Supporting Information

Direct Access to Chiral Tertiary Alcohols via Copper-Catalyzed Enantioconvergent *O*-Alkylation of Water with Racemic α-Tertiary Haloamides

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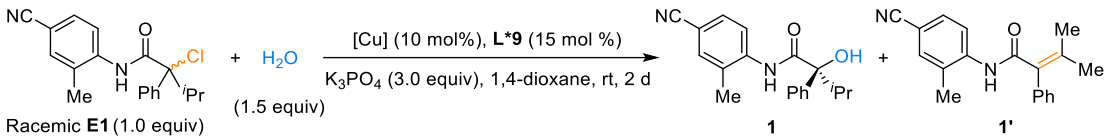
1. Supplementary tables for experiments

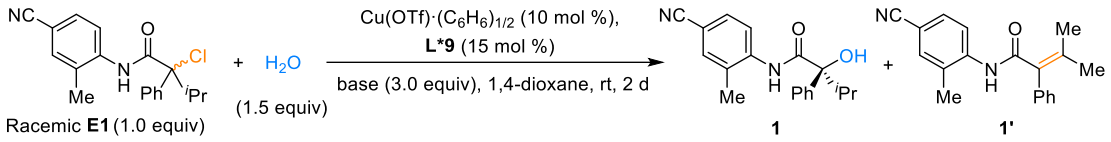
Table S1. Effect of copper salts in the model reaction.[a]



Entry	[Cu]	Conv. of **E1**	Yield of **1** (%)	Ee of **1** (%)	Yield of **1′**
1	CuCl	84	84	88	0
2	CuBr	84	82	87	Trace
3	CuI	84	79	56	Trace
4	CuTc	85	75	83	8
5	$CuBr{\bullet}SMe_2$	84	85	89	0
6	$Cu(PPh_3)_3{\bullet}CF_3$	86	77	<5	9
7	$Cu(MeCN)_4{\bullet}BF_4$	86	84	88	0
8	$Cu(OTf){\bullet}tol_{1/2}$	86	86	89	0
9	$Cu(OTf){\bullet}(C_6H_6)_{1/2}$	90	90	89	0
10	$Cu(OAc)_2$	89	86	84	0
11	$Cu(OTf)_2$	85	86	89	0

[a]Reaction conditions: Racemic **E1** (0.05 mmol), H_2O (0.075 mmol, 1.5 equiv), [Cu] (10 mol%), **L9*** (15 mol%), and K_3PO_4 (3.0 equiv) in 1,4-dioxane (0.50 mL) at room temperature (rt) for 2 days under argon. Conversion of **E1**, yields of **1** and **1'** were based on ^1H NMR analysis of the crude products using 1,3,5-trimethoxybenzene as an internal standard; ee values were based on HPLC analysis. Tc, 2-thiophenecarboxylate.

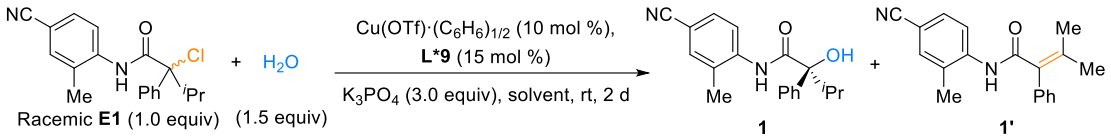
Table S2. Effect of bases in the model reaction.[a]



Entry	Base	Conv. of **E1** (%)	Yield of **1** (%)	Ee of **1** (%)	Yield of **1′** (%)
1	K_3PO_4	90	90	89	0
2	K_2CO_3	47	48	88	Trace
3	Rb_2CO_3	79	76	80	Trace
4	Cs_2CO_3	82	71	25	9
5	K_2HPO_4	0	0	–	0
6	KOAc	0	0	–	0
7	KO^{t}Bu	85	57	<5	26
8	DBU	83	31	<5	50
9	DIPEA	0	0	–	0

[a]Reaction conditions: Racemic **E1** (0.05 mmol), H_2O (0.075 mmol, 1.5 equiv), Cu(OTf)•$(C_6H_6)_{1/2}$ (10 mol%), **L9*** (15 mol%), and base (3.0 equiv) in 1,4-dioxane (0.50 mL) at room temperature (rt) for 2 days under argon. Conversion of **E1**, yields of **1** and **1'** were based on ^{1}H NMR analysis of the crude products using 1,3,5-trimethoxybenzene as an internal standard; ee values were based on chiral HPLC analysis. DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene. DIPEA, diisopropylethylamine.

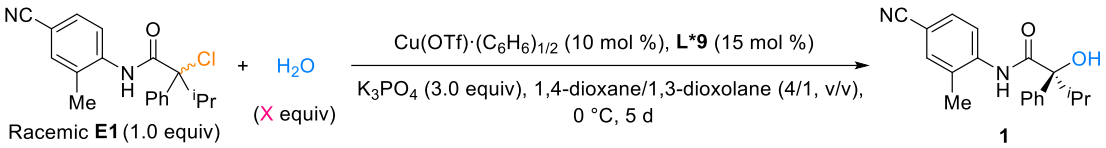
Table S3. Effect of solvents in the model reaction.[a]



Entry	Solvent	Conv. of **E1**	Yield of **1** (%)	Ee of **1** (%)	Yield of **1′**
1	1,4-dioxane	90	90	89	0
2	1,3-dioxolane	82	81	80	Trace
3	THF	84	81	68	Trace
4	MTBE	85	86	84	0
5	MeCN	84	85	<5	0
6	DCM	81	80	87	0
7	$CHCl_3$	66	50	85	0
8	DCE	86	83	86	0
9	PhCl	65	51	81	0
10	toluene	71	71	82	0
11	$PhCF_3$	82	80	80	0
12	EtOAc	84	85	37	0
13[b]	1,4-dioxane/ 1,3-dioxolane	86	81	86	Trace
14[c]	1,4-dioxane/ 1,3-dioxolane	85	86	88	0
15[c,d]	1,4-dioxane/ 1,3-dioxolane	>99	97	93	0

[a]Reaction conditions: Racemic **E1** (0.05 mmol), H_2O (0.075 mmol, 1.5 equiv), Cu(OTf)•$(C_6H_6)_{1/2}$ (10 mol%), **L9*** (15 mol%), and K_3PO_4 (3.0 equiv.) in solvent (0.50 mL) at room temperature (rt) for 2 days under argon. Conversion of **E1**, yields of **1** and **1'** were based on ^1H NMR analysis of the crude products using 1,3,5-trimethoxybenzene as an internal standard; ee values were based on chiral HPLC analysis. [b]A mixture of 1,4-dioxane/1,3-dioxolane (3/2, v/v) was used as solvent. [c]A mixture of 1,4-dioxane/1,3-dioxolane (4/1, v/v) was used as solvent. [d]At 0 °C for 5 days. MTBE, methyl *t*-butyl ether; DCE, 1,2-dichloroethane.

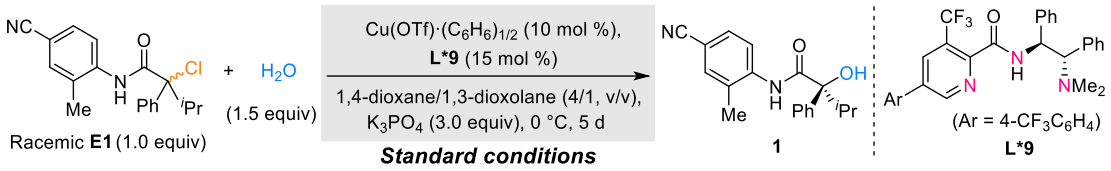
Table S4. Effect of water loading in the model reaction.[a]



Entry	X	Conv. of **E1** (%)	Yield of **1** (%)	Ee of **1** (%)
1	1.5	>99	97	93
2	5.0	57	54	90
3	10	47	44	86
4	50	32	32	67
5	100	30	28	12
6	200	28	27	11
7[b]	1.5	92	90	90

[a]Reaction conditions: Racemic **E1** (0.05 mmol, 1.0 equiv), H_2O (X equiv), Cu(OTf)•$(C_6H_6)_{1/2}$ (10 mol%), **L*9** (15 mol%), and K_3PO_4 (3.0 equiv) in 1,4-dioxane/1,3-dioxolane (0.50 mL, v/v = 4/1) at 0 °C for 5 days under argon. Conversion of **E1** and yield of **1** were based on ^1H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard; ee values were based on chiral HPLC analysis. [b]Performed under air.

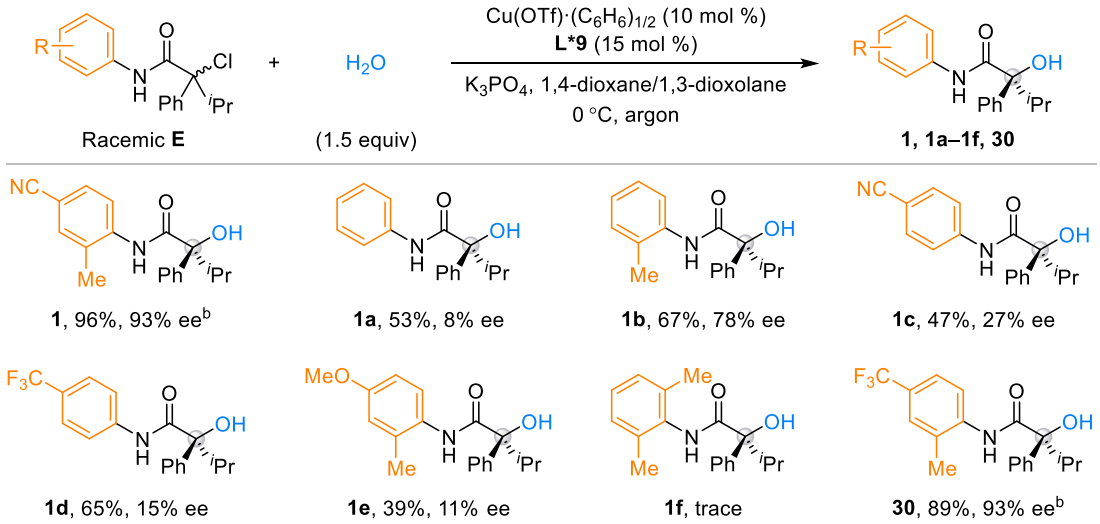
Table S5. Control experiments in the model reaction.[a]



Entry	Variations	Conv. of **E1** (%)	Yield of **1** (%)	Ee of **1** (%)
1	None	>99	97	93
2	Without [Cu]	5	6	<5
3	Without **L*9**	8	6	0
4	Without K_3PO_4	0	0	–

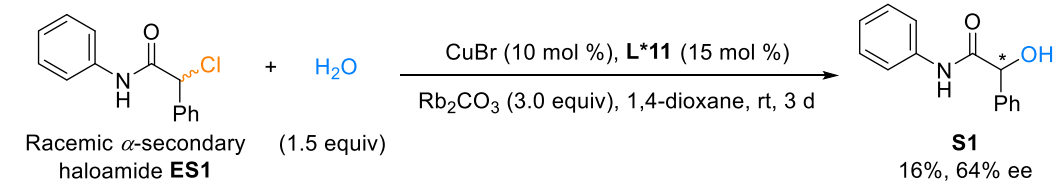
[a]Standard conditions: Racemic **E1** (0.05 mmol, 1.0 equiv), H_2O (1.5 equiv), Cu(OTf)•$(C_6H_6)_{1/2}$ (10 mol%), **L*9** (15 mol%), and K_3PO_4 (3.0 equiv) in 1,4-dioxane/1,3-dioxolane (0.50 mL, v/v = 4/1) at 0 °C for 5 days under argon. Yields were based on ^{1}H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard; ee values were based on chiral HPLC analysis.

Table S6. Effect of *N*-aryl substituent on the amide moiety in the substrate.[a]



[a]Reaction conditions: racemic α-tertiary haloamides **E** (0.10 mmol, 1.0 equiv), H_2O (1.5 equiv), Cu(OTf)•$(C_6H_6)_{1/2}$ (10 mol%), **L*9** (15 mol%), and K_3PO_4 (3.0 equiv) in 1,4-dioxane/1,3-dioxolane (1.0 mL, v/v = 4/1) at 0 °C for 5 days under argon. The yields were isolated yields, and ee values were based on chiral HPLC analysis. [b]0.20 mmol scale.

2. Supplementary figures for experiments



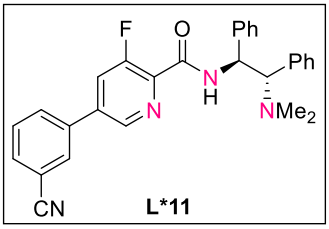
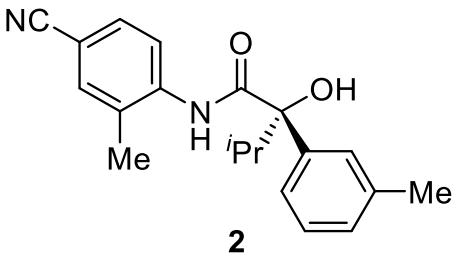


Figure S1. Preliminary investigation on the *O*-alkylation of water with racemic α-secondary haloamide. Reaction conditions: racemic α-tertiary haloamide **ES1** (0.20 mmol, 1.0 equiv), H_2O (1.5 equiv), CuBr (10 mol%), **L*11** (15 mol%), and Rb_2CO_3 (3.0 equiv) in 1,4-dioxane at rt for 3 days under argon. The yield was isolated yield, and ee value was based on chiral HPLC analysis.



2

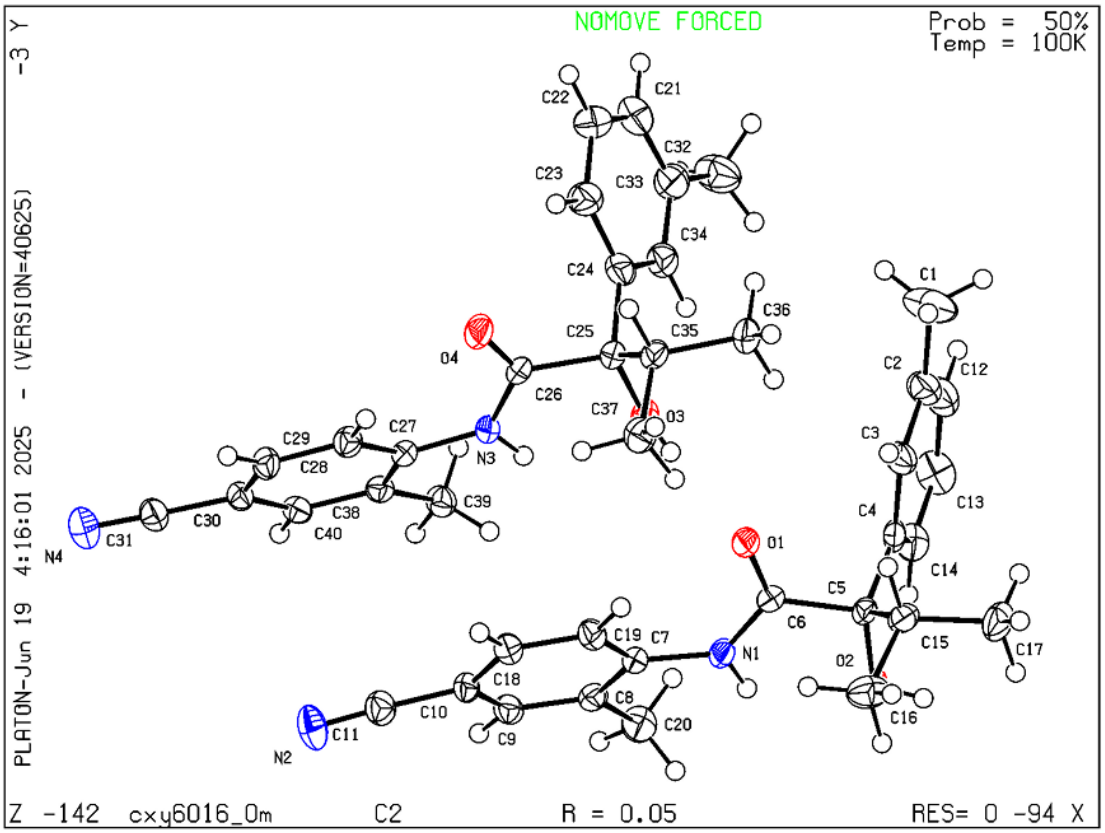
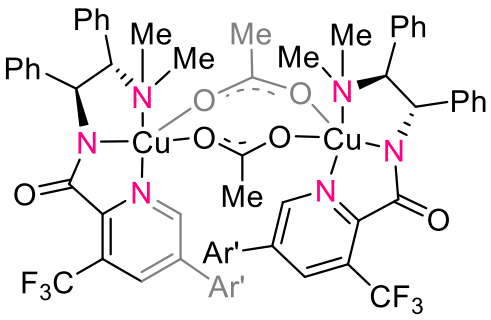


Figure S2. The X-ray structure of **2**. (CCDC 2526649, 50% probability ellipsoids).



(Cu-L*9)$_2$

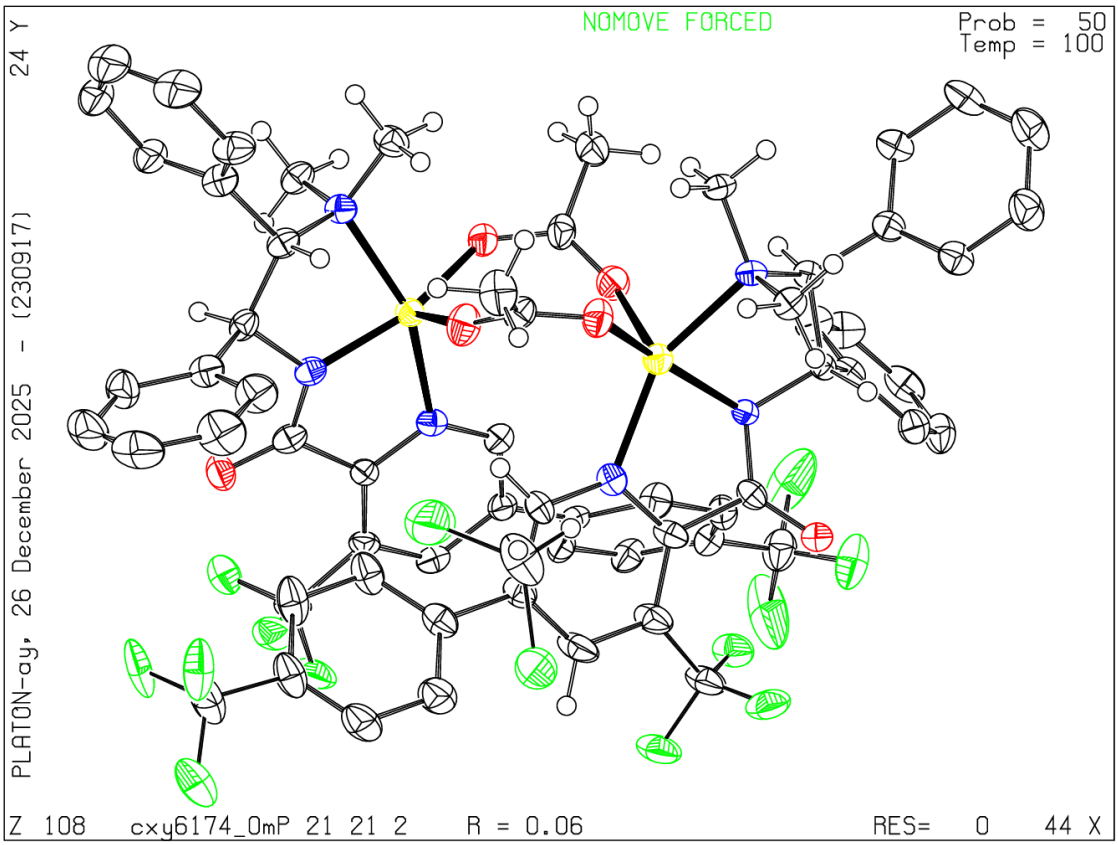
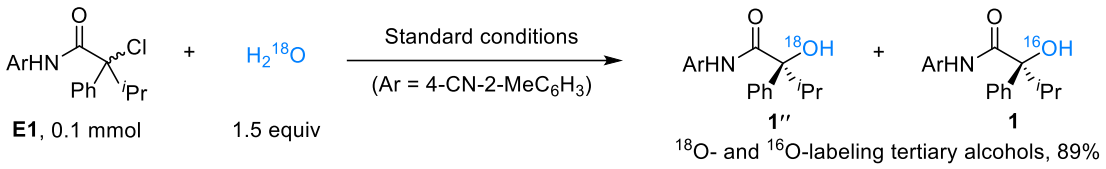


Figure S3. The X-ray structure of **(Cu-L*9)$_2$**. (CCDC 2526651, 50% probability ellipsoids). Ar', 4-$CF_3C_6H_4$.



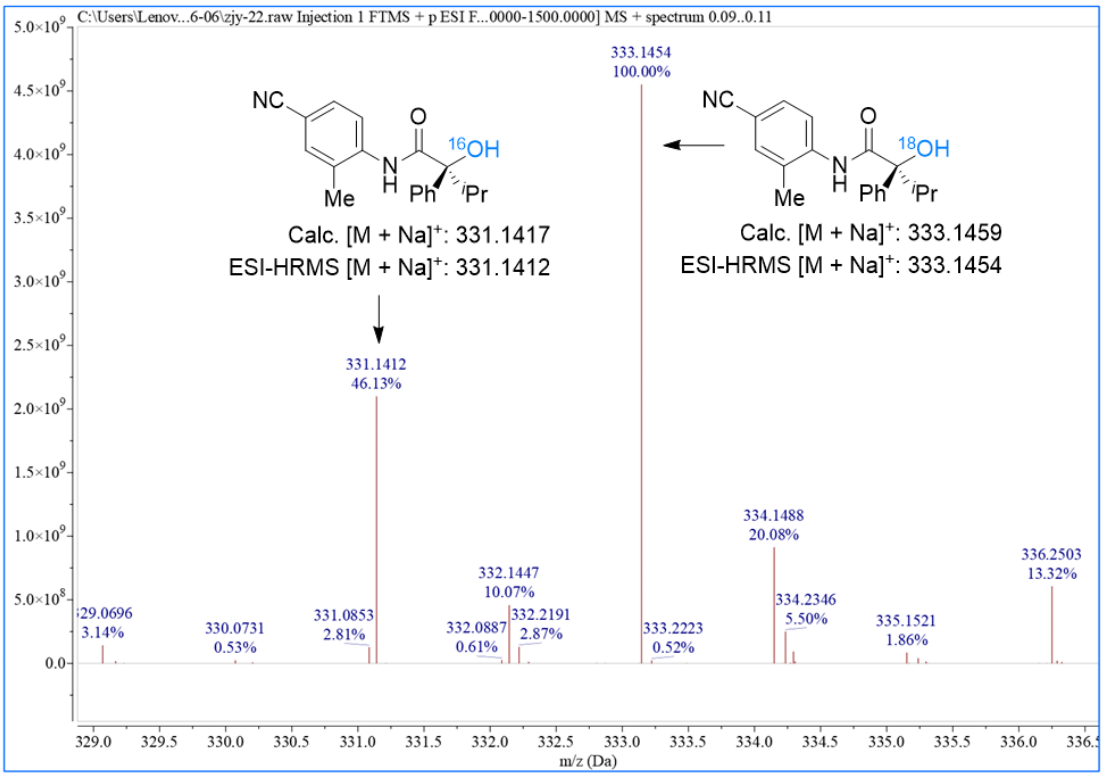


Figure S4. The ^{18}O-labeling experiment and high resolution mass spectrum (HRMS).

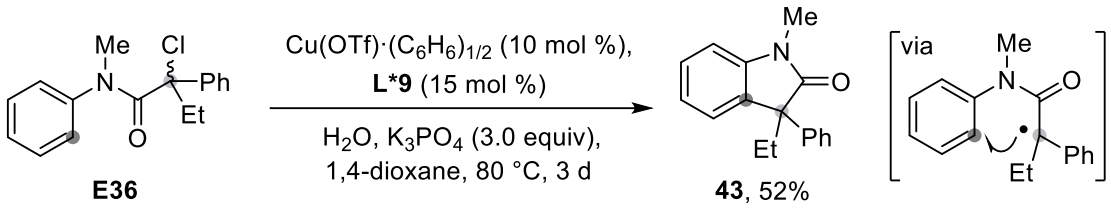


Figure S5. Radical clock experiment. Reaction conditions: racemic α-tertiary haloamides **E36** (0.20 mmol, 1.0 equiv), H_2O (1.5 equiv), Cu(OTf)•$(C_6H_6)_{1/2}$ (10 mol%), **L*9** (15 mol%), and K_3PO_4 (3.0 equiv) in 1,4-dioxane (2.0 mL) at 80 ℃ for 3 days under argon. The yield was isolated yield.

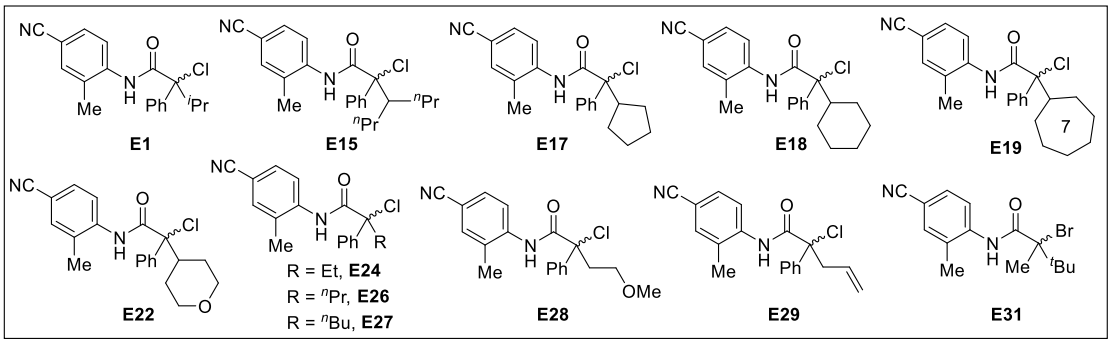
3. General information

Most of the reactions were carried out under argon atmosphere using Schlenk techniques. All the solvents used for the reactions were dried according to standard procedures. Schlenk tube was oven dried before use. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Cu(OTf)•$(C_6H_6)_{1/2}$ (CAS 37234-97-2) was purchased from Bide Pharmatech Ltd. CuI was purchased from Sigma-Aldrich. Anhydrous 1,4-dioxane and 1,3-dioxolane were purchased from J&K Scientific and stored under argon. K_3PO_4 was purchased from Bide Pharmatech Ltd, and pretreated prior to use by heating at 200 °C for 3 hours in vacuum. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 GF254 plates. Flash column chromatography was performed using Tsingdao silica gel (60, particle size 0.040–0.063 mm). As the eluent, the petroleum ether (PE) and EtOAc were purchased from Shanghai Titan Scientific Co. Ltd without further purification. Visualization on TLC was achieved by use of UV light (254 nm), iodine or basic $KMnO_4$ indicator. NMR spectra were recorded on Bruker DRX-400 spectrometers at 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR, respectively, in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. The chemical shifts are expressed in ppm and coupling constants were given in Hz. Data for ^1H NMR are recorded as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; p, pentet, m, multiplet; br, broad), coupling constant (Hz), integration. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Mass spectrometric data were obtained using Bruker Apex IV RTMS. Enantiomeric excess (ee) was determined using Agilent high-performance liquid chromatography (HPLC) with a Hitachi detector. Column conditions were reported in the experimental section below. Specific optical rotation was measured on a Rudolph-Autopol I. X-ray diffraction was measured on a ′Bruker APEX-II CCD′ diffractometer with Ga–Kα radiation.

4. The preparation of substrates and ligands

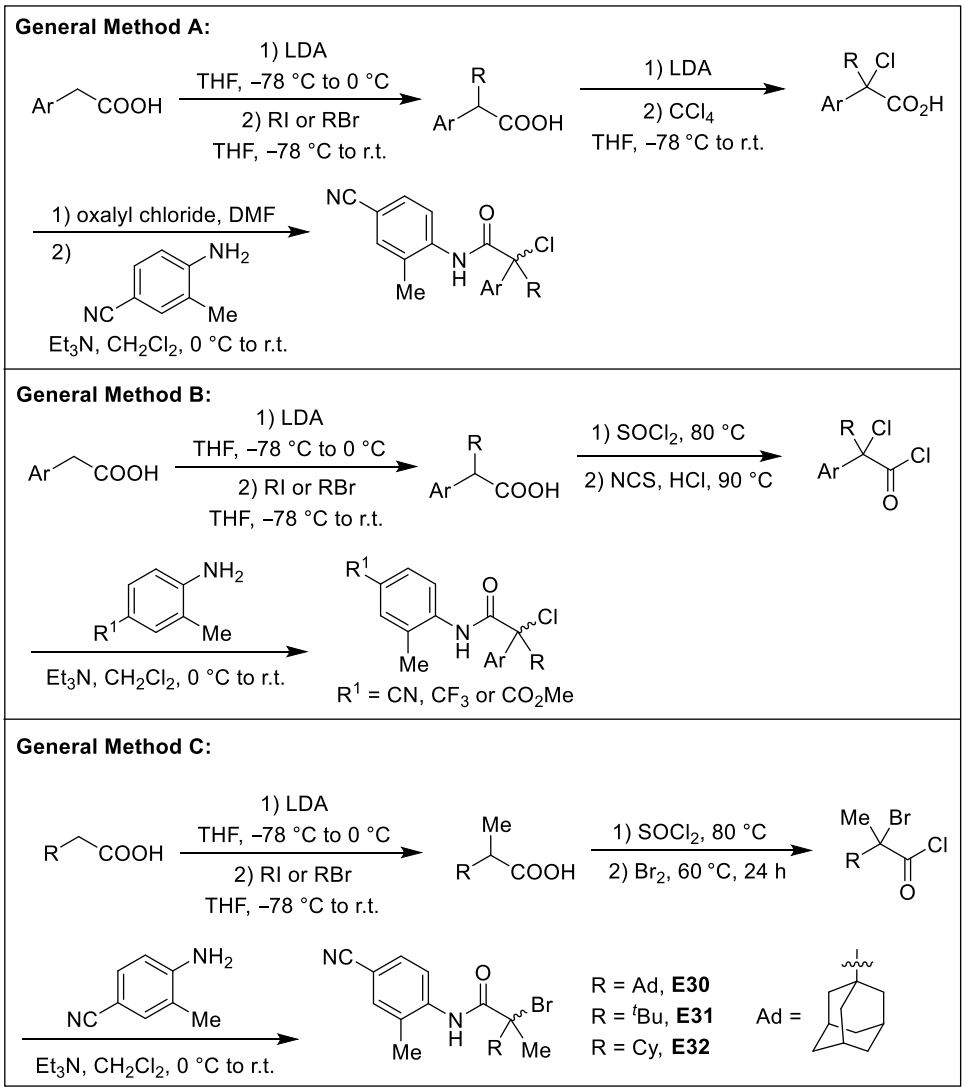
Preparation of α-tertiary haloamides

Table S7. Previously reported α-tertiary haloamides.

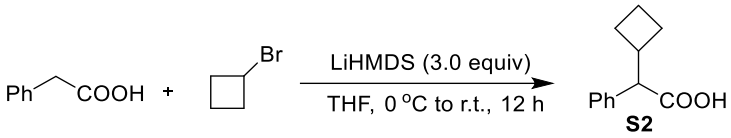


The α-tertiary haloamide substrates reported in the literature are listed in Table S7. The corresponding substrates **E1**, **E15**, **E17**, **E18**, **E19**, **E22**, **E24, E26-E29** and **E31** were prepared according to the reported procedure[1].

Table S8. General procedures for preparing new α-tertiary haloamides.

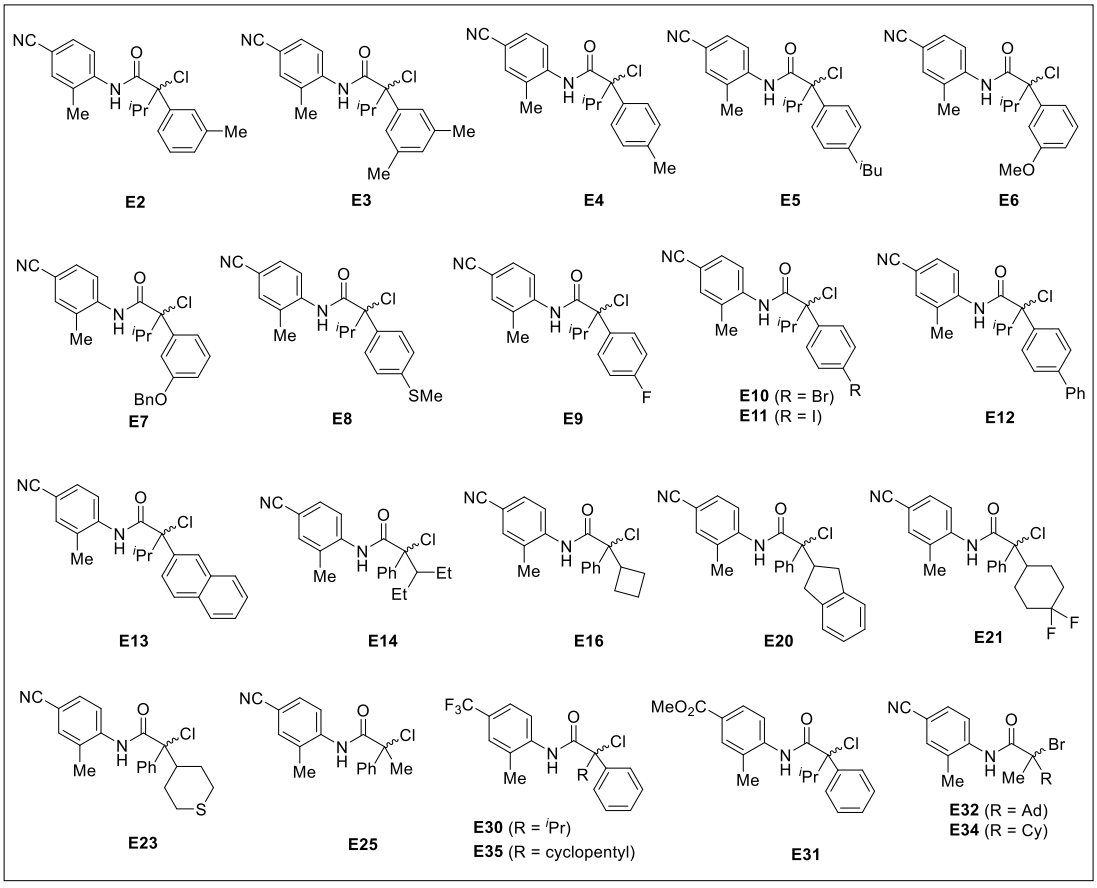


The synthesis of *α*-cyclobutyl substituted phenylacetic acid S2.



The *α*-cyclobutyl substituted phenylacetic acid **S2** was prepared according to the previously reported procedure[2]. A solution of phenylacetic acid (5.0 mmol) in dry THF (10 mL) was cooled in ice bath. Then LiHMDS (15 mL, 1M solution in THF) was added dropwise. After 1 h, a solution of bromocyclobutane (0.74 g, 5.5 mmol) in dry THF (5mL) was slowly added and the cold bath was removed. The reaction mixture was stirred overnight, then carefullyly quenched with water and extracted with EtOAc (10 mL x 3). The aqueous layer was acidified with 2.0 N HCI and extracted with EtOAc (10 mL x 3). The organic layers were combined and washed with brine, dried with Na_2SO_4, and purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 10/1 to 5/1) to afford the α-cyclobutyl substituted phenylacetic acid **S2** as a white solid.

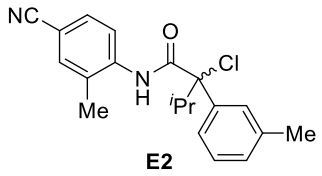
Table S9. The structures of new *α*-tertiary haloamide substrates.



The new *α*-tertiary haloamides are listed in Table S9. Substrates **E2**, **E3**, **E6**–**E8**, **E10**, **E12, E13**, **E20**, and **E23** were prepared using **General Method A** (Table S8); substrates **E4**, **E5**, **E9**, **E11**, **E14**, **E16**, **E21**, **E25**, **E30**, **E31**, and **E35** were prepared using **General Method B** (Table S8); and substrate **E32** and **E34** were prepared using **General Method C** (Table S8), according to the previously reported procedures[1].

Characterization data for new *α*-tertiary haloamides

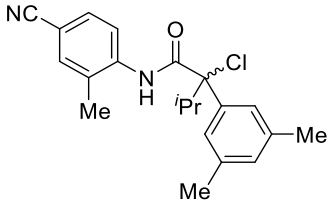
2-Chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl-2-(*m*-tolyl)butanamide (E2)



E2

According to **General Method A**, the synthesized substrate **E2** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.51 – 7.44 (m, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 7.31 – 7.22 (m, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 3.24 – 3.10 (m, 1H), 2.37 (s, 3H), 2.24 (s, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 139.6, 138.4, 138.1, 133.8, 131.1, 129.2, 128.3, 126.9, 123.4, 120.9, 118.7, 107.7, 86.1, 37.3, 21.6, 18.9, 17.2, 16.9.
HRMS (ESI) m/z calcd. for $C_{20}H_{21}ClN_2NaO$ $[M + Na]^+$ 363.1235, found 363.1229.

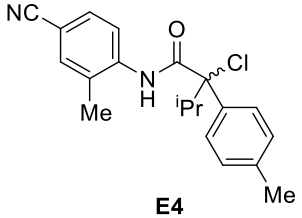
2-Chloro-*N*-(4-cyano-2-methylphenyl)-2-(3,5-dimethylphenyl)-3-methyl-butanamide (E3)



E3

According to **General Method A**, the synthesized substrate **E3** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.46 – 7.42 (m, 1H), 7.32 (s, 2H), 6.96 (s, 1H), 3.21 – 3.11 (m, 1H), 2.33 (s, 6H), 2.25 (s, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 139.7, 138.4, 138.0, 133.8, 131.1, 130.1, 128.3, 124.1, 120.9, 118.8, 107.7, 86.2, 37.3, 21.5, 19.0, 17.3, 17.1.
HRMS (ESI) m/z calcd. for $C_{21}H_{23}ClN_2NaO$ $[M + Na]^+$ 377.1391, found 377.1387.

2-Chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl-2-(*p*-tolyl)butanamide (E4)

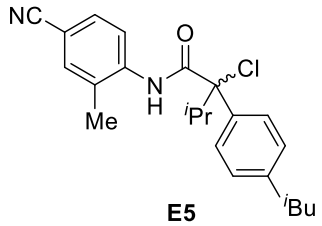


E4

According to **General Method B**, the synthesized substrate **E4** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.65 – 7.56 (m, 2H), 7.51 – 7.45 (m, 1H), 7.44 – 7.38 (m, 1H), 7.24 – 7.11 (m, 2H), 3.22 – 3.10 (m, 1H), 2.34 (s, 3H), 2.24 (s, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 139.6, 138.3, 135.6, 133.7, 131.0, 129.1, 128.3, 126.2, 120.9, 118.7, 107.7, 86.0, 37.3, 20.8, 18.9, 17.2, 16.9.
HRMS (ESI) m/z calcd. for $C_{20}H_{21}ClN_2NaO$ $[M + Na]^+$ 363.1235, found 363.1229.

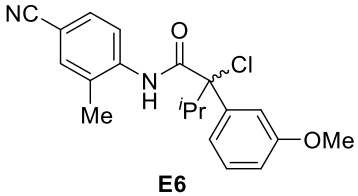
2-Chloro-*N*-(4-cyano-2-methylphenyl)-2-(4-isobutylphenyl)-3-methylbutanamide (E5)



E5

According to **General Method B**, the synthesized substrate **E5** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.62 (d, 2H), 7.52 – 7.44 (m, 1H), 7.45 – 7.39 (m, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 3.24 – 3.07 (m, 1H), 2.46 (d, *J* = 7.2 Hz, 2H), 2.23 (s, 3H), 1.94 – 1.78 (m, 1H), 1.16 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 6H), 0.82 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 142.1, 139.6, 135.8, 133.7, 131.0, 129.1, 128.4, 126.1, 121.0, 118.7, 107.7, 86.1, 44.7, 37.4, 30.0, 22.3, 22.2, 18.9, 17.2, 16.9.
HRMS (ESI) m/z calcd. for $C_{23}H_{27}ClN_2NaO$ $[M + Na]^+$ 405.1704, found 405.1704.

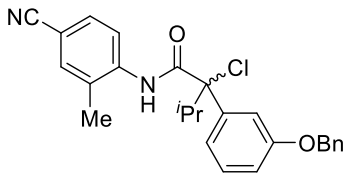
2-Chloro-*N*-(4-cyano-2-methylphenyl)-2-(3-methoxyphenyl)-3-methyl-butanamide (E6)



E6

According to **General Method A**, the synthesized substrate **E6** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a light yellow solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.49 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.43 (d, *J* = 1.9 Hz, 1H), 7.33 – 7.27 (m, 3H), 6.91 – 6.86 (m, 1H), 3.82 (s, 3H), 3.24 – 3.10 (m, 1H), 2.24 (s, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 159.6, 140.1, 139.6, 133.8, 131.1, 129.5, 128.4, 121.0, 118.7, 118.6, 113.2, 112.9, 107.8, 85.8, 55.3, 37.5, 19.0, 17.3, 16.9.
HRMS (ESI) m/z calcd. for $C_{20}H_{21}ClN_2NaO_2$ $[M + Na]^+$ 379.1184, found 379.1178.

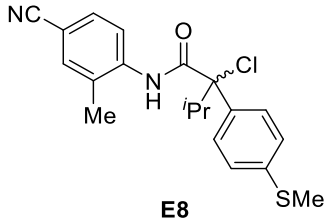
2-(3-(Benzyloxy)phenyl)-2-chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl-butanamide (E7)



E7

According to **General Method A**, the synthesized substrate **E7** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.53 – 7.31 (m, 10H), 7.01 – 6.95 (m, 1H), 5.11 (s, 2H), 3.26 – 3.10 (m, 1H), 2.25 (s, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 158.8, 140.2, 139.6, 136.6, 133.9, 131.2, 129.6, 128.7, 128.5, 128.1, 127.6, 121.1, 119.0, 118.8, 114.4, 113.8, 107.9, 85.9, 70.1, 37.6, 19.1, 17.3, 17.0.
HRMS (ESI) m/z calcd. for $C_{26}H_{25}ClN_2NaO_2$ $[M + Na]^+$ 455.1497, found 455.1493.

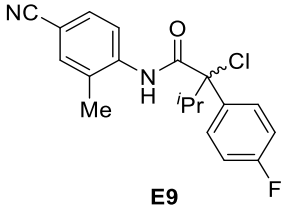
2-Chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl-2-(4-(methylthio)phenyl)-butanamide (E8)



E8

According to **General Method A**, the synthesized substrate **E8** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.72 – 7.63 (m, 2H), 7.55 – 7.42 (m, 2H), 7.31 – 7.20 (m, 2H), 3.32 – 3.08 (m, 1H), 2.49 (s, 3H), 2.27 (s, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 139.4, 139.3, 135.0, 133.8, 131.0, 128.4, 126.8, 125.8, 120.9, 118.6, 107.8, 85.8, 37.3, 18.8, 17.2, 16.8, 15.2.
HRMS (ESI) m/z calcd. for $C_{20}H_{21}ClN_2NaOS$ $[M + Na]^+$ 395.0955, found 395.0954.

2-Chloro-*N*-(4-cyano-2-methylphenyl)-2-(4-fluorophenyl)-3-methylbutanamide (E9)

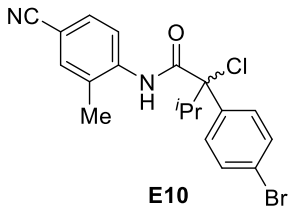


E9

According to **General Method B**, the synthesized substrate **E9** was purified by column

chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.92 – 7.67 (m, 2H), 7.53 – 7.37 (m, 2H), 7.19 – 6.95 (m, 2H), 3.26 – 3.08 (m, 1H), 2.25 (s, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 162.4 (d, *J* = 248.6 Hz), 139.3, 134.3 (d, *J* = 3.3 Hz), 133.7, 130.9, 128.6, 128.3 (d, *J* = 8.2 Hz), 121.1, 118.5, 115.2 (d, *J* = 21.5 Hz), 107.9, 85.3, 37.6, 18.8, 17.1, 16.7.
^{19}F NMR (376 MHz, $CDCl_3$) δ –113.7.
HRMS (ESI) m/z calcd. for $C_{19}H_{18}ClFN_2NaO$ $[M + Na]^+$ 367.0984, found 367.0979.

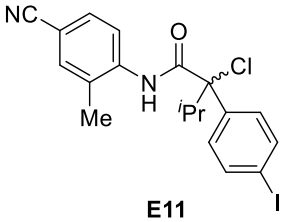
2-(4-Bromophenyl)-2-chloro-*N*-(4-cyano-2-methylphenyl)-3-methylbutanamide (E10)



E10

According to **General Method A**, the synthesized substrate **E10** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.71 – 7.58 (m, 2H), 7.57 – 7.47 (m, 3H), 7.45 (s, 1H), 3.22 – 3.05 (m, 1H), 2.26 (s, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 139.4, 137.7, 133.9, 131.6, 131.2, 128.63, 128.3, 122.9, 121.2, 118.7, 108.1, 85.6, 37.8, 19.0, 17.4, 16.9.
HRMS (ESI) m/z calcd. for $C_{19}H_{18}BrClN_2NaO$ $[M + Na]^+$ 427.0183, found 427.0179.

2-Chloro-*N*-(4-cyano-2-methylphenyl)-2-(4-iodophenyl)-3-methylbutanamide (E11)

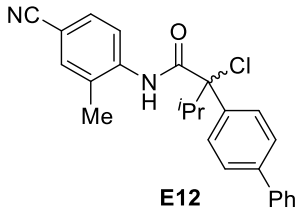


E11

According to **General Method B**, the synthesized substrate **E11** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.82 – 7.63 (m, 2H), 7.54 – 7.46 (m, 2H), 7.46 – 7.42 (m, 1H), 7.41 – 7.38 (m, 1H), 3.22 – 3.02 (m, 1H), 2.24 (s, 3H), 1.13 (d, *J* = 6.4 Hz, 3H), 0.79 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 139.1, 138.2, 137.3, 133.7, 130.8, 128.6, 128.2, 121.0, 118.4, 107.8, 94.5, 85.4, 37.4, 18.7, 17.2, 16.7.

HRMS (ESI) m/z calcd. for $C_{19}H_{18}ClIN_2NaO$ $[M + Na]^+$ 475.0045, found 475.0044.

2-([1,1'-Biphenyl]-4-yl)-2-chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl-butanamide (E12)



E12

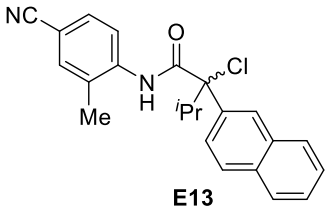
According to **General Method A**, the synthesized substrate **E12** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 2H), 7.68 – 7.58 (m, 4H), 7.55 – 7.44 (m, 4H), 7.42 – 7.35 (m, 1H), 3.34 – 3.20 (m, 1H), 2.30 (s, 3H), 1.24 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 141.3, 140.0, 139.6, 137.6, 133.9, 131.2, 128.9, 128.6, 127.8, 127.2, 127.1, 127.0, 121.1, 118.8, 107.9, 86.1, 37.6, 19.1, 17.4, 17.1.

HRMS (ESI) m/z calcd. for $C_{25}H_{23}ClN_2NaO$ $[M + Na]^+$ 425.1391, found 425.1387.

2-Chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl-2-(naphthalen-2-yl)butanamide (E13)



E13

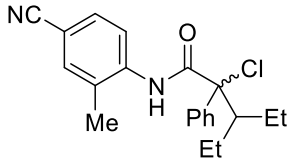
According to **General Method A**, the synthesized substrate **E13** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.31 (s, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 8.01 – 7.81 (m, 4H), 7.62 – 7.50 (m, 2H), 7.47 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.40 (s, 1H), 3.44 – 3.26 (m, 1H), 2.24 (s, 3H), 1.28 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 139.6, 136.0, 133.9, 133.0, 132.9, 131.1, 128.8, 128.6, 128.4, 127.5, 126.9, 126.7, 126.1, 123.9, 121.2, 118.8, 107.9, 86.3, 37.5, 19.2, 17.4, 17.1.

HRMS (ESI) m/z calcd. for $C_{23}H_{21}ClN_2NaO$ $[M + Na]^+$ 399.1235, found 399.1230.

2-Chloro-*N*-(4-cyano-2-methylphenyl)-3-ethyl-2-phenylpentanamide (E14)



E14

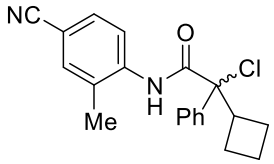
According to **General Method B**, the synthesized substrate **E14** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.81 – 7.70 (m, 2H), 7.50 – 7.30 (m, 5H), 2.75 – 2.59 (m, 1H), 2.22 (s, 3H), 1.67 – 1.50 (m, 2H), 1.36 – 1.22 (m, 2H), 1.06 (t, *J* = 7.5 Hz, 3H), 0.78 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 139.7, 138.7, 133.9, 131.1, 128.6, 128.5, 128.4, 126.6, 121.1, 118.8, 107.9, 86.7, 50.6, 26.5, 23.8, 17.3, 13.7, 13.4.

HRMS (ESI) m/z calcd. for $C_{21}H_{23}ClN_2NaO$ $[M + Na]^+$ 377.1391, found 377.1386.

2-Chloro-*N*-(4-cyano-2-methylphenyl)-2-cyclobutyl-2-phenylacetamide (E16)



E16

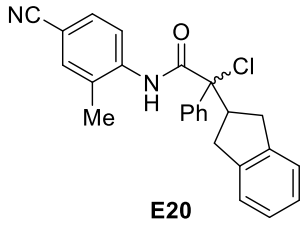
According to **General Method B**, the synthesized substrate **E16** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.52 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.46 (s, 1H), 7.43 – 7.34 (m, 3H), 3.76 – 3.58 (m, 1H), 2.33 – 2.26 (m, 1H), 2.24 (s, 3H), 2.21 – 2.10 (m, 2H), 2.03 – 1.89 (m, 2H), 1.88 – 1.77 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 139.6, 138.9, 133.9, 131.2, 128.8, 128.7, 128.5, 126.4, 121.2, 118.8, 107.9, 82.5, 43.7, 24.9, 24.5, 17.3, 17.1.

HRMS (ESI) m/z calcd. for $C_{20}H_{19}ClN_2NaO$ $[M + Na]^+$ 361.1078, found 361.1073.

2-Chloro-*N*-(4-cyano-2-methylphenyl)-2-(2,3-dihydro-1*H*-inden-2-yl)-2-phenylacetamide (E20)



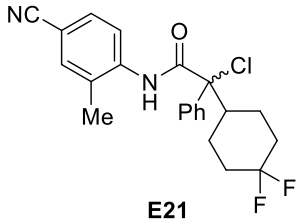
E20

According to **General method A**, the synthesized substrate **E20** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 7.4

Hz, 2H), 7.59 – 7.35 (m, 5H), 7.25 – 7.03 (m, 4H), 4.14 – 3.94 (m, 1H), 3.40 – 3.14 (m, 2H), 3.03 – 2.87 (m, 1H), 2.84 – 2.69 (m, 1H), 2.23 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 142.0, 141.6, 139.6, 138.7, 134.0, 131.2, 128.9, 128.6, 126.6, 126.5, 126.3, 124.5, 124.3, 121.2, 118.8, 108.1, 83.5, 48.4, 36.1, 34.9, 17.3.
HRMS (ESI) m/z calcd. for $C_{25}H_{21}ClN_2NaO$ $[M + Na]^+$ 423.1235, found 423.1234.

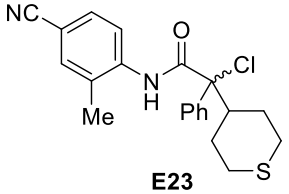
2-Chloro-*N*-(4-cyano-2-methylphenyl)-2-(4,4-difluorocyclohexyl)-2-phenylacetamide (E21)



E21

According to **General Method B**, the synthesized substrate **E21** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.53 – 7.47 (m, 1H), 7.46 – 7.34 (m, 4H), 2.85 (t, *J* = 11.0 Hz, 1H), 2.22 (s, 3H), 2.19 – 2.01 (m, 2H), 1.96 – 1.63 (m, 4H), 1.59 – 1.45 (m, 1H), 1.38 – 1.29 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 139.3, 137.7, 134.0, 131.2, 128.9, 128.8, 128.7, 126.1, 121.2, 118.7, 108.2, 83.16 (d, *J* = 2.4 Hz), 45.5, 33.3 (t, *J* = 24.6 Hz), 25.2 (d, *J* = 10.3 Hz), 23.1 (d, *J* = 10.3 Hz), 17.3.
^{19}F NMR (376 MHz, $CDCl_3$) δ –92.1 (d, *J* = 235.4 Hz), –102.8 (d, *J* = 235.7 Hz).
HRMS (ESI) m/z calcd. for $C_{22}H_{21}ClF_2N_2NaO$ $[M + Na]^+$ 425.1203, found 425.1202.

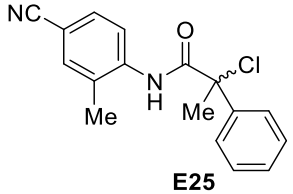
2-Chloro-*N*-(4-cyano-2-methylphenyl)-2-phenyl-2-(tetrahydro-2*H*-thiopyran-4-yl)acetamide (E23)



E23

According to **General Method A**, the synthesized substrate **E23** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.71 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.45 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.43 – 7.33 (m, 4H), 2.87 – 2.76 (m, 2H), 2.67 – 2.58 (m, 2H), 2.55 – 2.47 (m, 1H), 2.20 (s, 3H), 2.18 – 2.11 (m, 1H), 1.94 – 1.82 (m, 1H), 1.62 – 1.51 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 139.4, 137.2, 133.9, 131.1, 128.8, 126.5, 121.2, 118.7, 108.1, 84.6, 47.1, 31.0, 28.8, 28.7, 28.4, 17.3.
HRMS (ESI) m/z calcd. for $C_{21}H_{21}ClN_2NaOS$ $[M + Na]^+$ 407.0955, found 407.0954.

2-Chloro-*N*-(4-cyano-2-methylphenyl)-2-phenylpropanamide (E25)



E25

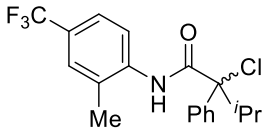
According to **General Method B**, the synthesized substrate **E25** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 7.67 – 7.57 (m, 2H), 7.51 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.47 – 7.33 (m, 4H), 2.23 (s, 3H), 2.19 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 140.7, 139.6, 133.9, 131.3, 129.0, 128.9, 128.4, 125.9, 121.0, 118.8, 108.0, 73.6, 30.1, 17.2.

HRMS (ESI) m/z calcd. for $C_{17}H_{15}ClN_2NaO$ $[M + Na]^+$ 321.0765, found 321.0762.

2-Chloro-3-methyl-*N*-(2-methyl-4-(trifluoromethyl)phenyl)-2-phenylbutanamide (E30)



E30

According to **General Method B**, the synthesized substrate **E30** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 25/1) to afford as a light yellow solid.

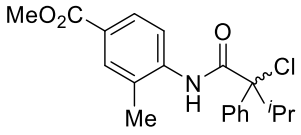
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.80 – 7.72 (m, 2H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.40 – 7.33 (m, 2H), 3.27 – 3.09 (m, 1H), 1.18 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 140.3, 138.6, 128.5, 128.4, 126.6 (q, *J* = 32.7 Hz), 126.5, 126.2 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 270.0 Hz), 119.6, 85.5, 37.7, 19.1, 17.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ –62.2.

HRMS (ESI) m/z calcd. for $C_{19}H_{20}ClF_3NO$ $[M + H]^+$ 370.1180, found 370.1178.

Methyl 4-(2-chloro-3-methyl-2-phenylbutanamido)-3-methylbenzoate (E31)



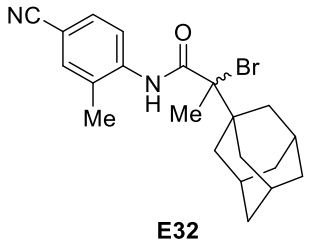
E31

According to **General Method B**, the synthesized substrate **E31** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.95 – 7.79 (m, 2H), 7.78 – 7.68 (m, 2H), 7.43 – 7.26 (m, 3H), 3.89 (s, 3H), 3.28 – 3.12 (m, 1H), 2.27

(s, 3H), 1.18 (d, J = 6.4 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 166.6, 139.6, 138.8, 131.7, 128.6, 128.5, 128.4, 127.7, 126.5, 126.2, 120.5, 86.2, 52.0, 37.5, 19.1, 17.5, 17.0.
HRMS (ESI) m/z calcd. for $C_{20}H_{23}ClNO_3$ $[M + H]^+$ 360.1361, found 360.1361.

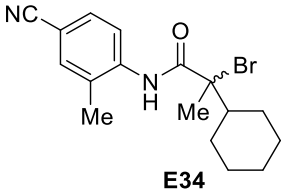
2-((1*S*,3*S*)-adamantan-1-yl)-2-bromo-N-(4-cyano-2-methylphenyl)propanamide (E32)



E32

According to **General Method C**, the synthesized substrate **E32** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.28 (d, J = 8.5 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.46 (s, 1H), 2.33 (s, 3H), 2.02 (s, 6H), 1.94 – 1.76 (m, 6H), 1.70 – 1.54 (m, 6H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 139.9, 133.9, 131.2, 128.1, 120.4, 118.9, 107.5, 84.7, 40.7, 38.2, 36.4, 28.6, 25.3, 17.7.
HRMS (ESI) m/z calcd. for $C_{21}H_{25}BrN_2NaO$ $[M + Na]^+$ 423.1042, found 423.1038.

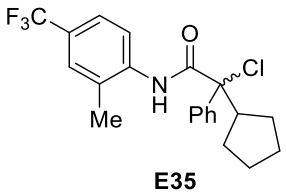
2-Bromo-*N*-(4-cyano-2-methylphenyl)-2-cyclohexylpropanamide (E34)



E34

According to **General Method C**, the synthesized substrate **E34** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 15/1) to afford as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.27 (d, J = 8.5 Hz, 1H), 7.57 – 7.46 (m, 2H), 2.35 (s, 3H), 1.99 (s, 3H), 1.93 – 1.73 (m, 6H), 1.34 – 1.18 (m, 5H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 139.7, 133.9, 131.2, 128.2, 120.7, 118.8, 107.8, 77.7, 48.2, 29.6, 28.4, 28.0, 26.0, 25.9, 25.8, 17.5.
HRMS (ESI) m/z calcd. for $C_{17}H_{22}BrN_2O$ $[M + H]^+$ 349.0910, found 349.0905.

2-Chloro-2-cyclopentyl-*N*-(2-methyl-4-(trifluoromethyl)phenyl)-2-phenylacetamide (E35)



E35

According to **General Method B**, the synthesized substrate **E35** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 25/1 to 20/1) to afford as a colorless oil.

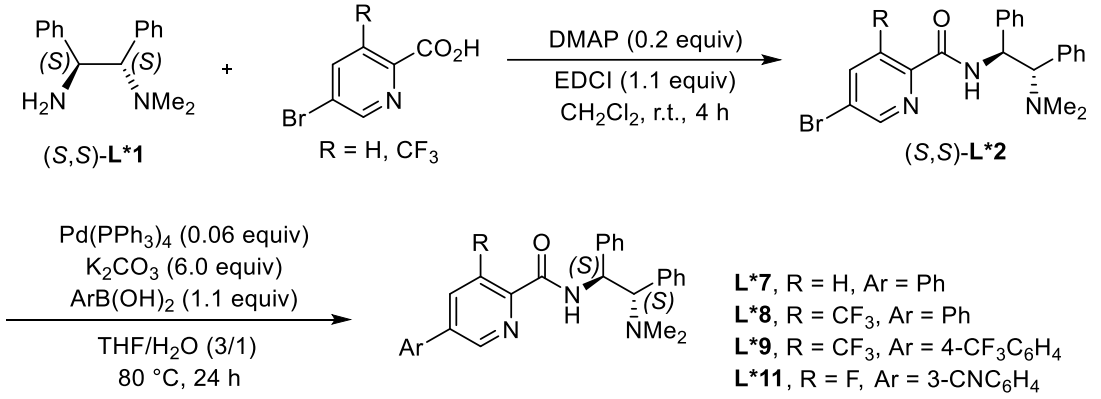
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 7.4 Hz, 2H), 7.51 – 7.32 (m, 5H), 3.52 – 3.33 (m, 1H), 2.26 (s, 3H), 2.09 – 1.91 (m, 1H), 1.81 – 1.63 (m, 4H), 1.60 – 1.42 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 139.8, 138.5, 128.8, 128.5, 128.4, 127.3 (q, *J* = 3.7 Hz), 126.8 (q, *J* = 32.3 Hz), 126.5, 124.1 (q, *J* = 270.1 Hz), 124.0 (q, *J* = 3.7 Hz), 121.5, 84.6, 48.7, 29.2, 28.2, 26.2, 25.9, 17.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ –62.2.

HRMS (ESI) m/z calcd. for $C_{21}H_{22}ClF_3NO$ $[M + H]^+$ 396.1337, found 396.1339.

The synthesis of chiral ligands



The chiral ligand **L*7-L*9** and **L*11** were synthesized according to the reported procedure[1].

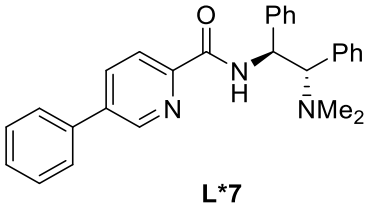
To a solution of chiral diamine (*S*,*S*)-**L*1** (5.0 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (10 mL) were successively added the substituted 5-bromo-picolinic acid (5.5 mmol, 1.1 equiv), DMAP (0.12 g, 1.0 mmol, 0.2 equiv) and EDCI (5.5 mmol, 1.1 equiv) under argon at room temperature. The reaction mixture was stirred at room temperature for 4 h. After completion (monitored by TLC), the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 10/1 to 5/1) to give the ligand intermediate (*S*, *S*)-**L*2** as a white solid.

To a solution of the ligand (*S*,*S*)-**L*2** in THF/H_2O (10 mL, v/v: 3/1) were successively added $Pd(PPh_3)_4$ (0.06 equiv), K_2CO_3 (6.0 equiv) and arylboronic acid (1.1 equiv) under argon. The reaction was reflux at 80 °C for 24 hours. Then the reaction was quenched by H_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 5/1 to 2/1) to give the ligands **L*7-L*9** and **L*11** as white solids.

The diamine (*S*,*S*)-**L*1** was synthesized according to the reported literature[3]. The chiral ligand *ent*-**L*9** was synthesized according to the same procedures as **L*9**. And the NMR date of *ent*-**L*9** were identical to those of **L*9**.

Characterization data for new chiral ligands

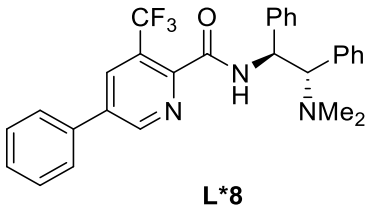
***N*-((1*S*,2*S*)-2-(dimethylamino)-1,2-diphenylethyl)-5-phenylpicolinamide (L*7)**



L*7

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (d, *J* = 5.4 Hz, 1H), 8.86 (d, *J* = 2.2 Hz, 1H), 8.21 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.98 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.56 – 7.47 (m, 2H), 7.45 – 7.41 (m, 1H), 7.28 – 7.26 (m, 1H), 7.25 – 7.17 (m, 4H), 7.15 – 7.08 (m, 4H), 7.07 – 7.03 (m, 1H), 5.49 – 5.41 (m, 1H), 3.95 (d, *J* = 10.6 Hz, 1H), 2.25 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 149.0, 146.8, 140.9, 138.8, 137.1, 135.3, 133.1, 129.7, 129.2, 128.5, 127.9, 127.7, 127.6, 127.5, 127.2, 126.9, 122.3, 73.5, 54.6, 41.0.
HRMS (ESI) m/z calcd. for $C_{28}H_{28}N_3O$ $[M + H]^+$ 422.2227, found 422.2228.

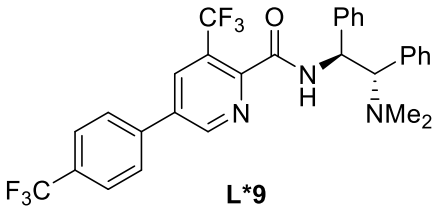
***N*-((1*S*,2*S*)-2-(dimethylamino)-1,2-diphenylethyl)-5-phenyl-3-(trifluoromethyl) picolinamide (L*8)**



L*8

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, *J* = 1.3 Hz, 1H), 8.87 (d, *J* = 4.8 Hz, 1H), 8.28 (s, 1H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.55 – 7.45 (m, 3H), 7.25 – 7.20 (m, 5H), 7.14 – 7.03 (m, 5H), 5.43 (dd, *J* = 10.6, 5.1 Hz, 1H), 3.85 (d, *J* = 10.6 Hz, 1H), 2.21 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 149.0, 148.7, 136.9 (q, *J* = 255.2 Hz), 134.0 (q, *J* = 5.6 Hz), 129.8, 129.5, 129.4, 128.0, 127.8, 127.7, 127.5, 127.3, 126.9, 125.8 (q, *J* = 33.8 Hz), 123.01 (q, *J* = 272.3 Hz), 73.7, 54.8, 41.0.
^{19}F NMR (376 MHz, $CDCl_3$) δ –59.2.
HRMS (ESI) m/z calcd. for $C_{29}H_{27}F_3N_3O$ $[M + H]^+$ 490.2101, found 490.2099.

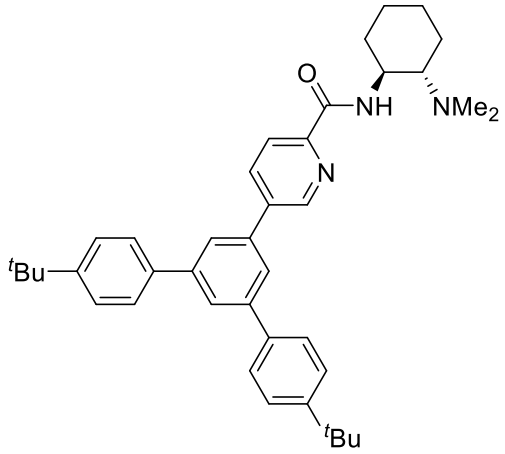
***N*-((1*S*,2*S*)-2-(dimethylamino)-1,2-diphenylethyl)-3-(trifluoromethyl)-5-(4-(trifluoromethyl)phenyl)picolinamide (L*9)**



L*9

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, *J* = 1.9 Hz, 1H), 8.88 (d, *J* = 4.6 Hz, 1H), 8.33 (d, *J* = 1.8 Hz, 1H), 7.90 – 7.73 (m, 4H), 7.32 – 7.22 (m, 5H), 7.21 – 7.03 (m, 5H), 5.44 (dd, *J* = 10.6, 5.0 Hz, 1H), 3.87 (d, *J* = 10.7 Hz, 1H), 2.24 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 149.6, 149.1, 140.6, 139.1, 136.8, 134.4 (q, *J* = 5.8 Hz), 133.0, 131.3 (q, *J* = 32.5 Hz), 129.8, 128.1, 127.9, 127.8, 127.7, 127.4, 127.0, 126.4 (q, *J* = 3.6 Hz), 126.0 (q, *J* = 34.2 Hz), 123.4 (q, *J* = 105.1 Hz), 73.7, 54.9, 41.0.
^{19}F NMR (376 MHz, $CDCl_3$) δ –59.3, –62.7.
HRMS (ESI) m/z calcd. for $C_{30}H_{26}F_6N_3O$ $[M + H]^+$ 558.1975, found 558.1974.

5-(4,4''-di-*tert*-butyl-[1,1':3',1''-terphenyl]-5'-yl)-*N*-((1*S*,2*S*)-2-(dimethylamino) cyclohexyl)picolinamide (L*10)



L*10

The chiral ligand **L*10** was synthesized according to the similar procedure as **L*9**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, *J* = 0.7 Hz, 1H), 8.43 – 8.25 (m, 2H), 8.17 – 8.08 (m, 1H), 7.87 (s, 1H), 7.77 (s, 2H), 7.64 (d, *J* = 8.2 Hz, 4H), 7.54 (d, *J* = 8.2 Hz, 4H), 3.96 – 3.80 (m, 1H), 2.60 – 2.50 (m, 2H), 2.31 (s, 6H), 1.98 – 1.82 (m, 2H), 1.80 – 1.70 (m, 1H), 1.40 (s, 18H), 1.33 – 1.27 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 150.9, 149.5, 146.9, 142.7, 138.9, 138.2, 137.8, 135.6, 127.0, 126.2, 126.0, 124.8, 122.3, 66.5, 51.1, 40.2, 34.7, 33.0, 31.4, 25.4, 24.9, 22.1.
HRMS (ESI) m/z calcd. for $C_{40}H_{50}N_3O$ $[M + H]^+$ 588.3948, found 588.3947.

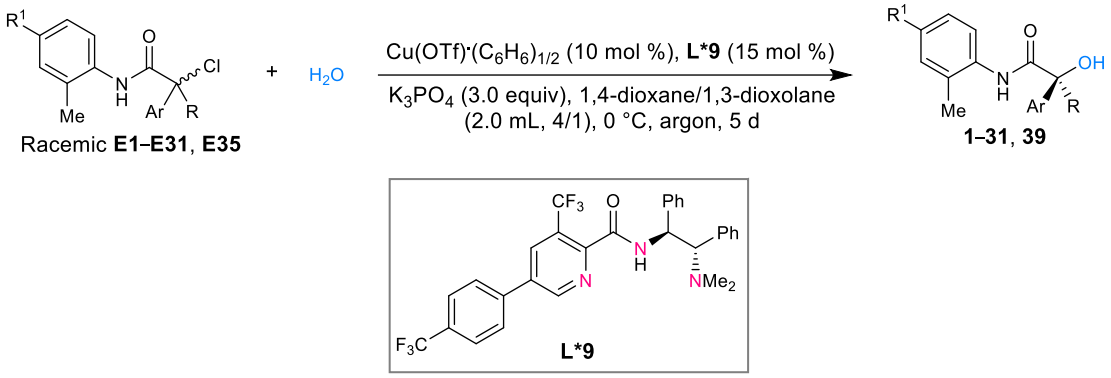
5. General procedure for the synthesis of products

The preparation of the mixed solvents for this reaction

Under argon atmosphere, an oven-dried resealable 100 mL Schlenk tube was charged with anhydrous 1,4-dioxane (40 mL) and 1,3-dioxolane (10 mL). Then water (7.5 mmol, 135.0 mg) was added to the mixed solvent, and the mixture was shaken thoroughly.

Note: *The other solvent or mixed solvents were prepared by analogy, and the corresponding prepared mixed solvent was used and stored under argon atmosphere.*

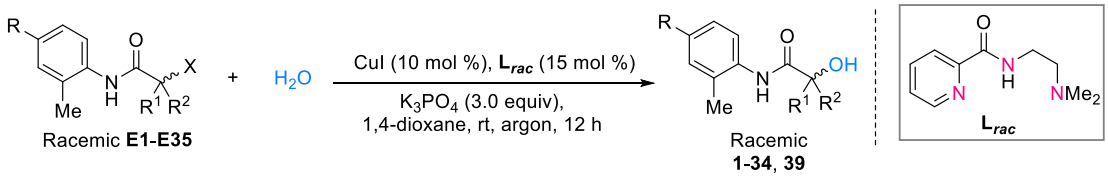
General procedure for the synthesis of chiral products



General Procedure A:

Under argon atmosphere, an oven-dried 10 mL resealable Schlenk tube equipped with a magnetic stir bar was charged with α-tertiary haloamides (0.20 mmol, 1.0 equiv), Cu(OTf)•$(C_6H_6)_{1/2}$ (5.03 mg, 0.02 mmol, 10 mol%), chiral ligand **L*9** (16.72 mg, 0.03 mmol, 15 mol%) and K_3PO_4 (128.0 mg, 0.60 mmol, 3.0 equiv). Then the mixed solvent (1,4-dioxane/1,3-dioxolane = 4/1, 2.0 mL) was added into the mixture, and the reaction mixture was stirred at 0 °C for 5 days. Upon completion (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2, filtered off and rinsed three times with CH_2Cl_2. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel to afford the desired product.

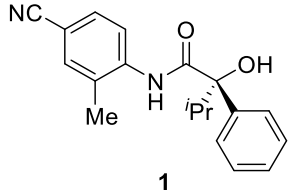
General procedure for the synthesis of racemates



Under argon atmosphere, an oven-dried 10 mL resealable Schlenk tube equipped with amagnetic stir bar was charged with CuI (0.95 mg, 0.005 mmol, 10 mol%), **L**$_{rac}$ (1.34 mg, 0.0075 mmol, 15 mol%), K_3PO_4 (32.0 mg, 0.15 mmol, 3.0 equiv), and anhydrous 1,4-dioxane (0.50 mL). Then α-tertiary haloamides (0.05 mmol, 1.0 equiv) and water (0.075 mmol, 1.5 equiv) were sequentially added into the mixture, and the resulting mixture was stirred at room temperature for 12 hours. Upon completion (monitored by TLC), the precipitate was filtered off and rinsed by CH_2Cl_2. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel to afford the desired racemic product.

Characterization data for products

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-3-methyl-2-phenylbutanamide (1)



1

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl-2-phenylbutanamide **E1** (65.4 mg, 0.20 mmol), the reaction was run at 0 ℃ for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **1** as a white solid (59.2 mg, 96% yield, 93% ee).

$[\alpha]_D^{25}$ = –25 (c 0.7, $CHCl_3$).

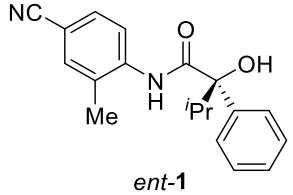
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (minor) = 11.90 min, t_R (major) = 17.31 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 7.75 – 7.55 (m, 2H), 7.52 – 7.28 (m, 5H), 3.05 – 2.91 (m, 1H), 2.81 (s, 1H), 2.26 (s, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.76 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 140.9, 139.8, 133.8, 131.2, 128.6, 127.9, 127.7, 125.2, 120.6, 119.0, 107.1, 82.8, 34.9, 17.3, 17.0, 15.8.

HRMS (ESI) m/z calcd. for $C_{19}H_{20}N_2NaO_2$ $[M + Na]^+$ 331.1417, found 331.1416.

(*R*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-3-methyl-2-phenylbutanamide (*ent*-1)



ent-**1**

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl-2-phenylbutanamide **E1** (65.4 mg, 0.20 mmol) using *ent*-**L*9** as the ligand, the reaction was run at 0 ℃ for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product *ent*-**1** as a white solid (58.0 mg, 94% yield, 93% ee).

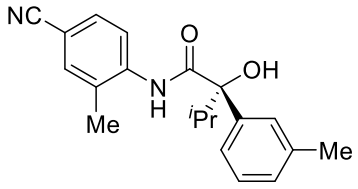
$[\alpha]_D^{25}$ = +20 (c 0.4, $CHCl_3$).

HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (major) = 12.01 min, t_R (minor) = 17.24 min.

HRMS (ESI) m/z calcd. for $C_{19}H_{20}N_2NaO_2$ $[M + Na]^+$ 331.1417, found 331.1416.

Note: The ^{1}H NMR and ^{13}C NMR data of *ent*-**1** was same as product **1**.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-3-methyl-2-(*m*-tolyl)butanamide (2)



2

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl-2-(*m*-tolyl)butanamide **E2** (68.2 mg, 0.20 mmol), the reaction was run in mixed solvent (1,4-dioxane:1,3-dioxolane:$CHCl_3$, 3:1:1, 2.0 mL) at –10 °C for 7 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **2** as a white solid (51.6 mg, 80% yield, 92% ee).

$[\alpha]_D^{25}$ = –16 (c 0.7, $CHCl_3$).

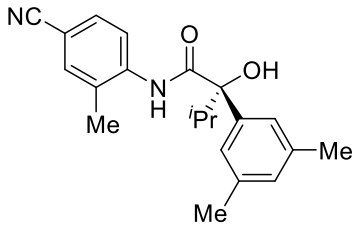
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (minor) = 9.84 min, t_R (major) = 16.73 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 7.50 – 7.38 (m, 4H), 7.29 – 7.22 (m, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 3.02 – 2.92 (m, 1H), 2.93 (s, 1H), 2.37 (s, 3H), 2.26 (s, 3H), 1.07 (d, *J* = 6.7 Hz, 3H), 0.76 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 140.8, 139.8, 138.1, 133.7, 131.1, 128.6, 128.4, 127.6, 125.9, 122.2, 120.5, 119.0, 106.9, 82.6, 34.8, 21.6, 17.2, 17.0, 15.8.

HRMS (ESI) m/z calcd. for $C_{20}H_{22}N_2NaO_2$ $[M + Na]^+$ 345.1573, found 345.1570.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-(3,5-dimethylphenyl)-2-hydroxy-3-methyl-butanamide (3)



3

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-(3,5-dimethylphenyl)-3-methyl-butanamide **E3** (71.0 mg, 0.20 mmol), the reaction was run at 0 °C for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **3** as a light yellow oil (63.9 mg, 95% yield, 92% ee).

$[\alpha]_D^{25}$ = –9 (c 0.7, $CHCl_3$).

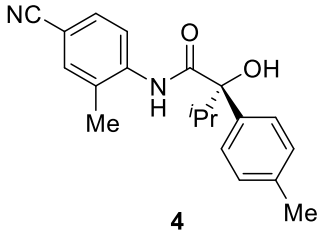
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (minor) = 7.90 min, t_R (major) = 14.45 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 7.47 – 7.40 (m, 1H), 7.42 – 7.37 (m, 1H), 7.30 – 7.24 (m, 2H), 6.93 (s, 1H), 3.01 (s, 1H), 3.00 – 2.89 (m, 1H), 2.32 (s, 6H), 2.26 (s, 3H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 140.8, 139.9, 138.0, 133.6, 131.1, 129.5, 127.5, 122.9, 120.4, 119.0, 106.8, 82.6, 34.7, 21.5, 17.2, 16.9, 15.9.

HRMS (ESI) m/z calcd. for $C_{21}H_{24}N_2NaO_2$ $[M + Na]^+$ 359.1730, found 359.1724.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-3-methyl-2-(*p*-tolyl)butanamide (4)



4

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl-2-(*p*-tolyl)butanamide **E4** (68.2 mg, 0.20 mmol), the reaction was run in mixed solvent (1,4-dioxane:1,3-dioxolane:$CHCl_3$, 3:1:1, 2.0 mL) at –10 ℃ for 7 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **4** as a white solid (50.3 mg, 78% yield, 88% ee).

$[\alpha]_D^{25}$ = –18 (c 0.7, $CHCl_3$).

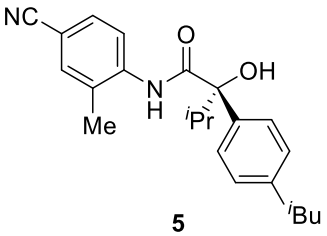
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (minor) = 11.80 min, t_R (major) = 16.03 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 7.61 – 7.51 (m, 2H), 7.49 – 7.37 (m, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 3.00 – 2.91 (m, 1H), 2.90 (s, 1H), 2.33 (s, 3H), 2.26 (s, 3H), 1.07 (d, *J* = 6.7 Hz, 3H), 0.76 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 139.8, 137.9, 137.6, 133.7, 131.1, 129.2, 127.5, 125.1, 120.5, 119.0, 106.9, 82.6, 34.7, 20.9, 17.2, 16.9, 15.8.

HRMS (ESI) m/z calcd. for $C_{20}H_{22}N_2NaO_2$ $[M + Na]^+$ 345.1573, found 345.1571.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-2-(4-isobutylphenyl)-3-methyl-butanamide (5)



5

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-(4-isobutylphenyl)-3-methylbutanamide **E5** (76.6 mg, 0.20 mmol), the reaction was run at 0 ℃ for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **5** as a white solid (54.7 mg, 75% yield, 86% ee).

$[\alpha]_D^{25}$ = –9 (c 0.7, $CHCl_3$).

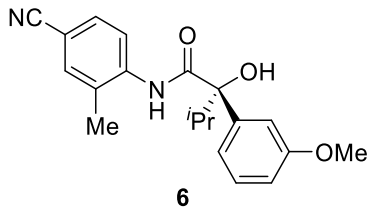
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (minor) = 9.98 min, t_R (major) = 13.25 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.29 (d, *J* = 8.5 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.51 – 7.36 (m, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 3.01 – 2.90 (m, 1H), 2.84 (s, 1H), 2.45 (d, *J* = 7.1 Hz, 2H), 2.25 (s, 3H), 1.92 – 1.76 (m, 1H), 1.07 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 6H), 0.76 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 141.5, 139.9, 138.2, 133.8, 131.2, 129.3, 127.6,

125.0, 120.6, 119.0, 107.0, 82.7, 45.0, 34.8, 30.2, 22.4, 22.3, 17.3, 17.0, 15.9.
HRMS (ESI) m/z calcd. for $C_{23}H_{28}N_2NaO_2$ $[M + Na]^+$ 387.2043, found 387.2042.

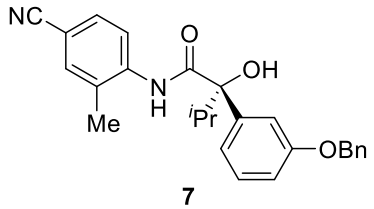
(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-2-(3-methoxyphenyl)-3-methyl-butanamide (6)



6

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-(3-methoxyphenyl)-3-methyl-butanamide **E6** (71.4 mg, 0.20 mmol), the reaction was run at 0 ℃ for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **6** as a white solid (59.5 mg, 88% yield, 94% ee).
$[\alpha]_D^{25}$ = –30 (c 0.7, $CHCl_3$).
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (minor) = 19.03 min, t_R (major) = 20.75 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 7.50 – 7.36 (m, 2H), 7.34 – 7.28 (m, 1H), 7.27 – 7.23 (m, 2H), 6.88 – 6.80 (m, 1H), 3.82 (s, 3H), 3.01 – 2.87 (m, 2H), 2.26 (s, 3H), 1.07 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 7.0 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 159.8, 142.7, 139.8, 133.8, 131.2, 129.6, 127.7, 120.6, 119.0, 117.6, 112.8, 111.6, 107.0, 82.7, 55.3, 34.9, 17.3, 17.0, 15.9.
HRMS (ESI) m/z calcd. for $C_{20}H_{22}N_2NaO_3$ $[M + Na]^+$ 361.1523, found 361.1520.

(*S*)-2-(3-(Benzyloxy)phenyl)-*N*-(4-cyano-2-methylphenyl)-2-hydroxy-3-methyl-butanamide (7)

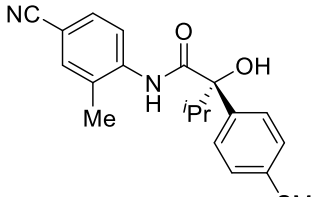


7

According to **General Procedure A** with 2-(3-(benzyloxy)phenyl)-2-chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl- butanamide **E7** (86.6 mg, 0.20 mmol), the reaction was run in mixed solvent (1,4-dioxane: DCM, 4:1, 2.0 mL) at 0 ℃ for 7 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **7** as a white solid (68.0 mg, 82% yield, 91% ee).
$[\alpha]_D^{25}$ = –30 (c 0.7, $CHCl_3$).
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (minor) = 19.05 min, t_R (major) = 41.02 min.
^{1}H NMR (400 MHz, CDCl3) δ 8.93 (s, 1H), 8.29 (d, J = 8.5 Hz, 1H), 7.59 – 7.29 (m,

10H), 7.04 – 6.87 (m, 1H), 5.09 (s, 2H), 3.09 (s, 1H), 3.02 – 2.90 (m, 1H), 2.26 (s, 3H), 1.10 (d, J = 6.7 Hz, 3H), 0.78 (d, J = 7.0 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 159.0, 142.8, 139.9, 136.8, 133.8, 131.2, 129.6, 128.6, 128.1, 127.8, 127.6, 120.6, 119.1, 117.9, 113.8, 112.6, 107.0, 82.7, 70.1, 35.0, 17.3, 17.1, 15.9.
HRMS (ESI) m/z calcd. for $C_{26}H_{26}N_2NaO_3$ $[M + Na]^+$ 437.1836, found 437.1832.

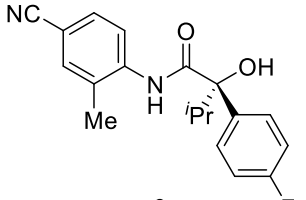
(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-3-methyl-2-(4-(methylthio)phenyl)-butanamide (8)



8

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl-2-(4-(methylthio)phenyl)-butanamide **E8** (74.6 mg, 0.20 mmol), the reaction was run at 0 ℃ for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **8** as a white solid (58.1 mg, 82% yield, 84% ee).
$[\alpha]_D^{25}$ = –8 (c 0.7, $CHCl_3$).
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (minor) = 18.44 min, t_R (major) = 28.94 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.25 (d, J = 8.5 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.46 – 7.35 (m, 2H), 7.23 (d, J = 8.5 Hz, 2H), 3.14 (s, 1H), 3.00 – 2.87 (m, 1H), 2.46 (s, 3H), 2.26 (s, 3H), 1.06 (d, J = 6.7 Hz, 3H), 0.75 (d, J = 7.0 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 139.9, 138.3, 137.8, 133.8, 131.2, 127.8, 126.3, 125.9, 120.6, 119.0, 107.0, 82.6, 34.9, 17.3, 17.0, 15.8, 15.6.
HRMS (ESI) m/z calcd. for $C_{20}H_{22}N_2NaO_2S$ $[M + Na]^+$ 377.1294, found 377.1291.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-(4-fluorophenyl)-2-hydroxy-3-methyl-butanamide (9)

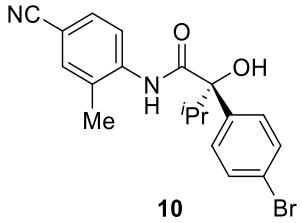


9

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-(4-fluorophenyl)-3-methylbutanamide **E9** (68.9 mg, 0.20 mmol), the reaction was run in mixed solvent (1,4-dioxane/1,3-dioxolane/$CHCl_3$, 3/1/1, 2.0 mL) at –10 ℃ for 7 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **9** as a white solid (52.2 mg, 80% yield, 90% ee).

$[\alpha]_D^{25}$ = –25 (c 0.7, $CHCl_3$).
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (minor) = 10.15 min, t_R (major) = 13.89 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 7.72 – 7.60 (m, 2H), 7.52 – 7.39 (m, 2H), 7.11 – 6.99 (m, 2H), 3.02 – 2.87 (m, 2H), 2.27 (s, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.75 (d, *J* = 7.0 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 162.3 (d, *J* = 246.9 Hz), 139.7, 136.6 (d, *J* = 2.9 Hz), 133.7, 131.2, 127.7, 127.1 (d, *J* = 8.1 Hz), 120.6, 118.9, 115.2 (d, *J* = 21.4 Hz), 107.1, 82.4, 35.1, 17.2, 16.9, 15.6.
^{19}F NMR (376 MHz, $CDCl_3$) δ –114.8.
HRMS (ESI) m/z calcd. for $C_{19}H_{19}FN_2NaO_2$ $[M + Na]^+$ 349.1323, found 349.1321.

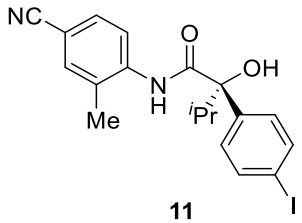
(*S*)-2-(4-Bromophenyl)-*N*-(4-cyano-2-methylphenyl)-2-hydroxy-3-methyl-butanamide (10)



10

According to **General Procedure A** with 2-(4-bromophenyl)-2-chloro-*N*-(4-cyano-2-methylphenyl)-3-methylbutanamide **E10** (81.1 mg, 0.20 mmol), the reaction was run at 0 °C for 7 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **10** as a white solid (46.1 mg, 84% yield, 85% ee).
$[\alpha]_D^{25}$ = –24 (c 0.7, $CHCl_3$).
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (minor) = 11.96 min, t_R (major) = 18.03 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.54 – 7.44 (m, 3H), 7.43 (s, 1H), 3.10 (s, 1H), 3.00 – 2.87 (m, 1H), 2.29 (s, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.76 (d, *J* = 7.0 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 140.1, 139.7, 133.8, 131.5, 131.2, 127.9, 127.3, 122.1, 120.7, 119.0, 107.1, 82.6, 35.1, 17.3, 17.0, 15.7.
HRMS (ESI) m/z calcd. for $C_{19}H_{19}BrN_2NaO_2$ $[M + Na]^+$ 409.0522, found 409.0519.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-2-(4-iodophenyl)-3-methyl-butanamide (11)



11

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-(4-

iodophenyl)-3-methylbutanamide **E11** (90.5 mg, 0.20 mmol), the reaction was run at 0 ℃ for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **11** as a white solid (62.5 mg, 72% yield, 87% ee).

$[\alpha]_D^{25}$ = –23 (c 0.7, $CHCl_3$).

