Supplementary Information:

A straightforward route to substituted 1-pyrrolines via photocatalyzed ring-opening cyclization of cyclopropyl enamines

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1. General information

^{1}H (600 MHz), ^{13}C (151 MHz), ^{19}F (565 MHz) and ^{31}P (243 MHz) spectra were recorded at ambient temperature using Bruker Avance III HD 600 (Bruker, Bremen, Germany) at 600 MHz. The chemical shifts (δ) are reported in parts per million downfield from residual solvent ($CDCl_3$, CD_3OD, $(CD_3)_2SO$).^{1}H NMR spectra are reported in parts per million (ppm) downfield relative to $CDCl_3$ (7.26 ppm) and all ^{13}C NMR spectra are reported in ppm relative to $CDCl_3$ (77.16 ppm) unless stated otherwise. The multiplicities of signals are designated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sext (sextet), hept (heptet), m (multiplet) and as combination of previously mentioned abbreviations. Coupling constants (J) are reported in hertz (Hz). NMR yields were calculated using trichloroethylene (TCE) as an internal standard by the integration of the selected peaks. In cases where diastereomer peaks could be distinguished, they are labelled as major and minor. TLC analysis was performed using Silica on aluminum foils TLC plates (F254, SILICYCLE) with visualization under ultraviolet light (254 nm and 365 nm) or appropriate TLC staining (Ninhydrin, $KMnO_4$, or Phosphomolybdic acid). Flash chromatography was performed using silica (P60, SILICYCLE). Flow equipment and parts were purchased from Darwin-microfluidics. Stainless Steel (1/8" OD x 1 mm ID) and FEP (internal diameter 0.5 mm, external diameter 1.6 mm) tubing were purchased from Darwin-microfluidics and cut into appropriate lengths. AL-1000 1 SyringeONE Aladdin Programmable syringe pump was purchased from World Precision Instruments Germany, Razel R99-E and syramed® µSP6000 syringe pumps were obtained from Razel scientific and Arcomed respectively. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator (in vacuo at 40 ºC, ~40 mbar). UV-Vis-spectra were collected (applying baseline corrections) by a Jasco V-750 spectrophotometer with a spectral bandwidth of 2 nm.

Photoluminescence spectra were obtained with a Jasco FP-8050 spectrofluorometer equipped with a 450 W xenon lamp as the excitation source. The luminescence was collected exciting at 440 nm with an emission range of 400–750 nm with a 5 nm spectral bandwidth for excitation and emission. Measurements were performed in a quartz cuvette (optical path: 1 cm) sealed with a rubber septum. The solution was bubbled with N_2 for 10 minutes before irradiation. Low Mass Spectra Analysis were recorded on an Agilent-HP GC-MS (E.I. 70 eV). High Resolution Mass Spectra (HRMS) were obtained using a Bruker High Resolution Mass Spectrometer in fast atom bombardment (FAB+) ionization mode. Photocyclization experiments were performed using Kessil PR160L 456 nm or Kessil Tuna Blue A160WE as light sources. The technical details relating to the light sources used in this work can be retrieved from the manufacturer's website (https://kessil.com/products/science_main.php).

1.1 Materials

Solvents were bought from VWR International and Carlo Erba and used as received without further purification. All reagents were purchased from the companies Fluorochem, TCI, Merck and BLD Pharm and used as received without further purification. The synthesis of cholesteryl acetoacetate **q'**(*2*) and N-tert-butyl-3-oxobutanamide **t'**(*3*) were performed according to literature procedures.

1.2 Experimental Setups

Thermal step batch setup

The condensation step in batch (procedures **GP1.1A** and **GP1.1B**) was conducted in a vial with a stirring bar, placed in an oil bath at a temperature of 50 °C (Figure S1).

Figure S1 Details of the condensation reaction in batch of **a** and **a'** (1 mmol scale). Left: t = 0 min; T= 25 °C; Center: t = 1 min; T= 25 °C; Right: t = 100 min; T= 50 °C.

Photochemical step batch setup

The ring opening-cyclization batch reactions (procedure **GP2.1**) were conducted inside a 7.5 mL (13 × 100 mm, Pyrex, Corning) screw-capped glass test tubes, placed into a UFO 3D-printed reactor (*4*) equipped with either a Kessil Tuna Blue lamp (Intensity 100% color 50%) or a 40W Kessil PR160L-456 nm LED lamp (Intensity 100%). A 24V fan placed in the bottom of the reactor ensured that the reaction temperature did not exceed 35 °C (Figure S2).

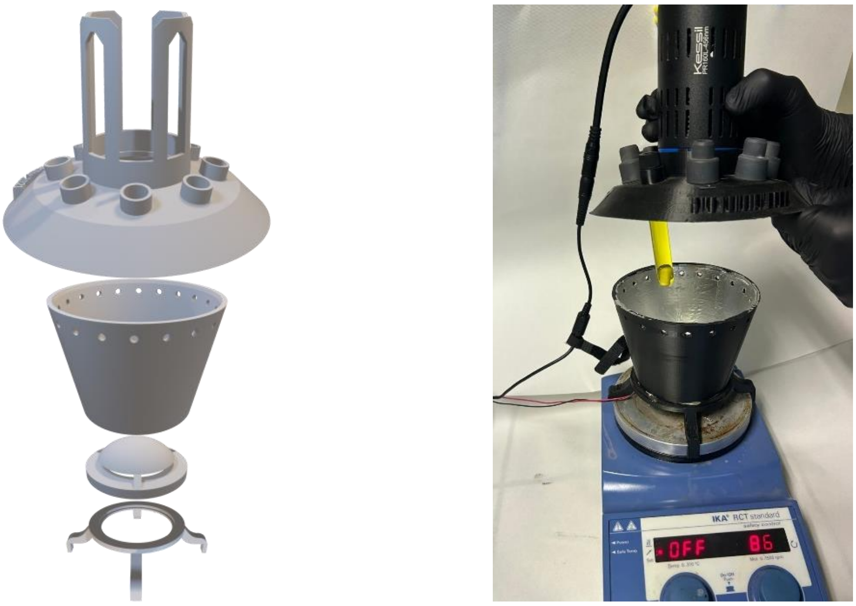
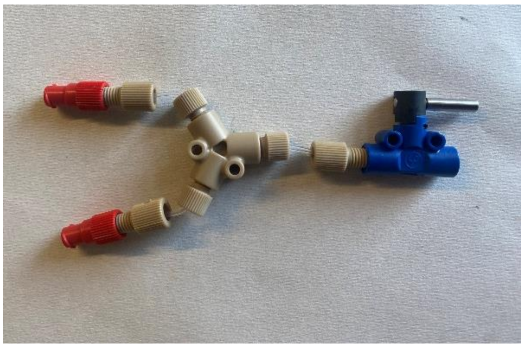


Figure S2 Details of the batch reactor used for the photocatalyzed ring opening-cyclization step.

Flow Equipment

Syringe pump model AL-1060

1 mL Coil Tubing, Stainless Steel 1/8" OD x 1 mm ID



Fitting and stop valve

Check valve

Figure S3 Flow equipment

Thermal step flow setup

The flow condensation reactions were performed inside a stainless steel coil tubing (V = 1 mL, ID = 1 mm) submerged into an oil bath kept at 50 °C. The outlet of the coil was connected to a check valve and the inlet to a Y-mixer, through which the starting materials were fed. In case of neat reactions (**GP1.2A**) the starting materials were delivered to the Y-mixer by two different syringe pumps (Figure S4).

Figure S4 Details of the setup used for the thermal step in flow.

In reactions that required the use of the solvent (**GP1.2B**) the solutions of the starting materials were pushed by the same syringe pump and the two streams converged into a Y-mixer, which mixed and delivered the reaction mixture to the Stainless steel coil (Figure S5).

Figure S5 Overview and details of the condensation step setup

Photochemical step flow setup

The flow photocatalyzed ring-opening cyclization reaction was carried out in a 3D-printed Uflow reactor equipped with a Kessil lamp and a 4 mL FEP coil (ID = 0.5 mm, OD = 1.6 mm) connected to a syringe pump. A 24 V fan positioned at the bottom of the reactor ensured that the reaction temperature did not exceed 35 °C (Figure S6).

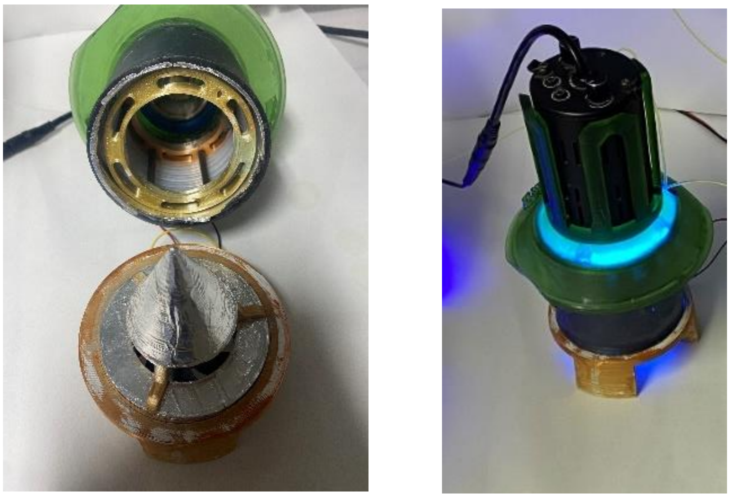


Figure S6 Overview and details of the UFlow system.

Telescoped reaction setup

The telescoped approach setup is composed by a syringe pump that pushes the starting materials, charged in two separate syringes, into a Y-mixer that delivers the resulting mixture to a stainless steel coil (V =1 mL, ID = 1 mm) submerged into an oil bath heated to 50 °C. The output of the steel coil is linked to a check valve followed by a second Y-mixer connected to a second syringe pump that delivers the photocatalyst solution to two FEP coils (V_1 = 4 mL, ID = 0.5 mm ; V_2 = 10 mL, ID = 0.5

mm) arranged in series and inserted in to two 3D-printed UFlow photochemical reactors, each equipped with a Kessil lamp.

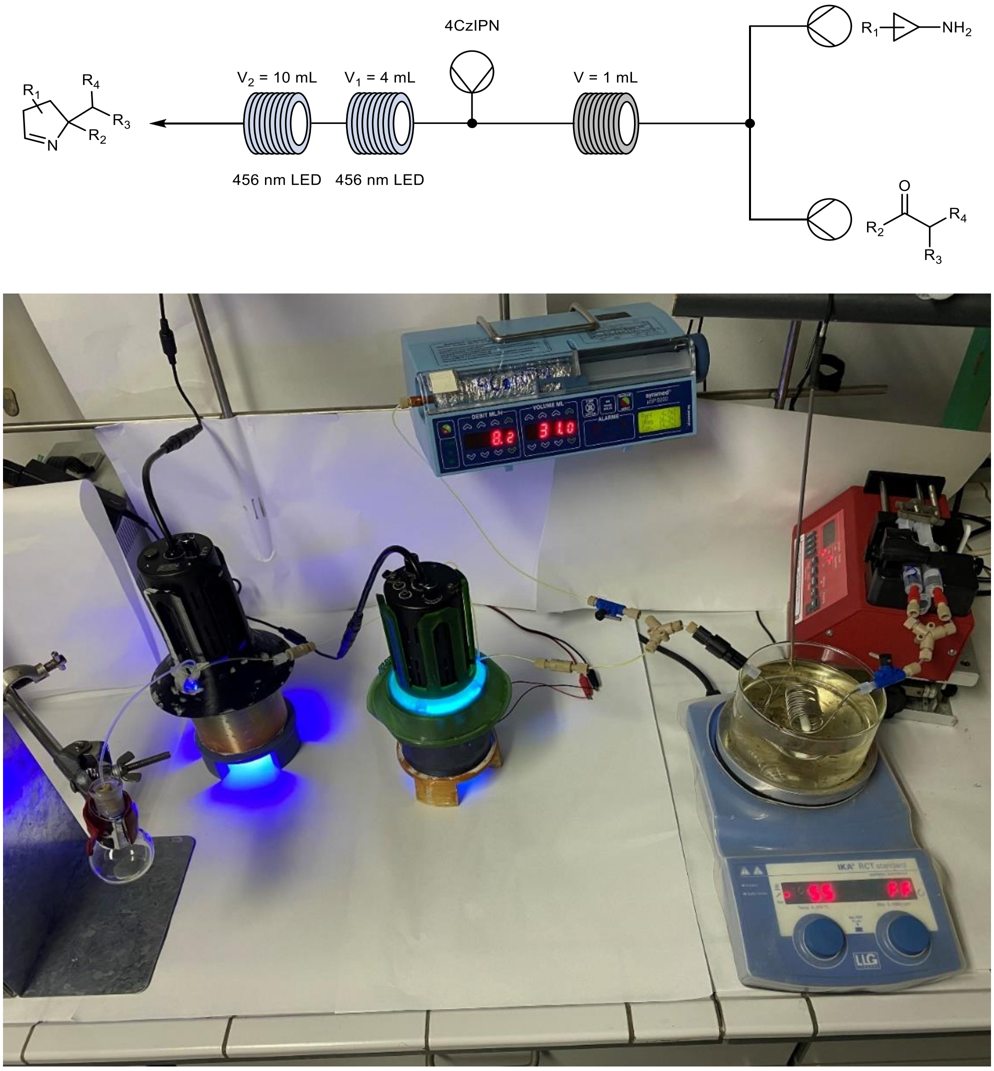


Figure S7 Schematic representation and pictures of the thermal and photocatalyzed reactions performed in continuous-telescoped mode.

Fed batch reaction

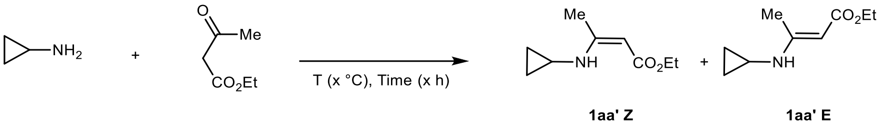
The telescoped fed-batch setup is composed by a syringe pump that pushes the starting materials, charged in two separate syringes, into a Y-mixer that delivers the resulting mixture to a stainless steel coil (V =1 mL, ID = 1 mm) submerged into an oil bath heated to 50 °C. The output of the steel coil is linked to a check valve followed by a second Y-mixer connected to a second syringe pump that delivers the photocatalyst solution to two FEP coils (V_1 = 4 mL, ID = 0.5 mm ; V_2 = 10 mL, ID = 0.5 mm) arranged in series and inserted in to two 3D-printed UFlow photochemical reactors, each equipped with a Kessil lamp. The outlet of the photochemical reactor was inserted into a round bottom flask containing $NaBH_4$, equipped with a stirring bar and immersed into an ice bath.

2. Optimization

2.1 Optimization of the thermal step for the synthesis of starting material

In a 2 mL vial, cyclopropylamine **a** (0.5 mmol) and ethyl acetoacetate **a’** (0.5 mmol) were added. The mixture was stirred at the given temperature for the given time. The crude residue was then dissolved in $CDCl_3$ (2 mL) and trichloroethylene added as the internal standard (0.5 mmol, 45 µL). An analytical sample was transferred into an NMR tube and analysed by ^1H NMR to obtain the reaction NMR yield.

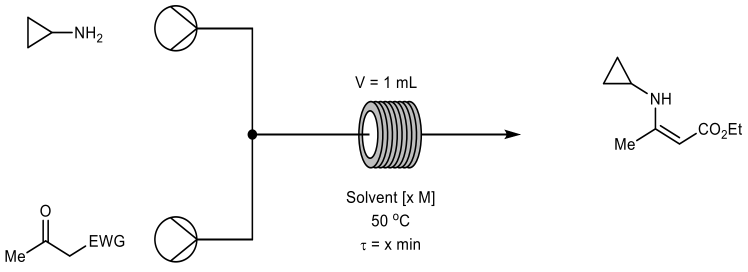
Table S1. Screening of Temperature and Time



Entry	Time	Reactor	Temperature	Conversion	Yield 1aa’ Z+E	Ratio 1aa’ Z /1aa’ E
1	8 h	Vial 4 mL	25 °C	80%	78%	5:1
2	6 h	Vial 4 mL	50 °C	86%	82%	>20:1
3	8 h	Vial 4 mL	50 °C	95%	90%	>20:1

Cyclopropylamine **a** (0.5 mmol) and ethyl acetoacetate **a’** (0.5 mmol) were charged in two syringe pumps (5 M in MeCN for entry 3) and delivered through a Y-mixture to a Stainless-Steel coil (1 mL) submerged into an oil bath kept at 50 °C. The solvent was evaporated to give a crude residue that was then dissolved in $CDCl_3$ (2 mL). Trichloroethylene was added as internal standard (0.5 mmol, 45 µL), and an analytical sample was transferred into an NMR tube and analysed by ^1H NMR to determine the reaction NMR yield.

Table S2. Optimization of the parameters for the flow process

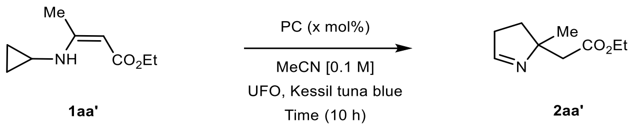


Entry	Residence time τ	Solvent	Conversion	Yield 1aa’ Z+E	Ratio 1aa’ Z /1aa’ E
1	2 h	Neat	88%	85%	>20:1
2	3 h	Neat	>99%	>99%	>20:1
3	3 h	CH_3CN (2.5 M)	>99%	>99%	>20:1

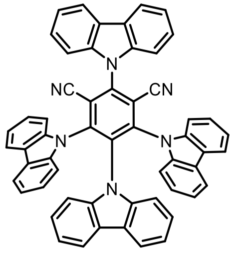
2.2 Optimization of the photocyclization step

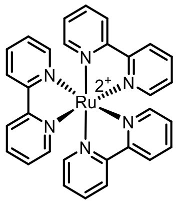
In a disposable reaction tube (7.5 mL, 13 × 100 mm, Pyrex, Corning) **1aa**’ (0.5 mmol), the photocatalyst **PC** (X mol%) and degassed solvent (5 mL) were charged and irradiated with a Kessil lamp placed in a UFO reactor. The solvent was evaporated to give a crude residue that was then dissolved in $CDCl_3$ (2 mL). Trichloroethylene was added as internal standard (0.5 mmol, 45 µL), and an analytical sample was transferred into an NMR tube and analysed by ^1H NMR to determine the reaction NMR yield.

Table S3. Screening of the Photocatalysts



Entry[a]	Photocatalyst	PC (mol%)	Conversion	Yield 2aa’
1	4CzIPN	2%	80%	75%
2	4CzIPN	5%	100%	93%
3	[Ru(bpy)$_3$]Cl$_2$·6H$_2$O	2%	15%	<10%
4	[Ir((dFCF$_3$)ppy)$_2$(dtbpy)](PF$_6$)	2%	27%	23%


4CzIPN


[Ru(bpy)$_3$]Cl$_2$·6H$_2$O

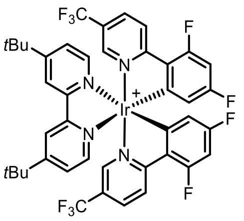
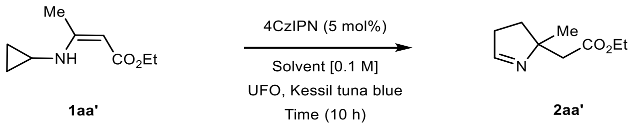

[Ir((dFCF$_3$)ppy)$_2$(dtbpy)]PF$_6$

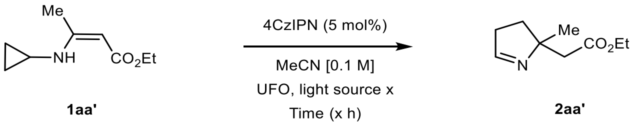
Table S4 Screening of the Solvents



Entry	Solvent	Conversion	Yield 2aa’
1	MeCN	>99%	93%
2	DMSO	98%	80%
3	DEC	97%	81%
4	EtOAc	88%	75%

5	Acetone	75%	69%
6	*t*-BuOH	56%	52%
7	Me-THF	40%	<20%
8	DCM	40%	<20%

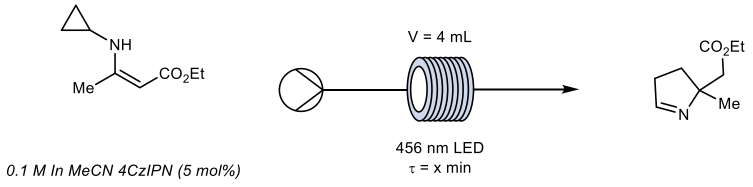
Table S5 Screening of Irradiation Sources and Time



Entry	Light source	Time	Conversion 1aa’	Yield 2aa’
1	Kessil Tuna Blue	10 h	>99%	93%
2	Kessil Tuna Blue	4 h	80%	74%
3	Kessil 456 nm	10 h	>99%	91%
4	Kessil 456 nm	4 h	90%	88%
5	Kessil 456 nm	8 h	>99%	94%
6	Kessil 456 nm	6 h	>95%	95%
7*	Kessil 456 nm	8 h	>99%	94%

[*] **1aa**’ was used without any workup from the previous step (one pot).

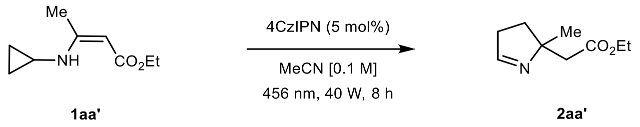
Table S6 Optimization of the Residence Time for the flow process



Entry[a]	Residence time τ (min)	Conversion	Yield 2aa
1	240	>99%	88%
2	120	>99%	95%
3	90	>95%	96%
4	60	93%	92%
5*	90	>95%	95%

[a] Uflow reactor with 4 mL FEP coil was used. [*] **1aa’** was used without any workup from the condensation.

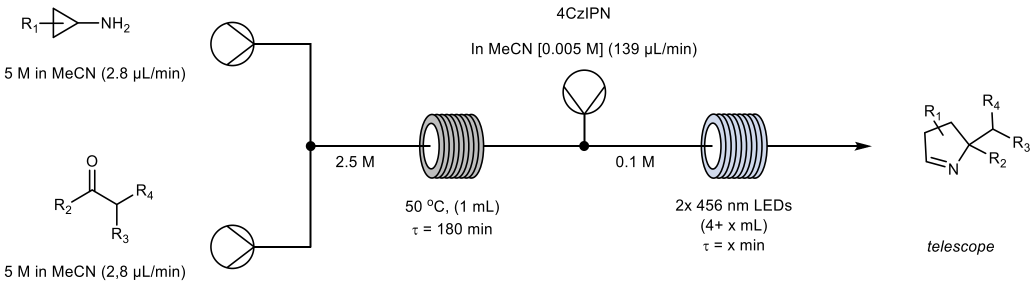
Table S7. Control experiments



Entry	Variation from standard conditions	Yield 2aa’
1	-	94%
2	No light	-
3	No light, 60 °C	-

2.3 Optimization of the telescoped reaction

Table S8 Optimization of the parameters for the telescoped approach



Entry	Variables screened in the photochemical step	τ	Yield 2aa	Productivity mg/h
1	1 lamp (Coil 4 mL)	28 min	59%	84
2	1 lamp (Coil 10 mL)	69 min	75%	107
4	1+1 lamps (Coil 4+4 mL)	55 min	78%	111
5	1+1 lamps (Coil 10+4 mL)	96 min	84%	119

The productivity of the telescoped process was enhanced by placing two UFlow reactors in series, each equipped with its own Kessil lamp.

3. General procedures and characterization data

3.1 General procedure for starting materials preparation GP1 (condensation)

List of the precursors for the starting materials synthesis

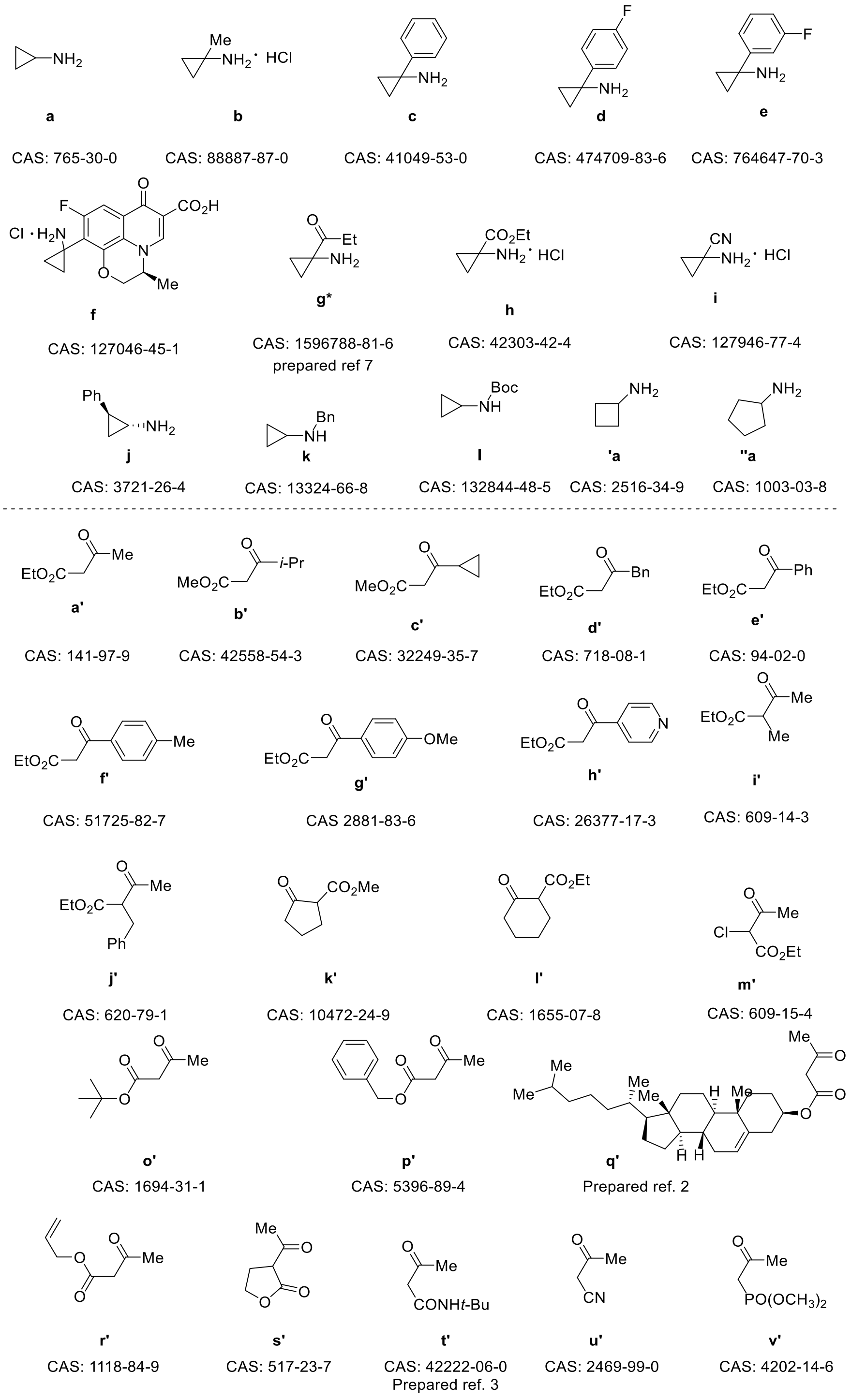
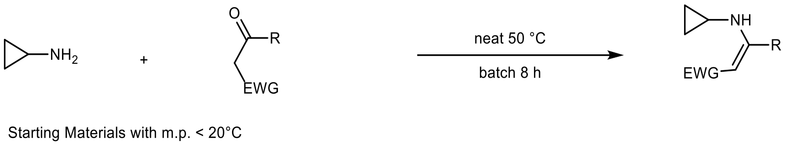


Figure S8

All the condensation reactions were monitored by NMR spectroscopy. NMR yields were determined using trichloroethylene (TCE) as internal standard (1 mmol, 90 µL). For reactions with an NMR yield above 95%, the crude was diluted with EtOAc, dried with Na_2SO_4, filtered. The solvent was then removed under vacuum and the obtained products were used without further purification. In case of lower NMR yields the product was purified by flash column chromatography on silica gel (petroleum ether/diethyl ether in increasing polarity) to remove the unconverted starting materials.

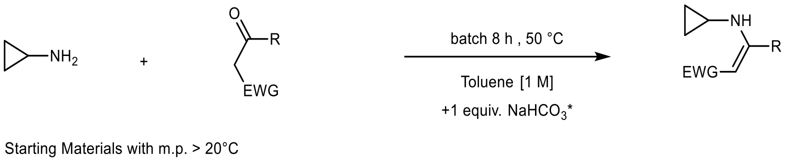
NOTE: The conversion of residual starting material can be pushed to completion by adding an excess (0.2 equiv.) of either the amine or the β-keto derivative. If cyclopropylamine is used as the excess reagent, final column chromatography is generally not required, as the compound is readily removed by evaporation under reduced pressure.

Condensation reaction neat, in batch GP1.1A



To a vial equipped with a stirring bar, the cyclopropylamine (1-10 mmol, 1 equiv.) and the β-keto derivative (1 equiv.) were added, the resulting mixture was stirred at 50 °C and monitored by NMR spectroscopy after 8 hours (see GP1).

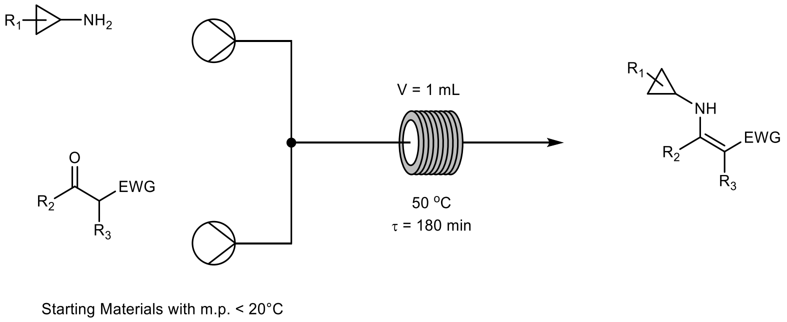
Condensation reaction with solvent, in batch GP1.1B



To an oven-dried 25 mL round-bottom flask equipped with a magnetic stirring bar, the cyclopropylamine* (1 mmol, 1 equiv.) and the β-keto derivative (1 mmol, 1 equiv.) were added. Toluene (1 mL) was then introduced, and the resulting suspension was stirred at 50 °C overnight. The crude reaction mixture was purified according to GP1.

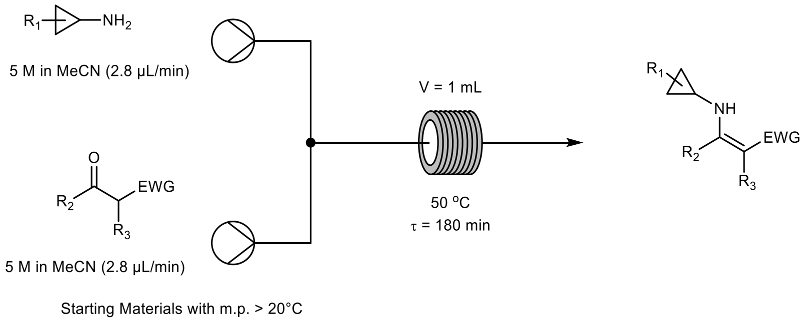
*When cyclopropyl amines hydrochloride salts are used $NaHCO_3$ (1 mmol, 1 equiv.) was added within the amine.

Condensation reaction neat, in flow GP1.2A



When starting materials were both liquid, cyclopropylamine (10 mmol) and the β-keto derivative (1 equiv.) were loaded separately into two 1 mL syringes. Using independent syringe pumps, the reagents were delivered to a 1 mL stainless-steel coil maintained at 50 °C (see Figure S3). The flow rates were adjusted to ensure a 1:1 molar ratio of the starting materials. The yield of the obtained compound was determined by NMR analysis as described in **GP1**.

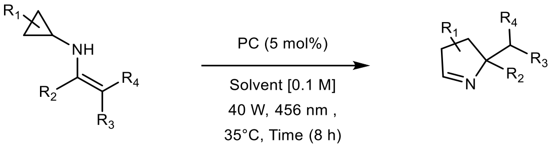
Condensation reaction with solvent, in flow, GP1.2B



A 5 M solution of cyclopropylamine (2.5 mL, 1.43 g, 25 mmol, 1 equiv.) in MeCN was charged into a syringe and a 5 M solution of the β-keto derivative (25 mmol, 1 equiv.) in MeCN into a separate one. The two syringes were pushed using a double channel syringe pump, delivering the two solutions, through a Y-mixer to a 1 mL Stainless Steel Coil kept at 50 °C (see Figure S4). Both flow rates were set to 2.8 µL/min. The crude was analyzed and purified according to **GP1**.

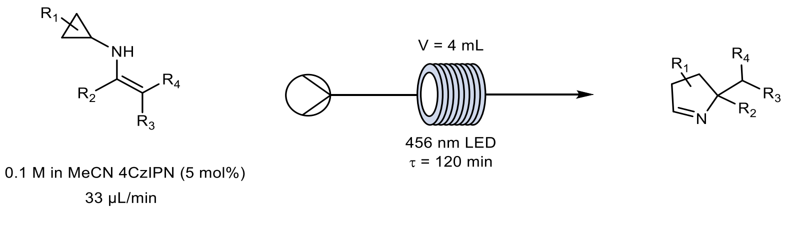
3.2 General procedure for photochemical reaction GP2 (ring opening-cyclization)

Ring opening-cyclization reaction in batch, GP2.1



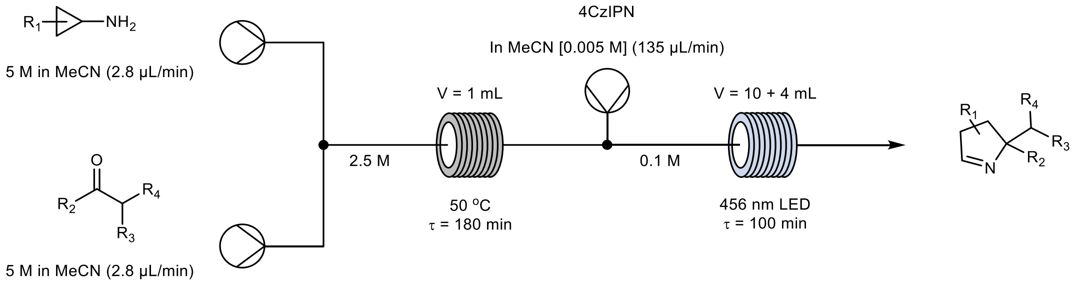
To an oven-dried argon-purged screw-capped vial, fitted with a rubber septum and charged with the photocatalyst 4CzIPN (19.7 mg, 5 mol%), the cyclopropyl enamine derivative (0.5 mmol, 1 equiv.) in degassed CH_3CN (5 mL, 0.1 M) was added. Subsequently the reaction vessel was sparged with argon, capped and sealed with parafilm. The vial was then placed in a 3D-printed UFO photoreactor equipped with a Kessil Lamp (456 nm, 100% intensity) and irradiated for 8 hours. The solvent was then removed under reduced pressure, and the resulting crude mixture was purified by flash column chromatography on silica gel to afford the corresponding product.

Ring opening-cyclization reaction in flow, GP2.2



A solution of the cyclopropyl enamine (0.5 mmol) 0.1 M in MeCN and the photocatalyst 4CzIPN (5 mol%) in MeCN 0.1 M was placed in a syringe and the solution was delivered using a syringe pump to a 4 mL FEP coil (ID = 1 mm) housed in a 3D-printed UFlow photoreactor (see Figure S6). The solvent was then removed under reduced pressure and the resulting crude mixture was purified by flash column chromatography on silica gel to afford the corresponding product.

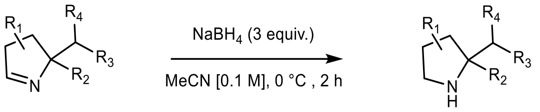
3.3 General procedure for the telescoped approach GP3



Two syringes containing the cyclopropylamine (5 M in MeCN), and the β-keto derivative (5 M in MeCN) respectively were pushed by the same syringe pump (2.8 μL/min). The two solutions were pushed through a Y-mixer that mixed and delivered the reaction mixture into a Stainless steel coil (V = 1 mL) submerged into an oil bath kept at 50 °C. The outlet of the thermal steel coil was equipped with a check valve connected to a Y-mixer in which the photocatalyst solution (0.005 M in MeCN) was pumped with a flow rate of 135 μL/min. The resulting mixture was delivered to two FEP coils (V_1 = 4 mL, ID = 0.5 mm ; V_2 = 10 mL, ID = 0.5 mm) connected in series and inserted into two 3D-printed UFlow photochemical reactors each equipped with a 456nm Kessil lamp (See Fig. S7).

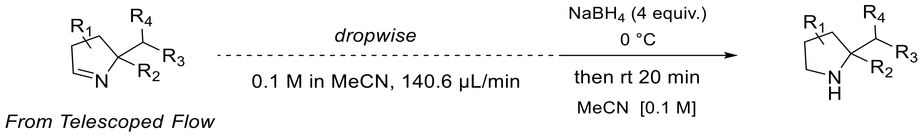
3.4 General procedure for the synthesis of pyrrolidine derivatives GP4

Reduction reaction in batch GP4.1



An oven-dried argon-purged screw-capped vial, fitted with a rubber septum, was charged with 5 mL of a solution of the pyrroline derivative (0.1 M in dry MeCN) and cooled down to 0 °C. 3 equivalents of sodium borohydride were added and then the suspension stirred at room temperature for 2 hours. The mixture was then quenched with a saturated aqueous solution of $NaHCO_3$, extracted with EtOAc, the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel to afford the desired compound, or alternatively, the product precipitated as the corresponding hydrochloride salt by bubbling HCl gas, generated in situ, into a solution of the crude product in diethyl ether (20 mL).

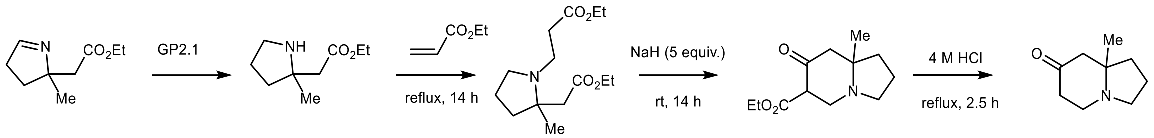
Reduction reaction fed-batch GP4.2



To an oven-dried, argon-purged round-bottom flask fitted with a rubber septum and connected to an argon balloon, sodium borohydride (76 mg, 2.0 mmol, 4.0 equiv.) was added and dispersed in dry MeCN (0.1 mL) at 0 °C. The outlet of the telescoped setup was connected to the flask and the crude reaction mixture from the telescoped process was directly added dropwise to this suspension kept at 0 °C under continuous stirring. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for an additional 30 minutes. The reaction was then quenched with a saturated aqueous solution of $NaHCO_3$, and the product was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel to afford the desired compound, or alternatively, the product was precipitated as the corresponding hydrochloride salt by bubbling HCl gas, generated in situ, into a solution of the crude product in diethyl ether (20 mL).

3.5 Procedures for the post functionalization

Compound **S5** was synthesized following a slightly modified version of the procedure reported in literature (*5*):

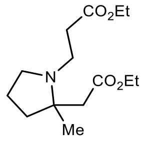


CAS 85358-22-1

2aa' **3aa'** **S4** **S'4** not purified **S5**

Compound **2aa’** and **3aa’** are obtained according to the general procedure **GP2.1** and **GP4.1** respectively.

ethyl 3-(2-(2-ethoxy-2-oxoethyl)-2-methylpyrrolidin-1-yl)propanoate (S4)

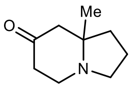


S4

To obtain compound **S4** the pyrrolidine **3aa’** (86 mg, 0.5 mmol) was dissolved in ethyl acrylate (0.5 mL) and refluxed overnight. The solvent was then evaporated, and the residue was purified by flash column chromatography (petroleum ether : AcOEt = 5:1 to 1:1) to afford product **S4** as yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.16 – 4.05 (m, 4H), 2.84 – 2.71 (m, 2H), 2.70 – 2.61 (m, 2H), 2.47 – 2.25 (m, 4H), 2.09 – 2.00 (m, 1H), 1.75 (p, *J* = 7.4 Hz, 2H), 1.65 – 1.58 (m, 1H), 1.28 – 1.22 (m, 6H), 1.06 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 172.8, 172.4, 62.4, 60.4, 60.2, 50.5, 44.4, 42.2, 37.2, 35.1, 20.8, 20.6, 14.4.

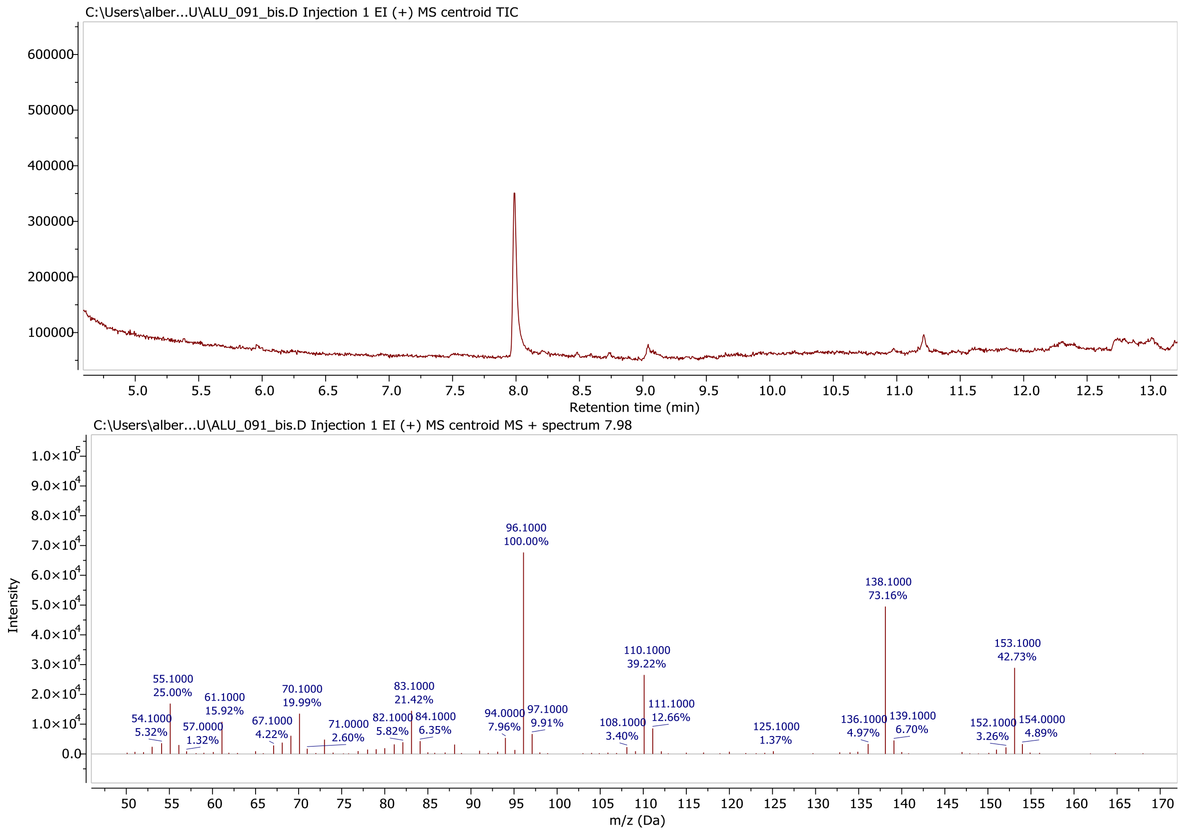
8a-methylhexahydroindolizin-7(1H)-one CAS 85358-22-1 (S5)

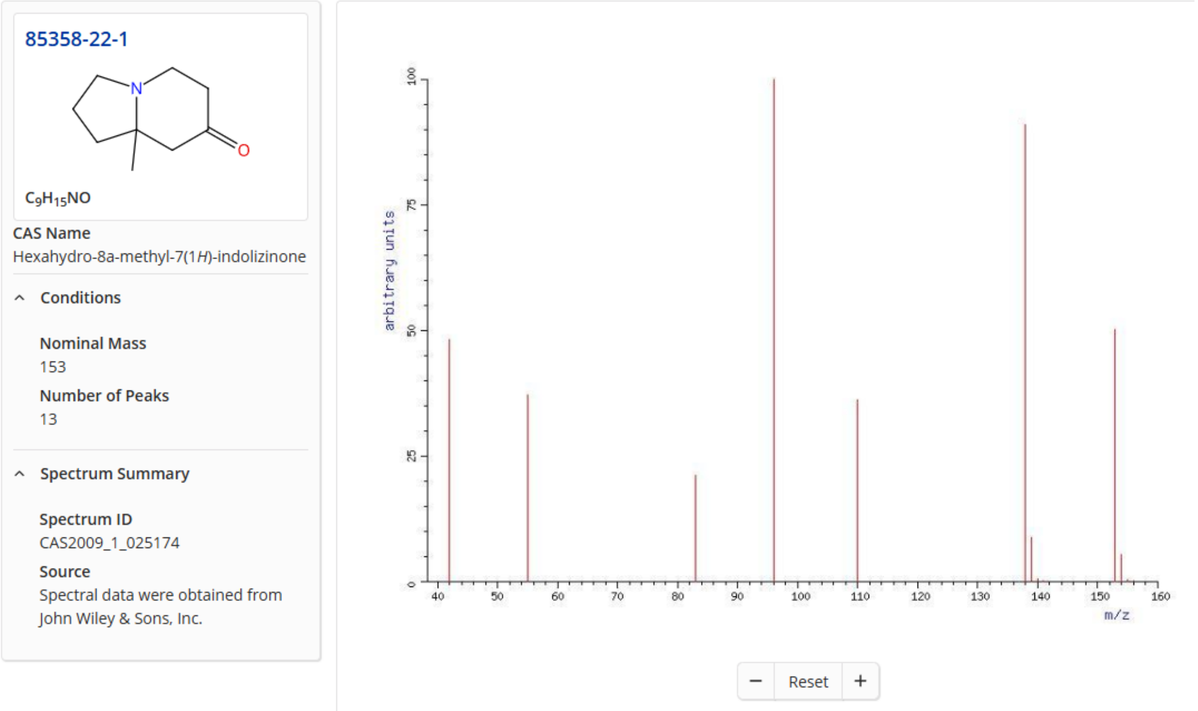


CAS 85358-22-1

S5

To a solution of compound **S4** (0.3 mmol) in dry THF (0.16 M) and drops of MeOH, NaH (5.0 equiv.) was added at room temperature. The solution was stirred overnight, quenched with EtOH and concentrated to give the desired α-keto ester product **S’4**, that was used for the next step without further purification. The ester starting material (e.g., methyl 8-methyl-7-oxooctahydroindolizine-6- carboxylate) was dissolved in 4M HCl and refluxed until the reaction was complete (approximately 3 h). The mixture was cooled to room temperature and K_2CO_3 was added until the pH reached 10. The solution was then extracted with CH_2Cl_2 (6 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and analyzed by GC–MS. The successful synthesis of compound **S5** (8a-methylhexahydroindolizin-7(1H)-one) was confirmed by comparison of the obtained spectrum with the data reported in the Wiley Mass Spectral Library (see Figure S9).





85358-22-1

$C_9H_{15}NO$

CAS Name

Hexahydro-8a-methyl-7(1*H*)-indolizinone

Conditions

Nominal Mass
153

Number of Peaks
13

Spectrum Summary

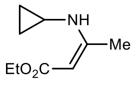
Spectrum ID
CAS2009_1_025174

Source
Spectral data were obtained from John Wiley & Sons, Inc.

Figure S9 GC-MS chromatogram and EI mass spectrum of 8a-methylhexahydroindolizin-7(1H)-one (**S5**) in agreement with literature data obtained from John Wiley Sons, Inc.

3.6 Characterization data of cyclopropylenamines (condensation reaction)

(Z)-ethyl 3-(cyclopropylamino) but-2-enoate (1aa')



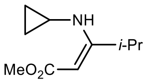
1aa'

Prepared according to general procedure **GP1.1A**, using cyclopropylamine **a** (70 µL, 1mmol, 1 equiv.) and ethyl acetoacetate **a'** (99 µL, 1 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : AcOEt = 10:1 to 1:1), to afford product **1aa'** (144 mg, 85% yield) as pale yellowish oil.

^{1}H NMR (600 MHz, CDCl$_3$) δ 8.53 (s, 1H), 4.47 (s, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 2.62 – 2.49 (m, 1H), 2.05 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.02 – 0.64 (m, 3H), 0.67 – 0.48 (m, 3H).
^{13}C NMR (151 MHz, CDCl$_3$) δ 170.6, 163.8, 82.8, 58.5, 24.8, 20.0, 14.8, 7.8.
The spectroscopic data are consistent with those reported previously (*6*).

In flow: Following **GP1.2A**, using **a** (35 µL, 0.5 mmol, 1 equiv.) and **a'** (50 µL, 0.5 mmol, 1 equiv.), gave **1aa'** in 95% NMR yield.

(Z)-methyl 3-(cyclopropylamino)-4-methylpent-2-enoate (1ab')



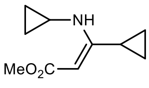
1ab'

Prepared according to general procedure **GP1.1A**, using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.) and methyl isobutyrylacetate **b'** (144 µL, 1 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : Et$_2$O = 10:1 to 5:1) to afford product **1ab'** (137 mg, 75% yield) as a colourless oil.

^{1}H NMR (600 MHz, CDCl$_3$) δ 8.68 (s, 1H), 4.51 (s, 1H), 3.61 (s, 3H), 3.10 (hept, *J* = 6.8 Hz, 1H), 2.62 – 2.51 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 6H), 0.82 – 0.70 (m, 2H), 0.65 – 0.53 (m, 2H).
^{13}C NMR (151 MHz, CDCl$_3$) δ 173.9, 171.7, 78.0, 50.1, 29.2, 24.1, 21.7, 18.0, 8.0.
MS (EI$^+$) calcd for $C_{10}H_{17}NO_2$ [M+]: 183.13; found: 183.20

In flow: Following **GP1.2A**, using **a** (35 µL, 0.5 mmol, 1 equiv.) and **b'** (72 µL, 0.5 mmol, 1 equiv.), gave **1ab'** in 93% NMR yield.

Methyl (Z)-3-cyclopropyl-3-(cyclopropylamino)acrylate (1ac')

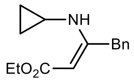


1ac'

Prepared according to general procedure **GP1.1A**, using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.) and methyl 3-cyclopropyl-3-oxopropanoate **c**' (129 µL, 1 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : Et$_2$O = 10:1 to 5:1) to afford product **1ac'** (87 mg, 48% yield) as a colourless oil.

^{1}H NMR (600 MHz, CDCl$_3$) δ 8.71 (s, 1H), 4.19 (s, 1H), 3.59 (s, 3H), 2.77 – 2.69 (m, 1H), 1.93 – 1.85 (m, 1H), 0.93 – 0.89 (m, 2H), 0.79 – 0.75 (m, 2H), 0.71 – 0.67 (m, 2H), 0.66 – 0.62 (m, 2H).
^{13}C NMR (151 MHz, CDCl$_3$) δ 171.1, 168.1, 51.2, 24.7, 12.3, 8.0, 7.7.
MS (EI$^+$) calcd for $C_{10}H_{15}NO_2$ [M$^+$]: 181.11; found: 181.10

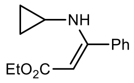
Ethyl (Z)-3-(cyclopropylamino)-4-phenylbut-2-enoate (1ad')


1ad'

Prepared according to general procedure **GP1.1A**, using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.) and ethyl 3-oxo-4-phenylbutanoate **d'** (201µL, 1 mmol, 1 equiv.). The crude mixture was evaporated in vacuum pump overnight to afford product **1ad'** (221 mg, 90% yield) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.26 – 7.15 (m, 5H), 4.45 – 4.41 (m, 1H), 4.06 – 3.99 (m, 2H), 3.67 – 3.62 (m, 2H), 2.34 – 2.28 (m, 1H), 1.21 – 1.15 (m, 3H), 0.61 – 0.56 (m, 2H), 0.50 – 0.44 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.3, 164.7, 136.5, 128.7, 128.4, 126.5, 84.3, 58.3, 39.1, 24.4, 14.4, 7.9.
HRMS (ESI$^+$) m/z calcd. for $C_{15}H_{19}NO_2H^+$ $[M+H]^+$: 246.1494; found: 246.1483

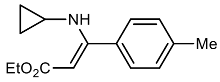
Ethyl (Z)-3-(cyclopropylamino)-3-phenylacrylate (1ae')


1ae'

Prepared according to general procedure **GP1.1A**, using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.) and ethyl 3-oxo-3-phenylpropanoate **e'** (192 mg, 1.0 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : Et_2O = 10:1 to 5:1) to afford product **1ae'** (139 mg, 60% yield) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.47 – 7.42 (m, 2H), 7.39 – 7.36 (m, 3H), 4.61 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.52 – 2.45 (m, 1H), 1.26 (t, *J* = 6.7 Hz, 3H), 0.55 – 0.46 (m, 4H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.5, 165.5, 137.0, 129.1, 128.2, 128.0, 85.4, 58.8, 26.9, 14.7, 8.7.
MS (EI$^+$) calcd for $C_{14}H_{17}NO_2$ [M+]: 231.13; found: 231.20

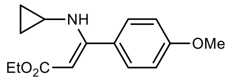
Ethyl (Z)-3-(cyclopropylamino)-3-(p-tolyl)acrylate (1af')


1af'

Prepared according to general procedure **GP1.1A.**, using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.) and ethyl 3-oxo-3-(m-tolyl)propanoate **f'** (206 mg, 1 mmol, 1 equiv.). The crude mixture was evaporated in vacuum pump overnight to afford product **1af'** (230,6 mg, 94% yield) as a pale yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.37 – 7.31 (m, 2H), 7.20 – 7.16 (m, 2H), 4.61 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.53 – 2.47 (m, 1H), 2.38 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.56 – 0.48 (m, 4H).
^{13}C NMR (151 MHz, $CDCl_3$): δ 170.6, 165.7, 139.2, 134.1, 128.9, 128.0, 85.1, 58.8, 27.0, 21.4, 14.7, 8.8.
HRMS (ESI$^+$) m/z calcd for $C_{15}H_{19}NO_2H^+$ $[M+H]^+$: 246.1494; 246.1500;

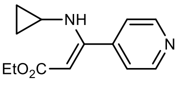
Ethyl (Z)-3-(cyclopropylamino)-3-(4-methoxyphenyl)acrylate (1ag')


1ag'

Prepared according to general procedure **GP1.1A**, using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.) and ethyl (4-Methoxybenzoyl) acetate **g'** (192 µL, 1 mmol, 1 equiv). The crude mixture was purified by flash column chromatography (petroleum ether 10:1 Et_2O to petroleum ether 5:1 Et_2O) to afford product **1ag’** (146 mg, 56% yield) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.60 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 2.53 – 2.47 (m, 1H), 1.26 (t, *J* = 7.0 Hz, 3H), 0.57 – 0.52 (m, 2H), 0.52 – 0.48 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 165.4, 160.4, 129.6, 129.3, 113.6, 85.0, 58.8, 55.4, 27.1, 14.8, 8.8.
HRMS (ESI$^+$) m/z calcd for $C_{15}H_{19}NO_3H^+$ $[M+H]^+$: 262.1443; found: 262.1435

Ethyl (Z)-3-(cyclopropylamino)-3-(pyridin-4-yl)acrylate (1ah’)



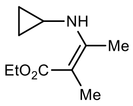
1ah'

Prepared according to general procedure **GP1.1B.**, using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.) and ethyl 3-oxo-3-(pyridin-4-yl)propanoate **h’** (193 mg, 1 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether 10:1 Et_2O to petroleum ether 5:1 Et_2O) to afford product **1ah’** (214 mg, 90% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.70 – 8.62 (m, 2H), 8.51 (s, 1H), 7.40 – 7.31 (m, 2H), 4.61 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.51 – 2.40 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.56 – 0.51 (m, 2H), 0.51 – 0.46 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.2, 162.3, 150.0, 144.8, 122.7, 86.5, 59.2, 26.8, 14.7, 9.0.
HRMS (ESI$^+$) m/z calcd for $C_{13}H_{16}N_2O_2H^+$ $[M+H]^+$: 233.1290; found: 233.1283.

In flow: Following **GP1.2B**, using **a** (35 µL, 0.5 mmol) and **h’** (97 mg, 0.5 mmol) gave **1ah’** in 94% NMR yield.

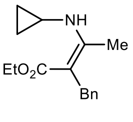
Ethyl (Z)-3-(cyclopropylamino)-2-methylbut-2-enoate (1ai’)



1ai'

Prepared according to general procedure **GP1.1A.**, using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.) and ethyl 2-methyl-3-oxobutanoate **i’** (144 mg, 1 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : Et_2O = 10:1 to 5:1) to afford product **1ai’** (169 mg, 92% yield) as a colourless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.17 (s, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.54 – 2.49 (m, 1H), 2.10 (s, 3H), 1.75 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.73 – 0.69 (m, 2H), 0.56 – 0.52 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.1, 161.1, 87.4, 58.8, 25.2, 16.2, 14.8, 12.7, 8.1.
HRMS (ESI$^+$) m/z calcd for $C_{10}H_{17}NO_2H^+$ $[M+H]^+$: 184.1338; found: 184.1326

Ethyl (Z)-2-benzyl-3-(cyclopropylamino)but-2-enoate (1aj’)

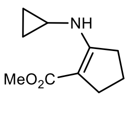


1aj'

Prepared according to general procedure **GP1.1A** using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.) and ethyl 2-benzyl-3-oxobutanoate **j’** (210 µL, 1 mmol, 1 equiv.) The crude mixture was purified by flash column chromatography (petroleum ether:AcOEt = 10:1 to 5:1 AcOEt) to afford product **1aj’** (224 mg, 86 % yield) as a colourless oil.

^{1}H NMR (600 MHz, CDCl$_3$) δ 9.45 (s, 1H), 7.27 – 7.23 (m, 2H), 7.19 – 7.13 (m, 3H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.65 (s, 2H), 2.59 – 2.52 (m, 1H), 2.10 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.78 – 0.71 (m, 2H), 0.63 – 0.57 (m, 2H).
^{13}C NMR (151 MHz, CDCl$_3$) δ 171.1, 162.8, 143.2, 128.2, 127.9, 125.4, 91.5, 58.9, 32.8, 25.2, 16.3, 14.7, 8.1.
HRMS (ESI$^+$) m/z calcd for $C_{16}H_{21}NO_2H^+$ [M+H]$^+$: 260.1650 found: 260.1637

Methyl 2-(cyclopropylamino)cyclopent-1-ene-1-carboxylate (1ak’)



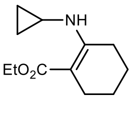
1ak'

Prepared according to general procedure **GP1.1B,** using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.), methyl 2-oxocyclopentan-1-carboxylate **k’** (125 µL, 1 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : Et$_2$O = 10:1 to 1:1), to afford product **1ak’** (145 mg, 80% yield) as colourless oil.

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.35 (s, 1H), 3.64 (s, 3H), 2.69 (t, *J* = 7.6 Hz, 2H), 2.60 – 2.53 (m, *J* = 3.9 Hz, 1H), 2.48 (t, *J* = 7.2 Hz, 2H), 1.81 (p, *J* = 7.5 Hz, 2H), 0.69 – 0.63 (m, 2H), 0.56 – 0.52 (m, 2H).
^{13}C NMR (151 MHz, CDCl$_3$) δ 168.8, 166.4, 93.2, 50.2, 32.8, 29.2, 25.8, 21.2, 7.6.
MS (EI$^+$) calcd for $C_{10}H_{15}NO_2$ [M+]: 181.24; found: 181.20.

In flow: Following **GP1.2B**, but at 80 °C, **a** (35 µL, 0.5 mmol) and **k’**(63 µL, 0.5 mmol), gave **1ak’** in 91% NMR yield.

Ethyl 2-(cyclopropylamino)cyclohex-1-ene-1-carboxylate (1al’)

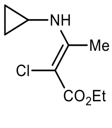


1al'

Prepared according to general procedure **GP1.1B**, using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.) and ethyl 2-oxocyclohexane-1-carboxylate **l’** (170 µL, 1 mmol, 1 equiv.). Compound **1al’** (198 mg, 95% yield), isolated as a yellowish oil, was used without further purification.

^{1}H NMR (600 MHz, CDCl$_3$) δ 8.87 (s, 1H), 4.11 – 4.02 (m, 2H), 2.54 – 2.43 (m, 3H), 2.26 – 2.20 (m, 2H), 1.68 – 1.61 (m, 2H), 1.57 – 1.51 (m, 2H), 1.26 – 1.20 (m, 3H), 0.71 – 0.65 (m, 2H), 0.56 – 0.50 (m, 2H).
^{13}C NMR (151 MHz, CDCl$_3$) δ 170.8, 161.2, 90.3, 58.7, 27.2, 24.2, 23.8, 22.9, 22.4, 14.7, 7.9.
HRMS (ESI$^+$) m/z calcd for $C_{12}H_{19}NO_2H^+$ [M+H]$^+$: 210.1494; found: 210.1493

Ethyl (E)-2-chloro-3-(cyclopropylamino)but-2-enoate (1am’)



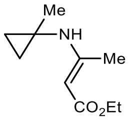
1am'

Prepared according to general procedure **GP1.1A**, using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.) and ethyl 2-chloro-3-oxobutanoate **m’** (139 µL, 1 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : Et$_2$O = 10:1 to 5:1) to afford product **1am’** (160 mg, 79% yield) as a brownish oil.

^{1}H NMR (600 MHz, CDCl$_3$) δ 9.03 (s, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 2.60 – 2.54 (m, 1H), 2.31 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.80 – 0.74 (m, 2H), 0.61 – 0.56 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.5, 161.7, 89.1, 60.3, 25.7, 17.6, 14.6, 8.1.
MS (EI$^+$) calcd for $C_9H_{14}ClNO_2$ [M+]: 203.08; found: 203.10

Ethyl (E)-3-((1-methylcyclopropyl)amino)but-2-enoate (1ba')

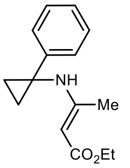


1ba'

Prepared according to general procedure **GP1.1B**, using 1-methylcyclopropan-1-amine hydrochloride **b** (108 mg, 1 mmol, 1 equiv.), ethyl acetoacetate **a'** (128 µL, 1 mmol, 1 equiv.) and $NaHCO_3$ (84 mg, 1 mmol, 1 equiv.). Compound **1ba'** (167 mg, 91% yield), isolated as a pale yellow oil, was used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.78 (s, 1H), 4.41 (s, 1H), 4.07 – 4.02 (m, 2H), 2.05 (s, 3H), 1.33 (s, 3H), 1.25 – 1.19 (m, 3H), 0.83 – 0.78 (m, 2H), 0.65 – 0.60 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.5, 163.2, 83.0, 58.4, 30.8, 25.1, 19.8, 15.8, 14.7.
HRMS (ESI$^+$) m/z calcd for $C_{10}H_{17}NO_2H^+$ [M+H]$^+$: 184.1337; found: 184.1323

Ethyl (E)-3-((1-phenylcyclopropyl)amino)but-2-enoate (1ca')

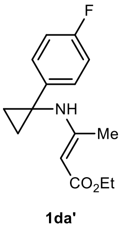


1ca'

Prepared according to general procedure **GP1.1A**, using 1-phenylcyclopropanamine **c** (133 mg , 1 mmol, 1 equiv.) and ethyl acetoacetate **a'** (128 µL, 1 mmol, 1 equiv.). Compound **1ca'** (225 mg, 92% yield), isolated as a yellowish oil, was used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.31 – 7.28 (m, 2H), 7.19 – 7.16 (m, 1H), 7.13 – 7.11 (m, 2H), 4.55 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 1.85 (s, 3H), 1.36 – 1.32 (m, 2H), 1.31 – 1.26 (m, 5H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 163.8, 144.1, 128.7, 126.1, 124.2, 84.2, 58.6, 36.8, 20.4, 20.2, 14.8.
HRMS (ESI$^+$) m/z calcd for $C_{15}H_{19}NO_2H^+$ [M+H]$^+$: 246,1494; found: 246.1482

Ethyl (E)-3-((1-(4-fluorophenyl)cyclopropyl)amino)but-2-enoate (1da')



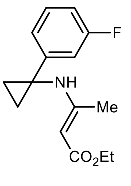
1da'

Prepared according to general procedure **GP1.1A**, using 1-(4-fluorophenyl)cyclopropanamine **d** (133 mg , 1 mmol, 1 equiv.) and ethyl acetoacetate **a'** (128 µL, 1 mmol, 1 equiv.). Compound **1da'** (248 mg, 94% yield), isolated as a yellowish oil, was used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.11 – 7.05 (m, 2H), 7.00 – 6.93 (m, 2H), 4.55 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 1.84 (s, 3H), 1.34 – 1.30 (m, 2H), 1.29 – 1.23 (m, 5H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 163.5, 161.5 (d, J = 244.6 Hz), 139.7 (d, *J* = 3.1 Hz), 126.0 (d, *J* = 8.0 Hz), 115.5 (d, *J* = 21.5 Hz), 84.5, 58.7, 36.5, 20.3, 19.8, 14.7.
^{19}F NMR (565 MHz, $CDCl_3$) δ -117.4.
HRMS (ESI$^+$) m/z calcd for $C_{15}H_{18}FNO_2H^+$ [M+H]$^+$: 264.1400; found: 264.1391

Ethyl (E)-3-((1-(3-fluorophenyl)cyclopropyl)amino)but-2-enoate (1ea’)

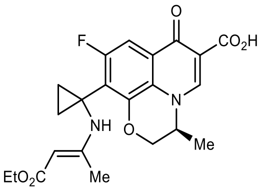


1ea'

Prepared according to general procedure **GP1.1A**, using 1-(3-fluorophenyl)cyclopropane-1-amine **e** (133 mg , 1 mmol, 1 equiv.) and ethyl acetoacetate **a’** (128 µL, 1 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : EtO_2 = 10:1 to 5:1) to afford the compound **1ea’** (155 mg, 59% yield) as a yellowish oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.12 (s, 1H), 7.26 – 7.22 (m, 1H), 6.90 – 6.84 (m, 2H), 6.81 (dt, J = 10.6, 2.1 Hz, 1H), 4.57 (s, 1H), 4.12 (q, J = 7.1 Hz, 2H), 1.84 (s, 3H), 1.38 – 1.35 (m, 2H), 1.31 – 1.26 (m, 5H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 164.2, 163.4 (d, J = 245.5 Hz), 147.2 (d, *J* = 6.9 Hz), 130.2 (d, *J* = 8.5 Hz), 119.7 (d, *J* = 2.7 Hz), 113.0 (d, *J* = 21.3 Hz), 111.4 (d, *J* = 23.0 Hz), 84.7, 58.7, 36.6 (d, *J* = 2.2 Hz), 20.6, 20.3, 14.7.
^{19}F NMR (565 MHz, $CDCl_3$) δ -112.9.
HRMS (ESI$^+$) m/z calcd for $C_{15}H_{18}FNO_2H^+$ $[M+H]^+$: 264.1400; found: 264.1391

(S,E)-10-(1-((4-ethoxy-4-oxobut-2-en-2-yl)amino)cyclopropyl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (1fa’)

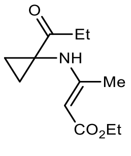


1fa'

The compound was prepared using a slightly modified **GP1.1B**: in a 25 mL round bottom flask pazufloxacin mesylate **f** (1g, 2,41 mmol), ethylacetoacetate **a’** (2 mL, 15 mmol, 6.5 equiv.), $NaHCO_3$ (1 equiv.) and 2 mL of toluene were added. The resulting slurry was stirred for 16 h at 80 °C. The reaction crude was then dried by rotary evaporation diluting with DCM to facilitate evaporation of toluene and acetoacetate. The resulting white solid was poured into a glass filter and washed with pentane to remove any residual acetoacetate. The product was then collected from the residual white powder adding 50 mL DCM which solubilized the product and let the impurities (salts) in the glass filter. Evaporation of the solvent affords the product **1fa’** (757 mg, 73% yield), as off-white solid.

^{1}H NMR (600 MHz, DMSO) δ 14.95 (s, 1H), 9.35 (s, 1H), 9.05 (s, 1H), 7.65 – 7.60 (m, 1H), 5.01 – 4.94 (m, 1H), 4.73 – 4.68 (m, 1H), 4.49 – 4.44 (m, 1H), 4.38 (s, 1H), 4.00 – 3.93 (m, 2H), 2.04 (s, 3H), 1.48 – 1.43 (m, 3H), 1.42 – 1.30 (m, 4H), 1.12 (t, *J* = 7.0 Hz, 3H).
^{13}C NMR (151 MHz, DMSO) δ 176.55 (d, J = 2.9 Hz), 169.02, 165.77, 162.42, 158.46 (d, J = 247.9 Hz), 146.49, 146.24 (d, J = 7.4 Hz), 125.76 (d, J = 10.1 Hz), 124.15, 122.18 (d, J = 18.0 Hz), 102.56 (d, J = 25.3 Hz), 84.24, 68.45, 57.82, 54.89, 28.91, 19.02 (d, J = 2.5 Hz), 17.76, 14.45.
^{19}F NMR (565 MHz, $CDCl_3$) δ -113.1.
HRMS (ESI$^+$) m/z calcd for $C_{22}H_{23}FN_2O_6H^+$ $[M+H]^+$: 431.1618; found: 431.1604

Ethyl (E)-3-((1-propionylcyclopropyl)amino)but-2-enoate (1*ga’)



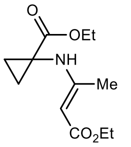
1*ga'

*This starting material was prepared according to ref. (*7*)

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.03 (s, 1H), 4.62 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.61 (q, *J* = 7.2 Hz, 2H), 1.89 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 4H), 1.04 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 211.5, 170.6, 162.2, 85.8, 58.9, 43.4, 32.8, 21.1, 20.0, 14. 7, 8.0.

The spectroscopic data are consistent with those previously reported (*7*).

Ethyl (E)-1-((4-ethoxy-4-oxobut-2-en-2-yl)amino)cyclopropane-1-carboxylate (1ha')

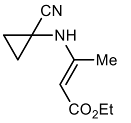


1ha'

Prepared according to general procedure **GP1.1B**, using ethyl 1-aminocyclopropanecarboxylate hydrochloride **h** (166 mg, 1 mmol, 1 equiv.), ethyl acetoacetate **a'** (128 µL, 1 mmol, 1 equiv.) and $NaHCO_3$ (84 mg, 1 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : AcOEt = 10:1 to 1:1), to afford product **1ha'** (103 mg, 85% yield) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.77 (s, 1H), 4.55 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 1.91 (s, 3H), 1.54 (q, *J* = 4.3 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 6H), 1.18 – 1.13 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 170.4, 162.9, 85.3, 61.6, 58.6, 35.9, 19.7, 19.3, 14.6, 14.3.
MS (EI$^+$) calcd for $C_9H_{14}ClNO_2$ [M+]: 241.14; found: 241.10.

Ethyl (E)-3-((1-cyanocyclopropyl)amino)but-2-enoate (1ia')

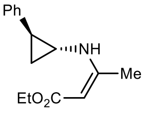


1ia'

Prepared according to general procedure **GP1.1B**, using 1-amino-1-cyclopropanecarbonitrile hydrochloride **i** (119 mg, 1 mmol, 1 equiv.), ethyl acetoacetate **a'** (128 µL, 1 mmol, 1 equiv.) and $NaHCO_3$ (84 mg, 1 mmol, 1 equiv.) The crude mixture was purified by flash column chromatography (petroleum ether : Et_2O = 10:1 to 5:1) to afford the compound **1ia'** in (147 mg, 76% yield) a yellowish oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.78 (s, 1H), 4.68 (s, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.17 (s, 3H), 1.55 – 1.51 (m, 2H), 1.32 – 1.29 (m, 2H), 1.24 (t, *J* = 7.0 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.2, 160.4, 120. 7, 88.3, 59.2, 23.0, 19.8, 18.2, 14.6.
MS (EI$^+$) calcd for $C_{10}H_{14}N_2O_2$ [M+]: 194.10; found: 194.10.

