Supporting Information

Aliphatic C–H Functionalization Using Pyridine *N*-Oxides as H-Atom Abstraction Agents

Marcel Schlegel, Siran Qian and David A. Nicewicz*

Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, 27599-3290, USA

E-mail: nicewicz@unc.edu

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General Information

General Reagent Information

Commercially available reagents were purchased from SigmaAldrich, Fischer Scientific, TCI Corporation, Atratech, Oakwood, Ambeed and were used without further purification. Pyridine *N*-oxide and 4-Nitropyridine *N*-oxide were purchased from TCI and used without further purification. They were stored in a desiccator. Anhydrous solvents were purchased through Sigma-Aldrich and used as is.

General Analytical Information

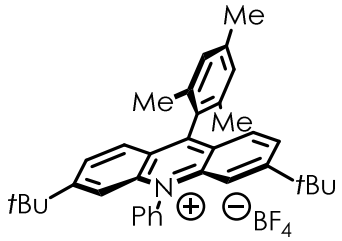
Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were obtained at 298 K using a Bruker Avance III 600 (^{1}H NMR at 600 MHz, ^{13}C NMR at 151 MHz), a Bruker Avance Neo Oxford 600 (^{1}H NMR at 600 MHz, ^{13}C NMR at 151 MHz), a Bruker Avance III 500 with Narrow-bore magnet (^{1}H NMR at 500 MHz, ^{13}C NMR at 126 MHz), a Bruker Avance Neo 400 (^{1}H NMR at 400 MHz, ^{13}C NMR at 101 MHz), and a Bruker Avance 400 with Narrow-bore magnet (^{1}H NMR at 400 MHz, ^{13}C NMR at 101 MHz) spectrometer unless otherwise noted. NMR spectra are referenced to Chloroform-d (^{1}H NMR: 7.26 ppm and ^{13}C NMR: 77.16 ppm) and reported as parts per million. ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublets of doublets, m = multiplet), coupling constants (Hz), and integration.

High Resolution Mass Spectra (HRMS) were obtained using a Thermo LTqFT mass spectrometer with electrospray ionization in positive or negative mode.

Flash chromatography was performed using SiliaFlash P60 silica gel (40-63 μm) that was purchased from Silicycle. Thin layer chromatography (TLC) was performed using SiliaPlate 250 μm silica gel plates provided by Silicycle. Visualization was accomplished with short wave UV light (254 nm), in an I_2 chamber or with a $KMnO_4$ or vanillin stain solution followed by heating.

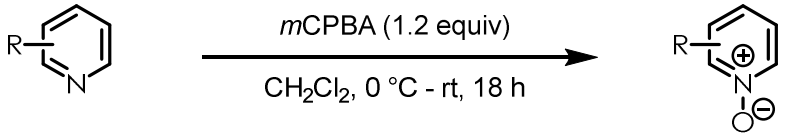
Catalyst Synthesis

Photoredox Catalyst



3,6-Di-*tert*-butyl-9-mesityl-10-phenylacridin-10-ium tetrafluoroborate was prepared according to literature precedent. Spectral data matched that reported in the literature.[1]

HAT Catalysts – General Procedure

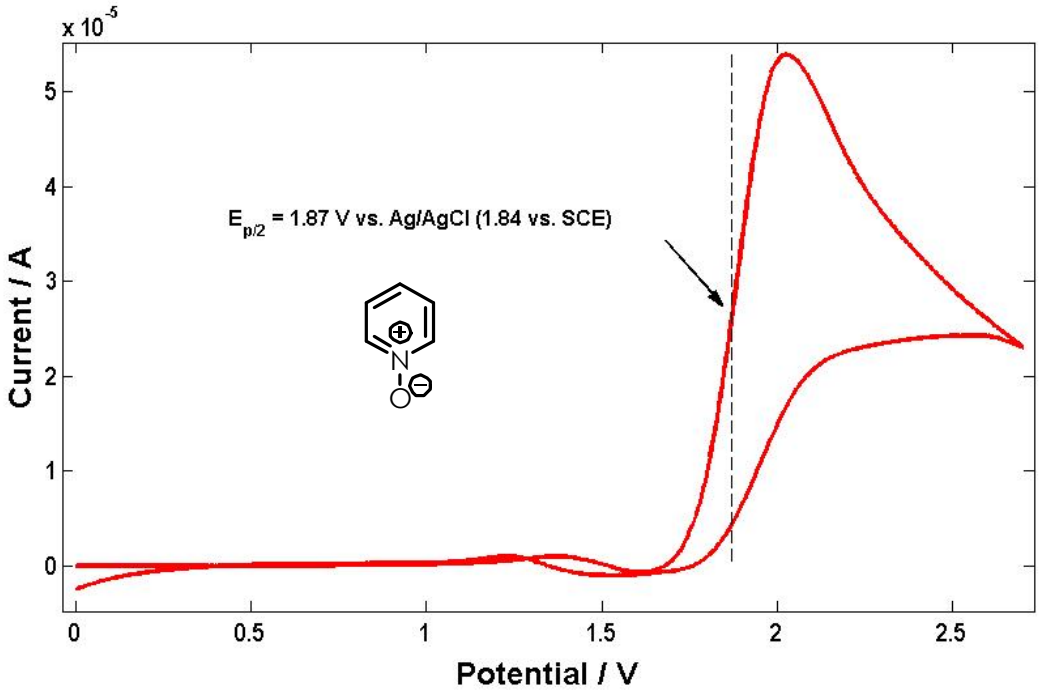


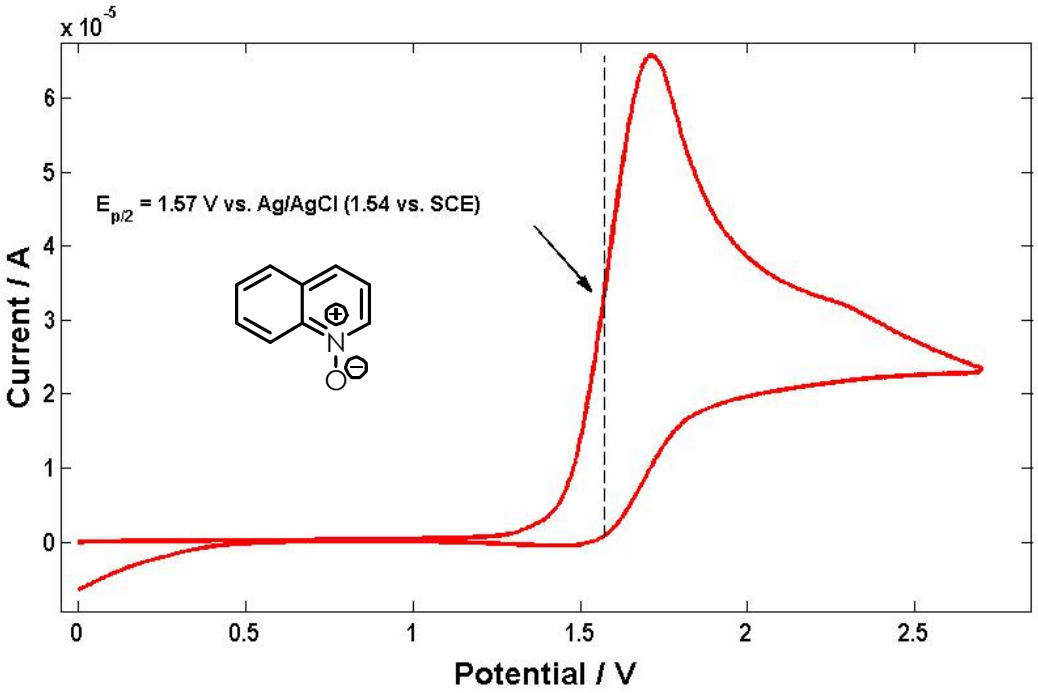
Following a modified version of literature known procedures,[2] *m*CPBA (1.2 equiv, 77% w/w) was added portionwise to a solution of the pyridine (1.0 equiv) in dry CH_2Cl_2 (0.17 M) at 0°C. The mixture was stirred at room temperature overnight, concentrated to ¼ of its volume and purified by flash-column chromatography (silica, EtOAc to 10% MeOH/EtOAc).

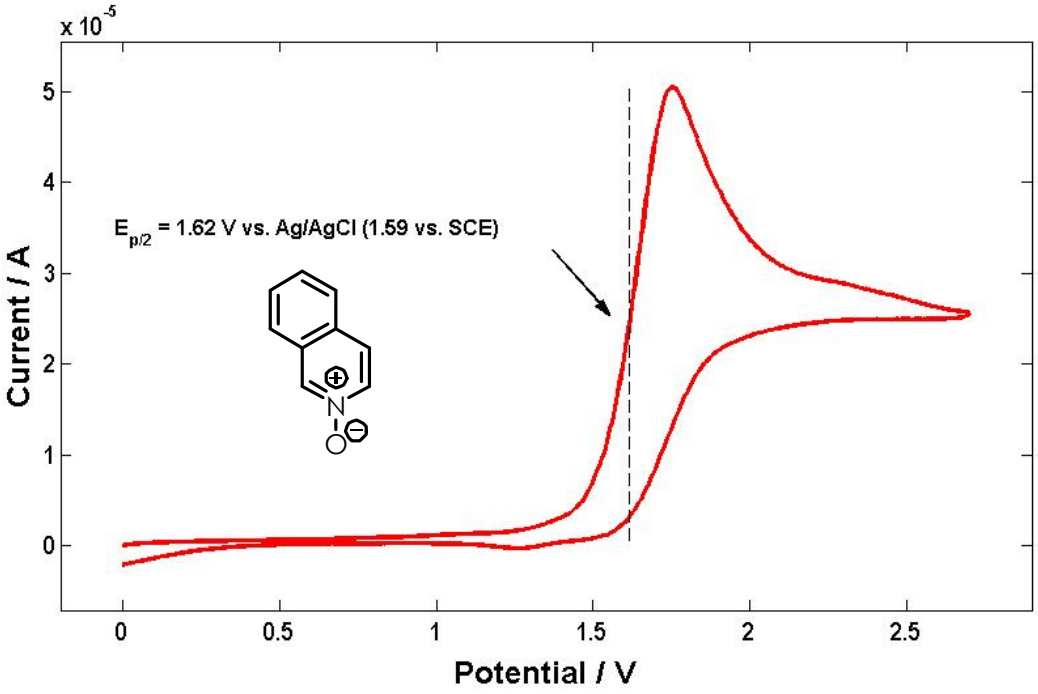
The spectroscopic data of quinoline *N*-oxide **B**,[2a] isoquinoline *N*-oxide **C**,[2a] 2,6-lutidine *N*-oxide **D**,[3] 2-acetylpyridine *N*-oxide **E**,[2b] 3-acetylpyridine *N*-oxide **F**[2a] and 4-acetylpyridine *N*-oxide **G**[2b] are in agreement with those reported in the literature.

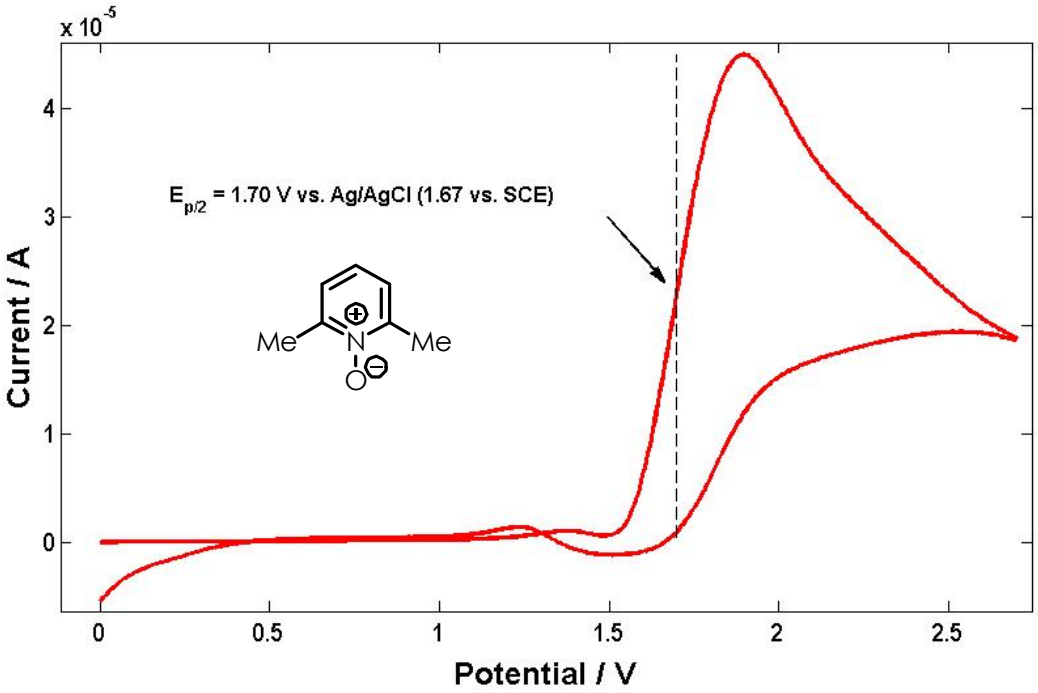
Cyclic Voltammetry

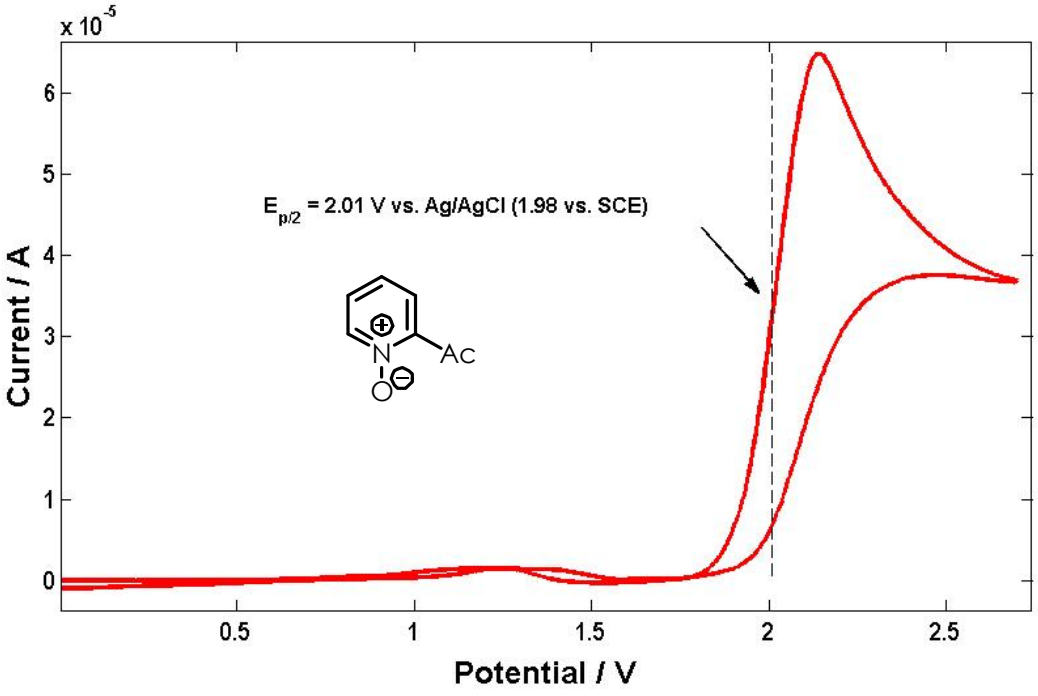
Electrochemical potentials were obtained with a standard set of conditions to main internal consistency. Cyclic voltammograms were collected with a Pine WaveNow Potentiostat. Samples were prepared with 0.05 mmol of substrate in 5 mL of 0.1 M tetra-*n*-butylammonium hexafluorophosphate in anhydrous, degassed acetonitrile. Measurements employed a glassy carbon working electrode, platinum wire counter electrode, 3 M NaCl silver-silver chloride reference electrode, and a scan rate of 100 mV/s. Oxidations were measured by scanning potentials in the positive direction with a starting point of 0 V and a vertex potential of +2.7 V. Data was analyzed using MATLAB by subtracting a background current prior to identifying the maximum current (Cp) and determining the potential (Ep/2) at half this value (Cp/2). The obtained value was referenced to Ag|AgCl and converted to SCE by subtracting 0.03V.

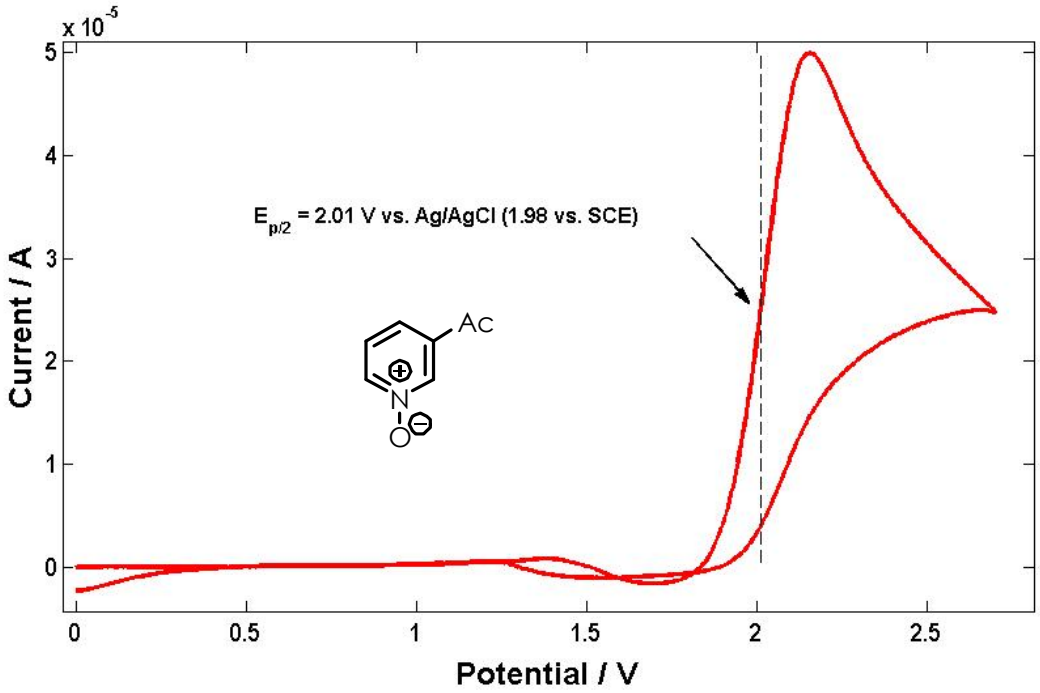


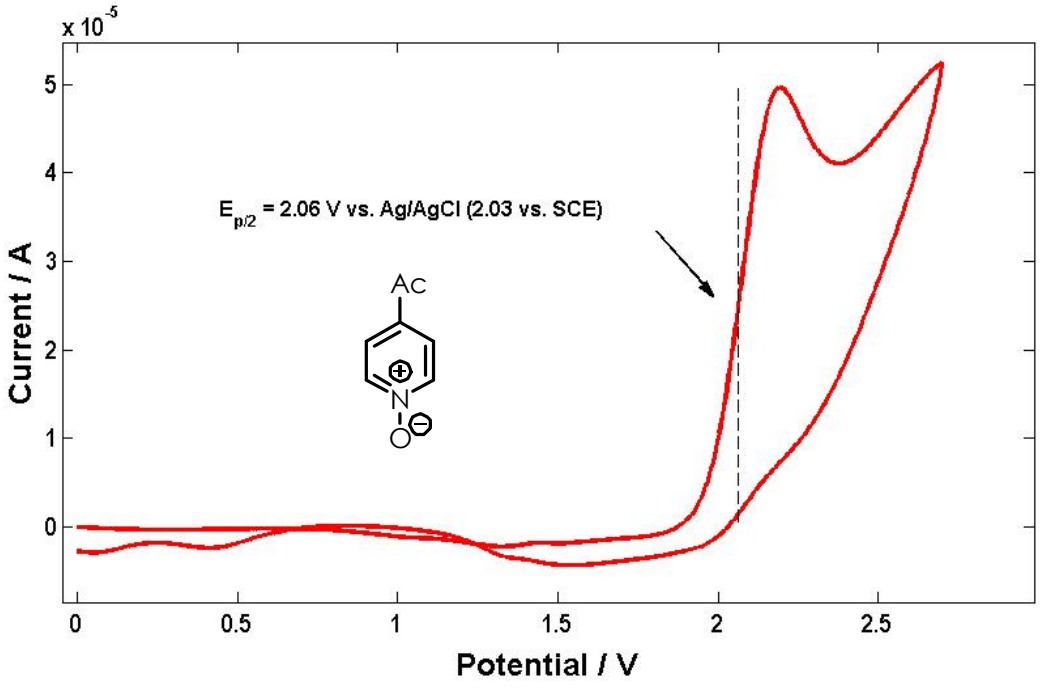

x 10^-5
Current / A
Potential / V
E_p/2 = 1.57 V vs. Ag/AgCl (1.54 vs. SCE)

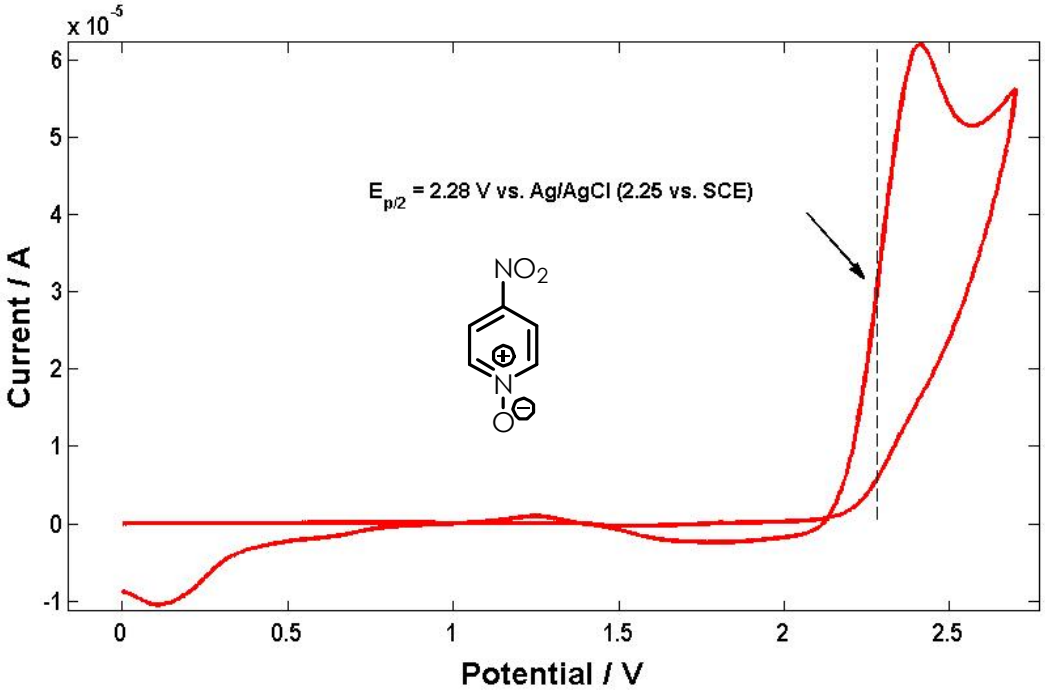

x 10^-5
Current / A
Potential / V
E_p/2 = 1.62 V vs. Ag/AgCl (1.59 vs. SCE)


x 10^-5
Current / A
Potential / V
E_p/2 = 1.70 V vs. Ag/AgCl (1.67 vs. SCE)
Me
Me
N
O


x 10^-5
Current / A
Potential / V
E_p/2 = 2.01 V vs. Ag/AgCl (1.98 vs. SCE)
Ac
N
O


x 10^-5
Current / A
Potential / V
E_p/2 = 2.01 V vs. Ag/AgCl (1.98 vs. SCE)
Ac
N
O


x 10^-5
Current / A
Potential / V
E_p/2 = 2.06 V vs. Ag/AgCl (2.03 vs. SCE)
Ac
N
O


x 10^-5
6
5
4
3
2
1
0
-1
Current / A
0
0.5
1
1.5
2
2.5
Potential / V
E_p/2 = 2.28 V vs. Ag/AgCl (2.25 vs. SCE)
NO2
N
O

Chemical Computations

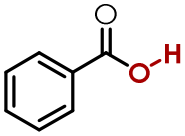
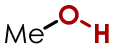
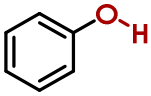
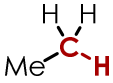
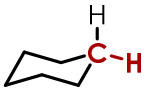
All geometry optimizations and frequency calculations were performed using the ORCA 5.0.3 program package. The reported data were calculated for the standard state of 298 K and 1 atm in the gas phase. All optimizations were checked for convergence to an energy minimum, which included checking for proper termination flags from ORCA and ensuring the resulting structure had no imaginary vibrational frequencies.
The bond dissociation energy (BDE) of the molecule M–H was calculated according to:

$$\mathrm{BDE(M–H)} = [H_{298}(\mathrm{M}\bullet) + H_{298}(\mathrm{H}\bullet)] - H_{298}(\mathrm{M–H})$$

where H_{298} is total enthalpy as sum of the total free energy and the thermal enthalpy correction for each molecule/radical provided by ORCA.

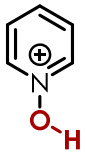
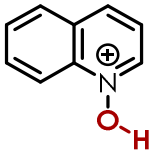
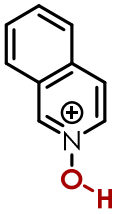
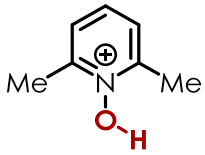
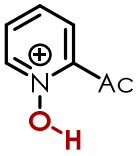
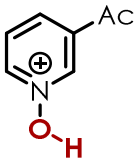
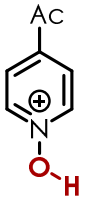
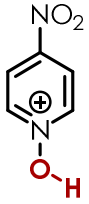
Previous reports provided good accuracy for BDE calculations of M–H bonds using the M06-2X functional.[4] Initially, we employed this functional along with two different basis sets to calculate the BDEs of different M–H substrates and compared those to experimental and literature values (Table S1).

Table S1. Calculated homolytic bond dissociation energies (BDEs) in kcal/mol of different X–H bonds using M06-2X with two different basis sets.

X–H bond	M06-2X/6-311+G(d,p)	M06-2X/def2-TZVP	Reference
	113.4	113.2	110.9 ± 4.0 (ref.[5]) 111 ± 4 (ref.[6])
	102.3	102.3	105.1 ± 0.7 (ref.[5]) 104.6 ± 0.7 (ref.[6]) 104.3 (ref.[7])
	88.4	88.9	86.6 ± 0.7 (ref.[5]) 90 ± 3 (ref.[6]) 87.9 (ref.[7])
	99.7	99.8	100.4 ± 0.3 (ref.[5]) 101.1 ± 0.4 (ref.[6]) 97.9 (ref.[7])
	95.3	95.3	99.4 (ref.[5]) 95.4 (ref.[7])

Both basis sets provided good approximations to literature values. The M06-2X/def2-TZVP method was employed for the calculation of BDEs for all pyridine *N*-oxide derivatives (Table S2).

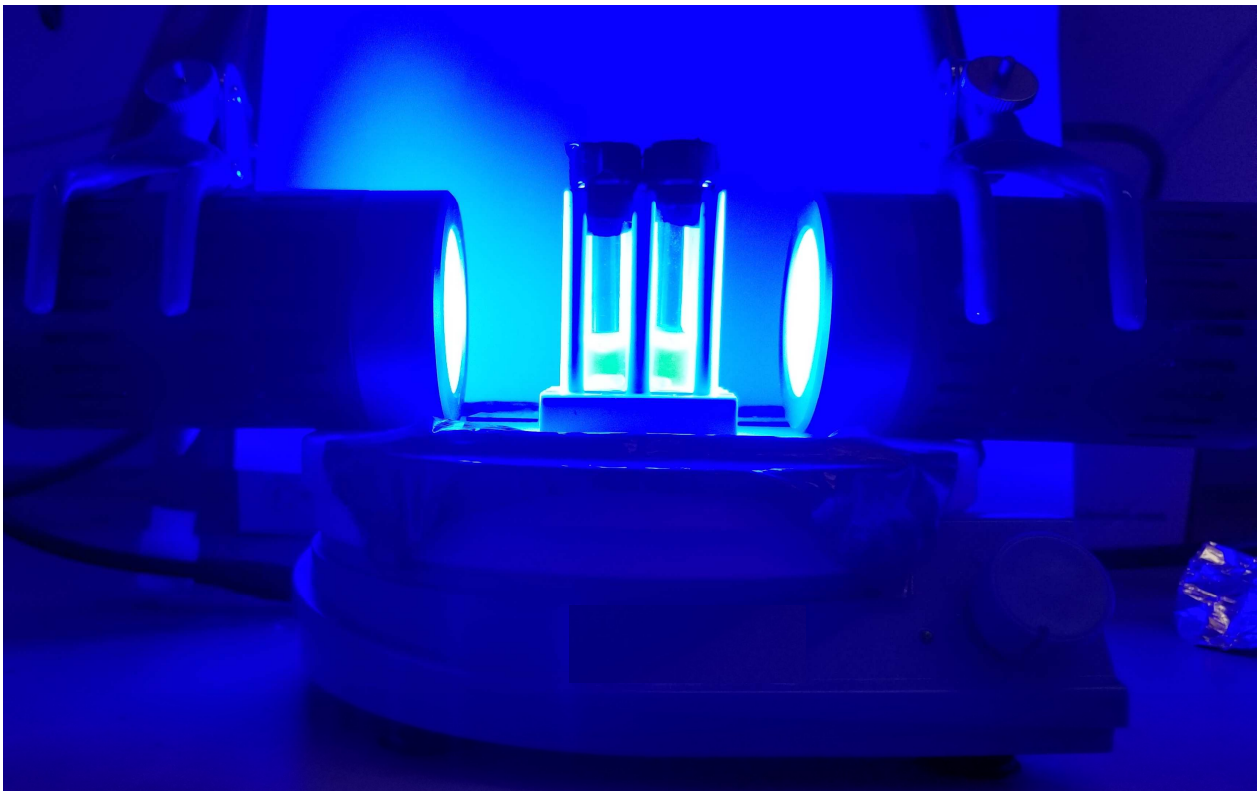
Table S2. Calculated homolytic bond dissociation energies (BDEs) of O–H bonds of different pyridine *N*-oxides in kcal/mol.

HAT catalyst:				
	A	**B**	**C**	**D**
M06-2X/ def2-TZVP	**99.4**	**92.7**	**94.7**	**95.8**[a]
HAT catalyst:				
	E	**F**	**G**	**H**
M06-2X/ def2-TZVP	**108.8**	**100.2**	**99.1**	**101.4**

[a]Calculated using M06-2X/6-311+G(d,p).

Photoreactor Configuration

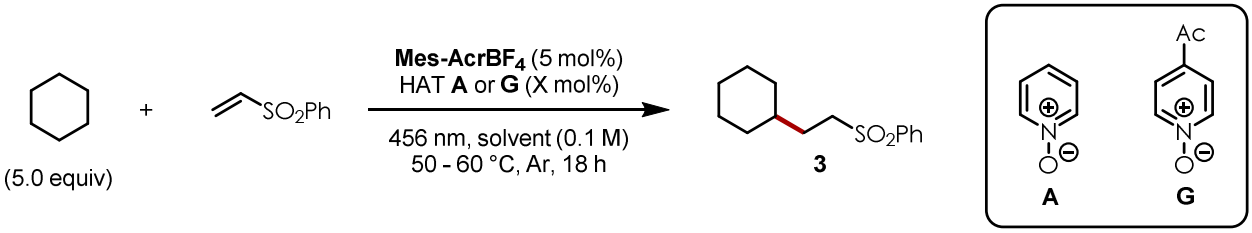
Reactions were irradiated using two Kessil lamps (456 nm) while stirring on stir plates (various models). The reactions were placed approximately 3 cm away from the LEDs, and an external cooling fan was used to adjust temperatures between 50-60 °C.



Reaction Optimizations

Cyclohexane with phenyl vinyl sulfone

Table S3. Optimization for the C–H alkylation with phenyl vinyl sulfone.

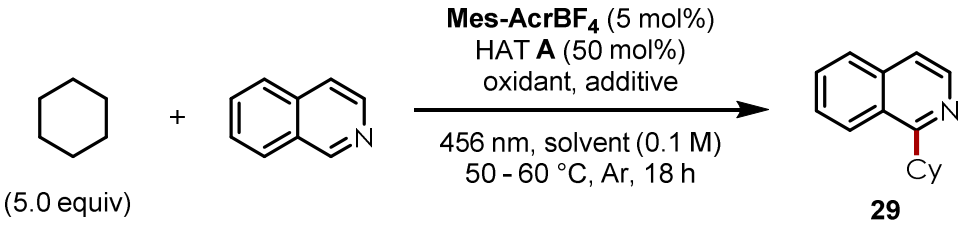


entry	HAT (X mol%)	solvent	conversion[a] [%]	yield[a] [%]
1	**G** (20)	MeCN	63	12
2	**A** (20)	MeCN	66	40
3	**A** (50)	MeCN	73	40
4	**A** (50)	MeCN/HFIP (9:1)	91	79
5	**A** (50)	MeCN/HFIP (7:3)	>99	91 (82)[b]
6	**A** (100)	MeCN/HFIP (7:3)	99	90
7	**A** (20)	MeCN/HFIP (7:3)	>99	91
8	**A** (10)	MeCN/HFIP (7:3)	>99	83
9	**G** (20)	MeCN/HFIP (7:3)	52	6

Scale: 0.100 mmol of phenyl vinyl sulfone. [a]Determined by ^{1}H NMR of the crude mixture with HMDSO as internal standard. [b]Average isolated yield in parenthesis (n = 2).

Cyclohexane with isoquinoline

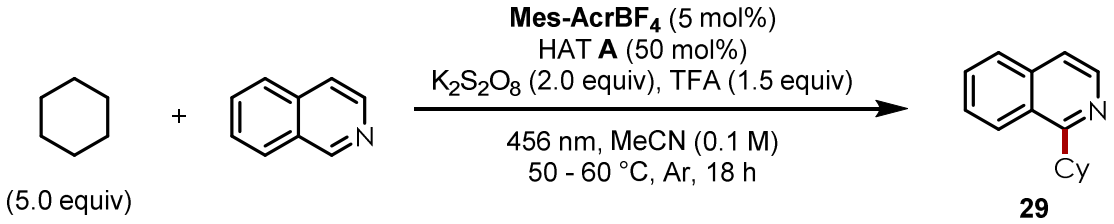
Table S4. Optimization for the C–H heteroarylation with isoquinoline.



entry	oxidant	additive	solvent	conversion[a] [%]	yield[a] [%]
1	$K_2S_2O_8$ (2 equiv)	---	MeCN/HFIP/H_2O (6:3:1)	95	41
2	$K_2S_2O_8$ (2 equiv)	---	MeCN/HFIP (7:3)	>99	46
3[b]	$K_2S_2O_8$ (2 equiv)	---	MeCN/HFIP (7:3)	62	trace
4	$K_2S_2O_8$ (2 equiv)	TFA (1.5 equiv)	MeCN	>99	72 (57)[c]
5	$K_2S_2O_8$ (2 equiv)	TFA (1.5 equiv)	MeCN/H_2O (9:1)	98	54
6	$K_2S_2O_8$ (2 equiv)	TFA (1.5 equiv)	MeCN/H_2O (7:3)	87	27
7	$K_2S_2O_8$ (2 equiv)	TFA (1.5 equiv)	MeCN/H_2O (1:1)	85	10
8	$K_2S_2O_8$ (2 equiv)	TFA (1.5 equiv)	MeCN/HFIP (9:1)	>99	38
9	$K_2S_2O_8$ (2 equiv)	TFA (1.5 equiv)	MeCN/HFIP (7:3)	>99	47
10	$K_2S_2O_8$ (2 equiv)	TFA (1.0 equiv)	MeCN	84	18
11	$K_2S_2O_8$ (2 equiv)	TFA (2.0 equiv)	MeCN	>99	69
12	$K_2S_2O_8$ (2 equiv)	TFA (3.0 equiv)	MeCN	>99	65
13	$K_2S_2O_8$ (1.2 equiv)	TFA (1.5 equiv)	MeCN	94	58

Scale: 0.100 mmol of isoquinoline. [a]Determined by ^{1}H NMR of the crude mixture with HMDSO as internal standard. [b]Without HAT **A**. [c]Average isolated yield in parenthesis (n = 2).

Table S5. Control experiments for the C–H heteroarylation with isoquinoline.

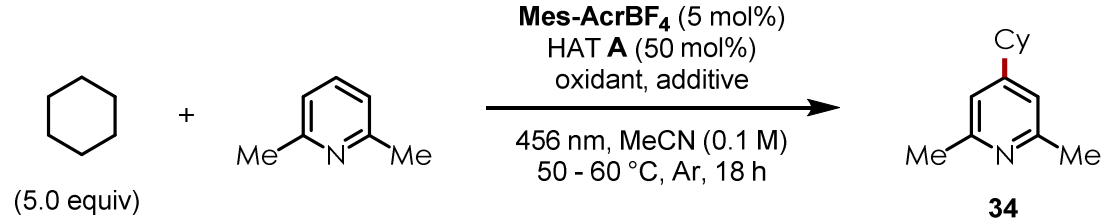


entry	Mes-AcrBF$_4$	HAT A	$K_2S_2O_8$	conversion[a] [%]	yield[a] [%]
1	X	X	X	>99	72
2	X	X	---	30	32
3	X	---	X	93	9
4	---	X	X	81	19
5	---	X	---	37	5
6	---	---	X	28	5

Scale: 0.100 mmol of isoquinoline. [a]Determined by ^{1}H NMR of the crude mixture with HMDSO as internal standard.

Cyclohexane with 2,6-lutidine

Table S6. Optimization for the C–H heteroarylation with 2,6-lutidine.



entry	oxidant	additive	solvent	conversion[a] [%]	yield[a] [%]
1	$K_2S_2O_8$ (2 equiv)	TFA (1.5 equiv)	MeCN	46	28
2	$(NH_4)_2S_2O_8$ (2 equiv)	TFA (1.5 equiv)	MeCN	76	28
3	$K_2S_2O_8$ (2 equiv)	TFA (2 equiv)	MeCN	74	46
4	$K_2S_2O_8$ (2 equiv)	TFA (3 equiv)	MeCN	62	39
5	$K_2S_2O_8$ (2 equiv)	TFA (2 equiv)	MeCN/H_2O (7:3)	70	28
6	$K_2S_2O_8$ (2 equiv)	TFA (3 equiv)	MeCN/H_2O (7:3)	83	21
7[b]	$K_2S_2O_8$ (2 equiv)	TFA (2 equiv)	MeCN	82	54 (48)[c]

Scale: 0.200 mmol of 2,6-lutidine. [a]Determined by ^{1}H NMR of the crude mixture with HMDSO as internal standard. [b]42 hours. [c]Average isolated yield in parenthesis (n = 2).

Stability of the HAT Catalysts under Optimized Reaction Conditions

During the optimization of the C–H functionalization we observed partial deoxygenation of the pyridine *N*-oxides. In order to gain further insights into the stability of these HAT catalysts under the established reaction conditions, control experiments without substrate and radical acceptors were performed.
All reactions were prepared according to the general procedures of the photochemical reactions. No additional substrate was added for reactions **I**-**IV** (*Figure S1*), whereas 5.0 equiv of cyclohexane were added to **V**-**VIII** (*Figure S2*).
Yields of the returned pyridine *N*-oxide derivative (blue color) and the deoxygenated pyridine derivative (red color) were determined by ^{1}H NMR spectroscopy (integral of *ortho*-protons) of the crude reaction mixtures with HMDSO as internal standard. ^{1}H NMR spectra are displayed for the aromatic areas.

All reactions resulted in a mixture of returned pyridine *N*-oxides and their pyridine counterparts, the latter ones ranging from trace to significant amounts. Moreover, the following results were obtained:

- Relatively clean mixtures of returned pyridine *N*-oxides and their deoxygenated products were observed without any additional substrates (**I**-**IV**). However, in the presence of cyclohexane (**V**-**VIII**), significantly lower amounts of both pyridine *N*-oxides and their corresponding pyridines were observed, along with several unidentified products of low intensity in the aromatic and aliphatic area.
- Unsubstituted pyridine *N*-oxide (**I**, **II**, **V** and **VI**) showed higher stability than its 4-acetyl counterpart (**III**, **IV**, **VII** and **VIII**) both without and with cyclohexane in MeCN or MeCN/HFIP (7:3).
- Without additional substrates, pyridine *N*-oxides revealed slightly higher stability in MeCN/HFIP (7:3) than in MeCN (**II** vs. **I**, **IV** vs. **III**), whereas with cyclohexane, the opposite trend was obtained (**VI** vs. **V**, **VIII** vs. **VII**).

These results indicate that the electronic nature of the pyridine *N*-oxide is one of the major factors determining its stability upon single electron oxidation with the acridinium photoredox catalyst (no deoxygenation was observed without Mes-Acr under the photochemical reaction conditions). Also, the chemical environment (solvents/mixtures, large excesses of C–H substrates) significantly contributes to the amount of decomposition products of pyridine *N*-oxides.
As a consequence, the gradually decreasing amount of active HAT-catalyst through deoxygenation/decomposition might partly inhibit the complete conversion of less reactive C–H substrates (e.g. with only primary C–H bonds),
Further mechanistic insights into the deoxygenation pathway will be reported in due course.

Figure S1: Stability test of pyridine *N*-oxide derivatives under the optimized reaction conditions.