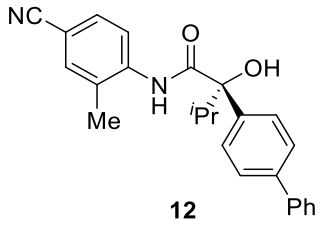
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (minor) = 13.38 min, t_R (major) = 21.15 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.55 – 7.38 (m, 4H), 3.00 – 2.88 (m, 2H), 2.29 (s, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.76 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 140.8, 139.7, 137.6, 133.8, 131.3, 127.8, 127.4, 120.7, 119.0, 107.2, 93.9, 82.7, 35.1, 17.3, 17.0, 15.7.

HRMS (ESI) m/z calcd. for $C_{19}H_{19}IN_2NaO_2$ $[M + Na]^+$ 457.0383, found 457.0378.

(*S*)-2-([1,1'-Biphenyl]-4-yl)-*N*-(4-cyano-2-methylphenyl)-2-hydroxy-3-methyl-butanamide (12)



12

According to **General Procedure A** with 2-([1,1'-biphenyl]-4-yl)-2-chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl-butanamide **E12** (80.6 mg, 0.20 mmol), the reaction was run in mixed solvent (1,4-dioxane/1,3-dioxolane/$CHCl_3$, 3/1/1, 2.0 mL) at –10 ℃ for 7 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **12** as a white solid (63.8 mg, 83% yield, 87% ee).

$[\alpha]_D^{25}$ = –15 (c 0.7, $CHCl_3$).

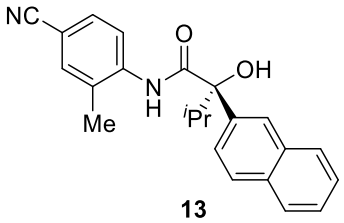
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (minor) = 15.96 min, t_R (major) = 26.41 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.30 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.64 – 7.53 (m, 4H), 7.48 – 7.39 (m, 4H), 7.37 – 7.31 (m, 1H), 3.08 – 2.96 (m, 1H), 2.92 (s, 1H), 2.28 (s, 3H), 1.10 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 140.7, 140.4, 140.0, 139.9, 133.8, 131.2, 128.9, 127.7, 127.5, 127.2, 127.1, 125.8, 120.6 119.0, 107.1, 82.8, 35.0, 17.3, 17.1, 15.9.

HRMS (ESI) m/z calcd. for $C_{25}H_{24}N_2NaO_2$ $[M + Na]^+$ 407.1730, found 407.1725.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-3-methyl-2-(naphthalen-2-yl)-butanamide (13)



13

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl-2-(naphthalen-2-yl)butanamide **E13** (75.4 mg, 0.20 mmol), the reaction was run at 0 ℃ for 7 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **13** as a white solid (61.7 mg, 86% yield, 92% ee).

$[\alpha]_D^{25}$ = –94 (c 0.7, $CHCl_3$).

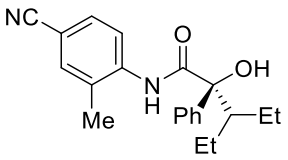
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (minor) = 16.21 min, t_R (major) = 23.46 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 8.18 (s, 1H), 7.92 – 7.79 (m, 4H), 7.55 – 7.47 (m, 2H), 7.46 – 7.35 (m, 2H), 3.33 (s, 1H), 3.23 – 3.05 (m, 1H), 2.27 (s, 3H), 1.16 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 139.9, 138.6, 133.8, 133.0, 132.8, 131.2, 128.4, 128.3, 127.8, 127.6, 126.4, 126.3, 124.3, 123.6, 120.7, 119.1, 107.0, 83.0, 34.9, 17.3, 17.1, 15.9.

HRMS (ESI) m/z calcd. for $C_{23}H_{22}N_2NaO_2$ $[M + Na]^+$ 381.1573, found 381.1567.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-3-ethyl-2-hydroxy-2-phenylpentanamide (14)



14

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-3-ethyl-2-phenylpentanamide **E14** (35.5 mg, 0.10 mmol), the reaction was run in 1.0 mL 1,4-dioxane at 12 ℃ for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **14** as a white solid (28.6 mg, 85% yield, 84% ee).

$[\alpha]_D^{25}$ = –32 (c 0.7, $CHCl_3$).

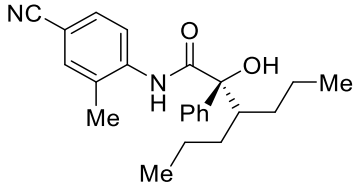
HPLC analysis: Chiralcel IG (*n*-hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 11.75 min, t_R (major) = 13.99 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 7.76 – 7.59 (m, 2H), 7.43 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.40 – 7.33 (m, 3H), 7.32 – 7.27 (m, 1H), 3.01 (s, 1H), 2.58 – 2.46 (m, 1H), 2.24 (s, 3H), 1.66 – 1.55 (m, 1H), 1.53 – 1.41 (m, 1H), 1.30 – 1.20 (m, 1H), 1.19 – 1.10 (m, 1H), 1.04 (t, *J* = 7.4 Hz, 3H), 0.81 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 141.2, 140.0, 133.8, 131.2, 128.4, 127.8, 127.7, 125.4, 120.6, 119.1, 106.9, 84.2, 47.7, 23.0, 21.4, 17.3, 13.1, 12.8.

HRMS (ESI) m/z calcd. for $C_{21}H_{24}N_2NaO_2$ $[M + Na]^+$ 359.1730, found 359.1730.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-2-phenyl-3-propylhexanamide (15)



15

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-phenyl-3-propylhexanamide **E15** (76.6 mg, 0.20 mmol), the reaction was run at 0 ℃ for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **15** as a white solid (52.5 mg, 72% yield, 86% ee).

$[\alpha]_D^{25}$ = –27 (c 0.4, $CHCl_3$).

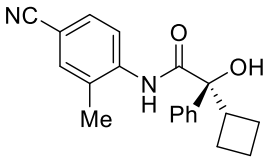
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 11.75 min, t_R (major) = 13.99 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.42 (s, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 2.71 (s, 1H), 2.68 – 2.59 (m, 1H), 2.25 (s, 3H), 1.54 – 1.23 (m, 6H), 1.15 – 1.07 (m, 2H), 0.91 (t, *J* = 6.3 Hz, 3H), 0.73 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 141.1, 139.9, 133.8, 131.2, 128.4, 127.8, 127.7, 125.3, 120.6, 119.0, 107.0, 84.1, 44.4, 33.3, 31.6, 21.7, 21.4, 17.3, 14.7, 14.5.

HRMS (ESI) m/z calcd. for $C_{23}H_{28}N_2NaO_2$ $[M + Na]^+$ 387.2043, found 387.2042.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-cyclobutyl-2-hydroxy-2-phenylacetamide (16)



16

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-cyclobutyl-2-phenylacetamide **E16** (67.8 mg, 0.20 mmol), the reaction was run at 0 ℃ for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **16** as a white solid (62.1 mg, 97% yield, 90% ee).

$[\alpha]_D^{25}$ = –6 (c 0.7, $CHCl_3$).

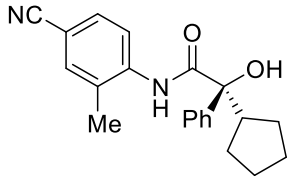
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (minor) = 16.65 min, t_R (major) = 23.59 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.63 – 7.50 (m, 2H), 7.47 – 7.28 (m, 5H), 3.66 (s, 1H), 3.62 – 3.49 (m, 1H), 2.22 (s, 3H), 2.19 – 2.08 (m, 1H), 1.97 – 1.81 (m, 4H), 1.80 – 1.69 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 140.5, 139.9, 133.8, 131.2, 128.7, 128.2, 127.9, 125.7, 120.8, 119.0, 107.1, 80.2, 41.9, 22.6, 22.0, 17.3.

HRMS (ESI) m/z calcd. for $C_{20}H_2N_2NaO_2$ $[M + Na]^+$ 343.1417, found 343.1412.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-cyclopentyl-2-hydroxy-2-phenylacetamide (17)



17

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-cyclopentyl-2-phenylacetamide **E17** (70.6 mg, 0.20 mmol), the reaction was run at 0 ℃ for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **17** as a white solid (63.5 mg, 95% yield, 91% ee).

$[\alpha]_D^{25}$ = –15 (c 0.4, $CHCl_3$).

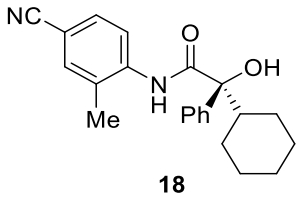
HPLC analysis: Chiralcel ID (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (minor) = 23.23 min, t_R (major) = 29.17 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.25 (d, *J* = 8.5 Hz, 1H), 7.72 – 7.64 (m, 2H), 7.48 – 7.44 (m, 1H), 7.43 – 7.34 (m, 3H), 7.34 – 7.27 (m, 1H), 3.34 – 3.14 (m, 1H), 2.95 (s, 1H), 2.25 (s, 3H), 1.89 – 1.74 (m, 1H), 1.68 – 1.53 (m, 6H), 1.23 – 1.07 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 141.6, 139.9, 133.8, 131.2, 128.6, 128.0, 127.7, 125.4, 120.7, 119.0, 107.1, 81.0, 46.7, 26.8, 26.6, 26.2, 25.9, 17.3.

HRMS (ESI) m/z calcd. for $C_{21}H_{22}N_2NaO_2$ $[M + Na]^+$ 357.1573, found 357.1572.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-cyclohexyl-2-hydroxy-2-phenylacetamide (18)



18

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-cyclohexyl-2-phenylacetamide **E18** (73.4 mg, 0.20 mmol), the reaction was run at 0 ℃ for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **18** as a white solid (64.8 mg, 93% yield, 90% ee).

$[\alpha]_D^{25}$ = –14 (c 0.7, $CHCl_3$).

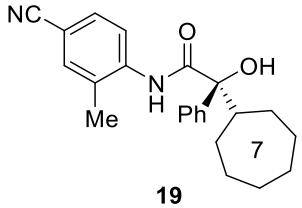
HPLC analysis: Chiralcel ID (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (minor) = 14.90 min, t_R (major) = 17.27 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 7.78 – 7.58 (m, 2H), 7.47 – 7.33 (m, 4H), 7.32 – 7.27 (m, 1H), 3.01 (s, 1H), 2.66 – 2.49 (m, 1H), 2.25 (s, 3H), 1.85 – 1.63 (m, 4H), 1.44 – 1.20 (m, 4H), 1.17 – 1.02 (m, 1H), 0.95 – 0.80 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 140.6, 139.9, 133.8, 131.2, 128.5, 127.8, 127.7, 125.4, 120.6, 119.1, 107.0, 82.7, 45.0, 27.4, 26.3, 26.2, 26.0, 17.3.

HRMS (ESI) m/z calcd. for $C_{22}H_{24}N_2NaO_2$ $[M + Na]^+$ 371.1730, found 371.1730.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-cycloheptyl-2-hydroxy-2-phenylacetamide (19)



19

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-cycloheptyl-2-phenylacetamide **E19** (76.2 mg, 0.20 mmol), the reaction was run in mixed solvent (1,4-dioxane/1,3-dioxolane/$CHCl_3$, 3/1/1, 2.0 mL) at –10 ℃ for 7 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **19** as a white solid (57.3 mg, 79% yield, 89% ee).

$[\alpha]_D^{25}$ = –21 (c 0.7, $CHCl_3$).

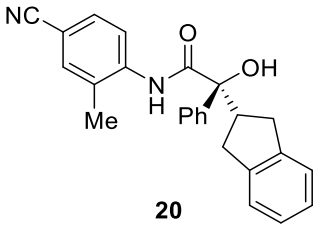
HPLC analysis: Chiralcel IF (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (minor) = 12.36 min, t_R (major) = 13.93 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.48 – 7.43 (m, 1H), 7.43 – 7.35 (m, 3H), 7.33 – 7.27 (m, 1H), 2.87 – 2.75 (m, 2H), 2.26 (s, 3H), 1.84 – 1.71 (m, 2H), 1.64 – 1.35 (m, 9H), 1.19 – 1.06 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 141.2, 139.9, 133.8, 131.2, 128.6, 127.8, 127.6, 125.3, 120.6, 119.0, 107.0, 84.3, 45.6, 29.3, 28.0, 27.7, 27.6, 27.3, 27.2, 17.3.

HRMS (ESI) m/z calcd. for $C_{23}H_{26}N_2NaO_2$ $[M + Na]^+$ 385.1886, found 385.1887.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-(2,3-dihydro-1*H*-inden-2-yl)-2-hydroxy-2-phenylacetamide (20)



20

According to **General Procedure A** with 2-([1,1'-biphenyl]-3-yl)-2-chloro-*N*-(4-cyano-2-methylphenyl)butanamide **E20** (77.8 mg, 0.20 mmol), the reaction was run at 0 ℃ for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **20** as a white solid (71.1 mg, 93% yield, 88% ee).

$[\alpha]_D^{25}$ = –3 (c 0.4, $CHCl_3$).

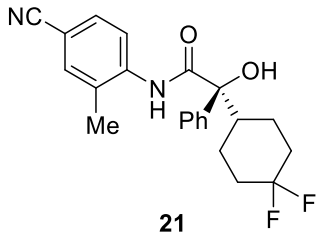
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 80/20, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 11.11 min, t_R (major) = 23.48 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 7.4 Hz, 2H), 7.51 – 7.31 (m, 5H), 7.24 – 7.08 (m, 4H), 3.97 – 3.81 (m, 1H), 3.22 – 3.11 (m, 1H), 3.11 – 2.99 (m, 2H), 2.88 (dd, *J* = 16.6, 8.9 Hz, 1H), 2.65 (dd, *J* = 16.6, 7.8 Hz, 1H), 2.24 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 142.1, 141.8, 140.8, 139.8, 133.8, 131.3, 128.8,

128.2, 127.8, 126.9, 126.7, 125.4, 124.7, 124.6, 120.7, 119.0, 107.2, 81.8, 45.7, 33.8, 33.4, 17.3.
HRMS (ESI) m/z calcd. for $C_{25}H_{22}N_2NaO_2$ $[M + Na]^+$ 405.1573, found 405.1572.

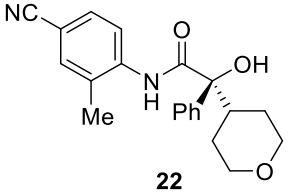
(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-(4,4-difluorocyclohexyl)-2-hydroxy-2-phenylacetamide (21)



21

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-(4,4-difluorocyclohexyl)-2-phenylacetamide **E21** (80.6 mg, 0.20 mmol), the reaction was run at 0 ℃ for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **21** as a white solid (70.7 mg, 92% yield, 90% ee).
$[\alpha]_D^{25}$ = –21 (c 0.7, $CHCl_3$).
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 95/5, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 35.04 min, t_R (major) = 39.38 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 2H), 7.48 – 7.28 (m, 5H), 3.22 (s, 1H), 2.68 (t, *J* = 12.1 Hz, 1H), 2.25 (s, 3H), 2.20 – 2.01 (m, 2H), 1.84 – 1.65 (m, 4H), 1.44 – 1.22 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 140.1, 139.7, 133.9, 131.2, 128.8, 128.2, 127.9, 125.0, 120.7, 118.9, 107.2, 81.8 (d, *J* = 1.8 Hz), 43.1, 33.83 – 32.92 (m), 23.4 (d, *J* = 10.2 Hz), 22.2 (d, *J* = 10.2 Hz), 17.3.
^{19}F NMR (376 MHz, $CDCl_3$) δ –92.0 (d, *J* = 235.8 Hz), –102.9 (d, *J* = 235.8 Hz).
HRMS (ESI) m/z calcd. for $C_{22}H_{22}F_2N_2NaO_2$ $[M + Na]^+$ 407.1542, found 407.1539.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-2-phenyl-2-(tetrahydro-2*H*-pyran-4-yl)acetamide (22)

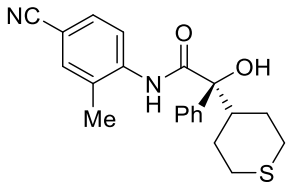


22

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-phenyl-2-(tetrahydro-2*H*-pyran-4-yl)acetamide **E22** (73.8 mg, 0.20 mmol), the reaction was run in 1,4-dioxane (2.0 mL) at room temperature for 3 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **22** as a white solid (62.4 mg, 89% yield, 90% ee).
$[\alpha]_D^{25}$ = –20 (c 0.7, $CHCl_3$).
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 92/8, flow rate 0.8 mL/min, λ = 254 nm), t_R (minor) = 20.67 min, t_R (major) = 22.60 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 7.72 – 7.60 (m, 2H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.44 – 7.36 (m, 3H), 7.35 – 7.29 (m, 1H), 4.10 – 3.92 (m, 2H), 3.55 – 3.35 (m, 2H), 3.04 (s, 1H), 2.94 – 2.80 (m, 1H), 2.27 (s, 3H), 1.80 – 1.67 (m, 2H), 1.36 – 1.25 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 139.7, 139.6, 133.8, 131.2, 128.7, 128.1, 127.7, 125.2, 120.6, 118.9, 107.2, 81.9, 67.9, 67.7, 42.4, 27.0, 25.8, 17.3.
HRMS (ESI) m/z calcd. for $C_{21}H_{22}N_2NaO_3$ $[M + Na]^+$ 373.1523, found 373.1522.

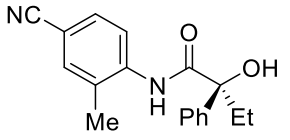
(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-2-phenyl-2-(tetrahydro-2*H*-thiopyran-4-yl)acetamide (23)



23

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-phenyl-2-(tetrahydro-2*H*-thiopyran-4-yl)acetamide **E23** (77.0 mg, 0.20 mmol), the reaction was run in 1,4-dioxane (2.0 mL) at room temperature for 3 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5/1 to 3/1) to yield the product **23** as a white solid (55.0 mg, 75% yield, 86% ee).
$[\alpha]_D^{25}$ = –24 (c 0.5, $CHCl_3$).
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 95/5, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 37.47 min, t_R (major) = 43.50 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 7.71 – 7.60 (m, 2H), 7.46 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.44 – 7.36 (m, 3H), 7.35 – 7.29 (m, 1H), 2.99 (s, 1H), 2.84 (t, *J* = 12.8 Hz, 1H), 2.74 – 2.51 (m, 4H), 2.26 (s, 3H), 2.12 – 2.05 (m, 1H), 1.82 – 1.71 (m, 1H), 1.67 – 1.61 (m, 1H), 1.37 – 1.29 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 139.7, 139.6, 133.8, 131.2, 128.8, 128.1, 127.7, 125.2, 120.6, 118.9, 107.3, 83.1, 44.6, 29.0, 28.9, 28.8, 27.4, 17.3.
HRMS (ESI) m/z calcd. for $C_{21}H_{22}N_2NaO_2S$ $[M + Na]^+$ 389.1294, found 389.1293.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-2-phenylbutanamide (24)



24

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-phenylbutanamide **E24** (62.4 mg, 0.20 mmol), the reaction was run at 0 °C for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **24** as a white solid (55.9 mg, 95% yield, 86% ee).

$[\alpha]_D^{25}$ = –23 (c 0.7, $CHCl_3$).

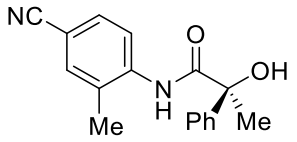
HPLC analysis: Chiralcel IB (*n*-hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 14.56 min, t_R (major) = 22.27 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.42 – 7.35 (m, 3H), 7.32 (t, *J* = 7.3 Hz, 1H), 3.07 (s, 1H), 2.52 – 2.38 (m, 1H), 2.25 (s, 3H), 2.22 – 2.10 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 141.5, 139.8, 133.8, 131.3, 128.7, 128.2, 127.7, 125.3, 120.6, 119.0, 107.1, 80.3, 32.4, 17.3, 7.8.

HRMS (ESI) m/z calcd. for $C_{18}H_{18}N_2NaO_2$ $[M + Na]^+$ 317.1260, found 317.1259.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-2-phenylpropanamide (25)



25

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-phenylpropanamide **E25** (59.7 mg, 0.20 mmol), the reaction was run at 0 °C for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **25** as a white solid (51.6 mg, 92% yield, 57% ee).

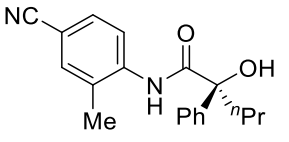
HPLC analysis: Chiralcel IB (*n*-hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 11.14 min, t_R (major) = 13.15 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.27 – 8.11 (m, 1H), 7.70 – 7.56 (m, 2H), 7.45 – 7.28 (m, 5H), 3.98 (s, 1H), 2.23 (s, 3H), 1.88 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 142.7, 139.9, 133.8, 131.2, 128.6, 128.1, 127.9, 125.2, 120.6, 119.0, 106.9, 77.3, 27.1, 17.2.

HRMS (ESI) m/z calcd. for $C_{17}H_{16}N_2NaO_2$ $[M + Na]^+$ 303.1104, found 303.1098.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-2-phenylpentanamide (26)



26

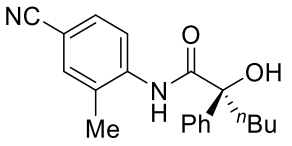
According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-phenylpentanamide **E26** (65.4 mg, 0.20 mmol), the reaction was run at 0 °C for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **26** as a white solid (57.4 mg, 93% yield, 80% ee).

$[\alpha]_D^{25}$ = –30 (c 0.5, $CHCl_3$).

HPLC analysis: Chiralcel IB (*n*-hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 12.47 min, t_R (major) = 22.70 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.25 (d, *J* = 8.5 Hz, 1H), 7.75 – 7.54 (m, 2H), 7.48 – 7.27 (m, 5H), 3.33 (s, 1H), 2.44 – 2.32 (m, 1H), 2.24 (s, 3H), 2.16 – 2.01 (m, 1H), 1.55 – 1.29 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 141.8, 139.9, 133.8, 131.2, 128.6, 128.1, 127.8, 125.3, 120.6, 119.0, 107.0, 80.0, 41.7, 17.3, 16.9, 14.2.
HRMS (ESI) m/z calcd. for $C_{19}H_{20}N_2NaO_2$ $[M + Na]^+$ 331.1417, found 331.1412.

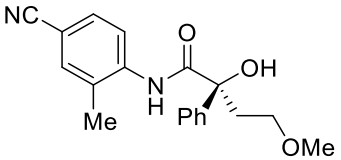
(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-2-phenylhexanamide (27)



27

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-phenylhexanamide **E27** (68.2 mg, 0.20 mmol), the reaction was run at 0 °C for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **27** as a white solid (57.4 mg, 89% yield, 77% ee).
$[\alpha]_D^{25}$ = –20 (c 0.4, $CHCl_3$).
HPLC analysis: Chiralcel IB (*n*-hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 12.03 min, t_R (major) = 20.88 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.29 (d, *J* = 8.5 Hz, 1H), 7.71 – 7.57 (m, 2H), 7.48 – 7.29 (m, 5H), 3.03 (s, 1H), 2.47 – 2.36 (m, 1H), 2.25 (s, 3H), 2.18 – 2.07 (m, 1H), 1.44 – 1.29 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 141.7, 139.9, 133.8, 131.3, 128.7, 128.1, 127.6, 125.2, 120.5, 119.0, 107.1, 80.0, 39.4, 25.6, 22.8, 17.3, 14.0.
HRMS (ESI) m/z calcd. for $C_{20}H_{22}N_2NaO_2$ $[M + Na]^+$ 345.1573, found 345.1567.

(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-4-methoxy-2-phenylbutanamide (28)

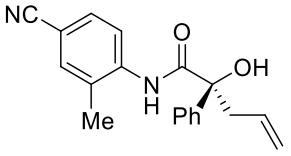


28

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-4-methoxy-2-phenylbutanamide **E28** (68.5 mg, 0.20 mmol), the reaction was run at 0 °C for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **28** as a light yellow oil (57.1 mg, 88% yield, 72% ee).
$[\alpha]_D^{25}$ = –62 (c 0.4, $CHCl_3$).
HPLC analysis: Chiralcel IB (*n*-hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, λ = 254 nm), t_R (major) = 13.36 min, t_R (minor) = 15.49 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.33 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 7.4 Hz, 2H), 7.50 – 7.28 (m, 5H), 5.69 (s, 1H), 3.76 – 3.66 (m, 1H), 3.55 – 3.43 (m, 1H),

3.32 (s, 3H), 2.65 – 2.54 (m, 1H), 2.50 – 2.40 (m, 1H), 2.28 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 141.3, 140.0, 133.8, 131.2, 128.4, 127.8, 127.6, 125.3, 120.3, 119.0, 107.0, 80.6, 70.7, 59.2, 38.0, 17.3.
HRMS (ESI) m/z calcd. for $C_{19}H_{20}N_2NaO_3$ $[M + Na]^+$ 347.1366, found 347.1359.

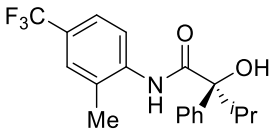
(*S*)-*N*-(4-Cyano-2-methylphenyl)-2-hydroxy-2-phenylpent-4-enamide (29)



29

According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-phenylpent-4-enamide **E29** (64.9 mg, 0.20 mmol), the reaction was run at 0 °C for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **29** as a light yellow oil (52.1 mg, 85% yield, 72% ee).
$[\alpha]_D^{25}$ = –45 (c 0.7, $CHCl_3$).
HPLC analysis: Chiralcel IB (*n*-hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 15.57 min, t_R (major) = 25.64 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 7.77 – 7.59 (m, 2H), 7.54 – 7.27 (m, 5H), 5.81 – 5.63 (m, 1H), 5.41 – 5.21 (m, 2H), 3.31 (s, 1H), 3.18 (dd, *J* = 14.0, 7.2 Hz, 1H), 2.90 (dd, *J* = 14.0, 7.5 Hz, 1H), 2.25 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 140.9, 139.8, 133.8, 132.1, 131.2, 128.6, 128.1, 127.8, 125.2, 122.0, 120.5, 119.0, 107.1, 78.3, 44.5, 17.3.
HRMS (ESI) m/z calcd. for $C_{19}H_{18}N_2NaO_2$ $[M + Na]^+$ 329.1260, found 329.1259.

(*S*)-2-Hydroxy-3-methyl-*N*-(2-methyl-4-(trifluoromethyl)phenyl)-2-phenylbutanamide (30)

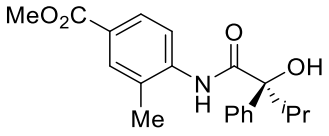


30

According to **General Procedure A** with 2-chloro-3-methyl-*N*-(2-methyl-4-(trifluoromethyl)phenyl)-2-phenylbutanamide **E30** (73.9 mg, 0.20 mmol), the reaction was run at 0 °C for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 15/1 to 10/1) to yield the product **30** as a white solid (62.5 mg, 89% yield, 93% ee).
$[\alpha]_D^{25}$ = –5 (c 0.7, $CHCl_3$).
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 6.53 min, t_R (major) = 10.19 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.80 – 7.64 (m, 2H), 7.50 – 7.28 (m, 5H), 3.07 – 2.91 (m, 2H), 2.25 (s, 3H), 1.10 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 141.2, 138.6, 128.5, 127.8, 127.7, 127.1 (q, J = 3.7 Hz), 126.2 (q, J = 32.2 Hz), 125.3, 124.1 (q, J = 270.2 Hz), 123.9 (q, J = 3.8 Hz), 120.9, 82.6, 34.8, 17.5, 17.0, 15.8.
^{19}F NMR (376 MHz, $CDCl_3$) δ –62.1.
HRMS (ESI) m/z calcd. for $C_{19}H_{21}F_3NO_2$ $[M + H]^+$ 352.1519, found 352.1517.

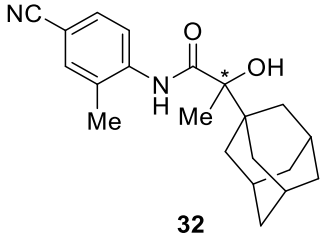
Methyl (*S*)-4-(2-Hydroxy-3-methyl-2-phenylbutanamido)-3-methylbenzoate (31)



31

According to **General Procedure A** with methyl 4-(2-chloro-3-methyl-2-phenylbutanamido)-3-methylbenzoate **E31** (72.0 mg, 0.20 mmol), the reaction was run at 0 °C for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **31** as a white solid (58.0 mg, 85% yield, 93% ee).
$[\alpha]_D^{25}$ = –17 (c 0.7, $CHCl_3$).
HPLC analysis: Chiralcel IB (*n*-hexane/*i*-PrOH = 92/8, flow rate 0.80 mL/min, λ = 254 nm), t_R (minor) = 16.94 min, t_R (major) = 18.15 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.18 (d, J = 9.0 Hz, 1H), 7.91 – 7.78 (m, 2H), 7.69 (d, J = 7.5 Hz, 2H), 7.44 – 7.33 (m, 2H), 7.32 – 7.27 (m, 1H), 3.86 (s, 3H), 3.19 (s, 1H), 3.06 – 2.86 (m, 1H), 2.24 (s, 3H), 1.09 (d, J = 6.7 Hz, 3H), 0.76 (d, J = 7.0 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 166.9, 141.2, 139.9, 131.7, 128.6, 128.5, 127.8, 126.8, 125.5, 125.4, 120.1, 82.6, 52.0, 34.9, 17.3, 17.1, 15.9.
HRMS (ESI) m/z calcd. for $C_{20}H_{24}NO_4$ $[M + H]^+$ 342.1700, found 342.1701.

2-(Adamantan-1-yl)-*N*-(4-cyano-2-methylphenyl)-2-hydroxypropanamide (32)

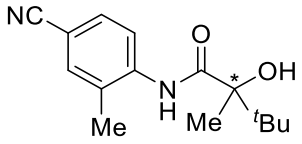


32

According to **General Procedure A** with 2-((1*S*,3*S*)-Adamantan-1-yl)-2-bromo-*N*-(4-cyano-2-methylphenyl)-propenamide **E32** (80.3 mg, 0.20 mmol), the reaction was run using **L*10** (17.6 mg, 15 mol%) as the ligand, K_2CO_3 (83.0 mg, 3.0 equiv.) as the base, in benzene (2.0 mL) at room temperature for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **32** as a white solid (48.7 mg, 72% yield, 65% ee).
$[\alpha]_D^{25}$ = –14 (c 0.4, $CHCl_3$).
HPLC analysis: Chiralcel IB (*n*-hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 8.28 min, t_R (major) = 11.99 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.41 (d, *J* = 8.5 Hz, 1H), 7.48 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.64 (s, 1H), 2.64 (s, 1H), 2.28 (s, 3H), 1.99 (s, 3H), 1.92 – 1.83 (s, 3H), 1.73 – 1.54 (m, 9H), 1.45 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 140.1, 133.8, 131.3, 127.5, 120.2, 119.1, 106.5, 80.8, 39.2, 36.7, 36.3, 28.4, 20.3, 17.4.
HRMS (ESI) m/z calcd. for $C_{21}H_{26}N_2NaO_2$ $[M + Na]^+$ 361.1886, found 361.1880.

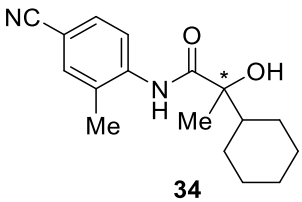
***N*-(4-Cyano-2-methylphenyl)-2-hydroxy-2,3,3-trimethylbutanamide (33)**



33

According to **General Procedure A** with 2-bromo-*N*-(4-cyano-2-methylphenyl)-2,3,3-trimethylbutanamide **E33** (64.6 mg, 0.20 mmol), the reaction was run using K_2CO_3 (83.0 mg, 3.0 equiv.) as the base at 0 °C for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **33** as a white solid (29.1 mg, 56% yield, 38% ee).
HPLC analysis: Chiralcel IB (*n*-hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 8.07 min, t_R (major) = 11.06 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.38 (d, *J* = 8.5 Hz, 1H), 7.55 – 7.47 (m, 1H), 7.45 (d, *J* = 0.9 Hz, 1H), 2.29 (s, 3H), 2.25 (s, 1H), 1.52 (s, 3H), 1.08 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 140.0, 133.8, 131.3, 127.5, 120.3, 119.1, 106.8, 80.8, 37.8, 25.4, 22.0, 17.4.
HRMS (ESI) m/z calcd. for $C_{15}H_{21}N_2O_2$ $[M + H]^+$ 261.1598, found 261.1592.

***N*-(4-Cyano-2-methylphenyl)-2-cyclohexyl-2-hydroxypropanamide (34)**

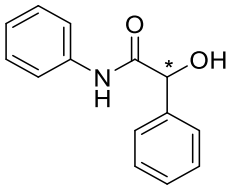


34

According to **General Procedure A** with 2-bromo-*N*-(4-cyano-2-methylphenyl)-2-cyclohexylpropanamide **E34** (69.8 mg, 0.20 mmol), the reaction was run using K_2CO_3 (83.0 mg, 3.0 equiv.) as the base at 0 °C for 5 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to yield the product **34** as a white solid (30.0 mg, 52% yield, 43% ee).
HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 9.79 min, t_R (major) = 12.22 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.37 (d, *J* = 8.5 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.44 (s, 1H), 2.57 (s, 1H), 2.29 (s, 3H), 1.92 – 1.72 (m, 4H), 1.70 – 1.62 (m, 1H), 1.48 (s, 3H), 1.34 – 1.19 (m, 4H), 1.18 – 1.02 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 139.9, 133.8, 131.3, 127.6, 120.4, 119.0, 106.9, 79.1, 45.4, 27.3, 26.3, 26.2, 26.1, 25.8, 24.4, 17.3.
HRMS (ESI) m/z calcd. for $C_{17}H_{23}N_2O_2$ $[M + H]^+$ 287.1754, found 287.1749.

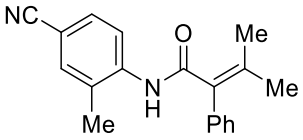
2-Hydroxy-*N*,2-diphenylacetamide (S1)



S1

According to **General Procedure A**, under argon atmosphere, an oven-dried 10 mL resealable Schlenk tube equipped with a magnetic stir bar was charged with **L*11** (13.9 mg, 0.03 mmol, 15 mol%), CuBr (2.87 mg, 0.02 mmol, 10 mol%), Rb_2CO_3 (89.0 mg, 0.60 mmol, 3.0 equiv), and 1,4-dioxane (2.0 mL) was added into the mixture, the reaction was stired at room temperature for 1 h. Then 2-chloro-*N*,2-diphenylacetamide **ES1** (49.1 mg, 0.20 mmol) and water (1.5 equiv) were added into the reaction mixture. The reaction was stired at room temperature for 3 days, and the reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 8/1 to 5/1) to yield the product **S1** as a white solid (7.3 mg, 16% yield, 64% ee).
HPLC analysis: Chiralcel IB (*n*-hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 15.53 min, t_R (major) = 26.59 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.55 – 7.44 (m, 4H), 7.41 – 7.34 (m, 3H), 7.33 – 7.28 (m, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 5.15 (s, 1H), 3.64 (s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 139.0, 137.1, 129.1, 129.0, 128.9, 126.9, 124.7, 119.8, 74.7.
HRMS (ESI) m/z calcd. for $C_{14}H_{13}NNaO_2$ $[M + Na]^+$ 250.0838, found 250.0835.

***N*-(4-Cyano-2-methylphenyl)-3-methyl-2-phenylbut-2-enamide (1')**

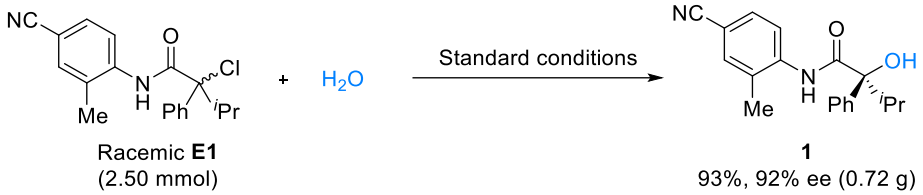


1′

The *β*-H elimination side product **1'** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 8/1) to afford as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.5 Hz, 1H), 7.56 – 7.36 (m, 4H), 7.33 – 7.25 (m, 3H), 7.03 (s, 1H), 2.34 (s, 3H), 1.73 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 148.3, 140.6, 138.3, 133.6, 131.4, 131.3, 129.9, 129.4, 128.3, 126.8, 120.1, 119.1, 106.5, 24.7, 22.5, 16.6.
HRMS (ESI) m/z calcd. for $C_{19}H_{18}N_2NaO$ $[M + Na]^+$ 313.1311, found 313.1306.

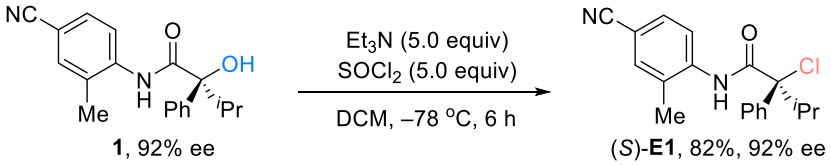
6. Synthetic utility

The scale-up experiment



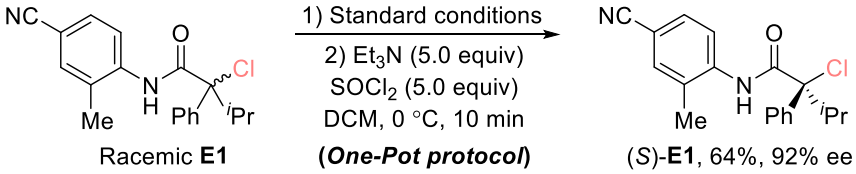
Under argon atmosphere, an oven-dried 50 mL resealable Schlenk tube equipped with a magnetic stir bar was charged with α-tertiary haloamide **E1** (817.0 mg, 2.50 mmol, 1.0 equiv), Cu(OTf)•$(C_6H_6)_{1/2}$ (62.4 mg, 0.25 mmol, 10 mol%), chiral ligand **L*9** (209.0 mg, 0.375 mmol, 15 mol%) and K_3PO_4 (1.60 g, 0.60 mmol, 3.0 equiv). Then the mixed solvent (1,4-dioxane/1,3-dioxolane = 4/1, 25.0 mL) was added into the reaction, and the resulting mixture was stirred at 0 °C for 7 days. Upon completion (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2, filtered off and rinsed three times with CH_2Cl_2. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel to afford the desired product **1** as a white solid (0.72 g, 93% yield, 92% ee).

The synthesis of enantioenriched α-tertiary haloamide ((*S*)-E1)



To a solution of **1** (61.7 mg, 0.20 mmol) in anhydrous DCM (1.0 mL) was slowly added Et_3N (101.0 mg, 1.0 mmol, 5.0 equiv) under argon atmosphere at –78 °C. After stirred at –78 °C for 10 mins, a solution of $SOCl_2$ (119.0 mg, 1.0 mmol, 5.0 equiv) in anhydrous DCM (0.50 mL) was slowly added into the reaction mixture, which was then allowed to warm slowly to room temperature over 6 h. Upon completion (monitored by TLC), the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 20/1 to 15/1) to give (*S*)-**E1** as a light yellow oil (53.6 mg, 82% yield, 92% ee).

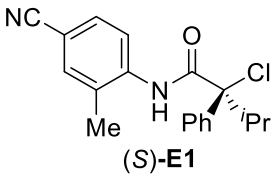
One-Pot protocol for synthesis of enantioenriched α-tertiary haloamide ((*S*)-E1)



According to **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl-2-phenylbutanamide **E1** (65.4 mg, 0.20 mmol), the reaction was run at 0 °C for 5 days under standard conditions. Upon completion (monitored by TLC), a solution of Et_3N (101.0 mg, 1.0 mmol, 5.0 equiv) in anhydrous DCM (0.50 mL) was slowly added

into the reaction mixture under argon atmosphere at 0 °C, and the resulting mixture was stirred for 5 min. Then, a solution of $SOCl_2$ (119.0 mg, 1.0 mmol, 5.0 equiv) in anhydrous DCM (0.50 mL) was slowly added, and the reaction mixture was stirred for an additional 10 min. Upon completion (monitored by TLC), the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 20/1 to 15/1) to give (*S*)-**E1** as a light yellow oil (41.8 mg, 64% yield, 92% ee).

2-Chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl-2-phenylbutanamide ((*S*)-E1)



(*S*)-**E1**

$[\alpha]_D^{25}$ = –102 (c 0.8, $CHCl_3$).

HPLC analysis: Chiralcel IB (*n*-hexane/*i*-PrOH = 95/5, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 9.19 min, t_R (major) = 9.76 min.

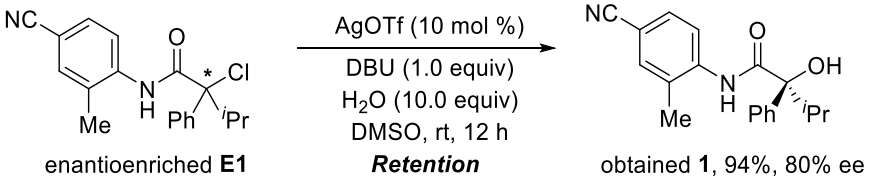
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.77 – 7.67 (m, 2H), 7.53 – 7.29 (m, 5H), 3.26 – 3.08 (m, 1H), 2.24 (s, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 139.6, 138.6, 133.9, 131.2, 128.6, 128.5, 126.4, 121.1, 118.8, 107.9, 86.2, 37.6, 19.0, 17.3, 17.0.

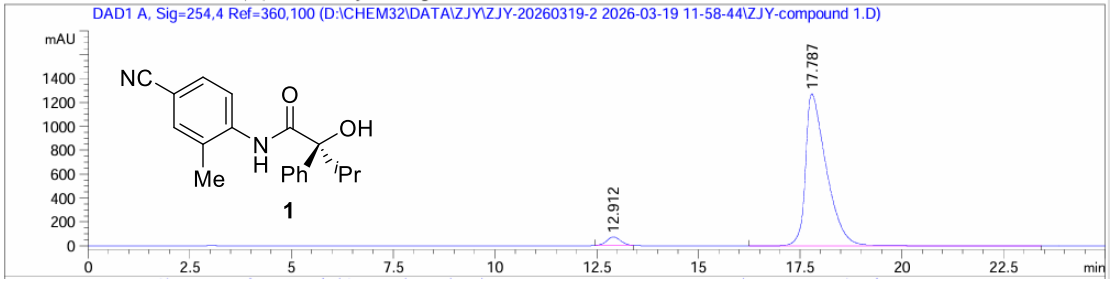
HRMS (ESI) m/z calcd. for $C_{19}H_{19}ClN_2NaO$ $[M + Na]^+$ 349.1078, found 349.1078.

Assignment of the absolute configuration of enantioenriched E1

To assign the absolute configuration of enantioenriched **E1**, we performed the AgOTf-catalyzed stereospecific hydroxylation of the above enantioenriched tertiary alkyl halide **E1** in a retentive manner, following the same procedures as reported in the literature[4]. By comparing the HPLC spectra of the obtained chiral compound **1** with those of an authentic sample **1** with known configuration prepared according to the **General Procedure A** of this work, the absolute configuration of enantioenriched **E1** was assigned as *S*.

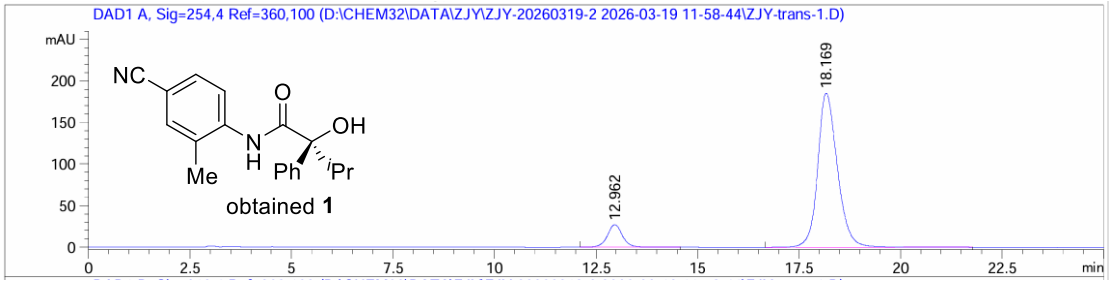


enantioenriched **E1** — obtained **1**, 94%, 80% ee



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

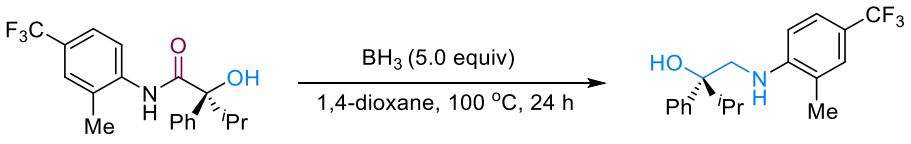
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.912	MM R	0.3941	1693.82764	71.63404	3.6016
2	17.787	BB	0.5260	4.53365e4	1271.58459	96.3984
Totals :				4.70303e4	1343.21864	



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.962	BB	0.3947	703.47168	27.11606	10.0967
2	18.169	BB	0.5113	6263.90527	185.80251	89.9033
Totals :				6967.37695	212.91856	

The synthesis of chiral *β*-amino alcohol 35

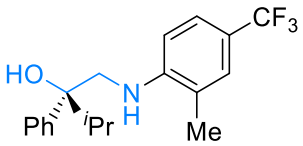


30, 93% ee

35, 86%, 93% ee

Under argon atmosphere, an oven-dried 10 mL resealable Schlenk tube equipped with a magnetic stir bar was charged with **30** (35.1 mg, 0.10 mmol, 1.0 equiv). Anhydrous 1,4-dioxane (1.0 mL) was added into the Schlenk tube under argon atmosphere at room temperature and stirred for 2 min. The BH_3 (0.50 mL, 5.0 equiv, 1.0 M in THF) was then added into the reaction mixture under argon atmosphere at room temperature. The tube was then heated in an oil bath at 100 ℃ and stirred for 24 h. Upon completion (monitored by TLC), the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 15/1 to 10/1) to give the chiral *β*-amino alcohol **35** as a colorless oil (29.0 mg, 86% yield, 93% ee).

(*S*)-3-Methyl-1-((2-methyl-4-(trifluoromethyl)phenyl)amino)-2-phenylbutan-2-ol (35)



35

$[\alpha]_D^{25}$ = –10 (c 0.4, $CHCl_3$).

HPLC analysis: Chiralcel IB (*n*-hexane/*i*-PrOH = 98/2, flow rate 1 mL/min, λ = 254 nm), t_R (major) = 12.91 min, t_R (minor) = 15.24 min.

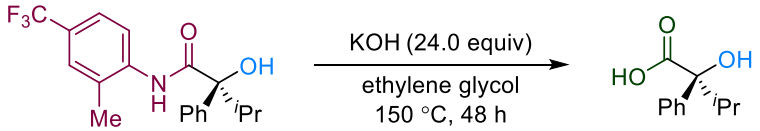
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.27 (m, 6H), 7.20 (s, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 3.68 (d, *J* = 11.5 Hz, 1H), 3.55 (s, 1H), 3.50 (d, *J* = 11.8 Hz, 1H), 2.28 (s, 1H), 2.24 – 2.13 (m, 1H), 1.83 (s, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 143.2, 128.4, 127.2, 126.8 (q, *J* = 3.6 Hz), 125.8, 124.9 (q, *J* = 268.8 Hz), 124.5 (q, *J* = 3.8 Hz), 122.5, 118.9 (q, *J* = 32.3 Hz), 109.3, 78.8, 51.8, 36.5, 17.4, 17.0, 16.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ –60.9.

HRMS (ESI) m/z calcd. for $C_{19}H_{23}F_3NO$ $[M + H]^+$ 338.1726, found 338.1726.

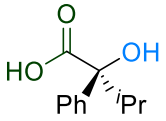
The synthesis of *α*-hydroxycarboxylic acid 36



30, 93% ee — **36**, 95%

An oven-dried 25 mL resealable Schlenk tube equipped with a magnetic stir bar was charged with **30** (440.0 mg, 1.0 mmol, 1.0 equiv), potassium hydroxide (1.35 g, 24.0 mmol) and ethylene glycol (5.0 mL). The reaction mixture was heated to 150 ℃ and stirred for 48 h. After cooling to room temperature, water (10.0 mL) was added. The resulting mixture was then washed three times with CH_2Cl_2 (10.0 mL), the aqueous layer was acidified with a 3 M aqueous HCl solution until pH = 1 and extracted with CH_2Cl_2 (10.0 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated to afford the corresponding *α*-hydroxycarboxylic acid **36** as a white solid (184.5 mg, 95% yield), which was used in the next step without further purification.

(*S*)-2-Hydroxy-3-methyl-2-phenylbutanoic acid (36)



36

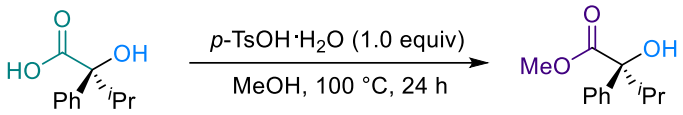
$[\alpha]_D^{25}$ = +27 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.4 Hz, 2H), 7.46 – 7.29 (m, 3H), 3.58 (s, 1H), 2.74 – 2.58 (m, 1H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 140.4, 128.2, 127.8, 125.9, 81.0, 35.8, 17.2, 15.7.

HRMS (ESI) m/z calcd. for $C_{11}H_{13}O_3$ $[M – H]^-$ 193.0870, found 193.0862.

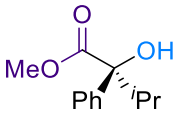
Synthesis of chiral *α*-hydroxyester 37



36 **37**, 73%, 93% ee

An oven-dried 10 mL resealable Schlenk tube equipped with a magnetic stir bar was charged with the *α*-hydroxycarboxylic acid **36** (97.0 mg, 0.50 mmol, 1.0 equiv) and *p*-toluenesulfonic acid monohydrate (115.0 mg, 0.50 mmol) in methanol (2 mL). The solution was heated at 100 ℃ for 24 h. Upon completion (monitored by TLC), the solvent was then removed under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 30/1 to 20/1) to give the chiral α-hydroxyester **37** as a colorless oil (76.0 mg, 73% yield, 93% ee).

Methyl (*S*)-2-Hydroxy-3-methyl-2-phenylbutanoate (37)



37

$[\alpha]_D^{25}$ = +35 (c 0.6, $CHCl_3$).

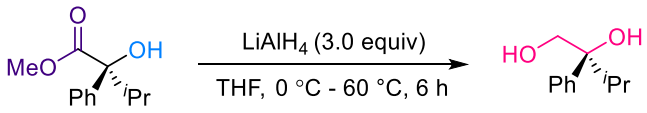
HPLC analysis: Chiralcel ODH (*n*-hexane/*i*-PrOH = 100/0, flow rate 1 mL/min, λ = 214 nm), t_R (major) = 14.15 min, t_R (minor) = 16.88 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.54 (m, 2H), 7.41 – 7.31 (m, 2H), 7.30 – 7.28 (m, 1H), 3.78 (s, 3H), 3.66 (s, 1H), 2.69 – 2.55 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.70 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 141.1, 128.1, 127.5, 126.0, 81.0, 53.3, 35.8, 17.2, 15.8.

HRMS (ESI) m/z calcd. for $C_{12}H_{16}NaO_3$ $[M + Na]^+$ 231.0992, found 231.0987.

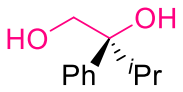
The synthesis of chiral diol 38



37, 93% ee **38**, 91%, 93% ee

An oven-dried 10 mL resealable Schlenk tube equipped with a magnetic stir bar was charged with **37** (20.8 mg, 0.10 mmol, 1.0 equiv). Anhydrous THF (1.0 mL) was added into the tube under argon atmosphere at room temperature and stirred at 0 ℃ for 5 min. Then $LiAlH_4$ (11.4 mg, 0.30 mmol, 3.0 equiv) was slowly added into the reaction mixture under argon atmosphere at 0 ℃. The resulting mixture was slowly warmed up to room temperature and stirred at 60 ℃ for 6 h. Upon completion (monitored by TLC), water (1.0 mL) was slowly added, and the reaction mixture was extracted with EtOAc (5.0 mL × 3). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 5/1 to 3/1) to give the chiral diol **38** as a colorless oil (16.5 mg, 91% yield, 93% ee).

(*S*)-3-Methyl-2-phenylbutane-1,2-diol (38)



38

$[\alpha]_D^{25}$ = –10 (c 0.3, $CHCl_3$).

HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, λ = 254 nm), t_R (major) = 8.08 min, t_R (minor) = 8.75 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.31 (m, 4H), 7.27 (d, *J* = 8.0 Hz, 1H), 3.98 (d, *J* = 11.2 Hz, 1H), 3.80 (d, *J* = 11.2 Hz, 1H), 2.55 – 1.55 (m, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H).

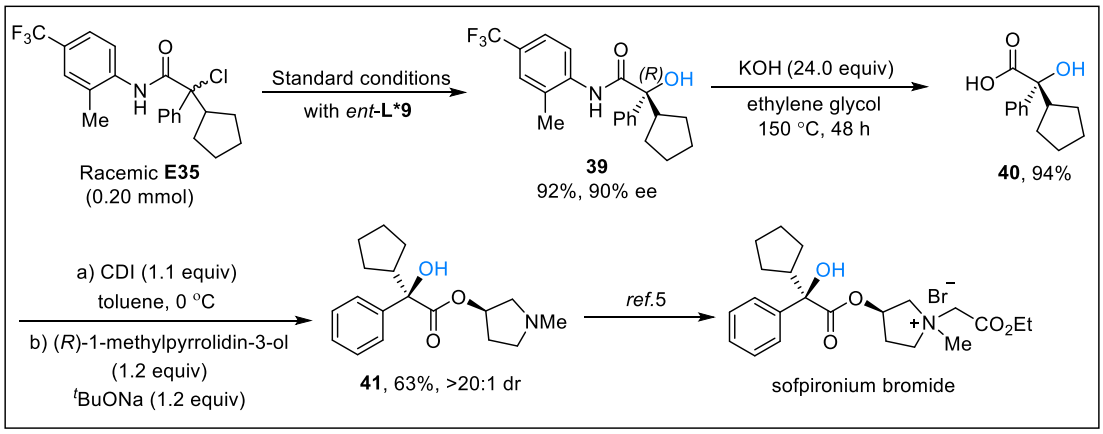
^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 128.2, 127.0, 126.2, 79.3, 68.4, 35.2, 17.4, 16.7.

HRMS (ESI) m/z calcd. for $C_{11}H_{17}O_2$ $[M + H]^+$ 181.1223, found 181.1222.

Enantioselective synthesis of drug molecules

(1) The synthesis of sofpironium bromide

Synthetic route for the key precursor **41** of sofpironium bromide.



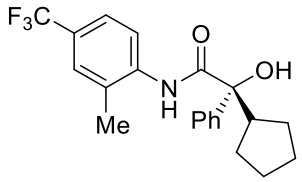
Step 1: According to the **General Procedure A** with 2-chloro-2-cyclopentyl-*N*-(2-methyl-4-(trifluoromethyl)phenyl)-2-phenylacetamide **E35** (79.2 mg, 0.20 mmol) using *ent*-**L*9**, the reaction was run at 0 °C for 6 d. The reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 15/1 to 10/1) to afford the desired product **39** as a white solid (69.5 mg, 92% yield, 90% ee).

Step 2: An oven-dried 10 mL resealable Schlenk tube equipped with a magnetic stir bar was charged with **39** (56.5 mg, 0.15 mmol, 1.0 equiv), potassium hydroxide (0.20 g, 3.6 mmol, 24.0 equiv) and ethylene glycol (3.0 mL). The reaction mixture was heated to 150 °C and stirred for 48 h. After cooling to room temperature, water (3.0 mL) was added. The resulting mixture was then washed three times with CH_2Cl_2 (10.0 mL), the aqueous layer was acidified with a 3 M aqueous HCl solution until the pH = 1 and extracted with CH_2Cl_2 (10.0 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated to give the corresponding α-hydroxycarboxylic acid **40** as a white solid (31.0 mg, 94% yield), which was used in the next step without further purification.

Step 3: An oven-dried 10 mL resealable Schlenk tube equipped with a magnetic stir bar was charged with **40** (22.0 mg, 0.10 mmol, 1.0 equiv). Anhydrous toluene (1.0 mL) was added into the tube under argon atmosphere at room temperature and stirred at 0 °C for 5 min. Then CDI (18.0 mg, 0.11 mmol, 1.1 equiv) was slowly added under argon

atmosphere. The reaction mixture was stirred at 0 ℃ for 0.5 h to prepare solution A. Another oven-dried 10 mL resealable Schlenk tube equipped with a magnetic stir bar was charged with (*R*)-1-methylpyrrolidin-3-ol (12.0 mg, 0.12 mmol, 1.2 equiv) and ^{t}BuONa (11.5 mg, 0.12 mmol, 1.2 equiv). Anhydrous toluene (1.0 mL) was added into the tube under argon atmosphere at room temperature and stirred at 50 ℃ for 2 hour to prepare solution B. Then solution A was slowly added into solution B under argon atmosphere, and the resulting mixture was stirred at 50 ℃ for 6 h. Upon completion (monitored by TLC), the mixture was cooled to room temperature and water (2.0 mL) was added. The reaction mixture was then washed with a 2M aqueous HCl solution until pH = 1. The organic layer was separated, and the aqueous layer was washed with saturated aqueous K_2CO_3 solution until pH = 10. The aqueous solution was extracted with EtOAc (5.0 mL × 3). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 2/1 to 1/1) to give the **41** as a colorless oil (20.0 mg, 63% yield, >20:1 dr).

(*R*)-2-Cyclopentyl-2-hydroxy-*N*-(2-methyl-4-(trifluoromethyl)phenyl)-2-phenylacetamide (39)



39

$[\alpha]_D^{25}$ = –3 (c 0.5, $CHCl_3$).

HPLC analysis: Chiralcel IB (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm), t_R (major) = 5.51 min, t_R (minor) = 6.17 min.

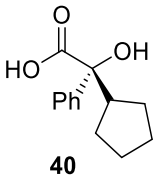
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 7.3 Hz, 2H), 7.47 – 7.25 (m, 5H), 3.28 – 3.16 (m, 1H), 3.12 (s, 1H), 2.23 (s, 3H), 1.88 – 1.72 (m, 1H), 1.67 – 1.47 (m, 6H), 1.26 – 1.08 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 141.9, 138.6, 128.6, 127.9, 127.2 (q, *J* = 3.8 Hz), 126.2 (q, *J* = 32.4 Hz), 125.5, 124.1 (q, *J* = 270.1 Hz), 124.0 (q, *J* = 3.8 Hz), 121.0, 80.9, 46.6, 26.8, 26.7, 26.2, 25.9, 17.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ –62.1.

HRMS (ESI) m/z calcd. for $C_{21}H_{23}F_3NO_2$ $[M + H]^+$ 378.1675, found 378.1677.

(*R*)-2-Cyclopentyl-2-hydroxy-2-phenylacetic acid (40)



40

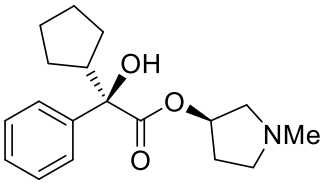
$[\alpha]_D^{25}$ = –12 (c 0.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (br, 1H), 7.73 – 7.57 (m, 2H), 7.37 – 7.29 (m, 2H), 7.28 – 7.24 (m, 1H), 3.00 – 2.84 (m, 1H), 1.75 – 1.25 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 141.0, 128.2, 127.8, 125.9, 79.2, 47.2, 26.9, 26.4, 26.3, 25.9.

HRMS (ESI) m/z calcd. for $C_{13}H_{15}O_3$ $[M - H]^-$ 219.1027, found 219.1020.
The NMR data match with those reported in literature[6].

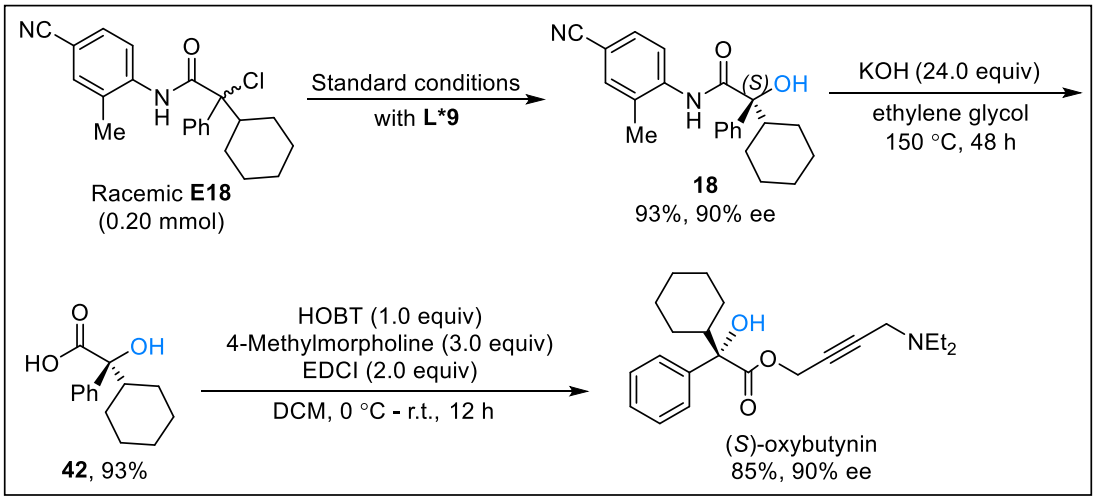
(*R*)-1-Methylpyrrolidin-3-yl (*R*)-2-cyclopentyl-2-hydroxy-2-phenylacetate (41)



41

$[\alpha]_D^{25}$ = –14 (c 0.4, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.56 (m, 2H), 7.40 – 7.30 (m, 2H), 7.30 – 7.25 (m, 1H), 5.31 – 5.16 (m, 1H), 3.89 (br, 1H), 2.98 – 2.89 (m, 1H), 2.87 – 2.75 (m, 2H), 2.64 – 2.57 (m, 1H), 2.56 – 2.47 (m, 1H), 2.37 (s, 3H), 2.34 – 2.23 (m, 1H), 1.95 – 1.85 (m, 1H), 1.74 – 1.22 (m, 9H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 141.7, 128.1, 127.4, 125.9, 79.3, 76.3, 61.5, 54.9, 47.0, 42.1, 32.6, 26.8, 26.5, 26.4, 26.1.
HRMS (ESI) m/z calcd. for $C_{18}H_{26}NO_3$ $[M + H]^+$ 304.1907, found 304.1903.
The NMR data match with those reported in literature[5].

(2) The synthesis of (*S*)-oxybutynin
Synthetic route for (*S*)-oxybutynin.



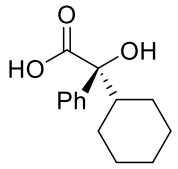
Step 1: According to the **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-2-cyclohexyl-2-phenylacetamide **E18** (73.4 mg, 0.20 mmol) using **L*9**, the reaction was run at 0 ℃ for 5 d. The reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1 to 5/1) to afford the desired product **18** as a white solid (64.8 mg, 93% yield, 90% ee).

Step 2: An oven-dried 10 mL resealable Schlenk tube equipped with a magnetic stir bar was charged with **18** (52.3 mg, 0.15 mmol, 1.0 equiv), potassium hydroxide (0.20 g, 3.6 mmol, 24.0 equiv) and ethylene glycol (2.0 mL). The reaction mixture was heated to 150 ℃ and stirred for 48 h. After cooling to room temperature, water (3.0 mL) was added. The resulting mixture was then washed three times with CH_2Cl_2 (10.0 mL), the

aqueous layer was acidified with a 3 M aqueous HCl solution until pH = 1 and extracted with CH_2Cl_2 (10.0 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated to give the corresponding α-hydroxycarboxylic acid **42** as a white solid (32.7 mg, 93% yield), which was used in the next step without further purification.

Step 3: An oven-dried 10 mL resealable Schlenk tube equipped with a magnetic stir bar was charged with the *α*-hydroxycarboxylic acid **42** (23.4 mg, 0.10 mmol, 1.0 equiv), 4-(diethylamino)but-2-yn-1-ol (14.1 mg, 0.10 mmol, 1.0 equiv) and anhydrous DCM (1.0 mL). Then 1-hydroxybenzotriazole hydrate (HOBT) (13.6 mg, 1.0 mmol, 1.0 equiv) and 4-methylmorpholine (34.0 uL, 0.30 mmol, 3.0 equiv) were added sequentially to the reaction mixture at 0 ℃ for 1 h. Then EDCI (38.3 mg, 0.20 mmol, 2.0 equiv.) was added and the reaction mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, and the residue was quenched with H_2O (4.0 mL) and washed with EtOAc (5.0 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (10.0 mL × 3). The combined organic layers were dried over Na_2SO_4, and the solvent was then removed under reduced pressure. The residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 5/1 to 3/1) to give the corresponding drug (*S*)-oxybutynin as a yellow oil (30.4 mg, 85% yield, 90% ee).

(*S*)-2-Cyclohexyl-2-hydroxy-2-phenylacetic acid (42)



42

$[\alpha]_D^{25}$ = +10 (c 0.5, $CHCl_3$).

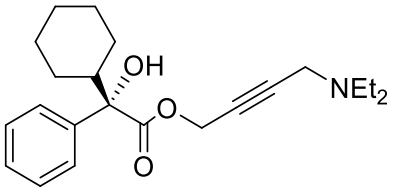
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.59 (m, 2H), 7.39 – 7.31 (m, 2H), 7.30 – 7.27 (m, 1H), 2.30 – 2.18 (m, 1H), 1.84 – 1.75 (m, 1H), 1.66 – 1.59 (m, 2H), 1.48 – 0.97 (m, 7H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 180.7, 139.9, 128.2, 127.7, 125.9, 80.9, 45.6, 27.3, 26.3, 26.2, 26.1, 25.4.

HRMS (ESI) m/z calcd. for $C_{14}H_{18}NaO_3$ $[M + Na]^+$ 257.1148, found 257.1146.

The analytical data are consistent with those reported in literature[7].

4-(Diethylamino)but-2-yn-1-yl (*S*)-2-Cyclohexyl-2-hydroxy-2-phenylacetate ((*S*)-oxybutynin)



(*S*)-oxybutynin

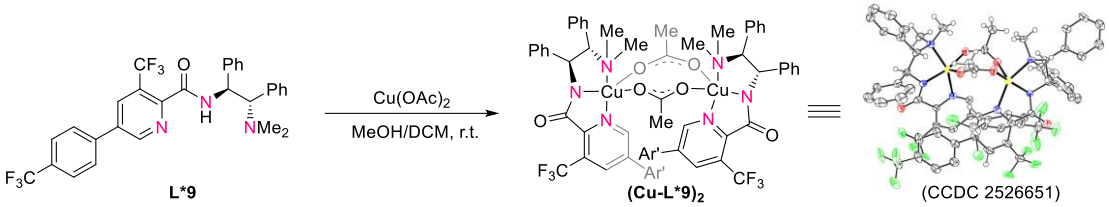
$[\alpha]_D^{25}$ = –32 (c 0.4, $CHCl_3$).

HPLC analysis: Chiralcel IA (*n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 214 nm), t_R (minor) = 5.73 min, t_R (major) = 6.53 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.58 (m, 2H), 7.38 – 7.29 (m, 2H), 7.28 – 7.23 (m, 1H), 4.83 (dt, *J* = 15.2, 1.9 Hz, 1H), 4.71 (dt, *J* = 15.2, 1.9 Hz, 1H), 3.64 (s, 1H), 3.42 (t, *J* = 1.8 Hz, 2H), 2.46 (q, *J* = 7.2 Hz, 4H), 2.31 – 2.20 (m, 1H), 1.83 – 1.72 (m, 1H), 1.69 – 1.59 (m, 2H), 1.58 – 1.50 (m, 1H), 1.48 – 1.36 (m, 1H), 1.36 – 1.26 (m, 1H), 1.23 – 1.06 (m, 4H), 1.03 (t, *J* = 7.2 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 140.4, 128.1, 127.5, 126.1, 82.6, 81.0, 77.8, 54.1, 47.2, 45.7, 40.7, 27.2, 26.3, 26.2, 25.4, 12.6.
HRMS (ESI) m/z calcd. for $C_{22}H_{32}NO_3$ $[M + H]^+$ 358.2377, found 358.2373.
The analytical data are consistent with those reported in literature[8].

7. Experimental mechanistic studies

The preparation of Cu(II)-ligand complex $(Cu\text{-}L^*9)_2$



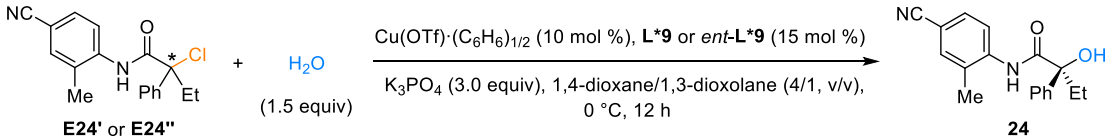
To a solution of ligand **L*9** (55.7 mg, 0.1 mmol) in MeOH/DCM (v/v = 1/1, 2.0 mL) was added $Cu(OAc)_2$ (36.5 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 6 h. Then the mixture was filtered off and washed three times by CH_2Cl_2. The filtrate was concentrated, and the residue was slowly diffused with a mixed solution of *n*-hexane and dichloromethane (v/v, 4/1) and recrystallized at room temperature to give the Cu(II)-ligand complex **$(Cu\text{-}L^*9)_2$** as a slightly blue solid. The structure of **$(Cu\text{-}L^*9)_2$** was confirmed by X-ray diffraction analysis.

The catalytic activity of $(Cu\text{-}L^*9)_2$ complex

With $(Cu\text{-}L^*9)_2$: According to the **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl-2-phenylbutanamide **E1** (16.4 mg, 0.05 mmol) using **$(Cu\text{-}L^*9)_2$** complex (5.2 mg, 15 mol%) under standard conditions. The reaction afforded the desired product **1** as a white solid (95% yield, 90% ee).

With $Cu(OAc)_2$**/L*9**: According to the **General Procedure A** with 2-chloro-*N*-(4-cyano-2-methylphenyl)-3-methyl-2-phenylbutanamide **E1** (16.4 mg, 0.05 mmol) using $Cu(OAc)_2$ (0.91 mg, 10 mol%) and **L*9** (4.18 mg, 15 mol%) under standard conditions. The reaction afforded the desired product **1** as a white solid (83% yield, 87% ee).

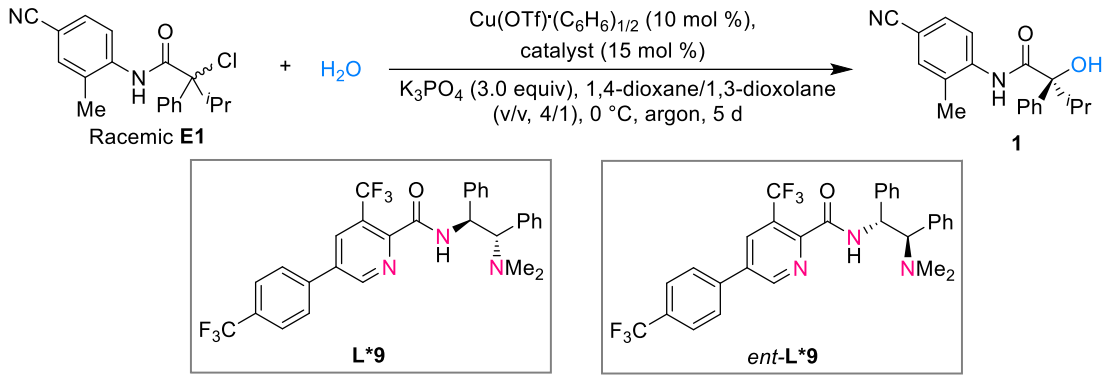
Enantiopurity of recovered *α*-tertiary alkyl chloride and tertiary alcohol



Entry	Substrate	Ee of **24** (%)	Ee of recovered substrate
1	**E24′** (>99% ee)	84 (with **L*9**)	>99 (**E24′**)
2	**E24′** (>99% ee)	−85 (with *ent*-**L*9**)	>99 (**E24′**)
3	**E24″** (> −99% ee)	85 (with **L*9**)	> −99 (**E24″**)

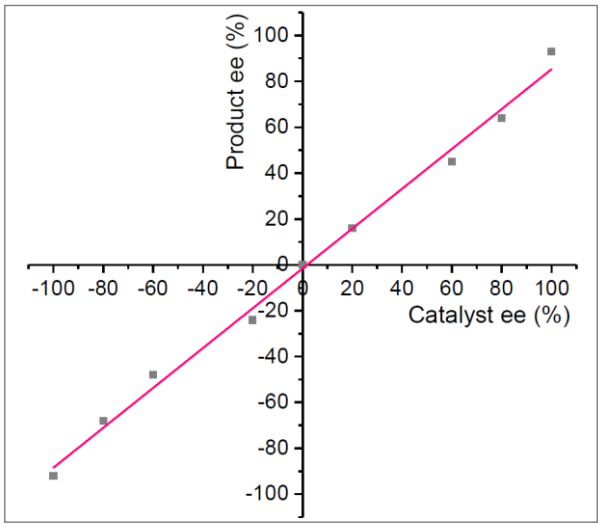
[a]Reaction conditions: Enantioenriched tertiary alkyl chloride **E24′** or **E24″** (0.05 mmol, 1.0 equiv), H_2O (1.5 equiv), $Cu(OTf)\cdot(C_6H_6)_{1/2}$ (10 mol%), **L*9** or *ent*-**L*9** (15 mol%), and K_3PO_4 (3.0 equiv) in 1,4-dioxane/1,3-dioxolane (0.50 mL, v/v = 4/1) at 0 °C for 12 h. Ee values were based on chiral HPLC analysis. *Note: **E24′** and **E24″** correspond to the two enantiomers of **E24**, respectively.*

The nonlinear effect experiments

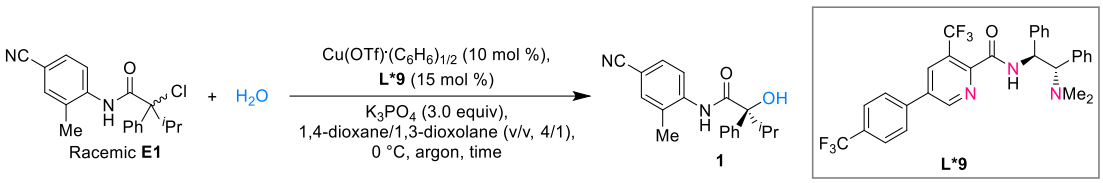


Under argon atmosphere, an oven-dried 10 mL resealable Schlenk tube equipped with a magnetic stir bar was charged with α-tertiary haloamide **E1** (0.05 mmol, 1.0 equiv), $Cu(OTf)\cdot(C_6H_6)_{1/2}$ (1.26 mg, 0.005 mmol, 10 mol%), ligand (4.18 mg, 0.0075 mmol, 15 mol%), K_3PO_4 (32.0 mg, 0.15 mmol, 3.0 equiv) and solvent (1,4-dioxane/1,3-dioxolane, v/v = 4/1, 0.50 mL). The resulting mixture was stirred at 0 °C for 5 d. Upon completion (monitored by TLC), the product was purified by preparative thin-layer chromatography (PTLC) on silica gel. The ee values of product **1** were determined by chiral HPLC, which revealed a linear relationship between the ee values of product **1** and those of the corresponding ligands. The ligands with different ee values were prepared by mixing **L*9** (99% ee) and *ent*-**L*9** (99% ee) in appropriate ratios.

Entry	Ee of ligand (%)	Ee of **1** (%)
1	100	93
2	80	64
3	60	45
4	20	16
5	0	0
6	–20	–24
7	–60	–48
8	–80	–68
9	–100	–92



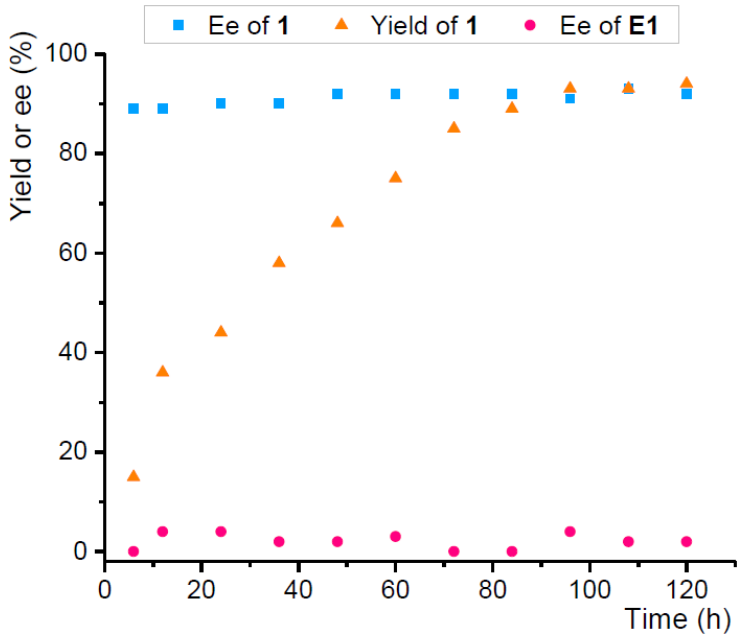
The time-course experiments



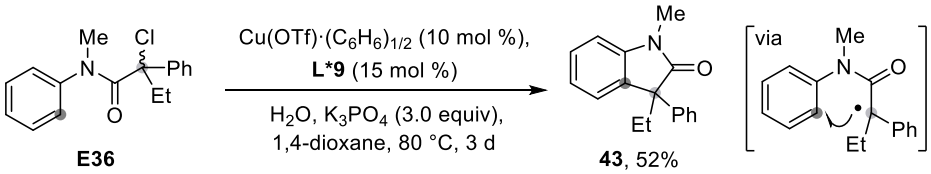
Under argon atmosphere, an oven-dried 10 mL resealable Schlenk tube equipped with a magnetic stir bar was charged with α-tertiary haloamide **E1** (0.05 mmol, 1.0 equiv), Cu(OTf)•$(C_6H_6)_{1/2}$ (1.26 mg, 0.005 mmol, 10 mol%), ligand (4.18 mg, 0.0075 mmol, 15 mol%), K_3PO_4 (32.0 mg, 0.15 mmol, 3.0 equiv) and solvent (1,4-dioxane/1,3-dioxolane, v/v = 4:1, 0.50 mL). The reaction mixture was stirred at 0 °C for a specified period of time. The reaction mixture was filtered off and washed with CH_2Cl_2 for three times. The combined organic layers were dried over Na_2SO_4 and concentrated to afford the crude product.

The yields of **1** were analyzed by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. The crude product was then purified by preparative thin-layer chromatography (PTLC) on silica gel, resulting in the isolation of product **1** and the recovery of **E1**. The ee values of **1** and the recovered **E1** were determined by chiral HPLC analysis.

Entry	Time (h)	Yield of **1** (%)	Recovered **E1** (%)	Ee of **1** (%)	Ee of **E1**(%)
1	6	15	84	89	0
2	12	36	62	89	4
3	24	44	52	90	4
4	36	58	38	90	2
5	48	66	31	92	2
6	60	75	21	92	3
7	72	85	13	92	0
8	84	89	9	92	0
9	96	93	5	91	4
10	108	93	4	93	2
11	120	94	2	92	2

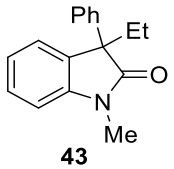


The radical clock experiment



Under argon atmosphere, an oven-dried 10 mL resealable Schlenk tube equipped with a magnetic stir bar was charged with *α*-tertiary haloamide **E36** (57.6 mg, 0.20 mmol, 1.0 equiv), Cu(OTf)•$(C_6H_6)_{1/2}$ (5.03 mg, 0.02 mmol, 10 mol%), chiral ligand **L*9** (16.72 mg, 0.03 mmol, 15 mol%) and K_3PO_4 (128.0 mg, 0.60 mmol, 3.0 equiv). Then the anhydrous solvent 1,4-dioxane (2.0 mL) and H_2O (1.5 equiv) was added into the mixture, and the reaction mixture was stirred at 80 ℃ for 3 days. Upon completion (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2, filtered off and rinsed three times with CH_2Cl_2. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel to afford the intramolecular cyclization product **43** (26.1 mg, 52% yield).

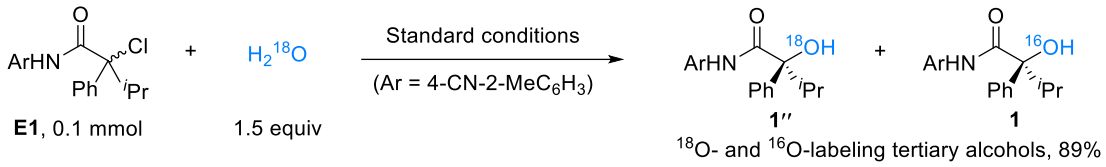
3-Ethyl-1-methyl-3-phenylindolin-2-one (43)



43

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.15 (m, 7H), 7.13 – 7.05 (m, 1H), 6.91 – 6.85 (m, 1H), 3.20 (s, 3H), 2.48 – 2.34 (m, 1H), 2.29 – 2.13 (m, 1H), 0.66 (t, J = 7.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 144.2, 140.3, 132.1, 128.5, 128.1, 127.2, 127.0, 124.8, 122.6, 108.2, 57.3, 30.9, 26.3, 9.0.
HRMS (ESI) m/z calcd. for $C_{17}H_{18}NO$ $[M + H]^+$ 252.1383, found 252.1383.

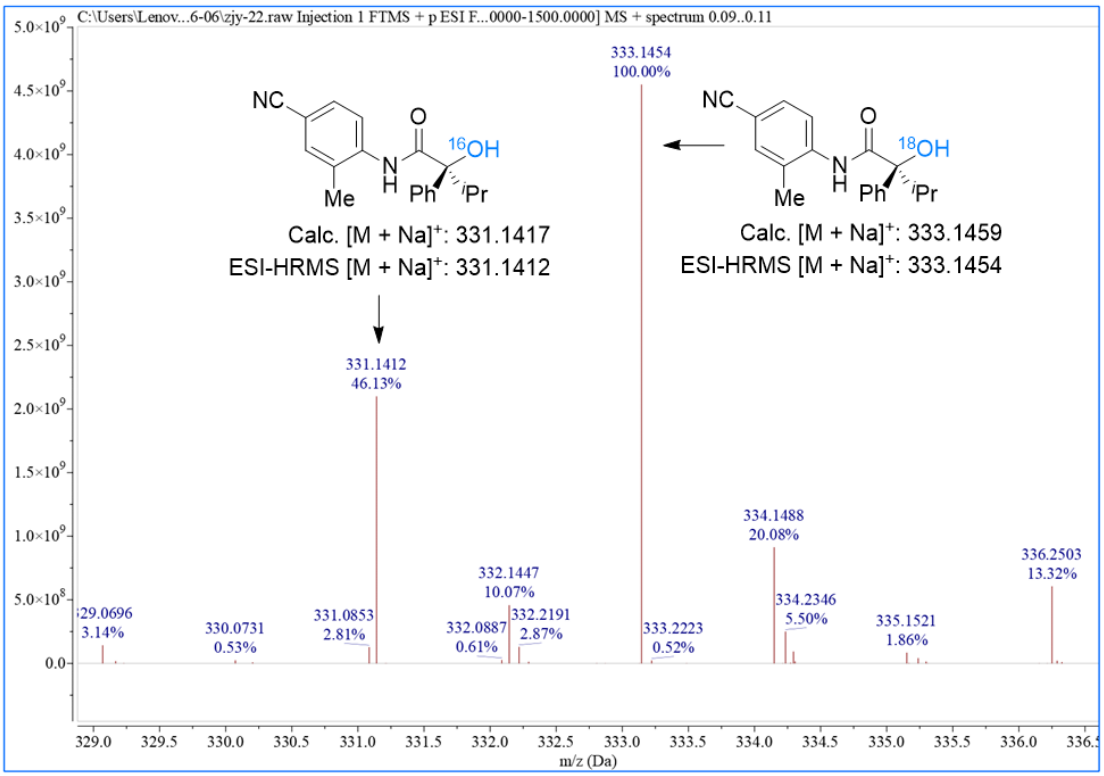
The ^{18}O labeling experiment



E1, 0.1 mmol 1.5 equiv ^{18}O- and ^{16}O-labeling tertiary alcohols, 89%

Under argon atmosphere, an oven-dried 10 mL resealable Schlenk tube equipped with a magnetic stir bar was charged with α-tertiary haloamide **E1** (32.7 mg, 0.10 mmol, 1.0 equiv), $Cu(OTf)\cdot(C_6H_6)_{1/2}$ (2.52 mg, 0.01 mmol, 10 mol%), **L*9** (8.36 mg, 0.015 mmol, 15 mol%), K_3PO_4 (64.0 mg, 0.30 mmol, 3.0 equiv) and anhydrous mixed solvents (1,4-dioxane/1,3-dioxolane, v/v = 4/1, 1.0 mL). Then the $H_2{}^{18}O$ (3.0 mg, 0.15 mmol, 1.5 equiv, 98% ^{18}O purity) was added into the reaction mixture. The reaction mixture was stirred at 0 °C for 5 days. Upon completion (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2, filtered off and rinsed three times with CH_2Cl_2. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel to afford the ^{18}O- and ^{16}O-labeled products (27.6 mg, 89% yield).

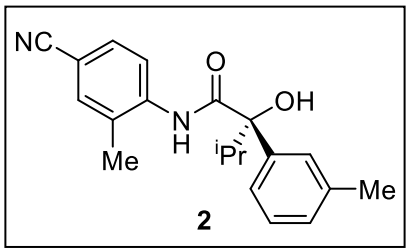
HRMS (ESI) m/z calcd. for $C_{19}H_{20}N_2NaO^{18}O$ $[M + Na]^+$ 333.1459, found 333.1454.

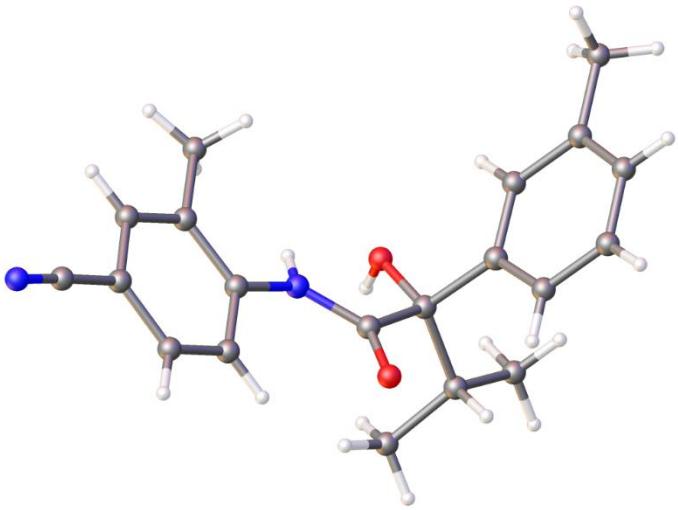


8. X-ray crystallographic data

Sample preparation of product 2

The single crystals of product **2** suitable for X-ray diffraction were obtained by slow evaporation of a mixed solution of **2** in *n*-hexane and dichloromethane (v/v, 3/1) at room temperature. The crystal data of compound **2** have been deposited at the Cambridge Crystallographic Data Centre (**CCDC 2526649**).



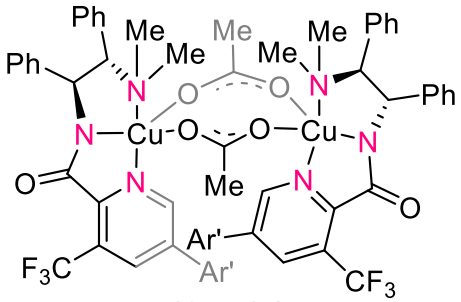


Crystal data and structure refinement for **2**.

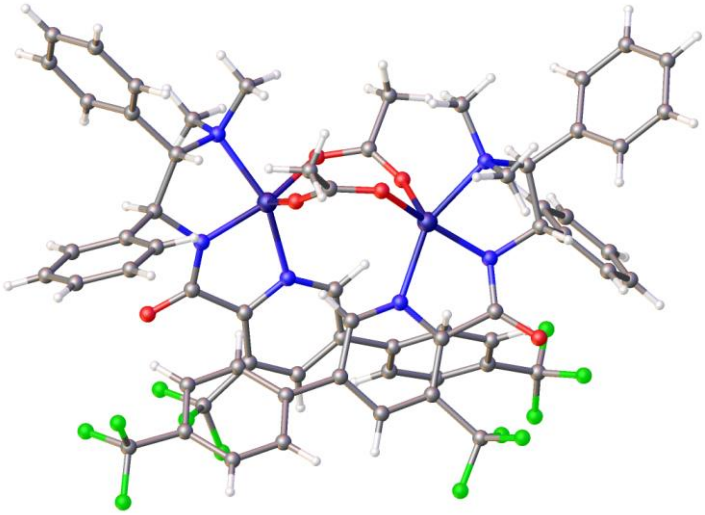
Identification code	**2**
Empirical formula	$C_{20}H_{22}N_2O_2$
Formula weight	322.39
Temperature/K	100.0(2)
Crystal system	monoclinic
Space group	C2
a/Å	22.2760(15)
b/Å	6.9882(5)
c/Å	23.4446(16)
α/°	90
β/°	102.237(3)
γ/°	90
Volume/Å^3	3566.7(4)
Z	8
ρ_{calc}g/cm^3	1.201
μ/mm^{-1}	0.411
F(000)	1376.0
Crystal size/mm^3	0.31 × 0.28 × 0.12
Radiation	GaKα (λ = 1.34138)
2Θ range for data collection/	6.712 to 113.988
Index ranges	–27≤ h ≤27, –8≤ k ≤8, –29≤ l ≤29
Reflections collected	61906
Independent reflections	7278 [R_{int} = 0.0531, R_{sigma} = 0.0320]
Data/restraints/parameters	7278/1/443
Goodness-of-fit on F^2	1.037
Final R indexes [I>=2σ (I)]	R_1 = 0.0456, wR_2 = 0.1165
Final R indexes [all data]	R_1 = 0.0489, wR_2 = 0.1191
Largest diff. peak/hole / e Å^{-3}	0.58/–0.27
Flack parameter	–0.01(7)

Sample preparation of complex (Cu-L*9)$_2$

The single crystals of complex **(Cu-L*9)$_2$** suitable for X-ray diffraction were obtained by slow evaporation of a mixed solution of **(Cu-L*9)$_2$** in *n*-hexane and dichloromethane (v/v, 4/1) at room temperature. The crystal data of complex **(Cu-L*9)$_2$** have been deposited at the Cambridge Crystallographic Data Centre (**CCDC 2526651**).



