
Supplementary information

Chiral Brønsted acid-catalyzed enantioselective synthesis of 3-azabicyclo[3.1.1]heptanes

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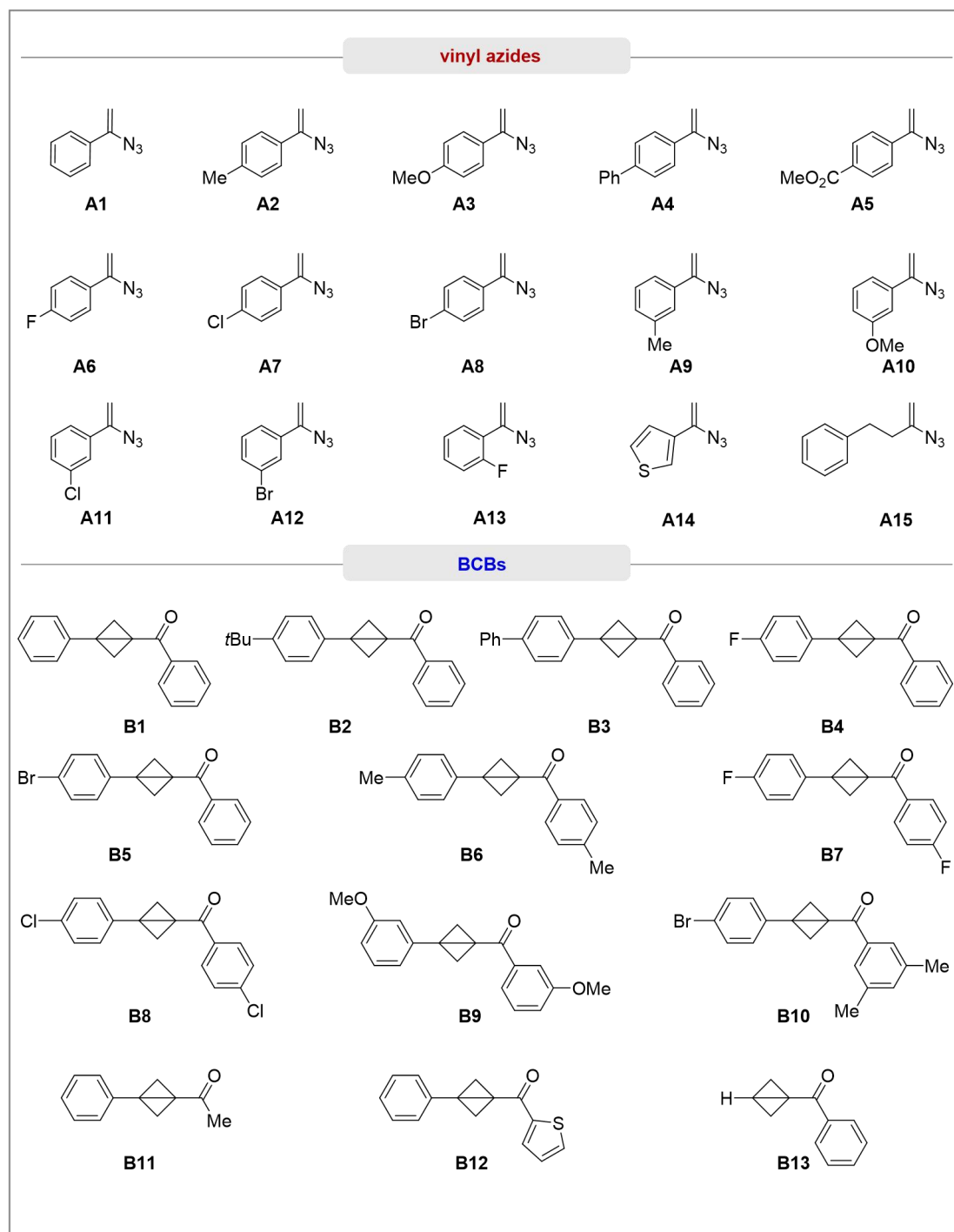
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1. General information

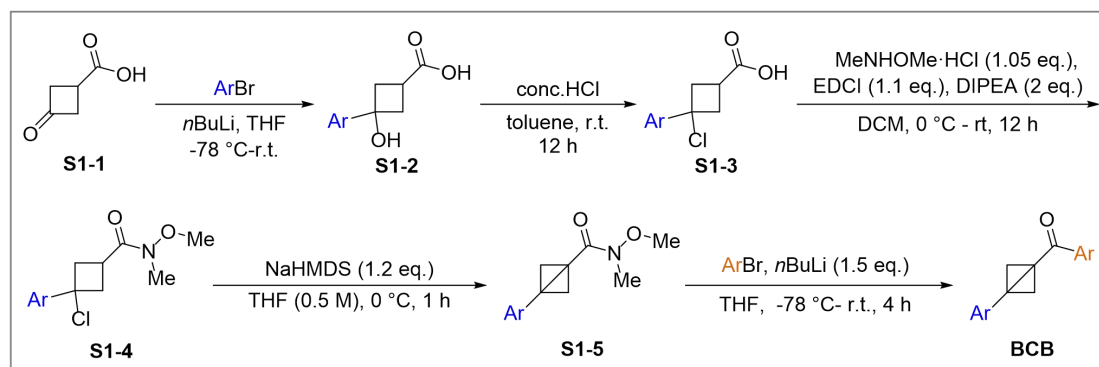
Chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. All Solvents were purified according to the standard procedures. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 GF254 plates. Flash column chromatography was performed using Tsingdao silica gel (60, particle size 0.040-0.063 mm). Visualization on TLC was achieved by use of UV light (254 nm). ^1H NMR spectra were recorded on Bruker 400 MHz spectrometer in CDCl_3 with tetramethylsilane (TMS) as internal standard, ^{13}C NMR spectra were measured at 101 MHz, ^{31}P NMR spectra were measured at 162 MHz, and ^{19}F NMR spectra were measured at 376 MHz. The chemical shifts are expressed in ppm and coupling constants are given in Hz. Data for ^1H NMR are recorded as follows: chemical shift (δ , ppm), multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; m = multiplet; brs = broad singlet), integration. Data for ^{13}C NMR are reported in terms of chemical shift (δ , ppm). The enantiomeric excess values were determined by chiral HPLC with an Agilent instrument and a Daicel CHIRALCEL and CHIRALPAK column. High resolution mass spectroscopy (HRMS) analyses were performed at a Q-Exactive (Thermo Scientific) Inc mass instrument. Optical rotations were measured using an Autopol I automatic polarimeter (1 mL cell, 1 dm path length; concentration (c) is in g/100 mL and $[\alpha]_{\text{D}}^{25}$ values are in degrees).

2. Substrates involved in the manuscript

Scheme S1. Vinyl azides **A1-A15** were synthesized according to the reported literature^[1-2], BCBs **B1, B2, B4, B8, B11-B13** were prepared according to literature^[3-7], and their spectral data are in accordance with the reported data.



a) General procedure A for synthesis of BCBs



To a solution of aryl bromides (44 mmol, 2.2 equiv.) in dry THF (60 mL) was added *n*-BuLi (2.5 M, 2.2 equiv.) dropwise at $-78\text{ }^{\circ}\text{C}$ under argon. The mixture was stirred for 1 h at $-78\text{ }^{\circ}\text{C}$, and then a solution of 3-oxocyclobutane-1-carboxylic acid **S1-1** (20 mmol, 1.0 equiv.) in dry THF (10 mL) was added in one portion at $25\text{ }^{\circ}\text{C}$. The mixture was stirred for 1 h, and quenched with a sat. solution of NH_4Cl . The organic layer was separated and aqueous layer was acidified with HCl (1 N) and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product **S1-2** was used for the next step without purification.

To a solution of **S1-2** in toluene (20 mL) was added conc. HCl (20 mL). The resulting mixture was stirred at room temperature for 12 h. The organic phase was separated, washed with water and brine, and concentrated under reduced pressure to give compound **S1-3**. The crude product was used for the next step without purification.

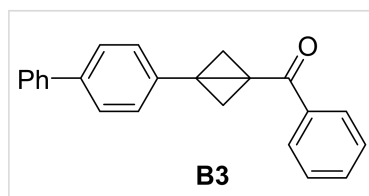
To an ice-cooled suspension of *N,O*-dimethylhydroxylamine hydrochloride (21 mmol, 1.05 equiv.) and crude mixture **S1-3** (20 mmol, 1.0 equiv.) in CH_2Cl_2 (0.4 M, 60 mL) was added *i*PrNEt₂ (40 mmol, 2 equiv.). After stirring for 5 min, EDCI·HCl (22 mmol, 1.1 equiv.) was added in one portion and the reaction mixture was stirred for 12 h while allowing it to warm to room temperature. The mixture was diluted with CH_2Cl_2 and organic layer was washed with saturated aqueous NaHCO_3 , water, brine, dried Na_2SO_4 . Then the solvent was evaporated in vacuum to give **S1-4**, which directly used in next reaction without further purification.

A round bottom flask under argon atmosphere was charged with **S1-4** (20 mmol, 1 equiv.) and THF (0.5 M, 40 mL). NaHMDS (2 M in THF, 1.2 equiv.) was added dropwise at $0\text{ }^{\circ}\text{C}$ and stirred for 3 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and the organic layer was extracted with CH_2Cl_2 . The

combined organic phase was washed with brine, dried over Na₂SO₄ and concentrated in vacuum. The crude reaction mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc = 4/1) to afford **S1-5** as white solid.

To a solution of ArBr (12 mmol, 1.5 equiv.) in dry THF (0.2 M, 40 mL) was added *n*BuLi (2.4 M, 12 mmol, 1.5 equiv.) dropwise under argon at -78 °C. After stirred at the same temperature for 2 h, a solution of **S1-5** (8 mmol, 1.0 equiv.) in THF (5 mL) was added. After 0.5 h, the resulting mixture was moved to room temperature for 1.5 h before quenched with saturated NH₄Cl solution. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous NaSO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1) to obtain BCB.

(3-([1,1'-Biphenyl]-4-yl)bicyclo[1.1.0]butan-1-yl)(phenyl)methanone (B3)



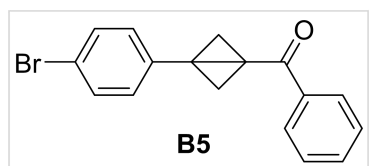
B3 was synthesized according to **General procedure A**. Flash chromatography on silica gel (petroleum ether/EtOAc = 10/1) provided the title compound as a white solid (1.36 g, 22% yield over five steps), m.p. 102-105 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.58 – 7.54 (m, 4H), 7.48 – 7.46 (m, 3H), 7.43 – 7.40 (m, 2H), 7.36 – 7.32 (m, 3H), 7.21 (d, *J* = 8.4 Hz, 2H), 3.21 (t, *J* = 1.1 Hz, 2H), 1.96 (t, *J* = 1.0 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 196.68, 140.60, 140.05, 138.39, 132.04, 128.91, 128.52, 128.18, 127.47, 127.19, 127.02, 126.62, 38.86, 38.02, 31.74.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₃H₁₉O, 311.1430; found, 311.1431.

(3-(4-Bromophenyl)bicyclo[1.1.0]butan-1-yl)(phenyl)methanone (B5)



B5 was synthesized according to General procedure A. Flash chromatography on silica gel (petroleum ether/EtOAc = 10/1) provided the title compound as a white solid (2.25 g, 36% yield over five steps), m.p. 82-85 °C.

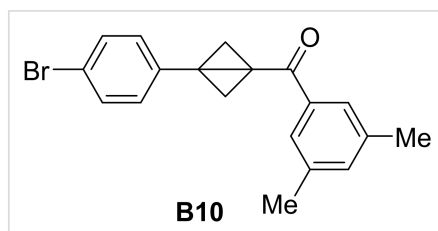
¹H NMR (400 MHz, CDCl₃): δ 7.57 (d, *J* = 7.2 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.37 – 7.33 (m, 4H), 7.00 (d, *J* = 8.5 Hz, 2H), 3.12 (t, *J* = 1.2 Hz, 2H), 1.92 (t, *J* = 1.2 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 196.27, 138.13, 132.30, 132.24, 131.65, 128.52, 128.26, 127.74, 121.29, 37.93, 37.68, 31.46.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₁₇H₁₄BrO, 313.0223; found, 313.0223.

(3-(4-Bromophenyl)bicyclo[1.1.0]butan-1-yl)(3,5-dimethylphenyl)methanone

(B10)



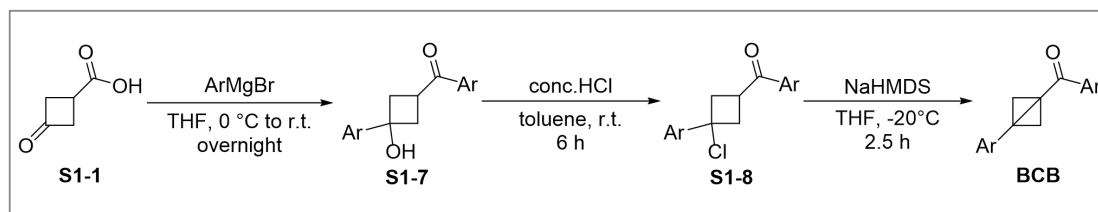
B10 was synthesized according to **General procedure A**. Flash chromatography on silica gel (petroleum ether/EtOAc = 10/1) provided the title compound as a white solid (3.20 g, 47% yield over five steps), m.p. 97-100 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.35 (d, *J* = 8.5 Hz, 2H), 7.17 (s, 2H), 7.11 (s, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 3.11 (t, *J* = 1.1 Hz, 2H), 2.30 (s, 6H), 1.89 (t, *J* = 1.1 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 196.54, 138.24, 137.85, 133.92, 132.50, 131.60, 127.83, 126.29, 121.17, 37.89, 37.34, 31.40, 21.34.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₁₉H₁₈BrO, 341.0536; found, 341.0538.

b) General procedure B for synthesis of BCBs

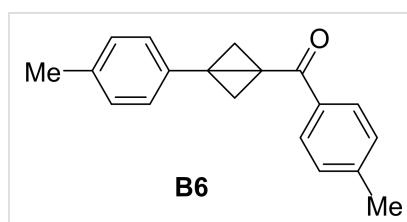


To a solution of 3-oxocyclobutane-1-carboxylic acid **S1-1** (20 mmol, 1.0 equiv.) in dry THF (100 mL) was added ArMgBr (2.0 M, 64 mmol, 3.2 equiv.) dropwise at 0 °C under argon. Move the reaction to room temperature, and the mixture was stirred for 12 h. Then, the mixture was quenched with a saturated aq. solution of NH₄Cl dropwise, and diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuum to give compound **S1-7**. The resulting mixture was used in next step without further purification.

To a solution of **S1-7** (20 mol, 1.0 equiv.) in toluene (20 mL) was added conc. HCl (20 mL). The resulted mixture was stirred at room temperature for 6 h. The organic phase was separated, and ethyl acetate to the resulted mixture, washed with water, saturated NaHCO₃, brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the **S1-8**. The crude product was used for next step without further purification.

S1-8 (20 mmol, 1.0 equiv.) was added to a 250 mL vial and dissolved in 100 mL THF under argon. NaHMDS (24 mmol, 1.2 equiv.) was added dropwise at -20 °C and stirred for 2.5 h. The mixture was quenched with saturated aq. solution of NH₄Cl and washed with water. The organic layer was extracted with EtOAc, washed with brine, dried with Na₂SO₄ and concentrated under reduced pressure. The resultant **BCB** was purified by column chromatography on silica gel.

***p*-Tolyl(3-(*p*-tolyl)bicyclo[1.1.0]butan-1-yl)methanone (B6)**



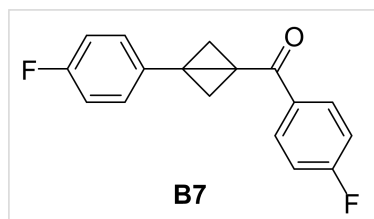
B6 was synthesized according to **General procedure B**. Flash chromatography on silica gel (petroleum ether/EtOAc = 25/1) provided the title compound as a white solid (1.05 g, 20%), m.p. 80-83 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.05 – 7.01 (m, 4H), 3.14 (t, *J* = 1.1 Hz, 2H), 2.37 (s, 3H), 2.28 (s, 3H), 1.87 (t, *J* = 1.1 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 196.29, 142.53, 137.02, 135.91, 129.87, 129.25, 128.81, 128.68, 126.12, 38.78, 37.83, 30.94, 21.72, 21.29.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₁₉H₁₉O, 263.1430; found, 263.1430.

(4-Fluorophenyl)(3-(4-fluorophenyl)bicyclo[1.1.0]butan-1-yl)methanone (B7)



B7 was synthesized according to **General procedure B**. Flash chromatography on silica gel (petroleum ether/EtOAc = 10/1) provided the title compound as a white solid (2.38 g, 44%), m.p. 110-114 °C.

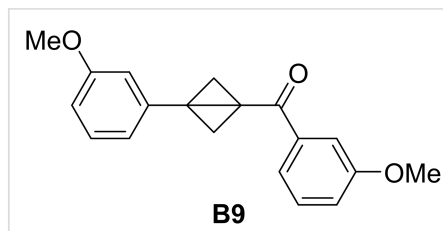
¹H NMR (400 MHz, CDCl₃): δ 7.63 – 7.58 (m, 2H), 7.13 – 7.08 (m, 2H), 7.05 – 7.00 (m, 2H), 6.96 – 6.90 (m, 2H), 3.11 (t, *J* = 1.1 Hz, 2H), 1.92 (t, *J* = 1.1 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 194.87, 165.20 (d, *J* = 253.3 Hz), 162.33 (d, *J* = 246.7 Hz), 134.49 (d, *J* = 3.1 Hz), 130.97 (d, *J* = 9.1 Hz), 128.64 (d, *J* = 3.0 Hz), 127.74 (d, *J* = 8.2 Hz), 115.65 (d, *J* = 21.8 Hz), 115.37 (d, *J* = 21.8 Hz), 38.20, 38.04, 30.74.

¹⁹F NMR (376 MHz, CDCl₃): δ -106.67, -114.42.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₁₇H₁₃F₂O, 271.0929; found, 271.0929.

(3-Methoxyphenyl)(3-(3-methoxyphenyl)bicyclo[1.1.0]butan-1-yl)methanone (B9)



B9 was synthesized according to **General procedure B**. Flash chromatography on silica gel (petroleum ether/EtOAc = 10/1) provided the title compound as a yellow oil (1.12 g, 19%).

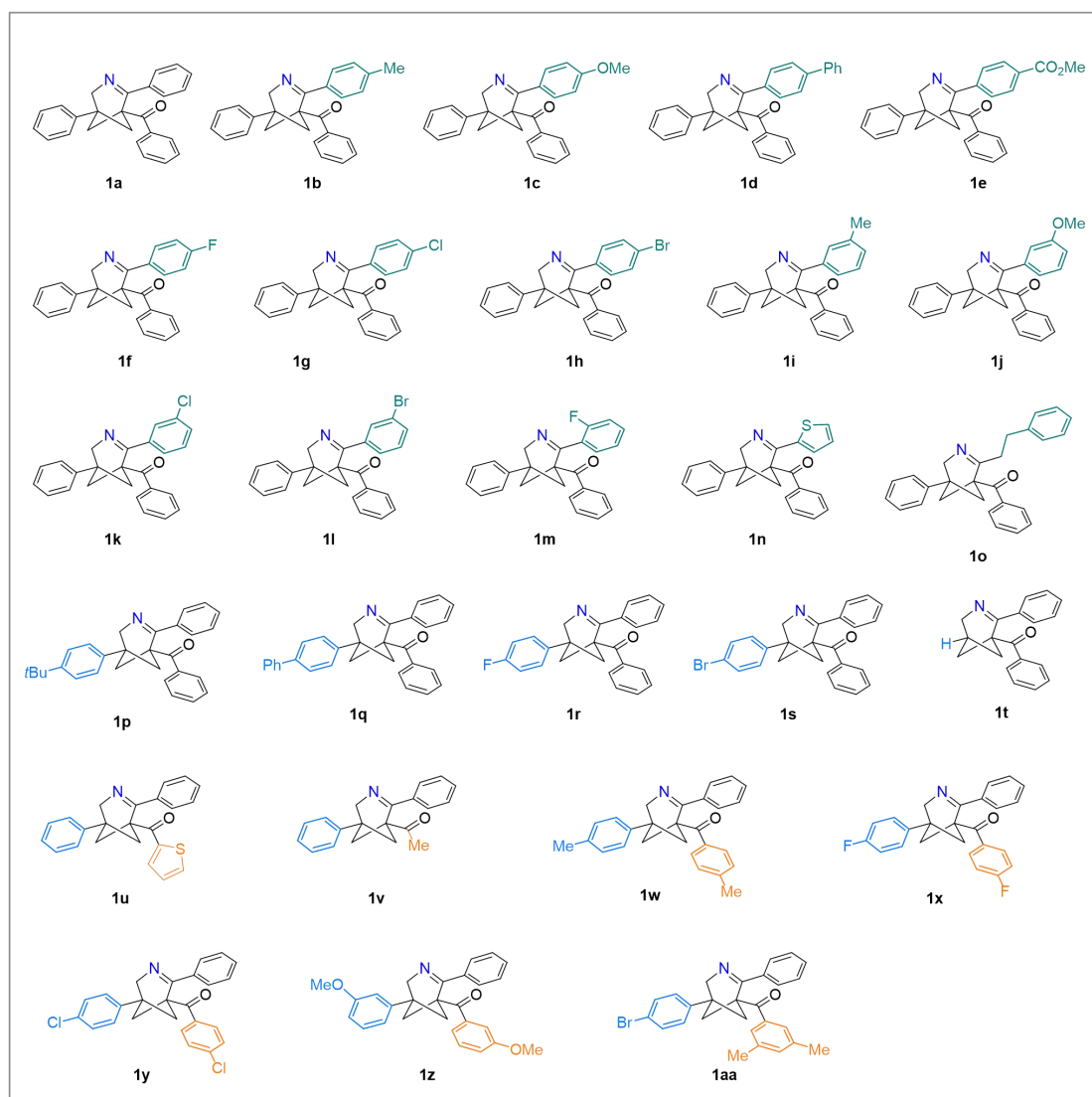
¹H NMR (400 MHz, CDCl₃): δ 7.27 – 7.18 (m, 2H), 7.12 (t, *J* = 8.0 Hz, 1H), 6.99 – 6.95 (m, 2H), 6.73 – 6.70 (m, 2H), 6.63 – 6.62 (m, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.11 (t, *J* = 1.2 Hz, 2H), 1.86 (t, *J* = 1.2 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 196.42, 159.63, 159.39, 139.73, 134.56, 129.54, 129.08, 121.38, 118.71, 118.47, 113.09, 112.47, 111.77, 55.47, 55.25, 38.79, 37.95, 31.49.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₁₉H₁₉O₃, 295.1329; found, 295.1331.

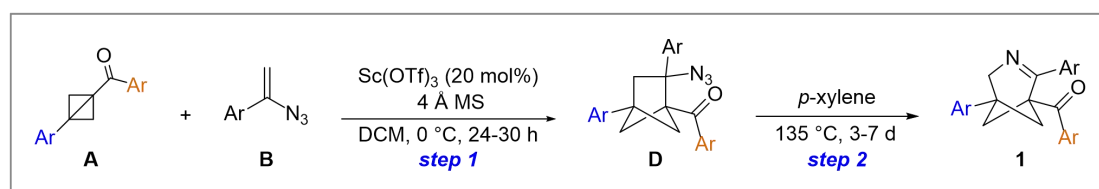
3. Preparation of imines

Scheme S2. Imines investigated in the manuscript



All imines were synthesized following a literature procedure^[5]. The characterization data for imines **1a–1h**, **1k** and **1u** were consistent with those reported previously.

General procedure C for synthesis of imines

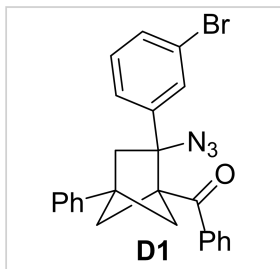


Step 1. A dried Schlenk-tube equipped with a magnetic stir was charged with 4 Å MS (200 wt%) and BCB **A** (2 mmol, 1.0 equiv.). The tube was evacuated and backfilled

with argon three times. CH₂Cl₂ (0.1 M, 20 mL) was added, followed by vinyl azides **B** (3 mmol, 1.5 equiv.) and Sc(OTf)₃ (0.4 mmol, 20 mol%) under a gentle counterflow of argon. The resulting mixture was stirred at 0 °C for 24-30 h. The reaction mixture was then passed through a short celite column (ca. 1 cm in length) and eluted with CH₂Cl₂ to remove the inorganic salts and other insoluble solids. The solvent was evaporated under reduced pressure, and the crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 50/1) to afford the pure products.

Step 2. To an oven-dried Schlenk-tube equipped with a magnetic stir was charged with compound **D** (1 mmol, 1.0 equiv.). The tube was evacuated and backfilled with argon three times. *p*-xylene (0.1 M, 10 mL) was added, and the resulting mixture was stirred at 135 °C until **D** was completely consumed (monitored by TLC, typically 3-7 d). After cooling, the crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 6/1) to afford the pure products **1**.

(2-Azido-2-(3-bromophenyl)-4-phenylbicyclo[2.1.1]hexan-1-yl)(phenyl)methanone (D1)

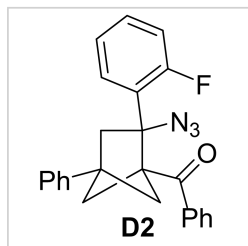


A pale yellow foam (448 mg, 49% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.82 (t, *J* = 7.3 Hz, 2H), 7.56 (t, *J* = 2.0 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.40 – 7.33 (m, 5H), 7.30 – 7.23 (m, 4H), 7.14 (t, *J* = 7.9 Hz, 1H), 3.06 – 2.98 (m, 2H), 2.60 (dd, *J* = 12.0, 3.5 Hz, 1H), 2.40 (dd, *J* = 7.1, 3.0 Hz, 1H), 2.33 (dd, *J* = 9.6, 7.9 Hz, 1H), 2.22 (dd, *J* = 7.9, 3.5 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 199.85, 140.83, 140.48, 137.42, 133.04, 131.49, 131.01, 130.04, 129.33, 128.62, 128.31, 127.10, 126.63, 125.94, 122.78, 75.80, 63.63, 48.70, 48.27, 47.15, 45.19.