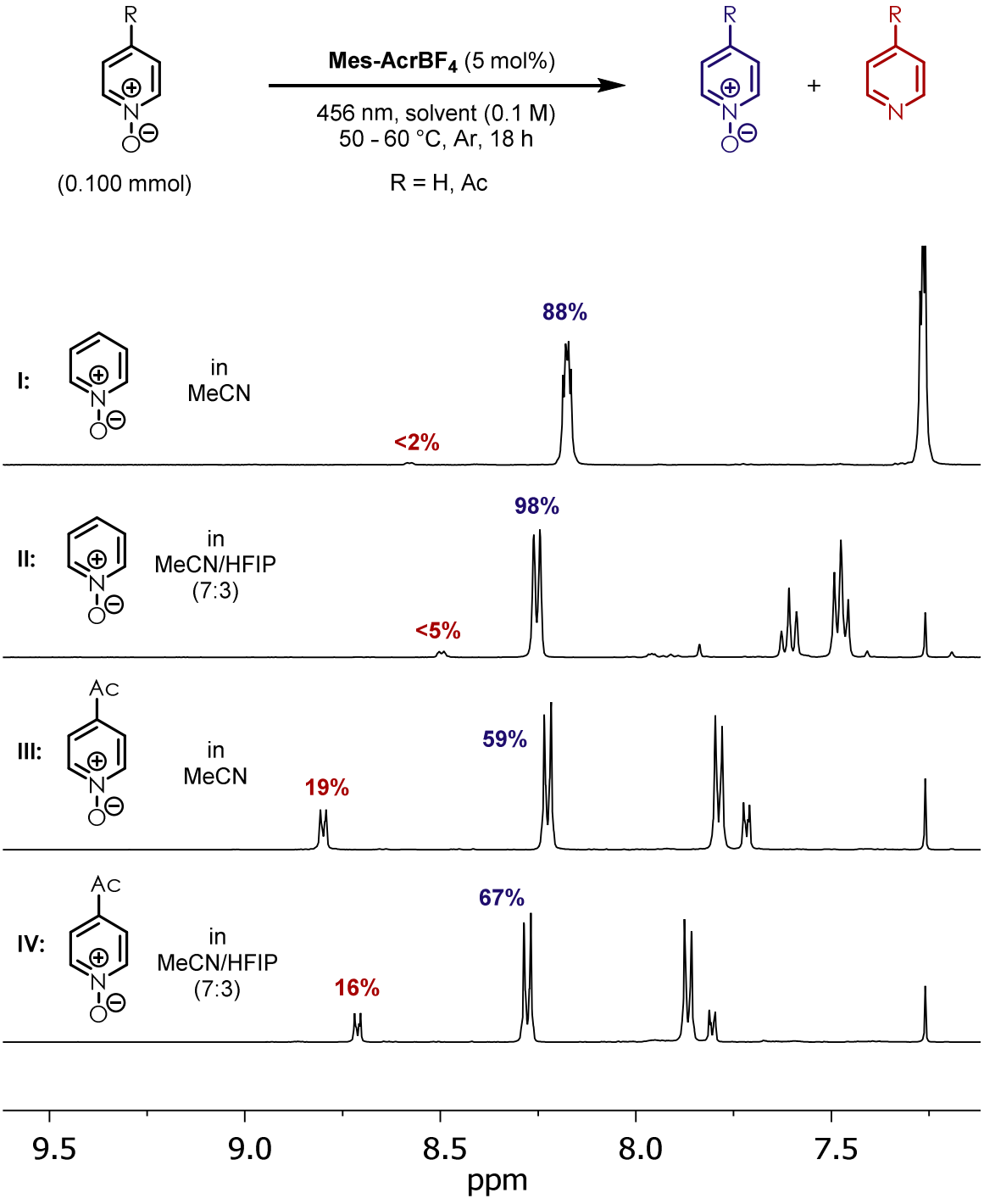
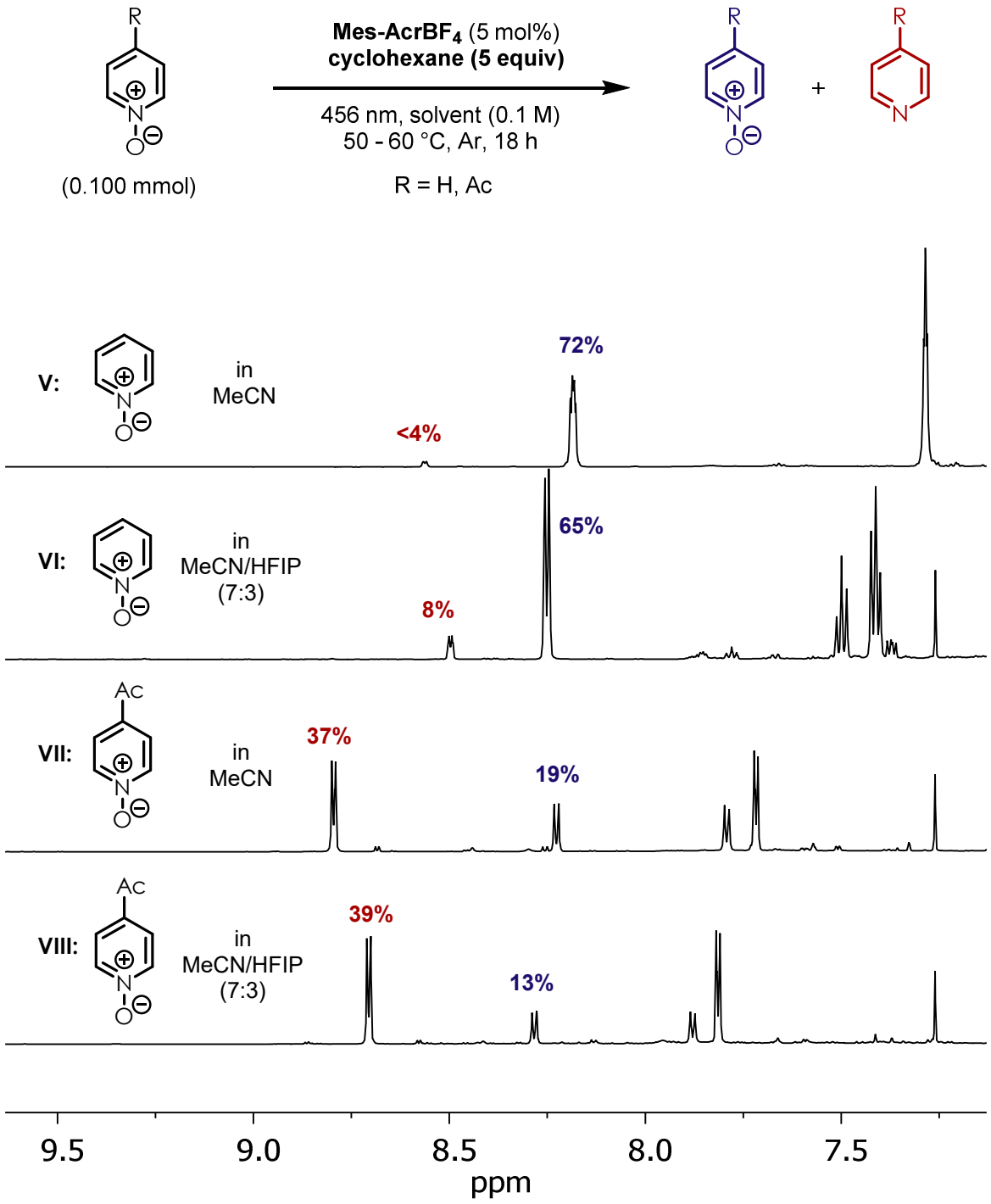
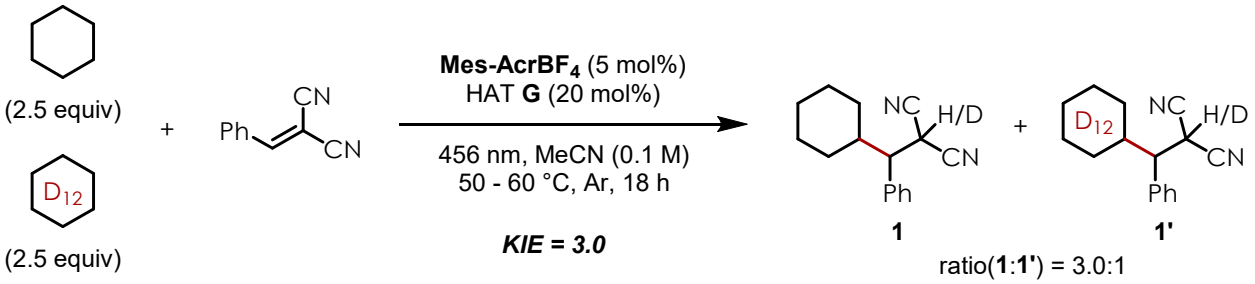


Figure S2: Stability test of pyridine *N*-oxide derivatives under the optimized reaction conditions with 5 equiv of cyclohexane.

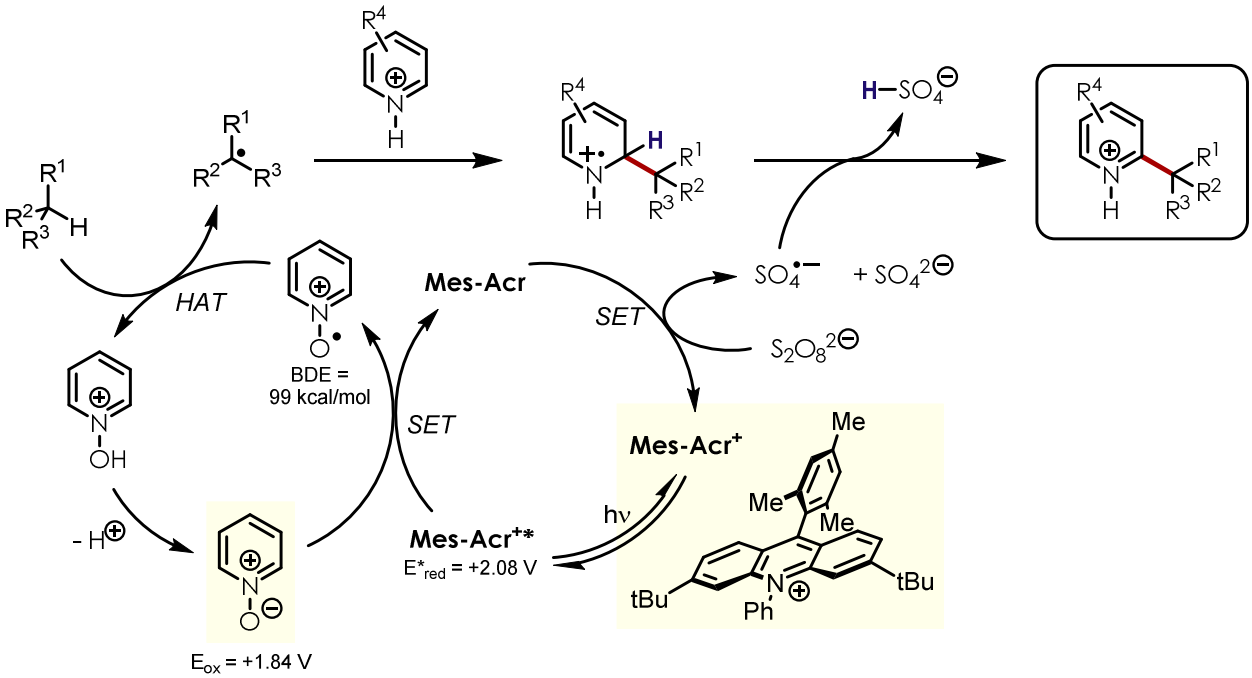


Deuterium Labeling Studies



A competition experiment using a 1:1 mixture of cyclohexane and cyclohexane-d12 revealed a KIE of 3.0, supporting the H-atom abstraction from unactivated C–H bonds by pyridine *N*-oxide **G**.

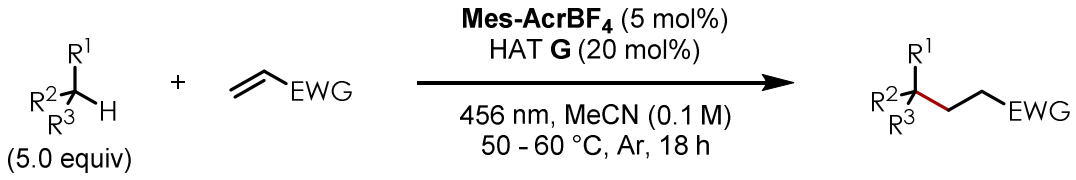
Proposed Mechanism of the Heteroarylation



General Procedures for Photochemical Reactions

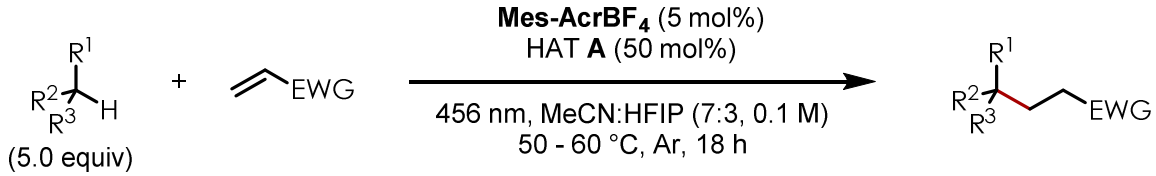
Note: *All reaction yields are shown as the average of two separate trials (including chromatography). Reported regio- and diastereoisomeric ratios were determined by ^1H NMR spectroscopy of the crude reaction mixtures. Unless otherwise stated, diastereoisomers of products were obtained with d.r. ~1:1.*

Method A



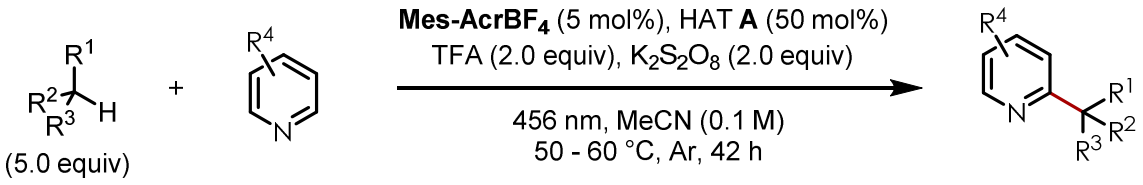
To a 2-dram vial with a stir bar and septa cap was added 3,6-di-*tert*-butyl-9-mesityl-10-phenylacridin-10-ium tetrafluoroborate (5 mol%), 4-acetylpyridine *N*-oxide **G** (20 mol%), the C–H substrate (if solid, 5.0 equiv), the radical acceptor (if solid, 1.0 equiv) and MeCN (1.0 mL/mmol). The vial was sealed and sparged with argon for five minutes. Then, liquid C–H substrates (5.0 equiv) and/or liquid radical acceptors (1.0 equiv) were added via microsyringe while maintaining an inert atmosphere. The vial was sealed with Teflon, placed in the photoreactor set up and stirred for 18 hours. The crude mixture was concentrated under reduced pressure and the residue was directly purified by flash column chromatography on silica gel using hexanes and EtOAc as eluent.

Method B



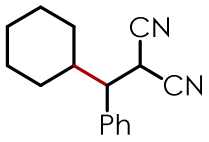
To a 2-dram vial with a stir bar and septa cap was added 3,6-di-*tert*-butyl-9-mesityl-10-phenylacridin-10-ium tetrafluoroborate (5 mol%), pyridine *N*-oxide **A** (50 mol%), the C–H substrate (if solid, 5.0 equiv), the radical acceptor (if solid, 1.0 equiv) and MeCN:HFIP (7:3 v/v, 1.0 mL/mmol). The vial was sealed and sparged with argon for five minutes. Then, liquid C–H substrates (5.0 equiv) and/or liquid radical acceptors (1.0 equiv) were added via microsyringe while maintaining an inert atmosphere. The vial was sealed with Teflon, placed in the photoreactor set up and stirred for 18 hours. The crude mixture was concentrated under reduced pressure and the residue was directly purified by flash column chromatography on silica gel using hexanes and EtOAc as eluent.

Method C - Heteroarylation

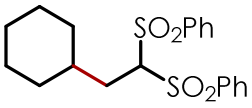


To a 2-dram vial with a stir bar and septa cap was added 3,6-di-*tert*-butyl-9-mesityl-10-phenylacridin-10-ium tetrafluoroborate (5 mol%), pyridine *N*-oxide **A** (50 mol%), potassium persulfate (2.0 equiv), the C–H substrate (if solid, 5.0 equiv), the heteroarene (if solid, 1.0 equiv) and MeCN (1.0 mL/mmol). The vial was sealed and sparged with argon for five minutes. Then, liquid C–H substrates (5.0 equiv) and/or liquid heteroarenes (1.0 equiv) along with trifluoroacetic acid (2.0 equiv) were added via microsyringe while maintaining an inert atmosphere. The vial was sealed with Teflon, placed in the photoreactor set up and stirred for 42 hours. The crude mixture was quenched with saturated $NaHCO_3$ and extracted three times with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by flash column chromatography on silica gel using hexanes and EtOAc as eluent.

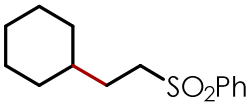
Product Synthesis and Characterization



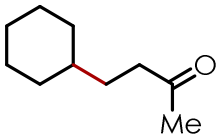
2-(Cyclohexyl(phenyl)methyl)malononitrile (1) was prepared using Method A on a 0.100 mmol scale. The title compound was isolated by column chromatography (5-10% EtOAc in hexanes) to provide a colorless oil (92%).
Analytical data matched that reported in literature.[8]



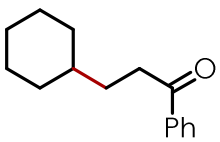
(2-Cyclohexylethane-1,1-diyldisulfonyl)dibenzene (2) was prepared using Method A on a 0.200 mmol scale. The title compound was isolated by column chromatography (20% EtOAc in hexanes) to provide a colorless solid (92%).
Analytical data matched that reported in literature.[9]



((2-Cyclohexylethyl)sulfonyl)benzene (3) was prepared using Method B on a 0.100 mmol scale. The title compound was isolated by column chromatography (10-15% EtOAc in hexanes) to provide a yellowish oil (85%).
Analytical data matched that reported in literature.[10]

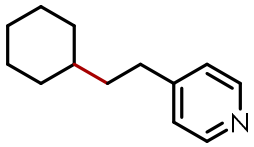


4-Cyclohexylbutan-2-one (4) was prepared using Method B on a 0.200 mmol scale. The title compound was isolated by column chromatography (2-5% Et_2O in pentane) to provide a yellowish oil (75%).
Analytical data matched that reported in literature.[11]

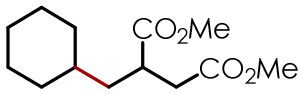


3-Cyclohexyl-1-phenylpropan-1-one (5) was prepared using Method B on a 0.100 mmol scale. The title compound was isolated by column chromatography (0-2% EtOAc in hexanes) to provide a colorless solid (31%).

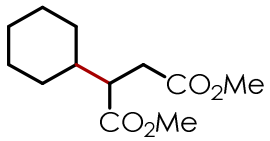
Analytical data matched that reported in literature.[12]



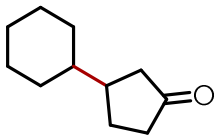
4-(2-Cyclohexylethyl)pyridine (6) was prepared using Method B on a 0.100 mmol scale. The title compound was isolated by column chromatography (20% EtOAc in hexanes) to provide a yellow oil (37%).
Analytical data matched that reported in literature.[13]



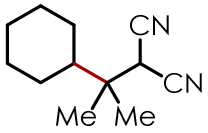
Dimethyl 2-(cyclohexylmethyl)succinate (7) was prepared using Method B on a 0.100 mmol scale. The title compound was isolated by column chromatography (5-10% EtOAc in hexanes) to provide a yellowish oil (67%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 3.66 (s, 3H), 2.93 (dddd, *J* = 9.4, 8.1, 6.6, 5.1 Hz, 1H), 2.68 (dd, *J* = 16.5, 9.4 Hz, 1H), 2.42 (dd, *J* = 16.6, 5.1 Hz, 1H), 1.82 – 1.72 (m, 1H), 1.73 – 1.52 (m, 5H), 1.35 – 1.08 (m, 5H), 0.95 – 0.79 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 176.05, 172.58, 51.95, 51.89, 39.81, 38.79, 36.42, 35.36, 33.27, 33.16, 26.59, 26.29, 26.27.
HRMS (ESI+): m/z calculated for $[M+Na]^+$: 265.14103; found: 265.14084.



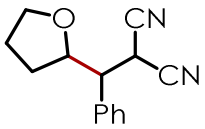
Dimethyl 2-cyclohexylsuccinate (8) was prepared using Method B on a 0.100 mmol scale. The title compound was isolated by column chromatography (5-10% EtOAc in hexanes) to provide a colorless oil (83%).
Analytical data matched that reported in literature.[10]



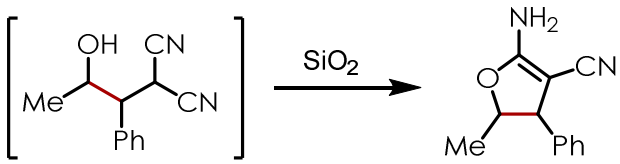
3-Cyclohexylcyclopentan-1-one (9) was prepared using Method B on a 0.200 mmol scale. The title compound was isolated by column chromatography (5% Et_2O in pentane) to provide a yellowish oil (37%).
Analytical data matched that reported in literature.[14]



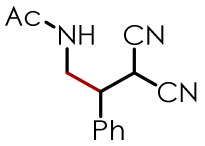
2-(2-Cyclohexylpropan-2-yl)malononitrile (10) was prepared using Method B on a 0.200 mmol scale. The title compound was isolated by column chromatography (5% EtOAc in hexanes) to provide a colorless solid (24%).
Analytical data matched that reported in literature.[15]



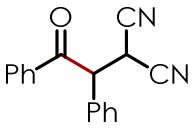
2-(Phenyl(tetrahydrofuran-2-yl)methyl)malononitrile (11) was prepared using Method A on a 0.200 mmol scale. The title compound was isolated by column chromatography (10% EtOAc in hexanes) to provide a colorless oil (87%).
Analytical data matched that reported in literature.[16]



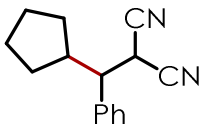
2-(2-Hydroxy-1-phenylpropyl)malononitrile (12) was prepared using Method A on a 0.100 mmol scale. The uncyclized product **12** was obtained with *d.r.* 1.4:1, which fully cyclized upon column chromatography (10-30% EtOAc in hexanes) to provide **2-amino-5-methyl-4-phenyl-4,5-dihydrofuran-3-carbonitrile 12'** as a colorless oil (95%).
Analytical data matched that reported in literature.[17]



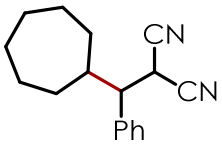
***N*-(3,3-Dicyano-2-phenylpropyl)acetamide (13)** was prepared using Method A on a 0.200 mmol scale. The title compound was isolated by column chromatography (70% EtOAc in hexanes) to provide a yellow oil (91%).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 3H), 7.36 – 7.31 (m, 2H), 6.24 (t, *J* = 5.8 Hz, 1H), 4.25 (d, *J* = 5.5 Hz, 1H), 3.85 (ddd, *J* = 14.5, 8.1, 6.8 Hz, 1H), 3.65 (ddd, *J* = 14.0, 6.4, 5.3 Hz, 1H), 3.60 (dt, *J* = 8.2, 5.9 Hz, 1H), 1.97 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.53, 134.95, 129.55, 129.46, 128.05, 112.08, 111.83, 45.69, 41.76, 27.60, 23.19.
HRMS (ESI+): m/z calculated for $[M+Na]^+$: 250.09508; found: 250.09479.



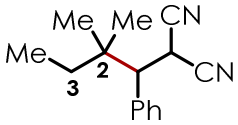
2-(2-Oxo-1,2-diphenylethyl)malononitrile (14) was prepared using Method A on a 0.100 mmol scale. After completion of the reaction, CH_2Cl_2 (2 mL) was added and the mixture was washed twice with sat. $NaHCO_3$ solution to remove benzoic acid observed as a by-product. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The title compound was isolated by column chromatography (5-20% EtOAc in hexanes) to provide a colorless solid (87%).
Analytical data matched that reported in literature.[8]



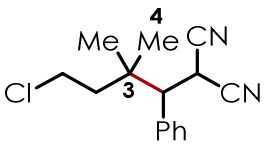
2-(Cyclopentyl(phenyl)methyl)malononitrile (15) was prepared using Method A on a 0.200 mmol scale. The title compound was isolated by column chromatography (5-10% EtOAc in hexanes) to provide a yellowish oil (89%).
Analytical data matched that reported in literature.[8]



2-(Cycloheptyl(phenyl)methyl)malononitrile (16) was prepared using Method A on a 0.200 mmol scale. The title compound was isolated by column chromatography (5-10% EtOAc in hexanes) to provide a colorless oil (88%).
Analytical data matched that reported in literature.[8]



2-(2,2-Dimethyl-1-phenylbutyl)malononitrile (17) (mixture of regioisomers) was prepared using Method A on a 0.100 mmol scale. The title compound was isolated by column chromatography (5-10% EtOAc in hexanes) to provide a colorless solid (91%, *C2*:*C3* = 5.1:1). Regioisomers could not be separated.
Analytical data matched that reported in literature.[9]



2-(4-Chloro-2,2-dimethyl-1-phenylbutyl)malononitrile (18) (mixture of regioisomers) was prepared using Method B on a 0.200 mmol scale. The title compound was isolated by column

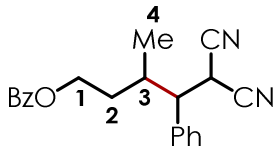
chromatography (5-10% EtOAc in hexanes) to provide a yellow oil (81%, *C3*:*C4* = 11:1). Regioisomers could not be separated.

Analytical data are reported for the *C3* regioisomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 5H), 4.26 (d, *J* = 5.5 Hz, 1H), 3.52 (dt, *J* = 9.1, 6.9 Hz, 2H), 3.10 (d, *J* = 5.5 Hz, 1H), 1.87 (dt, *J* = 8.9, 5.8 Hz, 2H), 1.20 (s, 3H), 1.11 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.35, 129.58, 129.10 (4C), 113.14, 112.90, 55.70, 43.60, 40.09, 37.87, 25.51, 25.01, 24.83.

HRMS (ESI+): m/z calculated for $[M+Na]^+$: 283.09725; found: 283.09732.



5,5-Dicyano-3-methyl-4-phenylpentyl benzoate (19) (mixture of regioisomers) was prepared using Method B on a 0.100 mmol scale. The title compound was isolated by column chromatography (5-15% EtOAc in hexanes) to provide a yellow oil (86%, *C3*:*C1*:*C2*:*C4* = 15:8.3:3.0:1). *C1*+*C2* regioisomers were separated from *C3*+*C4* regioisomers.

Analytical data are reported for the *C1*, *C2* and *C3* regioisomers.

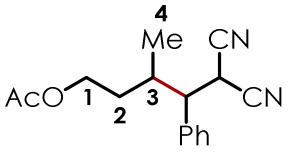
^{1}H NMR (400 MHz, $CDCl_3$) δ *C1* regioisomer (2 diastereoisomers): 8.12 (d, *J* = 7.2 Hz, 2H), 8.05 (d, *J* = 7.3 Hz, 2H), 7.66 – 7.36 (m, 16H), 5.78 (ddd, *J* = 10.6, 7.2, 3.6 Hz, 1H), 5.72 (ddd, *J* = 8.4, 5.4, 3.2 Hz, 1H), 4.25 – 4.17 (m, 2H), 3.59 – 3.53 (m, 2H), 1.69 – 1.29 (m, 8H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.80 (t, *J* = 7.3 Hz, 3H); *C2* regioisomer (2 diastereoisomers): 8.08 (d, *J* = 7.7 Hz, 2H), 8.00 (d, *J* = 7.3 Hz, 2H), 7.66 – 7.36 (m, 16H), 4.65 (dd, *J* = 12.2, 2.8 Hz, 1H), 4.54 (d, *J* = 5.7 Hz, 1H), 4.36 (d, *J* = 7.1 Hz, 1H), 4.34 (dd, *J* = 12.4, 5.6 Hz, 1H), 4.28 (dd, *J* = 11.8, 5.4 Hz, 1H), 4.04 (dd, *J* = 11.8, 4.2 Hz, 1H), 3.40 (t, *J* = 7.8 Hz, 1H), 3.25 (dd, *J* = 9.9, 5.7 Hz, 1H), 2.67 – 2.43 (m, 2H), 1.69 – 1.29 (m, 4H), 1.12 (t, *J* = 6.6 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ *C1* regioisomer (2 diastereoisomers): 166.25, 165.89, 134.26, 133.88, 133.82, 133.21, 130.07, 129.95, 129.84, 129.78, 129.76, 129.47, 129.38, 129.35, 128.84, 128.82 (4C), 128.64, 112.05, 111.95, 111.74, 111.44, 73.79, 73.27, 50.49, 50.47, 34.89, 34.67, 27.21, 27.06, 18.84, 17.81, 13.91, 13.81; *C2* regioisomer (2 diastereoisomers): 166.66, 166.15, 135.72, 135.10, 133.76, 133.54, 129.61, 129.59, 129.30, 129.25, 129.22, 128.85, 128.81, 128.52, 128.37, 112.21, 112.09, 112.00, 111.98, 63.95, 63.52, 48.53, 48.30, 41.36, 41.01, 28.13, 27.89, 22.36, 22.06, 11.46, 11.23. Three aromatic ^{13}C signals could not be detected due to their low intensity and the possible overlap with other signals.

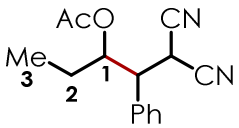
HRMS (ESI+) *C1*+*C2* regioisomers: m/z calculated for $[M+Na]^+$: 355.14170; found: 355.14117.

^{1}H NMR (400 MHz, $CDCl_3$) δ *C3* regioisomer (2 diastereoisomers): 8.06 (d, *J* = 7.4 Hz, 2H), 7.99 (d, *J* = 7.4 Hz, 2H), 7.61 – 7.55 (m, 2H), 7.51 – 7.28 (m, 14H), 4.50 (dt, *J* = 12.0, 6.2 Hz, 1H), 4.41 (ddd, *J* = 11.2, 7.6, 6.0 Hz, 1H), 4.33 (d, *J* = 7.2 Hz, 1H), 4.32 – 4.23 (m, 2H), 4.22 (d, *J* = 5.3 Hz, 1H), 3.16 (t, *J* = 7.7 Hz, 1H), 2.99 (dd, *J* = 10.2, 5.4 Hz, 1H), 2.57 – 2.45 (m, 2H), 2.11 – 2.00 (m, 1H), 1.84 – 1.76 (m, 1H), 1.68 – 1.59 (m, 1H), 1.45 – 1.36 (m, 1H), 1.25 (d, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ *C3* regioisomer (2 diastereoisomers): 166.72, 166.53, 136.48, 136.19, 135.63, 133.35, 133.23, 129.72, 129.65, 129.63, 129.47, 129.34, 129.25, 129.10, 128.65, 128.56, 128.54, 128.44, 112.11, 112.04, 111.95, 111.71, 62.35, 62.02, 52.31, 51.42, 33.31, 32.78, 32.36, 32.28, 27.96, 27.56, 17.74, 16.11.
HRMS (ESI+) *C3+C4* regioisomers: m/z calculated for $[M+Na]^+$: 355.14170; found: 355.14136.

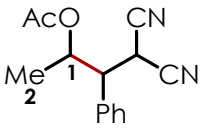


5,5-Dicyano-3-methyl-4-phenylpentyl acetate (20) (mixture of regioisomers) was prepared using Method B on a 0.200 mmol scale. The title compound was isolated by column chromatography (5-15% EtOAc in hexanes) to provide a yellow oil (90%, *C3*:*C1*:*C2*:*C4* = 16:6.7:4.0:1). The *C1* regioisomer was separated from *C2*+*C3*+*C4* regioisomers.
Analytical data are reported for the *C1* and *C3* regioisomers.
^{1}H NMR (400 MHz, $CDCl_3$) δ *C1* regioisomer (2 diastereoisomers): 7.46 – 7.35 (m, 10H), 5.52 – 5.42 (m, 2H), 4.14 (d, *J* = 7.5 Hz, 1H), 4.13 (d, *J* = 5.1 Hz, 1H), 3.43 – 3.37 (m, 2H), 2.20 (s, 3H), 2.16 (s, 3H), 1.53 – 1.23 (m, 6H), 0.86 (t, *J* = 7.1 Hz, 3H), 0.79 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ *C1* regioisomer (2 diastereoisomers): 170.64, 170.45, 134.50, 133.25, 129.79, 129.71, 129.44 (3C), 129.36, 129.32, 128.44, 111.96, 111.89, 111.78, 111.55, 73.49, 73.10, 50.19, 49.78, 34.67, 34.61, 27.33, 27.20, 21.17, 18.71, 17.73, 13.87, 13.78.
HRMS (ESI+) *C1* regioisomer: m/z calculated for $[M+Na]^+$: 293.12605; found: 293.12604.
^{1}H NMR (400 MHz, $CDCl_3$) δ *C3* regioisomer (2 diastereoisomers): 7.44 – 7.27 (m, 10H), 4.30 (d, *J* = 7.1 Hz, 1H), 4.28 – 4.22 (m, 1H), 4.21 (d, *J* = 5.5 Hz, 1H), 4.14 – 4.03 (m, 2H), 4.01 – 3.95 (m, 1H), 3.09 (t, *J* = 7.7 Hz, 1H), 2.95 (dd, *J* = 10.0, 5.5 Hz, 1H), 2.43 – 2.32 (m, 2H), 2.09 (s, 3H), 2.01 (s, 3H), 1.91 – 1.83 (m, 1H), 1.68 – 1.59 (m, 1H), 1.53 – 1.45 (m, 1H), 1.30 – 1.23 (m, 1H), 1.16 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ *C3* regioisomer (2 diastereoisomers): 171.26, 171.09, 136.12, 135.58, 129.38, 129.26, 129.17, 129.03, 128.52, 128.40, 112.15, 112.05, 111.94, 111.77, 61.79, 61.51, 52.19, 51.25, 33.10, 32.44, 32.14, 32.09, 27.88, 27.46, 21.06, 21.01, 17.55, 16.09.
HRMS (ESI+) *C2+C3+C4* regioisomers: m/z calculated for $[M+Na]^+$: 293.12605; found: 293.12610.

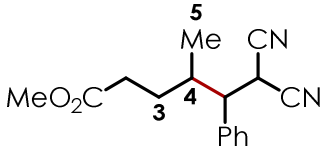


1,1-Dicyano-2-phenylpentan-3-yl acetate (21) (mixture of regioisomers) was prepared using Method B on a 0.200 mmol scale. The title compound was isolated by column chromatography (5-10% EtOAc in hexanes) to provide a yellow oil (71%, *C1*:*C2*:*C3* = 13:6.6:1). The *C1* regioisomer was separated from *C2*+*C3* regioisomers.
Analytical data are reported for *C1*, *C2* and *C3* regioisomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ *C1* regioisomer (2 diastereoisomers): 7.45 – 7.34 (m, 10H), 5.45 (ddd, *J* = 10.4, 6.5, 3.7 Hz, 1H), 5.36 (ddd, *J* = 7.6, 6.2, 3.7 Hz, 1H), 4.16 – 4.13 (m, 2H), 3.44 – 3.40 (m, 2H), 2.20 (s, 3H), 2.17 (s, 3H), 1.70 – 1.53 (m, 2H), 1.47 – 1.33 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ *C1* regioisomer (2 diastereoisomers): 170.61, 170.39, 134.37, 133.20, 129.76, 129.69, 129.44, 129.42, 129.30, 128.45, 111.96, 111.90, 111.80, 111.57, 74.56, 74.37, 49.50, 49.31, 27.32, 27.21, 25.67, 25.14, 21.13 (2x), 9.79, 8.42.
HRMS (ESI+) *C1* regioisomer: m/z calculated for $[M+Na]^+$: 279.11040; found: 279.11041.
^{1}H NMR (400 MHz, $CDCl_3$) δ *C2* regioisomer (2 diastereoisomers): 7.47 – 7.28 (m, 10H), 4.39 (d, *J* = 6.3 Hz, 1H), 4.32 (dd, *J* = 11.9, 3.7 Hz, 1H), 4.27 (d, *J* = 6.2 Hz, 1H), 3.93 – 3.83 (m, 2H), 3.78 (dd, *J* = 11.3, 5.2 Hz, 1H), 3.17 – 3.12 (m, 2H), 2.64 – 2.55 (m, 2H), 2.16 (s, 3H), 2.04 (s, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H); *C3* regioisomer: 7.47 – 7.28 (m, 5H), 4.10 – 3.99 (m, 2H), 3.93 – 3.83 (m, 1H), 3.25 (dt, *J* = 11.0, 5.8 Hz, 1H), 2.14 – 2.05 (m, 5H), 1.61 – 1.52 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ *C2* regioisomer (2 diastereoisomers): 170.81, 170.57, 135.50, 135.25, 129.56, 129.43, 129.40, 129.23, 128.42, 128.29, 112.06, 112.02, 112.00, 111.82, 66.65, 66.22, 49.62, 49.38, 34.95, 34.78, 27.98, 27.91, 21.05, 20.90, 16.00, 15.00; *C3* regioisomer: 171.11, 136.19, 129.60, 129.28, 127.92, 111.88, 111.80, 63.37, 46.31, 30.48, 28.70, 26.23, 21.04.
HRMS (ESI+) *C2*+*C3* regioisomers: m/z calculated for $[M+Na]^+$: 279.11040; found: 279.11002.



4,4-Dicyano-3-phenylbutan-2-yl acetate (22) was prepared using Method B on a 0.200 mmol scale. The title compound was isolated by column chromatography (5-10% EtOAc in hexanes) to provide a yellow oil (49%, *C1*:*C2* >20:1).
Analytical data are reported for the *C1* regioisomer (2 diastereoisomers).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.35 (m, 10H), 5.49 (qd, *J* = 6.3, 4.0 Hz, 1H), 5.39 (dq, *J* = 10.5, 6.1 Hz, 1H), 4.23 (d, *J* = 4.8 Hz, 1H), 4.17 (d, *J* = 8.4 Hz, 1H), 3.36 – 3.28 (m, 2H), 2.17 (s, 3H), 2.14 (s, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.16 (d, *J* = 6.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.06, 169.98, 134.25, 133.26, 129.78, 129.77 129.46, 129.36, 129.33, 128.41, 111.79, 111.75 (2x), 111.54, 70.90, 69.87, 51.53, 50.98, 27.07, 26.97, 21.27, 21.23, 18.87, 18.38.
HRMS (ESI+): m/z calculated for $[M+Na]^+$: 265.09475; found: 265.09470.



Methyl 6,6-dicyano-4-methyl-5-phenylhexanoate (23) (mixture of regioisomers) was prepared using Method B on a 0.100 mmol scale. The title compound was isolated by column chromatography (5-15% EtOAc in hexanes) to provide a yellow oil (89%, *C4*:*C3*:*C5* = 19:8.0:1). The *C3* regioisomer was separated from *C4*+*C5* regioisomers.

Analytical data are reported for the *C3* and *C4* regioisomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ *C3* regioisomer (2 diastereoisomers): 7.45 – 7.30 (m, 10H), 4.51 (d, *J* = 6.3 Hz, 1H), 4.28 (d, *J* = 5.9 Hz, 1H), 3.76 (s, 3H), 3.61 (s, 3H), 3.37 – 3.29 (m, 2H), 2.61 – 2.55 (m, 1H), 2.48 – 2.39 (m, 1H), 2.26 (dd, *J* = 16.3, 5.0 Hz, 1H), 2.14 (dd, *J* = 16.3, 6.6 Hz, 1H), 1.72 – 1.46 (m, 3H), 1.42 – 1.33 (m, 1H), 1.14 – 1.06 (m, 1H), 1.03 (t, *J* = 7.5 Hz, 3H), 0.90 – 0.82 (m, 4H).

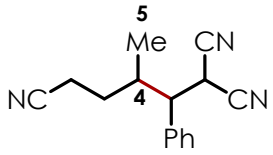
^{13}C NMR (101 MHz, $CDCl_3$) δ *C3* regioisomer (2 diastereoisomers): 172.55, 172.50, 135.95, 135.88, 129.49, 129.39, 129.27, 129.15, 128.57, 128.55, 112.17, 112.05, 112.04, 111.83, 52.25, 51.88, 49.16, 48.83, 39.12, 38.07, 34.64, 34.37, 27.80, 27.68, 24.18, 23.78, 11.31, 10.41.

HRMS (ESI+) *C3* regioisomer: m/z calculated for $[M+Na]^+$: 293.12605; found: 293.12625.

^{1}H NMR (400 MHz, $CDCl_3$) δ *C4* regioisomer (2 diastereoisomers): 7.44 – 7.27 (m, 10H), 4.33 (d, *J* = 6.8 Hz, 1H), 4.20 (d, *J* = 5.6 Hz, 1H), 3.71 (s, 3H), 3.62 (s, 3H), 3.02 (dd, *J* = 8.5, 6.8 Hz, 1H), 2.93 (dd, *J* = 9.7, 5.6 Hz, 1H), 2.48 – 2.18 (m, 6H), 1.93 – 1.86 (m, 1H), 1.72 – 1.64 (m, 1H), 1.52 – 1.44 (m, 1H), 1.30 – 1.20 (m, 1H), 1.13 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ *C4* regioisomer (2 diastereoisomers): 173.55, 173.41, 136.10, 135.71, 129.40, 129.27, 129.17, 129.03, 128.59, 128.42, 112.22, 112.11, 111.94, 111.83, 52.37, 52.05, 51.83, 51.56, 34.38, 34.38, 31.25, 31.17, 29.46, 28.69, 27.94, 27.55, 17.36, 16.17.

HRMS (ESI+) *C4*+*C5* regioisomers: m/z calculated for $[M+Na]^+$: 293.12605; found: 293.12582.



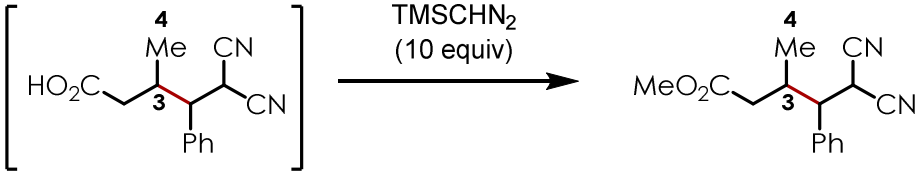
3-Methyl-2-phenylpentane-1,1,5-tricarbonitrile (24) (mixture of regioisomers) was prepared using Method B on a 0.100 mmol scale. The title compound was isolated by column chromatography (10-30% EtOAc in hexanes) to provide a yellow oil (50%, *C4*:*C5* = 8.2:1). Regioisomers could not be separated.

Analytical data are reported for the *C4* regioisomer (2 diastereoisomers).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.24 (m, 10H), 4.20 – 4.16 (m, 2H), 3.15 (t, *J* = 7.6 Hz, 1H), 2.92 (dd, *J* = 10.5, 4.9 Hz, 1H), 2.51 – 2.21 (m, 6H), 1.96 – 1.88 (m, 1H), 1.71 – 1.64 (m, 1H), 1.52 – 1.42 (m, 1H), 1.39 – 1.30 (m, 1H), 1.22 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.86, 134.92, 129.78, 129.58, 129.51, 129.36, 128.44, 128.23, 118.95, 118.89, 111.80, 111.79, 111.76, 111.51, 52.00, 51.25, 34.50, 34.47, 30.37, 29.82, 28.01, 27.36, 17.06, 15.08, 15.06, 14.94.

HRMS (ESI+): m/z calculated for $[M+Na]^+$: 260.11582; found: 260.11566.