(Cu-L*9)$_2$

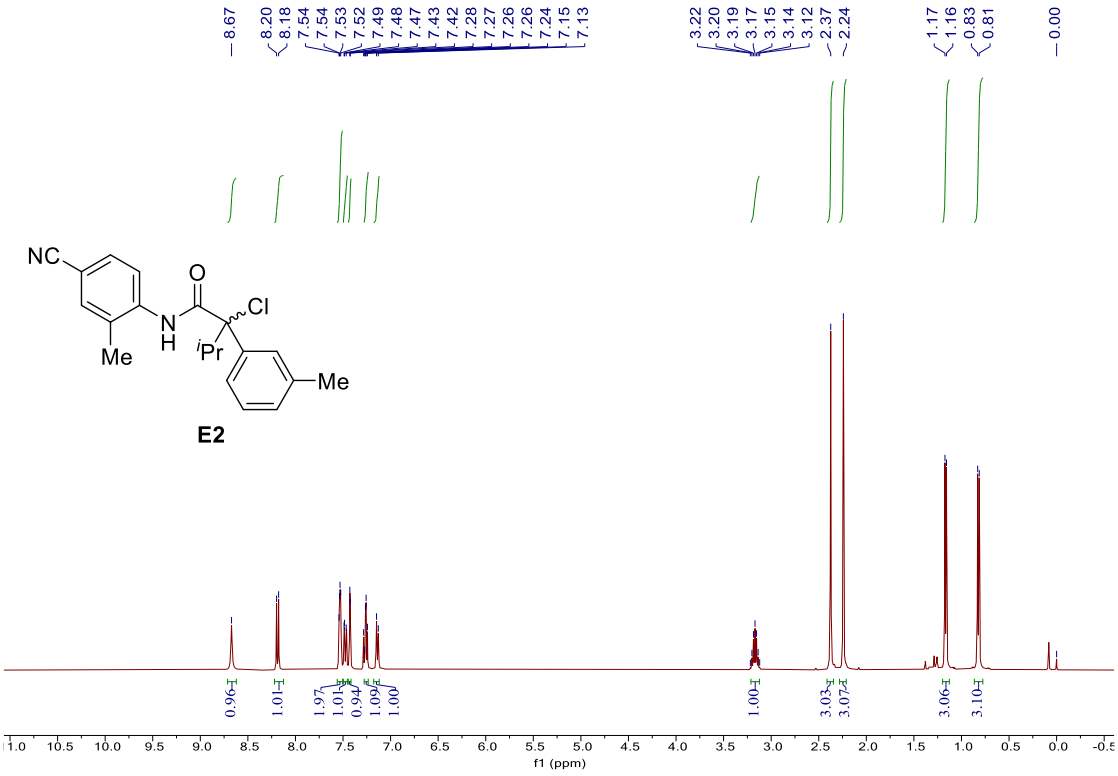


Crystal data and structure refinement for complex **(Cu-L*9)$_2$**.

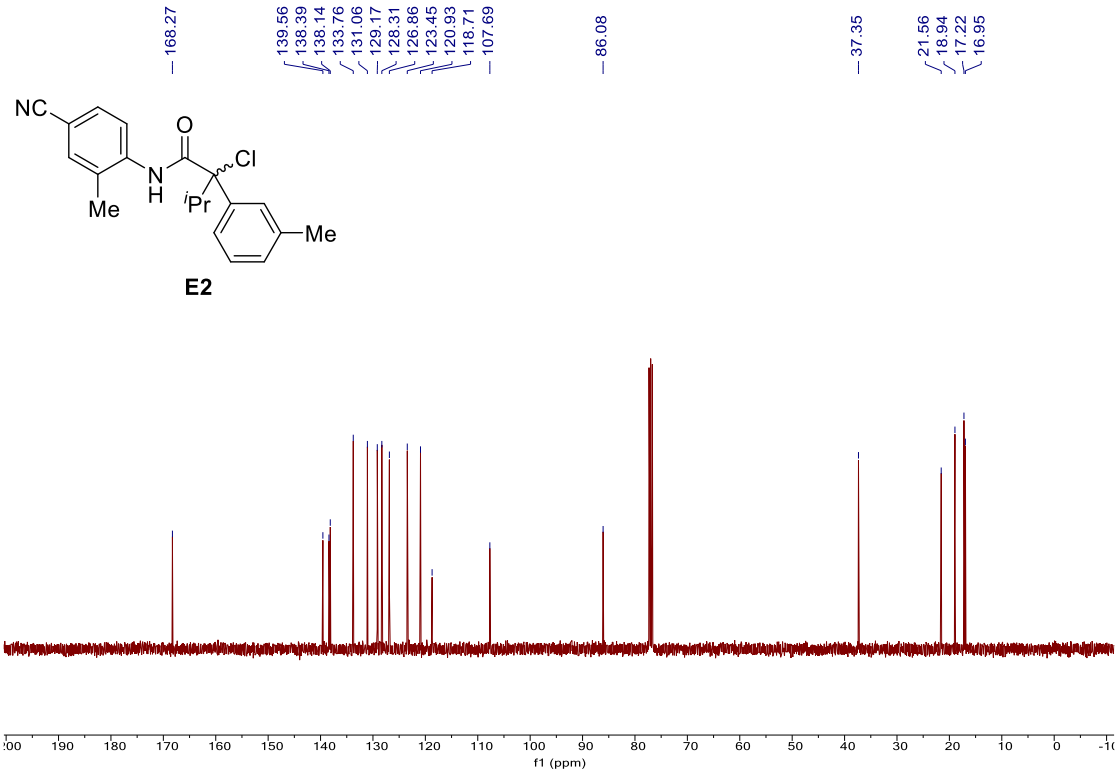
Identification code	**(Cu-L*9)$_2$**
Empirical formula	$C_{68}H_{63}Cl_2Cu_2F_{12}N_6O_6$
Formula weight	1486.22
Temperature/K	100.0(2)
Crystal system	orthorhombic
Space group	$P2_12_12$
a/Å	22.0556(15)
b/Å	31.513(2)
c/Å	9.5391(7)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	6630.0(8)
Z	4
ρ_{calc}g/cm^3	1.489
μ/mm^{-1}	4.433
F(000)	3044.0
Crystal size/mm^3	0.32 × 0.28 × 0.03
Radiation	GaKα (λ = 1.34138)
2Θ range for data collection/°	4.88 to 114.282
Index ranges	–27≤ h ≤27, –39≤ k ≤38, –11≤ l ≤11
Reflections collected	88592
Independent reflections	13590 [R_{int} = 0.0996, R_{sigma} = 0.0626]
Data/restraints/parameters	13590/456/975
Goodness-of-fit on F^2	1.121
Final R indexes [I>=2σ (I)]	R_1 = 0.0576, wR_2 = 0.1527
Final R indexes [all data]	R_1 = 0.0697, wR_2 = 0.1589
Largest diff. peak/hole / e Å^{-3}	1.04/–0.82
Flack parameter	–0.034(4)

9. NMR spectra

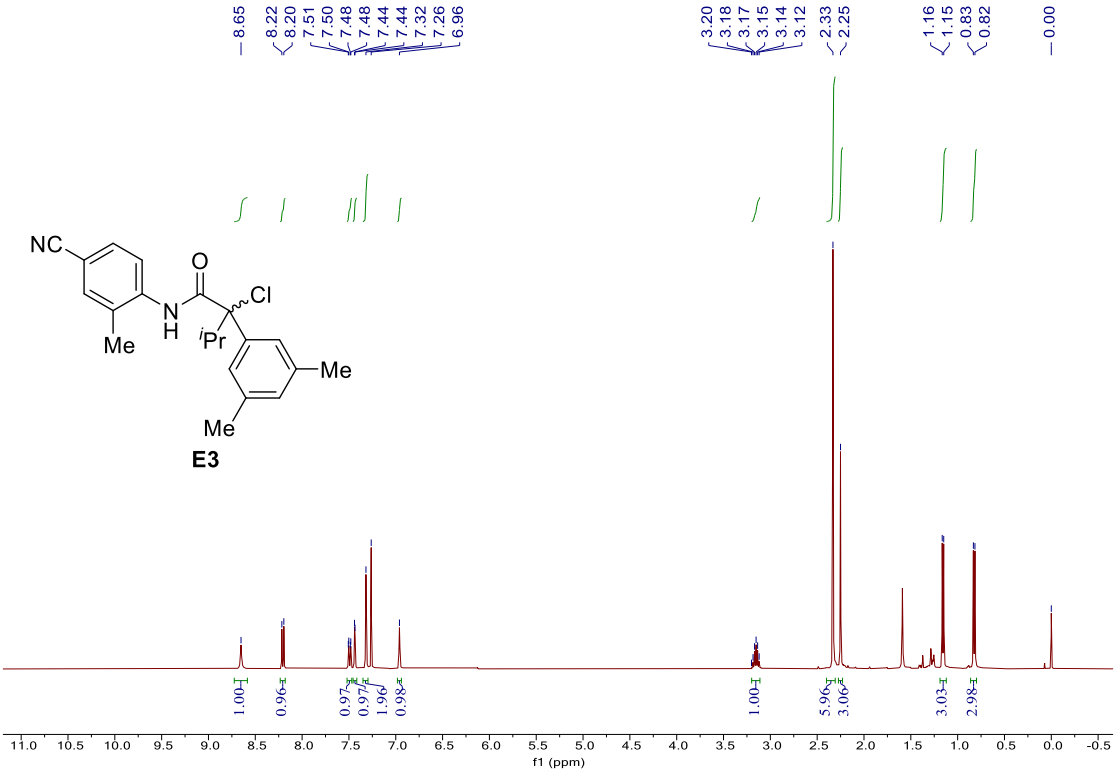
^{1}H NMR (400 MHz, $CDCl_3$)



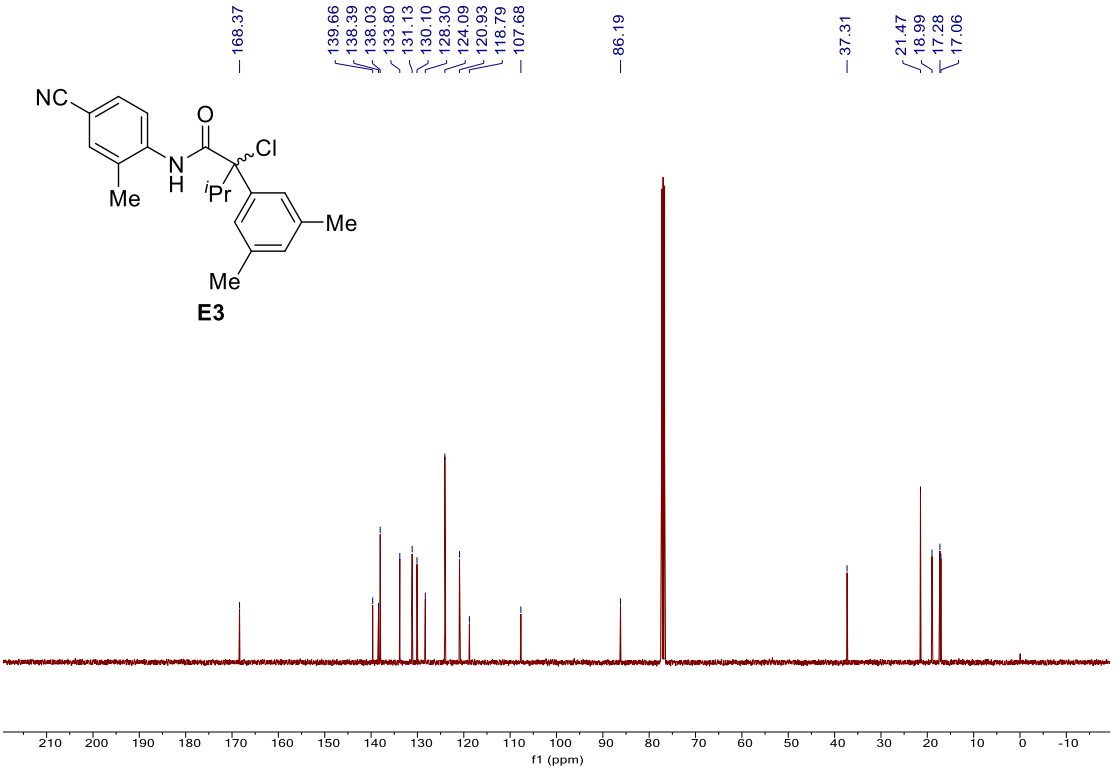
^{13}C NMR (100 MHz, $CDCl_3$)



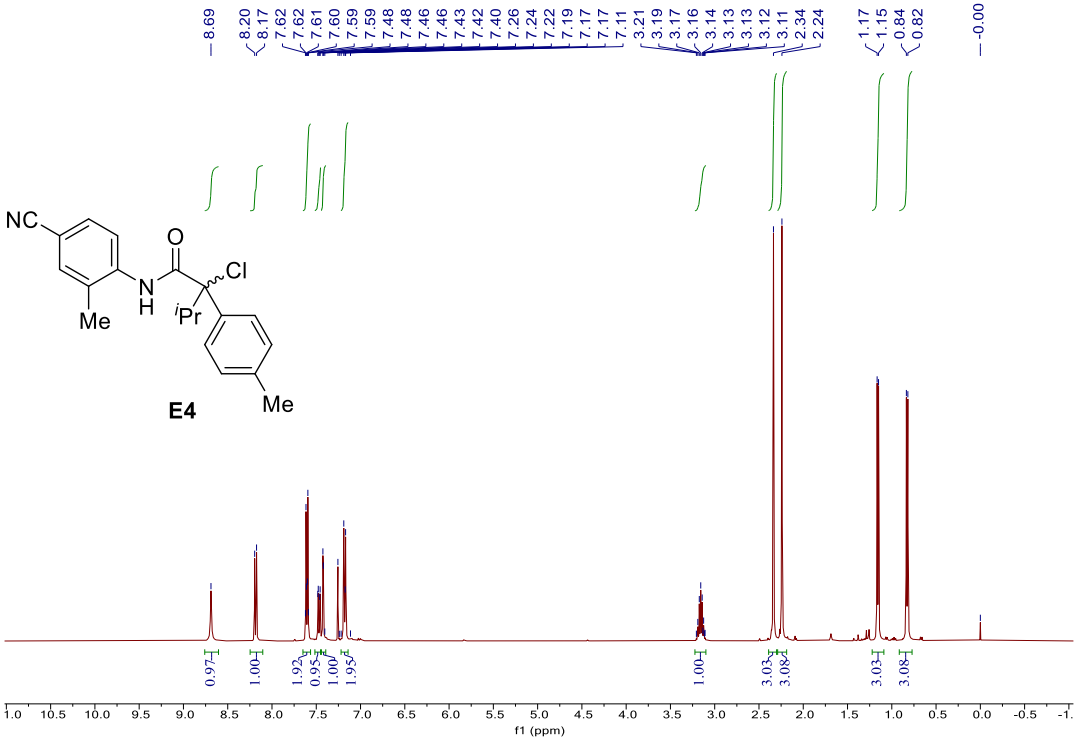
^{1}H NMR (400 MHz, $CDCl_3$)



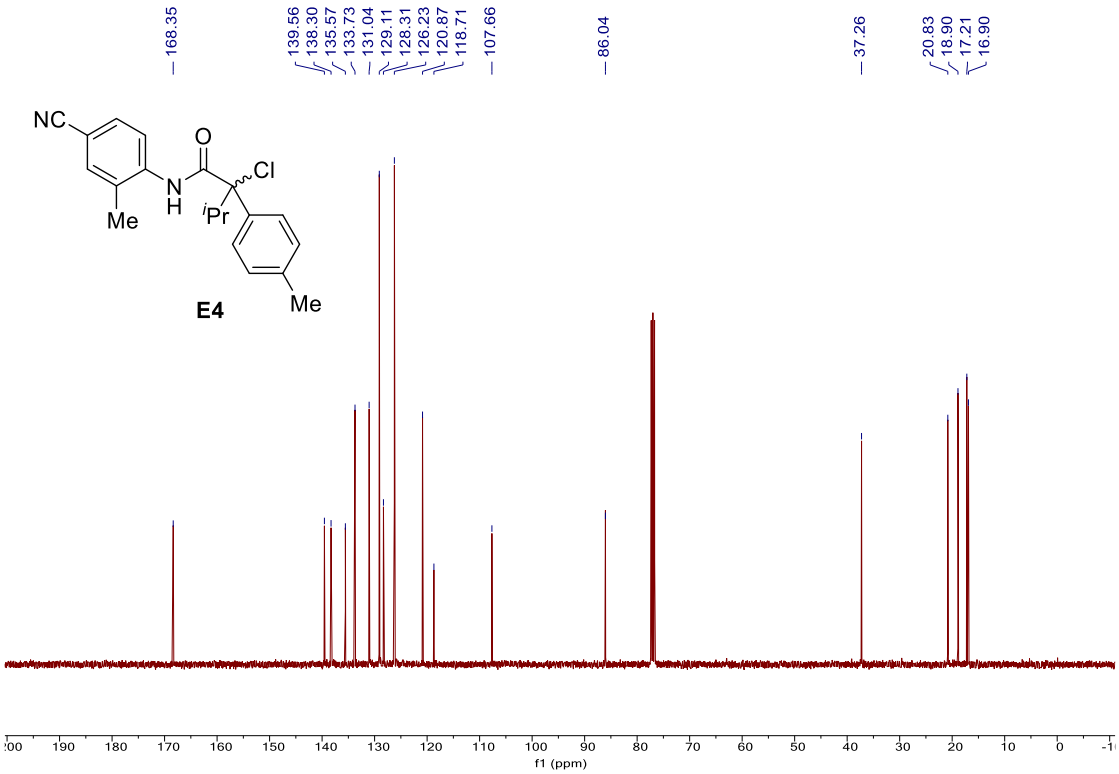
^{13}C NMR (100 MHz, $CDCl_3$)



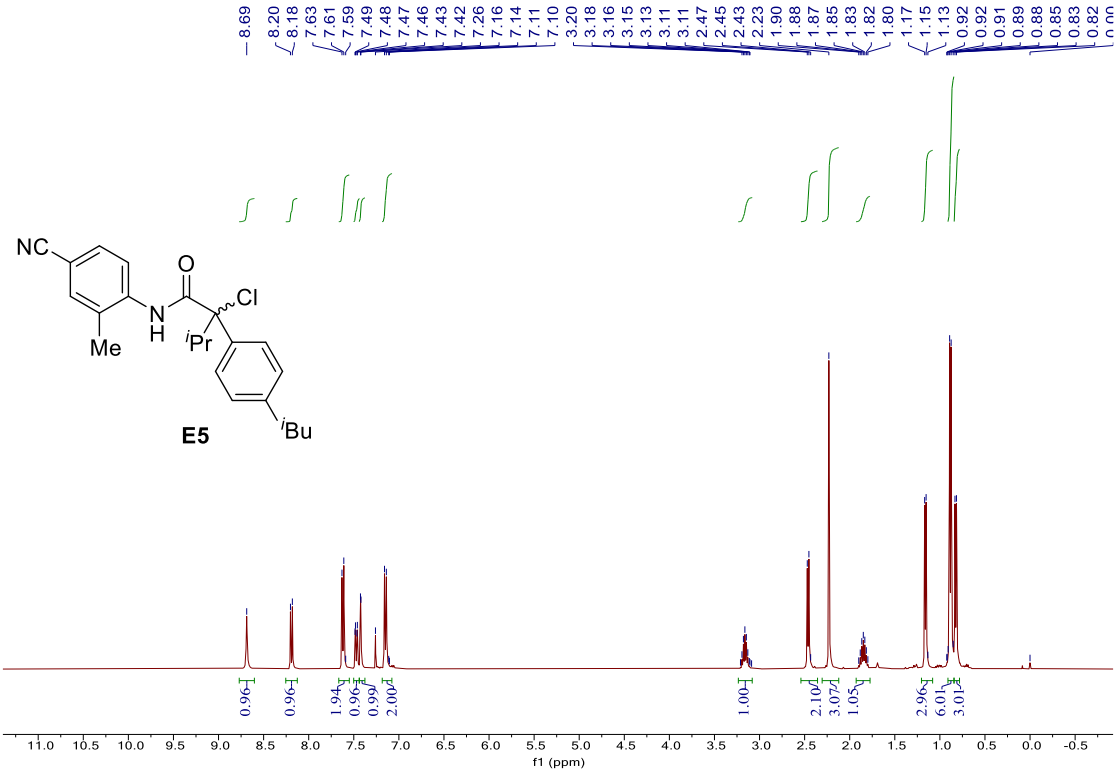
^{1}H NMR (400 MHz, $CDCl_3$)



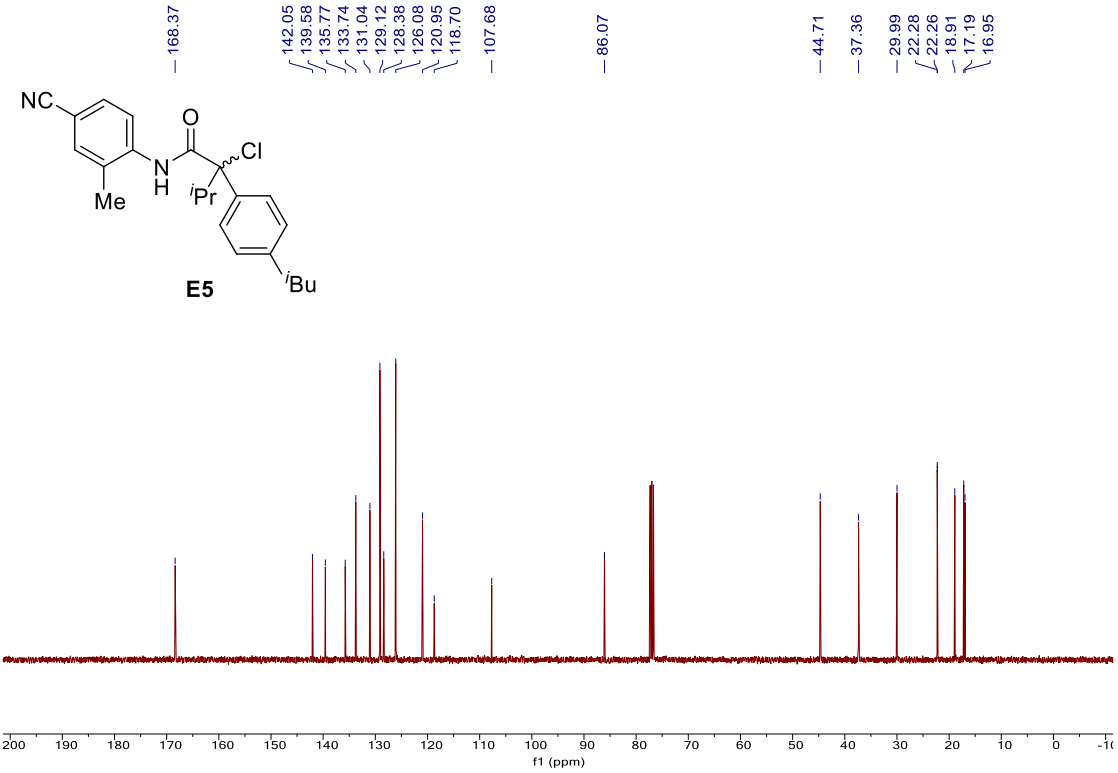
^{13}C NMR (100 MHz, $CDCl_3$)



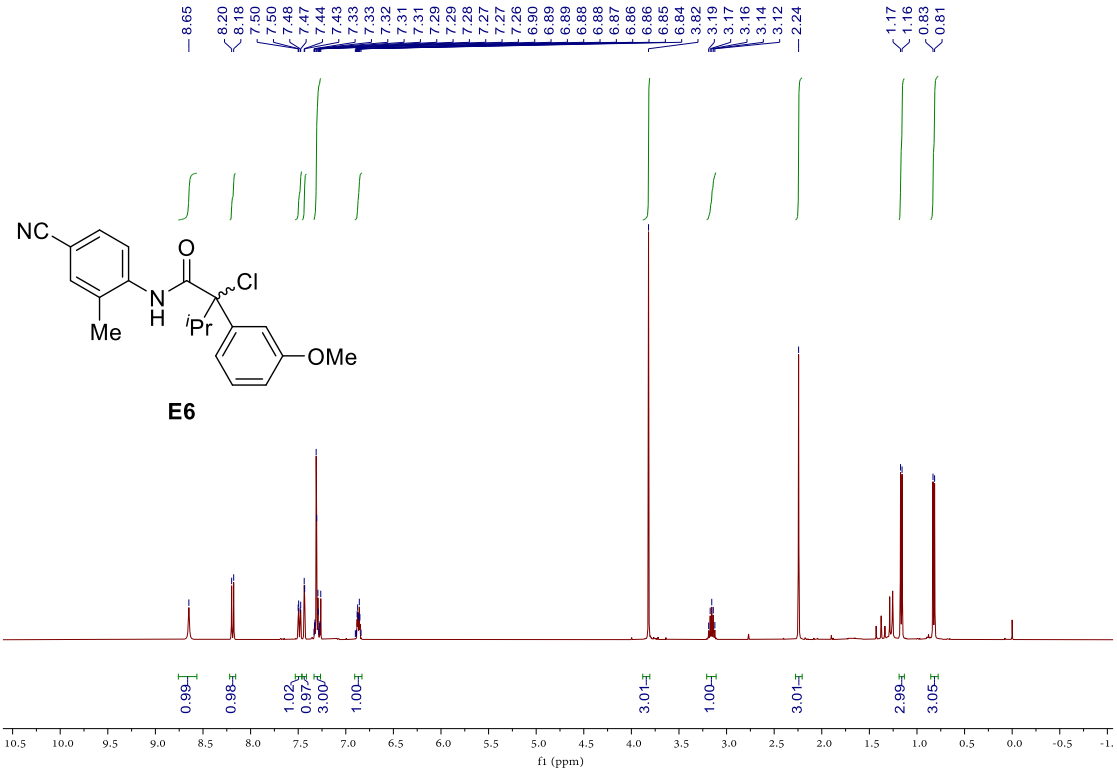
^{1}H NMR (400 MHz, $CDCl_3$)



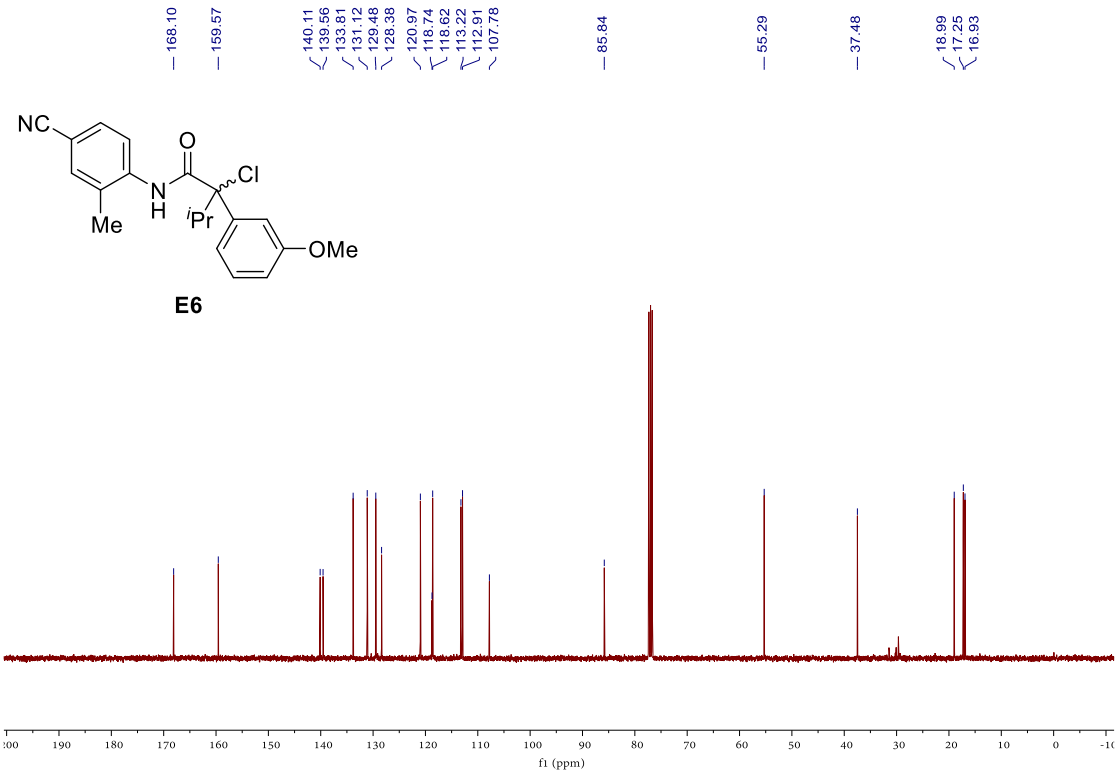
^{13}C NMR (100 MHz, $CDCl_3$)



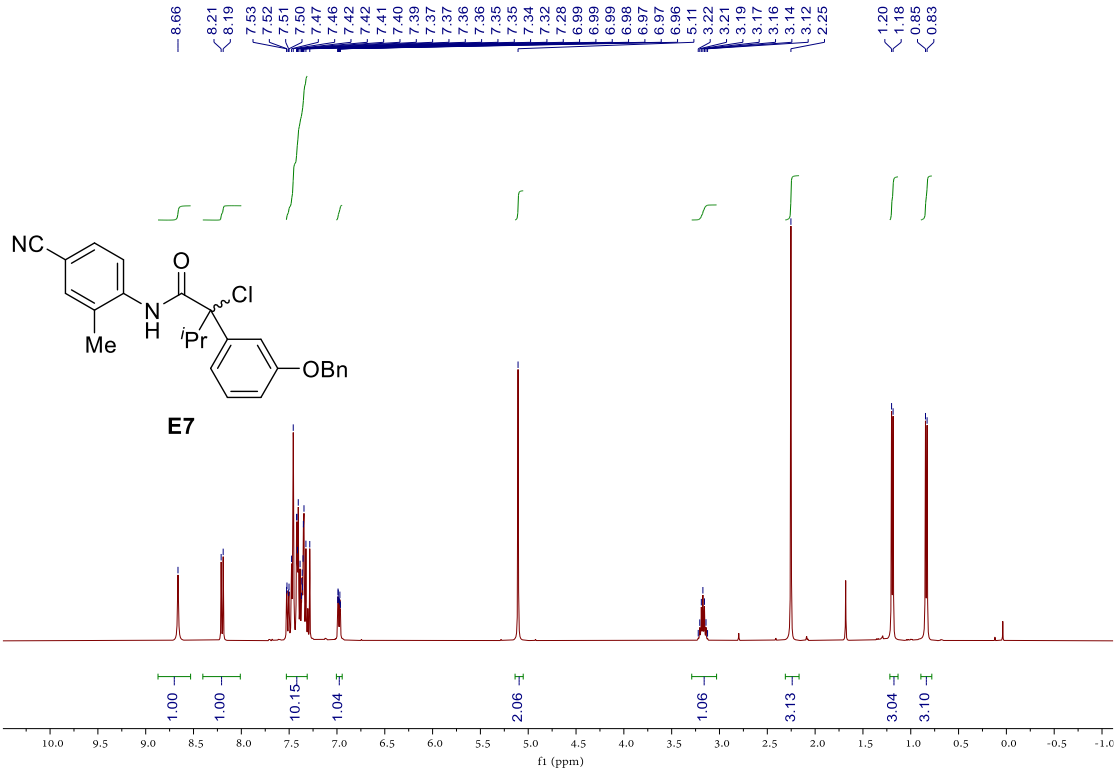
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



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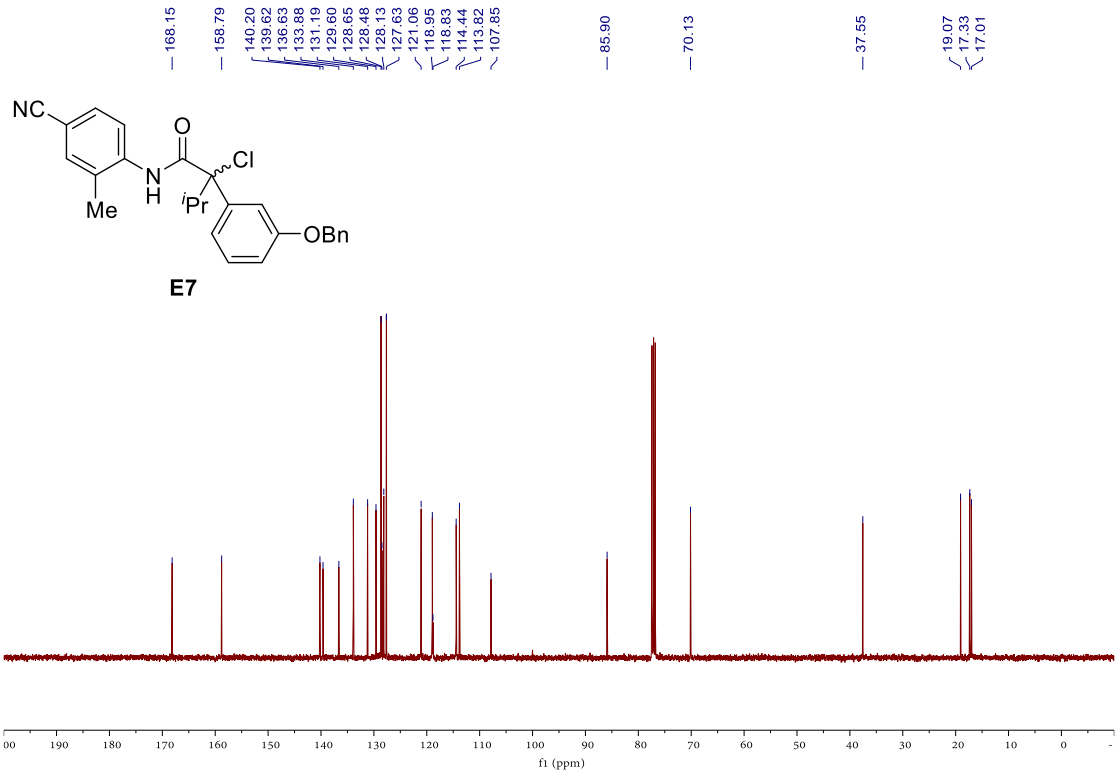

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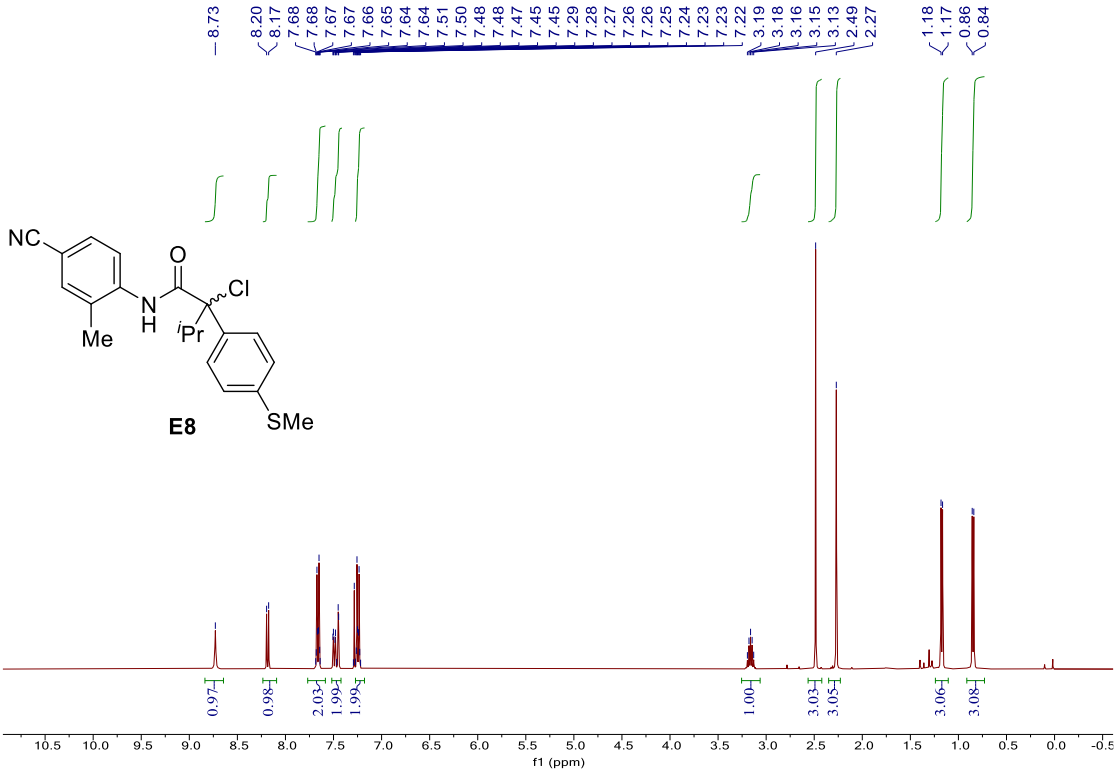

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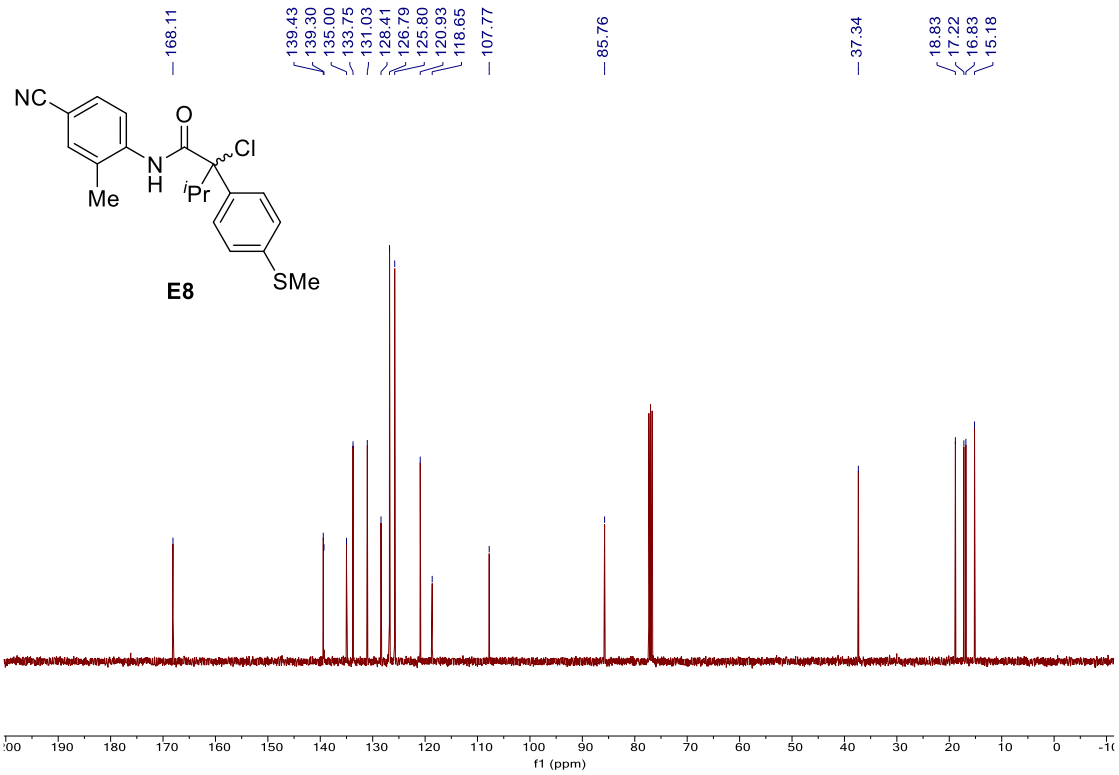

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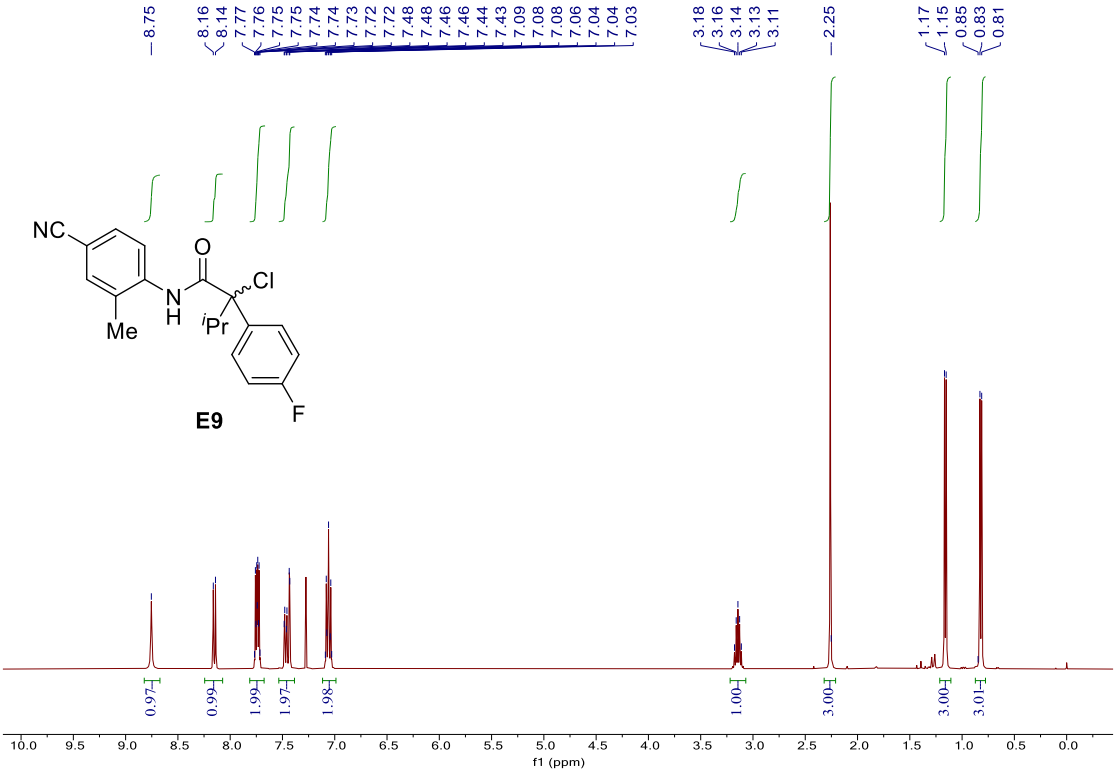
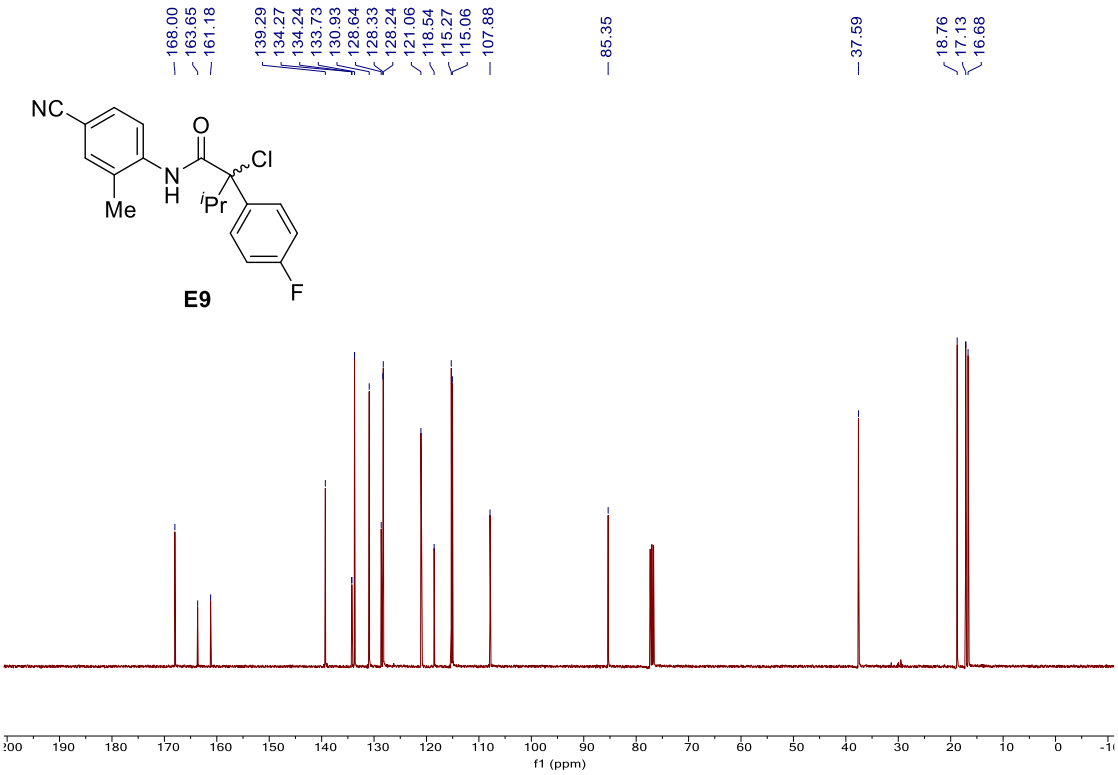
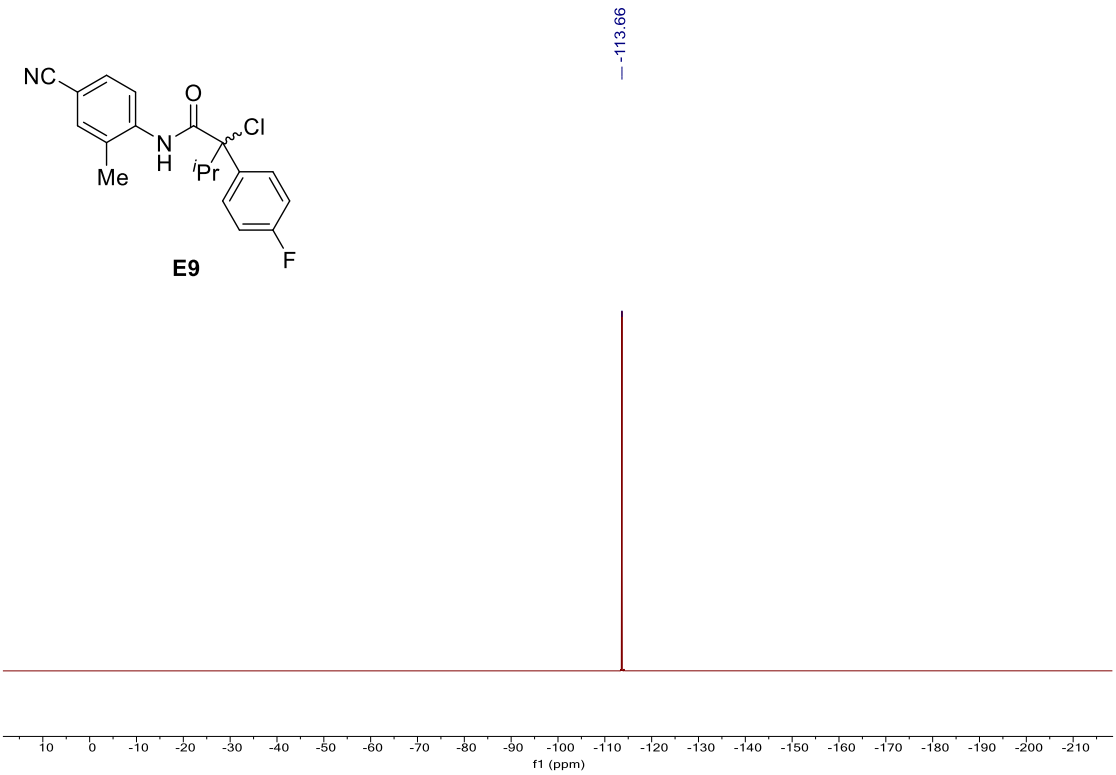


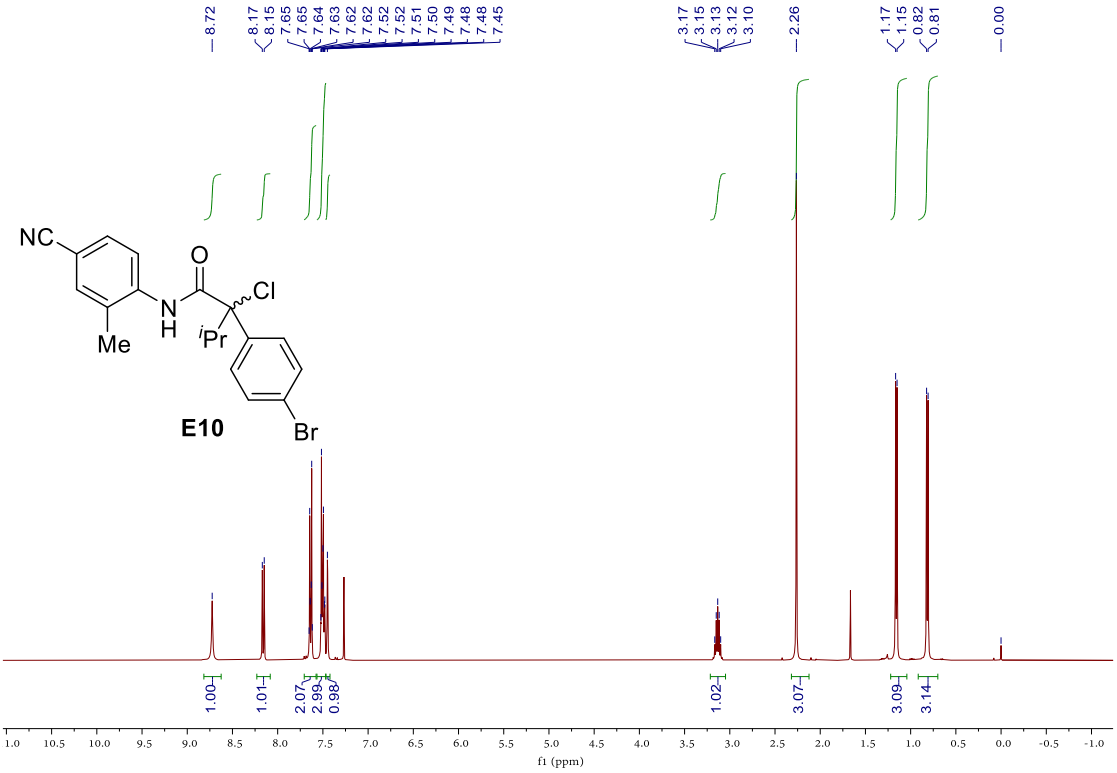
^{13}C NMR (100 MHz, $CDCl_3$)



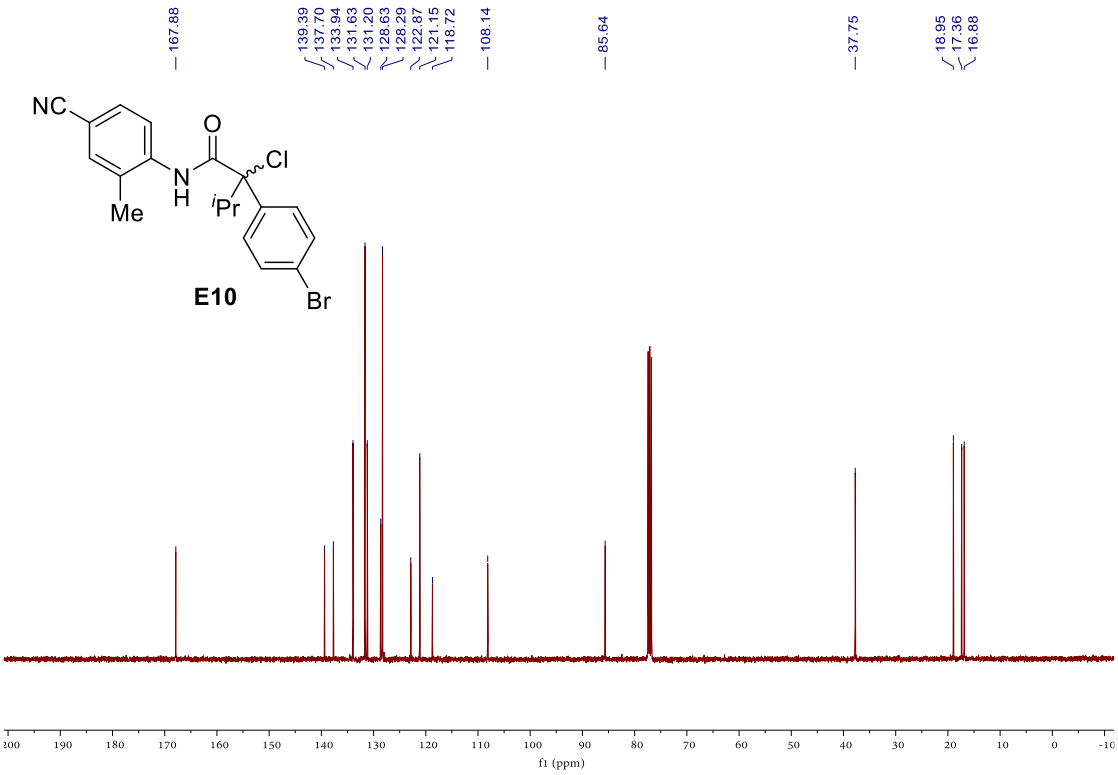
^{19}F NMR (376 MHz, $CDCl_3$)



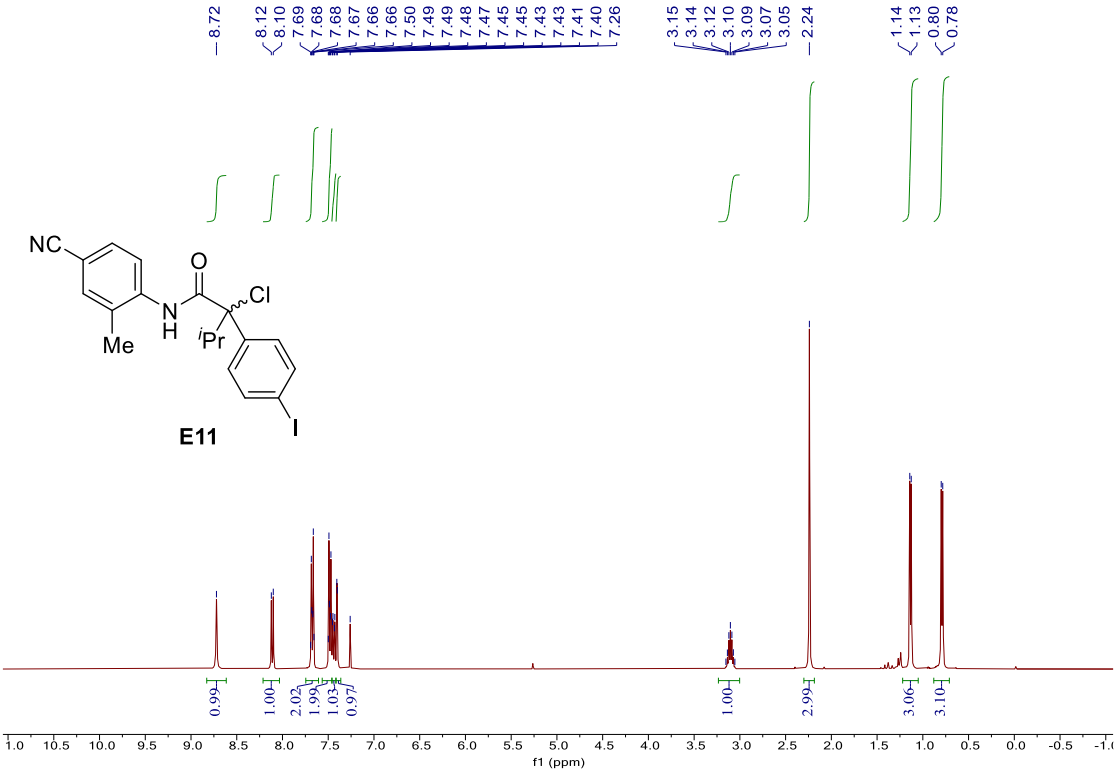
^{1}H NMR (400 MHz, $CDCl_3$)



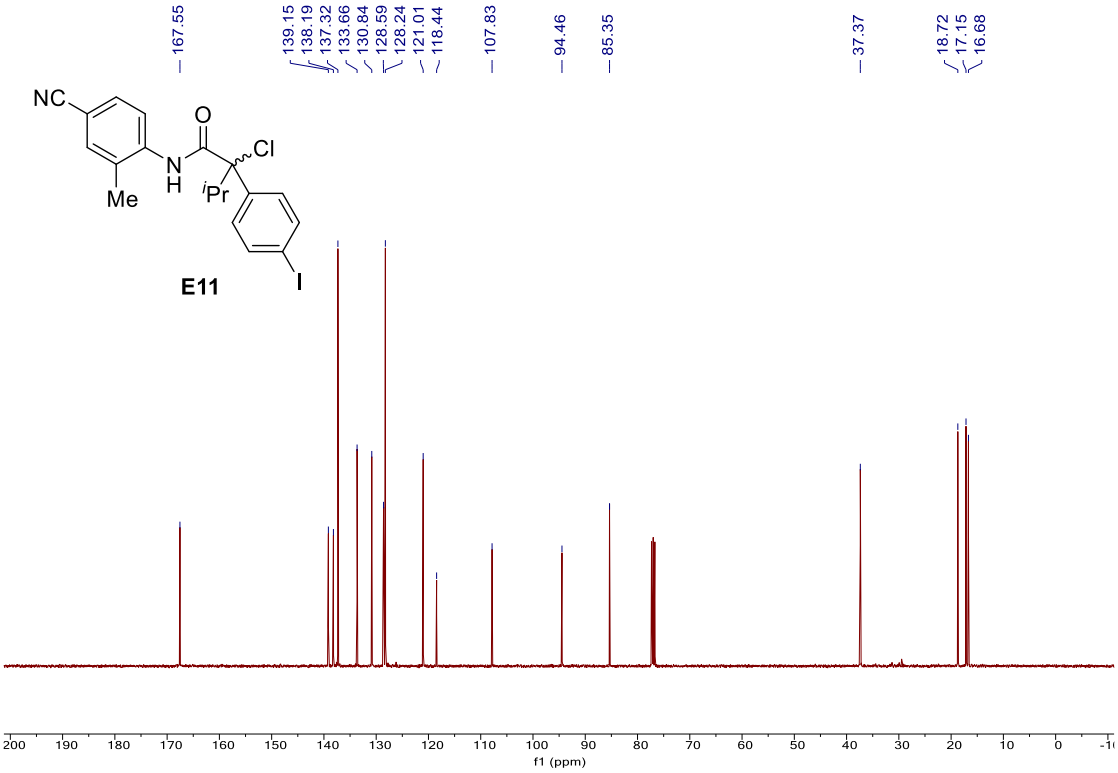
^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



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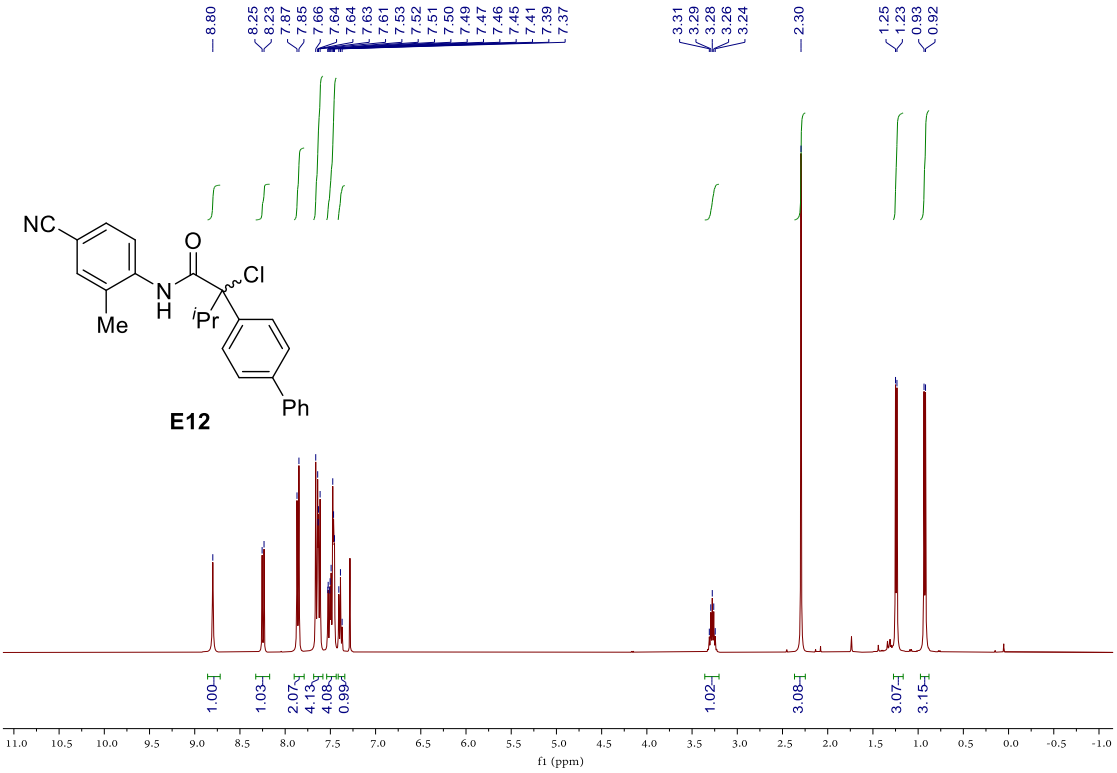
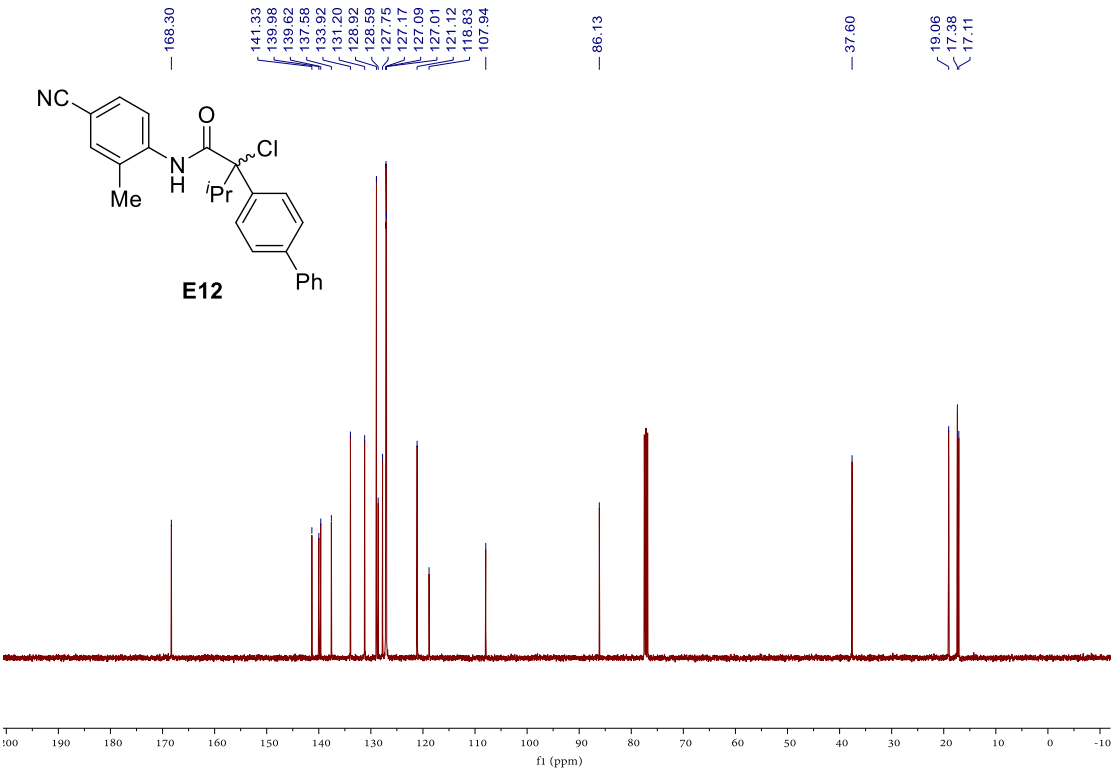


^{13}C NMR (100 MHz, $CDCl_3$)



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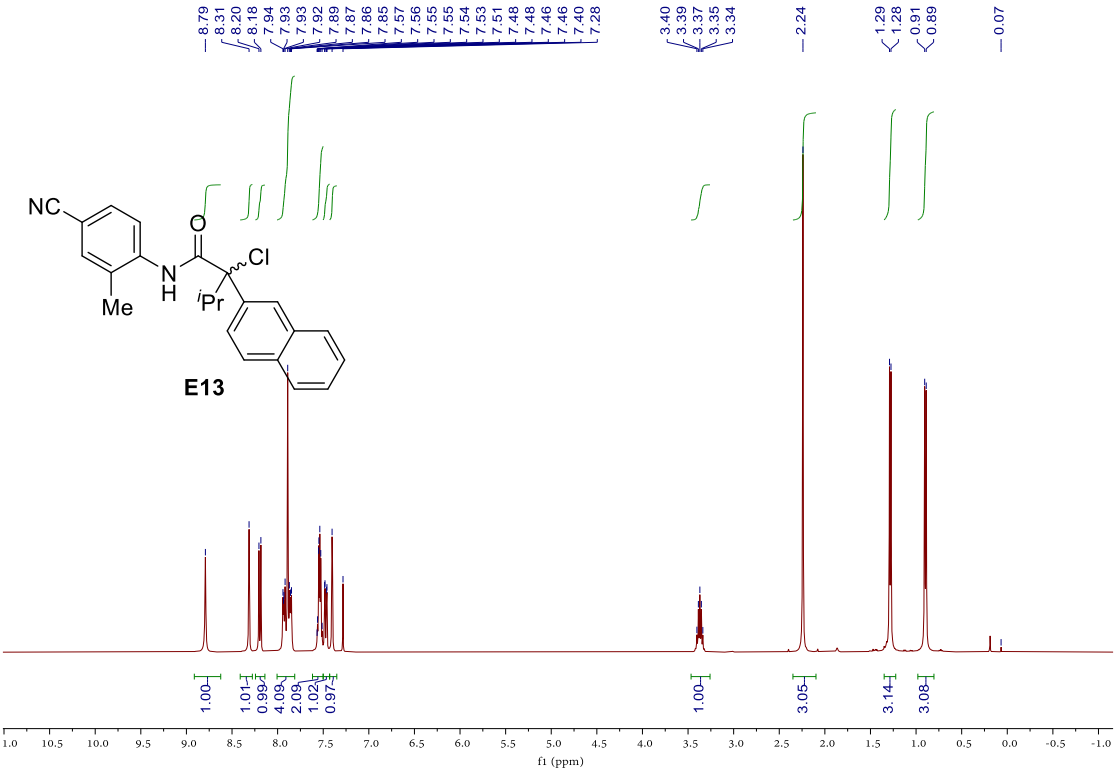
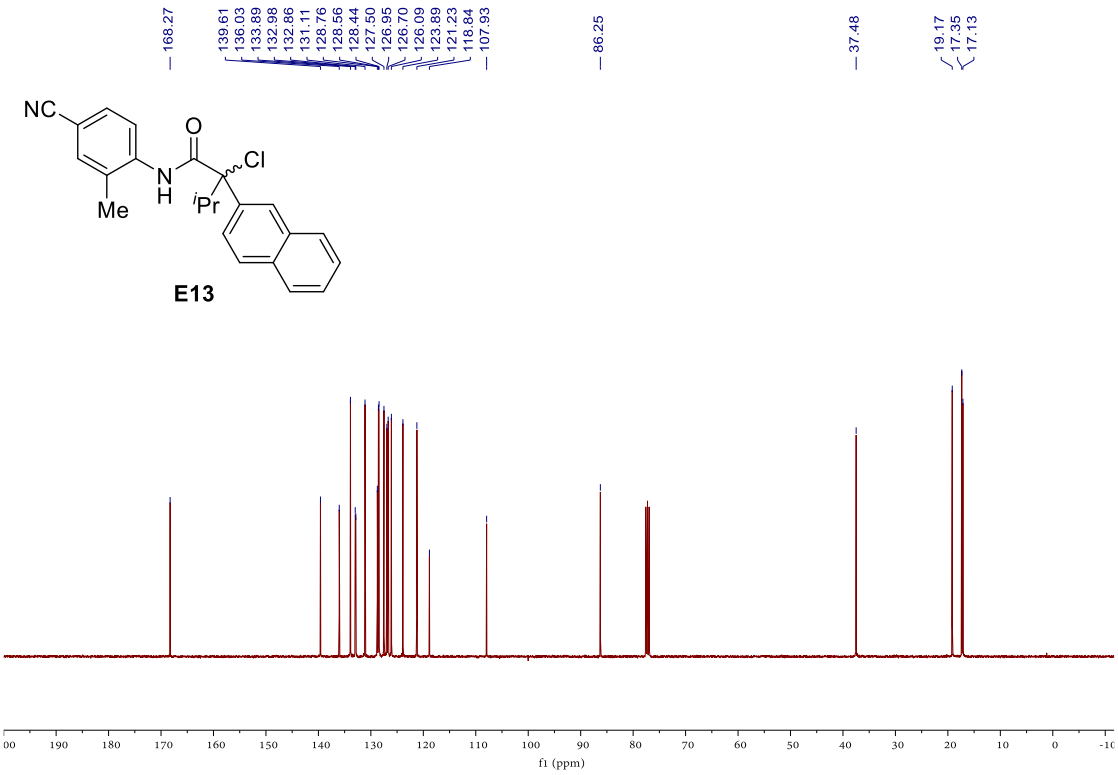
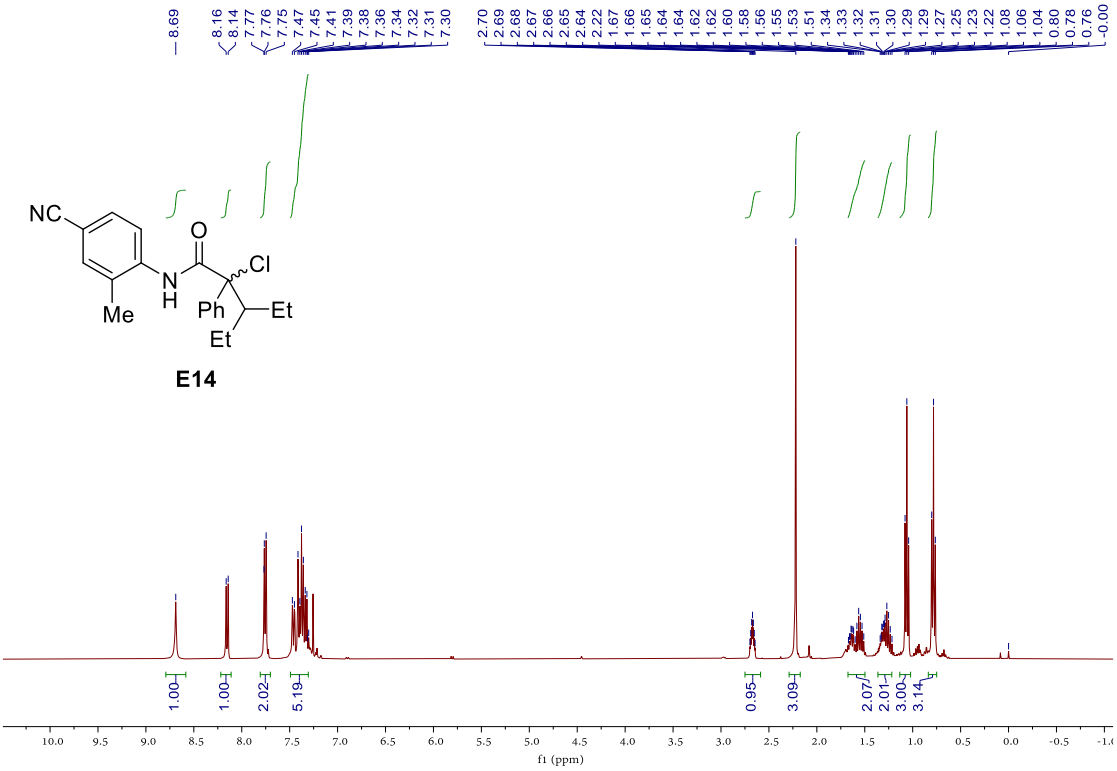


^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



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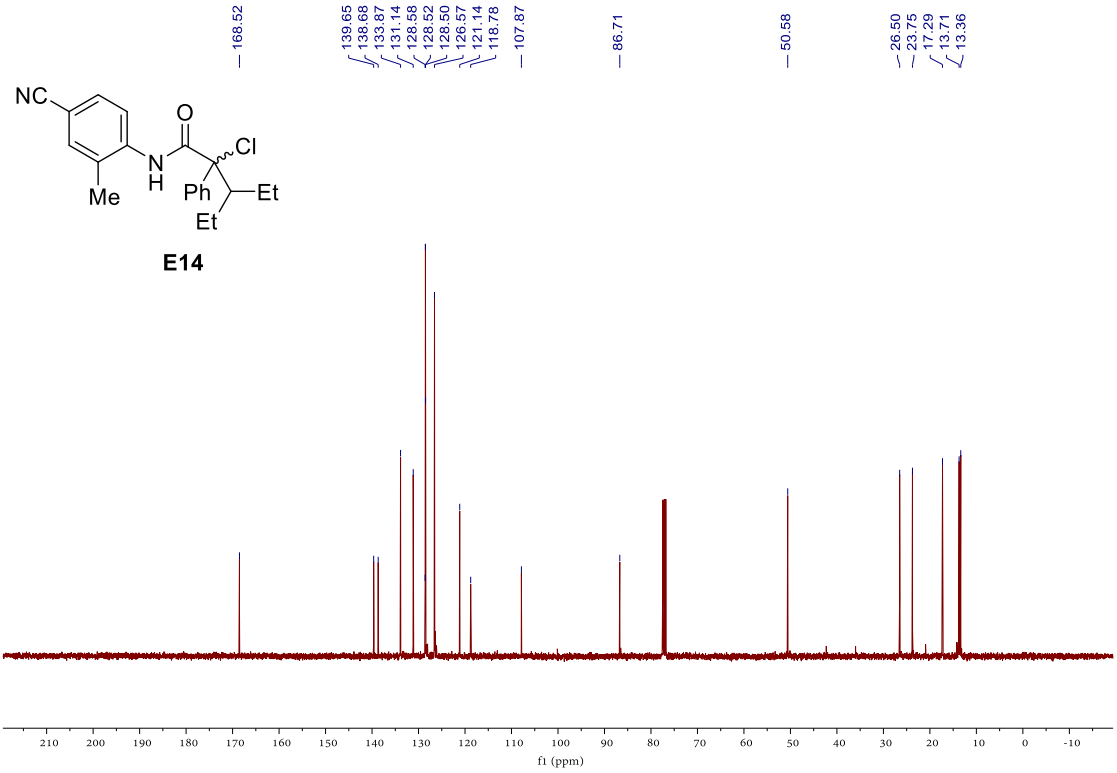
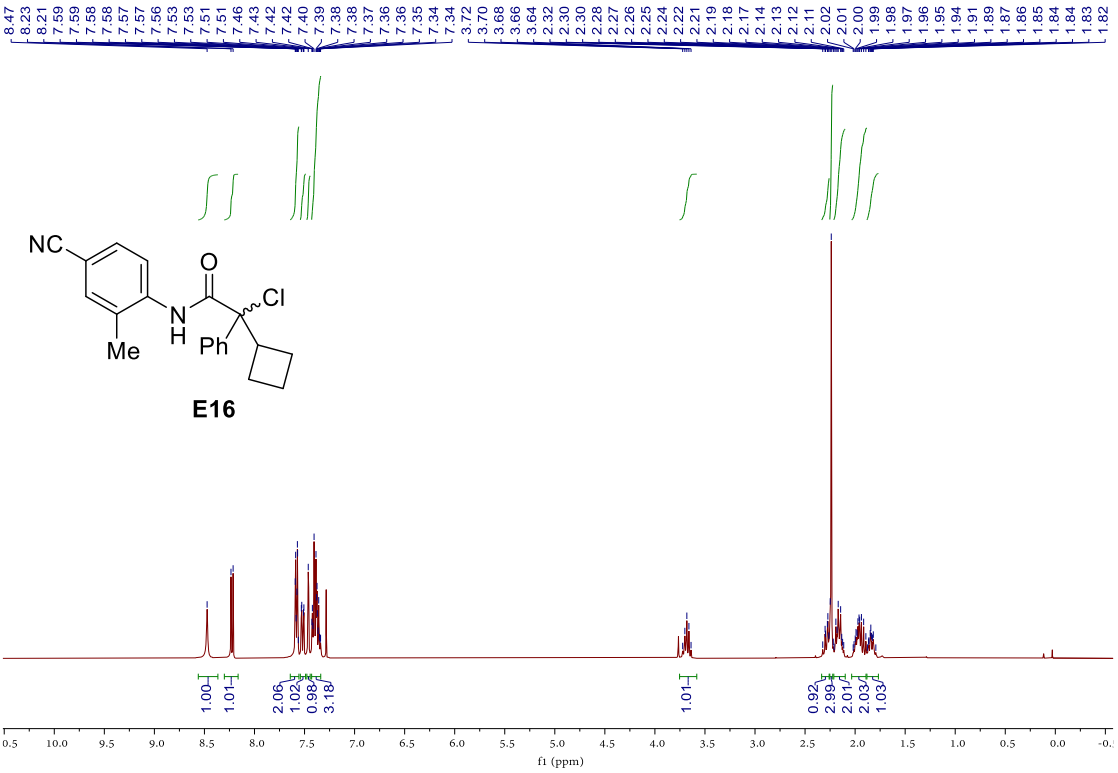


^{1}H NMR (400 MHz, $CDCl_3$)



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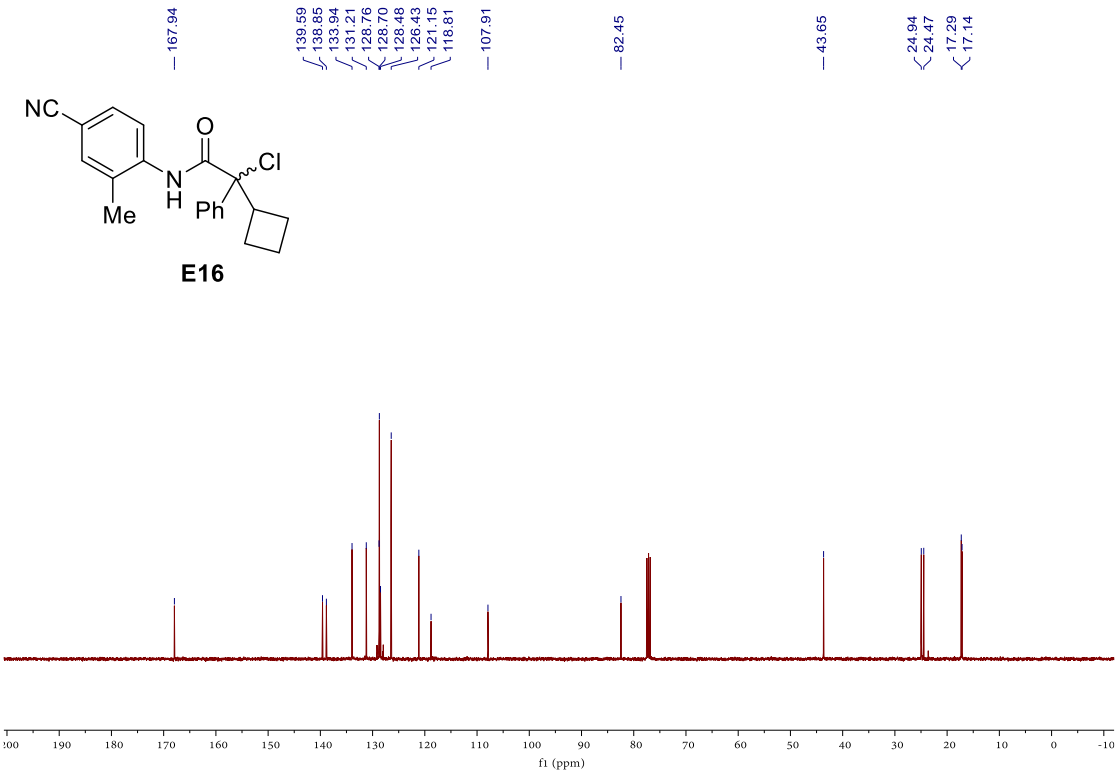
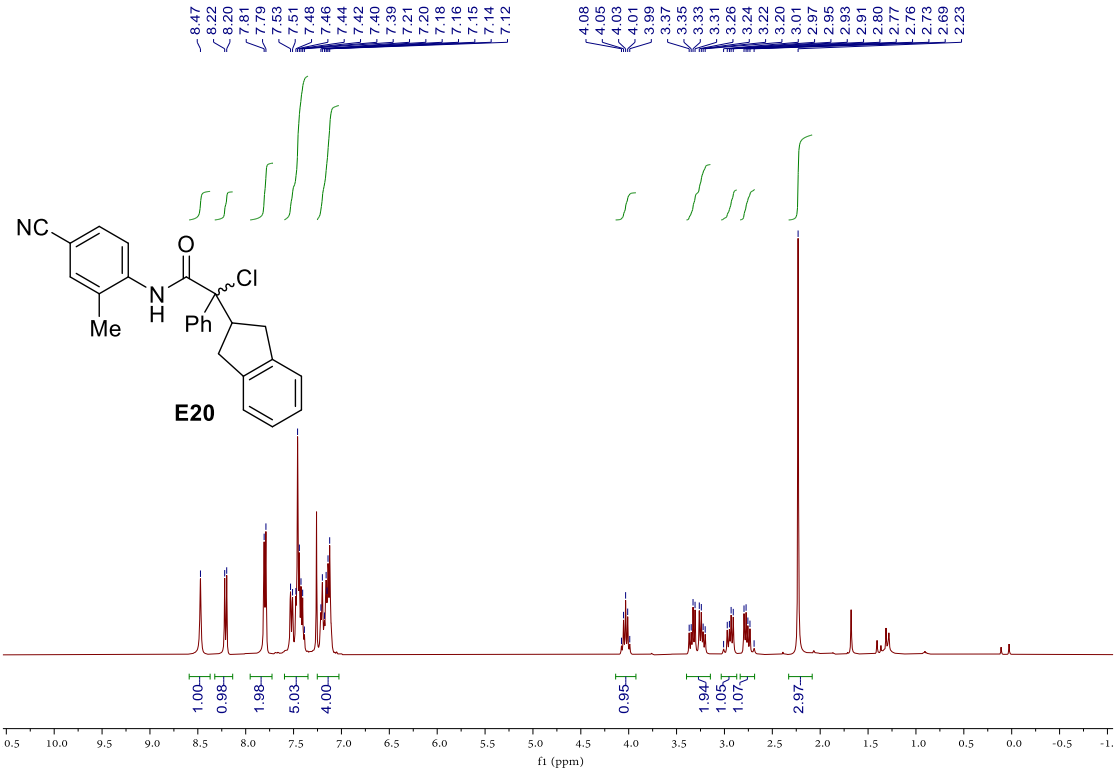


^{1}H NMR (400 MHz, $CDCl_3$)



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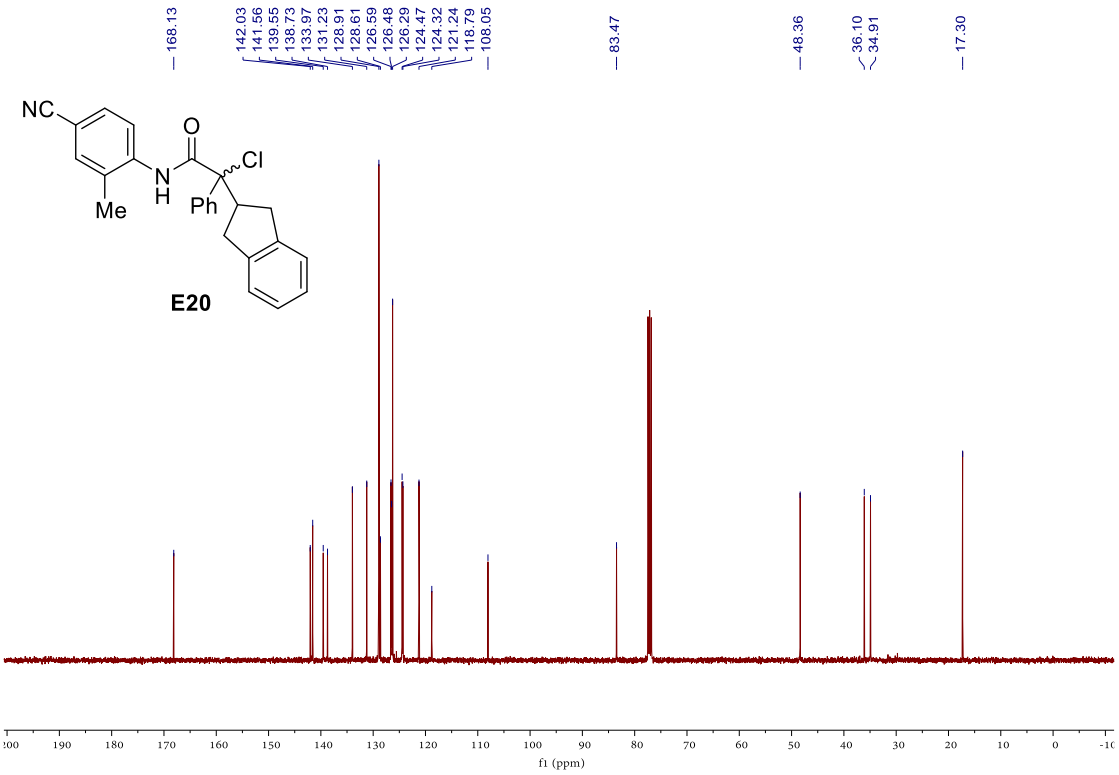
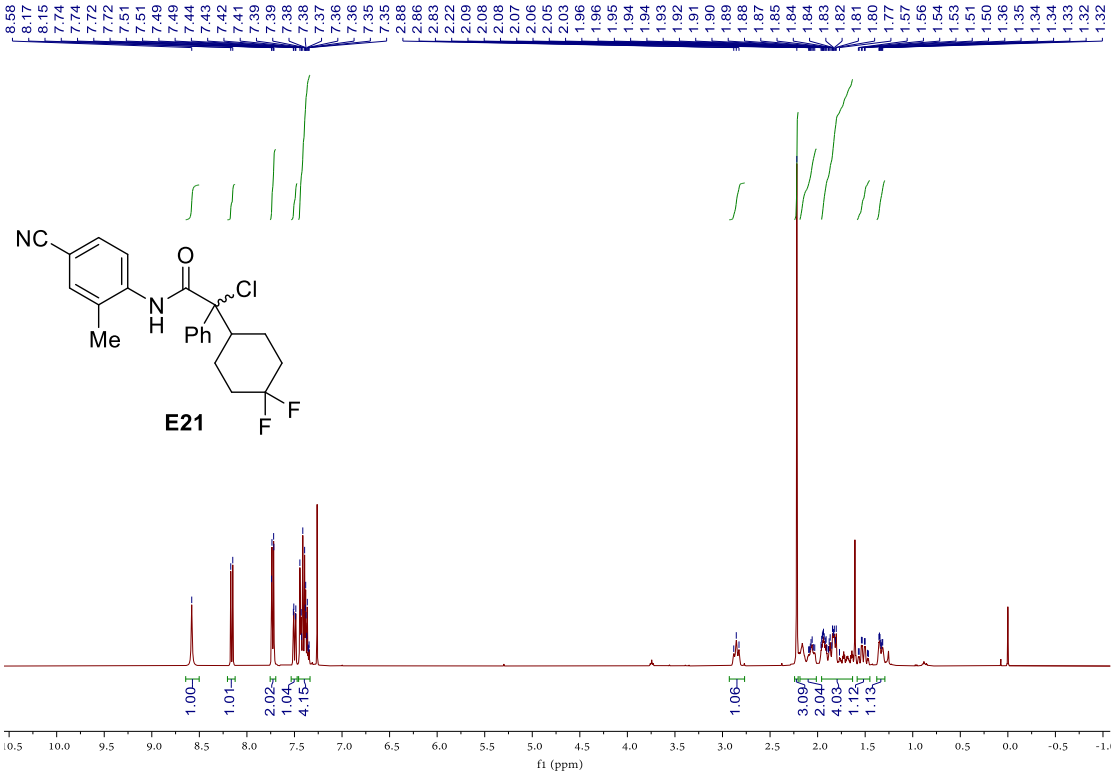
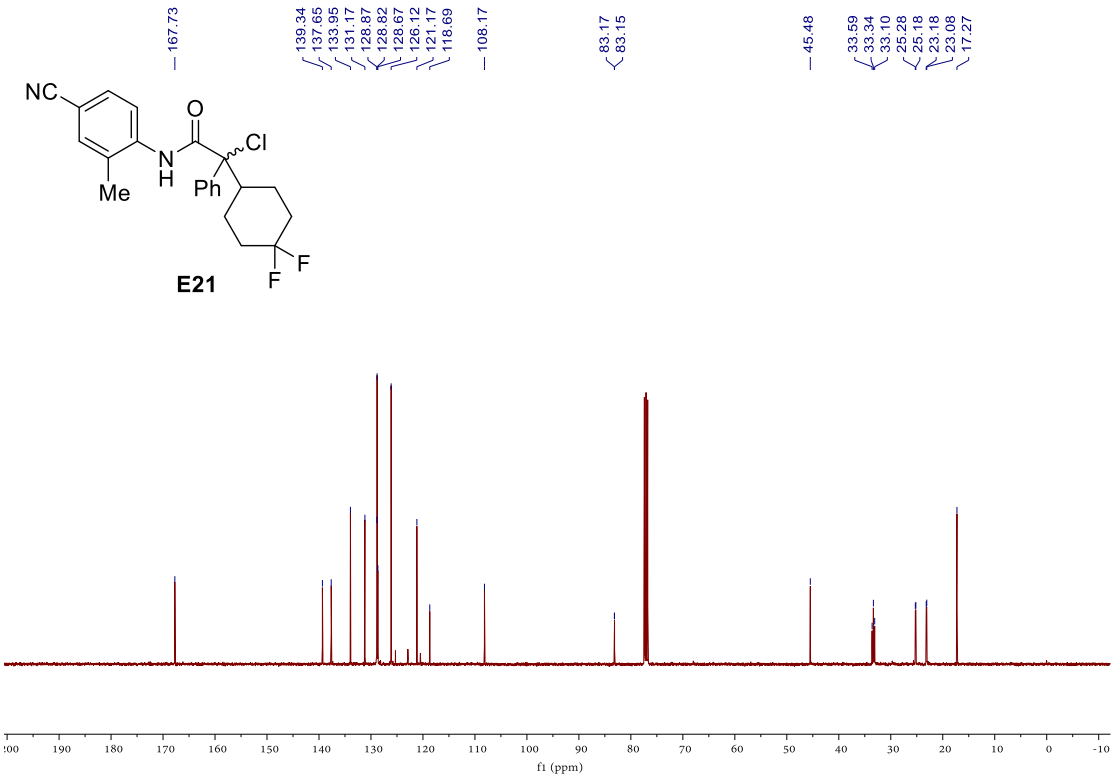


