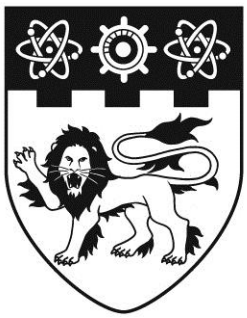

NANYANG TECHNOLOGICAL UNIVERSITY

I. MICHAEL ADDITIONS TO 1-BROMO-1-NITROALKENES

II. *N*-HETEROCYCLIC CARBENE-CATALYZED OXIDATIVE ESTERIFICATION OF ALDEHYDES

GE XIN

SCHOOL OF PHYSICAL & MATHEMATICAL SCIENCES

2015

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GE XIN

School of Physical and Mathematical Sciences

A thesis submitted to the Nanyang Technological University

in partial fulfilment of the requirement for the degree of

Doctor of Philosophy

2015

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ABSTRACT

Chapter 1 Michael Additions to 1-Bromo-1-nitroalkenes

The *β*-bromo-*β*-nitrostyrenes, due to the existence of bromo and nitro functionalities, were often shown to be versatile Michael acceptors. This thesis work focused on the development of new methodologies of Michael additions to *β*-bromo-*β*-nitrostyrenes. In the first part, the reaction of 1,3-diphenylthiourea and *β*-bromo-*β*-nitrostyrenes afforded 2-iminothiaozle in moderate to good yields. The domino reaction provided a new, mild and environmental benign process for the fast and efficient synthesis of highly-functionalized 2-iminothiazoles. In the second part, the Ag(I) catalyzed addition of *α*-ethereal carbon radicals to *β*-bromo-*β*-nitrostyrenes under mild conditions constituted the C−C bond formation at the otherwise unreactive *α*-C−H position of cyclic ethers. The reaction was conducted in the air to generate the dioxygen incorporated product. It provided a useful synthetic tool for the preparation of various ether derivatives.

Chapter 2 N-Heterocyclic Carbene-Catalyzed Oxidative Esterification of Aldehydes

N-Heterocyclic Carbenes (NHC)-catalyzed one pot esterification of aldehydes via internal redox esterification has become prominent. In this work, a mild NHC-catalyzed transformation of cinnamyl cinnamate from cinnamaldehyde by employing air oxygen as an oxidant has been developed. This is an alternative method for the synthesis of esters from reactive alkyl halides and *α*,*β*-unsaturated or aromatic aldelydes. Aldehydes with electron-withdrawing groups comparatively gave better yields than that with electron-donating groups. A significant feature of this protocol is that the reaction proceeds without cis-trans isomerization of the *α*,*β*-olefinic linkage in the cinnamyl cinnamate derivatives. When MnO_2 was use as oxidant instead of air oxygen, aromatic aldehydes generally provide ester in good yields.

INDEX OF ABBREVIATIONS

°C	degree centrigrade
δ	chemical shift
μg	microgram
μL	microliter
μM	micromolar
Ac	acetal
AIBN	azobisisobutyronitrile
aq	aqueous
Bn	benzyl
Bu	butyl
Bz	benzoyl
calcd.	calculated
CH_2Cl_2	dichloromethane
$CHCl_3$	chloroform
d	doublet
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DFT	density function theory
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N*, *N*-dimethylformamide
dr	diastereomeric ratio
DTBP	di-(*tert*-butyl)peroxide
ee	Enantiomeric excess
equiv	equivalent
ESI	electrospray ionization
FTIR	Fourier transform infrared spectroscopy
g	gram
h	hour
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometer
Hz	hertz
i-Pr	isopropyl
J	coupling constant
m	multiplet
M	Molar (mol/L)
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mmol	millimoles
mol	moles
NA	not active
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
OTf	trifluoromethanesulfonate
p	para
ph	phenyl
PMB	p-methoxybenzyl
ppm	part per million
py	pyridine
q	quartet
RT	room temperature
s	singlet
SAR	Structure activity relationship
sx	sextet
t	triplet
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	toluenesulfonyl
V	volumn

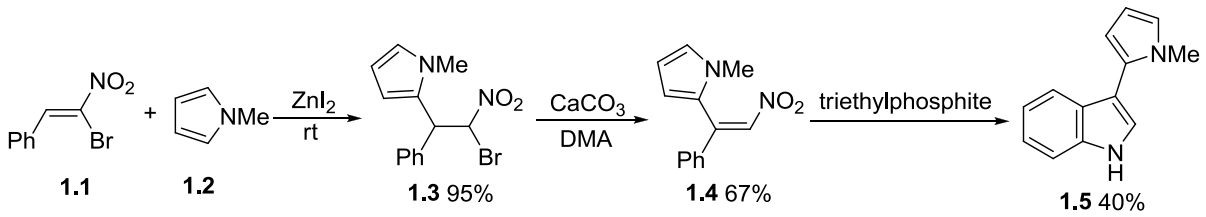
Chapter 1

Michael Additions to 1-Bromo-1-nitroalkenes

1.1 Introduction

Conjugated nitroalkenes are readily accessible synthetic building blocks of widespread use in organic chemistry.[1] While one of its derivatives, the 1-bromo-1-nitroalkenes, with 1-positions of the alkenes disubstituted, not only extends the synthetic potential of these compounds but also exhibit peculiar properties compared to that of bromoalkenes and nitroalkenes.[2-5] The information on reactions of 1-bromo-1-nitroalkenes showed their versatile reactivity as Michael acceptors,[2] dipolarophiles,[3] 1,3-dipoles,[4] dienophiles and heterodienes[4,5]. Here, we give a short review on the literatures of 1-bromo-1-nitroalkenes.

Initial 1-bromo-1-nitroalkenes were synthesized from available *β*-nitrostyrenes in one step.[3g] When used in Michael additions, *β*-bromo-*β*-nitrostyrenes were often shown to be effective dielectrophiles due to the existence of bromo and nitro functionalities. One of the early reports using *β*-bromo-*β*-nitrostyrenes as Michael acceptors is in a convenient synthesis of 3-heteroarylindoles (Scheme 1.1).[2f] The N-methylpyrrole reacted with *β*-bromo-*β*-nitrostyrene at room temperature in the presence of zinc iodide to give the adduct in high yield which underwent dehydrobromination and cyclisation to give the desired indole **1.5**. In another example, highly functionalized nitrocyclopropanes **1.6** were obtained by the conjugate addition of dimethyl malonate to *β*-bromo-*β*-nitrostyrenes in the presence of chiral bifunctional organocatalyst.[2e] (Scheme 1.2) In those attempts several Brønsted base were tested as additives. These experiments showed the route as unsatisfactory from an asymmetric catalysis standpoint: of the additives tested only NEt_3 provided **1.6** in racemic form. The incompatibility of less hindered yet both comparable and less basic amines to NEt_3 and isolation of racemic **1.6** from the reaction mediated by NEt_3 indicate that the relatively unhindered **1.8** is not involved in this catalytic reaction.

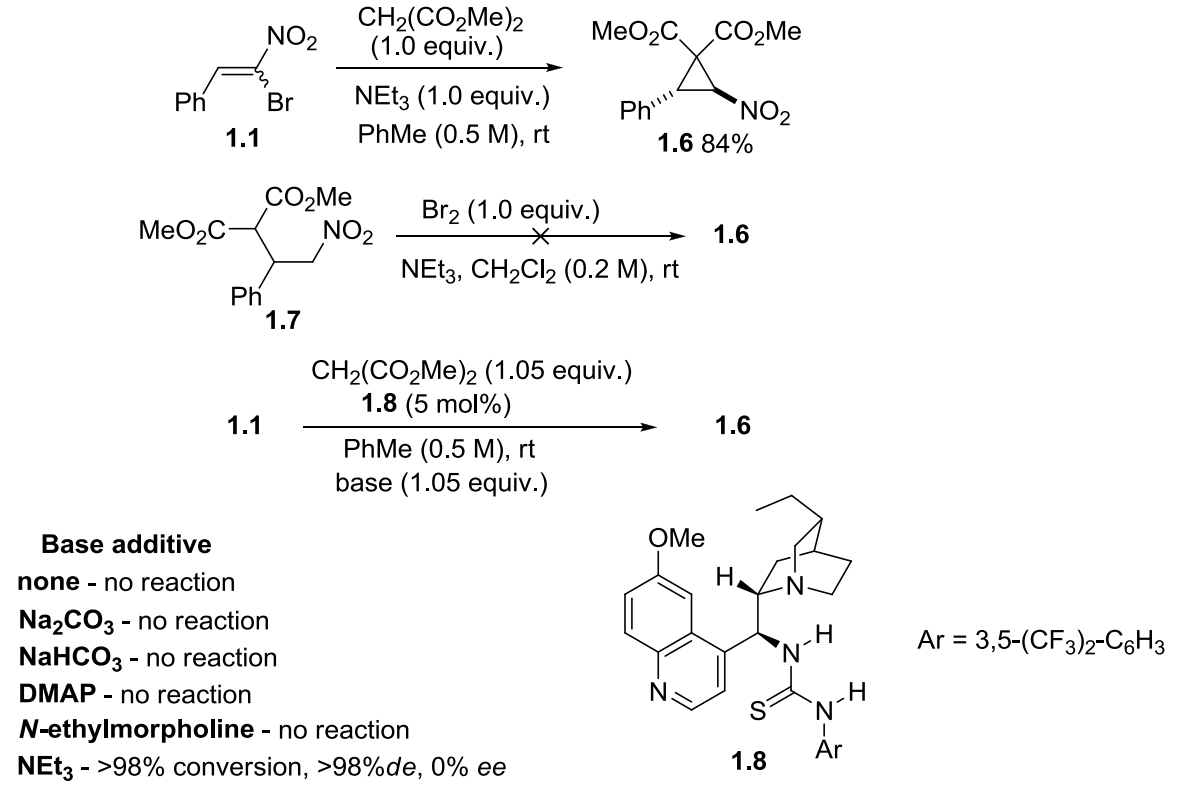


Scheme 1.1 A convenient route to 3-[2-(N-methylpyrrolyl)]indole

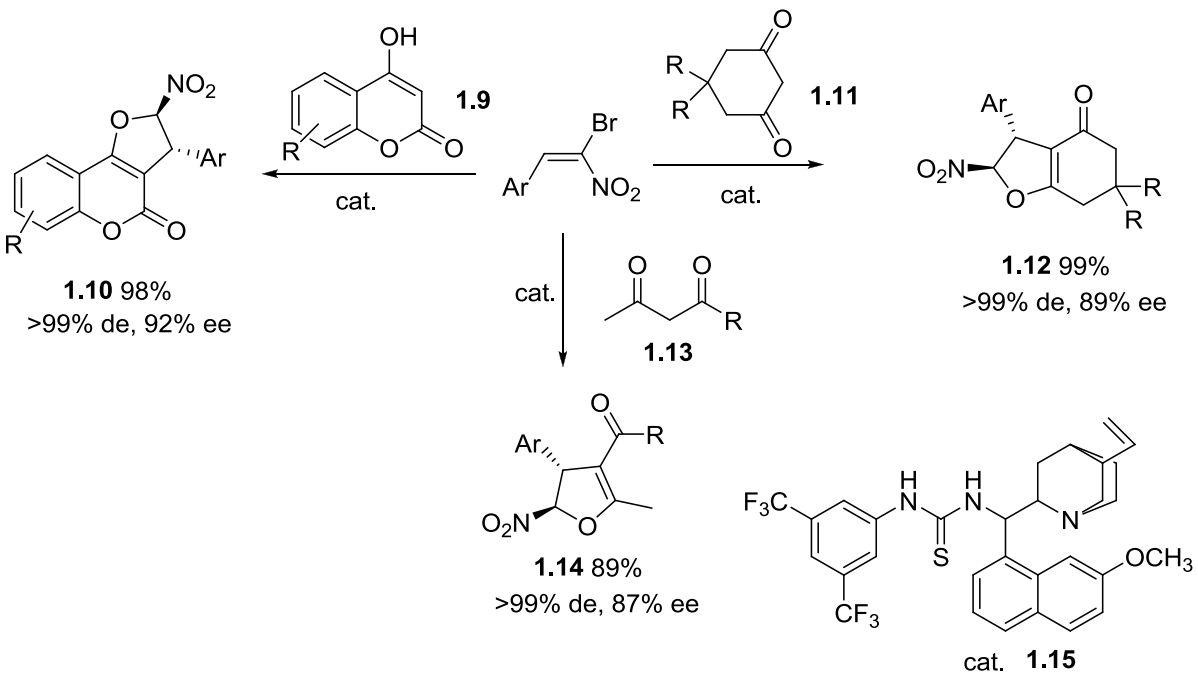
When using various 1,3-dicarbonyl compounds as dinucleophiles in the presence of bifunctional thiourea catalyst, chiral tricyclic 2,3-dihydrofurans, bicyclic 2,3-dihydrofurans, and tetrasubstituted 2,3-dihydrofurans with high regio-, chemo-, diastereo- and enantioselectivity were obtained as a result of domino Michael reactions.[2b,2c] (Scheme 1.3) In a similar strategy, pyrroles were obtained when enaminones were used as dinucleophiles. [2d] (Scheme 1.4) The reaction of curcumins **1.20** with nitroalkenes was also investigated.[2a] Highly functionalized cyclohexones with three contiguous chiral centers with complete diastereoselectivity were synthesized through an inter-intra molecular Michael addition involve curcumins and nitroalkenes. Under identical conditions, curcumin reacted with 1-bromo-1-nitroalkenes to provide dihydrofurans through an intermolecular Michael addition and intramolecular nucleophilic substitution (O-alkylation). (Scheme 1.5)

Just like their nitrostyrene counterpart, *β*-bromo-*β*-nitrostyrenes could serve as effective dipolarphiles. The facile synthesis of pyrazoles from hydrazones and nitroalkenes was also demonstrated.[3a] Based on a common 4-halo-4-nitropyrazolidine intermediate, the pyrazole product formed is dependent on the relative abilities of leaving group of the nitro and halo substituents. (Scheme 1.6)The condensation of diazomethane with *β*-bromo-*β*-nitrostyrenes gave 3-bromo-3-nitro-4-phenylpyrazoline as a result, which decomposed into 3-bromo- and 3-nitro-pyrazoles with acid and base.[3g] (Scheme 1.7) The decomposition of 3-bromo-3-nitro-4-phenylpyrazoline with hydrogen chloride was observed to give a 66% yield of 3-bromo-4-phenylpyrazole with a small amount of 3-nitro-4-phenylpyrazole (10.6%). When sodium

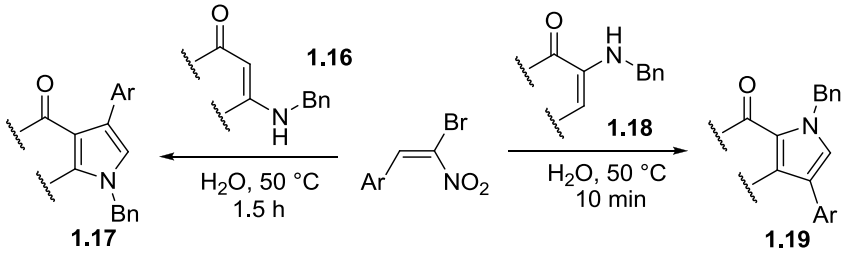
bicarbonate was used a 73.5% yield of the nitropyrazole was obtained together with a small amount of bromopyrazole (10.4%).



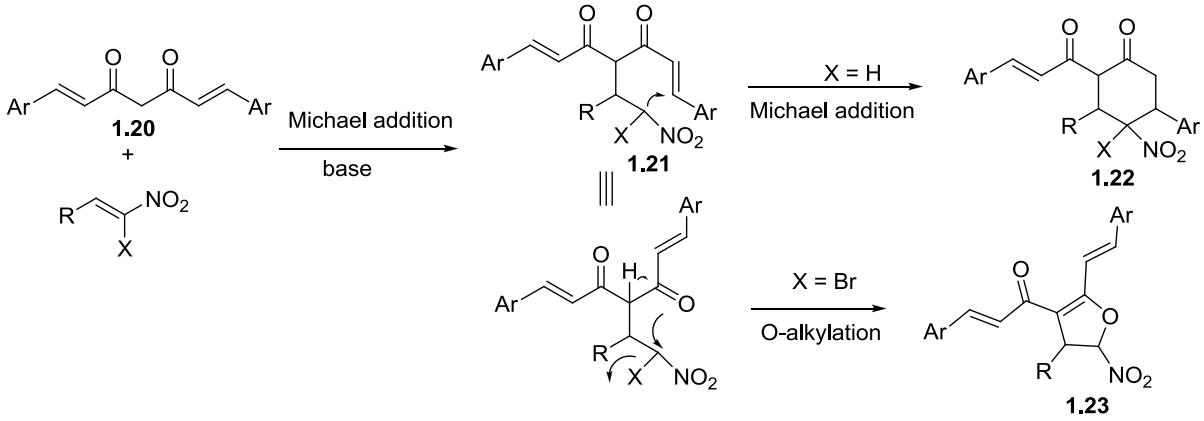
Scheme 1.2 Enantioselective cyclopropanation through organocatalytic conjugate addition to β-bromo-β-nitrostyrenes



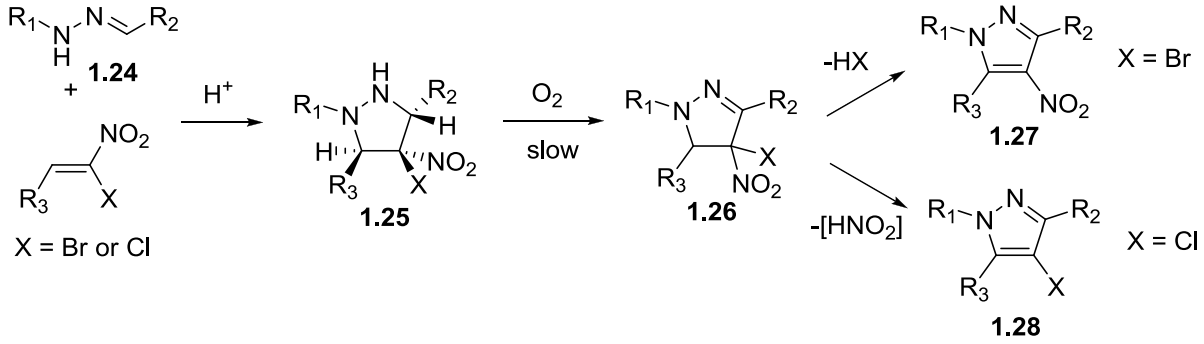
Scheme 1.3 Domino Michael reaction to chiral mono-, bi-, and tricyclic 2,3-dihydrofurans



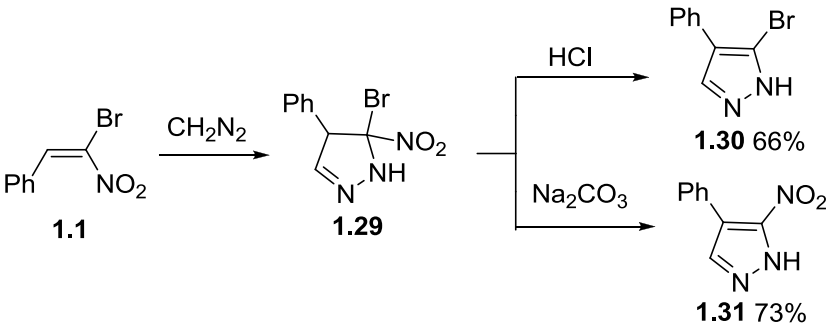
Scheme 1.4 Synthesis of pyrroles by domino reactions in water



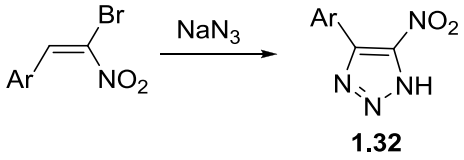
Scheme 1.5 Construction of carbocycles and heterocycles via cascade reaction involve curcumins and nitroalkenes



Scheme 1.6 Synthesis of 4-nitro or 4-chloro-tetrasubstituted pyrazoles from hydrazones and *β*-halo-*β*-nitrostyrenes

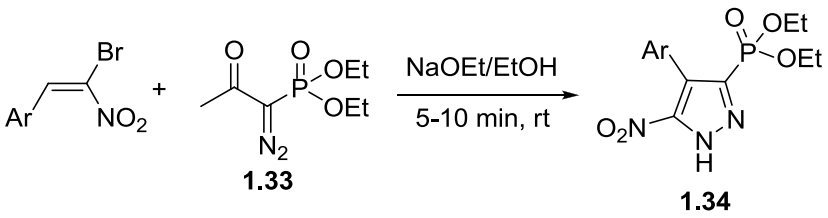


Scheme 1.7 Condensation of diazomethane with *β*-bromo-*β*-nitrostyrene



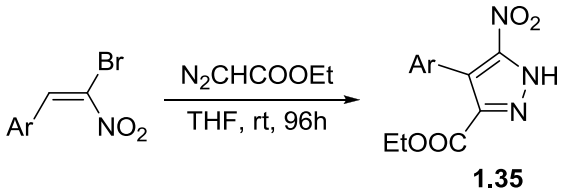
Scheme 1.8 Synthesis of nitro -1,2,3-triazoles by condensation with sodium azide

In another case, nitro-1,2,3-triazoles were obtained when sodium azide was used as 1,3-dipole.[3f] (Scheme 1.8) While when diethyl 1-diazo-2-oxopropylphosphonate (Bestmann-Ohira reagent) was used as cycloaddition partner, functionalized phosphonylpyrazole was synthesized through a one-pot regioselective reaction at room temperature. [3c,3e] (Scheme 1.9)



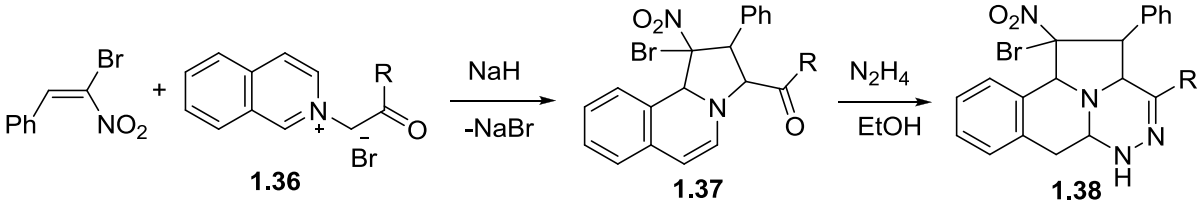
Scheme 1.9 Synthesis of phosphonylpyrazole by cycloaddition with Bestmann-Ohira reagent

When ethyl diazoacetate was used as cycloaddition reagent, multisubstituted pyrazoles were synthesized via catalyst-free 1,3-dipolar cycloaddition and elimination of the leaving group followed by intramolecular proton transfer.[3d] (Scheme 1.10) Azomethine ylides, generated in situ from *N*-onium salts, were also active cycloaddition partner, which reacted with *β*-bromo-*β*-nitrostyrenes to give tetrahydropyrroloisoquinolines. The latter one underwent cyclization with hydrazine hydrate to obtain substituted hexahydrotriazinoindolizine.[3b] (Scheme 1.11)



1.35

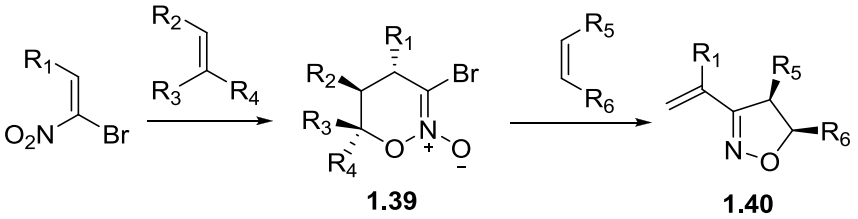
Scheme 1.10 Synthesis of functionalized pyrazole by cycloaddition with ethyl diazoacetate



1.36 **1.37** **1.38**

Scheme 1.11 Synthesis of tetrahydropyrroloisoquinoline by reaction with *N*-onium salts

Apart from its roles as Michael acceptors and dipolarophiles, *β*-bromo-*β*-nitrostyrenes could also serve as useful heterodienes and 1,3-dipoles.[4,5] (Scheme 1.12) In a recent report, 1,2-oxazine *N*-oxides were synthesized through [4+2] cycloaddition of *β*-bromo-*β*-nitrostyrenes to olefins. Then the adduct underwent [3+2] cycloaddition to give 3-vinyloxazoline as a final product.



1.39 **1.40**

Scheme 1.12 Synthesis and [3+2] cycloadditions of 1,2-oxazine *N*-oxides

In summary, all these information on *β*-bromo-*β*-nitrostyrenes, although limited, showed that the *β*-bromo-*β*-nitrostyrenes are versatile and promising agents in synthetic chemistry. We were interested in investigating the prospect of new transformations with the *β*-bromo-*β*-nitrostyrenes. In the following sections, we will describe these interesting discoveries.

1.2 Rapid Access to 2-Iminothiazoline from Thioureas and 1-Bromo-1-nitroalkenes

1.2.1 Introduction

Functionalized 2-iminothiazoline has been an important building block in synthetic chemistry.[6] The 2-iminothiazoline derivatives have been reported to have significant biological activities such as bactericidal, analgetic, fungicidal, insecticidal activity.[7] This structure has found applications in drug candidates for treatment of allergies, hypertension, schizophrenia, inflammations, and bacterial and HIV infections.[8] Pifithrin (Pft-α) (Figure 1.1), isolated by screening of chemical libraries containing 2-iminothiazoline skeletons, is the lead compound of p53 inactivators and have received increasing attention due to its possible applications in therapy of Alzheimer's disease, Parkinson's disease, stroke and other pathologies related to various signalling pathways.[9] Besides, 2-iminothiazolines derivatives were often used as chemical reaction accelerators and useful ligands in metal complexes.[10]

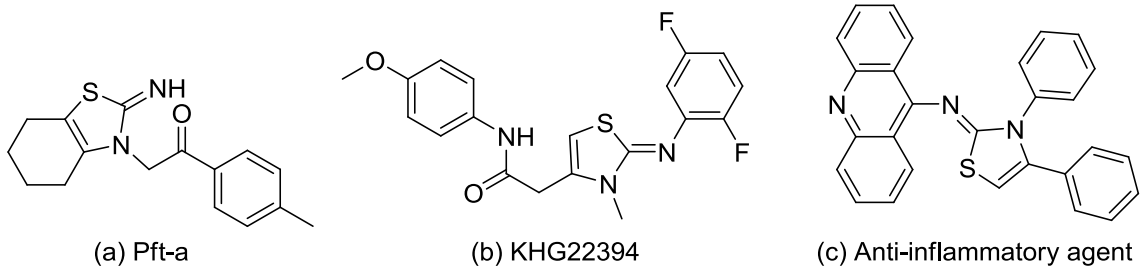
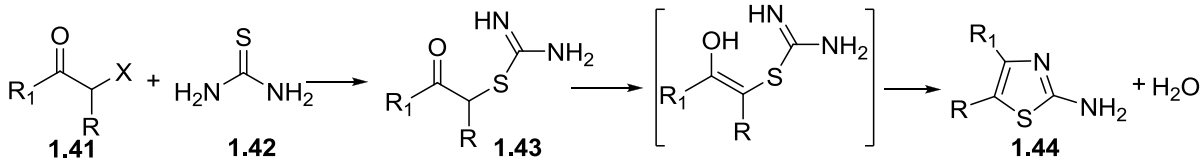


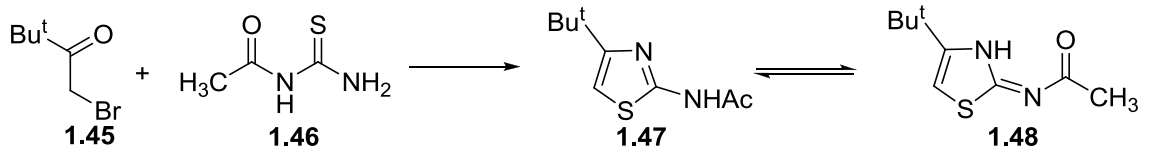
Figure 1.1 Structures of pharmacologically important molecules: (a) p53 inactivator; (b) skin whitening agent. (c) anti-inflammatory agent

The classical synthesis of 2-aminothiazole moieties involves the Hantzsch condensation by thiourea and α-haloketone.[11] (Scheme 1.13) This approach was subsequently used for the synthesis of *N*-alkylated iminothiazolines by replacing thioureas with mono-*N*-substituted thioureas.[12] (Scheme 1.14) Several alternative strategies have been devised. Highly functionalized thiazoles and 2-imino-thiazolines were synthesized by replacing α-haloketone with 2-chlorooxirane[13] and 2,2-dicyano-3,3-bis(trifluoromethy1)oxirane[14]. (Scheme 1.15)

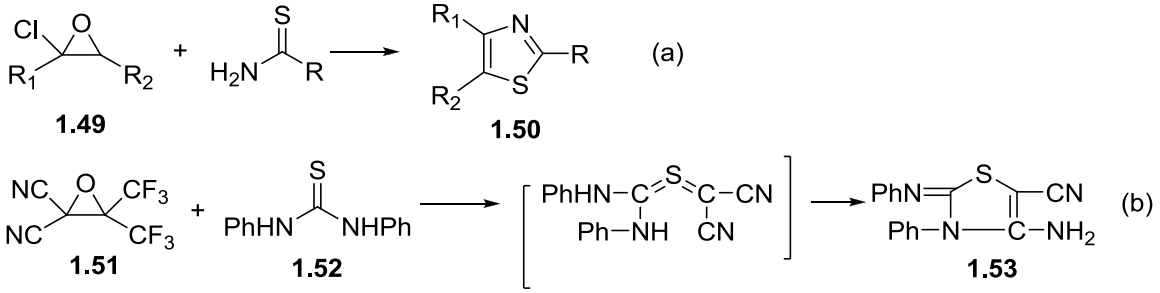
Treatment of α-bromoketimines with potassium thiocyanate[15] also could afford the 2-iminothiazolines. (Scheme 1.16) The reaction of *N*-monoalkylated thioureas with 3-bromomethyl-2-cyanocinnamonitrile gave the hydrobromides of 2-iminothiazolines.[16] (Scheme 1.17) Noteworthily, the thiazolines could be prepared from cycloaddition-elimination reaction of 5-imino-1,2,4-thiazolidin-3-ones with enamines and ester enolates.[17] (Scheme 1.18) The 2-iminothiazolines are also accessible from ring transformation of 2-(thiocyanomethyl)aziridines.[18] (Scheme 1.19)



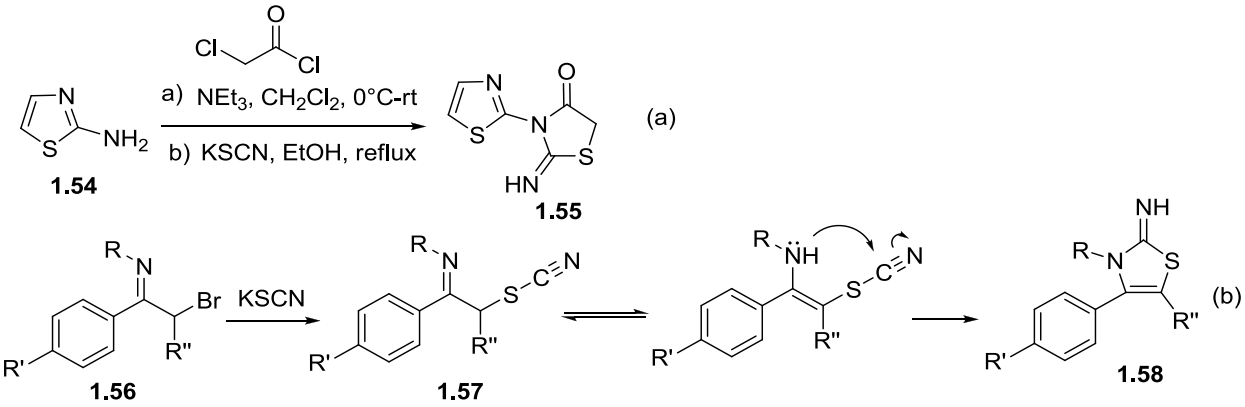
Scheme 1.13 Synthesis of 2-aminothiazoles by Hantzsch condensation



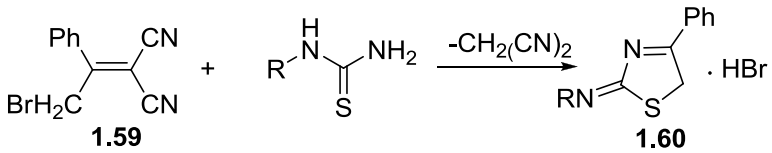
Scheme 1.14 Tautomerism in acetamidothiazoles



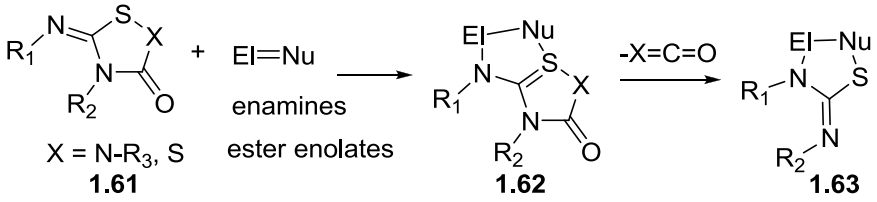
Scheme 1.15 Synthesis of thiazole and 2-iminothiazoline through 2-chlorooxirane and 2,2-dicyano-3,3-bis(trifluoromethyl)oxirane



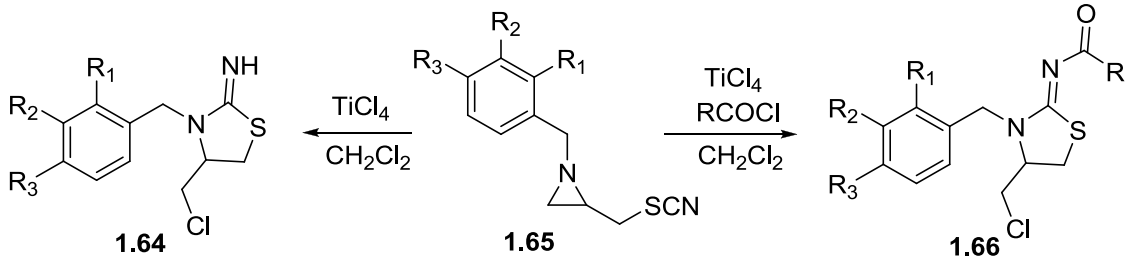
Scheme 1.16 Synthesis of 2-iminothiazolines by treatment of *α*-bromoketimines with potassium thiocyanate



Scheme 1.17 Synthesis of 2-iminothiazolinles by reaction of thioureas with 3-bromomethyl-2-cyanocinnamonitrile



Scheme 1.18 Reaction of 5-imino-1,2,4-thiazolidin-3-ones with enamines and ester enolates



Scheme 1.19 Synthesis of 2-imino-thiazolidines from 1-arylmethyl-2-(thiocyanomethyl)aziridines

Although some methods of preparation of 2-imino-thiazolines are effective, most procedures reported in literatures require arduous preparation of precursor substrates and harsh reaction conditions. Only a few reports are on the one-pot procedure for the synthesis of 2-imino-thiazoline from *N*,*N*'-dialkylthiourea and in situ generated α-bromoketones.[19] Since the 1-bromo-1-nitroalkenes share some structural similarity with the α-bromoketones, we were

interested to investigate the reaction of 1-bromo-1-nitroalkenes and thioureas. Here, we describe a novel and efficient synthesis of 2-imino-5-nitrothiazolines by 1,3-diphenylthioureas and 1-bromo-1-nitroalkenes with mild and facile conditions.

1.2.2 Results and Discussion

In our preliminary experiments, the reaction of 1,3-diphenylthiourea and *β*-bromo-*β*-nitrostyrene was studied. We found that when these two reactants were treated with base such as K_2CO_3 in THF at room temperature in the air, a red crystalline product was obtained (Table 1.1, entry 1), whose structure was confirmed to be **1.68a** by single crystal X-ray analysis (Figure 1.2). When the reaction temperature was increased to 70 °C, the reaction could be completed in shorter time but the yield was lower down due to the increase of side products (Table 1.1, entries 1-6). We tested several different bases such as K_2CO_3, Et_3N, DBU, $KHCO_3$, DIPEA and the Et_3N gave the best results. When no base was added, there is no desired product (Table 1.1, entry 10). The base loadings was examined and 0.2 equiv of base provided the best results (Table 1.1, entries 11-12). The solvents were also screened and THF proved to be the optimal solvent. (Table 1.1, entries 13-15).

Besides the 1,3-diphenylthiourea, we tested other thioureas including simple thiourea **2.2** and mono-*N*-substituted thioureas **2.6** and **2.28** (Figure 1.3) but there were no reaction for them. Other unsymmetrical thioureas such as benzoylthiourea **2.29** and other 1,3-disubstituted thiourea **2.30** were also tested but the yields were very low (< 5%) for them.

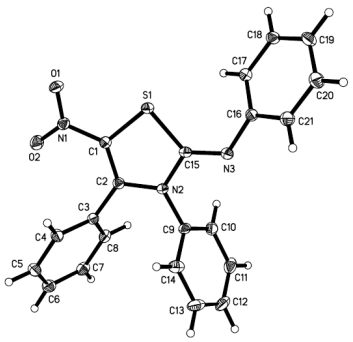
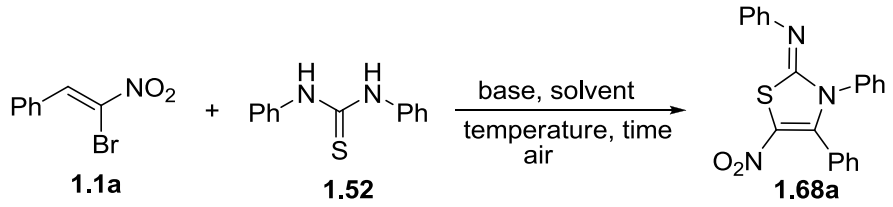


Figure 1.2 X-ray crystallography of **1.68a**

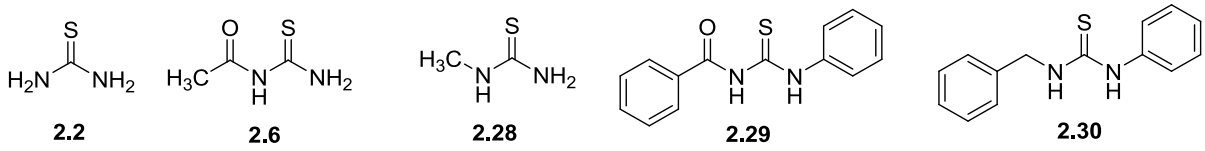
Table 1.1 Reaction of *β*-bromo-*β*-nitrostyrene **1.1a** and 1,3-diphenylthiourea **1.52** under different conditions



1.1a **1.52** **1.68a**

entry[a]	base	solvent	Temp (°C)	Time (h)	Yield (%)
1	K_2CO_3	THF	rt	24	62
2[b]	K_2CO_3	THF	70	10	60
3	Et_3N	THF	rt	24	72
4[b]	Et_3N	THF	70	10	65
5	DBU	THF	rt	24	63
6[b]	DBU	THF	70	10	58
7	$KHCO_3$	THF	rt	24	55
8[b]	$KHCO_3$	THF	70	10	60
9	DIPEA	THF	rt	24	48
10	None	THF	rt	24	0
11[c]	Et_3N	THF	rt	24	64
12[d]	Et_3N	THF	rt	24	58
13	Et_3N	CH_2Cl_2	rt	24	45
14	Et_3N	Toluene	rt	24	42
15	Et_3N	Toluene	110	5	40

[a] Reactions were performed with *β*-bromo-*β*-nitrostyrene **1.1a** (0.10 mmol) and 1,3-diphenylthiourea **1.52** (0.11 mmol) with the base (0.02 mmol) in the indicated solvent (2.0 ml) in the air. [b] The *β*-bromo-*β*-nitrostyrene was completely consumed. [c] The reaction was carried out with 0.04 mmol of base. [d] The reaction was carried out with 0.01 mmol of base.



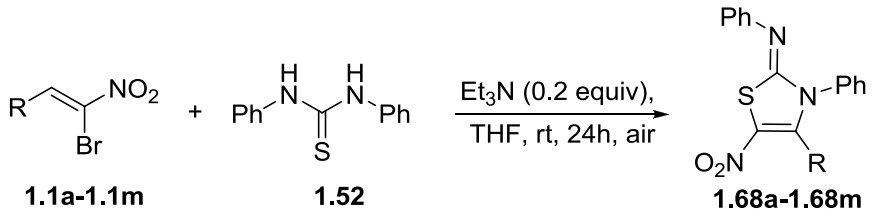
2.2 **2.6** **2.28** **2.29** **2.30**

Figure 1.3 Different thiourea substrates tested

Based on these results, we investigated the scope of the reaction by using different 1-bromo-1-nitroalkenes. The results were shown in Table 1.2. In general, *β*-bromo-*β*-nitrostyrenes with electron-withdrawing as well as electron-donating groups on the phenyl ring could give fair yields except that *β*-bromo-*β*-nitrostyrenes with $–NO_2$ substituent gave lower yields (Table 1.2, entries 8-9). Other 1-bromo-1-nitroalkenes with aromatic ring substituent such as naphthalene could give moderate yield (Table 1.2, entry 11). And nonconjugated

bromonitroalkene and bromonitroalkene with alkyl substituent gave rather low yields (Table 1.2, entries 12-13).

Table 1.2 Reaction of various 1-bromo-1-nitroalkenes **1.1a-1.1m** with 1,3-diphenylthiourea **1.52**

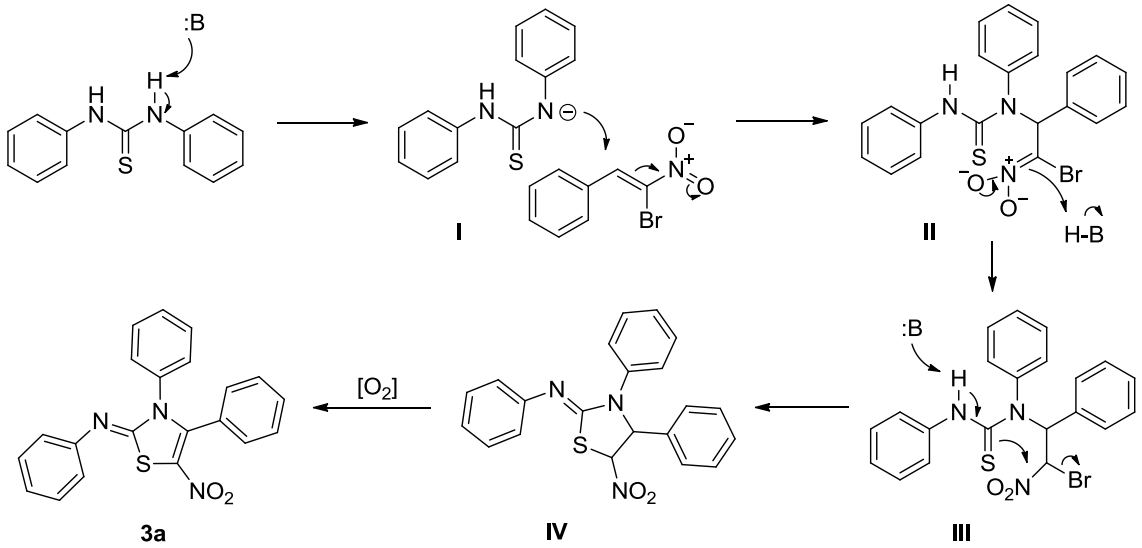


1.1a-1.1m **1.52** **1.68a-1.68m**

entry[a]	R	Product	Yield (%)[b]
1	Ph	3a	72
2	4-Br-C_6H_4-	3b	82
3	3-Br-C_6H_4-	3c	73
4	4-Cl-C_6H_4-	3d	75
5	3-Cl-C_6H_4-	3e	70
6	2-Cl-C_6H_4-	3f	60
7	4-F-C_6H_4-	3g	62
8	4-NO_2-C_6H_4-	3h	52
9	3-NO_2-C_6H_4-	3i	34
10	4-OMe-C_6H_4-	3j	56
11	2-napth-	3k	42
12	$PhCH_2CH_2$-	3l	45
13	Isopropyl-	3m	32

[a] Reaction were performed with 1-bromo-1-nitroalkenes **1.1a-1.1m** (0.10 mmol) and 1,3-diphenylthiourea **1.52** (0.11 mmol) with Et_3N (0.02 mmol) in THF (2.0 ml) at room temperature for 24 hours. [b] Yield after column chromatography.

A plausible mechanism for this reaction is shown in Scheme 1.20. Firstly, 1,3-diphenylthiourea was deprotonated by base to form intermediate **I** which was followed by Michael addition of the thiourea to the *β*-bromo-*β*-nitrostyrene to generate intermediate **II**. Further deprotonation of **III** by base results in an intramolecular nucleophilic substitution to form the five-membered ring **IV**. The **IV** undergoes a slow oxidation by air to give the desired product **1.68a**.



Scheme 1.20 Plausible Mechanism

1.2.3 Conclusion

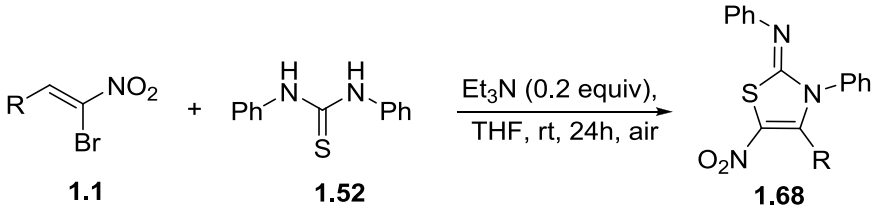
In summary, we have developed a facile and mild synthesis of functionalized 2-imino-5-nitrothiazoline by reaction of 1-bromo-1-nitroalkenes and 1,3-diphenylthiourea. Although this method is limited to 1,3-diphenylthiourea only, it provides a new approach for the synthesis of diverse 2-iminothiazolines, in which 1-bromo-1-nitroalkenes were used as a trifunctional synthon. This method is simple, versatile and the yield is fair.

1.2.4 Experimental Section

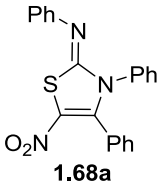
General: All reactions were conducted in the air. All reagents and solvents were obtained from commercial suppliers and used without further purification. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates. Product purification by flash column chromatography was accomplished using silica gel (0.010 - 0.063 mm). Technical grade solvents were used for chromatography and distilled prior to use. High-resolution mass spectra (HRMS) were obtained on a Finnigan/MAT LCQ quadrupole ion trap mass spectrometer, coupled with the TSP4000 HPLC system and the Crystal 310 CE system. Accurate masses are reported for the molecular ion $[M+H]^+$ or a suitable fragment ion. X-ray crystallographic data was collected by using a Bruker X8 Apex diffractometer with Mo K/α radiation (graphite monochromator). ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker AV 400 (400 MHz) NMR spectrometer. ^1H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm) and $CHCl_3$ (77.0 ppm), respectively. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from triethylsilane. Chemical shift (δ) is referred in terms of ppm, coupling constants (J) are given in Hz. Following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved.

Materials: 1-Bromo-1-nitroalkenes **1.1a-1.1m** were prepared according to the standard literature procedures[3g]. 1,3-Diphenylthiourea **1.52** was obtained from commercial suppliers and used without further purification.

General procedure for the Synthesis of 2-imino-5-nitro-thiazolines:

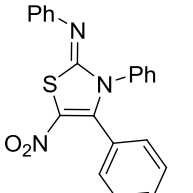


To a stirred solution of *β*-bromo-*β*-nitrostyrenes **1.1a** (22.8 mg, 0.1 mmol, 1.0 equiv, prepared as a mixture of *Z*- and *E*-isomer), 1,3-diphenylthiourea **1.52** (25.1 mg, 0.11 mmol, 1.1 equiv) in THF (2.0 mL) was added triethylamine (2.0 mg, 0.02 mmol, 0.2 equiv) slowly. The reaction mixture was stirred at room temperature in the air (TLC monitored). The resulting mixture was concentrated under reduced pressure to give the crude residue, which was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **1.68a** (26.8 mg, 0.07 mmol, 72% yield) as a red crystal.



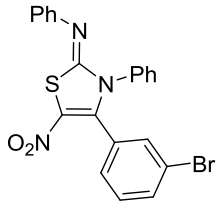
1.68a

(Z)-N-(5-nitro-3,4-diphenylthiazol-2(3H)-ylidene)aniline (**1.68a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.27 (m, 8H), 7.25-7.18 (m, 4H), 7.13 (t, J = 7.2 Hz, 1H), 7.00 (dd, J = 8.0, 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 149.7, 146.7, 135.5, 130.3, 129.8 (2C), 129.4 (2C), 129.2 (2C), 129.1 (2C), 129.0 (2C), 128.4 (2C), 127.5, 124.9, 120.7 (2C); HRMS (ESI): *m/z* calcd for $C_{21}H_{16}N_3O_2S$ $[M+H]^+$, 374.0963, found 374.0953.



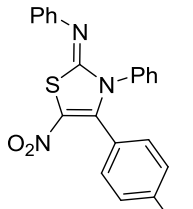
1.68b

(Z)-N-(4-(4-bromophenyl)-5-nitro-3-phenylthiazol-2(3H)-ylidene)aniline (**1.68b**): The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **1.68b** (37.1 mg, 0.08 mmol, 82% yield) as a red crystal. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 8.4 Hz, 2H), 7.39-7.31 (m, 5H), 7.19-7.09 (m, 5H), 6.99 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 149.6, 145.2, 135.4, 131.8 (2C), 131.1 (2C), 129.8 (2C), 129.4 (2C), 129.3 (2C), 129.0 (2C), 126.3, 125.1, 124.9, 120.6 (2C); HRMS (ESI): *m/z* calcd for $C_{21}H_{15}BrN_3O_2S$ $[M+H]^+$, 452.0068, found 452.0076.



1.68c

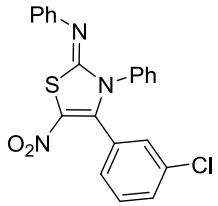
(Z)-N-(4-(3-bromophenyl)-5-nitro-3-phenylthiazol-2(3H)-ylidene)aniline (**1.68c**): The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **1.68c** (33.0 mg, 0.07 mmol, 73% yield) as a red crystal; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.30 (m, 8H), 7.20-7.11 (m, 4H), 6.97 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 149.5, 144.4, 135.2, 133.5, 132.3, 129.9 (2C), 129.8, 129.4 (3C), 129.3, 129.0 (2C), 128.1, 128.0, 124.9, 122.3, 120.6 (2C); HRMS (ESI): *m/z* calcd for $C_{21}H_{15}BrN_3O_2S$ $[M+H]^+$, 452.0068, found 452.0072.



1.68d

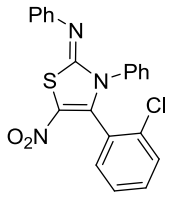
(Z)-N-(4-(4-chlorophenyl)-5-nitro-3-phenylthiazol-2(3H)-ylidene)aniline (**1.68d**): The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in

hexanes) to afford compound **1.68d** (30.6 mg, 0.08 mmol, 75% yield) as a yellow crystal. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.27 (m, 7H), 7.19-7.12 (m, 5H), 6.99 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 149.5, 145.2, 136.8, 135.3, 130.9 (2C), 129.8 (2C), 129.4 (2C), 129.3 (2C), 129.0 (2C), 128.8 (2C), 125.7, 124.9, 120.6 (2C); HRMS (ESI): *m/z* calcd for $C_{21}H_{15}ClN_3O_2S$ $[M+H]^+$, 408.0574, found 408.0582.



1.68e

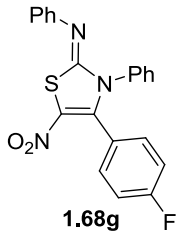
(Z)-N-(4-(3-chlorophenyl)-5-nitro-3-phenylthiazol-2(3H)-ylidene)aniline (**1.68e**): The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **1.68e** (28.6 mg, 0.07 mmol, 70% yield) as a yellow crystal; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.32 (m, 6H), 7.30-7.25 (m, 2H), 7.23 (d, J = 10.8 Hz, 2H), 7.18-7.10 (m, 2H), 6.99 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 149.5, 144.5, 135.2, 134.4, 130.5, 129.8 (2C), 129.7 (2C), 129.5, 129.4 (3C), 129.3, 129.0 (2C), 127.6, 124.9, 120.6 (2C); HRMS (ESI): *m/z* calcd for $C_{21}H_{15}ClN_3O_2S$ $[M+H]^+$, 408.0574, found 408.0569.



1.68f

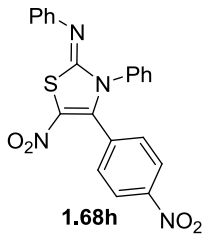
(Z)-N-(4-(2-chlorophenyl)-5-nitro-3-phenylthiazol-2(3H)-ylidene)aniline (**1.68f**): The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **1.68f** (24.4 mg, 0.06 mmol, 60% yield) as a yellow solid; ^{1}H

NMR (400 MHz, $CDCl_3$): δ 7.39-7.29 (m, 9H), 7.22-7.13 (m, 3H), 7.02 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 149.6, 143.2, 135.2, 133.6, 131.6, 130.4 (2C), 129.8 (2C), 129.7 (2C), 129.4 (2C), 129.3, 128.5, 127.7, 126.9, 124.9, 120.7 (2C); HRMS (ESI): *m/z* calcd for $C_{21}H_{15}ClN_3O_2S$ $[M+H]^+$, 408.0574, found 408.0583.



1.68g

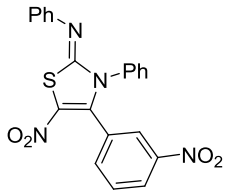
(Z)-N-(4-(4-fluorophenyl)-5-nitro-3-phenylthiazol-2(3H)-ylidene)aniline (**1.68g**): The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **1.68g** (24.3 mg, 0.06 mmol, 62% yield) as a yellow solid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34-7.27 (m, 5H), 7.26-7.11 (m, 5H), 7.02-6.97 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 162.2, 153.7, 149.7, 145.4, 135.4, 131.8, 131.7, 129.8 (2C), 129.4 (2C), 129.2 (2C), 129.0 (2C), 124.9, 120.6 (2C), 116.1, 115.7; HRMS (ESI): *m/z* calcd for $C_{21}H_{15}FN_3O_2S$ $[M+H]^+$, 392.0869, found 392.0853.



1.68h

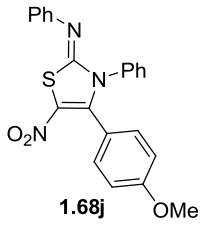
(Z)-N-(5-nitro-4-(4-nitrophenyl)-3-phenylthiazol-2(3H)-ylidene)aniline (**1.68h**): The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **1.68h** (21.7 mg, 0.05 mmol, 52% yield) as a yellow solid; ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 (dd, J = 7.2, 2.0 Hz, 2H), 7.45 (dd, J = 7.2, 2.0 Hz, 2H), 7.39-7.32 (m, 5H), 7.20-7.15 (m, 3H), 6.99 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 153.2, 149.3, 148.6, 143.5, 134.9, 134.1, 130.8 (2C), 129.9 (2C), 129.7 (4C), 128.9 (2C), 125.1, 123.6 (2C), 120.6 (2C); HRMS (ESI): *m/z* calcd for $C_{21}H_{15}N_4O_4S$ $[M+H]^+$, 419.0814, found 419.0821.



1.68i

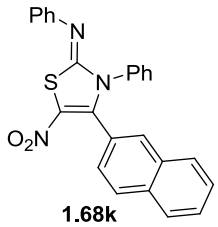
(Z)-N-(5-nitro-4-(3-nitrophenyl)-3-phenylthiazol-2(3H)-ylidene)aniline (**1.68i**): The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **1.68i** (14.2 mg, 0.03 mmol, 34% yield) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 8.8 Hz, 1H), 8.14 (t, J = 1.6 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.40-7.28 (m, 5H), 7.23-7.13 (m, 3H), 6.99 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 149.4, 147.9, 143.2, 135.5, 134.9, 129.9 (2C), 129.7 (4C), 129.6 (2C), 129.2, 129.0, 125.1 (2C), 124.8, 120.5 (2C); HRMS (ESI): *m/z* calcd for $C_{21}H_{15}N_4O_4S$ $[M+H]^+$, 419.0814, found 419.0824.



1.68j

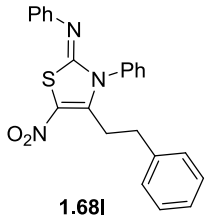
(Z)-N-(4-(4-methoxyphenyl)-5-nitro-3-phenylthiazol-2(3H)-ylidene)aniline (**1.68j**): The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **1.68j** (22.6 mg, 0.06 mmol, 56% yield) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-6.99 (m, 8H), 6.86-6.78 (m, 6H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 137.9, 131.3, 130.3 (2C), 129.8 (2C), 129.2 (2C), 129.1 (4C),

125.8, 124.0 (2C), 123.4, 120.8, 114.4 (2C), 113.9, 55.4; HRMS (ESI): *m/z* calcd for $C_{22}H_{18}N_3O_3S$ $[M+H]^+$, 404.1069, found 404.1055.



1.68k

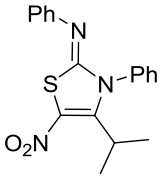
(Z)-N-(4-(naphthalen-2-yl)-5-nitro-3-phenylthiazol-2(3H)-ylidene)aniline (**1.68k**): The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **1.68k** (17.8 mg, 0.04 mmol, 42% yield) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.73 (m, 4H), 7.55-7.48 (m, 2H), 7.39-7.35 (m, 2H), 7.28-7.22 (m, 5H), 7.21-7.12 (m, 2H), 7.03 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 149.7, 146.6, 135.5, 133.5, 132.4, 130.3, 129.8 (2C), 129.3 (2C), 129.1 (2C), 129.0 (2C), 128.4, 128.2, 127.9, 127.8, 126.8, 125.6, 124.8, 124.8, 120.7 (2C); HRMS (ESI): *m/z* calcd for $C_{25}H_{18}N_3O_2S$ $[M+H]^+$, 424.1120, found 424.1124.



1.68l

(Z)-N-(5-nitro-4-phenethyl-3-phenylthiazol-2(3H)-ylidene)aniline (**1.68l**): The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **1.68l** (18.1 mg, 0.04 mmol, 45% yield) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.56 (m, 3H), 7.36-7.28 (m, 4H), 7.24-7.21 (m, 3H), 7.12-7.09 (m, 1H), 6.94 (d, J = 7.6 Hz, 4H), 3.12-3.08 (m, 2H), 2.86-2.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 150.0, 149.5, 139.3, 130.2 (2C), 130.1 (2C), 129.8 (2C), 128.9 (2C),

128.7 (2C), 128.4 (2C), 126.8, 124.9, 120.7 (2C), 33.5, 30.3; HRMS (ESI): *m/z* calcd for $C_{23}H_{20}N_3O_2S$ $[M+H]^+$, 402.1276, found 402.1283.

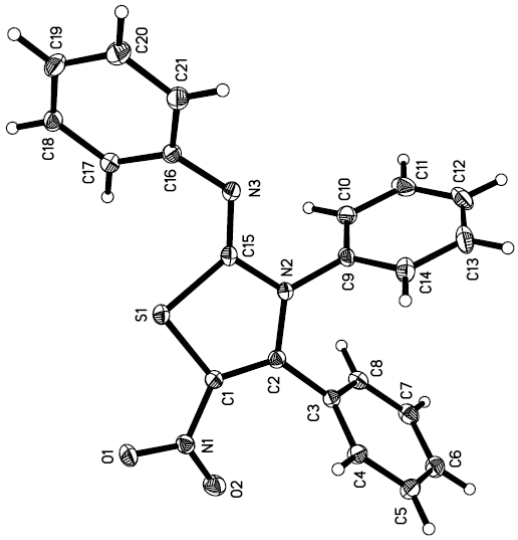


1.68m

(Z)-N-(4-isopropyl-5-nitro-3-phenylthiazol-2(3H)-ylidene)aniline (**1.68m**): The crude residue was then purified by flash column chromatography on silica gel (20% EtOAc in hexanes) to afford compound **1.68m** (10.9 mg, 0.03 mmol, 32% yield) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.52 (m, 3H), 7.39-7.29 (m, 4H), 7.10-7.06 (m, 1H), 6.95-6.90 (m, 2H), 3.28-3.23 (m, 1H), 1.29 (d, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.0, 149.7, 136.1, 130.2 (2C), 130.1 (3C), 129.7 (2C), 128.9 (2C), 124.7, 120.7 (2C), 29.0, 18.0; HRMS (ESI): *m/z* calcd for $C_{18}H_{18}N_3O_2S$ $[M+H]^+$, 340.1120, found 340.1126.

1.2.5 Supporting Information

1. X-ray data of compound 1.68a



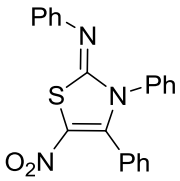


Table 1. Crystal data and structure refinement for compound **1.68a.**

Identification code	**1.68a**	
Empirical formula	C21 H15 N3 O2 S	
Formula weight	373.42	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 20.5389(5) Å	a= 90°.
	b = 9.3143(2) Å	b= 103.7740(10)°.
	c = 18.8825(4) Å	g = 90°.
Volume	3508.44(14) $Å^3$	
Z	8	
Density (calculated)	1.414 Mg/m^3	
Absorption coefficient	0.207 mm^{-1}	
F(000)	1552	
Crystal size	0.40 x 0.40 x 0.20 mm^3	
Theta range for data collection	2.04 to 31.03°.	
Index ranges	-29<=h<=29, -7<=k<=13, -26<=l<=27	
Reflections collected	26512	
Independent reflections	5604 [R(int) = 0.0259]	

Completeness to theta = 31.03°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9598 and 0.9219
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5604 / 0 / 244
Goodness-of-fit on F^2	1.169
Final R indices [I>2sigma(I)]	R1 = 0.0361, wR2 = 0.1008
R indices (all data)	R1 = 0.0508, wR2 = 0.1265
Largest diff. peak and hole	0.690 and -0.562 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **1.68a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	1747(1)	7370(1)	1985(1)	15(1)
C(2)	1595(1)	7296(1)	2650(1)	14(1)
C(3)	1712(1)	6112(1)	3185(1)	14(1)
C(4)	1452(1)	4755(1)	2973(1)	16(1)
C(5)	1534(1)	3651(1)	3480(1)	19(1)
C(6)	1867(1)	3904(2)	4201(1)	20(1)
C(7)	2130(1)	5251(2)	4412(1)	19(1)
C(8)	2055(1)	6361(1)	3907(1)	16(1)
C(9)	1015(1)	8721(1)	3426(1)	15(1)
C(10)	1314(1)	9738(2)	3934(1)	18(1)
C(11)	1092(1)	9884(2)	4571(1)	25(1)
C(12)	586(1)	9003(2)	4696(1)	27(1)
C(13)	285(1)	8005(2)	4176(1)	26(1)
C(14)	496(1)	7859(2)	3532(1)	20(1)
C(15)	1176(1)	9581(1)	2244(1)	13(1)
C(16)	811(1)	11833(1)	1777(1)	15(1)
C(17)	1354(1)	12329(1)	1520(1)	16(1)
C(18)	1271(1)	13473(1)	1034(1)	18(1)
C(19)	655(1)	14146(2)	811(1)	21(1)
C(20)	114(1)	13662(2)	1072(1)	23(1)
C(21)	190(1)	12512(2)	1554(1)	19(1)
N(1)	2113(1)	6370(1)	1672(1)	16(1)
N(2)	1268(1)	8518(1)	2785(1)	13(1)
N(3)	876(1)	10746(1)	2309(1)	15(1)
O(1)	2108(1)	6562(1)	1018(1)	20(1)
O(2)	2416(1)	5379(1)	2040(1)	20(1)
S(1)	1503(1)	8959(1)	1511(1)	15(1)

Table 3. Bond lengths [Å] and angles [°] for compound **1.68a**.

C(1)-C(2)	1.3656(16)
C(1)-N(1)	1.4125(16)
C(1)-S(1)	1.7401(13)
C(2)-N(2)	1.3756(16)
C(2)-C(3)	1.4761(17)
C(3)-C(4)	1.3927(17)
C(3)-C(8)	1.3978(17)
C(4)-C(5)	1.3884(18)
C(4)-H(4)	0.9500
C(5)-C(6)	1.391(2)
C(5)-H(5)	0.9500
C(6)-C(7)	1.387(2)
C(6)-H(6)	0.9500
C(7)-C(8)	1.3892(18)
C(7)-H(7)	0.9500
C(8)-H(8)	0.9500
C(9)-C(10)	1.3829(18)
C(9)-C(14)	1.3865(18)
C(9)-N(2)	1.4402(15)
C(10)-C(11)	1.3900(18)
C(10)-H(10)	0.9500
C(11)-C(12)	1.386(2)
C(11)-H(11)	0.9500
C(12)-C(13)	1.386(2)
C(12)-H(12)	0.9500
C(13)-C(14)	1.3922(19)
C(13)-H(13)	0.9500
C(14)-H(14)	0.9500
C(15)-N(3)	1.2687(16)
C(15)-N(2)	1.4030(15)
C(15)-S(1)	1.7714(12)
C(16)-C(21)	1.3968(18)
C(16)-C(17)	1.3973(18)
C(16)-N(3)	1.4095(16)
C(17)-C(18)	1.3902(18)
C(17)-H(17)	0.9500

C(18)-C(19)	1.385(2)
C(18)-H(18)	0.9500
C(19)-C(20)	1.392(2)
C(19)-H(19)	0.9500
C(20)-C(21)	1.3907(19)
C(20)-H(20)	0.9500
C(21)-H(21)	0.9500
N(1)-O(2)	1.2307(15)
N(1)-O(1)	1.2454(14)

C(2)-C(1)-N(1)	127.72(11)
C(2)-C(1)-S(1)	114.51(9)
N(1)-C(1)-S(1)	117.60(9)
C(1)-C(2)-N(2)	110.89(11)
C(1)-C(2)-C(3)	129.18(11)
N(2)-C(2)-C(3)	119.89(10)
C(4)-C(3)-C(8)	120.06(12)
C(4)-C(3)-C(2)	119.51(11)
C(8)-C(3)-C(2)	120.37(11)
C(5)-C(4)-C(3)	119.92(12)
C(5)-C(4)-H(4)	120.0
C(3)-C(4)-H(4)	120.0
C(4)-C(5)-C(6)	120.02(13)
C(4)-C(5)-H(5)	120.0
C(6)-C(5)-H(5)	120.0
C(7)-C(6)-C(5)	120.09(12)
C(7)-C(6)-H(6)	120.0
C(5)-C(6)-H(6)	120.0
C(6)-C(7)-C(8)	120.31(12)
C(6)-C(7)-H(7)	119.8
C(8)-C(7)-H(7)	119.8
C(7)-C(8)-C(3)	119.58(12)
C(7)-C(8)-H(8)	120.2
C(3)-C(8)-H(8)	120.2
C(10)-C(9)-C(14)	121.75(12)
C(10)-C(9)-N(2)	118.95(11)
C(14)-C(9)-N(2)	119.26(12)
C(9)-C(10)-C(11)	118.92(13)

C(9)-C(10)-H(10)	120.5
C(11)-C(10)-H(10)	120.5
C(12)-C(11)-C(10)	120.18(14)
C(12)-C(11)-H(11)	119.9
C(10)-C(11)-H(11)	119.9
C(13)-C(12)-C(11)	120.19(13)
C(13)-C(12)-H(12)	119.9
C(11)-C(12)-H(12)	119.9
C(12)-C(13)-C(14)	120.29(14)
C(12)-C(13)-H(13)	119.9
C(14)-C(13)-H(13)	119.9
C(9)-C(14)-C(13)	118.64(14)
C(9)-C(14)-H(14)	120.7
C(13)-C(14)-H(14)	120.7
N(3)-C(15)-N(2)	121.13(11)
N(3)-C(15)-S(1)	129.69(10)
N(2)-C(15)-S(1)	109.13(9)
C(21)-C(16)-C(17)	119.58(12)
C(21)-C(16)-N(3)	117.70(11)
C(17)-C(16)-N(3)	122.48(11)
C(18)-C(17)-C(16)	120.02(12)
C(18)-C(17)-H(17)	120.0
C(16)-C(17)-H(17)	120.0
C(19)-C(18)-C(17)	120.46(12)
C(19)-C(18)-H(18)	119.8
C(17)-C(18)-H(18)	119.8
C(18)-C(19)-C(20)	119.63(13)
C(18)-C(19)-H(19)	120.2
C(20)-C(19)-H(19)	120.2
C(21)-C(20)-C(19)	120.49(13)
C(21)-C(20)-H(20)	119.8
C(19)-C(20)-H(20)	119.8
C(20)-C(21)-C(16)	119.82(13)
C(20)-C(21)-H(21)	120.1
C(16)-C(21)-H(21)	120.1
O(2)-N(1)-O(1)	123.45(11)
O(2)-N(1)-C(1)	120.47(10)
O(1)-N(1)-C(1)	116.07(11)

C(2)-N(2)-C(15)	115.85(10)
C(2)-N(2)-C(9)	123.66(10)
C(15)-N(2)-C(9)	120.48(10)
C(15)-N(3)-C(16)	120.72(11)
C(1)-S(1)-C(15)	89.60(6)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for compound **1.68a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

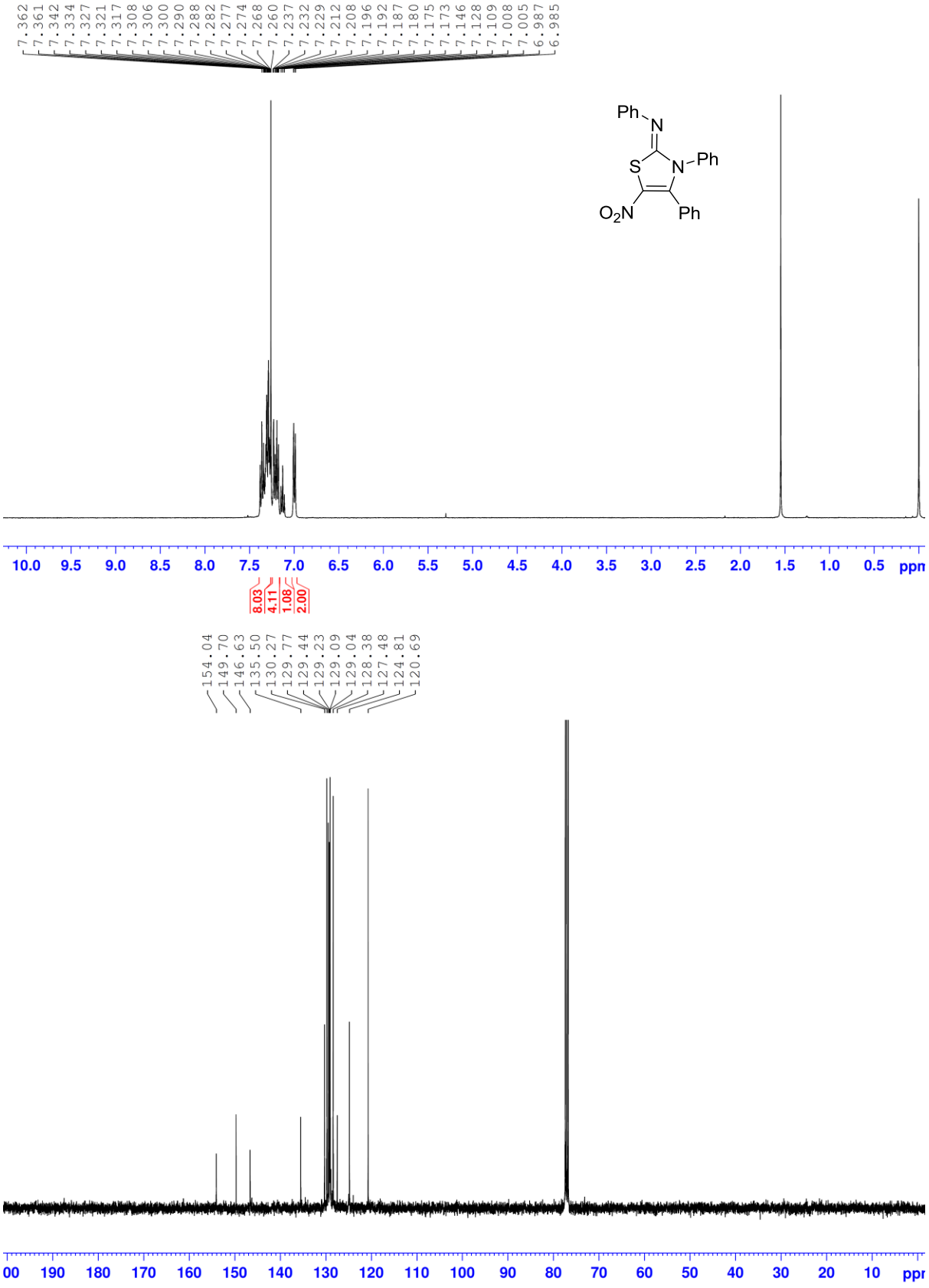
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	18(1)	13(1)	14(1)	0(1)	5(1)	0(1)
C(2)	14(1)	13(1)	14(1)	0(1)	3(1)	-1(1)
C(3)	14(1)	14(1)	14(1)	1(1)	5(1)	1(1)
C(4)	17(1)	14(1)	16(1)	0(1)	4(1)	0(1)
C(5)	20(1)	15(1)	23(1)	2(1)	7(1)	0(1)
C(6)	23(1)	21(1)	20(1)	7(1)	8(1)	6(1)
C(7)	20(1)	24(1)	14(1)	2(1)	4(1)	6(1)
C(8)	16(1)	18(1)	15(1)	-2(1)	4(1)	2(1)
C(9)	17(1)	17(1)	12(1)	4(1)	6(1)	4(1)
C(10)	24(1)	17(1)	15(1)	1(1)	6(1)	4(1)
C(11)	36(1)	24(1)	16(1)	0(1)	8(1)	11(1)
C(12)	31(1)	35(1)	19(1)	10(1)	14(1)	19(1)
C(13)	19(1)	36(1)	25(1)	14(1)	12(1)	8(1)
C(14)	17(1)	25(1)	19(1)	6(1)	5(1)	1(1)
C(15)	14(1)	15(1)	11(1)	1(1)	4(1)	-2(1)
C(16)	18(1)	13(1)	12(1)	0(1)	4(1)	0(1)
C(17)	18(1)	15(1)	16(1)	1(1)	5(1)	0(1)
C(18)	23(1)	14(1)	17(1)	-1(1)	8(1)	-3(1)
C(19)	29(1)	17(1)	18(1)	5(1)	6(1)	2(1)
C(20)	23(1)	24(1)	23(1)	7(1)	5(1)	6(1)
C(21)	18(1)	20(1)	20(1)	3(1)	6(1)	2(1)
N(1)	15(1)	16(1)	17(1)	-3(1)	6(1)	-2(1)
N(2)	17(1)	13(1)	11(1)	1(1)	6(1)	1(1)
N(3)	16(1)	15(1)	15(1)	2(1)	5(1)	1(1)
O(1)	29(1)	20(1)	15(1)	-2(1)	11(1)	-3(1)
O(2)	19(1)	21(1)	22(1)	1(1)	6(1)	6(1)
S(1)	20(1)	15(1)	12(1)	1(1)	6(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **1.68a**.