HRMS (ESI) *m/z*: [M+Na]⁺ calcd. for C₂₅H₂₀BrN₃NaO, 480.0682; found, 480.0687.



(2-Azido-2-(2-fluorophenyl)-4-phenylbicyclo[2.1.1]hexan-1-yl)(phenyl)methanone (D2)

A white solid (341 mg, 43% yield), m.p. 153-155 °C.

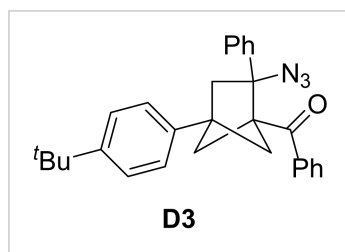
¹H NMR (400 MHz, CDCl₃): δ 7.99 (d, *J* = 7.4 Hz, 2H), 7.57 –

7.52 (m, 2H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.35 – 7.29 (m, 3H), 7.26 – 7.22 (m, 3H), 7.14 – 7.07 (m, 2H), 2.98 (dd, $J = 9.4, 7.0$ Hz, 1H), 2.92 (dt, $J = 12.0, 2.4$ Hz, 1H), 2.73 (ddd, $J = 12.0, 3.5, 1.7$ Hz, 1H), 2.43 (dt, $J = 6.4, 3.2$ Hz, 2H), 2.30 (dd, $J = 9.3, 8.0$ Hz, 1H). **^{13}C NMR (101 MHz, CDCl_3):** δ 201.99, 161.02 (d, $J = 250.7$ Hz), 140.86, 138.05, 132.81, 130.59 (d, $J = 8.9$ Hz), 129.26, 128.63, 128.47, 128.44, 127.05, 126.72 (d, $J = 11.7$ Hz), 125.91, 124.22 (d, $J = 3.4$ Hz), 117.11, 116.89, 73.07, 63.42, 50.85, 48.58, 48.11, 45.61.

^{19}F NMR (376 MHz, CDCl_3): δ -107.39.

HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{25}\text{H}_{20}\text{FN}_3\text{NaO}$, 420.1483; found, 420.1483.

(2-Azido-4-(4-(*tert*-butyl)phenyl)-2-phenylbicyclo[2.1.1]hexan-1-yl)(phenyl)methanone (D3)



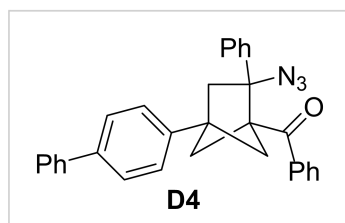
A yellow oil (635 mg, 73% yield).

^1H NMR (400 MHz, CDCl_3): δ 7.80 (d, $J = 7.5$ Hz, 2H), 7.50 (t, $J = 7.4$ Hz, 1H), 7.42 – 7.28 (m, 9H), 7.26 – 7.23 (m, 2H), 3.15 (dd, $J = 11.9, 2.9$ Hz, 1H), 3.02 (dd, $J = 9.5, 7.1$ Hz, 1H), 2.63 (dd, $J = 11.9, 3.5$ Hz, 1H), 2.41 – 2.34 (m, 2H), 2.23 (dd, $J = 7.8, 3.5$ Hz, 1H), 1.34 (s, 9H).

^{13}C NMR (101 MHz, CDCl_3): δ 200.53, 150.02, 138.55, 137.92, 137.57, 132.87, 129.47, 128.62, 128.43, 128.27, 127.97, 125.80, 125.56, 76.48, 63.71, 49.02, 48.04, 47.30, 45.40, 34.65, 31.48.

HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{29}\text{H}_{29}\text{N}_3\text{O}$, 458.2203; found, 458.2204.

(4-([1,1'-Biphenyl]-4-yl)-2-azido-2-phenylbicyclo[2.1.1]hexan-1-yl)(phenyl)methanone (D4)



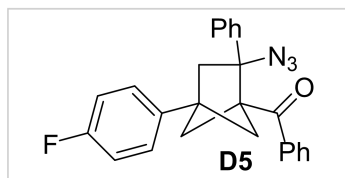
A white solid (592 mg, 65% yield), m.p. 170-174 °C.

^1H NMR (400 MHz, CDCl_3): δ 7.83 (d, $J = 7.3$ Hz, 2H), 7.62 (d, $J = 8.1$ Hz, 4H), 7.53 (t, $J = 7.4$ Hz, 1H), 7.48 – 7.44 (m, 4H), 7.40 – 7.31 (m, 8H), 3.20 (dd, $J = 11.9, 2.9$ Hz, 1H), 3.09 (dd, $J = 9.5, 7.1$ Hz, 1H), 2.69 (dd, $J = 11.9, 3.5$ Hz, 1H), 2.47 – 2.41 (m, 2H), 2.28 (dd, $J = 7.7, 3.5$ Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 200.44, 140.84, 140.06, 140.01, 138.46, 137.54, 132.92, 129.46, 128.93, 128.65, 128.49, 128.29, 127.97, 127.45, 127.40, 127.17, 126.51, 76.47, 63.71, 48.98, 48.13, 47.46, 45.40.

HRMS (ESI) m/z : $[M+Na]^+$ calcd. for $C_{31}H_{25}N_3NaO$, 478.1890; found, 478.1891.

(2-Azido-4-(4-fluorophenyl)-2-phenylbicyclo[2.1.1]hexan-1-yl)(phenyl)methanone (D5)



A white solid (643 mg, 81% yield), m.p. 141-143 °C.

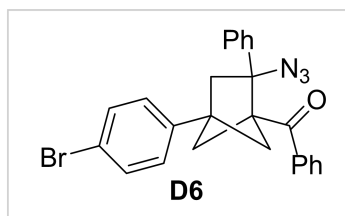
1H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 7.5 Hz, 2H), 7.52 (t, J = 7.4 Hz, 1H), 7.43 – 7.30 (m, 7H), 7.29 – 7.24 (m, 2H), 7.06 (t, J = 8.6 Hz, 2H), 3.13 (dd, J = 11.9, 2.8 Hz, 1H), 3.04 (dd, J = 9.5, 7.2 Hz, 1H), 2.62 (dd, J = 11.9, 3.5 Hz, 1H), 2.39 – 2.35 (m, 2H), 2.21 (dd, J = 7.7, 3.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.33, 161.86 (d, J = 245.5 Hz), 138.36, 137.49, 136.75 (d, J = 3.2 Hz), 132.93, 129.42, 128.66, 128.51, 128.29, 127.92, 127.60 (d, J = 8.0 Hz), 115.60, 115.39, 76.40, 63.55, 48.93, 47.74, 47.58, 45.40.

^{19}F NMR (376 MHz, $CDCl_3$): δ -115.50.

HRMS (ESI) m/z : $[M+Na]^+$ calcd. for $C_{25}H_{20}FN_3NaO$, 420.1483; found, 420.1485.

(2-Azido-4-(4-bromophenyl)-2-phenylbicyclo[2.1.1]hexan-1-yl)(phenyl)methanone (D6)

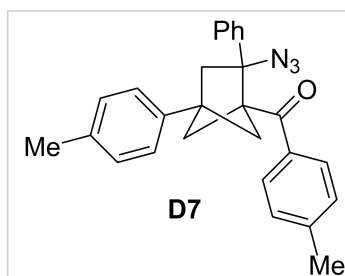


A white solid (695 mg, 76% yield), m.p. 76-79 °C.

1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 7.3 Hz, 2H), 7.52 – 7.47 (m, 3H), 7.41 – 7.29 (m, 7H), 7.16 (d, J = 8.4 Hz, 2H), 3.12 (dd, J = 11.9, 3.0 Hz, 1H), 3.03 (dd, J = 9.5, 7.1 Hz, 1H), 2.60 (dd, J = 11.9, 3.5 Hz, 1H), 2.38 – 2.34 (m, 2H), 2.19 (dd, J = 7.8, 3.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.23, 139.99, 138.28, 137.45, 132.97, 131.75, 129.43, 128.68, 128.54, 128.31, 127.91, 127.81, 120.89, 76.35, 63.60, 48.75, 47.87, 47.48, 45.24.

HRMS (ESI) m/z : $[M+Na]^+$ calcd. for $C_{25}H_{20}BrN_3NaO$, 480.0682; found, 480.0685.



(2-Azido-2-phenyl-4-(p-tolyl)bicyclo[2.1.1]hexan-1-yl)(p-tolyl)methanone (D7)

A yellow foam (391 mg, 48% yield).

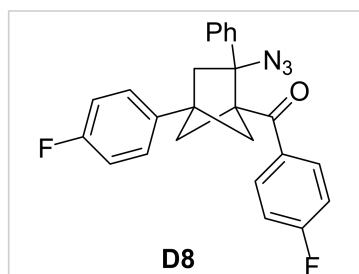
1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.2 Hz, 2H),

7.47 – 7.44 (m, 2H), 7.38 – 7.31 (m, 3H), 7.25 – 7.20 (m, 6H), 3.18 (dd, $J = 11.9$, 3.0 Hz, 1H), 3.06 (dd, $J = 9.5$, 7.1 Hz, 1H), 2.65 (dd, $J = 11.9$, 3.5 Hz, 1H), 2.45 – 2.37 (m, 8H), 2.23 (dd, $J = 7.8$, 3.5 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 199.91, 143.68, 138.54, 138.03, 136.65, 135.00, 129.66, 129.29, 128.95, 128.56, 128.37, 127.97, 125.92, 76.49, 63.62, 49.00, 47.98, 47.31, 45.38, 21.78, 21.22.

HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{27}\text{H}_{25}\text{N}_3\text{NaO}$, 430.1890; found, 430.1893.

(2-Azido-4-(4-fluorophenyl)-2-phenylbicyclo[2.1.1]hexan-1-yl)(4-fluorophenyl)methanone (D8)



A yellow foam (631mg, 76% yield).

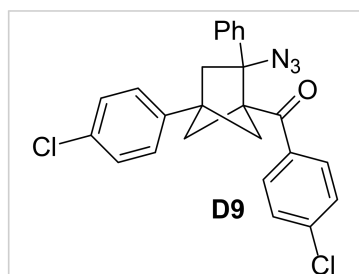
^1H NMR (400 MHz, CDCl_3): δ 7.77 – 7.72 (m, 2H), 7.33 – 7.29 (m, 2H), 7.26 – 7.20 (m, 3H), 7.19 – 7.15 (m, 2H), 6.99 – 6.91 (m, 4H), 3.06 (dd, $J = 11.9$, 3.0 Hz, 1H), 2.92 (dd, $J = 9.6$, 7.1 Hz, 1H), 2.52 (dd, $J = 11.9$, 3.5 Hz, 1H), 2.30 – 2.26 (m, 2H), 2.09 (dd, $J = 7.8$, 3.5 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 198.46, 165.62 (d, $J = 255.3$ Hz), 161.89 (d, $J = 245.6$ Hz), 138.16, 136.62 (d, $J = 3.2$ Hz), 133.75 (d, $J = 3.0$ Hz), 132.22 (d, $J = 9.3$ Hz), 128.69, 128.61, 127.90, 127.61 (d, $J = 8.0$ Hz), 115.58 (d, $J = 11.7$ Hz), 115.36 (d, $J = 12.1$ Hz), 76.44, 63.55, 48.91, 47.70, 47.27, 45.38.

^{19}F NMR (376 MHz, CDCl_3): δ -105.01, -115.36.

HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{25}\text{H}_{19}\text{F}_2\text{N}_3\text{NaO}$, 438.1388; found, 438.1392.

(2-Azido-4-(4-chlorophenyl)-2-phenylbicyclo[2.1.1]hexan-1-yl)(4-chlorophenyl)methanone (D9)



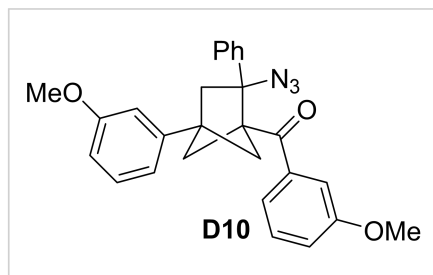
A yellow foam (787 mg, 88% yield).

^1H NMR (400 MHz, CDCl_3): δ 7.73 (d, $J = 8.6$ Hz, 2H), 7.39 – 7.36 (m, 2H), 7.34 – 7.30 (m, 7H), 7.25 – 7.18 (m, 2H), 3.14 (dd, $J = 11.9$, 2.9 Hz, 1H), 3.00 (dd, $J = 9.5$, 7.1 Hz, 1H), 2.59 (dd, $J = 11.9$, 3.5 Hz, 1H), 2.37 – 2.33 (m, 2H), 2.15 (dd, $J = 7.7$, 3.5 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 198.83, 139.51, 139.28, 138.04, 135.58, 132.91, 130.92, 128.83, 128.74, 128.68, 128.63, 127.87, 127.44, 76.41, 63.60, 48.78, 47.83, 47.13, 45.20.

HRMS (ESI) *m/z*: [M+Na]⁺ calcd. for C₂₅H₁₉Cl₂N₃NaO, 470.0797; found, 470.0802.

(2-Azido-4-(4-methoxyphenyl)-2-phenylbicyclo[2.1.1]hexan-1-yl)(4-methoxyphenyl)methanone (D10)



A colorless oil (439 mg, 50% yield).

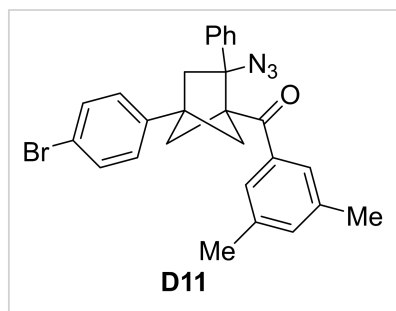
¹H NMR (400 MHz, CDCl₃): δ 7.44 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.41 – 7.27 (m, 7H), 7.08 – 7.06 (m, 1H), 6.92 – 6.89 (m, 1H), 6.84 – 6.81 (m, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.16 (dd, *J* = 11.9, 2.9 Hz, 1H), 3.04 (dd, *J* = 9.5, 7.1 Hz, 1H), 2.63 (dd, *J* = 11.9, 3.5

Hz, 1H), 2.41 – 2.36 (m, 2H), 2.22 (dd, *J* = 7.7, 3.5 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 200.10, 159.91, 159.48, 142.65, 138.71, 138.42, 129.77, 129.28, 128.65, 128.50, 128.00, 122.22, 119.54, 118.35, 113.64, 112.15, 112.04, 76.50, 63.58, 55.50, 55.40, 48.90, 48.26, 47.41, 45.40.

HRMS (ESI) *m/z*: [M+Na]⁺ calcd. for C₂₇H₂₅N₃NaO₃, 462.1788; found, 462.1789.

(2-Azido-4-(4-bromophenyl)-2-phenylbicyclo[2.1.1]hexan-1-yl)(3,5-dimethylphenyl)methanone (D11)



A white solid (825 mg, 85% yield), m.p. 134-137 °C.

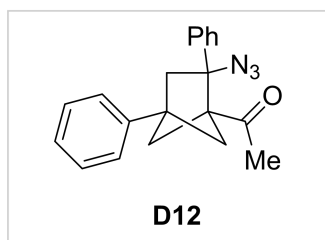
¹H NMR (400 MHz, CDCl₃): δ 7.49 – 7.46 (m, 2H), 7.44 – 7.41 (m, 2H), 7.35 – 7.30 (m, 3H), 7.28 (s, 2H), 7.18 – 7.12 (m, 2H), 7.12 (s, 1H), 3.12 (dd, *J* = 11.9, 3.0 Hz, 1H), 3.01 (dd, *J* = 9.5, 7.1 Hz, 1H), 2.59 (dd, *J* = 11.9, 3.5 Hz, 1H), 2.38 (dd, *J* = 9.5, 7.9 Hz, 1H), 2.33

(dd, *J* = 7.1, 3.0 Hz, 1H), 2.27 (s, 6H), 2.18 (dd, *J* = 7.7, 3.5 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 200.46, 140.10, 138.45, 137.83, 137.47, 134.63, 131.74, 128.66, 128.51, 128.00, 127.83, 127.12, 120.86, 76.37, 63.66, 48.79, 47.80, 47.39, 45.37, 21.37.

HRMS (ESI) *m/z*: [M+Na]⁺ calcd. for C₂₇H₂₄BrN₃NaO, 508.0995; found, 508.0998.

1-(2-azido-2,4-diphenylbicyclo[2.1.1]hexan-1-yl)ethan-1-one (D12)



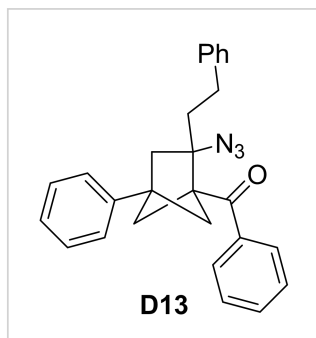
A pale yellow solid (574 mg, 44% yield), m.p. 134-137 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.44 – 7.37 (m, 4H), 7.36 – 7.31 (m, 3H), 7.27 – 7.21 (m, 3H), 2.86 (dd, *J* = 11.7, 3.0 Hz, 1H), 2.73 (dd, *J* = 9.5, 6.9 Hz, 1H), 2.63 (dd, *J* = 11.7, 3.5 Hz, 1H), 2.28 (s, 3H), 2.18 (dd, *J* = 7.7, 3.5 Hz, 1H), 2.14 (dd, *J* = 6.9, 3.0 Hz, 1H), 2.05 (dd, *J* = 9.5, 7.8 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 208.35, 140.97, 139.52, 128.99, 128.65, 128.44, 127.36, 127.07, 125.92, 75.09, 63.63, 49.50, 47.98, 47.33, 43.07, 28.85.

HRMS (ESI) *m/z*: [M+H-N₂]⁺ calcd. for C₂₀H₂₀NO, 290.1545; found, 290.1539.

(2-azido-2-phenethyl-4-phenylbicyclo[2.1.1]hexan-1-yl)(phenyl)methanone (D13)



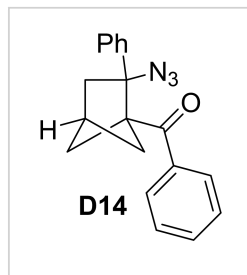
A yellow oil (254 mg, 34% yield).

¹H NMR (400 MHz, CDCl₃): δ 8.06 – 7.99 (m, 2H), 7.61 – 7.54 (m, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.37 – 7.31 (m, 2H), 7.29 – 7.22 (m, 5H), 7.21 – 7.16 (m, 3H), 2.89 (dd, *J* = 9.6, 7.0 Hz, 1H), 2.83 – 2.70 (m, 2H), 2.39 (dd, *J* = 9.5, 7.8 Hz, 2H), 2.34 – 2.30 (m, 2H), 2.29 – 2.15 (m, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 200.77, 141.24, 140.99, 137.36, 133.34, 129.44, 128.65, 128.64, 128.46, 127.03, 126.28, 125.97, 73.52, 63.38, 48.48, 47.46, 47.38, 46.19, 37.82, 31.17.

HRMS (ESI) *m/z*: [M+H-N₂]⁺ calcd. for C₂₇H₂₆NO, 380.2014; found, 380.2007.

(2-azido-2-phenylbicyclo[2.1.1]hexan-1-yl)(phenyl)methanone (D14)



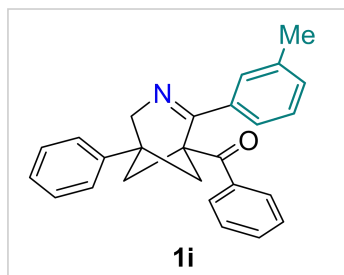
A colorless oil (1.04 g, 66% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.73 – 7.69 (m, 2H), 7.48 – 7.43 (m, 1H), 7.37 – 7.34 (m, 2H), 7.33 – 7.29 (m, 2H), 7.28 – 7.23 (m, 3H), 2.94 (ddd, *J* = 11.9, 2.6, 1.4 Hz, 1H), 2.59 (dt, *J* = 3.0, 1.7 Hz, 1H), 2.53 (dd, *J* = 9.6, 7.2 Hz, 1H), 2.36 (ddd, *J* = 11.9, 3.2, 1.2 Hz, 1H), 2.22 (dt, *J* = 7.0, 2.9 Hz, 1H), 2.00 (dd, *J* = 7.8, 3.1 Hz, 1H), 1.91 (dd, *J* = 9.6, 7.9 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 200.98, 138.86, 137.57, 132.69, 129.35, 128.43, 128.22, 128.13, 127.95, 75.50, 67.20, 45.09, 41.82, 41.76, 34.08.

HRMS (ESI) *m/z*: [M+Na]⁺ calcd. for C₁₉H₁₇N₃NaO, 326.1269; found, 326.1262.

Phenyl(5-phenyl-2-(*m*-tolyl)-3-azabicyclo[3.1.1]hept-2-en-1-yl)methanone (1i)



A white solid (237 mg, 38% yield over two steps), m.p. 177-180 °C.

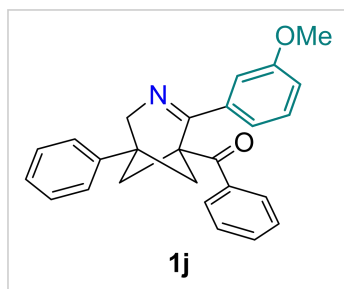
¹H NMR (400 MHz, CDCl₃): δ 7.67 (d, *J* = 7.5 Hz, 2H), 7.39 – 7.34 (m, 3H), 7.21 – 7.16 (m, 4H), 7.18 (dd, *J* = 11.0, 7.7 Hz, 3H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 4.22 (s, 2H), 2.68 (dt, *J* = 6.8, 3.5 Hz, 2H), 2.55 (dt, *J*

= 6.4, 3.6 Hz, 2H), 2.21 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 200.02, 175.33, 144.68, 139.34, 138.07, 134.97, 132.90, 130.14, 129.12, 128.90, 128.21, 128.18, 127.43, 126.94, 124.95, 123.84, 65.41, 54.21, 42.95, 39.92, 21.36.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₆H₂₄NO, 366.1852; found, 366.1853.

(2-(3-Methoxyphenyl)-5-phenyl-3-azabicyclo[3.1.1]hept-2-en-1-yl)(phenyl)methanone (1j)



A white solid (259 mg, 44% yield over two steps), m.p. 136-138 °C.

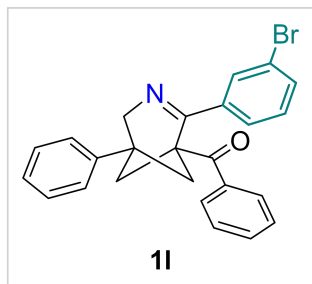
¹H NMR (400 MHz, CDCl₃): δ 7.70 – 7.67 (m, 2H), 7.39 – 7.36 (m, 3H), 7.29 – 7.23 (m, 3H), 7.21 – 7.18 (m, 2H), 7.06 (t, *J* = 7.8 Hz, 1H), 7.00 – 6.97 (m, 2H), 6.70 (ddd, *J*

= 8.2, 2.5, 1.1 Hz, 1H), 4.23 (s, 2H), 3.69 (s, 3H), 2.68 (dt, *J*

= 7.0, 3.5 Hz, 2H), 2.60 – 2.52 (dt, *J* = 6.4, 2.5 Hz, 2H).
¹³C NMR (101 MHz, CDCl₃): δ 200.04, 175.03, 159.45, 144.63, 140.68, 134.93, 132.98, 129.48, 129.10, 128.91, 128.29, 126.96, 124.95, 119.35, 116.14, 111.47, 65.39, 55.36, 54.25, 42.95, 39.93.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₆H₂₄NO₂, 382.1802; found, 382.1803.

(2-(3-Bromophenyl)-5-phenyl-3-azabicyclo[3.1.1]hept-2-en-1-yl)(phenyl)methanone (1l)



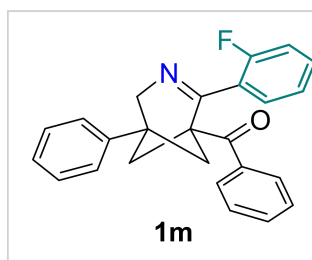
A white solid (305 mg, 71% yield), m.p. 138-140 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.68 – 7.65 (m, 3H), 7.41 – 7.36 (m, 3H), 7.27 (t, *J* = 7.3 Hz, 5H), 7.19 (d, *J* = 7.5 Hz, 2H), 6.99 (t, *J* = 7.9 Hz, 1H), 4.23 (s, 2H), 2.70 (dt, *J* = 7.0, 3.5 Hz, 2H), 2.55 (dt, *J* = 6.4, 3.6 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 199.65, 173.84, 144.36, 141.10, 134.82, 133.22, 132.37, 130.01, 129.76, 129.06, 128.95, 128.43, 127.06, 125.26, 124.93, 122.64, 65.50, 54.09, 42.93, 39.87.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₅H₂₁BrNO, 430.0801; found, 430.0805.

(2-(2-Fluorophenyl)-5-phenyl-3-azabicyclo[3.1.1]hept-2-en-1-yl)(phenyl)methanone (1m)



A white solid (232 mg, 63% yield), m.p. 174-177 °C.

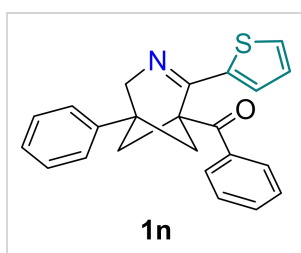
¹H NMR (400 MHz, CDCl₃): δ 7.69 (d, *J* = 7.3 Hz, 2H), 7.41 – 7.35 (m, 3H), 7.30 – 7.21 (m, 6H), 7.12 – 7.07 (m, 1H), 6.94 (td, *J* = 7.5, 0.9 Hz, 1H), 6.83 – 6.79 (m, 1H), 4.24 (s, 2H), 2.75 (dt, *J* = 7.3, 3.7 Hz, 2H), 2.65 – 2.60 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 198.59, 172.22, 158.82 (d, *J* = 247.7 Hz), 144.57, 135.14, 132.90, 130.82 (d, *J* = 8.2 Hz), 129.21 (d, *J* = 3.3 Hz), 128.92 (d, *J* = 5.9 Hz), 128.18, 127.54 (d, *J* = 15.6 Hz), 127.03, 124.95, 124.06 (d, *J* = 3.4 Hz), 115.77, 115.56, 65.44, 54.70, 43.12, 39.54.

