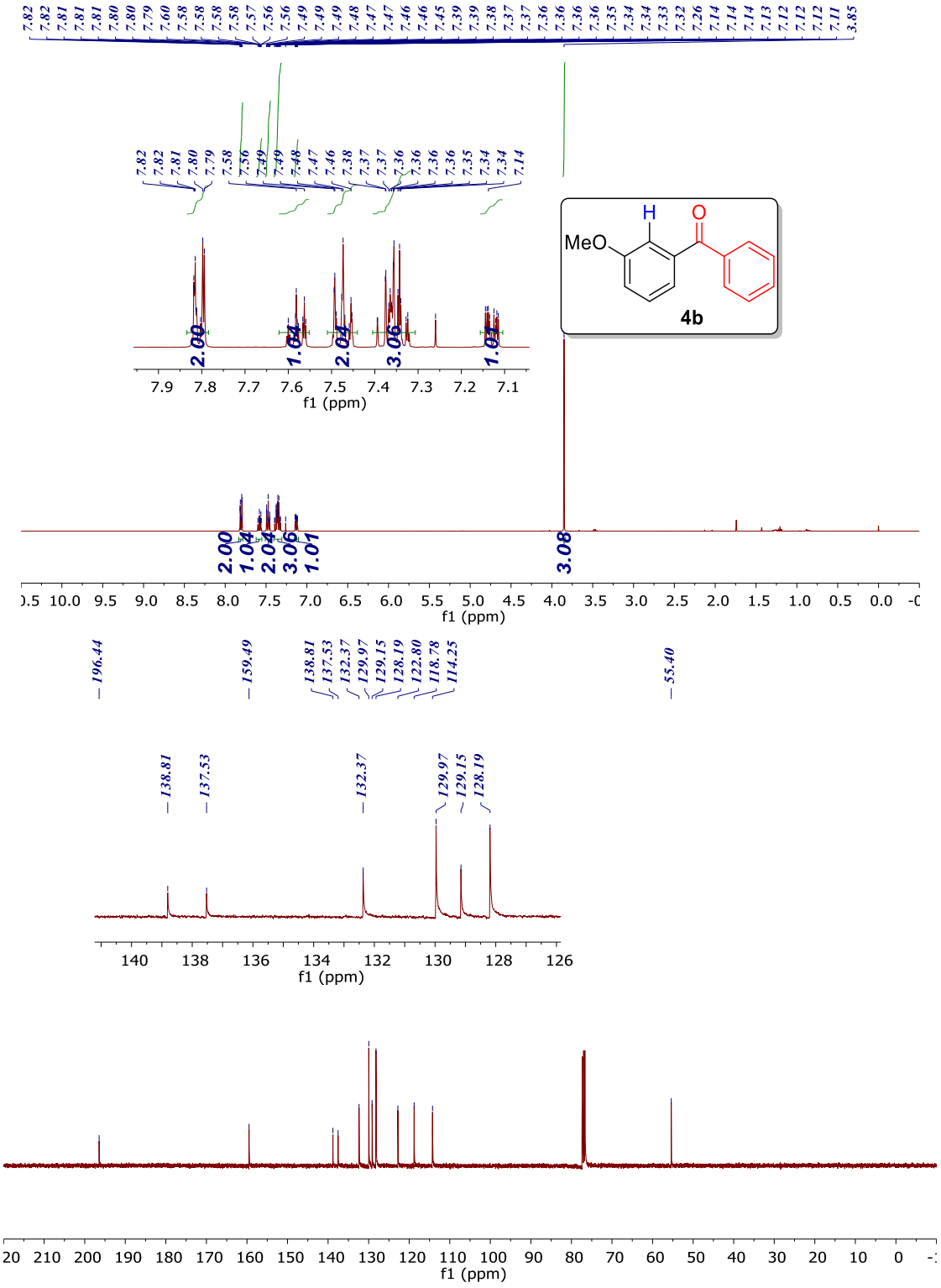


Figure 3.24 ^{1}H and ^{13}C NMR spectrum of compound **4c**.

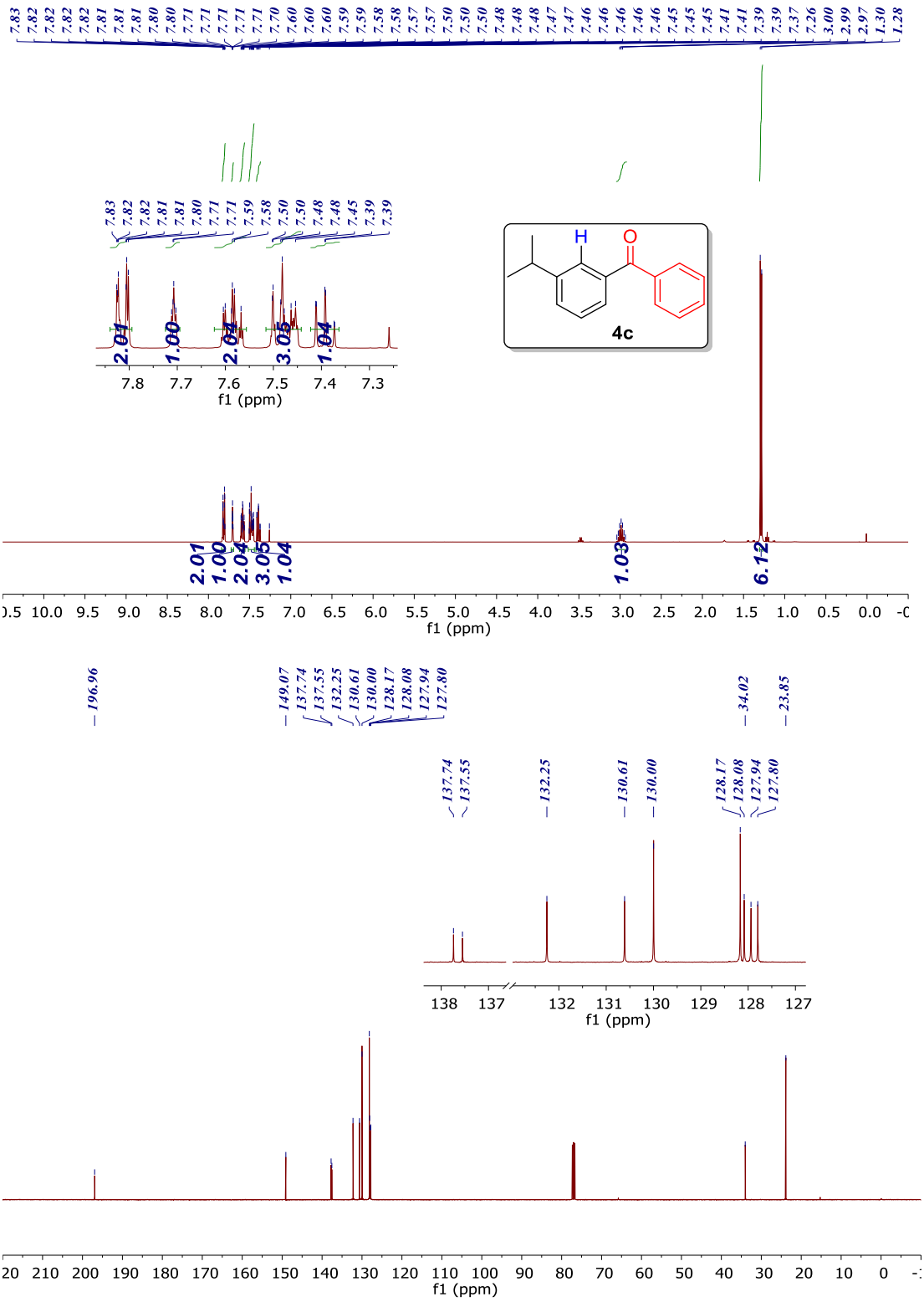


Figure 3.25 ^{1}H and ^{13}C NMR spectrum of compound **4d**.

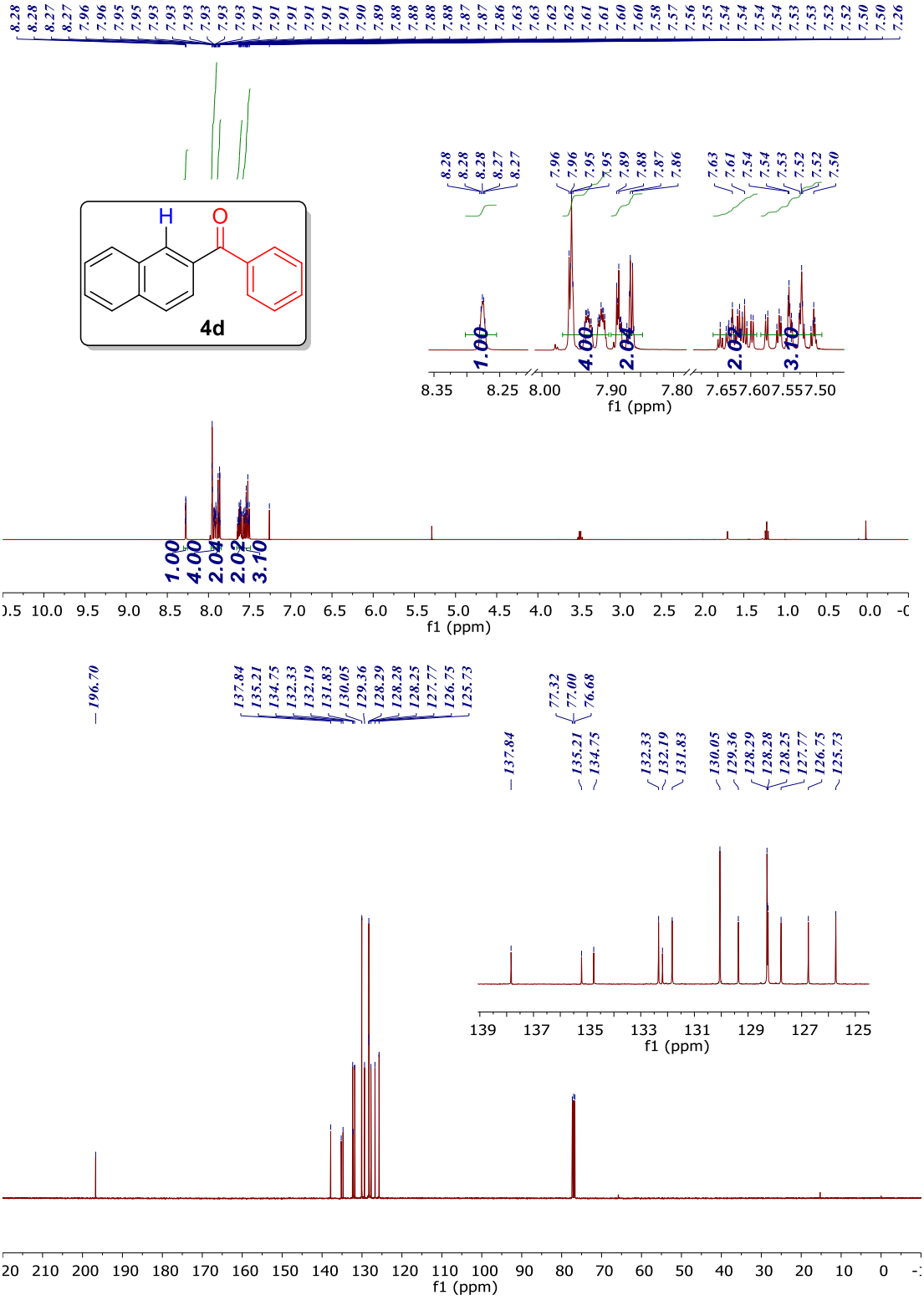


Figure 3.26 ^{1}H and ^{13}C NMR spectrum of compound **4e**.

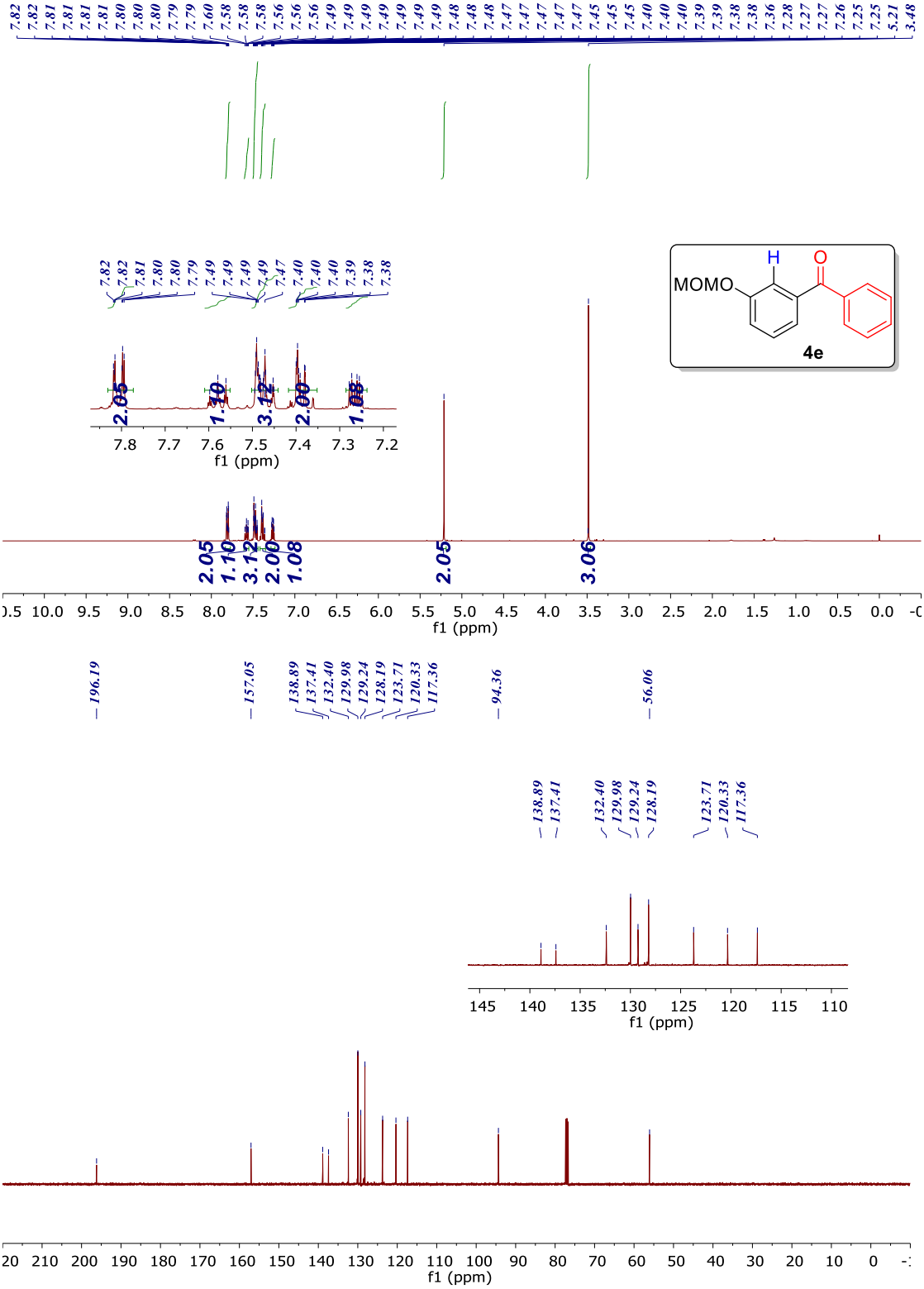


Figure 3.27 ^{1}H and ^{13}C NMR spectrum of compound **4f**.

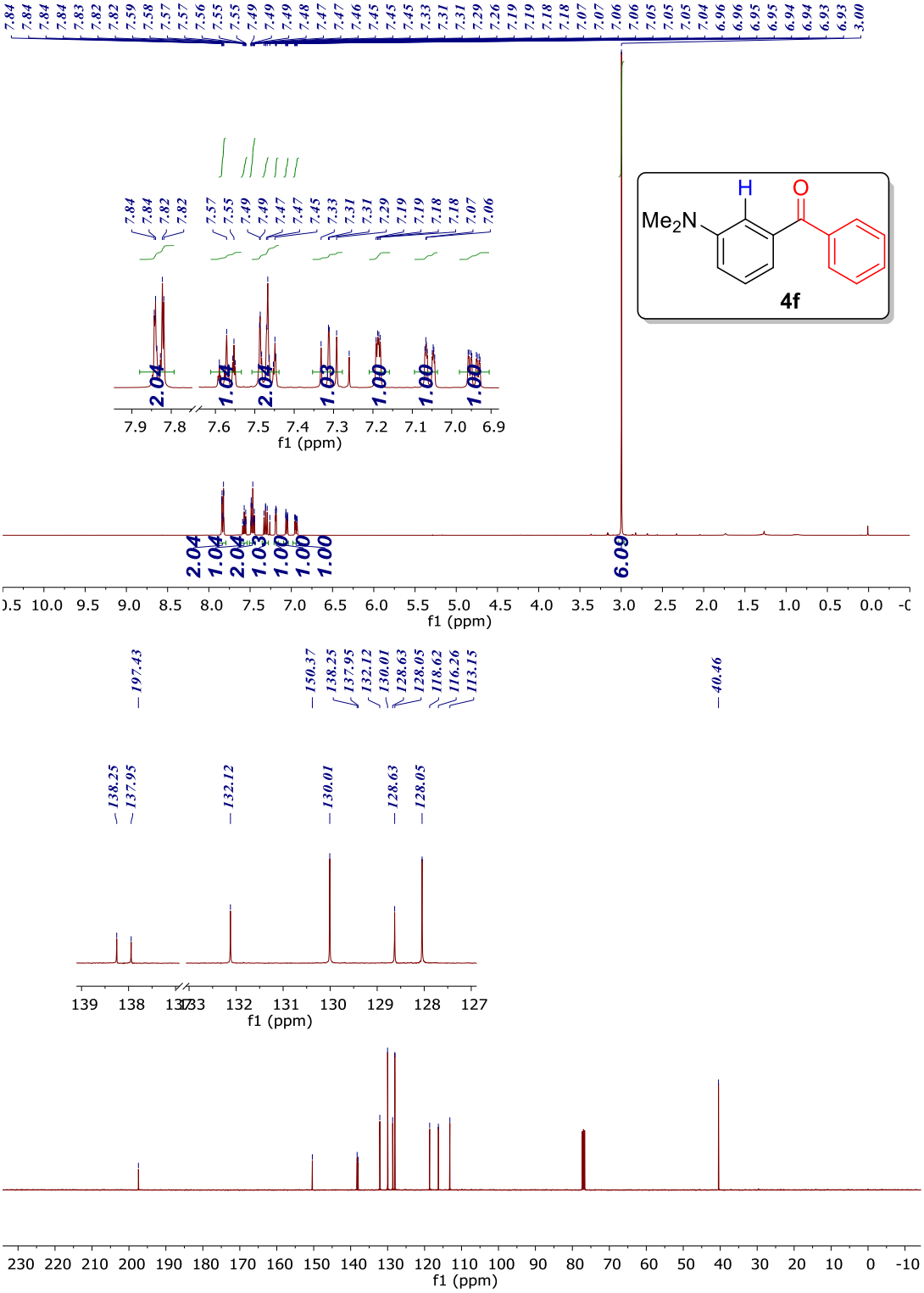


Figure 3.28 ^{1}H and ^{13}C NMR spectrum of compound **4g**.

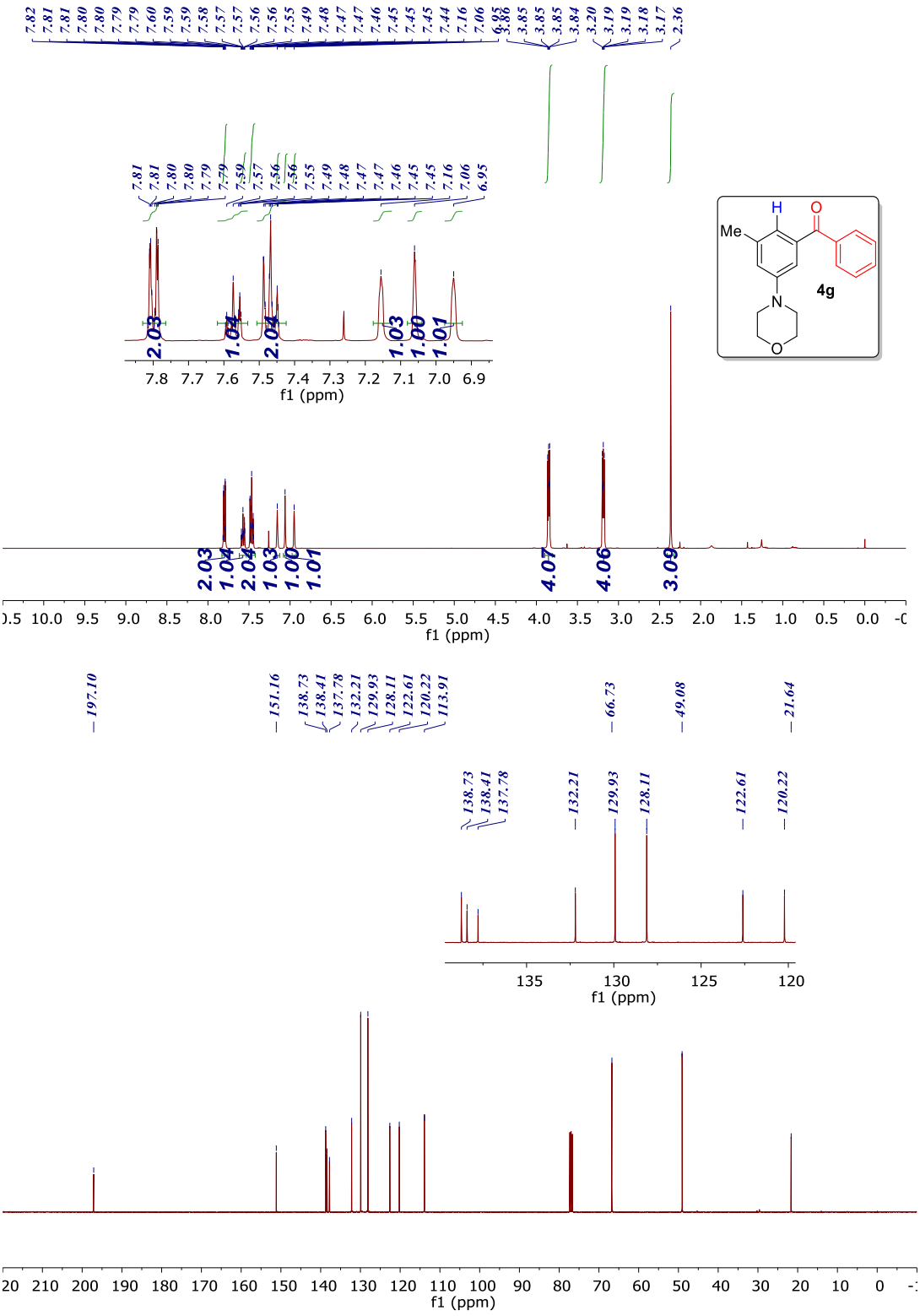


Figure 3.29 ^{1}H and ^{13}C NMR spectrum of compound **4h**.

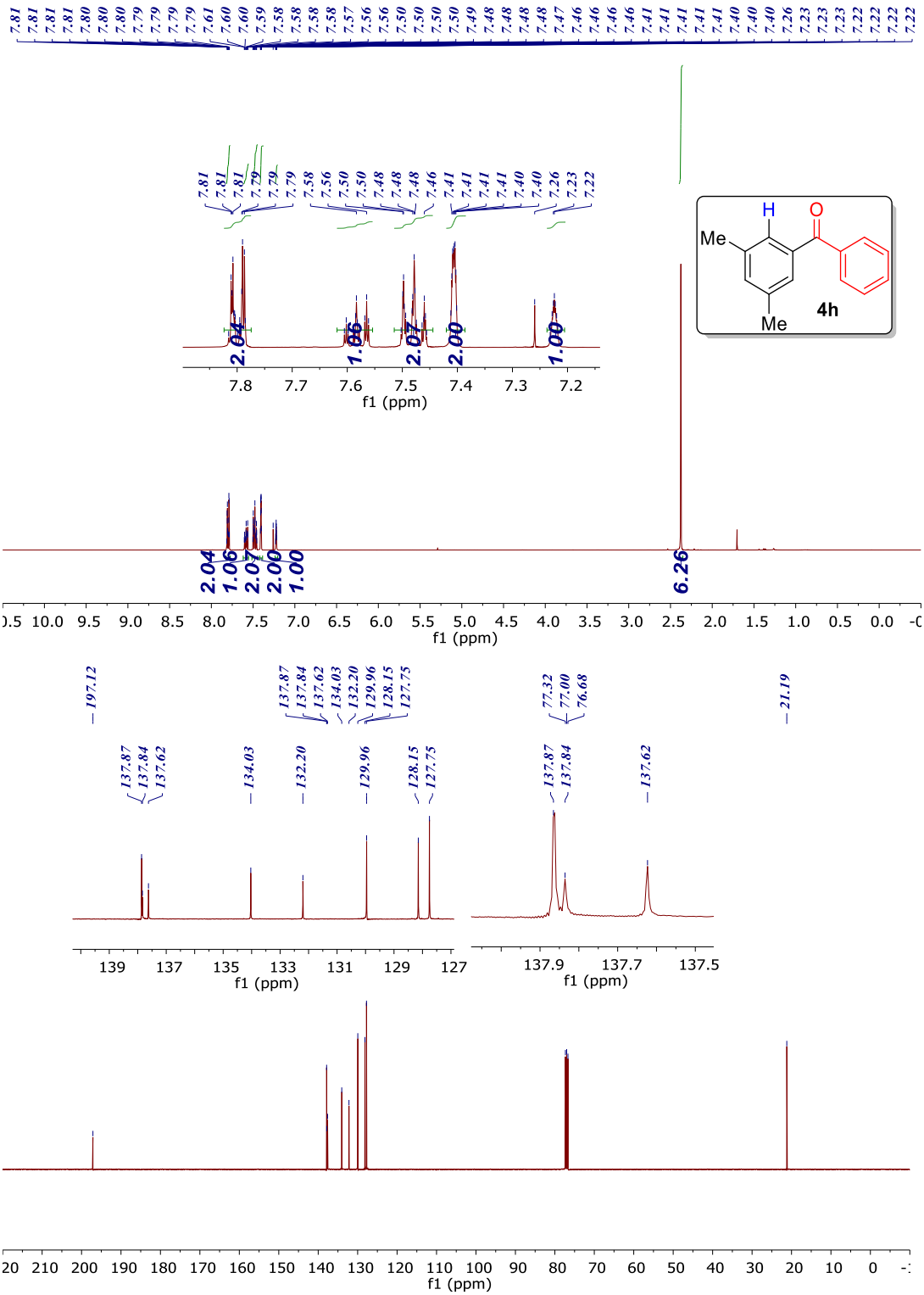


Figure 3.30 ^{1}H and ^{13}C NMR spectrum of compound **4i**.

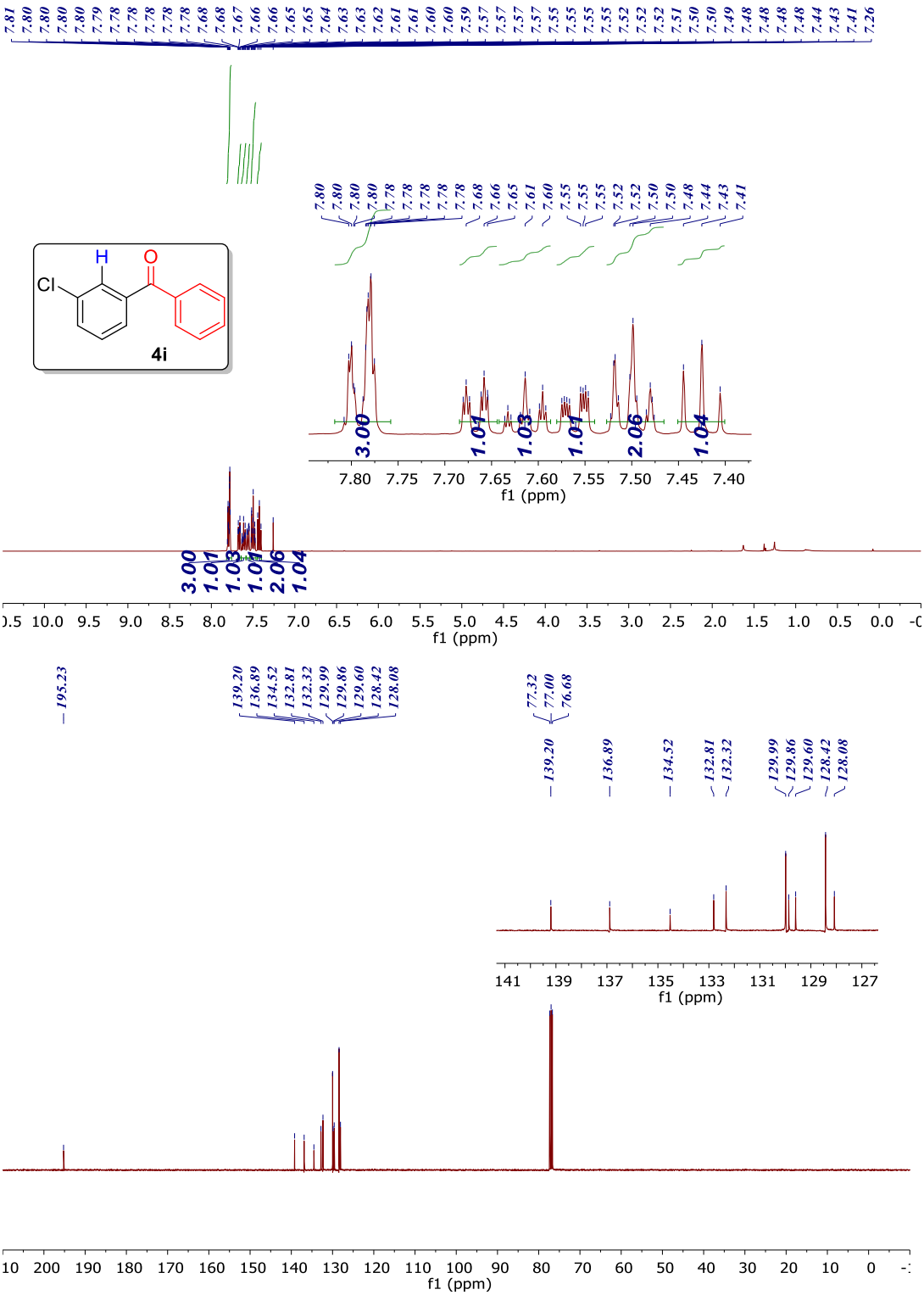


Figure 3.31 ^{1}H and ^{13}C NMR spectrum of compound **4j**.

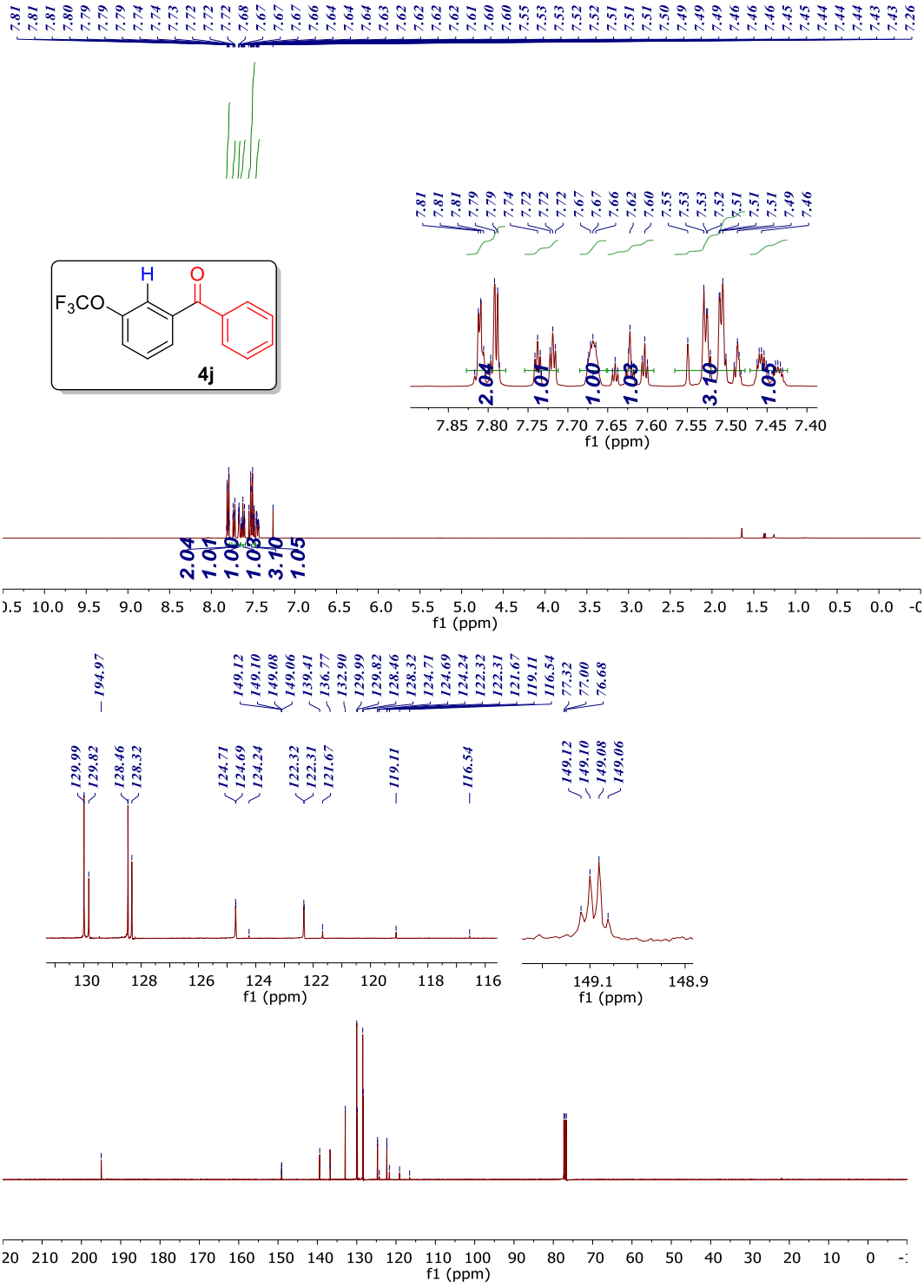


Figure 3.32 ^{19}F NMR spectrum of compound **4j**.

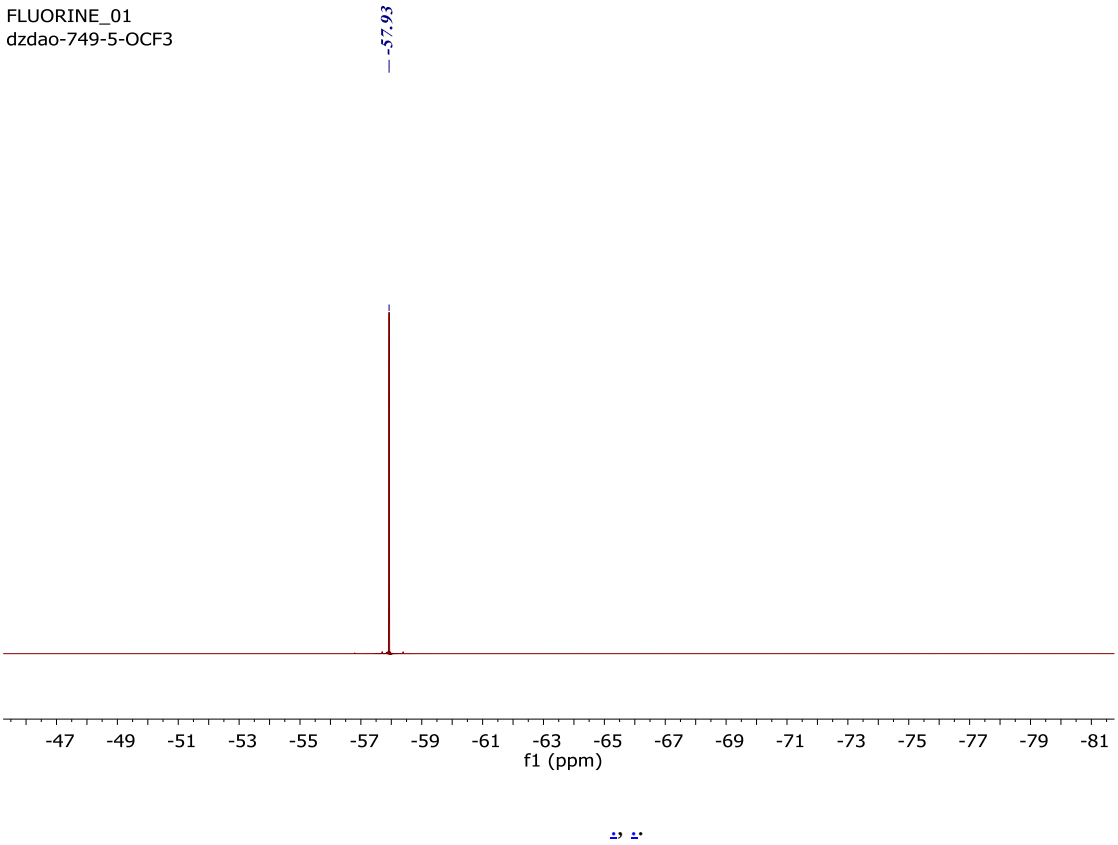


Figure 3.33 ^{1}H and ^{13}C NMR spectrum of compound **4k**.

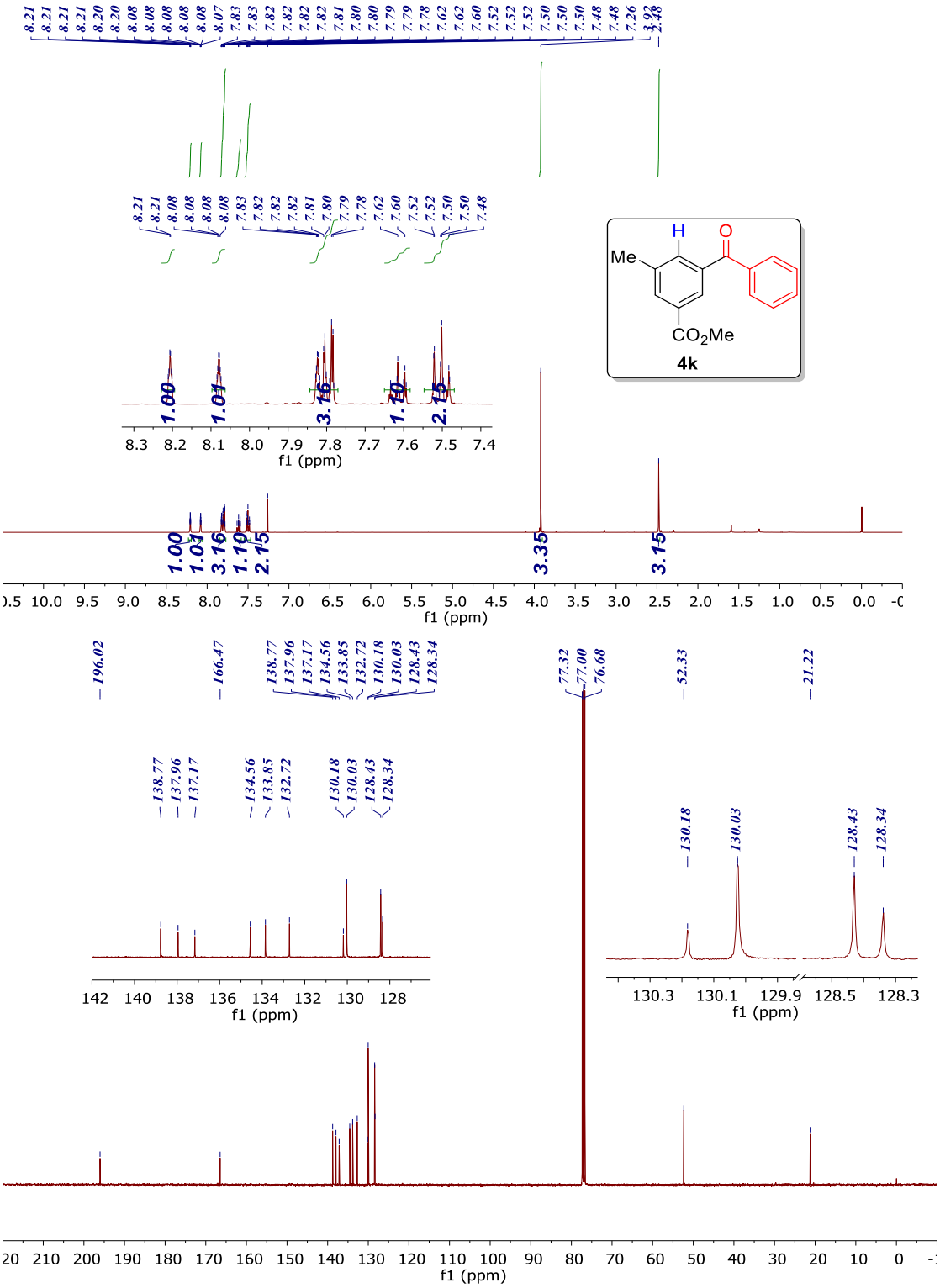


Figure 3.34 ^{1}H and ^{13}C NMR spectrum of compound **4l**.

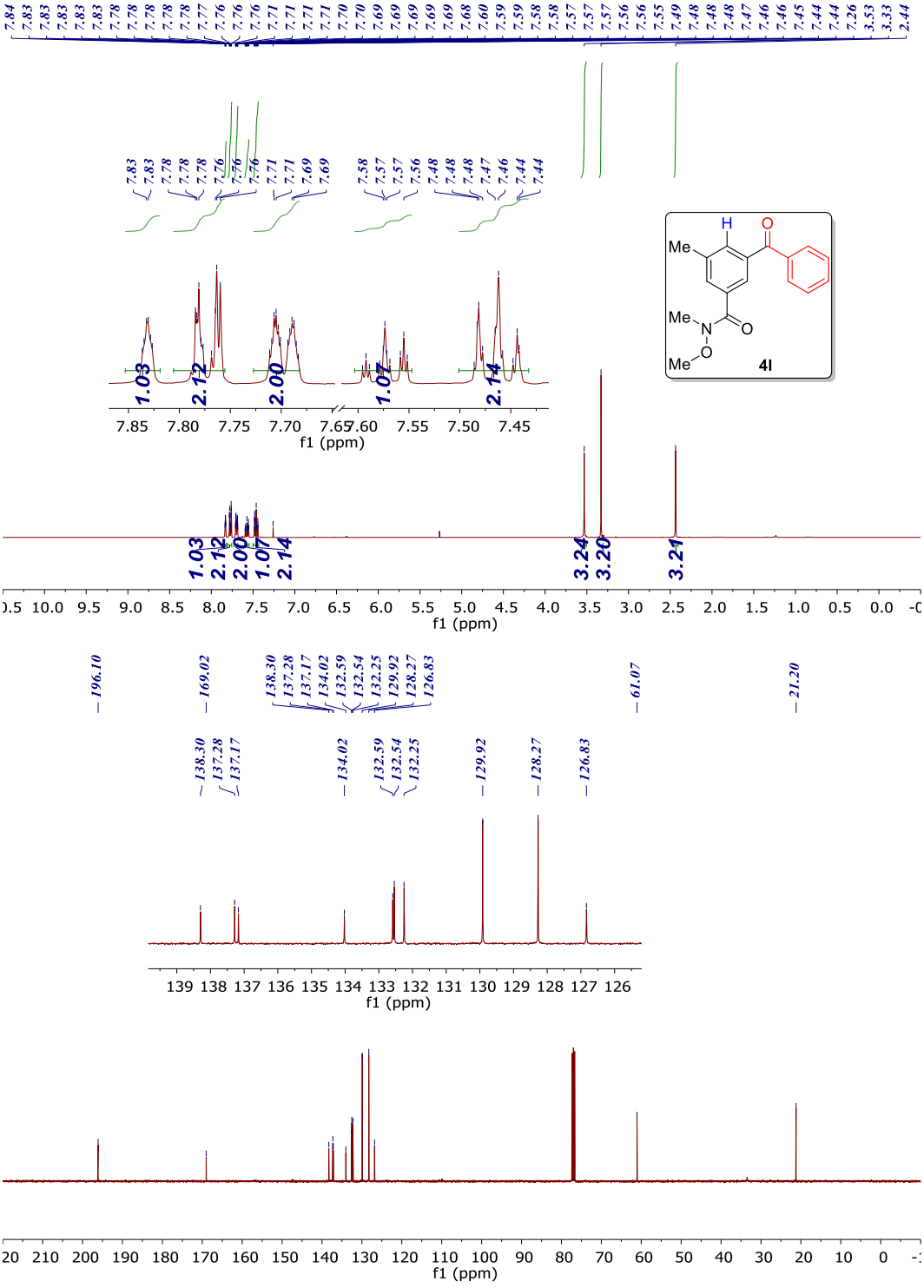


Figure 3.35 ^{1}H and ^{13}C NMR spectrum of compound **4m**.

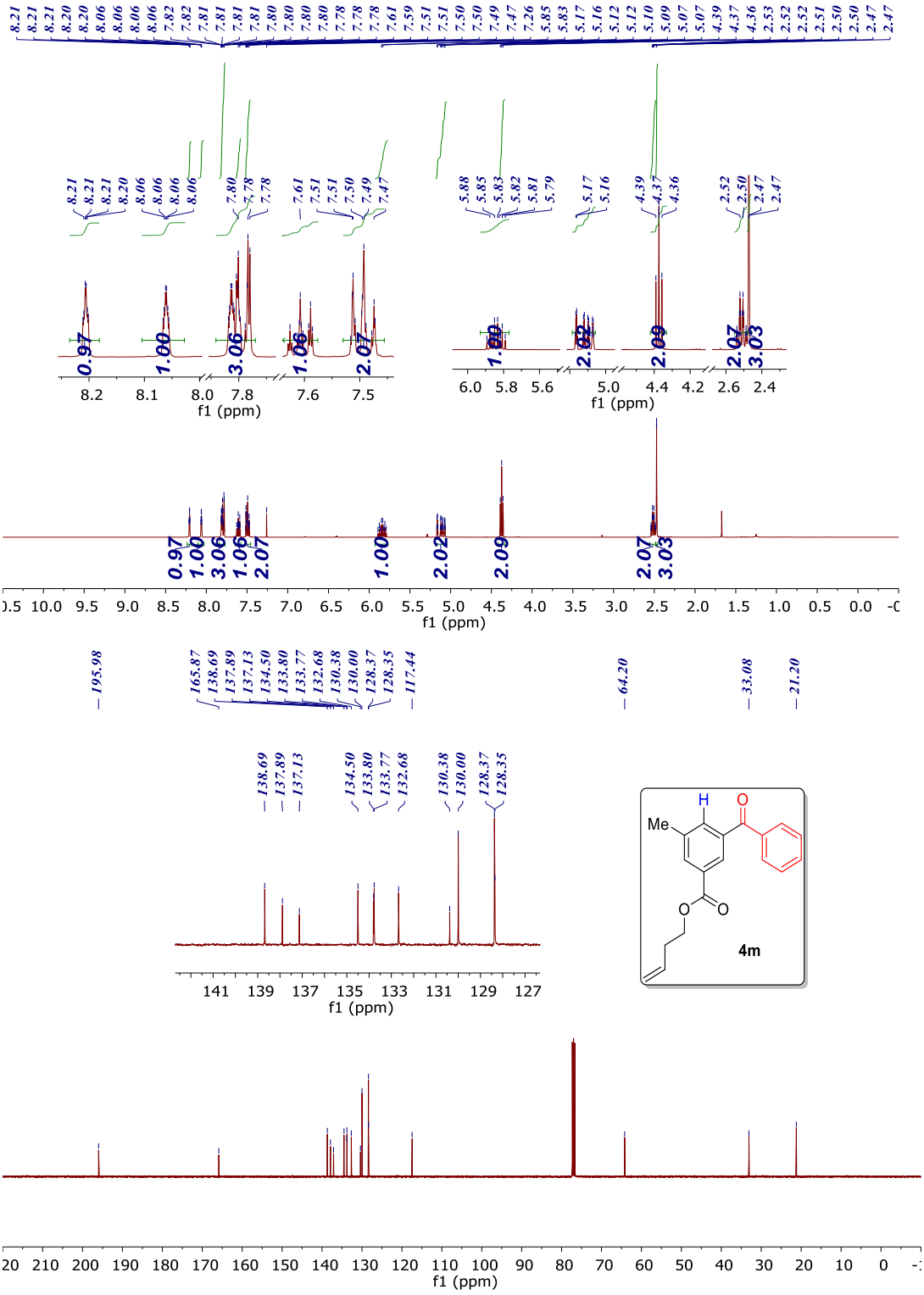


Figure 3.36 ^{1}H and ^{13}C NMR spectrum of compound **4n**.

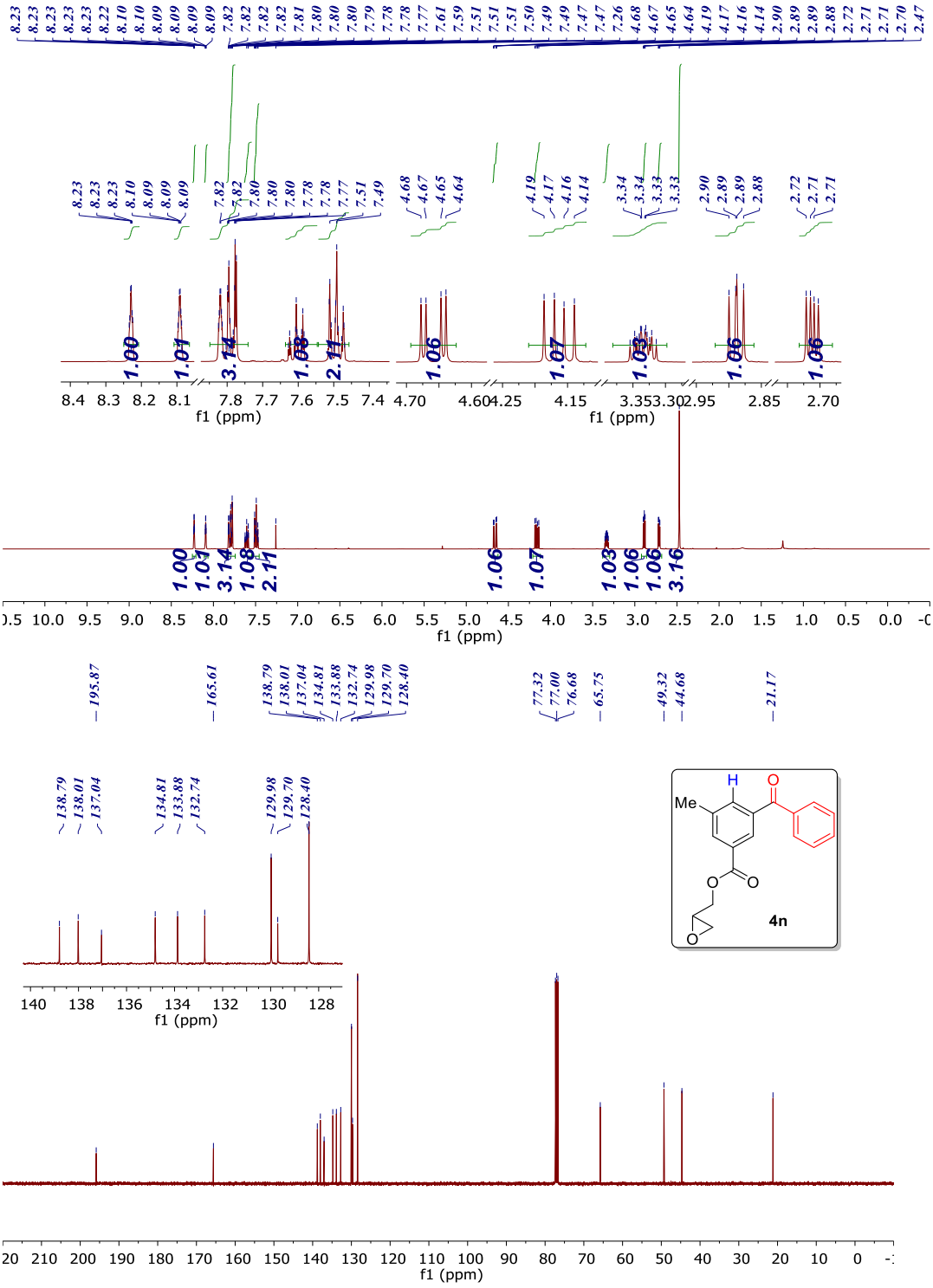


Figure 3.37 ^{1}H and ^{13}C NMR spectrum of compound **4o**.

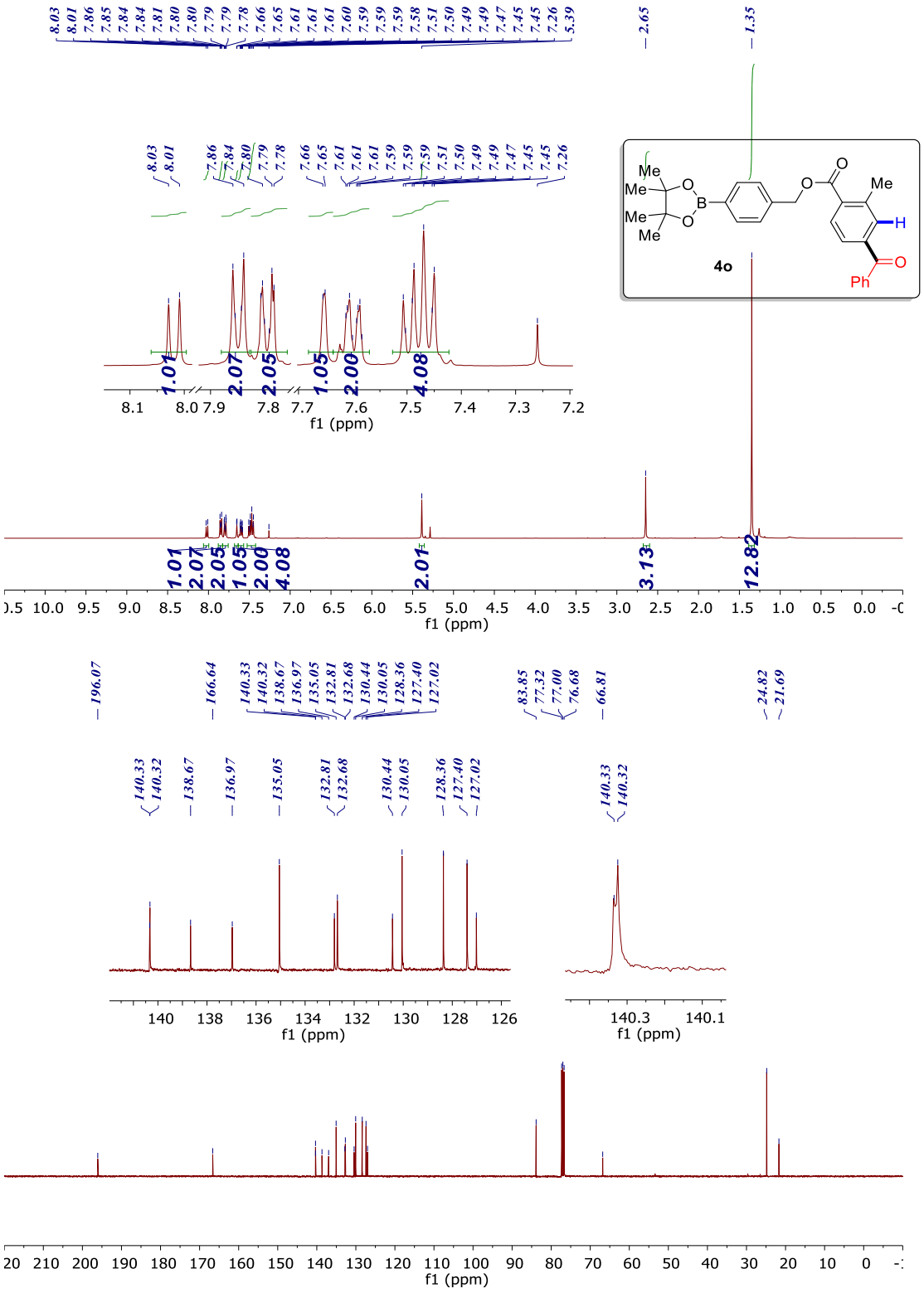


Figure 3.38 ^{1}H and ^{13}C NMR spectrum of compound **4p**.

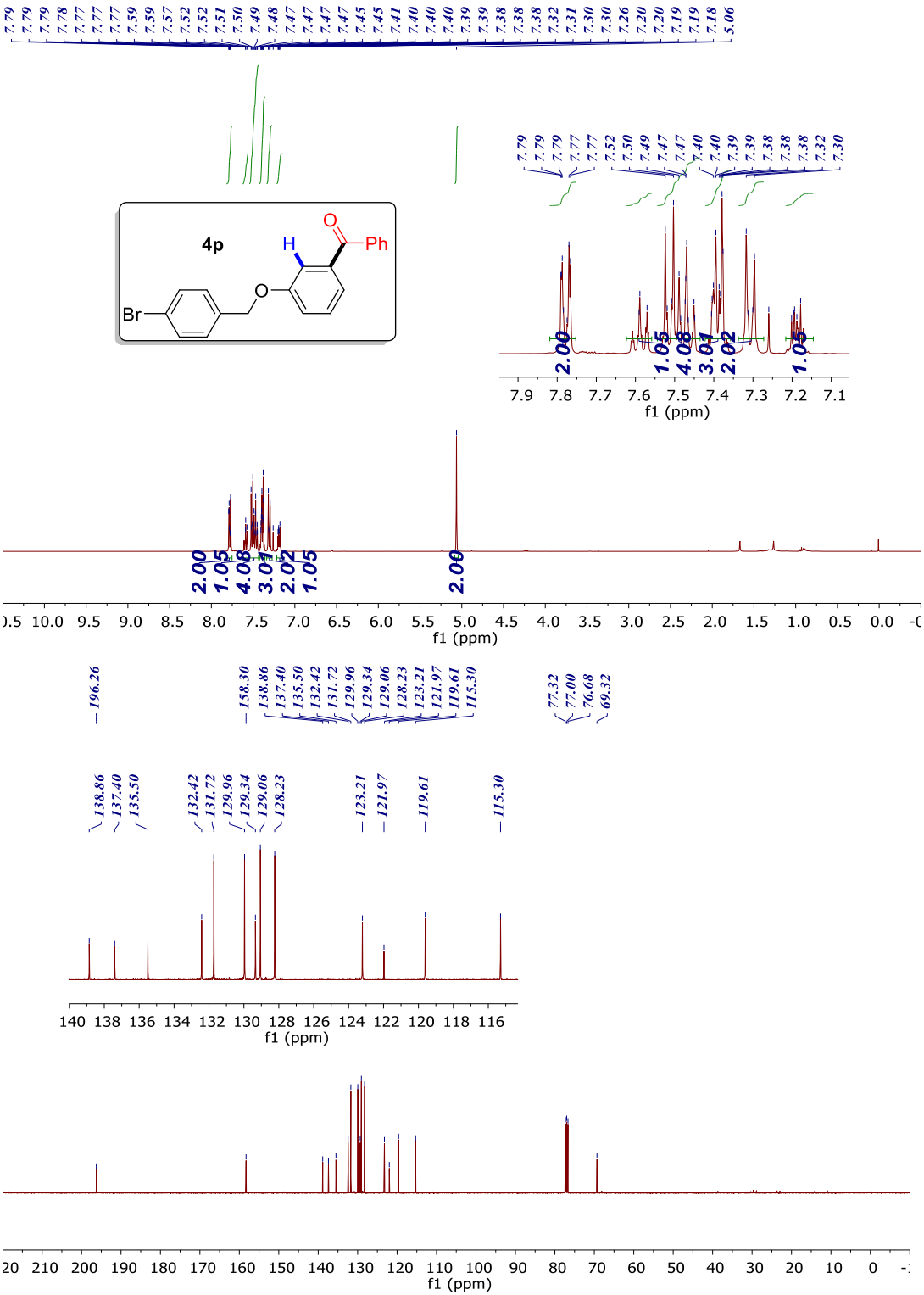


Figure 3.39 ^{1}H and ^{13}C NMR spectrum of compound **4q**.

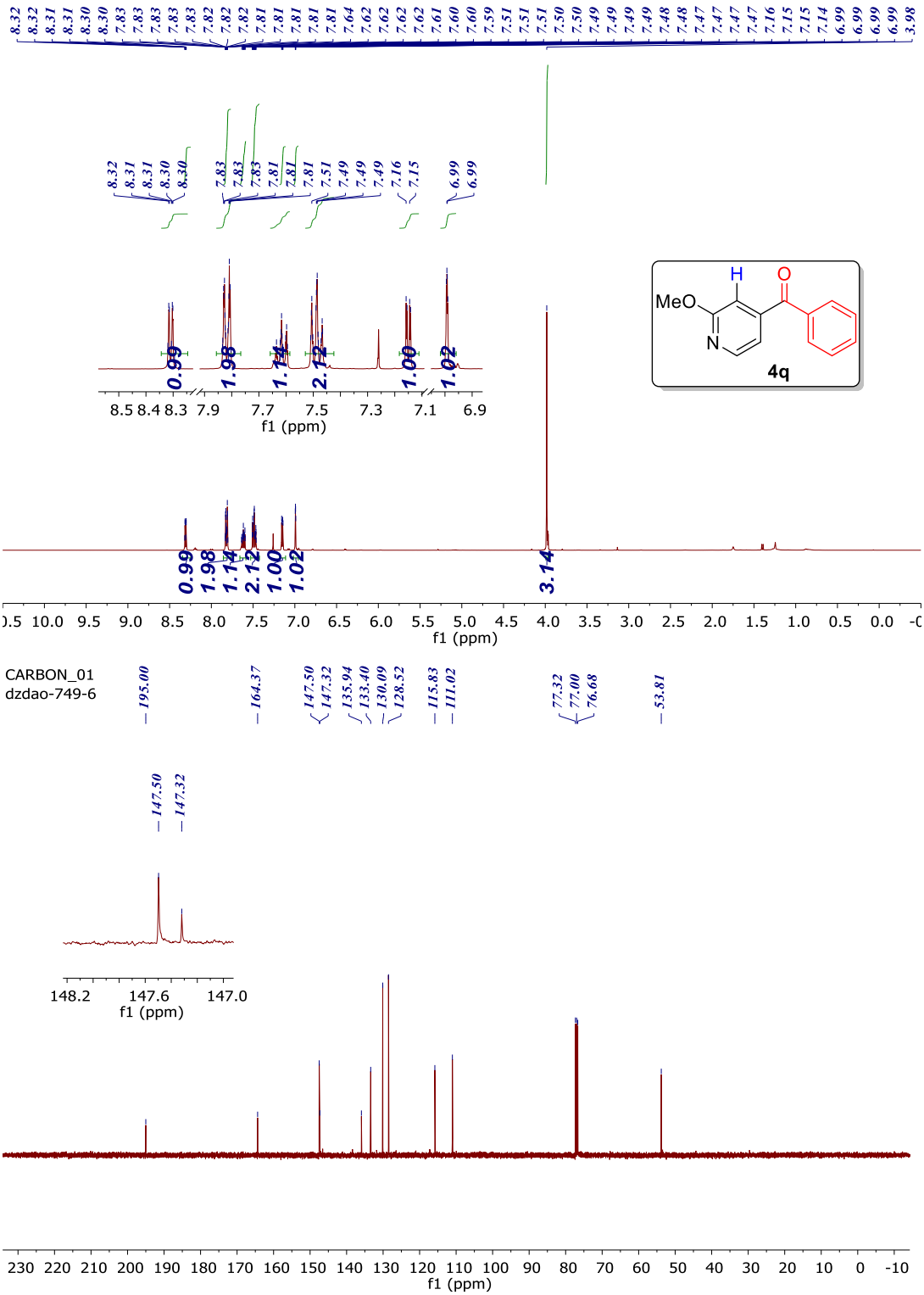


Figure 3.40 ^{1}H and ^{13}C NMR spectrum of compound **4r**.

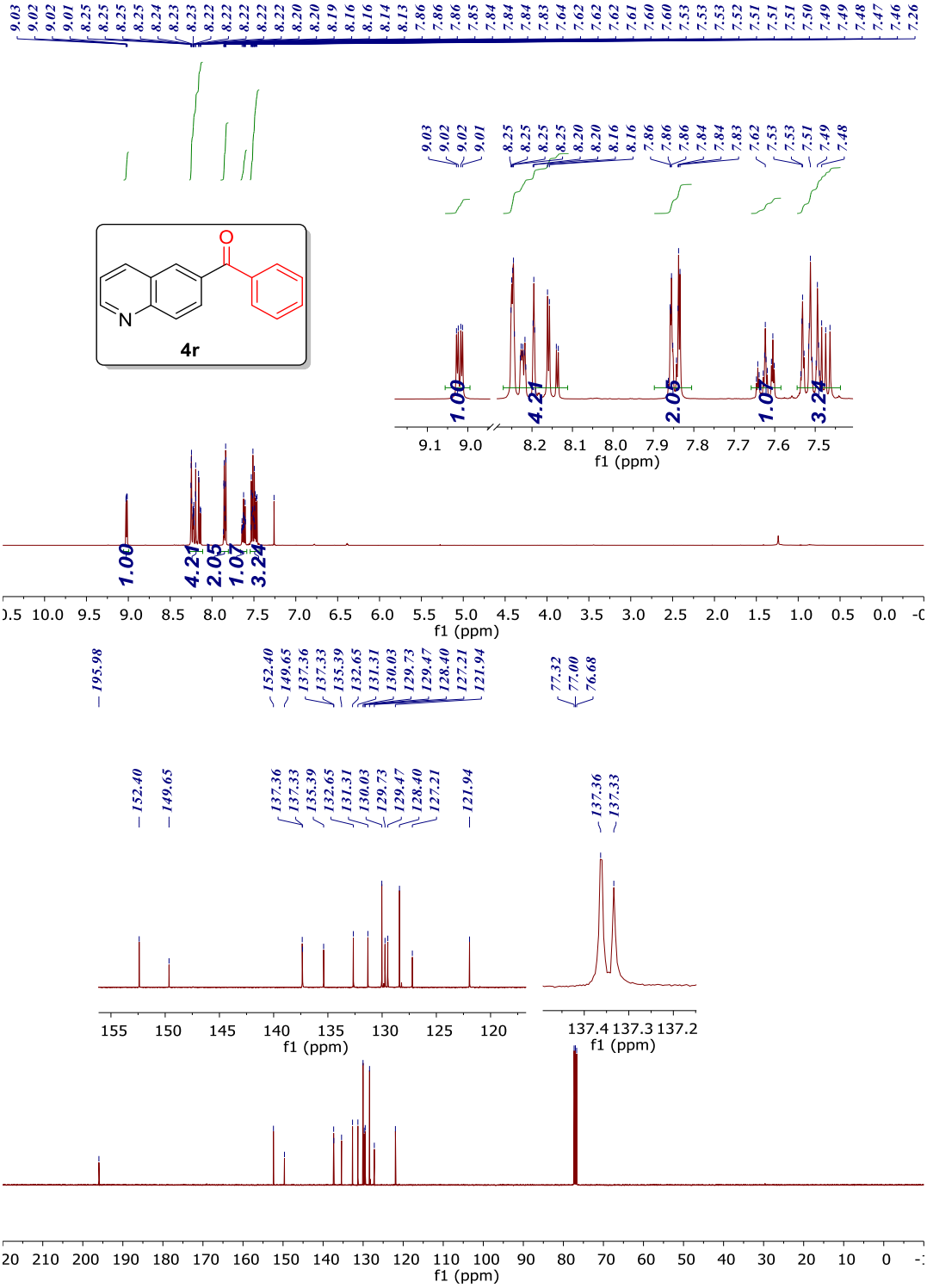


Figure 3.41 ^{1}H and ^{13}C NMR spectrum of compound **4s**.

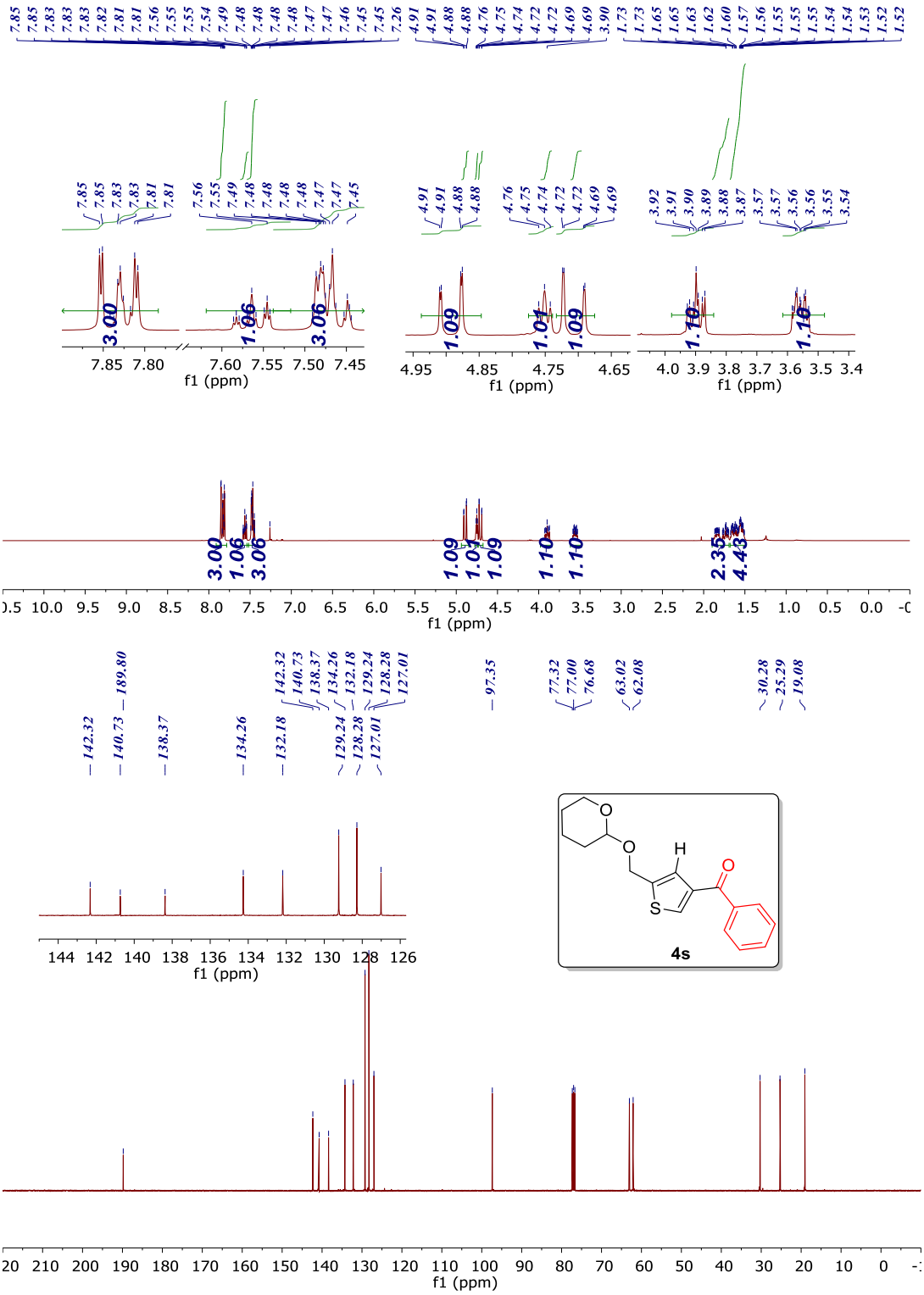


Figure 3.42 ^{1}H and ^{13}C NMR spectrum of compound **4t**.

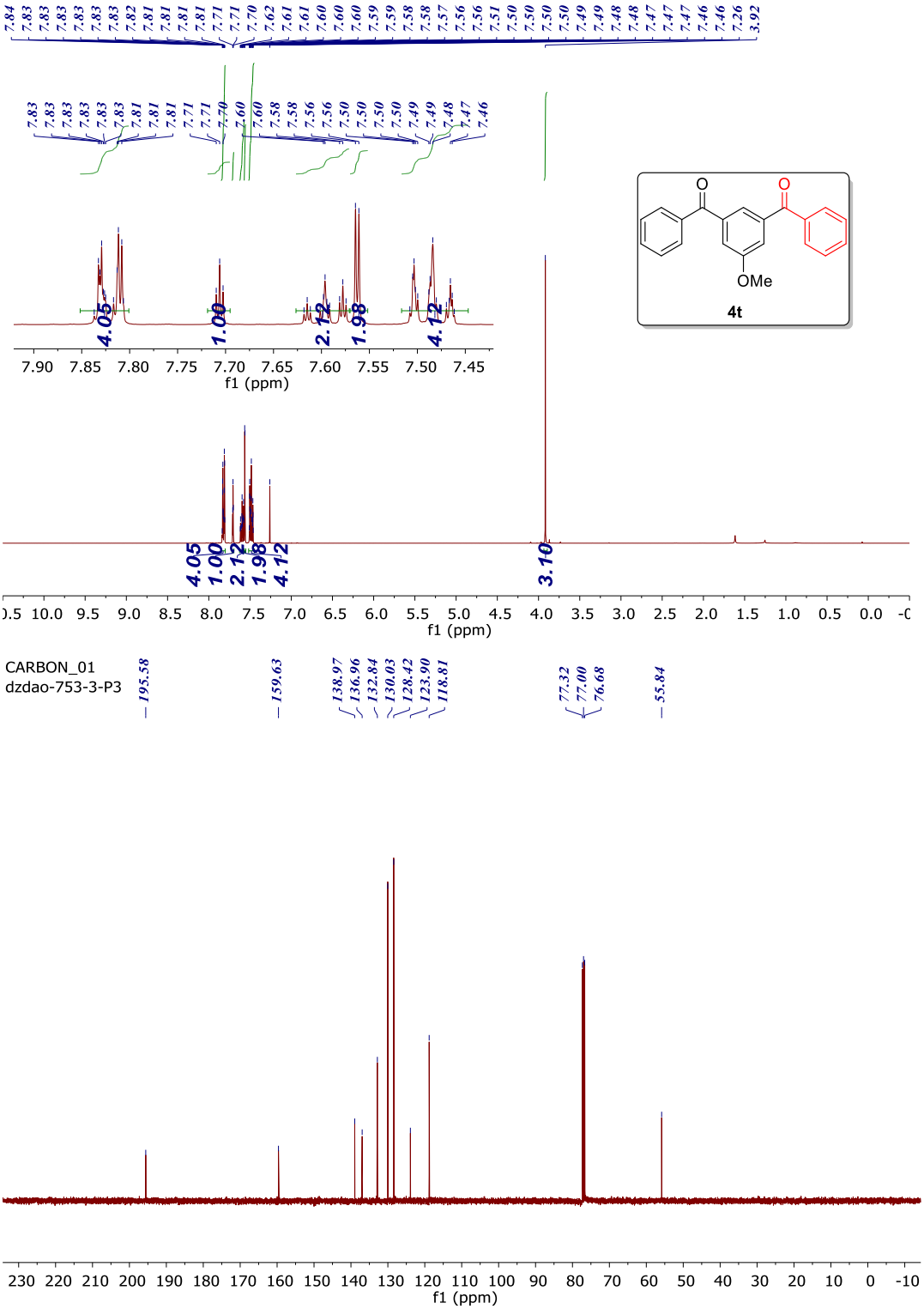


Figure 3.43 ^{1}H and ^{13}C NMR spectrum of compound **4t'**.

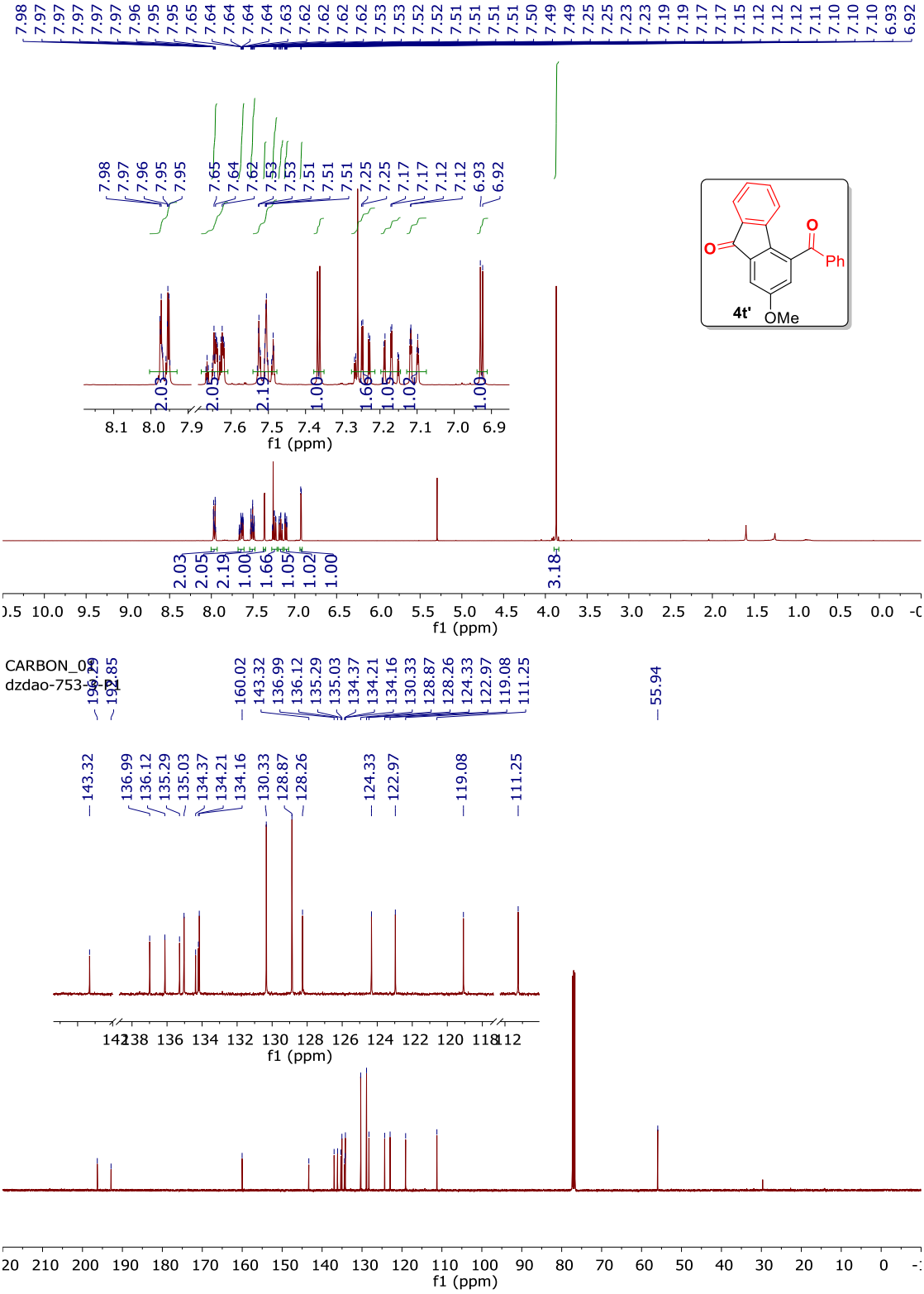


Figure 3.44 ^{1}H and ^{13}C NMR spectrum of compound **5b**.

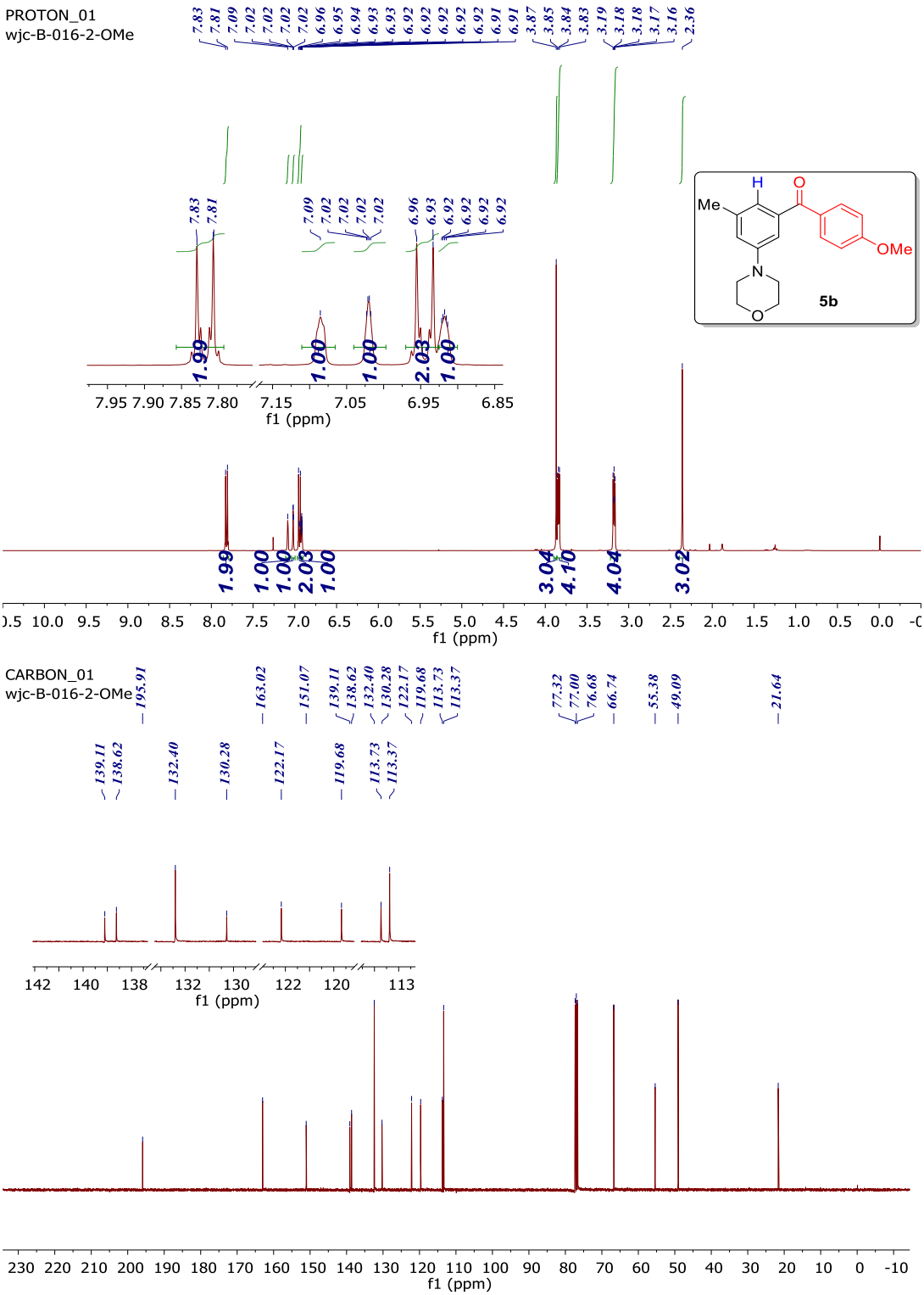


Figure 3.45 ^{1}H and ^{13}C NMR spectrum of compound **5c**.

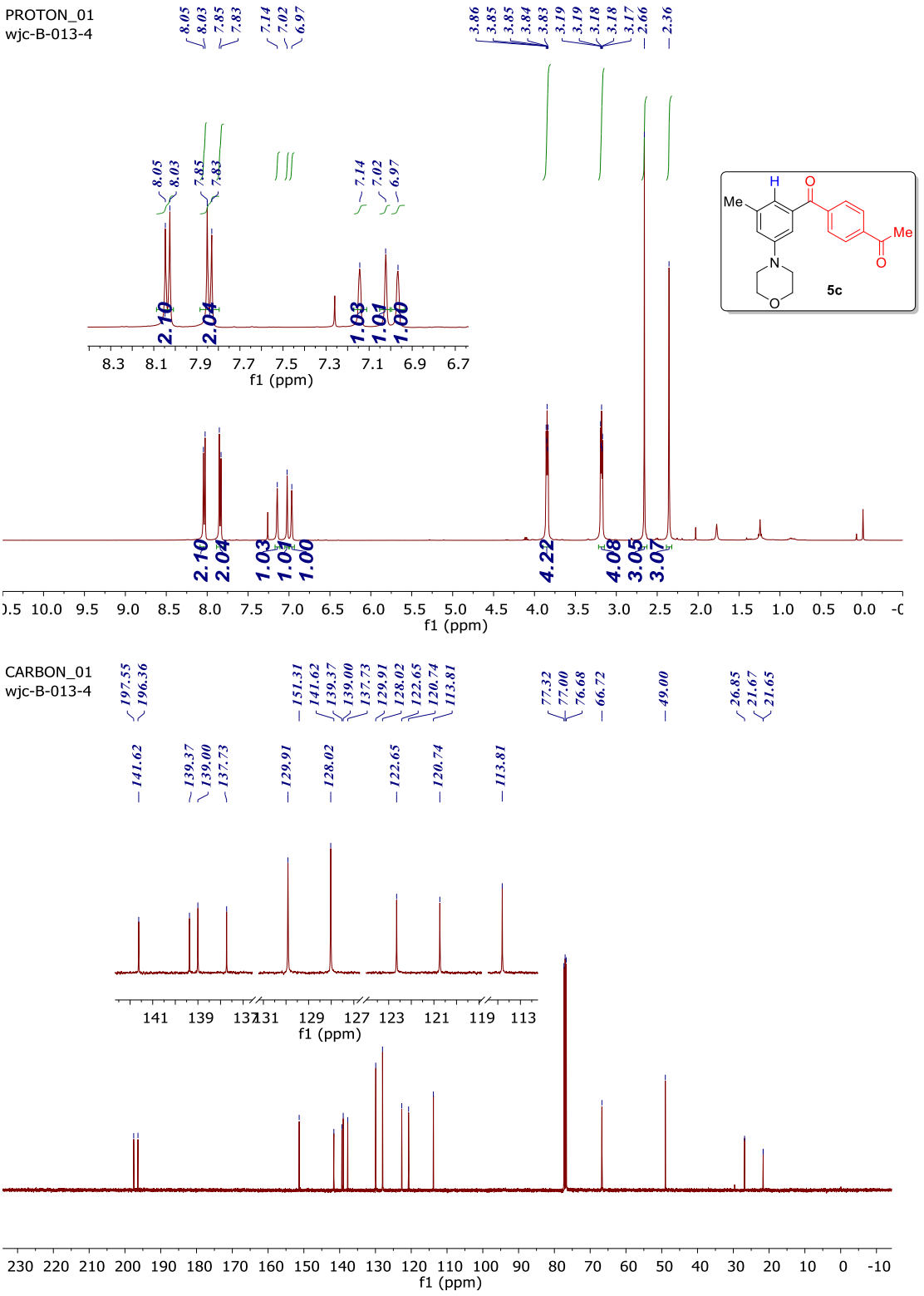


Figure 3.46 ^{1}H and ^{13}C NMR spectrum of compound **5d**.

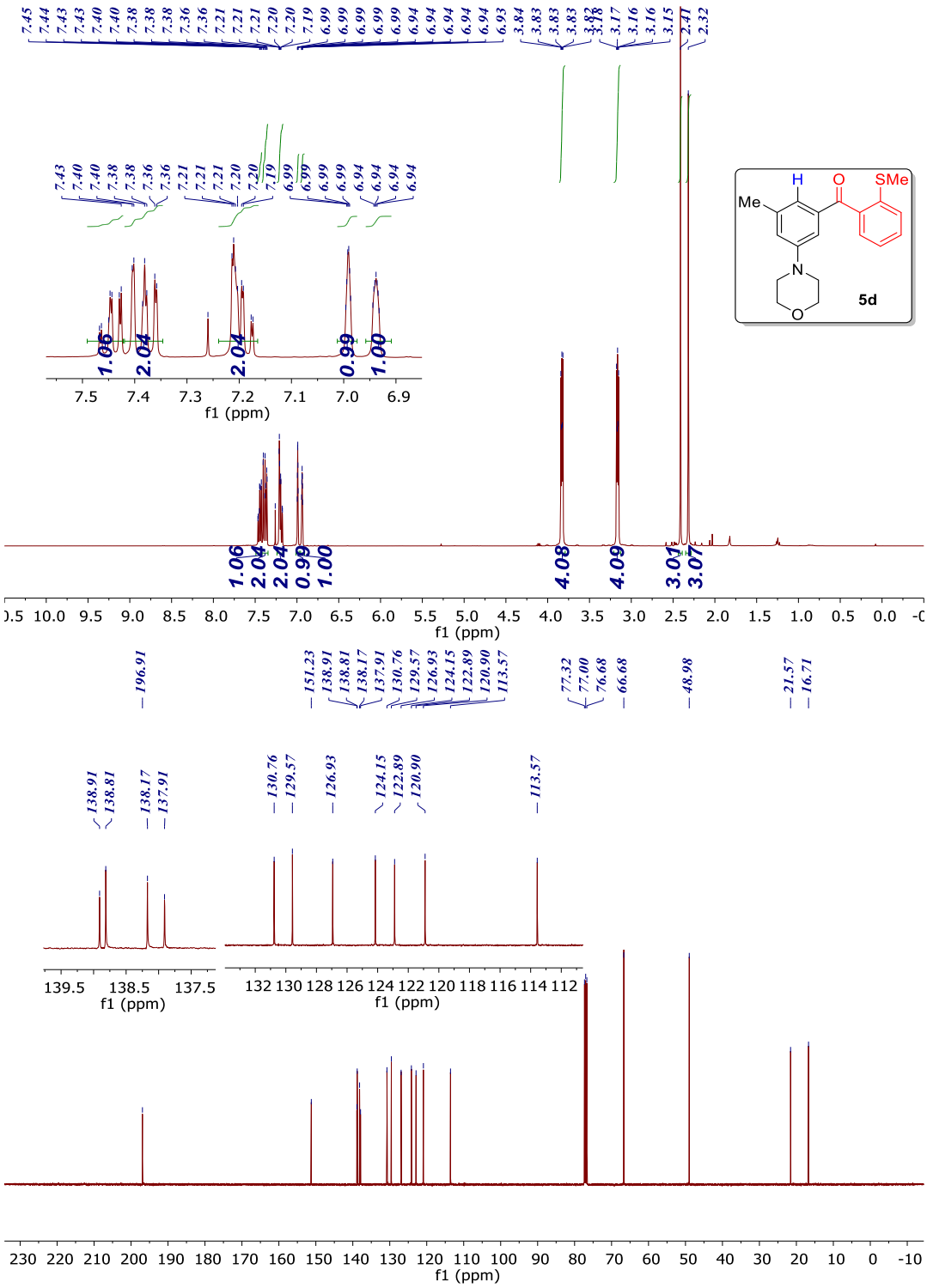


Figure 3.47 ^{1}H and ^{13}C NMR spectrum of compound **5e**.

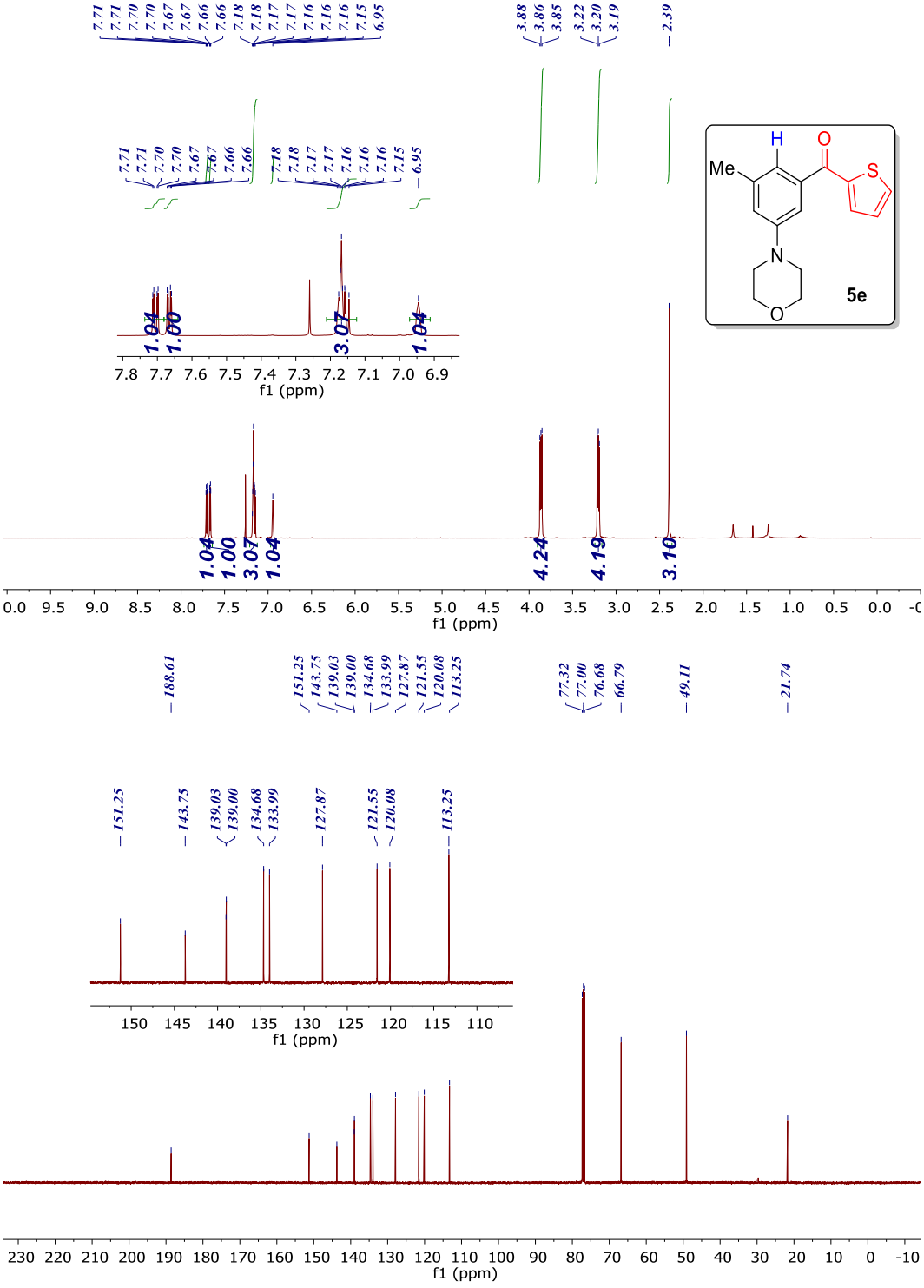


Figure 3.48 ^{1}H and ^{13}C NMR spectrum of compound **5f**.

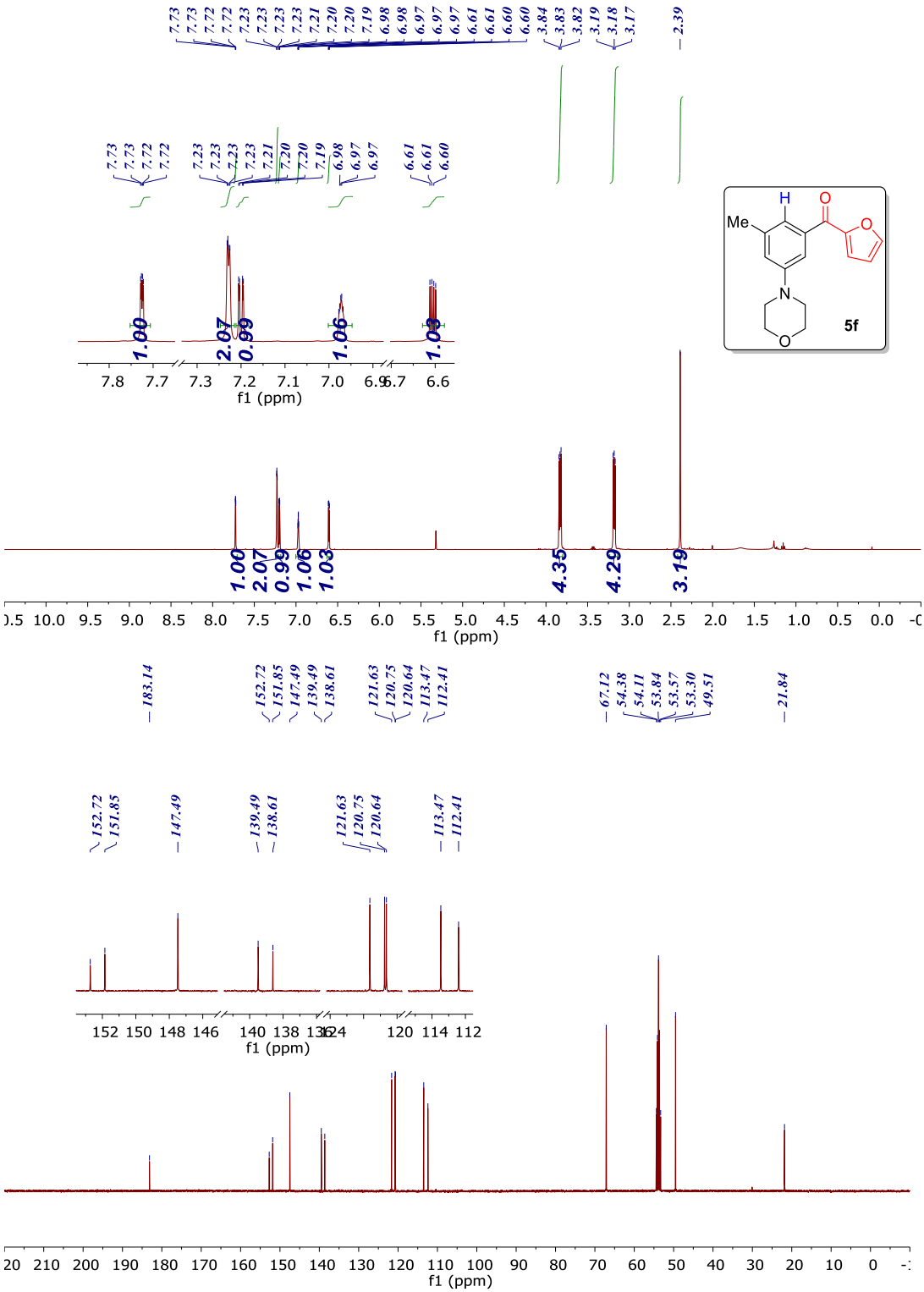


Figure 3.49 ^{1}H and ^{13}C NMR spectrum of compound **5g**.

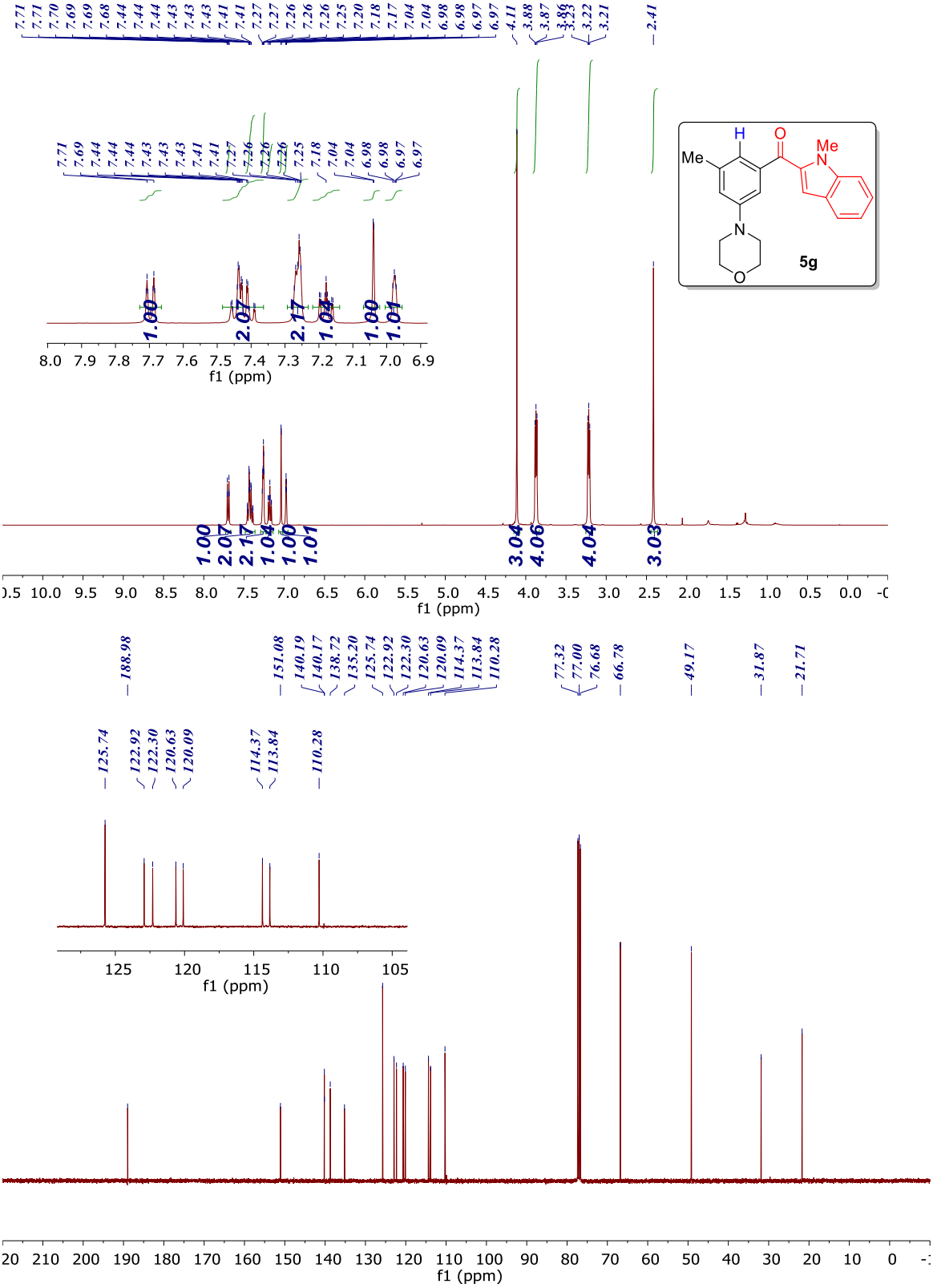


Figure 3.50 ^{1}H and ^{13}C NMR spectrum of compound **5h**.

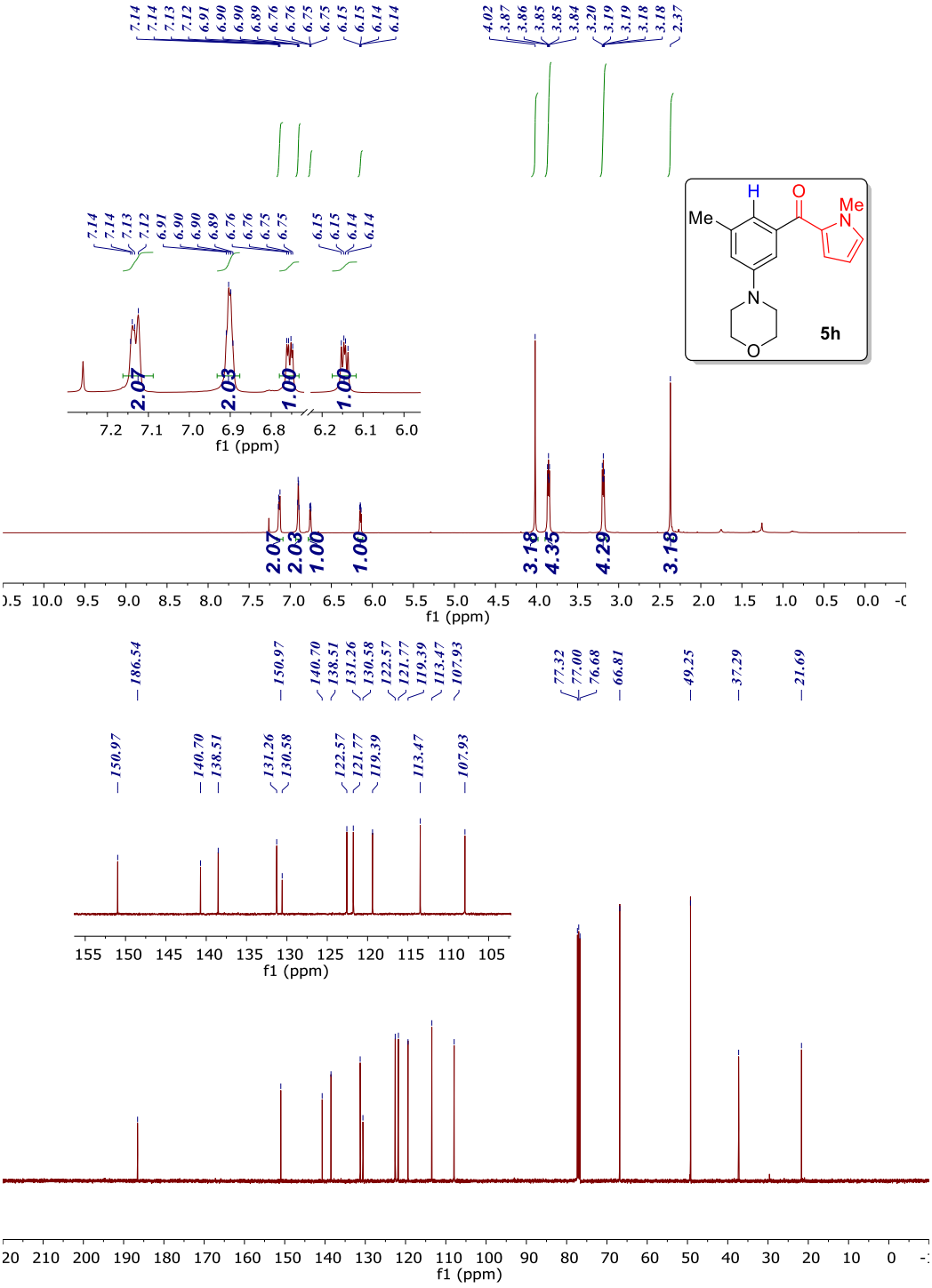


Figure 3.51 ^{1}H and ^{13}C NMR spectrum of compound **5i**.

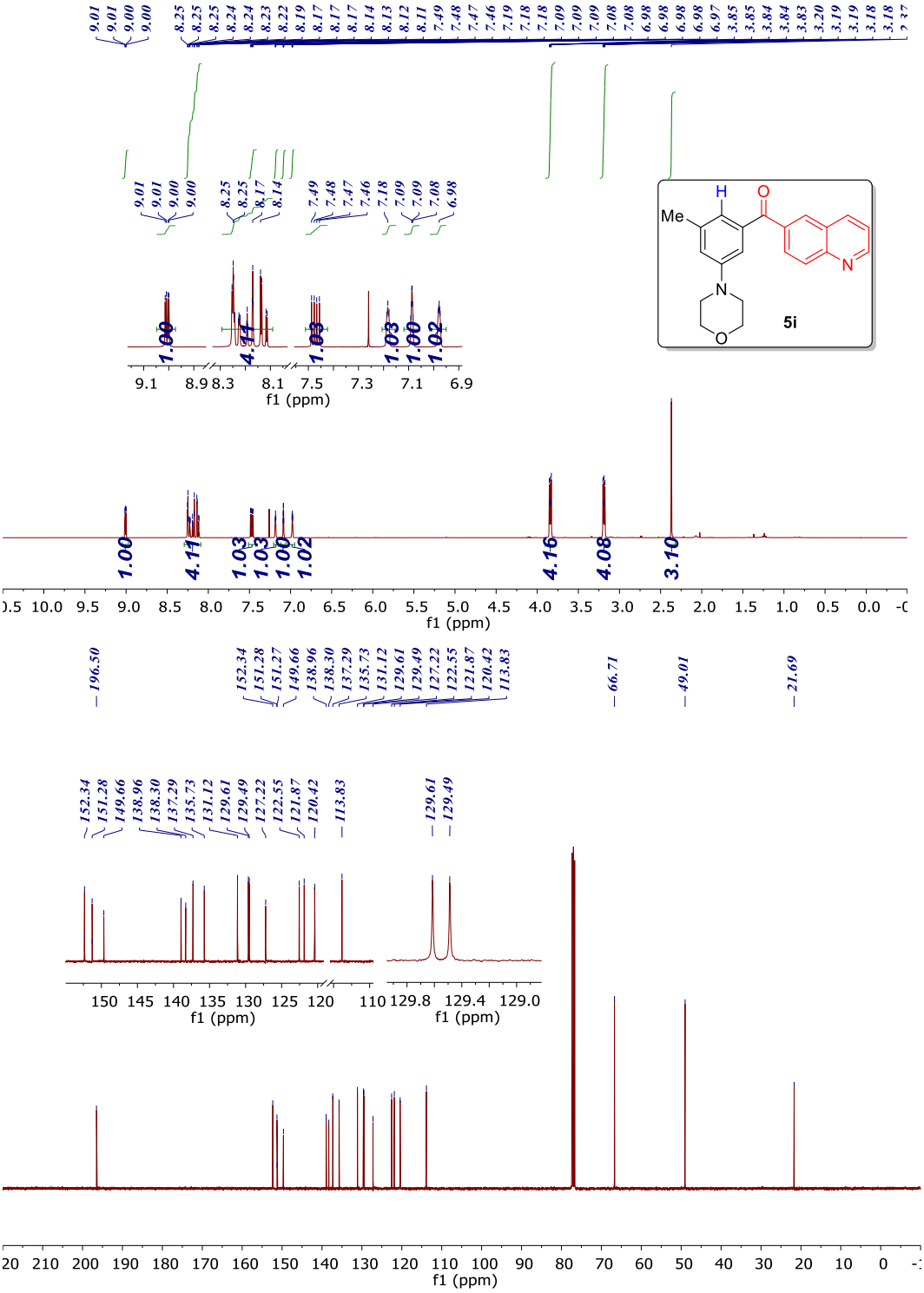


Figure 3.52 ^{1}H and ^{13}C NMR spectrum of compound **5j**.

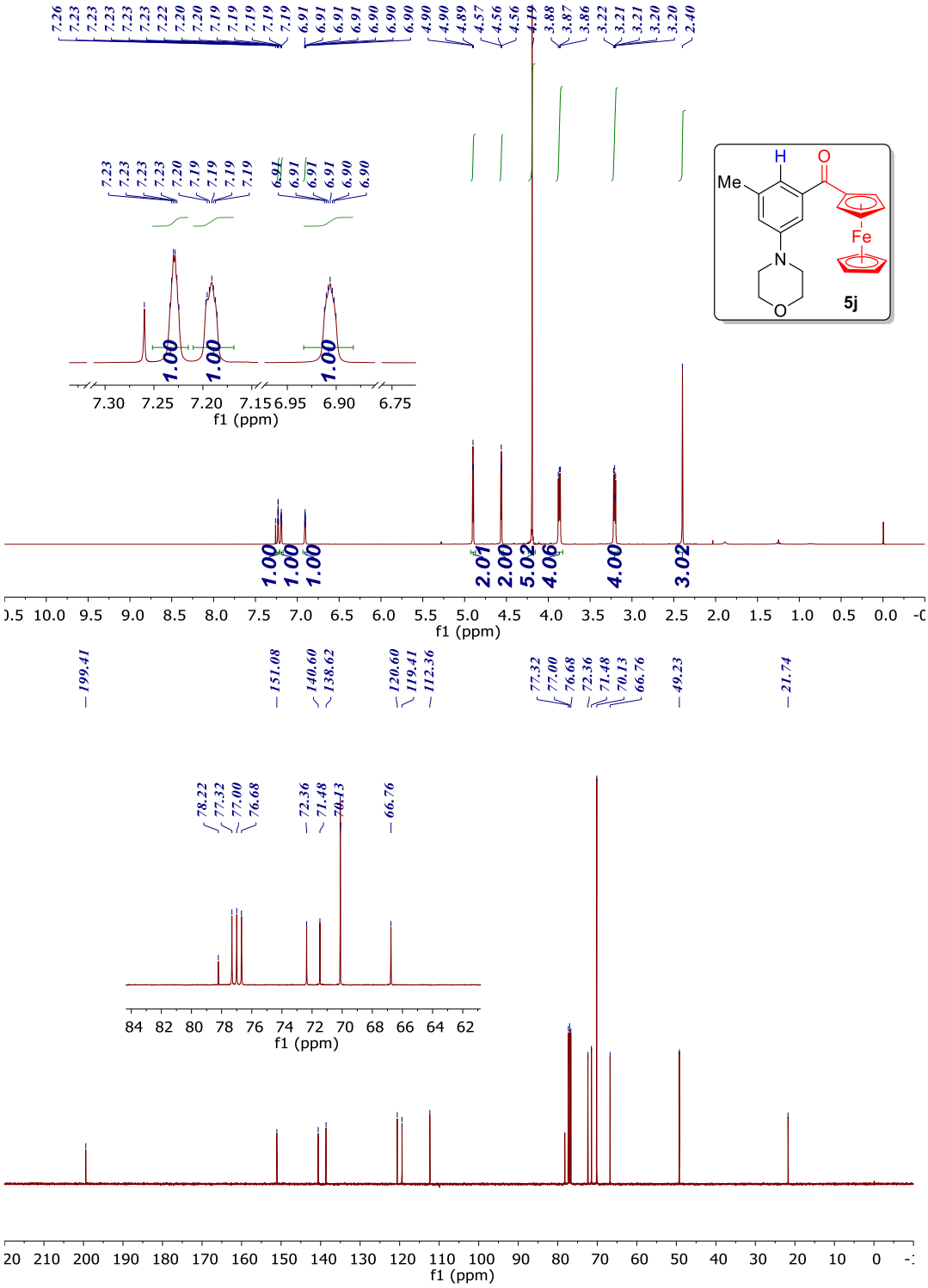


Figure 3.53 ^{1}H and ^{13}C NMR spectrum of compound **5k**.