5,5-Dicyano-3-methyl-4-phenylpentanoic acid (25) (mixture of regioisomers) was prepared using a modified procedure of Method B, in which MeCN/HFIP (7:3 v/v, 1.0 mL/mmol) was replaced by CH_2Cl_2 (1.0 mL/mmol), on a 0.200 mmol scale. After completion of the reaction, trimethylsilyldiazomethane (2M in hexanes, 10.0 equiv) was added directly to the reaction vial and it was allowed to react for another 2 h. The crude mixture was then concentrated under reduced pressure. **Methyl 5,5-dicyano-3-methyl-4-phenylpentanoate (25')** was isolated by column chromatography (10% EtOAc in hexanes) to provide a yellow oil (74%, *C2*:*C3* = 1.5:1). One diastereoisomer of the product (*C3* regioisomer) was separated from a mixture of the other diastereoisomer and the *C4* regioisomer.

Analytical data are reported for the *C3* and *C4* regioisomers.

^{1}H NMR (600 MHz, $CDCl_3$) δ *C3* regioisomer (diastereoisomer 1): 7.44 – 7.37 (m, 3H), 7.31 – 7.27 (m, 2H), 4.36 (d, *J* = 7.3 Hz, 1H), 3.75 (s, 3H), 3.29 (t, *J* = 7.8 Hz, 1H), 2.72 (hept, *J* = 6.7 Hz, 1H), 2.46 (dd, *J* = 15.5, 5.6 Hz, 1H), 2.34 (dd, *J* = 15.5, 6.3 Hz, 1H), 0.91 (d, *J* = 6.8 Hz, 3H).

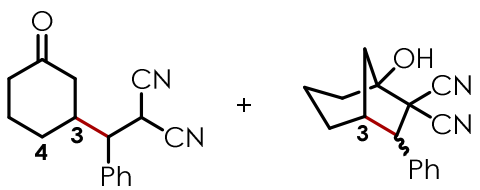
^{13}C NMR (151 MHz, $CDCl_3$) δ *C3* regioisomer (diastereoisomer 1): 172.10, 135.37, 129.39, 129.21, 128.56, 111.98 (2x), 52.17, 50.09, 38.73, 32.47, 27.51, 17.02.

HRMS (ESI+) *C3* regioisomer (diastereoisomer 1): m/z calculated for $[M+Na]^+$: 279.11040; found: 279.11044.

^{1}H NMR (600 MHz, $CDCl_3$) δ *C3* regioisomer (diastereoisomer 2): 7.44 – 7.35 (m, 5H), 4.23 (d, *J* = 5.1 Hz, 1H), 3.62 (s, 3H), 3.15 (dd, *J* = 10.5, 5.1 Hz, 1H), 2.77 – 2.70 (m, 1H), 2.34 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.07 – 2.02 (m, 1H), 1.24 (d, *J* = 6.6 Hz, 3H); *C4* regioisomer: 7.44 – 7.35 (m, 3H), 7.32 – 7.31 (m, 2H), 3.90 (d, *J* = 6.2 Hz, 1H), 3.66 (s, 3H), 3.22 (dt, *J* = 9.6, 6.0 Hz, 1H), 2.38 – 2.28 (m, 2H), 2.08 – 2.01 (m, 2H), 1.58 – 1.53 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ *C3* regioisomer (diastereoisomer 2): 172.19, 136.06, 129.37, 129.24, 128.41, 111.99, 111.64, 51.86, 51.16, 38.65, 32.46, 27.89, 18.22; *C4* regioisomer: 173.31, 136.26, 129.57, 129.56, 127.95, 111.88, 111.84, 51.86, 46.57, 33.37, 31.50, 30.43, 22.43.

HRMS (ESI+) *C3* regioisomer (diastereoisomer 2) + *C4* regioisomer: m/z calculated for $[M+Na]^+$: 279.11040; found: 279.11026.



2-((3-Oxocyclohexyl)(phenyl)methyl)malononitrile (26) was prepared using Method B on a 0.200 mmol scale. The title compound was isolated by column chromatography (10-30% EtOAc in hexanes) to provide a yellowish oil (91%, *C3*:*C4* >10:1, *d.r.*(*C3*) = 1.4:1). Both diastereoisomers of the product (*C3* regioisomer) could be separated from each other. One

diastereoisomer was collected along with its cyclized product **5-hydroxy-7-phenyl-bicyclo[3.2.1]octane-6,6-dicarbonitrile 26'** (single diastereoisomer).

Analytical data are reported for both diastereoisomers and the bicyclic product of the *C3* regioisomer.

^{1}H NMR (500 MHz, $CDCl_3$) δ diastereoisomer 1: 7.44 – 7.39 (m, 3H), 7.29 – 7.27 (m, 2H), 4.19 (d, *J* = 5.4 Hz, 1H), 3.06 (dd, *J* = 9.7, 5.4 Hz, 1H), 2.54 (dtd, *J* = 15.2, 11.8, 11.4, 3.7 Hz, 1H), 2.45 – 2.40 (m, 1H), 2.28 – 2.16 (m, 4H), 1.92 – 1.86 (m, 1H), 1.84 – 1.75 (m, 1H), 1.56 – 1.48 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ diastereoisomer 1: 208.73, 135.26, 129.70, 129.50, 128.13, 111.70, 111.68, 51.69, 45.12, 40.80, 40.36, 29.55, 27.46, 24.53.

HRMS (ESI+) diastereoisomer 1: m/z calculated for $[M+Na]^+$: 275.11548; found: 275.11540.

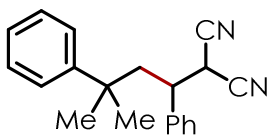
^{1}H NMR (400 MHz, $CDCl_3$) δ diastereoisomer 2: 7.45 – 7.30 (m, 5H), 4.15 (d, *J* = 6.1 Hz, 1H), 3.05 (dd, *J* = 8.9, 6.4 Hz, 1H), 2.67 – 2.51 (m, 2H), 2.47 – 2.40 (m, 1H), 2.27 – 2.23 (m, 1H), 2.13 (t, *J* = 12.3 Hz, 1H), 2.01 – 1.95 (m, 1H), 1.77 – 1.63 (m, 2H), 1.35 – 1.24 (m, 1H); bicyclic product: 7.45 – 7.30 (m, 5H), 3.63 (bs, 1H), 2.79 (bs, 1H), 2.56 – 2.51 (m, 1H), 2.28 – 2.23 (m, 1H), 2.02 – 1.93 (m, 3H), 1.82 (d, *J* = 12.0 Hz, 1H), 1.77 – 1.70 (m, 1H), 1.57 – 1.50 (m, 1H), the ^{1}H-signal of the OH group could not be detected.

^{13}C NMR (101 MHz, $CDCl_3$) δ diastereoisomer 2: 208.68, 135.22, 129.46, 128.89, 128.40, 111.71, 111.45, 51.21, 45.92, 41.05, 40.25, 28.21, 27.20, 24.29; bicyclic product: 138.81, 129.59, 129.42, 127.97, 114.78, 113.14, 84.30, 56.52, 52.66, 43.83, 38.91, 35.86, 30.39, 18.66.

HRMS (ESI+) diastereoisomer 2 + bicyclic product: m/z calculated for $[M+Na]^+$: 275.11548; found: 275.11536.

Notes:

1) Previously reported C–H alkylation reactions of cyclohexanone typically resulted in an detectable mixture of *C3* and *C4* functionalized products with moderate to good regioselectivity favoring the *C3*-position.[18,9] Careful investigation of the ^{1}H NMR spectrum of the crude reaction mixture did not reveal signals that could doubtlessly be assigned to a *C4*-functionalized product. However, an overlap of signals with the *C3*-isomers could not be ruled out. A potential *C4*-alkylated product was never isolated or observed in a product fraction upon column chromatography.
2) Partial cyclization of keto-substituted malononitriles to cyclopentanoles was also reported in other approaches.[18]
3) The structures of the *C3*-regioisomer (diastereoisomer 2) and the bicyclic product **26'** were supported by two-dimensional NMR spectroscopy (COSY, HSQC and HMBC). See the Spectral Data section for details.



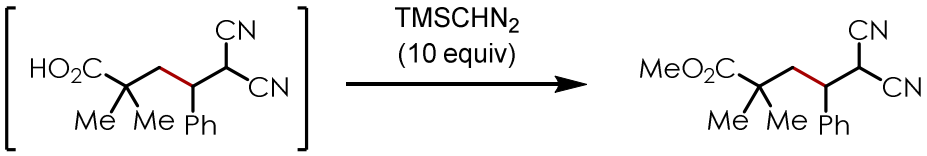
2-(3-Methyl-1,3-diphenylbutyl)malononitrile (27) was prepared using Method B on a 0.200 mmol scale (42 hours reaction time). ^{1}H NMR spectroscopy of the crude reaction mixtures with

HMDSO as an internal standard showed an average NMR yield of 23%. The title compound was isolated by column chromatography (2-5% EtOAc in hexanes), but could not be separated from unreacted benzylidene malononitrile (several solvent mixtures for column chromatography as well as isolation by preparative TLC failed). The calculated average yield of the fractions containing the title compound matched the NMR yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 7H), 7.25 – 7.17 (m, 3H), 3.37 (d, *J* = 5.6 Hz, 1H), 2.95 (dt, *J* = 7.2, 5.5 Hz, 1H), 2.38 – 2.34 (m, 2H), 1.36 (s, 3H), 1.16 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.66, 138.40, 129.19, 128.80, 128.74, 128.10, 126.66, 125.93, 112.09, 111.99, 46.46, 43.64, 38.15, 31.60, 30.89, 27.24.

HRMS (ESI+): m/z calculated for $[M+Na]^+$: 311.15187; found: 311.15207.

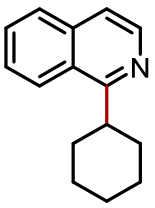


5,5-Dicyano-2,2-dimethyl-4-phenylpentanoic acid (28) was prepared using a modified procedure of Method B, in which MeCN/HFIP (7:3 v/v, 1.0 mL/mmol) was replaced by CH_2Cl_2 (1.0 mL/mmol), on a 0.200 mmol scale (66 hours reaction time). After completion of the reaction, trimethylsilyldiazomethane (2M in hexanes, 10.0 equiv) was added directly to the reaction vial and it was allowed to react for another 2 h. The crude mixture was then concentrated under reduced pressure. **Methyl 5,5-dicyano-2,2-dimethyl-4-phenylpentanoate (28')** was isolated by column chromatography (15% EtOAc in hexanes) to provide a yellow oil (33%).

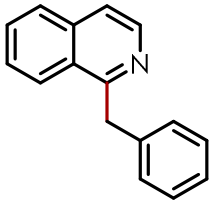
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 5H), 3.92 (d, *J* = 6.0 Hz, 1H), 3.85 (s, 3H), 3.29 (ddd, *J* = 9.5, 6.0, 2.7 Hz, 1H), 2.42 (dd, *J* = 14.2, 10.0 Hz, 1H), 2.15 (dd, *J* = 14.2, 2.7 Hz, 1H), 1.23 (s, 3H), 1.09 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.89, 137.00, 129.31, 129.16, 128.38, 111.97, 111.92, 51.93, 44.04, 42.54, 42.03, 31.51, 26.24, 25.53.

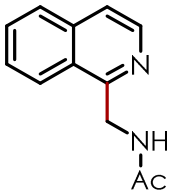
HRMS (ESI+): m/z calculated for $[M+Na]^+$: 293.12605; found: 293.12570.



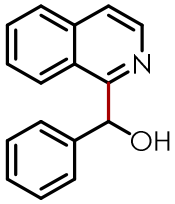
1-Cyclohexylisoquinoline (29) was prepared using a modified procedure of Method C, in which TFA (1.5 equiv) was used, on a 0.200 mmol scale (18 hours reaction time). The title compound was isolated by column chromatography (5% EtOAc in hexanes) to provide a colorless oil (57%). Analytical data matched that reported in literature.[19]



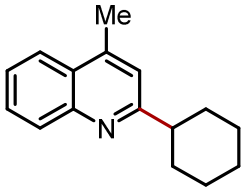
1-Benzylisoquinoline (30) was prepared using Method C on a 0.200 mmol scale. The title compound was isolated by column chromatography (10% EtOAc in hexanes) to provide a colorless oil (69%).
Analytical data matched that reported in literature.[20]



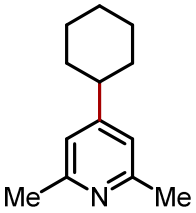
***N*-(Isoquinolin-1-ylmethyl)acetamide (31)** was prepared using Method C on a 0.200 mmol scale. The title compound was isolated by column chromatography (EtOAc) to provide a colorless solid (66%).
Analytical data matched that reported in literature.[21]



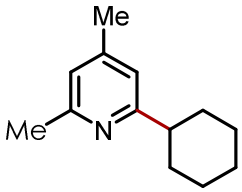
Isoquinolin-1-yl(phenyl)methanol (32) was prepared using a modified procedure of Method C in the absence of $K_2S_2O_8$ and with benzaldehyde as the C–H substrate on a 0.200 mmol scale. The title compound was isolated by column chromatography (15% EtOAc in hexanes) to provide a yellow oil (45%).
Analytical data matched that reported in literature.[22]



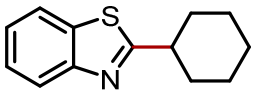
2-Cyclohexyl-4-methylquinoline (33) was prepared using Method C on a 0.200 mmol scale. The title compound was isolated by column chromatography (5% EtOAc in hexanes) to provide a colorless oil (81%).
Analytical data matched that reported in literature.[19,23]



4-Cyclohexyl-2,6-dimethylpyridine (34) was prepared using Method C on a 0.200 mmol scale. The title compound was isolated by column chromatography (30% EtOAc in hexanes) to provide yellow oil (48%).
Analytical data matched that reported in literature.[23]



2-Cyclohexyl-4,6-dimethylpyridine (35) was prepared using Method C on a 0.200 mmol scale. The title compound was isolated by column chromatography (10% EtOAc in hexanes) to provide a colorless oil (20%).
Analytical data matched that reported in literature.[24]



2-Cyclohexylbenzo[d]thiazole (36) was prepared using Method C on a 0.200 mmol scale. The title compound was isolated by column chromatography (1% EtOAc in hexanes) to provide a colorless oil (60%).
Analytical data matched that reported in literature.[23]

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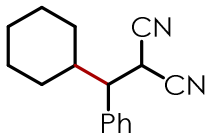
Spectral Data



1

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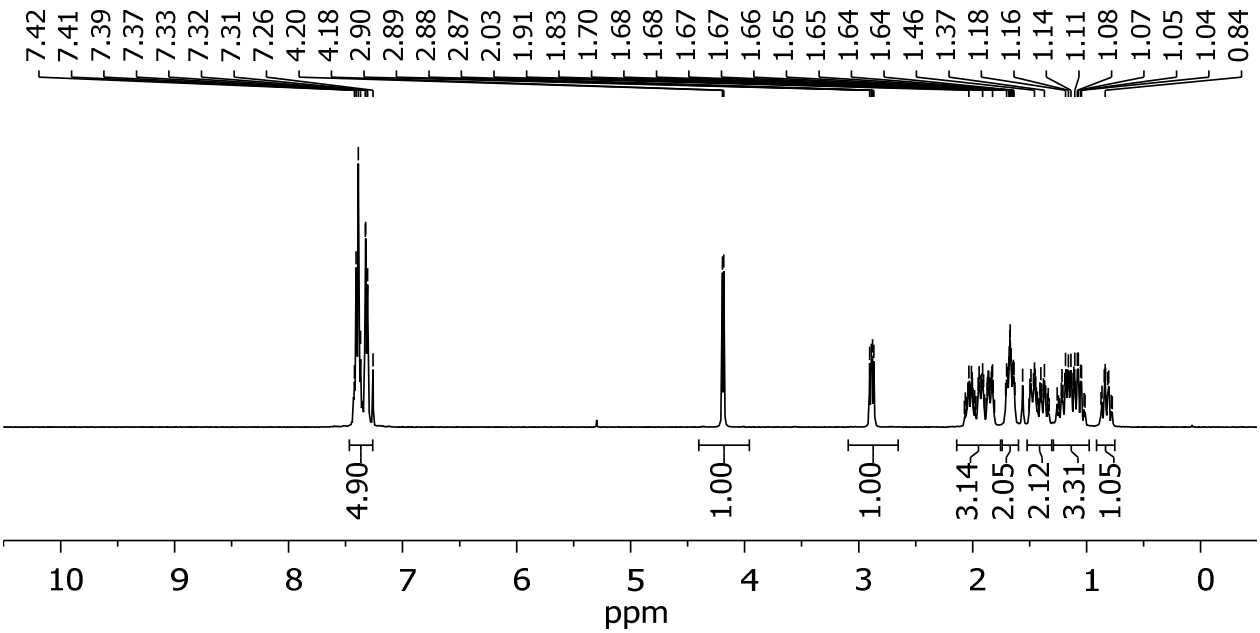

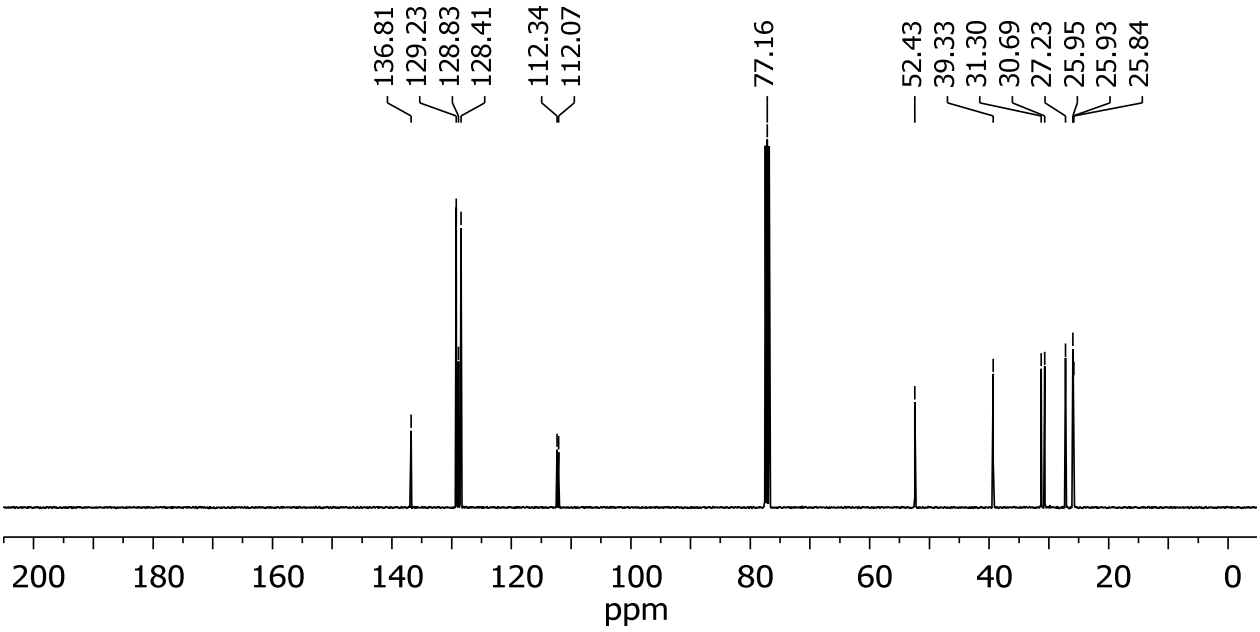

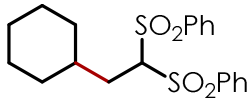

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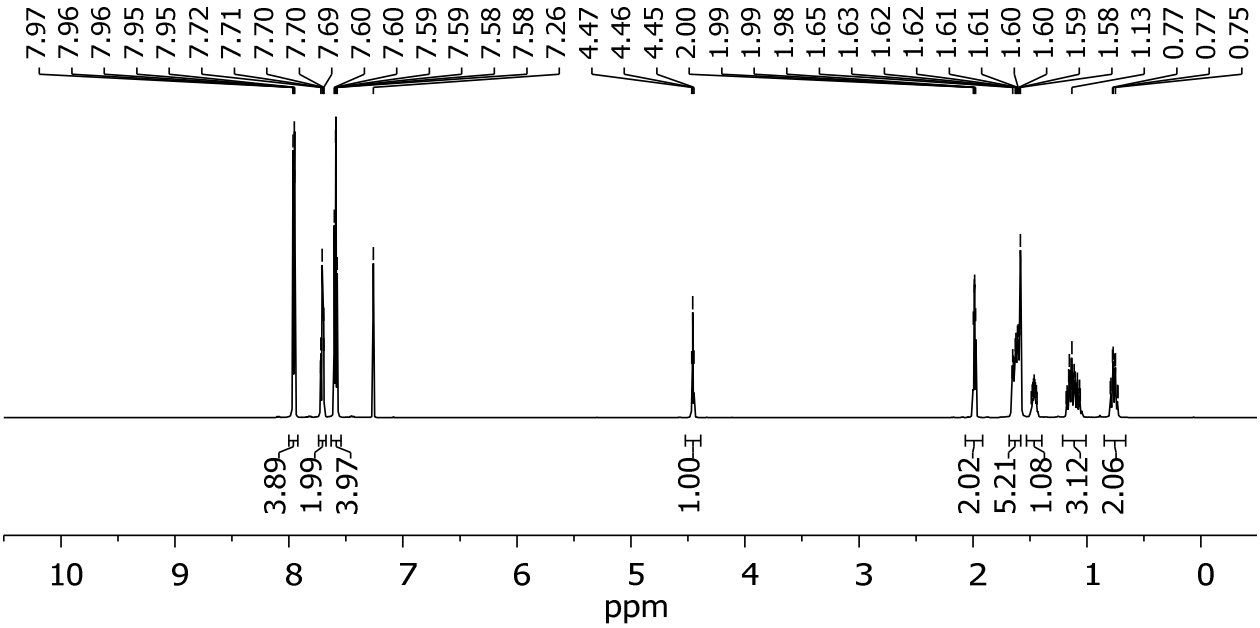

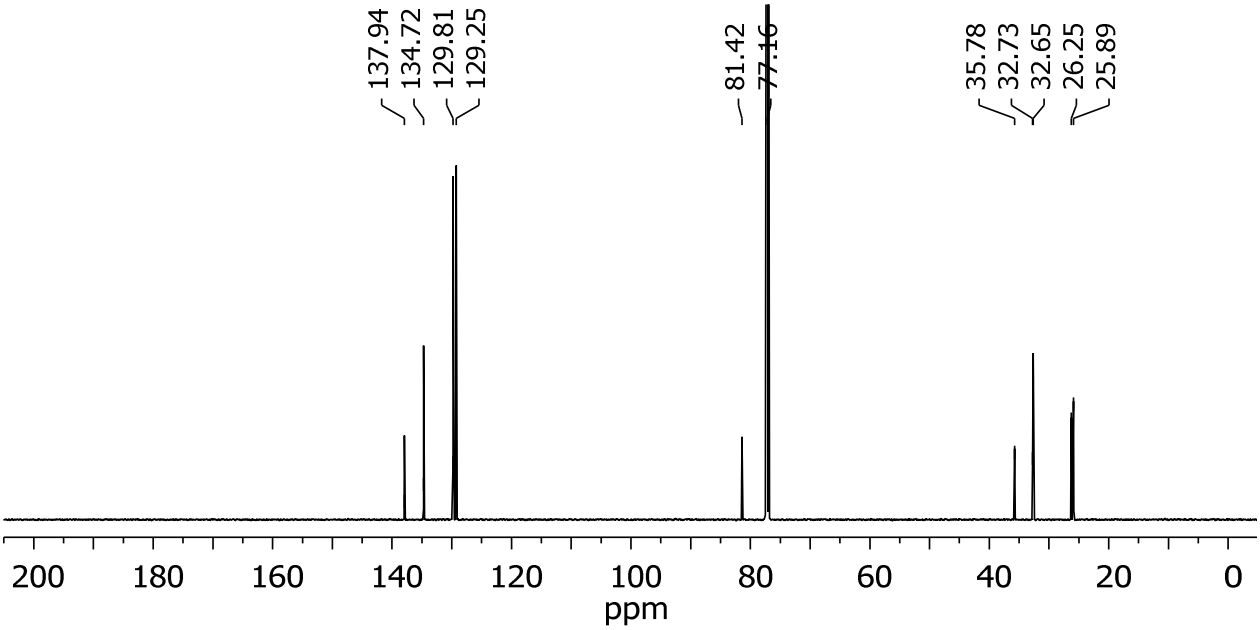

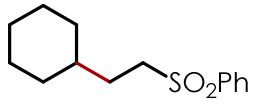

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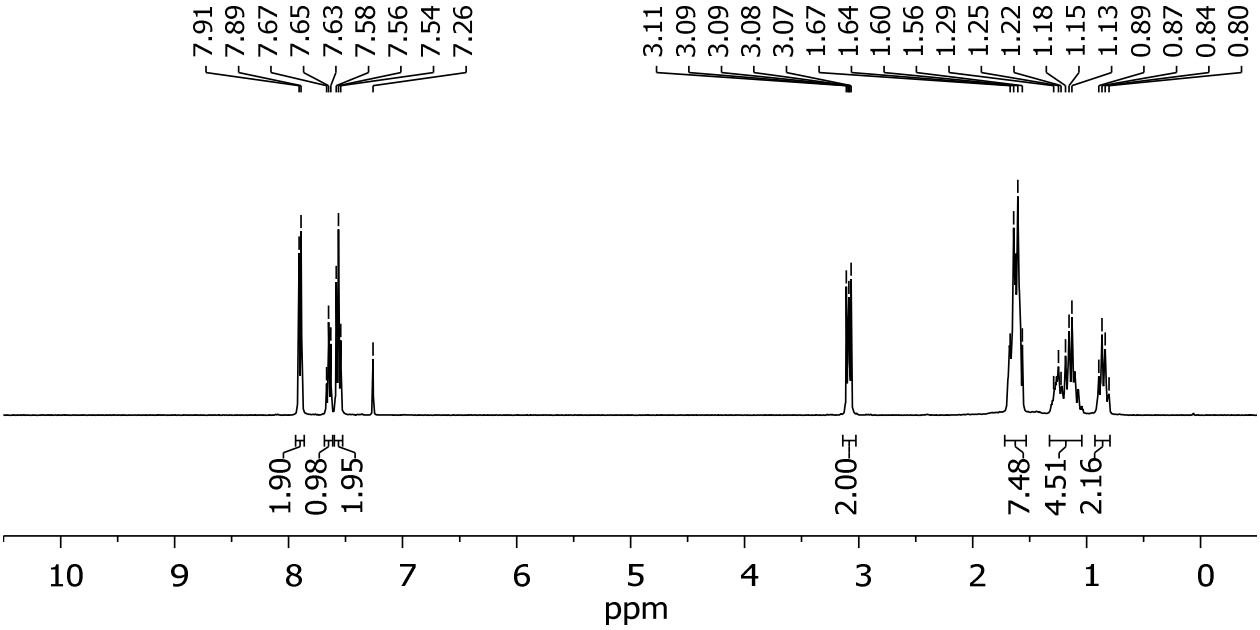

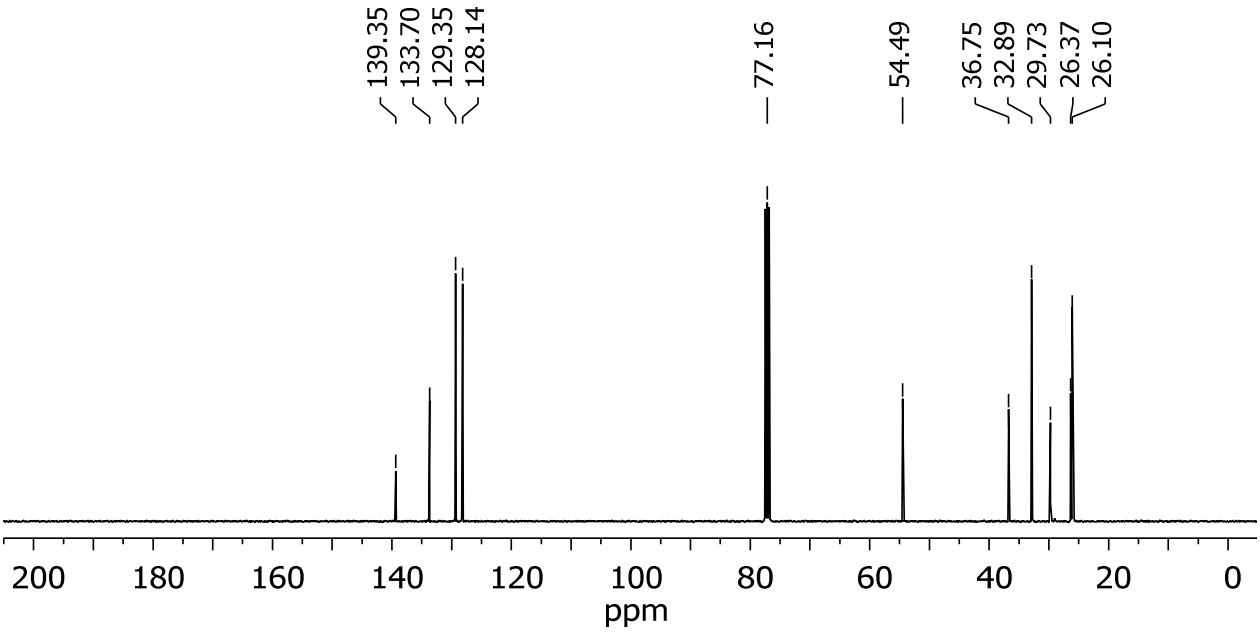

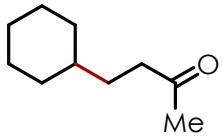

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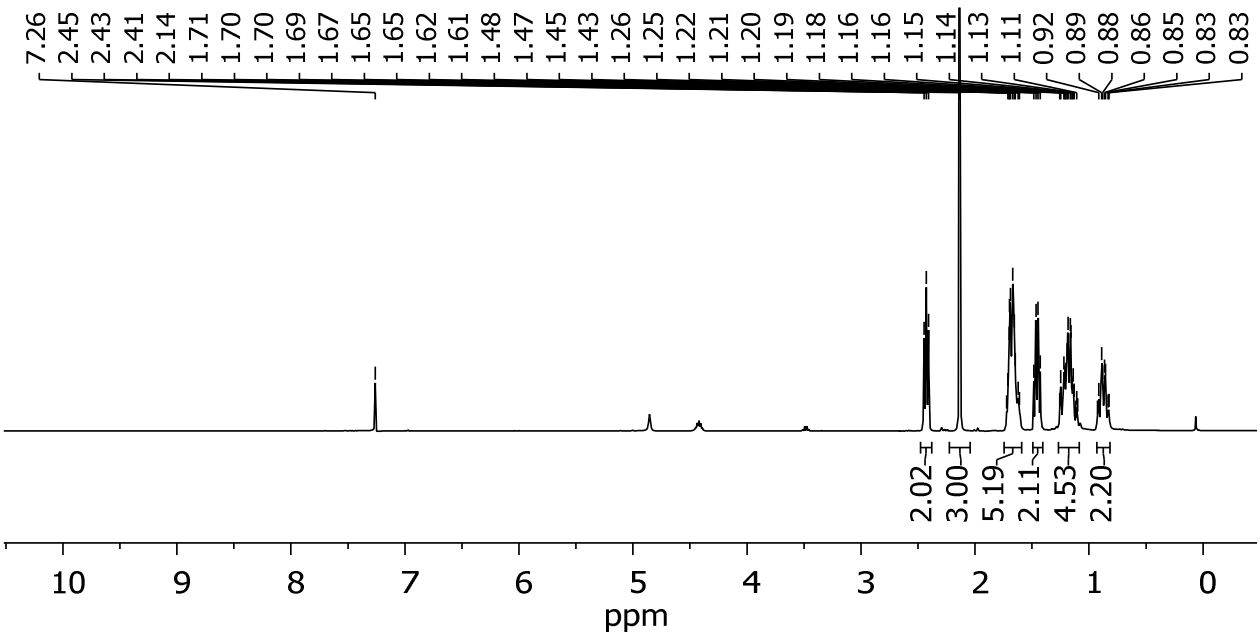

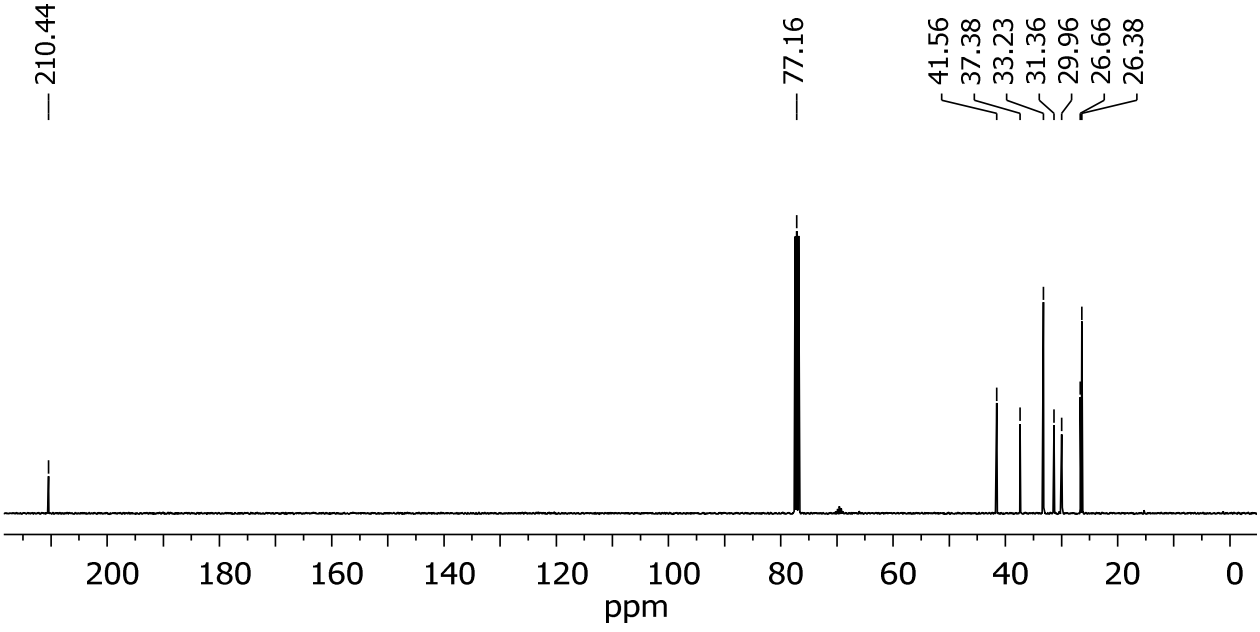

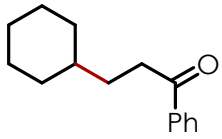

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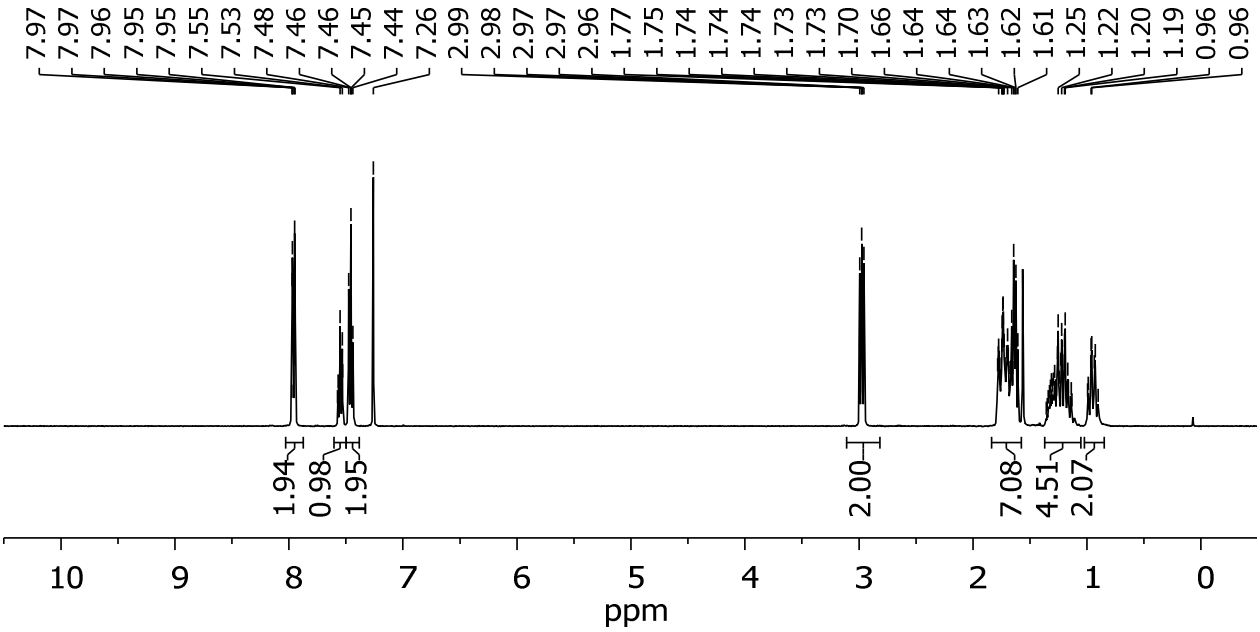

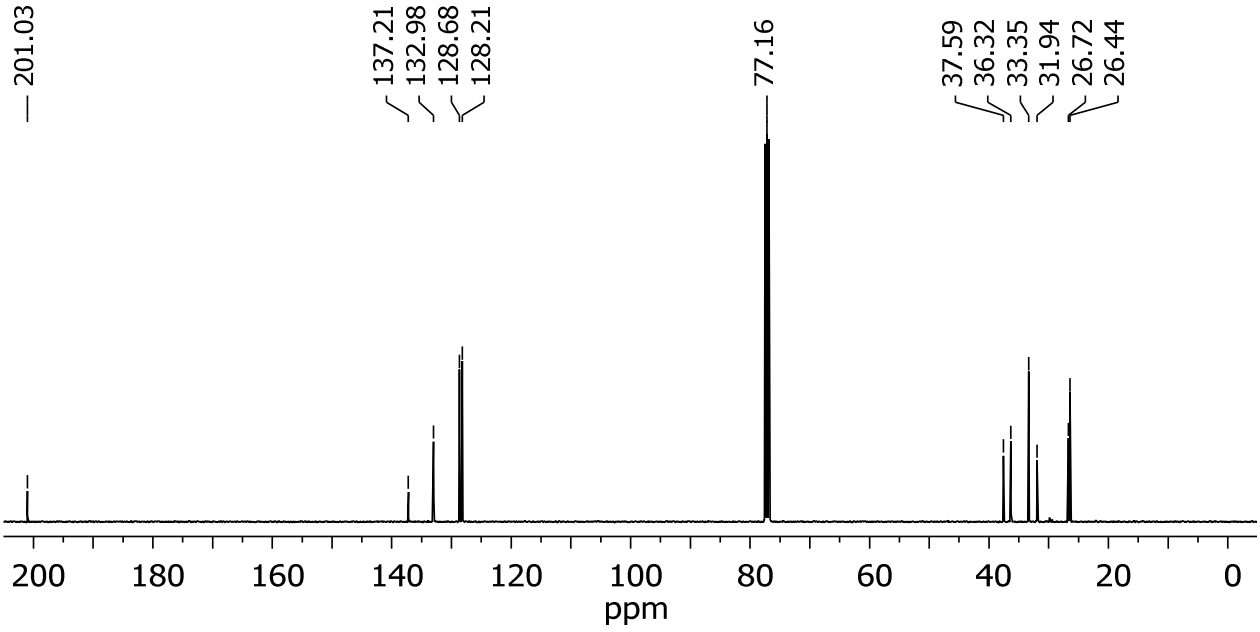

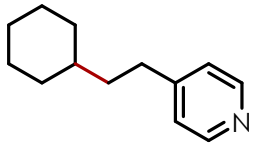

6

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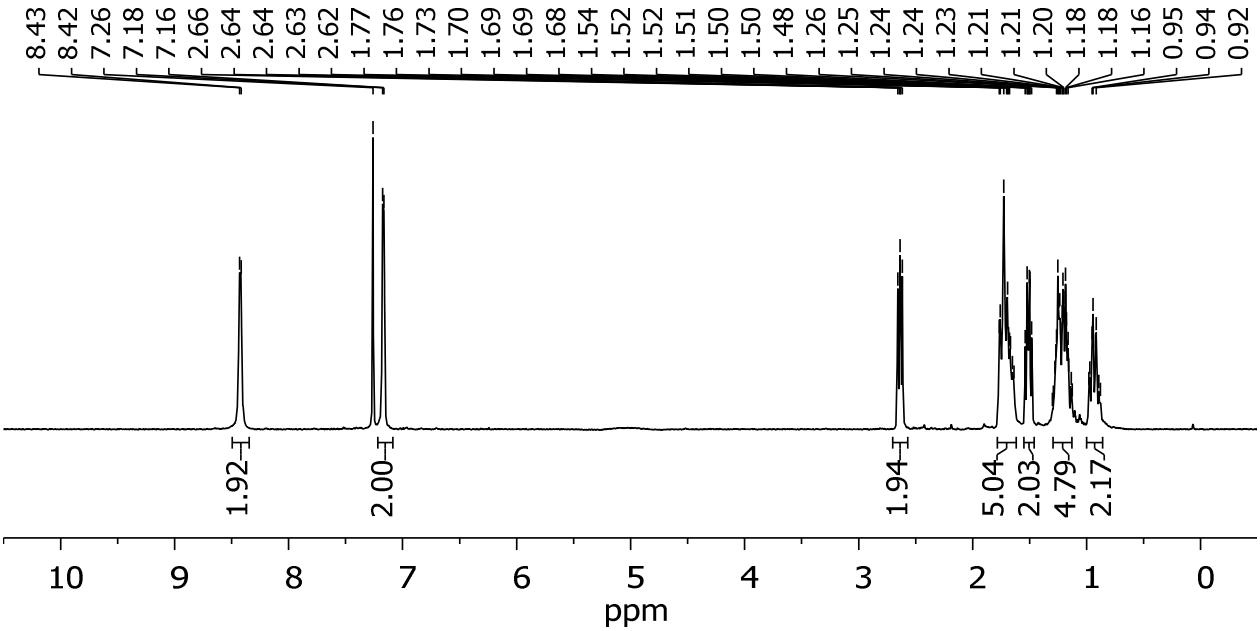
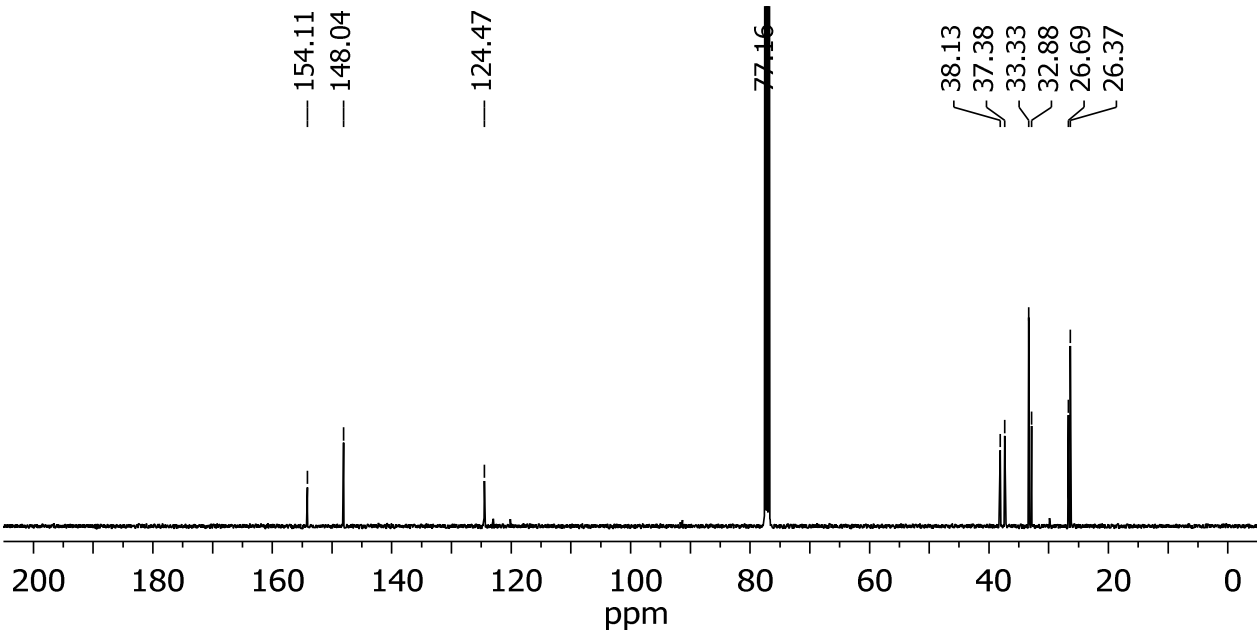
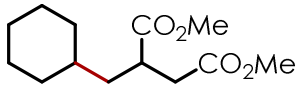
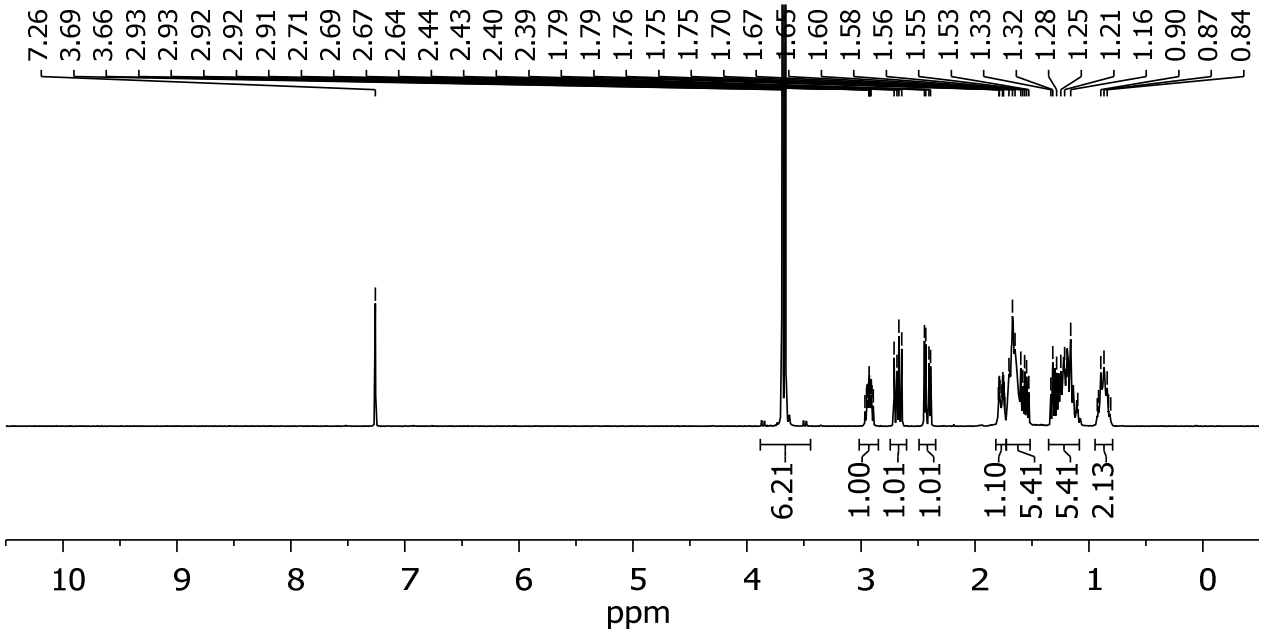