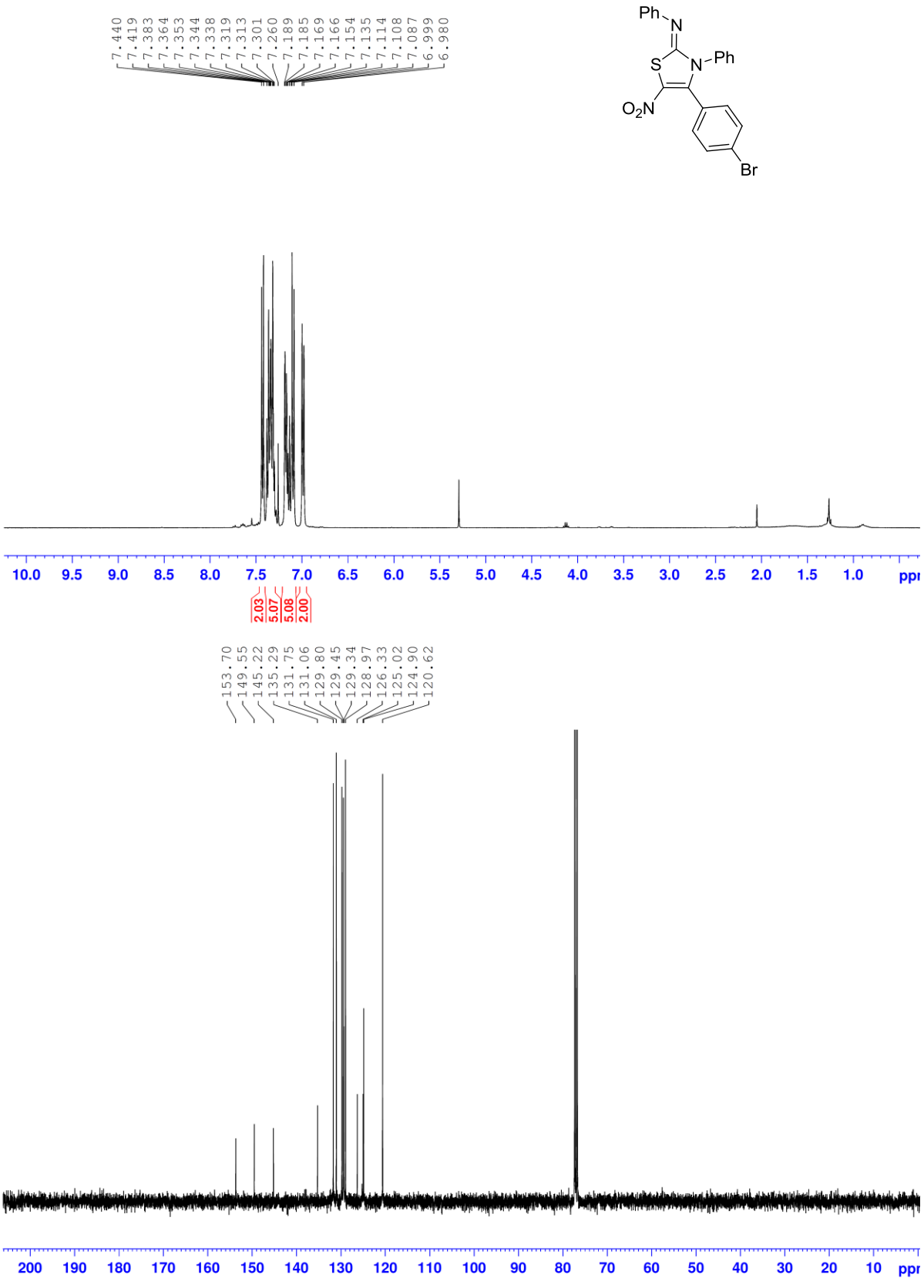
	x	y	z	U(eq)
H(4)	1220	4585	2481	19
H(5)	1361	2722	3335	23
H(6)	1914	3153	4550	25
H(7)	2363	5416	4903	23
H(8)	2236	7283	4052	19
H(10)	1666	10326	3850	22
H(11)	1286	10589	4921	30
H(12)	446	9085	5138	32
H(13)	-67	7417	4261	31
H(14)	289	7183	3172	24
H(17)	1781	11886	1678	19
H(18)	1640	13795	853	21
H(19)	601	14932	482	26
H(20)	-309	14122	920	28
H(21)	-181	12189	1731	23

2. ^{1}H and ^{13}C NMR spectral data of compounds 1.68a-1.68m

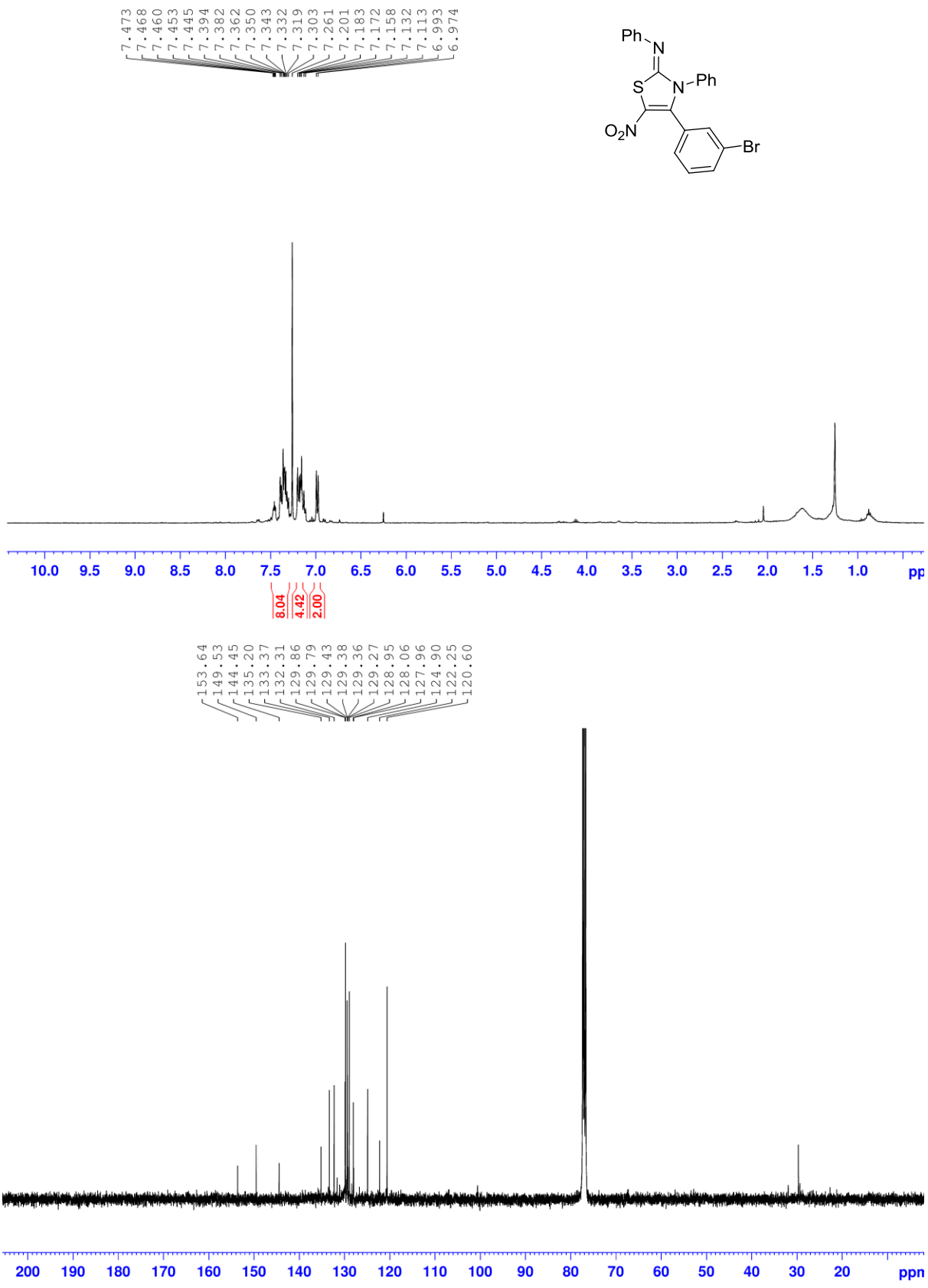
^{1}H and ^{13}C NMR of compound 1.68a



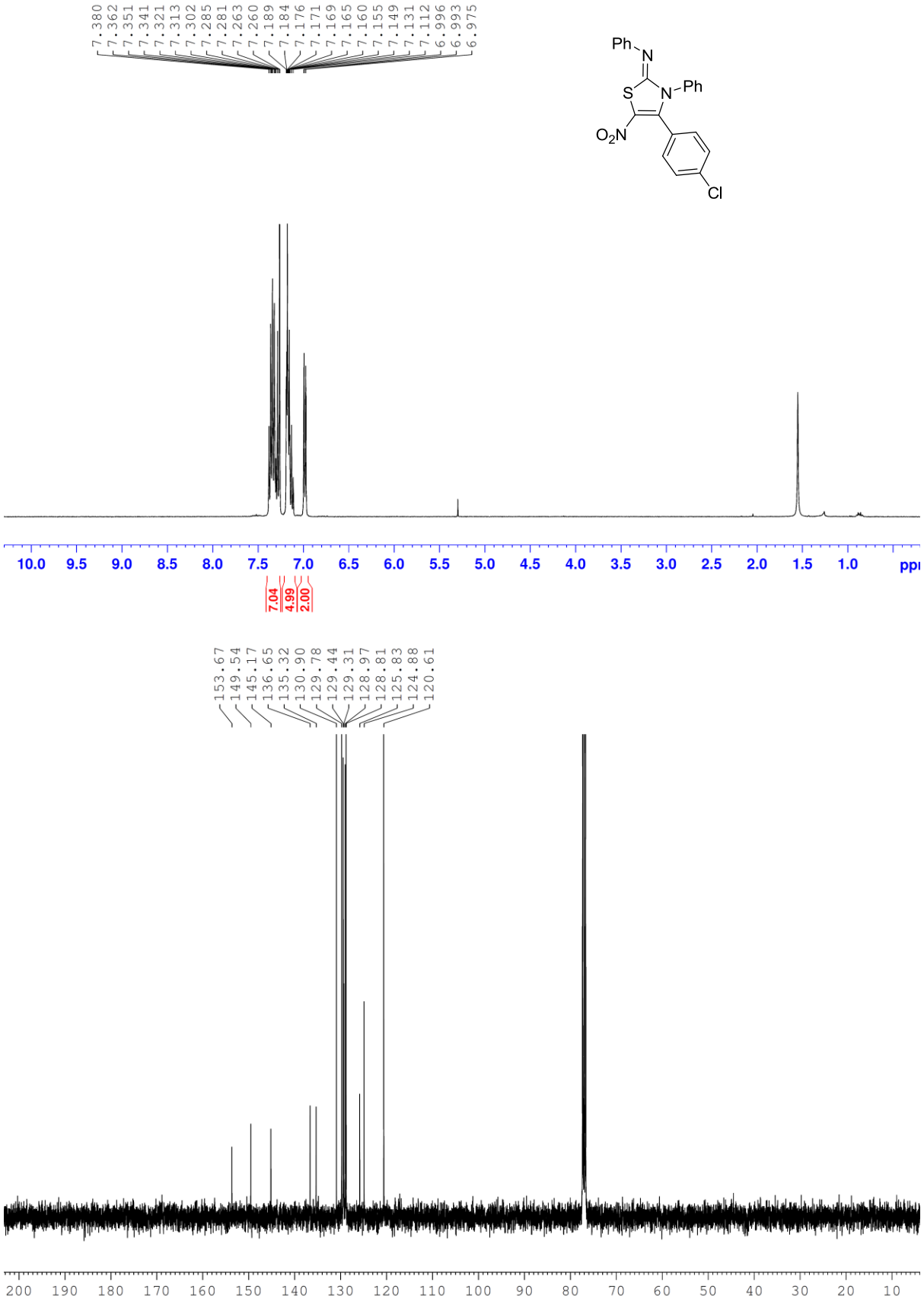
^{1}H and ^{13}C NMR of compound 1.68b



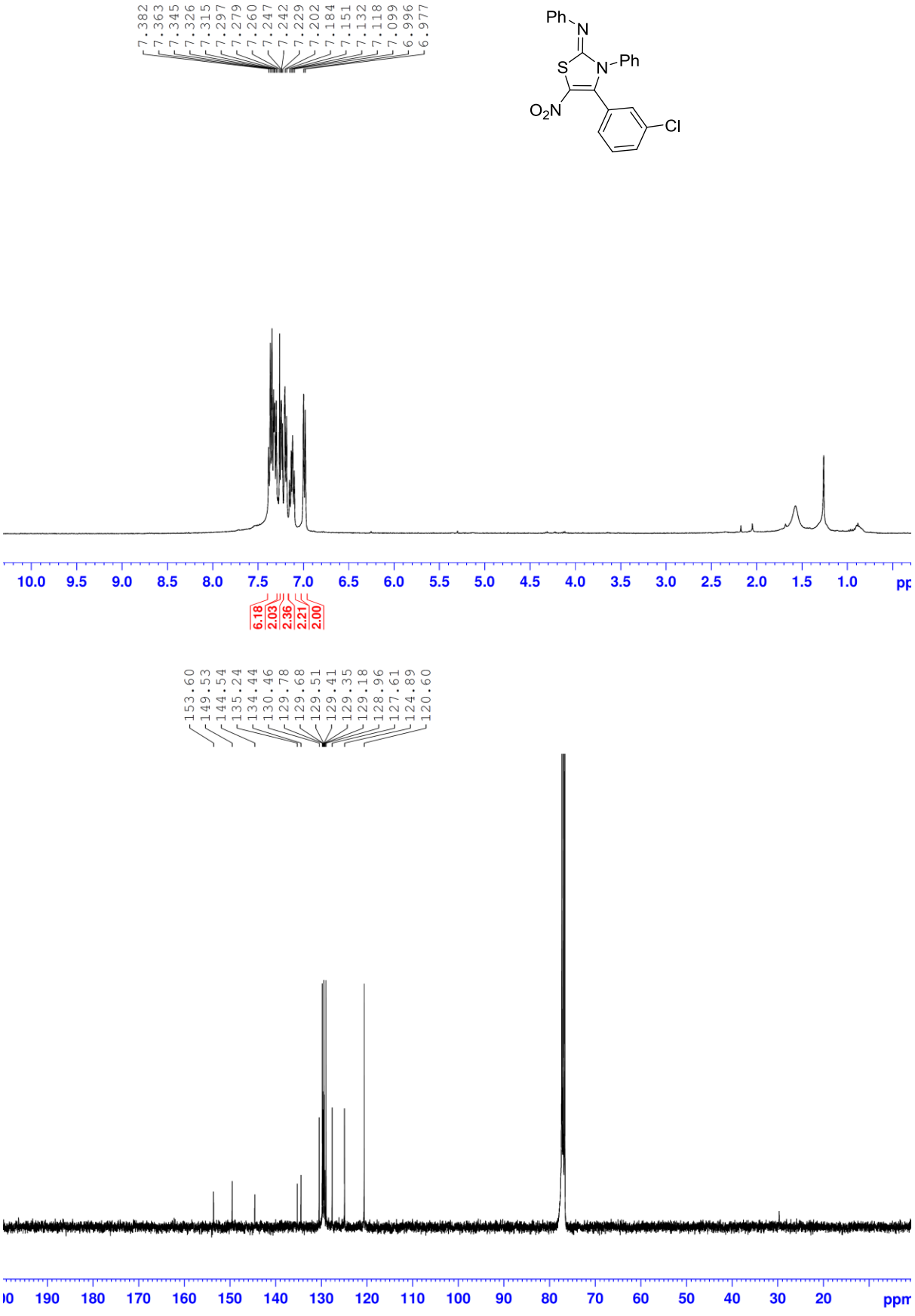
^{1}H and ^{13}C NMR of compound 1.68c



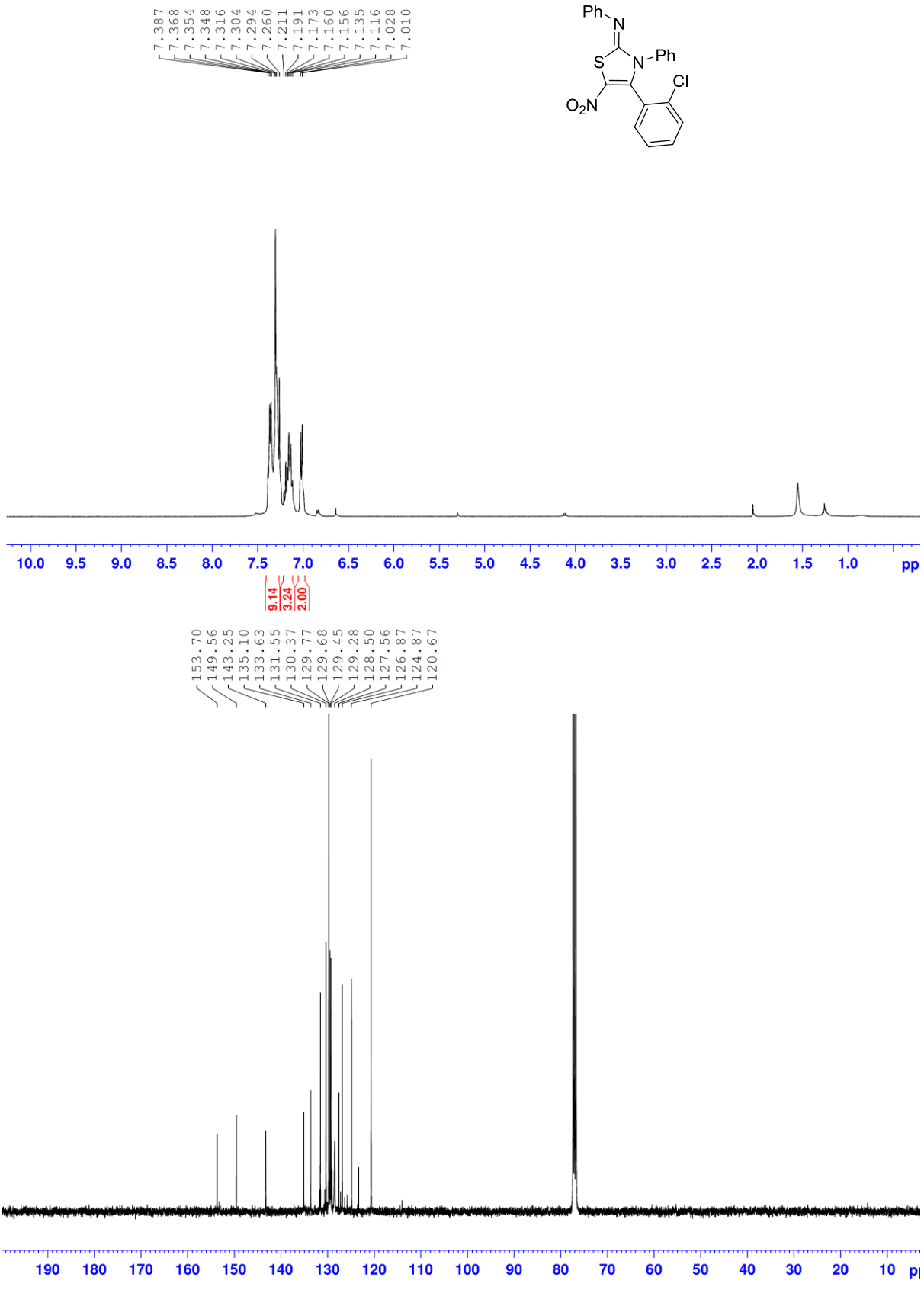
^{1}H and ^{13}C NMR of compound 1.68d



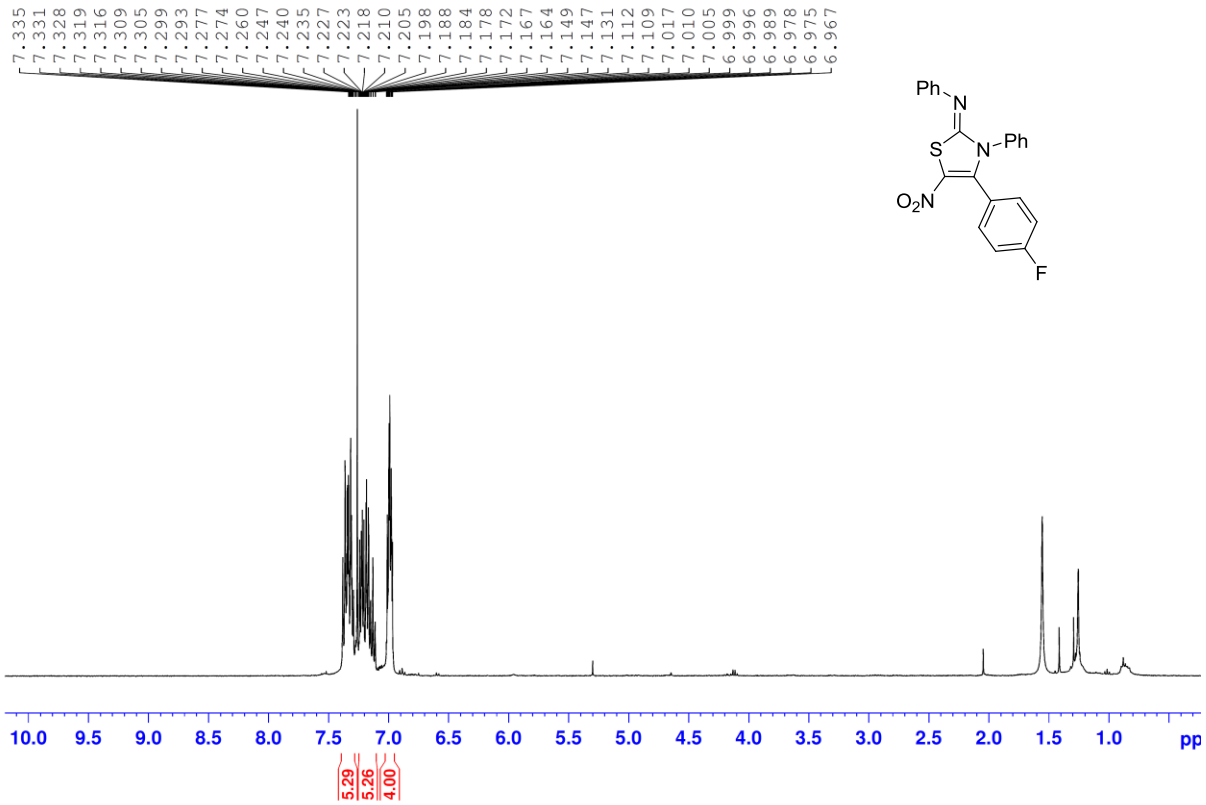
^{1}H and ^{13}C NMR of compound 1.68e

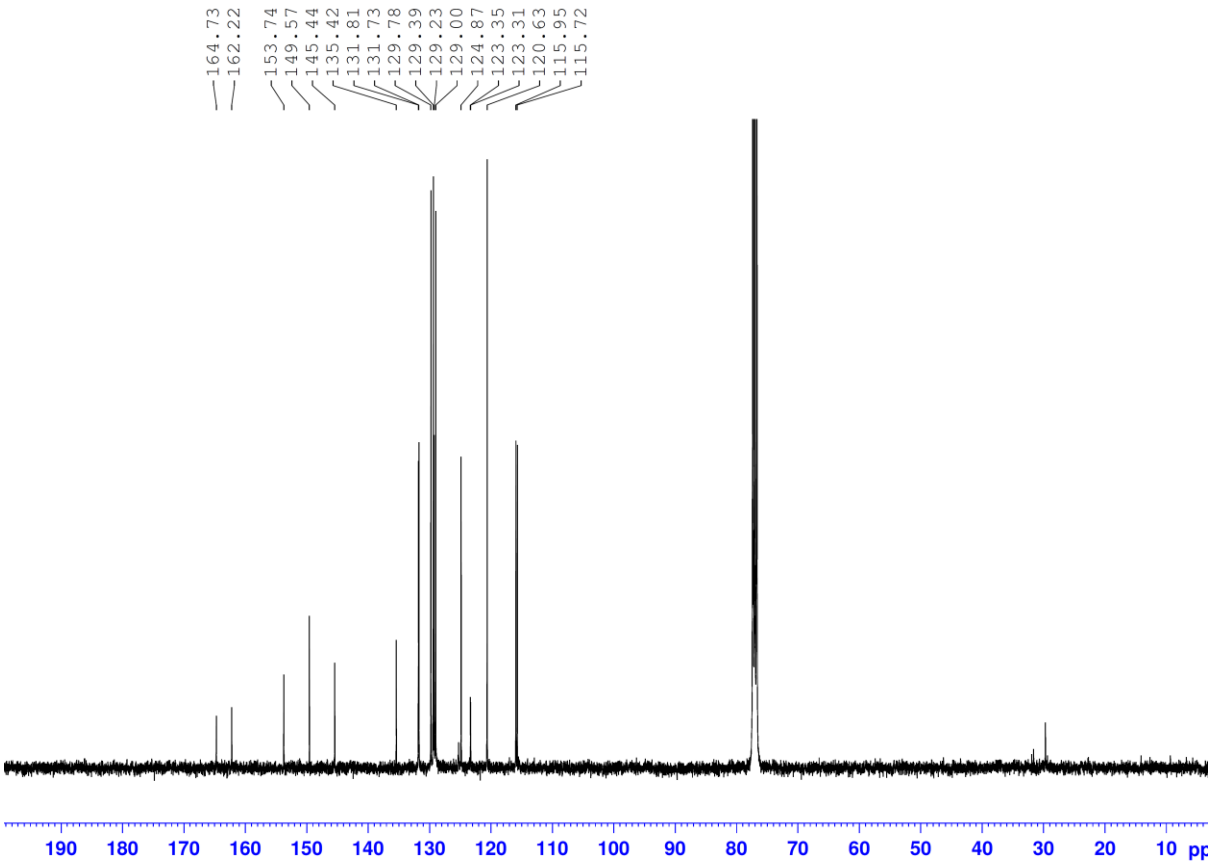


^{1}H and ^{13}C NMR of compound 1.68f

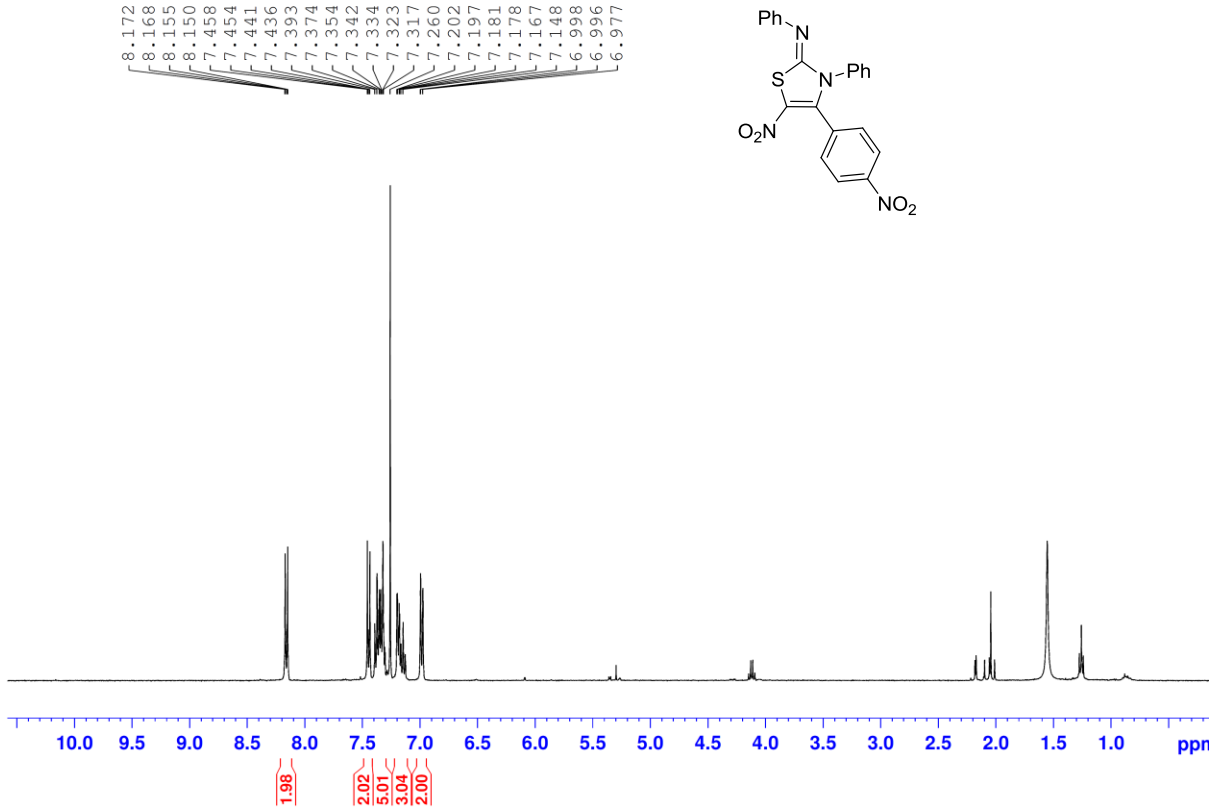


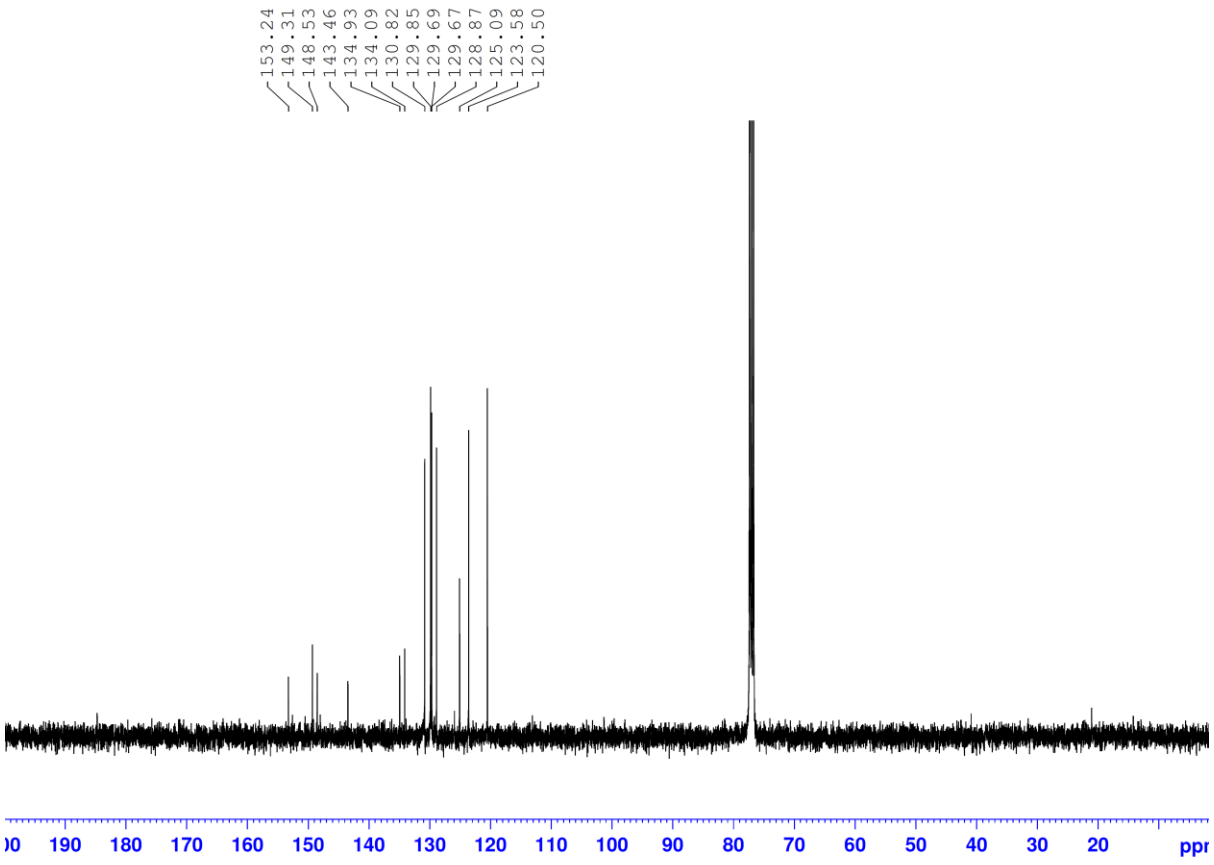
^{1}H and ^{13}C NMR of compound 1.68g



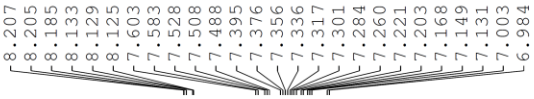


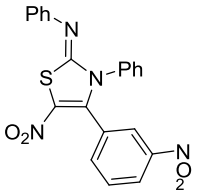
^{1}H and ^{13}C NMR of compound 1.68h

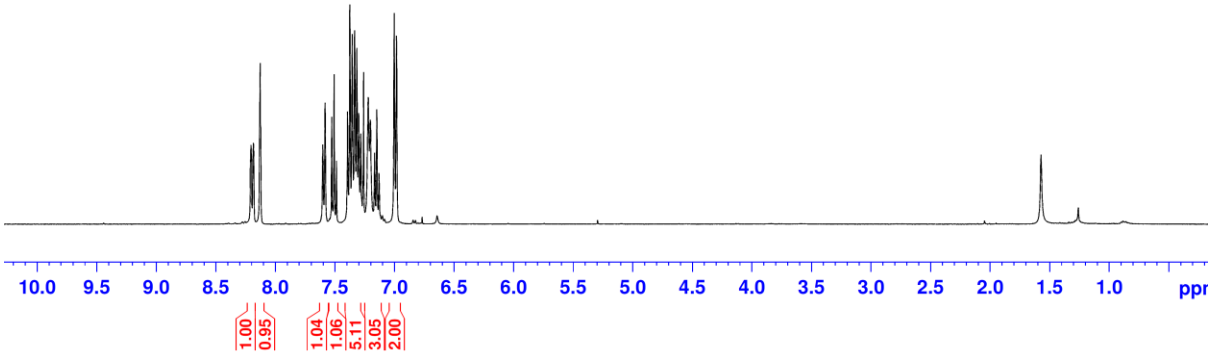


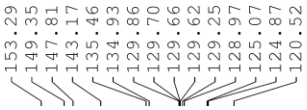


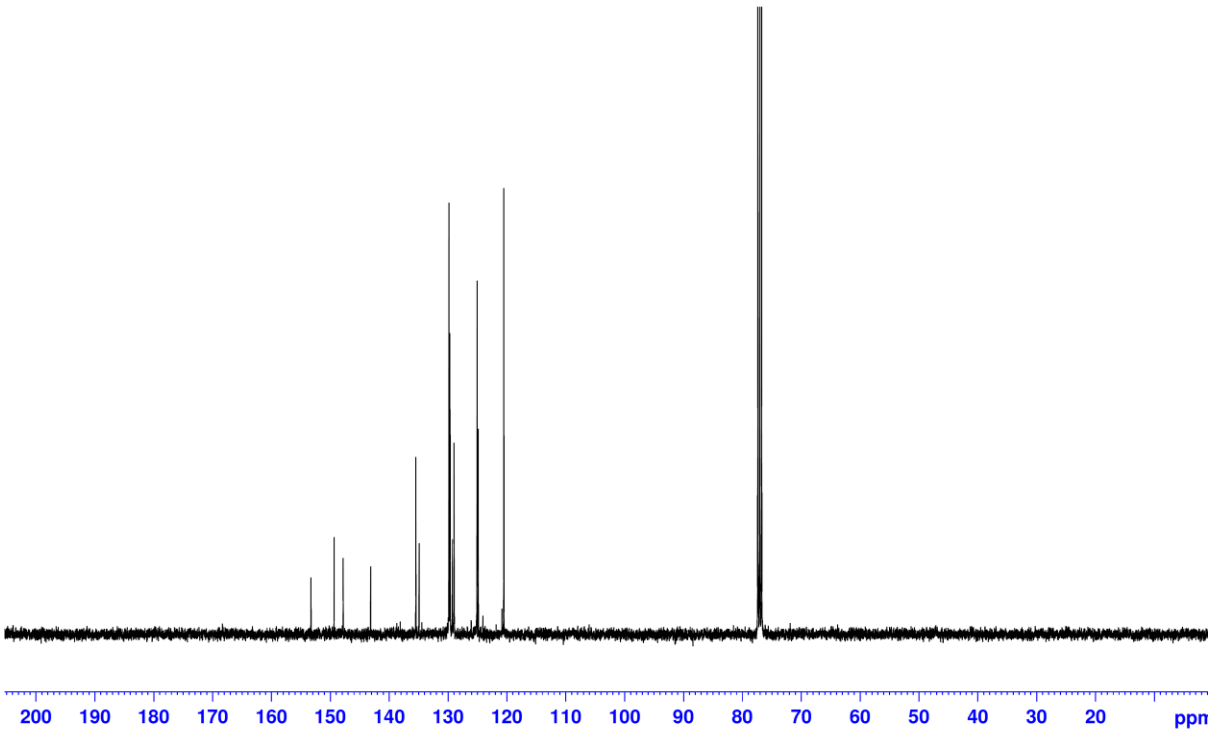
^{1}H and ^{13}C NMR of compound 1.68i



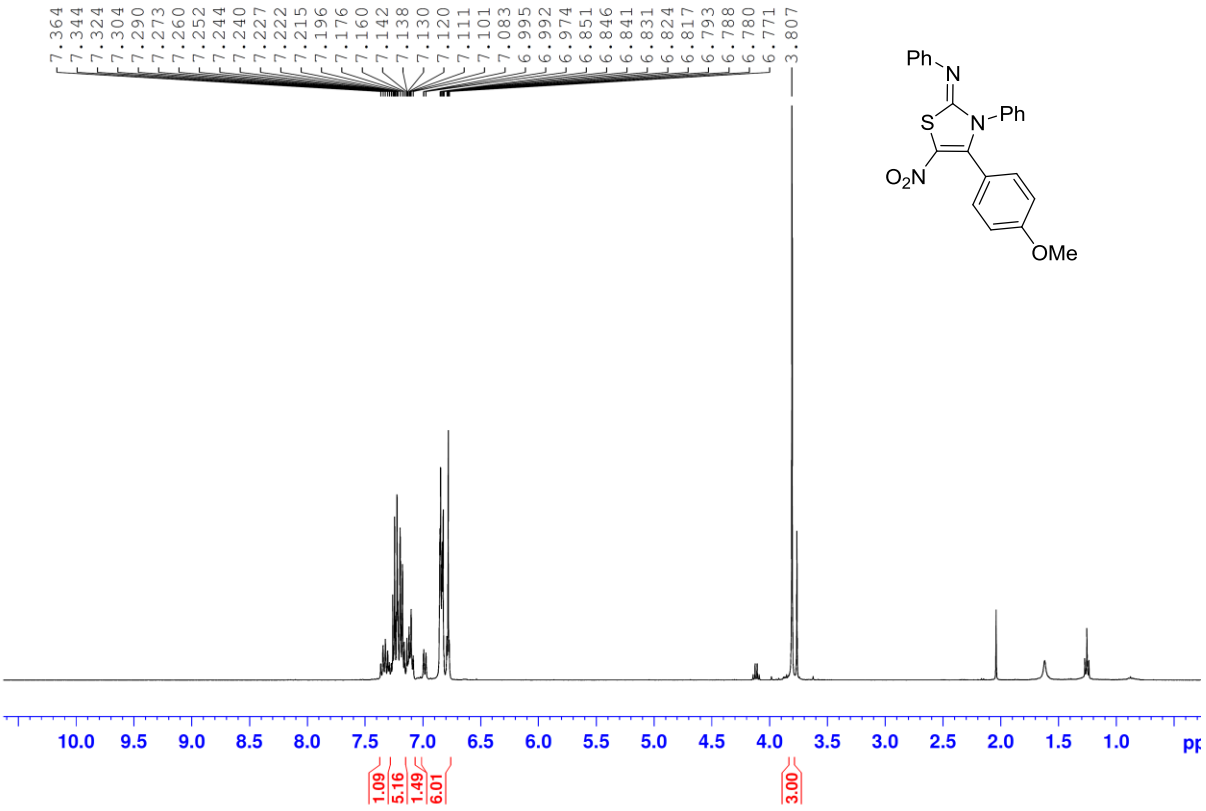


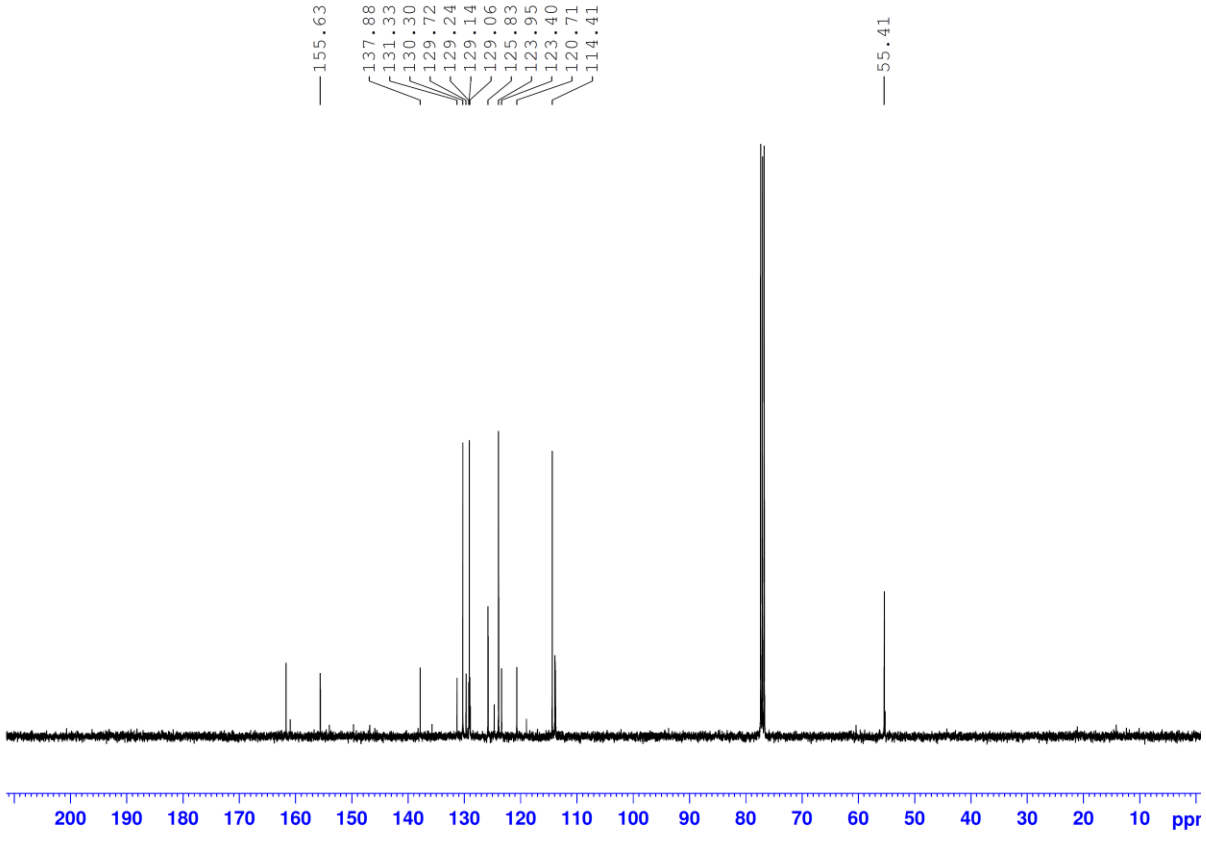




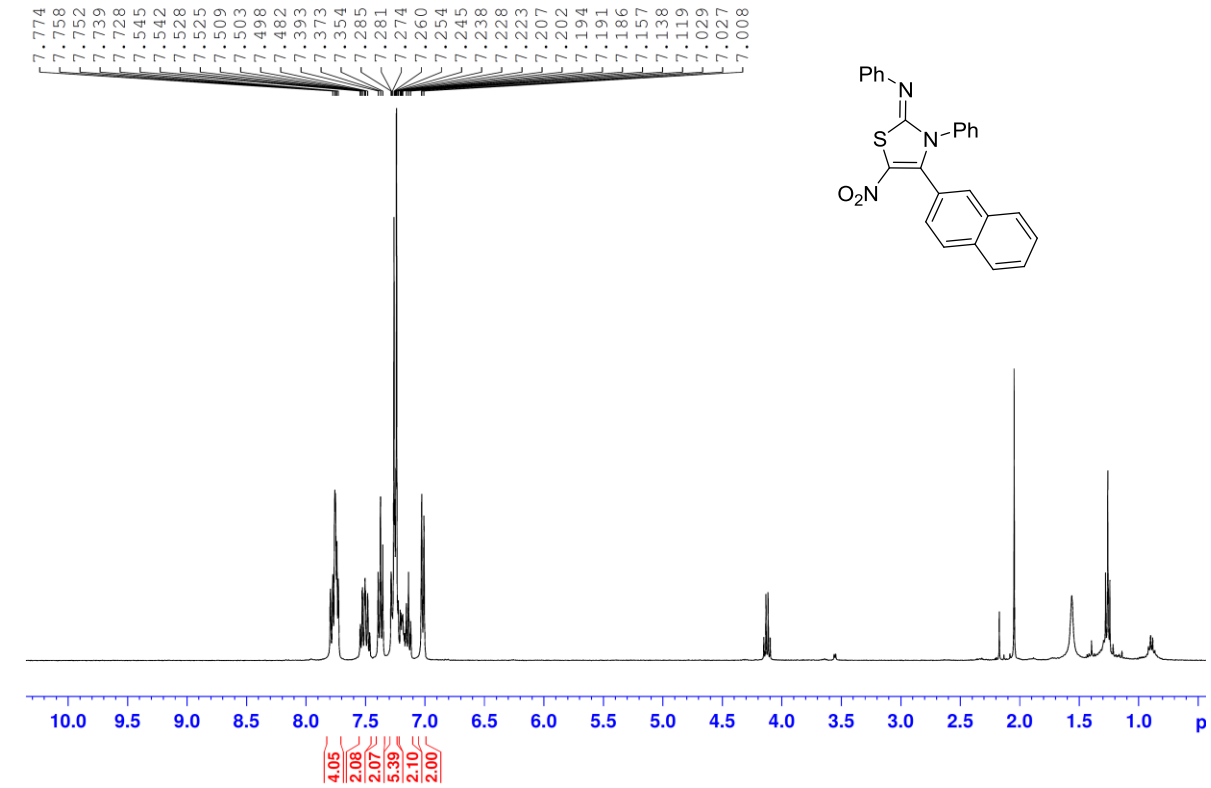


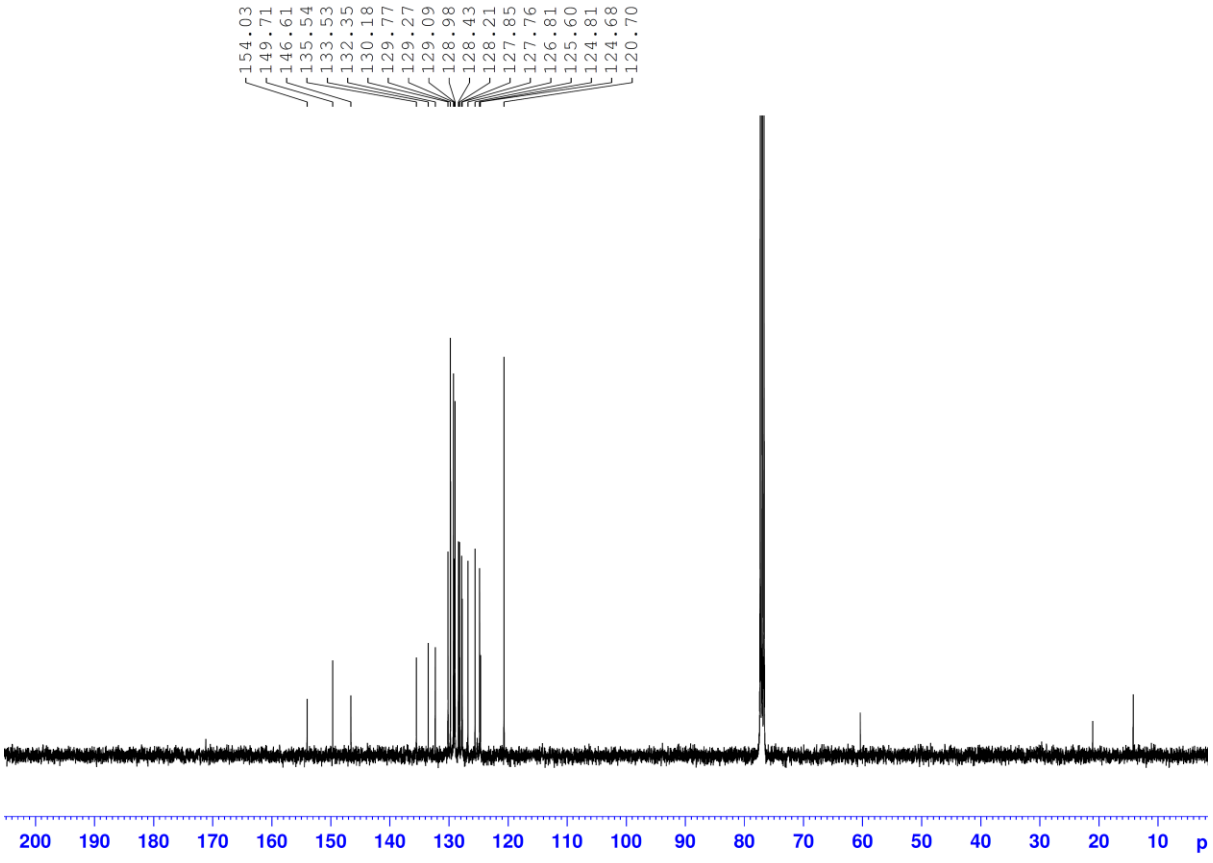
^{1}H and ^{13}C NMR of compound 1.68j





^{1}H and ^{13}C NMR of compound 1.68k





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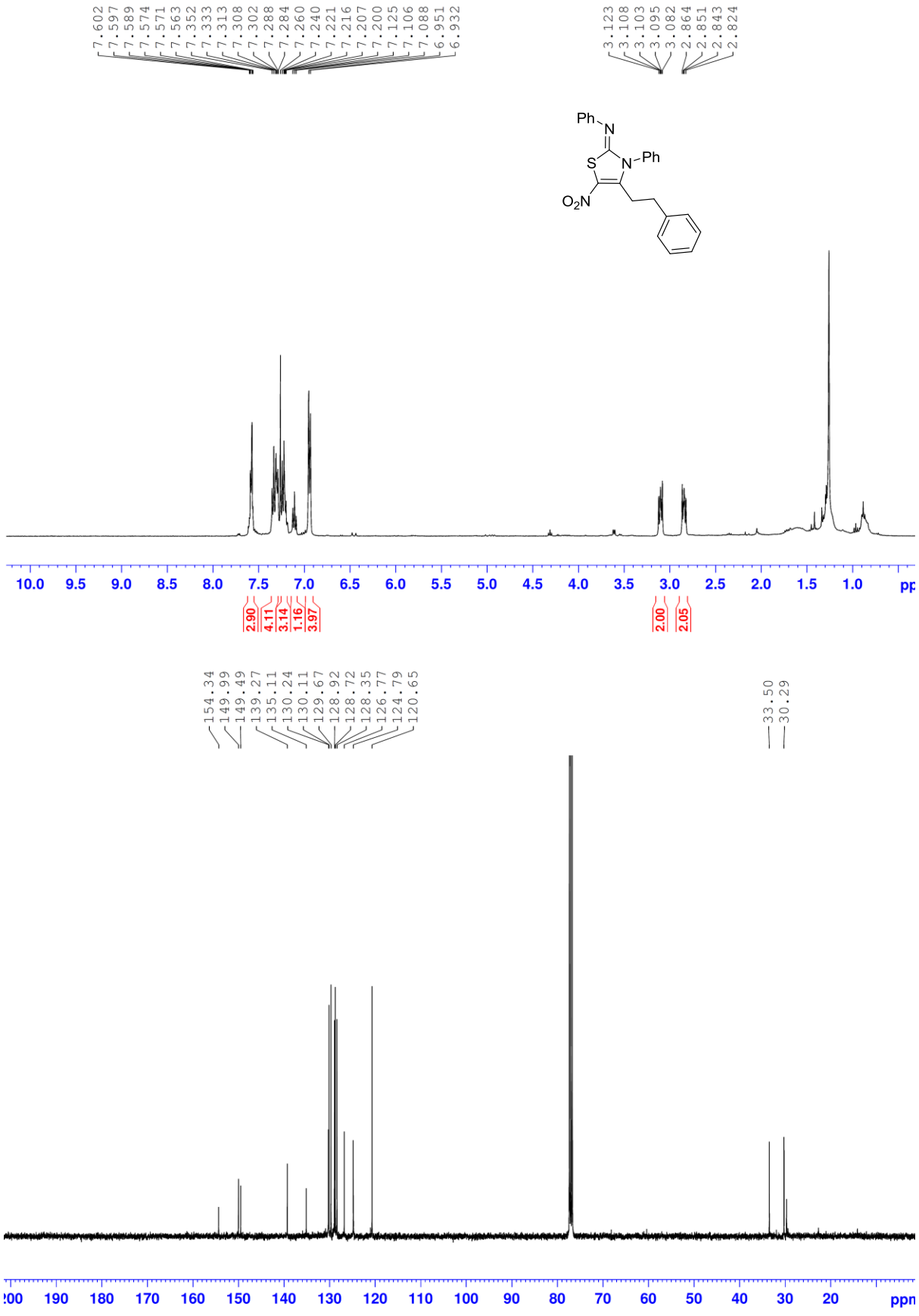

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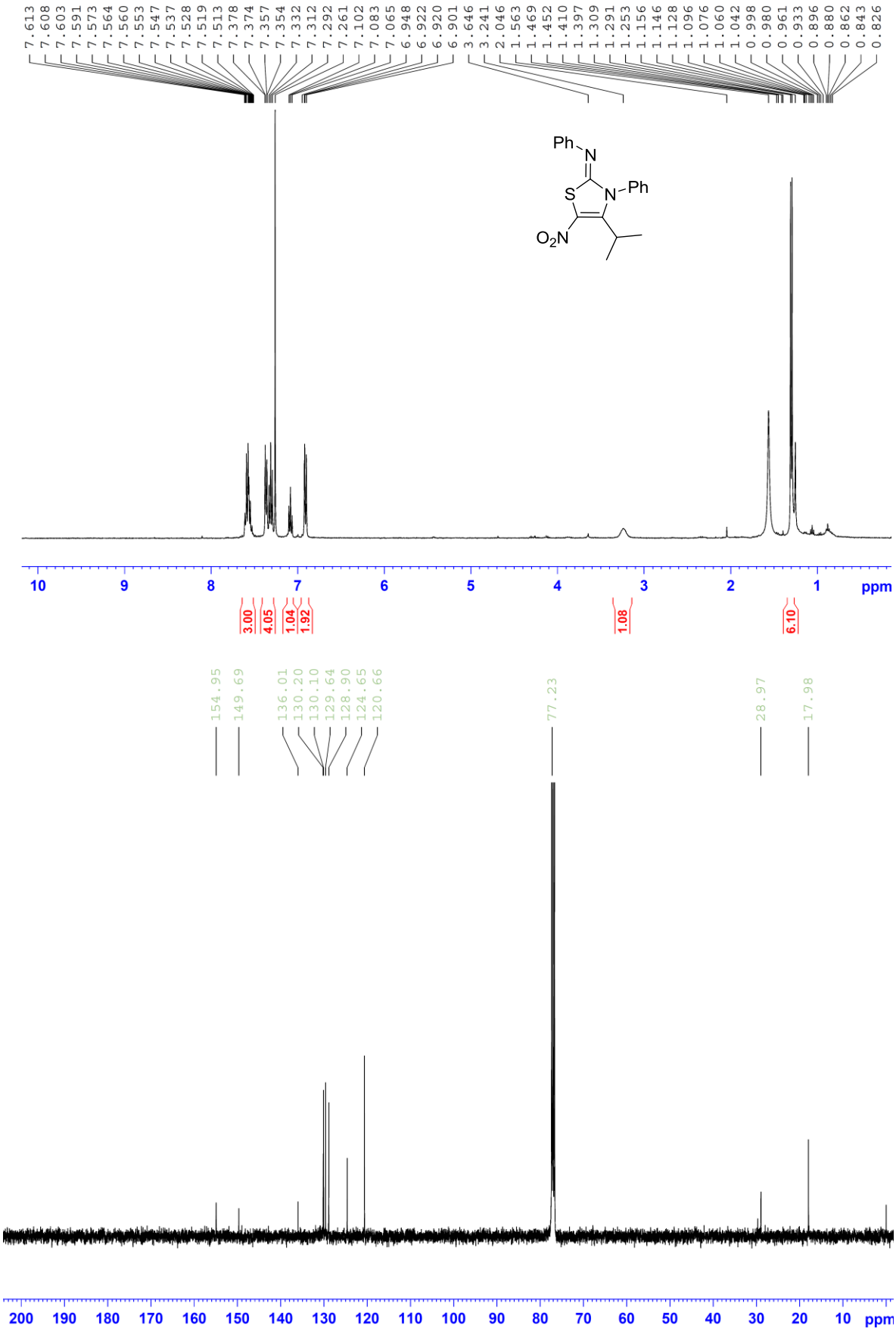
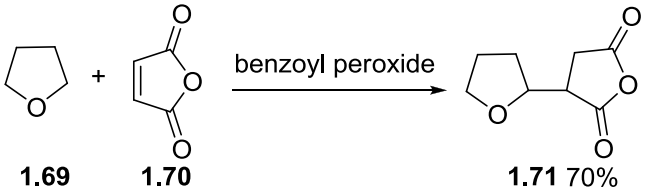


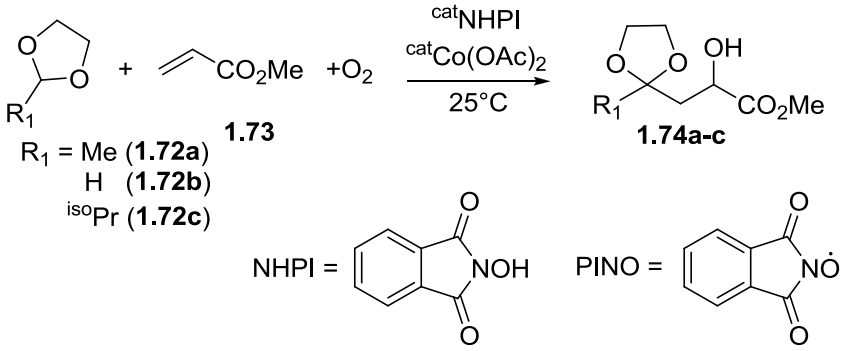
1.3 Cascade Reactions Initiated by Radical Addition of Tetrahydrofuran to β-Bromo-β-nitrostyrenes

1.3.1 Introduction

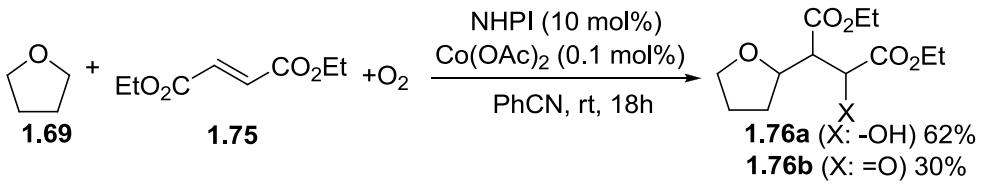
The addition of carbon radicals to alkenes are important tools of forming C−C bonds in organic synthesis.[20] Among numerous reports, one interesting example is the C−C bond formation at the otherwise unreactive *α*-C−H position of cyclic ethers by the addition of *α*-ethereal carbon radicals to alkenes, which provides rapid access to *α*-substituted cyclic ethers, the common moieties of bioactive molecules. A wide variety of methods have appeared for the generation of α-ethereal carbon radicals, usually mediated by initiators such as peroxides, AIBN or Et_3B in heating or light irradiation conditions. Previous literatures reported the addition of ether radicals to substituted alkenes like *α*,*β*-unsaturated carbonyl compounds[21] and *α*,*β*-unsaturated sulfonyl compounds[22]. The reaction of tetrahydrofuran with maleic anhydride in the presence of benzoyl peroxide was found to give a 70% yield of (tetrahydro-2-furyl)-succinic anhydride. [21e] (Scheme 1.21) In another case, the reaction of 2-methyl-1,3-dioxolane with methyl acrylate under dioxygen atmosphere in the presence of catalytic amounts of *N*-hydroxyphthalimide (NHPI) and $Co(OAc)_2$ produced the *β*-oxycarbonyl compounds in 81% yield. [21d] (Scheme 1.22) Similarly, the treatment of electron-deficient alkenes with ethers and dioxygen in the presence of NHPI and $Co(OAc)_2$ produced the corresponding adducts in which oxygen is incorporated into the alkenes in good yields. [21b] (Scheme 1.23) Photosensitized hydrogen abstraction from 2-alkyl-1,3-dioxolanes by benzophenones gave 1,3-dioxolan-2-yl-radicals which were trapped by α,β-unsaturated ketones yielding monoprotected 1,4-diketones. [21c] (Scheme 1.24) Futhermore, the conjugate addition of ether or acetal radicals generated by dimethylzinc-air with alkylidenemalonates afforded the corresponding adducts in high yields. [21a] (Scheme 1.25)



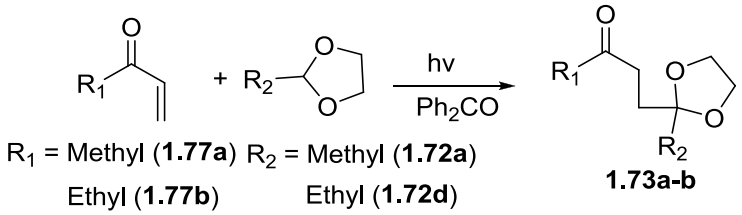
Scheme 1.21 Free radical addition of tetrahydrofuran to maleic anhydride



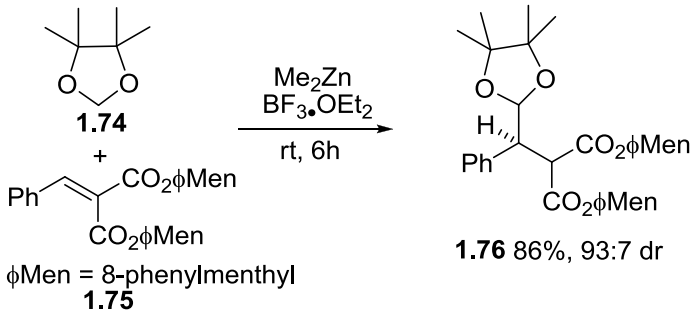
Scheme 1.22 NHPI catalyzed radical addition of 1,3-dioxolanes and molecular oxygen to alkenes



Scheme 1.23 NHPI catalyzed radical addition of ethers and molecular oxygen to alkenes



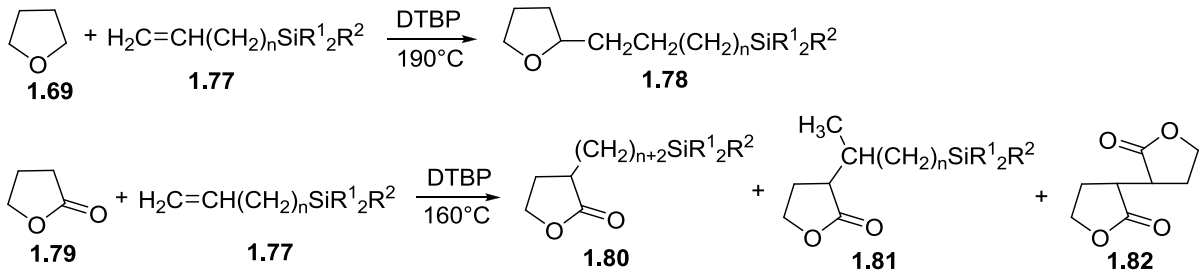
Scheme 1.24 Synthesis of monoprotected 1,4-diketones by alkylation of enones with 2-substituted-1,3-dioxolanes



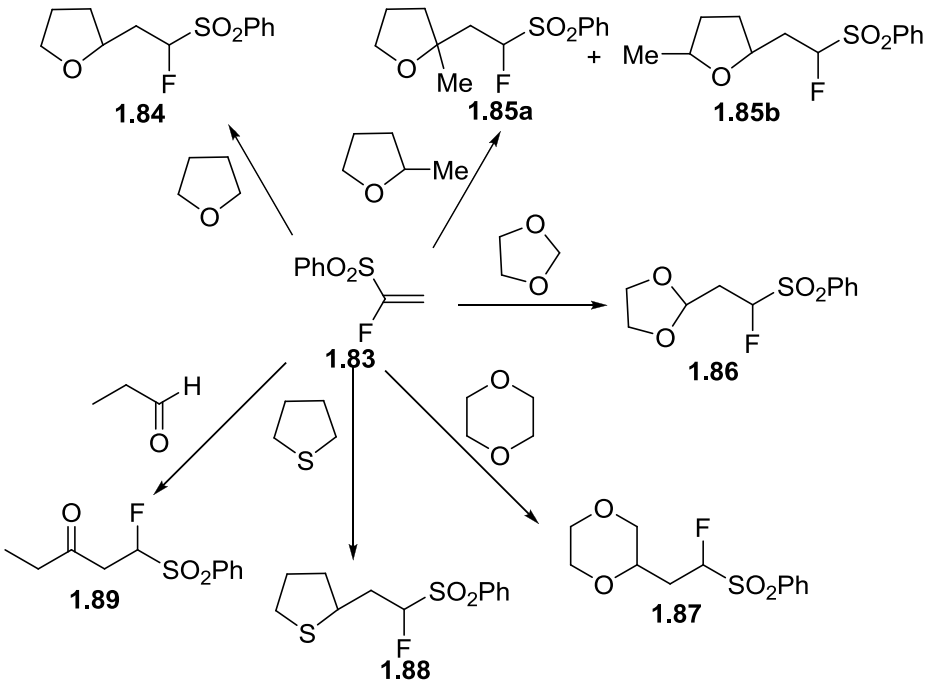
Scheme 1.25 Dimethylzinc mediated conjugate addition of ether and acetal radicals to alkylidenemalonates

When di(t-butyl) peroxide (DTBP) was used as initiator, *β*-(silylethyl)- and γ-(silylpropyl)-tetrahydrofurans and tetrahydro-2-furanones containing alkyl and phenyl groups at the Si

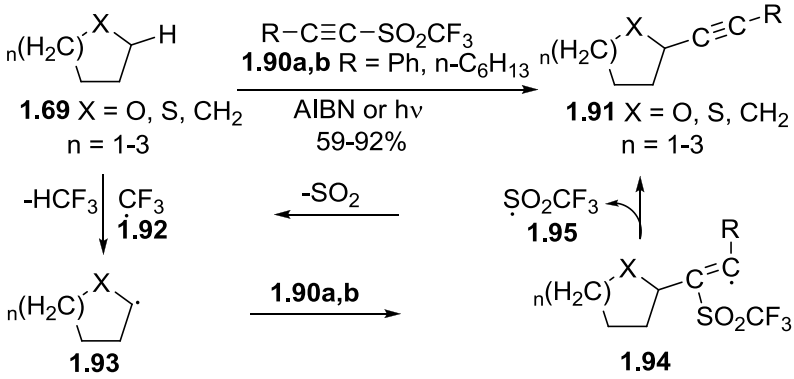
atom were obtained by the reactions of tetrahydrofuran and tetrahydro-2-furanone with vinyl and allylsilanes.[22g] (Scheme 1.26) 1-Fluoro-1-(phenylsulfonyl)ethylene was synthesized and its utility for the synthesis of fluorinated tetrahydrofurans and dioxanes was investigated. 1-Fluoro-1-(phenylsulfonyl)ethylene readily reacted with α-oxyradicals to provide 1-fluoro-1-(phenylsulfonyl) alkanes in good yield.[22f] (Scheme 1.27) Besides the monofluoroethyl-substituted tetrahydrofuran and dioxanes, the preparation of the protected aldehydes and ketones demonstrated the utility of this reaction for the preparation of monofluorinated intermediates. Fuchs et al reported the reaction of ethers, sulfides, hydrocarbons with acetylenic triflones such as **1.90a, 1.90b** provides facile access to substituted alkynes **1.91**.[22e] (Scheme 1.28) The reaction proceeded via radical C-H abstraction by the electrophilic trifluoromethyl radical **1.92** in a process involving addition of alkyl radical **1.93** to the α-carbon of the acetylenic triflone **1.90** followed by elimination of the vinyl radical **1.94** to alkyne **1.91** and trifluoromethylsulfonyl radical **1.95**. Fragmentation of **1.95** to sulfur dioxide and the trifluoromethyl radical **1.92** propagates the chain. The C-H functionalization protocol could be extended to the domain of olefins. The reaction of THF and cyclohexane with the vinyl triflone **1.96** and dienyl triflone **1.98** provide direct access to C-H functionalized olefins **1.97** and dienes **1.99**.[22d] (Scheme 1.29) Aryl and alkyl β-heteroatom-trisubstituted vinyl triflones reacted with THF and cyclohexane to undergo trifluoromethyl radical-mediated C-H functionalization reaction to afford *Z* and *E* olefins. Most reaction proceeded with both high yields and high stereospecificity.[22c] (Scheme 1.30) TIPS-substituted acetylenic triflones extended the versatility of the trifluoromethyl radical mediated C-H alkynylation reaction.[22b] (Scheme 1.31) Alkynes bearing propargylic oxygen functionality cannot be prepared, but silyl ethers in remote positions may be carried through the reaction. Furthermore, allylation of C-H bonds was realized by allylic triflones.[22a] (Scheme 1.32) Ethers and hydrocarbons were good substrates in the reaction with **1.107**.