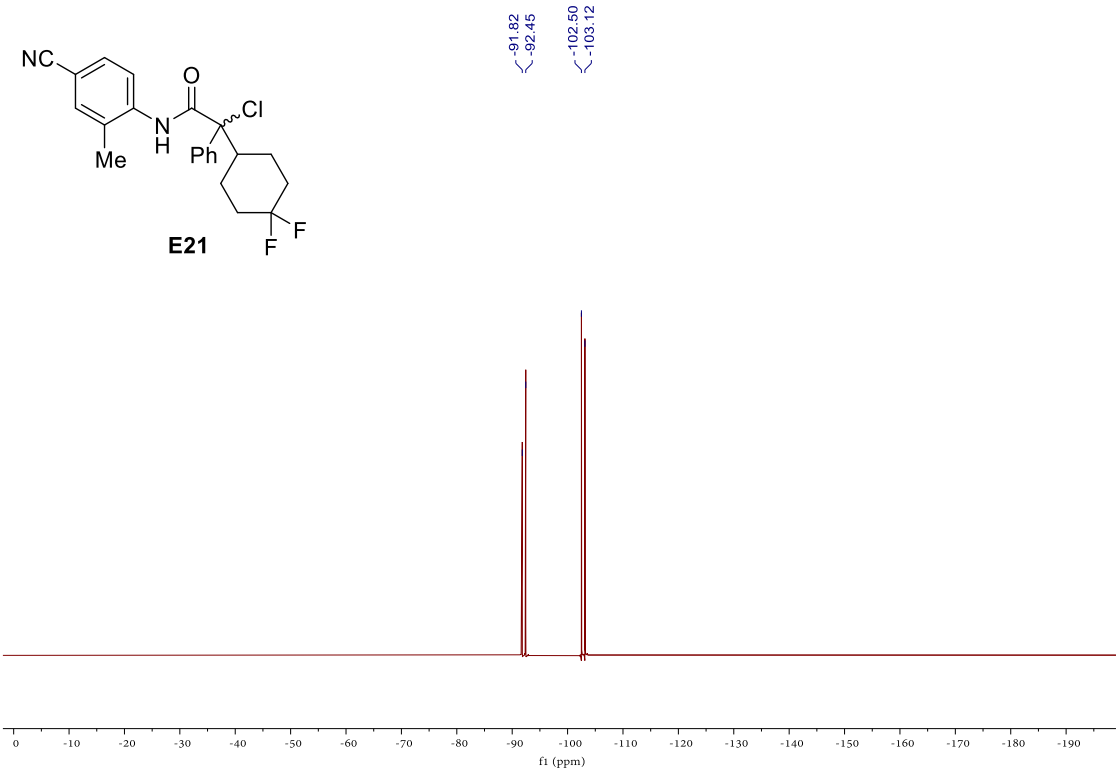
^{1}H NMR (400 MHz, $CDCl_3$)



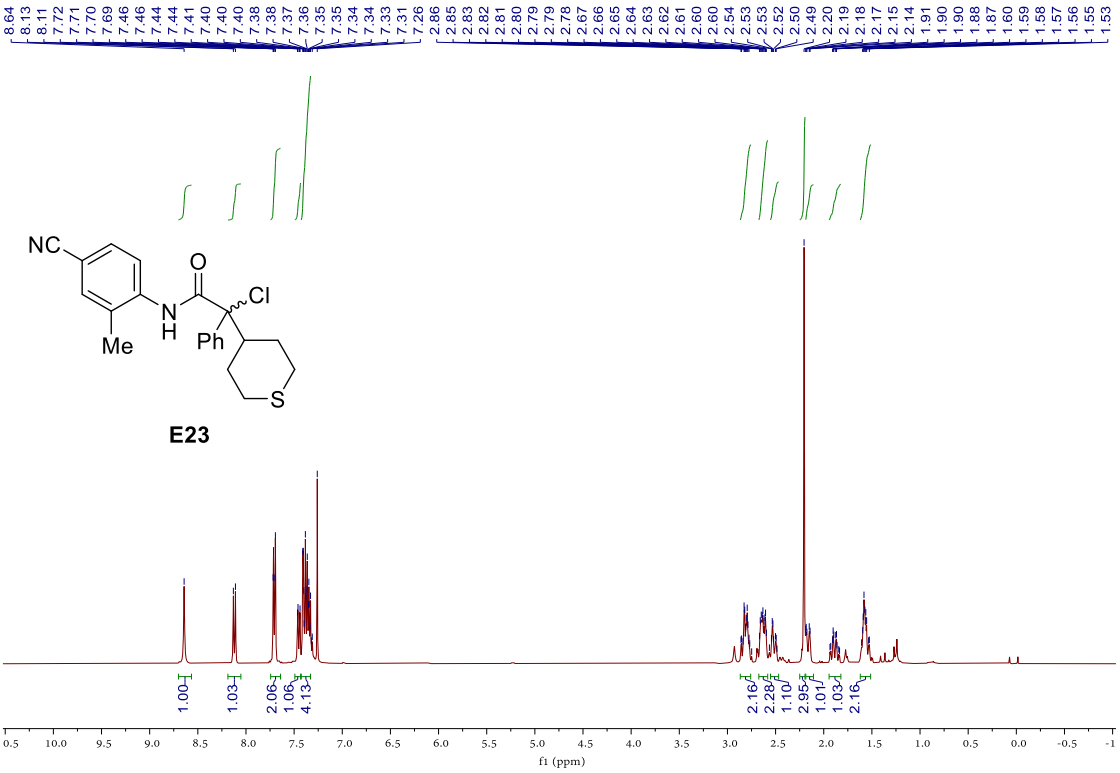
^{13}C NMR (100 MHz, $CDCl_3$)



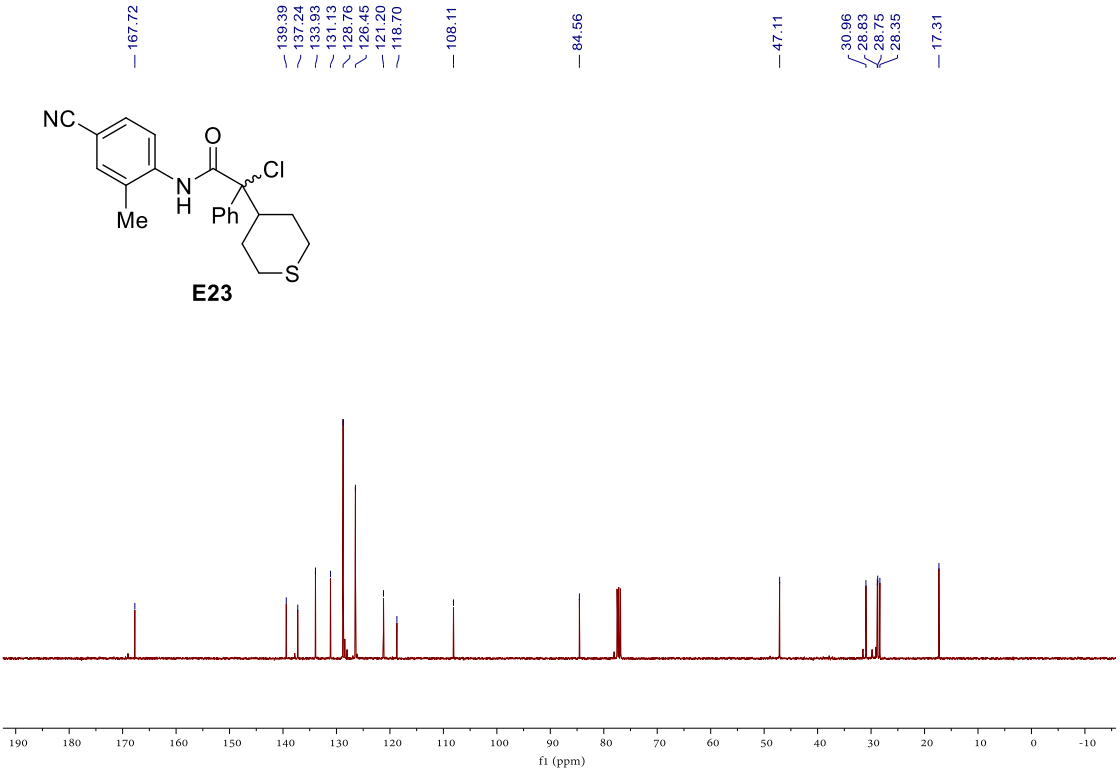
^{19}F NMR (376 MHz, $CDCl_3$)



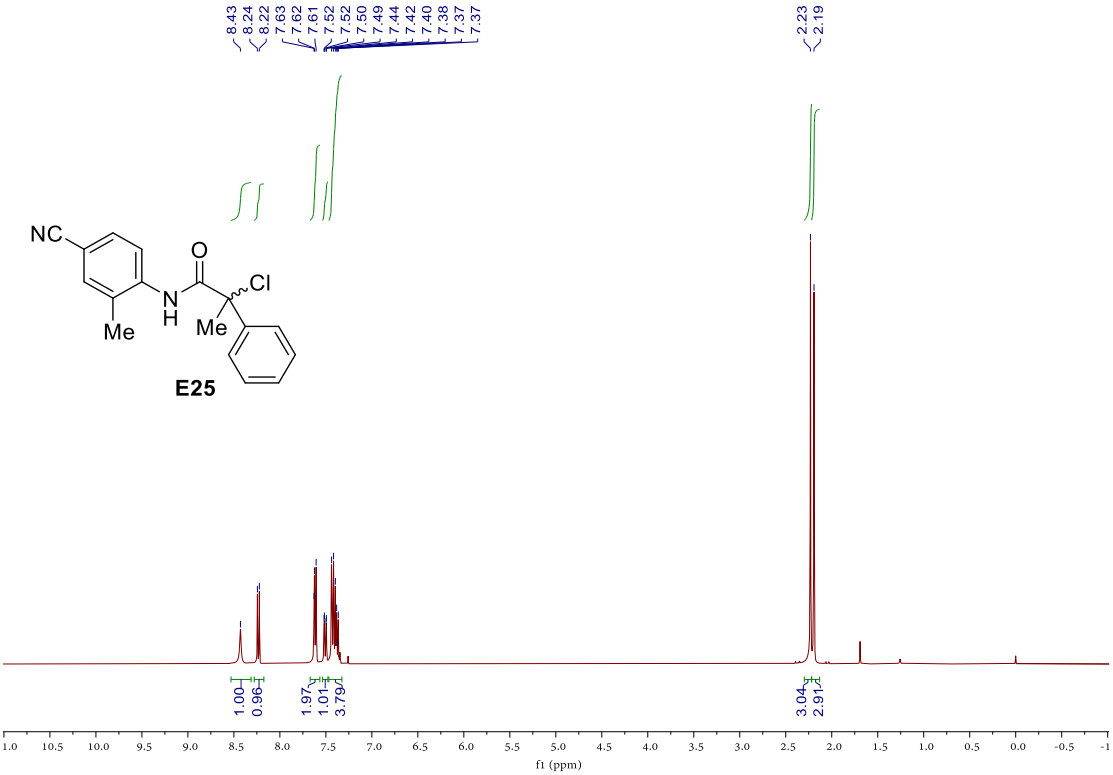
^{1}H NMR (400 MHz, $CDCl_3$)



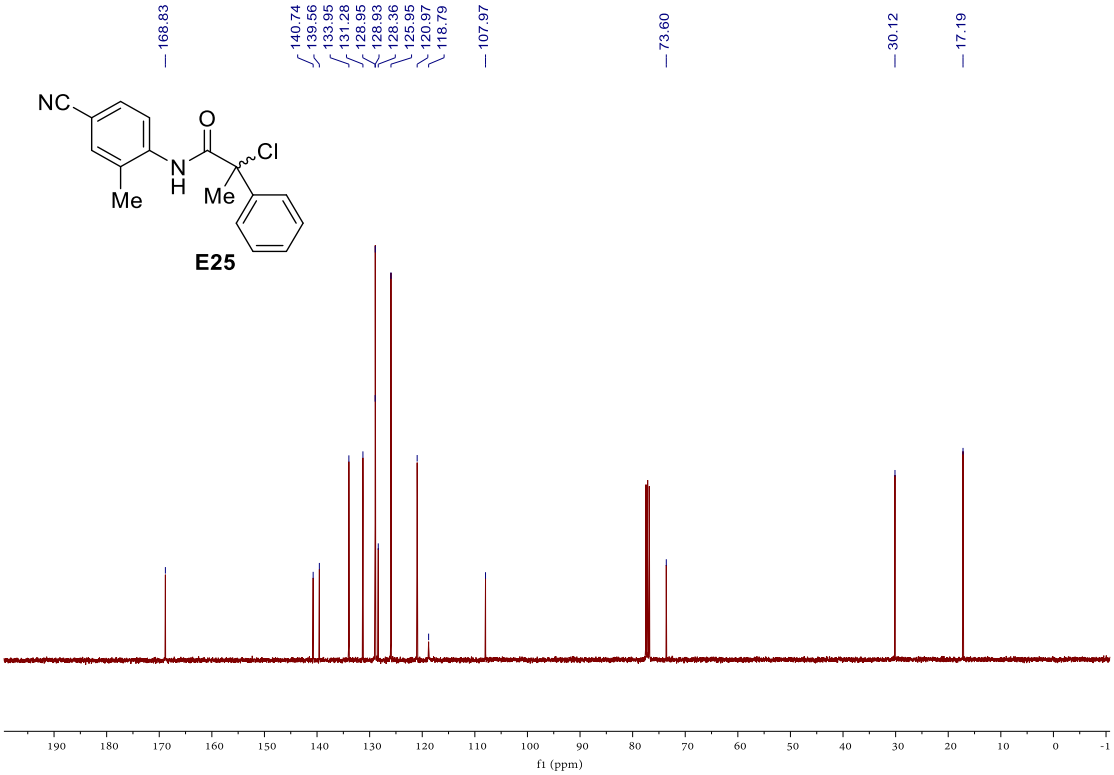
^{13}C NMR (100 MHz, $CDCl_3$)



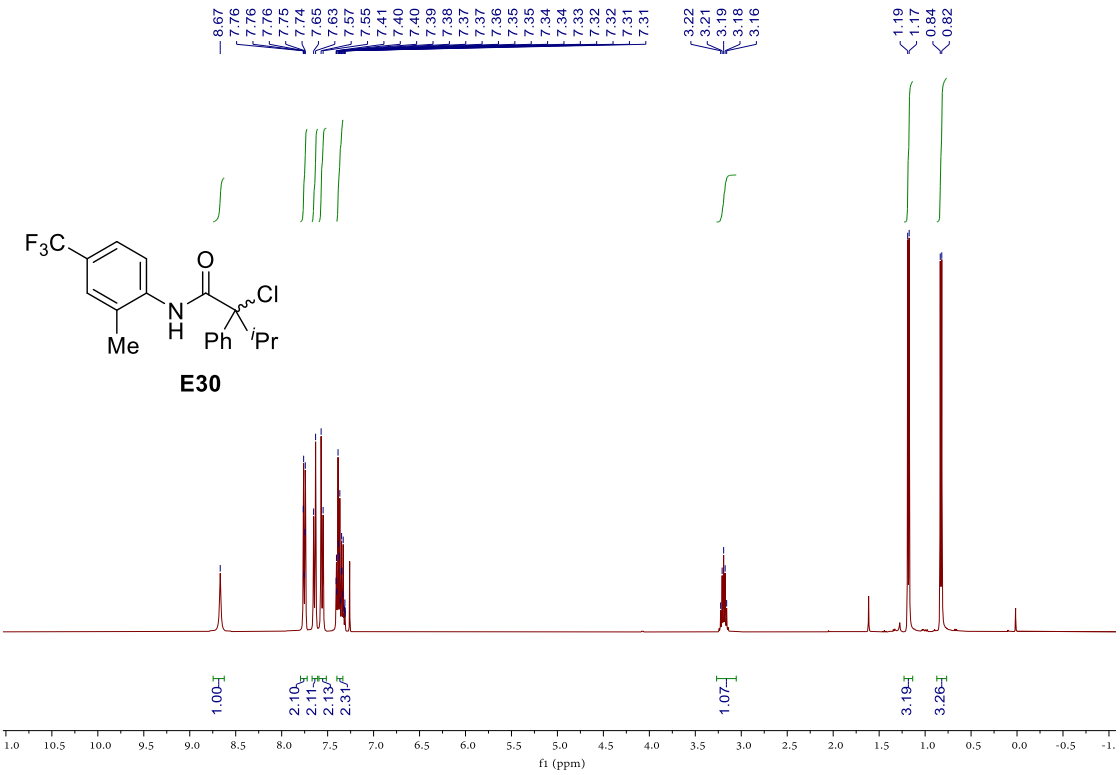
^{1}H NMR (400 MHz, $CDCl_3$)



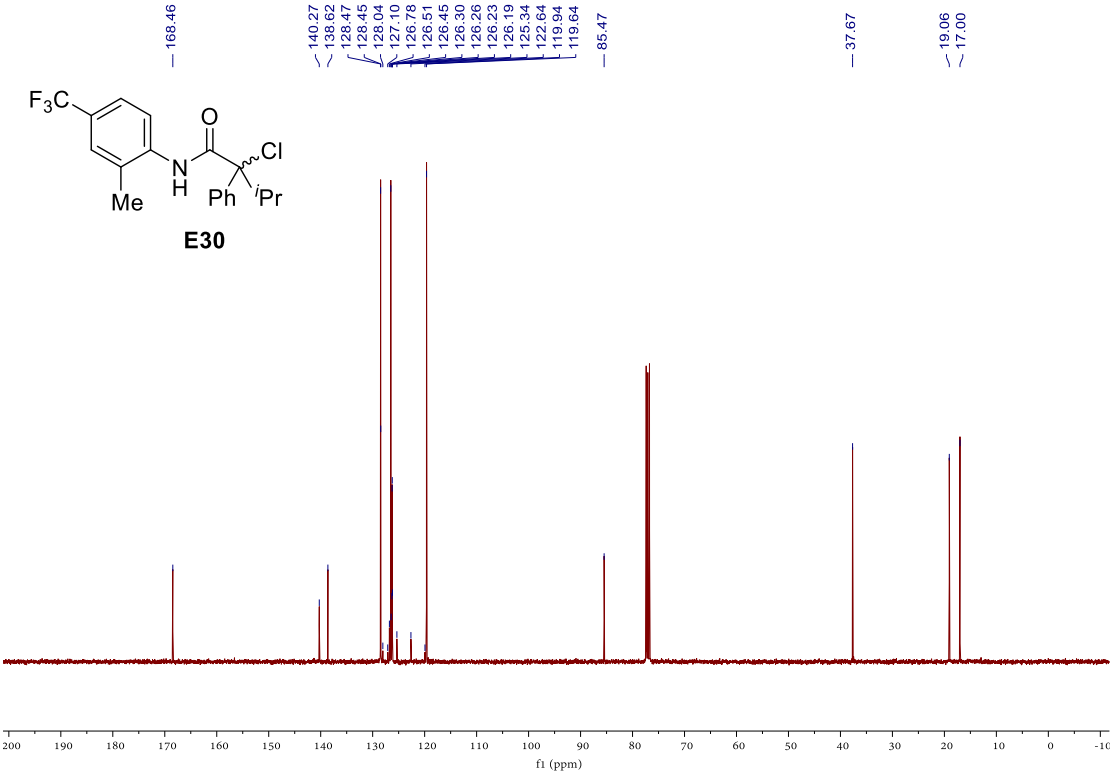
^{13}C NMR (100 MHz, $CDCl_3$)



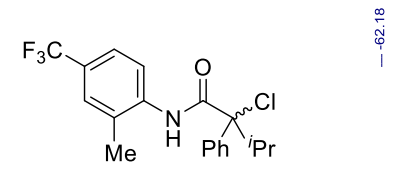
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)



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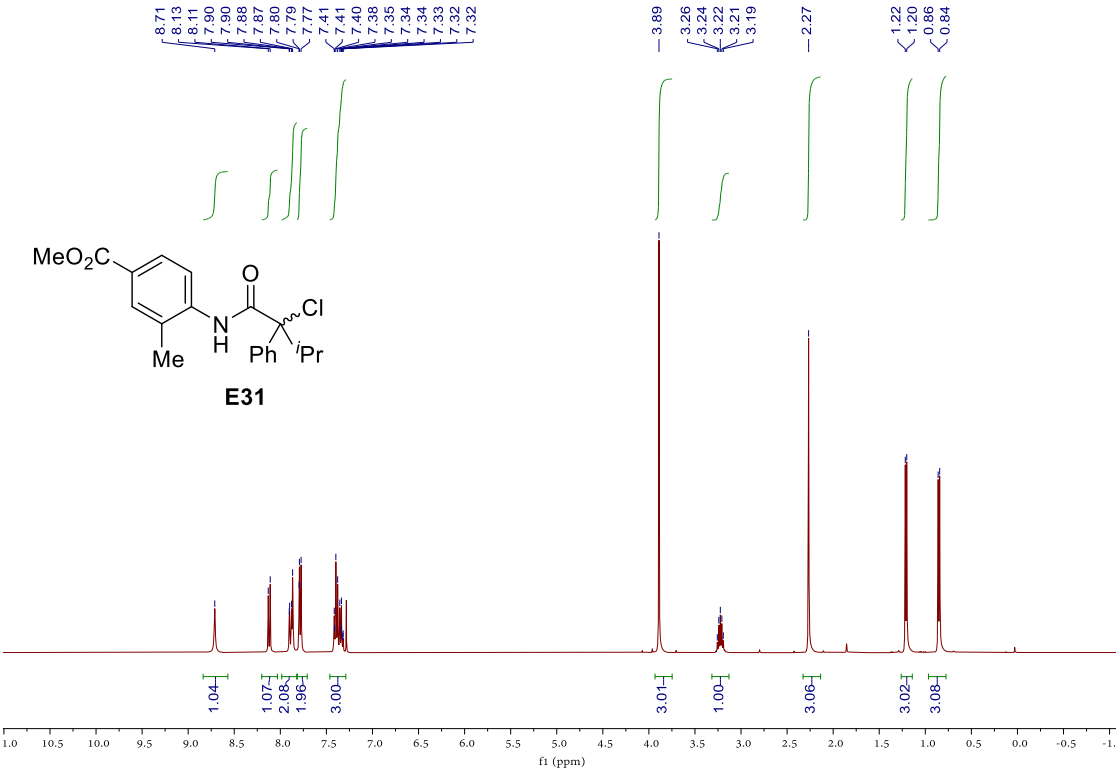
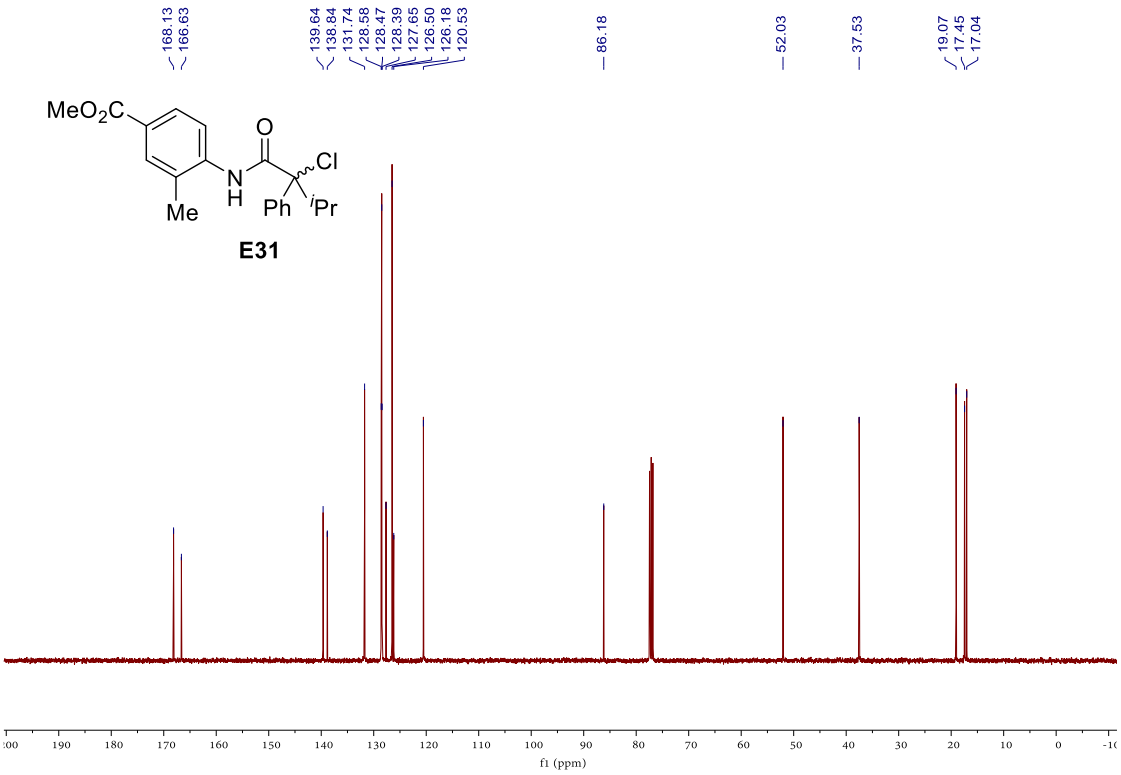
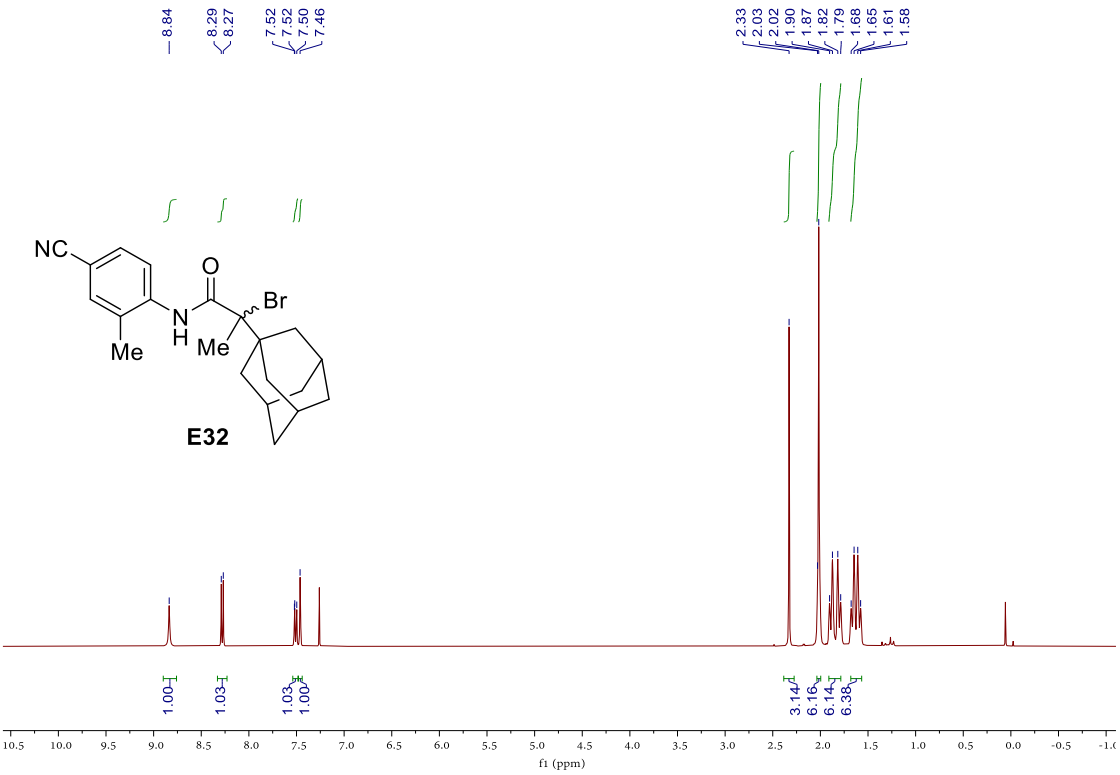
^{1}H NMR (400 MHz, $CDCl_3$)



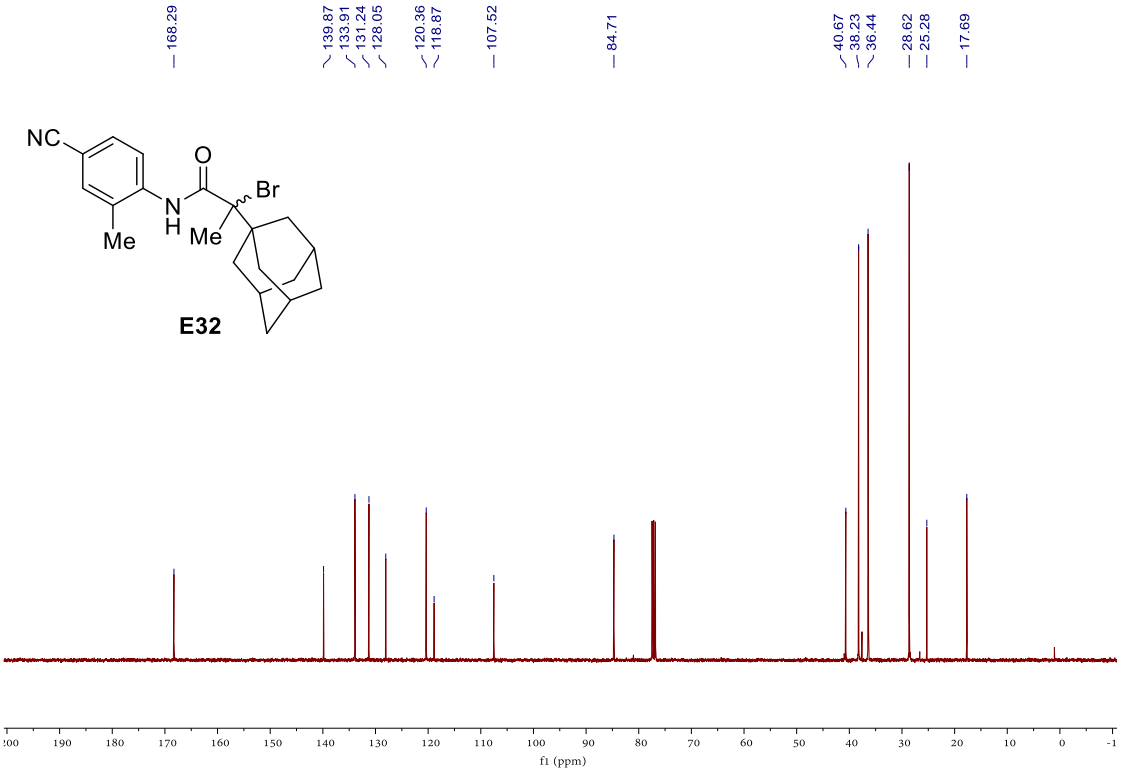
^{13}C NMR (100 MHz, $CDCl_3$)



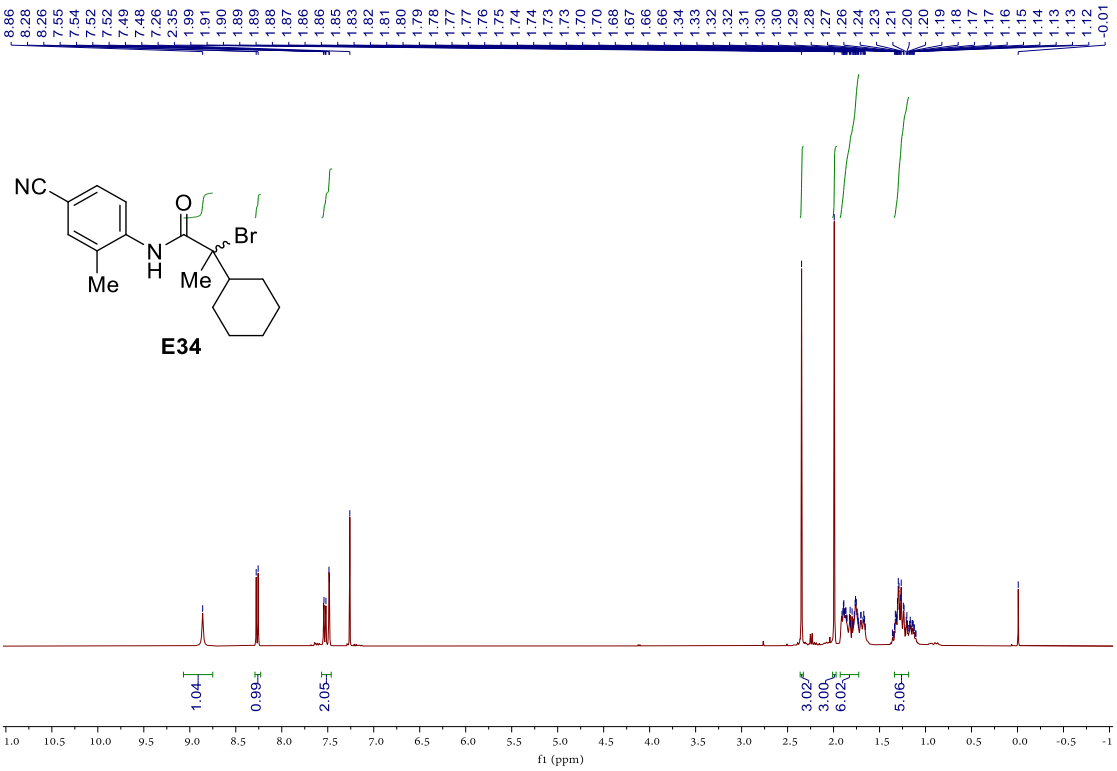
^{1}H NMR (400 MHz, $CDCl_3$)



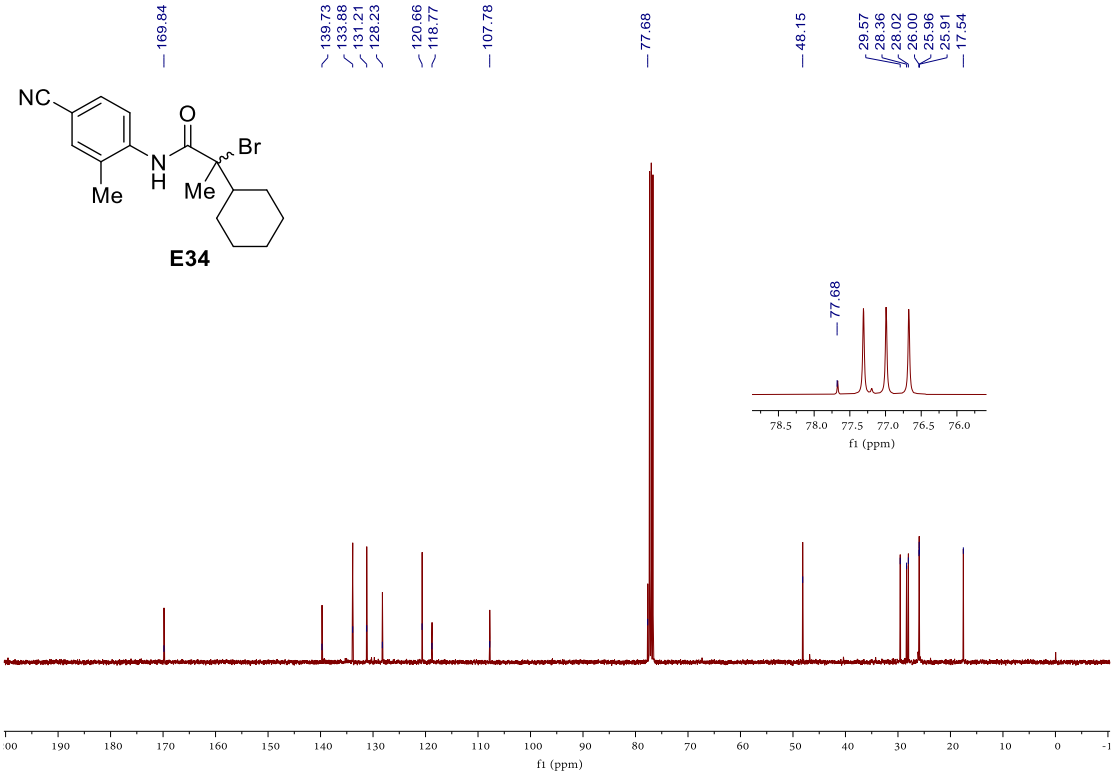
^{13}C NMR (100 MHz, $CDCl_3$)



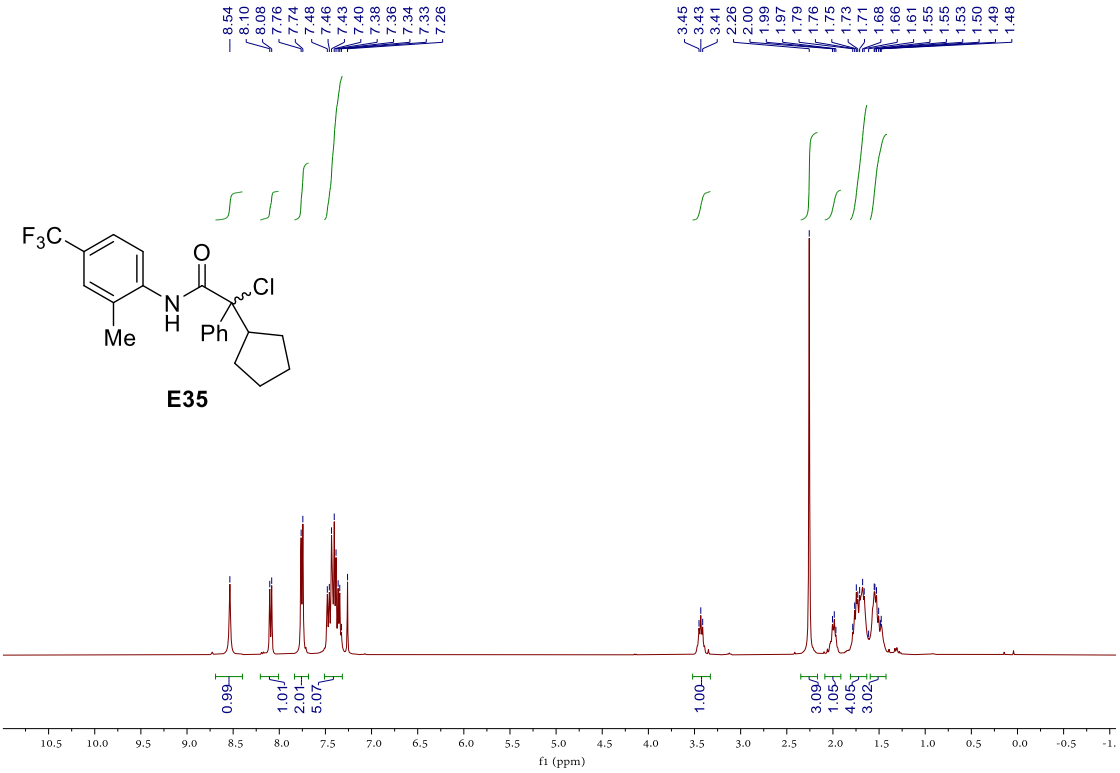
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



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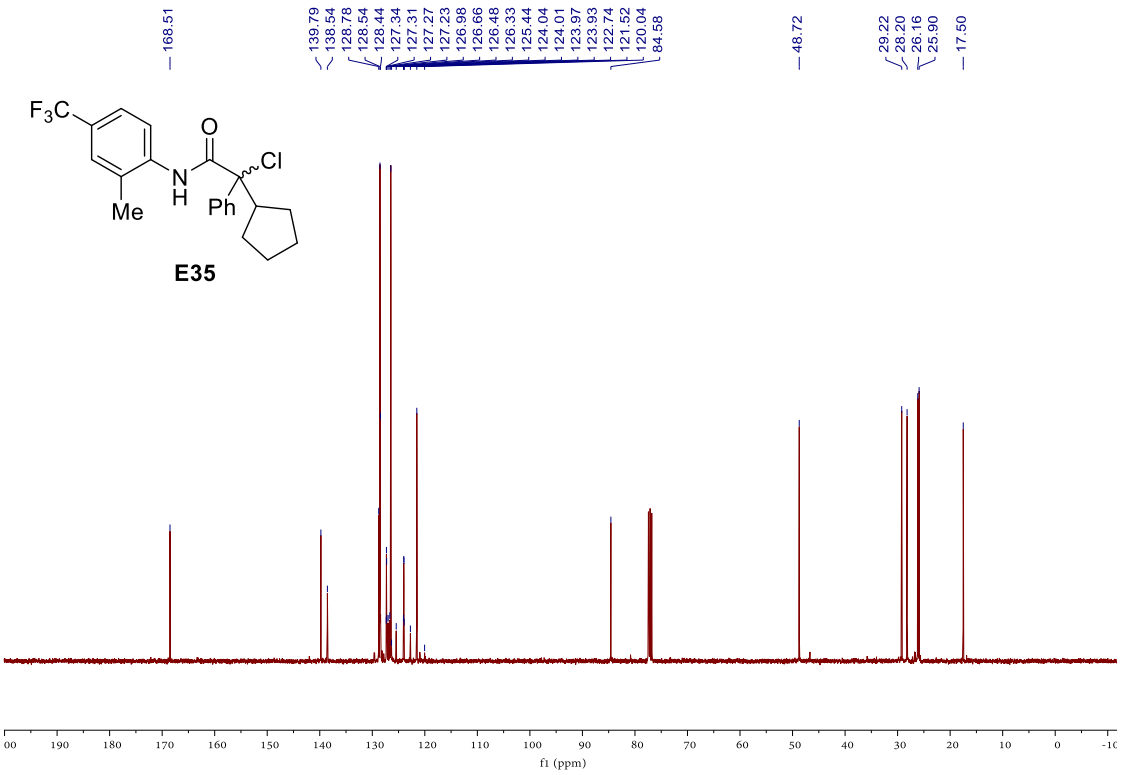

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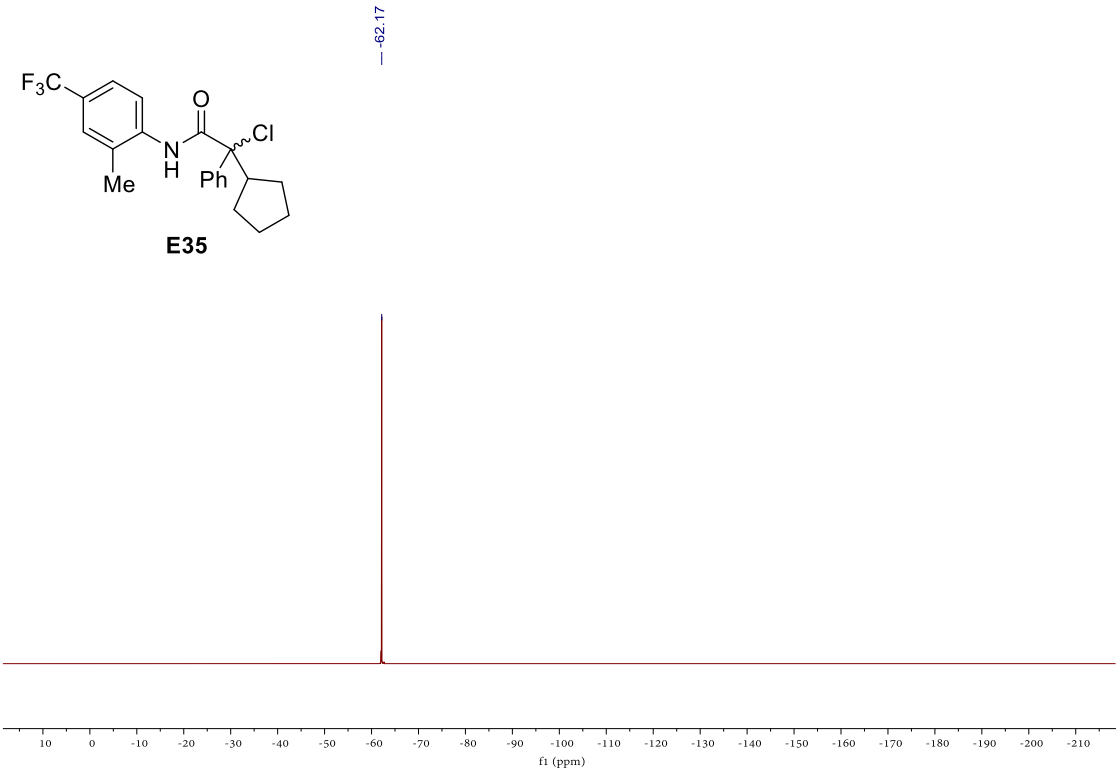

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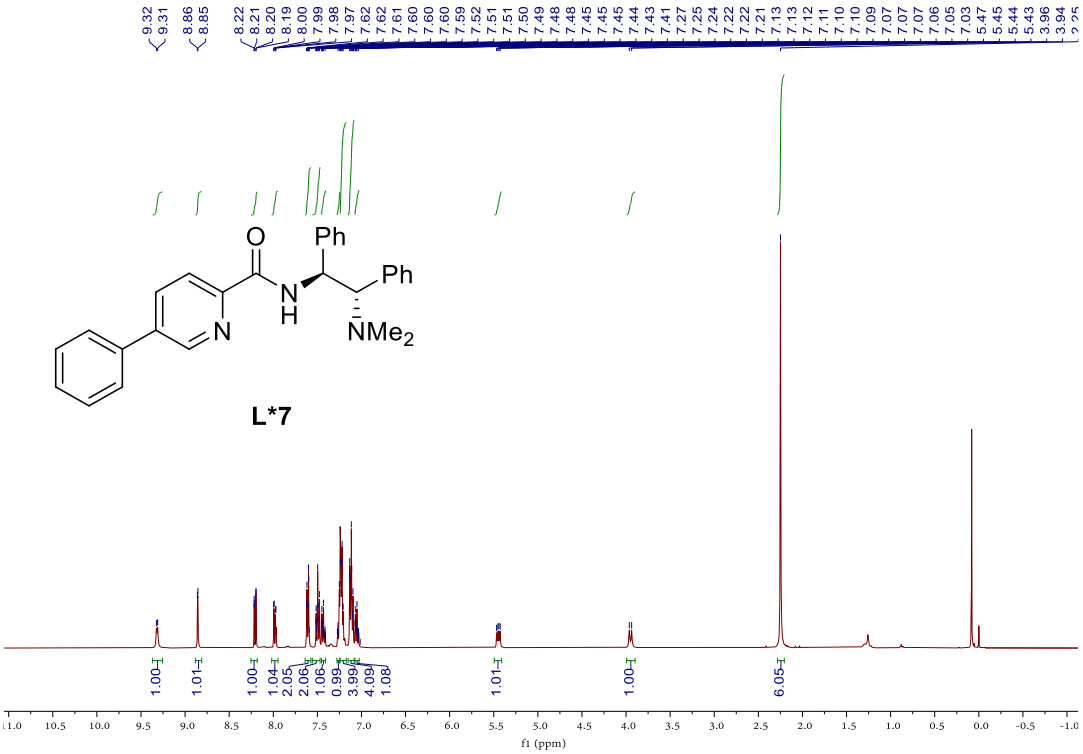
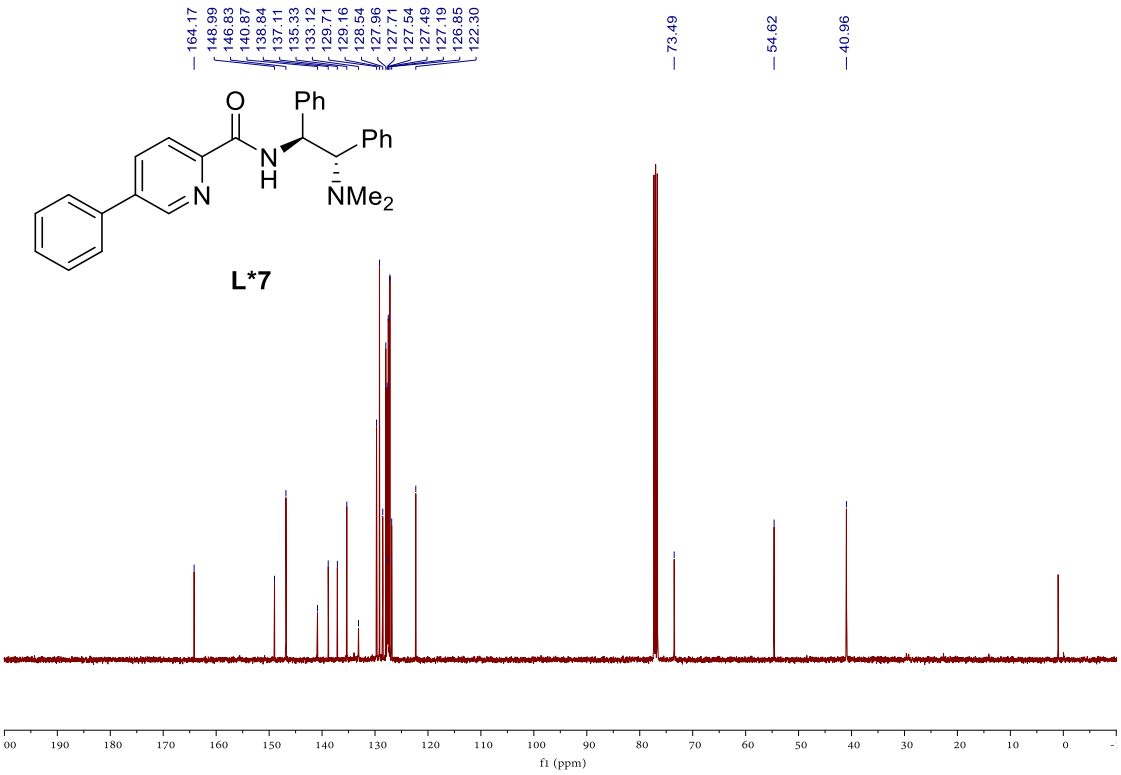
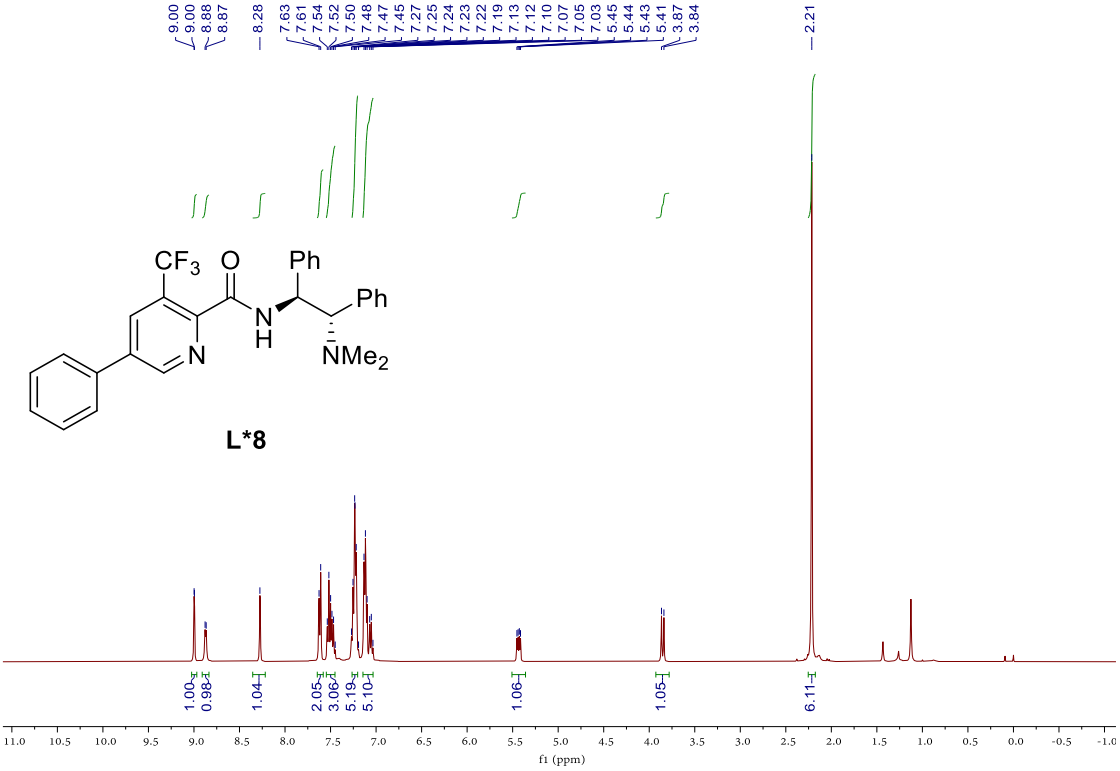


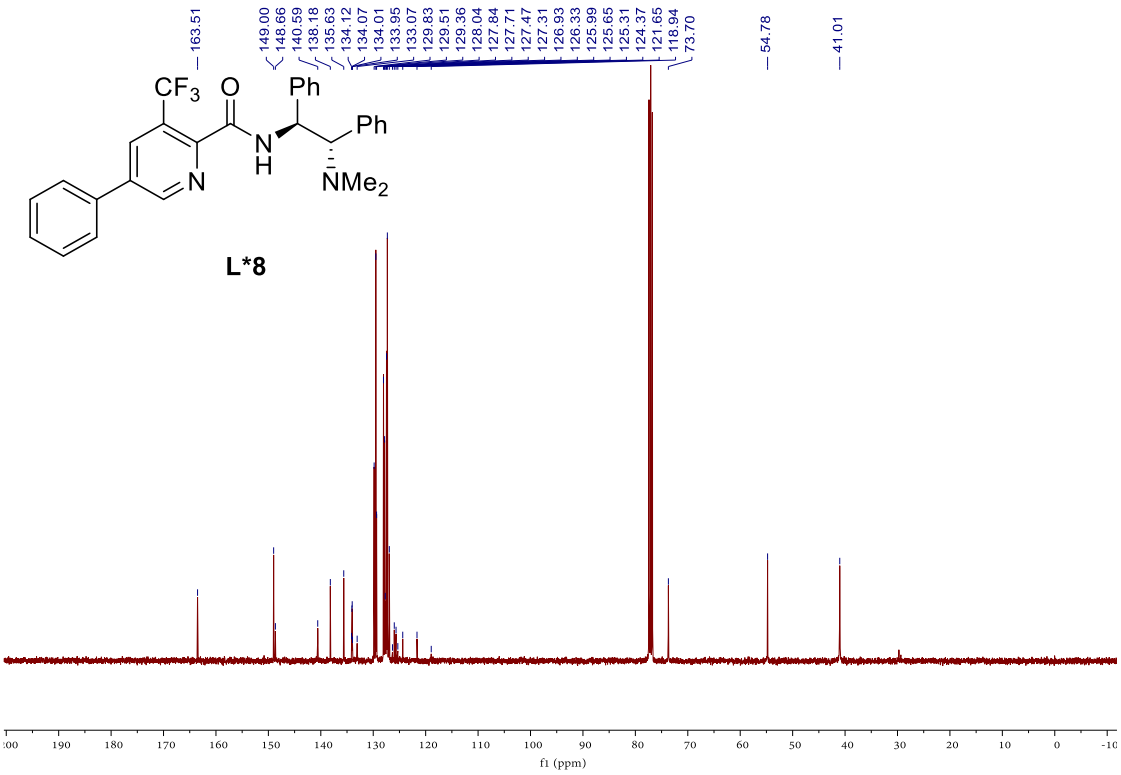
^{13}C NMR (100 MHz, $CDCl_3$)



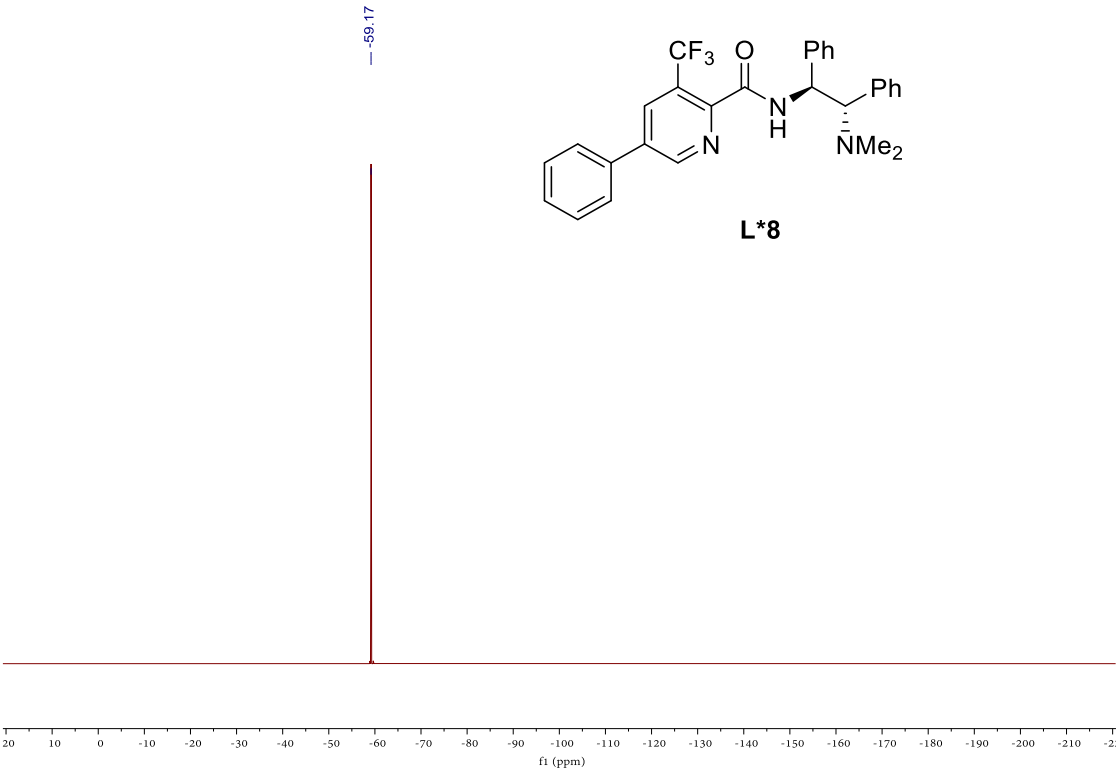
^{1}H NMR (400 MHz, $CDCl_3$)



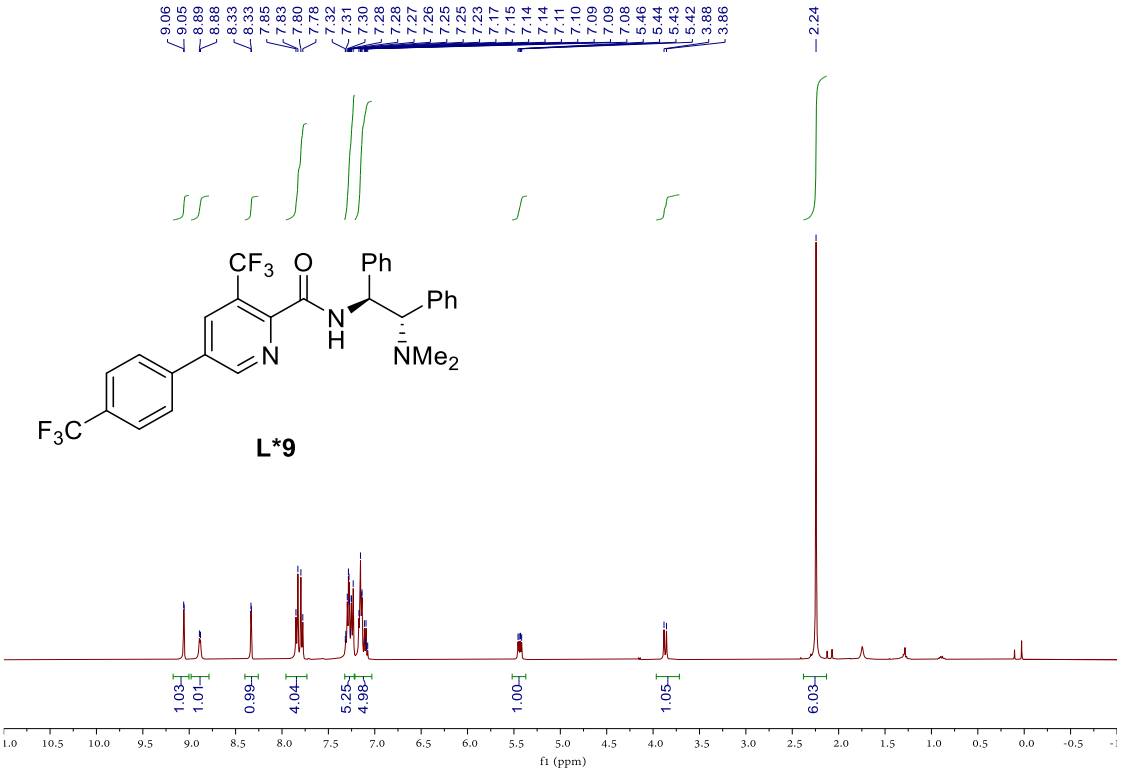
^{13}C NMR (100 MHz, $CDCl_3$)



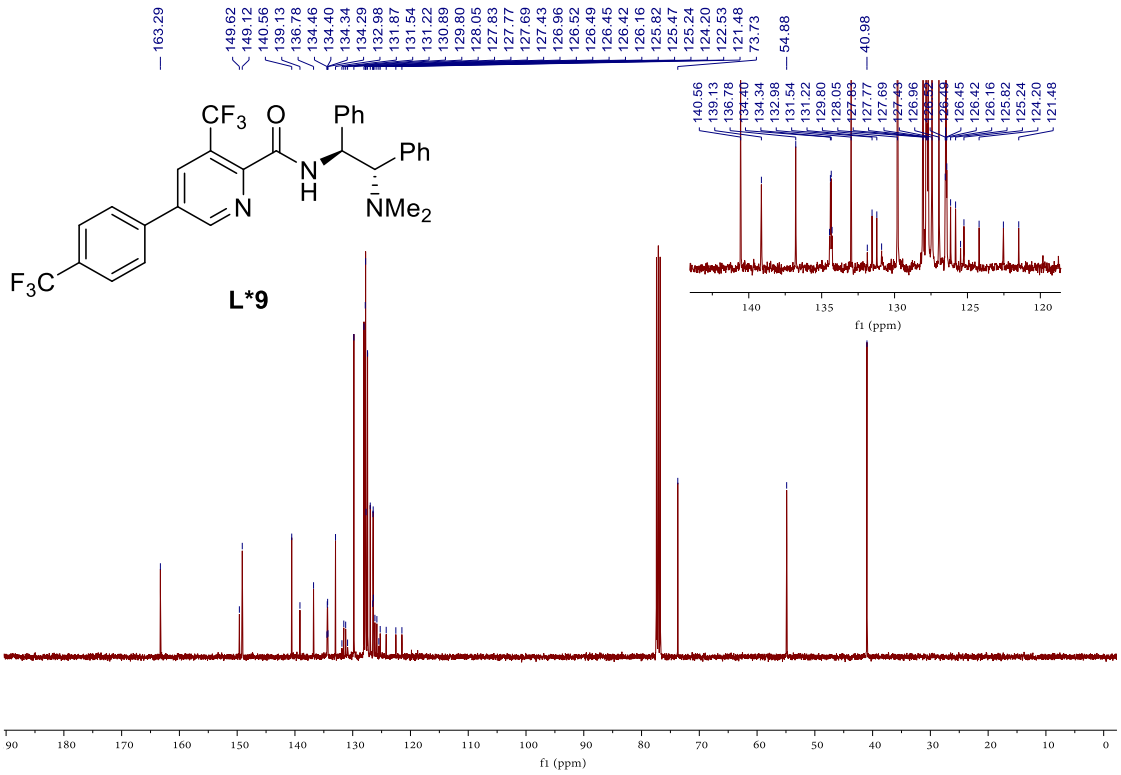
^{19}F NMR (376 MHz, $CDCl_3$)



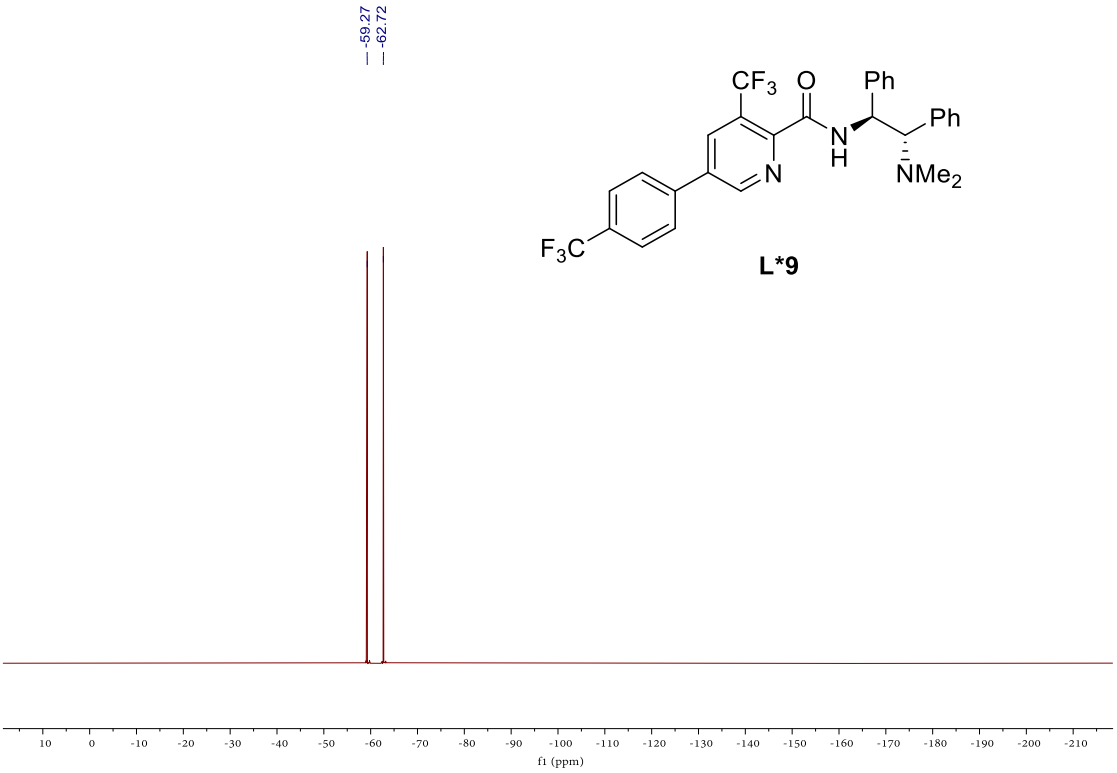
^{1}H NMR (400 MHz, $CDCl_3$)



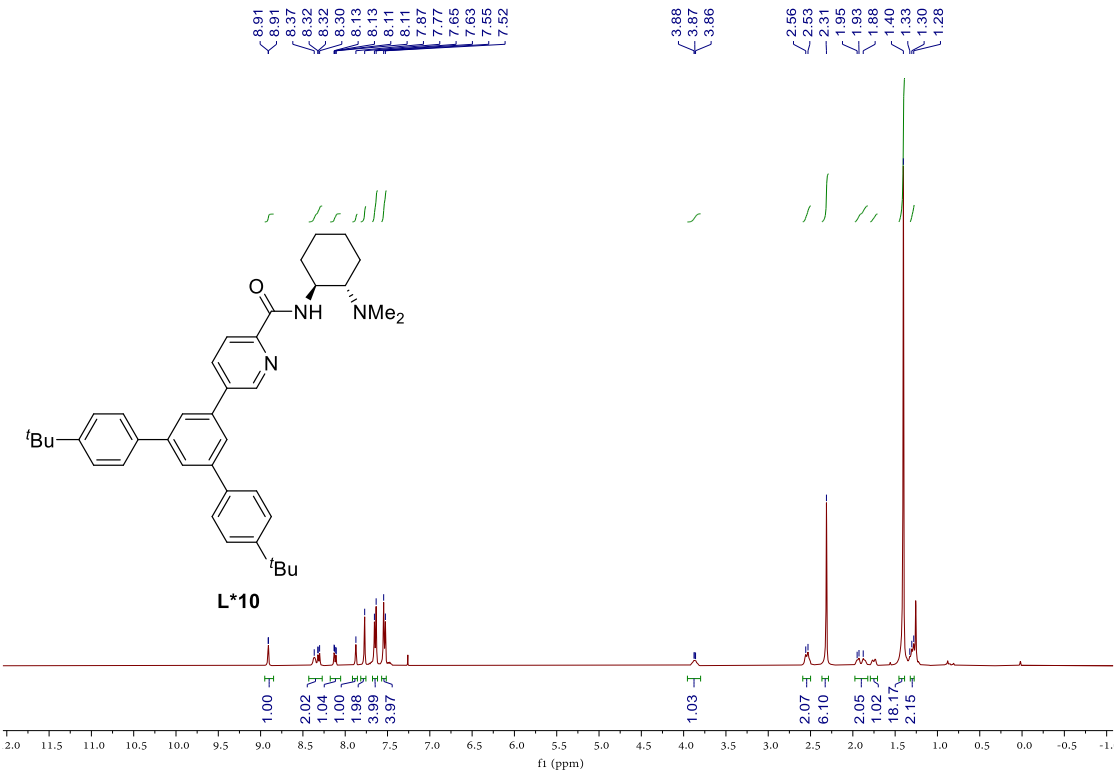
^{13}C NMR (100 MHz, $CDCl_3$)



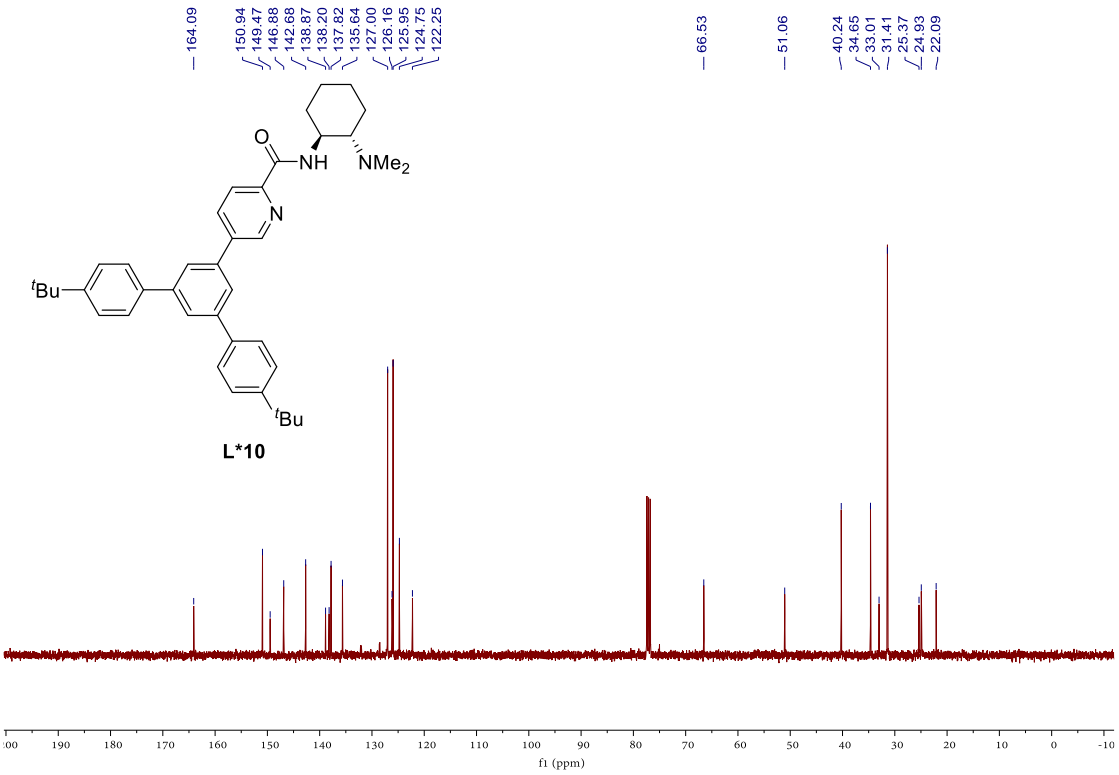
^{19}F NMR (376 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



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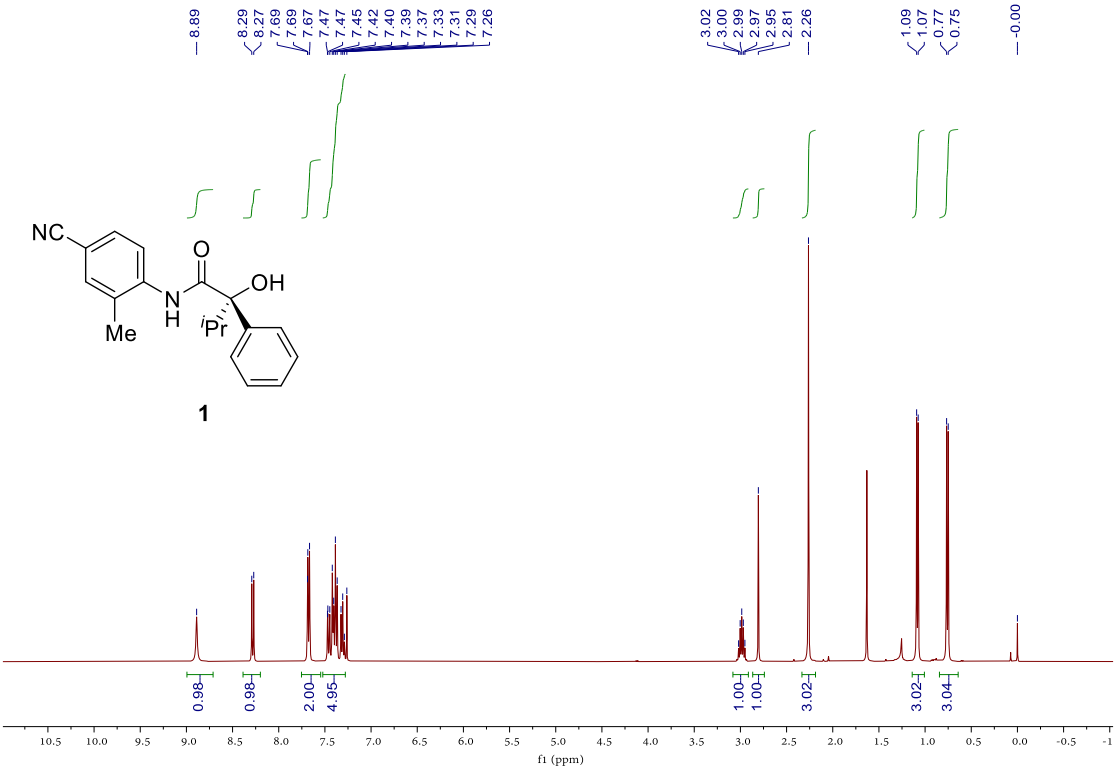
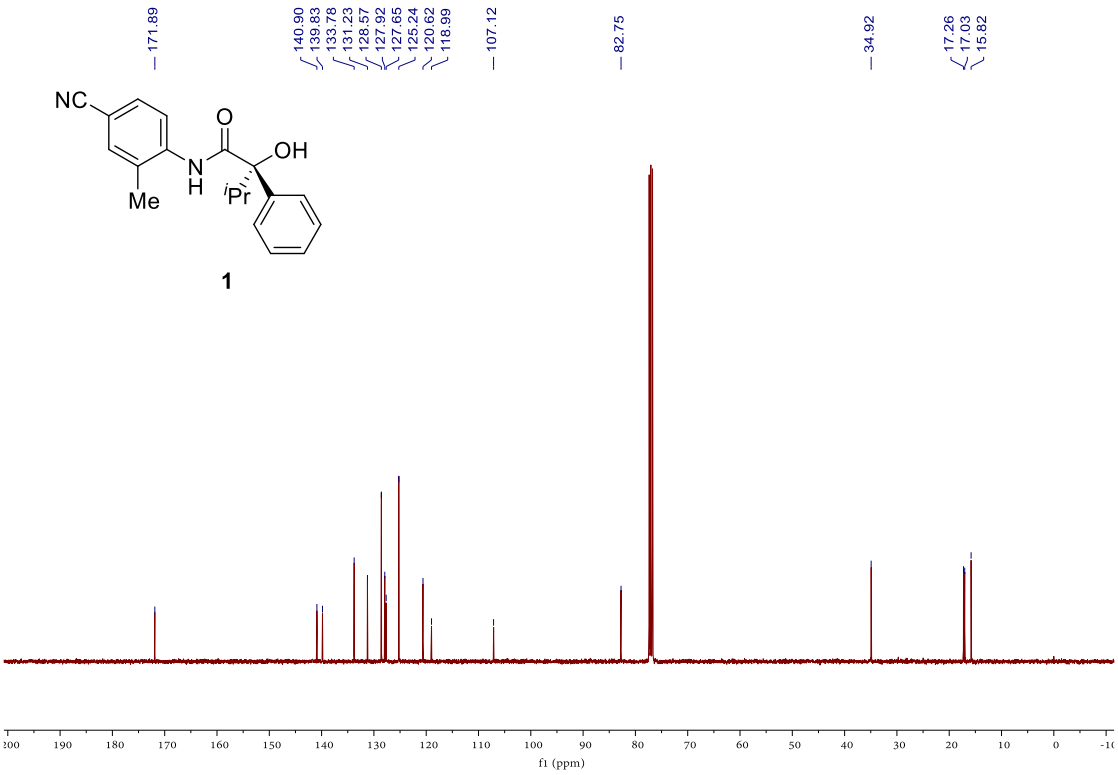
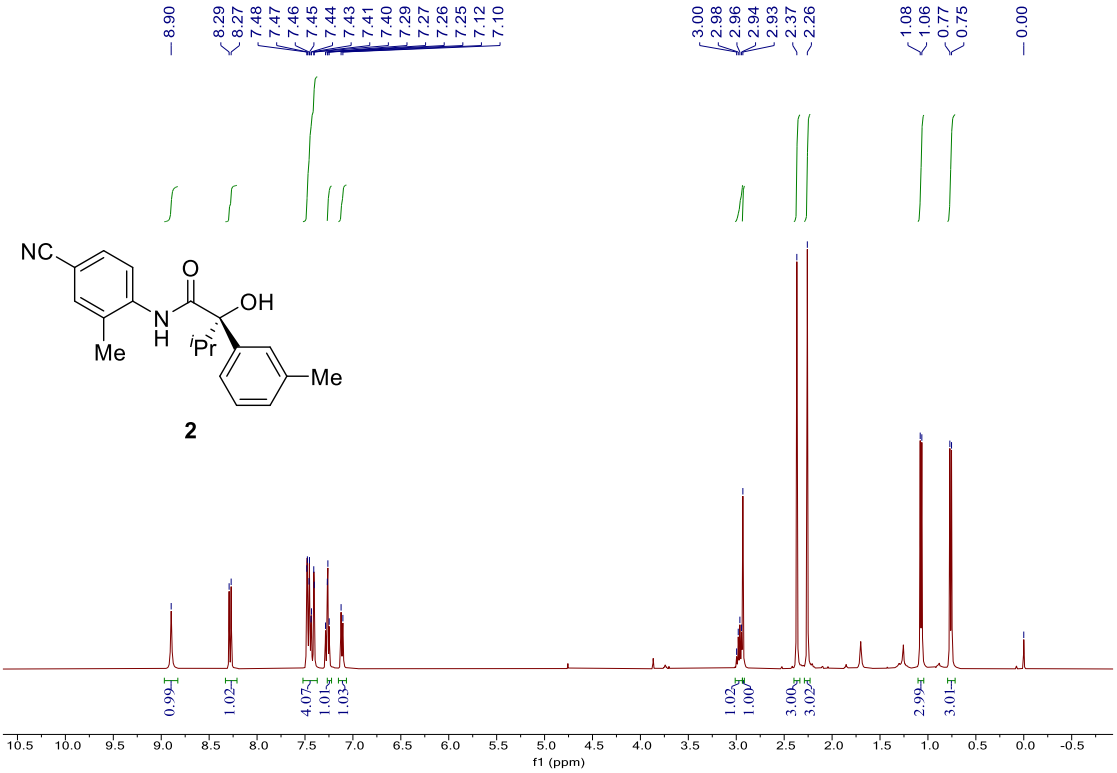


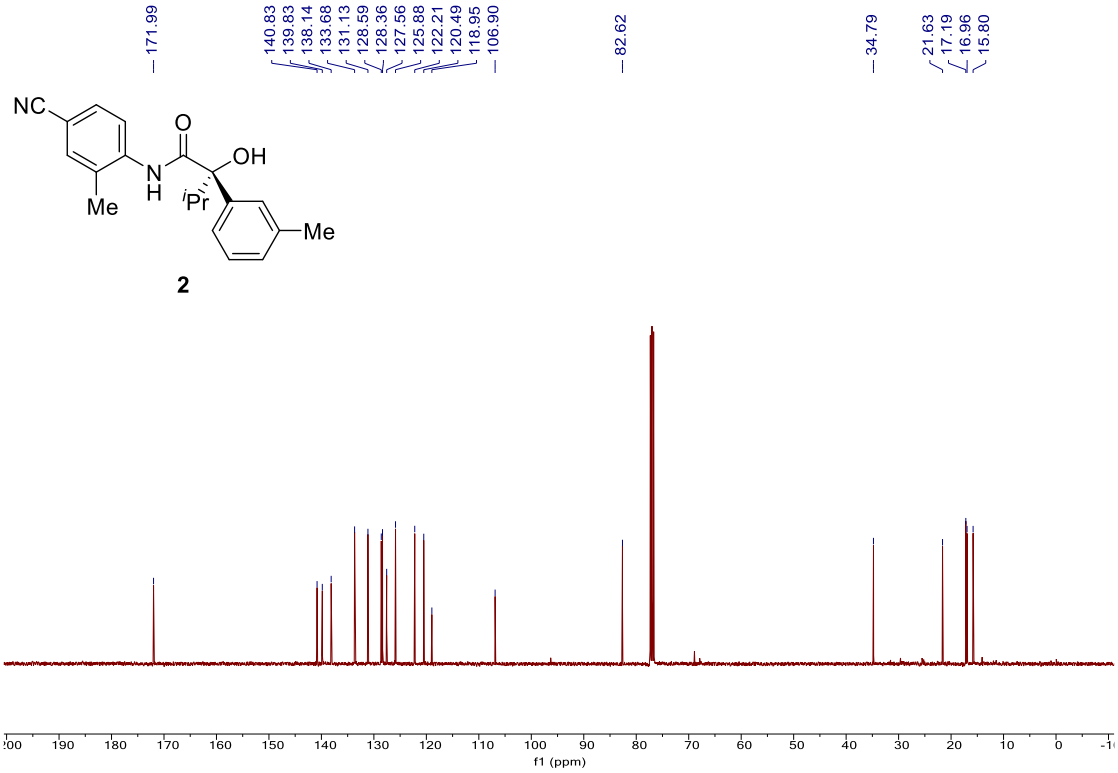
^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



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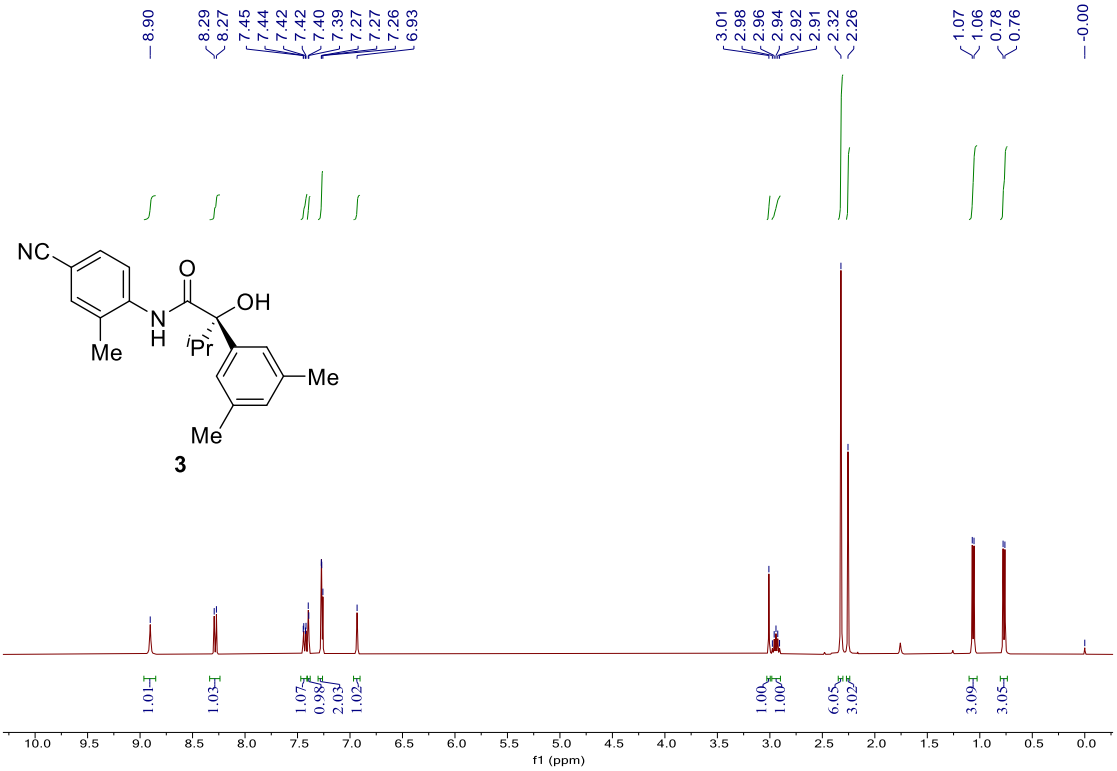

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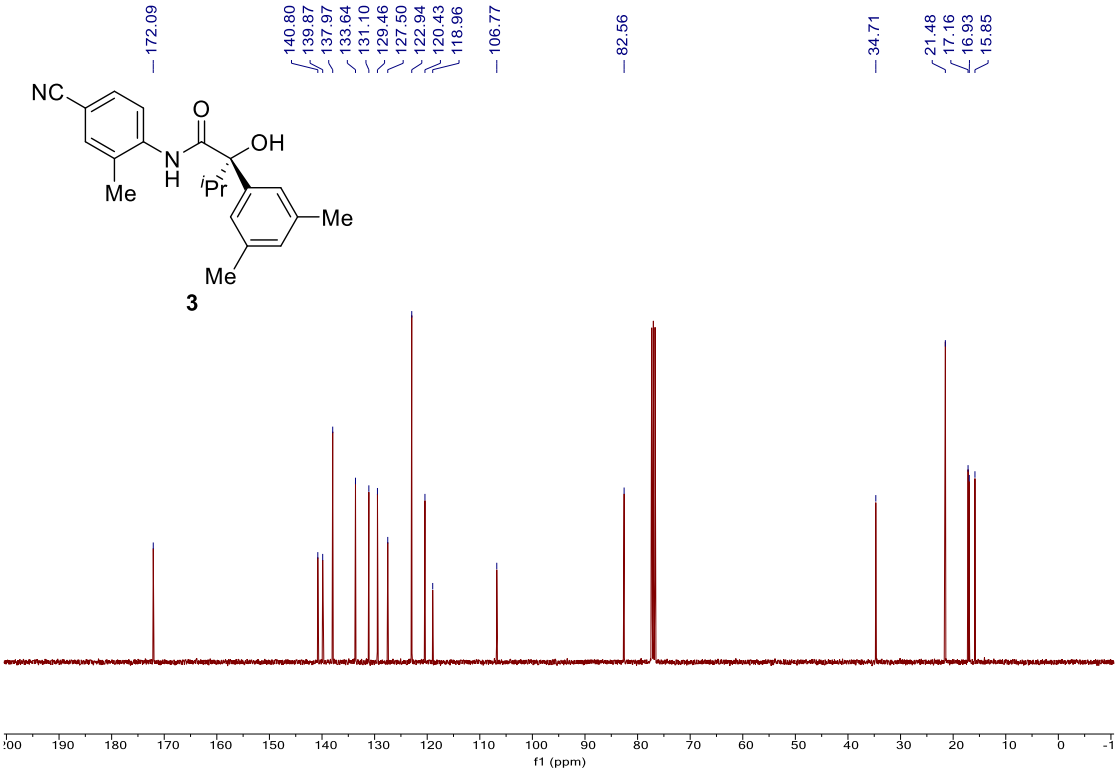