Ethyl (Z)-3-(((1S,2R)-2-phenylcyclopropyl)amino)but-2-enoate (1ja')



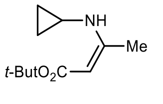
1ja'

Prepared according to general procedure **GP1.1A**, (1S,2R)-2-phenylcyclopropan-1-amine **j** (133 mg, 1 mmol, 1 equiv.) and ethyl acetoacetate **a'** (128 µL, 1 mmol, 1 equiv.). The compound **1ja'** (231 mg, 94% yield), isolated as a yellowish oil, was used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.28 – 7.22 (m, 2H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 2H), 4.50 (s, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 2.70 (dq, *J* = 7.3, 3.3 Hz, 1H), 2.06 – 2.00 (m, 1H), 1.96 (s, 3H), 1.31 – 1.24 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.7, 163.2, 140.5, 128.6, 126.3, 125.8, 83.5, 58.6, 35.5, 26.5, 20.2, 17.2, 14.8.
MS (EI^+) calcd for $C_{15}H_{19}NO_2$ [M+]: 254.20; found: 254.20

Tert-butyl (Z)-3-(cyclopropylamino)but-2-enoate (1ao')

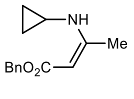


1ao'

Prepared according to general procedure **GP1.1A**, using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.) and *tert*-butyl acetoacetate **o'** (166 µL, 1 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : AcOEt = 10:1 to 1:1), to afford product **1ao'** (144 mg, 73% yield) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (s, 1H), 4.41 (s, 1H), 2.57 – 2.49 (m, 1H), 2.01 (s, 3H), 1.44 (s, 9H), 0.75 – 0.65 (m, 2H), 0.62 – 0.54 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.5, 162.9, 84.3, 77.9, 28.6, 24.6, 19.8, 7.6.
HRMS (ESI^+) m/z calcd for $C_{11}H_{19}NO_2H^+$ $[M+H]^+$: 198.1494; found: 198.1493

Benzyl (Z)-3-(cyclopropylamino)but-2-enoate (1ap')

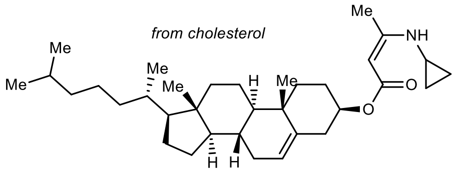


1ap'

Prepared according to general procedure **GP1.1A,** using cyclopropylamine **a** (70 µL 1 mmol, 1 equiv.) and benzyl acetoacetate **p'** (172 µL, 1 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : AcOEt = 10:1 to 1:1) to afford product **1ap'** (160 mg, 69% yield) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.35 – 7.19 (m, 5H), 5.02 (d, *J* = 1.6 Hz, 2H), 4.51 (s, 1H), 2.54 – 2.46 (m, 1H), 2.00 (s, 3H), 0.72 – 0.62 (m, 2H), 0.58 – 0.48 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.2, 164.3, 137.6, 128.5, 127.8, 127.7, 82.5, 64.4, 24.8, 20.0, 7.8.
HRMS (ESI^+) m/z calcd for $C_{14}H_{17}NO_2Na^+$ $[M+Na]^+$: 253.1080; found: 253.1082

(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl (Z)-3-(cyclopropylamino)but-2-enoate (1aq')

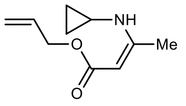


1aq'

Prepared according to general procedure **GP1.1B**, using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.), cholesteryl acetoacetate **q'** (470 mg, 1 mmol, 1 equiv.) The compound **1aq'** (443 mg, 87% yield), isolated as a white wax, was used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (s, 1H), 5.36 (s, 1H), 4.54 (dp, *J* = 10.9, 5.7 Hz, 1H), 4.46 (s, 1H), 2.57 – 2.52 (m, 1H), 2.32 – 2.27 (m, 2H), 2.04 (s, 3H), 2.02 – 1.92 (m, 2H), 1.86 – 1.79 (m, 2H), 1.59 – 1.39 (m, 7H), 1.37 – 1.31 (m, 3H), 1.29 – 1.22 (m, 2H), 1.19 – 1.04 (m, 8H), 1.03 – 0.97 (m, 5H), 0.93 – 0.89 (m, 3H), 0.87 – 0.84 (m, 6H), 0.72 (d, *J* = 5.7 Hz, 2H), 0.67 (s, 3H), 0.58 (d, *J* = 7.3 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.1, 163.7, 140.4, 122.2, 83.2, 72.0, 56.8, 56.3, 50.2, 42.4, 39.9, 39.6, 38.8, 37.3, 36.8, 36.3, 35.9, 32.0, 32.0, 28.4, 28.3, 28.1, 24.8, 24.4, 24.0, 22.9, 22.7, 21.2, 20.0, 19.5, 18.8, 12.0, 7.8, 7.8.
HRMS (ESI^+) m/z calcd for $C_{34}H_{55}NO_2H^+$ $[M+H]^+$: 510,4311 found: 510,4297

Allyl (Z)-3-(cyclopropylamino)but-2-enoate (1ar')

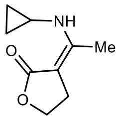


1ar'

Prepared according to general procedure **GP1.1A**, using cyclopropylamine (70 µL, 1 mmol, 1 equiv.) and allyl 3-oxobutanoate **r'** (137 µL, 1 mmol, 1 equiv.). Compound **1ar'** (141 mg, 78% yield), isolated as a colourless oil, was used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (s, 1H), 5.93 (ddt, *J* = 16.3, 10.3, 5.2 Hz, 1H), 5.31 – 5.15 (m, 2H), 4.56 – 4.49 (m, 3H), 2.61 – 2.51 (m, 1H), 2.06 (s, 3H), 0.78 – 0.69 (m, 2H), 0.62 – 0.56 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.1, 164.2, 133.7, 117.1, 82.5, 63.4, 24.9, 20.1, 7.8.
MS (EI$^+$) calcd for $C_{10}H_{15}NO_2$ [M+]: 181.11; found: 181.11

(Z)-3-(1-(cyclopropylamino)ethylidene)dihydrofuran-2(3H)-one (1as')

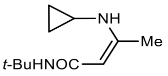


1as'

Prepared according to general procedure **GP1.1A**, using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.) and 3-acetyldihydrofuran-2(3H)-one **s'** (144 µL, 1 mmol, 1 equiv.). The compound **1as'** (144 mg, 86% yield), isolated as a pale yellow oil, was used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (s, 1H), 4.23 (t, *J* = 7.9 Hz, 2H), 2.78 (t, *J* = 7.9 Hz, 2H), 2.55 – 2.47 (m, 1H), 2.05 (s, 3H), 0.77 – 0.69 (m, 2H), 0.58 – 0.52 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 174.0, 158.6, 85.5, 65.2, 26.4, 24.7, 17.1, 7.9.
MS (EI$^+$) calcd for $C_9H_{13}NO_2$ [M+]: 167.10; found: 167.10

(Z)-N-(tert-butyl)-3-(cyclopropylamino)but-2-enamide) (1at')

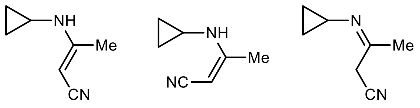


1at'

Prepared according to general procedure **GP1.1B**., using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.), N-tert-butyl-3-oxobutanamide **t'** (157 mg, 1,0 mmol, 1 equiv.). Compound **1at'** (182 mg, 93% yield), isolated as a white solid, was used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.92 (s, 1H), 4.72 (s, 1H), 4.22 (s, 1H), 2.49 (dh, *J* = 6.6, 3.7 Hz, 1H), 1.97 (s, 3H), 1.33 (s, 9H), 0.68 – 0.63 (m, 2H), 0.59 – 0.55 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.1, 159.1, 89.3, 50.5, 29.6, 28.8, 24.7, 20.1, 7.7.
HRMS (ESI$^+$) m/z calcd for $C_{11}H_{20}N_2OH^+$ $[M+H]^+$: 197,1654; found: 197,1658

(E)-3-(cyclopropylamino)but-2-enenitrile, (Z)-3-(cyclopropylamino)but-2-enenitrile, (Z)-3-(cyclopropylimino)butanenitrile (64 :9: 27) (1au')



E en Z en Z im

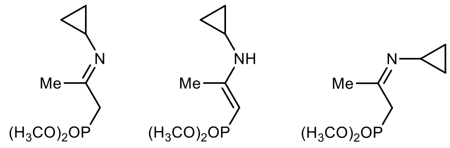
64 9 27

1 au'

Prepared according to general procedure **GP1.1A**, using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.) and 3-oxobutanenitrile **u'** (86 µL, 1,0 mmol, 1 equiv.). Compound **1au'** (111 mg, 91% yield), isolated as a white solid, was used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$, mixture of isomers) δ 8.43 (s, 1H), 4.53 (s, 2H), 4.25 (s, 1H), 2.76 – 2.59 (m, 1H), 2.35 – 2.25 (m, 1H), 2.04 (s, 3H), 1.05 (q, *J* = 6.8 Hz, 2H), 0.83 (q, *J* = 6.8 Hz, 2H).0.82 – 0.76 (m, 2H), 0.79 – 0.68 (m, 2H), 0.63 – 0.57 (m, 2H), 0.55 – 0.48 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 160.8, 121.8, 63.0, 61.0, 24.8, 23.3, 19.9, 7.3, 4.4.
HRMS (ESI^+) m/z calcd for $C_7H_{10}N_2H^+$ $[M+H]^+$: 123.0922; found: 123.0904

Dimethyl (E)-(2-(cyclopropylimino)propyl)phosphonate, dimethyl (E)-(2-(cyclopropylamino)prop-1-en-1-yl)phosphonate, dimethyl (Z)-(2-(cyclopropylimino)propyl)phosphonate (33 : 25 :42) (1av')



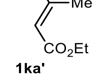
33 25 42

1av'

Prepared according to general procedure **GP1.1B**, using cyclopropylamine **a** (70 µL, 1 mmol, 1 equiv.) and dimethyl (2-oxopropyl)phosphonate **v'** (166 mg, 1 mmol, 1 equiv.). Compound **1av'** (185 mg, 90% yield), isolated as an orange oil, was used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (s, 1H), 4.38 (s, 1H), 4.32 (d, *J* = 11.6 Hz, 1H), 3.79 (d, *J* = 11.2 Hz, 4H), 3.74 (d, *J* = 11.0 Hz, 1H), 3.68 (d, *J* = 11.1 Hz, 4H), 3.62 (d, *J* = 11.2 Hz, 5H), 3.52 (d, *J* = 13.5 Hz, 1H), 3.10 (d, *J* = 22.8 Hz, 1H), 2.46 (dh, *J* = 6.4, 3.4 Hz, 1H), 2.37 – 2.30 (m, 3H), 2.13 – 2.06 (m, 6H), 0.88 – 0.79 (m, 2H), 0.78 – 0.75 (m, 1H), 0.72 (td, *J* = 6.7, 5.1 Hz, 1H), 0.67 (td, *J* = 6.8, 4.9 Hz, 2H), 0.56 – 0.52 (m, 2H), 0.52 – 0.48 (m, 1H), 0.48 – 0.44 (m, 1H), 0.39 – 0.35 (m, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 199.9, 199.8, 166.1, 166.0, 160.3, 74.7, 73.2, 69.5, 68.2, 53.2, 53.2, 52.9, 52.9, 51.9, 51.9, 51.8, 51.8, 42.8, 42.0, 40.5, 33.7, 31.6, 25.1, 24.8, 23.9, 22.1, 22.0, 19.6, 19.6, 19.1, 8.6, 8.5, 8.4, 7.9, 7.3, 7.3.
^{31}P NMR (243 MHz, $CDCl_3$) δ 29.5, 29.4, 22.4.
HRMS (ESI^+) m/z calcd for $C_8H_{16}NO_3PH^+$ $[M+H]^+$: 206.0946; found: 206.0931

Ethyl (E)-3-(benzyl(cyclopropyl)amino)but-2-enoate (1ka')



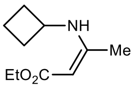
1ka'

Prepared according to general procedure **GP1.1B**, using N-Cyclopropylbenzylamine **k** (146 µL, 1 mmol, 1 equiv.), ethyl acetoacetate **a'** (128 µL, 1 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : AcOEt = 10:1 to 1:1), to afford product **1ka'** (181 mg, 70 % yield) as colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 – 7.30 (m, 2H), 7.25 – 7.22 (m, 1H), 7.12 – 7.08 (m, 2H), 5.15 (s, 1H), 4.55 (s, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.55 – 2.51 (m, 1H), 2.49 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.85 – 0.80 (m, 2H), 0.72 – 0.67 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.4, 162.4, 138.7, 128.8, 127.2, 126.2, 89.0, 58.7, 54.0, 32.8, 16.1, 14.8, 9.4.
HRMS (ESI$^+$) m/z calcd for $C_{16}H_{21}NO_2H^+$ $[M+H]^+$: 260,1651; found: 260,1635

Ethyl (Z)-3-(cyclobutylamino)but-2-enoate (1'aa')

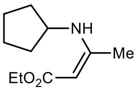


1'aa'

Prepared according to general procedure **GP1.1A**, using cyclobutylamine (85 μL, 1 mmol, 1 equiv.) and ethyl acetoacetate **a'** (128 μL, 1 mmol, 1 equiv.). Compound **l'aa'** (165 mg, 90% yield), isolated as a yellowish oil, was used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 (s, 1H), 4.38 (s, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.97 – 3.90 (m, 1H), 2.31 – 2.25 (m, 2H), 1.98 – 1.90 (m, 2H), 1.83 (s, 3H), 1.74 – 1.62 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.7, 160.7, 82.1, 58.3, 48.1, 32.0, 19.4, 14.9, 14.7.
HRMS (ESI$^+$) m/z calcd for $C_{10}H_{17}NO_2H^+$ $[M+H]^+$: 184.1338; found: 184.1338

Ethyl (Z)-3-(cyclopentylamino)but-2-enoate (1''aa')



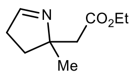
1''aa'

Prepared according to general procedure **GP1.1A**, using cyclopentylamine (99 μL, 1 mmol, 1 equiv.), and ethyl acetoacetate **a'** (128 μL, 1 mmol, 1 equiv.). Compound **l''aa'** (177 mg, 90% yield), isolated as a colourless oil, was used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.61 (s, 1H), 4.38 (s, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.86 – 3.77 (m, 1H), 1.96 – 1.88 (m, 5H), 1.77 – 1.68 (m, 2H), 1.58 – 1.52 (m, 2H), 1.50 – 1.44 (m, 2H), 1.28 – 1.22 (m, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.7, 161.4, 81.8, 58.2, 54.4, 34.4, 23.8, 19.7, 14.7.
HRMS (ESI$^+$) m/z calcd for $C_{11}H_{19}NO_2H^+$ $[M+H]^+$: 198.1494; 198.1498

3.7 Characterization data of the pyrrolines (ring-opening cyclization)

Ethyl 2-(2-methyl-3,4-dihydro-2H-pyrrol-2-yl) acetate (2aa')



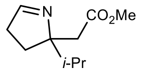
2aa'

Prepared according to general procedure **GP2.1**, using ethyl 3-(cyclopropylamino) but-2-enoate **1aa'** (85 mg, 0.5 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : AcOEt = 5:1 to 1:1), to afford product **2aa'** (62 mg, 73% yield) as a yellow oil.

^{1}H NMR (600 MHz, CDCl$_3$) ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.46 (s, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.65 – 2.45 (m, 4H), 2.05 – 1.94 (m, 1H), 1.73 – 1.59 (m, 1H), 1.28 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, CDCl$_3$) δ 170.6, 163.8, 82.8, 58.5, 24.8, 20.0, 14.8, 7.8.
HRMS (ESI$^+$) m/z calcd for $C_9H_{15}NO_2H^+$ [M+H]$^+$: 170.1181; found: 170.1180.

In flow: Following **GP2.2**, **1aa'** (85 mg, 0.5 mmol, 1.0 equiv.), gave **2aa'** in 95% NMR yield
Telescoped scale-up: Following **GP3**, **1aa'** (845 mg, 5 mmol, 1.0 equiv.), gave **2aa'** (84% NMR yield; 617 mg, 73% yield), as a yellow oil.

Methyl 2-(2-isopropyl-3,4-dihydro-2H-pyrrol-2-yl)acetate (2ab')

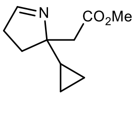


2ab'

Prepared according to general procedure **GP2.1**, using (Z)-methyl 3-(cyclopropylamino)-4-methylpent-2-enoate **1ab'** (92 mg, 0.5 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : AcOEt = 5:1 to 1:1), to afford product **2ab'** (60 mg, 65% yield) as a yellow oil.

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.49 (s, 1H), 3.58 (s, 3H), 2.64 – 2.55 (m, 3H), 2.50 – 2.43 (m, 1H), 1.94 (hept, *J* = 6.8 Hz, 1H), 1.89 – 1.81 (m, 1H), 1.75 – 1.68 (m, 1H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR (151 MHz, CDCl$_3$) δ 172.2, 165.4, 81.4, 51.4, 42.6, 38.2, 36.3, 26.2, 17.4, 17.2.
HRMS (ESI+) m/z calcd for $C_{10}H_{17}NO_2H^+$ [M+H]$^+$: 184.1338; found: 184.1330

Methyl 2-(2-cyclopropyl-3,4-dihydro-2H-pyrrol-2-yl)acetate (2ac')

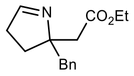


2ac'

Prepared according to general procedure **GP2.1**, using methyl (Z)-3-cyclopropyl-3-(cyclopropylamino)acrylate **1ac'** (91 mg, 0.5 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : AcOEt = 5:1 to 1:1), to afford product **2ac'** (66 mg, 73% yield) as a yellow oil.

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.51 (s, 1H), 3.63 (s, 3H), 2.76 – 2.46 (m, 4H), 2.00 (ddd, *J* = 13.2, 10.0, 6.0 Hz, 1H), 1.63 (ddd, *J* = 13.2, 9.8, 6.0 Hz, 1H), 1.22 – 1.05 (m, 1H), 0.47 – 0.40 (m, 1H), 0.39 – 0.28 (m, 2H), 0.05 – -0.02 (m, 1H).
^{13}C NMR (151 MHz, CDCl$_3$) δ 171.9, 166.8, 76.9, 51.5, 45.1, 37.7, 29.6, 20.2, 0.7, 0.7.
HRMS (ESI$^+$) m/z calcd for $C_{10}H_{15}NO_2H^+$ [M+H]$^+$: 182.1181; found: 182.1164
Telescoped scale-up – Following **GP3**, **1ac'** (905 mg, 5 mmol, 1.0 equiv.), gave **2ac'** (80% NMR yield; 652 mg, 76% yield) as a yellow oil.

Ethyl 2-(2-benzyl-3,4-dihydro-2H-pyrrol-2-yl)acetate (2ad')

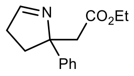


2ad'

Prepared according to general procedure **GP2.1**, using ethyl (E)-3-(cyclopropylamino)-4-phenylbut-2-enoate **1ad'** (123 mg, 0.5 mmol, 1 equiv.). The crude was purified by flash column chromatography (petroleum ether 5:1 AcOEt to 1:1), to afford product **2ad'** (98 mg, 80% yield) as a yellow oil.

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.45 (s, 1H), 7.25 – 7.09 (m, 5H), 4.12 (q, J = 7.1 Hz, 2H), 3.01 – 2.90 (m, 2H), 2.71 – 2.58 (m, 2H), 2.45 – 2.37 (m, 1H), 1.96 – 1.83 (m, 3H), 1.25 (t, J = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, CDCl$_3$) δ 171.3, 166.3, 137.3, 130.8, 127.9, 126.3, 78.1, 60.3, 45.7, 44.7, 37.7, 29.2, 14.3.
HRMS (ESI$^+$) m/z calcd for C$_{15}$H$_{19}$NO$_2$H$^+$ [M+H]$^+$: 246.1494; found: 246.1483

Ethyl 2-(2-phenyl-3,4-dihydro-2H-pyrrol-2-yl)acetate (2ae')



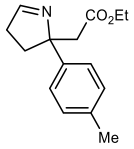
2ae'

Prepared according to general procedure **GP2.1**, using ethyl (Z)-3-(cyclopropylamino)-3-phenylacrylate **1ae'** (116 mg, 0.5 mmol, 1 equiv.). The crude was purified by flash column chromatography (petroleum ether 5:1 AcOEt to 1:1), to afford product **2ae'** (81 mg, 70% yield) as a yellow oil.

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.74 (s, 1H), 7.46 – 7.42 (m, 2H), 7.35 – 7.29 (m, 2H), 7.24 – 7.21 (m, 1H), 4.06 – 3.97 (m, 2H), 2.85 (q, J = 14.2 Hz, 2H), 2.77 – 2.70 (m, 1H), 2.64 – 2.53 (m, 2H), 2.20 – 2.14 (m, 1H), 1.12 (t, J = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, CDCl$_3$) δ 170.8, 166.7, 146.9, 128.4, 126.9, 125.8, 80.3, 60.4, 47.3, 37.6, 32.9, 14.2.
HRMS (ESI$^+$) m/z calcd for C$_{14}$H$_{17}$NO$_2$H$^+$ [M+H]$^+$: 232.1332; found 232.1330.

In flow: Following **GP2.2**, **1ae'** (116 mg, 0.5 mmol, 1.0 equiv.), gave **2ae'** in 80% NMR yield.

Ethyl 2-(2-(p-tolyl)-3,4-dihydro-2H-pyrrol-2-yl)acetate (2af')

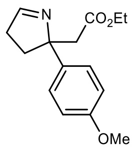


2af'

Prepared according to general procedure **GP2.1**, using ethyl (Z)-3-(cyclopropylamino)-3-(p-tolyl)acrylate **1af'** (123 mg, 0.5 mmol, 1 equiv.). The crude was purified by flash column chromatography (petroleum ether 5:1 AcOEt to 1:1), to afford product **2af'** (109 mg, 89% yield) as a orange/yellow oil.

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.72 (s, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 4.06 – 3.97 (m, 2H), 2.93 – 2.79 (m, 2H), 2.75 – 2.68 (m, 1H), 2.62 – 2.47 (m, 2H), 2.32 (s, 3H), 2.18 – 2.13 (m, 1H), 1.13 (t, J = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, CDCl$_3$) δ 170.7, 166.5, 143.8, 136.3, 128.9, 125.6, 79.9, 60.3, 47.2, 37.4, 32.8, 21.0, 14.1.
HRMS (ESI$^+$) m/z calcd for C$_{15}$H$_{19}$NO$_2$H$^+$ [M+H]$^+$: 246.1494; found 246.1500

Ethyl 2-(2-(4-methoxyphenyl)-3,4-dihydro-2H-pyrrol-2-yl)acetate (2ag')

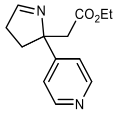


2ag'

Prepared according to general procedure **GP2.1**, using ethyl (Z)-3-(cyclopropylamino)-3-(4-methoxyphenyl)acrylate **1ag'** (131 mg, 0.5 mmol, 1 equiv.). The crude was purified by flash column chromatography (petroleum ether 5:1 AcOEt to 1:1), to afford product **2ag'** (86 mg, 66% yield) as a orange/yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.36 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.07 – 3.95 (m, 2H), 3.79 (s, 3H), 2.89 – 2.77 (m, 2H), 2.76 – 2.68 (m, 1H), 2.64 – 2.57 (m, 1H), 2.54 – 2.48 (m, 1H), 2.18 – 2.12 (m, 1H), 1.13 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.8, 166.5, 158.5, 138.9, 127.0, 113.7, 79.8, 60.4, 55.4, 47.4, 37.5, 32.9, 14.3.
HRMS (ESI$^+$) m/z calcd for $C_{15}H_{19}NO_3H^+$ [M+H]$^+$: 262.1443; found 262.1463

Ethyl 2-(2-(pyridin-4-yl)-3,4-dihydro-2H-pyrrol-2-yl)acetate (2ah')

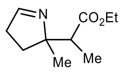


2ah'

Prepared according to general procedure **GP2.1**, using ethyl (Z)-3-(cyclopropylamino)-3-(pyridin-4-yl)acrylate **1ah'** (116 mg, 0.5 mmol, 1 equiv.). The crude was purified by flash column chromatography (petroleum ether 5:1 AcOEt to 1:1), to afford product **2ah'** (87 mg, 75% yield) as yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 – 8.52 (m, 2H), 7.77 (s, 1H), 7.36 – 7.32 (m, 2H), 4.06 – 3.98 (m, 2H), 2.87 – 2.80 (m, 2H), 2.80 – 2.73 (m, 1H), 2.67 – 2.59 (m, 1H), 2.57 – 2.49 (m, 1H), 2.13 – 2.05 (m, 1H), 1.12 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.1, 167.8, 155.4, 150.0, 121.1, 79.6, 60.6, 46.4, 37.6, 32.6, 14.2.
HRMS (ESI$^+$) m/z calcd for $C_{13}H_{16}N_2O_2H^+$ [M+H]$^+$: 233.1290; found: 233.1282

Ethyl 2-(2-methyl-3,4-dihydro-2H-pyrrol-2-yl)propanoate (2ai')

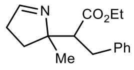


2ai'
d.r. = 60:40

Prepared according to general procedure **GP2.1**, but irradiating for 12 h, using ethyl (Z)-3-(cyclopropylamino)-2-methylbut-2-enoate **1ai'** (92 mg, 0.5 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : AcOEt = 5:1 to 1:1), to afford product **2ai'** (49 mg, 53% yield) as an inseparable mixture of diastereomers (60 :40), as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$, mixture of two diastereoisomers) δ 7.49 (s, 1H, major), 7.44 (s, 1H, minor), 4.16 – 4.05 (m, 2H), 2.79 – 2.75 (m, 1H major), 2.71 – 2.67 (1H minor), 2.65 – 2.51 (2H), 2.11 – 2.01 (m, 1H), 1.55 – 1.47 (m, 1H,), 1.28 – 1.01 (m, 9H)
^{13}C NMR (151 MHz, $CDCl_3$, mixture of two diastereoisomers) δ 175.1, 175.1, 164.8, 164.7, 78.0, 77.8, 60.3, 60.2, 48.5, 48.2, 37.6, 37.0, 30.0, 28.8, 26.2, 24.6, 14.4, 14.3, 13.2, 12.8.
HRMS (ESI$^+$) m/z calcd for $C_{10}H_{17}NO_2H^+$ [M+H]$^+$: 184.1338; found 184.1329

Ethyl 2-(2-methyl-3,4-dihydro-2H-pyrrol-2-yl)-3-phenylpropanoate (2aj')



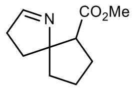
2aj'
d.r. = 55 : 45

Prepared according to general procedure **GP2.1**, but irradiating for 12 h, using ethyl (Z)-3-(cyclopropylamino)-4-phenylbut-2-enoate **1aj'** (130 mg, 0.5 mmol, 1 equiv.). The crude was purified by flash column chromatography (petroleum ether : AcOEt = 10:1 to 1:1)) to afford product **2aj'** (77 mg, 59% yield) as an inseparable mixture of diastereomers (55 :45), as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$, mixture of two diastereoisomers) δ 7.57 (s, 1H, major), 7.51 (s, 1H minor), 7.28 – 7.20 (m, 2H), 7.19 – 7.13 (m, 3H), 4.05 – 3.91 (m, 2H), 3.18 – 2.48 (m, 5H), 2.24 – 2.11 (m, 1H), 1.62 – 1.55 (m, 2H), 1.31 (s, 3H minor), 1.29 (s, 3H major), 1.06 – 0.99 (m, 3H).

^{13}C NMR (151 MHz, CDCl$_3$, mixture of two diastereoisomers) δ 173.8, 173.7, 165.2, 165.0, 139.9, 139.5, 129.0, 129.0, 128.4, 126.3, 126.3, 77.8, 77.8, 60.2, 60.1, 57.5, 57.1, 37.6, 37.0, 34.5, 34.2, 30.7, 29.5, 26.4, 24.5, 14.2.
HRMS (ESI$^+$) m/z calcd for $C_{16}H_{21}NO_2H^+$ [M+H]$^+$: 260.1650; found: 260.1636

Methyl 1-azaspiro[4.4]non-1-ene-6-carboxylate (2ak')



2ak'
d.r. = 60 : 40

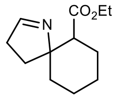
Prepared according to general procedure **GP2.1**, but irradiating for 12 h, using methyl 2-(cyclopropylamino)cyclopent-1-ene-1-carboxylate **1ak'** (91 mg, 0.5 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether: DCM = 1:1) to afford product **2ak'** (68 mg, 75% yield) as an inseparable mixture of diastereomers (60 :40), as a yellow oil.

^{1}H NMR (600 MHz, CDCl$_3$, mixture of two diastereoisomers) δ 7.50 (s, 1H, minor), 7.48 (s, 1H, major), 3.63 (s, 3H, minor), 3.61 (s, 3H, major), 2.94 (t, *J* = 8.4 Hz, 1H, minor), 2.77 (t, *J* = 8.6 Hz, 1H, major), 2.66 – 2.47 (m, 2H), 2.39 – 2.28 (m, 1H), 2.21 – 2.08 (m, 1H), 2.08 – 1.51 (m, 6H).
^{13}C NMR (151 MHz, CDCl$_3$, mixture of two diastereoisomers) δ 175.1, 173.7, 165.4, 165.1, 86.0, 55.1, 51.6, 51.5, 40.9, 40.5, 37.3, 37.1, 32.3, 28.0, 27.6, 23.1, 22.7.
HRMS (ESI$^+$) m/z calcd for $C_{10}H_{15}NO_2H^+$ [M+H]$^+$: 182.1181; found: 182.120.

In flow: Following **GP2.2**, **1ak'** (91 mg, 0.5 mmol, 1.0 equiv.), gave **2ak'** in 90% NMR yield.

Telescoped scale-up – Following **GP3**, **1ak'** (905 mg, 5 mmol, 1.0 equiv.), gave **2ak'** (81% NMR yield; 634 mg, 70% yield) as a yellow oil.

Ethyl 1-azaspiro[4.5]dec-1-ene-6-carboxylate (2al')

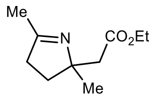


2al'
d.r. = 60 : 40

Prepared according to general procedure **GP2.1**, but irradiating for 12 h, using ethyl 2-(cyclopropylamino)cyclohex-1-ene-1-carboxylate **1al'** (105 mg, 0.5 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : AcOEt = 5:1 to 1:1), to afford product **2al'** (77 mg, 74% yield) as an inseparable mixture of diastereomers (60:40), as yellow oil.

^{1}H NMR (600 MHz, CDCl$_3$, mixture of two diastereoisomers) δ 7.54 (s, 1H major.), 7.44 (s, 1H minor), 4.06 (m, 2H), 2.76 (dd, J = 12.1, 3.4 Hz, 1H minor), 2.59-2.45 (m, 2H), 2,24-2.17 (m, 1H major) 2,12-1.20 (m, 13H).
^{13}C NMR (151 MHz, CDCl$_3$, mixture of two diastereoisomers) δ 174.5, 173.8, 165.1, 164.7, 79.2, 77.5, 60.1, 60.0, 52.0, 50.9, 37.3, 36.5, 32.5, 26.9, 26.4, 22.9, 22.8, 14.4.
HRMS (ESI$^+$) m/z calcd for $C_{12}H_{19}NO_2H^+$ [M+H]$^+$: 210.1494; found: 210.1493.

Ethyl 2-(2,5-dimethyl-3,4-dihydro-2H-pyrrol-2-yl)acetate (2ba')



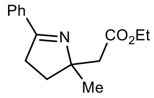
Prepared according to general procedure **GP2.1**, using ethyl (E)-3-((1-methylcyclopropyl)amino)but-2-enoate **1ba’** (92 mg, 0.5 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : AcOEt = 5:1 to 1:1), to afford product **2ba’** (72 mg, 79% yield) as a yellow oil.

2ba'

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.16 – 4.06 (m, 2H), 2.63 – 2.37 (m, 4H), 2.13 – 2.08 (m, 1H), 1.99 (s, 3H), 1.76 – 1.70 (m, 1H), 1.28 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 171.7, 74.2, 60.2, 46.0, 39.4, 34.2, 27.6, 19.8, 14.4.
HRMS (ESI$^+$) m/z calcd for $C_{10}H_{17}NO_2H^+$ [M+H]$^+$: 184.1337; found 184.1326.

In flow: Following **GP2.2**, **1ba’** (92 mg, 0.5 mmol, 1.0 equiv.), gave **2ba’** in 93% NMR yield.

Ethyl 2-(2-methyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)acetate (2ca’)

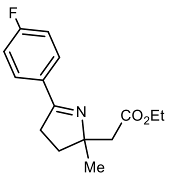


Prepared according to general procedure **GP2.1**, using ethyl (E)-3-((1-phenylcyclopropyl)amino)but-2-enoate **1ca’** (123 mg, 0.5 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : AcOEt = 5:1 to 1:1), to afford product **2ca’** (92 mg, 75% yield) as a yellow oil.

2ca'

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 – 7.76 (m, 2H), 7.42 – 7.33 (m, 3H), 4.09 (q, J = 7.1 Hz, 2H), 3.03 (t, J = 7.9 Hz, 2H), 2.82 – 2.52 (m, 2H), 2.29 – 2.22 (m, 1H), 1.92 – 1.84 (m, 1H), 1.39 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.5, 171.1, 134.6, 130.4, 128.4, 127.8, 74.6, 60.2, 46.0, 35.5, 33.8, 27.5, 14.3.
HRMS (ESI$^+$) m/z calcd for $C_{15}H_{19}NO_2H^+$ [M+H]$^+$: 246.1494; found: 246.1478

Ethyl 2-(5-(4-fluorophenyl)-2-methyl-3,4-dihydro-2H-pyrrol-2-yl)acetate (2da’)

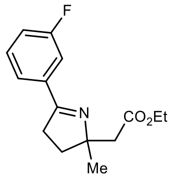


Prepared according to general procedure **GP2.1**, using ethyl (E)-3-((1-(4-fluorophenyl)cyclopropyl)amino)but-2-enoate **1da’** (132 mg, 0.5 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : AcOEt = 5:1 to 1:1), to afford product **2da’** (96 mg, 73% yield) as a yellow oil.

2da'

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 2H), 7.11 – 7.03 (m, 2H), 4.10 (q, J = 7.1 Hz, 2H), 3.02 (t, J = 7.9 Hz, 2H), 2.77 – 2.51 (m, 2H), 2.31 – 2.23 (m, 1H), 1.94 – 1.87 (m, 1H), 1.39 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ. ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.6, 170.0, 164.35 (d, J = 250.4 Hz), 131.02 (d, J = 2.7 Hz), 129.94 (d, J = 8.7 Hz), 115.52 (d, J = 21.6 Hz), 74.8, 60.3, 46.1, 35.7, 34.0, 27.7, 14.4.
^{19}F NMR (565 MHz, $CDCl_3$) δ -110.14.
HRMS (ESI$^+$) m/z calcd for $C_{15}H_{18}FNO_2H^+$ [M+H]$^+$: 264.1400; found: 264.1384.

Ethyl 2-(5-(3-fluorophenyl)-2-methyl-3,4-dihydro-2H-pyrrol-2-yl)acetate (2ea’)

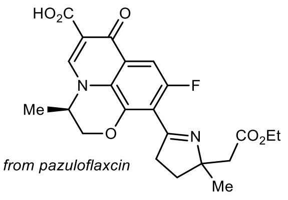


2ea

Prepared according to general procedure **GP2.1**, using ethyl (E)-3-((1-(3-fluorophenyl)cyclopropyl)amino)but-2-enoate **1ea'** (132 mg, 0.5 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : AcOEt = 5:1 to 1:1), to afford product **2ea'** (76 mg, 58% yield) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 – 7.44 (m, 2H), 7.45 – 7.31 (m, 1H), 7.13 – 7.03 (m, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.04 – 2.98 (m, 2H), 2.82 – 2.54 (m, 2H), 2.32 – 2.19 (m, 1H), 2.01 – 1.72 (m, 1H), 1.39 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.5, 170.1 (d, *J* = 2.5 Hz), 162.9 (d, *J* = 246.1 Hz), 137.0 (d, *J* = 7.3 Hz), 130.0 (d, *J* = 7.8 Hz), 123.6 (d, *J* = 3.0 Hz), 117.4 (d, *J* = 21.5 Hz), 114.6 (d, *J* = 22.6 Hz), 74.9, 60.3, 46.0, 35.7, 33.9, 27.6, 14.4.
^{19}F NMR (565 MHz, $CDCl_3$) δ -113.04.
HRMS (ESI$^+$) m/z calcd for $C_{15}H_{18}FNO_2H^+$ $[M+H]^+$: 264.1400; found 264.139.

(3S)-10-(2-(2-ethoxy-2-oxoethyl)-2-methyl-3,4-dihydro-2H-pyrrol-5-yl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (2fa')



from pazuloflaxcin

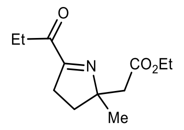
2fa'

d.r. = 52 : 48

Prepared according to general procedure **GP2.1**, but using DMSO instead of MeCN, using (S,E)-10-(1-((4-ethoxy-4-oxobut-2-en-2-yl)amino)cyclopropyl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid **1fa'** (215 mg, 0.5 mmol, 1 equiv.). The product was extracted from the crude mixture with DCM and purified by flash column chromatography (petroleum ether : AcOEt = 5:1 to 1:1), to afford product (**2fa'**) (110 mg, 51% yield) as an inseparable mixture of diastereomers (52:48), as a yellow oil.

^{1}H NMR (600 MHz, DMSO, mixture of two diastereomers) δ 14.88 (s, 1H), 9.07 (s, 1H), 7.63 (d, *J* = 9.5 Hz, 1H), 5.00 – 4.95 (m, 1H), 4.63 – 4.57 (m, 1H), 4.50 – 4.44 (m, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.06 – 2.91 (m, 2H), 2.71 – 2.54 (m, 2H), 2.24 – 2.15 (m, 1H), 1.88 – 1.80 (m, 1H), 1.48 – 1.45 (m, 3H), 1.36 – 1.29 (m, 3H), 1.21 – 1.16 (m, 3H).
^{13}C NMR (151 MHz, DMSO, mixture of two diastereomers) δ 176.53 (d, *J* = 3.3 Hz), 170.40 (d, *J* = 3.0 Hz), 165.70, 164.17, 157.66, 156.00, 146.52 (d, *J* = 2.5 Hz), 145.79, 145.75, 126.54 (d, *J* = 9.5 Hz), 123.90, 117.69 (d, *J* = 1.9 Hz), 117.55 (d, *J* = 1.6 Hz), 107.65, 102.51 (d, *J* = 24.4 Hz), 79.15, 75.23, 68.68 (d, *J* = 5.2 Hz), 59.70, 54.85 (d, *J* = 3.2 Hz), 45.09, 45.06, 33.26, 27.09 (d, *J* = 5.2 Hz), 17.82 (d, *J* = 11.0 Hz), 14.05.
^{19}F NMR (565 MHz, DMSO) δ -114.27, -114.31.
HRMS (ESI$^+$) m/z calcd for $C_{22}H_{23}FN_2O_6H^+$ $[M+H]^+$: 431.1618; found: 431.1606.

Ethyl 2-(2-methyl-5-propionyl-3,4-dihydro-2H-pyrrol-2-yl)acetate (2ga')

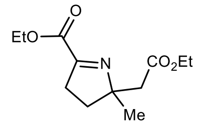


2ga'

Prepared according to general procedure **GP2.1**, using ethyl (E)-3-((1-propionylcyclopropyl)amino)but-2-enoate **1ga'** (113 mg, 0.5 mmol, 1 equiv.). The crude was purified by flash column chromatography (petroleum ether : AcOEt = 10:1 to 1:1), to afford product **2ga'** (34 mg, 30% yield) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.11 (q, *J* = 7.1 Hz, 2H), 2.96 – 2.88 (m, 2H), 2.85 – 2.77 (m, 2H), 2.72 – 2.51 (m, 2H), 2.15 – 2.05 (m, 1H), 1.89 – 1.72 (m, 1H), 1.55 – 1.31 (m, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 201.3, 171.3, 171.0, 76.2, 60.5, 45.5, 34.1, 33.2, 32.0, 30.5, 27.3, 14.4, 7.7.
HRMS (ESI$^+$) m/z calcd for $C_{12}H_{19}NO_3H^+$ $[M+H]^+$: 226.1443; found: 226.1439

Ethyl 2-(2-ethoxy-2-oxoethyl)-2-methyl-3,4-dihydro-2H-pyrrole-5-carboxylate (2ha')

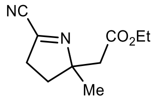


2ha'

Prepared according to general procedure **GP2.1**, using ethyl (E)-1-((4-ethoxy-4-oxobut-2-en-2-yl)amino)cyclopropane-1-carboxylate **1ha'** (120 mg, 0.5 mmol, 1 equiv.). The crude was purified by flash column chromatography (petroleum ether : AcOEt = 10:1 to 1:1), to afford product **2ha'** (96 mg, 80% yield) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.32 (q, *J* = 7.1 Hz, 2H), 4.19 – 3.86 (m, 2H), 2.98 – 2.82 (m, 2H), 2.76 – 2.57 (m, 2H), 2.21 – 2.13 (m, 1H), 1.87 – 1.79 (m, 1H), 1.36 – 1.31 (m, 6H), 1.22 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 166.3, 163.1, 76.2, 62.0, 60.4, 45.2, 36.1, 33.1, 27.1, 14.3.
HRMS (ESI$^+$) m/z calcd for $C_{12}H_{19}NO_4H^+$ $[M+H]^+$: 242.1392; found: 242.1404.

Ethyl 2-(5-cyano-2-methyl-3,4-dihydro-2H-pyrrol-2-yl)acetate (2ia')

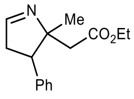


2ia'

Prepared according to general procedure **GP2.1**, but irradiating for 12 h, using ethyl (E)-3-((1-cyanocyclopropyl)amino)but-2-enoate **1ia'** (97 mg, 0.5 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : AcOEt = 5:1 to 1:1), to afford product **2ia'** (72 mg, 74% yield) as a yellow oil. In this case the compound was isolated with inseparable starting material **1ia'** (23mol%).

^{1}H NMR (600 MHz, $CDCl_3$) ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.24 – 4.10 (m, 2H), 3.09 – 2.78 (m, 2H), 2.76 – 2.47 (m, 2H), 2.23 (ddd, *J* = 13.2, 10.2, 6.8 Hz, 1H), 1.88 (ddd, *J* = 13.1, 9.6, 5.5 Hz, 1H), 1.35 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.4, 149.4, 114.1, 77.0, 60.6, 44.8, 39.8, 32. 6, 27.2, 14.3.
HRMS (ESI$^+$) m/z calcd for $C_{10}H_{14}N_2O_2H^+$ $[M+H]^+$: 195.1134; found: 195.1129.

Ethyl 2-(2-methyl-3-phenyl-3,4-dihydro-2H-pyrrol-2-yl)acetate (2ja')



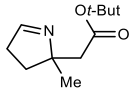
2ja'

d.r. = 75 : 25

Prepared according to general procedure **GP2.1**, using ethyl (Z)-3-(((1S,2R)-2-phenylcyclopropyl)amino)but-2-enoate **1ja'** (123 mg, 0.5 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether: AcOEt = 5:1 to 1:1), to afford product **2ja'** (61 mg, 50% yield) as an inseparable mixture of diastereomers (75:25), as a yellow oil.

^{1}H NMR (600 MHz, CDCl$_3$, mixture of two diastereomers) δ 7.73 (s, 1H minor), 7.69 (s, 1H, major), 7.36 – 7.07 (m, 5H), 4.16 (q, *J* = 7.1 Hz, 2H, major), 3.95 (q, *J* = 7.1 Hz, 2H, minor) 3.67 (t, *J* = 8.5 Hz, 1H, major), 3.38 – 3.23 (m, 1H, minor), 3.17– 2.93 (m, 2H), 2.67 – 2.60 (m, 2H, major), 2.42 – 1.96 (m, 2H, minor), 1.55 (s, 3H, minor), 1.27 (t, *J* = 7.1 Hz, 3H, major), 1.13 (t, *J* = 7.1 Hz, 3H, minor),0.88 (s, 3H, major),
^{13}C NMR (151 MHz, CDCl$_3$, mixture of two diastereomers) δ 171.2, 165.0, 164.9, 140.4, 128.5, 128.5, 128.4, 127.0, 126.9, 76.8, 60.5, 60.2, 52.1, 48.6, 45.3, 43.9, 43.2, 42.1, 27.2, 23.4, 14.4, 14.2.
HRMS (ESI$^+$) m/z calcd for $C_{15}H_{19}NO_2H^+$ [M+H]$^+$: 246.1490; found: 246.1478.

Tert-butyl 2-(2-methyl-3,4-dihydro-2H-pyrrol-2-yl)acetate (2ao')

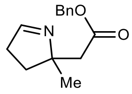


2ao'

Prepared according to general procedure **GP2.1**, using tert-butyl (E)-3-(cyclopropylamino)but-2-enoate **1ao'** (99 mg, 0.5 mmol, 1 equiv.). The crude was purified by flash column chromatography (petroleum ether: AcOEt = 5:1 to 1:1)) to afford product **2ao'** (85 mg, 86 % yield) as a yellow oil.

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.44 (s, 1H), 2.66 – 2.57 (m, 2H), 2.58 – 2.35 (m, 2H), 2.05 – 1.96 (m, 1H), 1.67 – 1.59 (m, 1H), 1.42 (s, 9H), 1.26 (s, 3H).
^{13}C NMR (151 MHz, CDCl$_3$) δ 170.5, 164.4, 80.2, 74. 6, 46.7, 37.0, 31.7, 28.0, 27.1.
HRMS (ESI$^+$) m/z calcd for $C_{11}H_{19}NO_2H^+$ [M+H]$^+$: 198.1494; found: 198.1496

Benzyl 2-(2-methyl-3,4-dihydro-2H-pyrrol-2-yl)acetate (2ap')

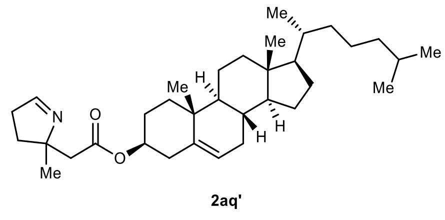


2ap'

Prepared according to general procedure **GP2.1**, using benzyl (E)-3-(cyclopropylamino) but-2-enoate **1ap'** (116 mg, 0.5 mmol, 1 equiv.). The crude was purified by flash column chromatography (petroleum ether : AcOEt = 5:1 to 1:1) to afford product **2ap'** (67 mg, 58% yield) as a yellow oil.

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.35 (s, 1H), 7.28 – 7.20 (m, 5H), 5.06 – 4.98 (m, 2H), 2.65 – 2.44 (m, 4H), 1.96 – 1.86 (m, 1H), 1.61 – 1.52 (m, 1H), 1.21 (s, 3H).
^{13}C NMR (151 MHz, CDCl$_3$) δ 171.1, 165.0, 136.0, 128.6, 128.4, 128.3, 74.6, 66.2, 45.7, 37.3, 32.0, 27.4.
HRMS (ESI$^+$) m/z calcd for $C_{14}H_{17}NO_2H^+$ [M+H]$^+$: 232.1337; found: 232.1328

(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl 2-(2-methyl-3,4-dihydro-2H-pyrrol-2-yl)acetate (2aq')



2aq'

d.r. = 60 : 40

Prepared according to general procedure **GP2.1**, using **1aq'** (255 mg, 0.5 mmol, 1 equiv.) but using ethyl acetate as solvent instead of MeCN. The crude mixture was purified by flash column chromatography (petroleum ether : AcOEt = 5:1 to 1:1), to afford product **2aq'** (143 mg, 56% yield) as an inseparable mixture of diastereomers (60:40), as yellowish wax.

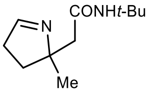
^{1}H NMR (600 MHz, CDCl$_3$, mixture of two diastereomers) δ 7.48 – 7.41 (m, 1H), 5.35 (dt, *J* = 5.2, 1.7 Hz, 1H), 4.59 (tdd, *J* = 9.7, 7.4, 4.2 Hz, 1H), 2.62 (tdd, *J* =

8.5, 4.0, 1.7 Hz, 2H), 2.46 (dd, *J* = 14.2, 1.8 Hz, 1H), 2.32 – 2.25 (m, 2H), 2.05 – 1.91 (m, 3H), 1.82 (tq, *J* = 13.2, 5.9, 4.4 Hz, 3H), 1.64 (ddd, *J* = 13.0, 8.8, 6.4 Hz, 1H), 1.61 – 1.39 (m, 8H), 1.38 – 1.30 (m, 3H), 1.28 (s, 3H), 1.26 – 1.19 (m, 2H), 1.19 – 1.02 (m, 8H), 0.99 (s, 3H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.84 (dd, *J* = 6.6, 2.7 Hz, 6H), 0.66 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$, mixture of two diastereomers**)** δ 170.7, 164.8, 139.7, 122.7, 74.7, 74.0, 56.8, 56.3, 50.1, 46.0, 46.0, 42.4, 39.8, 39.6, 38.2, 37.3, 37.1, 36.7, 36.3, 35.9, 32.0, 32.0, 32.0, 28.3, 28.1, 27.9, 27.5, 27.4, 24.4, 23.9, 22.9, 22.7, 21.1, 19.4, 18.8, 12.0.

HRMS (ESI$^+$) m/z calcd for $C_{34}H_{55}NO_2H^+$ [M+H]$^+$: 510.4311 found: 510.4297.

N-(tert-butyl)-2-(2-methyl-3,4-dihydro-2H-pyrrol-2-yl)acetamide (2at')



2at'

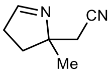
Prepared according to general procedure **GP2.1**, using (Z)-N-(tert-butyl)-3-(cyclopropylamino)but-2-enamide) **1at'** (98 mg, 0.5 mmol, 1 equiv.). The crude was purified by flash column chromatography (petroleum ether: AcOEt = 5:1 to 1:1) to afford product **2at'** (81 mg, 82 % yield) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (s, 1H), 6.71 (s, 1H), 2.63 – 2.57 (m, 2H), 2.44 – 2.16 (m, 2H), 1.93 – 1.78 (m, 1H), 1.72 – 1.65 (m, 1H), 1.32 (s, 9H), 1.24 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.5, 165.3, 74.7, 50.9, 50.0, 36.8, 33.0, 28.9, 26.6.

HRMS (ESI$^+$) m/z calcd for $C_{11}H_{20}N_2OH^+$ [M+H]$^+$: 197,1654 found: 197,1639

2-(2-methyl-3,4-dihydro-2H-pyrrol-2-yl)acetonitrile (2au')



2au'

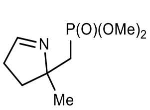
Prepared according to general procedure **GP2.1**, using (Z)-N-(tert-butyl)-3-(cyclopropylamino)but-2-enamide) **1au'** (61 mg, 0.5 mmol, 1 equiv.). The crude was purified by flash column chromatography (petroleum ether: AcOEt = 5:1 to 1:1) to afford product **2au'** (34 mg, 56 % yield) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (s, 1H), 2.80 – 2.66 (m, 2H), 2.59 (s, 2H), 1.92 – 1.84 (m, 1H), 1.81 – 1.73 (m, 1H), 1.36 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.7, 117.9, 74.3, 37.7, 32.2, 30.61, 27.1.

HRMS (ESI$^+$) m/z calcd for $C_7H_{10}N_2H^+$ [M+H]$^+$: 123.0922; found: 123.0908

Dimethyl ((2-methyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)phosphonate (2av')



2av'

Prepared according to general procedure **GP2.1**, using dimethyl (E)-(2-(cyclopropylamino)prop-1-en-1-yl)phosphonate **1av'** (103 mg, 0.5 mmol, 1 equiv.). The crude mixture was purified by flash column chromatography (petroleum ether : AcOEt = 5:1 to 1:1), to afford product **2av'** (87 mg, 85% yield) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (s, 1H), 3.74 – 3.67 (m, 6H), 2.70 – 2.66 (m, 2H), 2.28 – 2.18 (m, 1H), 2.09 – 2.05 (m, 1H), 2.04 – 1.98 (m, 1H), 1.75 – 1.67 (m, 1H), 1.33 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 164.8, 73.5, 52.3 (d, *J* = 6.6 Hz), 52.2 (d, *J* = 6.7 Hz), 37.3, 37.30, 36.4, 33.0 (d, *J* = 3.3 Hz), 28.1 (d, *J* = 7.2 Hz).

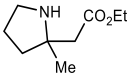
^{31}P NMR (243 MHz, $CDCl_3$) δ 30.76

HRMS (ESI$^+$) m/z calcd for $C_8H_{16}NO_3PH^+$ [M+H]$^+$: 206.0946; found: 206.0936

In flow: Following **GP2.2**, **1av'** (103 mg, 0.5 mmol, 1.0 equiv.), gave **2av'** in 94% NMR yield

3.8 Characterization data of the pyrrolidines (reduction reaction)

Ethyl 2-(2-methylpyrrolidin-2-yl)acetate (3aa')

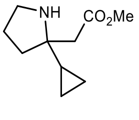

3aa'

Prepared according to the general procedure **GP4.1 (Method A),** using **2aa'** (86 mg, 0,5 mmol, 1 equiv.). The crude was purified by flash column chromatography (petroleum ether: AcOEt = 5:1 to 1:1) to afford product **3aa'** (60 mg, 70 % yield) as a yellow oil.

^{1}H NMR (600 MHz, DMSO) δ 4.19 – 3.93 (m, 2H), 3.03 – 2.85 (m, 1H), 2.51 – 2.42 (m, 2H), 1.84 – 1.65 (m, 2H), 1.55 – 1.15 (m, 9H).
^{13}C NMR (151 MHz, DMSO) δ 170.9, 60. 8, 59.7, 44.6, 37.3, 25.4, 24.1, 14.1, 14.1, 14.0.
HRMS (ESI$^+$) $C_9H_{17}NO_2H^+$ $[M+H]^+$: 172.1338; found 172.1329

Fed batch (Method B): according to **GP4.2** using **a** and **a'** (0.5 mmol) to afford product the **3aa'** in 61% NMR yield.

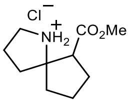
Methyl 2-(2-cyclopropylpyrrolidin-2-yl)acetate (3ac')


3ac'

Prepared according to the general procedure **GP4.1,** using **2ac'** (98 mg, 0.5 mmol, 1 equiv.). The crude was purified by flash column chromatography (petroleum ether: AcOEt = 5:1 to 1:1) to afford product **3ac'** (60 mg, 61 % yield) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.00 – 2.77 (m, 2H), 2.61 – 2.32 (m, 2H), 1.80 – 1.63 (m, 3H), 1.62 – 1.46 (m, 2H), 1.02 – 0.92 (m, 1H), 0.40 – 0.16 (m, 4H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 172.7, 62.6, 51.6, 46.5, 45.5, 35.7, 25.3, 20.4, 1.2, 0.8.
HRMS (ESI$^+$) $C_{10}H_{17}NO_2H^+$ $[M+H]^+$: 184.1338; found: 184.1331.

(5S)-6-(methoxycarbonyl)-1-azaspiro[4.4]nonan-1-ium chloride (3ak')

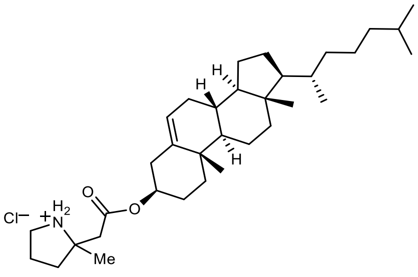

3ak'

Prepared according to general procedure **GP4.1**, using **2ak'** (91 mg, 0.5 mmol, 1 equiv.). The compound was precipitated as hydrochloride salt by bubbling HCl gas into a solution of the crude product in diethyl ether (20 mL) to afford the compound **3ak**' (75 mg, 68% yield) as an inseparable mixture of diastereomers (60:40), as white solid.

^{1}H NMR (600 MHz, D_2O) δ 3.89 – 3.62 (m, 4H), 3.51 – 3.07 (m, 3H), 2.13 – 1.88 (m, 6H), 1.88 – 1.72 (m, 4H).
^{13}C NMR (151 MHz, D_2O) δ 174.5, 75.1, 52.7, 50.4, 44.9, 36.1, 31.8, 26.4, 22.6, 20.8.
HRMS (ESI$^+$) $C_{10}H_{18}NO_2^+$ $[M+]^+$: 184.1337 found: 184.1339

Fed batch (Method B): according to **GP4.2** using **a** and **k'** (0.5 mmol) to afford product the **3ak'** in 60% NMR yield.

2-(2-(((3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)oxy)-2-oxoethyl)-2-methylpyrrolidin-1-iumchloride (3aq')



3aq'

Prepared according to general procedure **GP2.1**, using **2aq'** (255 mg, 0.5 mmol, 1 equiv.). The compound was precipitated as hydrochloride salt by bubbling HCl gas into a solution of the crude product in diethyl ether (20 mL) to afford the compound **3aq'** (200 mg, 73 yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.65 – 9.46 (m, 2H), 5.42 – 5.33 (m, 1H), 4.67 – 4.55 (m, 1H), 3.56 – 3.37 (m, 2H), 3.11 – 2.81 (m, 2H), 2.36 – 2.27 (m, 2H), 2.11 – 1.79 (m, 8H), 1.61 – 1.40 (m, 10H), 1.36 – 1.30 (m, 4H), 1.25 (m, 2H), 1.17 – 1.03 (m, 8H), 1.00 (s, 4H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.85 (dd, *J* = 6.6, 2.6 Hz, 6H), 0.66 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.4, 139.4, 139.4, 123.1, 123.0, 75.2, 65.1, 65.0, 56.8, 56.4, 50.1, 44.1, 42.5, 42.4, 39.8, 39.6, 38.1, 37.0, 36.9, 36.9, 36.7, 36.3, 35.9, 35.9, 32.0, 32.0, 28.3, 28.1, 27.9, 24.4, 24.0, 23.0, 23.0, 22.9, 22.7, 22.5, 22.5, 21.2, 19.4, 18.8, 12.0.
HRMS (ESI$^+$) $C_{34}H_{58}NO_2^+$ [M]$^+$: 512.4468; found: 512.4445

4. Mechanistic Studies

4.1 Photophysical Studies

UV-Vis spectroscopy

The absorption spectrum of a $2.0 \cdot 10^{-5}$ M solution of the photocatalyst **4CzIPN** in CH_3CN was recorded (Figure S10 left). To 2 mL of the latter solution **1aa'** was added (6.8 mg, 0.04 mmol, 1000 equiv.) and the absorption spectra recorded again (Fig. S10 right).

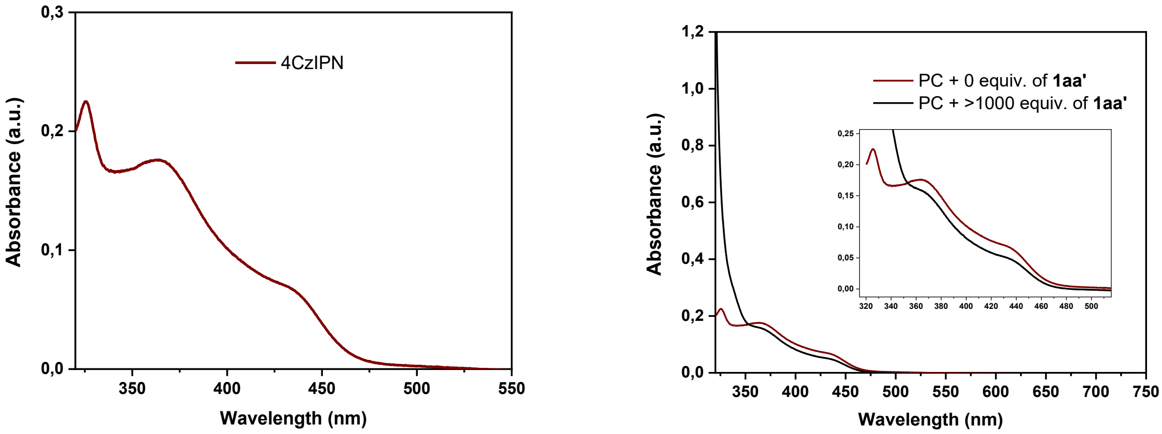


Figure S10 Absorption spectrum of **4CzIPN** $2.0 \cdot 10^{-5}$ M in CH3CN (left) and the mixture of **4CzIPN** $2.0 \cdot 10^{-5}$ M solution and **1aa'** (1000 equiv.).

Emission spectroscopy Stern-Volmer

To conduct the Stern-Volmer experiments, a N_2-bubbled solution of **4CzIPN** ($2.0 \cdot 10^{-5}$ M in CH_3CN) was irradiated with a 440 nm exciting source and the luminescence spectrum was recorded as shown Figure S11 (black line, 0 mM).

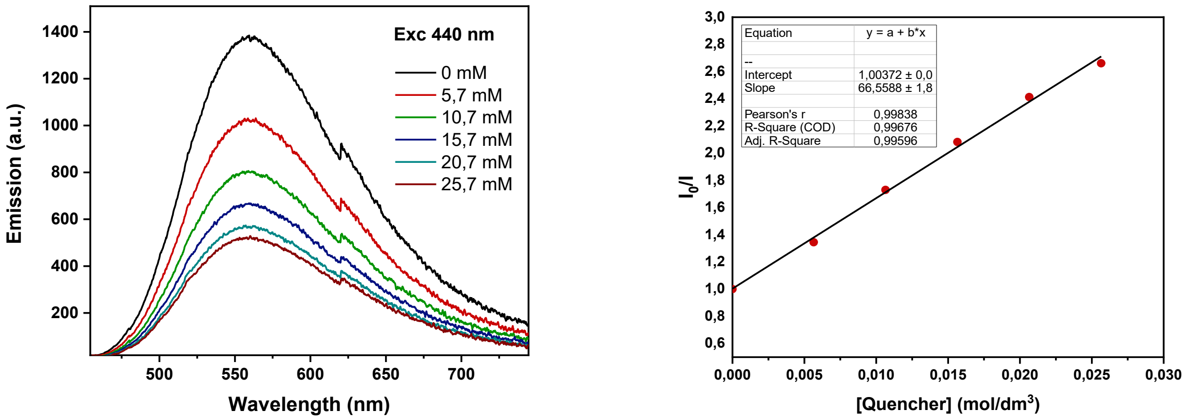


Figure S11 Luminescence spectrum of the photocatalyst **4CzIPN** ($2.0 \cdot 10^{-5}$ M in CH_3CN); exc = 440 nm.

Subsequentially, we monitored the photoluminescence spectra in the presence of increasing amounts of **1aa’**. A quenching of the signal was observed (Figure S11 left). The corresponding Stern-Volmer plot was built by monitoring the luminescence decay at 560 nm (Figure S11 right); a Stern-Volmer constant (Ksv) of 67 M^{-1} was calculated using the following equation (Eq. S1):

$$\frac{I_0}{I} = 1 + K_{SV}[Q] \qquad \text{[Eq. S1]}$$

4.2 Experimental Studies

Ring opening cyclization step in NMR tube

To an oven-dried, argon-purged screw-capped vial fitted with a rubber septum, 4CzIPN (19.7 mg, 5 mol%) and compound **1aa'** (Z:E = 90:10, 0.5 mmol, 1 equiv.) were added in degassed CD_3CN (5 mL, 0.1 M). The reaction vessel was subsequently sparged with argon, and 500 µL of the resulting solution was transferred to an NMR tube for spectral acquisition (Figure S12, **1aa’** : **2aa**’ = 100:0). The tube was then placed in a UFO photoreactor equipped with a 456 nm Kessil Lamp (100% intensity) as light source, irradiated and analysed by NMR (0 min, 30 min, 50 min, 130 min).

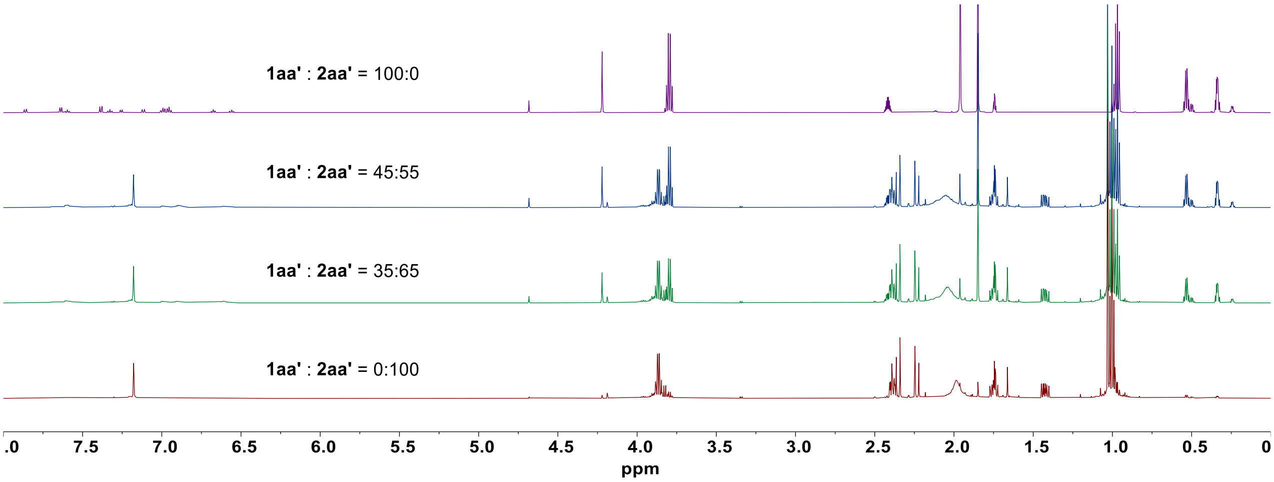
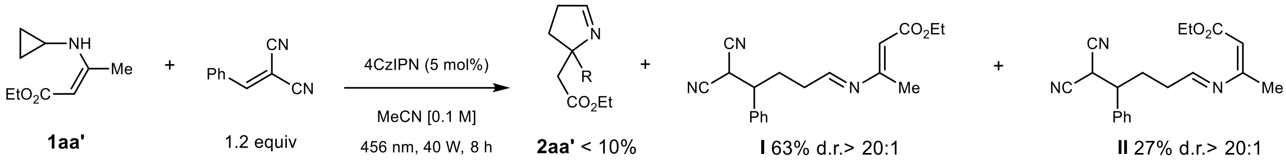


Figure S12 ^{1}H NMR monitoring of the ring opening cyclization

Trapping experiments



To an oven-dried argon-purged screw-capped vial, fitted with a rubber septum, charged with 4CzIPN (19.7 mg, 5 mol%), **1aa’** (84.5 mg, 0.5 mmol, 1 equiv.) and benzylidenemalononitrile (93 mg, 0.6 mmol, 1.2 equiv.) in degassed CH_3CN (5 mL, 0.1 M) was added. Subsequently the reaction vessel was sparged with argon. The vial was then placed in a UFO photoreactor equipped with a 456 nm Kessil Lamp 100% intensity as light source and irradiated for four hours. The solvent of the resulting crude mixture was then removed under reduced pressure and analyzed by GC-MS and NMR. Purification by flash column chromatography on silica gel gave compounds **I** and **II** as an inseparable mixture of diastereomers (70:30). The ^{1}H NMR spectrum of the mixture is reported in figure S13.

I and **II**, ^{1}H NMR (600 MHz, $CDCl_3$)

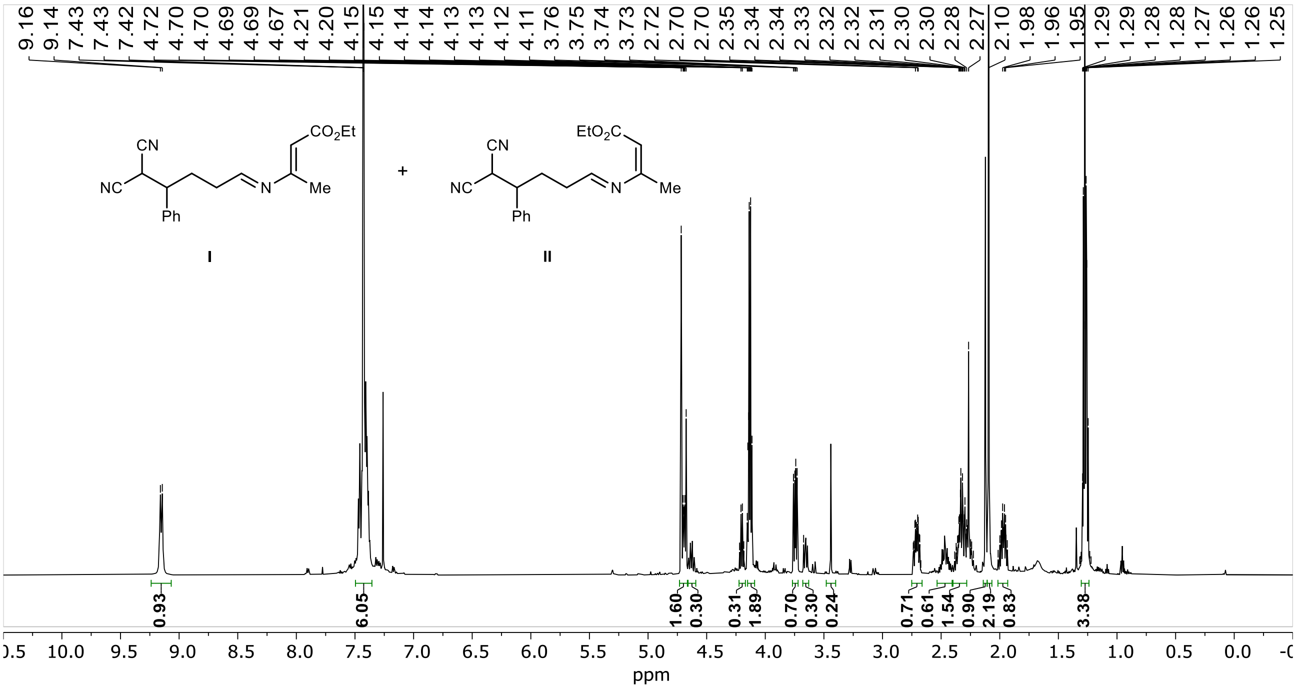
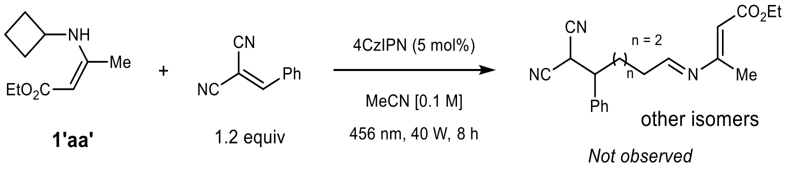


Figure S13

The same trapping experiment was conducted using the four-member derivative **1’aa’** in place of **1aa’**:



To an oven-dried argon-purged screw-capped vial, fitted with a rubber septum, charged with 4CzIPN (19,7 mg, 5 mol%), **1’aa’** (92 mg, 0.5 mmol, 1 equiv.) and benzylidenemalononitrile (93 mg, 0.6 mmol, 1.2 equiv.) in degassed CH_3CN (5 mL, 0.1 M) was added. Subsequently the reaction vessel was sparged with argon. The vial was then placed in a 3D-printed UFO photoreactor equipped with a 450 nm Kessil Lamp (100%) intensity as light source and irradiated for four hours. The solvent of the crude mixture was then removed under reduced pressure and analyzed by GC-MS and NMR.

Less than 20 % of conversion of **1'aa'** and less than 10% yield of the trapped product were detected. This result does not support the existence of an efficient ring opening of the four-member ring and is in line with the observations of previous experiments.

5. Batch and flow comparison

The efficiency of the continuous process was evaluated by selecting entries **2aa'**, **2ae'**, **2ak'**, **2ba'** and **2av'** and comparing the productivities (Equation S2) obtained by applying the optimized conditions for the flow and batch approach (Figure S14). The values reported, were determined on a reaction scale of 0.4 mmol of the corresponding starting material for each entry, which translates to a process time of 6 h for the batch protocol and 1.5 h for the flow approach (Table S9).

Table S9

	2aa'	**2ae'**	**2ak'**	**2ba'**	**2av'**
Batch Process Time (h)	6	6	6	6	6
Batch Yield %	95	71	80	88	92
Amount of product obtained in batch (mg)	64	66	58	65	76
Batch productivity (mg/h)	11	11	10	11	13
Flow Process Time (h)	1.5	1.5	1.5	1.5	1.5
Flow Yield %	96	80	90	93	94
Amount of product obtained in flow (mg)	65	74	65	68	77
Flow productivity (mg/h)	43	49	43	45	51

$$\text{Productivity} = \frac{\text{Mass of desidered product (mg)}}{\text{Process time (h)}} \qquad \text{[Eq. S2]}$$

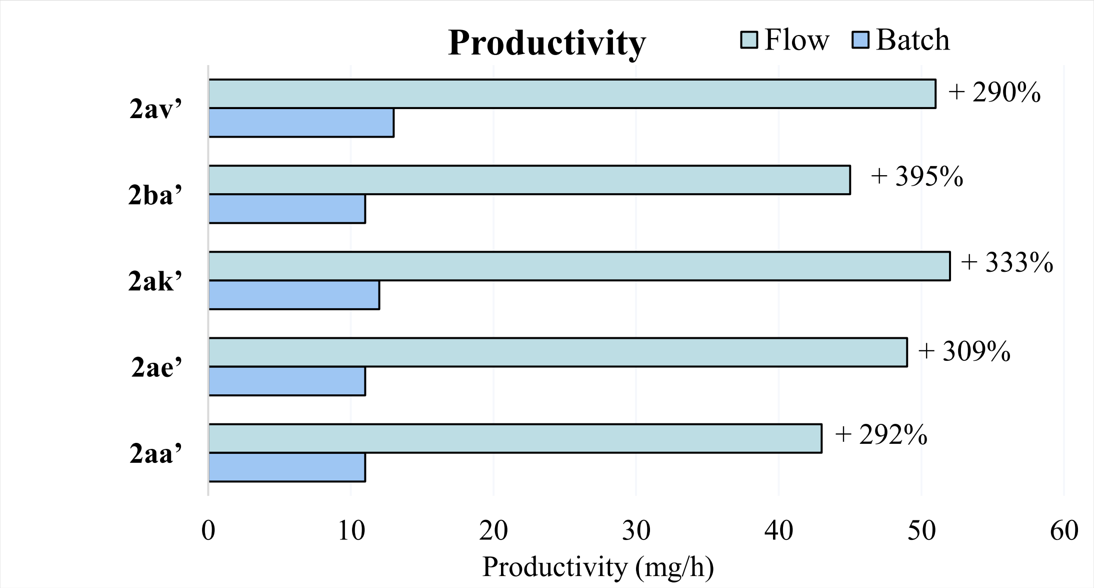

Productivity
Flow
Batch
2av’
2ba’
2ak’
2ae’
2aa’
+ 290%
+ 395%
+ 333%
+ 309%
+ 292%
0
10
20
30
40
50
60
Productivity (mg/h)

Figure S14

Finally the efficiency of the telescoped method was evaluated by selecting the model substrate **2aa'** and comparing the productivity obtained with this approach to the one-pot methods (Figure S15). The values reported were obtained processing 0.4 mmol of staring materials. The first step in the one-pot experiments was carried out following GP1.1A and GP1.2A (batch condensation and flow condensation respectively) and the crude processed without any purification according to GP2.1 and GP2.2 (batch cyclization and flow cyclization respectively). Overall Yields for the one-pot experiments were calculated as the product of the individual yields of the two steps considered (Table S10). Process times for the one-pot experiments were calculated as the sum of the process times of the two steps considered. Productivities were calculated according to Equation 2.