¹⁹F NMR (376 MHz, CDCl₃): δ -113.45.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₅H₂₁FNO, 370.1602; found, 370.1610.

Phenyl(5-phenyl-2-(thiophen-3-yl)-3-azabicyclo[3.1.1]hept-2-en-1-yl)methanone (1n)



A white solid (225 mg, 63% yield over two steps), m.p. 149-151 °C.

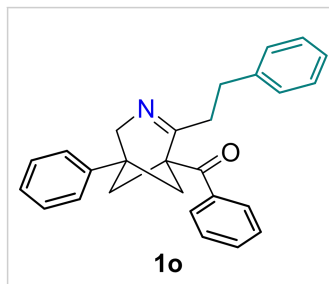
¹H NMR (400 MHz, CDCl₃): δ 7.74 – 7.72 (m, 2H), 7.45 – 7.42 (m, 1H), 7.39 – 7.30 (m, 6H), 7.27 – 7.24 (m, 1H), 7.19 – 7.17 (m, 2H), 7.13 (dd, *J* = 5.1, 2.9 Hz, 1H), 4.19 (s, 2H), 2.61 (dt, *J*

= 7.2, 3.6 Hz, 2H), 2.56 – 2.51 (dt, J = 6.5, 3.5 Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3): δ 200.91, 169.83, 144.63, 140.33, 135.23, 133.12, 129.18, 128.89, 128.47, 127.09, 126.95, 126.10, 125.80, 124.96, 65.08, 54.06, 42.74, 40.00.

HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{23}\text{H}_{20}\text{NOS}$, 358.1260; found, 358.1260.

(2-Phenethyl-5-phenyl-3-azabicyclo[3.1.1]hept-2-en-1-yl)(phenyl)methanone (1o)



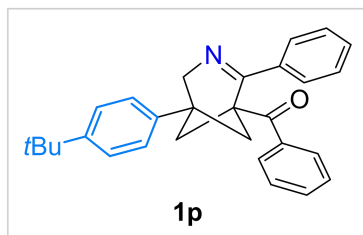
A yellow solid (309 mg, 65% yield), m.p. 112-115 °C.

^1H NMR (400 MHz, CDCl_3): δ 7.89 – 7.83 (m, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.25 – 7.17 (m, 3H), 7.16 – 7.05 (m, 5H), 4.01 (s, 2H), 2.97 – 2.90 (m, 2H), 2.66 – 2.58 (m, 2H), 2.48 (dt, J = 6.9, 3.5 Hz, 2H), 2.41 (dt, J = 6.3, 3.5 Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3): δ 200.73, 175.59, 144.66, 141.38, 135.45, 133.50, 128.99, 128.80, 128.76, 128.42, 128.37, 126.76, 125.97, 124.87, 64.56, 54.09, 42.63, 39.64, 39.18, 32.10.

HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{27}\text{H}_{26}\text{NO}$, 380.2014; found, 380.2006.

(5-(4-(*tert*-Butyl)phenyl)-2-phenyl-3-azabicyclo[3.1.1]hept-2-en-1-yl)(phenyl)methanone (1p)

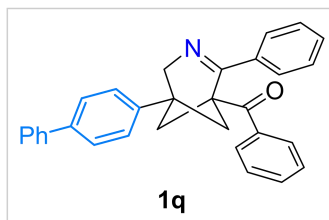


A white solid (277 mg, 68% yield), m.p. 188-190 °C.

^1H NMR (400 MHz, CDCl_3): δ 7.67 (d, J = 7.4 Hz, 2H), 7.42 – 7.39 (m, 4H), 7.35 (t, J = 7.4 Hz, 1H), 7.25 – 7.21 (m, 2H), 7.16 – 7.14 (m, 5H), 4.24 (s, 2H), 2.69 (dt, J = 7.0, 3.5 Hz, 2H), 2.56 – 2.52 (m, 2H), 1.33 (s, 9H).

^{13}C NMR (101 MHz, CDCl_3): δ 200.06, 175.20, 149.86, 141.57, 139.54, 134.92, 132.92, 129.35, 129.18, 128.34, 128.24, 126.78, 125.79, 124.68, 65.41, 54.28, 42.54, 40.03, 34.64, 31.49.

HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{29}\text{H}_{30}\text{NO}$, 408.2322; found, 408.2322.



(5-([1,1'-Biphenyl]-4-yl)-2-phenyl-3-azabicyclo[3.1.1]hept-2-en-1-yl)(phenyl)methanone (1q)

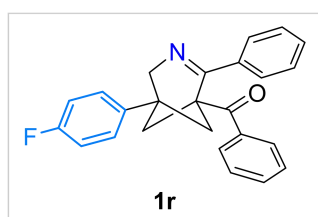
A white solid (256 mg, 60% yield), m.p. 195-197 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.68 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 4H), 7.46 – 7.41 (m, 4H), 7.37 – 7.32 (m, 2H), 7.29 – 7.22 (m, 4H), 7.18 – 7.15 (m, 3H), 4.28 (s, 2H), 2.72 (dt, *J* = 6.8, 3.5 Hz, 2H), 2.62 – 2.57 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 199.98, 175.18, 143.65, 140.87, 139.98, 139.48, 134.86, 132.98, 129.41, 129.19, 128.91, 128.37, 128.26, 127.67, 127.42, 127.19, 126.79, 125.45, 65.35, 54.22, 42.76, 40.02.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₃₁H₂₆NO, 428.2009; found, 428.2012.

(5-(4-Fluorophenyl)-2-phenyl-3-azabicyclo[3.1.1]hept-2-en-1-yl)(phenyl)methanone (1r)



A white solid (244 mg, 66% yield), m.p. 199-202 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.67 – 7.65 (m, 2H), 7.42 – 7.39 (m, 2H), 7.37 – 7.33 (m, 1H), 7.23 (t, *J* = 7.7 Hz, 2H), 7.17 – 7.13 (m, 5H), 7.08 – 7.02 (m, 2H), 4.20 (s, 1H), 2.66

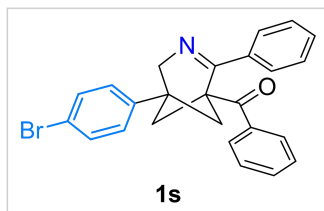
(dt, *J* = 7.0, 3.5 Hz, 2H), 2.56 – 2.51 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 199.86, 175.19, 161.82 (d, *J* = 245.2 Hz), 140.42 (d, *J* = 3.1 Hz), 139.37, 134.79, 133.02, 129.46, 129.18, 128.33 (d, *J* = 10.8 Hz), 126.78, 126.59 (d, *J* = 8.0 Hz), 115.90, 115.69, 65.38, 54.11, 42.45, 39.94.

¹⁹F NMR (376 MHz, CDCl₃): δ -115.66.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₅H₂₁FNO, 370.1602; found, 370.1603.

(5-(4-Bromophenyl)-2-phenyl-3-azabicyclo[3.1.1]hept-2-en-1-yl)(phenyl)methanone (1s)



A white solid (227 mg, 53% yield), m.p. 189-191 °C.

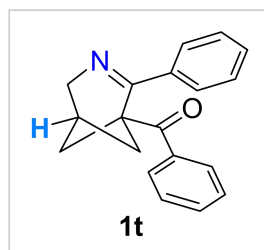
¹H NMR (400 MHz, CDCl₃): δ 7.66 (d, *J* = 7.4 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.40 (dd, *J* = 6.6, 2.9 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 2H), 7.17 – 7.13 (m, 3H), 7.07 (d, *J* = 8.3 Hz, 2H), 4.19 (s, 2H), 2.65 (dt, *J* = 6.9, 3.5 Hz,

2H), 2.56 – 2.51 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 199.77, 175.13, 143.61, 139.32, 134.73, 133.04, 132.03, 129.48, 129.17, 128.38, 128.28, 126.81, 126.76, 120.82, 65.11, 54.05, 42.65, 39.77.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₅H₂₁BrNO, 430.0801; found, 430.0805.

Phenyl(2-phenyl-3-azabicyclo[3.1.1]hept-2-en-1-yl)methanone (1t)



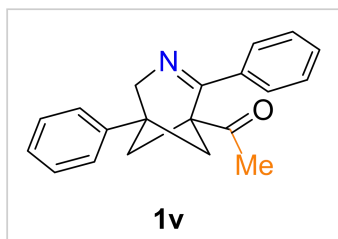
A white solid (745 mg, 81% yield), m.p. 137-140 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.65 – 7.58 (m, 2H), 7.38 – 7.30 (m, 3H), 7.20 (t, *J* = 7.7 Hz, 2H), 7.12 – 7.08 (m, 3H), 4.22 (d, *J* = 2.0 Hz, 2H), 2.76 – 2.68 (m, 1H), 2.60 (tt, *J* = 6.3, 3.7 Hz, 2H), 2.19 – 2.09 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 200.71, 175.33, 139.84, 134.87, 132.82, 129.13, 128.24, 128.16, 126.67, 58.51, 57.50, 35.80, 31.01.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₁₉H₁₈NO, 276.1388; found, 276.1381.

1-(2,5-Diphenyl-3-azabicyclo[3.1.1]hept-2-en-1-yl)ethan-1-one (1v)



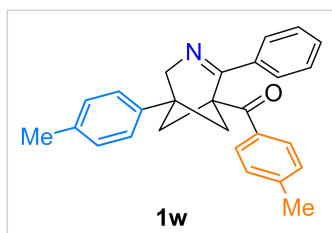
A white solid (292 mg, 64% yield), m.p. 123-125 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.44 – 7.36 (m, 7H), 7.31 – 7.25 (m, 1H), 7.21 – 7.16 (m, 2H), 4.13 (s, 2H), 2.49 – 2.45 (m, 2H), 2.37 – 2.31 (m, 2H), 1.76 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 200.07, 143.71, 137.77, 134.70, 134.67, 132.01, 129.41, 128.32, 127.06, 126.82, 126.66, 120.78, 65.10, 54.13, 42.62, 21.23.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₀H₂₀NO, 290.1545; found, 290.1537.

(2-Phenyl-5-(*p*-tolyl)-3-azabicyclo[3.1.1]hept-2-en-1-yl)(*p*-tolyl)methanone (1w)



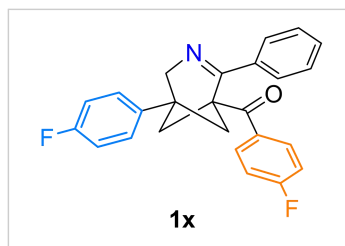
A white solid (265 mg, 70% yield), m.p. 128-131 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.45 – 7.42 (m, 2H), 7.20 – 7.15 (m, 5H), 7.10 (d, *J* = 8.1 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 4.22 (s, 2H), 2.65 (dt, *J* = 6.8, 3.4 Hz, 2H), 2.55 – 2.51 (m, 2H), 2.35 (s, 3H), 2.27 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 199.73, 175.24, 143.69, 141.72, 139.53, 136.48, 132.35, 129.51, 129.28, 129.27, 128.92, 128.26, 126.74, 124.82, 65.49, 54.11, 42.52, 40.01, 21.68, 21.19.

HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{27}\text{H}_{26}\text{NO}$, 380.2009; found, 380.2013.

(4-Fluorophenyl)(5-(4-fluorophenyl)-2-phenyl-3-azabicyclo[3.1.1]hept-2-en-1-yl)methanone (1x)



A white solid (314 mg, 81% yield), m.p. 194-197 °C.

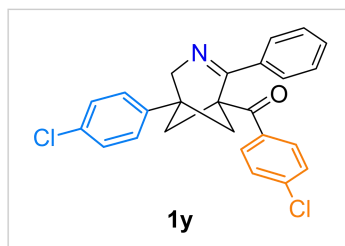
^1H NMR (400 MHz, CDCl_3): δ 7.68 (dd, J = 8.3, 5.6 Hz, 2H), 7.39 – 7.37 (m, 2H), 7.17 – 7.13 (m, 5H), 7.05 (t, J = 8.6 Hz, 2H), 6.90 (t, J = 8.5 Hz, 2H), 4.20 (s, 2H), 2.65 (d, J = 7.3 Hz, 2H), 2.54 – 2.51 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3): δ 198.25, 174.84, 165.33 (d, J = 255.6 Hz), 161.83 (d, J = 245.3 Hz), 140.29 (d, J = 3.2 Hz), 139.26, 131.78 (d, J = 9.4 Hz), 131.24 (d, J = 3.0 Hz), 129.58, 128.44, 126.69, 126.56 (d, J = 8.0 Hz), 115.81 (d, J = 21.4 Hz), 115.48 (d, J = 21.9 Hz), 65.37, 54.00, 42.44, 39.85.

^{19}F NMR (376 MHz, CDCl_3): δ -104.57, -115.56.

HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{25}\text{H}_{20}\text{F}_2\text{NO}$, 388.1507; found, 388.1508.

(4-Chlorophenyl)(5-(4-chlorophenyl)-2-phenyl-3-azabicyclo[3.1.1]hept-2-en-1-yl)methanone (1y)



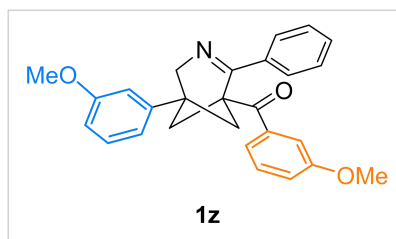
A white solid (335 mg, 80% yield), m.p. 193-195 °C.

^1H NMR (400 MHz, CDCl_3): δ 7.60 – 7.57 (m, 2H), 7.41 (dd, J = 6.5, 3.1 Hz, 2H), 7.35 – 7.32 (m, 2H), 7.22 – 7.16 (m, 5H), 7.13 – 7.10 (m, 2H), 4.19 (s, 2H), 2.65 (dt, J = 6.5, 3.3 Hz, 2H), 2.54 (dt, J = 6.4, 3.6 Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3): δ 198.53, 174.61, 142.89, 139.38, 139.17, 133.05, 132.81, 130.47, 129.66, 129.09, 128.63, 128.48, 126.67, 126.39, 65.12, 53.98, 42.57, 39.72.

HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{25}\text{H}_{20}\text{Cl}_2\text{NO}$, 420.0916; found, 420.0928.

(3-Methoxyphenyl)(5-(3-methoxyphenyl)-2-phenyl-3-azabicyclo[3.1.1]hept-2-en-1-yl)methanone (1z)



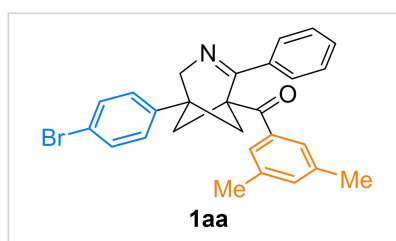
A colorless oil (345 mg, 84% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.41 (dd, *J* = 6.0, 2.6 Hz, 2H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.22 – 7.16 (m, 5H), 7.12 (t, *J* = 7.9 Hz, 1H), 6.90 (dd, *J* = 8.1, 2.5 Hz, 1H), 6.82 – 6.78 (m, 2H), 6.73 (s, 1H), 4.22 (s, 2H), 3.81 (s, 3H), 3.74 (s, 3H), 2.69 – 2.65 (m, 2H), 2.53 (dt, *J* = 6.5, 3.2 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 199.85, 175.06, 160.10, 159.39, 146.31, 139.49, 136.17, 130.00, 129.41, 129.16, 128.37, 126.73, 121.94, 119.57, 117.23, 113.21, 111.99, 110.96, 65.34, 55.44, 55.34, 54.19, 42.94, 40.01.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₇H₂₆NO₃, 412.1907; found, 412.1917.

(5-(4-Bromophenyl)-2-phenyl-3-azabicyclo[3.1.1]hept-2-en-1-yl)(3,5-dimethylphenyl)methanone (1aa)



A white solid (288 mg, 63% yield), m.p. 224-226 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.39 (dd, *J* = 6.5, 2.9 Hz, 2H), 7.24 (s, 2H), 7.18 – 7.15 (m, 3H), 7.08 – 7.05 (m, 2H), 6.98 (s, 1H), 4.19 (s, 2H), 2.62 (dt, *J* = 6.5, 3.3 Hz, 2H), 2.53 – 2.49 (m, 2H), 2.20 (s, 6H).

¹³C NMR (101 MHz, CDCl₃): δ 200.07, 143.71, 137.77, 134.70, 134.67, 132.01, 129.41, 128.32, 127.06, 126.82, 126.66, 120.78, 65.10, 54.13, 42.62, 21.23.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₇H₂₅BrNO, 458.1114; found, 458.1117.

4. Supplementary optimization of the reaction conditions

Table S1. Screening of chiral Brønsted acid catalyst

C1, R = 1-pyrenyl

C2, R = 1-naphthyl

C3, R = 9-anthryl

C4, R = 3,5-(CF₃)₂C₆H₃

C5, R = 9-anthryl

C6, R = 9-anthryl

C7, R = 9-[10-[(3,5-(CF₃)₂C₆H₃)]anthryl]

entry ^a	Cat.	yield (%) ^b	ee (%) ^c
1	None	0	0
2	C1	49	70
3	C2	82	76
4	C3	74	90
5	C4	85	77
6	C5	66	-28
7	C6	50	-8
8	C7	78	94

^aReaction conditions: **1a** (0.05 mmol), HE1 (0.15 mmol) and catalyst (10 mol%) in mesitylene (1 mL) at 50 °C for 48 h. ^bYield were determined by ¹H NMR analysis of the crude reaction mixture using triphenylmethane as an internal standard. ^cThe ee values were determined by chiral HPLC analysis.

Table S2. Screening of reductant

BT1, R = F

BT2, R = OH

entry ^a	hydrogen source	yield (%) ^b	ee (%) ^c
1	BT1	8	6
2	BT2	45	46
3	HE1	78	94
4	HE2	66	93
5	HE3	62	72

HE1, R = Et

HE2, R = Me

HE3, R = *t*Bu

^aReaction conditions: **1a** (0.05 mmol), hydrogen source (0.15 mmol) and **C7** (10 mol%) in mesitylene (1 mL) at 50 °C for 48 h. ^bYield were determined by ¹H NMR analysis of the crude

reaction mixture using triphenylmethane as an internal standard. ^cThe ee values were determined by chiral HPLC analysis.

Table S3. Optimization of Hantzsch ester equivalents

1a $\xrightarrow[\text{mesitylene (0.05 M), 50 } ^\circ\text{C, 48 h}]{\text{C7 (10 mol\%), HE1 (x eq.)}}$ **2a**

entry ^a	HE1 (x eq.)	yield (%) ^b	ee (%) ^c
1	1.0	75 (75)	94
2	1.5	78 (77)	94
3	2.0	81 (76)	94
4	2.5	81 (78)	94
5	3.0	78 (76)	94

^aReaction conditions: **1a** (0.05 mmol), HE1 and **C7** (10 mol%) in mesitylene (1 mL) at 50 °C for 48 h. ^bYield were determined by ¹H NMR analysis of the crude reaction mixture using triphenylmethane as an internal standard. Isolated yield was provided in parentheses. ^cThe ee values were determined by chiral HPLC analysis.

Table S4. Evaluation the effect of solvent

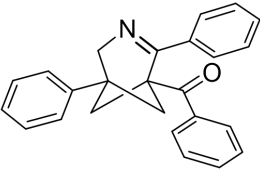
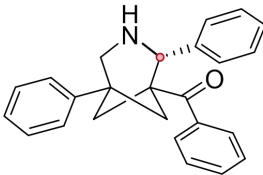
1a $\xrightarrow[\text{mesitylene (0.05 M), temp., time}]{\text{C7 (10 mol\%), HE1 (2.5 eq.)}}$ **2a**

entry ^a	solvent	temp. (°C)	time (h)	yield (%) ^b	ee (%) ^c
1	benzene	50	48	78	92
2	PhCF ₃	50	48	81	90
3	mesitylene	50	48	81	94
4	toluene	50	48	78	92
5	EtOAc	50	48	45	84
6	THF	50	48	39	84
7	CH ₂ Cl ₂	50	48	62	86
8	mesitylene	60	48	80	92
9	mesitylene	70	48	86	87
10	mesitylene	80	48	85	80
11	mesitylene	50	24	78	94
12	mesitylene	50	72	94(89)	94
13	mesitylene (0.01 M)	50	72	75	94
14	mesitylene (0.1 M)	50	72	81	94

^aReaction conditions: **1a** (0.05 mmol), HE1 (0.125 mmol) and **C7** (10 mol%) in solvent. ^bYield were determined by ¹H NMR analysis of the crude reaction mixture using triphenylmethane as an internal

standard. Isolated yield was provided in parentheses. ^cThe ee values were determined by chiral HPLC analysis.

Table S5. Evaluation of catalyst loading

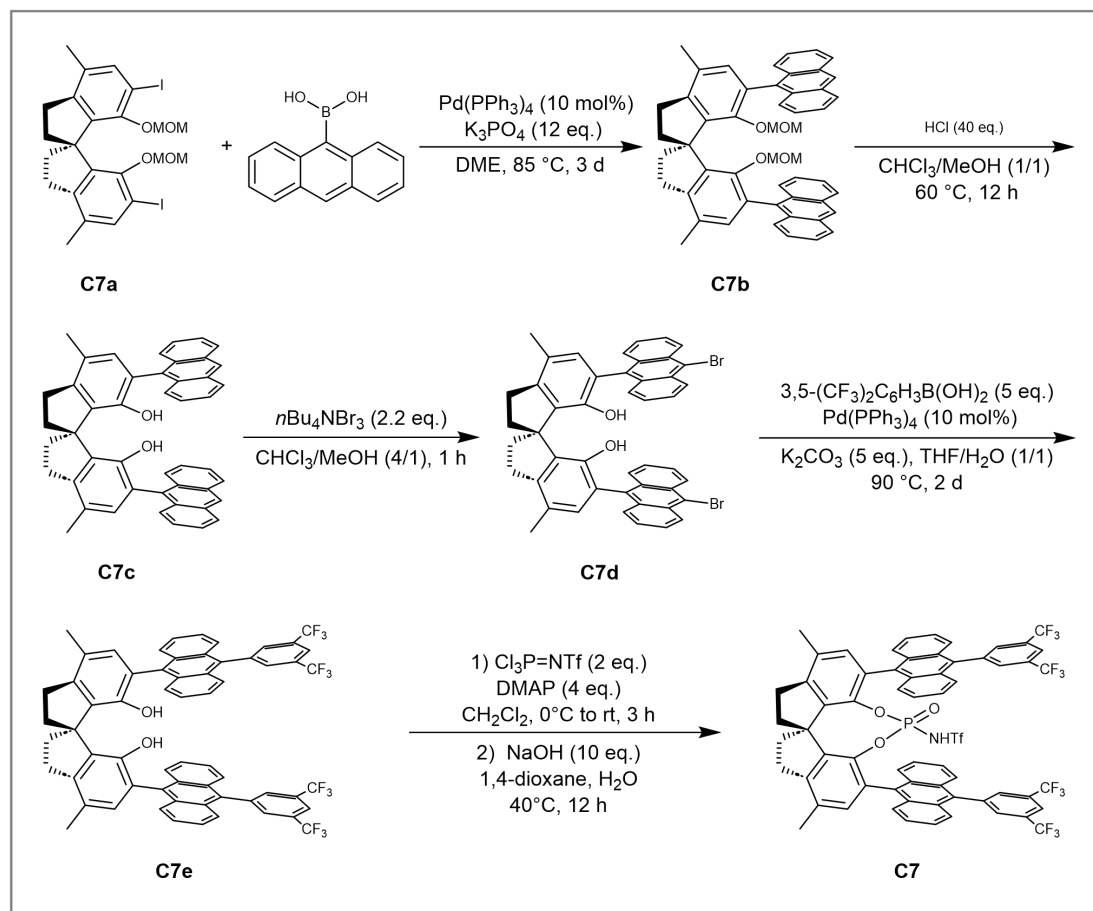
 1a (0.05 mmol) C7 (x mol%) HE1 (2.5 eq.) mesitylene (0.05 M) 50 °C, 72 h  2a			
entry	x	yield ^{NMR} (%)	ee (%)
1	1	77	90
2	5	93	93
3	10	94	94

^aReaction conditions: **1a** (0.05 mmol), HE1 (0.125 mmol) and **C7** (x mol%) in mesitylene (1 mL).

^bYield were determined by ¹H NMR analysis of the crude reaction mixture using triphenylmethane as an internal standard. ^cThe ee values were determined by chiral HPLC analysis.

5. Synthetic procedures and characterization of C7

Scheme S3. Synthesis of C7. C7a was prepared according to the reported procedure^[8].



A 250 mL round- bottom flask was charged with **C7a** (3.10 g, 5 mmol), 9-anthracene boronic acid (6.66 g, 30 mmol) and K_3PO_4 (12.72 g, 60 mmol) in air. Then the flask was evacuated and refilled with argon triple times. Next, DME (100 mL) was added under argon atmosphere and the flask was quickly evacuated and refilled with argon triple times. Finally, $Pd(PPh_3)_4$ (578 mg, 10 mol%) was added under argon atmosphere and again quickly evacuated and refilled with argon three times. Upon completion, the reaction mixture was stirred at 85 °C for 3 d. After cooling to room temperature, H_2O and CH_2Cl_2 were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 , the combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure. Purification of the residue by repeated column chromatography on silica gel (petroleum ether/ CH_2Cl_2 = 2/1) to afford **C7b** as a yellow solid.

To a solution of **C7b** in a mixture of $CHCl_3$ (50 mL) and MeOH (50 mL) was treated with conc. HCl (25 mL) and heated to 60 °C for 12 h. After cooling to room

temperature, diluted with CH₂Cl₂. The separated aqueous layer was extracted with CH₂Cl₂. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (petroleum ether/CH₂Cl₂ = 2/1) to give **C7c** as a white solid (2.40 g, 76% yield over two steps).

To a solution of **C7c** (2.21 g, 3.5 mmol) in a mixture of CHCl₃ (20 mL) and MeOH (5 mL), tetrabutylammonium tribromide (3.71 g, 7.7 mmol) was added slowly in batches. The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched with 1N HCl (aq.), and extracted with CH₂Cl₂. The combined organic layers were dried with anhydrous Na₂SO₄ and then concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/CH₂Cl₂ = 5/1) to give **C7d** as a light-yellow solid (2.24 g, 81% yield).