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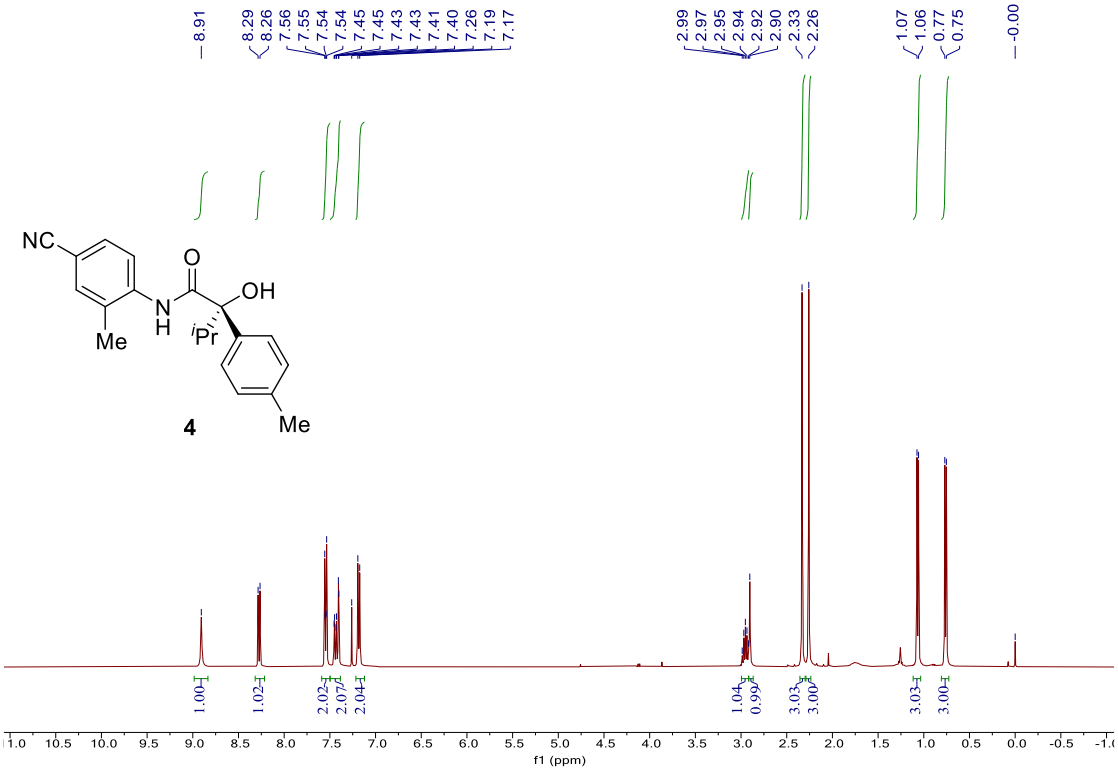

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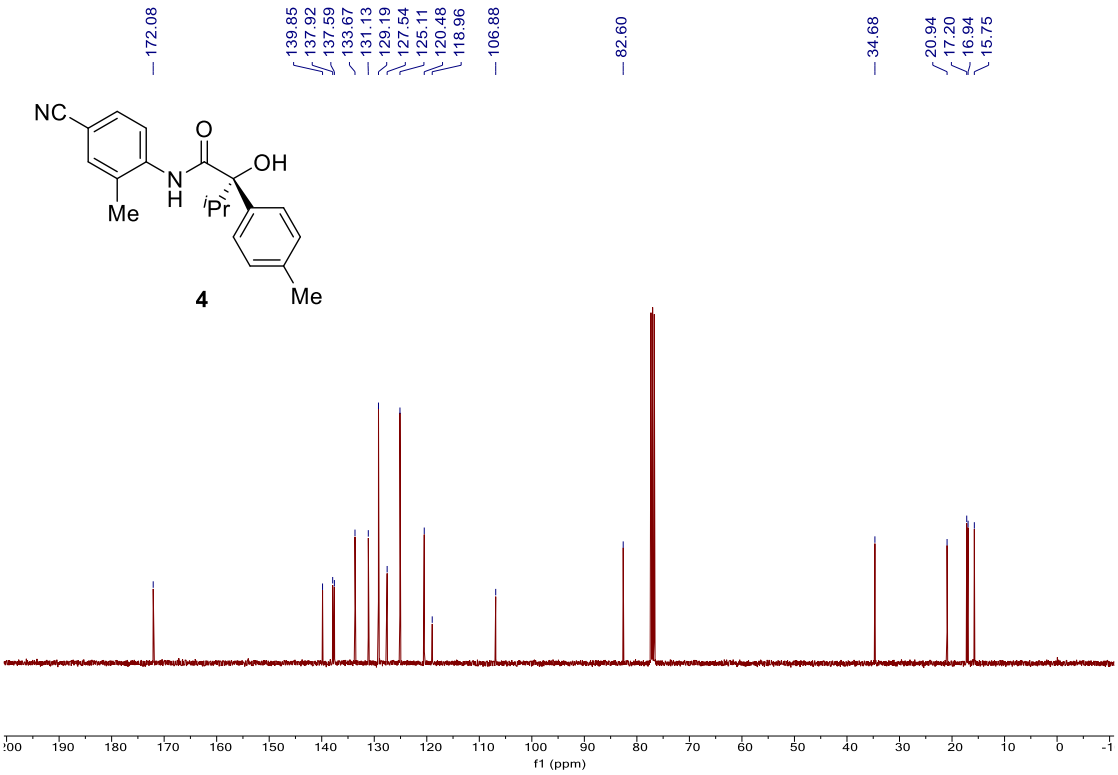

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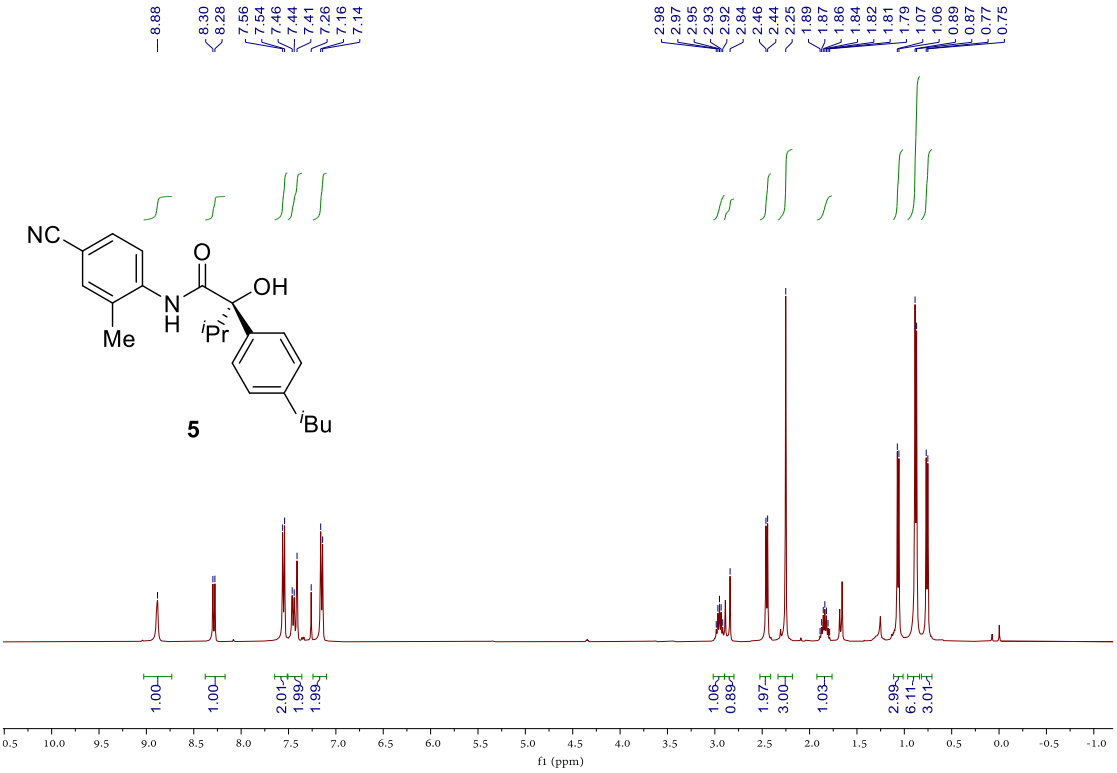

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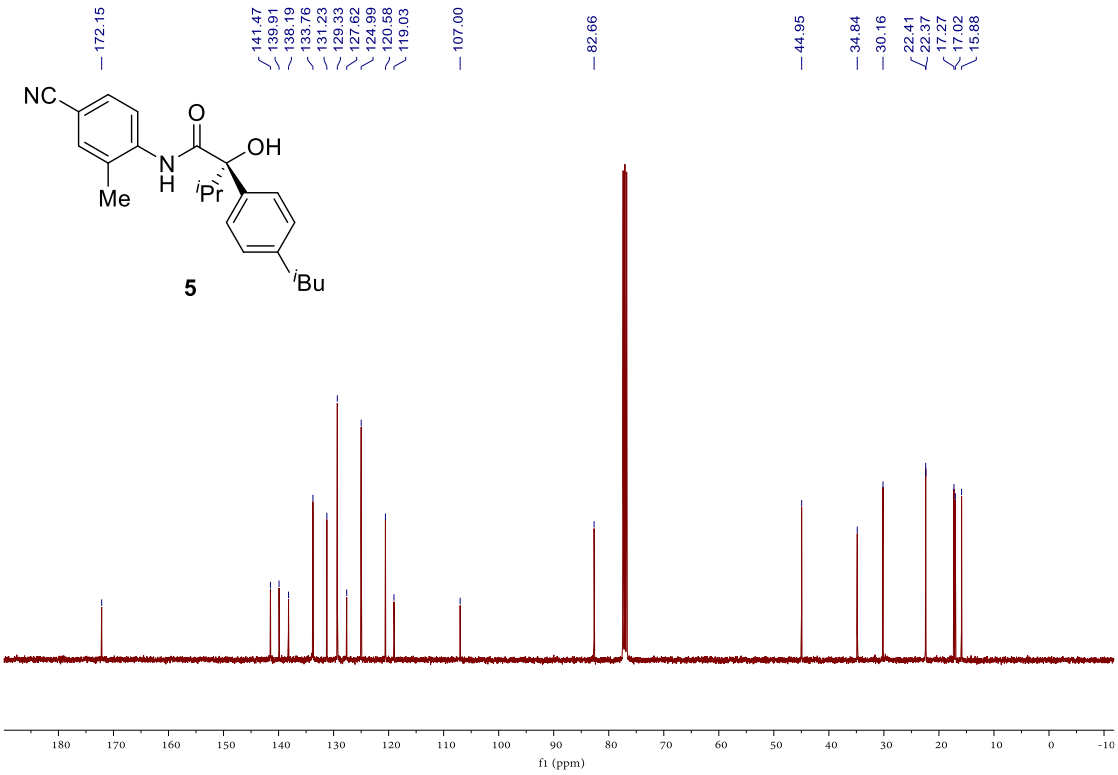
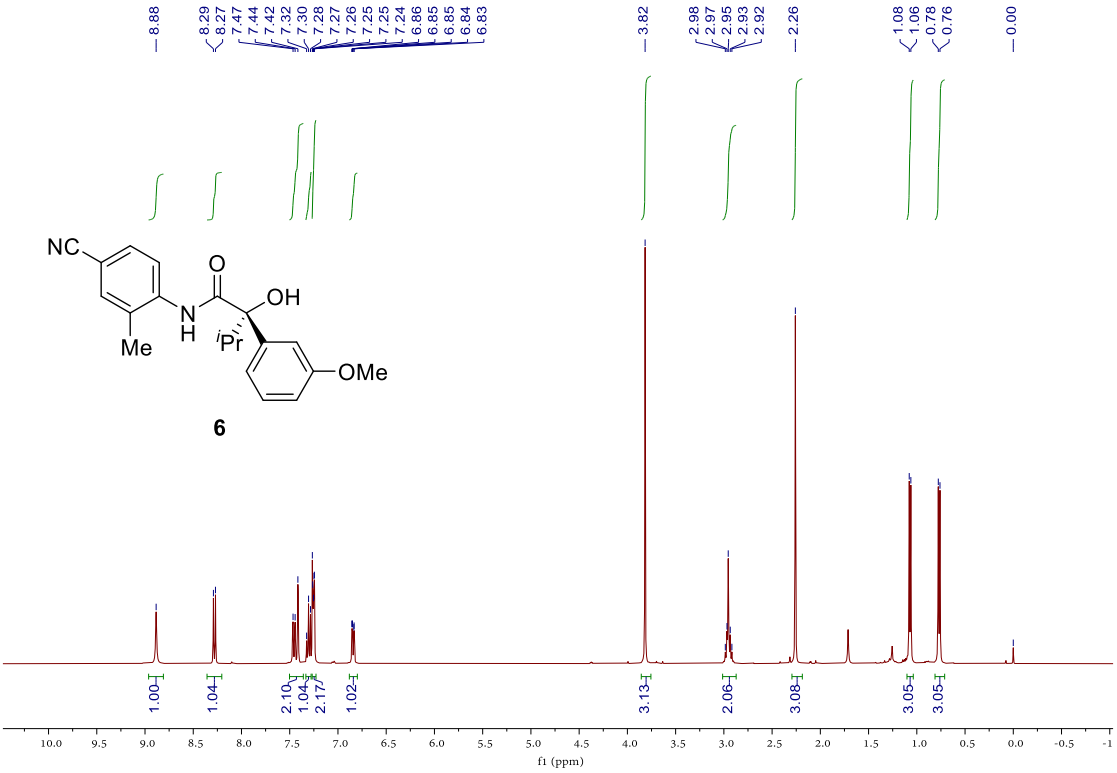


^{1}H NMR (400 MHz, $CDCl_3$)



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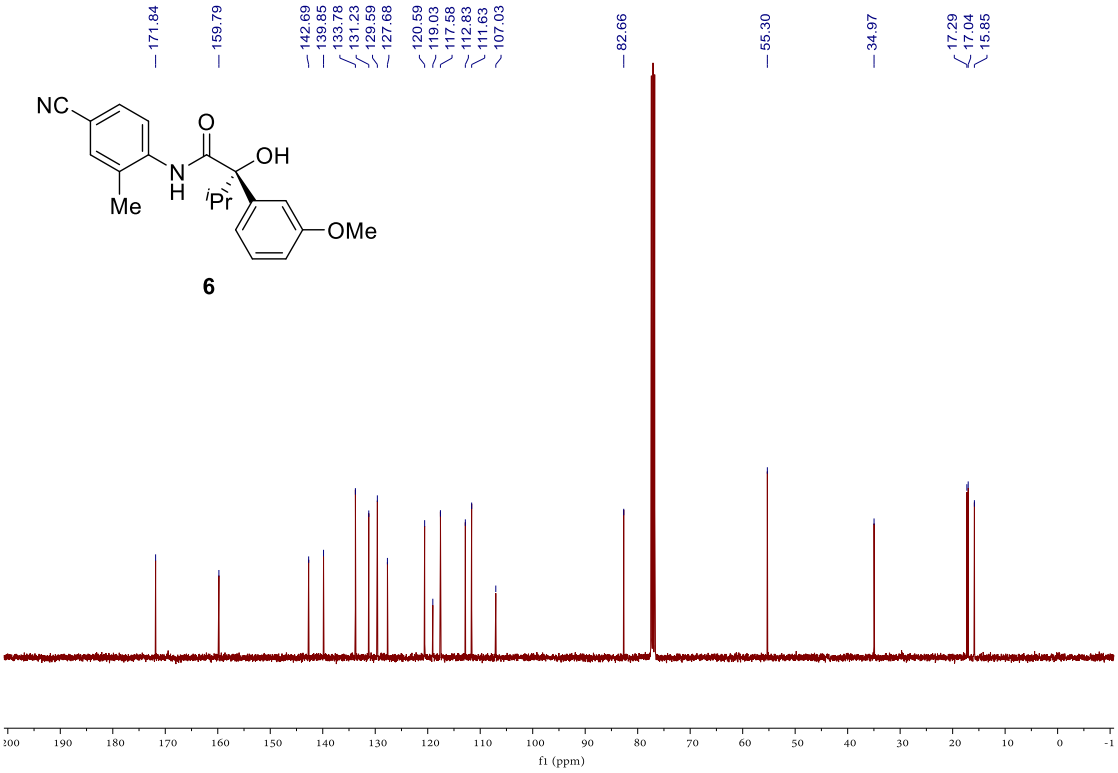
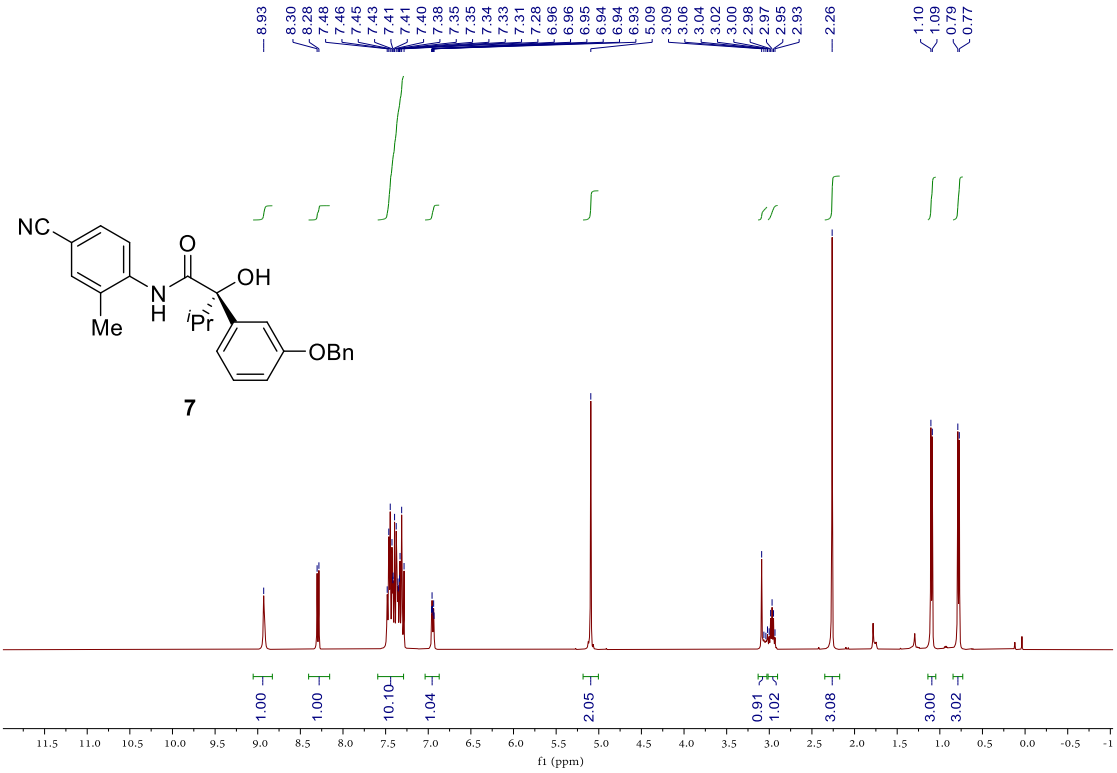


^{1}H NMR (400 MHz, $CDCl_3$)



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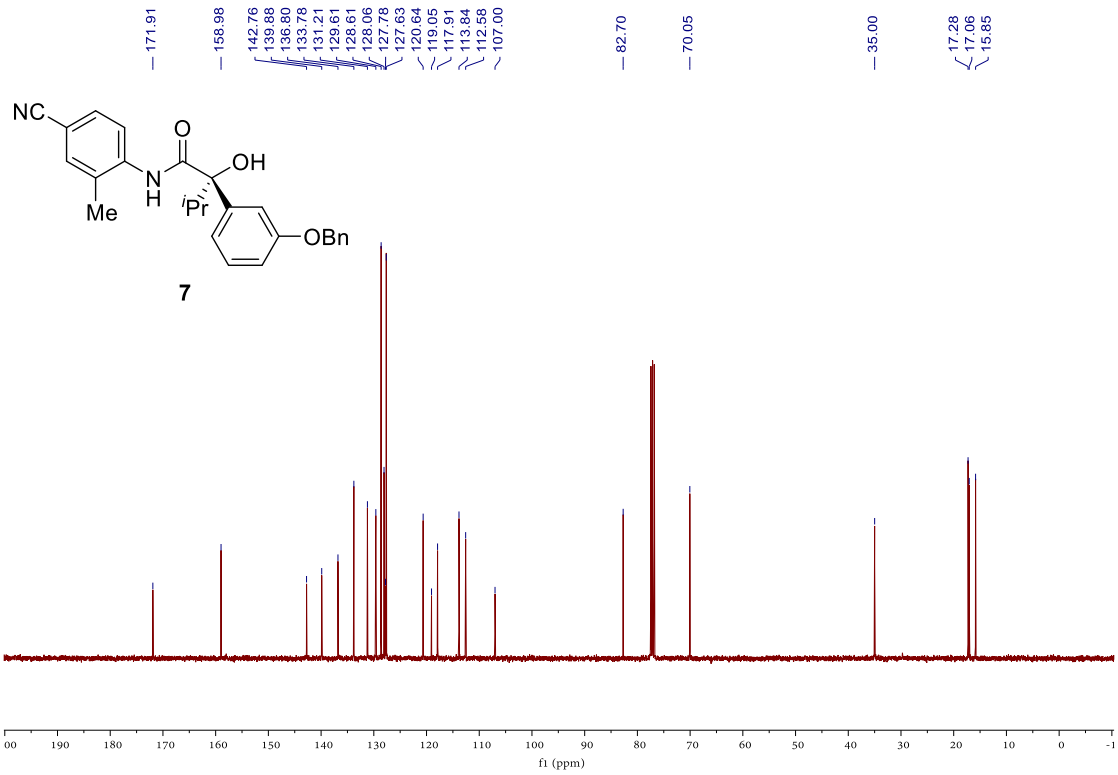

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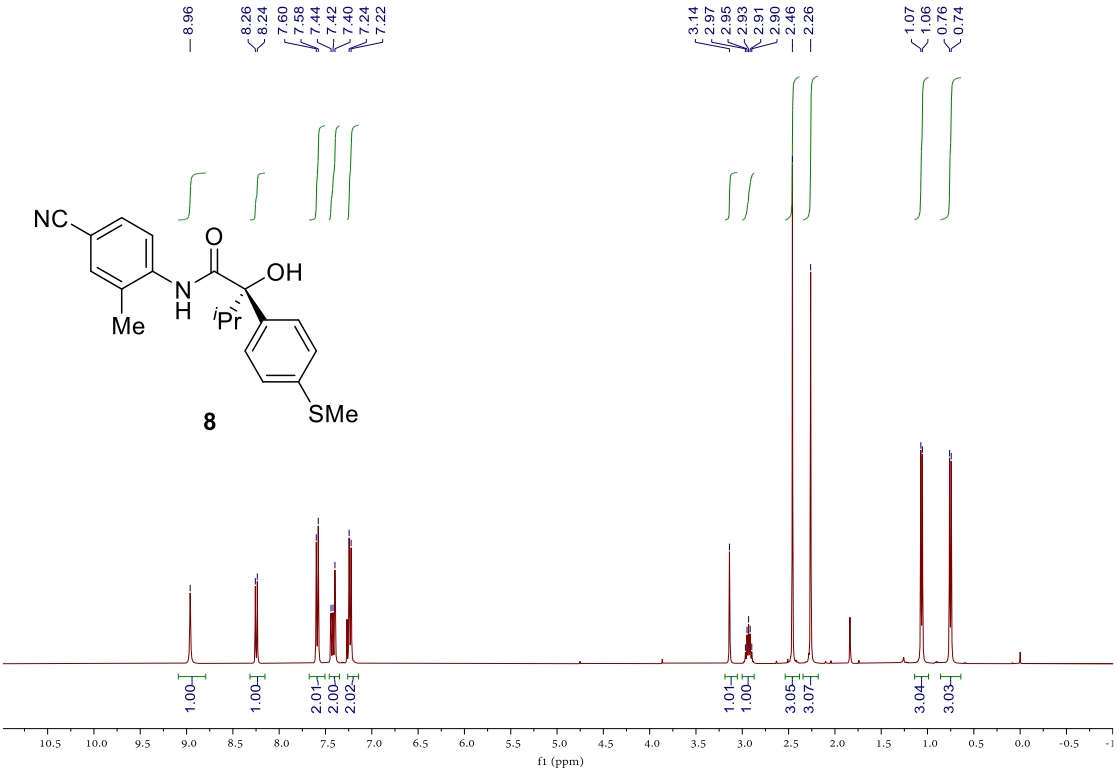

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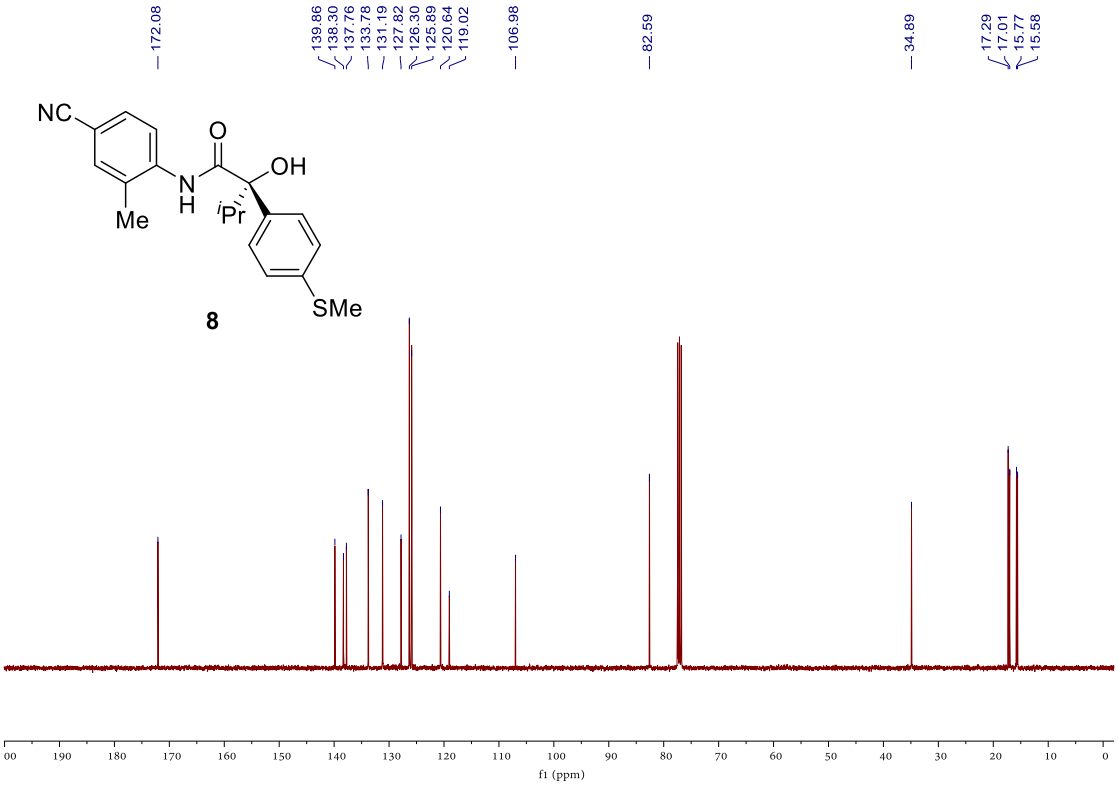

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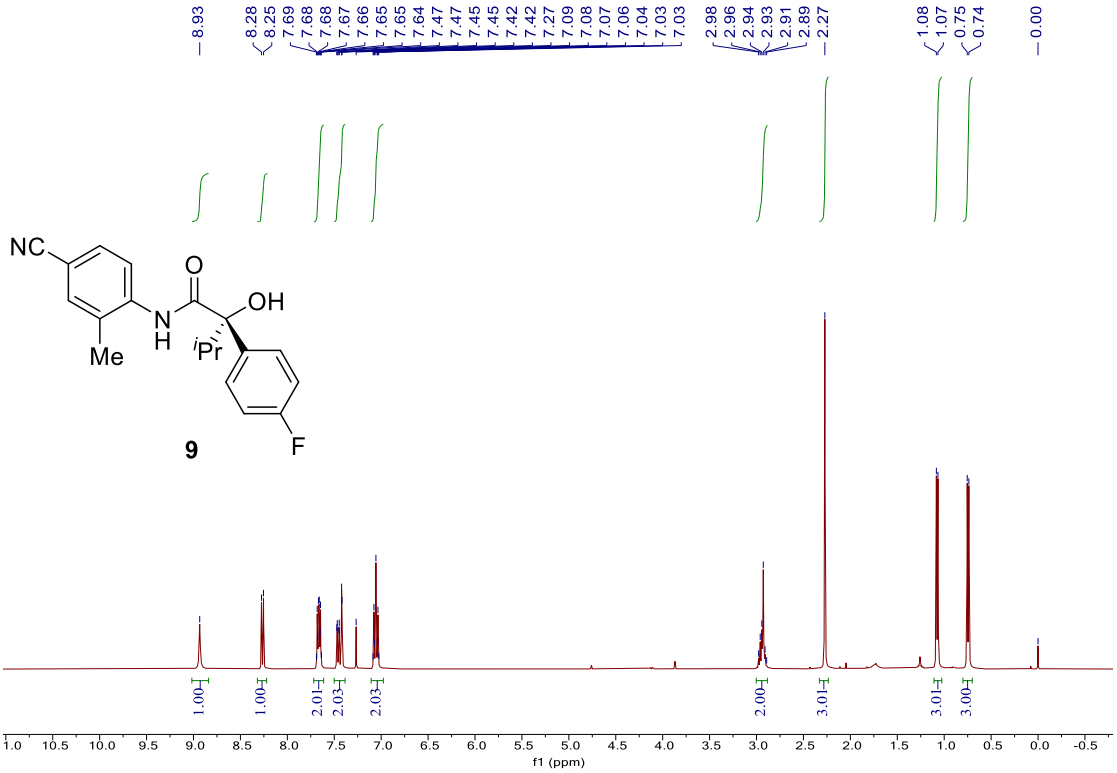
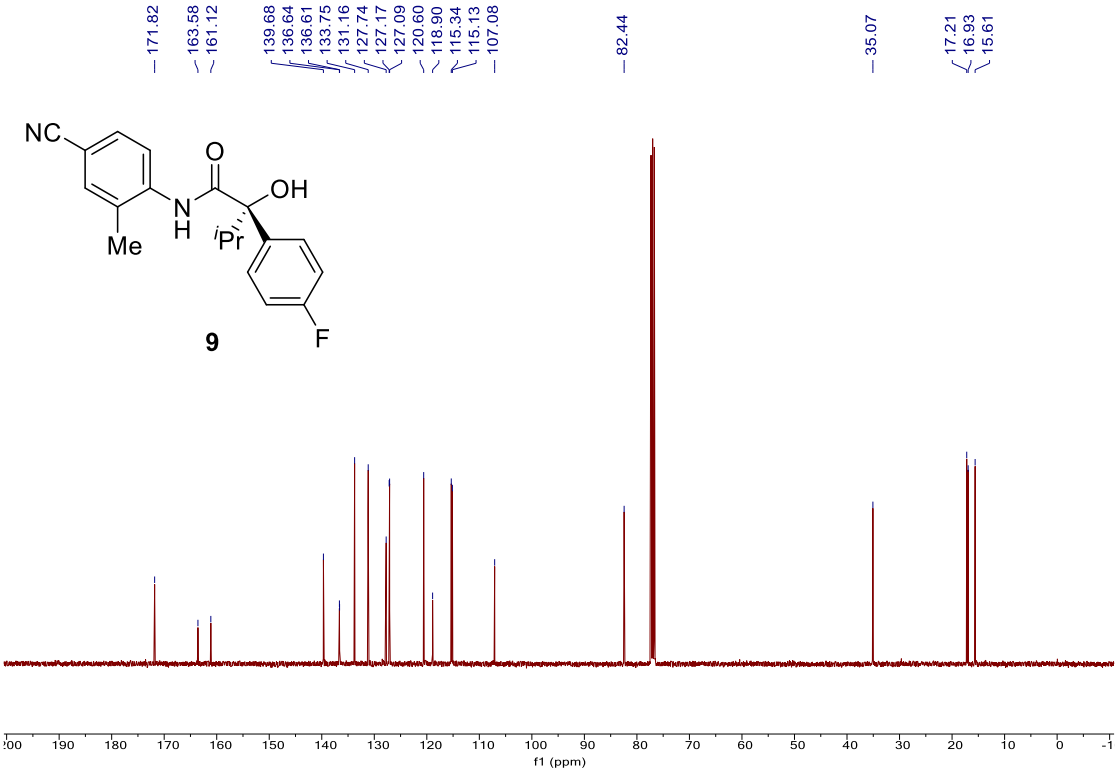
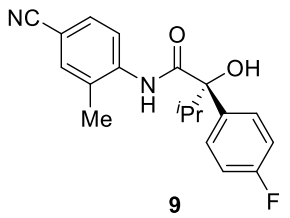


^{13}C NMR (100 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)



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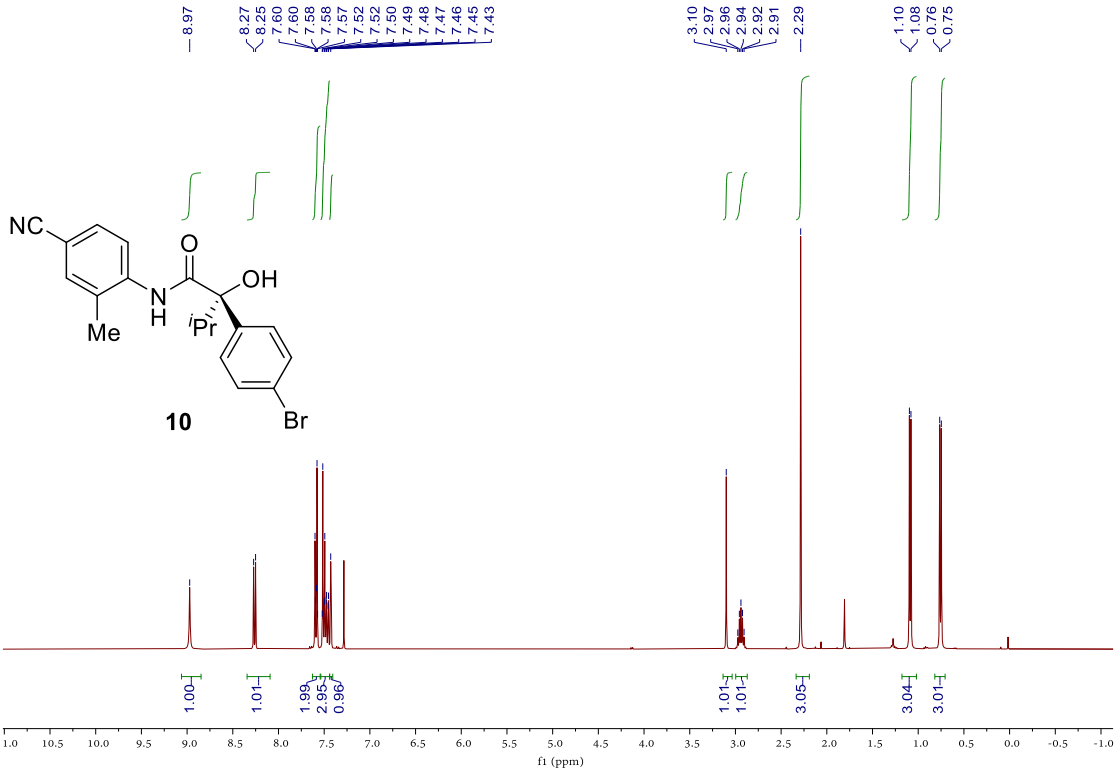
^{1}H NMR (400 MHz, $CDCl_3$)



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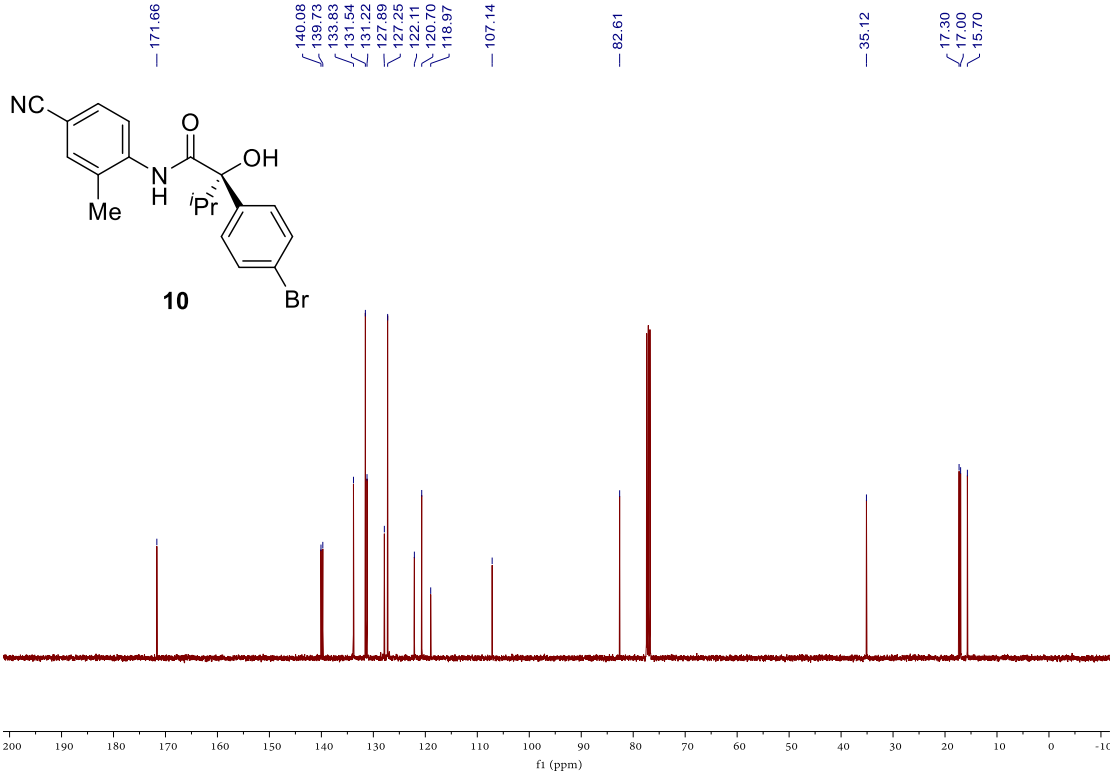
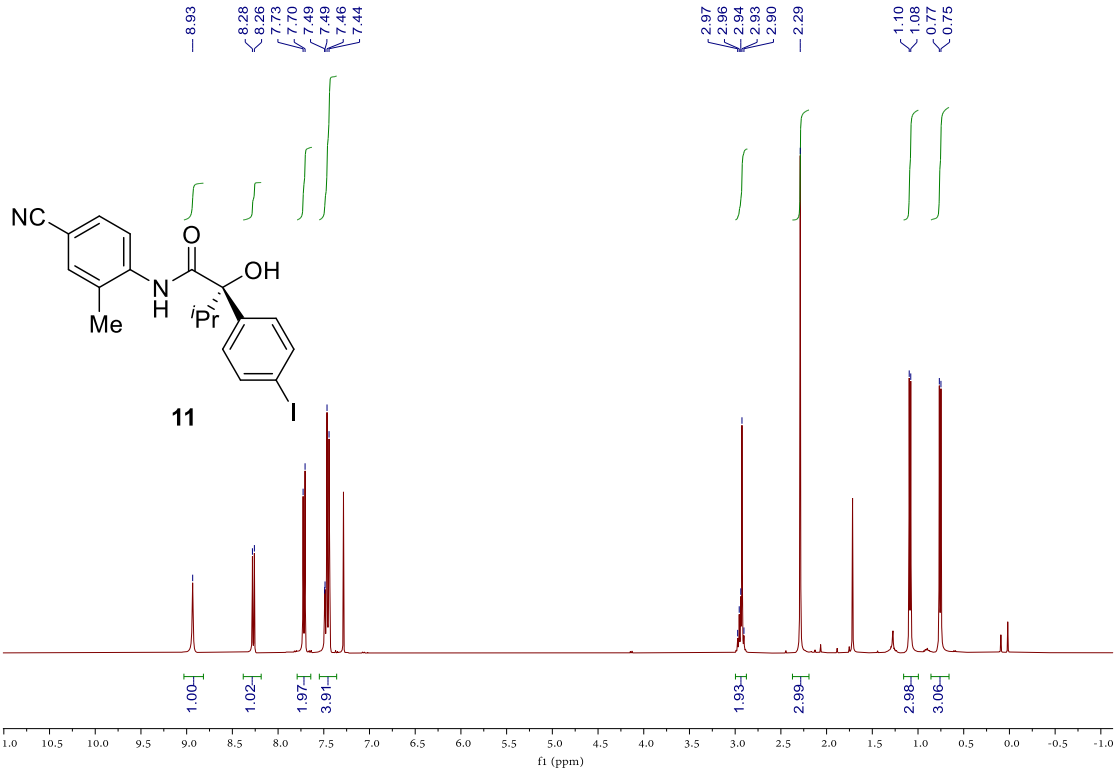


^{1}H NMR (400 MHz, $CDCl_3$)



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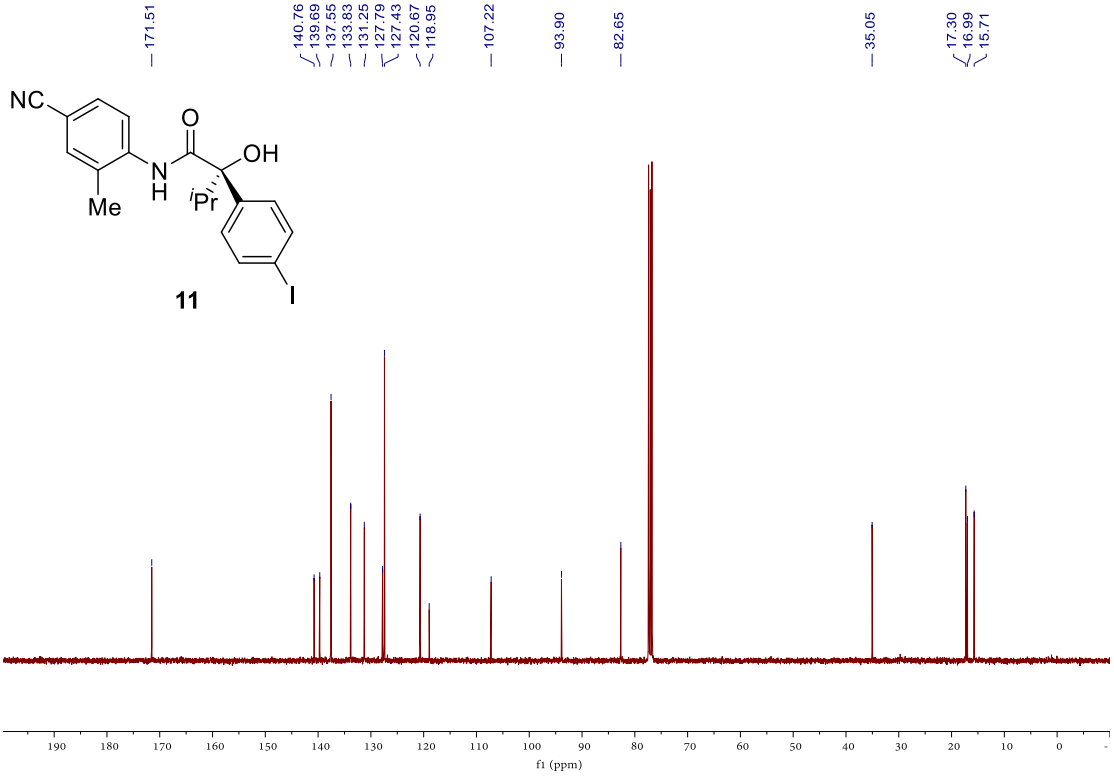
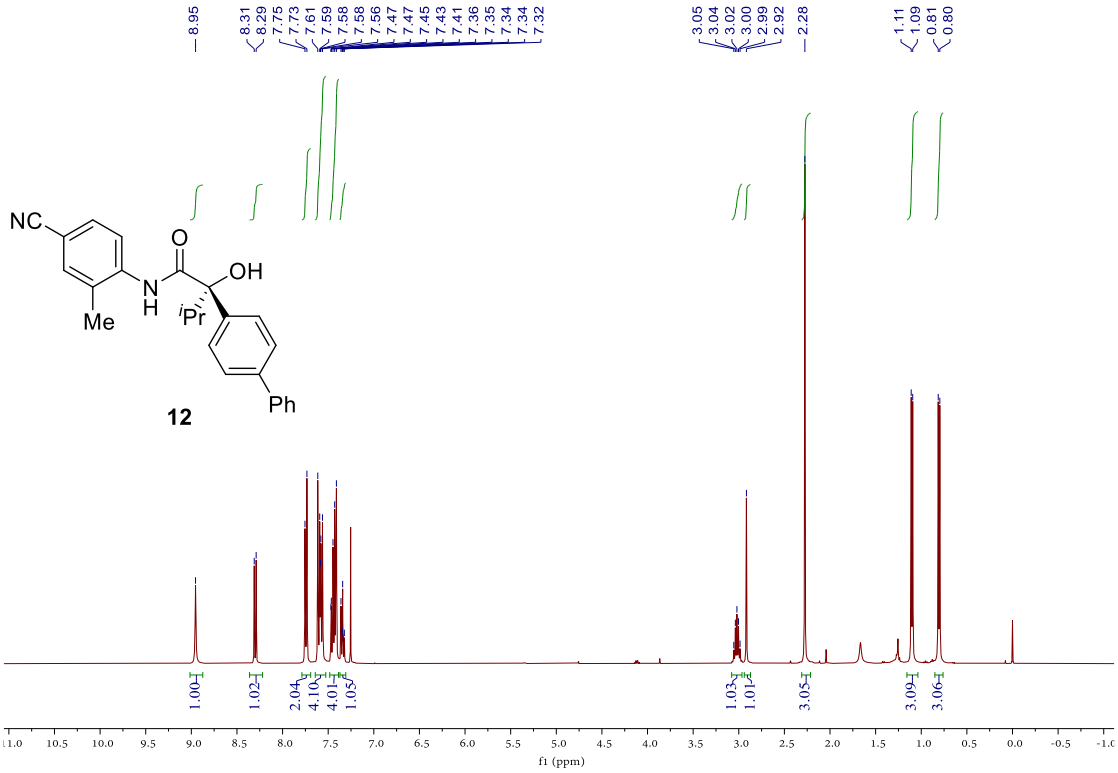


^{1}H NMR (400 MHz, $CDCl_3$)



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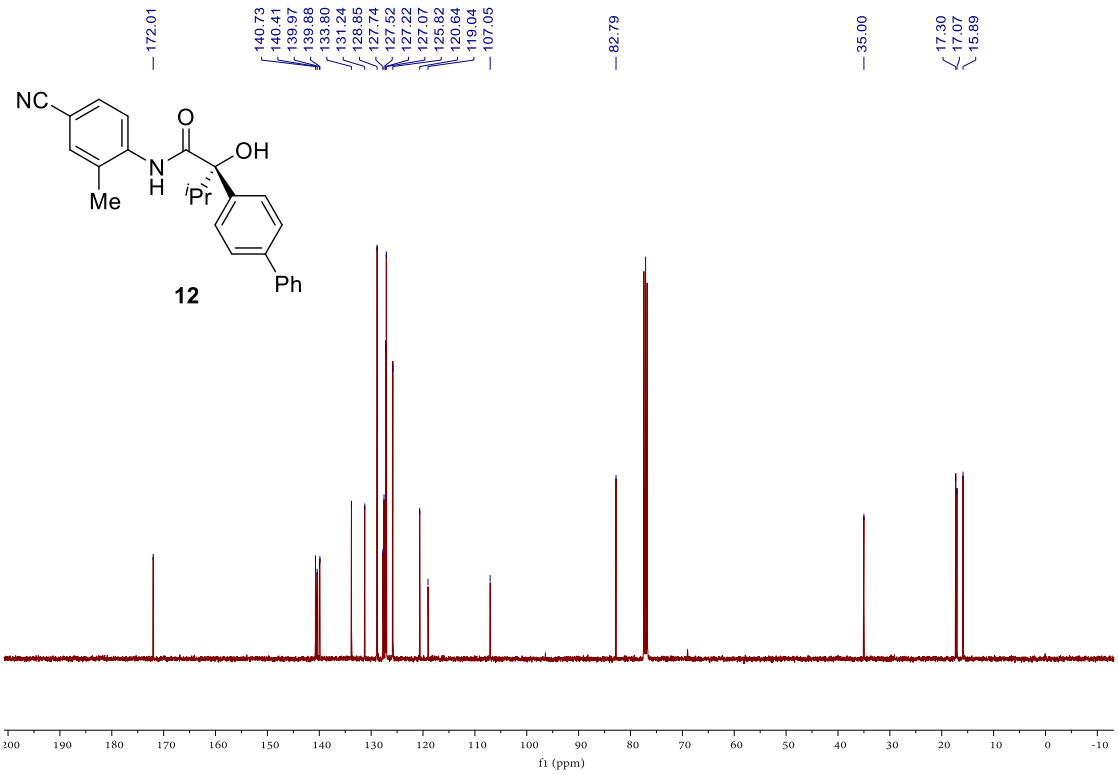

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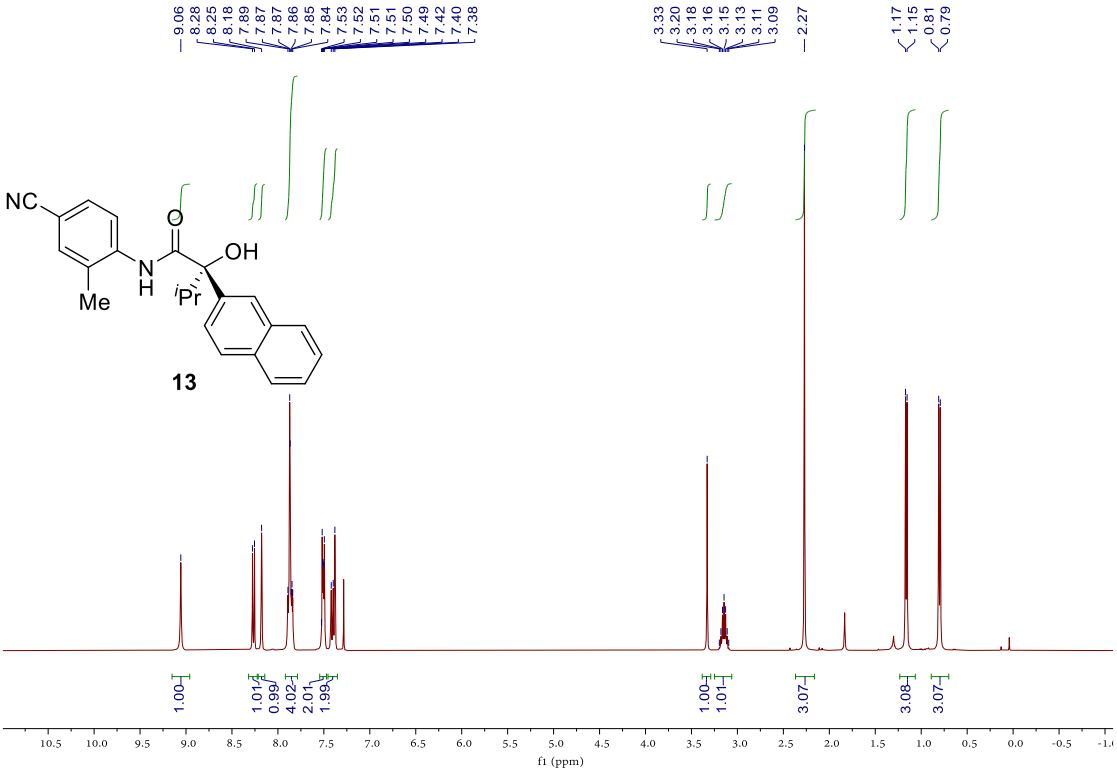

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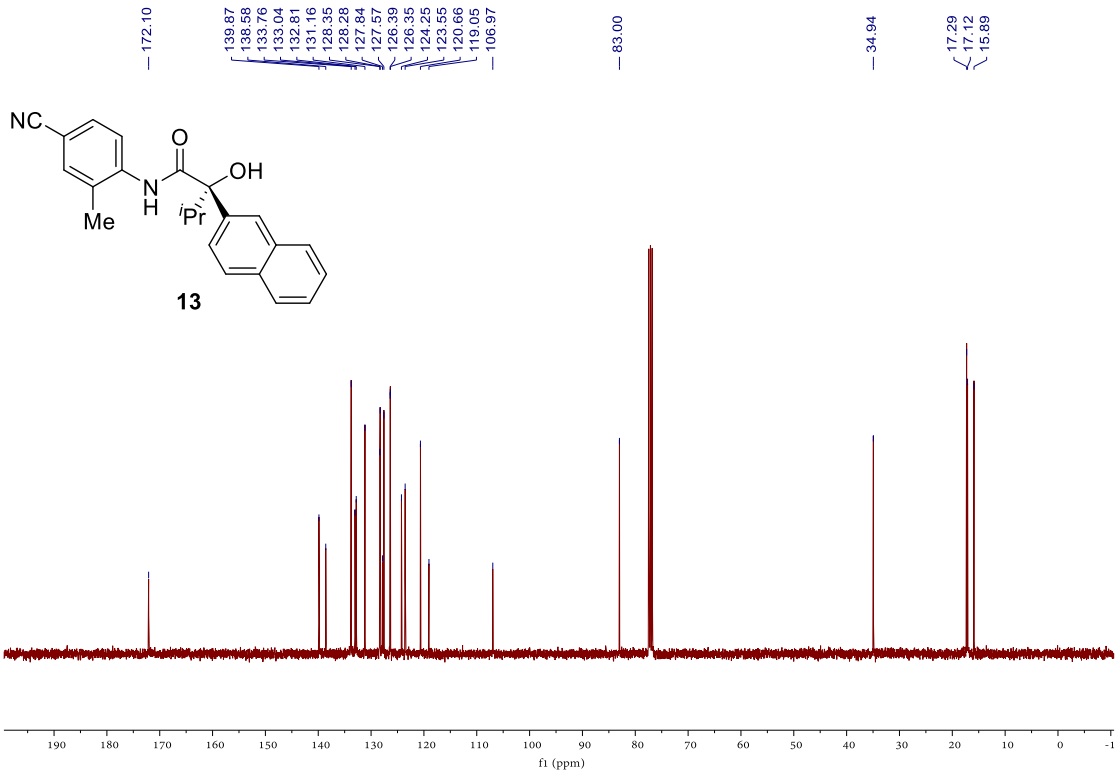

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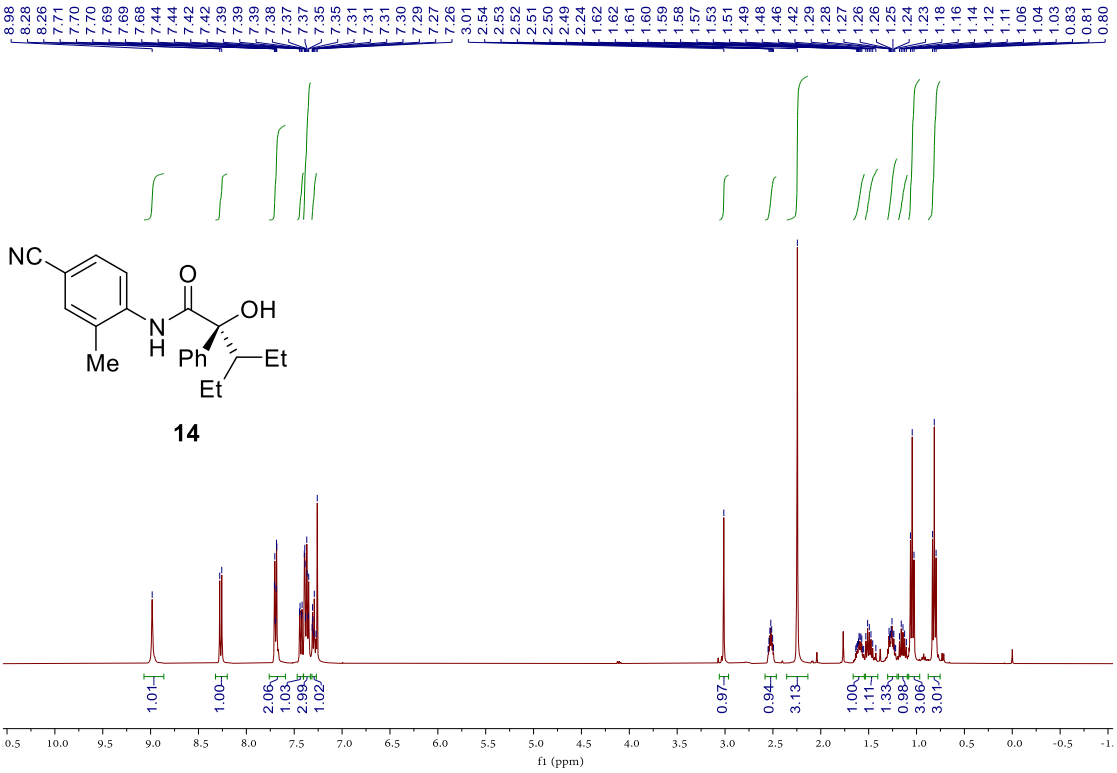
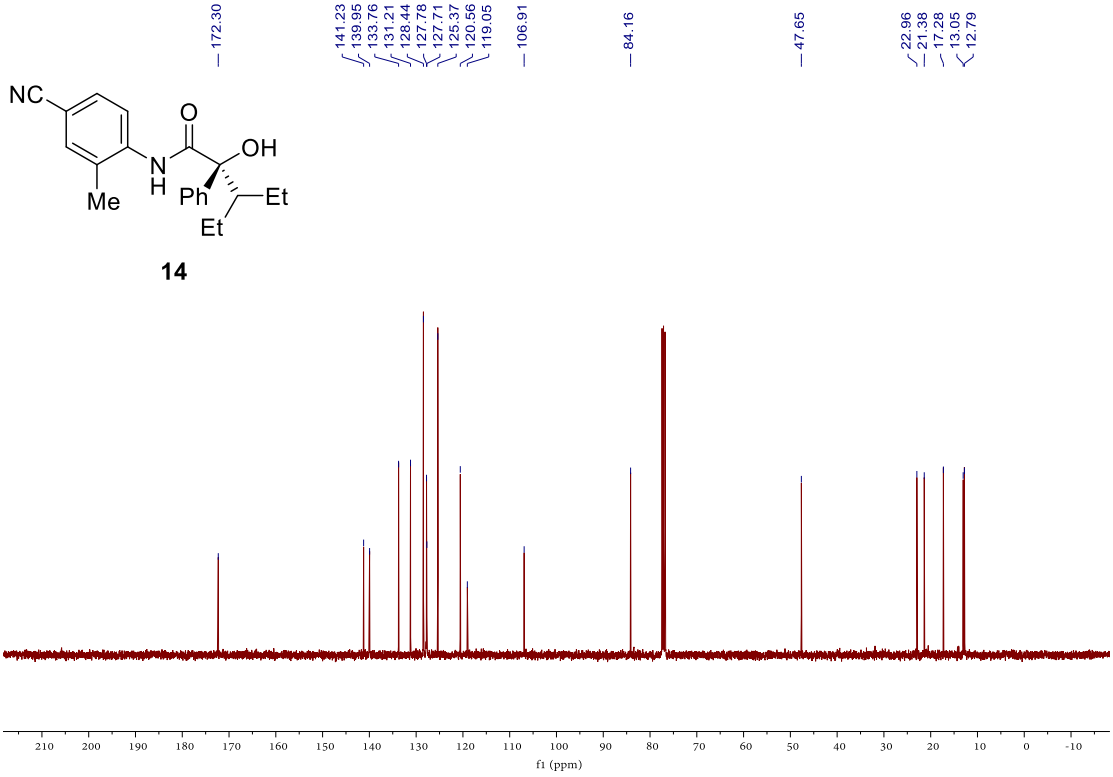


^{13}C NMR (100 MHz, $CDCl_3$)



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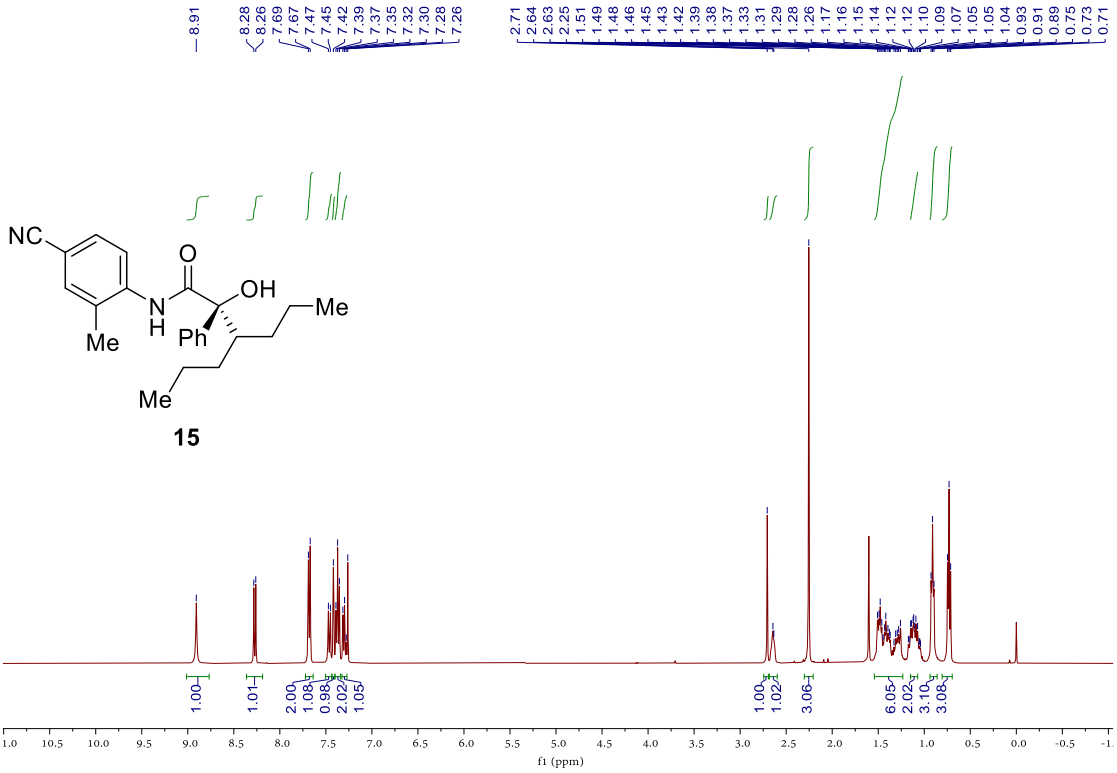

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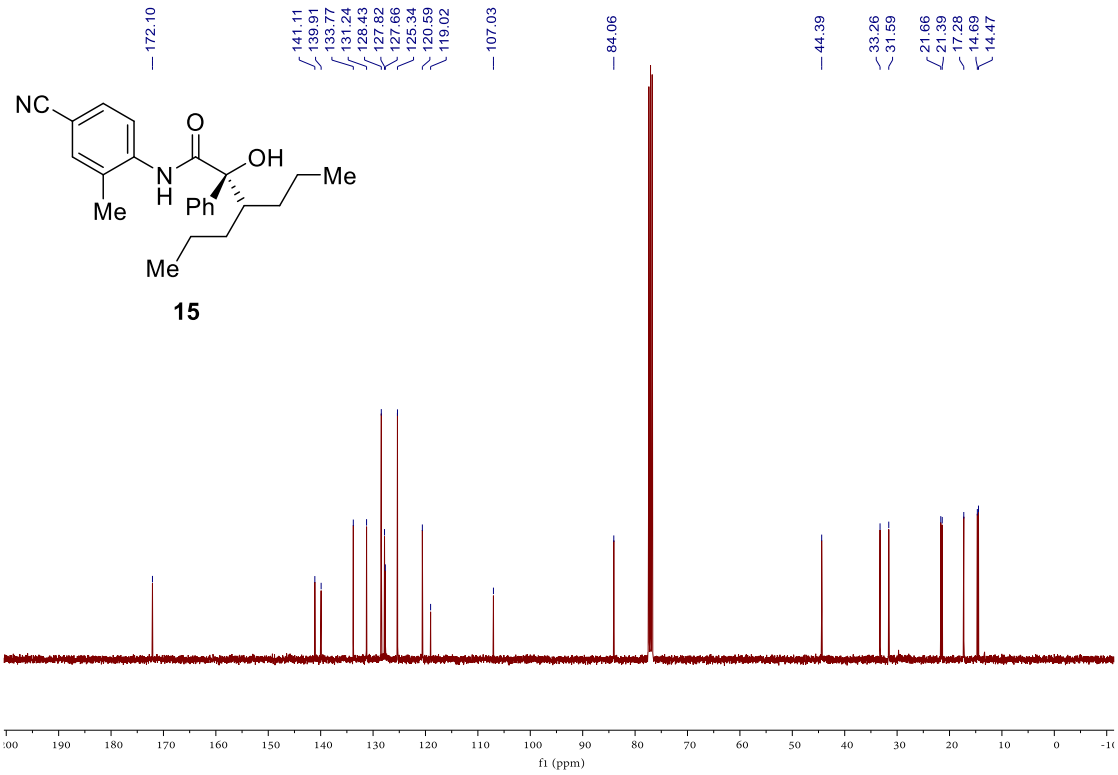

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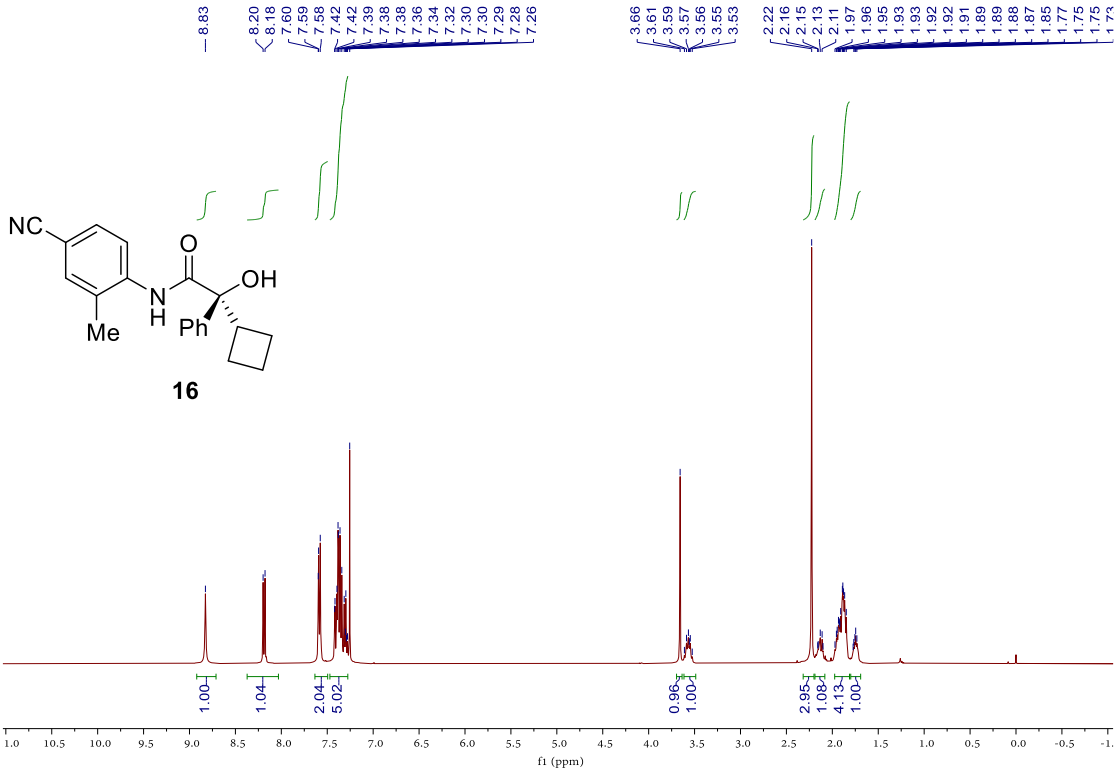
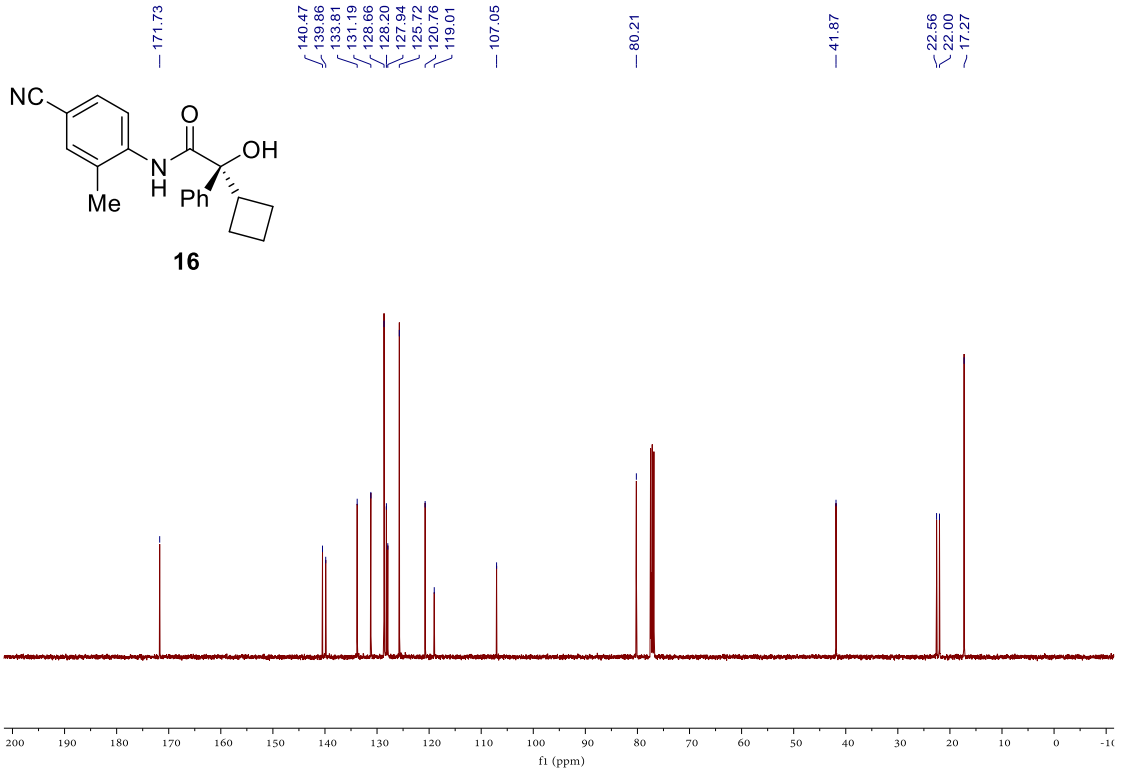


^{13}C NMR (100 MHz, $CDCl_3$)



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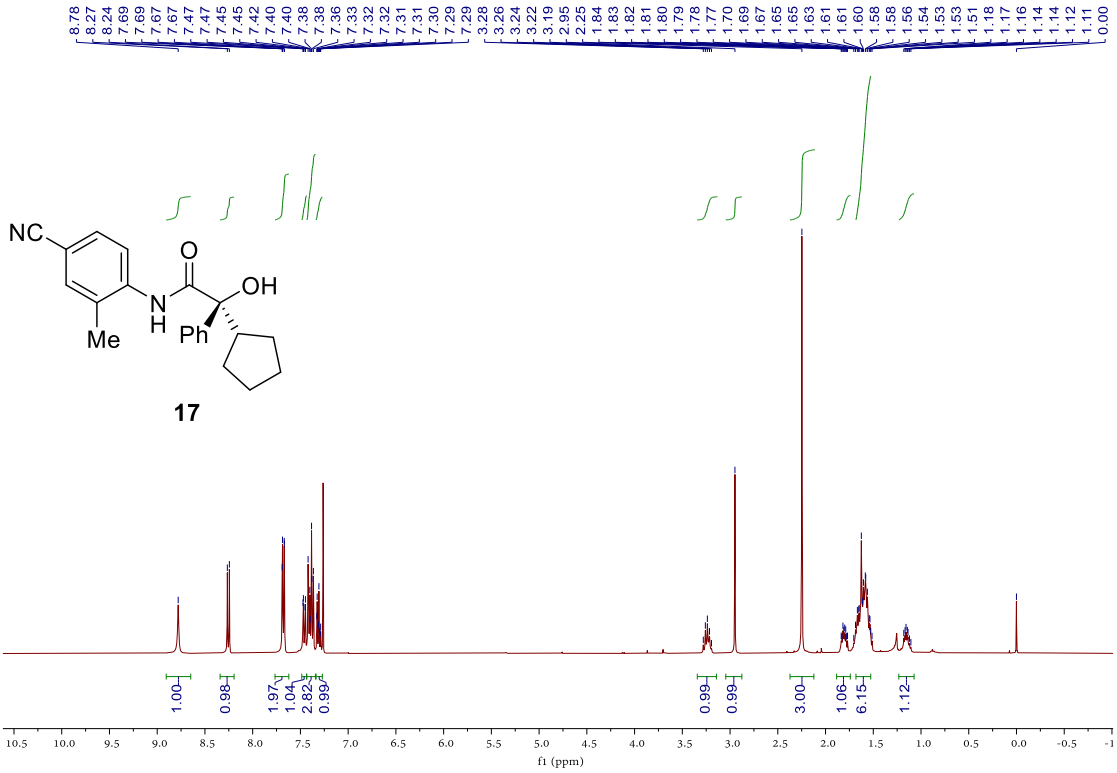

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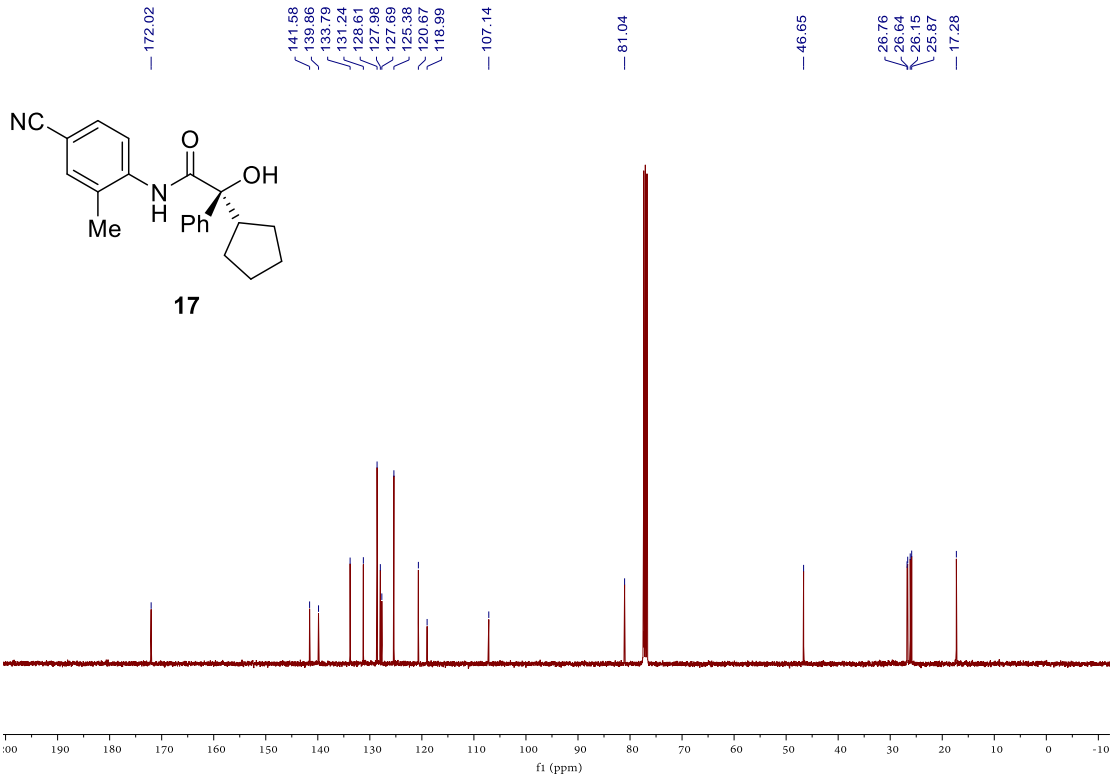

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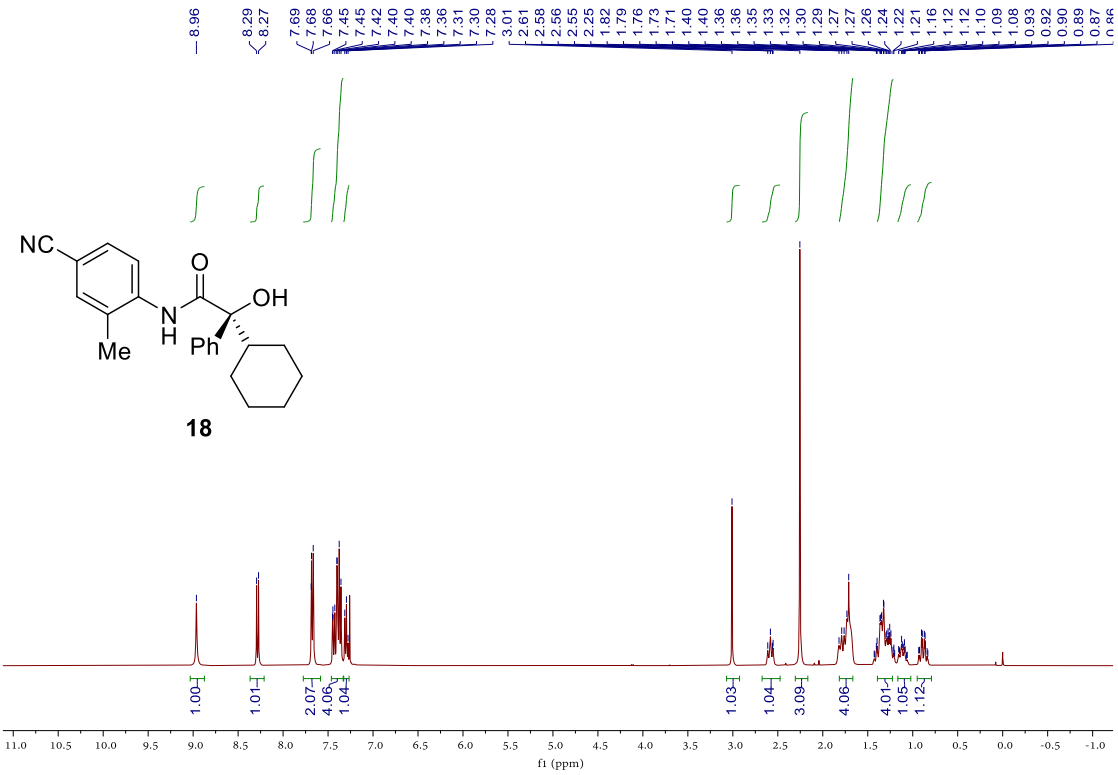

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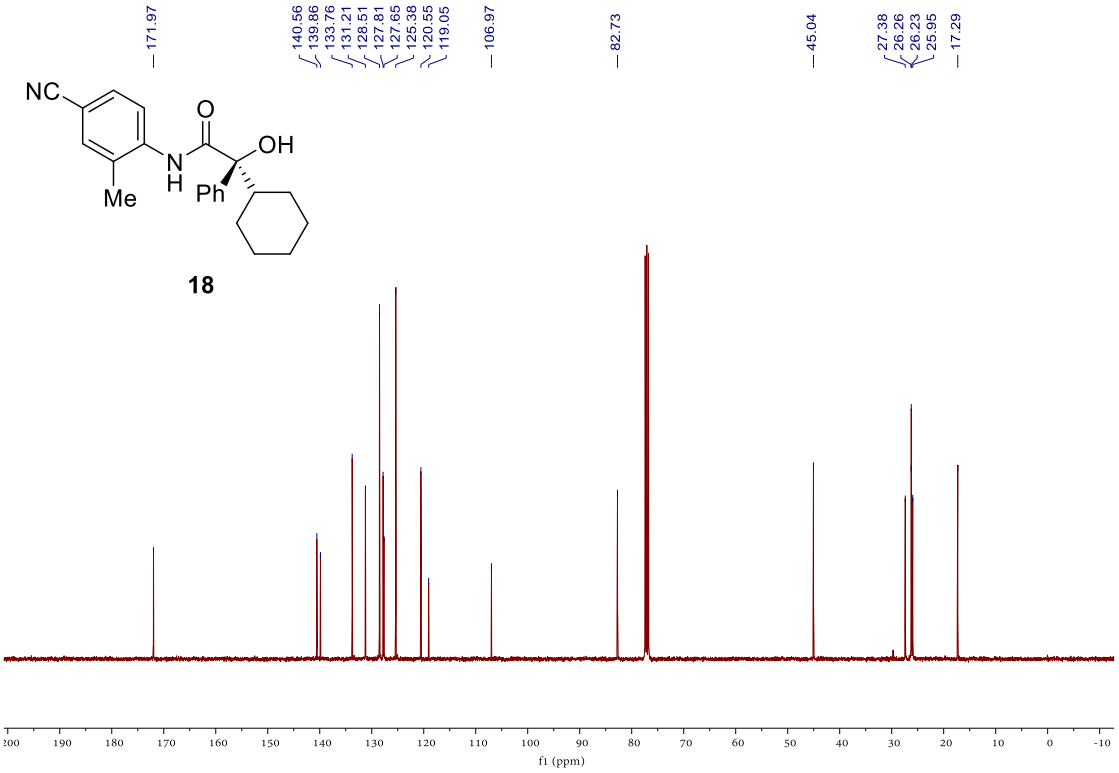
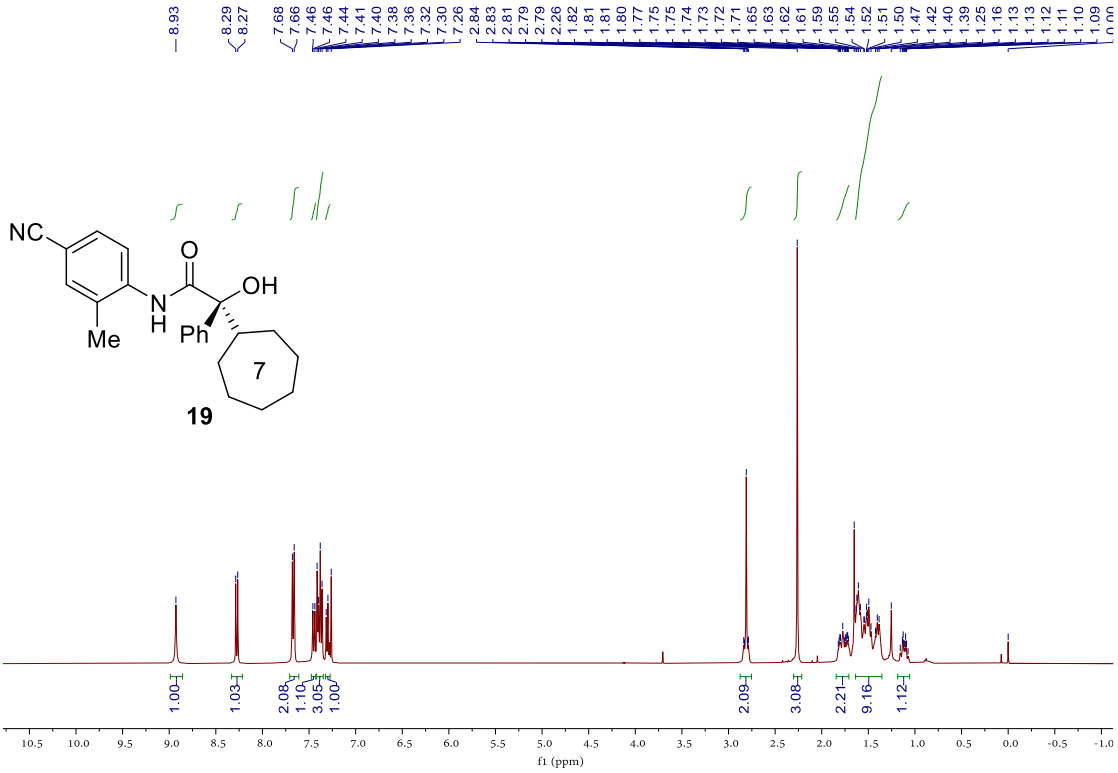
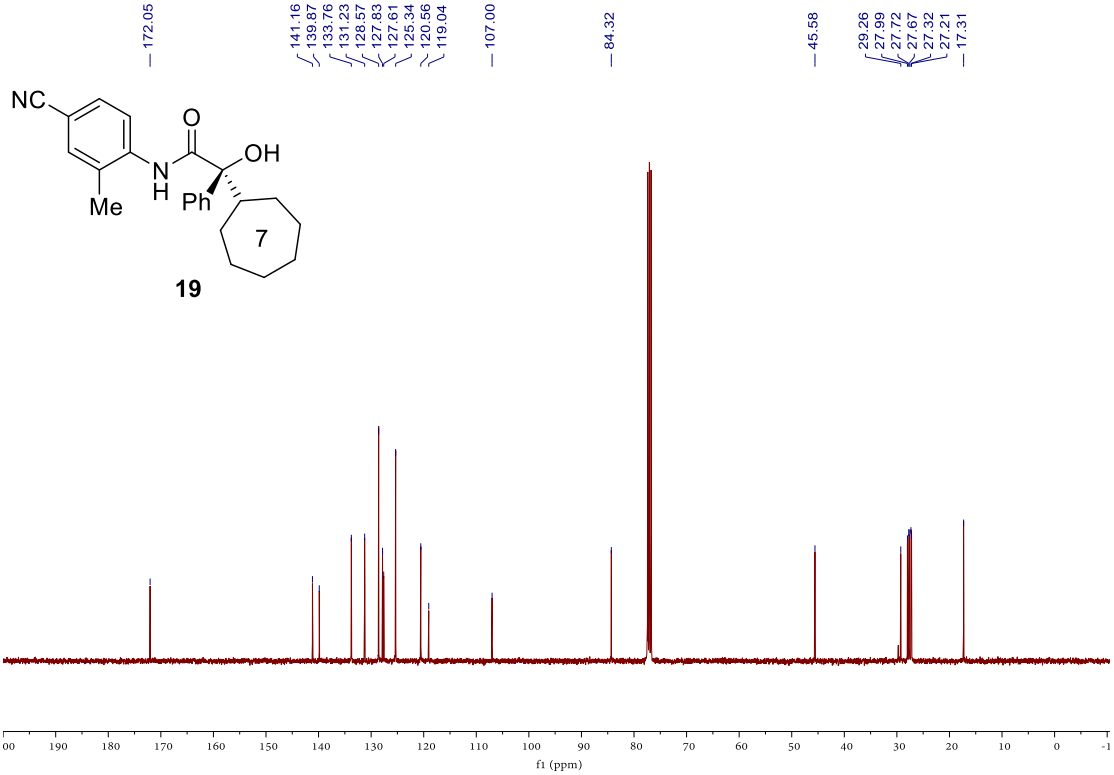


^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



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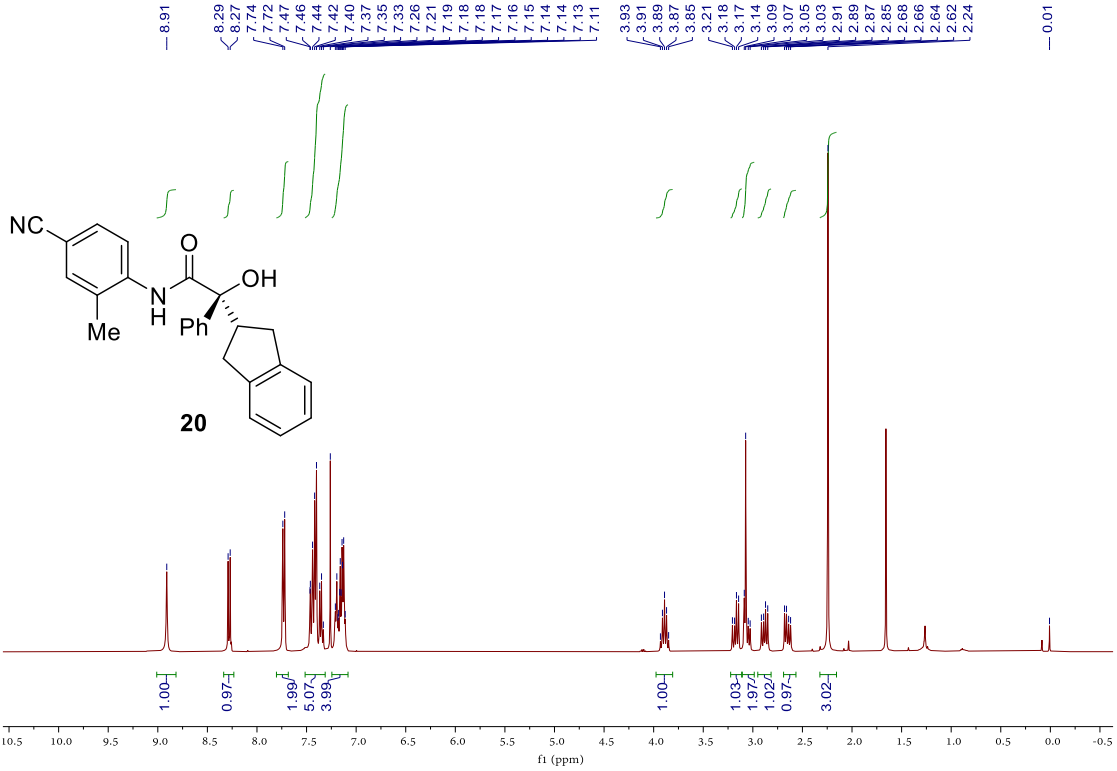