Table S10

	Batch condensation + batch cyclization	**Flow condensation + batch cyclization**	**Flow condensation + flow cyclization**	**Telescope**
Overall Yield %	85%	93%	94%	84%
Process Time (h)	16	8.2	1.7	0.476
Amount of **2aa'** obtained (mg)	57.26	63.02	63.66	56.86
Productivity (mg/h)	3.58	7.68	37.45	119.45

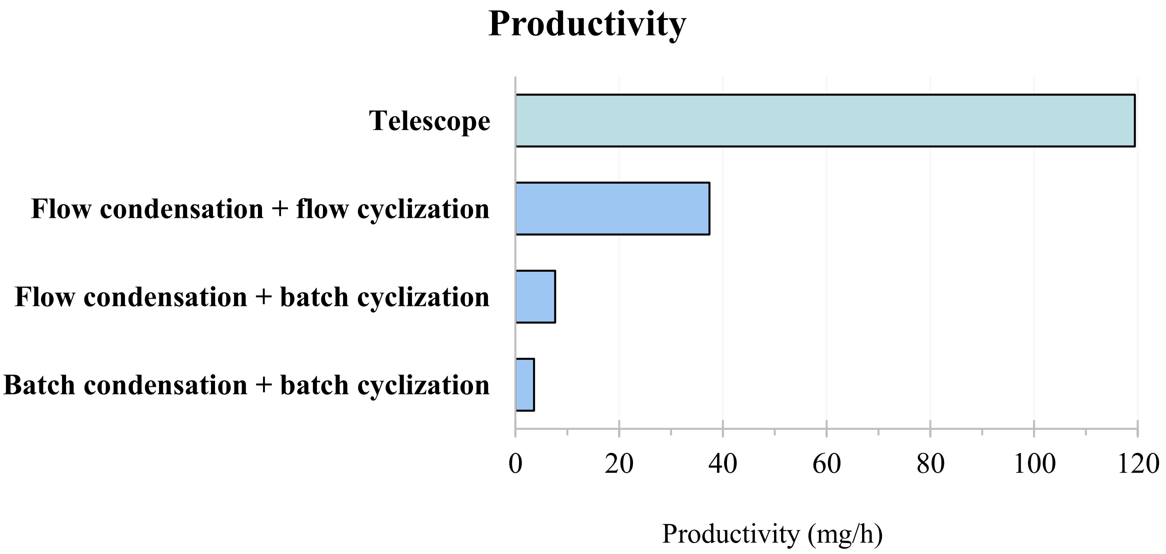


Figure S15

6. Reference

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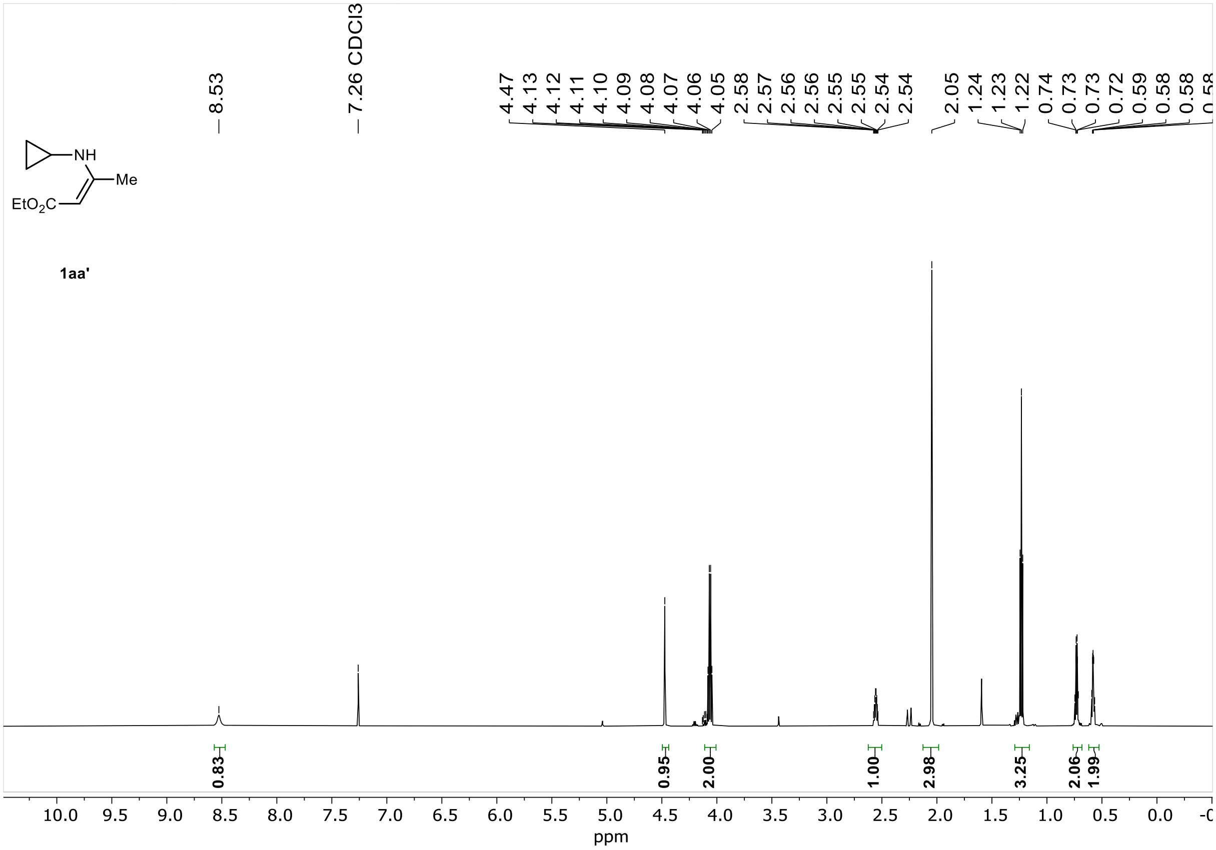
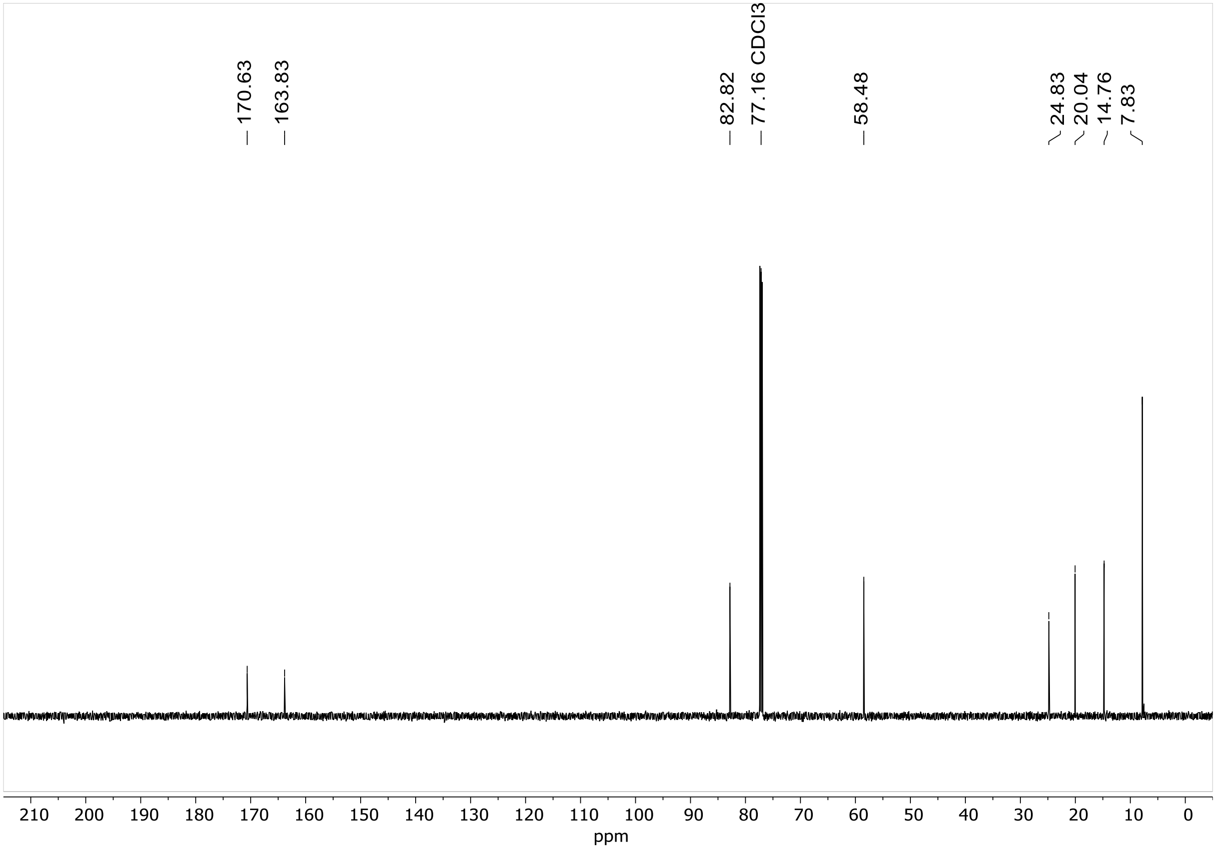
7. NMR Spectra starting material

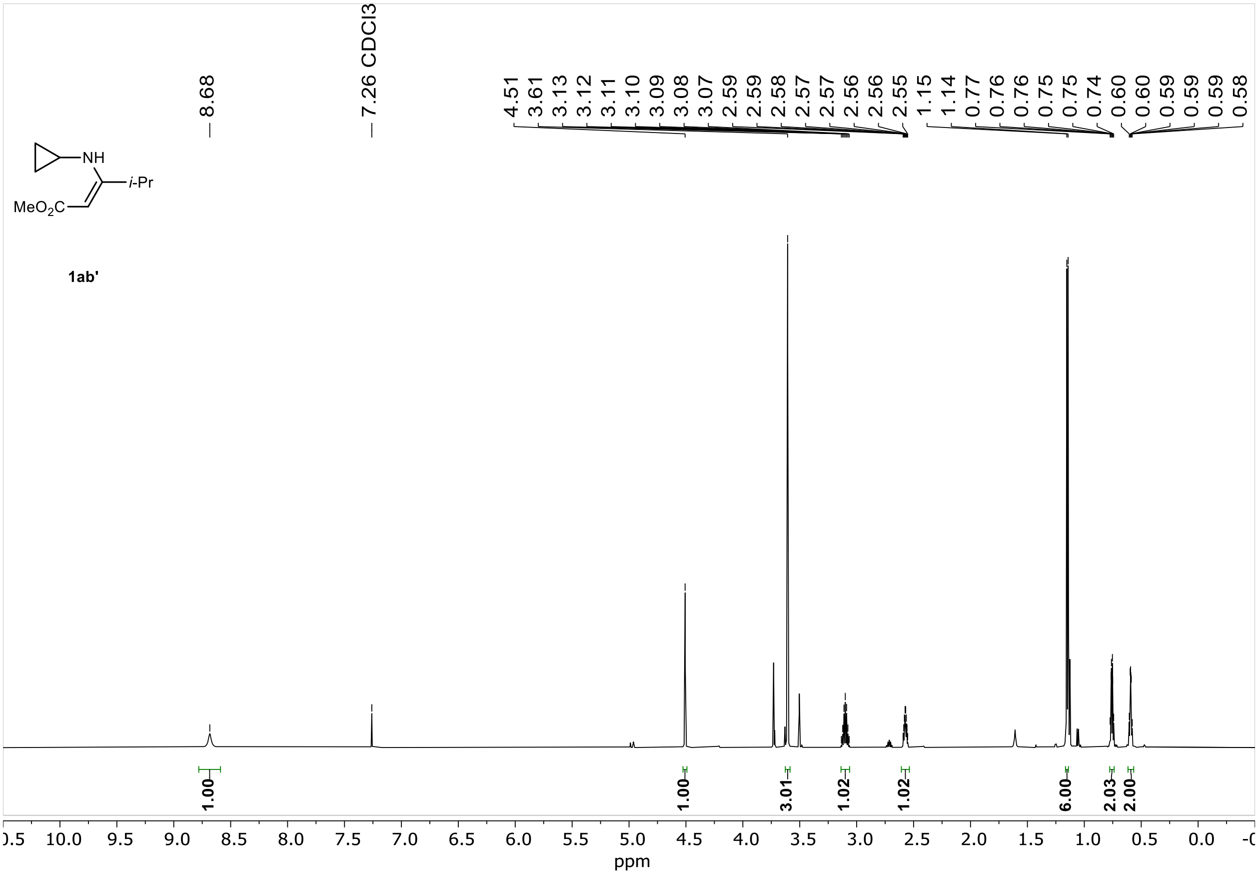
1aa', ^{1}H NMR (600 MHz, CDCl$_3$)



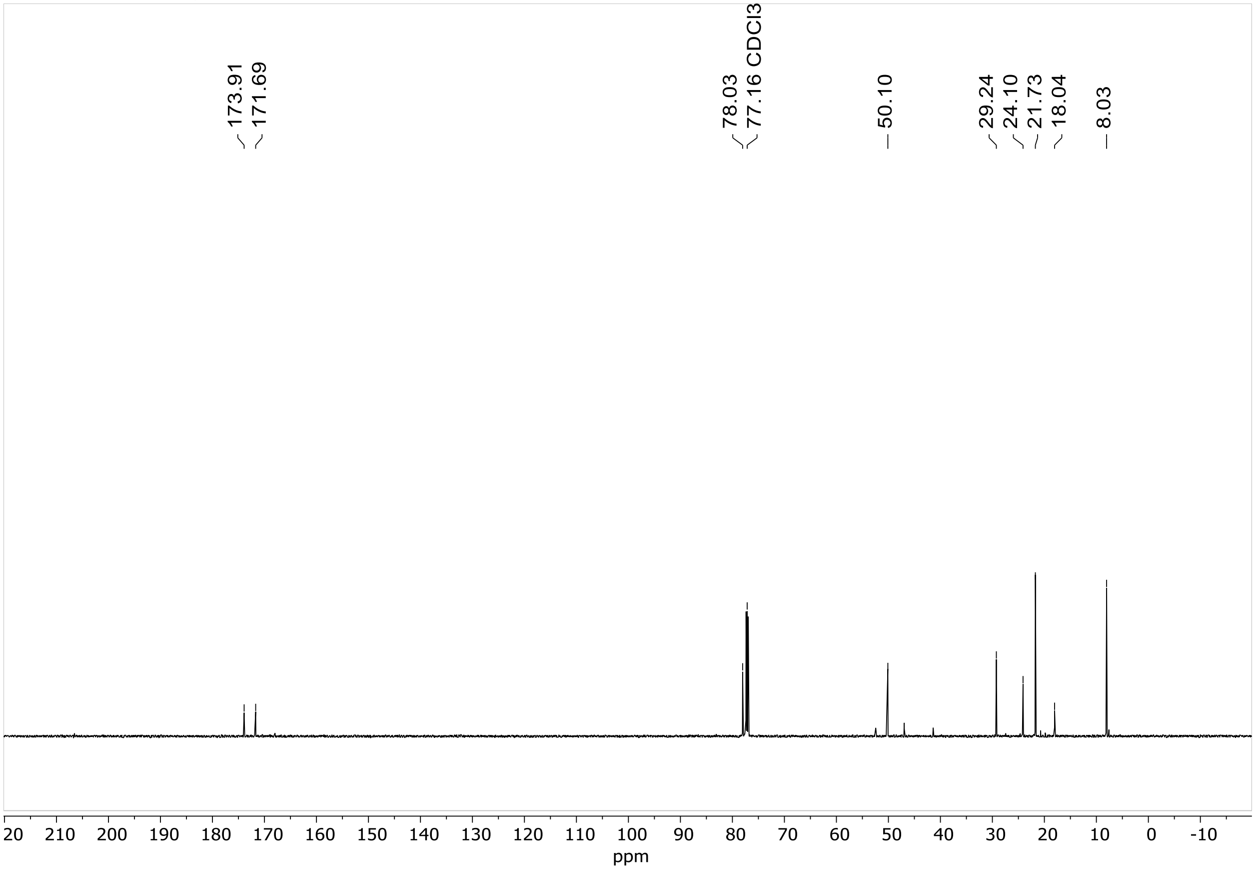
1aa',^{13}C NMR (151 MHz, CDCl$_3$)



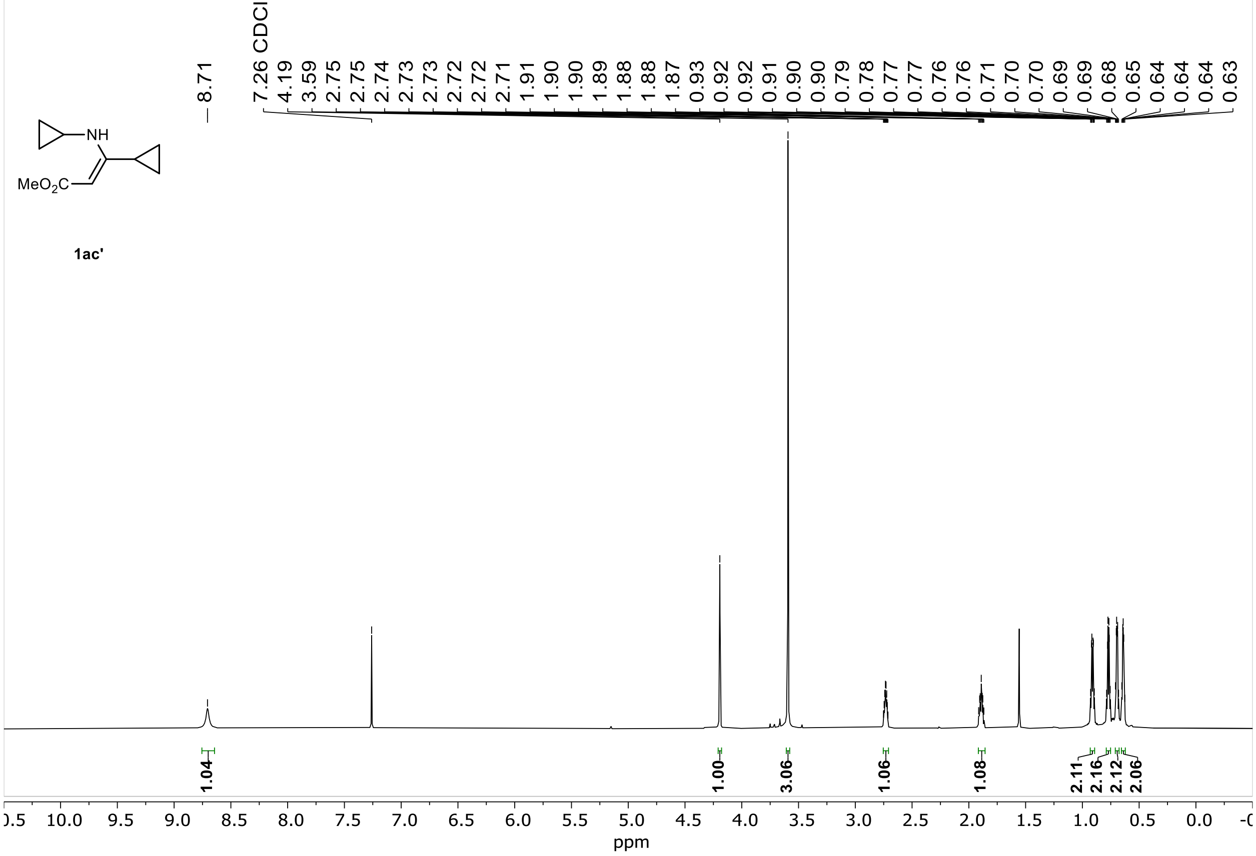
1ab’, ^{1}H NMR (600 MHz, CDCl$_3$)



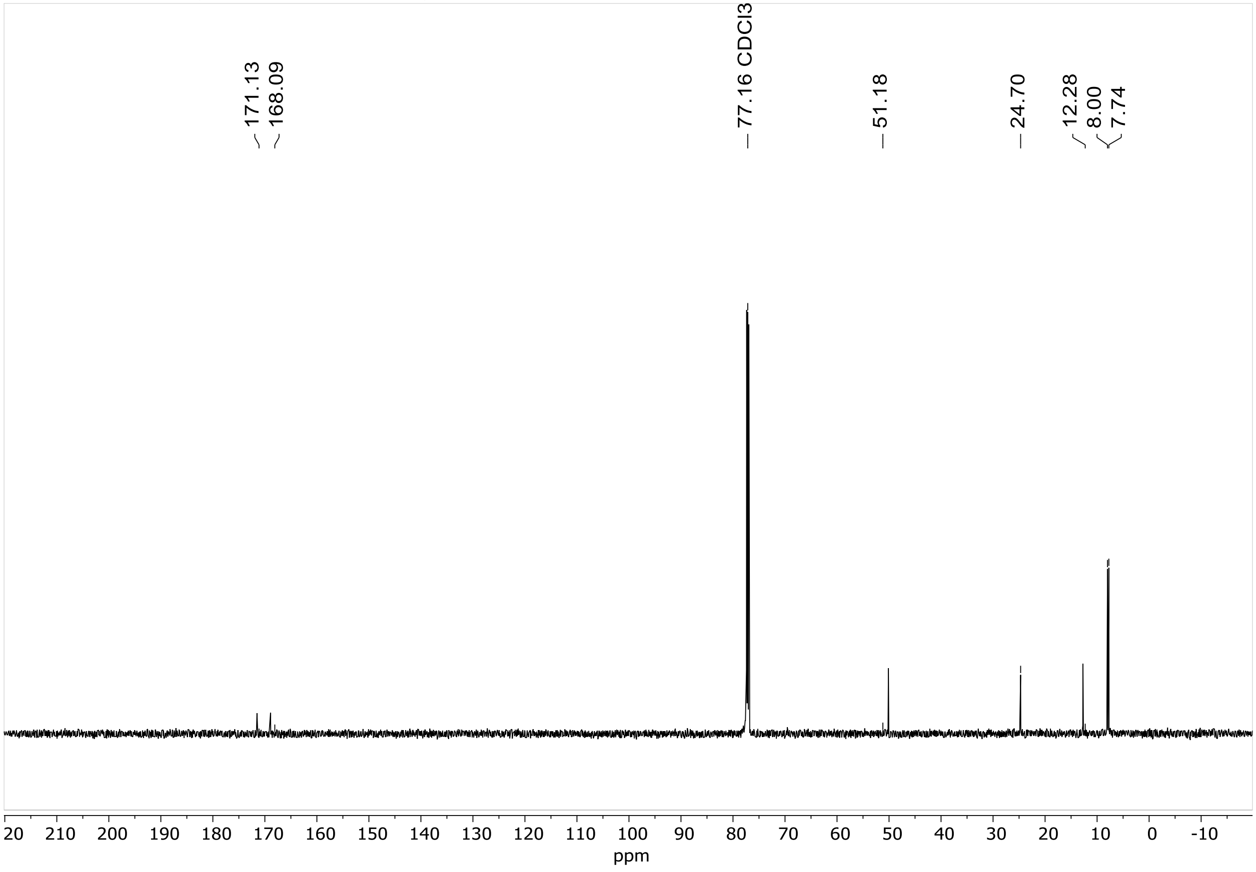
1ab’,^{13}C NMR (151 MHz, CDCl$_3$)



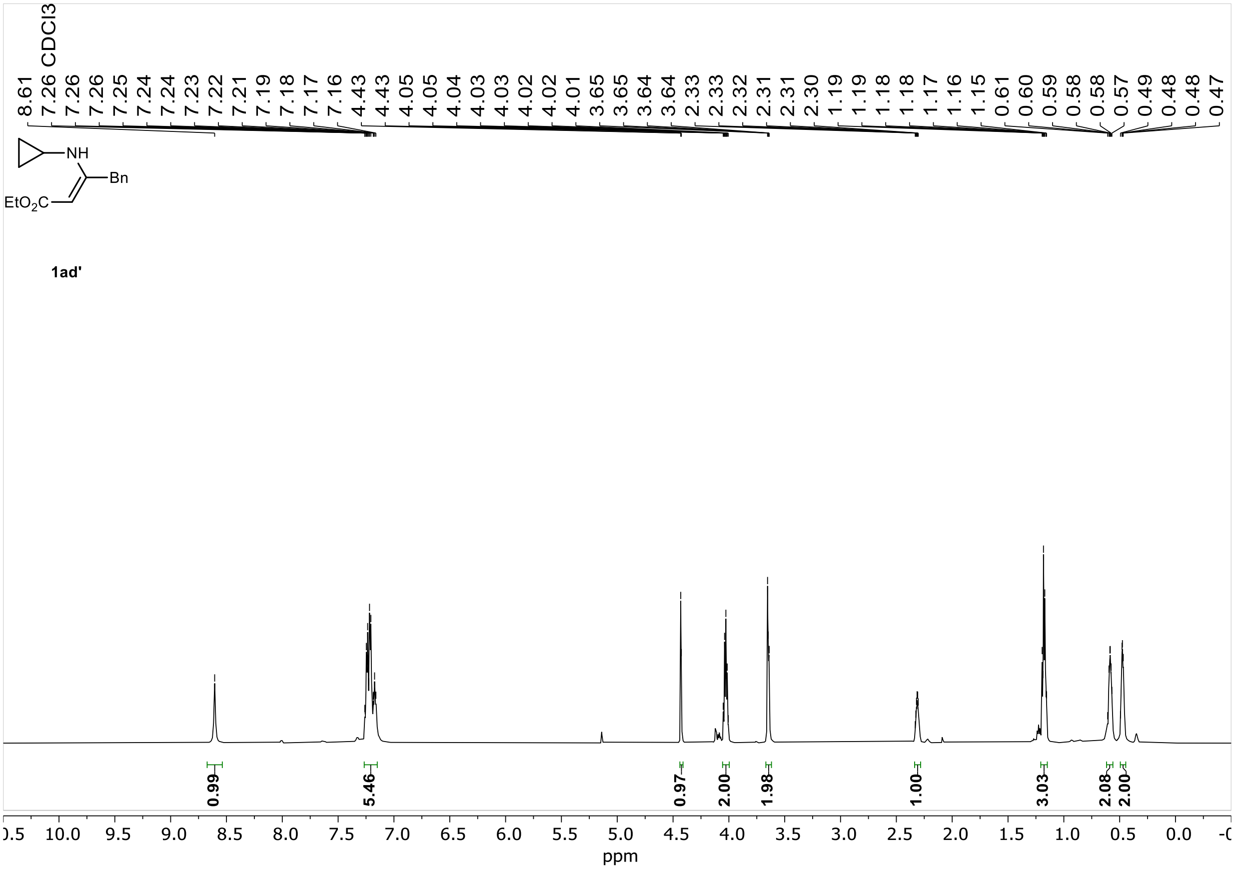
1ac’, ^{1}H NMR (600 MHz, CDCl$_3$)



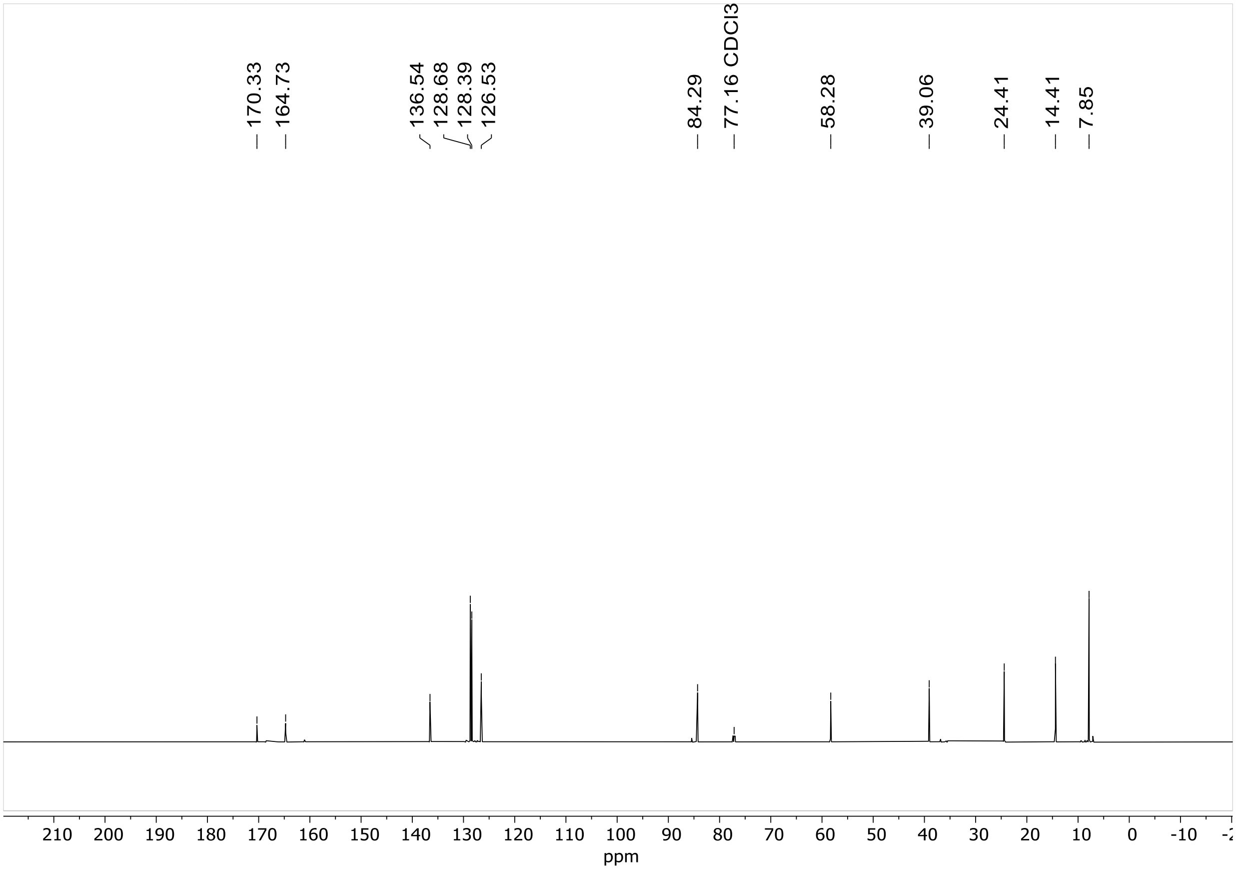
1ac’, ^{13}C NMR (151 MHz, CDCl$_3$)



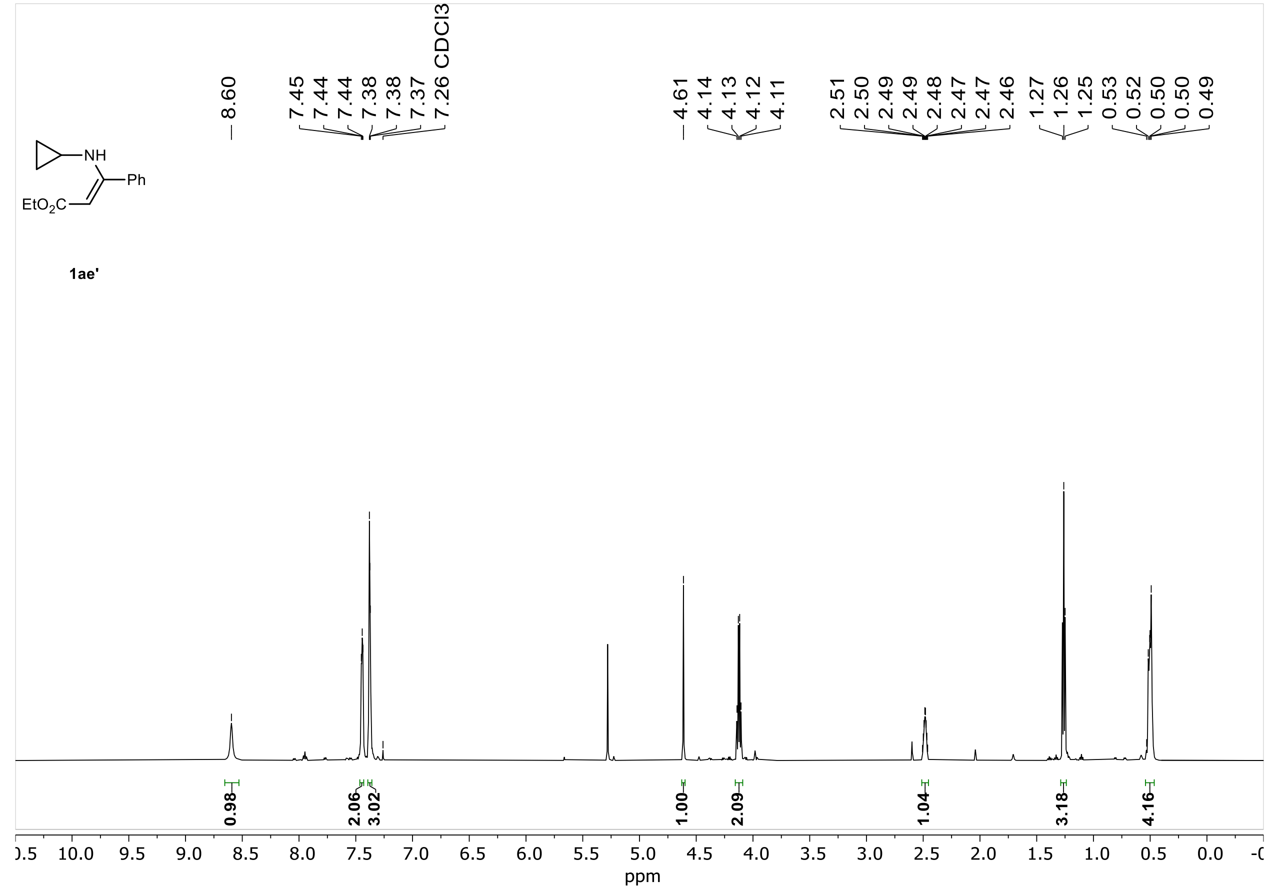
1ad',^{1}H NMR (600 MHz, CDCl$_3$)



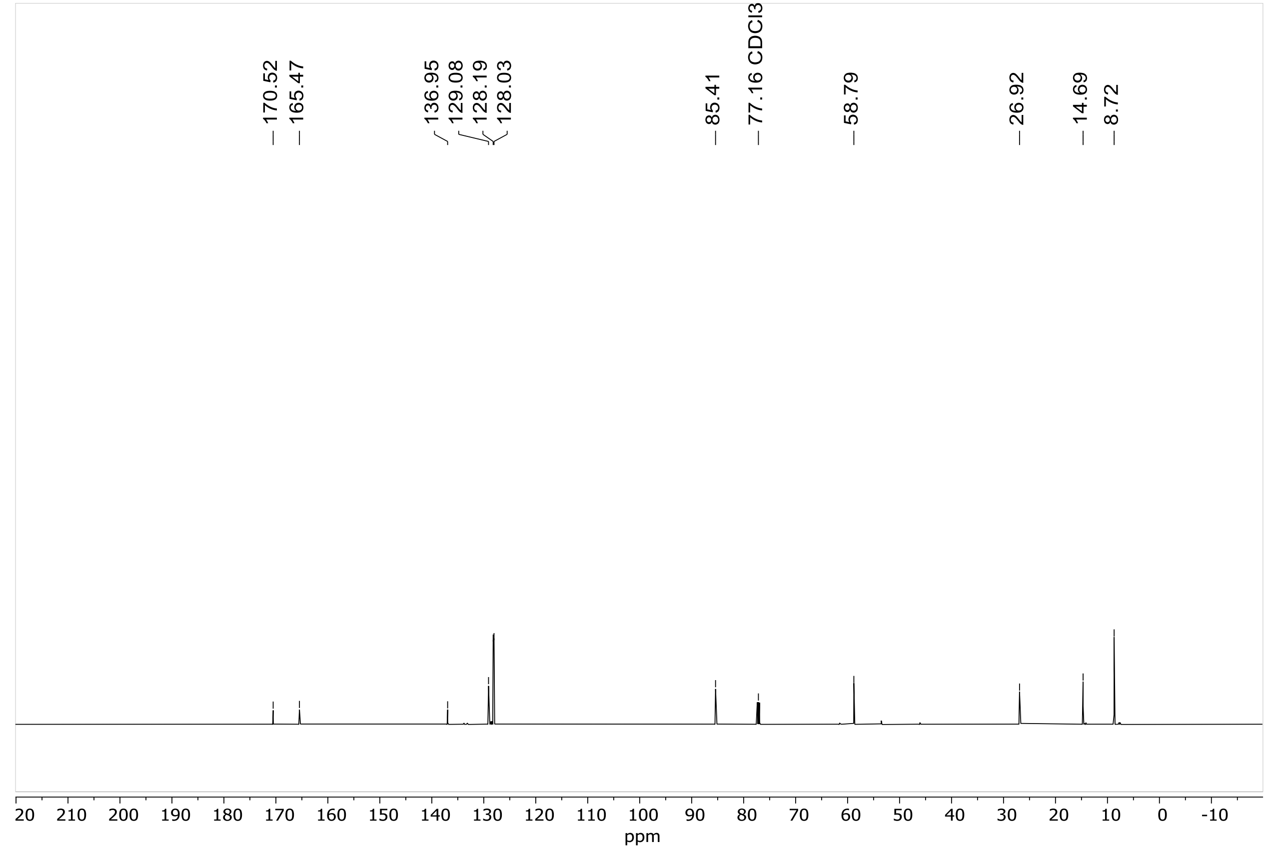
1ad',^{13}C NMR (151 MHz, CDCl$_3$)



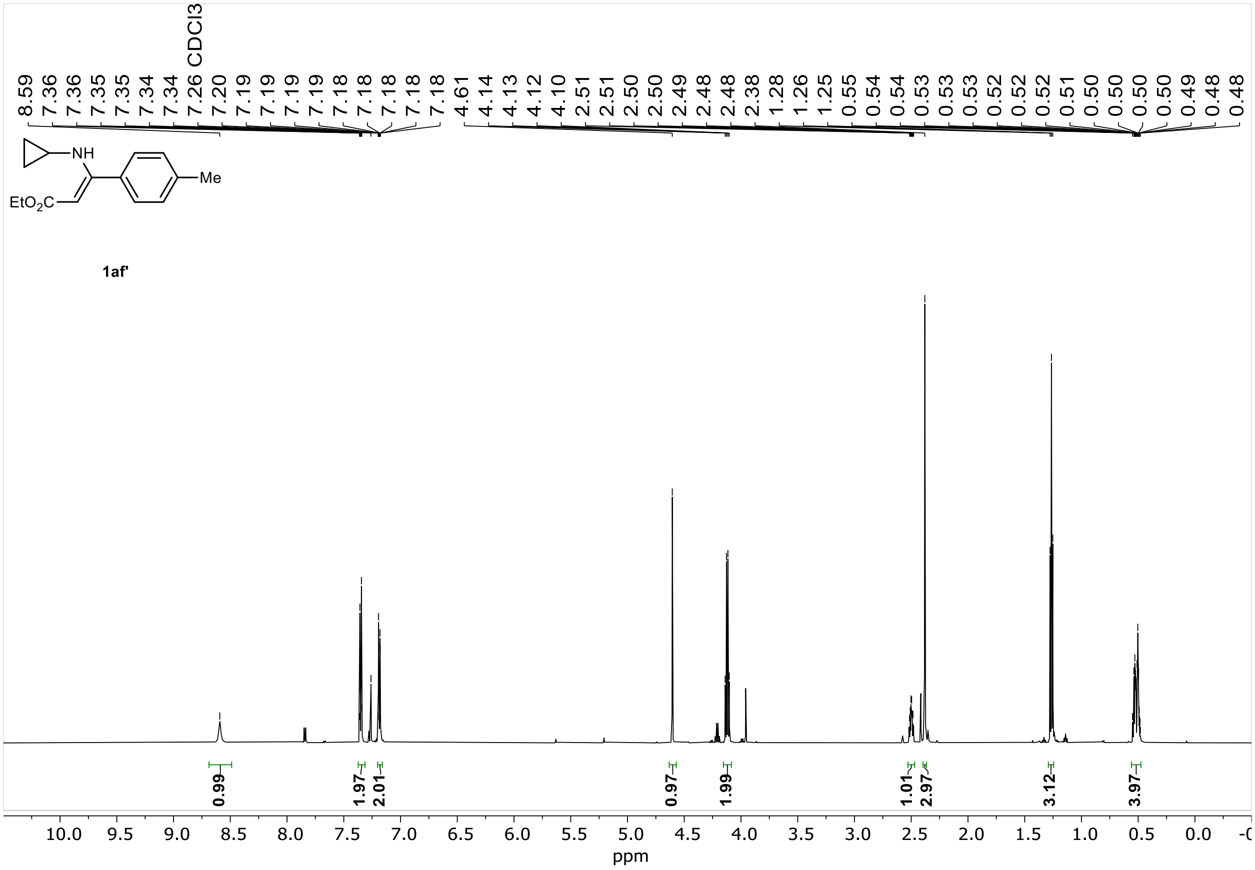
1ae’,^{1}H NMR (600 MHz, CDCl$_3$)



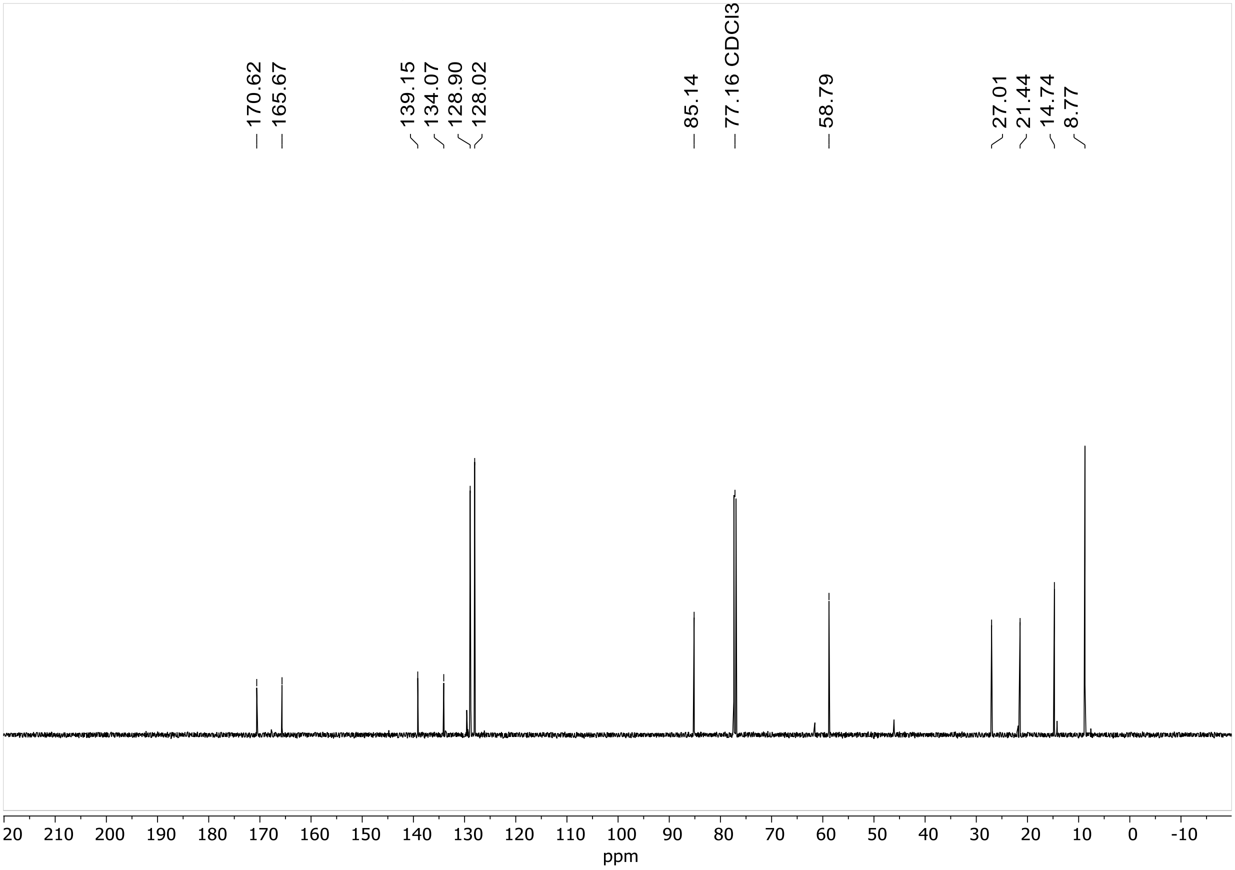
1ae’,^{13}C NMR (151 MHz, CDCl$_3$)



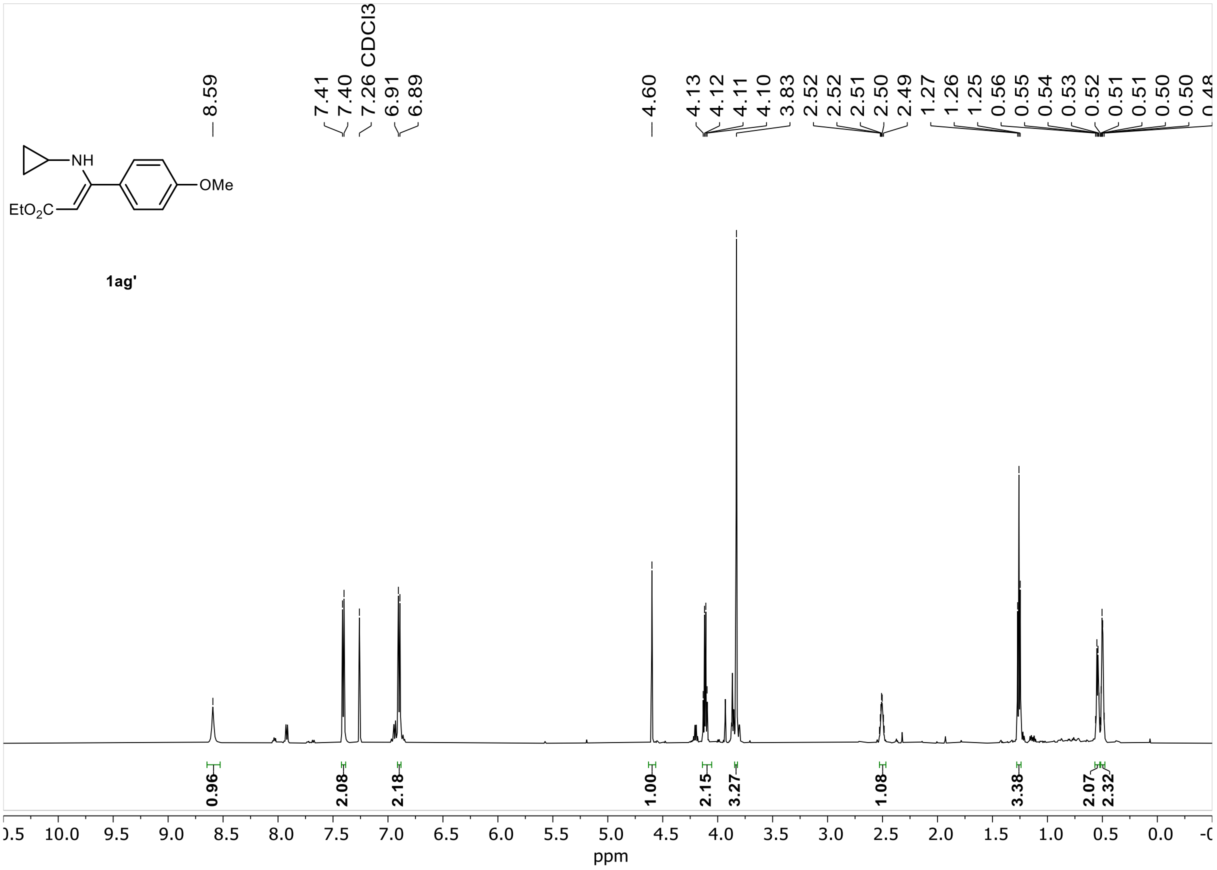
1af’,^{1}H NMR (600 MHz, CDCl$_3$)



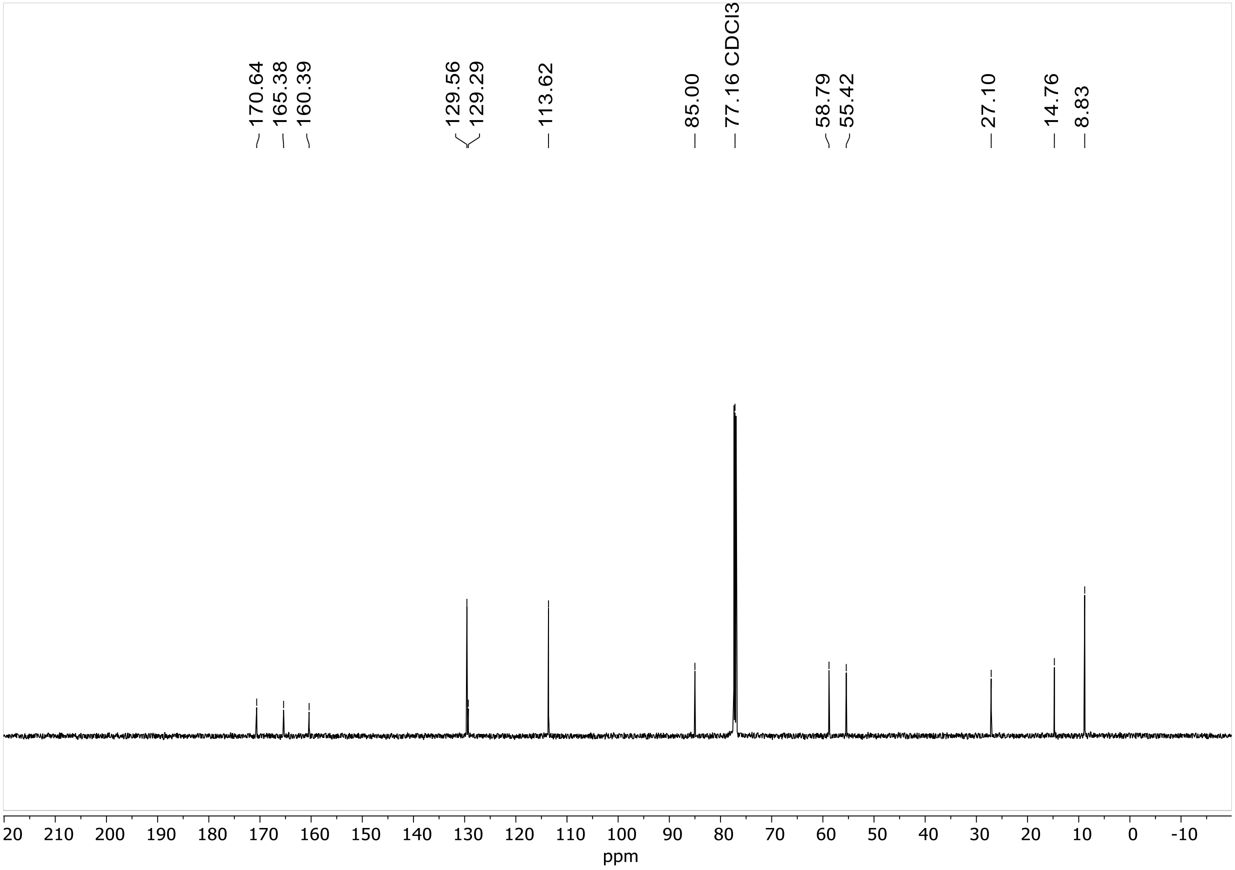
1af’,^{13}C NMR (151 MHz, CDCl$_3$)



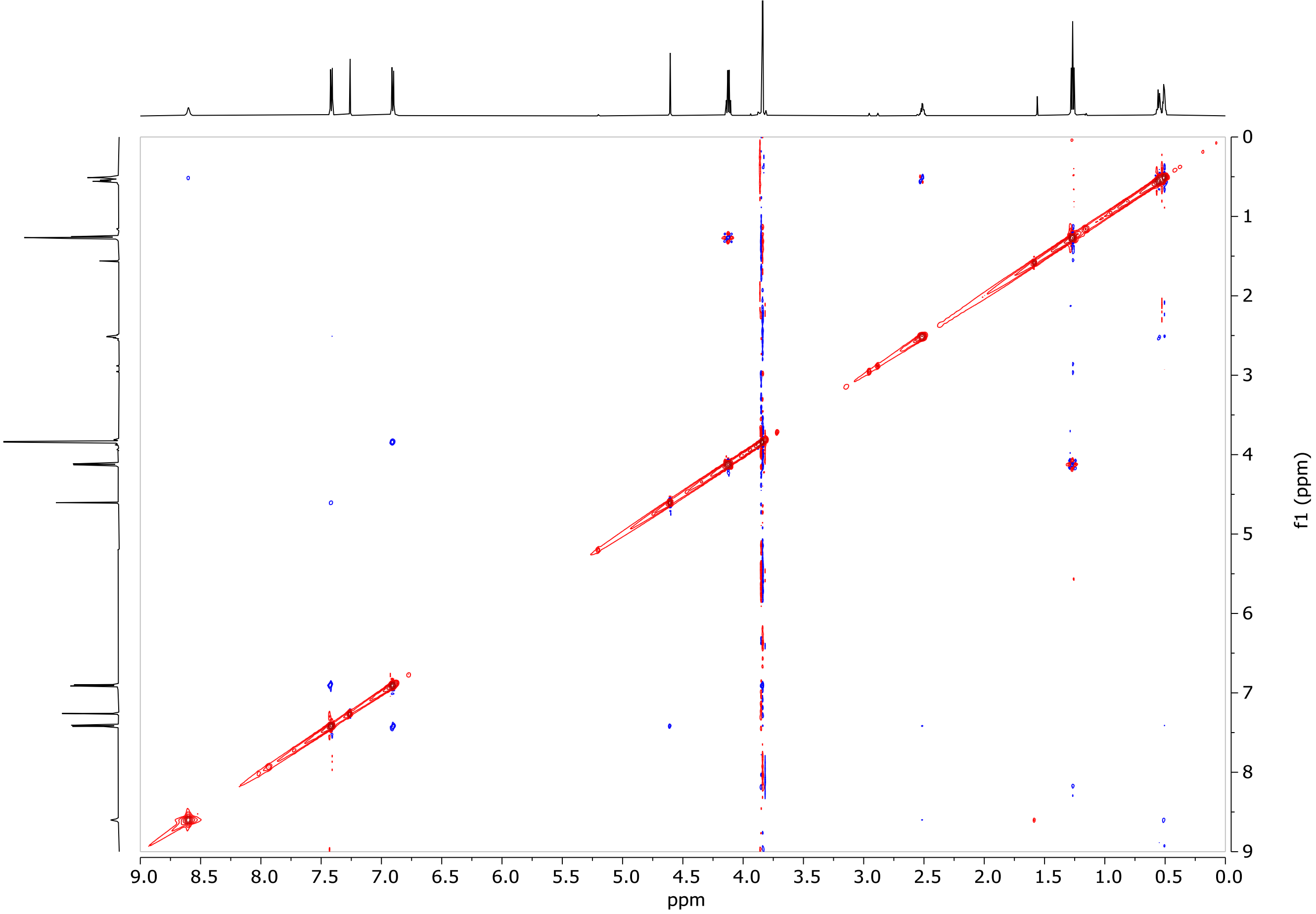
1ag’,^{1}H NMR (600 MHz, CDCl$_3$)



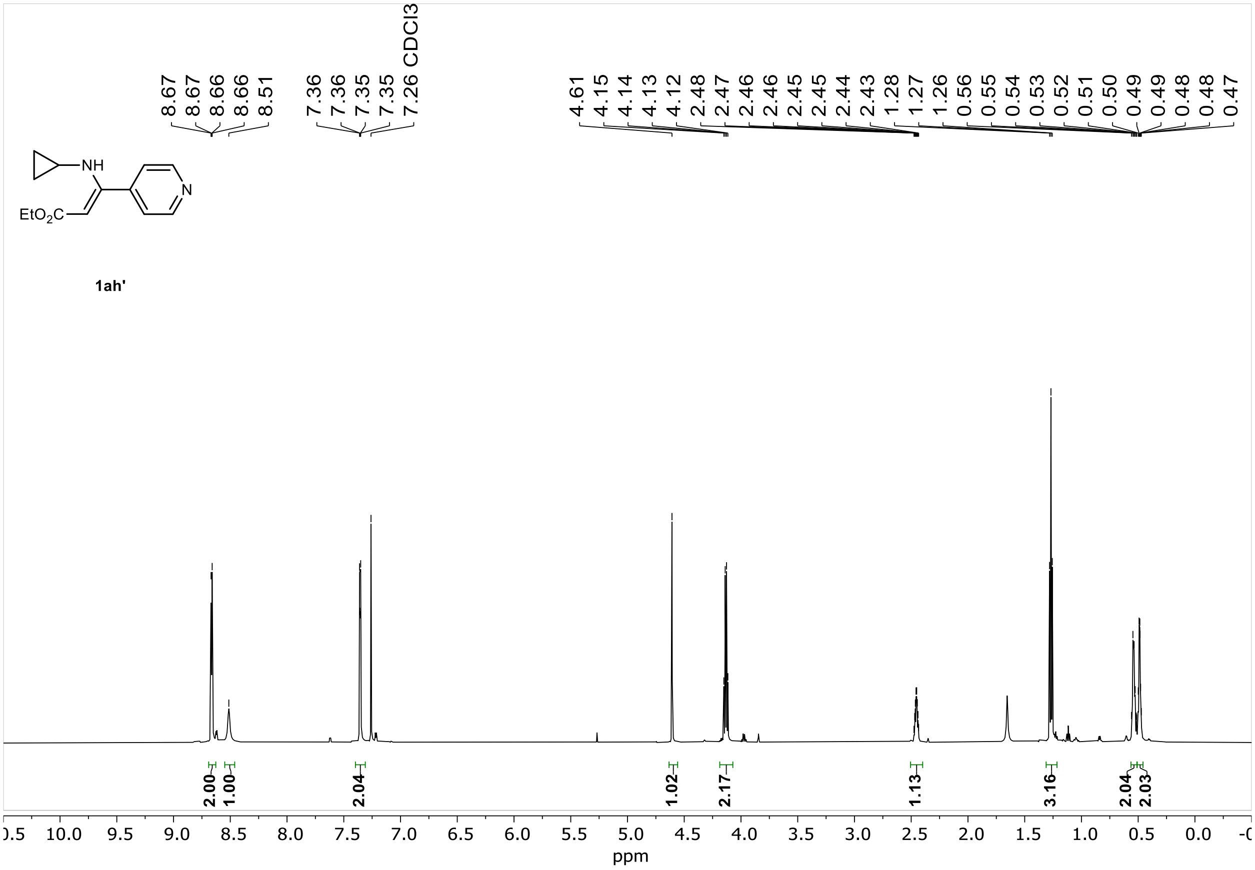
1ag’,^{13}C NMR (151 MHz, CDCl$_3$)



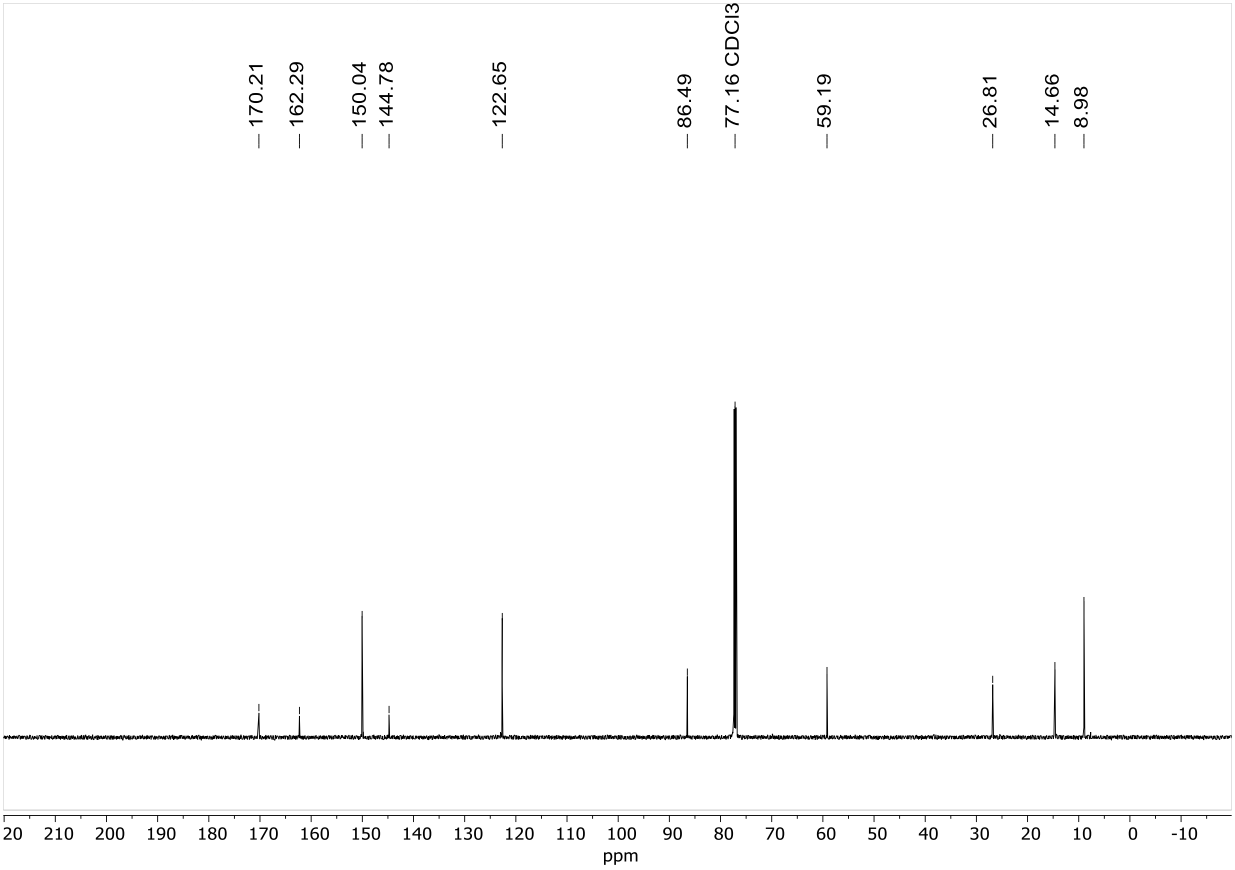
1ag', 2D NOESY (600 MHz, 600 MHz, $CDCl_3$)



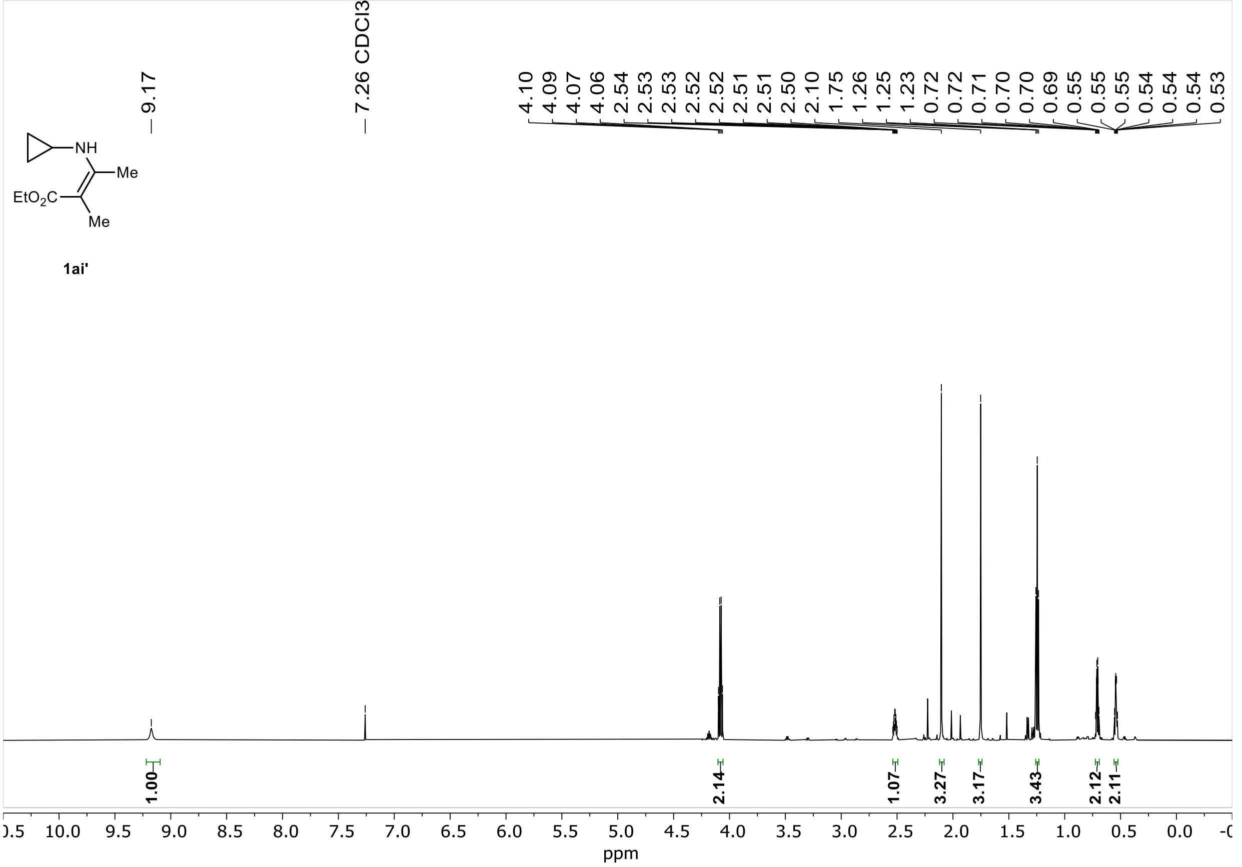
1ah’, ^{1}H NMR (600 MHz, CDCl$_3$)



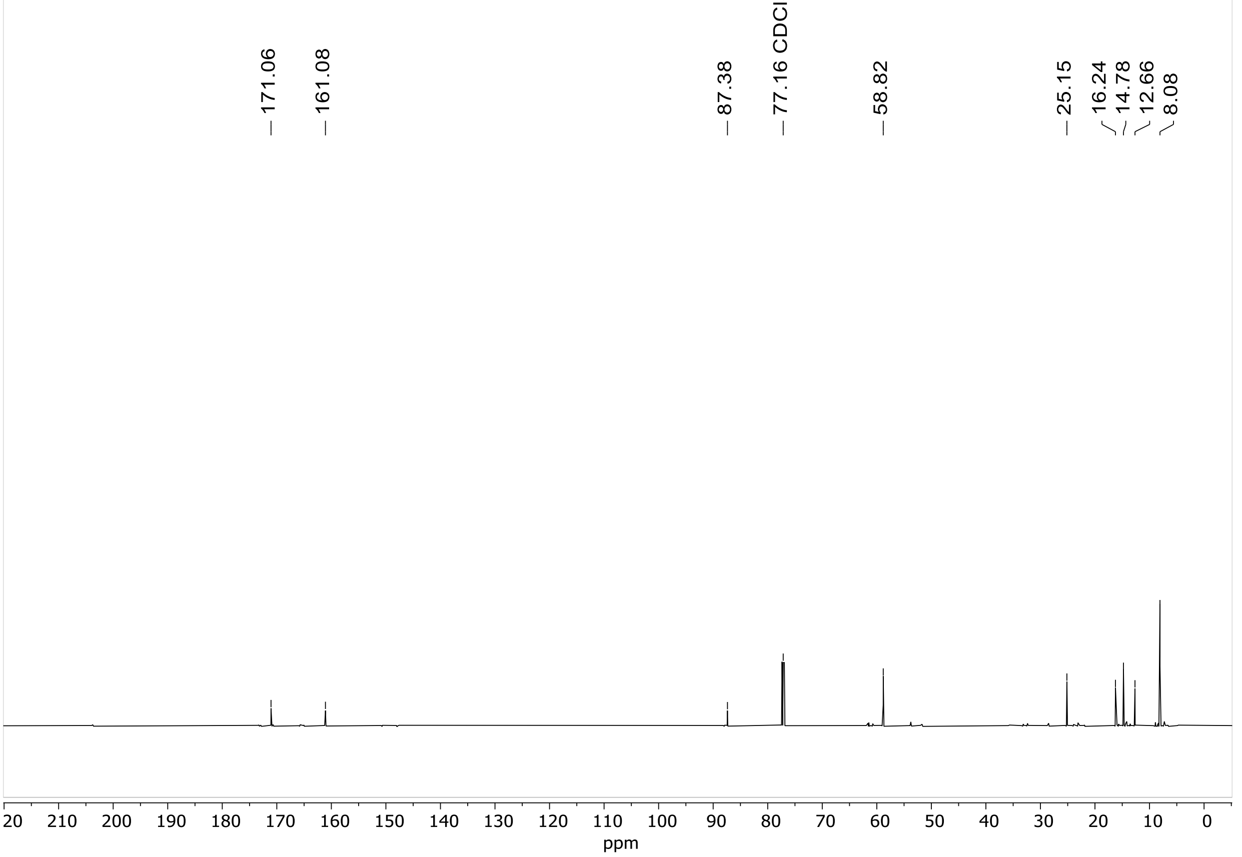
1ah’, ^{13}C NMR (151 MHz, CDCl$_3$)



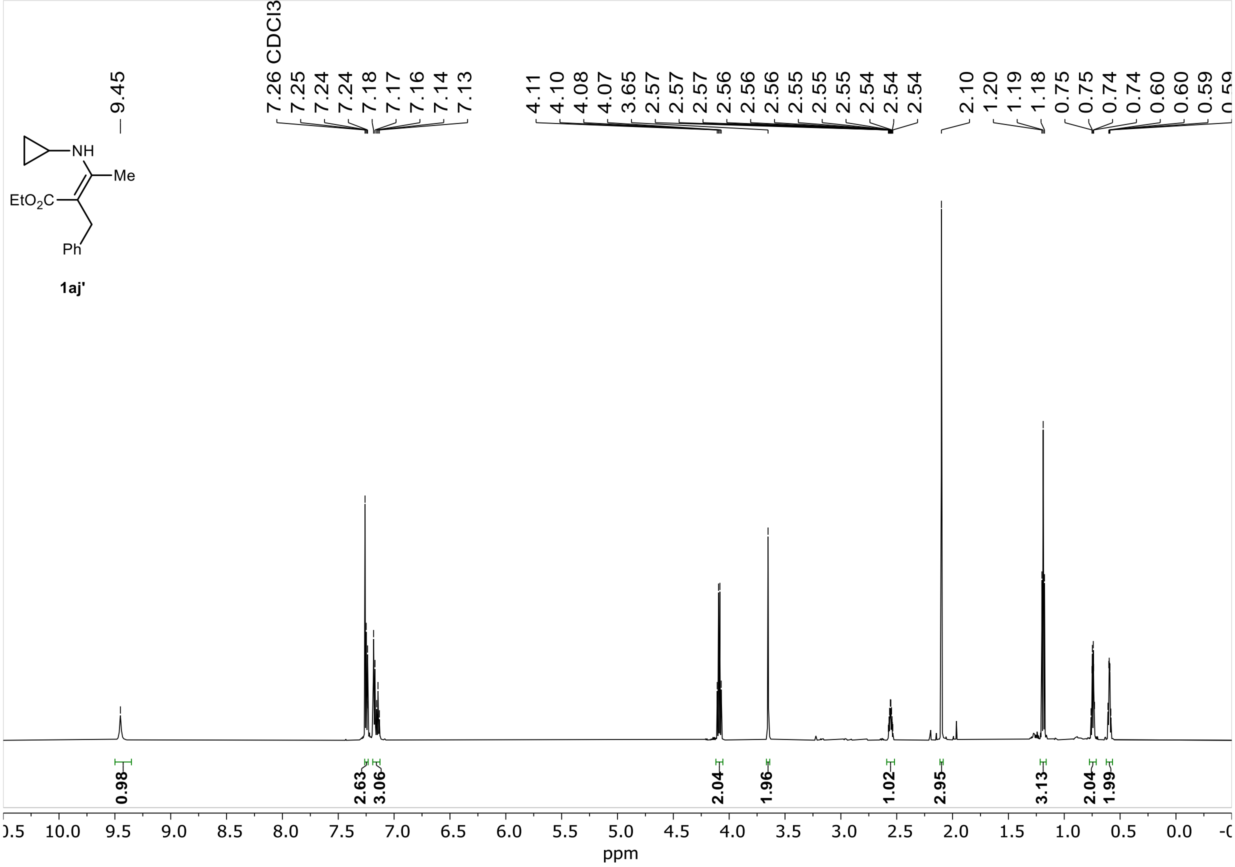
1ai' ^{1}H NMR (600 MHz, $CDCl_3$)



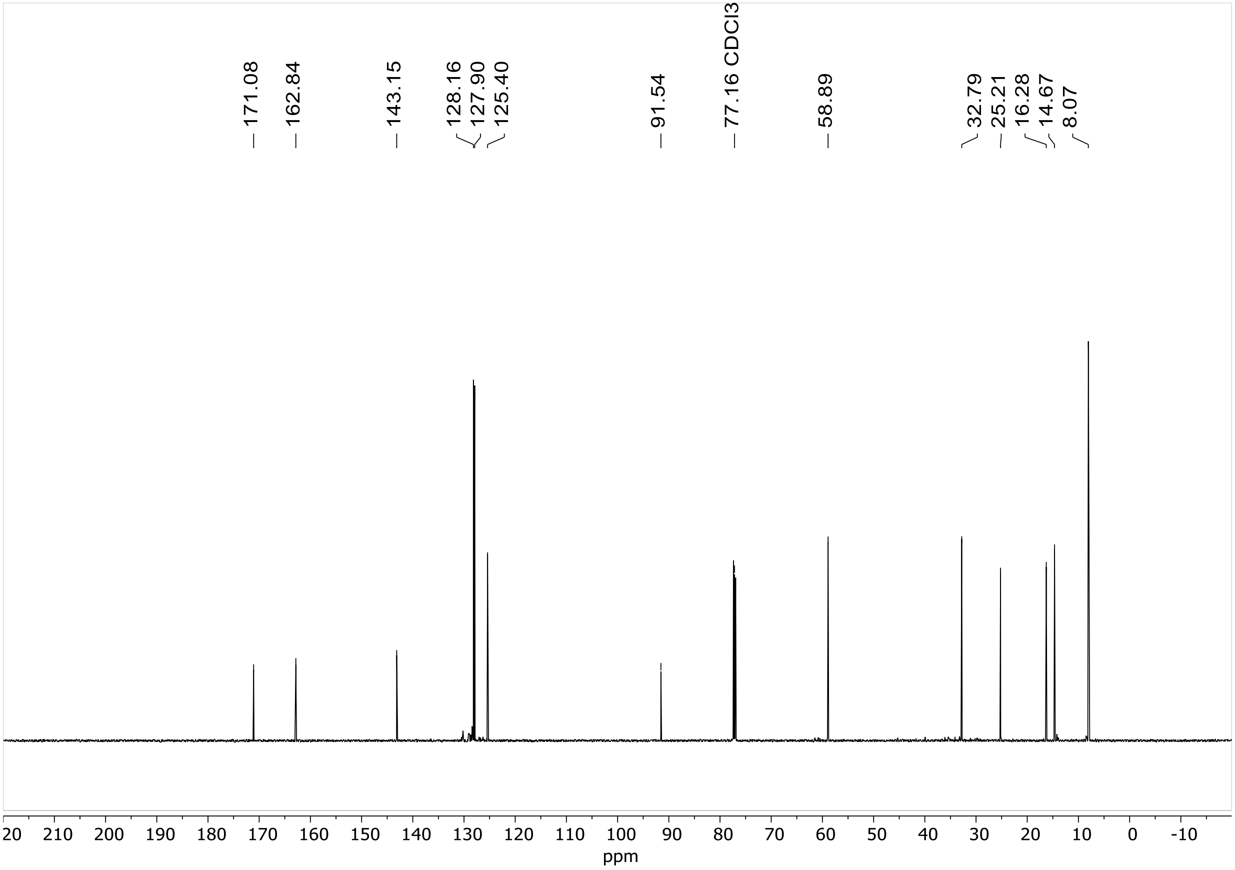
1ai' ^{13}C NMR (151 MHz, $CDCl_3$)



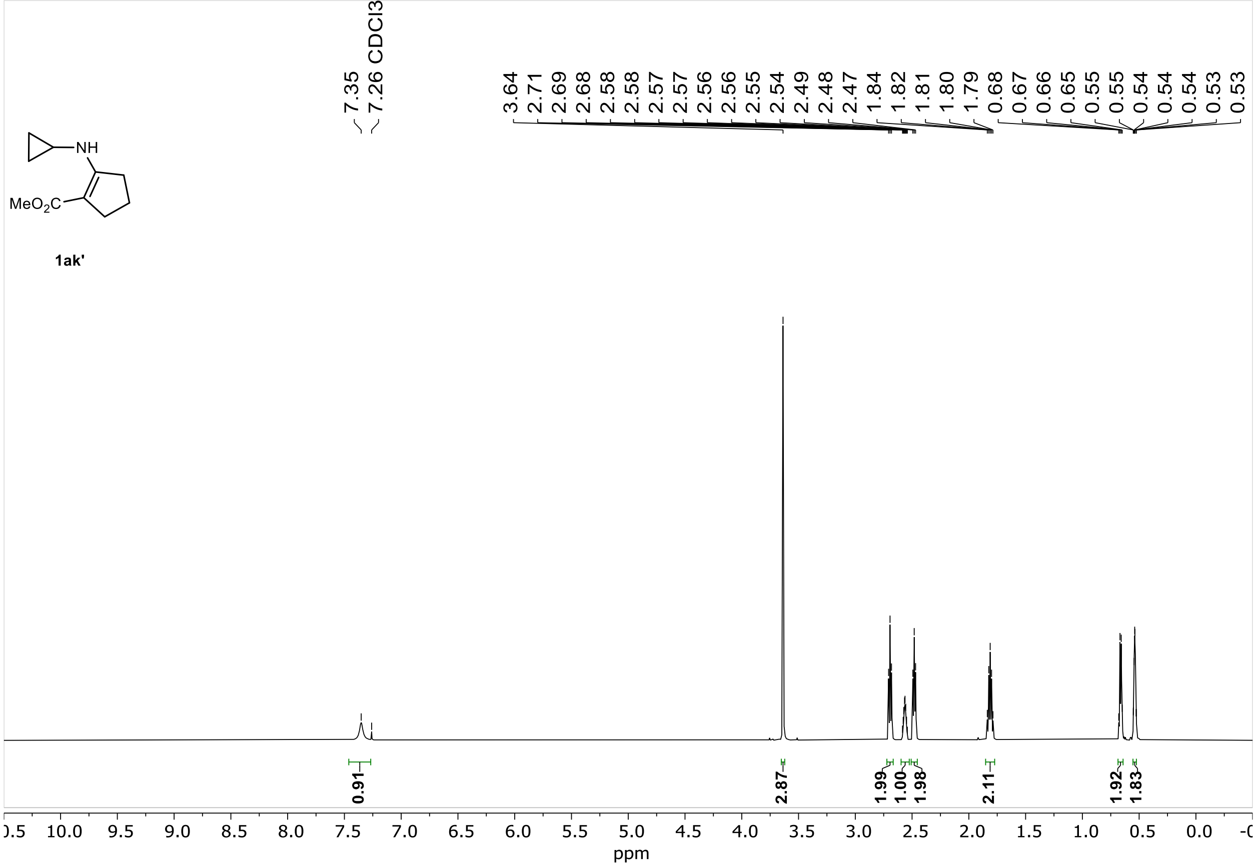
1aj’ ^{1}H NMR (600 MHz, CDCl$_3$)



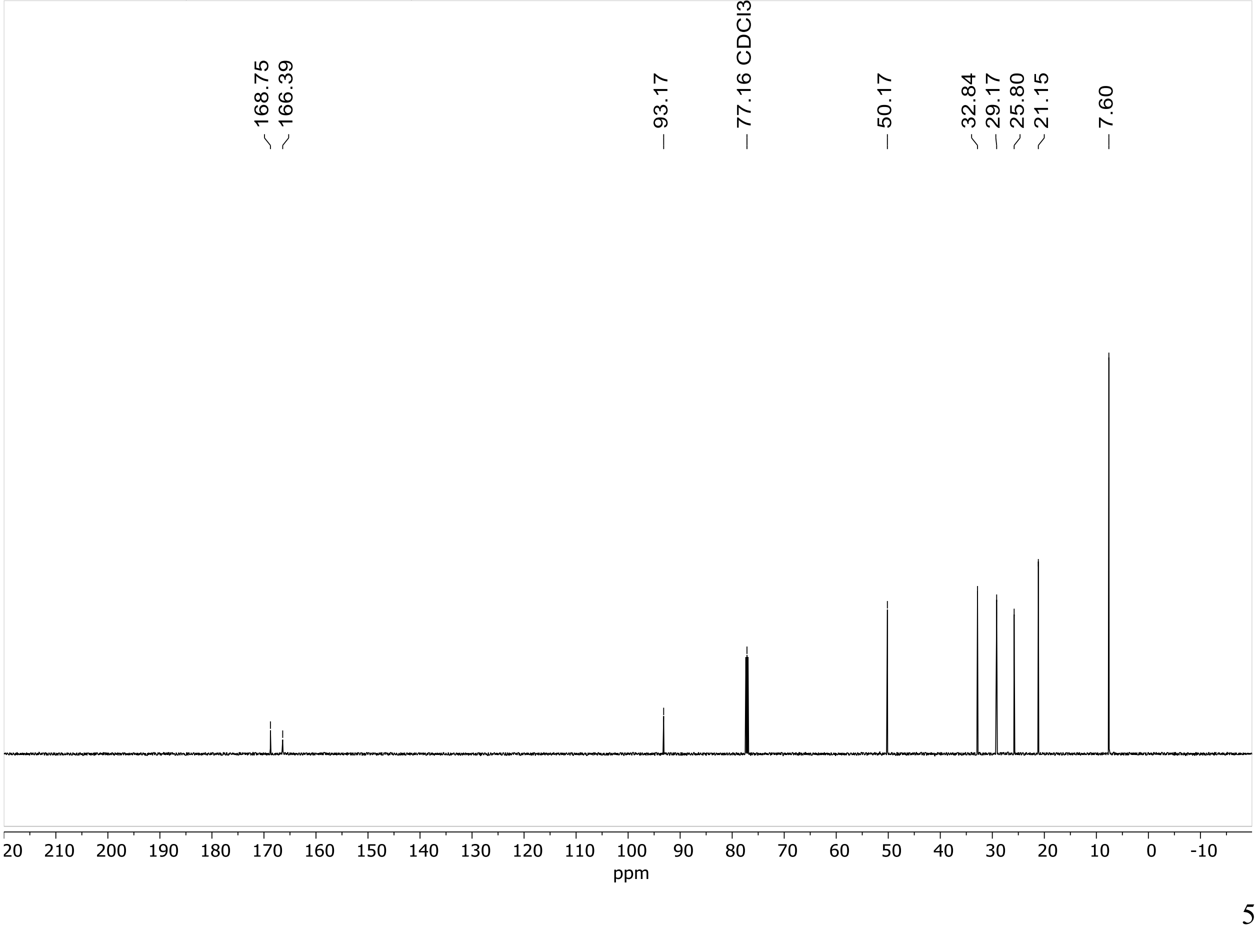
1aj’ ^{13}C NMR (151 MHz, CDCl$_3$)



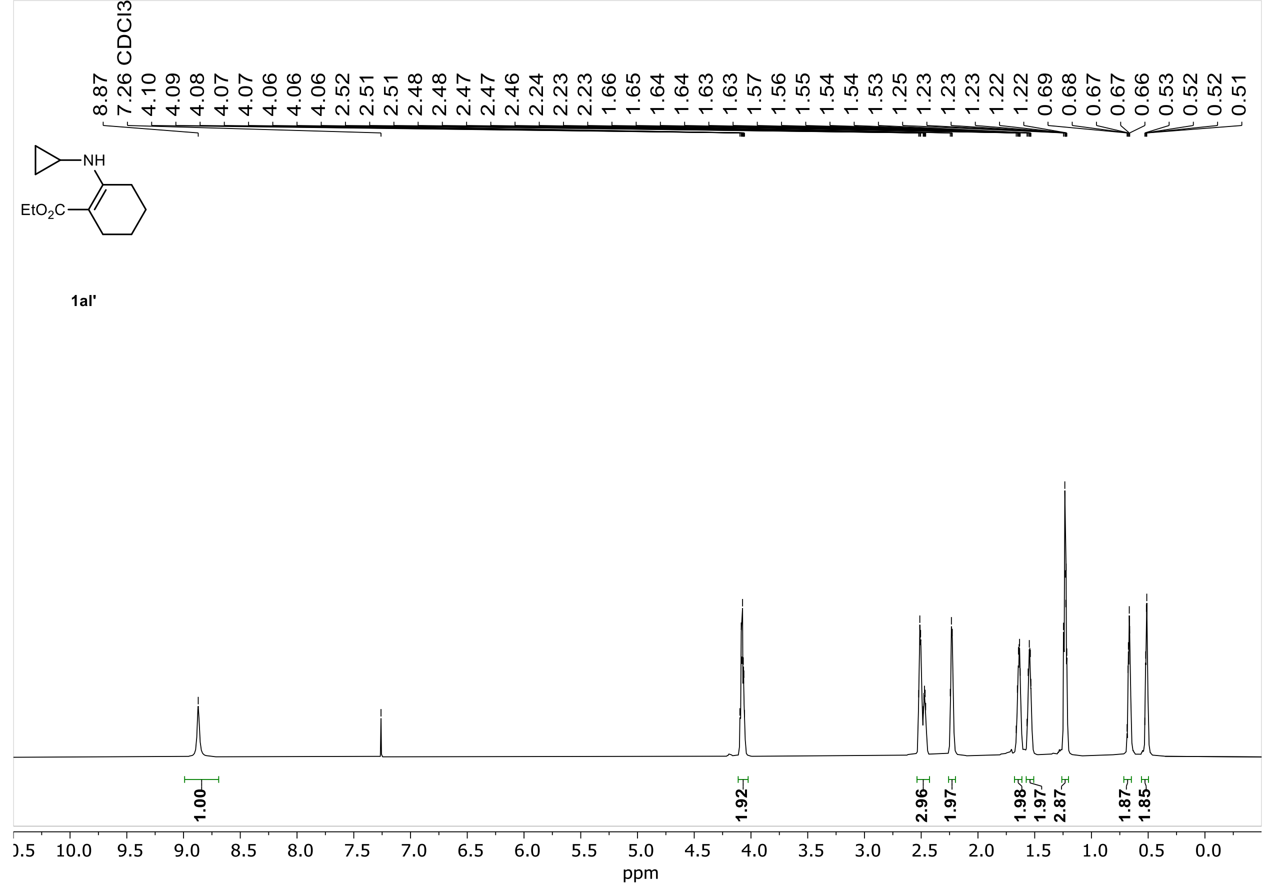
1ak’ ^{1}H NMR (600 MHz, $CDCl_3$)



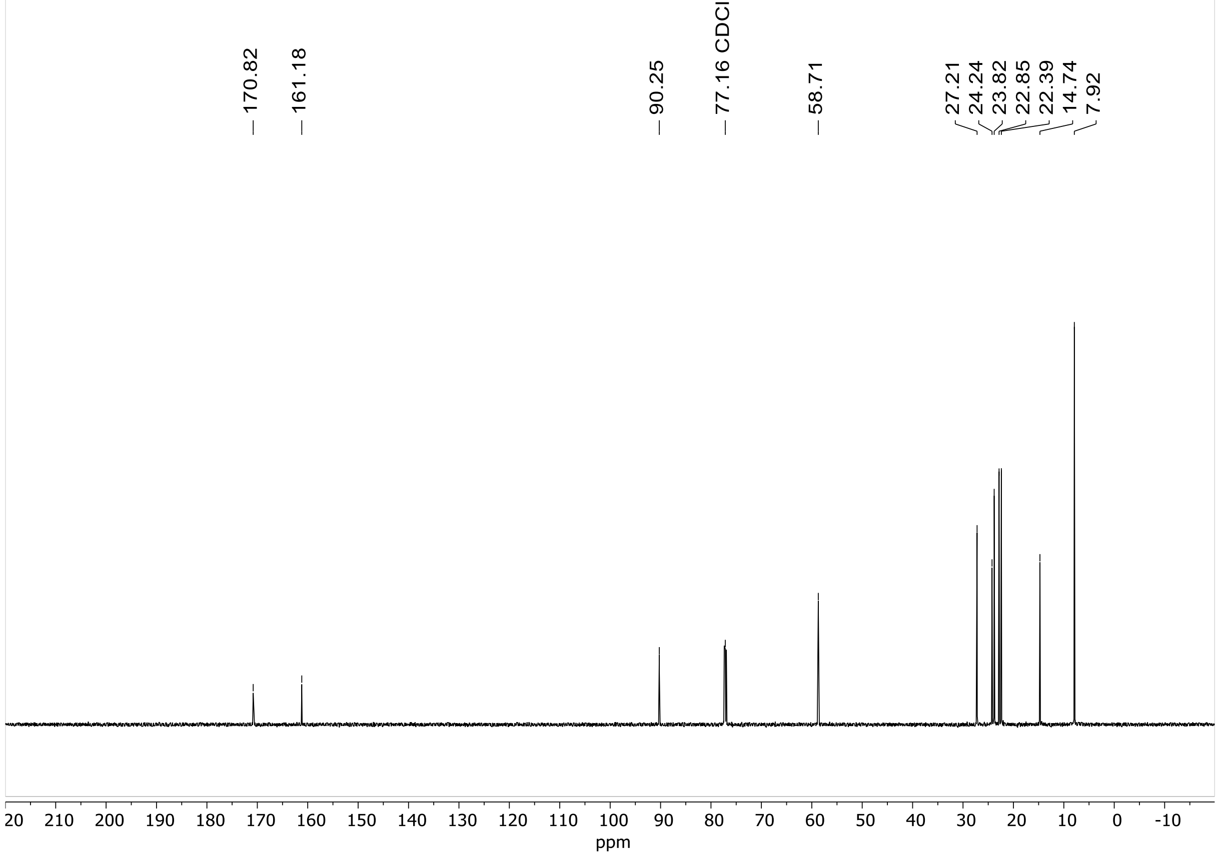
1ak’,^{1}H NMR (600 MHz, $CDCl_3$)