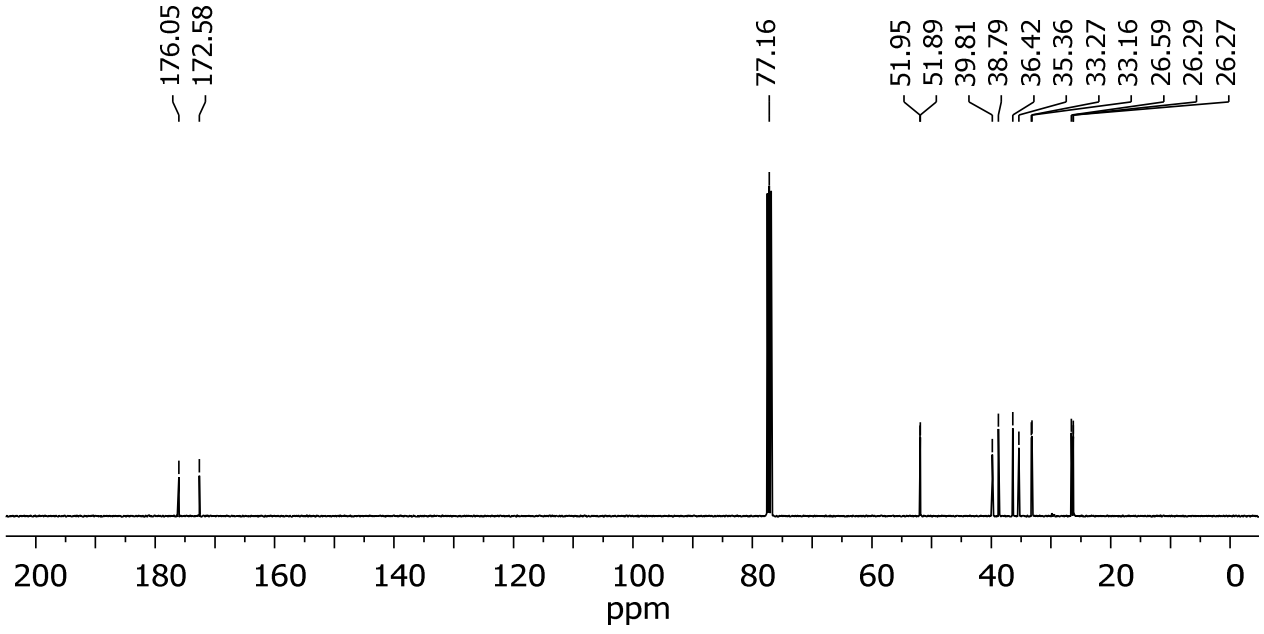


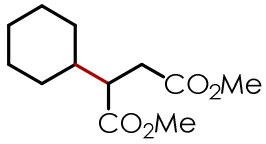


7

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

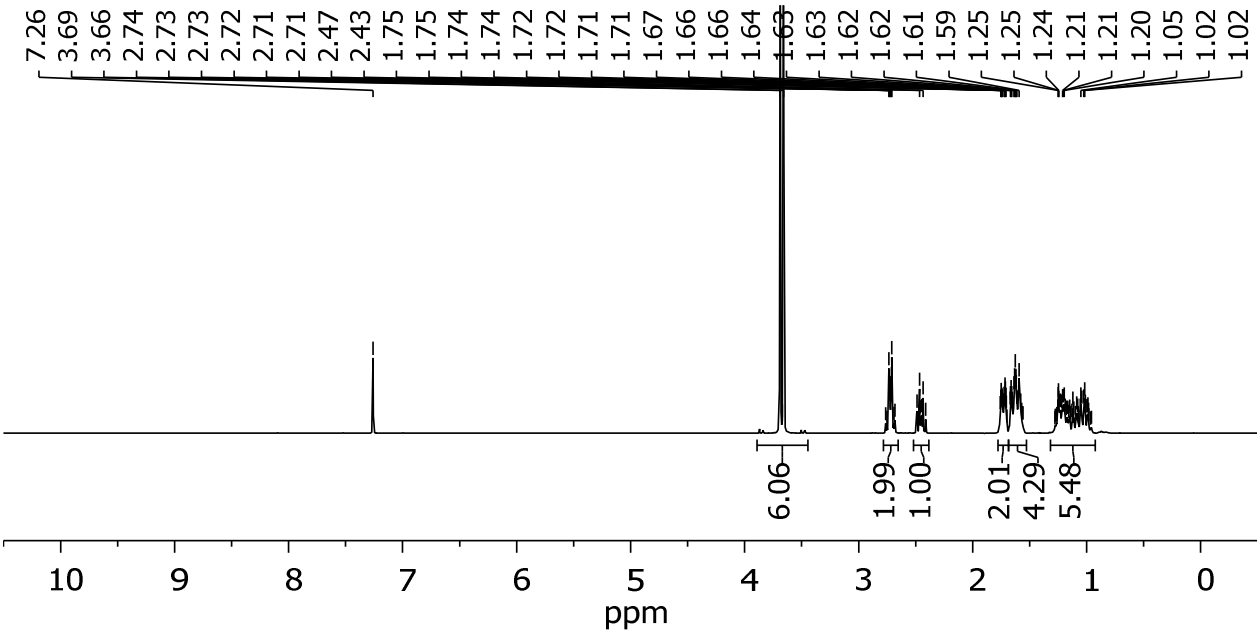


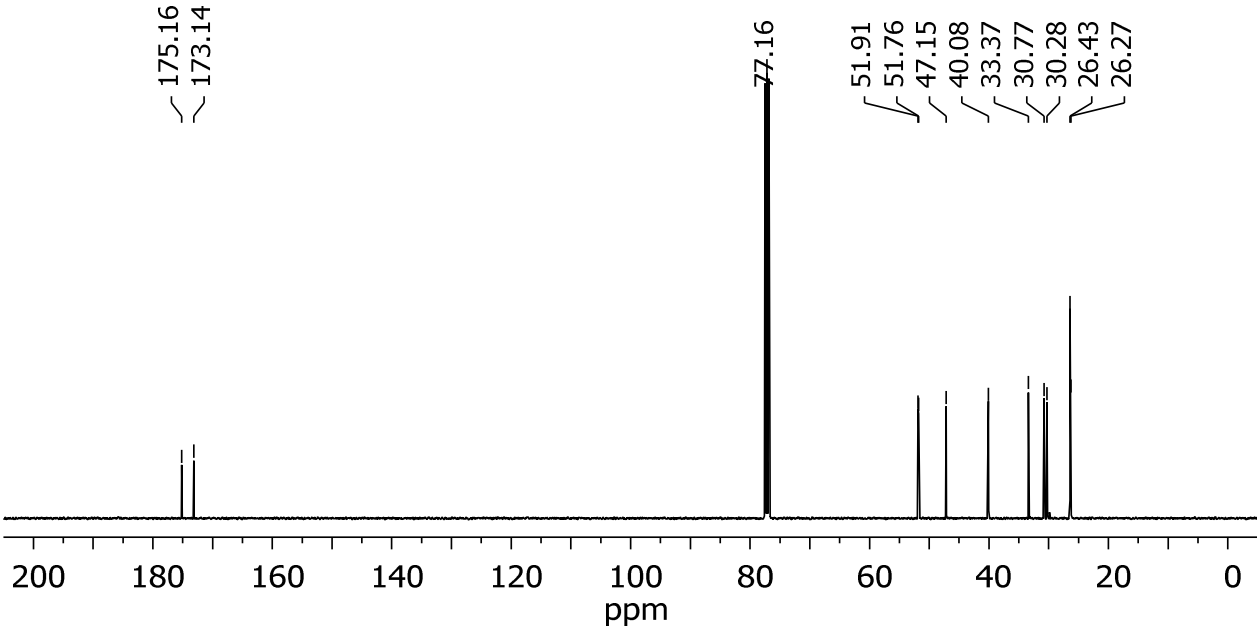


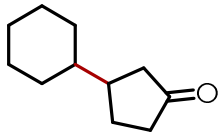


8

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

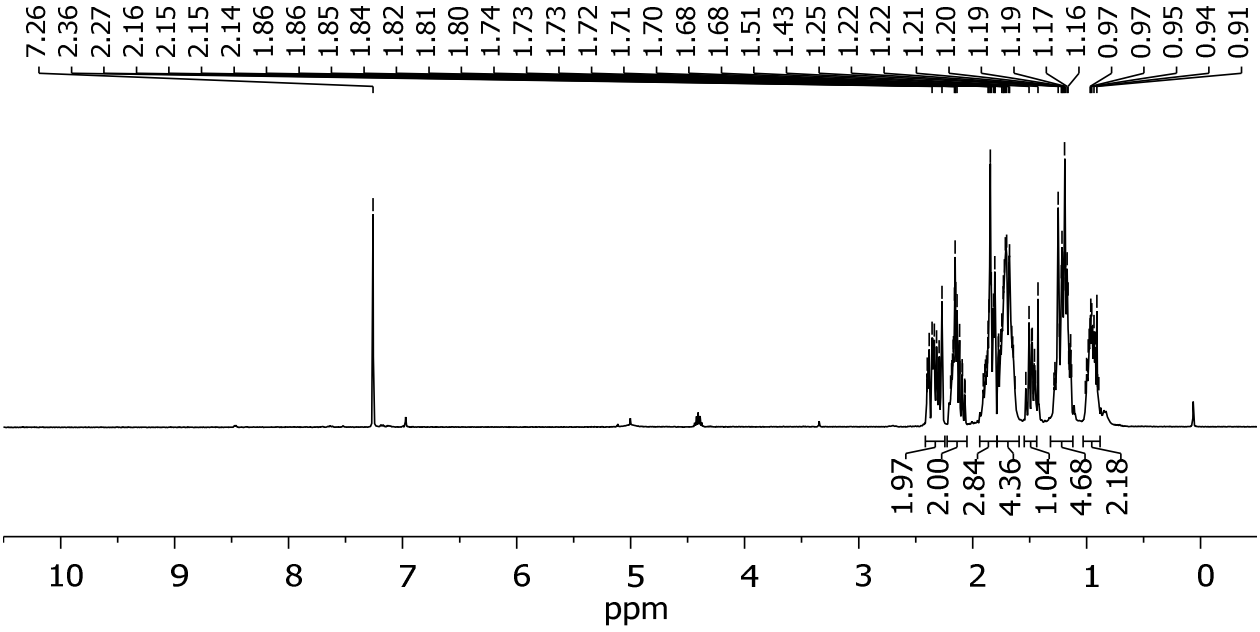


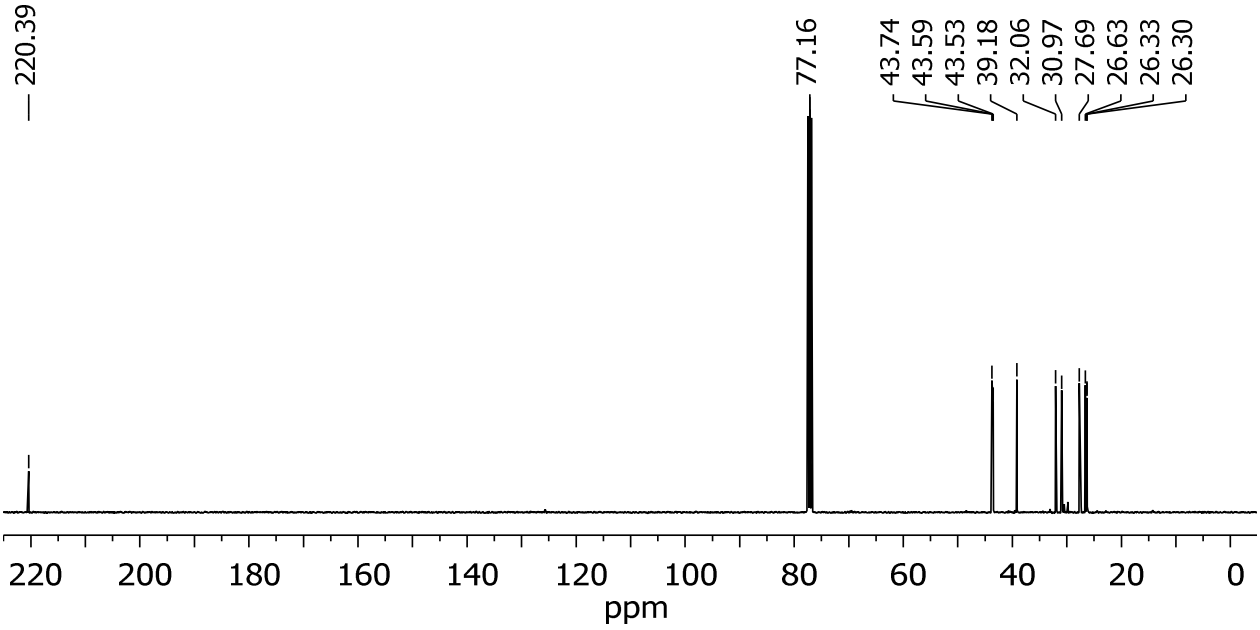


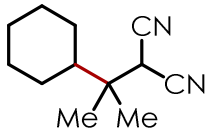


9

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

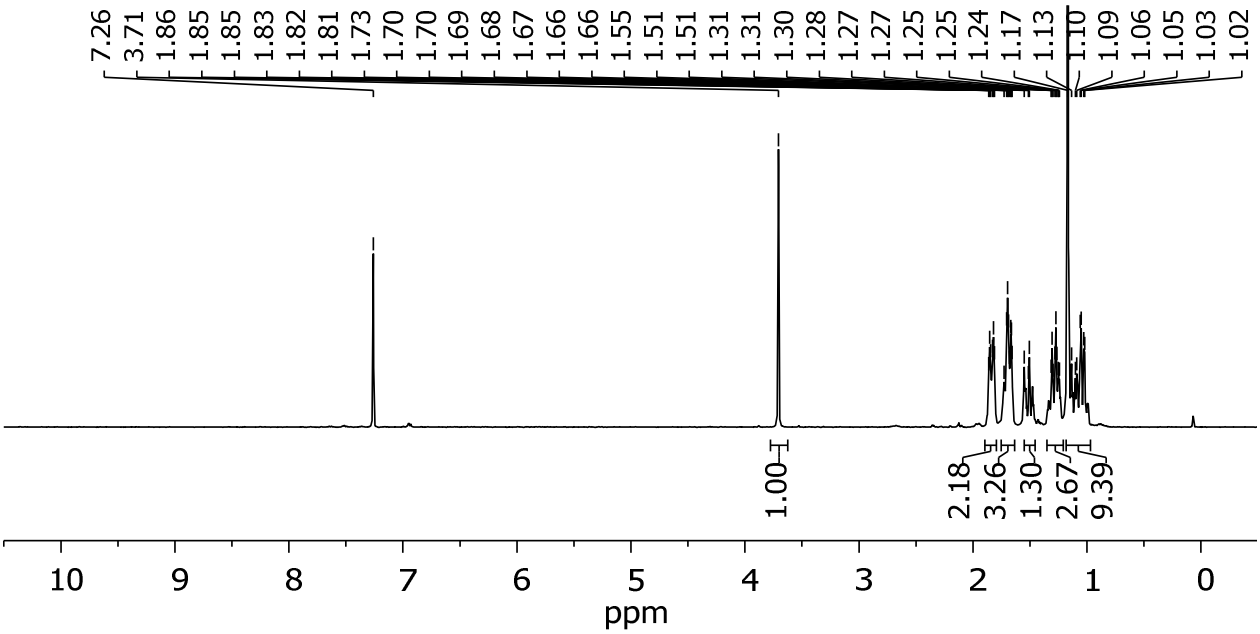


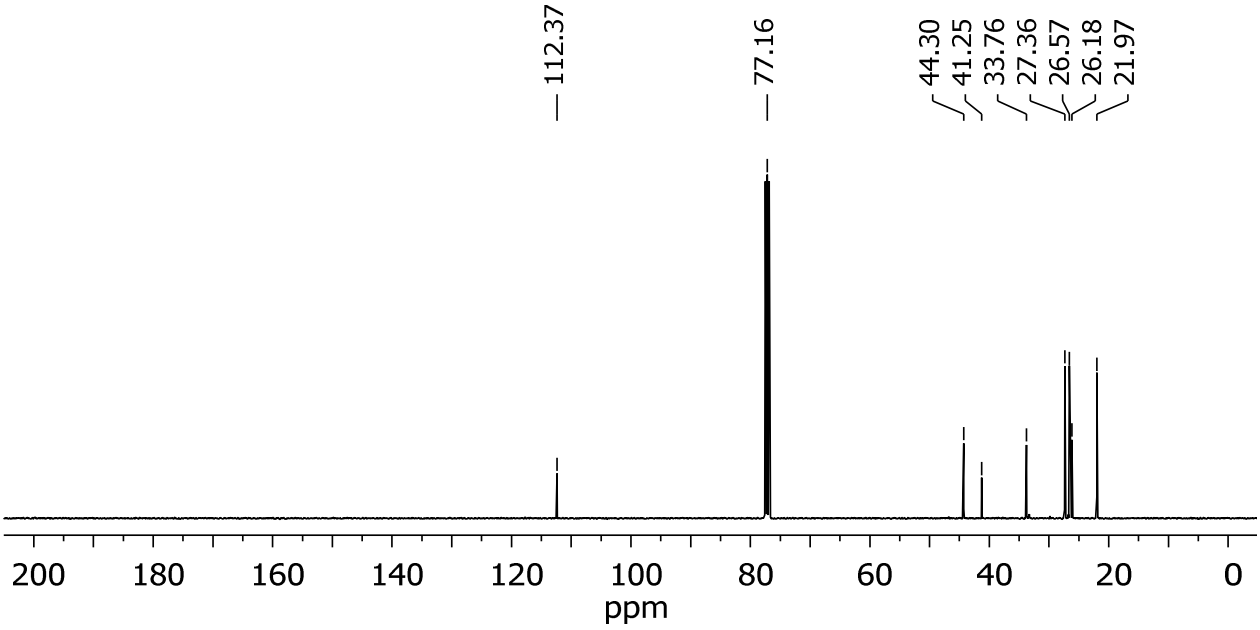


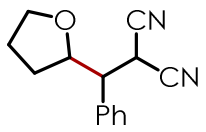


10

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

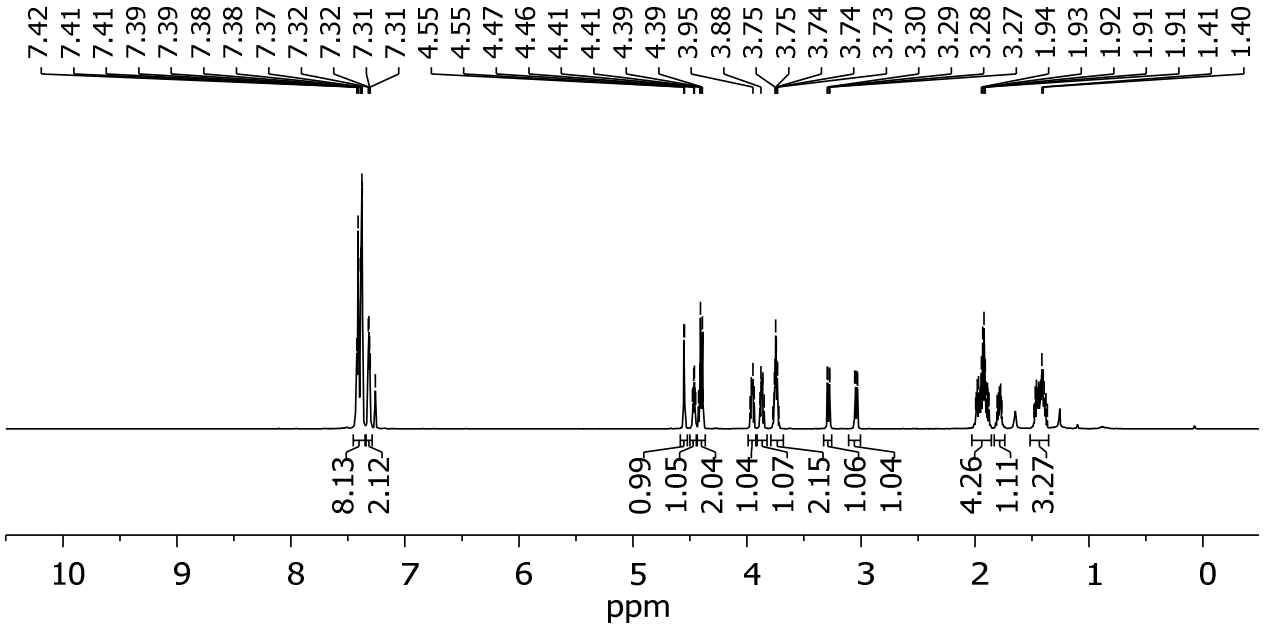


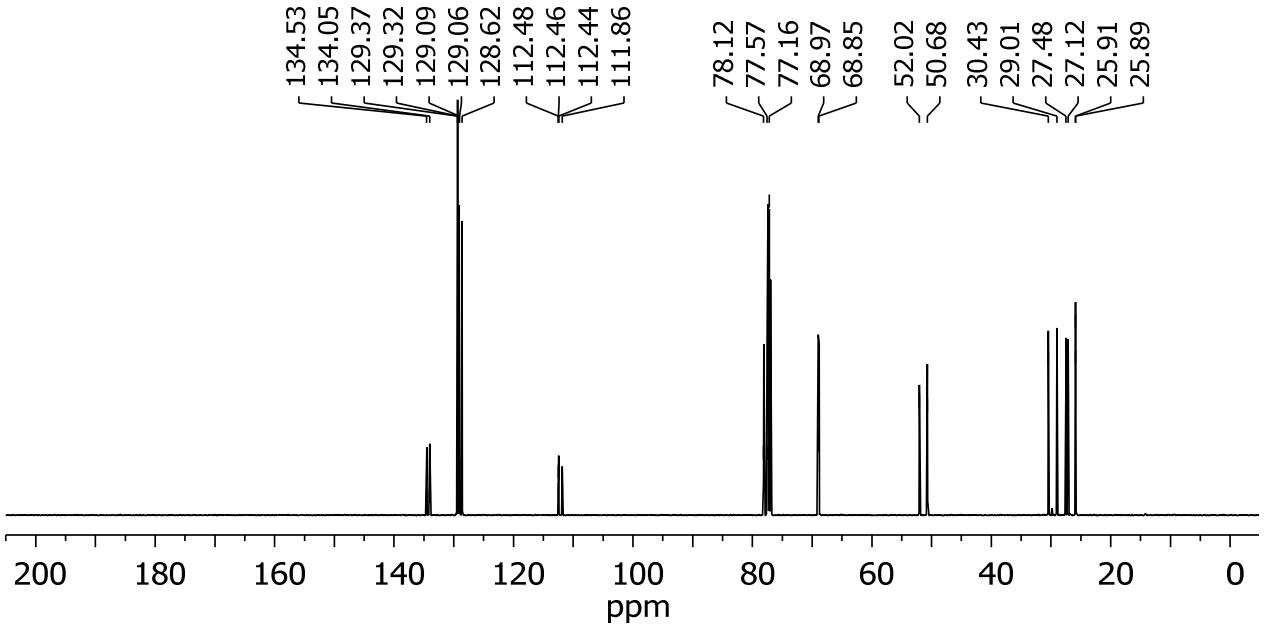


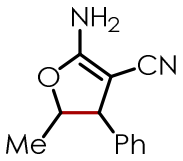


11

($CDCl_3$, ^1H NMR: 600 MHz, ^{13}C NMR: 151 MHz)

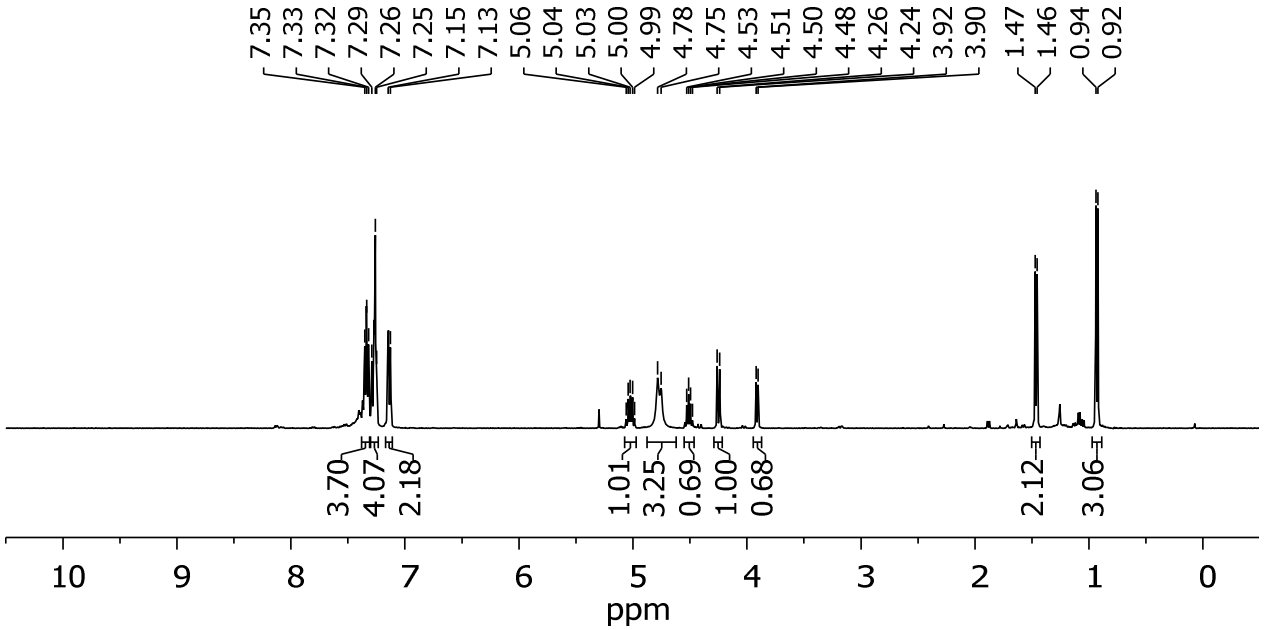


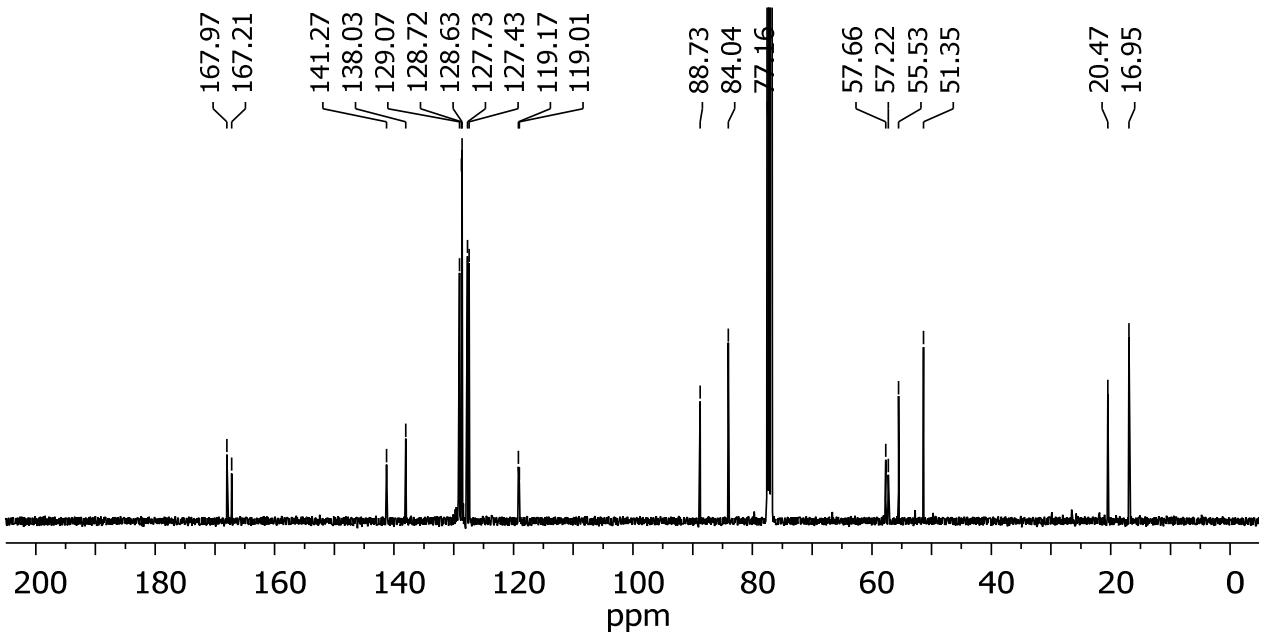


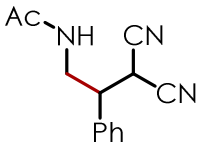


12

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

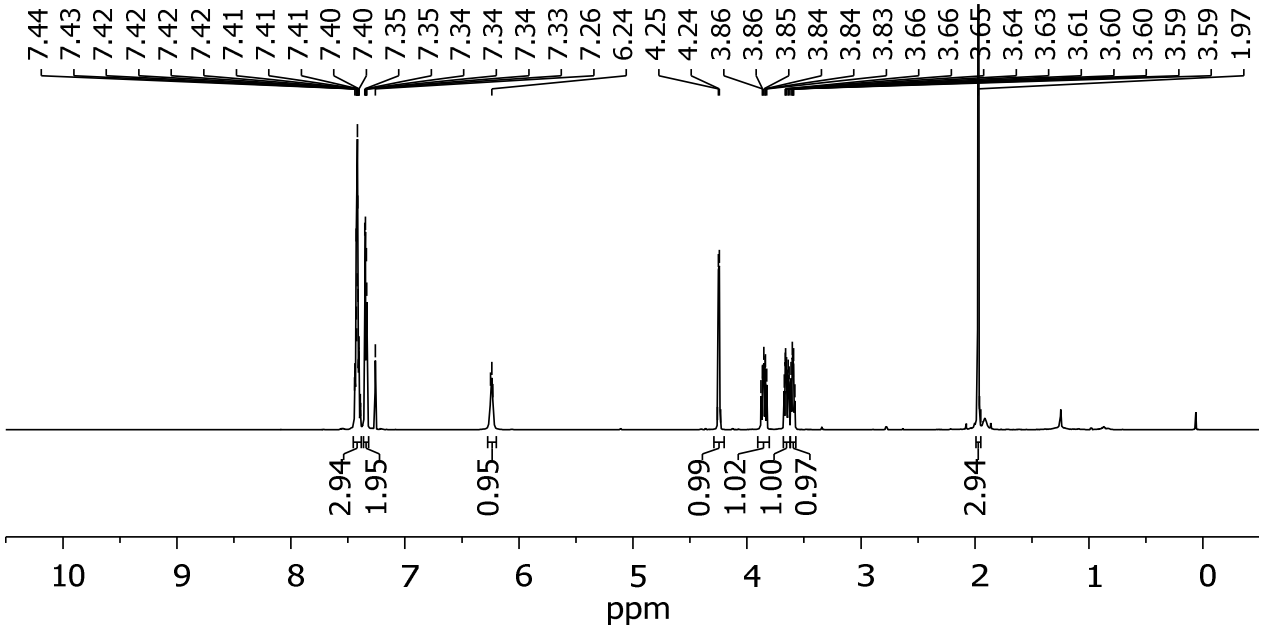


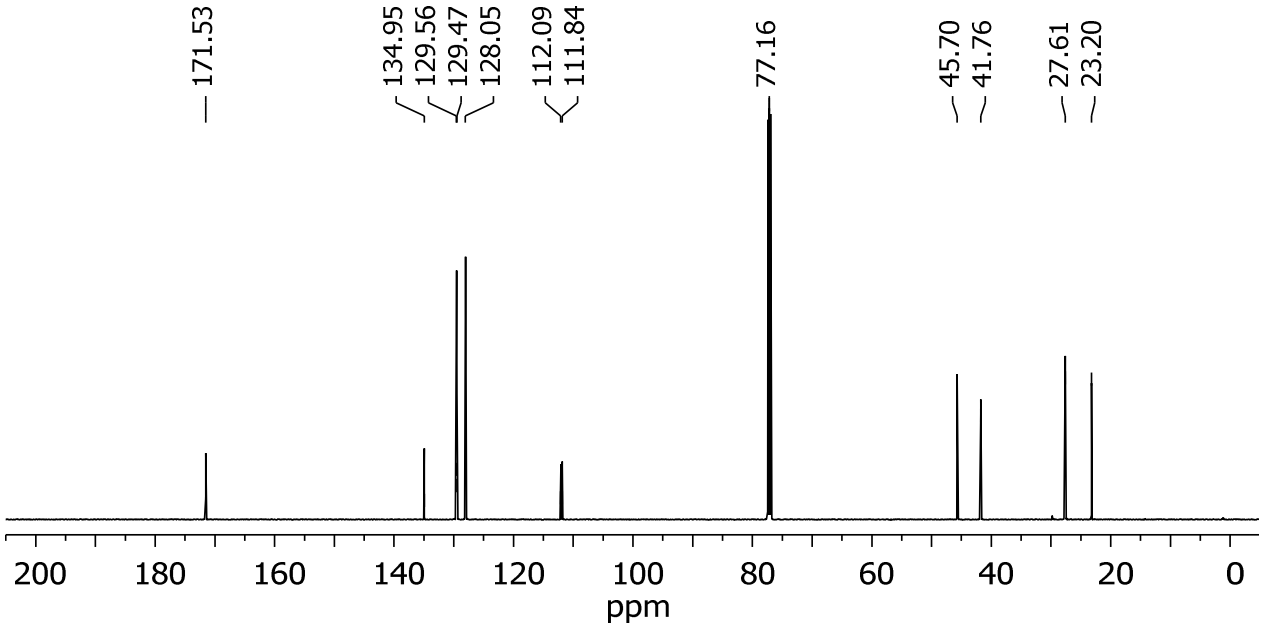


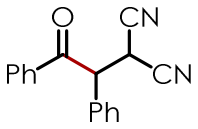


13

($CDCl_3$, ^1H NMR: 600 MHz, ^{13}C NMR: 151 MHz)