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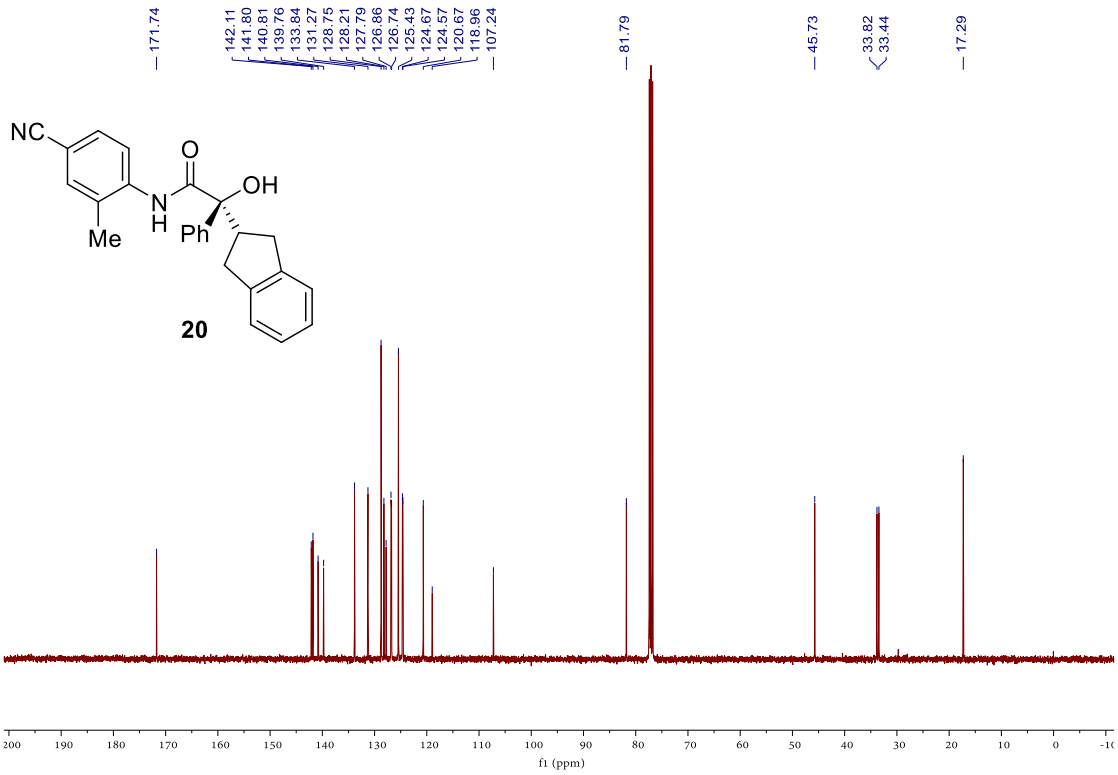

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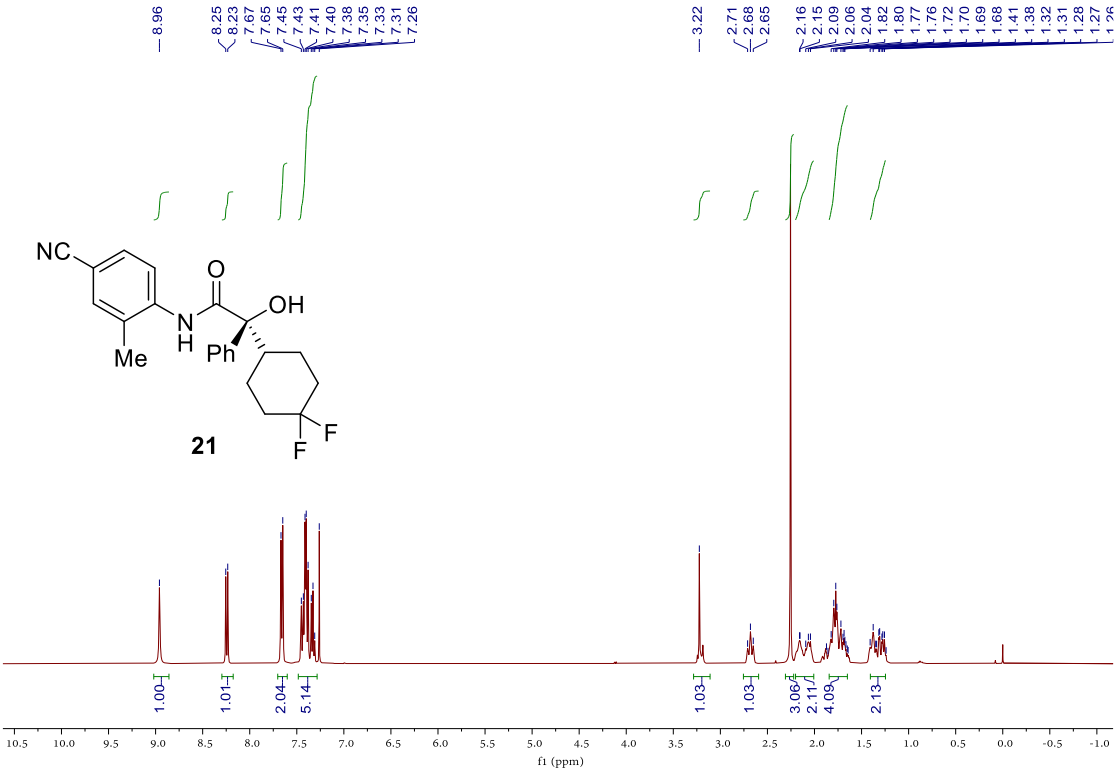
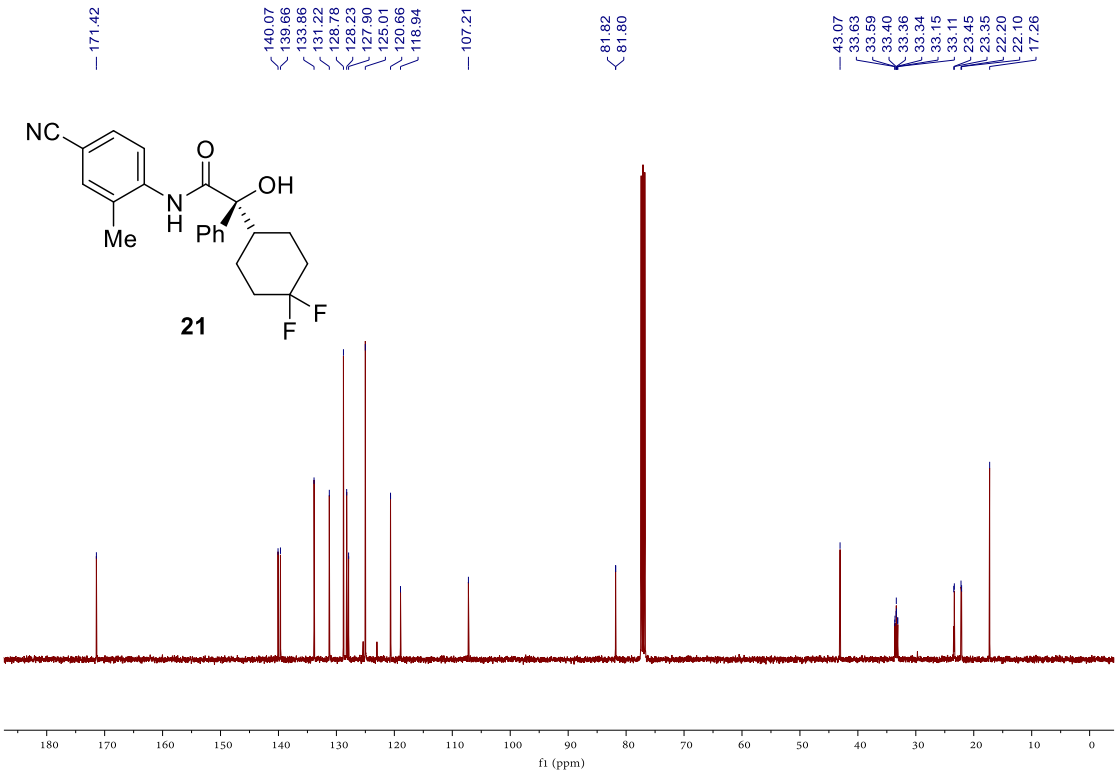


^{13}C NMR (100 MHz, $CDCl_3$)



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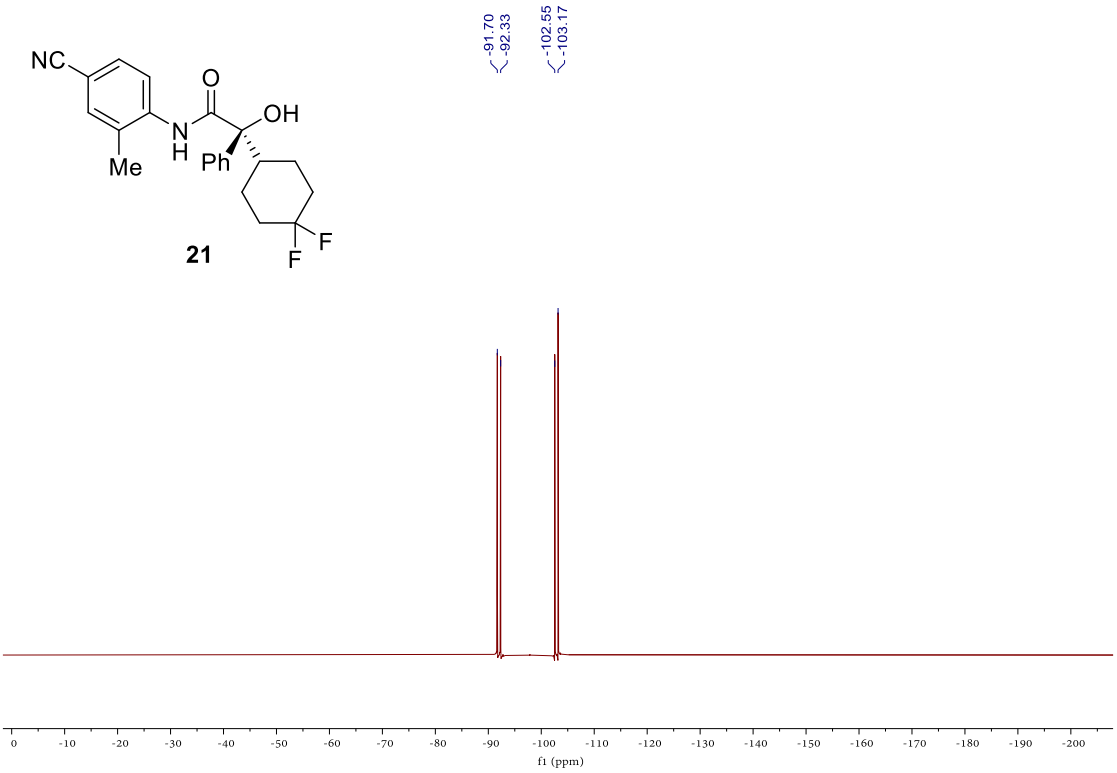

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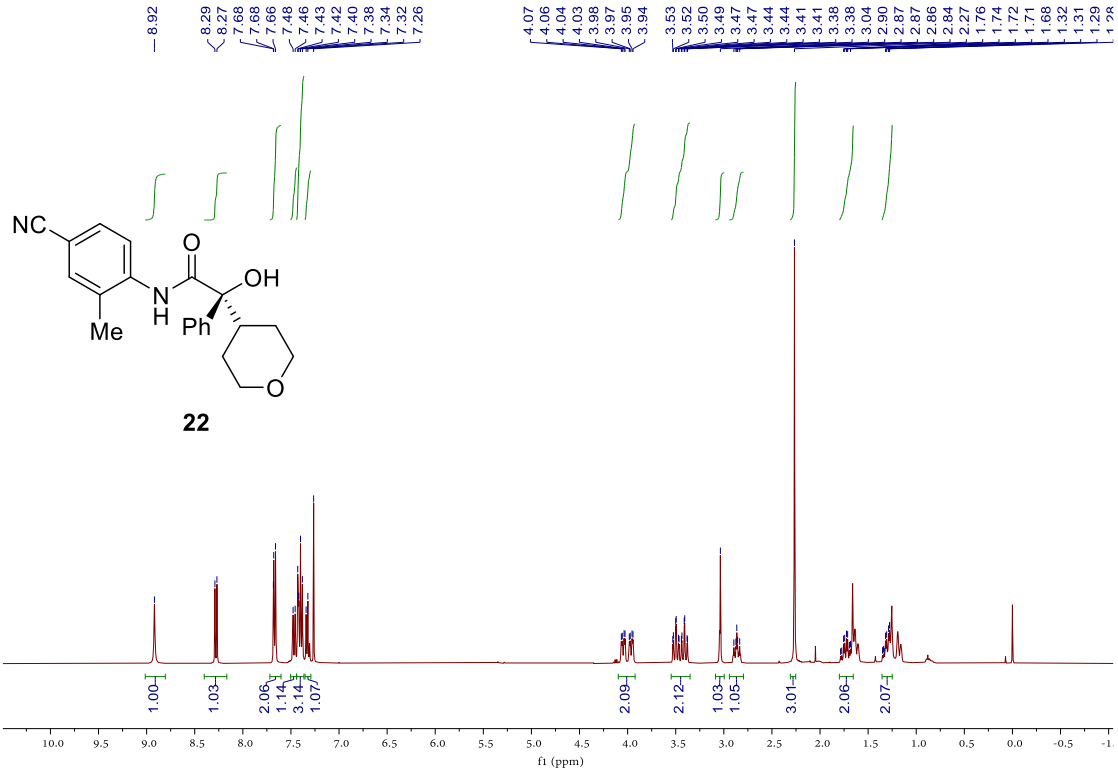

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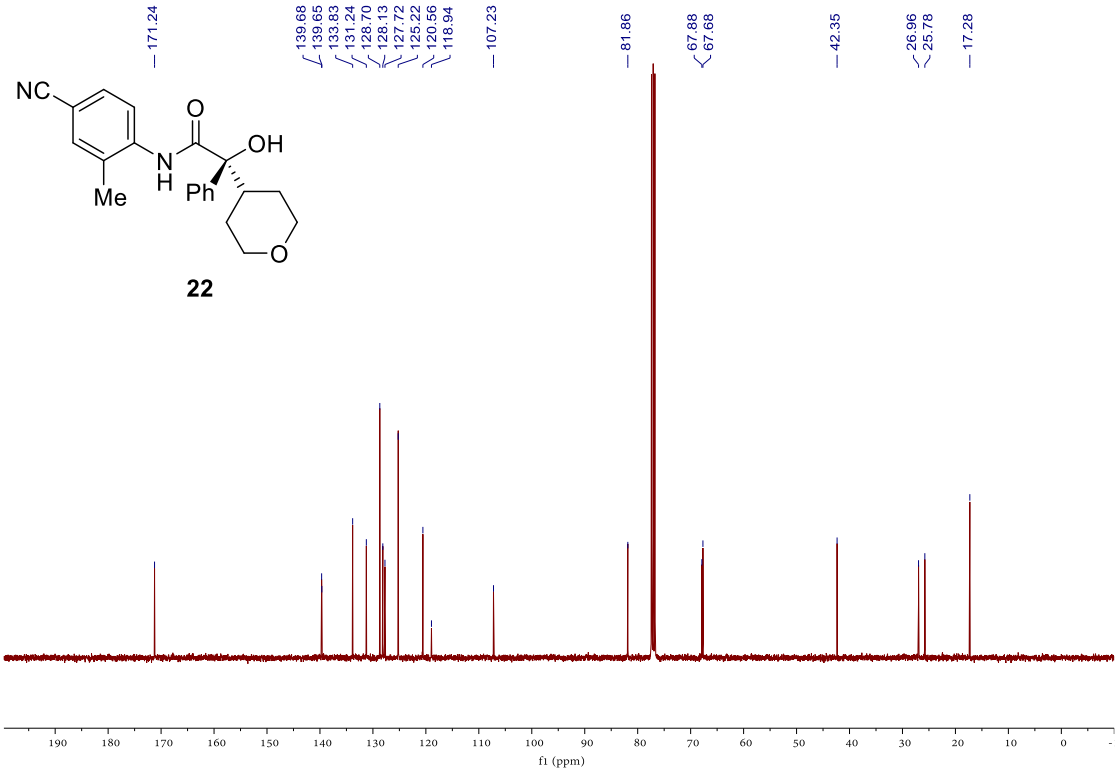

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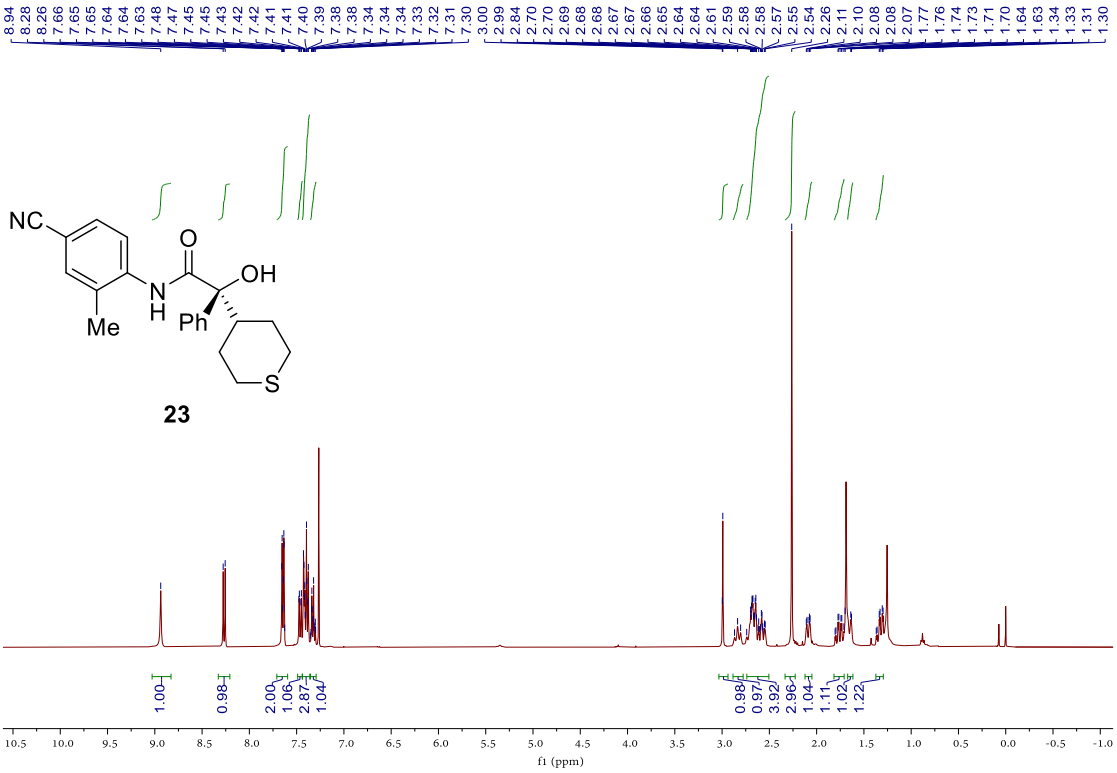

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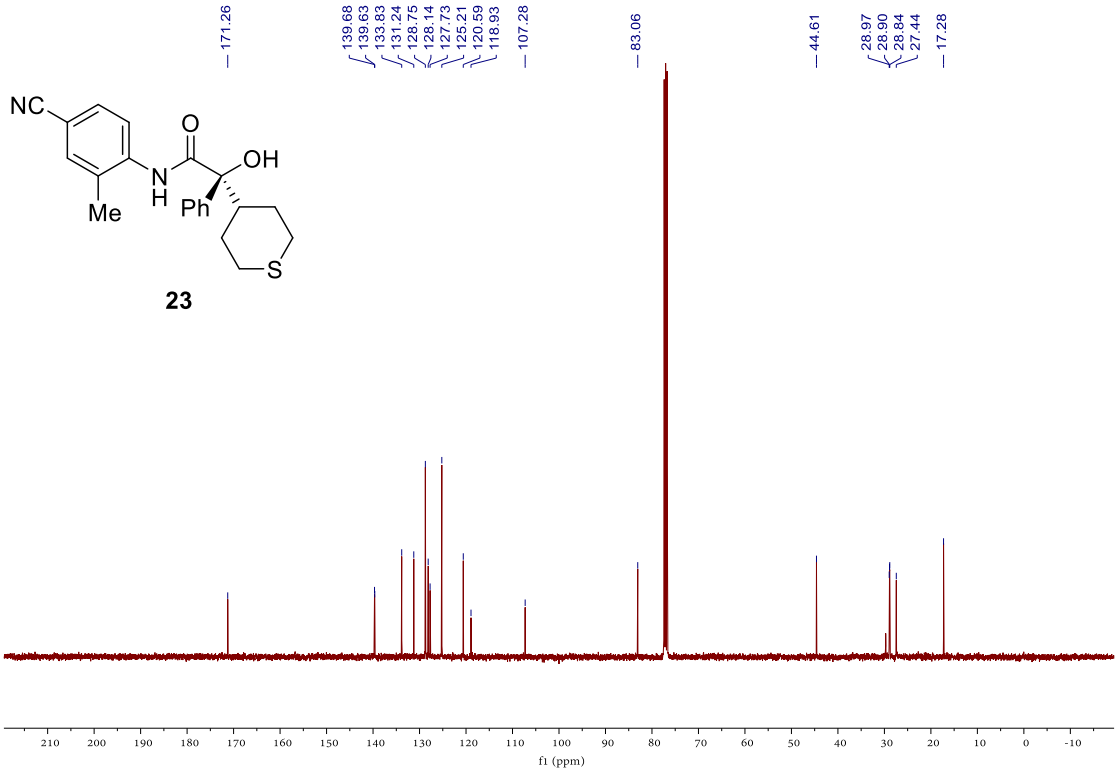
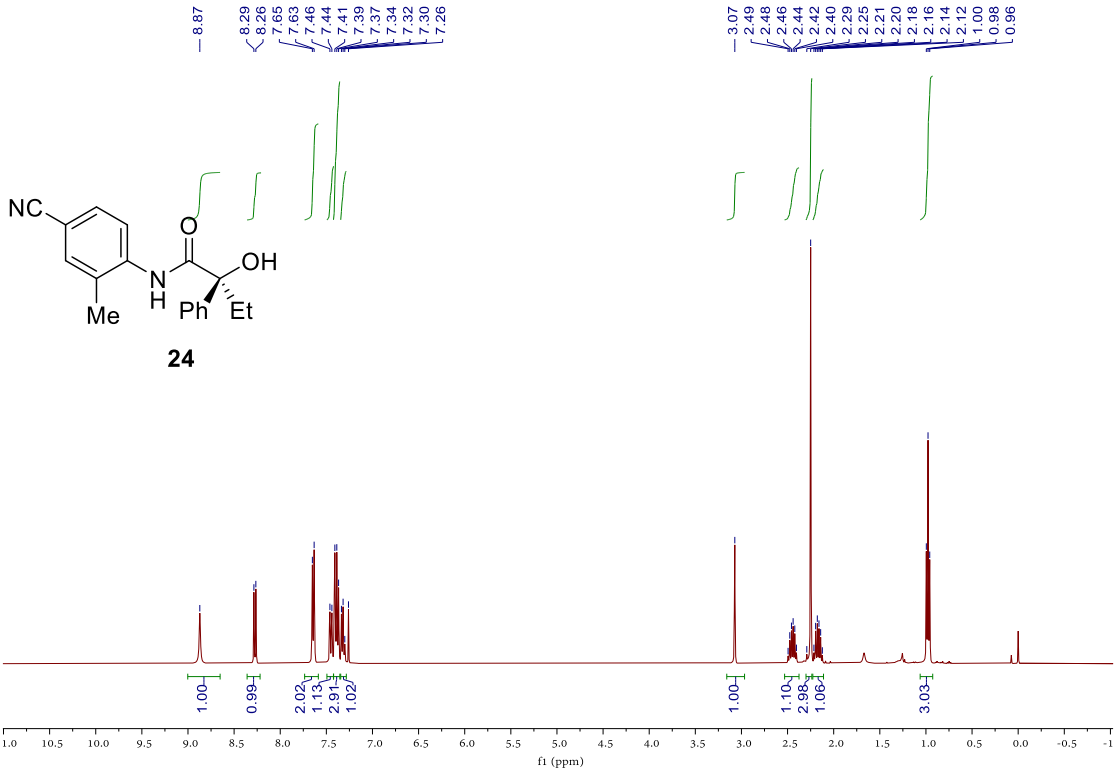
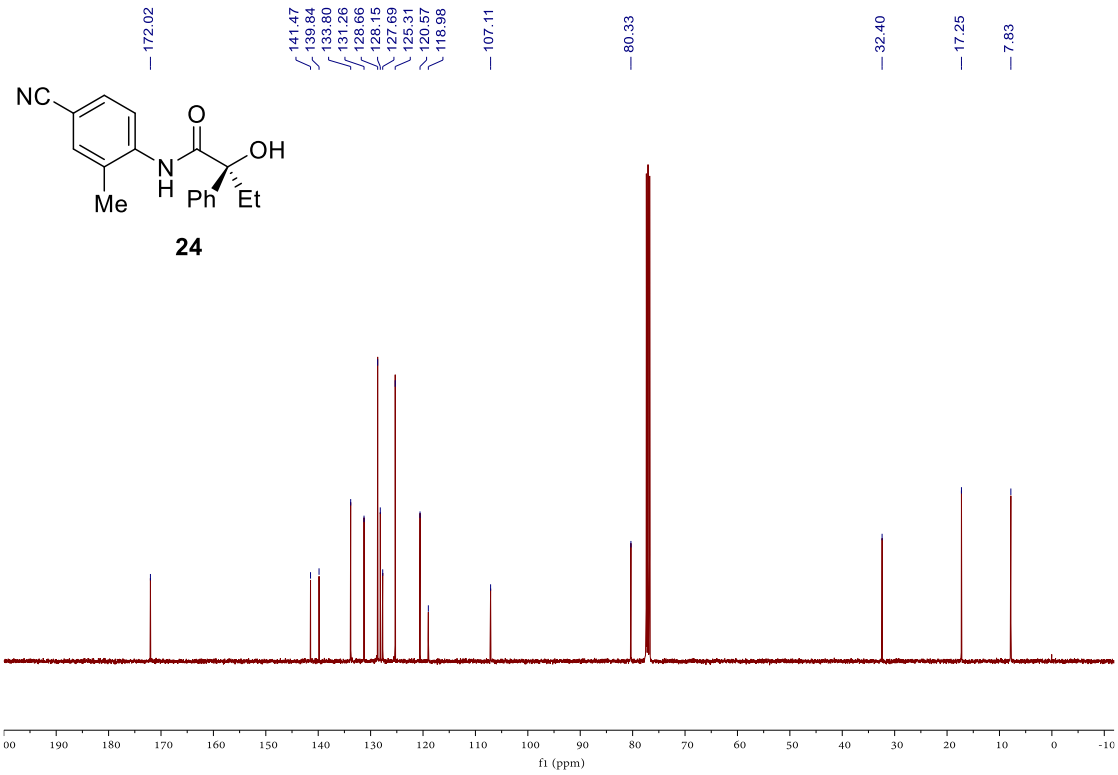


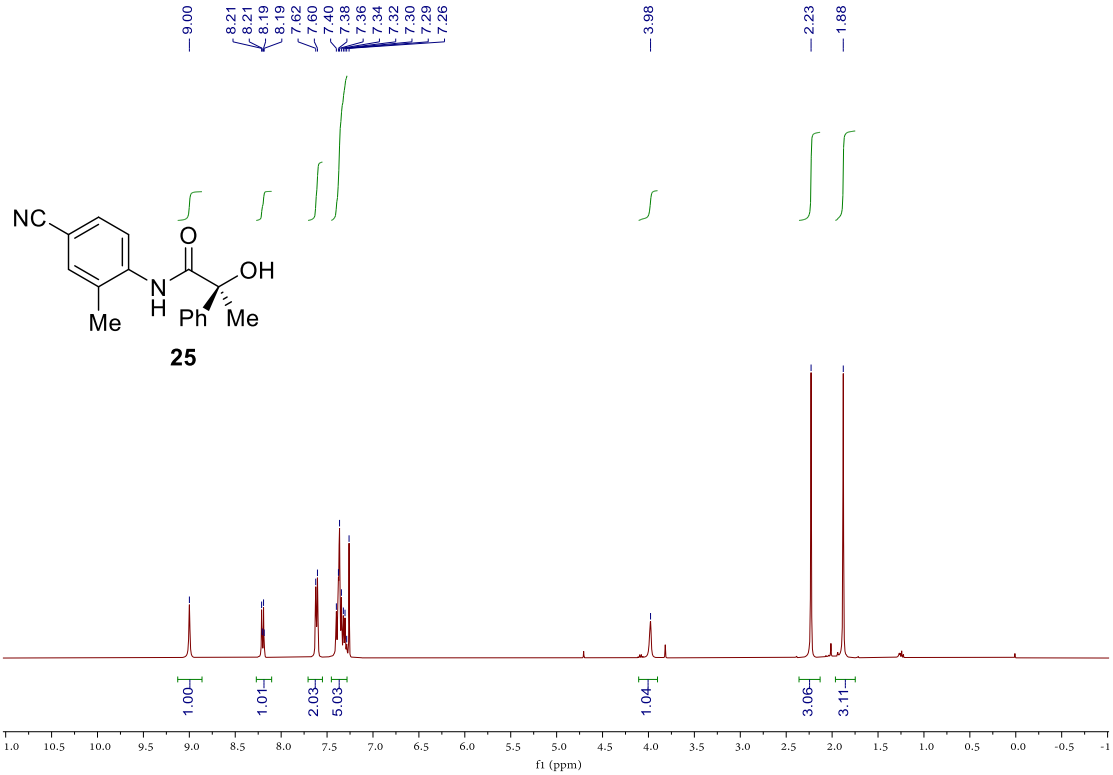
^{1}H NMR (400 MHz, $CDCl_3$)



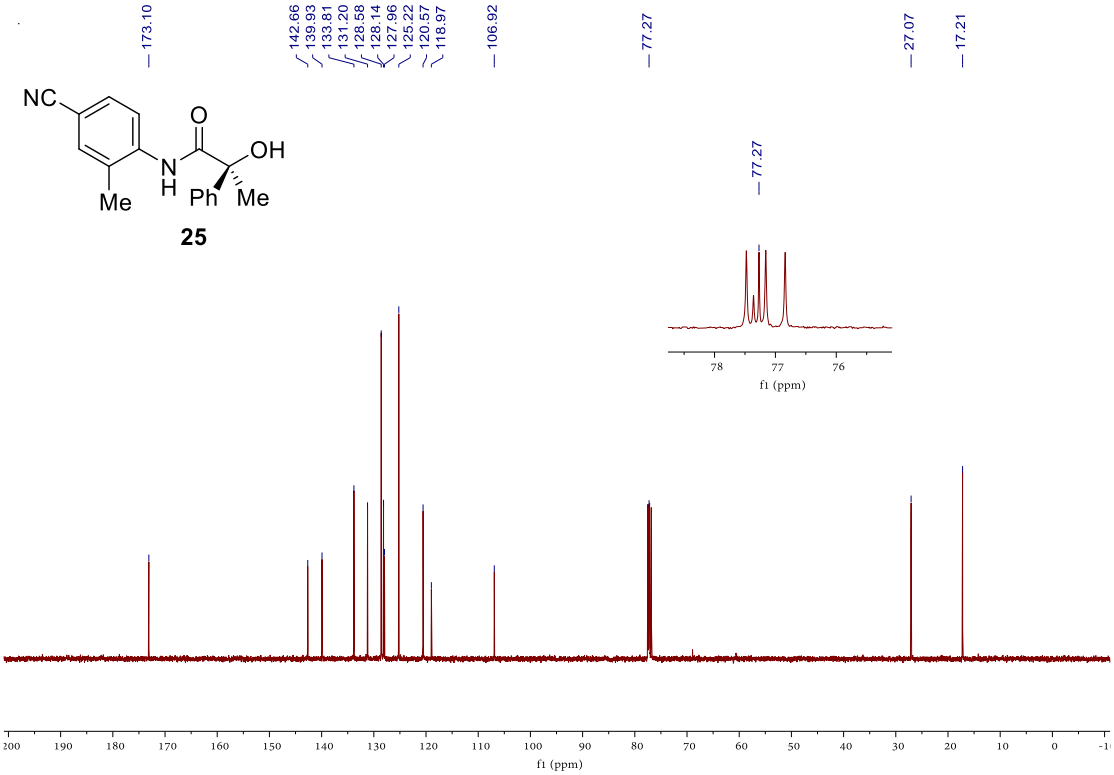
^{13}C NMR (100 MHz, $CDCl_3$)



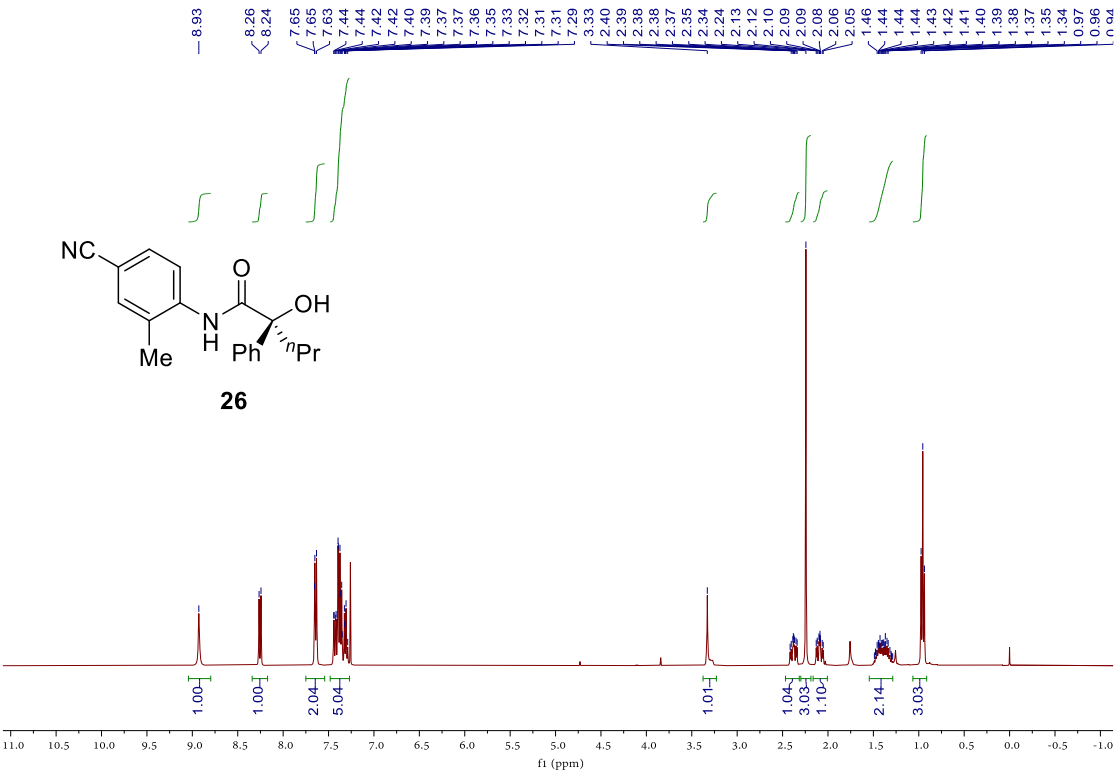
^{1}H NMR (400 MHz, $CDCl_3$)



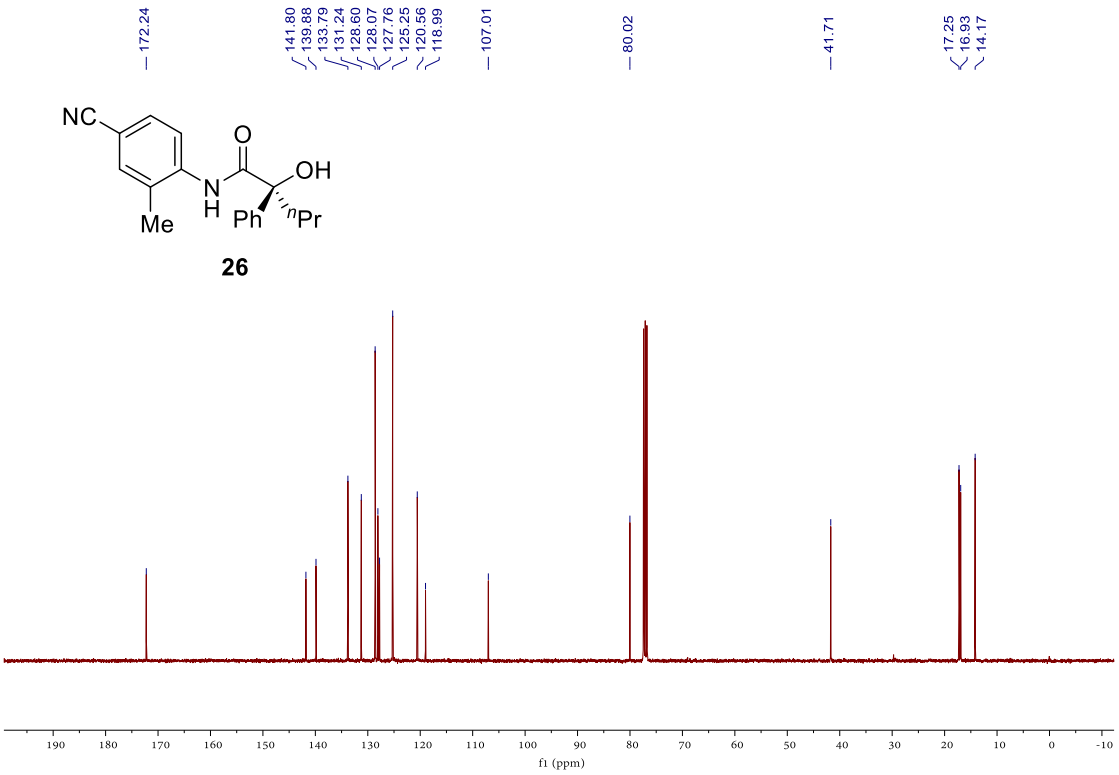
^{13}C NMR (100 MHz, $CDCl_3$)



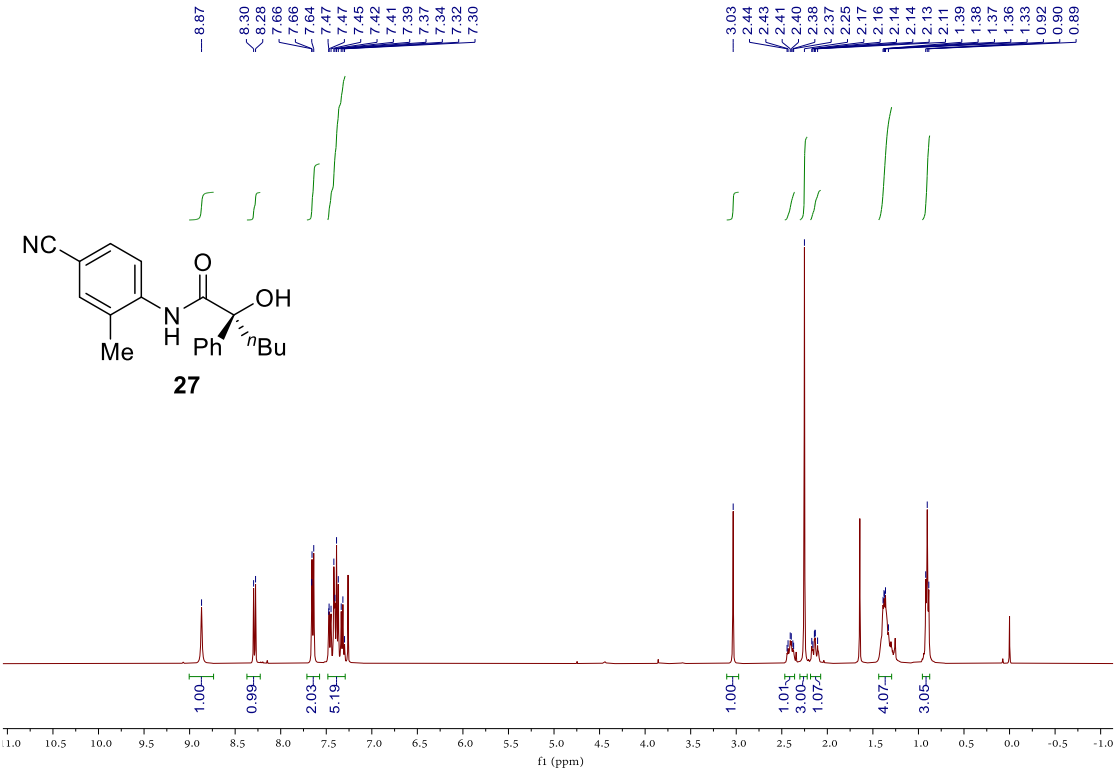
^{1}H NMR (400 MHz, $CDCl_3$)



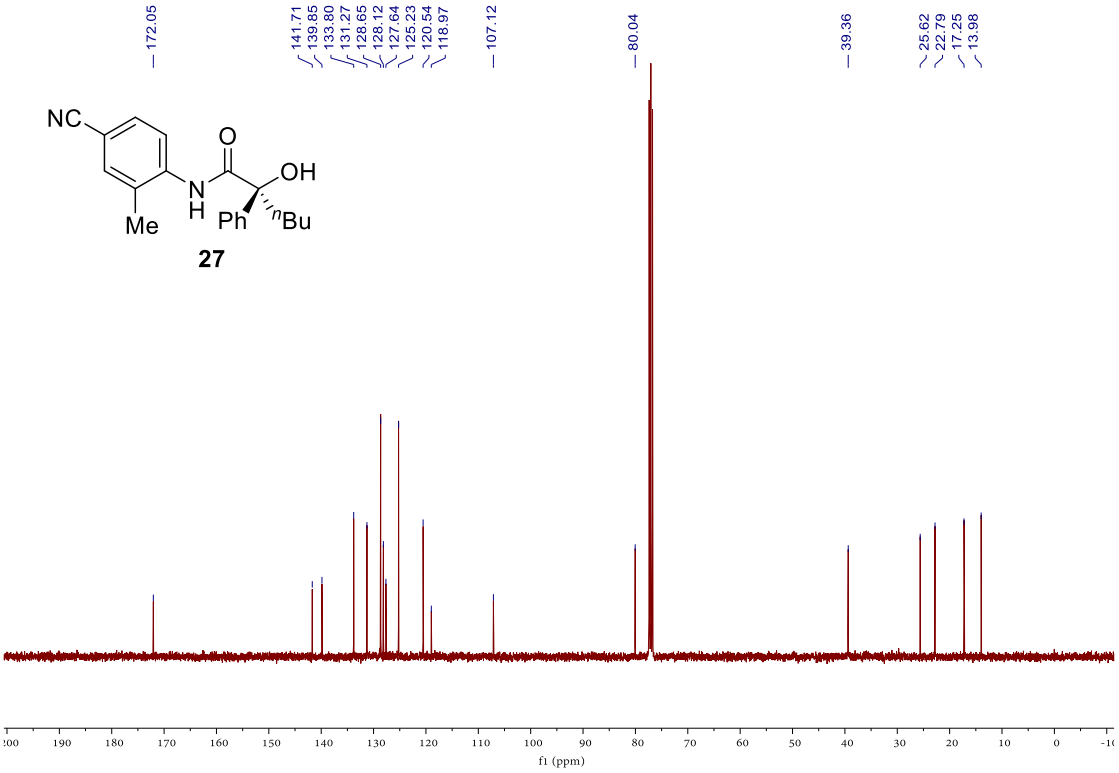
^{13}C NMR (100 MHz, $CDCl_3$)



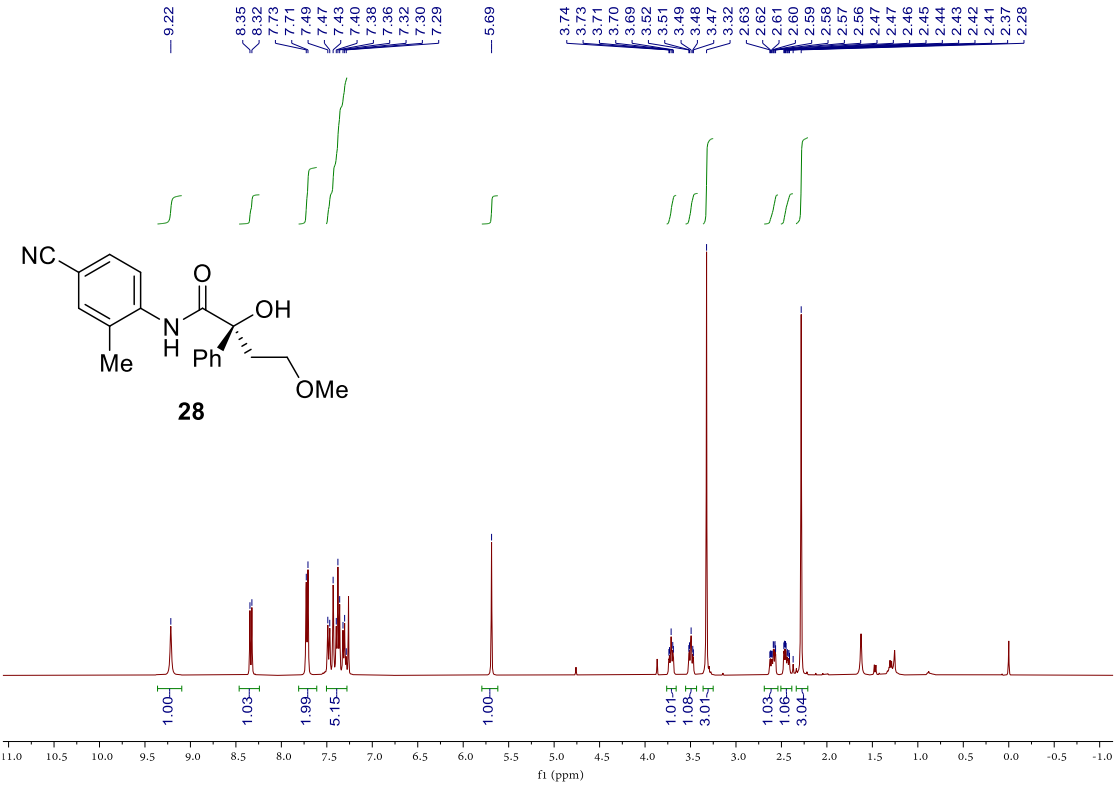
^{1}H NMR (400 MHz, $CDCl_3$)



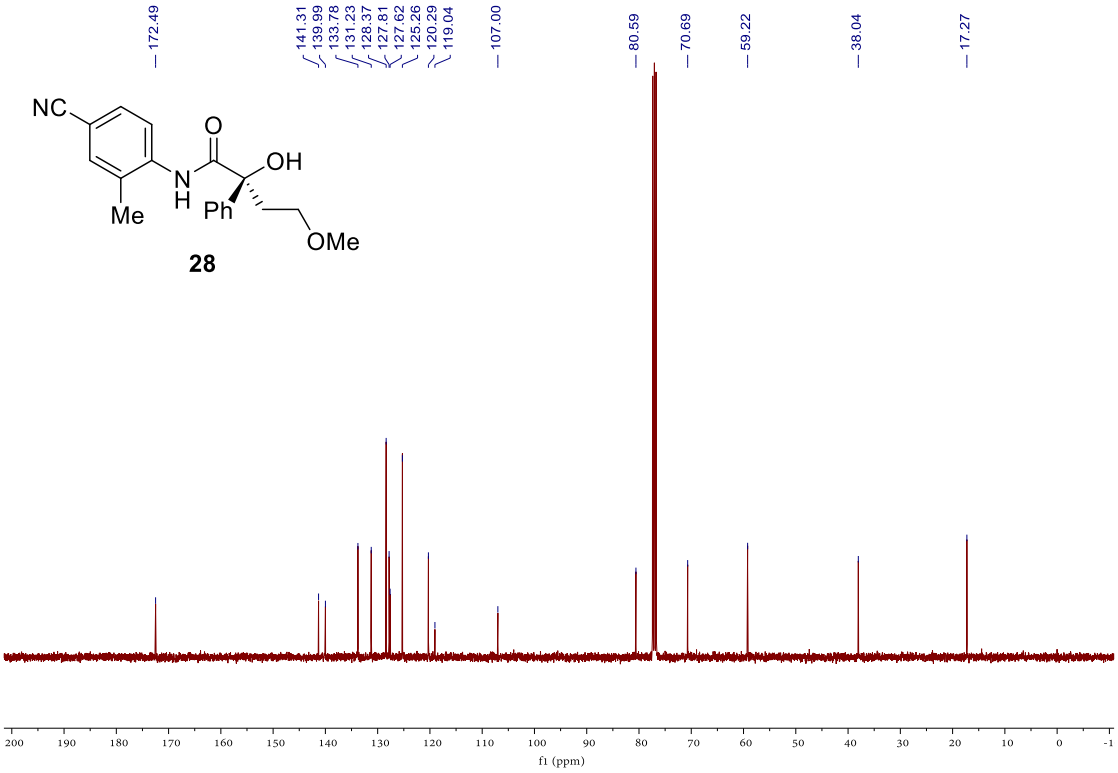
^{13}C NMR (100 MHz, $CDCl_3$)



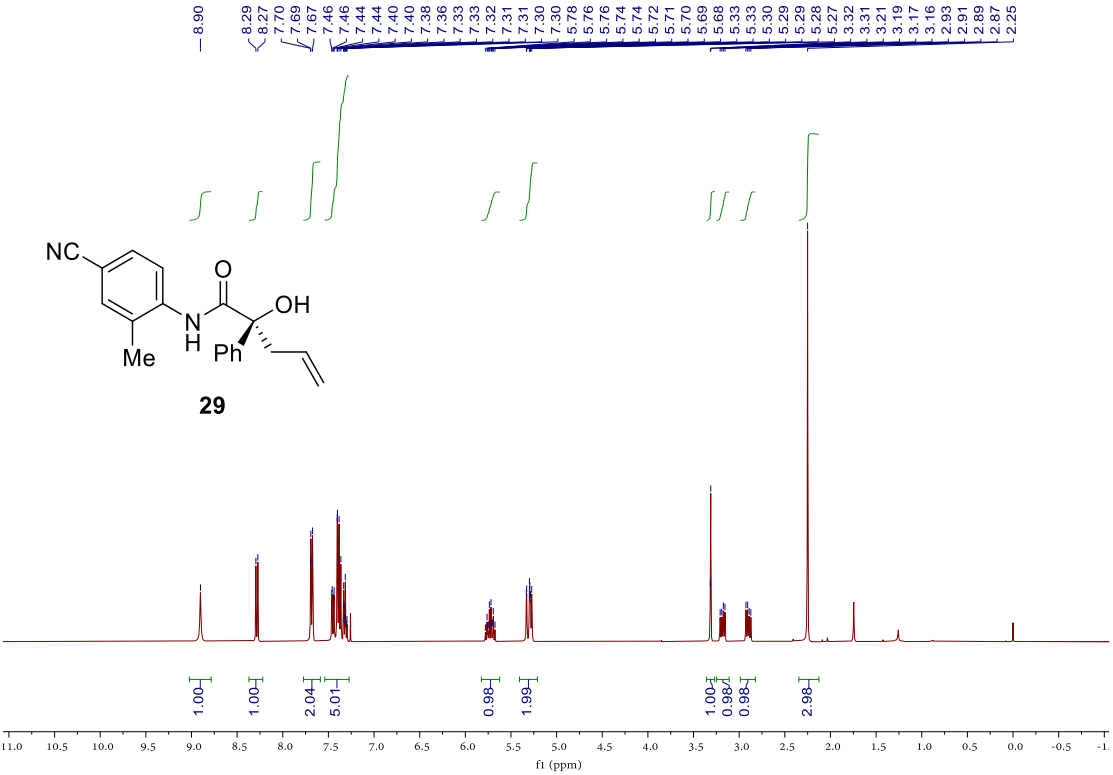
^{1}H NMR (400 MHz, $CDCl_3$)



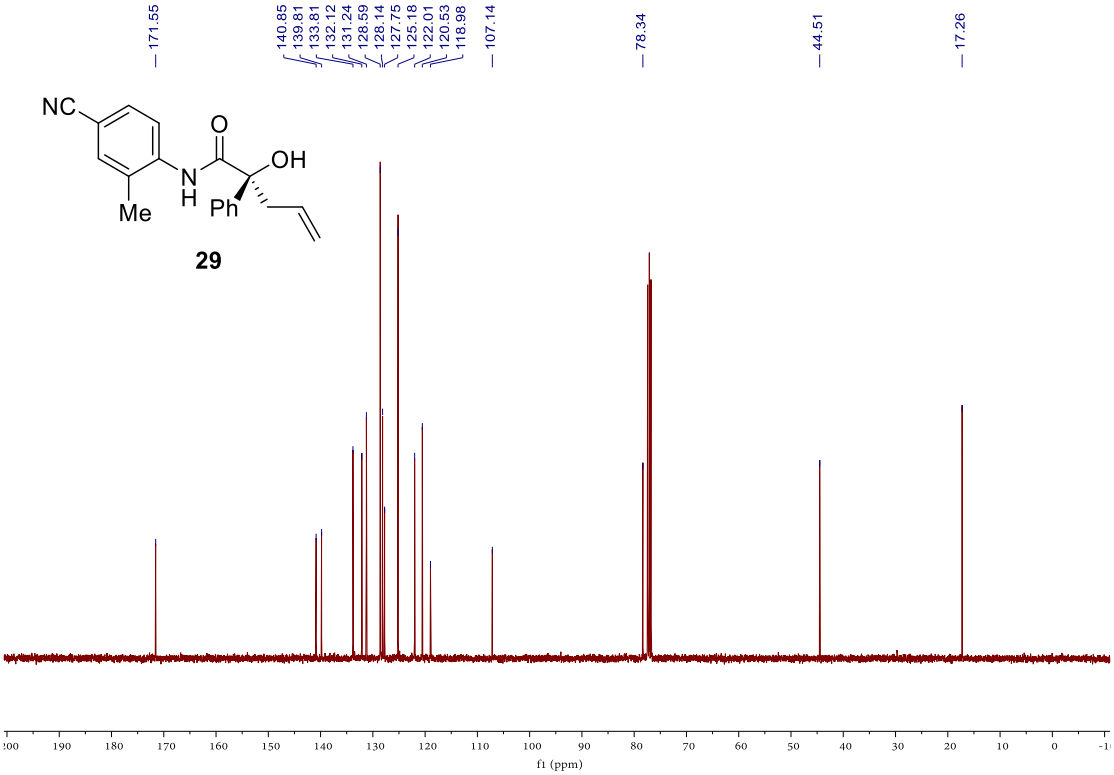
^{13}C NMR (100 MHz, $CDCl_3$)



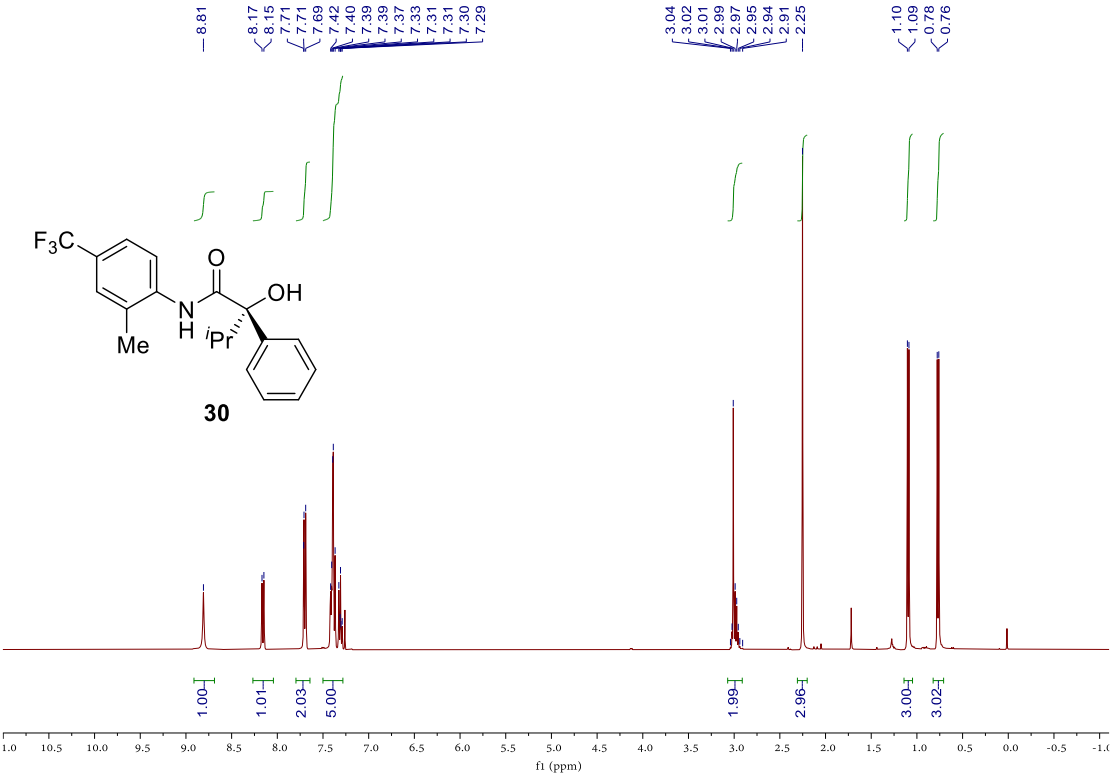
^{1}H NMR (400 MHz, $CDCl_3$)



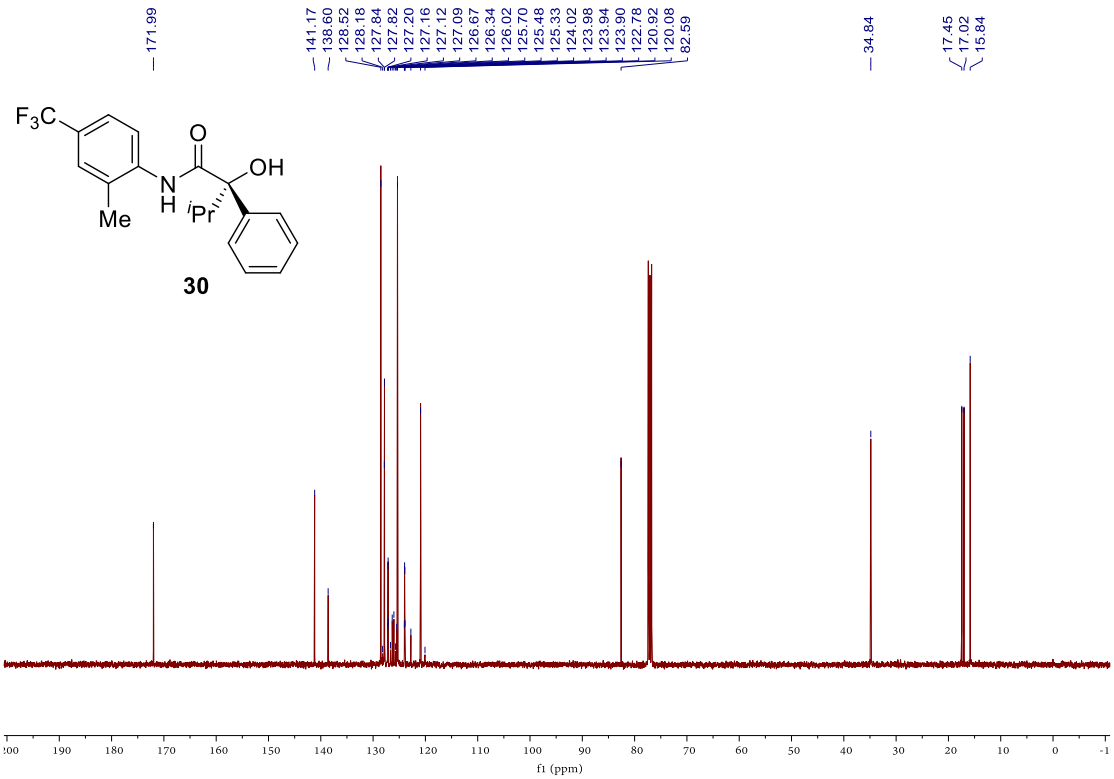
^{13}C NMR (100 MHz, $CDCl_3$)



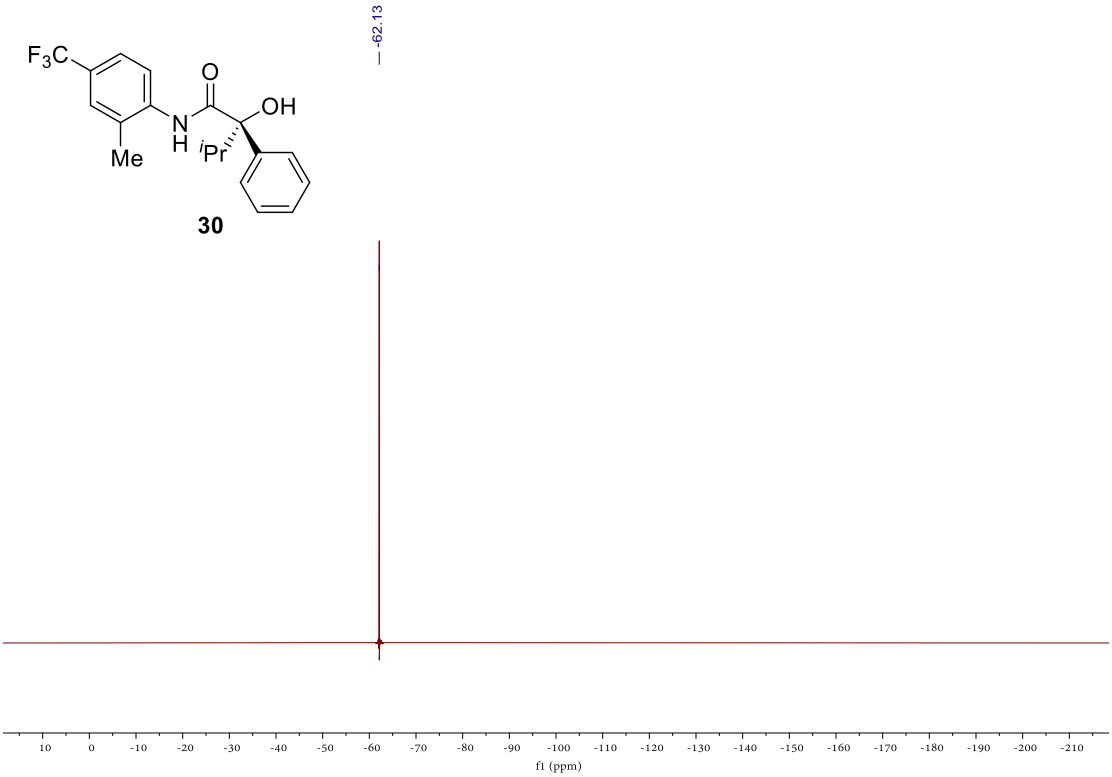
^{1}H NMR (400 MHz, $CDCl_3$)



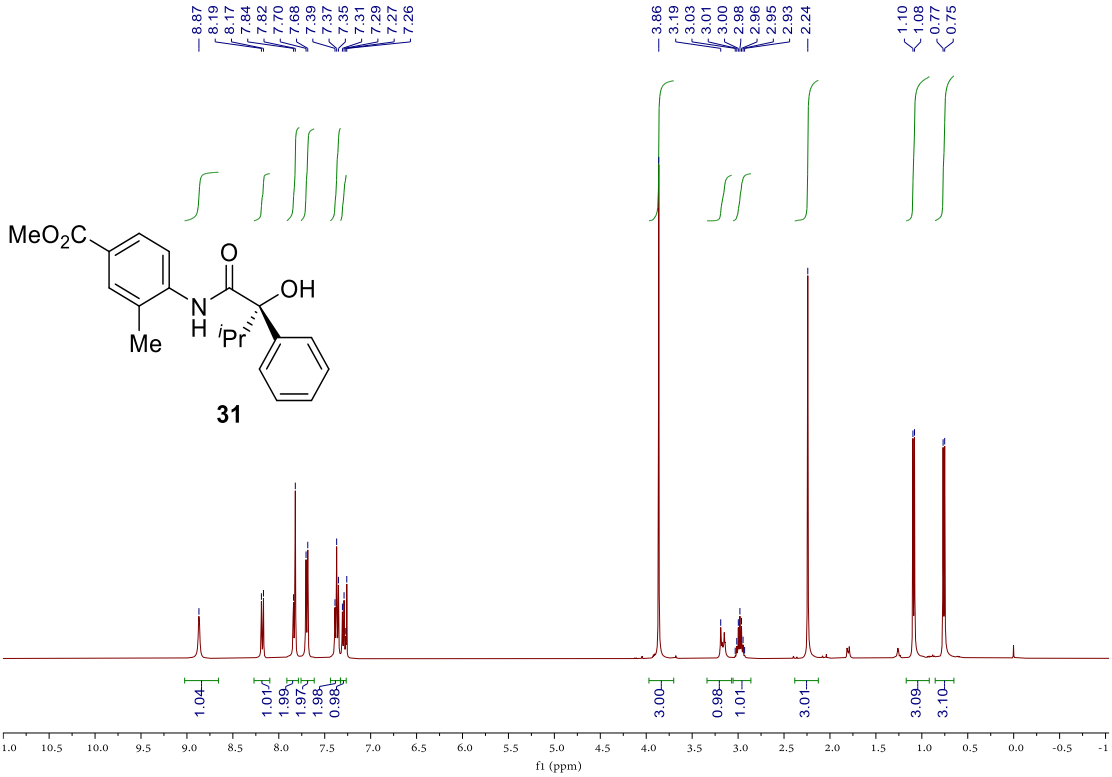
^{13}C NMR (100 MHz, $CDCl_3$)



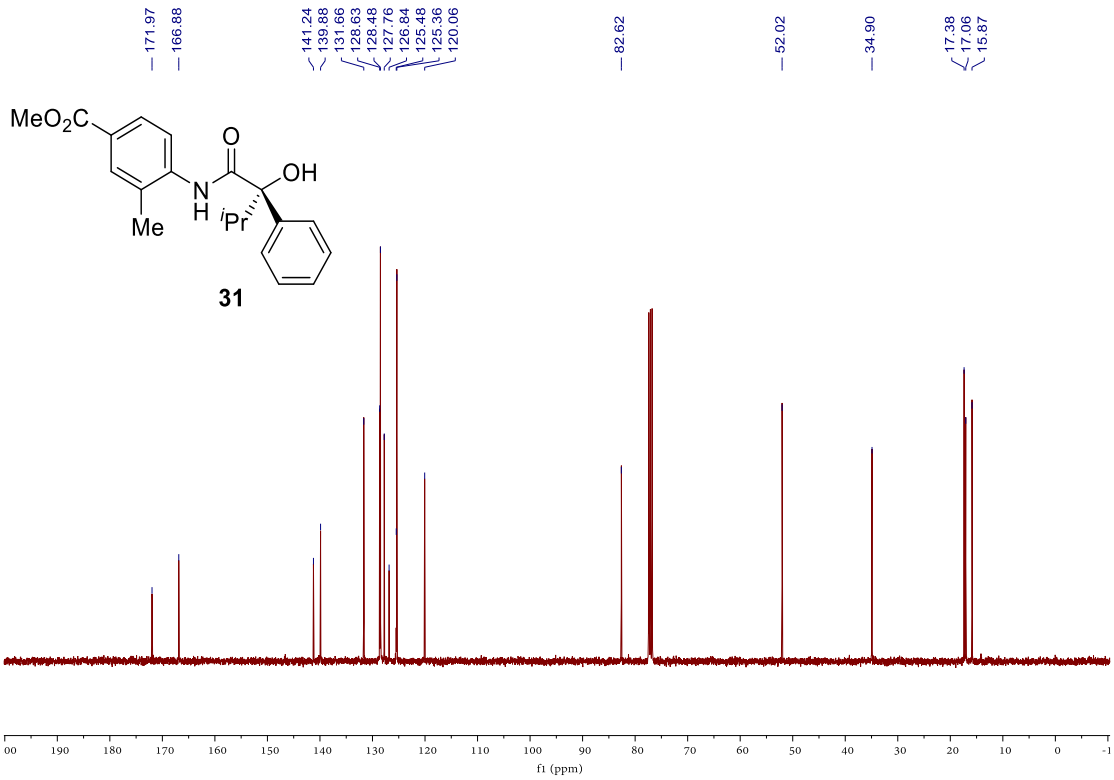
^{19}F NMR (376 MHz, $CDCl_3$)



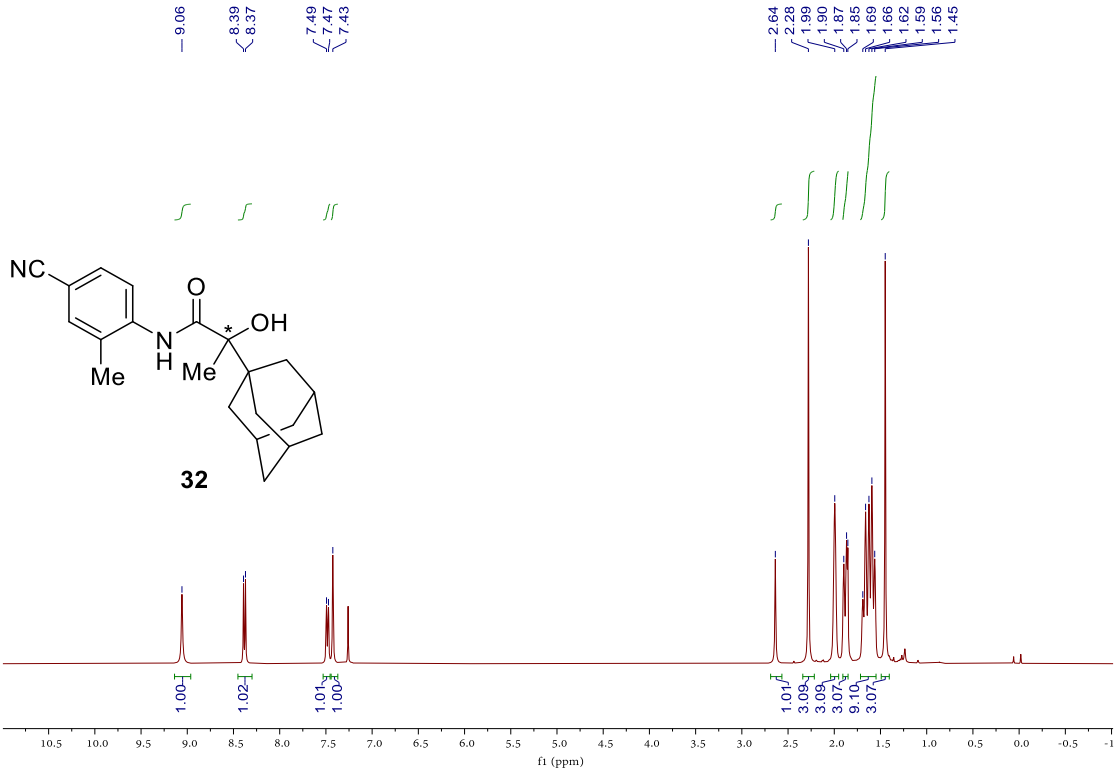
^{1}H NMR (400 MHz, $CDCl_3$)



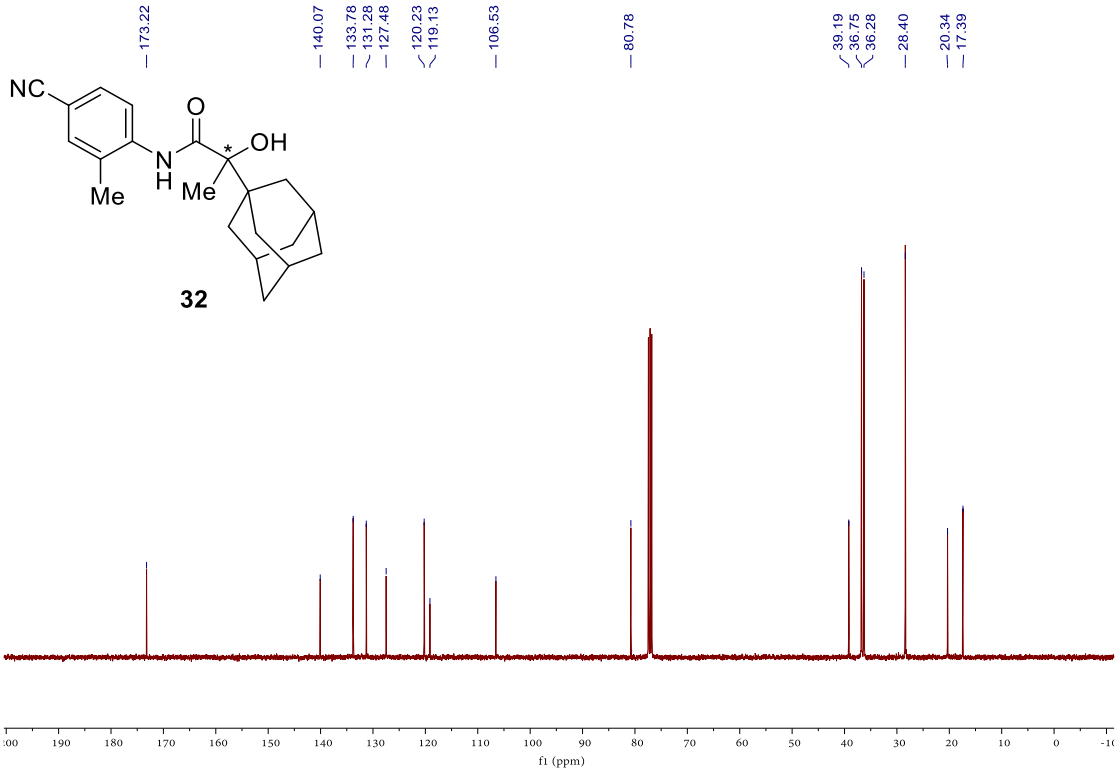
^{13}C NMR (100 MHz, $CDCl_3$)



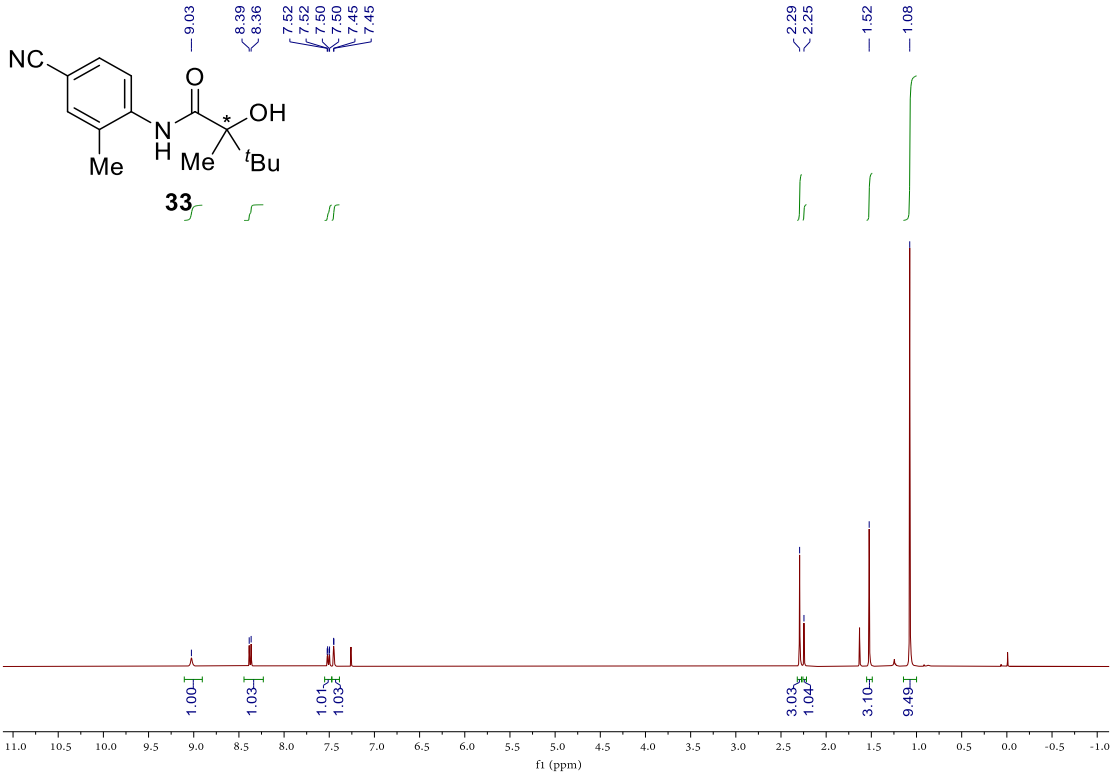
^{1}H NMR (400 MHz, $CDCl_3$)



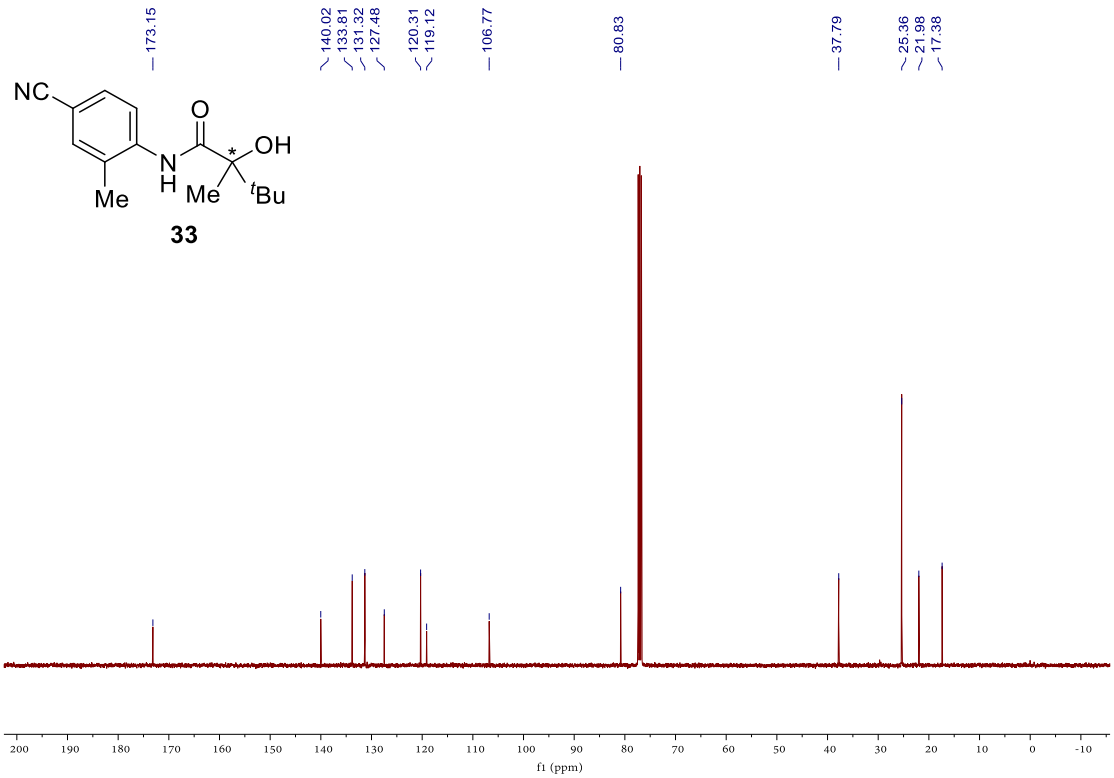
^{13}C NMR (100 MHz, $CDCl_3$)



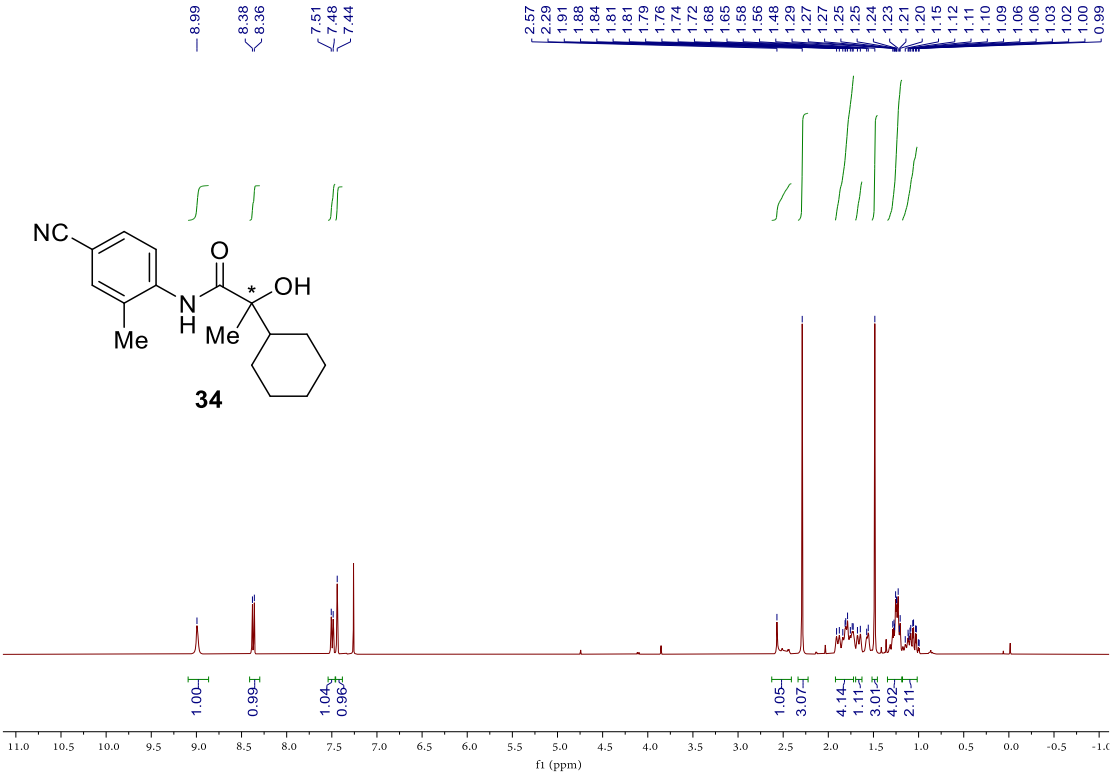
^{1}H NMR (400 MHz, $CDCl_3$)



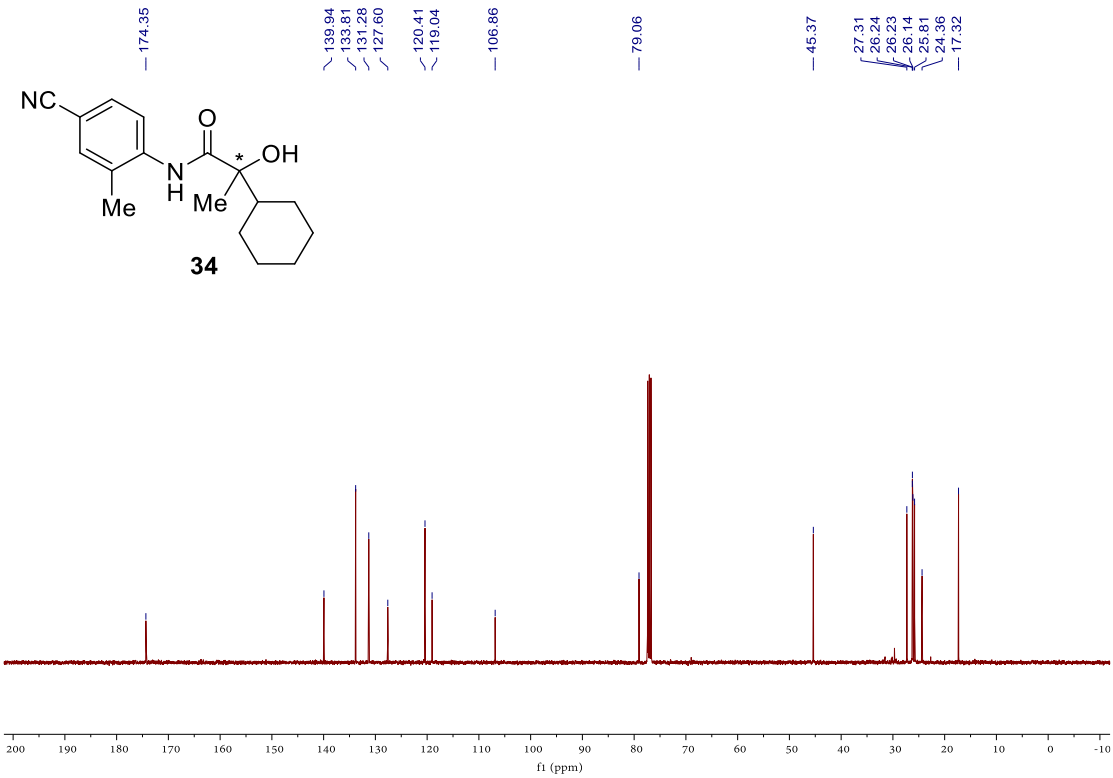
^{13}C NMR (100 MHz, $CDCl_3$)



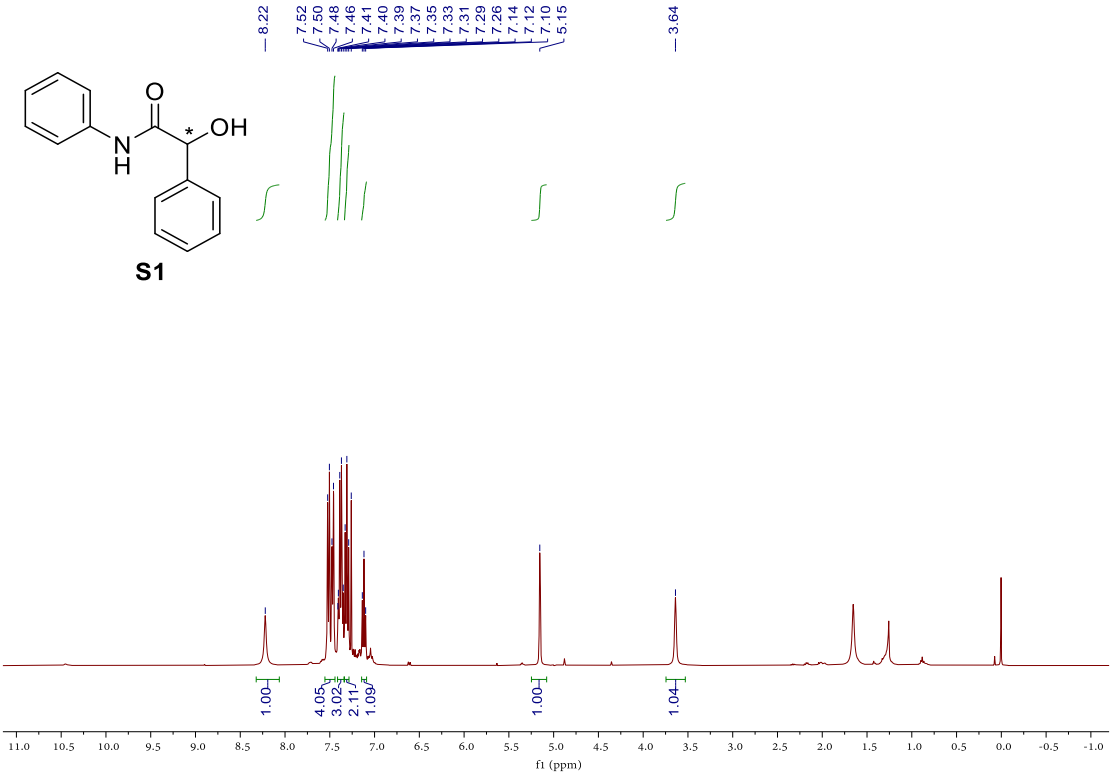
^{1}H NMR (400 MHz, $CDCl_3$)