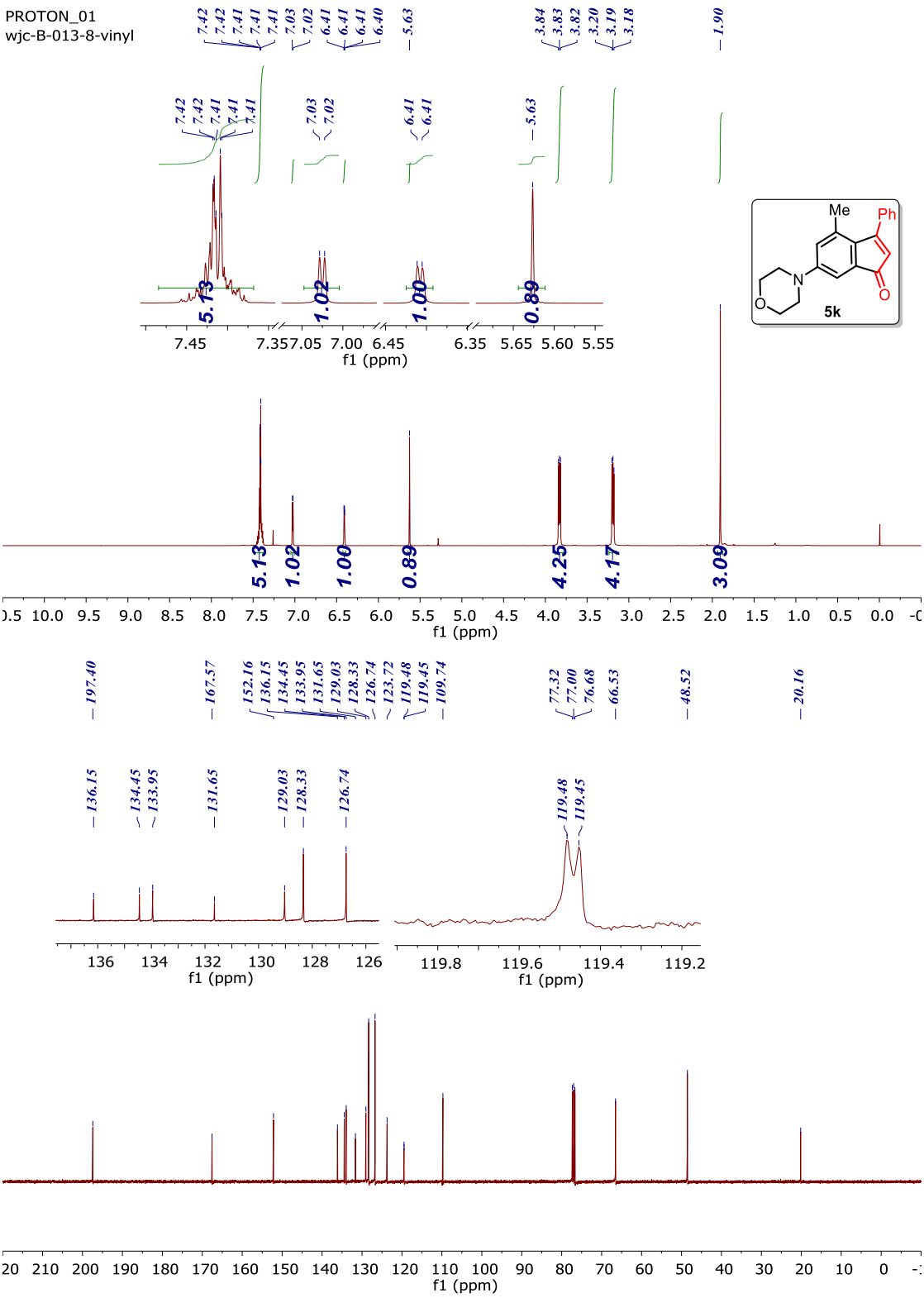


Figure 3.54 1D-NOE NMR spectrum of compound **5k**.

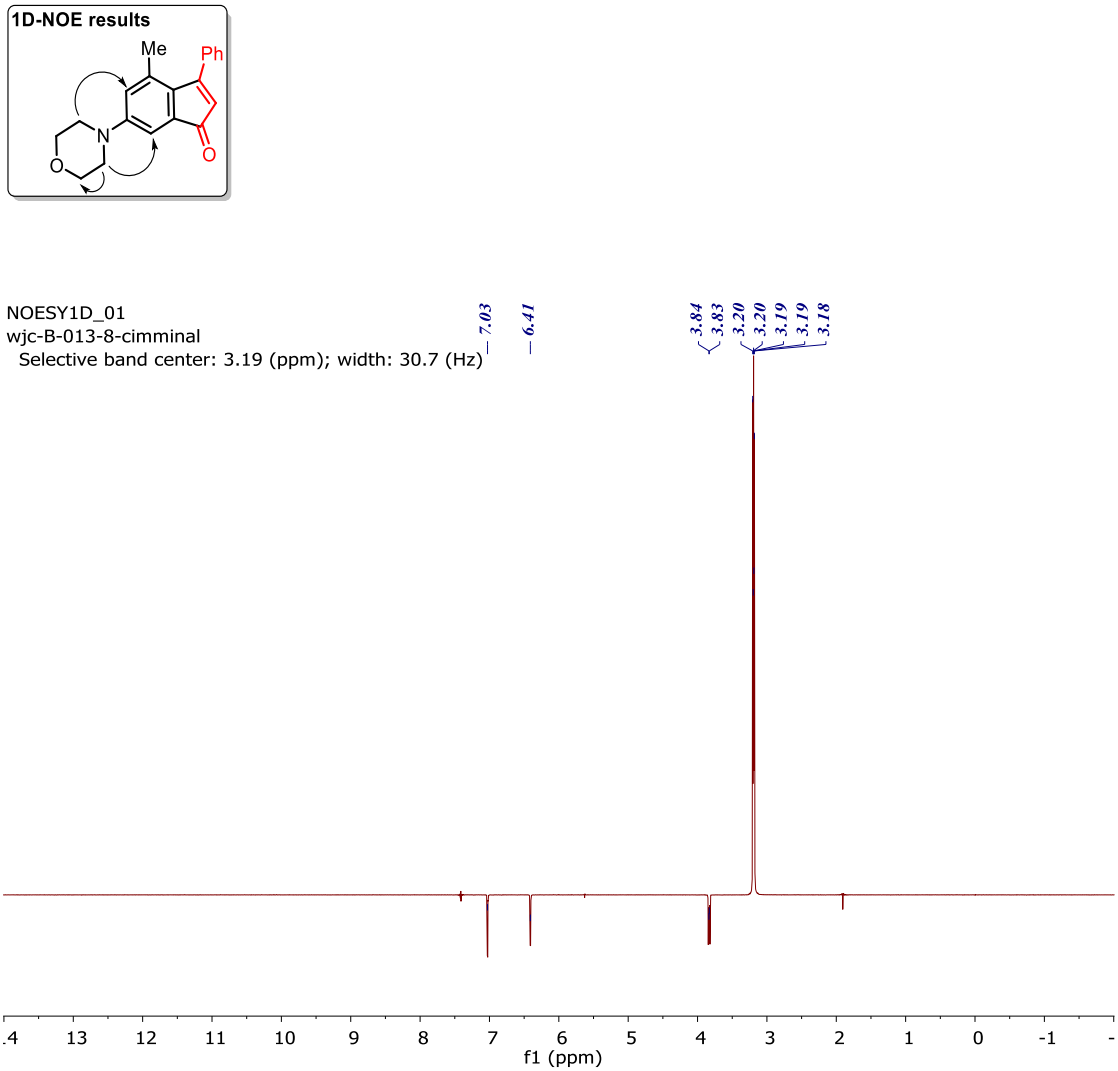


Figure 3.55 ^{1}H and ^{13}C NMR spectrum of compound **5l**.

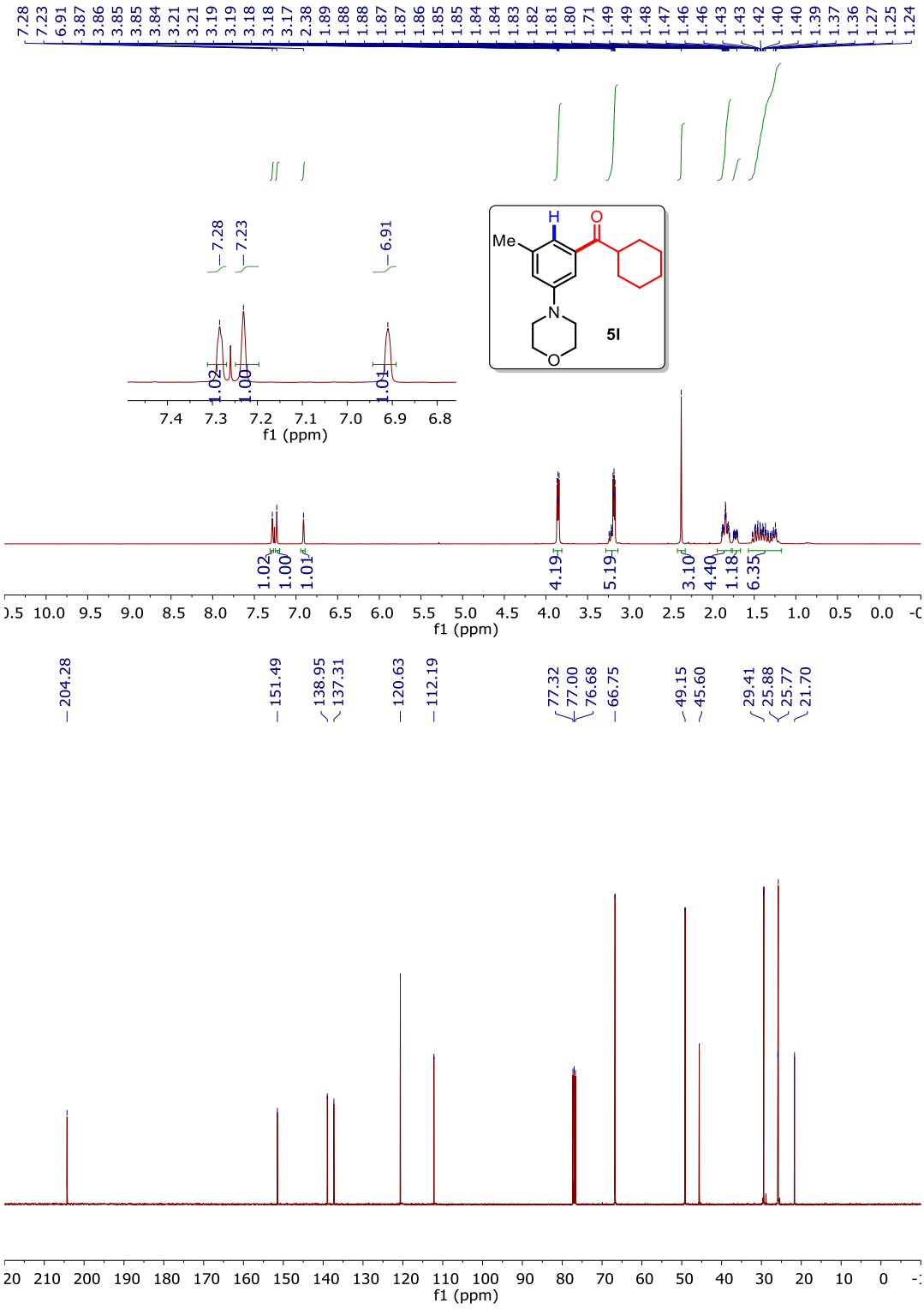


Figure 3.56 ^{1}H and ^{13}C NMR spectrum of compound **5m**.

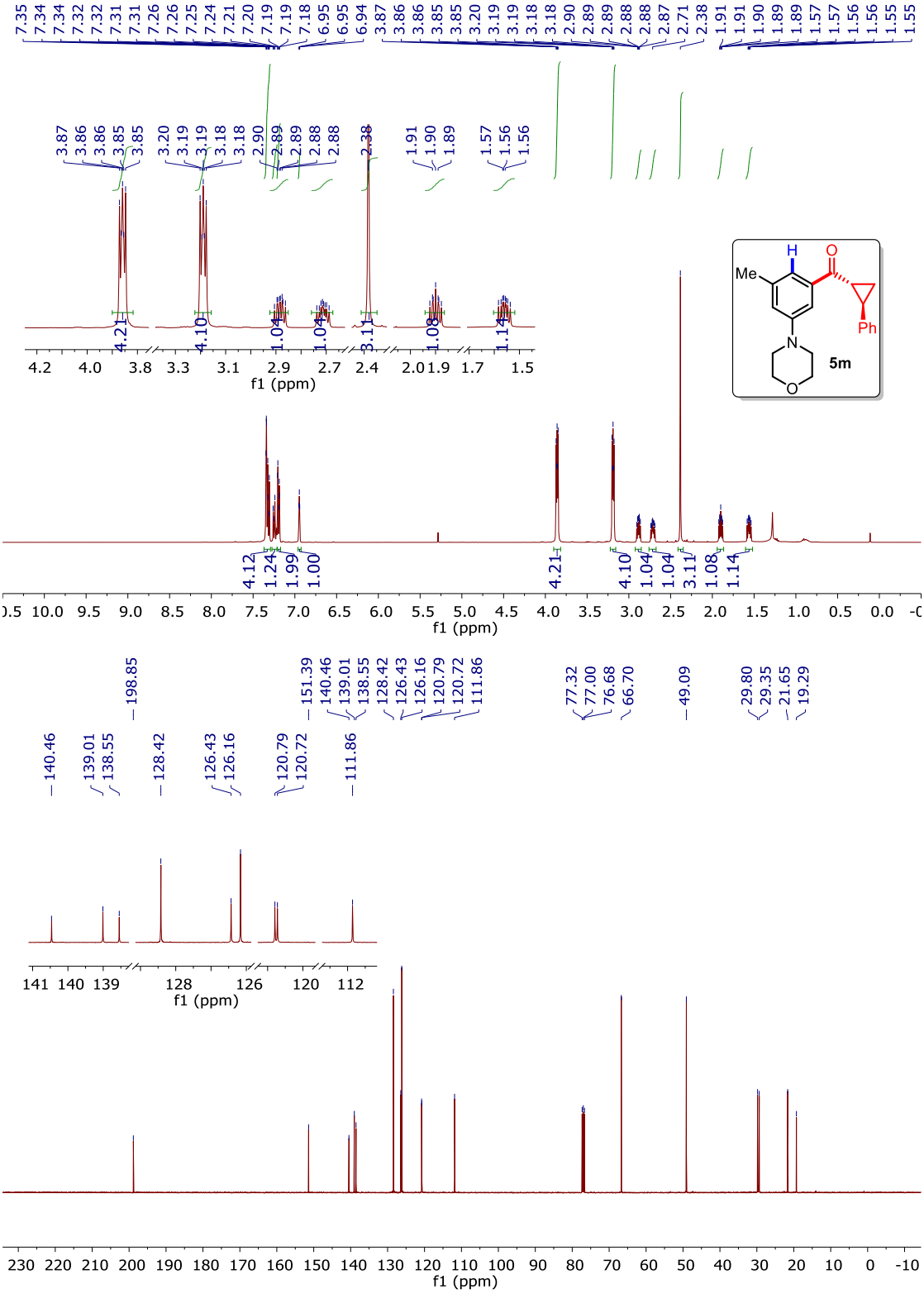


Figure 3.57 ^{1}H and ^{13}C NMR spectrum of compound **5n**.

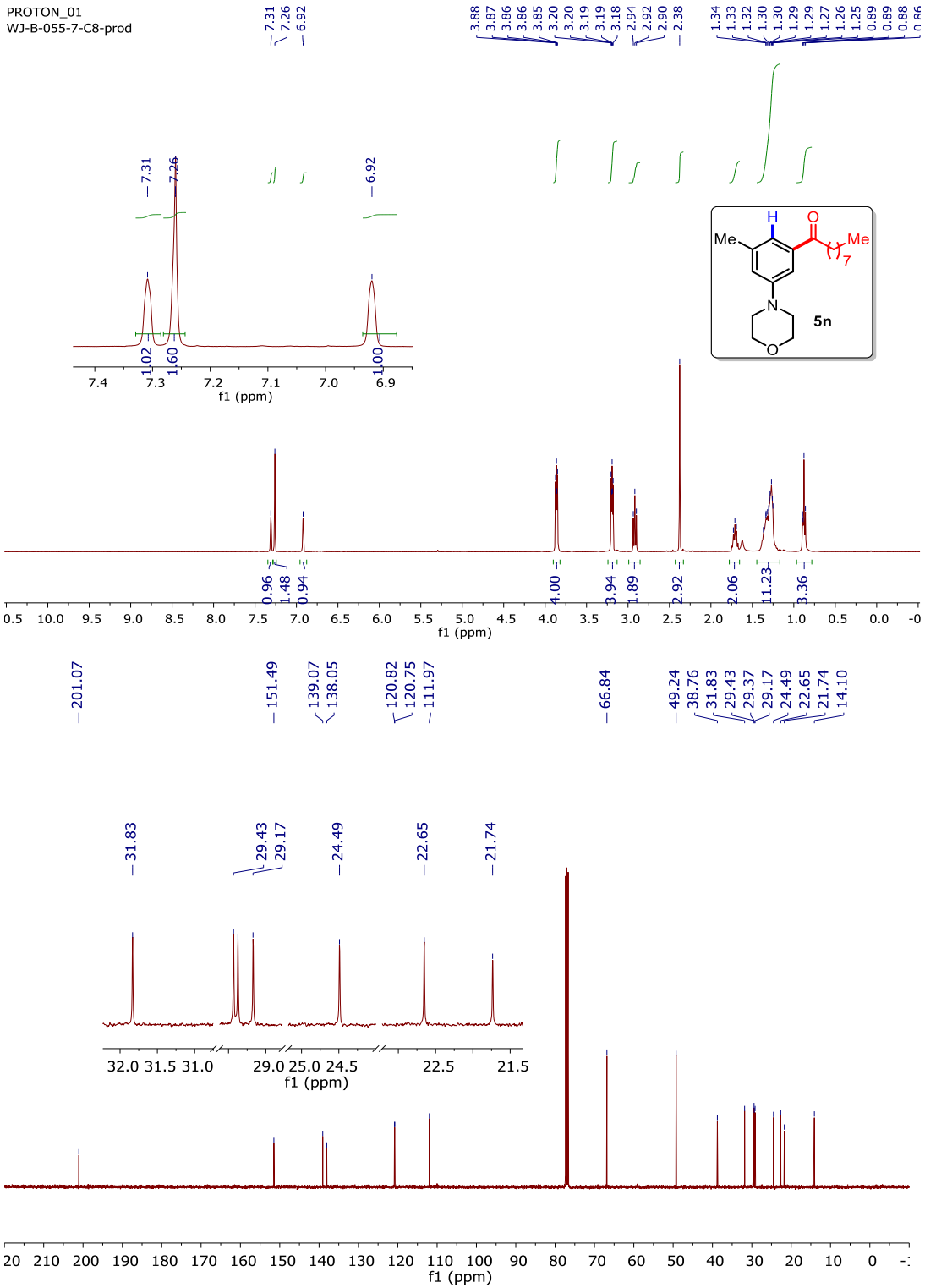


Figure 3.58 ^{1}H and ^{13}C NMR spectrum of compound **6**.

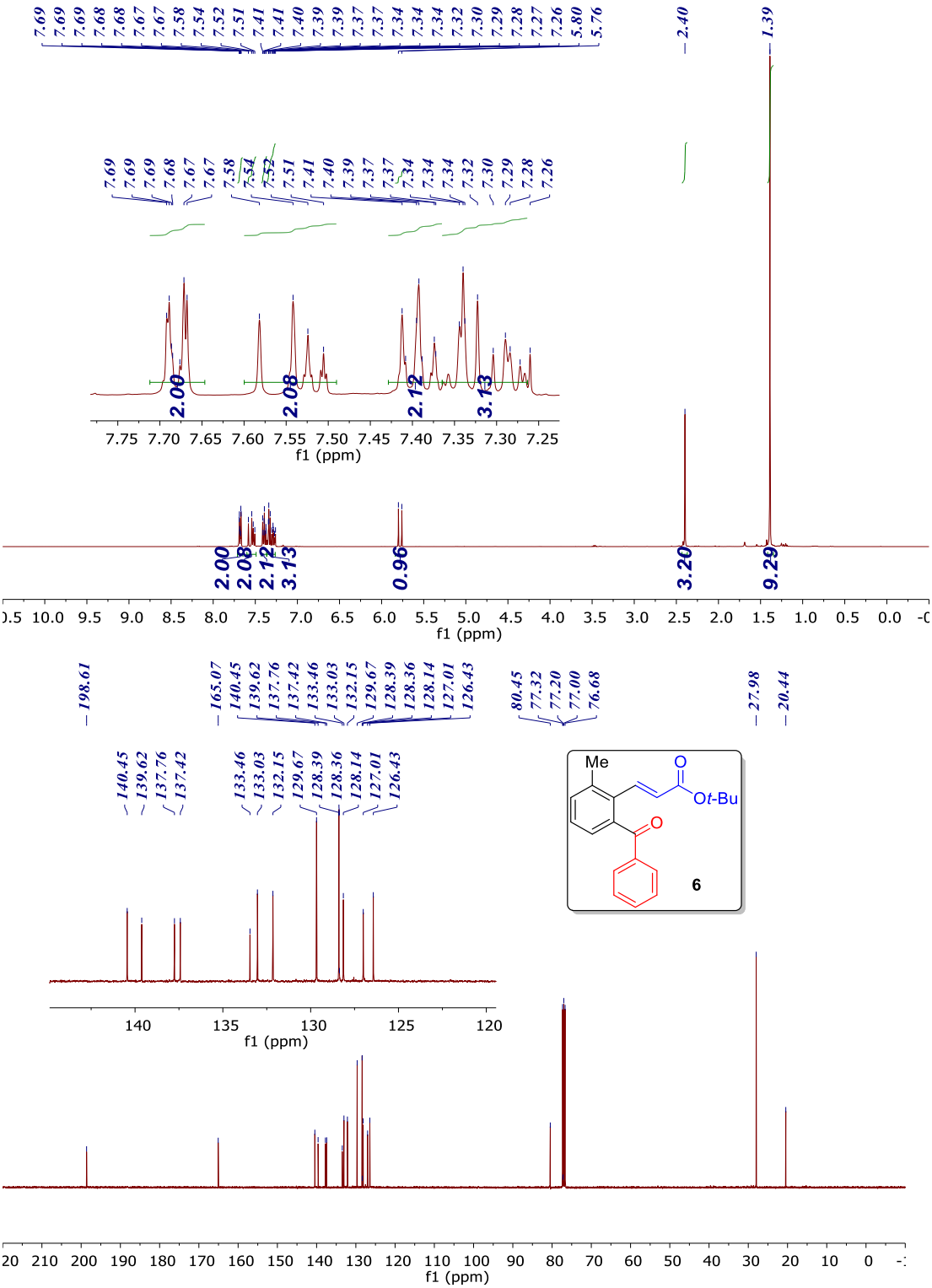


Figure 3.59 ^{1}H and ^{13}C NMR spectrum of compound **7**.

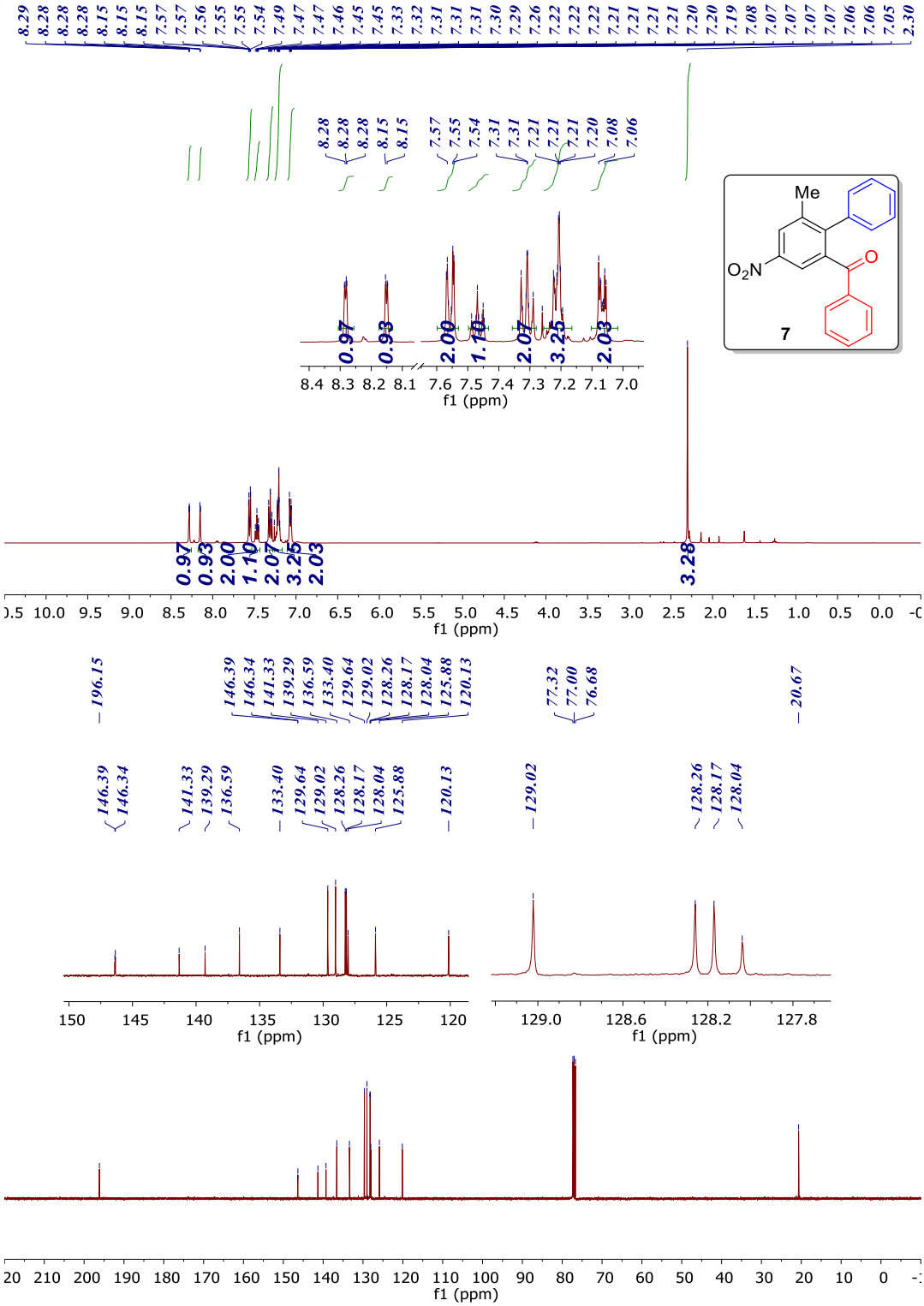


Figure 3.60 ^{1}H and ^{13}C NMR spectrum of compound **2a'**.

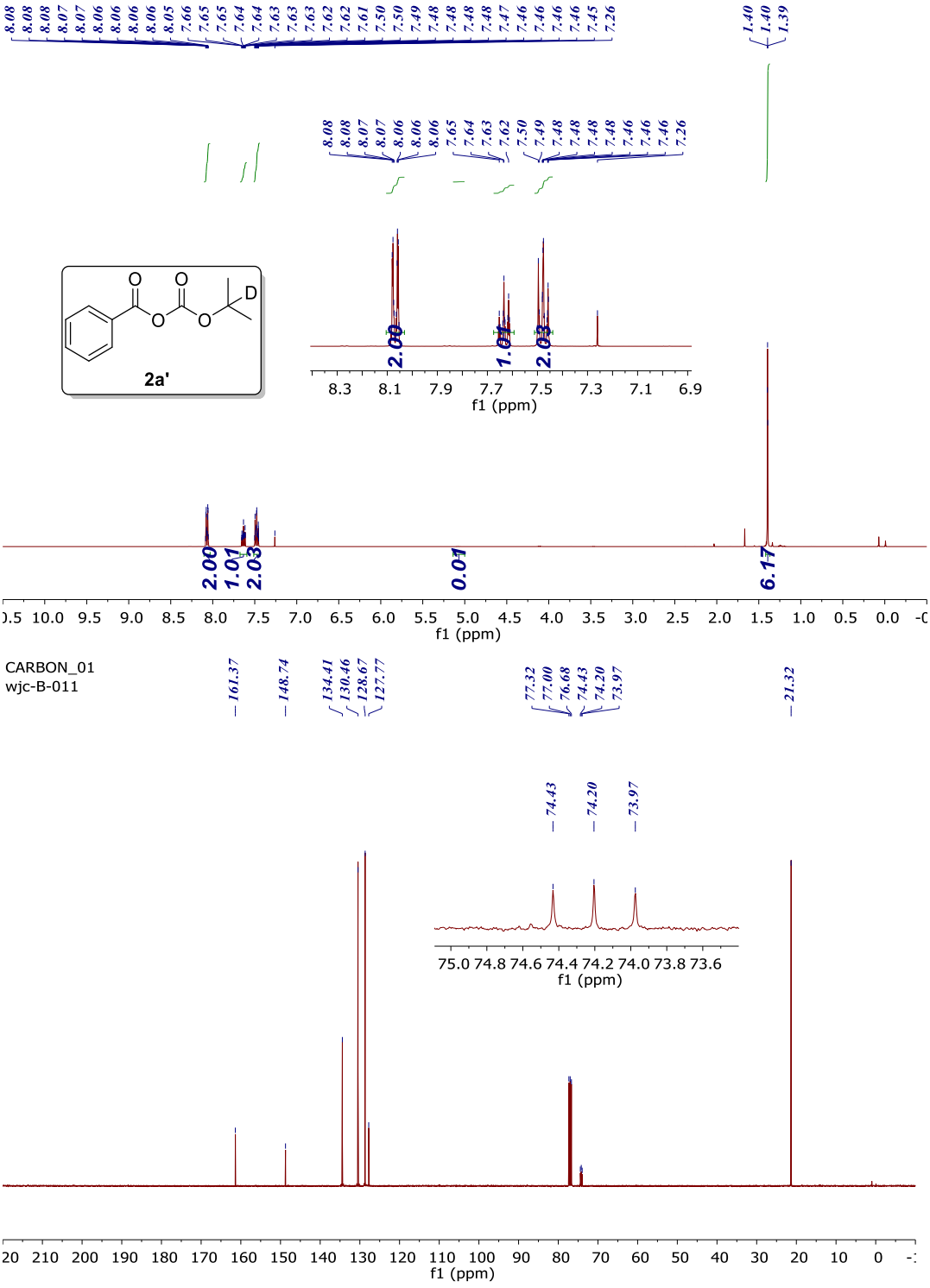


Figure 3.61 ^{1}H and ^{13}C NMR spectrum of compound **4g'**.

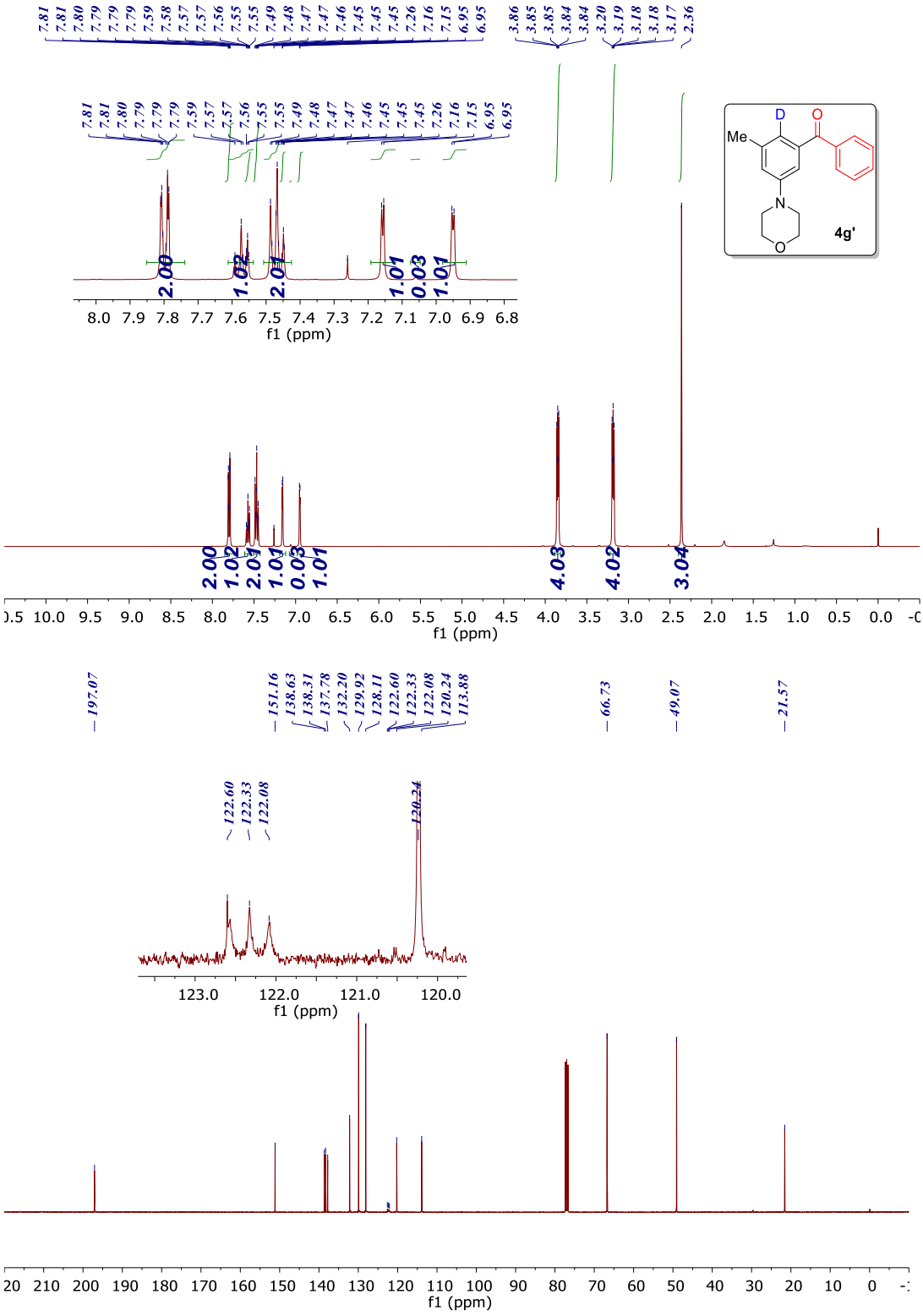


Figure 3.62 Comparison between ^{1}H NMR spectrum for compound **4g** and **4g'**.

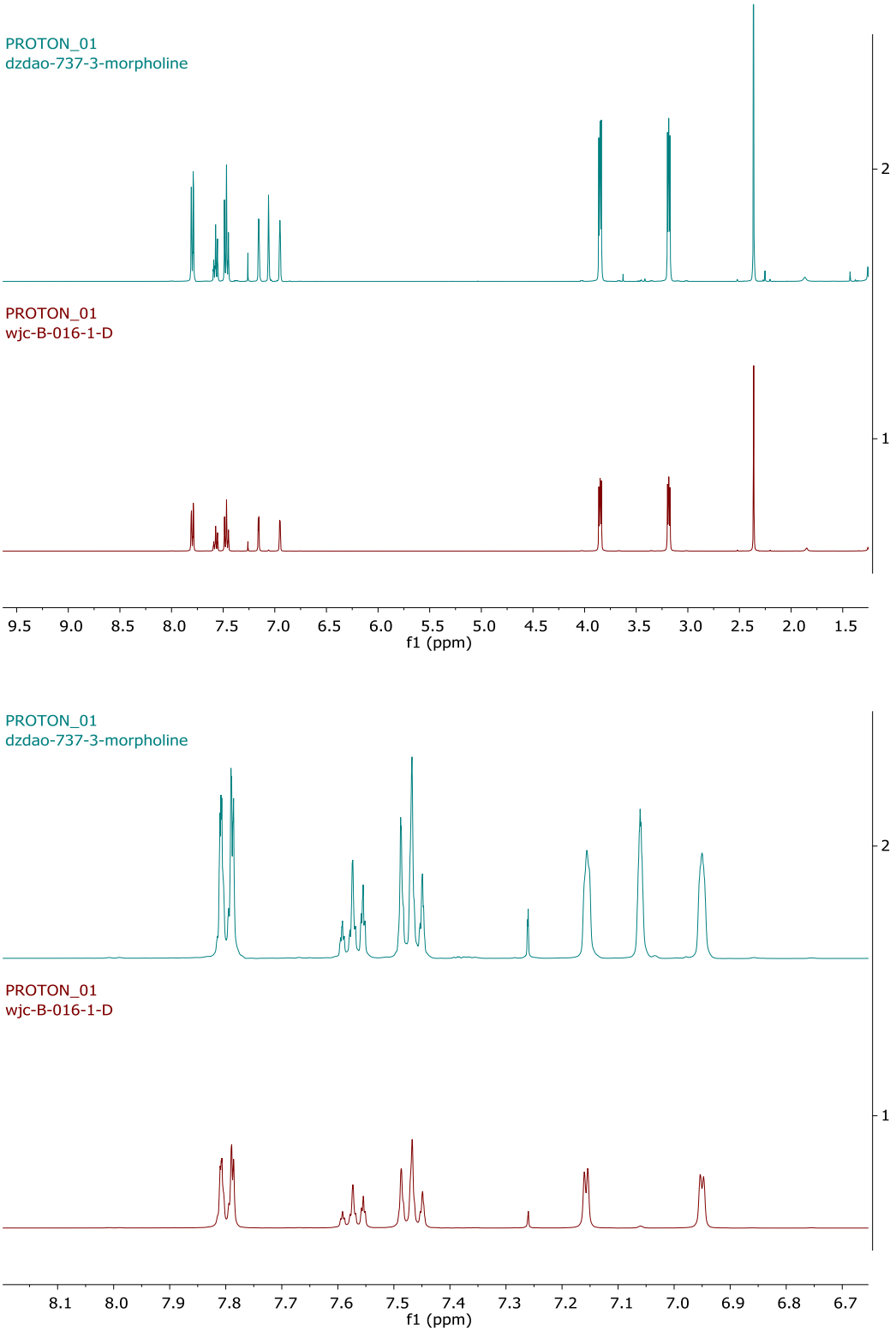
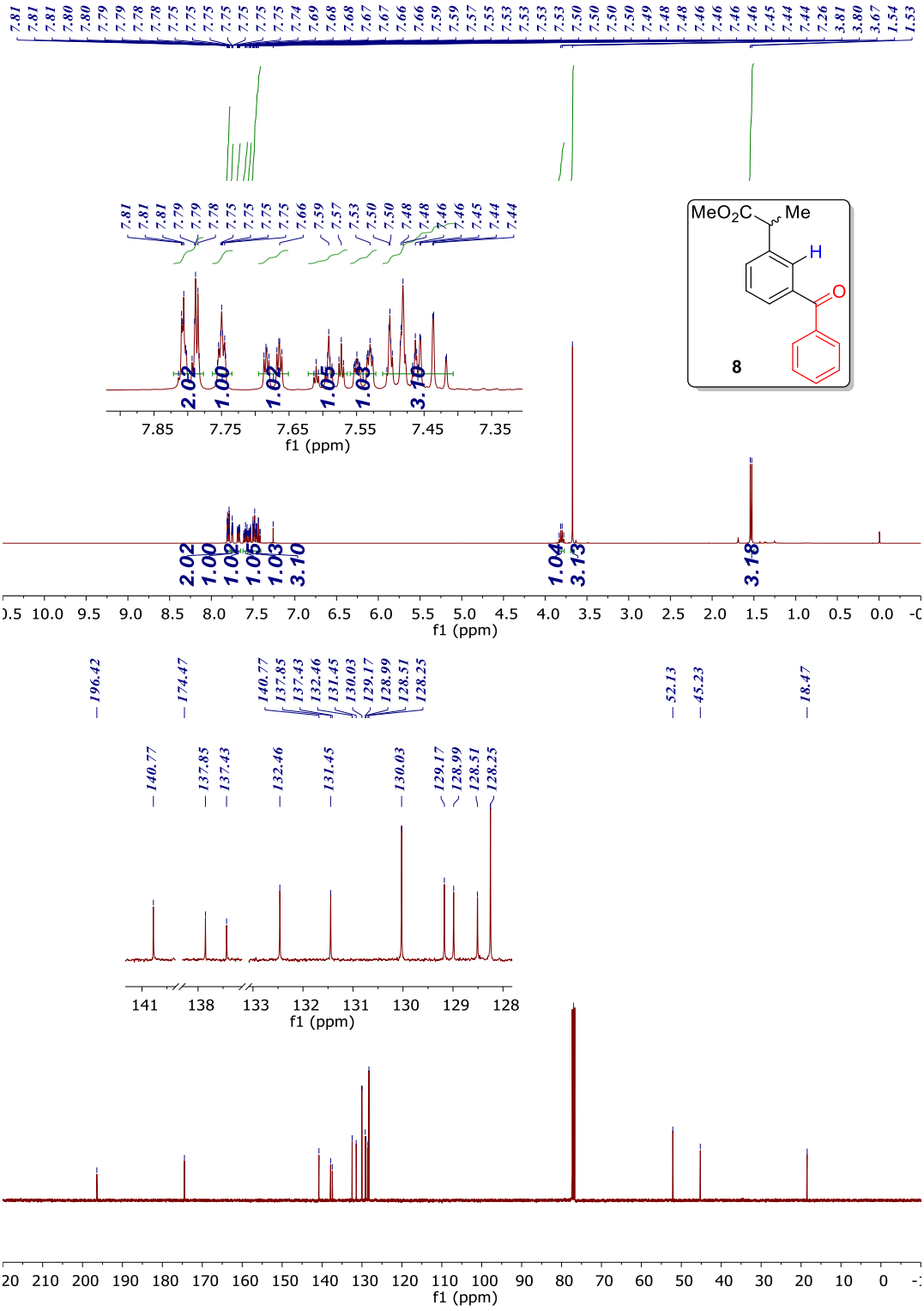
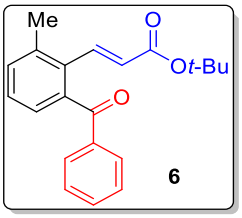
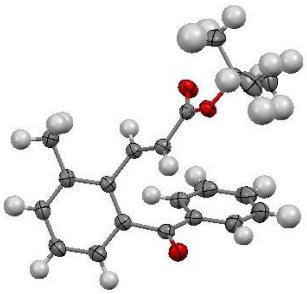


Figure 3.63 ^{1}H and ^{13}C NMR spectrum of compound **8**.

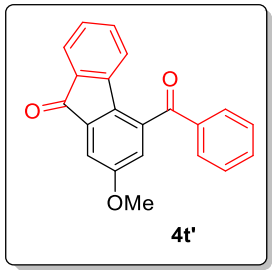


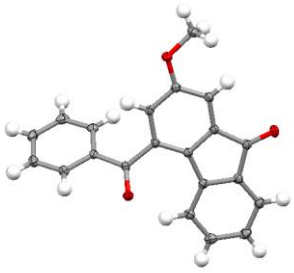




CCDC Number	1411116
Empirical formula	C21 H22 O3
Formula weight	322.39
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 8.4927(1) Å α= 73.378(18)°.
	b = 11.0891(4) Å β= 73.320(16)°.
	c = 11.3329(1) Å γ = 68.496(17)°.
Volume	931.43(16) $Å^3$
Z	2
Density (calculated)	1.150 Mg/m^3
Absorption coefficient	.076 mm^{-1}
F(000)	344.0
Crystal size	0.40 x 0.21 x 0.20 mm^3

Theta range for data collection	1.916 to 31.867°.
Index ranges	-11<=h<=11, -15<=k<=16, -16<=l<=16
Reflections collected	5971
Independent reflections	4659 [R(int) = 0.0523]
Completeness to theta = 31.867°	93.2 %
Absorption correction	None
Max. and min. transmission	0.985 and 0.970
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5971 / 0 / 305
Goodness-of-fit on F^2	1.027
Final R indices [I>2sigma(I)]	R1 = 0.0523, wR2 = 0.1225
R indices (all data)	R1 = 0.0701, wR2 = 0.1363
Largest diff. peak and hole	0.36 and –0.23 e.$Å^{-3}$





CCDC Number	1416066
Empirical formula	C21 H14 O3
Formula weight	314.32
Temperature	100(2) K
Wavelength	0.71075 Å
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	a = 11.883(7) Å α= 90°.
	b = 8.177(5) Å β= 96.828(10)°.
	c = 15.646(9) Å γ= 90°.
Volume	1509.4(15) $Å^3$
Z	4
Density (calculated)	1.383 Mg/m^3
Absorption coefficient	0.092 mm^{-1}
F(000)	656
Crystal size	0.830 x 0.720 x 0.140 mm^3

Theta range for data collection	1.726 to 30.922°.
Index ranges	-16<=h<=16, -11<=k<=11, -21<=l<=21
Reflections collected	19532
Independent reflections	4386 [R(int) = 0.0543]
Completeness to theta = 25.242°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.9250
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4386 / 0 / 218
Goodness-of-fit on F^2	0.955
Final R indices [I>2sigma(I)]	R1 = 0.0427, wR2 = 0.1114
R indices (all data)	R1 = 0.0520, wR2 = 0.1193
Extinction coefficient	n/a
Largest diff. peak and hole	0.303 and -0.250 e.$Å^{-3}$

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Chapter 4: Palladium and Norbornene Catalyzed *ipso/ortho* Difunctionalization of Aryl Bromides

4.1 INTRODUCTION

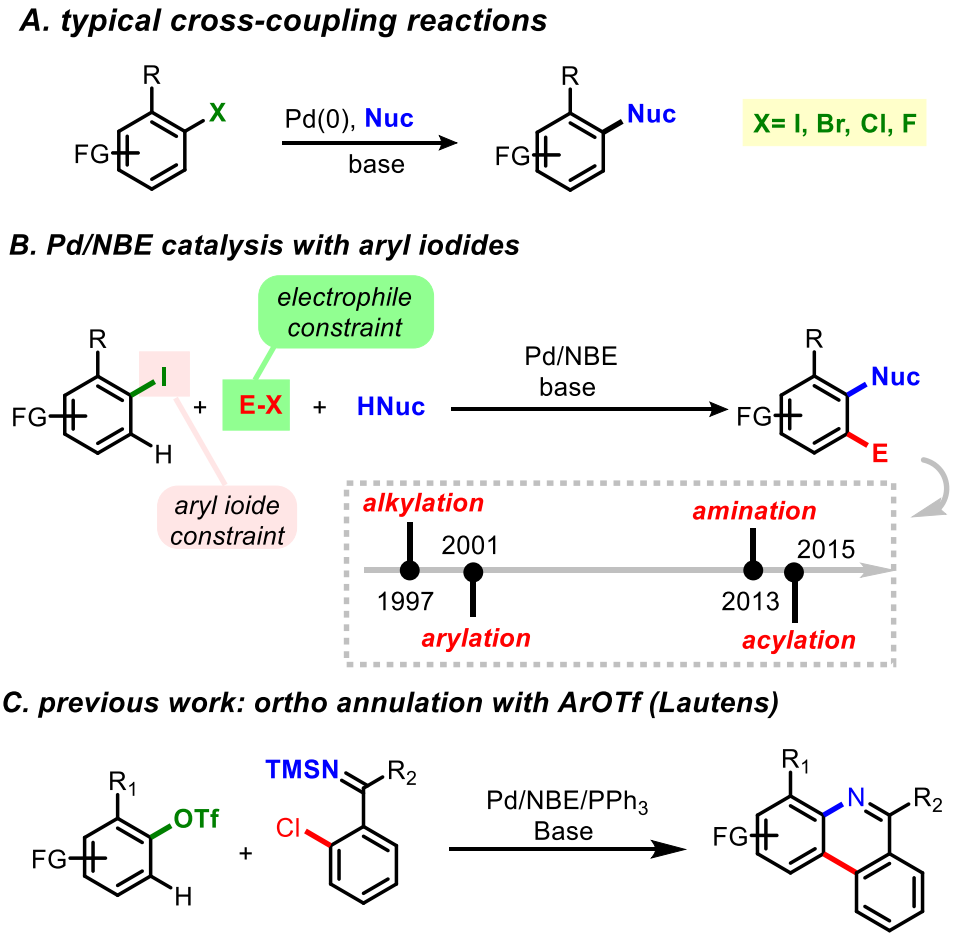
Poly-substituted aromatics are ubiquitously found in pharmaceuticals[1], agrochemicals[2-3] and organic materials.[4] During the past decades, cross-couplings[5] and nucleophilic aromatic substitutions[6] (S_NAr) have clearly become indispensable tools for preparing poly-functionalized arenes from readily available aryl halides through introducing a nucleophile at the *ipso* position (Scheme 4.1A). While powerful, these approaches typically only introduce one substituent at one time and the position of the newly installed functional group (FG) is dictated by the position of the halogen substituent.[7] (Scheme 4.1A) As a complementary approach for arene functionalization using aryl iodides, palladium/norbornene (Pd/NBE) cooperative catalysis, namely Catellani-type reactions, allows for vicinal difunctionalization of arenes through coupling a nucleophile at the *ipso* position and an electrophile at the *ortho* position simultaneously.[8-14](Scheme 4.1B) It can be envisioned that, through using different combinations of nucleophiles and electrophiles, a diverse range of multi-substituted arene products would be easily obtained in one step from simple starting materials, thereby providing a modular approach for *ipso/ortho* difunctionalization.

4.2 BACKGROUND

Important contributions by Catellani and Lautens have demonstrated that, analogous to the cross coupling reactions, a broad scope of nucleophiles can be coupled at the *ipso* position;[8,15-31] however, the scope of the electrophiles had been primarily restricted to alkyl and aryl halides since the seminal works by Catellani in 1997[8] and 2001[16]. In addition, except a single elegant report by Lautens on aryl triflate-mediated annulation reaction[32] (Scheme 4.1C), the arene substrates in

Catellani-type reactions have been limited to aryl iodides, and use of aryl bromides remained elusive.

Scheme 4.1 Arene functionalization with aryl halides**.**



Such constraints might be better understood from the proposed catalytic cycle (Figure 4.1). It starts with oxidative addition of Pd(0) into the aryl-iodide bond (Step A), followed by *syn*-migratory insertion[33] into NBE (Step B) and C−H metalation, to generate an aryl-NBE-palladacycle (**ANP**)[34-35] (Step C), which can react with an electrophile to introduce a FG at the *ortho* position[36] (Step D). The following de-insertion of NBE through β-carbon elimination gives an electrophilic aryl-palladium species[37] (Step E), which is then trapped by a nucleophile to furnish

the *ipso* functionalization and regenerate the Pd(0) catalyst[8] (Step F). Thus, to successfully implement the Pd/NBE catalysis, the electrophile employed should selectively oxidize or react with the **ANP** Pd(II) intermediate instead of the electron-rich Pd(0) catalyst (Step G); on the other hand, the aryl halide substrate must selectively react with the Pd(0) instead of **ANP** to avoid self-dimerization (Figure 4.2). Given the simultaneous presence of two oxidants (aryl halides and the electrophiles) and two electron-rich Pd species (Pd(0) and **ANP**), developing new *ortho* functionalization with expanded electrophile and aryl halide scopes is not a trivial issue.[14]

Figure 4.1 Simplified Catalytic Cycle

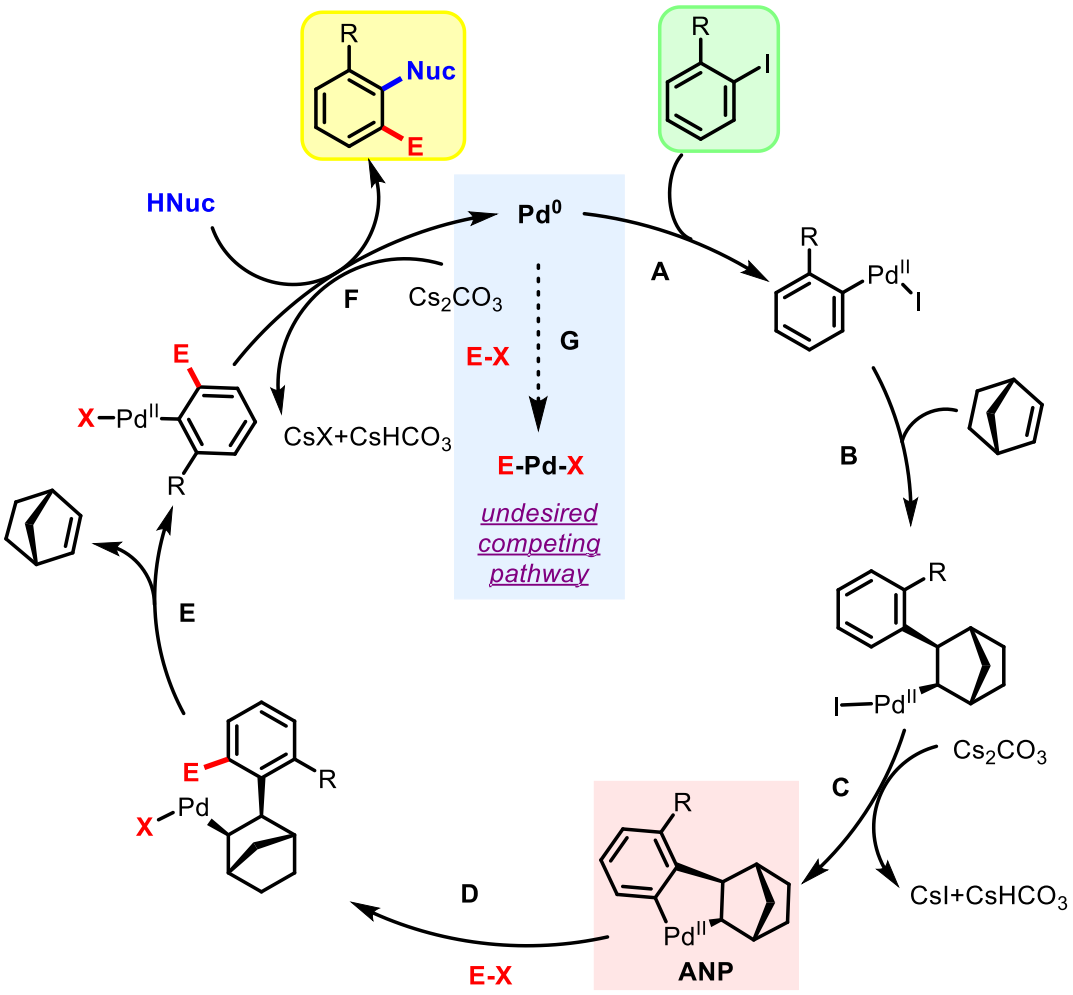
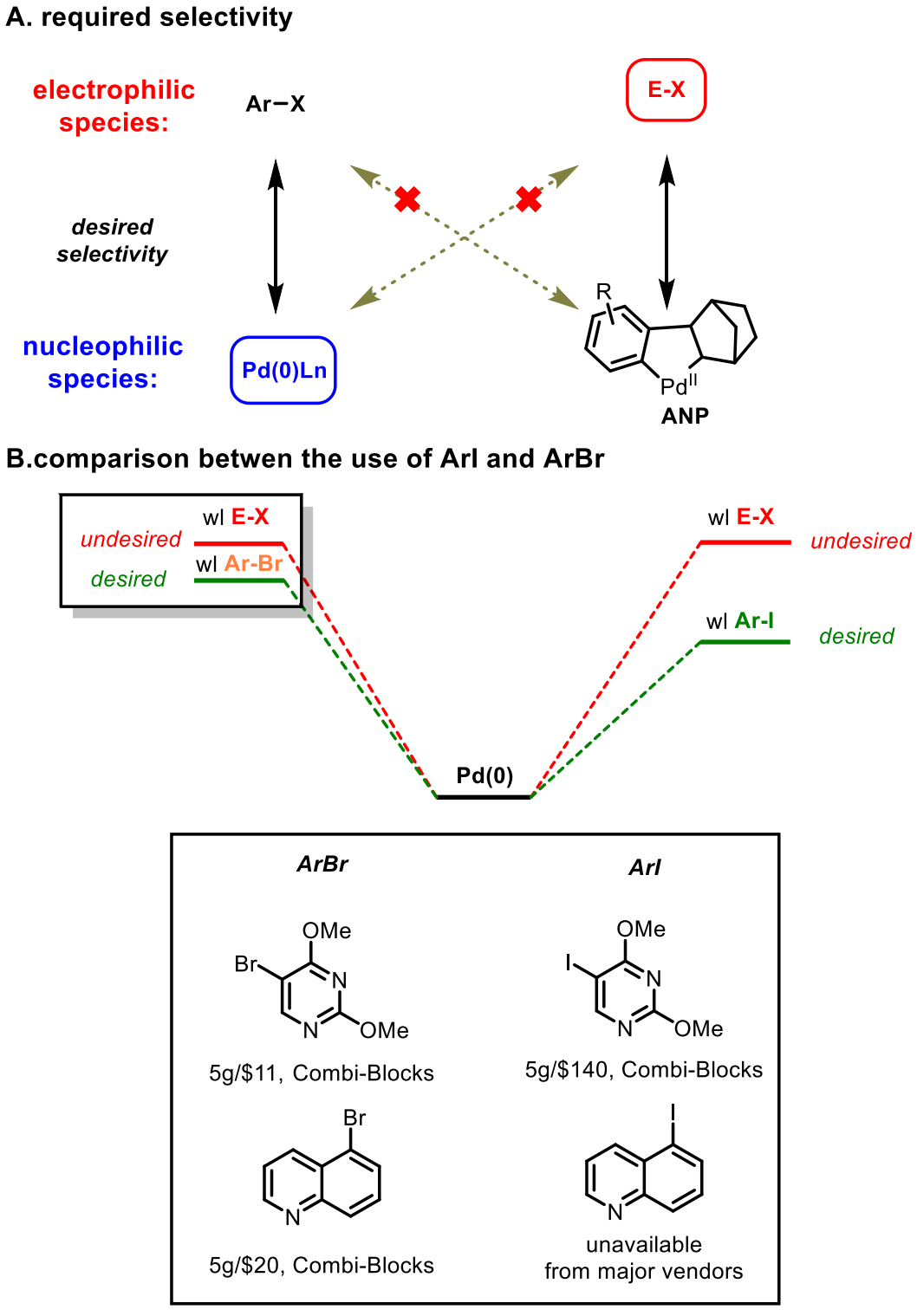


Figure 4.2 Mechanistic considerations



To address the challenge of the "electrophile constraint", we hypothesized that *electrophiles that have certain coordinating capability with the more Lewis acidic Pd(II) center at **ANP** might be suitable to afford desired selectivity in the Pd/NBE catalysis*. In 2013 we reported our preliminary study of developing *ortho* amination using *O*-benzoyl hydroxylamines as the electrophile[38], illustrating that heteroatoms can be introduced arene *ortho* positions (Scheme 4.1B). Subsequently, a series of elegant works on *ortho* amination-derived different *ipso* functionalization have been disclosed.[39-51] In 2015, the Liang, Gu and our laboratories concurrently described *ortho* acylation using anhydrides as the electrophiles.[52-54] Recently, *ortho* acylation/*ipso* thiolation with thioesters[55] and *ortho* carboxylation with carbonate anhydrides[56] were reported by Gu and us respectively.

The challenge of the "aryl iodide constraint" may seem to be rather surprising, as aryl bromides have proved to be a suitable coupling partner in the Pd-catalyzed cross-coupling reactions for more than three decades.[57] It is well known that aryl bromides undergo significantly slower oxidative addition with Pd(0) than aryl iodides,[58-59] which inevitably increases the chance for the "external" electrophile to compete for the oxidation with Pd(0) (Figure 4.2 B). Thus, it is reasonable to imagine the catalytic conditions that work well for aryl iodides may not work for aryl bromides. Hence, fine-tuning of the steric and electronic properties of the Pd(0) catalyst to *match* the electrophile or nucleophile employed would become critical to enable the reactions with aryl bromides.

From the practicality viewpoint, aryl bromides are generally much cheaper and more accessible than the corresponding aryl iodides (Figure 4.2B).[60] For example, 5-iodo-2,4-dimethoxypyrimidine is ten times more expensive than the bromo counterpart;[61] 5-bromoquinoline is about $4 per gram, whereas 5-iodoquinoline is not available from major vendors.[62] In addition,

for heterocycles and complex nature product derivatives, the aryl bromides are often more stable towards light or heat.[63] Moreover, availing the Pd/NBE catalysis with aryl bromides would also enable sequential cross coupling/*ortho* functionalization reactions or consecutive difunctionalization with polyhaloarenes[64-66] (*vide infra*, Scheme 4.3). Therefore, efficient and general methods for *ipso/ortho* difunctionalization of aryl bromides via Pd/NBE catalysis would be of high synthetic value.

In this chapter, we describe systematic efforts for developing various *ortho* functionalization reactions with different classes of electrophiles using aryl bromides as substrates. Diverse *ipso*–functionalization with different nucleophiles has also been exemplified. These methods have allowed for rapid access of a broad range of poly-substituted arenes and heteroarenes with complete control of site-selectivity.

4.3 REACTION DEVELOPMENT AND SCOPE

4.3.1 *Ortho* amination. Inspired by Johnson's seminal study on copper-catalyzed electrophilic amination with organozinc reagents,[67-68] we found *O*-benzoyl hydroxylamines could serve as an excellent electrophile for Pd/NBE catalysis. In combination with isopropanol as the hydride reductant, the *ortho* amination/*ipso* hydrogenation with aryl iodides was successfully developed.[38] Using different nucleophiles as quenching reagents, various *ipso* functionalization reactions based on *ortho* amination have been developed (Figure 4.3), including Mizoroki-Heck reaction with olefins,[39,45] vinylation with hydrazines,[40] Suzuki coupling with aryl and alkyl boronic acids,[41,46] Sonogashira reaction with alkynes,[43-44] Miyaura borylation with diboranes,[42] cyanation with cyanides,[47-48] ketone α-arylation with enol equivalents,[49] dearomatization with phenols[50] and intramolecular amidation with amides.[51] It is clear that the *ortho* amination chemistry holds broad

applicability and potential for practical utility;[69] however, aryl iodides have been the sole substrates employed in these reactions except a single example in our *ortho* amination/*ipso* reductant report with a special electron-deficient aryl bromide.[38]

Figure 4.3 Examples of intermolecular *ortho* amination of aryl iodides

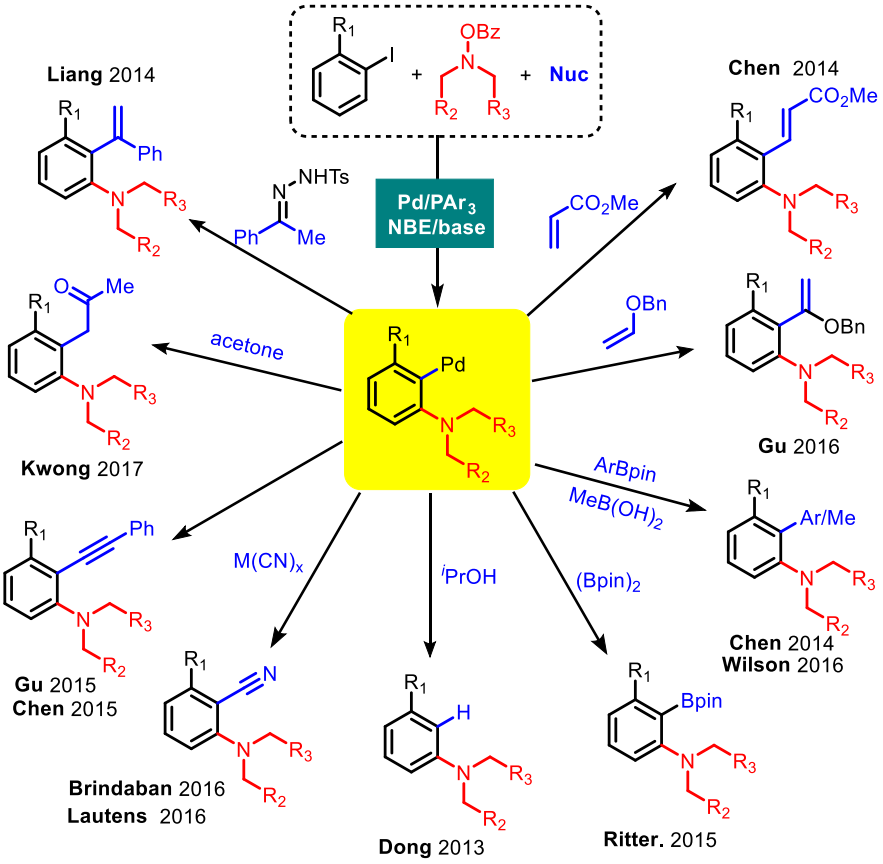
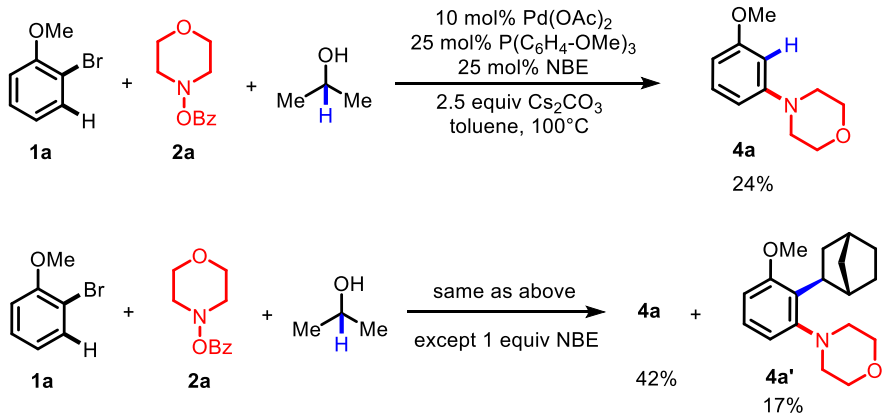


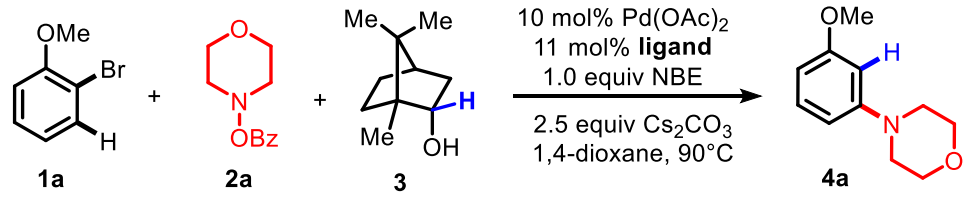
Figure 4.4 Initial Optimization

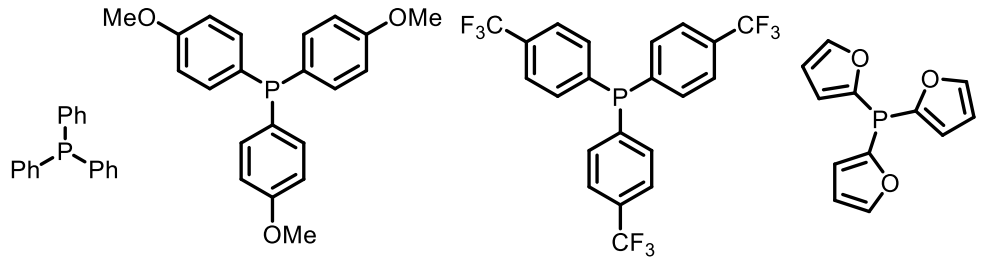


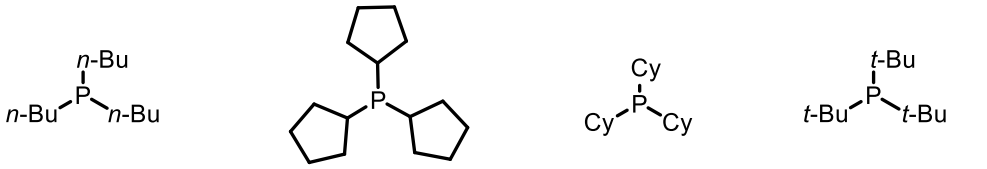
To explore a general *ortho* amination method with aryl bromides, 2-bromoanisole **1a** was employed as the model substrate and the *ipso* hydrogenation was chosen as the model reaction. Under the previously reported conditions for aryl iodides,[38] poor mass balance of aryl bromide and low yield of desired product **4a** were observed (Figure 4.4). Further effort to optimize the reaction identified that the major side-product was norbornene attached reduction compound **4a'** (Figure 4.4). The formation of **4a'** indicated that β-carbon elimination of NBE from the Pd(II) center was slower than hydride transfer from the alcohol reductant. We proposed that more hinder secondary alcohol could significantly decrease β-hydride elimination speed to diminish the side-product. After additional survey of the reaction conditions, using more sterically hindered (−)-borneol **3** and 1,4-dioxane proved to be the best reductant and solvent combination to reduce the formation of **4a'**. The ligand effect was then carefully investigated. The yields with mono-dentate phosphines were generally moderate. Compared to triaryl phosphines, trialkyl phosphines appear more effective, and by large, electron-rich and less sterically hindered ligands gave higher yields. Bulky ligands, such as P*t*Bu$_3$ and Ruphos gave no desired product. It is rather surprisingly that bidentate ligands worked well in this case, as they are typically less effective than monodentate ligands when aryl iodides were used as substrates.[12] In particular, bidentate phosphine ligands with a flexible backbone, such as dppb, DPEphos and dppf, gave reasonable yields. On the contrary, those with a

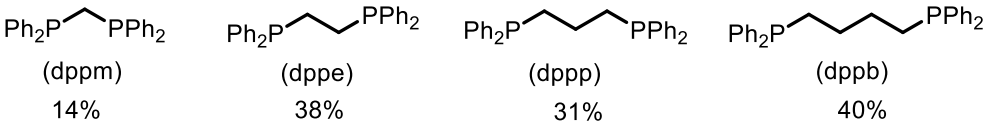
rigid backbone, such as dppBz, Xantphos and BINAP, gave very low yields. Inspired by the fact that PCy_3 gave higher yield than PPh_3, several bidentate trialkylphosphines were examined. Gratifyingly, the dCypb ligand gave the desired product in 90% yield, though the same trend was not observed for DPEphos and dppf-type ligands. It is noteworthy that reducing the NBE loading to 50 mol% still afforded product **4a** in 88% yield. In addition, the related dCpentpb ligand was also found efficient (82% yield).[70]

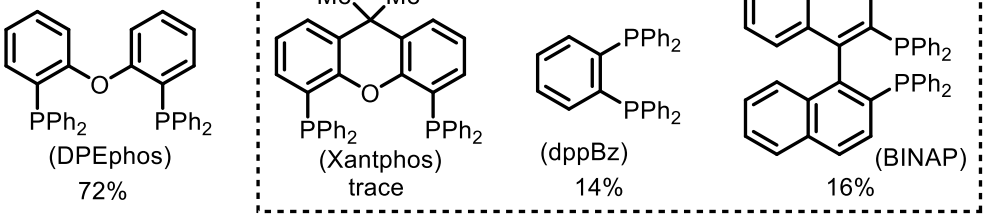
Table 4.1 Ligand Effect for *ortho*-Amination with Aryl Bromides.[a]

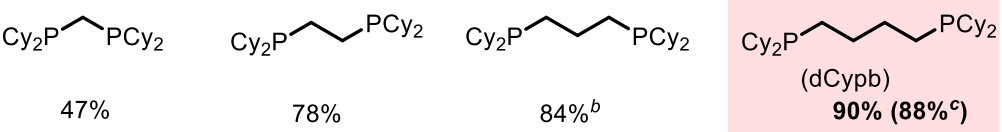


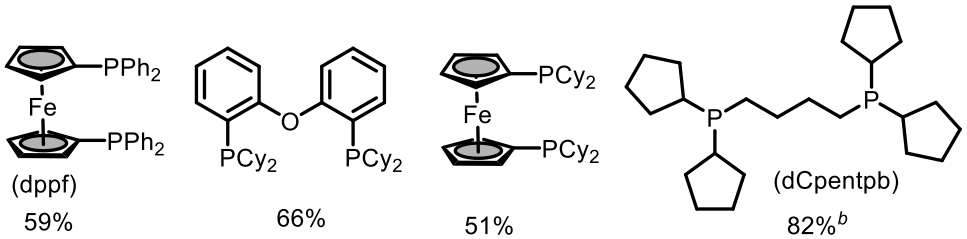








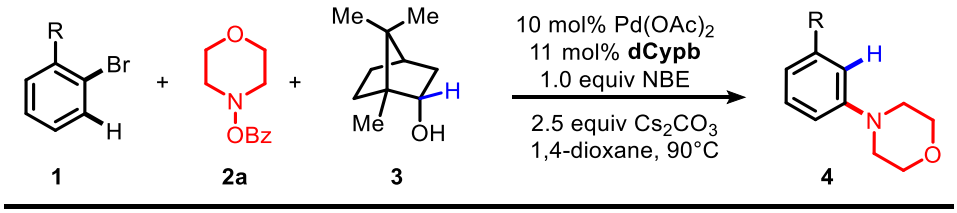




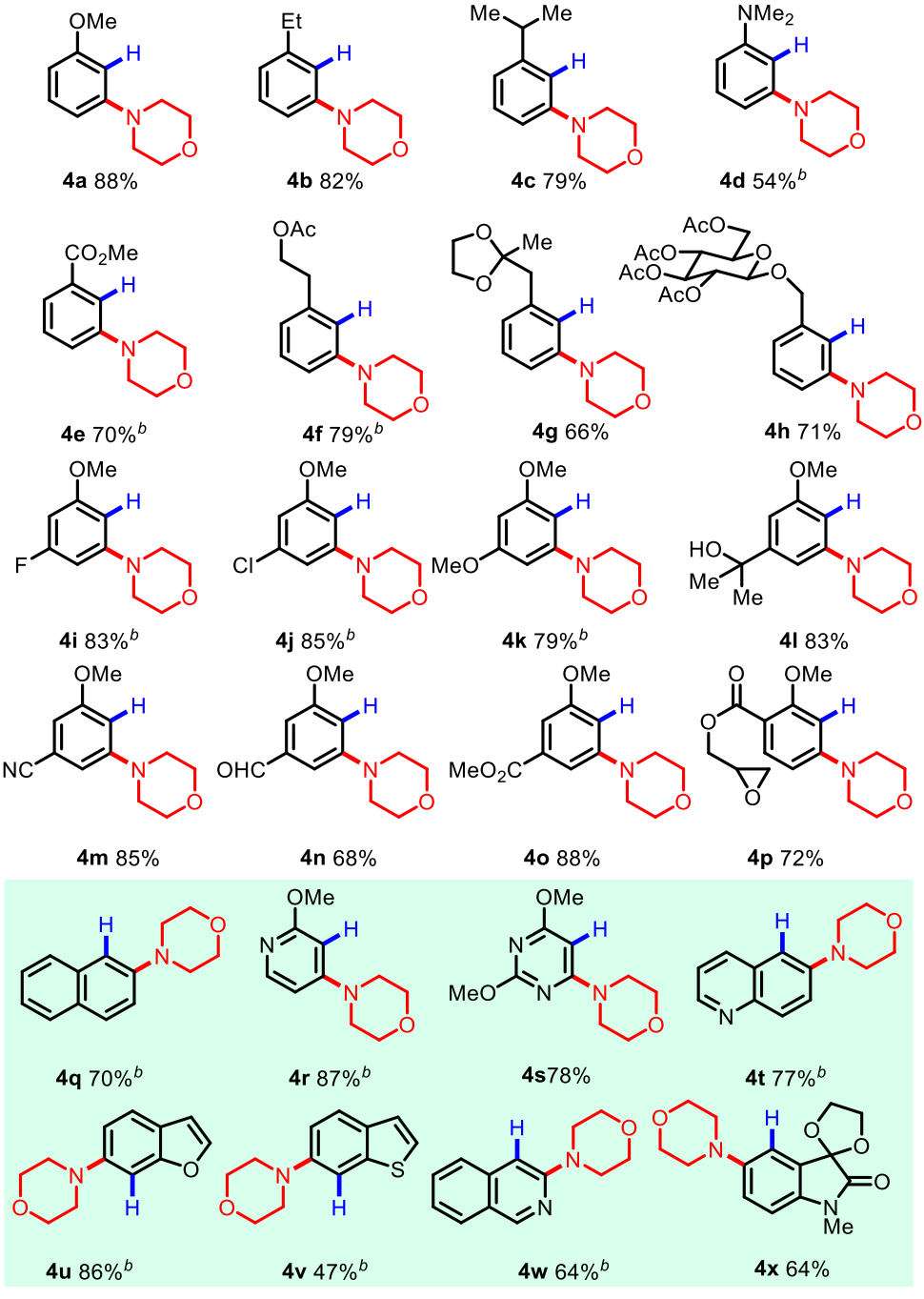
[a] Run on a 0.2 mmol scale (0.1 M) for 14h with 1.6 equiv of **2a** and 1.0 equiv of **3**; yields were determined by ^{1}H-NMR using 1,3,5-trimethoxylbenzene as the internal standard. [b] The corresponding HBF_4 salts were used. Cy, cyclohexyl. [c] The reaction was run with 50 mol% norbornene instead.

Regarding the efficacy of dCypb and DPEphos ligands in the ArBr-mediated reactions, we rationalize that the electron richness and large bite-angle should promote formation of 14e Pd(0) species, thereby lowering the activation barrier for the oxidative addition into the aryl-bromide bond. Meanwhile, the flexible backbone may allow one phosphine moiety dissociates and leaves a vacant site for NBE coordination and subsequent transformations.[71]

Table 4.2 Aryl Bromide Scope for *ortho*-Amination[a]



1 2a 3 4



4a 88% **4b** 82% **4c** 79% **4d** 54%[b]

4e 70%[b] **4f** 79%[b] **4g** 66% **4h** 71%

4i 83%[b] **4j** 85%[b] **4k** 79%[b] **4l** 83%

4m 85% **4n** 68% **4o** 88% **4p** 72%

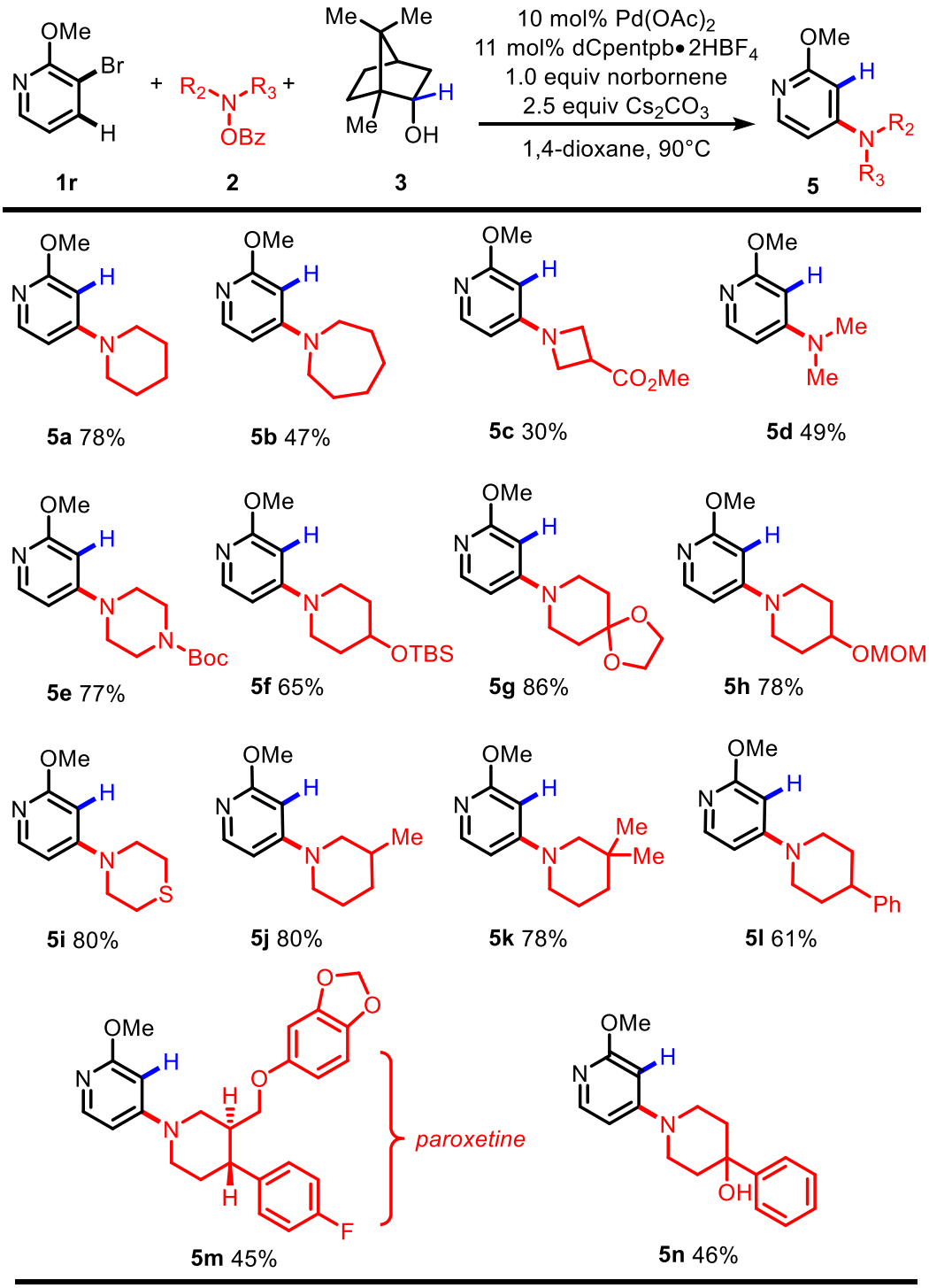
4q 70%[b] **4r** 87%[b] **4s**78% **4t** 77%[b]

4u 86%[b] **4v** 47%[b] **4w** 64%[b] **4x** 64%

[a] 1.6 Equiv of **2a** and 1.0 equiv of **3** were used. All yields are isolated yields. [b] 11 mol % dCpentapb·2HBF$_4$ was used instead of dCypb.

With the optimized reaction conditions in hands, the scope of aryl bromides was investigated next (Table 4.2). We first tested different FGs at the *ortho* position of aryl bromides. Both electron-rich (**4a**, **4d**) and -deficient (**4e)** substrates smoothly gave the desired products in good yields. Bulky substituents at the *ortho* position, such as *iso*propyl (**4c**) and ketal (**4g**), were tolerated. Ester, ketal and glycoside moieties proved compatible under the reaction conditions (**4f**-**h**). The FG tolerance was further examined with different 2-bromoanisole derived substrates (**4i**-**p**). A broad range of FGs, including methoxy ether (**4k**), fluoride (**4i**), chloride (**4j**), free tertiary benzyl alcohol (**4l**), nitrile (**4m**), aldehyde (**4n**), methyl ester (**4o**) and epoxide (**4p**), are tolerated. The scope can be further expanded to naphthalene and heteroarenes. Bromo-substituted pyridine (**4r**), pyrimidine (**4s**), quinoline (**4t**), benzo[b]furan (**4u**), benzo[b]thiophene (**4v**), isoquinoline (**4w**) and isatin (**4x**) all delivered the desired *ortho*-amination products in reasonably good yields, therefore showing promise for medicinal applications. Note that for certain substrates the analogous dCpentpb ligand gave slightly higher yields.

Table 4.3 *O*-benzoyl hydroxylamine Scope for *ortho*-Amination[a]

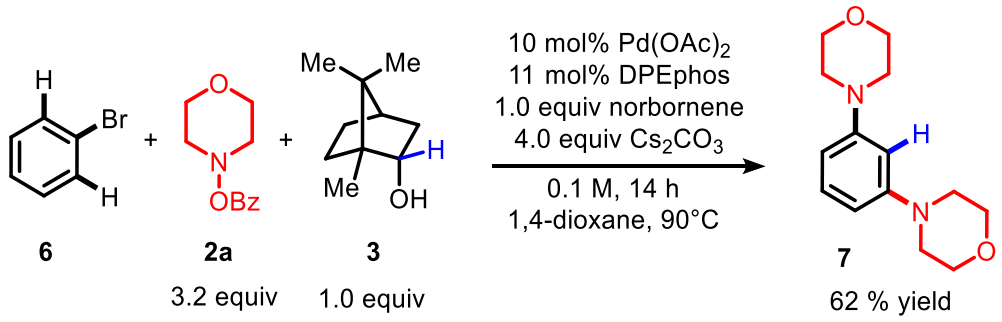


[a]1.6 Equiv of **2** and 1.0 equiv of **3** were used. All yields are isolated yields.

We then continued to explore the scope of the amine coupling partners and bromopyridine **3r** was used as the model substrate (Table 4.3). Piperidine, azepane, dimethylamine, azetidine and Boc-protected piperazine-derived amination reagents all provided the desired products in moderate to good yields (**5a**-**5e**). Additional FG tolerance was observed with alkyl sulfide (**5i**), tertiary benzylic alcohol (**5n**), TBS and MOM-protected secondary alcohols (**5f** and **5h**), carbamate (**5e**) and benzodioxole (**5m**). The protected 4-piperidone moiety (**5g**) could be converted to free aniline through ketal hydrolysis and retro-aza-1,4-addition.[42,72] The complex *O*-benzoyl hydroxylamine, derived from commercial drug paroxetine, was successfully coupled to give an interesting product (**5m**).

Besides *ortho*-substituted aryl bromides, *para* and *meta*-substituted substrates have also been evaluated. Similar to the prior observation when using aryl iodides,[38] *para*-substituted aryl bromides only afforded the 1,3-diaminated products (for a representative example, see scheme 4.2), while *meta*-substituted ones, such as the 1-bromo-3-isopropylbenzene, did not give either mono- or di-substituted products, instead forming NBE-attached side-products under the standard reaction conditions.

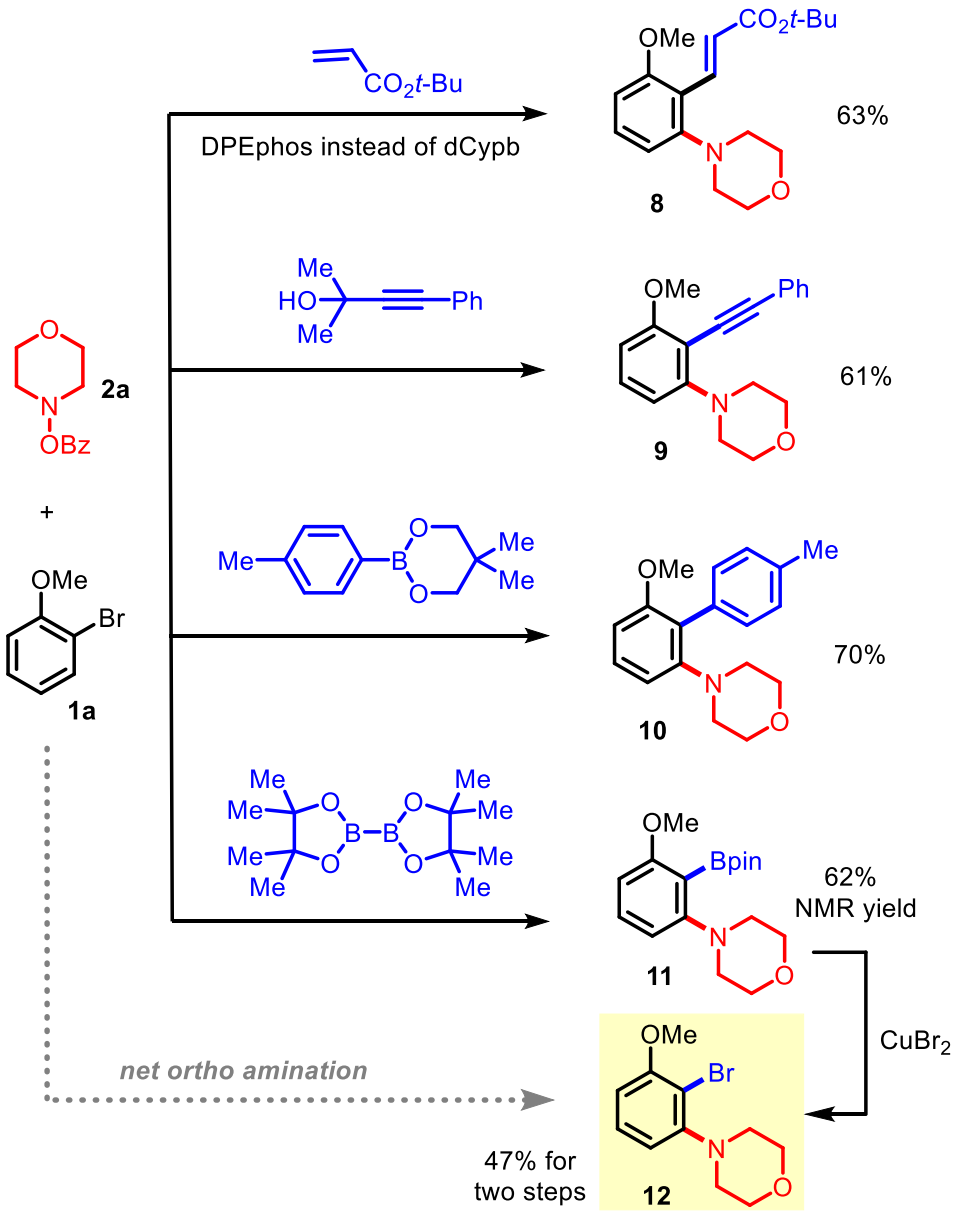
Scheme 4.2 *Ortho*-amination of aryl bromide without *ortho* substitution**.**



Besides coupling with hydride as the nucleophile, other classes of *ipso* coupling with different nucleophiles also worked smoothly using large-bite-angle ligands with flexible backbones

(Scheme 4.3). DPEphos proved to be a better ligand than dcypb for Chen's *ipso* Mizoroki-Heck *ortho* amination reaction.[39] Sonogashira quench with masked terminal acetylides[44] afforded the desired alkynylation product. Neopentyl diol-derived boronates were found to be a better coupling partner to deliver *ipso* arylation products.[41] Finally, Ritter's *ipso* borylation with $B_2(pin)_2$ also provided the desired aryl boronic ester **11**.[42] Due to its instability on column chromatography, compound **11** was further transformed to the corresponding aryl bromide (**12**),[73] offering an intriguing net-*ortho* amination of **1a**.

Scheme 4.3 Different *ipso* functionalization in the *ortho* amination of aryl bromides[a]



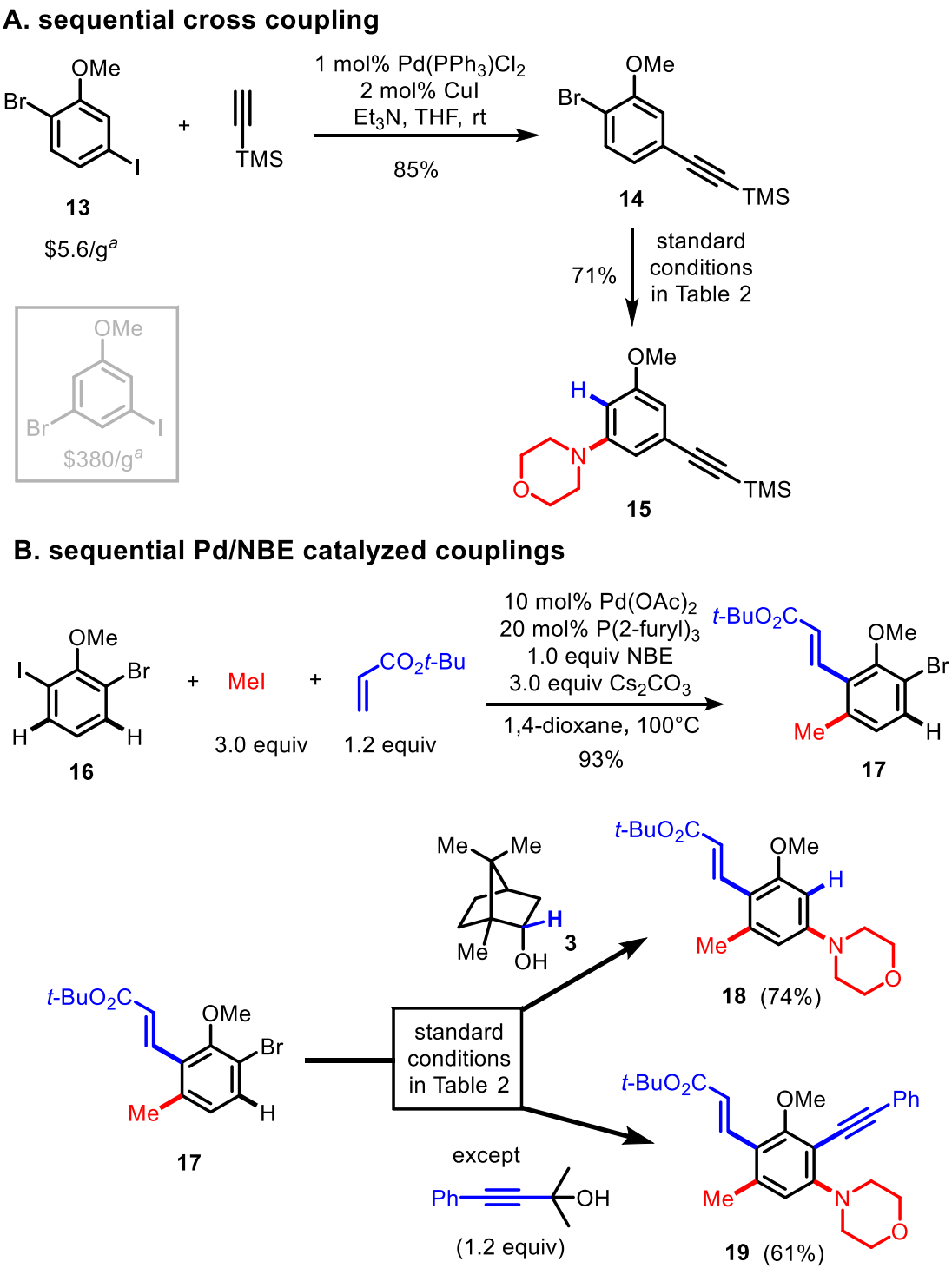
[a] The reactions were operated using the conditions described in Table 4.2 except replacing alcohol 3 with the corresponding nucleophiles.

The synthetic utility of this method was then tested. Sequential cross-coupling[74] plays an important role in synthesis of complex aromatic compounds and is often employed in pharmaceutical research.[75] Using commercially available bromo-iodoarene **13**, selective coupling

at the iodide site via Sonogashira reaction afforded alkyne **14**. Subsequently, *ortho* amination occurred smoothly to afford 3,5-disubstituted anisole **15** (Scheme 4.4A). In contrast, the alternative potential substrate for more typical sequential couplings, i.e. 3-bromo-5-iodoanisole, is significantly less available or much more expensive. Hence, the ArBr-based Pd/NBE catalysis offers additional options for preparing *meta*-substituted arenes.

Encouraged by the success of the sequential cross-coupling, we envisioned that merging the classical ArI-based Catellani reaction with the current ArBr-based method would realize a rapid access to multi-and diverse-substituted aromatic compounds from polyhaloarenes. Starting with 2-bromo-6-iodoanisole **16**, *ortho* methylation/*ipso* Heck reaction,[46] followed by *ortho* amination with either hydride or Sonogashira quench, provided tetra- or penta-substituted arenes efficiently (Scheme 4.4B). It is noteworthy that for the penta-substituted product (19) all the five substituents are different from each other, containing all three hybridized forms of carbons (*sp* to sp^3), oxygen and nitrogen groups. To the best of knowledge, this represents the first example of combining two different Pd/NBE catalysis reactions into a single arene substrate, showing promise for efficient generation of a diverse range of poly-substituted arenes.

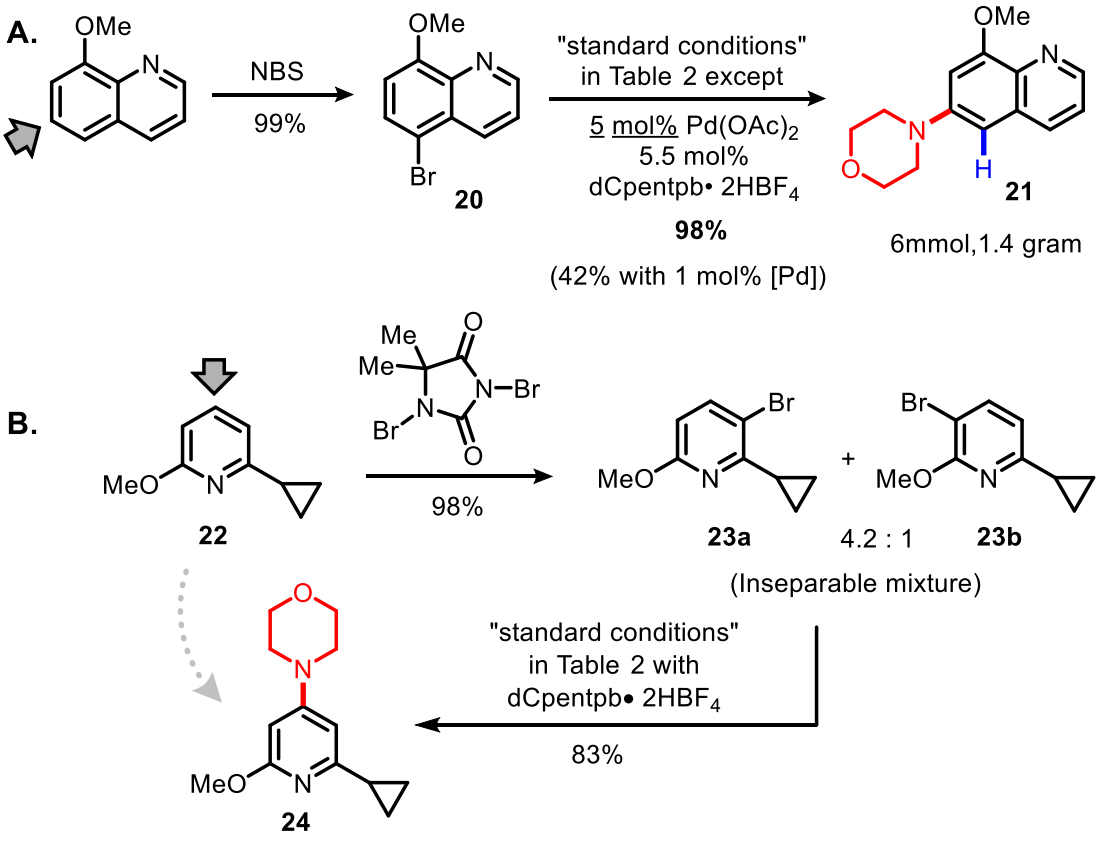
Scheme 4.4 Synthetic utility of ArBr-based *ortho* amination



[a] The prices are estimated from the catalogue of Combi-Blocks, Inc.

Finally, this method is applied in a two-step *meta*-amination of heterocycles. One merit of this protocol is the avoidance of using directing groups.[76-77] Bromination of the commercially available 8-methoxyquinoline with NBS gave exclusively C5-brominated product **20** in nearly a quantitative yield (Scheme 4.5A). Subsequent *ortho* amination afforded C6-aminated quinoline **21** in 98% yield on a gram scale with 5 mol% Pd. Further lowering the Pd loading to 1 mol% still gave the desired product with 42 turnovers. On the other hand, amination of pyridine **22** resulted in an inseparable mixture of 4.2: 1 regio-isomers; however, directly subjecting this mixture to the *ortho* amination conditions provided a *single* regioisomer of the C4-amination product **24** in 83% yield (Scheme 4.5B).

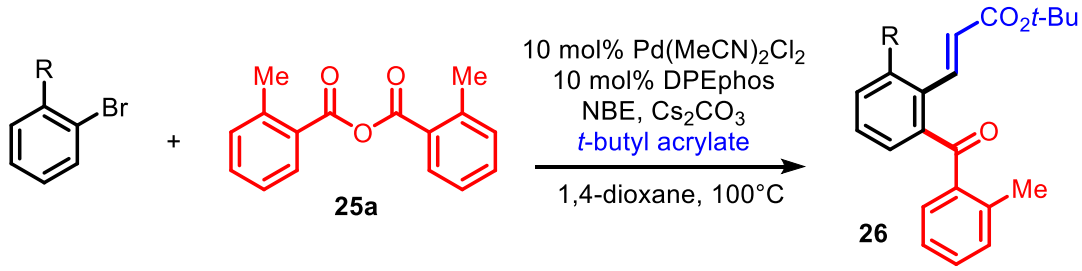
Scheme 4.5 Stepwise *meta*-amination of heterocycles

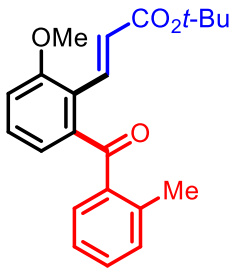


2.2 *Ortho* acylation. In 2015, we reported an initial study on *ortho* acylation/*ipso* hydrogenation using a bifunctional mixed anhydride.[53] Concurrently, the Liang and Gu groups developed *ortho* acylation/*ipso* Heck using symmetrical anhydrides or acyl chlorides as electrophiles.[52,54] In all these cases, only aryl iodides were used as substrates and electron-deficient trifurylphosphine was found to give the best results.[78-79] To enable the use of aryl bromides as substrates, *ortho* acylation/*ipso* Heck coupling was chosen as the model reactions. Unsurprisingly, applying the trifurylphosphine conditions directly to aryl bromides led to very low conversion. To our delight, analogous to the *ortho* amination reaction, large bite-angle bidentate phosphine ligands with flexible backbones also worked well for the *ortho* acylation. A survey of ligand effects revealed DPEphos to be optimal.

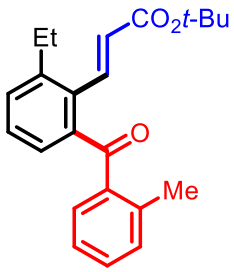
The aryl bromide scope was then explored using anhydride **25a** as the coupling partner (Table 4.4). A range of substituents and FGs, such as ketals (**26e**) and tertiary alcohols (**26g**), can be tolerated on the arene substrates. Quinoline (**26h**) and benzofuran-derived (**26i**) substrates also participated in this transformation. When 1-bromonaphthylene was used, 90% yield of the desired acylation product (**25c**) was obtained. The acid anhydride scope is also reasonably broad (Table 4.5). Sterically hindered anhydrides, such as 2-methyl and 2,6-dimethoxyl benzoic acid anhydrides (**27a**), gave significantly higher yields than the simple benzoic anhydride (**27b**). Aryl chloride (**27c**) is compatible in this reaction. Heteroarenes, such as thiophene, and ferrocenes were also tolerated (**27d** and **27f**). Besides aromatic acyl groups, the cyclopropyl-derived one was also successfully introduced with aryl bromides (**27e**), in which epimerization was not observed.

Table 4.4 Aryl bromide scope for *ortho* acylation/*ipso* Heck reaction[a]

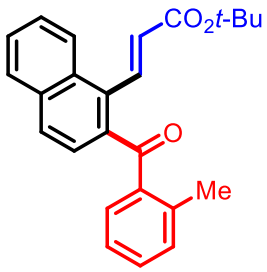




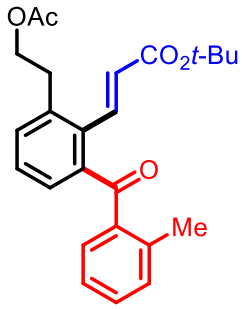
26a 68%



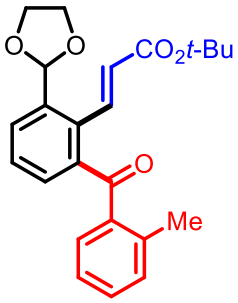
26b 86%



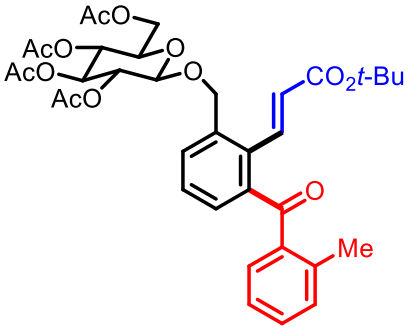
26c 90%



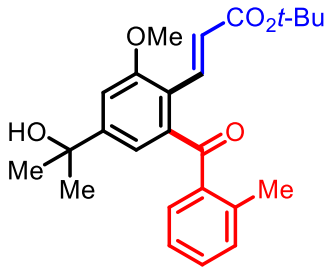
26d 80%



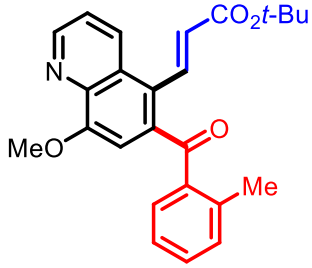
26e 69%



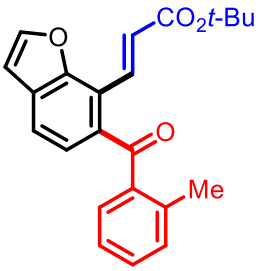
26f 72%



26g 57%



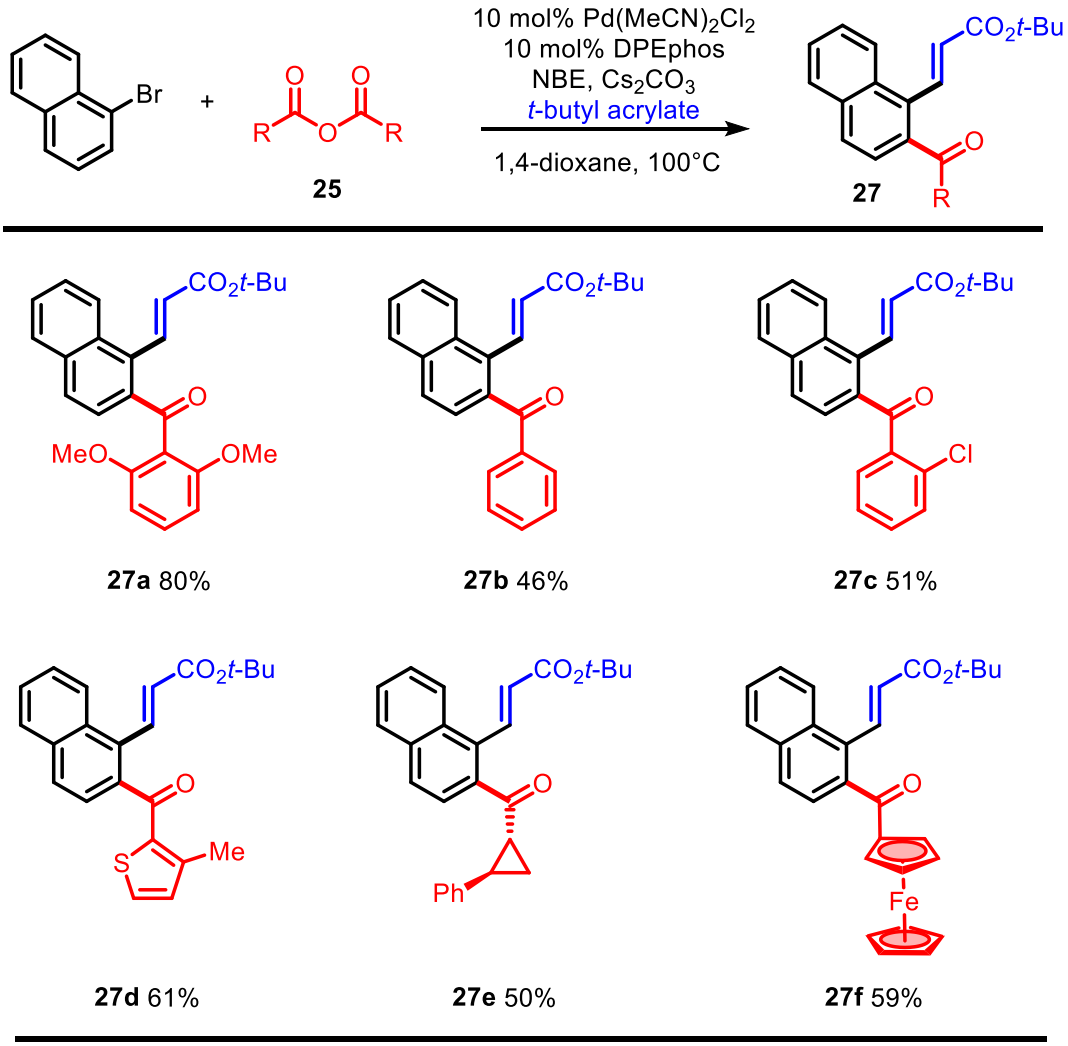
26h 56%



26i 38%

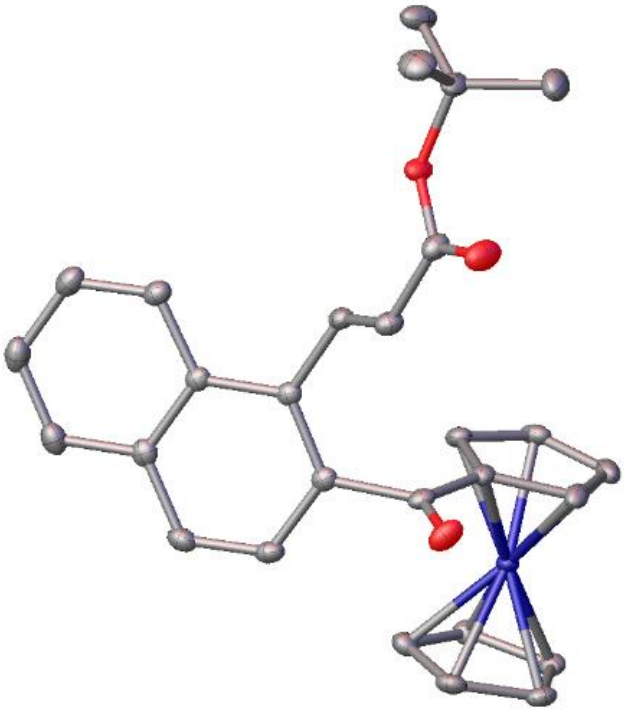
[a] Run on a 0.3 mmol scale (0.1 M) for 14 h with 1.8 equiv of **25a**, 1.0 equiv of **3**, 1.5 equiv of *t*-butyl acrylate, 2.0 equiv of NBE and 3.0 equiv of Cs_2CO_3; all yields are isolated yields.