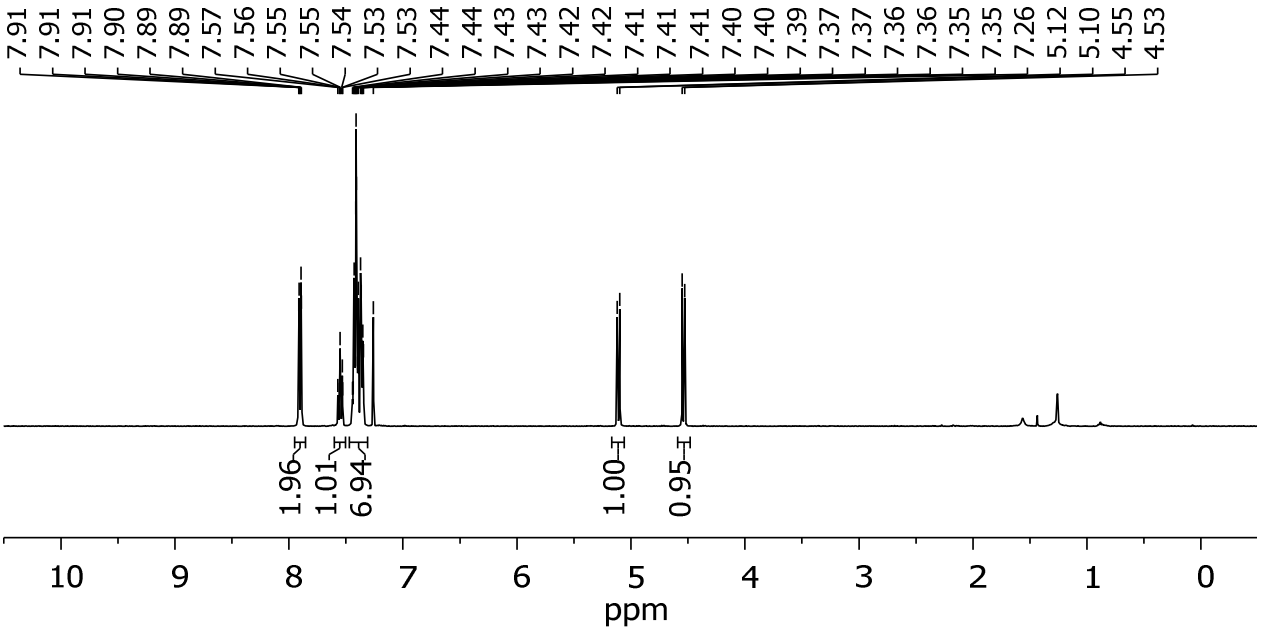


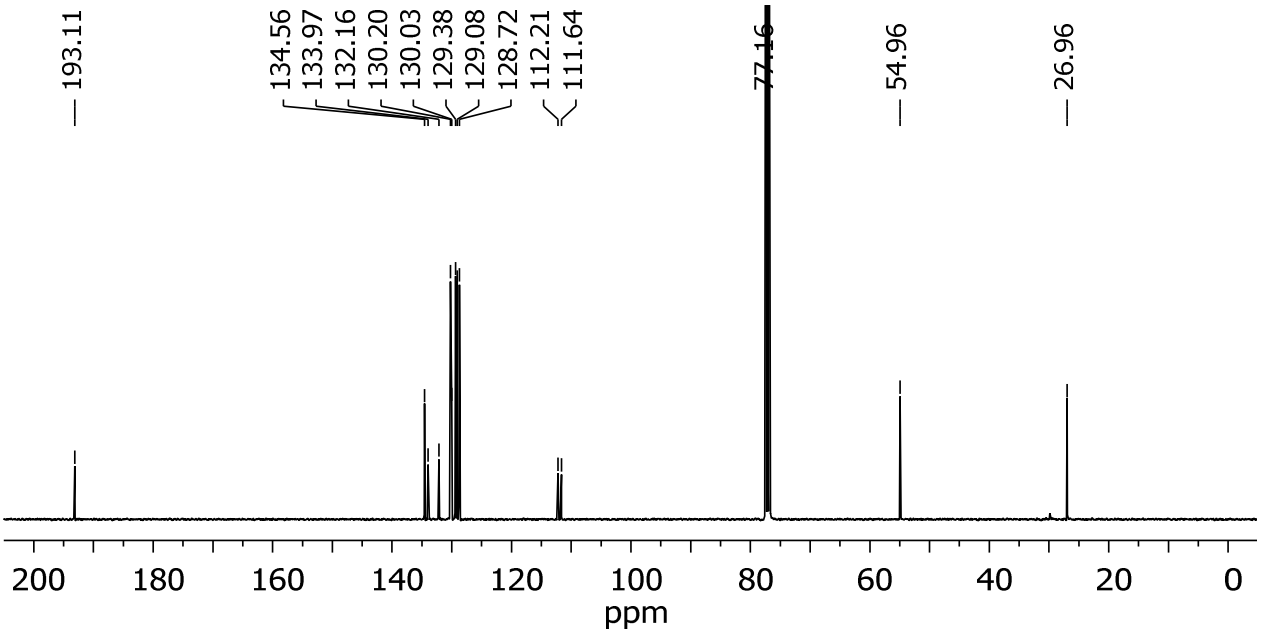


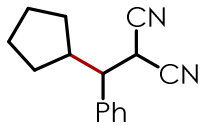


14

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

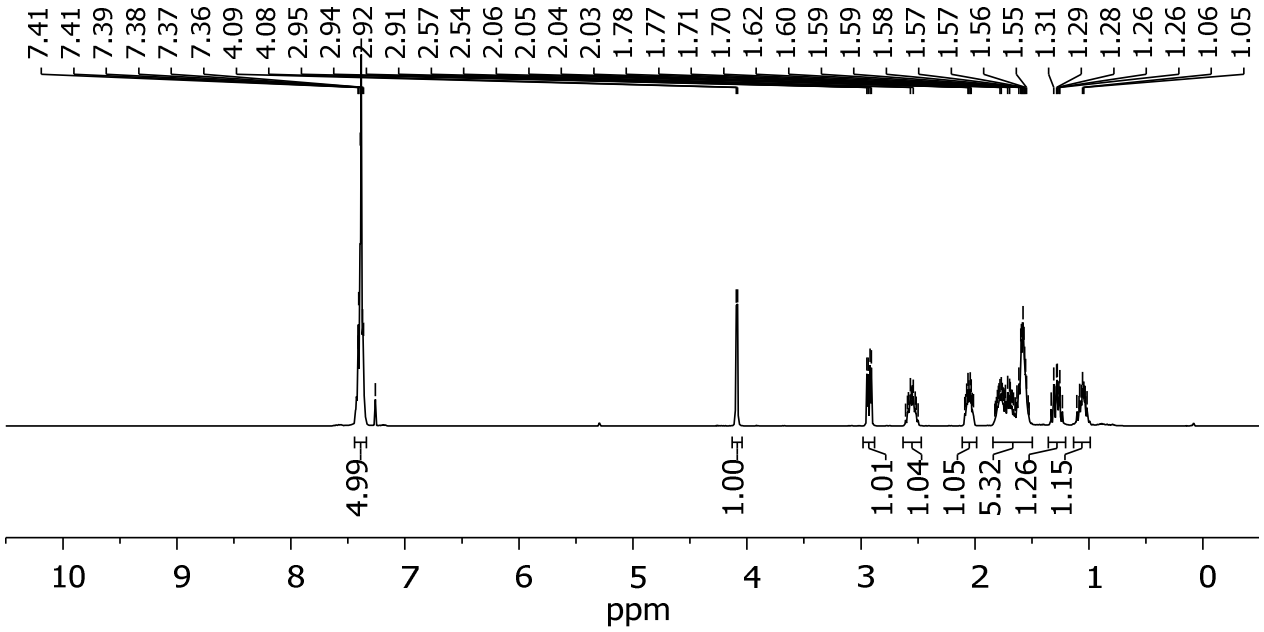


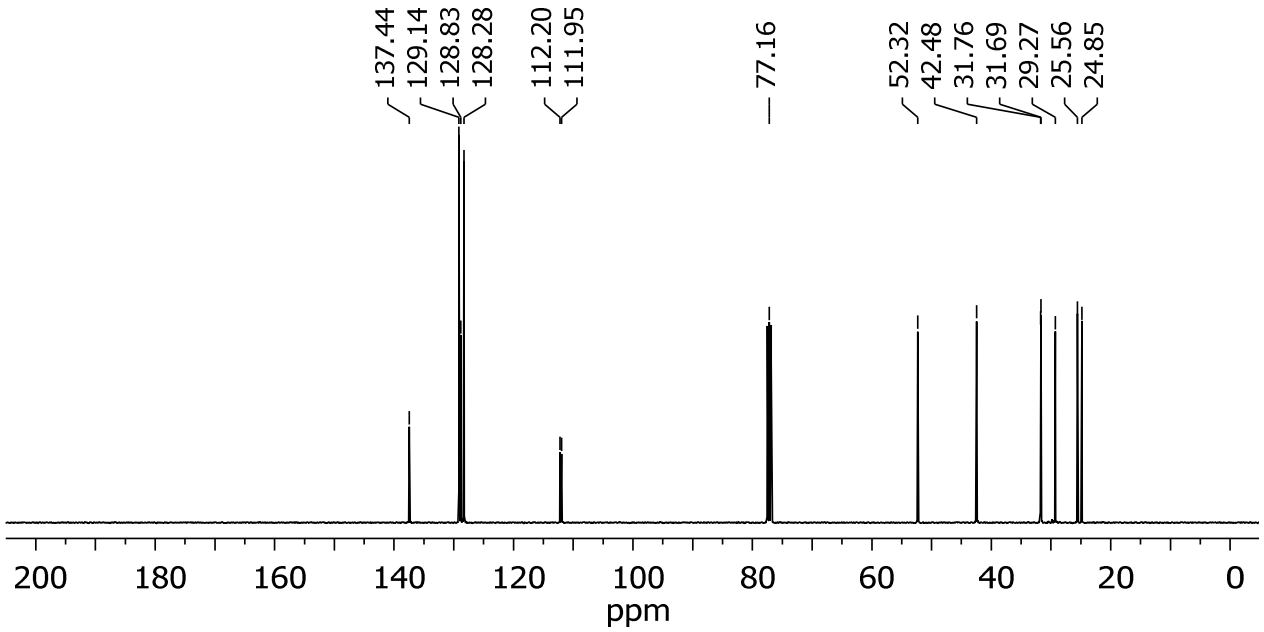


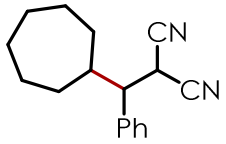


15

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

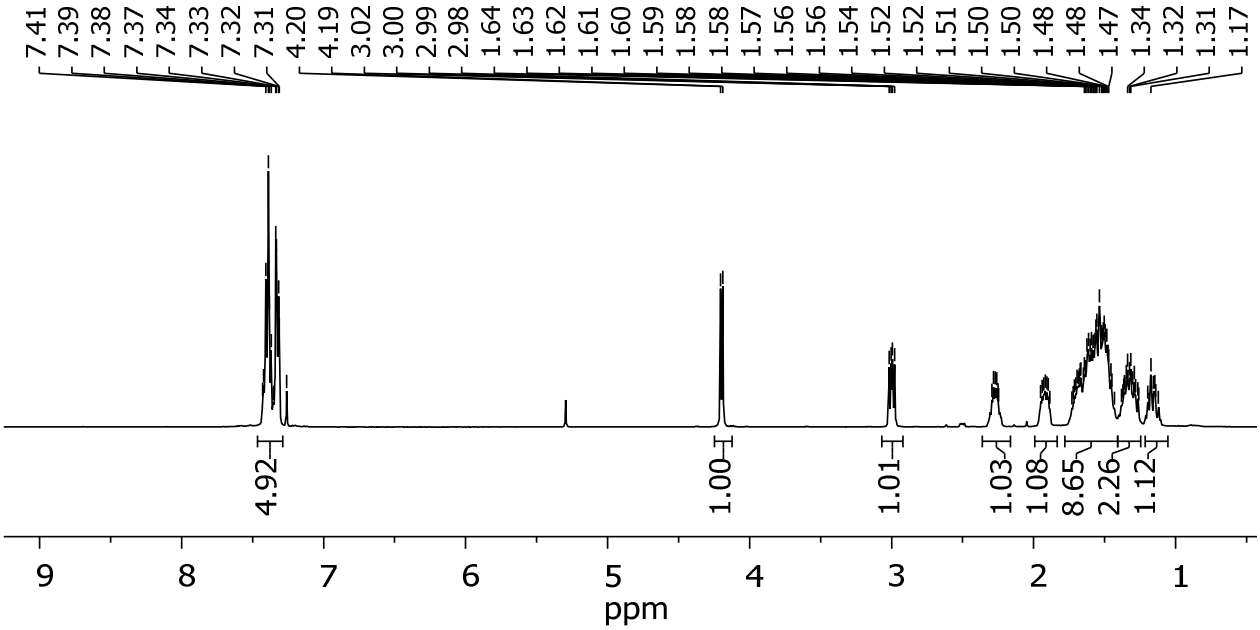


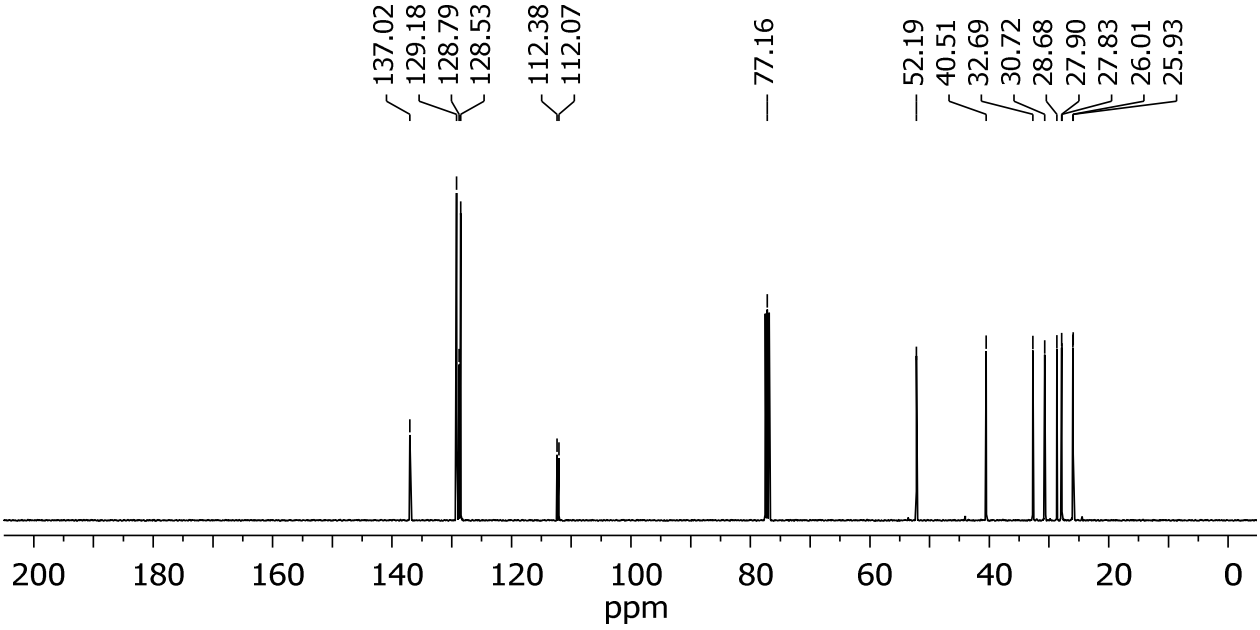




16

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

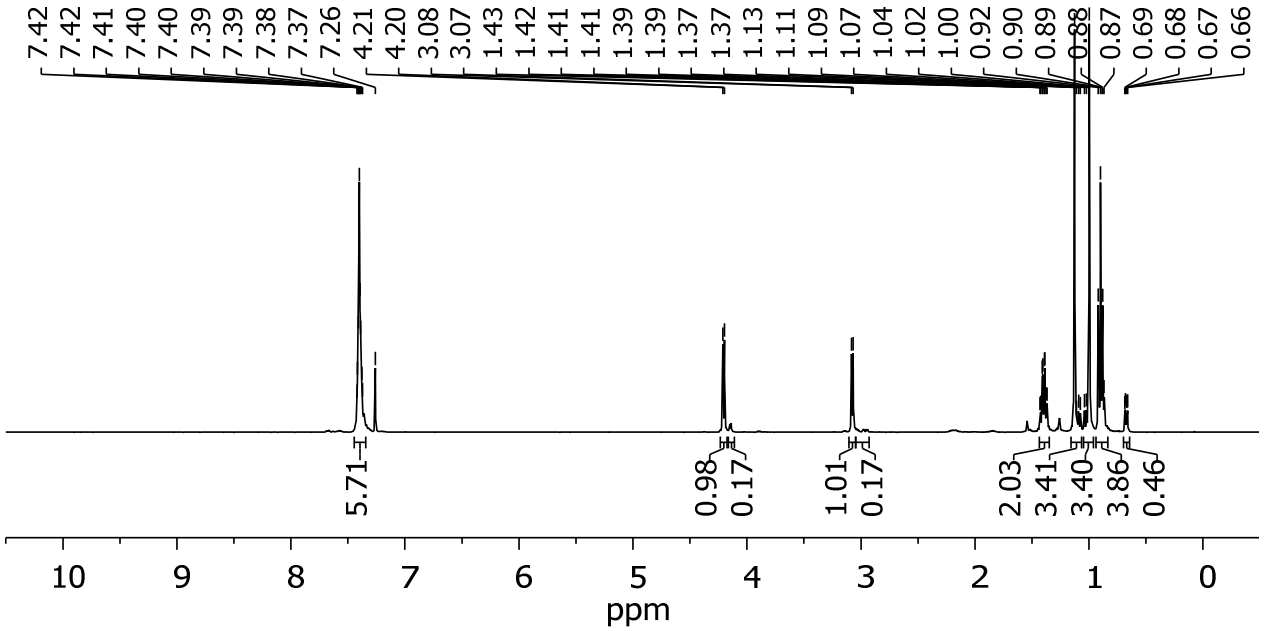


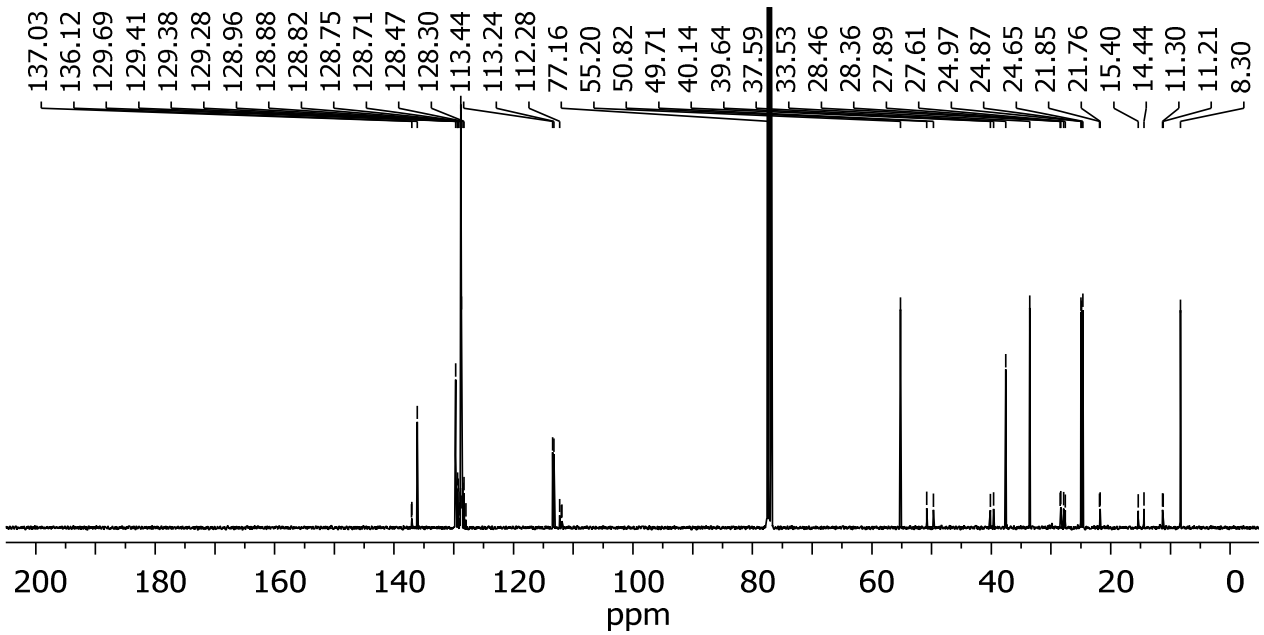


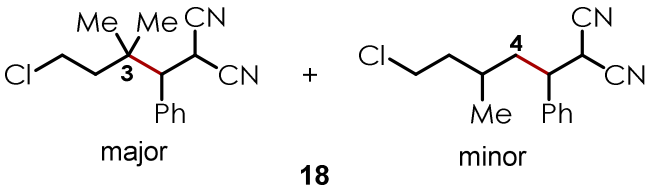
major + minor

17

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

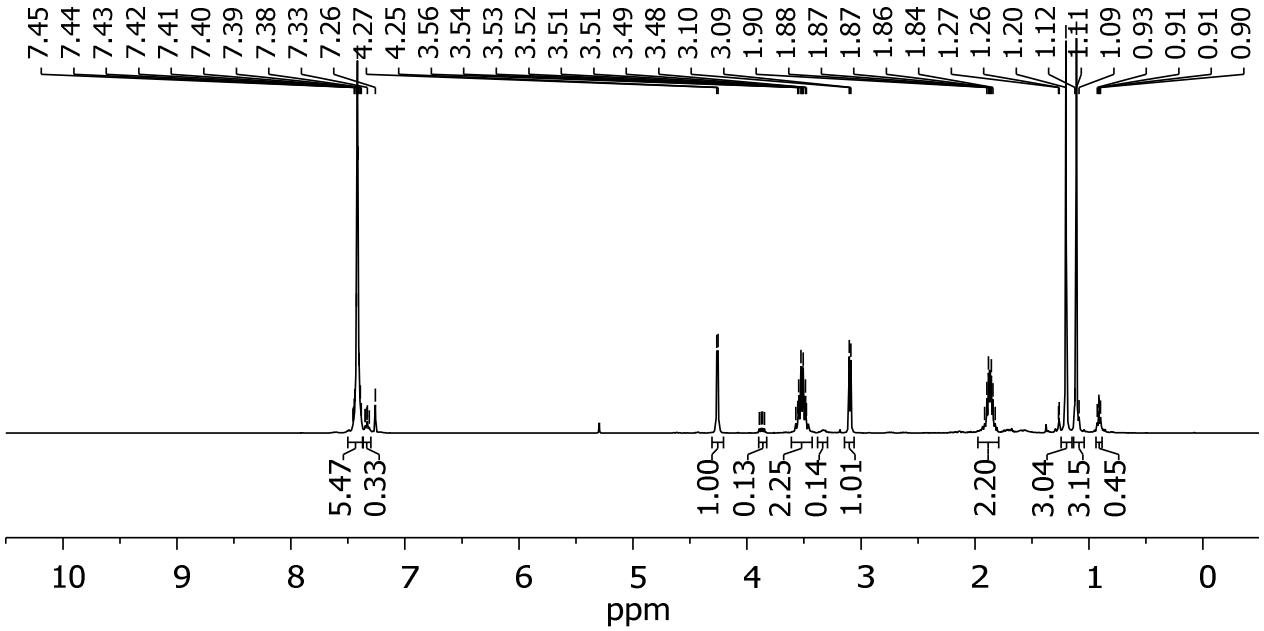


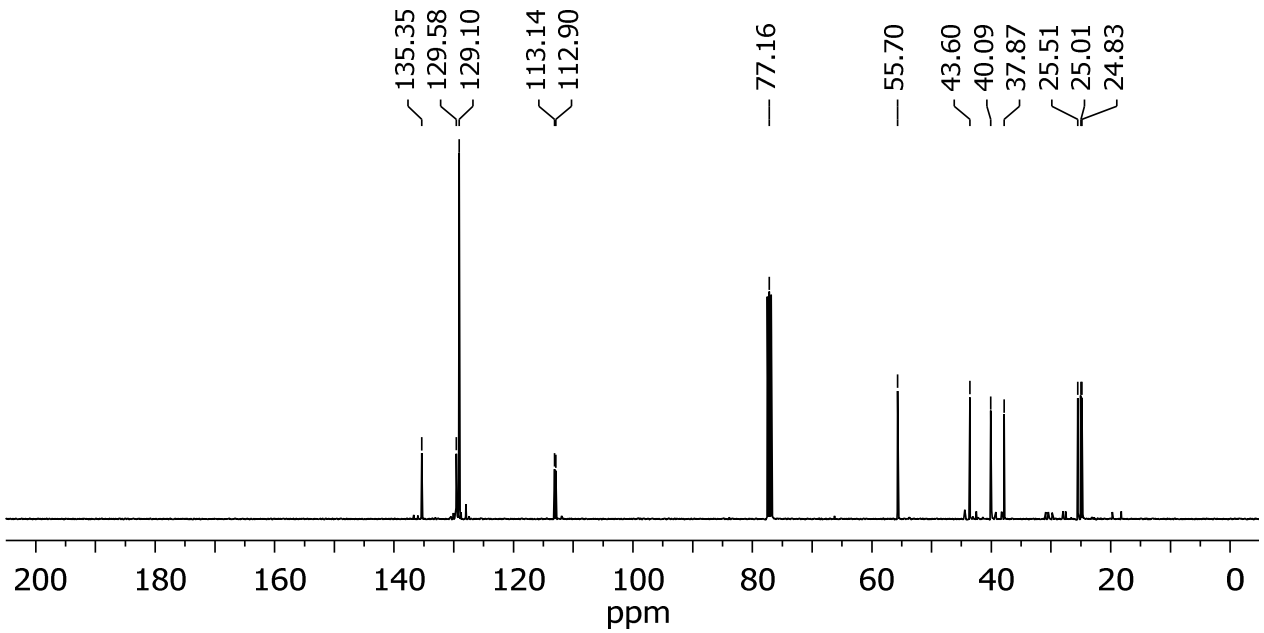


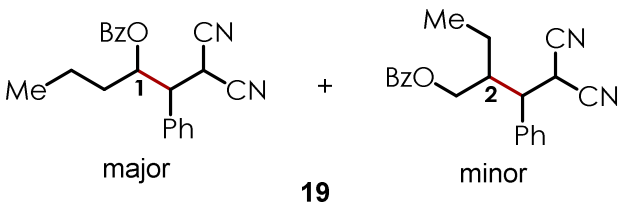


18

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

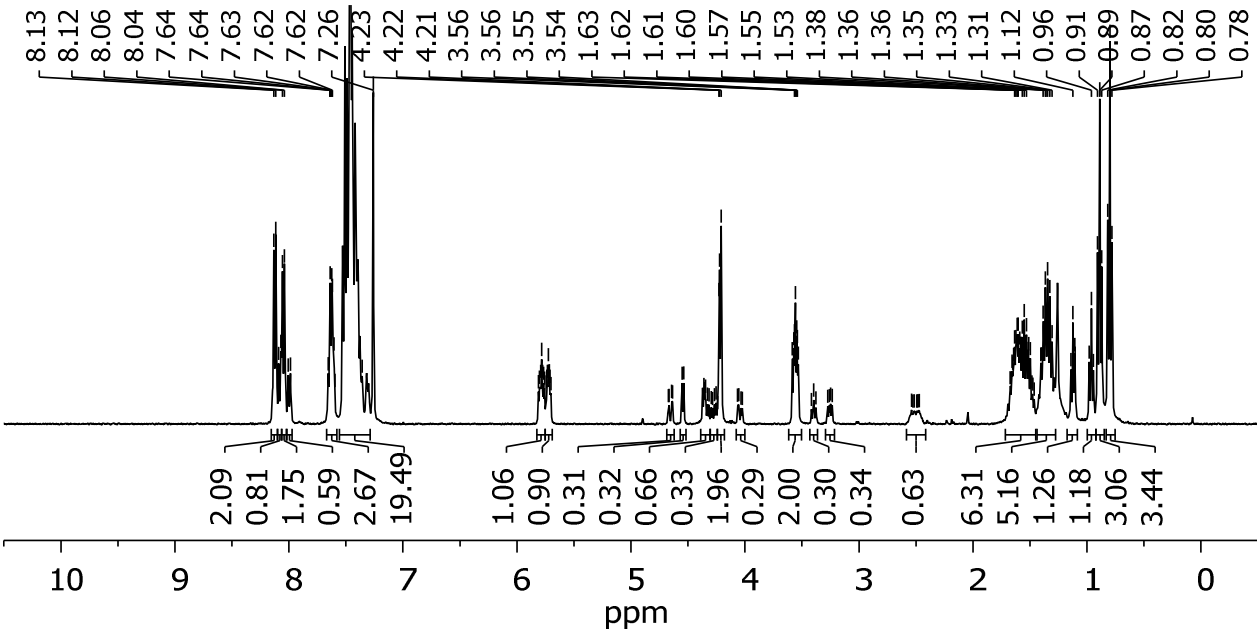


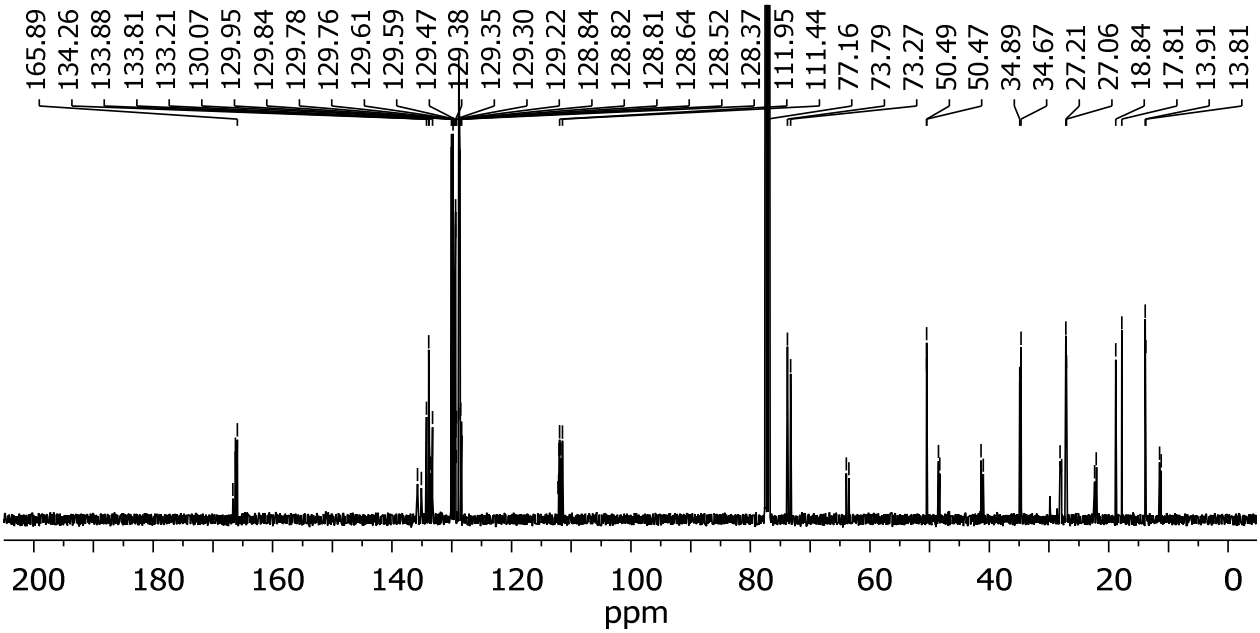


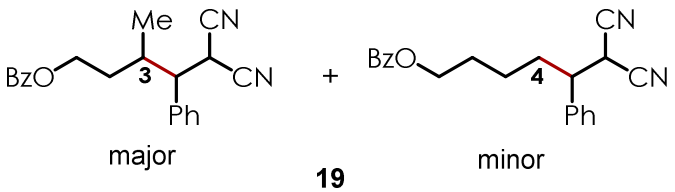


19

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

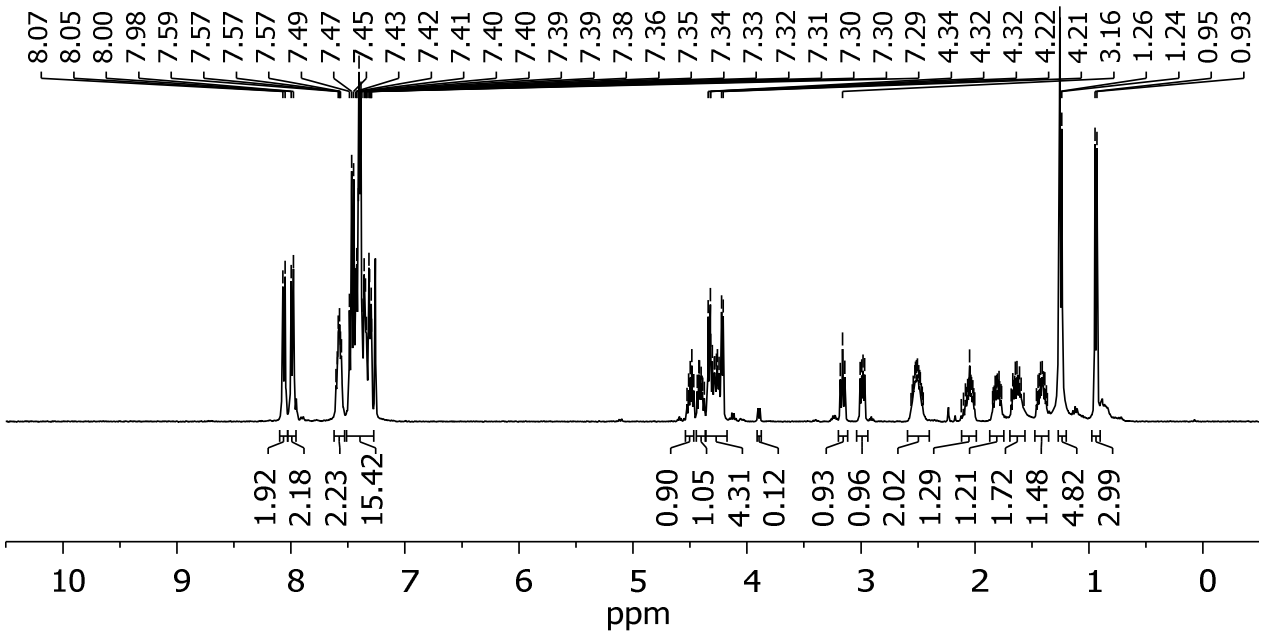


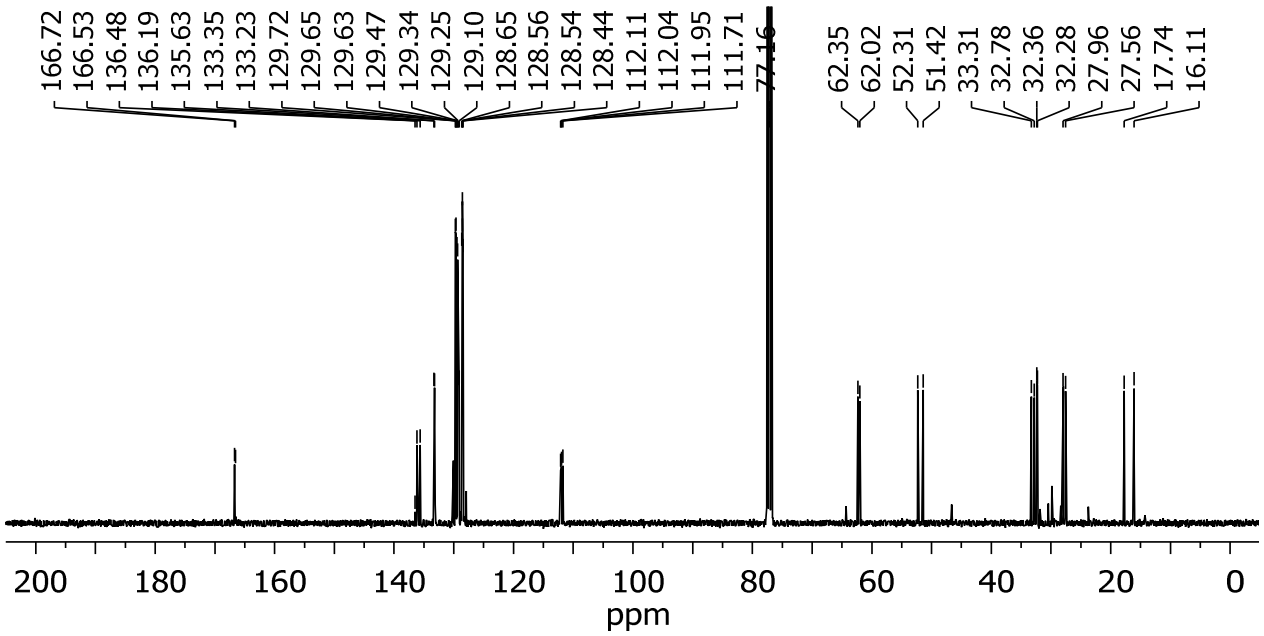


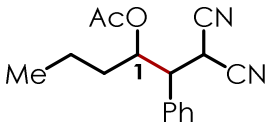


19

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

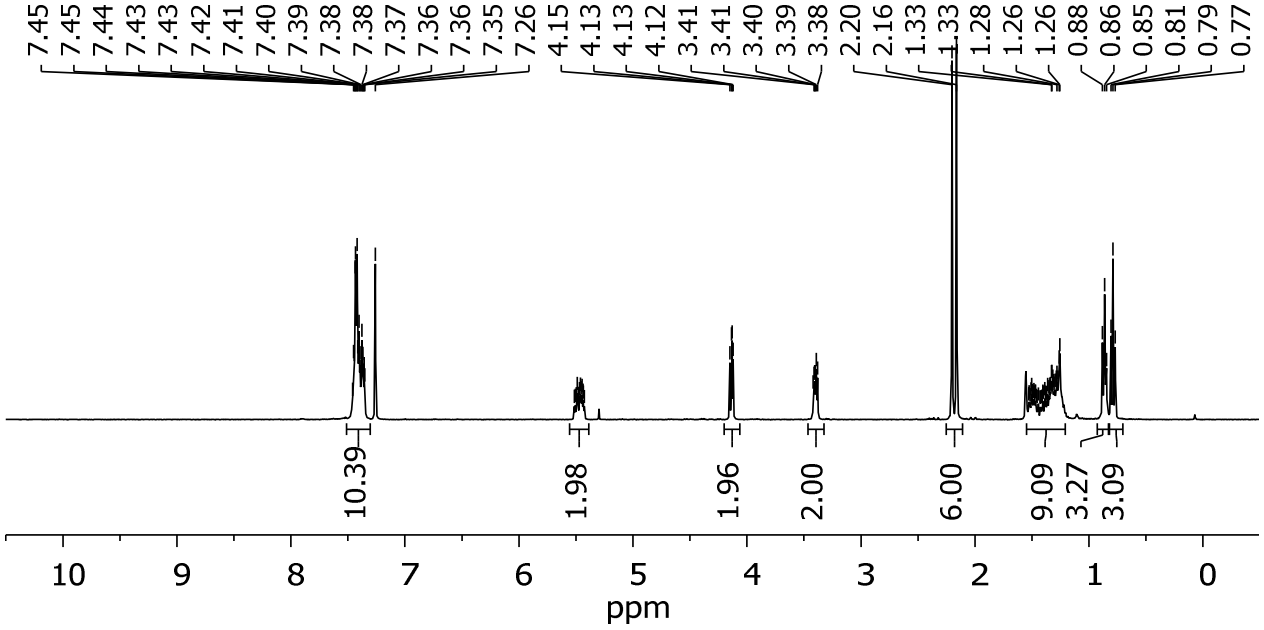


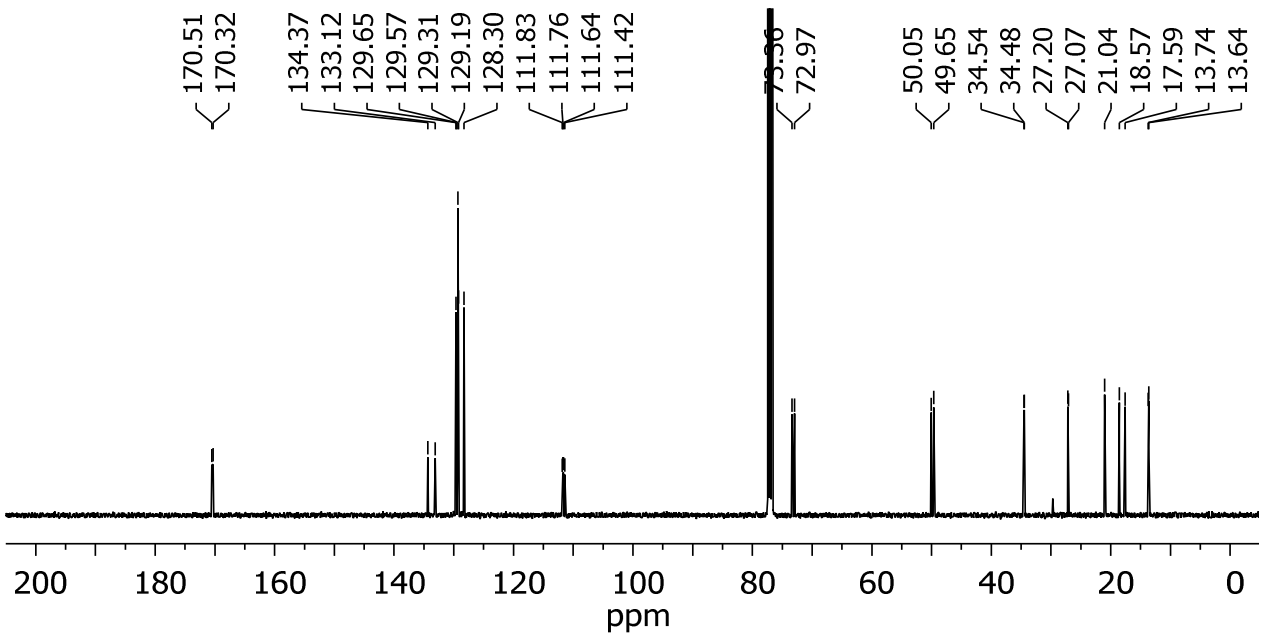


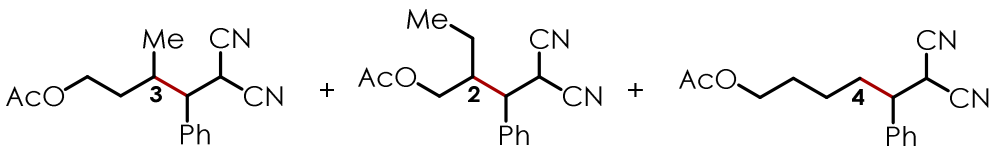


20

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)