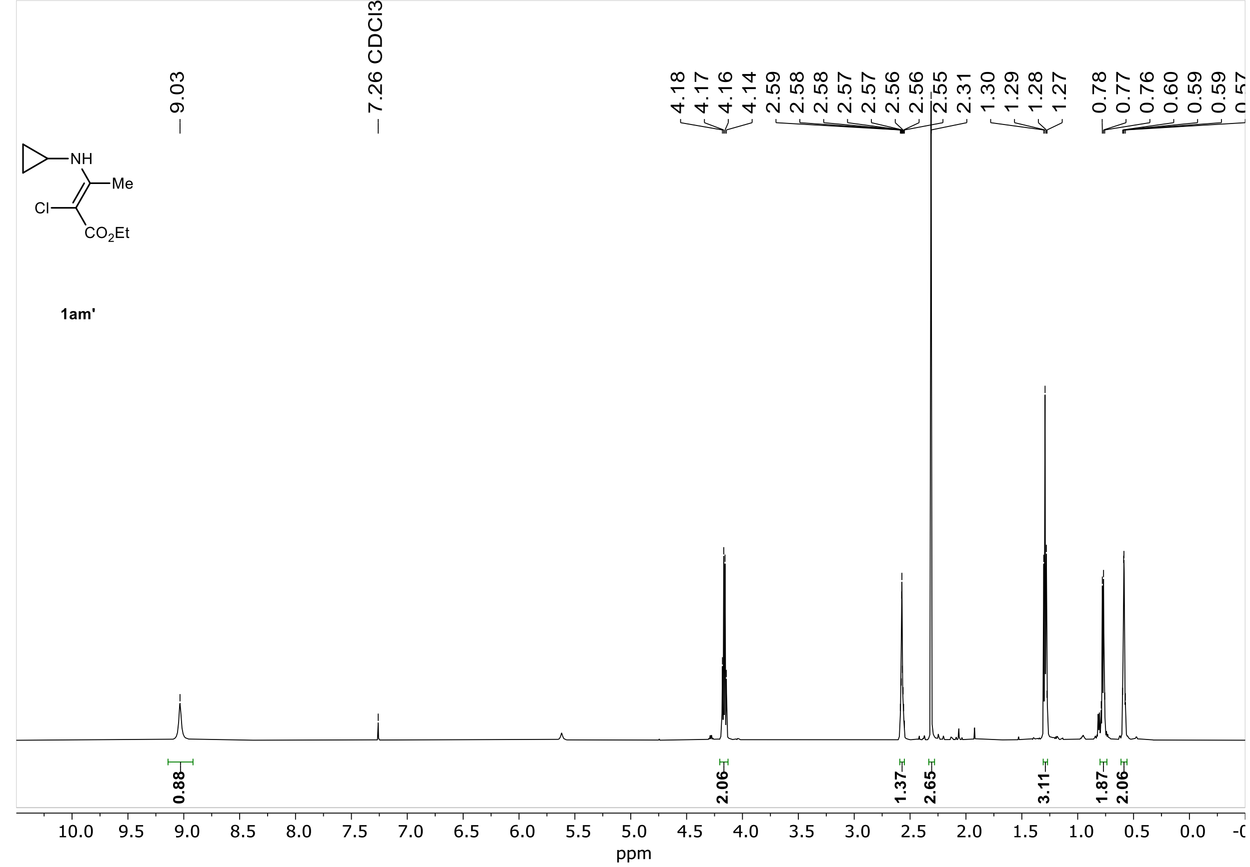
1al', ^{1}H NMR (600 MHz, CDCl$_3$)



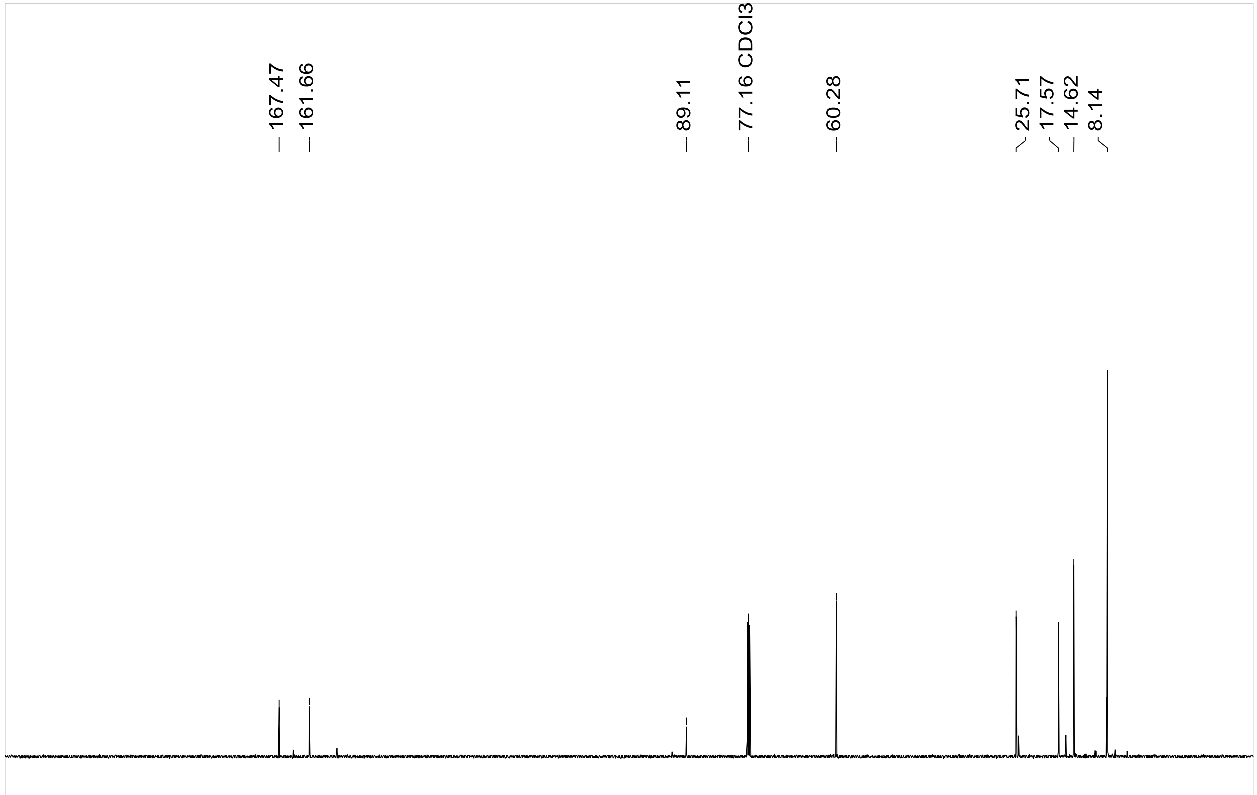
1al', ^{13}C NMR (151 MHz, CDCl$_3$)



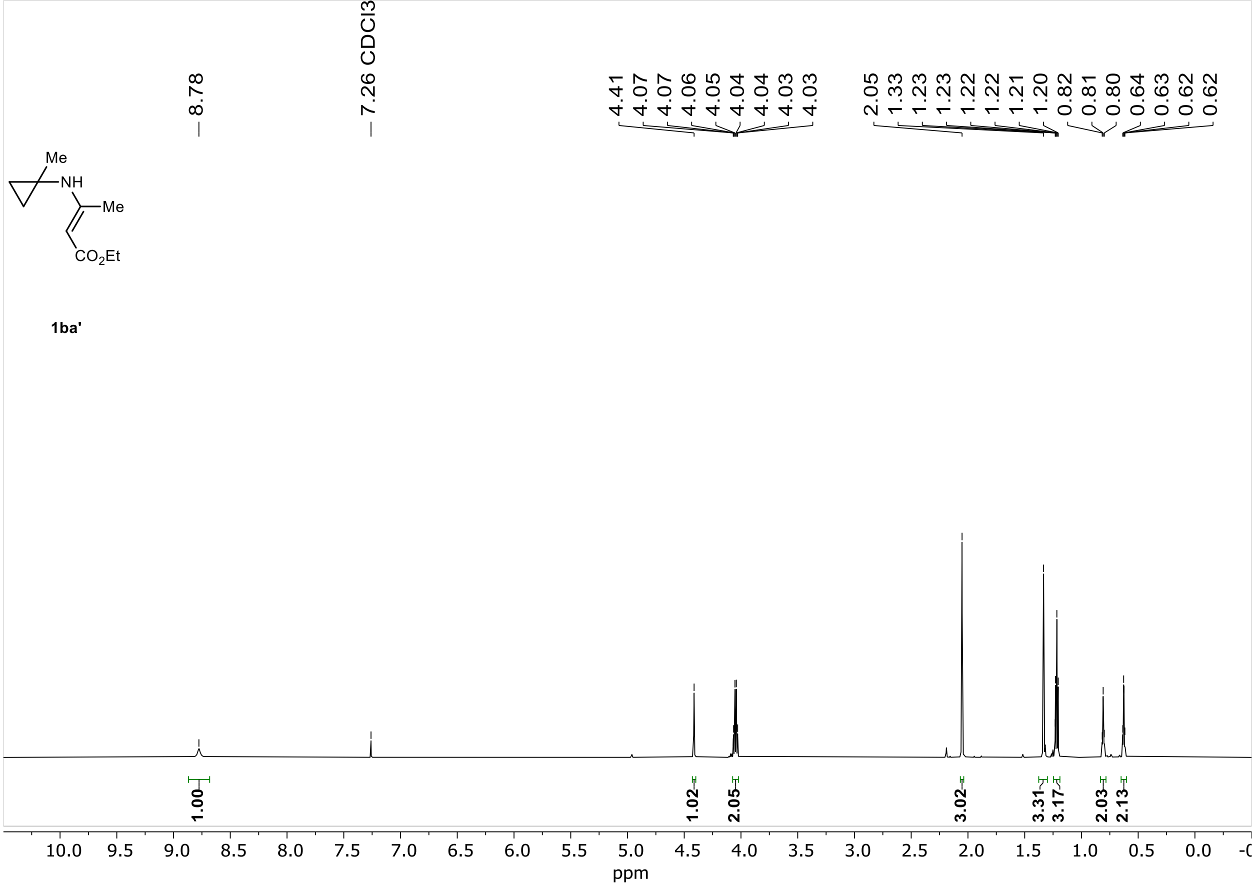
1am', ^{1}H NMR (600 MHz, CDCl$_3$)



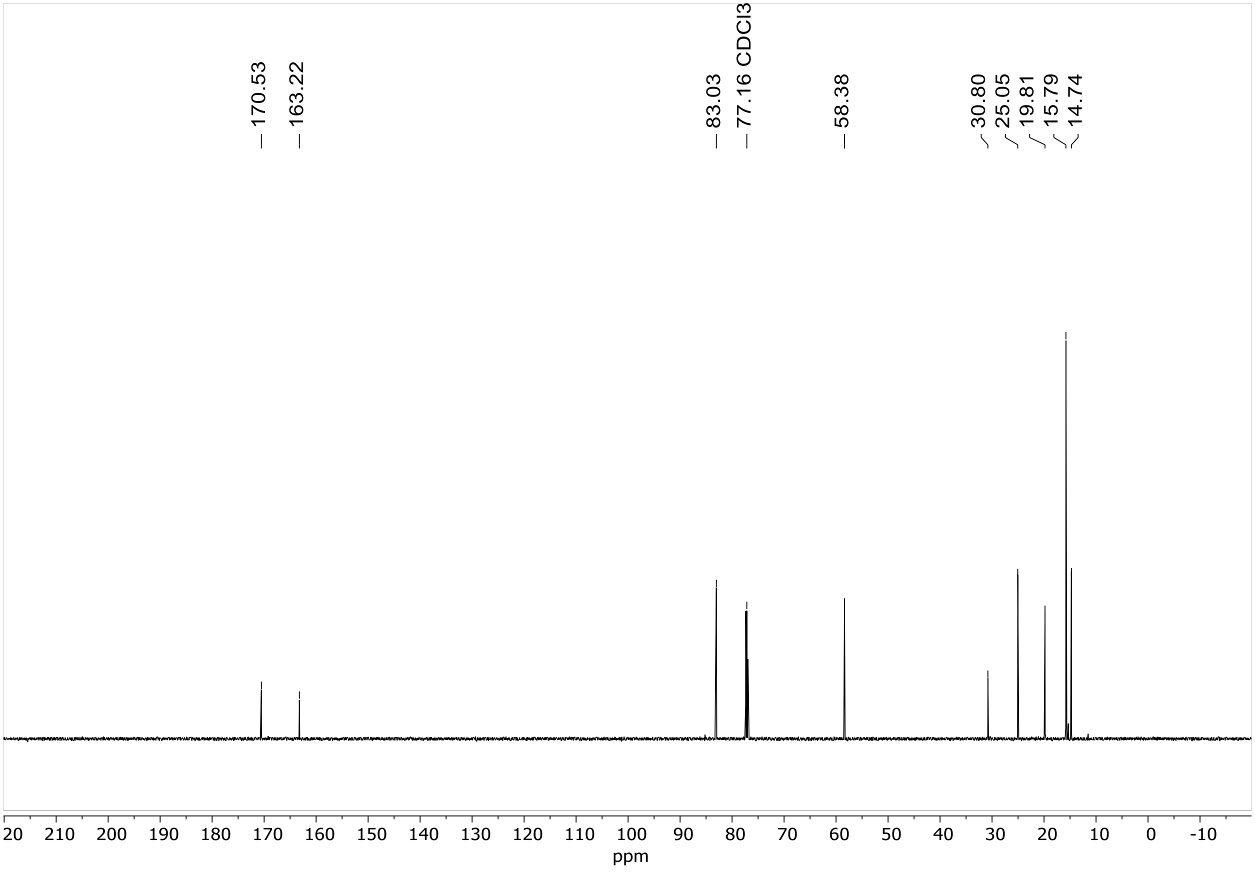
1am', ^{13}C NMR (151 MHz, CDCl$_3$)



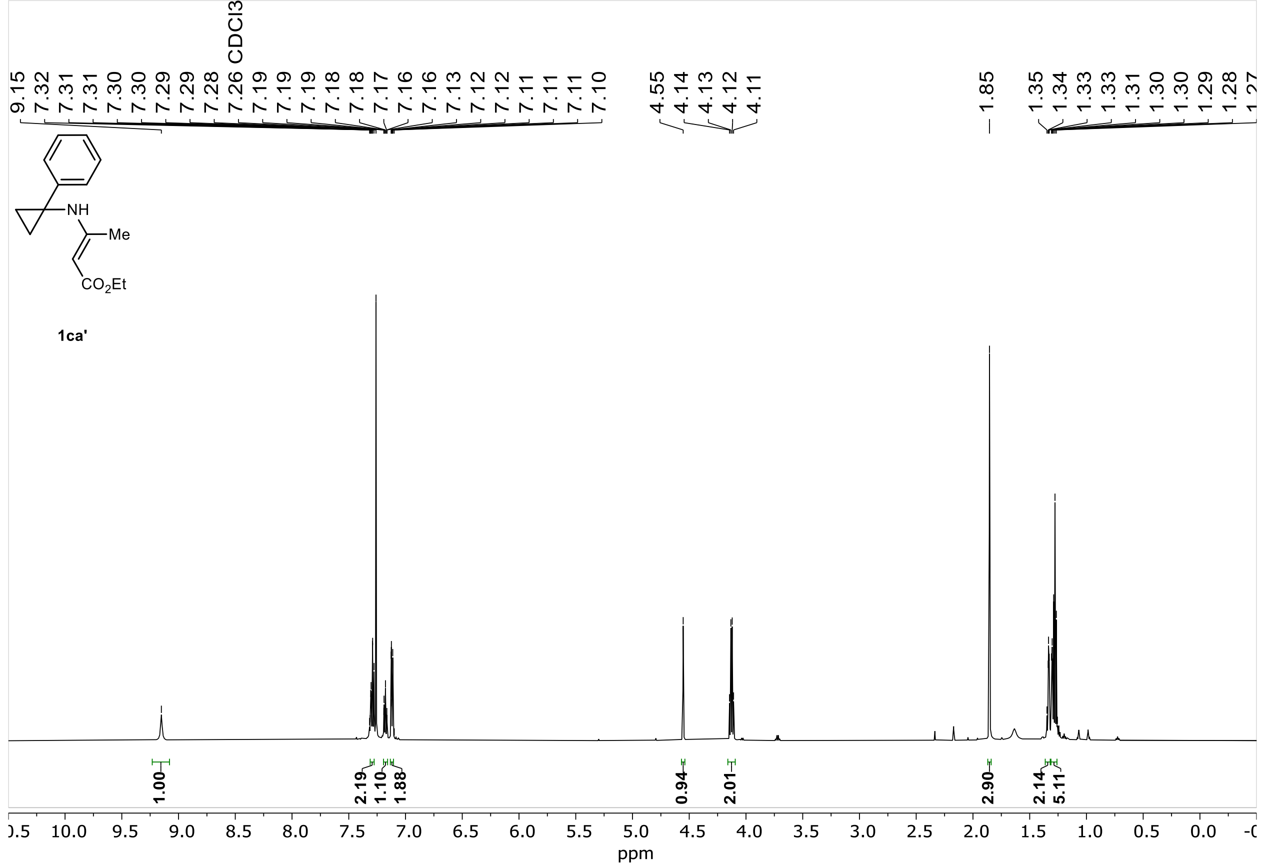
1ba',^{1}H NMR (600 MHz, CDCl$_3$)



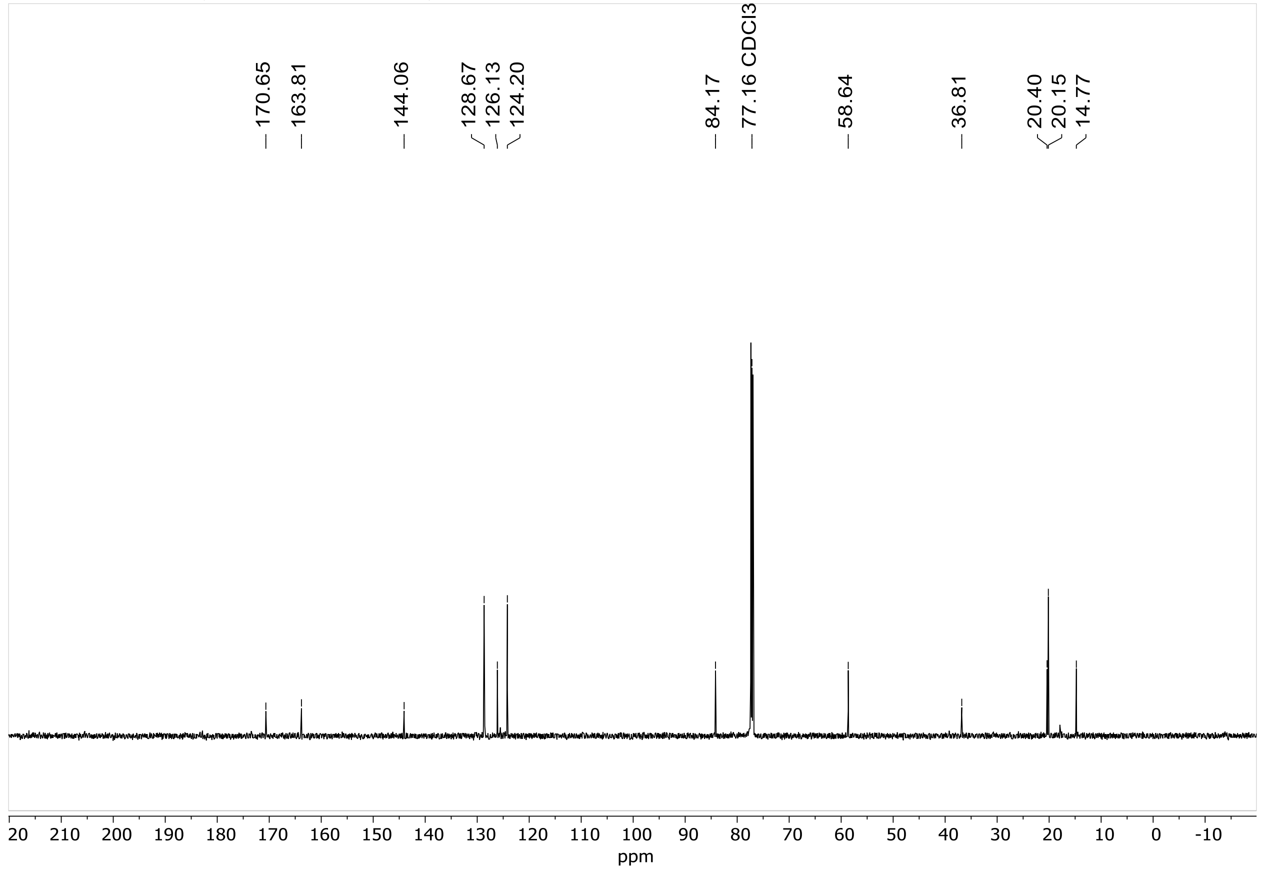
1ba',^{13}C NMR (151 MHz, CDCl$_3$)



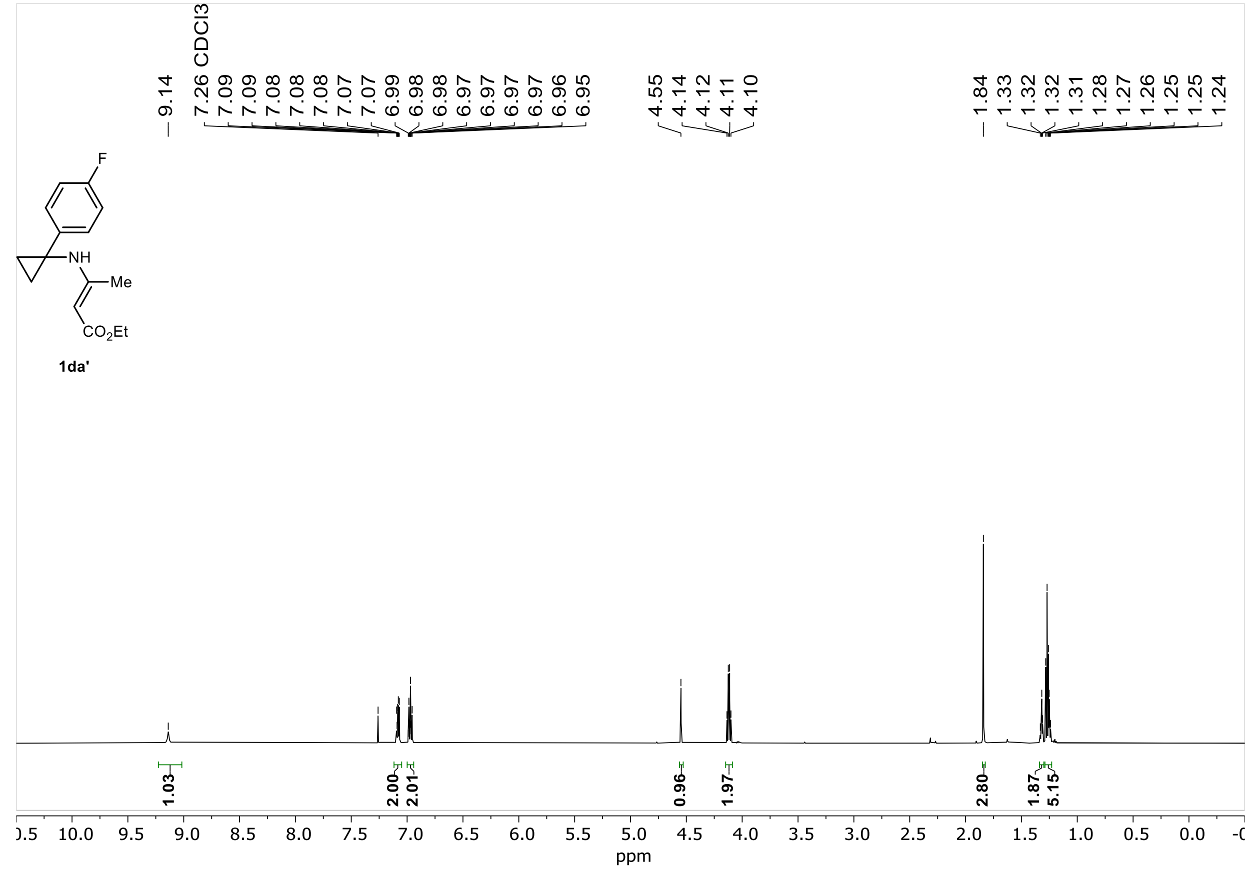
1ca', ^{1}H NMR (600 MHz, CDCl$_3$)



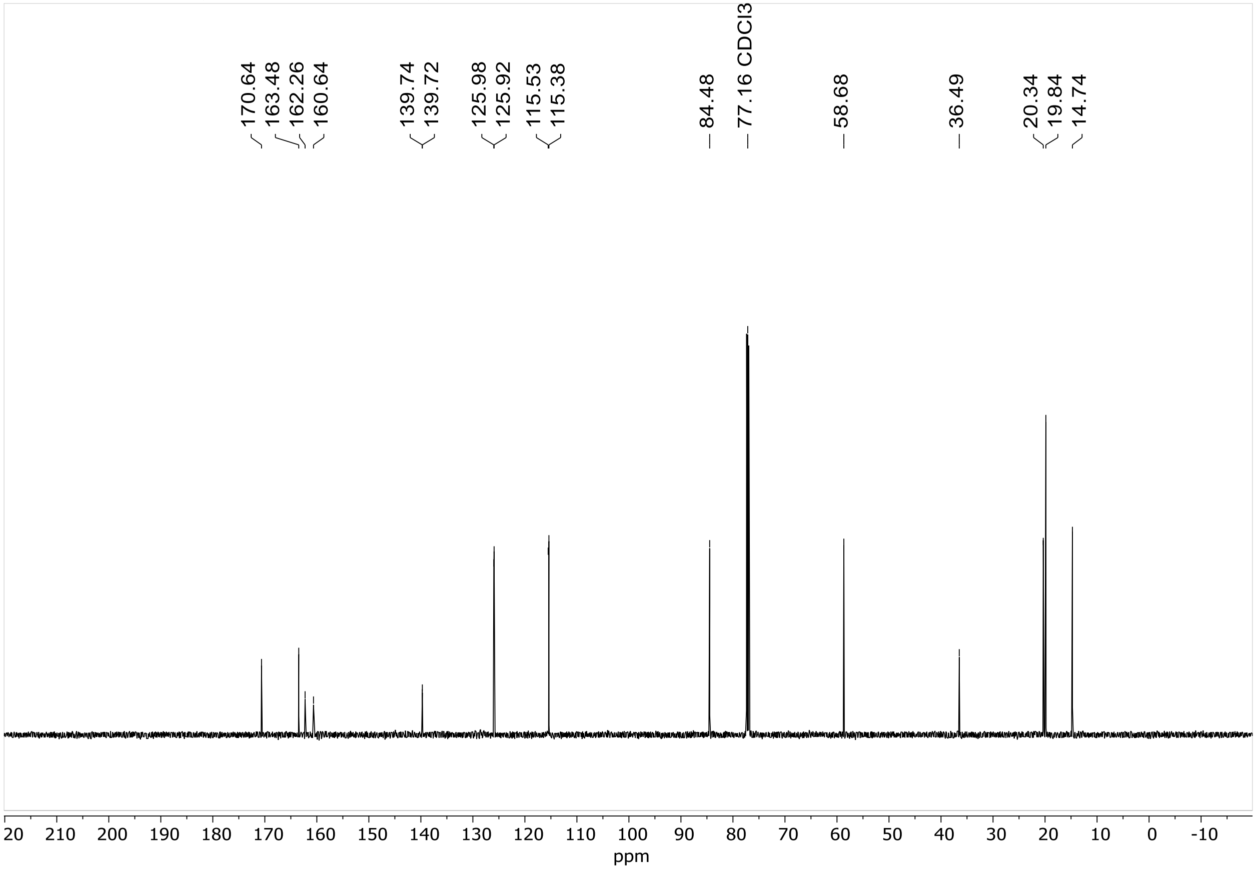
1ca', ^{13}C NMR (151 MHz, CDCl$_3$)



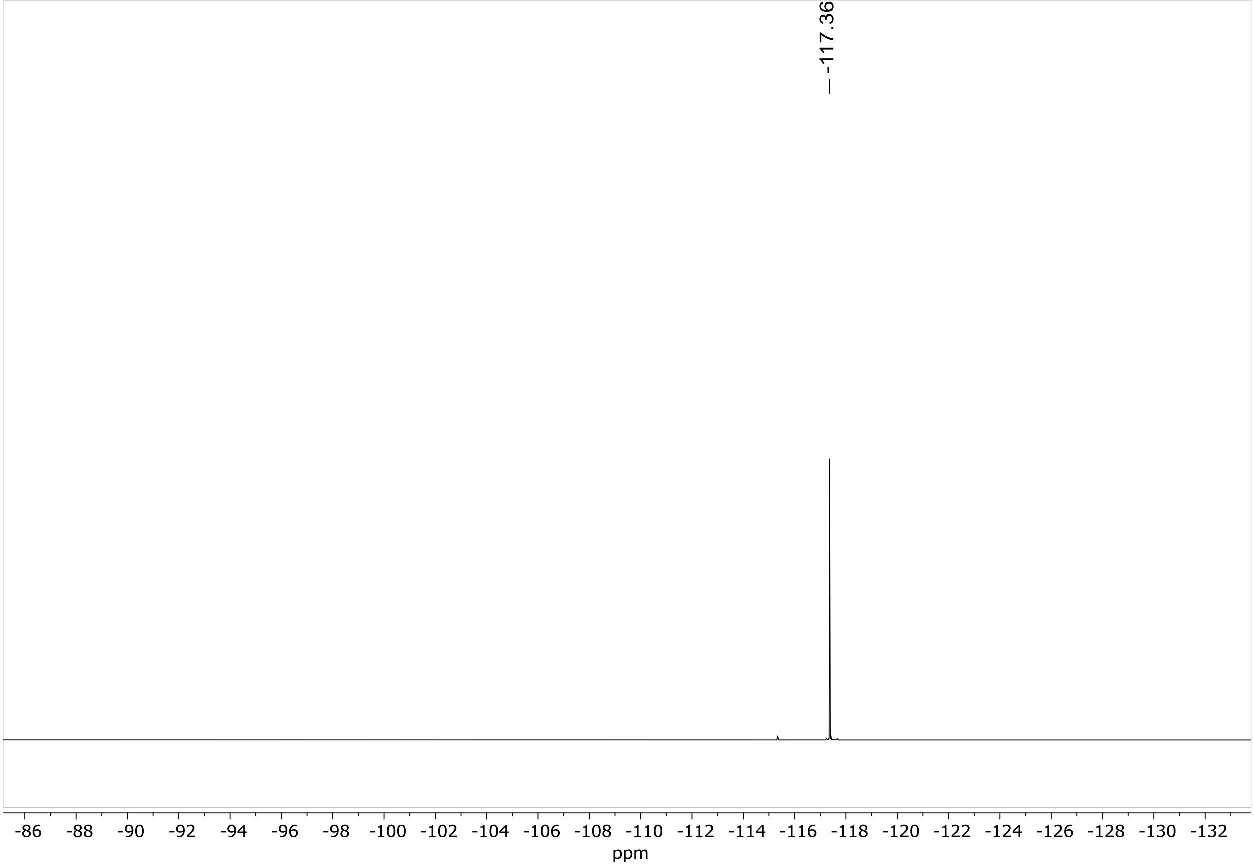
1da', ^{1}H NMR (600 MHz, CDCl$_3$)



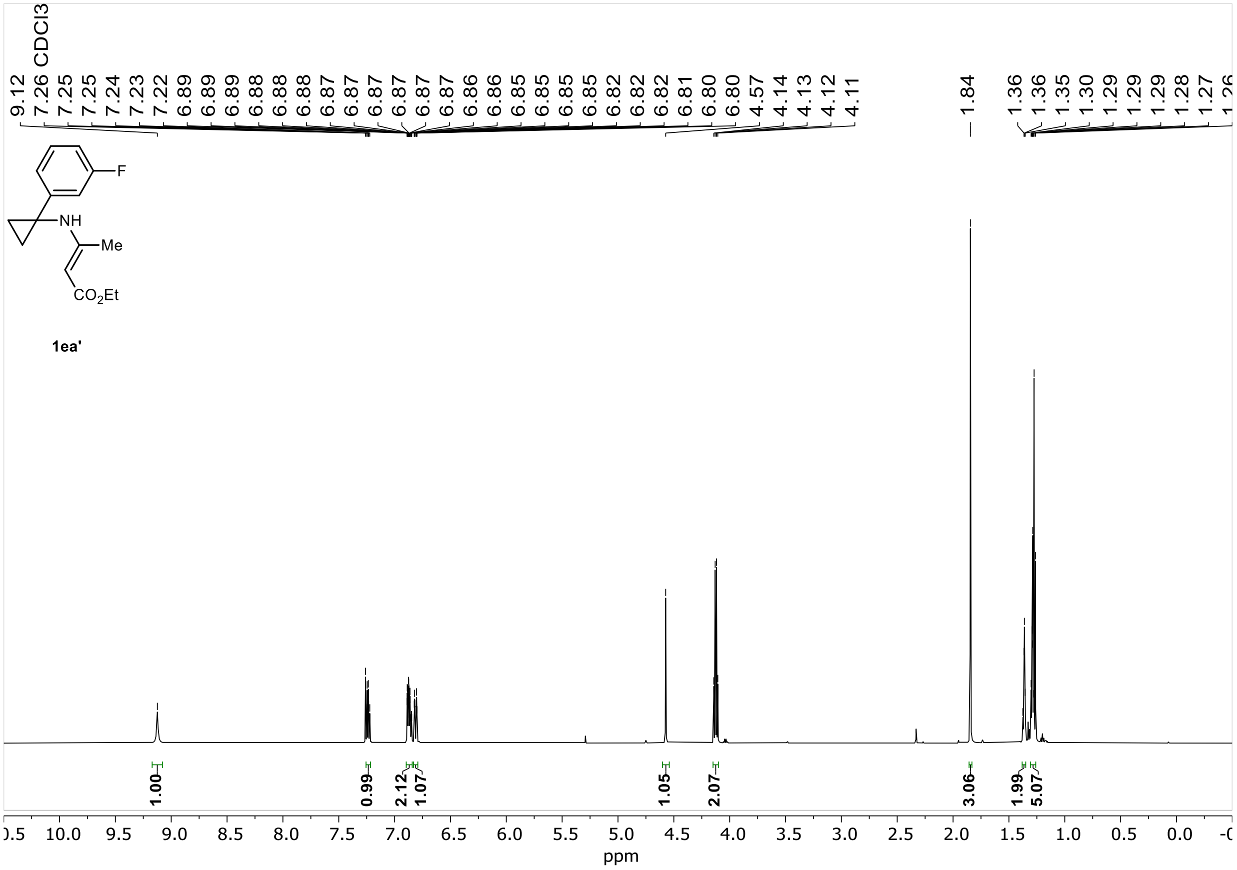
1da', ^{13}C NMR (151 MHz, CDCl$_3$)



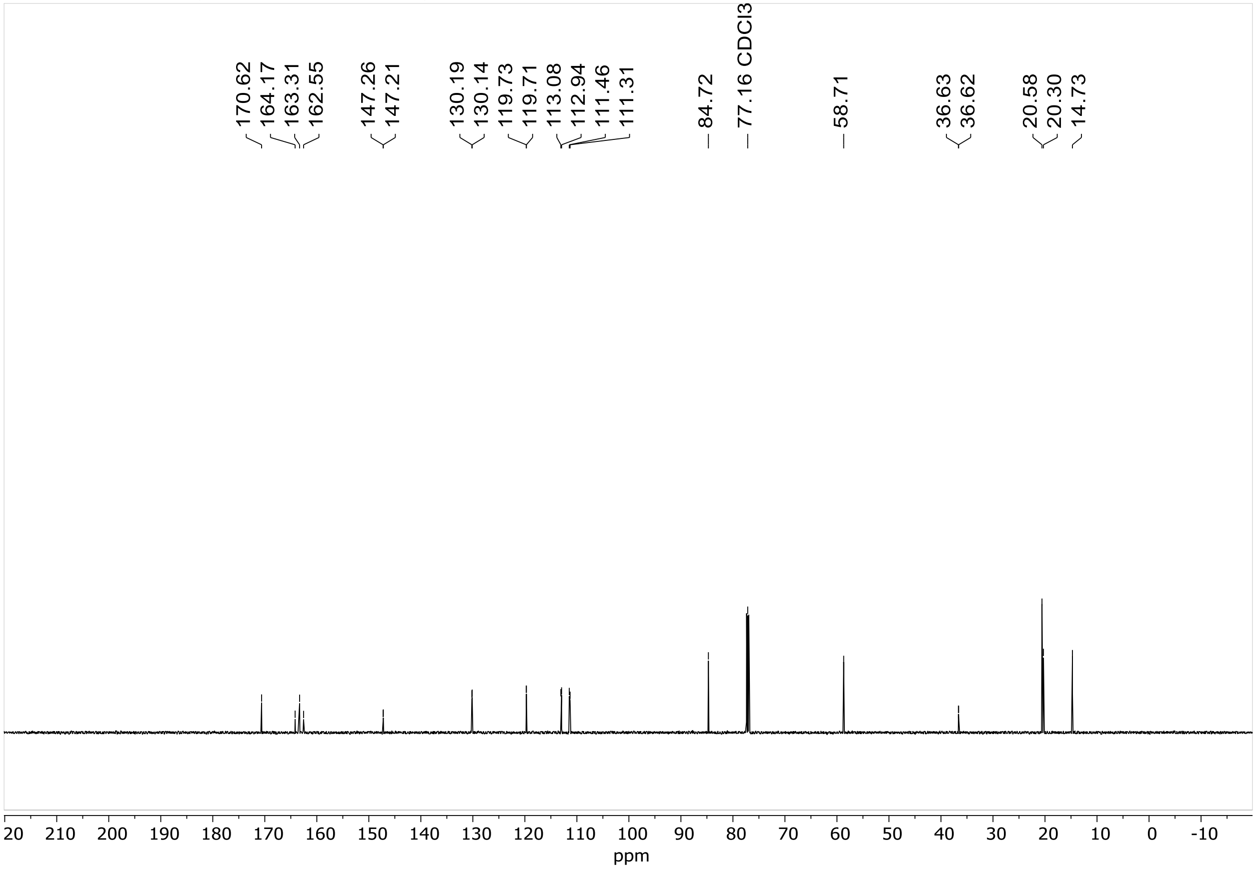
1da', ^{19}F NMR (565 MHz, CDCl$_3$)



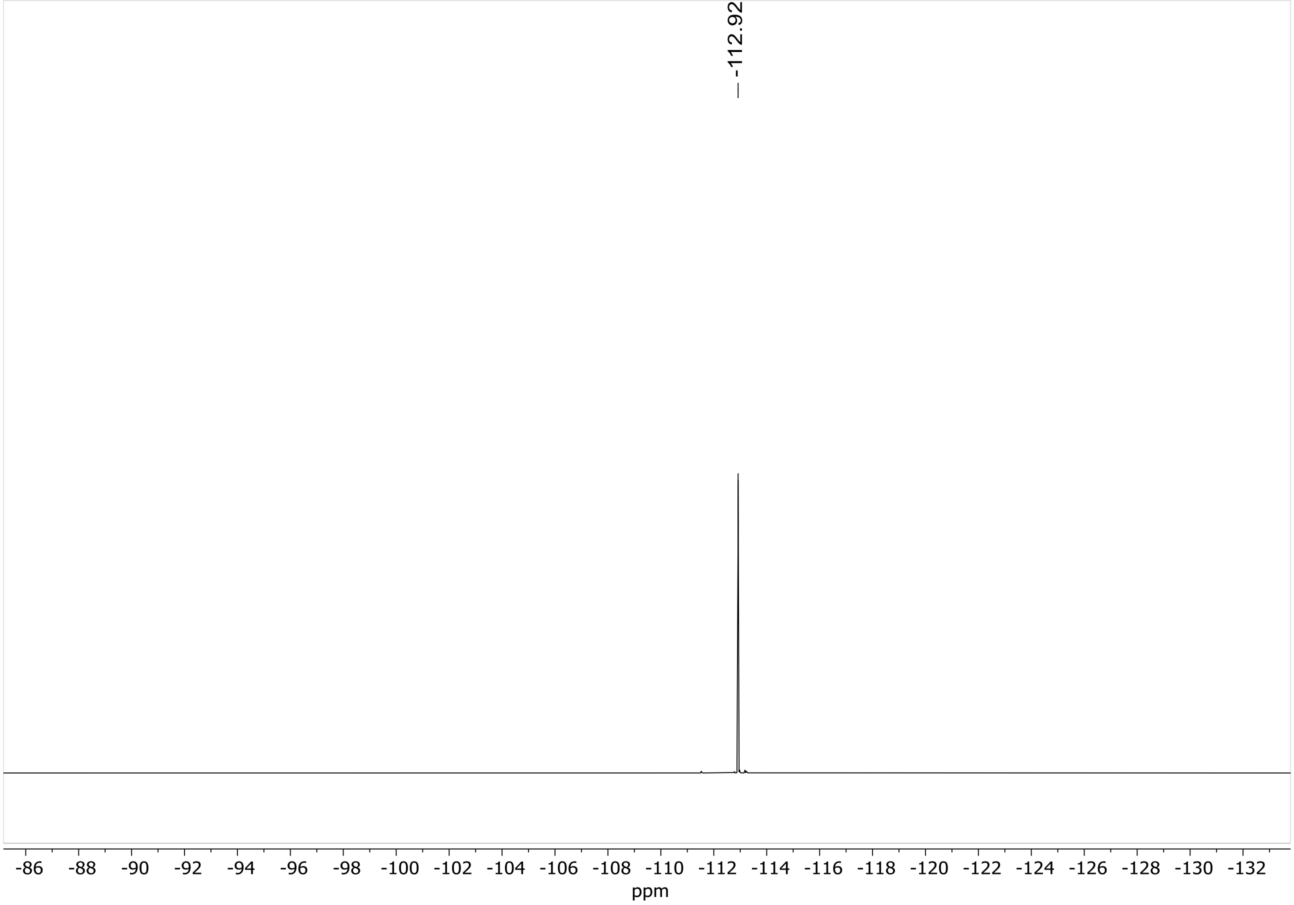
1ea', ^{1}H NMR (600 MHz, CDCl$_3$)



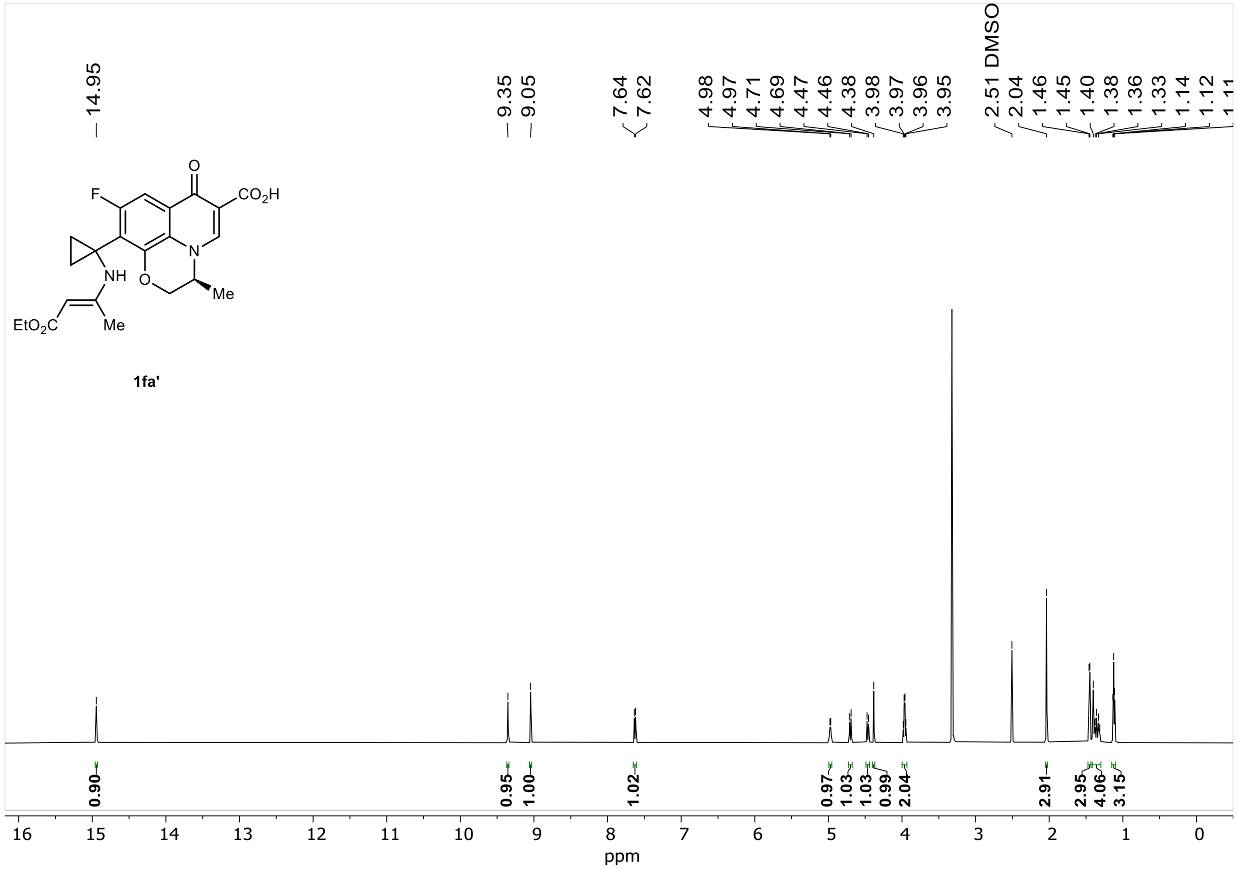
1ea', ^{13}C NMR (151 MHz, CDCl$_3$)



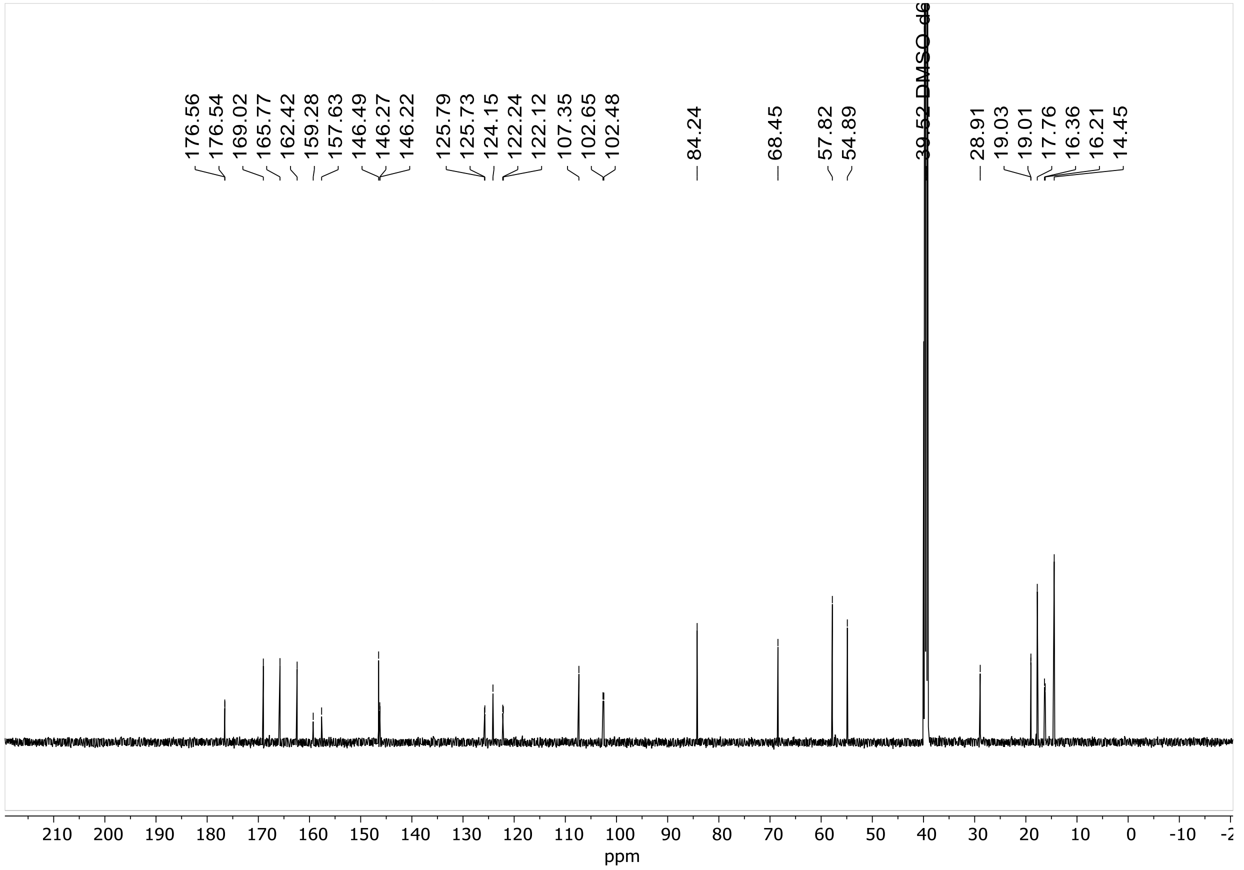
1ea’, ^{19}F NMR (565 MHz, CDCl$_3$)



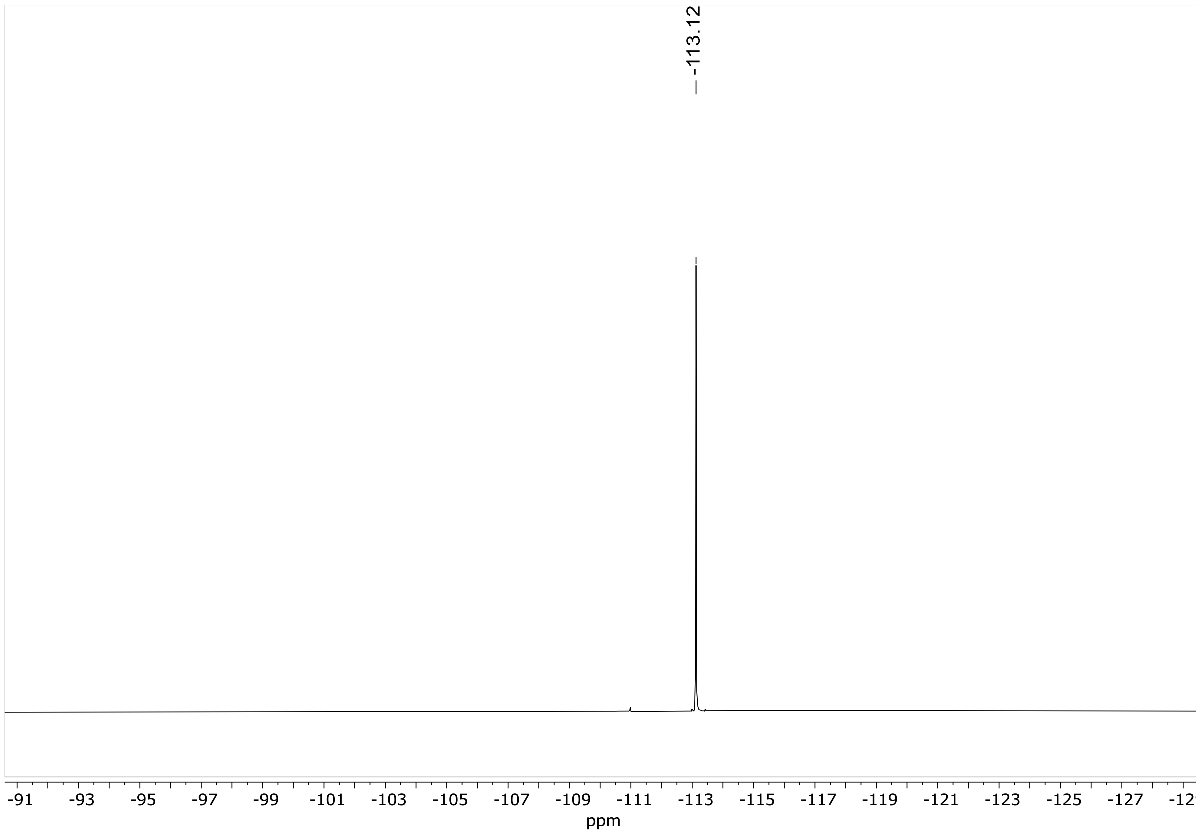
1fa', ^{1}H NMR (600 MHz, CDCl$_3$)



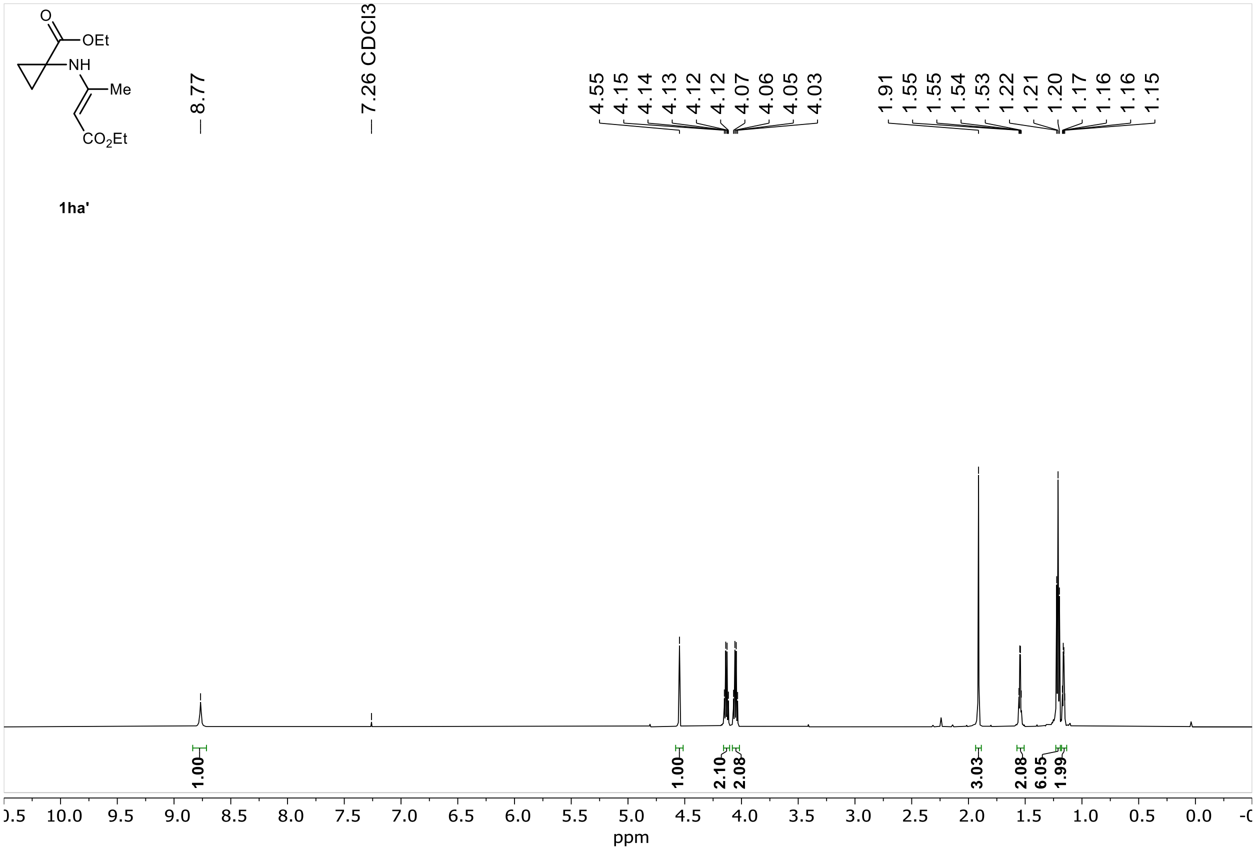
1fa', ^{13}C NMR (151 MHz, CDCl$_3$)



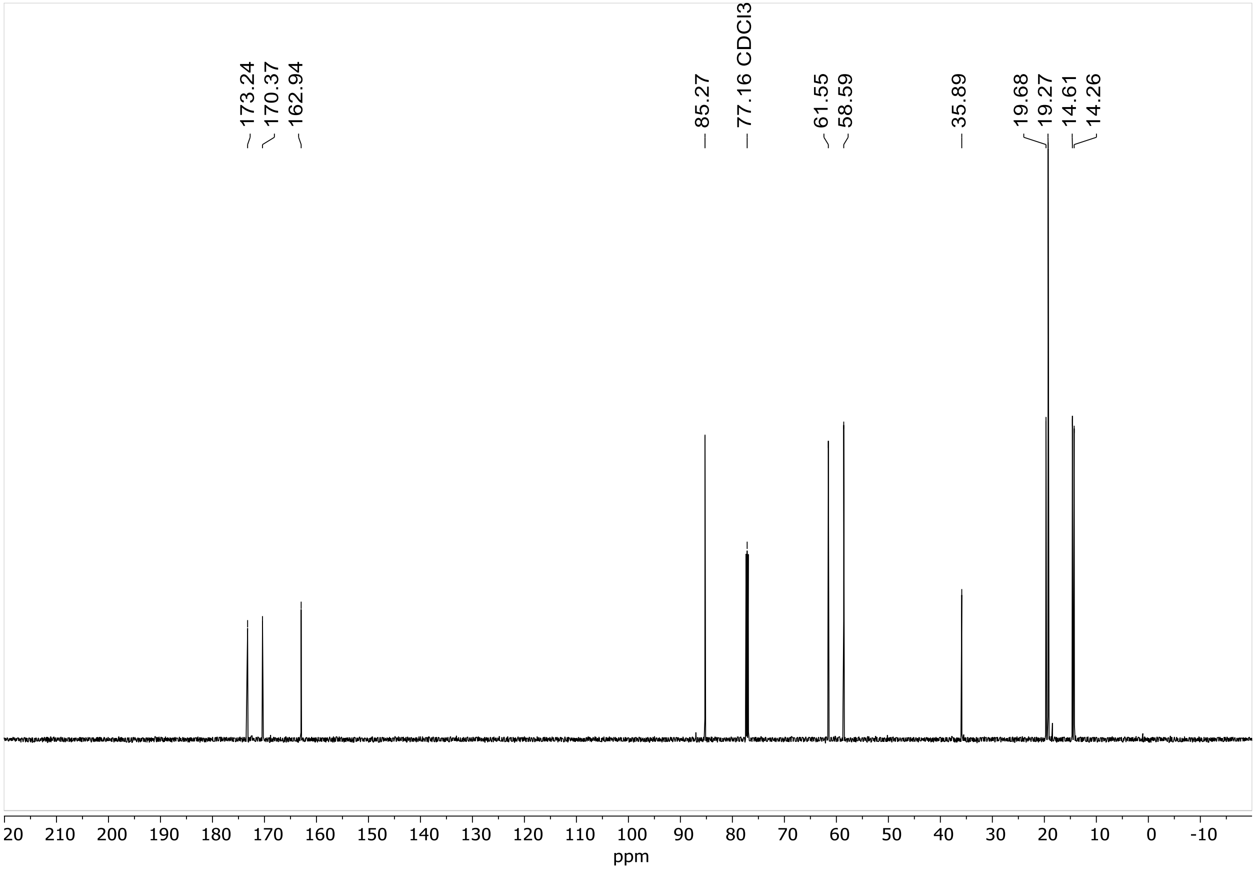
1fa’, ^{19}F NMR (565 MHz, CDCl$_3$)



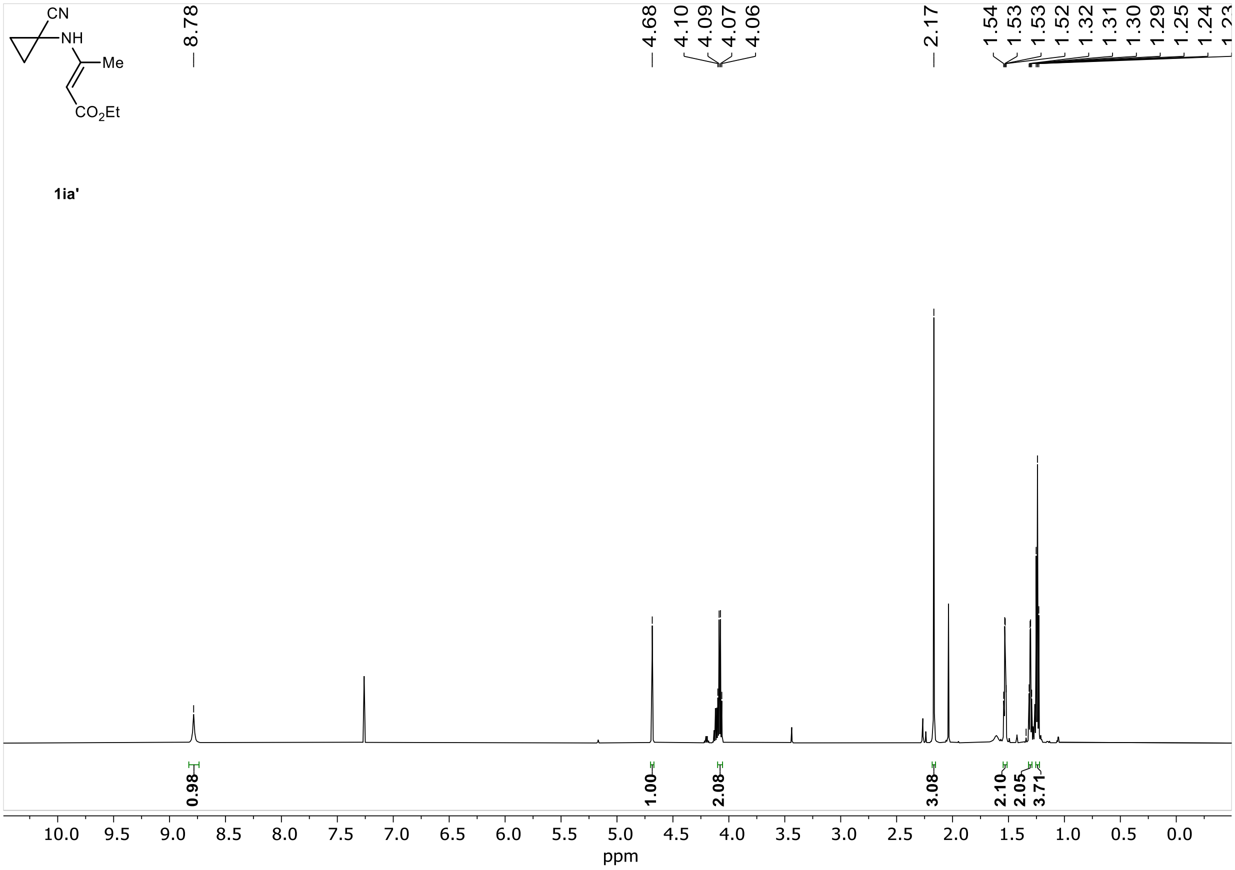
1ha', ^{1}H NMR (600 MHz, CDCl$_3$)



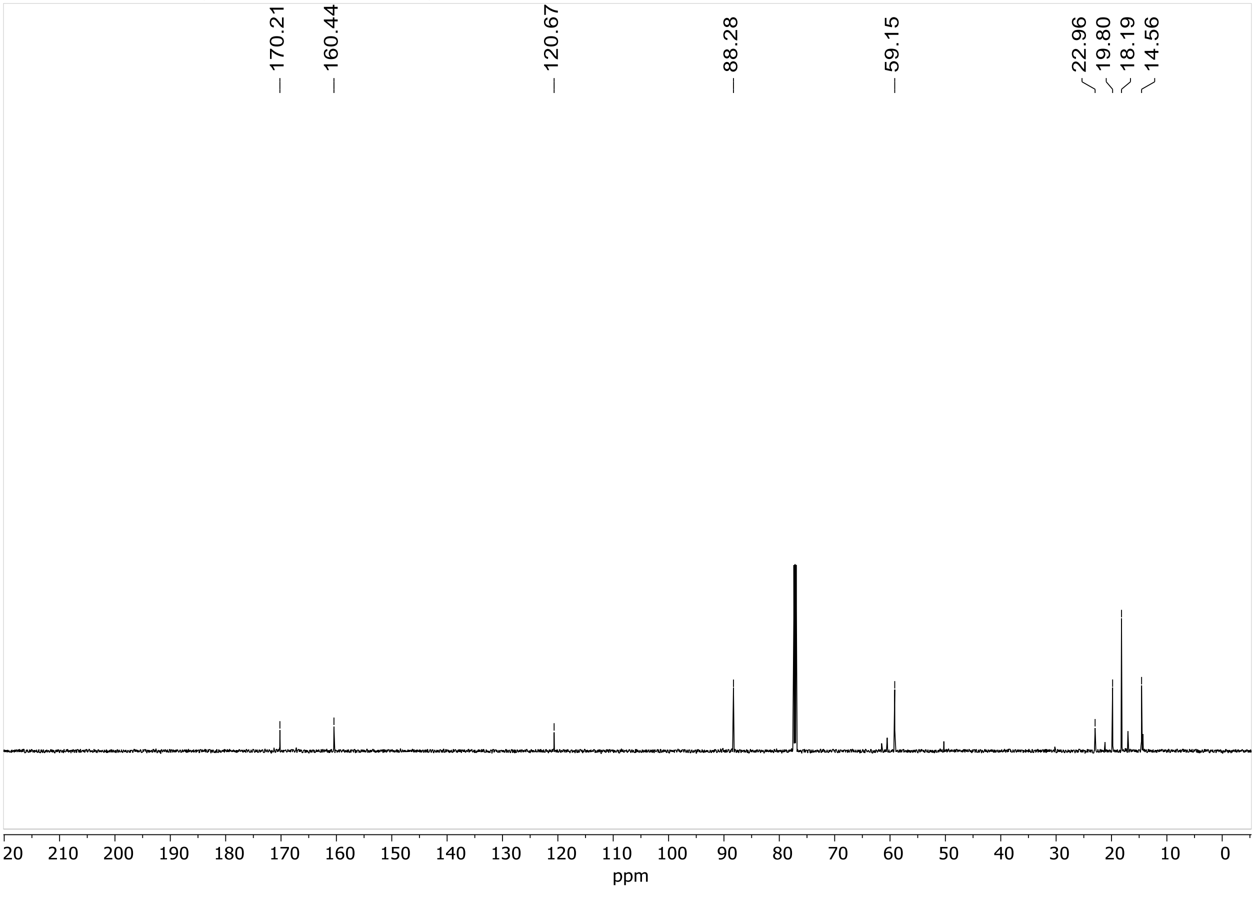
1ha',^{13}C NMR (151 MHz, CDCl$_3$)



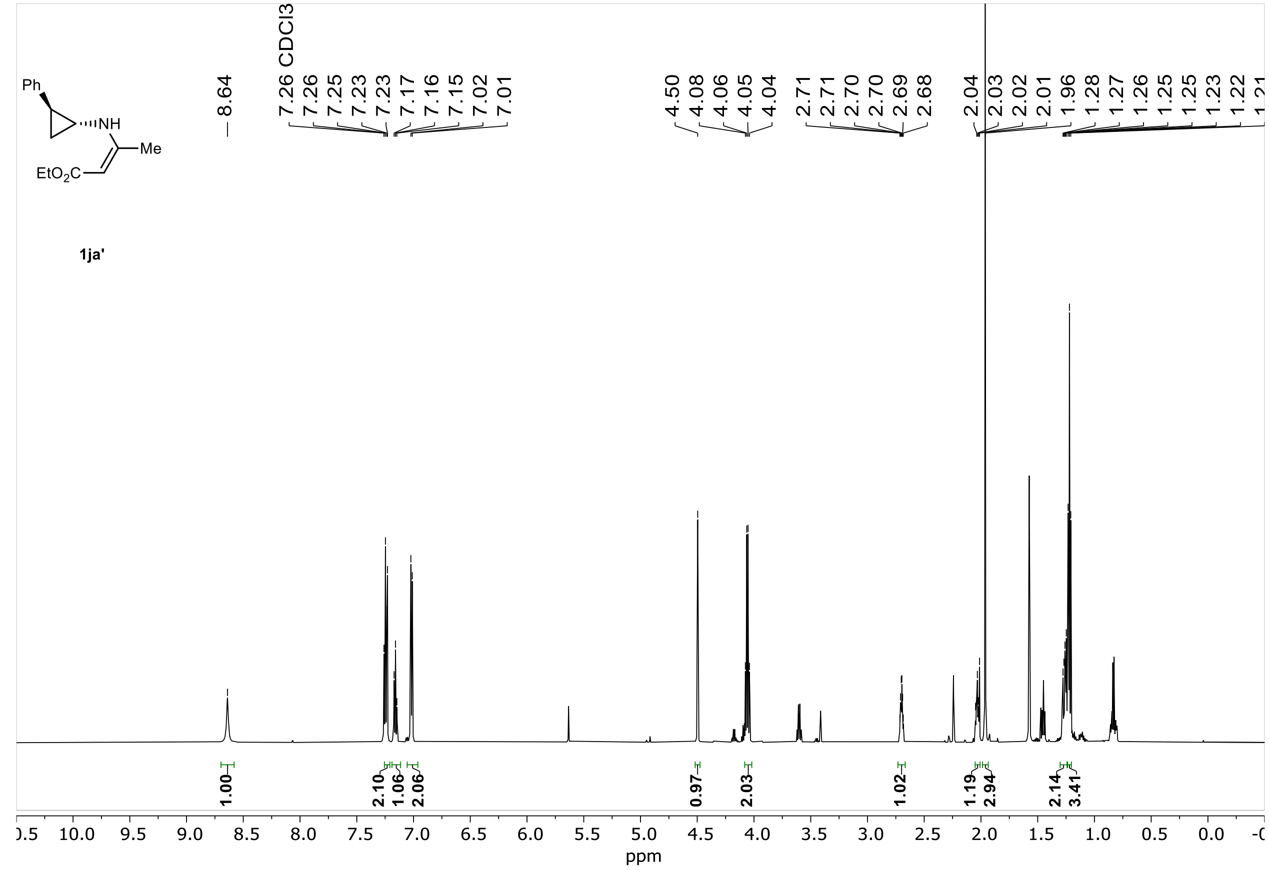
1ia’,^{1}H NMR (600 MHz, CDCl$_3$)



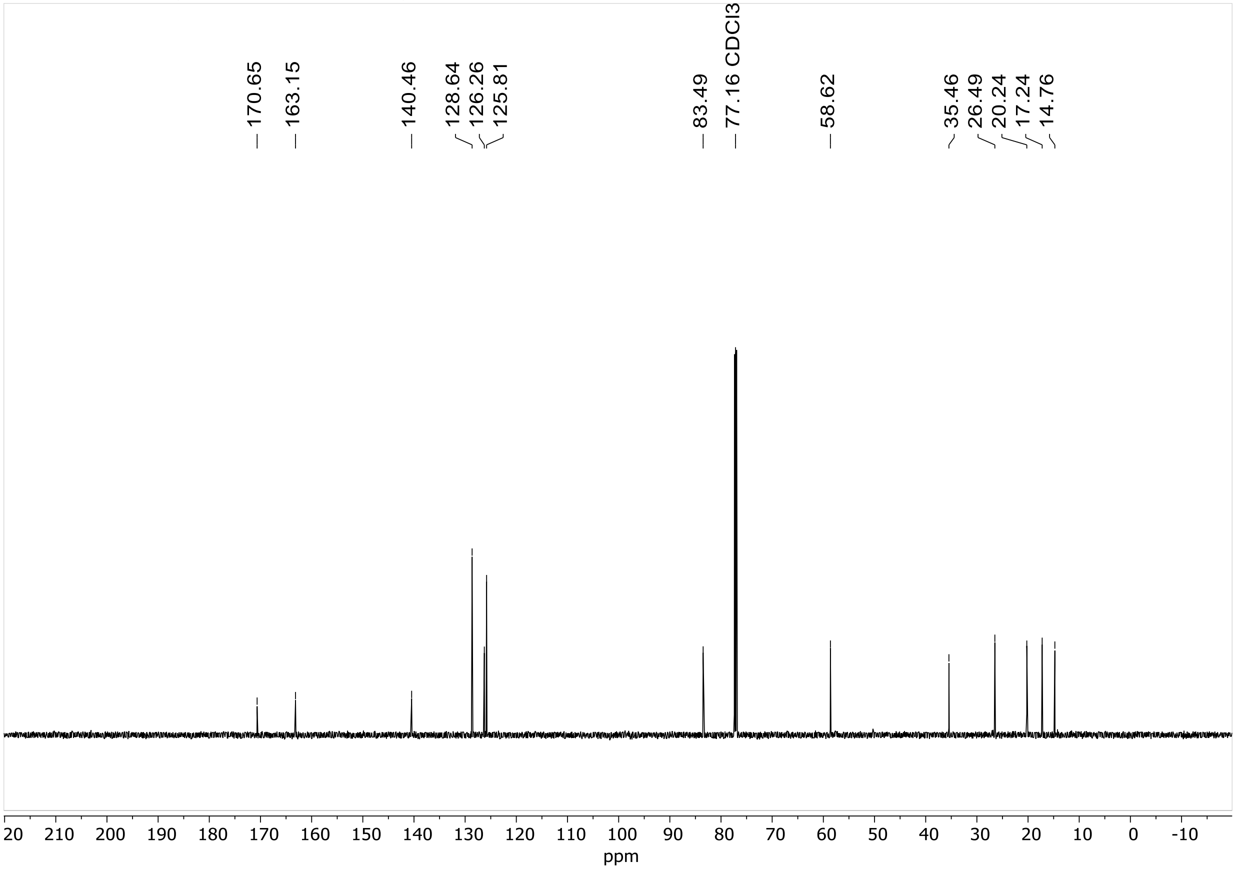
1ia’,^{13}C NMR (151 MHz, CDCl$_3$)



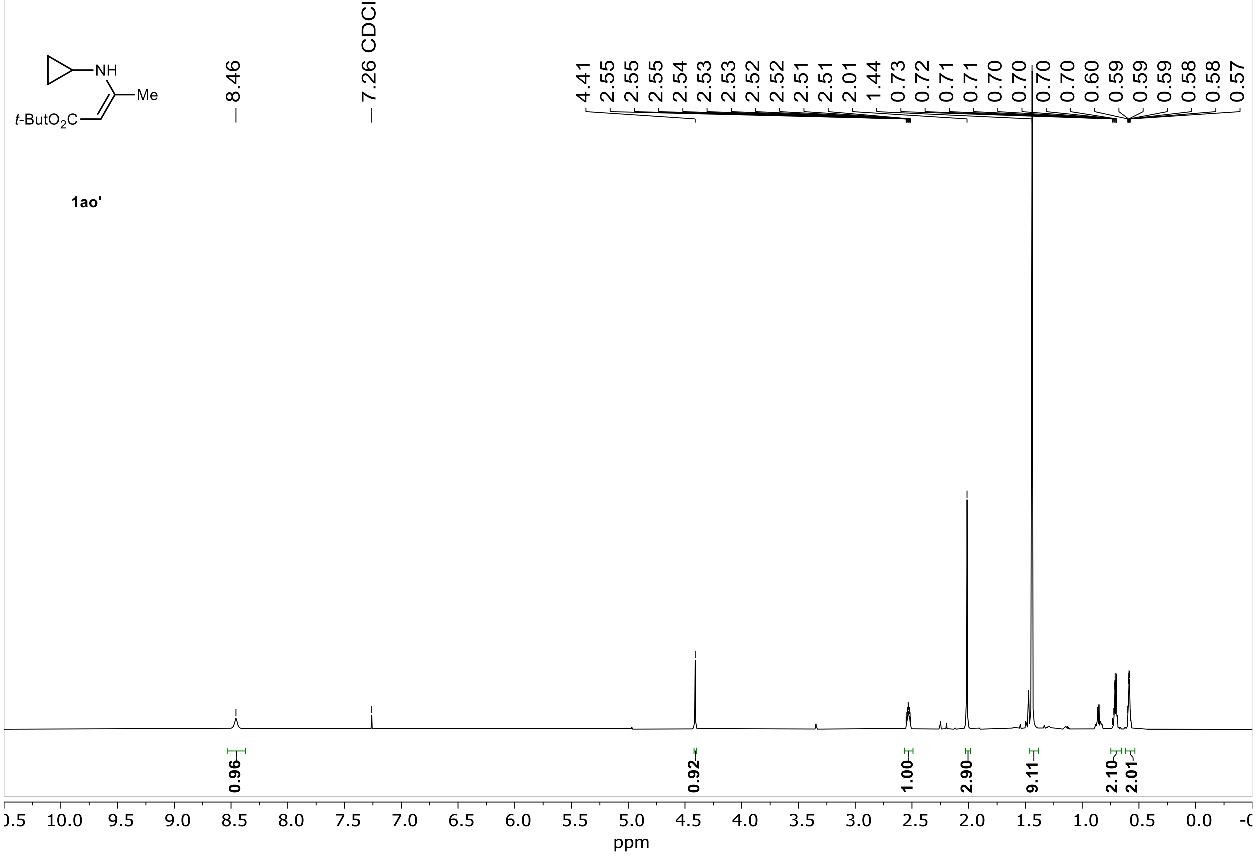
1ja', ^{1}H NMR (600 MHz, CDCl$_3$)