Table 4.5 Carboxylic acid anhydride scope[a]



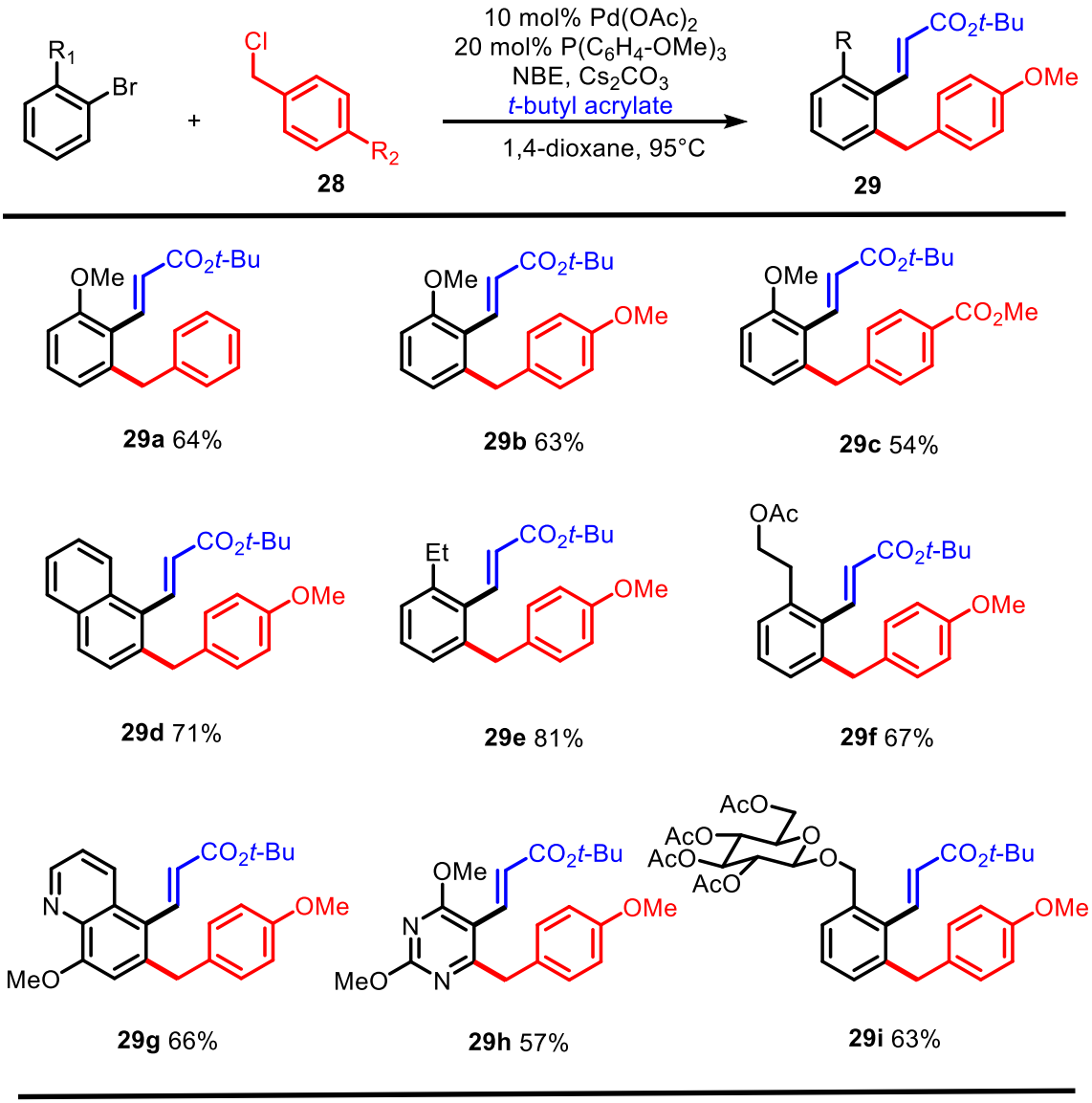
[a] Run on a 0.3 mmol scale (0.1 M) for 14 h with 1.8 equiv of **25**; 1.0 equiv of **3**; 1.5 equiv of *t*-butyl acrylate, 2.0 equiv of NBE and 3.0 equiv of Cs_2CO_3; all yields are isolated yields.

Figure 4.5 X-ray Crystal structure of compound **27f**.



2.3 *Ortho* alkylation. *Ortho* alkylation with alkyl halides has been the first Catellani reaction reported.[8] However, the use of aryl bromides for *ortho* alkylation remained to be developed. The feasibility of aryl bromide-mediated *ortho* alkylation was first explored with benzyl electrophiles, in which the corresponding reactions with aryl iodides were reported by Lautens and Liang.[80-81] When benzyl bromides were employed as the electrophile, no desired benzylation product was observed, which is likely due to the strong oxidative ability of benzyl bromides compared to aryl bromides. However, combining benzyl chlorides as the electrophile and tris(4-methoxyphenyl)phosphine as the ligand,[82] the desired benzylation products **29a** was isolated in 64% yield with 2-bromoanisole as the substrate (Table 4.6). In addition, both electron-rich and -deficient benzyl chlorides gave the desired products in comparable yields (**29b** and **29c**). Besides aryl bromides, bromo-heteroarenes, such as quinoline **29g** and pyrimidine **29h**, are also competent substrates.

Table 4.6 *Ortho* alkylation/*ipso* Heck reaction of aryl bromides with benzyl chlorides[a]

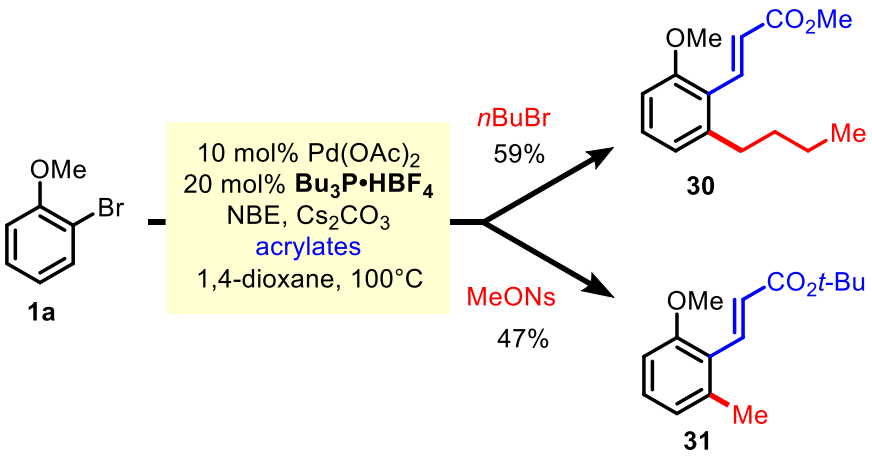


[a] Run on a 0.3 mmol scale (0.1 M) for 14 h with 2.0 equiv of **28**; 1.0 equiv of **3**; 1.5 equiv of *t*-butyl acrylate, 2.0 equiv of NBE and 3.0 equiv of Cs_2CO_3; All yields are isolated yields.

With preliminary success of the reactions using activated benzyl halides, *ortho* alkylation with unactivated alkyl halides,[83-87] which has been utilized in several elegant total syntheses,[88-91] was investigated next using 2-bromoanisole **1a** as the model substrate. When alkyl iodides (e.g. BuI)

were employed as the alkylating reagent, regardless the choice of phosphine ligands, the reaction proceeded with a low conversion without forming any desired product. It is likely that alkyl iodides may react with Pd(0) faster than 2-bromoanisole. Hence, a weaker alkylating reagent, such as alkyl bromides, was tested. To our delight, when BuBr was used as the electrophile, tributylphosphine was found to give optimal results at this stage (Scheme 4.6). In addition, *ortho* methylation was realized using methyl 4-nitrobenzenesulfonate as the electrophile, given that methyl bromide, a toxic gas, is not convenient to handle. Considering the importance of methylation of arenes[92-93] and heteroarenes[94] in drug design,[95] this method is expected to be useful for medicinal chemistry. While the efficiency of these *ortho* alkylation reactions remains to be further improved, they nevertheless show the feasibility of employing widely available aryl bromides as suitable substrates.

Scheme 4.6 *Ortho* alkylation of aryl bromides with unactivated alkyl electrophiles.



4.4. Conclusion

In summary, we describe the efforts of developing general aryl-bromide-mediated Pd/norbornene cooperative catalysis, in which *ortho*-amination, acylation and alkylation have been realized using

O-benzoyl hydroxylamines, carboxylic acid anhydrides and alkyl halides respectively as electrophiles. For *ortho* amination and acylation of aryl bromides, electron-rich bidentate phosphines with large bite angles and flexible backbones generally worked efficiently. For ortho benzylation and alkylation, mono-dentate tris(4-methoxyphenyl)phosphine and tributylphosphine were found to be superior than bidentate ligands. The conditions (at least for *ortho* amination) are also general for introducing various substituents, such as vinyl, alkynyl, boryl groups or hydrogen, at *ipso* positions. The high chemoselectivity and tolerance of various heterocycles observed in this study should make these methods attractive for medicinal chemistry study. Allowing aryl bromides to be suitable for Pd/NBE catalysis also permits development of sequential functionalization strategies for constructing more complex and diverse aromatic compounds, therefore offering new strategic insights for bond disconnection approaches. Further improvement of the catalyst efficiency and detailed mechanistic study for expanding the substrate scope to more challenging aryl chlorides are ongoing.

4.5. Experimental Procedure and Characterization of New Compound

4.5.1 General Information

Unless noted otherwise, all solvents were dried by filtration through a Pure-Solv MD-5 Solvent Purification System (Innovative Technology). 1,4-dioxane was distilled freshly over sodium. Reaction temperatures were reported as the temperatures of the bather surrounding the flasks or vials. Sensitive reagents and solvents were transferred under nitrogen into a nitrogen-filled glovebox with standard techniques. Cesium carbonate was purchased from Strem, stored in the glovebox and used as recieved. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (silica gel 60, F254, EMD chemical). Vials (15 x 45 mm 1 dram (4 mL) with PTFE lined cap attached) were purchased from Qorpak and flame-dried prior to use. Mass spectra were recorded on an Agilent 6530 LC Q-TOF mass spectrometer using electrospray ionization with fragmentation voltage set at 115 V and processed with an Agilent MassHunter Operating System. X-ray diffraction data were collected at 100(2) K on a Bruker-Nonius Kappa CCD or Agilent SuperNova AtlasS2 CCD. Infrared spectra were recorded on a Nicolet 380 FTIR using neat thin film technique.

Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded with a Bruker Model DMX 500 or 400. Chemical shifts are reported in parts per million (ppm, δ), downfield from tetramethylsilane (TMS, δ=0.00ppm) and are referenced to residual solvent ($CDCl_3$, δ=7.26 ppm (^{1}H) and 77.00 ppm (^{13}C)). Coupling constants were reported in Hertz (Hz). Data for ^{1}H NMR spectra were reported as follows: chemical shift (ppm, referenced to protium, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet, coupling constant (Hz), and integration). All

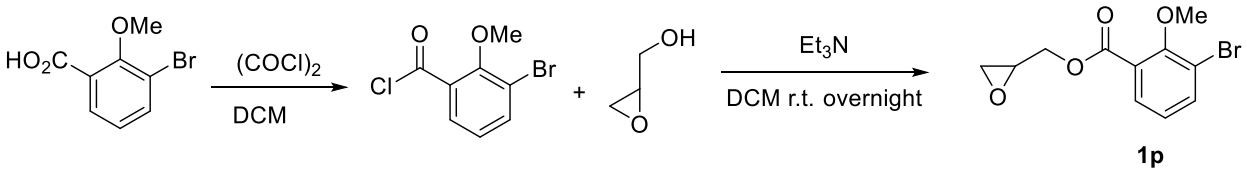
other chemicals were obtained from Aldrich Chemical Company/Combi-blocks/ Ark Pharm, Inc. and were used as received.

4.5.2 Supplemental Experimental Procedure and Characterization Data

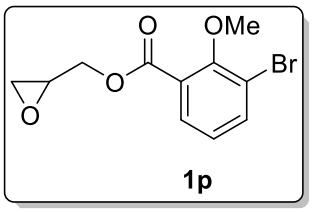
Preparation of aryl-bromide substrates:

Aryl iodides **1a**, **1b**, **1c**, **1d**, **1e**, **1i**, **1j**, **1k**, **1m**, **1n**, **1o**, **1q**, **1r, 1s, 1t, 1u, 1v** and **1w** were all commercially available from Combi-blocks or Ark Pharm, Inc. and were used without further purification. Aryl bromides **1f**,[96] **1g**,[97] **1h,**[98] **1l**,[99] **1x,**[100] **14**[101] and **16**[102] were known compounds and were synthesized according to reported procedures.

Scheme 4.7 Synthesis of aryl bromide **1p**:

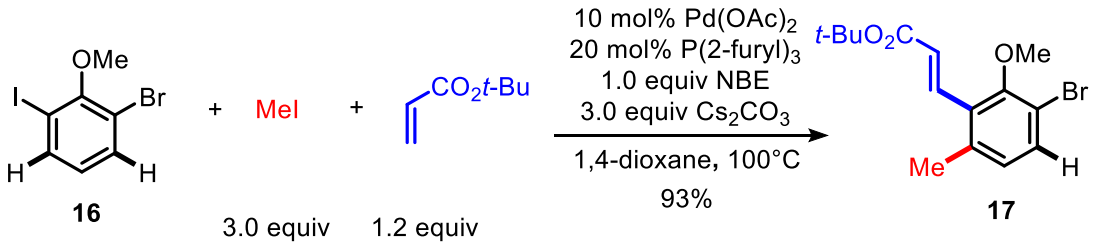


To a solution of the 3-bromo-2-methoxylbenzoic acid (2.50 g, 10 mmol, 1.0 equiv) in dichloromethane (40 mL) was added 3 drops of dimethylformamide. Oxalyl chloride (1.05 mL, 11 mmol, 1.1 equiv) was then added dropwise under N_2 atmosphere. After stirring at room temperature for 3 hours, the solvent was removed under vacuum. The residue was dissolved in the 30 mL dry dichloromethane. A solution of triethylamine (3.0 mL, 21 mmol, 2.1 equiv) and (±)-glycidol (1.33 g, 18.0 mmol, 1.8 equiv) in 15 ml dichloromethane was added in one portion. The mixture was allowed to stir at room temperature overnight. The reaction mixture was quenched with water, the organic phase was washed with brine, and dried over MgSO4. After the filtration, the solution was concentrated under vacuum, and purified by chromatography on silica gel using (20:1 hexanes/EtOAc) the eluent to afford **1p** (2.11 g, 74%) as a colorless oil.



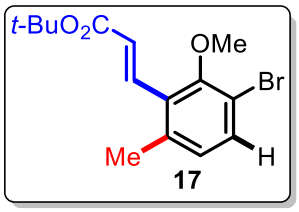
1p: Colorless oil; Rf=0.26 (hexane/ethyl acetate=10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.73 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.05 (t, *J* = 7.9 Hz, 1H), 4.66 (dd, *J* = 12.3, 3.0 Hz, 1H), 4.17 (dd, *J* = 12.3, 6.3 Hz, 1H), 3.94 (s, 3H), 3.38 – 3.28 (m, 2H), 2.89 (dd, *J* = 4.9, 4.1 Hz, 1H), 2.74 (dd, *J* = 4.9, 2.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.79, 156.96, 137.54, 130.77, 126.26, 124.95, 119.16, 65.74, 62.12, 49.27, 44.64. **IR** (KBr): v 3067, 2941, 2383, 2314, 1741, 1589, 1464, 1416, 1344, 1284 cm^{-1}; **HRMS** (ESI): Calcd for $C_{11}H_{12}BrO_4$ ($M+H^+$): 285.9913; found: 285.9911.

Scheme 4.8 Synthesis of aryl bromide **17**:



An oven-dried 40 mL vial was charged with 2-bromo-6-iodoanisole (1.21 g, 4.0 mmol 1.0 equiv), iodomethane (0.78 mL, 12.0 mmol, 3.0 equiv), cesium carbonate (3.90 g, 12.0 mmol, 3.0 equiv), *tert*-butyl acrylate (670 mg, 4.8 mmol, 1.2 equiv), norbornene (374 mg, 4.0 mmol, 1.0 equiv), palladium acetate (89.5 mg, 0.4 mmol, 0.1 equiv), tri(2-furyl)phosphine (186 mg, 0.80 mmol, 0.20 equiv) and a X-shape stir bar, which was sealed outside and transferred in a nitrogen-filled glovebox. 1,4-dioxane (33 ml) was added into the vial. The vial was sealed with PTFE lined cap in the glovebox and stirred at RT for 10 minutes. The vial was then transferred out of glovebox and stirred on a pie-block preheated to 90 ℃ for 14 hours. After that, the mixture was filtered through a thin pad of celite. The filter cake was washed with diethyl ether, and the combined filtrate was concentrated. The residue was directly purified by flash column

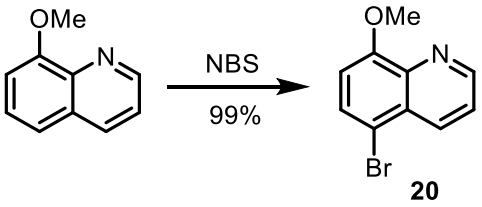
chromatography (from hexane : ethyl acetate = 50 : 1 to hexane : ethyl acetate = 30 : 1) on silica gel to give the desired product **17** 1.182 g (93% yield) as a white solid.



17: A white solid mp=95-96°C Rf=0.42 (hexane/ethyl acetate=20:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, J = 16.3 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.51 (dd, J = 16.3, 0.6 Hz, 1H), 3.76 (s, 3H), 2.36 (s, 3H), 1.54 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.53, 156.00, 138.61, 137.11, 133.23, 129.43, 127.65, 126.01, 115.22, 80.63, 60.40, 28.20, 20.67; **IR** (KBr):*v* 2976, 1708, 1661, 1458, 1367, 1301, 1271, 1254, 1154 cm^{-1}; **HRMS** (ESI): Calcd for $C_{15}H_{20}O_3Br(M+H^+)$: 327.0590; found: 327.0583.

5-bromo-8-methylquinoline is known compound[103], we synthesize it through direct bromonation pathway.

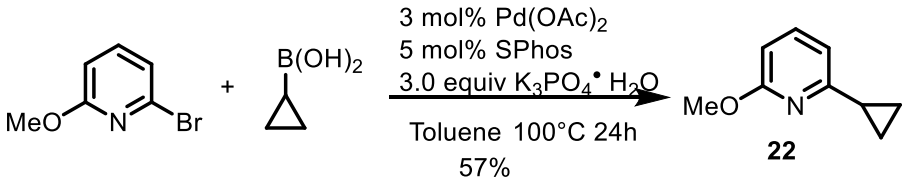
Scheme 4.9 Synthesis of aryl bromide **20**:



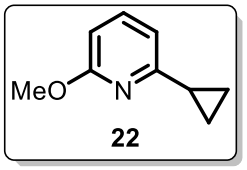
An 20 mL vial was charged with 8-methylquinoline (3.21 g, 20 mmol 1.0 equiv), n-bromosuccinimide (3.65 g, 20.0 mmol, 1.0 equiv), 15 mL chloroform and a X-shape stir bar. The vial was sealed in the air and heated to 60 ℃ for 24 hours. The solid precipitated out upon cooling, the solvent was directly removed under vacuum. The residue was dissolved in the 100 mL ethyl acetate / 30 mL 1.0 M NaOH aqueous solution. The organic phase was washed twice with 1.0 M

NaOH aqueous solution (20 mL X 2), 50 mL pure water and 50 mL brine. The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum. The residue (4.75 g pink solid, 99% yield) is pure enough for direct use in the next step. No further purification was required.

Scheme 4.10 Synthesis of pyridine **22**:



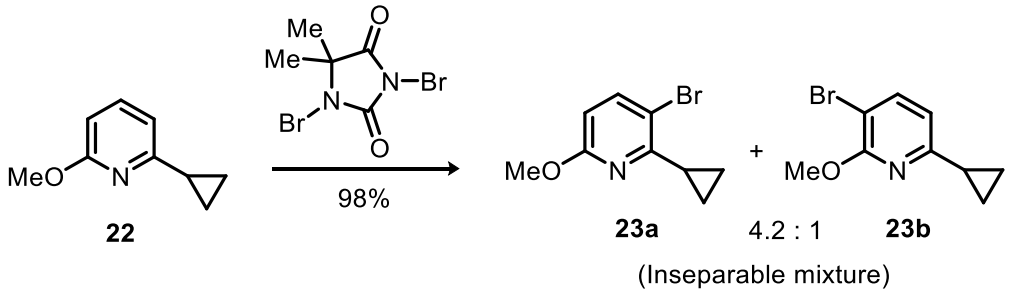
An oven-dried 40 mL vial was charged with 2-bromo-6-methoxylpyridine (1.50 g, 8.0 mmol 1.0 equiv), cyclopropylboronic acid (1.38 g, 16.0 mmol, 2.0 equiv), potassium phosphate tribasic monohydrate (5.52 g, 12.0 mmol, 3.0 equiv), palladium acetate (54.0 mg, 0.24 mmol, 0.03 equiv), SPhos (164.2 mg, 0.40 mmol, 0.05 equiv) and a X-shape stir bar. Dry Toluene (30 ml) was added in one portion. The vial was purged with nitrogen gas flow and sealed. The vial was stirred on a pie-block preheated to 100℃ for 24 hours. After that, the mixture was filtered through a thin pad of celite. The filter cake was washed with diethyl ether, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography (from hexane : diethyl ether = 100 : 1 to hexane : diethyl ether = 40 : 1) on silica gel to give the desired product **22** 647mg (93% yield) as a colorless oil.



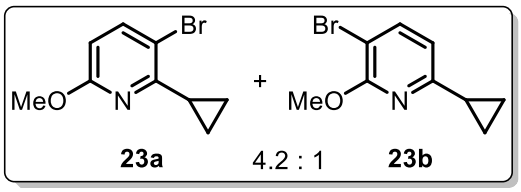
22: colorless oil. R_f = 0.32 (hexane/ethyl acetate = 50:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 –

7.35 (m, 1H), 6.74 (d, J = 7.4 Hz, 1H), 6.46 (d, J = 8.2 Hz, 1H), 3.86 (s, 3H), 1.94 (tt, J = 7.9, 4.7 Hz, 1H), 1.09 – 1.01 (m, 2H), 0.95 – 0.84 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.78, 160.58, 138.28, 113.88, 106.60, 52.87, 16.76, 9.28. **IR** (KBr, cm^{-1}): *v* 3008, 2948, 1596, 1579, 1467, 1440, 1382, 1287, 1023; **HRMS** (ESI): Calcd for $C_9H_{12}NO$ ($M+H^+$): 150.0913, found: 150.0912.

Scheme 4.11 Synthesis of bromopyridine **23**:



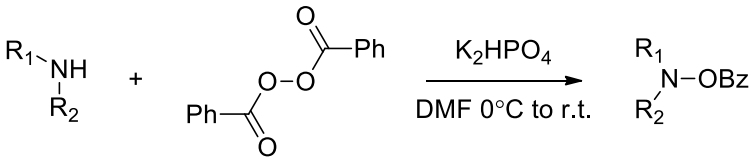
An 4 mL vial was charged with **22** (154 mg, 1.04 mmol 1.0 equiv), dibromantin (328 mg, 1.15 mmol, 1.1 equiv), 3 mL chloroform and a stir bar. The vial was sealed in the air and heated to 60 ℃ for 24 hours. The solvent was directly removed under vacuum. The residue was dissolved in the 15 mL ethyl acetate / 4 mL 1.0 M NaOH aqueous solution. The organic phase was washed twice with 1.0 M NaOH aqueous solution (3 mL X 2), 5 mL pure water and 5 mL brine. The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum. The desired product was obtained as a yellow oil (234 mg, 98% yield), ^{1}H-NMR show a 4.2:1 mixture. to isolate two regio-isomers by column chromatography all failed at this stage.



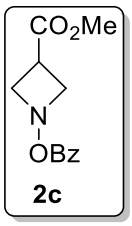
23a/23b: colorless oil. R_f = 0.34 (hexane/ethyl acetate = 50:1). Major isomer **23a**: **^{1}H NMR** (400

MHz, $CDCl_3$) δ 7.58 (d, J = 8.5 Hz, 1H), 6.37 (d, J = 8.5,Hz, 1H), 3.82 (s, 3H), 2.50 – 2.38 (m, 1H), 1.09 (ddd, J = 4.7, 2.6, 1.1 Hz, 2H), 1.00 – 0.89 (m, 2H); The minor isomer is badly overlapped with some major peaks. **HRMS** (ESI): Calcd for $C_9H_{11}NOBr$ ($M+H^+$): 228.0019, found: 228.0017.

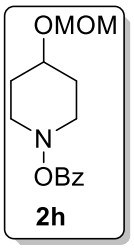
Scheme 4.12 General preparation of *O*-Benzoyl Hydroxylamines:



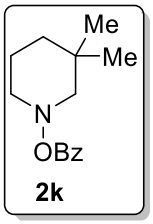
O-benzoyl hydroxylamines were synthesized using a modified procedure[104]: To a 50 mL flask equipped with a stir bar and a rubber septum was charged with benzoyl peroxide (3.46 g, 70% purity 10 mmol, 1 equiv), dipotassium hydrogen phosphate (3.50 g, 20 mmol, 2 equiv), and *N*,*N*-dimethylformamide (25 mL). A solution of corresponding amine (1.5 equiv) was added dropwise at 0 degree. Upon completion, the reaction was further stirred at room temperature overnight. After monitored by TLC to see the full conversion of benzoyl peroxide, water (100 mL) was added, and the products were extracted with ether (4 × 30 mL). The combined organic extract was washed with brine (60 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel to give the *O*-benzoyl hydroxylamine product.



2n: White solid, 22% isolation yield. Melting point: 76 – 78 °C. R_f = 0.14 (hexane/ethyl acetate = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.2 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.7 Hz, 2H), 4.39 – 4.11 (m, 2H), 4.08 – 3.89 (m, 2H), 3.72 (s, 3H), 3.45 – 3.15 (m, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.63, 164.63, 133.14, 129.34, 128.48, 128.35, 61.64, 52.30, 31.10. **IR** (KBr, cm^{-1}): *ν* 2996, 2953, 1739, 1451, 1437, 1369, 1266, 1205, 1086, 1064*;* **HRMS** (ESI): Calcd for $C_{12}H_{14}NO_4$ ($M+H^+$): 236.0917, found: 236.0901.

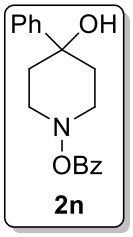


2h: colorless oil, 67% isolation yield. R_f = 0.19 (hexane/ethyl acetate = 15:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.8 Hz, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.7 Hz, 2H), 4.66 (s, 2H), 3.88 – 3.46 (br, 2H), 3.35 (s, 3H), 3.24 (br, 2H), 2.84 (br, 1H), 2.18 – 1.74 (br, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.54, 132.85, 129.24, 128.22, 94.62, 71.89, 68.76, 55.17, 54.16, 52.24, 30.17, 29.38. **IR** (KBr, cm^{-1}): *ν* 2933, 2888, 2850, 1740, 1706, 1652, 1451, 1251, 1154, 1042; **HRMS** (ESI): Calcd for $C_{14}H_{20}NO_4$ ($M+H^+$): 266.1387,, found: 266.1380.



2k: colorless oil, 63% isolation yield. R_f = 0.39 (hexane/ethyl acetate = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 – 7.94 (m, 2H), 7.58 – 7.50 (m, 1H), 7.46 – 7.39 (m, 2H), 3.54 (s, 1H), 3.21 (s, 1H),

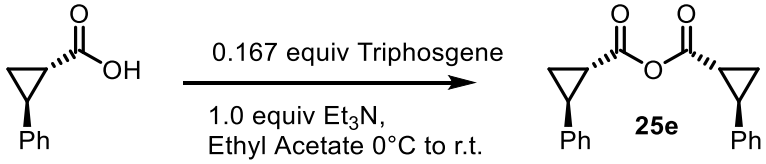
2.55 (d, J = 67.5 Hz, 2H), 1.97 (s, 1H), 1.72 (s, 1H), 1.47 – 1.26 (m, 1H), 1.26 – 0.84 (m, 7H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.65, 132.74, 129.74, 129.25, 128.26, 68.28, 57.32, 36.57, 33.68, 29.98, 24.69, 22.00. **IR** (KBr, cm^{-1}): *v* 2951, 1743, 1475, 1450, 1365, 1246, 1178; **HRMS** (ESI): Calcd for $C_{14}H_{20}NO_2$ ($M+H^+$): 234.1489, found: 234.1475.



2n

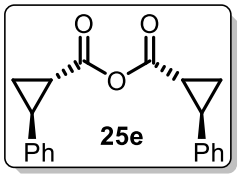
2n: White solid. 83% isolation yield. Mp=135-136 °C. R_f = 0.10 (hexane/ethyl acetate = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 – 7.98 (m, 2H), 7.63 – 7.57 (m, 1H), 7.55 (d, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 7.3 Hz, 1H), 3.80 – 3.26 (m, 4H), 2.50 (s, 2H), 2.07 – 1.71 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.93, 147.21, 133.08, 129.46, 128.55, 128.44, 127.38, 124.44, 70.30, 52.59, 37.91. **IR** (KBr, cm^{-1}): *v* 3448, 3060, 2958, 2863, 1734, 1451, 1260, 1089, 1067, 1045. **HRMS** (ESI): Calcd for $C_{18}H_{19}NNaO_3$+ ($M+Na^+$): 320.1257, found: 320.1262.

Scheme 4.13 Preparation of carboxylic acid anhydride:



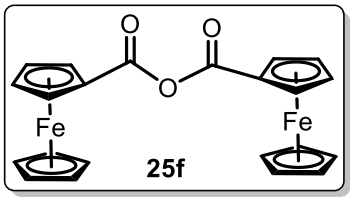
A solution of *trans*-2-phenylcyclopropane-1-carboxylic acid (3.40 g, 21 mmol) and dry Et_3N (2.10 g, 21 mmol) in 200 mL of ethyl acetate was stirred in an ice bath. Triphosgene (1.05g, 3.5mmol) was added in one portion, upon which the formation of an immediate precipitate of triethylamine

hydrochloride was observed. The reaction was allowed to mix in the ice bath for 5 min, followed by additional 30 min of stirring at room temperature. The solid (Et_3N-HCl) was filtered and washed with a small portion of (20 ml X 3) of ethyl acetate. The filtrate was evaporated to dryness, and the resulting residue was purified by flash column chromatograph (Hexane/EtOAc = 20 : 1) to afford the product as a white solid (2.81g 87% yield).



25e

25e: A white solid mp=85-87℃ Rf=0.42 (hexane/ethyl acetate=10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 4H), 7.25 – 7.19 (m, 2H), 7.15 – 7.05 (m, 4H), 2.69 (ddd, *J* = 9.1, 6.8, 4.0 Hz, 2H), 1.96 (ddd, *J* = 8.3, 5.2, 4.0 Hz, 2H), 1.76 (dt, *J* = 9.7, 5.0 Hz, 2H), 1.50 (ddd, *J* = 8.3, 6.8, 4.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.94, 138.81, 128.55, 126.92, 126.27, 28.25, 24.73, 18.12. **IR** (KBr):*v* 3031,1801,1734,1604,13971322,1220,1065 cm^{-1}; **HRMS** (ESI): Calcd for $C_{20}H_{18}O_3Na$ ($M+Na^+$):329.1148; found: 329.1148.



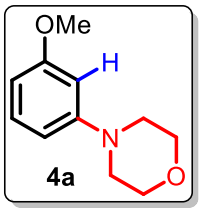
25f

25f: synthesized following the same protocol as **25e**, 67% isolation yield. A red solid, mp=145-146℃ Rf=0.25 (hexane/ethyl acetate=10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.93 – 4.87 (m, 2H), 4.59 – 4.53 (m, 2H), 4.37 (s, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.61, 72.66, 70.77, 70.16, 69.34. **IR** (KBr):*v* 1767, 1712, 1444, 1373, 1243, 1067, 1044, 1007 cm^{-1}; **HRMS** (ESI): Calcd

for $C_{22}H_{18}Fe_2O_3Na$ ($M+Na^+$): 464.9847; found: 464.9829.

General procedure of Pd and nobornene catalyzed C–H amination of aryl bromides:

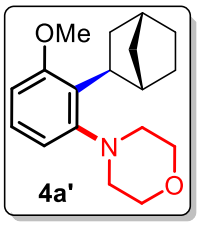
Unless otherwise noted, An oven-dried 4 mL vial was charged with aryl bromide (0.3 mmol, 1.0 equiv), *O*-benzoyl hydroxylamine (0.3 mmol, 1.6 equiv), (-)-borneol (46.2 mg, 0.3 mmol, 1.0 equiv), norbornene (28.2 mg, 0.3 mmol, 1.0 equiv), palladium acetate (6.7 mg, 0.03 mmol, 0.1 equiv) and a magnetic stir bar. The vial was sealed in the air and transferred in a nitrogen-filled glovebox. 1,4-Bis(dicyclo-hexylphosphino)butane (14.9 mg, 0.033 mmol, 0.11 equiv) and cesium carbonate (245 mg, 0.75 mmol, 2.5 equiv) were added to the vial in the glove box. 1,4-dioxane (3 ml) was added, and the vial was then sealed with PTFE lined cap in the glovebox. The resulting mixture was stirred at room temperature for 10 minutes until the all the palladium acetate was fully dissolved. The vial was subsequently transferred out of glovebox and stirred on a pie-block preheated to 90°C for 14 hours. After completion of the reaction, the mixture was filtered through a thin pad of celite. The filter cake was washed with ethyl acetate, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography on silica gel to yield the desired product. (Note: vigorous stirring is critical to achieve reproducible yields)



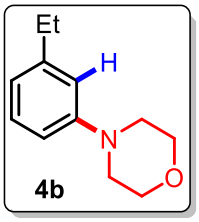
4a

4a: 88% yield. A colorless oil. Rf=0.27 (hexane/ethyl acetate=5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21-.7.15 (m, 1H), 6.55 – 6.49 (m, 1H), 6.47 – 6.40 (m, 2H), 3.86 – 3.81 (m, 4H), 3.78 (s, 3H), 3.17 – 3.10 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ **^{13}C NMR** (101 MHz, CDCl3) δ 160.56,

152.61, 129.78, 108.39, 104.65, 102.14, 66.81, 55.11, 49.22. Both the proton and carbon NMR match the literature reported data.[105]

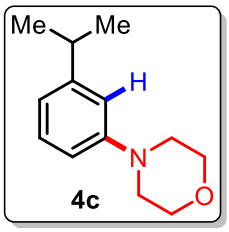


4a': A white solid, mp = 52 to 54 °C. Rf=0.29 (hexane/ethyl acetate=30:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 (t, J = 8.1 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 7.6 Hz, 1H), 3.79 (m, 7H), 3.49 (t, J = 8.4 Hz, 1H), 3.18 – 2.75 (m, 4H), 2.37 (d, J = 4.3 Hz, 1H), 2.29 (d, J = 9.2 Hz, 1H), 2.15 (d, J = 2.2 Hz, 1H), 2.04 – 1.92 (m, 1H), 1.75 – 1.45 (m, 4H), 1.43 – 1.27 (m, 2H), 1.18 (dt, J = 9.2, 1.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.13, 153.16, 129.93, 126.63, 113.05, 107.96, 77.32, 77.00, 76.68, 67.54, 54.85, 42.74, 39.13, 38.21, 37.80, 37.24, 33.36, 28.23. **IR** (KBr): *v* 2974, 2851, 1706, 1497, 132, 1291, 1151, 1117 cm^{-1}; **HRMS** (ESI): Calcd for $C_{18}H_{26}O_2N$ ($M+H^+$):288.1985; found: 288.1996.

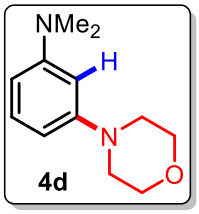


4b: 82% yield. A colorless oil. Rf=0.32 (hexane/ethyl acetate=10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (t, J = 7.8 Hz, 1H), 6.82 – 6.70 (m, 3H), 3.97 – 3.75 (m, 3H), 3.28 – 3.06 (m, 3H), 2.64 (q, J = 7.6 Hz, 2H), 1.25 (t, J = 7.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.34, 145.28, 129.05, 119.74, 115.46, 113.03, 66.94, 49.49, 29.18, 15.62. **IR** (KBr): *v* 2929, 2854, 2821, 1727, 1682,

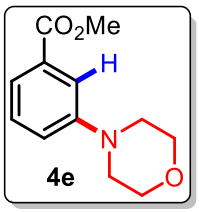
1602, 1582, 1447, 1242, 1123 cm^{-1}; **HRMS** (ESI): Calcd for $C_{12}H_{18}ON$ ($M+H^+$):192.1383; found: 192.1384.



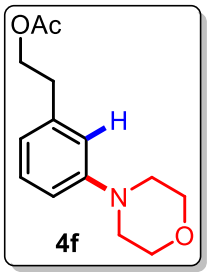
4c: 79% yield. A colorless oil. Rf=0.34 (hexane/ethyl acetate=10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (t, J = 7.8 Hz, 1H), 6.85 – 6.72 (m, 3H), 3.93 – 3.82 (m, 4H), 3.23 – 3.10 (m, 4H), 2.88 (hept, J = 6.9 Hz, 1H), 1.26 (d, J = 6.9 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.29, 149.95, 129.05, 118.31, 114.24, 113.14, 66.95, 49.57, 34.44, 24.00. **IR** (KBr):*v* 2959, 2855, 1601, 1582, 1492, 1447, 1240, 1123, 963 cm^{-1}; **HRMS** (ESI): Calcd for $C_{13}H_{20}ON$ ($M+H^+$):206.1539; found: 206.1550.



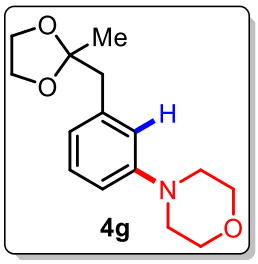
4d: 54% yield (run with 11 mol% dCpentpb2HBF$_4$). A blue oil. Rf=0.19 (hexane/ethyl acetate=5:1); **^{1}H NMR** (400 MHz, Acetone-d_6) δ 7.10 – 6.99 (m, 1H), 6.36 – 6.23 (m, 3H), 3.80 – 3.71 (m, 4H), 3.15 – 3.05 (m, 4H), 2.90 (s, 6H); **^{13}C NMR** (101 MHz, Acetone-d_6) δ 153.70, 152.75, 130.17, 105.90, 105.63, 101.50, 67.62, 50.53, 40.88. Both the proton and carbon NMR match the literature reported data.[106]



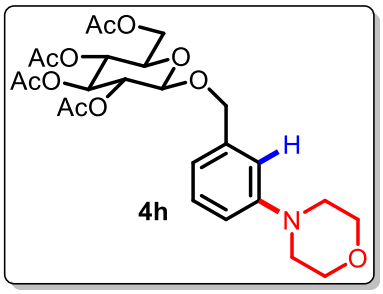
4e: 70% yield (run with 11 mol% dCpentpb2HBF$_4$). A colorless oil. Rf=0.20 (hexane/ethyl acetate=5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (dd, J = 2.7, 1.5 Hz, 1H), 7.54 (ddd, J = 7.6, 1.6, 1.0 Hz, 1H), 7.33 (t, J = 7.9 Hz, 0H), 7.09 (ddd, J = 7.9, 2.7, 1.0 Hz, 1H), 3.90 (s, 3H), 3.90 – 3.83 (m, 4H), 3.24 – 3.16 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.29, 151.22, 130.98, 129.12, 120.93, 119.95, 116.32, 66.77, 52.08, 49.06. Both the proton and carbon NMR match the literature reported data.[107]



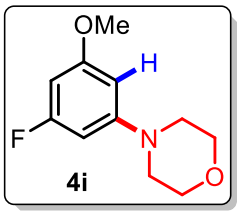
4f: 79% yield (run with 11 mol% dCpentpb2HBF$_4$). A colorless oil. Rf=0.24 (hexane/ethyl acetate=5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 (t, J = 7.7 Hz, 1H), 6.82 – 6.68 (m, 3H), 4.27 (t, J = 7.4 Hz, 2H), 3.91 – 3.80 (m, 4H), 3.19 – 3.05 (m, 4H), 2.90 (t, J = 7.2 Hz, 2H), 2.04 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.91, 151.36, 138.69, 129.19, 120.51, 116.21, 113.84, 66.82, 64.89, 49.28, 35.32, 20.93. **IR** (KBr):*v* 2956, 2854, 1739, 1681, 1602, 1583, 1448, 1364, 1241, 1123, 1034 cm^{-1}; **HRMS** (ESI): Calcd for $C_{14}H_{20}O_3N$ ($M+H^+$):250.1438; found: 250.1458.



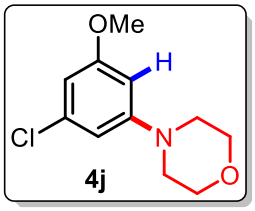
4g: 66% yield. A colorless oil. Rf=0.17 (hexane/ethyl acetate=10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (t, J = 7.8 Hz, 1H), 6.88 – 6.76 (m, 3H), 3.94 – 3.88 (m, 2H), 3.88 – 3.83 (m, 4H), 3.80 – 3.74 (m, 2H), 3.21 – 3.09 (m, 4H), 2.89 (s, 2H), 1.31 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.96, 137.86, 128.60, 122.43, 118.07, 113.78, 109.73, 66.89, 64.78, 49.50, 45.59, 24.34. **IR** (KBr):*v* 2958, 2884, 1726, 1680, 1602, 1493, 1448, 1377, 1244, 1123 cm^{-1}; **HRMS** (ESI): Calcd for $C_{15}H_{22}O_3N$ ($M+H^+$):264.1594; found: 264.1613.



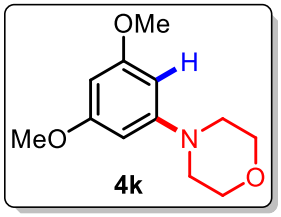
4h: 71% yield. A pink oil. Rf=0.19 (hexane/ethyl acetate=3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 – 7.17 (m, 1H), 6.86 – 6.79 (m, 2H), 6.76 (d, J = 7.2 Hz, 1H), 5.20 – 4.99 (m, 3H), 4.84 (d, J = 12.3 Hz, 1H), 4.60 – 4.50 (m, 2H), 4.26 (dd, J = 12.3, 4.6 Hz, 1H), 4.14 (dd, J = 12.3, 2.4 Hz, 1H), 3.88 – 3.79 (m, 4H), 3.66 (ddd, J = 9.7, 4.6, 2.5 Hz, 1H), 3.19 – 3.06 (m, 4H), 2.07 (s, 3H), 2.02 – 1.94 (m, 9H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.52, 170.12, 169.27, 169.14, 151.36, 137.55, 129.11, 119.03, 115.00, 114.75, 99.18, 72.69, 71.66, 71.19, 70.80, 68.28, 66.74, 61.80, 49.10, 20.64, 20.57, 20.49, 20.47. **IR** (KBr):*v* 2960, 2857, 1756, 2604, 1494, 1449, 1367, 1226, 1122, 1040 cm^{-1}; **HRMS** (ESI): Calcd for $C_{25}H_{34}O_{11}N$ ($M+H^+$): 524.2126; found: 524.2139.



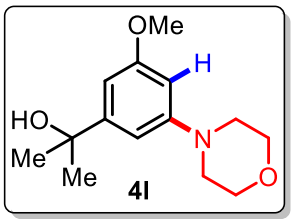
4i: 83% yield (run with 11 mol% dCpentpb2HBF$_4$). A white solid, mp = 42.0 – 43.7 ℃. Rf=0.22 (hexane/ethyl acetate=10:1); **^{1}H NMR** (500 MHz, $CDCl_3$) 6.25 – 6.18 (m, 2H), 6.17 – 6.12 (m, 1H), 3.89 – 3.79 (m, 4H), 3.76 (s, 3H), 3.18 – 3.05 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.46 (d, J = 241.3 Hz), 161.46 (d, J = 13.5 Hz), 153.13 (d, J = 12.5 Hz), 95.17 (d, J = 25.7 Hz), 92.40 (d, J = 25.9 Hz), 97.23, 66.60, 55.32, 48.68. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -111.14. **IR** (KBr):*v* 2967, 2851, 1637, 1588, 1490, 1446, 1375, 1270, 1140, 1123 cm^{-1}; **HRMS** (ESI): Calcd for $C_{11}H_{15}FO_2N$ ($M+H^+$): 212.1081; found: 212.1101.



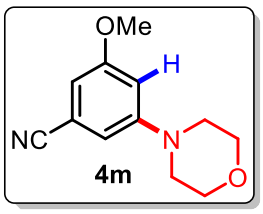
4j: 85% yield (run with 11 mol% dCpentpb2HBF$_4$). A colorless oil. Rf=0.22 (hexane/ethyl acetate=10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.51 – 6.48 (m, 1H), 6.43 – 6.40 (m, 1H), 6.30 (t, J = 2.2 Hz, 1H), 3.86 – 3.80 (m, 4H), 3.77 (s, 3H), 3.17 – 3.08 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.99, 152.94, 135.44, 108.49, 105.03, 100.30, 66.63, 55.37, 48.77. **IR** (KBr):*v* 2956, 2854, 1739, 1681, 1602, 1583, 1448, 1364, 1241, 1123, 1034 cm^{-1}; **HRMS** (ESI): Calcd for $C_{11}H_{15}ClO_2N$ ($M+H^+$): 228.0786; found: 228.0804.



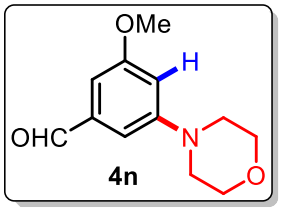
4k: 79% yield (run with 11 mol% dCpentpb2HBF$_4$). A white solid. Rf=0.23 (hexane/ethyl acetate=5:1); **^{1}H NMR** (400 MHz, CDCl3) δ 6.08 (d, J = 2.2 Hz, 2H), 6.04 (t, J = 2.1 Hz, 1H), 3.87 – 3.81 (m, 4H), 3.77 (s, 6H), 3.19 – 3.10 (m, 4H); **^{13}C NMR** (100 MHz, CDCl3) δ 161.44, 153.22, 94.65, 91.76, 66.78, 55.16, 49.26. Both the proton and carbon NMR match the literature reported data.[108]



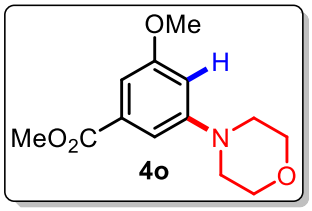
4l: 83% yield. A bright yellow oil. Rf=0.17 (hexane/ethyl acetate=2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.69 (dd, J = 2.3, 1.5 Hz, 1H), 6.56 (dd, J = 2.3, 1.5 Hz, 1H), 6.33 (t, J = 2.2 Hz, 1H), 3.88 – 3.81 (m, 4H), 3.80 (s, 3H), 3.19 – 3.12 (m, 4H), 1.97 (br, 1H), 1.55 (s, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.43, 152.41, 151.57, 104.87, 101.83, 100.22, 72.69, 66.82, 55.19, 49.47, 31.67. **IR** (KBr):*ν* 3433, 2969, 2854, 1592, 1450, 1270, 1202, 1171, 1120 cm^{-1}; **HRMS** (ESI): Calcd for $C_{14}H_{22}O_3N$ ($M+H^+$): 252.1594; found: 252.1614.



4m: 85% yield. A white solid, mp = 85.8 – 88.2 ℃. Rf=0.21 (hexane/ethyl acetate=5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.74 (dd, J = 2.4, 1.2 Hz, 1H), 6.62 (dd, J = 2.3, 1.2 Hz, 1H), 6.59 (t, J = 2.3 Hz, 1H), 3.87 – 3.81 (m, 4H), 3.79 (s, 3H), 3.19 – 3.11 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.66, 152.60, 119.16, 113.37, 111.69, 107.19, 106.18, 66.45, 55.47, 48.36. **IR** (KBr):*v* 2960, 2872, 2228, 1603, 1585, 1461, 1324, 1270, 1118 cm^{-1}; **HRMS** (ESI): Calcd for $C_{12}H_{15}O_2N_2$ ($M+H^+$): 219.1128; found: 219.1143.

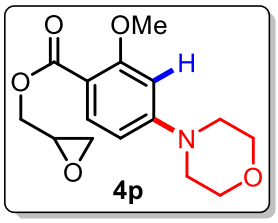


4n: 68% yield. A yellow oil. Rf=0.30 (hexane/ethyl acetate=5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.03 (dd, J = 2.4, 1.2 Hz, 1H), 6.90 (dd, J = 2.3, 1.2 Hz, 1H), 6.67 (t, J = 2.3 Hz, 1H), 3.89 – 3.82 (m, 7H), 3.24 – 3.17 (m, 4H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.37, 161.12, 152.78, 138.22, 110.32, 108.11, 104.15, 66.62, 55.49, 48.78. **IR** (KBr):*v* 2960, 2851, 1697, 1600, 1451, 1389, 1271, 1206, 1122 cm^{-1}; **HRMS** (ESI): Calcd for $C_{12}H_{16}O_3N$ ($M+H^+$): 222.1125; found: 222.1145.

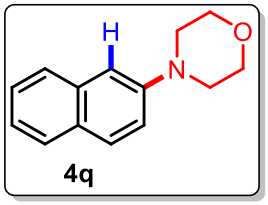


4o: 88% yield. A colorless oil. Rf=0.22 (hexane/ethyl acetate=5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (dd, J = 2.4, 1.3 Hz, 1H), 7.07 (dd, J = 2.3, 1.3 Hz, 1H), 6.61 (t, J = 2.4 Hz, 1H), 3.89 (s, 3H), 3.86 – 3.82 (m, 4H), 3.82 (s, 3H), 3.21 – 3.13 (m, 4H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.09,

160.45, 152.27, 131.72, 109.75, 106.77, 104.83, 66.66, 55.40, 52.11, 48.95. **IR** (KBr):*v* 2955, 2842, 1720, 1594, 1440, 1360, 1278, 1205, 1121, 1054 cm^{-1}; **HRMS** (ESI): Calcd for $C_{13}H_{18}O_4N$ ($M+H^+$): 252.1230; found: 252.1253.

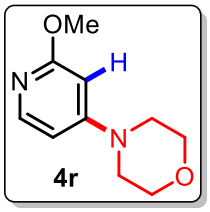


4p: 72% yield. A white solid, mp = 110 - 112℃. Rf=0.20 (hexane/ethyl acetate=3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.8 Hz, 1H), 6.43 (dd, J = 8.9, 2.3 Hz, 1H), 6.34 (d, J = 2.3 Hz, 1H), 4.55 (dd, J = 12.4, 3.1 Hz, 1H), 4.10 (dd, J = 12.4, 5.9 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 4H), 3.34 – 3.22 (m, 5H), 2.84 (dd, J = 5.0, 4.1 Hz, 1H), 2.72 (dd, J = 5.0, 2.6 Hz, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.89, 161.64, 155.58, 133.72, 108.93, 105.87, 97.48, 66.46, 64.33, 55.74, 49.66, 47.60, 44.71. **IR** (KBr):*v* 2960, 2853, 1715, 1606, 1449, 1243, 1212, 1122, 976 cm^{-1}; **HRMS** (ESI): Calcd for $C_{15}H_{20}O_5N$ ($M+H^+$): 294.1336; found: 294.1340.

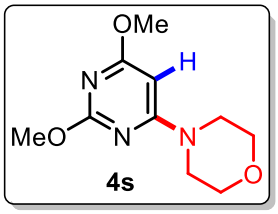


4q: 70% yield (run with 11 mol% dCpentpb2HBF$_4$). A white solid. Rf=0.22 (hexane/ethyl acetate= 10:1); **^{1}H NMR** (400 MHz, CDCl3) 7.82 – 7.68 (m, 3H), 7.44 (t, J = 7.5 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.27 (dd, J = 8.8, 2.7 Hz, 1H), 7.13 (d, J = 2.3 Hz, 1H), 3.97 – 3.89 (m, 4H), 3.30 – 3.25 (m, 4H); **^{13}C NMR** (100 MHz, CDCl3) δ 149.02, 134.47, 128.77, 128.62, 127.40, 126.72, 126.30, 123.50, 118.85, 110.05, 66.88, 49.75. Both the proton and carbon NMR match the literature

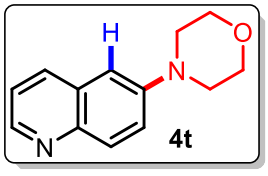
reported data.[38]



4r: 87% yield (run with 11 mol% dCpentpb2HBF$_4$). A colorless oil. Rf=0.31 (hexane/ethyl acetate= 3:1); **^{1}H NMR** (400 MHz, CDCl3) 7.91 (d, J = 6.1 Hz, 1H), 6.39 (dd, J = 6.1, 2.4 Hz, 1H), 6.05 (d, J = 2.3 Hz, 1H), 3.90 (s, 3H), 3.86 – 3.76 (m, 4H), 3.29 – 3.19 (m, 4H); **^{13}C NMR** (100 MHz, CDCl3) δ 165.76, 157.82, 146.97, 103.96, 92.98, 66.32, 53.25, 46.47. Both the proton and carbon NMR match the literature reported data.[109]

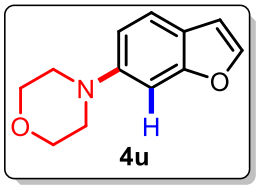


4s: 78% yield. A white solid. Rf=0.23 (hexane/ethyl acetate= 5:1); **^{1}H NMR** (400 MHz, CDCl3) 5.46 (s, 1H), 3.88 (m, 6H), 3.76 – 3.70 (m, 4H), 3.56 – 3.48 (m, 4H); **^{13}C NMR** (100 MHz, CDCl3) δ 172.47, 165.33, 164.80, 79.22, 66.40, 54.13, 53.50, 44.55. Both the proton and carbon NMR match the literature reported data.[110]



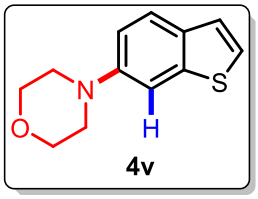
4t: 77% yield (run with 11 mol% dCpentpb2HBF$_4$). A white solid. Rf=0.18 (hexane/ethyl acetate= 1:1); **^{1}H NMR** (400 MHz, CDCl3) 8.70 (dd, J = 4.2, 1.7 Hz, 1H), 7.98 (s, 1H), 7.96 (s, 1H), 7.45

(dd, J = 9.3, 2.7 Hz, 1H), 7.29 (dd, J = 8.2, 4.2 Hz, 1H), 6.99 (d, J = 2.8 Hz, 1H), 3.91 – 3.87 (m, 4H), 3.29 – 3.21 (m, 4H); **^{13}C NMR** (100 MHz, CDCl3) δ 149.23, 147.68, 143.91, 134.68, 130.10, 129.30, 122.01, 121.38, 108.90, 66.77, 49.35. Both the proton and carbon NMR match the literature reported data.[38]



4u

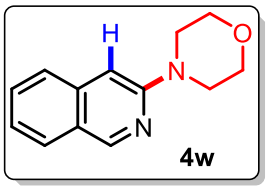
4u: 86% yield (run with 11 mol% dCpentpb2HBF$_4$). A white solid, mp = 83 - 86℃. Rf=0.20 (hexane/ethyl acetate=10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.7 Hz, 1H), 7.37 (d, J = 2.2 Hz, 1H), 7.31 – 7.22 (m, 2H), 7.09 (dd, J = 8.7, 2.3 Hz, 1H), 3.98 – 3.88 (m, 4H), 3.29 – 3.18 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) 148.94, 141.38, 133.37, 123.79, 123.54, 123.32, 115.65, 108.04, 66.93, 50.25. **IR** (KBr):*v* 2962, 2828,1625, 1494, 1448, 1265, 1220, 1162, 1123 cm^{-1}; **HRMS** (ESI): Calcd for $C_{12}H_{14}O_2N$ ($M+H^+$): 204.1019; found: 204.1016.



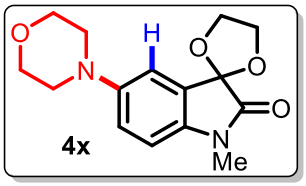
4v

4v: 47% yield (run with 11 mol% dCpentpb2HBF$_4$). A white solid, mp = 96 – 98 ℃. Rf=0.21 (hexane/ethyl acetate=10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (d, J = 2.2 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.04 (q, J = 0.9 Hz, 1H), 6.94 (dd, J = 8.6, 2.2 Hz, 1H), 6.68 (dd, J = 2.2, 1.0 Hz, 1H), 3.98 – 3.69 (m, 4H), 3.27 – 3.07 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) 156.18, 149.62, 143.82, 121.06, 120.45, 113.44, 106.18, 98.62, 66.90, 50.44. **IR** (KBr):*v* 2852, 2825, 2360, 2342, 1601,

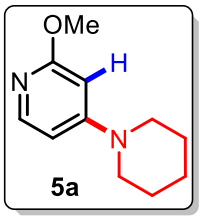
1495, 1446, 1264, 1232, 1120 cm^{-1}; **HRMS** (ESI): Calcd for $C_{12}H_{14}ONS$ ($M+H^+$): 220.0791; found: 220.0786.



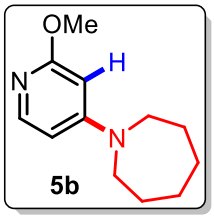
4w: 64% yield (run with 11 mol% dCpentpb2HBF$_4$). A green solid. Rf=0.23 (hexane/ethyl acetate= 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.80 (dd, J = 8.2, 1.0 Hz, 1H), 7.63 – 7.57 (m, 1H), 7.56 – 7.48 (m, 1H), 7.29 (ddd, J = 8.1, 6.7, 1.2 Hz, 1H), 6.77 (s, 1H), 3.96 – 3.84 (m, 4H), 3.60 – 3.50 (m, 4H). **^{13}C NMR** (100 MHz, CDCl3) δ 156.79, 151.23, 138.63, 130.32, 127.60, 125.30, 123.92, 123.51, 98.97, 66.83, 46.66. Both the proton and carbon NMR match the literature reported data.[111]



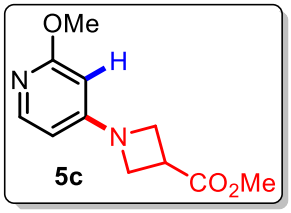
4x: 64% yield. An orange solid, mp = 156 – 158 °C. Rf=0.34 (hexane/ethyl acetate=3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.02 (d, J = 2.5 Hz, 1H), 6.90 (dd, J = 8.5, 2.5 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 4.64 – 4.52 (m, 2H), 4.34 – 4.22 (m, 2H), 3.88 – 3.78 (m, 4H), 3.14 – 3.03 (m, 7H). **^{13}C NMR** (101 MHz, $CDCl_3$) 173.05, 148.32, 137.85, 124.58, 119.01, 113.99, 109.02, 102.43, 66.82, 65.71, 50.38, 25.76. **IR** (KBr):*v* 2961, 2900, 2854, 1724, 1504, 1287, 1244, 1119, 1032 cm^{-1}; **HRMS** (ESI): Calcd for $C_{15}H_{19}O_4N_2$ ($M+H^+$): 291.1339; found: 291.1334.



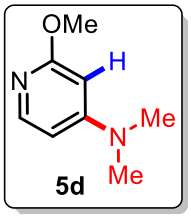
5a: 78% yield (run with 11 mol% dCpentpb2HBF$_4$). A colorless oil. Rf=0.36 (hexane/ethyl acetate=5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, J = 6.1 Hz, 1H), 6.36 (dd, J = 6.2, 2.4 Hz, 1H), 6.02 (d, J = 2.3 Hz, 1H), 3.87 (s, 3H), 3.27 (t, J = 4.5 Hz, 4H), 1.67 – 1.53 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.89, 157.53, 146.81, 104.23, 92.60, 53.12, 47.54, 25.01, 24.33. **IR** (KBr):*v* 2937, 2854, 1605, 1543, 1499, 1453, 1288, 1225, 1205, 1053 cm^{-1}; **HRMS** (ESI): Calcd for $C_{11}H_{17}ON_2$ ($M+H^+$): 193.1335; found: 193.1352.



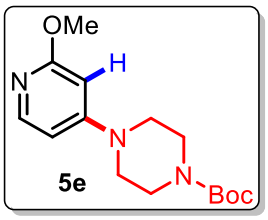
5b: 47% yield (run with 11 mol% dCpentpb2HBF$_4$). A colorless oil. Rf=0.38 (hexane/ethyl acetate=5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, J = 6.2 Hz, 1H), 6.22 (dd, J = 6.2, 2.4 Hz, 1H), 5.87 (d, J = 2.3 Hz, 1H), 3.87 (s, 3H), 3.46 – 3.35 (m, 4H), 1.78 – 1.69 (m, 4H), 1.56 – 1.45 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.71, 155.66, 146.63, 102.29, 89.95, 53.17, 48.92, 27.18, 26.77. **IR** (KBr):*v* 2927, 2853, 1606, 1540, 1504, 1461, 1296, 1191, 1057 cm^{-1}; **HRMS** (ESI): Calcd for $C_{12}H_{19}ON_2$ ($M+H^+$): 207.1492; found: 207.1507.



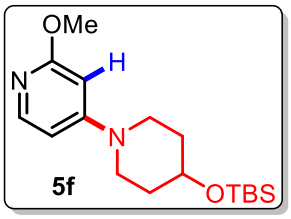
5c: 30% yield (run with 11 mol% dCpentpb2HBF$_4$). A colorless oil. Rf=0.19 (hexane/ethyl acetate=5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (d, J = 5.8 Hz, 1H), 5.99 (dd, J = 5.8, 2.1 Hz, 1H), 5.65 (d, J = 2.0 Hz, 1H), 4.16 – 4.03 (m, 4H), 3.87 (s, 3H), 3.75 (s, 3H), 3.61 – 3.50 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.75, 165.11, 157.57, 146.66, 101.75, 90.15, 53.49, 53.30, 52.34, 33.26. **IR** (KBr):*v* 2951, 2870, 1737, 1609, 1551, 1463, 1311, 1264, 1221 cm^{-1}; **HRMS** (ESI): Calcd for $C_{11}H_{15}O_3N_2$ ($M+H^+$): 223.1077; found: 223.1063.



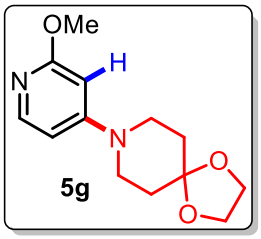
5d: 49% yield (run with 11 mol% dCpentpb2HBF$_4$, moderate yield may due to volatility). A colorless oil. Rf=0.29 (hexane/ethyl acetate=10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (d, J = 6.1 Hz, 1H), 6.23 (dd, J = 6.1, 2.4 Hz, 1H), 5.86 (d, J = 2.3 Hz, 1H), 3.89 (s, 3H), 2.95 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.53, 156.86, 146.50, 102.63, 90.60, 53.17, 39.25. **IR** (KBr):*v* 2946, 1611, 1544, 1454, 1260, 1156, 1116, 1051 cm^{-1}; **HRMS** (ESI): Calcd for $C_8H_{13}ON_2$ ($M+H^+$): 153.1022; found: 153.1034.



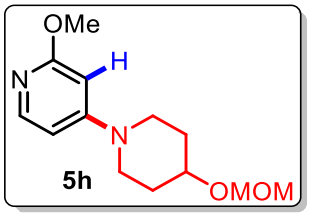
5d: 77% yield (run with 11 mol% dCpentpb2HBF$_4$). A colorless oil. Rf=0.19 (hexane/ethyl acetate=5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (d, J = 6.1 Hz, 1H), 6.35 (dd, J = 6.2, 2.3 Hz, 1H), 6.01 (d, J = 2.3 Hz, 1H), 3.86 (s, 3H), 3.58 – 3.45 (m, 4H), 3.31 – 3.18 (m, 4H), 1.44 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.80, 157.35, 154.50, 147.03, 104.28, 93.21, 80.07, 53.21, 46.17, 42.97(br), 28.31. **IR** (KBr):*v* 2976, 1695, 1607, 1547, 1412, 1287, 1202, 1168, 1044 cm^{-1}; **HRMS** (ESI): Calcd for $C_{15}H_{24}O_3N_3$ ($M+H^+$): 294.1812; found: 294.1830.



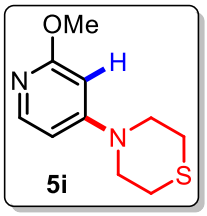
5f: 65% yield (run with 11 mol% dCpentpb2HBF$_4$). A colorless oil. Rf=0.24 (hexane/ethyl acetate=20:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (d, J = 6.2 Hz, 1H), 6.38 (dd, J = 6.2, 2.4 Hz, 1H), 6.04 (d, J = 2.3 Hz, 1H), 3.92 (dt, J = 7.0, 3.5 Hz, 1H), 3.88 (s, 3H), 3.52 (ddd, J = 12.2, 7.9, 3.6 Hz, 2H), 3.17 (ddd, J = 13.0, 7.6, 3.7 Hz, 2H), 1.78 (ddt, J = 11.8, 7.6, 3.6 Hz, 2H), 1.57 (dtd, J = 16.2, 7.3, 3.5 Hz, 2H), 0.88 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.89, 157.25, 146.86, 104.25, 92.74, 66.91, 53.20, 43.48, 33.45, 25.76, 18.04, -4.75. **IR** (KBr):*v* 2950, 2893, 2856, 1606, 1545, 1463, 1253, 1206, 1103, 1052. cm^{-1}; **HRMS** (ESI): Calcd for $C_{17}H_{31}O_2N_2Si$ ($M+H^+$): 323.2149; found: 323.2181.



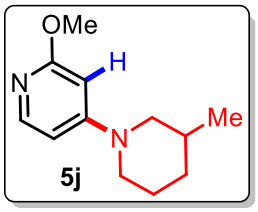
5g: 86% yield (run with 11 mol% dCpentpb2HBF$_4$). A colorless oil. Rf=0.21 (hexane/ethyl acetate=10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, J = 6.1 Hz, 1H), 6.36 (dd, J = 6.2, 2.4 Hz, 1H), 6.03 (d, J = 2.3 Hz, 1H), 3.94 (s, 4H), 3.86 (s, 3H), 3.47 – 3.34 (m, 4H), 1.76 – 1.67 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.87, 156.70, 146.96, 106.94, 104.27, 92.94, 64.32, 53.16, 44.73, 33.95. **IR** (KBr):*v* 2956, 2887, 1605, 1545, 1465, 1290, 1205, 1100, 1053 cm^{-1}; **HRMS** (ESI): Calcd for $C_{13}H_{19}O_3N_2$ ($M+H^+$): 251.1390; found: 251.1400.



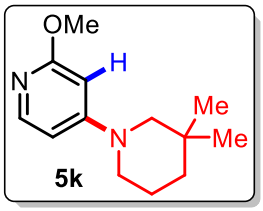
5h: 78% yield (run with 11 mol% dCpentpb2HBF$_4$). A colorless oil. Rf=0.24 (hexane/ethyl acetate= 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, J = 6.1 Hz, 1H), 6.36 (dd, J = 6.2, 2.4 Hz, 1H), 6.03 (d, J = 2.3 Hz, 1H), 4.68 (s, 2H), 3.86 (s, 3H), 3.76 (tt, J = 8.0, 3.8 Hz, 1H), 3.59 (ddd, J = 13.1, 6.7, 4.2 Hz, 2H), 3.35 (s, 3H), 3.07 (ddd, J = 12.9, 9.0, 3.4 Hz, 2H), 1.98 – 1.82 (m, 2H), 1.64 (dtd, J = 12.7, 8.6, 3.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.86, 157.08, 146.92, 104.27, 94.61, 92.87, 72.08, 55.26, 53.15, 44.14, 30.75. **IR** (KBr):*v* 2945, 1605, 1544, 1463, 1203, 1150, 1105, 1039 cm^{-1}; **HRMS** (ESI): Calcd for $C_{13}H_{21}O_3N_2$ ($M+H^+$): 253.1547; found: 253.1557.



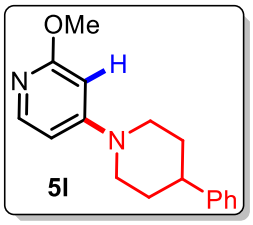
5i: 80% yield (run with 11 mol% dCpentpb2HBF$_4$). A brown oil. Rf=0.28 (hexane/ethyl acetate= 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (dd, J = 6.2, 0.4 Hz, 1H), 6.32 (dd, J = 6.2, 2.4 Hz, 1H), 5.99 (d, J = 2.3 Hz, 1H), 3.88 (s, 3H), 3.76 – 3.69 (m, 4H), 2.67 – 2.59 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.97, 156.05, 147.21, 104.20, 93.10, 53.28, 49.38, 25.31. **IR** (KBr):*v* 2947, 2907, 1604, 1543, 1499, 1276, 1188, 1058 cm^{-1}; **HRMS** (ESI): Calcd for $C_{10}H_{15}OSN_2$ ($M+H^+$): 211.0900; found: 211.0916.



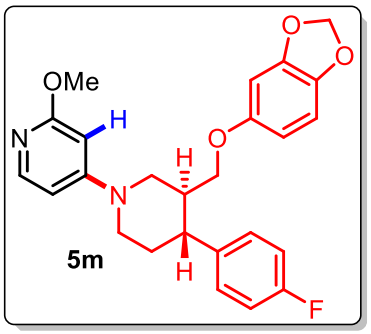
5j: 80% yield (run with 11 mol% dCpentpb2HBF$_4$). A colorless oil. Rf=0.41 (hexane/ethyl acetate=10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, J = 6.2 Hz, 1H), 6.37 (dd, J = 6.2, 2.4 Hz, 1H), 6.02 (d, J = 2.3 Hz, 1H), 3.88 (s, 3H), 3.78 – 3.62 (m, 2H), 2.76 (ddd, J = 12.9, 11.9, 3.1 Hz, 1H), 2.45 (dd, J = 12.8, 10.7 Hz, 1H), 1.81 (ddt, J = 13.1, 3.6, 1.6 Hz, 1H), 1.75 – 1.60 (m, 2H), 1.60 – 1.48 (m, 1H), 1.11 (tdd, J = 12.3, 11.1, 4.0 Hz, 1H), 0.91 (d, J = 6.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.89, 157.35, 146.81, 104.20, 92.52, 54.42, 53.18, 47.02, 32.98, 30.25, 24.51, 19.21; **IR** (KBr):*v* 2958, 2852, 2813, 1603, 1577, 1504, 1448, 1229, 1122 cm^{-1}; **HRMS** (ESI): Calcd for $C_{12}H_{19}ON_2$ ($M+H^+$): 207.1492; found: 207.1506.



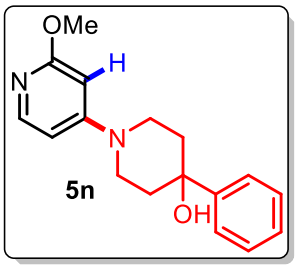
5k: 78% yield (run with 11 mol% dCpentpb2HBF$_4$). A colorless oil. Rf=0.40 (hexane/ethyl acetate=10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, J = 6.2 Hz, 1H), 6.33 (dd, J = 6.2, 2.4 Hz, 1H), 5.99 (d, J = 2.4 Hz, 1H), 3.86 (s, 3H), 3.25 – 3.17 (m, 2H), 2.97 (s, 2H), 1.69 – 1.57 (m, 2H), 1.44 – 1.35 (m, 2H), 0.92 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.89, 157.70, 146.75, 103.90, 91.96, 58.43, 53.12, 46.62, 37.68, 31.47, 26.40, 21.61; **IR** (KBr):*v* 2948, 2864, 1603, 1542, 1398, 1199, 1160, 1051 cm^{-1}; **HRMS** (ESI): Calcd for $C_{13}H_{21}ON_2$ ($M+H^+$): 221.1648; found: 221.1639.



5l: 61% yield (run with 11 mol% dCpentpb2HBF$_4$). A colorless oil. Rf=0.31 (hexane/ethyl acetate=10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, J = 6.1 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.22 (td, J = 6.5, 1.6 Hz, 3H), 6.44 (dd, J = 6.2, 2.4 Hz, 1H), 6.11 (d, J = 2.3 Hz, 1H), 3.96 (dt, J = 13.4, 2.6 Hz, 2H), 3.91 (s, 3H), 2.94 (td, J = 12.8, 2.7 Hz, 2H), 2.74 (tt, J = 12.2, 3.7 Hz, 1H), 2.00 – 1.86 (m, 2H), 1.87 – 1.69 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.94, 157.37, 146.96, 145.36, 128.49, 126.68, 126.39, 104.39, 92.95, 53.21, 47.39, 42.53, 32.43; **IR** (KBr):*v* 2940, 2847, 1605, 1543, 1493, 1257, 1199, 1053, 1011 cm^{-1}; **HRMS** (ESI): Calcd for $C_{17}H_{21}ON_2$ ($M+H^+$): 269.1648; found: 269.1672.

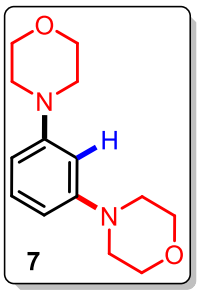


5m: 45% yield (run with 11 mol% dCpentpb2HBF$_4$). A yellow oil. Rf=0.28 (hexane/ethyl acetate= 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, J = 6.2 Hz, 1H), 7.13 (dd, J = 8.6, 5.4 Hz, 2H), 6.98 (t, J = 8.7 Hz, 2H), 6.64 (d, J = 8.5 Hz, 1H), 6.47 (dd, J = 6.2, 2.3 Hz, 1H), 6.38 (d, J = 2.5 Hz, 1H), 6.16 (dd, J = 8.5, 2.5 Hz, 1H), 6.13 (d, J = 2.3 Hz, 1H), 5.89 (s, 2H), 4.19 (ddd, J = 13.3, 4.0, 1.9 Hz, 1H), 3.97 (dt, J = 13.3, 1.9 Hz, 1H), 3.92 (s, 3H), 3.63 (dd, J = 9.5, 3.0 Hz, 1H), 3.50 (dd, J = 9.5, 7.3 Hz, 1H), 3.04 – 2.86 (m, 2H), 2.72 (td, J = 11.5, 4.6 Hz, 1H), 2.18 (dtq, J = 11.0, 7.0, 3.4 Hz, 1H), 1.94 – 1.75 (m, 2H); **^{19}F NMR** (470 MHz, $CDCl_3$) δ -115.89. **^{13}C NMR** (101 MHz, $CDCl_3$) 165.87, 162.83, 160.40, 157.13, 154.04, 148.18, 146.92, 141.75, 138.73, 138.69, 128.72, 128.64, 115.66, 115.45, 107.85, 105.53, 104.34, 101.12, 97.92, 92.95, 68.92, 53.37, 50.42, 47.43, 44.23, 40.98, 33.09; **IR** (KBr):*v* : 2895, 1603, 1509, 1488, 1467, 1186, 1039, 832 cm^{-1}; **HRMS** (ESI): Calcd for $C_{25}H_{26}FO_4N_2$ ($M+H^+$): 437.1871; found: 437.1898.

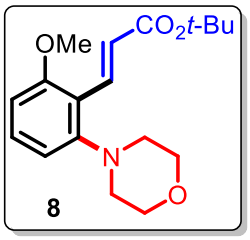


5n: 46% yield (run with 11 mol% dCpentpb2HBF$_4$). A yellow oil. Rf=0.21 (hexane/ethyl acetate=2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (d, J = 6.2 Hz, 1H), 7.50 – 7.43 (m, 2H), 7.39

– 7.33 (m, 2H), 7.30 – 7.25 (m, 1H), 6.44 (dd, J = 6.2, 2.4 Hz, 1H), 6.11 (d, J = 2.3 Hz, 1H), 3.89 (s, 3H), 3.73 (dt, J = 12.9, 2.4 Hz, 2H), 3.39 (td, J = 12.9, 2.7 Hz, 2H), 2.12 (td, J = 13.1, 4.7 Hz, 2H), 1.89 – 1.73 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.91, 157.18, 147.65, 146.92, 128.45, 127.29, 124.38, 104.30, 92.83, 71.35, 53.30, 42.93, 37.24; **IR** (KBr):*v* 3349, 2948, 2853, 1606, 1541, 1461, 1194, 1021 cm^{-1}; **HRMS** (ESI): Calcd for $C_{17}H_{21}O_2N_2$ ($M+H^+$): 285.1598; found: 285.1617.

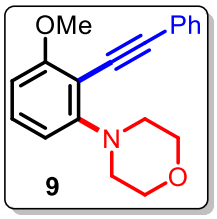


7: 62% yield (run with 11 mol% DPEphos, 3.2 equiv **2a** and 4.0 equiv Cs_2CO_3). A white solid. Rf=0.14 (hexane/ethyl acetate= 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.23 – 7.15 (m, 1H), 6.51 – 6.42 (m, 3H), 3.91 – 3.81 (m, 8H), 3.21 – 3.09 (m, 8H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.39, 129.69, 108.11, 103.85, 66.91, 49.61. Both the proton and carbon NMR match the literature reported data.[112]

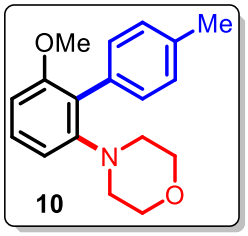


8: 63% yield (run with 11 mol% DPEphos, 1.5 equiv *tert*-butyl acrylate instead of **3**). A colorless oil. Rf=0.23 (hexane/ethyl acetate= 15:1); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.97 (d, J = 16.4 Hz, 1H), 7.28 (t, J = 8.2 Hz, 1H), 6.79 (d, J = 16.3 Hz, 1H), 6.69 (dd, J = 8.2, 4.3 Hz, 2H), 3.93 – 3.86 (m,

7H), 3.00 – 2.94 (m, 4H), 1.56 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.70, 159.87, 154.08, 136.68, 130.54, 123.10, 117.03, 111.16, 105.97, 79.74, 67.14, 55.50, 53.14, 28.28. Both the proton and carbon NMR match the literature reported data.[39]



9: 61% yield (run with 1.2 equiv 2-methyl-4-phenylbut-3-yn-2-ol instead of **3**). A colorless oil. Rf=0.34 (hexane/ethyl acetate= 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 2H), 7.39 – 7.31 (m, 3H), 7.24 (t, J = 8.3 Hz, 1H), 6.65 – 6.54 (m, 2H), 3.97 – 3.88 (m, 7H), 3.31 – 3.20 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.60, 155.60, 131.29, 129.73, 128.28, 127.96, 123.90, 110.28, 105.74, 104.83, 99.55, 84.08, 67.29, 56.09, 51.77. Both the proton and carbon NMR match the literature reported data.[44]



10: 70% yield (run with 1.5 equiv *p*Tol-B(neop) instead of **3**). A colorless oil. Rf=0.32 (hexane/ethyl acetate= 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 2H), 7.27 (t, J = 8.2 Hz, 1H), 7.24 – 7.18 (m, 2H), 6.75 – 6.68 (m, 2H), 3.73 (s, 3H), 3.54 – 3.45 (m, 4H), 2.81 – 2.74 (m, 4H), 2.40 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.46, 151.72, 136.03, 132.68, 130.74, 128.46, 128.44, 124.16, 111.19, 106.02, 66.96, 55.80, 51.49, 21.33. Both the proton and carbon

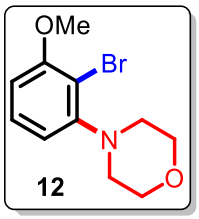
NMR match the literature reported data.[41]

Synthesis of Compounds **11** and **12**

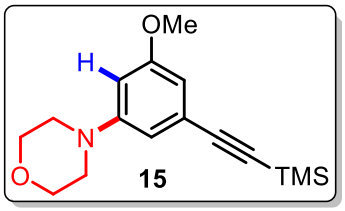
An oven-dried 4 mL vial was charged with 2-bromoanisole (57.1mg 0.3 mmol, 1.0 equiv), *O*-benzoyl hydroxylamine (0.3 mmol, 1.6 equiv), bis(pinacolato)diboron (92.5 mg, 0.36 mmol, 1.2 equiv), norbornene (28.2 mg, 0.3 mmol, 1.0 equiv), palladium acetate (6.7 mg, 0.03 mmol, 0.1 equiv) and a magnetic stir bar. The vial was sealed in the air and transferred in a nitrogen-filled glovebox. 1,4-Bis(dicyclo-hexylphosphino)butane (14.9 mg, 0.033 mmol, 0.11 equiv) and cesium carbonate (245 mg, 0.75 mmol, 2.5 equiv) were added to the vial in the glove box. 1,4-Dioxane (3 ml) was added, and the vial was then sealed with PTFE lined cap in the glovebox. The resulting mixture was stirred at room temperature for 10 minutes until the all the palladium acetate was fully dissolved. The vial was subsequently transferred out of glovebox and stirred on a pie-block preheated to 90^{o}C for 14 hours. After completion of the reaction, the mixture was filtered through a thin pad of celite. The filter cake was washed with ethyl acetate, and the combined filtrate was concentrated. Crude NMR Analysis showed full conversion and 62% NMR yield using 1,3,5-trimethoxylbenzene as the internal standard. Attempts to isolate the compound **11** by column chromatography or distillation all failed at this stage.

The crude product containing compound **11** was dissolved in methanol (3 mL). Water (3 mL) was added and stirring was initiated. $CuBr_2$ (201 mg, 0.9 mmol, 3.0 equiv) was added and the reaction mixture was heated to 80 °C. After the reaction was complete, as judged by TLC, methanol was removed under reduced pressure. The residue was dissolved in EtOAc and washed with water (3 × 5 mL). The organic layer was washed with brine (1 × 4 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel

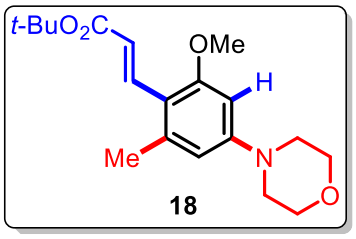
chromatography (hexanes/ethyl acetate = 30 : 1 to 20 :1) to afford the compound **12** (39.0 mg, 47% yield for two steps) as a colorless oil.



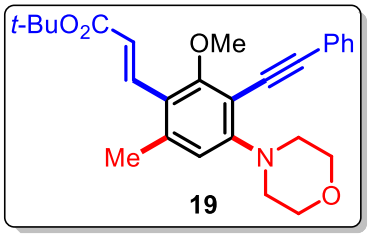
12: a colorless oil. Rf=0.24 (hexane/ethyl acetate= 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (t, J = 8.2 Hz, 1H), 6.70 (dd, J = 8.1, 1.3 Hz, 1H), 6.67 (dd, J = 8.2, 1.3 Hz, 1H), 3.95 – 3.84 (m, 7H), 3.09 – 2.98 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.07, 151.94, 128.27, 113.16, 109.10, 107.14, 67.17, 56.40, 52.20. Both the proton and carbon NMR match the literature reported data.[73]



15: 71% yield. A yellow oil. Rf=0.31 (hexane/ethyl acetate= 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.65 (dd, J = 2.3, 1.2 Hz, 1H), 6.53 (dd, J = 2.3, 1.2 Hz, 1H), 6.41 (t, J = 2.3 Hz, 1H), 3.87 – 3.79 (m, 4H), 3.77 (s, 3H), 3.17 – 3.07 (m, 4H), 0.25 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.23, 152.23, 124.22, 112.26, 107.63, 105.50, 103.46, 93.17, 66.75, 55.30, 49.00, -0.03; **IR** (KBr):*v* 2959, 2896, 2854, 2153, 1593, 1450, 1204, 1124, 1006 cm^{-1}; **HRMS** (ESI): Calcd for $C_{16}H_{24}O_2NSi$ ($M+H^+$): 290.1571; found: 290.1550.



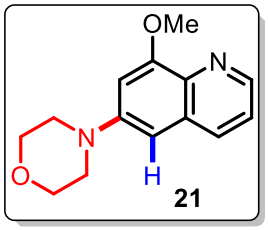
18: 74% yield. A colorless oil. Rf=0.13 (hexane/ethyl acetate= 10:1); **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.78 (d, J = 16.0 Hz, 1H), 6.47 (d, J = 16.0 Hz, 1H), 6.36 (d, J = 2.4 Hz, 1H), 6.29 (d, J = 2.4 Hz, 1H), 3.87 (s, 3H), 3.84 – 3.77 (m, 4H), 3.28 – 3.17 (m, 4H), 2.41 (s, 3H), 1.51 (s, 9H); **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 168.21, 161.34, 152.97, 141.32, 137.69, 120.23, 114.07, 109.73, 96.24, 79.76, 67.05, 55.61, 48.64, 28.44, 21.88; **IR** (KBr):*v* 2972, 2855, 1697, 1597, 1365, 1314, 1145, 994 cm^{-1}; **HRMS** (ESI): Calcd for $C_{19}H_{27}O_4N$ ($M+H^+$): 334.2013; found: 334.2017.



19: 61% yield (run with 3.0 equiv norbornene and 1.2 equiv 2-methyl-4-phenylbut-3-yn-2-ol instead of **3**). A yellow oil. Rf=0.17 (hexane/ethyl acetate= 5 :1); **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.73 (d, J = 16.2 Hz, 1H), 7.60 – 7.47 (m, 2H), 7.43 – 7.33 (m, 3H), 6.61 (s, 1H), 6.49 (d, J = 16.2 Hz, 1H), 3.94 (s, 3H), 3.93 – 3.87 (m, 4H), 3.34 – 3.25 (m, 4H), 2.44 (s, 3H), 1.54 (s, 9H); **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 167.30, 163.06, 155.53, 141.18, 137.25, 131.41, 128.93, 128.72, 124.02, 123.59, 121.61, 116.15, 108.96, 99.58, 84.49, 80.33, 67.43, 61.00, 51.85, 28.39, 21.93; **IR** (KBr):*v* 2974, 2932, 2853, 2361, 1705, 1626, 1583, 1295, 1149, 1118 cm^{-1}; **HRMS** (ESI): Calcd for $C_{27}H_{32}O_4N$ ($M+H^+$): 434.2326; found: 434.2329.

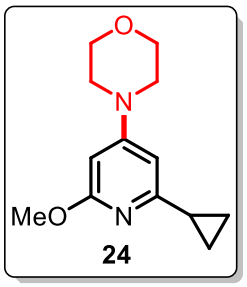
Gram Scale Synthesis of compound **21**

Compound **20** (1.43 g, 6.0 mmol, 1.0 equiv), **2a** (1.87 g, 9.0 mmol, 1.5 equiv), (-)borneol (926 mg, 6.0 mmol, 1.0 equiv), palladium acetate (70.1 mg, 0.3 mmol, 0.05 equiv.), dCpentpb·2HBF4 (188.9 mg, 0.033 mmol, 0.055 equiv), norbornene (564 mg, 6.0 mmol, 1.0 equiv)and Cs_2CO_3 (4.89 g, 15.0 mmol, 2.5 equiv) were added into a flame-dried, 50 mL Schlenk flask. The Schlenk tube was evacuated and back-filled with nitrogen three times. Dry 1,4-dioxane (30 mL) was added and stirring was initiated. The Schlenk tube was plcaed in a pre-heated oil bath at 90 °C. After 14 h, the oil bath was removed, and the reaction mixture was allowed to cool to room temperature. The reaction mixture was filtered through Celite, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane : ethyl acetate = 1 : 2) to give desired product **21** as a yellow solid. (1.44 g, 98% yield)



21

21: A yellow solid, mp =134 to 136 ℃. Rf=0.21 (hexane/ethyl acetate= 1:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.69 (dd, J = 4.2, 1.7 Hz, 1H), 7.92 (dd, J = 8.3, 1.7 Hz, 1H), 7.30 (dd, J = 8.3, 4.2 Hz, 1H), 6.77 (d, J = 2.4 Hz, 1H), 6.60 (d, J = 2.4 Hz, 1H), 4.04 (s, 3H), 3.94 – 3.83 (m, 4H), 3.29 – 3.19 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.87, 149.72, 146.65, 136.54, 134.49, 130.05, 122.03, 101.48, 100.94, 66.75, 55.78, 49.68; **IR** (KBr):*v* 2957, 2852, 1617, 1498, 1384, 1258, 1120, 985 cm^{-1}; **HRMS** (ESI): Calcd for $C_{14}H_{17}O_2N_2$ ($M+H^+$): 245.1285; found: 245.1286.



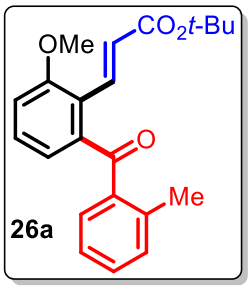
24

24: 83% yield (run with 11 mol% dCpentpb2HBF$_4$). A white solid, mp =79 to 81 ℃. Rf=0.21 (hexane/ethyl acetate= 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.31 (d, J = 2.1 Hz, 1H), 5.84 (d, J = 2.0 Hz, 1H), 3.86 – 3.75 (m, 7H), 3.27 – 3.18 (m, 4H), 1.84 (tt, J = 8.0, 4.7 Hz, 1H), 1.07 – 0.98 (m, 2H), 0.88 – 0.78 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.46, 160.64, 158.19, 101.05, 90.05, 66.46, 52.87, 46.88, 17.14, 8.62 ; **IR** (KBr):*v* 2970, 2854, 1605, 1555, 1452, 1383, 1275, 1206, 1125 cm^{-1}; **HRMS** (ESI): Calcd for $C_{13}H_{19}O_2N_2$ ($M+H^+$): 235.1441; found: 235.1445.

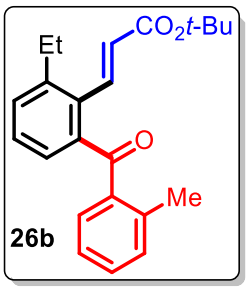
General procedure of palladium/norbornene-catalyzed ortho acylation of aryl bromides.

An oven-dried 4 mL vial was charged with aryl bromide (0.3 mmol, 1.0 equiv), carboxylic acid anhydride (0.54 mmol, 1.8 equiv), *tert*-butyl acrylate (56.7 mg, 0.45 mmol, 1.5 equiv), norbornene (56.4 mg, 0.6 mmol, 2.0 equiv), dichlorobis(acetonitrile)palladium(II) (7.8 mg, 0.03 mmol, 0.10 equiv), bis[2-(diphenylphosphino)phenyl] ether (16.1 mg, 0.03 mmol, 0.10 equiv) and a magnetic stir bar. The vial was sealed in the air and transferred in a nitrogen-filled glovebox. Cesium carbonate (294.0 mg, 0.9 mmol, 3.0 equiv) was added to the vial in the glove box. 1,4-Dioxane (3 ml) was added, and the vial was then sealed with PTFE lined cap in the glovebox. The resulting mixture was stirred at room temperature for 15 minutes until the all the dichlorobis(acetonitrile)palladium(II) was fully dissolved. The vial was subsequently transferred out of glovebox and stirred on a pie-block preheated to 100^{o}C for 14 hours. After completion of the reaction, the mixture was filtered through a thin pad of celite. The filter cake was washed with

ethyl acetate, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography on silica gel to yield the desired product.

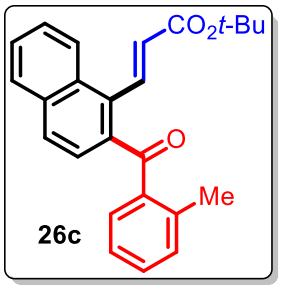


26a: 68% yield. A yellow oil. Rf=0.21 (hexane/ethyl acetate= 20:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (d, J = 16.0 Hz, 1H), 7.43 – 7.33 (m, 2H), 7.29 – 7.25 (m, 1H), 7.25 – 7.19 (m, 1H), 7.17 – 7.10 (m, 1H), 7.09 – 7.02 (m, 2H), 6.28 (d, J = 16.1 Hz, 1H), 3.92 (s, 3H), 2.60 (s, 3H), 1.44 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.76, 165.81, 158.33, 142.83, 139.50, 137.46, 137.15, 131.82, 131.66, 131.23, 129.70, 125.92, 125.40, 122.85, 121.15, 112.63, 80.06, 55.70, 28.01, 21.19; **IR** (KBr):*v* 2976, 2932, 1707, 1666, 1571, 1315, 1271, 1151, 1069 cm^{-1}; **HRMS** (ESI): Calcd for $C_{22}H_{24}O_4Na$ ($M+Na^+$): 375.1567; found: 375.1559.

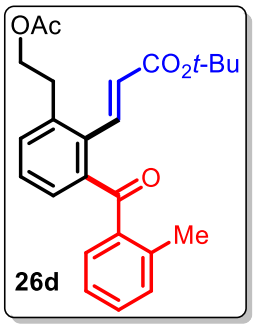


26b: 86% yield. A colorless oil. Rf=0.34 (hexane/ethyl acetate= 20:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, J = 16.0 Hz, 1H), 7.42 – 7.29 (m, 4H), 7.25 – 7.19 (m, 1H), 7.13 – 7.04 (m, 2H), 5.75 (d, J = 16.0 Hz, 1H), 2.67 (q, J = 7.5 Hz, 2H), 2.52 (s, 3H), 1.42 (s, 9H), 1.23 – 1.14 (t, J = 7.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.49, 164.80, 143.18, 141.19, 140.99, 139.03,

138.29, 133.73, 131.52, 131.47, 130.74, 130.17, 128.37, 127.18, 126.88, 125.38, 80.40, 27.99, 26.37, 20.93, 15.00; **IR** (KBr):*v* 2973, 2932, 1713, 1665, 1456, 1315, 1301, 1151, 978 cm^{-1}; **HRMS** (ESI): Calcd for $C_{23}H_{26}O_3Na$ ($M+Na^+$): 373.1774; found: 373.1779.

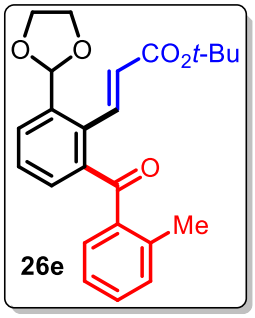


26c: 90% yield. A colorless oil. Rf=0.34 (hexane/ethyl acetate= 20:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 – 8.03 (m, 1H), 7.98 – 7.86 (m, 3H), 7.68 (d, J = 8.5 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.38 (td, J = 7.4, 1.7 Hz, 1H), 7.32 – 7.24 (m, 1H), 7.20 – 7.08 (m, 2H), 5.99 (d, J = 16.0 Hz, 1H), 2.57 (s, 3H), 1.49 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.47, 164.59, 140.46, 138.85, 138.60, 137.58, 134.19, 133.33, 131.55, 131.53, 130.96, 130.15, 128.75, 128.41, 128.40, 127.59, 127.23, 125.70, 125.67, 125.48, 80.58, 28.00, 20.88; **IR** (KBr):*v* 2977, 2930, 1711, 1663, 1368, 1340, 1283, 1249, 1152 cm^{-1}; **HRMS** (ESI): Calcd for $C_{25}H_{25}O_3$ ($M+H^+$): 373.1798; found: 373.1813.

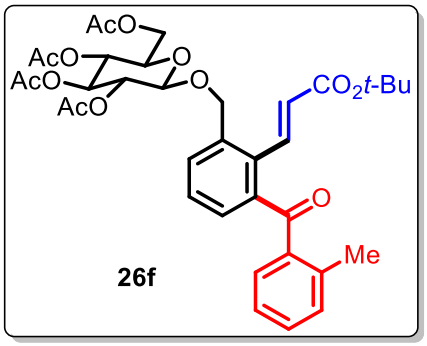


26d: 80% yield. A colorless oil. Rf=0.24 (hexane/ethyl acetate= 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, J = 16.0 Hz, 1H), 7.46 – 7.29 (m, 4H), 7.21 (d, J = 7.6 Hz, 1H), 7.07 (dd, J = 6.6, 1.5 Hz,

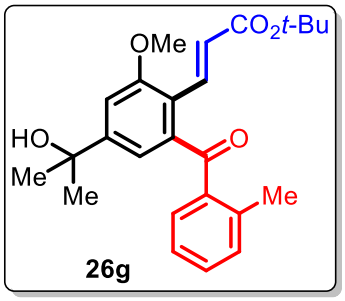
2H), 5.75 (d, J = 16.0 Hz, 1H), 4.21 (t, J = 6.8 Hz, 2H), 2.97 (t, J = 6.8 Hz, 2H), 2.50 (s, 3H), 1.99 (s, 3H), 1.41 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.07, 170.69, 164.46, 141.18, 140.84, 139.03, 138.09, 136.91, 134.62, 131.98, 131.54, 130.05, 128.35, 128.03, 127.57, 125.36, 80.50, 63.97, 32.16, 27.93, 20.88, 20.79; **IR** (KBr):*v* 3063, 2977, 2930, 1742, 1712, 1665, 1456, 1367, 1235, 1152, 1037 cm^{-1}; **HRMS** (ESI): Calcd for $C_{25}H_{29}O_5$ ($M+H^+$): 391.1904; found: 391.1895.



26e: 69% yield. A colorless oil. Rf=0.16 (hexane/ethyl acetate= 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 7.7, 1.4 Hz, 1H), 7.61 (d, J = 16.0 Hz, 1H), 7.56 (dd, J = 7.7, 1.5 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.25 – 7.20 (m, 1H), 7.15 – 7.08 (m, 2H), 5.88 – 5.82 (m, 2H), 4.21 – 4.14 (m, 2H), 4.07 – 3.99 (m, 2H), 2.50 (s, 3H), 1.42 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.81, 164.70, 140.89, 140.03, 138.96, 138.10, 136.17, 134.71, 131.61, 131.58, 130.42, 130.30, 129.14, 128.28, 127.65, 125.53, 101.28, 80.48, 65.52, 28.01, 20.94.; **IR** (KBr):*v* 2976, 1709, 1663, 1500, 1370, 1242, 1151, 1138 cm^{-1}; **HRMS** (ESI): Calcd for $C_{24}H_{27}O_5$ ($M+H^+$): 377.1747; found: 377.1750.

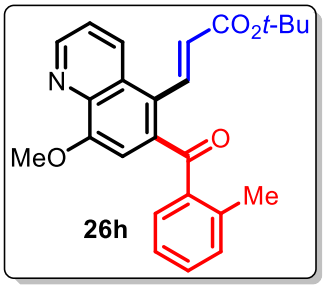


26f: 72% yield. A yellow oil. Rf=0.19 (hexane/ethyl acetate= 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 7.5, 1.4 Hz, 1H), 7.50 – 7.37 (m, 3H), 7.31 (td, J = 7.2, 2.0 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.12 – 7.04 (m, 2H), 5.77 (d, J = 16.0 Hz, 1H), 5.16 (t, J = 9.4 Hz, 1H), 5.06 (dt, J = 11.7, 9.4 Hz, 2H), 4.86 (d, J = 12.3 Hz, 1H), 4.64 – 4.50 (m, 2H), 4.26 (dd, J = 12.3, 4.7 Hz, 1H), 4.13 (dd, J = 12.3, 2.3 Hz, 1H), 3.67 (ddd, J = 10.0, 4.7, 2.3 Hz, 1H), 2.47 (s, 3H), 2.06 (s, 3H), 2.00 – 1.96 (m, 6H), 1.93 (s, 3H), 1.39 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.66, 170.47, 170.05, 169.25, 169.20, 164.41, 140.84, 139.64, 138.91, 137.89, 135.25, 134.13, 131.55, 131.50, 130.97, 130.16, 129.31, 128.29, 127.52, 125.43, 99.26, 80.59, 72.69, 71.81, 71.04, 68.22, 68.13, 61.73, 27.88, 20.80, 20.60, 20.46, 20.44; **IR** (KBr):*v* 2978, 2256, 1757, 1712, 1665, 1367, 1226, 1153, 1041 cm^{-1}; **HRMS** (ESI): Calcd for $C_{36}H_{42}O_{13}Na$ ($M+Na^+$): 705.2518; found: 705.2495.

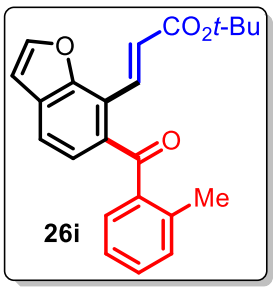


26g: 57% yield. A colorless oil. Rf=0.26 (hexane/ethyl acetate= 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, J = 16.1 Hz, 1H), 7.35 (td, J = 7.5, 1.5 Hz, 1H), 7.24 (s, 2H), 7.19 (dd, J = 7.8, 1.5 Hz, 1H), 7.13 – 7.05 (m, 2H), 6.23 (d, J = 16.0 Hz, 1H), 3.92 (s, 3H), 2.59 (s, 3H), 2.26 (br, 1H), 1.58

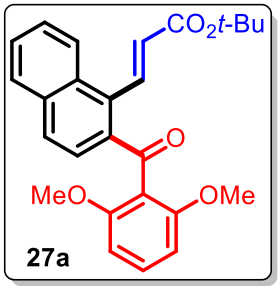
(s, 6H), 1.41 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.05, 165.96, 158.45, 151.61, 142.74, 139.71, 137.22, 137.00, 131.95, 131.74, 131.48, 125.43, 121.06, 117.06, 109.06, 80.06, 72.48, 55.70, 31.63, 28.00, 21.33; **IR** (KBr):*v* 3467, 2975, 2932, 1707, 1665, 1598, 1455, 1317, 1285, 1151 cm^{-1}; **HRMS** (ESI): Calcd for $C_{25}H_{30}O_5Na$ ($M+Na^+$): 433.1985; found: 433.1987.



26h: 56% yield. A pink oil. Rf=0.26 (hexane/ethyl acetate= 1:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.05 (dd, J = 4.2, 1.6 Hz, 1H), 8.40 (dd, J = 8.6, 1.6 Hz, 1H), 7.71 (d, J = 15.9 Hz, 1H), 7.55 (dd, J = 8.6, 4.1 Hz, 1H), 7.38 (td, J = 7.4, 1.7 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.24 (s, 1H), 7.19 – 7.09 (m, 2H), 5.92 (d, J = 15.5 Hz, 1H), 4.16 (s, 3H), 2.59 (s, 3H), 1.45 (s, 9H).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.86, 164.53, 155.72, 150.57, 140.73, 139.31, 138.74, 138.57, 137.81, 133.93, 131.96, 131.72, 130.40, 128.43, 127.39, 125.60, 124.93, 122.58, 107.49, 80.69, 56.35, 27.98, 21.02; **IR** (KBr):*v* 2977, 2886, 1711, 1665, 1315, 1301, 1152, 1103 cm^{-1}; **HRMS** (ESI): Calcd for $C_{25}H_{26}O_4N$ ($M+H^+$): 404.1856; found: 404.1839.

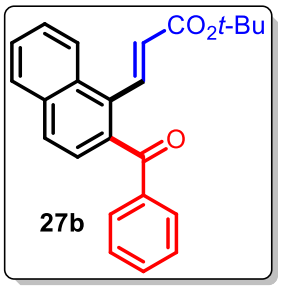


26i: 38% yield. A yellow oil. Rf=0.36 (hexane/ethyl acetate= 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.79 (m, 2H), 7.58 (dd, J = 8.0, 1.0 Hz, 1H), 7.40 (td, J = 7.5, 1.5 Hz, 1H), 7.31 (ddd, J = 7.1, 4.1, 1.1 Hz, 3H), 7.18 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 16.1 Hz, 1H), 6.86 (d, J = 2.2 Hz, 1H), 2.50 (s, 3H), 1.50 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.25, 166.11, 153.02, 147.39, 138.72, 138.70, 136.94, 135.76, 131.57, 131.50, 131.00, 130.50, 126.75, 125.43, 125.20, 121.42, 119.83, 106.81, 80.46, 28.14, 20.90; **IR** (KBr):*v* 2977, 1756, 1708, 1660, 1367, 1271, 1253, 1155, 1031 cm^{-1}; **HRMS** (ESI): Calcd for $C_{23}H_{22}O_4Na$ ($M+Na^+$): 385.1410; found: 385.1399.

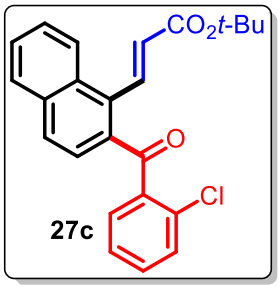


27a

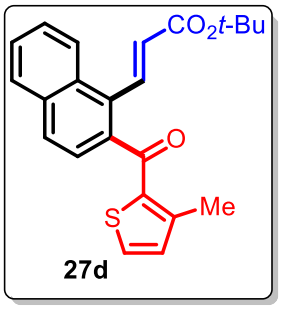
27a: 80% yield. A colorless oil. Rf=0.21 (hexane/ethyl acetate= 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (dd, J = 8.1, 1.6 Hz, 1H), 8.01 (d, J = 16.1 Hz, 1H), 7.87 – 7.71 (m, 3H), 7.61 – 7.45 (m, 2H), 7.31 (t, J = 8.4 Hz, 1H), 6.56 (d, J = 8.4 Hz, 2H), 5.96 (d, J = 16.1 Hz, 1H), 3.66 (s, 6H), 1.54 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.20, 165.10, 157.65, 141.43, 135.68, 134.98, 134.89, 131.49, 130.99, 128.09, 128.05, 127.62, 127.23, 126.83, 126.62, 125.97, 119.72, 104.07, 80.30, 55.77, 28.14; **IR** (KBr):*v* 2976, 2838, 1708, 1672, 1594, 1473, 1368, 1254, 1151, 1112 cm^{-1}; **HRMS** (ESI): Calcd for $C_{26}H_{26}O_5Na$ ($M+Na^+$): 441.1672; found: 441.1664.



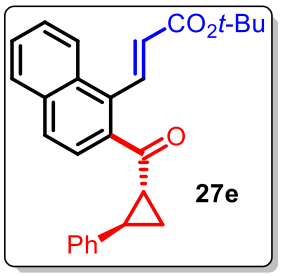
27b: 46% yield. A colorless oil. Rf=0.43 (hexane/ethyl acetate= 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 – 8.07 (m, 1H), 8.02 – 7.90 (m, 3H), 7.71 (dd, J = 8.2, 1.4 Hz, 2H), 7.64 – 7.58 (m, 2H), 7.57 – 7.51 (m, 2H), 7.44 – 7.37 (m, 2H), 5.99 (d, J = 16.0 Hz, 1H), 1.43 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.64, 164.82, 139.71, 137.91, 136.56, 133.94, 133.12, 132.32, 130.98, 129.69, 128.87, 128.83, 128.51, 128.49, 127.42, 127.37, 125.42, 125.11, 80.65, 28.02; **IR** (KBr):*v* 3059, 2977, 1710, 1664, 1368, 1280, 1250, 1151 cm^{-1}; **HRMS** (ESI): Calcd for $C_{24}H_{22}O_3Na$ ($M+Na^+$): 381.1461; found: 381.1459.



27b: 51% yield. A orange oil. Rf=0.43 (hexane/ethyl acetate= 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (dd, J = 8.4, 1.4 Hz, 1H), 7.96 – 7.84 (m, 3H), 7.69 (d, J = 8.5 Hz, 1H), 7.58 (dddd, J = 17.0, 8.3, 6.9, 1.5 Hz, 2H), 7.43 – 7.35 (m, 2H), 7.35 – 7.30 (m, 1H), 7.25 (td, J = 5.6, 3.2 Hz, 1H), 5.99 (d, J = 16.0 Hz, 1H), 1.49 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.99, 164.59, 140.27, 139.06, 135.69, 134.71, 134.65, 132.54, 132.08, 130.97, 130.63, 130.40, 129.09, 128.74, 128.36, 128.03, 127.23, 126.66, 126.12, 125.87, 80.65, 28.03; **IR** (KBr):*v* 3060, 2977, 1710, 1669, 1368, 1289, 1152, 1058 cm^{-1}; **HRMS** (ESI): Calcd for $C_{24}H_{21}O_3ClNa$ ($M+Na^+$): 415.1071; found: 415.1064.

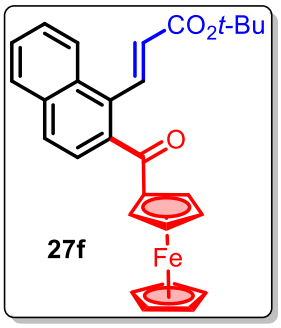


27b: 61% yield. A yellow oil. Rf=0.37 (hexane/ethyl acetate= 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1H NMR (400 MHz, Chloroform-d) δ 8.17 – 8.01 (m, 2H), 7.91 (d, J = 8.9 Hz, 2H), 7.63 – 7.51 (m, 3H), 7.43 (d, J = 4.9 Hz, 1H), 6.92 (d, J = 4.9 Hz, 1H), 6.11 (d, J = 16.1 Hz, 1H), 2.37 (s, 3H), 1.47 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.16, 165.03, 145.88, 139.14, 138.32, 137.28, 133.84, 132.29, 132.08, 131.31, 130.97, 129.01, 128.53, 128.38, 127.33, 127.30, 125.32, 124.28, 80.64, 28.05, 16.28; **IR** (KBr):*ν* 2976, 2928, 1709, 1637, 1400, 1369, 1284, 1152 cm^{-1}; **HRMS** (ESI): Calcd for $C_{23}H_{22}O_3SNa$ ($M+Na^+$): 401.1182; found: 401.1174.



27e: 50% yield. A colorless oil. Rf=0.32 (hexane/ethyl acetate= 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34 (d, J = 16.0 Hz, 1H), 8.17 – 8.10 (m, 1H), 7.86 (d, J = 8.6 Hz, 2H), 7.62 – 7.53 (m, 3H), 7.29 – 7.24 (m, 2H), 7.21 – 7.15 (m, 1H), 7.14 – 7.09 (m, 2H), 6.13 (d, J = 16.0 Hz, 1H), 2.83 (ddd, J = 9.0, 6.7, 4.0 Hz, 1H), 2.60 (ddd, J = 8.1, 5.2, 4.1 Hz, 1H), 1.90 (ddd, J = 9.2, 5.3, 4.0 Hz, 1H), 1.53 (m, 10H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.41, 165.02, 140.29, 139.99, 138.07,

134.12, 132.11, 131.04, 129.27, 129.05, 128.50, 128.38, 127.52, 127.28, 126.56, 126.08, 125.61, 124.21, 80.87, 34.47, 31.17, 28.15, 21.59; **IR** (KBr):*v* 2977, 1710, 1674, 1457, 1394, 1285, 1151 cm^{-1}; **HRMS** (ESI): Calcd for $C_{27}H_{26}O_3Na$ ($M+Na^+$): 421.1774; found: 421.1762.



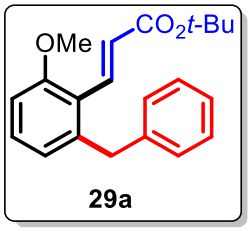
27f

27f: 59% yield. A dark red solid, mp = 95 to 97℃. Rf=0.32 (hexane/ethyl acetate= 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) 8.22 – 8.10 (m, 2H), 7.91 (d, J = 8.7 Hz, 2H), 7.66 (d, J = 8.5 Hz, 1H), 7.60 (dd, J = 6.4, 3.3 Hz, 2H), 6.12 (d, J = 16.0 Hz, 1H), 4.64 (t, J = 1.9 Hz, 2H), 4.52 (t, J = 2.0 Hz, 2H), 4.21 (s, 5H), 1.46 (s, 9H) ; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 13C NMR (101 MHz, CDCl3) δ 202.18, 165.14, 139.84, 137.92, 133.80, 131.12, 130.97, 128.66, 128.50, 128.45, 127.24, 127.13, 125.58, 124.70, 80.66, 79.58, 72.61, 71.05, 70.04, 28.11; **IR** (KBr):*v* 3097, 2977, 2929, 1709, 1644, 1444, 1286, 1152 cm^{-1}; **HRMS** (ESI): Calcd for $C_{28}H_{26}O_3FeNa$ ($M+Na^+$): 499.1609; found: 499.1617.

General procedure of palladium/norbornene-catalyzed ortho benzylation of aryl bromides**.**

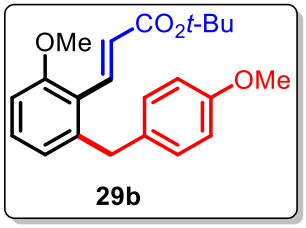
An oven-dried 4 mL vial was charged with aryl bromide (0.30 mmol, 1.0 equiv), benzyl chloride (0.60 mmol, 2.0 equiv), *tert*-butyl acrylate (56.7 mg, 0.45 mmol, 1.5 equiv), norbornene (56.4 mg, 0.6 mmol, 2.0 equiv, 2.0 equiv) and a magnetic stir bar (“substrate vial”). Palladium acetate (6.7 mg, 0.03 mmol, 0.1 equiv) and tris(4-methoxyphenyl)-phosphine (21.1 mg, 0.06 mmol, 0.2 equiv)

were put in another oven-dried 4 mL vial ("Pd/ligand vial"). Both vials were transferred in a nitrogen-filled glovebox. 1,4-Dioxane (1 ml) was added to the Pd/ligand vial. The resulting mixture was stirred at room temperature for 10 minutes until the all the palladium acetate was fully dissolved to give a bright yellow homogenous solution. 1,4-Dioxane (2 ml) and cesium carbonate (294.0 mg, 0.9 mmol, 3.0 equiv) were added to another vial in the glove box. The palladium/ligand solution was transferred to the substrate vial that was then sealed inside the glovebox. The vial was subsequently transferred out of glovebox and stirred on a pie-block preheated to 95°C for 14 hours. After completion of the reaction, the mixture was filtered through a thin pad of celite. The filter cake was washed with ethyl acetate, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography on silica gel to yield the desired product.



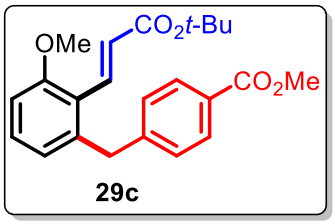
29a

29a: 64% yield. A colorless oil. Rf=0.24 (hexane/ethyl acetate= 30:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, J = 16.1 Hz, 1H), 7.30 – 7.09 (m, 6H), 6.86 – 6.77 (m, 2H), 6.51 (d, J = 16.2 Hz, 1H), 4.12 (s, 2H), 3.86 (s, 3H), 1.50 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.02, 159.14, 141.95, 140.34, 137.34, 129.76, 128.75, 128.41, 126.04, 124.80, 123.18, 122.60, 109.23, 80.01, 55.47, 39.70, 28.21; **IR** (KBr):*v* 2976, 2932, 1704, 1469, 1367, 1313, 1266, 1149, 1069 cm^{-1}; **HRMS** (ESI): Calcd for $C_{21}H_{24}O_3Na$ ($M+Na^+$): 347.1618; found: 347.1602.