A 250 mL round-bottom flask was charged with **C7d** (2.0 g, 2.5 mmol), 3,5-Bis(trifluoromethyl)benzene boronic acid (3.22 g, 12.5 mmol) and K₂CO₃ (1.7 g, 12.5 mmol) in air. Then the flask was evacuated and refilled with argon three times. Next, THF/H₂O (50 mL) was added under argon atmosphere and the flask was quickly evacuated and refilled with argon triple times. Finally, Pd(PPh₃)₄ (289 mg, 10 mol%) was added under argon atmosphere and again quickly evacuated and refilled with argon triple times. Upon completion, the reaction mixture was stirred at 90 °C for 48 h. After cooling to room temperature, H₂O and CH₂Cl₂ were added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂, the combined extracts were dried over Na₂SO₄ and evaporated under reduced pressure. Purification of the residue by repeated column chromatography on silica gel (petroleum ether/CH₂Cl₂ = 5/1) to afford **C7e** (2.53 g, 96% yield) as a light-yellow solid.

To an oven-dried round-bottom flask was charged with **C7e** (2.11 g, 2.0 mmol). After evacuating and refilling with argon three times, anhydrous CH₂Cl₂ (40 mL) was added. To this solution was added DMAP (977 mg, 8.0 mmol) and TfN=PCl₃ (628 µL, 4.0 mmol) dropwise at 0 °C. The mixture was then stirred at room temperature for 3 h. After full consumption of **C7e**, to the suspension of **C7e** was added 1,4-dioxane (20 mL) and 2 M NaOH (aq.) (10 mL, 20 mmol). The suspension was stirred at 40 °C for 12 h. The solution was cooled to room temperature and carefully acidified to pH<7 with 6 N HCl (aq.). The mixture was extracted by CH₂Cl₂ and the combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtrated and concentrated. The

crude product was purified by a flash chromatography on silica gel (petroleum ether/EtOAc = 1/1) to give the desired product **C7**, which sometime existed as a salt form.

The pure **C7** was obtained by re-dissolving it in CH₂Cl₂, stirring with conc. HCl overnight. Upon completion, the mixture was diluted with CH₂Cl₂ and the separated aqueous layer was extracted with CH₂Cl₂, the combined organic layer was washed with distilled water for three times and evaporated under reduced pressure to afford **C7** as a pale white foam (2.25 g, 90% yield over two steps).

¹H NMR (400 MHz, CDCl₃): δ 8.01 (d, *J* = 6.3 Hz, 2H), 7.91 (s, 1H), 7.87 – 7.83 (m, 3H), 7.72 – 7.66 (m, 4H), 7.38 – 7.22 (m, 10H), 7.24 – 7.22 (m, 2H), 7.01 (s, 2H), 3.80 (brs, 1H), 3.23 (dt, *J* = 16.4, 8.2 Hz, 2H), 3.09 (ddd, *J* = 16.4, 7.7, 4.2 Hz, 2H), 2.66 – 2.59 (m, 2H), 2.50 – 2.37 (m, 8H).

¹³C NMR (101 MHz, CDCl₃): δ 146.49, 144.67, 142.07, 141.73, 141.62, 141.10, 140.44, 140.36, 139.37, 139.34, 139.30, 139.27, 134.94, 134.44, 134.00, 133.90, 133.18, 133.08, 132.77, 132.65, 132.46, 132.32, 132.13, 132.11, 131.99, 131.85, 131.80, 131.58, 131.52, 131.29, 131.10, 130.98, 130.95, 130.30, 130.13, 130.10, 130.05, 129.96, 129.86, 129.72, 129.33, 128.63, 128.24, 128.15, 127.72, 127.46, 127.34, 126.84, 126.79, 126.64, 126.52, 126.40, 126.27, 126.17, 126.04, 125.83, 125.49, 125.46, 125.17, 125.01, 124.86, 124.75, 124.63, 124.35, 122.76, 122.30, 122.15, 122.04, 121.92, 121.52, 119.56, 116.36, 113.15, 61.22, 39.45, 38.42, 29.40, 18.67.

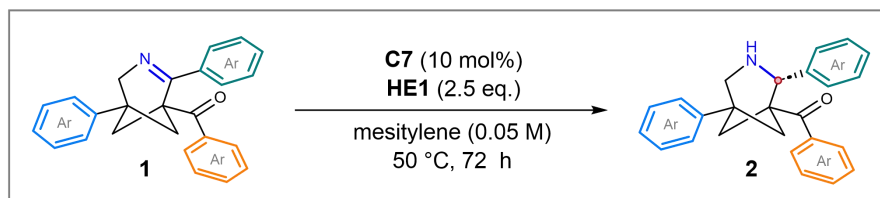
¹⁹F NMR (376 MHz, CDCl₃): δ -62.61, -62.64, -62.73, -63.00, -78.12.

³¹P NMR (162 MHz, CDCl₃): δ -15.28.

HRMS (ESI) calcd for [M+H]⁺ C₆₄H₄₀F₁₅NO₅PS, m/z: 1250.2120; found: 1250.2120.

6. Synthesis and characterization of 3-aza-BCHeps

General procedure for asymmetric reduction

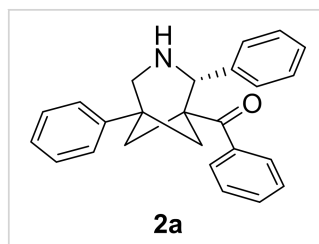


An oven-dried 25 mL Schlenk tube equipped with a magnetic stir bar was charged with imine **1** (0.2 mmol, 1.0 equiv.), Hantzsch ester (0.5 mmol, 2.5 equiv.), and **C7** (10 mol%). The tube was evacuated and backfilled with argon three times. Mesitylene (4 mL) was then added, and the mixture was stirred at 50 °C for 72 h. After cooling to room temperature, chloranil (0.2 mmol, 1.0 equiv.) was added, and the mixture was stirred for an additional 20 min. The reaction was quenched with saturated aqueous NaHCO₃. The mixture was washed with aqueous NaOH (2 M, 2 × 10 mL), the aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL), and the combined organic layers were dried over Na₂SO₄, filtered. The filtrate was concentrated under reduced pressure, and the residue was purified via column chromatography on silica gel (petroleum ether/EtOAc/CH₂Cl₂ = 11/1/1 to 2/1/1) basified with triethylamine to give product **2**. (For those samples with unsatisfactory purity, additional separation was achieved by preparative TLC.)

The racemic products were synthesized with (*rac*)-**C7** (5 mol%) as catalyst.

Characterization of 3-aza-BCHeps

(*R*)-(2,5-Diphenyl-3-azabicyclo[3.1.1]heptan-1-yl)(phenyl)methanone



According to the general procedure, **2a** was obtained as a white solid in 92% yield with 94% ee, m.p. 147-150 °C, $[\alpha]_D^{25}$ -20.0 (c 0.5, CH₂Cl₂).

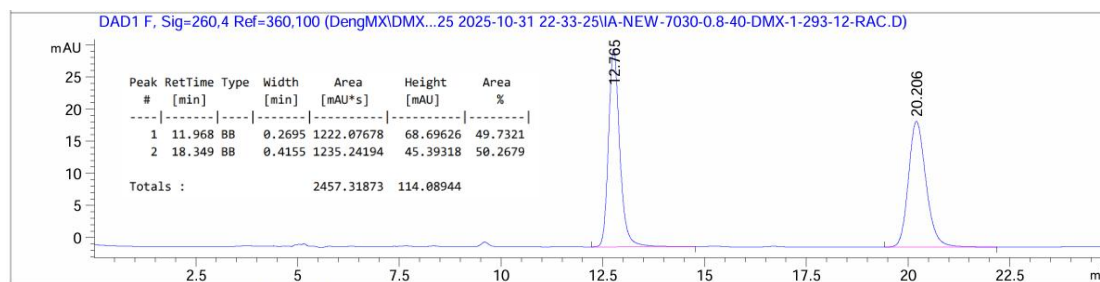
¹H NMR (400 MHz, CDCl₃): δ 7.57 (d, J = 7.6 Hz, 2H), 7.45 (t, J = 7.4 Hz, 1H), 7.35 – 7.30 (m, 4H), 7.24 – 7.14 (m, 8H), 4.85 (s, 1H), 3.41 (d, J = 11.5 Hz, 1H), 3.36 (d, J = 11.5 Hz, 1H), 2.88 – 2.80 (m, 1H), 2.73 – 2.68 (m, 2H), 2.53 (d, J = 9.6 Hz, 1H), 2.42 (brs, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 202.49, 146.22, 141.51, 136.53, 132.47, 128.63, 128.52, 128.34, 128.30, 127.82, 127.36, 126.42, 125.18, 64.43, 56.84, 54.18, 46.50, 42.59, 33.21.

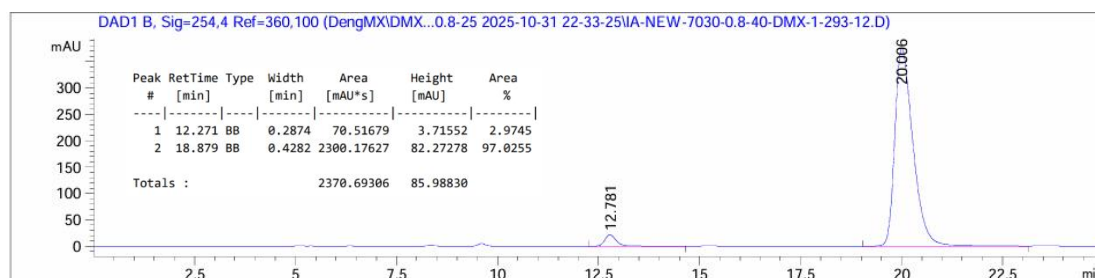
HRMS (ESI) m/z : $[M+H]^+$ calcd. for C₂₅H₂₄NO, 354.1852; found, 354.1851.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, t_R (minor) = 12.8 min, t_R (major) = 20.0 min, ee = 94%.

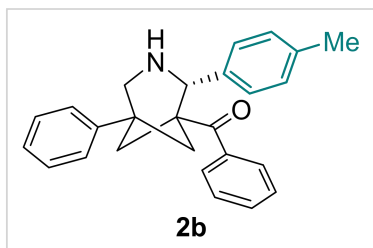
Chiral HPLC spectrum of (*rac*)-**2a**



Chiral HPLC spectrum of (*R*)-**2a**



(R)-Phenyl(5-phenyl-2-(*p*-tolyl)-3-azabicyclo[3.1.1]heptan-1-yl)methanone



According to the general procedure, **2b** was obtained as a pale yellow solid in 85% yield with 92% ee, m.p. 139-141 °C, $[\alpha]_D^{25}$ -10.0 (*c* 0.5, CH₂Cl₂).

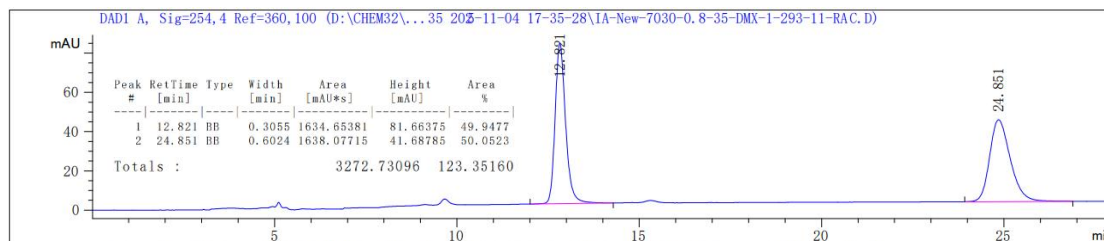
¹H NMR (400 MHz, CDCl₃): δ 7.62 (d, *J* = 7.6 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 4H), 7.24 – 7.17 (m, 3H), 7.08 (d, *J* = 7.9 Hz, 2H), 6.96 (d, *J* = 7.9 Hz, 2H), 4.83 (s, 1H), 3.40 (d, *J* = 11.5 Hz, 1H), 3.34 (d, *J* = 11.6 Hz, 1H), 2.83 (dd, *J* = 9.4, 5.7 Hz, 1H), 2.73 – 2.68 (m, 2H), 2.52 (d, *J* = 9.6 Hz, 1H), 2.44 (brs, 1H), 2.24 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 202.38, 146.29, 138.40, 137.39, 136.50, 132.45, 129.01, 128.69, 128.50, 128.30, 127.17, 126.38, 125.16, 64.22, 56.89, 54.24, 46.59, 42.58, 33.10, 21.16.

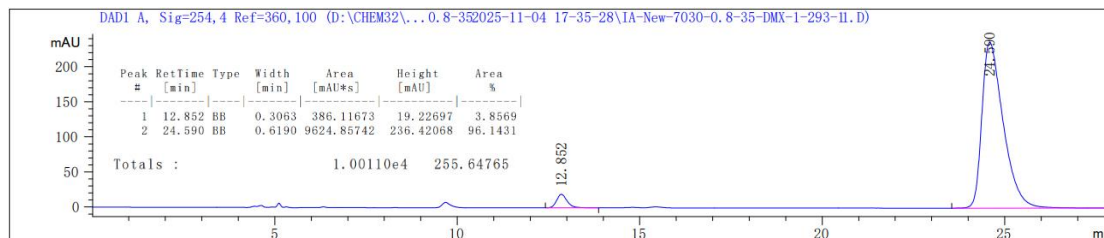
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₆H₂₆NO, 368.2009; found, 368.2009.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, *t_R* (minor) = 12.9 min, *t_R* (major) = 24.6 min, ee = 92%.

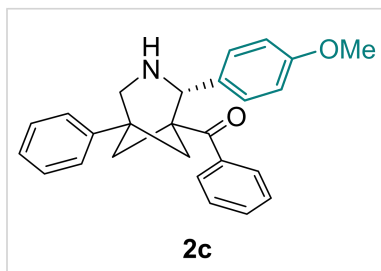
Chiral HPLC spectrum of (*rac*)-2b****



Chiral HPLC spectrum of (*R*)-2b****



(R)-(2-(4-Methoxyphenyl)-5-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)(phenyl)methanone



According to the general procedure, **2c** as obtained as a pale yellow solid in 80% yield with 78% ee, m.p. 126-129 °C, $[\alpha]_D^{25}$ -2.0 (*c* 0.5, CH₂Cl₂).

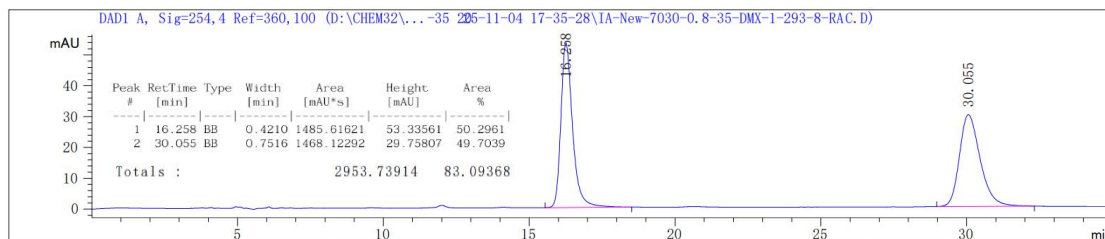
¹H NMR (400 MHz, CDCl₃): δ 7.60 (d, *J* = 7.4 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 4H), 7.24 – 7.20 (m, 1H), 7.19 – 7.17 (m, 2H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.68 (d, *J* = 8.7 Hz, 2H), 4.80 (s, 1H), 3.70 (s, 3H), 3.39 (d, *J* = 11.6 Hz, 1H), 3.32 (dd, *J* = 11.5, 1.3 Hz, 1H), 2.84 (dd, *J* = 9.5, 7.1 Hz, 1H), 2.73 (dd, *J* = 8.7, 1.4 Hz, 1H), 2.68 (dd, *J* = 8.4, 7.1 Hz, 1H), 2.54 – 2.52 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 202.40, 159.06, 146.23, 136.54, 133.45, 132.45, 128.62, 128.50, 128.44, 128.31, 126.39, 125.15, 113.67, 63.93, 56.80, 55.22, 54.23, 46.83, 42.50, 32.87.

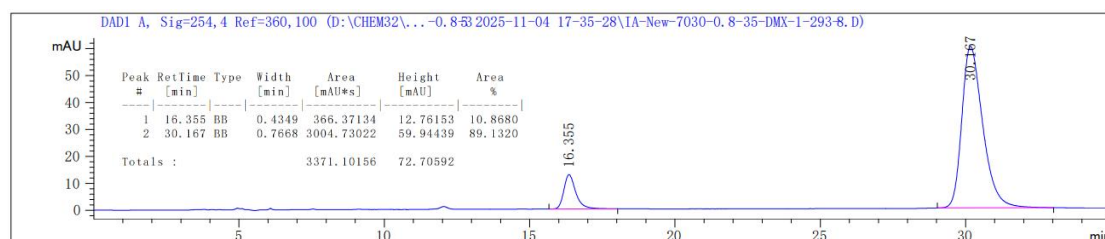
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₆H₂₆NO₂, 384.1958; found, 384.1958.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, *t_R* (minor) = 16.4 min, *t_R*(major) = 30.2 min, ee = 78%.

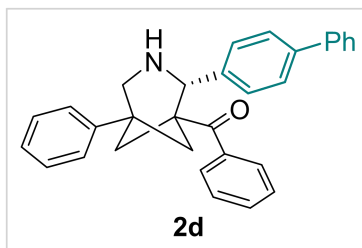
Chiral HPLC spectrum of (*rac*)-2c****



Chiral HPLC spectrum of (*R*)-2c****



**(R)-(2-([1,1'-Biphenyl]-4-yl)-5-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)
(phenyl)methanone**



According to the general procedure, **2d** as obtained as a white solid in 91% yield with 90% ee, m.p. 165-168 °C, $[\alpha]_D^{25} +56.0$ (*c* 0.5, CH₂Cl₂).

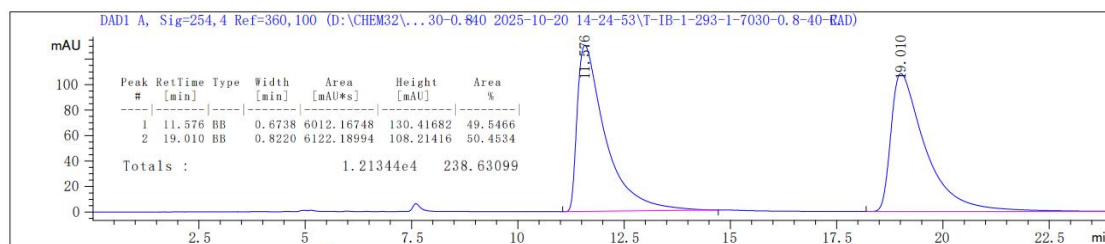
¹H NMR (400 MHz, CDCl₃): δ 7.61 – 7.59 (m, 2H), 7.49 – 7.47 (m, 2H), 7.44 – 7.36 (m, 5H), 7.33 – 7.27 (m, 5H), 7.26 – 7.16 (m, 5H), 4.88 (s, 1H), 3.41 (d, *J* = 11.6 Hz, 1H), 3.36 (d, *J* = 11.5 Hz, 1H), 2.85 (dt, *J* = 9.5, 3.2 Hz, 1H), 2.72 – 2.68 (m, 2H), 2.53 (d, *J* = 9.5 Hz, 1H), 2.42 (brs, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 202.44, 146.20, 140.77, 140.65, 140.49, 136.50, 132.51, 128.77, 128.69, 128.51, 128.32, 127.79, 127.29, 127.05, 126.98, 126.41, 125.17, 64.06, 56.81, 54.19, 46.34, 42.60, 33.28.

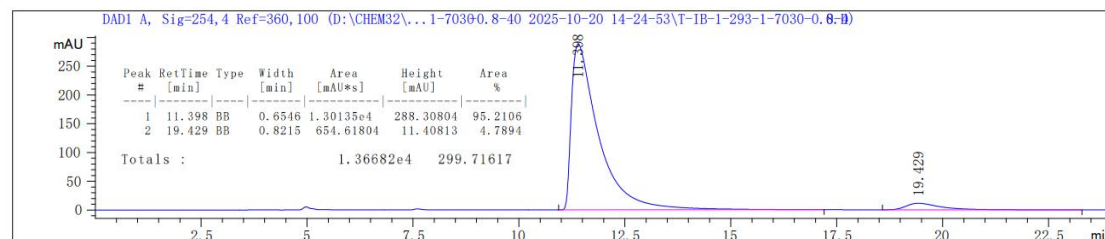
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₃₁H₂₈NO, 430.2165; found, 430.2166.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, *t_R* (major) = 11.4 min, *t_R* (minor) = 19.4 min, ee = 90%.

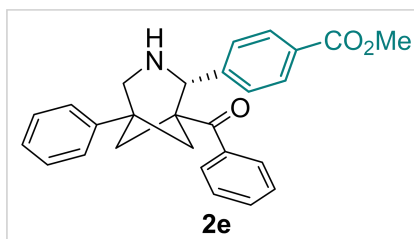
Chiral HPLC spectrum of (*rac*)-**2d**



Chiral HPLC spectrum of (*R*)-**2d**



(R)-Methyl 4-(1-benzoyl-5-phenyl-3-azabicyclo[3.1.1]heptan-2-yl)benzoate



According to the general procedure, **2e** as obtained as a white solid in 92% yield with 95% ee, m.p. 163-166 °C, $[\alpha]_D^{25} +24.0$ (c 0.5, CH₂Cl₂).

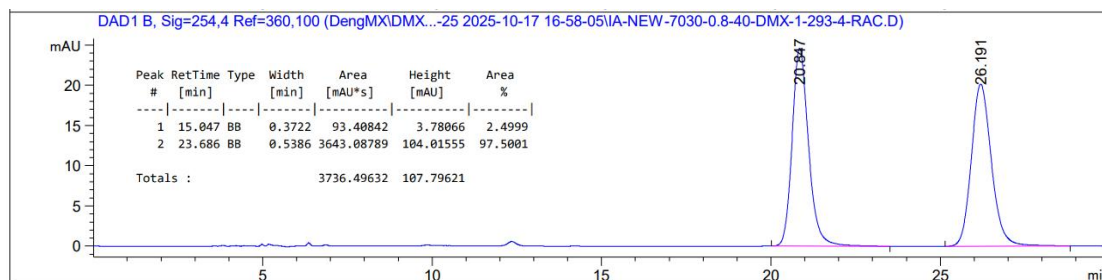
¹H NMR (400 MHz, CDCl₃): δ 7.84 – 7.82 (m, 2H), 7.59 – 7.57 (m, 2H), 7.48 – 7.43 (m, 1H), 7.32 (t, J = 7.6 Hz, 4H), 7.28 – 7.26 (m, 2H), 7.24 – 7.19 (m, 1H), 7.18 – 7.15 (m, 2H), 4.91 (s, 1H), 3.85 (s, 3H), 3.40 (d, J = 11.7 Hz, 1H), 3.38 (d, J = 11.7 Hz, 1H) 2.83 – 2.76 (m, 1H), 2.74 – 2.69 (m, 2H), 2.49 (d, J = 9.5 Hz, 1H), 2.36 (brs, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 202.16, 166.95, 147.01, 146.04, 136.29, 132.76, 129.65, 129.52, 128.69, 128.57, 128.48, 127.51, 126.53, 125.18, 64.02, 56.71, 54.08, 52.17, 46.16, 42.64, 33.44.

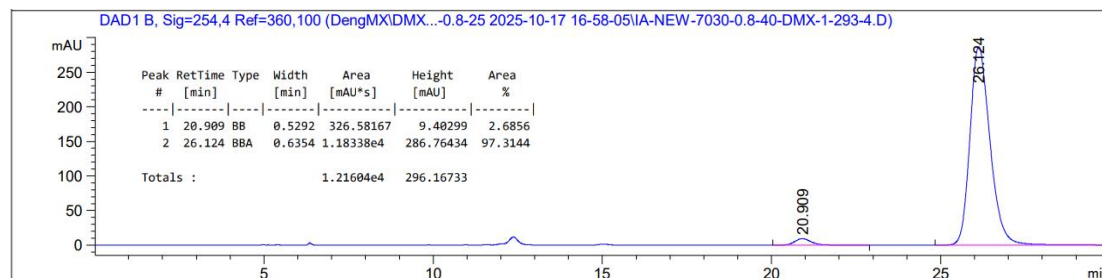
HRMS (ESI) m/z : $[M+H]^+$ calcd. for C₂₇H₂₆NO₃, 412.1907; found, 412.1906.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, t_R (minor) = 20.9 min, t_R (major) = 26.1 min, ee = 95%.

Chiral HPLC spectrum of (*rac*)-**2e**

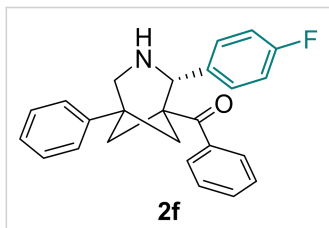


Chiral HPLC spectrum of (*R*)-**2e**



(*R*)-(2-(4-Fluorophenyl)-5-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)

(phenyl)methanone



According to the general procedure, **2f** as obtained as a pale yellow solid in 87% yield with 96% ee, m.p. 169-174 °C, $[\alpha]_D^{25}$ -18.0 (*c* 0.5, CH₂Cl₂).

¹H NMR (400 MHz, CDCl₃): δ 7.58 (d, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 4H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.18 – 7.15 (m, 4H), 6.83 (t, *J* = 8.6 Hz, 2H), 4.83 (s, 1H), 3.40 (d, *J* = 11.4 Hz, 1H), 3.34 (d, *J* = 11.4 Hz, 1H), 2.83 (dd, *J* = 9.4, 7.1 Hz, 1H), 2.73 (d, *J* = 8.8 Hz, 1H), 2.70 – 2.66 (m, 1H), 2.51 (d, *J* = 9.6 Hz, 1H), 2.46 (brs, 1H).