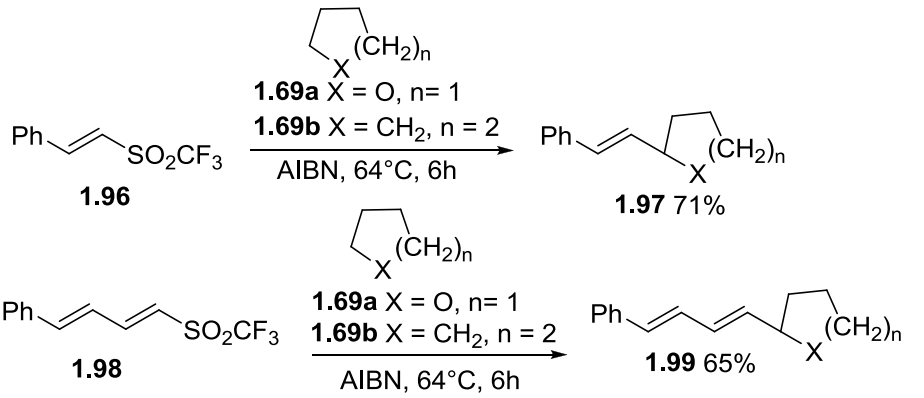
Scheme 1.26 Radical addition of tetrahydrofuran and tetrahydro-2-furanone to alkenylsilanes



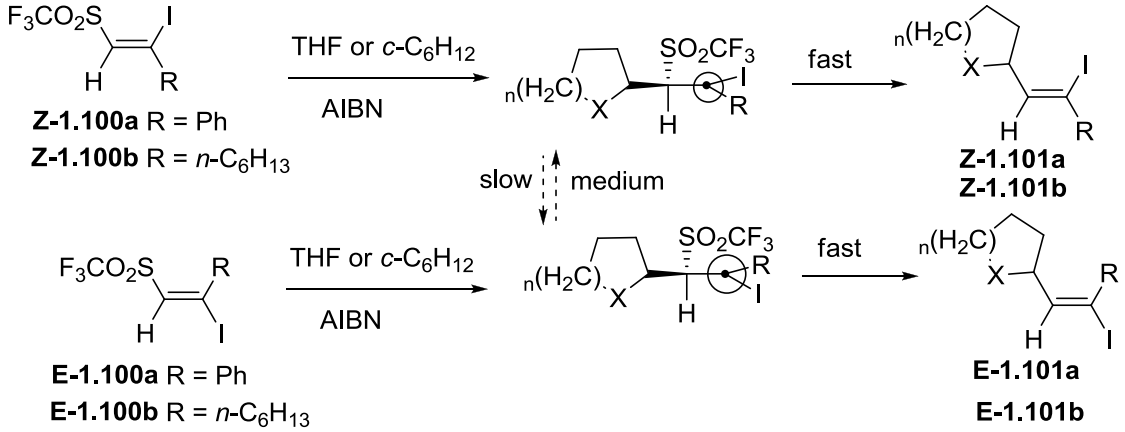
Scheme 1.27 Addition of *α*-oxyradicals to 1-fluoro-1-(phenylsulfonyl)ethylene



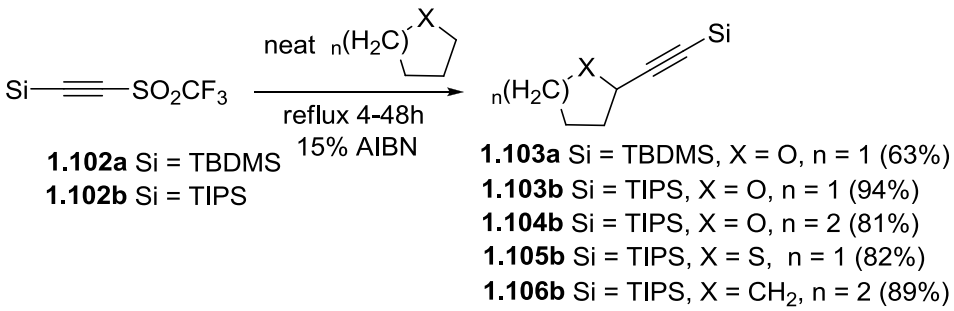
Scheme 1.28 Alkynylation of C-H bonds via reaction with acetylenic triflones



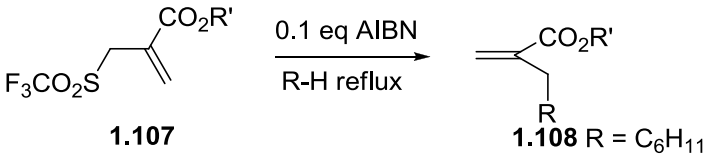
Scheme 1.29 Alkenylation of C-H bonds via reaction with vinyl and dienyl triflones



Scheme 1.30 Alkenylation of C-H bonds via reaction with trisubstituted vinyl triflones



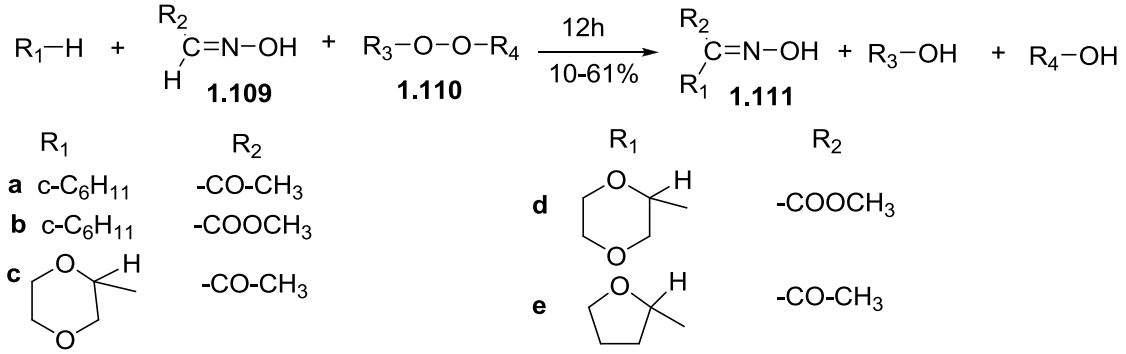
Scheme 1.31 Alkynylation of C-H bonds via reaction with TIPS-substituted acetylenic triflones



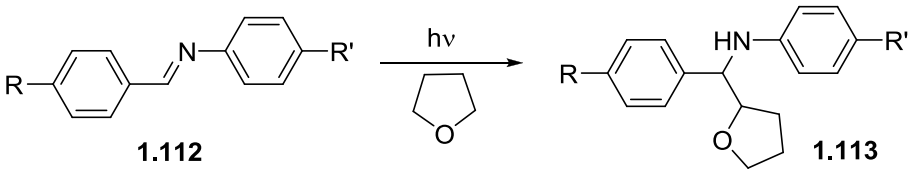
Scheme 1.32 Allylation of C-H bonds using allylic triflones

Additions of ether radicals to C=N bonds such as imines[23a-c] and azirines[23d] and C=O bonds of aldehydes[24] have also been reported. Aldoximes with the radical source **1.110** in the hydrogen-donor solvents such as cycloalkanes or ethers were found to afford ketoximes.[23f] (Scheme 1.33) Photoirradiation of benzalaniline in THF afforded a 1: 1 THF adduct.[23e]

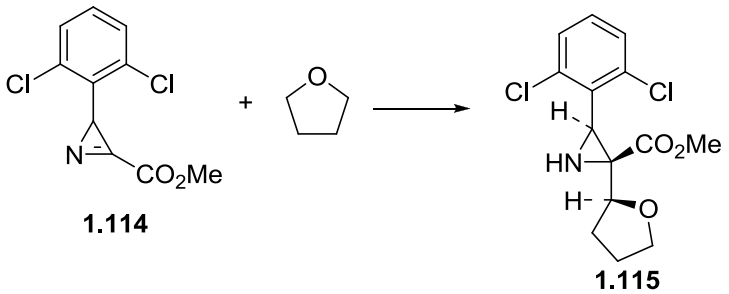
(Scheme 1.34) THF reacted readily with azirine **1.114** to give aziridine **1.115** with high stereoselectivity of the addition (only one isomer was detected).[23d] (Scheme 1.35) Tomioka et al reported a radical initiated three component reaction of aldehyde, arylamines and THF to give the THF adducts of imines with Me_2Zn and adducts of aldehyde with Et_3B.[23c] (Scheme 1.36) Asymmetric radical addition of ethers to enantiopure *N*-*p*-toluenesulfinyl aldimines to give sulfonamide products in enantiomerically enriched form was achieved.[23b] (Scheme 1.37) The reaction of THF radical with *α,β*-unsaturated *N*-tosyl aldimines was demonstrated to proceed preferentially in a conjugate addition manner to give 2-(3-hydroxyalkyl)- or 2-(3-aminoalkyl)tetrahydrofurans in good yield.[23a] (Scheme 1.38)



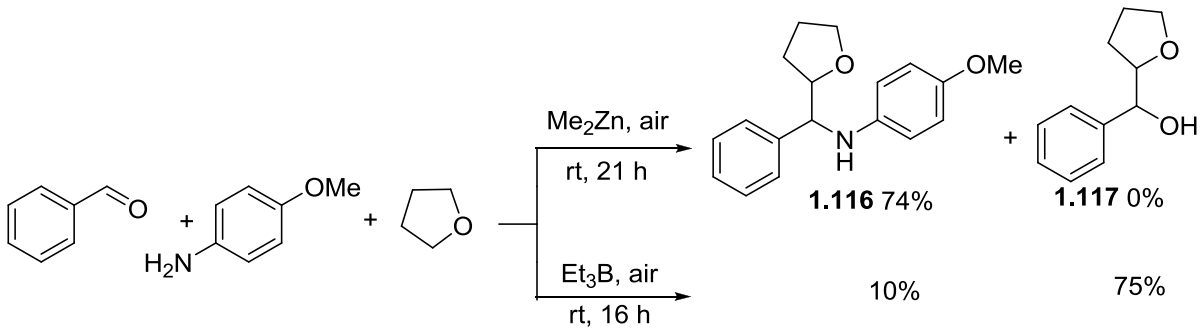
Scheme 1.33 C-alkylation of aldoximes



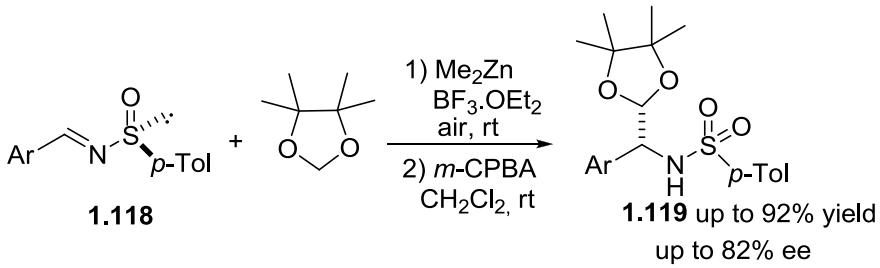
Scheme 1.34 Addition of THF to benzalaniline



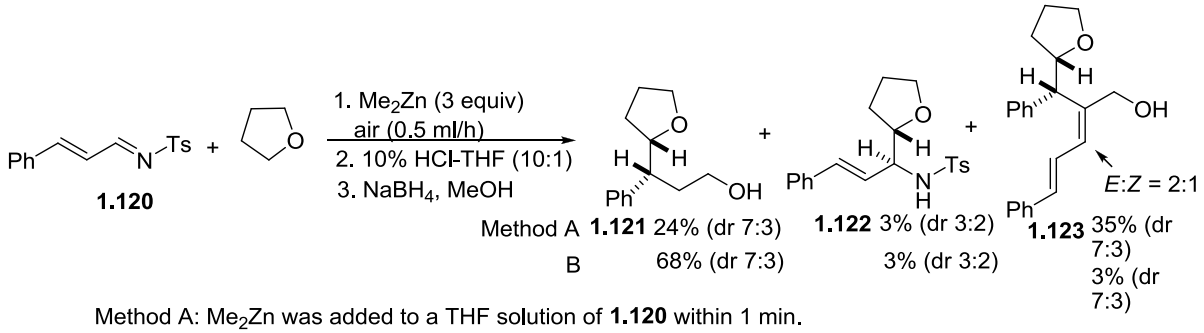
Scheme 1.35 Addition of THF to C=N bond of azirines



Scheme 1.36 Addition of THF radical to aldehyde and aldimine



Scheme 1.37 Radical addition of ethers to *N*-*p*-toluenesulfinyl aldimines

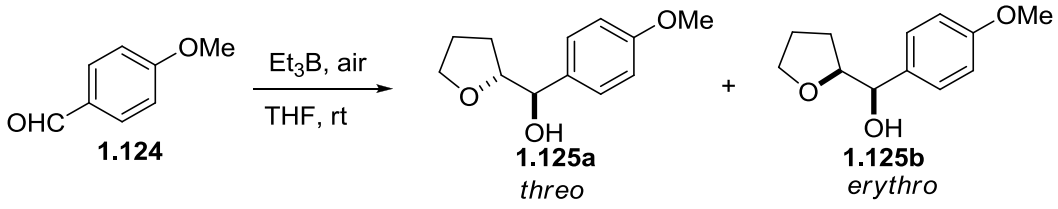


Method A: Me_2Zn was added to a THF solution of **1.120** within 1 min.

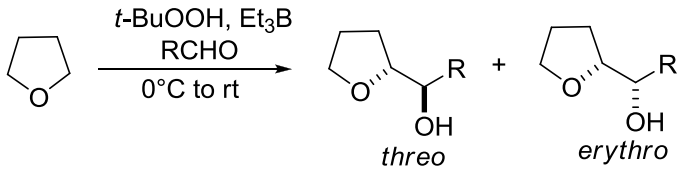
Method B: A THF solution of **1.120** was added to a THF solution of Me_2Zn over 6h

Scheme 1.38 Conjugate addition of THF radical to α,β-unsaturated *N*-tosyl imines

The THF radical was also found to react with aldehyde *threo*-selectively to afford *α*-substituted tetrahydrofuran-2-methanols. [24a,24b] Different reagent systems were reported for the promotion of this reaction, which including triethylborane/air system and the combination of triethylborane and *tert*-butyl hydroperoxide. (Scheme 1.39 and 1.40)



Scheme 1.39 Synthesis of tetrahydrofuran-2-methanols through addition of THF to aldehydes



Scheme 1.40 Addition of THF to aldehyde in the presence of triethylborane and *tert*-butyl hydroperoxide

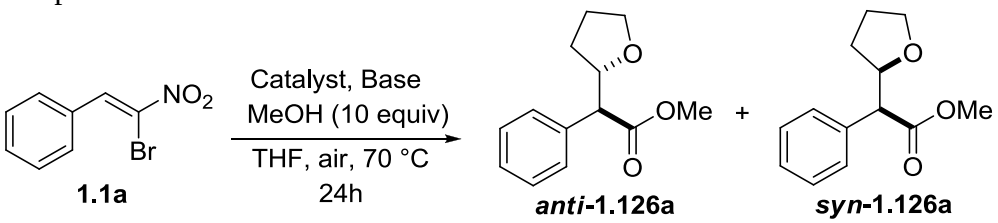
In summary, the addition of ether radicals to all these substrates showed the versatile reactivity of α-ethereal radicals. Inspired by these examples (especially by Scheme 1.22 and 1.23), we were interested to investigate the prospect of addition of ether radicals to the specially active alkene, the β-bromo-β-nitrostyrene. Here, we will describe these discoveries.

1.3.2 Results and Discussion

Here, we described a THF radical addition to the active alkene, the *β*-bromo-*β*-nitrostyrene, in the presence of air to generate the dioxygen incorporated adduct. Due to the versatile reactivity of *β*-bromo-*β*-nitrostyrene, we were interested in investigating the prospect of addition of ether radicals to the *β*-bromo-*β*-nitrostyrene. In an initial attempt, we tested the addition of THF to the *β*-bromo-*β*-nitrostyrene with triethylborane-air[23b,24a] as radical initiator, but there was no desired THF adduct products. Other radical initiators such as dimethylzinc-air,[23b] *N*-hydroxyphthalimide-$Co(OAc)_2$-dioxygen,[21b] AIBN (reflux),[22a,22b] benzoyl peroxide (reflux),[22c] di-*tert*-butyl peroxide (heating)[24b] still did not give any desired THF adduct products. As transition metals such as Mn(III), Ce(IV), Fe(III), V(V), Cu(II), Co(II)[25] and Ag(I)[26] were often used in oxidative radical formations, the possibilities of these catalytic species were explored. We found that the treatment of *β*-bromo-*β*-nitrostyrene with $AgNO_3$ and K_2CO_3 in THF-MeOH solution at reflux in air gave the methyl ester **1.126a**[27] in 50% yield (Table 1.3, entry 1) while other metals didn't produce such results. During this, AgBr was precipitated from the reaction solution and we speculate that it facilitates the removal of the bromide in the mixture and catalyses the reaction to some extent. Other solvents such as toluene, DCM, CH_3CN containing THF-MeOH were not so effective for this reaction. Further we examined the efficacy of various silver salts (Table 1.3). It showed that most of the silver salts could catalyze the reaction and AgOTf give the best yield (Table 1.3, entry 2). Besides K_2CO_3, a series of base were also screened for this reaction. When Na_2CO_3, Cs_2CO_3, $KHCO_3$, KOH were used, the product could also be obtained albeit in a lower yield (Table 1.3, entries 10-13). When DBU, Et_3N were used, no desired products were formed (Table 1.3, entries 14-15). The decreased silver(I) salts loading resulted in a slightly lower yield of products and a longer reaction time (Table 1.3, entry 16), while increased catalyst loading led to no higher yield (Table 1.3, entry 17). No obvious differences were observed in

the reaction when increasing the amount of base (Table 1.3, entry 18). The reaction time under a pure O_2 atmosphere instead of air was shorter, but it led to a decreased yield of product (Table 1.3, entry 19). No reaction was detected in the absence of either silver catalyst or base or oxygen in the reaction system. Since the *β*-bromo-*β*-nitrostyrene was a mixture of *Z*- and *E*-isomer, it is explicable that the product was a pair of *syn*- and *anti*-isomer. Besides the THF, tetrahydropyran and cyclohexane were also tested for the reaction but there were no reaction for them.

Table 1.3 Optimization of the reaction conditions[a]



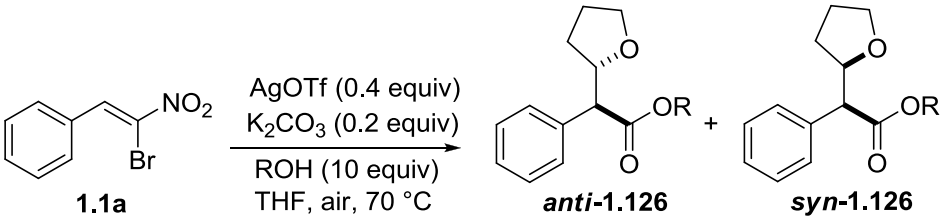
1.1a ***anti*-1.126a** ***syn*-1.126a**

entry	catalyst (equiv)	base (equiv)	yield[b] (%)	*anti*:*syn*[c]
1	$AgNO_3$ (0.4)	K_2CO_3 (0.2)	50	1.3:1
2	AgOTf (0.4)	K_2CO_3 (0.2)	58	1.2:1
3	$AgSbF_6$ (0.4)	K_2CO_3 (0.2)	52	1.2:1
4	$AgPF_6$ (0.4)	K_2CO_3 (0.2)	51	1.1:1
5	$AgBF_4$ (0.4)	K_2CO_3 (0.2)	34	1.4:1
6	AgOAc (0.4)	K_2CO_3 (0.2)	22	2.5:1
7[d]	Ag_2O (0.4)	K_2CO_3 (0.2)	trace	-
8[d]	Ag_2CO_3 (0.4)	K_2CO_3 (0.2)	trace	-
9	Silver *p*-toluene sulfonate	K_2CO_3 (0.2)	29	1.5:1
10	AgOTf (0.4)	Na_2CO_3 (0.2)	52	1.2:1
11	AgOTf (0.4)	Cs_2CO_3 (0.2)	54	1.3:1
12[d]	AgOTf (0.4)	$KHCO_3$ (0.2)	42	1.3:1
13	AgOTf (0.4)	KOH (0.2)	12	1.6:1
14[d]	AgOTf (0.4)	DBU (0.2)	n.r.[e]	-
15[d]	AgOTf (0.4)	Et_3N (0.2)	n.r.[e]	-
16[d]	AgOTf (0.2)	K_2CO_3 (0.2)	45	1.3:1
17	AgOTf (0.6)	K_2CO_3 (0.2)	42	1.2:1
18	AgOTf (0.4)	K_2CO_3 (1.0)	57	1.2:1
19[f]	AgOTf (0.4)	K_2CO_3 (0.2)	48	1.3:1

[a] Reactions were performed using 0.2 mmol of **1.1a**. [b] Isolated yield. [c] The ratios of *anti*:*syn* isomers were determined by the crude ^1H NMR spectra. [d] The reaction time was 48 hr. [e] No reaction. [f] The reaction was carried out in O_2 atmosphere and finished in 10 hr.

Based on these results, we examined the scope of the reaction by replacing methanol with different alcohols (Table 1.4). When ethanol was used the corresponding ethyl ester product could be obtained but in a much lower yield, while 1-propanol could give only 10% yield (Table 1.4, entries 2-3). And other alcohols could not afford the product.

Table 1.4 Radical reactions of *β*-bromo-*β*-nitrostyrene with various alcohols[a]

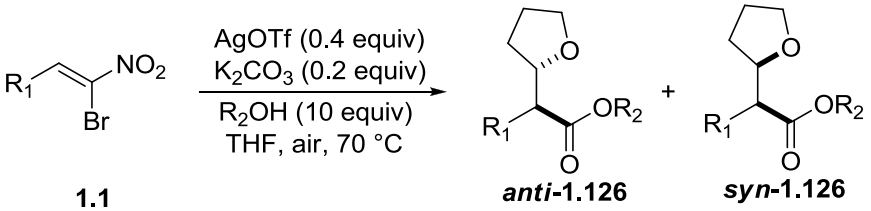


entry	ROH	T (h)	yield[b] (%)	*anti*:*syn*[c]
1	methanol	24	58	1.2:1
2	ethanol	48	39	1.5:1
3	1-propanol	48	10	2.2:1
4	2-propanol	48	trace	-
5	1-butanol	48	trace	-
6	*tert*-butanol	48	n.r.[d]	-

[a] Reactions were performed using 0.2 mmol of **1.1a**. [b] Isolated yield. [c] The ratios of *anti*:*syn* isomers were determined by the crude ^{1}H NMR spectra. [d] No reaction.

Next, we investigated the generality of this silver catalyzed radical reaction with different bromonitroalkenes. *β*-Bromo-*β*-nitrostyrene bearing electro-withdrawing groups such as - F, -Cl, -Br on the phenyl ring generally gave good yields (Table 1.5, entries 2−7), while substrates with -NO_2 group gave lower yields (Table 1.5, entries 8 and 9). When the substituent of the phenyl ring was changed to *p*-CH_2Br, it could give moderate yield (Table 1.5, entry 10). In cases of electron-donating substituents such as *p*-OMe on the phenyl ring or other aromatic systems with increased electron-density such as furan ring, there were no observed products (Table 1.5, entries 11 and 12). Lower yield was observed for the nonconjugated bromonitroalkene (Table 1.5, entry 13). There was no reaction when alkyl substituent was used (Table 1.5, entry 14). When ethanol was used instead of methanol, longer reaction times were required and the yields were decreased (Table 1.5, entries 15−19).

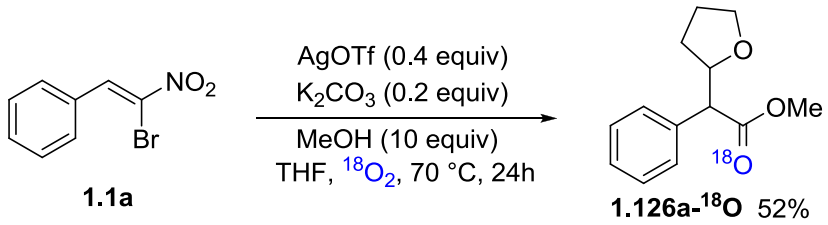
Table 1.5 Radical reactions of various *β*-bromo-*β*-nitrostyrenes[a]



entry	R_1	R_2	T (h)		yield[b] (%)	*anti*:*syn*[c]
1	Ph	Me	24	**1.126a**	58	1.2:1
2	4-BrC_6H_4	Me	24	**1.126b**	69	1.3:1
3	3-BrC_6H_4	Me	24	**1.126c**	62	1.5:1
4	4-ClC_6H_4	Me	24	**1.126d**	68	1.2:1
5	3-ClC_6H_4	Me	24	**1.126e**	61	1.3:1
6	2-ClC_6H_4	Me	24	**1.126f**	59	1.4:1
7	4-FC_6H_4	Me	24	**1.126g**	60	1.3:1
8	4-$NO_2C_6H_4$	Me	48	**1.126h**	15	1.8:1
9	3-$NO_2C_6H_4$	Me	48	**1.126i**	37	1.5:1
10	4-$CH_2BrC_6H_4$	Me	24	**1.126j**	50	1.2:1
11	4-$OMeC_6H_4$	Me	48	**1.126k**	trace	-
12	2-Furyl	Me	48	**1.126l**	trace	-
13	$PhCH_2CH_2$	Me	24	**1.126m**	35	1.5:1
14	$(CH_3)_2CH$	Me	48	**1.126n**	n.r.[d]	-
15	Ph	Et	48	**1.126o**	39	1.5:1
16	4-BrC_6H_4	Et	48	**1.126p**	45	1.6:1
17	3-BrC_6H_4	Et	48	**1.126q**	40	1.8:1
18	4-ClC_6H_4	Et	48	**1.126r**	42	1.6:1
19	4-FC_6H_4	Et	48	**1.126s**	40	1.5:1

[a] Reactions were performed in standard procedures (see Supporting information) using 0.5 mmol of **1.1**. [b] Isolated yield. [c] The ratios of *anti*:*syn* isomers were determined by the crude ^{1}H NMR spectra. [d] No reaction.

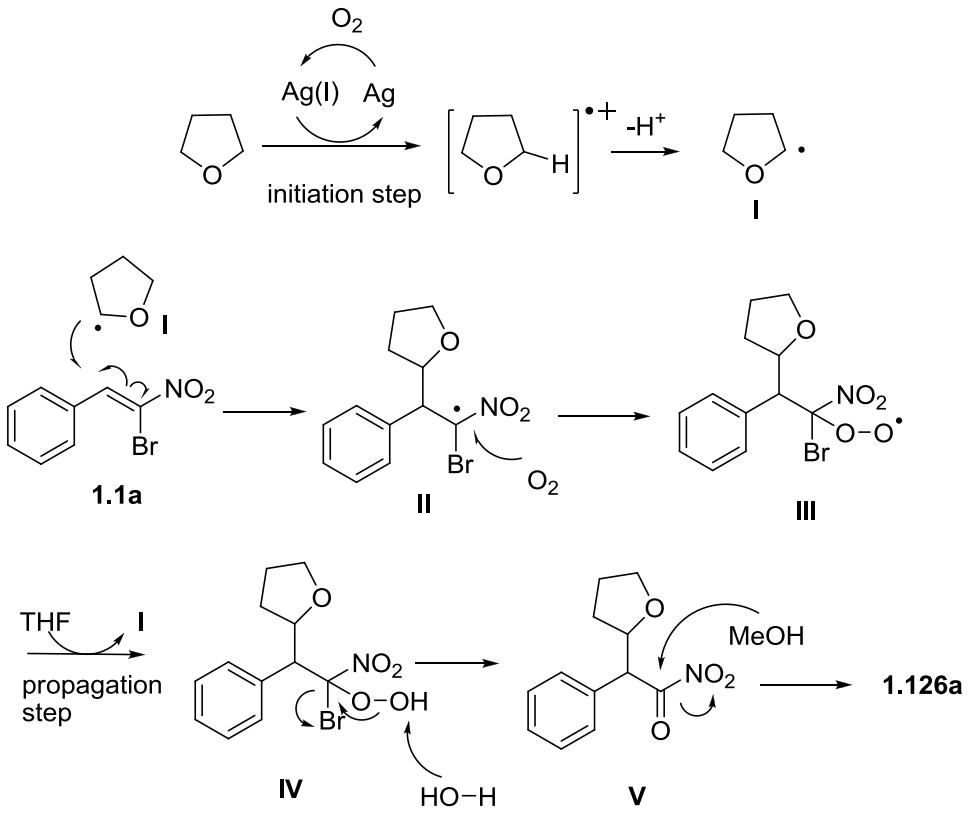
Several reactions were conducted to investigate the possible reaction mechanism. When 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added into the reaction system, no reaction could be observed. And when the reaction was conducted in the absence of light, the products were obtained only in a trace amount. These evidences indicated that the reaction might proceed through a radical process. Through an isotope labelling experiment by using $^{18}O_2$ in replace of air, it showed that the molecular oxygen was incorporated into the carbonyl group (Scheme 1.41).



Scheme 1.41 Isotope labeling experiment by $^{18}O_2$

A plausible mechanism for this reaction is shown in Scheme 3.22. The THF radical **I** generated from THF and Ag(I) in the presence of oxygen adds to *β*-bromo-*β*-nitrostyrene **1.1a** to form an radical adduct **II** which is trapped by dioxygen giving a peroxy radical **III**, followed by hydrogen abstraction from THF to generate a hydroperoxide **IV**. The O−O bond

of hydroperoxide **IV** undergoes cleavage to form the intermediate **V** with the release of bromo group. The intermediate **V** is subjected to nucleophilic attack by alcohols to give the desired ester **1.126a**. Since the intermediate **V** is less active than the acyl halide (the latter one would be formed if the nitro group leaves first after the cleavage of the hydroperoxide), it is difficult for bulky alcohols to attack the intermediate **V** to form the corresponding ester. This could explain the inactivity of most alcohols toward the reaction (Table 1.4). The base K_2CO_3 may serve to neutralize the acids generated from the reaction system. Since the content of water in the reaction system is essential to the reaction, too much water may quench the reaction to some extent. This could explain why the base KOH gave extremely low yield (Table 1, entry 13). For KOH is hydroscopic and the use of KOH may introduce some water into the reaction system so the yield is low. In addition, since other free radical initiators such as triethylborane-air, dimethylzinc-air, N-hydroxyphthalimide-$Co(OAc)_2$-dioxygen, AIBN (reflux), benzoyl peroxide (reflux) or di-tert-butyl peroxide (heating) fail to initiate the reaction, we believe a strong affinity of Ag(I) towards Br plays a key role in this reaction. The precipitation of AgBr makes the leaving of Br^- more readily and catalyze the reaction to some extent.



Scheme 1.42 Plausible Mechanism

1.3.3 Conclusion

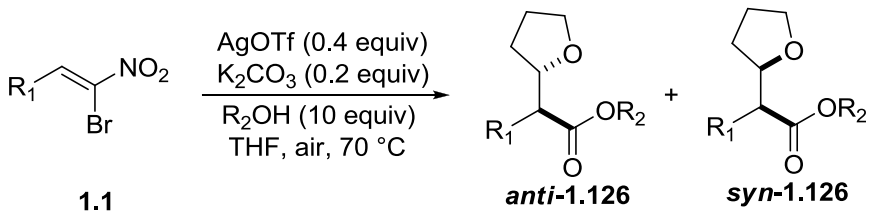
In summary, a Ag(I) catalyzed addition of THF radical to *β*-bromo-*β*-nitrostyrenes under mild conditions has been developed. The molecular oxygen was incorporated into the carbonyl group. *β*-Bromo-*β*-nitrostyrenes bearing electro-withdrawing groups such as - F, -Cl, -Br on the phenyl ring generally gave good yields. It provides a useful synthetic tool for the preparation of various ether derivatives.

1.3.4 Experimental Section

General: All reactions were conducted in the air. All reagents and solvents were obtained from commercial suppliers and used without further purification. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates. Product purification by flash column chromatography was accomplished using silica gel (0.010 - 0.063 mm). Technical grade solvents were used for chromatography and distilled prior to use. High-resolution mass spectra (HRMS) were obtained on a Finnigan/MAT LCQ quadrupole ion trap mass spectrometer, coupled with the TSP4000 HPLC system and the Crystal 310 CE system. Accurate masses are reported for the molecular ion $[M+H]^+$ or a suitable fragment ion. X-ray crystallographic data was collected by using a Bruker X8 Apex diffractometer with Mo K/α radiation (graphite monochromator). ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker AV 400 (400 MHz) NMR spectrometer. ^1H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm) and $CHCl_3$ (77.0 ppm), respectively. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from triethylsilane. Chemical shift (δ) is referred in terms of ppm, coupling constants (J) are given in Hz. Following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved.

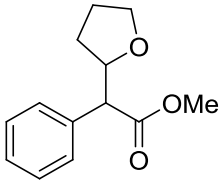
Materials: 1-Bromo-1-nitroalkenes **1.1a-1.1n** were prepared from the standard literature procedures[3g].

General procedure for Addition of THF radical to *β*-bromo-*β*-nitrostyrene.



1.1 ***anti*-1.126** ***syn*-1.126**

A mixture of the β-bromonitrostyrene **1.1** (0.5 mmol, prepared as a mixture of *Z*- and *E*-isomer), silver triflate (51.4 mg, 0.2 mmol) and K_2CO_3 (13.8 mg, 0.1 mmol) in MeOH (0.2 mL, 5 mmol) and THF (2.5 mL) was heated at 70 °C with continuous air bubbling (flow rate: 0.5 mL/h). After the indicated period, the solvent was removed under reduced pressure. The residue was purified by silica-gel chromatography (hexane/EtOAc). **Caution**: THF tends to form highly-explosive peroxides in the presence of oxygen. Although we have never detected peroxides in this reaction, appropriate caution should always be paid when the reaction is carried out in a large scale.

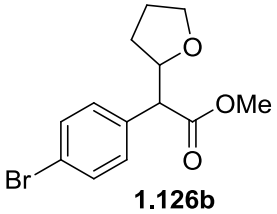


1.126a

methyl 2-phenyl-2-(tetrahydrofuran-2-yl)acetate (**1.126a**): The diastereomer ratio was 1.2:1 (*anti:syn*). The diastereomers were separated by column chromatography (hexane/EtOAc = 10/1).

The *anti*-isomer (**1.126a-1**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.28 (m, 5H), 4.52 (dt, J = 10.0, 7.2 Hz, 1H), 3.93 (q, J = 6.8 Hz, 1H), 3.83 (q, J = 7.2 Hz, 1H), 3.70 (s, 3H), 3.53 (d, J = 10.0 Hz, 1H), 1.89-1.80 (m, 2H), 1.72-1.67 (m, 1H), 1.47-1.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 135.9, 128.8, 128.4, 127.7, 80.6, 68.5, 57.7, 52.1, 29.5, 25.5; IR (neat) 3062, 3030, 2950, 2873, 1732, 1604, 1453, 1230, 1071, 736, 700 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{17}O_3$ $[M + H]^+$ 221.1178, found 221.1177.

The *syn*-isomer (**1.126a-2**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.27 (m, 5H), 4.45 (dt, *J* = 8.0, 7.6 Hz, 1H), 3.81 (q, *J* = 7.2 Hz, 1H), 3.74-3.66 (m, 4H), 3.63 (d, *J* = 8.4 Hz, 1H), 2.16-2.06 (m, 1H), 1.91-1.85 (m, 2H), 1.70-1.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 136.6, 128.6, 127.5, 80.1, 68.3, 56.8, 52.0, 30.2, 25.6; IR (neat) 3061, 3030, 2951, 2872, 1730, 1603, 1344, 1229, 1204, 1022, 735, 700 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{17}O_3$ $[M + H]^+$ 221.1178, found 221.1171.

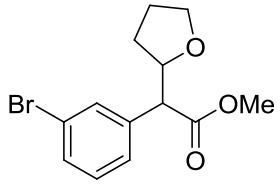


1.126b

methyl 2-(4-bromophenyl)-2-(tetrahydrofuran-2-yl)acetate (**1.126b**): The diastereomer ratio was 1.3:1 (*anti:syn*). The diastereomers were separated by column chromatography (hexane/EtOAc = 10/1).

The *anti*-isomer (**1.126b-1**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 6.4, 1.6 Hz, 2H), 7.24 (dd, *J* = 6.4, 1.6 Hz, 2H), 4.45 (dt, *J* = 10.0, 7.2 Hz, 1H), 3.90 (q, *J* = 6.8 Hz, 1H), 3.82 (q, *J* = 6.8 Hz, 1H), 3.71 (s, 3H), 3.49 (d, *J* = 10.0 Hz, 1H), 1.88-1.81 (m, 2H), 1.74-1.66 (m, 1H), 1.45-1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 134.9, 131.9, 130.1, 121.9, 80.4, 68.5, 56.9, 52.3, 29.5, 25.4; IR (neat) 3009, 2971, 2870, 1734, 1489, 1409, 1300, 1204, 1013, 819, 765 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{16}O_3Br$ $[M + H]^+$ 299.0283, found 299.0290.

The *syn*-isomer (**1.126b-2**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 4.42 (q, *J* = 7.2 Hz, 1H), 3.81-3.73 (m, 1H), 3.72-3.67 (m, 4H), 3.57 (d, *J* = 8.4 Hz, 1H), 2.15-2.08 (m, 1H), 1.90-1.82 (m, 2H), 1.67-1.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 135.6, 131.7, 130.5, 121.7, 79.8, 68.4, 56.3, 52.1, 30.3, 25.6; IR (neat) 3008, 2970, 2869, 1734, 1435, 1328, 1299, 1159, 1073, 819, 766 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{16}O_3Br$ $[M + H]^+$ 299.0283, found 299.0279.

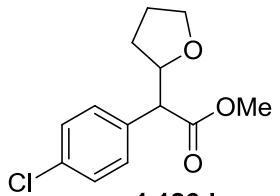


1.126c

methyl 2-(3-bromophenyl)-2-(tetrahydrofuran-2-yl)acetate (**1.126c**): The diastereomer ratio was 1.5:1 (*anti:syn*). The diastereomers were separated by column chromatography (hexane/EtOAc = 8/1).

The *anti*-isomer (**1.126c-1**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (t, J = 1.6 Hz, 1H), 7.42 (dt, J = 8.0, 1.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 4.46 (dt, J = 10.0, 7.2 Hz, 1H), 3.90 (q, J = 6.8 Hz, 1H), 3.82 (q, J = 6.8 Hz, 1H), 3.70 (s, 3H), 3.48 (d, J = 9.6 Hz, 1H), 1.89-1.82 (m, 2H), 1.75-1.67 (m, 1H), 1.44-1.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 138.0, 131.4, 130.9, 130.4, 127.1, 122.8, 80.5, 68.6, 57.1, 52.2, 29.6, 25.5; IR (neat) 3010, 2972, 2865, 1736, 1480, 1406, 1302, 1205, 1015, 820, 752 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{16}O_3Br$ $[M + H]^+$ 299.0283, found 299.0284.

The *syn*-isomer (**1.126c-2**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (t, J = 1.6 Hz, 1H), 7.41 (dt, J = 6.4, 1.2 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 4.42 (dt, J = 8.4, 6.8 Hz, 1H), 3.79 (q, J = 6.8 Hz, 1H), 3.74-3.71 (m, 1H), 3.68 (s, 3H), 3.56 (d, J = 8.4 Hz, 1H), 2.16-2.08 (m, 1H), 1.92-1.88 (m, 2H), 1.67-1.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 138.8, 131.7, 130.8, 130.0, 127.4, 122.6, 79.8, 68.4, 56.5, 52.2, 30.3, 25.6; IR (neat) 3010, 2973, 2870, 1735, 1483, 1405, 1301, 1205, 1012, 806, 761 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{16}O_3Br$ $[M + H]^+$ 299.0283, found 299.0281.

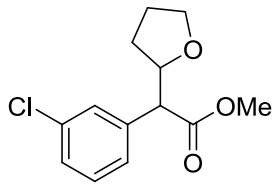


1.126d

methyl 2-(4-chlorophenyl)-2-(tetrahydrofuran-2-yl)acetate (**1.126d**): The diastereomer ratio was 1.2:1 (*anti:syn*). The diastereomers were separated by column chromatography (hexane/EtOAc = 15/1).

The *anti*-isomer (**1.126d-1**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (s, 4H), 4.46 (dt, *J* = 9.6, 6.8 Hz, 1H), 3.91 (q, *J* = 6.8 Hz, 1H), 3.82 (q, *J* = 6.8 Hz, 1H), 3.70 (s, 3H), 3.50 (d, *J* = 9.6 Hz, 1H), 1.88-1.81 (m, 2H), 1.75-1.68 (m, 1H), 1.44-1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 134.4, 133.7, 129.9, 128.9, 80.5, 68.5, 56.8, 52.2, 29.4, 25.4; IR (neat) 3080, 3011, 2950, 2872, 1735, 1435, 1303, 1228, 1070, 816, 750 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{16}O_3Cl$ $[M + H]^+$ 255.0788, found 255.0795.

The *syn*-isomer (**1.126d-2**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (s, 4H), 4.41 (dt, *J* = 8.4, 7.2 Hz, 1H), 3.78 (q, *J* = 7.2 Hz, 1H), 3.74-3.68 (m, 4H), 3.58 (d, *J* = 8.4 Hz, 1H), 2.14-2.08 (m, 1H), 1.89-1.84 (m, 2H), 1.67-1.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 135.1, 133.5, 130.0, 128.8, 79.9, 68.4, 56.2, 52.2, 30.2, 25.6; IR (neat) 3080, 3012, 2949, 2870, 1734, 1435, 1334, 1302, 1227, 1071, 815, 750 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{16}O_3Cl$ $[M + H]^+$ 255.0788, found 255.0795.



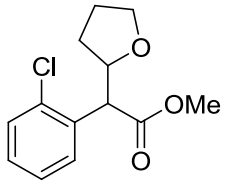
1.126e

methyl 2-(3-chlorophenyl)-2-(tetrahydrofuran-2-yl)acetate (**1.126e**): The diastereomer ratio was 1.3:1 (*anti:syn*). The diastereomers were separated by column chromatography (hexane/EtOAc = 10/1).

The *anti*-isomer (**1.126e-1**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 1.6 Hz, 1H), 7.27-7.24 (m, 3H), 4.48 (dt, *J* = 9.6, 6.8 Hz, 1H), 3.90 (q, *J* = 6.8 Hz, 1H), 3.82 (q, *J* = 6.4 Hz, 1H), 3.71 (s, 3H), 3.51 (d, *J* = 10.0 Hz, 1H), 1.89-1.81 (m, 2H), 1.76-1.68 (m, 1H), 1.47-1.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 137.7, 134.6,

130.0, 128.5, 128.0, 126.7, 80.4, 68.5, 57.1, 52.4, 29.6, 25.5; IR (neat) 2952, 2873, 1735, 1596, 1478, 1205, 1162, 1071, 1021, 774 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{16}O_3Cl$ $[M + H]^+$ 255.0788, found 255.0786.

The *syn*-isomer (**1.126e-2**) was obtained as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (s, 1H), 7.27-7.24 (m, 3H), 4.43 (dt, *J* = 8.4, 7.2 Hz, 1H), 3.80 (q, *J* = 6.8 Hz, 1H), 3.71 (q, *J* = 6.8 Hz,1H), 3.69 (s, 3H), 3.59 (d, *J* = 8.4 Hz, 1H), 2.15-2.10 (m, 1H), 1.90-1.84 (m, 2H), 1.66-1.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 138.6, 134.3, 129.7, 128.8, 127.8, 126.9, 79.8, 68.4, 56.5, 52.3, 30.2, 25.6; IR (neat) 2951, 2872, 1734, 1598, 1477, 1433, 1161, 1070, 1002, 773 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{16}O_3Cl$ $[M + H]^+$ 255.0788, found 255.0780.



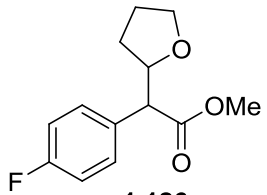
1.126f

methyl 2-(2-chlorophenyl)-2-(tetrahydrofuran-2-yl)acetate (**1.126f**): The diastereomer ratio was 1.4:1 (*anti:syn*). The diastereomers were separated by column chromatography (hexane/EtOAc = 10/1).

The *anti*-isomer (**1.126f-1**) was obtained as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.27-7.19 (m, 2H), 4.52 (dt, *J* = 9.6, 6.8 Hz, 1H), 4.29 (d, *J* = 9.6 Hz, 1H), 3.96 (q, *J* = 6.8 Hz, 1H), 3.86 (q, *J* = 6.8 Hz, 1H), 3.70 (s, 3H), 1.94-1.84 (m, 2H), 1.73-1.68 (m, 1H), 1.58-1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 134.2, 133.8, 129.8, 129.2, 128.8, 127.2, 81.0, 68.6, 52.2, 51.9, 28.9, 25.5; IR (neat) 3060, 2948, 2870, 1738, 1629, 1476, 1437, 1205, 1165, 1071, 752 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{16}O_3Cl$ $[M + H]^+$ 255.0788, found 255.0780.

The *syn*-isomer (**1.126f-2**) was obtained as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.30-7.19 (m, 2H), 4.55 (dt, *J* = 7.6, 6.8 Hz,

1H), 4.33 (d, *J* = 8.0 Hz, 1H), 3.79-3.71 (m, 2H), 3.69 (s, 3H), 2.15-2.09 (m, 1H), 1.88-1.83 (m, 2H), 1.76-1.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 134.7, 134.3, 129.9, 129.5, 128.5, 126.9, 79.5, 68.4, 52.2, 51.8, 30.2, 25.6; IR (neat) 3061, 2949, 2871, 1737, 1630, 1476, 1436, 1207, 1071, 751 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{16}O_3Cl$ $[M + H]^+$ 255.0788, found 255.0786.

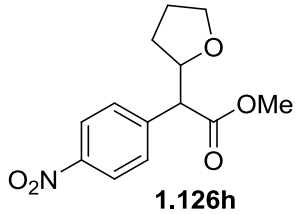


1.126g

methyl 2-(4-fluorophenyl)-2-(tetrahydrofuran-2-yl)acetate (**1.126g**): The diastereomer ratio was 1.3:1 (*anti:syn*). The diastereomers were separated by column chromatography (hexane/EtOAc = 10/1).

The *anti*-somer (**1.126g-1**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.30 (m, 2H), 7.04-6.99 (m, 2H), 4.47 (dt, *J* = 10.0, 7.2 Hz, 1H), 3.90 (q, *J* = 6.8 Hz, 1H), 3.83 (q, *J* = 7.2 Hz, 1H), 3.70 (s, 3H), 3.52 (d, *J* = 10.0 Hz, 1H), 1.89-1.81 (m, 2H), 1.74-1.66 (m, 1H), 1.45-1.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 131.7, 131.6, 130.0, 129.9, 115.7, 115.6, 80.6, 68.5, 56.7, 52.2, 29.5, 25.4; IR (neat) 2990, 2871, 1734, 1602, 1510, 1369, 1225, 1159, 1068, 839, 812 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{16}O_3F$ $[M + H]^+$ 239.1083, found 239.1078.

The *syn*-isomer (**1.126g-2**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.32 (m, 2H), 7.05-7.00 (m, 2H), 4.43 (dt, *J* = 8.0, 7.2 Hz, 1H), 3.79 (q, *J* = 6.8 Hz, 1H), 3.71 (q, *J* = 7.2 Hz, 1H), 3.68 (s, 3H), 3.61 (d, *J* = 8.4 Hz, 1H), 2.14-2.07 (m, 1H), 1.89-1.83 (m, 2H), 1.67-1.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 132.3, 130.4, 130.2, 115.5, 115.3, 79.9, 68.4, 56.1, 52.1, 30.1, 25.6; IR (neat) 2991, 2872, 1735, 1601, 1370, 1226, 1159, 1068, 841, 811 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{16}O_3F$ $[M + H]^+$ 239.1083, found 239.1091.

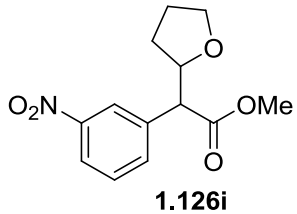


1.126h

methyl 2-(4-nitrophenyl)-2-(tetrahydrofuran-2-yl)acetate (**1.126h**): The diastereomer ratio was 1.8:1 (*anti:syn*). The diastereomers were separated by column chromatography (hexane/EtOAc = 10/1).

The *anti*-isomer (**1.126h-1**) was obtained as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 4.50 (dt, J = 9.6, 7.2 Hz, 1H), 3.91 (q, J = 6.8 Hz, 1H), 3.84 (q, J = 6.8 Hz, 1H), 3.72 (s, 3H), 3.68 (d, J = 9.6 Hz, 1H), 1.90-1.83 (m, 2H), 1.75-1.70 (m, 1H), 1.46-1.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 147.6, 143.1, 129.5, 123.9, 80.4, 68.6, 57.3, 52.5, 29.6, 25.5; IR (neat) 2955, 2851, 1735, 1602, 1520, 1347, 1209, 1066, 841 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{16}NO_5$ $[M + H]^+$ 266.1028, found 266.1033.

The *syn*-isomer (**1.126h-2**) was obtained as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 4.46 (dt, J = 8.0, 7.2 Hz, 1H), 3.79 (q, J = 7.2 Hz, 1H), 3.74-3.68 (m, 5H), 2.18-2.13 (m, 1H), 1.92-1.84 (m, 2H), 1.67-1.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 147.4, 144.0, 129.7, 123.7, 79.8, 68.4, 56.7, 52.5, 30.3, 25.6; IR (neat) 2955, 2852, 1735, 1602, 1520, 1349, 1211, 1066, 841 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{16}NO_5$ $[M + H]^+$ 266.1028, found 266.1021.

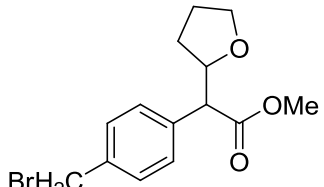


1.126i

methyl 2-(3-nitrophenyl)-2-(tetrahydrofuran-2-yl)acetate (**1.126i**): The diastereomer ratio was 1.5:1 (*anti:syn*). The diastereomers were separated by column chromatography (hexane/EtOAc = 15/1).

The *anti*-isomer (**1.126i-1**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (t, *J* = 1.6 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 4.52 (dt, *J* = 9.2, 7.2 Hz, 1H), 3.92 (q, *J* = 6.8 Hz, 1H), 3.84 (q, *J* = 6.8 Hz, 1H), 3.72 (s, 3H), 3.68 (d, *J* = 9.6 Hz, 1H), 1.91-1.85 (m, 2H), 1.77-1.72 (m, 1H), 1.47-1.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 148.4, 137.9, 134.5, 129.7, 123.6, 122.8, 80.4, 68.7, 57.0, 52.5, 29.6, 25.5; IR (neat) 2945, 2875, 1733, 1528, 1345, 1160, 1071, 736 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{16}NO_5$ $[M + H]^+$ 266.1028, found 266.1016.

The *syn*-isomer (**1.126i-2**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (t, *J* = 2.0 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 4.48 (dt, *J* = 8.0, 7.2 Hz, 1H), 3.82-3.69 (m, 6H), 2.17-2.13 (m, 1H), 1.92-1.86 (m, 2H), 1.66-1.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 138.6, 135.1, 129.4, 124.0, 123.7, 122.6, 79.7, 68.4, 56.5, 52.5, 30.3, 25.6; IR (neat) 2946, 2874, 1734, 1529, 1346, 1161, 1071, 735 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{16}NO_5$ $[M + H]^+$ 266.1028, found 266.1036.

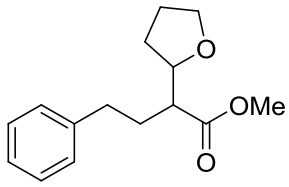


1.126j

methyl 2-(4-(bromomethyl)phenyl)-2-(tetrahydrofuran-2-yl)acetate (**1.126j**): The diastereomer ratio was 1.2:1 (*anti:syn*). The diastereomers were separated by column chromatography (hexane/EtOAc = 15/1).

The *anti*-isomer (**1.126j-1**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.31(m, 4H), 4.52-4.47 (m, 3H), 3.92 (q, *J* = 7.2 Hz, 1H), 3.82 (q, *J* = 7.6 Hz, 1H), 3.70 (s, 3H), 3.53 (d, *J* = 10.0 Hz, 1H), 1.89-1.81 (m, 2H), 1.75-1.68 (m, 1H), 1.46-1.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 137.3, 136.1, 129.5, 128.9, 80.5, 68.5, 57.2, 52.3, 33.0, 29.6, 25.5; IR (neat) 2958, 2870, 1731, 1611, 1517, 1160, 1067, 736 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{18}O_3Br$ $[M + H]^+$ 313.0439, found 313.0440.

The *syn*-isomer (**1.126j-2**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 4H), 4.47 (s, 2H), 4.44 (dt, *J* = 8.0, 7.2 Hz, 1H), 3.79 (q, *J* = 7.2 Hz, 1H), 3.71 (q, *J* = 7.2 Hz, 1H), 3.69 (s, 3H), 3.62 (d, *J* = 8.8 Hz, 1H), 2.15-2.11 (m, 1H), 1.91-1.84 (m, 2H), 1.69-1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 137.0, 136.8, 129.3, 129.1, 79.9, 68.3, 56.6, 52.1, 33.3, 30.2, 25.6; IR (neat) 2959, 2871, 1732, 1611, 1518, 1160, 1068, 735 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{18}O_3Br$ $[M + H]^+$ 313.0439, found 313.0427.

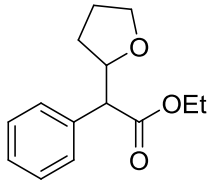


1.126m

methyl 4-phenyl-2-(tetrahydrofuran-2-yl)butanoate (**1.126m**): The diastereomer ratio was 1.5:1 (*anti:syn*). The diastereomers were separated by column chromatography (hexane/EtOAc = 15/1).

The *anti*-isomer (**1.126m-1**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 2H), 7.21-7.16 (m, 3H), 3.98 (dt, *J* = 8.0, 7.2 Hz, 1H), 3.85 (q, *J* = 7.2 Hz, 1H), 3.75-3.70 (m, 4H), 2.64-2.45 (m, 3H), 2.01-1.94 (m, 2H), 1.89-1.83 (m, 2H), 1.73-1.69 (m, 1H), 1.53-1.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 141.4, 128.3, 126.0, 80.1, 68.1, 51.7, 51.3, 33.7, 31.1, 29.7, 25.5; IR (neat) 3050, 3030, 2951, 2868, 1736, 1456, 1205, 1161, 1067, 742, 700 cm^{-1}; HRMS (ESI) Calcd for $C_{15}H_{21}O_3$ $[M + H]^+$ 249.1491, found 249.1488.

The *syn*-isomer (**1.126m-2**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.25 (m, 2H), 7.19-7.17 (m, 3H), 3.97 (dt, *J* = 8.0, 7.2 Hz, 1H), 3.80-3.67 (m, 5H), 2.69-2.62 (m, 1H), 2.60-2.50 (m, 2H), 2.05-1.99 (m, 2H), 1.96-1.84 (m, 2H), 1.68-1.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 141.5, 128.5, 128.4, 125.9, 79.6, 68.0, 51.6, 50.6, 33.7, 31.3, 29.3, 25.6; IR (neat) 3051, 3030, 2949, 2869, 1737, 1456, 1205, 1162, 1069, 742, 700 cm^{-1}; HRMS (ESI) Calcd for $C_{15}H_{21}O_3$ $[M + H]^+$ 249.1491, found 249.1485.

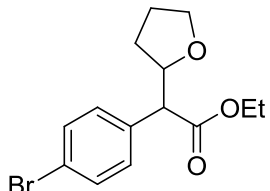


1.126o

ethyl 2-phenyl-2-(tetrahydrofuran-2-yl)acetate (**1.126o**): The diastereomer ratio was 1.5:1 (*anti:syn*). The diastereomers were separated by column chromatography (hexane/EtOAc = 12/1).

The *anti*-isomer (**1.126o-1**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 4.53 (dt, J = 10.0, 7.2 Hz, 1H), 4.22-4.16 (m, 1H), 4.15-4.10 (m, 1H), 3.93-3.89 (m, 1H), 3.86-3.82 (m, 1H), 3.50 (d, J = 10.0 Hz, 1H), 1.87-1.82 (m, 2H), 1.71-1.66 (m, 1H), 1.46-1.40 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 136.1, 128.7, 128.4, 127.8, 80.7, 68.5, 60.9, 57.8, 29.5, 25.4, 14.1; IR (neat) 3060, 3028, 2975, 2862, 1739, 1549, 1453, 1372, 1157, 736, 698 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{19}O_3$ $[M + H]^+$ 235.1334, found 235.1337.

The *syn*-isomer (**1.126o-2**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.27 (m, 5H), 4.45 (dt, J = 8.8, 7.2 Hz, 1H), 4.17-4.10 (m, 2H), 3.82-3.78 (m, 1H), 3.74-3.70 (m, 1H), 3.60 (d, J = 8.8 Hz, 1H), 2.15-2.12 (m, 1H), 1.90-1.85 (m, 2H), 1.71-1.66 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 136.7, 128.6, 128.5, 127.4, 80.1, 68.3, 60.8, 57.1, 30.3, 25.6, 14.1; IR (neat) 3061, 3029, 2976, 2863, 1738, 1550, 1372, 1159, 737, 697 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{19}O_3$ $[M + H]^+$ 235.1334, found 235.1339.

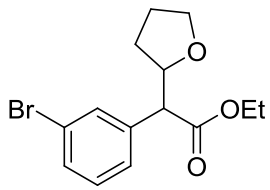


1.126p

ethyl 2-(4-bromophenyl)-2-(tetrahydrofuran-2-yl)acetate (**1.126p**): The diastereomer ratio was 1.6:1 (*anti:syn*). The diastereomers were separated by column chromatography (hexane/EtOAc = 15/1).

The *anti*-somer (**1.126p-1**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 6.4, 2.0 Hz, 2H), 7.26 (dd, *J* = 6.4, 2.0 Hz, 2H), 4.45 (dt, *J* = 9.6, 7.2 Hz, 1H), 4.16 (tq, *J* = 18.0, 3.6 Hz, 2H), 3.90 (q, *J* = 7.2 Hz, 1H), 3.82 (q, *J* = 7.2 Hz, 1H), 3.47 (d, *J* = 10.0 Hz, 1H), 1.88-1.81 (m, 2H), 1.72-1.67 (m, 1H), 1.42-1.38 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 135.0, 131.8, 130.2, 121.8, 80.4, 68.5, 61.1, 57.1, 29.5, 25.4, 14.0; IR (neat) 2980, 2879, 1734, 1493, 1375, 1204, 1164, 1075, 1018, 824 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{18}O_3Br$ $[M + H]^+$ 313.0439, found 313.0428.

The *syn*-isomer (**1.126p-2**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 6.4, 2.0 Hz, 2H), 7.28 (dd, *J* = 6.4, 2.0 Hz, 2H), 4.40 (dt, *J* = 8.4, 7.2 Hz, 1H), 4.18-4.09 (m, 2H), 3.79 (q, *J* = 6.8 Hz, 1H), 3.71 (q, *J* = 6.8 Hz, 1H), 3.54 (d, *J* = 8.8 Hz, 1H), 2.14-2.08 (m, 1H), 1.90-1.84 (m, 2H), 1.68-1.61 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 135.8, 131.6, 130.5, 121.6, 79.9, 68.3, 61.0, 56.5, 30.2, 25.7, 14.1; IR (neat) 2982, 2880, 1732, 1528, 1493, 1374, 1308, 1075, 1018, 828 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{18}O_3Br$ $[M + H]^+$ 313.0439, found 313.0449.



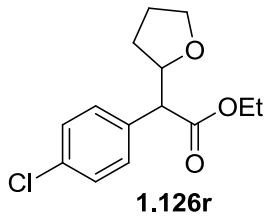
1.126q

ethyl 2-(3-bromophenyl)-2-(tetrahydrofuran-2-yl)acetate (**1.126q**): The diastereomer ratio was 1.8:1 (*anti:syn*). The diastereomers were separated by column chromatography (hexane/EtOAc = 15/1).

The *anti*-isomer (**1.126q-1**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (t, *J* = 1.6 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.6 Hz,

1H), 4.46 (dt, *J* = 4.4, 2.8 Hz, 1H), 4.23-4.11 (m, 2H), 3.91 (q, *J* = 6.8 Hz, 1H), 3.84 (q, *J* = 6.8 Hz, 1H), 3.46 (q, *J* = 10.0 Hz, 1H), 1.88-1.83 (m, 2H), 1.73-1.68 (m, 1H), 1.44-1.40 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 138.3, 131.4, 130.9, 130.2, 127.1, 122.7, 80.5, 68.5, 61.3, 57.2, 29.5, 25.4, 14.1; IR (neat) 2970, 2871, 1736, 1568, 1475, 1162, 1072, 1032, 709 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{18}O_3Br$ $[M + H]^+$ 313.0439, found 313.0436.

The *syn*-isomer (**1.126q-2**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (t, *J* = 1.6 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 4.41 (dt, *J* = 8.4, 6.8 Hz, 1H), 4.19-4.08 (m, 2H), 3.80 (q, *J* = 6.8 Hz, 1H), 3.71 (q, *J* = 6.8 Hz, 1H), 3.54 (d, *J* = 8.8 Hz, 1H), 2.14-2.09 (m, 1H), 1.90-1.85 (m, 2H), 1.67-1.62 (m, 1H), 1.23 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 139.0, 131.6, 130.6, 130.0, 127.3, 122.6, 79.9, 68.4, 61.0, 56.8, 30.2, 25.6, 14.1; IR (neat) 2971, 2869, 1736, 1568, 1476, 1161, 1072, 1034, 710 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{18}O_3Br$ $[M + H]^+$ 313.0439, found 313.0441.



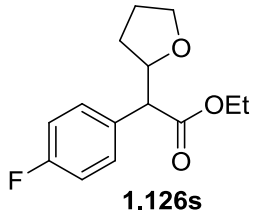
1.126r

ethyl 2-(4-chlorophenyl)-2-(tetrahydrofuran-2-yl)acetate (**1.126r**): The diastereomer ratio was 1.6:1 (*anti:syn*). The diastereomers were separated by column chromatography (hexane/EtOAc = 15/1).

The *anti*-isomer (**1.126r-1**) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (br s, 4H), 4.45 (dt, *J* = 10.0, 6.8 Hz, 1H), 4.22-4.11 (m, 2H), 3.90 (q, *J* = 7.2 Hz, 1H), 3.82 (q, *J* = 7.2 Hz, 1H), 3.49 (d, *J* = 10.0 Hz, 1H), 1.88-1.82 (m, 2H), 1.74-1.68 (m, 1H), 1.44-1.36 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 134.5, 133.6, 129.8, 128.8, 80.5, 68.5, 61.1, 57.0, 29.4, 25.4, 14.1; IR (neat) 2969, 2868, 1739, 1490,

1160, 1090, 1066, 1016, 669 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{18}O_3Cl$ $[M + H]^+$ 269.0944, found 269.0946.

The *syn*-isomer (**1.126r-2**) was obtained as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34-7.28 (m, 4H), 4.41 (dt, J = 8.4, 6.8 Hz, 1H), 4.18-4.09 (m, 2H), 3.79 (q, J = 6.8 Hz, 1H), 3.71 (q, J = 6.8 Hz, 1H), 3.55 (d, J = 8.8 Hz, 1H), 2.15-2.09 (m, 1H), 1.91-1.84 (m, 2H), 1.68-1.62 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 135.3, 133.4, 130.0, 128.7, 79.8, 68.3, 61.0, 56.5, 30.3, 25.6, 14.1; IR (neat) 2970, 2868, 1738, 1491, 1161, 1090, 1066, 1018, 670 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{18}O_3Cl$ $[M + H]^+$ 269.0944, found 269.0945.



1.126s

ethyl 2-(4-fluorophenyl)-2-(tetrahydrofuran-2-yl)acetate (**1.126s**): The diastereomer ratio was 1.5:1 (*anti:syn*). The diastereomers were separated by column chromatography (hexane/EtOAc = 15/1).

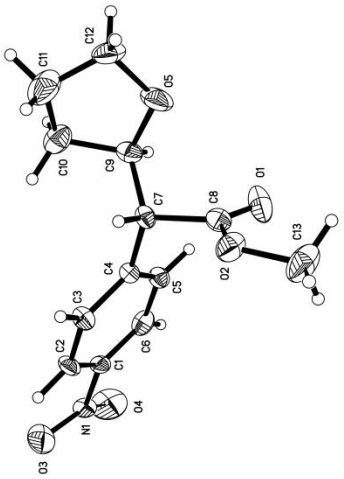
The *anti*-isomer (**1.126s-1**) was obtained as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.31 (m, 2H), 7.03-6.97 (m, 2H), 4.46 (dt, J = 9.6, 6.8 Hz, 1H), 4.22-4.10 (m, 2H), 3.90 (q, J = 7.2 Hz, 1H), 3.84 (q, J = 7.2 Hz, 1H), 3.48 (d, J = 9.6 Hz, 1H), 1.87-1.82 (m, 2H), 1.72-1.67 (m, 1H), 1.43-1.38 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 131.9, 131.8, 130.0, 129.8, 115.7, 115.5, 80.6, 68.5, 61.0, 56.7, 29.5, 25.4, 14.1; IR (neat) 2985, 2876, 1735, 1608, 1530, 1370, 1228, 1159, 1072, 841, 810 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{18}O_3F$ $[M + H]^+$ 253.1240, found 253.1235.

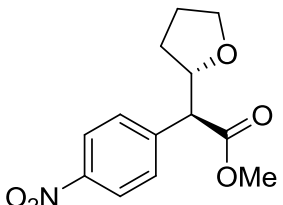
The *syn*-isomer (**1.126s-2**) was obtained as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.34 (m, 2H), 7.04-7.00 (m, 2H), 4.41 (dt, J = 8.4, 6.8 Hz, 1H), 4.18-4.10 (m, 2H), 3.79 (q, J = 6.8 Hz, 1H), 3.71 (q, J = 6.8 Hz, 1H), 3.58 (d, J = 8.4 Hz, 1H), 2.13-2.10 (m, 1H),

1.90-1.86 (m, 2H), 1.67-1.62 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 132.5, 130.2, 130.1, 115.6, 115.3, 80.0, 68.3, 60.9, 56.4, 30.2, 25.6, 14.1; IR (neat) 2984, 2876, 1734, 1608, 1530, 1372, 1228, 1158, 1072, 840, 809 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{18}O_3F$ $[M + H]^+$ 253.1240, found 253.1237.

1.3.5 Supporting Information

1. X-ray structure and data of compound 1.126h-1





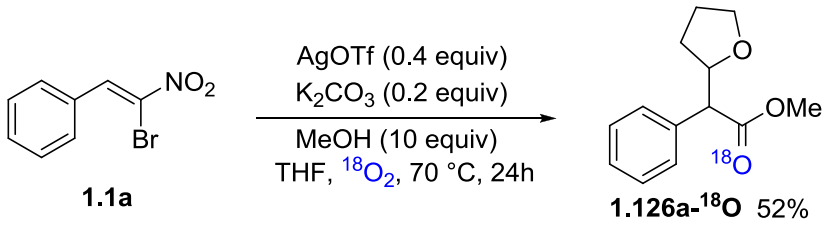
1.126h-1

Crystal data and structure refinement for compound **1.126h-1**

Identification code	compound **1.126h-1**	
Empirical formula	C13 H15 N O5	
Formula weight	265.26	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.0104(6) Å	a= 102.106(2)°.
	b = 8.0179(8) Å	b= 109.539(3)°.
	c = 10.7954(7) Å	g = 95.818(2)°.
Volume	627.73(9) $Å^3$	
Z	2	
Density (calculated)	1.403 Mg/m^3	
Absorption coefficient	0.109 mm^{-1}	
F(000)	280	

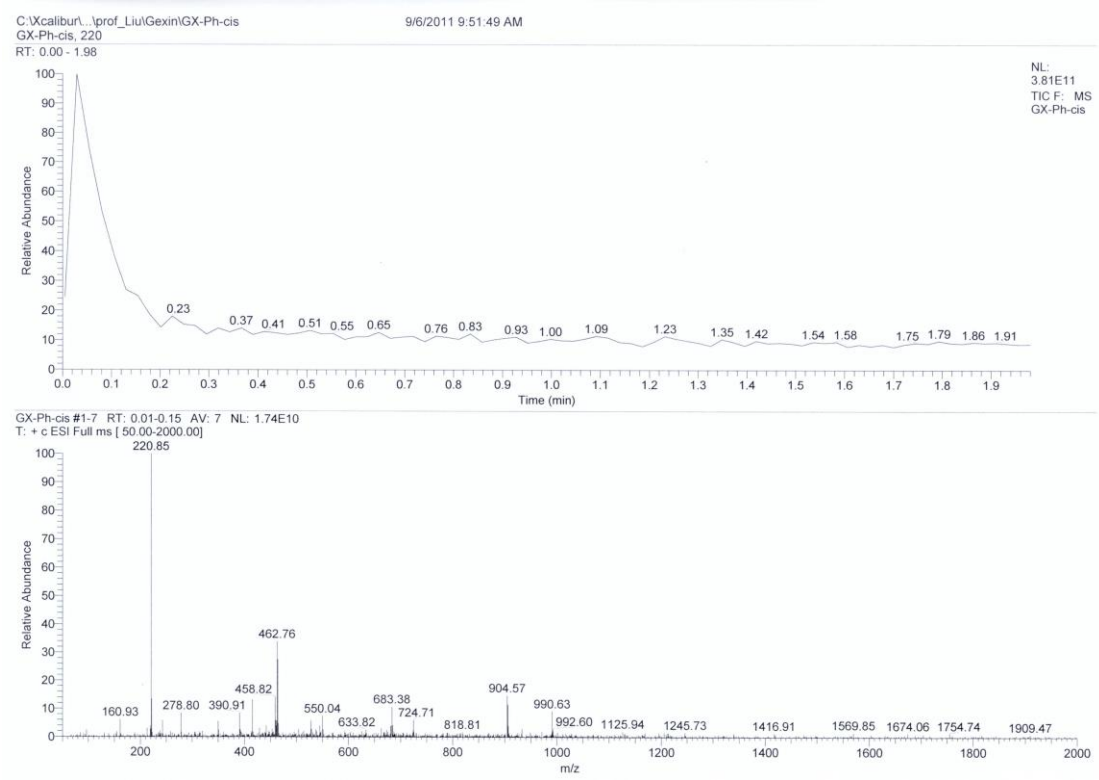
Crystal size	0.40 x 0.24 x 0.20 mm^3
Theta range for data collection	2.07 to 32.02°.
Index ranges	-11<=h<=11, -11<=k<=11, -16<=l<=16
Reflections collected	13070
Independent reflections	4334 [R(int) = 0.0180]
Completeness to theta = 32.02°	99.8 %
Absorption correction	None
Max. and min. transmission	0.9786 and 0.9578
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4334 / 915 / 346
Goodness-of-fit on F^2	1.038
Final R indices [I>2sigma(I)]	R1 = 0.0462, wR2 = 0.1126
R indices (all data)	R1 = 0.0675, wR2 = 0.1230
Largest diff. peak and hole	0.223 and -0.205 $e.Å^{-3}$

2. Isotope Labeling Experiments



When the reaction was conducted under an $^{18}O_2$ atmosphere, the ester was obtained in 52% yield. The differences in mass spectroscopy showed that an ^{18}O atom was incorporated into the ester.