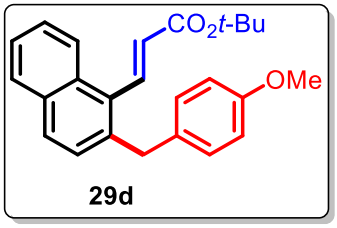
29b

29b: 63% yield. A colorless oil. Rf=0.35 (hexane/ethyl acetate= 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, J = 16.1 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.10 – 7.02 (m, 2H), 6.86 – 6.77 (m, 4H), 6.53 (d, J = 16.2 Hz, 1H), 4.07 (s, 2H), 3.87 (s, 3H), 3.77 (s, 3H), 1.52 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.05, 159.13, 157.86, 142.42, 137.36, 132.42, 129.74, 129.66, 124.66, 123.02, 122.44, 113.82, 109.14, 79.97, 55.43, 55.18, 38.81, 28.21.; **IR** (KBr):*v* 2976, 2836, 1704, 1625, 1511, 1469, 1251, 1150, 1071 cm^{-1}; **HRMS** (ESI): Calcd for $C_{23}H_{26}O_5Na$ ($M+Na^+$): 377.1723; found: 377.1693.



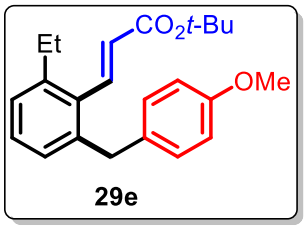
29c

29c: 54% yield. A colorless oil. Rf=0.27 (hexane/ethyl acetate= 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 16.1 Hz, 1H), 7.29 – 7.16 (m, 3H), 6.85 (d, J = 8.3 Hz, 1H), 6.80 (d, J = 7.7 Hz, 0H), 6.80 (dd, J = 7.7, 1.0 Hz, 1H), 6.48 (d, J = 16.1 Hz, 1H), 4.16 (s, 2H), 3.91 – 3.84 (m, 6H), 1.50 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.97, 166.86, 159.19, 145.81, 140.89, 137.04, 129.90, 129.75, 128.71, 128.04, 124.95, 123.16, 122.60, 109.53, 80.11, 55.48, 51.94, 39.73, 28.18; **IR** (KBr):*v* 2977, 1722, 1470, 1313, 1279, 1150, 1107, 1070 cm^{-1}; **HRMS** (ESI): Calcd for $C_{23}H_{26}O_5Na$ ($M+Na^+$): 405.1672; found: 405.1658.



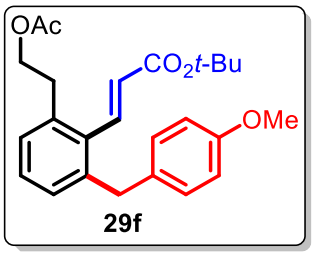
29d

29d: 71%yield. A colorless oil. Rf=0.31 (hexane/ethyl acetate= 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 – 8.06 (m, 2H), 7.85 (dd, J = 8.0, 1.6 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.58 – 7.45 (m, 2H), 7.34 (d, J = 8.5 Hz, 1H), 7.13 – 7.05 (m, 2H), 6.89 – 6.80 (m, 2H), 6.14 (d, J = 16.3 Hz, 1H), 4.18 (s, 2H), 3.80 (s, 3H), 1.61 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.64, 157.92, 141.34, 136.82, 132.68, 132.25, 131.54, 131.47, 129.79, 128.52, 128.29, 128.21, 127.78, 126.44, 125.47, 125.16, 113.85, 80.70, 55.20, 38.83, 28.21; **IR** (KBr):*v* 2977, 1709, 1510, 1367, 1288, 1247, 1152, 1037 cm^{-1}; **HRMS** (ESI): Calcd for $C_{25}H_{24}O_2Na$ ($M-H_2O+Na^+$): 379.1669; found: 379.1671.



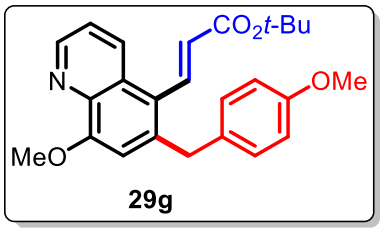
29e

29e: 81% yield. A colorless oil. Rf=0.35 (hexane/ethyl acetate= 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, J = 16.3 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.16 – 7.10 (m, 1H), 7.07 – 6.98 (m, 3H), 6.85 – 6.78 (m, 2H), 5.86 (d, J = 16.3 Hz, 1H), 3.95 (s, 2H), 3.78 (s, 3H), 2.66 (q, J = 7.5 Hz, 2H), 1.54 (s, 9H), 1.19 (t, J = 7.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.69, 157.82, 142.45, 142.23, 139.33, 134.24, 132.70, 129.86, 128.08, 127.70, 126.57, 126.22, 113.76, 80.47, 55.18, 39.03, 28.18, 26.70, 15.29; **IR** (KBr):*v* 2972, 2932, 1710, 1639, 1511, 1312, 1247, 1150, 1038 cm^{-1}; **HRMS** (ESI): Calcd for $C_{23}H_{26}O_2Na$ ($M-H_2O+Na^+$): 357.1825; found: 357.1824.



29f

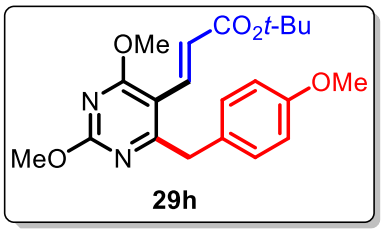
29f: 67% yield. A colorless oil. Rf=0.19 (hexane/ethyl acetate= 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, J = 16.3 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.13 (dd, J = 7.8, 1.4 Hz, 1H), 7.06 (dd, J = 7.6, 1.4 Hz, 1H), 7.00 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 5.86 (d, J = 16.3 Hz, 1H), 4.22 (t, J = 7.0 Hz, 2H), 3.93 (s, 2H), 3.77 (s, 3H), 2.97 (t, J = 7.0 Hz, 2H), 2.02 (s, 3H), 1.53 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.86, 165.38, 157.88, 141.87, 139.65, 135.94, 135.21, 132.42, 129.84, 128.57, 128.07, 127.79, 126.97, 113.79, 80.63, 64.44, 55.19, 39.04, 32.54, 28.16, 20.91; **IR** (KBr):*v* 2977, 1741, 1710, 1511, 1462, 1367, 1246, 1151, 1036 cm^{-1}; **HRMS** (ESI): Calcd for $C_{25}H_{28}O_4Na$ ($M-H_2O+Na^+$): 415.1880; found: 415.1887.



29g

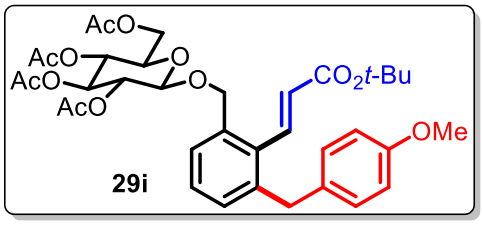
29g: 66% yield. A yellow oil. Rf=0.19 (hexane/acetone = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.89 (dd, J = 4.1, 1.6 Hz, 1H), 8.42 (dd, J = 8.7, 1.5 Hz, 1H), 7.99 (d, J = 16.2 Hz, 1H), 7.43 (dd, J = 8.6, 4.1 Hz, 1H), 7.05 (d, J = 8.6 Hz, 2H), 6.86 (s, 1H), 6.81 (d, J = 8.6 Hz, 2H), 6.03 (d, J = 16.2 Hz, 1H), 4.14 (s, 2H), 4.01 (s, 3H), 3.76 (s, 3H), 1.54 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.59, 158.03, 155.28, 148.65, 139.79, 139.30, 138.61, 133.44, 131.93, 129.67, 127.64, 127.21, 123.39, 121.89, 113.93, 110.09, 80.74, 55.94, 55.17, 39.16, 28.16; **IR** (KBr):*v* 2976, 1707, 1582,

1511, 1503, 1369, 1302, 1247, 1149, 1133 cm^{-1}; **HRMS** (ESI): Calcd for $C_{25}H_{28}O_4N$ (M +H^+): 406.2013; found: 406.2000.



29h

29h: 57% yield. A colorless oil. Rf=0.27 (hexane/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, J = 15.9 Hz, 1H), 7.22 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 6.54 (d, J = 16.0 Hz, 1H), 4.10 (s, 2H), 4.04 (s, 3H), 4.00 (s, 3H), 3.76 (s, 3H), 1.53 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.01, 169.95, 166.80, 163.72, 158.27, 133.62, 129.78, 129.72, 123.46, 113.94, 107.79, 80.30, 55.19, 54.90, 54.35, 40.46, 28.22; **IR** (KBr):*v* 2977, 1704, 1575, 1512, 1480, 1379, 1227, 1150, 1081 cm^{-1}; **HRMS** (ESI): Calcd for $C_{21}H_{27}O_5N_2$ (M +H^+): 387.1914 found: 387.1917.



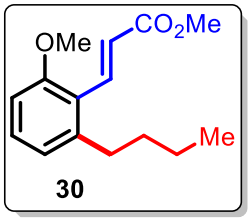
29i

29i: 63% yield. A white solid, mp = 45 to 47℃. Rf=0.17 (hexane/ethyl acetate = 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, J = 16.2 Hz, 1H), 7.35 – 7.23 (m, 2H), 7.18 (dd, J = 7.3, 1.6 Hz, 1H), 7.03 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.92 (d, J = 16.3 Hz, 1H), 5.23 – 5.03 (m, 3H), 4.86 (d, J = 12.1 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 7.9 Hz, 1H), 4.31 (dd, J = 12.3, 4.7 Hz, 1H), 4.18 (dd, J = 12.3, 2.3 Hz, 1H), 3.97 (s, 2H), 3.79 (s, 3H), 3.69 (ddd, J = 9.5, 4.8, 2.3 Hz, 1H), 2.12 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.54 (s, 9H); **^{13}C NMR** (101 MHz,

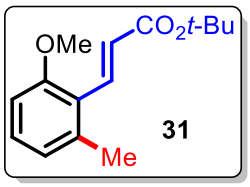
$CDCl_3$) δ 157.95, 140.56, 140.16, 134.77, 134.35, 132.03, 130.12, 129.81, 128.20, 127.71, 126.82, 113.83, 98.81, 80.72, 72.89, 71.80, 71.18, 68.71, 68.37, 61.91, 55.19, 38.93, 28.17, 20.71, 20.57, 20.56, 20.53.; **IR** (KBr):*v* 2977, 1757, 1709, 1512, 1367, 1227, 1153, 1039 cm^{-1}; **HRMS** (ESI): Calcd for $C_{36}H_{44}O_{13}Na$ ($M + Na^+$): 707.2674 found: 707.2658.

General procedure of palladium/norbornene-catalyzed ortho alkylation of aryl bromides with $Bu_3P{\cdot}HBF_4$**.**

An oven-dried 4 mL vial was charged with 2-bromoanisole (56.1 mg 0.30 mmol, 1.0 equiv), palladium acetate (6.7 mg, 0.03 mmol, 0.1 equiv) and tri-*n*-butylphosphonium tetrafluoroborate (17.4 mg, 0.06 mmol, 0.2 equiv) and a magnetic stir bar ("substrate vial"). Alkyl halide (0.60 mmol, 2.0 equiv), *tert*-butyl acrylate (56.7 mg, 0.45 mmol, 1.5 equiv), norbornene (56.4 mg, 0.6 mmol, 2.0 equiv, 2.0 equiv) were put in another oven-dried 4 mL vial ("reagent vial"). Both vials were transferred in a nitrogen-filled glovebox. 1,4-Dioxane (1 ml) was added to the reagent vial. The resulting mixture was stirred at room temperature for 5 mins. 1,4-Dioxane (2 ml) and cesium carbonate (294.0 mg, 0.9 mmol, 3.0 equiv) were added to substrate vial in the glove box. The substrate vial stirred at room temperature for 15 mins until all the palladium acetate fully dissolved. The reagent solution was transferred to the substrate vial that was then sealed inside the glovebox. The vial was subsequently transferred out of glovebox and stirred on a pie-block preheated to 100ºC for 14 hours. After completion of the reaction, the mixture was filtered through a thin pad of celite. The filter cake was washed with ethyl acetate, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography on silica gel to yield the desired product.



30: 59% yield**.** A colorless oil. Rf=0.26 (hexane/ethyl acetate = 30:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, J = 16.1 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 6.81 (d, J = 8.3 Hz, 1H), 6.75 (d, J = 16.2 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 2.84 – 2.72 (m, 2H), 1.64 – 1.53 (m, 2H), 1.47 – 1.35 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.50, 159.25, 144.79, 138.72, 130.02, 122.37, 121.83, 121.60, 108.67, 55.37, 51.49, 33.60, 22.51, 13.86; **IR** (KBr):*v* 2955, 1716, 1626, 1470, 1311, 1265, 1166 cm^{-1}; **HRMS** (ESI): Calcd for $C_{15}H_{21}O_3$ ($M+H^+$): 249.1485 found: 249.1489.



31: 47% yield. A colorless oil. Rf=0.22(hexane/ethyl acetate = 30:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (d, J = 16.2 Hz, 1H), 7.25 – 7.15 (m, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 6.60 (d, J = 16.2 Hz, 1H), 3.89 (s, 3H), 2.46 (s, 3H), 1.57 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.43, 159.10, 139.63, 137.56, 129.73, 123.99, 123.12, 122.41, 108.65, 80.08, 55.42, 28.24, 20.96; **IR** (KBr):*v* 2958, 2853, 2819, 2360, 1720, 1589, 1470, 1269, 1115, 1091, 1046 cm^{-1}; **HRMS** (ESI): Calcd for $C_{15}H_{21}O_3$ ($M+H^+$): 249.1485 found: 249.1475.

4.6 NMR Spectra

Figure 4.6 ^{1}H and ^{13}C NMR spectrum of compound **1p**.

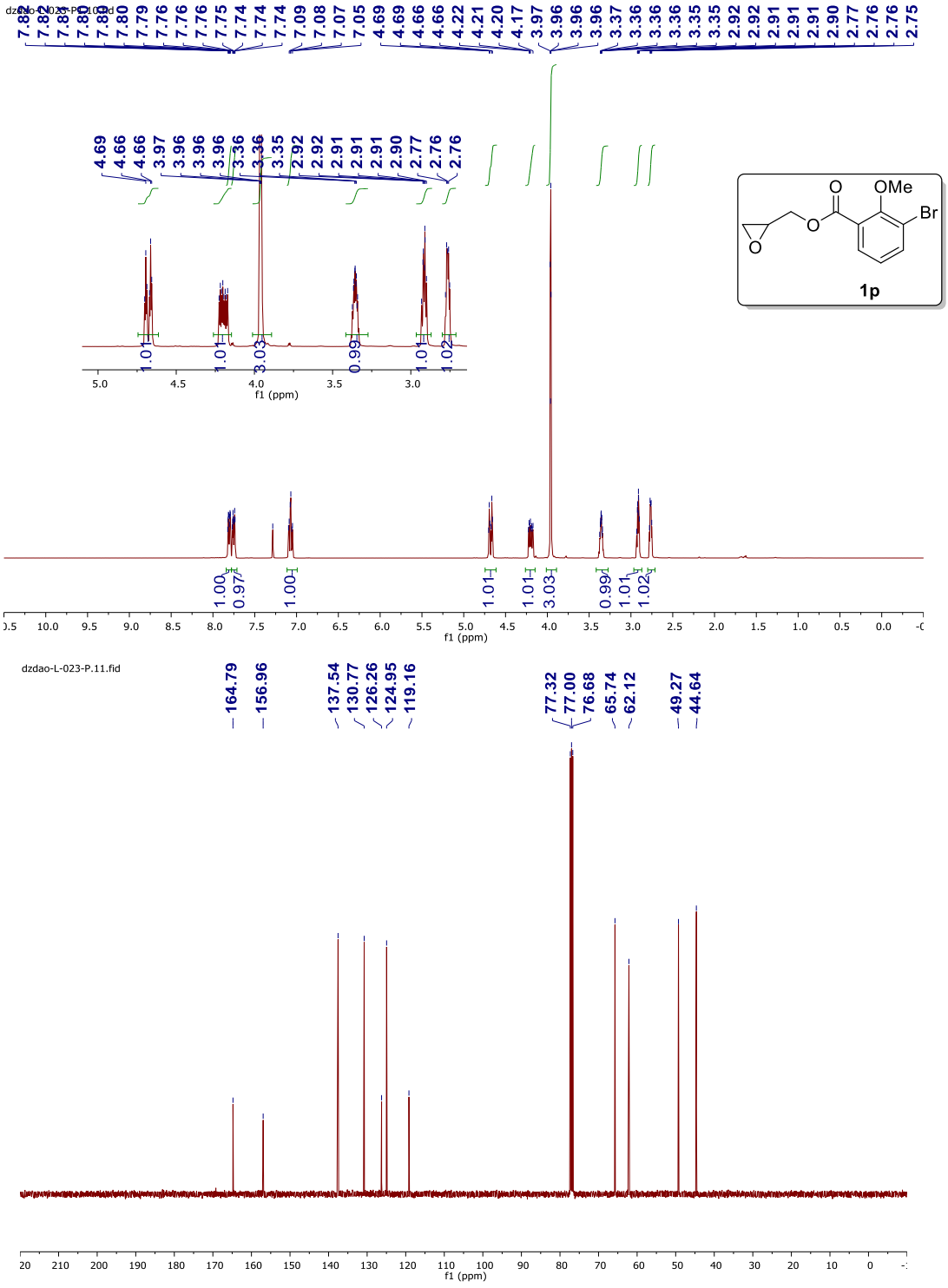


Figure 4.7 ^{1}H and ^{13}C NMR spectrum of compound **17**.

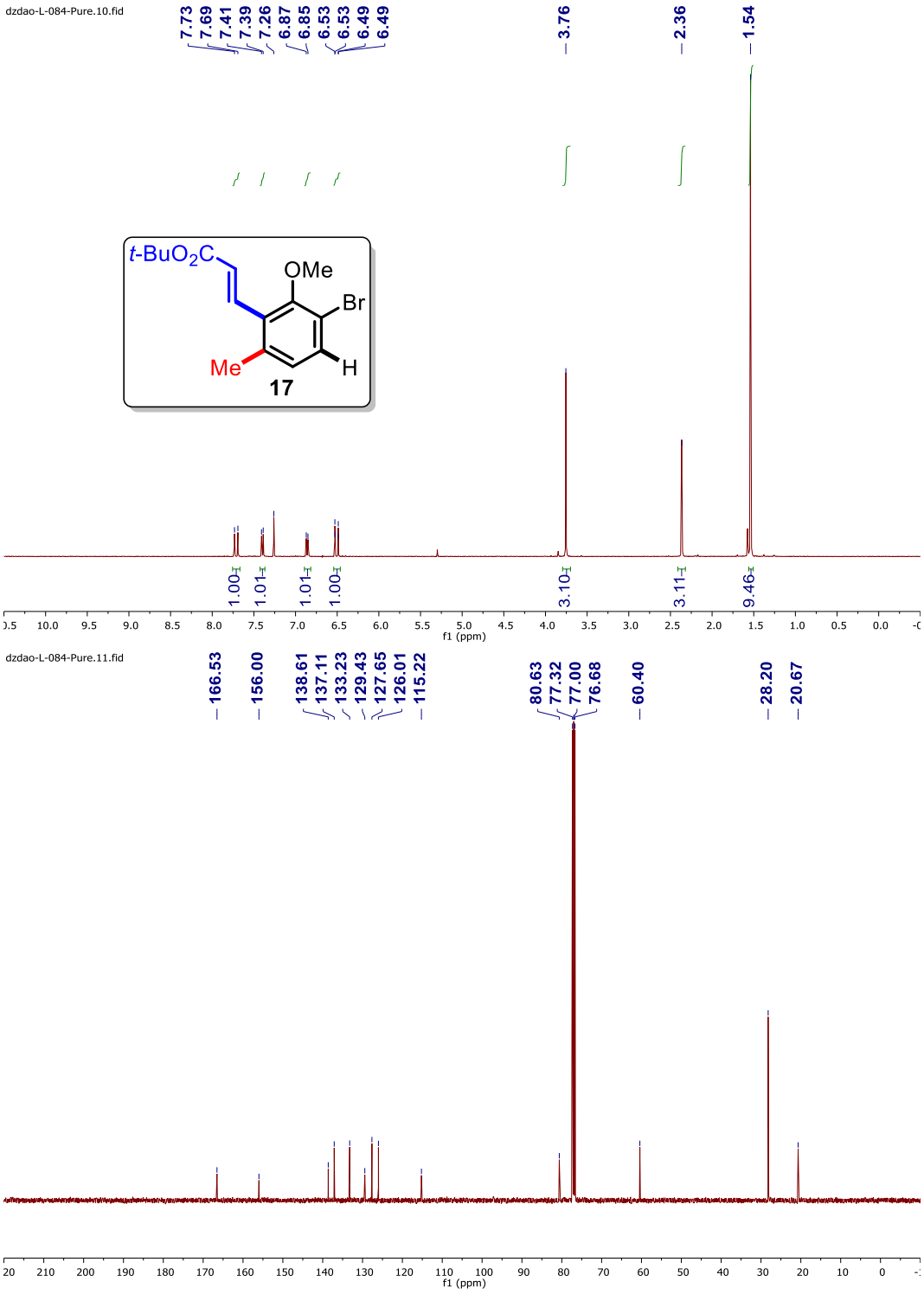


Figure 4.8 ^{1}H and ^{13}C NMR spectrum of compound **22**.

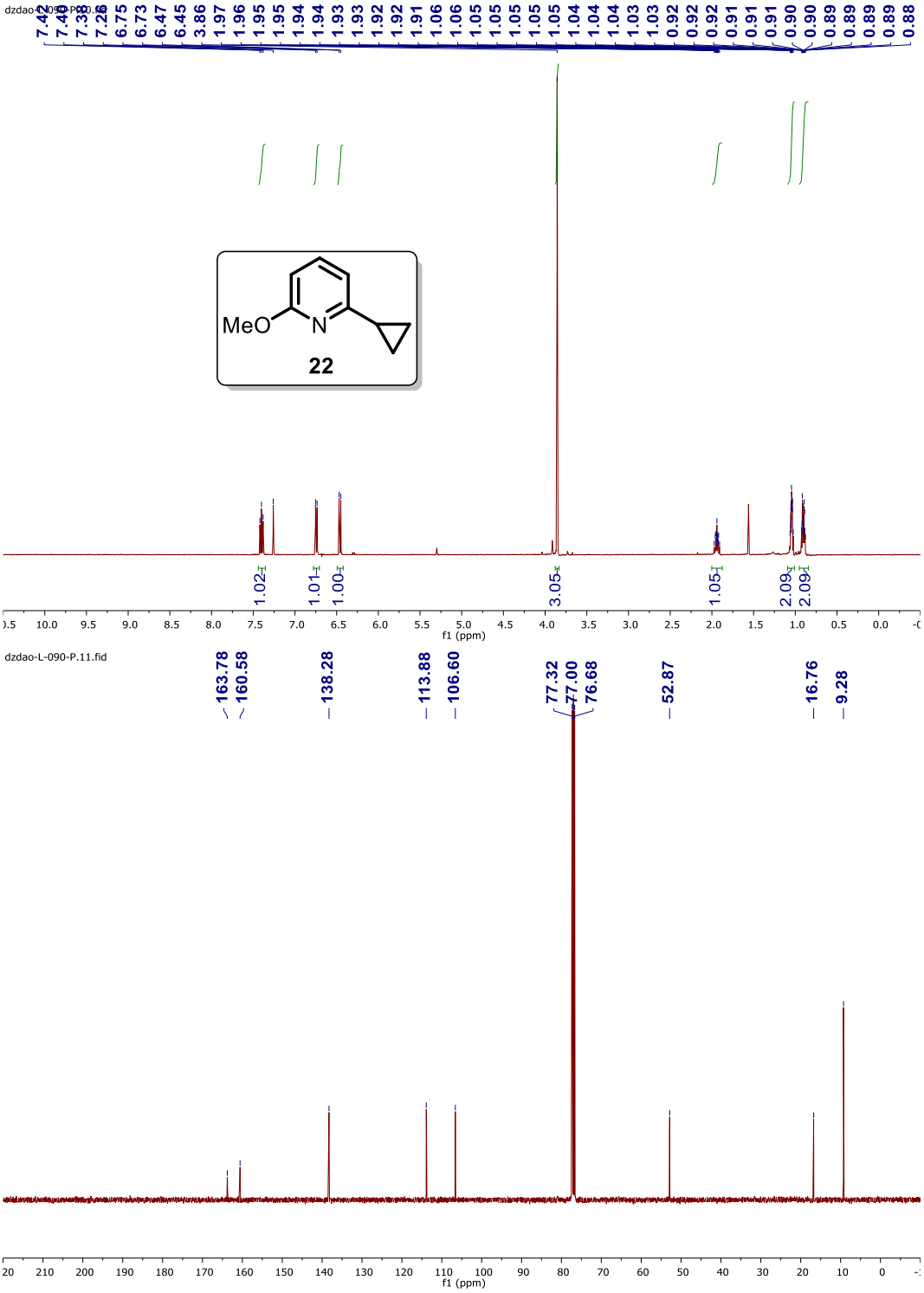


Figure 4.9 ^{1}H NMR spectrum of compound **23**.

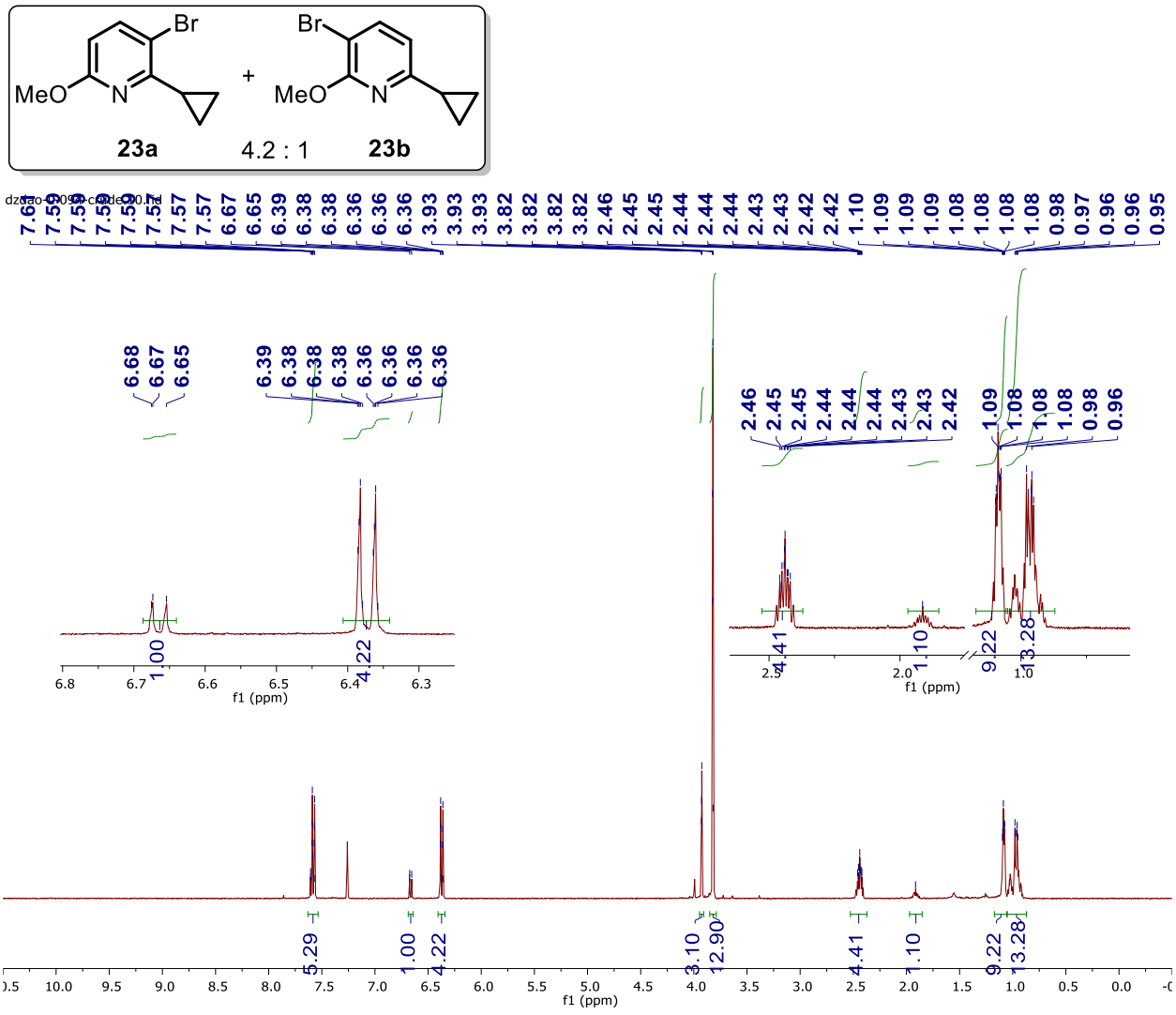


Figure 4.10 ^{1}H and ^{13}C NMR spectrum of compound **2c**.

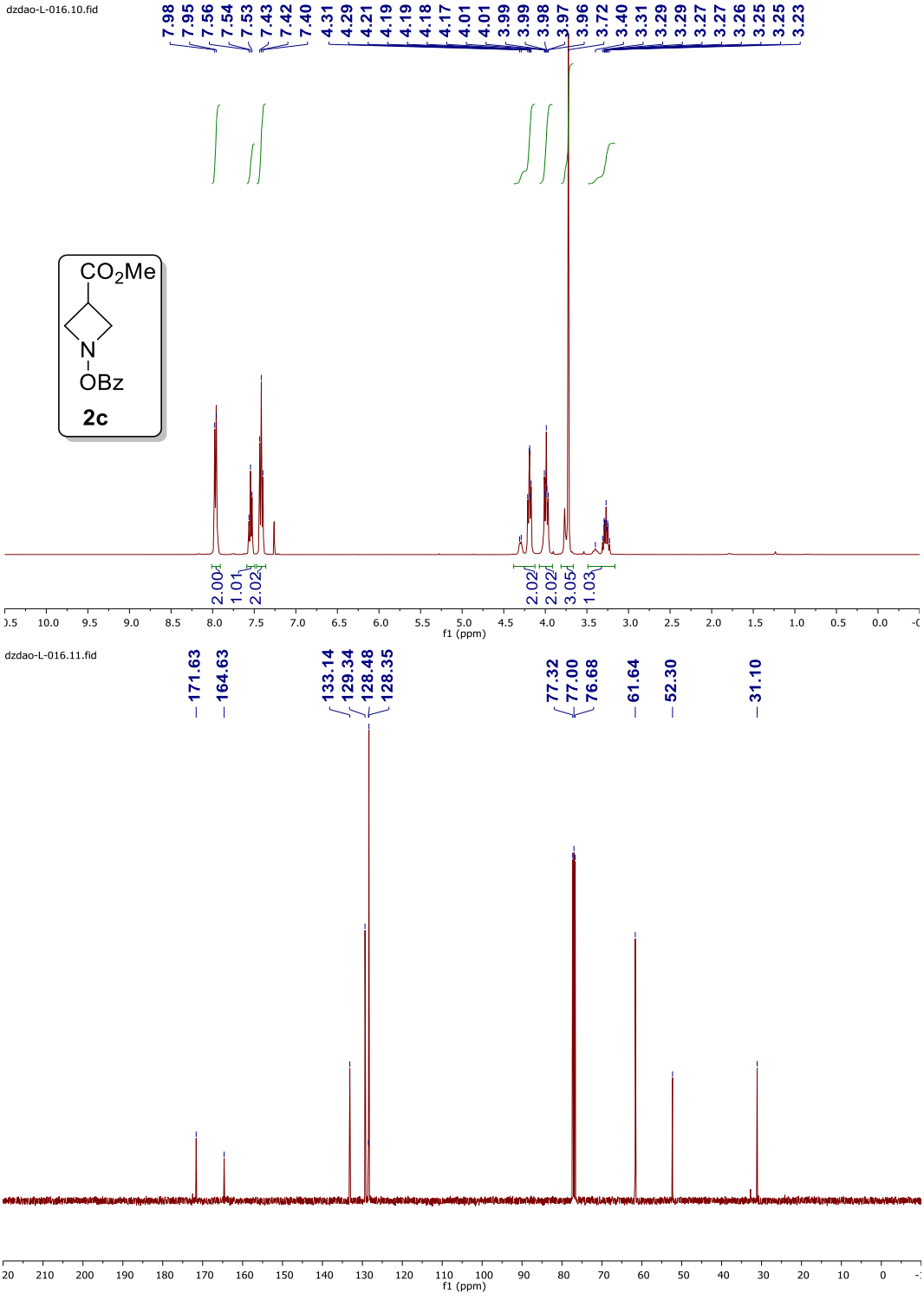


Figure 4.11 ^{1}H and ^{13}C NMR spectrum of compound **2h**.

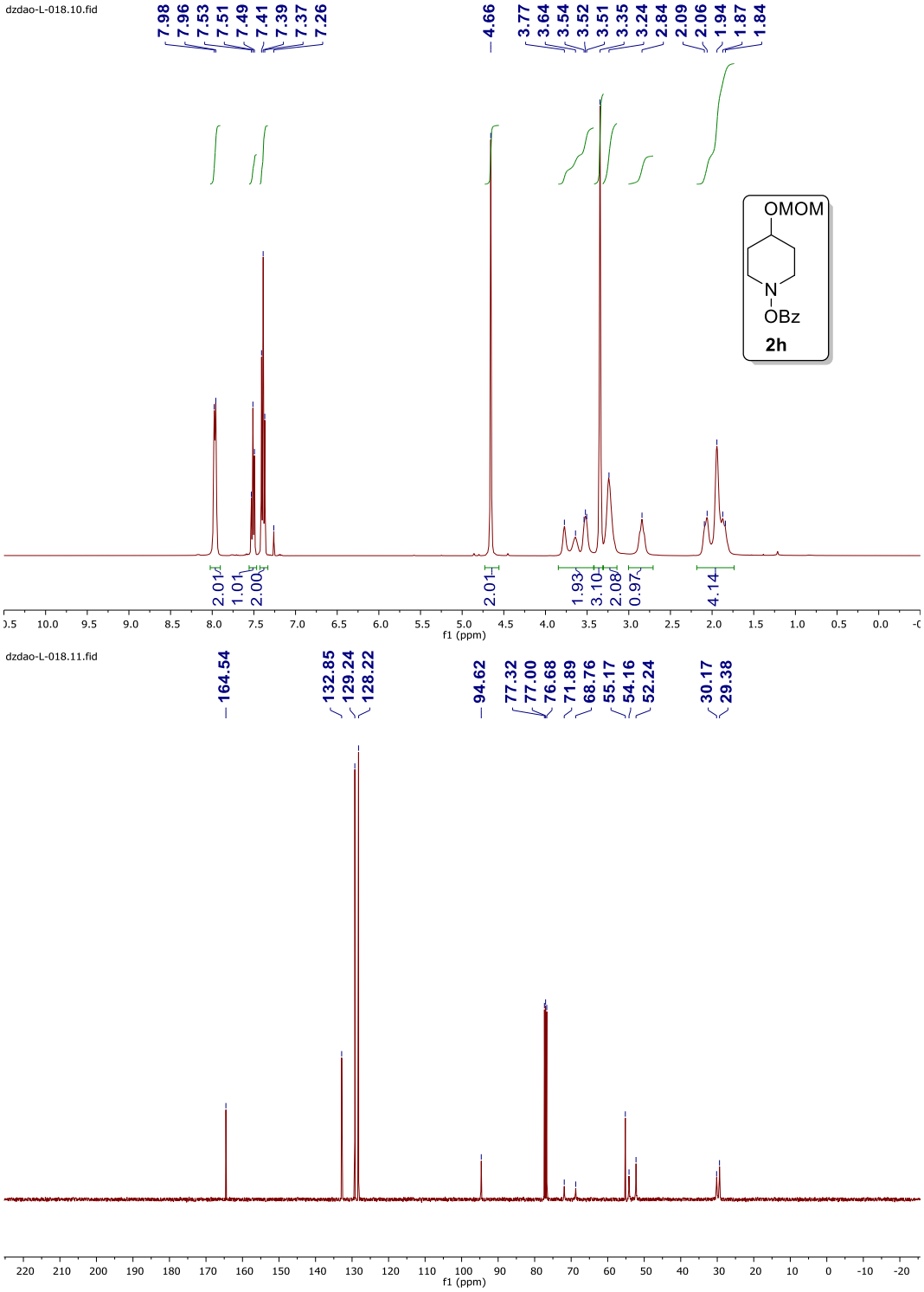


Figure 4.12 ^{1}H and ^{13}C NMR spectrum of compound **2k**.

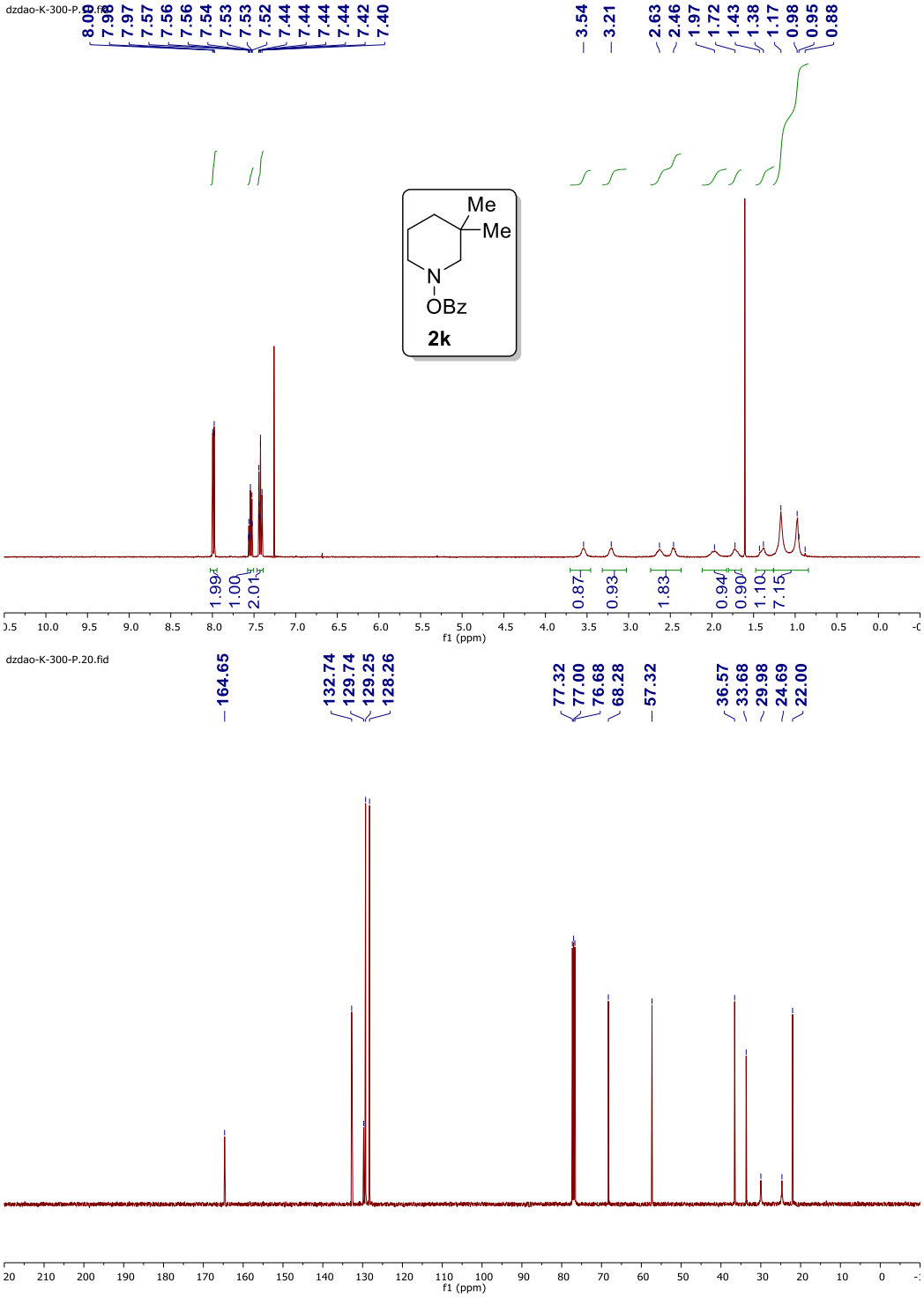


Figure 4.13 ^{1}H and ^{13}C NMR spectrum of compound **2n**.

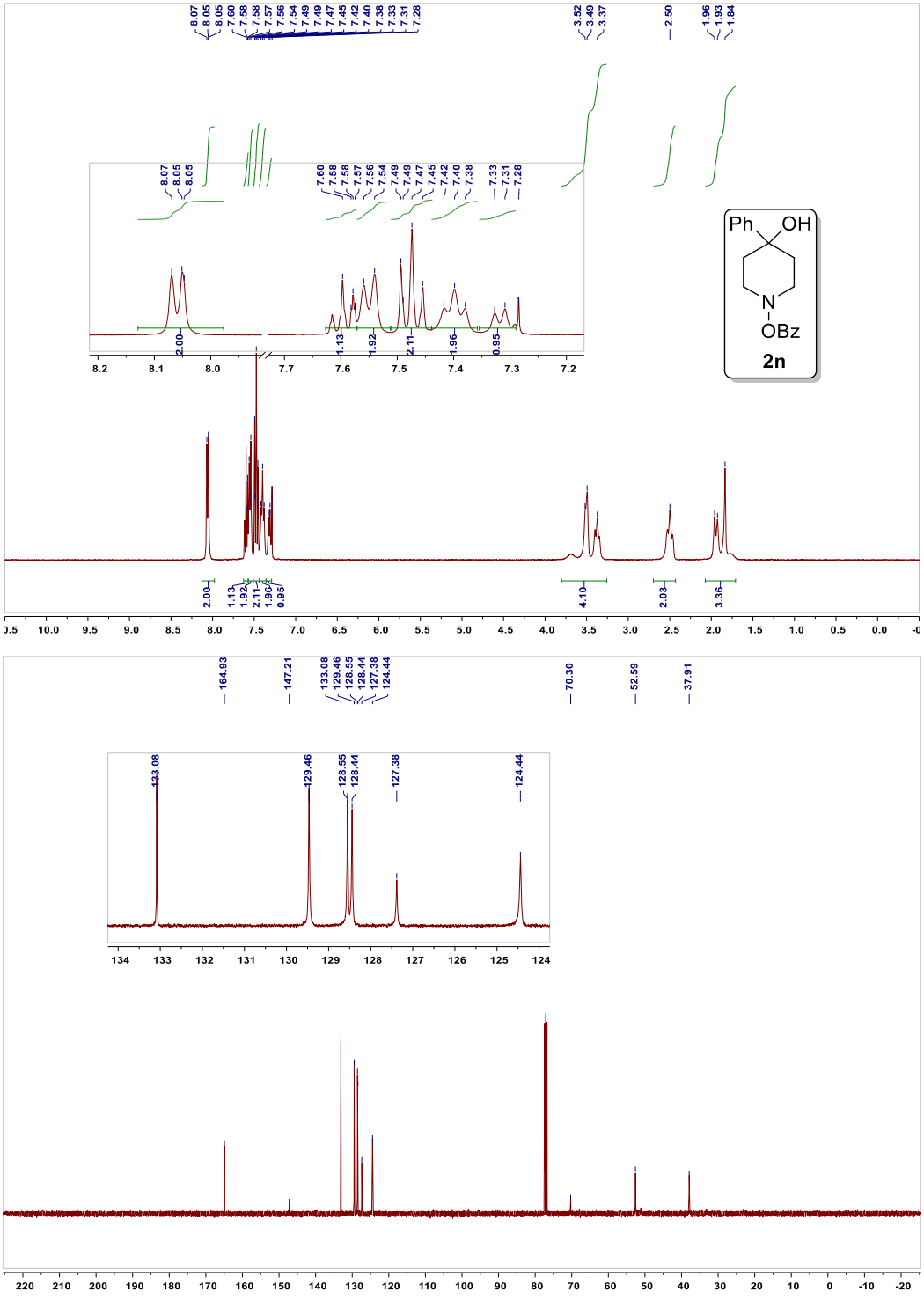


Figure 4.14 ^{1}H and ^{13}C NMR spectrum of compound **24e**.

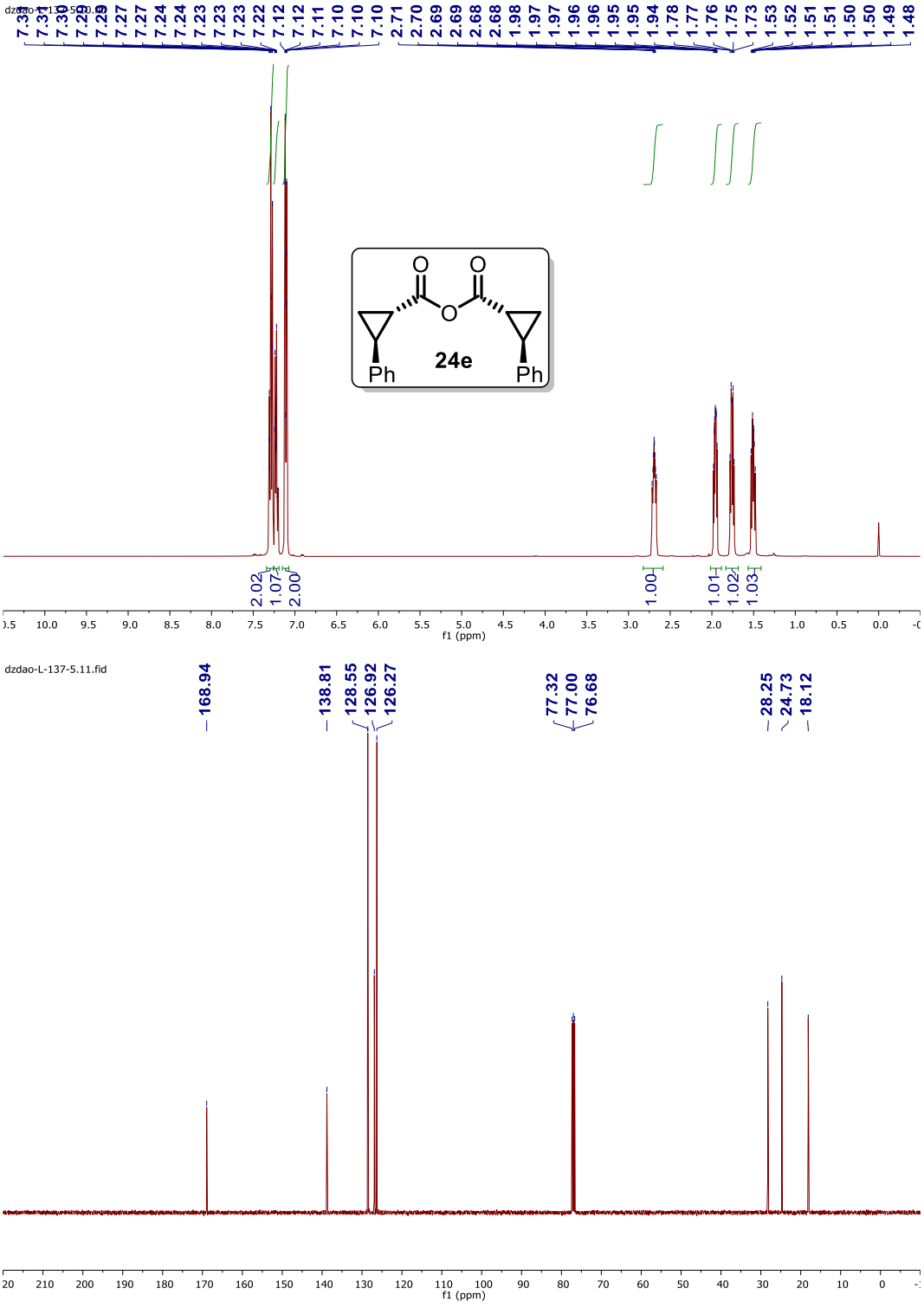


Figure 4.15 ^{1}H and ^{13}C NMR spectrum of compound **24f**.

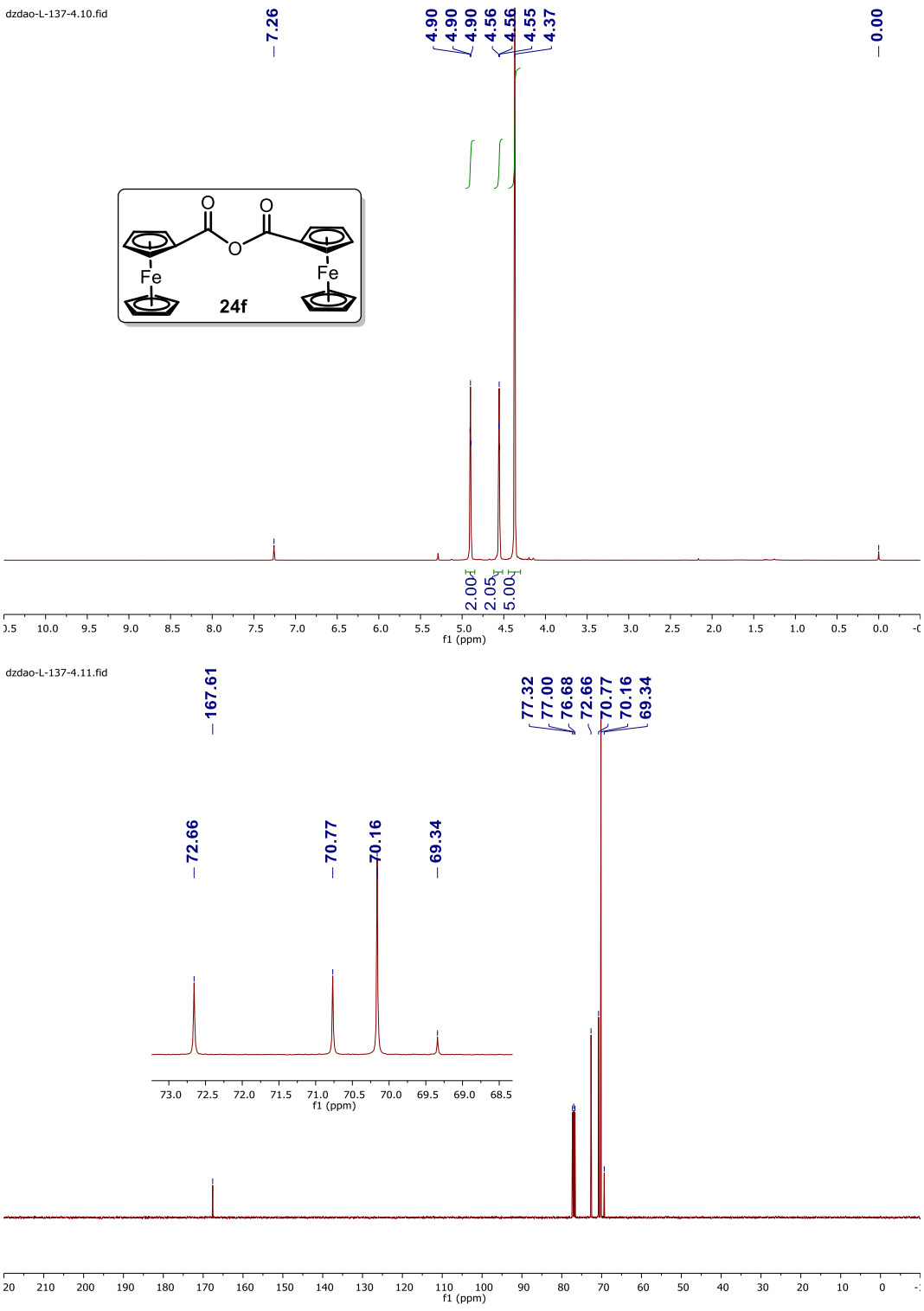


Figure 4.16 ^{1}H and ^{13}C NMR spectrum of compound **4a**.

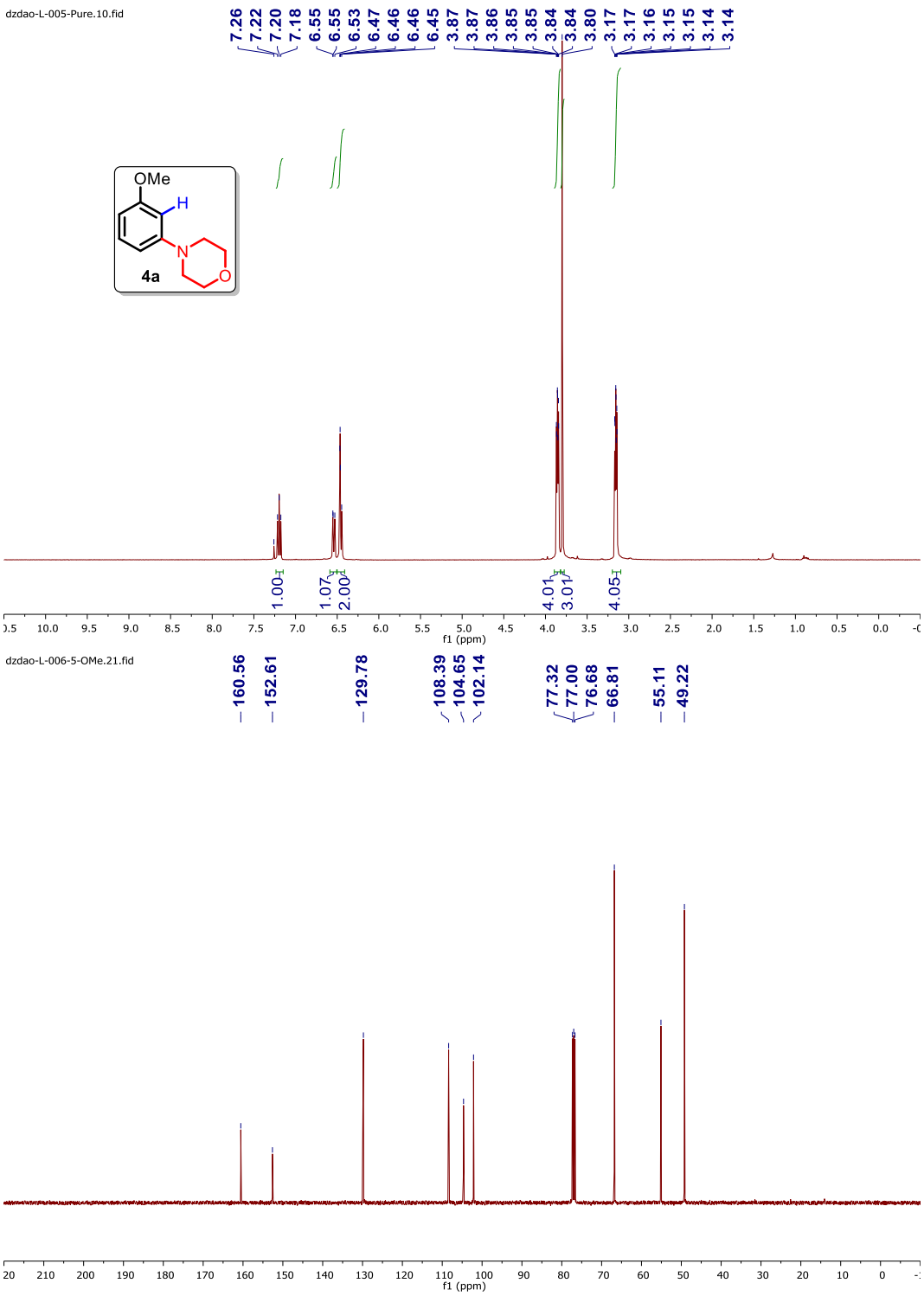


Figure 4.17 ^{1}H and ^{13}C NMR spectrum of compound **4a'**.

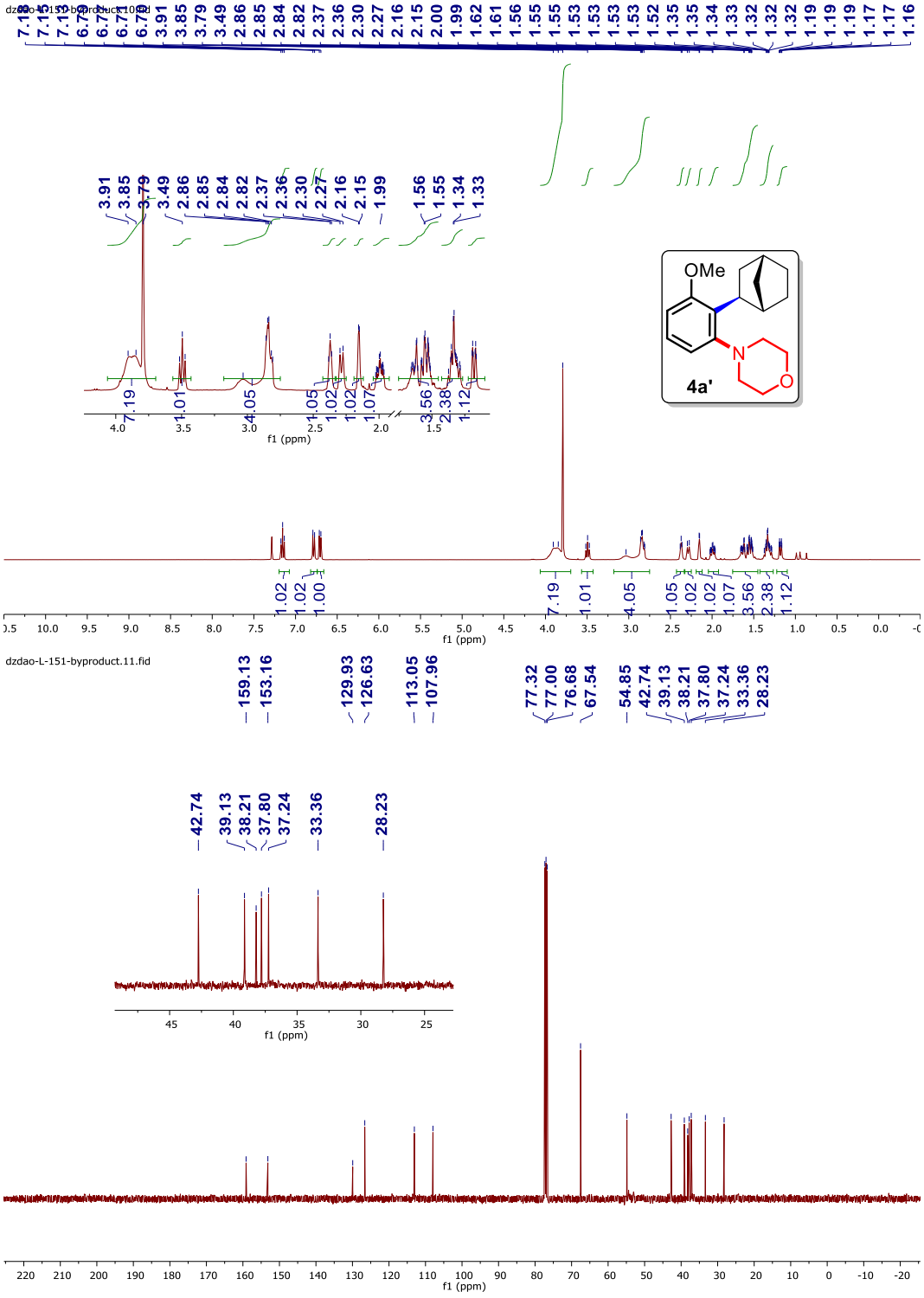


Figure 4.18 ^{1}H and ^{13}C NMR spectrum of compound **4b**.

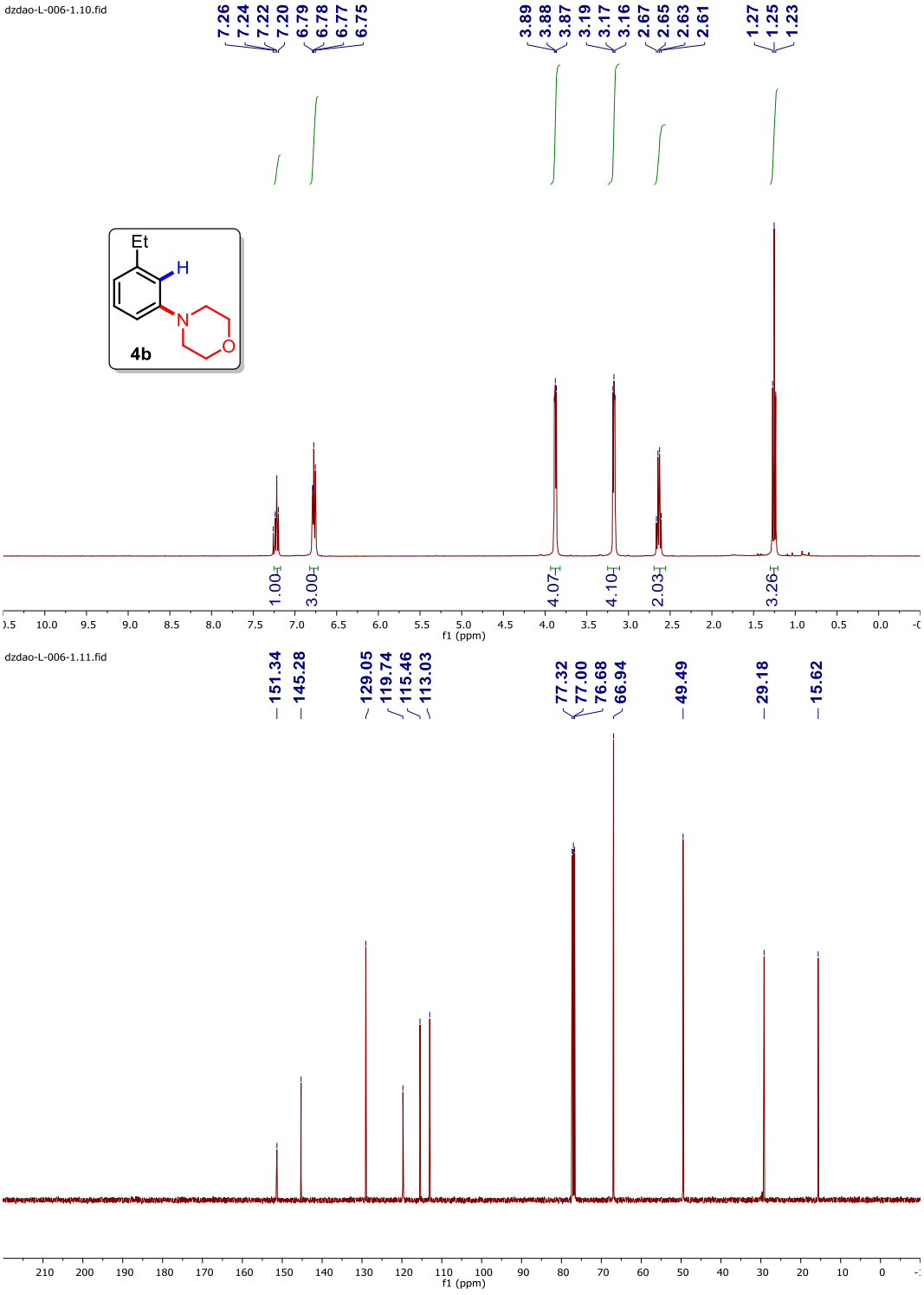


Figure 4.19 ^{1}H and ^{13}C NMR spectrum of compound **4c**.

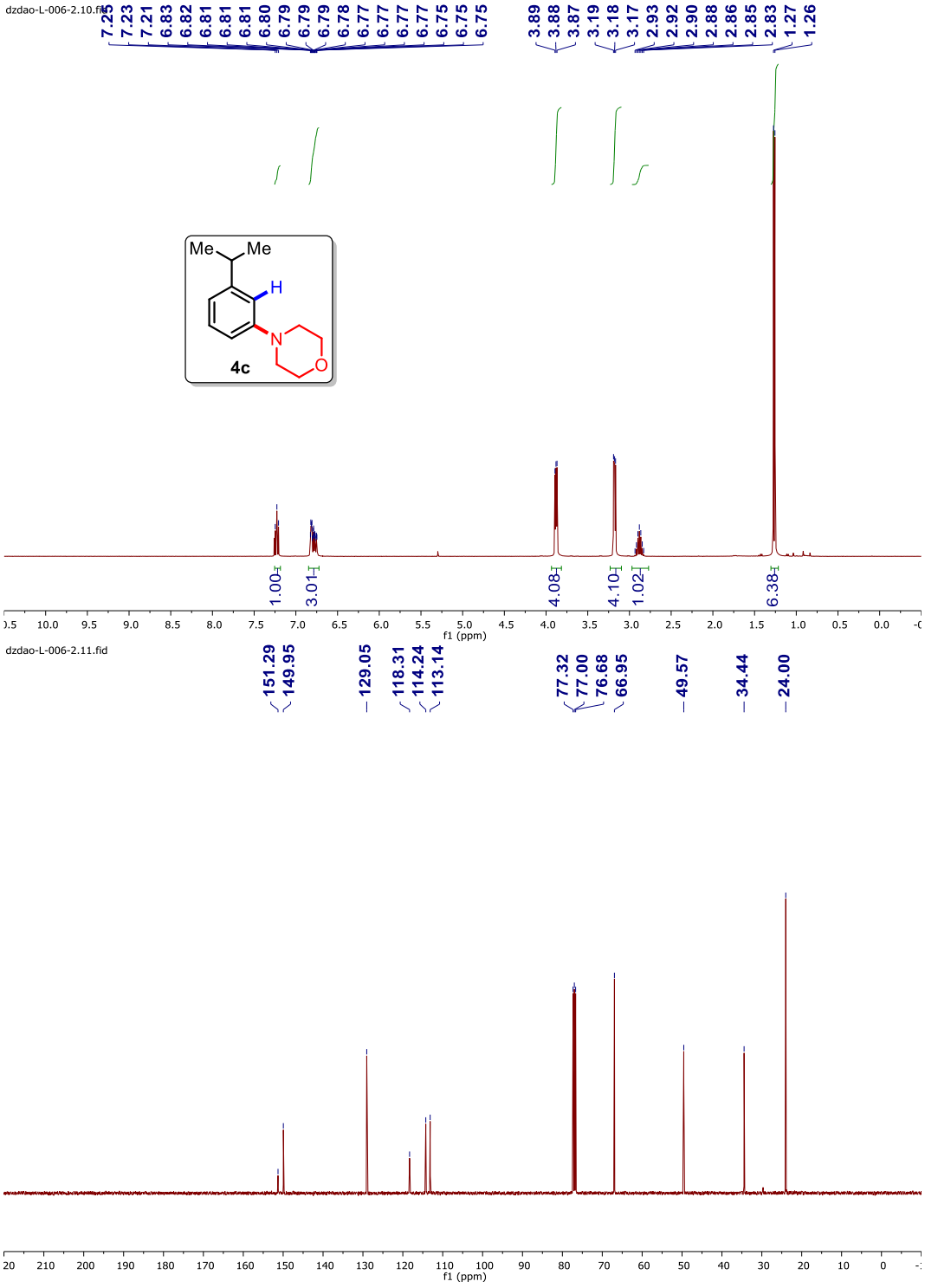


Figure 4.20 ^{1}H and ^{13}C NMR spectrum of compound **4d**.

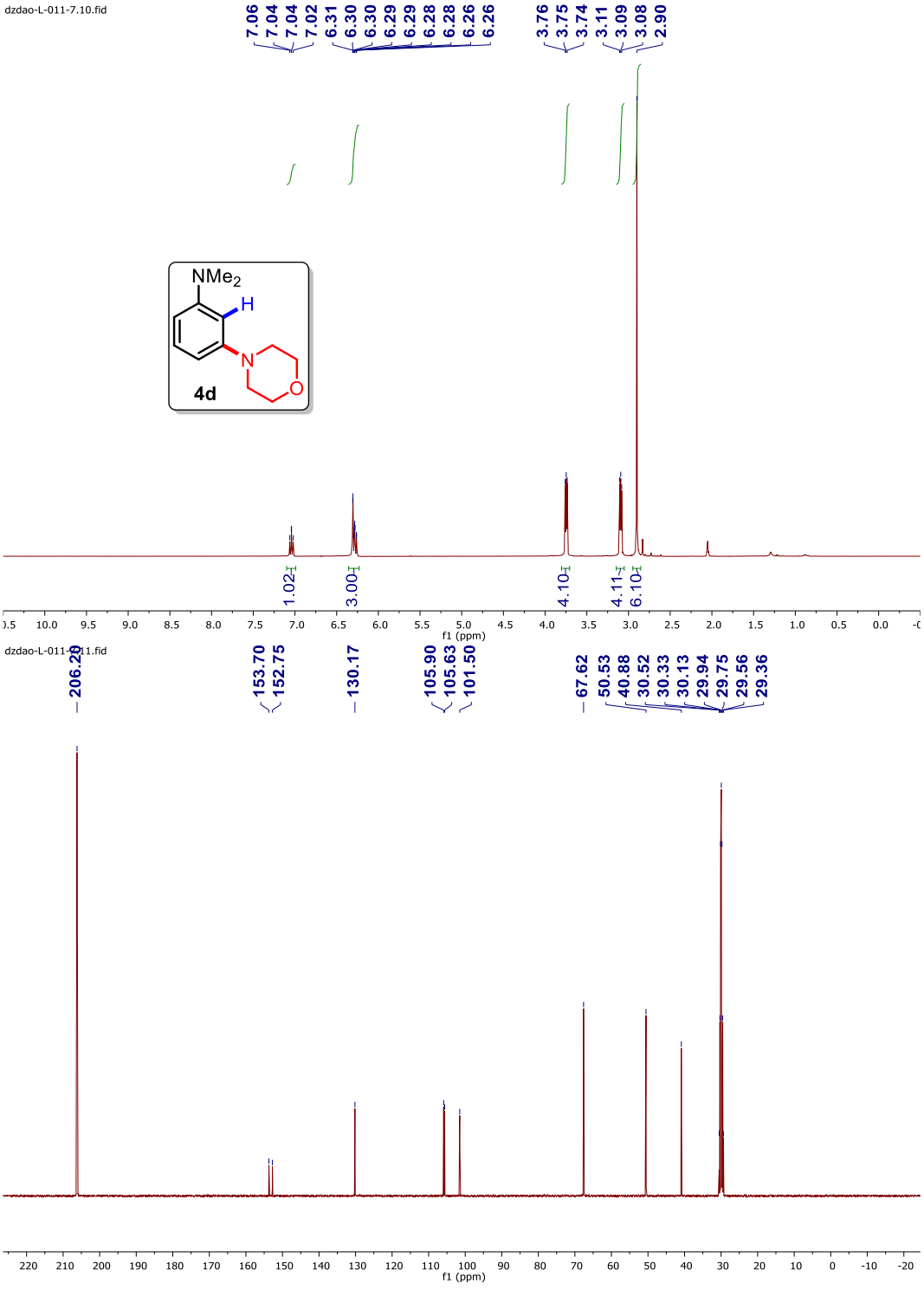


Figure 4.21 ^{1}H and ^{13}C NMR spectrum of compound **4e**.

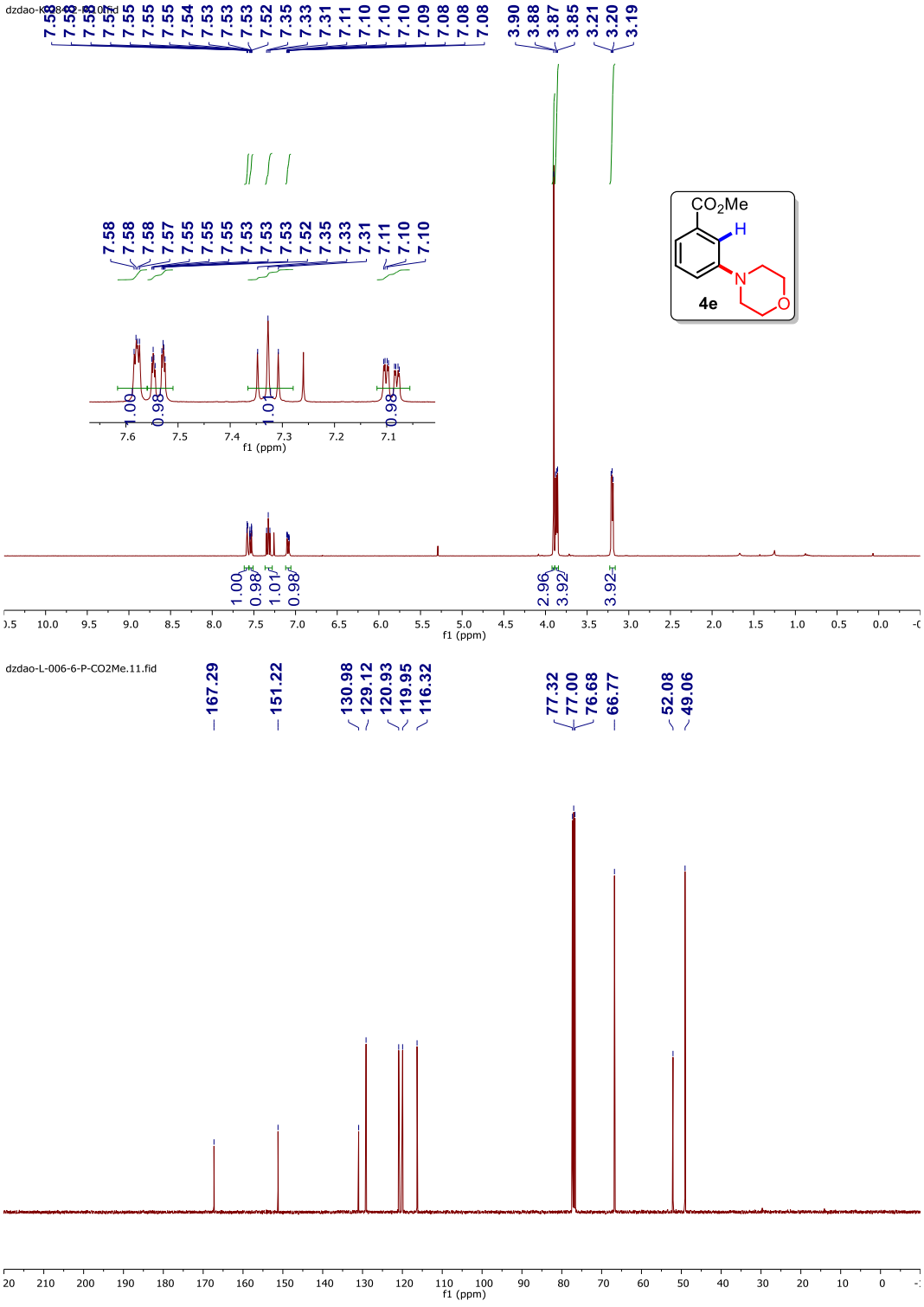


Figure 4.22 ^{1}H and ^{13}C NMR spectrum of compound **4f**.

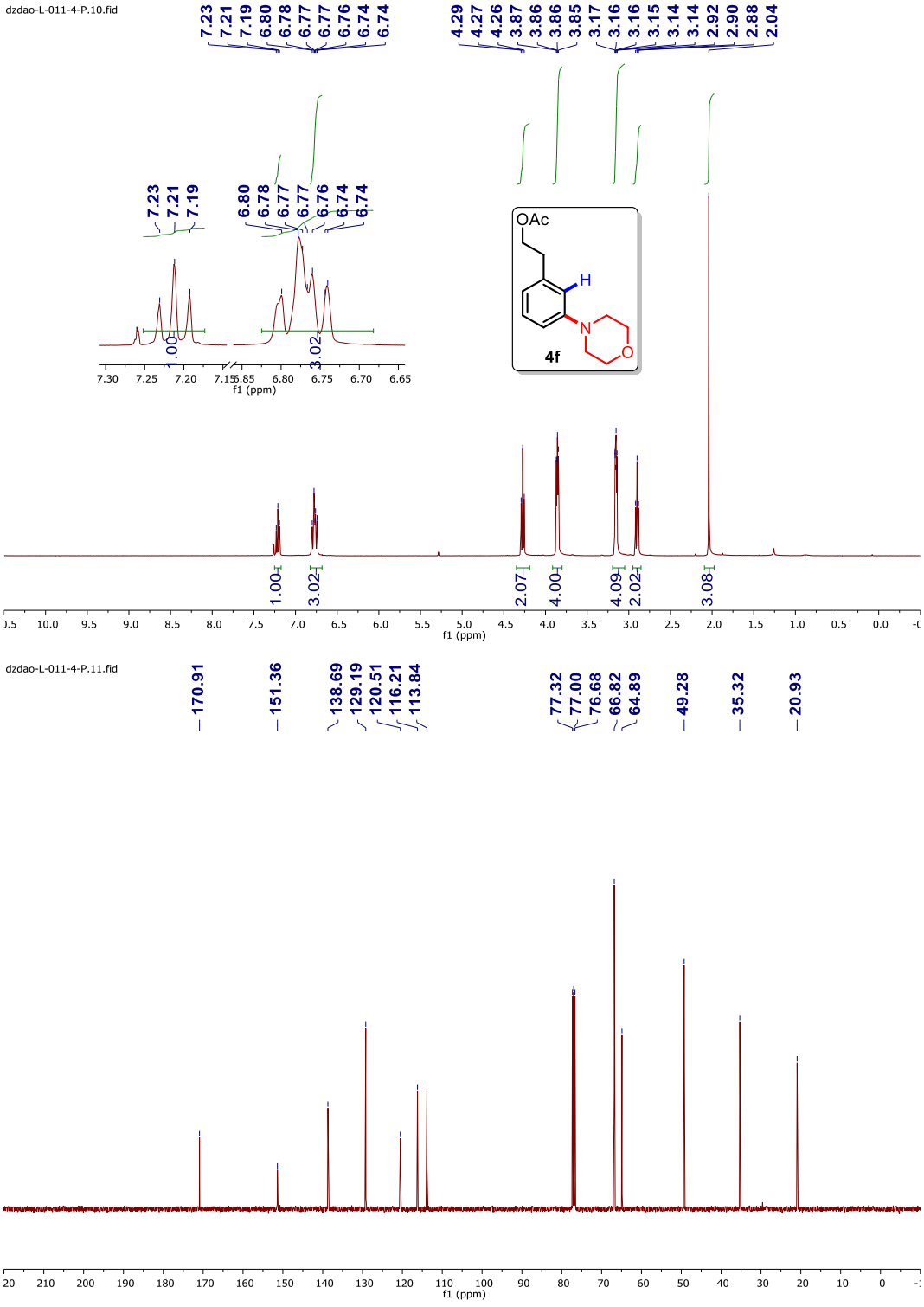


Figure 4.23 ^{1}H and ^{13}C NMR spectrum of compound **4g**.

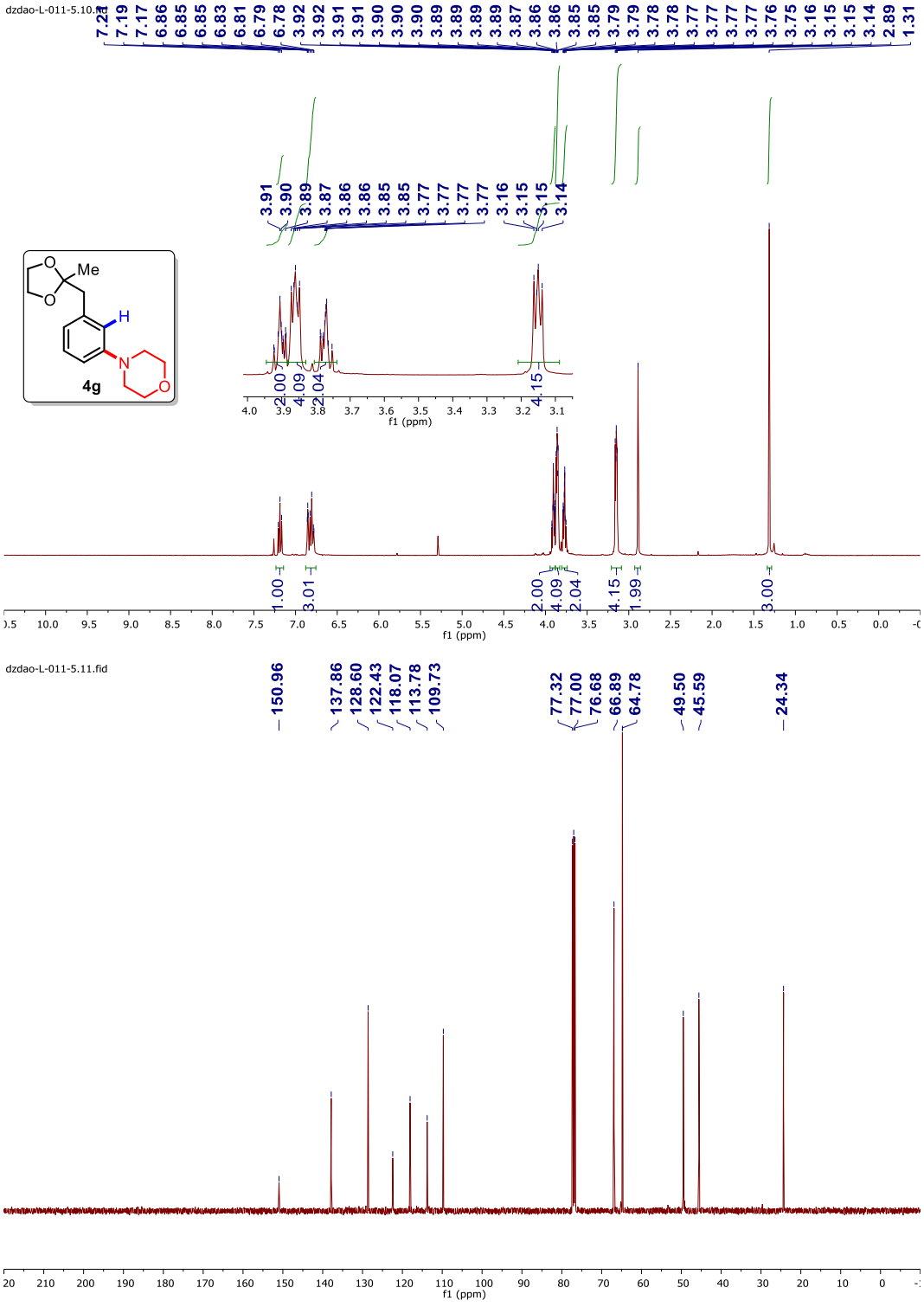


Figure 4.24 ^{1}H and ^{13}C NMR spectrum of compound **4h**.

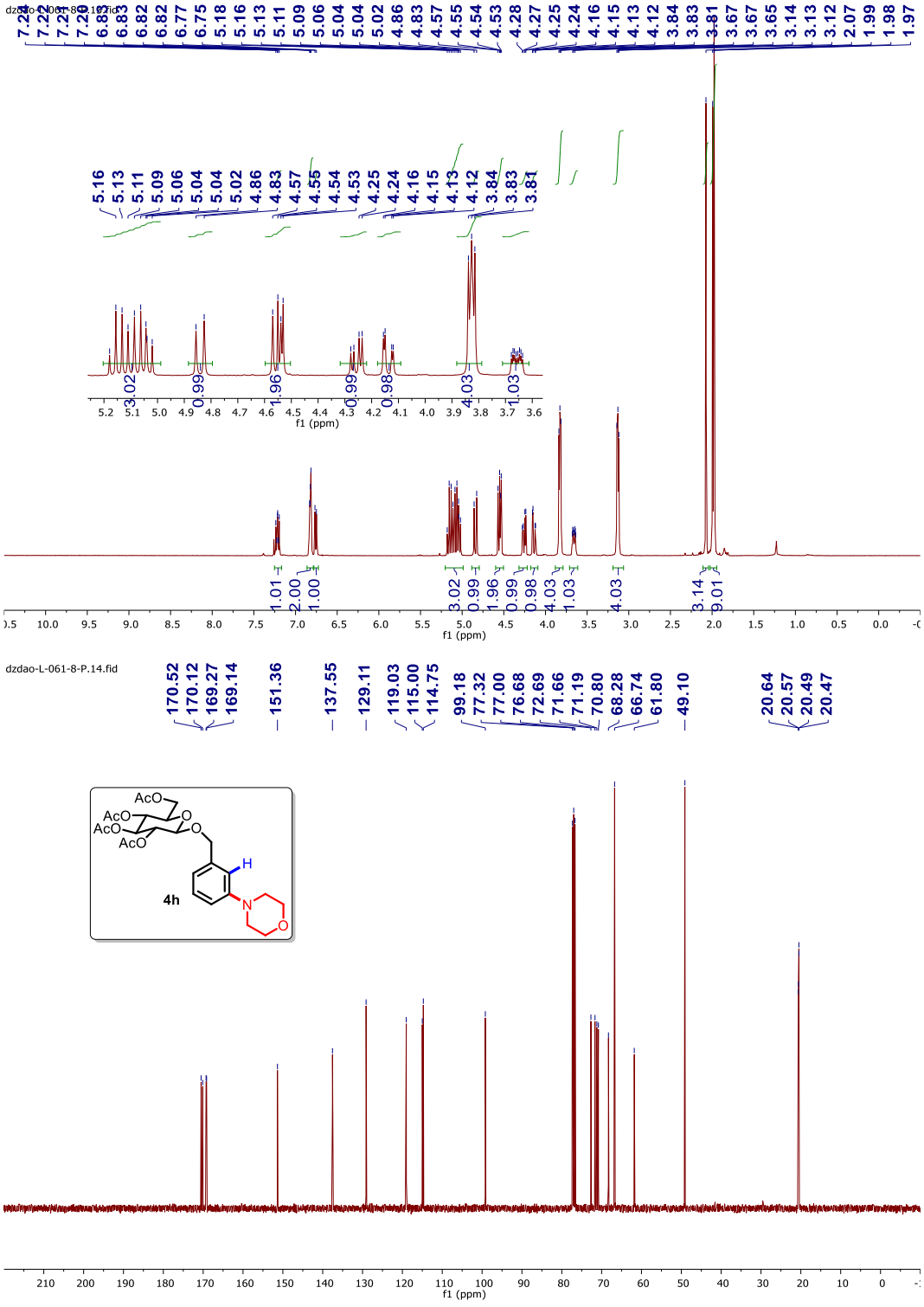


Figure 4.25 ^{1}H and ^{13}C NMR spectrum of compound **4i**.

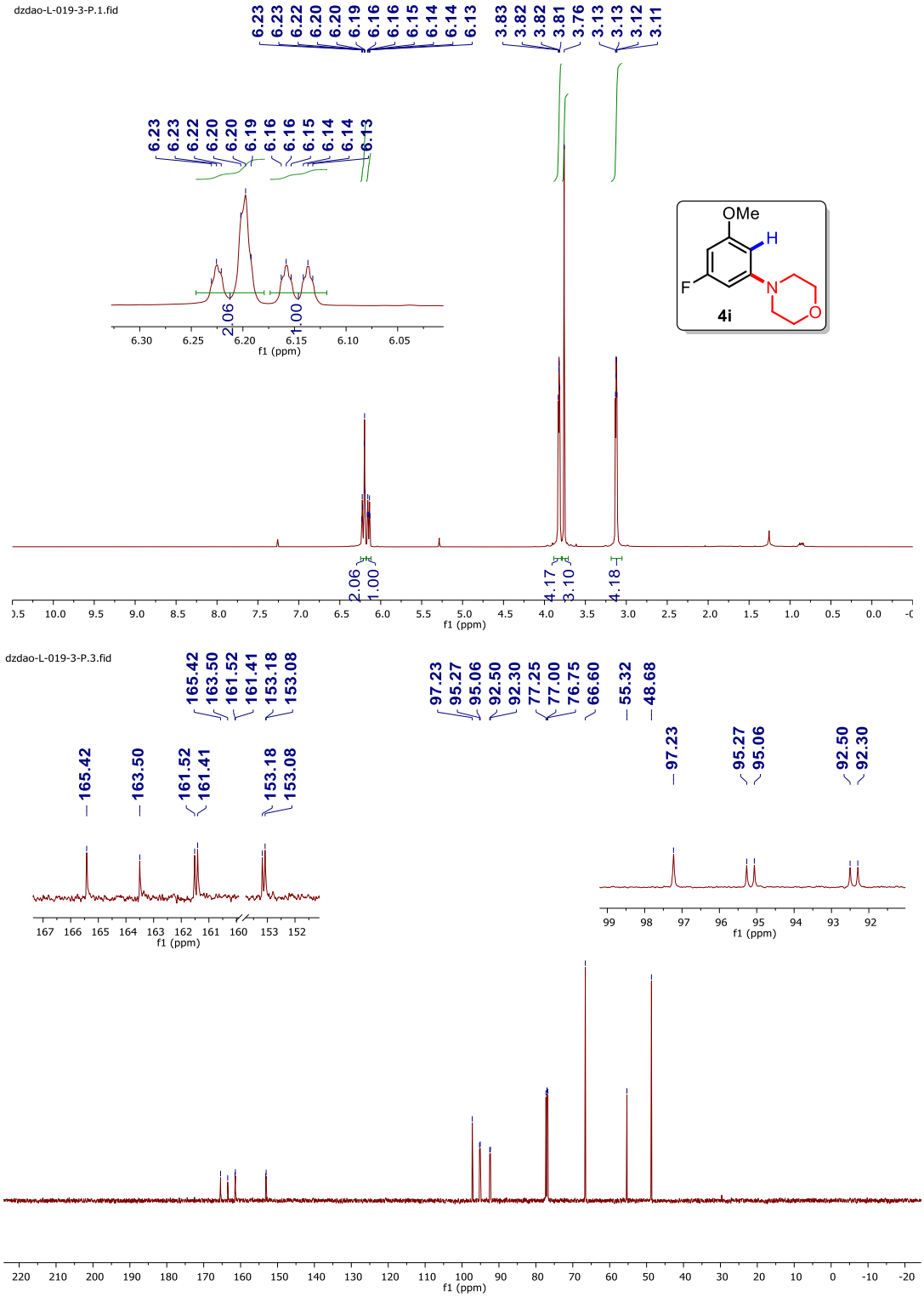


Figure 4.26 ^{19}F NMR spectrum of compound **4i**.

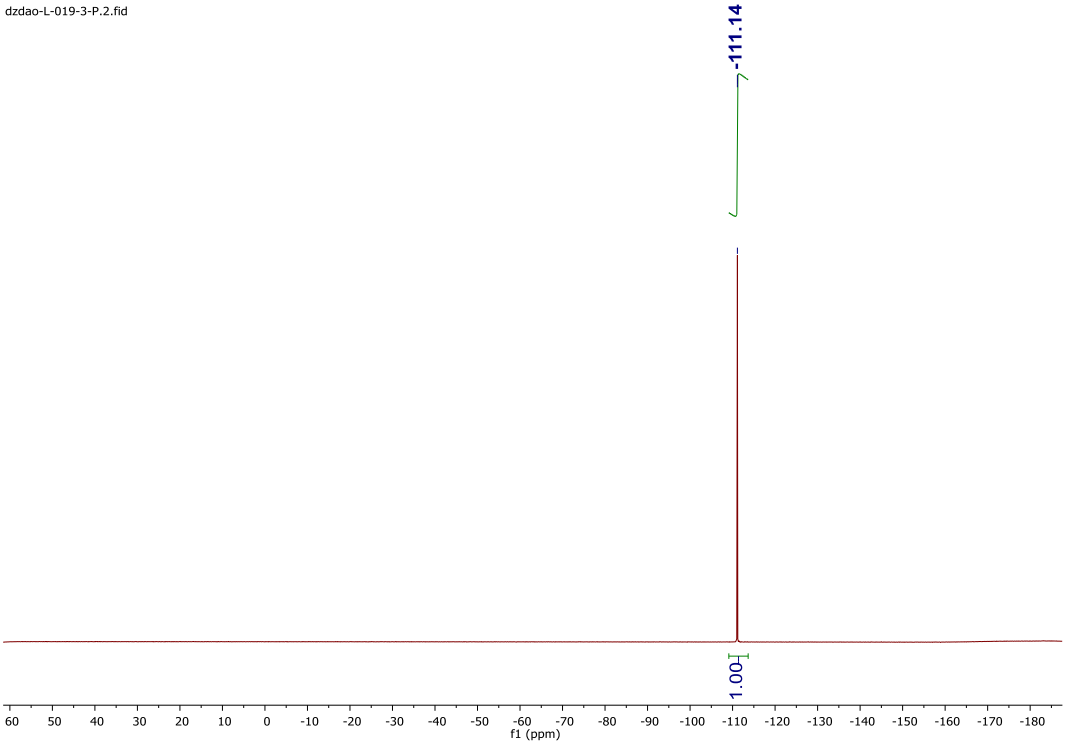


Figure 4.27 ^{1}H and ^{13}C NMR spectrum of compound **4j**.

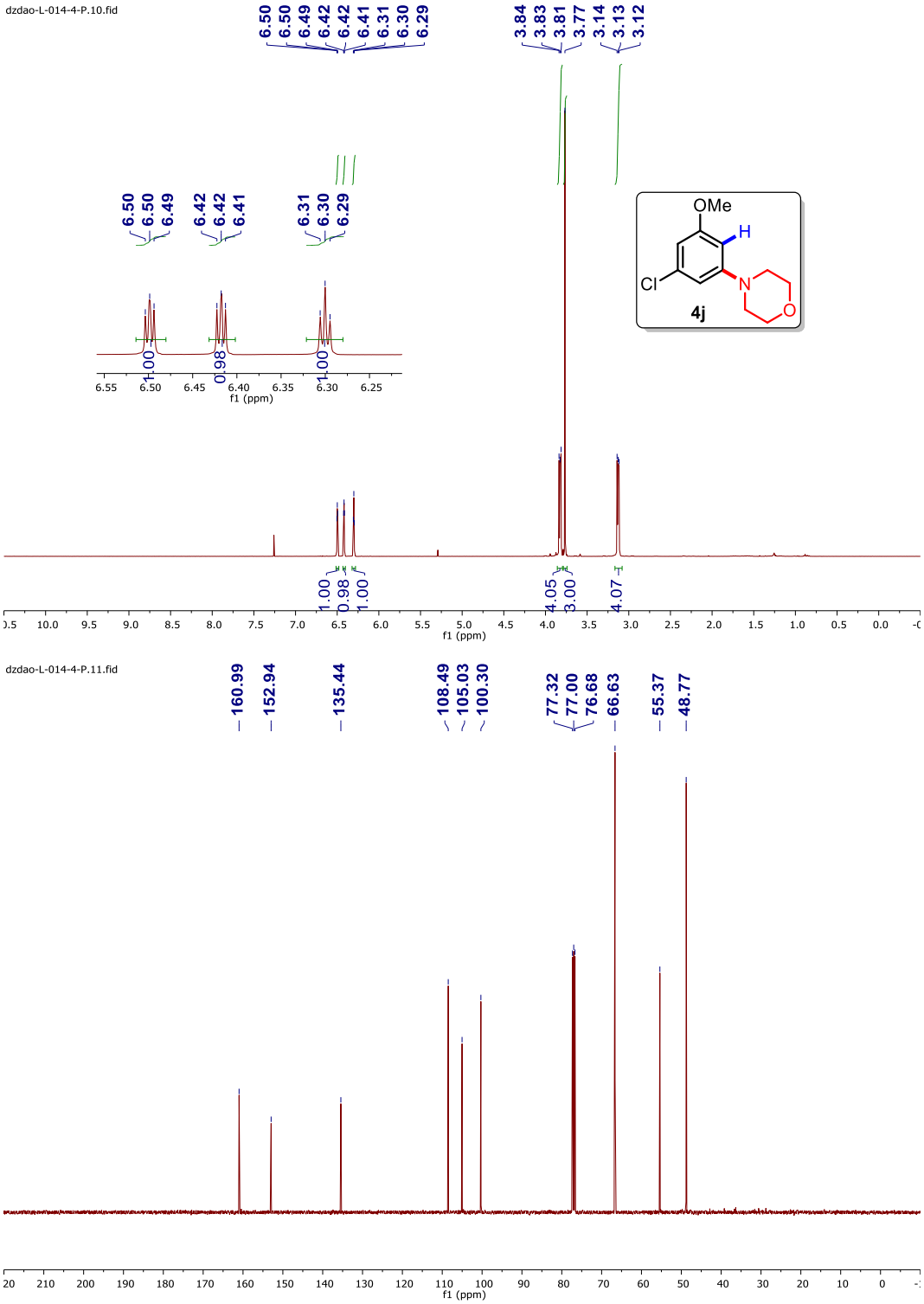


Figure 4.28 ^{1}H and ^{13}C NMR spectrum of compound **4k**.

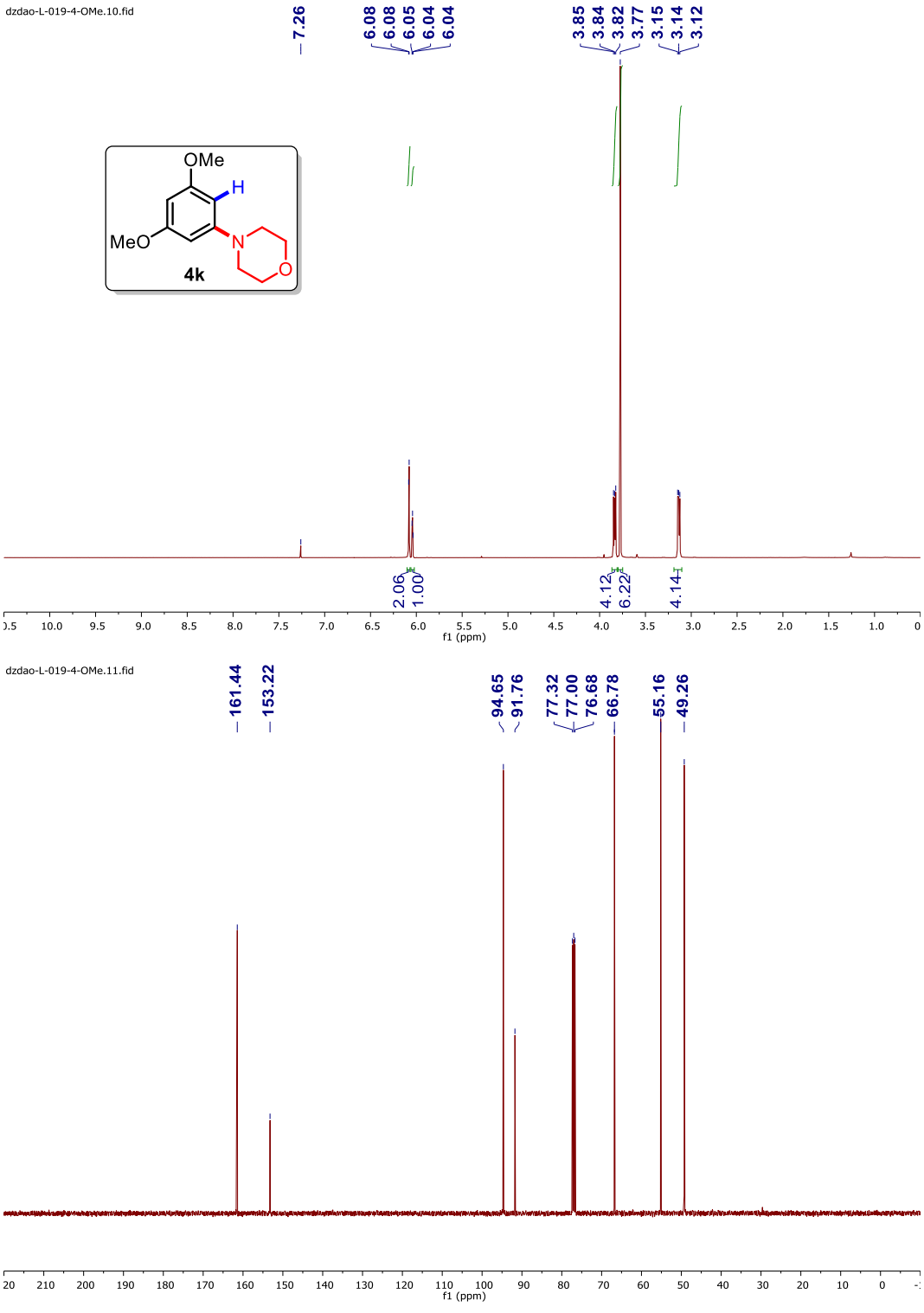


Figure 4.29 ^{1}H and ^{13}C NMR spectrum of compound **4l**.

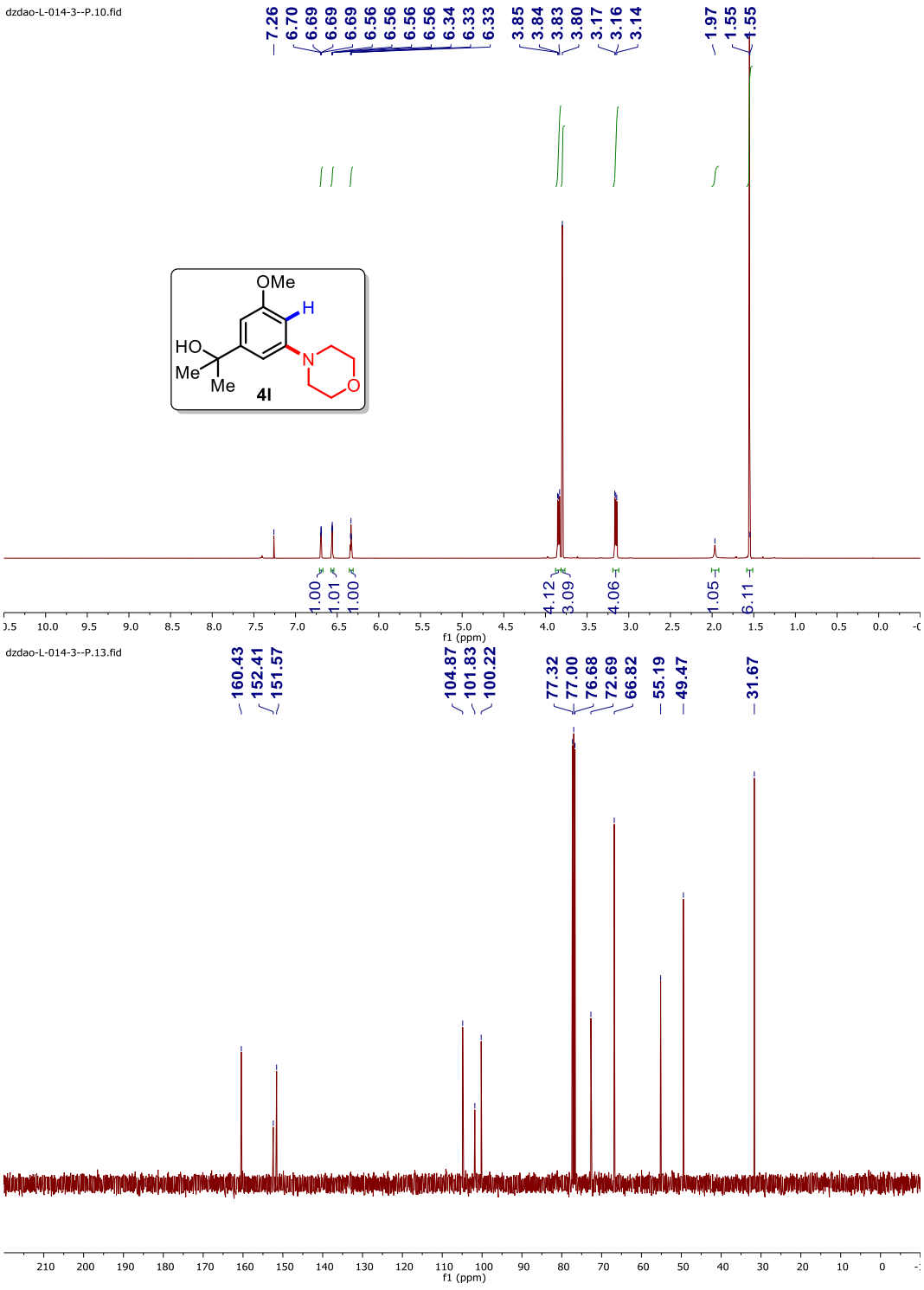


Figure 4.30 ^{1}H and ^{13}C NMR spectrum of compound **4m**.

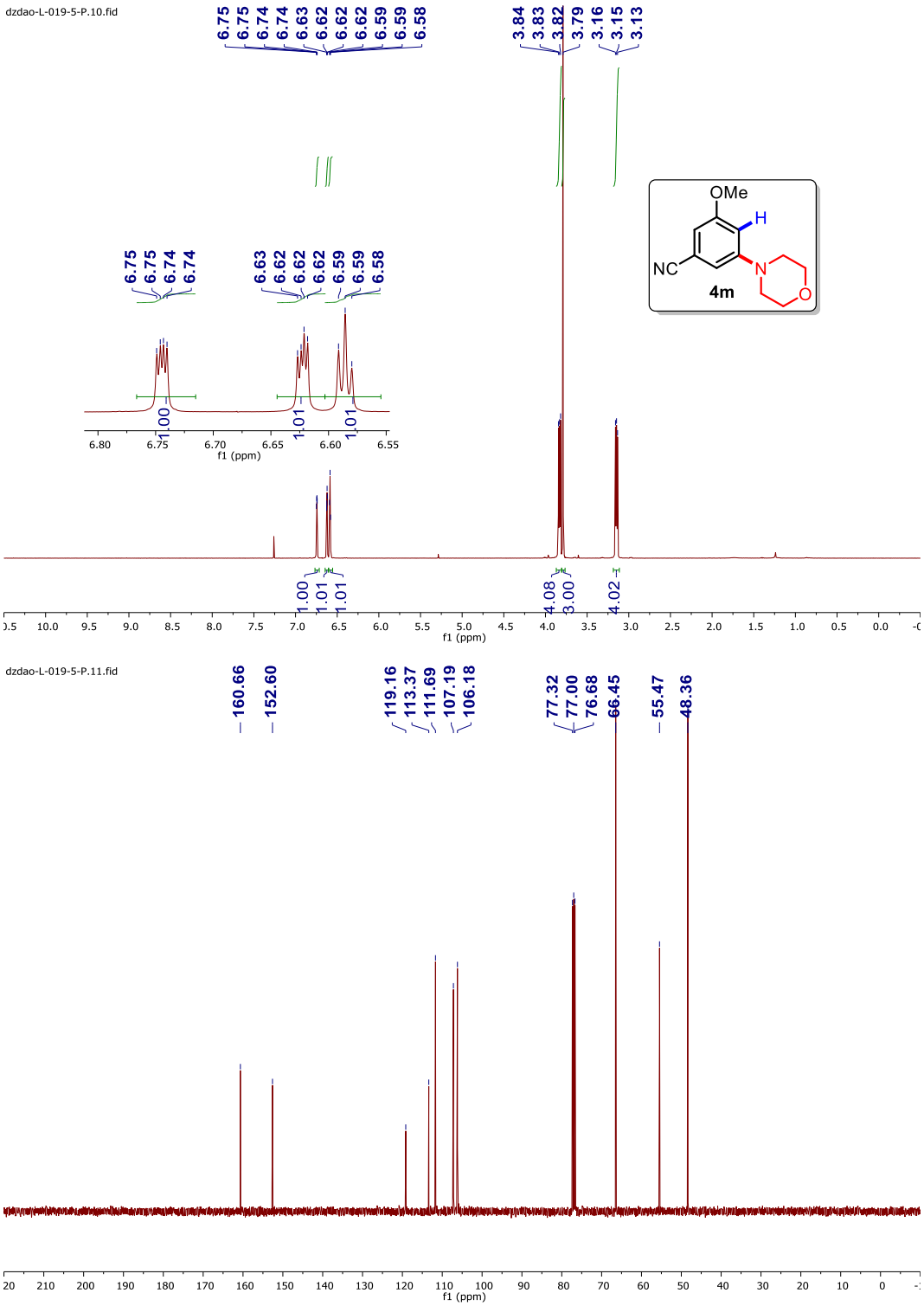


Figure 4.31 ^{1}H and ^{13}C NMR spectrum of compound **4n**.

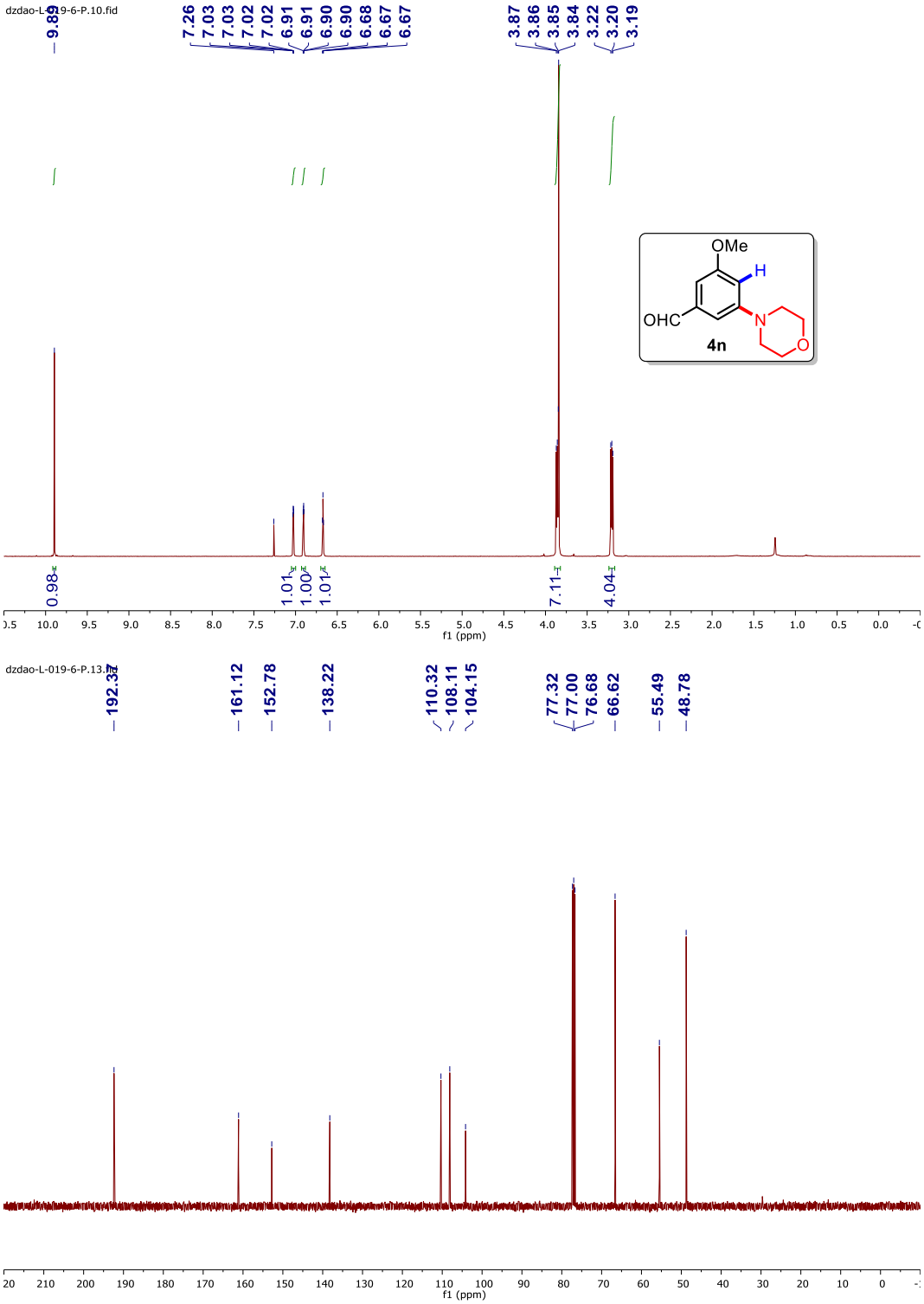


Figure 4.32 ^{1}H and ^{13}C NMR spectrum of compound **4o**.