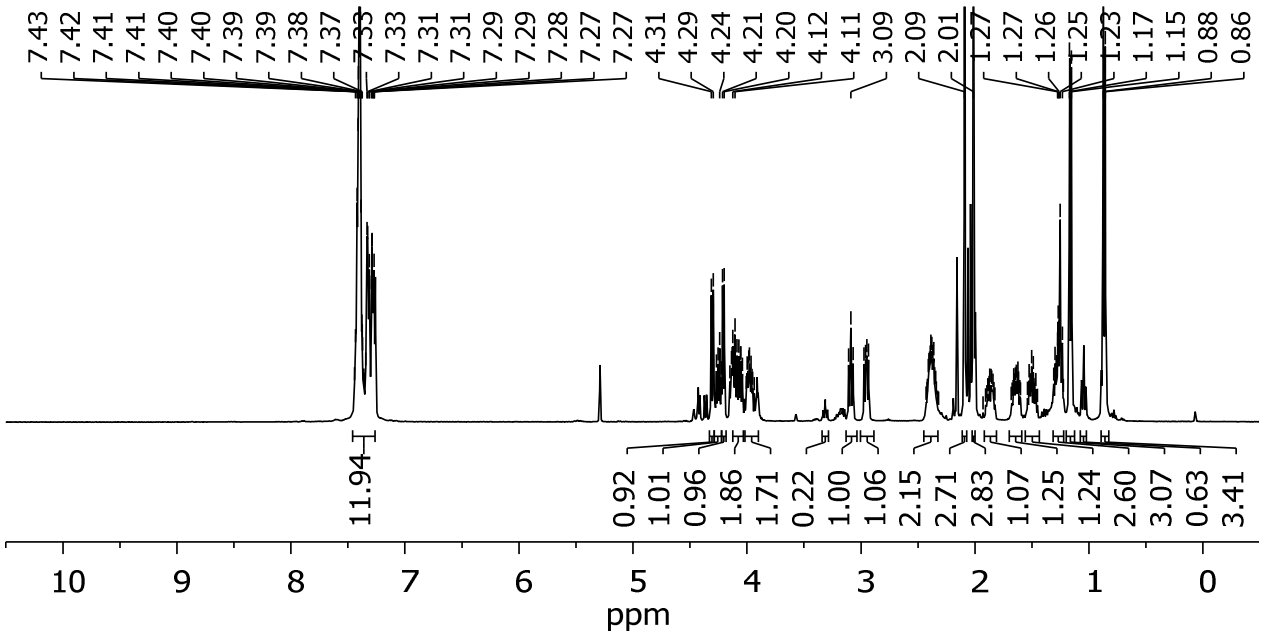


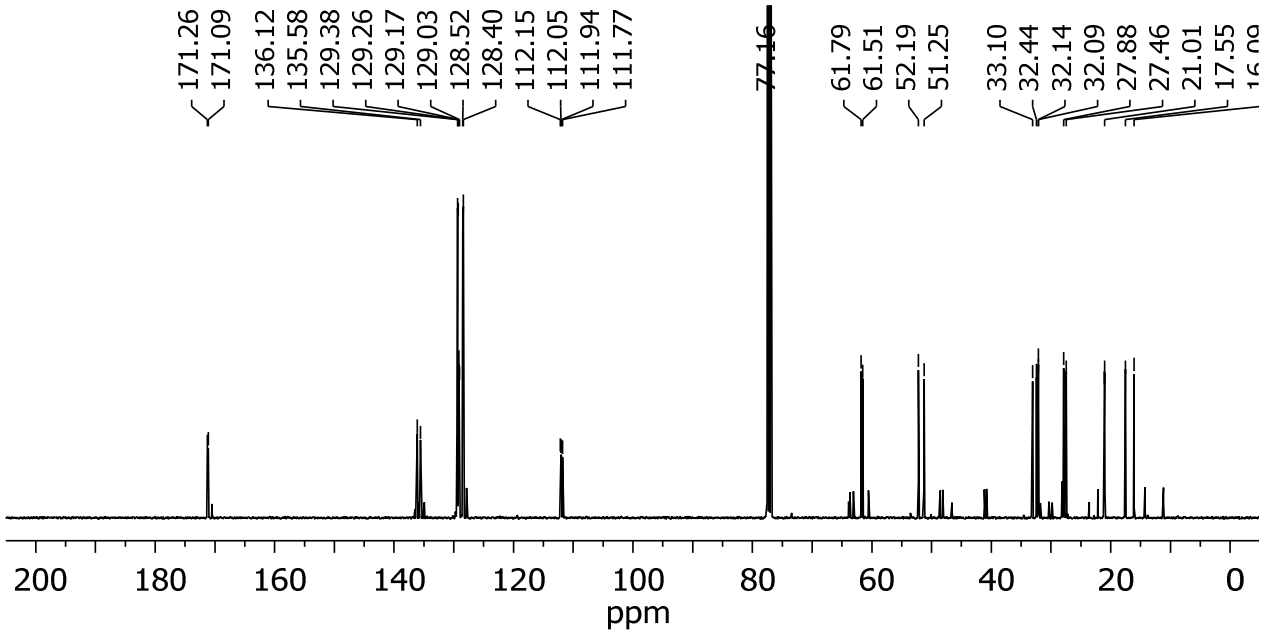


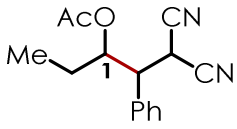
major minor traces

20

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

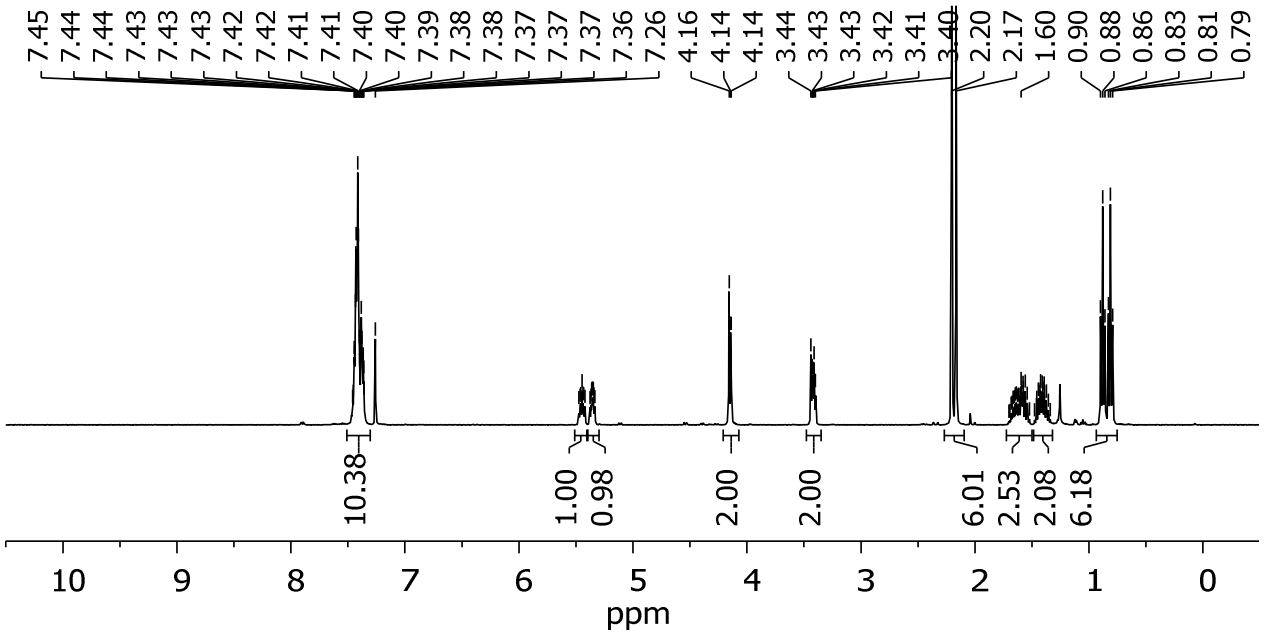


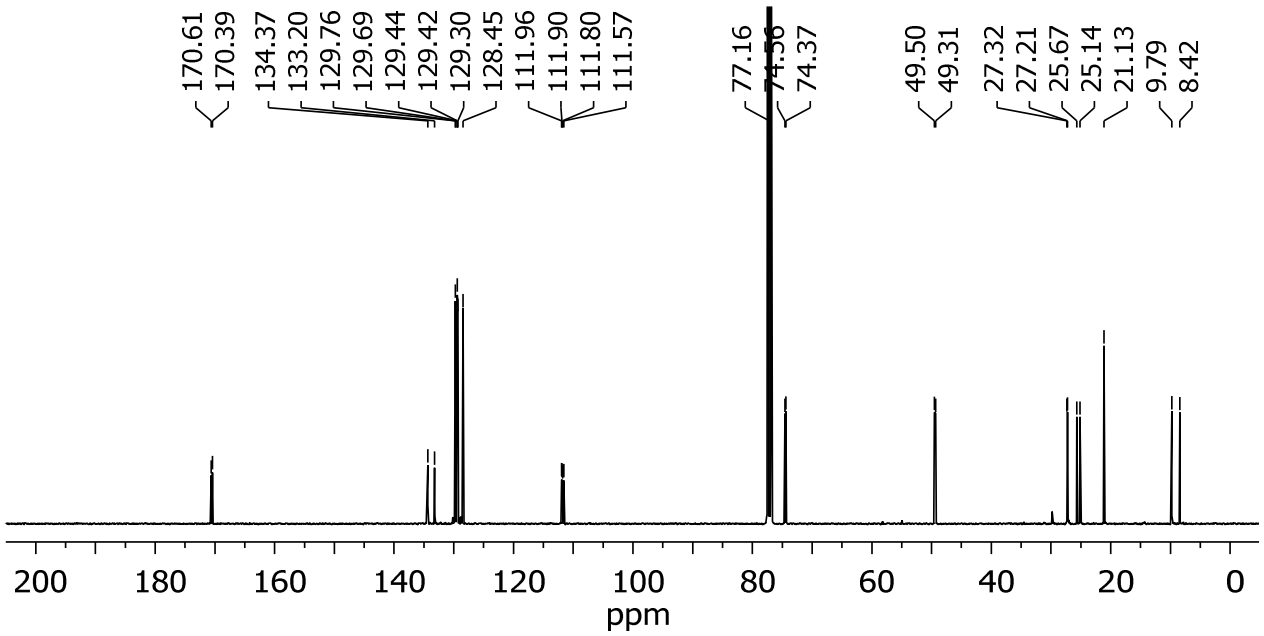




21

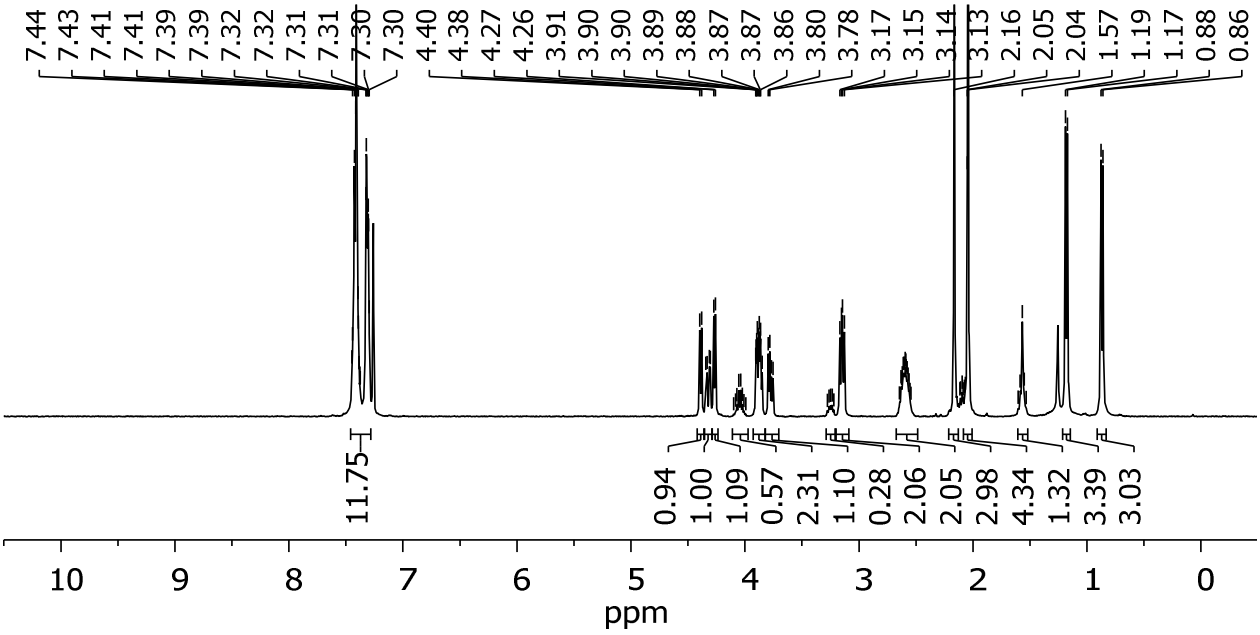
($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

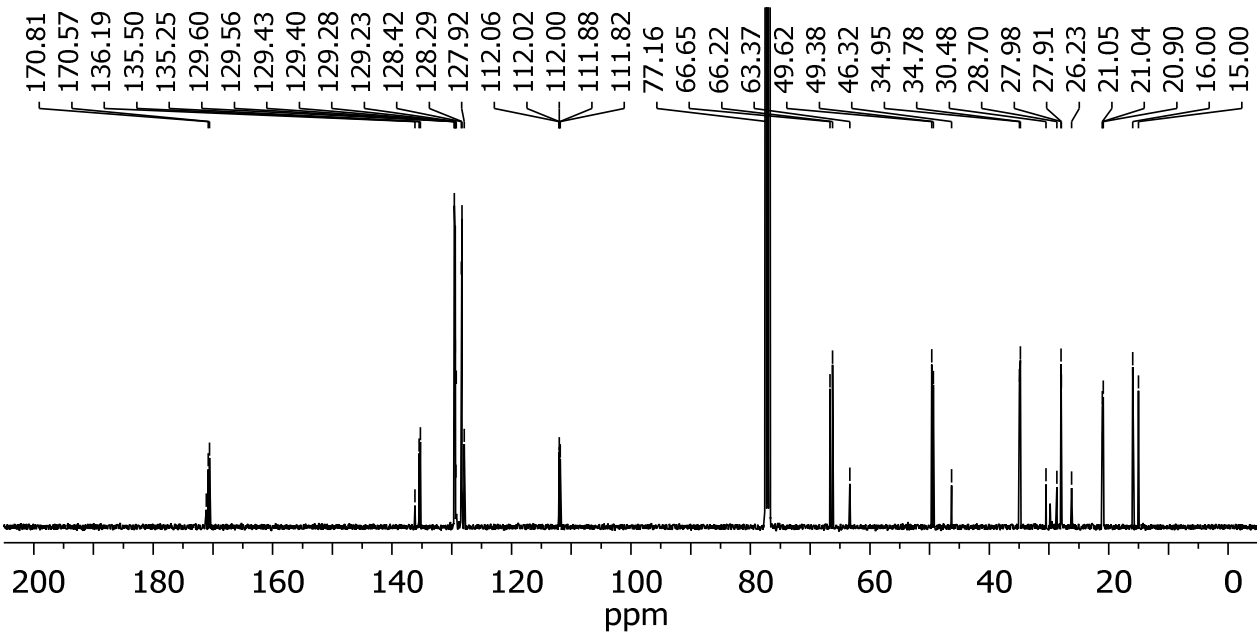


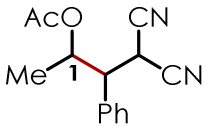


21

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

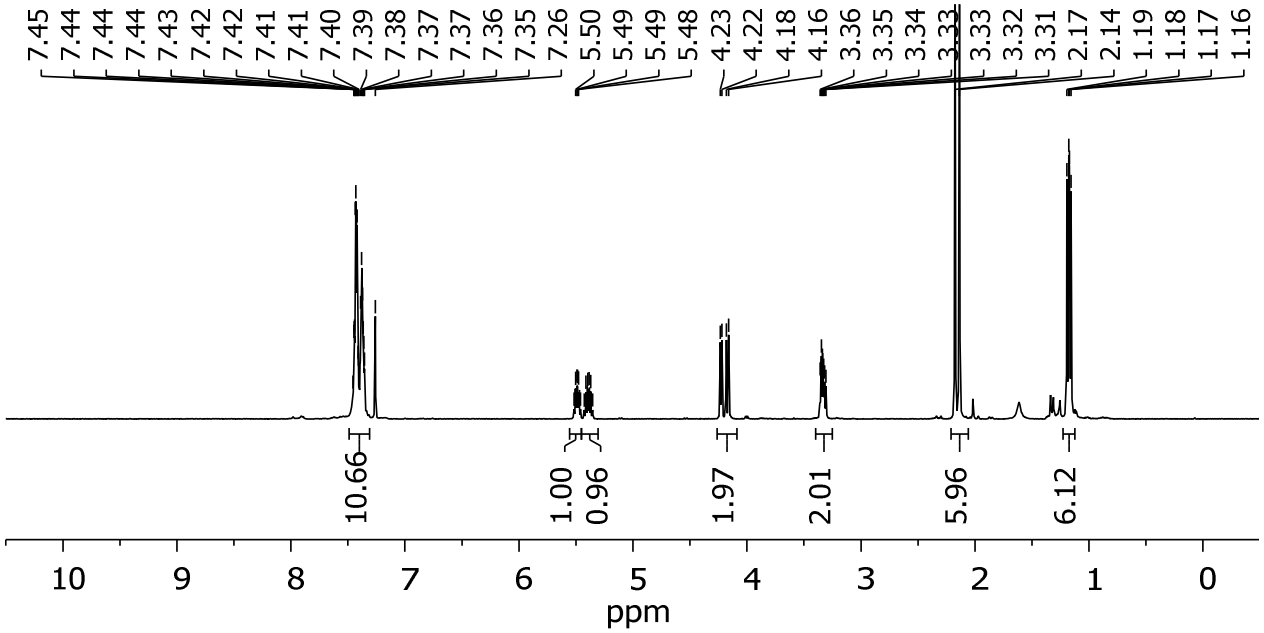


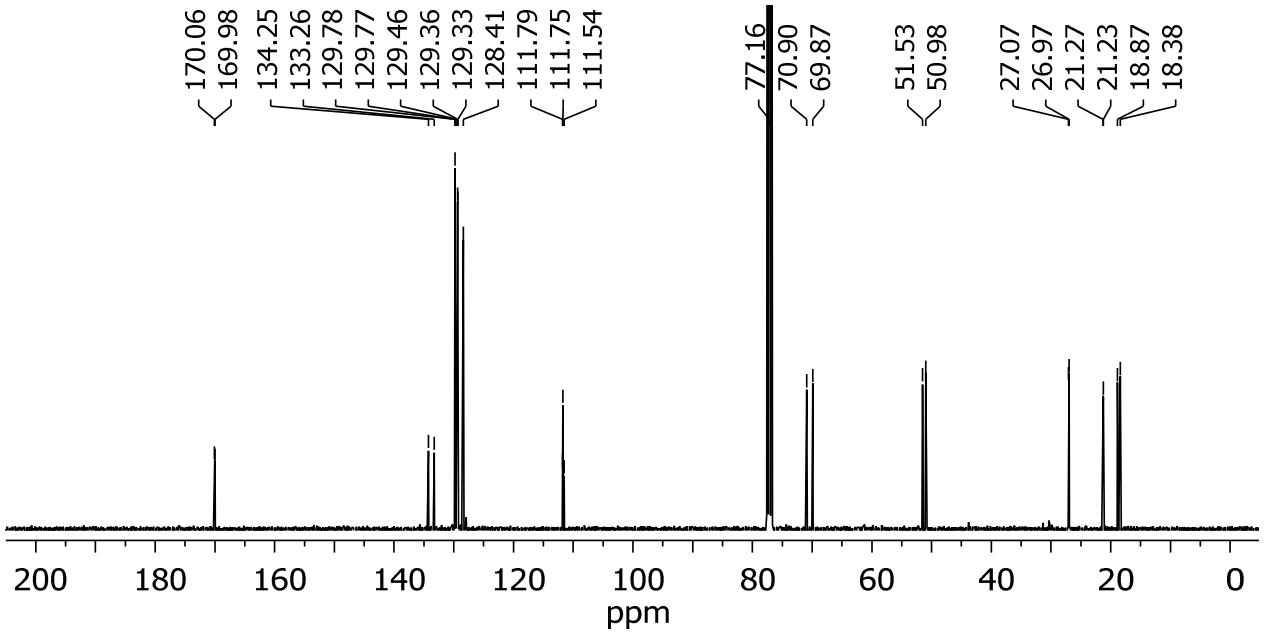


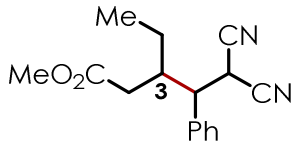


22

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

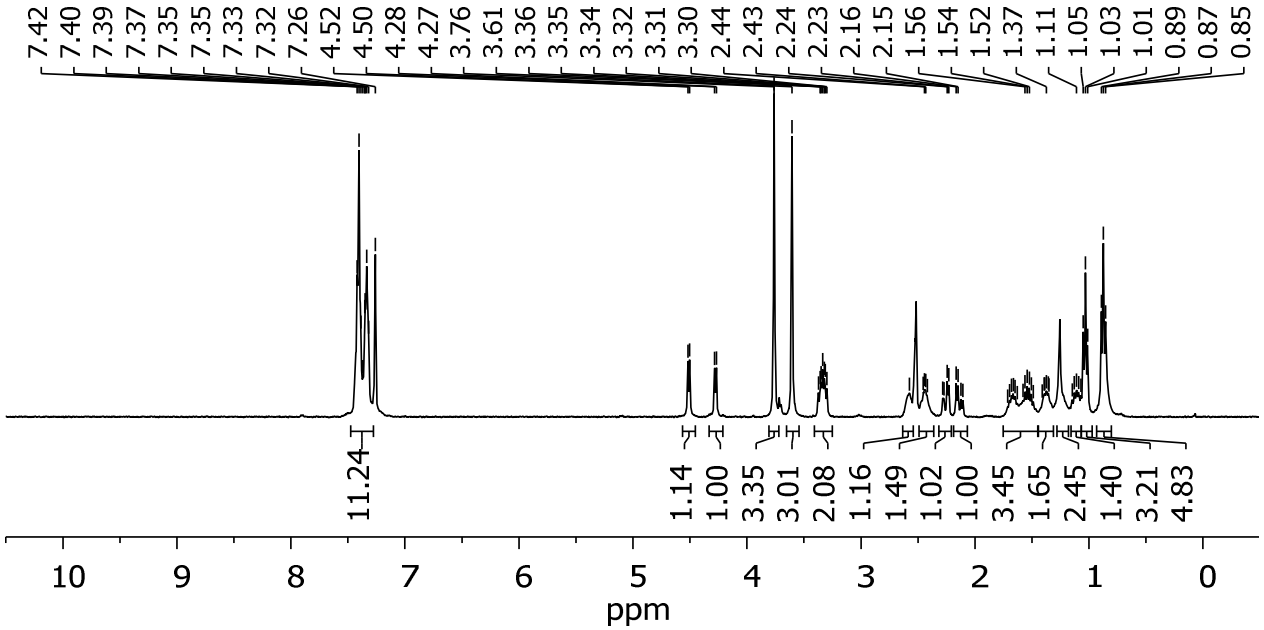


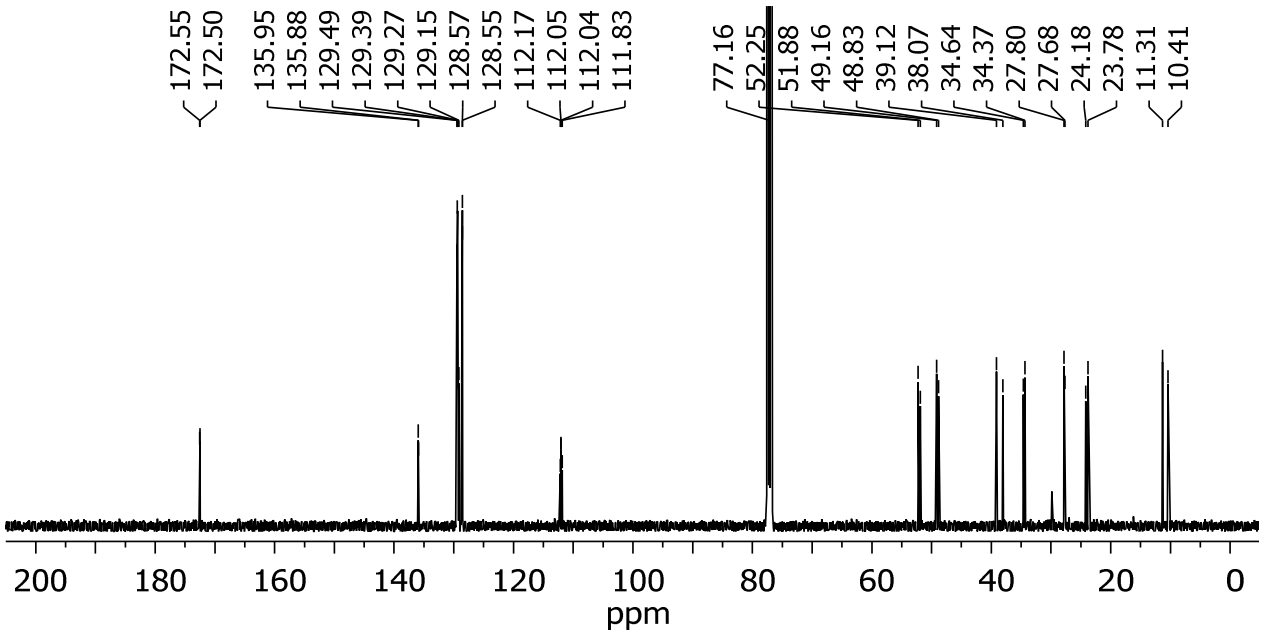


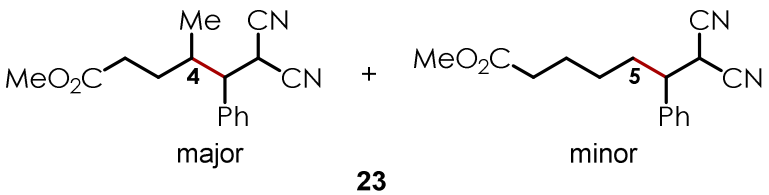


23

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

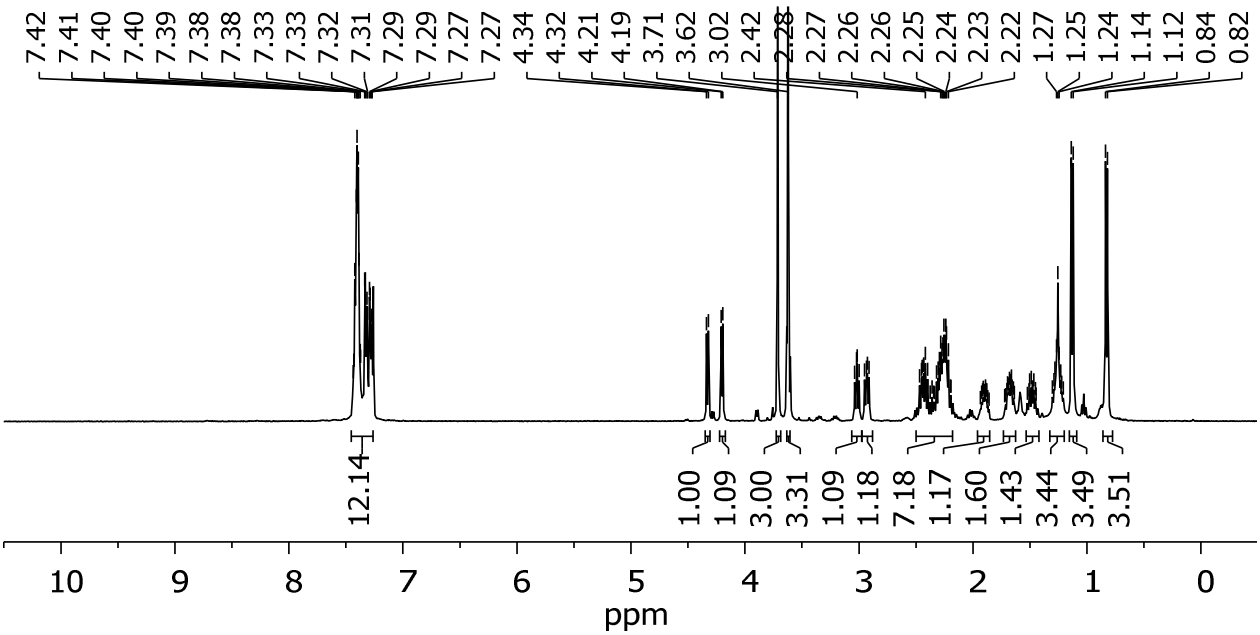


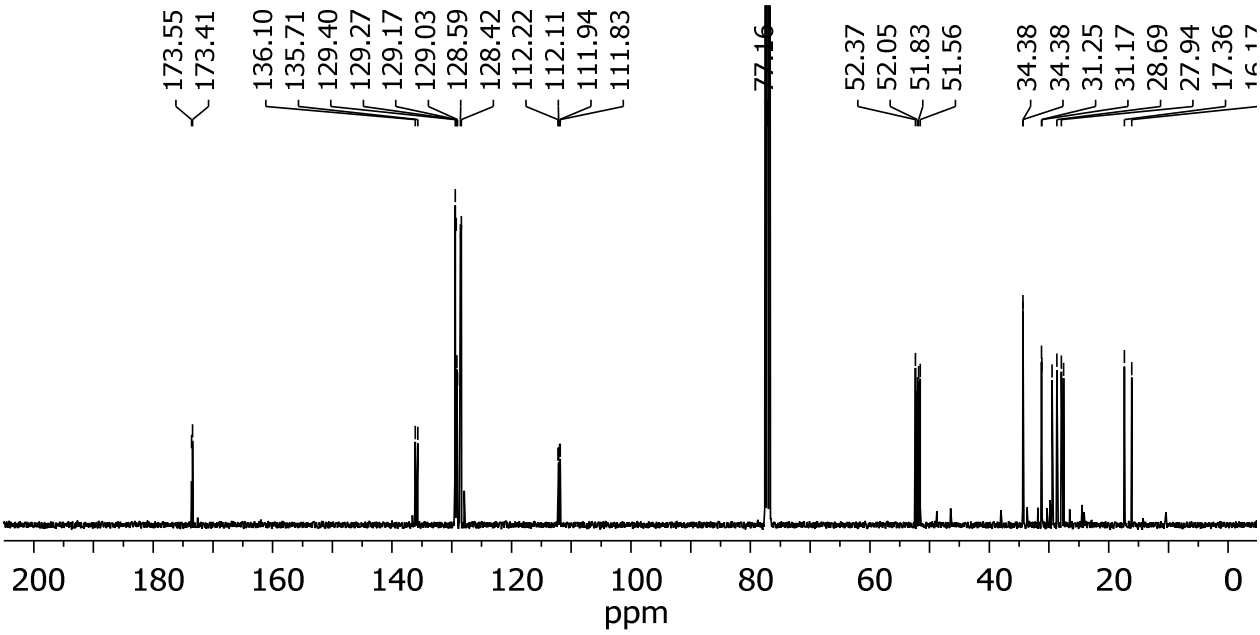


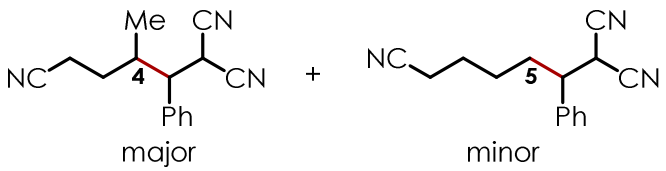


23

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

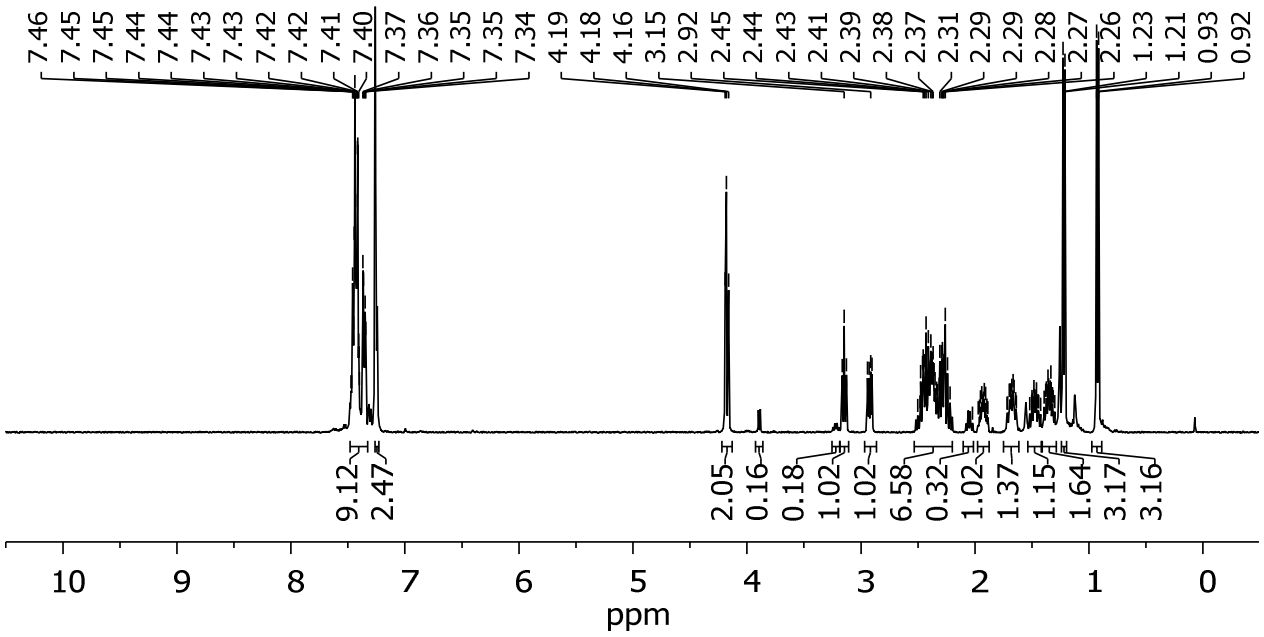


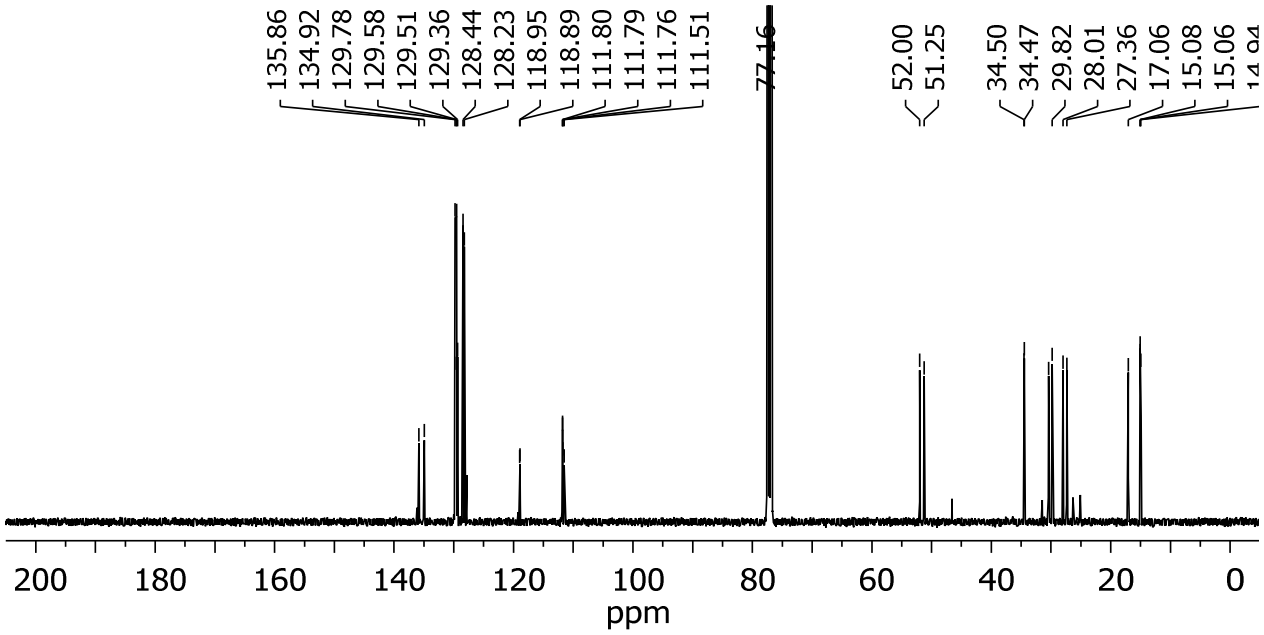


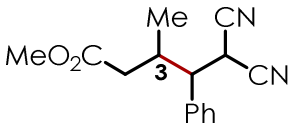


24

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

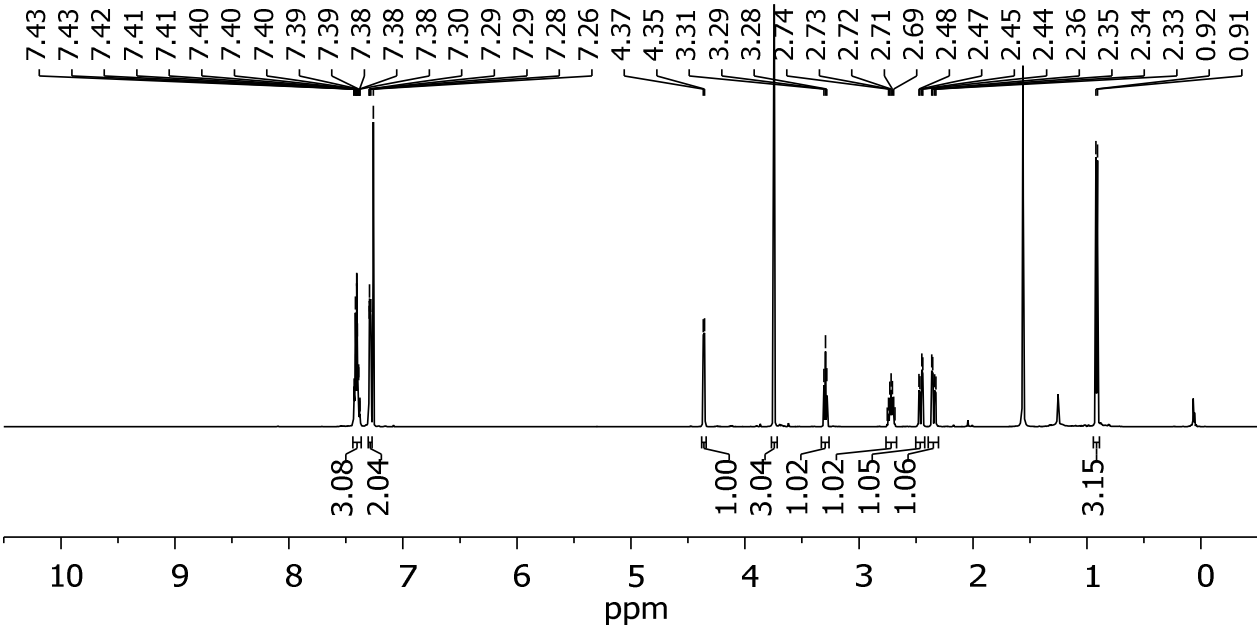


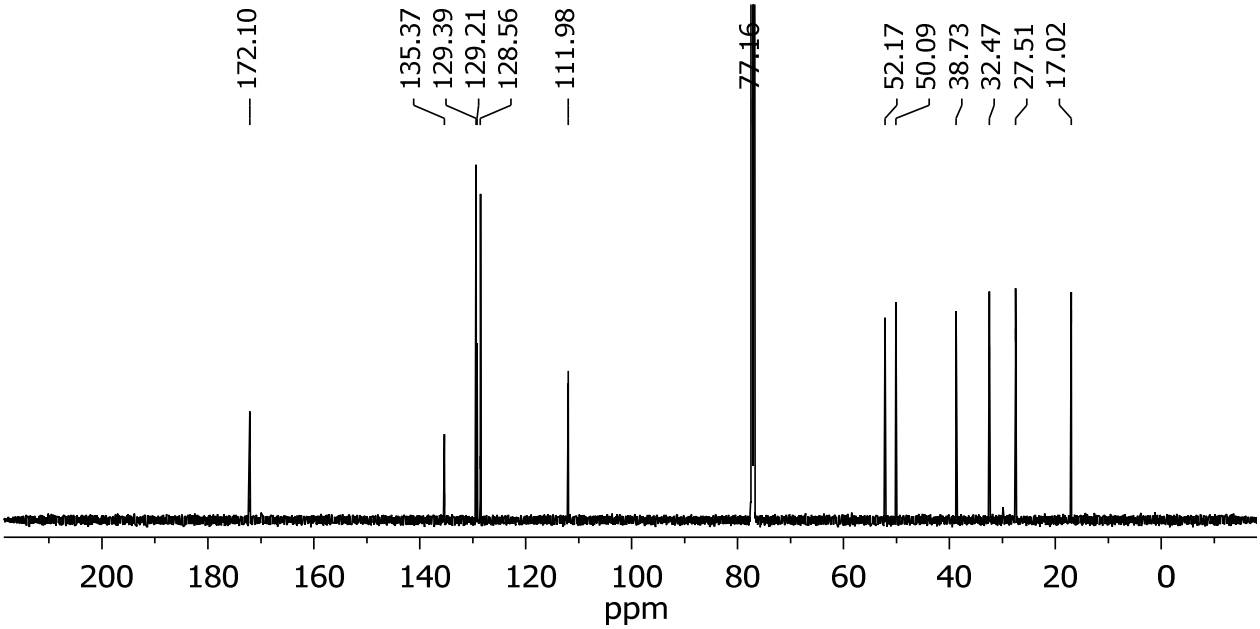


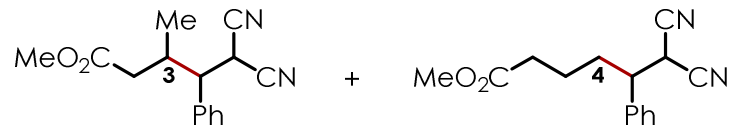


25' (diastereoisomer 1)

($CDCl_3$, ^1H NMR: 600 MHz, ^{13}C NMR: 151 MHz)



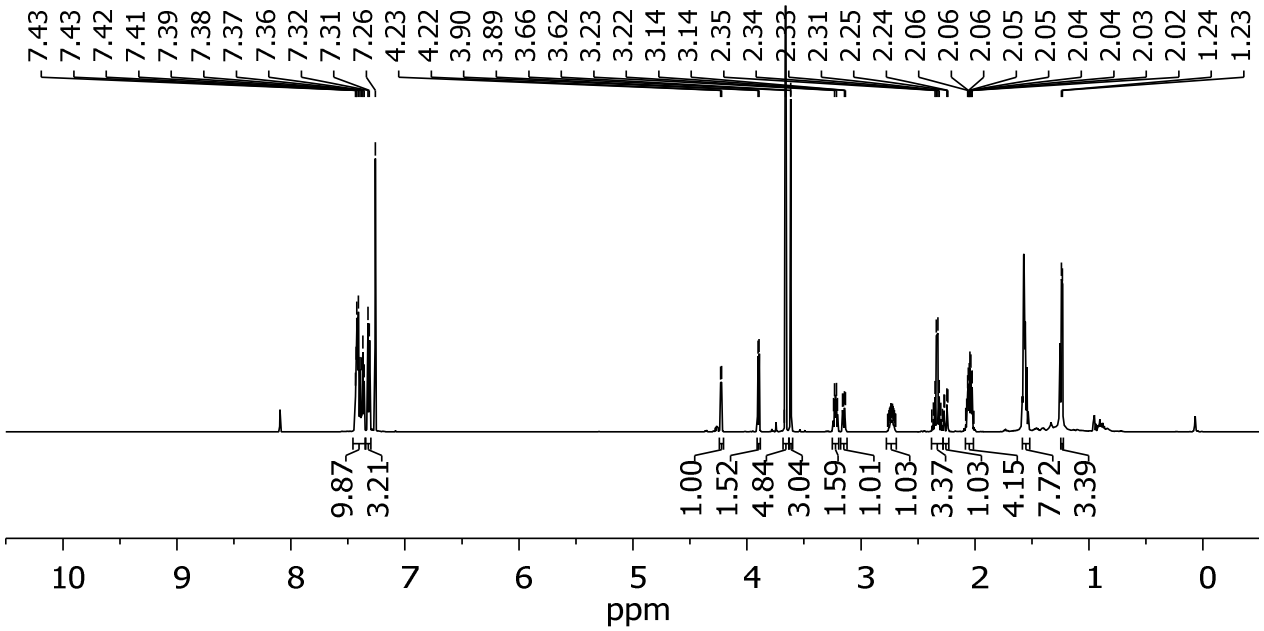


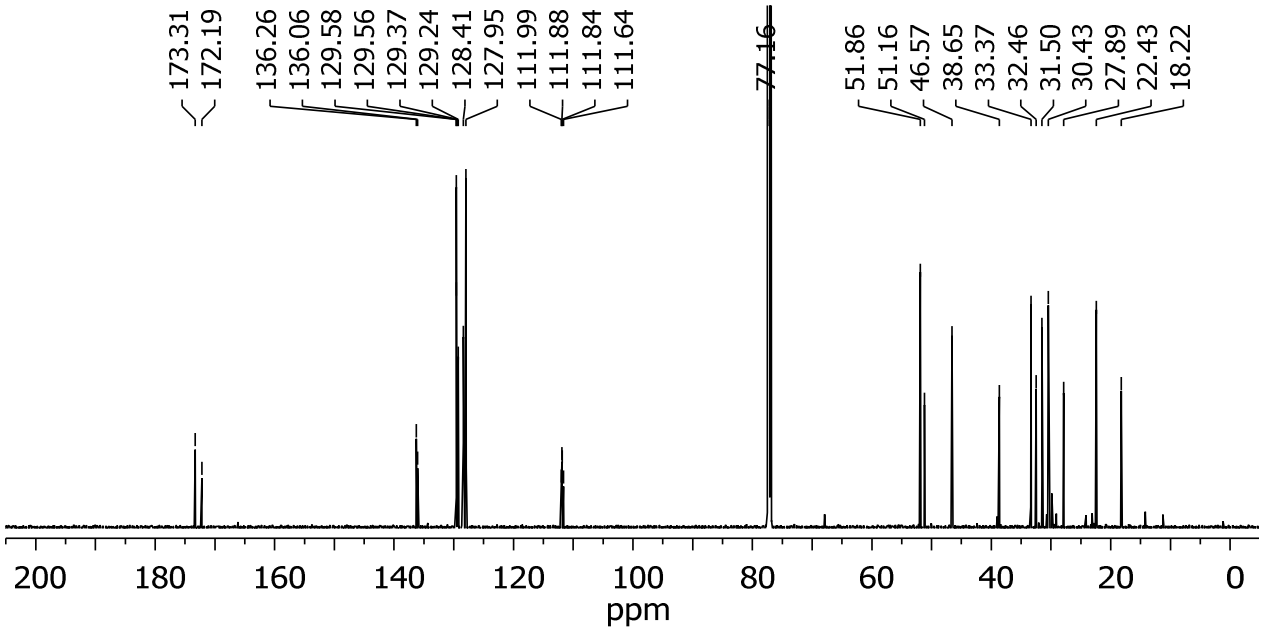


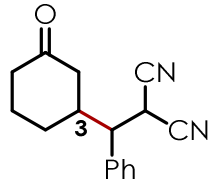
minor (diastereoisomer 2) major

25'