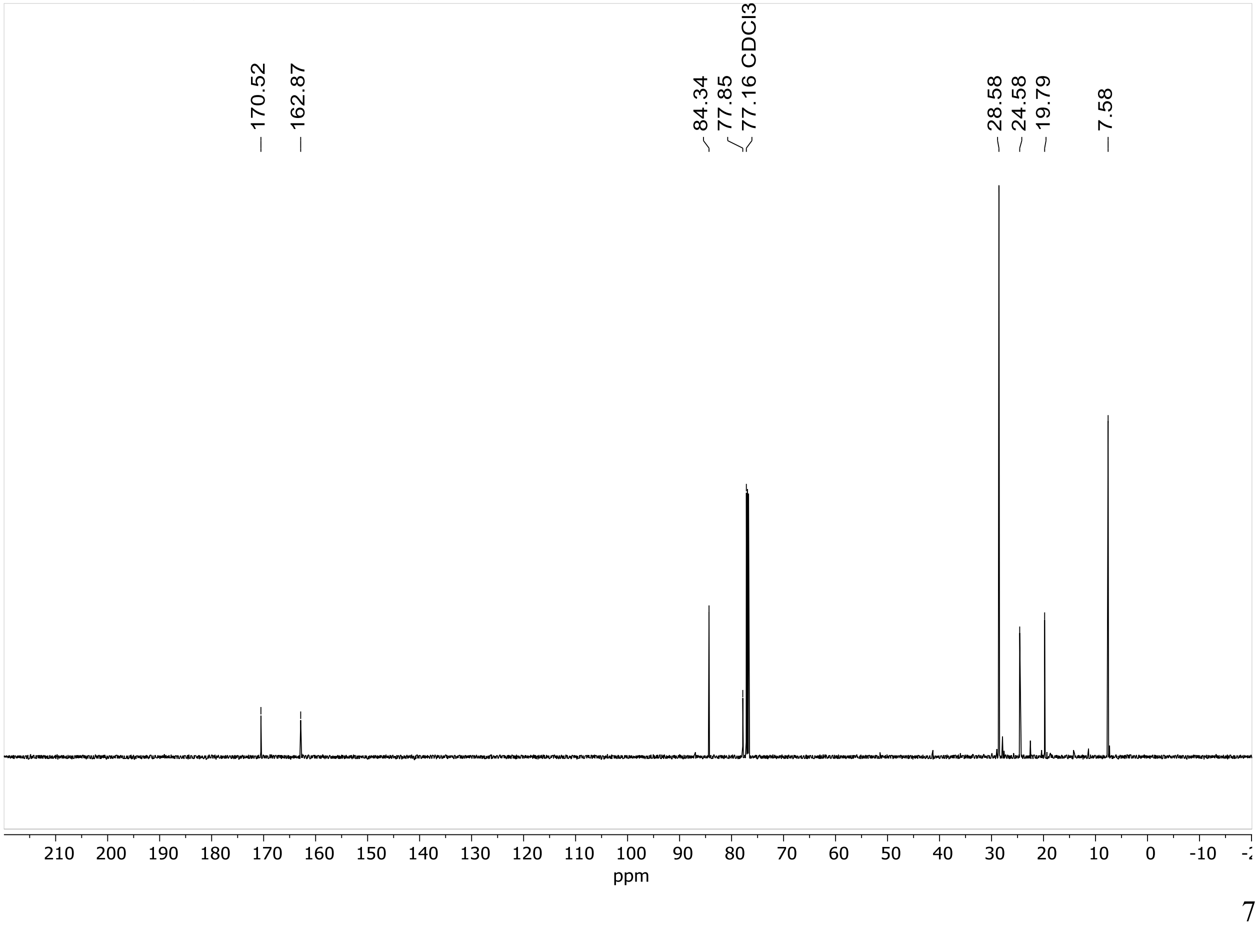
1ja',^{13}C NMR (151 MHz, CDCl$_3$)



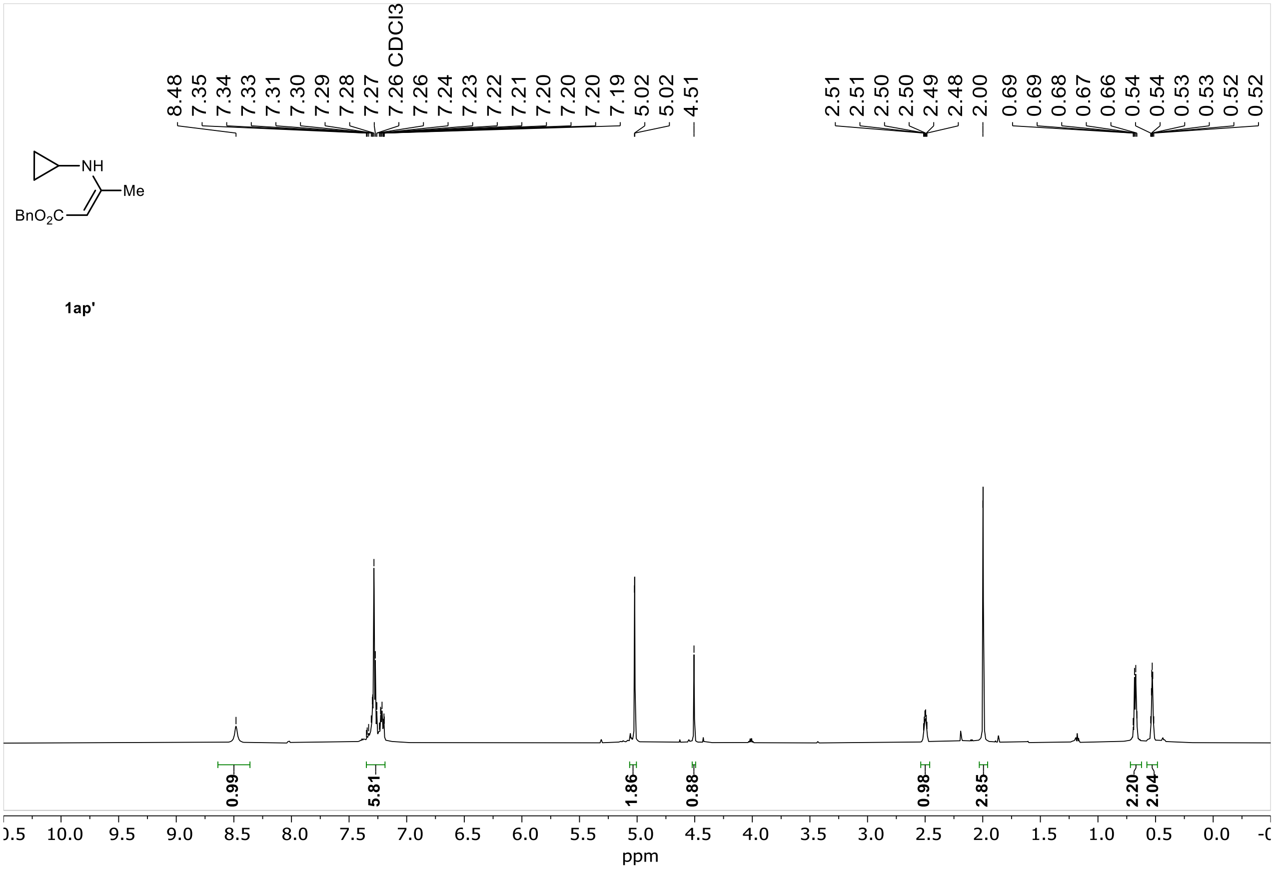
1ao’, ^{1}H NMR (600 MHz, CDCl$_3$)



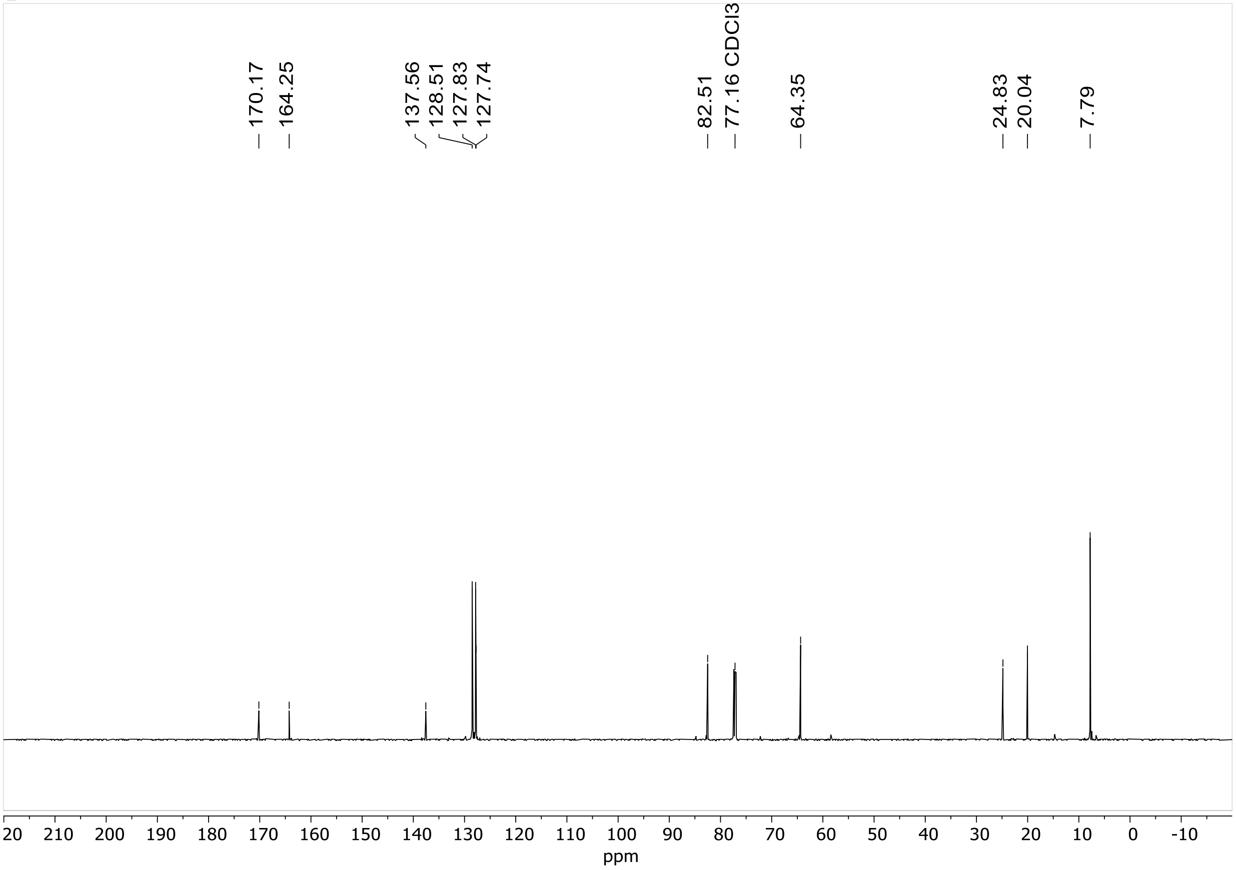
1ao’, ^{13}C NMR (151 MHz, CDCl$_3$)



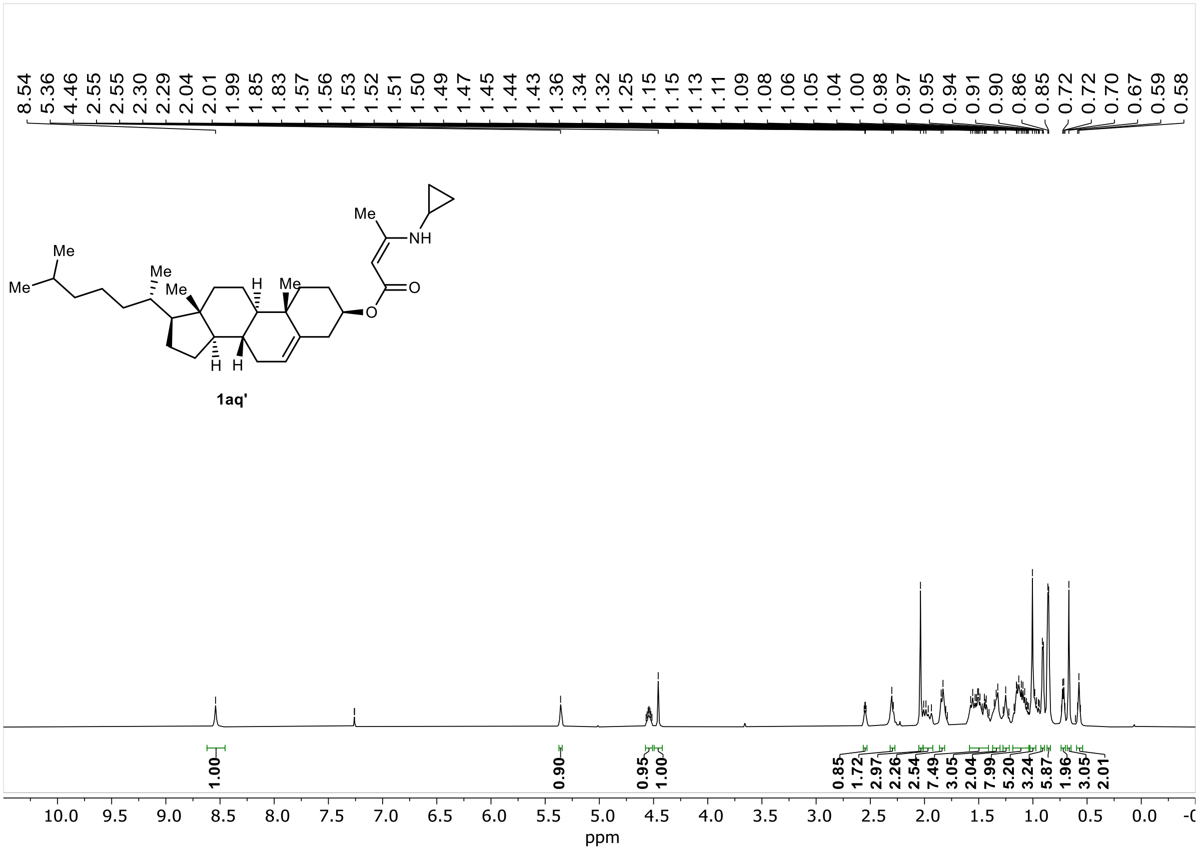
1ap’,^{1}H NMR (600 MHz, CDCl$_3$)



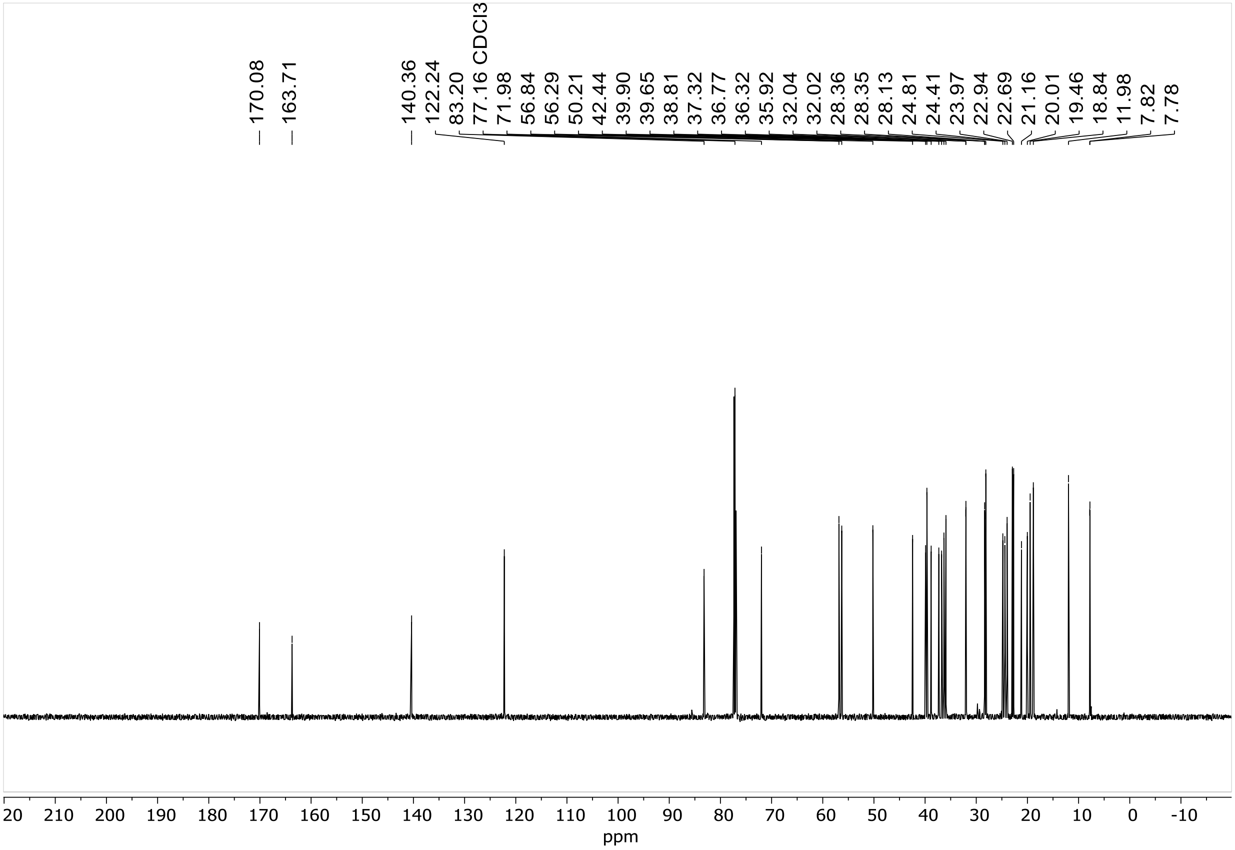
1ap’,^{13}C NMR (151 MHz, CDCl$_3$)



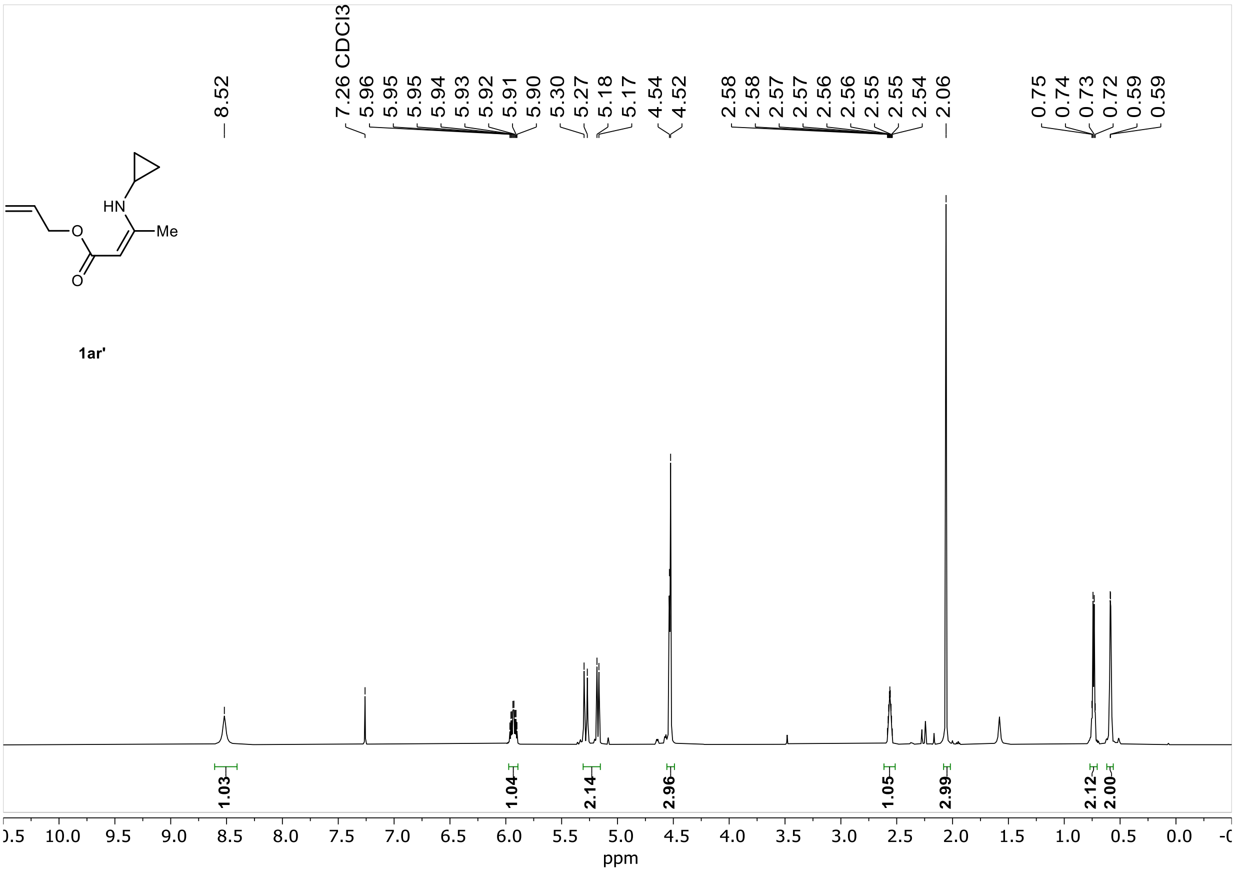
1aq',^{1}H NMR (600 MHz, CDCl$_3$)



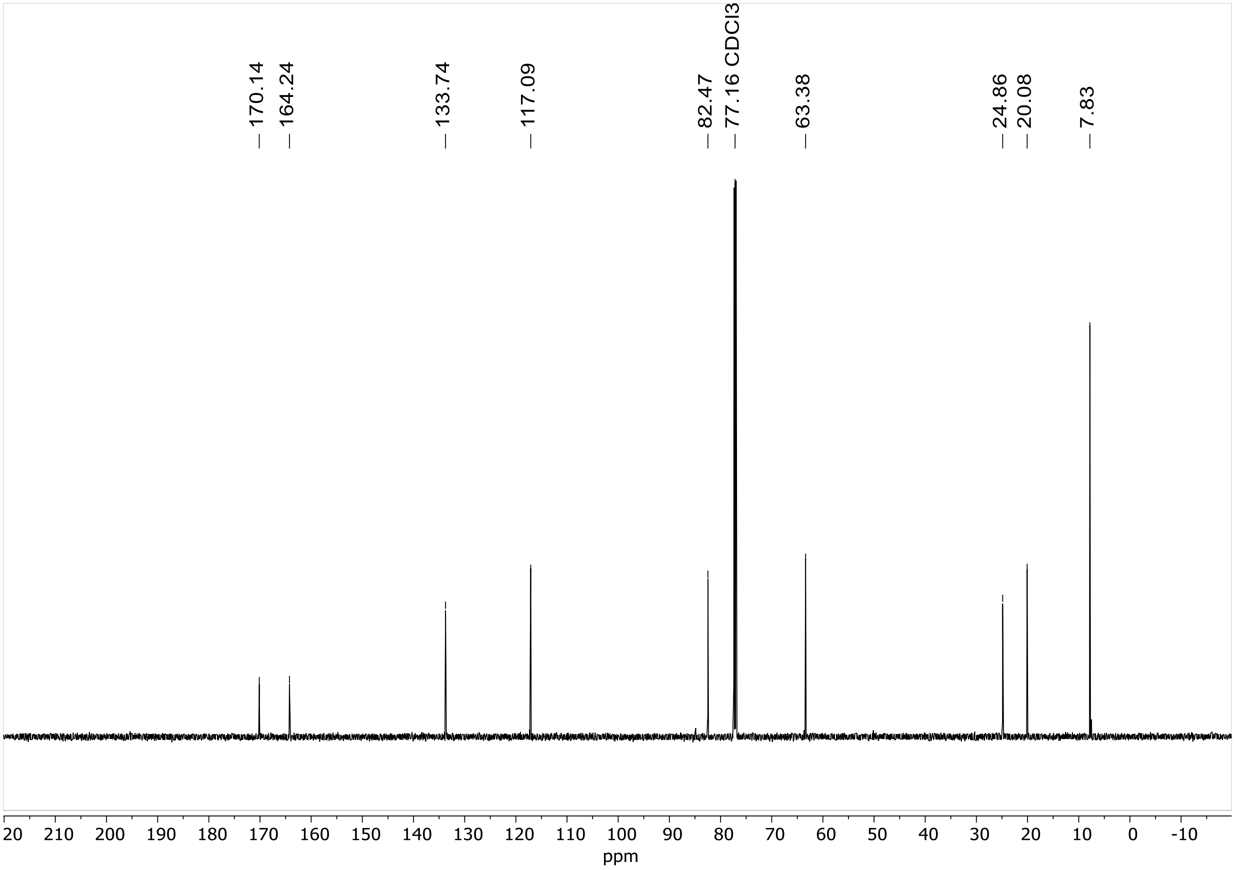
1aq',^{13}C NMR (151 MHz, CDCl$_3$)



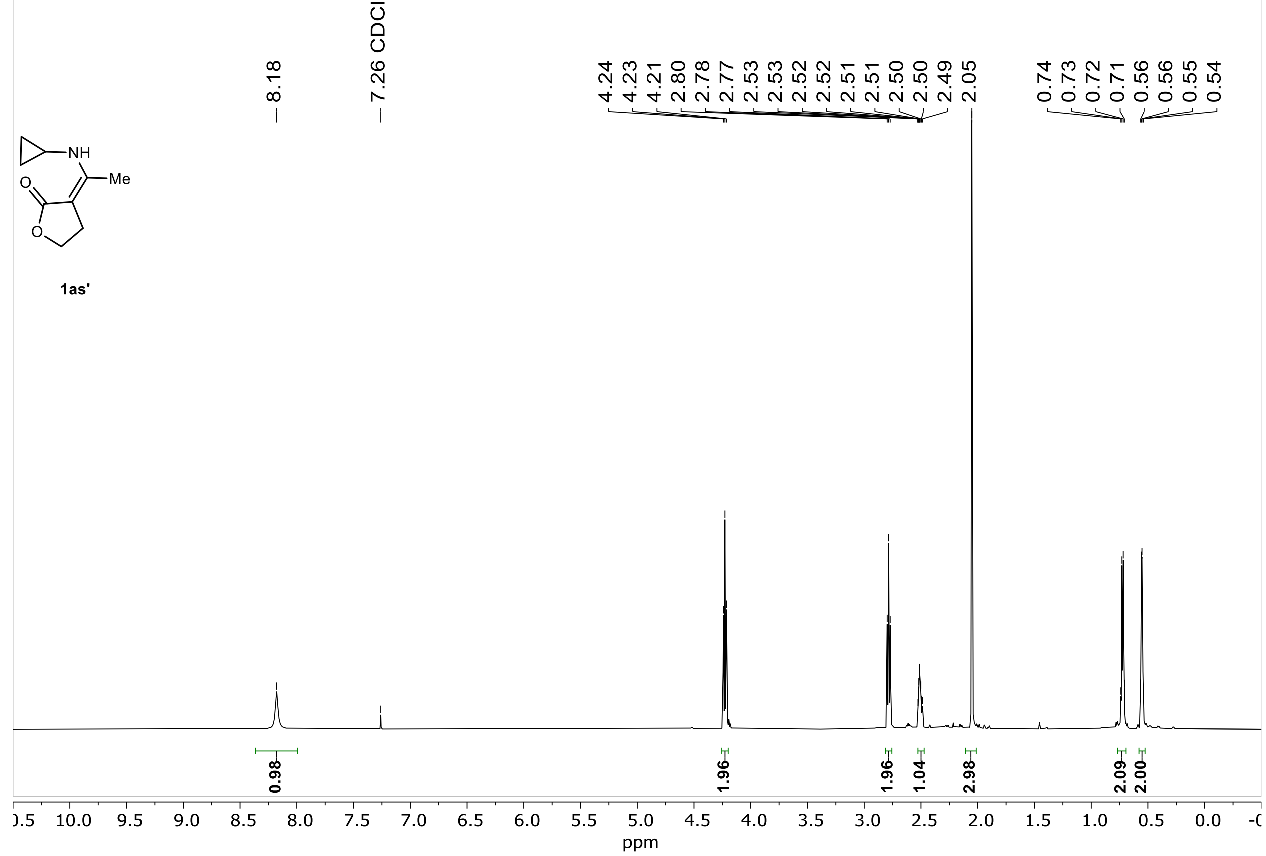
1ar',^{1}H NMR (151 MHz, CDCl$_3$)



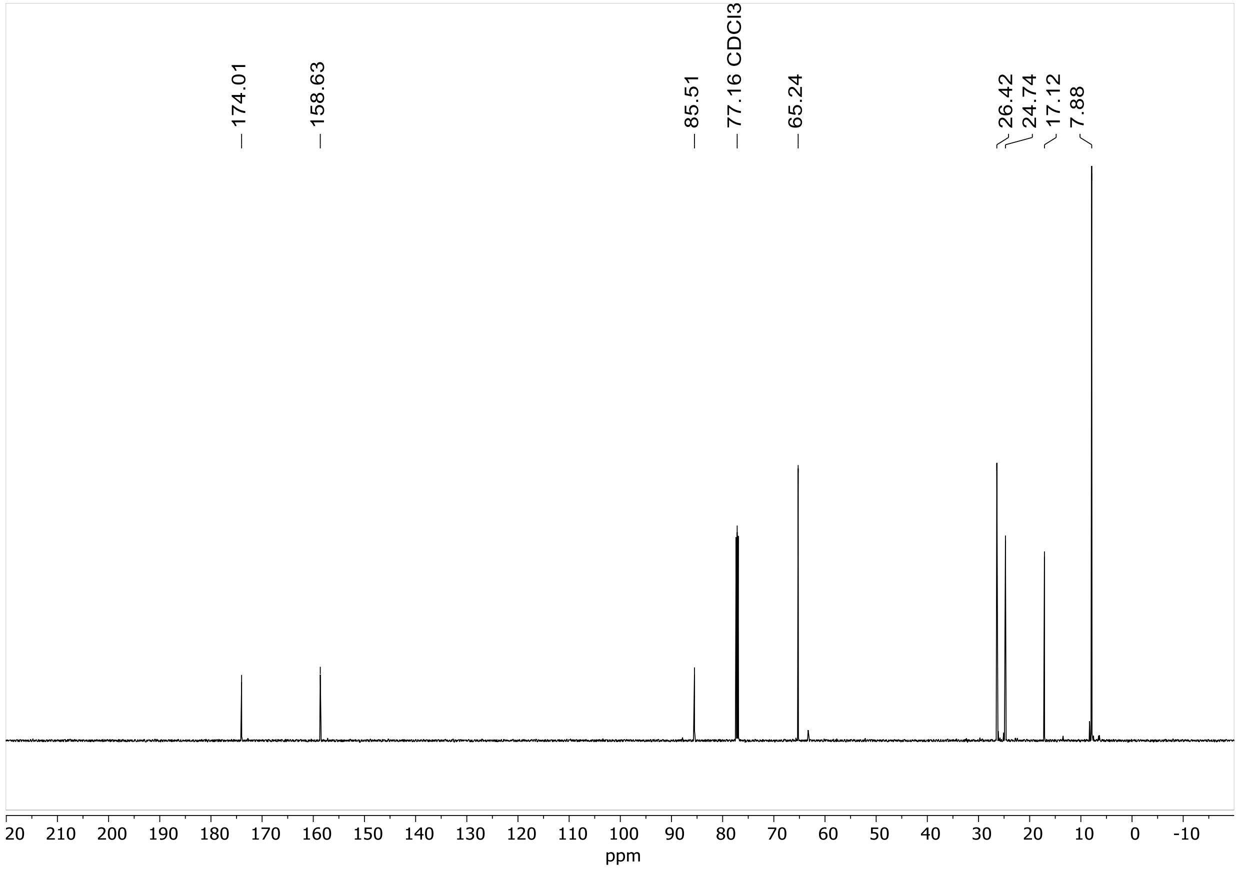
1ar',^{13}C NMR (151 MHz, CDCl$_3$)



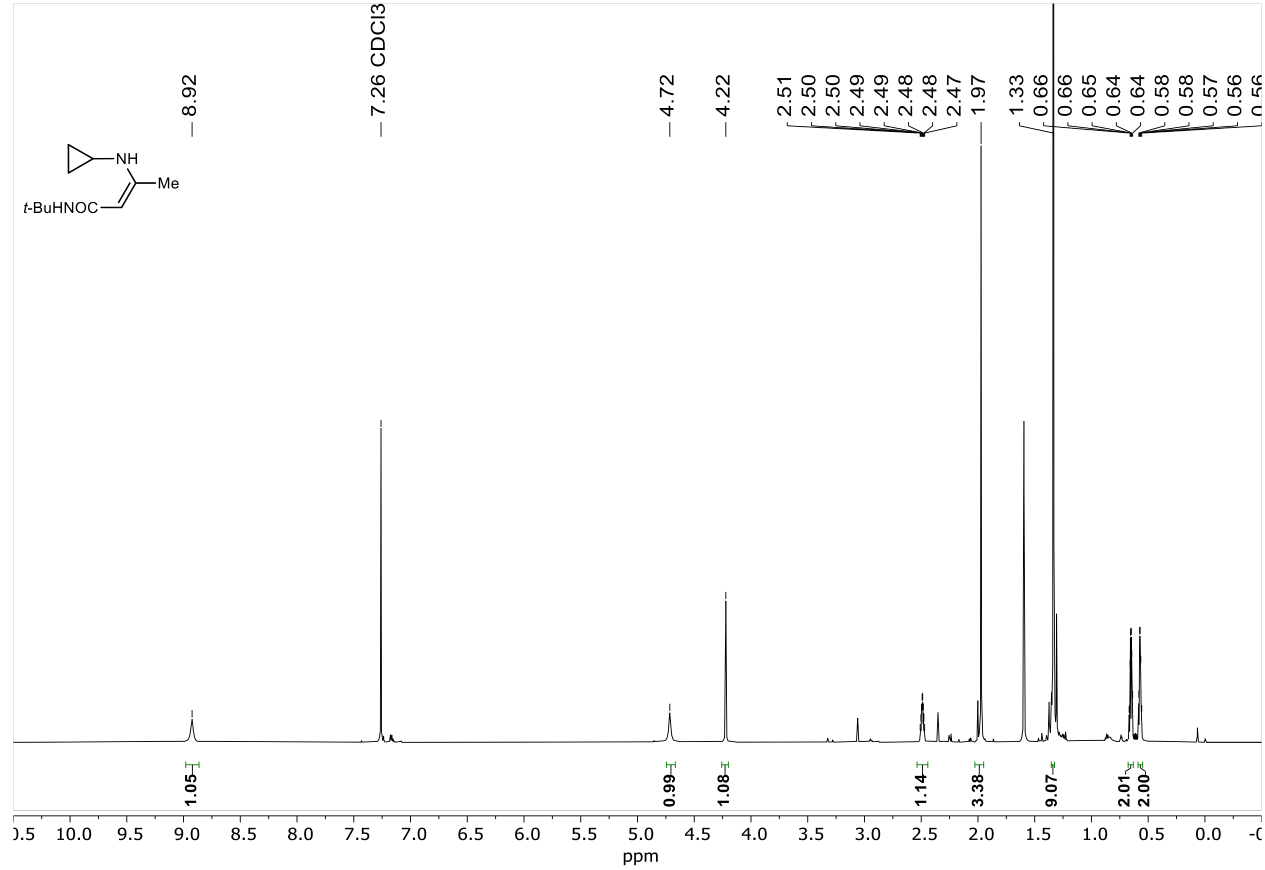
1as’,^{1}H NMR (600 MHz, CDCl$_3$)



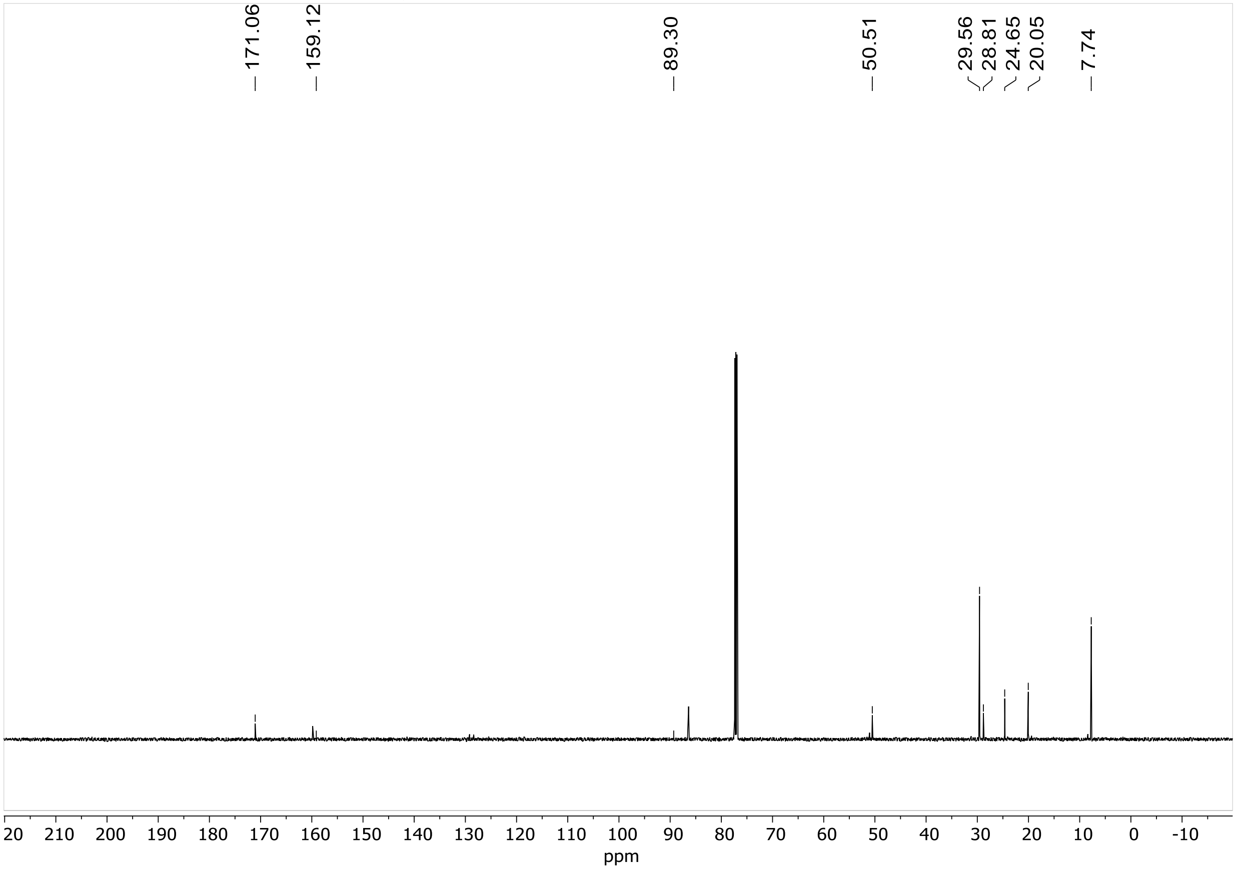
1as’,^{13}C NMR (151 MHz, CDCl$_3$)



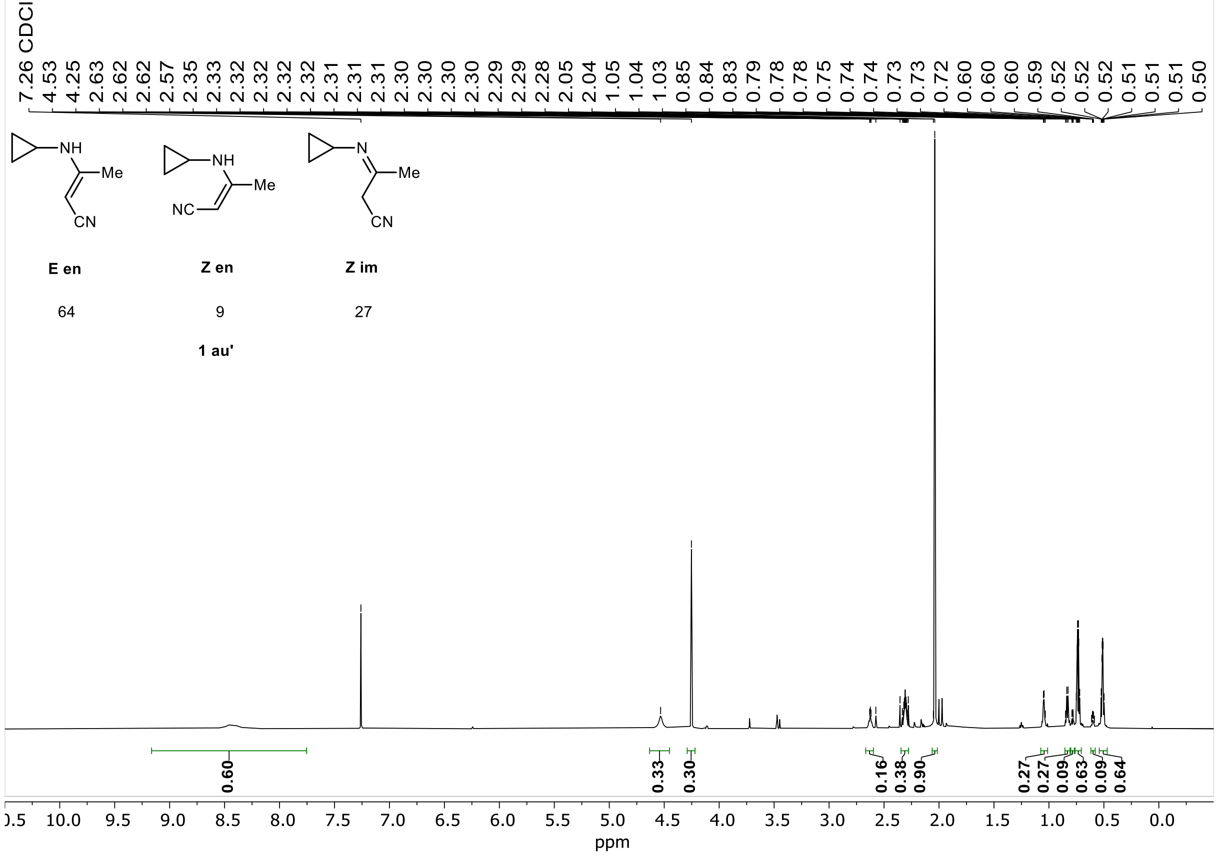
1at',^{1}H NMR (600 MHz, CDCl$_3$)



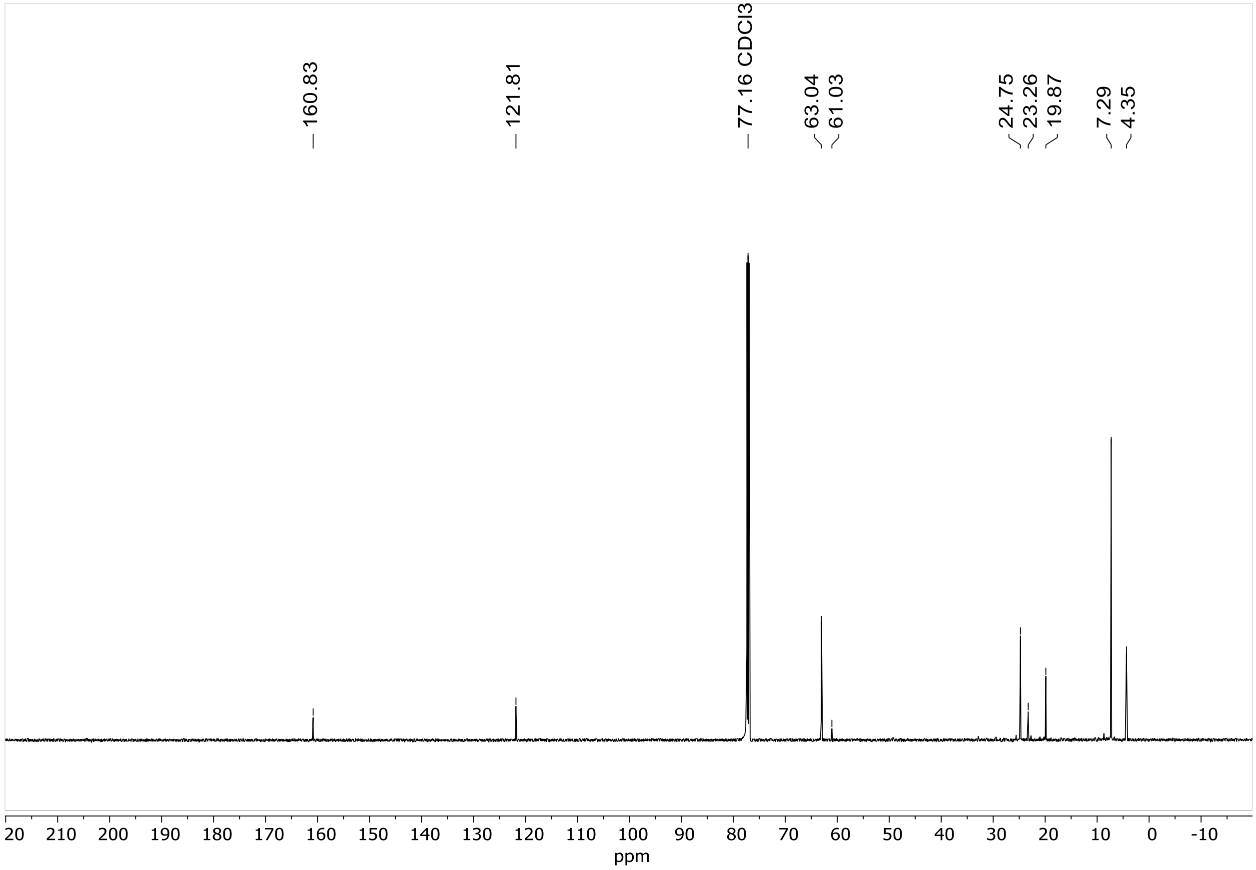
1at',^{13}C NMR (151 MHz, CDCl$_3$)



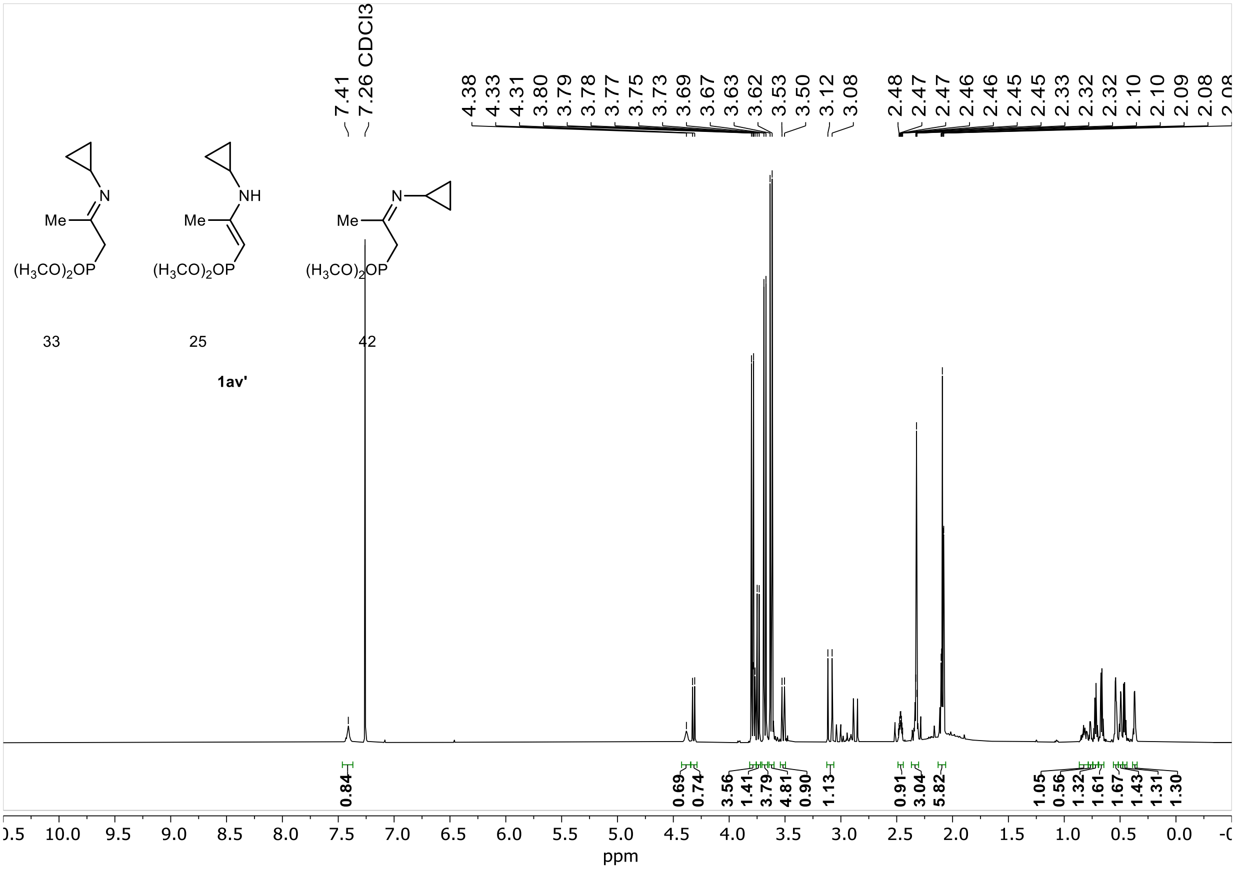
1au', ^{1}H NMR (600 MHz, CDCl$_3$)



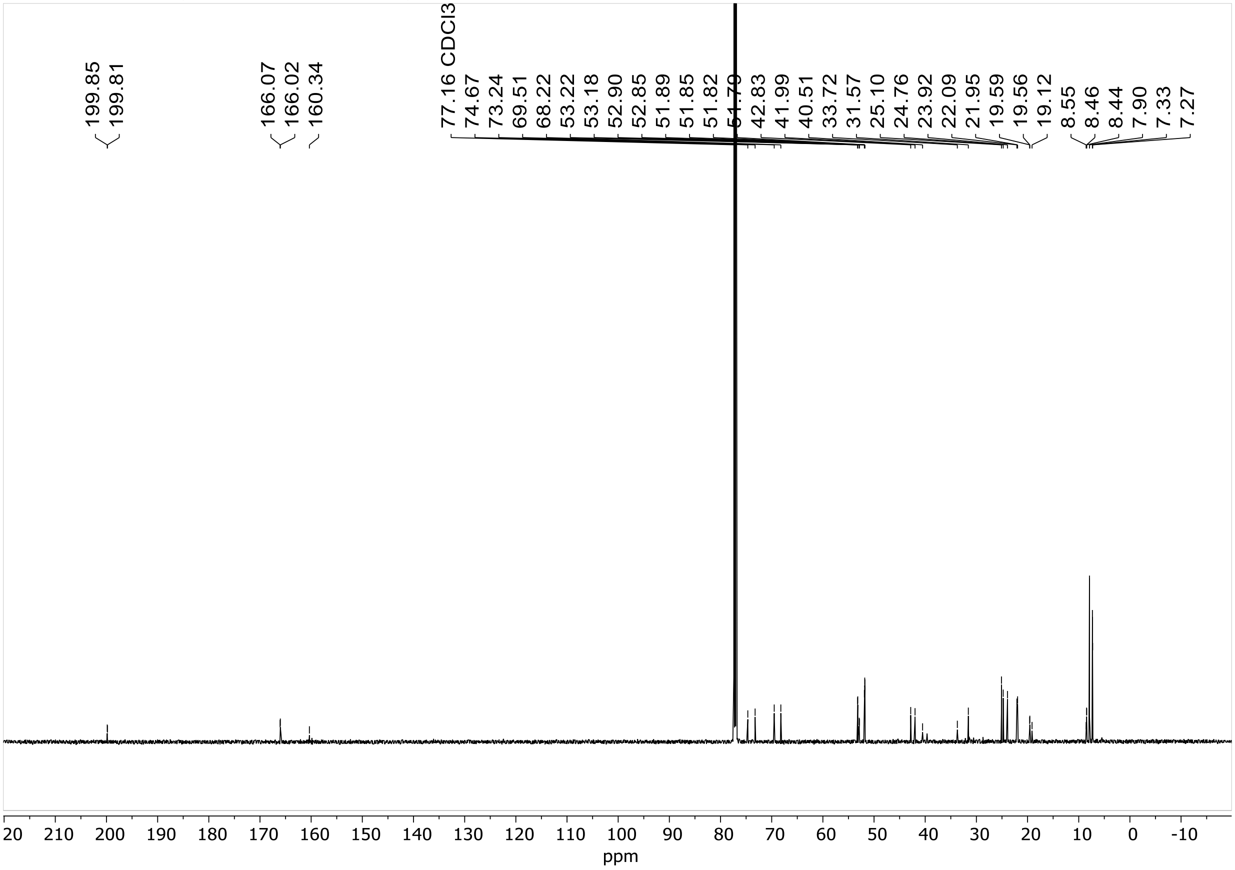
1au', ^{13}C NMR (151 MHz, CDCl$_3$)



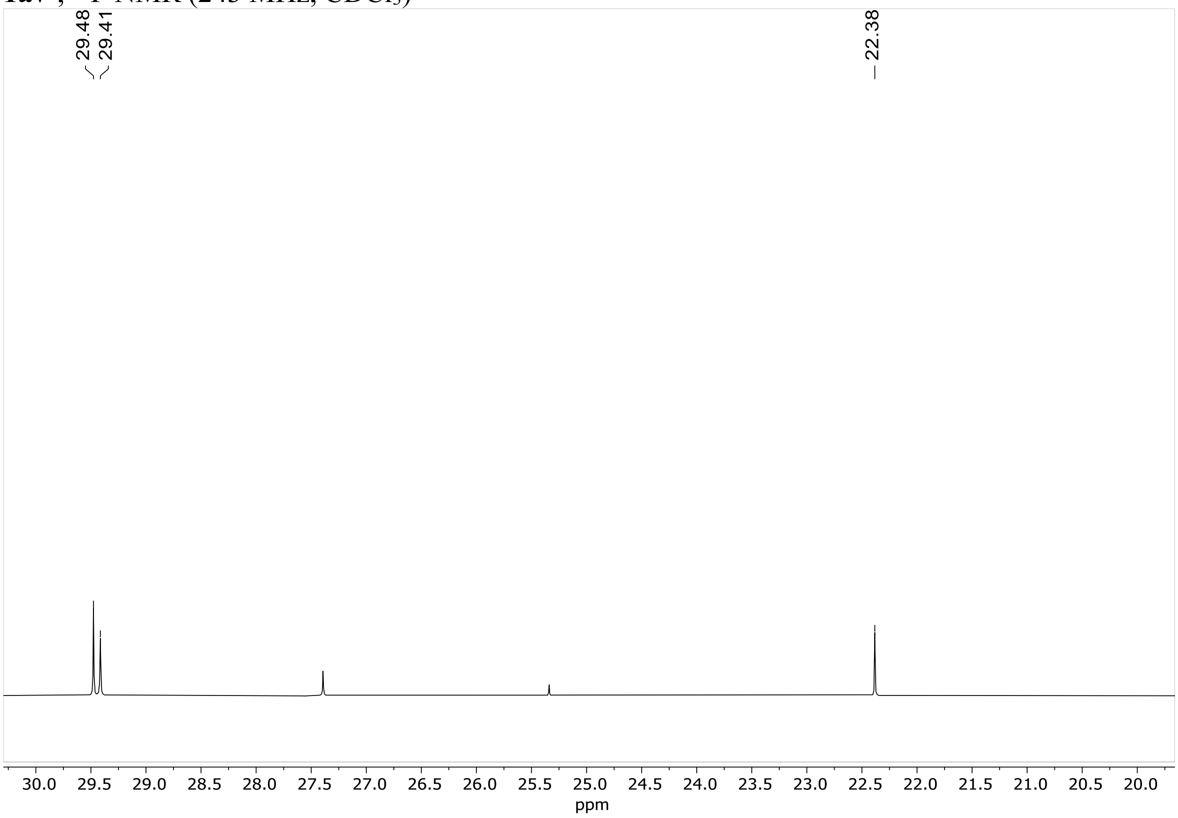
1av’, ^{1}H NMR (600 MHz, CDCl$_3$)



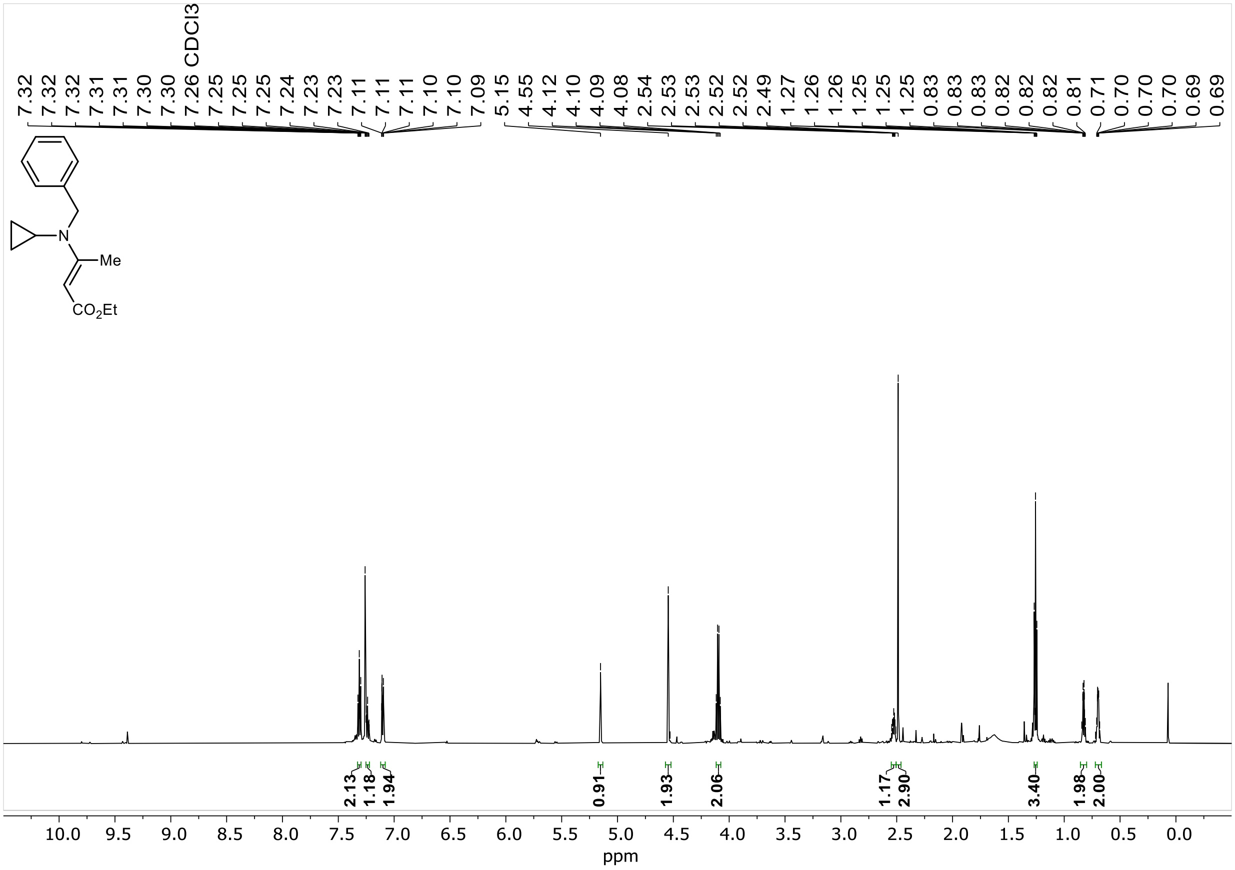
1av’, ^{13}C NMR (151 MHz, CDCl$_3$)



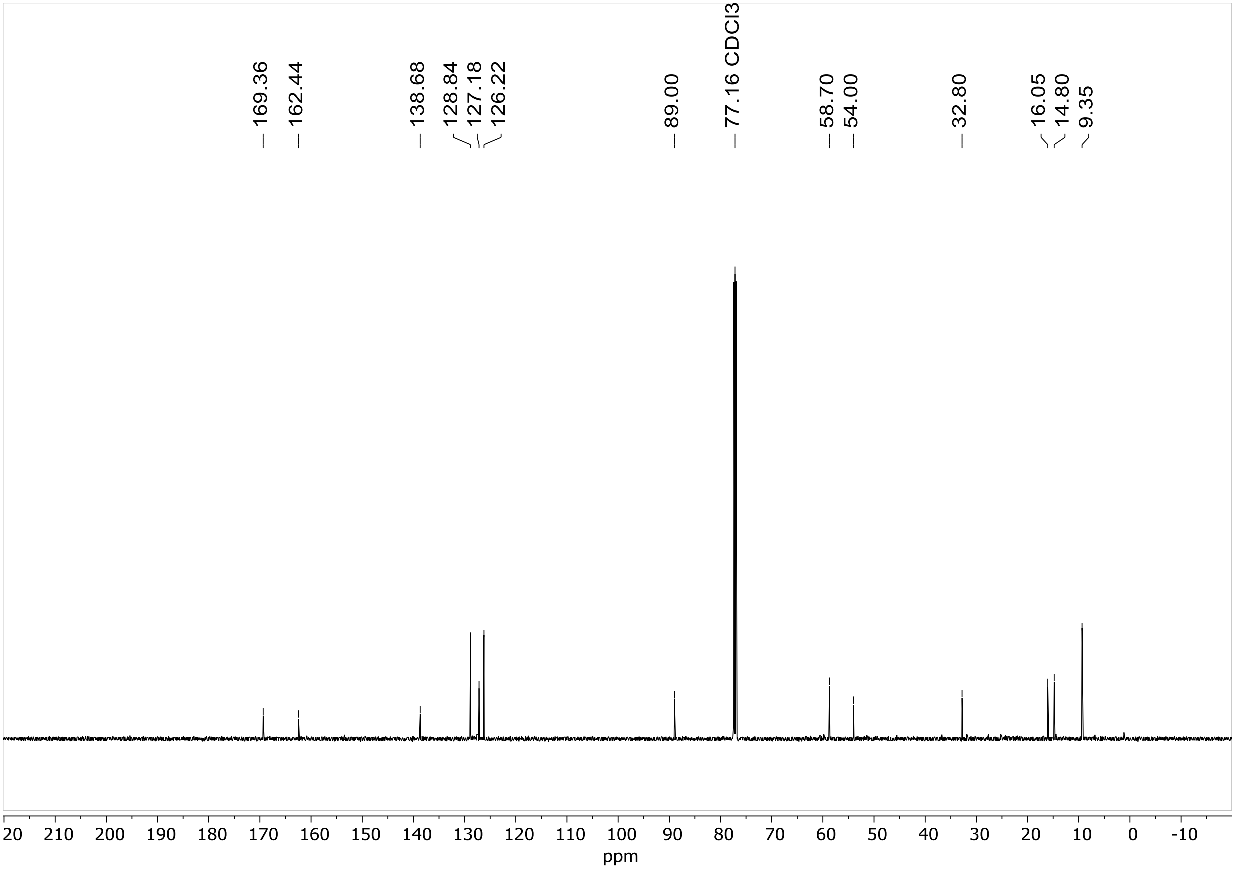
1av', ^{31}P NMR (243 MHz, CDCl$_3$)



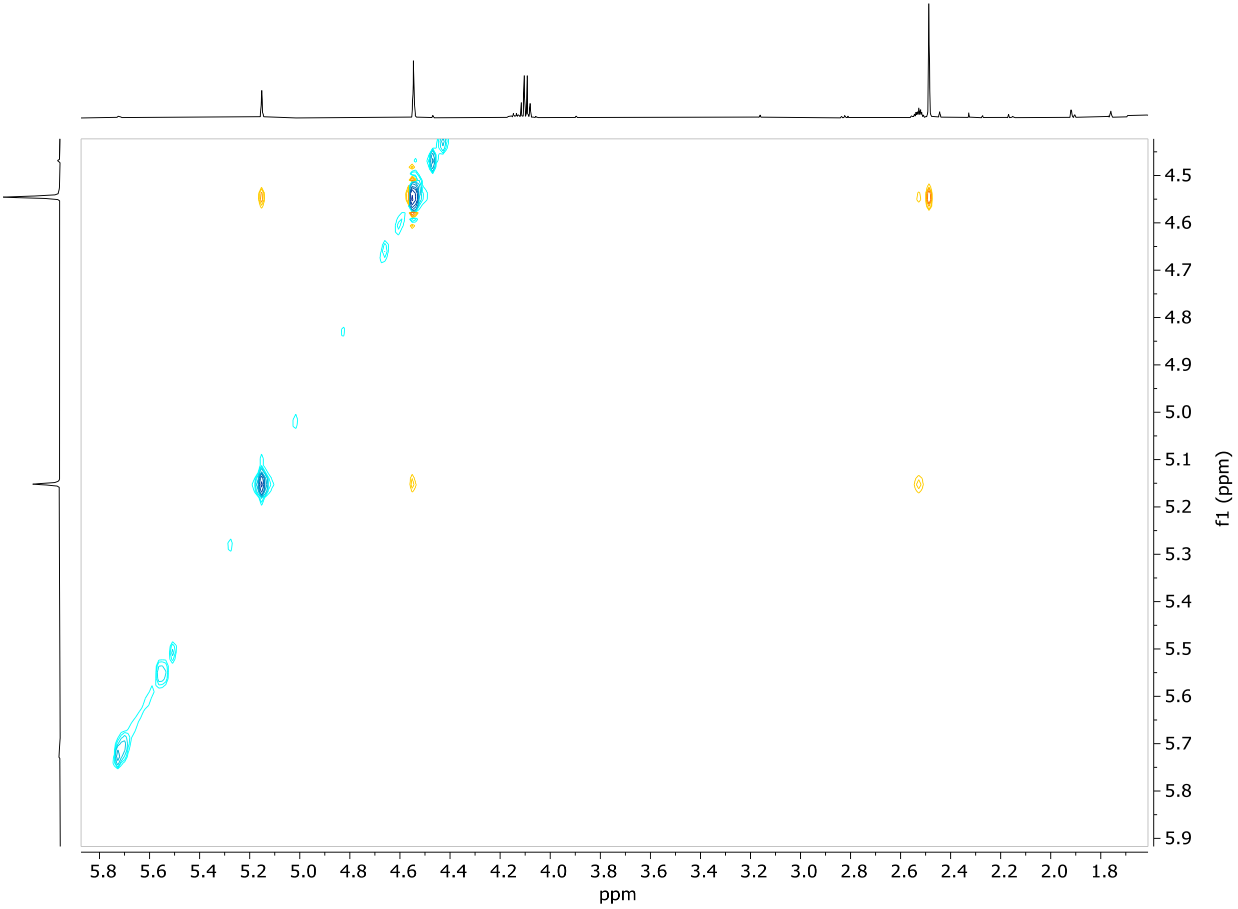
1ka’, ^{1}H NMR (600 MHz, $CDCl_3$)



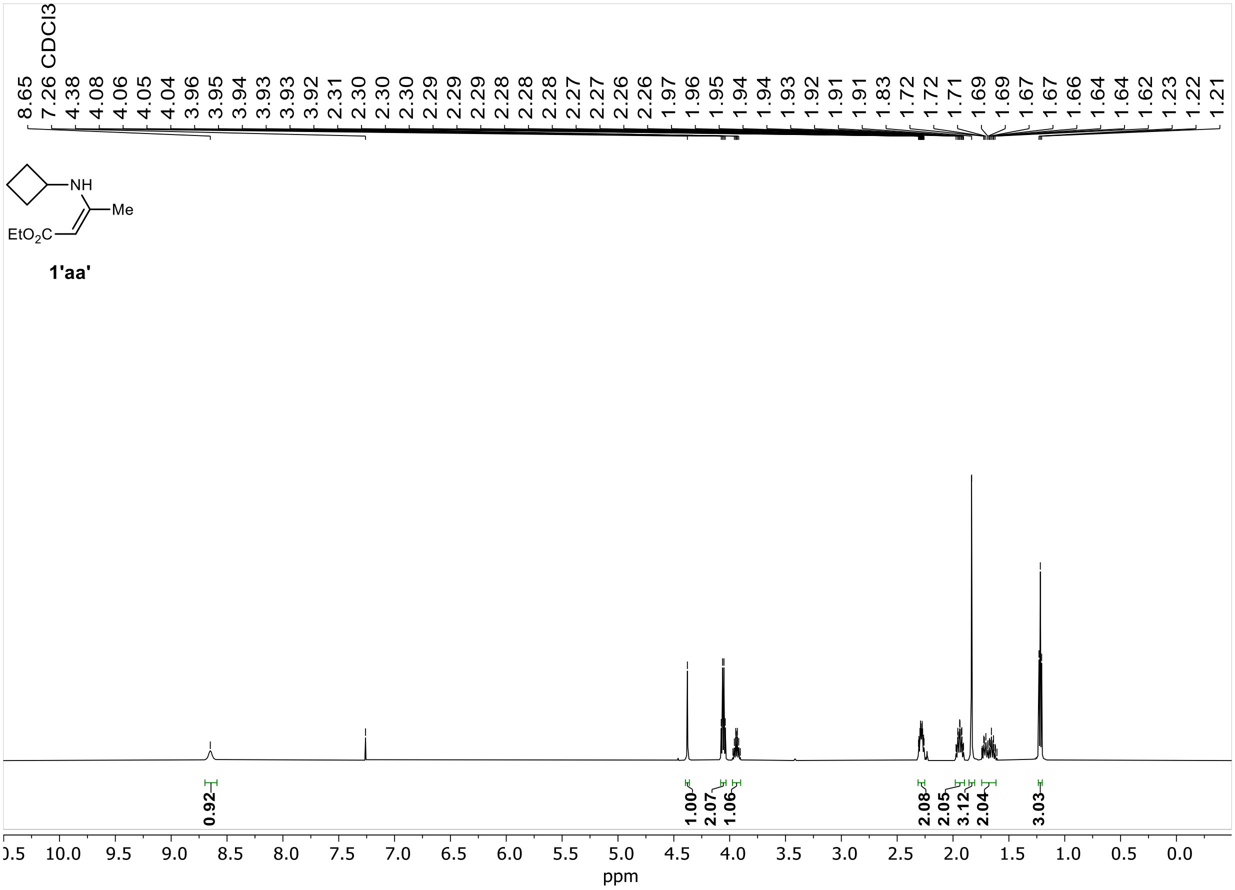
1ka’, ^{13}C NMR (151 MHz, $CDCl_3$)



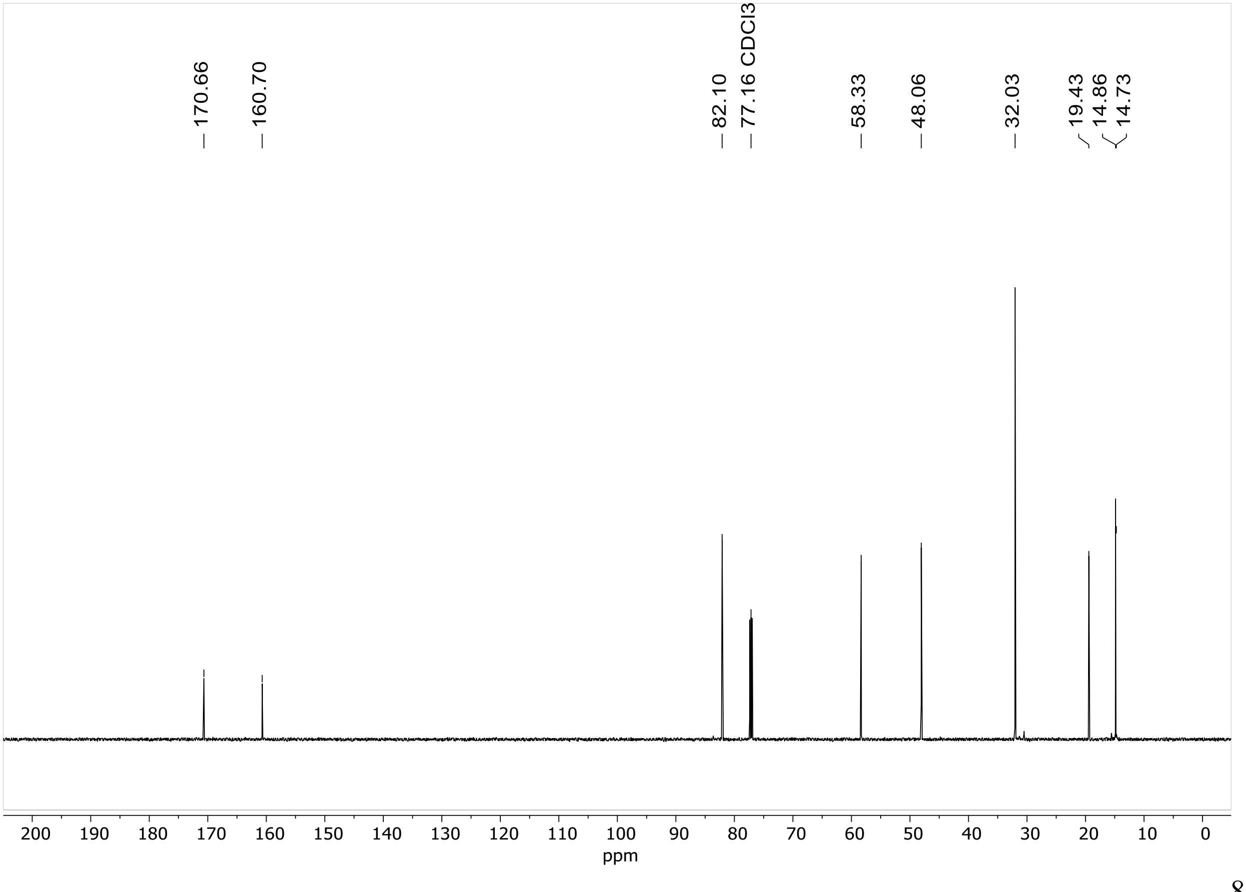
1ka’, 2D NOESY (600MHz, 600MHz, CDCl$_3$)



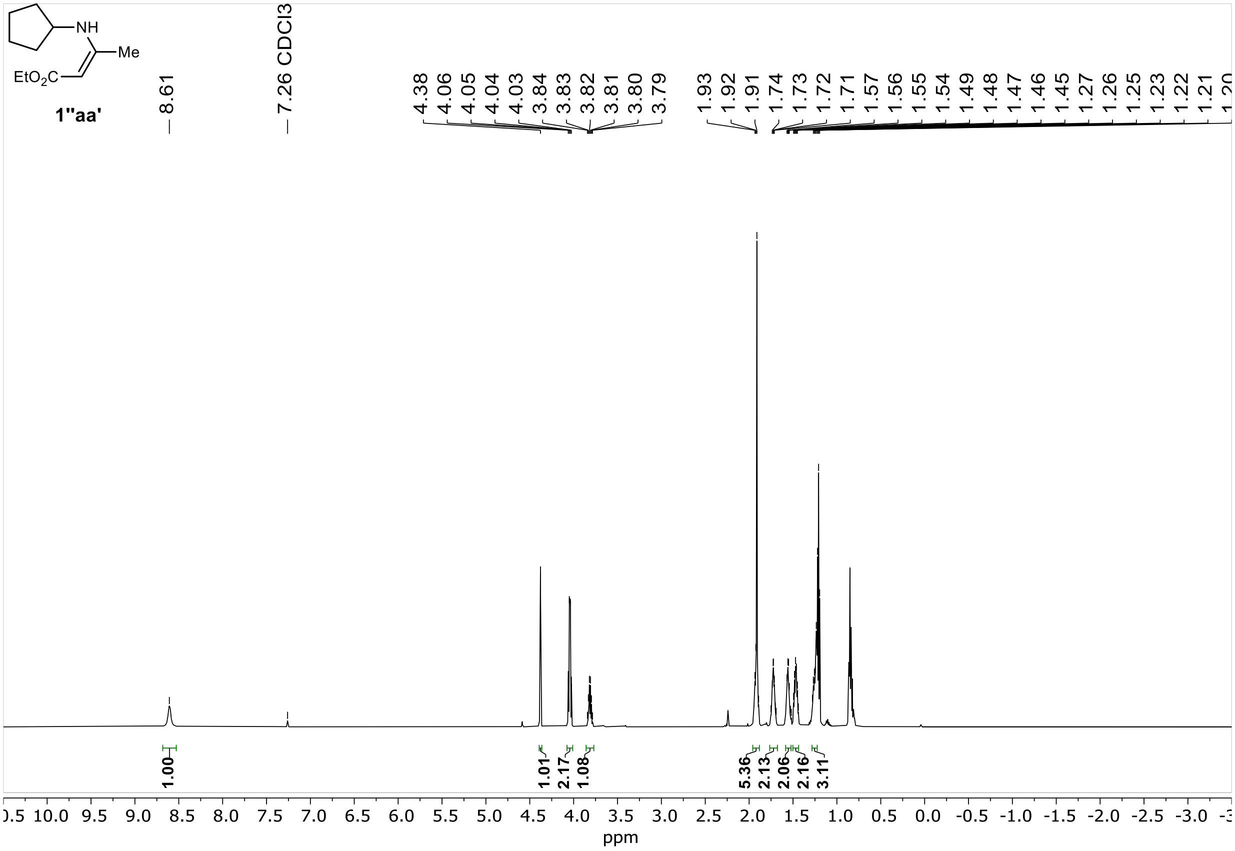
1’aa’, ^{1}H NMR (600 MHz, $CDCl_3$)



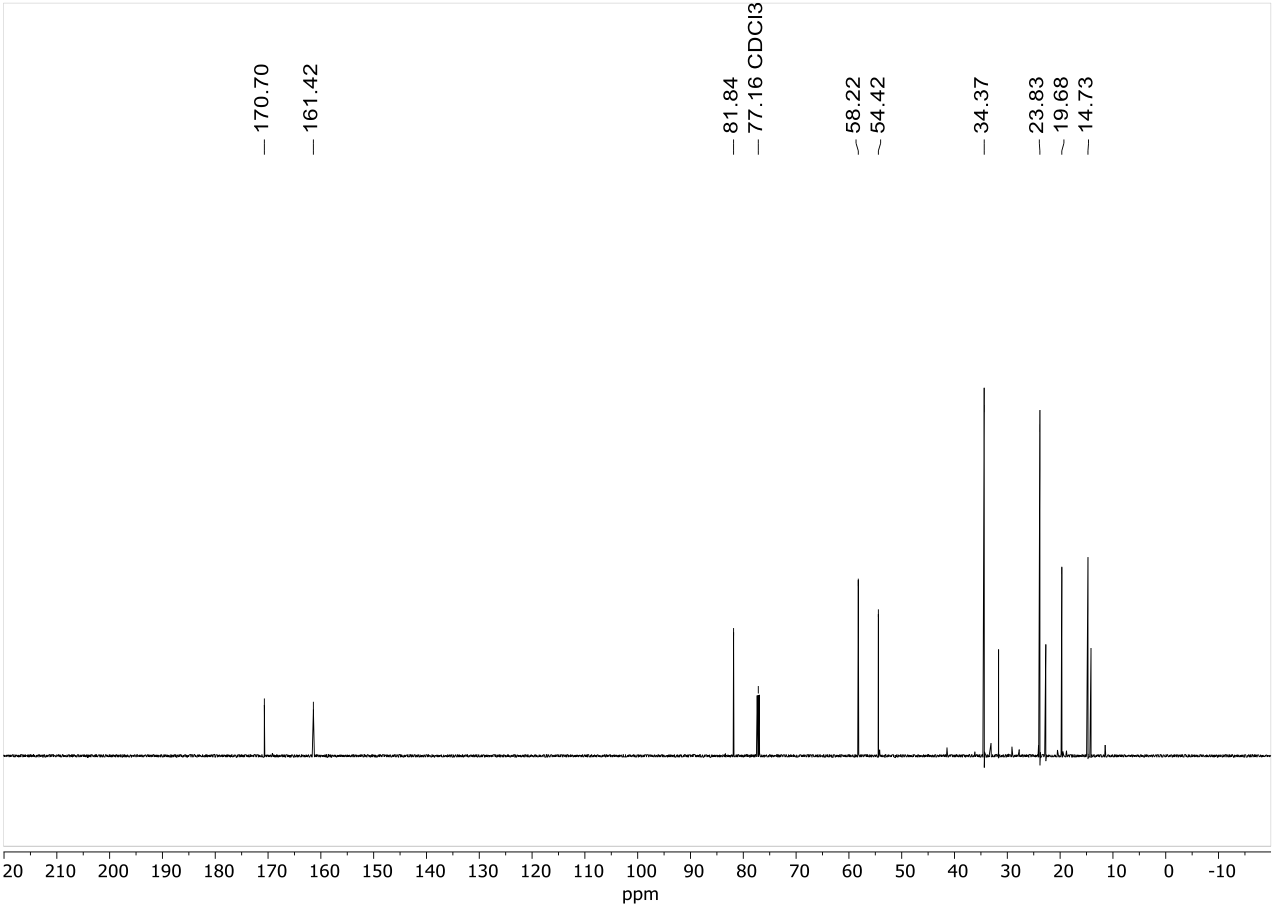
1’aa’, ^{13}C NMR (151 MHz, $CDCl_3$)