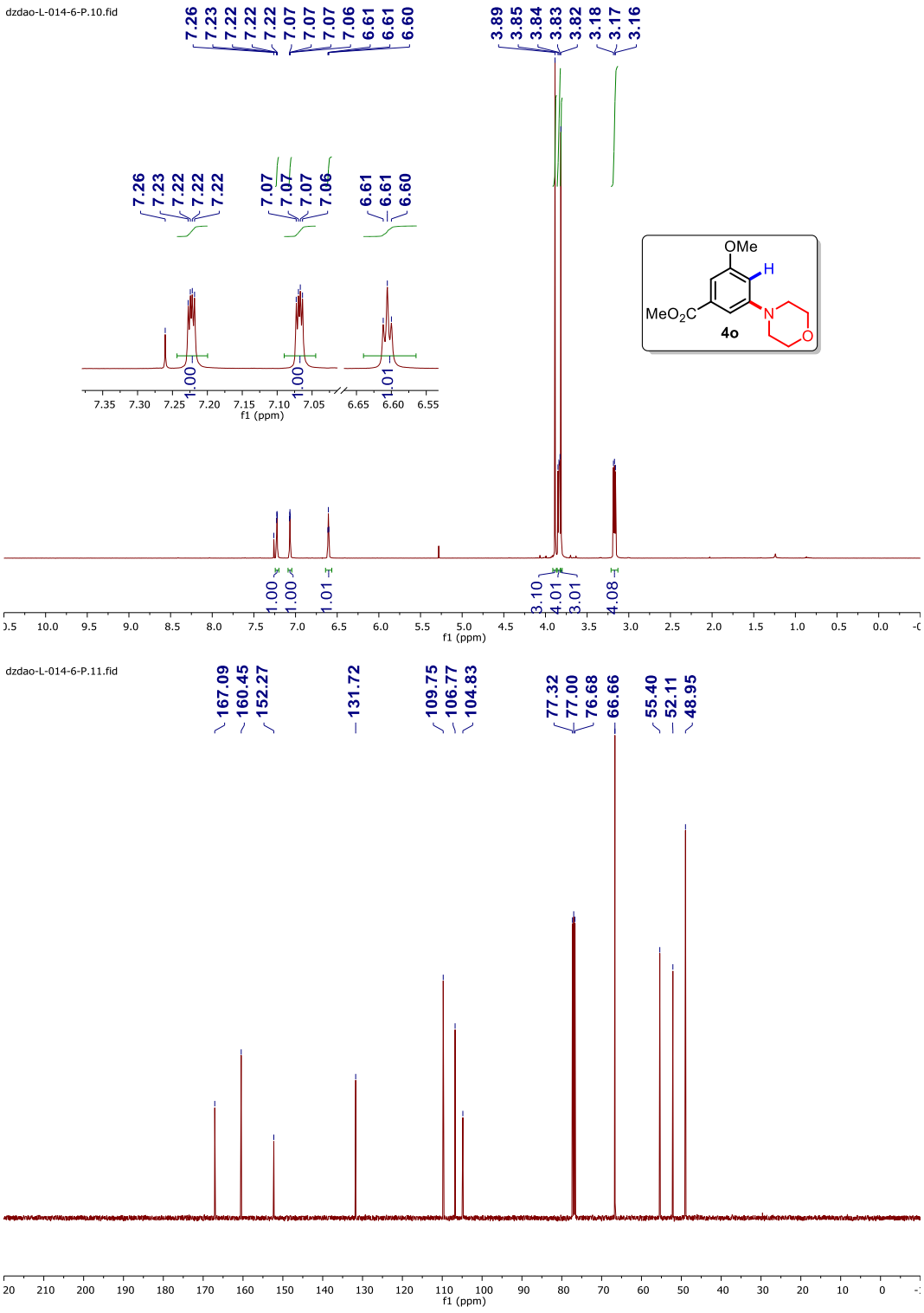


Figure 4.33 ^{1}H and ^{13}C NMR spectrum of compound **4p**.

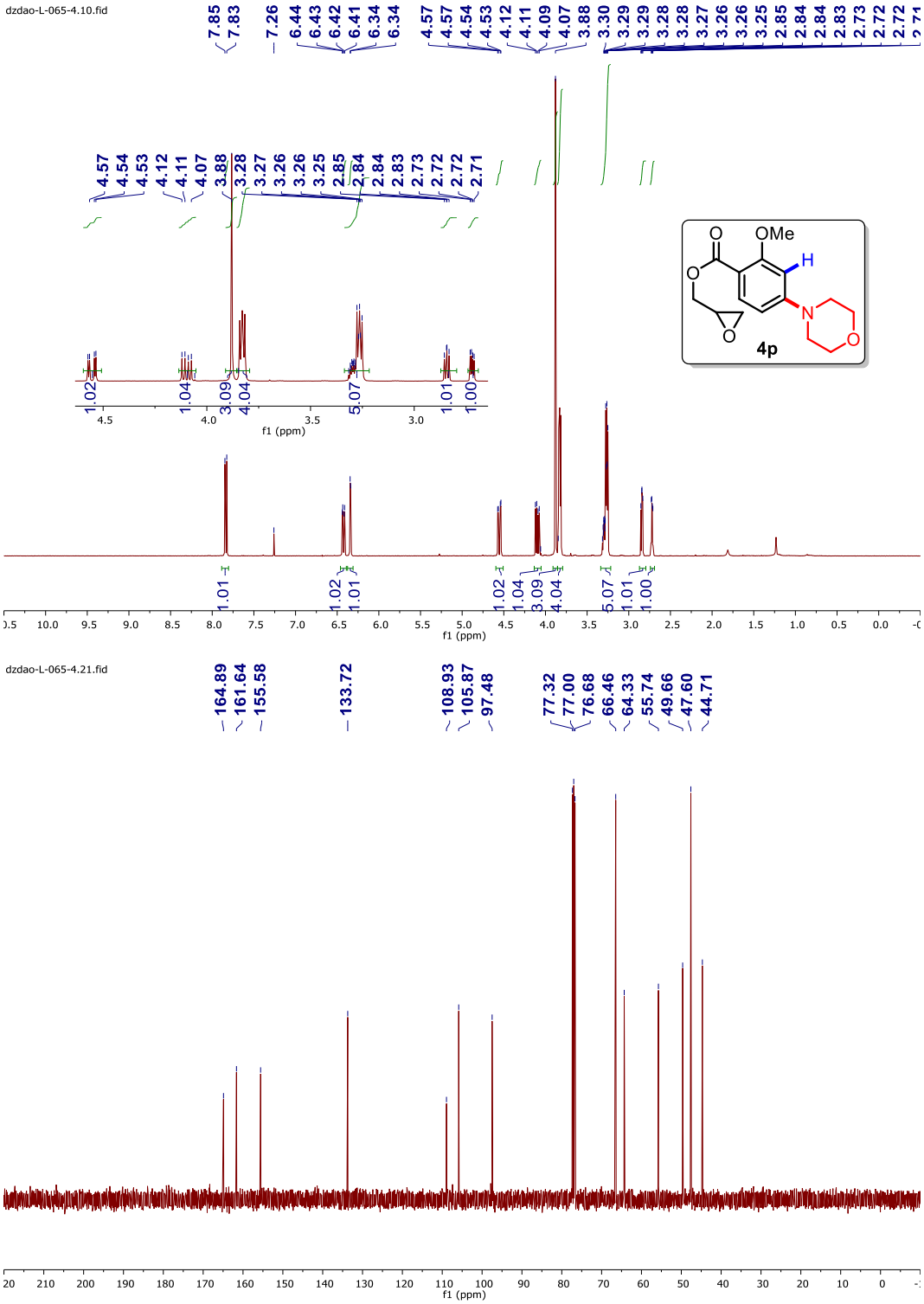


Figure 4.34 ^{1}H and ^{13}C NMR spectrum of compound **4q**.

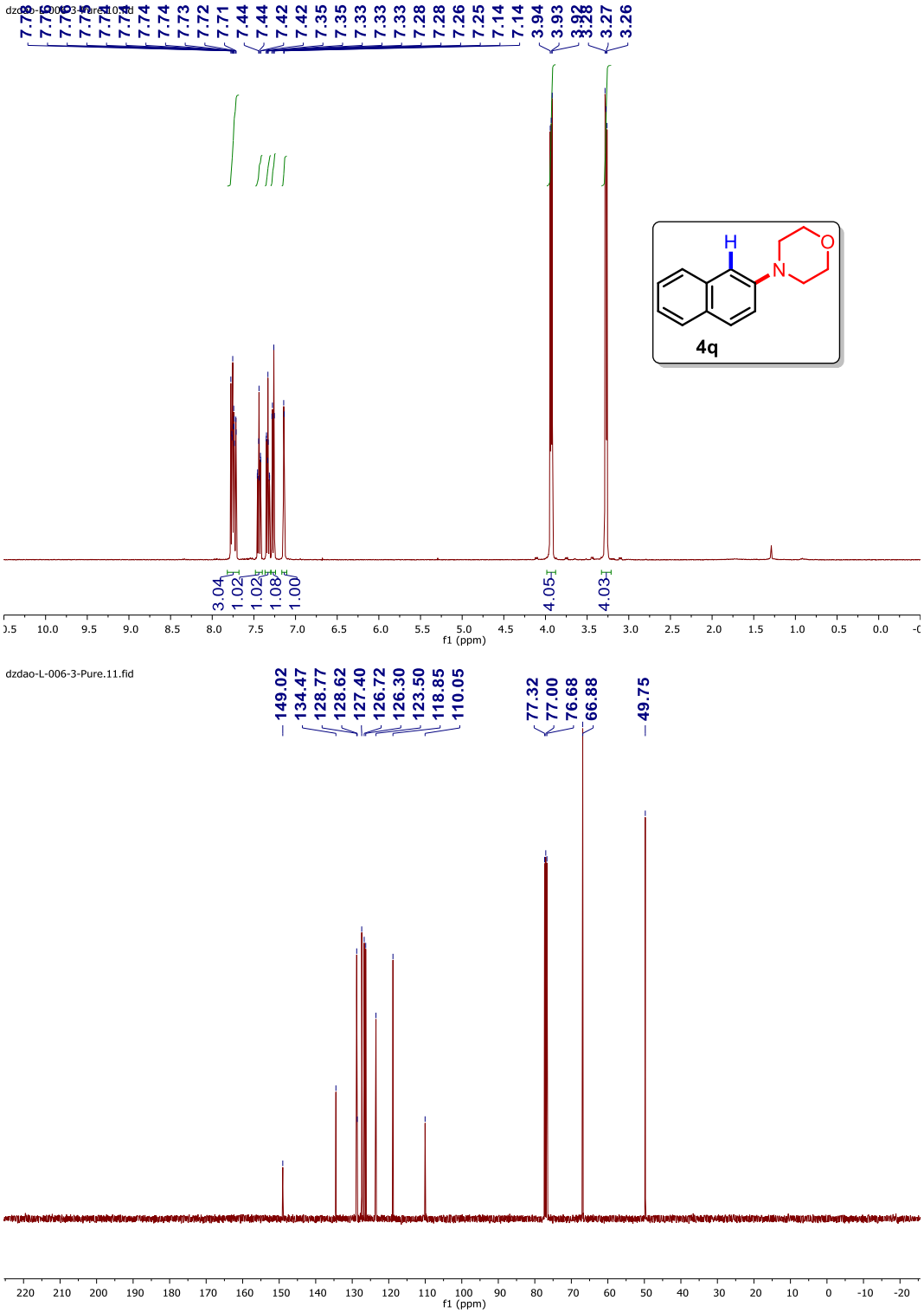


Figure 4.35 ^{1}H and ^{13}C NMR spectrum of compound **4r**.

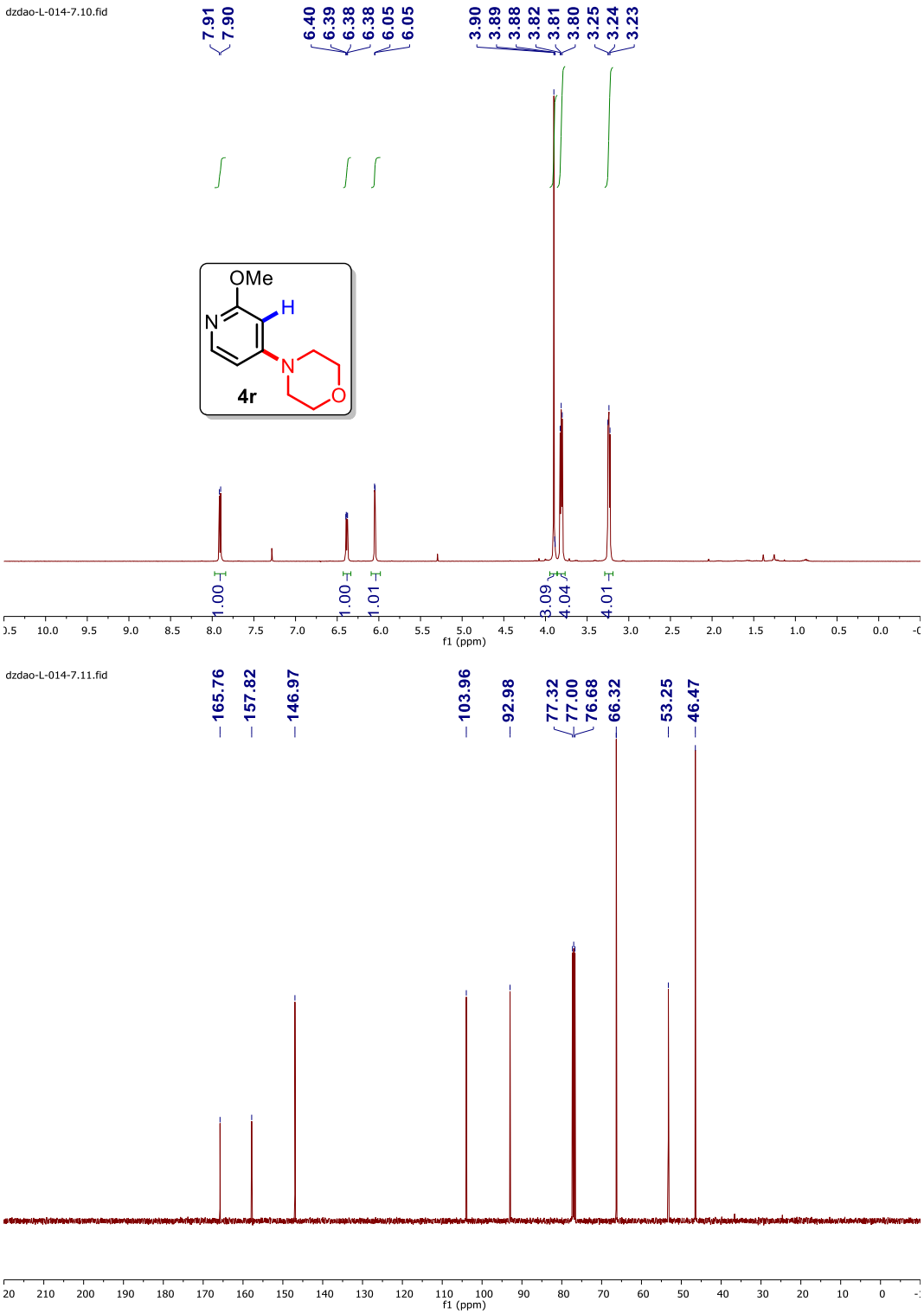


Figure 4.36 ^{1}H and ^{13}C NMR spectrum of compound **4s**.

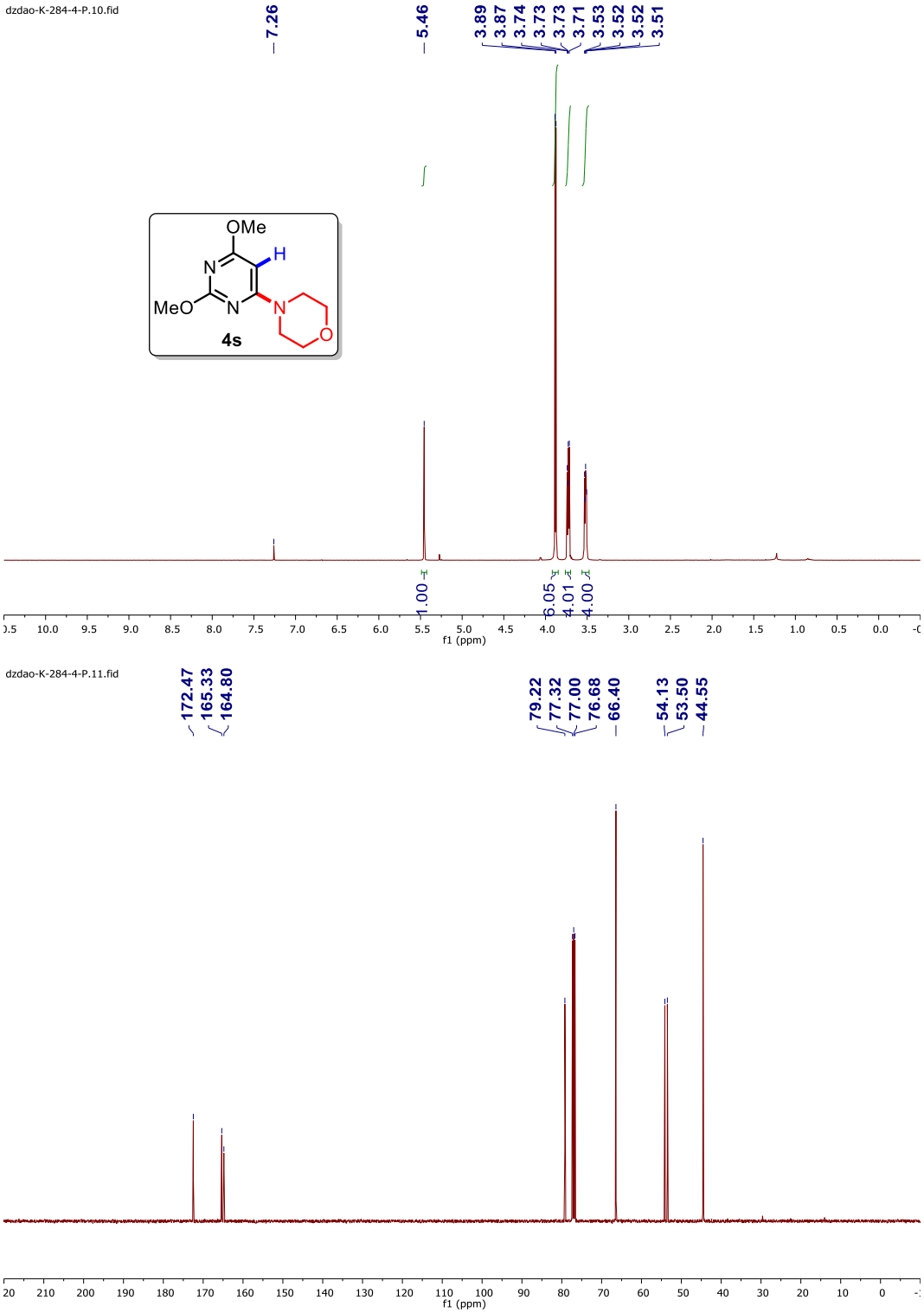


Figure 4.37 ^{1}H and ^{13}C NMR spectrum of compound **4t**.

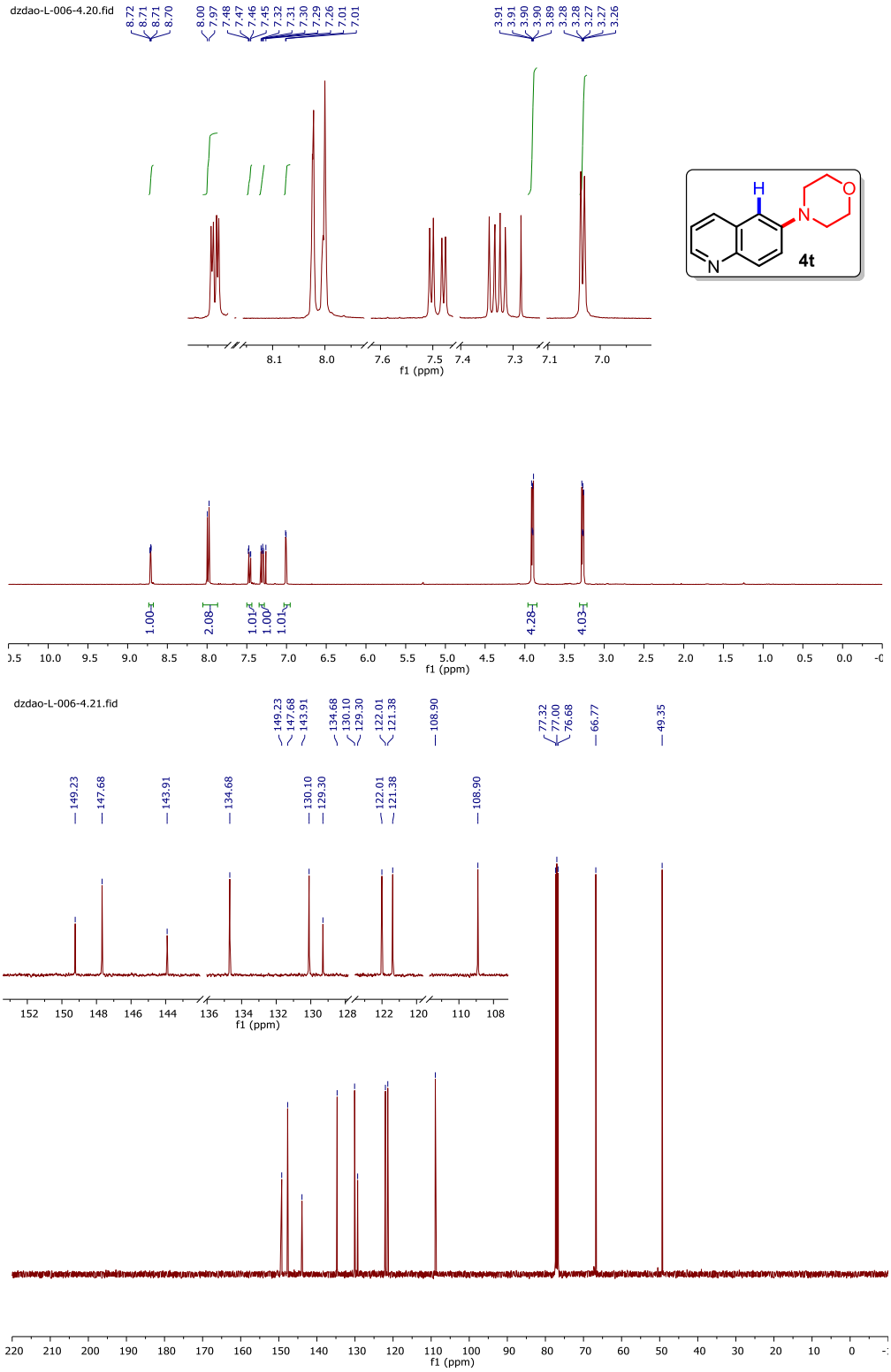


Figure 4.38 ^{1}H and ^{13}C NMR spectrum of compound **4u**.

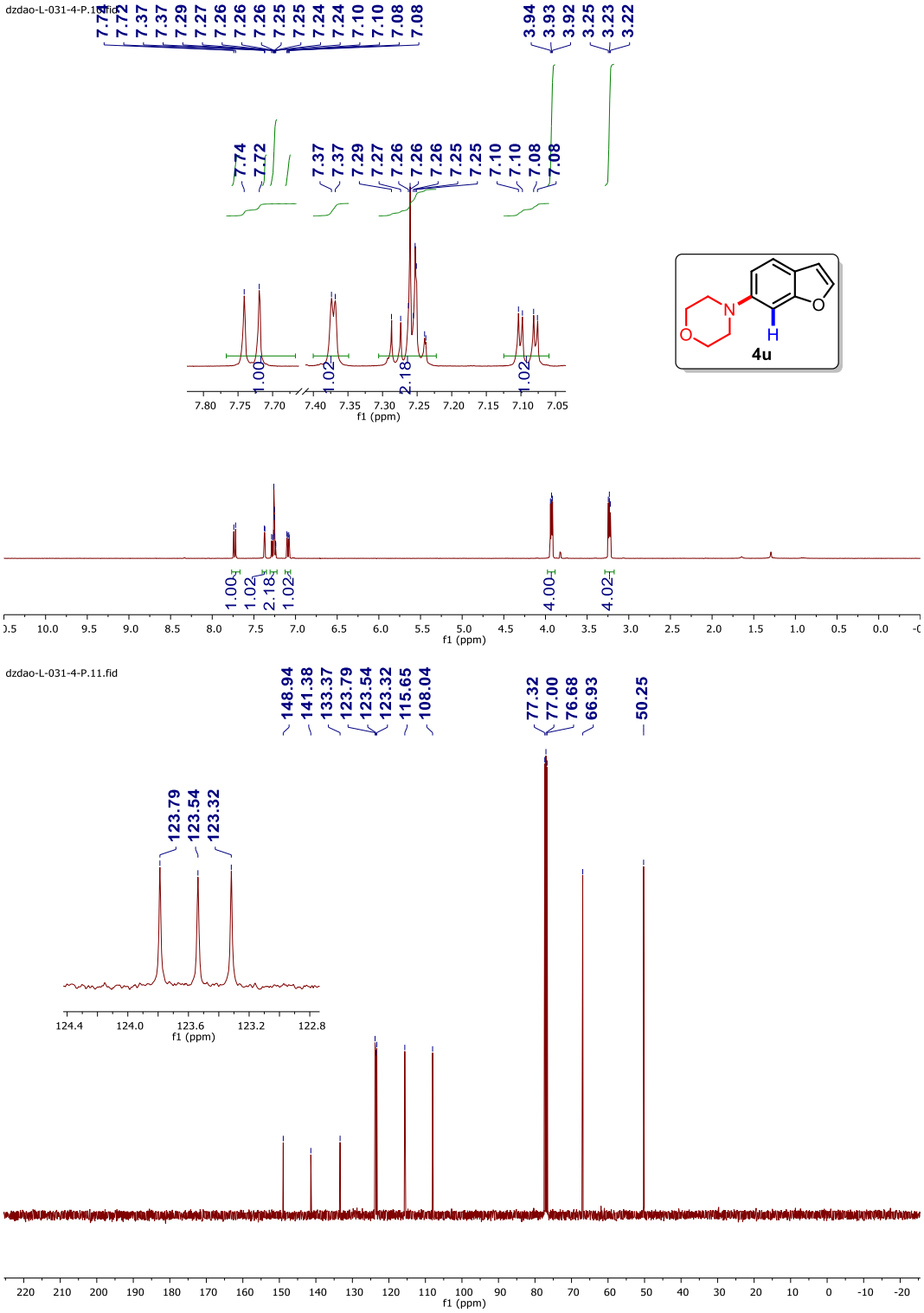


Figure 4.39 ^{1}H and ^{13}C NMR spectrum of compound **4v**.

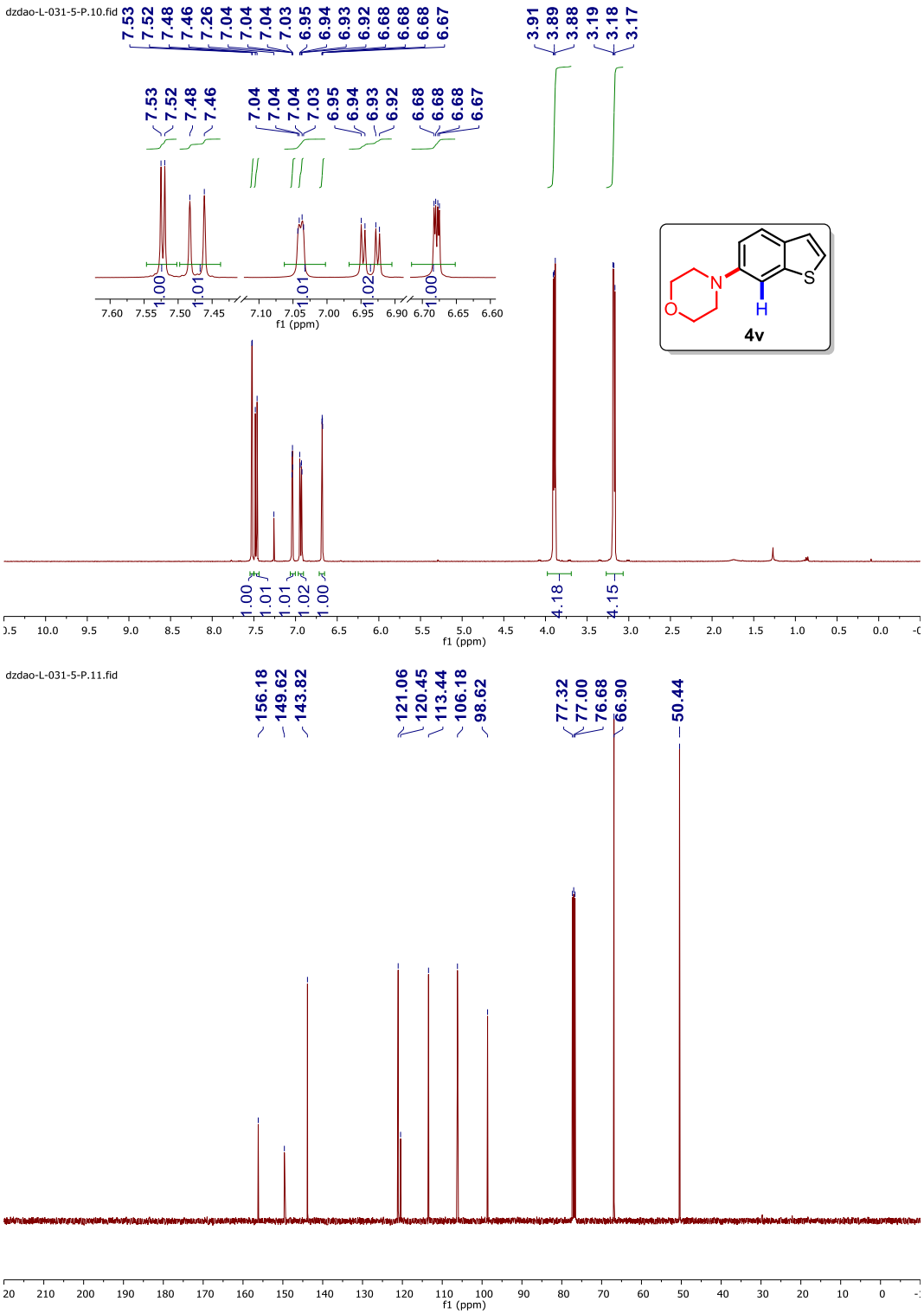


Figure 4.40 ^{1}H and ^{13}C NMR spectrum of compound **4w**.

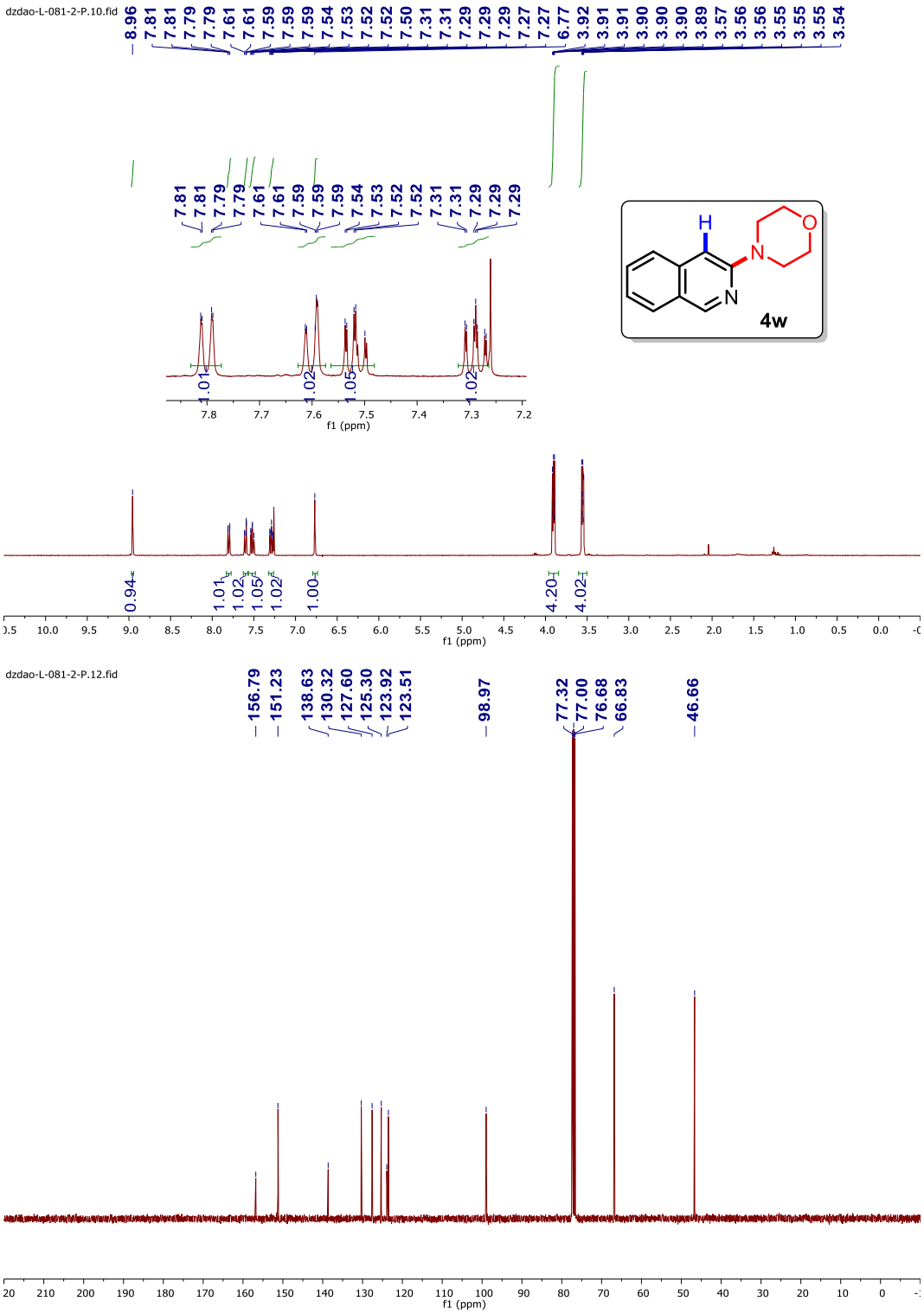


Figure 4.41 ^{1}H and ^{13}C NMR spectrum of compound **4x**.

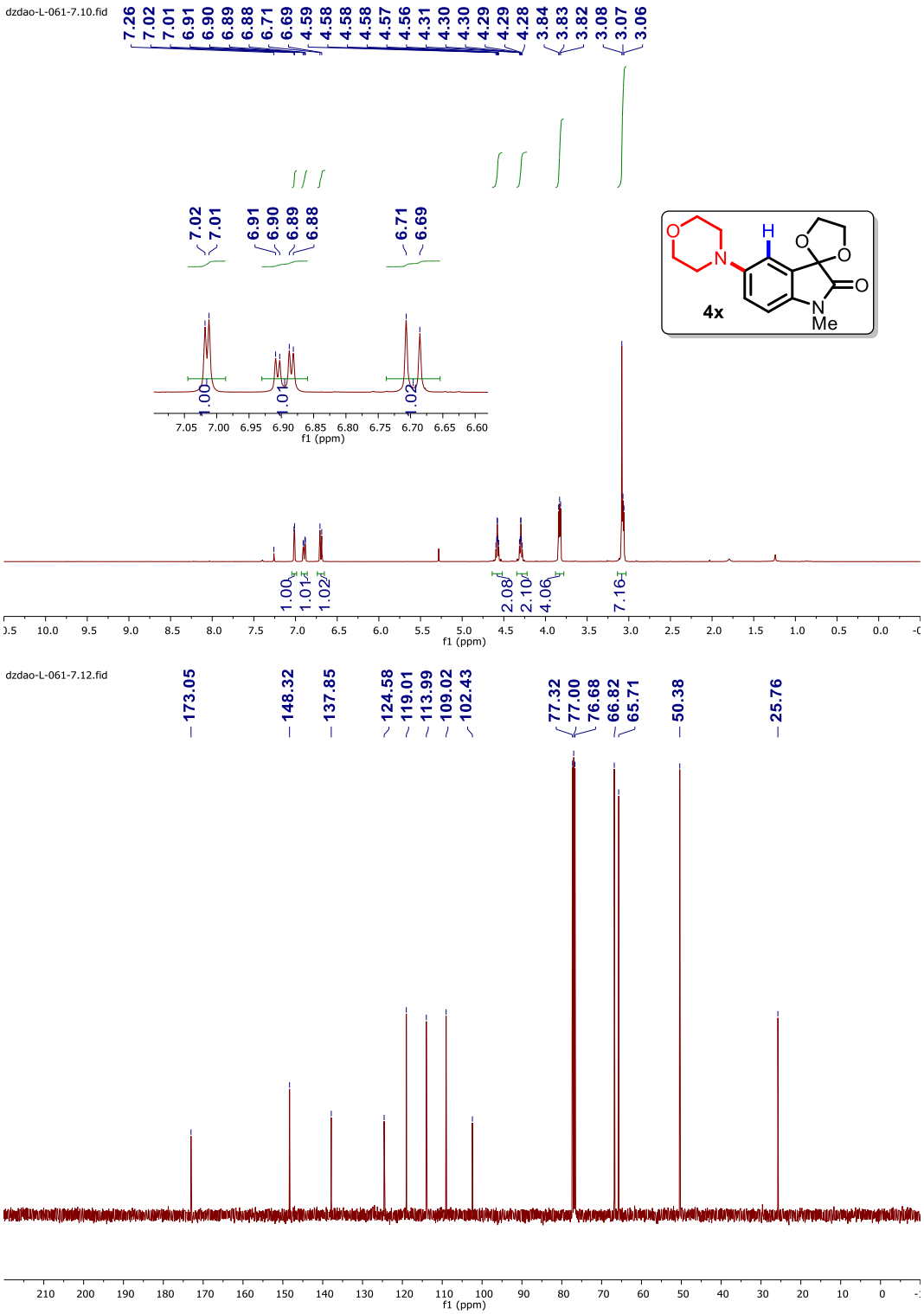


Figure 4.42 ^{1}H and ^{13}C NMR spectrum of compound **5a**.

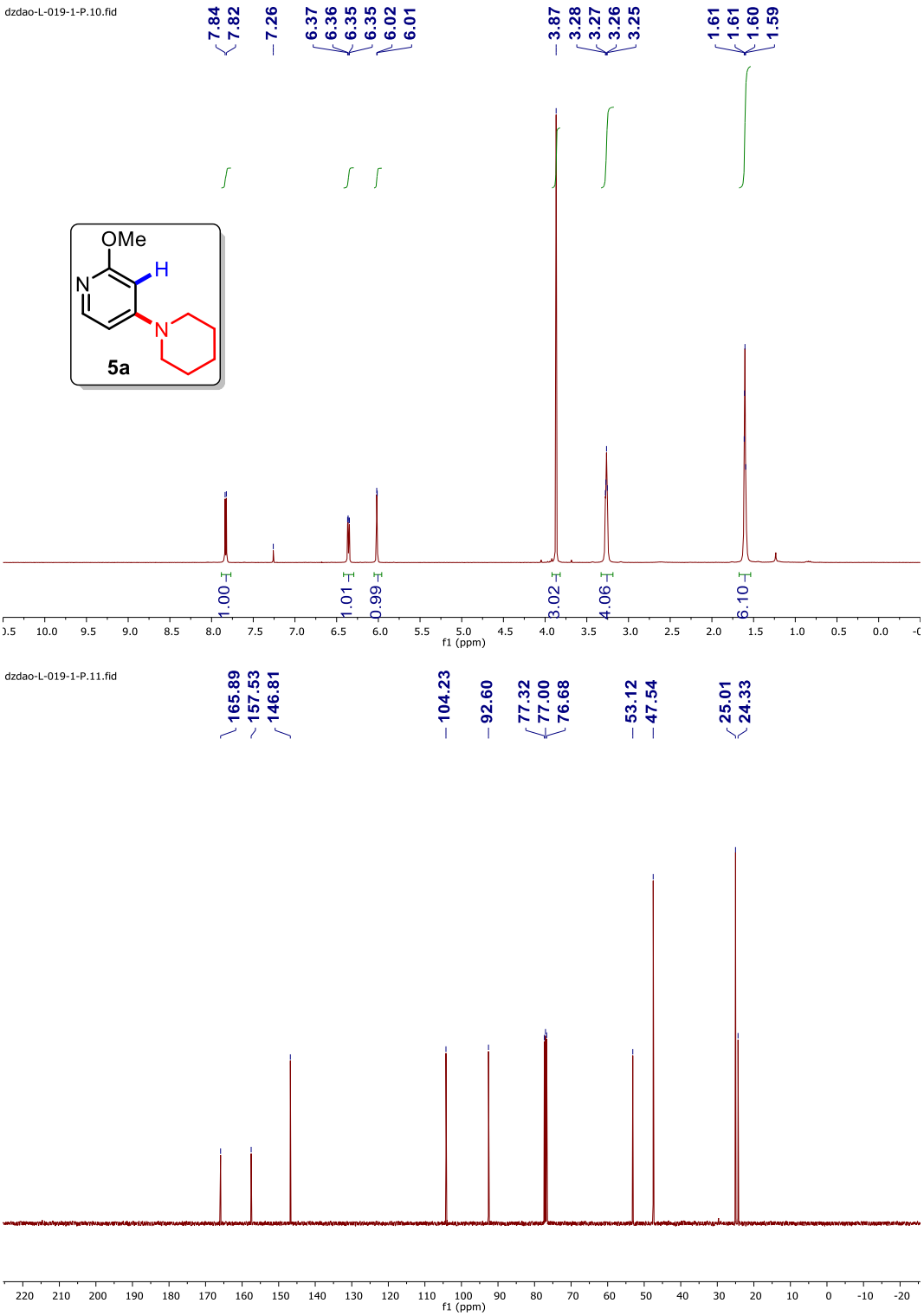


Figure 4.43 ^{1}H and ^{13}C NMR spectrum of compound **5b**.

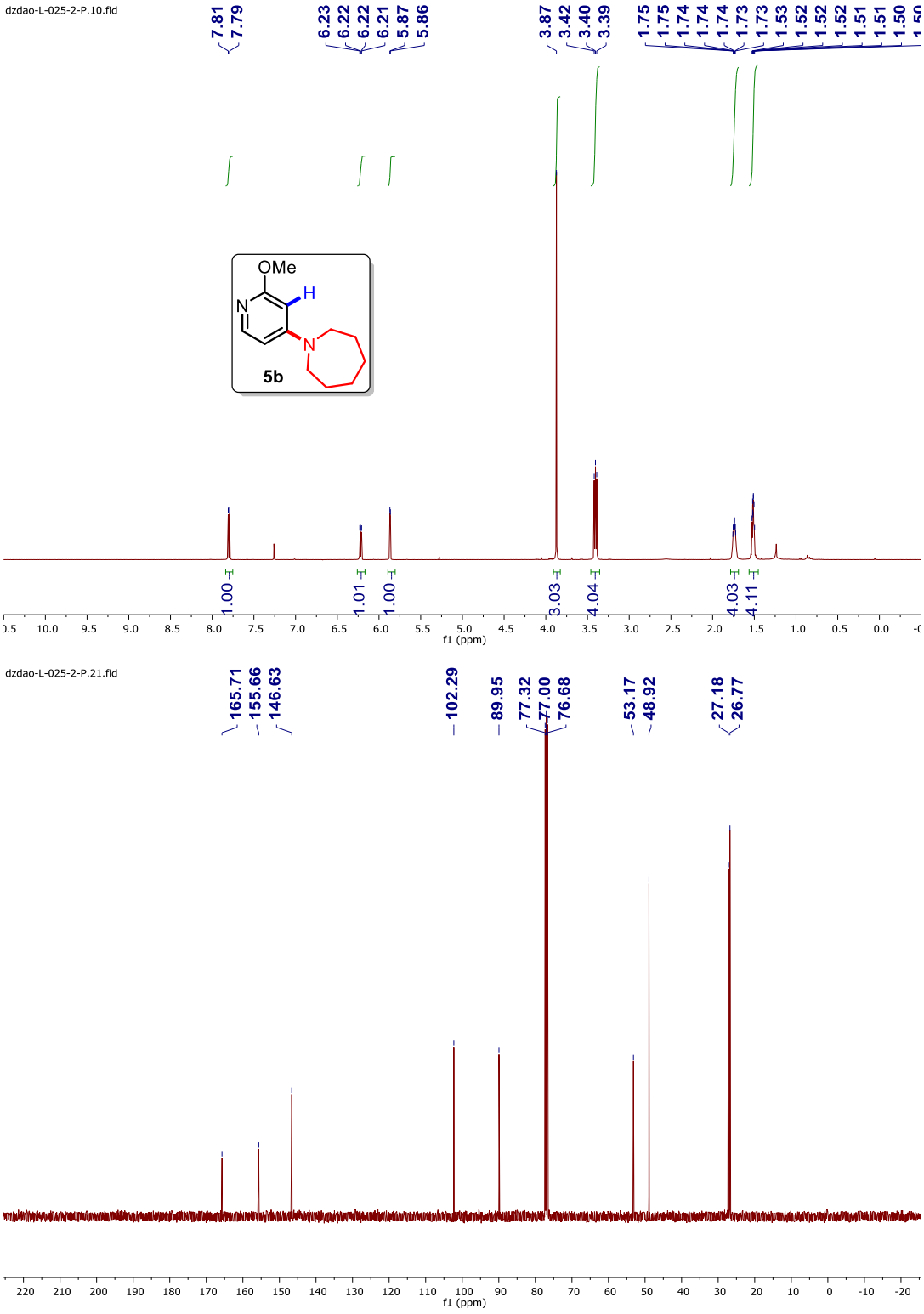


Figure 4.44 ^{1}H and ^{13}C NMR spectrum of compound **5c**.

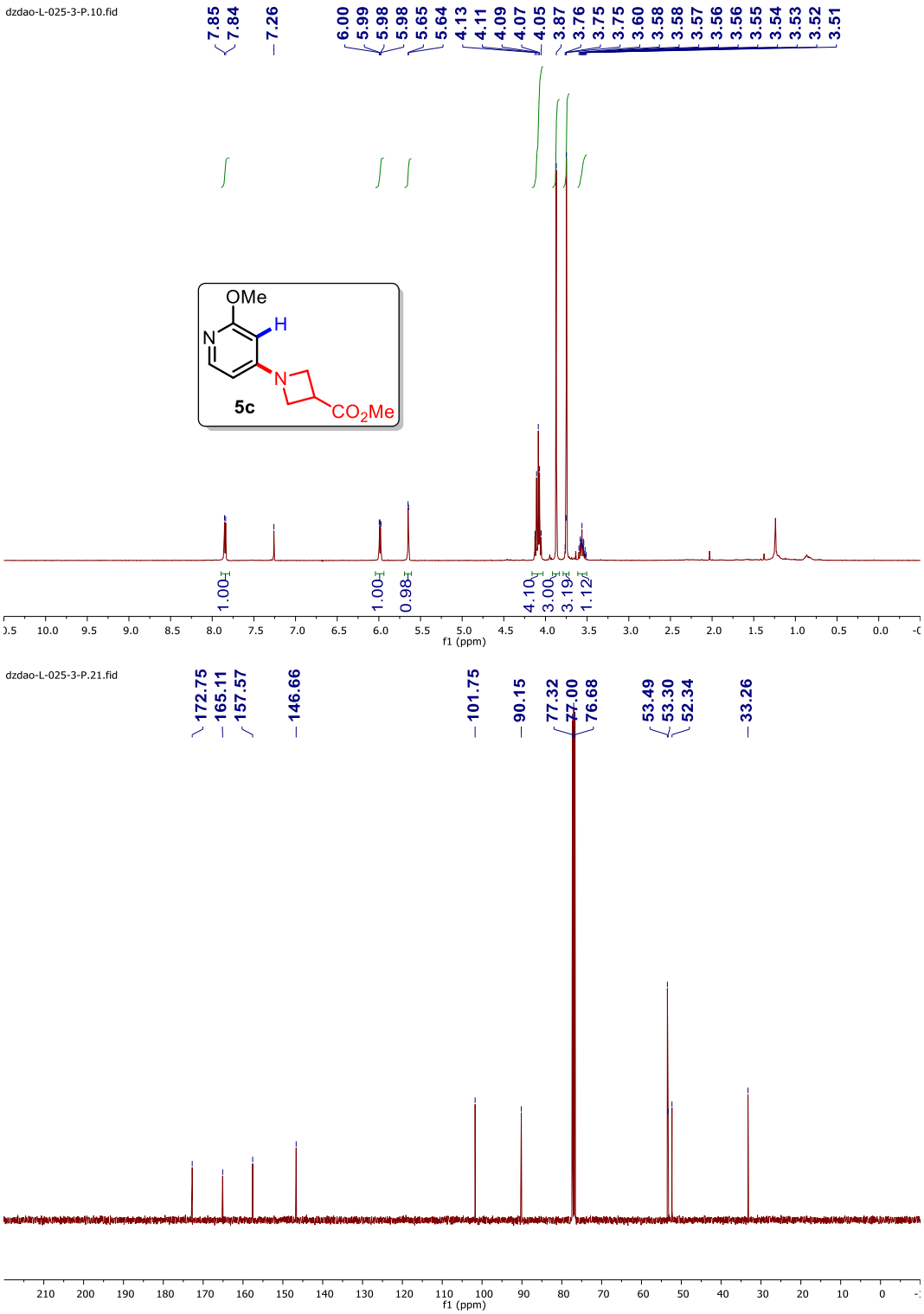


Figure 4.45 ^{1}H and ^{13}C NMR spectrum of compound **5d**.

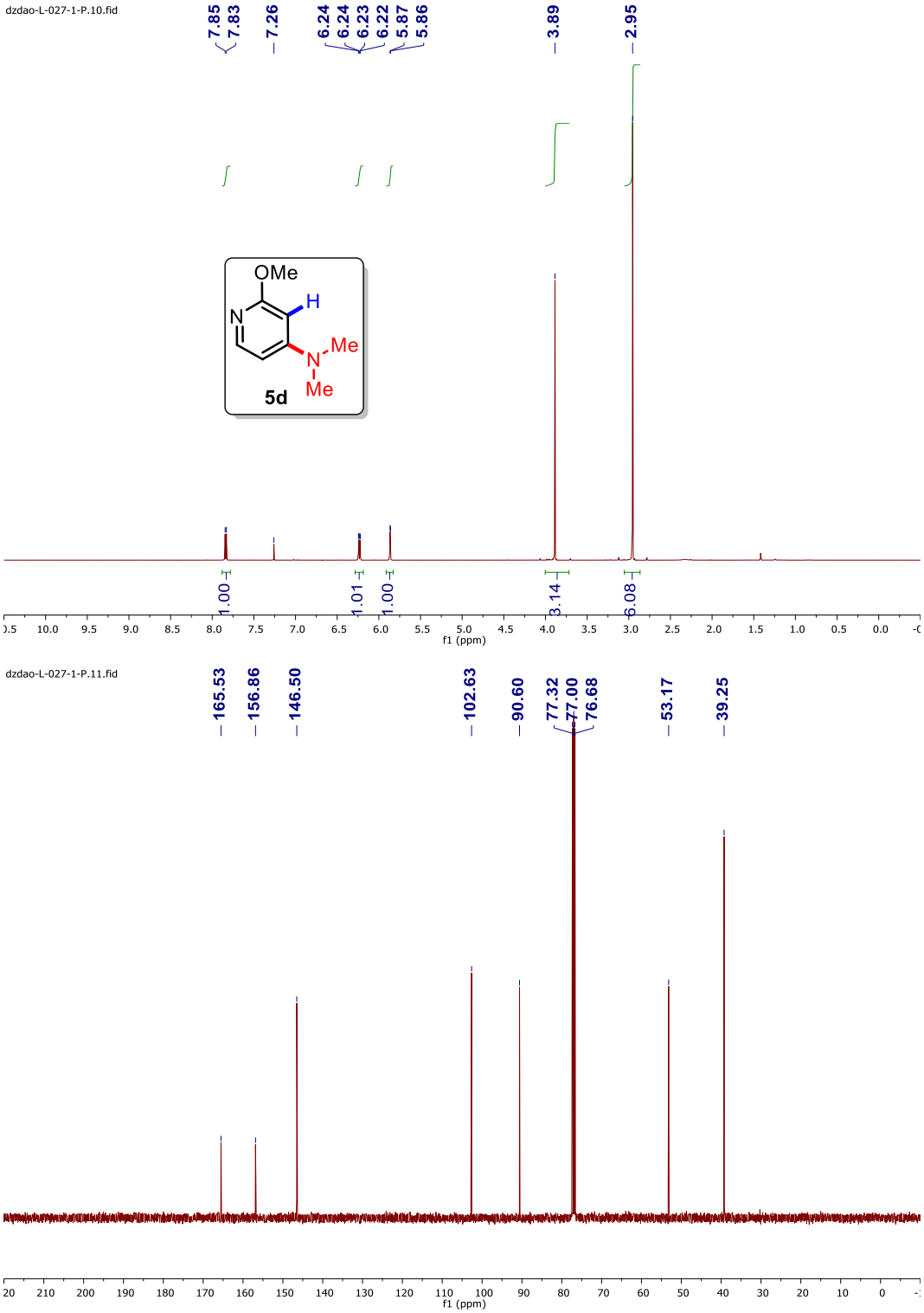


Figure 4.46 ^{1}H and ^{13}C NMR spectrum of compound **5e**.

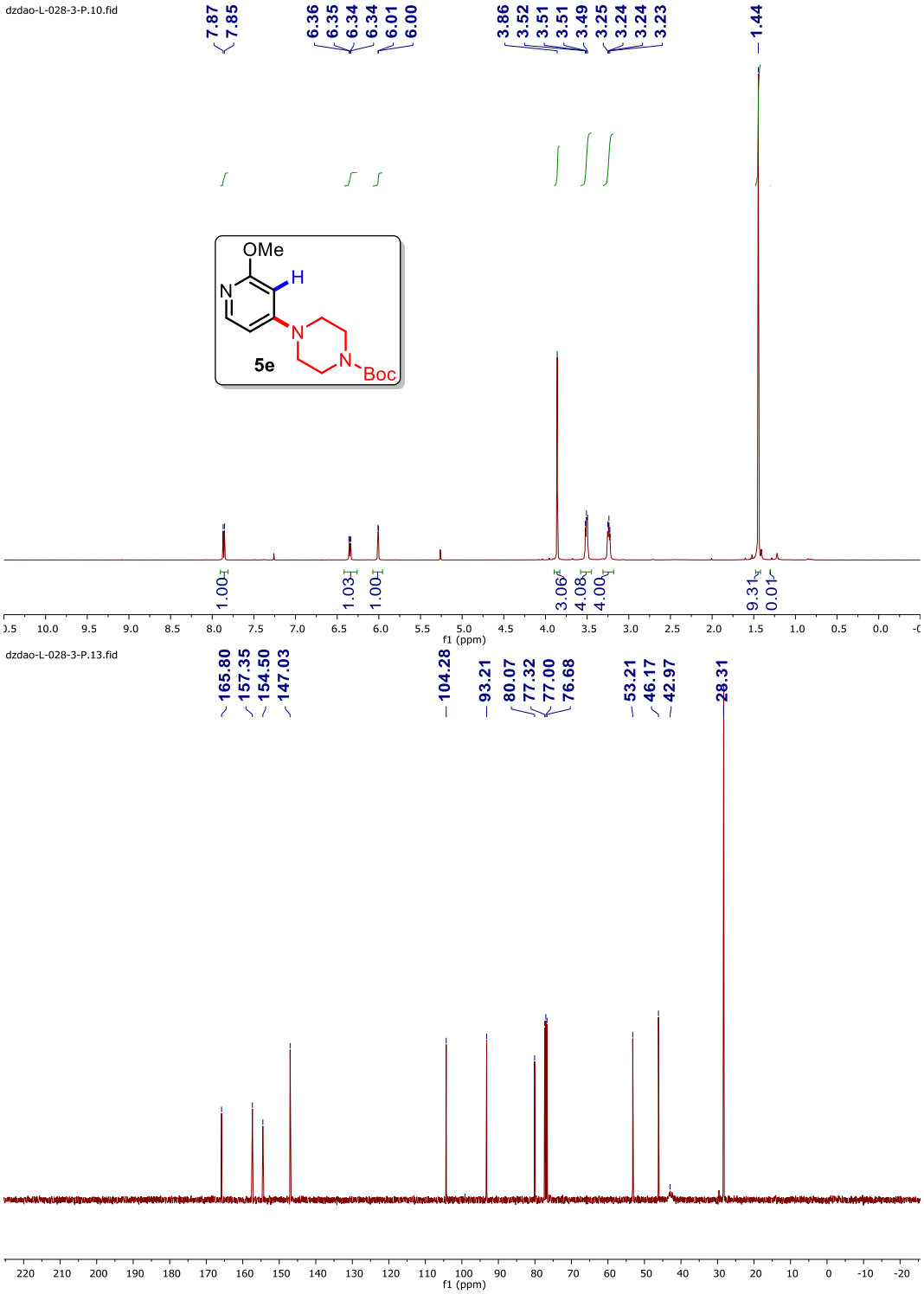


Figure 4.47 ^{1}H and ^{13}C NMR spectrum of compound **5f**.

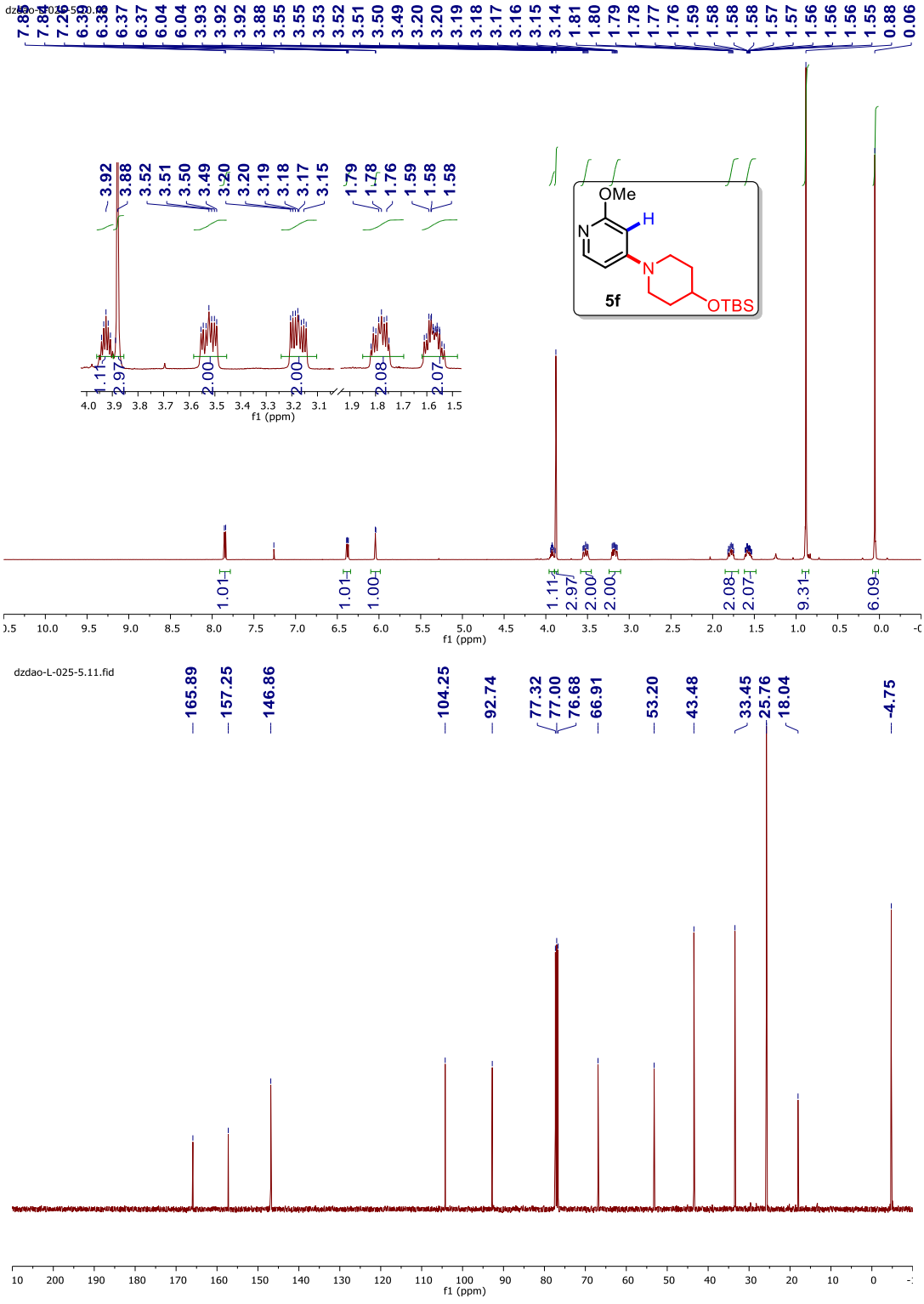


Figure 4.48 ^{1}H and ^{13}C NMR spectrum of compound **5g**.

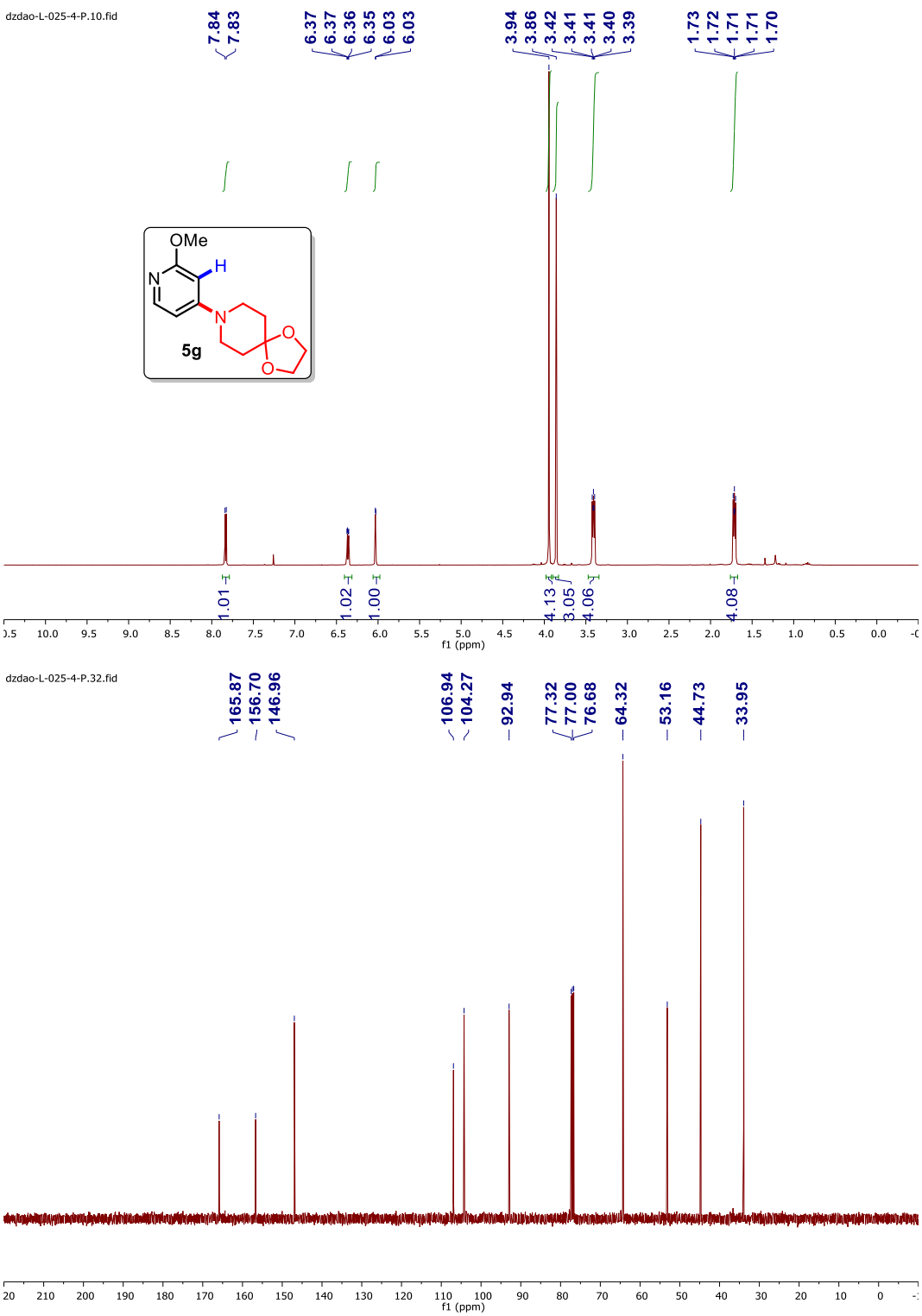


Figure 4.49 ^{1}H and ^{13}C NMR spectrum of compound **5h**.

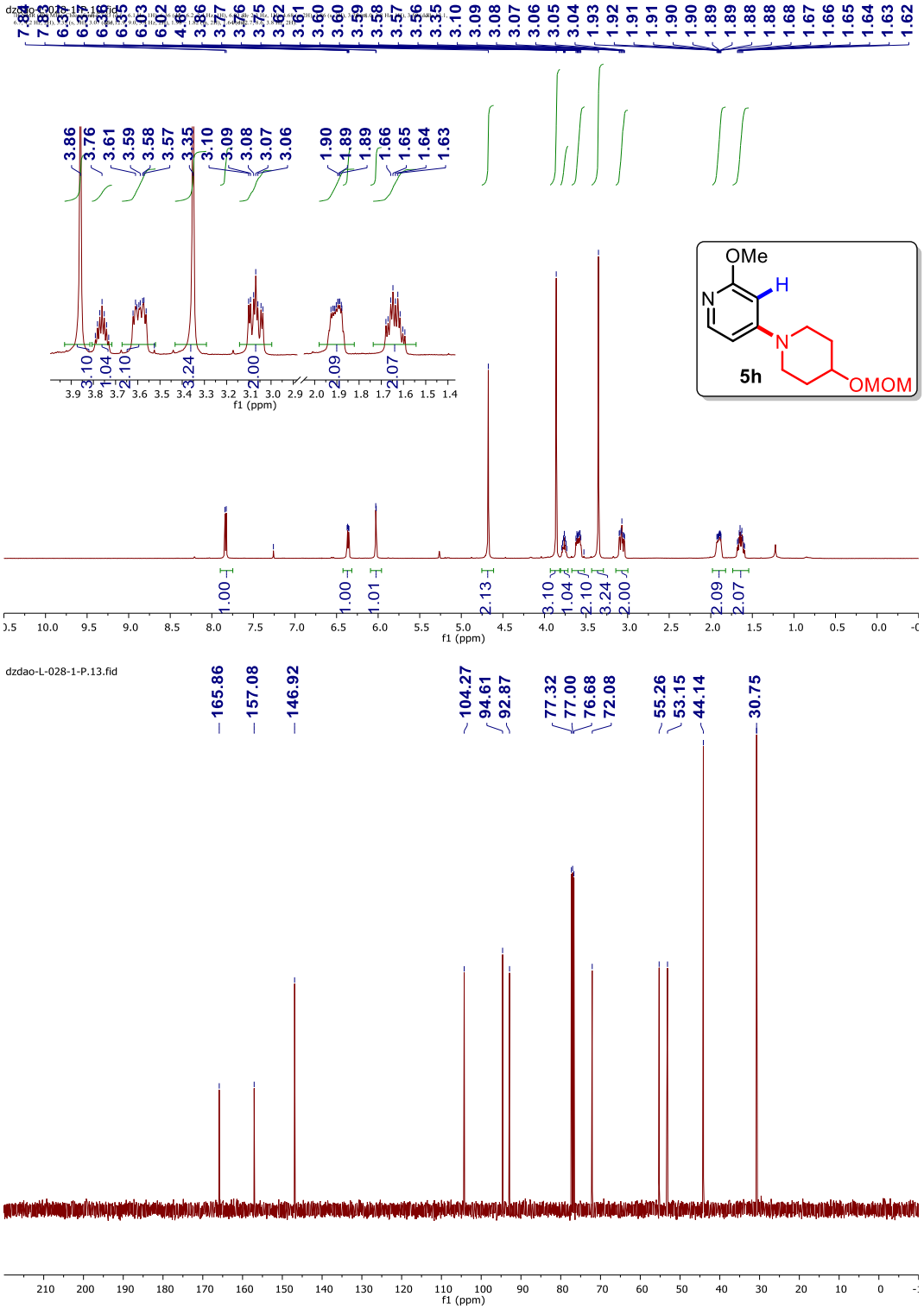


Figure 4.50 ^{1}H and ^{13}C NMR spectrum of compound **5i**.

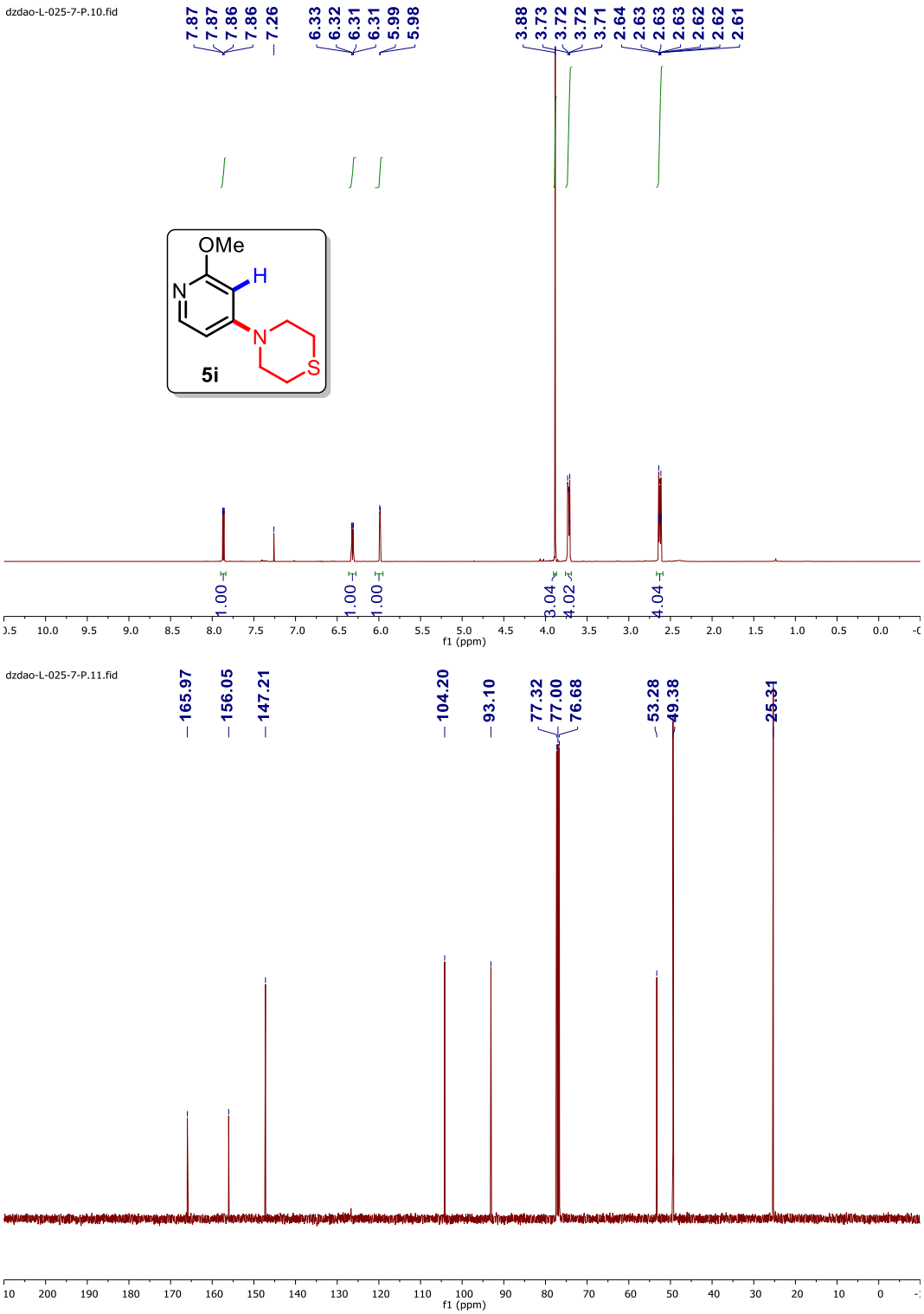


Figure 4.51 ^{1}H and ^{13}C NMR spectrum of compound **5j**.

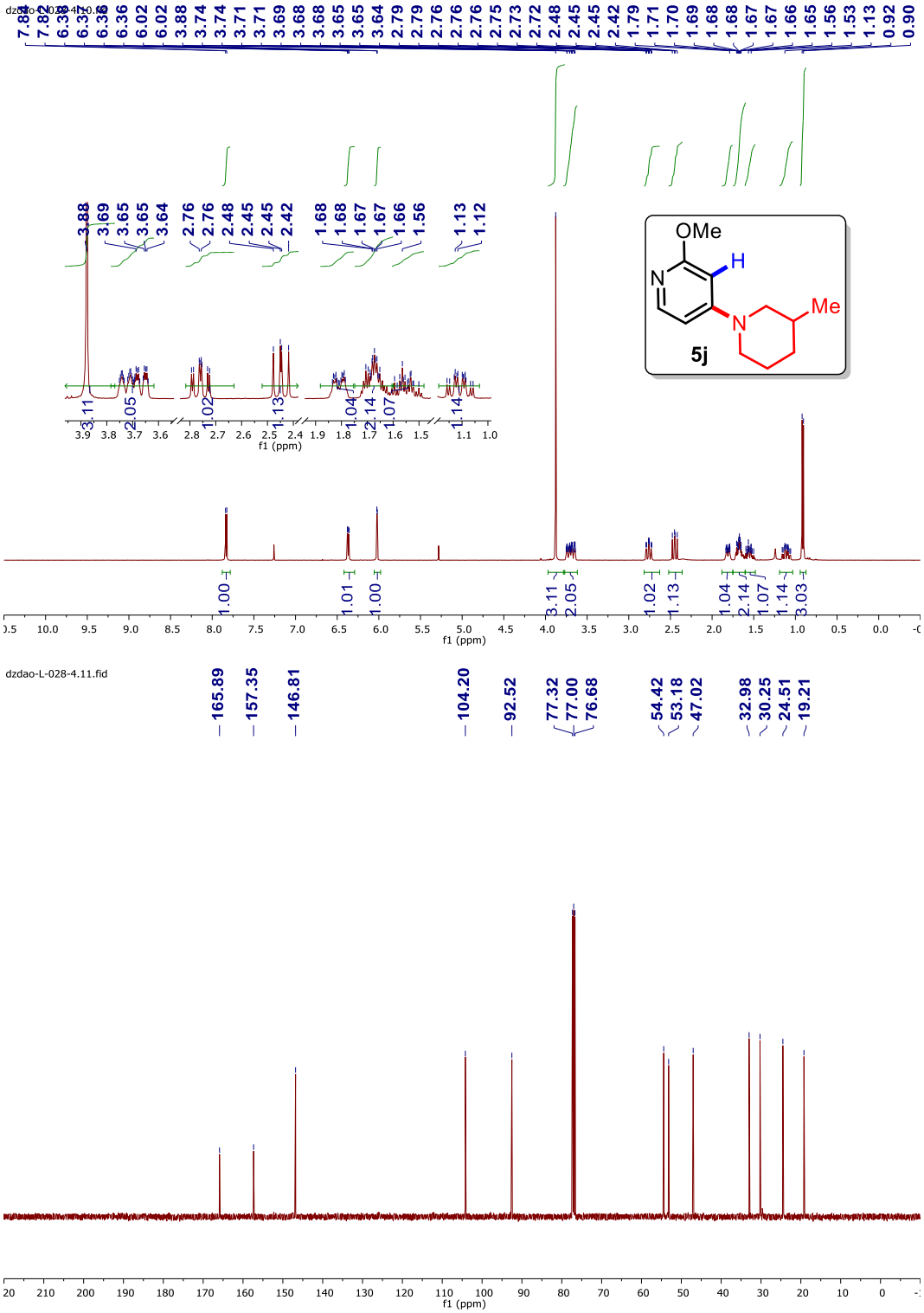


Figure 4.52 ^{1}H and ^{13}C NMR spectrum of compound **5k**.

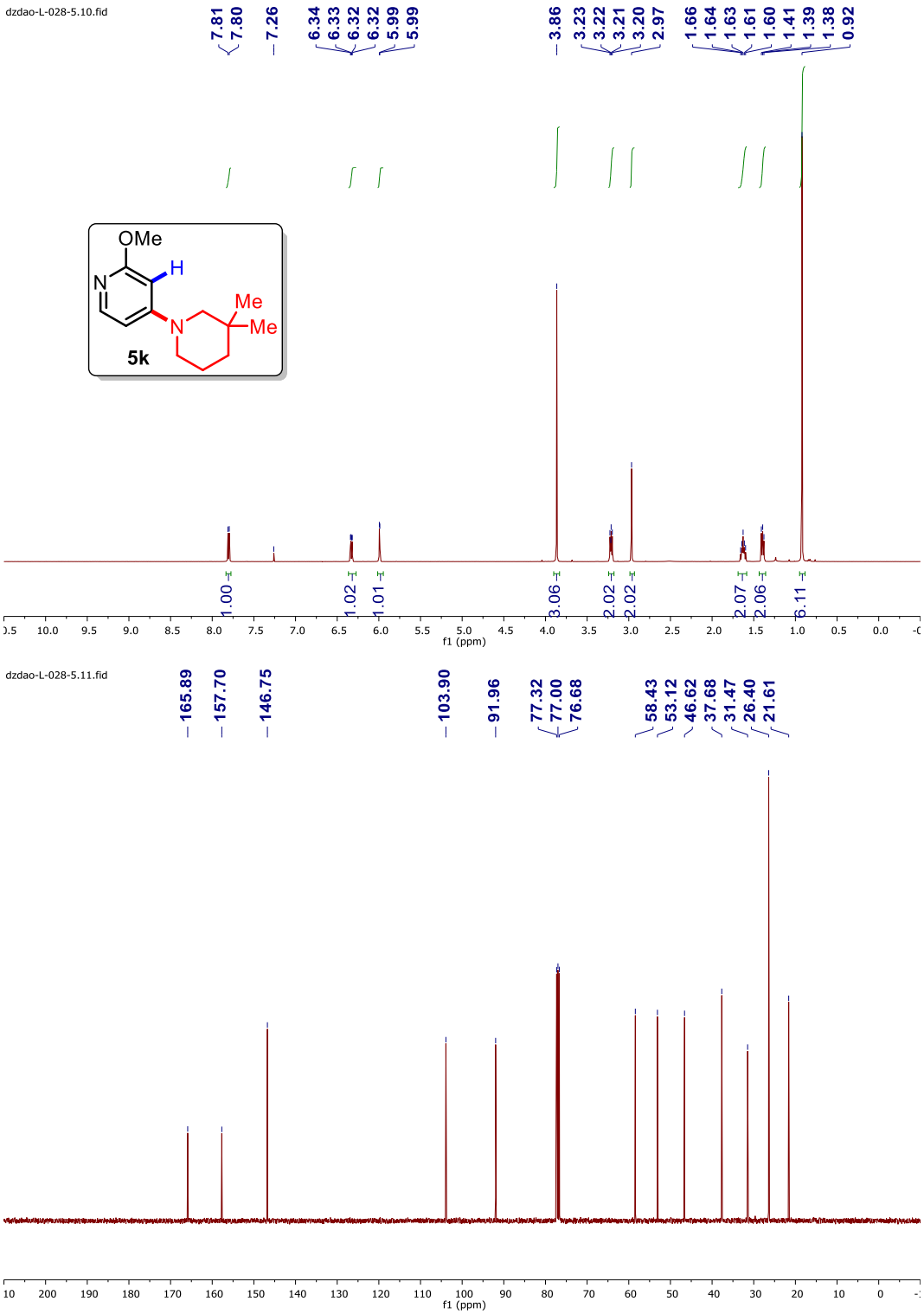


Figure 4.53 ^{1}H and ^{13}C NMR spectrum of compound **5l**.

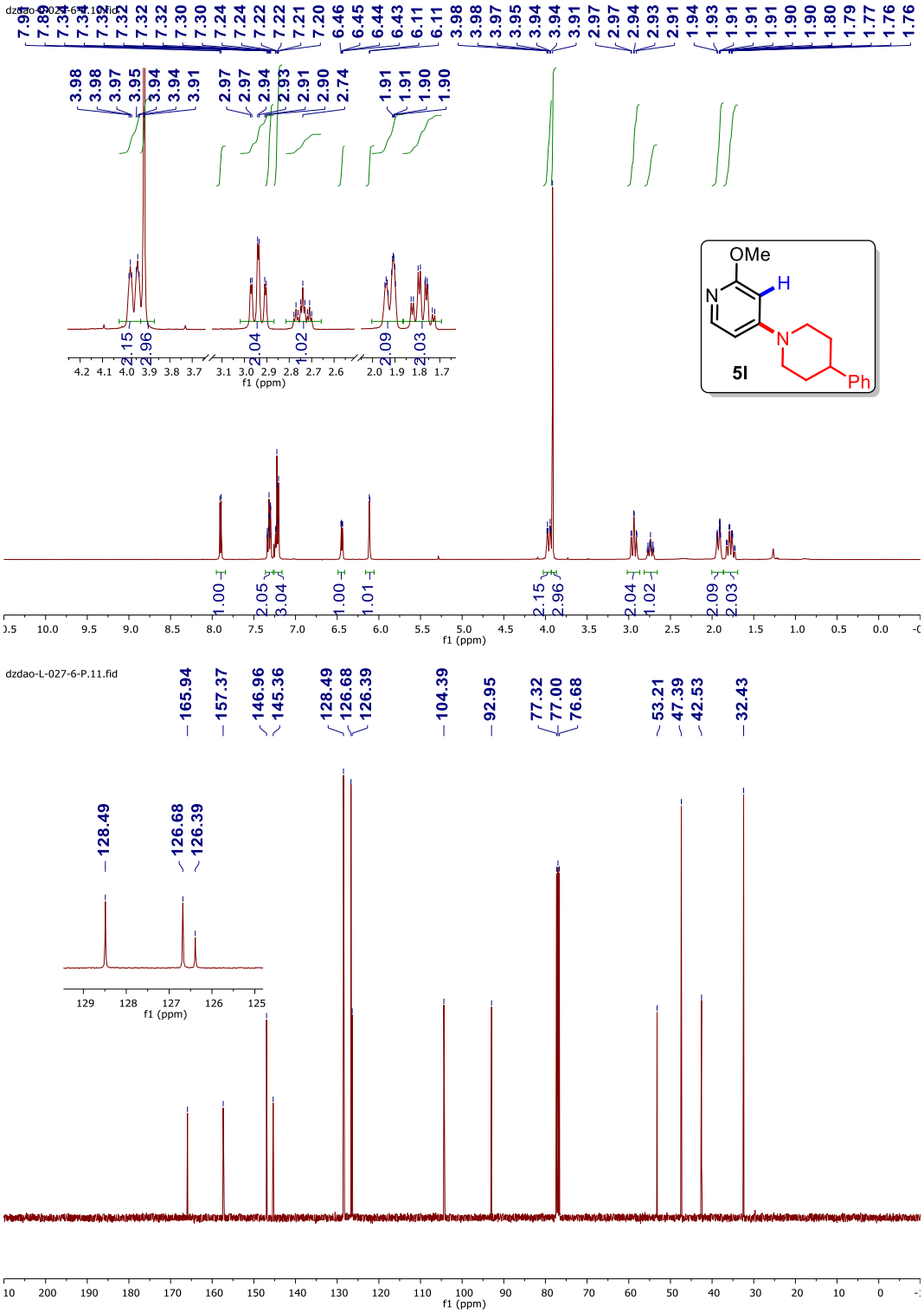


Figure 4.54 ^{1}H and ^{13}C NMR spectrum of compound **5m**.

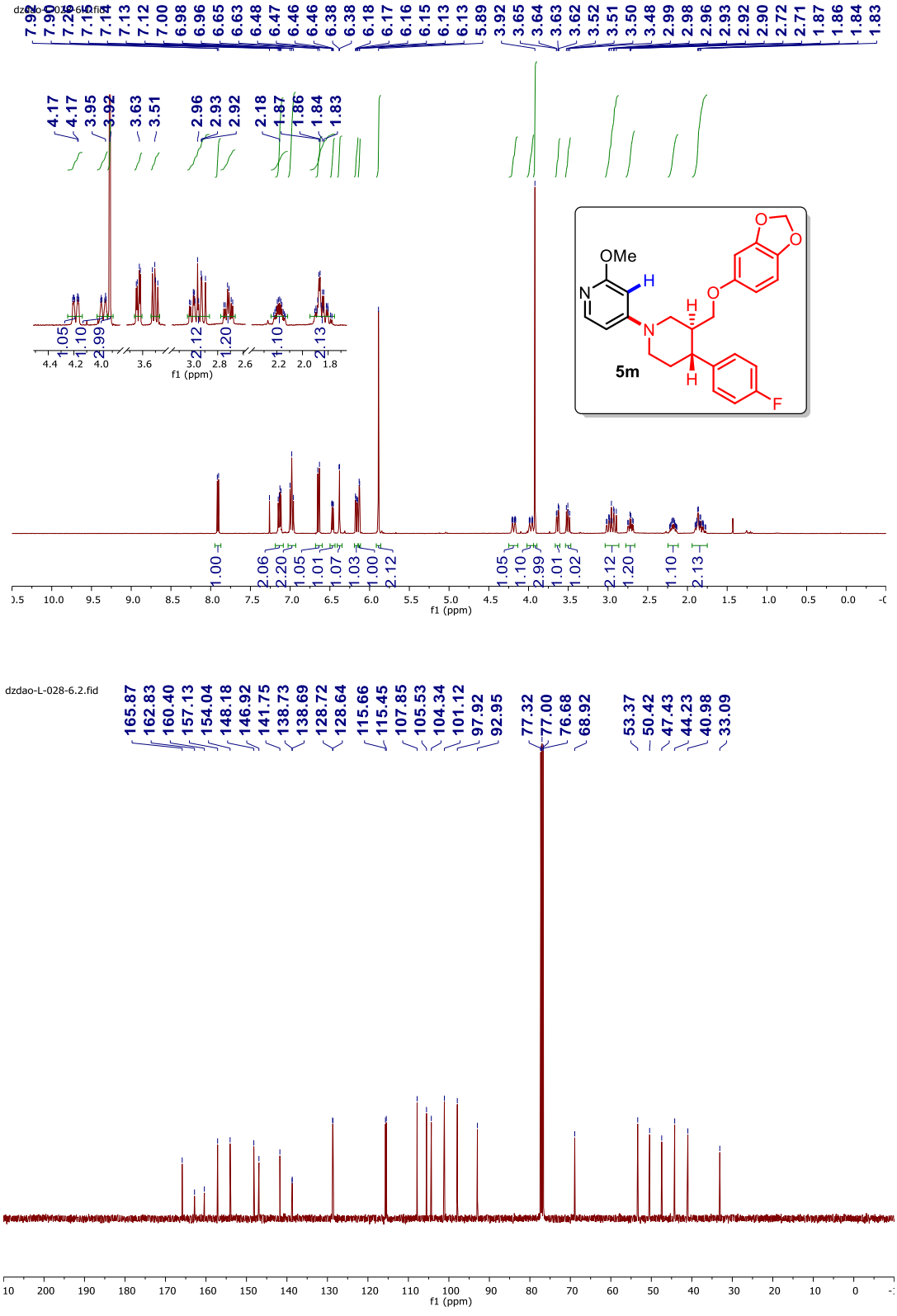


Figure 4.55 ^{19}F NMR spectrum of compound **5m**.

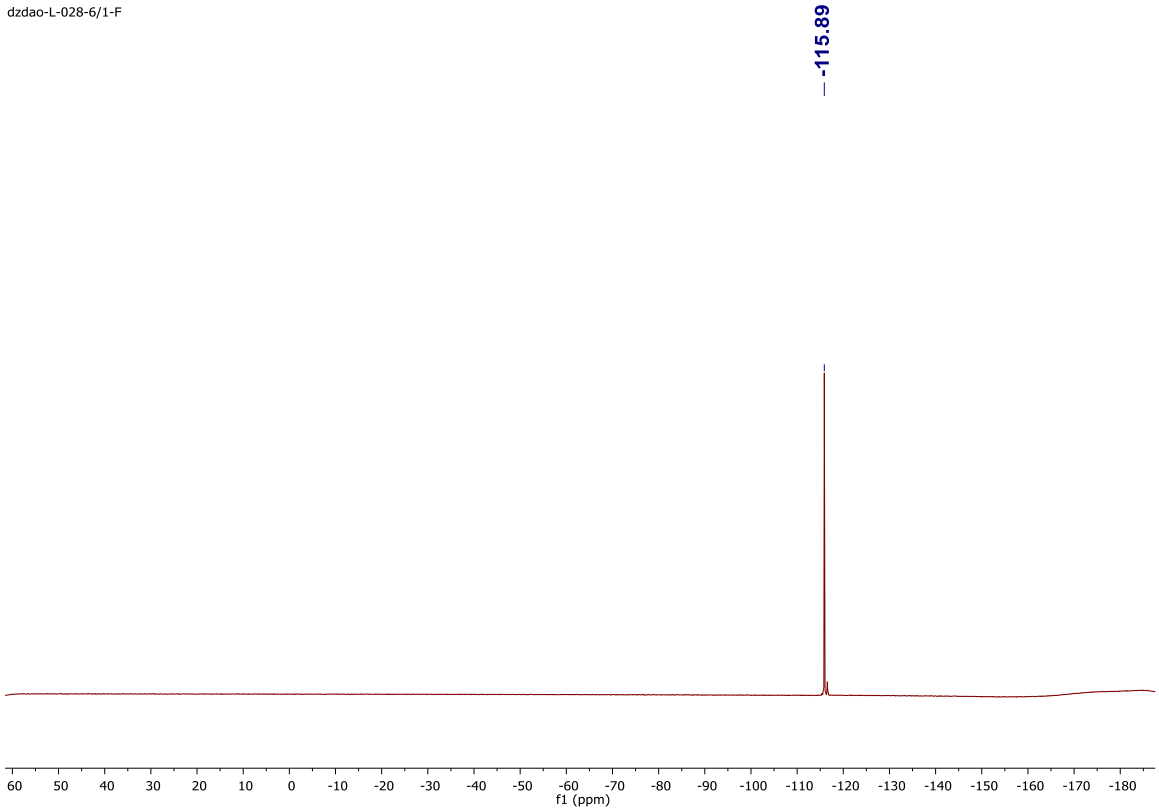


Figure 4.56 ^{1}H and ^{13}C NMR spectrum of compound **5n**.

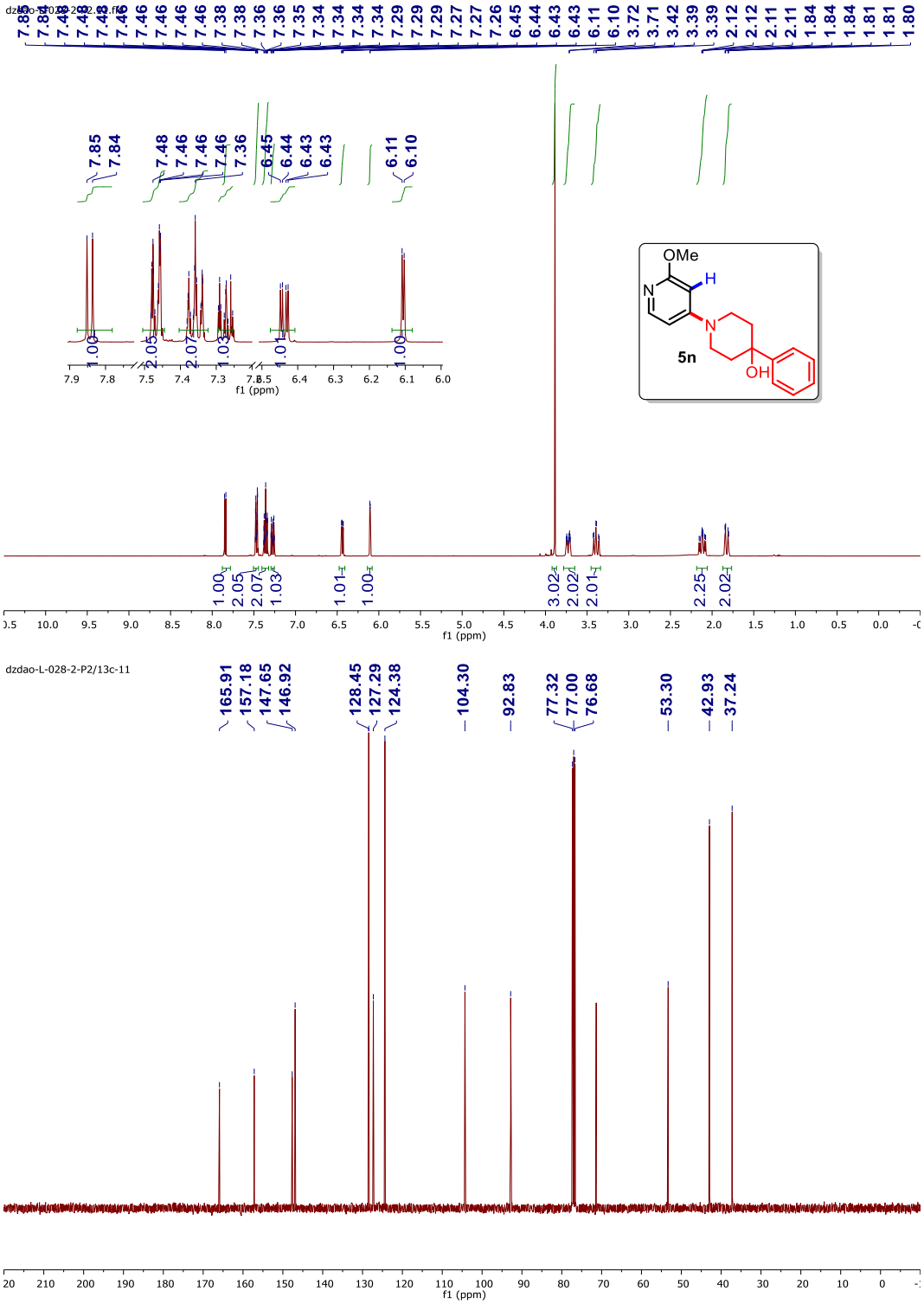


Figure 4.57 ^{1}H and ^{13}C NMR spectrum of compound **7**.

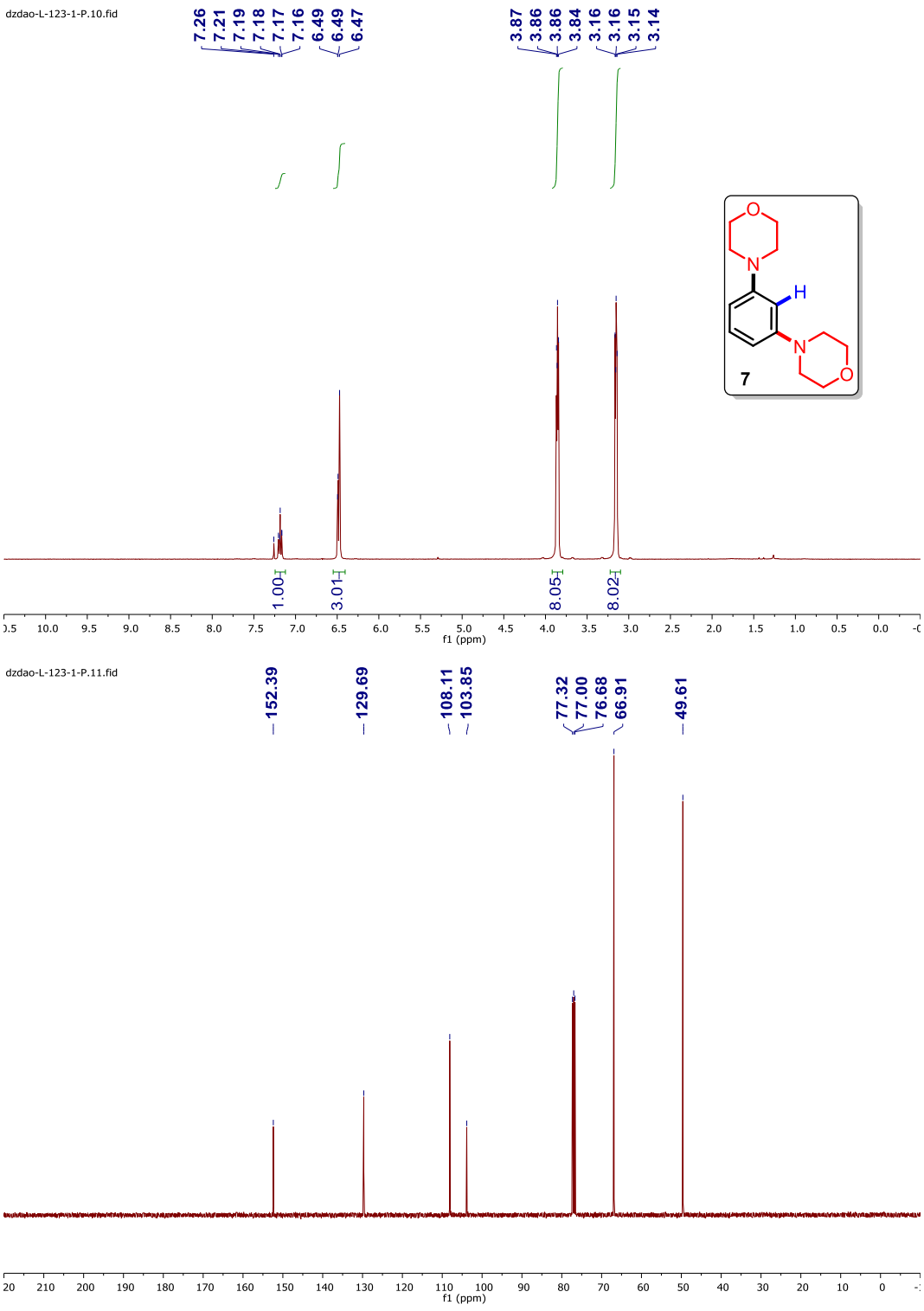


Figure 4.58 ^{1}H and ^{13}C NMR spectrum of compound **8**.

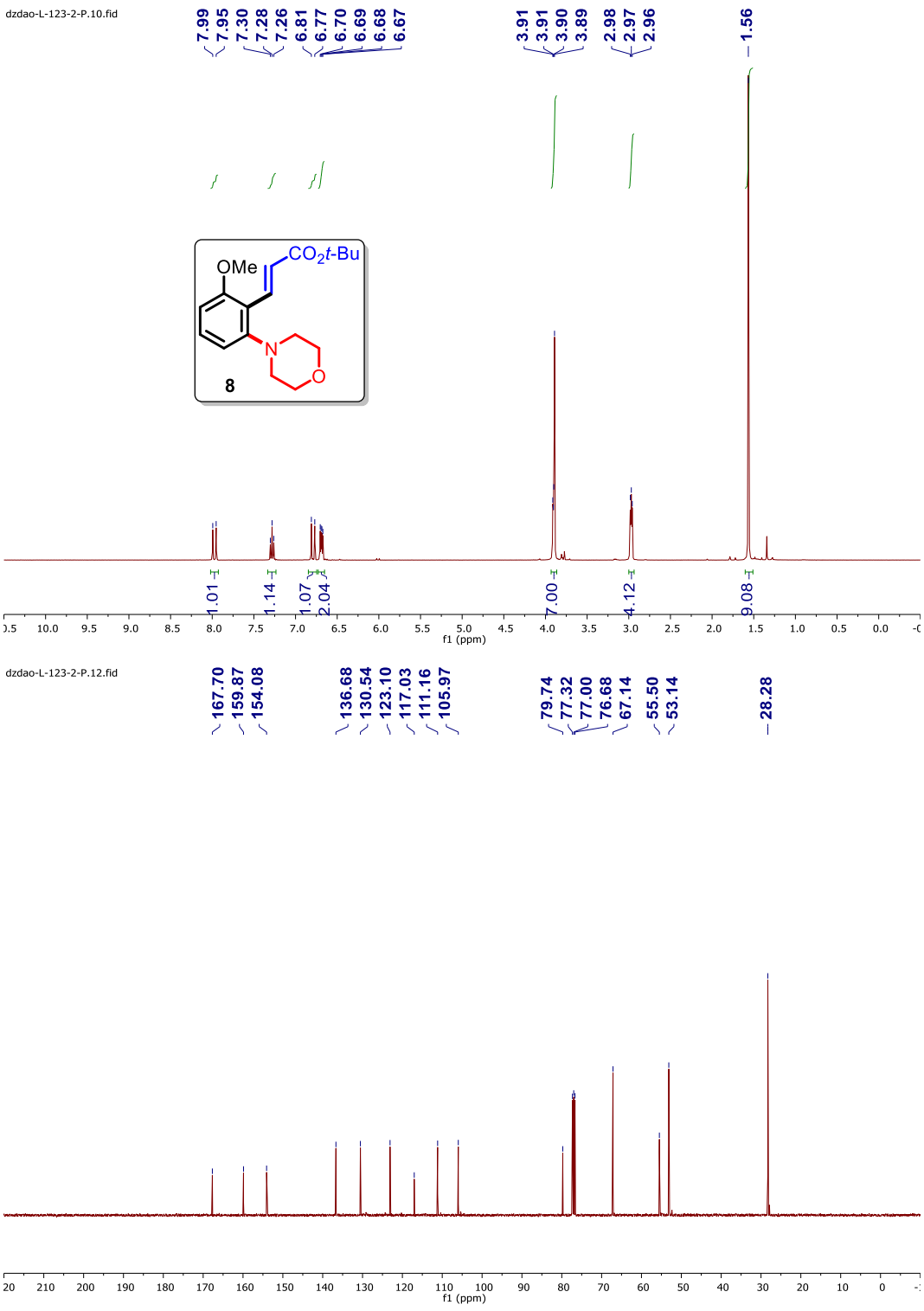


Figure 4.59 ^{1}H and ^{13}C NMR spectrum of compound **9**.

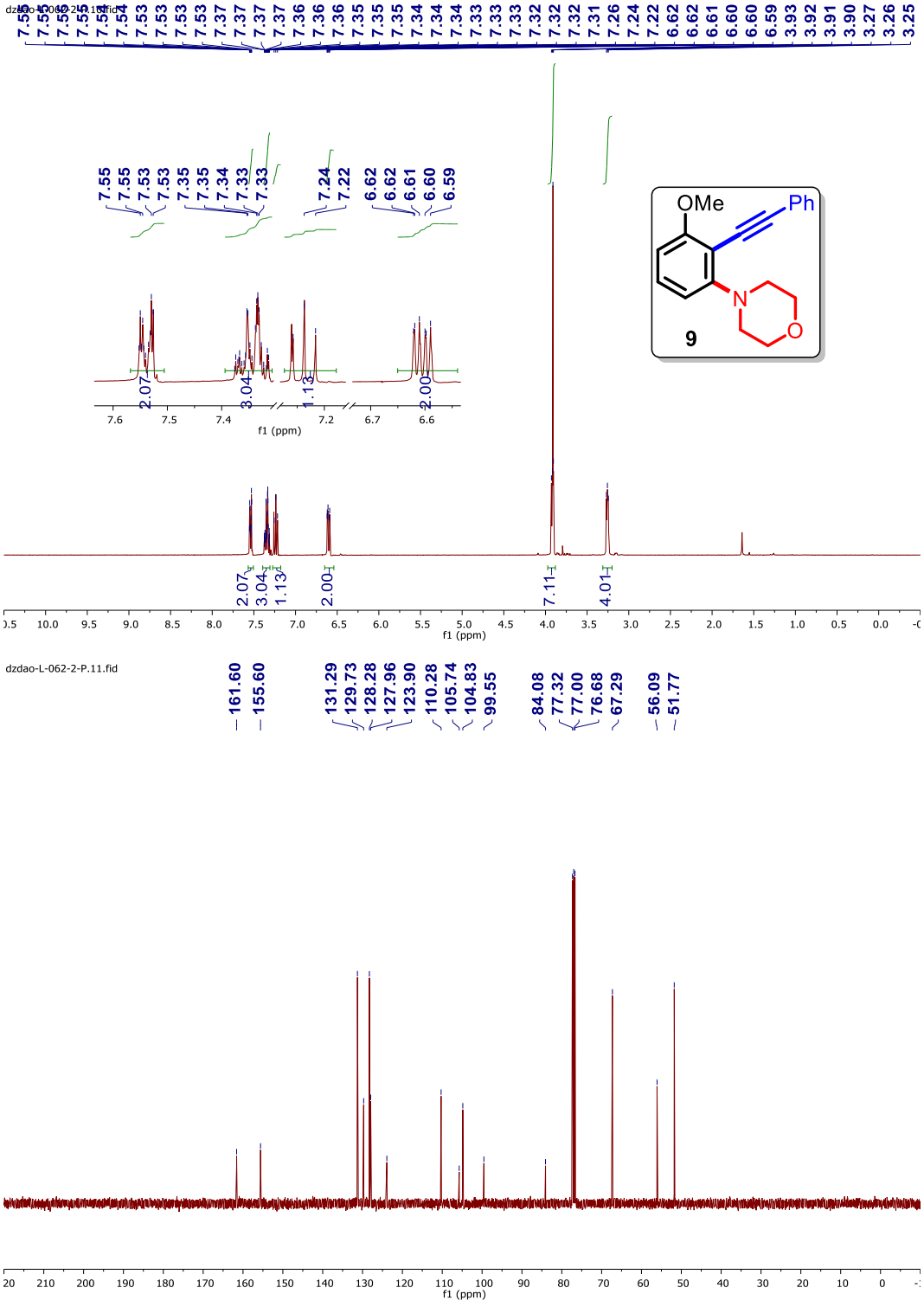


Figure 4.60 ^{1}H and ^{13}C NMR spectrum of compound **10**.

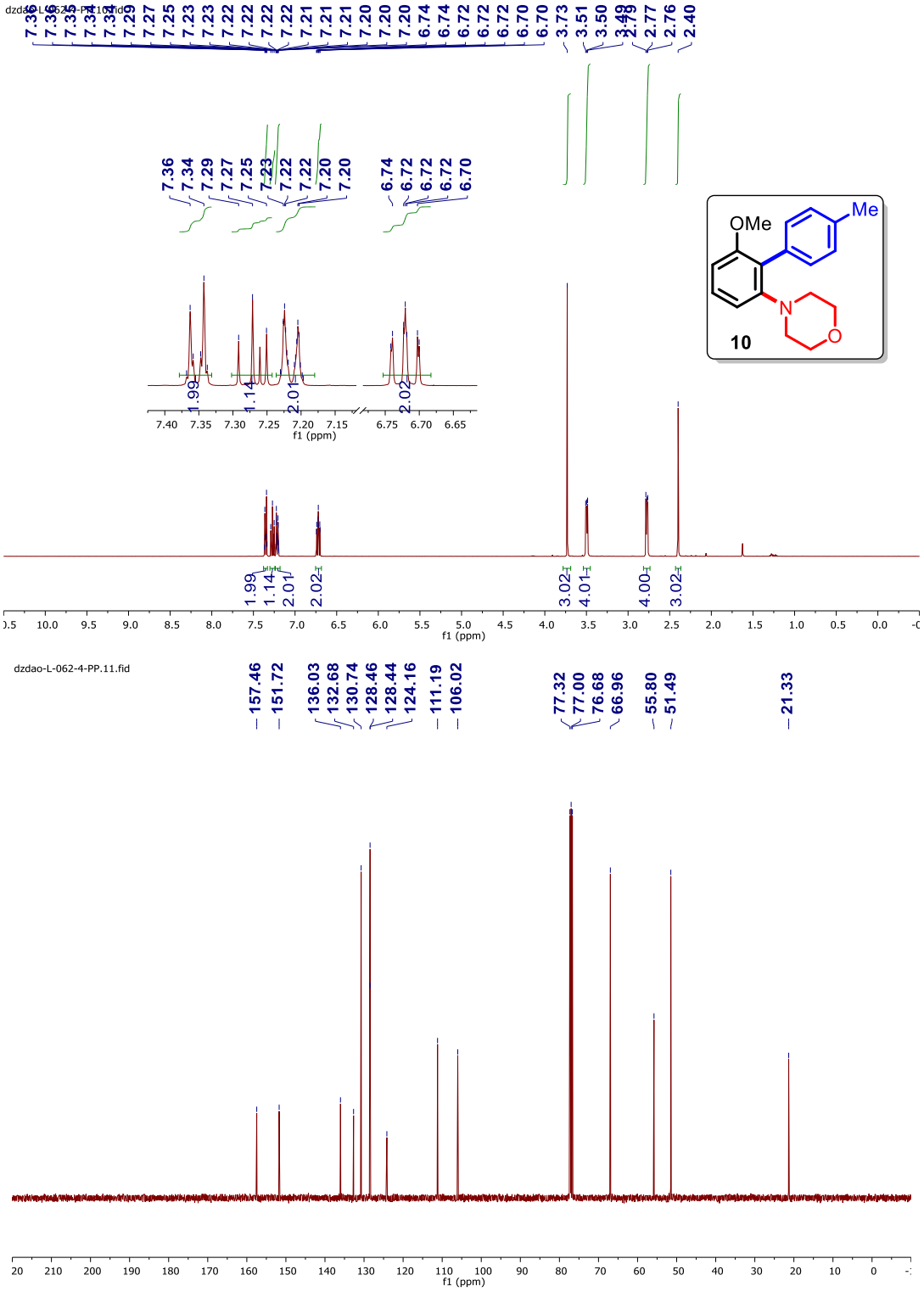


Figure 4.61 ^{1}H and ^{13}C NMR spectrum of compound **12**.

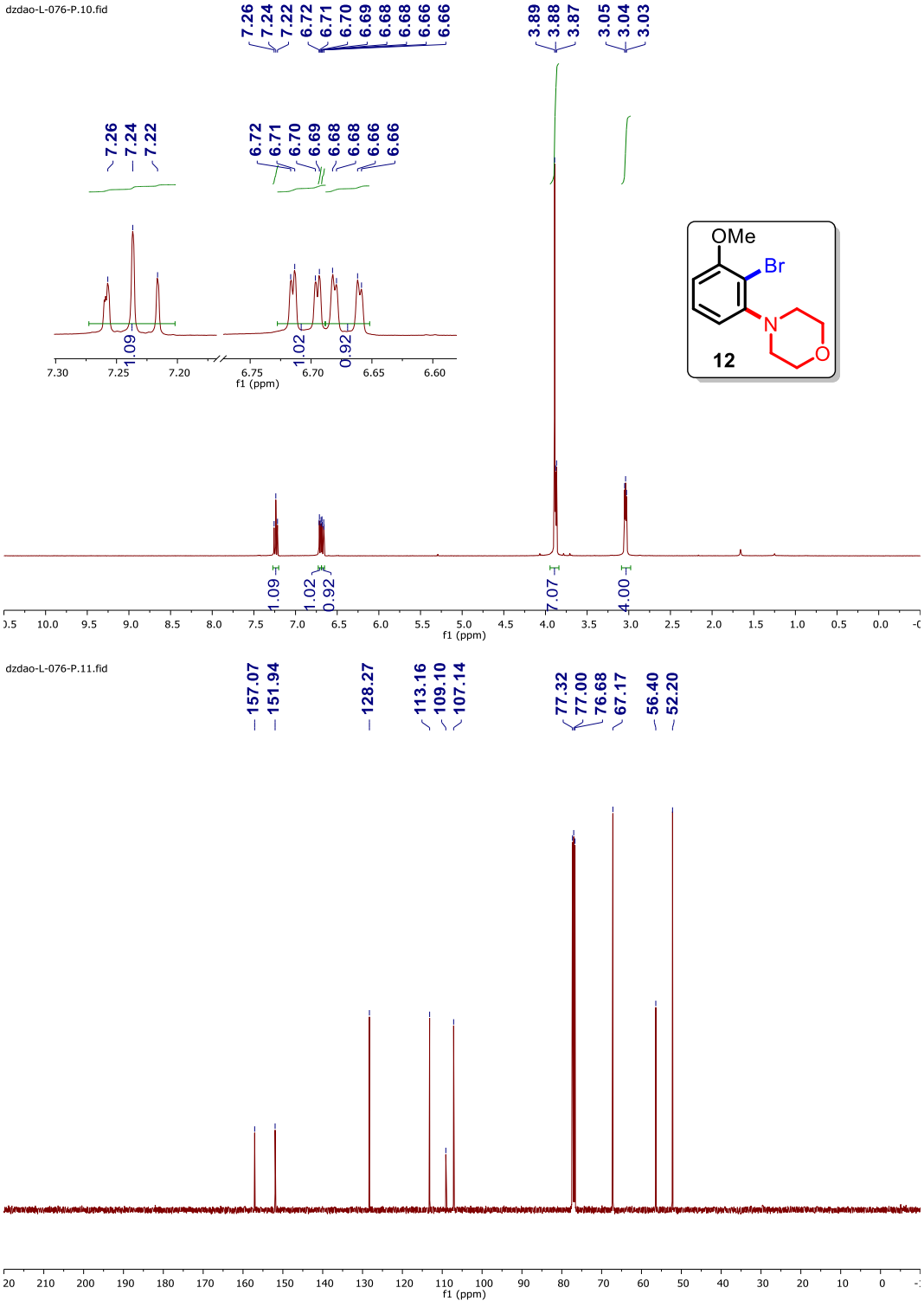


Figure 4.62 ^{1}H and ^{13}C NMR spectrum of compound **15**.