Spectrum of ESI (LRMS) of 1.126a



Spectrum of ESI (HRMS) of 1.126a

Elemental Composition Report **Page 1**

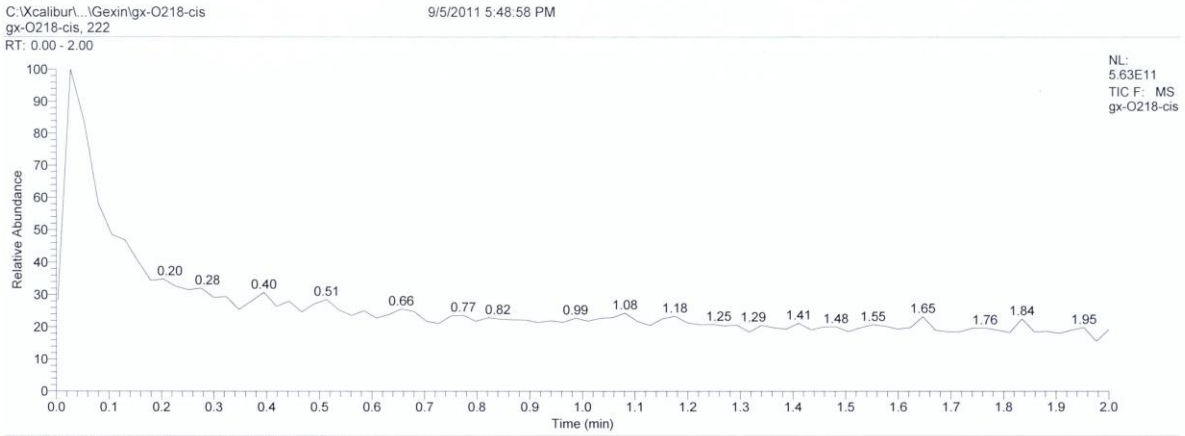
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.8, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

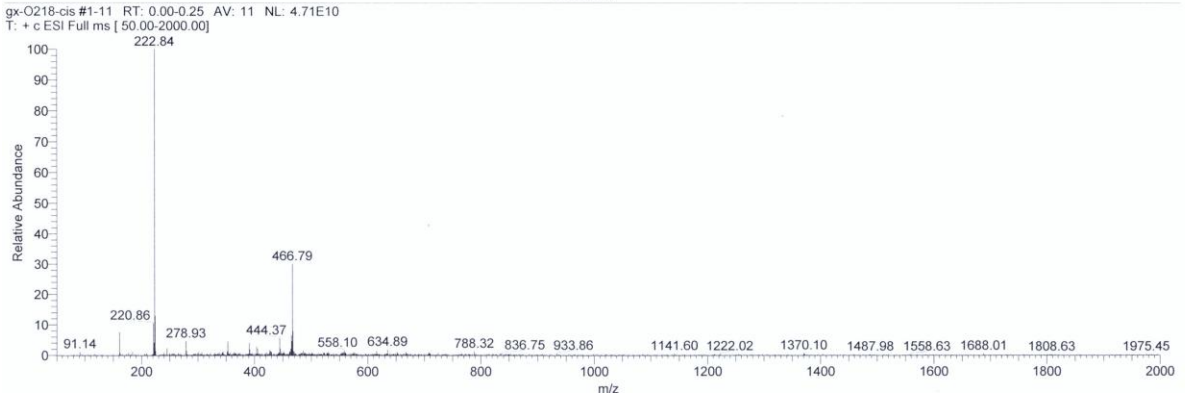
Monoisotopic Mass, Even Electron Ions
36 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-15 H: 1-21 O: 1-4 Cl: 0-2 Br: 0-1

C13H16O3
GX-23 152 (3.328)

Minimum:				-1.8			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
221.1177	221.1178	-0.1	-0.5	5.5	12.1	0.0	C13 H17 O3

Spectrum of ESI (LRMS) of 1.126a-^{18}O





Spectrum of ESI (HRMS) of 1.126a-^{18}O

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.8, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

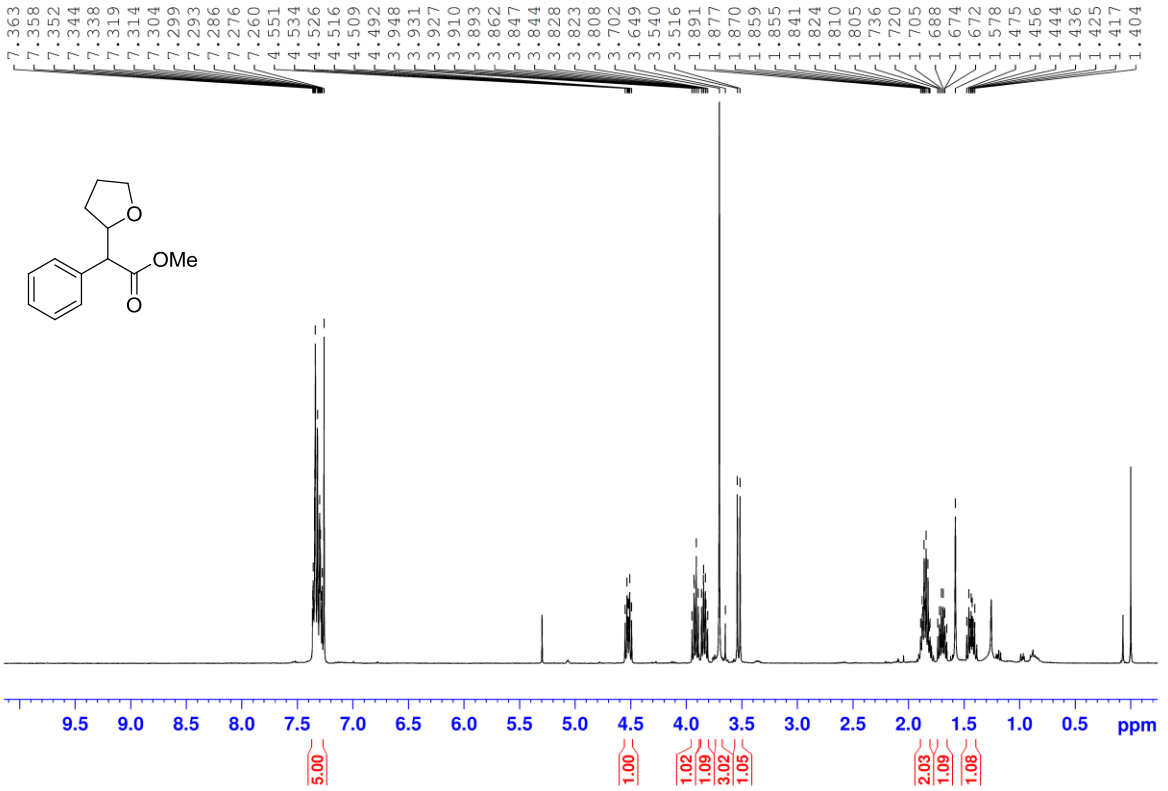
Monoisotopic Mass, Even Electron Ions
66 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-14 H: 0-17 N: 0-1 16O: 0-2 17O: 0-2 18O: 0-2
C13H16O3
GX-17 24 (0.526)

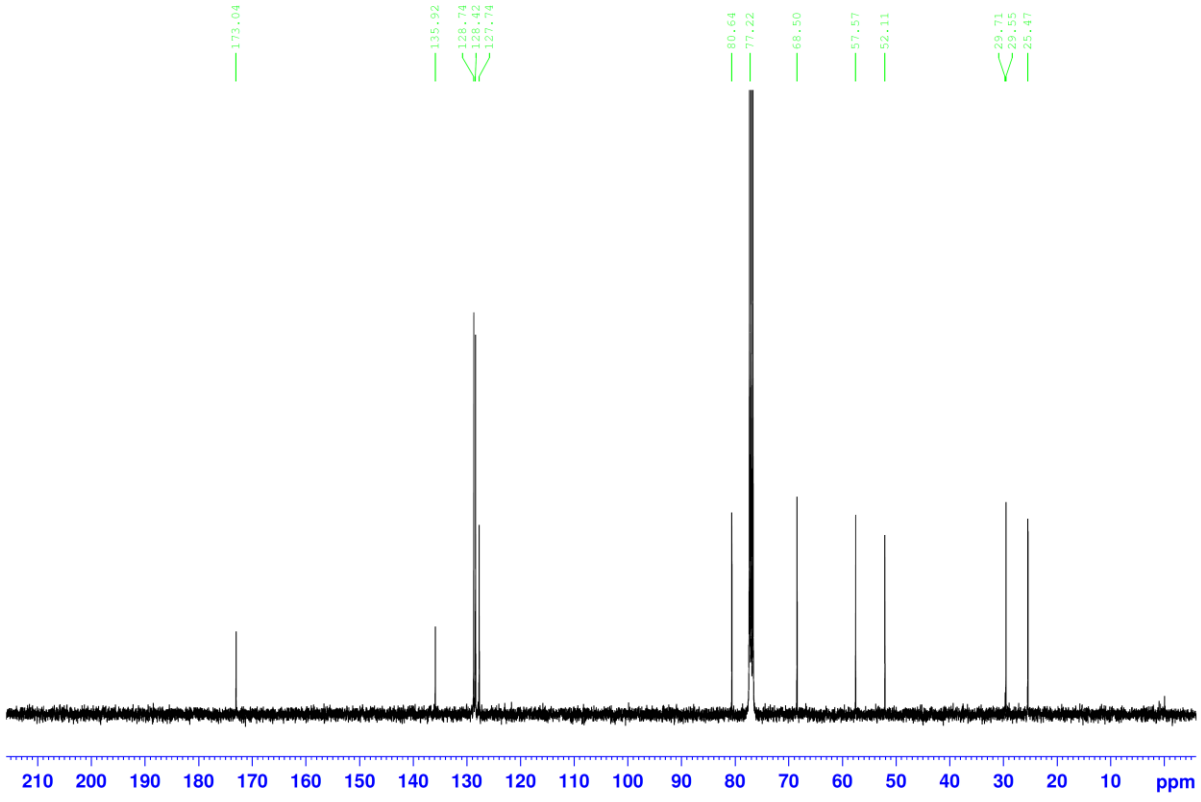
1: TOF MS ES+
2.84e+001

Minimum:		5.0	5.0	-1.8			
Maximum:				50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
223.1222	223.1220	0.2	0.9	5.5	13.1	0.0	C13 H17 16O2 18O

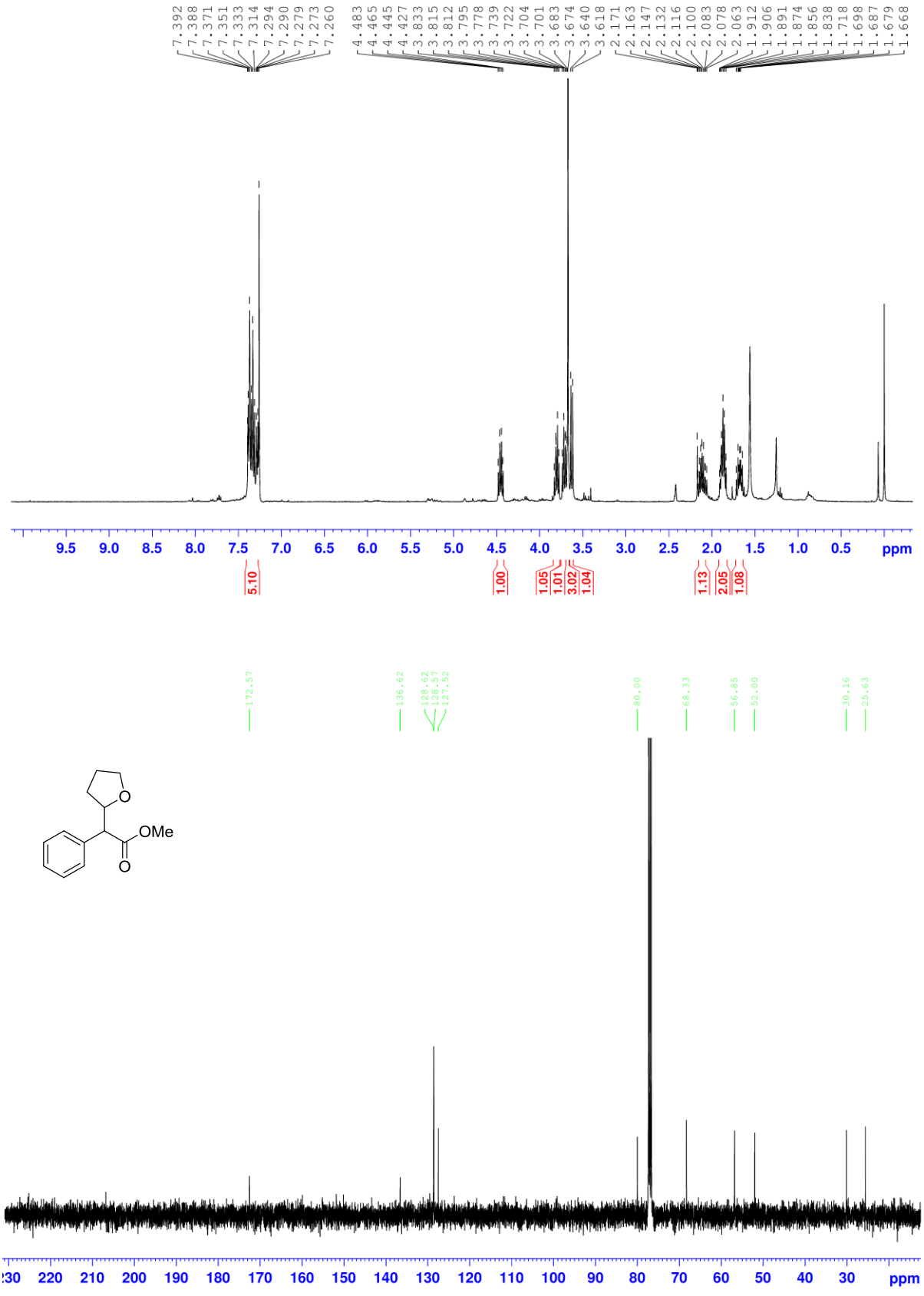
3. ^{1}H and ^{13}C NMR spectra of compounds 1.126a-1.126s

^{1}H and ^{13}C NMR spectra of compound 1.126a-1 (the *anti*-isomer)

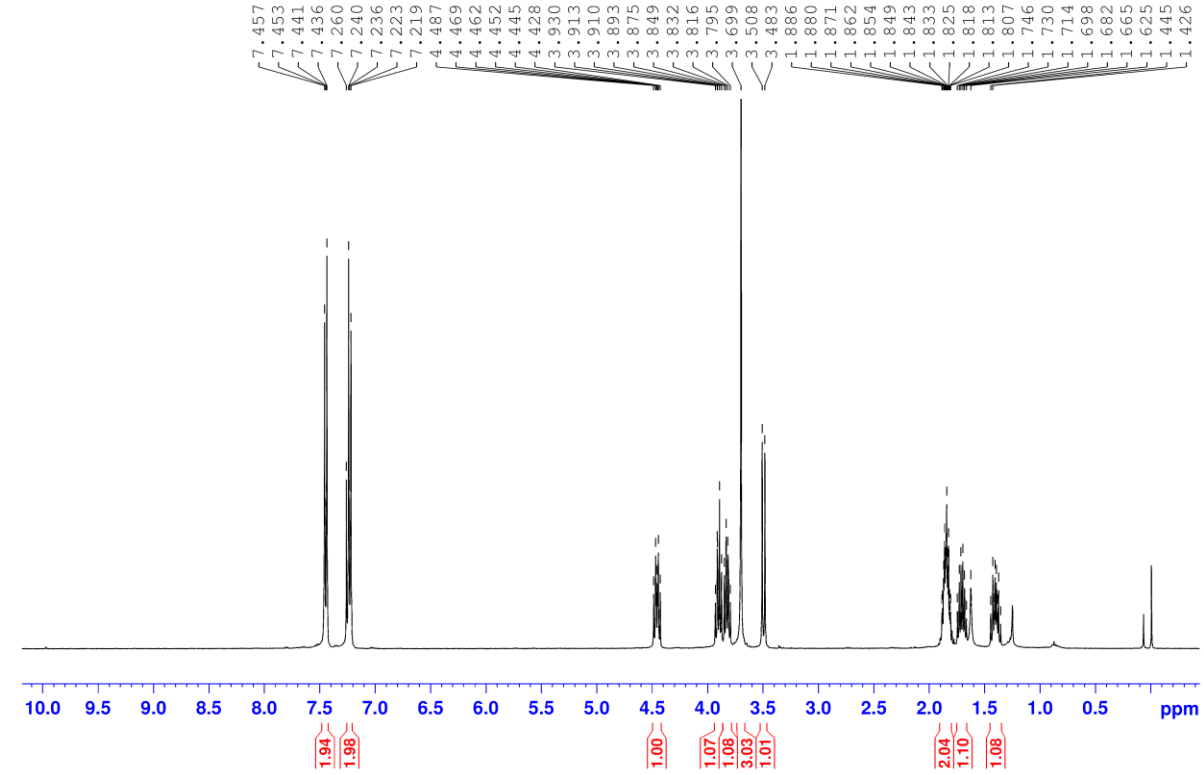


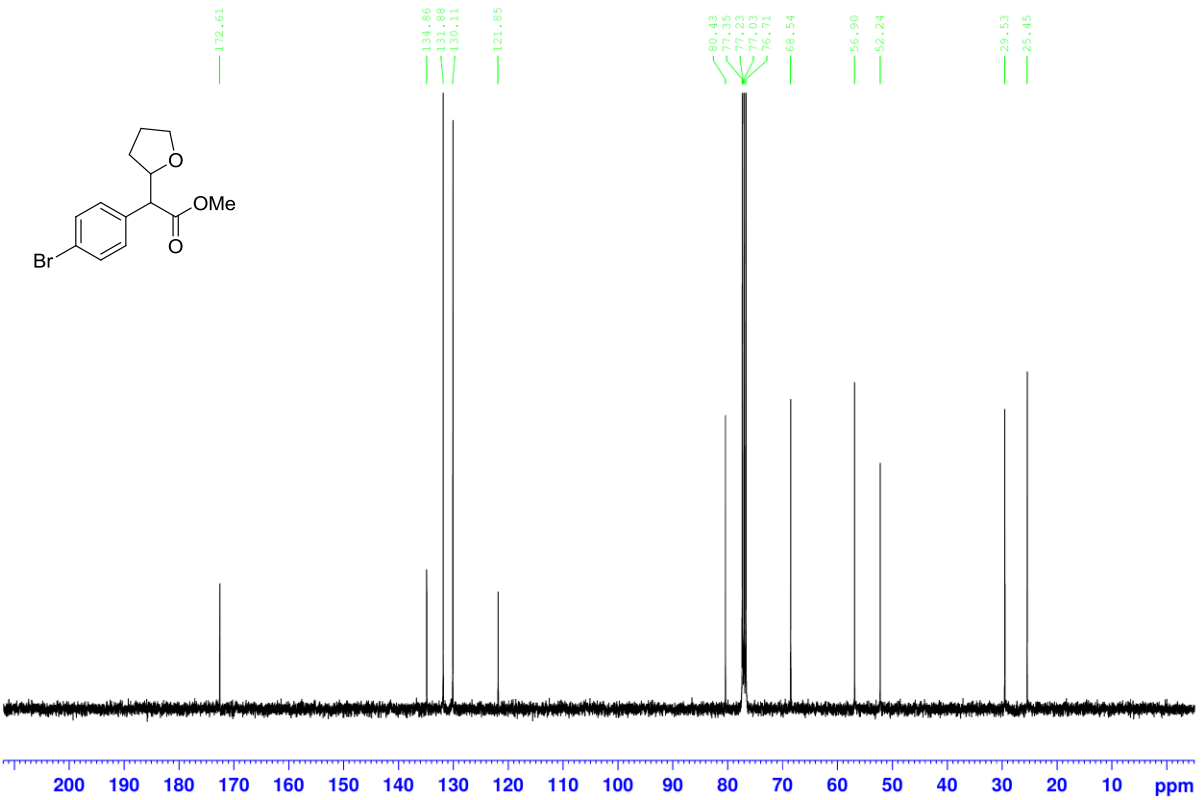


^{1}H and ^{13}C NMR spectra of compound 1.126a-2 (the *syn*-isomer)

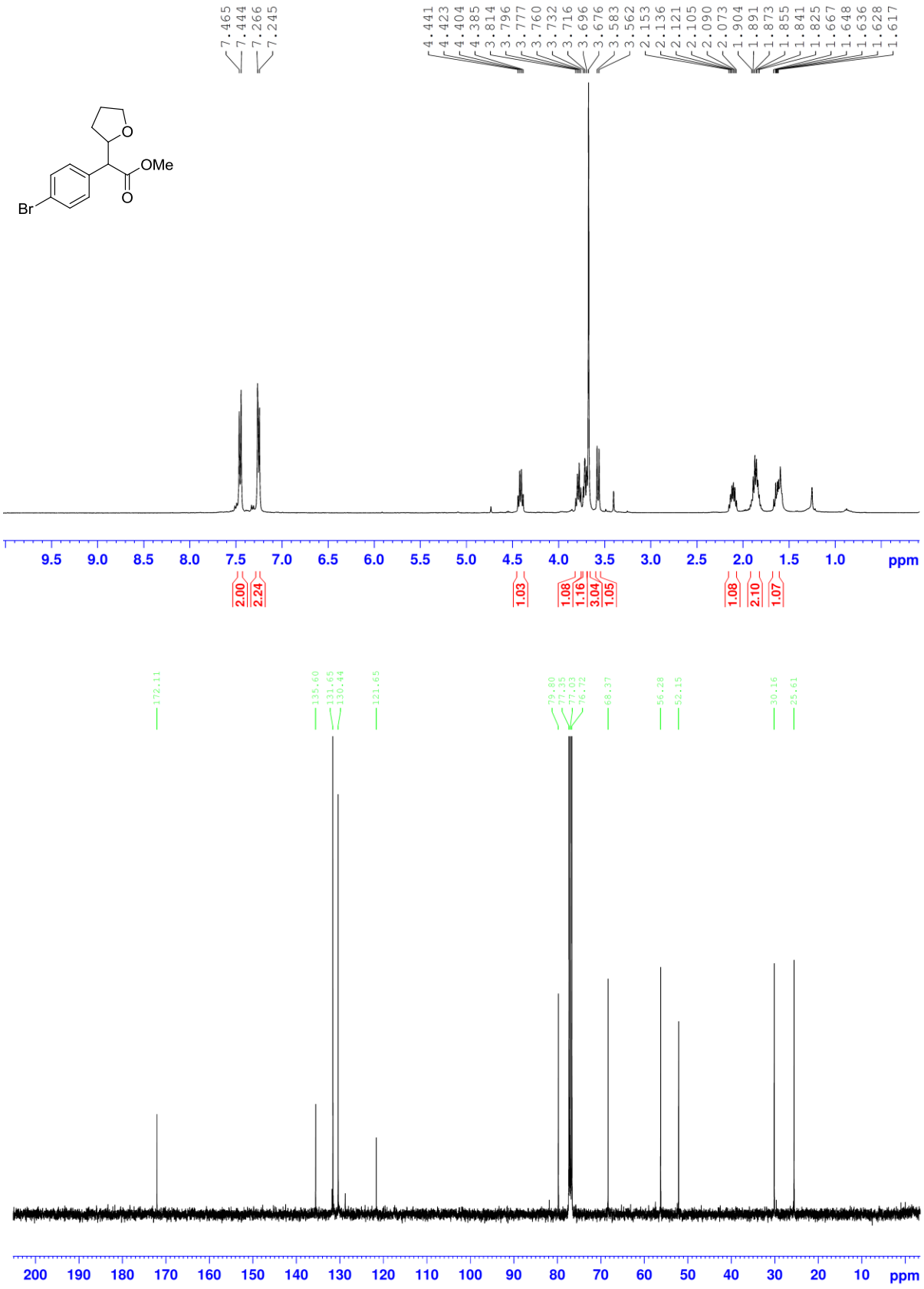


^{1}H and ^{13}C NMR spectra of compound 1.126b-1 (the *anti*-isomer)

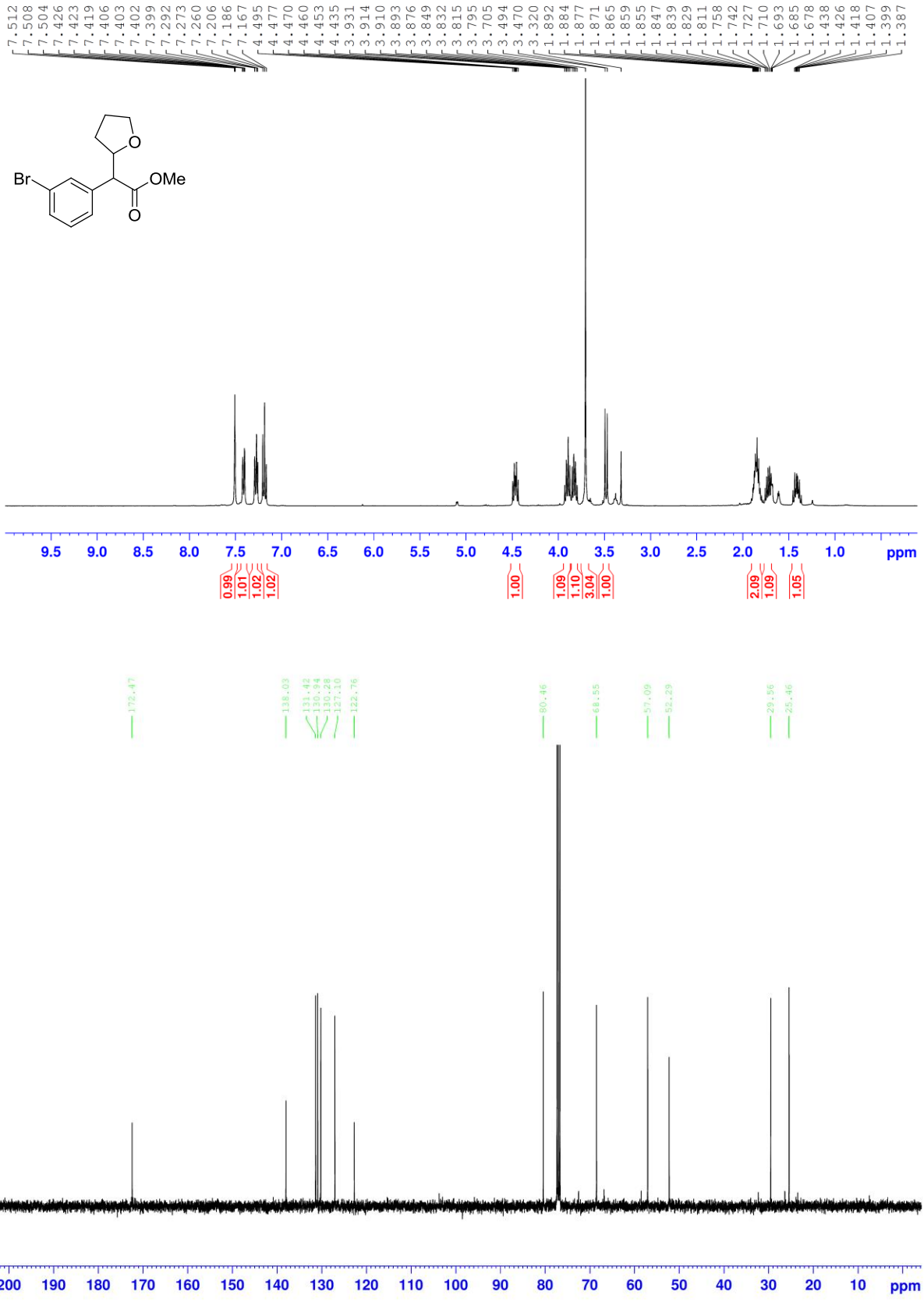




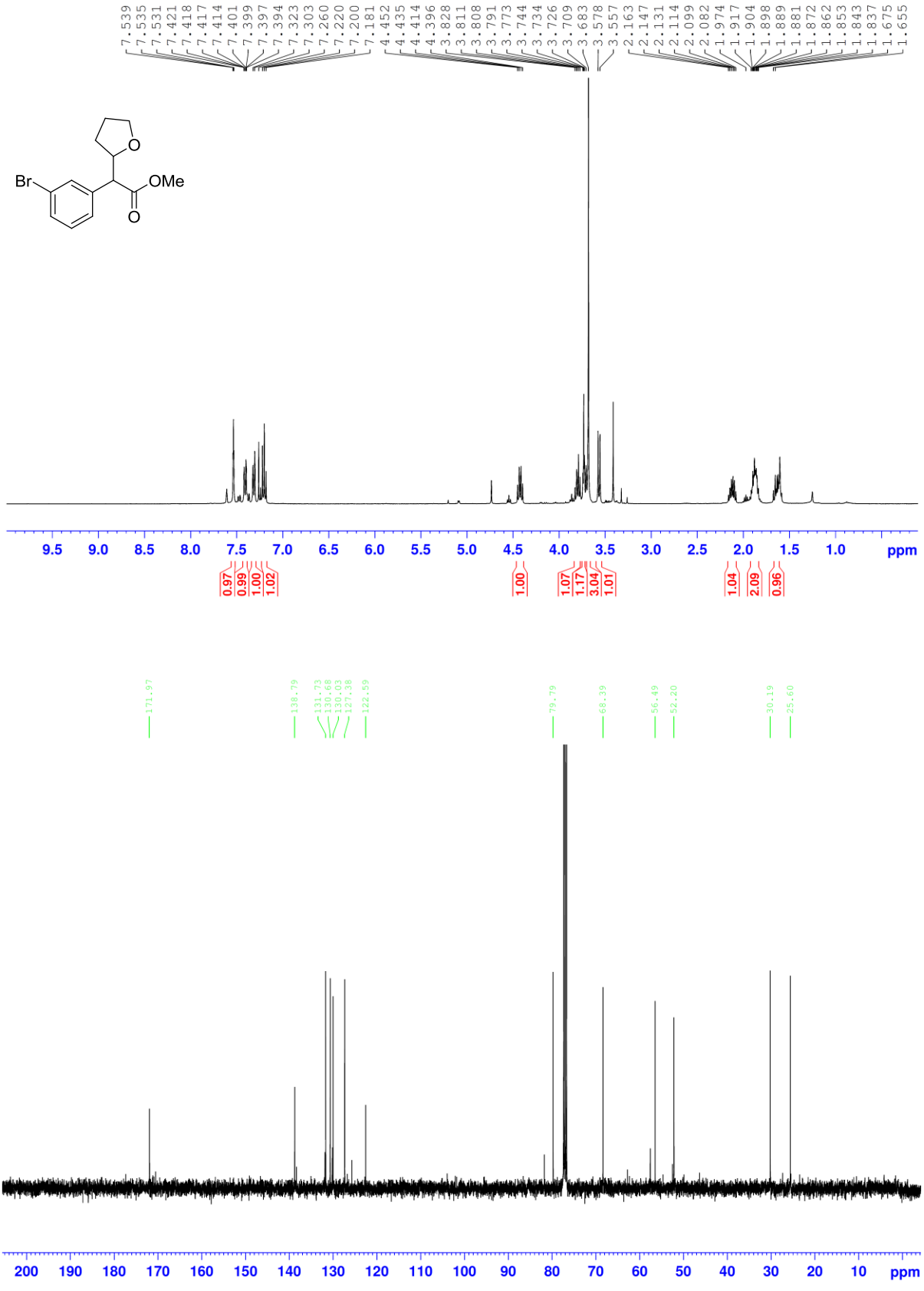
^{1}H and ^{13}C NMR spectra of compound 1.126b-2 (the *syn*-isomer)



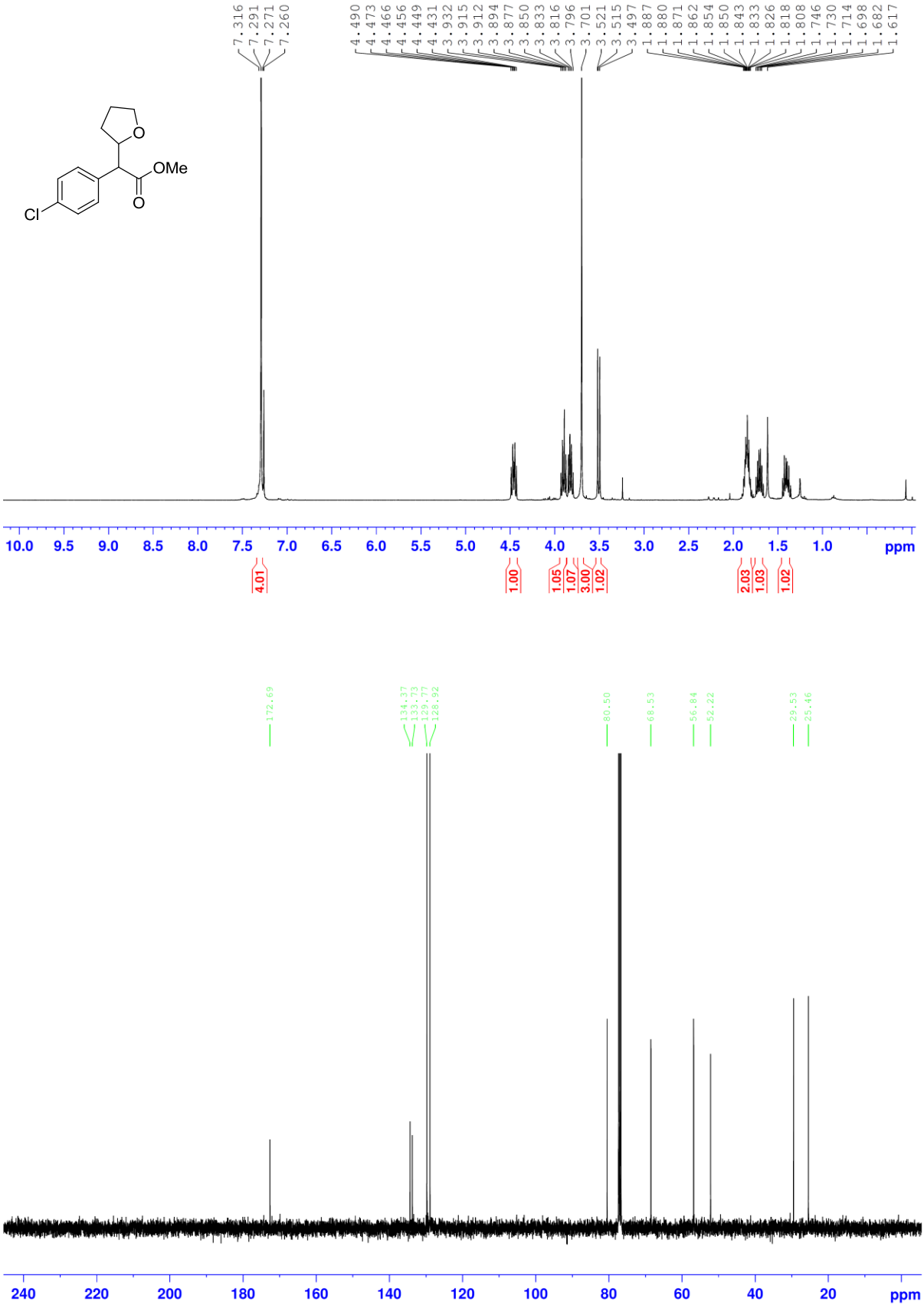
^{1}H and ^{13}C NMR spectra of compound 1. 126c-1 (the *anti*-isomer)



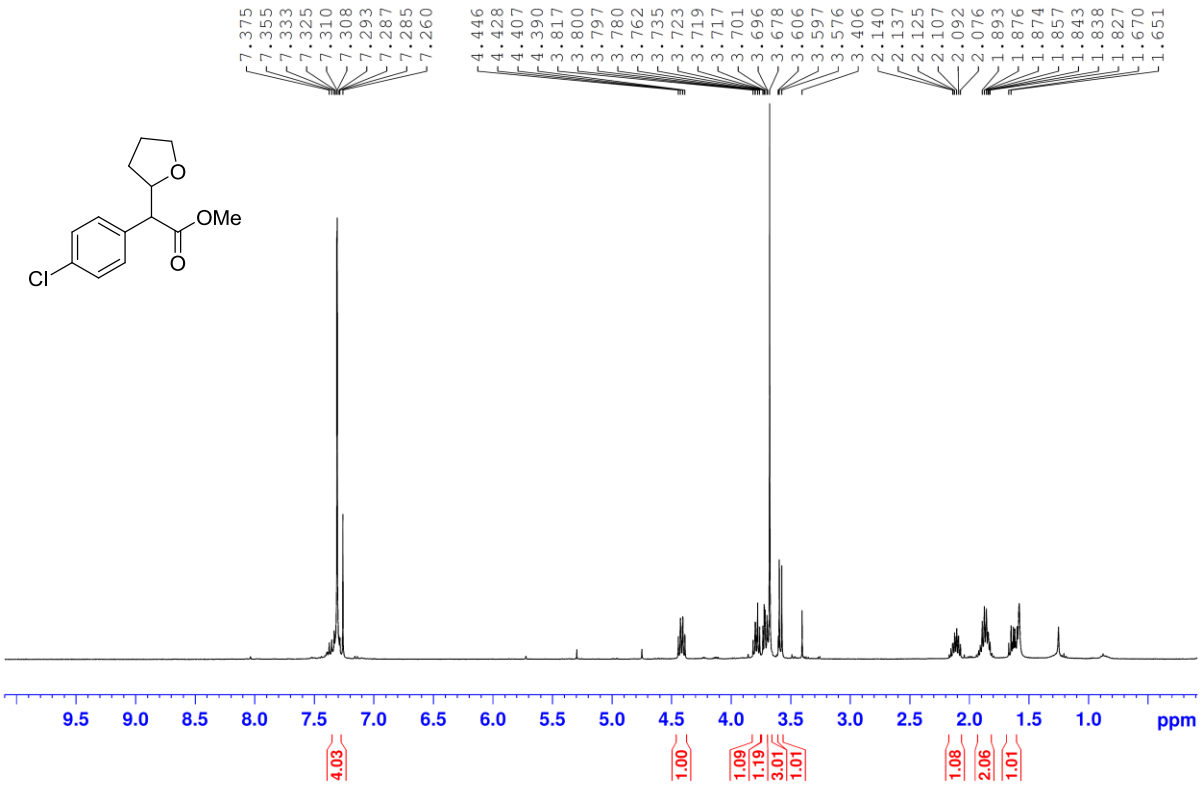
^{1}H and ^{13}C NMR spectra of compound 1.126c-2 (the *syn*-isomer)

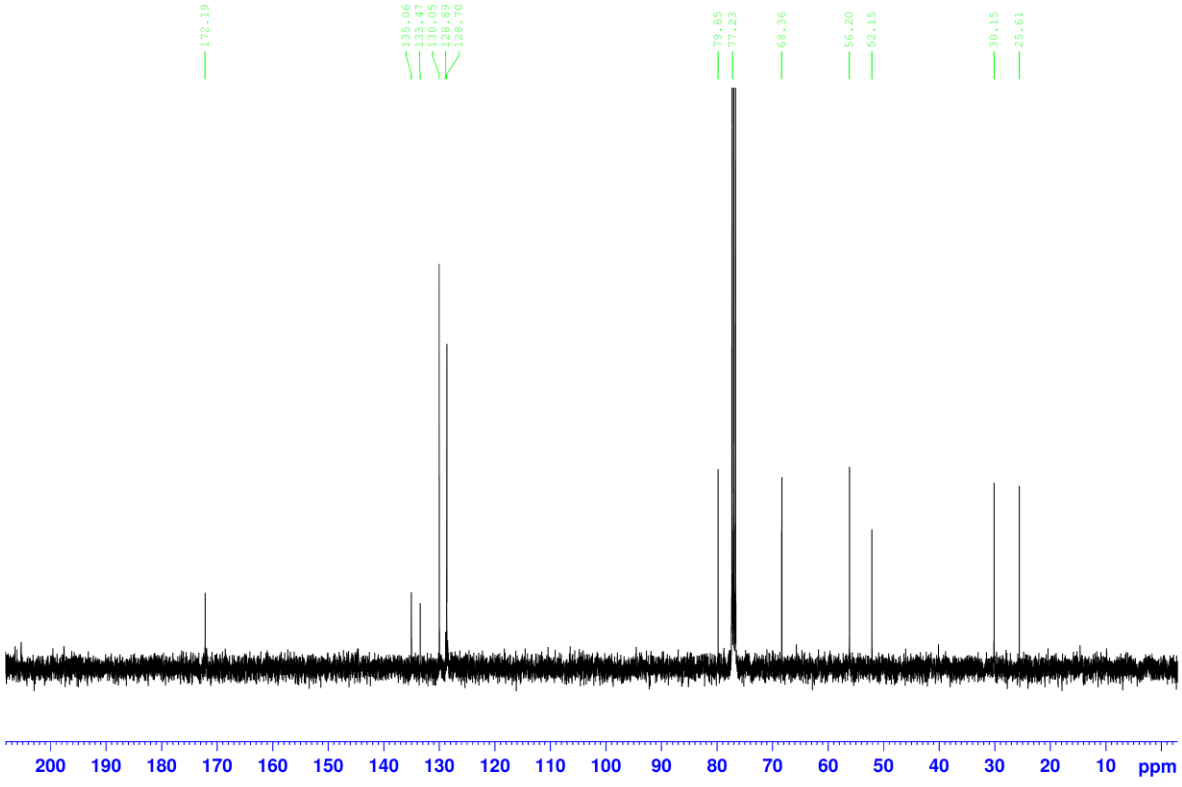


^{1}H and ^{13}C NMR spectra of compound 1.126d-1 (the *anti*-isomer)

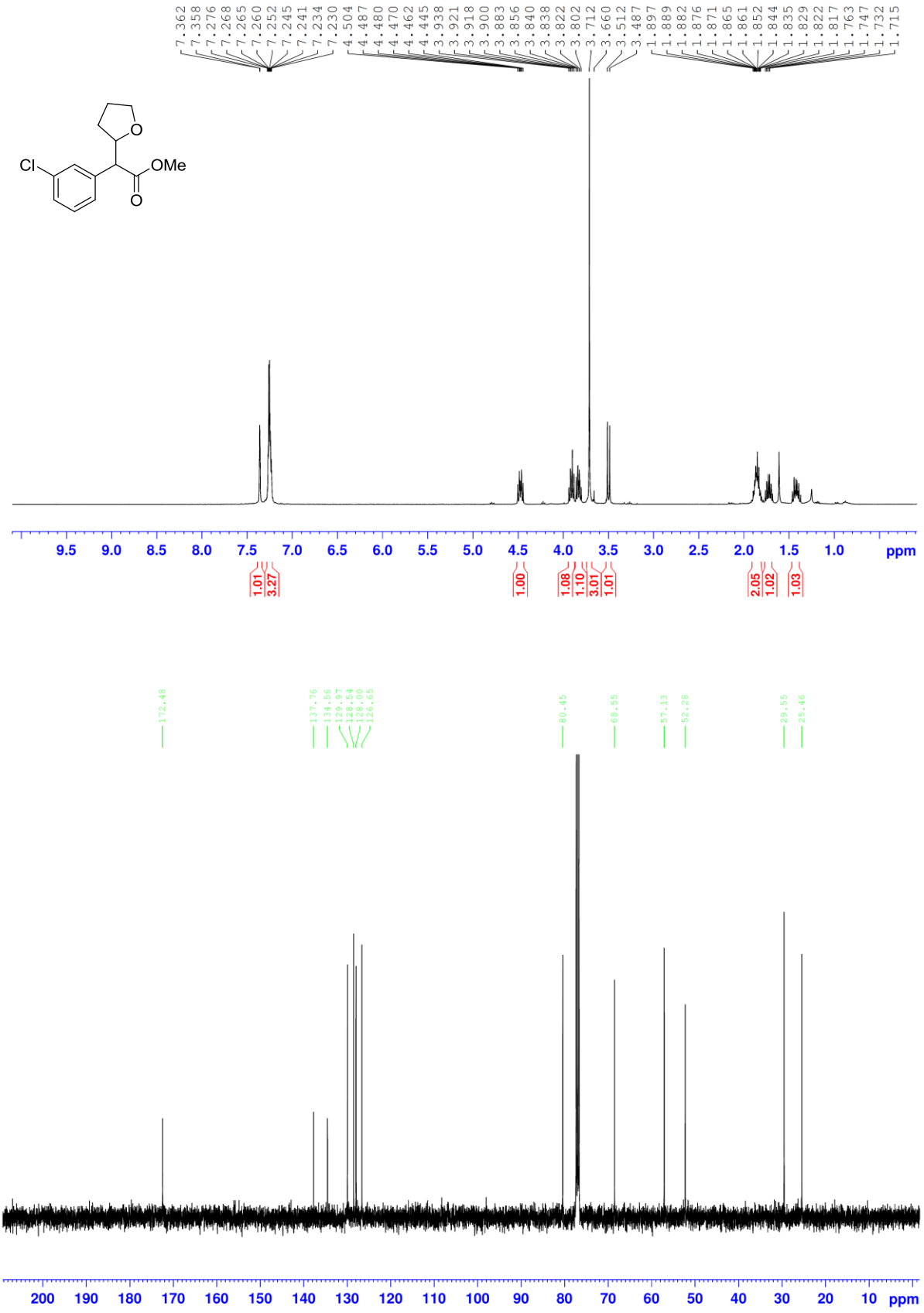


^{1}H and ^{13}C NMR spectra of compound 1.126d-2 (the *syn*-isomer)

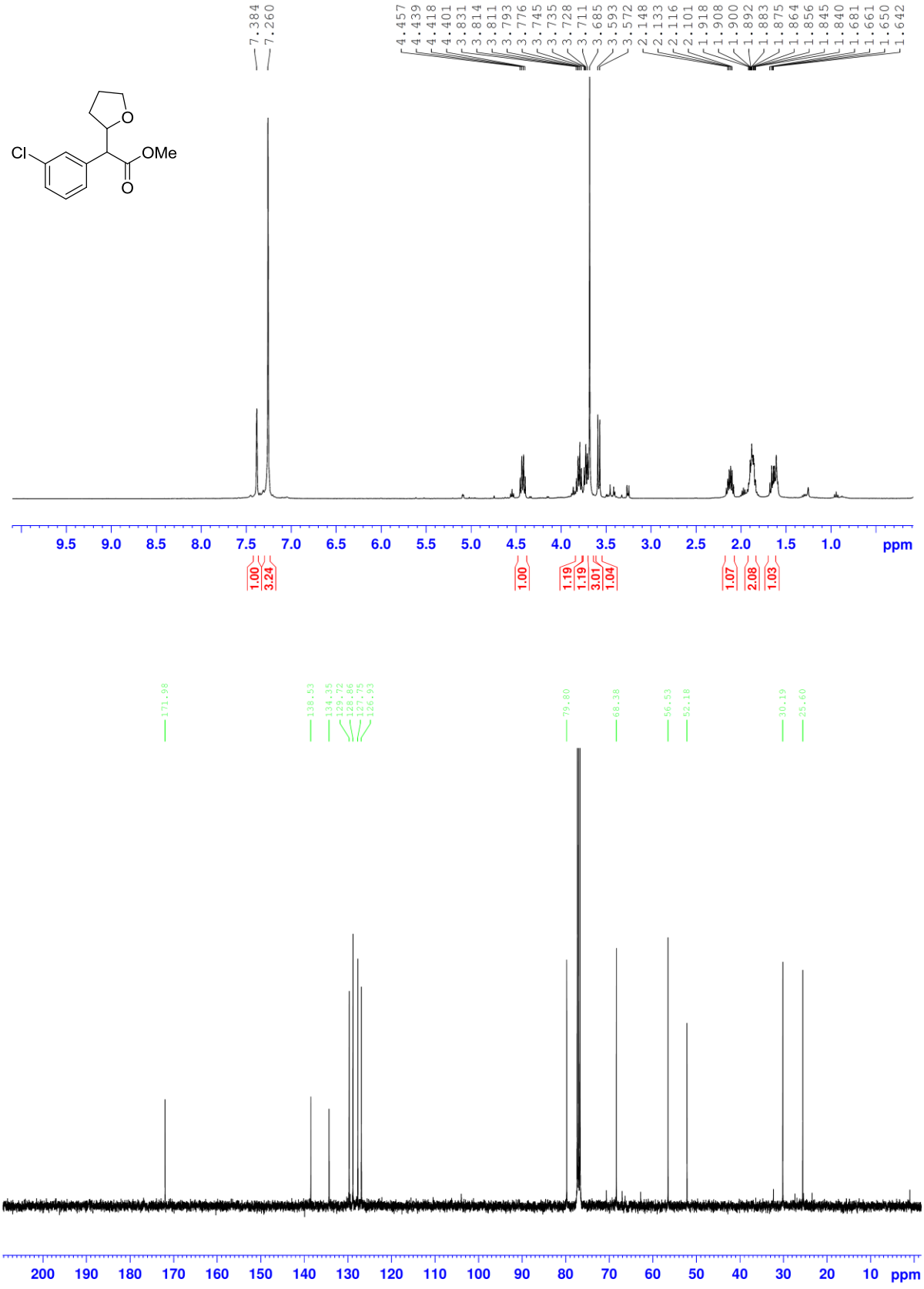




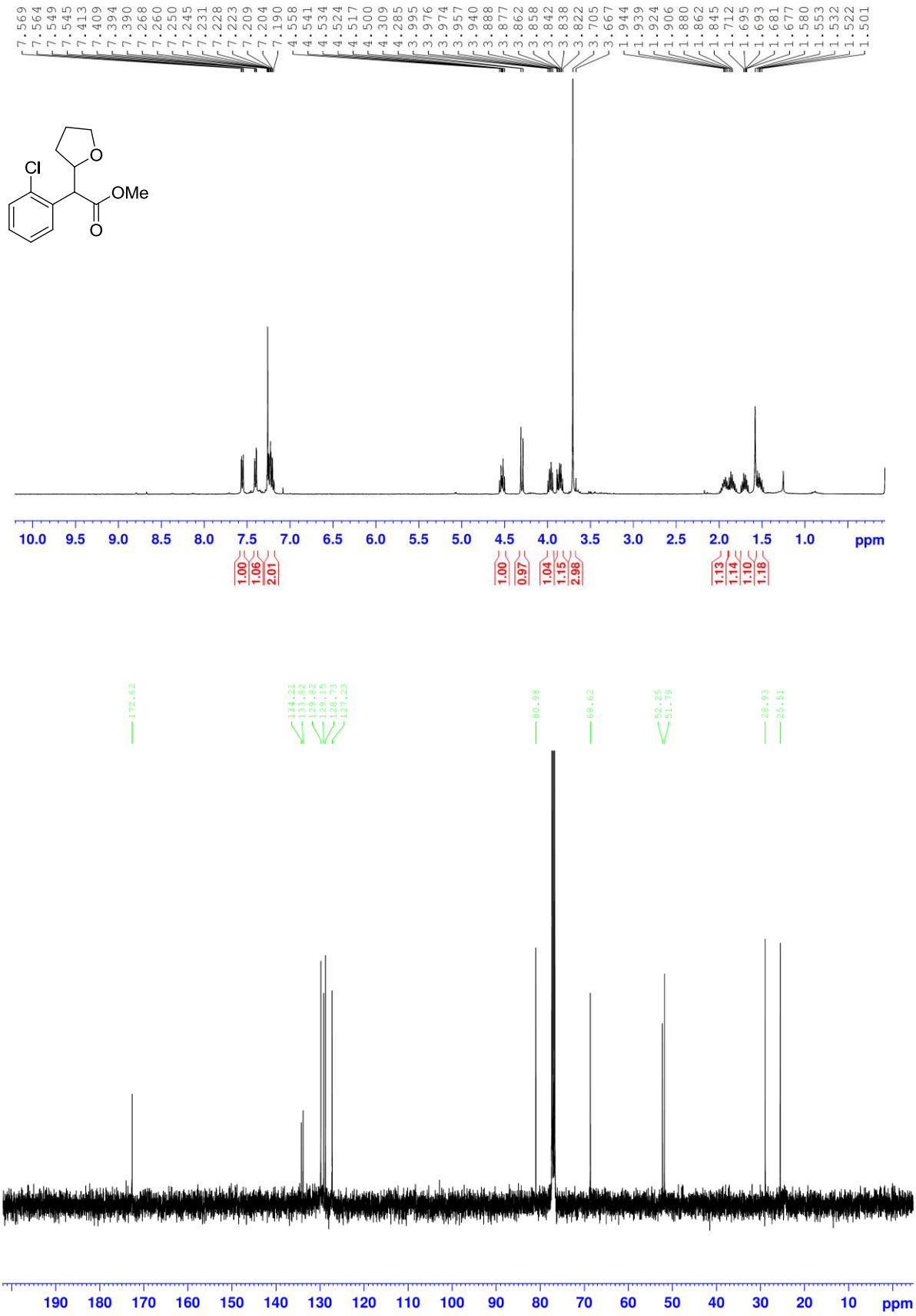
^{1}H and ^{13}C NMR spectra of compound 1.126e-1 (the *anti*-isomer)



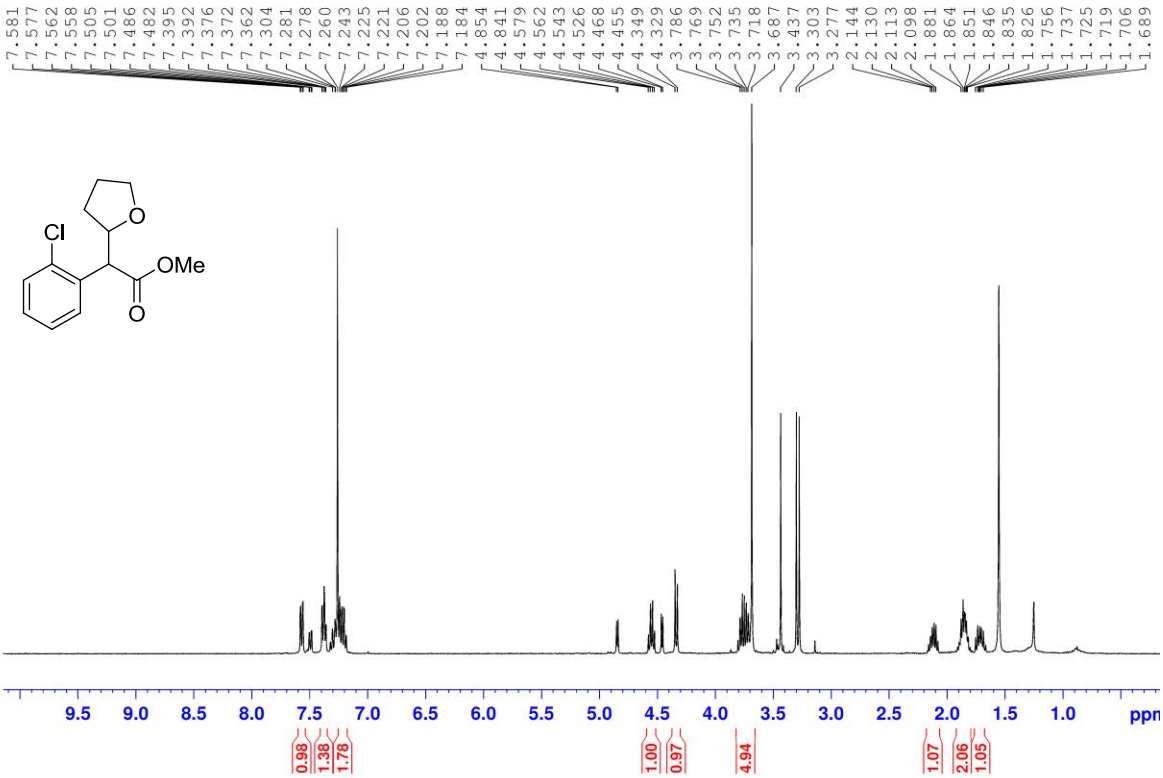
^{1}H and ^{13}C NMR spectra of compound 1.126e-2 (the *syn*-isomer)

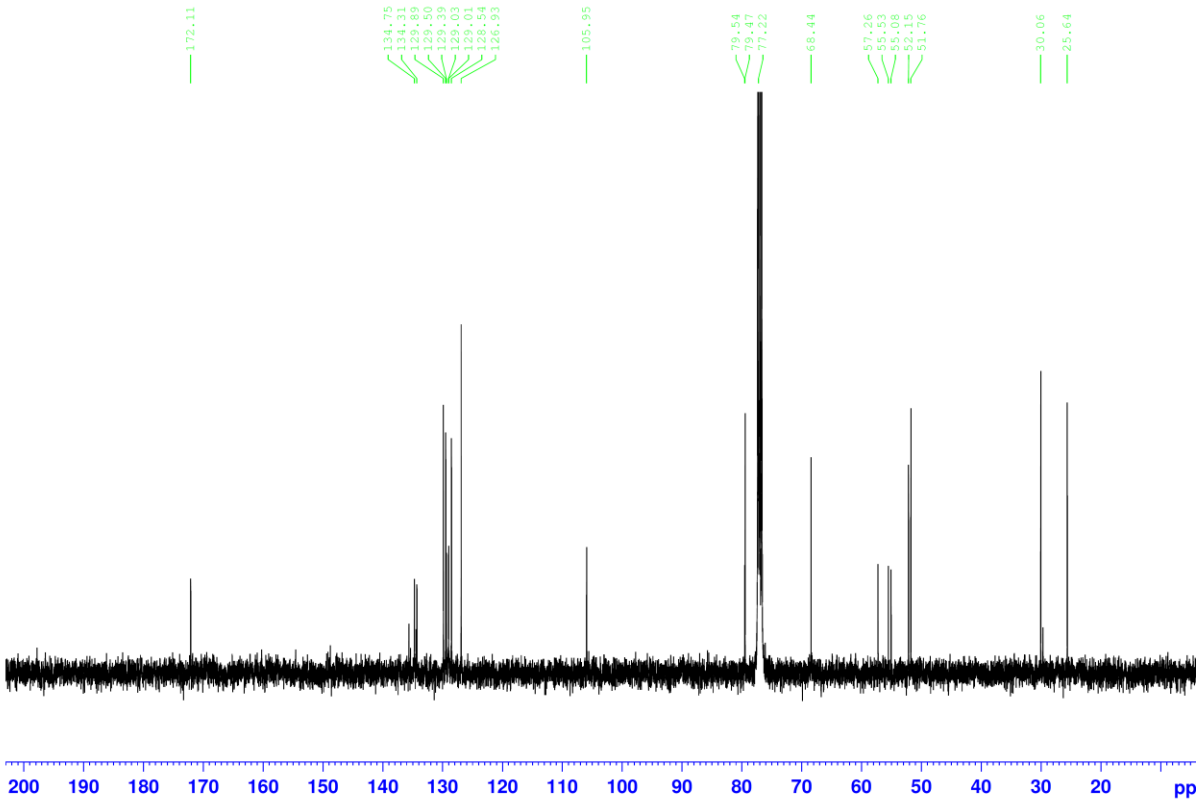


^{1}H and ^{13}C NMR spectra of compound 1.126f-1 (the *anti*-isomer)

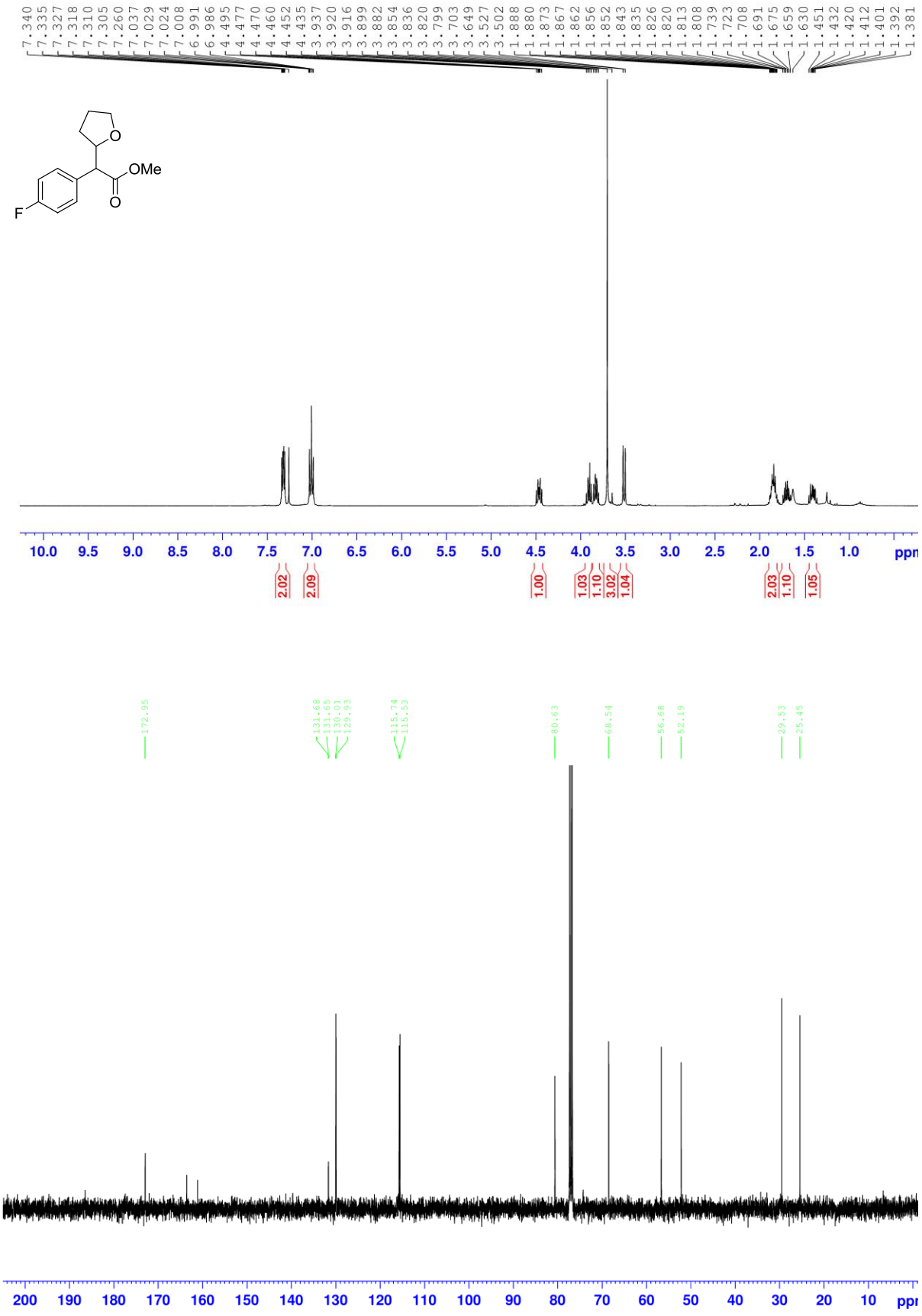


^{1}H and ^{13}C NMR spectra of compound 1.126f-2 (the *syn*-isomer)

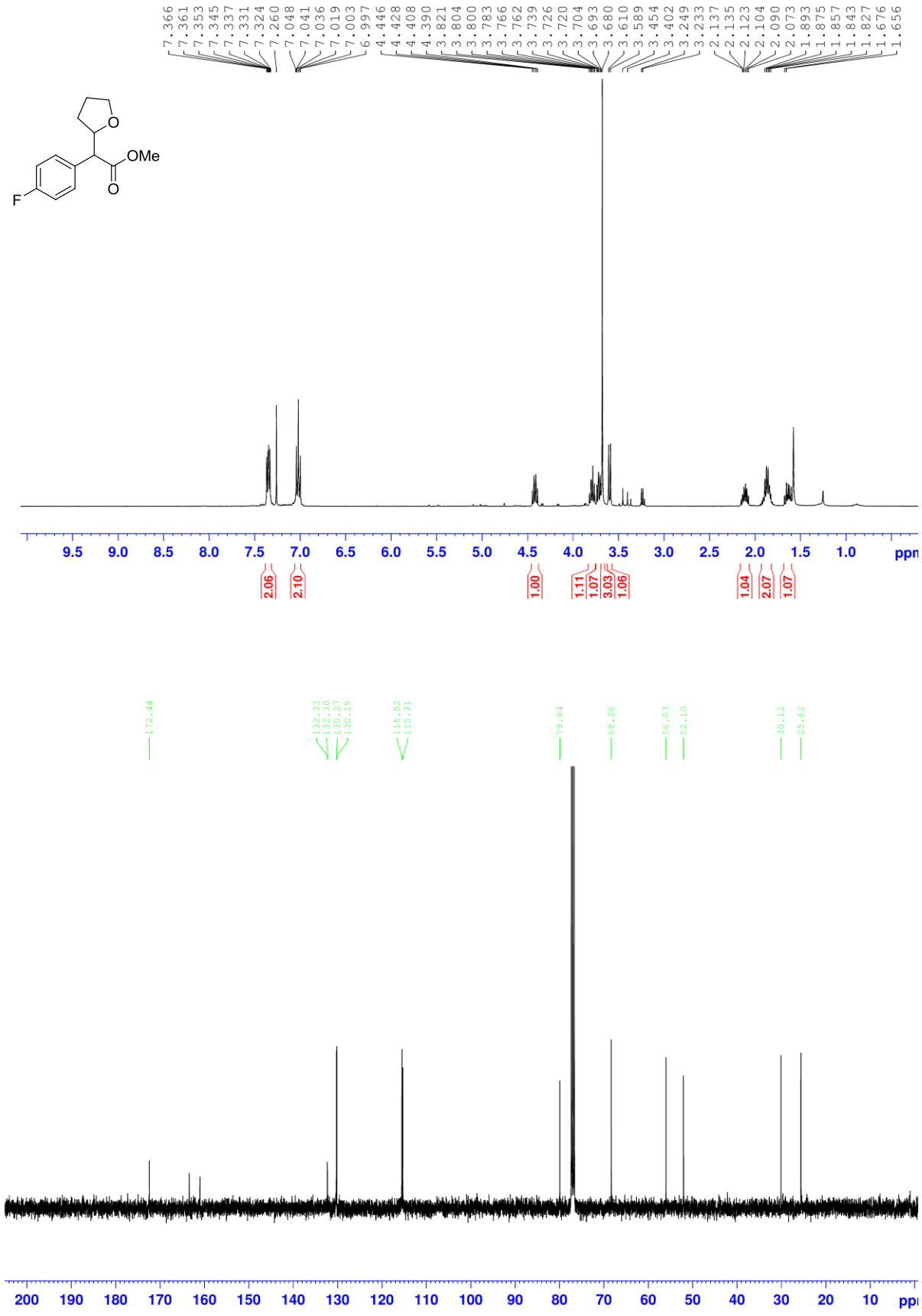




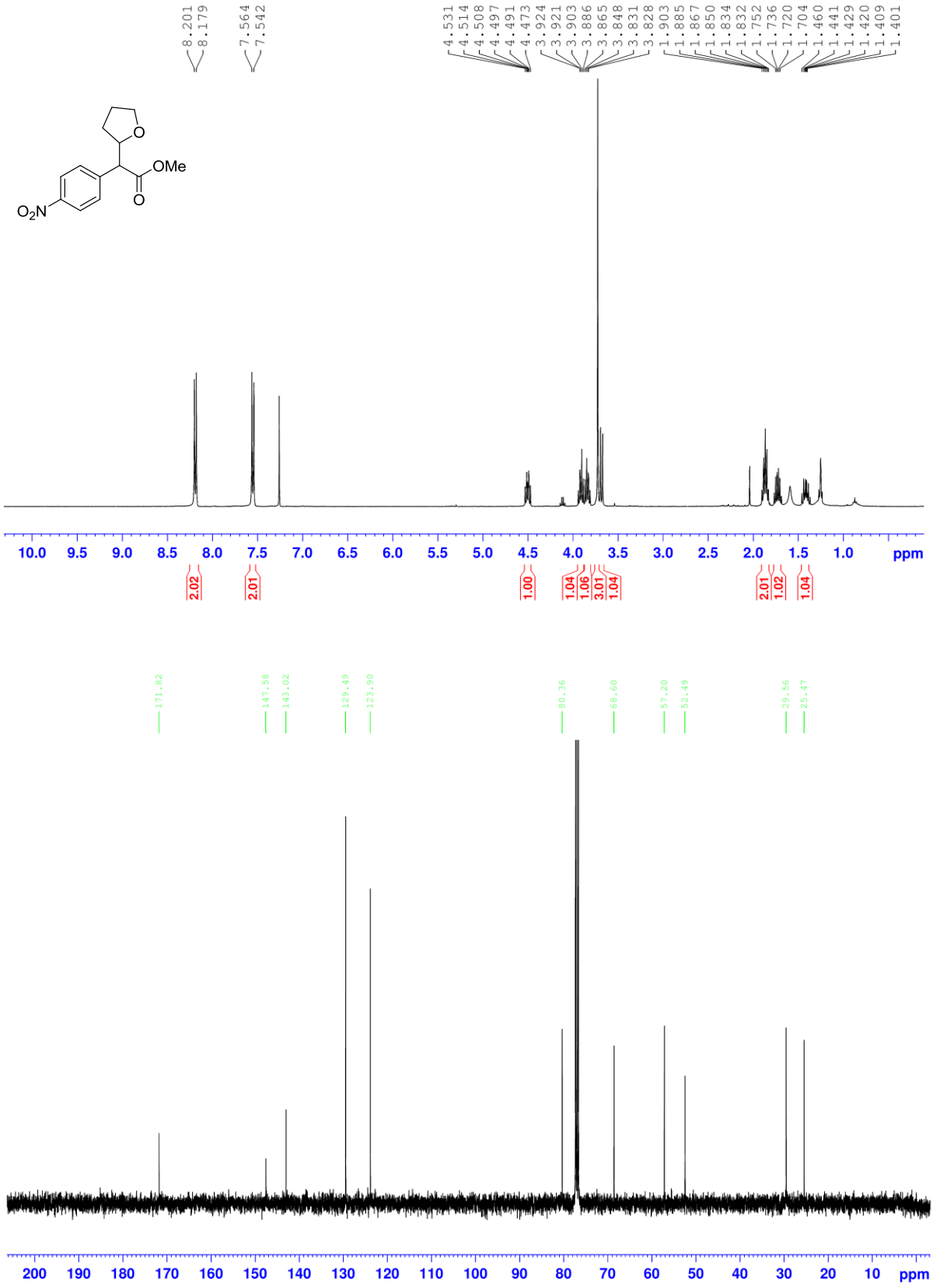
^{1}H and ^{13}C NMR spectra of compound 1.126g-1 (the *anti*-isomer)



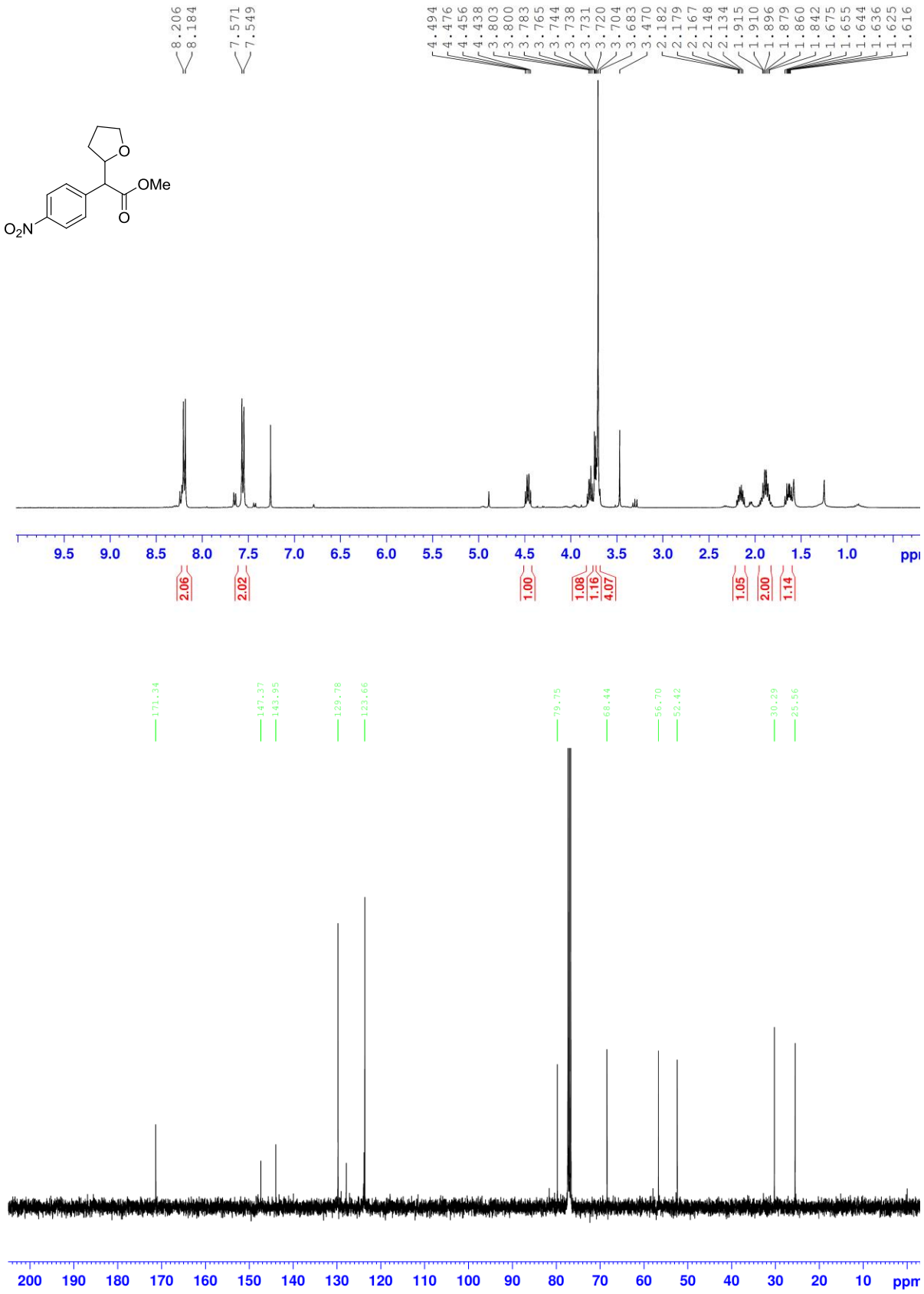
^{1}H and ^{13}C NMR spectra of compound 1.126g-2 (the *syn*-isomer)



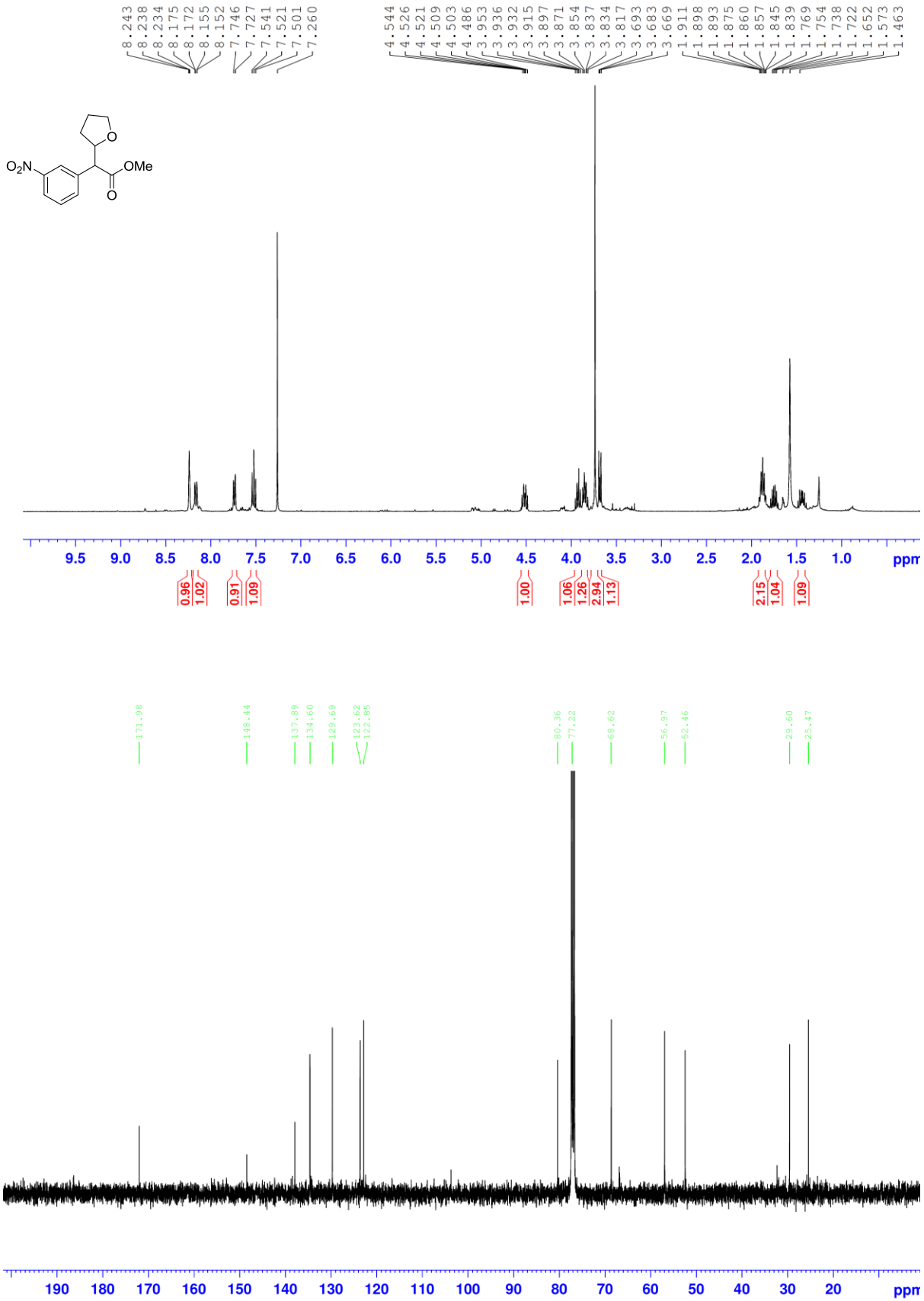
^{1}H and ^{13}C NMR spectra of compound 1.126h-1 (the *anti*-isomer)



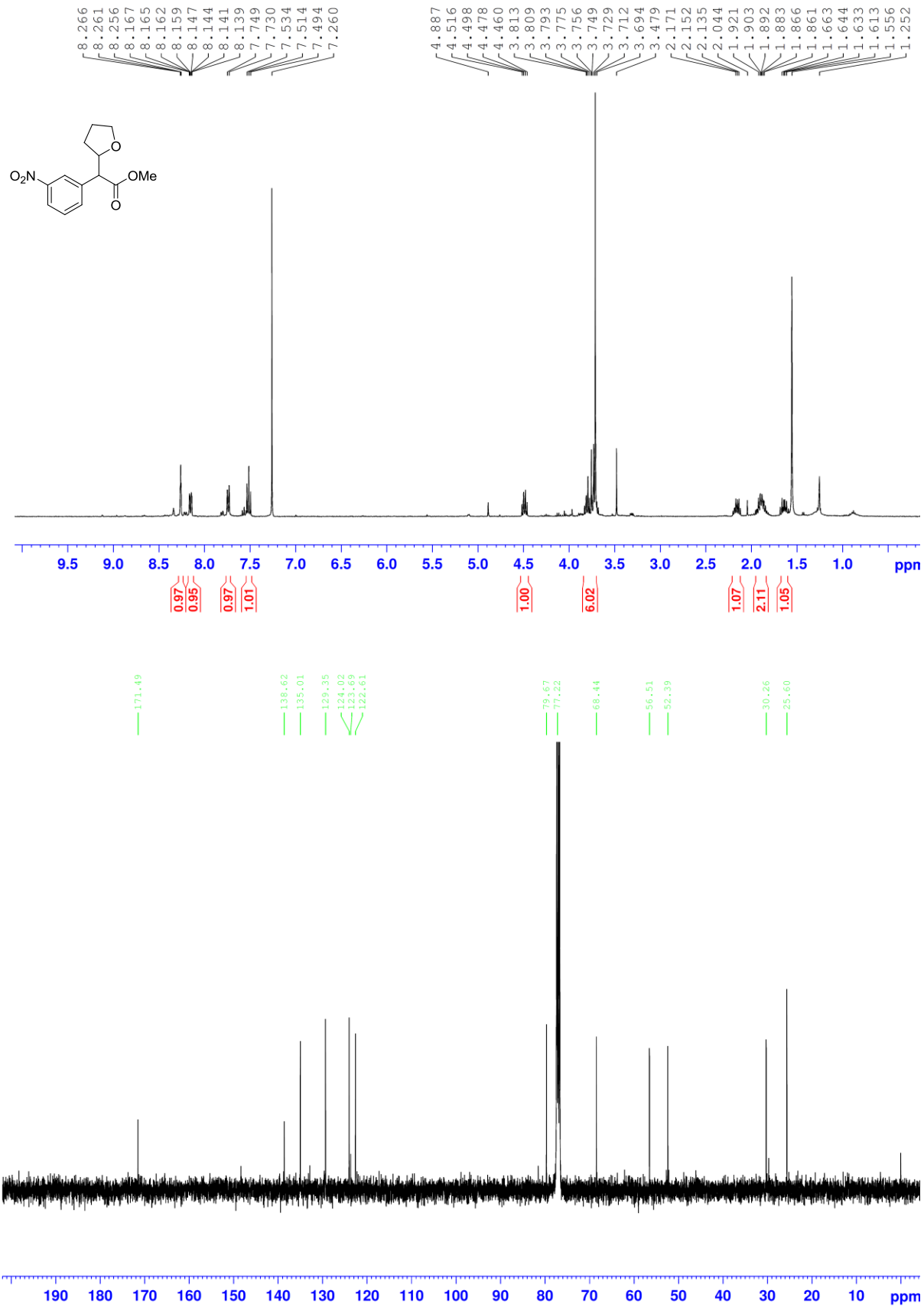
^{1}H and ^{13}C NMR spectra of compound 1.126h-2 (the *syn*-isomer)



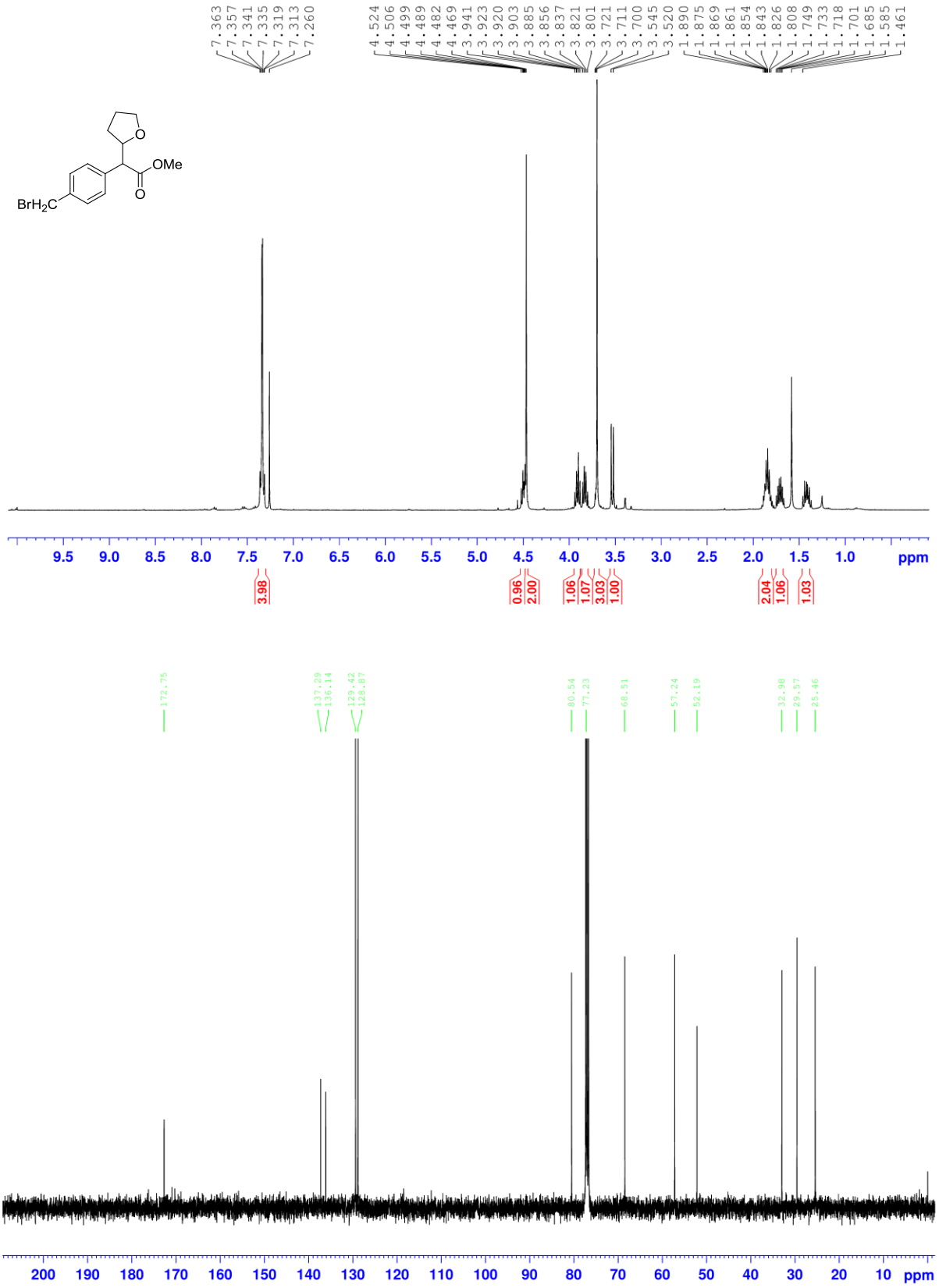
^{1}H and ^{13}C NMR spectra of compound 1.126i-1 (the *anti*-isomer)