($CDCl_3$, ^1H NMR: 600 MHz, ^{13}C NMR: 151 MHz)

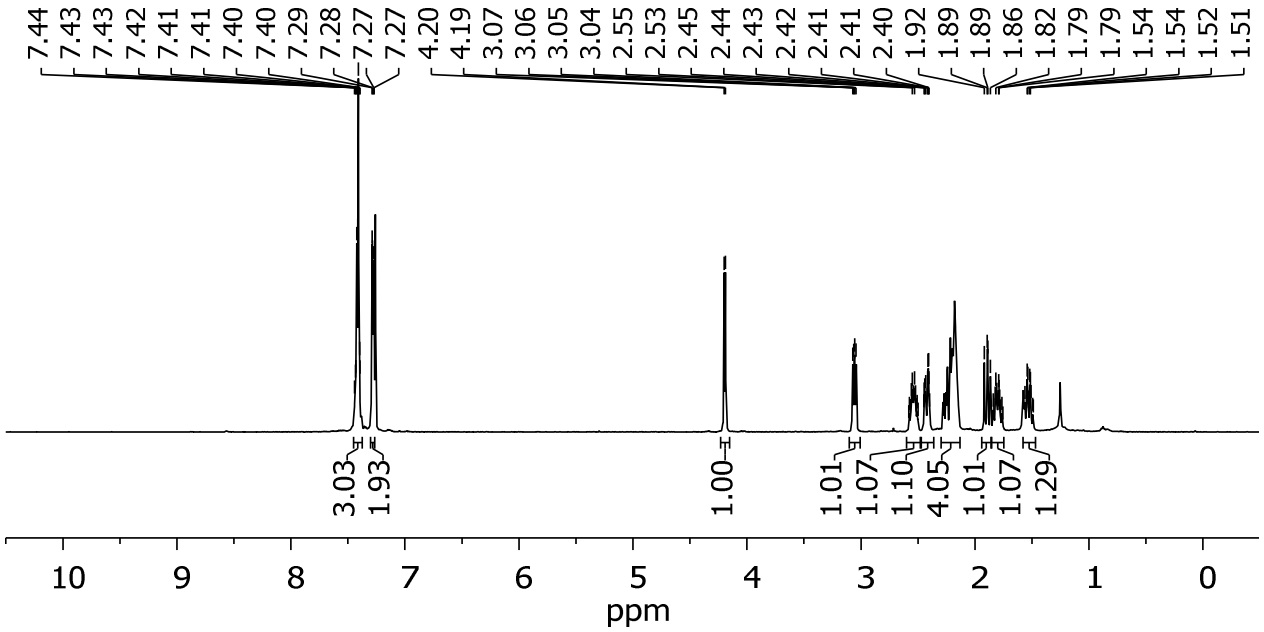


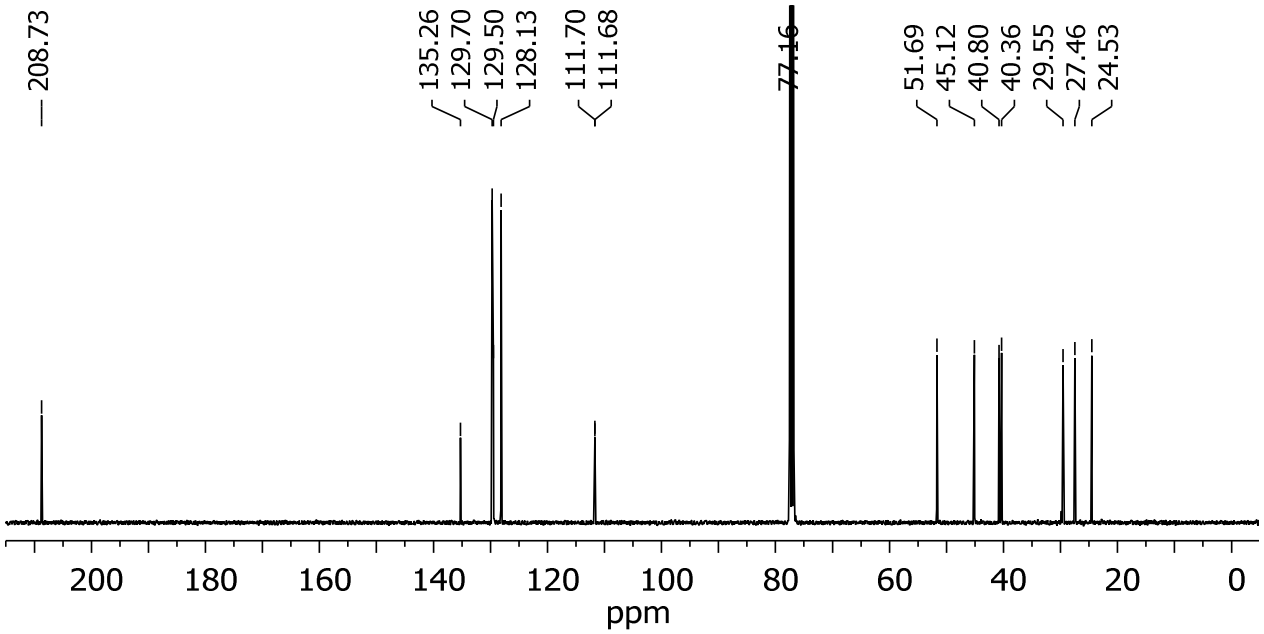


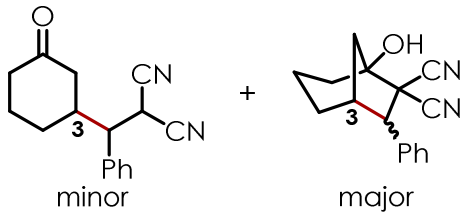


26 (diastereoisomer 1)

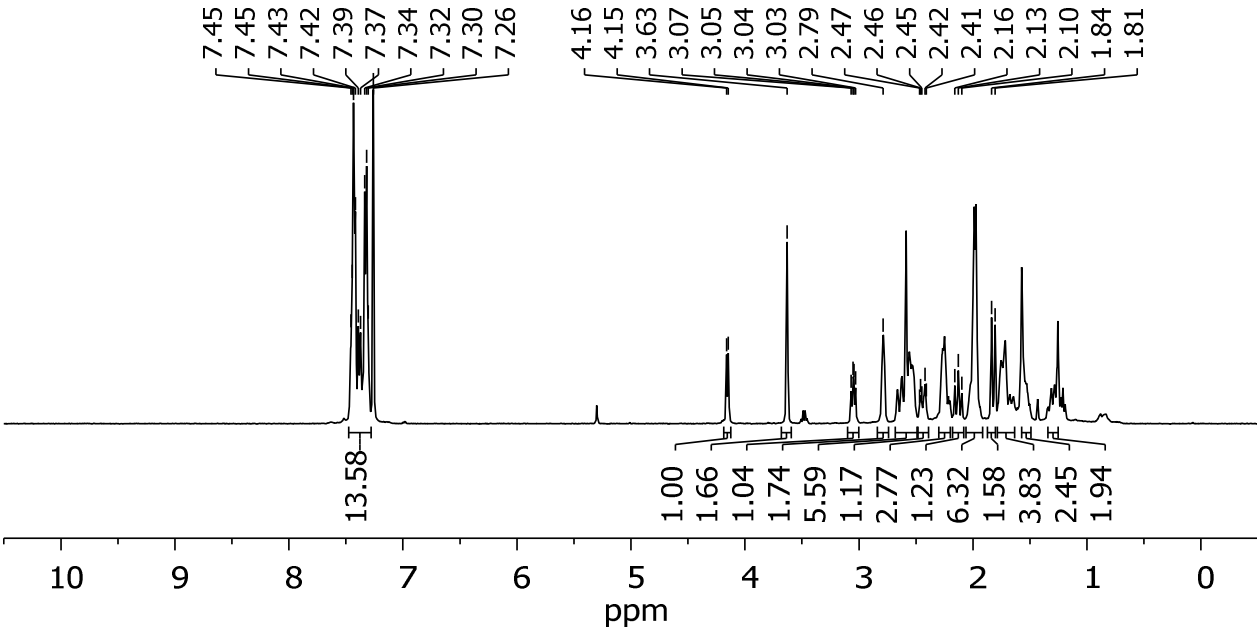
($CDCl_3$, ^1H NMR: 500 MHz, ^{13}C NMR: 101 MHz)

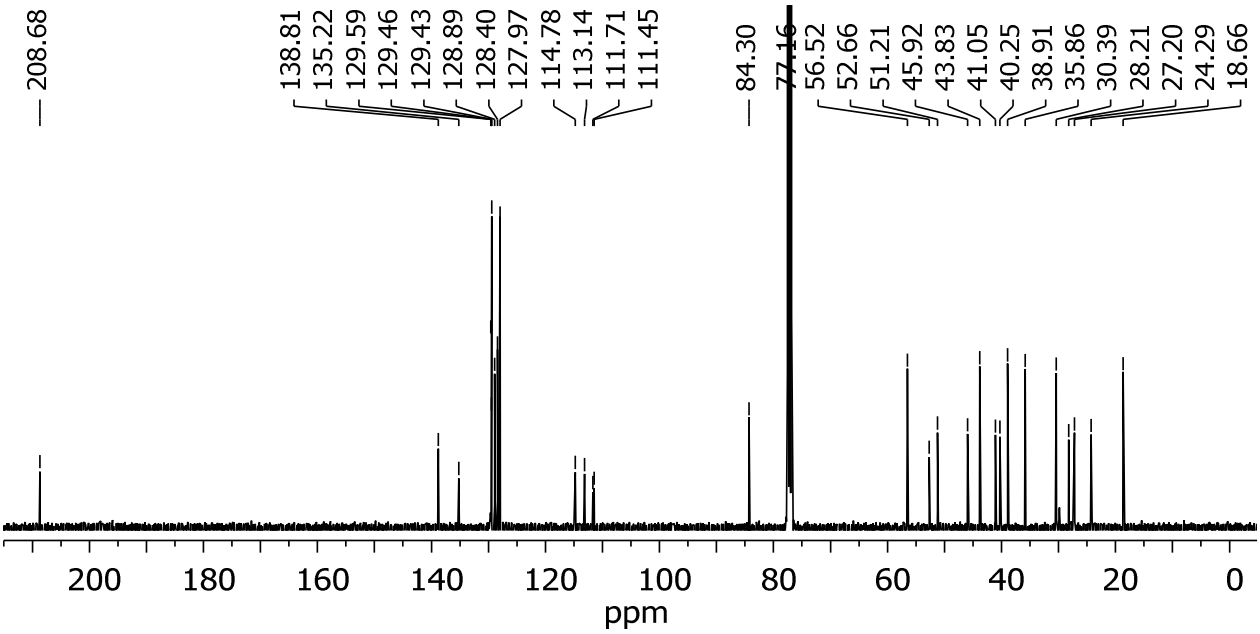






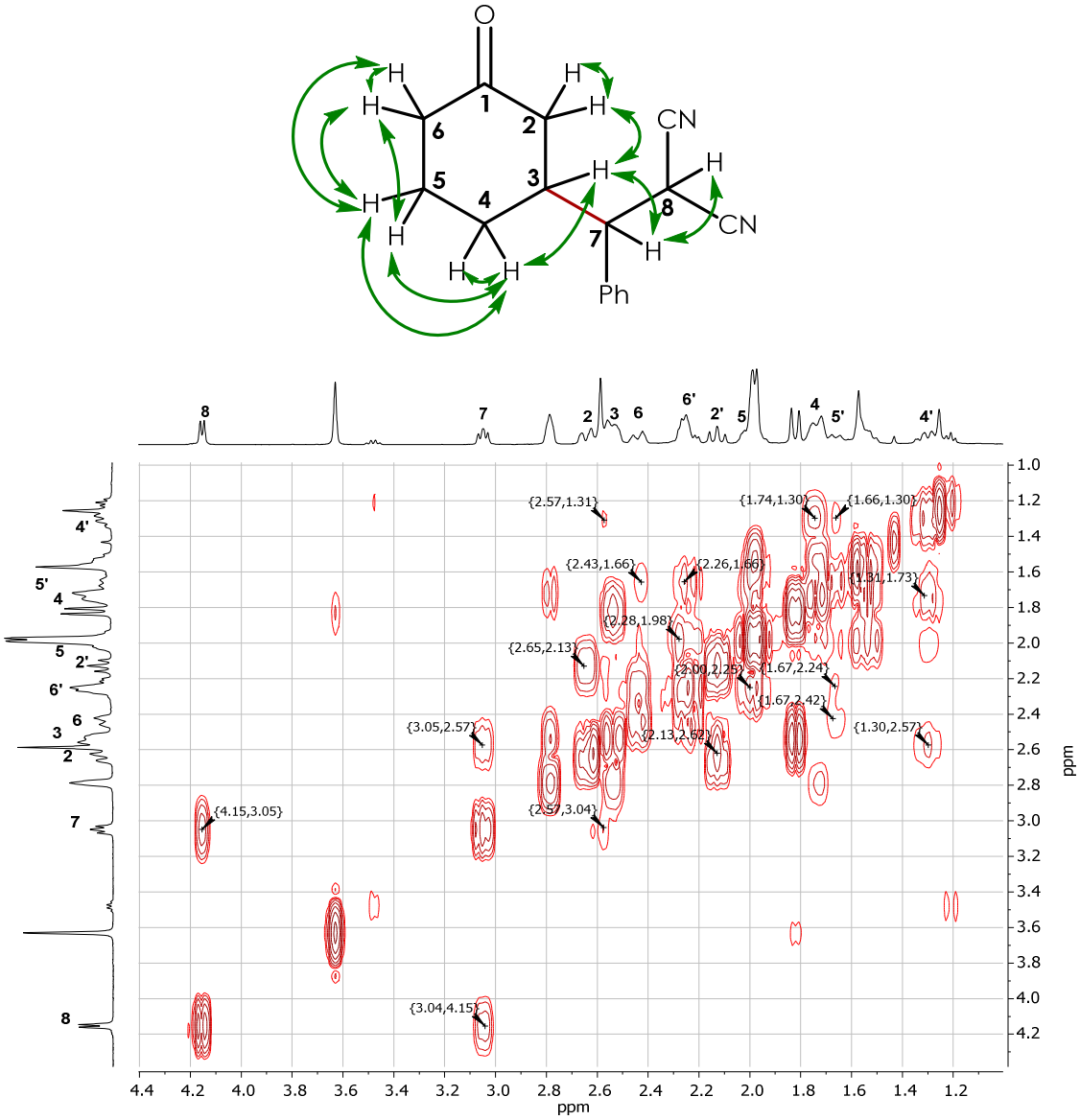
26 (diastereoisomer 2 + bicyclic product)
($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)



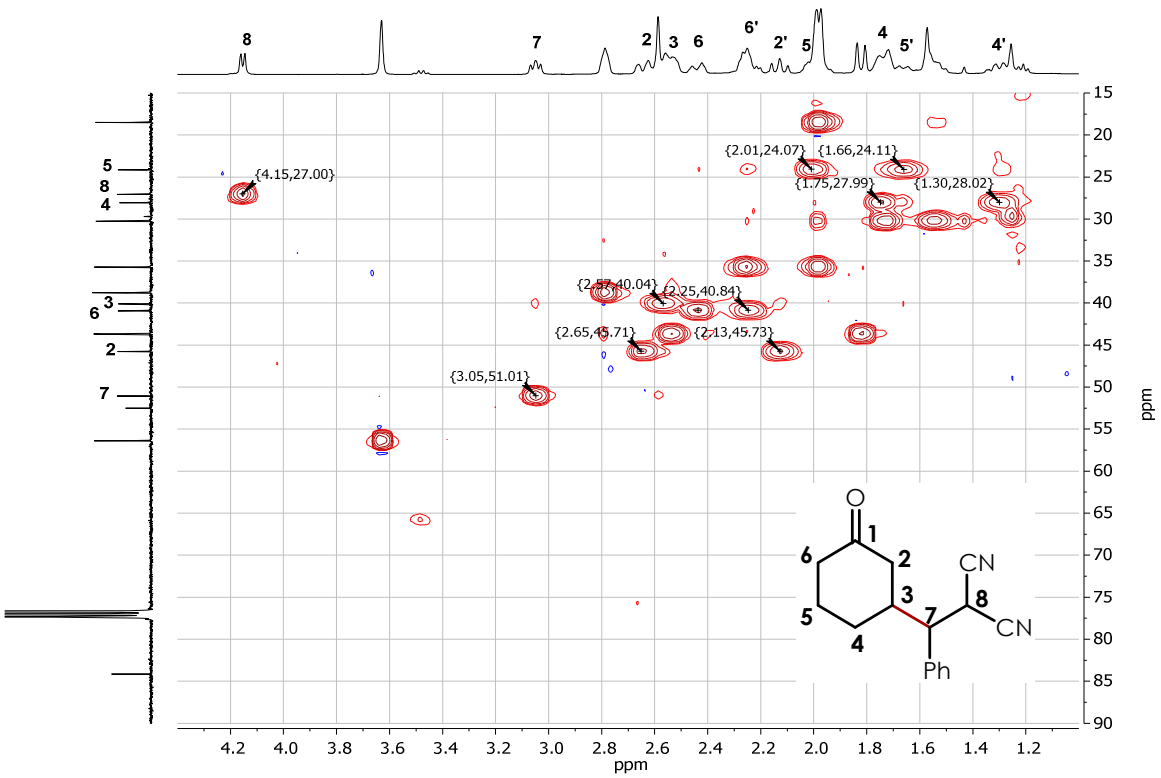


2D-NMR Data of Diastereoisomer 2

(^{1}H,^{1}H)-COSY Spectrum (aliphatic section, $CDCl_3$, ^{1}H NMR: 400 MHz)

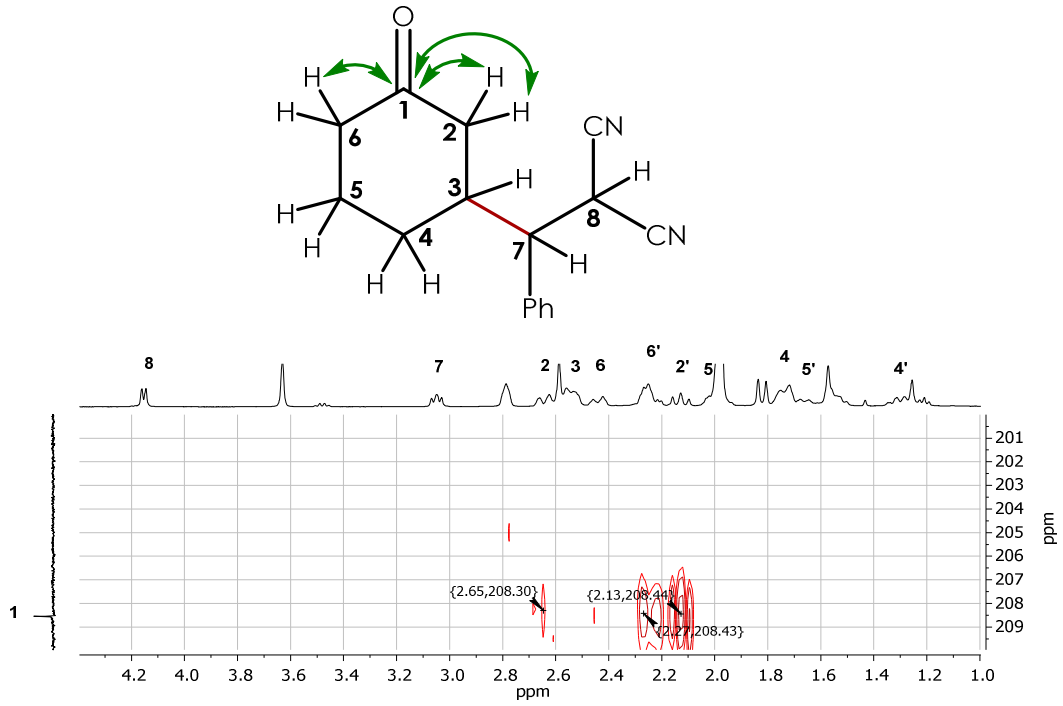


(¹H,¹³C)-HSQC spectrum (aliphatic section, $CDCl_3$, ¹H NMR: 400 MHz, ¹³C NMR: 101 MHz)

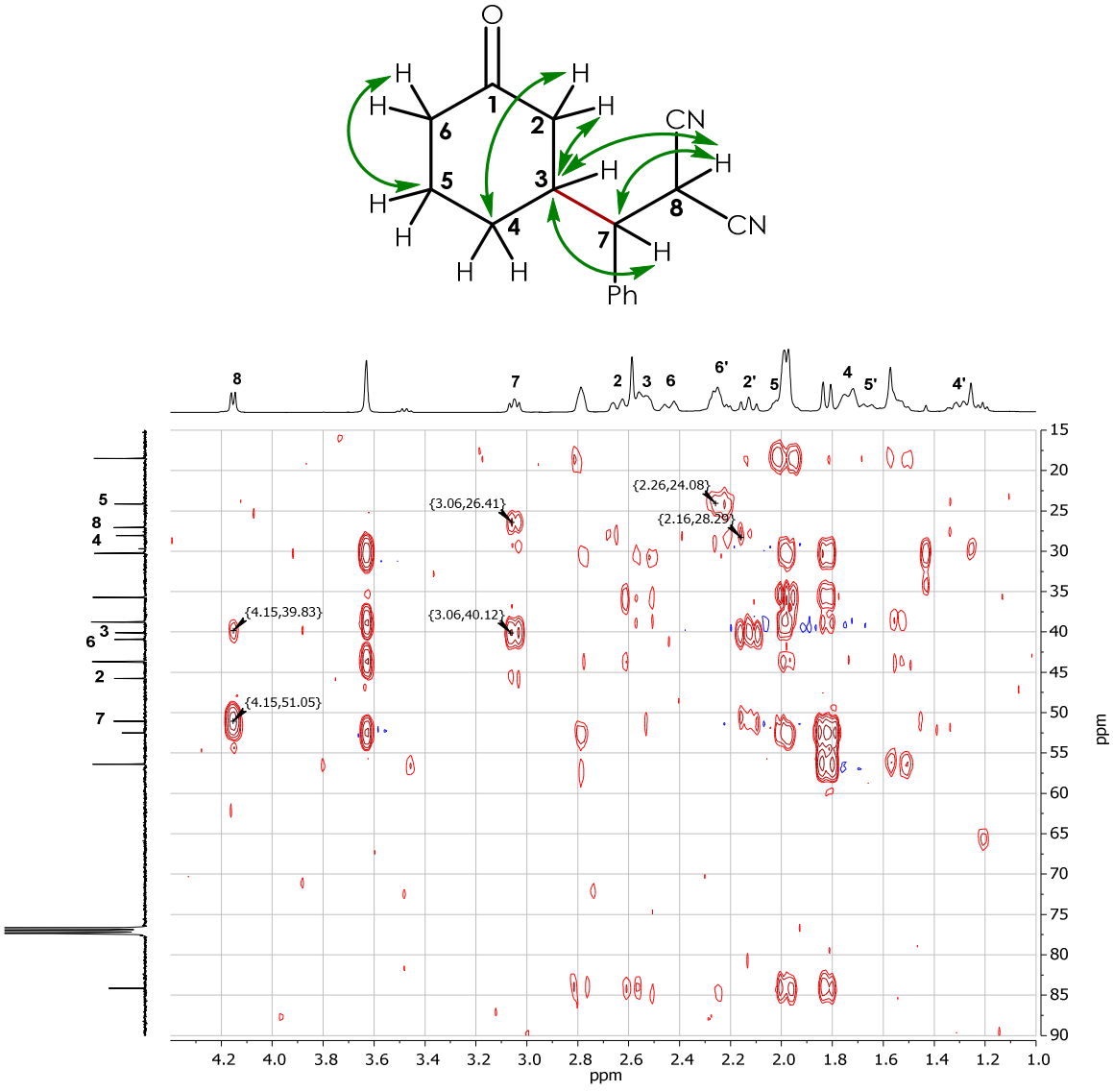


(¹H,¹³C)-HMBC spectrum ($CDCl_3$, ¹H NMR: 400 MHz, ¹³C NMR: 101 MHz)

carbonyl section:

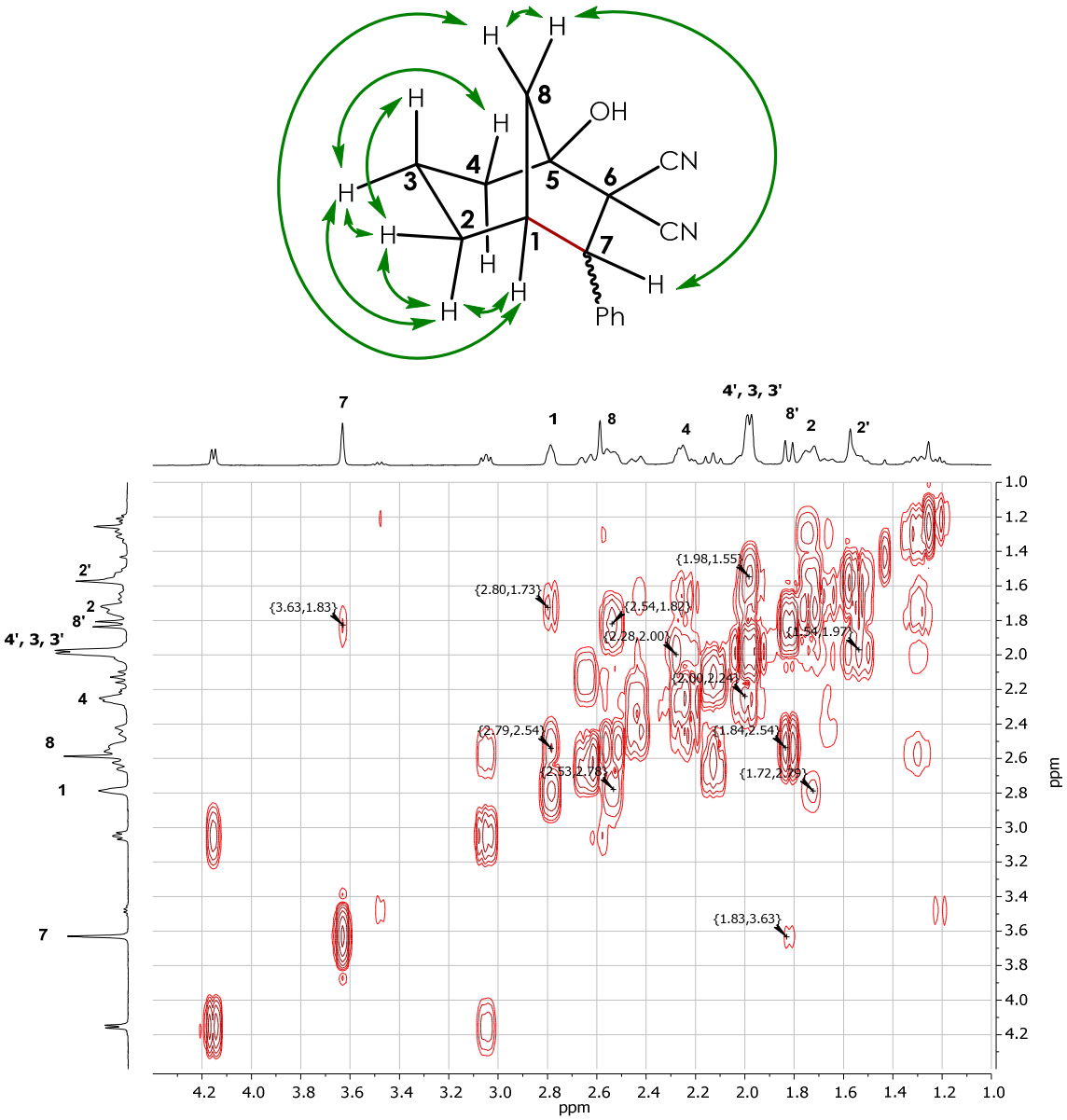


aliphatic section:

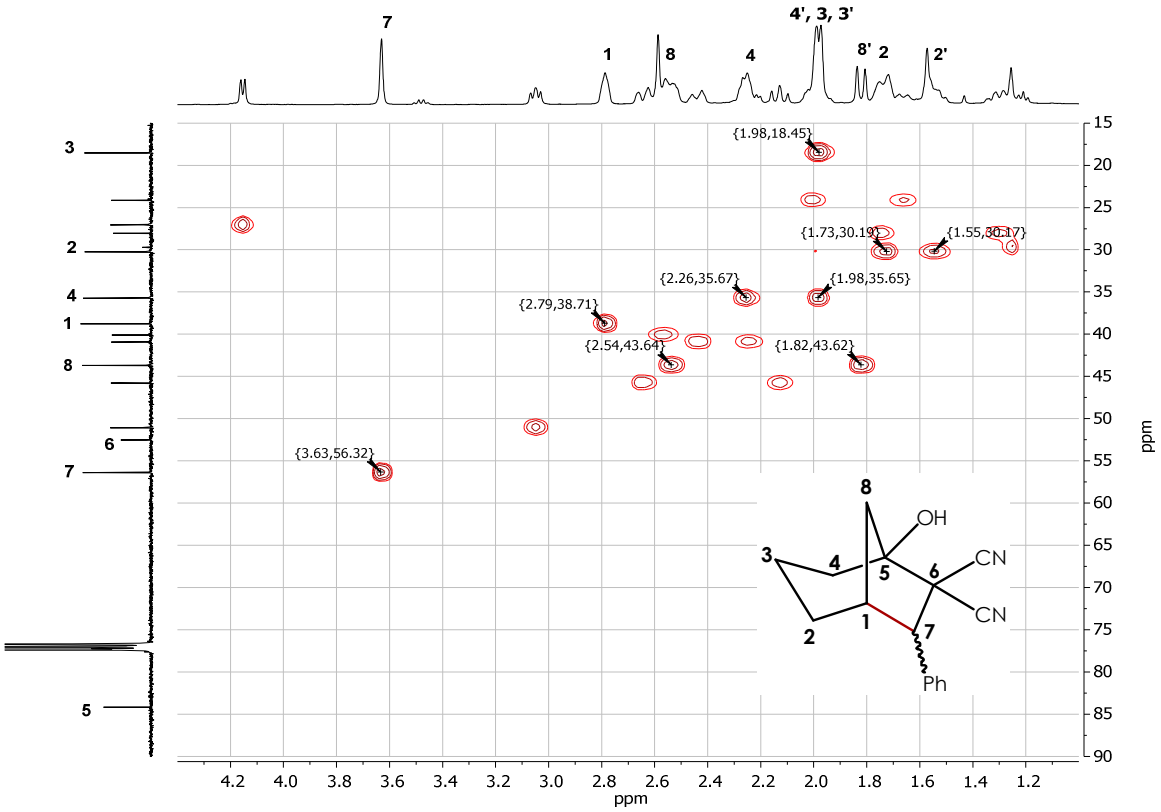


2D-NMR Data of the Bicyclic Product

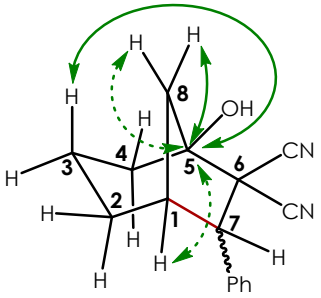
(^{1}H,^{1}H)-COSY Spectrum (aliphatic section, $CDCl_3$, ^{1}H NMR: 400 MHz)



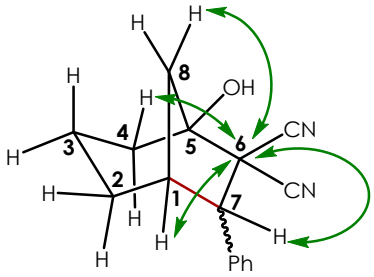
(<u>$^{1}H,^{13}C$)-HSQC spectrum</u> (aliphatic section, $CDCl_3$, ^{1}H NMR: 400 MHz, ^{13}C NMR: 101 MHz)



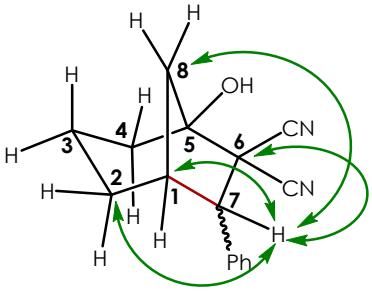
(^{1}H,^{13}C)-HMBC spectrum (aliphatic section, $CDCl_3$, ^{1}H NMR: 400 MHz, ^{13}C NMR: 101 MHz)



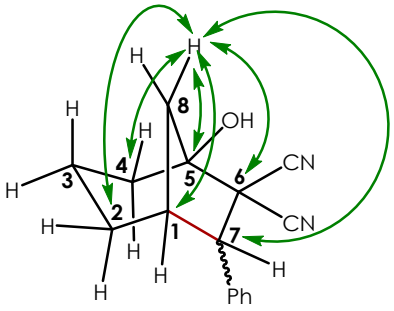
HMBC-signals of C5



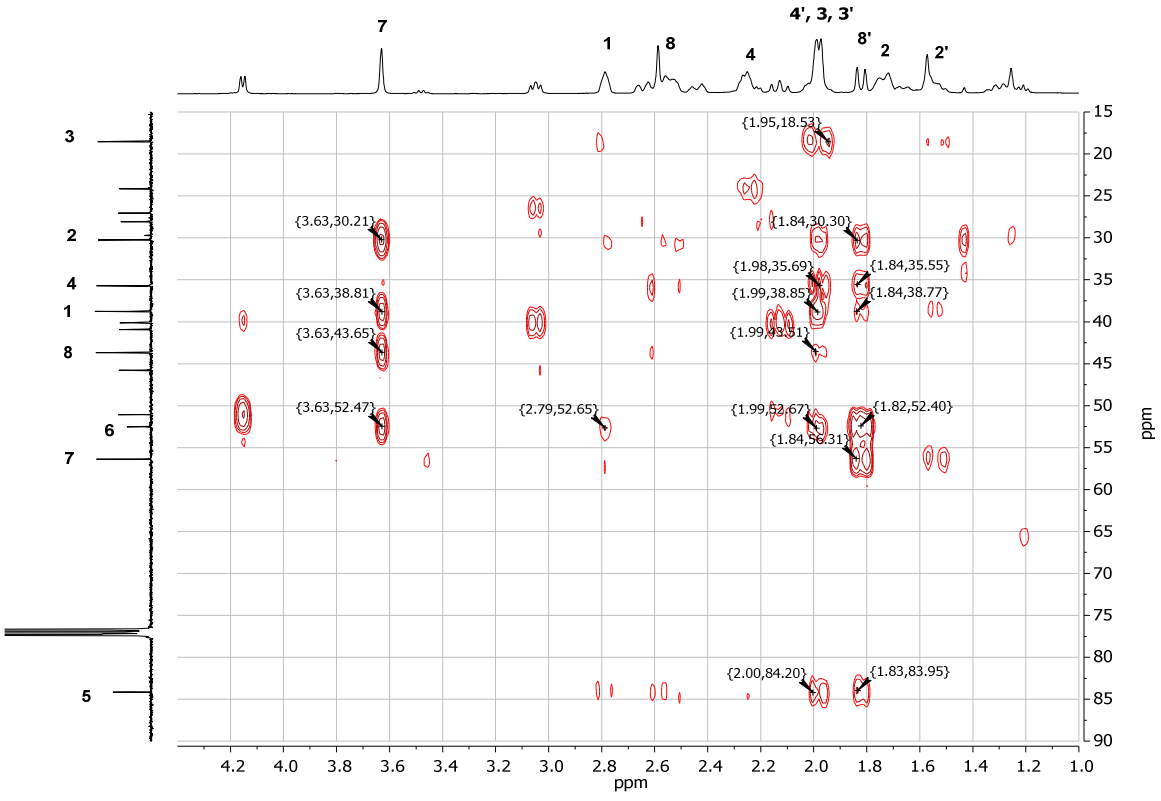
HMBC-signals of C6

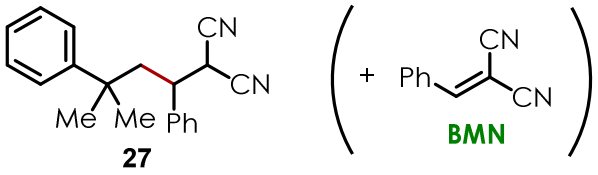


HMBC-signals of H7



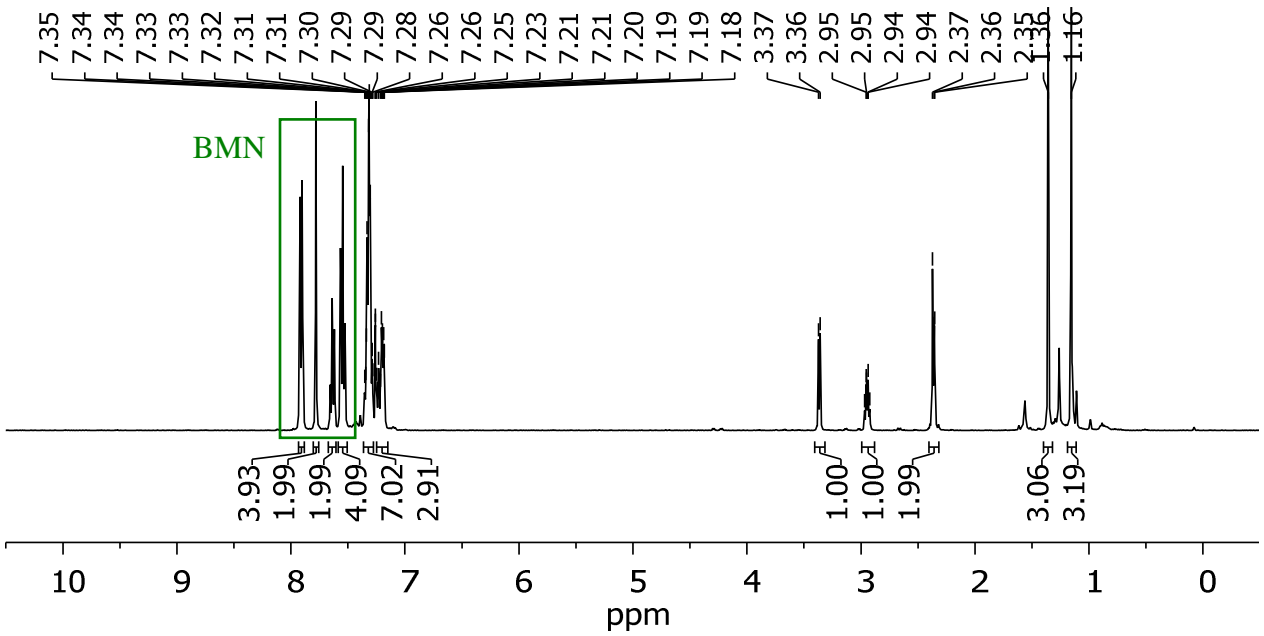
HMBC-signals of H8'

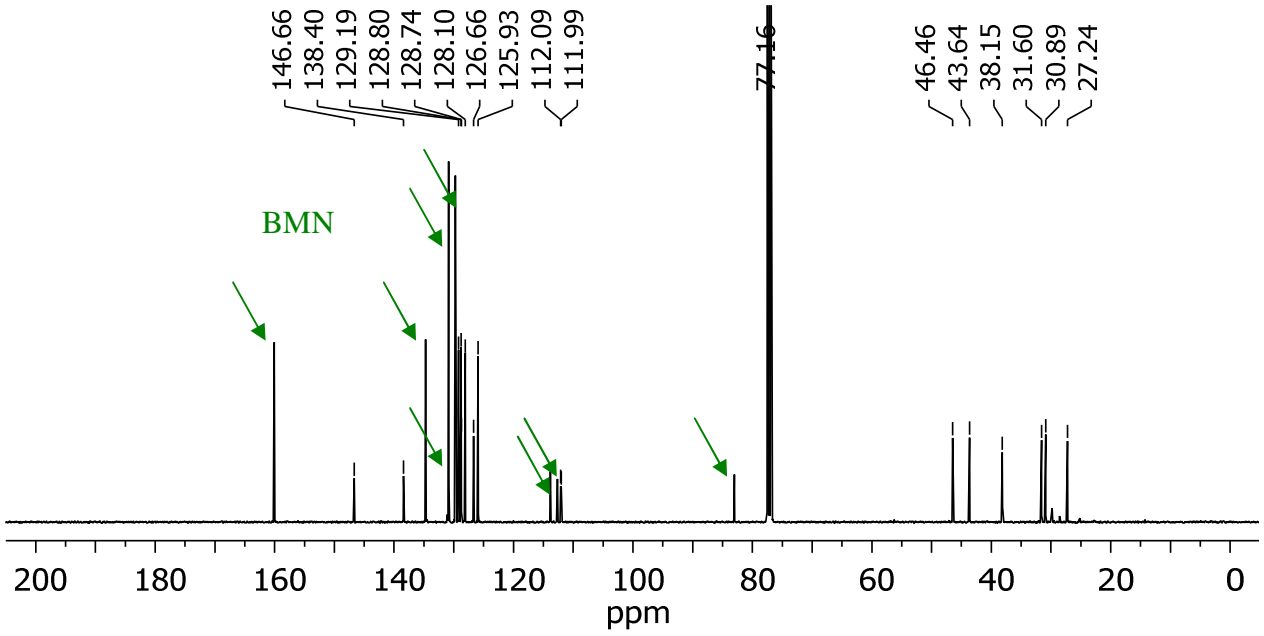


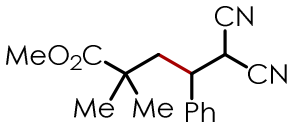


27

($CDCl_3$, ^1H NMR: 400 MHz, ^{13}C NMR: 101 MHz)