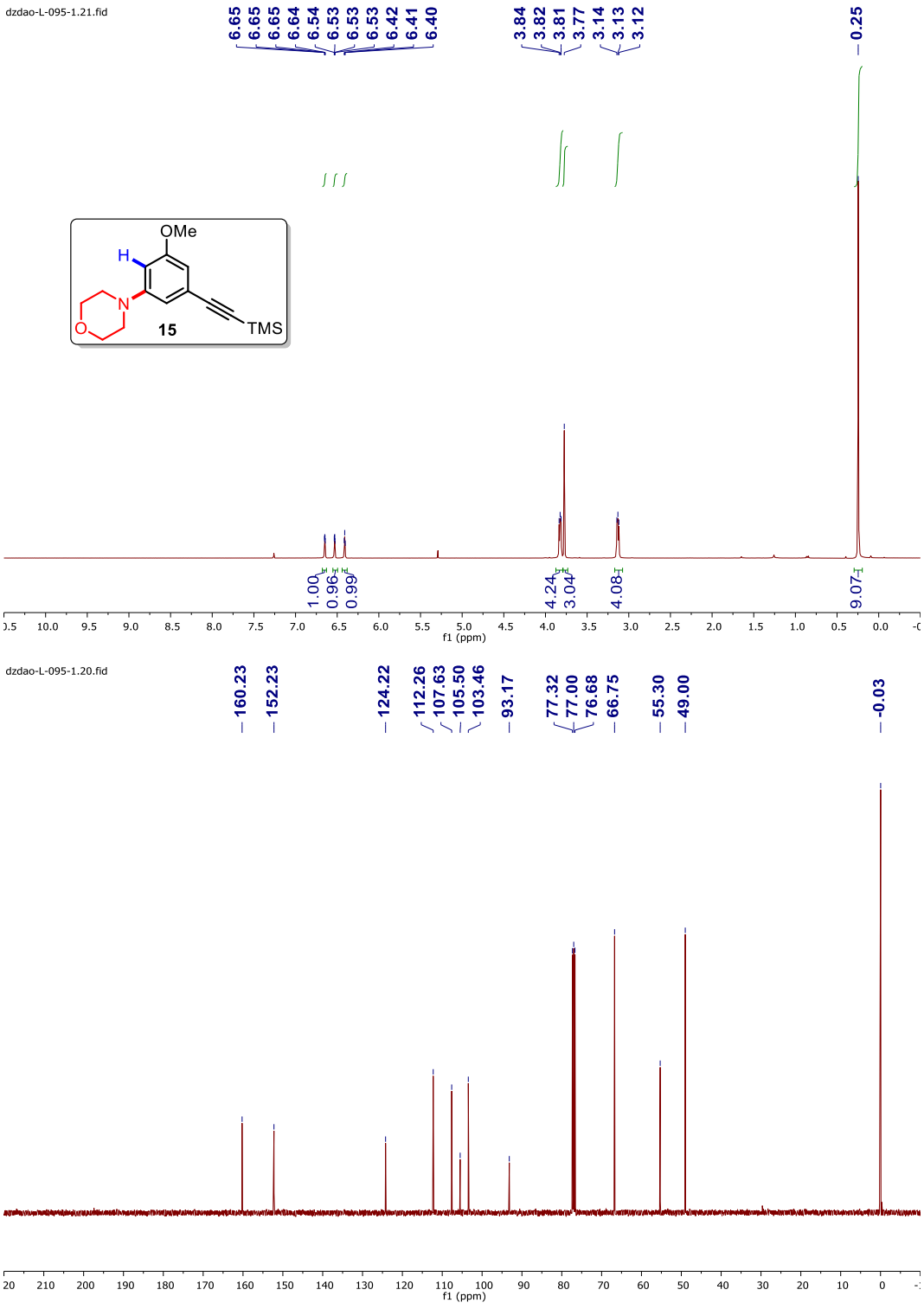


Figure 4.63 ^{1}H and ^{13}C NMR spectrum of compound **18**.

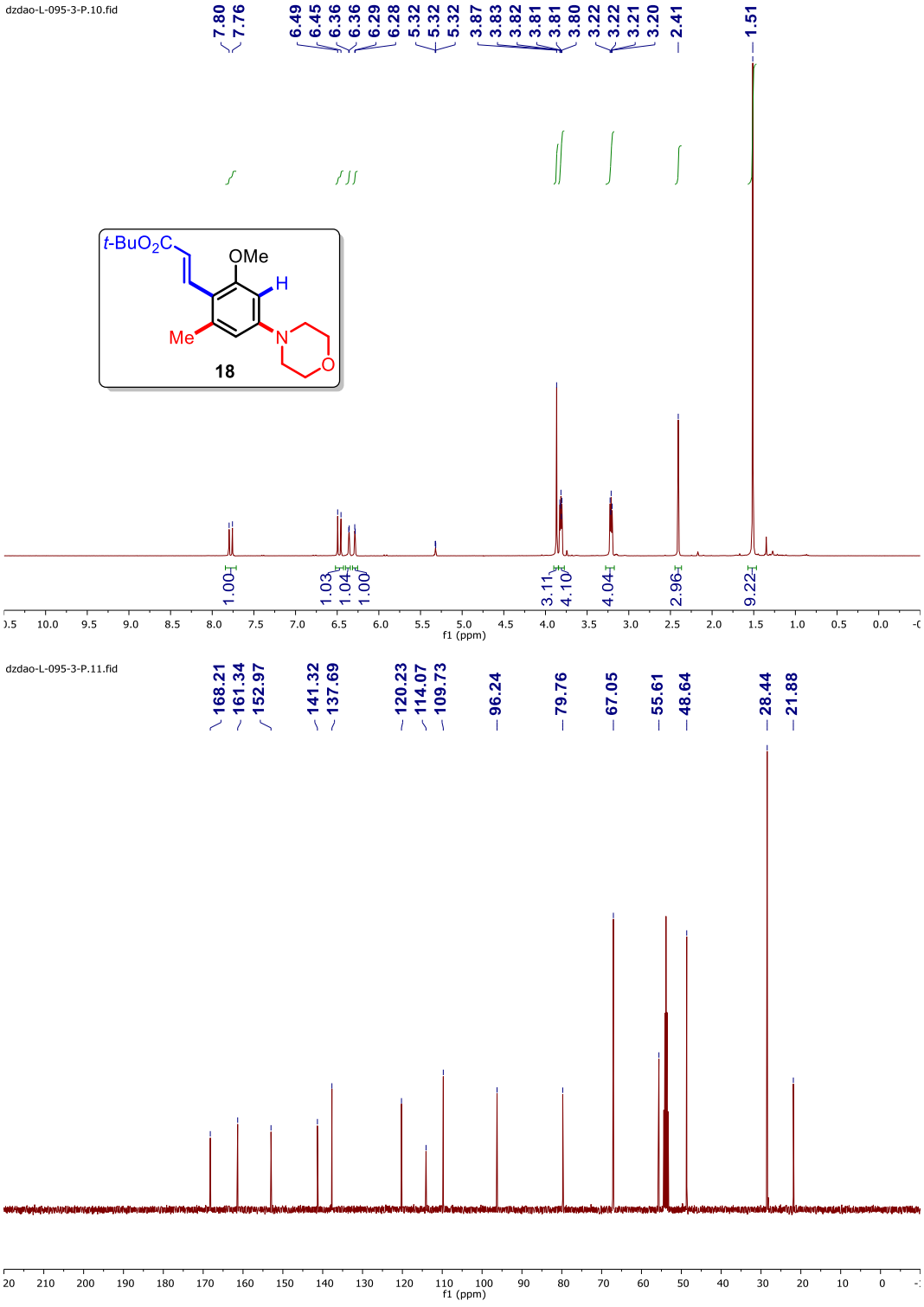


Figure 4.64 ^{1}H and ^{13}C NMR spectrum of compound **19**.

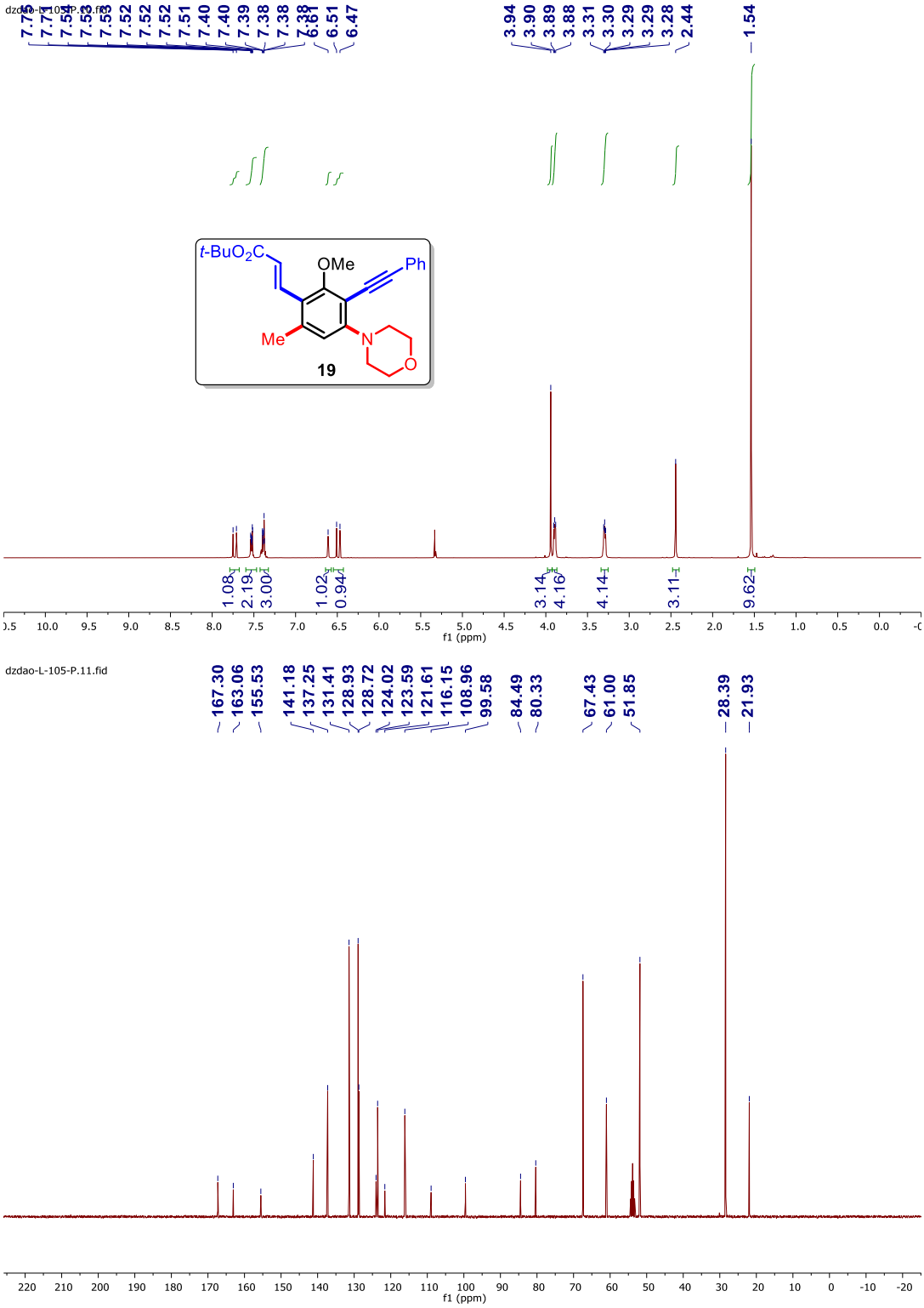


Figure 4.65 ^{1}H and ^{13}C NMR spectrum of compound **21**.

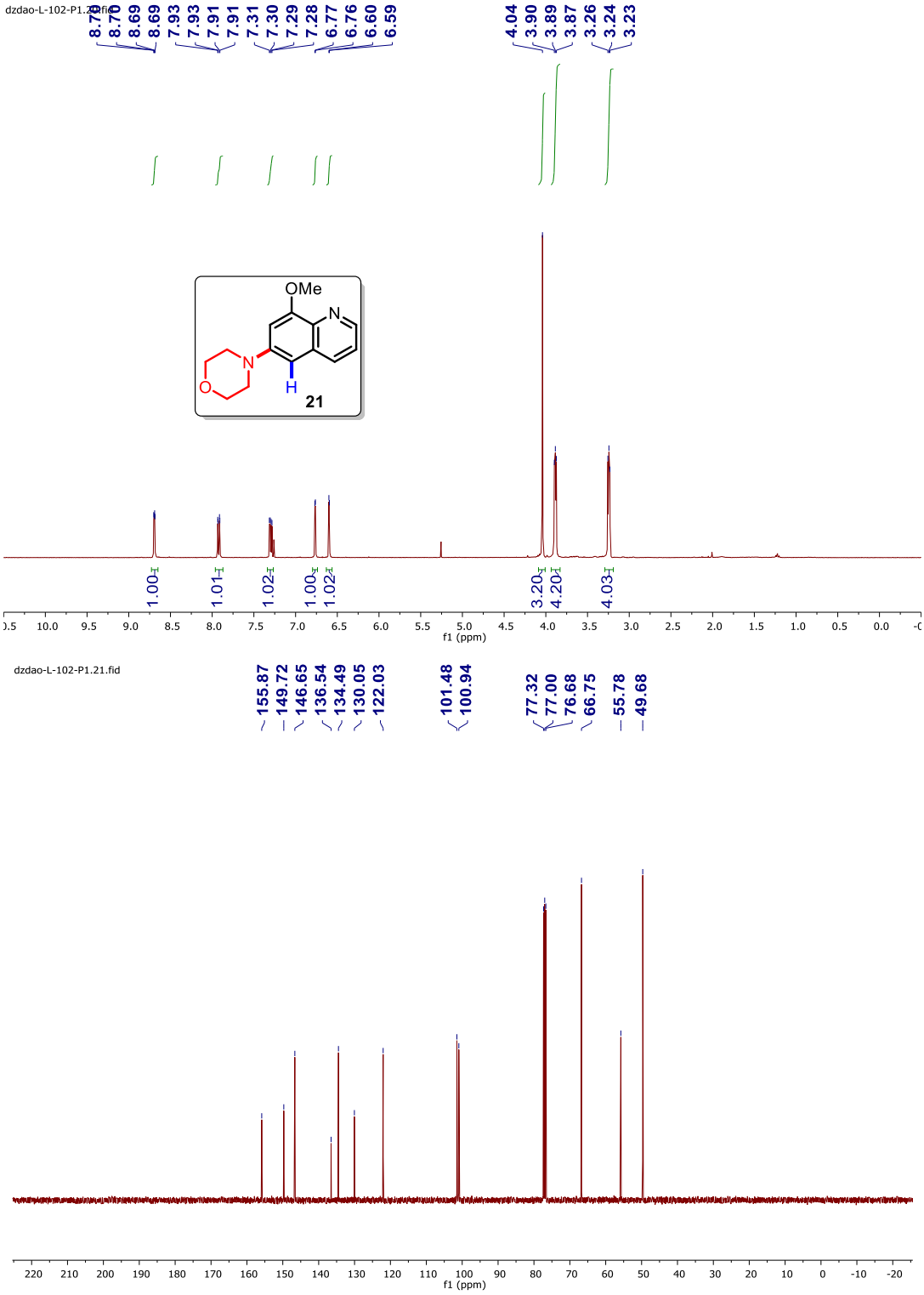


Figure 4.66 ^{1}H and ^{13}C NMR spectrum of compound **24**.

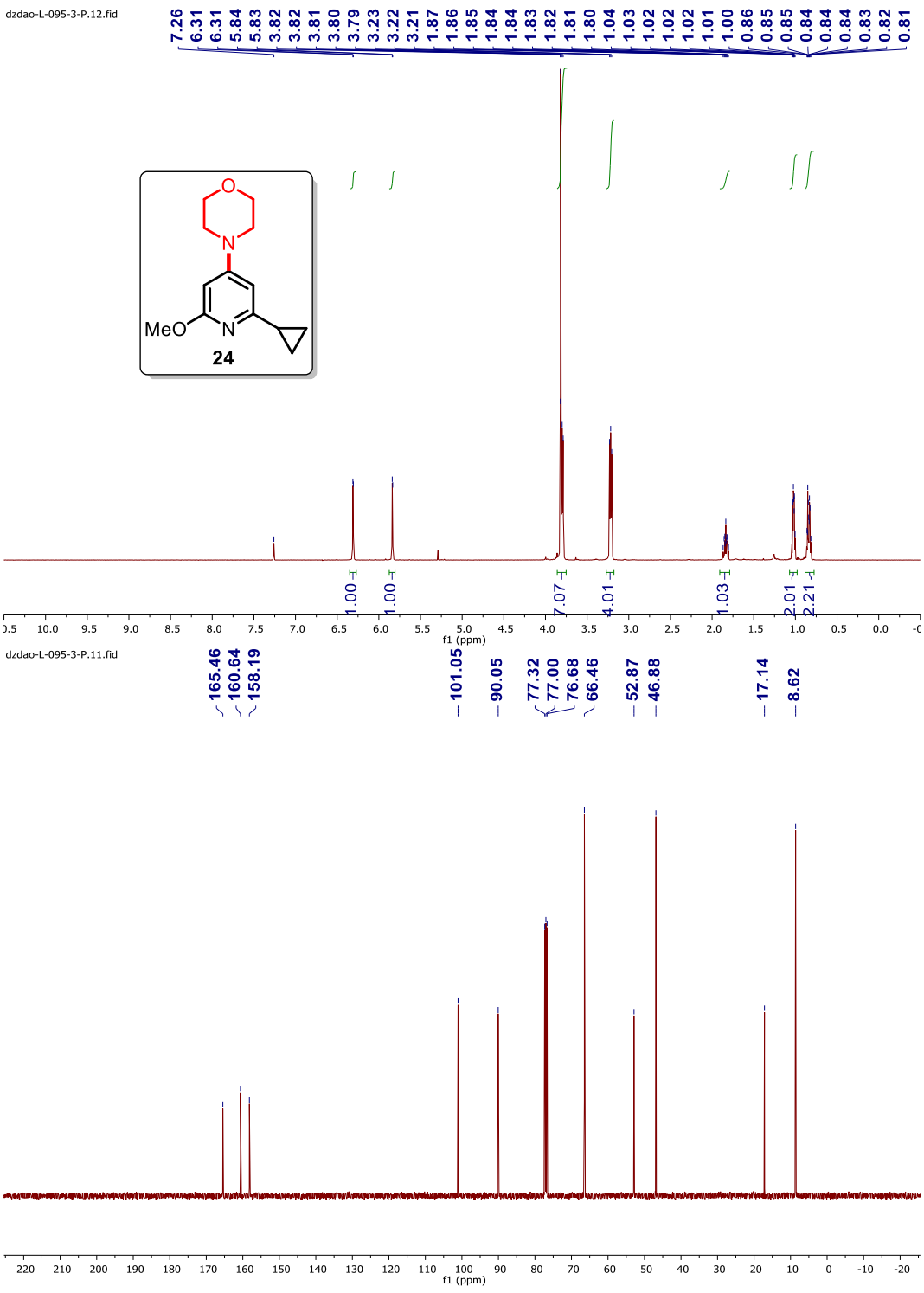


Figure 4.67 ^{1}H and ^{13}C NMR spectrum of compound **26a**.

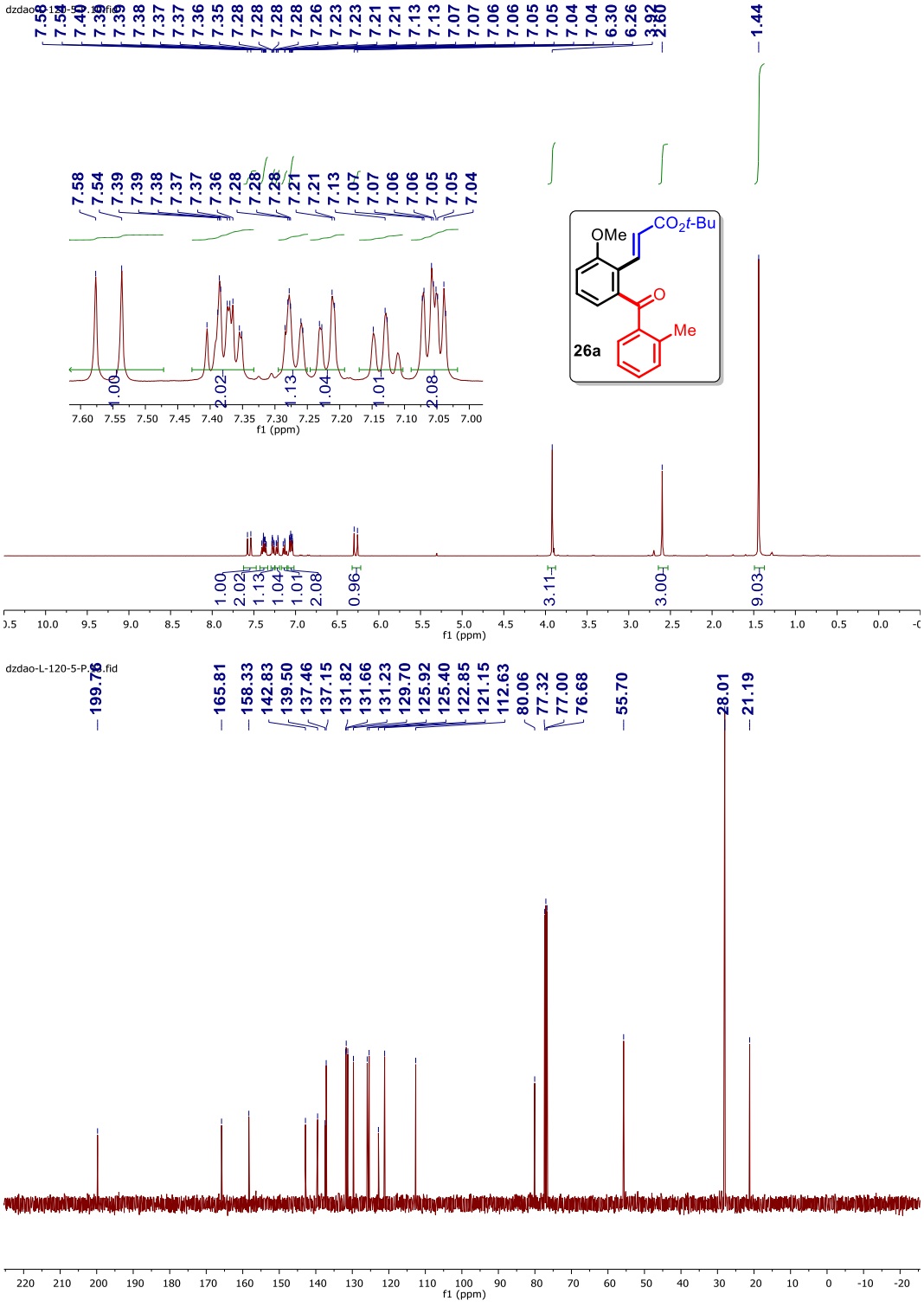


Figure 4.68 ^{1}H and ^{13}C NMR spectrum of compound **26b**.

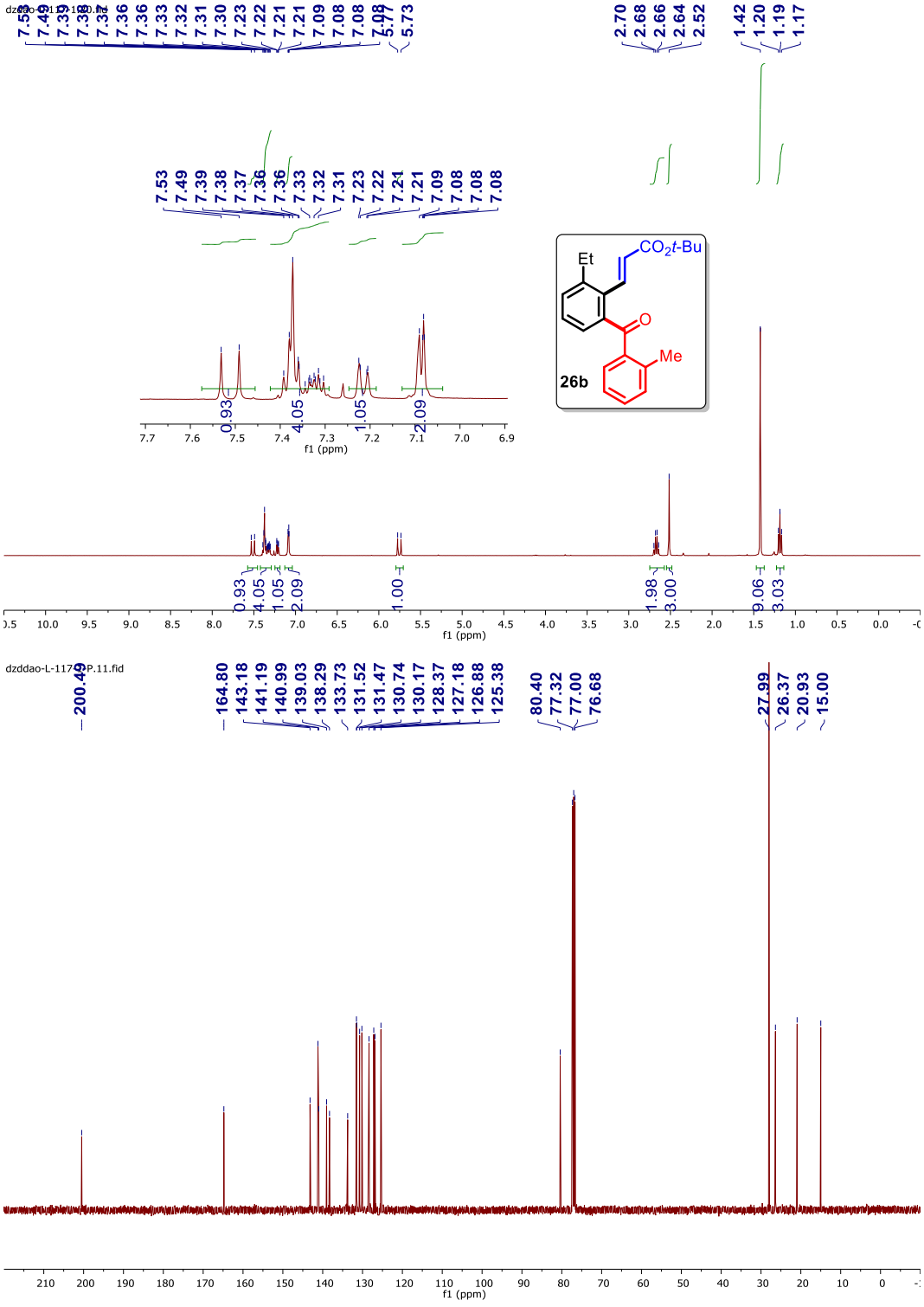


Figure 4.69 ^{1}H and ^{13}C NMR spectrum of compound **26c**.

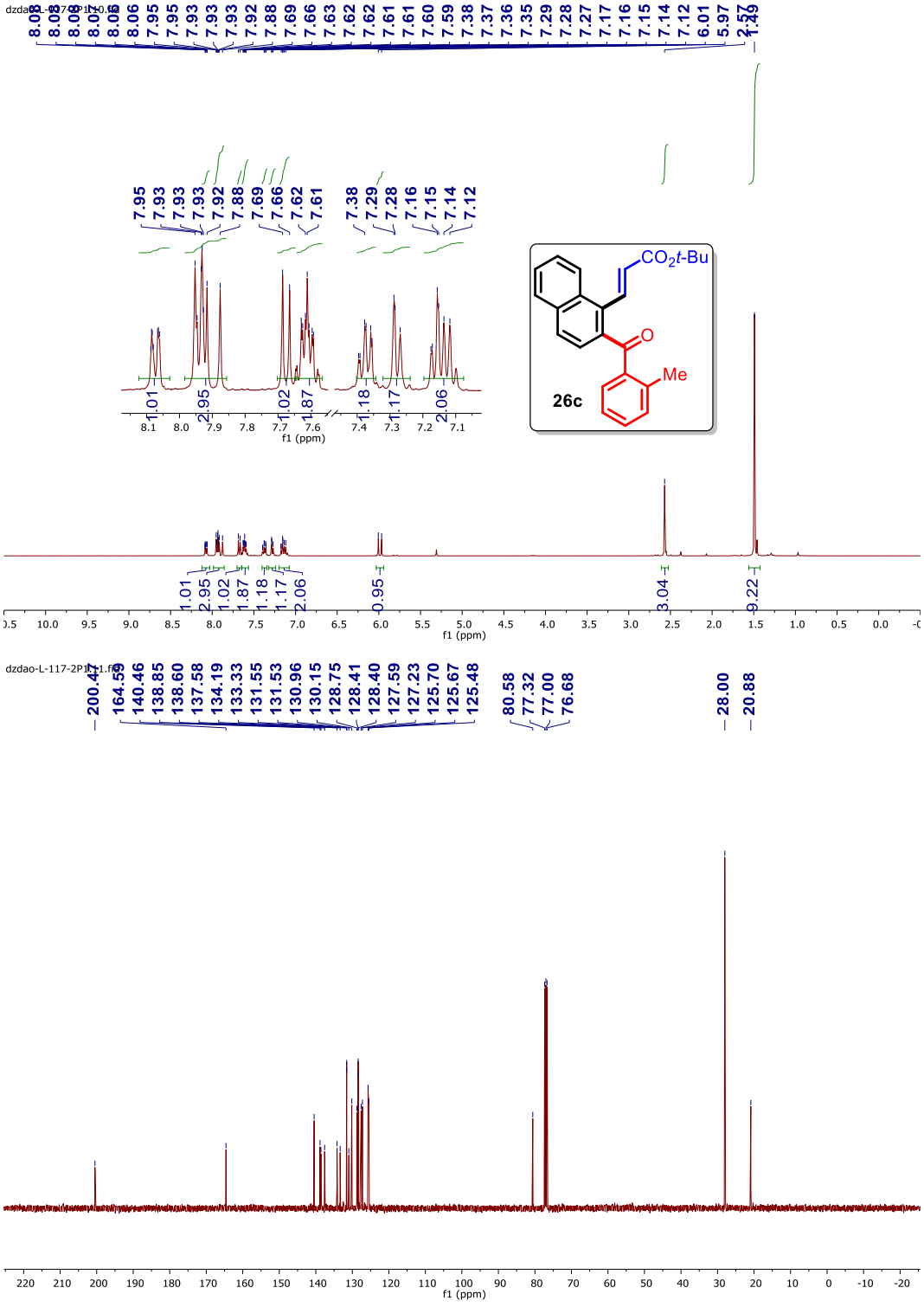


Figure 4.70 ^{1}H and ^{13}C NMR spectrum of compound **26d**.

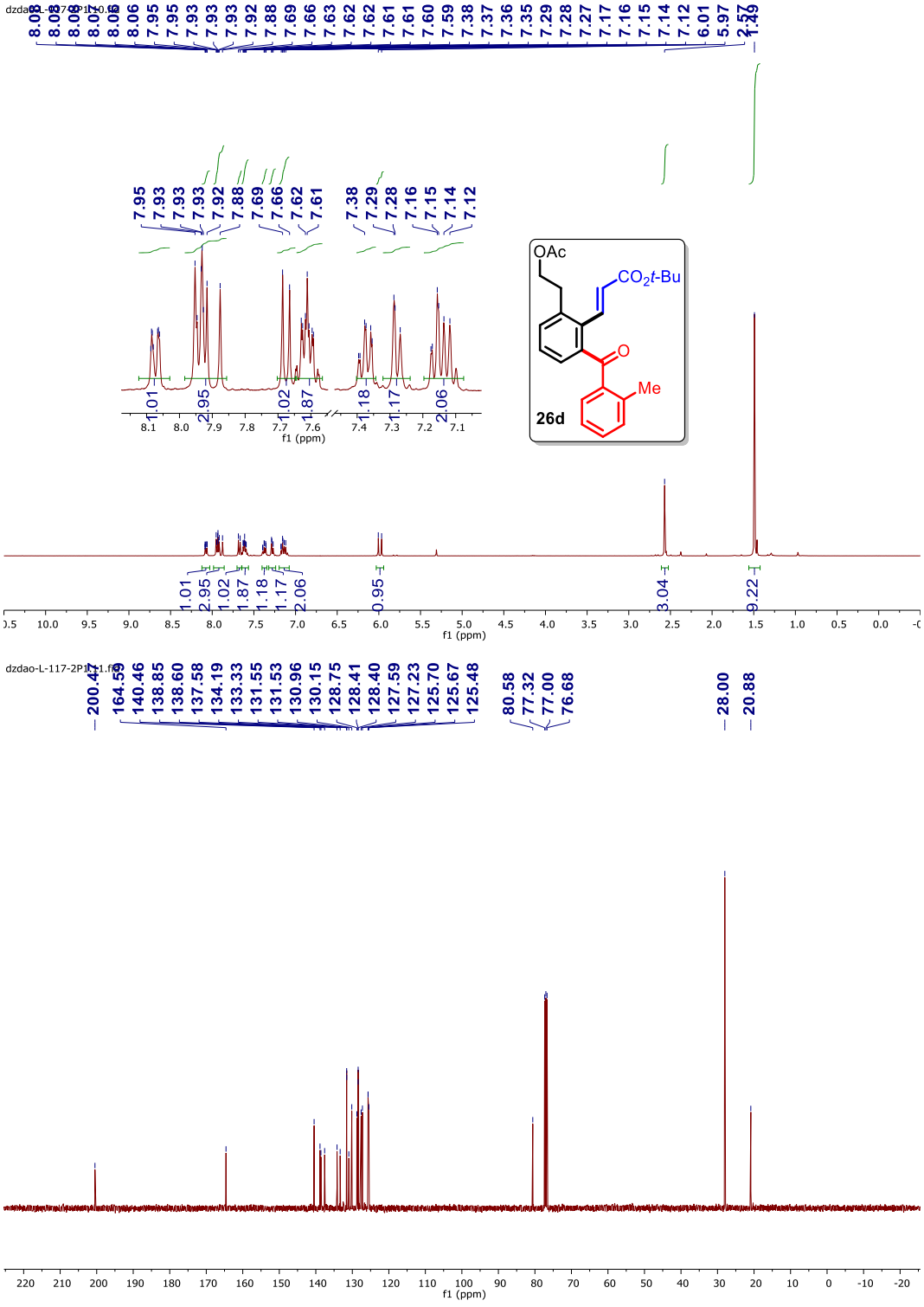


Figure 4.71 ^{1}H and ^{13}C NMR spectrum of compound **26e**.

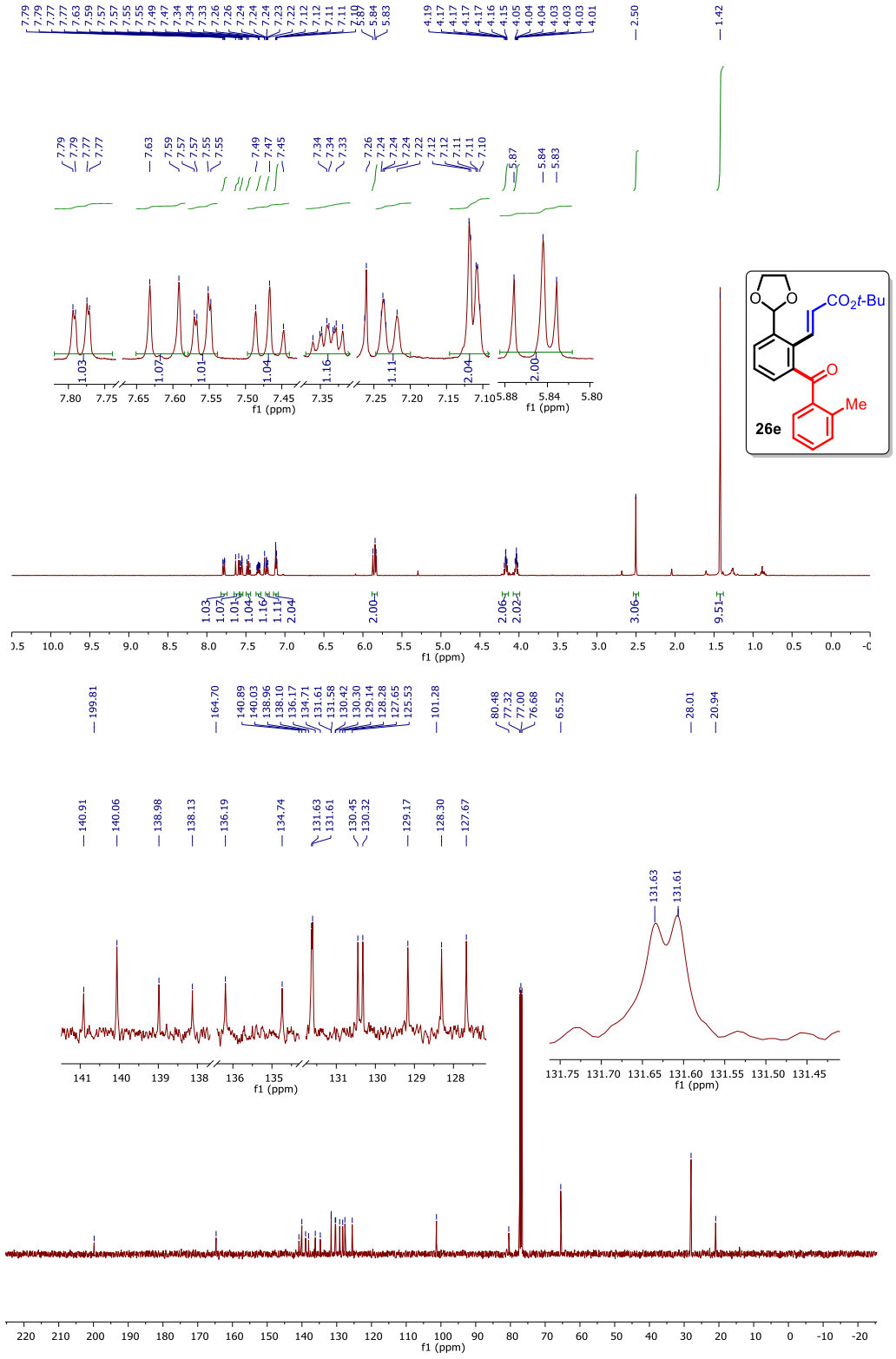


Figure 4.72 ^{1}H and ^{13}C NMR spectrum of compound **26f**.

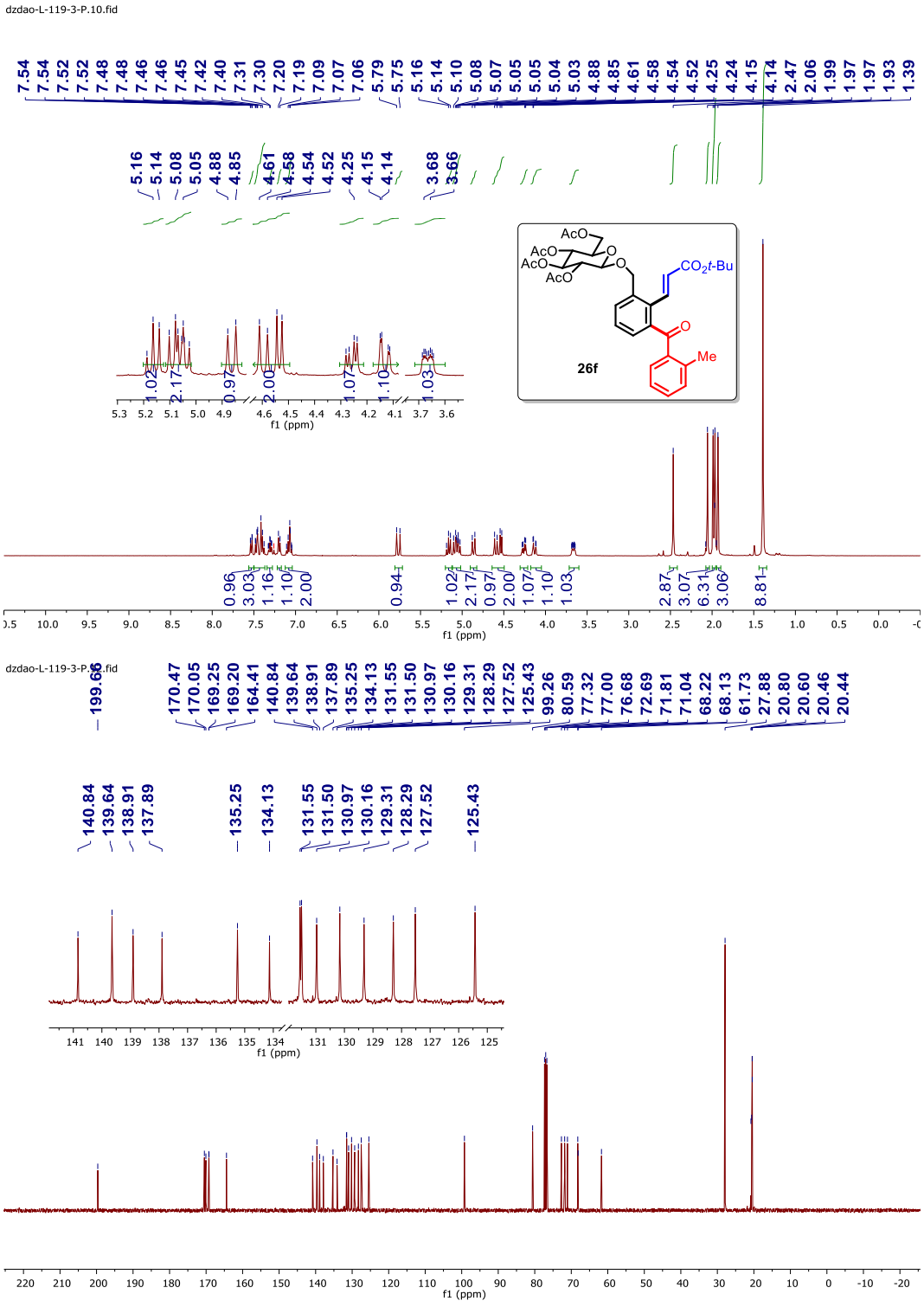


Figure 4.73 ^{1}H and ^{13}C NMR spectrum of compound **26g**.

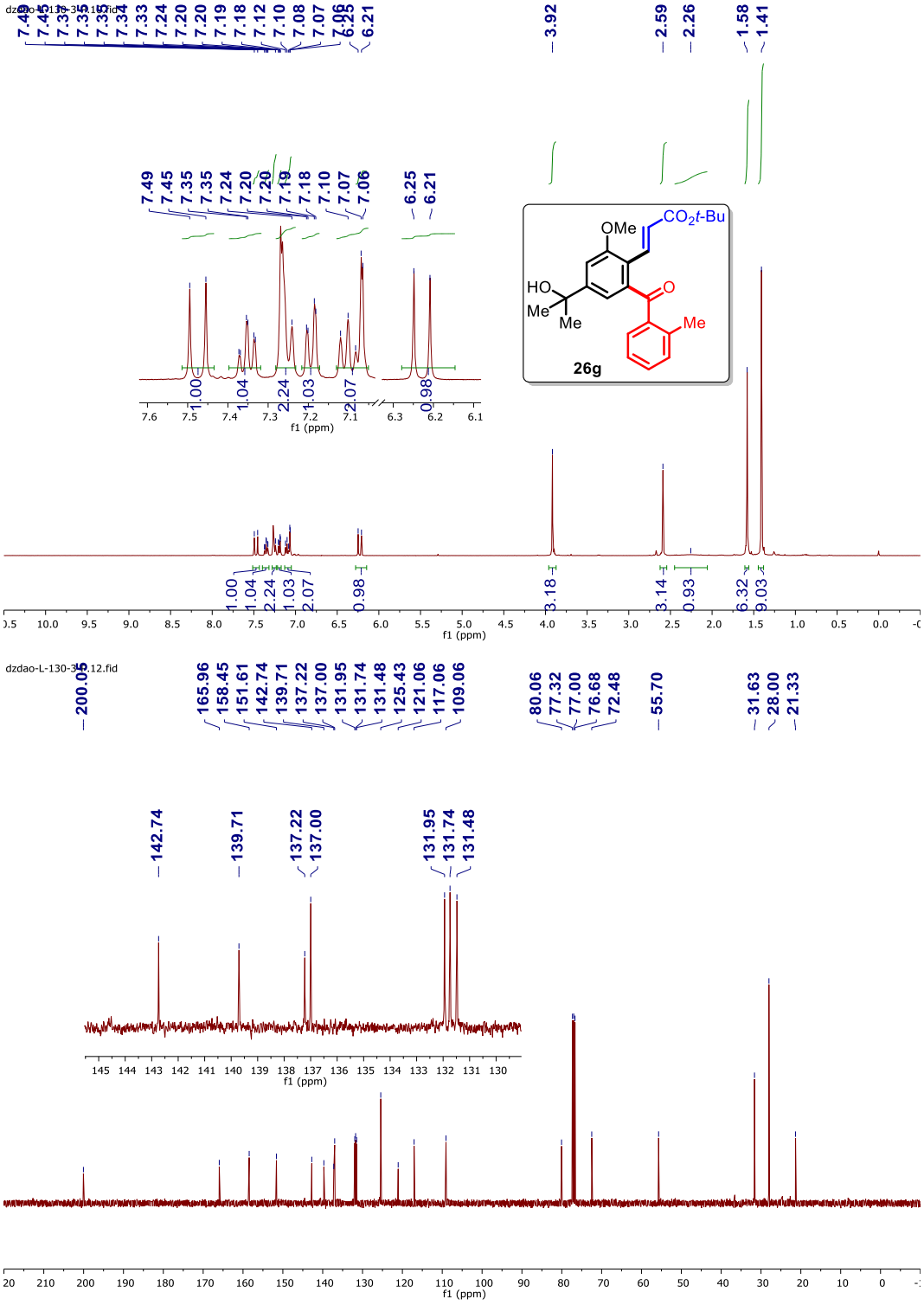


Figure 4.74 ^{1}H and ^{13}C NMR spectrum of compound **26h**.

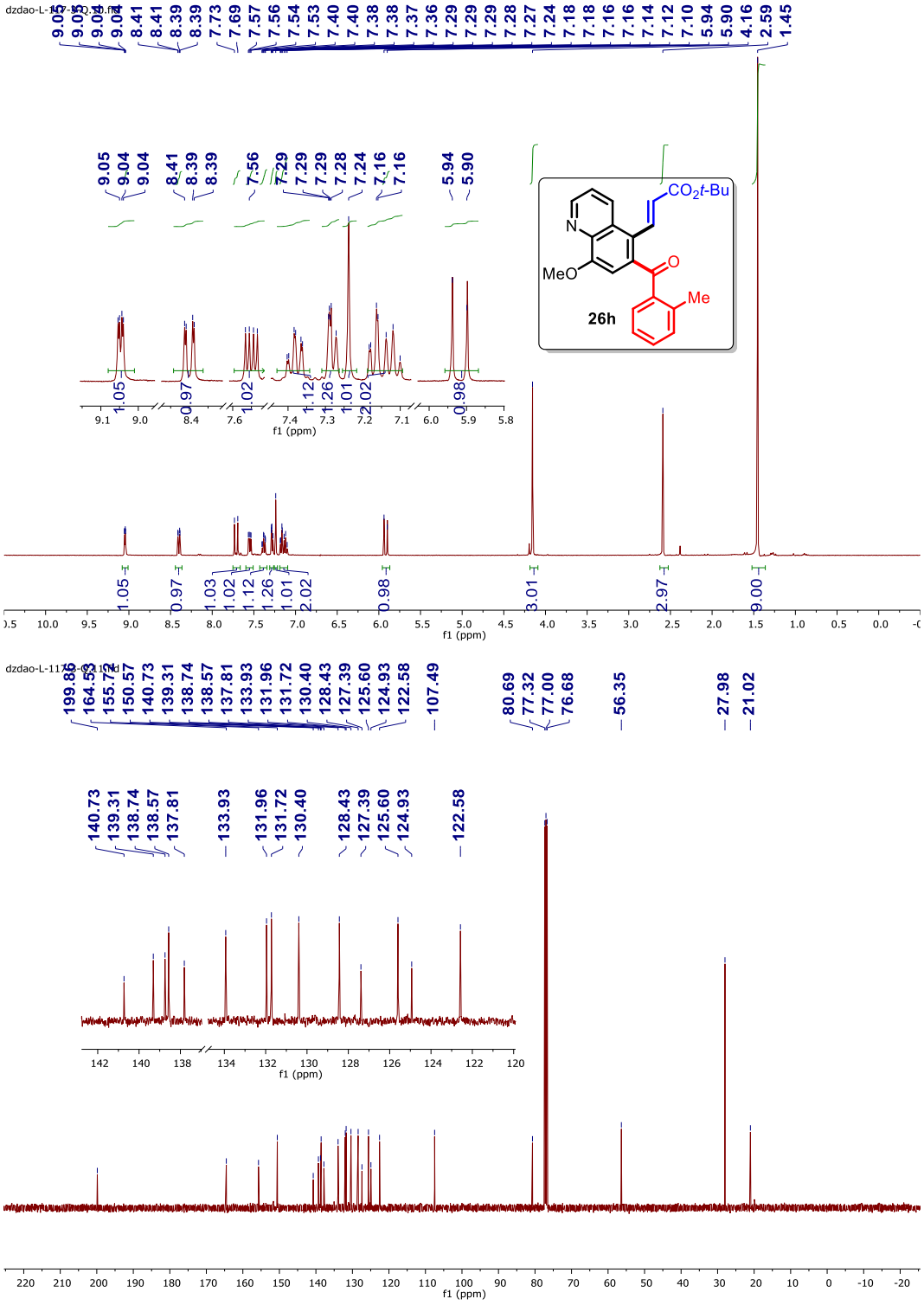


Figure 4.75 ^{1}H and ^{13}C NMR spectrum of compound **26i**.

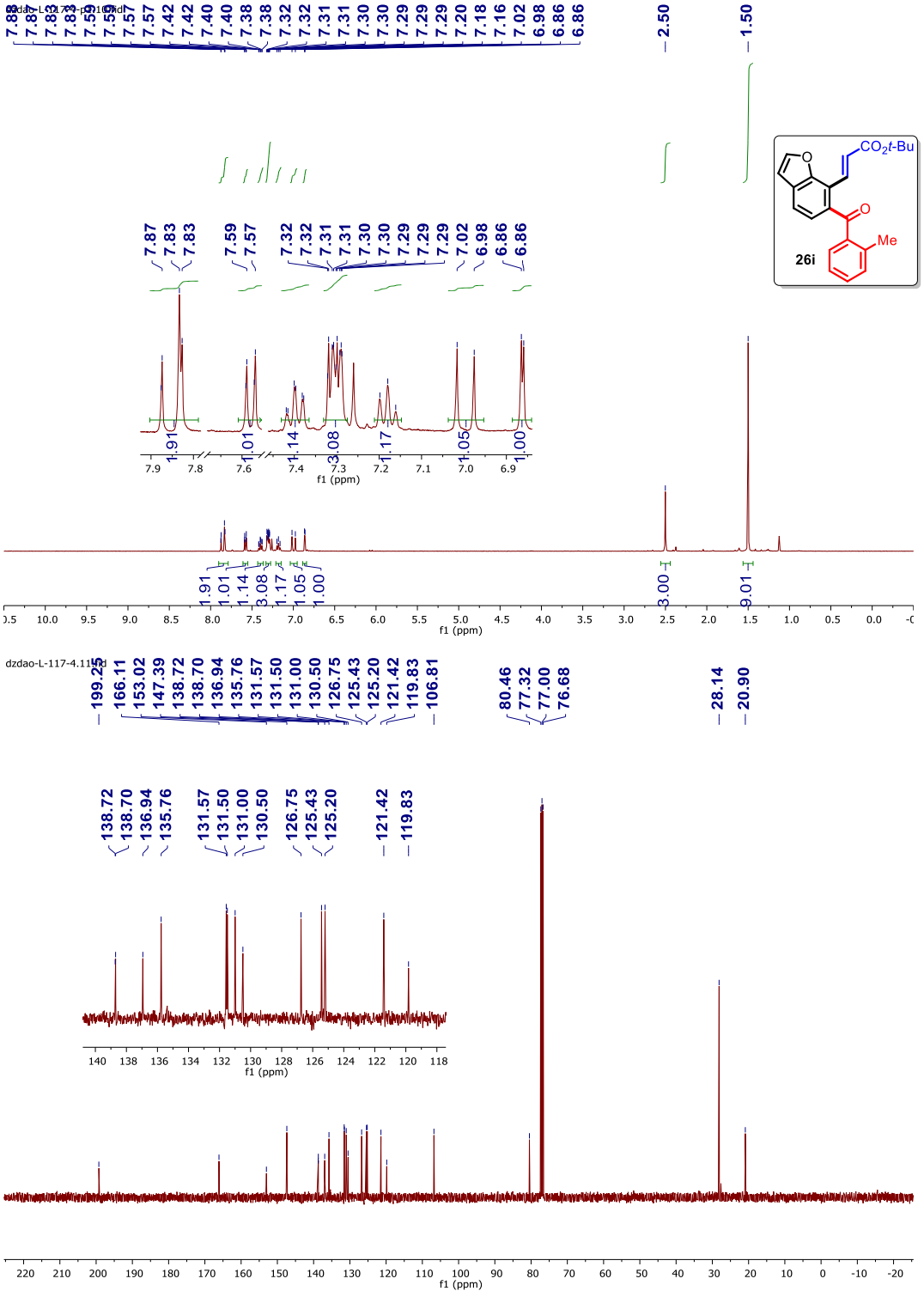


Figure 4.76 ^{1}H and ^{13}C NMR spectrum of compound **27a**.

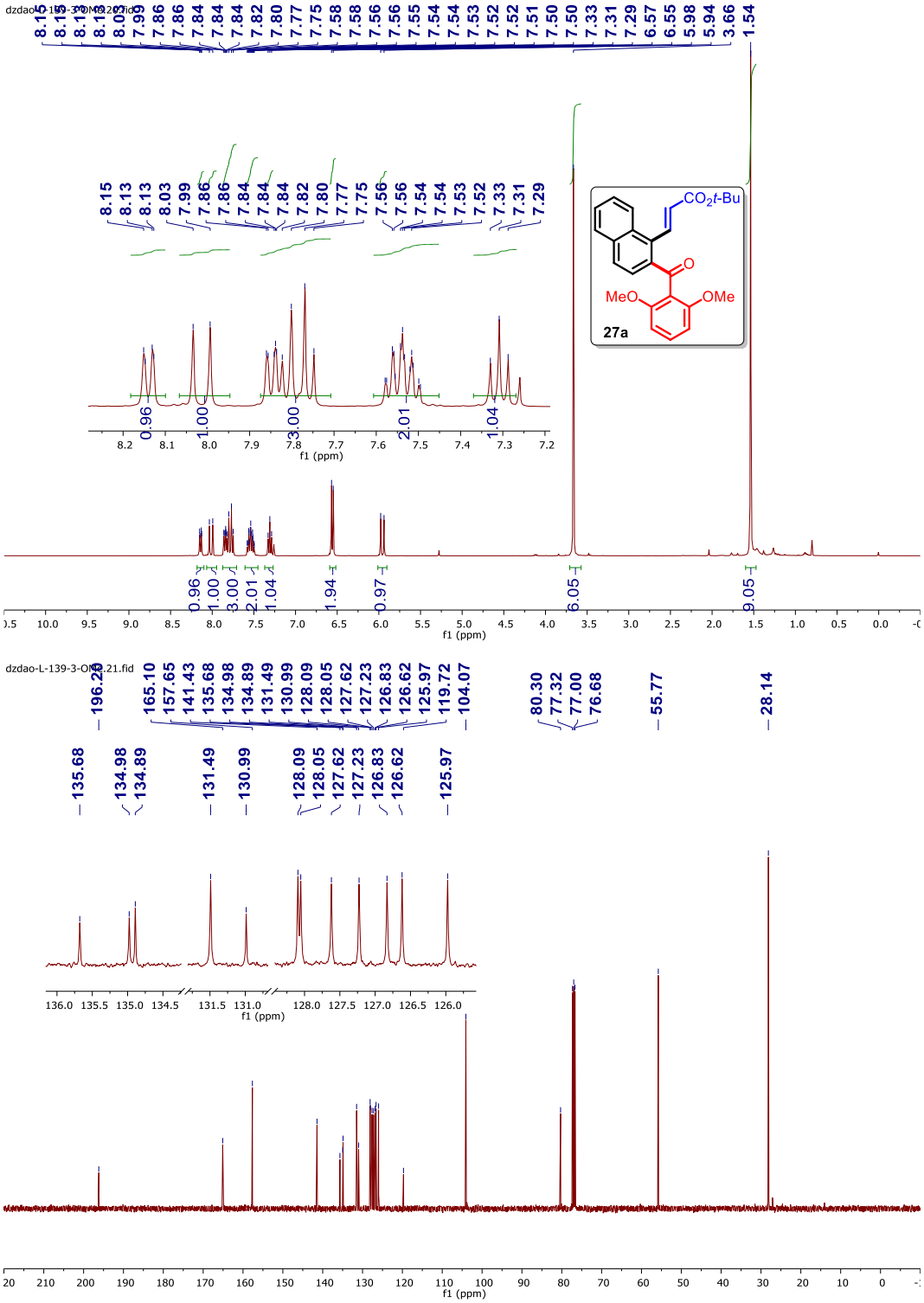


Figure 4.77 ^{1}H and ^{13}C NMR spectrum of compound **27b**.

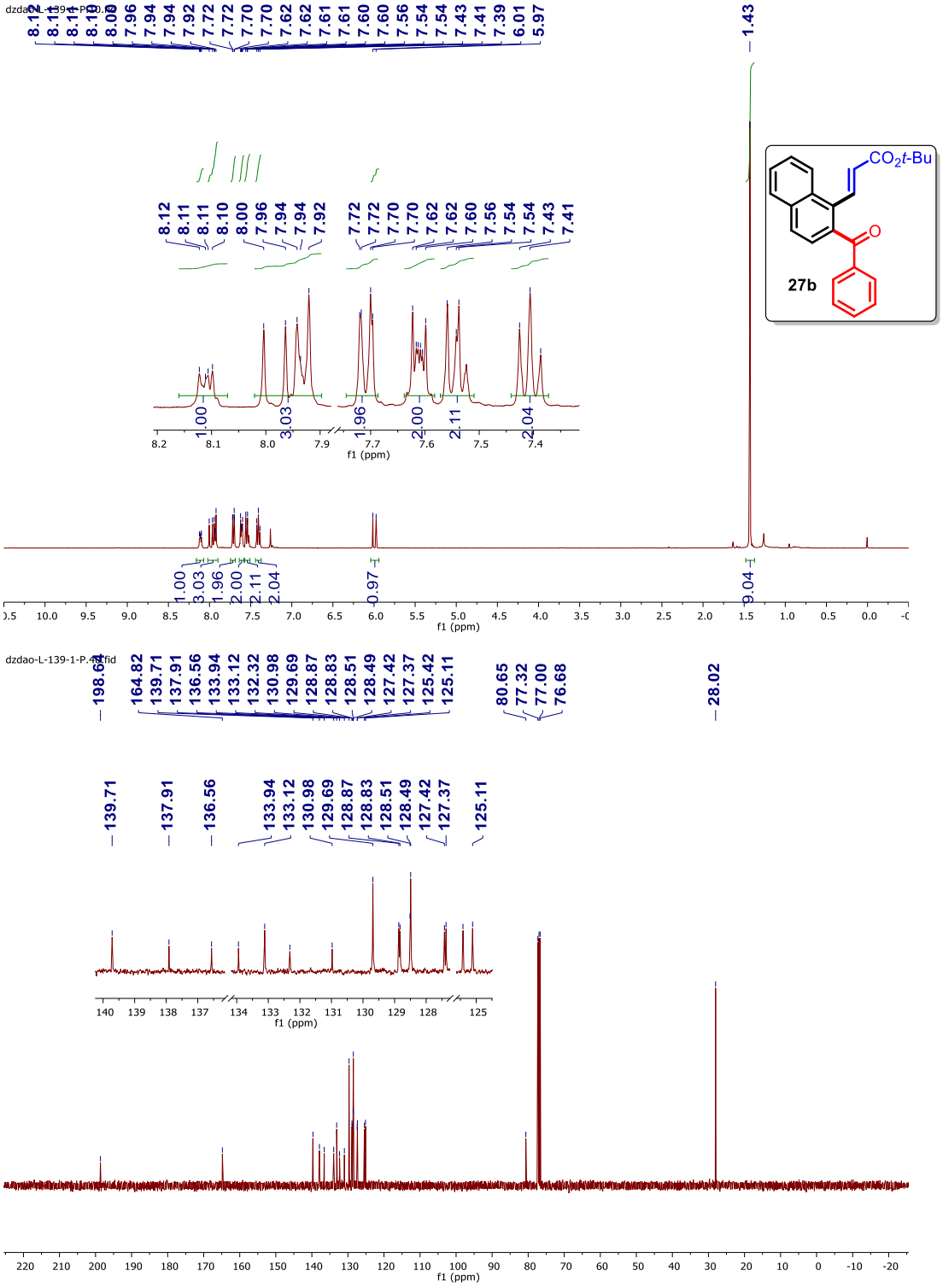


Figure 4.78 ^{1}H and ^{13}C NMR spectrum of compound **27c**.

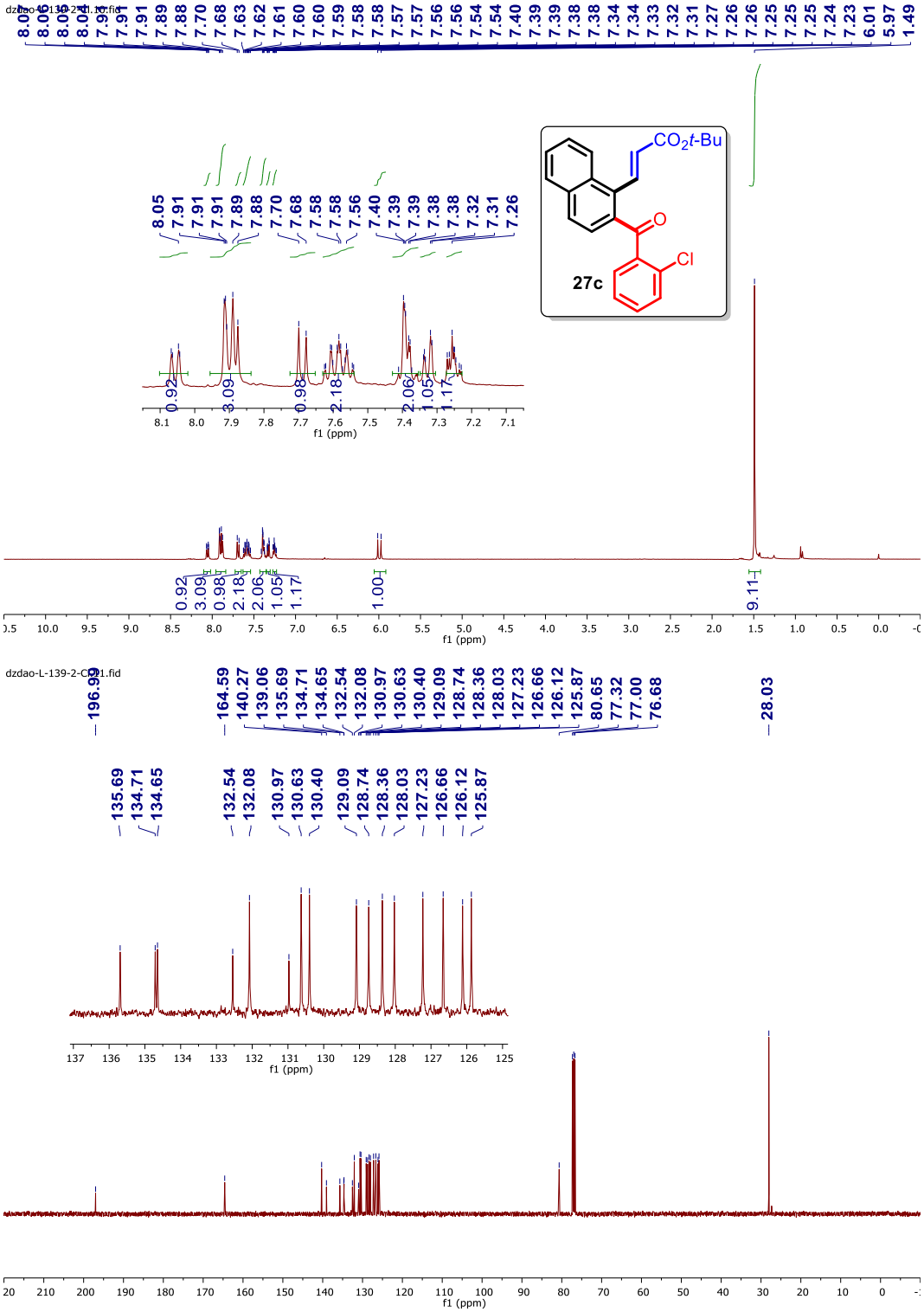


Figure 4.79 ^{1}H and ^{13}C NMR spectrum of compound **27d**.

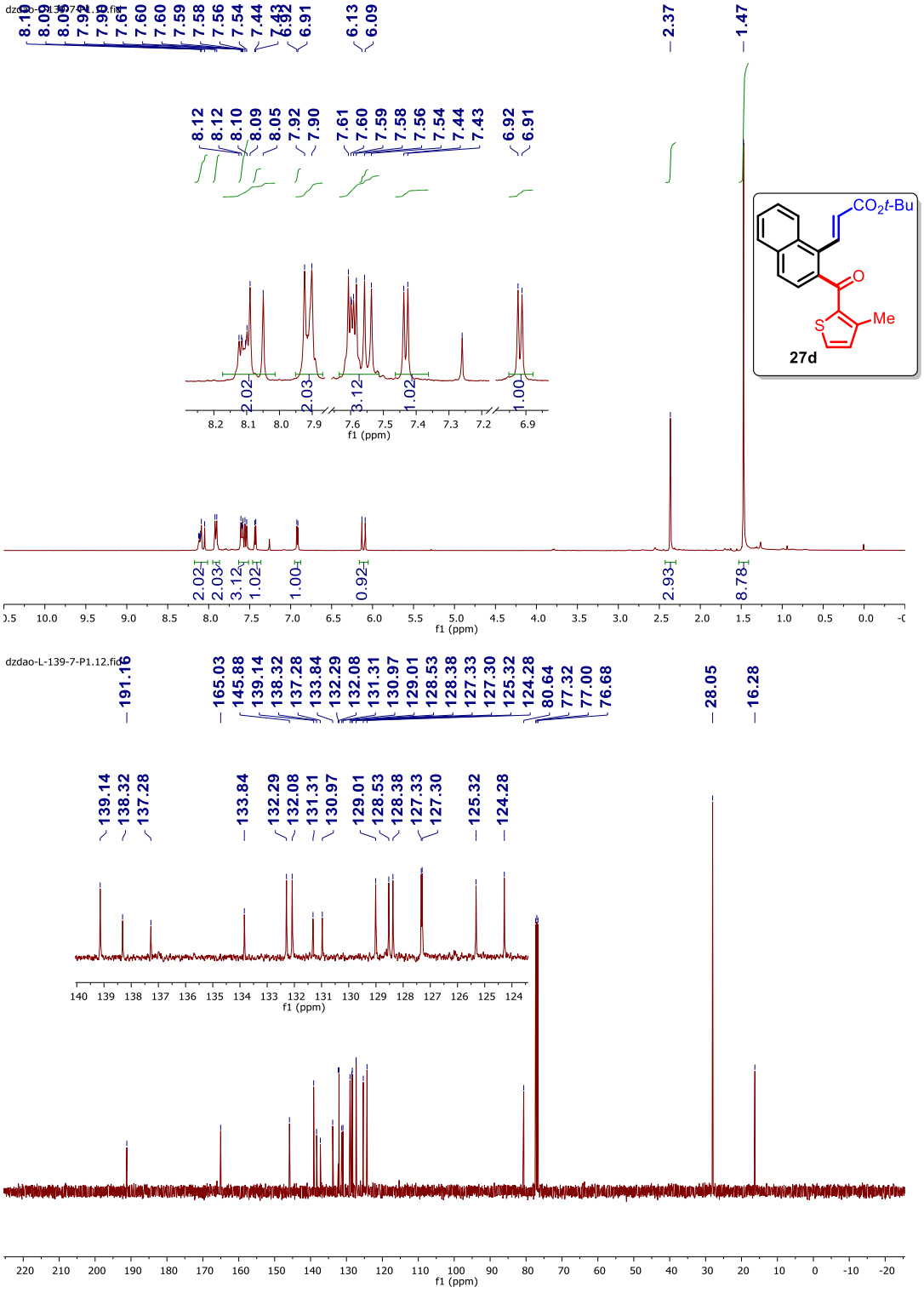


Figure 4.80 ^{1}H and ^{13}C NMR spectrum of compound **27e**.

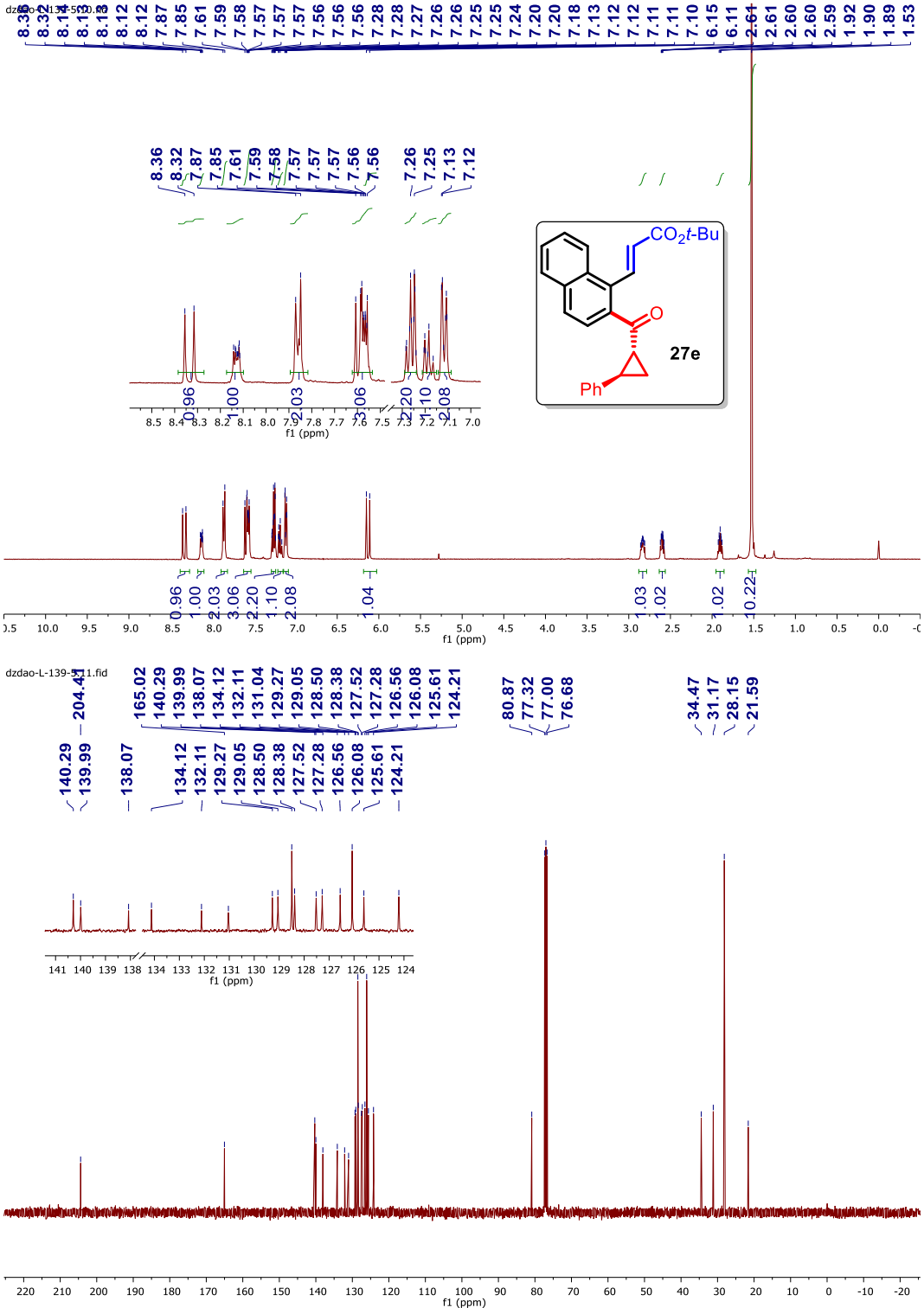


Figure 4.81 ^{1}H and ^{13}C NMR spectrum of compound **27f**.

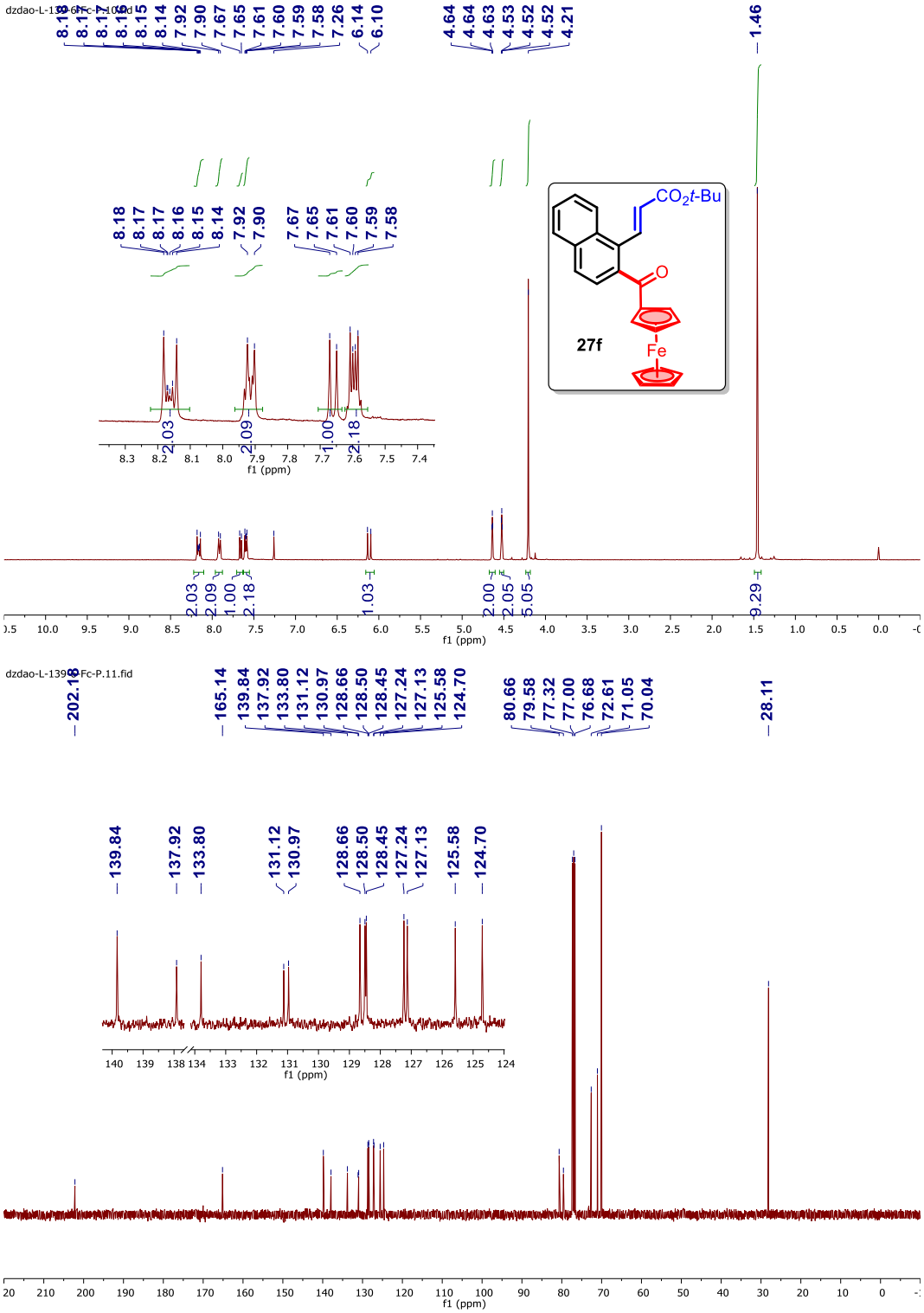


Figure 4.82 ^{1}H and ^{13}C NMR spectrum of compound **29a**.

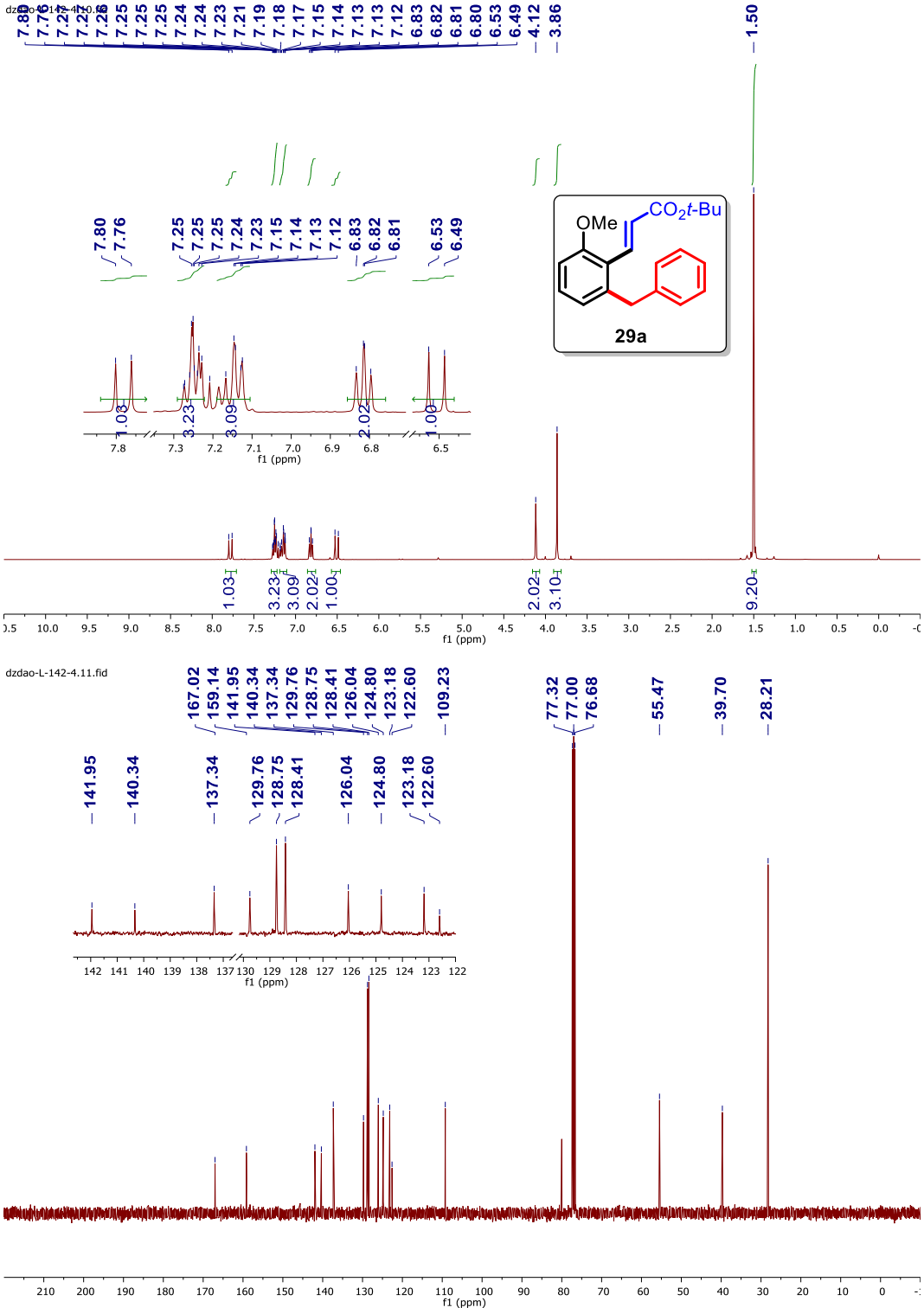


Figure 4.83 ^{1}H and ^{13}C NMR spectrum of compound **29b**.

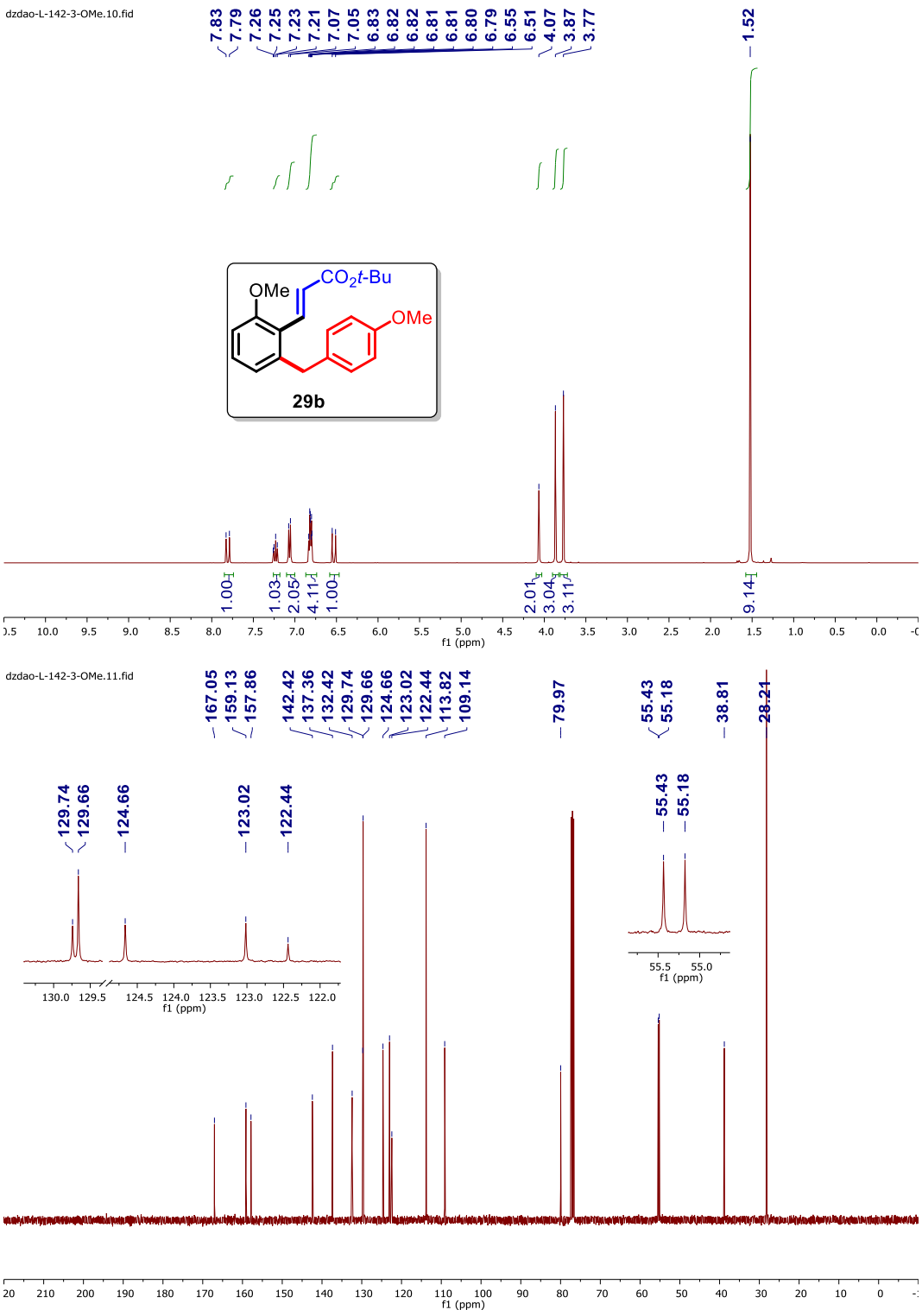


Figure 4.84 ^{1}H and ^{13}C NMR spectrum of compound **29c**.

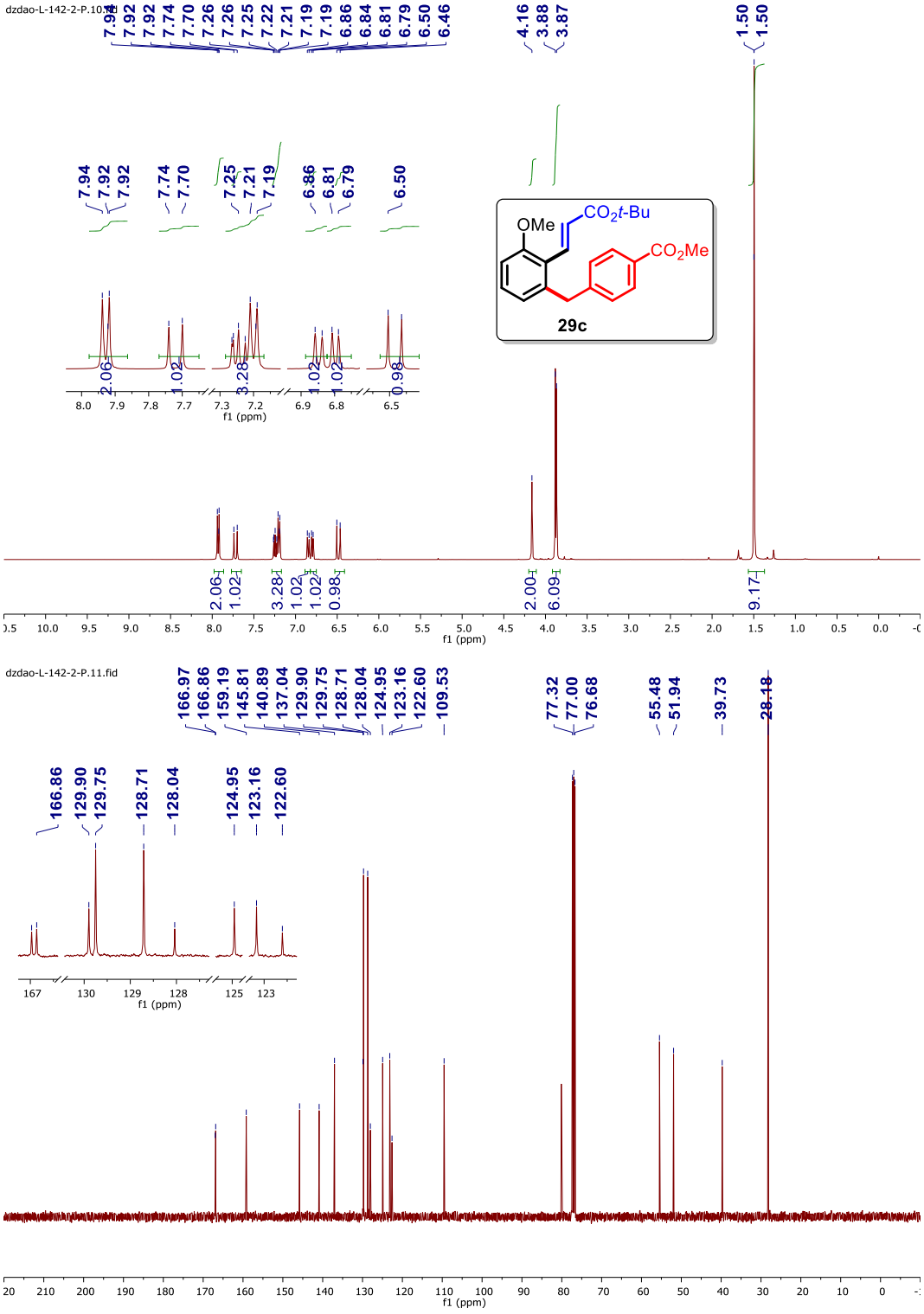


Figure 4.85 ^{1}H and ^{13}C NMR spectrum of compound **29d**.

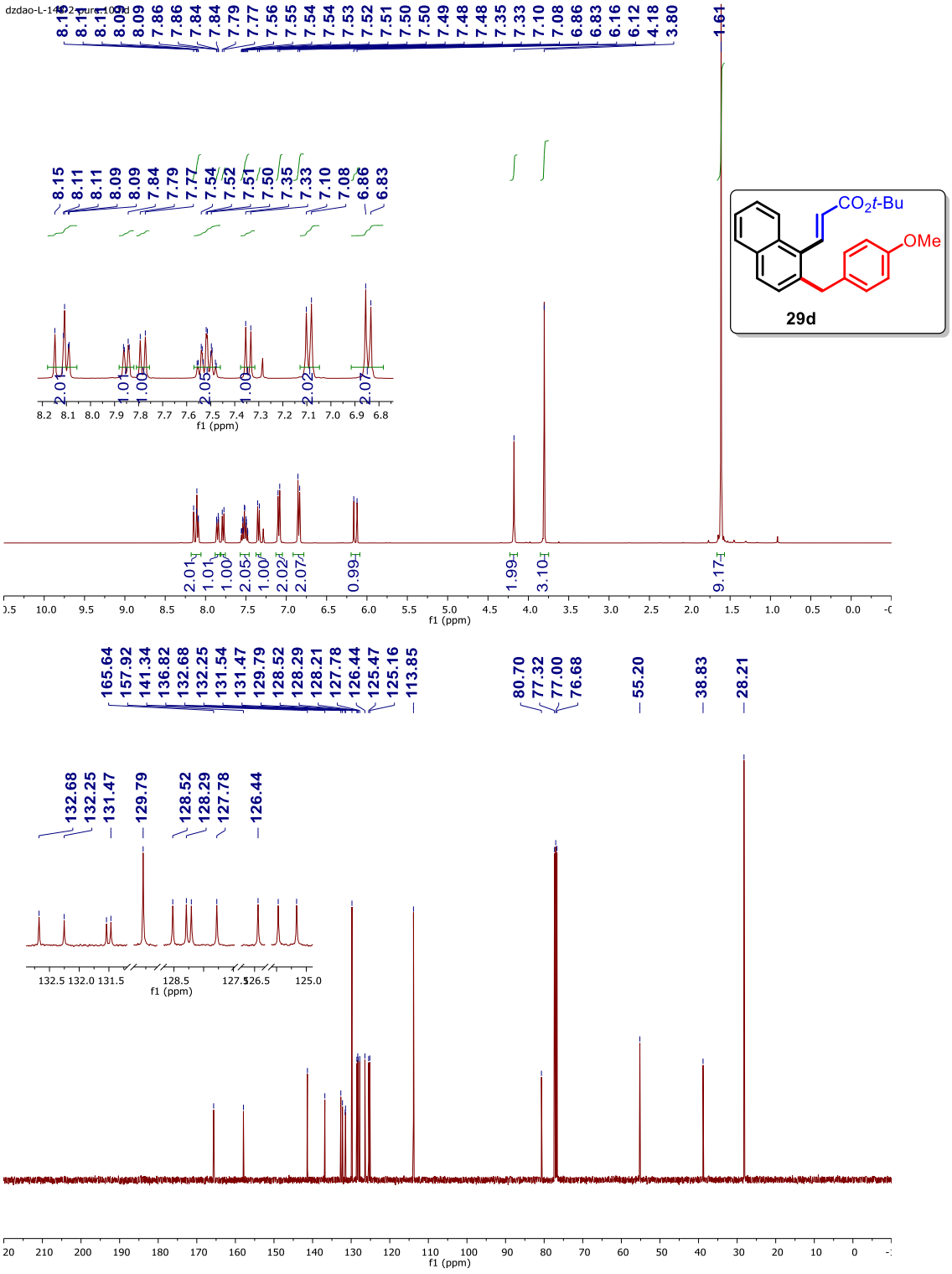


Figure 4.86 ^{1}H and ^{13}C NMR spectrum of compound **29e**.

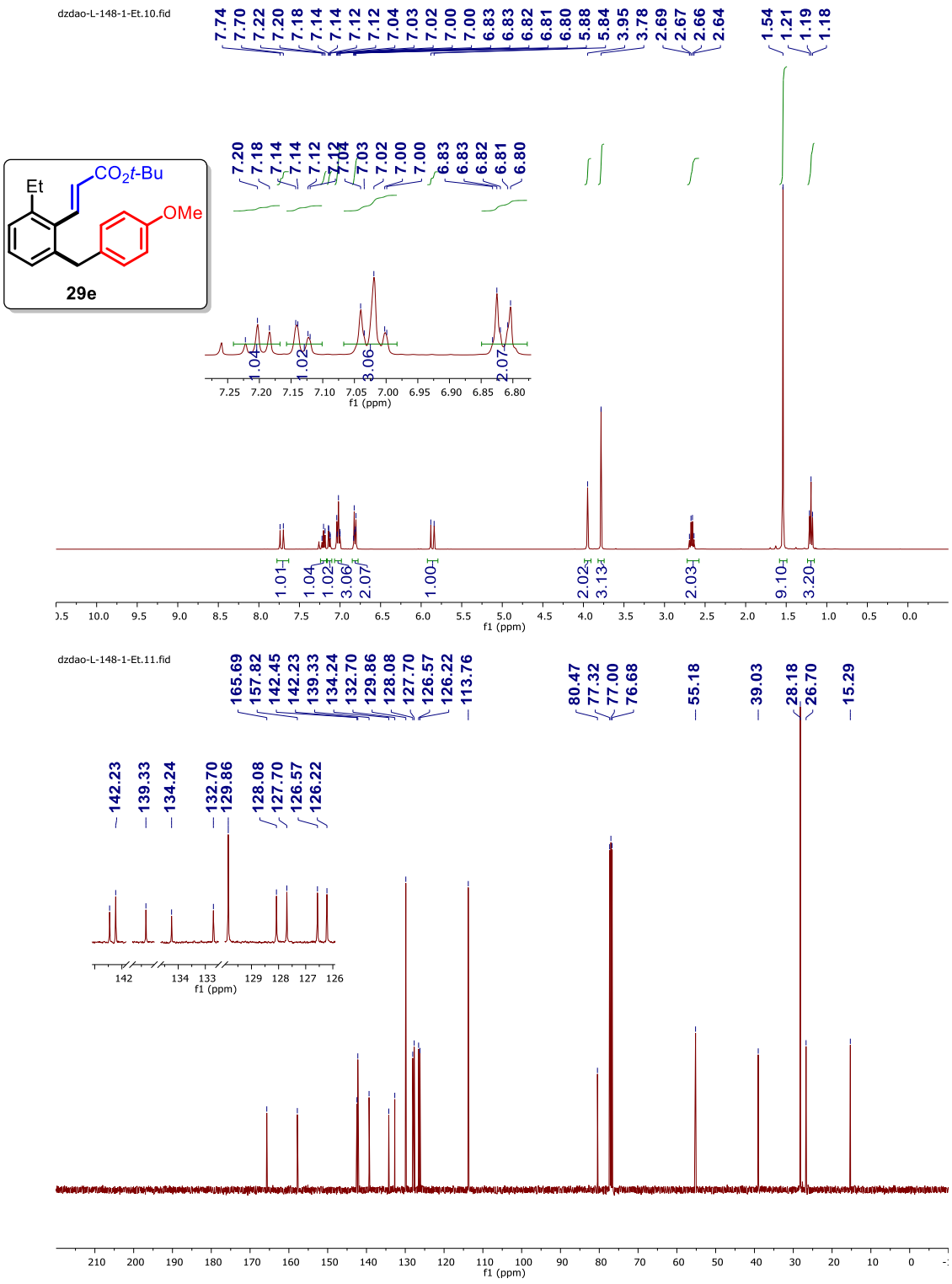


Figure 4.87 ^{1}H and ^{13}C NMR spectrum of compound **29f**.

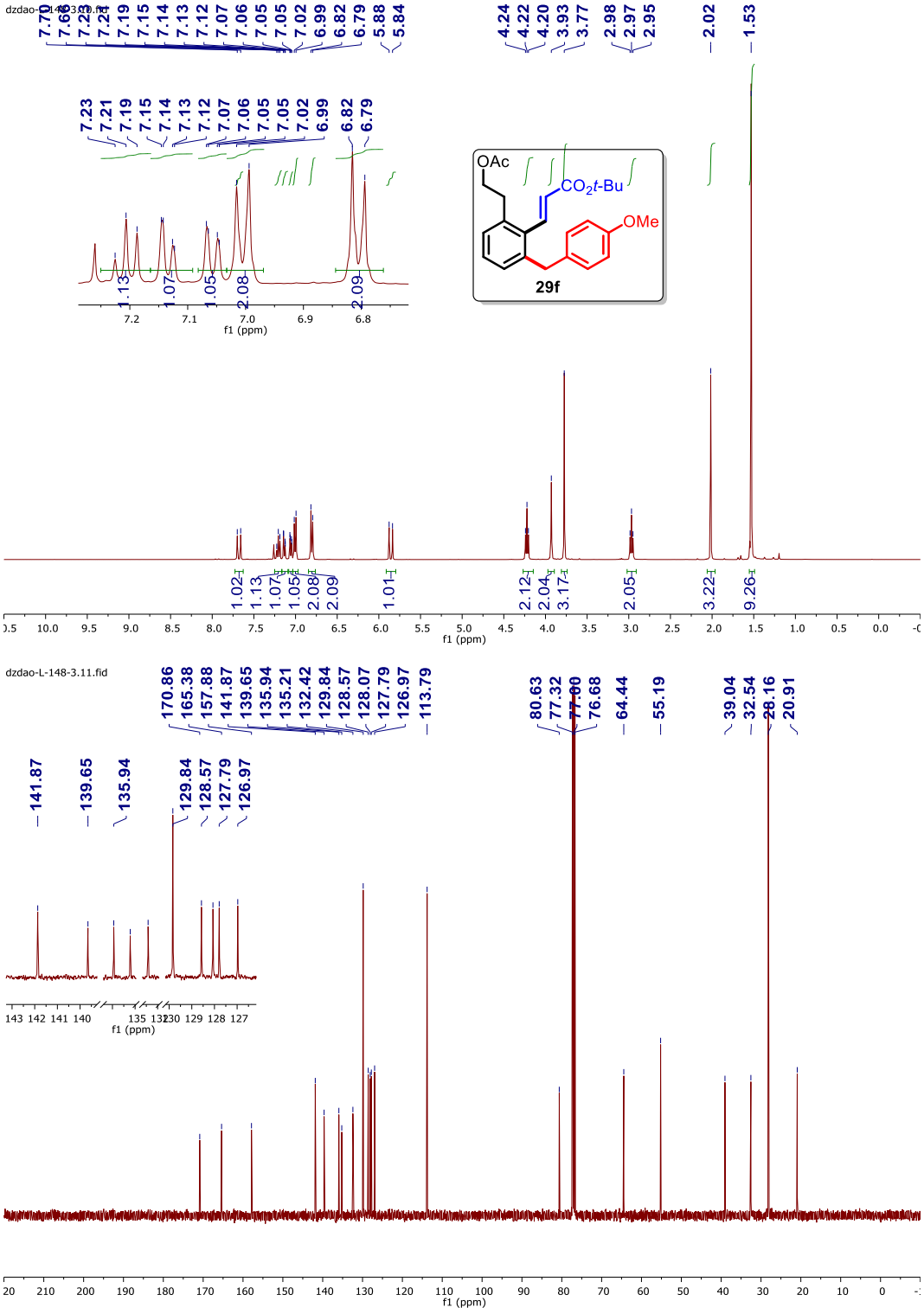


Figure 4.88 ^{1}H and ^{13}C NMR spectrum of compound **29g**.

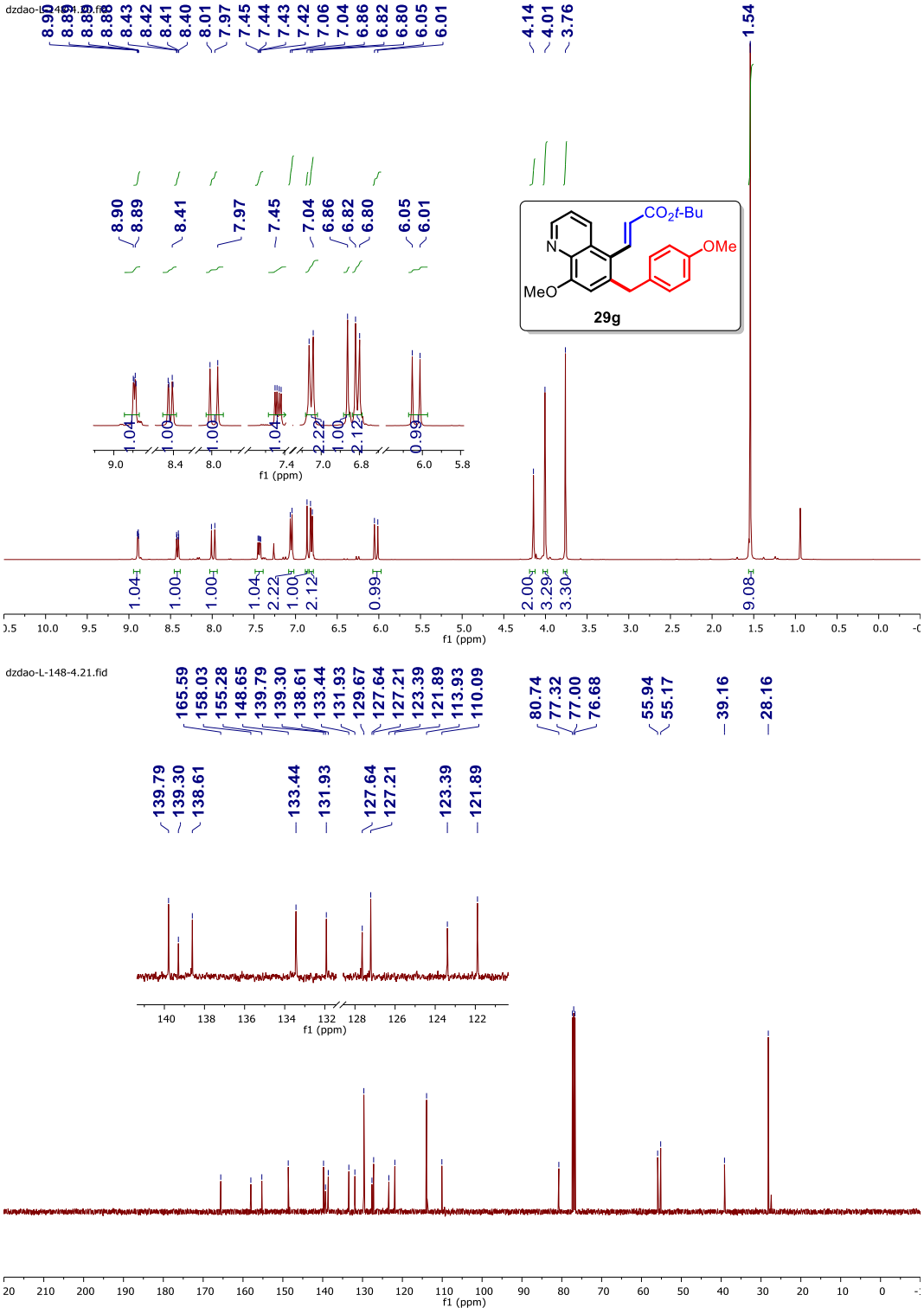


Figure 4.89 ^{1}H and ^{13}C NMR spectrum of compound **29h**.

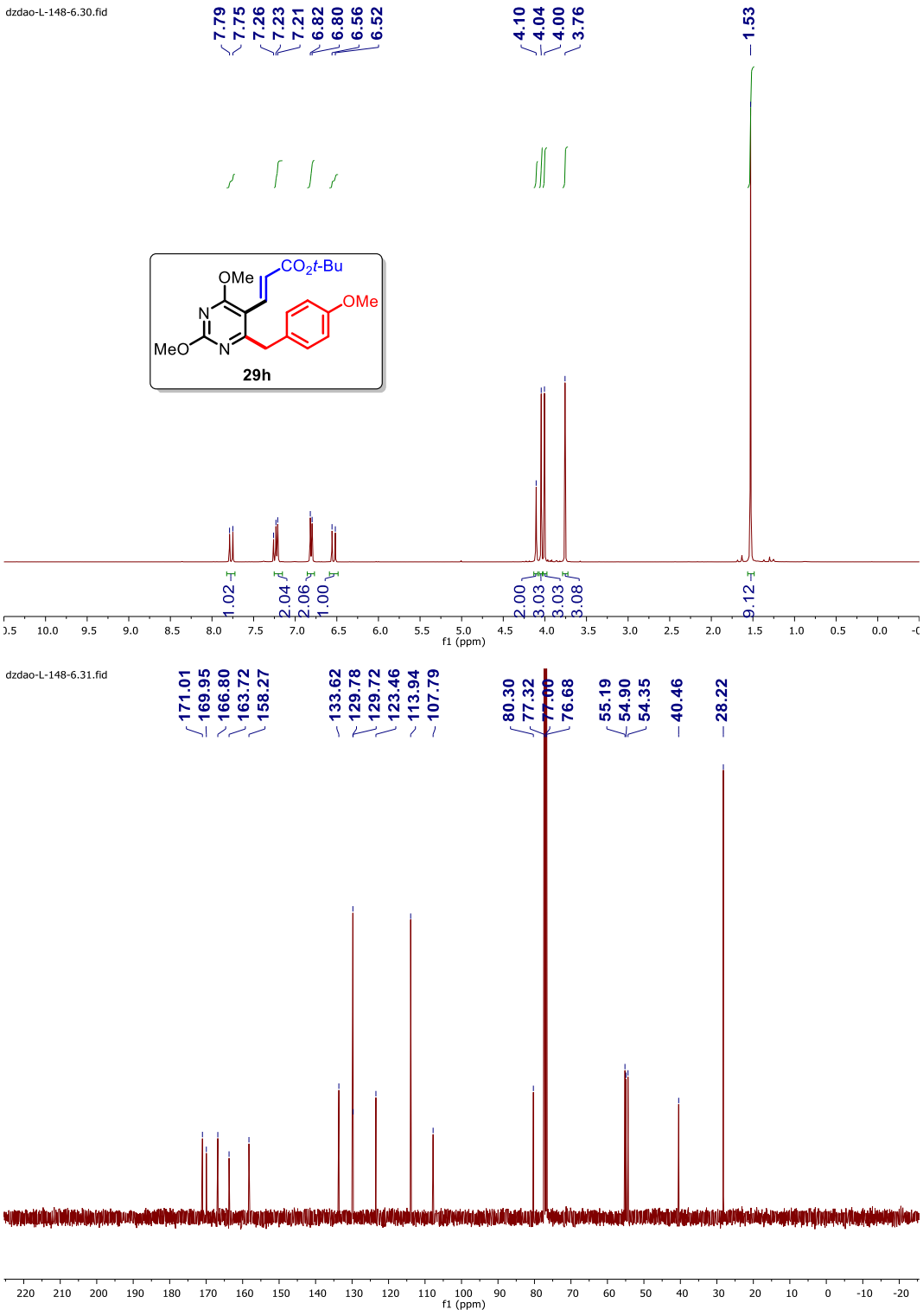


Figure 4.90 ^{1}H and ^{13}C NMR spectrum of compound **29i**.

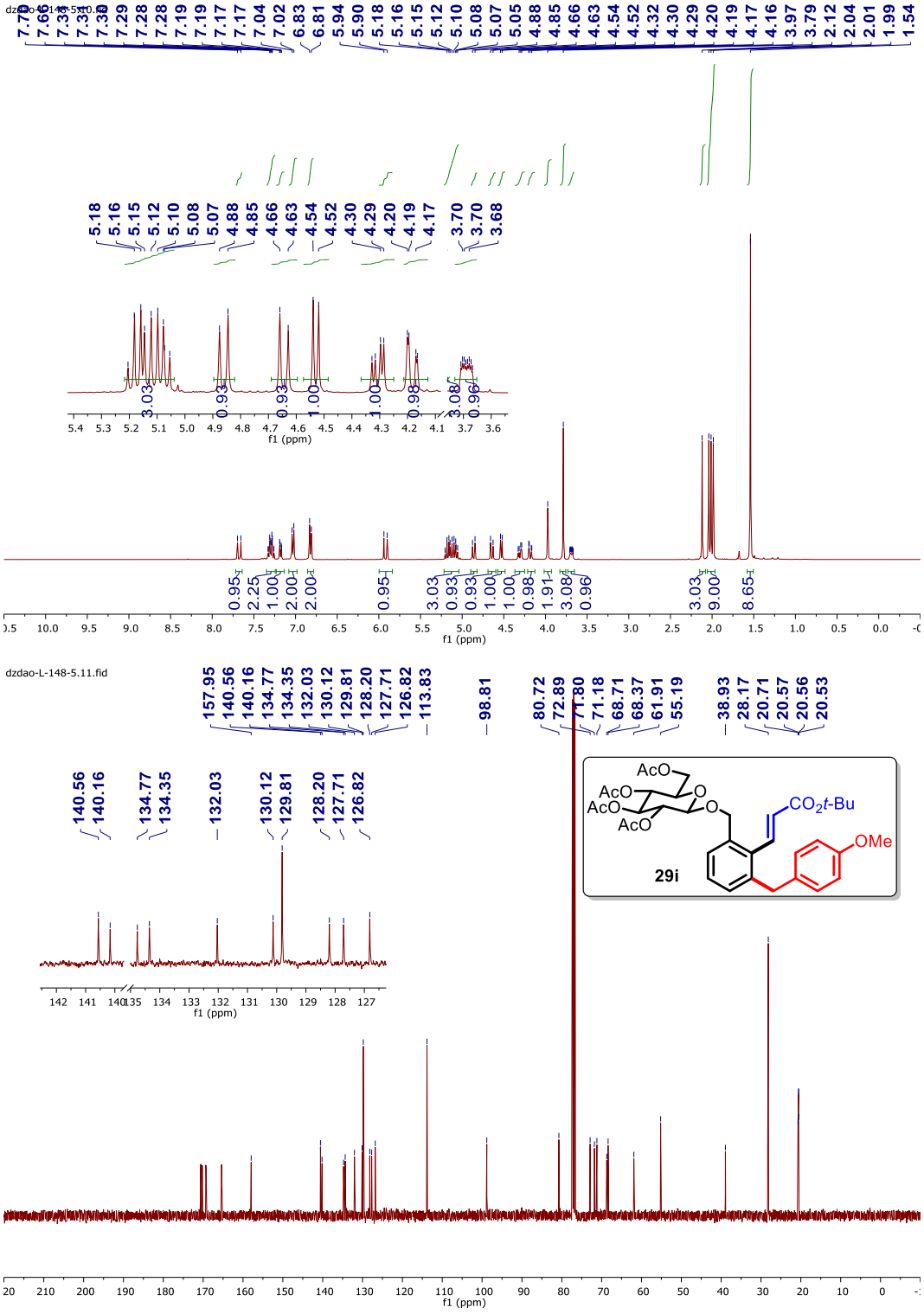


Figure 4.91 ^{1}H and ^{13}C NMR spectrum of compound **30**.