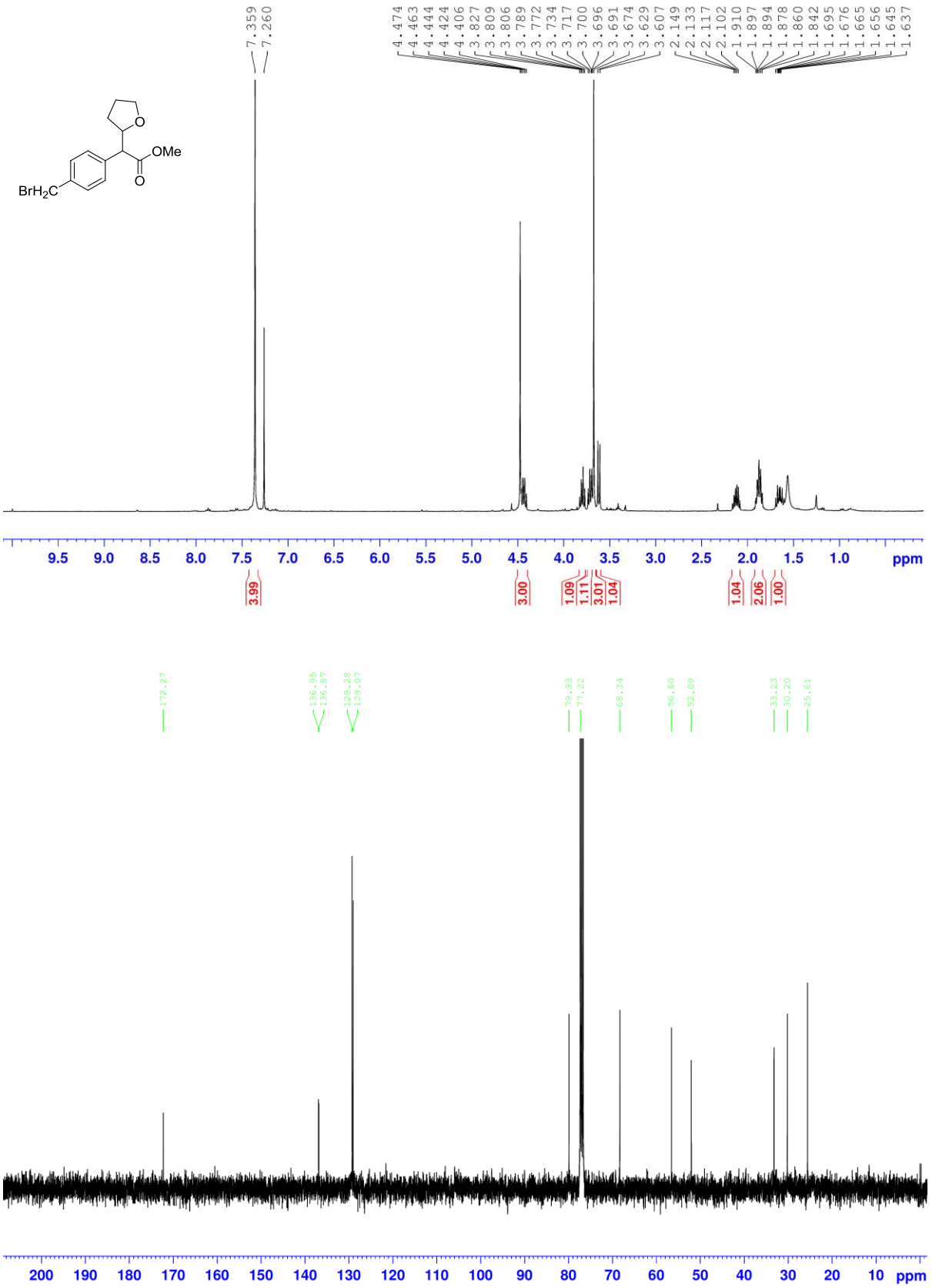
^{1}H and ^{13}C NMR spectra of compound 1.126i-2 (the *syn*-isomer)



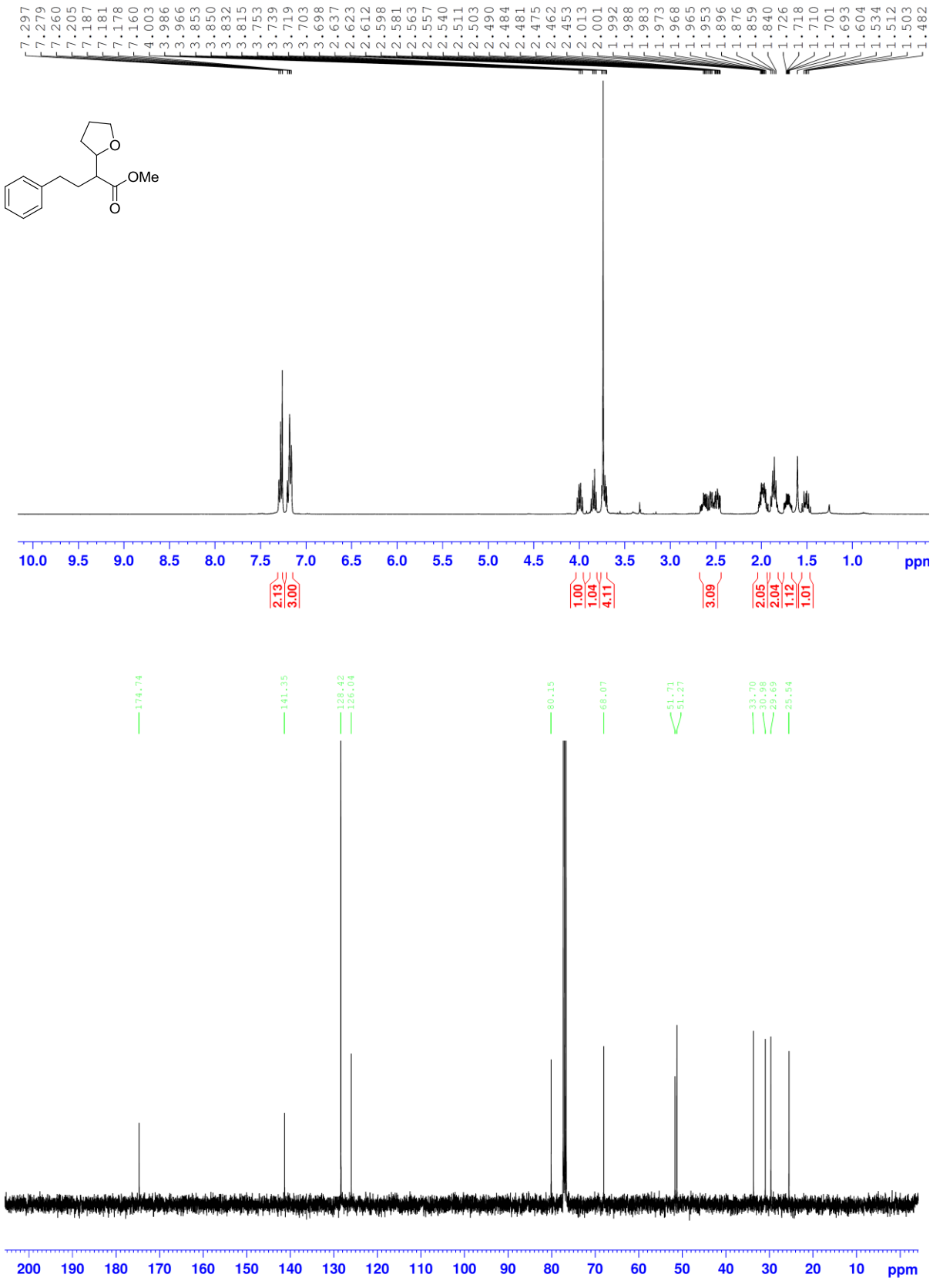
^{1}H and ^{13}C NMR spectra of compound 1.126j-1 (the *anti*-isomer)



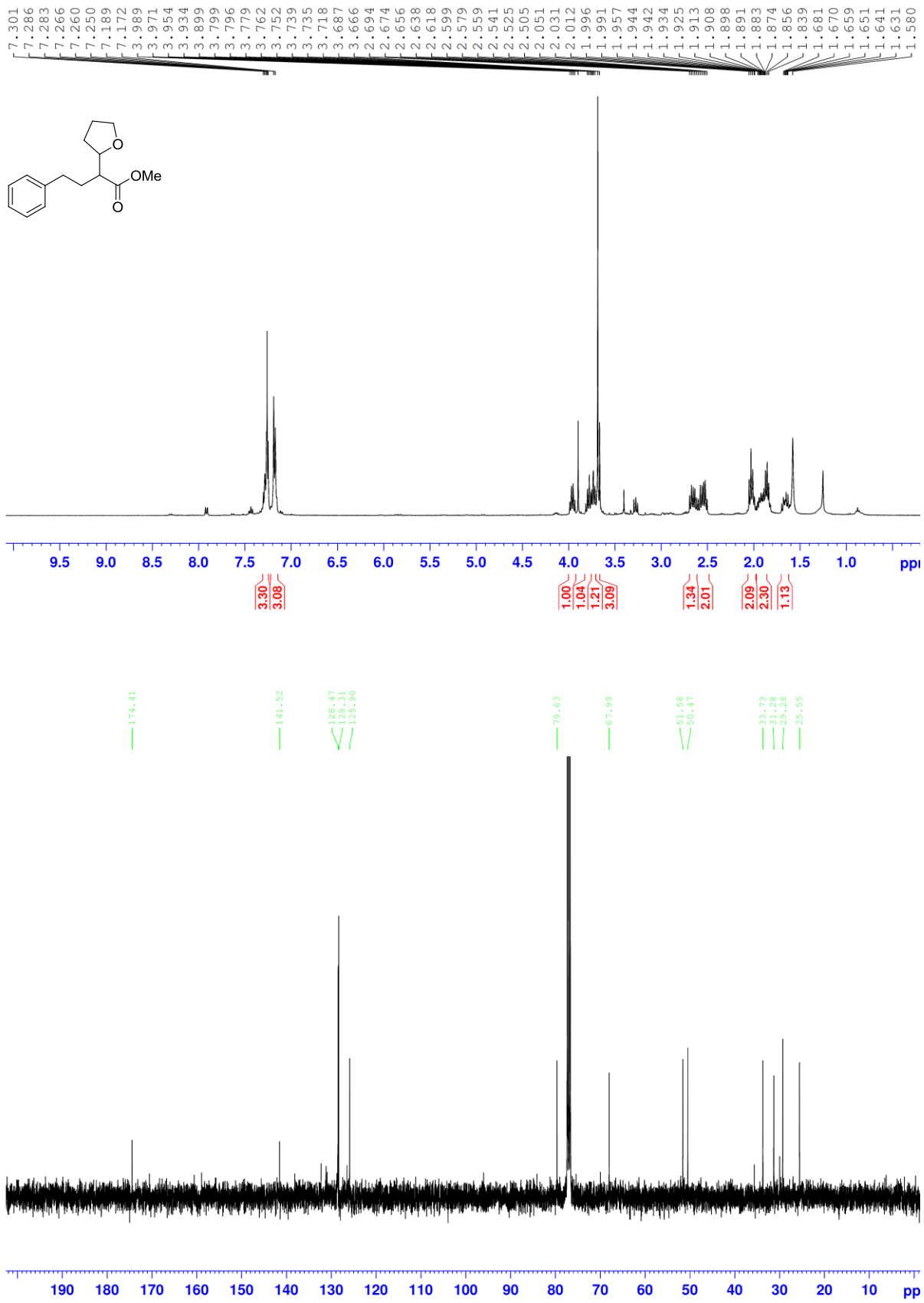
^{1}H and ^{13}C NMR spectra of compound 1.126j-2 (the *syn*-isomer)



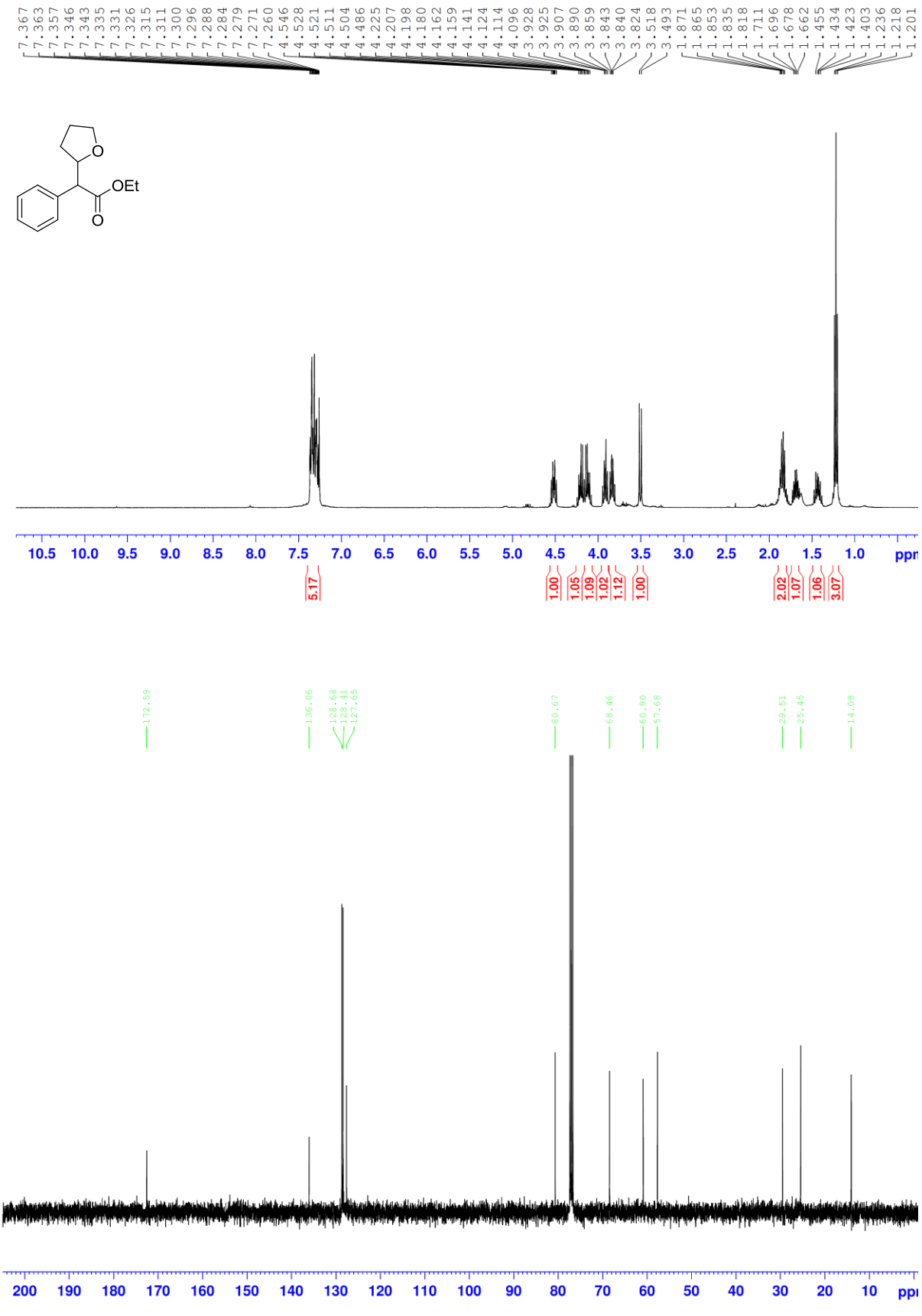
^{1}H and ^{13}C NMR spectra of compound 1.126m-1 (the *anti*-isomer)



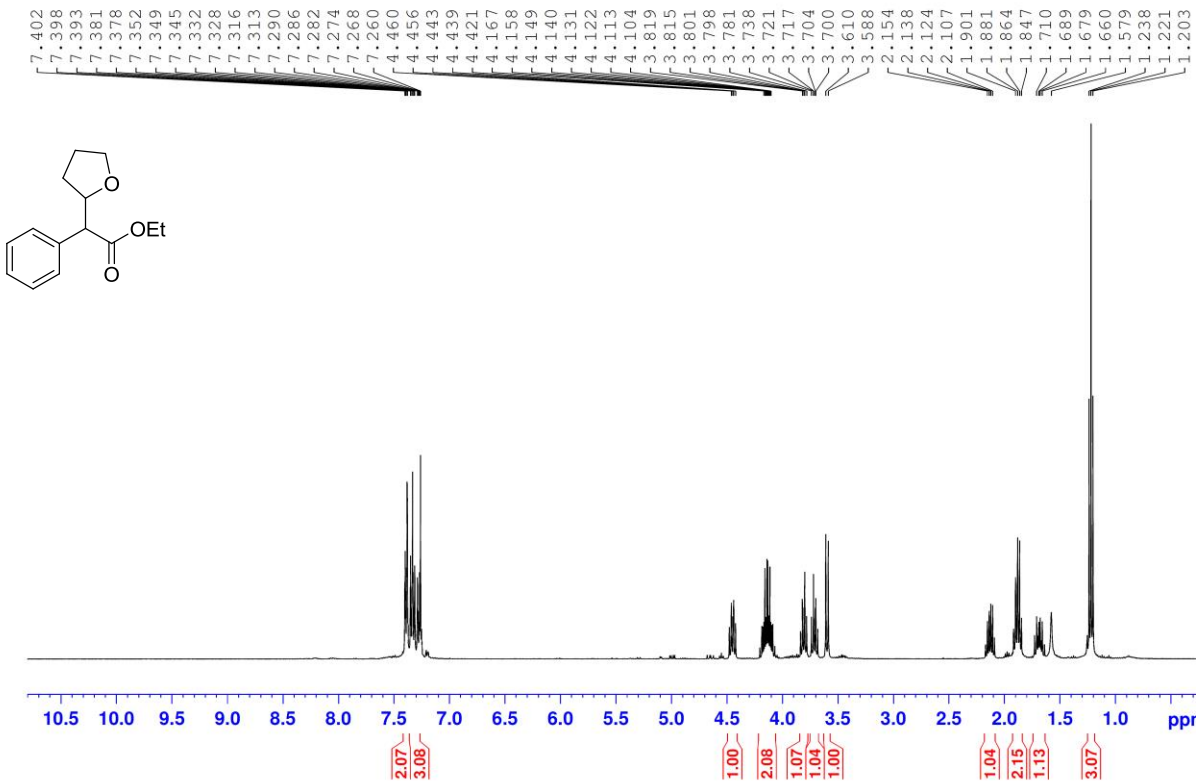
^{1}H and ^{13}C NMR spectra of compound 1.126m-2 (the *syn*-isomer)

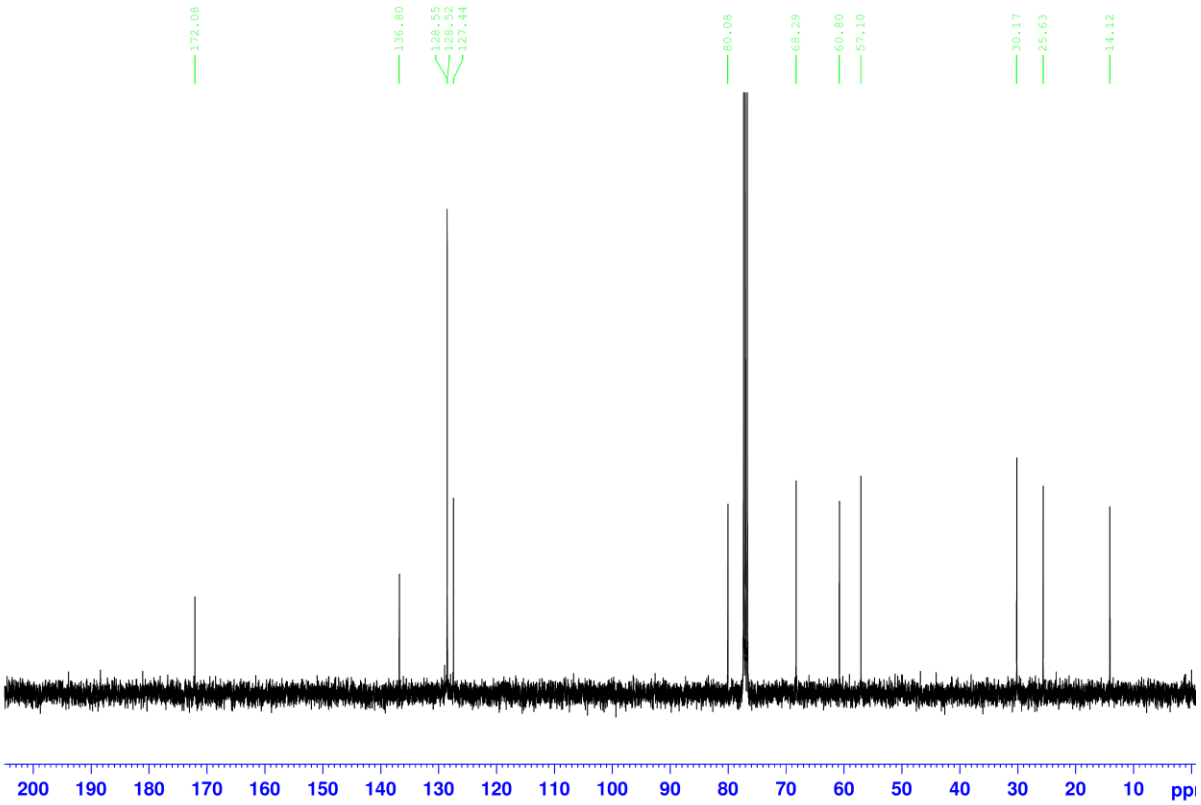


^{1}H and ^{13}C NMR spectra of compound 1.126o-1 (the *anti*-isomer)

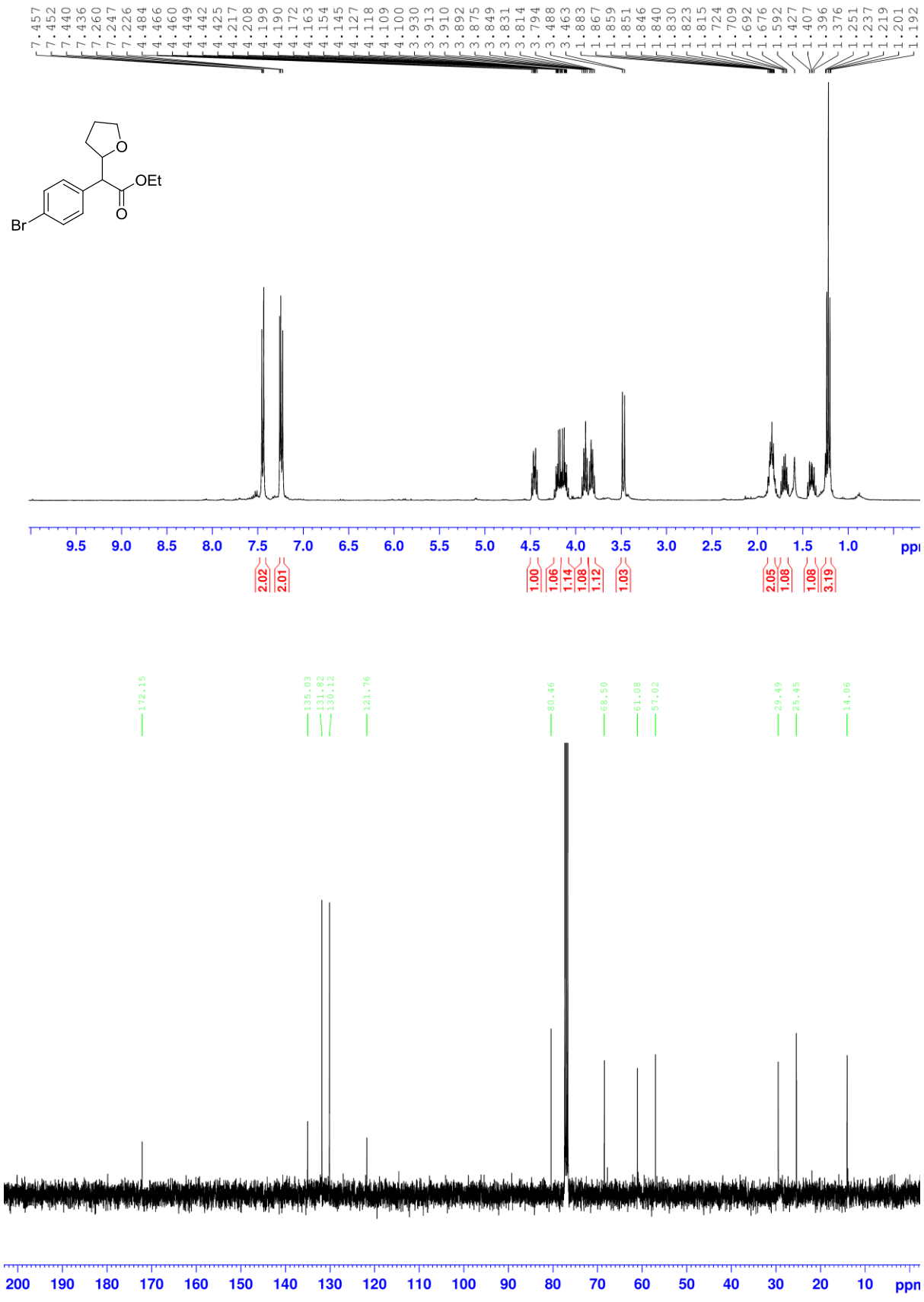


^{1}H and ^{13}C NMR spectra of compound 1.126o-2 (the *syn*-isomer)

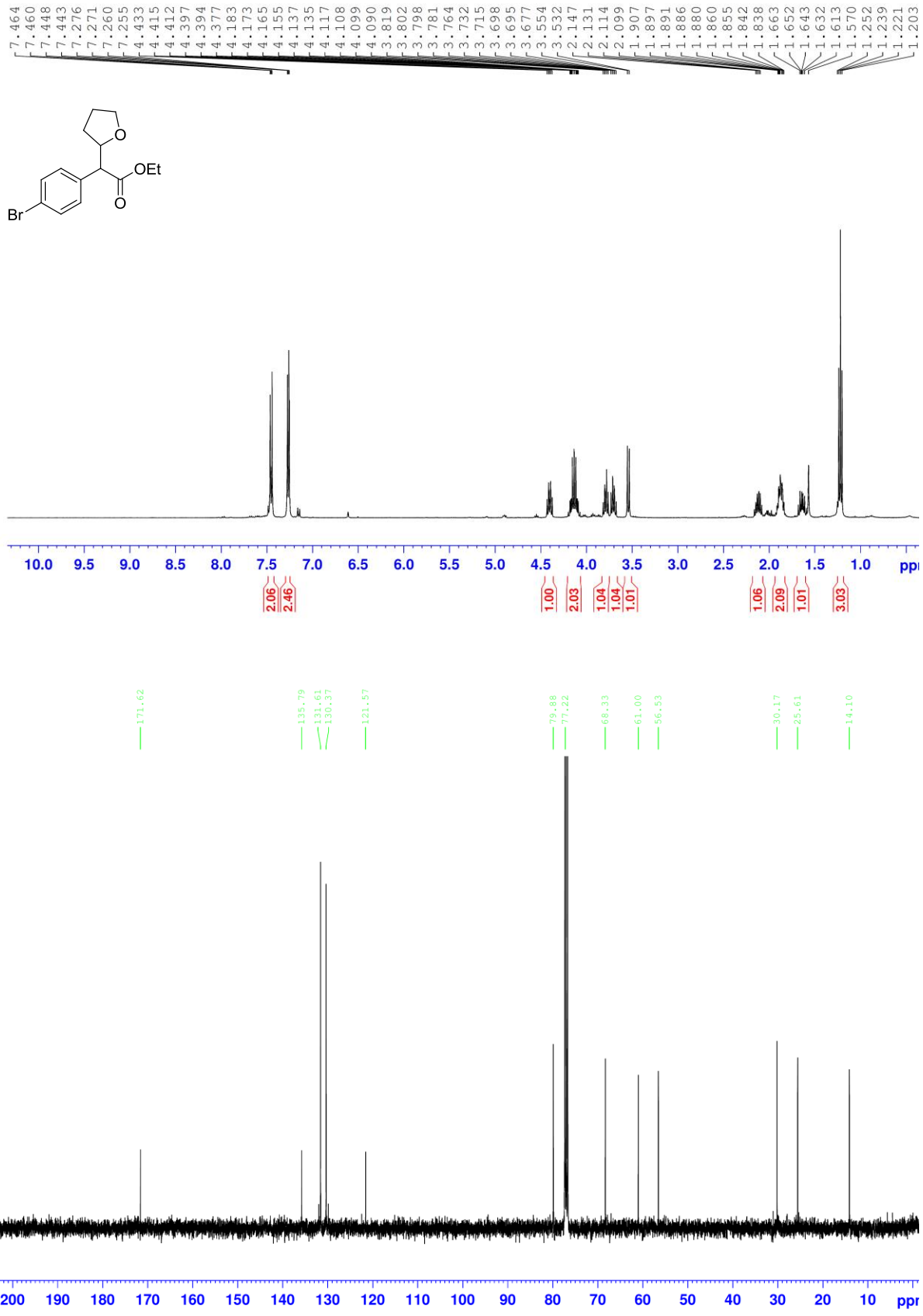




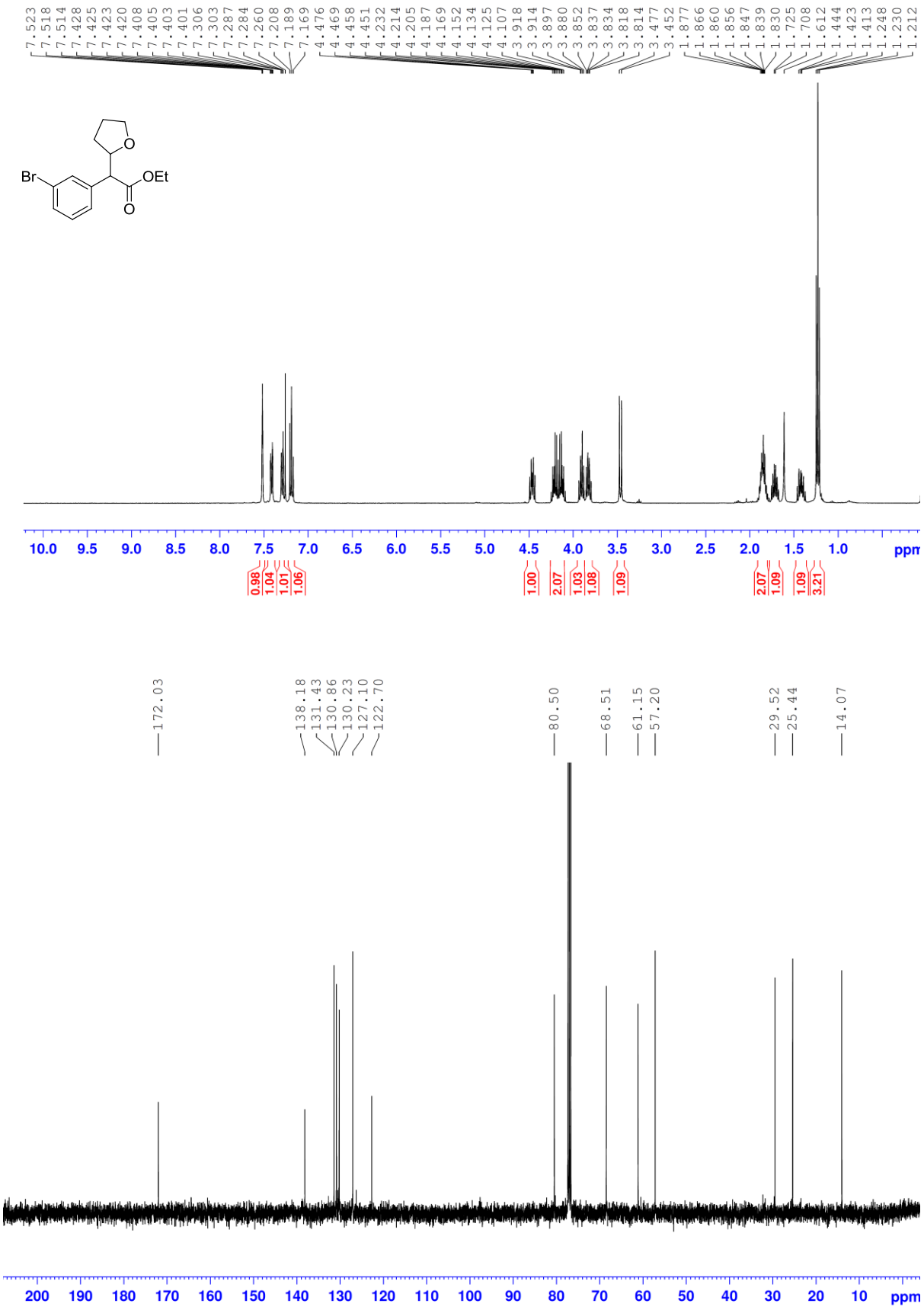
^{1}H and ^{13}C NMR spectra of compound 1.126p-1 (the *anti*-isomer)



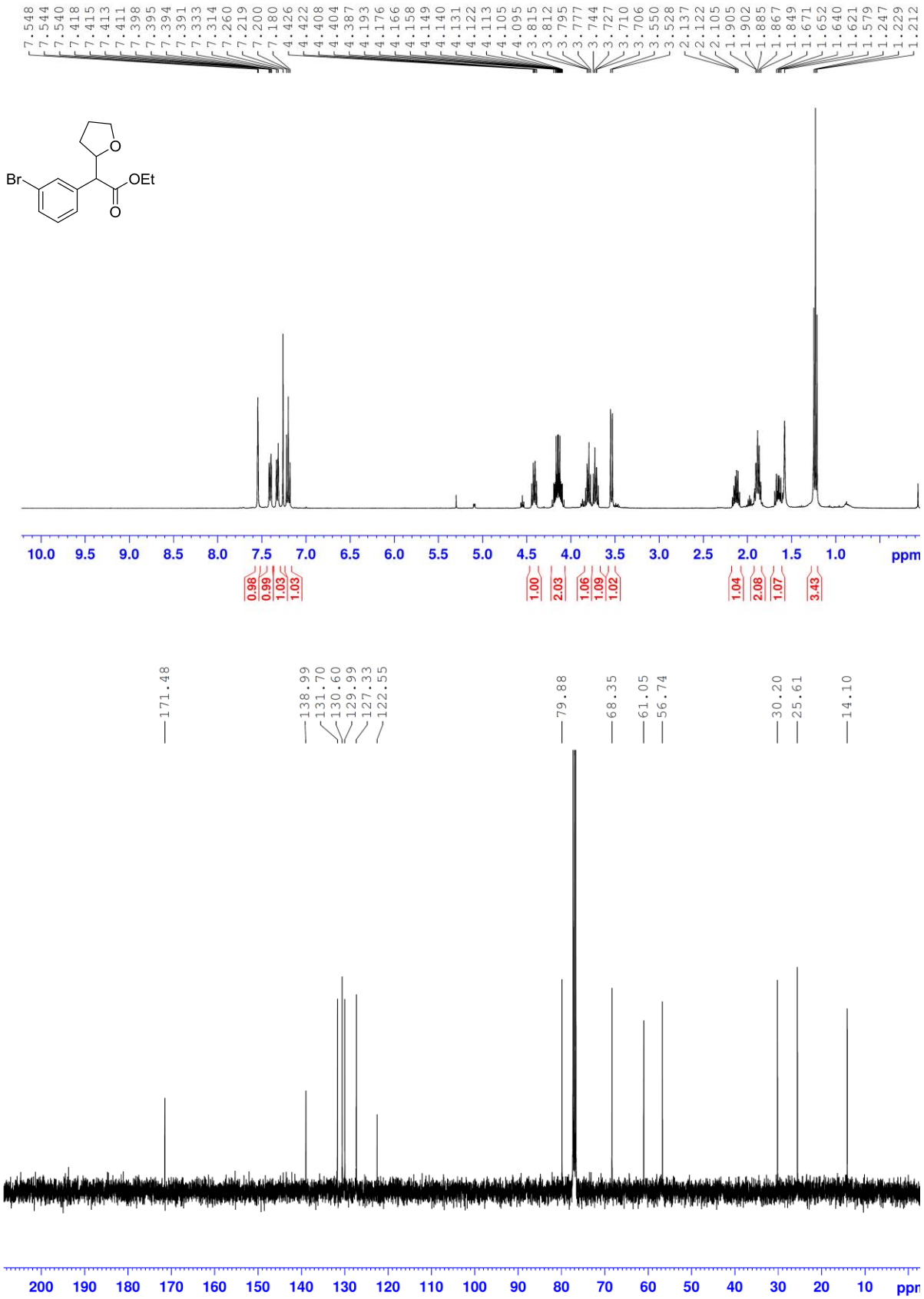
^{1}H and ^{13}C NMR spectra of compound 1.126p-2 (the *syn*-isomer)



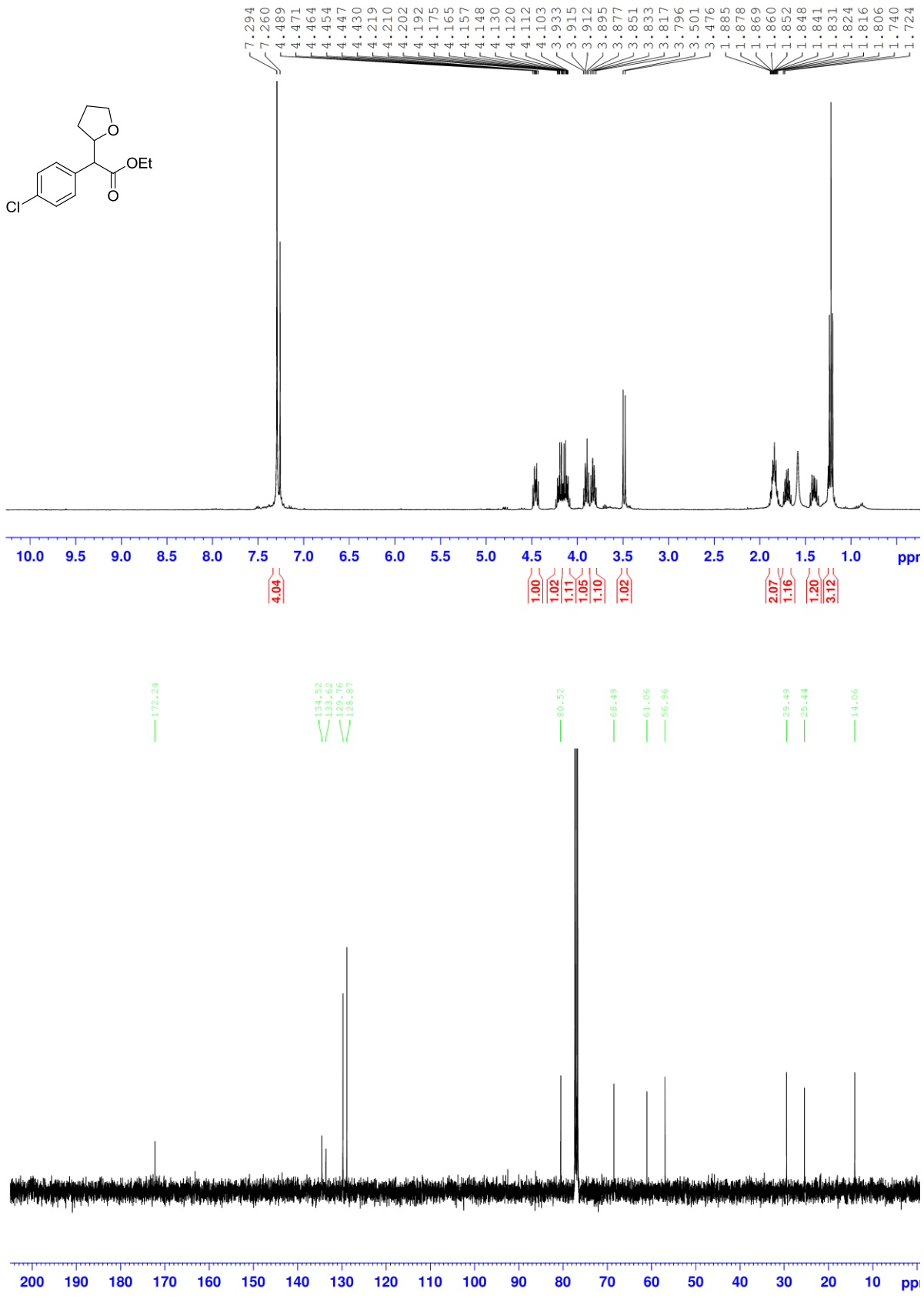
^{1}H and ^{13}C NMR spectra of compound 1.126q-1 (the *anti*-isomer)



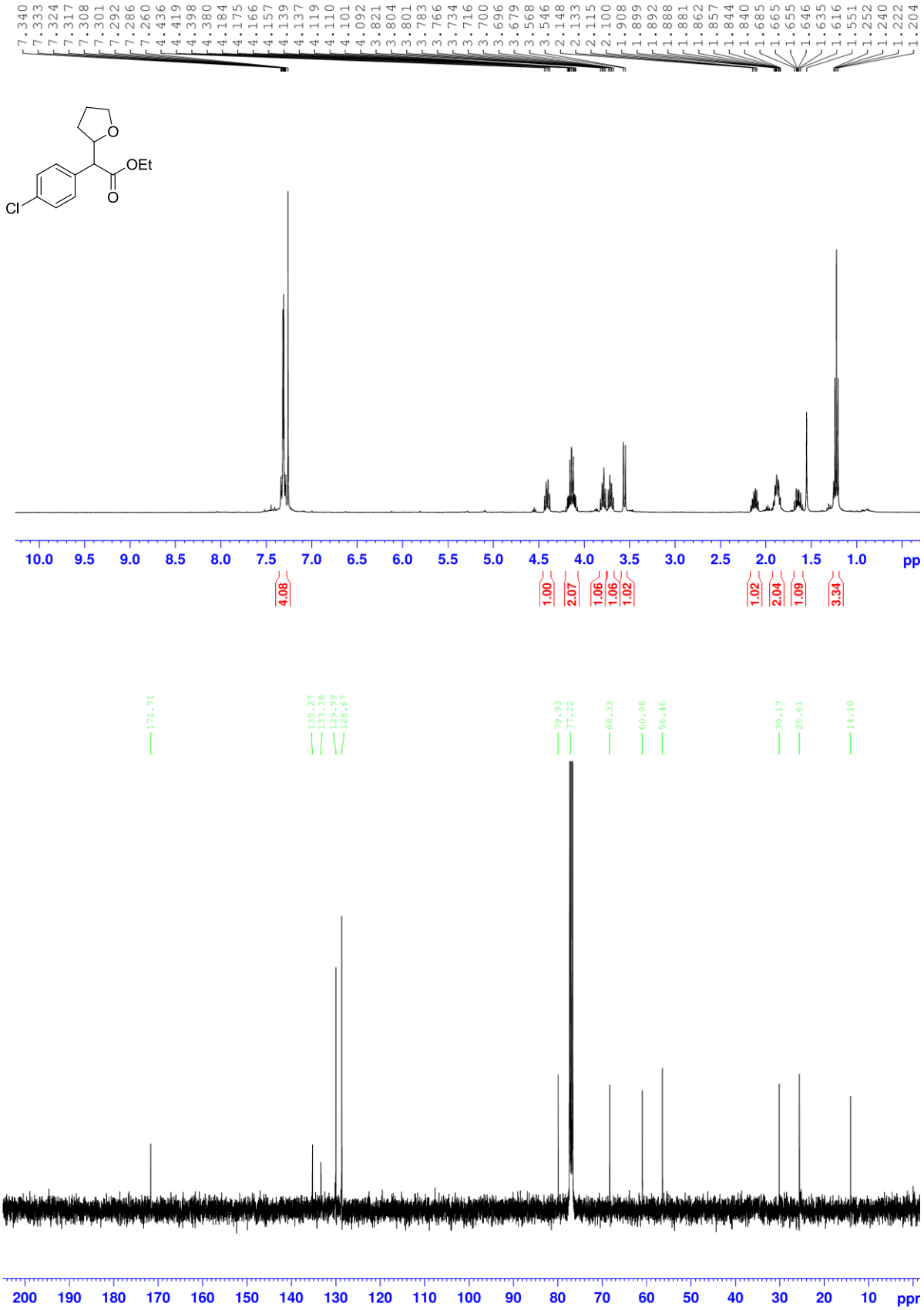
^{1}H and ^{13}C NMR spectra of compound 1.126q-2 (the *syn*-isomer)



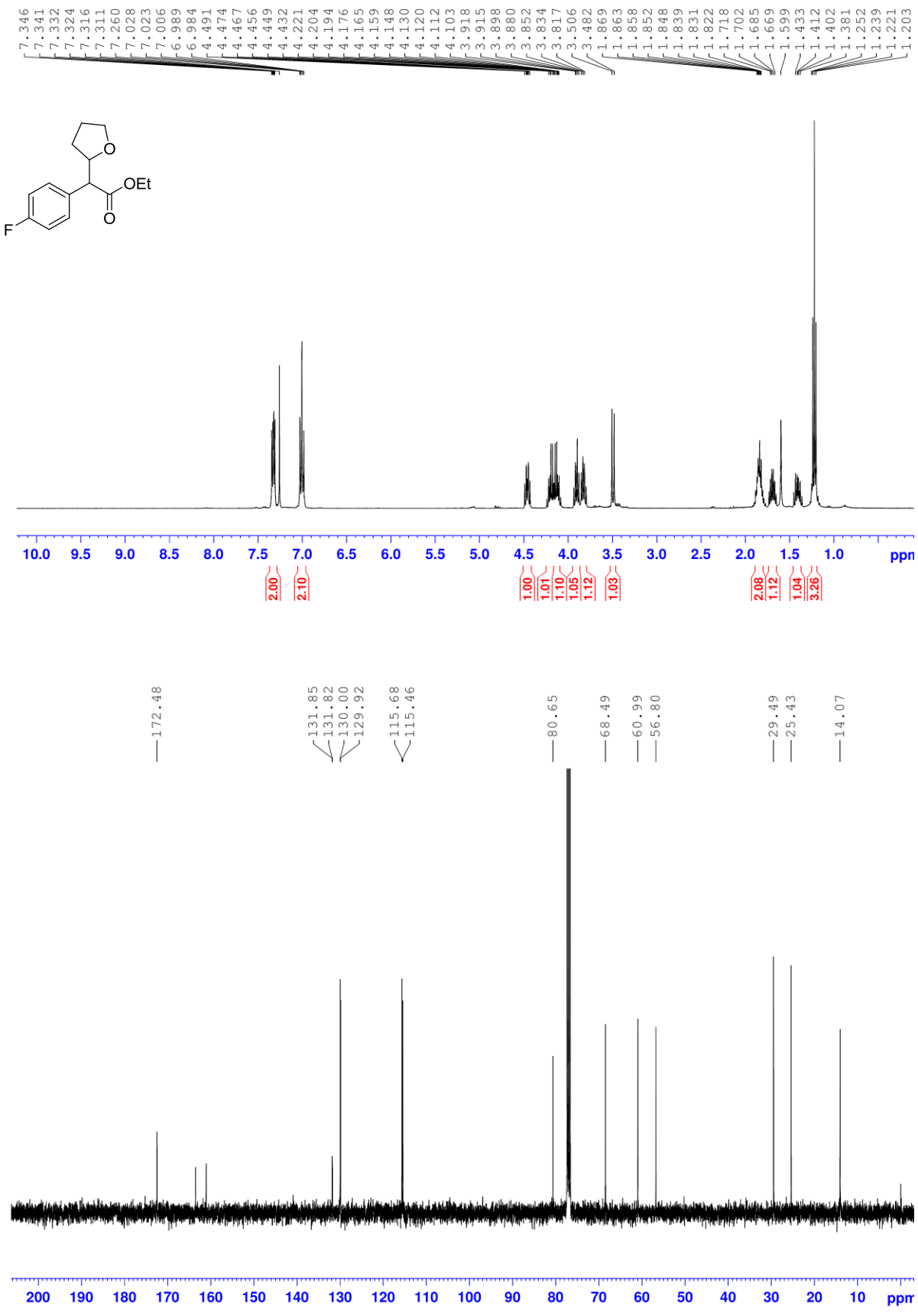
^{1}H and ^{13}C NMR spectra of compound 1.126r-1 (the *anti*-isomer)



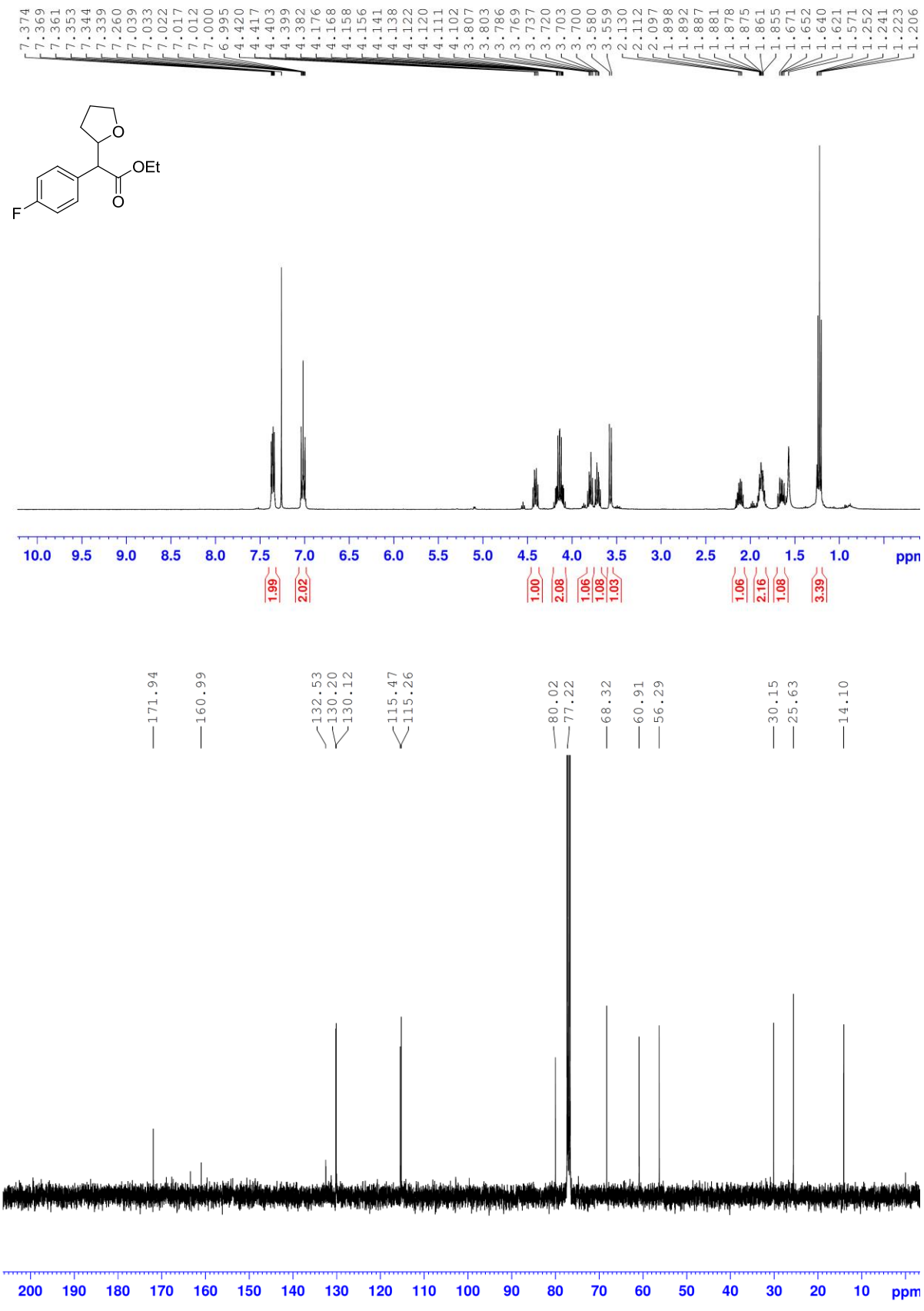
^{1}H and ^{13}C NMR spectra of compound 1.126r-2 (the *syn*-isomer)



^{1}H and ^{13}C NMR spectra of compound 1.126s-1 (the *anti*-isomer)



^{1}H and ^{13}C NMR spectra of compound 1.126s-2 (the *syn*-isomer)



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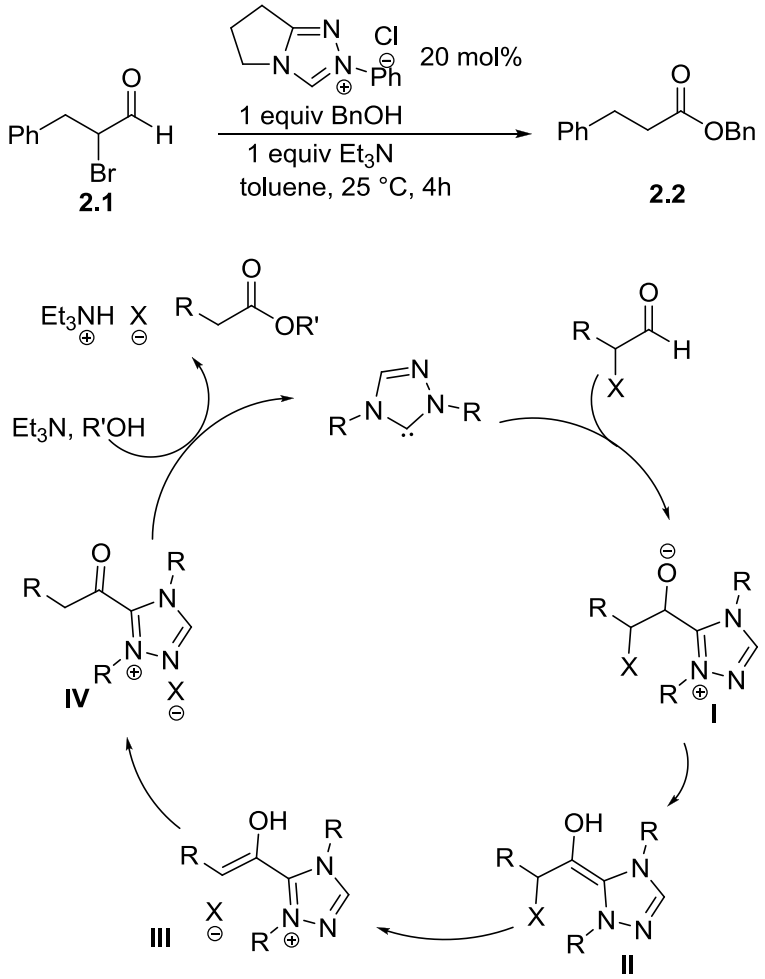
Chapter 2

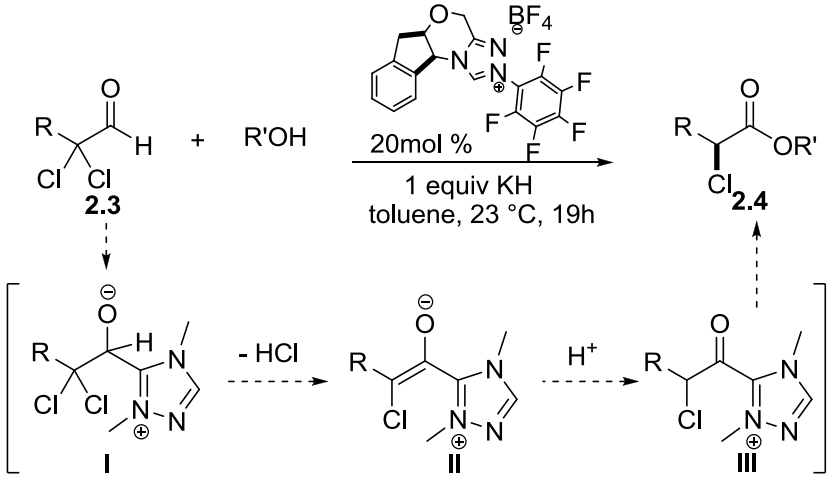
N-Heterocyclic Carbene-Catalyzed Oxidative Esterification of Aldehydes

2.1 Introduction

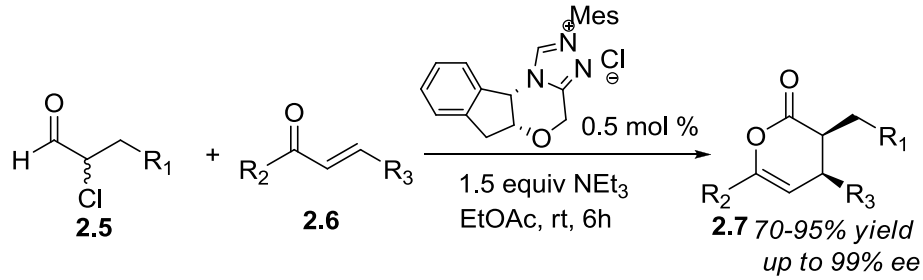
The umpolung reactions catalyzed by *N*-heterocyclic carbenes (NHC) provide an unconventional access to various important target molecules.[1,2] One important example among these cases is NHC-catalyzed one-pot esterification of aldehydes.[3-5] Recently, Rovis and Bode groups have reported the NHC-catalyzed synthesis of dehalogenated esters from α-halogenated aldehydes via intramolecular redox reaction (Scheme 1-3).[3b-d] In the internal redox reaction of *α*-haloaldehydes (Scheme 1), the activation of aldehydes is proposed to proceed through the nucleophilic alkene intermediate **II**. Since this intermediate contains a *β*-leaving group, we may access the enol **III** that, following tautomerization, provides the acyl azolium **IV**. Interception of this activated ester with an appropriate nucleophile regenerates this catalyst. In the synthesis of α-chloroesters from 2,2-dichloroaldehydes (Scheme 2), the carbene, generated upon deprotonation of the azolium salt by base, adds to the *α*-haloaldehyde to form **I**, which subsequently undergoes an elimination of HCl to provide azolium enolate. Protonation of this intermediate produces an acyl azolium species, which performs an acylation to provide catalyst turnover. Chiral NHC-catalyzed enantioselective oxodiene Diels-Alder reaction was also reported (Scheme 3). The highly enantio- and diastereoselective process proceeded via the catalytic generation of a chiral enolate that serves as a remarkably reactive dienophile, leading to dihydropyran-2-ones products under mild conditions.



Scheme 1 The internal redox reaction of α-haloaldehydes



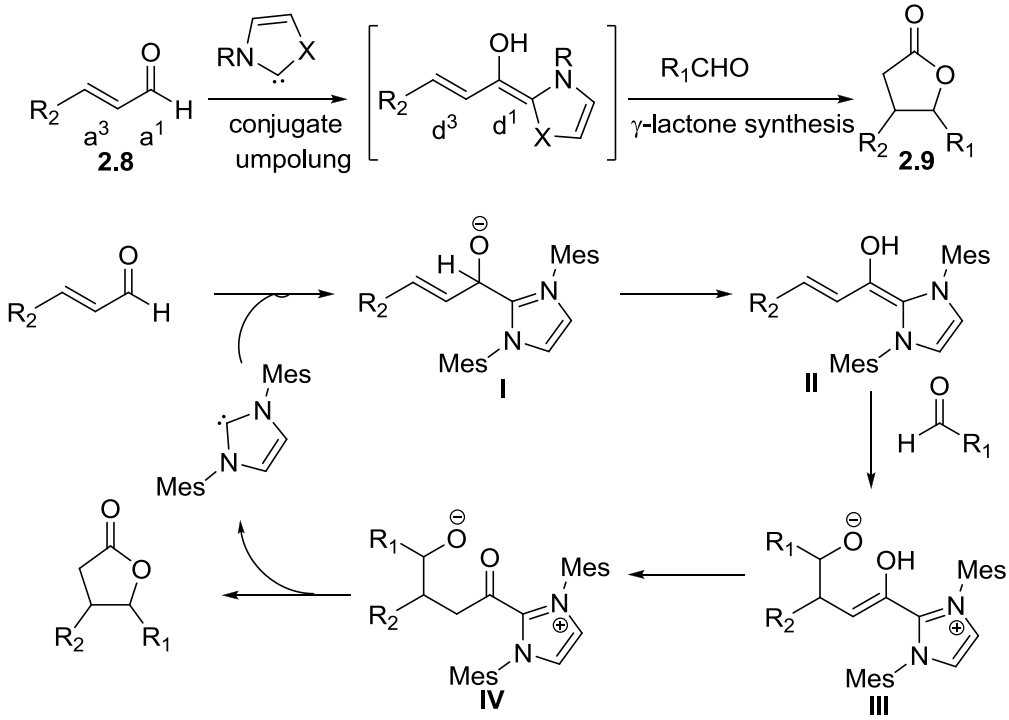
Scheme 2 The synthesis of α-chloroesters from 2,2-dichloroaldehydes



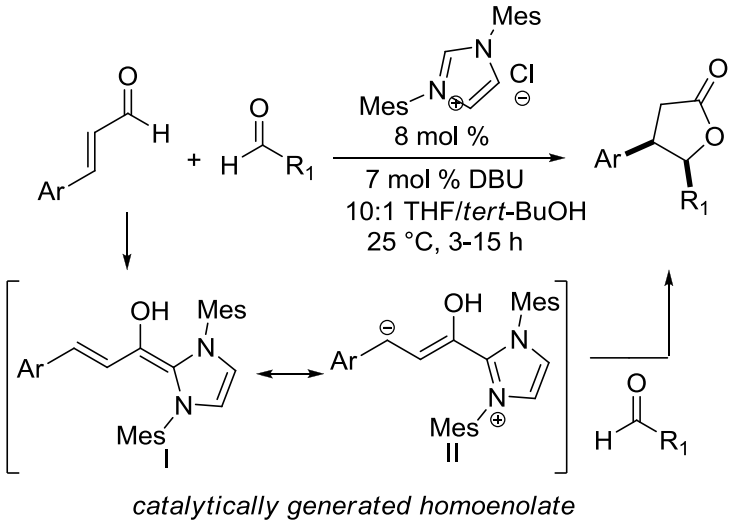
Scheme 3 Chiral NHC-catalyzed enantioselective oxodiene Diels-Alder reaction

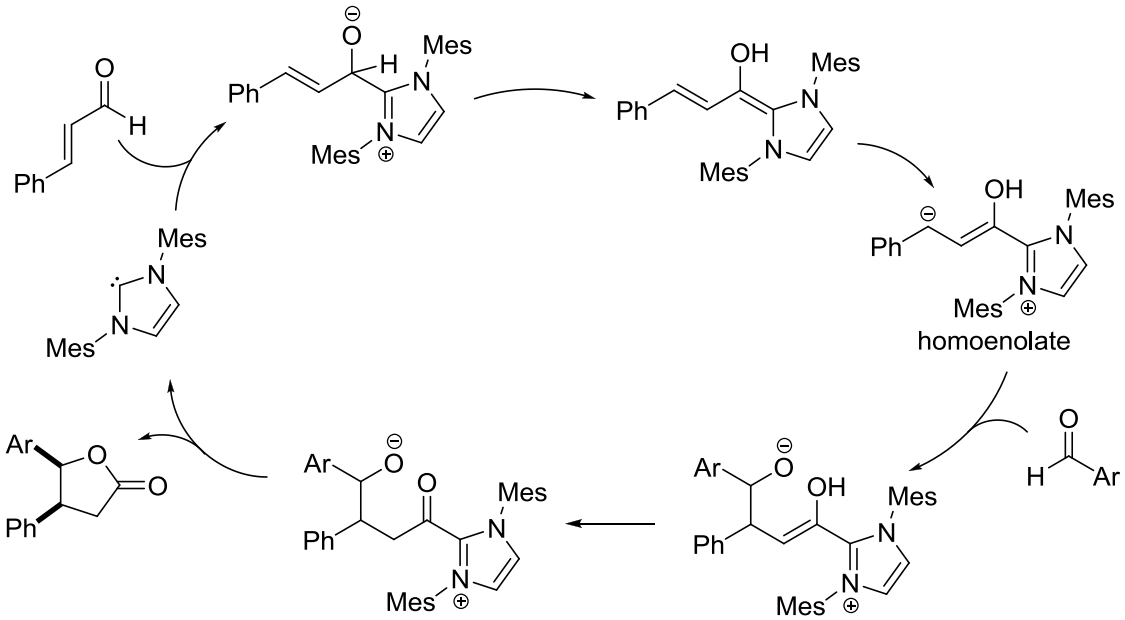
Later, the same strategy has been applied to other unlikely precursors such as *α*,*β*-unsaturated aldehydes (Scheme 4-8),[3e-k] epoxy aldehydes (Scheme 9),[3l] and formylcyclopropanes[3m]. In the synthesis of *γ*-butyrolactones (Scheme 4), reaction of NHC with the *α*, *β*-unsaturated aldehydes give rise to a zwitterionic structure **I**, which isomerize by protonation/deprotonation to the conjugated dienamine **II**. Nucleophilic attack of II or its zwitterionic homoenolate tautomer at the aromatic aldehyde results in the formation of alcoholate **III**, followed by isomerization to give the corresponding tautomer **IV**. These activated carboxylates are thought to be intermediates in NHC-catalyzed in transesterification reactions, lead to ester formation when attacked by alcohol nucleophiles. Analogously, intramolecular attack of the alkoxide IV or its protonated form at the carbonyl group leads to the closing of the lactone ring and the regeneration of the nucleophilic catalyst. In the conversion of *α*,*β*-unsaturated aldehydes into saturated esters (Scheme 6), the addition of a nucleophilic carbene catalyst to the carbonyl compounds generates the intermediate **II**, and subsequent hydrogen migration would generate the reactive dienamine **III**. Enol **IV** is produced in the presence of an electrophile. After tautomerization of **IV** to the activated acyl azolium **V**, the attack of a suitable nucleophile completes the catalytic cycle. Bode reported the catalytic generation of activated carboxylates from enals (Scheme 7). Carbenes react with enals to generate homoenolates. Strong base such as ^{t}BuOK leads to the carbon-carbon bond formation, while weaker bases allow protonation of the homoenolate and subsequent generation of activated carboxylates. In the synthesis of *α*,*β*-unsaturated esters via carbene-

catalyzed redox esterification (Scheme 8), the nucleophilic carbene, generated from the deprotonation of the heterazolium salt, adds to the alkynyl aldehyde **I** to form intermediate **II**, which subsequently undergoes H-migration to produce an alkynyl enaminol **III**. Protonation of **III** provides allenol **IV**, a tautomer of activated carboxylate **V**, which regenerates the catalyst upon acylation of appropriate nucleophiles.

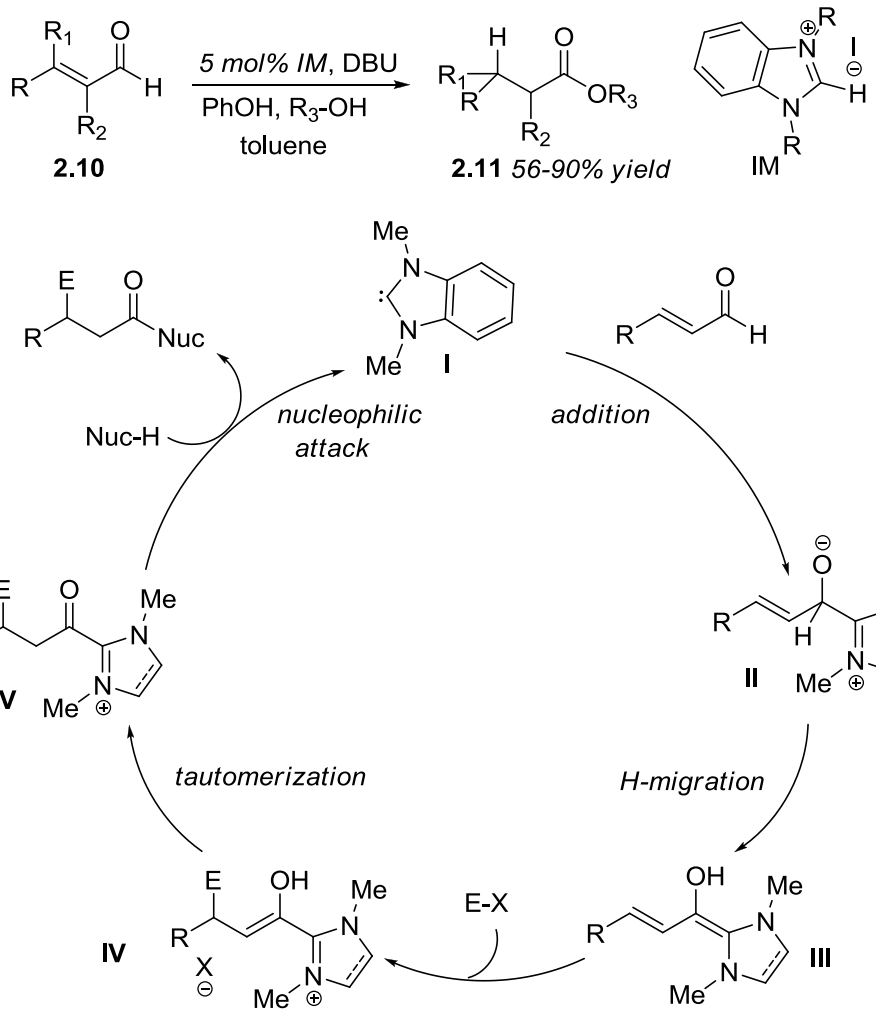


Scheme 4 Conjugate umpolung of *α,β*-unsaturated aldehydes for the synthesis of γ-butyrolactones

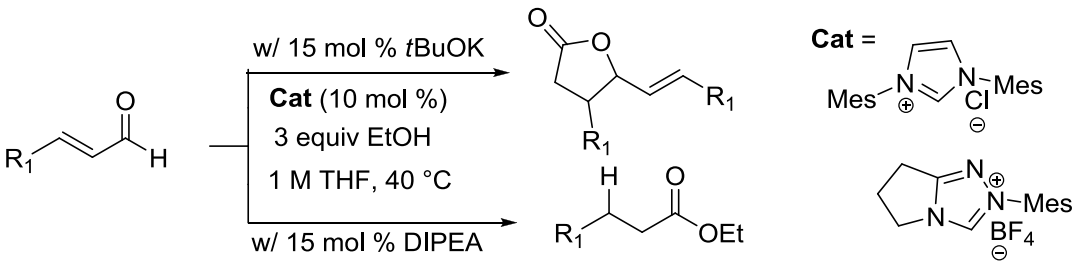




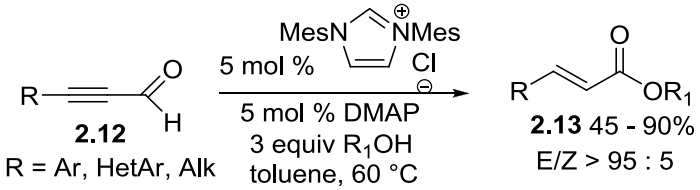
Scheme 5 Synthesis of γ-butyrolactones by direct annulations of enals and aldehydes

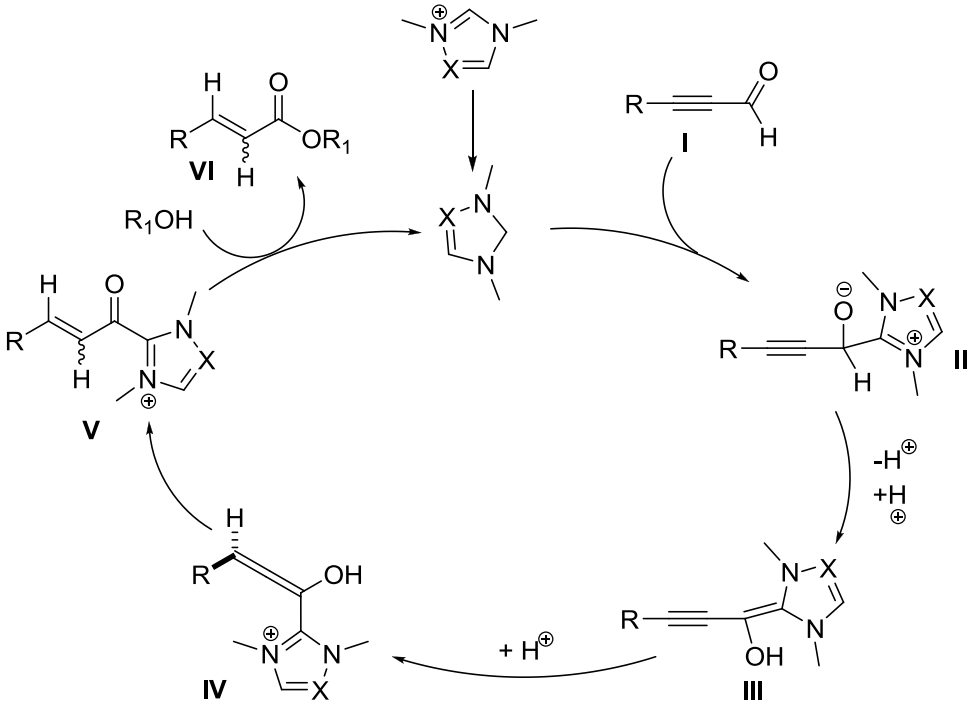


Scheme 6 Conversion of *α,β*-unsaturated aldehydes into saturated esters

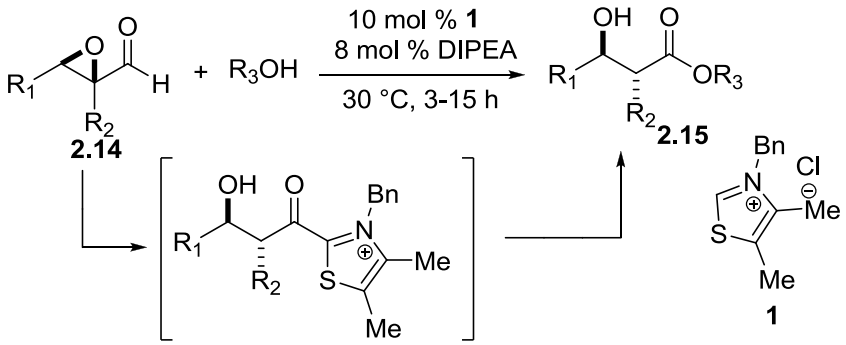


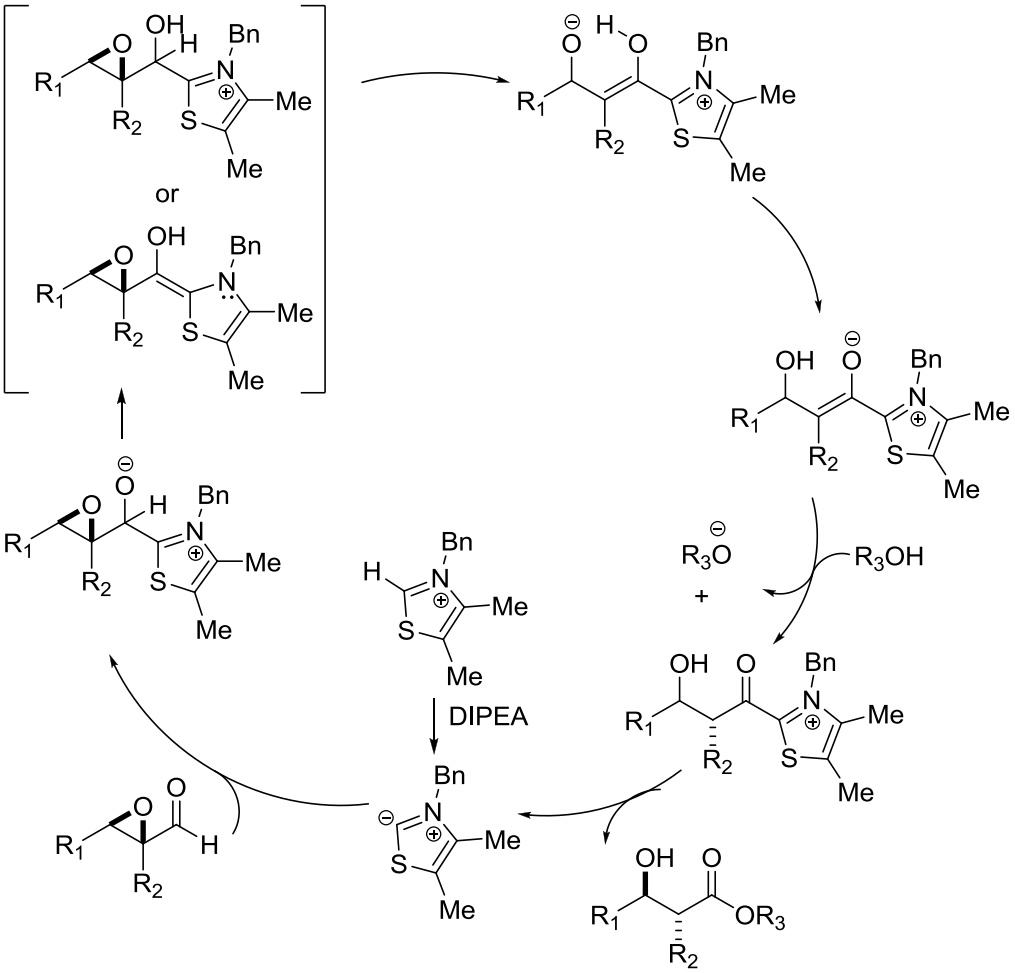
Scheme 7 Catalytic generation of activated carboxylates from enals





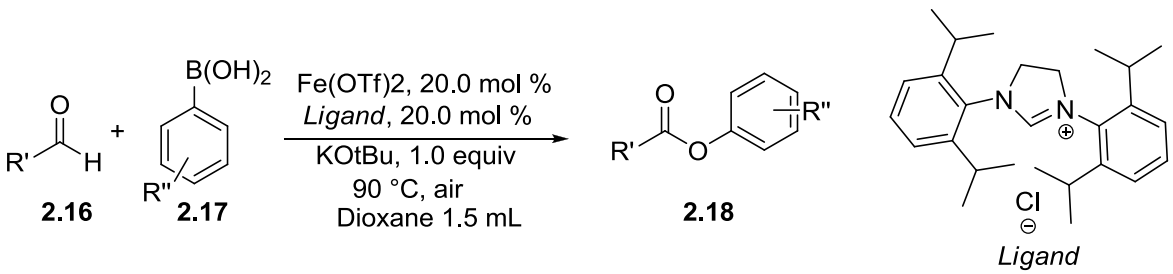
Scheme 8 Synthesis of *α,β*-unsaturated esters via carbene-catalyzed redox esterification



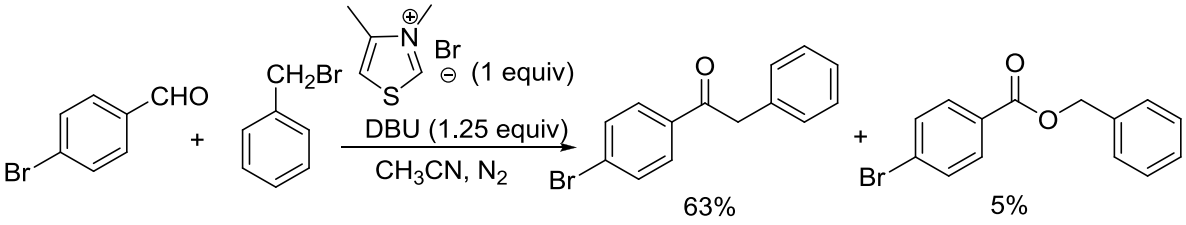


Scheme 9 Synthesis of *β*-hydroxyesters from epoxyaldehydes

Although NHC-catalyzed reaction of the Breslow intermediate with sp^2-carbon-centered electrophiles are being immensely explored,[1,2] the reaction of the Breslow intermediate with sp^3-centered electrophiles is comparatively fewer.[6] Recently, Gois (Scheme 10) and Deng (Scheme 11) groups reported aerobic oxidative aromatic esterification of aldehydes with boronic acids and benzyl bromides, respectively.[6a, 7]



Scheme 10 NHC-iron-catalyzed aerobic oxidative aromatic esterification of aldehydes

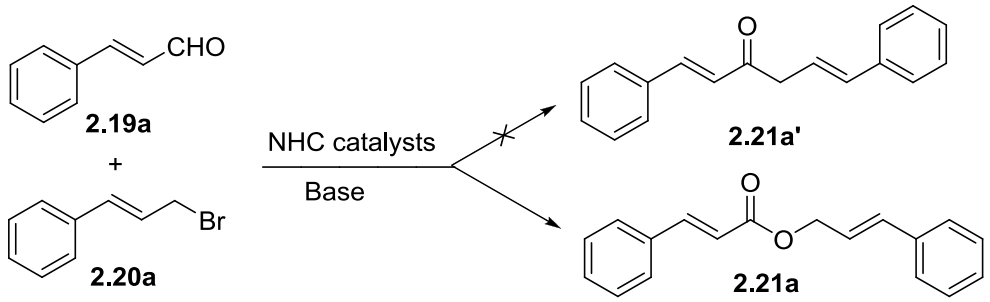


Scheme 11 NHC-mediated cross-coupling of aromatic aldehydes and benzyl bromides

Inspired by Deng's work, we would like to extend the substrates to cinnamaldehyde and cinnamyl bromide, which constitute an important class of compound in organic chemistry and wondered if the same ketones would be produced. But unexpectively, the totally different outcome was produced. Here, we will describe these discoveries.