1’’aa’,^{1}H NMR (600 MHz, CDCl$_3$)

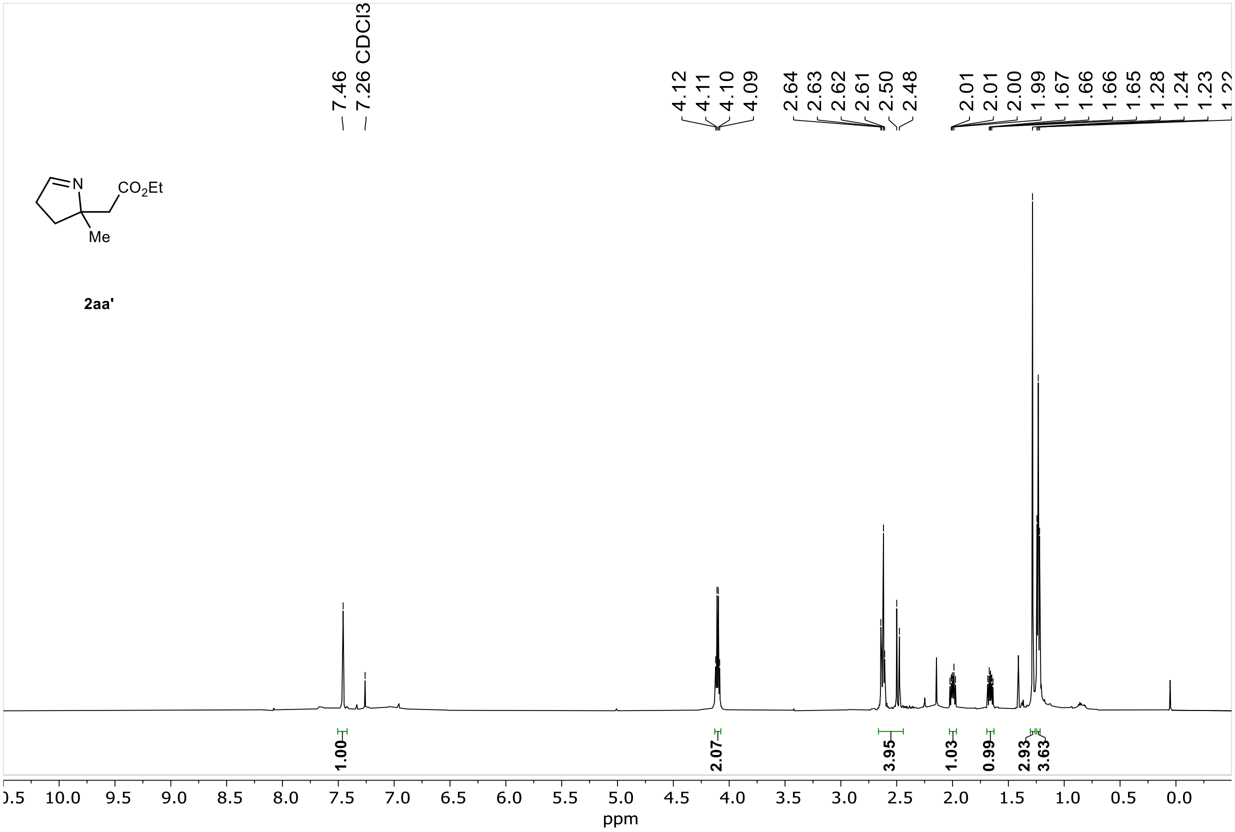


1’’aa’,^{13}C NMR (600 MHz, CDCl$_3$)

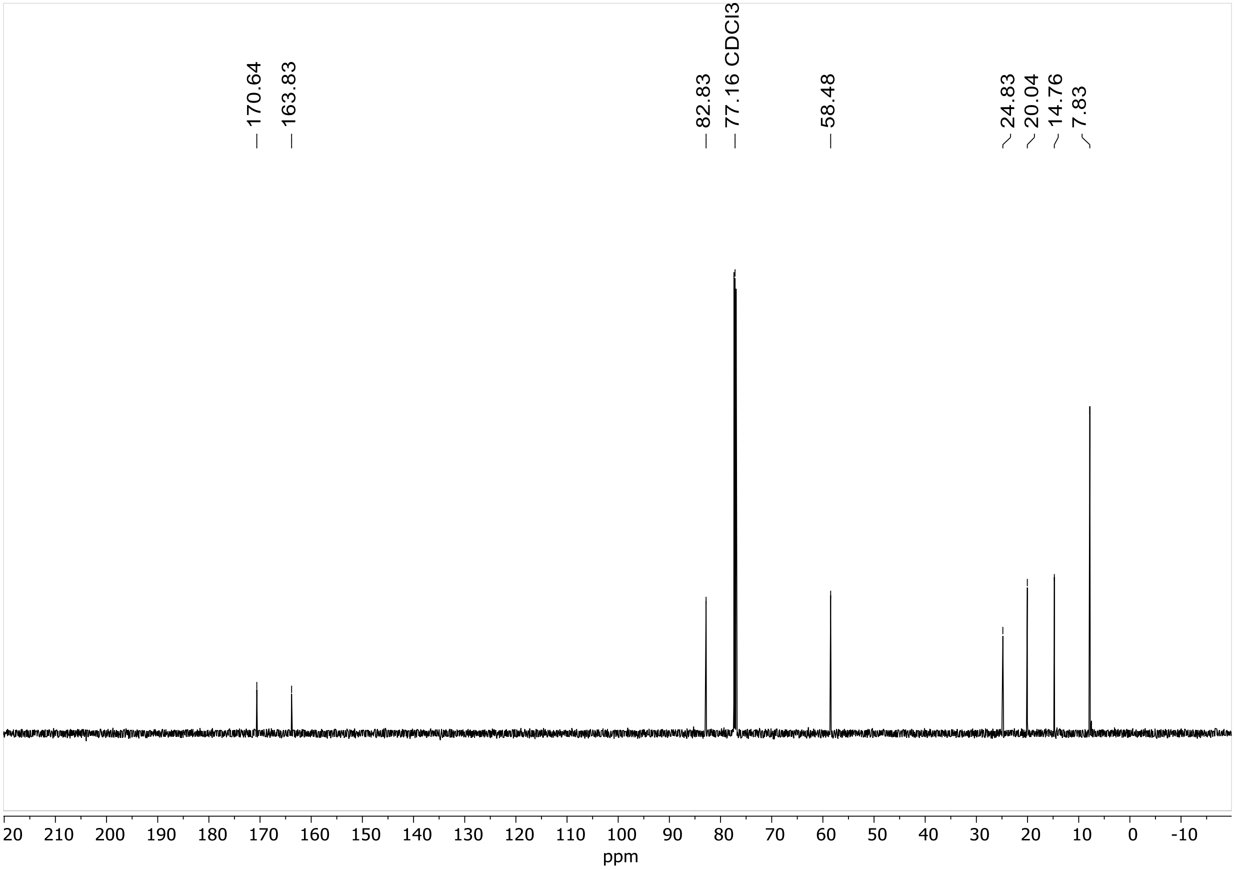


8. NMR Spectra product

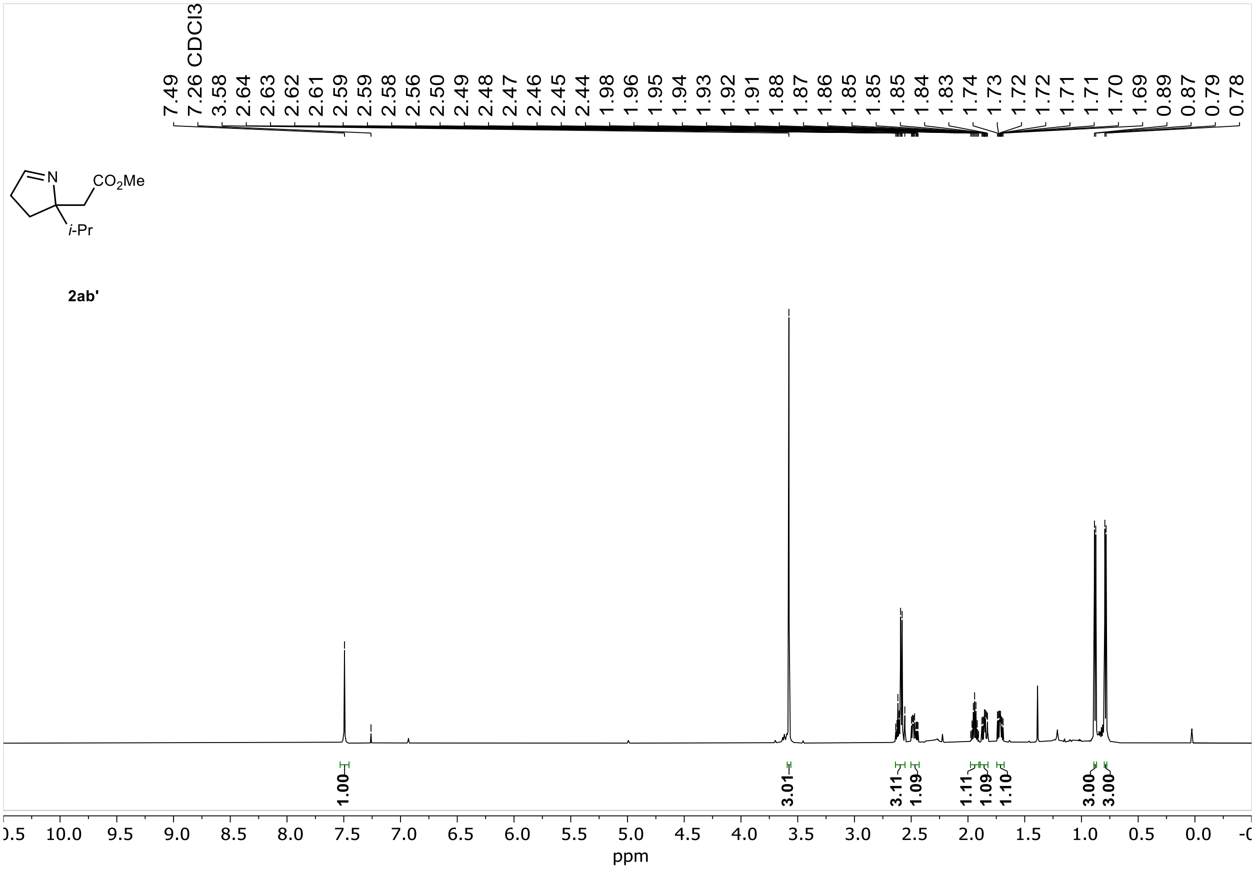
2aa’,^{1}H NMR (600 MHz, CDCl$_3$)



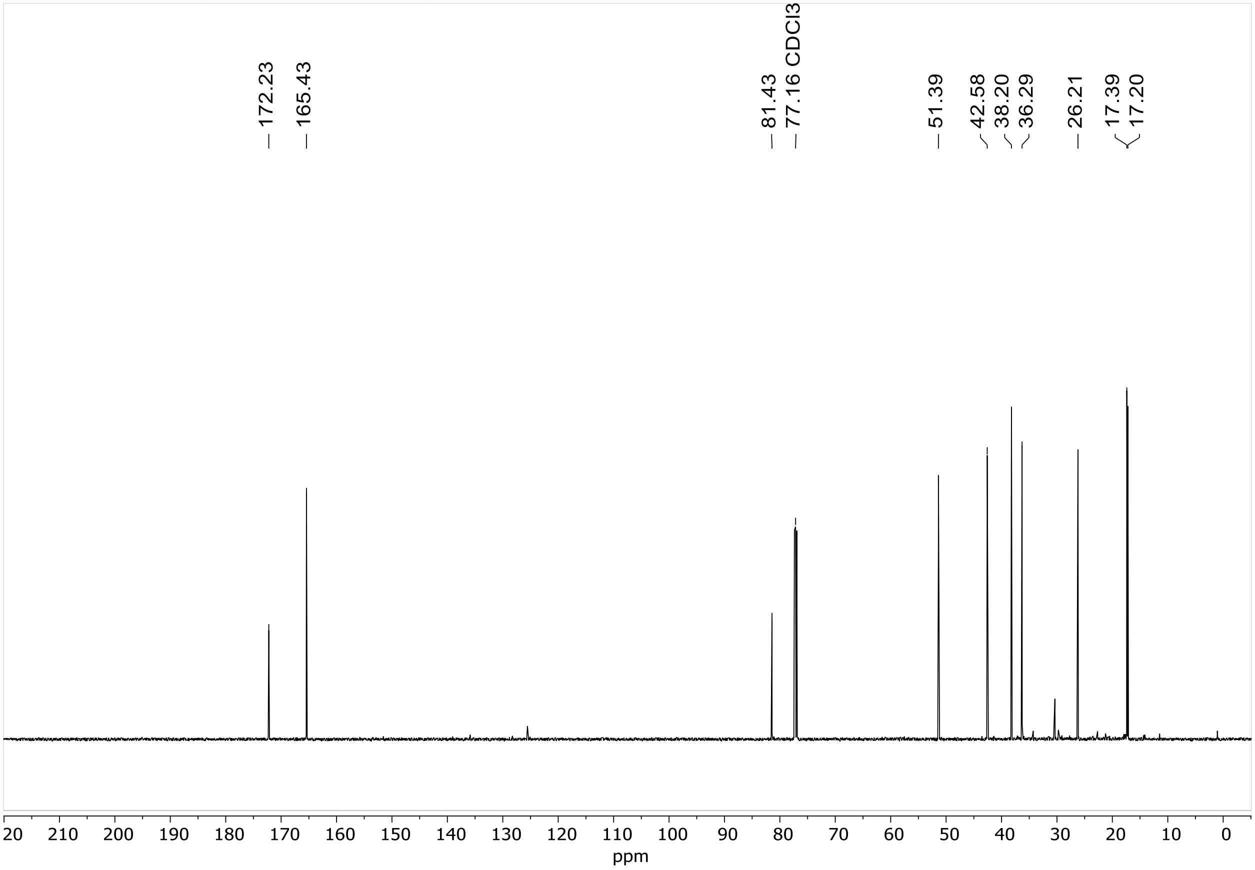
2aa’,^{13}C NMR (151 MHz, CDCl$_3$)



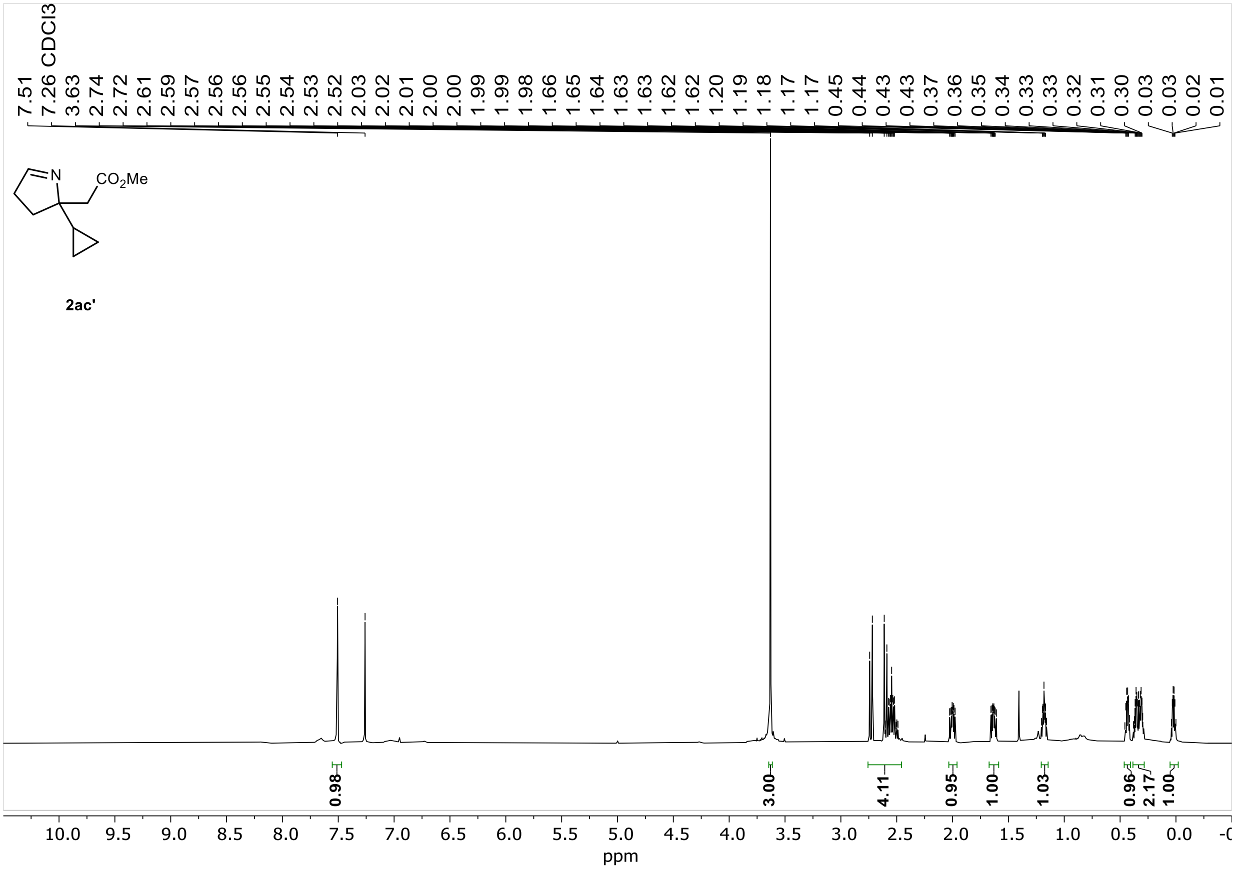
2ab’, ^{1}H NMR (600 MHz, CDCl$_3$)



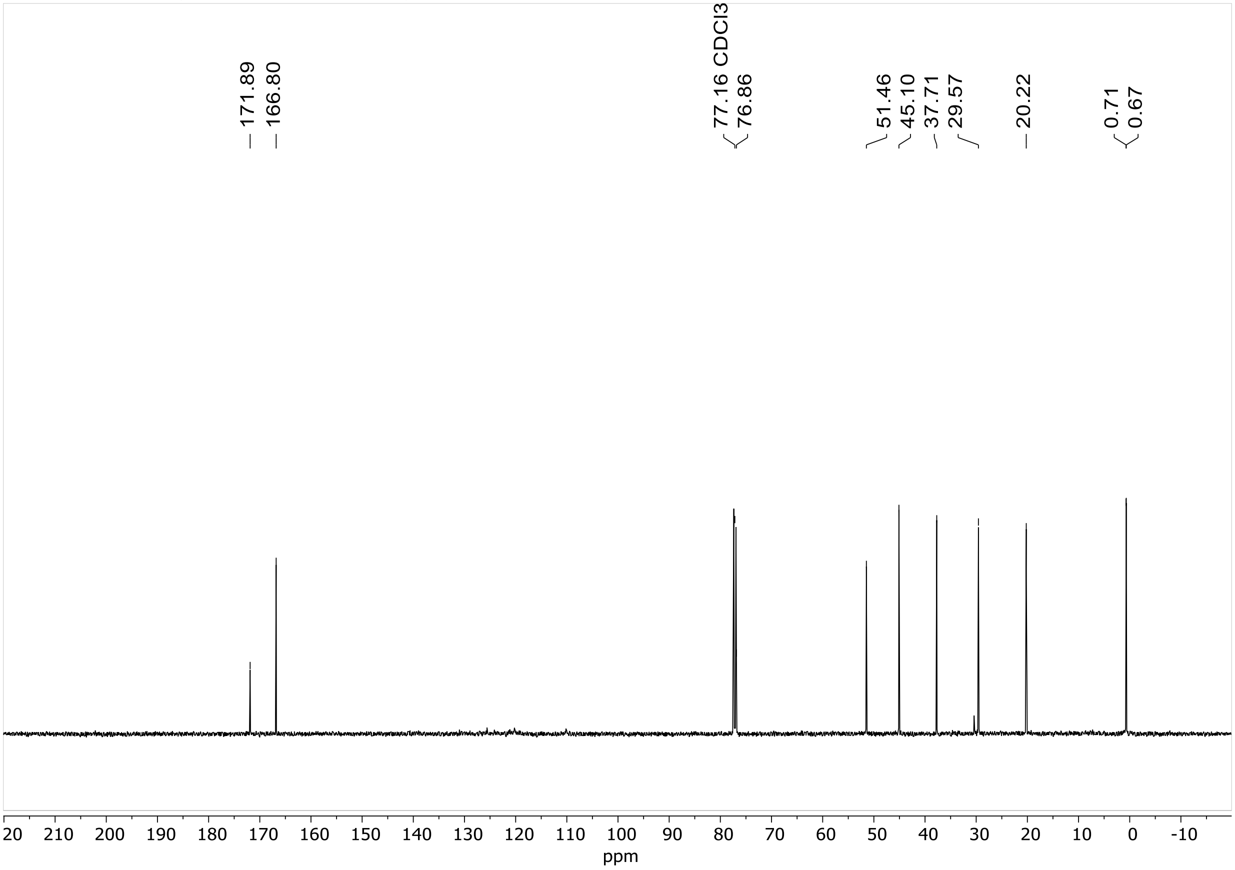
2ab’, ^{13}C NMR (151 MHz, CDCl$_3$)



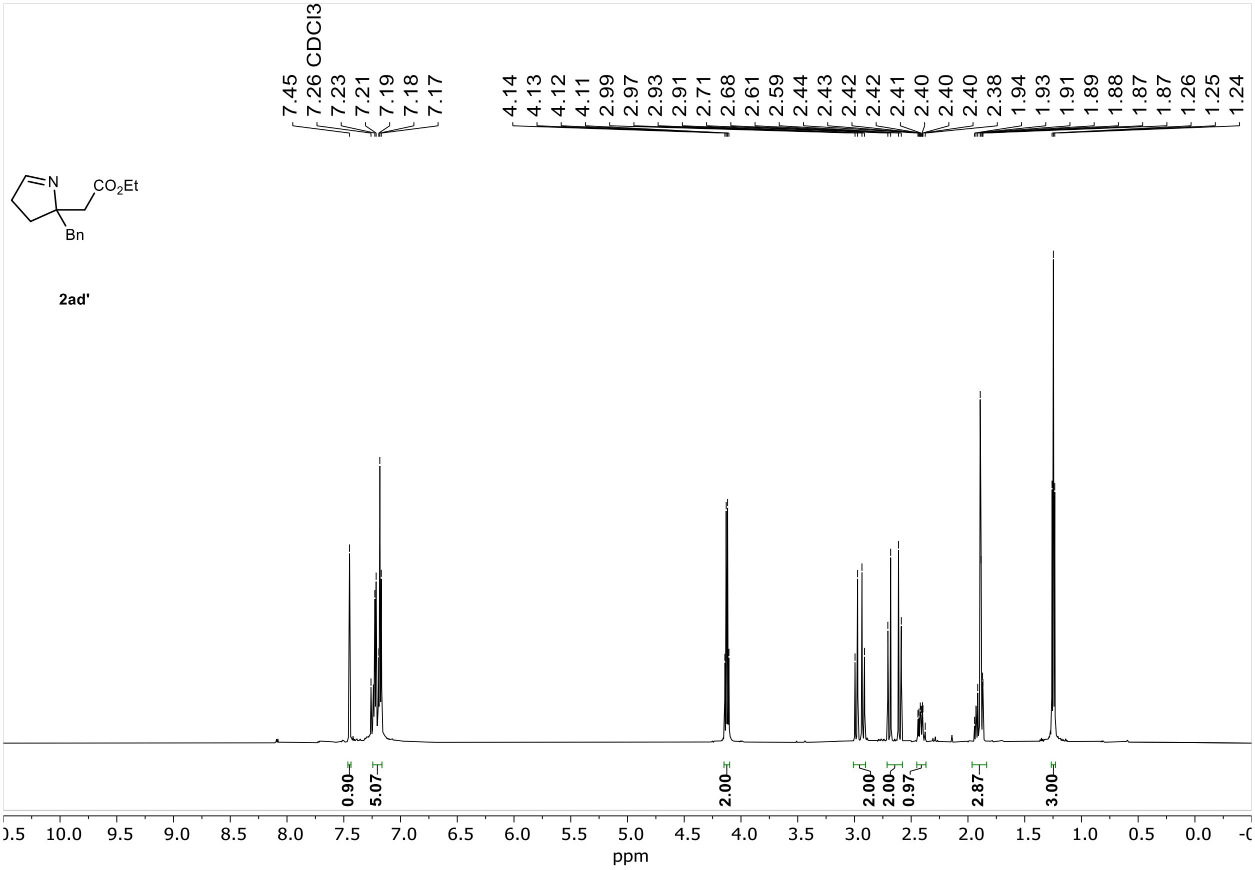
2ac', ^{1}H NMR (600 MHz, CDCl$_3$)



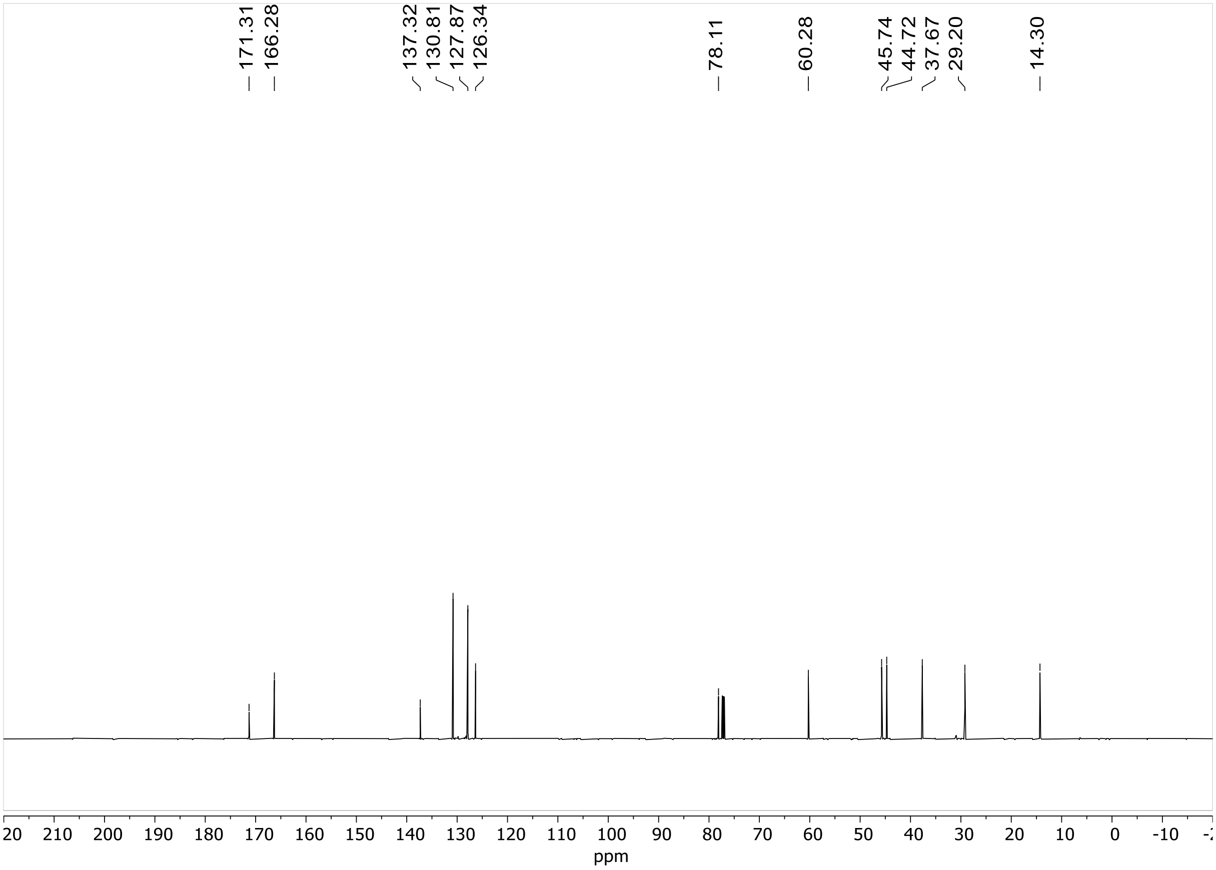
2ac' ^{13}C NMR (151 MHz, CDCl$_3$)



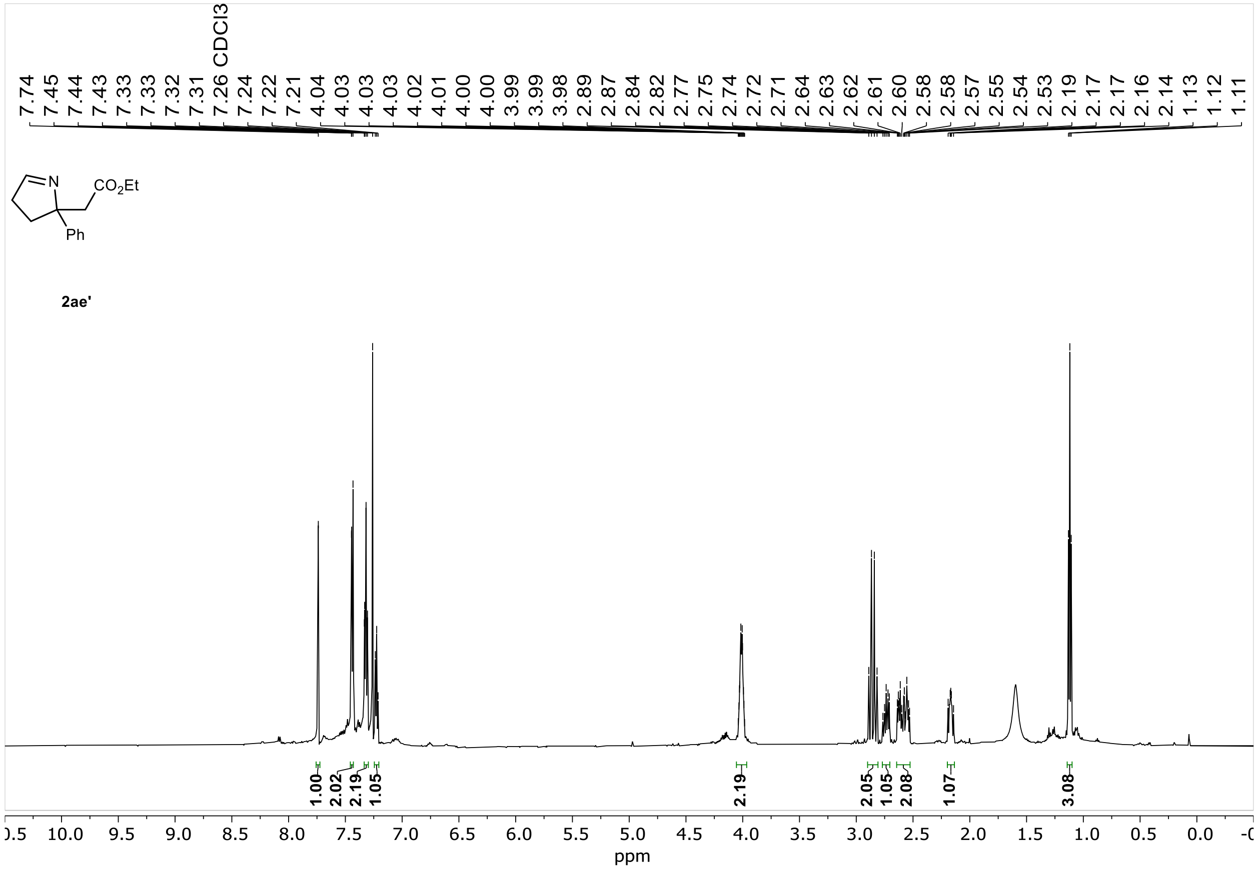
2ad’, ^{1}H NMR (600 MHz, CDCl$_3$)



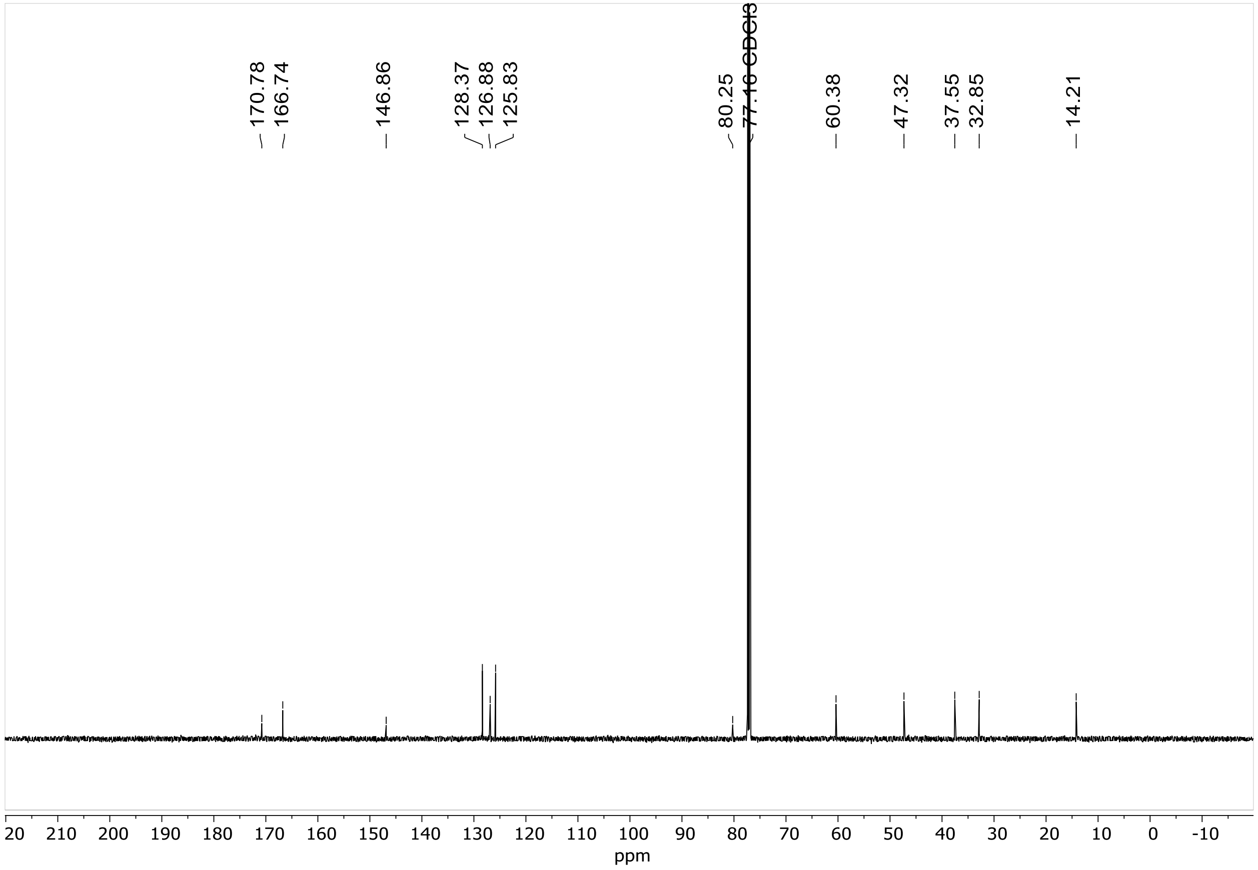
2ad’, ^{13}C NMR (151 MHz, CDCl$_3$)



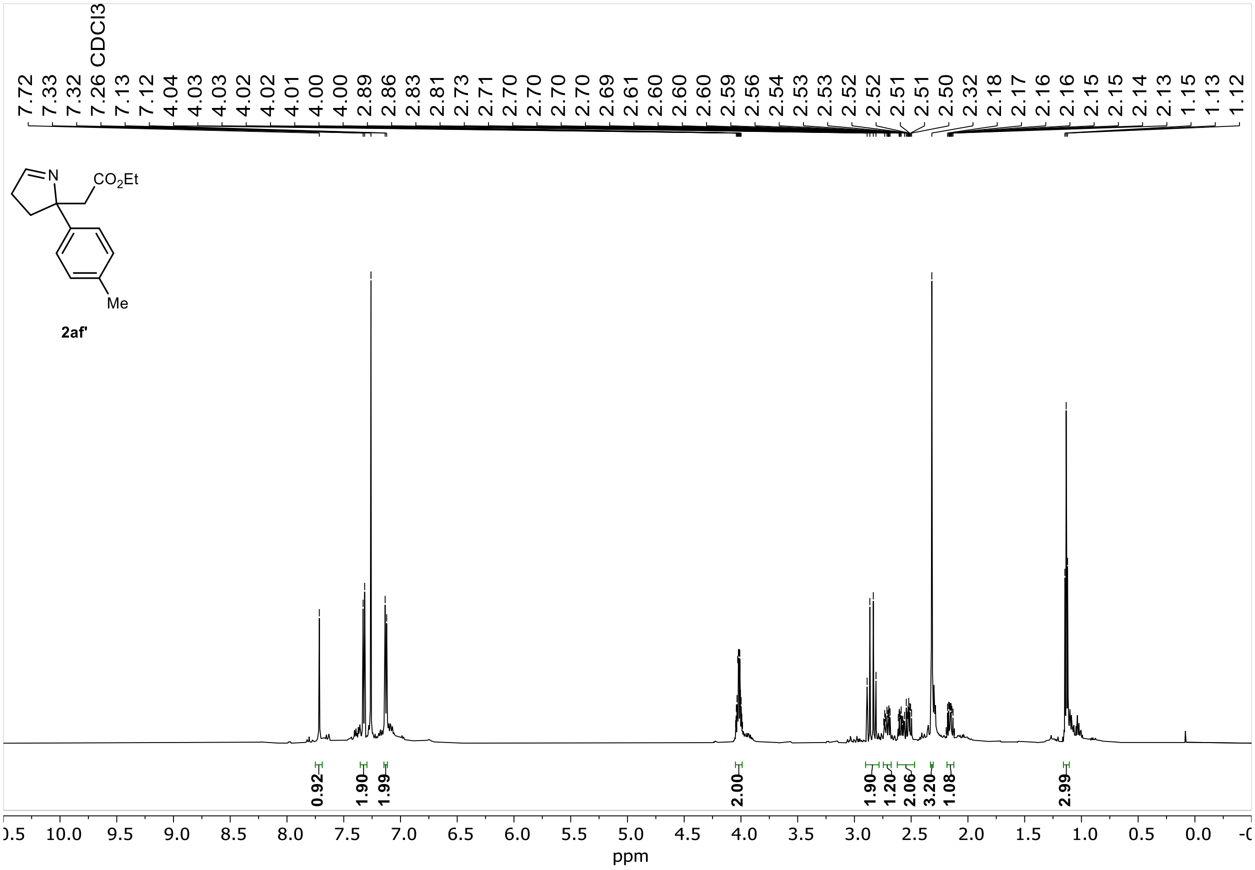
2ae', ^{1}H NMR (600 MHz, CDCl$_3$)



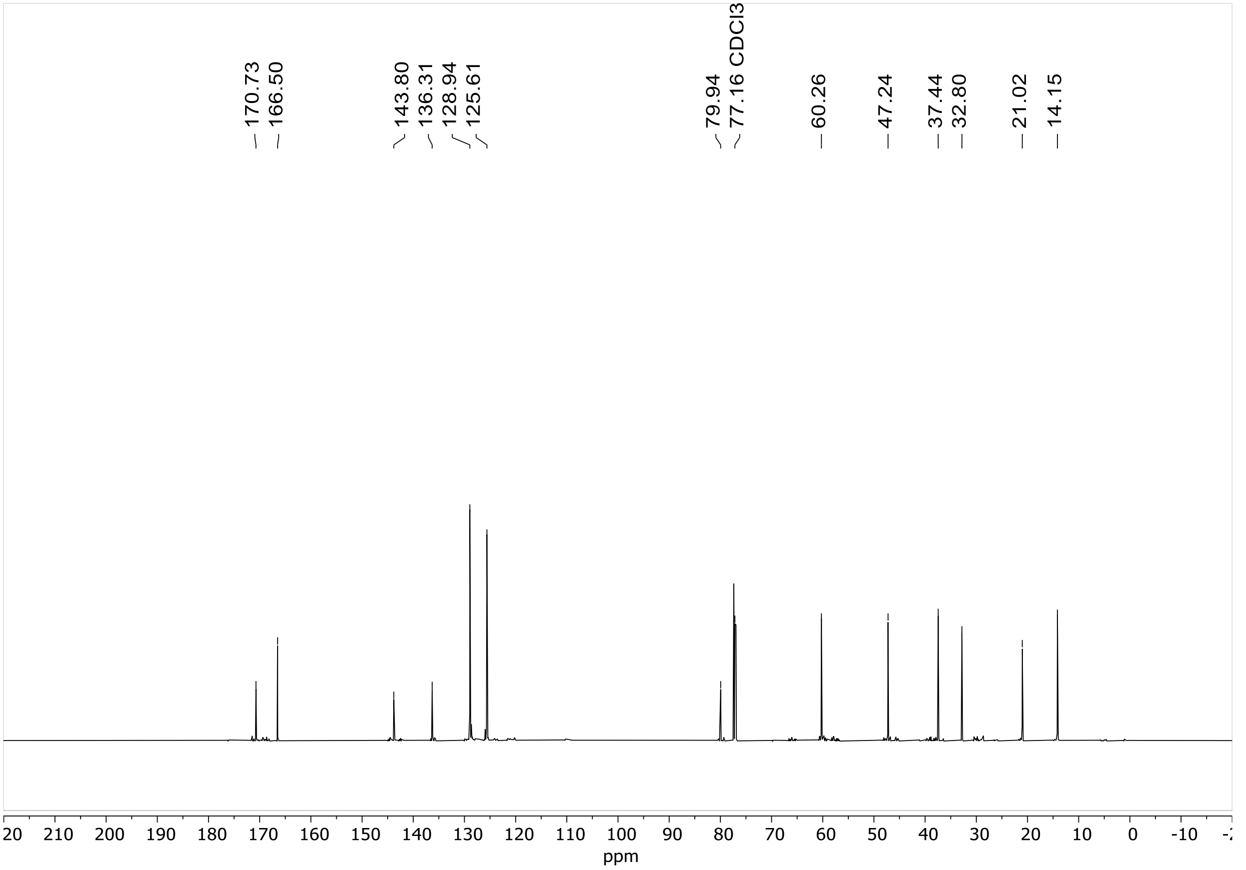
2ae' ^{13}C NMR (151 MHz, CDCl$_3$)



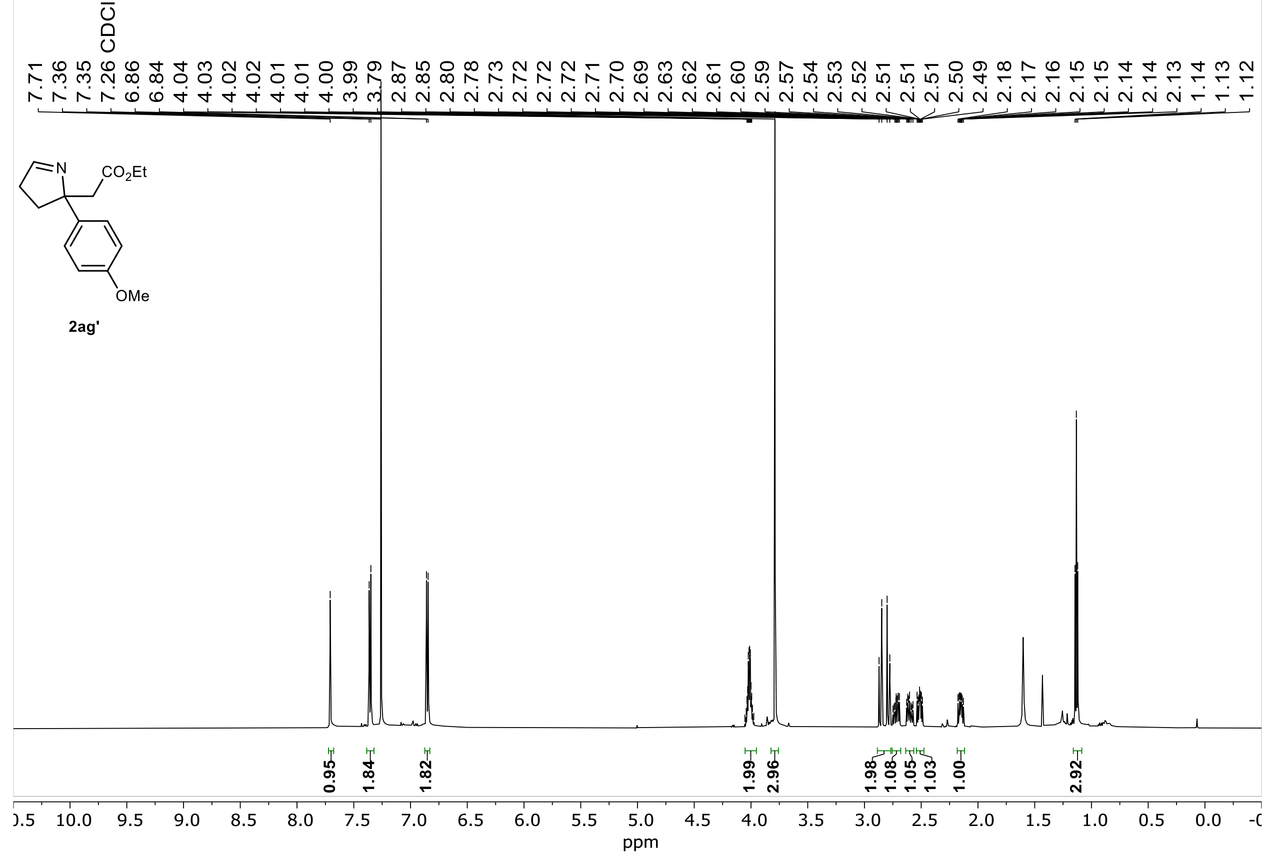
2af’, ^{1}H NMR (600 MHz, CDCl$_3$)



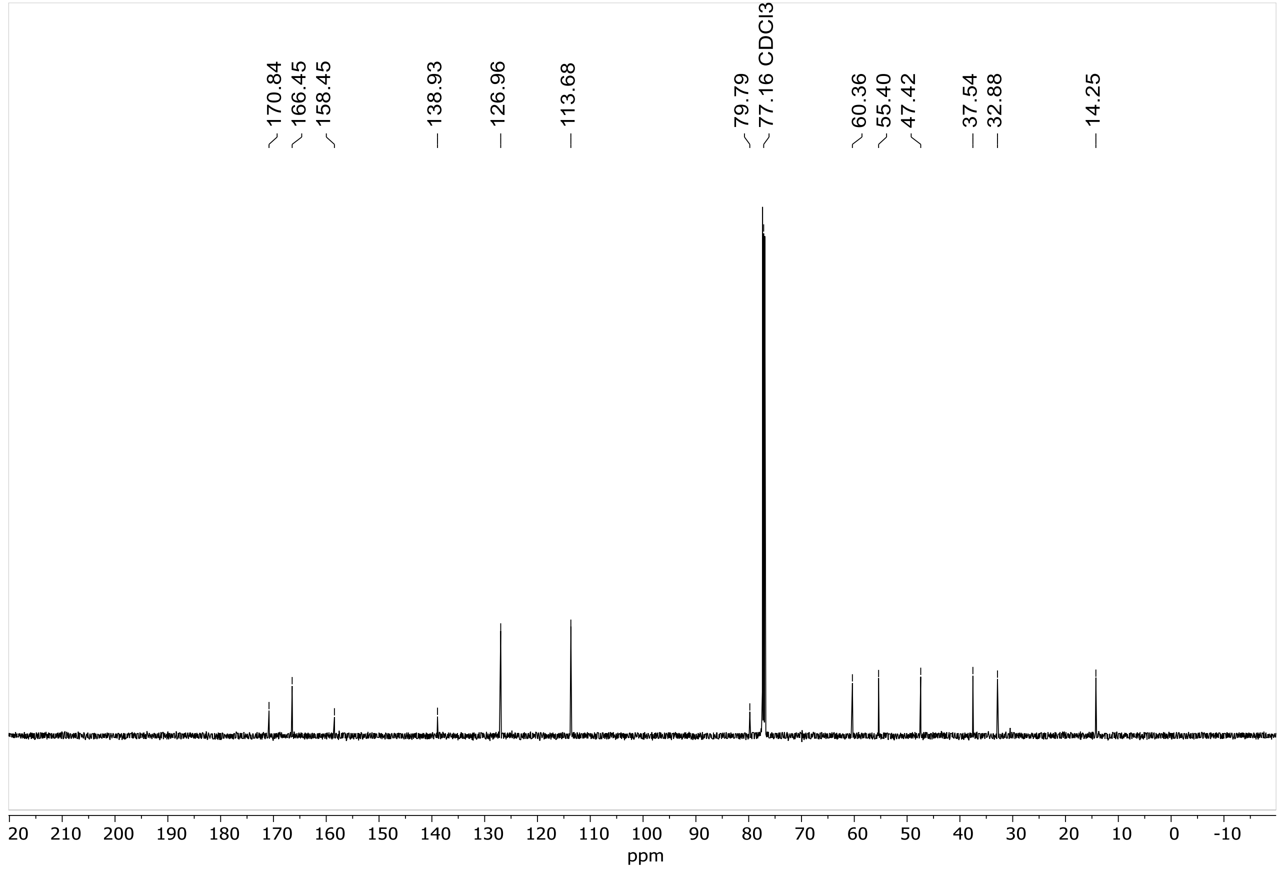
2af’, ^{13}C NMR (151 MHz, CDCl$_3$)



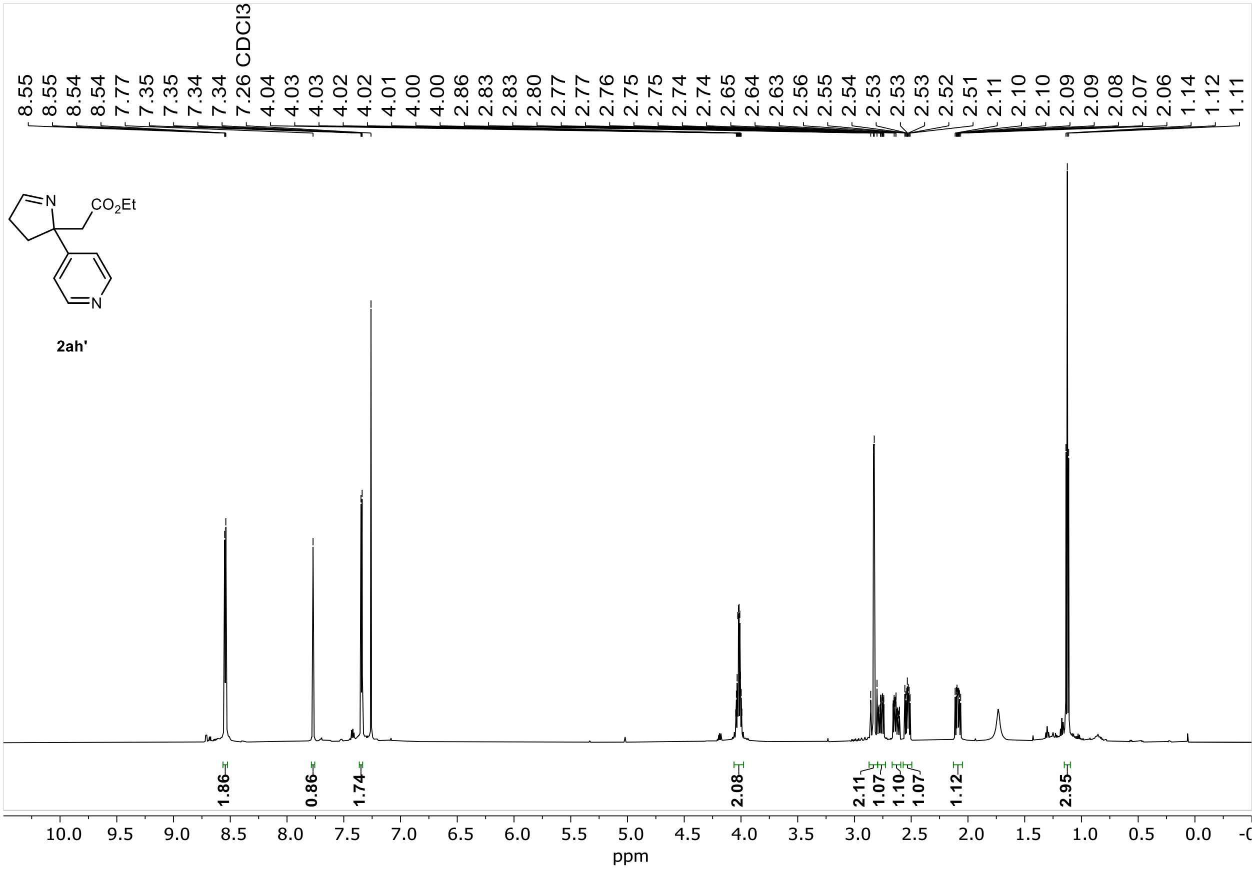
2ag’, ^{1}H NMR (600 MHz, CDCl$_3$)



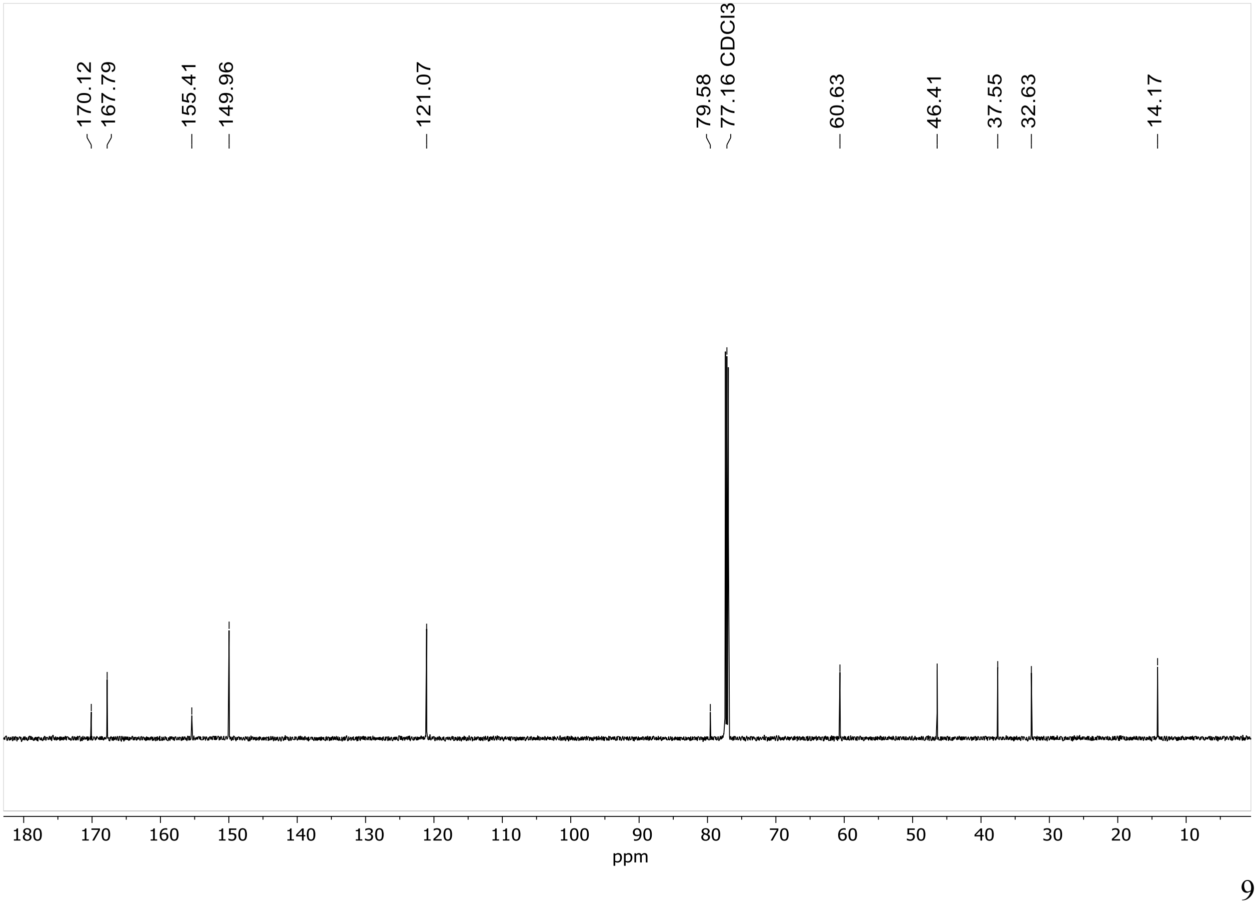
2ag’, ^{13}C NMR (151 MHz, CDCl$_3$)



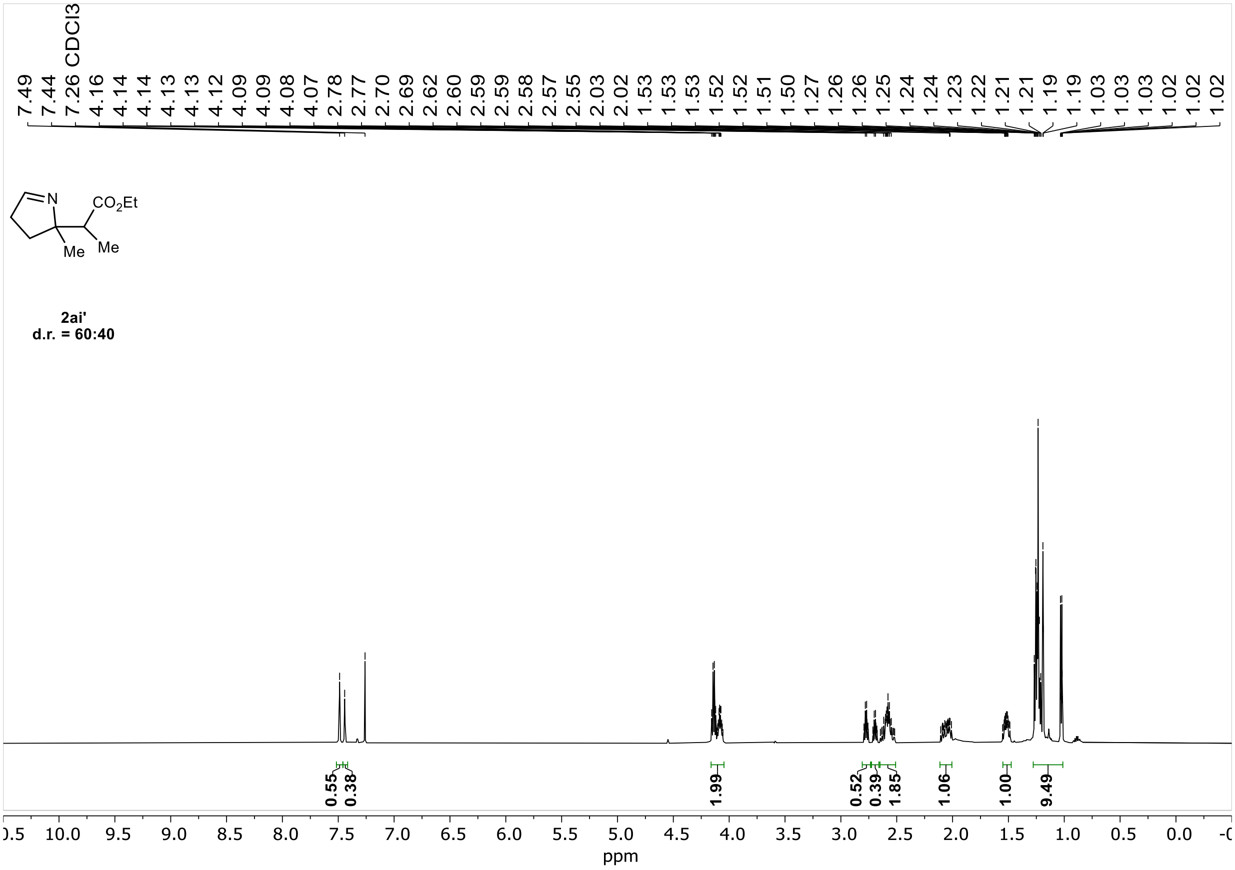
2ah’, ^{1}H NMR (600 MHz, CDCl$_3$)



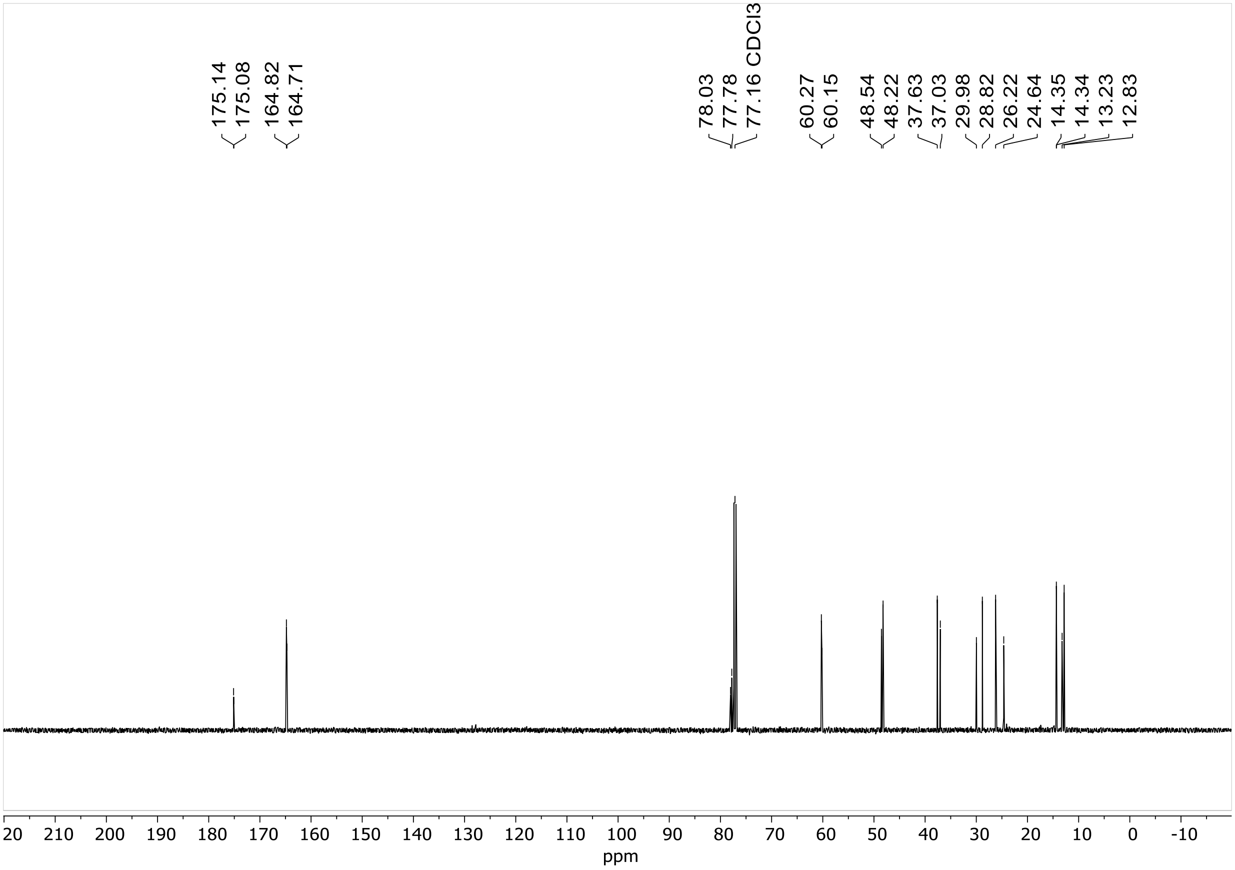
2ah’, ^{13}C NMR (151 MHz, CDCl$_3$)



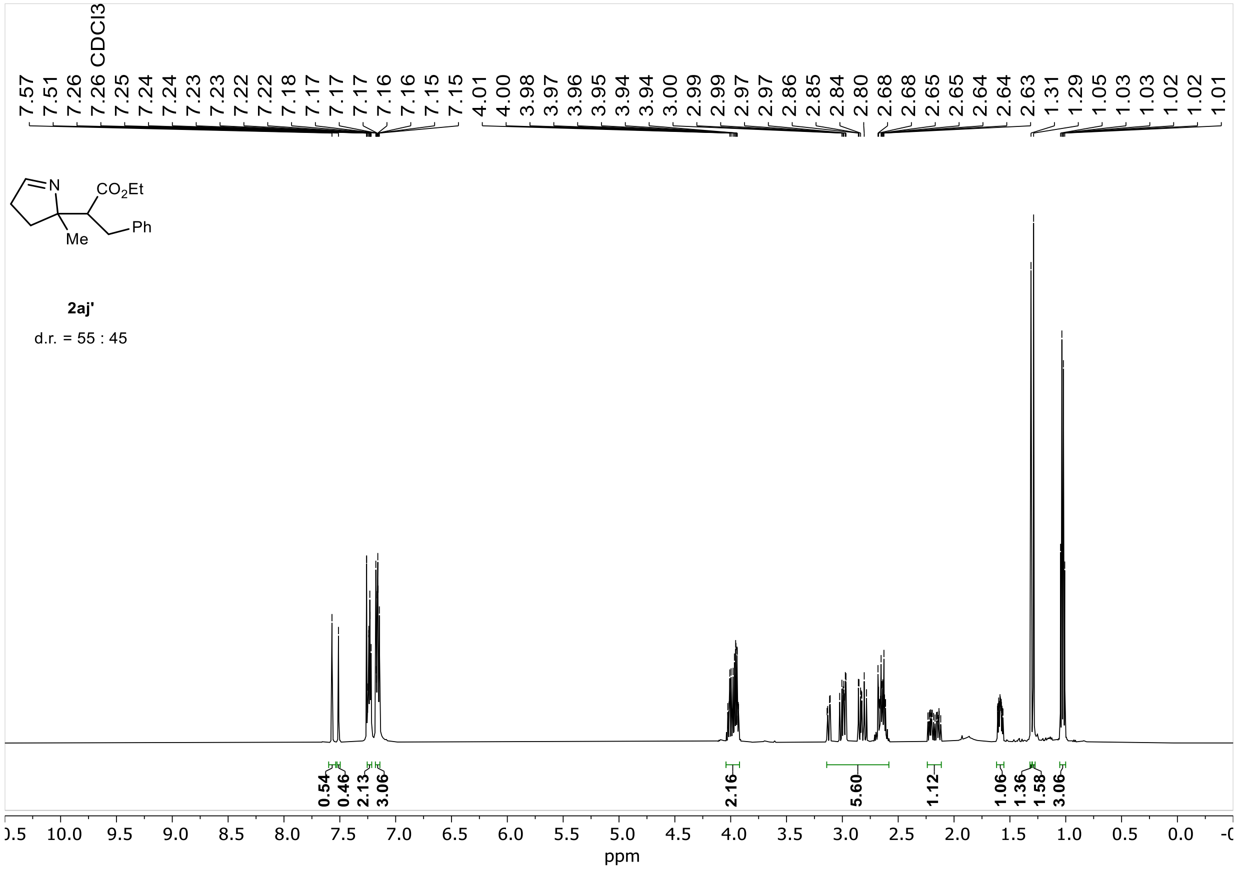
2ai', ^{1}H NMR (600 MHz, CDCl$_3$)



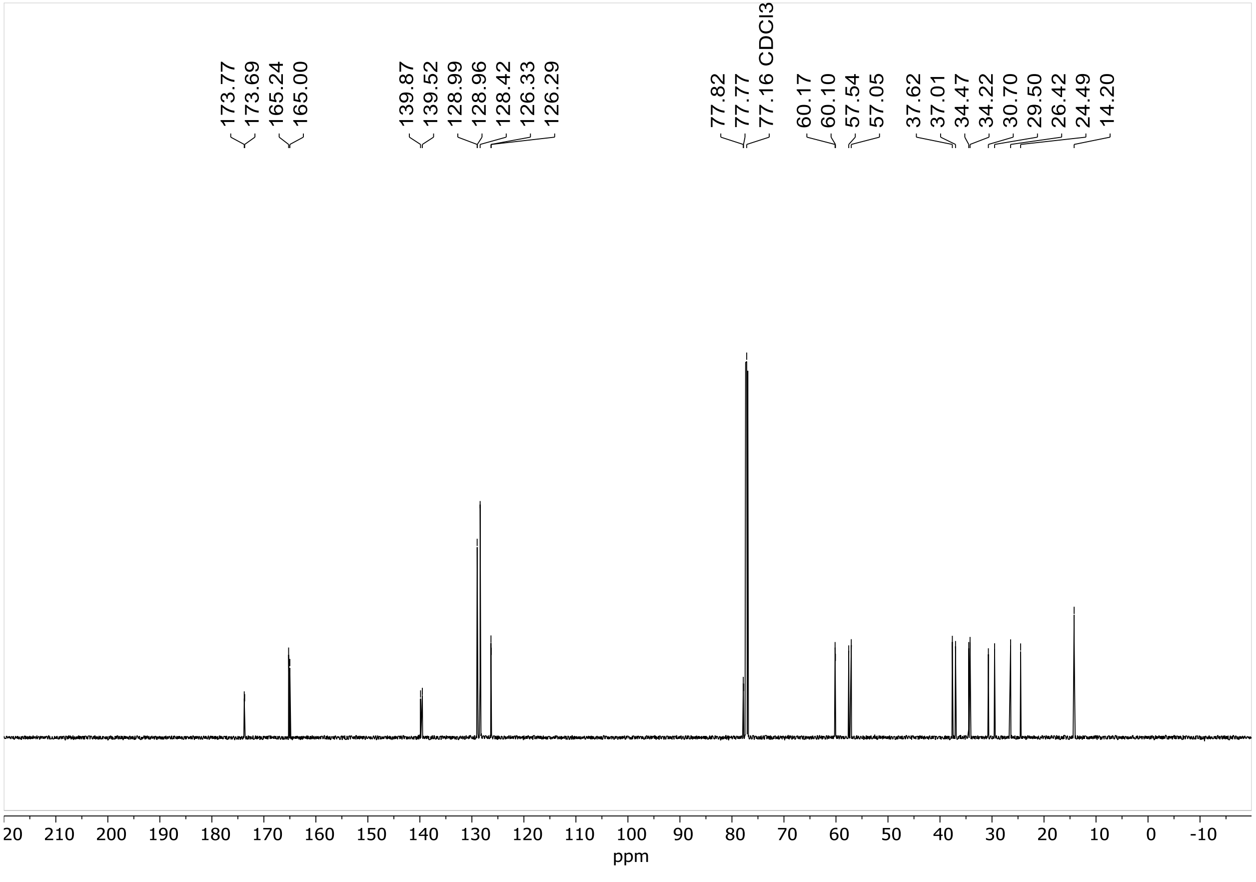
2ai', ^{13}C NMR (151 MHz, CDCl$_3$)



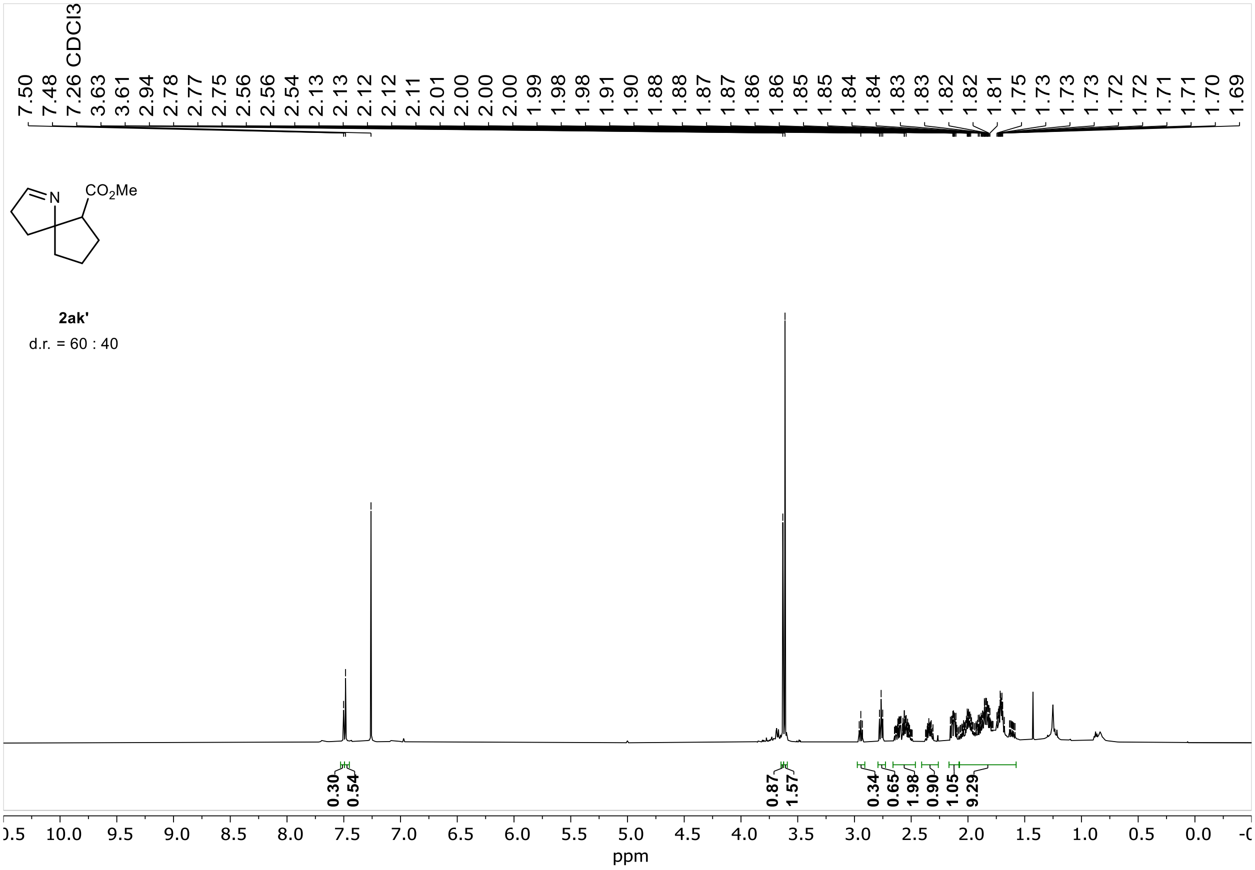
2aj', ^{1}H NMR (600 MHz, CDCl$_3$)



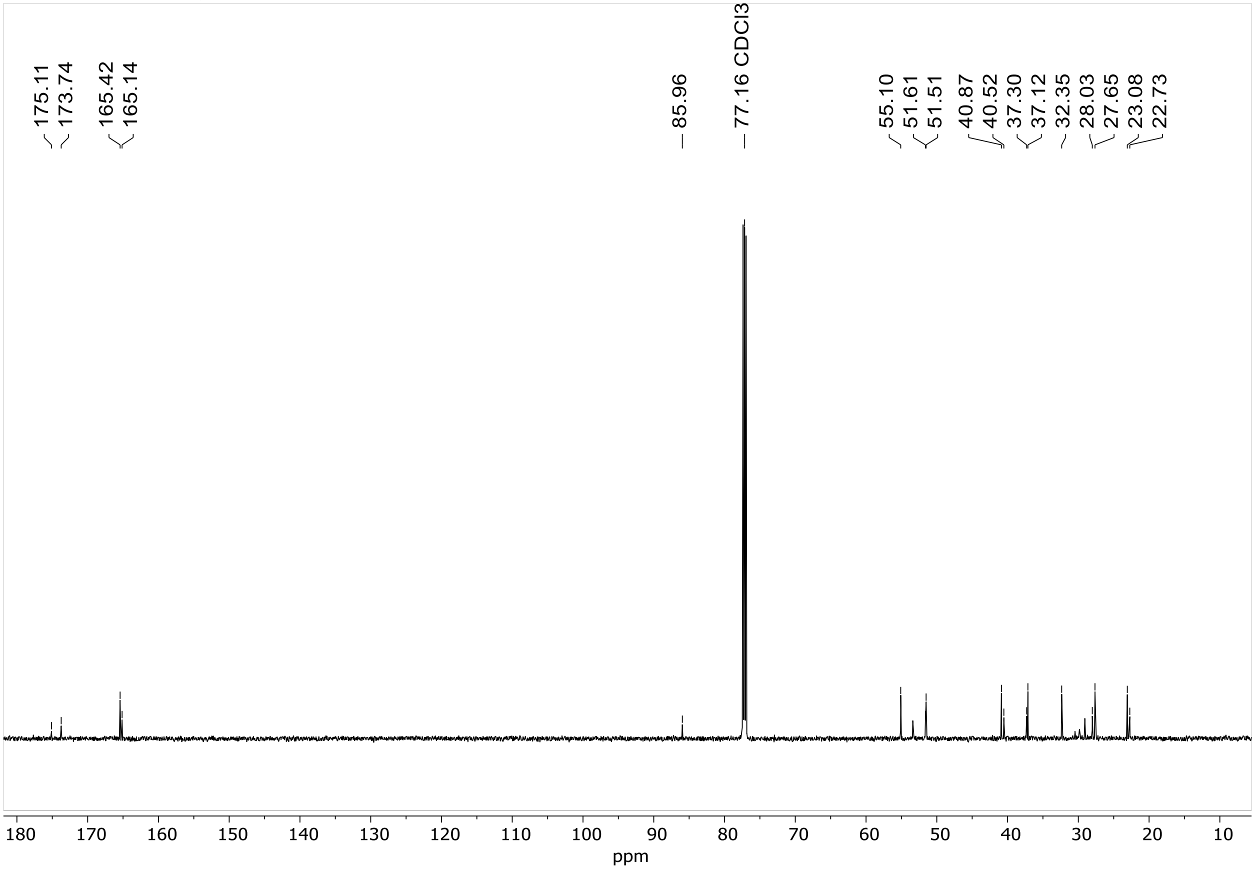
2aj', ^{13}C NMR (151 MHz, CDCl$_3$)