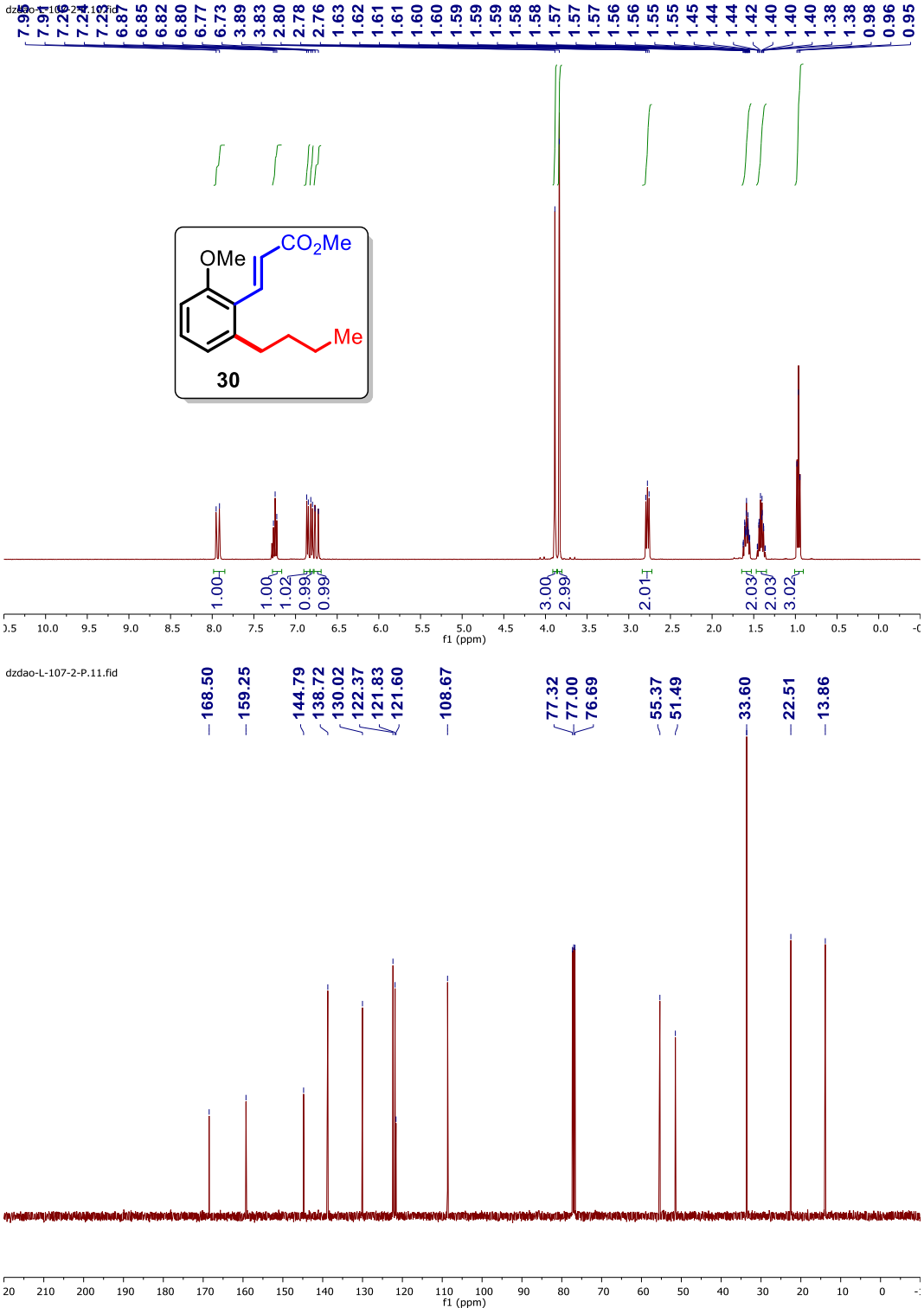
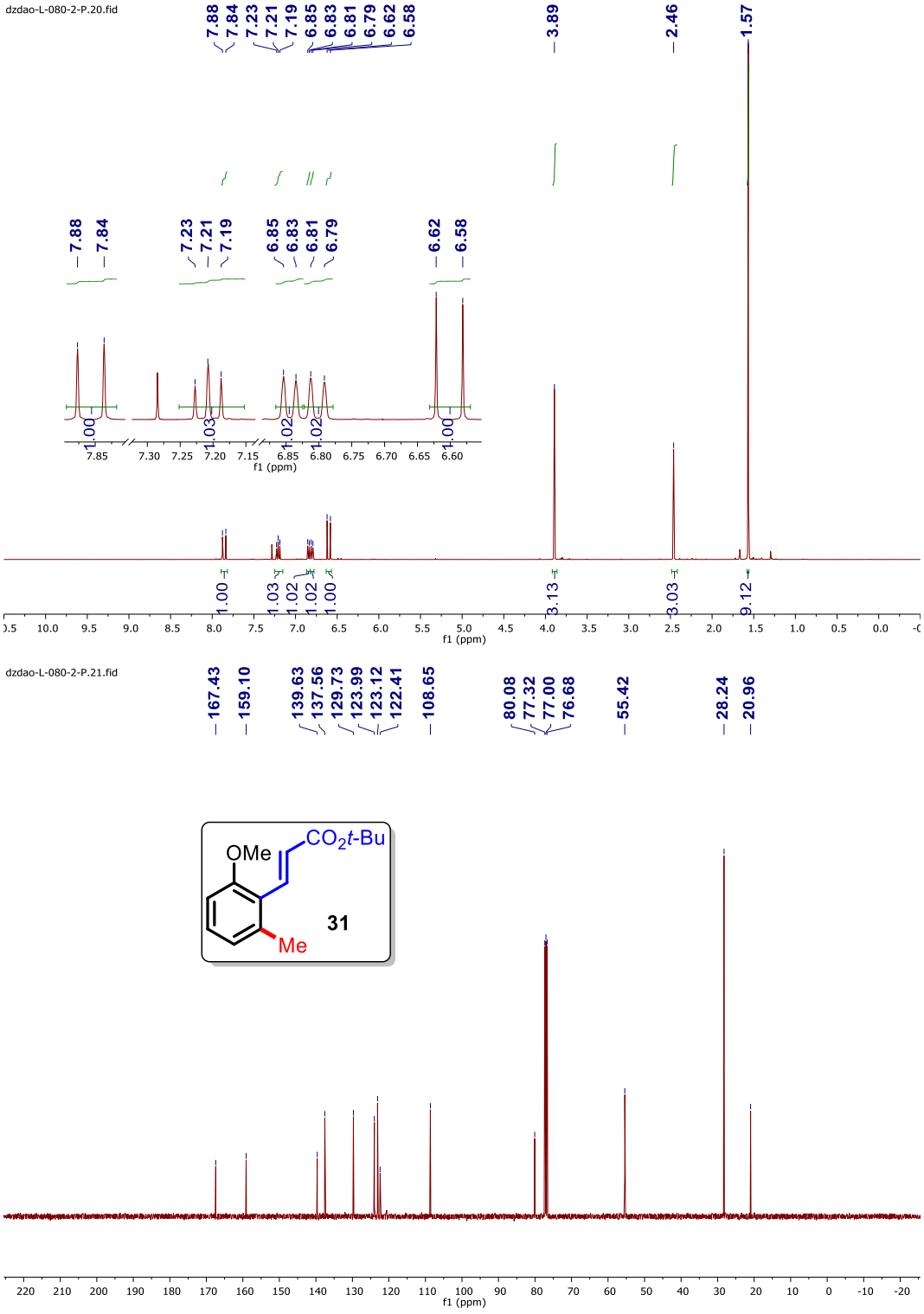
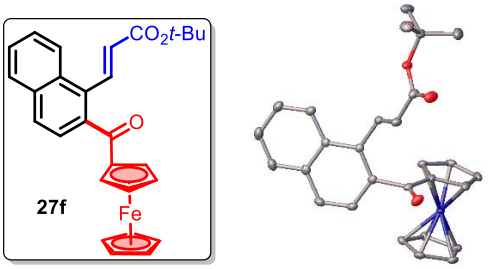


Figure 4.92 ^{1}H and ^{13}C NMR spectrum of compound **31**.



X-ray Crystallography Data



Crystal data and structure refinement for dzdao-L-139-6.

Identification code	dzdao-L-139-6
Empirical formula	$C_{28}H_{26}FeO_3$
Formula weight	466.34
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	10.8154(5)
b/Å	18.7822(10)
c/Å	11.4495(6)
α/°	90
β/°	109.7420(10)
γ/°	90
Volume/Å^3	2189.11(19)
Z	4
ρ_{calc}g/cm^3	1.415

μ/mm^{-1}	0.717
F(000)	976.0
Crystal size/mm^3	0.05 × 0.03 × 0.03
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.002 to 60.622
Index ranges	$-15 \leq h \leq 15$, $-26 \leq k \leq 26$, $-16 \leq l \leq 16$
Reflections collected	31677
Independent reflections	5949 [R_{int} = 0.0318, R_{sigma} = 0.0289]
Data/restraints/parameters	5949/0/292
Goodness-of-fit on F^2	1.038
Final R indexes [I>=2σ (I)]	R_1 = 0.0341, wR_2 = 0.0737
Final R indexes [all data]	R_1 = 0.0481, wR_2 = 0.0788
Largest diff. peak/hole / e $Å^{-3}$	0.41/-0.25

4.7 References

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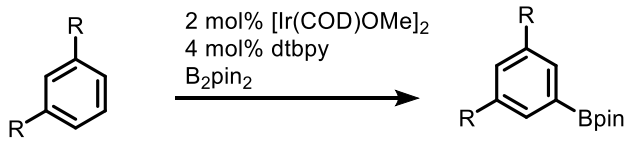
Chapter 5: Simple Amine-Directed *meta*-Selective C−H Arylation via Pd/Norbornene Catalysis

5.1 Introduction

Site-selective arene functionalization has been continuously impacting the fields of drug discovery, material science and chemical industry.[1-10] While numerous *ortho*-selective arene functionalization methods have been extensively developed, the *meta*-selective functionalization of an electronically unbiased arene remains a difficult task.[11] Recently, a number of elegant approaches have been developed, including steric-sensitive borylation and silylation,[12-17] cluster-templated metalation,[18-19] diaryliodonium salt-mediated arylation,[20-21] use of a traceless directing group (DG),[22-23] *ortho*-metalation-triggered ArS_E,[24-25] use of a U-shape template,[26-32] and others.[33-34] Despite these seminal efforts, a broadly applicable C−H functionalization strategy, that is completely *meta*-selective, overrides intrinsic steric and electronic preference of the arene substrates and tolerates a broad range of functional groups (FGs), remains highly sought after. (Scheme 5.1).

Scheme 5.1. Representative examples for *meta*-selective C-H functionalization.



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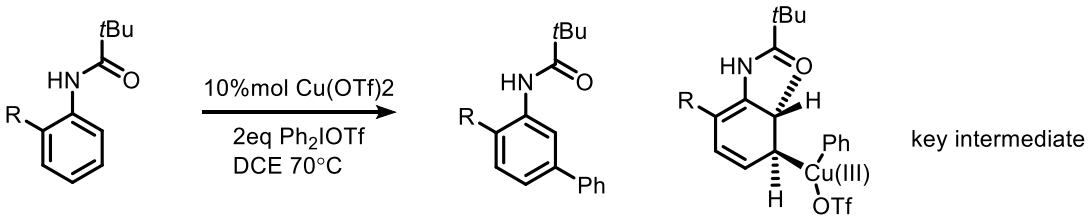

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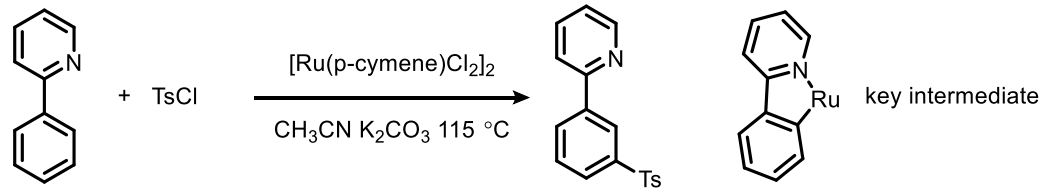
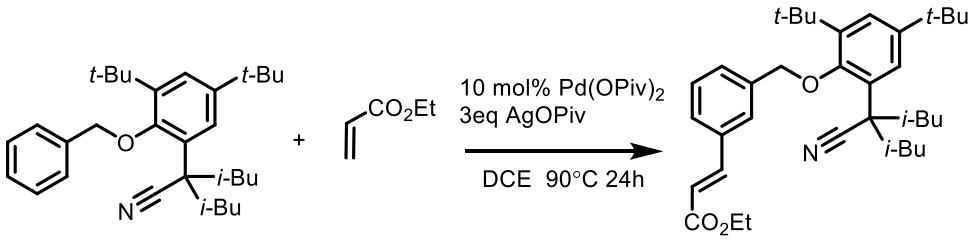
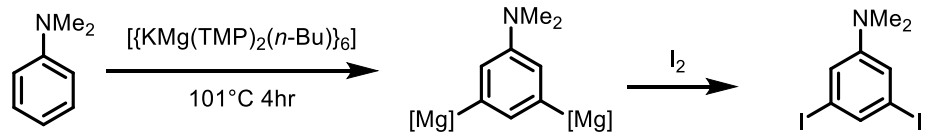


Saidi, O.;Marafie, J.; Ledger, A. E. W.; Liu, P. M.; Mahon, M. F.; Kociok-Kohn,
G.; Whittlesey, M. K.; Frost, C. G. *J. Am. Chem. Soc.* **2011**, 133, 19298



Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature*,**2012**,486-518.



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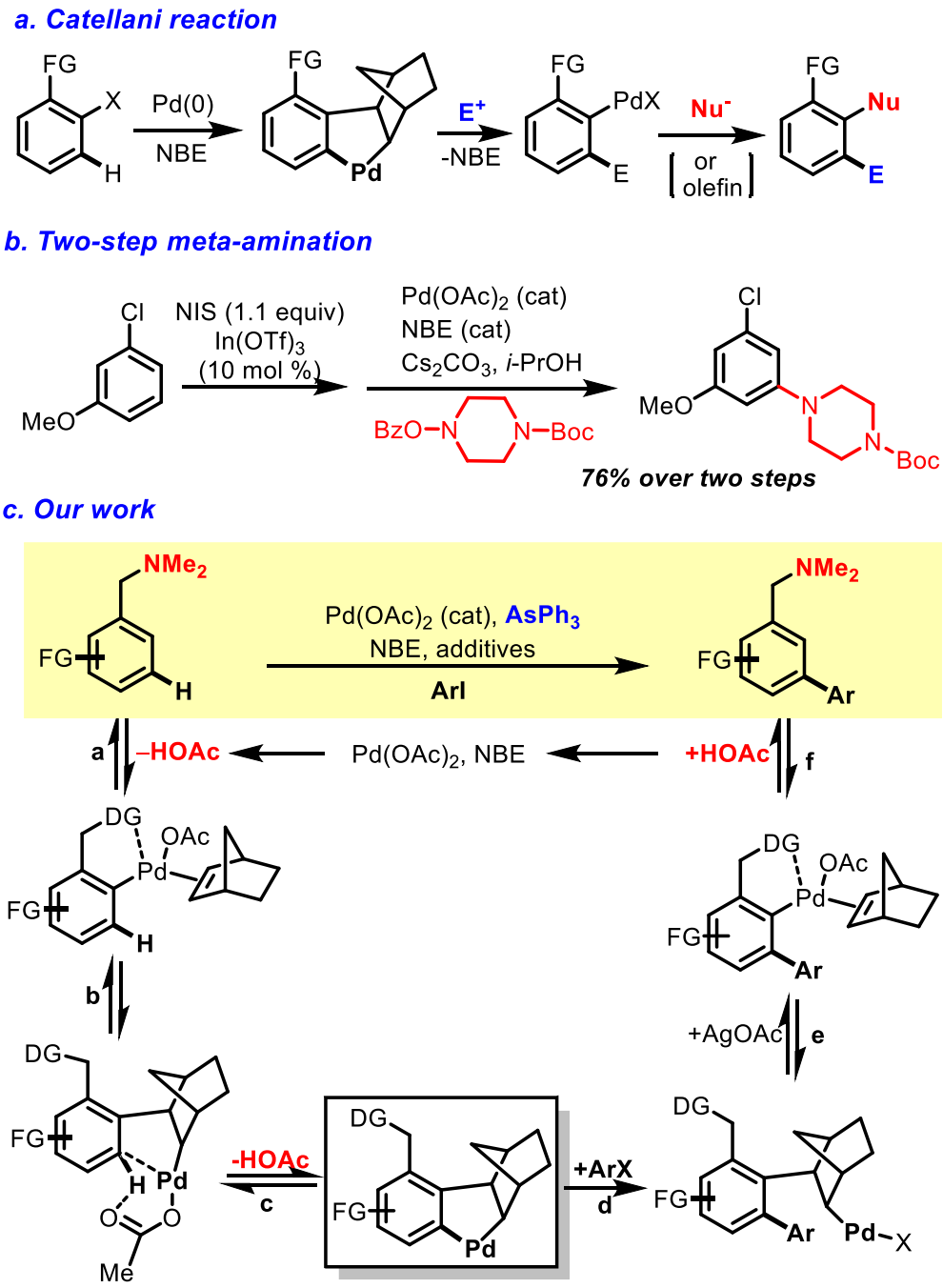
5.2 BACKGROUND

We foresaw the potential of employing the Pd/norbornene(NBE) catalysis, namely the Catellani reaction,[10] to control the site-selectivity for arene C−H functionalization. The Catellani reaction generally uses aryl halides as the substrates allowing *ipso* and *ortho* di-functionalization of arenes, through a NBE-mediated vicinal C−H metalation reaction (Scheme 5.2a).[3,6,35] Seminal work by Catellani and Lautens has shown that various carbon FGs can be installed at the *ortho*-position of the arene,[36-48] which has been employed to prepare *meta*-substituted arenes.[44,47] Our group recently demonstrated the first *ortho* C−N bond forming transformations with an electrophilic amination reagent, and further illustrated a two-step *meta*-amination sequence via electrophilic halogenation followed by reductive *ortho*-amination (Scheme 5.2b).[49] In this chapter, we extend our efforts towards developing a direct approach for catalytic *meta*-functionalization of arenes based on the unique features of the Pd/NBE catalysis.[50]

Scheme 5.2 *meta*-Selective Arene C−H functionalization via Pd/NBE catalysis



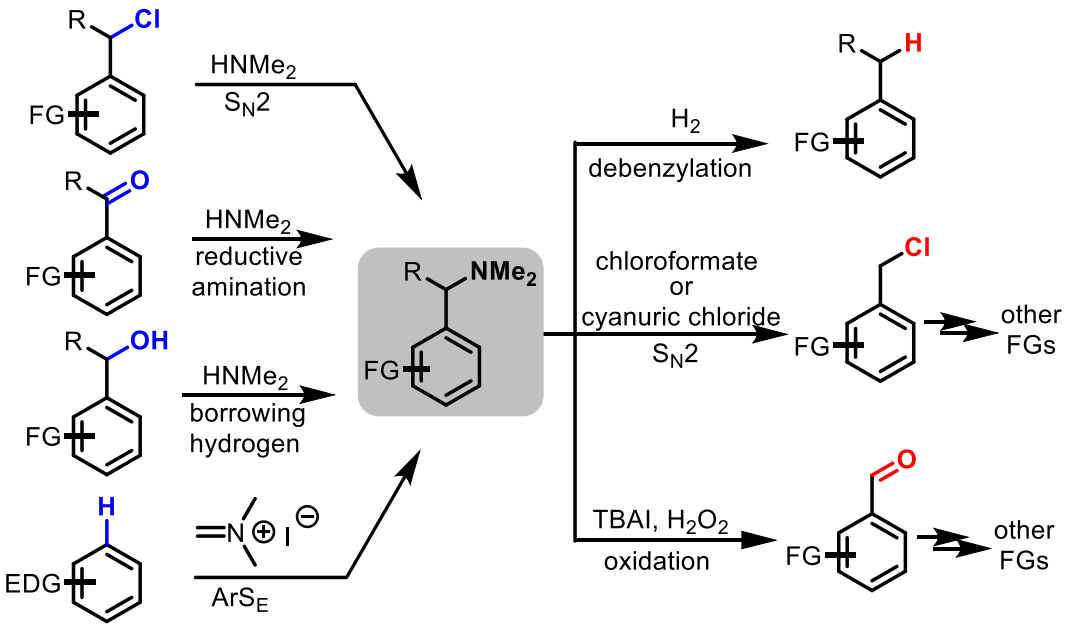
We postulated that the NBE-bridged five-membered palladacycle, the key intermediate in the Catellani reaction, could also be generated via a C−H metalation-initiated pathway.[51-53] A proposed *meta*-arylation is depicted in Scheme 5.2c, guided by a DG, *ortho*-metalation should give a Pd(II)

intermediate (step a), which should be able to undergo an analogous Catellani reaction pathway (steps b and c). The five-membered palladacycle is expected to react with an electrophile, e.g. an aryl halide, through either a Pd(IV) intermediate or a transmetalation pathway,[54-56] to generate a *meta*-substituted complex (step d). The resulting Pd(II) intermediate would then undergo β-carbon elimination followed by re-protonation at the *ortho*-position to furnish the desired *meta*-product (steps e and f). However, the challenges of the proposed pathway are three-fold. First, both the *ortho*-metalation-deprotonation (step a), its reverse step (step f, demetalation-protonation) and the metalation at the *meta*-position (step c) must be accommodated under the same reaction conditions. Second, the electrophile can possibly react with either the *ortho*-palladated arene species or the intermediate after *meta*-metalation. Thus, finding an appropriate ligand to control the relative reactivity of these aryl-palladium intermediates is nontrivial. For broad applicability purposes, it would be more attractive to utilize a common and versatile FG as the DG.

5.3 REACTION DEVELOPMENT AND SCOPE

Finally, Stimulated by the aforementioned challenges, we sought the use of a simple tertiary amine, i.e. dimethyl amine, as the DG.[57-61] A number of benefits with this type of DG can be envisioned: 1) it was demonstrated three decades ago by Ryabov that the dimethylamine can direct a *reversible ortho*-metalation under mildly acidic conditions;[62-63] 2) amines are widely available and frequently found in bio-active and pharma-interesting molecules; 3) it is small and light (the MW of the Me_2N group is only 44); 4) it can be easily installed from a number of common starting materials, e.g. benzaldehydes and halides, etc (Scheme 5.3);[64] 5) it is also known that the dimethylamino group at the benzylic position can be easily removed under hydrogenolysis conditions[58-59,65] or converted to other FGs (*vide infra*, Scheme 5.4).

Scheme 5.3 Availability and versatility of the amine DG.

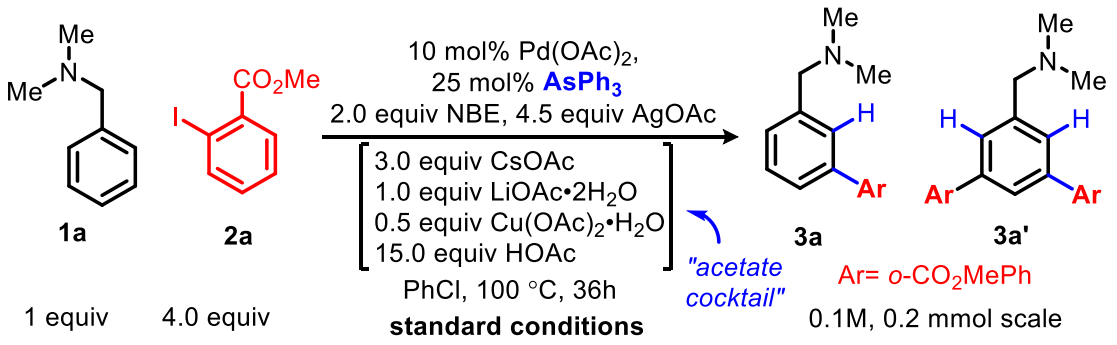


Benzylamine **1a** was employed as the initial model substrate. After extensively examining a range of Pd, ligand, additive and solvent combinations (for detailed optimization studies, see SI), to our delight, the desired *meta*-arylation can be obtained when using $Pd(OAc)_2$/$AsPh_3$ as the metal/ligand choice, aryl iodide **2a** as the aryl source, and chlorobenzene as the solvent. Given that substrate **1a** has two *meta*-positions, both mono and diarylation are possible; nevertheless, by controlling the amount of the aryl halide used, the diarylation product (**3a'**) can be formed as the dominate product (72% yield, entry 1, Table 5.1).

A series of control experiments were subsequently conducted to understand the role of each reactant (Table 5.1). In the absence of either Pd precatalyst or NBE, no desired product was observed (entries 2 and 4). The commercially available $AsPh_3$ proved to be the most efficient ligand for promoting the arylation (entry 3); in contrast, use of more electron-rich ligands, such as PPh_3 or S-Phos, gave significantly lower yields. The silver salt was employed to accelerate the oxidative addition of aryl iodide. In the absence of AgOAc, the mono-arylation product (**3a**) can

still be obtained in 6% yield (entry 5). We further discovered that the reaction rate can be improved by using an interesting "acetate cocktail" containing $LiOAc \cdot 2H_2O$, CsOAc and $Cu(OAc)_2 \cdot H_2O$ (1: 3: 0.5) in acetic acid (entries 6-8). Although the exact reason remains to be further explored, we speculate that HOAc and LiOAc would help dechelation of the DG from the palladium (through protonation or complexation) after the initial *ortho*-C−H activation, which is required for the second metalation (*vide supra*, step b, Scheme 5.2c); CsOAc might work as a stronger acetate source to assist the deprotonation/metalation step; the Cu(II) salt may act as an efficient Pd(0) scavenger to minimize Pd(0)-mediated reactions. It should be noted that in the absence of the "acetate cocktail", the desired *meta*-products can be still be formed albeit in lower yields (entry 10). Interestingly, while in the absence of acetic acid the reaction became more sluggish, its use as solvent completely shut down the reaction (entry 11). Finally, shortening the reaction time or using less NBE led to incomplete conversion and more mono-arylation product (entries 12 and 13). Further control experiments showed that no *ortho* and *para*-arylation products were observed during the reaction with **1a**.[66] One major side reaction arises from the self-dimerization of aryl ioide **2a** with NBE.[11j,67]

Table 5.1 Control experiments for the *meta*-arylation



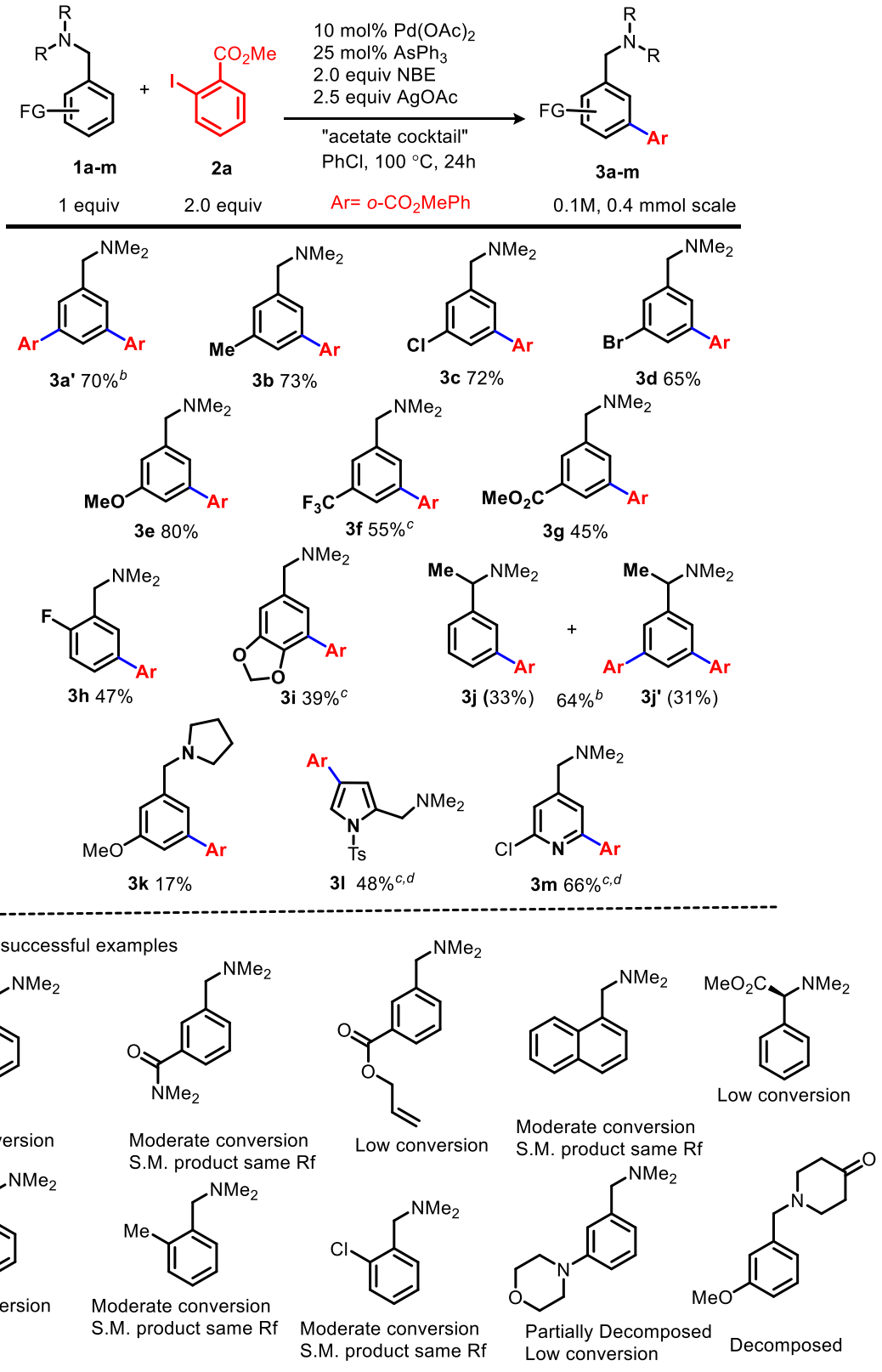
Entry	Change from standard conditions	Yield of 3a[a]	Yield of 3a'[a]
1	None	**2%**	**72%**
2	No $Pd(OAc)_2$	0%	0%
3	No $AsPh_3$	11%	7%
4	No NBE	0%	0%
5	No AgOAc	6%	0%
6	No CsOAc	7%	34%
7	No $LiOAc^{\bullet 2}H_2O$	3%	60%
8	No $Cu(OAc)_2•H_2O$	8%	45%
9	No HOAc	19%	14%
10	No acetate cocktail	21%	20%
11	HOAc instead of PhCl	0%	0%
12	12h instead of 36h	23%	29%
13	0.5 equiv of NBE instead of 2.0 equiv	22%	13%

[a] *Determined by GC using dodecane as the internal standard.*

With the optimal conditions established, we first examined the scope of benzylamine substrates (Table 5.2). When substituted benzylamines were employed as the substrate, the amount of aryl iodide and AgOAc can be reduced to 2 equiv and 2.5 equiv respectively. To our delight, both electron-rich and deficient arenes provided the desired *meta*-arylated products in moderate to good yields. In particular, the highly electron-rich 3-methoxy substrate, with a strong electron bias on the *ortho* and *para*-positions, still afford the *meta*-product (**3e**) in 80% yield.

Substitutions on various positions of the arenes can be tolerated. Moreover, this transformation is compatible with a number of functional groups, including tertiary amines, aryl fluorides, chlorides, bromides, anisoles, trifluoromethyl, methylenedioxy groups and esters. In addition, the substrate with a methyl substituent at the benzylic position still provided the desired mono and diarylation products (**3j** and **3j'**). When enantiopure **1j** was used, no racemization was observed. Besides the dimethylamino group, other tertiary amines[68] can also be employed as the DG (e.g. **3k**) albeit with a lower efficiency. In contrast, use of Ac-protected benzylamines did not lead to the desired products. Further investigation of this transformation with other DGs is ongoing in our laboratory. It is noteworthy that heteroarenes, such as protected pyrrole and pyridine-derived substrates, are also amenable for this transformation (**3l** and **3m**). Table 5.2 also listed several representative unsuccessful examples, when ortho position of benzyl amine was blocked by large group, the reaction has a low conversion. Very electronic deficient substrates also has conversion issue. The major problem for the moderate conversion substrate is the difficult isolation.

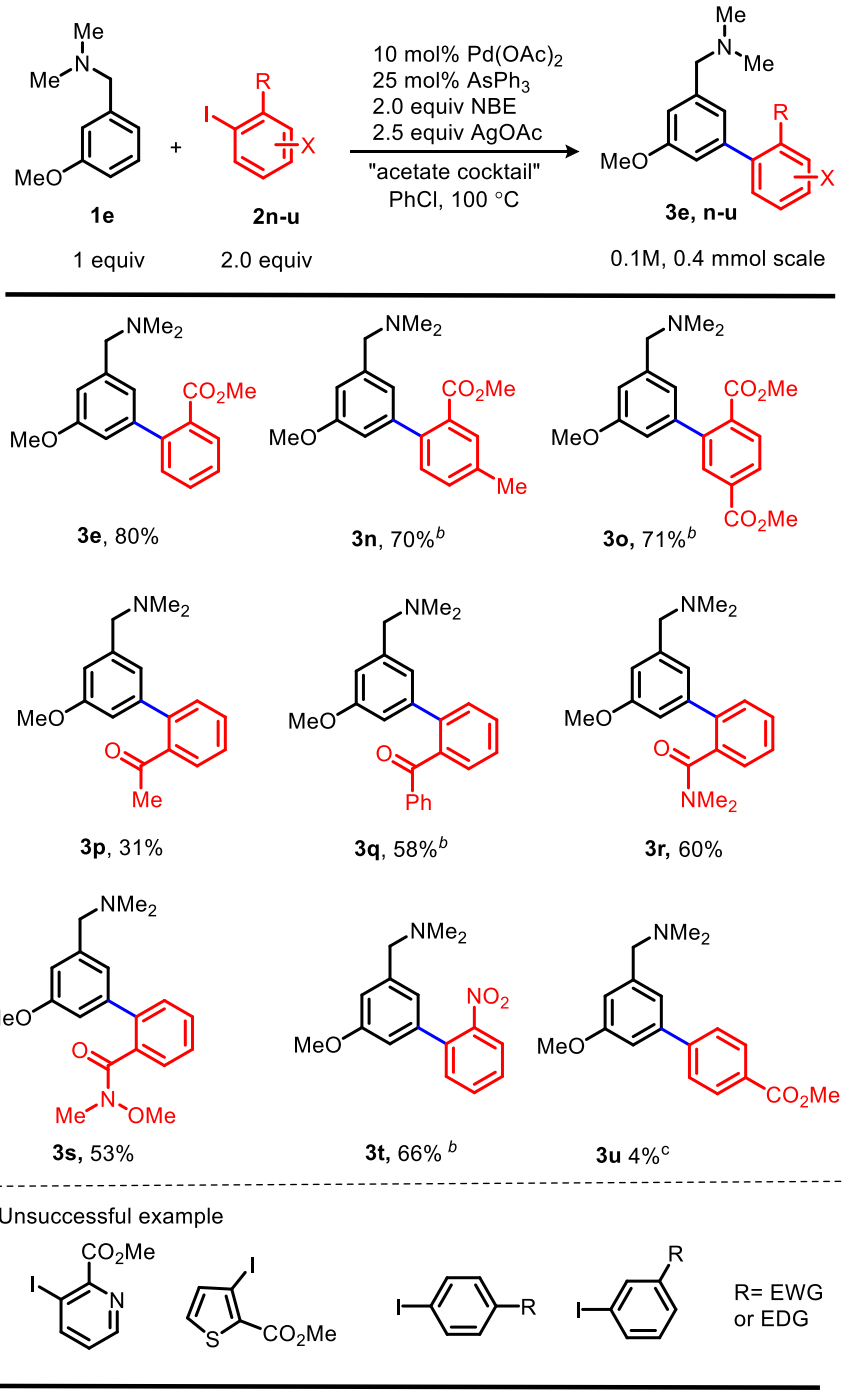
Table 5.2. Substrate scope with different benzylamines[a]



[a] All yields are isolated yields. [b] The reaction time was 36h; 4.0 equiv of **2a** and 4.5 equiv of AgOAc were used. [c] The reaction was run at 130°C. [d] 3.0 equiv of **2a** and 3.5 equiv of AgOAc were used.

The scope of the aryl halides was investigated next (Table 5.3). Aryl halides containing an *ortho* electron-withdrawing group (EWG) proved to be most efficient, which is consistent with the previous observation in the typical Catellani arylation reaction.[42,69] It is likely that the EWGs can accelerate oxidative addition of the aryl iodide (step d, Scheme 5.2c) through a combined electronic and weak-directing effect. Aryl iodides with only a *para* or *meta*-substituent proved to be much less reactive. For example, when methyl 4-iodobenzoate **2u** was used, a low conversion was observed (<10%) but still giving the desired *meta*-arylation product (**3u**).[24] Nevertheless, besides ester group, amide, Weinreb amide, alkyl and aryl ketone and nitro groups were all found suitable for this transformation. Hetero aryl iodide such as thiophene and pyridine gave a poor conversion under standard reaction condition.

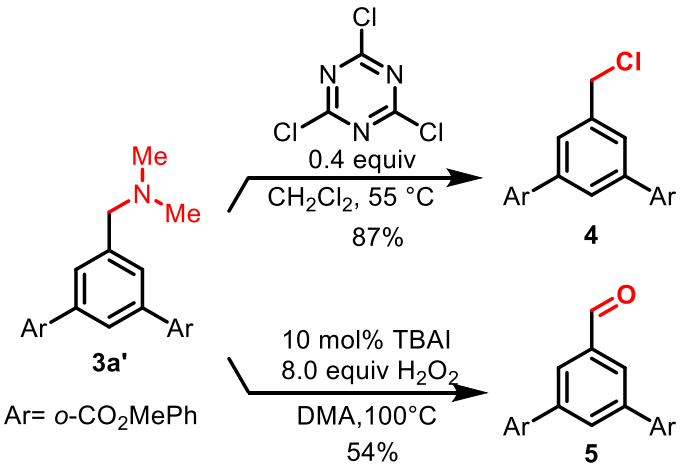
Table 5.3. Substrate scope with different aryl iodides[a]



[a] All yields are isolated yields. [b] The reaction time was 36h. [c] The reaction was run at 130°C with 4.0 equiv of the aryl iodide and 4.5 equiv of AgOAc.

Finally, as an example to demonstrate the potential usage of this *meta*-arylation reaction, we showed the triaryl product **3a'** can be easily transformed to a benzyl chloride or an aldehyde by using established procedures.[25](Scheme 5.4) Both moieties are well known as versatile synthetic precursors, and can be readily transformed to various other FGs.

Scheme 5.4 Derivatization of the *meta*-arylation product



5.4. CONCLUSION

In summary, we have developed a distinct highly meta-selective arylation using Pd/NBE catalysis. This transformation uses a simple tertiary amine as the DG and commercially avail-able AsPh3 as the ligand. In addition, arenes with various elec-tronic and steric properties can be used as the substrates, and a significant number of FGs, including some heteroarenes, can be tolerated. We expect this mode of reactivity should have high potential to be generalized allowing other meta-functionalization, e.g. forming C−X (X≠C) bonds at the meta-position.

5.5 Experimental procedure and characterization of new compound

Materials and methods

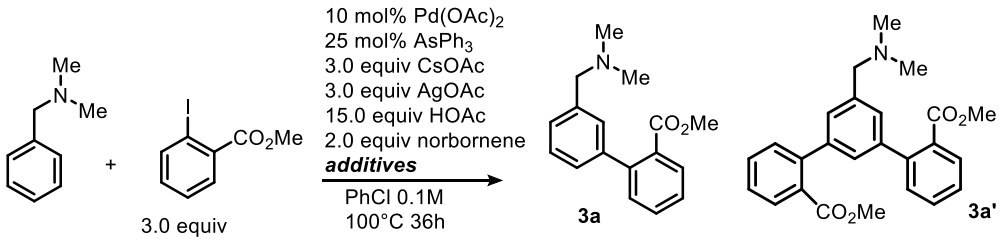
Unless stated otherwise, all reactions were run in vials sealed with PTFE lined caps, purchased from Qorpak. Chlorobenzene (99% HPLC level) was directly used as received from Arcos. Triphenylarsine ($AsPh_3$, 99%), Copper acetate monohydrate (99%) and palladium acetate (98%) were purchased from Strem and used as received. Cesium acetate (CsOAc) and lithium acetate dihydrate were purchased from Alfa and used as received. 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). Gas chromatography (GC) data was obtained from Agilent 7820A GC system, equipped with Agilent 19091J-413 column and a FID detector. GC yield of **3a** and **3a'** was determined using standard curves with dodecane as internal standard. Mass spectra were recorded on an Autospec or Agilent 6150. Accurate masses from high-resolution mass spectra were reported for the molecular ion $[M+Na]^+$, $[M]^+$ or $[M+H]^+$. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini (400 MHz for ^1H, 100 MHz for ^{13}C). Chemical shifts are reported as parts per million (ppm) using residual solvent signals as internal standard ($CDCl_3$, δ = 7.26 ppm for ^1H NMR, δ = 77.00 ppm for ^{13}C NMR; DMSO-d_6, δ = 2.50 ppm for ^1H NMR, δ = 39.50 ppm for ^{13}C NMR; MeCN-d_3, δ = 1.94 ppm for ^1H NMR, δ = 1.32, 118.26 ppm for ^{13}C NMR). Data for ^1H NMR were presented as following: chemical shifts (δ, ppm), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, tt = triplet of triplets, td = triplet of doublets, m = multiplet), coupling constant (Hz), and integration. The chemical shifts of peaks found were reported for ^{13}NMR spectra. Infrared spectra were obtained from a Nicolet iS5 FTIR spectrometer.

5.5.1 General procedure for reaction-condition screening and condition optimization table

The reaction was run at a 0.2 mmol scale based on the limiting reagent. A 4 mL vial was charged with palladium salt, ligand, additives, benzylamine derivative, aryl iodide, 1.8 mL chlorobenzene and HOAc as cosolvent. The vial was sealed with a PTFE lined cap and heated in a pie-block at 100 °C for 36 hours under stirring. Then the mixture was allowed to cool to room temperature. The saturated potassium carbonate aqueous solution 2ml was carefully added to the vial to make the whole solution basic. The vial were kept stirring at room temperature for 15min before the solid was filtered. The filter cake was further washed with ethyl acetate (containing 8% trimethylamine), filtrate were collected together with the aqueous phase. The appropriate amount of dodecane (~10 mg) was added as the internal standard to the filtrate. The mixture was stirred for an additional 5 min to fully mix.. The filtrate was directly used for GC analysis.

GC instrument conditions: inlet temperature: 250 °C, detector temperature: 300 °C, hydrogen flow: 40 mL/min, air flow: 400 mL/min, column + makeup flow: 30 mL/min. Method: 50 °C hold for 0 min, followed by a temperature increase of 10°C/min to 320 °C, hold 0 min (total run time: 27 min). Yields of product and byproducts are calculated using standard curves with dodecane as the internal standard. Full details of the control reactions are listed below (Tables 5.S1-5.S4).

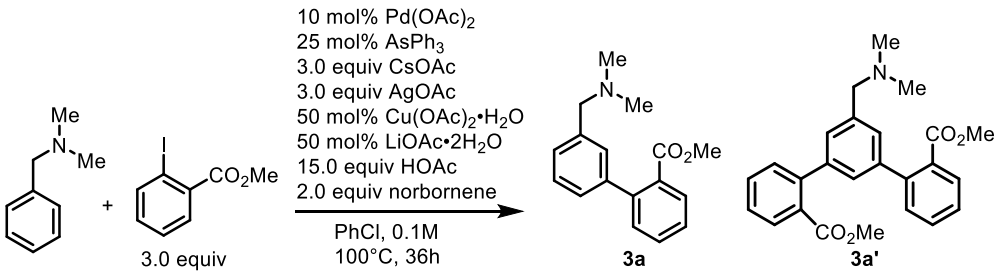
Table 5.4 Full details of salts effect:[a]



Additives	yield of **3a**	yield of **3a'**	**Total yield**
None	7%	53%	60%
50 mol% $Cu(OAc)_2 \cdot H_2O$	8%	48%	54%
50 mol% $LiOAc \cdot 2H_2O$	10%	54%	64%
50 mol% $Cu(OAc)_2 \cdot H_2O$ and 50 mol% $LiOAc \cdot 2H_2O$	9%	60%	69%
KOAc instead of CsOAc	8%	46%	54%
NaOAc instead of CsOAc	9%	42%	51%
50 mol% of $Zn(OAc)_2$	10%	47%	57%
None 130°C 18h	13%	47%	60%

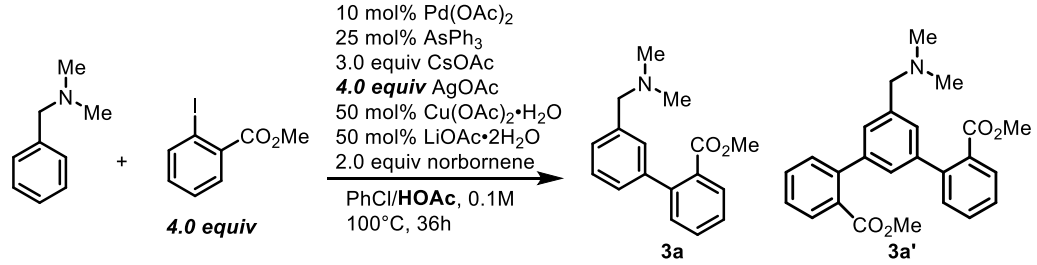
[a]*All yields were determined by GC using dodecane as the internal standard.*

Table 5.5 Selected ligand and solvent effect: [a]



Change from above conditions	yield of **3a**	yield of **3a'**	**Total yield**
None	2%	60%	62%
tAmyOH instead of PhCl	15.5%	26.5%	42%
TFE instead of PhCl	0%	0%	0%
PPh_3 instead of $AsPh_3$	15%	12%	27%
SPhos instead of $AsPh_3$	13%	12%	25%

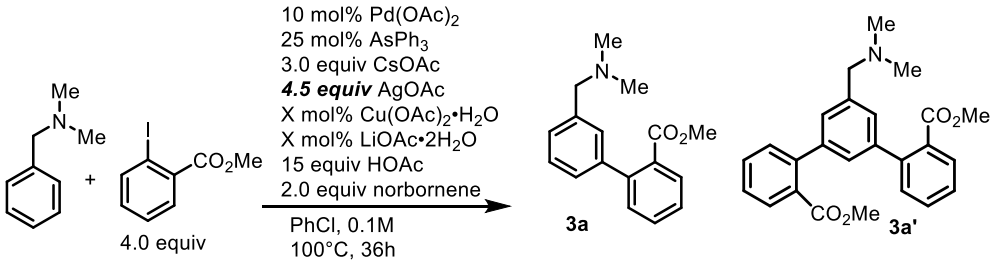
Table 5.6 Acetic acid equivalent effect: [a]



	recovery yield of **1a**	yield of **3a**	yield of **3a'**	**Total yield**
PhCl/HOAc = 1 : 1	39%	4%	2.2%	6.2%
PhCl/HOAc = 3 : 1	6%	14%	19%	33%
PhCl/HOAc = 5 : 1	3%	12.3%	27.6%	40%
PhCl/HOAc = 10 : 1 (15 equiv)	1%	12.4%	43.5%	56%
HOAc 5.0 equiv	33%	20%	6%	26%
HOAc 1.0 equiv	41%	7%	4%	11%

[a]*All yields were determined by GC using dodecane as the internal standard.*

Table 5.7 The salts equivalent effect: [a]



	yield of **3a**	yield of **3a'**	**Total yield**
No $Cu(OAc)_2•H_2O$ and $LiOAc•2H_2O$	4%	54%	58%
No $Cu(OAc)_2•H_2O$ No $LiOAc•2H_2O$ with 1.0 equiv CsOAc	4%	48%	33%
50 mol% $Cu(OAc)_2•H_2O$ 50 mol% $LiOAc•2H_2O$	2%	67%	69%
50 mol% $Cu(OAc)_2•H_2O$ No $LiOAc•2H_2O$	2%	63%	65%
No $Cu(OAc)_2•H_2O$ 50 mol% $LiOAc•2H_2O$	6%	53%	59%
100 mol% $Cu(OAc)_2•H_2O$ 50 mol% $LiOAc•2H_2O$	2%	66%	68%
50 mol% $Cu(OAc)_2•H_2O$ 100 mol% $LiOAc•2H_2O$	2%	72%	74%
100 mol% $Cu(OAc)_2•H_2O$ 100 mol% $LiOAc•2H_2O$	1%	70%	71%
50 mol% $Cu(OAc)_2•H_2O$ 50 mol% $LiOAc•2H_2O$ Under N_2	15%	43%	58%

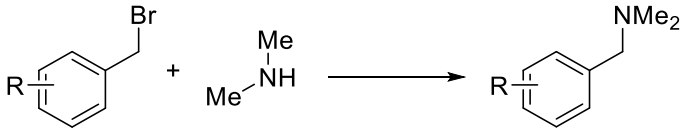
[a]*All yields were determined by GC using dodecane as the internal standard.*

5.5.2 Experimental procedure

Synthesis of benzylamine derivatives

Most benzylamine substrates used in this work are known compounds expect **1l** and **1m**. **1a, 1d** and**1j** are commercially available. The known benzylamine were all synthesized from corresponding benzyl halide and dimethyl amine. We used a slight modified protocol.[70]

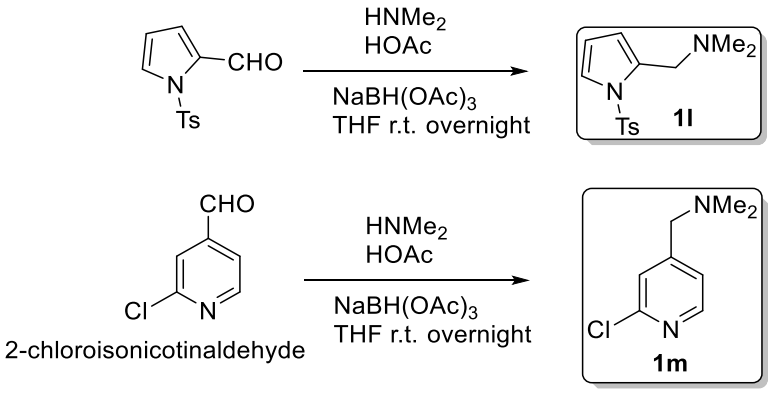
Scheme 5.5 General Synthesis of benzylamine derivatives through substitution.



To a solution of benzylic bromide (1.0 equiv, 10 mmol) in ether (1 M) was added 50 wt.% aqueous dimethylamine solution (5 equiv) at room temperature. After stirring for 12 hours at the same temperature, the resulting mixture was transferred to a separatory funnel. The aqueous phase was removed and the organic phase was extracted with 10 wt.% aqueous citric acid solution twice. The combined aqueous extracts were treated with sodium hydroxide to keep pH slightly above 12. The mixture was extracted with ether and the combined organic extracts were washed with brine. The solution was dried over mageniusm sulfate and concentrated. The crude product were found pure based on NMR, was used without further purification. Further vacuum distillation can be adapted to remove all the colorful impurity.

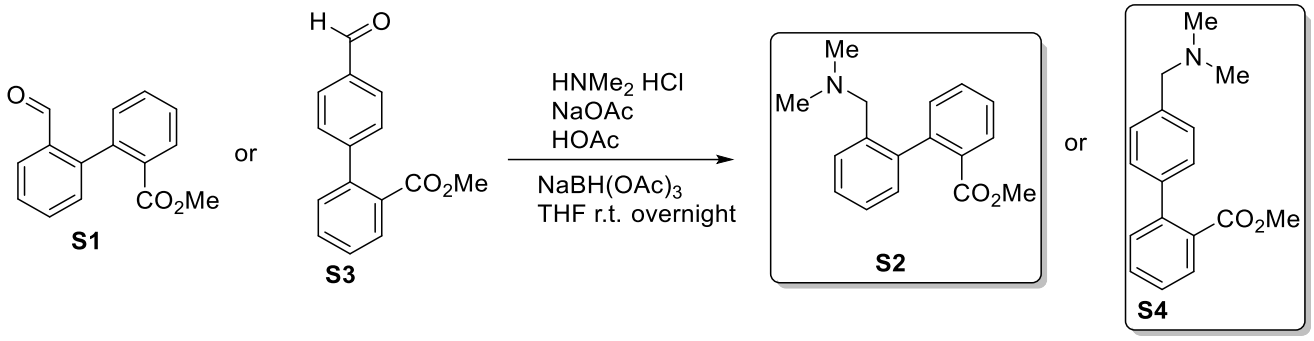
1l and **1m** were synthesized from corresponding benzaldehyde through reductive amination：

Scheme 5.6 Synthesis of hetero-benzylamine derivatives through reductive amination.



To solution of 1-tosyl-1*H*-pyrrole-2-carbaldehyde[71] or 2-chloroisonicotinaldehyde (10 mmol) in 20 mL tetrahydrofuran was added 2.0M dimethylamine solution in THF (10 ml, 20 mmol), acetic acid (1.2 g, 20 mmol). After being cooled in an ice bath for 5 minutes, sodium triacetoxyborohydride (4.2 g, 20 mmol) was added portion wise with stirring. The solution was further stirred at room temperature overnight. After monitored by TLC till full conversion, the solution was concentrated under vacuum. The residue was then dissolved by diethyl ether (20 mL) and extracted by 10% citric acid solution (30 mL x 3). The aqueous layer was neutralized by adding potassium hydroxide at zero degree and extracted by diethyl ether (30 mL x 3). The Combined organic layer was dried over magnesium sulfate and concertrated under vacuum to give the desired product **1l** as pale brown solid or **1m** as an oil which were analytically pure and directly used as in the C-H activation reaction.

Scheme 5.7 General Procedure for synthesis *ortho* and *para* products.



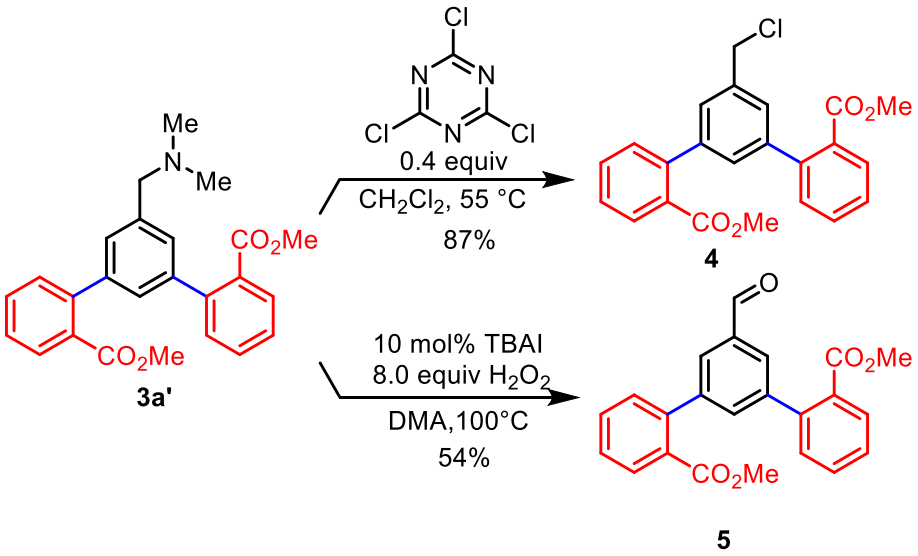
To solution of aldehyde **S1**[72] or **S3**[73] (0.55 g, 2.29 mmol) in 20 mL tetrahydrofuran was added dimethylamine hydrochloride (0.37g, 4.58 mmol), sodium acetate (0.18 g, 3.66 mmol), acetic acid (0.07 g, 1.15 mmol). After being cooled in an ice bath for 5 minutes, sodium triacetoxyborohydride (1.07 g, 5.04 mmol) was added portion wise with stirring. The solution was further stirred at room temperature overnight. After monitored by TLC till full conversion, the solution was concentrated under vacuum. The residue was then dissolved by diethyl ether (20 mL) and extracted by 10% citric acid solution (30 mL x 3). The aqueous layer was neutralized by adding potassium hydroxide at zero degree and extracted by diethyl ether (30 mL x 3). The Combined organic layer was dried over magnesium sulfate and concertrated under vacuum to give the desired product **S2** or **S4** as an oil which were analytically pure and directly used as the standard for GC-analysis.

General Procedure for the meta-Arylation of benzylamine derivative with simple aryl iodide.

Unless stated otherwise, an 8 mL vial was charged with benzyl amine (0.4 mmol, 1.0 equiv), aryl iodide (1.6 mmol, 4.0 equiv), $Pd(OAc)_2$ (9.0 mg, 0.1 equiv), norbornene (75.7 mg, 2.0 equiv), triphenylarsine (30.6 mg, 0.25 equiv), AgOAc (300 mg, 4.5 equiv), $Cu(OAc)_2$ H_2O (40.2 mg, 0.5 equiv.), LiOAc $2H_2O$ (40.1 mg, 1.0 equiv), CsOAc (235 mg, 1.2eq), HOAc (360 μL, 15.0 equiv) and PhCl (3.5 mL). The vial was sealed with a PTFE lined cap and heated in a pie-block at 100 °C for 36 hours under stirring. The mixture was allowed to cool to room temperature. The saturated potassium carbonate aqueous solution (4ml) was carefully added to the vial to make the whole solution alkaline. The vial were kept stirring at room temperature for 15min before the solid was filtered. The filter cake was further washed with ethyl acetate (containing 8% trimethylamine, roughly about 20 ml), the filtrate were collected together with aqueous phase. The aqueous phase was isolated and further extracted with dichloromethane three times (8ml X 3). The organic phase were combined and dried with magnesium sulfate. The magnesium sulfate were removed by filtration and solution were concentrated under vacuum, the residue was purified by chromatography on silica gel.

For other substrates in the Table 5.2 and Table 5.3, the equiv of aryl iodide, the equiv of AgOAc and reaction temperature were used as indicated in the manuscript. The rest of procedure was exactly same as we described here.

Scheme 5.8 Conversion of the amine directing group to other functional groups:



Chlorination:

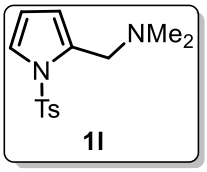
In a 4 mL vial, a solution of **3a'** (72.1 mg, 0.179 mmol) and cyanuric chloride (12.9 mg, 0.07 mmol) in 1 mL dicholoromethane was sealed and heated at 55 °C for 18 hours. When the reaction show full conversion monitored by TLC, the solvent directly was removed under vacuum. The residue was directly purified by silica gel flash column chromatography (from hexane : ethyl acetate = 20:1 to hexane : ethyl acetate = 10:1) to give product **4** (61.1 mg, 87% yield) as a colorless oil.

Oxidation:

In a 4 mL vial, **3a'** (150.1 mg, 0.40 mmol) and tetrabutylammonium iodide (15.0 mg, 0.04 mmol) were dissolved in 1.5 mL dimethylacetamide. 30% hydrogen peroxide solution (0.33 mL,

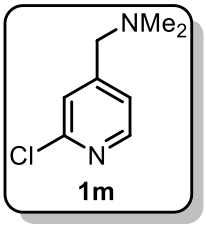
3.2 mmol) was quickly added to the vial. The vial was then sealed and heated with stirring at 100 °C for 24 hours. (Positive pressure was generated in the vial, be careful when opened it.) The reaction was worked up with aqueous $NaHCO_3$ solution, and extracted with ethyl acetate (10 mL x 4). Combined organic layer was dried over magnesium sulfate, concentrated under vacuum, and purified by silica gel column chromatography (from hexane : ethyl acetate = 10:1 to hexane : ethyl acetate = 5:1) to give product **5** 74.5 mg (54% yield) as colorless oil.

5.5.3 Characterization of new compound



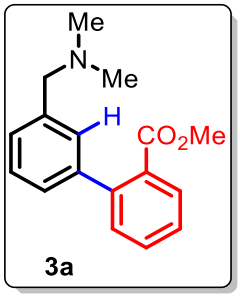
1l

(1l): sight brown solid, mp = 71.5°C to 73.0°C. R_f = 0.37 (Hex/EA = 3:1 with 3% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.30 (dd, *J* = 3.4, 1.8 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.19 (t, *J* = 3.3 Hz, 1H), 6.13 – 6.10 (m, 1H), 3.50 (s, 2H), 2.38 (s, 3H), 2.04 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.16, 136.89, 132.73, 129.21, 127.11, 123.16, 114.67, 110.78, 55.00, 44.53, 21.53. **IR** (KBr, cm^{-1}) 2942, 2816, 2774, 1366, 1175, 1148, 1131, 1091, 1054. **HRMS** calcd $C_{14}H_{19}N_2O_2S$ $[M+H]^+$: 279.1162. Found: 279.1164.



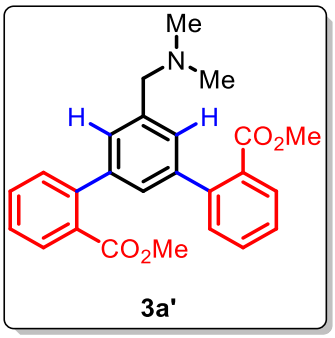
1m

(1m): yellow oil. R_f = 0.38 (Hex/EA = 3:1 with 3% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 5.1Hz, 1H), 7.32–7.27 (m, 1H), 7.18–7.14 (m, 1H), 3.38 (s, 2H), 2.22 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.82, 151.66, 149.47, 124.00, 122.41, 62.51, 45.45.**IR** (KBr, cm^{-1}) 2970,2870, 2823, 2776, 1594, 1551, 1384, 1143, 913. **HRMS** calcd $C_8H_{12}ClN_2$ $[M+H]^+$: 171.0684. Found: 171.0681.



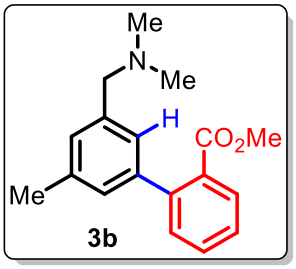
3a

(3a): 23% yield when the reaction was worked up after 12 hours. Colorless oil. R_f = 0.33 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 – 7.75 (m, 1H), 7.50 – 7.44 (m, 1H), 7.38 – 7.23 (m, 5H), 7.21 – 7.16 (m, 1H), 3.59 (s, 3H), 3.44 (s, 2H), 2.23 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.81, 142.10, 141.00, 138.20, 130.91, 130.62, 130.45, 129.45, 128.87, 127.76, 127.73, 126.84, 63.94, 51.59, 45.02. **IR** (KBr, cm^{-1}) 2947, 2815, 2769, 1724, 1288, 1253, 1125, 1090, 1050. **HRMS** calcd $C_{17}H_{20}NO_2$ $[M+H]^+$: 270.1489. Found: 270.1490.

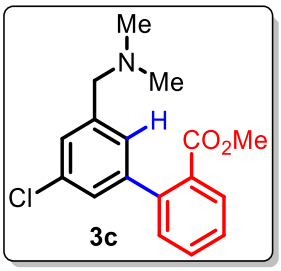


3a'

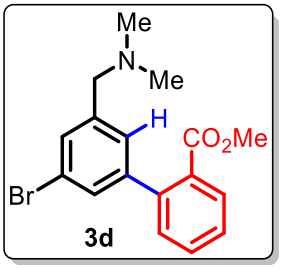
(3a'): 70% isolated from 36hour's reaction. Yellow oil. R_f = 0.19 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (ddd, *J* = 7.7, 1.5, 0.6 Hz, 2H), 7.56 – 7.48 (m, 2H), 7.44 – 7.36 (m, 4H), 7.25 (d, *J* = 1.8 Hz, 2H), 7.17 (t, *J* = 1.7 Hz, 1H), 3.65 (s, 6H), 3.49 (s, 2H), 2.27 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.12, 142.08, 141.12, 138.43, 131.12, 130.98, 130.73, 129.71, 128.02, 127.14, 127.04, 64.18, 51.90, 45.34.. **IR** (KBr, cm^{-1}) 2948, 2815, 2771, 1727, 1293, 1254, 1126, 1097, 1074. **HRMS** calcd $C_{25}H_{26}NO_4$ $[M+H]^+$: 404.1862. Found: 404.1859.



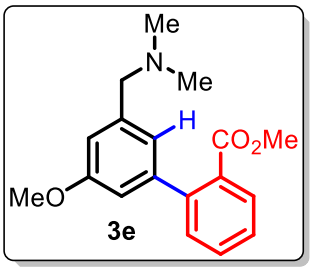
(3b): 73% yield. Yellow oil. R_f = 0.29 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 – 7.76 (m, 1H), 7.53 – 7.46 (m, 1H), 7.41 – 7.34 (m, 2H), 7.14 (s, 1H), 7.03 (s, 2H), 3.63 (s, 3H), 3.41 (s, 2H), 2.38 (s, 3H), 2.25 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.27, 142.35, 141.03, 138.59, 137.62, 131.02, 130.93, 130.61, 129.54, 128.70, 127.69, 126.92, 126.28, 64.29, 51.84, 45.39, 21.29. **IR** (KBr, cm^{-1}) 2947, 2815, 2771, 1724, 1598, 1433, 1291, 1253, 1125, 1098, 1071, 1042. **HRMS** calcd $C_{18}H_{22}NO_2$ $[M+H]^+$: 284.1645. Found: 284.1647.



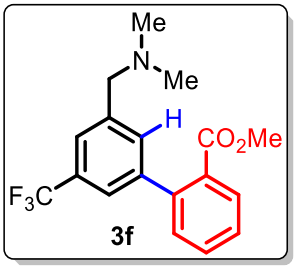
(3c): 72% yield. Colorless oil. R_f = 0.36 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (ddd, *J* = 7.7, 1.5, 0.5 Hz, 1H), 7.51 (td, *J* = 7.5, 1.5 Hz, 1H), 7.41 (td, *J* = 7.6, 1.4 Hz, 1H), 7.37 – 7.28 (m, 1H), 7.34 – 7.28 (m, 1H), 7.20 (t, *J* = 1.8 Hz, 1H), 7.12 (t, *J* = 1.5 Hz, 1H), 3.65 (s, 3H), 3.41 (s, 2H), 2.24 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.52, 142.85, 141.04, 140.62, 133.69, 131.30, 130.55, 130.54, 129.90, 127.66, 127.54, 127.24, 126.95, 63.65, 51.92, 45.31. **IR** (KBr, cm^{-1}) 2947, 2818, 2772, 1730, 1577, 1456, 1435, 1289, 1254, 1126, 1095, 1065. **HRMS** calcd $C_{17}H_{19}ClNO_2$ $[M+H]^+$: 304.1104. Found: 304.1101.



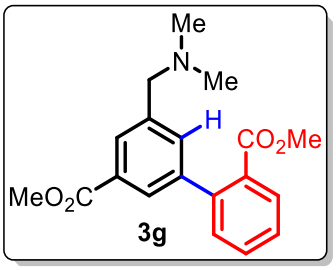
(3d): 65% yield. Colorless oil. R_f = 0.39 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.52 (td, *J* = 7.5, 1.5 Hz, 1H), 7.48 – 7.46 (m, 1H), 7.42 (td, *J* = 7.6, 1.3 Hz, 1H), 7.36 (t, *J* = 1.8 Hz, 1H), 7.34 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.17 (t, *J* = 1.6 Hz, 1H), 3.66 (s, 3H), 3.42 (s, 2H), 2.25 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.57, 143.15, 140.96, 140.87, 131.35, 130.62, 130.60, 130.57, 129.96, 129.88, 127.77, 127.61, 121.93, 63.65, 51.99, 45.36. **IR** (KBr, cm^{-1}) 2947, 2818, 2772, 1730, 1456, 1434, 1289, 1254, 1126, 1095, 1064, 1042. **HRMS** calcd $C_{17}H_{19}BrNO_2$ $[M+H]^+$: 348.0594. Found: 348.0597



(3e): 80% yield. Colorless oil. R_f = 0.21 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 – 7.76 (m, 1H), 7.53 – 7.47 (m, 1H), 7.42 – 7.36 (m, 2H), 6.88 (s, 1H), 6.83 (s, 1H), 6.77 (s, 1H), 3.82 (s, 3H), 3.63 (s, 3H), 3.42 (s, 2H), 2.25 (s, 6H).**^{13}C NMR** (101 MHz, $CDCl_{33}$) δ 169.16, 159.36, 142.34, 142.06, 140.15, 131.04, 130.96, 130.50, 129.51, 127.10, 121.65, 113.15, 112.75, 64.29, 55.24, 51.90, 45.36. **IR** (KBr, cm^{-1}) 2947, 2816, 2773, 1727, 1594, 1456, 1292, 1255, 1212, 913. **HRMS** calcd $C_{18}H_{21}NNaO_3$ $[M+Na]^+$: 322.1414. Found: 322.1404.

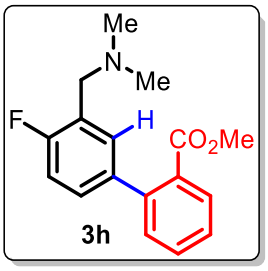


(3f): 55% yield. Colorless oil. R_f = 0.41 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, Acetonitrile-d_3) δ 7.83 (ddd, *J* = 7.7, 1.5, 0.5 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.53 – 7.46 (m, 3H), 7.42 (ddd, *J* = 7.6, 1.3, 0.5 Hz, 1H), 3.62 (s, 3H), 3.49 (s, 2H), 2.20 (s, 6H).**^{13}C NMR** (101 MHz, Acetonitrile-d_3) δ 169.23 , 143.05 , 141.98 , 141.52 , 133.60 (d, *J* = 1.5 Hz), 132.57 , 131.93 , 131.63 , 130.75 , 130.68 (q, *J* = 31.9 Hz), 128.98 , 125.44 (q, *J* = 271.6 Hz), 125.12 (q, *J* = 3.9 Hz), 124.51 (q, *J* = 3.8 Hz), 63.88 , 52.60 , 45.54 . **^{19}F NMR** (376 MHz, Acetonitrile-d_3) δ -62.83. **IR** (KBr, cm^{-1}) 2950, 2820, 2776, 1726, 1458, 1437, 1346, 1293, 1253, 1164, 1125. **HRMS** calcd $C_{18}H_{19}F_3NO_2$ $[M+H]^+$: 338.1362. Found: 338.1364.

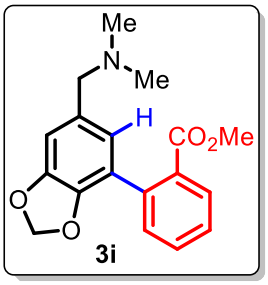


(3g): 45% yield. Colorless oil. R_f = 0.41 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (t, *J* = 1.7 Hz, 1H), 7.90 (t, *J* = 1.7 Hz, 1H), 7.86 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.52 (td, *J* = 7.5, 1.4 Hz, 1H), 7.45 (t, *J* = 1.7 Hz, 1H), 7.42 (td, *J* = 7.6, 1.4 Hz, 1H), 7.36 (dd, *J* = 7.6, 1.3 Hz, 1H), 3.90 (s, 3H), 3.62 (s, 3H), 3.48 (s, 2H), 2.25 (s, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.47, 166.94, 141.65, 141.57, 139.13, 133.54, 131.38, 130.77, 130.42, 130.01, 129.93, 128.89, 128.23,

127.49, 63.81, 52.05, 51.90, 45.32. **IR** (KBr, cm^{-1}) 2950, 2818, 2774, 1724, 1457, 1436, 1328, 1292, 1238, 1126, 1097, 913. **HRMS** calcd $C_{19}H_{22}NO_4$ $[M+H]^+$: 328.1543. Found: 328.1541.

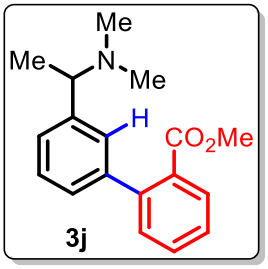


(3h): 47% yield. Colorless oil. R_f = 0.46 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 – 7.80 (m, 1H), 7.54 – 7.46 (m, 1H), 7.43 – 7.37 (m, 1H), 7.34 (d, *J* = 7.6, 0.7 Hz, 1H), 7.29 (dd, *J* = 7.0, 2.4 Hz, 1H), 7.21 – 7.12 (m, 1H), 7.06 (t, *J* = 9.4, 8.4, 0.9 Hz, 1H), 3.65 (s, 3H), 3.56 – 3.42 (m, 2H), 2.28 (s, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.68 , 160.71 (d, *J* = 246.8 Hz), 141.46 , 137.00 (d, *J* = 3.7 Hz), 131.41 (d, *J* = 4.7 Hz), 131.16 , 130.69 , 130.58 , 129.75 , 128.55 (d, *J* = 8.3 Hz), 127.12 , 124.87 (d, *J* = 15.2 Hz), 114.81 (d, *J* = 22.8 Hz), 56.53 (d, *J* = 1.6 Hz), 51.82 , 45.12. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -120.43 . **IR** (KBr, cm^{-1}) 2948, 2820, 2778, 1729, 1503, 1479, 1289, 1249, 1126, 1087, 913. **HRMS** calcd $C_{17}H_{19}FNO_2$ $[M+H]^+$: 288.1394. Found: 288.1395.

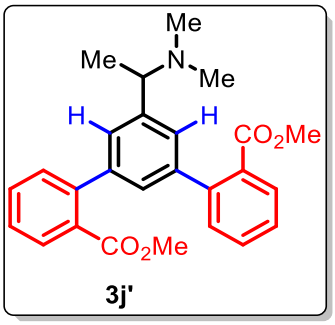


(3i): 32% yield. Colorless oil. R_f = 0.21 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.54 (td, *J* = 7.5, 1.4 Hz, 1H), 7.47 – 7.38 (m, 2H), 6.84 (d, *J* = 1.6 Hz, 1H), 6.75 (d, *J* = 1.5 Hz, 1H), 5.91 (s, 2H), 3.72 (s, 3H), 3.37 (s, 2H), 2.25 (s, 6H).**^{13}C**

NMR (101 MHz, $CDCl_3$) δ 168.45, 147.13, 143.68, 136.35, 132.80, 131.58, 130.97, 130.80, 130.04, 127.62, 122.72, 122.15, 108.69, 100.94, 64.12, 52.00, 45.22. **IR** (KBr, cm^{-1}) 2948, 2617, 2772, 1726, 1420, 1291, 1256, 1192, 1126, 1096, 1046, 913. **HRMS** calcd $C_{19}H_{22}NO_4$ $[M+H]^+$: 314.1389. Found: 314.1387.



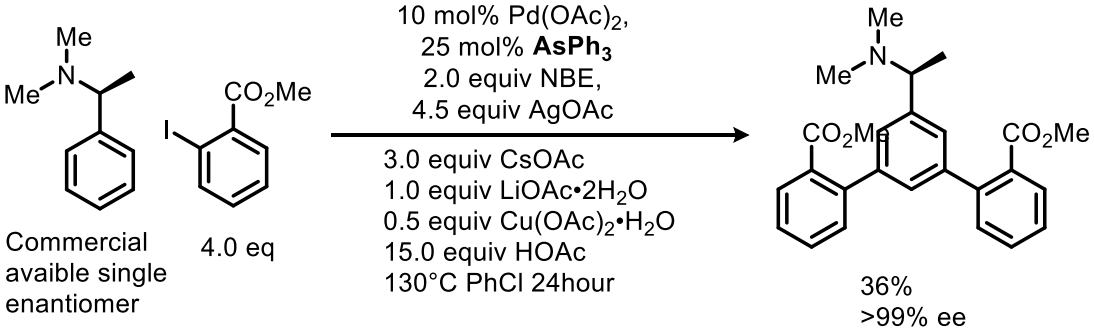
(3j): 33% yield. Colorless oil. R_f = 0.43 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 1H), 7.55 – 7.49 (m, 1H), 7.43 – 7.38 (m, 2H), 7.38 – 7.33 (m, 1H), 7.31 – 7.26 (m, 1H), 7.25 – 7.18 (m, 2H), 3.61 (s, 3H), 3.27 (q, *J* = 6.7 Hz, 1H), 2.21 (s, 6H), 1.39 (d, *J* = 6.7 Hz, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.21, 143.87, 142.42, 141.15, 131.08, 130.98, 130.65, 129.63, 127.95, 127.60, 127.02, 126.78, 126.37, 65.89, 51.86, 43.24, 20.34. **IR** (KBr, cm^{-1}) 2976, 2950, 2816, 2769, 1725, 1290, 1126, 1088, 1050, 931. **HRMS** calcd $C_{18}H_{21}NNaO_2$ $[M+Na]^+$: 306.1465. Found: 306.1467.



(3j'): 31% yield. Colorless oil. R_f = 0.23 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (ddd, *J* = 7.7, 1.5, 0.6 Hz, 2H), 7.51 (ddd, *J* = 7.7, 7.2, 1.4 Hz, 2H), 7.44 – 7.36 (m,

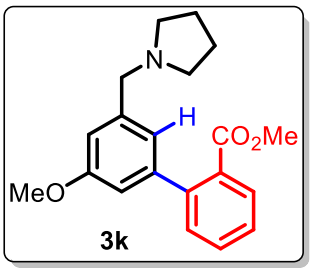
4H), 7.22 (dd, *J* = 1.7, 0.5 Hz, 2H), 7.18 (t, *J* = 1.7 Hz, 1H), 3.65 (s, 6H), 3.30 (q, *J* = 6.7 Hz, 1H), 2.23 (s, 6H), 1.40 (d, *J* = 6.7 Hz, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.20, 143.70, 142.13, 141.11, 131.13, 131.07, 130.68, 129.66, 127.11, 126.76, 126.56, 65.81, 51.89, 43.26, 20.47.**IR** (KBr, cm^{-1}) 2950, 2817, 2769, 1727, 1595, 1433, 1293, 1254, 1126, 913. **HRMS** calcd $C_{26}H_{27}NNaO_4$ $[M+Na]^+$: 440.1832. Found: 440.1837.

Scheme 5.9 Chiral Substrates in the *meta* C-H activation,

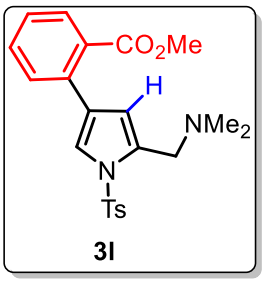


For chiral (S)-(-)-**3j',** it is directly synthesized from commercial available (S)-(-)-N,N-Dimethyl-1-phenylethylamine following general procedure at 130°C.

Chiral HPLC (Chiralpak IA, hexane : isopropanol (with 0.5% V/V diethylamine) = 98.5:1.5, 1 mL/min, 254 nm): t_s = 28.65 min, t_r =31.34min. $[a]_D^{20}$ = -13° (c 1.0, $CDCl_3$) at >99 %e.e..

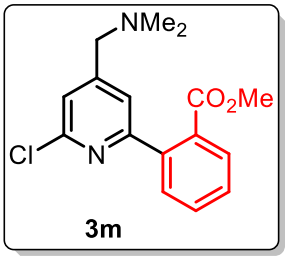


(3k): 17% yield. Yellow oil. R_f = 0.54 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 – 7.74 (m, 1H), 7.54 – 7.46 (m, 1H), 7.44 – 7.36 (m, 2H), 6.91 (dd, *J* = 2.5, 1.4 Hz, 1H), 6.86 (t, *J* = 1.5 Hz, 1H), 6.76 (dd, *J* = 2.5, 1.6 Hz, 1H), 3.82 (s, 3H), 3.64 (s, 3H), 3.62 (s, 2H), 2.58 – 2.47 (m, 4H), 1.83 – 1.74 (m, 4H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.25, 159.35, 142.32, 142.16, 140.62, 131.06, 131.03, 130.56, 129.53, 127.12, 121.51, 113.27, 112.48, 60.62, 55.30, 54.12, 51.95, 23.44. **IR** (KBr, cm^{-1}) 2951, 2784, 1727, 1594, 1292, 1252, 1211, 1126, 913. **HRMS** calcd $C_{20}H_{23}NNaO_3$ $[M+Na]^+$: 348.1570. Found: 348.1559.

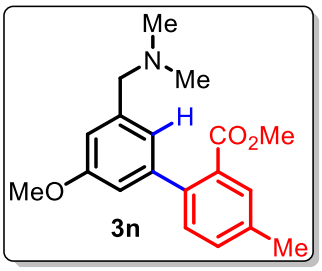


3l

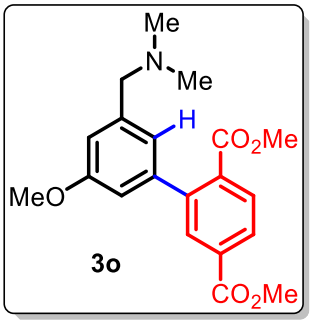
(3k): 48% yield. Brown oil. R_f = 0.36 (Hex/EA = 3:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 2H), 7.67 (ddd, *J* = 7.7, 1.5, 0.5 Hz, 1H), 7.47 - 7.43 (m, 1H), 7.41 - 7.37 (m, 2H), 7.35 – 7.29 (m, 1H), 7.28 – 7.24 (m, 2H), 6.21 (dd, *J* = 1.9, 0.9 Hz, 1H), 3.71 (s, 3H), 3.52 (s, 2H), 2.39 (s, 3H), 2.07 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.41, 144.27, 136.80, 133.63, 132.70, 131.04, 130.79, 129.93, 129.33, 129.24, 127.16, 126.88, 125.43, 120.57, 115.68, 54.95, 51.99, 44.50, 21.52. **IR** (KBr, cm^{-1}) 2949, 2869, 2818, 1727, 1366, 1291, 1175, 1133, 1103, 913. **HRMS** calcd $C_{22}H_{25}N_2O_4S$ $[M+H]^+$: 413.1530. Found: 413.1535.



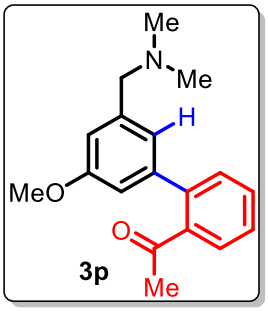
(3m): 66% yield. Brown oil. R_f = 0.35 (Hex/EA = 3:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (ddd, *J* = 7.6, 1.4, 0.6 Hz, 1H), 7.61 – 7.51 (m, 2H), 7.49 – 7.44 (m, 1H), 7.39 (dd, *J* = 1.2, 0.6 Hz, 1H), 7.28 (dd, *J* = 1.3, 0.7 Hz, 1H), 3.75 (s, 3H), 3.46 (s, 2H), 2.28 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.05, 158.67, 152.06, 150.68, 139.04, 131.70, 131.00, 129.59, 128.72, 122.38, 121.19, 62.71, 52.14, 45.56. **IR** (KBr, cm^{-1}) 2979, 2947, 2869, 1728, 1595, 1548, 1291, 1258, 1127, 913. **HRMS** calcd $C_{16}H_{18}ClN_2O_2$ $[M+H]^+$: 305.1051. Found: 305.1056.



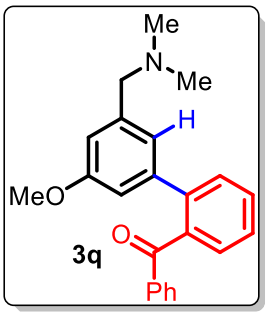
(3l): 70% yield. Colorless oil. R_f = 0.21 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (dt, *J* = 1.6, 0.7 Hz, 1H), 7.33 – 7.27 (m, 2H), 6.86 (dd, *J* = 2.5, 1.4 Hz, 1H), 6.81 (t, *J* = 1.5 Hz, 1H), 6.75 (dd, *J* = 2.5, 1.6 Hz, 1H), 3.81 (s, 3H), 3.63 (s, 3H), 3.41 (s, 2H), 2.40 (s, 3H), 2.24 (s, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.34, 159.32, 142.27, 140.06, 139.18, 136.95, 131.75, 130.74, 130.40, 129.98, 121.67, 112.92, 112.78, 64.30, 55.19, 51.84, 45.34, 20.84.**IR** (KBr, cm^{-1}) 2946, 2816, 2772, 1732, 1594, 1456, 1434, 1296, 1253, 1204, 826. **HRMS** calcd $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1751. Found: 314.1752.



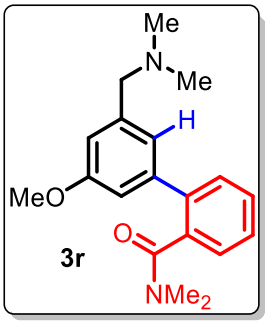
(3m): 71% yield. Colorless oil. R_f = 0.19 (Hex/EA = 3:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (d, J = 1.7 Hz, 1H), 7.97 (dd, J = 8.0, 1.7 Hz, 1H), 7.74 (dd, J = 7.9, 1.4 Hz, 1H), 6.84 (s, 1H), 6.79 (s, 1H), 6.72 (s, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 3.60 (s, 3H), 3.36 (s, 2H), 2.18 (s, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.38, 165.91, 159.37, 141.93, 141.10, 140.40, 134.89, 132.04, 131.33, 129.32, 127.91, 121.31, 113.44, 112.54, 64.10, 55.11, 52.20, 52.02, 45.23.**IR** (KBr, cm^{-1}) 2950, 2817, 2773, 1727, 1594, 1456, 1434, 1284, 1250, 1209, 1116, 913. **HRMS** calcd $C_{20}H_{23}NO_5$ $[M+H]^+$: 358.1649. Found: 358.1649.



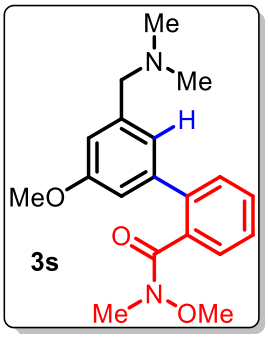
(3n): 31% yield. Colorless oil. R_f = 0.24 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 – 7.45 (m, 2H), 7.43 – 7.35 (m, 2H), 6.92 (s, 1H), 6.86 (s, 1H), 6.78 (s, 1H), 3.82 (s, 3H), 3.42 (s, 2H), 2.24 (s, 6H), 2.02 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.81, 159.80, 141.84, 141.03, 140.82, 140.32, 130.58, 130.03, 127.71, 127.44, 122.11, 113.78, 113.29, 64.14, 55.33, 45.35, 30.37. **IR** (KBr, cm^{-1}) 2941, 2816, 2772, 1688, 1592, 1456, 1361, 1332, 1276, 1238, 1211, 1146, 1030. **HRMS** calcd $C_{18}H_{21}NO_2$ $[M+H]^+$: 284.1645. Found: 284.1646.



(3o): 58% yield. Colorless oil. R_f = 0.22 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 2H), 7.58 – 7.42 (m, 4H), 7.39 – 7.33 (m, 1H), 7.22 (s, 2H), 6.77 (t, *J* = 1.5 Hz, 1H), 6.71 – 6.68 (m, 1H), 6.67 – 6.61 (m, 1H), 3.67 (s, 3H), 3.25 (s, 2H), 2.09 (s, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.83, 159.31, 141.18, 140.70, 140.45, 138.95, 137.21, 132.63, 130.21, 129.71, 129.63, 128.57, 127.92, 127.20, 122.25, 113.57, 113.40, 64.04, 55.16, 45.24.. **IR** (KBr, cm^{-1}) 2942, 2817, 2771, 1728, 1667, 1594, 1456, 1285, 1254, 1212, 1148, 928. **HRMS** calcd $C_{23}H_{24}NO_2$ $[M+H]^+$: 346.1802. Found: 346.1804.

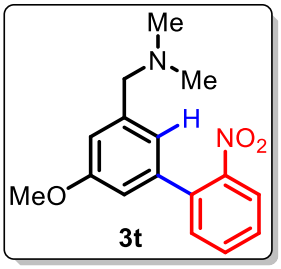


(3p): 60% yield. Colorless oil. R_f = 0.29 (Hex/EA = 1:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.33 (m, 4H), 6.97 (s, 1H), 6.93 – 6.90 (m, 1H), 6.89 – 6.85 (m, 1H), 3.80 (s, 3H), 3.46 – 3.35 (m, 2H), 2.85 (s, 3H), 2.44 (s, 3H), 2.23 (s, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.25, 159.57, 141.06, 140.56, 138.45, 135.64, 129.29, 129.15, 127.66, 127.31, 121.56, 113.99, 112.47, 64.20, 55.32, 45.35, 37.99, 34.54.**IR** (KBr, cm^{-1}) 2939, 2856, 2816, 2772, 1633, 1593, 1456, 1394, 1210, 913. **HRMS** calcd $C_{19}H_{25}N_2O_2$ $[M+H]^+$: 313.1911. Found: 313.1913.



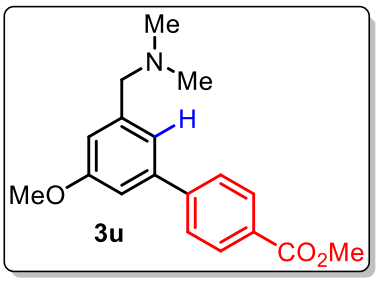
(3q): 53% yield. Colorless oil. R_f = 0.37 (Hex/EA = 1:1 with 4% v/v Et_3N). This compound has several rotamers at r.t. in $CDCl_3$. Both proton and 13 carbon are taken in DMSO-*d6* at 100°C.

^{1}H NMR (600 MHz, DMSO-d_6) δ 7.49 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.43 (ddd, *J* = 14.6, 7.4, 1.4 Hz, 2H), 7.38 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.94 (d, *J* = 1.7 Hz, 1H), 6.87 (dt, *J* = 7.8, 2.1 Hz, 2H), 3.79 (s, 3H), 3.41 (s, 2H), 3.06 – 2.90 (m, 6H), 2.20 (s, 6H).**^{13}C NMR** (151 MHz, DMSO-d_6) δ 158.84, 140.44, 140.18, 138.20, 134.67, 128.63, 128.57, 126.38, 126.19, 120.72, 113.04, 112.25, 62.94, 59.73, 54.71, 54.69, 44.32.**IR** (KBr, cm^{-1}): 2938, 2816, 2773, 1652, 1593, 1457, 1364, 1332, 1214. **HRMS** calcd $C_{19}H_{25}N_2O_3$ $[M+H]^+$: 329.1860. Found: 329.1862.



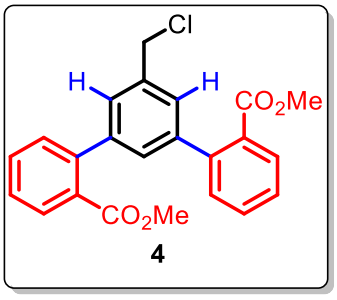
(3r): 66% yield. Yellow oil. R_f = 0.43 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.62 – 7.55 (m, 1H), 7.49 – 7.41 (m, 2H), 6.91 (s, 1H), 6.83 (s, 1H), 6.79 – 6.73 (m, 1H), 3.81 (s, 3H), 3.41 (s, 2H), 2.24 (s, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.70, 149.23, 140.96, 138.38, 136.11, 132.08, 131.78, 128.07, 123.88, 120.86, 113.95, 112.42, 64.11, 55.27,

45.33.**IR** (KBr, cm^{-1}) 2942, 2818, 2774, 1572, 1529, 1457, 1361, 1213, 913. **HRMS** calcd $C_{16}H_{19}N_2O_3$ $[M+H]^+$: 287.1390. Found: 287.1390.



3u

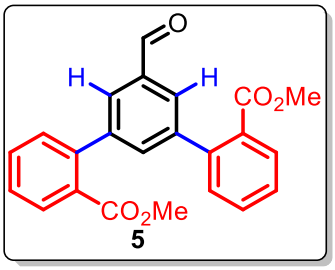
(3u): 4% yield. Pale yellow oil. R_f = 0.41 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 – 8.05 (m, 2H), 7.69 – 7.62 (m, 2H), 7.16 (t, *J* = 1.5 Hz, 1H), 7.05 (dd, *J* = 2.5, 1.6 Hz, 1H), 6.92 (dd, *J* = 2.5, 1.3 Hz, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 3.46 (s, 2H), 2.28 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.99, 160.10, 145.45, 141.24, 129.98, 129.06, 128.94, 127.11, 120.40, 113.91, 111.91, 64.43, 55.43, 52.12, 45.48. **IR** (KBr, cm^{-1}) 2979, 2949, 2869, 1726, 1363, 1286, 1175, 1134, 913. **HRMS** calcd $C_{18}H_{22}NO_3$ $[M+H]^+$: 300.1594. Found: 300.1599.



4

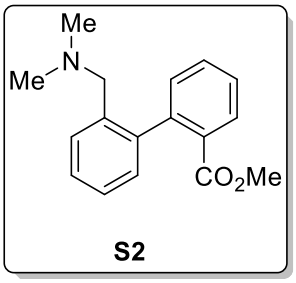
(4): 87% yield. Colorless oil. R_f = 0.34 (Hex/EA = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (ddd, *J* = 7.7, 1.4, 0.6 Hz, 2H), 7.54 (td, *J* = 7.5, 1.5 Hz, 2H), 7.46 – 7.39 (m, 4H), 7.33 (d, *J* = 1.7 Hz, 2H),

7.25 (t, *J* = 1.7 Hz, 1H), 4.65 (s, 2H), 3.68 (s, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.90, 141.68, 141.46, 136.99, 131.30, 130.87, 130.64, 129.90, 128.37, 127.48, 52.04, 46.04. **IR** (KBr, cm^{-1}) 2950, 1725, 1596, 1434, 1294, 1255, 1127, 1098, 1074, 913. **HRMS** calcd $C_{23}H_{19}ClNaO_4$ $[M+Na]^+$: 417.0864. Found: 417.0859.



5

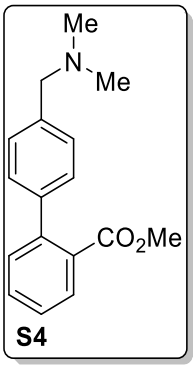
(5): 55% yield. Colorless oil. R_f = 0.23 (Hex/EA = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 7.92 (ddd, *J* = 7.8, 1.5, 0.5 Hz, 2H), 7.82 (d, *J* = 1.8 Hz, 2H), 7.56 (td, *J* = 7.5, 1.4 Hz, 2H), 7.50 (t, *J* = 1.7 Hz, 1H), 7.49 – 7.44 (m, 2H), 7.40 (ddd, *J* = 7.6, 1.4, 0.5 Hz, 2H), 3.68 (s, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.95, 168.18, 142.14, 141.10, 135.98, 134.40, 131.59, 130.80, 130.34, 130.24, 128.35, 127.85, 52.03.**IR** (KBr, cm^{-1}) 2951, 1726, 1699, 1597, 1434, 1294, 1258, 1166, 1127, 913. **HRMS** calcd $C_{23}H_{18}NaO_5$ $[M+Na]^+$: 397.1046. Found: 397.1047.



S2

(S2): 43% yield. Colorless oil. R_f = 0.44 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (ddd, *J* = 7.8, 1.5, 0.5 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.42 (td, *J* = 7.6, 1.4 Hz, 1H), 7.33 (td, *J* = 7.5, 1.5 Hz, 1H), 7.29 – 7.20 (m, 2H), 7.12 – 7.06 (m, 1H), 3.57 (s, 3H), 3.21 – 2.95 (m, 2H),

2.06 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.67, 142.15, 141.70, 136.36, 131.08, 131.04, 130.79, 129.70, 128.76, 128.71, 127.15, 127.07, 126.11, 61.21, 51.70, 45.26.**IR** (KBr, cm^{-1}) 2947, 2815, 2769, 1732, 1456, 1289, 1253, 1127, 1085, 913. **HRMS** calcd $C_{17}H_{20}NO_2$ $[M+H]^+$: 270.1489. Found: 270.1488.



(S2): 45% yield. Colorless oil. R_f = 0.35 (Hex/EA = 5:1 with 4% v/v Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (ddd, *J* = 7.6, 1.4, 0.7 Hz, 1H), 7.52 (td, *J* = 7.5, 1.4 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.36 – 7.31 (m, 2H), 7.27 (d, *J* = 7.0 Hz, 2H), 3.62 (s, 3H), 3.47 (s, 2H), 2.27 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.27 , 142.20 , 140.03 , 137.83 , 131.19 , 130.89 , 130.65 , 129.72 , 128.81 , 128.18 , 127.05 , 64.12 , 51.88 , 45.41 .**IR** (KBr, cm^{-1}) 2947, 2816, 2769, 1727, 1447, 1433, 1287, 1253, 1126, 1089. **HRMS** calcd $C_{17}H_{20}NO_2$ $[M+H]^+$: 270.1489. Found: 270.1481.