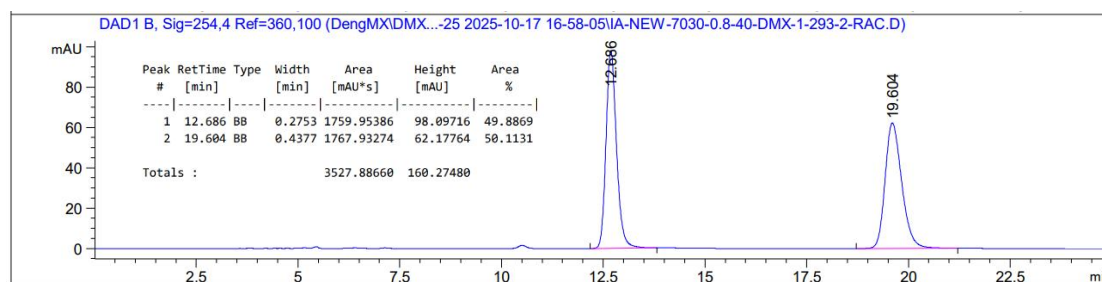
¹³C NMR (101 MHz, CDCl₃): δ 202.31, 162.27 (d, *J* = 246.1 Hz), 146.06, 137.25 (d, *J* = 3.1 Hz), 136.42, 132.67, 129.04 (d, *J* = 8.1 Hz), 128.59 (d, *J* = 6.5 Hz), 128.42, 126.50, 125.17, 115.29, 115.08, 63.71, 56.67, 54.12, 46.63, 42.51, 32.99.

¹⁹F NMR (376 MHz, CDCl₃): δ -114.52.

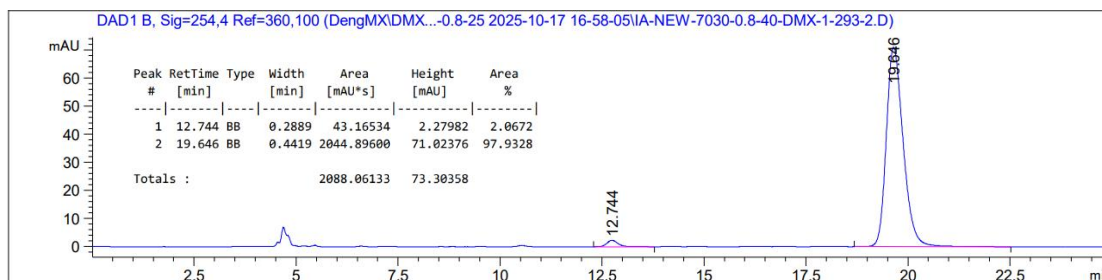
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₅H₂₃FNO, 372.1758; found, 372.1759.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, *t_R* (minor) = 12.7 min, *t_R* (major) = 19.6 min, ee = 96%.

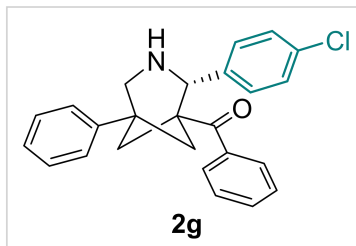
Chiral HPLC spectrum of (*rac*)-2f****



Chiral HPLC spectrum of (*R*)-2f****



**(*R*)-(2-(4-Chlorophenyl)-5-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)
(phenyl)methanone**



According to the general procedure, **2g** as obtained as a pale yellow solid in 86% yield with 94% ee, m.p. 137-140 °C, $[\alpha]_D^{25} +10.0$ (*c* 0.5, CH₂Cl₂).

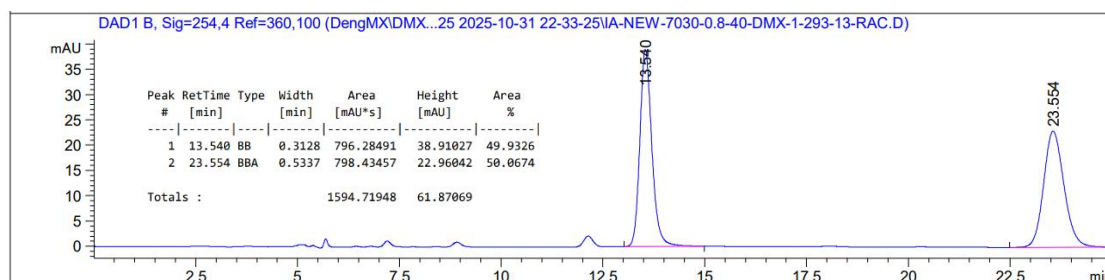
¹H NMR (400 MHz, CDCl₃): δ 7.62 – 7.60 (m, 2H), 7.49 – 7.46 (m, 1H), 7.37 – 7.31 (m, 4H), 7.24 – 7.21 (m, 1H), 7.18 – 7.10 (m, 6H), 4.83 (s, 1H), 3.40 (d, *J* = 11.4 Hz, 1H), 3.35 (d, *J* = 11.4 Hz, 1H), 2.80 (dd, *J* = 9.5, 6.5 Hz, 1H), 2.73 – 2.66 (m, 2H), 2.49 (d, *J* = 9.5 Hz, 1H), 2.29 (brs, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 202.16, 146.05, 140.22, 136.30, 133.37, 132.70, 128.79, 128.66, 128.52, 128.43, 128.40, 126.46, 125.14, 63.65, 56.67, 54.05, 46.32, 42.52, 33.15.

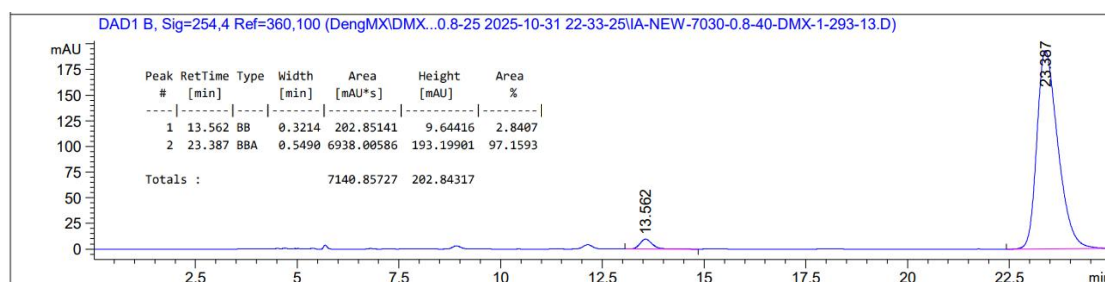
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₅H₂₃ClNO, 388.1463; found, 388.1461.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, t_R (minor) = 13.6 min, t_R (major) = 23.4 min, ee = 94%.

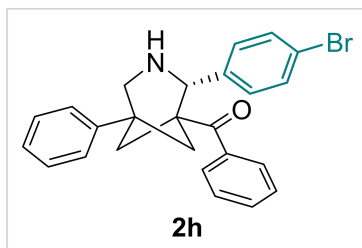
Chiral HPLC spectrum of (*rac*)-**2g**



Chiral HPLC spectrum of (*R*)-**2g**



**(R)-(2-(4-Bromophenyl)-5-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)
(phenyl)methanone**



According to the general procedure, **2h** as obtained as a pale yellow solid in 88% yield with 93% ee, m.p. 103-105 °C, $[\alpha]_D^{25} +16.0$ (*c* 0.5, CH₂Cl₂).

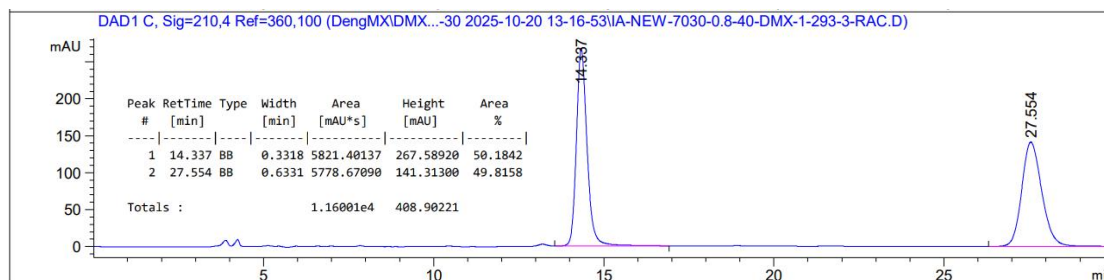
¹H NMR (400 MHz, CDCl₃): δ 7.60 – 7.58 (m, 2H), 7.50 – 7.46 (m, 1H), 7.37 – 7.31 (m, 4H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.18 – 7.15 (m, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 4.82 (s, 1H), 3.40 (d, *J* = 11.5 Hz, 1H), 3.35 (d, *J* = 11.5 Hz, 1H), 2.79 (dd, *J* = 9.5, 6.3 Hz, 1H), 2.73 – 2.66 (m, 2H), 2.50 (d, *J* = 9.6 Hz, 1H), 2.22 (brs, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 202.16, 146.03, 140.67, 136.31, 132.76, 131.41, 129.16, 128.70, 128.57, 128.49, 126.52, 125.17, 121.65, 63.70, 56.66, 54.02, 46.33, 42.55, 33.20.

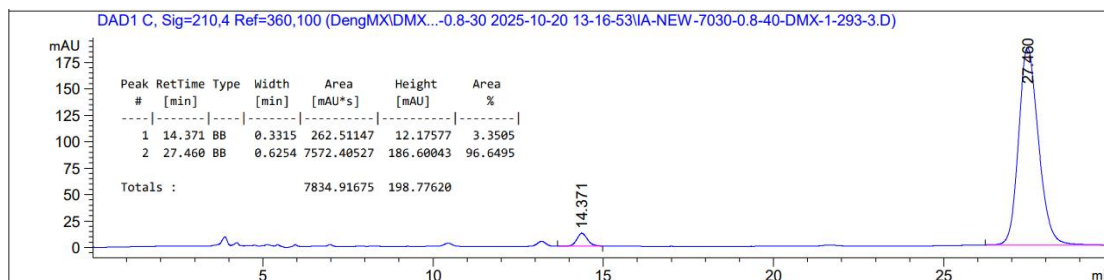
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₅H₂₃BrNO, 432.0958; found, 432.0958.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 210 nm, *t_R* (minor) = 14.4 min, *t_R* (major) = 27.5 min, ee = 93%.

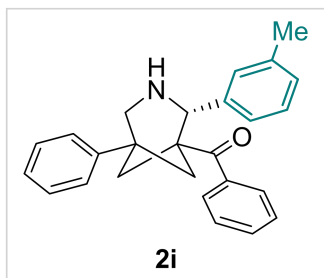
Chiral HPLC spectrum of (*rac*)-**2h**



Chiral HPLC spectrum of (*R*)-**2h**



(R)-Phenyl(5-phenyl-2-(*m*-tolyl)-3-azabicyclo[3.1.1]heptan-1-yl)methanone



According to the general procedure, **2i** as obtained as a pale yellow solid in 84% yield with 97% ee, m.p. 144-147 °C, $[\alpha]_D^{25}$ -18.0 (*c* 0.5, CH₂Cl₂).

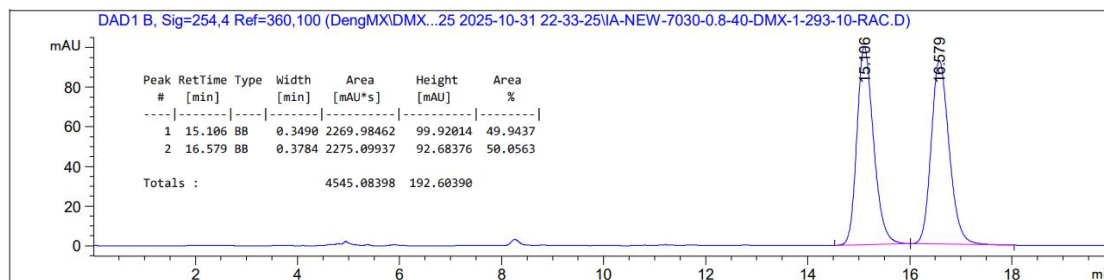
¹H NMR (400 MHz, CDCl₃): δ 7.59 – 7.57 (m, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.36 – 7.31 (m, 4H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 7.1 Hz, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 7.01 – 6.94 (m, 3H), 4.80 (s, 1H), 3.41 (d, *J* = 11.6 Hz, 1H), 3.35 (d, *J* = 11.6 Hz, 1H), 2.84 (dd, *J* = 9.5, 5.8 Hz, 1H), 2.74 – 2.68 (m, 2H), 2.54 (d, *J* = 9.5 Hz, 1H), 2.44 (brs, 1H), 2.20 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 202.44, 146.27, 141.35, 137.82, 136.69, 132.39, 128.63, 128.53, 128.51, 128.25, 128.21, 128.15, 126.39, 125.17, 124.28, 64.44, 56.86, 54.20, 46.54, 42.61, 33.13, 21.48.

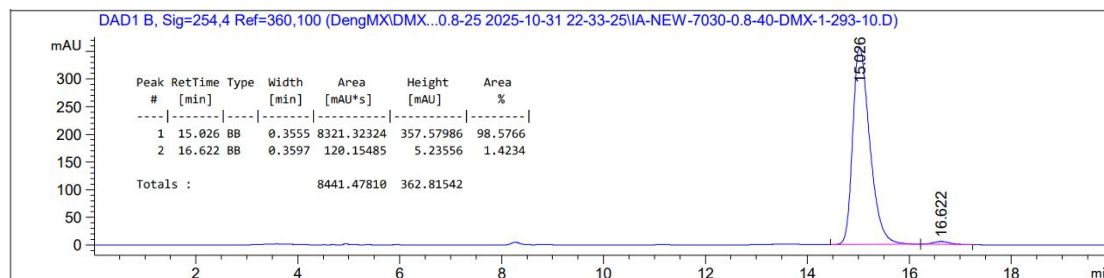
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₆H₂₆NO, 368.2009; found, 368.2008.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, *t_R* (major) = 15.0 min, *t_R* (minor) = 16.6 min, ee = 97%.

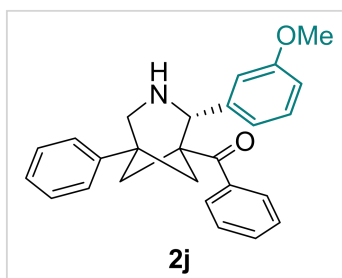
Chiral HPLC spectrum of (*rac*)-**2i**



Chiral HPLC spectrum of (*R*)-**2i**



**(*R*)-(2-(3-Methoxyphenyl)-5-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)
(phenyl)methanone**



According to the general procedure, **2j** as obtained as a pale yellow solid in 84% yield with 96% ee, m.p. 145-148 °C, $[\alpha]_D^{25}$ -14.0 (*c* 0.5, CH₂Cl₂).

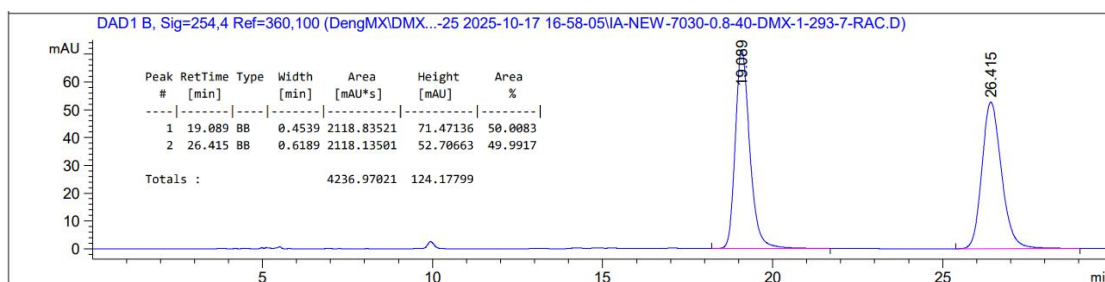
¹H NMR (400 MHz, CDCl₃): δ 7.62 – 7.60 (m, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 4H), 7.24 – 7.20 (m, 1H), 7.18 – 7.16 (m, 2H), 7.08 (t, *J* = 7.9 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.73 – 6.67 (m, 2H), 4.84 (s, 1H), 3.63 (s, 3H), 3.40 (d, *J* = 11.7 Hz, 1H), 3.36 (d, *J* = 11.5 Hz, 1H), 2.81 (dt, *J* = 9.4, 3.3 Hz, 1H), 2.73 – 2.68 (m, 2H), 2.52 (d, *J* = 9.5 Hz, 1H), 2.45 (brs, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 202.32, 159.41, 146.19, 143.12, 136.55, 132.47, 129.36, 128.66, 128.50, 128.30, 126.40, 125.16, 119.49, 113.50, 112.99, 64.31, 56.73, 55.14, 54.12, 46.27, 42.60, 33.30.

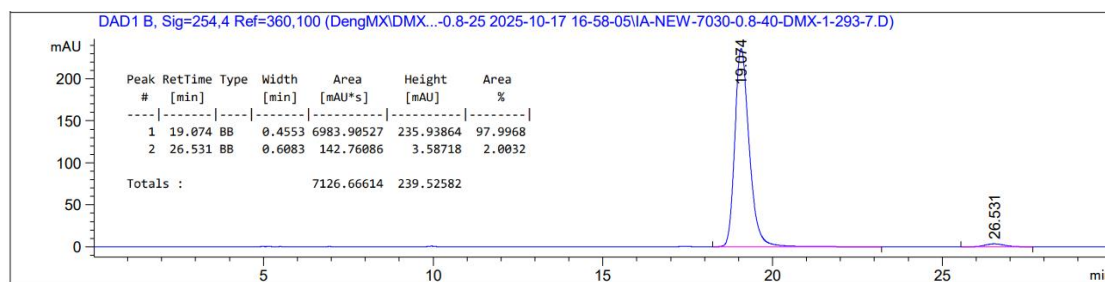
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₆H₂₆NO₂, 384.1958; found, 384.1957.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, *t_R* (major) = 19.1 min, *t_R* (minor) = 26.5 min, ee = 96%.

Chiral HPLC spectrum of (*rac*)-**2j**

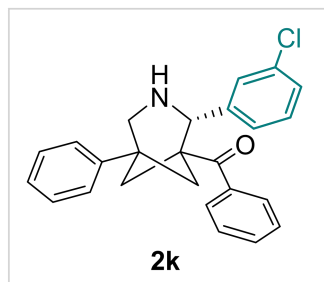


Chiral HPLC spectrum of (*R*)-**2j**



(R)-(2-(3-Chlorophenyl)-5-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)

(phenyl)methanone



According to the general procedure, **2k** as obtained as a pale yellow solid in 79% yield with 95% ee, m.p. 124-127 °C, $[\alpha]_D^{25} +2.0$ (c 0.5, CH₂Cl₂).

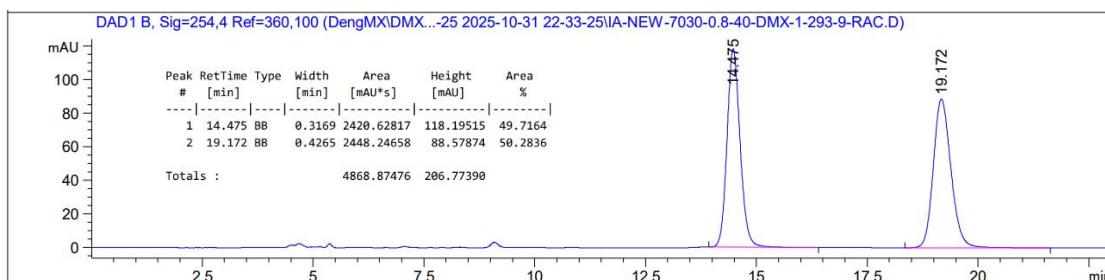
¹H NMR (400 MHz, CDCl₃): δ 7.59 (d, J = 7.6 Hz, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.36 – 7.31 (m, 4H), 7.25 – 7.20 (m, 2H), 7.17 (d, J = 7.3 Hz, 2H), 7.12 – 7.09 (m, 1H), 7.06 – 7.00 (m, 2H), 4.81 (s, 1H), 3.41 – 3.34 (m, 2H), 2.80 (dd, J = 9.3, 5.4 Hz, 1H), 2.71 – 2.65 (m, 2H), 2.48 (d, J = 9.5 Hz, 1H), 2.32 (brs, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 202.20, 146.04, 143.92, 136.37, 134.13, 132.68, 129.47, 128.65, 128.51, 128.41, 127.87, 127.63, 126.46, 125.63, 125.16, 63.68, 56.58, 53.98, 46.06, 42.53, 33.32.

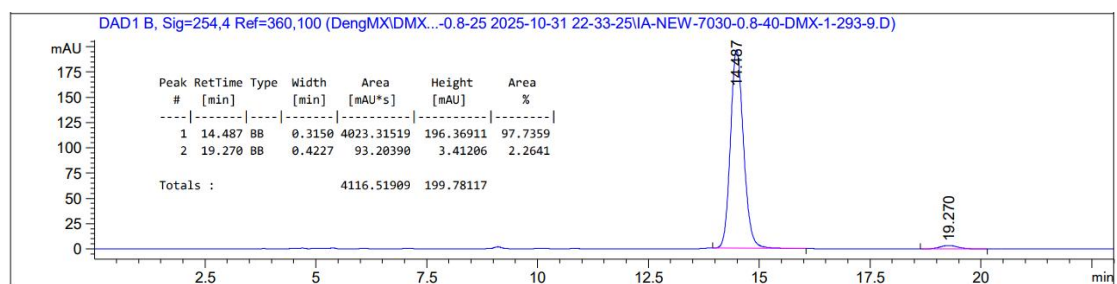
HRMS (ESI) m/z : $[M+H]^+$ calcd. for C₂₅H₂₃ClNO, 388.1463; found, 388.1461.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, t_R (major) = 14.5 min, t_R (minor) = 19.3 min, ee = 95%.

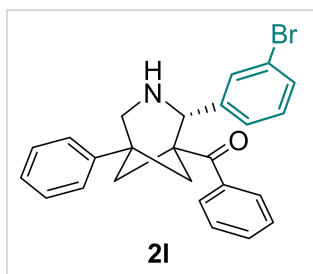
Chiral HPLC spectrum of (*rac*)-**2k**



Chiral HPLC spectrum of (*R*)-**2k**



**(R)-(2-(3-Bromophenyl)-5-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)
(phenyl)methanone**



According to the general procedure, **21** as obtained as a pale yellow solid in 79% yield with 96% ee, m.p. 125-128 °C, $[\alpha]_D^{25} +8.0$ (*c* 0.5, CH₂Cl₂).

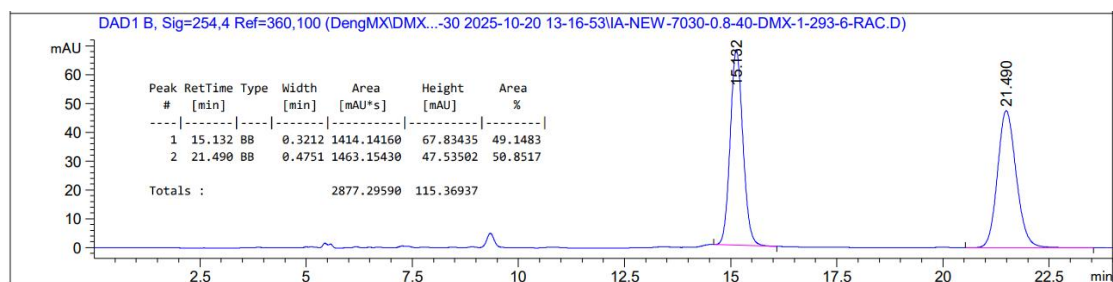
¹H NMR (400 MHz, CDCl₃): δ 7.60 – 7.58 (m, 2H), 7.50 – 7.45 (m, 1H), 7.41 (t, *J* = 1.7 Hz, 1H), 7.37 – 7.31 (m, 4H), 7.27 – 7.20 (m, 2H), 7.18 – 7.16 (m, 2H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 4.80 (s, 1H), 3.41 – 3.35 (m, 2H), 2.80 (dd, *J* = 9.5, 6.0 Hz, 1H), 2.72 – 2.66 (m, 2H), 2.49 (d, *J* = 9.5 Hz, 1H), 2.32 (brs, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 202.20, 146.02, 144.13, 136.39, 132.70, 130.84, 130.57, 129.79, 128.65, 128.53, 128.43, 126.49, 126.09, 125.18, 122.42, 63.65, 56.55, 54.00, 46.09, 42.52, 33.30.

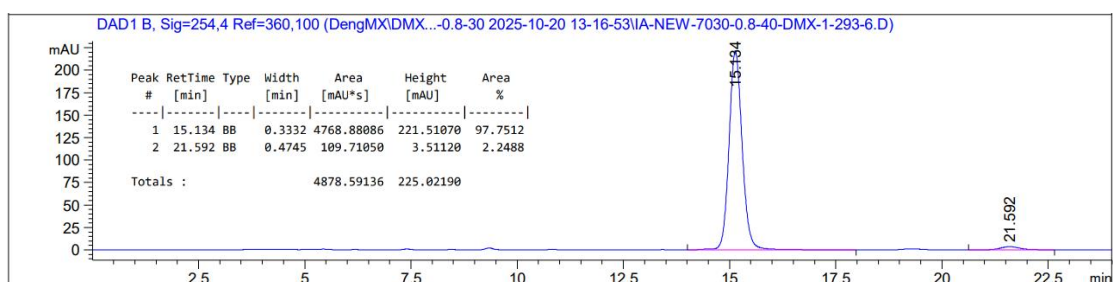
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₅H₂₃BrNO, 432.0958; found, 432.0956.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, *t_R* (major) = 15.1 min, *t_R* (minor) = 21.6 min, ee = 96%.

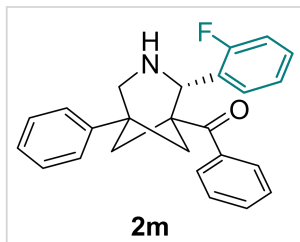
Chiral HPLC spectrum of (*rac*)-**21**



Chiral HPLC spectrum of (*R*)-**21**



**(*R*)-(2-(2-Fluorophenyl)-5-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)
(phenyl)methanone**



According to the general procedure, **2m** as obtained as a pale yellow solid in 68% yield with 22% ee, m.p. 172-175 °C, $[\alpha]_D^{25}$ -30.0 (*c* 0.5, CH₂Cl₂).