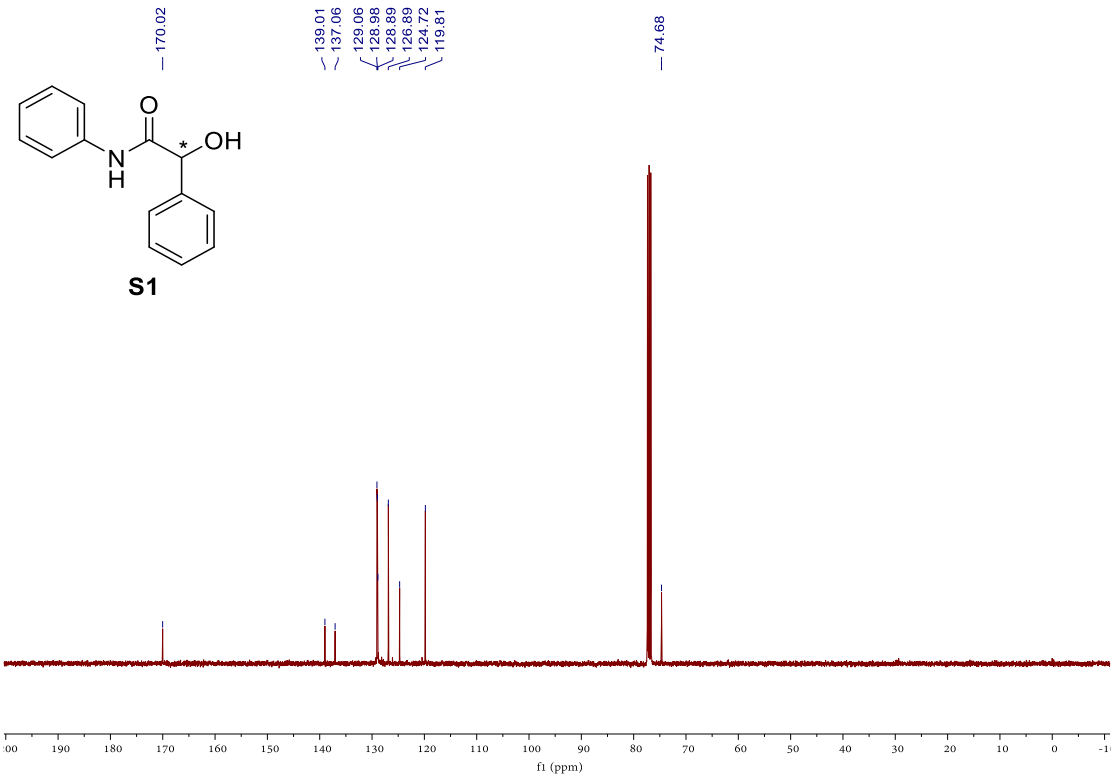
^{13}C NMR (100 MHz, $CDCl_3$)



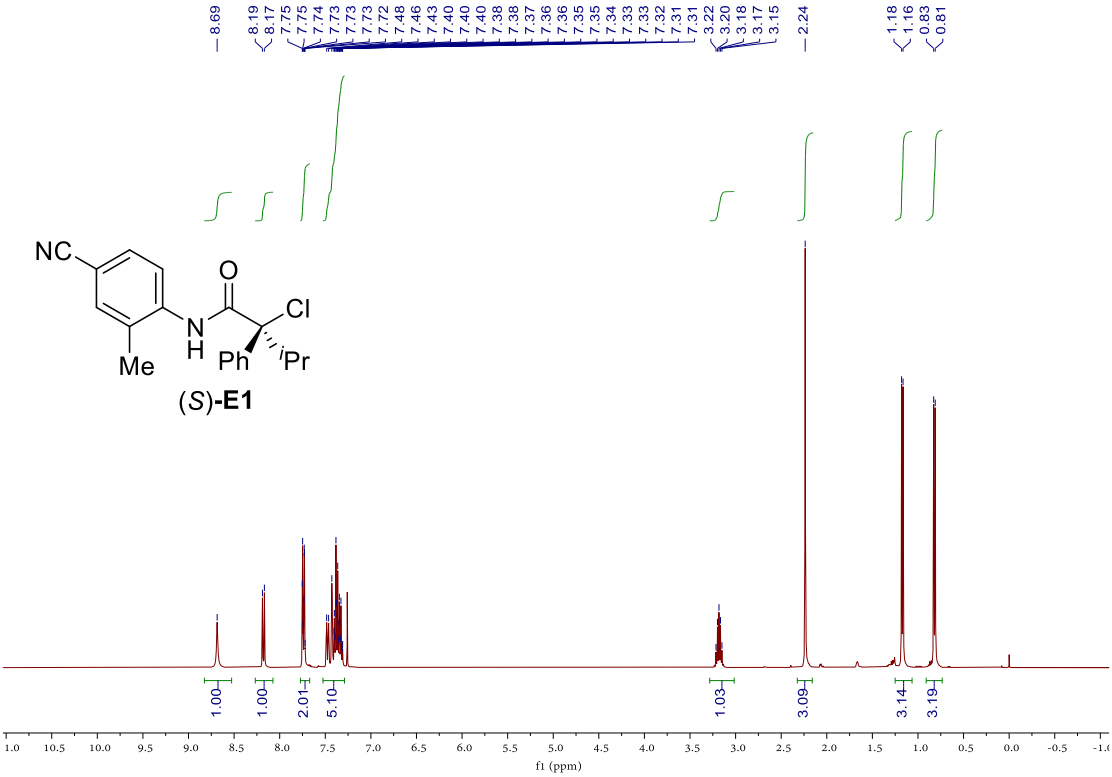
^{1}H NMR (400 MHz, $CDCl_3$)



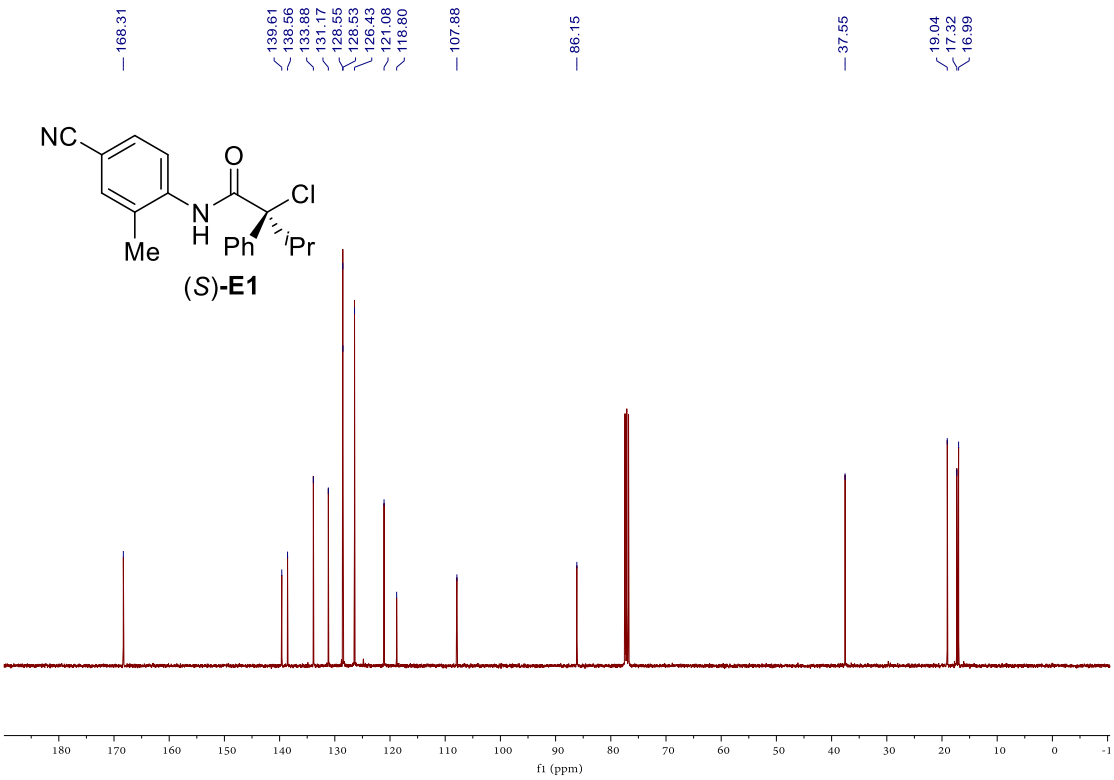
^{13}C NMR (100 MHz, $CDCl_3$)



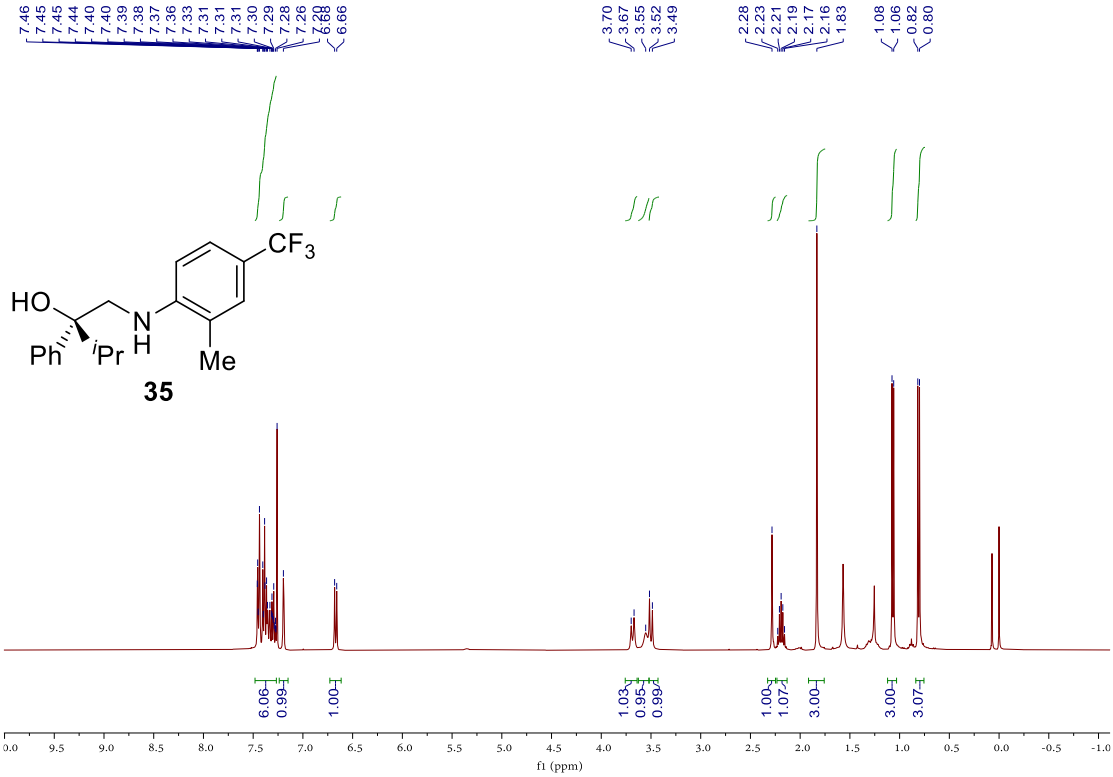
^{1}H NMR (400 MHz, $CDCl_3$)



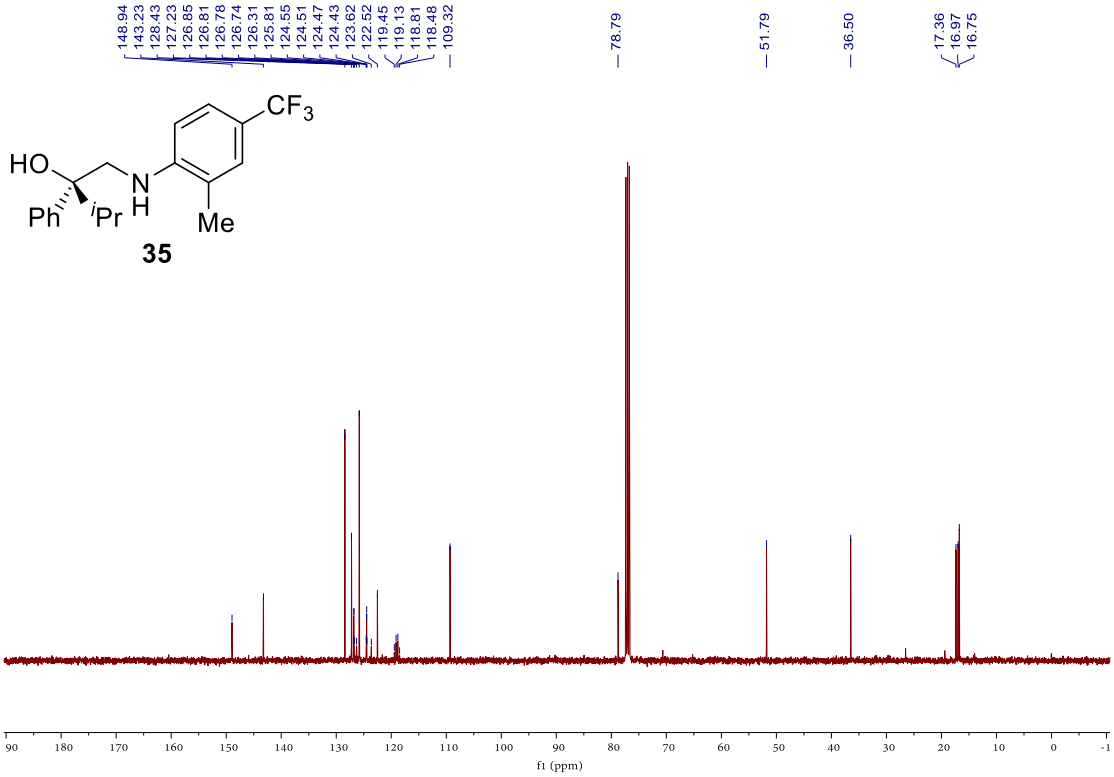
^{13}C NMR (100 MHz, $CDCl_3$)



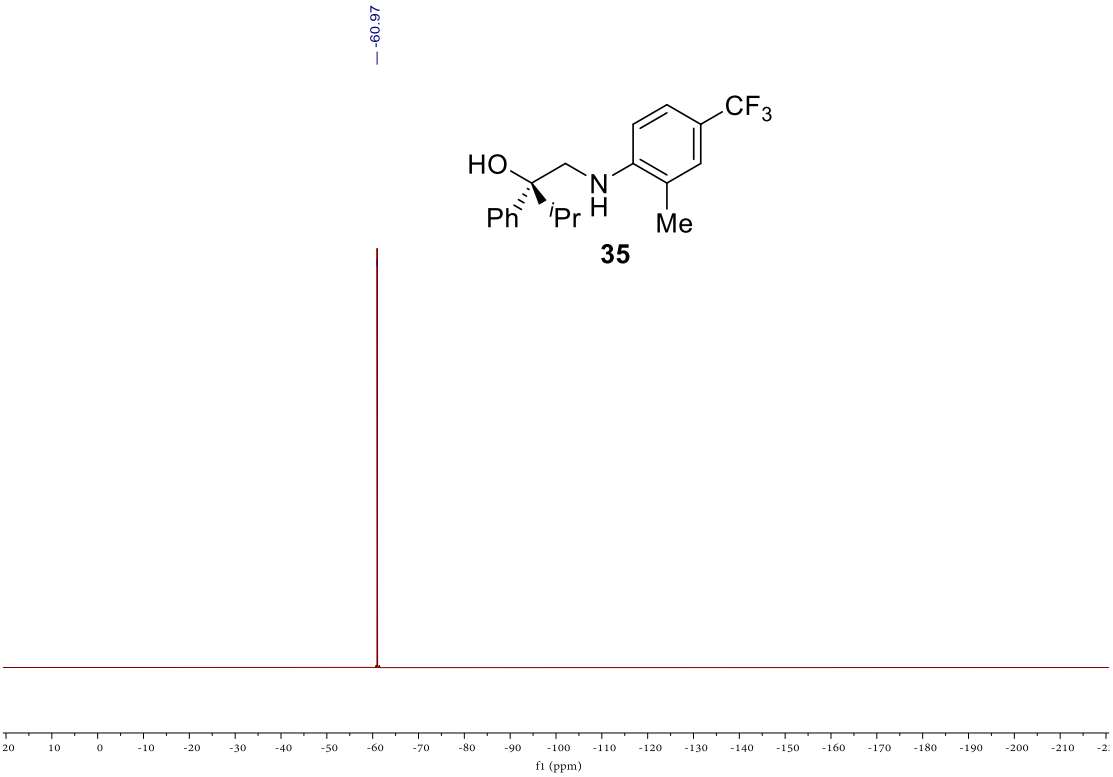
^{1}H NMR (400 MHz, $CDCl_3$)



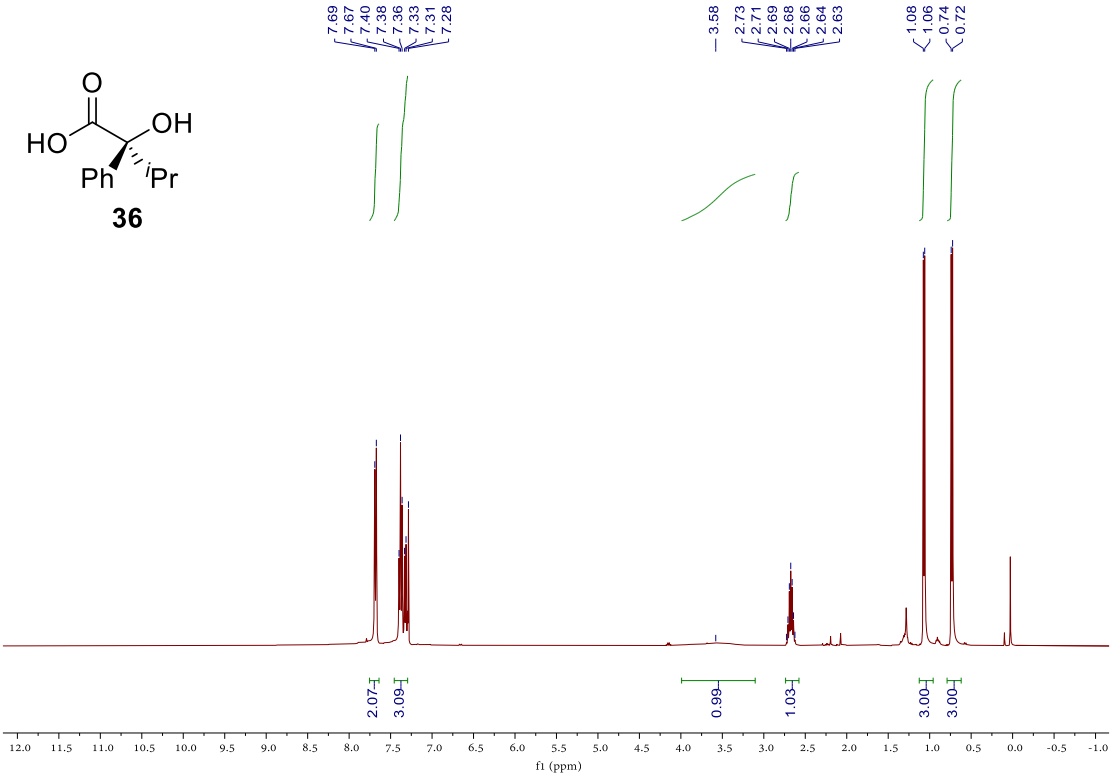
^{13}C NMR (100 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

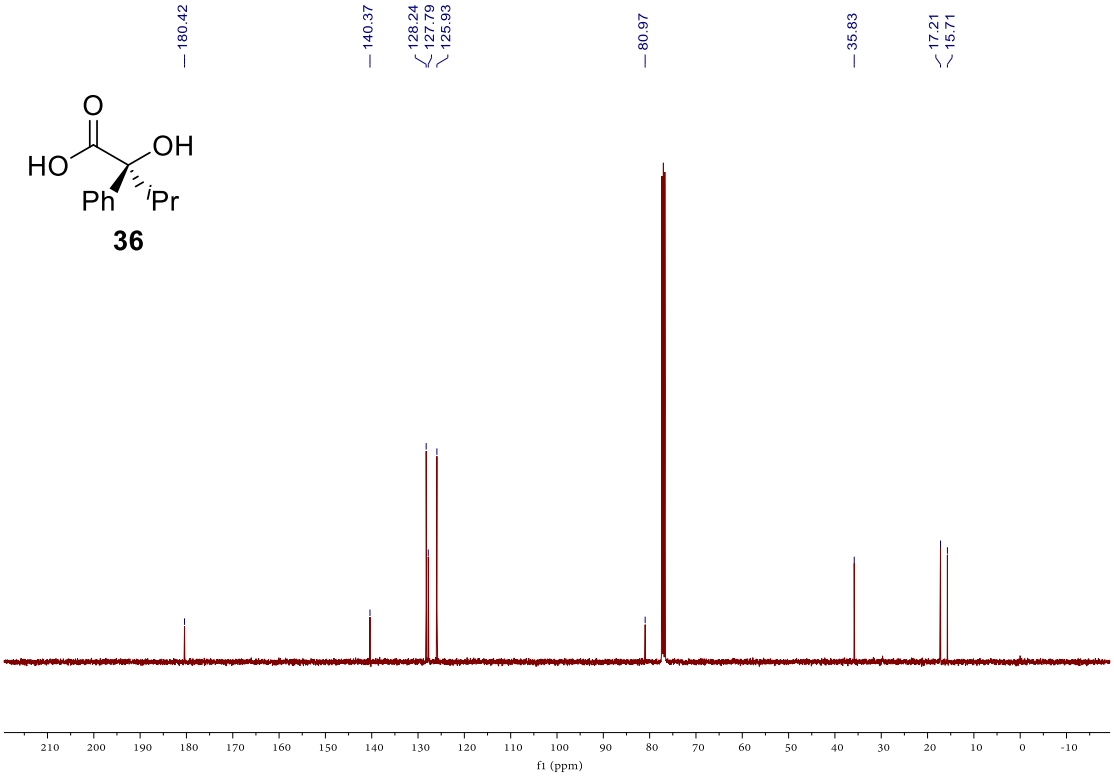


^{1}H NMR (400 MHz, $CDCl_3$)



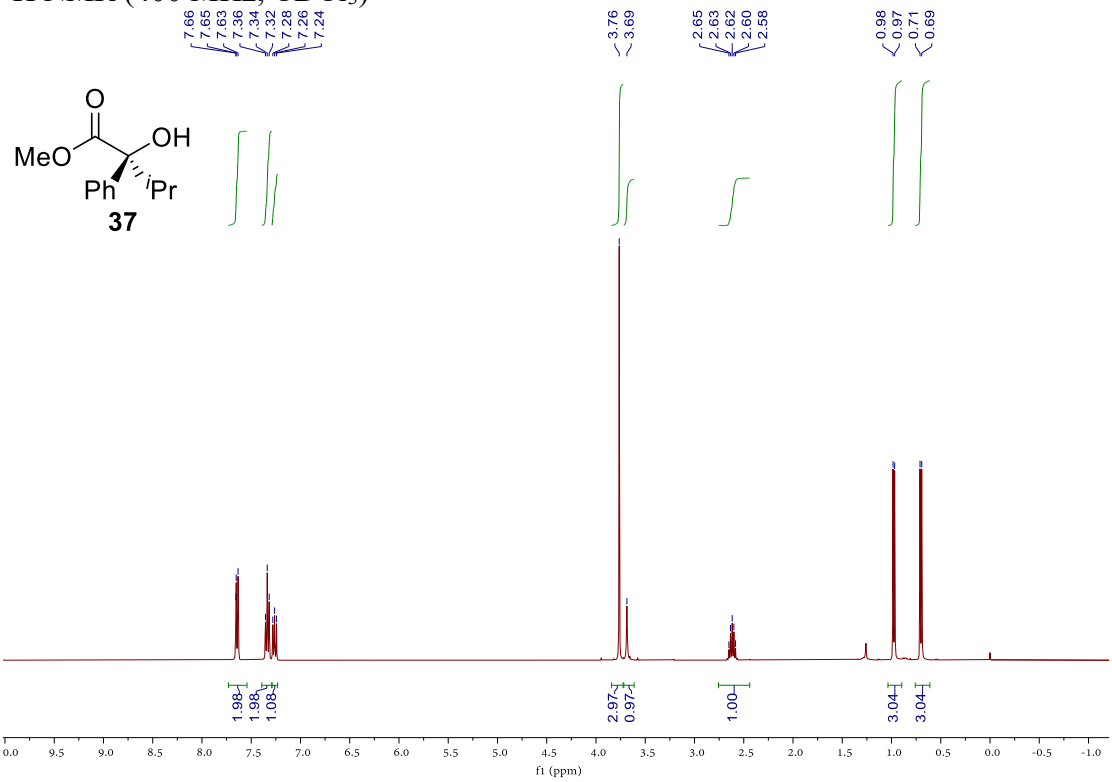
36

^{13}C NMR (100 MHz, $CDCl_3$)

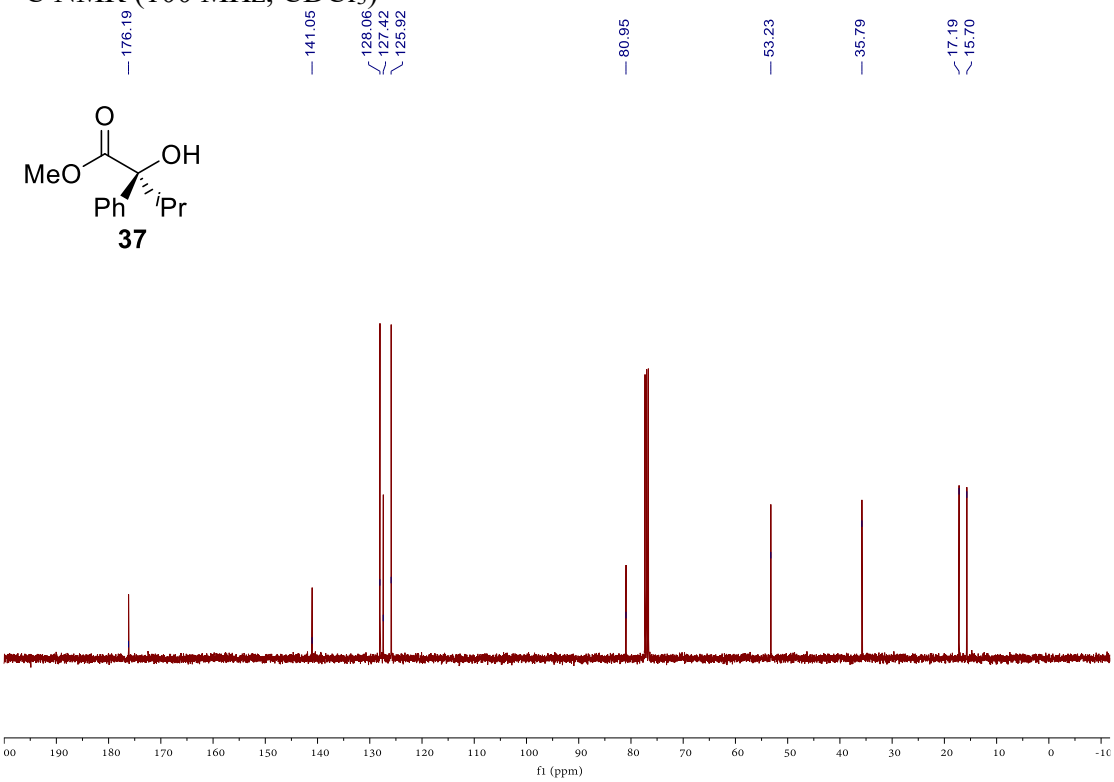


36

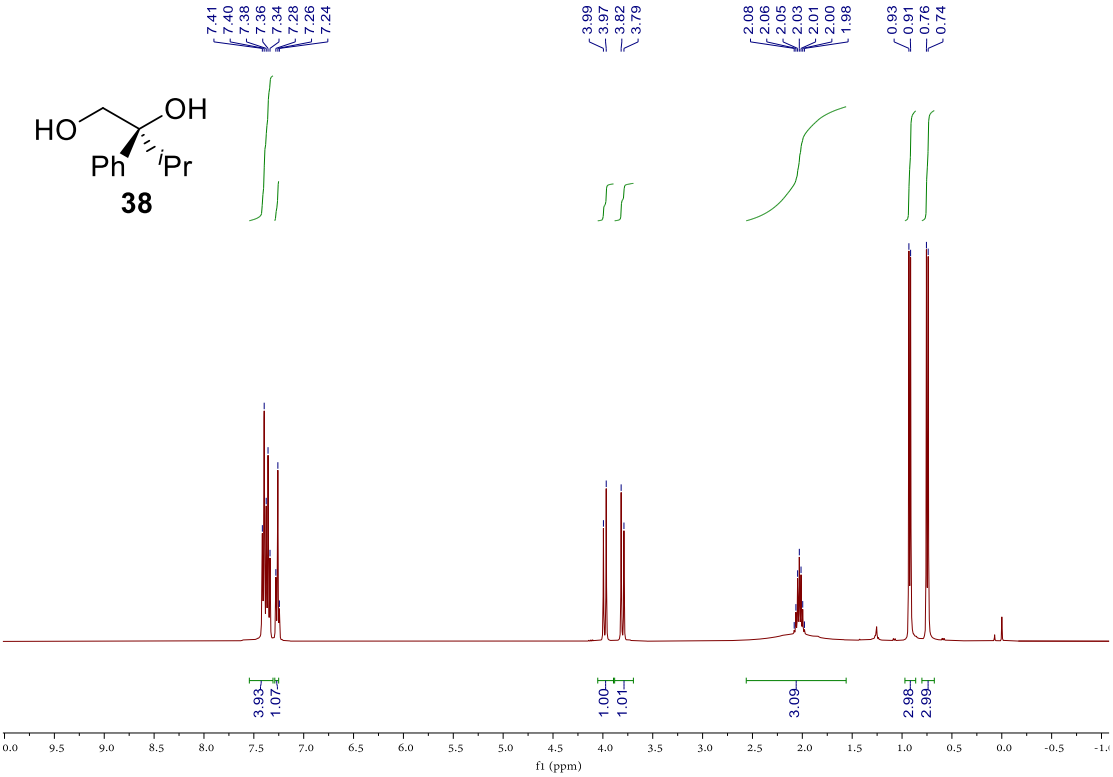
^{1}H NMR (400 MHz, $CDCl_3$)



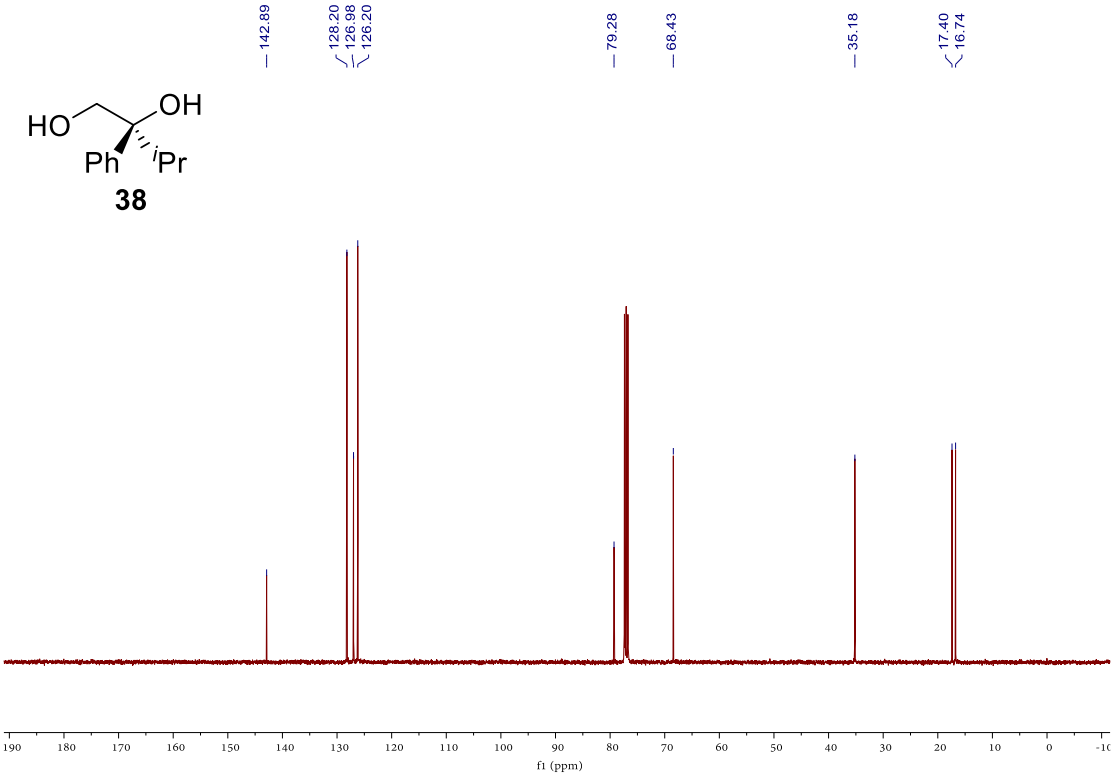
^{13}C NMR (100 MHz, $CDCl_3$)



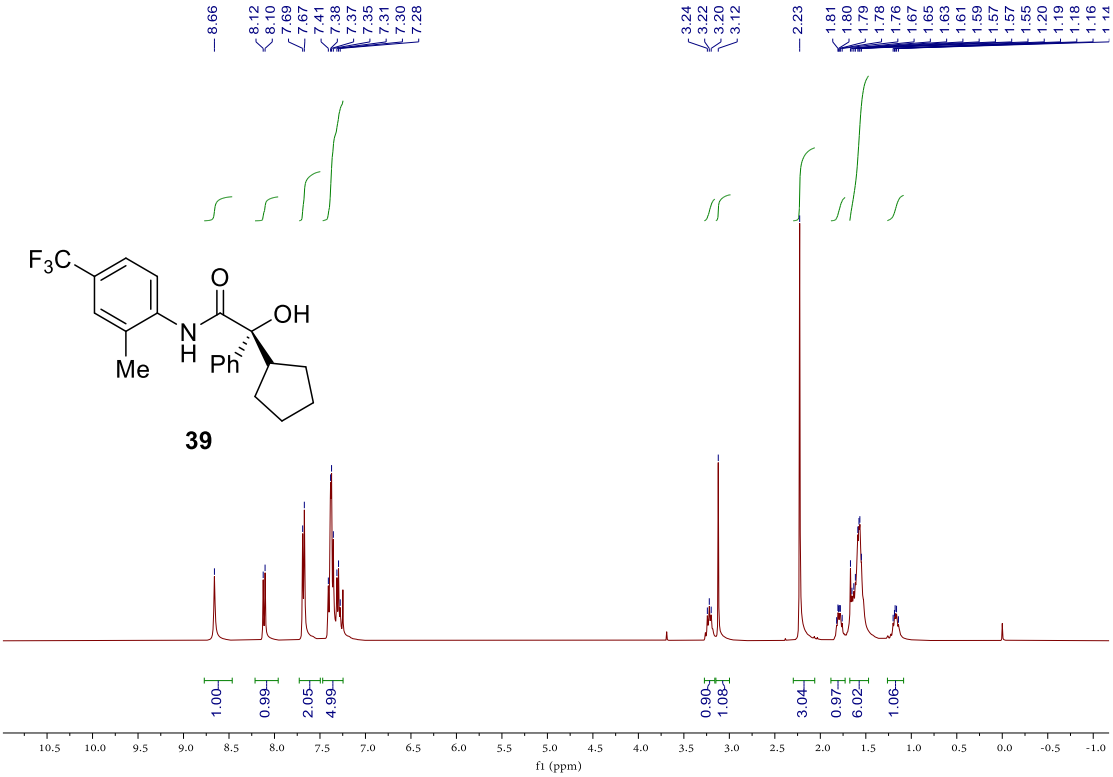
^{1}H NMR (400 MHz, $CDCl_3$)



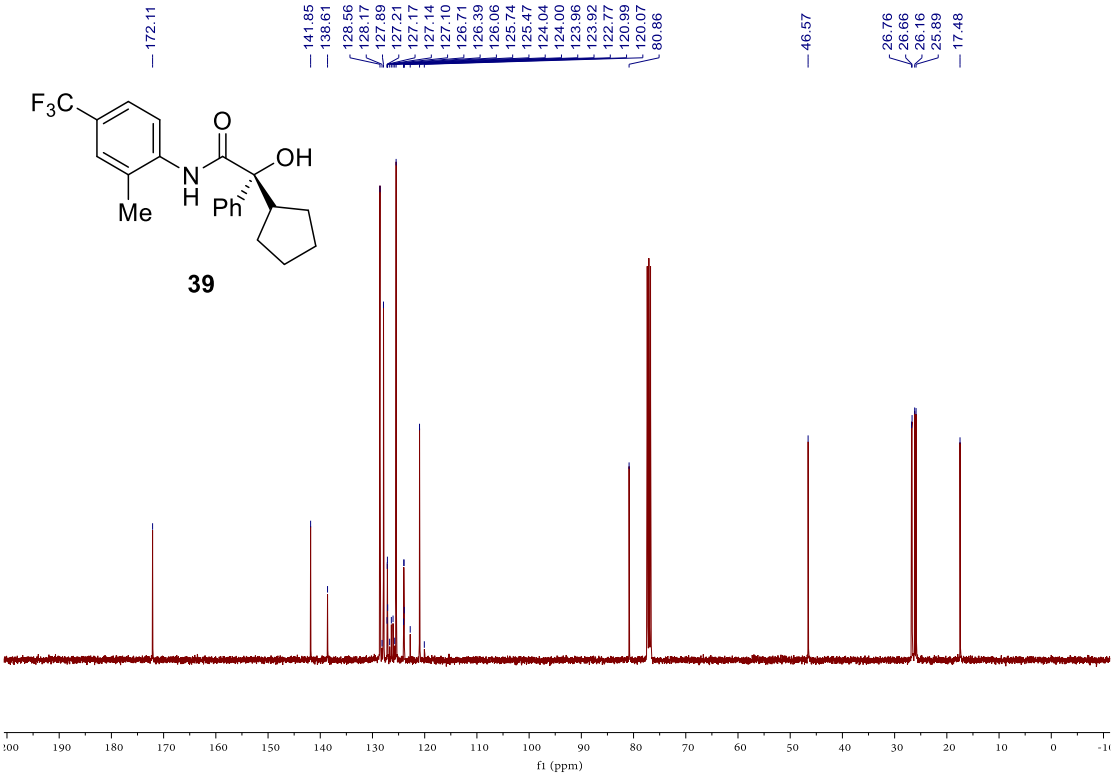
^{13}C NMR (100 MHz, $CDCl_3$)



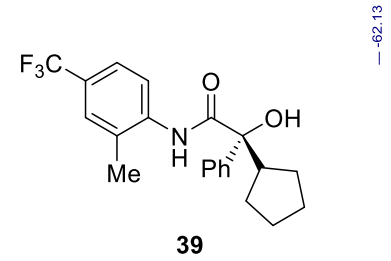
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

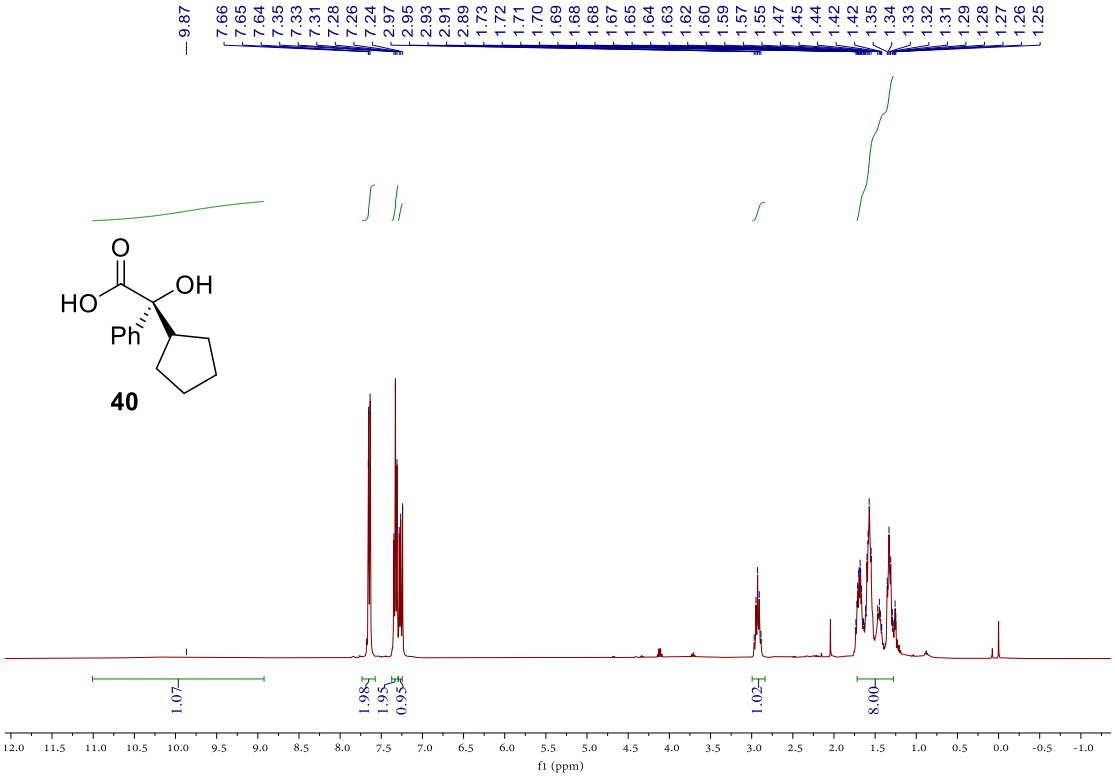


^{19}F NMR (376 MHz, $CDCl_3$)

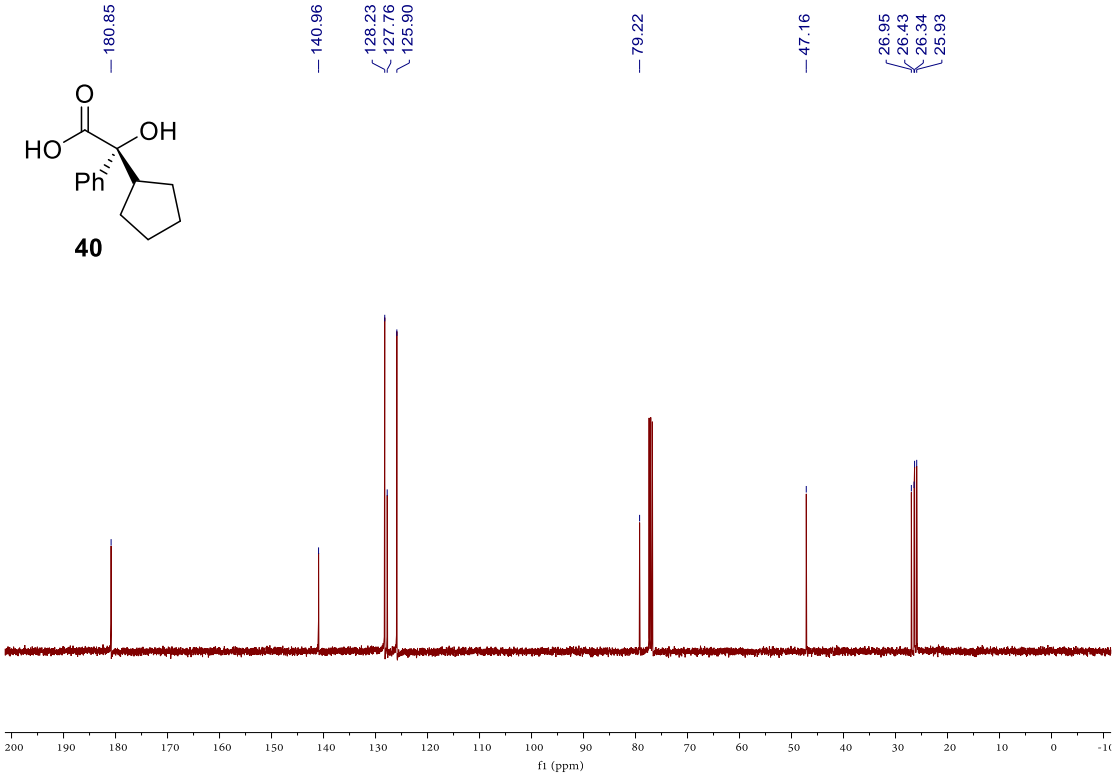


39

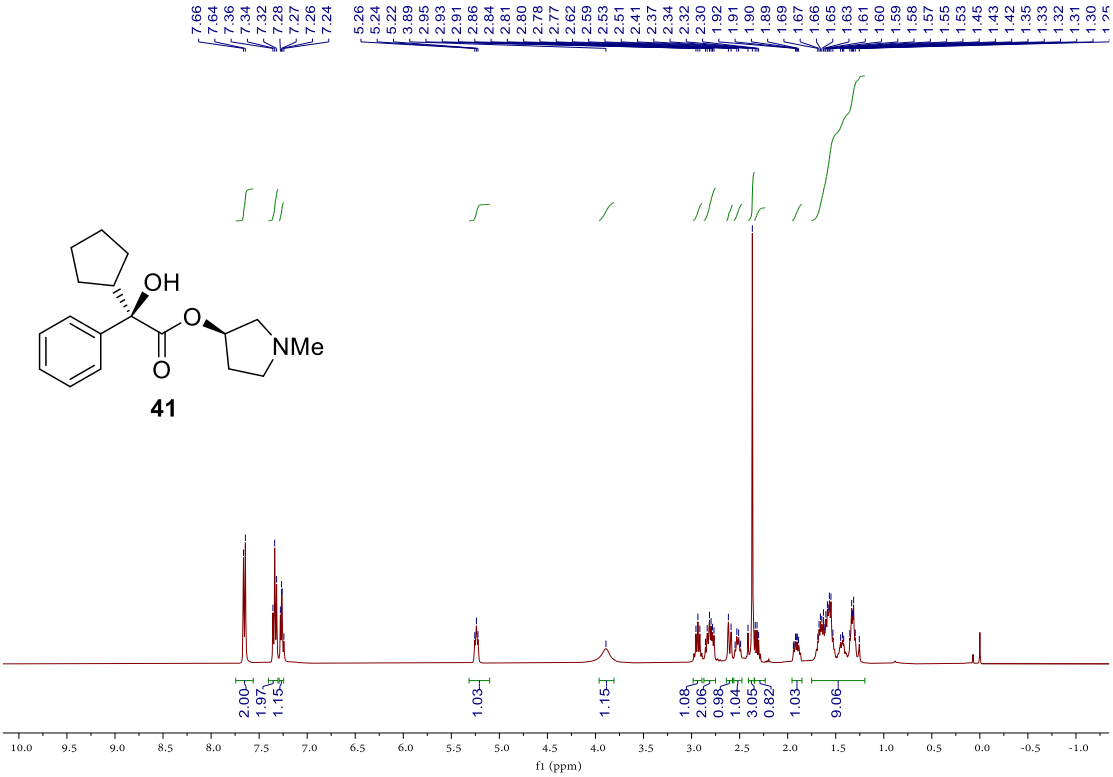
^{1}H NMR (400 MHz, $CDCl_3$)



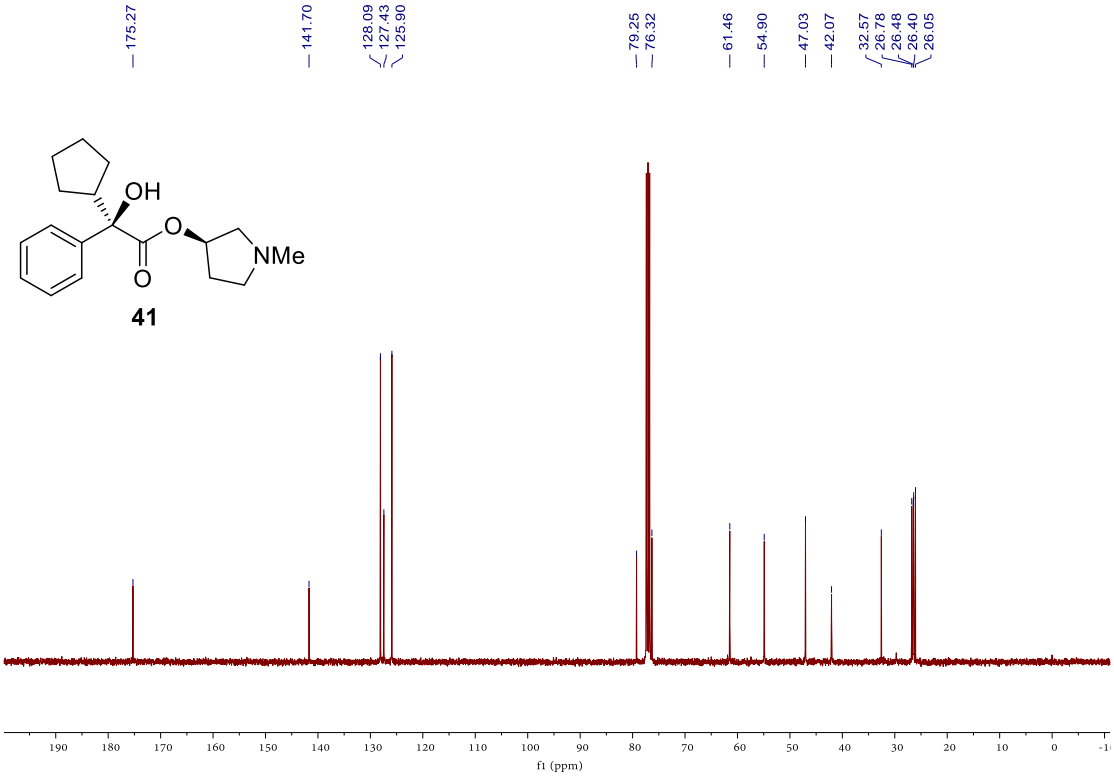
^{13}C NMR (100 MHz, $CDCl_3$)



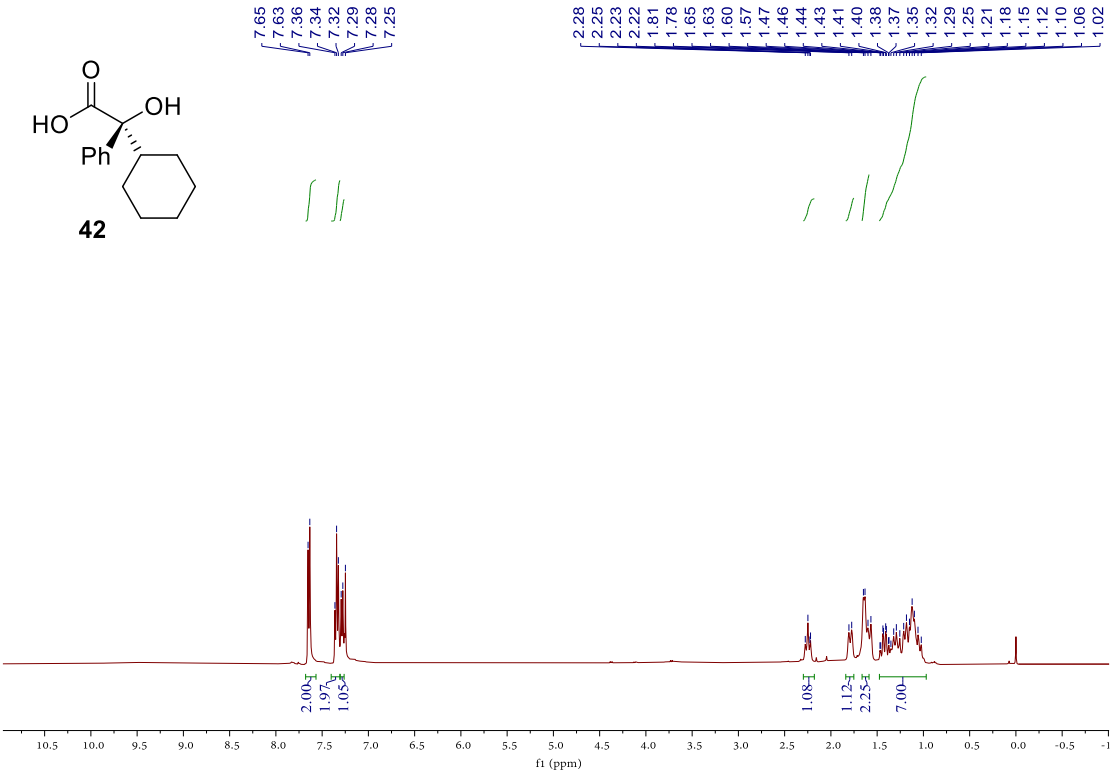
^{1}H NMR (400 MHz, $CDCl_3$)



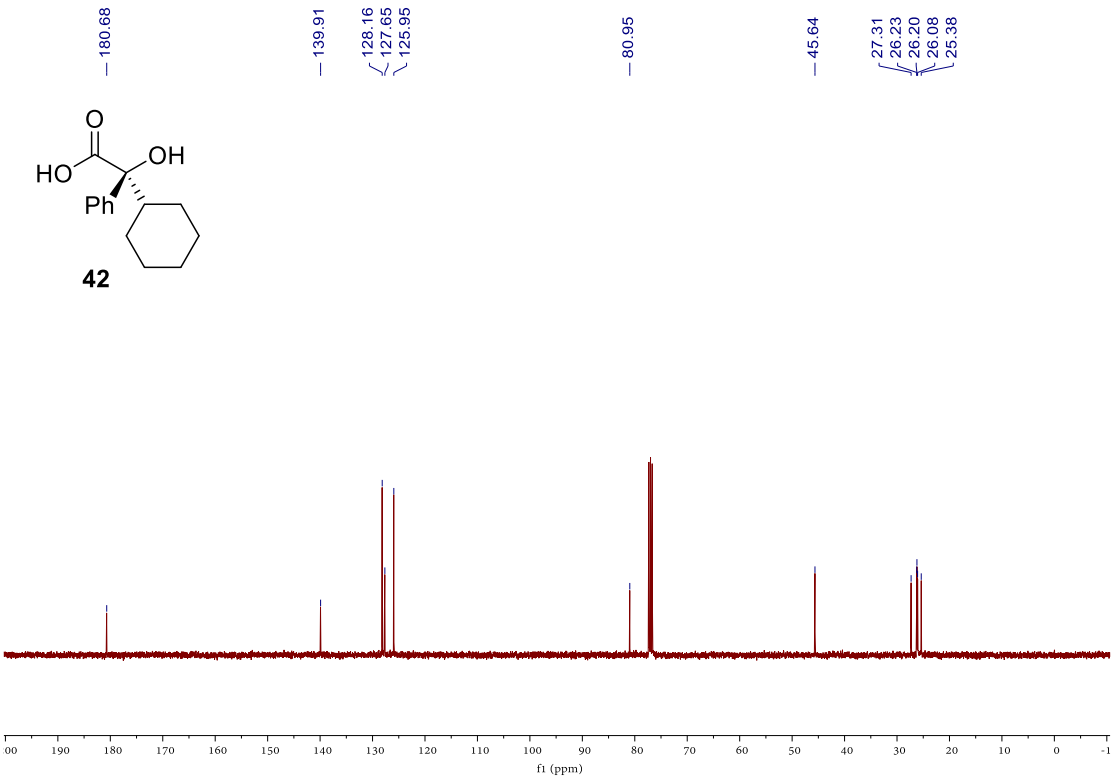
^{13}C NMR (100 MHz, $CDCl_3$)



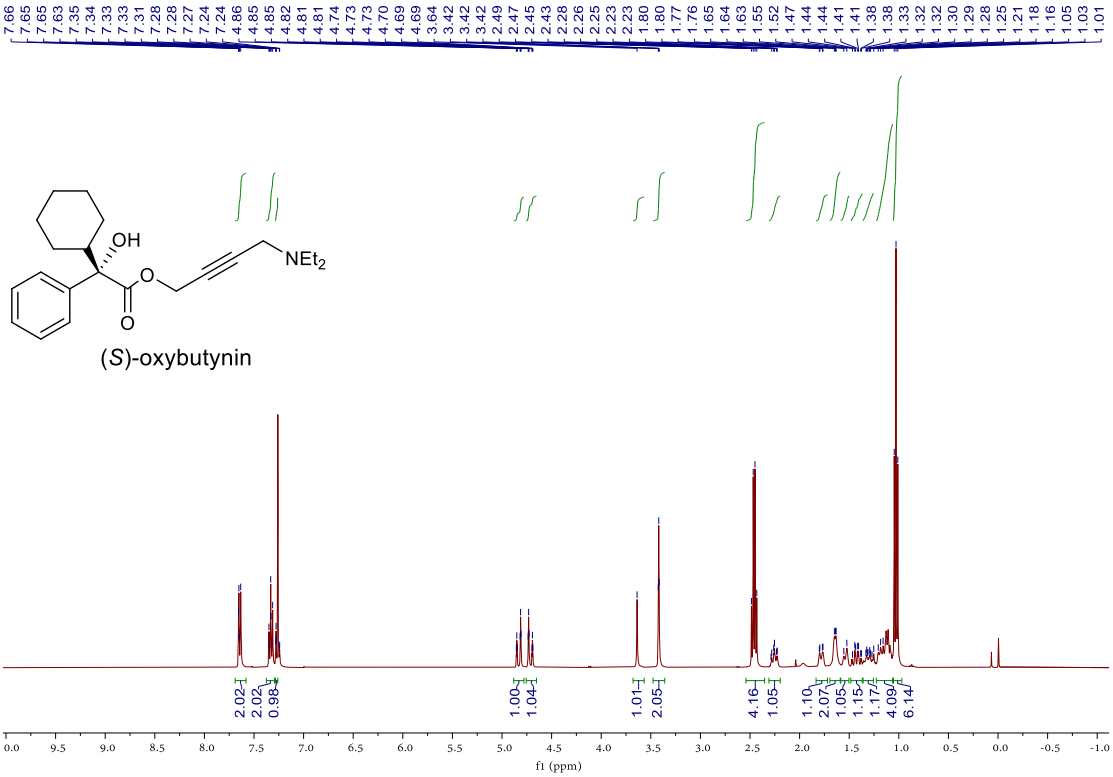
^{1}H NMR (400 MHz, $CDCl_3$)



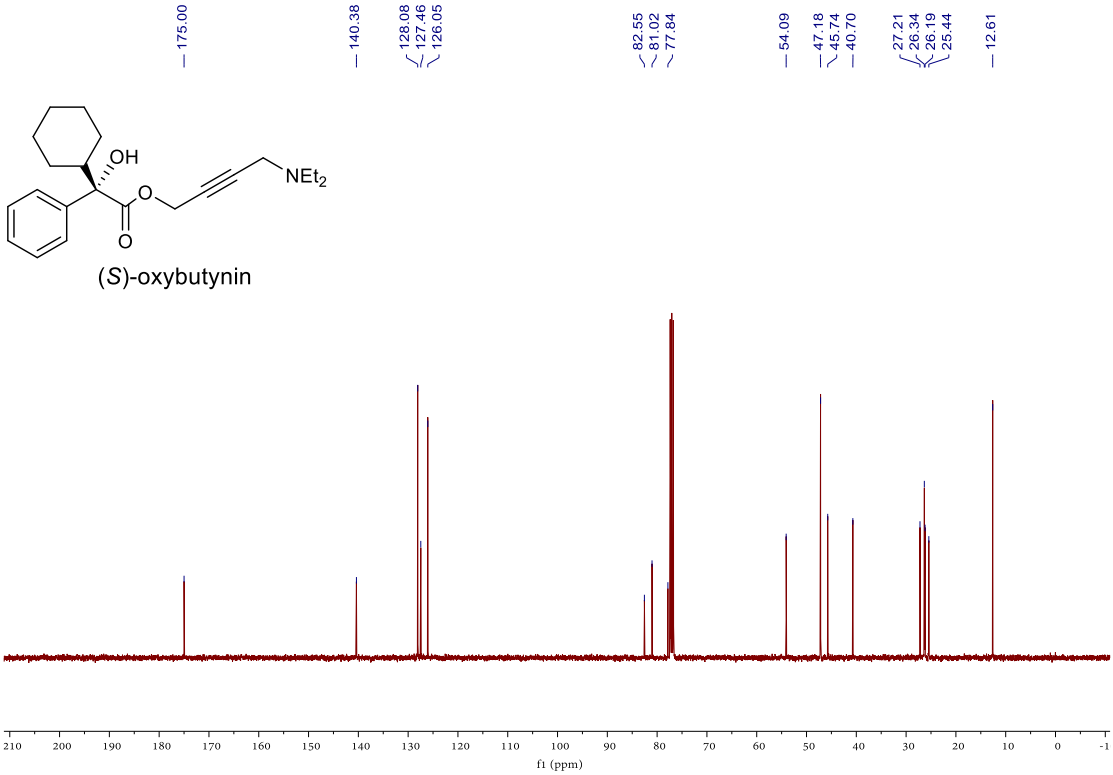
^{13}C NMR (100 MHz, $CDCl_3$)



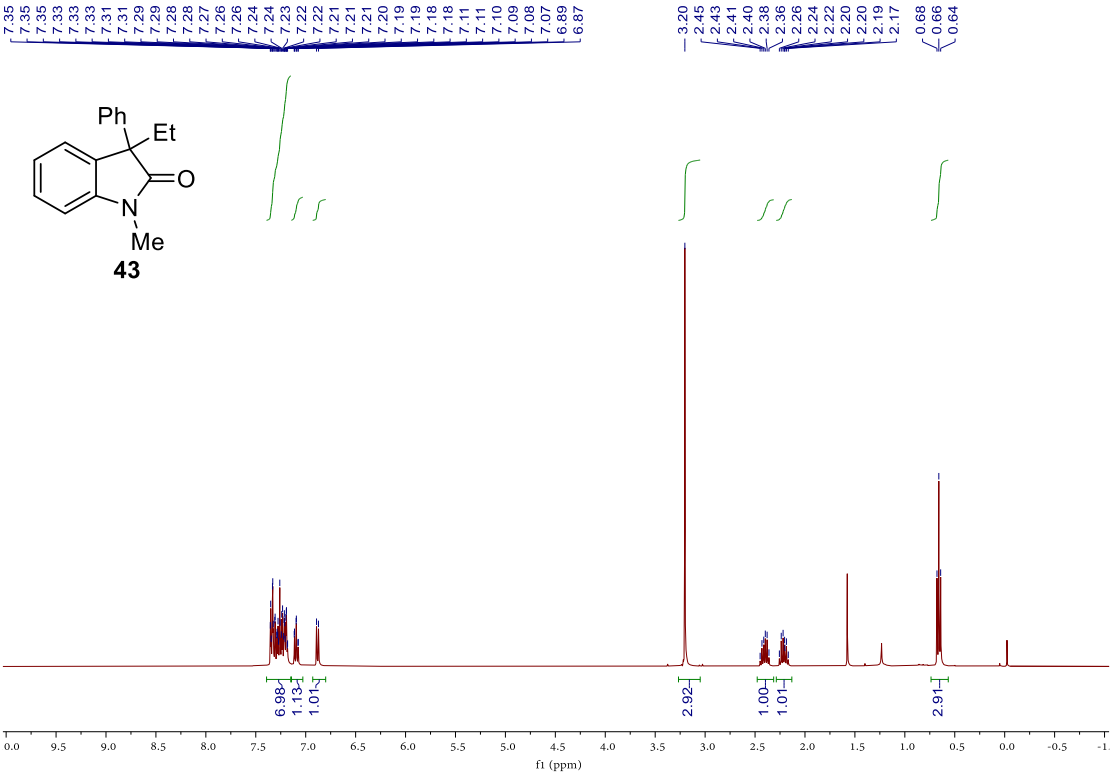
^{1}H NMR (400 MHz, $CDCl_3$)



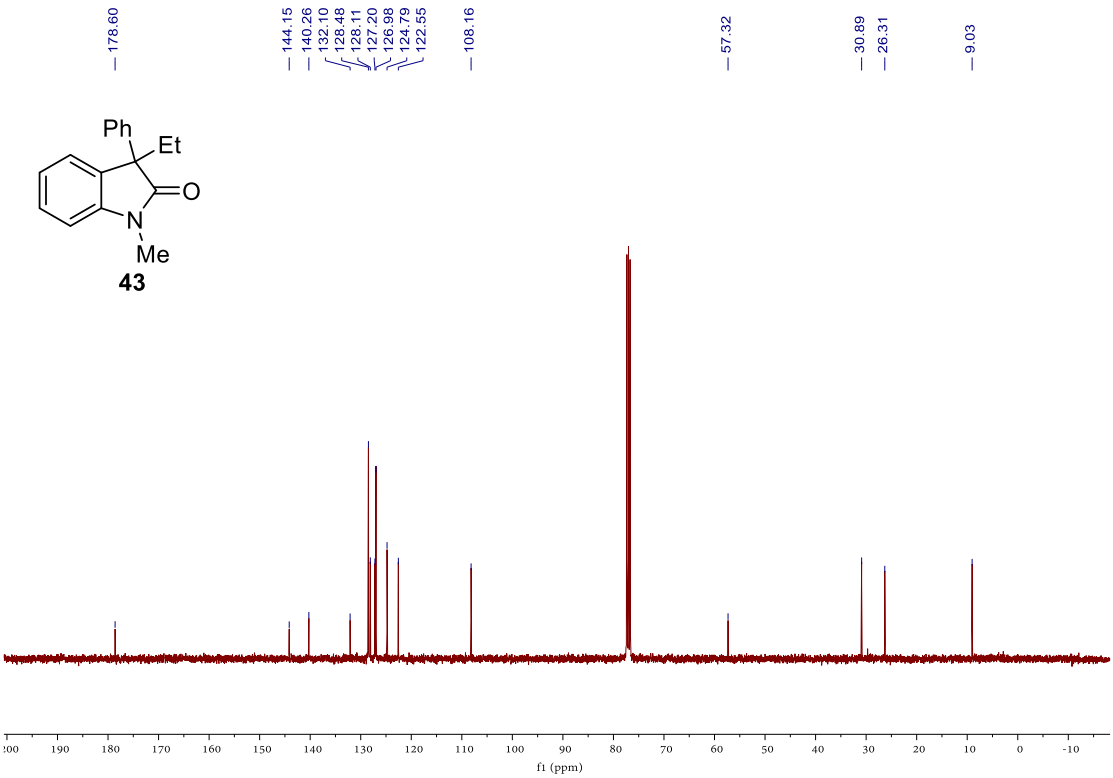
^{13}C NMR (100 MHz, $CDCl_3$)



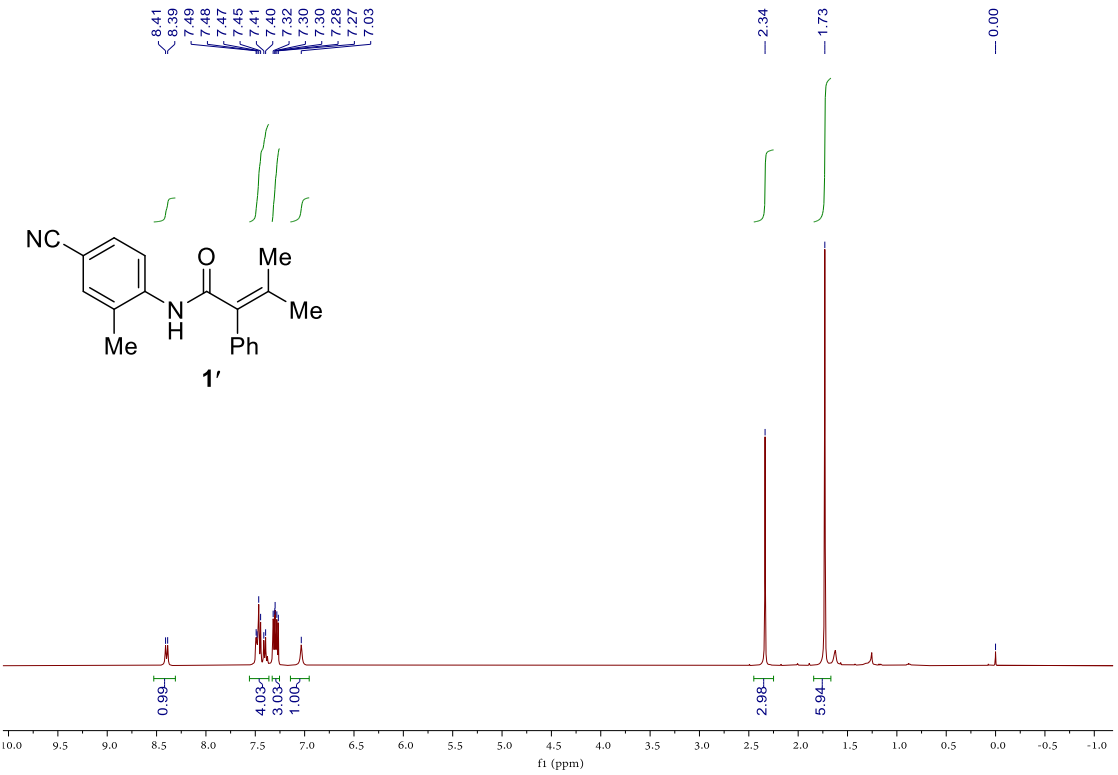
^{1}H NMR (400 MHz, $CDCl_3$)



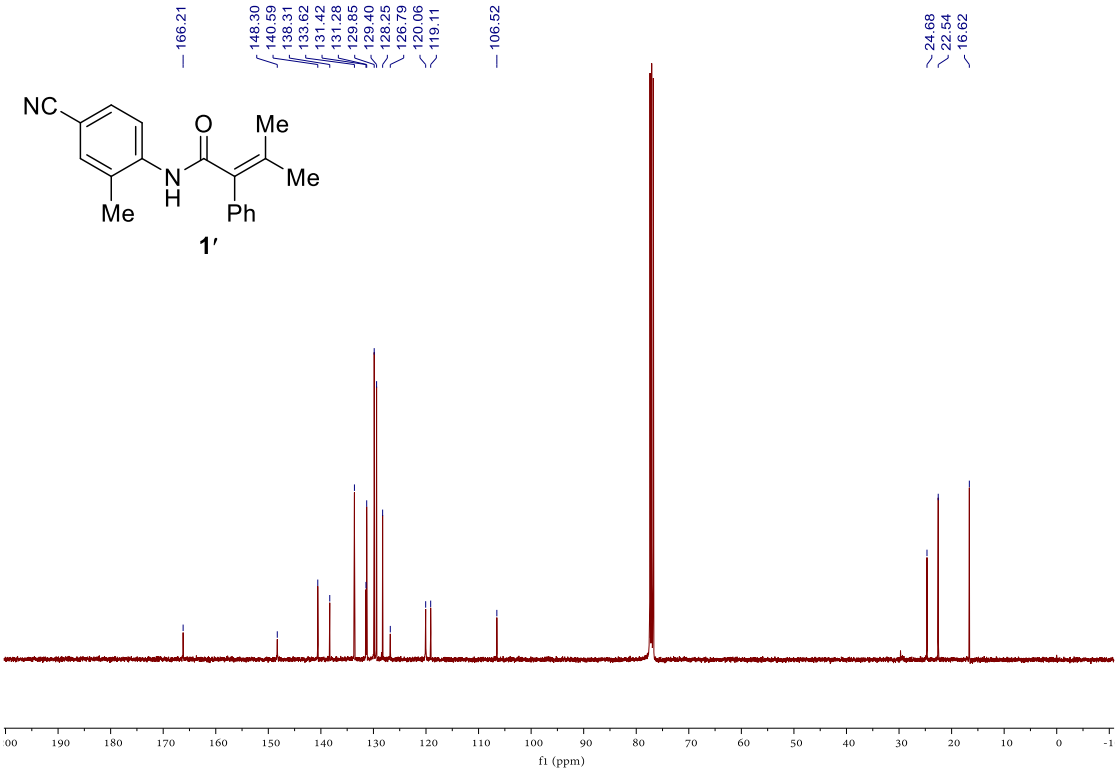
^{13}C NMR (100 MHz, $CDCl_3$)



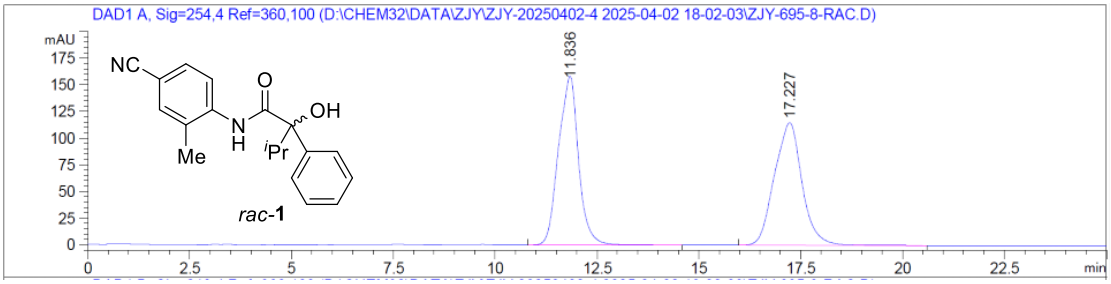
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

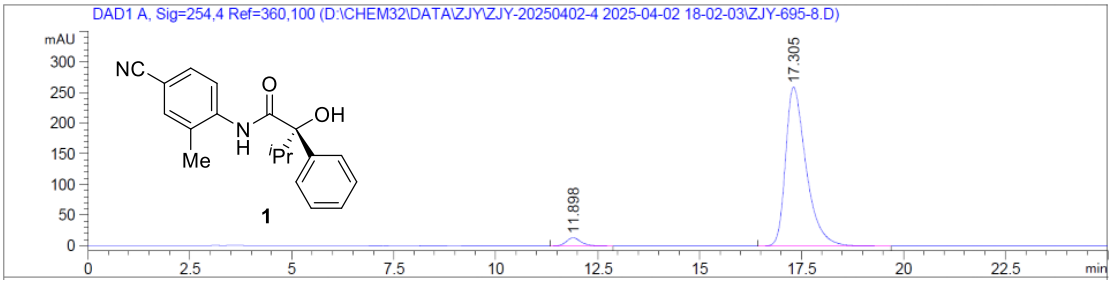


10. HPLC spectra



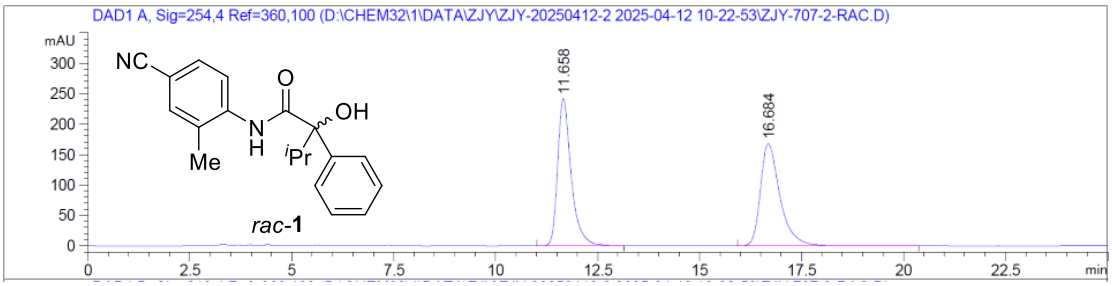
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.836	BB	0.4803	5406.39893	158.34593	50.0455
2	17.227	BB	0.6756	5396.56396	114.97403	49.9545
Totals :				1.08030e4	273.31996	



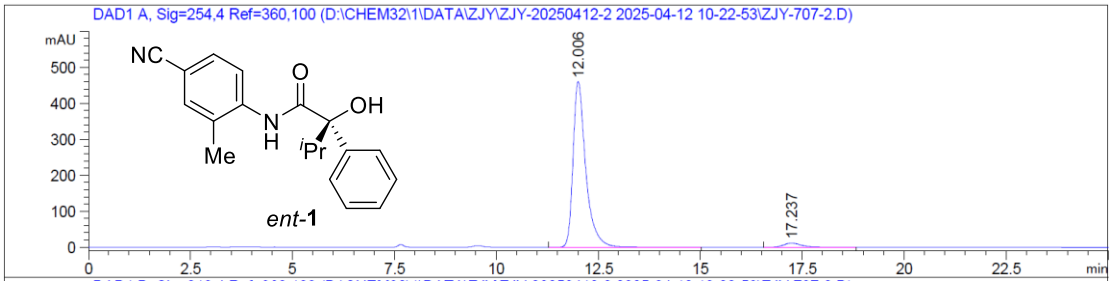
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.898	MM R	0.4200	338.42050	13.42942	3.5641
2	17.305	MF R	0.5884	9156.80469	259.35315	96.4359
Totals :				9495.22519	272.78257	



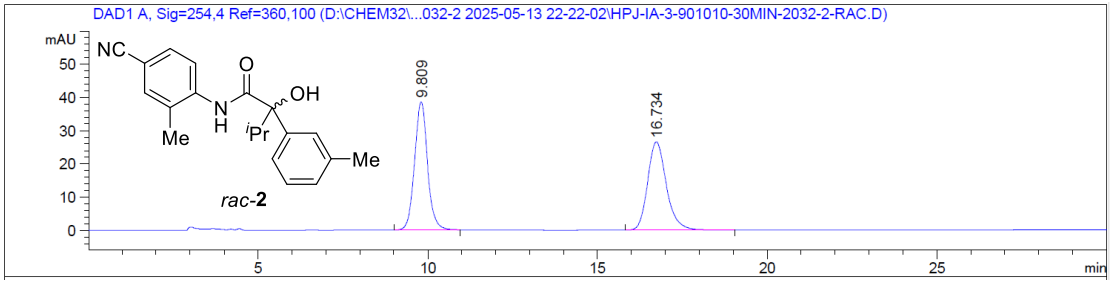
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.658	BB	0.3441	5548.80957	241.46722	49.9133
2	16.684	BB	0.5015	5568.07520	167.62025	50.0867
Totals :				1.11169e4	409.08748	



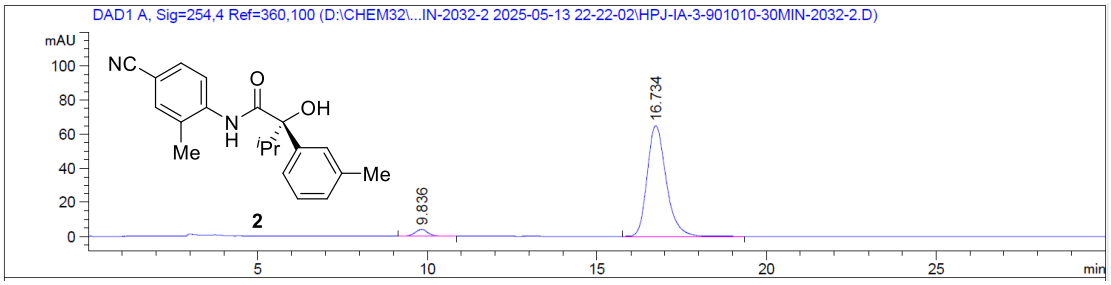
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.006	BB	0.3228	9995.69043	461.26974	96.4797
2	17.237	BB	0.4717	364.71765	11.63673	3.5203
Totals :				1.03604e4	472.90647	



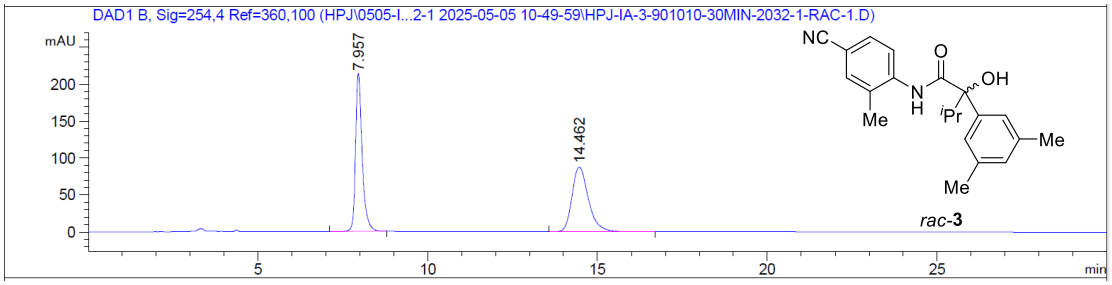
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.809	BB	0.4073	1020.05676	38.47350	50.0265
2	16.734	BB	0.5898	1018.97809	26.54789	49.9735
Totals :				2039.03485	65.02139	



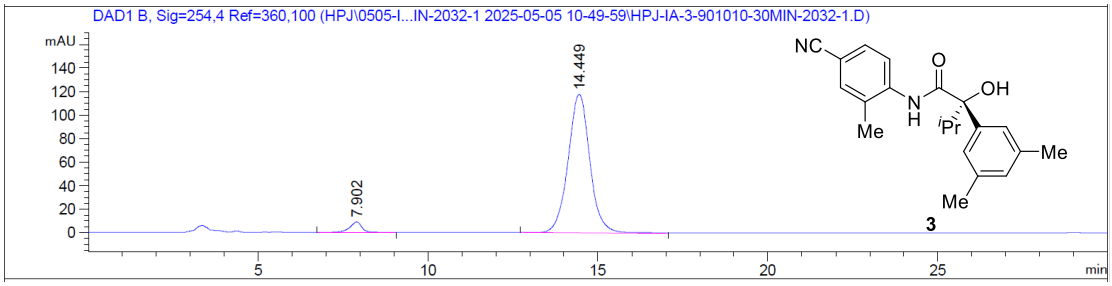
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.836	BB	0.4054	106.77150	4.05188	4.0493
2	16.734	BB	0.6010	2530.03564	64.87897	95.9507
Totals :				2636.80714	68.93085	



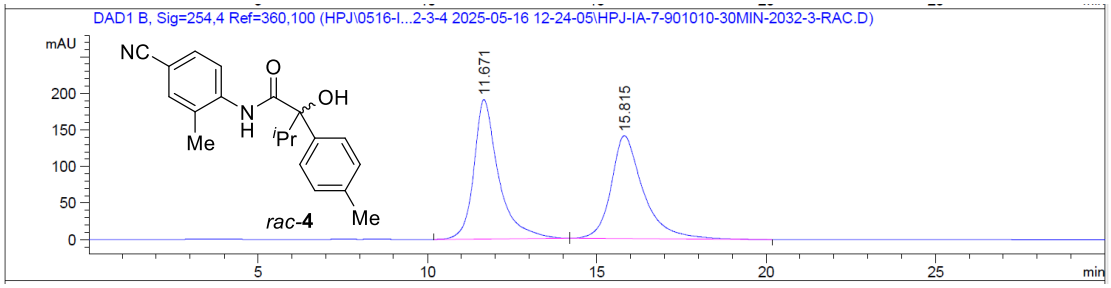
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.957	BB	0.2022	2906.55225	214.31767	49.7046
2	14.462	BB	0.5182	2941.10449	87.48328	50.2954
Totals :				5847.65674	301.80095	



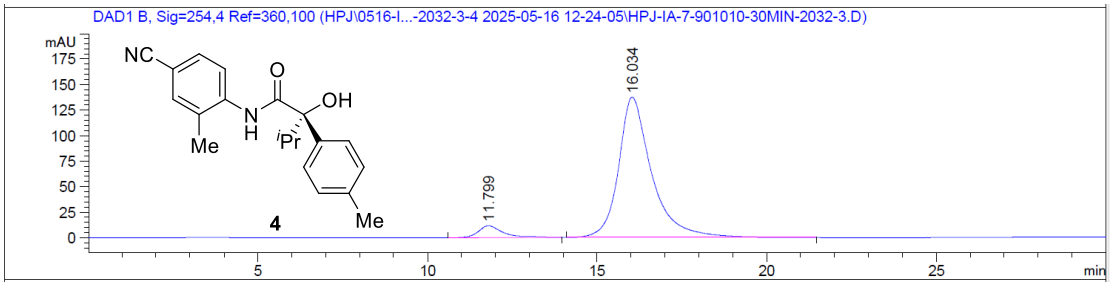
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.902	BB	0.3712	226.66423	8.95746	4.1286
2	14.449	MM R	0.7456	5263.47217	117.66261	95.8714
Totals :				5490.13640	126.62007	



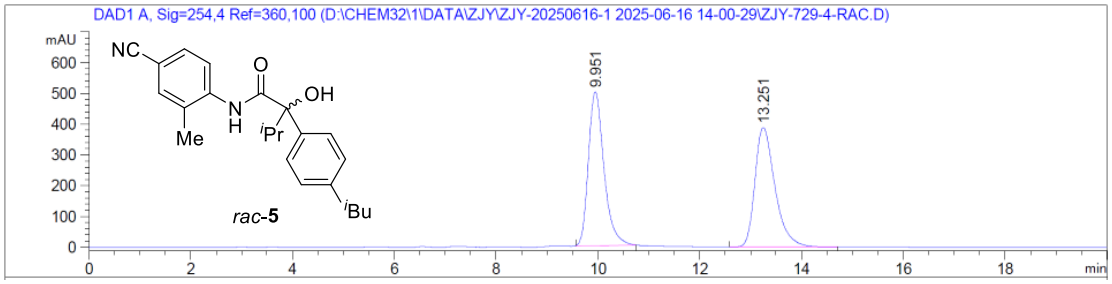
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.671	BB	0.7317	9677.04492	190.81821	50.8889
2	15.815	BB	0.9654	9338.99414	140.87032	49.1111
Totals :				1.90160e4	331.68852	



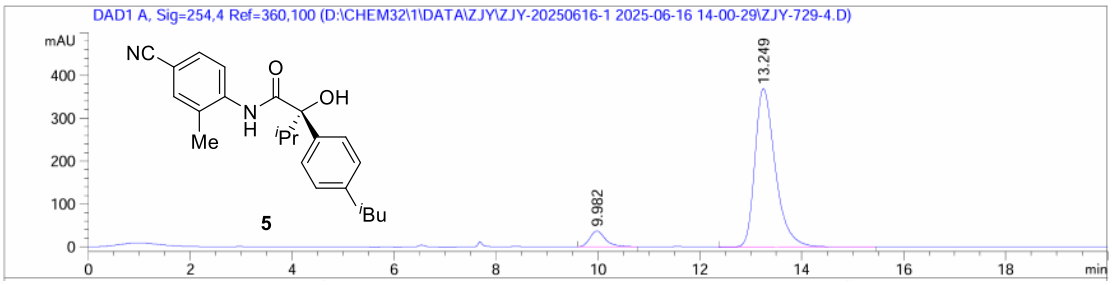
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.799	BB	0.7368	594.96118	11.74809	5.9962
2	16.034	BB	0.9802	9327.32813	137.35864	94.0038
Totals :				9922.28931	149.10673	



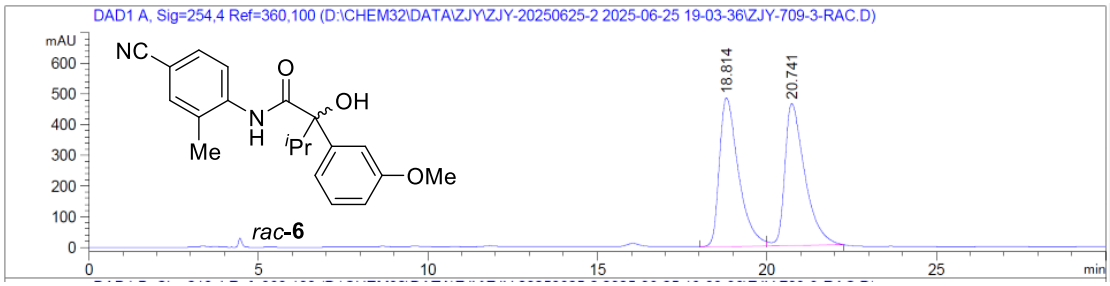
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.951	MM R	0.3547	1.06213e4	499.13025	50.0277
2	13.251	BB	0.4175	1.06095e4	387.44147	49.9723
Totals :				2.12308e4	886.57172	



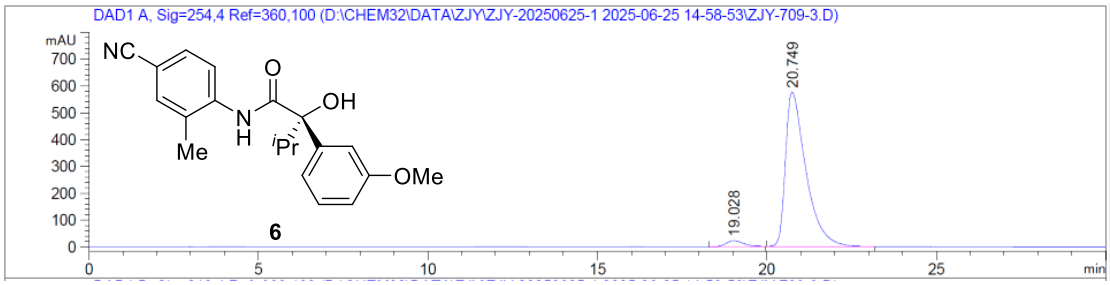
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.982	MM R	0.3569	782.29926	36.53171	7.0708
2	13.249	MM R	0.4642	1.02815e4	369.11557	92.9292
Totals :				1.10638e4	405.64728	



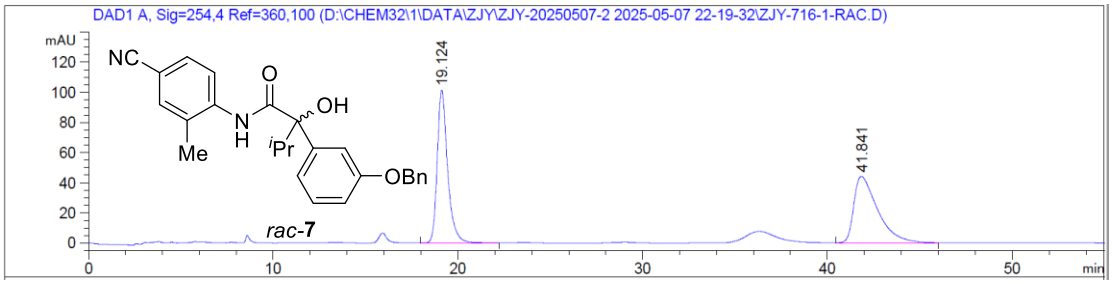
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.814	MF R	0.6545	1.90316e4	484.60330	49.9810
2	20.741	FM R	0.6861	1.90460e4	462.69299	50.0190
Totals :				3.80776e4	947.29630	