5.6 NMR spectra

Figure 5.1 ^{1}H and ^{13}C NMR spectrum of compound **1m.**

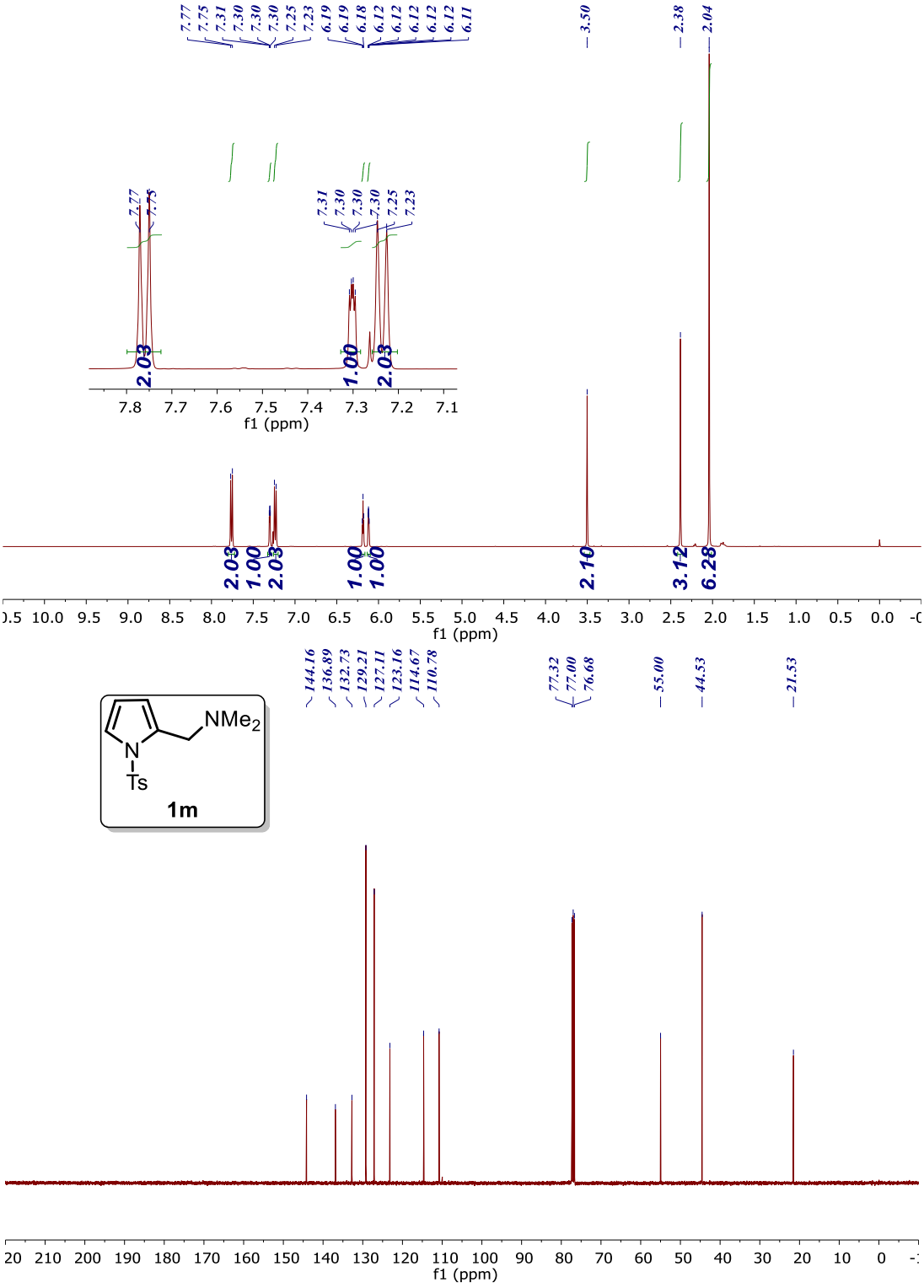


Figure 5.2 ^{1}H and ^{13}C NMR spectrum of compound **1l.**

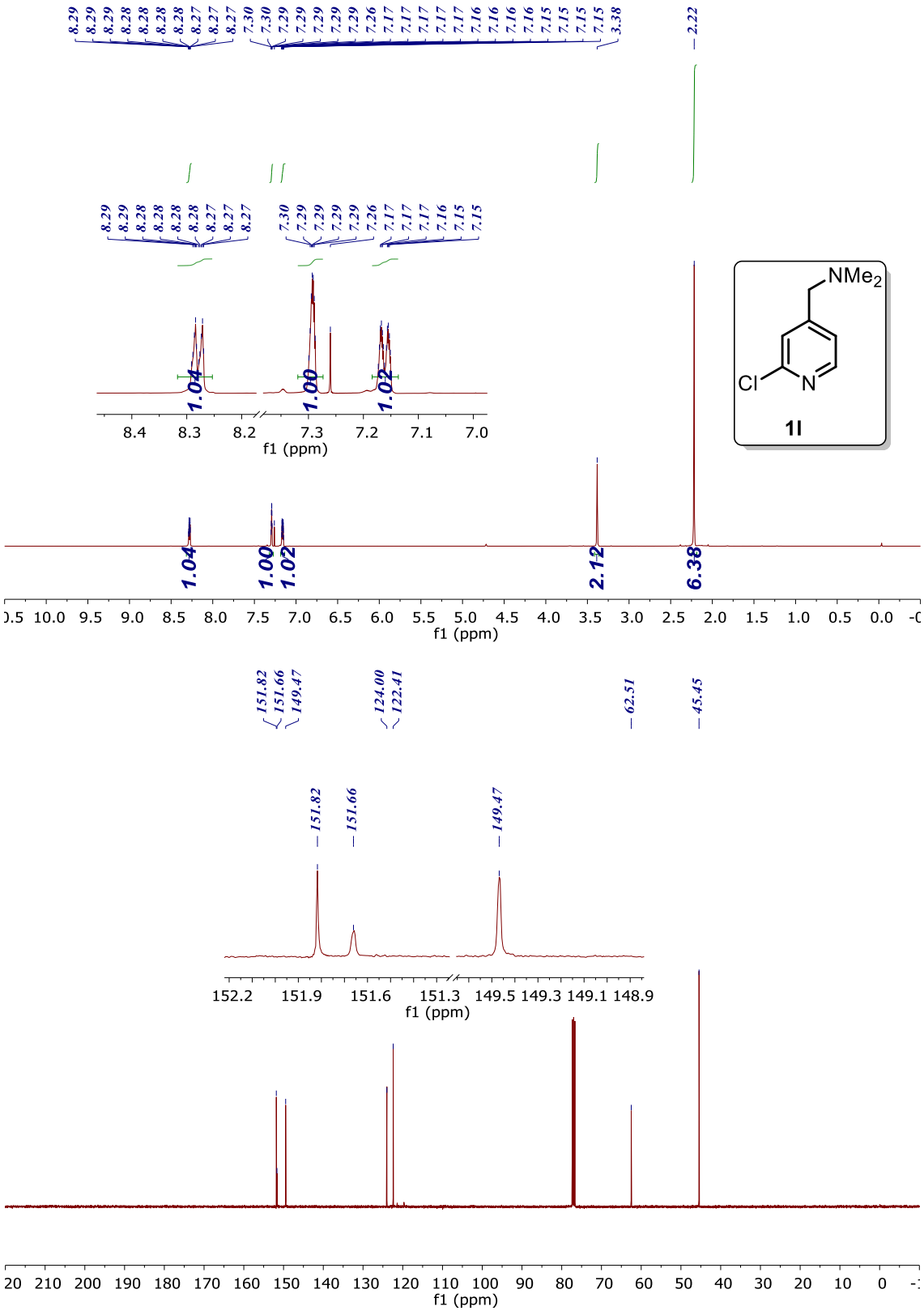


Figure 5.3 ^{1}H and ^{13}C NMR spectrum of compound **3a.**

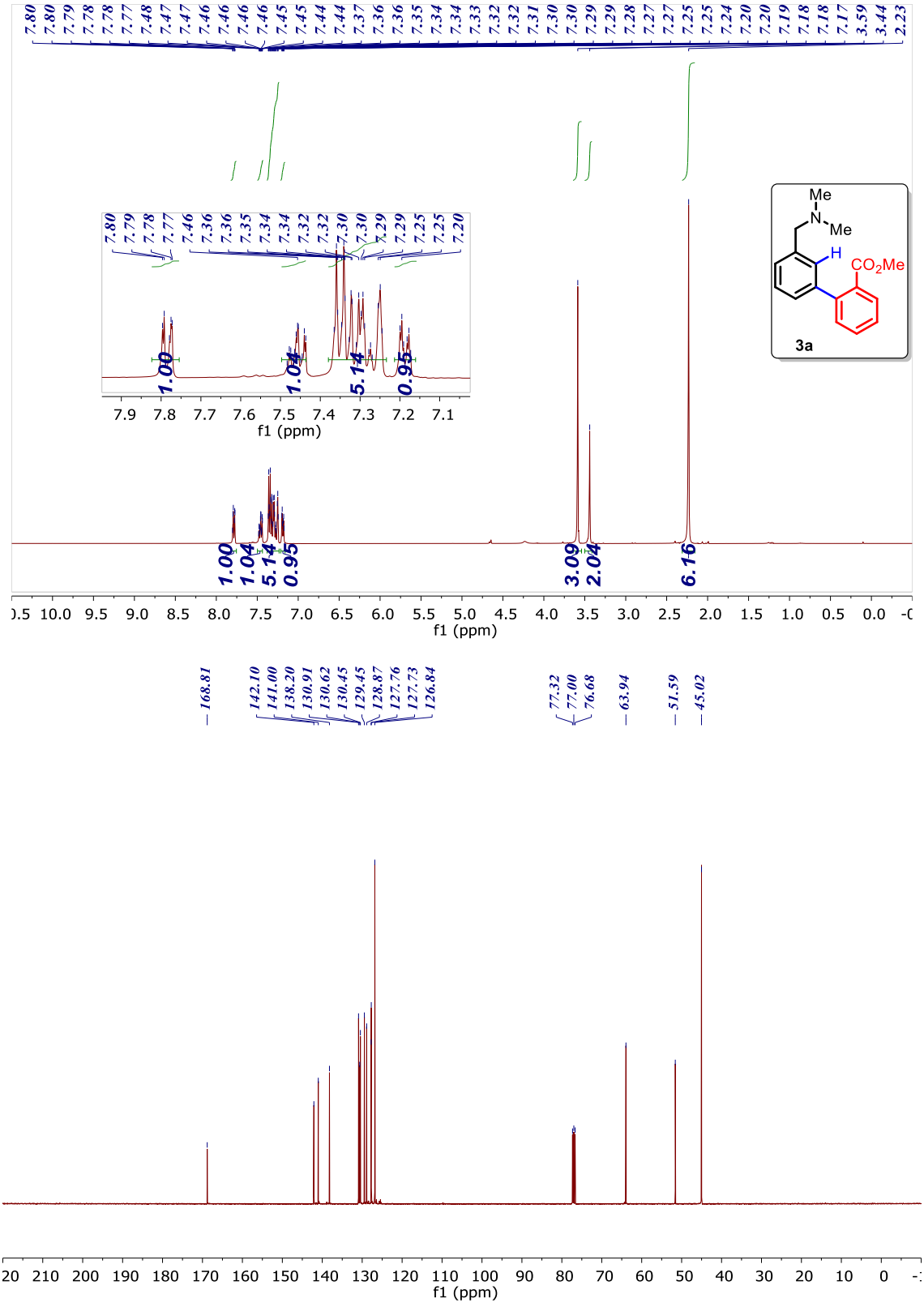


Figure 5.4 ^{1}H and ^{13}C NMR spectrum of compound **3a'.**

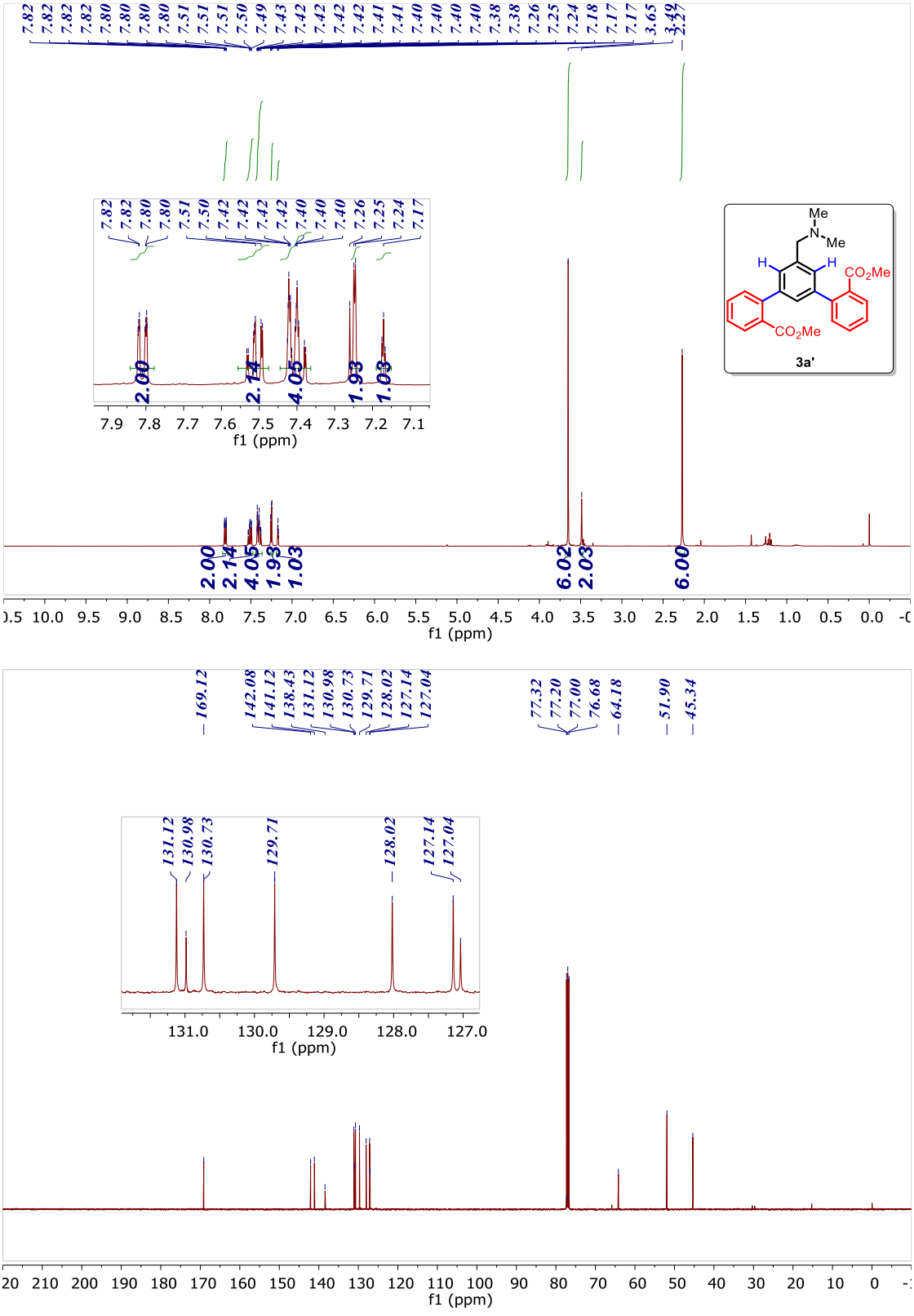


Figure 5.5 ^{1}H and ^{13}C NMR spectrum of compound **3b.**

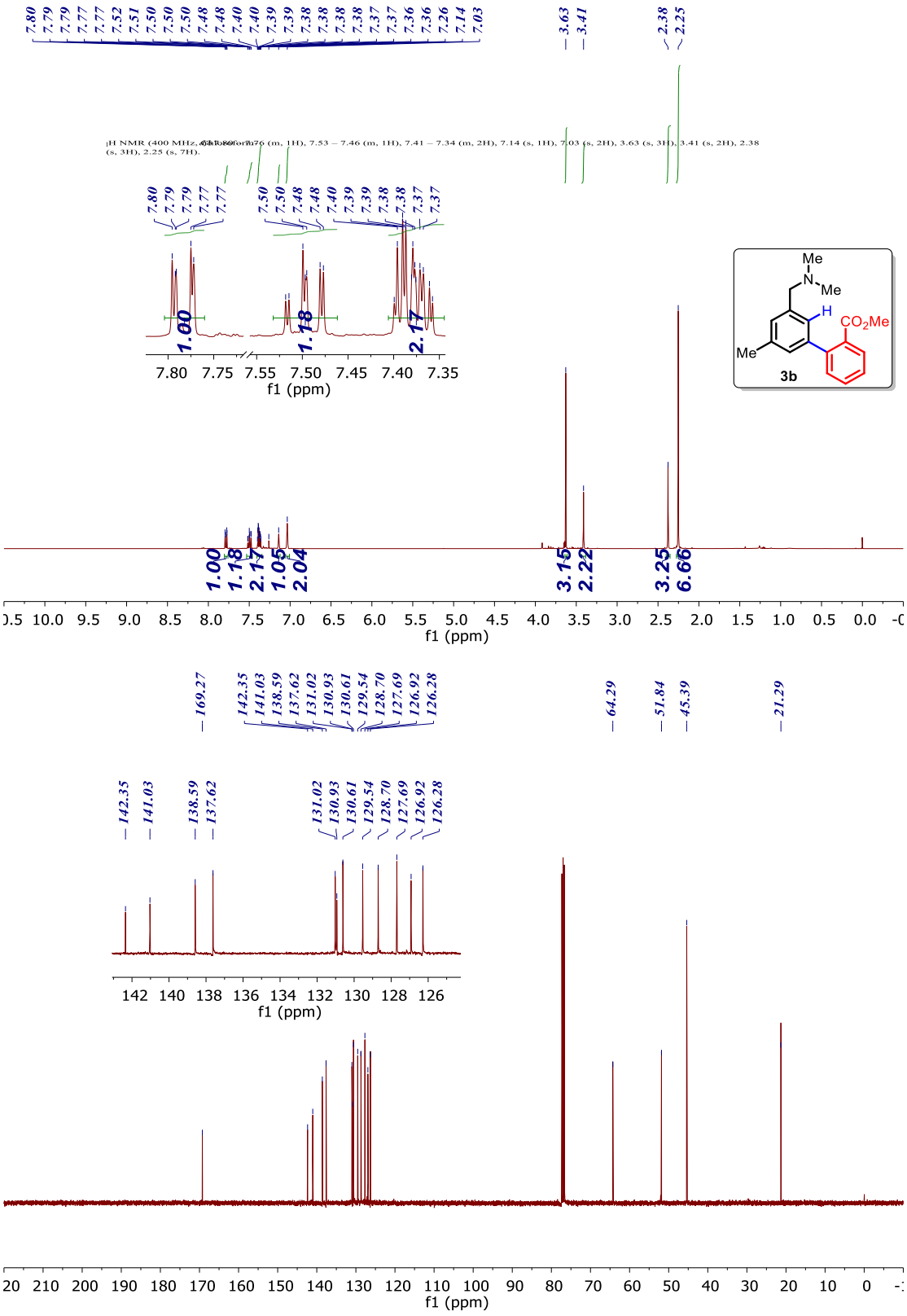


Figure 5.6 ^{1}H and ^{13}C NMR spectrum of compound **3c.**

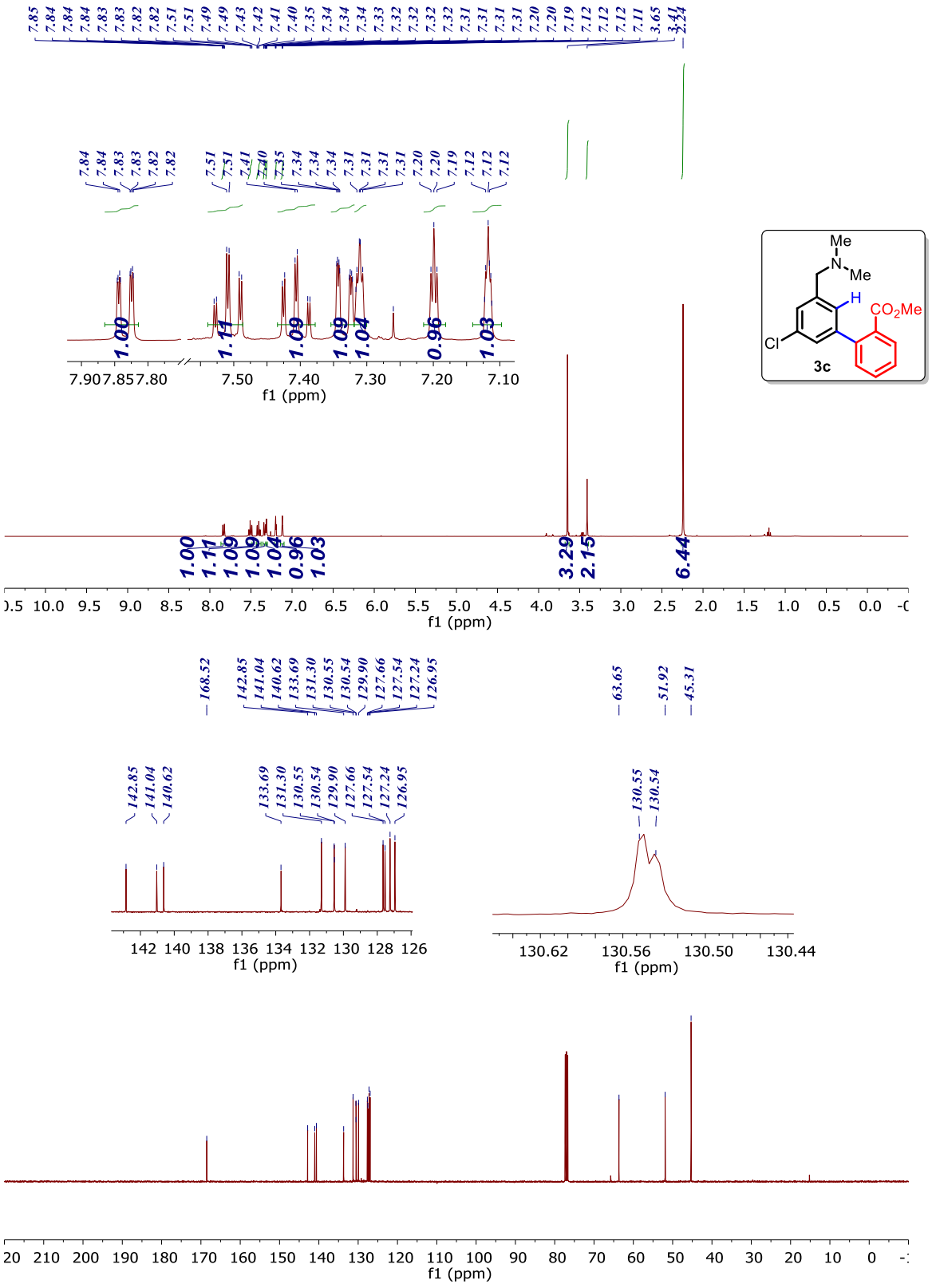


Figure 5.7 ^{1}H and ^{13}C NMR spectrum of compound **3d.**

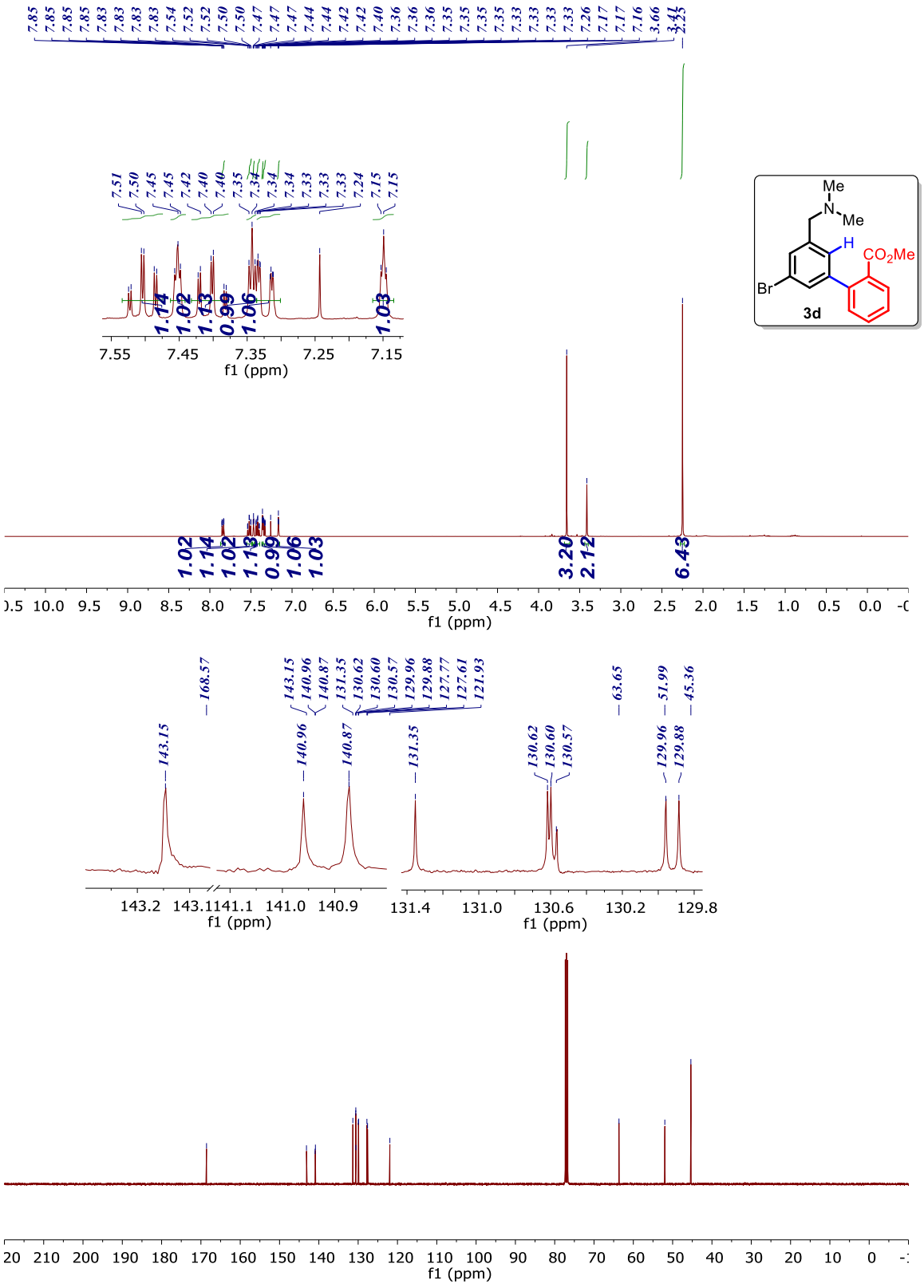


Figure 5.8 ^{1}H and ^{13}C NMR spectrum of compound **3e.**

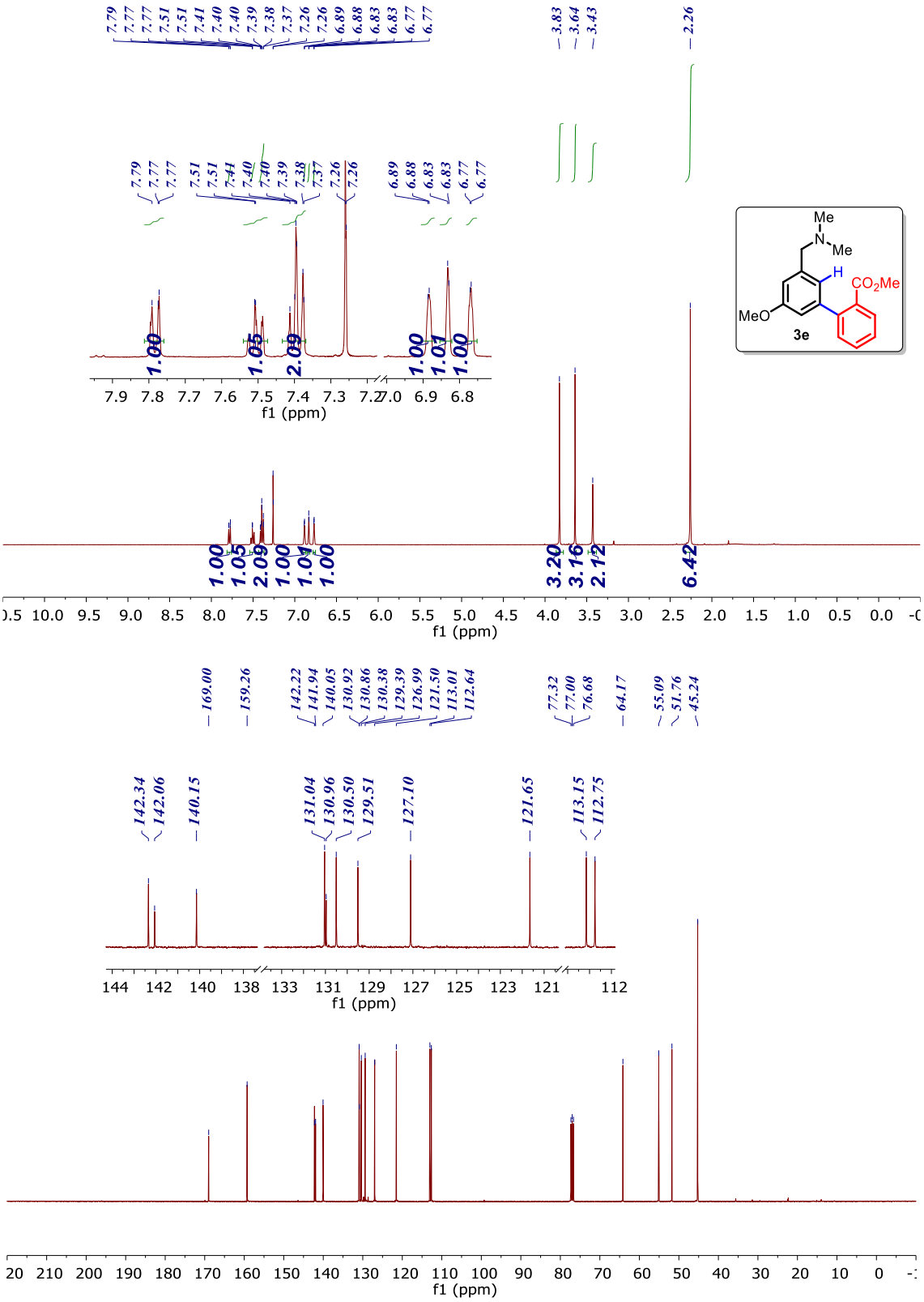


Figure 5.9 ^{1}H and ^{13}C NMR spectrum of compound **3f.**

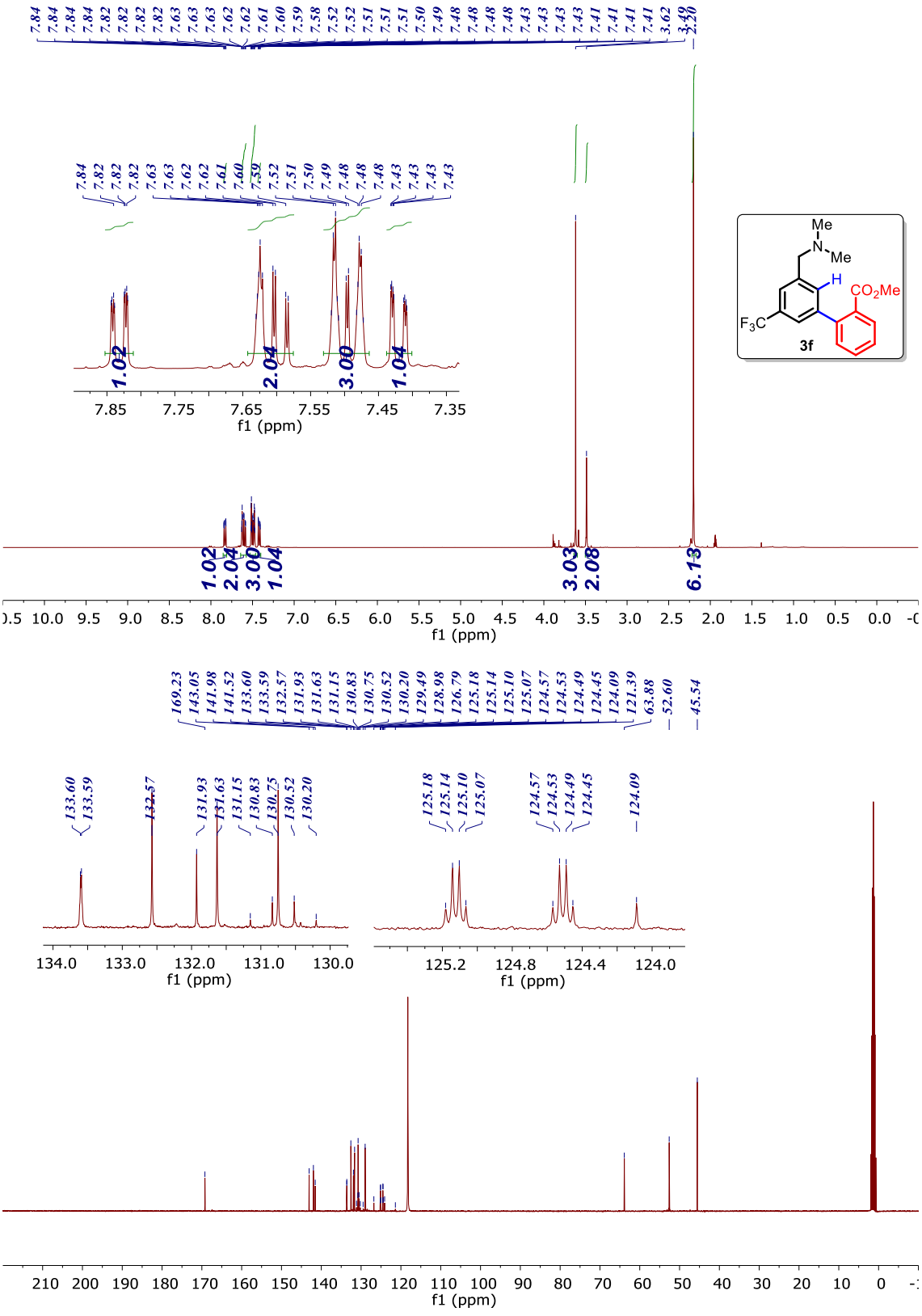


Figure 5.10 ^{19}F NMR spectrum of compound **3f.**

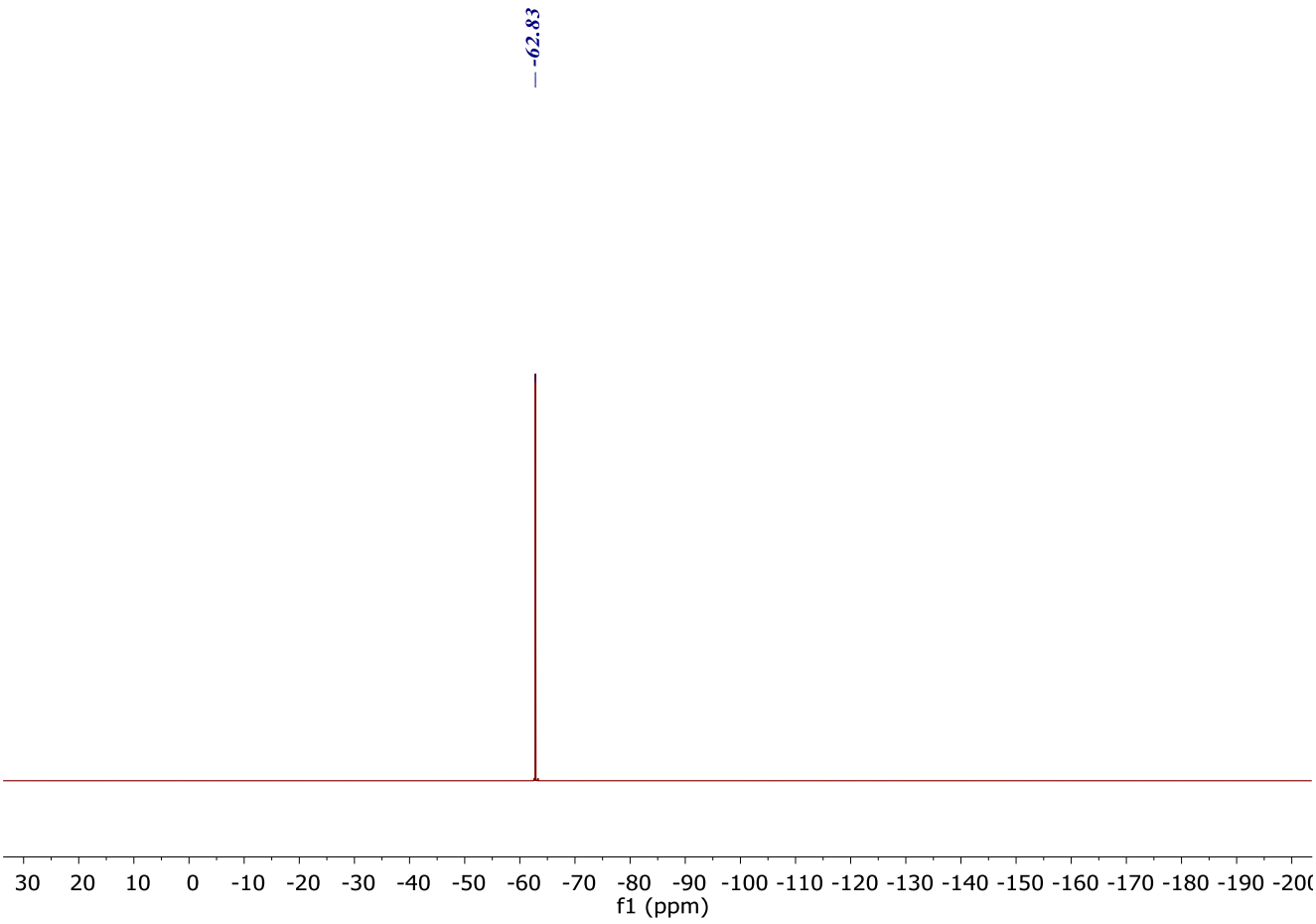


Figure 5.11 ^{1}H and ^{13}C NMR spectrum of compound **3g.**

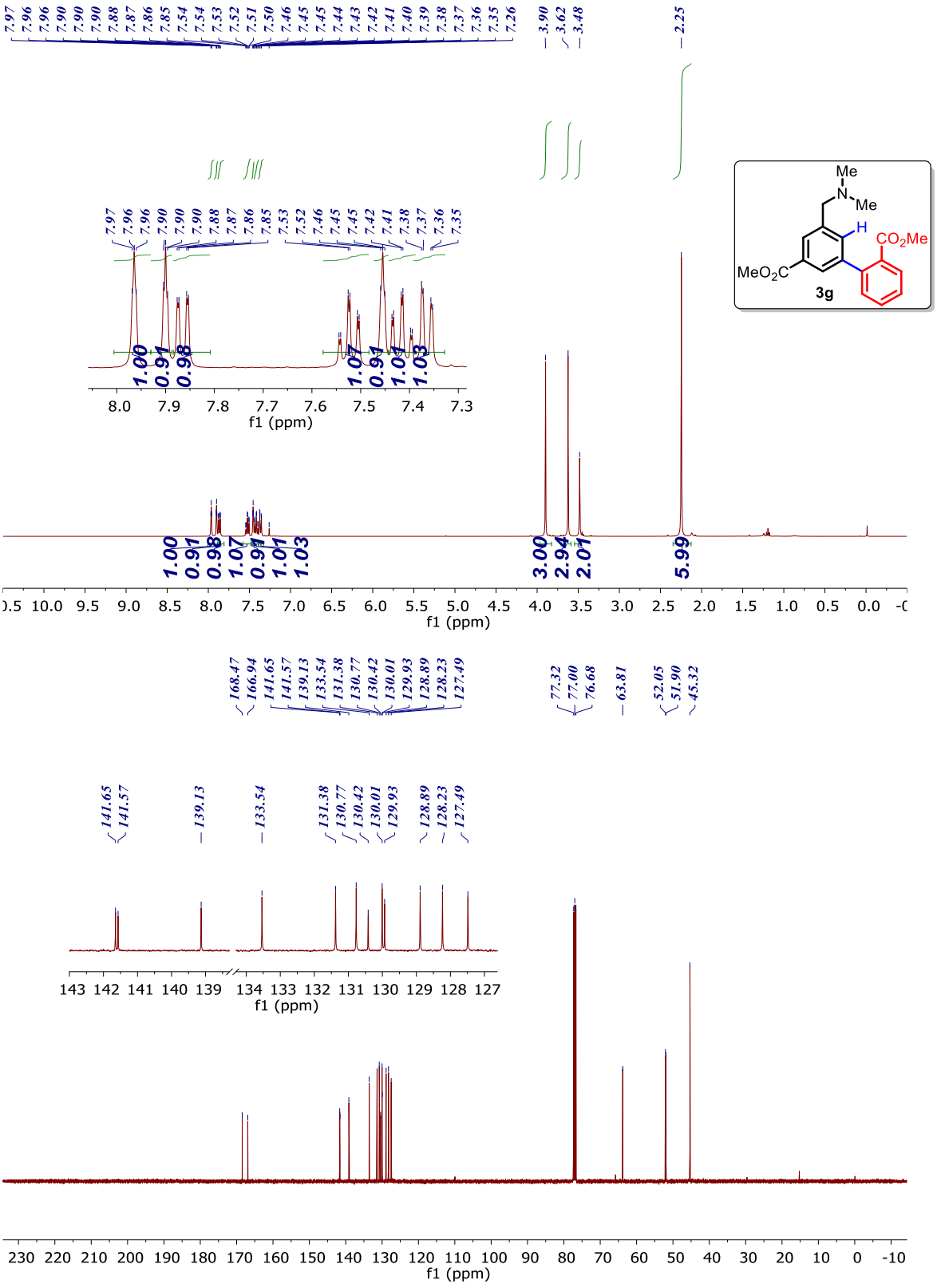


Figure 5.12 ^{1}H and ^{13}C NMR spectrum of compound **3h.**

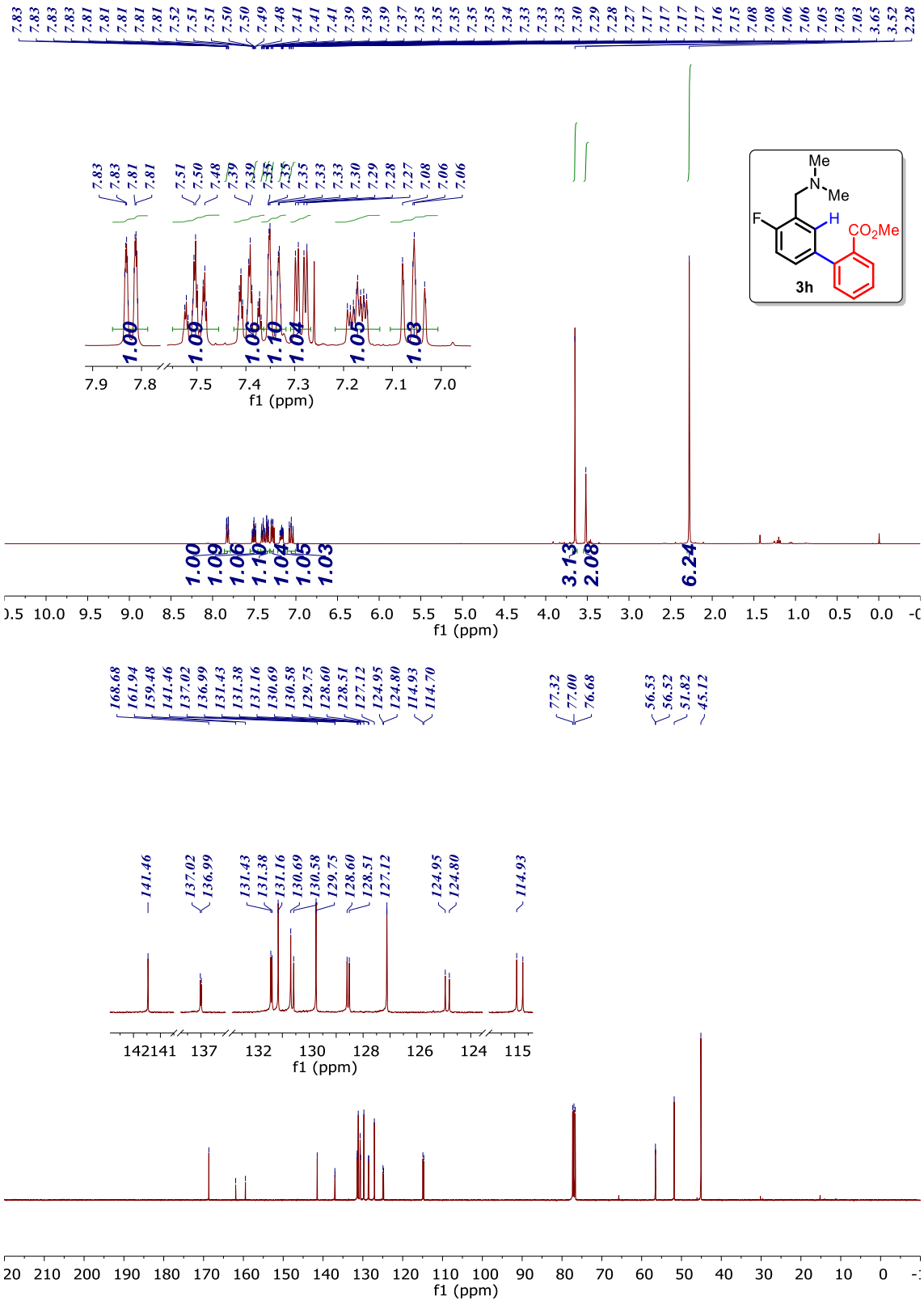


Figure 5.13 ^{19}F NMR spectrum of compound **3h.**

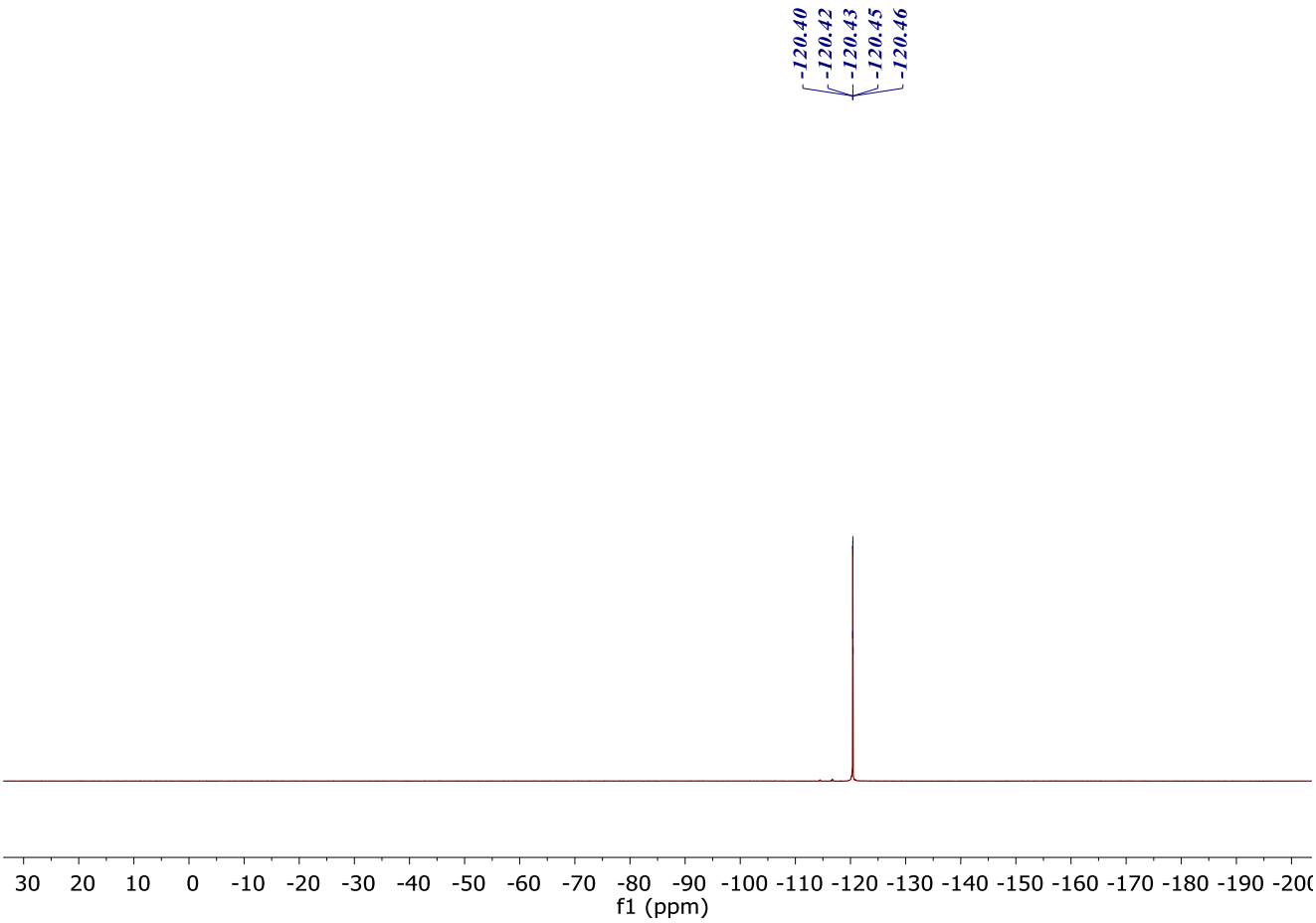


Figure 5.14 ^{1}H and ^{13}C NMR spectrum of compound **3i.**

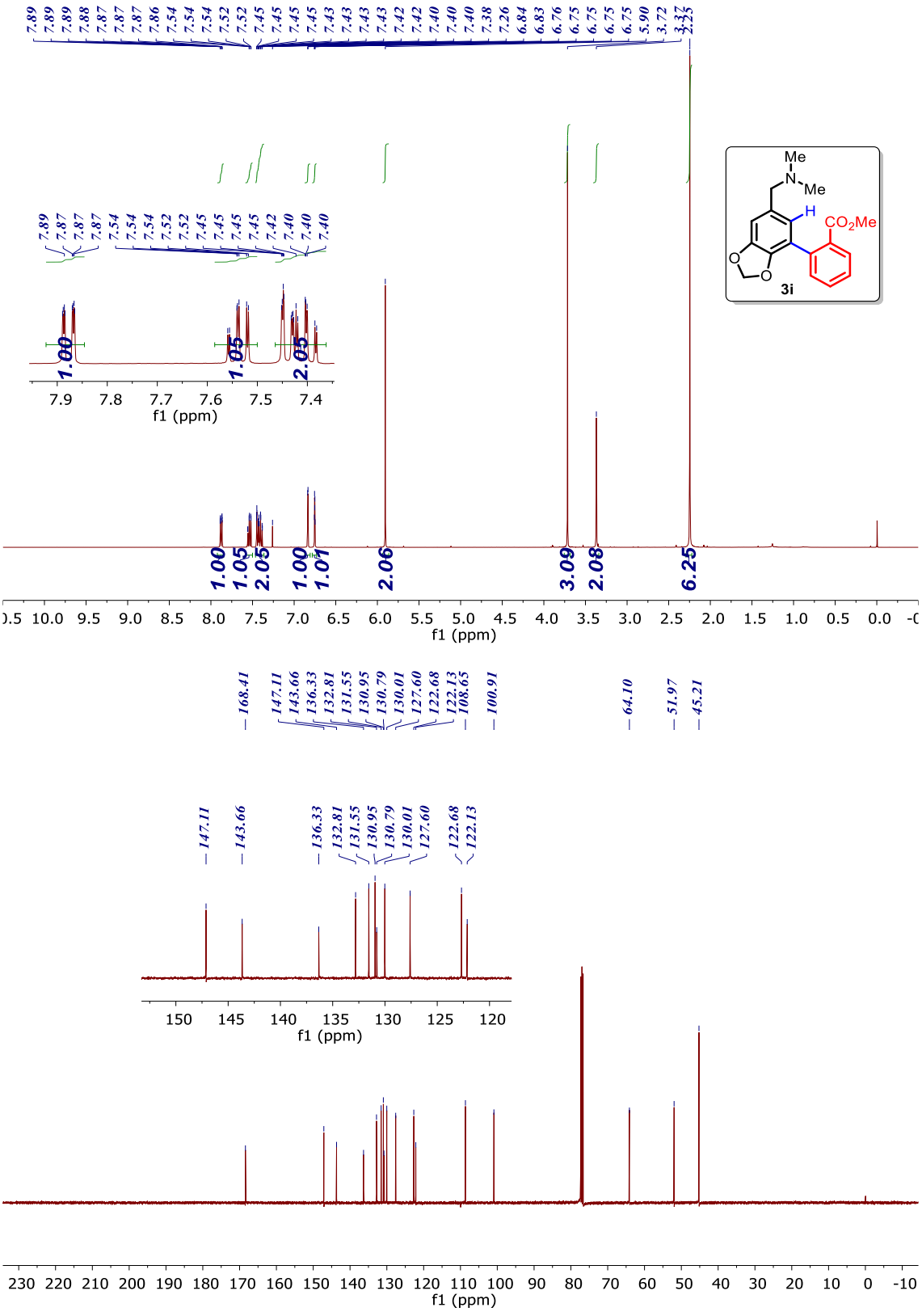


Figure 5.15 1D-NOE NMR spectrum of compound **3i.**

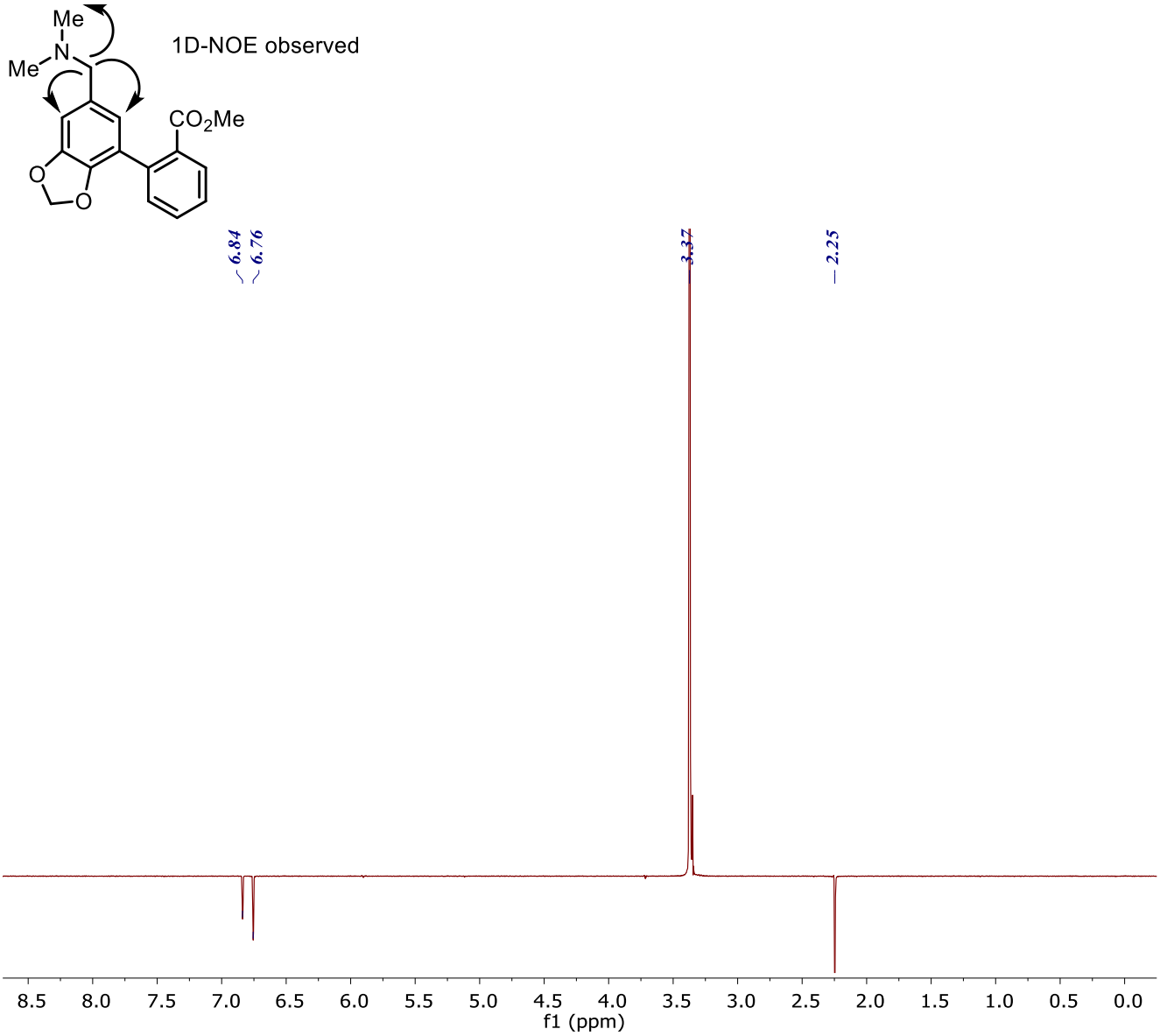


Figure 5.16 ^{1}H and ^{13}C NMR spectrum of compound **3j.**

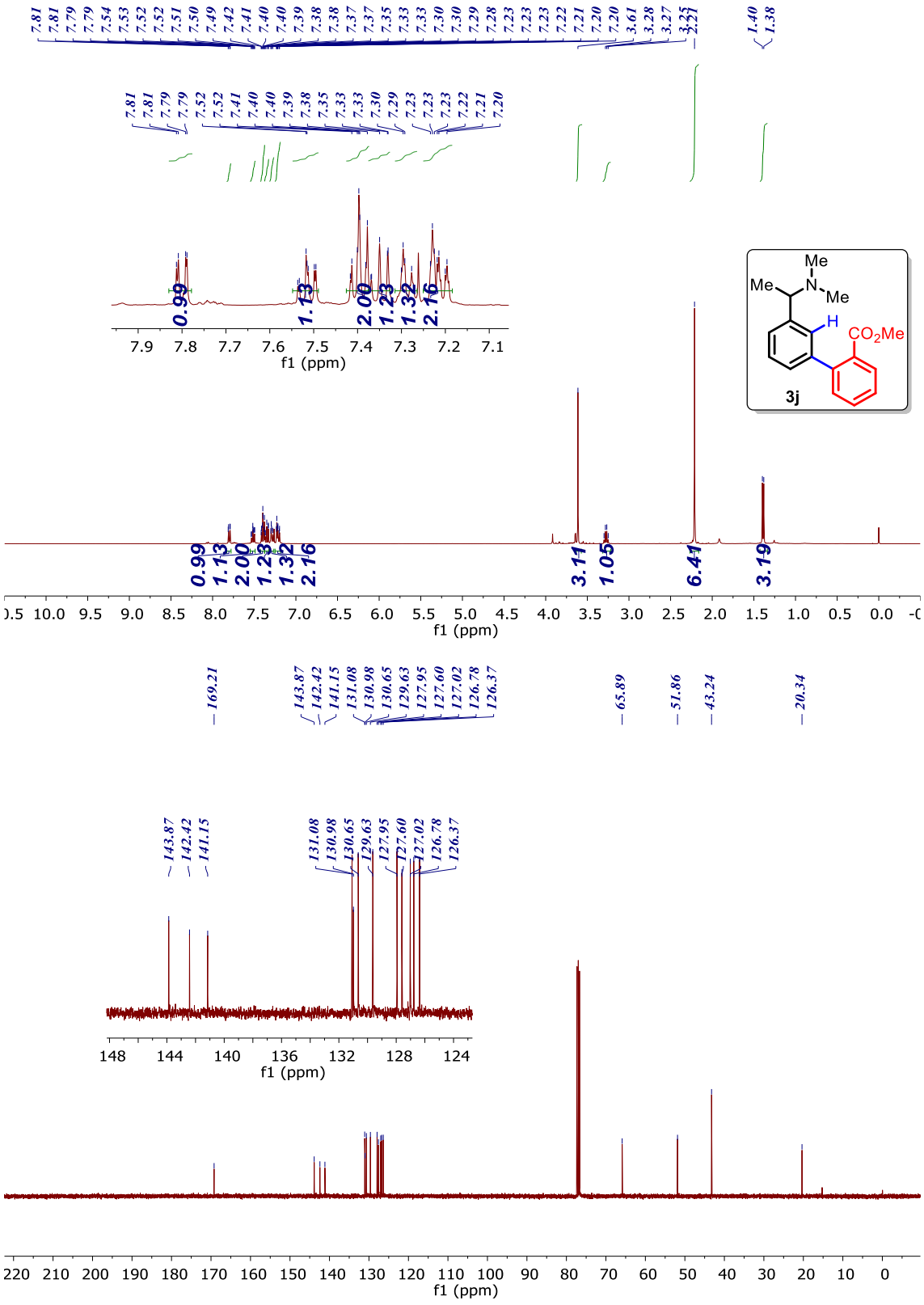


Figure 5.17 ^{1}H and ^{13}C NMR spectrum of compound **3j'.**

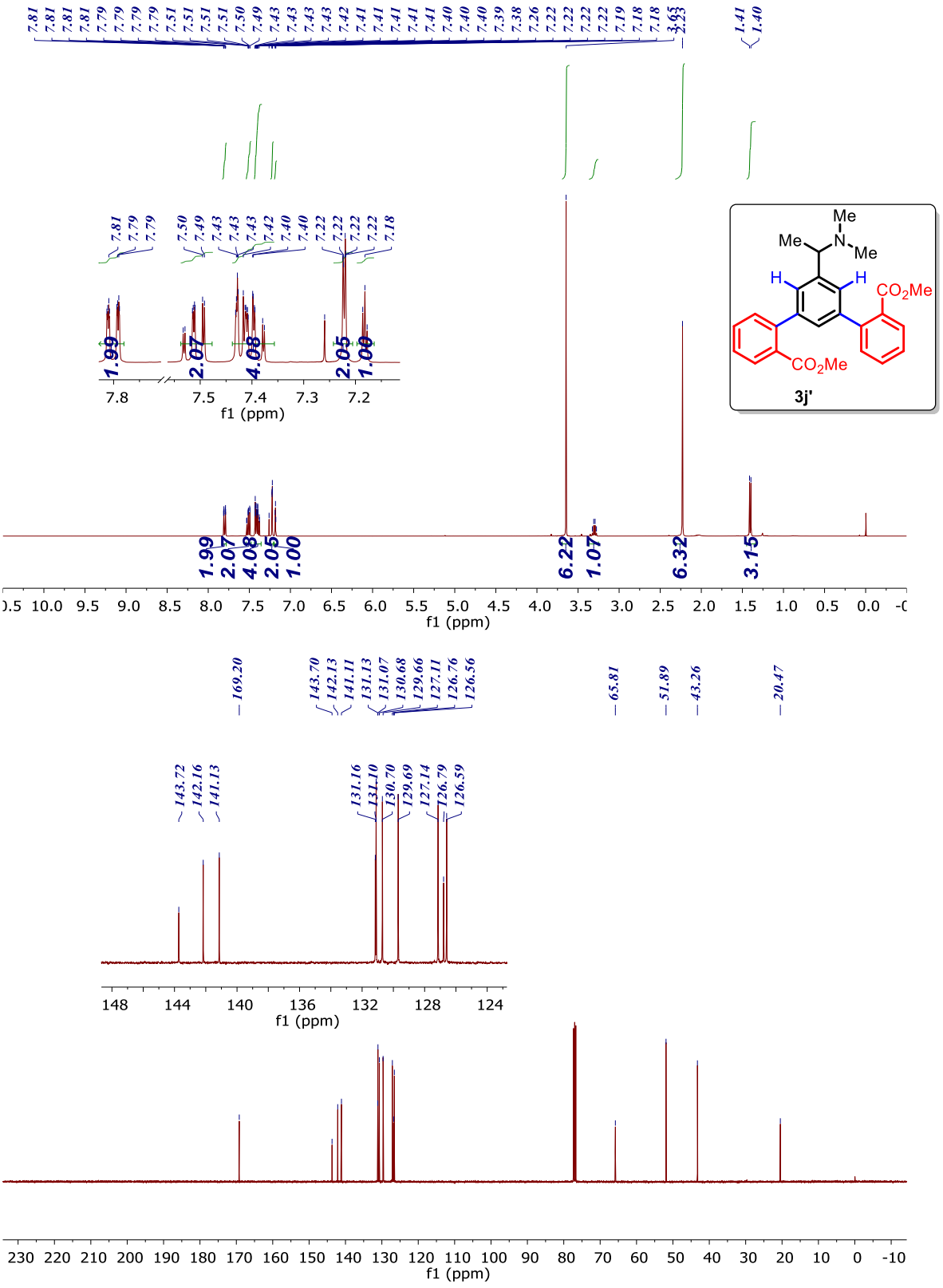
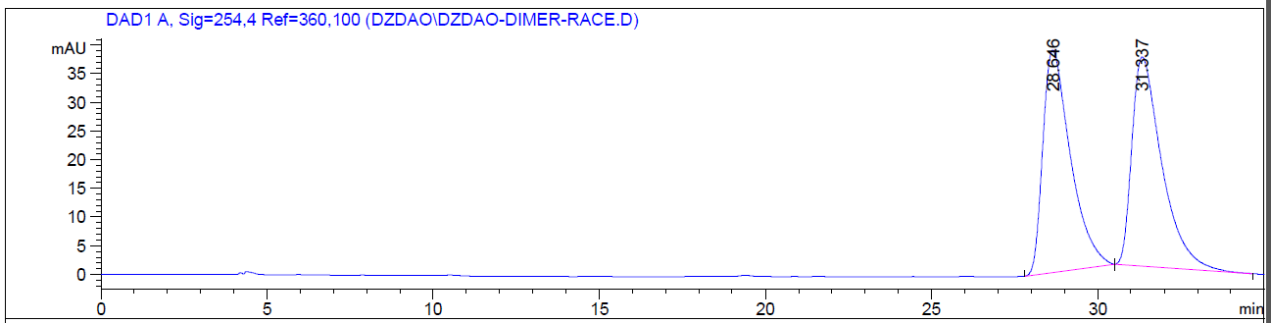


Figure 5.18 Isolation conditions of racemic sample **3j'** on Chiral HPLC

```
Data File C:\CHEM32\2\DATA\DZDAO\DZDAO-DIMER-RACE.D
Sample Name: dzdao-dimer-race

    ======================================================================
    Acq. Operator   : SYSTEM
    Acq. Instrument : 1260                          Location : Vial 1
    Injection Date  : 4/17/2015 9:57:54 PM
                                                   Inj Volume : 1.000 µl
    Acq. Method     : C:\CHEM32\2\METHODS\LIN.M
    Last changed    : 4/17/2015 9:27:49 PM by SYSTEM
                      (modified after loading)
    Analysis Method : C:\CHEM32\2\METHODS\DEF_LC.M
    Last changed    : 4/9/2015 11:01:36 PM by SYSTEM
    Sample Info     : IF 1.0 mL/min Hex:IPA:Et2NH=98.5:1.5:0.01
```




```
Data File C:\CHEM32\2\DATA\DZDAO\DZDAO-DIMER-RACE.D
Sample Name: dzdao-dimer-race


    Signal 1: DAD1 A, Sig=254,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  28.646 BB    0.8614 2246.63452   38.80727  49.5323
       2  31.337 BBA   0.9459 2289.05762   36.49050  50.4677

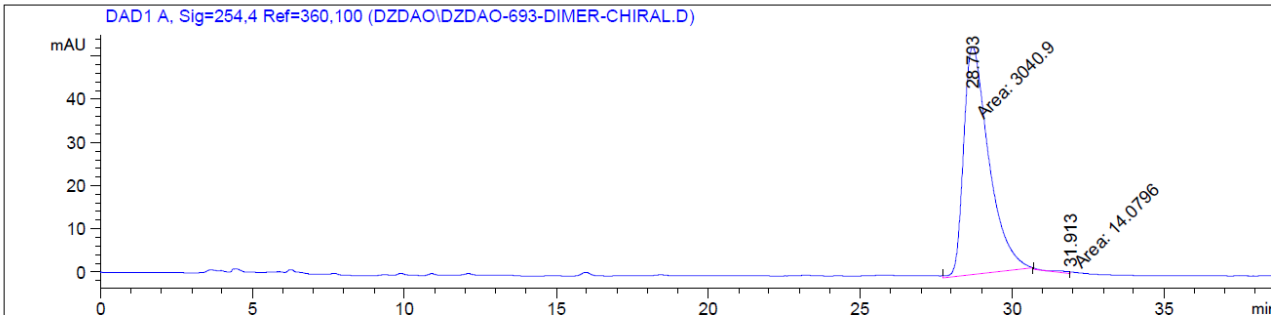
    Totals :                  4535.69214   75.29777
```

Figure 5.19 Isolation conditions of enantiopure sample **3j'** on Chiral HPLC

```
Data File C:\CHEM32\2\DATA\DZDAO\DZDAO-693-DIMER-CHIRAL.D
Sample Name: dzdao-693-dimer-chiral

    ========================================================================
    Acq. Operator   : SYSTEM
    Acq. Instrument : 1260                          Location : Vial 1
    Injection Date  : 4/17/2015 10:35:56 PM
                                                    Inj Volume : 1.000 µl
    Acq. Method     : C:\CHEM32\2\METHODS\LIN.M
    Last changed    : 4/17/2015 9:27:49 PM by SYSTEM
                      (modified after loading)
    Analysis Method : C:\CHEM32\2\METHODS\DEF_LC.M
    Last changed    : 4/9/2015 11:01:36 PM by SYSTEM
    Sample Info     : IF 1.0 mL/min Hex:IPA:Et2NH=98.5:1.5:0.01


    Additional Info : Peak(s) manually integrated
```

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Data File C:\CHEM32\2\DATA\DZDAO\DZDAO-693-DIMER-CHIRAL.D
Sample Name: dzdao-693-dimer-chiral


    Signal 1: DAD1 A, Sig=254,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  28.703 MM    0.9604 3040.89551   52.76996  99.5391
       2  31.913 MM    0.6126   14.07957 3.83043e-1   0.4609

    Totals :                  3054.97507   53.15300
```

Figure 5.20 ^{1}H and ^{13}C NMR spectrum of compound **3k.**

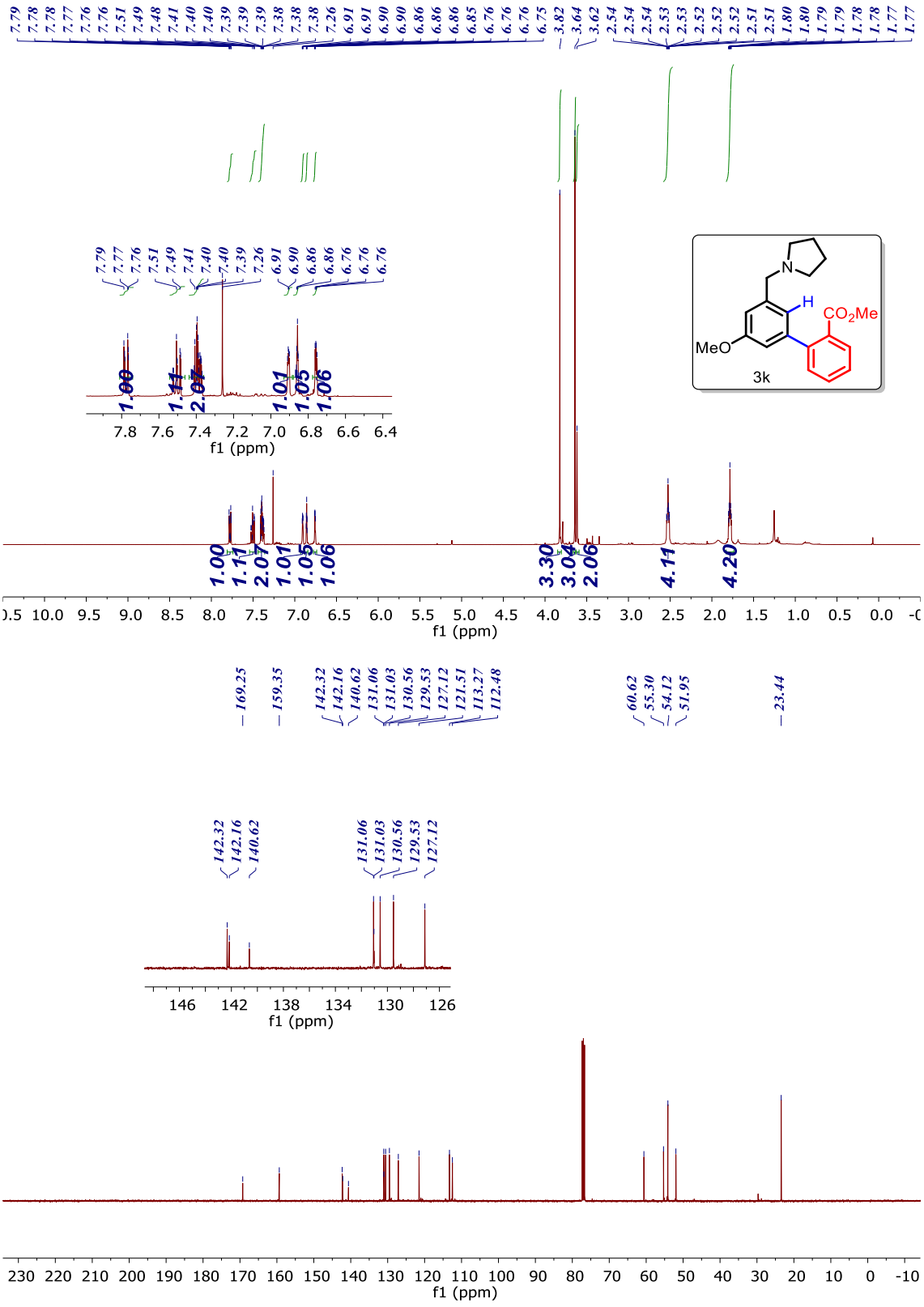


Figure 5.21 ^{1}H and ^{13}C NMR spectrum of compound **3l.**

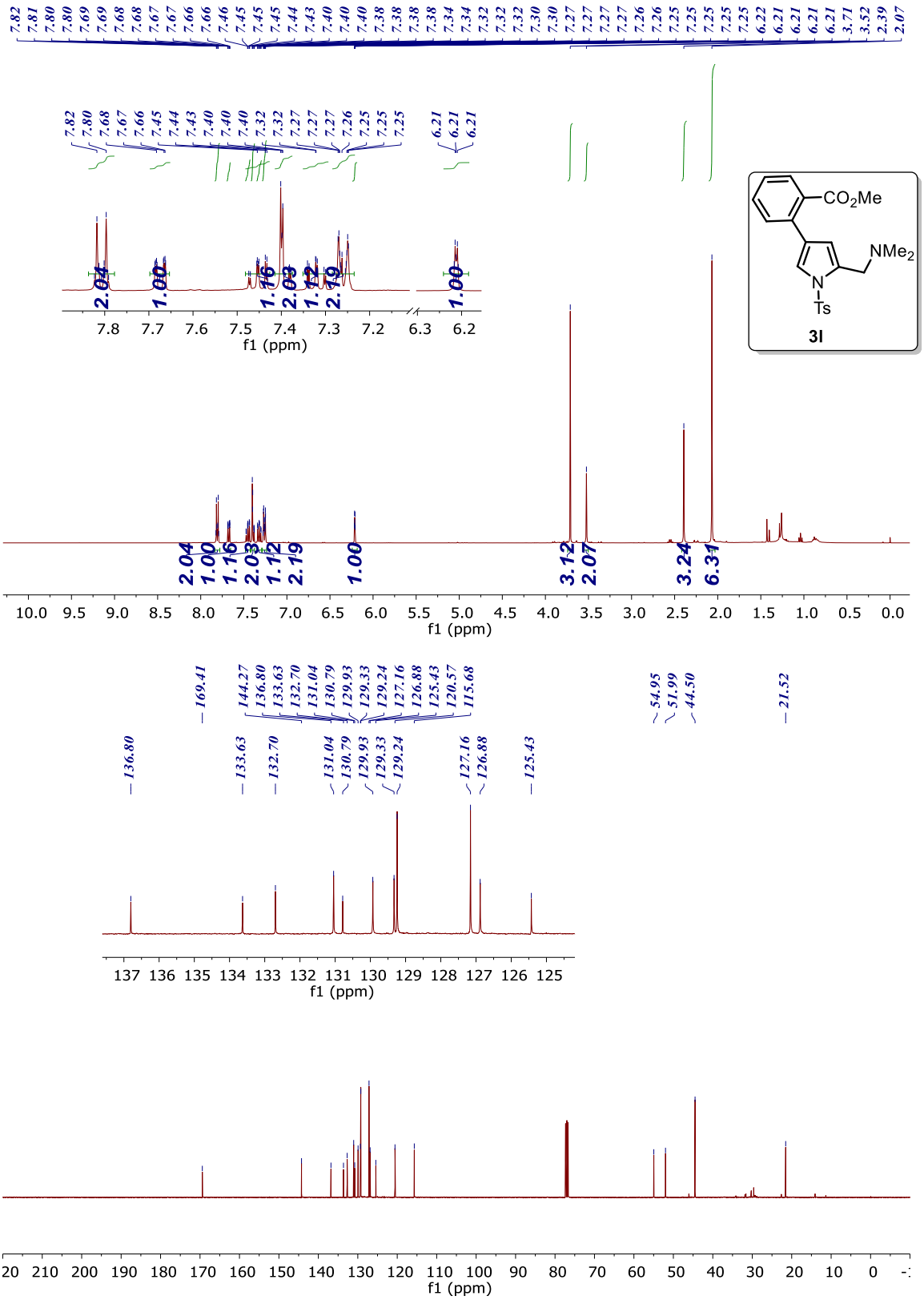


Figure 5.22 ^{1}H and ^{13}C NMR spectrum of compound **3m.**

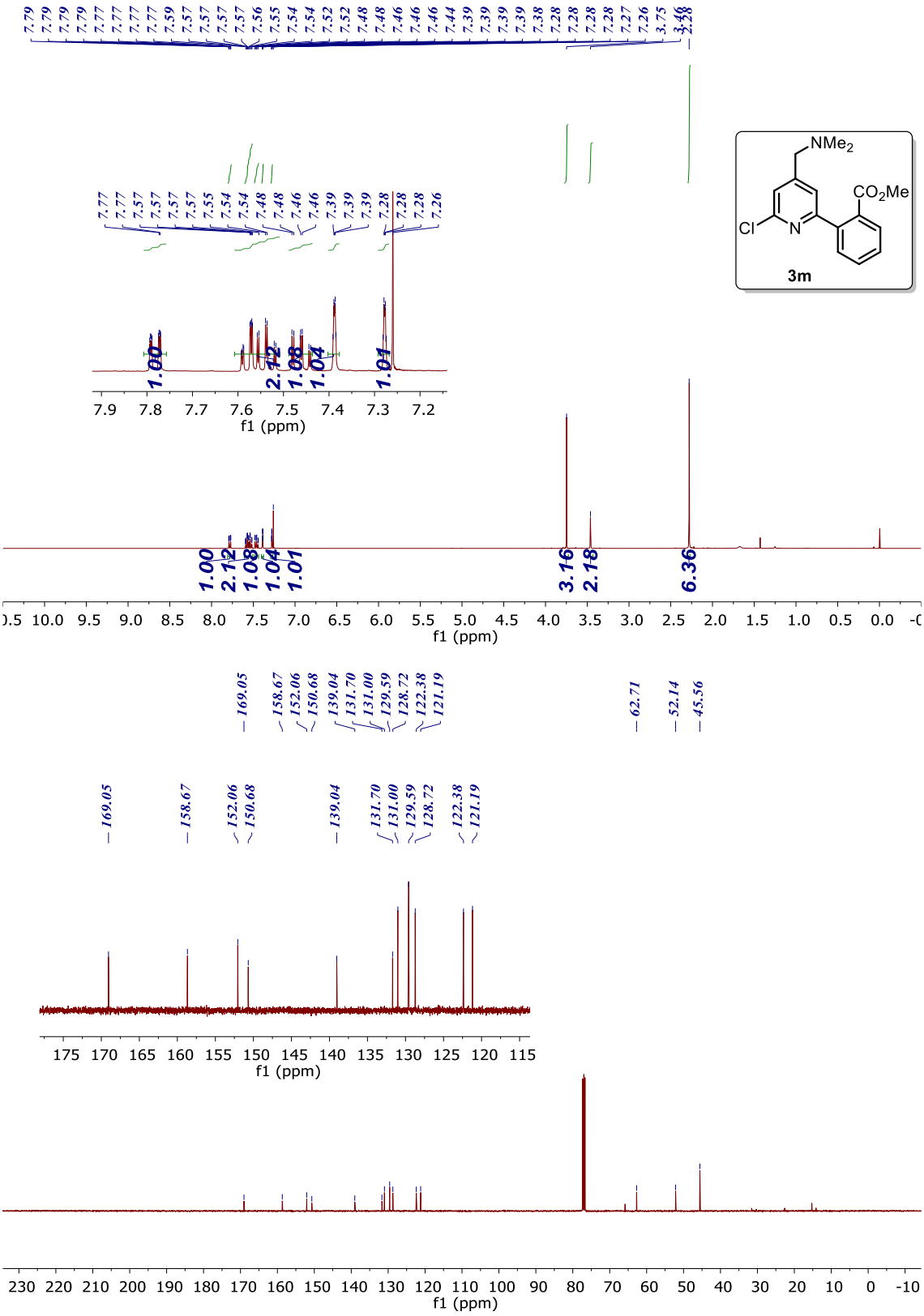


Figure 5.23 1D-NOE NMR spectrum of compound **3l.**

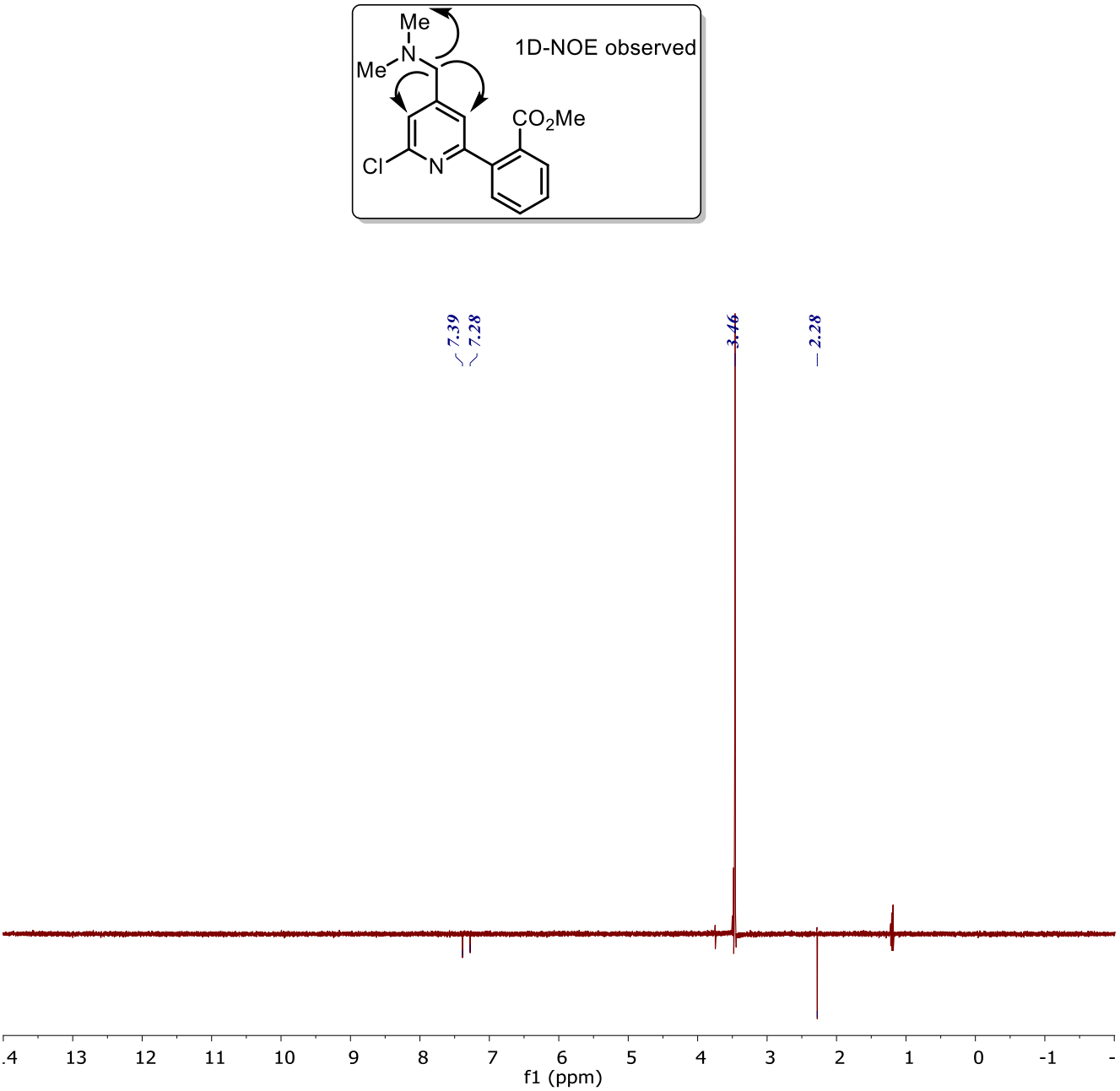


Figure 5.24 ^{1}H and ^{13}C NMR spectrum of compound **3n.**

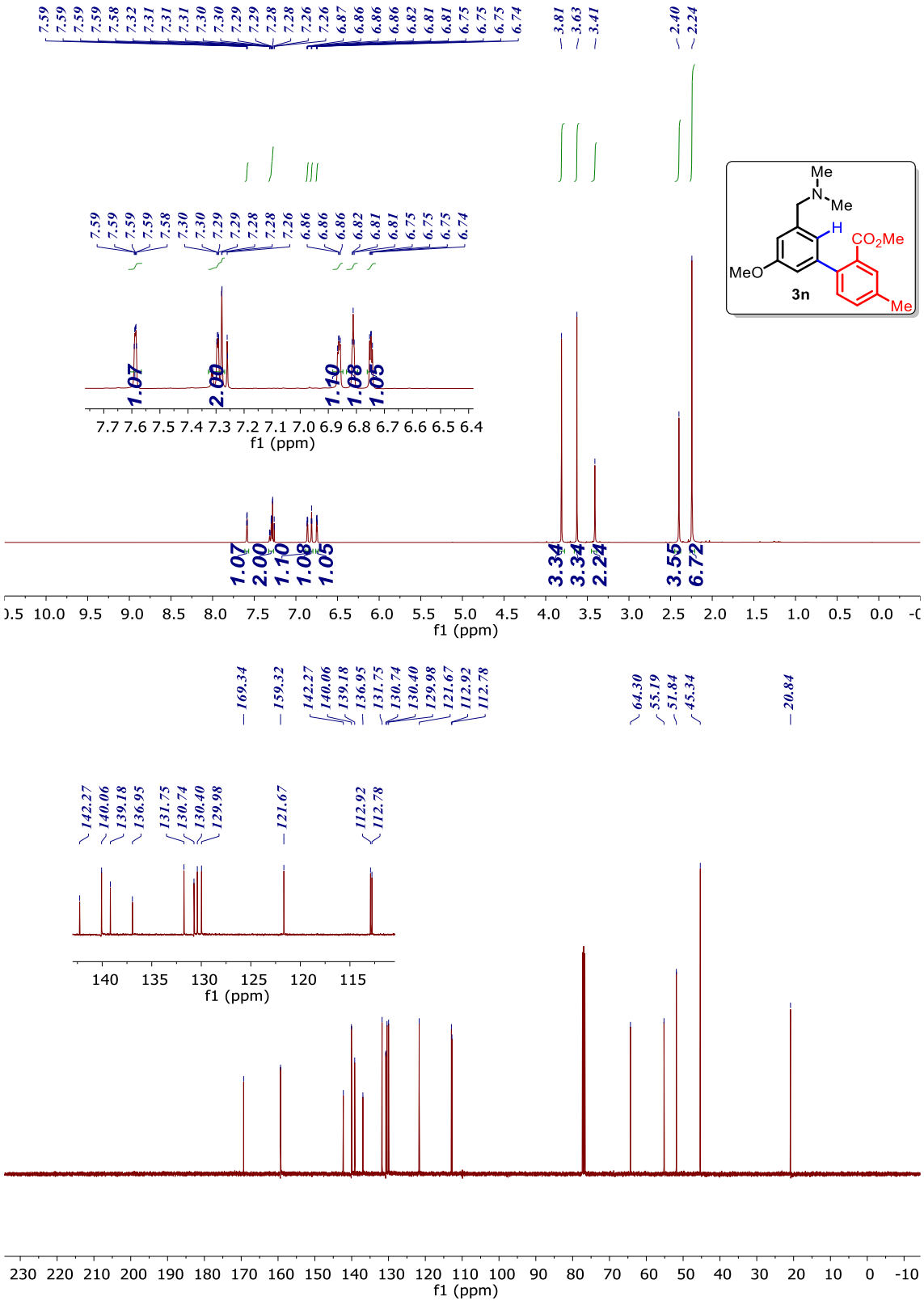


Figure 5.25 ^{1}H and ^{13}C NMR spectrum of compound **3o.**

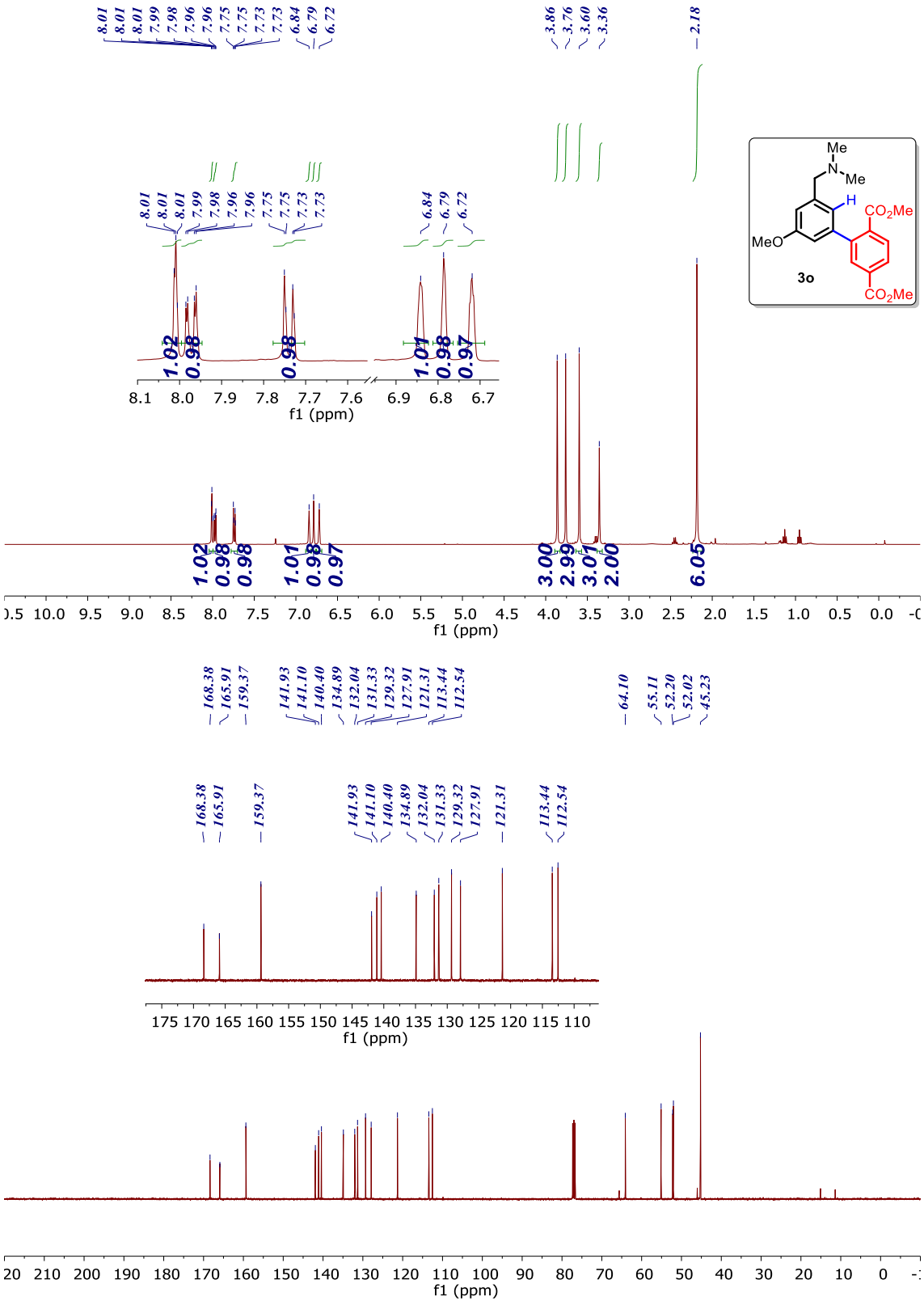


Figure 5.26 ^{1}H and ^{13}C NMR spectrum of compound **3p.**

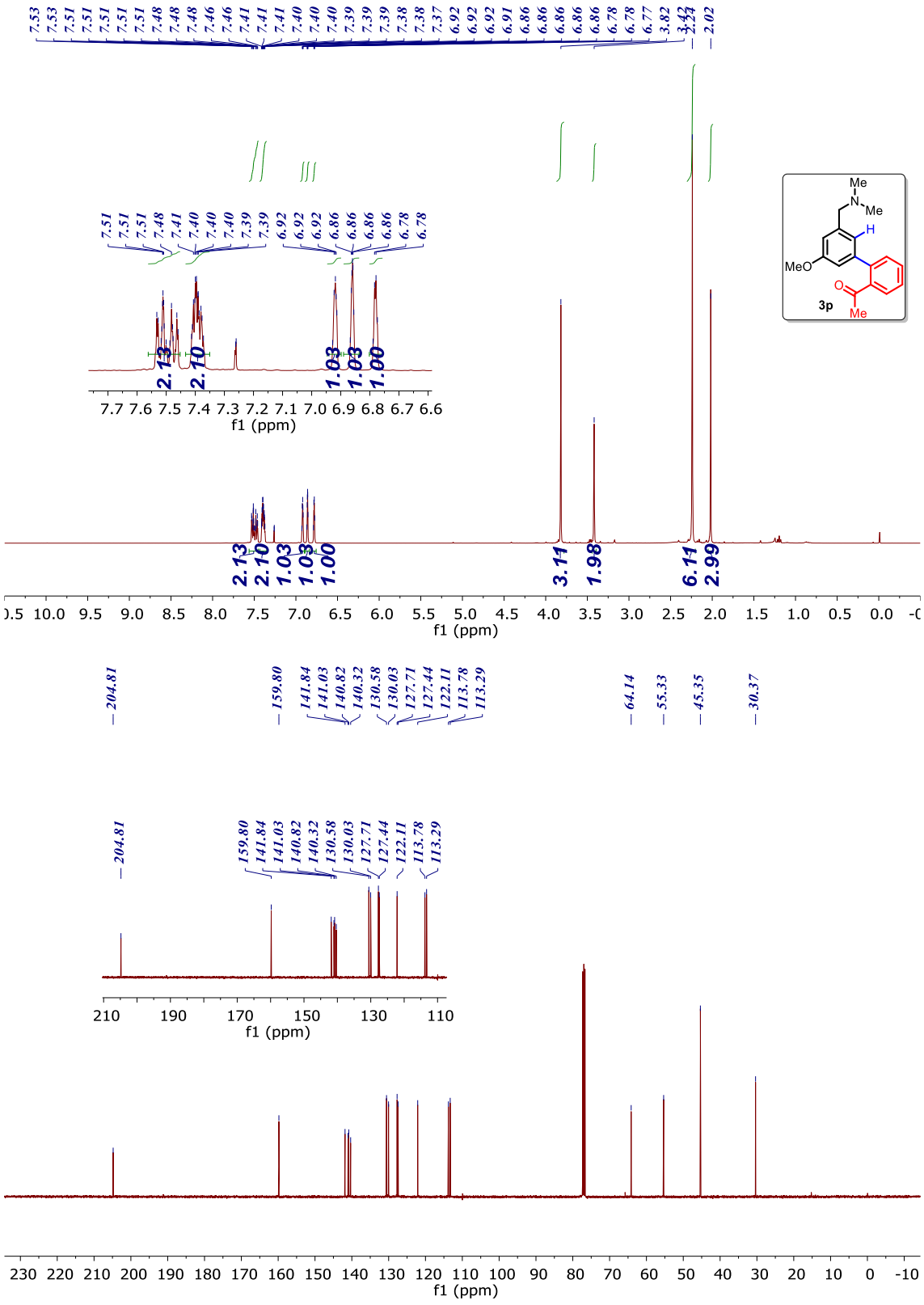


Figure 5.27 ^{1}H and ^{13}C NMR spectrum of compound **3q.**

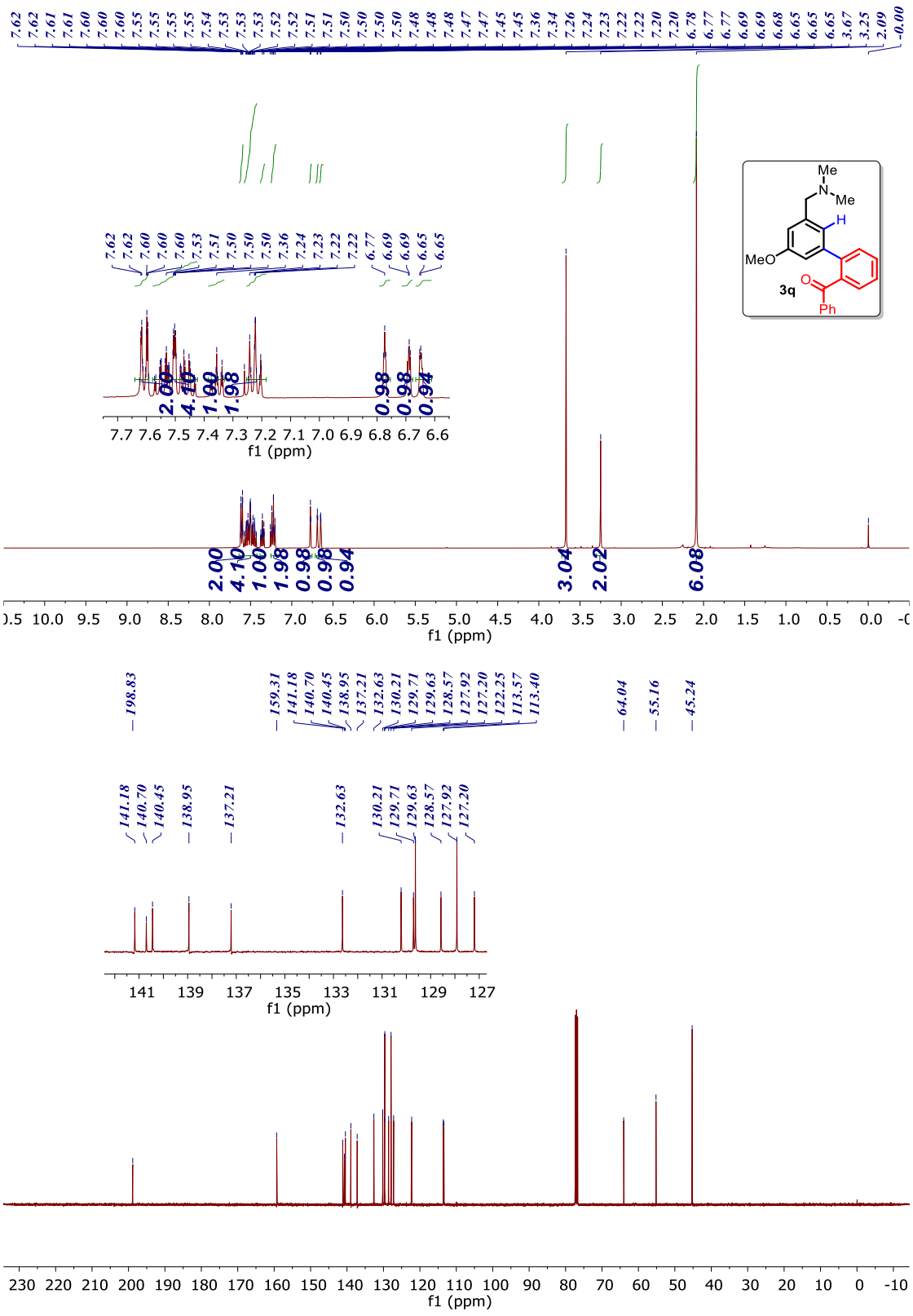


Figure 5.28 ^{1}H and ^{13}C NMR spectrum of compound **3r.**

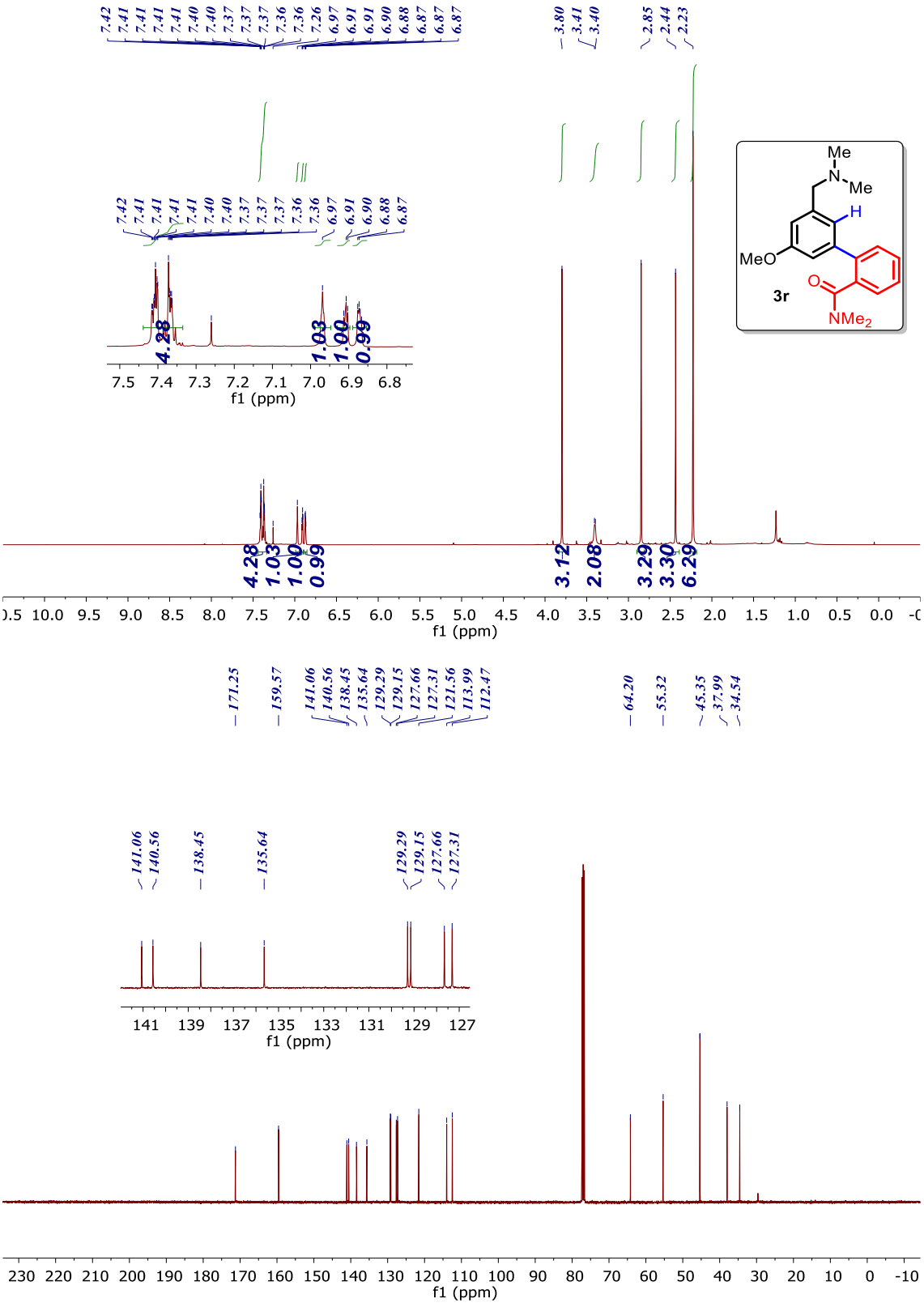


Figure 5.29 ^{1}H and ^{13}C NMR spectrum of compound **3s.**

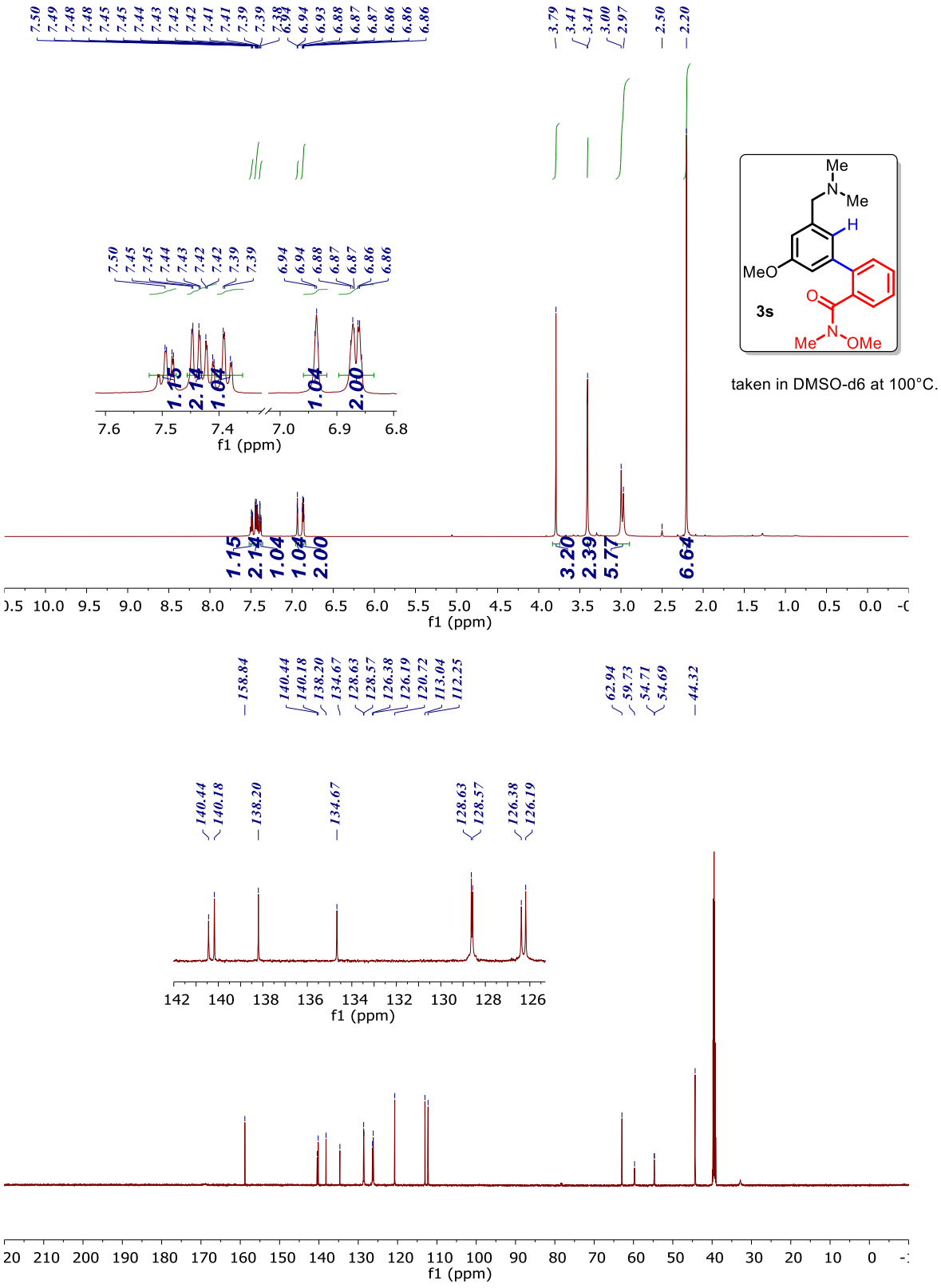


Figure 5.30 ^{1}H and ^{13}C NMR spectrum of compound **3t.**

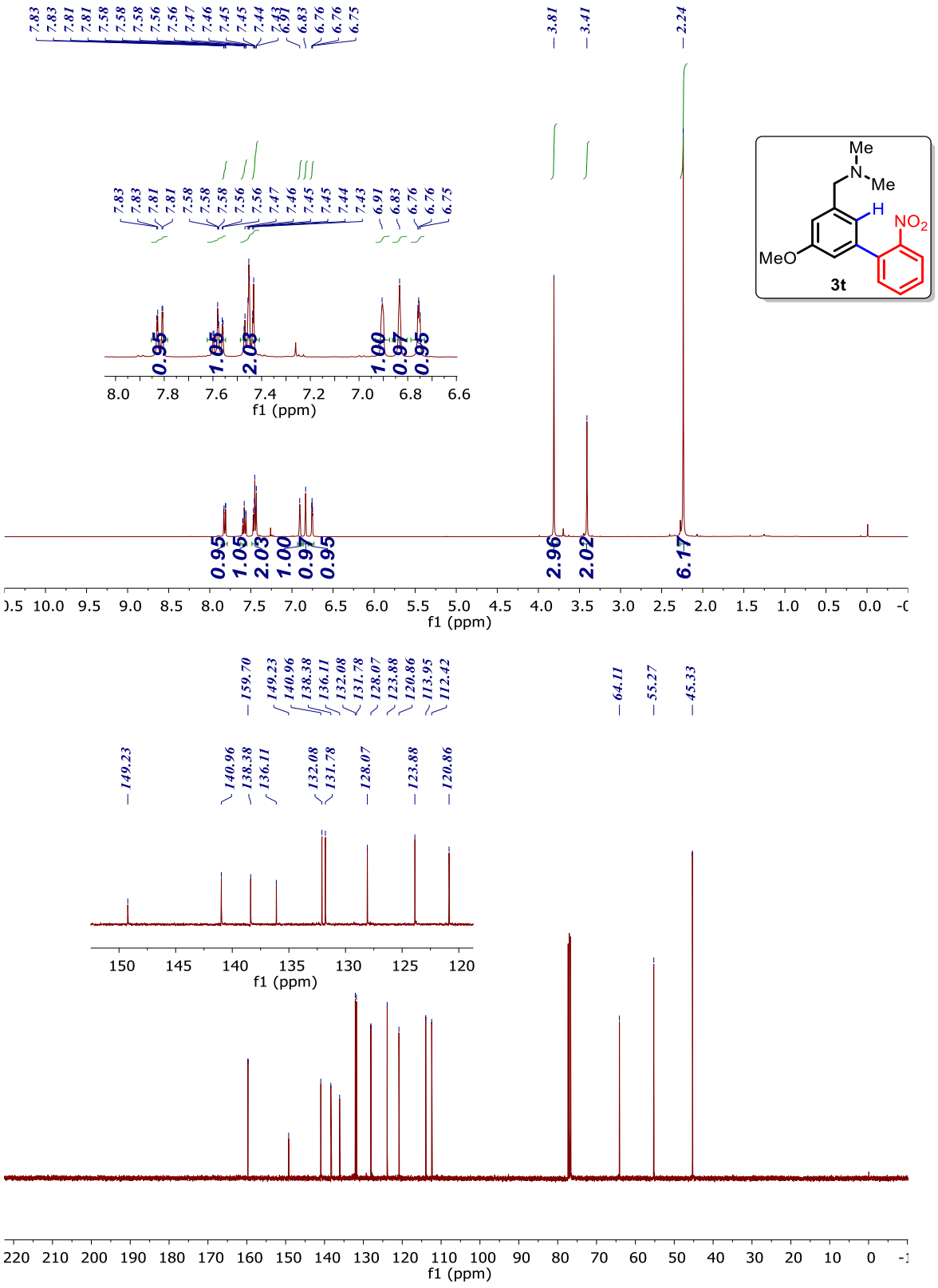


Figure 5.31 ^{1}H and ^{13}C NMR spectrum of compound **3u.**

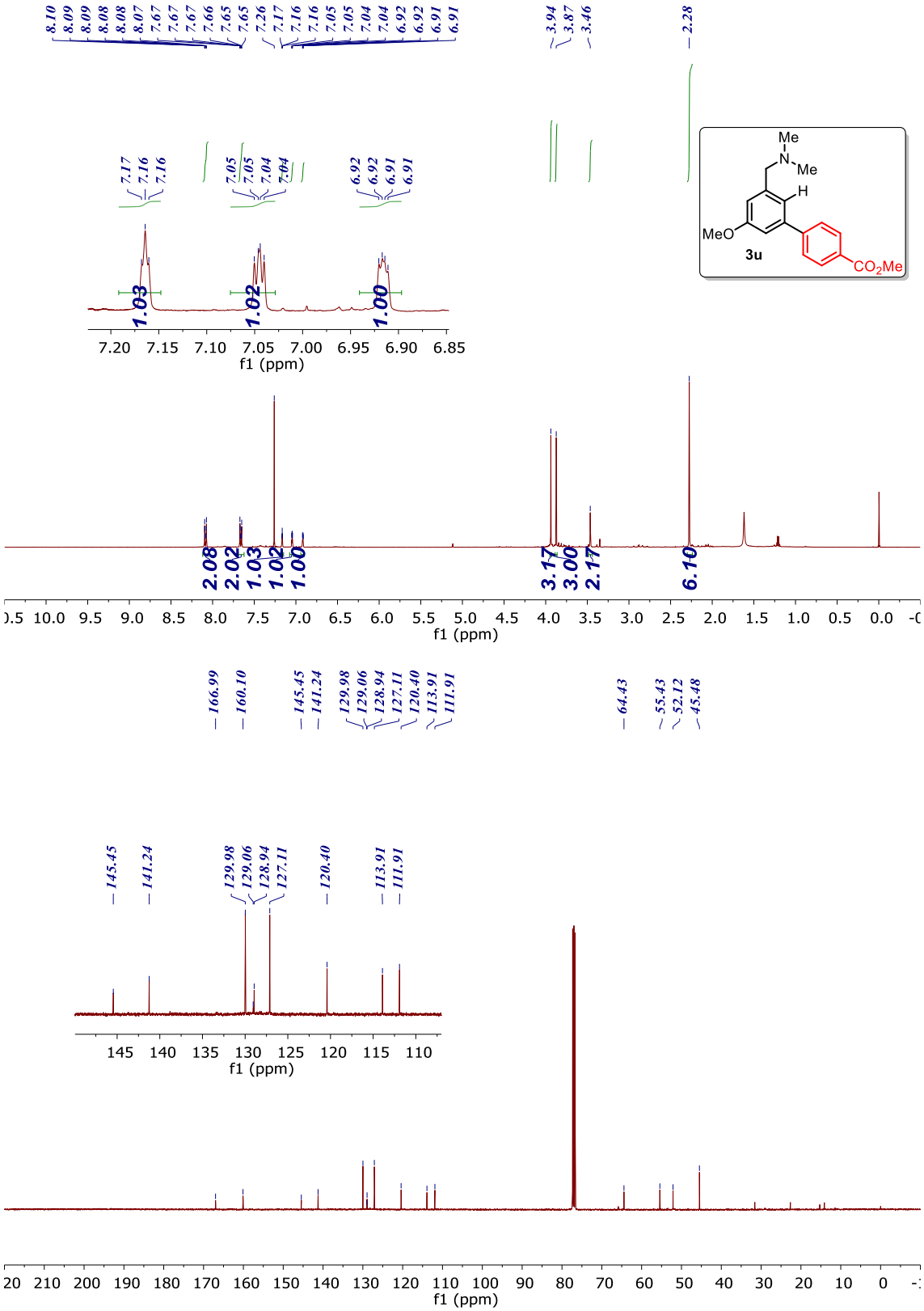


Figure 5.32 ^{1}H and ^{13}C NMR spectrum of compound **4.**

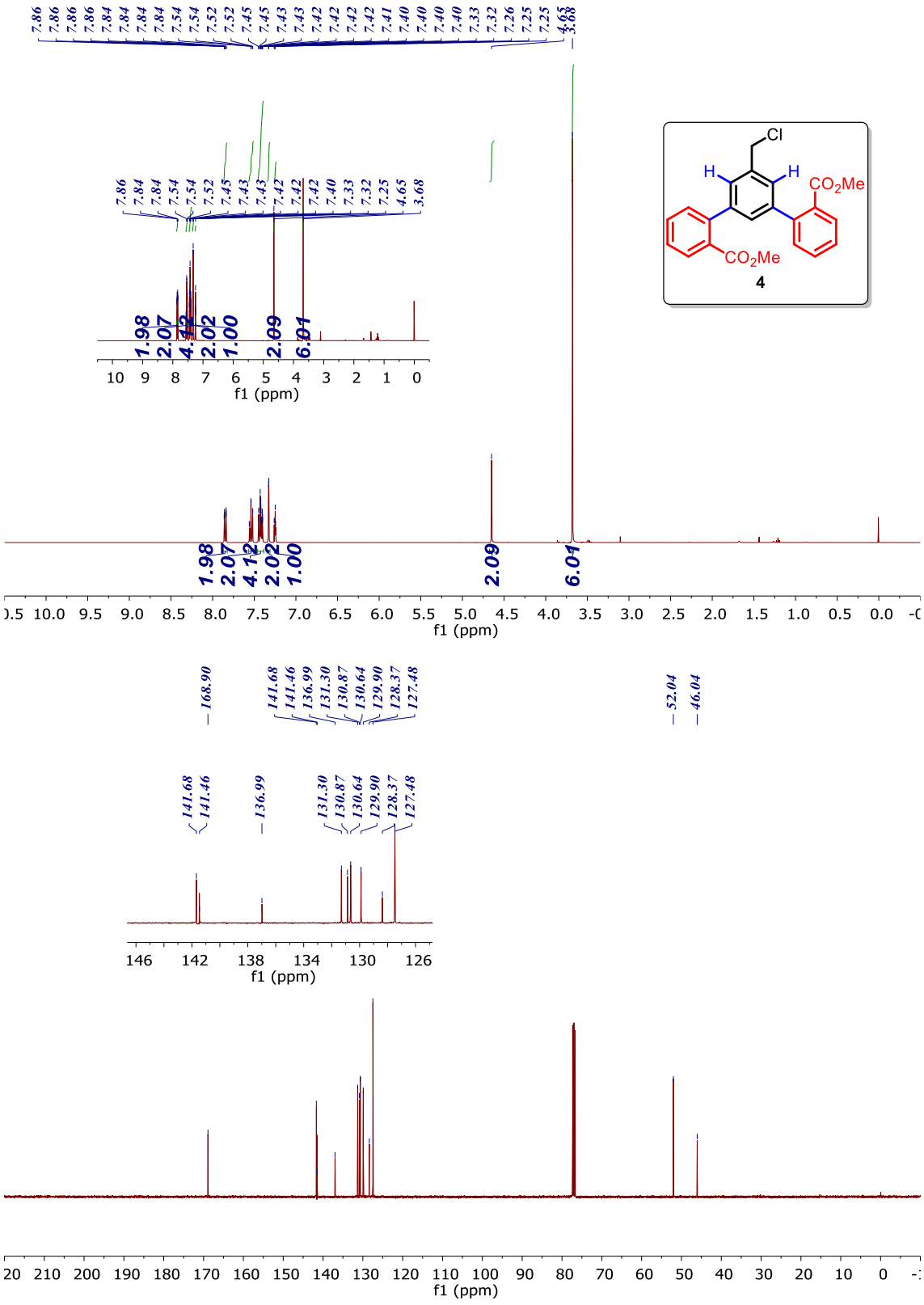


Figure 5.33 ^{1}H and ^{13}C NMR spectrum of compound **5.**

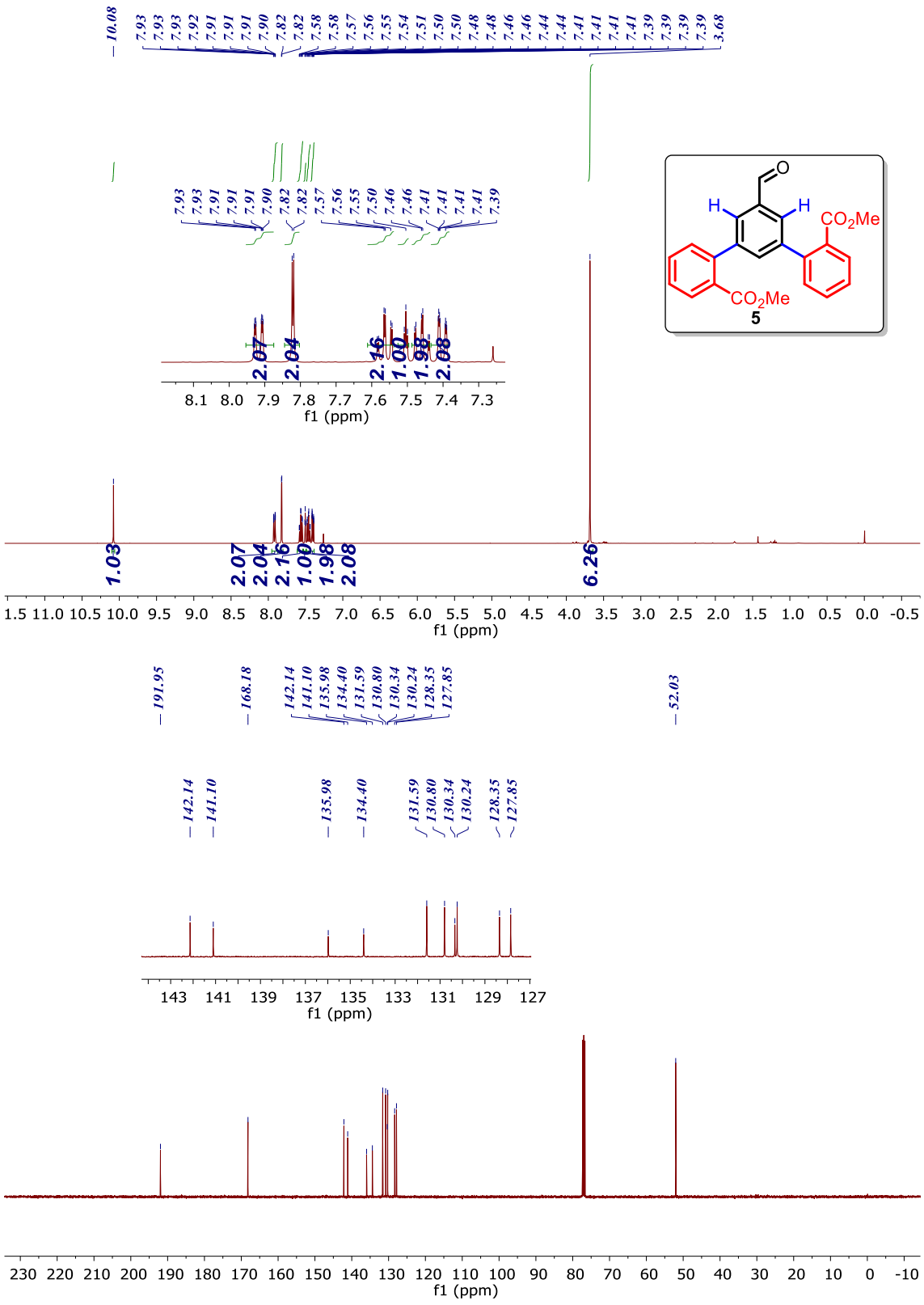


Figure 5.34 ^{1}H and ^{13}C NMR spectrum of compound **S2.**

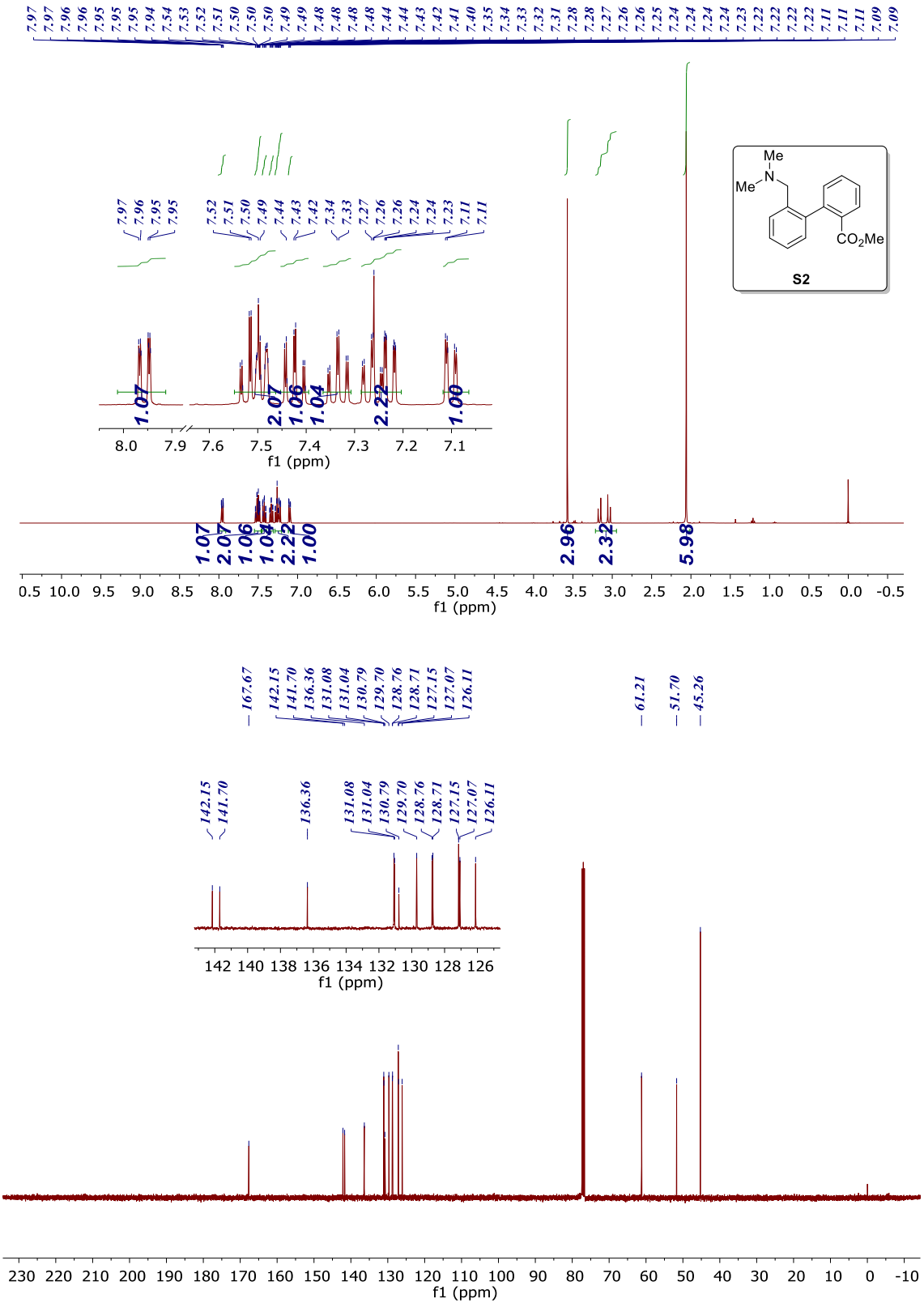
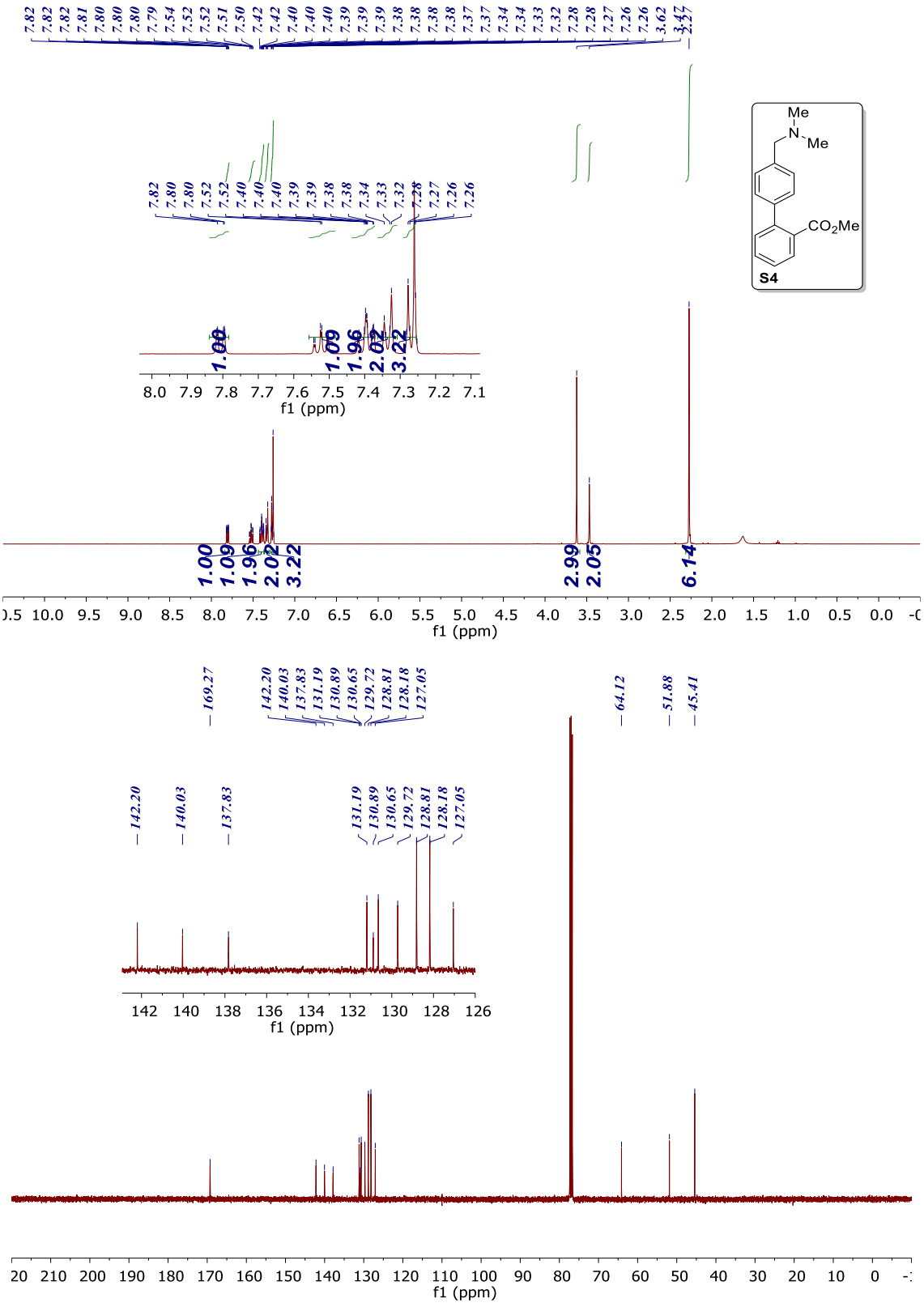


Figure 5.35 ^{1}H and ^{13}C NMR spectrum of compound **S4.**



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