¹H NMR (400 MHz, CDCl₃): δ 7.66 – 7.64 (m, 2H), 7.53 – 7.48 (m, 1H), 7.47 – 7.43 (m, 1H), 7.35 – 7.31 (m, 4H), 7.24 – 7.20 (m, 1H), 7.19 – 7.17 (m, 2H), 7.15 – 7.09 (m, 1H), 7.08 – 7.04 (m, 1H), 6.76 (ddd, *J* = 10.4, 8.1, 1.1 Hz, 1H), 5.16 (s, 1H), 3.40 (d, *J* = 11.9 Hz, 1H), 3.34 (d, *J* = 11.9 Hz, 1H), 2.85 (dd, *J* = 9.3, 5.7 Hz, 1H), 2.77 – 2.71 (m, 2H), 2.57 (d, *J* = 9.6 Hz, 1H), 2.42 (brs, 1H).

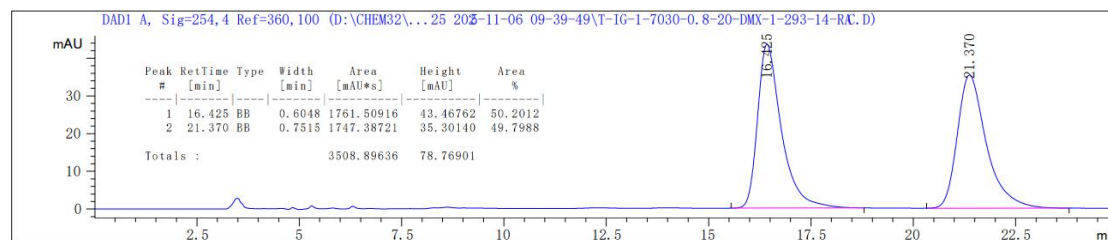
¹³C NMR (101 MHz, CDCl₃): δ 201.80, 160.15 (d, *J* = 246.6 Hz), 146.12, 136.15, 132.59, 129.35 (d, *J* = 8.6 Hz), 128.95 (d, *J* = 4.2 Hz), 128.54 (d, *J* = 4.3 Hz), 128.29, 128.32 (d, *J* = 13.3 Hz), 126.47, 125.15, 124.29 (d, *J* = 3.4 Hz), 115.50, 115.27, 57.67 (d, *J* = 2.4 Hz), 56.87, 53.85, 46.61, 42.64, 33.45.

¹⁹F NMR (376 MHz, CDCl₃): δ -116.00.

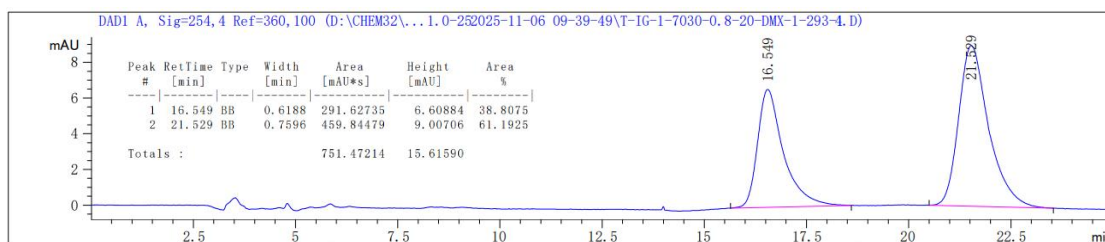
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₅H₂₃FNO, 372.1758; found, 372.1757.

HPLC analysis: DAICEL CHIRALPAK IG, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, *t_R* (minor) = 16.5 min, *t_R* (major) = 21.5 min, ee = 22%.

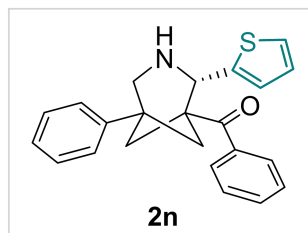
Chiral HPLC spectrum of (*rac*)-**2m**



Chiral HPLC spectrum of (*R*)-**2m**



**(R)-Phenyl(5-phenyl-2-(thiophen-2-yl)-3-azabicyclo[3.1.1]heptan-1-yl)
methanone**



According to the general procedure, **2n** as obtained as a pale yellow solid in 81% yield with 95% ee, m.p. 173-176 °C, $[\alpha]_D^{25}$ -24.0 (*c* 0.5, CH₂Cl₂).

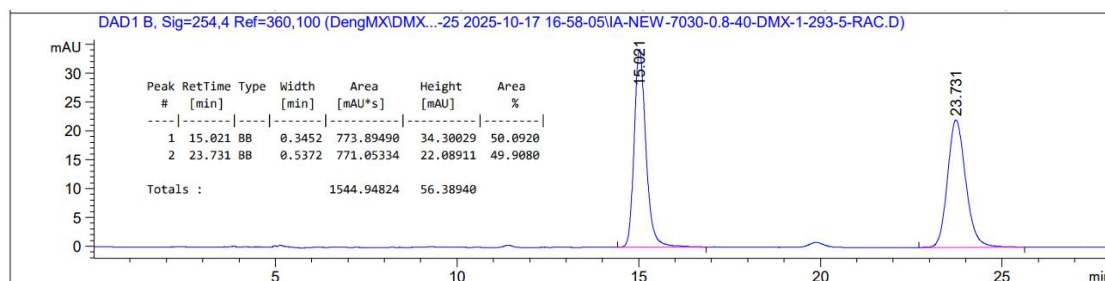
¹H NMR (400 MHz, CDCl₃): δ 7.62 – 7.60 (m, 2H), 7.49 – 7.45 (m, 1H), 7.37 – 7.31 (m, 4H), 7.24 – 7.20 (m, 1H), 7.18 – 7.15 (m, 2H), 7.12 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.04 – 7.03 (m, 1H), 6.90 (dd, *J* = 5.0, 1.2 Hz, 1H), 4.96 (s, 1H), 3.36 (d, *J* = 11.6 Hz, 1H), 3.30 (d, *J* = 11.7 Hz, 1H), 2.75 (dd, *J* = 9.3, 5.8 Hz, 1H), δ 2.70 – 2.65 (m, 2H), 2.53 (d, *J* = 9.4 Hz, 1H), 2.36 (brs, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 202.52, 146.18, 142.53, 136.46, 132.54, 128.53, 128.38, 126.50, 126.42, 125.80, 125.16, 122.27, 60.22, 56.56, 53.82, 45.87, 42.72, 33.24.

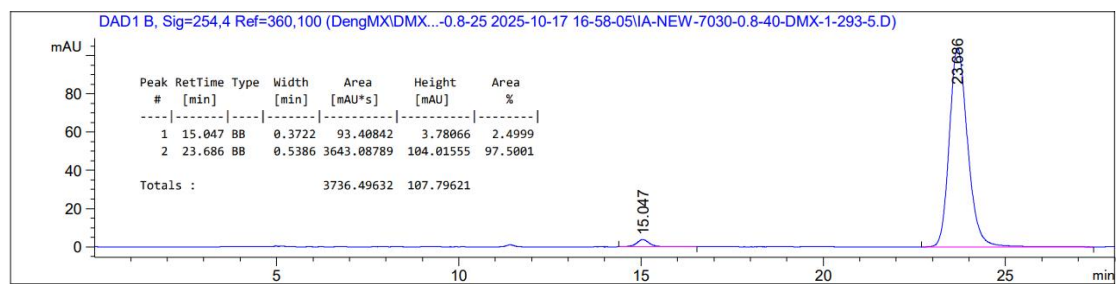
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₃H₂₂NOS, 360.1417; found, 360.1414.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, *t_R* (minor) = 15.0 min, *t_R* (major) = 23.7 min, ee = 95%.

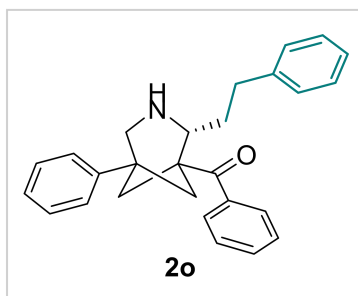
Chiral HPLC spectrum of (*rac*)-**2n**



Chiral HPLC spectrum of (*R*)-**2n**



(R)-(2-phenethyl-5-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)(phenyl)methanone



According to the general procedure, **2o** as obtained as a white solid in 76% yield with 93% ee, m.p. 152-155 °C, $[\alpha]_D^{25}$ -32.0 (*c* 0.5, CH₂Cl₂).

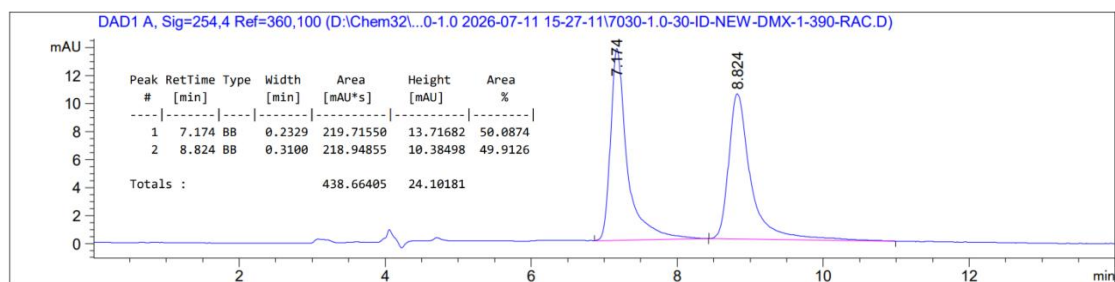
¹H NMR (400 MHz, CDCl₃): δ 7.91 – 7.83 (m, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.24 – 7.09 (m, 6H), 7.00 (d, *J* = 6.8 Hz, 2H), 3.71 (dd, *J* = 9.7, 2.8 Hz, 1H), 3.26 (d, *J* = 12.4 Hz, 1H), 3.17 (dd, *J* = 12.3, 1.7 Hz, 1H), 2.86 – 2.79 (m, 2H), 2.66 – 2.43 (m, 5H), 1.79 – 1.70 (m, 1H), 1.64 – 1.55 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 202.32, 146.04, 141.39, 135.77, 133.01, 128.77, 128.72, 128.51, 128.36, 128.31, 126.35, 125.86, 125.06, 59.16, 56.50, 53.44, 45.99, 42.89, 34.14, 32.94, 32.37.

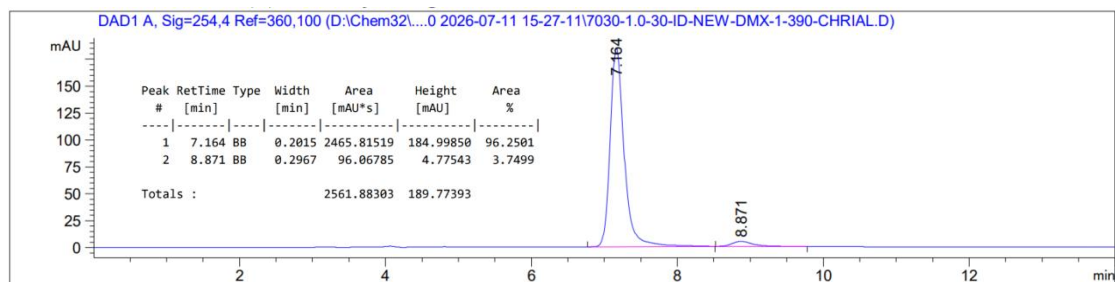
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₇H₂₈NO, 382.2171; found, 382.2165.

HPLC analysis: DAICEL CHIRALPAK ID, *n*-hexane/isopropanol = 70/30, 1.0 mL/min, λ = 254 nm, *t_R* (major) = 7.2 min, *t_R* (minor) = 8.9 min, ee = 93%.

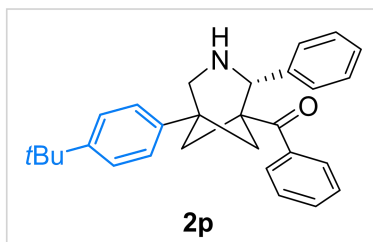
Chiral HPLC spectrum of (*rac*)-**2o**



Chiral HPLC spectrum of (*R*)-**2o**



(R)-(5-(4-(*tert*-Butyl)phenyl)-2-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)(phenyl)methanone



According to the general procedure, **2p** as obtained as a pale yellow solid in 93% yield with 95% ee, m.p. 189-192 °C, $[\alpha]_D^{25}$ -24.0 (*c* 0.5, CH₂Cl₂).

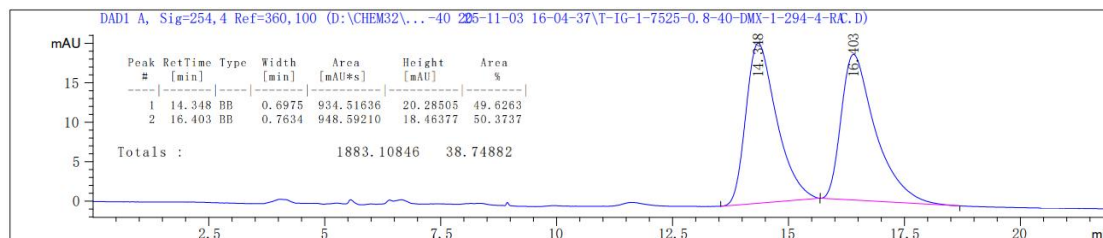
¹H NMR (400 MHz, CDCl₃): δ 7.57 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.23 – 7.12 (m, 7H), 4.86 (s, 1H), 3.42 (d, *J* = 11.6 Hz, 1H), 3.38 (d, *J* = 11.6 Hz, 1H), 2.84 (dd, *J* = 9.3, 6.4 Hz, 1H), 2.74 – 2.68 (m, 2H), 2.55 – 2.53 (m, 2H), 1.33 (s, 9H).

¹³C NMR (101 MHz, CDCl₃): δ 202.57, 149.20, 143.12, 141.54, 136.57, 132.40, 128.59, 128.31, 128.26, 127.77, 127.36, 125.38, 124.87, 64.42, 56.77, 54.20, 46.54, 42.18, 34.53, 33.30, 31.47.

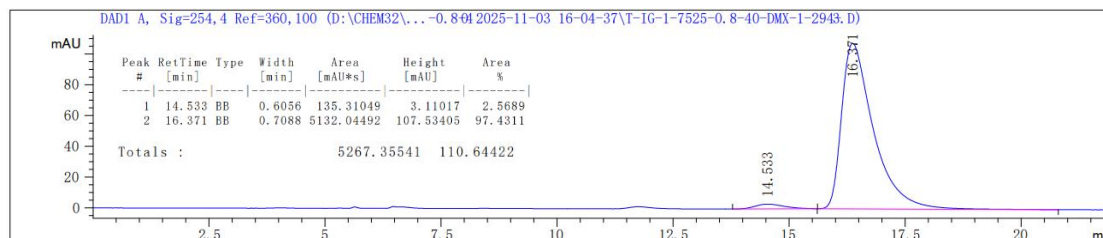
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₉H₃₂NO, 410.2478; found, 410.2477.

HPLC analysis: DAICEL CHIRALPAK IG, *n*-hexane/isopropanol = 75/25, 0.8 mL/min, λ = 254 nm, *t_R* (minor) = 14.5 min, *t_R* (major) = 16.4 min, ee = 95%.

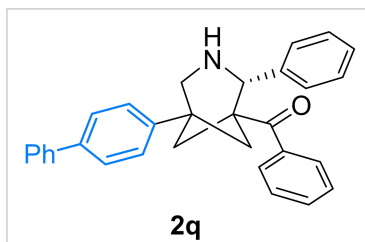
Chiral HPLC spectrum of (*rac*)-2p****



Chiral HPLC spectrum of (*R*)-2p****



(R)-(5-([1,1'-Biphenyl]-4-yl)-2-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)(phenyl)methanone



According to the general procedure, **2q** as obtained as a white solid in 91% yield with 90% ee, m.p. 170-172 °C, $[\alpha]_D^{25}$ -38.0 (*c* 0.5, CH₂Cl₂).

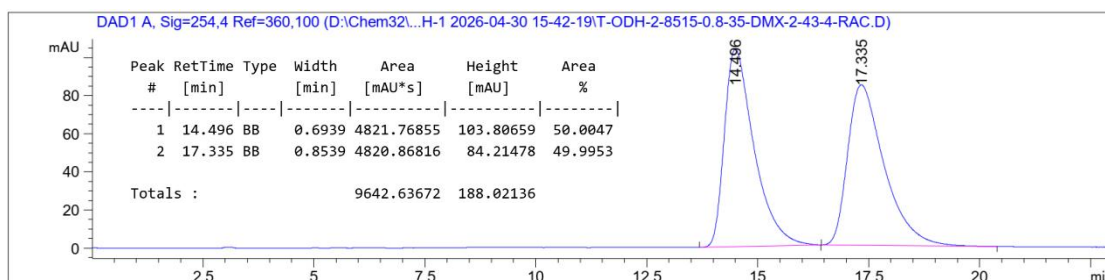
¹H NMR (400 MHz, CDCl₃): δ 7.59 – 7.55 (m, 6H), 7.47 – 7.42 (m, 3H), 7.36 – 7.30 (m, 3H), 7.27 – 7.25 (m, 2H), 7.22 – 7.15 (m, 5H), 4.87 (s, 1H), δ 3.46 (d, *J* = 11.6 Hz, 1H), 3.41 (d, *J* = 11.6 Hz, 1H), 2.87 (dd, *J* = 9.5, 5.6 Hz, 1H), 2.77 – 2.71 (m, 2H), 2.56 (d, *J* = 9.5 Hz, 1H), 2.22 (brs, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 202.46, 145.26, 141.47, 140.98, 139.44, 136.53, 132.52, 128.88, 128.66, 128.37, 128.33, 127.87, 127.39, 127.31, 127.17, 125.68, 64.44, 56.76, 54.20, 46.58, 42.41, 33.33.

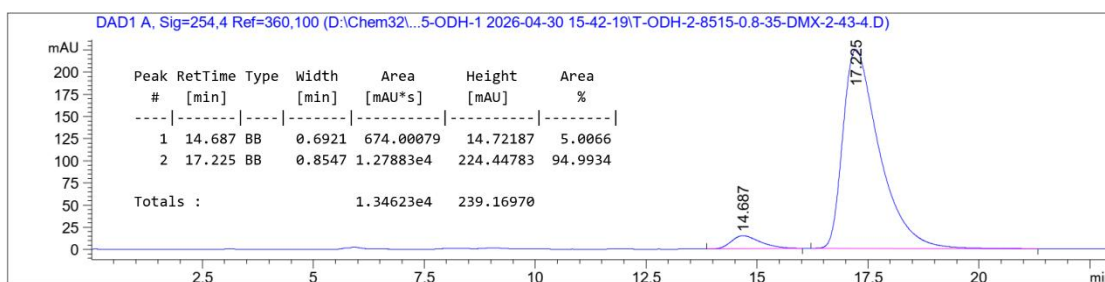
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₃₁H₂₈NO, 430.2165; found, 430.2165.

HPLC analysis: DAICEL CHIRALPAK OD-H, *n*-hexane/isopropanol = 85/15, 0.8 mL/min, λ = 254 nm, *t_R* (minor) = 14.7 min, *t_R* (major) = 17.2 min, ee = 90%.

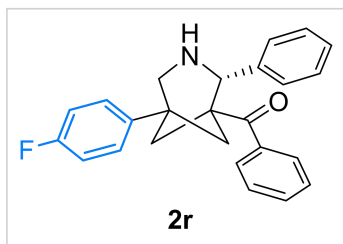
Chiral HPLC spectrum of (*rac*)-**2q**



Chiral HPLC spectrum of (*R*)-**2q**



**(R)-(5-(4-Fluorophenyl)-2-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)
(phenyl)methanone**



According to the general procedure, **2r** as obtained as a pale yellow solid in 79% yield with 92% ee, m.p. 149-152 °C, $[\alpha]_D^{25}$ -18.0 (*c* 0.5, CH₂Cl₂).

¹H NMR (400 MHz, CDCl₃): δ 7.57 – 7.55 (m, 2H), 7.47 – 7.42 (m, 1H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.20 – 7.11 (m, 7H), 7.03 – 6.97 (m, 2H), 4.84 (s, 1H), 3.38 (d, *J* = 11.5 Hz, 1H), 3.33 (d, *J* = 11.4 Hz, 1H), 2.86 – 2.79 (m, 1H), 2.71 – 2.66 (m, 2H), 2.48 (d, *J* = 9.5 Hz, 1H), 2.36 (brs, 1H).

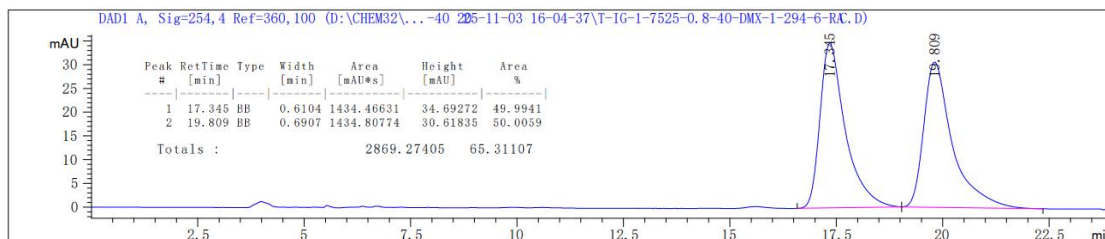
¹³C NMR (101 MHz, CDCl₃): δ 202.33, 161.52 (d, *J* = 244.5 Hz), 142.03 (d, *J* = 3.1 Hz), 141.47, 136.44, 132.54, 128.65, 128.34 (d, *J* = 2.7 Hz), 127.86, 127.34, 126.75 (d, *J* = 8.0 Hz), 115.43, 115.22, 64.35, 56.85, 54.08, 46.53, 42.09, 33.30.

¹⁹F NMR (376 MHz, CDCl₃): δ -116.56.

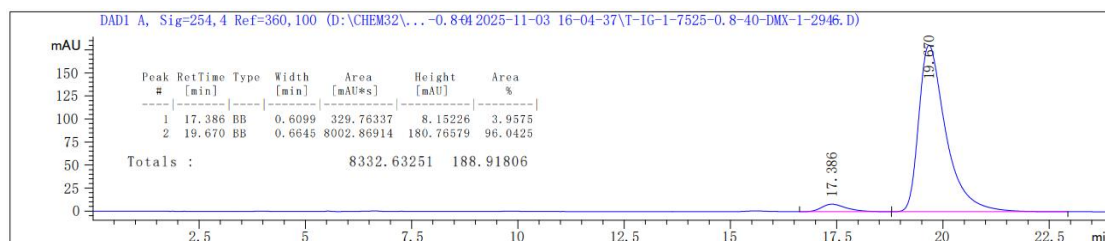
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₅H₂₃FNO, 372.1758; found, 372.1757.

HPLC analysis: DAICEL CHIRALPAK IG, *n*-hexane/isopropanol = 75/25, 0.8 mL/min, λ = 254 nm, *t_R* (minor) = 17.4 min, *t_R* (major) = 19.7 min, ee = 92%.

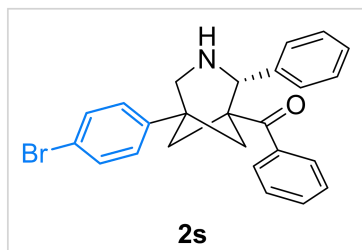
Chiral HPLC spectrum of (*rac*)-2r****



Chiral HPLC spectrum of (*R*)-2r****



**(*R*)-(5-(4-Bromophenyl)-2-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)
(phenyl)methanone**



According to the general procedure, **2s** as obtained as a pale yellow solid in 87% yield with 92% ee, m.p. 192-195 °C, $[\alpha]_D^{25}$ -26.0 (*c* 0.5, CH₂Cl₂).

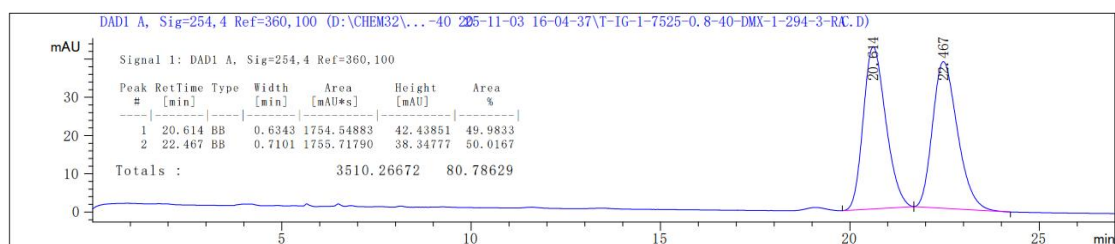
¹H NMR (400 MHz, CDCl₃): δ 7.56 (d, *J* = 7.6 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 3H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.19 – 7.13 (m, 5H), 7.04 (d, *J* = 8.3 Hz, 2H), 4.83 (s, 1H), 3.37 (d, *J* = 11.4 Hz, 1H), 3.31 (d, *J* = 11.4 Hz, 1H), 2.82 (dd, *J* = 9.3, 5.5 Hz, 1H), 2.70 – 2.65 (m, 2H), 2.47 (d, *J* = 9.5 Hz, 1H), 2.36 (brs, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 202.20, 145.21, 141.37, 136.37, 132.57, 131.60, 128.64, 128.35, 128.33, 127.87, 127.32, 127.04, 120.27, 64.32, 56.57, 54.05, 46.34, 42.27, 33.15.

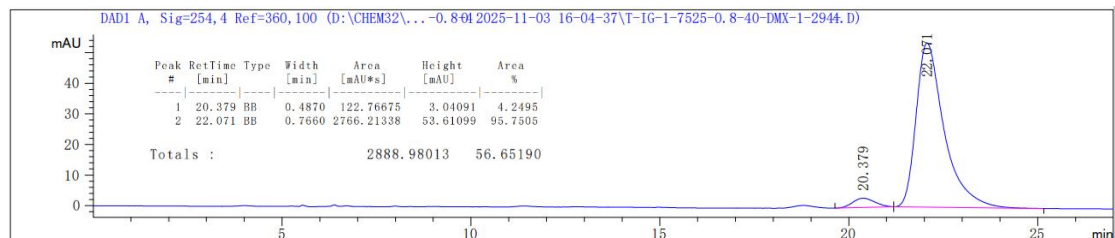
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₅H₂₃BrNO, 432.0958; found, 432.0958.