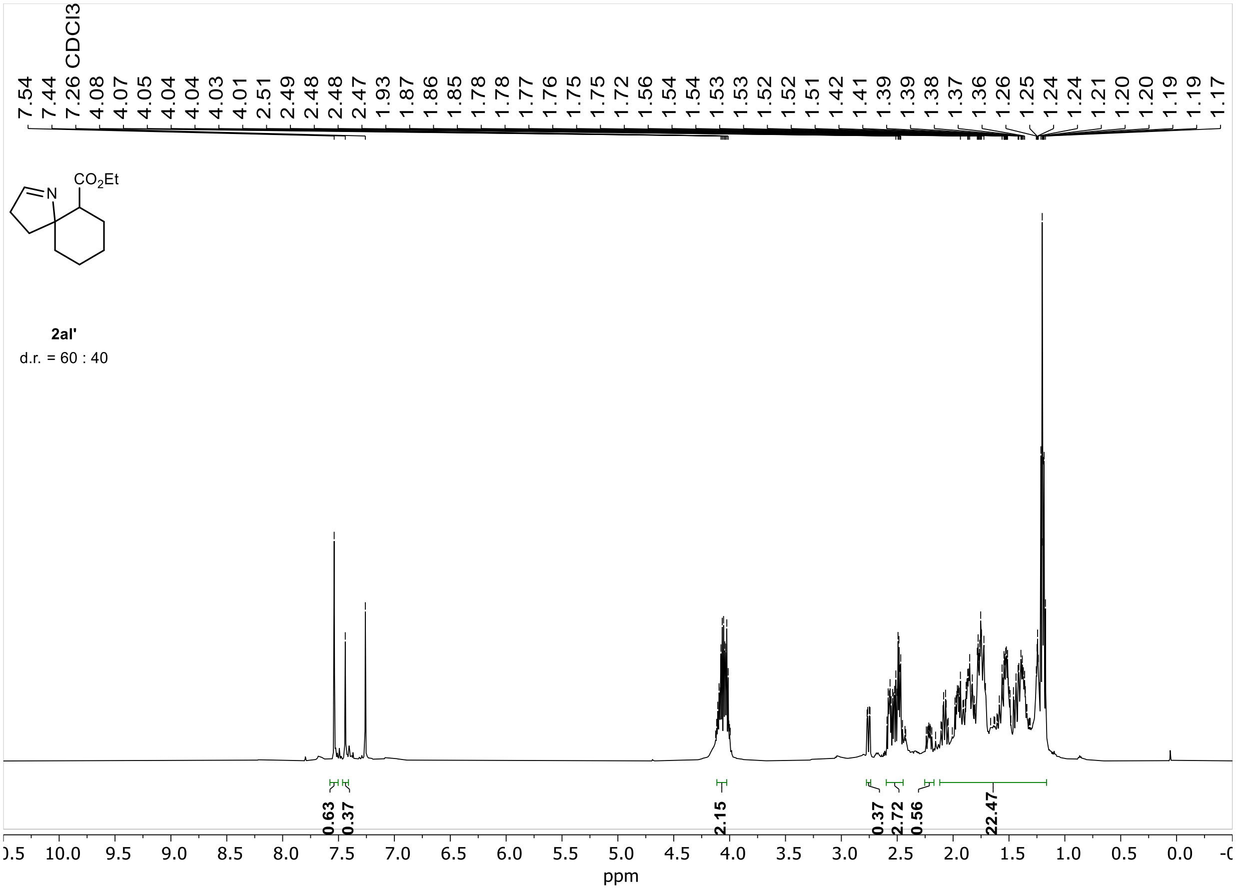
2ak', ^{1}H NMR (600 MHz, $CDCl_3$)



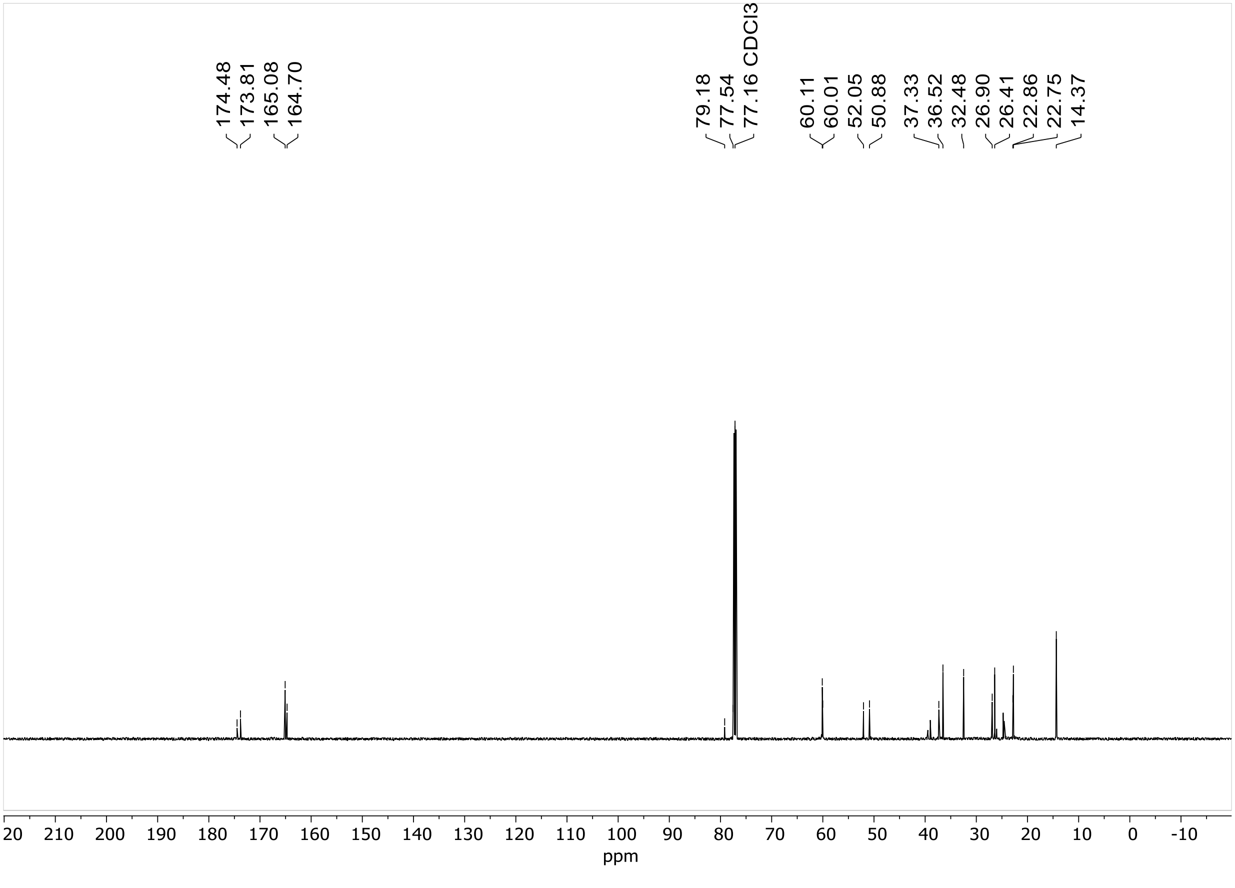
2ak', ^{13}C NMR (151 MHz, $CDCl_3$)



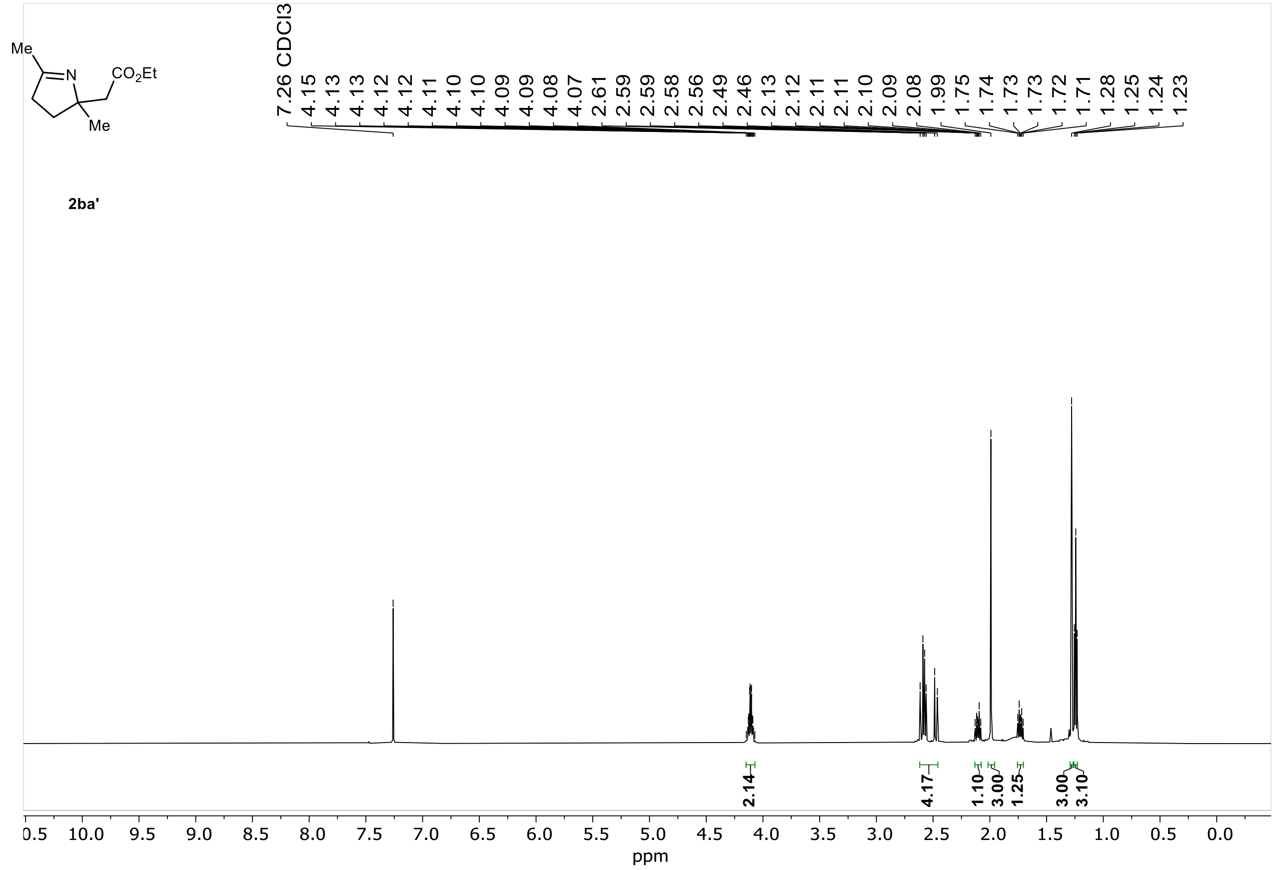
2al’,^{1}H NMR (600 MHz, CDCl$_3$)



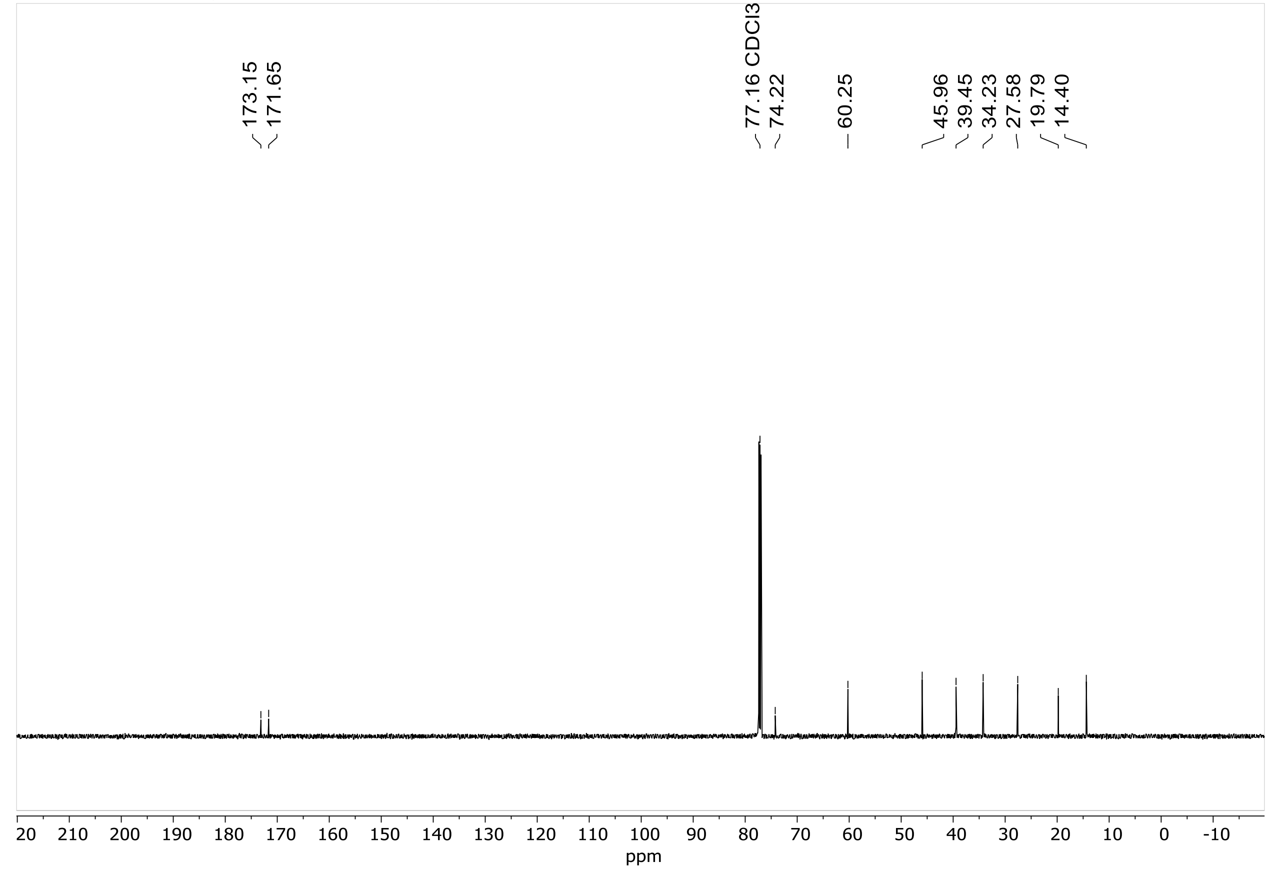
2al’,^{13}C NMR (151 MHz, CDCl$_3$)



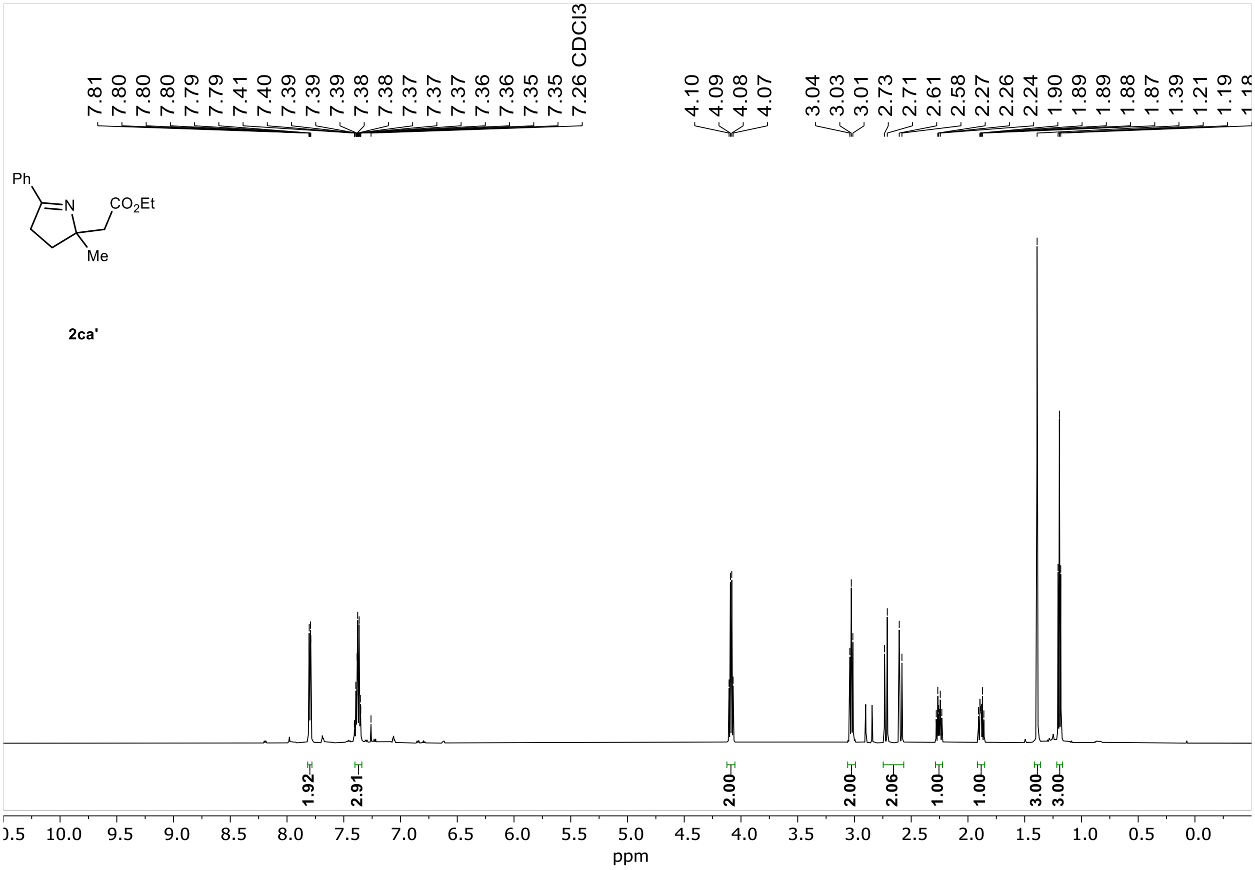
2ba', ^{1}H NMR (600 MHz, CDCl$_3$)



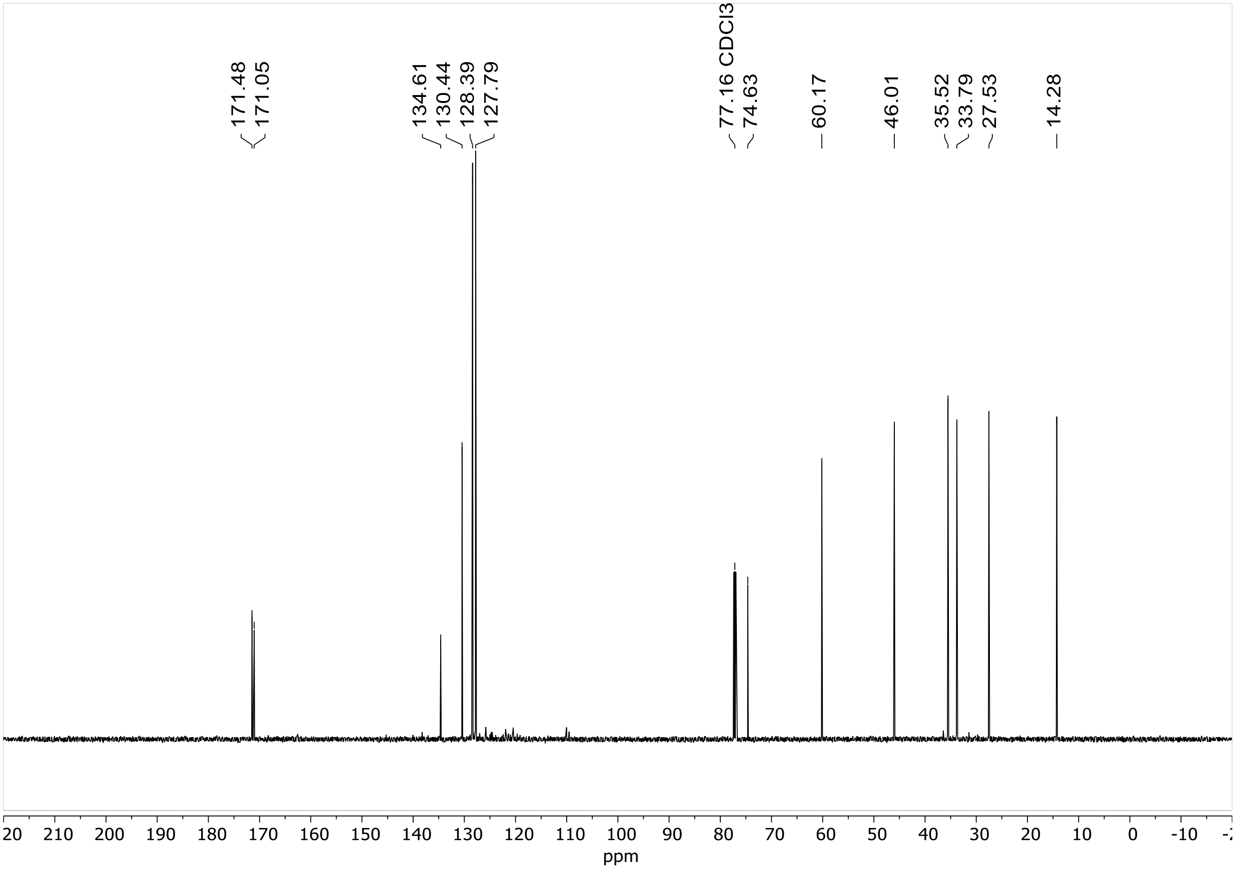
2ba', ^{13}C NMR (151 MHz, CDCl$_3$)



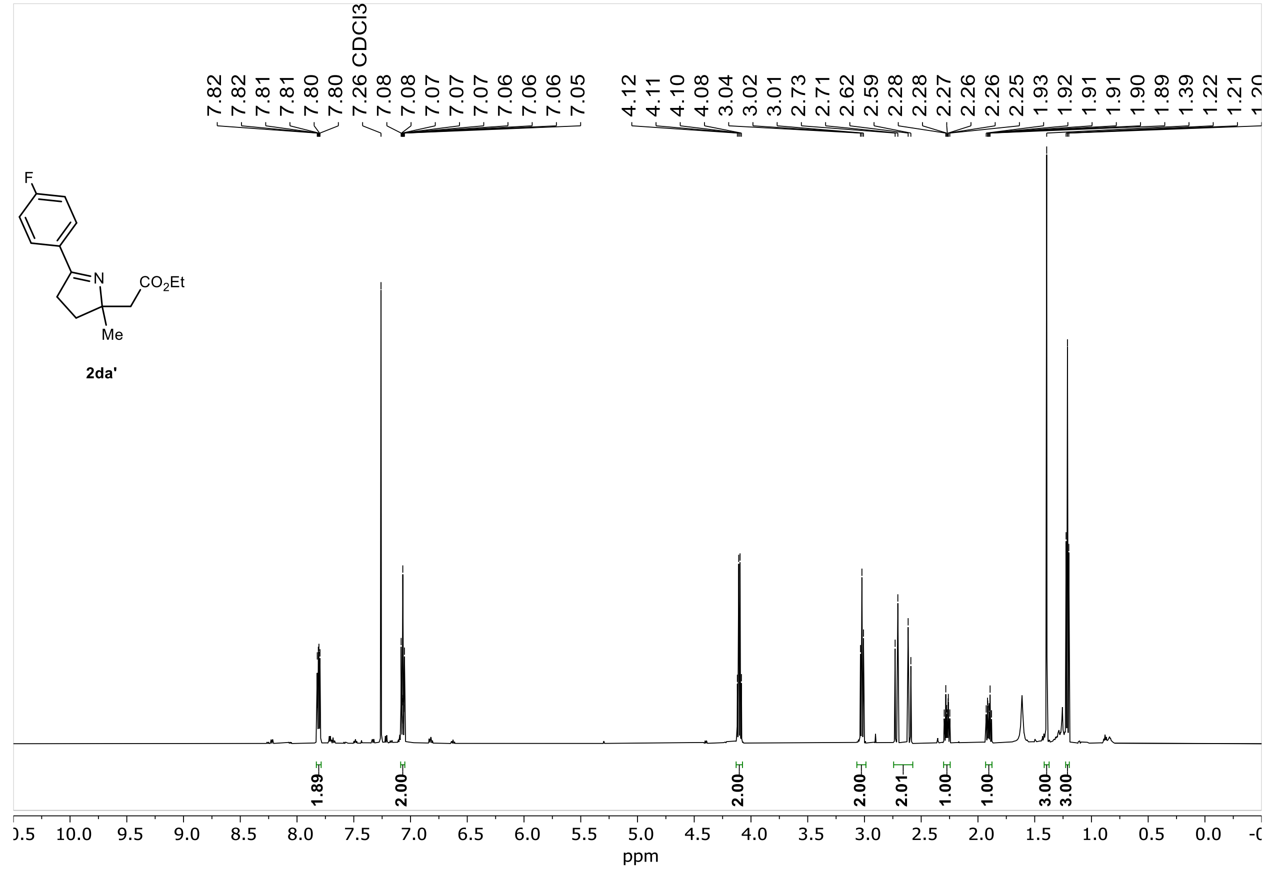
2ca', ^{1}H NMR (600 MHz, CDCl$_3$)



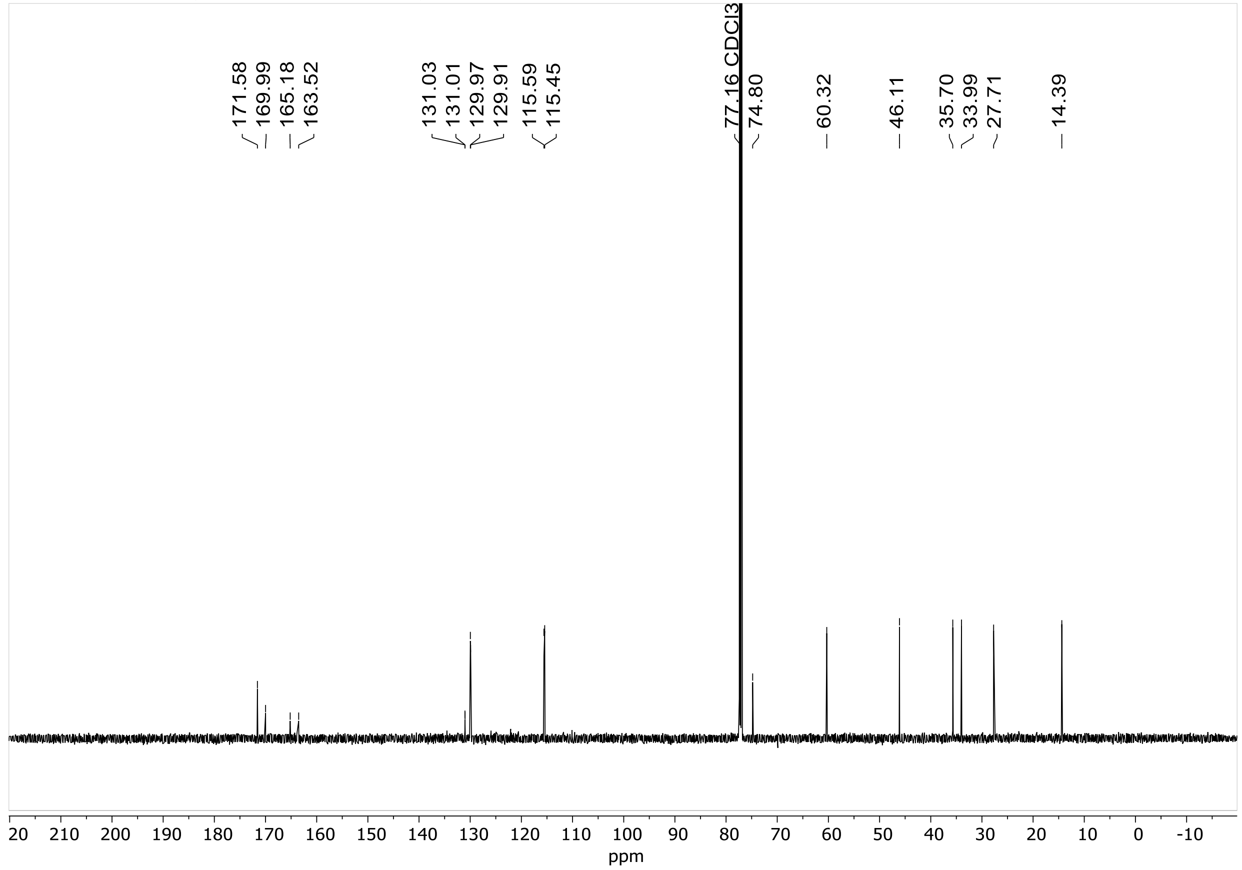
2ca', ^{13}C NMR (151 MHz, CDCl$_3$)



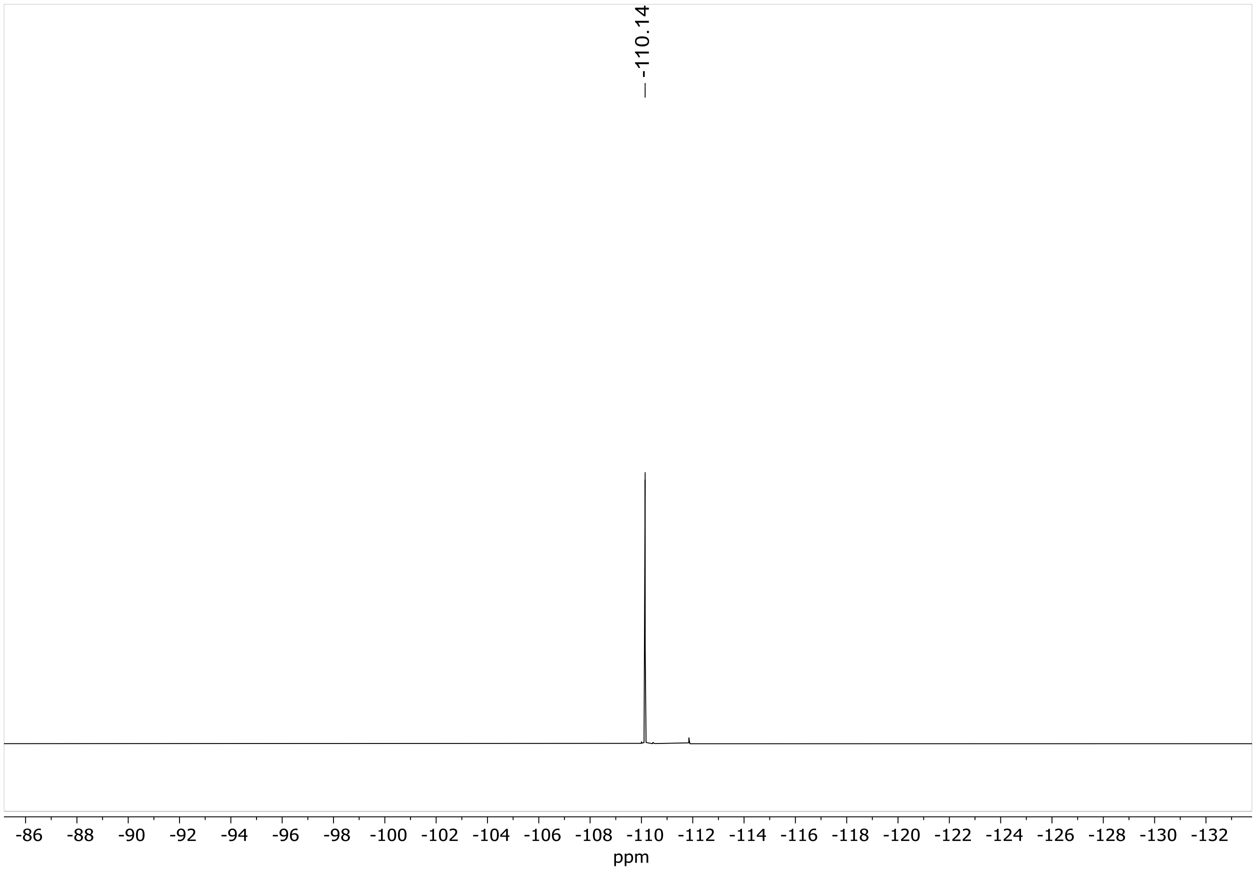
2da', ^{1}H NMR (600 MHz, CDCl$_3$)



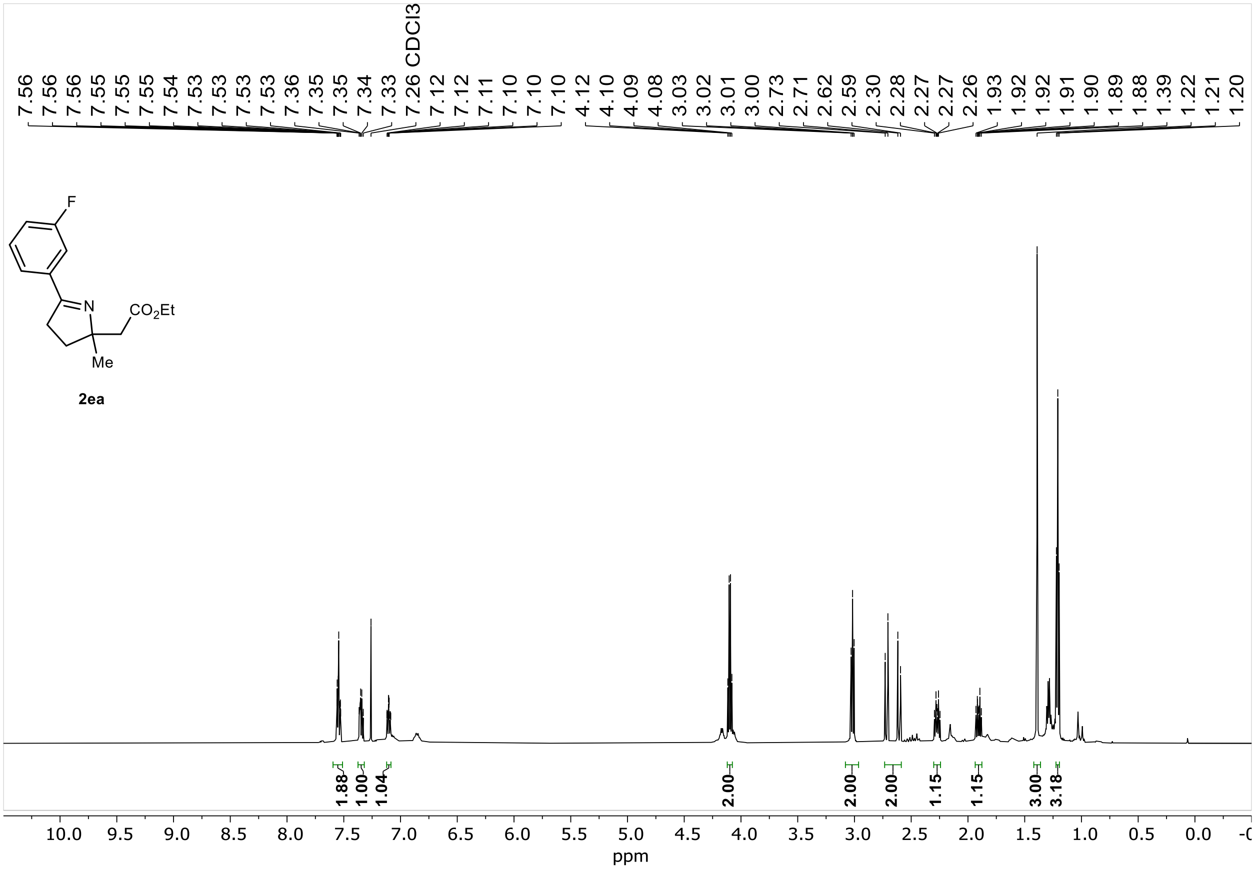
2da', ^{13}C NMR (151 MHz, CDCl$_3$)



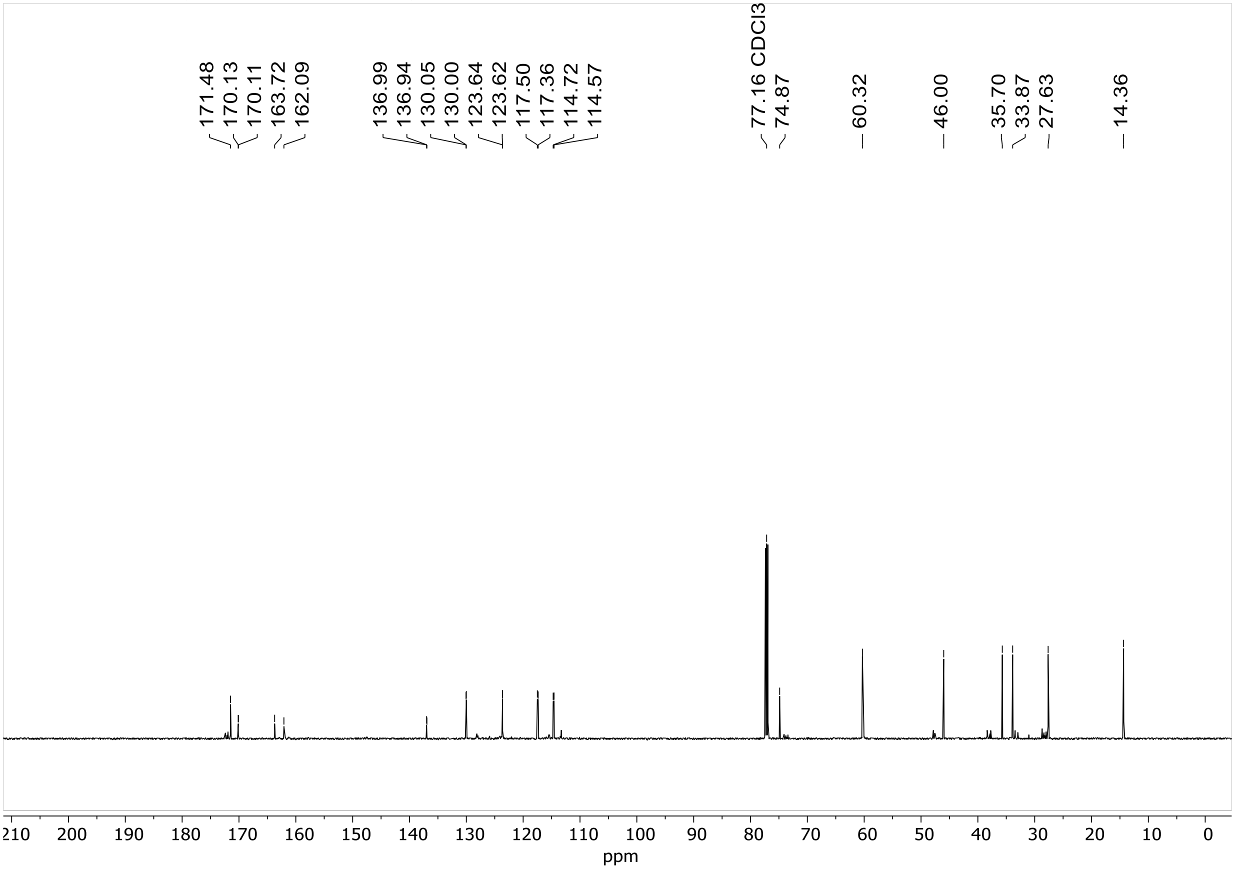
2da’, ^{19}F NMR (565 MHz, CDCl$_3$)



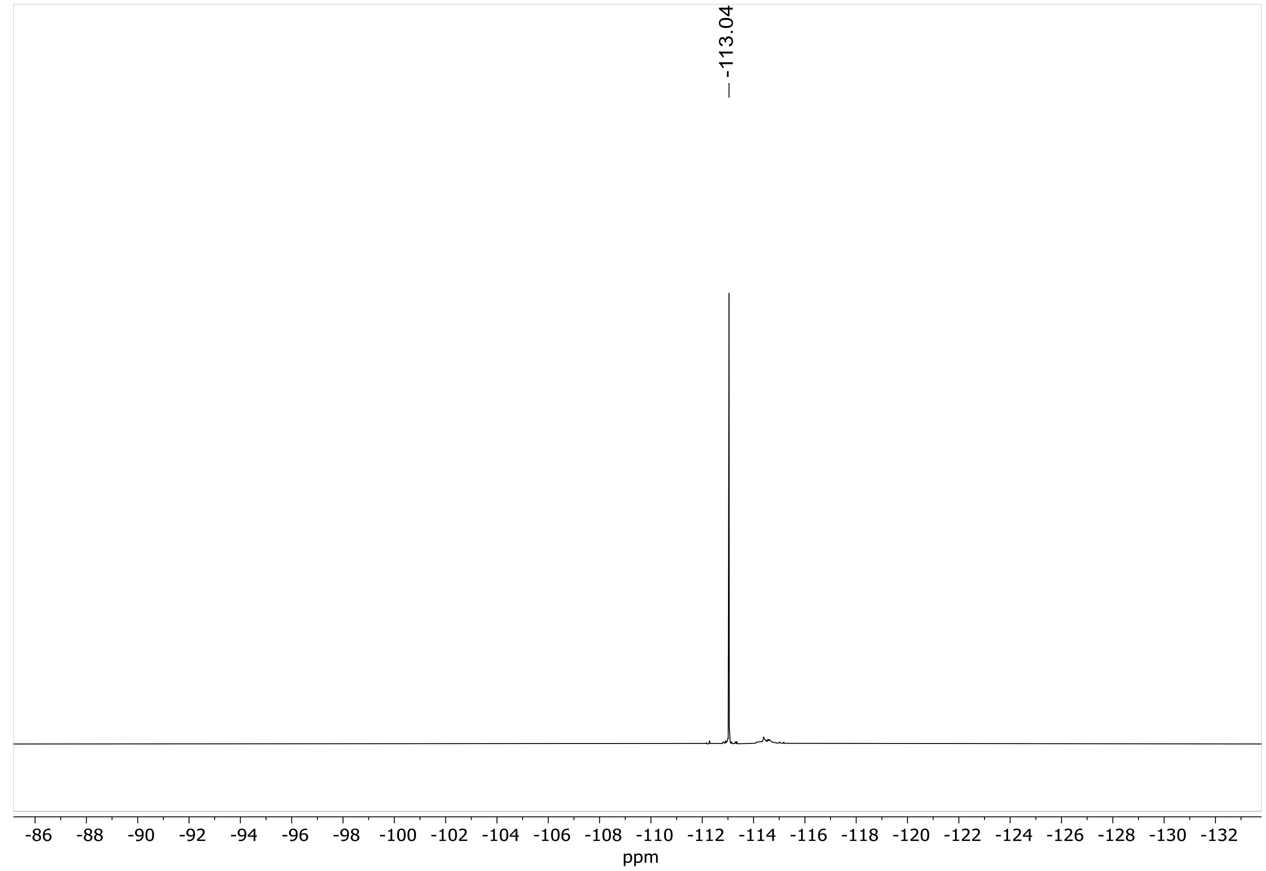
2ea', ^{1}H NMR (600 MHz, CDCl$_3$)



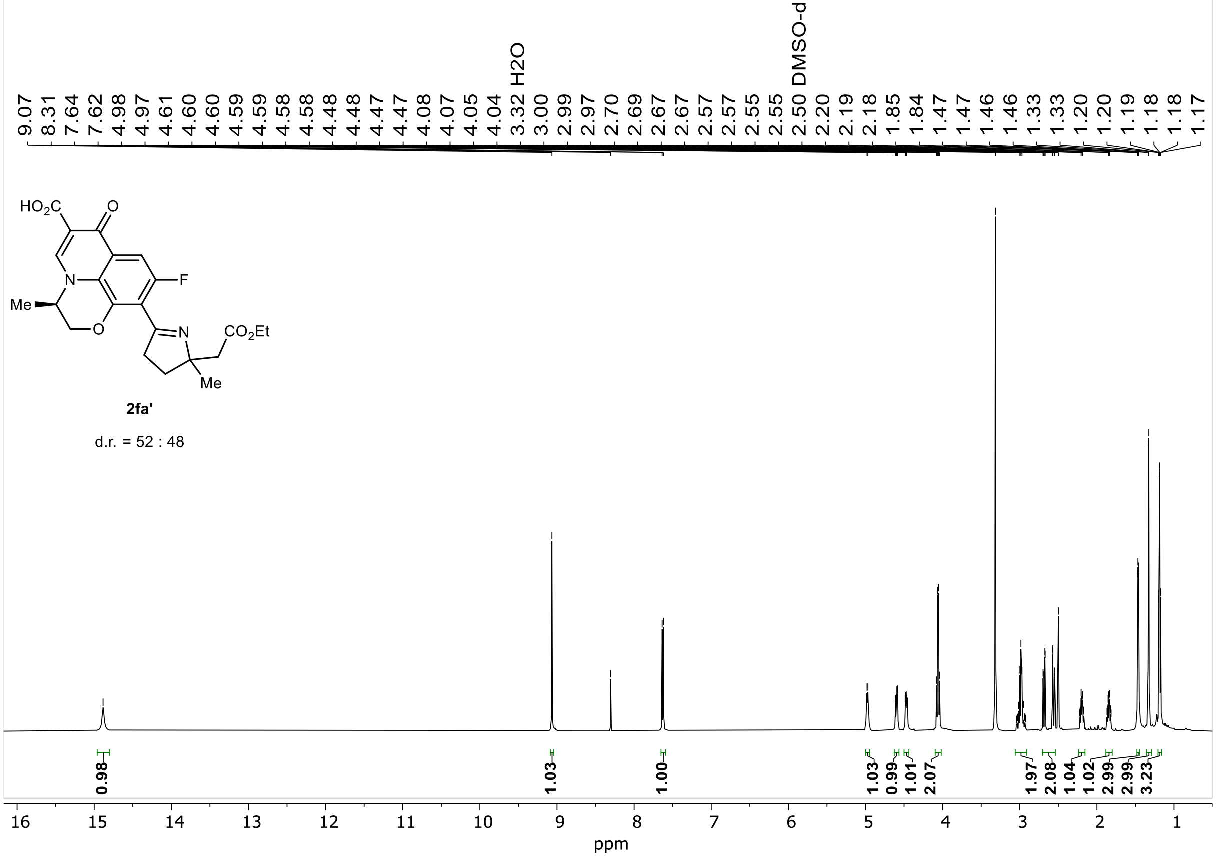
2ea', ^{13}C NMR (151 MHz, CDCl$_3$)



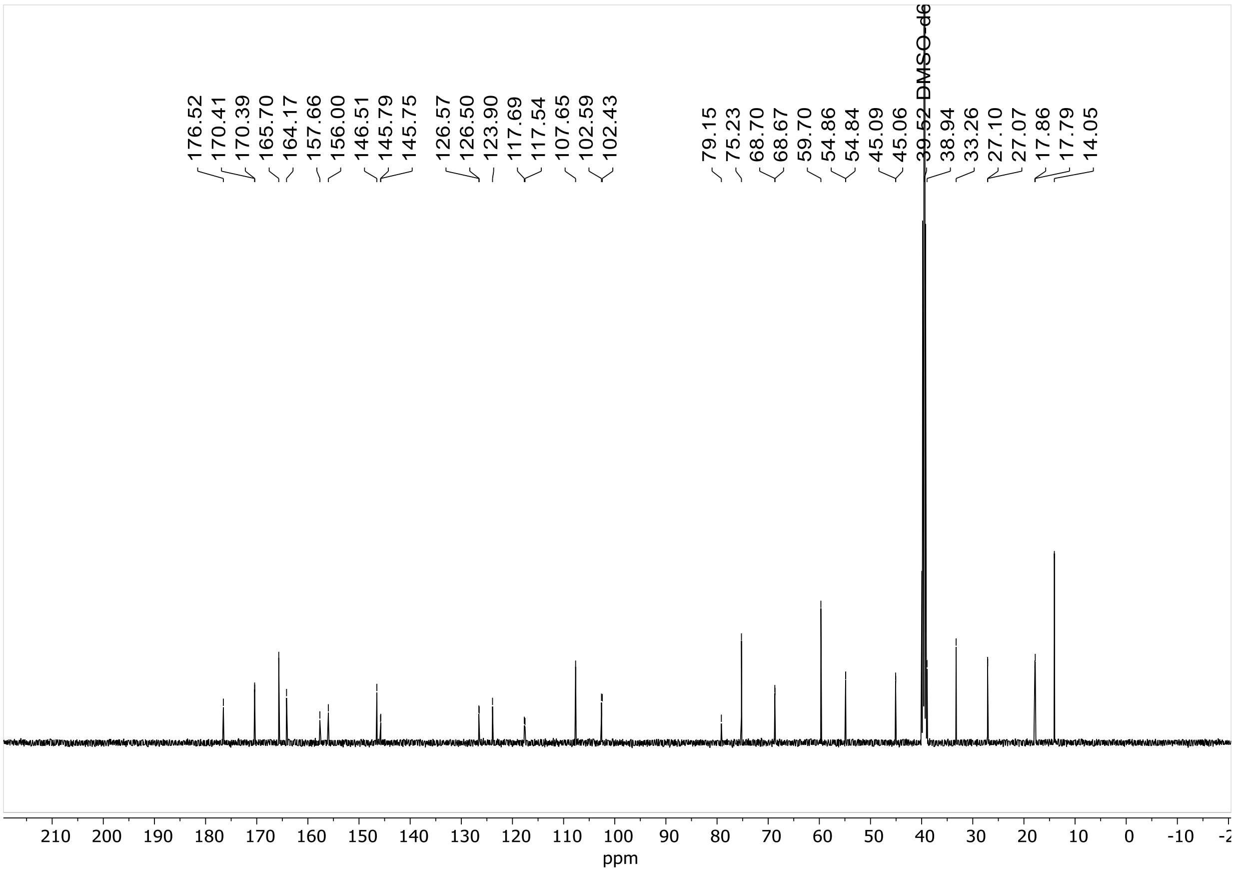
2ea', ^{19}F NMR (565 MHz, CDCl$_3$)



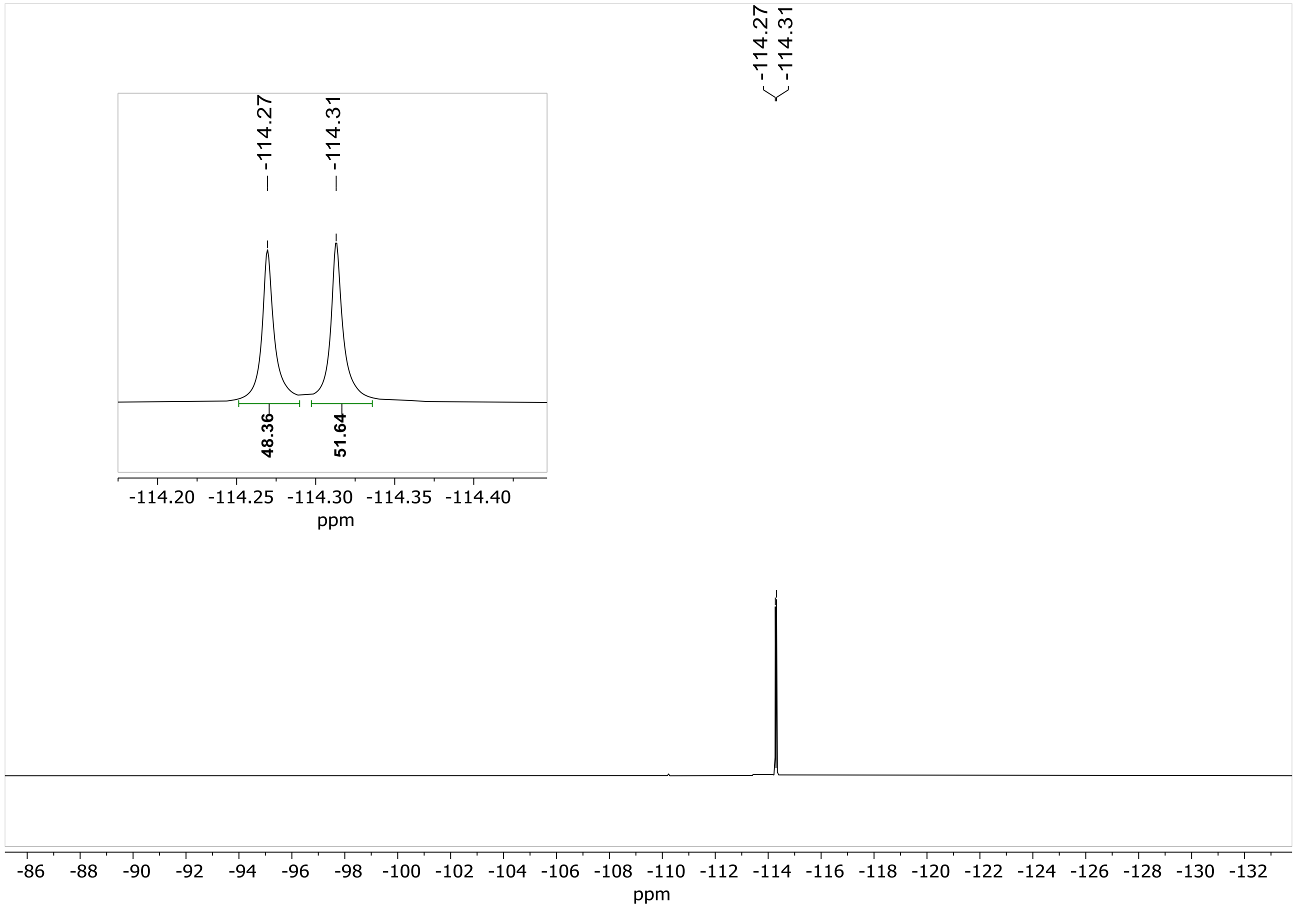
2fa', ^{1}H NMR (600 MHz, DMSO)



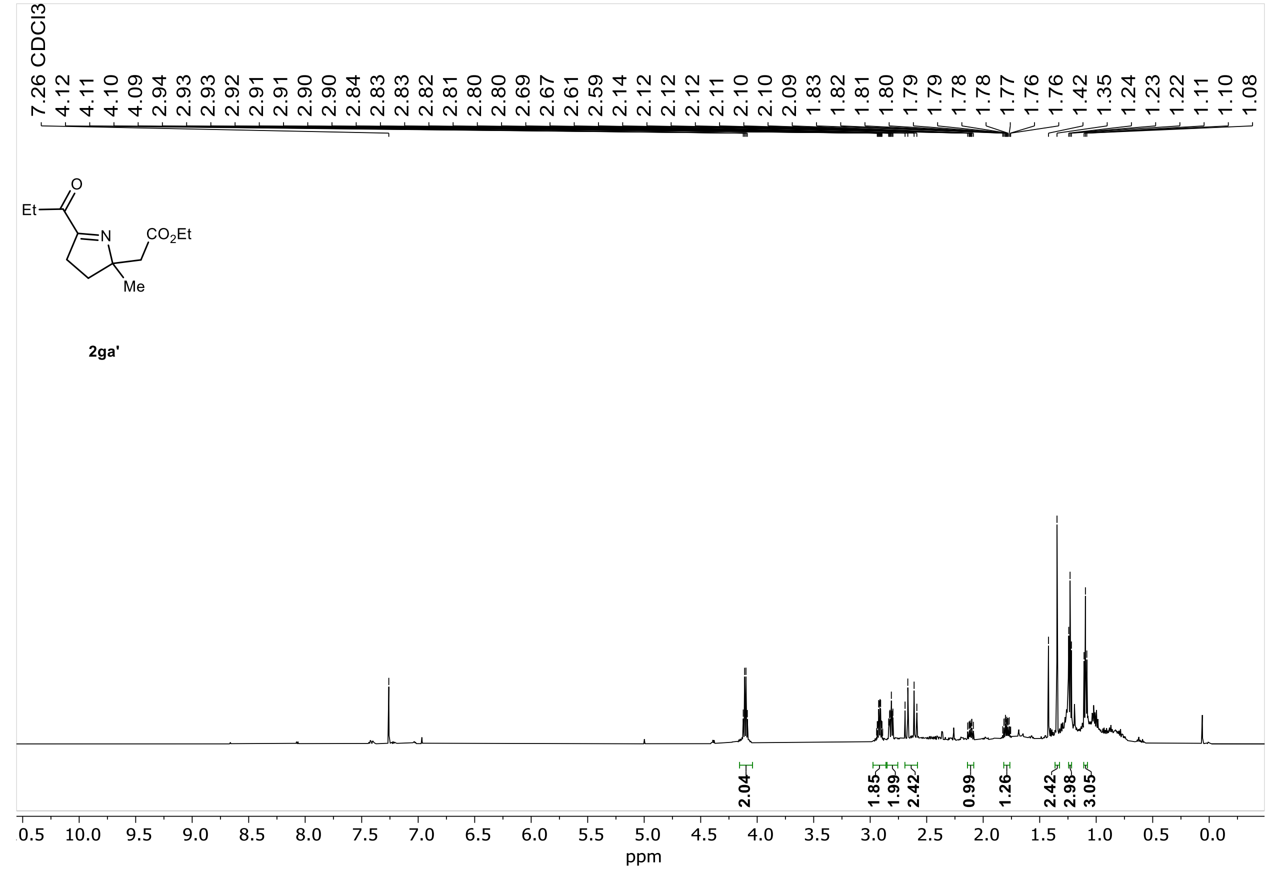
2fa', ^{13}C NMR (151 MHz, DMSO)



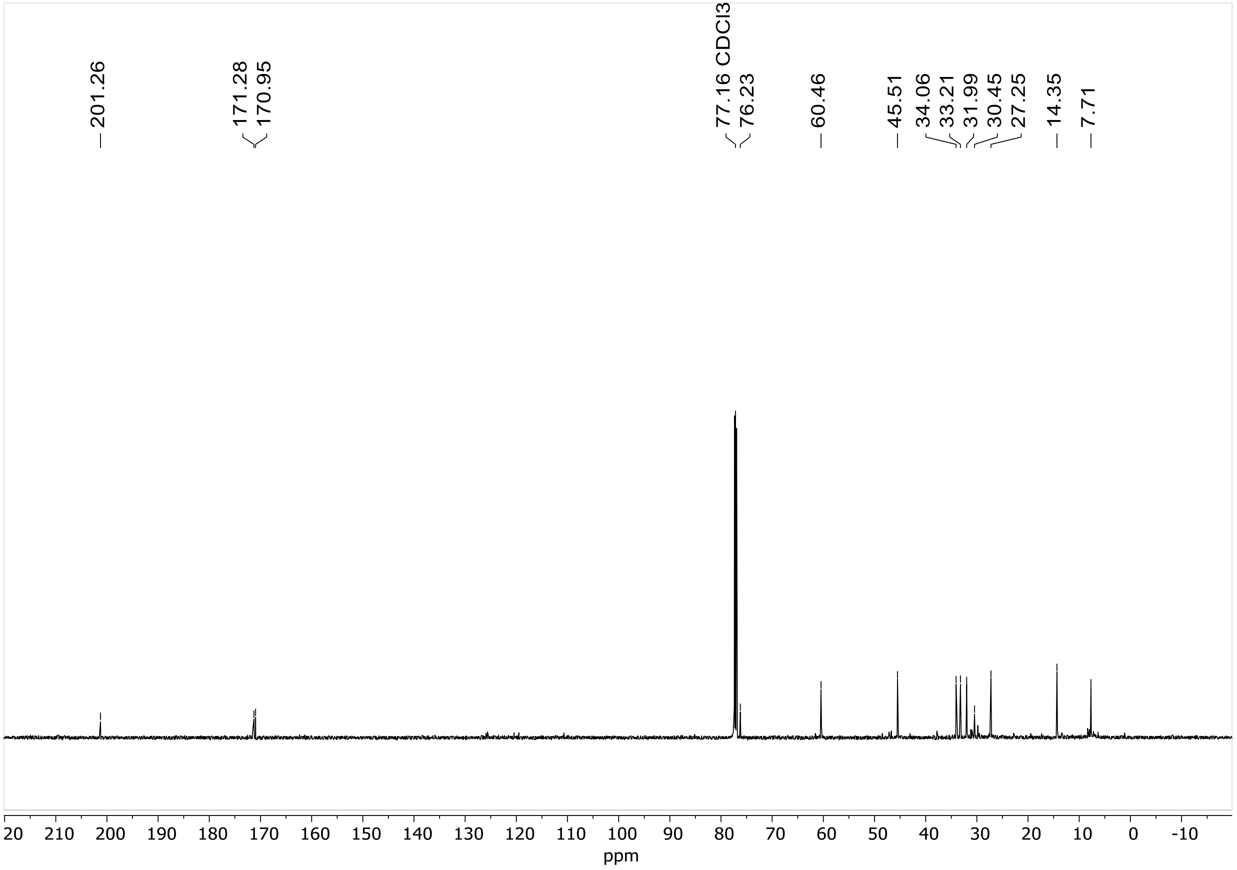
2fa',^{19}F NMR (565 MHz, DMSO)



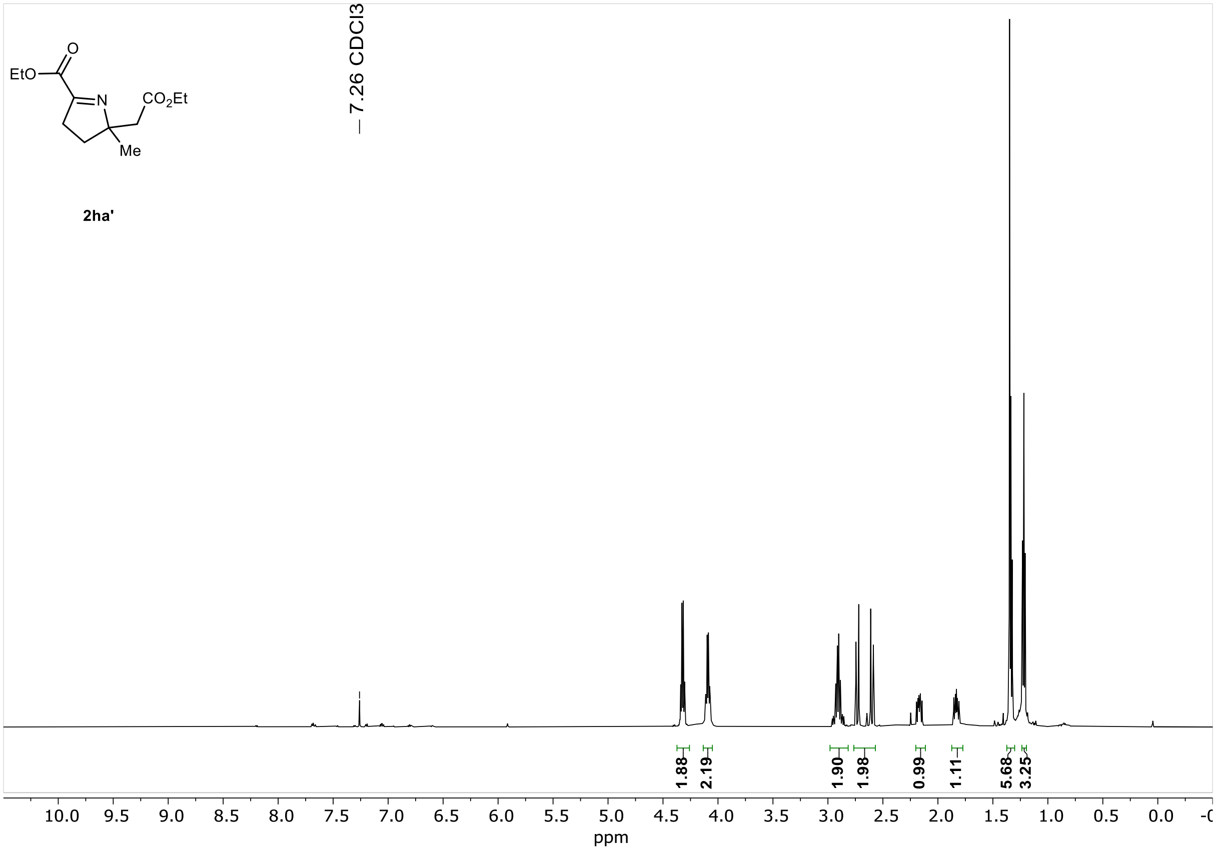
2ga', ^{1}H NMR (600 MHz, $CDCl_3$)



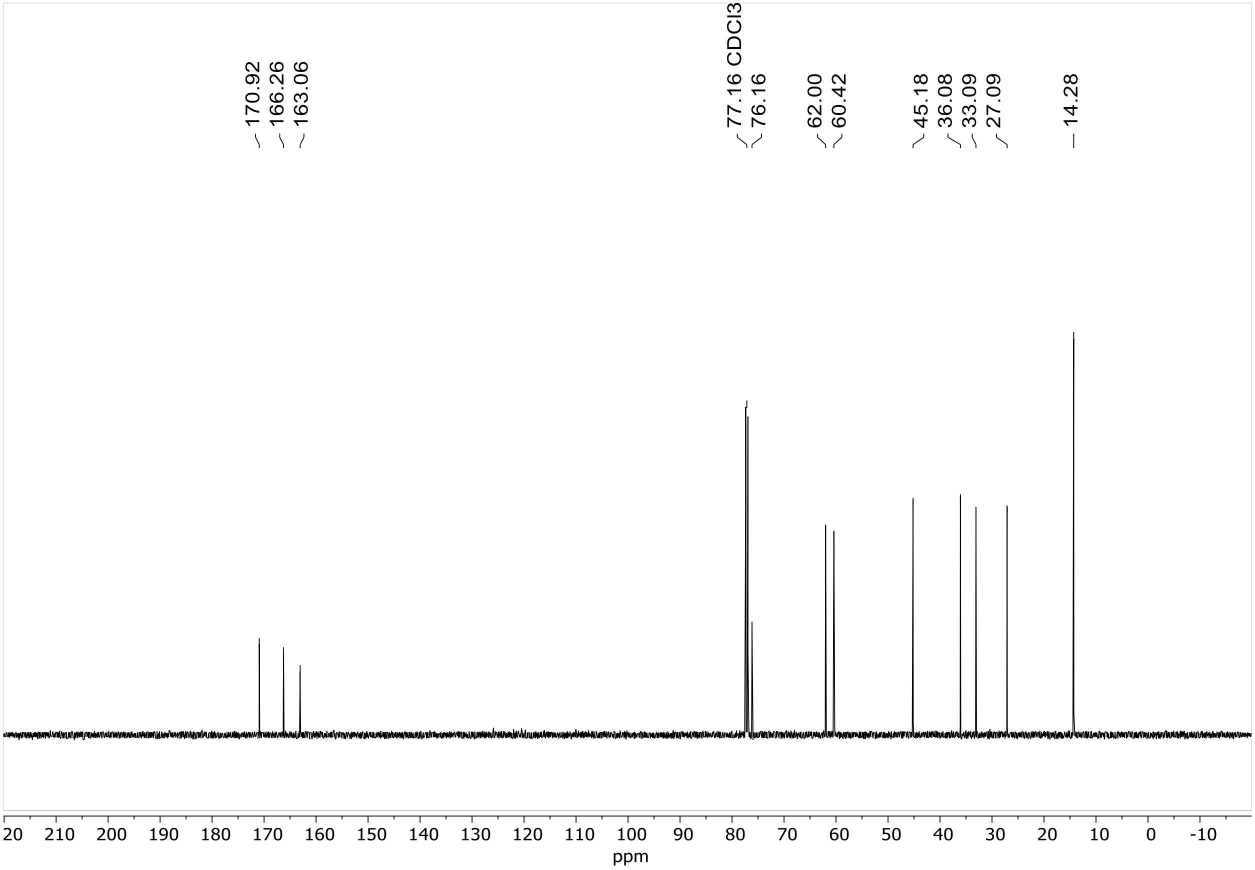
2ga', ^{13}C NMR (600 MHz, $CDCl_3$)



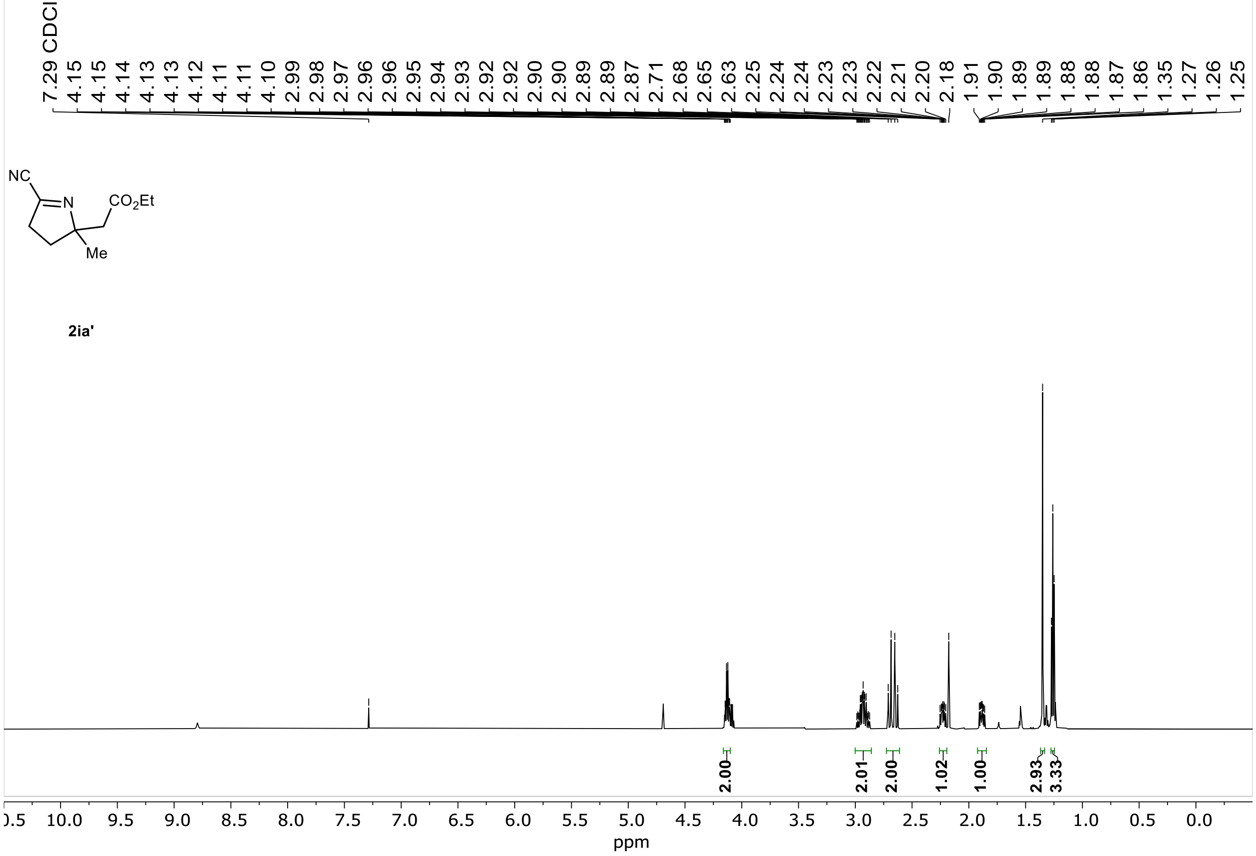
2ha’, ^{1}H NMR (600 MHz, $CDCl_3$)



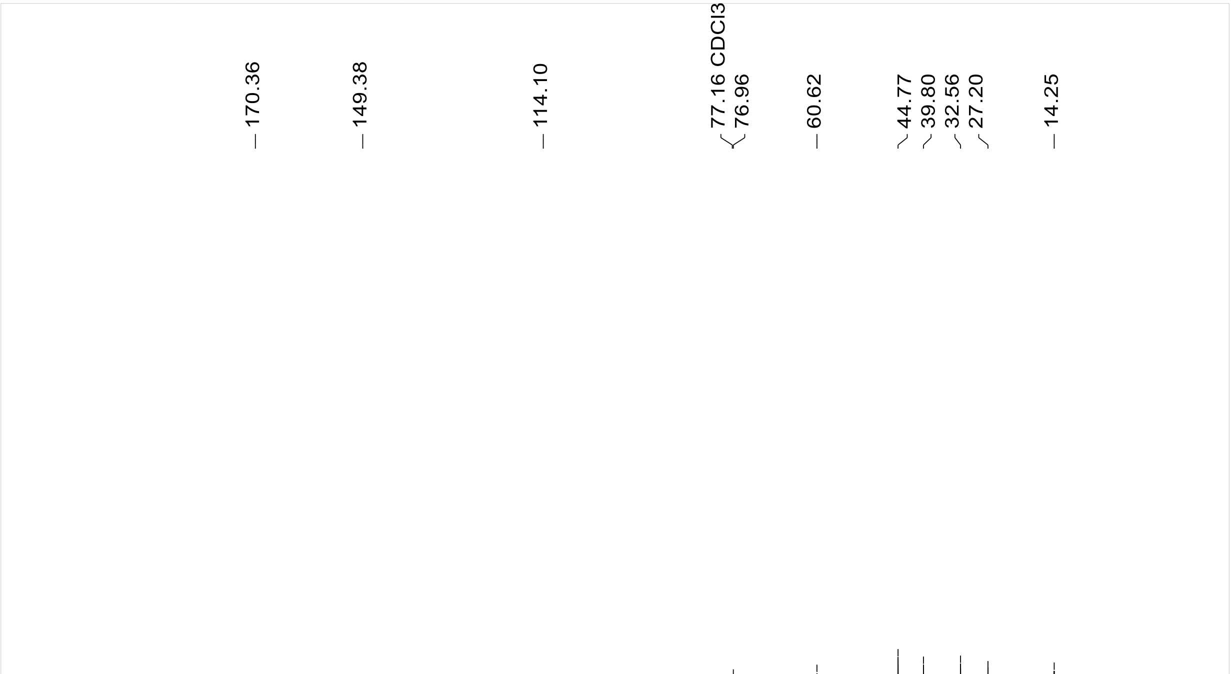
2ha’, ^{13}C NMR (600 MHz, $CDCl_3$)



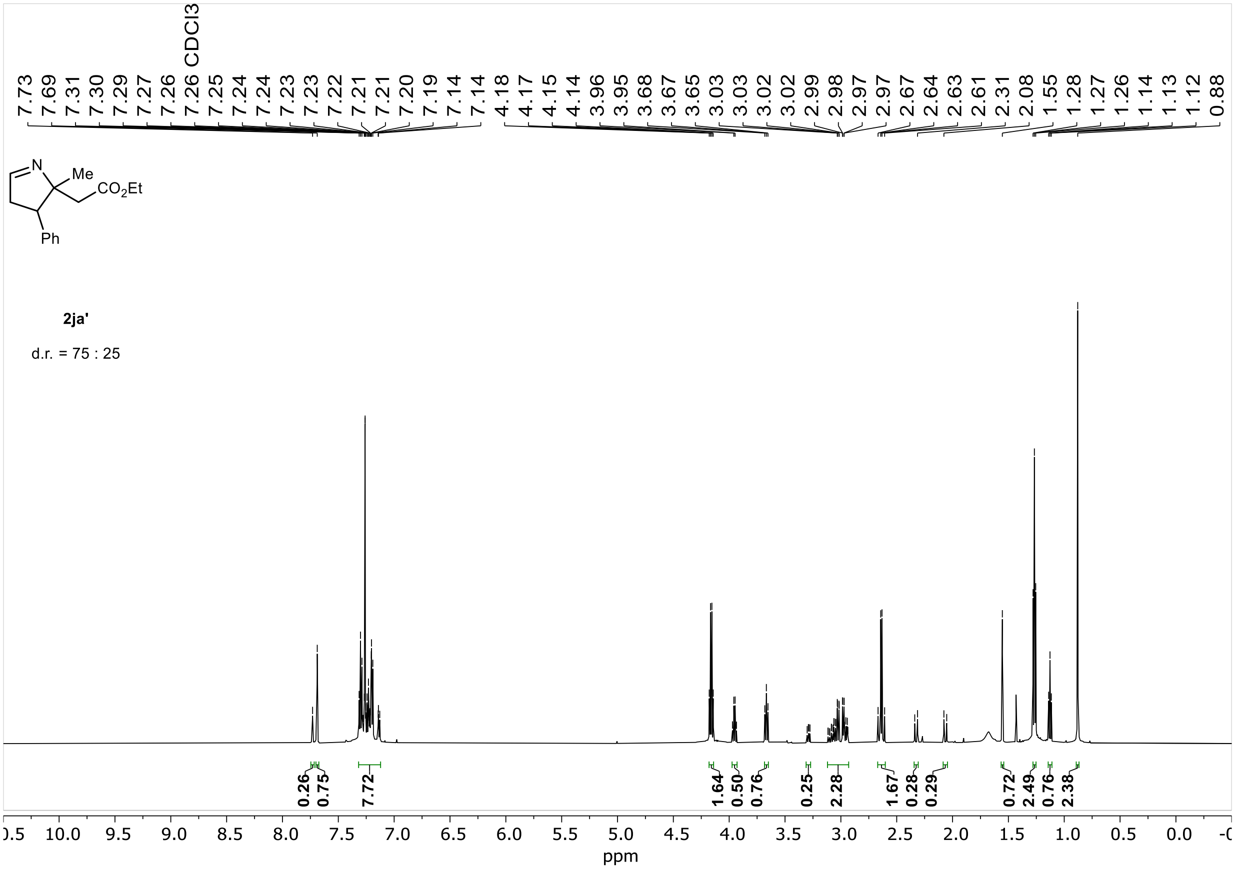
2ia', ^{1}H NMR (600 MHz, $CDCl_3$)