2.2 Results and Discussion

Inspired by these examples (especially by Deng's work, Scheme 11), we envisaged the carbon-carbon bond formation reaction between cinnamaldehyde **2.19a** and cinnamyl bromide **2.20a** (Scheme 12). Unexpectively, the above reaction gave cinnamyl cinnamate **2.21a** instead of desired C-C bond forming product **2.21a'**. Since cinnamates derivatives play an important role in organic, medicinal, and material chemistry, we were motivated to investigate this NHC-catalyzed esterification reaction.



Scheme 12 Unexpected formation of Cinnamyl Cinnamate

In the beginning, the reaction was carried out with cinnamaldehyde **2.19a** (1.0 equiv) and cinnamyl bromide **2.20a** (1.2 equiv) catalyzed by the most encouterable NHC catalysts **A**-**F** (0.2 equiv) (Figure 1) and DBU as base under N_2 atmosphere in THF-*t*-BuOH (9:1). After 48h, only benzimidazolium catalyst **D1** gave cinnamyl cinnamate **2.21a** in 10% yield instead of compound **2.21a'**. When the same reaction was performed in the air atmosphere, the yield of **2.21a** was increased to 27%. With this fact in mind, we anticipated that this reaction goes through an oxygen incorporation mechanism, which is quite similar to the results reported by Deng[6a] and Chen[8] groups.

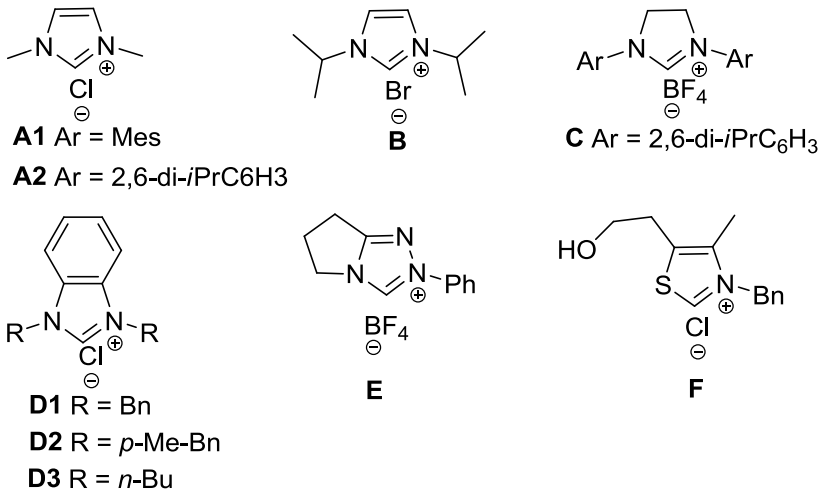
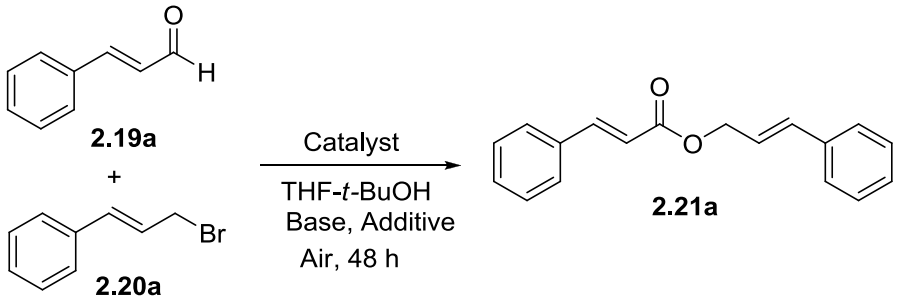


Figure 1 Screening of N-heterocyclic carbene catalysts in the reaction

Next, the reaction was examined using various catalysts **A-F** in the presence of air. Catalysts **A1**, **A2**, **B**, and **C** gave very low yields of ester **2.21a** after 48 h (Table 1, entries 1-4). And the catalysts **E** and **F** gave no product toward the reaction (Table 1, entries 6 and 7). With catalyst **D1**, the reactions were screened using different bases such as K_2CO_3, *t*-BuOK, NaH, and NaOMe. However, there was no obvious enhancement in the yield of **2.21a** (Table 1, entries 8-11). To sequester the HBr generated from the reaction which might decrease the yield of **2.21a**, additional organic or inorganic bases such as pyridine, 2,6-dimethylpyridine, K_2CO_3, Cs_2CO_3 and $KHCO_3$ were added to the reaction. When organic bases such as pyridine, 2,6-dimethylpyridine, and DMAP were used as additives, the yield of ester **2.21a** was low along with undesired and inseperable side products (Table 1, entries 12-14). Inorganic base K_2CO_3 gave the best yield of 72% after 48h (Table 1, entry 15). Other inorganic base such as $KHCO_3$ and Cs_2CO_3 gave ester **2.21a** in 30% and 43% of yield, respectively (Table 1, entries 16 and 17). In addition, when the reaction was conducted with an excess of DBU (i.e., 1.5 equiv, for 30 min), the cinnamyl bromide began to decompose and only trace amount of ester **2.21a** was detected from TLC. Benzimidazolium catalysts **D2** and **D3** were also tested for the reaction and they gave 48% and 38% of yield respectively (Table 1, entries 18 and 19). It can be seen that catalyst **D1** was most suitable for the esterification reaction.

Table 1 Optimization of reaction conditions for the ester formation[a] reaction



entry	catalyst	base	additive	Yield (%)
1	**A1**	DBU	none	<5
2	**A2**	DBU	none	<5
3	**B**	DBU	none	trace
4	**C**	DBU	none	<5
5	**D1**	DBU	none	27
6	**E**	DBU	none	0
7	**F**	DBU	none	0
8	**D1**	K_2CO_3	none	0
9	**D1**	NaH	none	trace
10	**D1**	NaOMe	none	<5
11	**D1**	*t*-BuOK	none	8
12	**D1**	DBU	pyridine	34[b]
13	**D1**	DBU	2,6-lutidine	35[b]
14	**D1**	DBU	DMAP	23[b]
15	**D1**	DBU	K_2CO_3	72
16	**D1**	DBU	$NaHCO_3$	30
17	**D1**	DBU	Cs_2CO_3	43
18	**D2**	DBU	K_2CO_3	48
19	**D3**	DBU	K_2CO_3	38

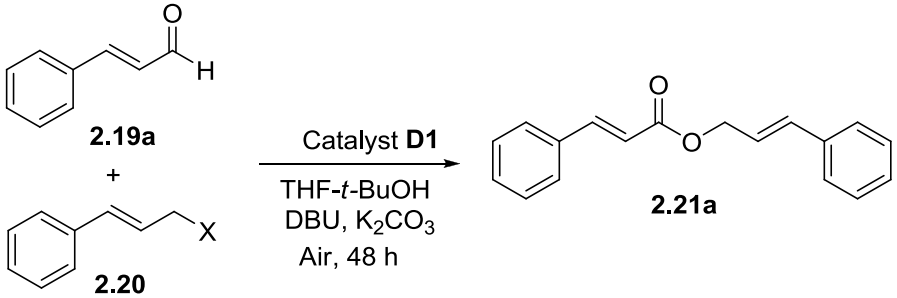
[a] Reaction conditions: aldehyde **2.19a** (1 equiv), cinnamyl bromide **2.20a** (1.2 equiv), catalyst (0.2 equiv), and additive (1.5 equiv) were mixed together in 5mL/mmol of THF-*t*-BuOH (9: 1 ratio) in the air atmosphere at room temperaturea and finally the base was added and stirred for 48 h. [b] Desired ester **2.21a** was produced in low yield along with inseparable and unidentified side products.

Furthermore, the leaving fitness of the cinnamyl halides was screened. Among –Cl, –Br, –OAc, $–OCO_2Et$, and –OTs, bromo was found to be the best leaving group for the reaction (Table 2, entries 1-5). In summary, the optimal condition for the NHC-catalyzed esterification involved a suspended solution of NHC catalyst **D1**(0.2 equiv), cinnamaldehyde (1.0 equiv), cinnamyl bromide (1.2 equiv), and K_2CO_3 (1.5 equiv) in THF-*t*-BuOH (9: 1) solution with DBU (0.2 equiv) to give the cinnamyl cinnamate **2.21a** in 72% yield after 48 h.

Based on these results, we investigated the scope of this method for the synthesis of various cinnamyl cinnamates (Table 3). Under the optimal conditions, different cinnamaldehyde were

tested as shown in Table 3. Electron-withdrawing substituents such as *o*-bromo, *p*-bromo, *o*-chloro, *p*-chloro, and *p*-nitro generally could give the corresponding cinnamyl cinnamate derivatives in good to excellent yields (Table 3, entries 2-6). Whereas cinnamaldehyde with electron-donating groups such as *o*-OMe produced the desired cinnamate in moderate yield at 70 °C after 48h (Table 3, entry 9). 2-Furan cinnamaldehyde and aliphatic *α,β*-unsaturated aldehydes such as crotonaldehyde also produced the cinnamate in fair yield of 58% and 51%, respectively (Table 3, entries 7 and 8). Next, we extended the catalytic method toward

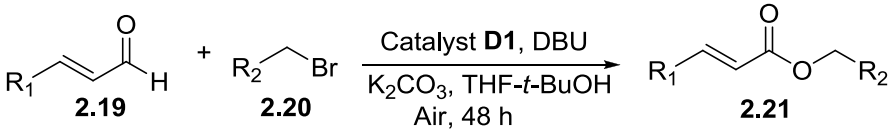
Table 2 Investigating effects of leaving groups on the reaction[a]



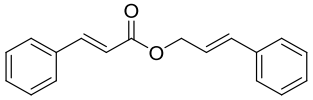
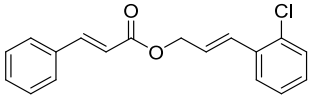
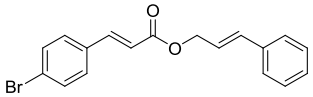
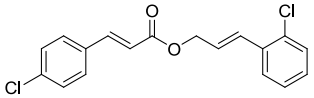
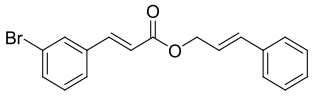
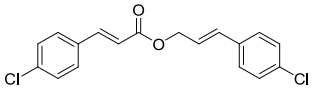
entry	leaving group (X)	time (h)	yield (%)
1	Cl	48	63
2	Br	48	72
3	OTs	48	trace
4	OCO_2Et	48	0
5	OAc	48	0

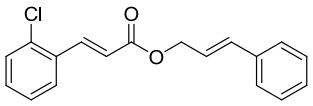
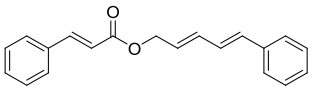
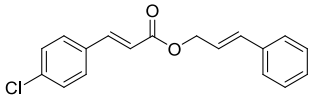
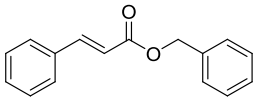
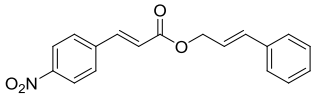
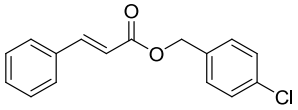
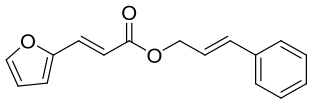
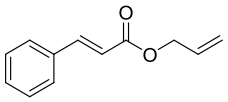
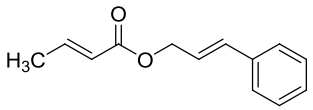
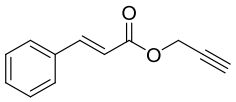
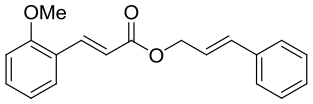
[a] Reaction conditions are identical to that of Table 1.

Table 3 Exploring the substrates scope in the synthesis of cinnamyl cinnamate derivatives[a]



R_1 = Aryl, alkyl R_2 = Ar=CH, Ar=CH=CH, Ar

entry	product **2.21**	yield (%)	entry	product **2.21**	yield (%)
1	 **2.21a**	72	10	 **2.21j**	61
2	 **2.21b**	86	11	 **2.21k**	76
3	 **2.21c**	78	12	 **2.21l**	81

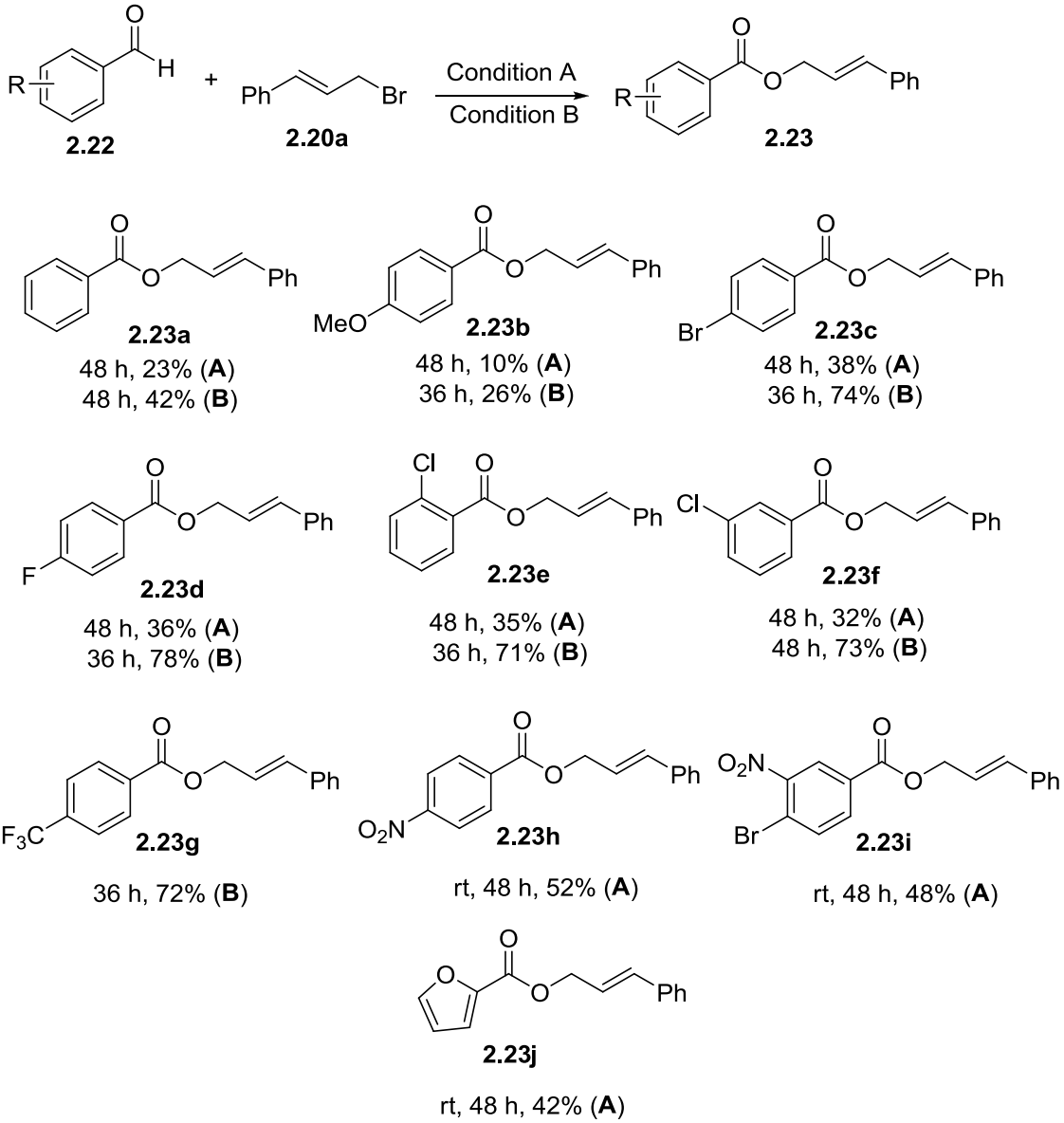
4		**2.21d**	76	13		**2.21m**	68
5		**2.21e**	86	14[d]		**2.21n**	46(23)[e]
6		**2.21f**	56	15[d]		**2.21o**	48(21)[e]
7		**2.21g**	58	16[d]		**2.21p**	13(34)[e]
8		**2.21h**	51[b]	17[d]		**2.21q**	11(42)[e]
9		**2.21i**	53[c]				

[a] Reaction conditions: aldehyde **2.19** (1.0 equiv), alkyl bromide **2.20** (1.2 equiv), benzimidazolium catalyst **D1** (0.2 equiv), and K_2CO_3 (1.5 equiv) were mixed together in 5mL/mmol of THF-*t*-BuOH (9: 1) in the air at room temperature and then DBU (0.2 equiv) was added to stir for 48 h. [b] Aldehyde (1.5 equiv) was used. [c] Reaction was performed at 70 °C. [d] Alkyl bromide (1.5 equiv) was used for 72 h. [e] Yields in parentheses refer to the recovery of unreacted cinnamaldehyde.

different cinnamyl bromide derivatives. 2-Chloro, 4-chloro-cinnamyl bromide, and extended cinnamyl bromide derivatives (i.e., (5-bromopenta-1,3-dienyl)benzene) smoothly underwent this catalytic reaction and gave good yields (Table 3, entries 10-13). Simple benzyl bromides also produced benzyl cinnnamates in moderate yield along with unreacted cinnamaldehyde after 72 h (Table 3, entries 14 and 15). Next we tested simple allyl and propargyl bromides as alkylating reagents. Both of them provided the esters in 13% an 11% yield, respectively (Table 3, entries 16 and 17).

After successful development of aerobic oxidation of enals with reactive cinnamyl bromides, we applied this method to simple aromatic aldehydes. Initially, benzaldehyde was reacted with cinnamyl bromide under the optimized conditions in the air. Only trace amount of cinnamyl benzoate **2.23a** was obtained after 48 h at room temperature. However, when the reaction temperature was increased to 70 °C, the yield was increase to 23%. The lower yields could attribute to the lower activity of the benzaldehydes. When we employed MnO_2 as an oxidant instead of O_2 and added 1.5 equiv of water into the reaction system at 70 °C, the

cinnamyl benzoate was obtained in 42% yield after 48 h. Here the reaction proceeds mostly via acid formation and then simple alkylation in the presence of base. Therefore, by using MnO_2 as an oxidant, we carried out of the reaction with a series of aromatic aldehydes and conducted a comparative study with air oxygen and MnO_2 as oxidants (Scheme 13). Electron-rich 4-methoxybenzaldehyde delivered the desired ester in low yield of 26%. On the contrary, When MnO_2 was used as an oxidant, aromatic aldehydes with electron-withdrawing halogen constituents such as 4-BrC_6H_4CHO, 4-FC_6H_4CHO, 2-ClC_6H_4CHO, 3-ClC_6H_4CHO, and 4-$CF_3C_6H_4CHO$ underwent reaction smoothly with cinnamyl bromide to give esters **2.23c-2.23g** in excellent yields (Scheme 13). Other substituents with electron-withdrawing groups such as 4-$NO_2C_6H_4CHO$ and 4-Br-3-$NO_2C_6H_3CHO$ also gave the esters in good yields even at room temperature in the presence of air (Scheme 13, **2.23h** and **2.23i**). Heteroaromatic aldehydes such as furfural also could give fair yield with cinnamyl bromide at room temperature in the air.

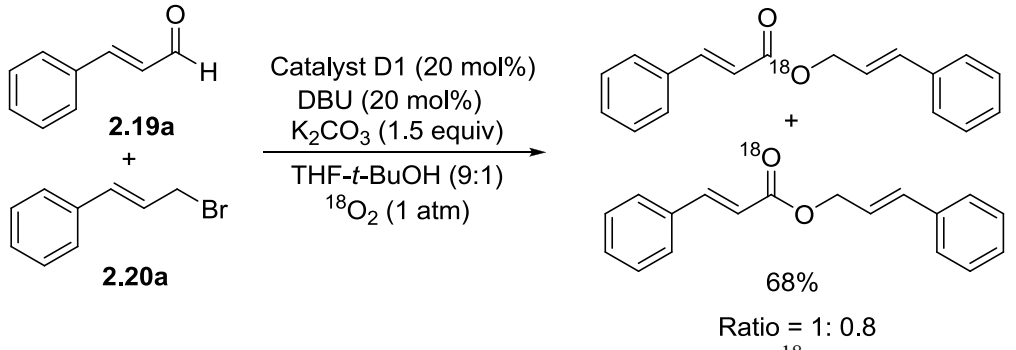


Scheme 13 Synthesis of esters from aromatic aldehydes[a]

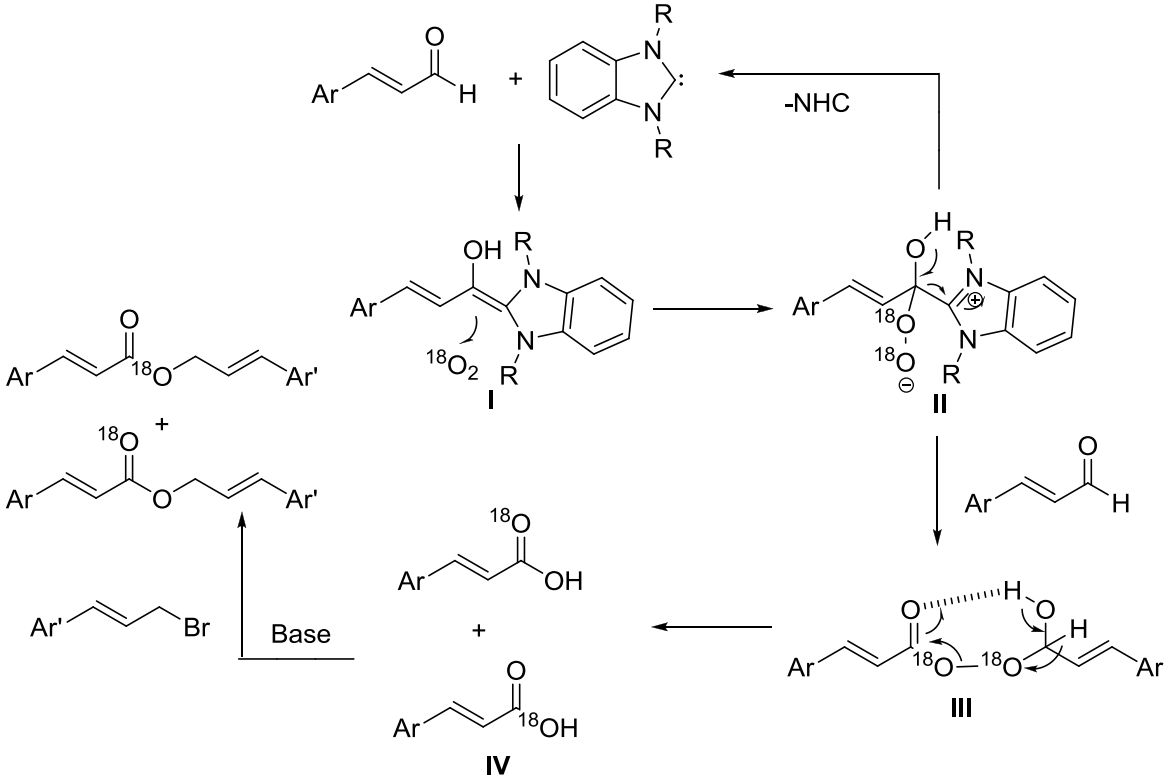
[a] Condition A: catalyst **D1** (0.3 equiv), DBU (0.3 equiv), K_2CO_3 (1.5 equiv), 5 mL/mmol of THF-*t*-BuOH (9:1), air, 70 °C or rt. Condition B: catalyst **D1** (0.3 equiv), DBU (0.3 equiv), K_2CO_3 (1.5 equiv), MnO_2 (5 equiv), H_2O (1.5 equiv), 5 mL/mmol of THF-*t*-BuOH (9:1), 70 °C).

2.3 Mechanism Studies

To investigate the possible reaction mechanism, several experiments were conducted. First, cinnamaldehyde was reacted with methanol (2.5 equiv) under the same catalytic conditions with an oxygen balloon (1 atm). However, no considerable amount of product was detected even after 48 h. This experiment clearly suggested that active acyl imidazolium intermediate was not formed during the reaction when oxygen was used as an oxidant. Second, when the same reaction was conducted in the presence of water, the yield of the ester **2.21a** was decreased to lower than 10%. Therefore, the concentration of water in the reacton system is essential to obtain the good yields of the ester. Further, to elucidate the mechanism clearly, an isotope labeling experiment was conducted using $^{18}O_2$ (Scheme 14). It was observed that the reaction proceeded smmothly in the presence of $^{18}O_2$ to produce the ester in 68% yield. The GC-MS[7,9] spectrum of the precursor ion at *m*/*z* at 266.1 exhibited an intensive charateristic fragment at *m*/*z* 131.0 and 133.0 with 1: 0.8 ratio, which could be attributed to the fragments of $[PhCH=CHC=^{16}O]^+$ and $[PhCH=CHC=^{18}O]^+$. This isotope labeling experiment clearly proved that dioxygen plays an important role in the transformation of enals to esters. On the basis of isotope labeling experiment, an oxygen insertion mechanism is proposed. As shown in Scheme 15, the Breslow intermediate **I** reacts with $^{18}O_2$ (dioxygen) to give the corresponding peroxide intermediate **II**. After the carbene liberation the peroxide intermediate **II** forms a corresponding deprotonated peracid intermediate (doubly ^{18}O-marked at the peracid moiety). The peracid reacts with another molecule of aldehyde to produce hydroxy peroxyl adduct **III**,[10] which in turn generates 2 equiv of corresponding acids **IV**. At this juncture, the acid (carboxylate under the conditions) bear exactly one labeled ^{18}O atom. Alkylation with the allyl bromide leads to the ester **2.21** which bear the ^{18}O labeling both at the carbonyl O atmo and at the alcohol O atom (around 1: 1 ratio).

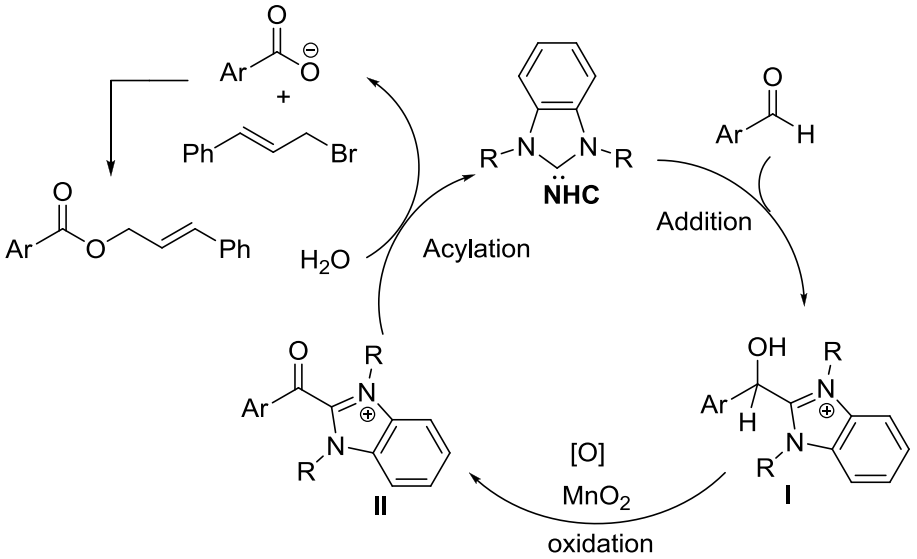


Scheme 14 Isotopic labeling experiment using $^{18}O_2$



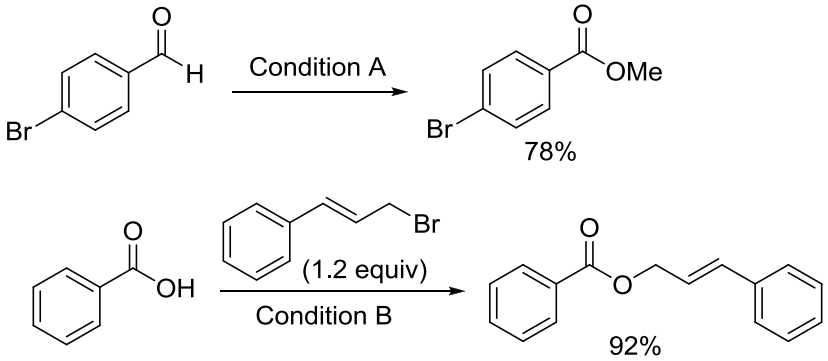
Scheme 15 Mechanism illustrating the insertion of oxygen in the reaction

When MnO_2 was used as oxidant, the reaction proceeds via a different pathway. As shown in Scheme 16, the catalytic cycle is initiated by generation of carbene, which undergoes nucleophlic addition to the aldehyde, forming a tetrahedral intermediate **I**. This intermediate is oxidized to acyl benzimidazolium intermidate **II** by MnO_2.[11] Next, the intermediate **II**[12] is trapped by H_2O to form acid[13] as an intermediate with regeneration of carbene **D**. In the presence of base, the carboxylic anion reacts with cinnamyl bromides to generate ester **2.23**[14].



Scheme 16 Esterification of aromatic aldehydes with MnO_2 as an oxidant

To support the above elucidated mechanism, we conducted an experiment in the presence of methanol (2.5 equiv) with 4-bromobenzaldehyde under the same reaction conditions. When MnO_2 was usesd as oxidant, methyl 4-bromobenzoate was formed in 78% yield, which confirmed the formation of an active acyl imidazolium intermediate during the course of reaction (Scheme 17). Another parallel experiment was carried out with simple benzoic acid and cinnamyl bromide as an alkylating agent with the same reaction condition where ester **2.23a** was obtained in 92% yield after 24 h (Scheme 17).



Condition A: catalyst D1 (0.3 equiv), DBU (0.3 equiv), THF-*t*-BuOH, MnO_2 (5 equiv), MeOH (2.5 equiv), 70 °C, 24h; Condition B: catalyst D1 (0.3 equiv), DBU (0.3 equiv), K_2CO_3 (1.5 equiv), THF-*t*-BuOH, 70 °C, 24 h.

Scheme 17 Experimental reactions with 4-bromobenzaldehyde and benzoic acid

2.4 Conclusion

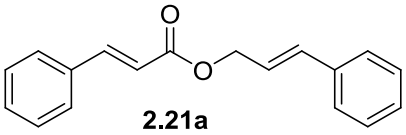
In conclusion, we presented a mild NHC-catalyzed transformation of cinnamyl cinnamate from cinnamaldehyde derivatives by employing air oxygen as as oxidant. This is an alternative method for the synthesis of esters from reactive alkyl halides and *α,β*-unsaturated or aromatic aldelydes. Aldehydes with electron-withdrawing groups comparatively gave better yields than that with electron-donating groups. A significant feature of this protocol is that the reaction proceeds without cis-trans isomerization of the *α,β*-olefinic linkage in the cinnamyl cinnamate derivatives. When MnO_2 was use as oxidant instead of air oxygen, aromatic aldehydes generally provide ester in good yields. Great efforts have been made on mechanistic studies and which constituted a useful supplementation to previous groups' work.

2.5 Experimental Section

General: All reagents and solvents were obtained from commercial suppliers and used without further purification. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates. Product purification by flash column chromatography was accomplished using silica gel (0.010 - 0.063 mm). Technical grade solvents were used for chromatography and distilled prior to use. High-resolution mass spectra (HRMS) were obtained on a Finnigan/MAT LCQ quadrupole ion trap mass spectrometer, coupled with the TSP4000 HPLC system and the Crystal 310 CE system. Accurate masses are reported for the molecular ion $[M+H]^+$ or a suitable fragment ion. X-ray crystallographic data was collected by using a Bruker X8 Apex diffractometer with Mo K/α radiation (graphite monochromator). ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker AV 400 (400 MHz) NMR spectrometer. ^1H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm) and $CHCl_3$ (77.0 ppm), respectively. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from triethylsilane. Chemical shift (δ) is referred in terms of ppm, coupling constants (J) are given in Hz. Following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved.

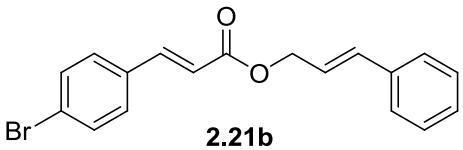
Materials: α,β-unsaturated aldehydes **2.19a**, **2.19f**, **2.19h**, and **2.19i** and all aromatic aldehydes were purchased from commercial suppliers and used without further purification. Other cinnamaldehydes were prepared according to standard literature procedures.[15] Cinnamyl bromides were prepared from their corresponding alcohols with PBr_3 treatment.[16] NHC catalyst were purchased from commercial suppliers, and catalysts **D1**, **D2**, and **D3** were prepared from standard literature procedures.[17]

General procedure for synthesis of cinnamyl cinnamates 2.21. To a well-stirred suspended solution of NHC catalyst **D1**(50 mg, 0.15 mmol), cinnamaldehyde (100 mg, 0.76 mmol), cinnamyl bromide (180 mg, 0.91 mmol), and K_2CO_3 (160 mg, 1.14 mmol) in THF-*t*-BuOH (4 mL, 9: 1 ratio) was added a catalytic amount of DBU (25 mg, 0.15 mmol) in the air atmosphere. Then the reaction mixture was stirred at room temperature. On completion, the mixture was diluted with EtOAc (5 mL) and filtered through Celite. The combined organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvents under reduced pressure, the crude reaction mixture was subjected to purification by flash column chromatography using hexane/EtOAc as eluent to afford 144 mg of cinnamyl cinnamate **2.21a** in 72% yield.



2.21a

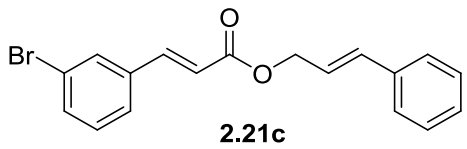
3-Phenylacrylic acid-3-phenyl allyl ester (**2.21a**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, J = 16.0 Hz, 1H), 7.53-7.51 (m, 2H), 7.42-7.25 (m, 8H), 6.71 (d, J = 16.0 Hz, 1H), 6.48 (d, J = 16.0 Hz, 1H), 6.39-6.34 (m, 1H), 4.86 (dd, J = 6.4, 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 145.1, 136.3, 134.4, 130.5, 128.9 (2C), 128.6 (2C), 128.2 (2C), 128.1 (3C), 126.7, 123.4, 117.9, 65.2; HRMS (EI) calcd for $C_{18}H_{17}O_2$ 265.1229 *m*/*z* $[M+H]^+$, found 265.1232 *m*/*z*.



2.21b

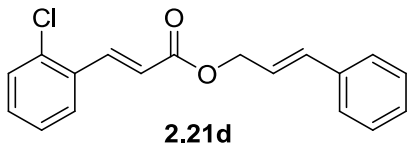
3-(4-Bromophenyl)acrylic acid-3phenyl allyl ester (**2.21b**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66 (d, J = 16.0 Hz, 1H), 7.52-7.48 (m, 2H), 7.41-7.25 (m, 7H), 6.71 (d, J = 16.0 Hz, 1H), 6.45 (d, J = 16.0 Hz, 1H), 6.38-6.32 (m, 1H), 4.85 (dd, J = 6.4, 1.2 Hz, 2H); ^{13}C NMR (100

MHz, $CDCl_3$): δ 166.6, 143.7, 136.4, 134.5, 133.5, 132.3 (2C), 129.5 (2C), 128.8 (2C), 128.3, 126.8 (2C), 124.8, 123.4, 118.8, 65.3; HRMS (EI) calcd for $C_{18}H_{15}O_2BrNa$ 365.0153 *m*/*z* $[M+Na]^+$, found 365.0148 *m*/*z*.



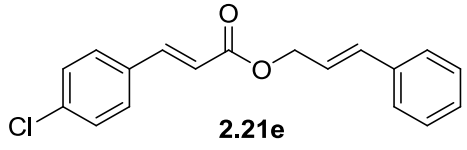
2.21c

3-(3-Bromophenyl)acrylic acid-3phenyl allyl ester (**2.21c**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, *J* = 4.1 Hz, 1H), 7.64 (d, *J* = 16.0 Hz, 1H), 7.51-7.47 (m, 1H), 7.43-7.34 (m, 3H), 7.33-7.31 (m, 2H), 7.30-7.24 (m, 2H), 6.71 (d, *J* = 16.0 Hz, 1H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.38-6.32 (m, 1H), 4.88 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 143.3, 136.4, 136.4, 134.6, 133.3, 130.8, 130.6, 128.8 (2C), 128.3, 126.8 (2C), 126.7, 123.3, 123.1, 119.5, 65.4; HRMS (EI) calcd for $C_{18}H_{15}O_2BrNa$ 365.0153 *m*/*z* $[M+Na]^+$, found 365.0151 *m*/*z*.



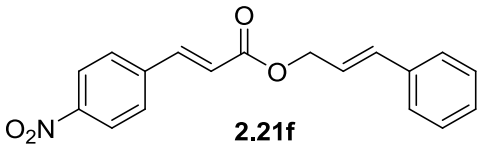
2.21d

3-(2-Chlorophenyl)acrylic acid-3phenyl allyl ester (**2.21d**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (d, *J* = 16.4 Hz, 1H), 7.63-7.62 (m, 1H), 7.42-7.26 (m, 8H), 6.73 (d, *J* = 16.0 Hz, 1H), 6.48 (d, *J* = 16.0 Hz, 1H), 6.39-6.33 (m, 1H), 4.88 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 141.2, 136.4, 135.2, 134.4, 132.9, 131.4, 130.4, 128.9 (2C), 128.3, 127.9, 127.3, 126.7 (2C), 123.4, 120.8, 65.6; HRMS (EI) calcd for $C_{18}H_{15}O_2ClNa$ 321.0658 *m*/*z* $[M+Na]^+$, found 321.0653 *m*/*z*.



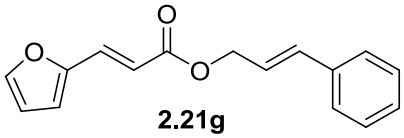
2.21e

3-(4-Chlorophenyl)acrylic acid-3phenyl allyl ester (**2.21e**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, J = 16.4 Hz, 1H), 7.46-7.27 (m, 9H), 6.71 (d, J = 16.0 Hz, 1H), 6.48 (d, J = 16.0 Hz, 1H), 6.38-6.32 (m, 1H), 4.87 (d, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 143.8, 136.4, 136.1, 134.5, 132.8, 129.5 (2C), 129.4 (2C), 128.8 (2C), 128.3, 126.8 (2C), 123.3, 118.7, 63.4; HRMS (EI) calcd for $C_{18}H_{15}O_2ClNa$ 321.0658 *m*/*z* $[M+Na]^+$, found 321.0655 *m*/*z*.



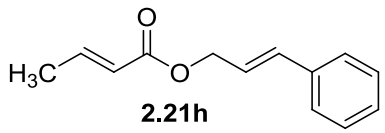
2.21f

3-(4-Nitrophenyl)acrylic acid-3phenyl allyl ester (**2.21f**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26 (d, J = 8.7 Hz, 2H), 7.76 (d, J = 16.0 Hz, 1H), 7.69 (d, J = 9.1 Hz, 2H), 7.44-7.25 (m, 5H), 6.73 (d, J = 16.0 Hz, 1H), 6.61 (d, J = 16.0 Hz, 1H), 6.39-6.32 (m, 1H), 4.88 (dd, J = 6.4, 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 148.6, 142.2, 140.5, 136.2, 134.8, 128.8 (4C), 128.3, 126.7 (2C), 124.3 (2C), 122.8, 122.3, 65.7; HRMS (EI) calcd for $C_{18}H_{15}O_4NNa$ 322.0899 *m*/*z* $[M+Na]^+$, found 322.0902 *m*/*z*.



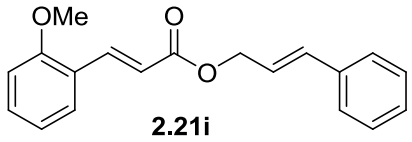
2.21g

3-Furan-2-yl acrylic acid-3phenyl allyl acetate (**2.21g**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49-7.23 (m, 7H), 6.69 (d, J = 16.0 Hz, 1H), 6.60 (d, J = 3.2 Hz, 1H), 6.47-6.45 (m, 1H), 6.38-6.30 (m, 2H), 4.84 (dd, J = 6.4, 1.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 151.0, 144.9, 136.4, 134.2, 131.5, 128.7 (2C), 128.1, 126.7 (2C), 123.4, 115.6, 115.0, 112.4, 65.2; HRMS (EI) calcd for $C_{16}H_{15}O_3$ 255.1021 *m*/*z* $[M+H]^+$, found 255.1029 *m*/*z*.



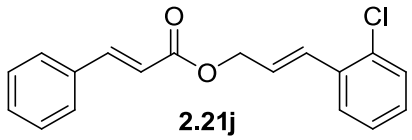
2.21h

But-2-enoic acid-3phenyl allyl ester(**2.21h**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.20 (m, 5H), 7.07-6.97 (m, 1H), 6.65 (d, *J* = 16.0 Hz, 1H), 6.34-6.27 (m, 1H), 5.88 (dd, *J* = 16.0, 1.4 Hz, 1H), 4.78 (dd, *J* = 6.4, 1.4 Hz, 2H), 1.88 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 145.2, 136.4, 134.1, 128.7 (2C), 128.2, 126.7 (2C), 123.5, 122.6, 64.9, 18.1; HRMS (EI) calcd for $C_{13}H_{15}O_2$ 203.1072 *m*/*z* $[M+H]^+$, found 203.1072 *m*/*z*.



2.21i

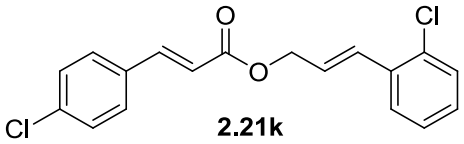
3-(2-Methoxyphenyl)acrylic acid-3phenyl allyl ester (**2.21i**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (d, *J* = 16.0 Hz, 1H), 7.52-7.50 (m, 1H), 7.44-7.23 (m, 6H), 6.97-6.90 (m, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 16.0 Hz, 1H), 6.59 (d, *J* = 16.0 Hz, 1H), 6.40-6.35 (m, 1H), 4.87 (dd, *J* = 6.4, 1.2 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 158.4, 140.6, 136.3, 134.0, 131.6, 129.0, 128.6 (2C), 128.0, 126.7 (2C), 123.6, 123.4, 118.4, 111.2, 65.0, 55.5; HRMS (EI) calcd for $C_{19}H_{19}O_3$ 295.1334 *m*/*z* $[M+Na]^+$, found 295.1333 *m*/*z*.



2.21j

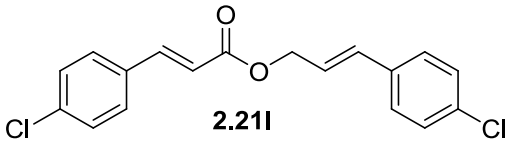
3-Phenylacrylic acid-3-(2-chlorophenyl)allyl ester (**2.21j**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (d, *J* = 16.0 Hz, 1H), 7.59-7.55 (m, 3H), 7.41-7.36 (m, 4H), 7.26-7.20 (m, 2H), 7.13 (d, *J* = 16.0 Hz, 1H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.41-6.34 (m, 1H), 4.93 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 145.2, 134.4 (2C), 133.3, 130.4, 130.1, 129.8, 129.1,

128.9 (2C), 128.1 (2C), 127.0, 126.9, 126.2, 117.8, 65.0; HRMS (EI) calcd for $C_{18}H_{15}O_2ClNa$ 321.0658 *m*/*z* $[M+Na]^+$, found 321.0655 *m*/*z*.



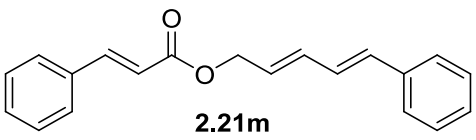
2.21k

3-(4-Chlorophenyl)acrylic acid-3-(2-chlorophenyl)allyl ester (**2.21k**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, J = 16.0 Hz, 1H), 7.56-7.54 (m, 1H), 7.47-7.44 (m, 2H), 7.38-7.28 (m, 3H), 7.26-7.18 (m, 2H), 7.10 (d, J = 16.0 Hz, 1H), 6.46 (d, J = 16.0 Hz, 1H), 6.38-6.30 (m, 1H), 4.91 (dd, J = 6.4, 1.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 143.8, 136.4, 134.5, 133.4, 132.9, 130.2, 129.8, 129.4 (2C), 129.3 (2C), 129.2, 127.1, 127.0, 126.1, 118.5, 65.1; HRMS (EI) calcd for $C_{18}H_{14}O_2Cl_2Na$ 355.0269 *m*/*z* $[M+Na]^+$, found 355.0273 *m*/*z*.



2.21l

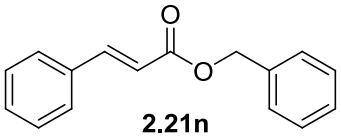
3-(4-Chlorophenyl)acrylic acid-3-(4-chlorophenyl)allyl ester (**2.21l**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, J = 16.0 Hz, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.36-7.23 (m, 6H), 6.65 (d, J = 16.0 Hz, 1H), 6.44 (d, J = 16.0 Hz, 1H), 6.36-6.28 (m, 1H), 4.86 (dd, J = 6.4, 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 143.9, 136.4, 134.8, 133.9, 133.1, 132.9, 129.4 (2C), 129.3 (2C), 128.9 (2C), 127.9 (2C), 123.4, 118.5, 65.1; HRMS (EI) calcd for $C_{18}H_{14}O_2Cl_2Na$ 355.0269 *m*/*z* $[M+Na]^+$, found 355.0271 *m*/*z*.



2.21m

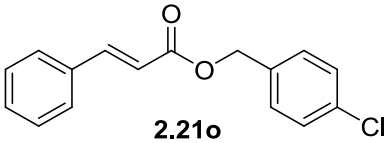
3-Phenylacrylic acid-5-phenylpenta-2,4-dienyl ester (**2.21m**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, J = 16.0 Hz, 1H), 7.55-7.52 (m, 2H), 7.43-7.20 (m, 8H), 6.83-6.77 (m, 1H), 6.61 (d, J

= 16.0 Hz, 1H), 6.54-6.47 (m, 2H), 6.00-5.91 (m, 1H), 4.80 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 145.2, 137.0, 134.7, 134.5, 133.9, 130.4, 129.0 (2C), 128.7 (2C), 128.2 (2C), 127.9, 127.8, 127.1, 126.6 (2C), 118.0, 65.0; HRMS (EI) calcd for $C_{20}H_{18}O_2Na$ 313.1204 *m*/*z* $[M+Na]^+$, found 313.1215 *m*/*z*.



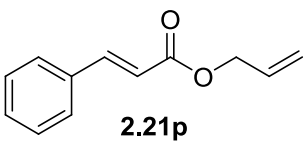
2.21n

3-phenylacrylic acid-benzyl ester (**2.21n**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (d, *J* = 16.0 Hz, 1H), 7.51-7.50 (m, 2H), 7.45-7.31 (m, 8H), 6.48 (d, *J* = 16.0 Hz, 1H), 5.24 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 145.3, 136.1, 134.4, 130.4, 129.0 (2C), 128.7 (2C), 128.4, 128.2, 128.3 (2C), 128.2 (2C), 118.0, 66.4; HRMS (EI) calcd for $C_{16}H_{14}O_2Na$ 261.0891 *m*/*z* $[M+Na]^+$, found 261.0904 *m*/*z*.



2.21o

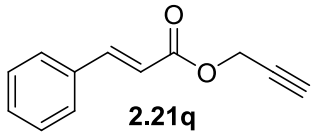
3-phenylacrylic acid-4-chlorobenzyl ester (**2.21o**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (d, *J* = 16.0 Hz, 1H), 7.53-7.50 (m, 2H), 7.41-7.32 (m, 7H), 6.47 (d, *J* = 16.0 Hz, 1H), 5.21 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 145.5, 134.7, 134.4, 134.3, 130.6, 129.8 (2C), 129.0 (2C), 128.9 (2C), 128.2 (2C), 117.7, 65.6; HRMS (EI) calcd for $C_{16}H_{13}O_2ClNa$ 295.0502 *m*/*z* $[M+Na]^+$, found 295.0514 *m*/*z*.



2.21p

3-phenylacrylic acid-allyl ester (**2.21p**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, *J* = 16.0 Hz, 1H), 7.55-7.52 (m, 2H), 7.40-7.38 (m, 3H), 6.48 (d, *J* = 16.0 Hz, 1H), 6.08-5.96 (m, 1H),

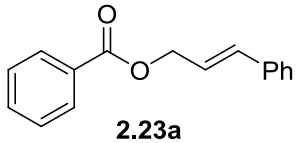
5.38 (dd, *J* = 16.0, 1.4 Hz, 1H), 4.72 (dd, *J* = 6.0, 1.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 145.2, 134.5, 132.4, 130.5, 129.0 (2C), 128.2 (2C), 118.4, 118.0, 65.4; HRMS (EI) calcd for $C_{12}H_{13}O_2$ 189.0916 *m*/*z* $[M+Na]^+$, found 189.0909 *m*/*z*.



2.21q

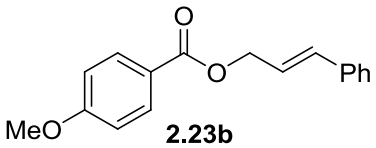
3-phenylacrylic acid-3-phenyl-2-ynyl ester (**2.21q**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, *J* = 16.0 Hz, 1H), 7.55-7.52 (m, 2H), 7.42-7.37 (m, 3H), 6.47 (d, *J* = 16.0 Hz, 1H), 4.82 (d, *J* = 2.3 Hz, 2H), 2.51 (t, *J* = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 146.2, 134.3, 130.8, 129.1 (2C), 128.4 (2C), 117.2, 78.0, 75.1, 52.2; HRMS (EI) calcd for $C_{12}H_{10}O_2Na$ 209.0578 *m*/*z* $[M+Na]^+$, found 209.0584 *m*/*z*.

General procedure for synthesis of cinnamyl benzoates 2.23 using MnO_2 as an oxidant. To a well-stirred suspended solution of NHC catalyst **D1**(54.0 mg, 0.16 mmol), 4-bromobenzaldehyde (100 mg, 0.54 mmol), cinnamyl bromide (130 mg, 0.65 mmol), K_2CO_3 (120 mg, 0.81 mmol) and MnO_2 (240 mg, 2.7 mmol) in THF-*t*-BuOH (4 mL, 9: 1 ratio) was added a catalytic amount of DBU (24 mg, 0.16 mmol). After a few minutes, water was added into the reaction mixture and stirred for 36 h at 70 °C. On completion, the mixture was diluted with EtOAc (5 mL) and filtered through Celite. The combined organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvents under reduced pressure, the crude reaction mixture was subjected to purification by flash column chromatography using hexane/EtOAc as eluent to afford 126 mg of cinnamyl benzoate **2.23c** in 74% yield.



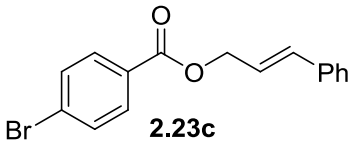
2.23a

Benzoic acid-3-phenyl allyl ester (**2.23a**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (d, J = 7.76 Hz, 2H), 7.56-7.52 (m, 1H), 7.44-7.39 (m, 4H), 7.33-7.23 (m, 3H), 6.72 (d, J = 16.0 Hz, 1H), 6.43-6.36 (m, 1H), 4.97 (d, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 136.4, 134.4, 133.2, 130.4, 129.8 (2C), 128.8 (2C), 128. 5 (2C), 128.2, 126.8 (2C), 123.4, 65.7; HRMS (EI) calcd for $C_{16}H_{14}O_2Na$ 261.0891 *m*/*z* $[M+Na]^+$, found 261.0875 *m*/*z*.



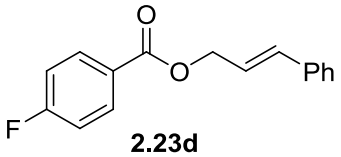
2.23b

4-Methoxybenzoic acid-3-phenyl allyl ester (**2.23b**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (d, J = 9.1 Hz, 2H), 7.42-7.40 (m, 1H), 7.32 (t, J = 7.6 Hz, 2H), 7.27-7.23 (m, 1H), 6.91 (d, J = 9.1 Hz, 2H), 6.72 (d, J = 15.6 Hz, 1H), 6.44-6.36 (m, 1H), 4.95 (dd, J = 6.4, 1.4 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 163.6, 136.4, 134.2, 131.8 (2C), 128.8 (2C), 128.2, 126. 8 (2C), 123.7, 122.8, 113.8 (2C), 65.4, 55.6; HRMS (EI) calcd for $C_{17}H_{16}O_3Na$ 291.0997 *m*/*z* $[M+Na]^+$, found 291.0982 *m*/*z*.



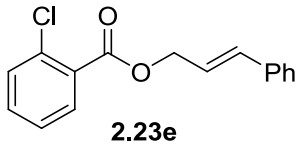
2.23c

4-Bromobenzoic acid-3-phenyl allyl ester (**2.23c**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 8.7 Hz, 2H), 7.42-7.26 (m, 5H), 6.72 (d, J = 16.0 Hz, 1H), 6.41-6.34 (m, 1H), 4.95 (dd, J = 6.6, 1.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 136.2, 134.7, 131.9 (2C), 131.4 (2C), 129.2, 128.8 (2C), 128.4, 128.3, 126.8 (2C), 123.1, 66.0; HRMS (EI) calcd for $C_{17}H_{16}O_3Na$ 291.0997 *m*/*z* $[M+Na]^+$, found 291.0982 *m*/*z*.



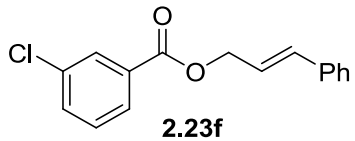
2.23d

4-Fluorobenzoic acid-3-phenyl allyl ester (**2.23d**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12-8.05 (m, 2H), 7.44-7.24 (m, 5H), 7.13-7.05 (m, 2H), 6.73 (d, J = 16.0 Hz, 1H), 6.43-6.35 (m, 1H), 4.96 (dd, J = 6.8, 1.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 165.6, 136.3, 134.7, 132.4, 128.8 (2C), 128.3, 126.8 (2C), 126.6, 123.3, 115.7, 65.9; HRMS (EI) calcd for $C_{16}H_{13}O_2FNa$ 279.0797 m/z $[M+Na]^+$, found 279.0787 m/z.



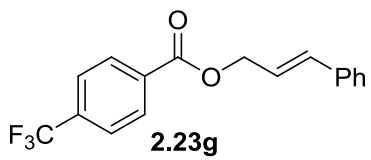
2.23e

2-Chlorobenzoic acid-3-phenyl allyl ester (**2.23e**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84 (dd, J = 7.8, 1.8 Hz, 1H), 7.43-7.22 (m, 8H), 6.73 (d, J = 16.0 Hz, 1H), 6.41-6.34 (m, 1H), 4.97 (dd, J = 6.8, 1.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 136.2, 134.8, 133.9, 132.7, 131.6, 131.2, 130.1, 128.7 (2C), 128.3, 126.8 (2C), 126.7, 122.8, 66.2; HRMS (EI) calcd for $C_{16}H_{13}O_2ClNa$ 295.0502 m/z $[M+Na]^+$, found 295.0508 m/z.



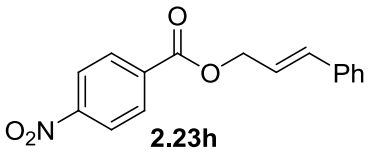
2.23f

3-Chlorobenzoic acid-3-phenyl allyl ester (**2.23f**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (m, 1H), 7.97-7.94 (m, 1H), 7.54-7.51 (m, 1H), 7.42-7.22 (m, 6H), 6.74 (d, J = 16.0 Hz, 1H), 6.43-6.35 (m, 1H), 4.98 (dd, J = 6.8, 1.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 136.3, 134.9, 134.7, 133.2, 132.1, 129.9 (2C), 128.8 (2C), 128.4, 128.0, 126.9 (2C), 123.0, 66.1; HRMS (EI) calcd for $C_{16}H_{13}O_2ClNa$ 295.0502 m/z $[M+Na]^+$, found 295.0514 m/z.



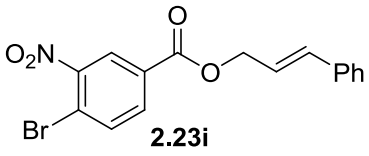
2.23g

4-Trifluoromethylbenzoic acid-3-phenyl allyl ester (**2.23g**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (d, J = 8.0, 2H), 7.80 (d, J = 8.0, 2H), 7.36-7.24 (m, 5H), 6.74 (d, J = 16.0 Hz, 1H), 6.43-6.35 (m, 1H), 4.98 (dd, J = 6.4, 1.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 152.8, 136.3, 134.8, 131.8 (2C), 128.9 (2C), 128.8, 120.4, 126.8 (2C), 123.1, 120.5, 120.4 (2C), 66.0; HRMS (EI) calcd for $C_{17}H_{13}O_2F_3Na$ 329.0765 *m*/*z* $[M+Na]^+$, found 329.0767 *m*/*z*.



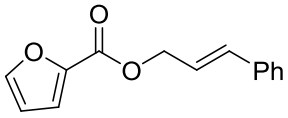
2.23h

4-Nitrobenzoic acid-3-phenyl allyl ester (**2.23h**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30-8.20 (m, 4H), 7.45-7.39 (m, 2H), 7.38-7.25 (m, 3H), 6.75 (d, J = 16.0 Hz, 1H), 6.43-6.36 (m, 1H), 5.02 (dd, J = 6.8, 1.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 150.6, 136.0, 135.6, 135.3, 130.9 (2C), 128.8 (2C), 128.5, 126.8 (2C), 123.6 (2C), 122.4, 66.6; HRMS (EI) calcd for $C_{16}H_{13}NO_4Na$ 306.0742 *m*/*z* $[M+Na]^+$, found 306.0749 *m*/*z*.



2.23i

4-Bromo-3-nitrobenzoic acid-3-phenyl allyl ester (**2.23i**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.48 (d, J = 1.8 Hz, 1H), 8.08 (dd, J = 8.2, 1.8 Hz, 1H), 7.82 (d, J = 8.6 Hz, 1H), 7.42-7.40 (m, 2H), 7.36-7.25 (m, 3H), 6.75 (d, J = 16.0 Hz, 1H), 6.41-6.34 (m, 1H), 5.08 (dd, J = 6.4, 1.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 150.0, 135.7, 135.6, 133.7, 131.0, 128.8 (2C), 128.6, 126.9 (2C), 126.6, 122.3, 119.8, 66.8; HRMS (EI) calcd for $C_{16}H_{12}NO_4BrNa$ 383.9874 *m*/*z* $[M+Na]^+$, found 383.9860 *m*/*z*.



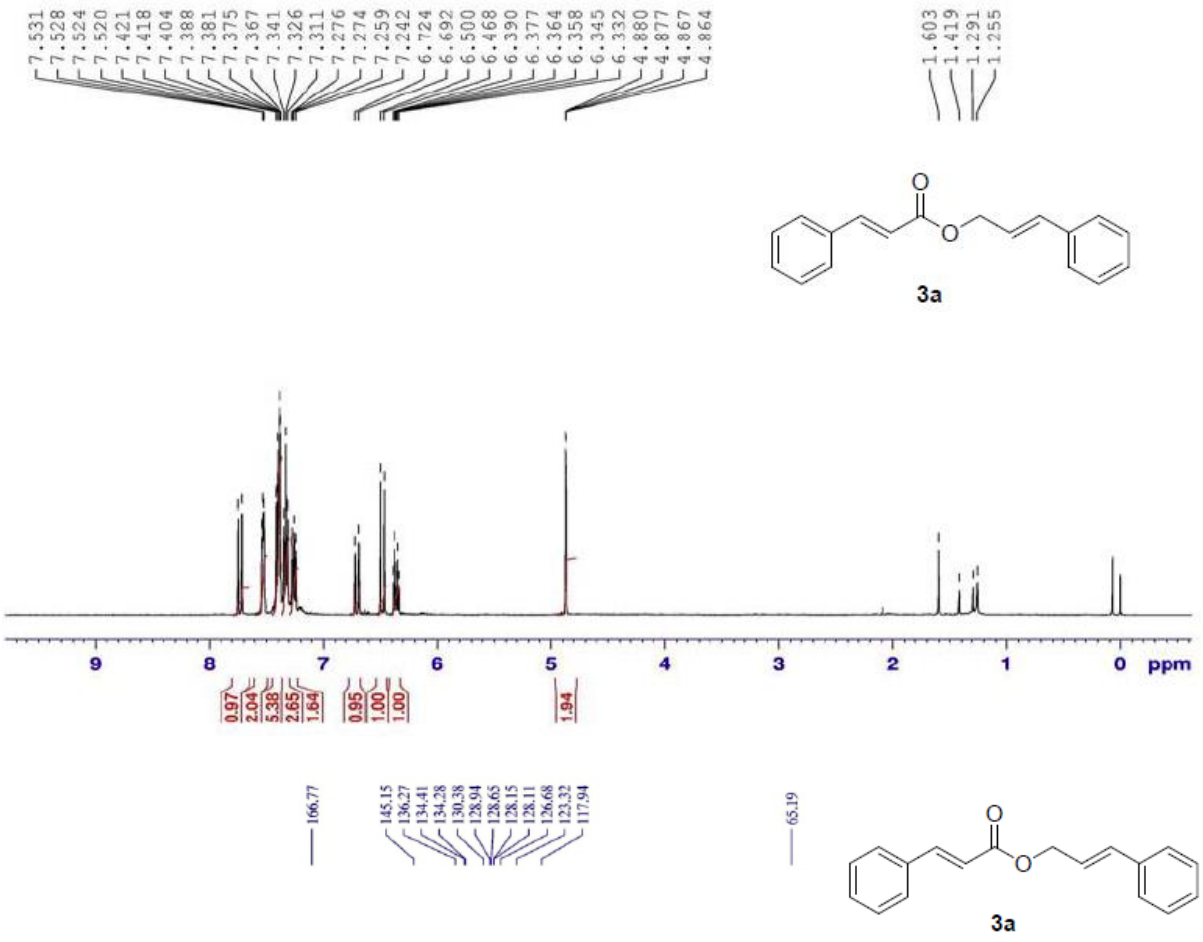
2.23j

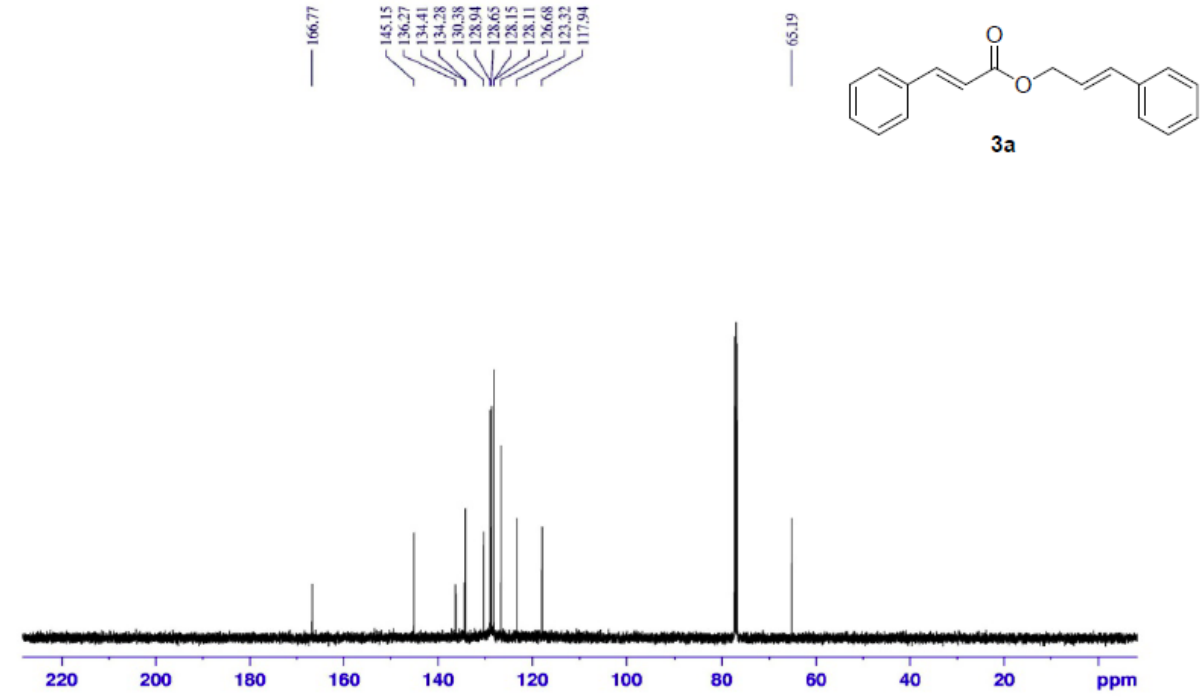
Furan-2 carboxylic acid-3-phenyl allyl ester (**2.23j**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (s, 1H), 7.41-7.38 (m, 2H), 7.35-7.21 (m, 4H), 6.72 (d, J = 15.6 Hz, 1H), 6.50-6.48 (m, 1H), 6.40-6.32 (m, 1H), 4.95 (dd, J = 6.4, 1,4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 146.5, 144.7, 136.2, 134.9, 128.7 (2C), 128.3, 126.8 (2C), 122.9, 118.3, 112.0, 65.6; HRMS (EI) calcd for $C_{14}H_{12}O_3Na$ 251.0684 *m*/*z* $[M+Na]^+$, found 251.0694 *m*/*z*.