HPLC analysis: DAICEL CHIRALPAK IG, *n*-hexane/isopropanol = 75/25, 0.8 mL/min, λ = 254 nm, *t_R* (minor) = 20.4 min, *t_R* (major) = 22.1 min, ee = 92%.

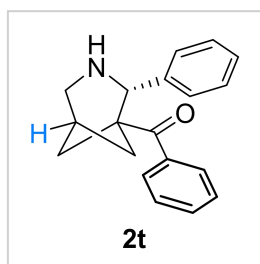
Chiral HPLC spectrum of (*rac*)-2s****



Chiral HPLC spectrum of (*R*)-2s****



(R)-Phenyl(2-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)methanone



According to the general procedure, **2t** as obtained as a white solid in 68% yield with 73% ee, m.p. 84-87 °C, $[\alpha]_D^{25} +30.0$ (c 0.5, CH₂Cl₂).

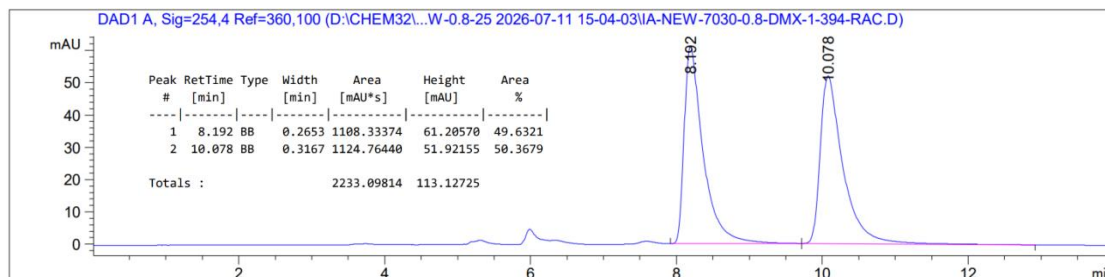
¹H NMR (400 MHz, CDCl₃): δ 7.56 (dd, J = 8.3, 1.2 Hz, 2H), 7.47 – 7.41 (m, 1H), 7.31 (t, J = 7.7 Hz, 2H), 7.18 – 7.10 (m, 5H), 4.80 (s, 1H), 3.46 – 3.39 (m, 1H), 3.34 (d, J = 11.3 Hz, 1H), 2.70 – 2.62 (m, 1H), 2.44 – 2.38 (m, 4H), 2.28 – 2.20 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 202.86, 141.75, 136.53, 132.28, 128.59, 128.16, 128.16, 127.62, 127.26, 65.25, 57.77, 49.38, 42.94, 30.09, 28.83.

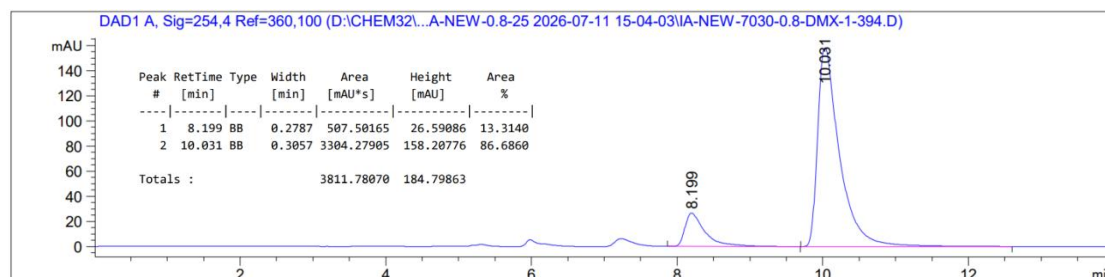
HRMS (ESI) m/z : $[M+H]^+$ calcd. for C₁₉H₂₀NO, 278.1545; found, 278.1537.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, t_R (minor) = 8.2 min, t_R (major) = 10.0 min, ee = 73%.

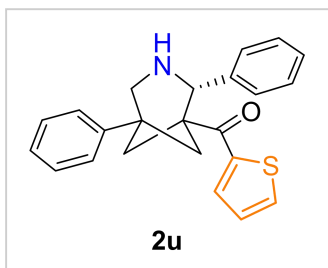
Chiral HPLC spectrum of (*rac*)-**2t**



Chiral HPLC spectrum of (*R*)-**2t**



(R)-(2,5-Diphenyl-3-azabicyclo[3.1.1]heptan-1-yl)(thiophen-2-yl)methanone



According to the general procedure, **2u** as obtained as a white solid in 86% yield with 93% ee, m.p. 176-179 °C, $[\alpha]_{\text{D}}^{25}$ -42.0 (*c* 0.5, CH₂Cl₂).

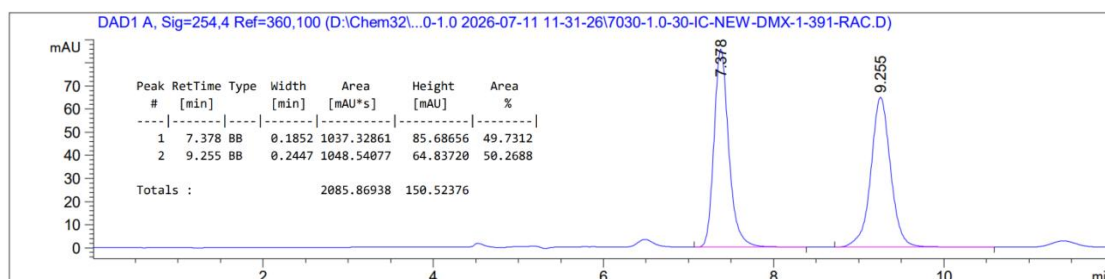
¹H NMR (400 MHz, CDCl₃): δ 7.51 (dd, *J* = 4.9, 0.8 Hz, 1H), 7.47 (d, *J* = 3.6 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.21 (m, 3H), 7.20 – 7.13 (m, 5H), 7.00 (dd, *J* = 4.8, 4.0 Hz, 1H), 4.83 (s, 1H), 3.40 (d, *J* = 11.6 Hz, 1H), 3.35 (dd, *J* = 11.4, 1.3 Hz, 1H), 2.83 (dd, *J* = 9.4, 7.0 Hz, 1H), 2.68 (dd, *J* = 8.8, 1.3 Hz, 1H), 2.65 – 2.59 (m, 1H), 2.48 (d, *J* = 9.5 Hz, 1H), 2.18 (brs, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 194.77, 146.14, 142.76, 141.37, 133.25, 132.20, 128.53, 128.34, 127.88, 127.85, 127.31, 126.45, 125.19, 64.87, 56.81, 54.02, 45.90, 42.61, 33.12.

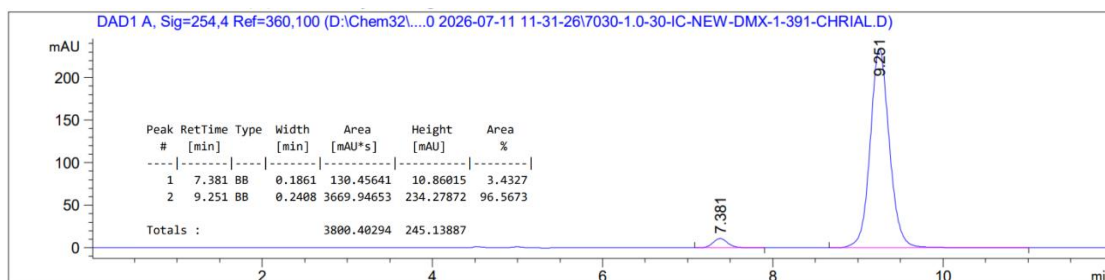
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₃H₂₂NOS, 360.1422; found, 360.1415.

HPLC analysis: DAICEL CHIRALPAK IC, *n*-hexane/isopropanol = 70/30, 1.0 mL/min, λ = 254 nm, *t_R* (minor) = 7.4 min, *t_R* (major) = 9.3 min, ee = 93%.

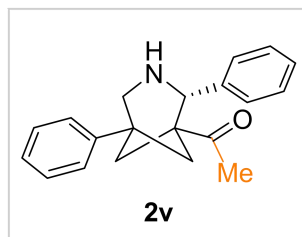
Chiral HPLC spectrum of (*rac*)-**2u**



Chiral HPLC spectrum of (*R*)-**2u**



(R)-1-(2,5-Diphenyl-3-azabicyclo[3.1.1]heptan-1-yl)ethan-1-one



According to the general procedure, **2v** as obtained as a white solid in 67% yield with 95% ee, m.p. 112-114 °C, $[\alpha]_D^{25}$ -38.0 (*c* 0.5, CH₂Cl₂).

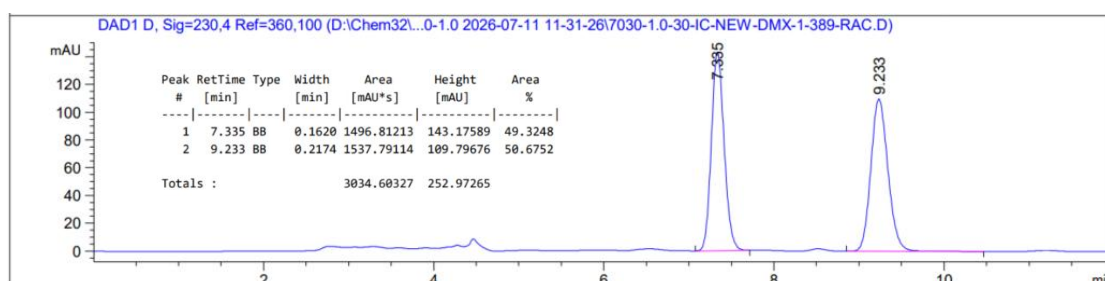
¹H NMR (400 MHz, CDCl₃): δ 7.45 – 7.40 (m, 2H), 7.38 – 7.33 (m, 4H), 7.32 – 7.21 (m, 2H), 7.19 – 7.14 (m, 2H), 4.56 (s, 1H), 3.33 (d, *J* = 11.7 Hz, 1H), 3.26 (dd, *J* = 11.5, 1.8 Hz, 1H), 2.70 (dd, *J* = 9.4, 7.3 Hz, 1H), 2.44 (dd, *J* = 8.7, 1.8 Hz, 1H), 2.39 (d, *J* = 9.4 Hz, 1H), 2.33 (dd, *J* = 8.5, 7.4 Hz, 1H), 2.26 (brs, 1H), 1.74 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 209.96, 146.17, 141.64, 128.78, 128.51, 128.14, 127.30, 126.42, 125.13, 63.41, 56.78, 54.39, 45.19, 41.55, 31.13, 26.23.

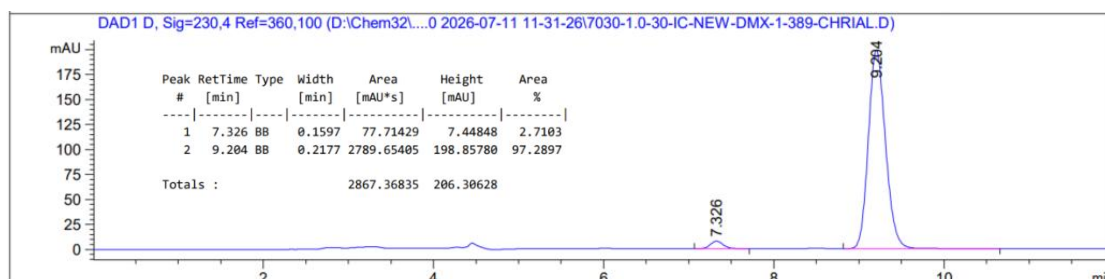
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₀H₂₂NO, 292.1701; found, 292.1693.

HPLC analysis: DAICEL CHIRALPAK IC, *n*-hexane/isopropanol = 70/30, 1.0 mL/min, λ = 230 nm, *t_R* (minor) = 7.3 min, *t_R* (major) = 9.2 min, ee = 95%.

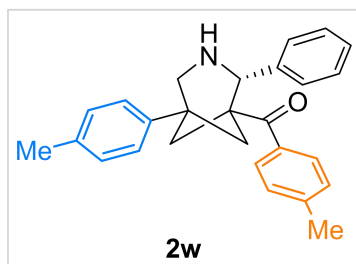
Chiral HPLC spectrum of (*rac*)-**2v**



Chiral HPLC spectrum of (*R*)-**2v**



(R)-(2-Phenyl-5-(*p*-tolyl)-3-azabicyclo[3.1.1]heptan-1-yl)(*p*-tolyl)methanone



According to the general procedure, **2w** was obtained as a pale yellow solid in 93% yield with 93% ee, m.p. 142–146 °C, $[\alpha]_D^{25} -22.0$ (*c* 0.5, CH₂Cl₂).

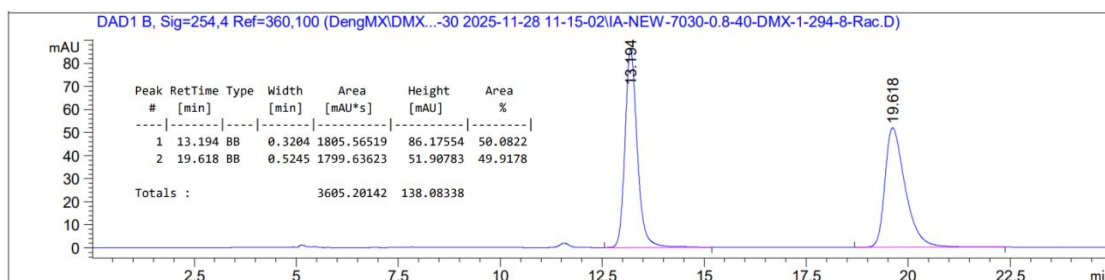
¹H NMR (400 MHz, CDCl₃): δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.23 – 7.19 (m, 2H), 7.18 – 7.12 (m, 7H), 7.09 – 7.06 (m, 2H), 4.87 (s, 1H), 3.40 (d, *J* = 11.5 Hz, 1H), 3.35 (d, *J* = 11.6 Hz, 1H), 2.80 (dd, *J* = 9.5, 5.9 Hz, 1H), 2.72 – 2.66 (m, 3H), 2.49 (d, *J* = 9.6 Hz, 1H), 2.36 (s, 3H), 2.34 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 201.97, 143.27, 143.19, 141.52, 135.90, 133.84, 129.16, 129.00, 128.83, 128.27, 127.73, 127.34, 125.07, 64.38, 56.83, 54.11, 46.39, 42.21, 33.41, 21.70, 21.15.

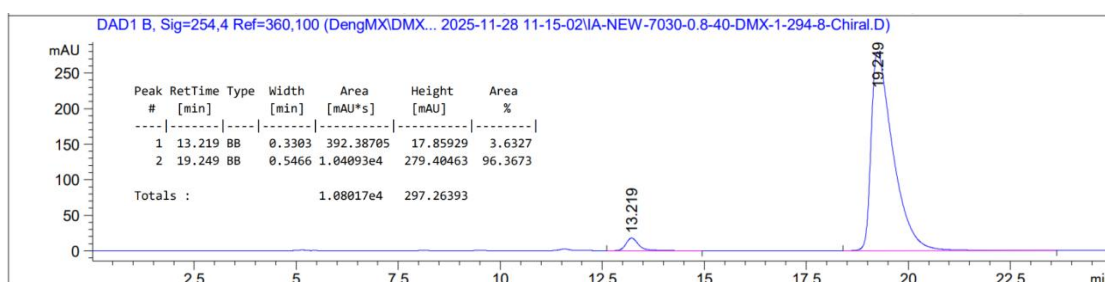
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₇H₂₈NO, 382.2165; found, 382.2163.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, *t_R* (minor) = 13.2 min, *t_R* (major) = 19.2 min, ee = 93%.

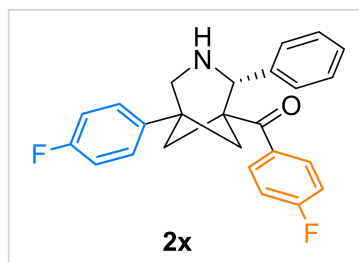
Chiral HPLC spectrum of (*rac*)-**2w**



Chiral HPLC spectrum of (*R*)-**2w**



(*R*)-(4-Fluorophenyl)(5-(4-fluorophenyl)-2-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)methanone



According to the general procedure, **2x** as obtained as a pale yellow solid in 81% yield with 92% ee, m.p. 173-176 °C, $[\alpha]_D^{25}$ -12.0 (*c* 0.5, CH₂Cl₂).

¹H NMR (400 MHz, CDCl₃): δ 7.60 – 7.55 (m, 2H), 7.20 – 7.17 (m, 2H), 7.16 – 7.09 (m, 5H), 7.03 – 6.94 (m, 4H), 4.79 (s, 1H), 3.38 (d, *J* = 11.5 Hz, 1H), 3.32 (d, *J* = 11.5 Hz, 1H), 2.85 (dd, *J* = 9.5, 6.0 Hz, 1H), 2.68 – 2.62 (m, 2H), 2.45 (d, *J* = 9.5 Hz, 1H), 2.34 (brs, 1H).

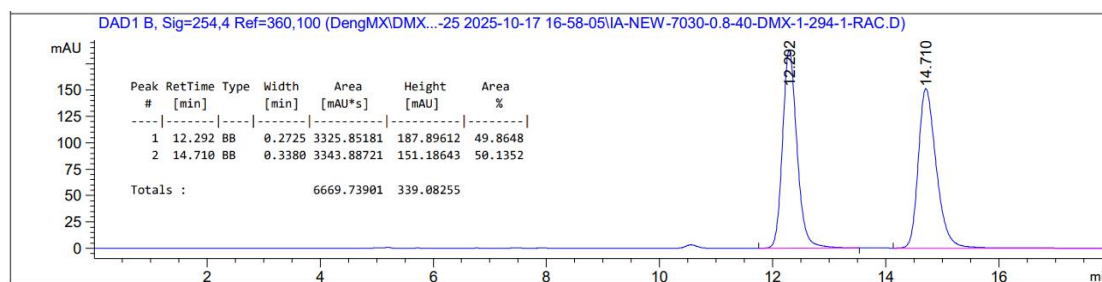
¹³C NMR (101 MHz, CDCl₃): δ 200.82, 165.21 (d, *J* = 254.5 Hz), 161.54 (d, *J* = 244.6 Hz), 141.89 (d, *J* = 3.1 Hz), 141.33, 132.74 (d, *J* = 3.0 Hz), 131.28 (d, *J* = 9.2 Hz), 128.40, 127.99, 127.31, 126.74 (d, *J* = 8.0 Hz), 115.50 (d, *J* = 8.4 Hz), 115.28 (d, *J* = 8.0 Hz), 64.50, 56.76, 53.94, 46.55, 42.00, 33.38.

¹⁹F NMR (376 MHz, CDCl₃): δ -105.62, -116.46.

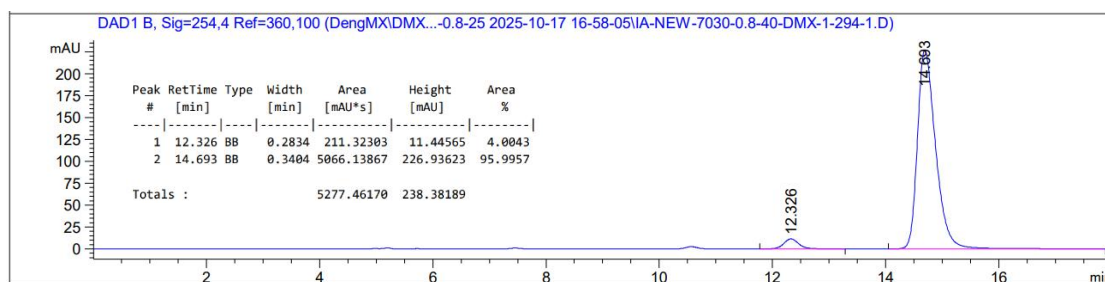
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₅H₂₂F₂NO, 390.1664; found, 390.1663.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, *t_R* (minor) = 12.3 min, *t_R* (major) = 14.7 min, ee = 92%.

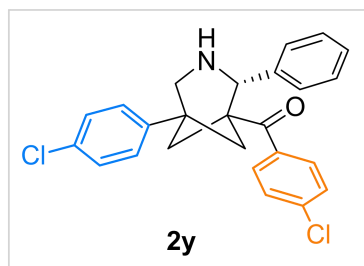
Chiral HPLC spectrum of (*rac*)-**2x**



Chiral HPLC spectrum of (*R*)-**2x**



(R)-(4-Chlorophenyl)(5-(4-chlorophenyl)-2-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)methanone



According to the general procedure, **2y** as obtained as a pale yellow solid in 92% yield with 91% ee, m.p. 174-176 °C, $[\alpha]_D^{25}$ -6.0 (*c* 0.5, CH₂Cl₂).

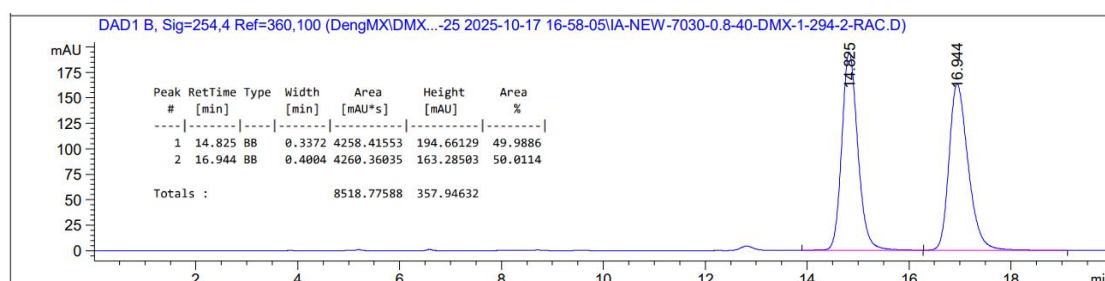
¹H NMR (400 MHz, CDCl₃): δ 7.45 – 7.42 (m, 2H), 7.28 – 7.22 (m, 4H), 7.15 – 7.10 (m, 5H), 7.06 – 7.03 (m, 2H), 4.76 (s, 1H), δ 3.34 (d, *J* = 11.4 Hz, 1H), 3.27 (d, *J* = 11.4 Hz, 1H), 2.80 (dt, *J* = 9.4, 3.2 Hz, 1H), 2.63 – 2.58 (m, 3H), 2.41 (d, *J* = 9.6 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 201.02, 144.41, 140.95, 139.00, 134.60, 132.38, 130.07, 128.74, 128.69, 128.52, 128.15, 127.33, 126.66, 64.31, 56.39, 53.95, 46.42, 42.13, 33.22.

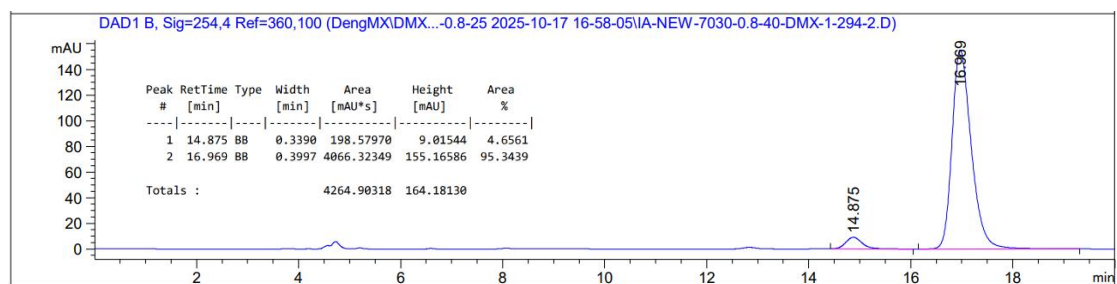
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₅H₂₂Cl₂NO, 422.1073; found, 422.1074.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, *t_R* (minor) = 14.9 min, *t_R* (major) = 17.0 min, ee = 91%.

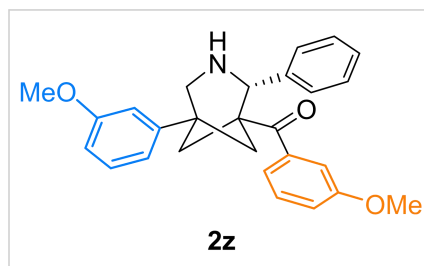
Chiral HPLC spectrum of (*rac*)-**2y**



Chiral HPLC spectrum of (*R*)-**2y**



**(*R*)-(3-Methoxyphenyl)(5-(3-methoxyphenyl)-2-phenyl-3-azabicyclo
[3.1.1]heptan-1-yl)methanone**



According to the general procedure, **2z** as obtained as a pale yellow solid in 85% yield with 93% ee, m.p. 96-99 °C, $[\alpha]_D^{25}$ -30.0 (*c* 0.5, CH₂Cl₂).

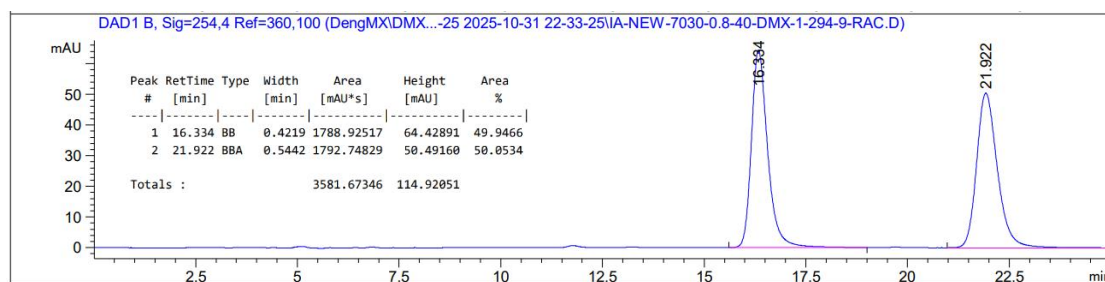
¹H NMR (400 MHz, CDCl₃): δ 7.25 – 7.23 (m, 1H), 7.22 – 7.13 (m, 7H), 7.01 – 6.97 (m, 2H), 6.76 (dd, *J* = 7.9, 2.1 Hz, 2H), 6.71 – 6.68 (m, 1H), 4.83 (s, 1H), 3.80 (s, 3H), 3.73 (s, 3H), δ 3.39 (d, *J* = 11.6 Hz, 1H), 3.34 (d, *J* = 11.6 Hz, 1H), 2.80 (dd, *J* = 9.5, 6.0 Hz, 1H), 2.70 – 2.64 (m, 2H), 2.49 (d, *J* = 9.5 Hz, 1H), 2.39 (brs, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 202.32, 159.74, 159.47, 147.90, 141.54, 137.81, 129.57, 129.22, 128.32, 127.78, 127.36, 121.09, 119.00, 117.52, 112.91, 111.52, 111.15, 64.41, 56.72, 55.40, 55.28, 54.12, 46.51, 42.59, 33.25.