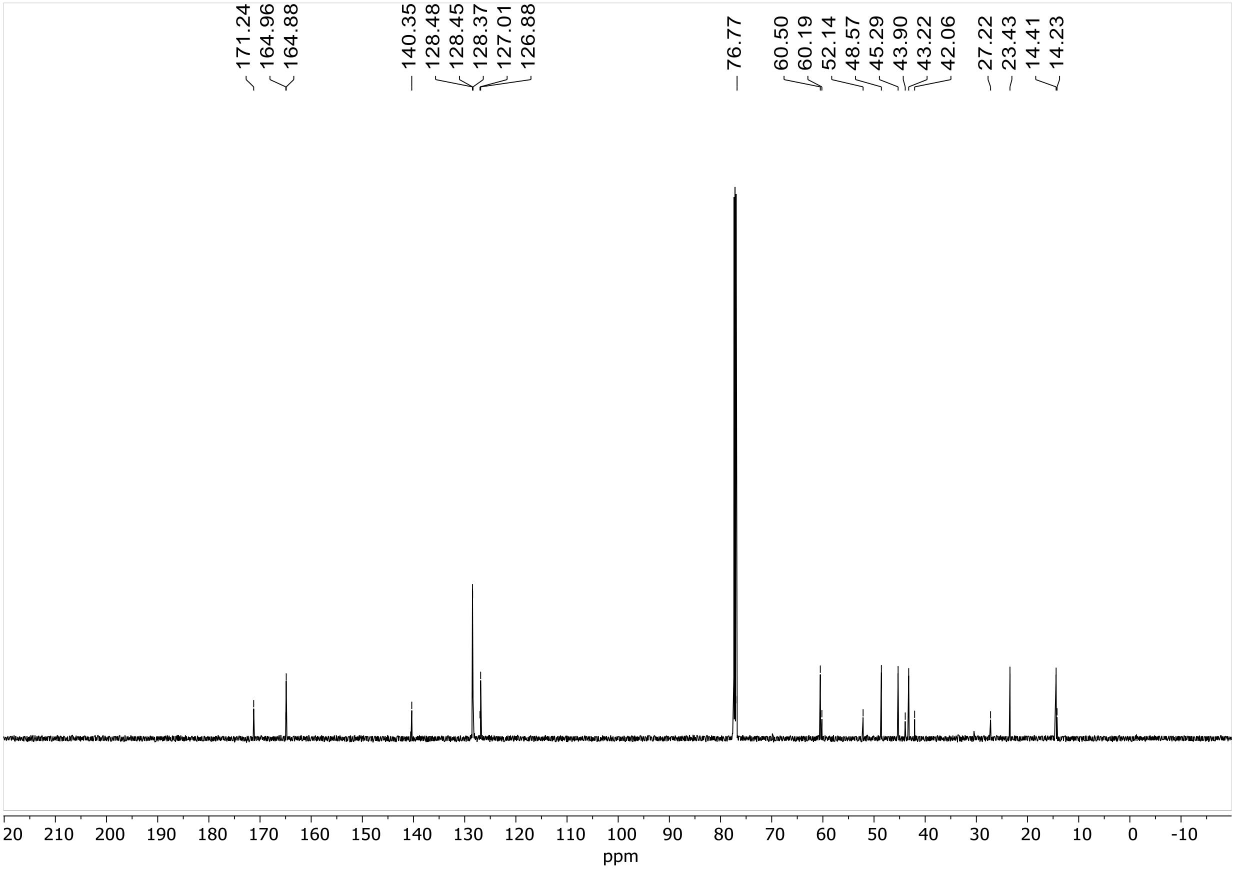
2ia', ^{13}C NMR (151 MHz, $CDCl_3$)



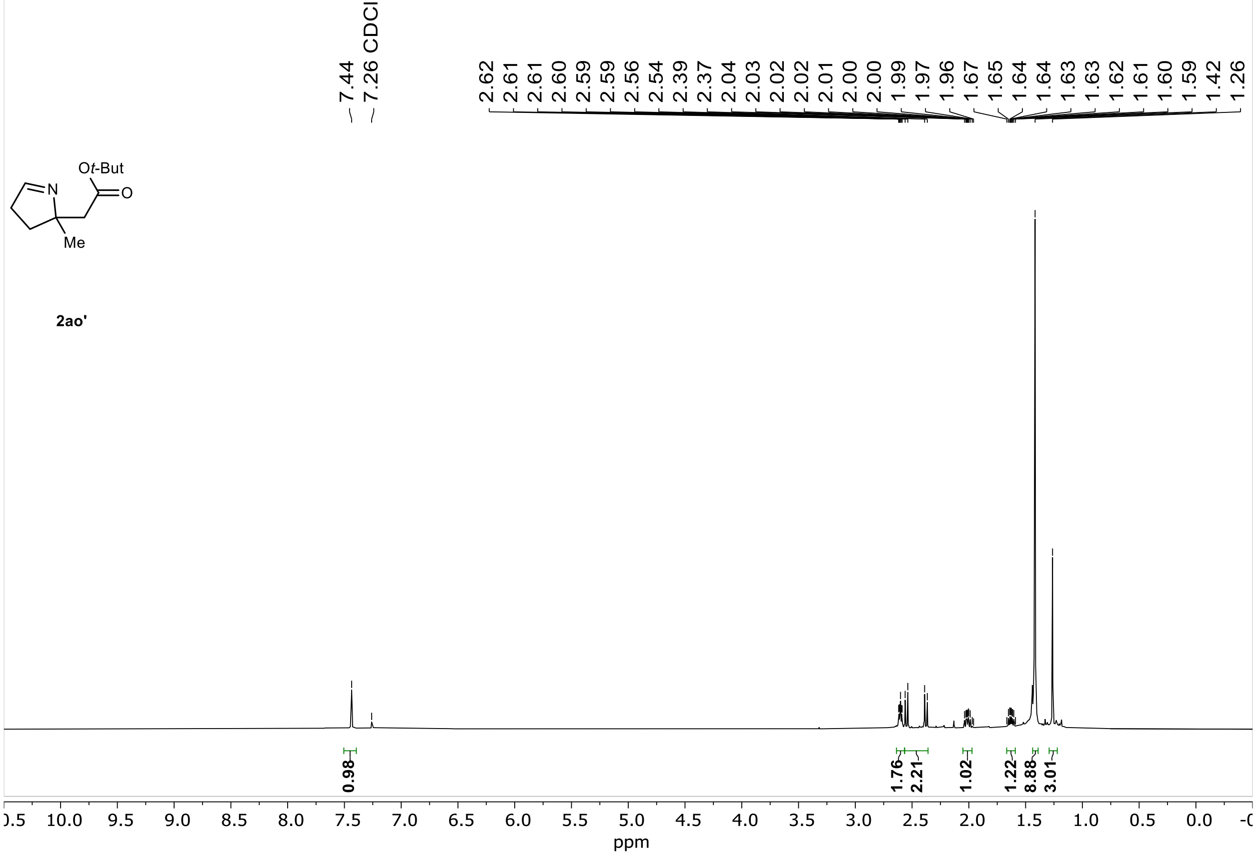
2ja', ^{1}H NMR (600 MHz, CDCl$_3$)



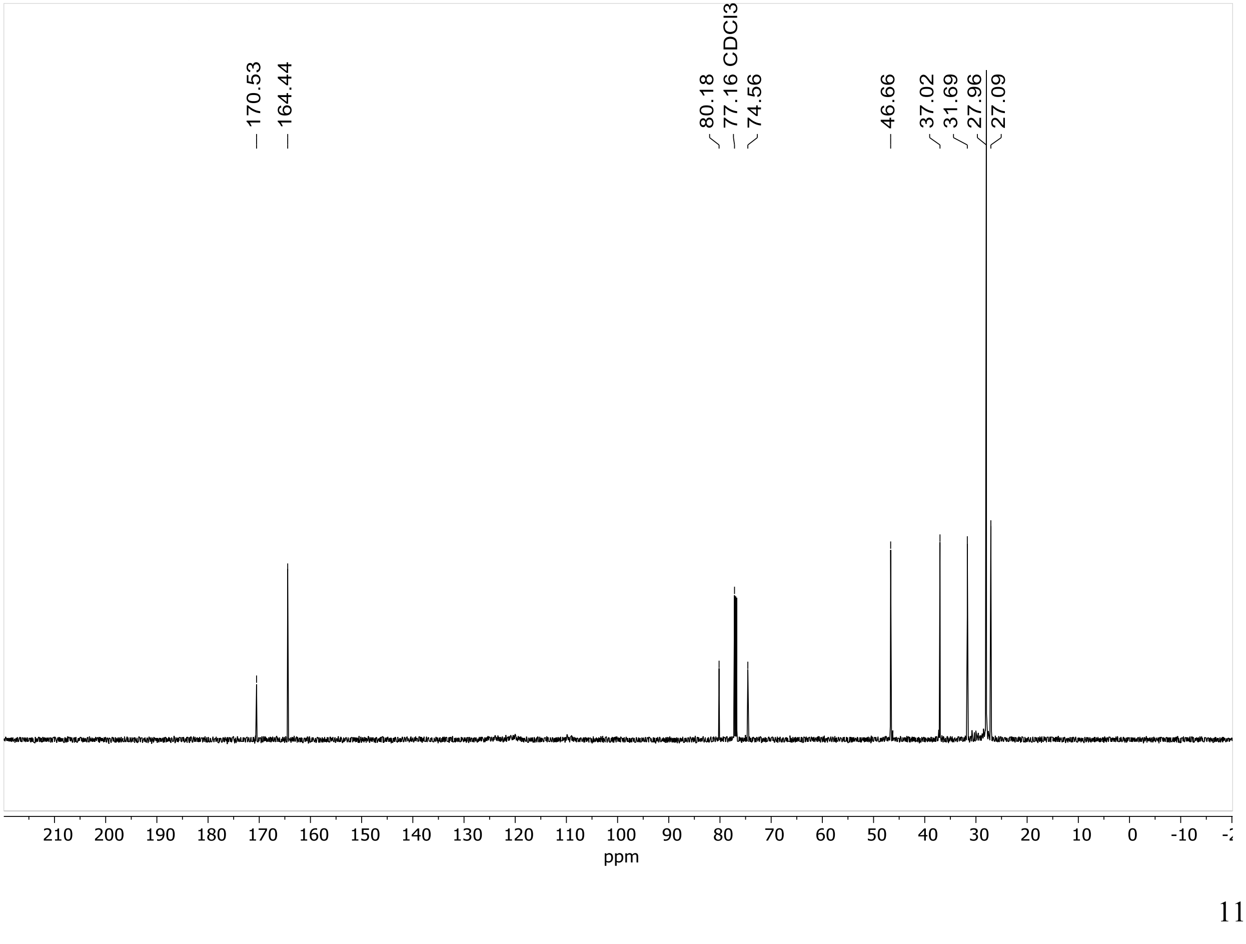
2ja', ^{13}C NMR (151 MHz, CDCl$_3$)



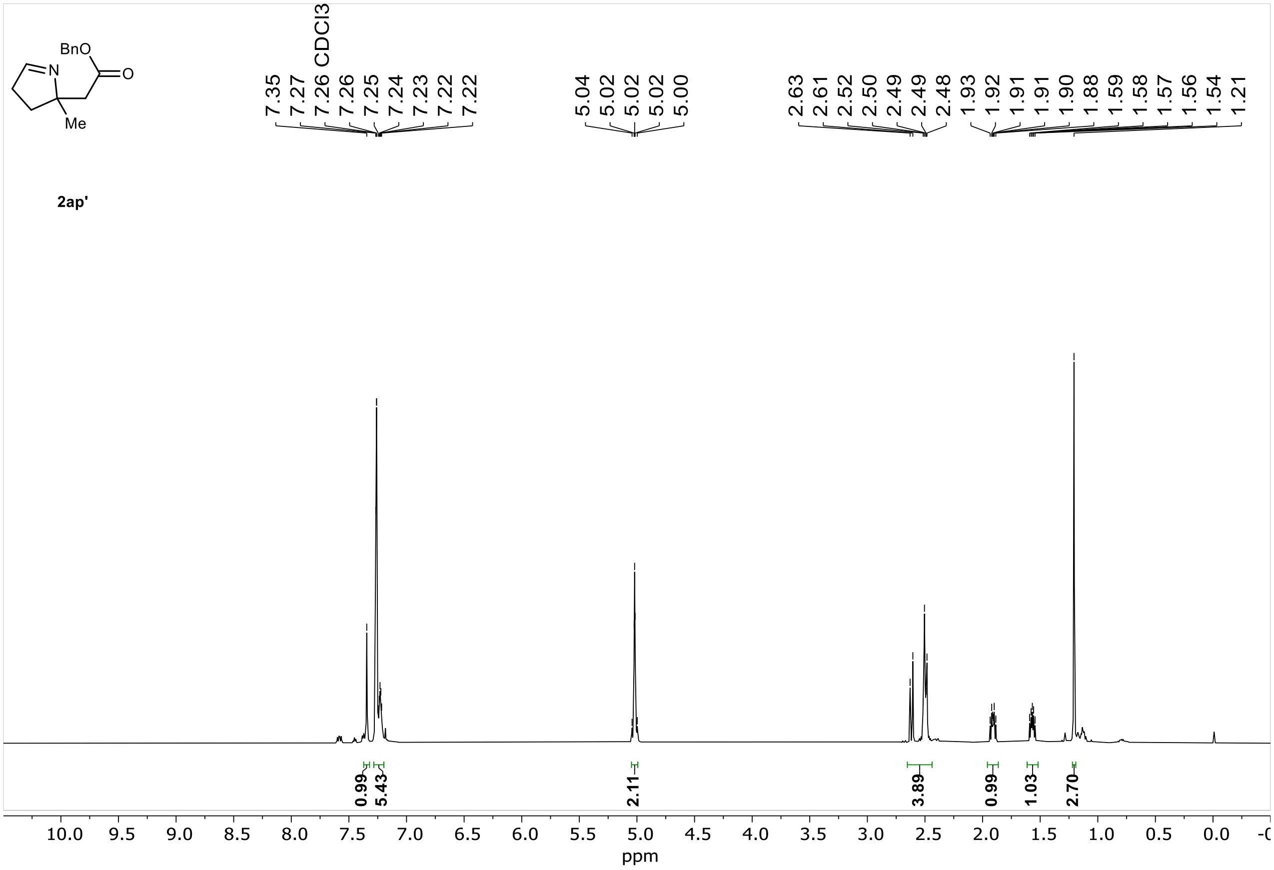
2ao', ^{1}H NMR (600 MHz, CDCl$_3$)



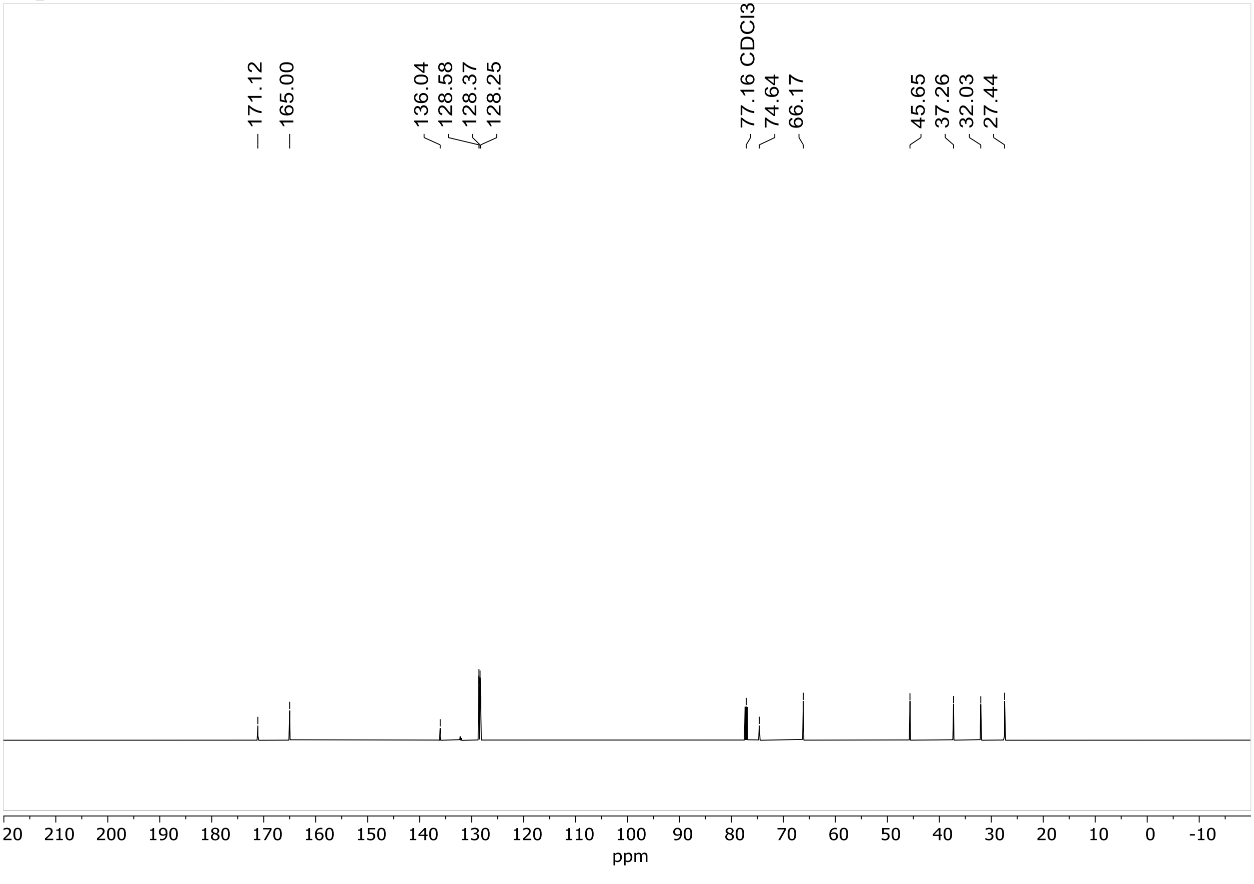
2ao', ^{13}C NMR (151 MHz, CDCl$_3$)



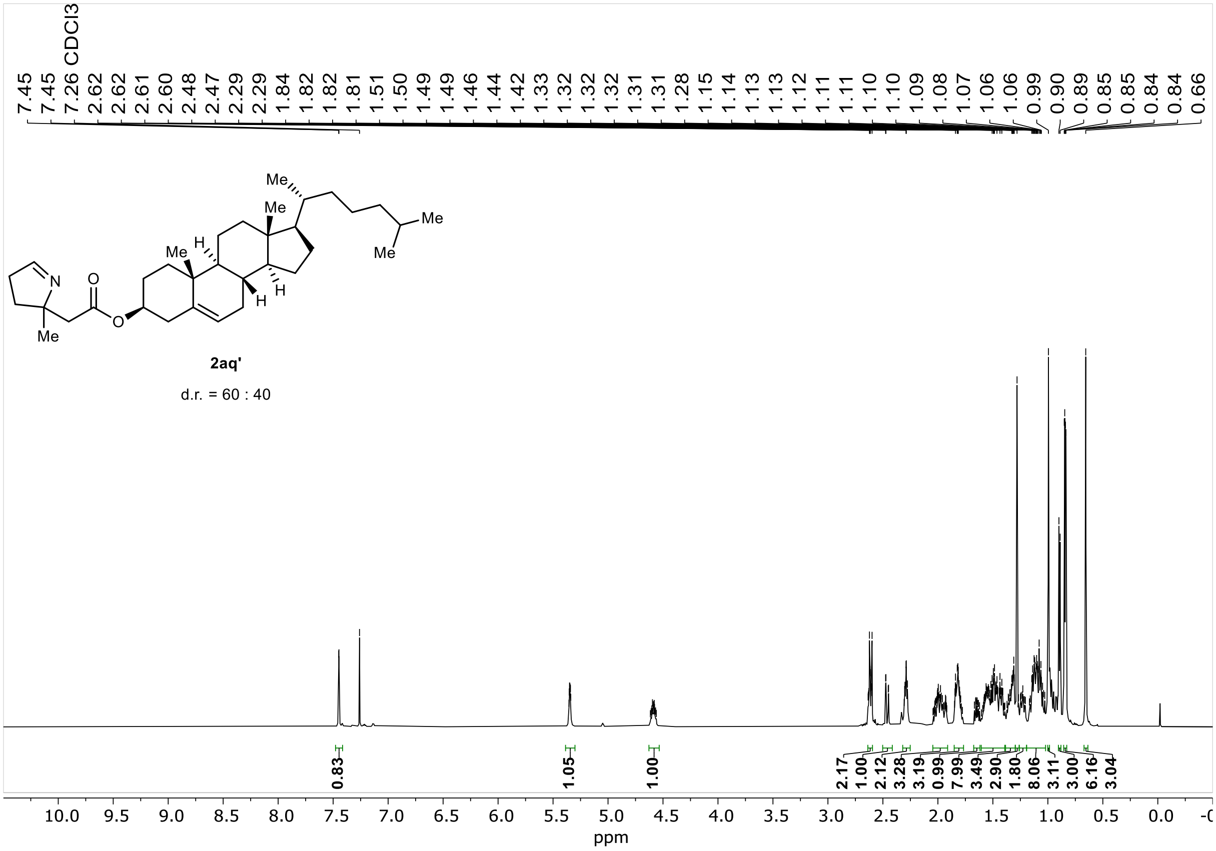
2ap', ^{1}H NMR (600 MHz, CDCl$_3$)



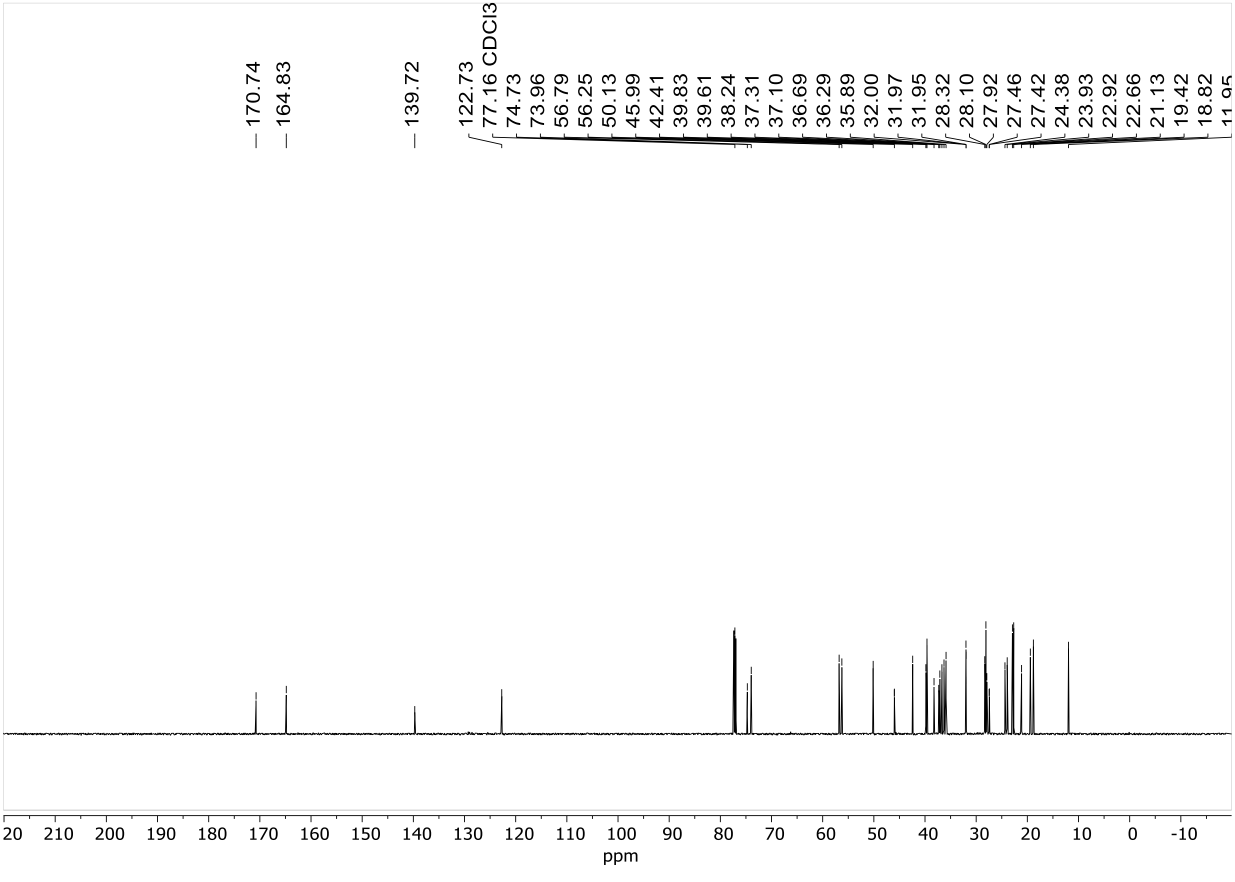
2ap', ^{13}C NMR (151 MHz, CDCl$_3$)



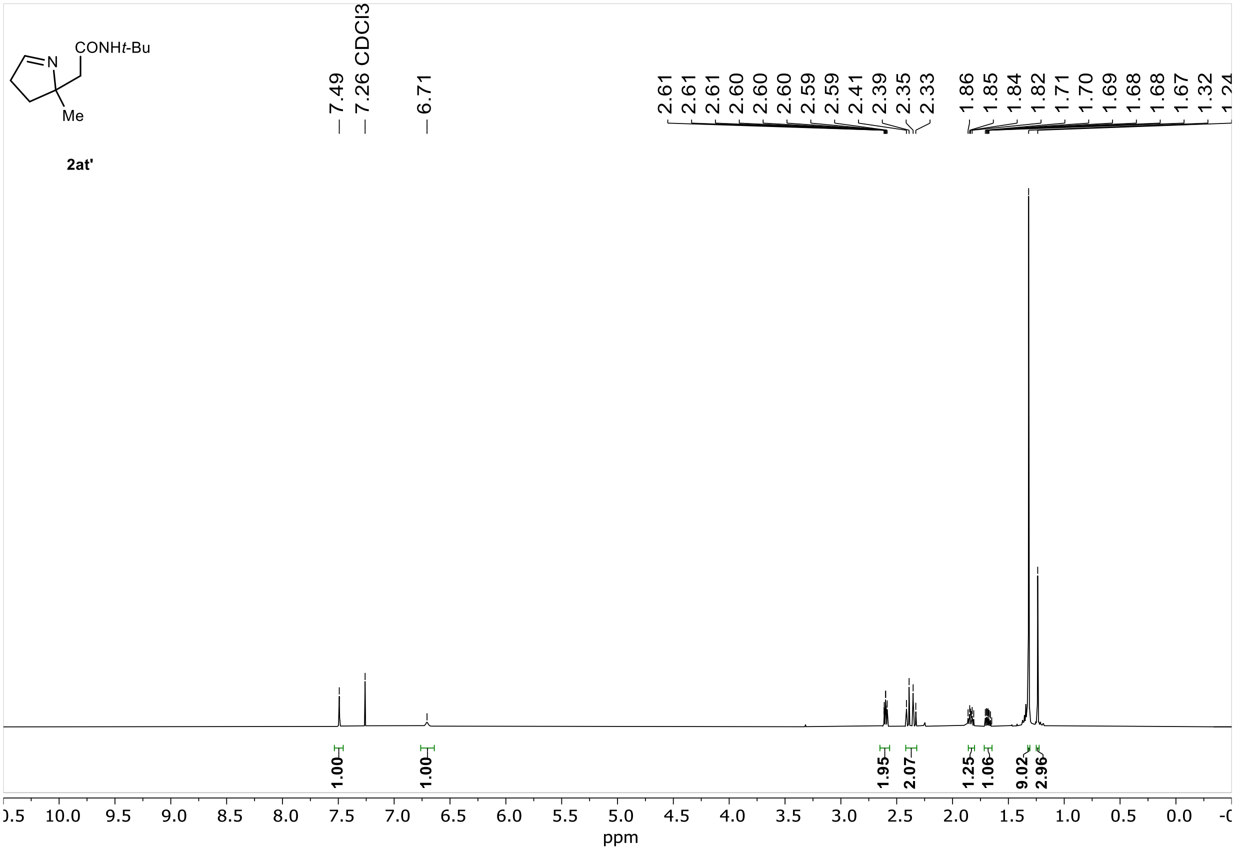
2aq', ^{1}H NMR (600 MHz, CDCl$_3$)



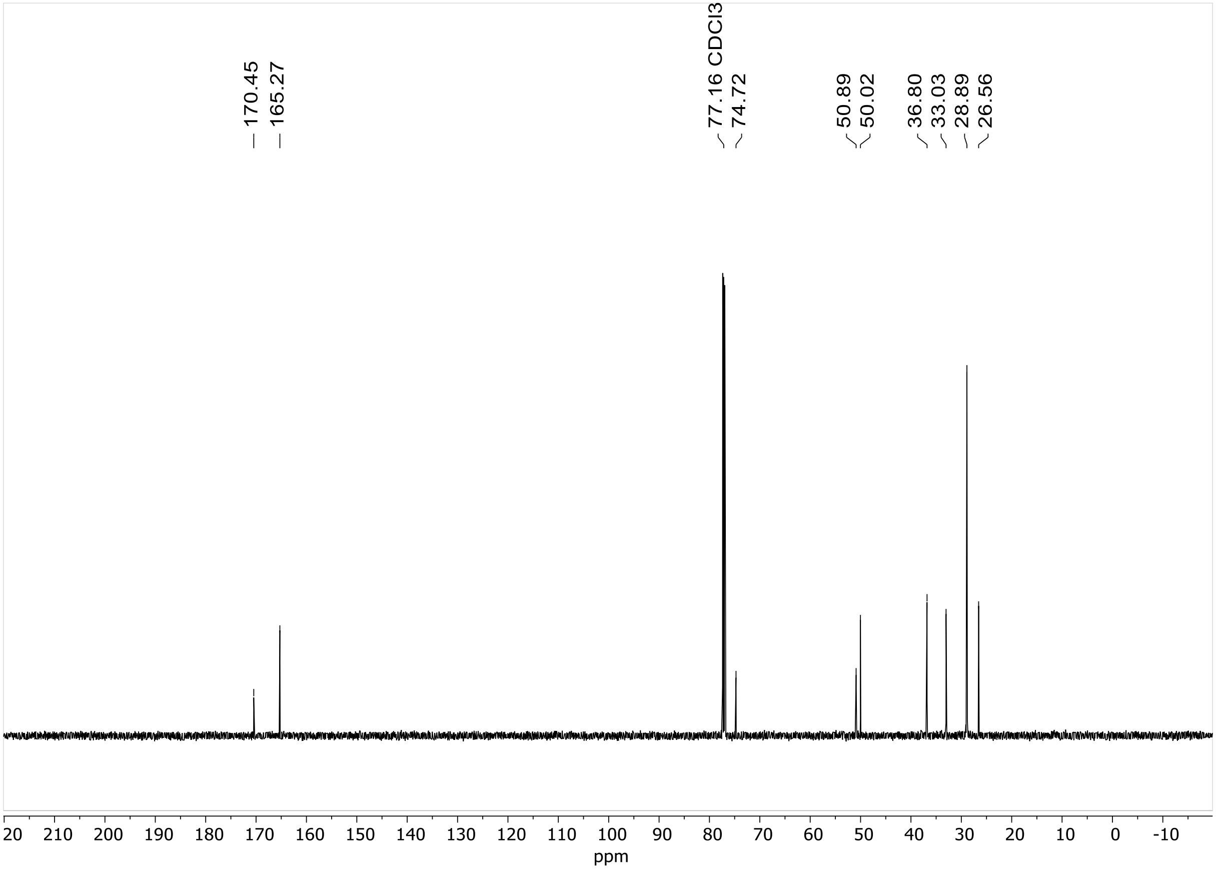
2aq', ^{13}C NMR (151 MHz, CDCl$_3$)



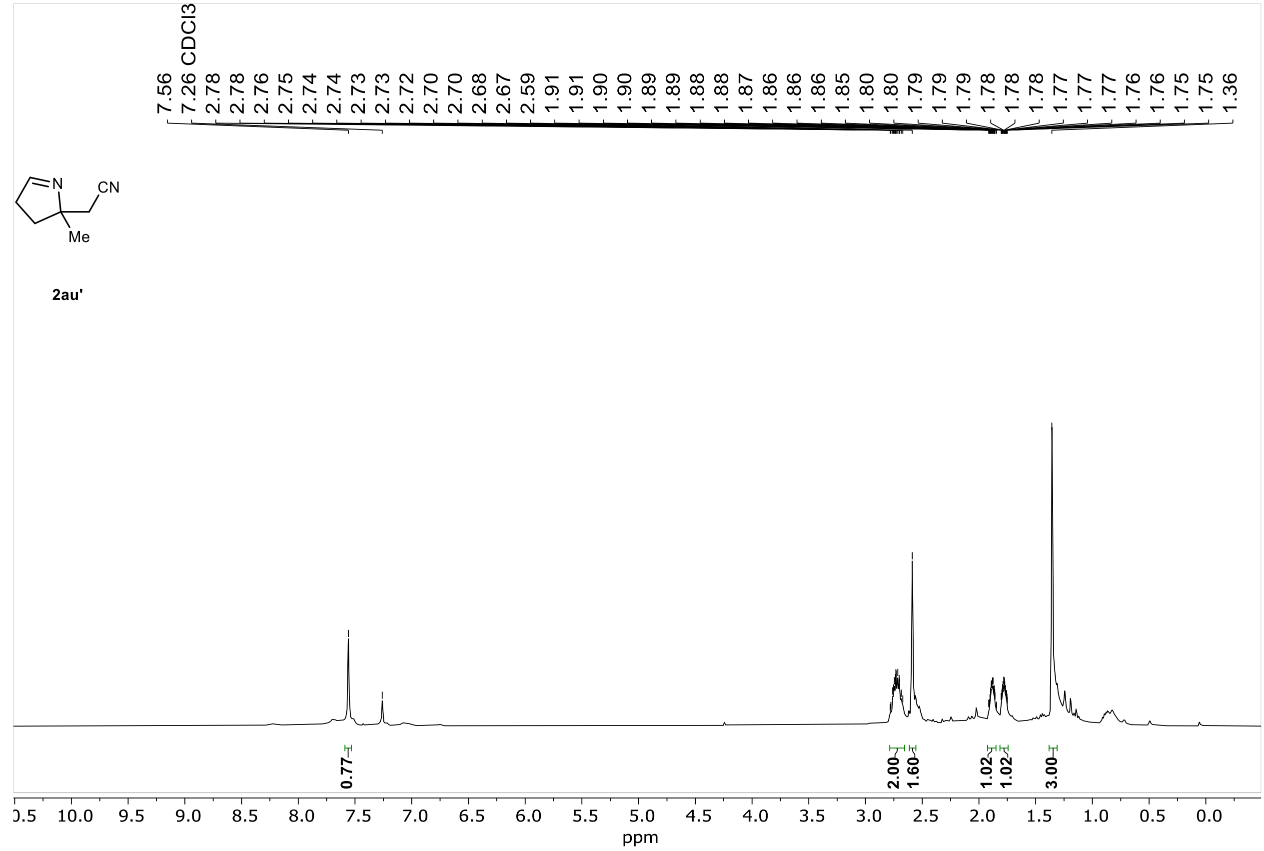
2at', ^{1}H NMR (600 MHz, CDCl$_3$)



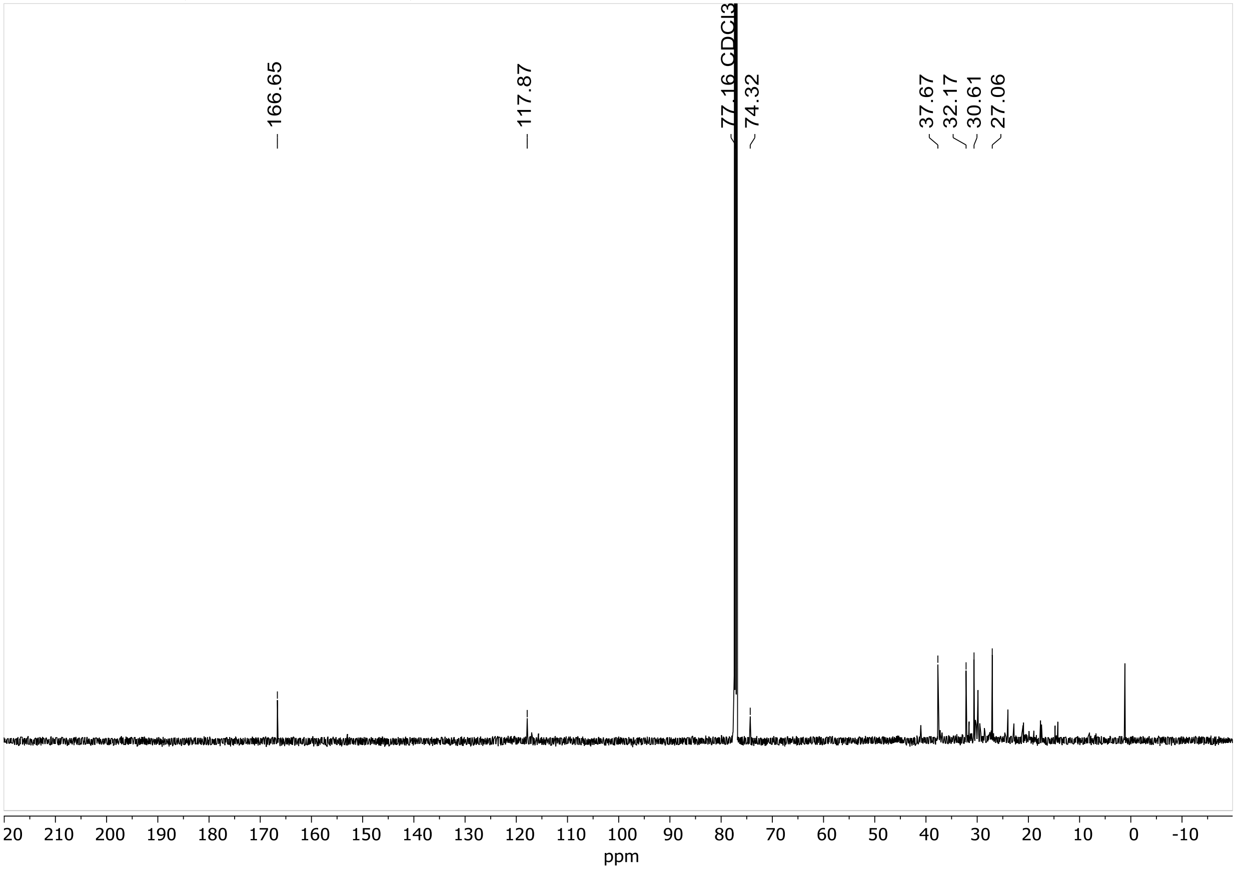
2at', ^{13}C NMR (151 MHz, CDCl$_3$)



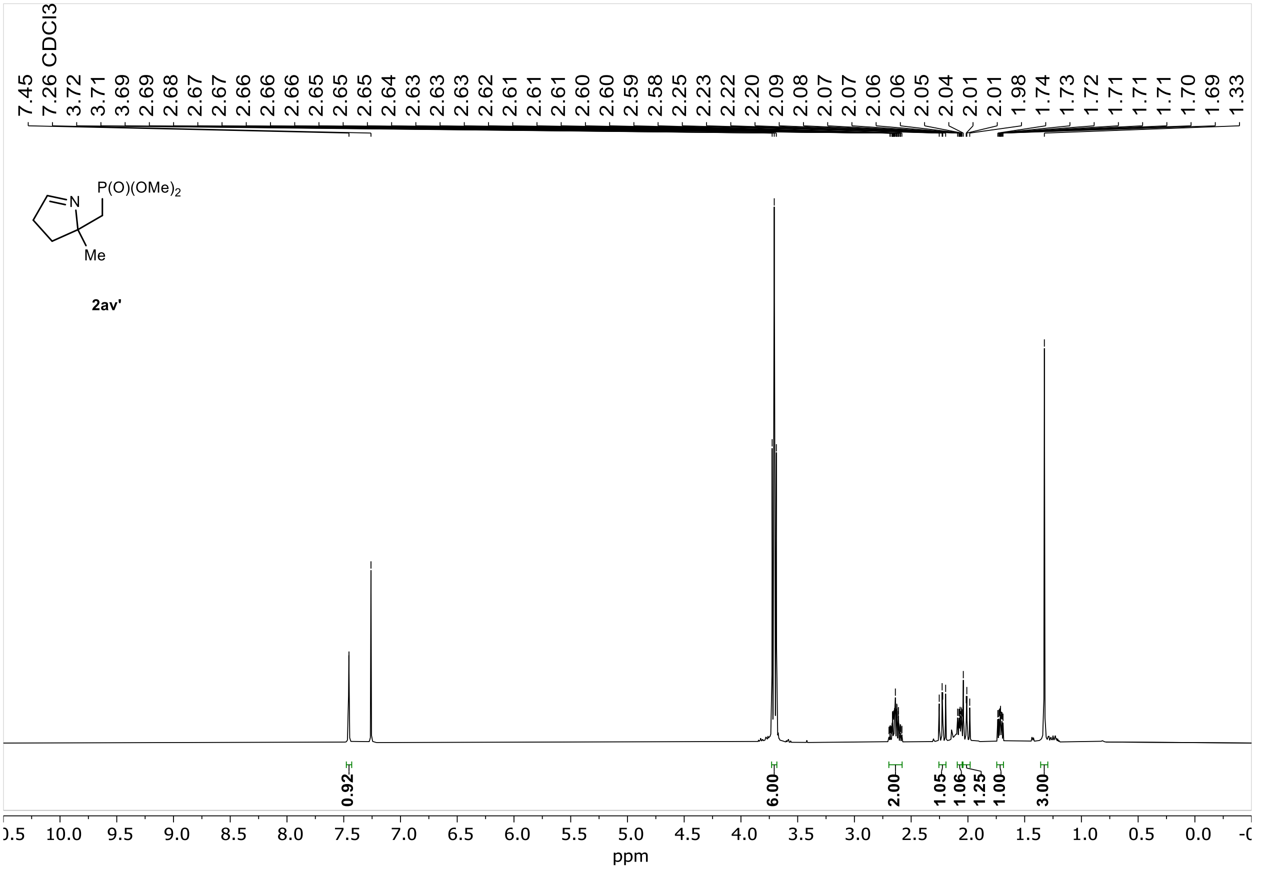
2au', ^{1}H NMR (600 MHz, $CDCl_3$)



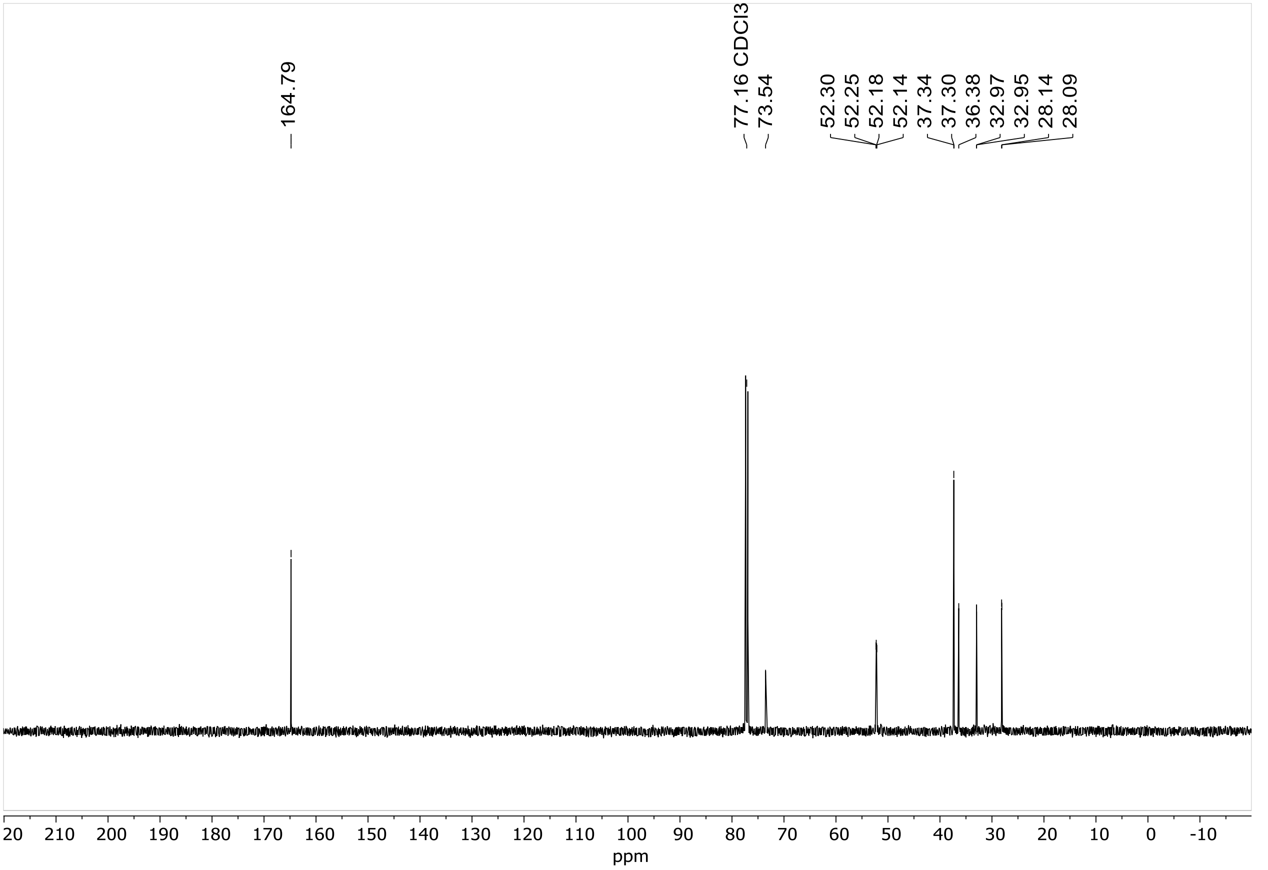
2au', ^{13}C NMR (151 MHz, $CDCl_3$)



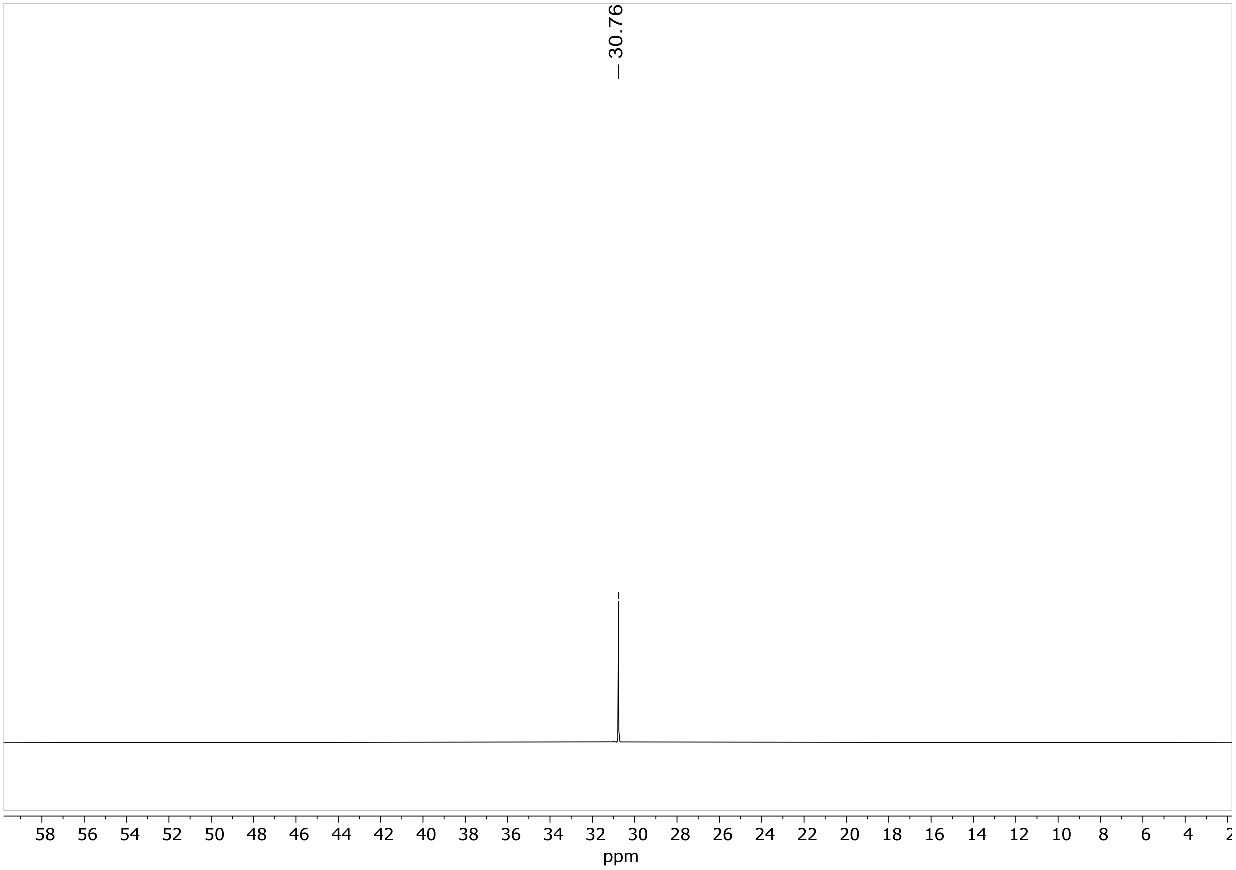
2av', ^{1}H NMR (600 MHz, $CDCl_3$)



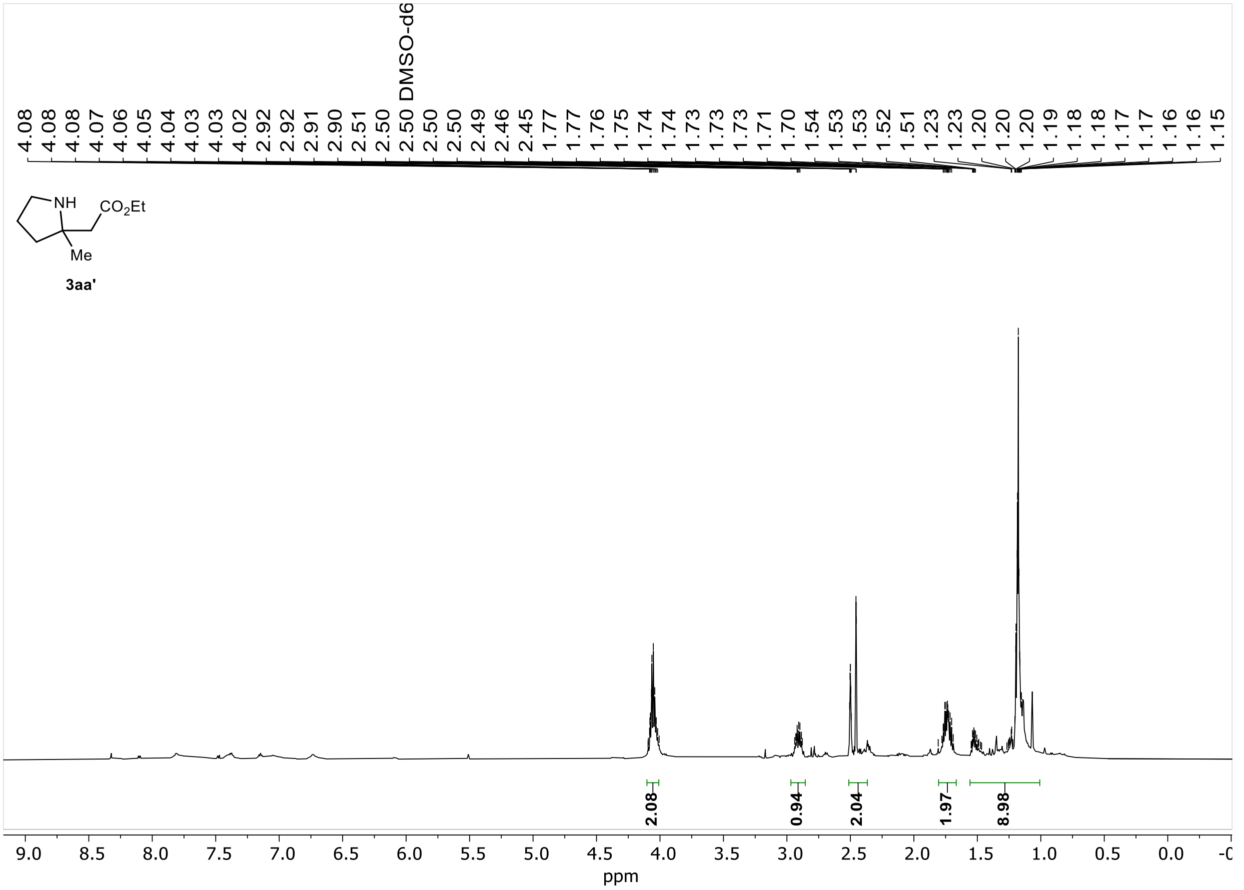
2av', ^{13}C NMR (151 MHz, $CDCl_3$)



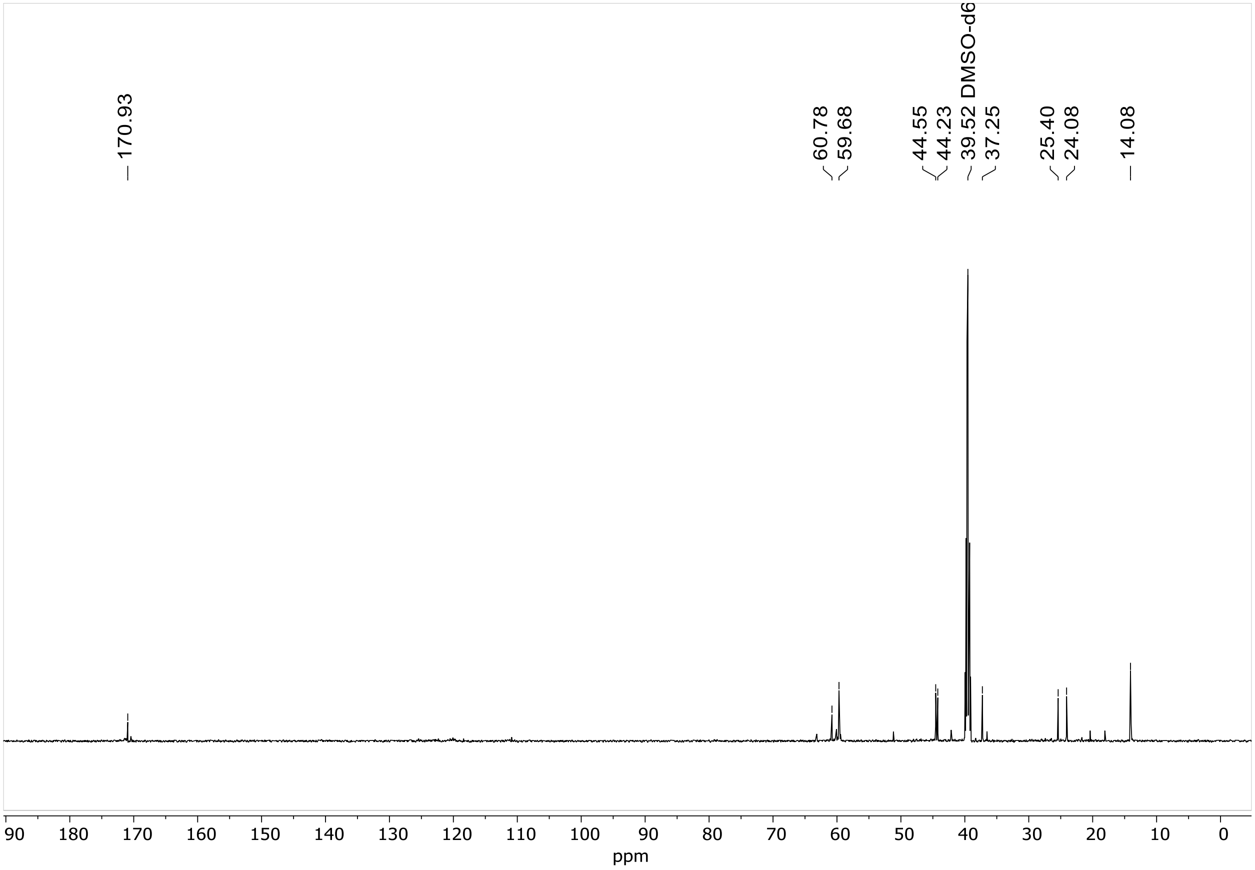
2av’,^{31}P NMR (243 MHz, CDCl$_3$)



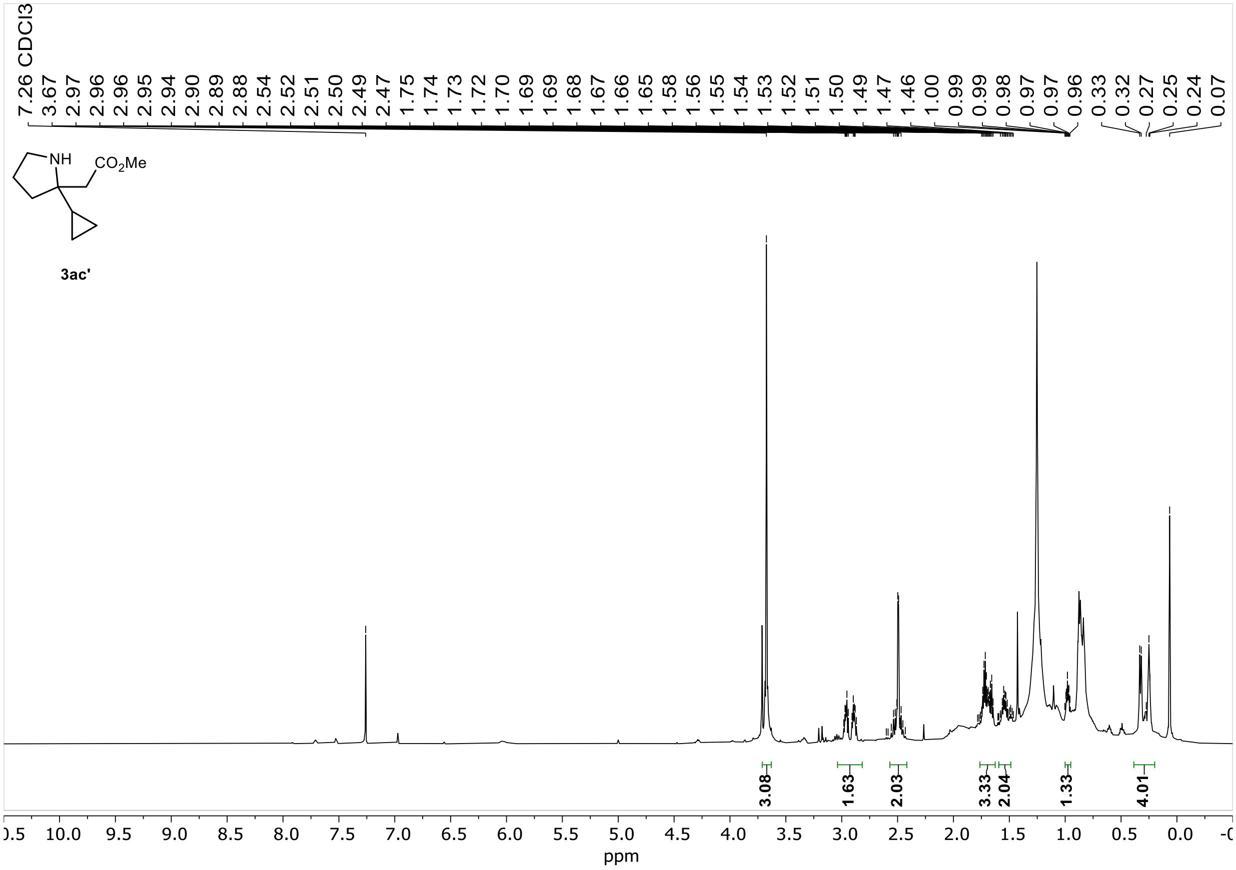
3aa’, ^{1}H NMR (600 MHz, DMSO)



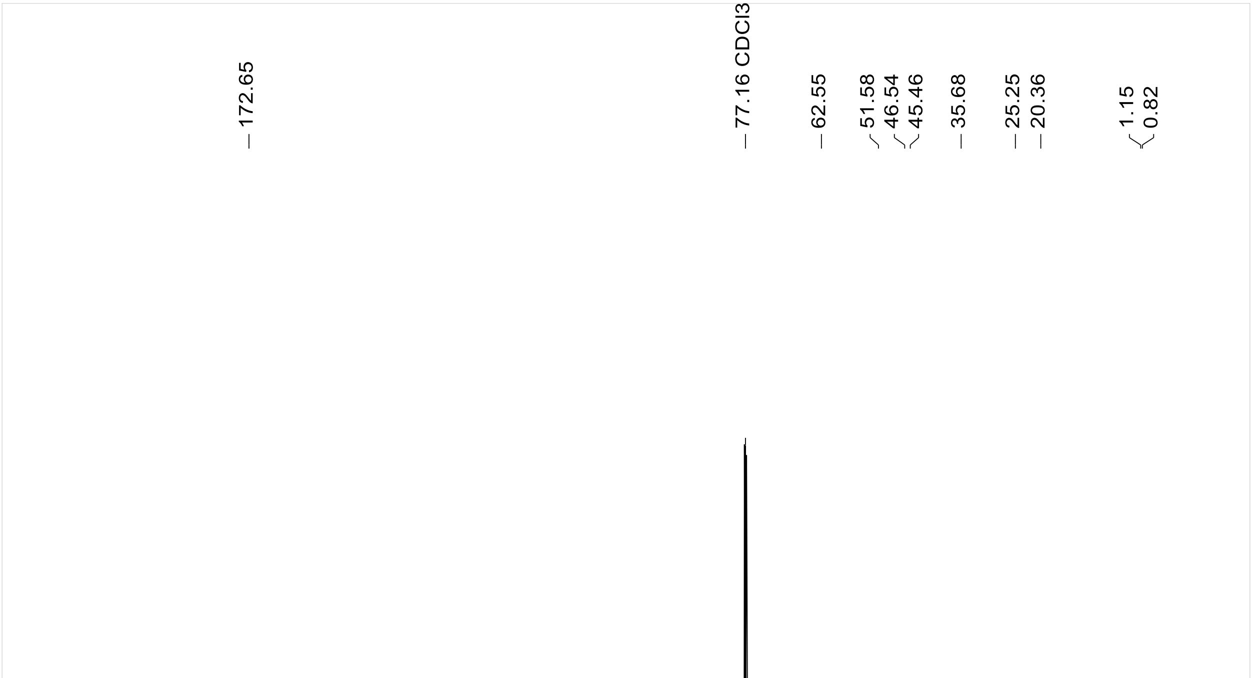
3aa’,^{13}C NMR (151 MHz, DMSO)



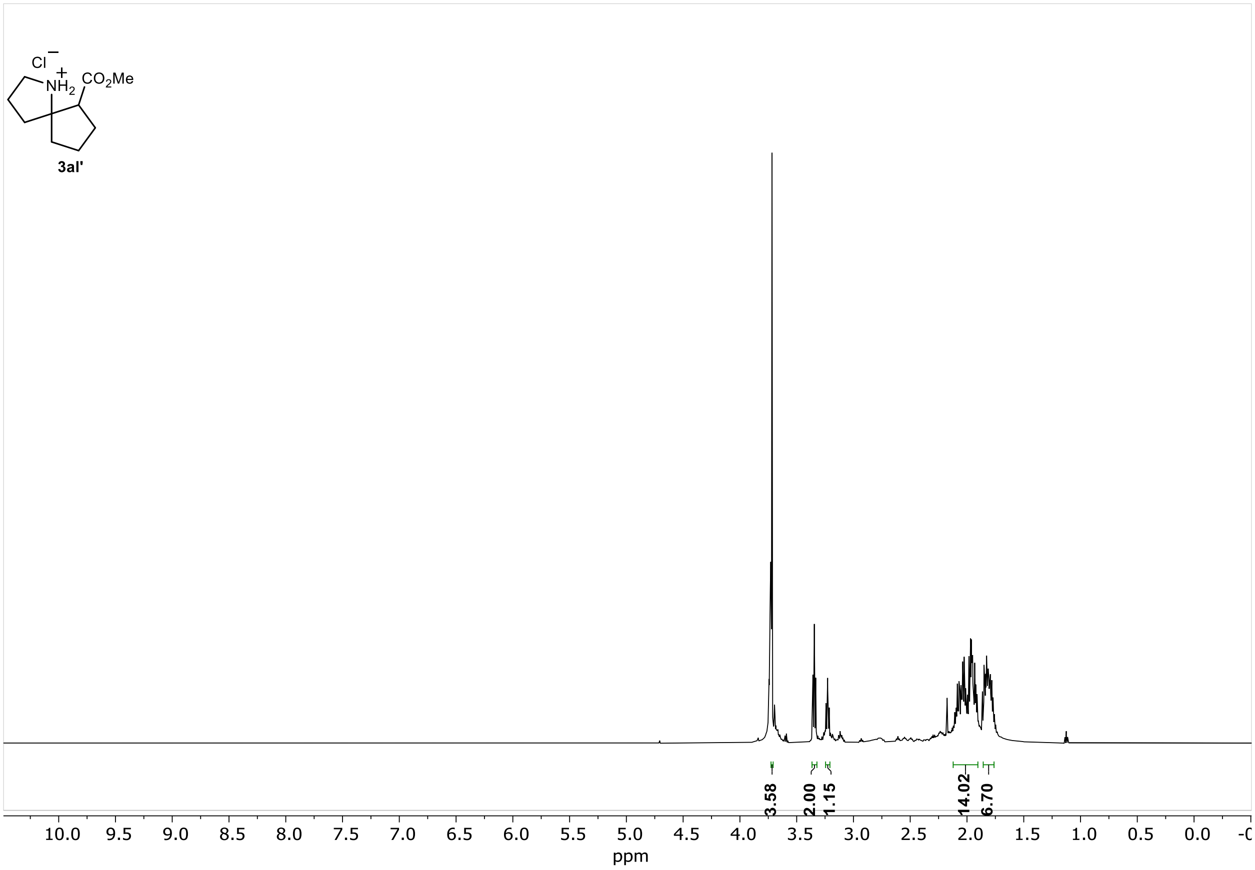
3ac', ^{1}H NMR (600 MHz, CDCl$_3$)



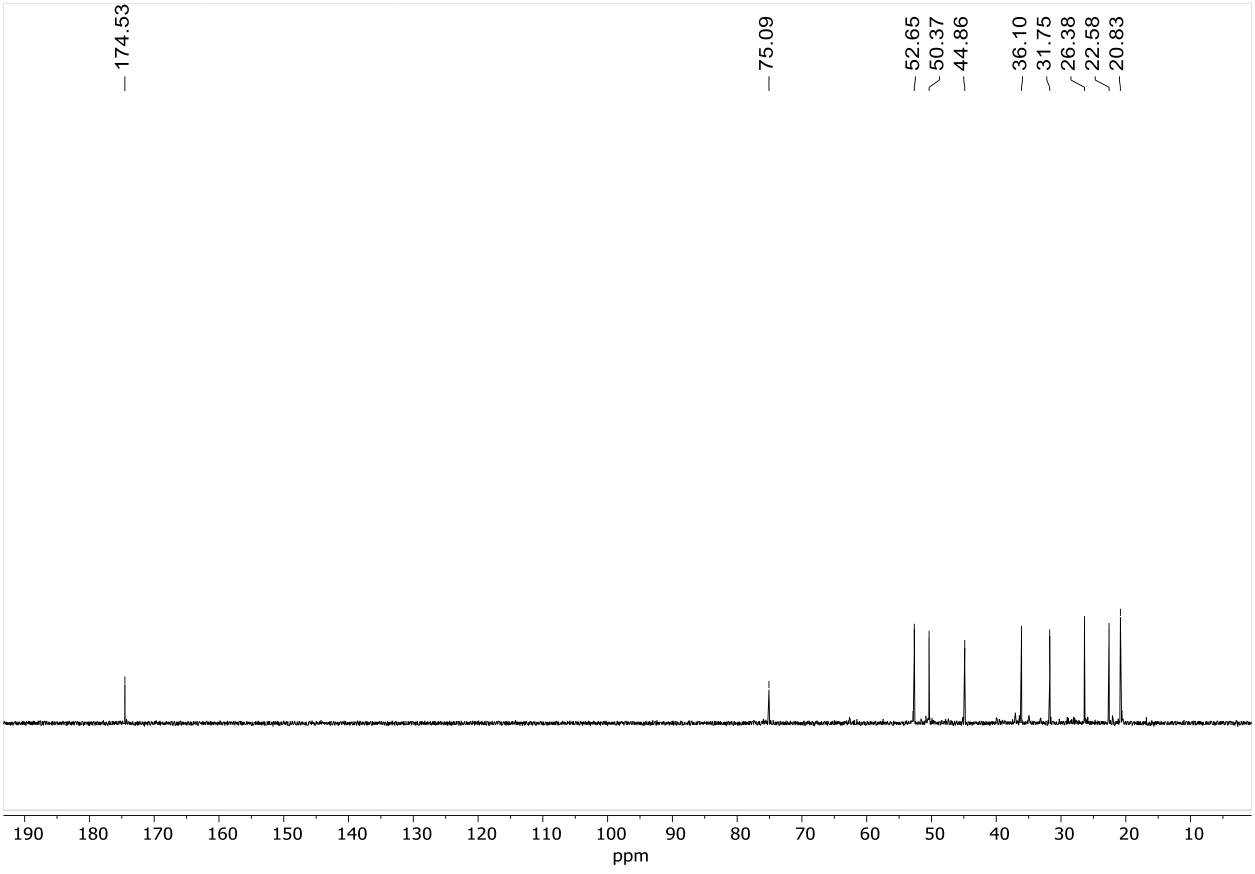
3ac', ^{13}C NMR (600 MHz, CDCl$_3$)



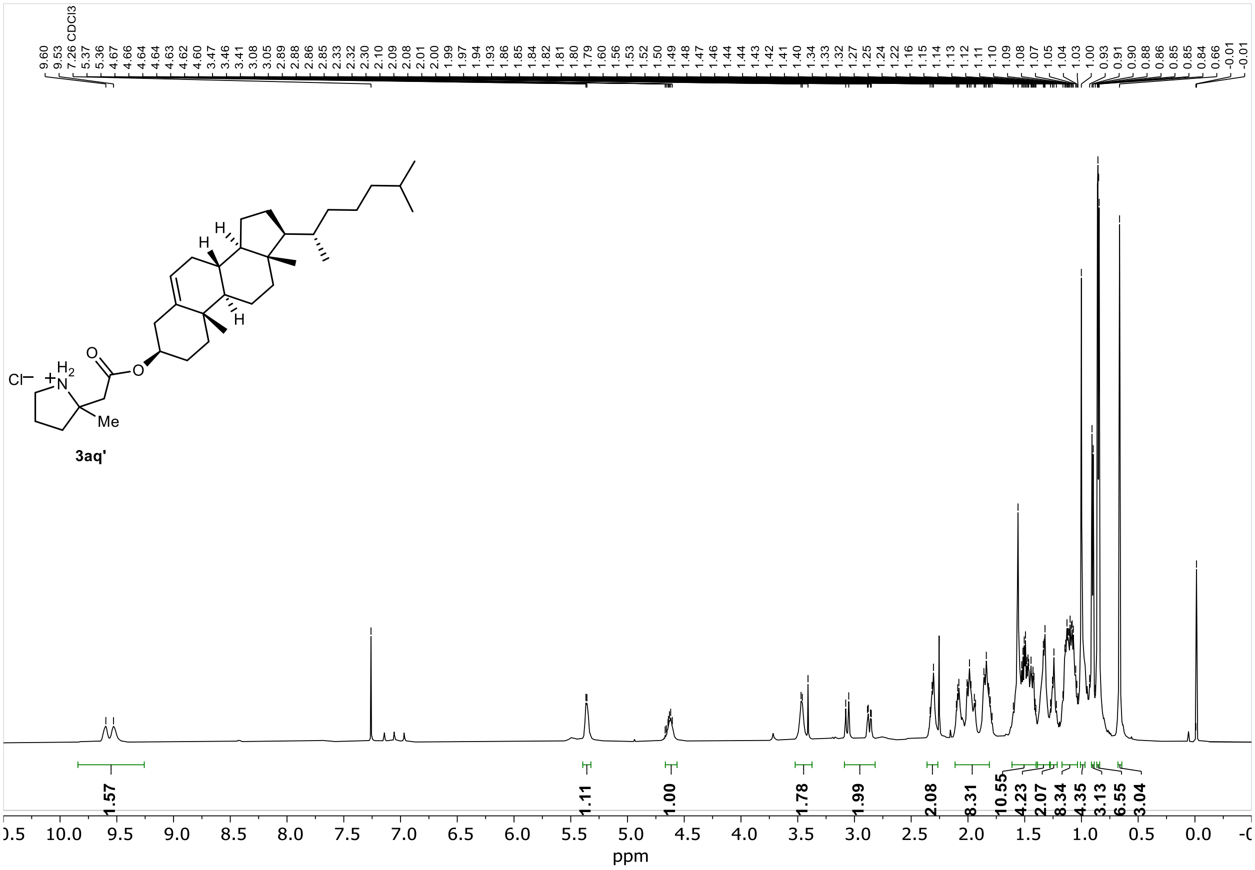
3ak’, ^{1}H NMR (600 MHz, D_2O Presat)



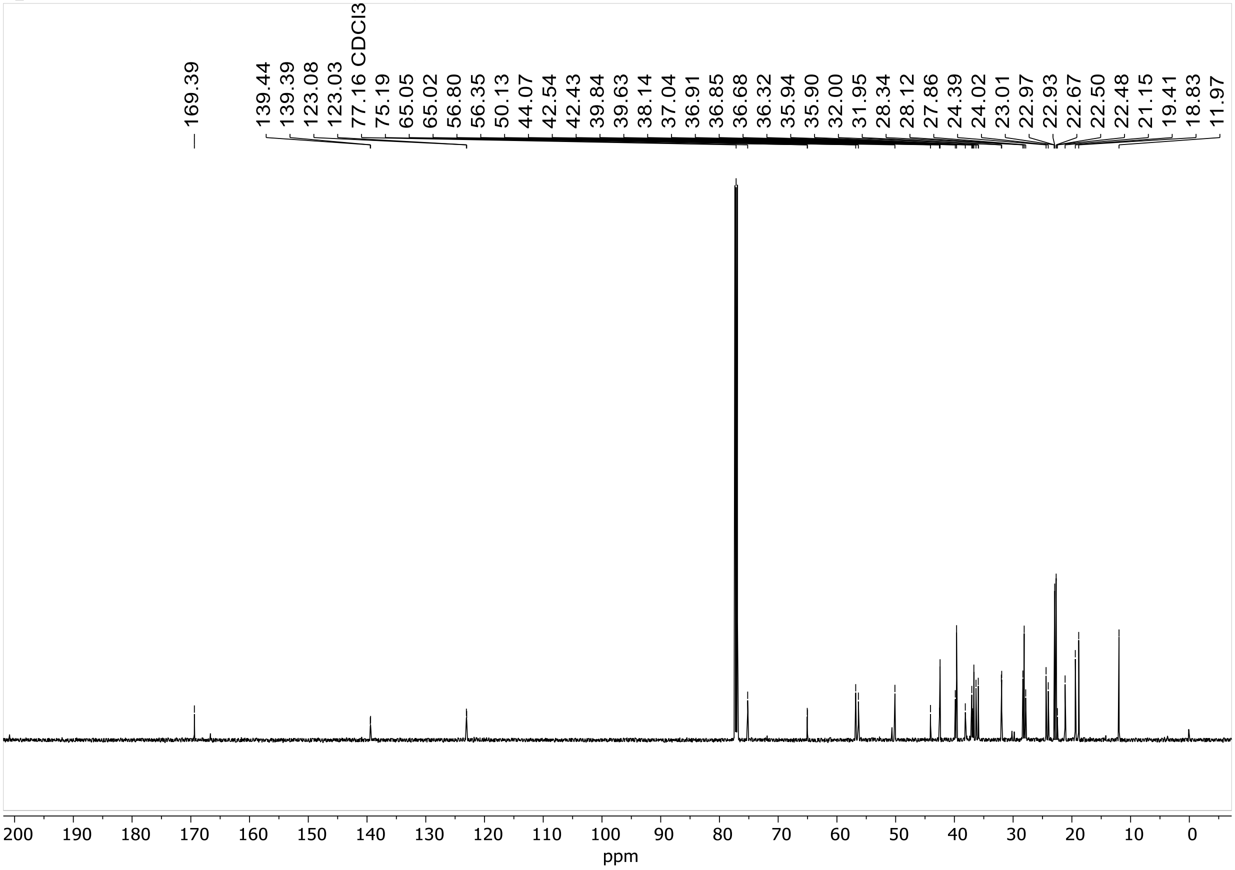
3ak’, ^{13}C NMR (151 MHz, D_2O)



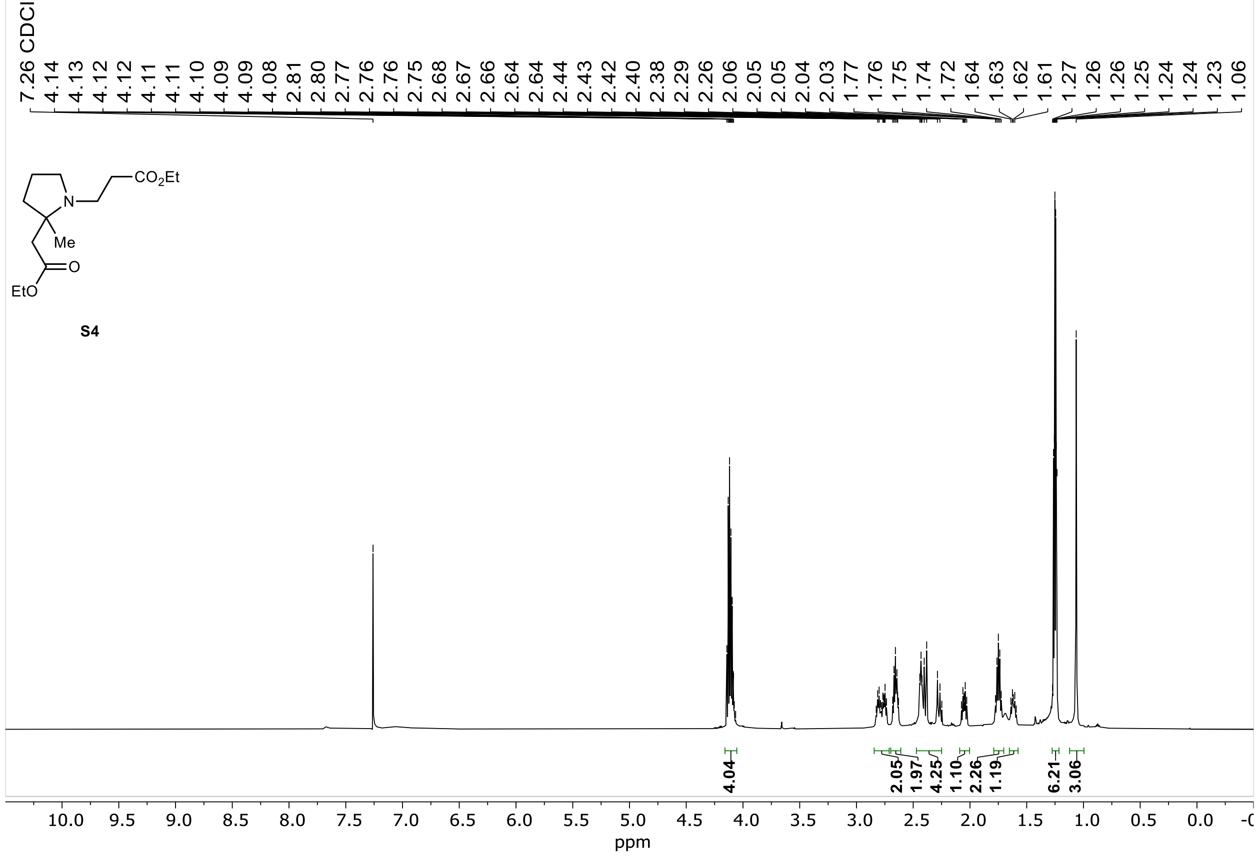
3aq’, ^{1}H NMR (600 MHz, CDCl$_3$)



3aq’, ^{13}C NMR (125 MHz, CDCl$_3$)



S4, ^{1}H NMR (600 MHz, CDCl$_3$).



S4, ^{13}C NMR (151 MHz, CDCl$_3$)