2.6 Supporting Information

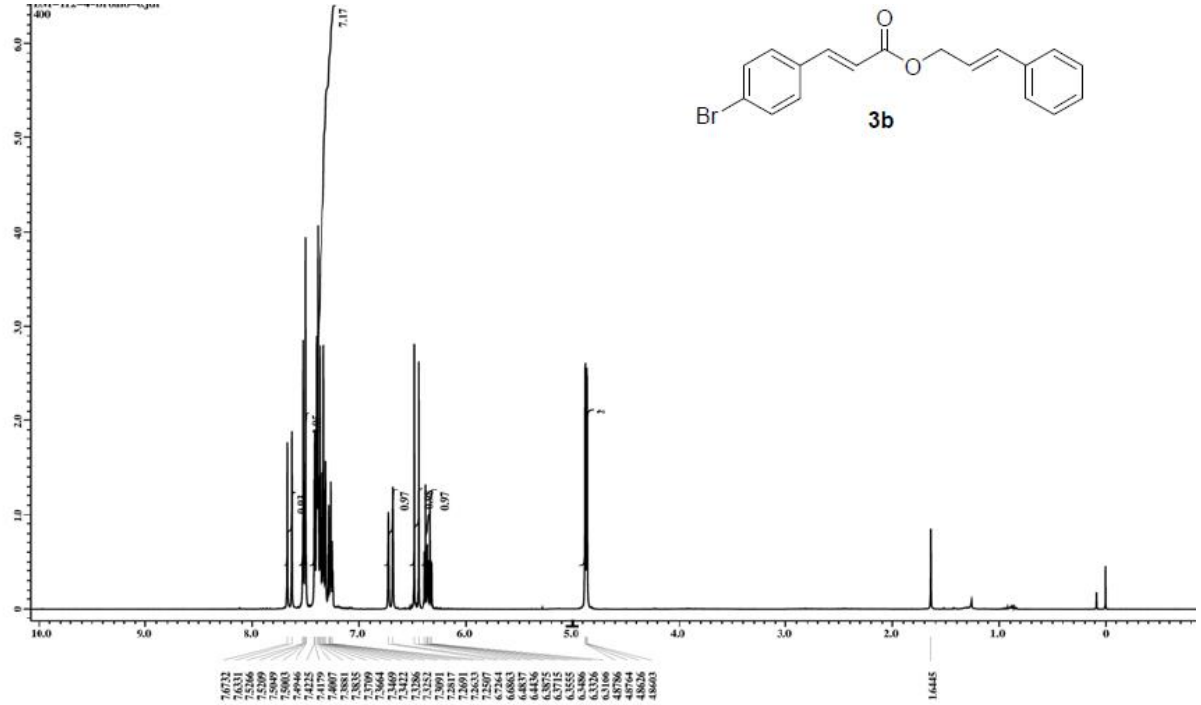
1. ^{1}H and ^{13}C NMR spectra data of compounds 2.21a-2.21q and 2.23a-2.23j

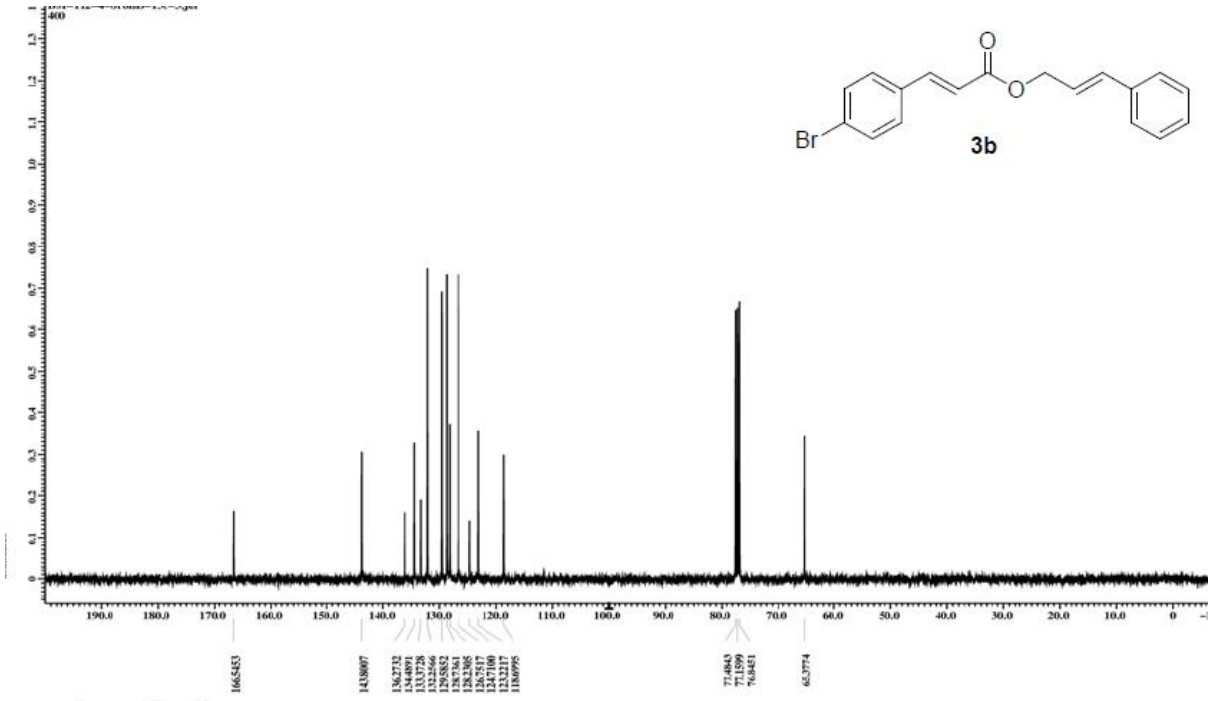
^{1}H and ^{13}C NMR spectra of compound 2.21a



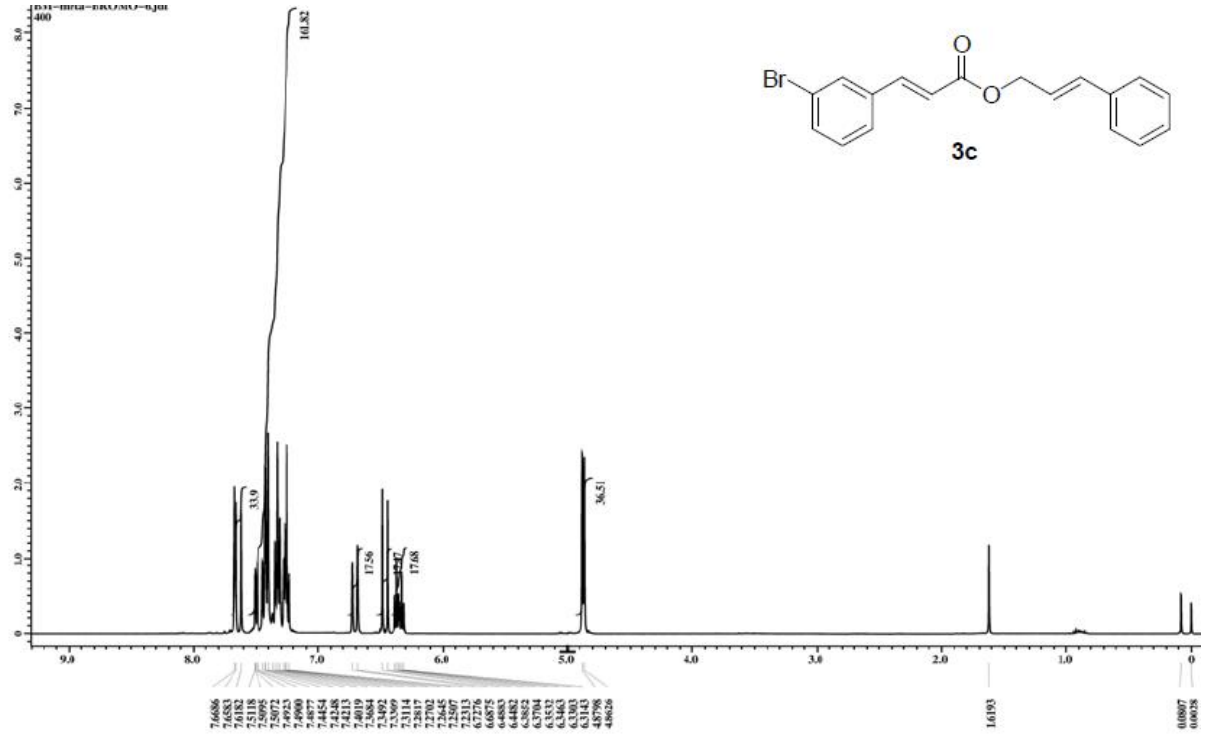


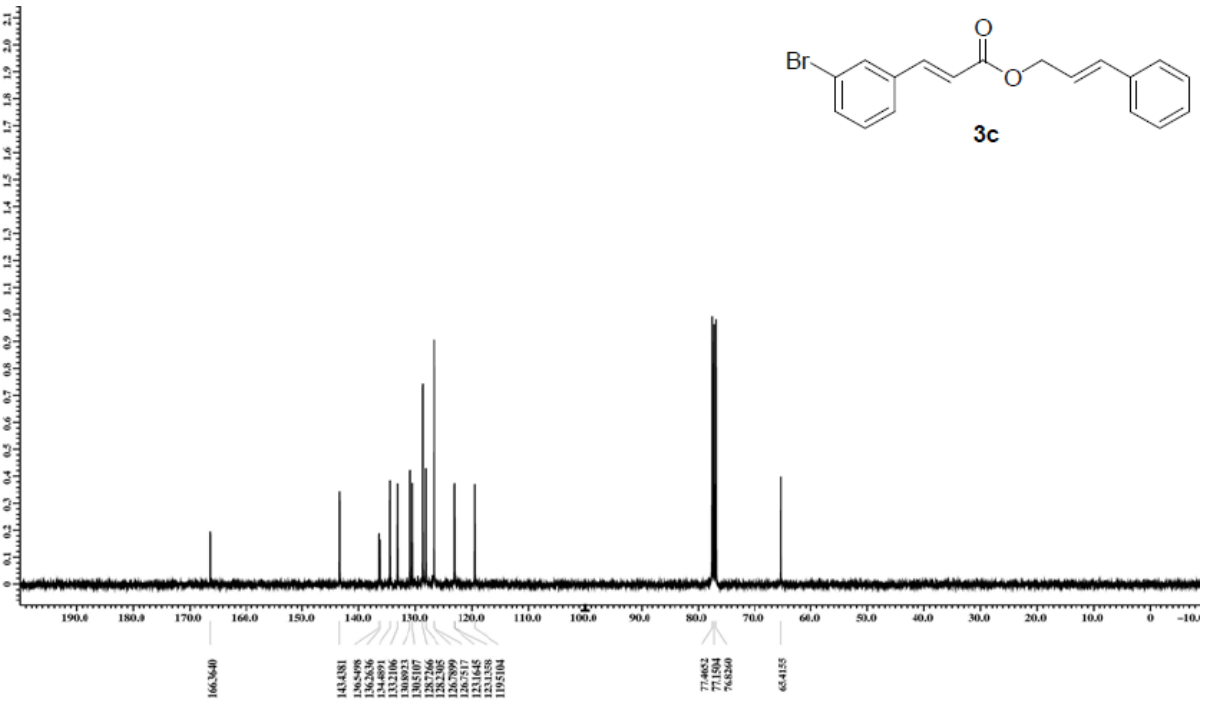
^{1}H and ^{13}C NMR spectra of compound 2.21b



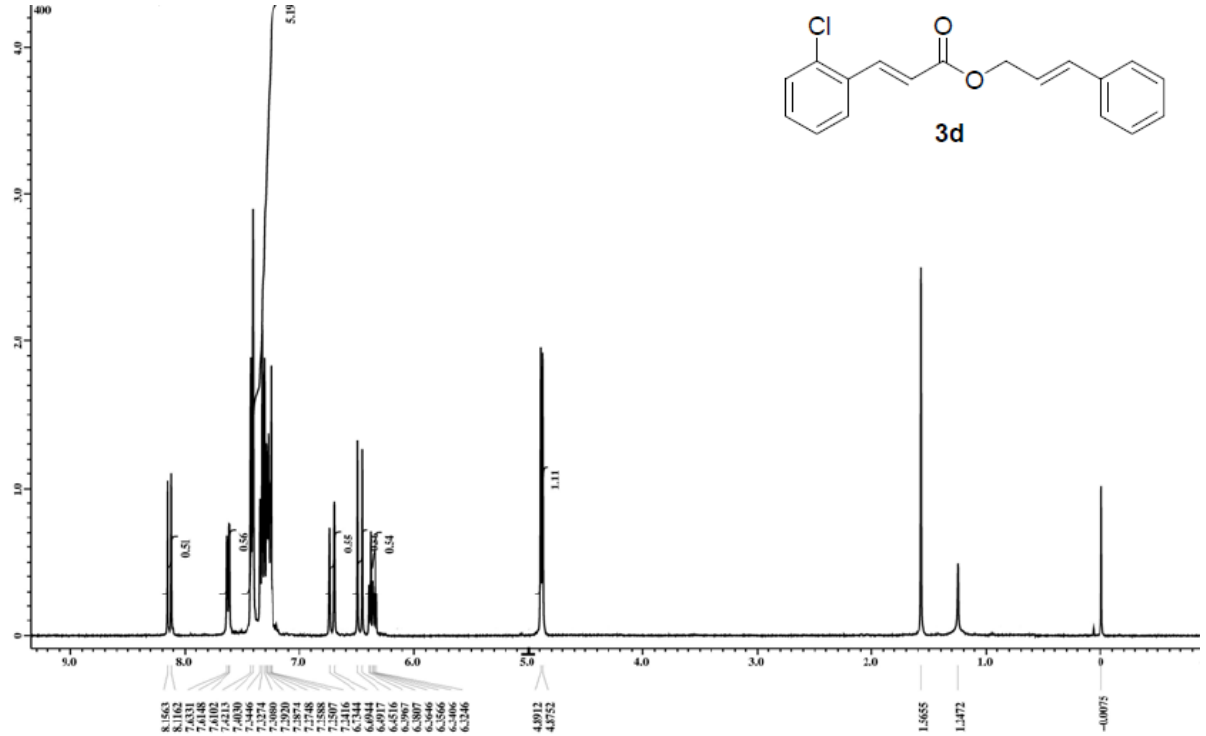


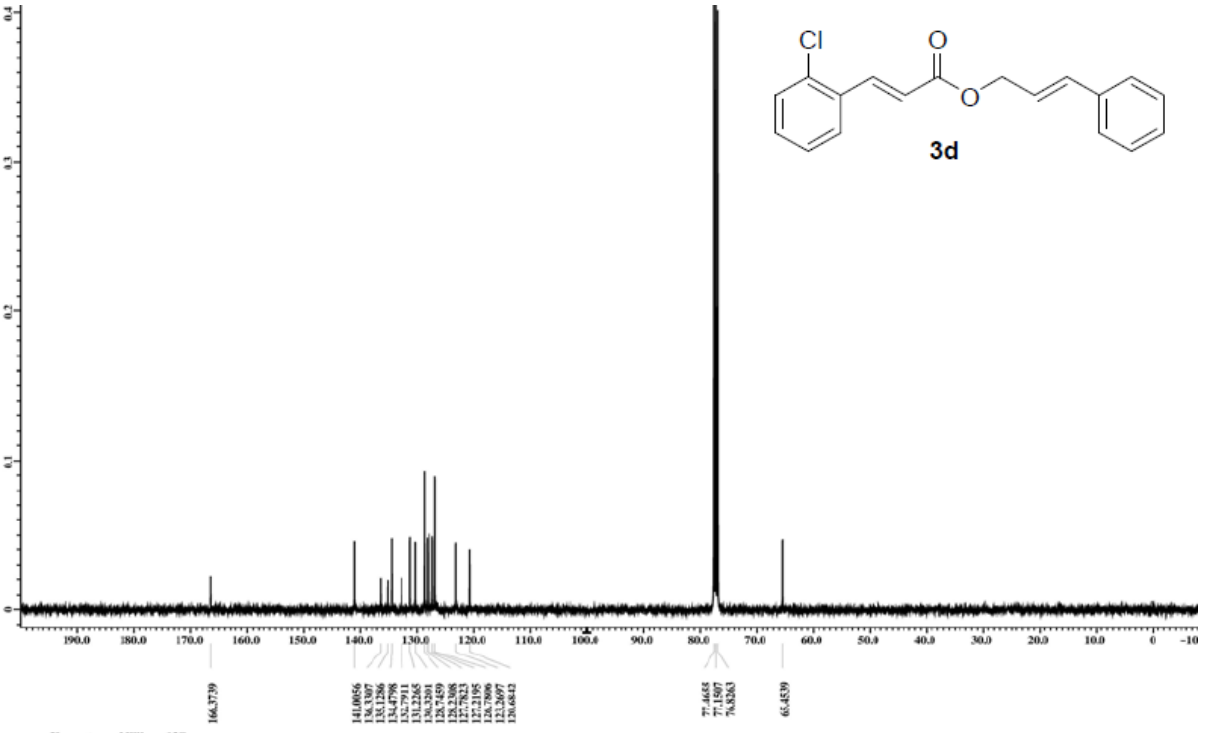
^{1}H and ^{13}C NMR spectra of compound 2.21c



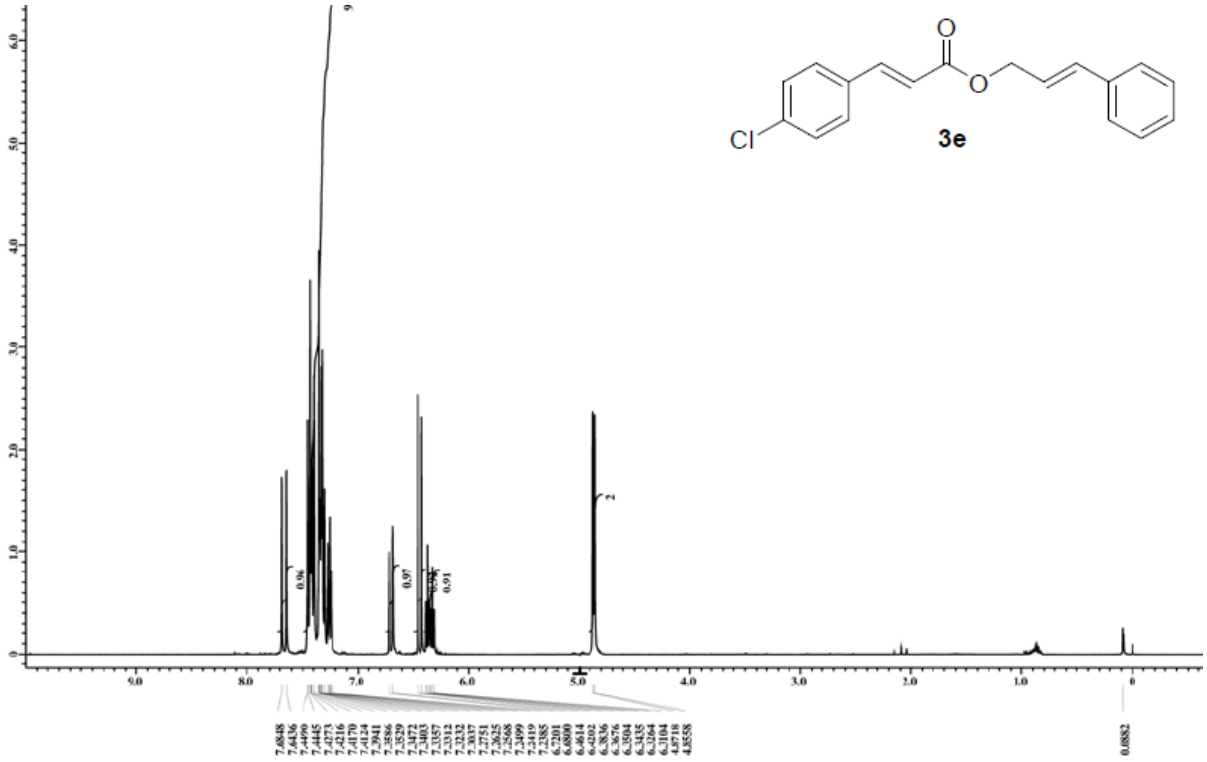


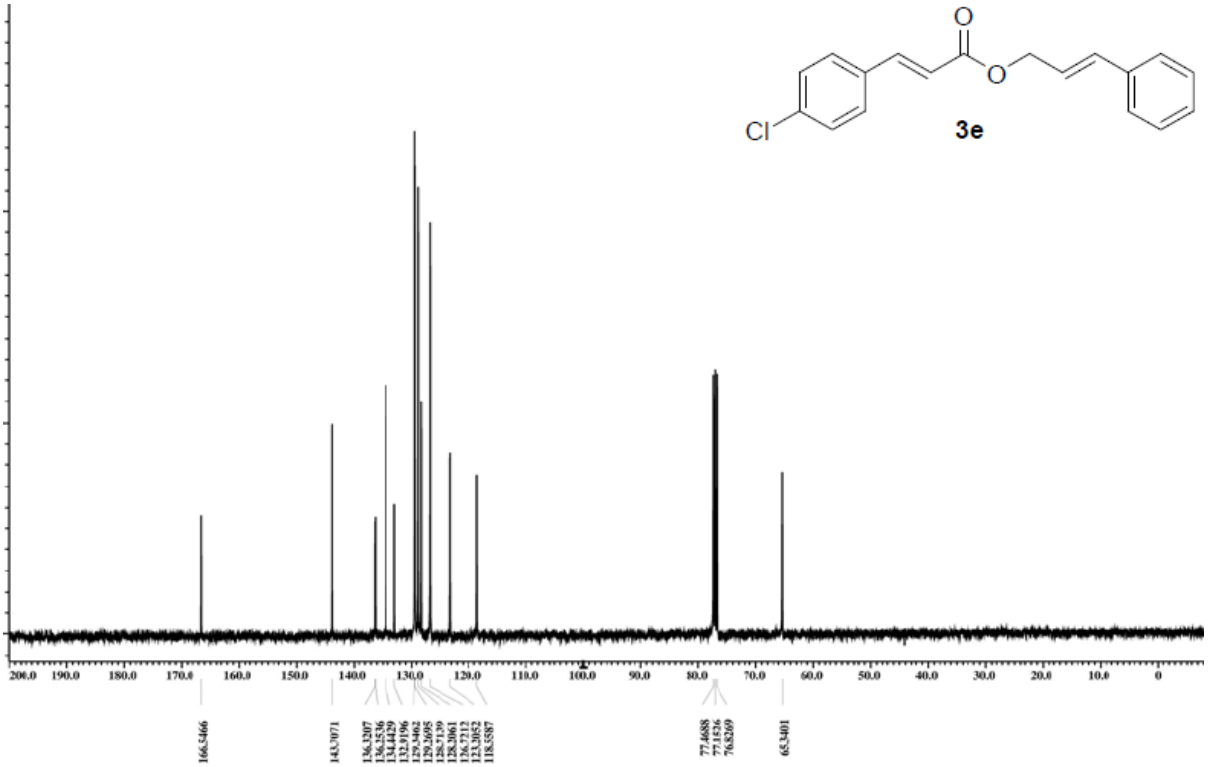
^{1}H and ^{13}C NMR spectra of compound 2.21d



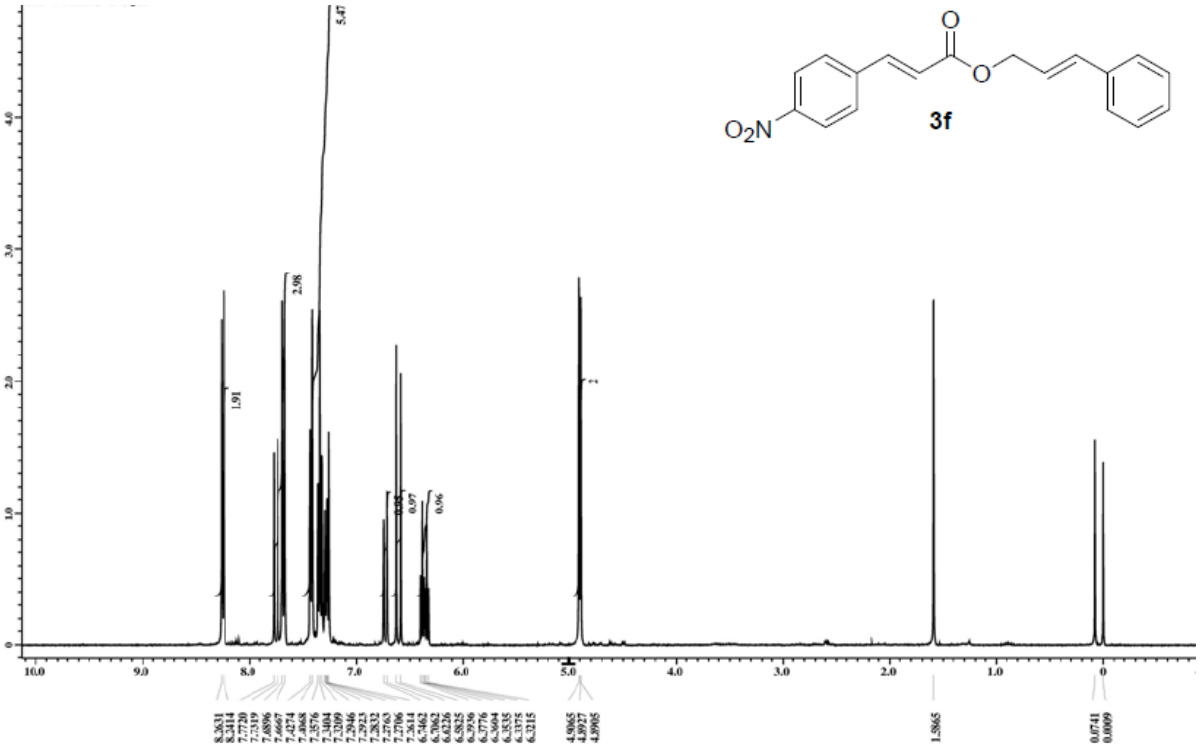


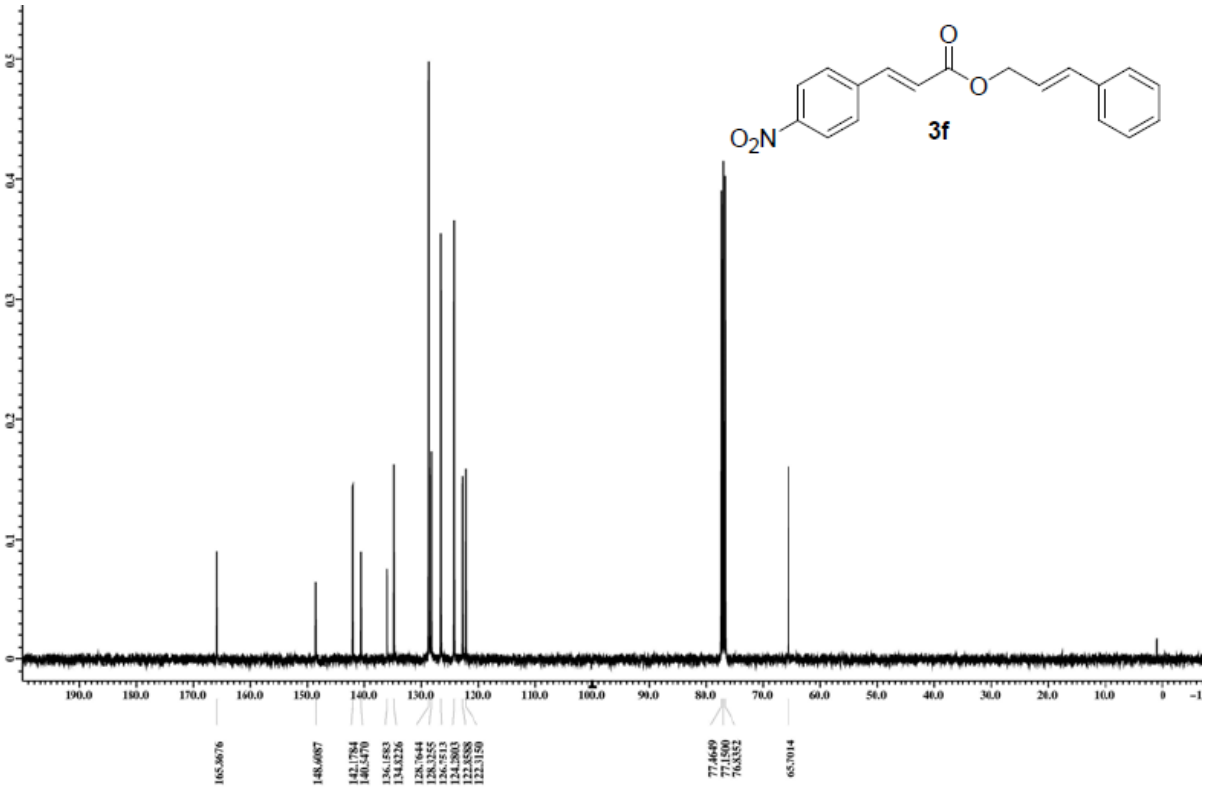
^{1}H and ^{13}C NMR spectra of compound 2.21e



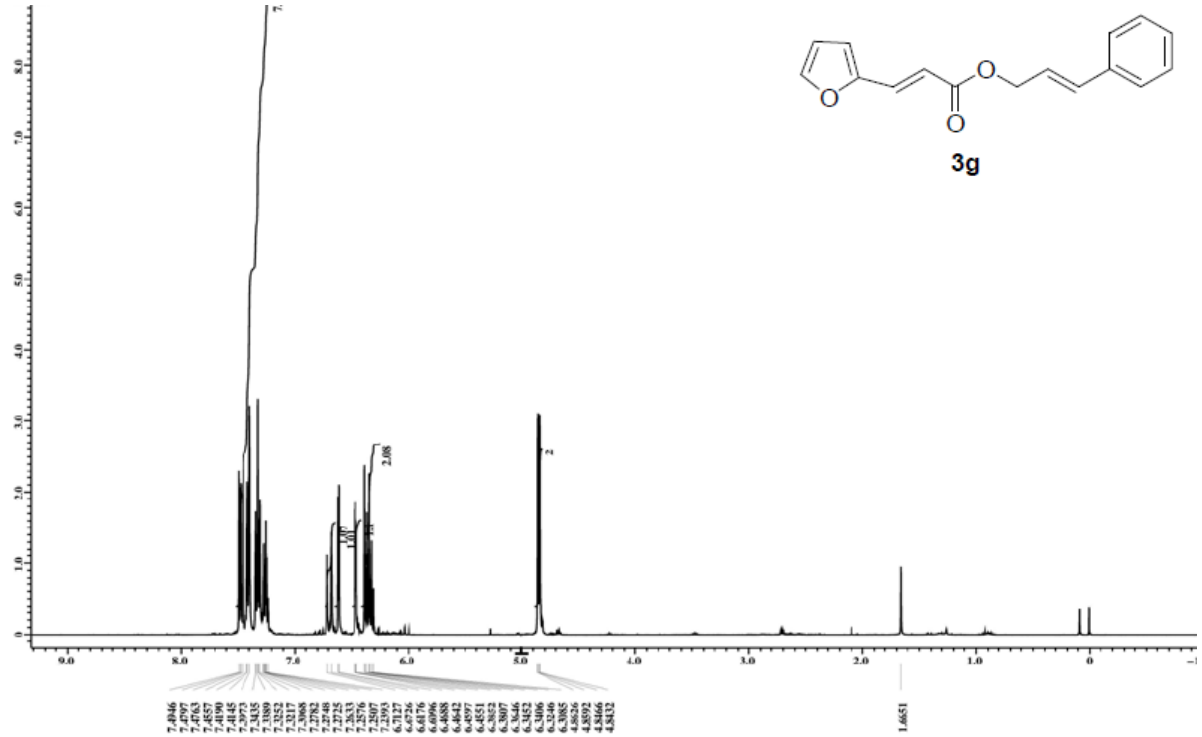


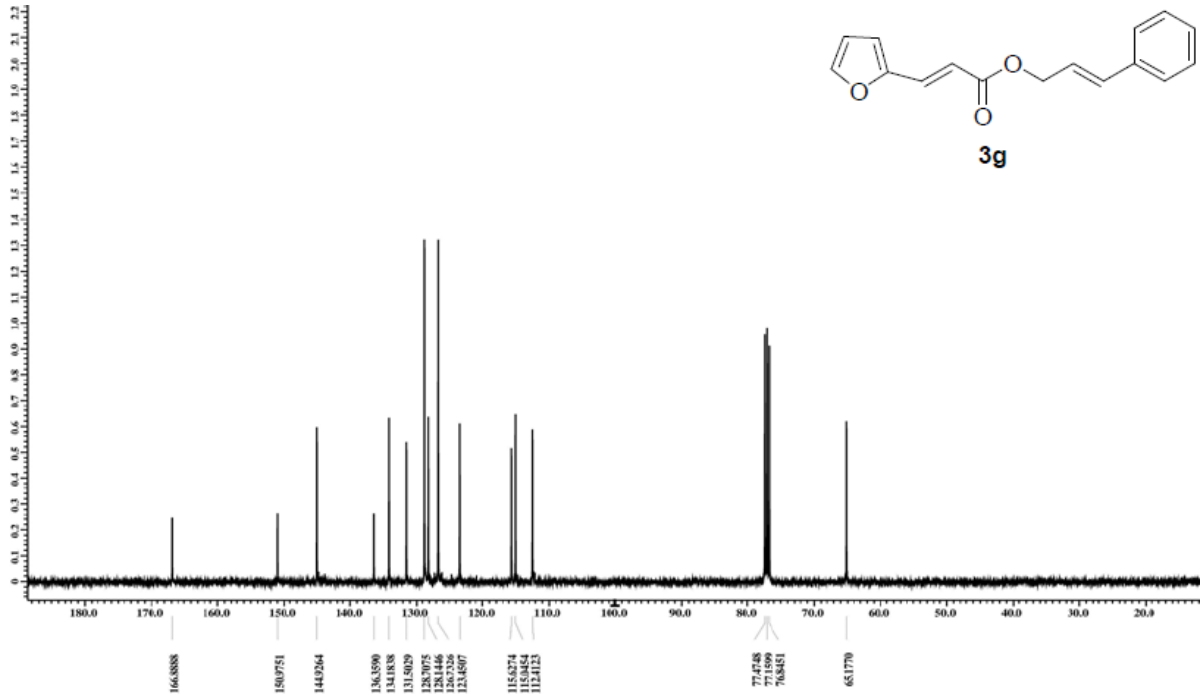
^{1}H and ^{13}C NMR spectra of compound 2.21f



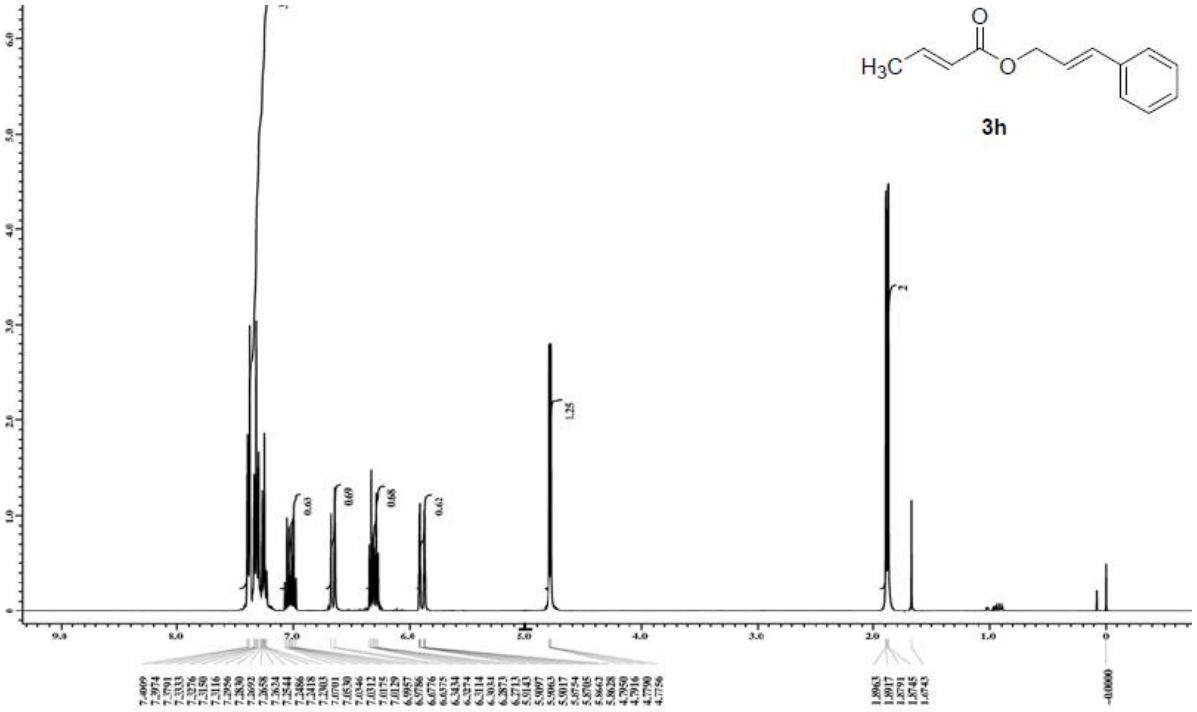


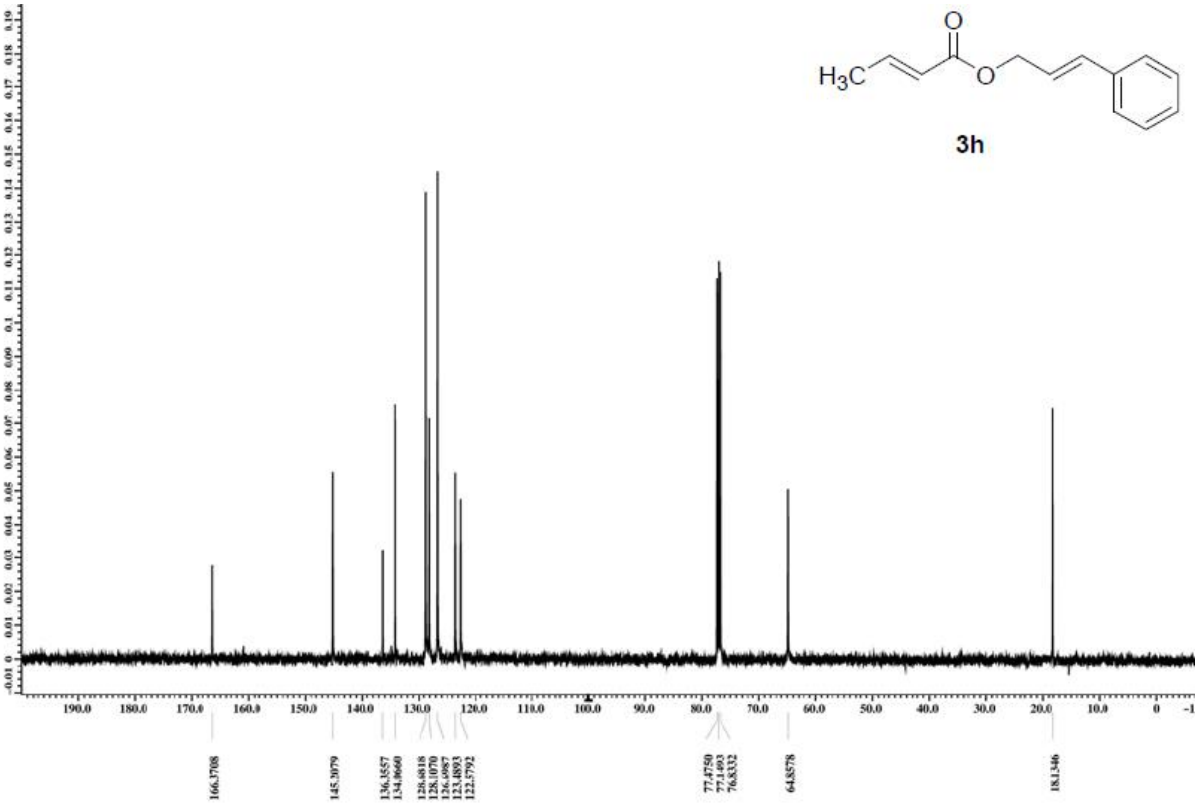
^{1}H and ^{13}C NMR spectra of compound 2.21g



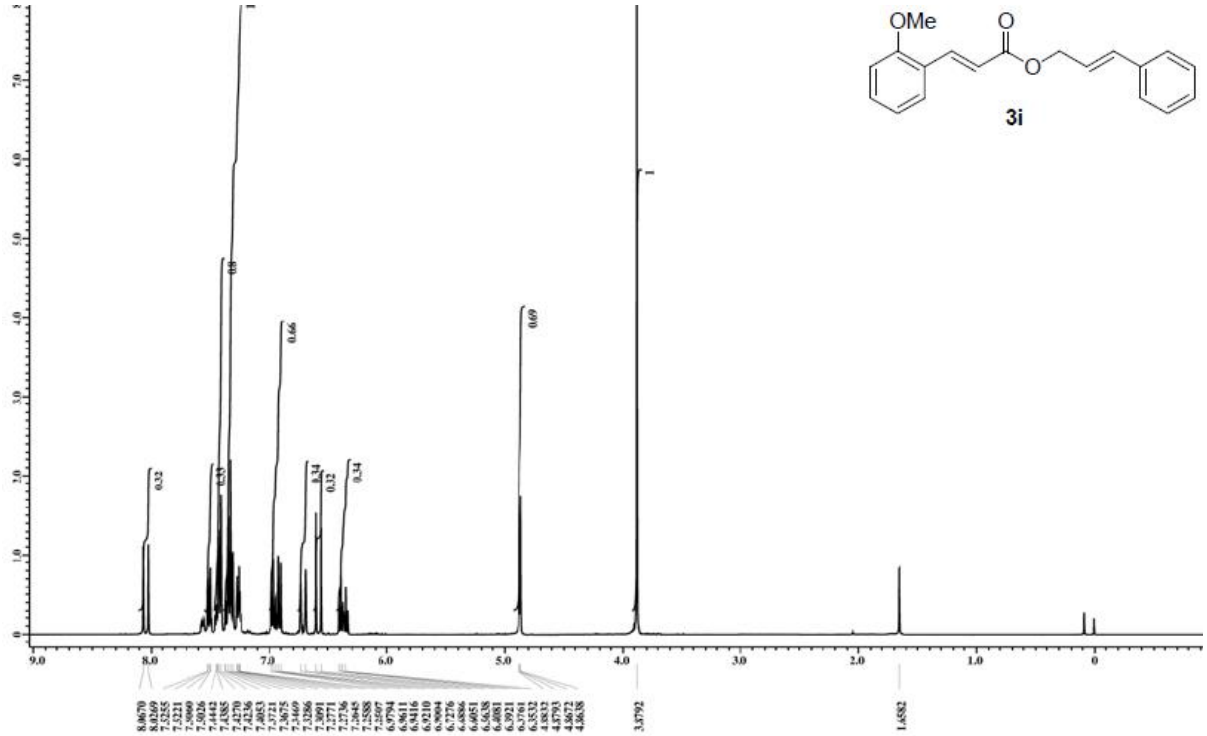


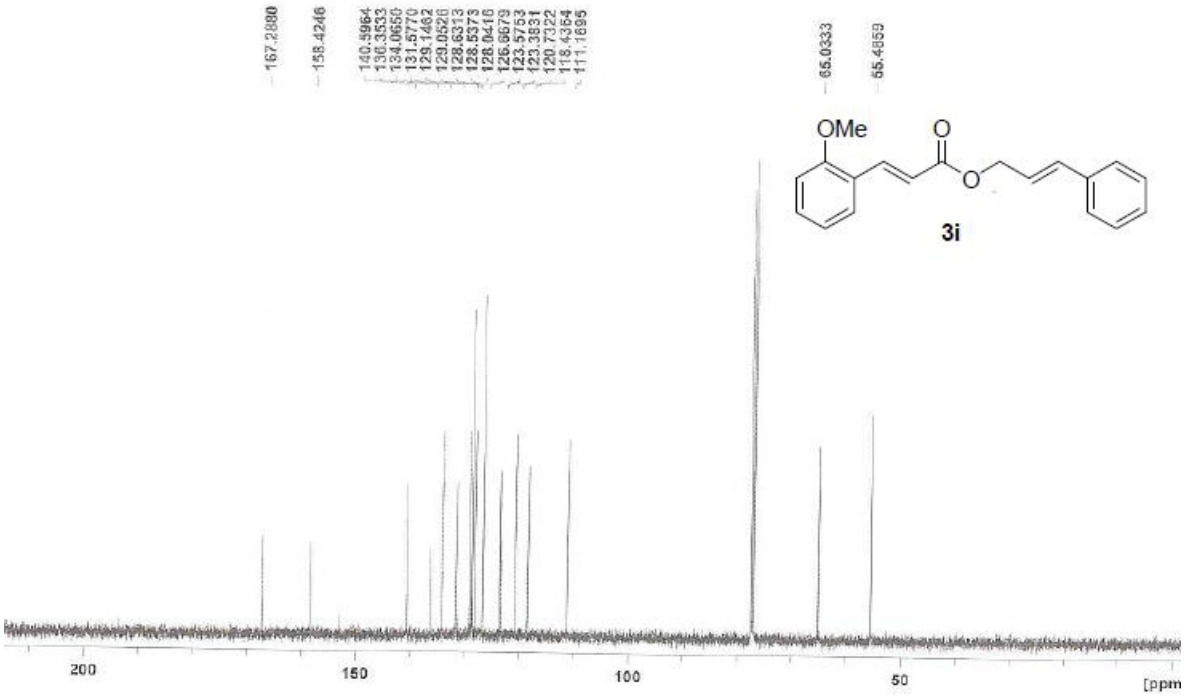
^{1}H and ^{13}C NMR spectra of compound 2.21h



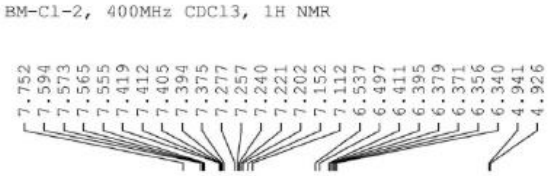


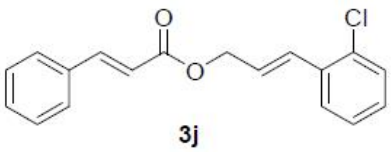
^{1}H and ^{13}C NMR spectra of compound 2.21i

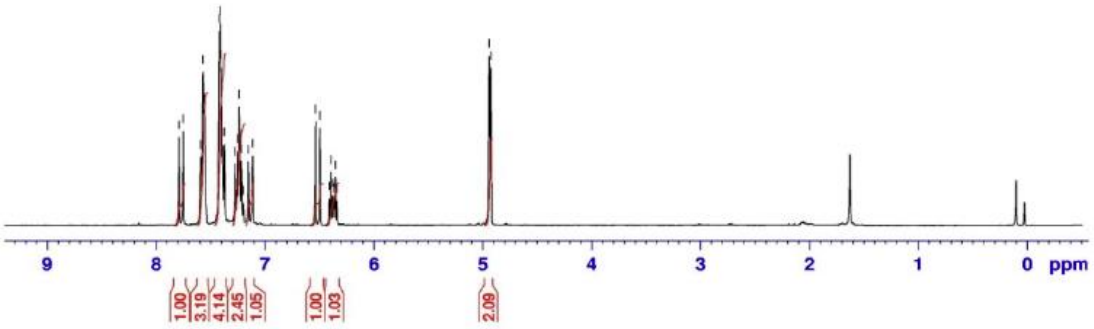


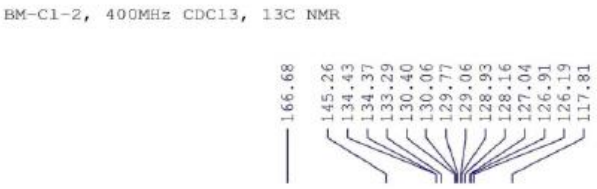


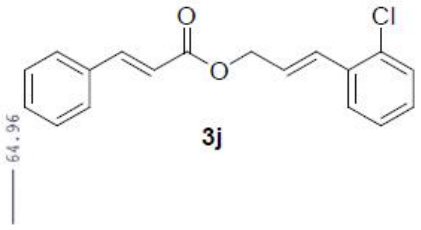
^{1}H and ^{13}C NMR spectra of compound 2.21j

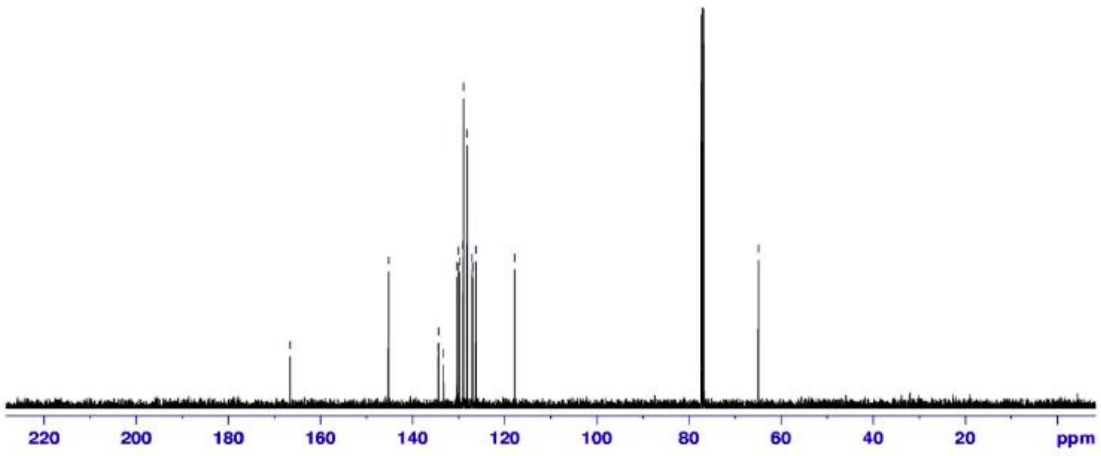




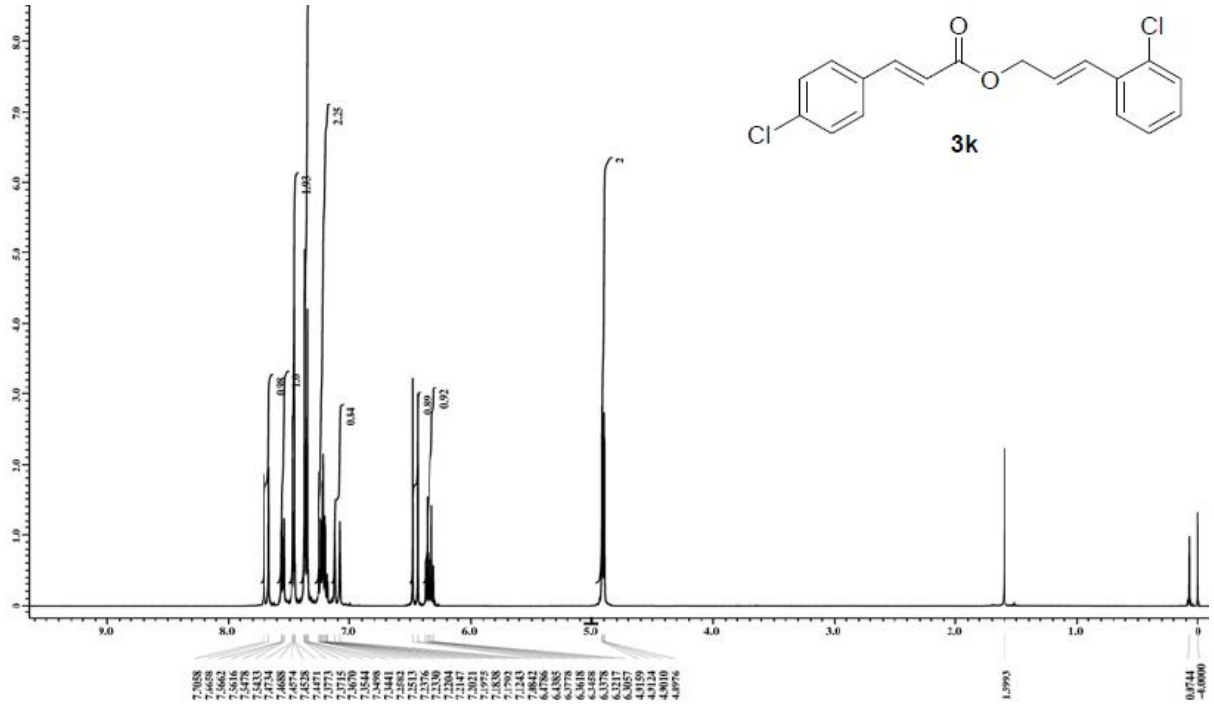


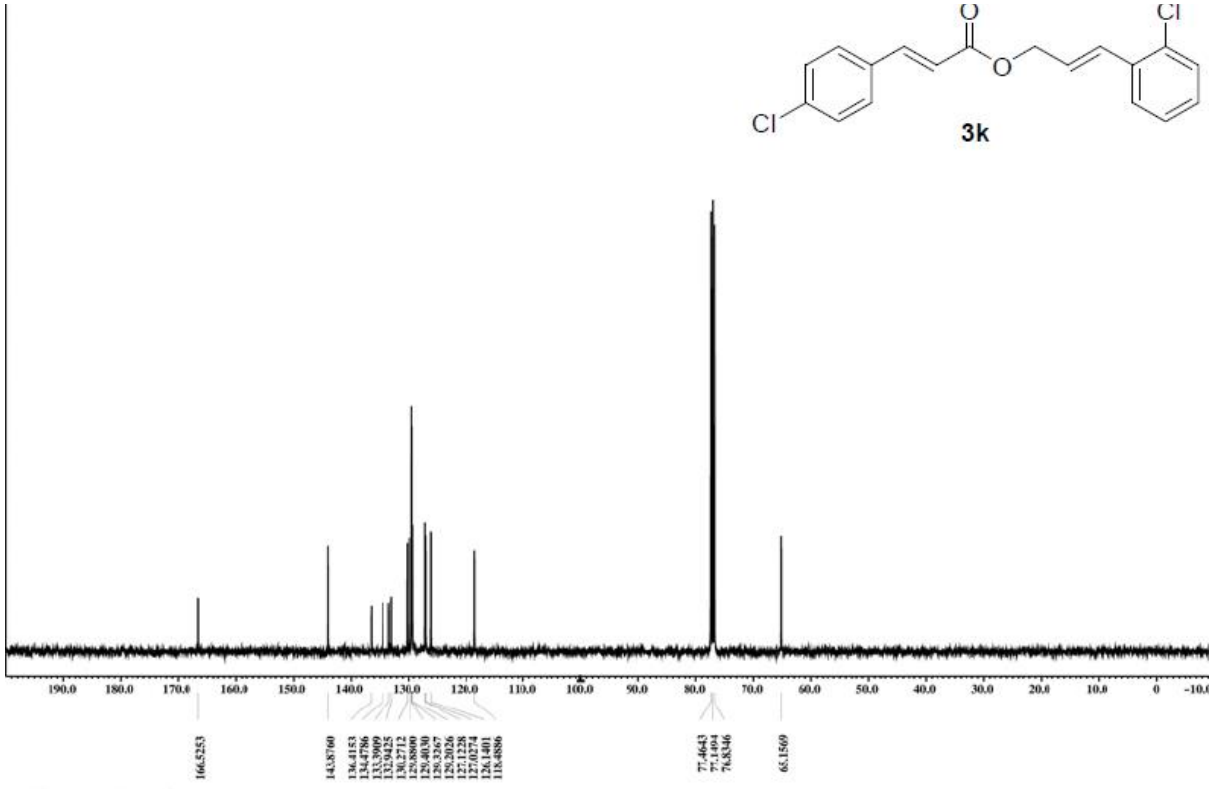




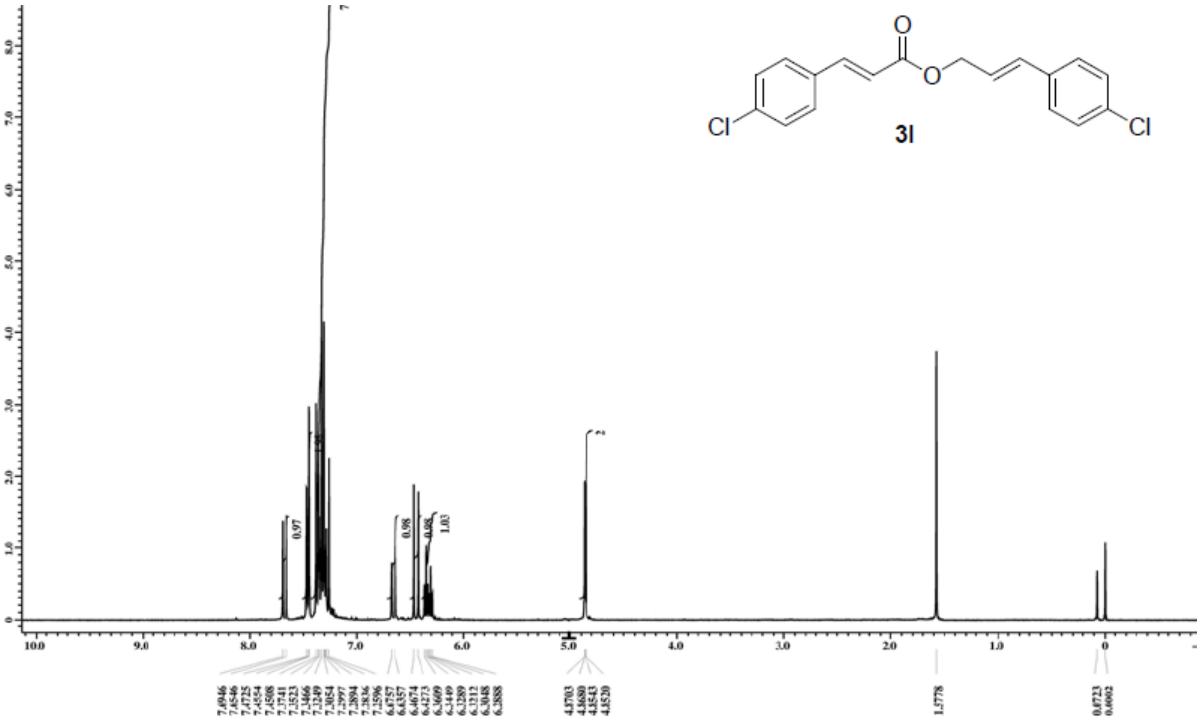


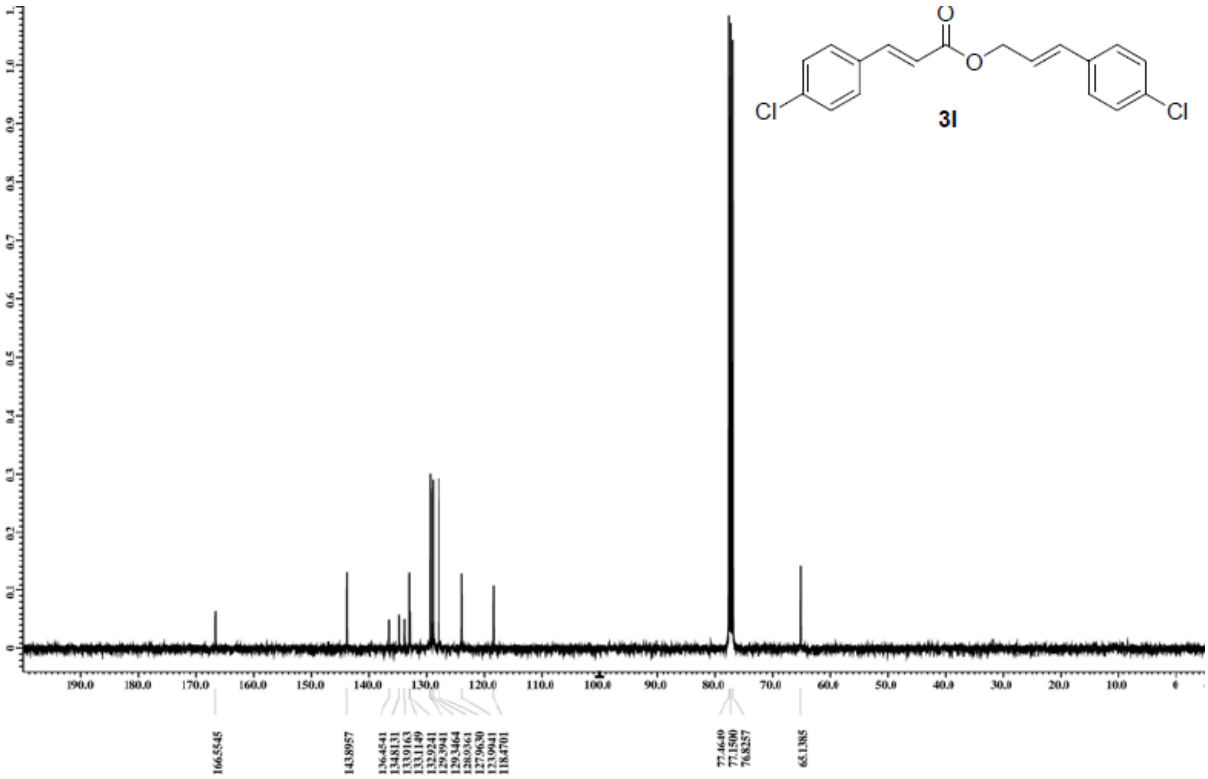
^{1}H and ^{13}C NMR spectra of compound 2.21k



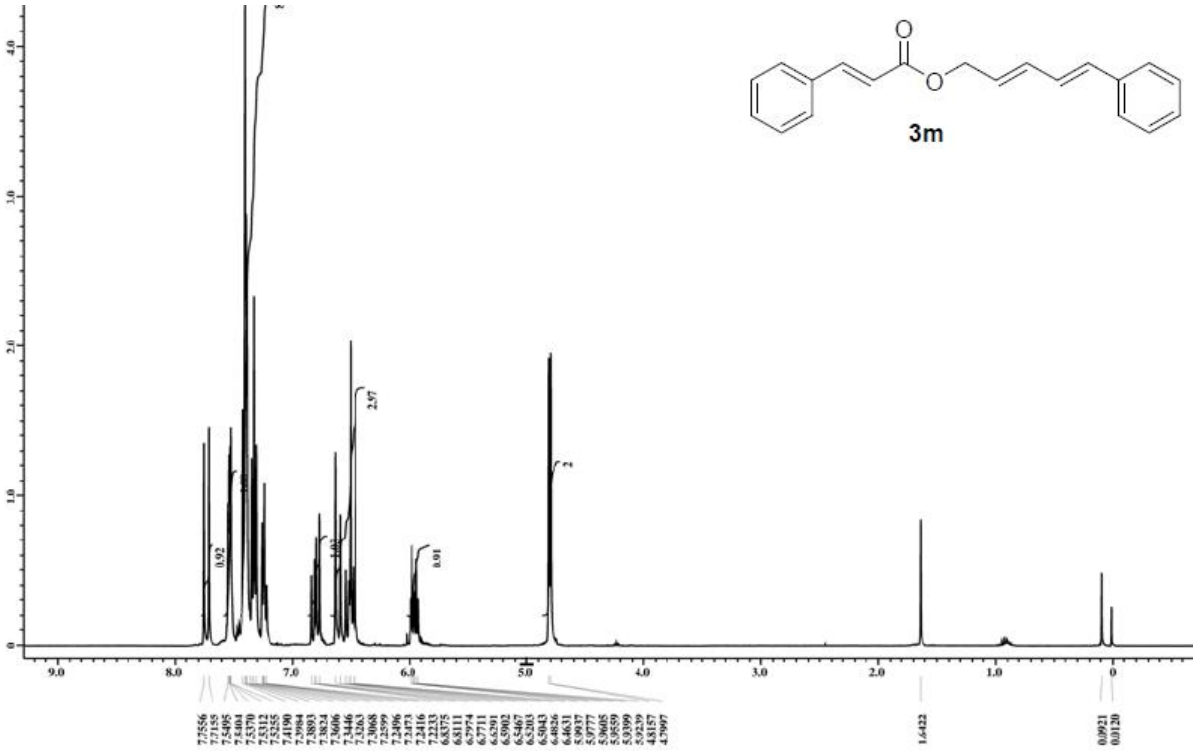


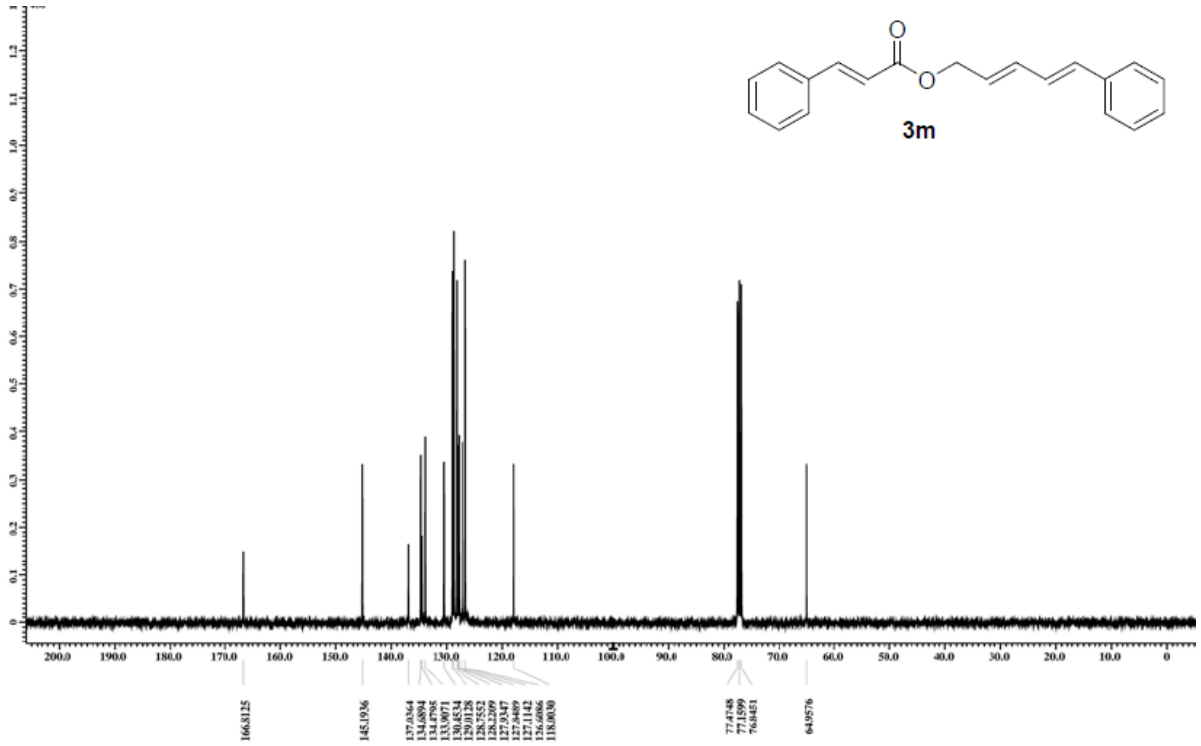
^{1}H and ^{13}C NMR spectra of compound 2.21l



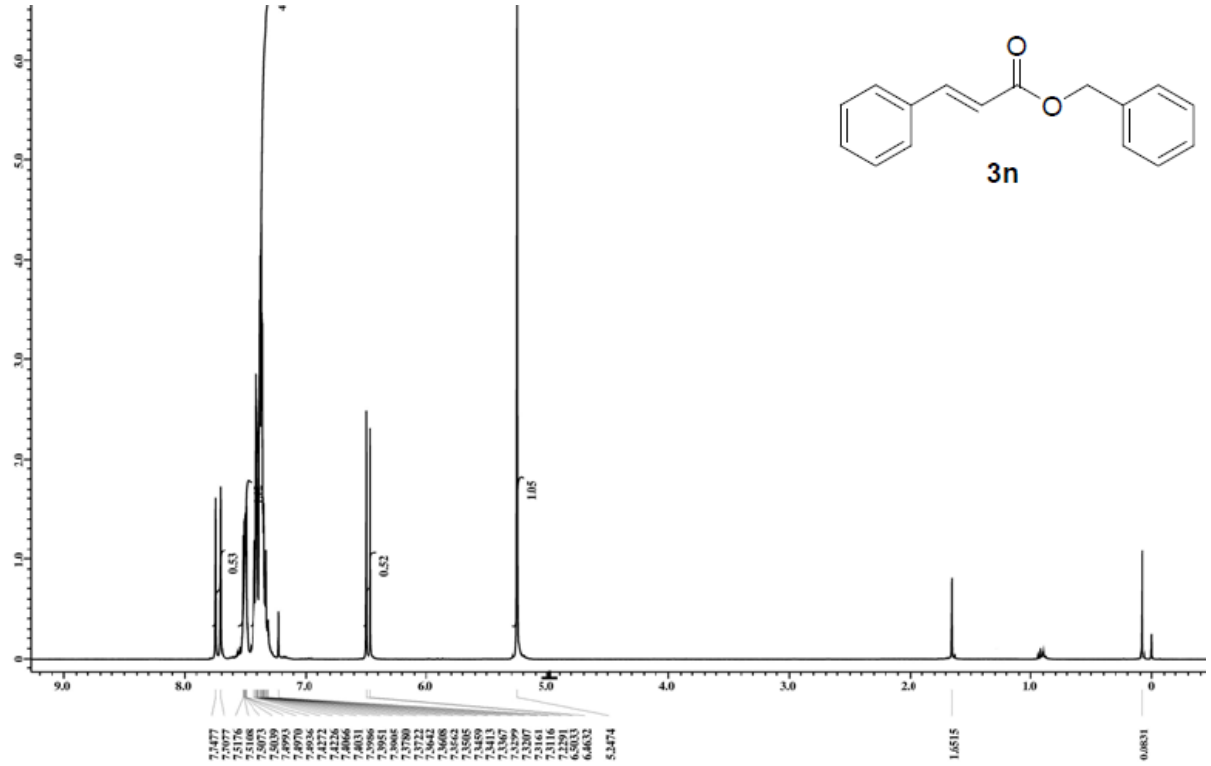


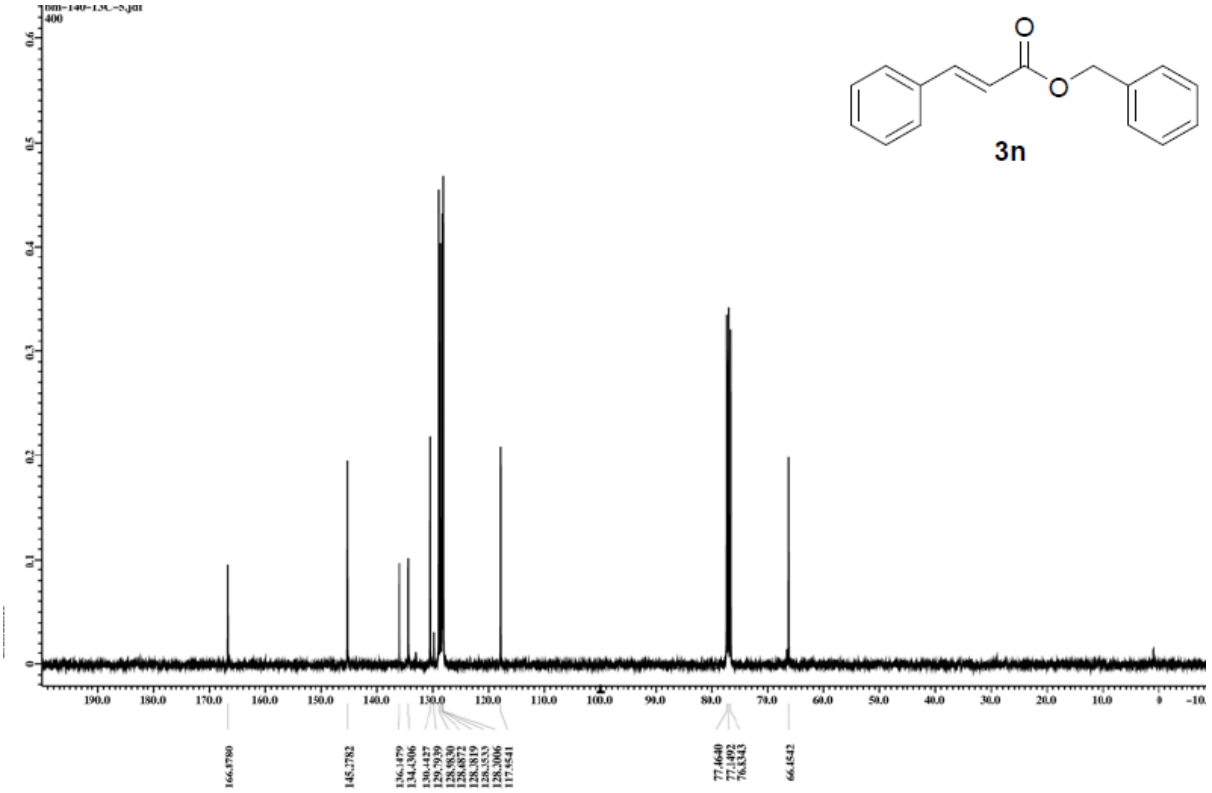
^{1}H and ^{13}C NMR spectra of compound 2.21m



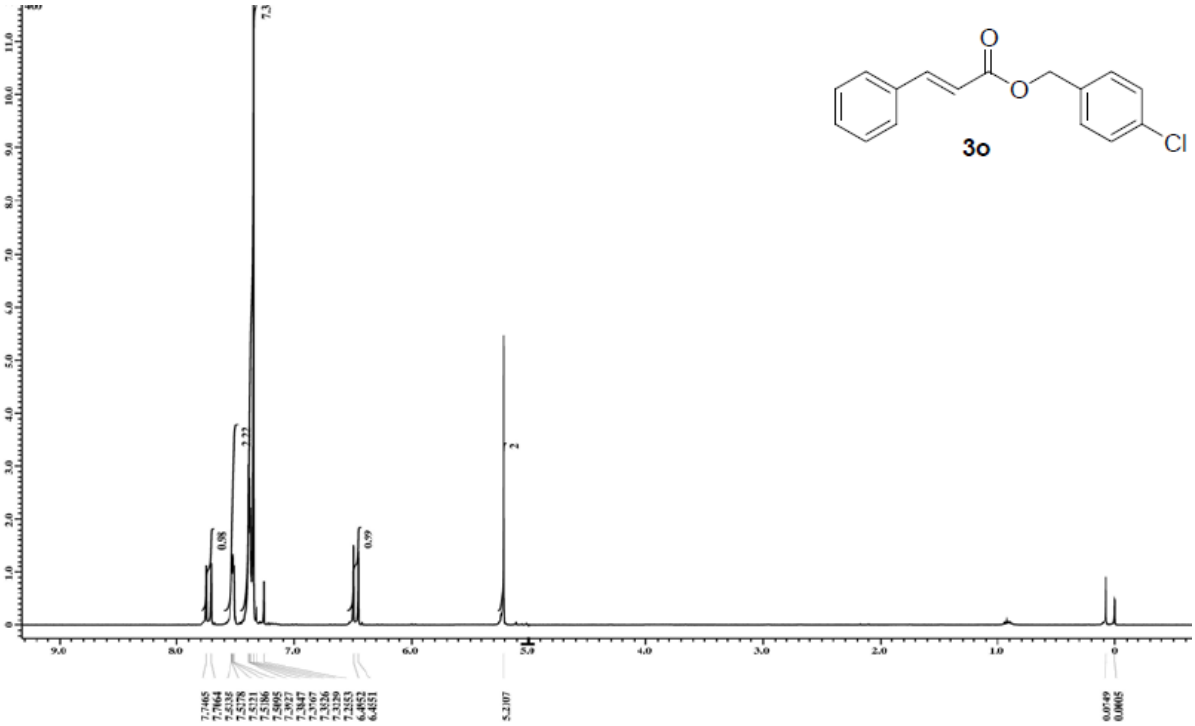


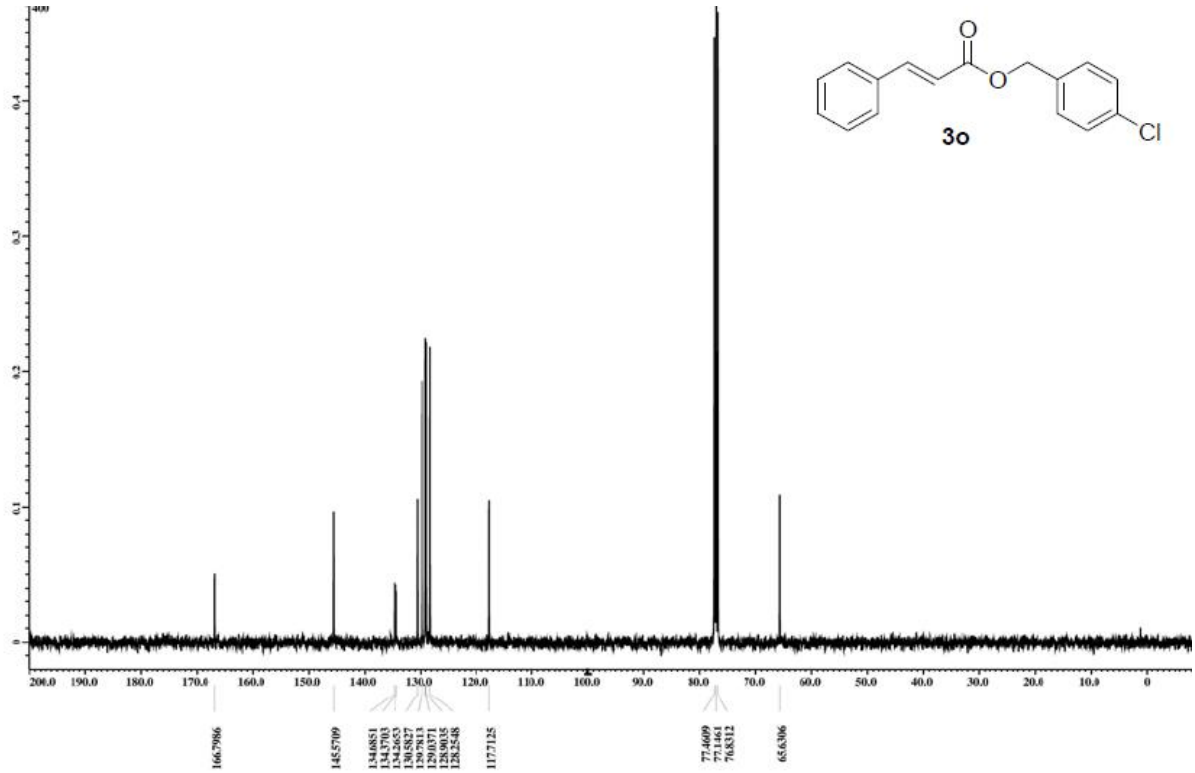
^{1}H and ^{13}C NMR spectra of compound 2.21n



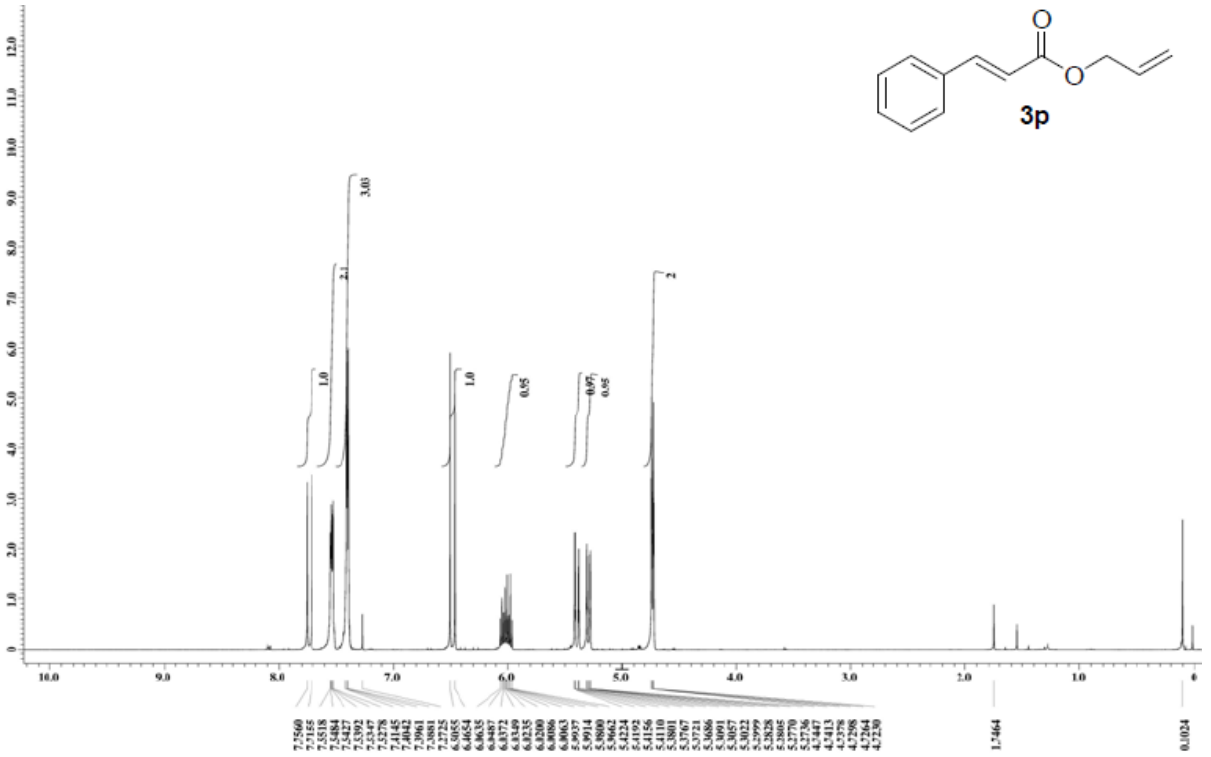


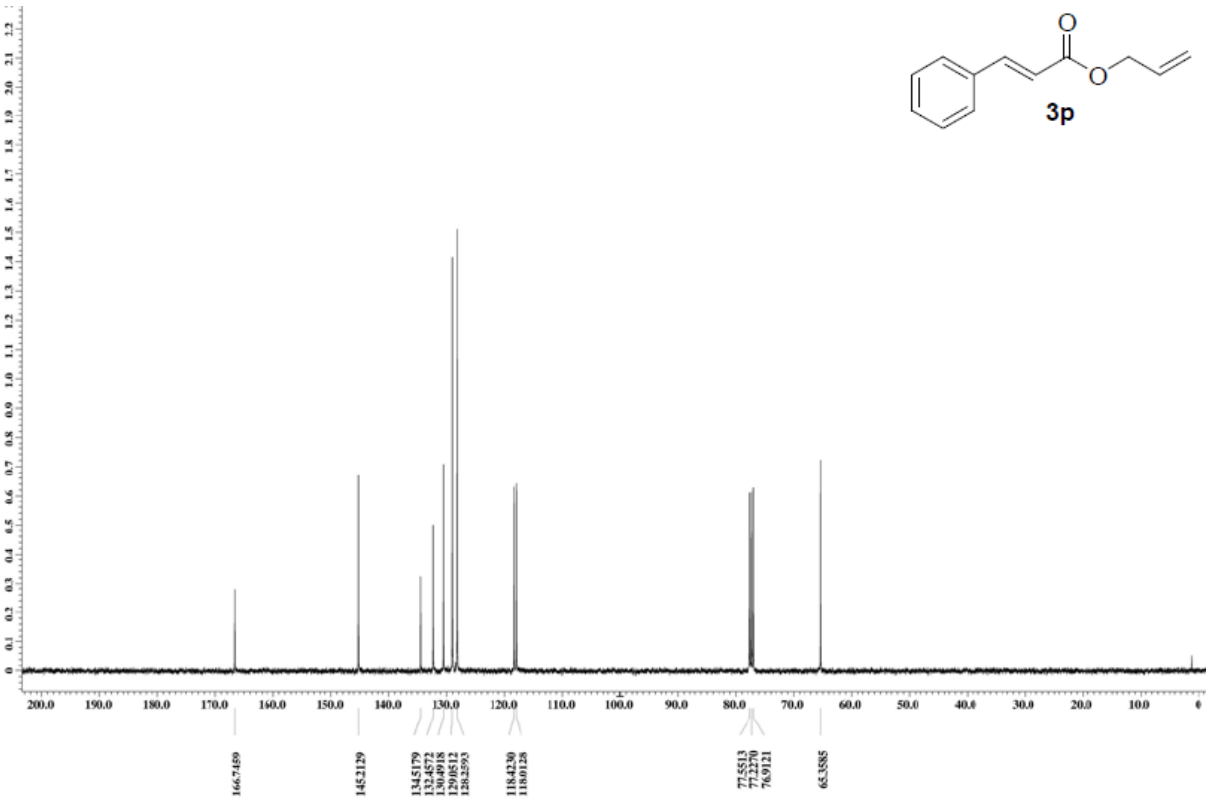
^{1}H and ^{13}C NMR spectra of compound 2.21o