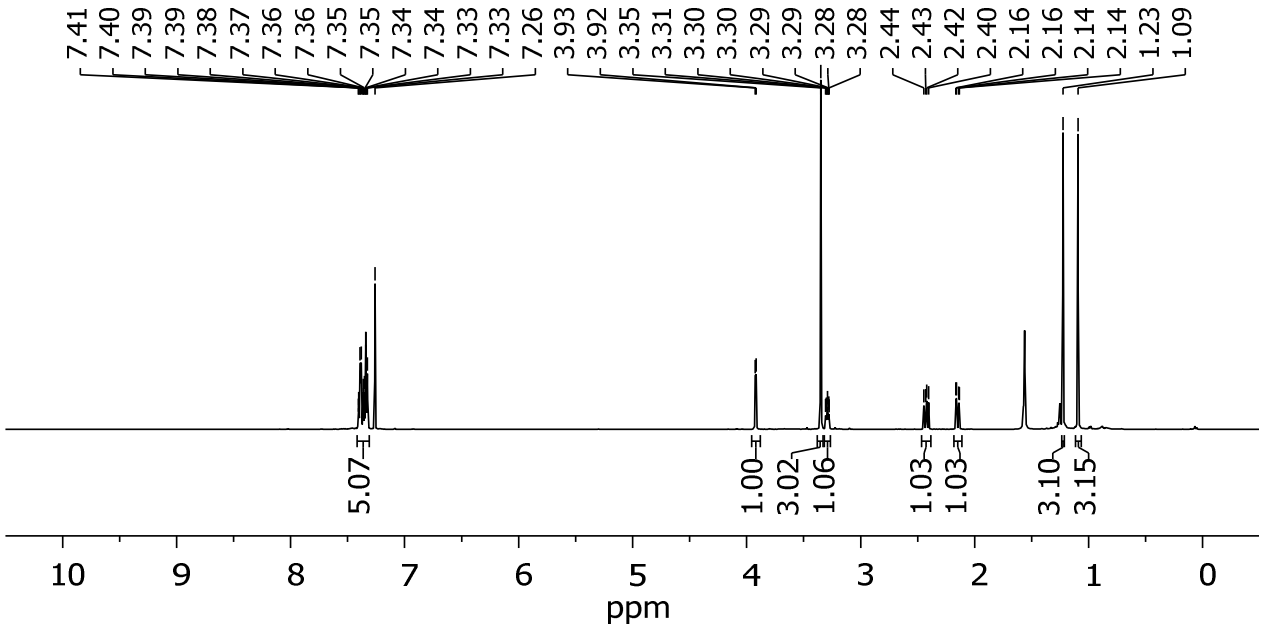


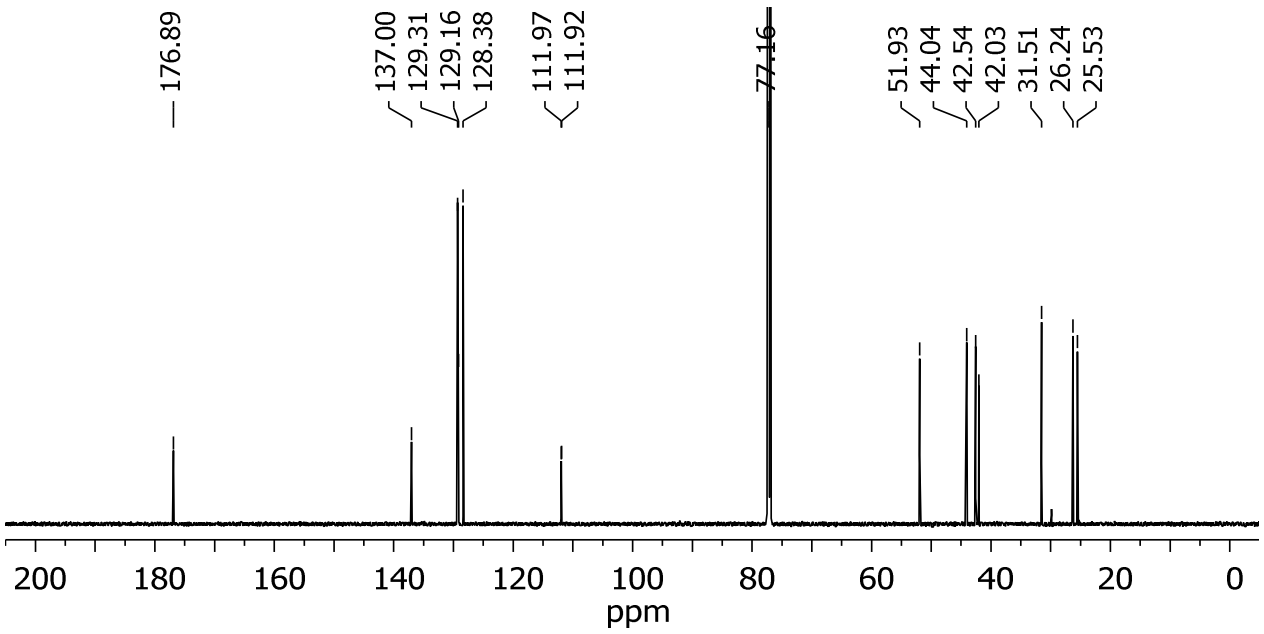


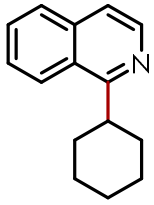


28'

($CDCl_3$, ^1H NMR: 600 MHz, ^{13}C NMR: 151 MHz)

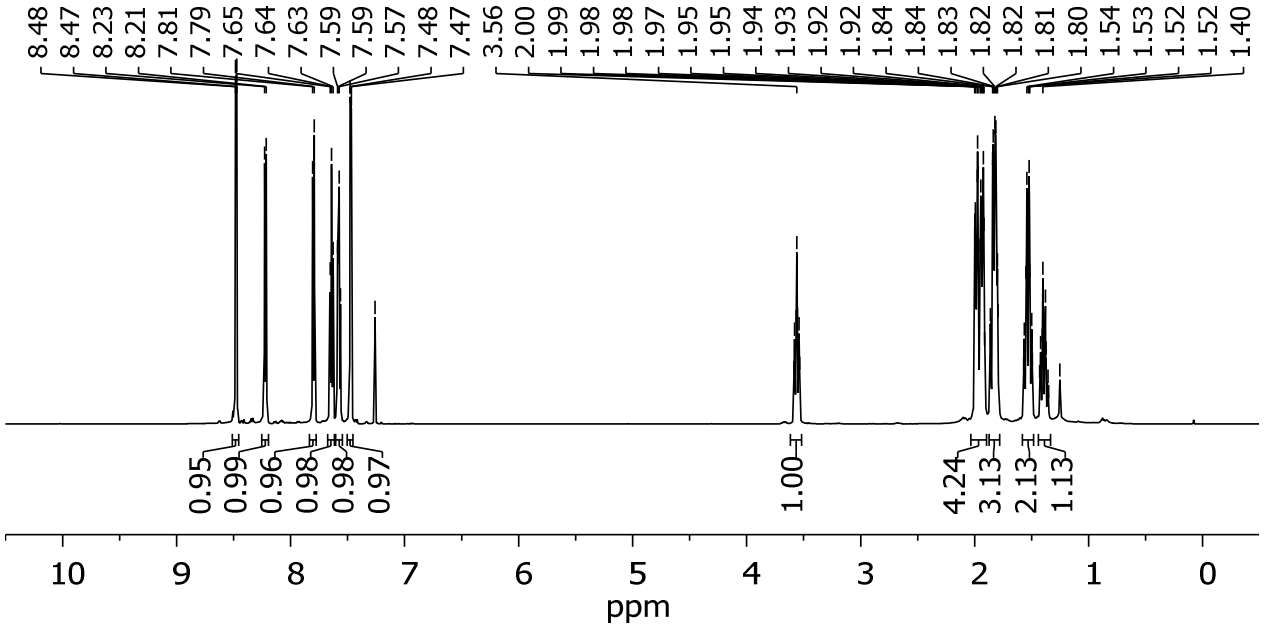


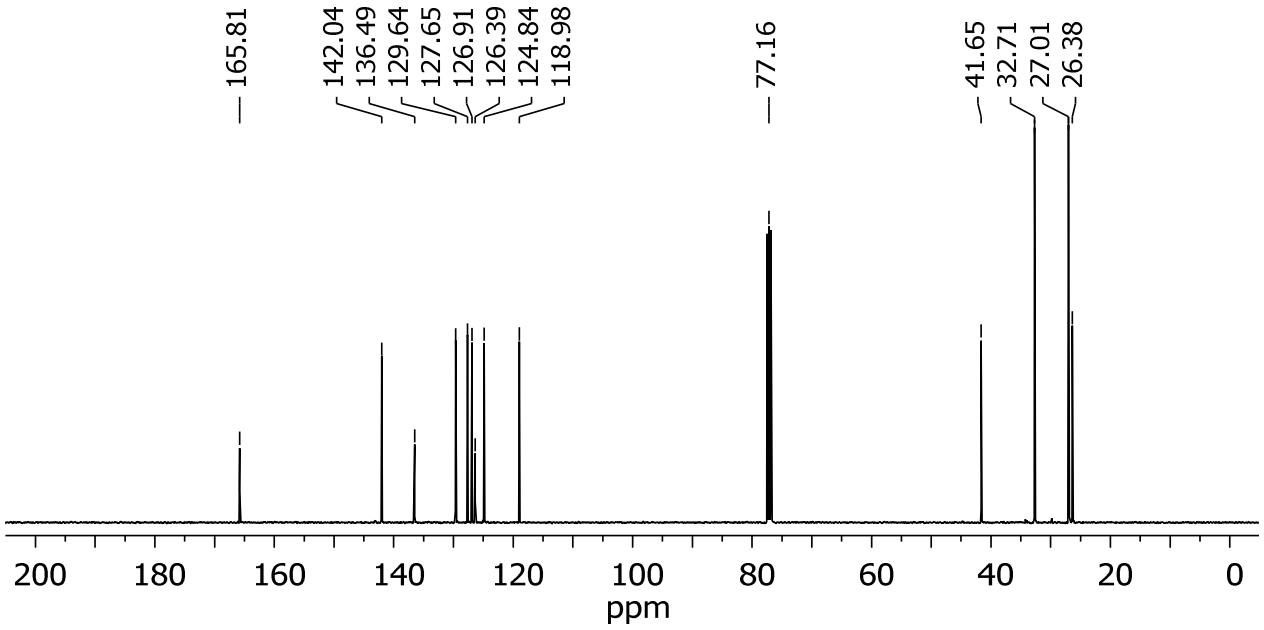


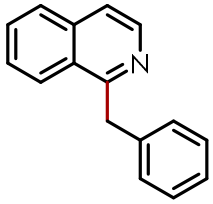


29

($CDCl_3$, ^1H NMR: 600 MHz, ^{13}C NMR: 101 MHz)

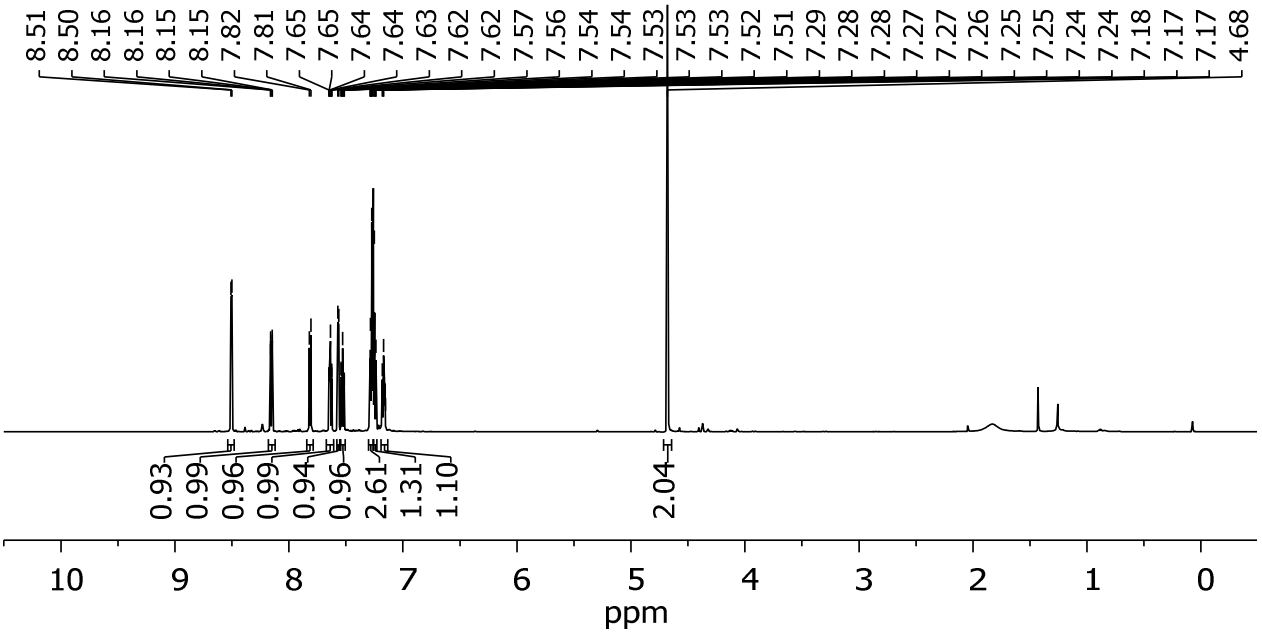


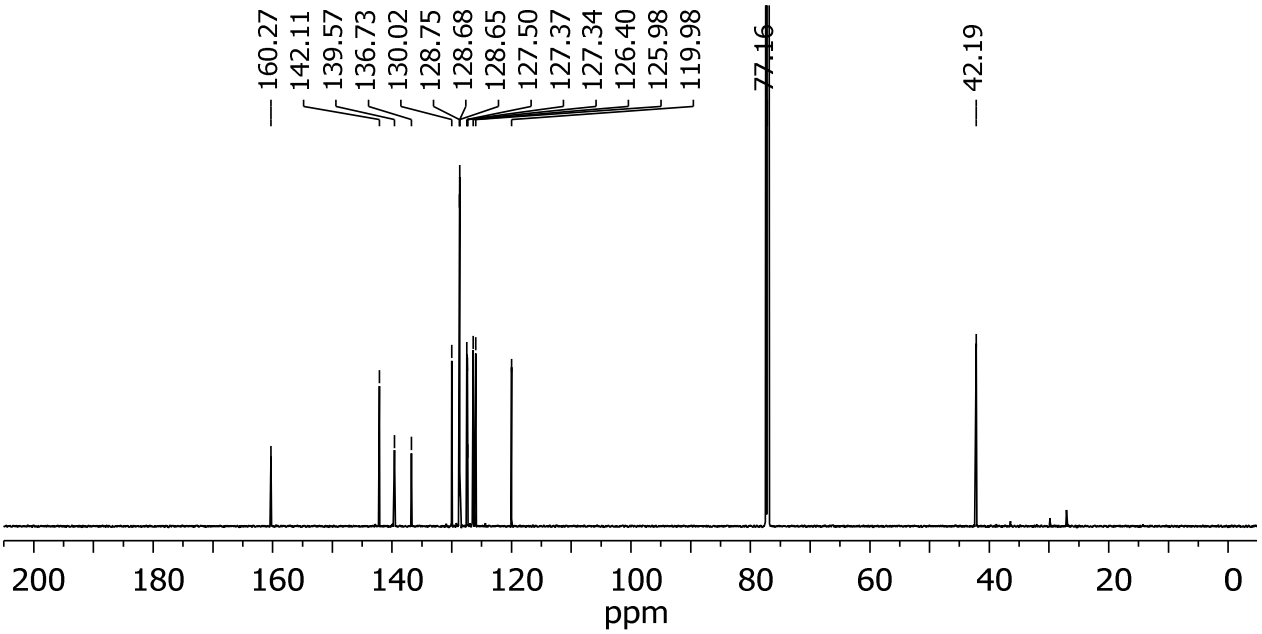


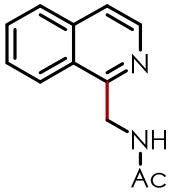


30

($CDCl_3$, ^1H NMR: 600 MHz, ^{13}C NMR: 151 MHz)

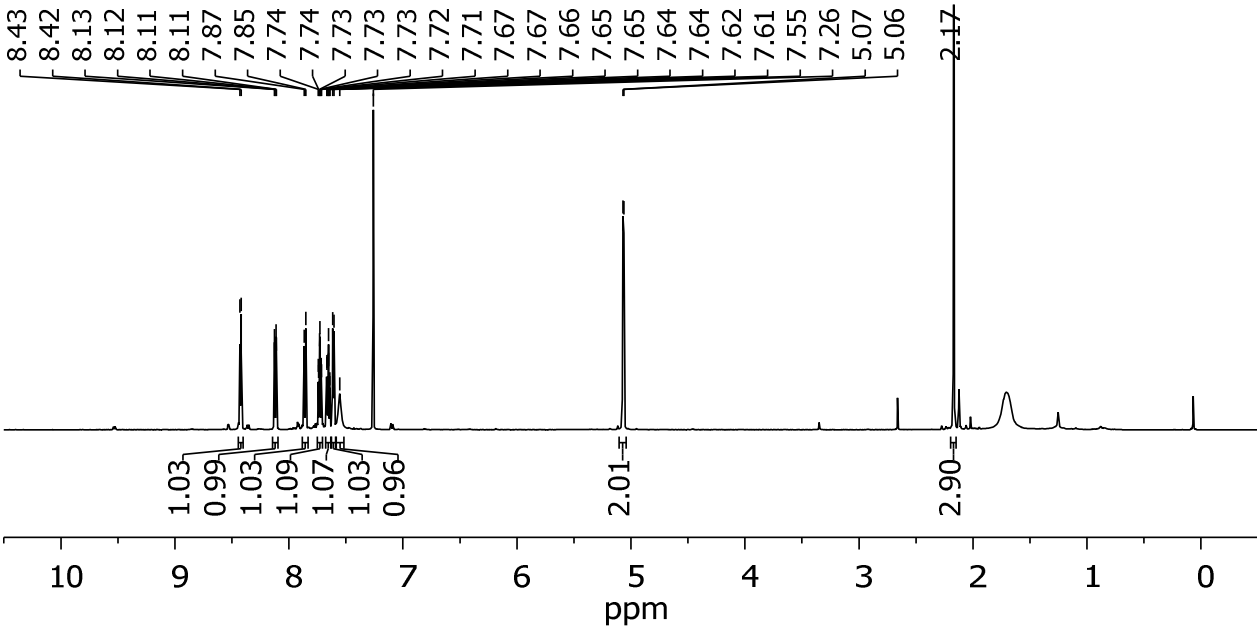


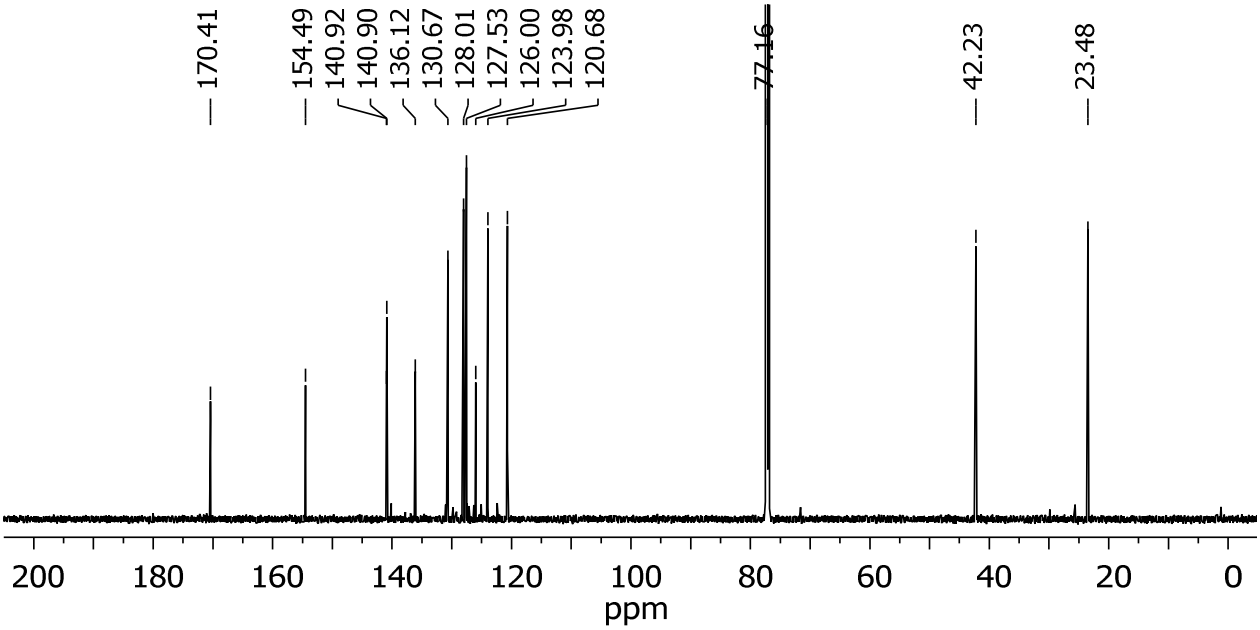


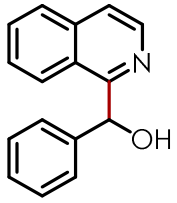


31

($CDCl_3$, ^1H NMR: 600 MHz, ^{13}C NMR: 151 MHz)

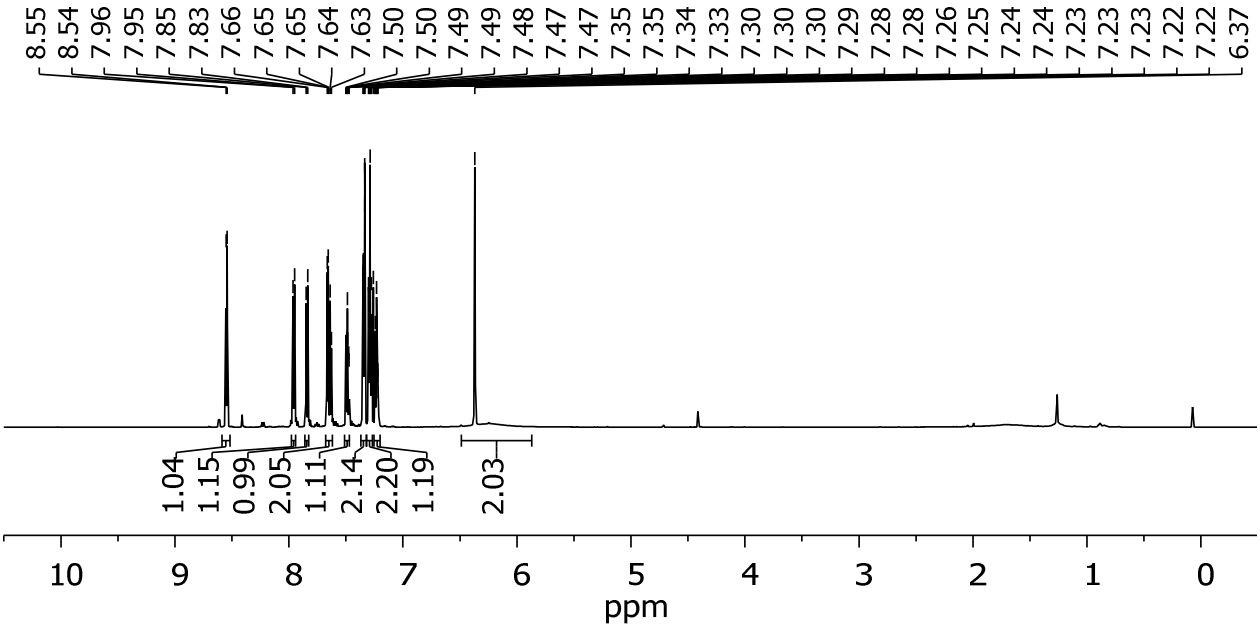


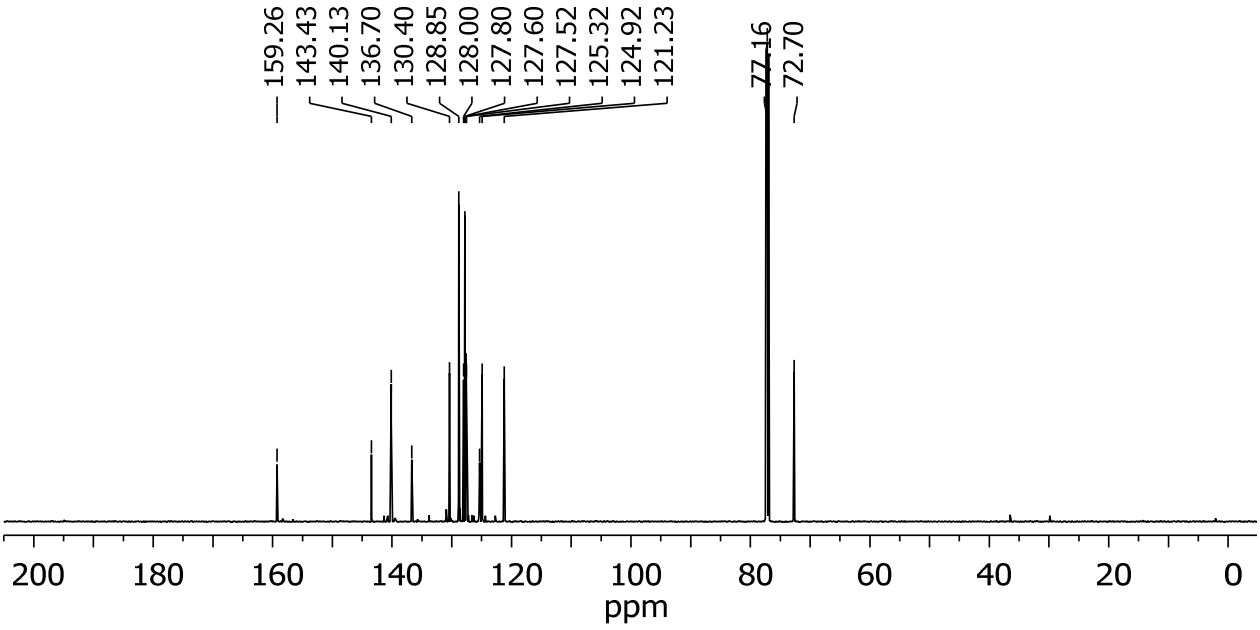


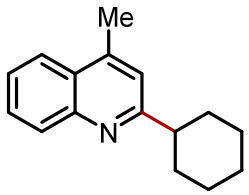


32

($CDCl_3$, ^1H NMR: 600 MHz, ^{13}C NMR: 151 MHz)

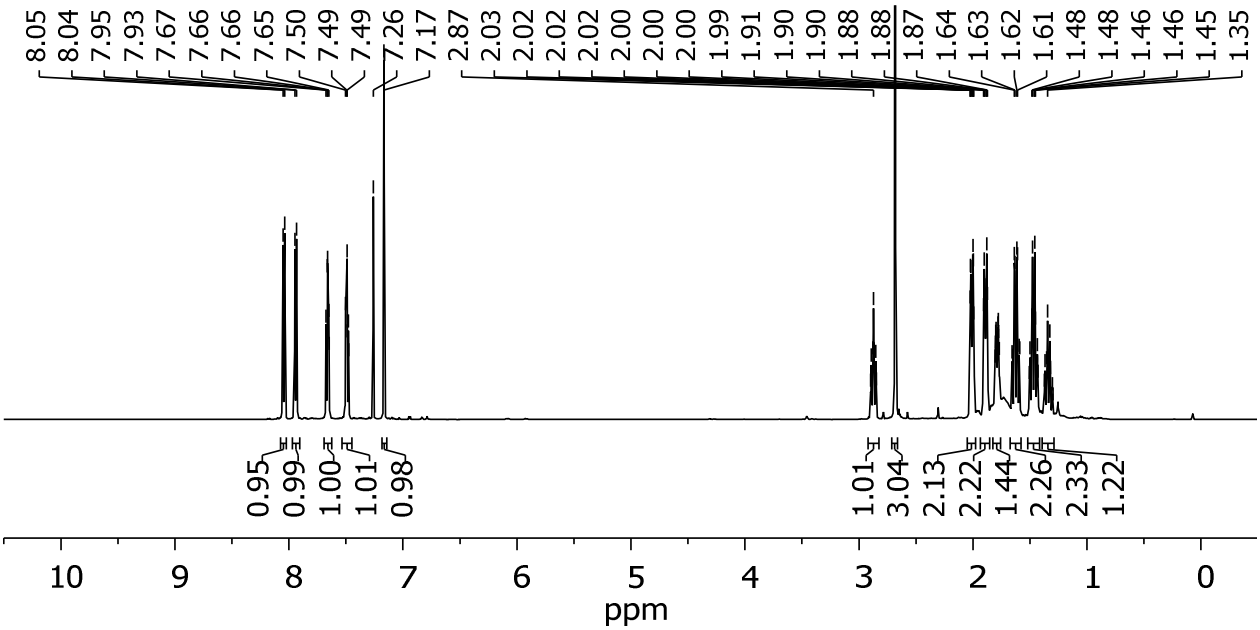


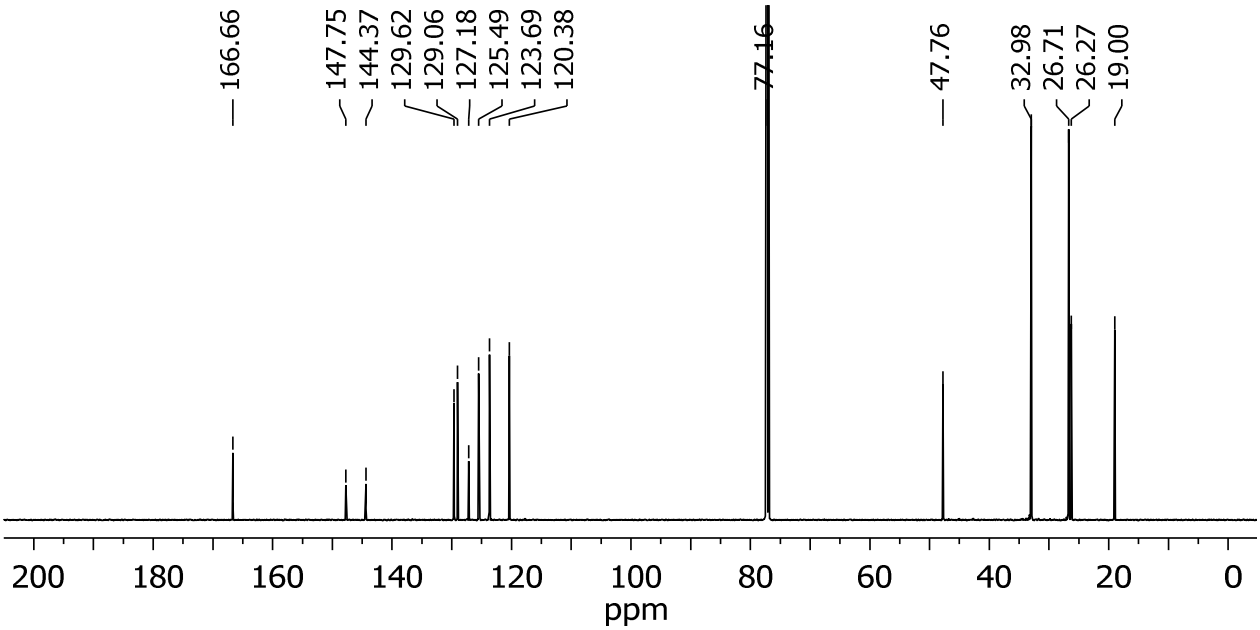


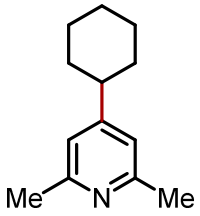


33

($CDCl_3$, ^1H NMR: 600 MHz, ^{13}C NMR: 151 MHz)

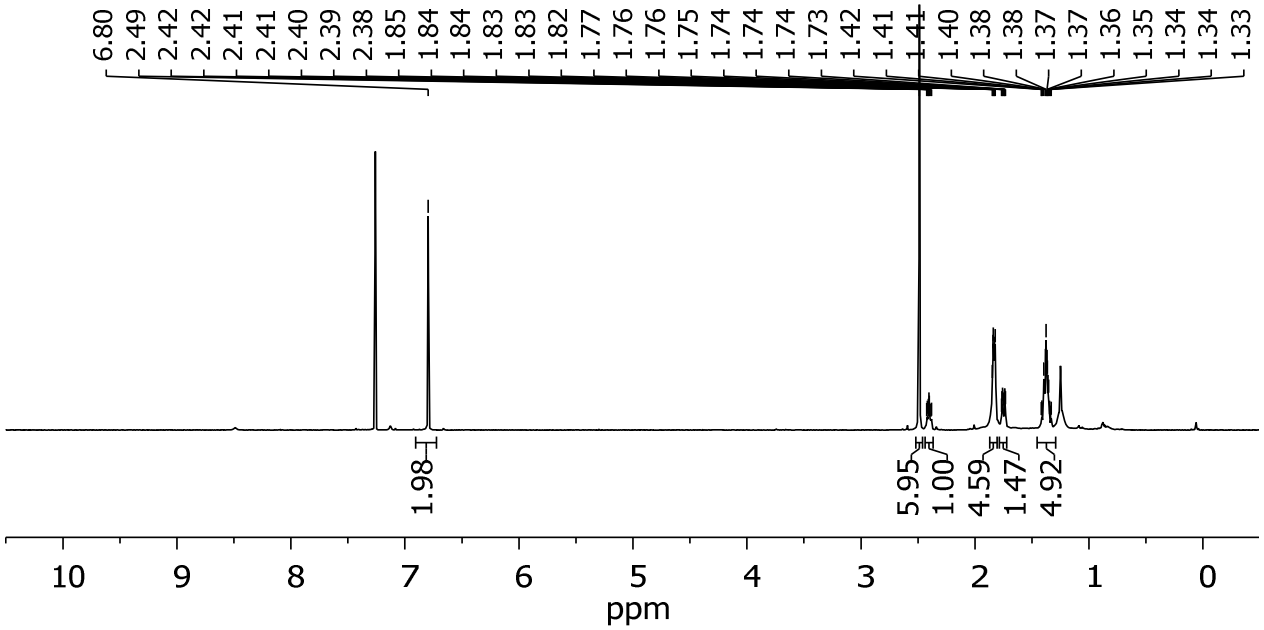


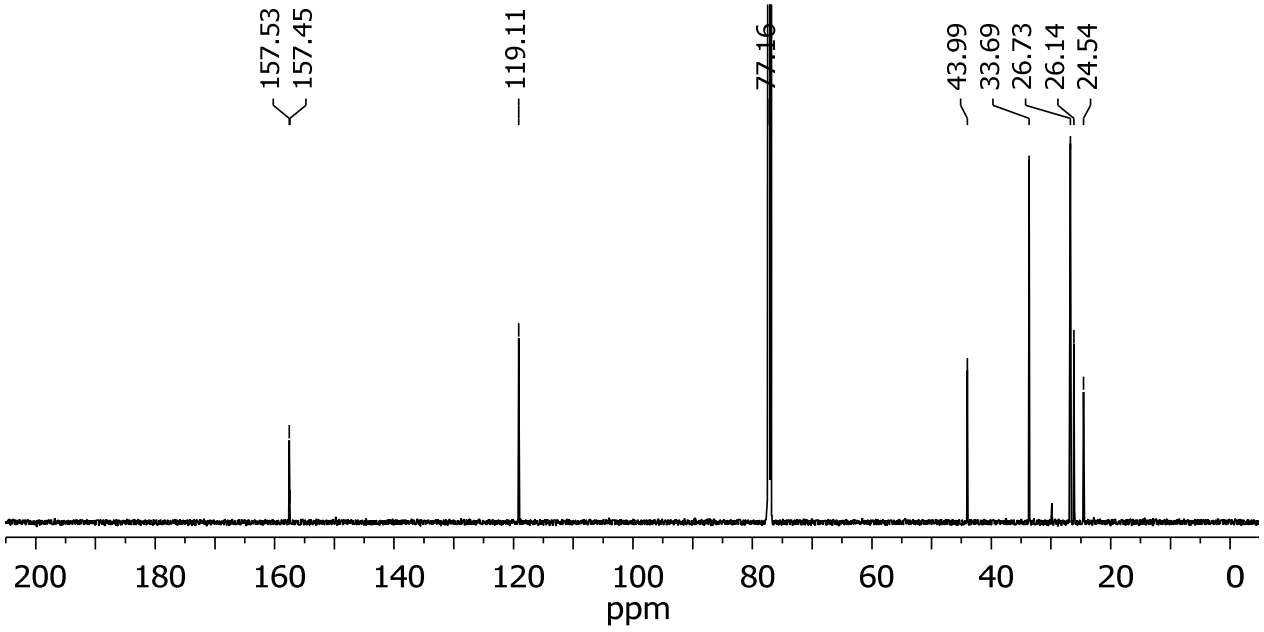


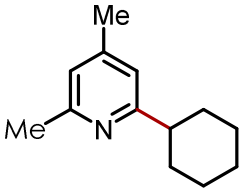


34

($CDCl_3$, ^1H NMR: 600 MHz, ^{13}C NMR: 151 MHz)

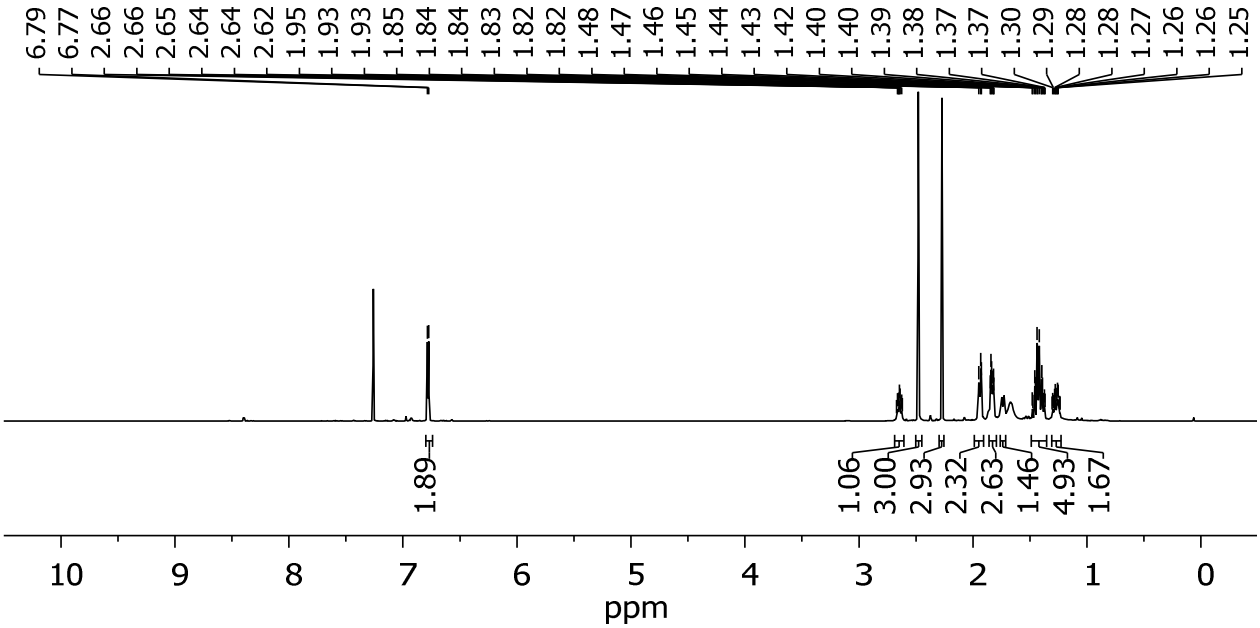


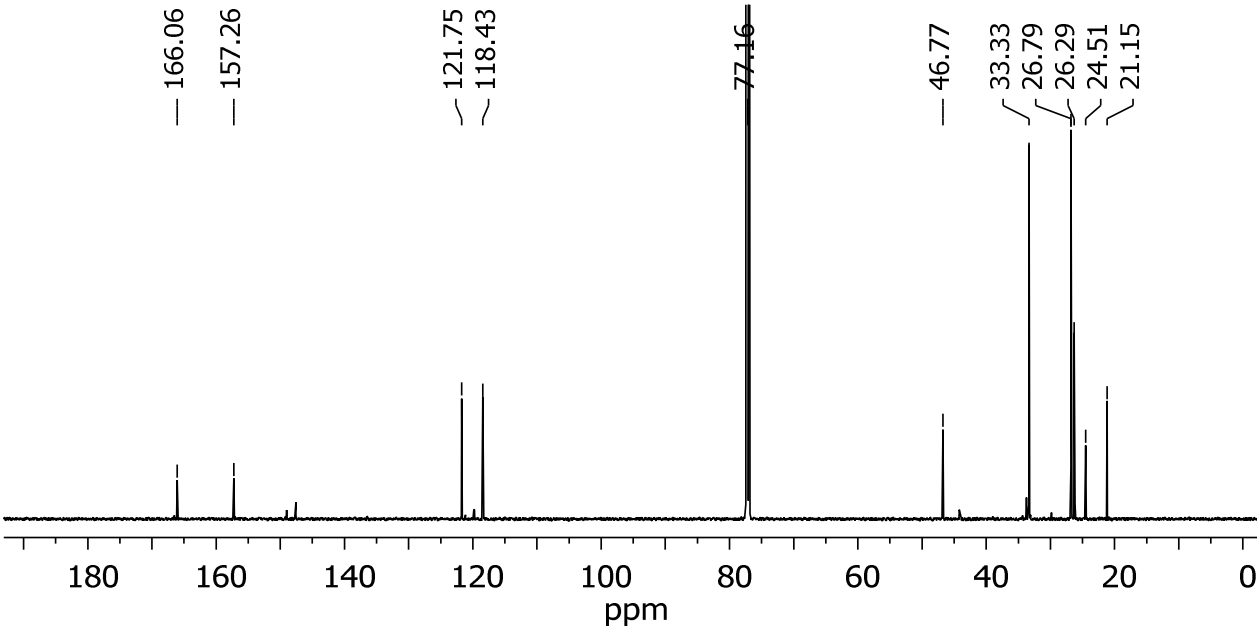


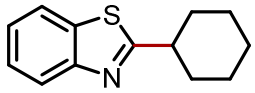


35

($CDCl_3$, ^1H NMR: 600 MHz, ^{13}C NMR: 151 MHz)







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($CDCl_3$, ^1H NMR: 600 MHz, ^{13}C NMR: 151 MHz)