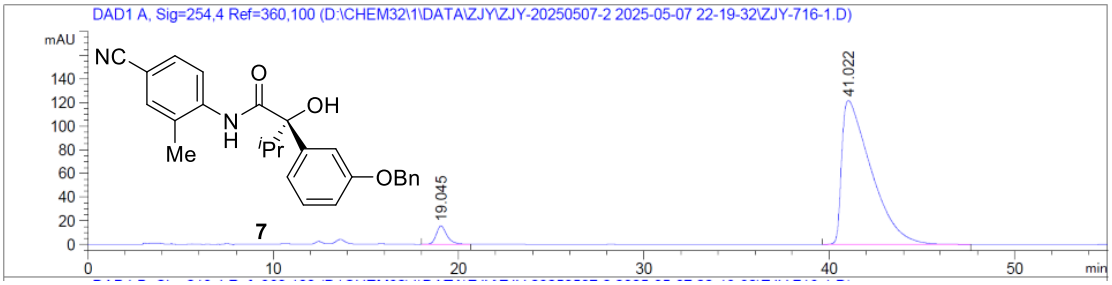
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.028	BB	0.5416	790.98834	22.31295	3.1827
2	20.749	BB	0.6222	2.40616e4	575.06152	96.8173
Totals :				2.48526e4	597.37447	



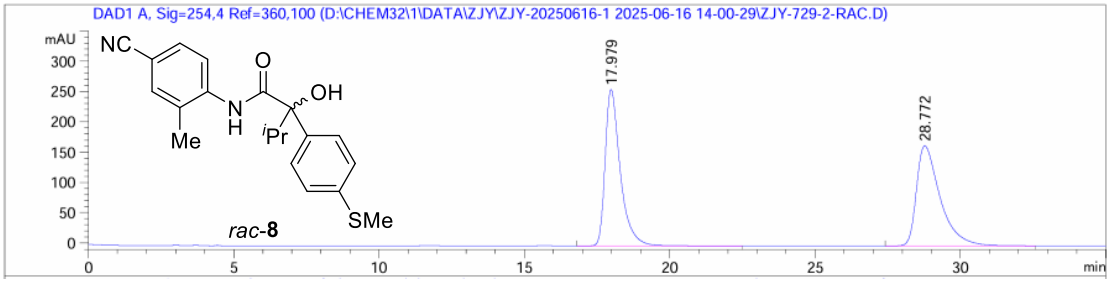
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.124	BB	0.5901	3963.95386	101.39977	50.0090
2	41.841	MM R	1.4943	3962.53442	44.19672	49.9910
Totals :				7926.48828	145.59649	



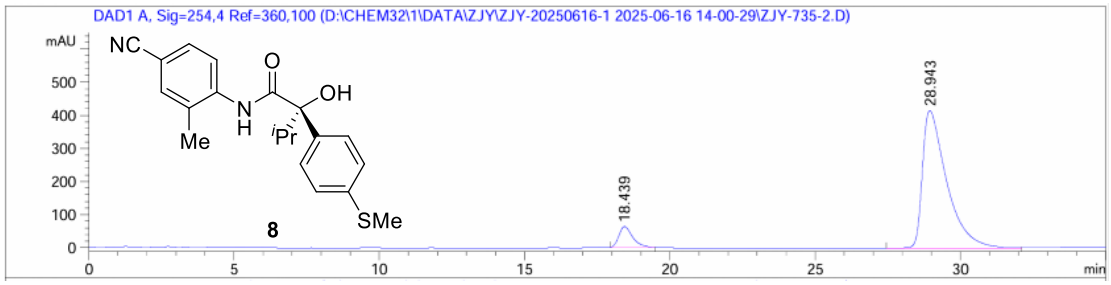
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.045	BB	0.6005	613.99475	15.42150	4.3797
2	41.022	BB	1.5437	1.34051e4	121.64255	95.6203
Totals :				1.40191e4	137.06404	



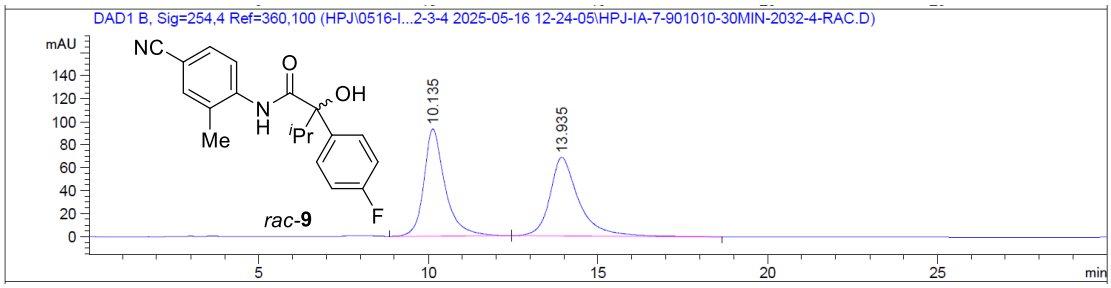
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.979	BB	0.5403	9341.46289	258.08118	49.9528
2	28.772	BB	0.8455	9359.13477	165.07408	50.0472
Totals :				1.87006e4	423.15526	



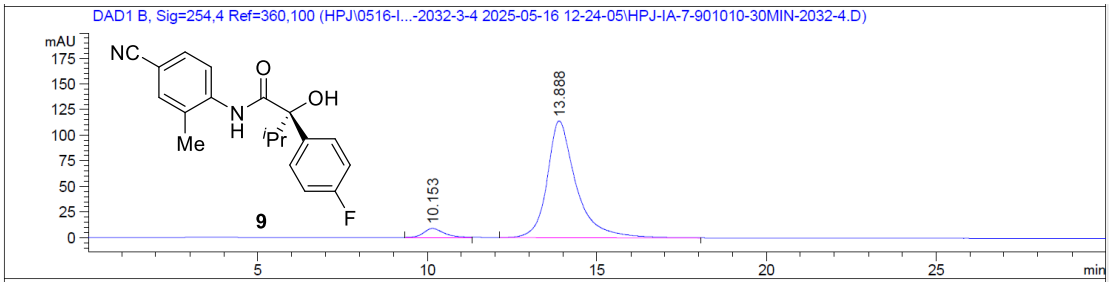
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.439	MM R	0.5468	2069.44678	63.08145	7.8980
2	28.943	MM R	0.9695	2.41328e4	414.85495	92.1020
Totals :				2.62022e4	477.93640	



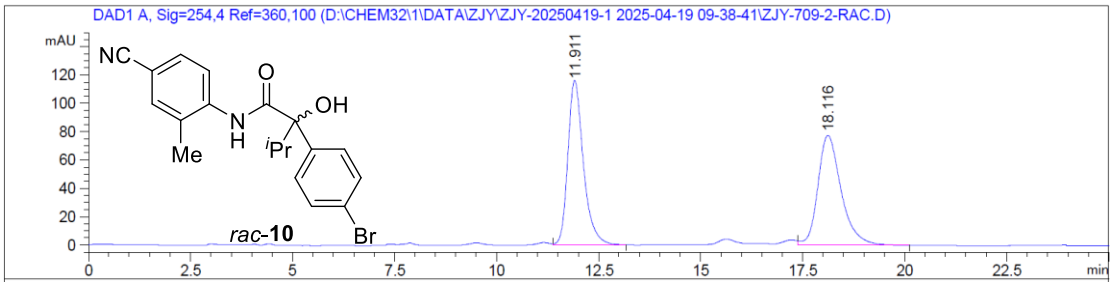
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.135	BB	0.6343	4038.01758	93.04272	49.8470
2	13.935	BB	0.8639	4062.81079	68.30505	50.1530
Totals :				8100.82837	161.34778	



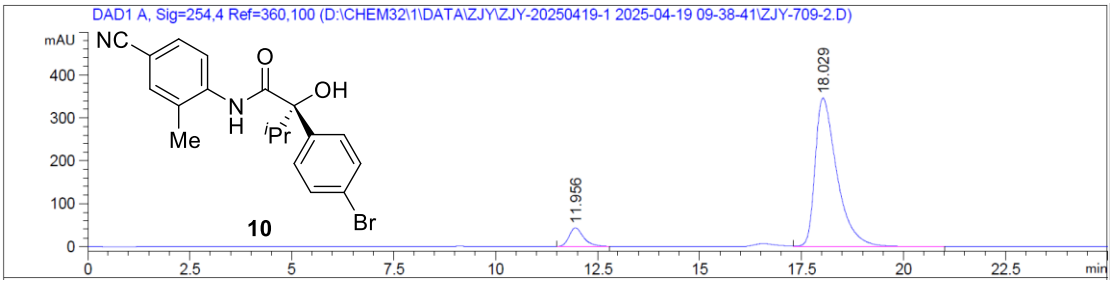
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.153	FM R	0.7058	375.26877	8.86189	5.2472
2	13.888	MF R	0.9911	6776.46680	113.95090	94.7528
Totals :				7151.73557	122.81280	



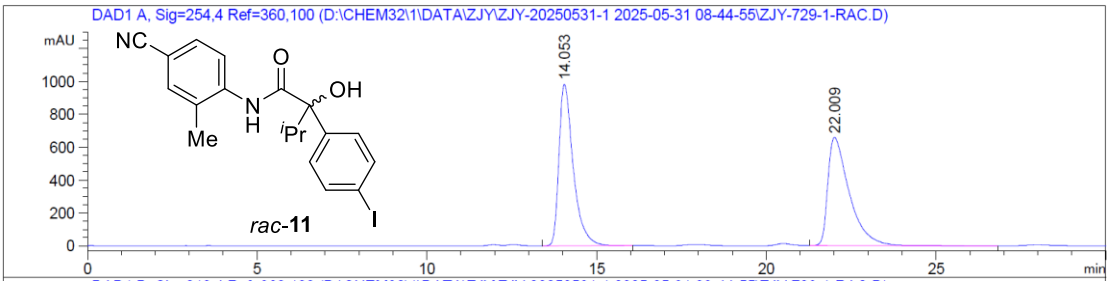
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.911	MM R	0.4439	3097.80933	116.30872	50.0520
2	18.116	MM R	0.6635	3091.36694	77.64870	49.9480
Totals :				6189.17627	193.95743	



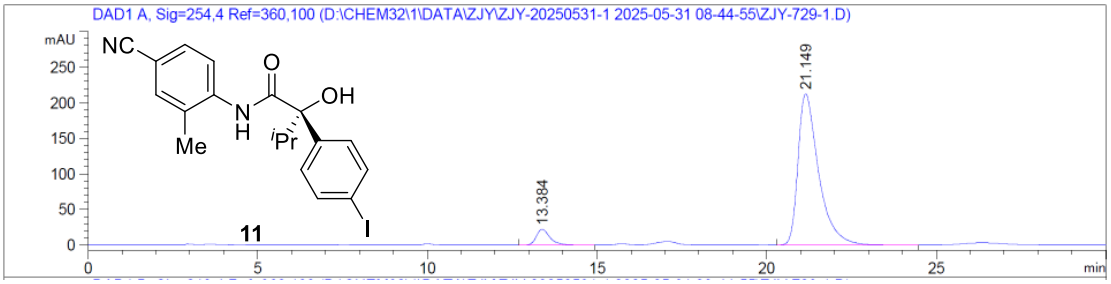
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.956	MM R	0.4096	1069.84460	43.53201	7.6484
2	18.029	MM R	0.6220	1.29179e4	346.14148	92.3516
Totals :				1.39878e4	389.67349	



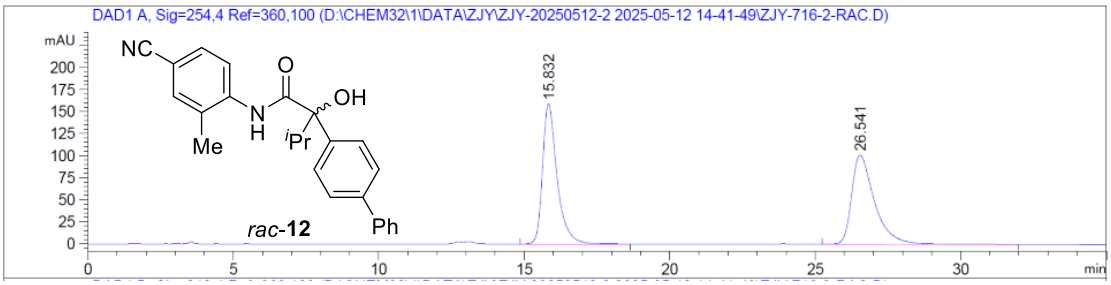
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.053	BB	0.4427	2.87992e4	980.56372	49.9344
2	22.009	BB	0.6498	2.88750e4	658.21484	50.0656
Totals :				5.76742e4	1638.77856	



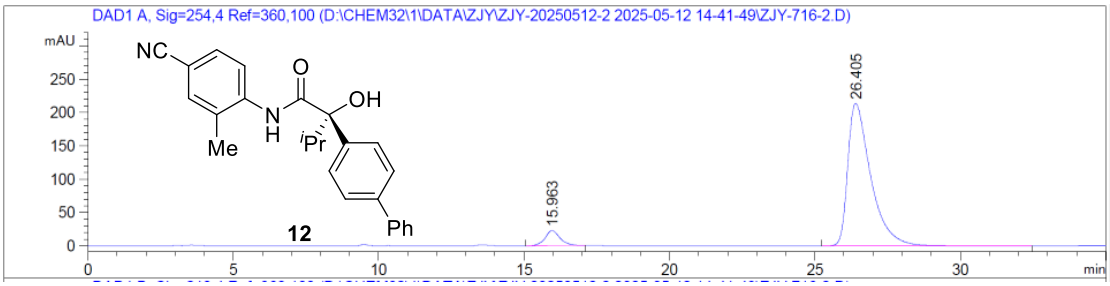
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.384	BB	0.4230	627.94135	22.40265	6.5322
2	21.149	BB	0.6336	8985.06445	212.37263	93.4678
Totals :				9613.00580	234.77529	



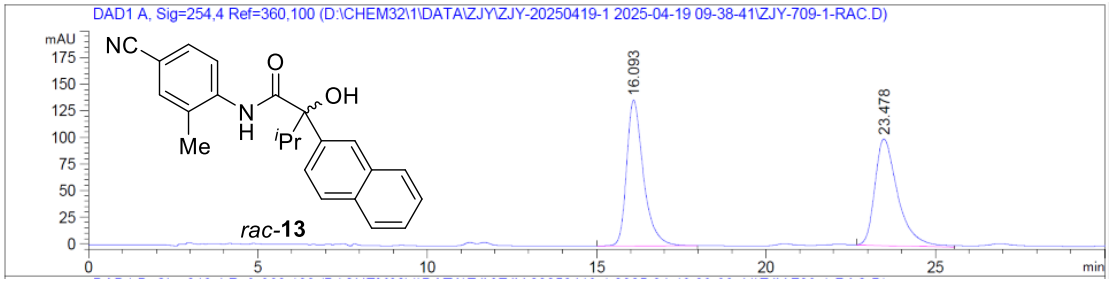
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.832	BB	0.5235	5553.48340	159.00227	50.1229
2	26.541	BB	0.8175	5526.25977	101.14093	49.8771
Totals :				1.10797e4	260.14320	



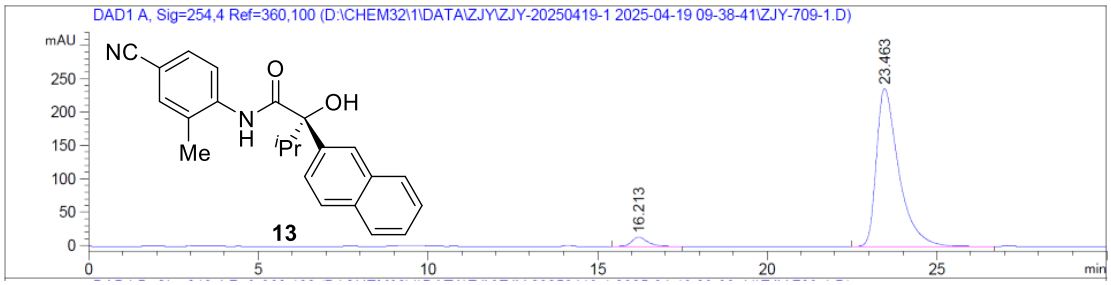
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.963	BB	0.5350	832.96417	22.97599	6.6170
2	26.405	BB	0.8198	1.17552e4	213.68042	93.3830
Totals :				1.25882e4	236.65641	



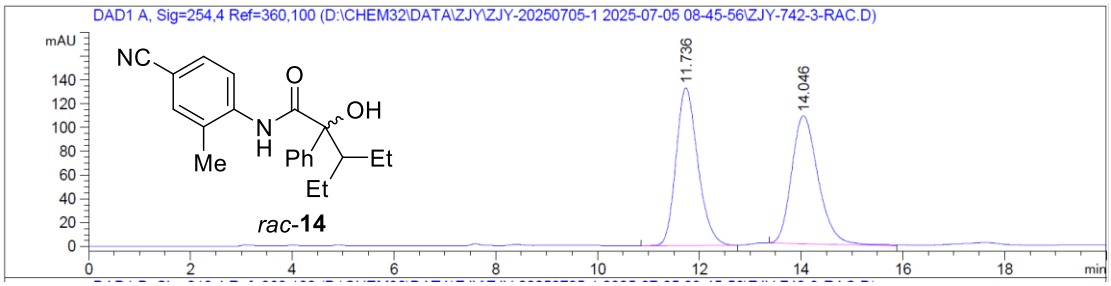
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.093	BB	0.5202	4733.05176	137.28860	50.0710
2	23.478	MM R	0.7860	4719.63525	100.08295	49.9290
Totals :				9452.68701	237.37156	



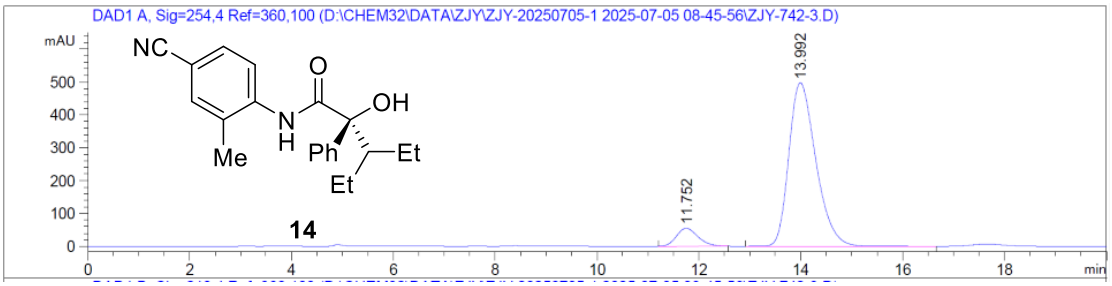
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.213	MM R	0.5652	479.67462	14.14455	4.2094
2	23.463	MM R	0.7679	1.09156e4	236.91074	95.7906
Totals :				1.13952e4	251.05528	



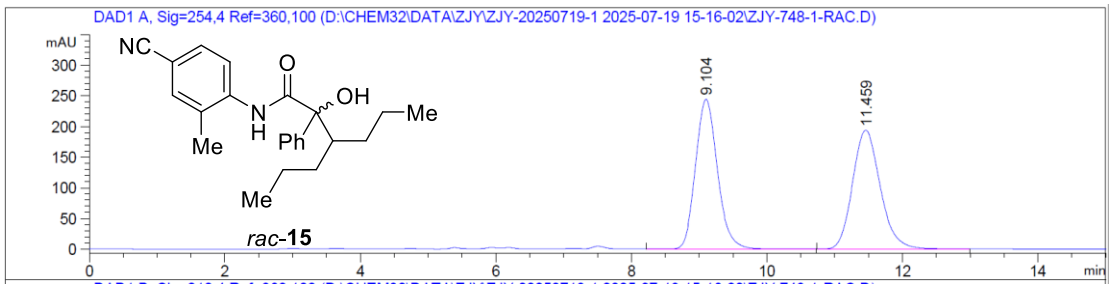
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.736	BB	0.4579	3948.72583	132.40881	50.0933
2	14.046	MM R	0.6083	3934.01978	107.78139	49.9067
Totals :				7882.74561	240.19021	



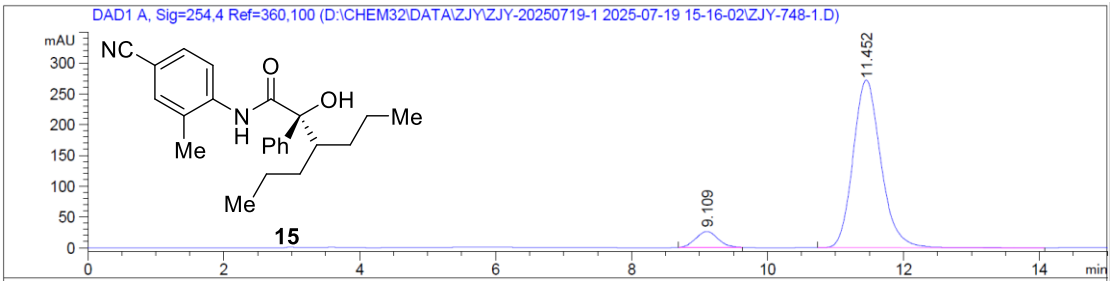
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.752	MM R	0.4909	1616.62927	54.88396	8.0944
2	13.992	MM R	0.6149	1.83556e4	497.48807	91.9056
Totals :				1.99723e4	552.37203	



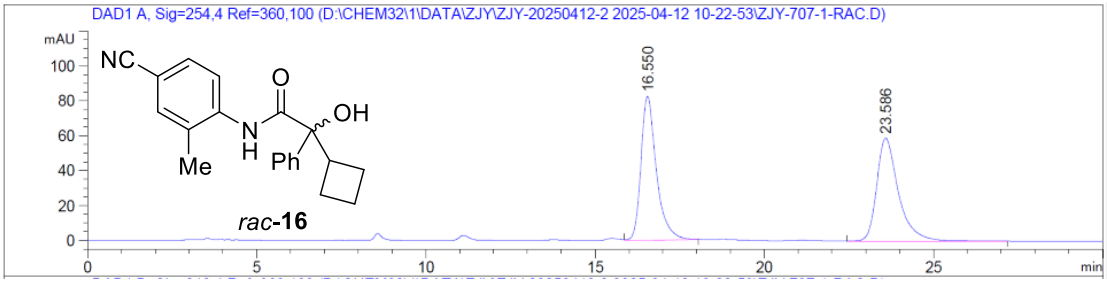
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.104	BB	0.3506	5499.06787	244.31459	49.9878
2	11.459	BB	0.4376	5501.74902	193.54573	50.0122
Totals :				1.10008e4	437.86032	



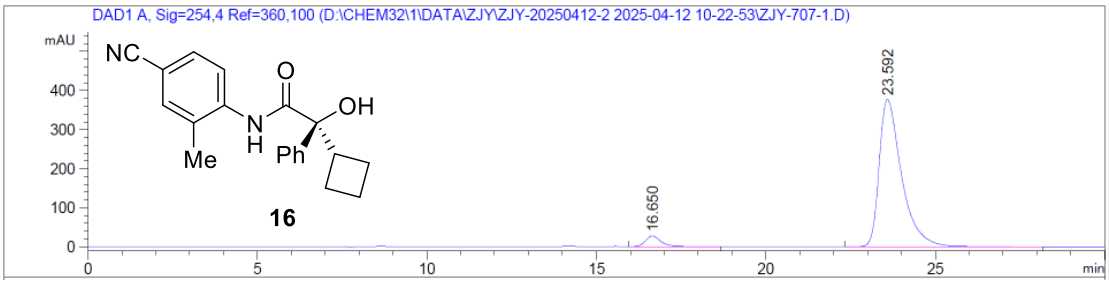
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.109	MM R	0.3810	600.19281	26.25214	7.2082
2	11.452	MM R	0.4732	7726.30762	272.11951	92.7918
Totals :				8326.50043	298.37164	



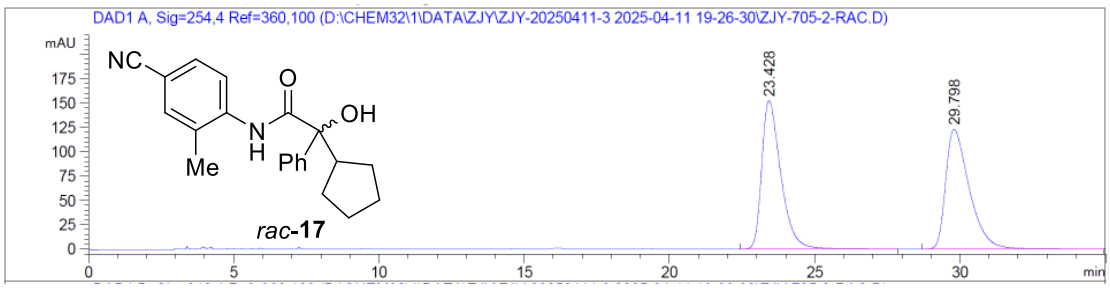
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.550	MM R	0.5281	2609.39917	82.35350	49.9816
2	23.586	BB	0.6644	2611.31982	58.99294	50.0184
Totals :				5220.71899	141.34644	



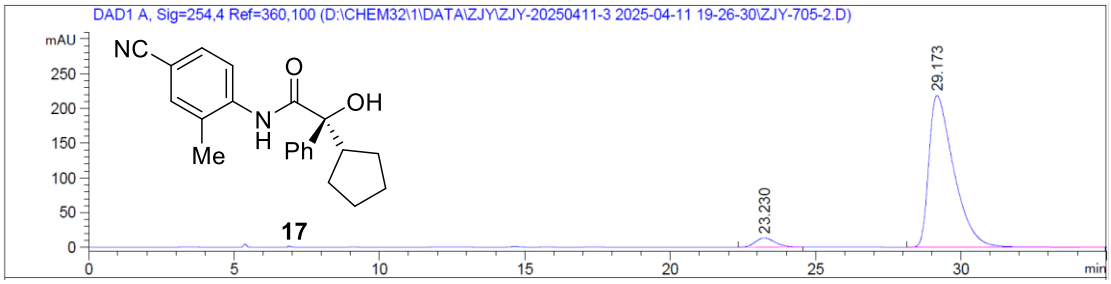
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.650	BB	0.4772	877.79175	27.58794	4.8138
2	23.592	BB	0.6880	1.73571e4	377.80411	95.1862
Totals :				1.82349e4	405.39204	



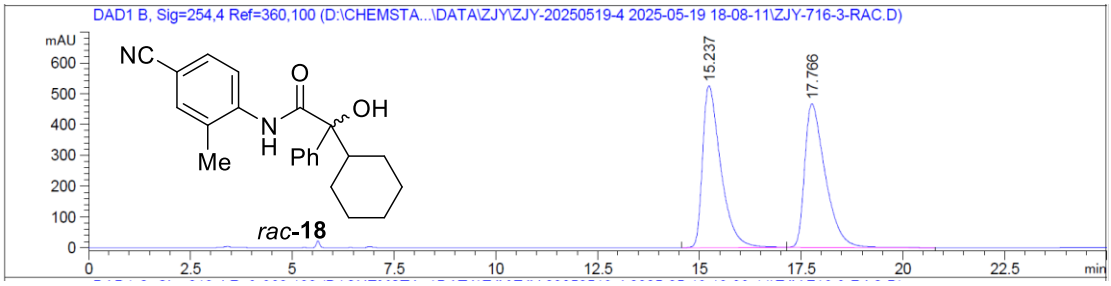
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.428	BB	0.6884	6947.84131	152.25319	50.0685
2	29.798	BBA	0.8520	6928.82471	122.84574	49.9315
Totals :				1.38767e4	275.09893	



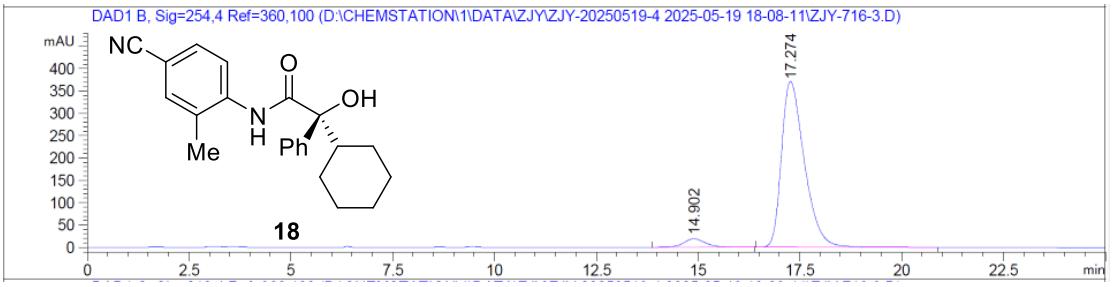
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.230	MM R	0.7942	632.19440	13.26735	4.6278
2	29.173	BBA	0.8934	1.30286e4	218.59309	95.3722
Totals :				1.36608e4	231.86045	



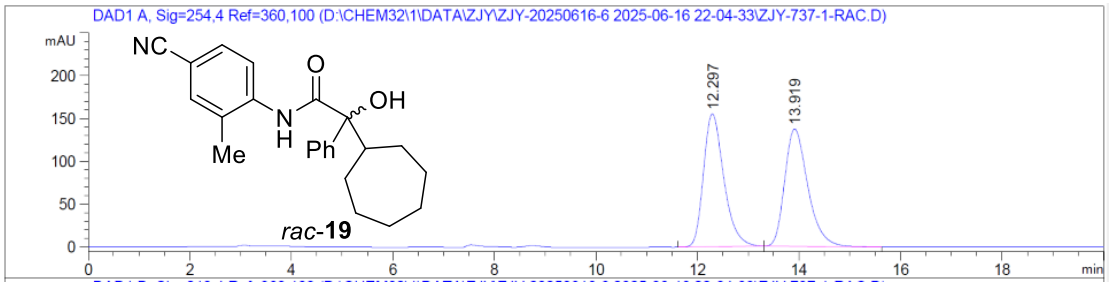
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.237	BB	0.4638	1.62805e4	525.00568	49.9536
2	17.766	BB	0.5266	1.63108e4	465.76324	50.0464
Totals :				3.25913e4	990.76892	



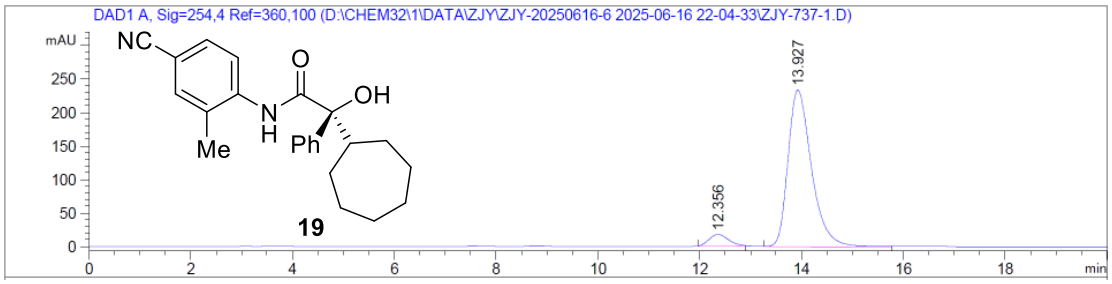
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.902	BB	0.5703	717.52106	19.01376	4.7118
2	17.274	BB	0.5899	1.45107e4	371.34204	95.2882
Totals :				1.52283e4	390.35580	



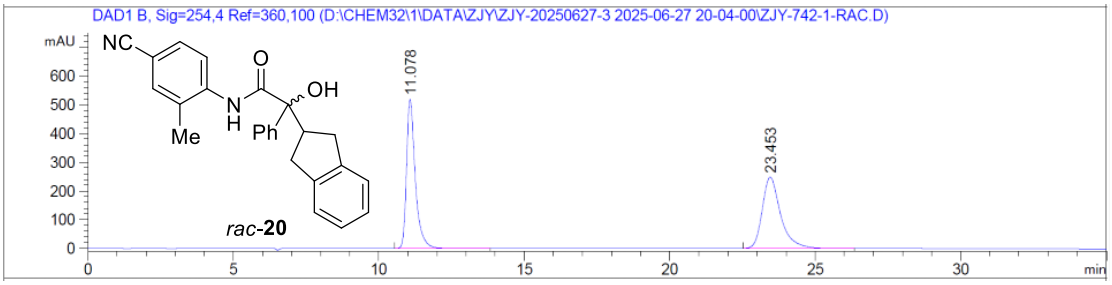
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.297	BB	0.4294	4317.13281	154.80367	49.9617
2	13.919	BB	0.4869	4323.75928	136.74925	50.0383
Totals :				8640.89209	291.55292	



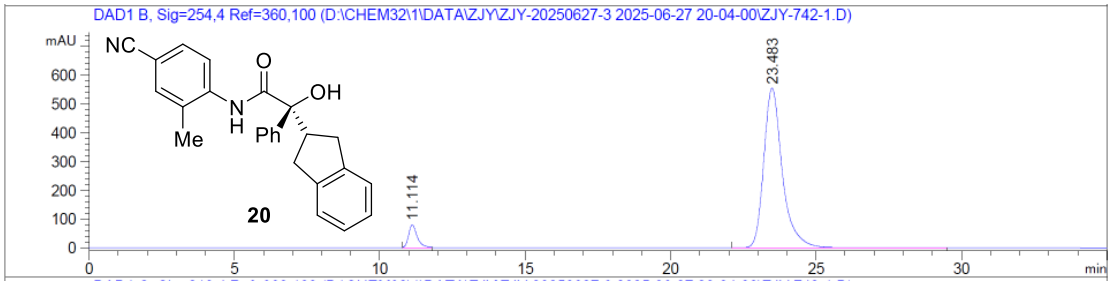
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.356	MM R	0.4324	444.91733	17.14773	5.5381
2	13.927	MM R	0.5407	7588.76904	233.91710	94.4619
Totals :				8033.68637	251.06483	



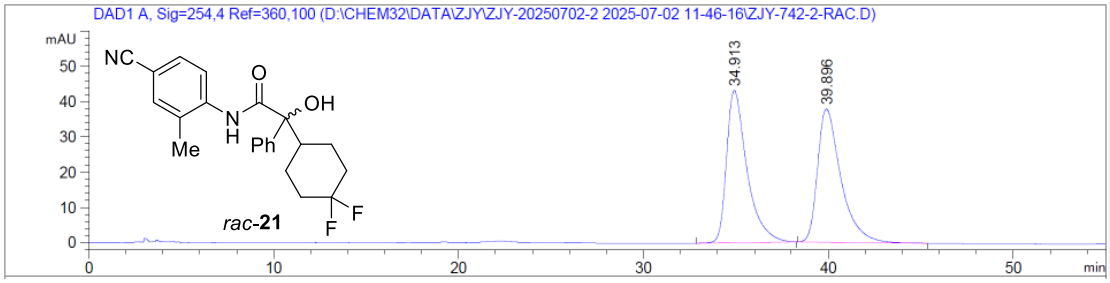
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.078	BB	0.3146	1.08693e4	518.45599	49.9059
2	23.453	FM R	0.7333	1.09103e4	247.97775	50.0941
Totals :				2.17796e4	766.43375	



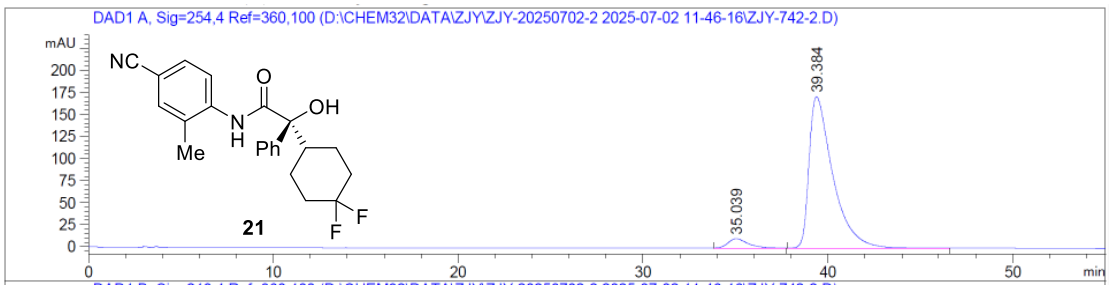
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.114	MM R	0.3416	1629.82910	79.52686	6.1366
2	23.483	MM R	0.7473	2.49292e4	556.00873	93.8634
Totals :				2.65590e4	635.53558	



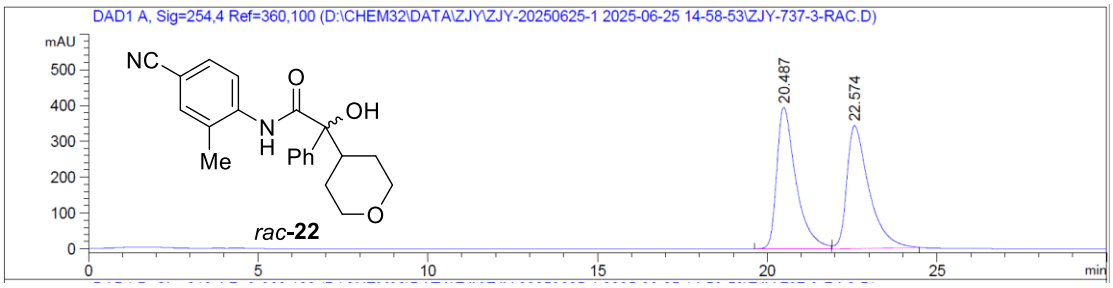
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.913	BB	1.1447	3319.34790	43.18784	50.0411
2	39.896	BB	1.2949	3313.89233	37.79785	49.9589
Totals :				6633.24023	80.98569	



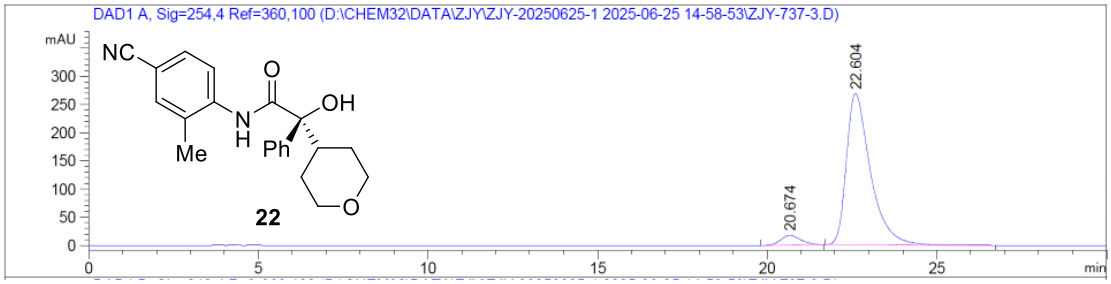
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.039	BB	1.0694	776.56738	10.44453	4.8339
2	39.384	BB	1.3223	1.52884e4	171.46307	95.1661
Totals :				1.60650e4	181.90761	



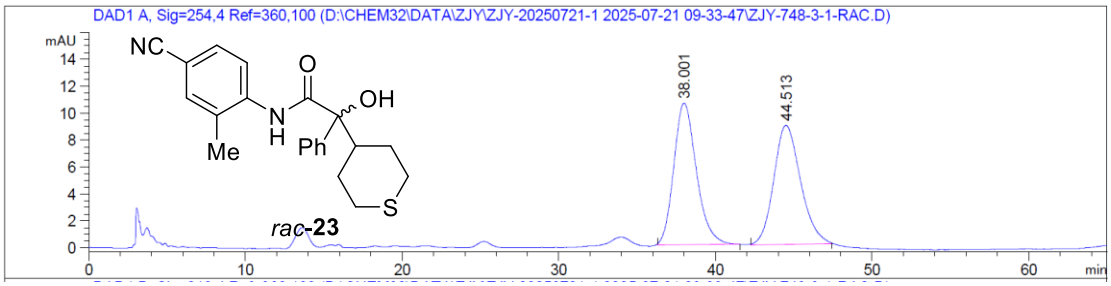
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.487	MM R	0.6577	1.55808e4	394.83990	50.0497
2	22.574	MM R	0.7566	1.55498e4	342.53177	49.9503
Totals :				3.11306e4	737.37167	



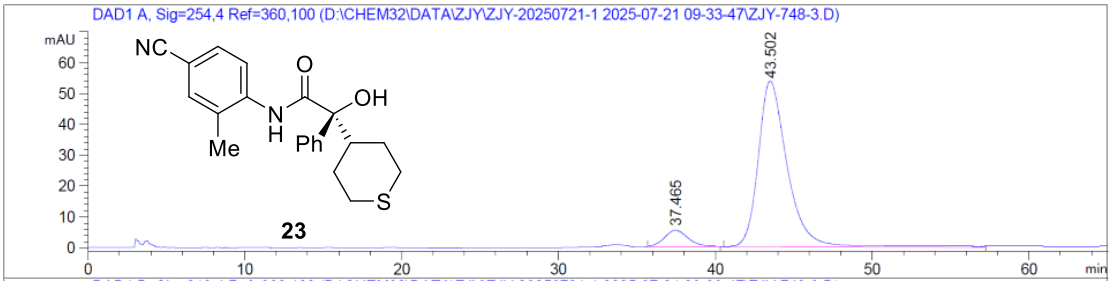
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.674	BB	0.6287	704.96405	17.25260	5.0541
2	22.604	BB	0.7402	1.32434e4	268.16928	94.9459
Totals :				1.39483e4	285.42188	



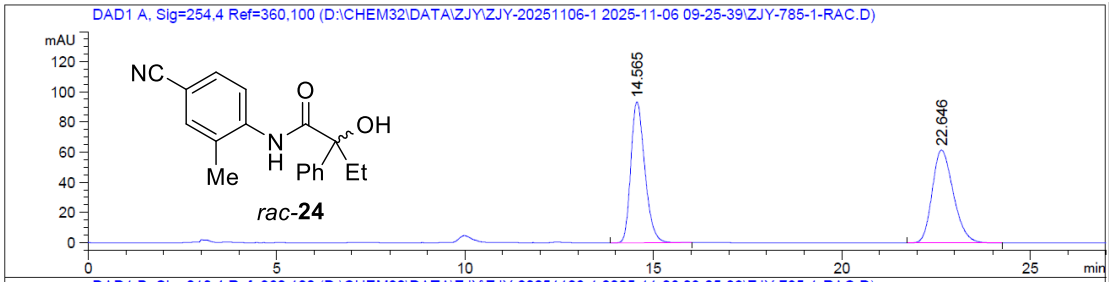
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	38.001	MM R	1.6726	1057.88391	10.54133	50.0634
2	44.513	MM R	1.9851	1055.20618	8.85943	49.9366
Totals :				2113.09009	19.40076	



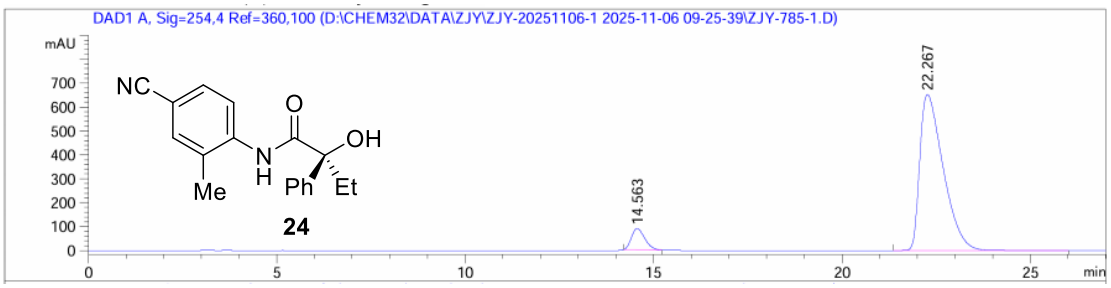
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.465	MM R	1.7283	547.78894	5.28268	7.2430
2	43.502	MM R	2.1778	7015.24121	53.68713	92.7570
Totals :				7563.03015	58.96981	



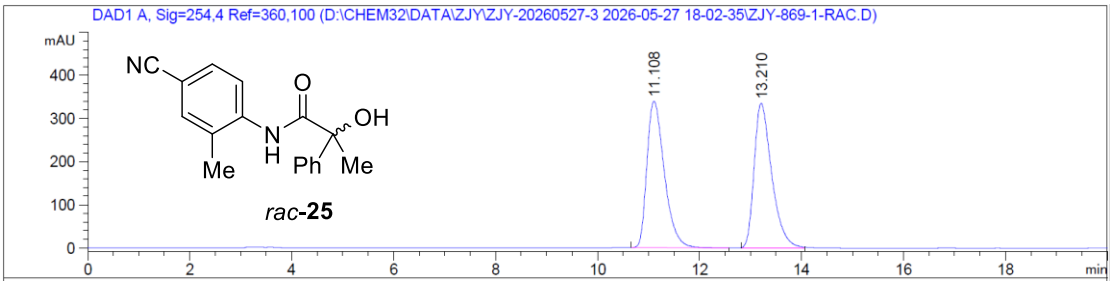
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.565	BB	0.3994	2414.55347	93.45667	50.0411
2	22.646	BB	0.5999	2410.58301	61.68615	49.9589
Totals :				4825.13647	155.14282	



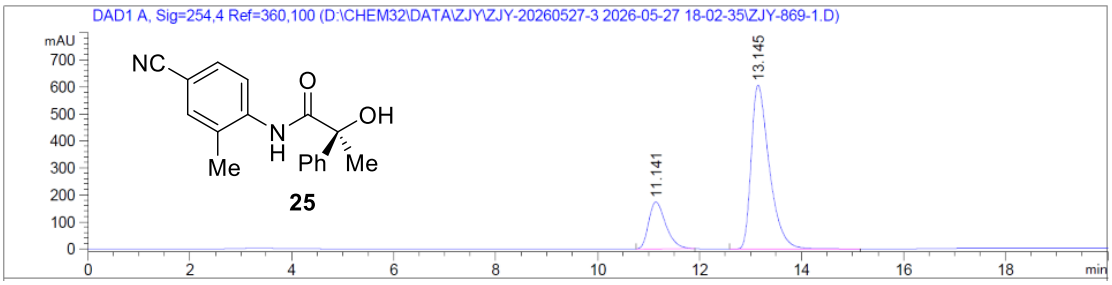
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.563	MM R	0.4107	2199.42920	89.25930	7.1915
2	22.267	MM R	0.7242	2.83842e4	653.26324	92.8085
Totals :				3.05836e4	742.52254	



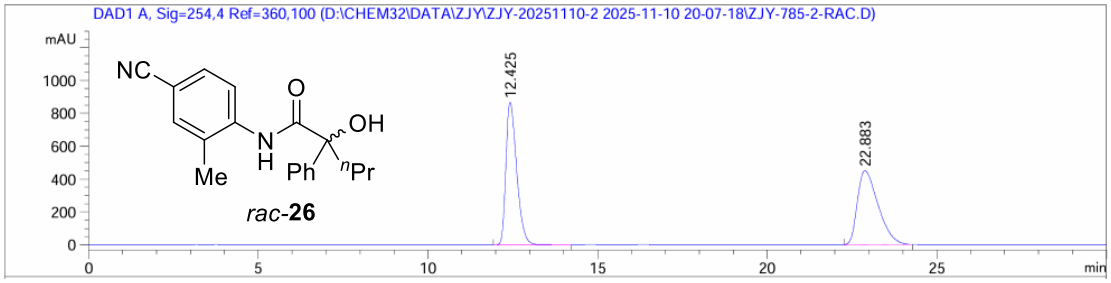
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.108	BB	0.3671	8055.74561	339.17111	50.0754
2	13.210	MM R	0.3998	8031.49365	334.84692	49.9246
Totals :				1.60872e4	674.01804	



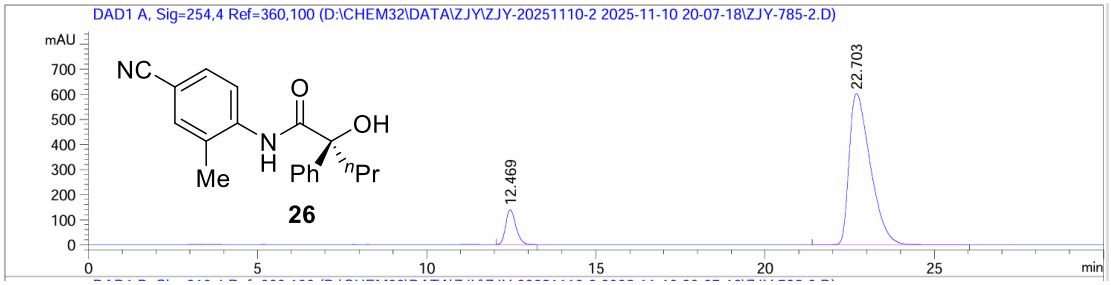
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.141	MM R	0.3912	4072.69067	173.52132	21.4151
2	13.145	BB	0.3715	1.49452e4	606.52509	78.5849
Totals :				1.90179e4	780.04640	



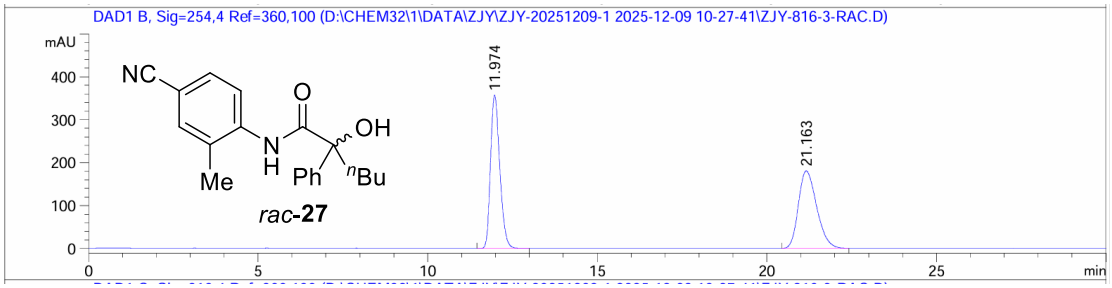
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.425	BB	0.3397	1.91337e4	866.39160	49.9886
2	22.883	MM R	0.7102	1.91424e4	449.23212	50.0114
Totals :				3.82761e4	1315.62372	



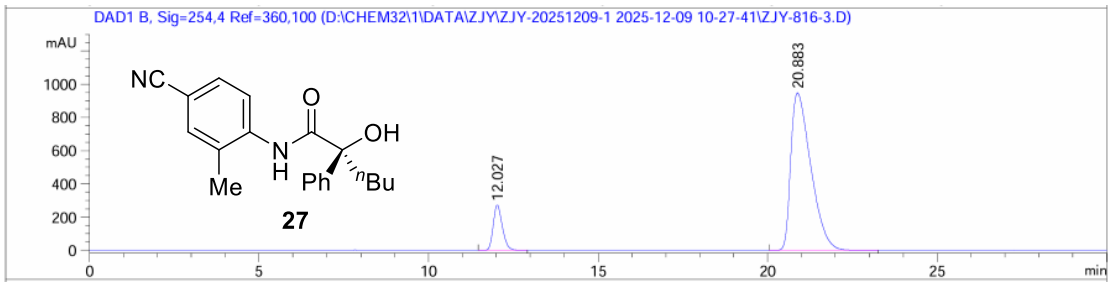
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.469	MM R	0.3530	2950.69141	139.30421	10.0756
2	22.703	MM R	0.7286	2.63349e4	602.39838	89.9244
Totals :				2.92856e4	741.70259	



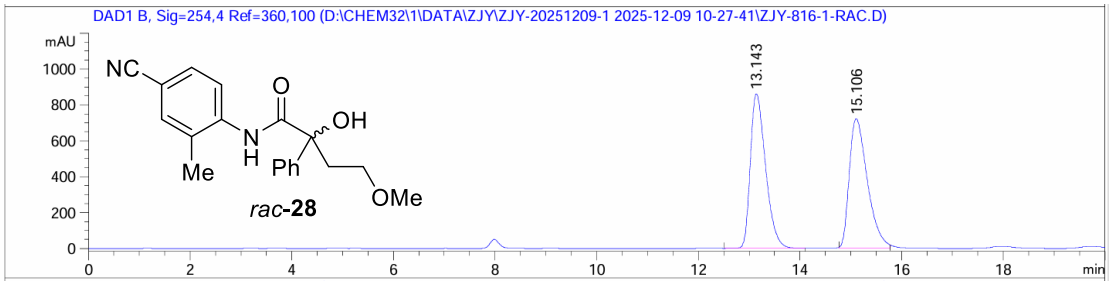
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.974	BB	0.2939	6785.37109	356.75858	49.9571
2	21.163	MM R	0.6257	6797.03809	181.05424	50.0429
Totals :				1.35824e4	537.81282	



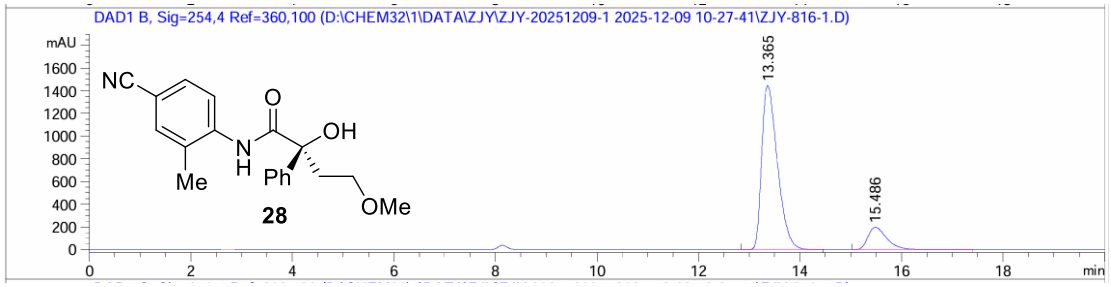
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.027	BB	0.2862	5057.42041	272.85208	11.5446
2	20.883	BB	0.6269	3.87503e4	948.05365	88.4554
Totals :				4.38077e4	1220.90573	



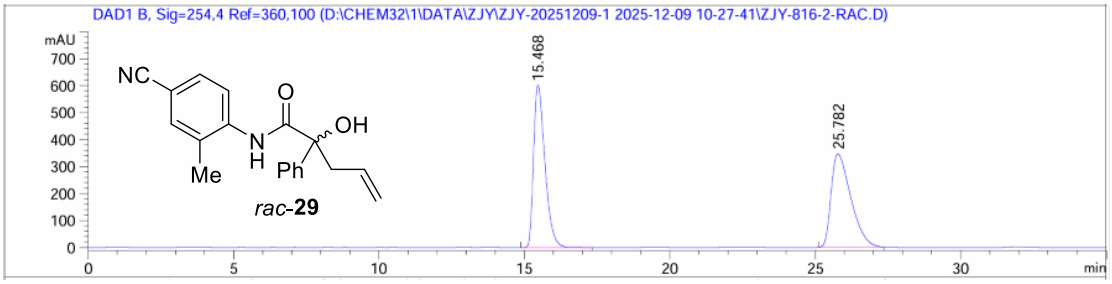
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.143	BB	0.3208	1.79103e4	860.57751	50.0184
2	15.106	MF R	0.4128	1.78971e4	722.57605	49.9816
Totals :				3.58075e4	1583.15356	



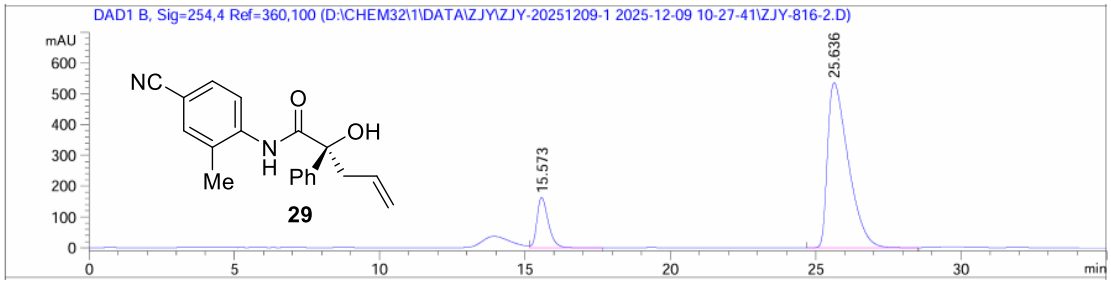
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.365	BB	0.3326	3.10335e4	1444.87805	85.9457
2	15.486	BB	0.3953	5074.78760	196.51381	14.0543
Totals :				3.61083e4	1641.39186	



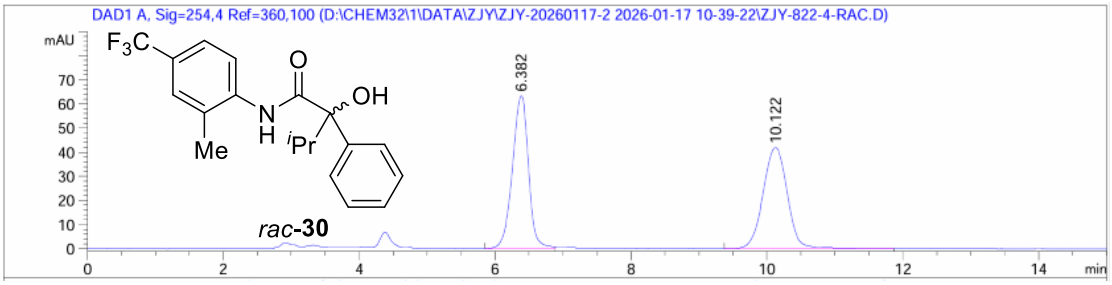
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.468	BB	0.4151	1.62370e4	601.11505	49.9664
2	25.782	MM R	0.7829	1.62588e4	346.14609	50.0336
Totals :				3.24958e4	947.26114	



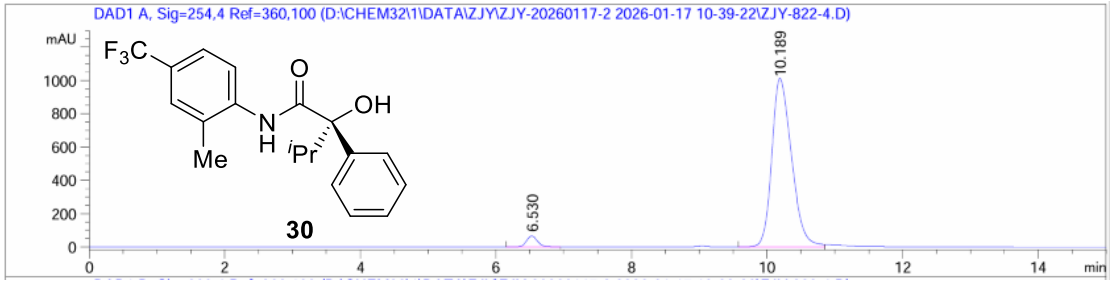
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.573	VB	0.4114	4382.96826	163.15613	14.1574
2	25.636	MM R	0.8259	2.65758e4	536.27850	85.8426
Totals :				3.09588e4	699.43463	



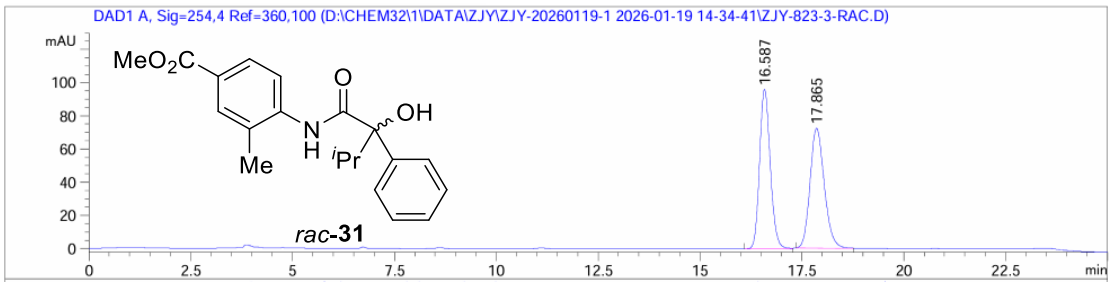
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.382	MF R	0.2731	1037.85718	63.32822	50.0478
2	10.122	BB	0.3907	1035.87488	41.85410	49.9522
Totals :				2073.73206	105.18232	



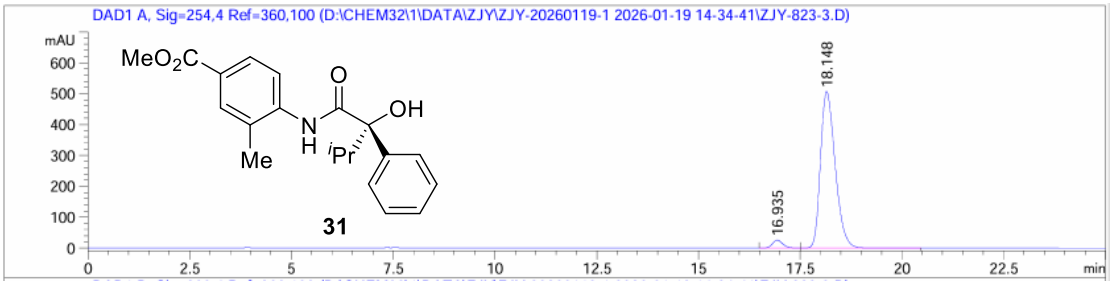
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.530	MF R	0.1882	740.30859	65.54549	3.4838
2	10.189	MF R	0.3373	2.05095e4	1013.43146	96.5162
Totals :				2.12498e4	1078.97695	



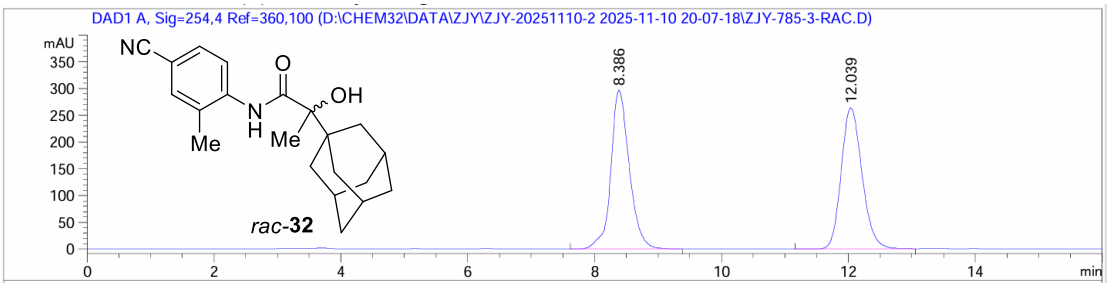
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.587	MM R	0.3041	1754.30884	96.13198	49.9911
2	17.865	MM R	0.4051	1754.93262	72.20422	50.0089
Totals :				3509.24146	168.33620	



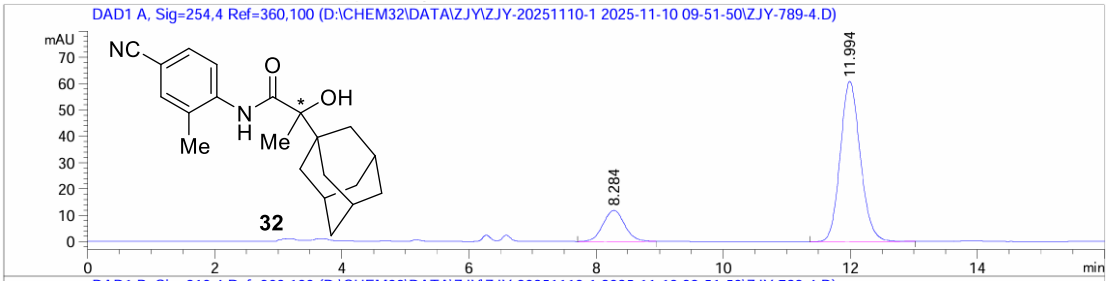
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.935	BB	0.2739	447.55847	25.36481	3.4088
2	18.148	BB	0.3879	1.26818e4	506.80045	96.5912
Totals :				1.31294e4	532.16525	



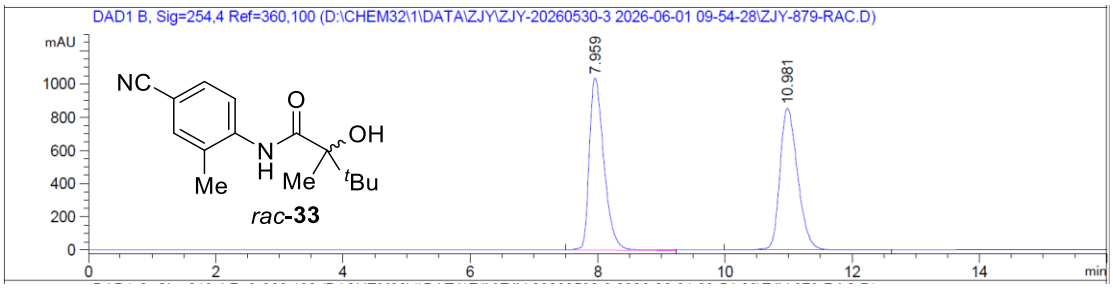
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.386	BB	0.3032	5987.46289	296.93918	49.9448
2	12.039	BB	0.3537	6000.69727	263.47778	50.0552
Totals :				1.19882e4	560.41696	



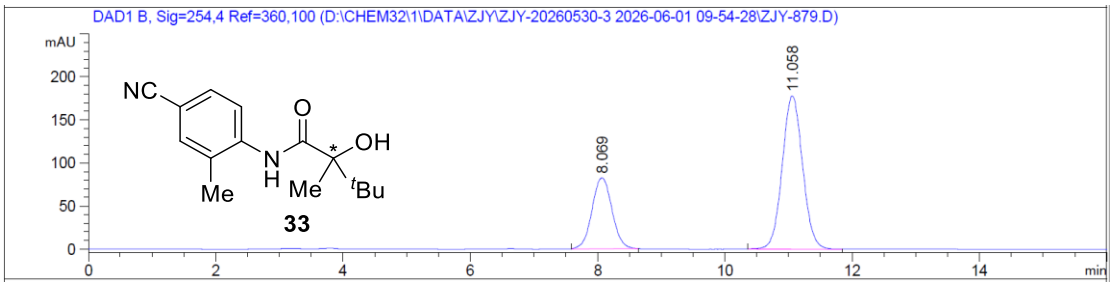
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.284	BB	0.3706	280.64508	11.83529	17.3276
2	11.994	BB	0.3405	1338.99500	60.89240	82.6724
Totals :				1619.64008	72.72769	



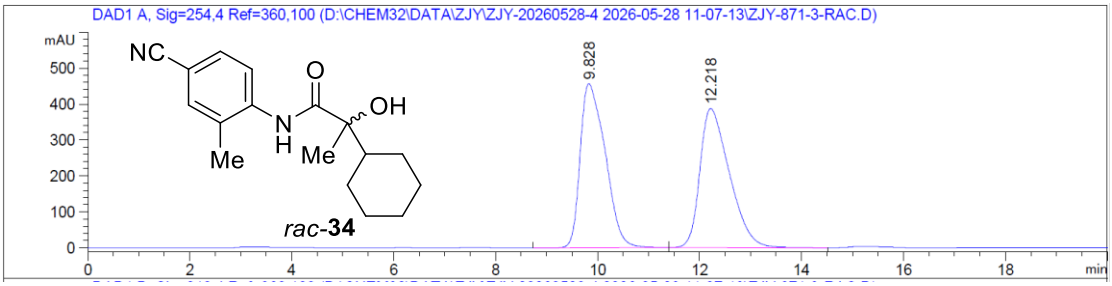
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.959	MM R	0.2659	1.65136e4	1035.18701	49.9007
2	10.981	BB	0.3009	1.65793e4	852.65613	50.0993
Totals :				3.30930e4	1887.84314	



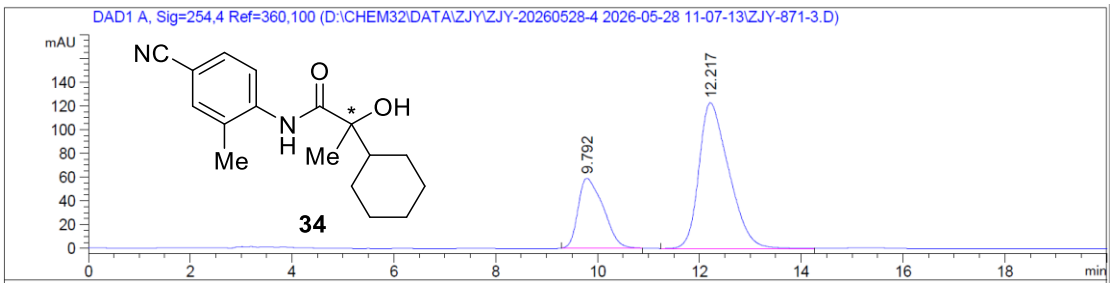
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.069	MM R	0.3622	1790.97363	82.41676	31.0879
2	11.058	MM R	0.3718	3970.02344	177.95221	68.9121
Totals :				5760.99707	260.36897	



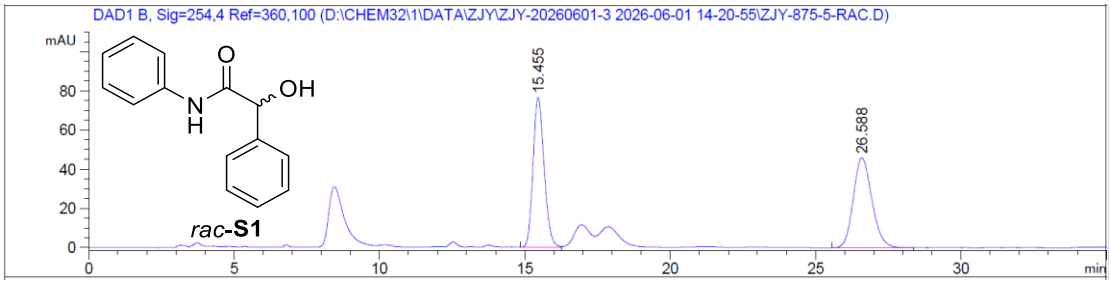
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.828	BB	0.5649	1.55261e4	456.38425	49.9568
2	12.218	BB	0.6131	1.55530e4	386.83139	50.0432
Totals :				3.10791e4	843.21564	



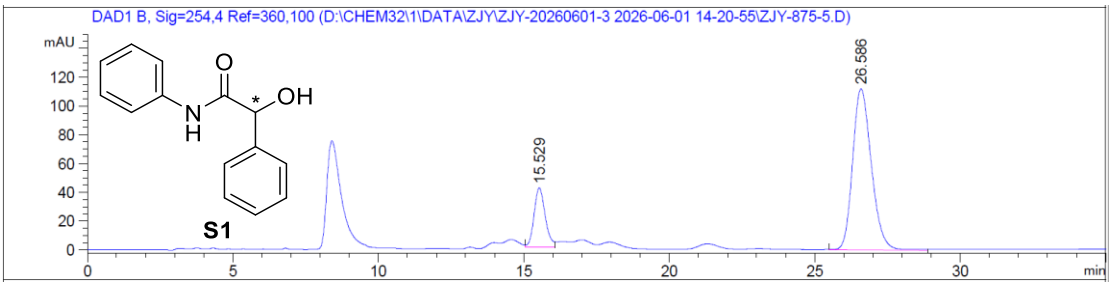
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.792	MM R	0.5689	2013.10535	58.97418	28.5468
2	12.217	MM R	0.6837	5038.84961	122.83995	71.4532
Totals :				7051.95496	181.81413	



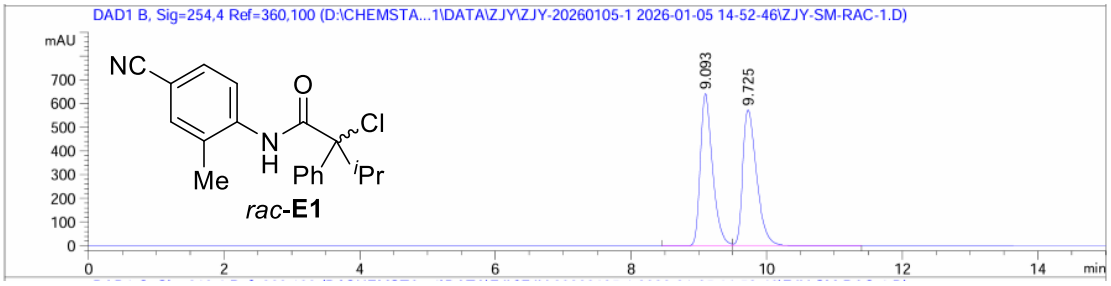
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.455	MM R	0.4432	2029.97241	76.33259	49.9224
2	26.588	BB	0.6840	2036.28345	45.85831	50.0776
Totals :				4066.25586	122.19090	



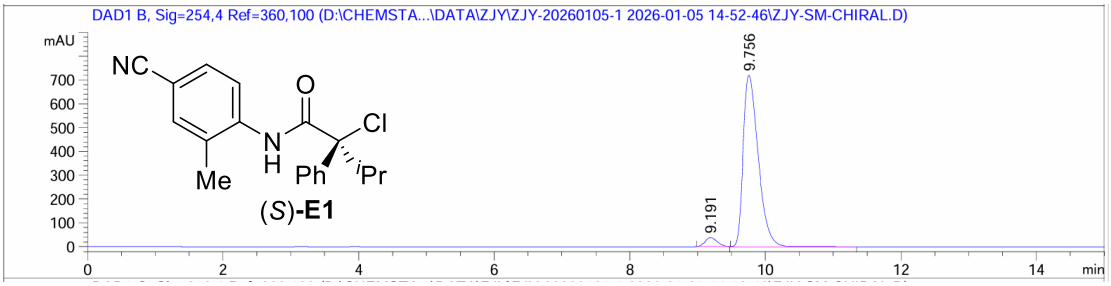
Signal 2: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.529	MM R	0.4453	1100.84021	41.19957	17.9514
2	26.586	MM R	0.7486	5031.50342	112.02131	82.0486
Totals :				6132.34363	153.22087	



Signal 2: DAD1 B, Sig=254,4 Ref=360,100

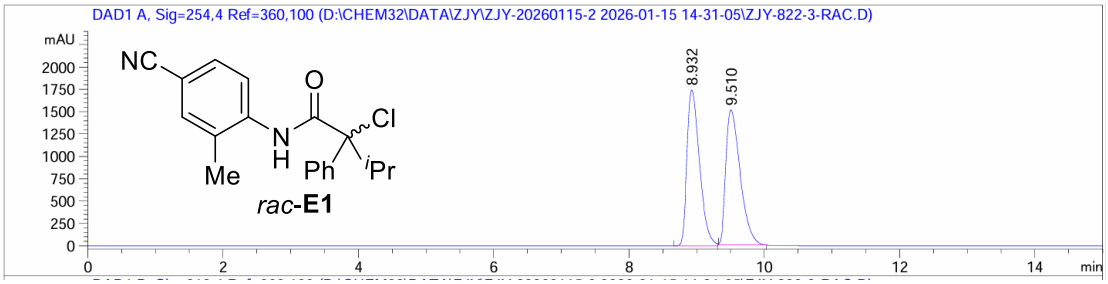
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.093	BV	0.1953	8083.25000	640.34473	49.7627
2	9.725	VB	0.2184	8160.35693	572.04858	50.2373
Totals :				1.62436e4	1212.39331	



Signal 2: DAD1 B, Sig=254,4 Ref=360,100

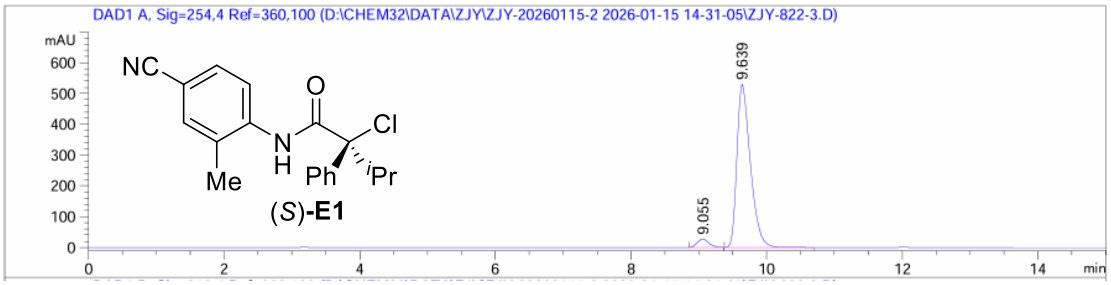
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.191	MM R	0.2129	487.55161	38.16169	4.1962
2	9.756	MM R	0.2574	1.11314e4	720.74292	95.8038
Totals :				1.16190e4	758.90461	

The HPLC spectra for one-pot protocol



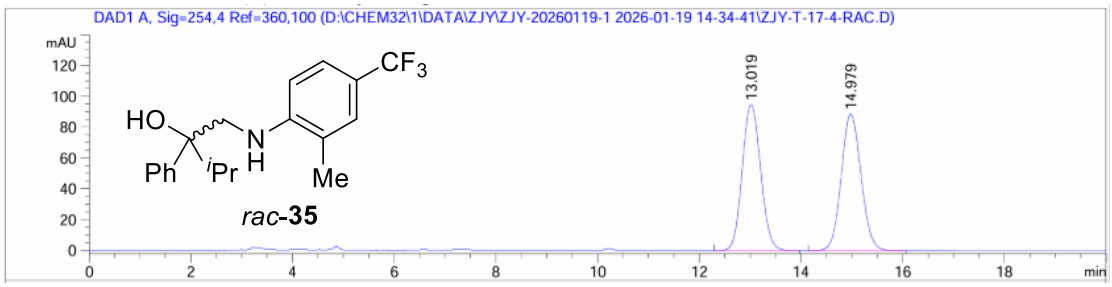
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.932	BV	0.1974	2.23380e4	1744.17993	50.0364
2	9.510	MM R	0.2455	2.23055e4	1514.05164	49.9636
Totals :				4.46435e4	3258.23157	



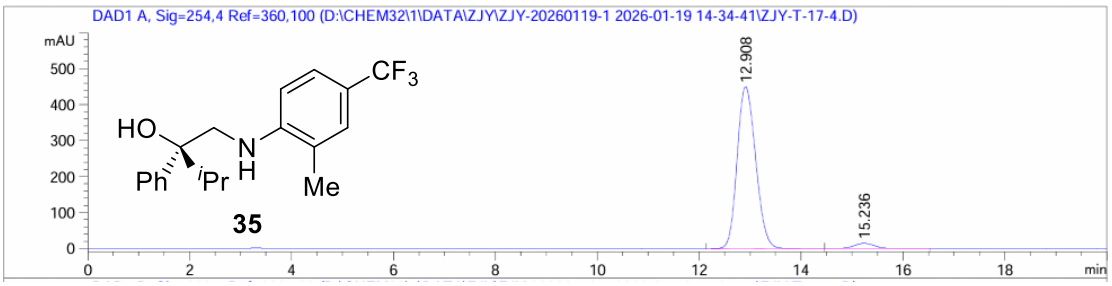
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.055	MM R	0.1950	313.29178	26.78301	4.0956
2	9.639	MM R	0.2308	7336.14648	529.69159	95.9044
Totals :				7649.43826	556.47460	



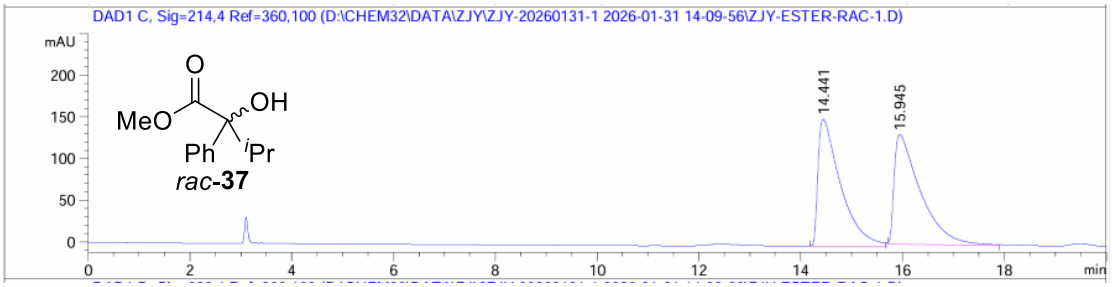
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.019	BB	0.3962	2388.61670	94.71024	50.0254
2	14.979	BB	0.4208	2386.19189	88.43827	49.9746
Totals :				4774.80859	183.14851	



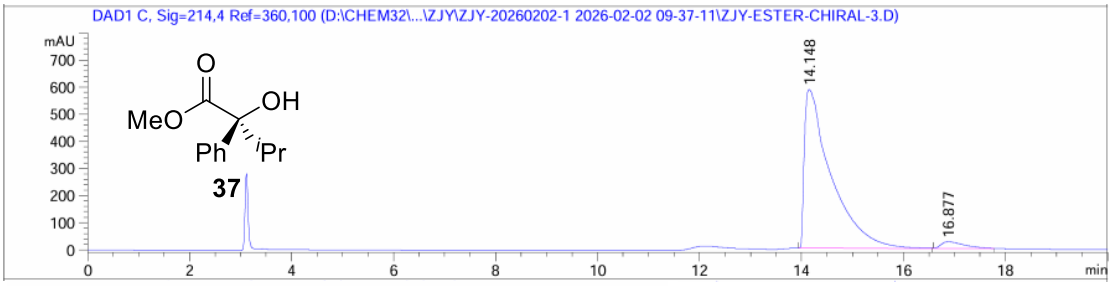
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.908	BB	0.3960	1.13424e4	450.02972	96.5202
2	15.236	BB	0.4350	408.91980	14.67722	3.4798
Totals :				1.17514e4	464.70695	



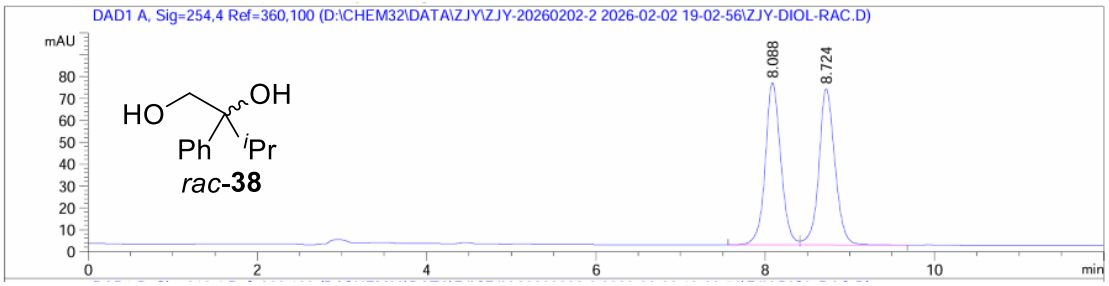
Signal 3: DAD1 C, Sig=214,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.441	MM R	0.5106	4672.34229	152.50262	49.9018
2	15.945	MM R	0.5924	4690.73633	131.97124	50.0982



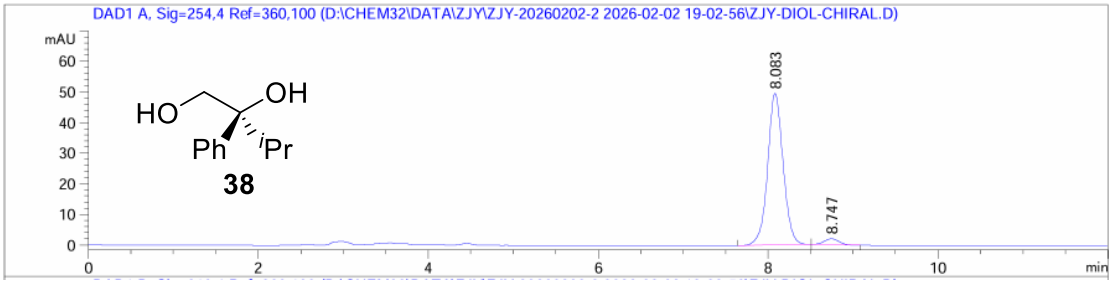
Signal 3: DAD1 C, Sig=214,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.148	MM R	0.6069	2.13012e4	584.94171	96.4494
2	16.877	MM R	0.5271	784.15247	24.79357	3.5506
Totals :				2.20853e4	609.73528	



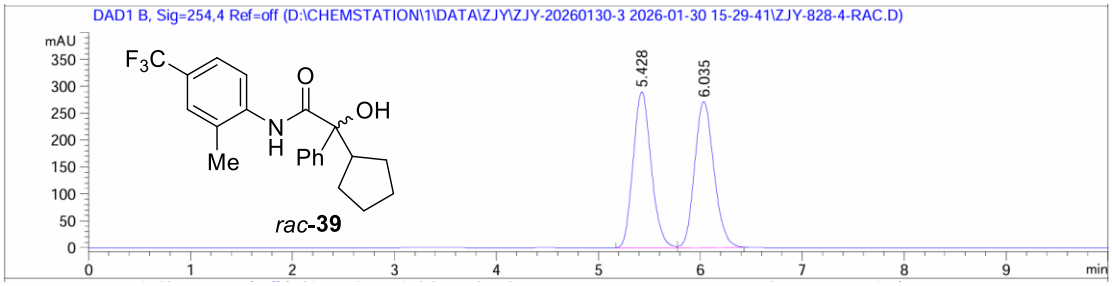
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.088	BV	0.1921	940.65082	74.11330	49.9652
2	8.724	VB	0.1997	941.96222	71.49957	50.0348
Totals :				1882.61304	145.61287	



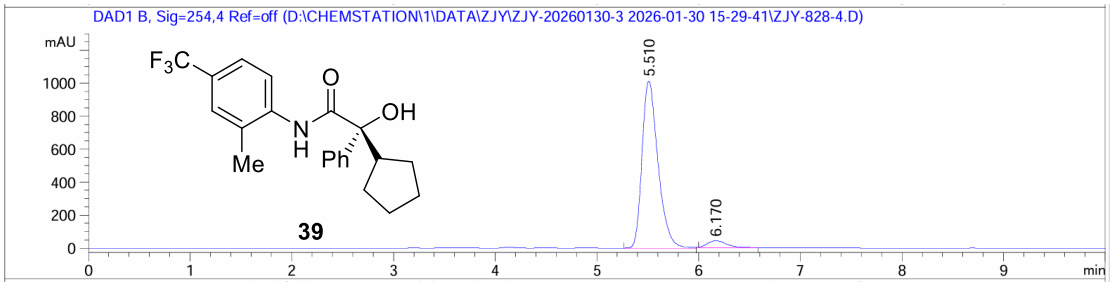
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.083	BB	0.1938	628.32593	49.59962	96.3762
2	8.747	BB	0.1853	23.62535	1.97832	3.6238
Totals :				651.95128	51.57794	



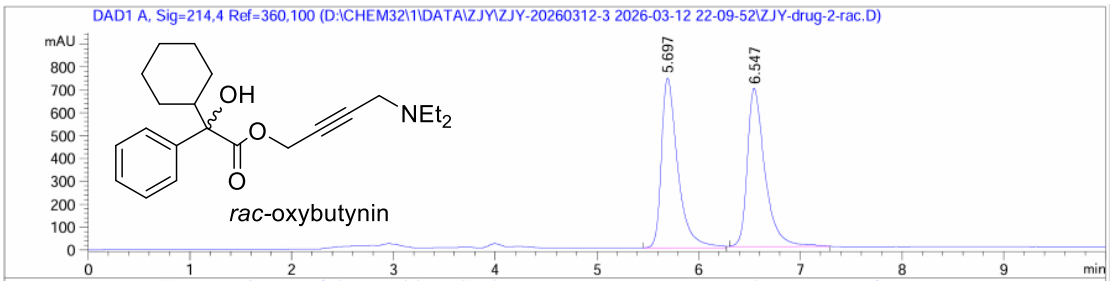
Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.428	MF R	0.2059	3586.30054	290.27826	50.0521
2	6.035	FM R	0.2199	3578.84033	271.29404	49.9479
Totals :				7165.14087	561.57230	



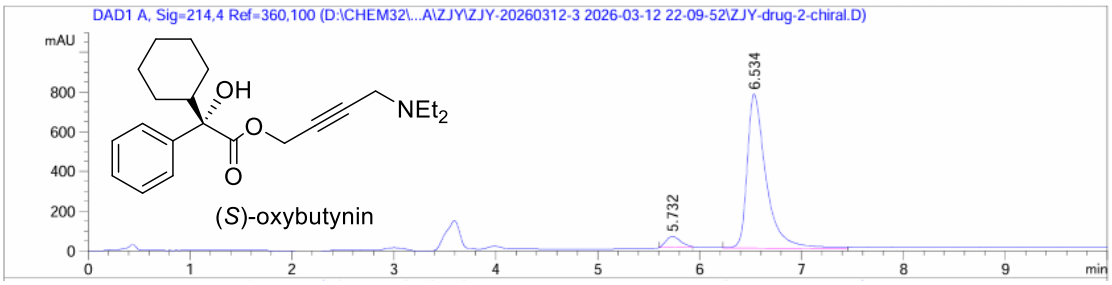
Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.510	MM R	0.1810	1.10034e4	1013.09473	95.0123
2	6.170	MM R	0.2274	577.62708	42.32753	4.9877
Totals :				1.15810e4	1055.42226	



Signal 1: DAD1 A, Sig=214,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.697	MF R	0.1871	8360.56348	744.89545	50.0042
2	6.547	MM R	0.2008	8359.17383	693.96899	49.9958
Totals :				1.67197e4	1438.86444	



Signal 1: DAD1 A, Sig=214,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.732	MM R	0.1620	531.81665	54.69880	5.0402
2	6.534	MM R	0.2151	1.00196e4	776.22900	94.9598
Totals :				1.05514e4	830.92781	

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