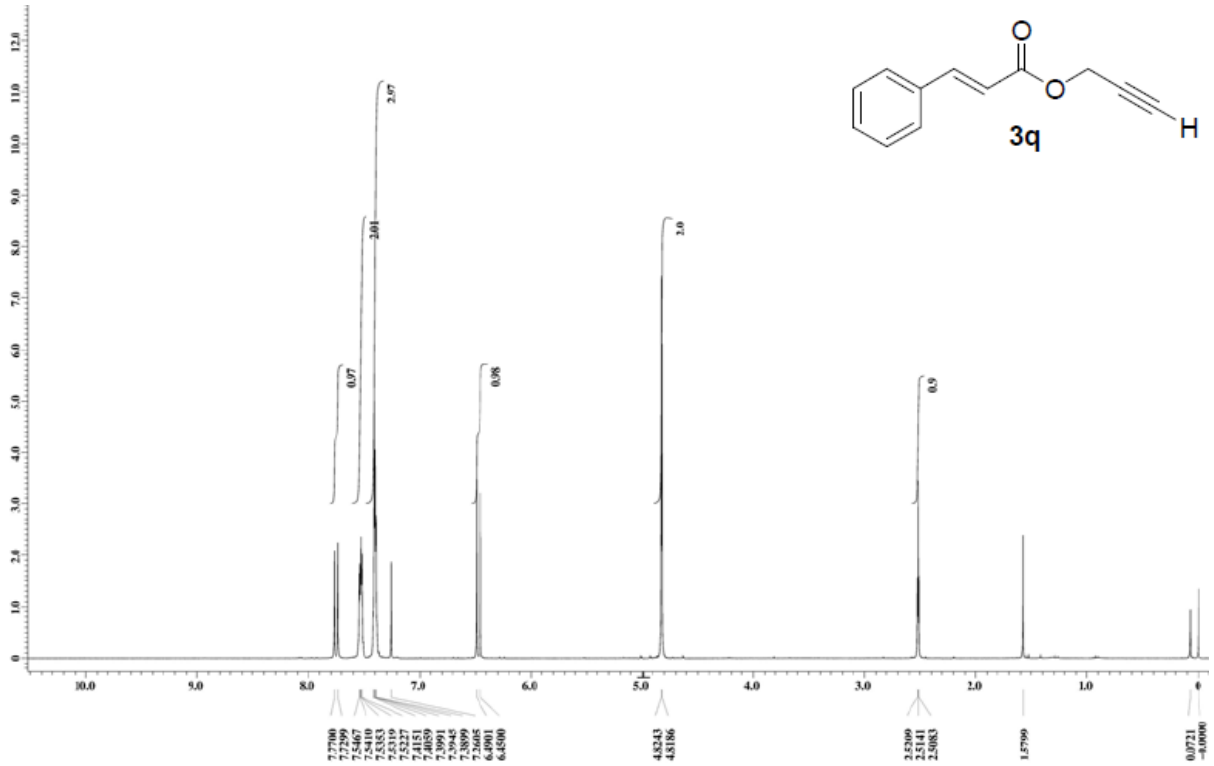


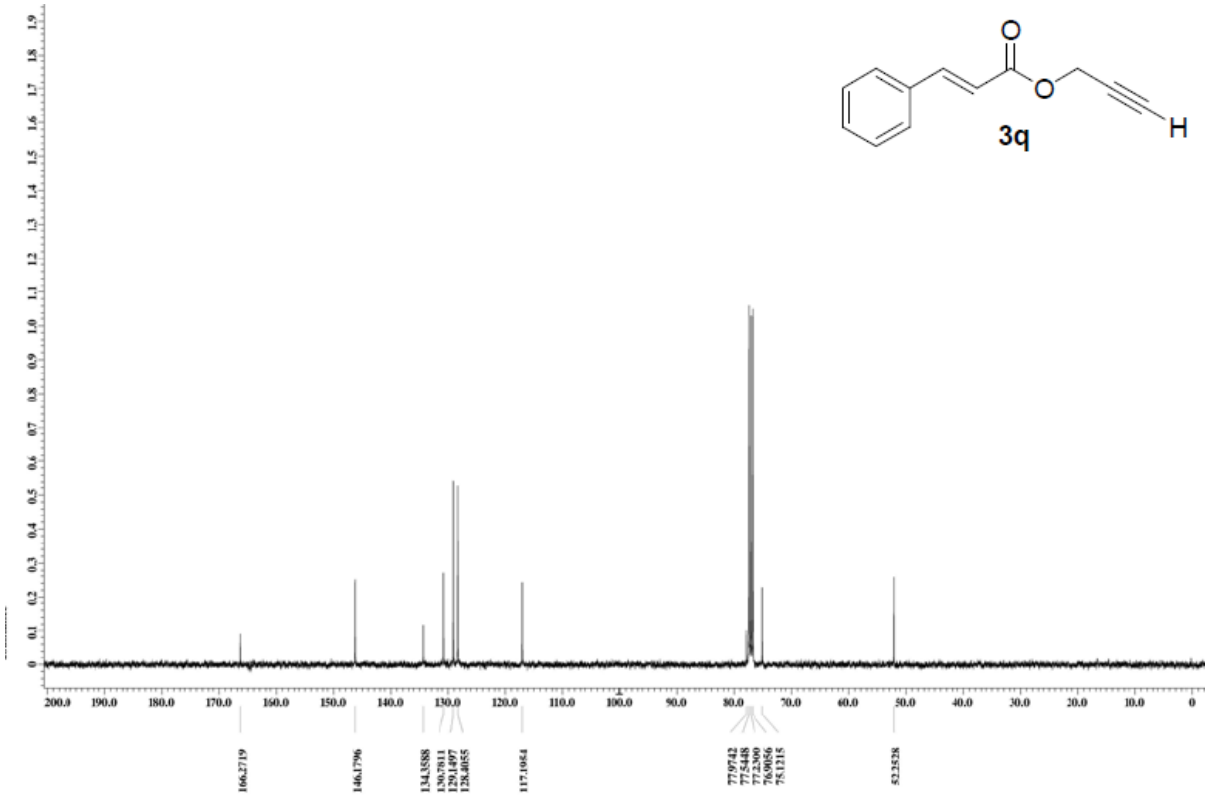
^{1}H and ^{13}C NMR spectra of compound 2.21p



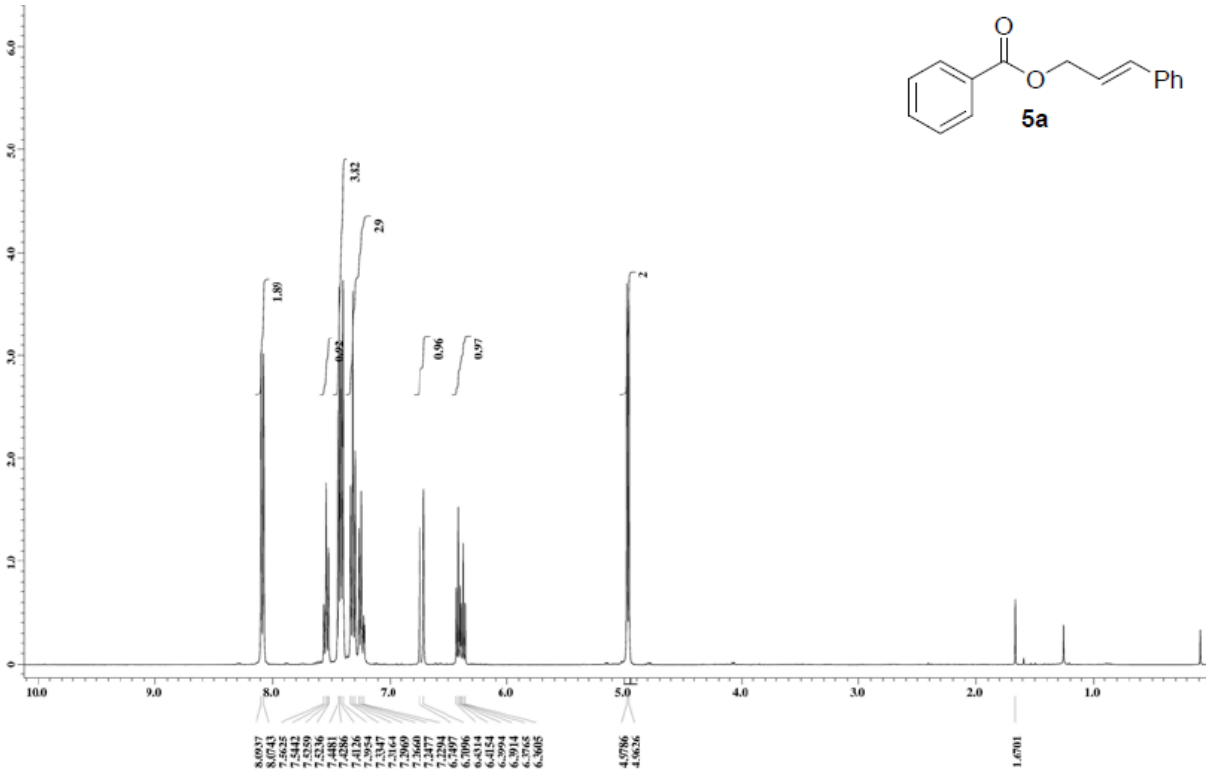


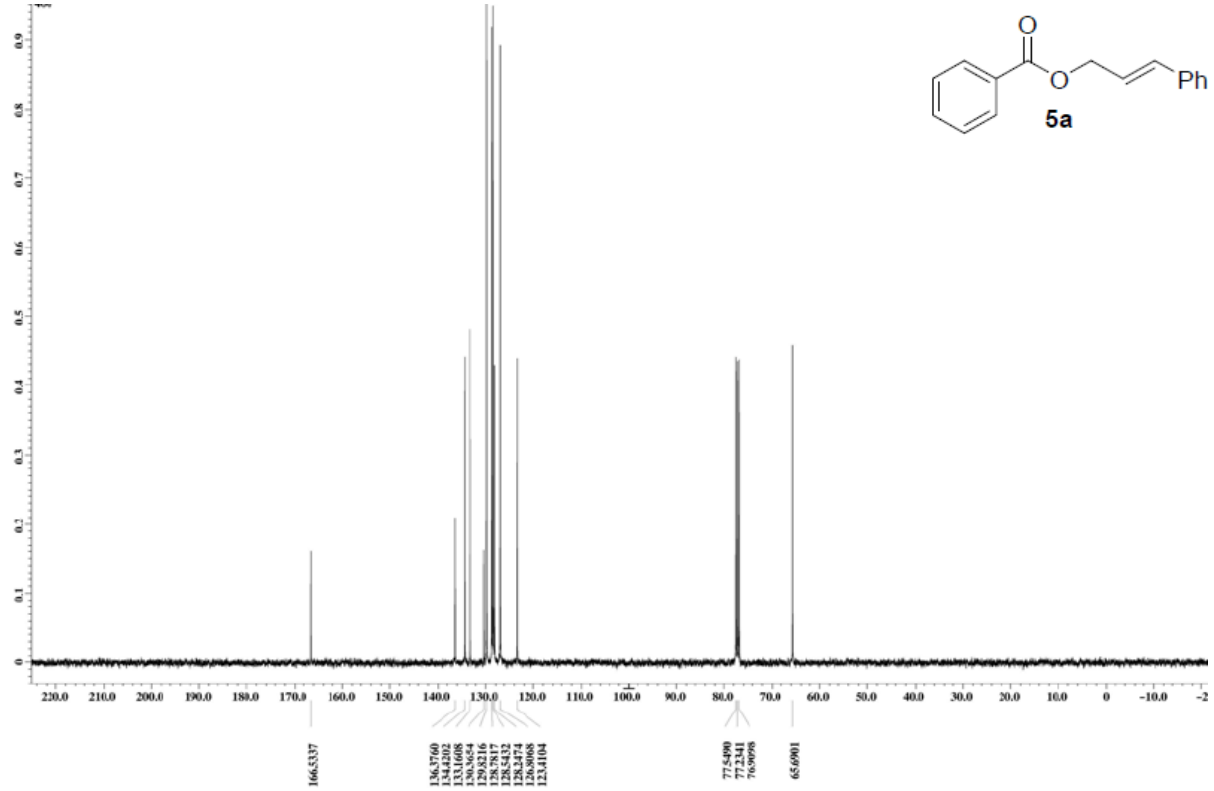
^{1}H and ^{13}C NMR spectra of compound 2.21q



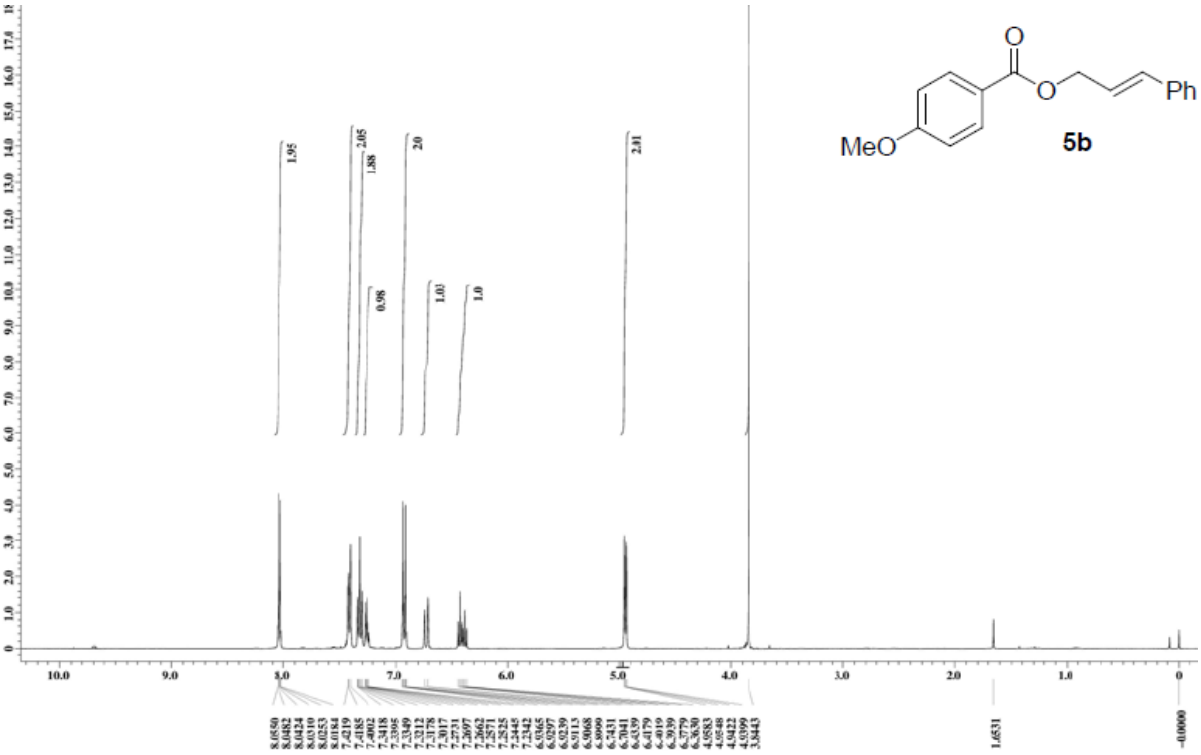


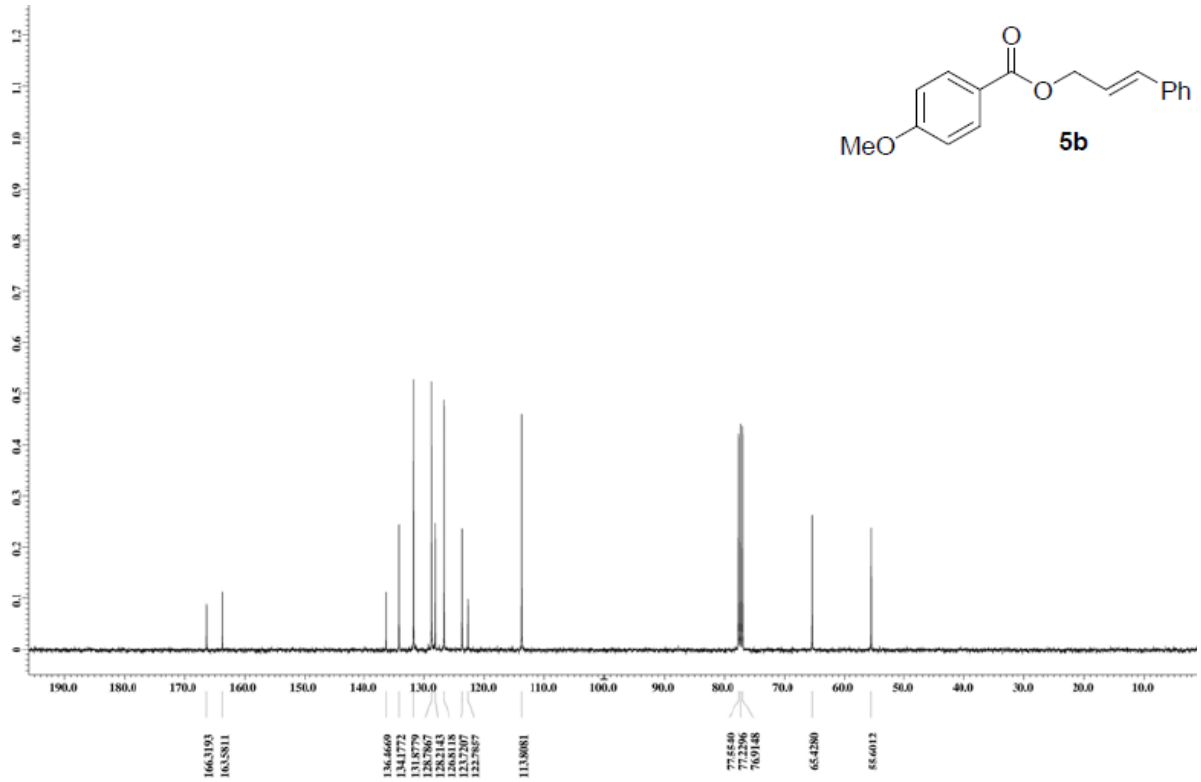
^{1}H and ^{13}C NMR spectra of compound 2.23a



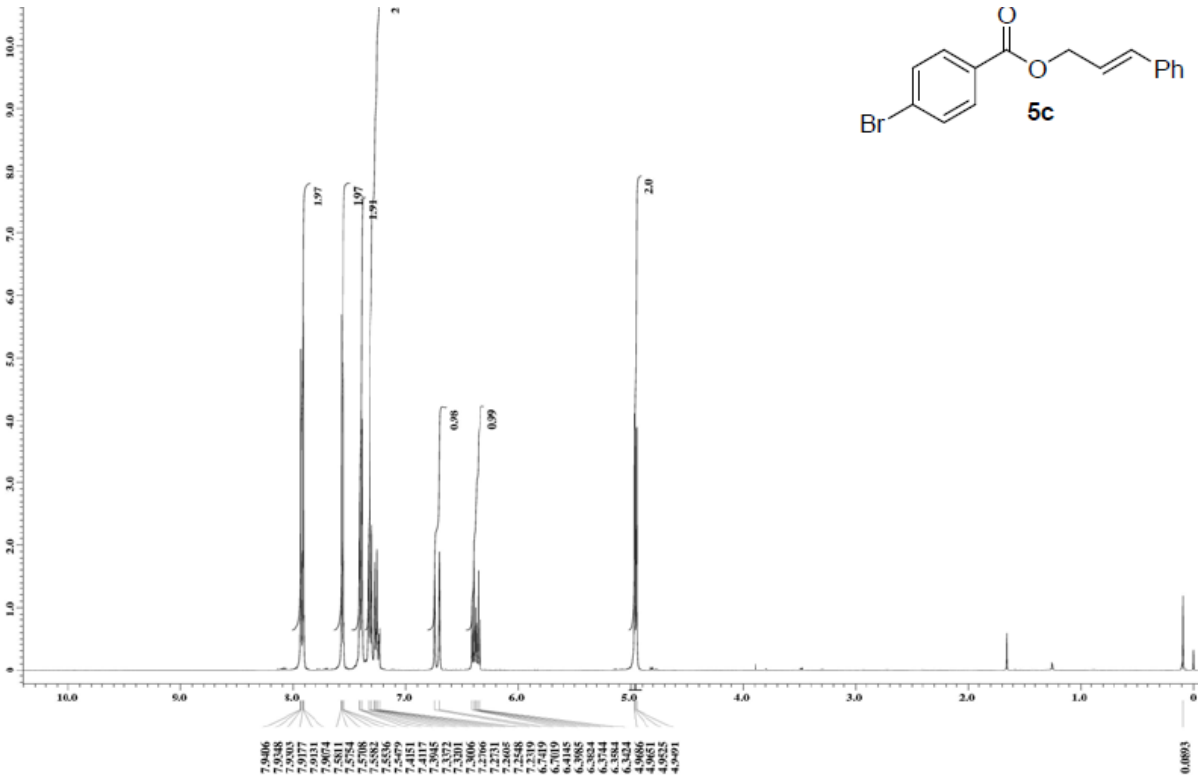


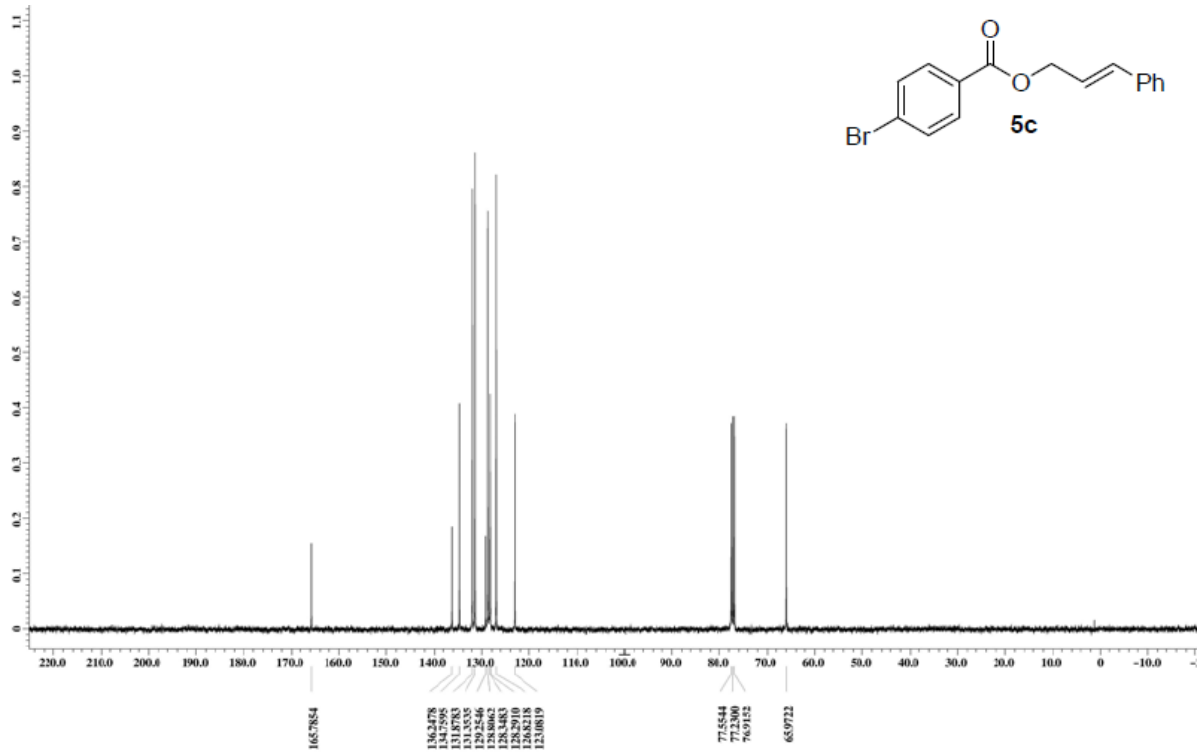
^{1}H and ^{13}C NMR spectra of compound 2.23b



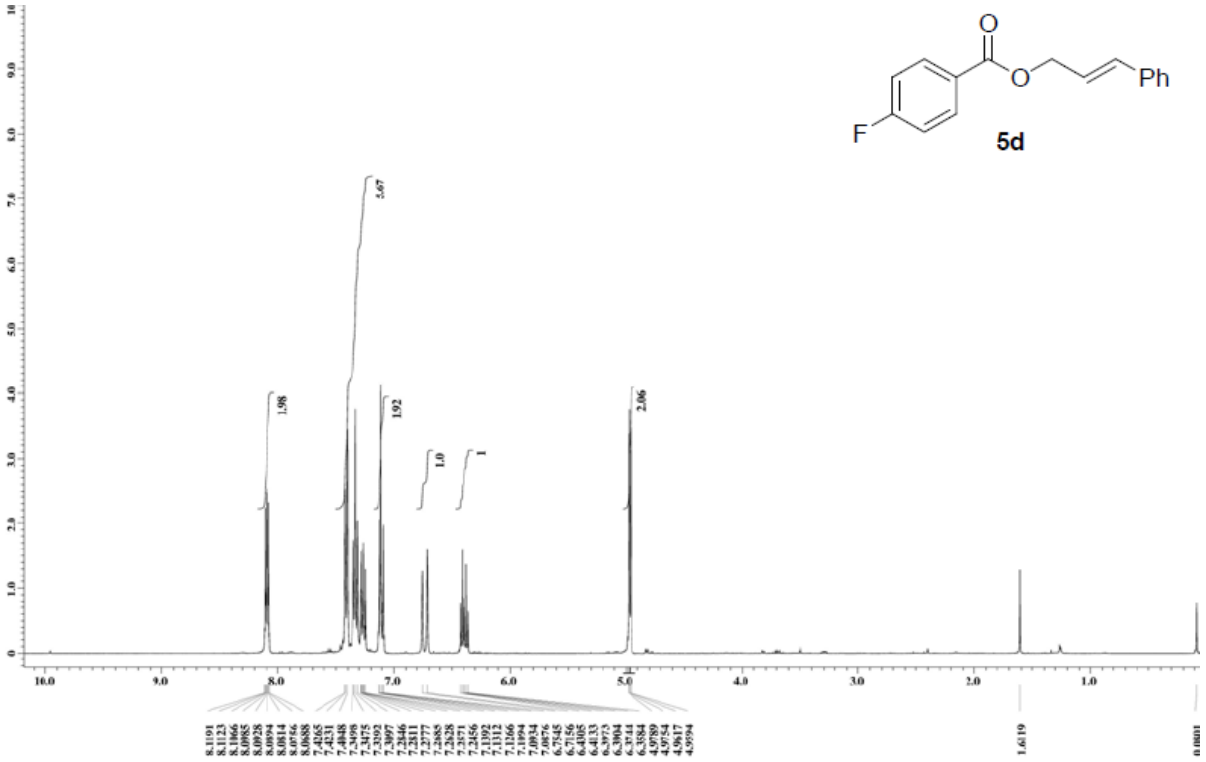


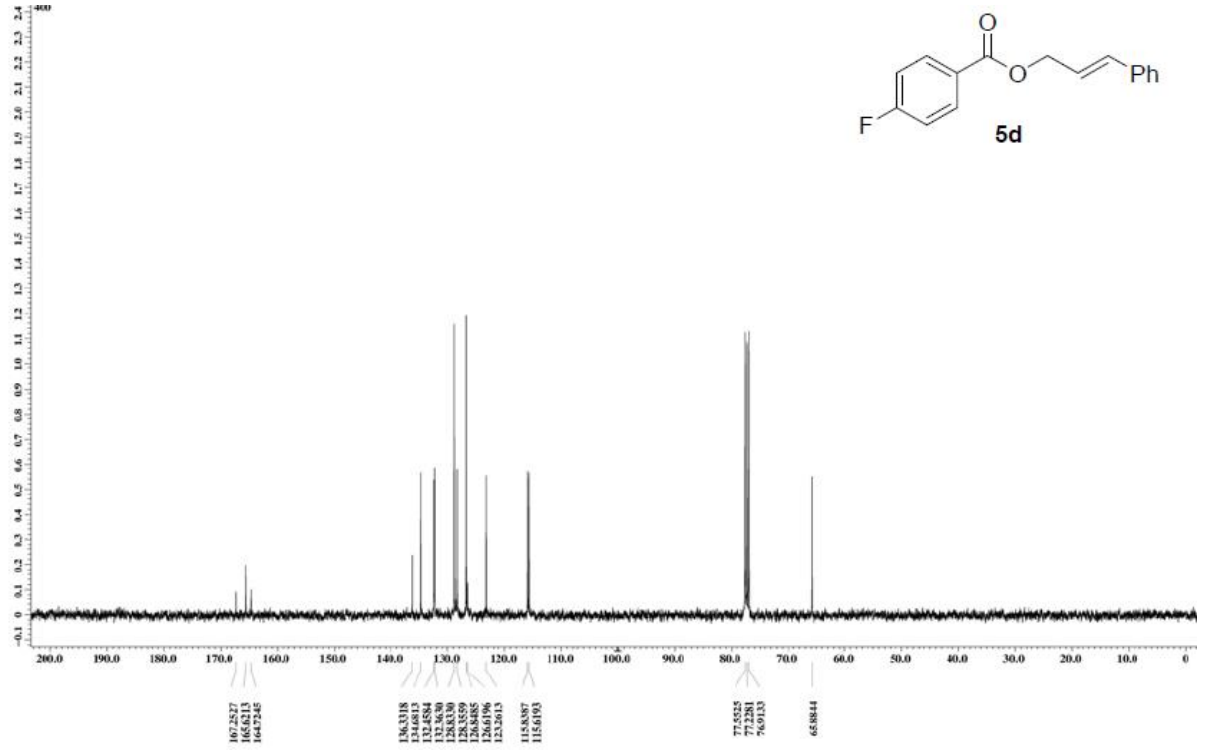
^{1}H and ^{13}C NMR spectra of compound 2.23c



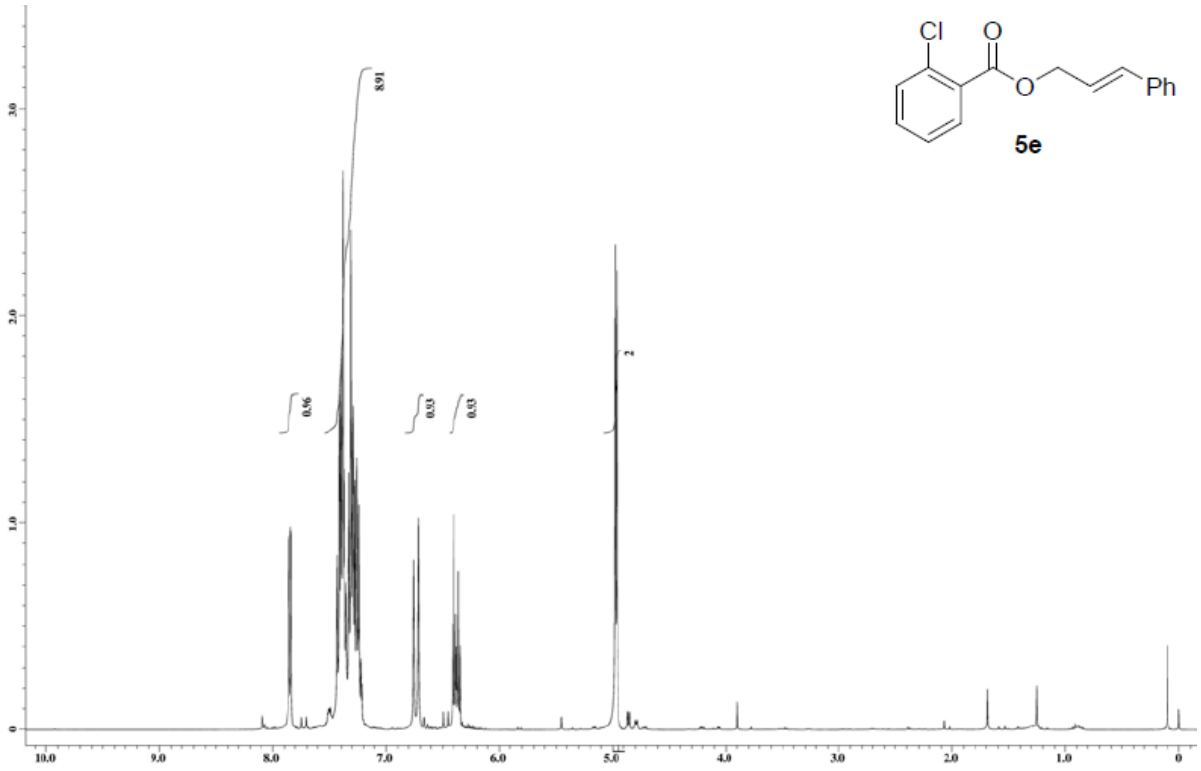


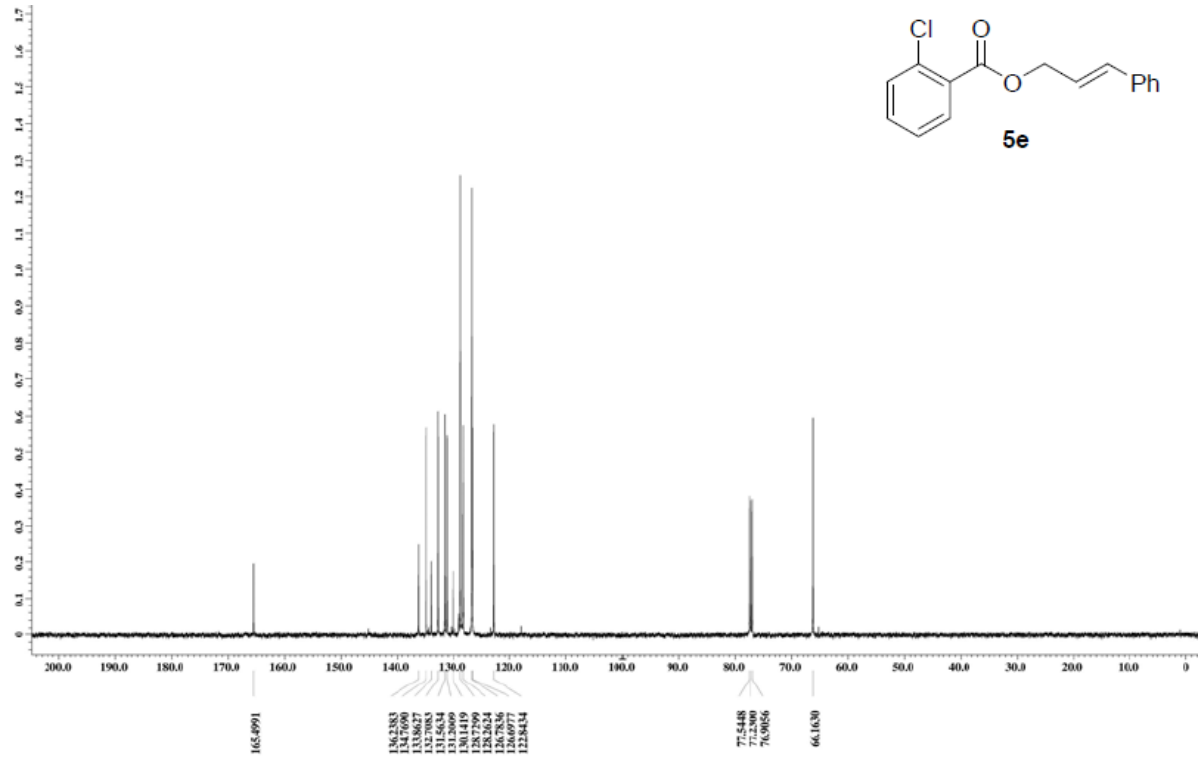
^{1}H and ^{13}C NMR spectra of compound 2.23d



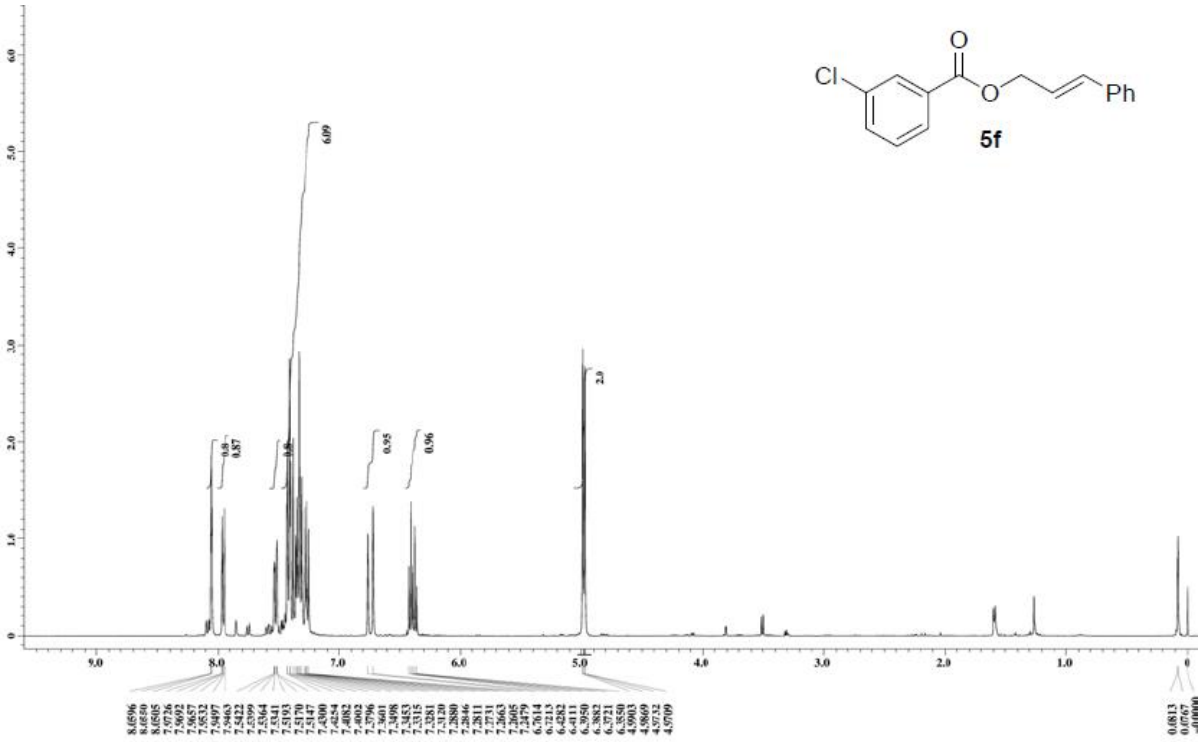


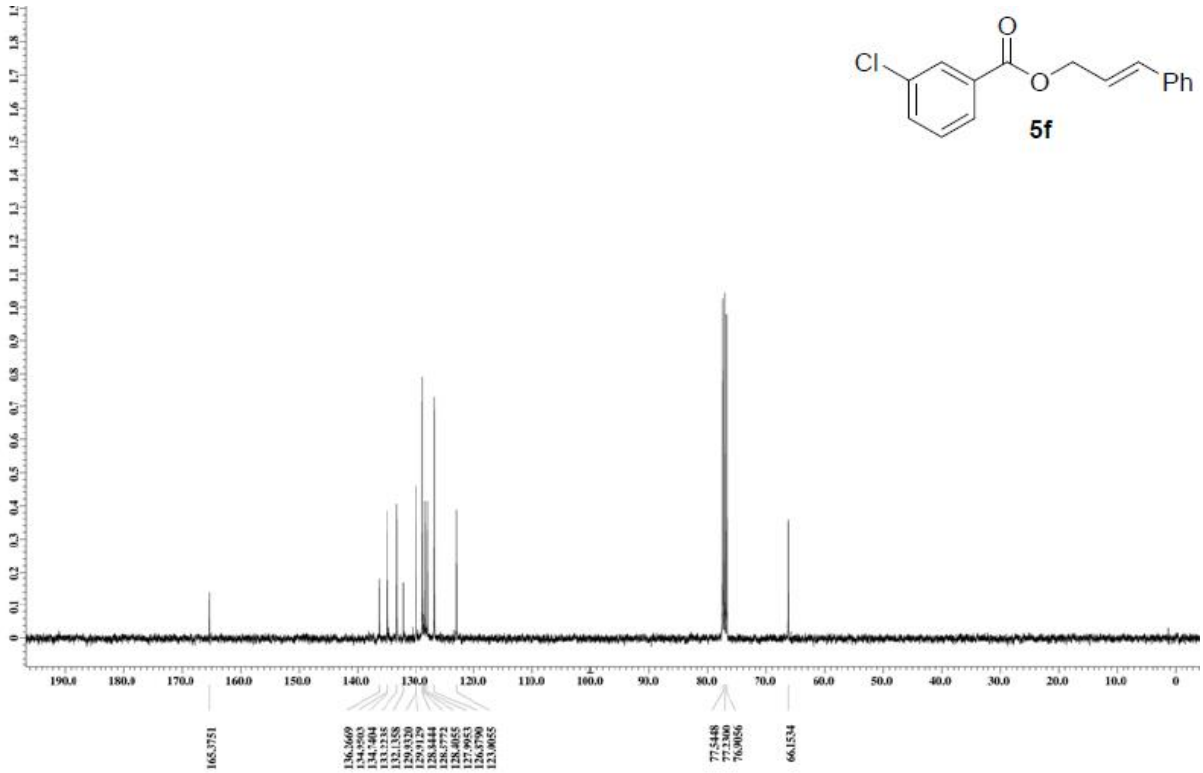
^{1}H and ^{13}C NMR spectra of compound 2.23e



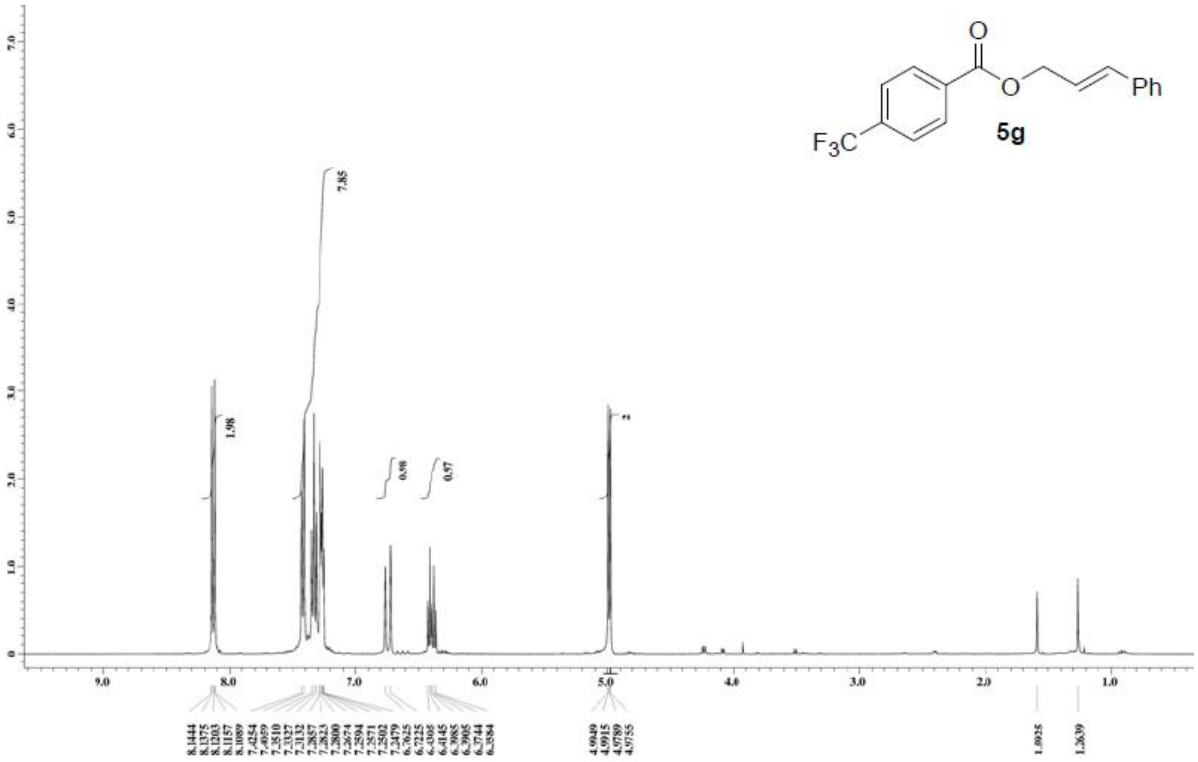


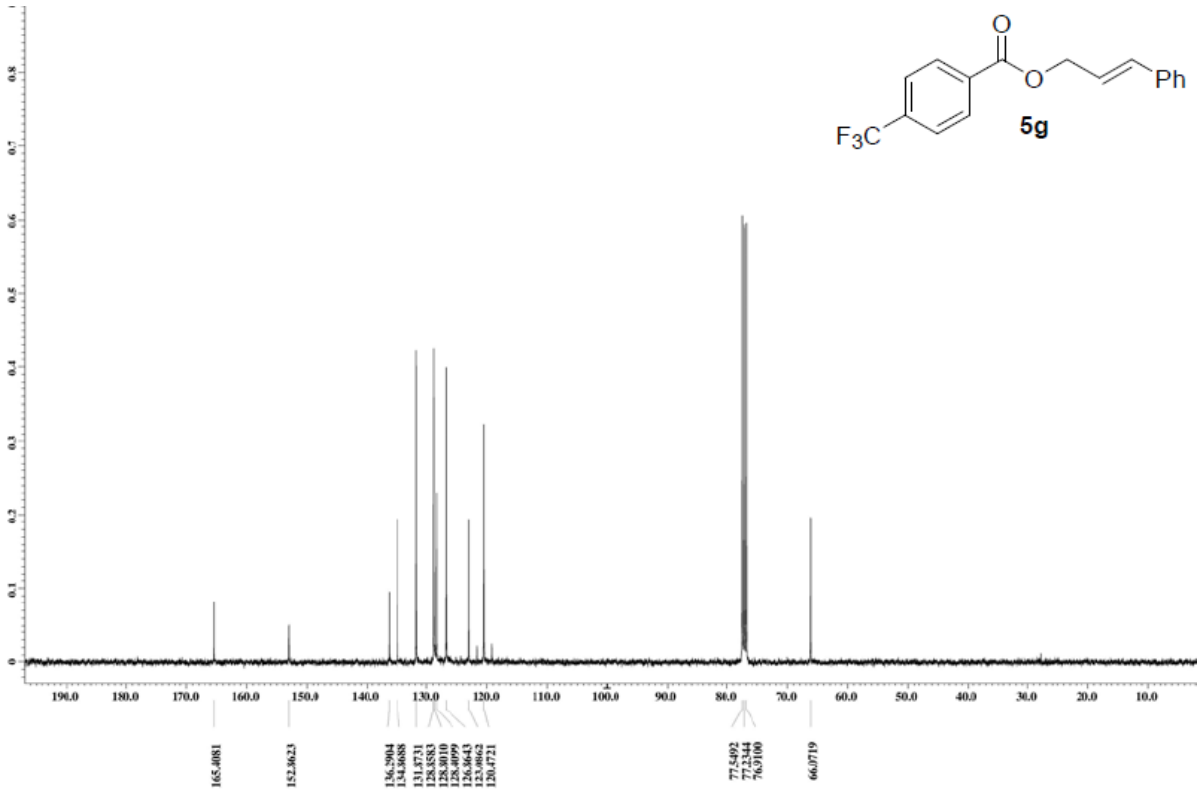
^{1}H and ^{13}C NMR spectra of compound 2.23f



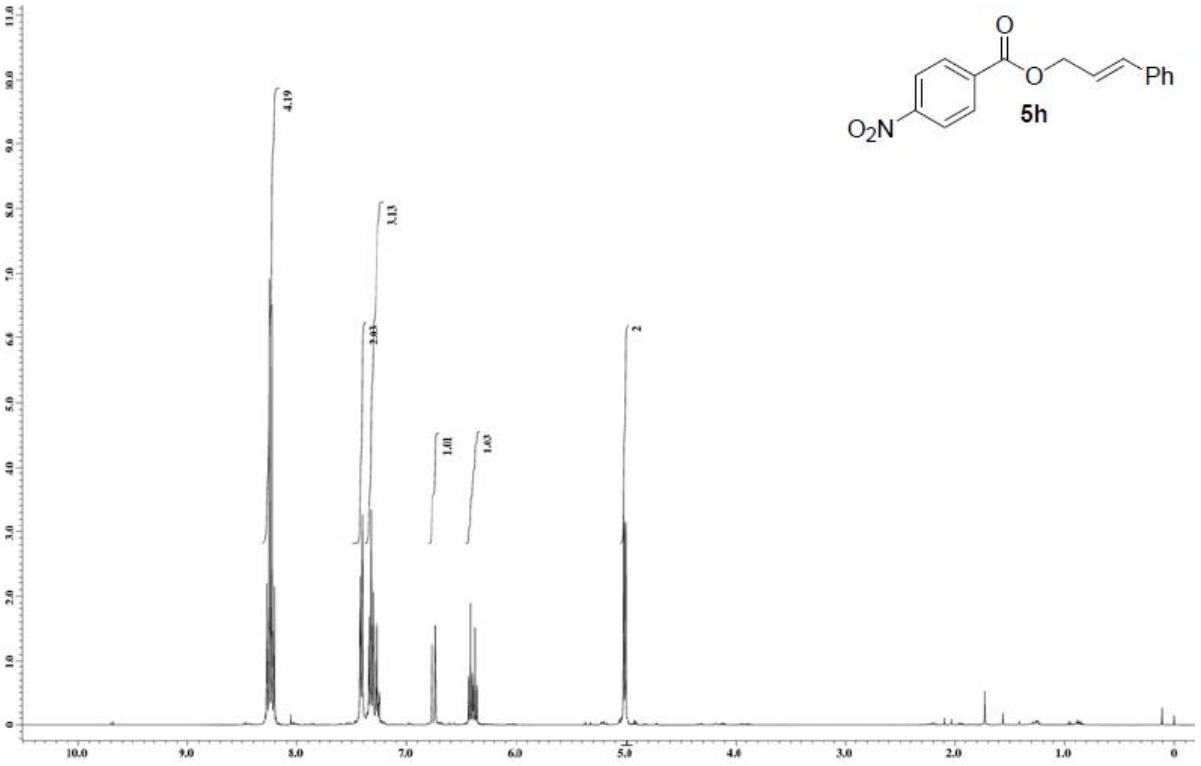


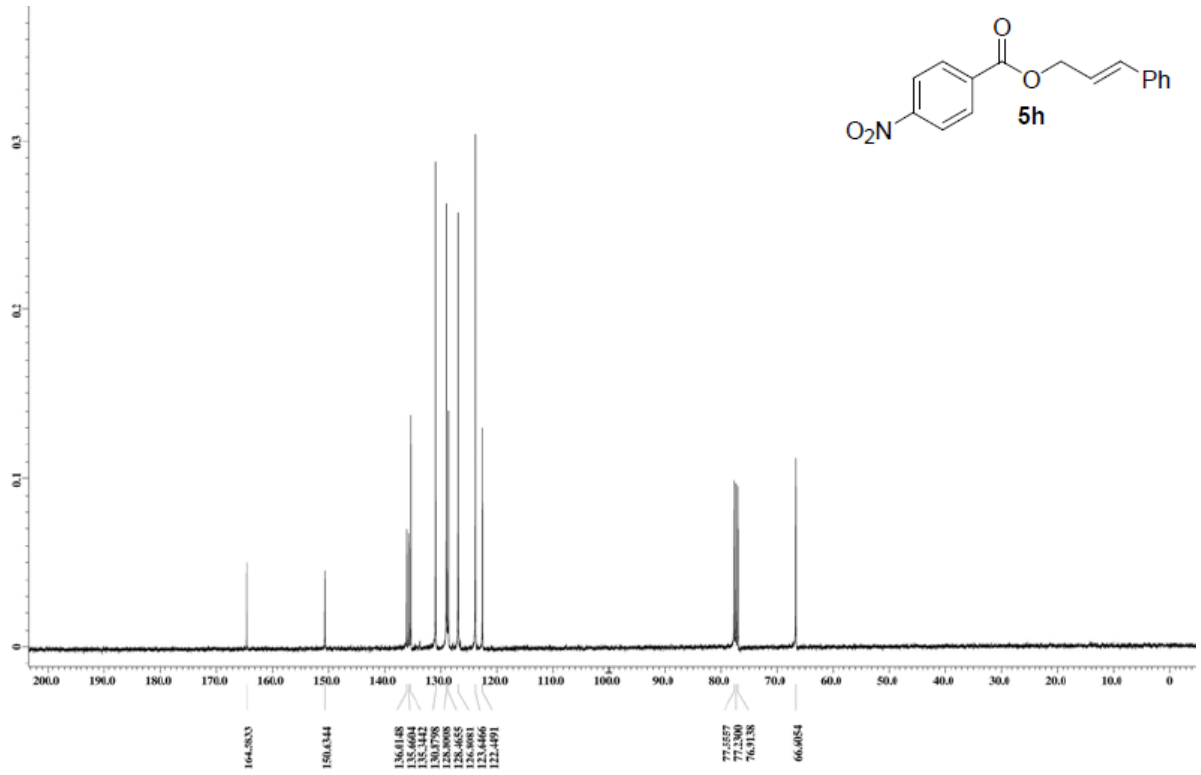
^{1}H and ^{13}C NMR spectra of compound 2.23g



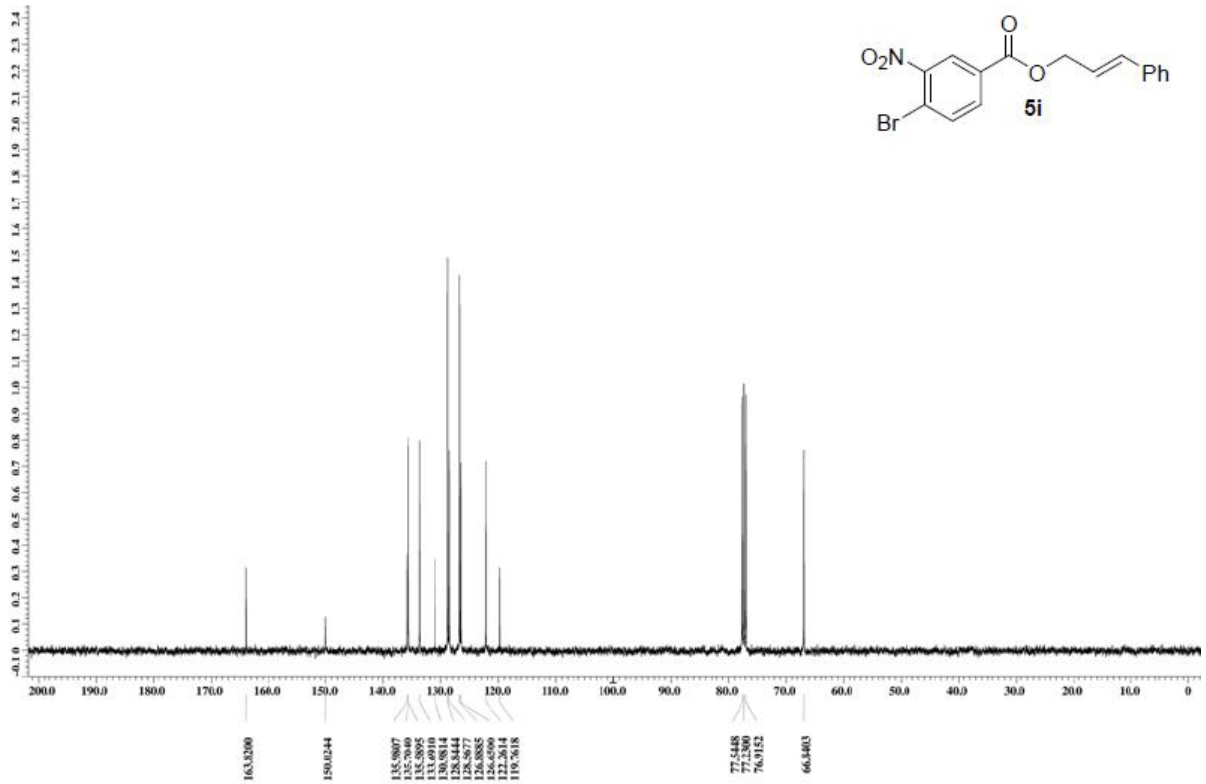


^{1}H and ^{13}C NMR spectra of compound 2.23h

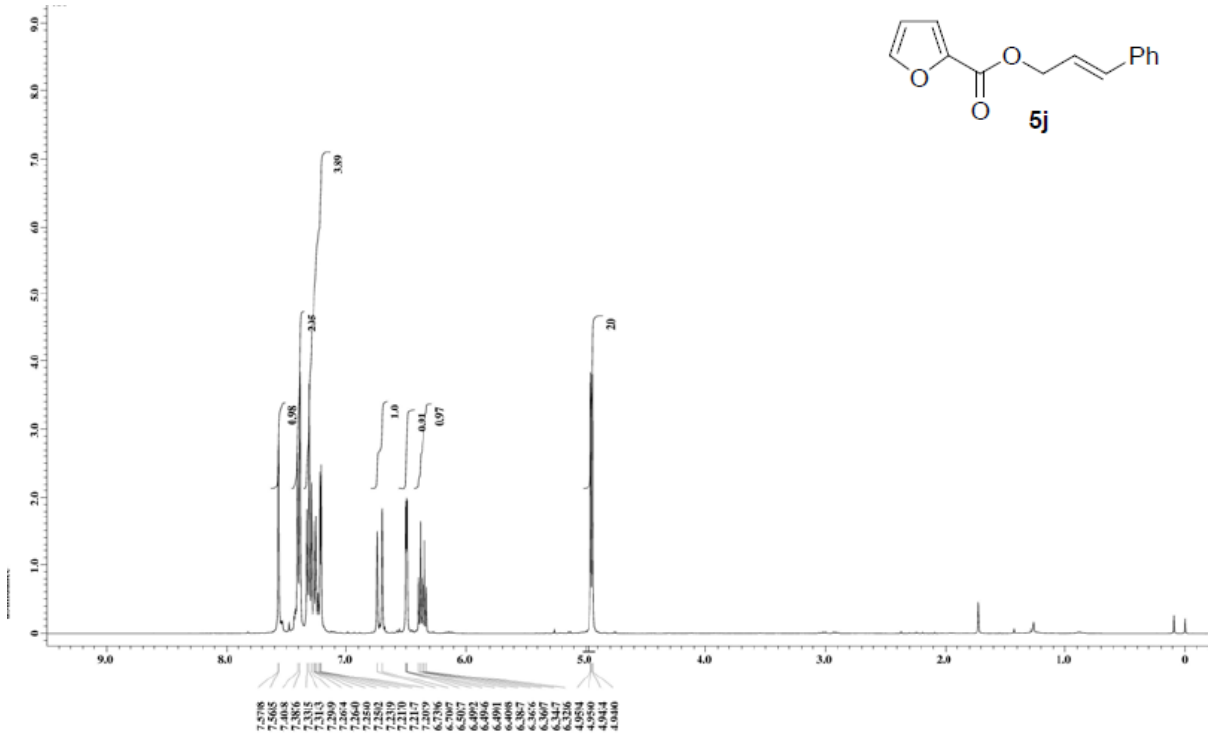


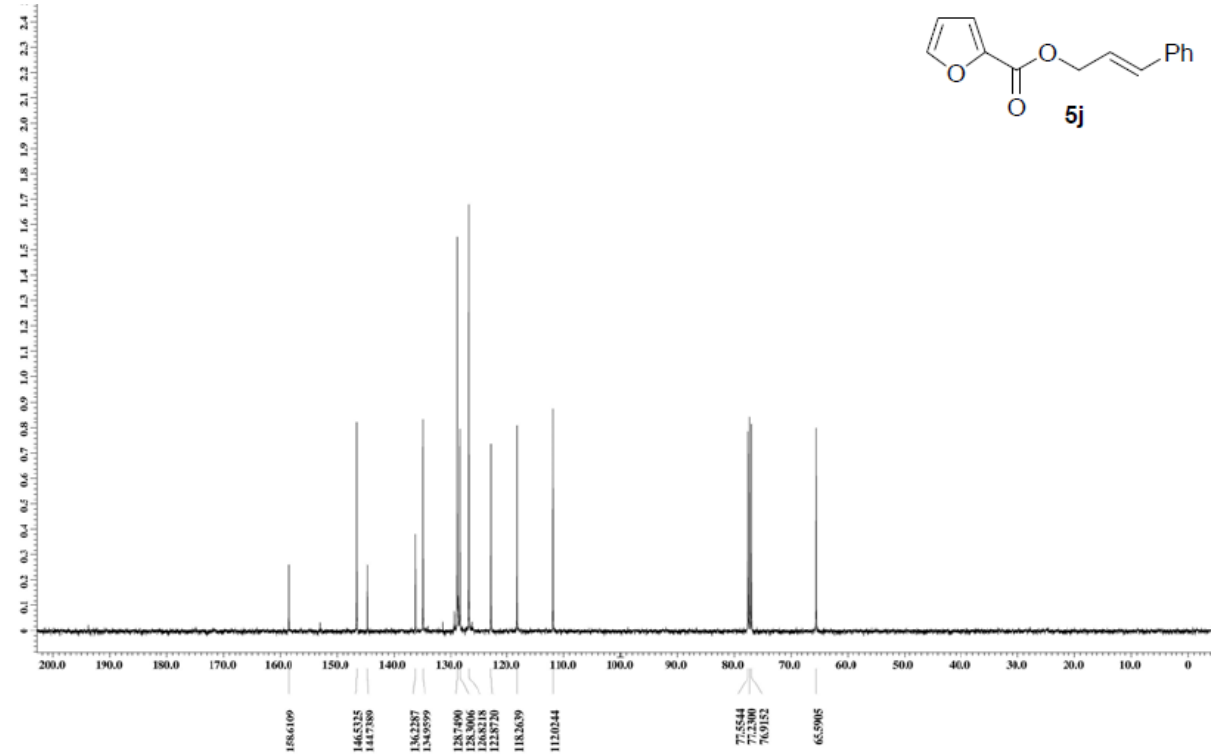


^{1}H and ^{13}C NMR spectra of compound 2.23i

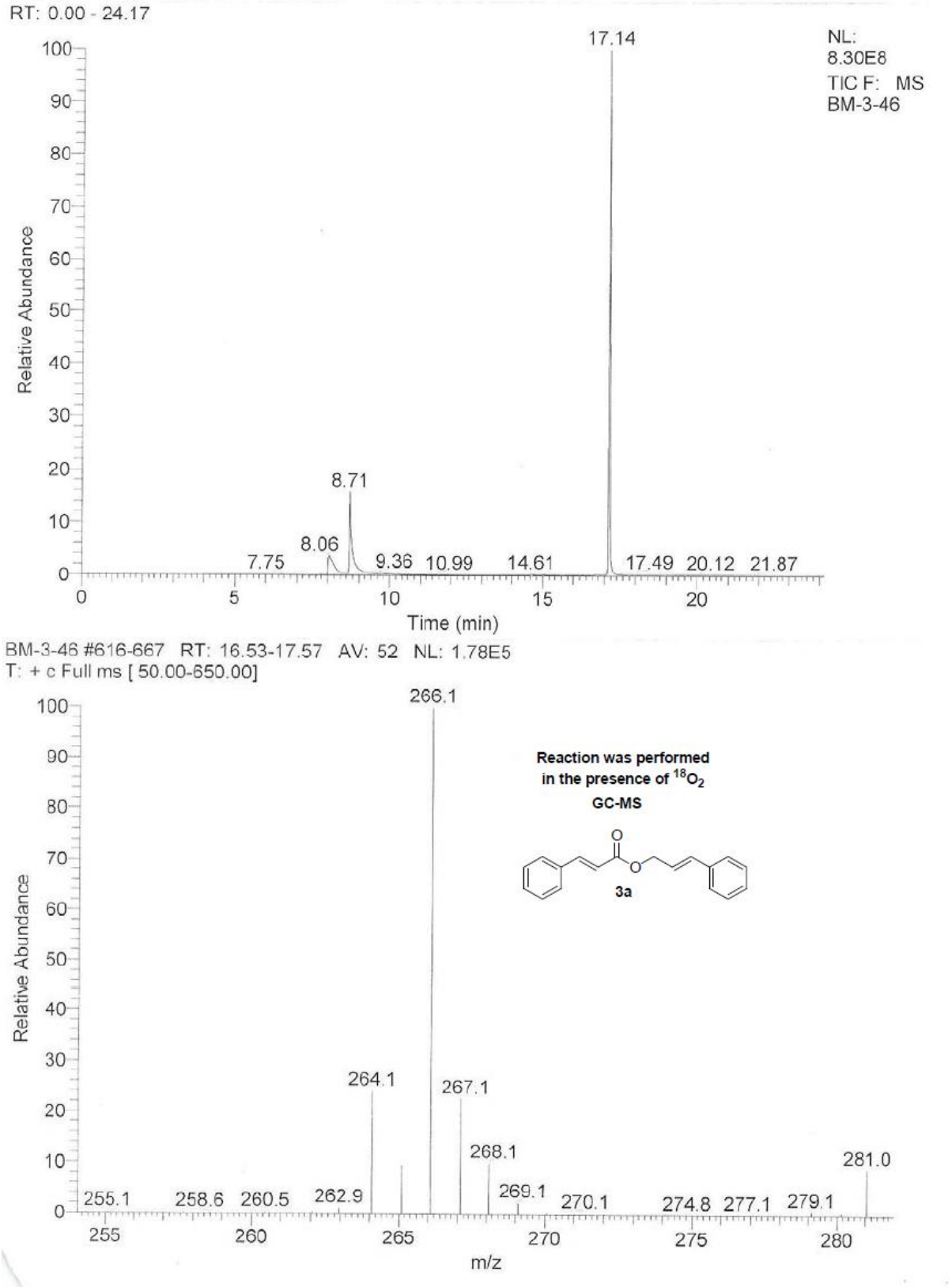


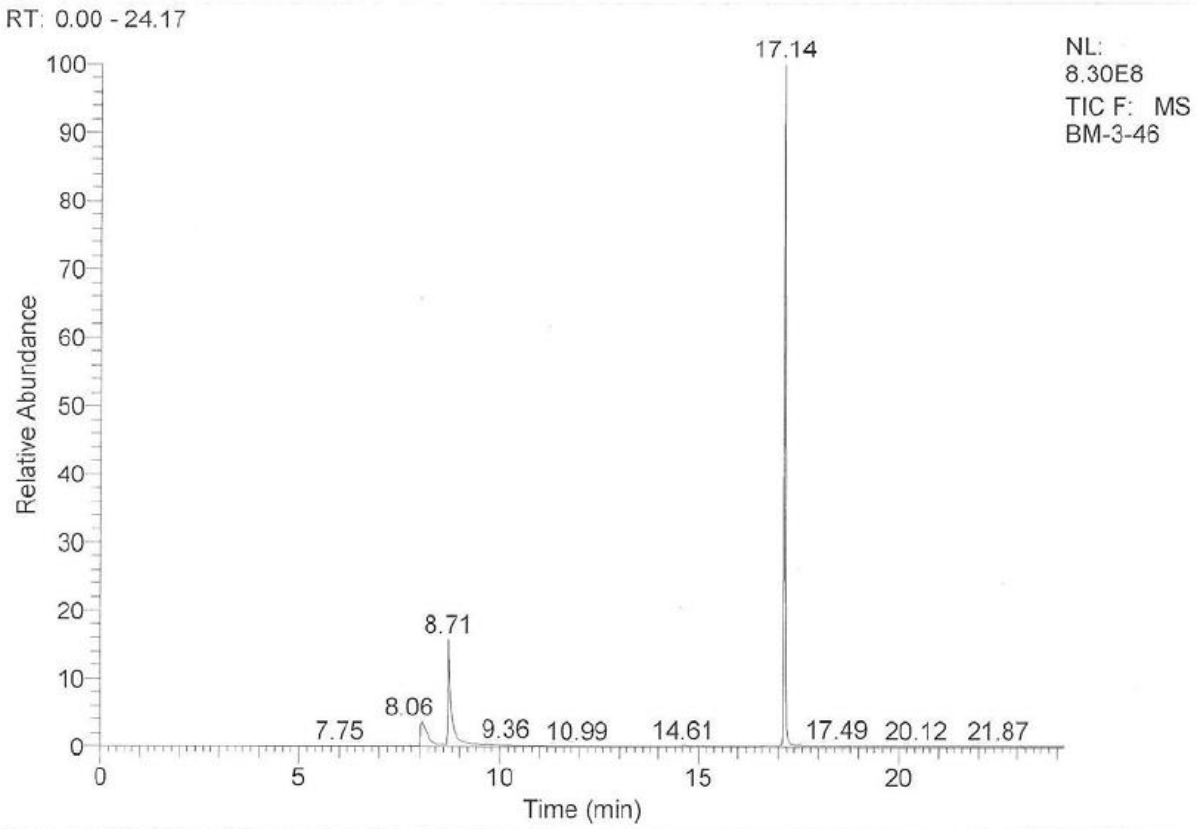
^{1}H and ^{13}C NMR spectra of compound 2.23j

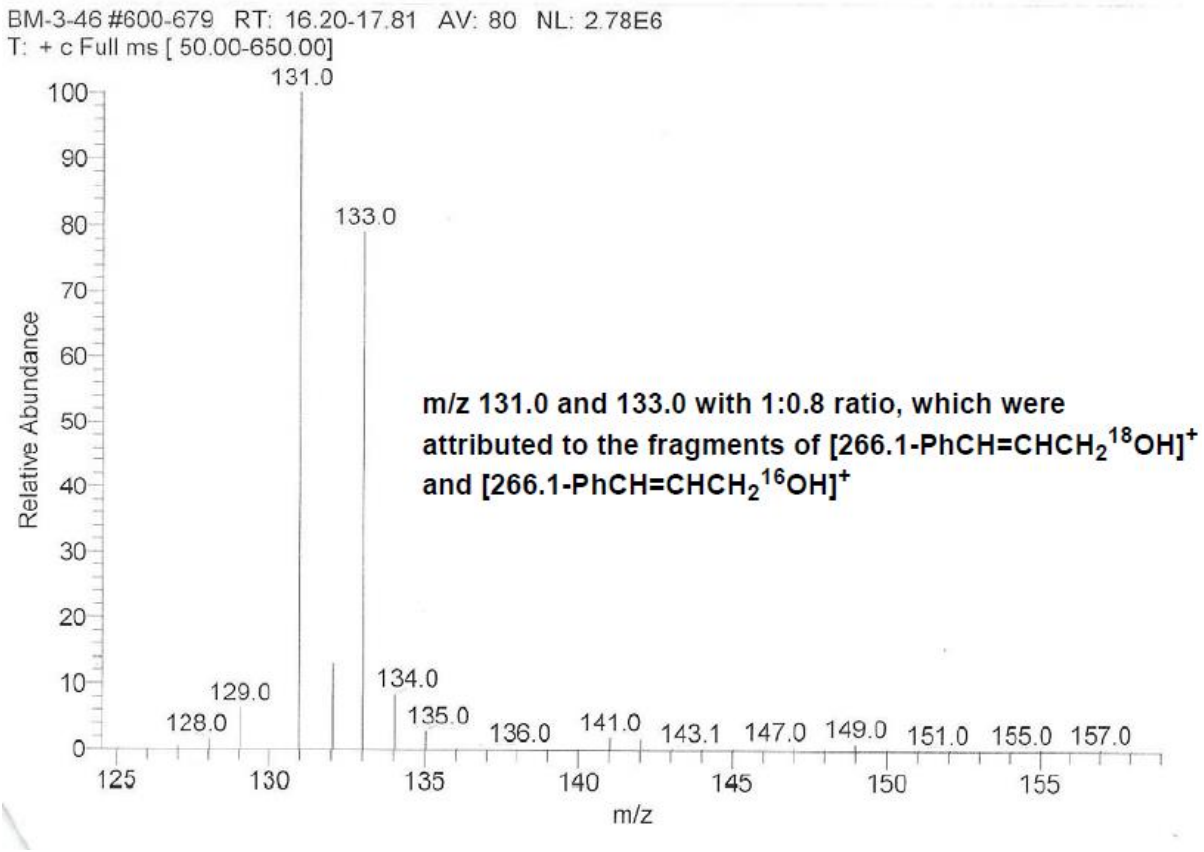




2. Isotope Labeling Experiment




RT: 0.00 - 24.17
NL:
8.30E8
TIC F: MS
BM-3-46
Relative Abundance
Time (min)
17.14
8.71
8.06
7.75
9.36
10.99
14.61
17.49
20.12
21.87


BM-3-46 #600-679 RT: 16.20-17.81 AV: 80 NL: 2.78E6
T: + c Full ms [50.00-650.00]
Relative Abundance
m/z
131.0
133.0
129.0
128.0
134.0
135.0
136.0
141.0
143.1
147.0
149.0
151.0
155.0
157.0
m/z 131.0 and 133.0 with 1:0.8 ratio, which were attributed to the fragments of [266.1-PhCH=CHCH2 18OH]+ and [266.1-PhCH=CHCH2 16OH]+

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(12) When MnO_2 was used as an oxidant, another important pathway is not overruled, where allylic alcohol was generated in situ from the allyl bromide and reacted with acyl benzimidazolium intermediate II (Scheme 15) to provide ester **2.23**.

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