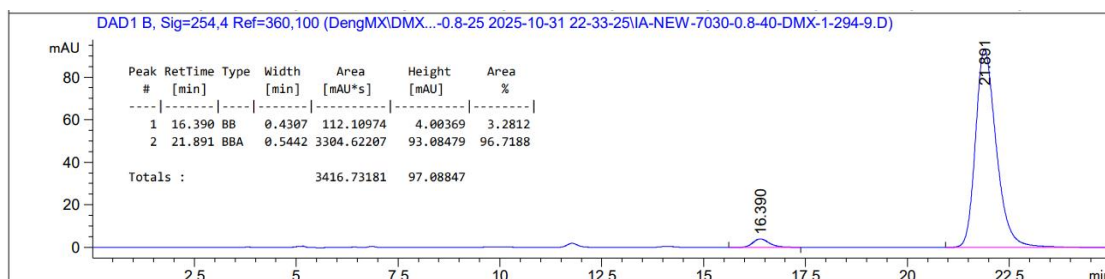
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₇H₂₈NO₃, 414.2064; found, 414.2062.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, λ = 254 nm, *t_R* (minor) = 16.4 min, *t_R* (major) = 21.9 min, ee = 93%.

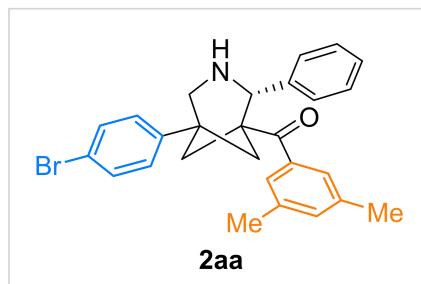
Chiral HPLC spectrum of (*rac*)-**2z**



Chiral HPLC spectrum of (*R*)-**2z**



(R)-(5-(4-Bromophenyl)-2-phenyl-3-azabicyclo[3.1.1]heptan-1-yl)(3,5-dimethylphenyl)methanone



According to the general procedure, **2aa** as obtained as a pale yellow solid in 86% yield with 86% ee, m.p. 225-228 °C, $[\alpha]_D^{25}$ -26.0 (*c* 0.5, CH₂Cl₂).

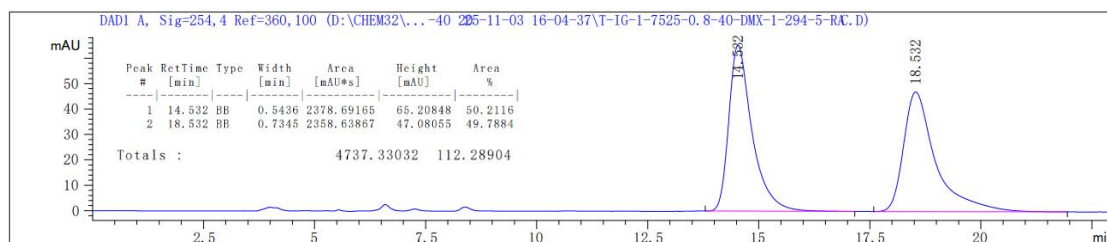
¹H NMR (400 MHz, CDCl₃): δ 7.43 (d, *J* = 8.3 Hz, 2H), 7.22 – 7.15 (m, 5H), 7.12 (s, 2H), 7.08 – 7.03 (m, 3H), 4.84 (s, 1H), 3.37 (d, *J* = 11.4 Hz, 1H), 3.33 (d, *J* = 11.9 Hz, 1H), 2.77 (dd, *J* = 9.4, 7.2 Hz, 1H), 2.70 – 2.66 (m, 1H), 2.62 (d, *J* = 8.8 Hz, 1H), 2.42 (d, *J* = 9.5 Hz, 1H), 2.29 – 2.27 (m, 7H).

¹³C NMR (101 MHz, CDCl₃): δ 202.81, 145.29, 141.63, 137.85, 136.45, 134.21, 131.58, 128.29, 127.80, 127.38, 127.09, 126.42, 120.24, 64.20, 56.60, 54.08, 46.03, 42.24, 33.47, 21.34.

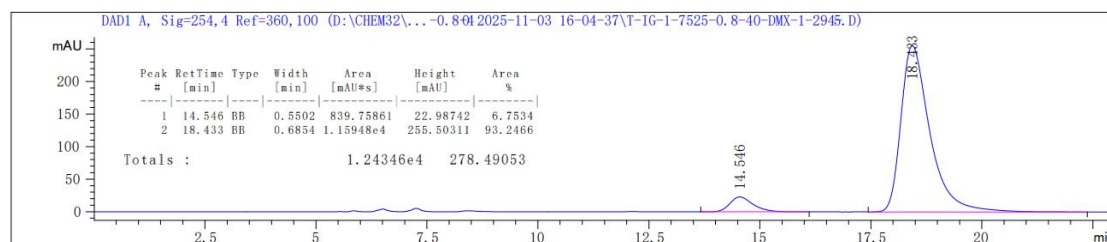
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₇H₂₇BrNO, 460.1271; found, 460.1268.

HPLC analysis: DAICEL CHIRALPAK IG, *n*-hexane/isopropanol = 75/25, 0.8 mL/min, λ = 254 nm, *t_R* (minor) = 14.5 min, *t_R* (major) = 18.4 min, ee = 86%.

Chiral HPLC spectrum of (rac)-2aa

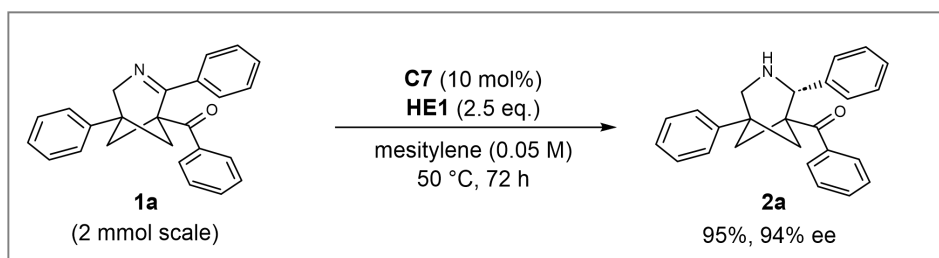


Chiral HPLC spectrum of (R)-2aa

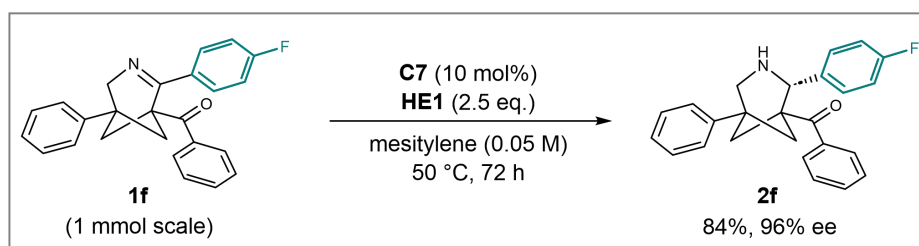


7. Gram Scale Synthesis and Synthetic transformations

a) Gram scale synthesis



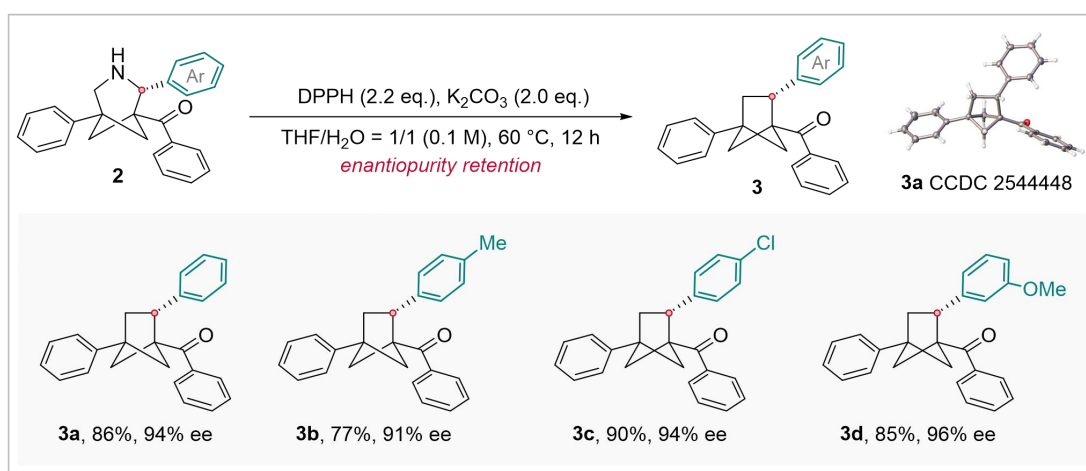
An oven-dried 25 mL Schlenk tube equipped with a magnetic stir bar was charged with imine **1** (2 mmol, 1.0 equiv.), **HE1** (5 mmol, 2.5 equiv.), and **C7** (10 mol%). The tube was evacuated and backfilled with argon three times. Mesitylene (40 mL) was then added, and the mixture was stirred at 50 °C for 72 h. After cooling to room temperature, chloranil (2 mmol, 1.0 equiv.) was added, and the mixture was stirred for an additional 30 min. The reaction was quenched with saturated aqueous NaHCO₃. The mixture was washed with aqueous NaOH (2 M, 2 × 20 mL) to remove tetrachloroquinol, then extracted with CH₂Cl₂ (3 × 20 mL), the combined organic layers were dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified via column chromatography on silica gel basified with triethylamine (petroleum ether/EtOAc/CH₂Cl₂ = 11/1/1) to afford product **2a** (670 mg, 95% yield, 94% ee).



An oven-dried 25 mL Schlenk tube equipped with a magnetic stir bar was charged with imine **1** (1 mmol, 1.0 equiv.), **HE1** (2.5 mmol, 2.5 equiv.), and **C7** (10 mol%). The tube was evacuated and backfilled with argon three times. Mesitylene (20 mL) was then added, and the mixture was stirred at 50 °C for 72 h. After cooling to room temperature, chloranil (1 mmol, 1.0 equiv.) was added, and the mixture was stirred for an additional

30 min. The reaction was quenched with saturated aqueous NaHCO₃. The mixture was washed with aqueous NaOH (2 M, 2 × 10 mL) to remove tetrachloroquinol, then extracted with CH₂Cl₂ (3 × 10 mL), the combined organic layers were dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified via column chromatography on silica gel basified with triethylamine (petroleum ether/EtOAc/CH₂Cl₂ = 10/1/1) to afford product **2f** (312 mg, 84% yield, 96% ee).

b) Synthesis of chiral bicyclo[2.1.1]hexanes



To a Schlenk tube (10 mL) with a magnetic stir bar, the 3-aza-BCHeP **2** (0.1 mmol, 1 equiv.), THF (0.5 mL), H₂O (0.5 mL), DPPH (*O*-(diphenylphosphoryl)hydroxylamine, 0.22 mmol, 2.2 equiv.), K₂CO₃ (0.2 mmol, 2 equiv.) was added sequentially. The reaction mixture was stirred at 60 °C for 18 h (monitored by TLC). The reaction was cooled to room temperature, diluted with 2 mL of water, extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were then saturated with brine, dried over Na₂SO₄ and concentrated by evaporation. The residue was purified by preparative TLC (petroleum ether/EtOAc = 10/1) to afford the product **3**.

(*R*)-(2,4-Diphenylbicyclo[2.1.1]hexan-1-yl)(phenyl)methanone (**3a**)

A white solid (31 mg, 86% yield, 94% ee), m.p. 88-91 °C, [α]_D²⁵ +12.0 (*c* 0.5, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃): δ 7.69 (d, *J* = 7.4 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.36 – 7.30 (m, 6H), 7.27 – 7.22 (m, 1H), 7.21 – 7.09 (m, 5H), 4.12 (dd, *J* = 8.9, 3.8 Hz, 1H),

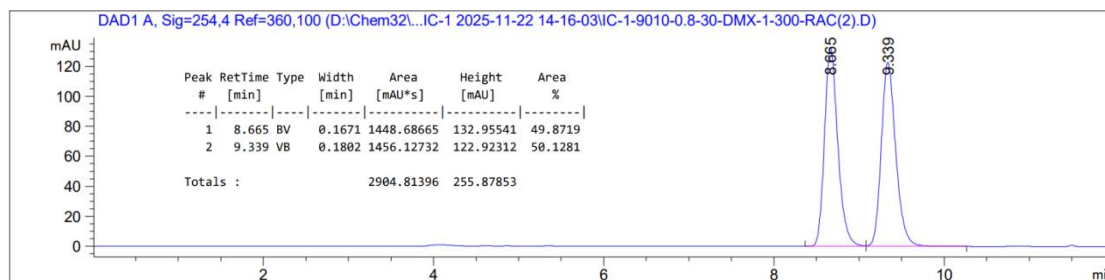
2.64 (ddd, $J = 10.3, 9.1, 2.6$ Hz, 1H), 2.55 – 2.46 (m, 2H), 2.41 (ddd, $J = 11.2, 4.3, 3.1$ Hz, 1H), 2.36 (dd, $J = 5.5, 2.9$ Hz, 1H), 2.18 (d, $J = 6.1$ Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 202.18, 142.36, 141.56, 137.20, 132.67, 128.53, 128.48, 128.43, 128.42, 127.95, 126.72, 126.69, 126.09, 61.06, 52.03, 50.45, 49.81, 41.65, 41.36.

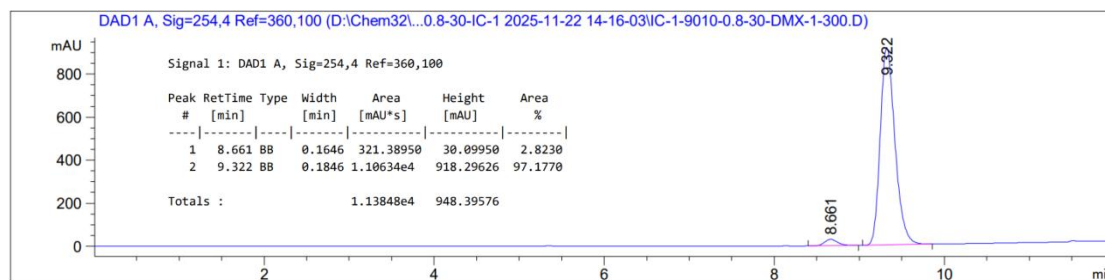
HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{25}\text{H}_{22}\text{NaO}$, 361.1563; found, 361.1571.

HPLC analysis: DAICEL CHIRALPAK IC, n -hexane/isopropanol = 90/10, 0.8 mL/min, $\lambda = 254$ nm, t_R (minor) = 8.7 min, t_R (major) = 9.3 min, ee = 94%.

Chiral HPLC spectrum of (*rac*)-**3a**



Chiral HPLC spectrum of (*R*)-**3a**



(*R*)-4-Phenyl-2-(*p*-tolyl)bicyclo[2.1.1]hexan-1-yl(phenyl)methanone (**3b**)

A white foam (27 mg, 77% yield, 91% ee), $[\alpha]_D^{25} +20.0$ (c 0.5, CH_2Cl_2).

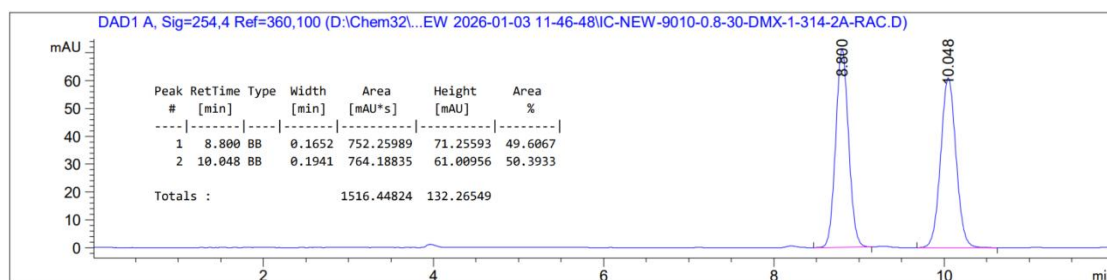
^1H NMR (400 MHz, CDCl_3): δ 7.73 (d, $J = 7.9$ Hz, 2H), 7.48 (t, $J = 7.1$ Hz, 1H), 7.38 – 7.31 (m, 6H), 7.27 – 7.21 (m, 1H), 7.06 (d, $J = 8.0$ Hz, 2H), 7.00 (d, $J = 8.0$ Hz, 2H), 4.10 (dd, $J = 8.7, 3.3$ Hz, 1H), 2.68 – 2.59 (m, 1H), 2.58 – 2.44 (m, 2H), 2.41 – 2.36 (m, 2H), 2.24 (s, 3H), 2.16 (d, $J = 6.7$ Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 202.19, 142.45, 138.47, 137.19, 136.22, 132.65, 129.11, 128.51, 128.49, 128.46, 127.81, 126.65, 126.09, 61.13, 52.04, 50.11, 49.74, 41.57, 41.44, 21.05.

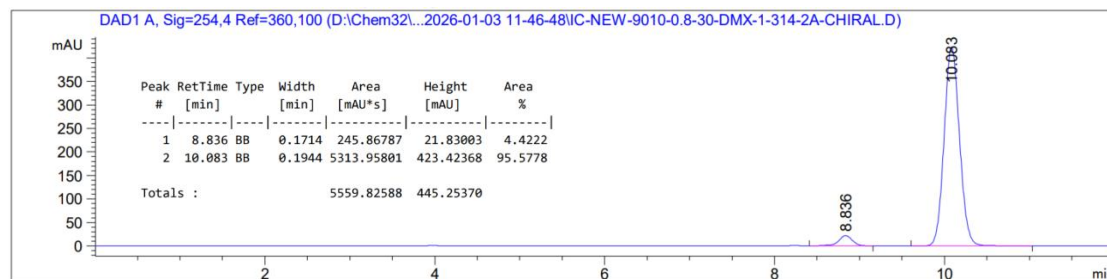
HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{26}\text{H}_{24}\text{NaO}$, 375.1719; found, 375.1722.

HPLC analysis: DAICEL CHIRALPAK IC, n -hexane/isopropanol = 90/10, 0.8 mL/min, $\lambda = 254$ nm, t_R (minor) = 8.8 min, t_R (major) = 10.1 min, ee = 91%.

Chiral HPLC spectrum of (*rac*)-**3b**



Chiral HPLC spectrum of (*R*)-**3b**



(*R*)-2-(4-Chlorophenyl)-4-phenylbicyclo[2.1.1]hexan-1-yl(phenyl)methanone (**3c**)

A white foam (36 mg, 90% yield, 94% ee), $[\alpha]_D^{25} +29.0$ (*c* 1.0, CH₂Cl₂).

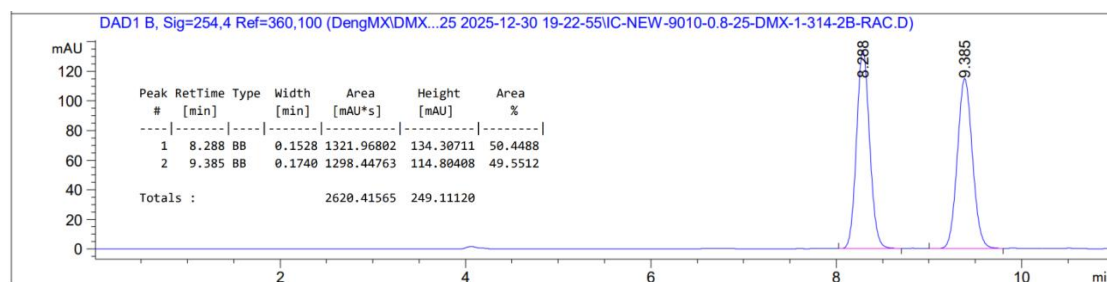
¹H NMR (400 MHz, CDCl₃): δ 7.79 – 7.71 (m, 2H), 7.55 – 7.50 (m, 1H), 7.44 – 7.31 (m, 6H), 7.30 – 7.24 (m, 1H), 7.20 – 7.15 (m, 2H), 7.15 – 7.09 (m, 2H), 4.10 (dd, *J* = 8.9, 3.8 Hz, 1H), 2.67 (ddd, *J* = 11.6, 9.1, 2.7 Hz, 1H), 2.53 (dd, *J* = 9.4, 6.4 Hz, 1H), 2.47 – 2.39 (m, 2H), 2.35 (ddd, *J* = 11.3, 4.3, 3.0 Hz, 1H), 2.22 (ddd, *J* = 7.3, 2.6, 1.6 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 201.79, 142.04, 140.07, 137.03, 132.89, 132.49, 129.27, 128.62, 128.56, 128.52, 128.38, 126.79, 126.06, 61.04, 52.01, 49.82, 41.56, 41.53.

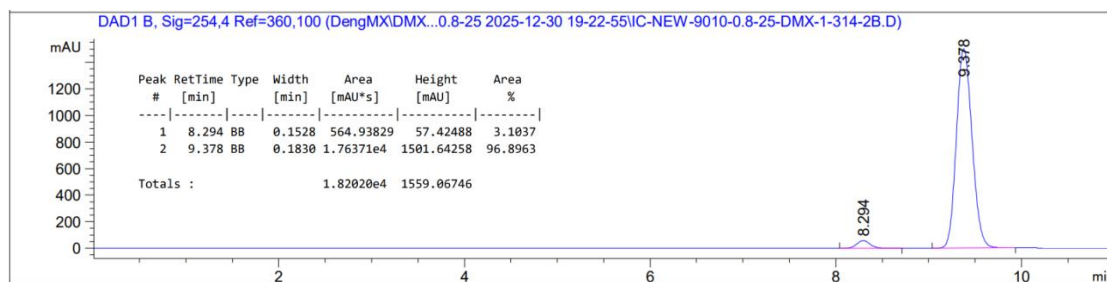
HRMS (ESI) *m/z*: [M+Na]⁺ calcd. for C₂₅H₂₁ClNaO, 395.1173; found, 395.1175.

HPLC analysis: DAICEL CHIRALPAK IC, *n*-hexane/isopropanol = 90/10, 0.8 mL/min, λ = 254 nm, *t_R* (minor) = 8.3 min, *t_R* (major) = 9.4 min, ee = 94%.

Chiral HPLC spectrum of (*rac*)-**3c**



Chiral HPLC spectrum of (*R*)-**3c**



(*R*)-2-(3-Methoxyphenyl)-4-phenylbicyclo[2.1.1]hexan-1-yl(phenyl)methanone (**3d**)

A white foam (31 mg, 85% yield, 96% ee), $[\alpha]_D^{25} +4.0$ (*c* 1.0, CH₂Cl₂).

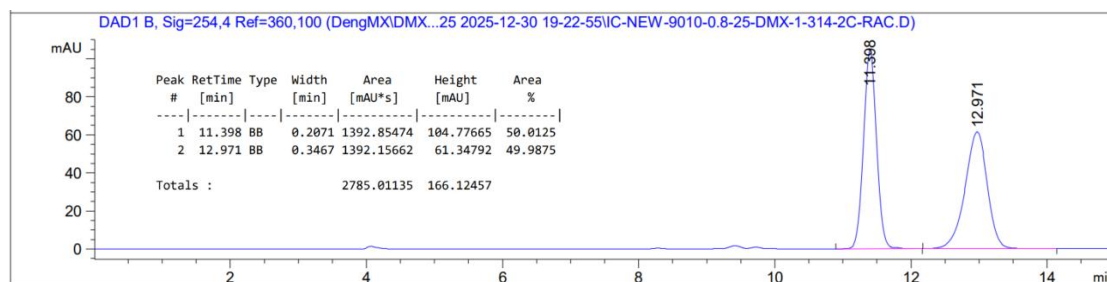
¹H NMR (400 MHz, CDCl₃): δ 7.73 (d, *J* = 7.3 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.37 – 7.29 (m, 6H), 7.28 – 7.21 (m, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 6.69 – 6.66 (m, 2H), 4.10 (dd, *J* = 8.7, 3.7 Hz, 1H), 3.63 (s, 3H), 2.63 (td, *J* = 10.1, 9.0, 2.5 Hz, 1H), 2.53 – 2.44 (m, 2H), 2.41 – 2.33 (m, 2H), 2.19 (d, *J* = 6.0 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 202.03, 159.53, 143.20, 142.32, 137.20, 132.69, 129.37, 128.51, 128.49, 128.43, 126.68, 126.07, 120.21, 113.88, 112.12, 61.02, 55.14, 51.99, 50.43, 49.72, 41.71, 41.36.

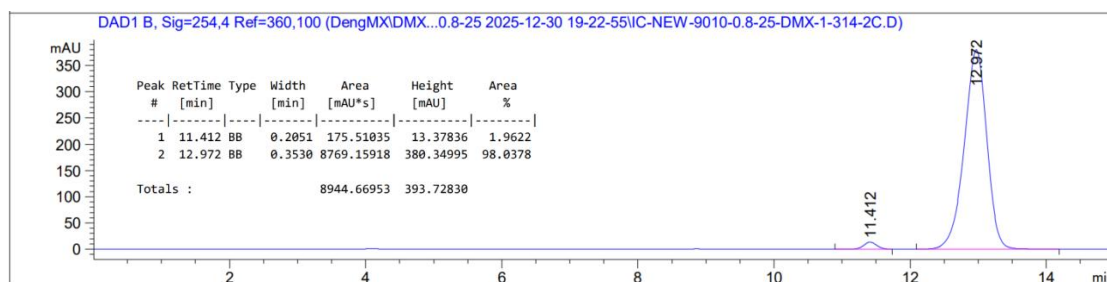
HRMS (ESI) *m/z*: [M+Na]⁺ calcd. for C₂₆H₂₄NaO₂, 391.1669; found, 391.1672.

HPLC analysis: DAICEL CHIRALPAK IC, *n*-hexane/isopropanol = 90/10, 0.8 mL/min, λ = 254 nm, *t_R* (minor) = 11.4 min, *t_R* (major) = 13.0 min, ee = 96%.

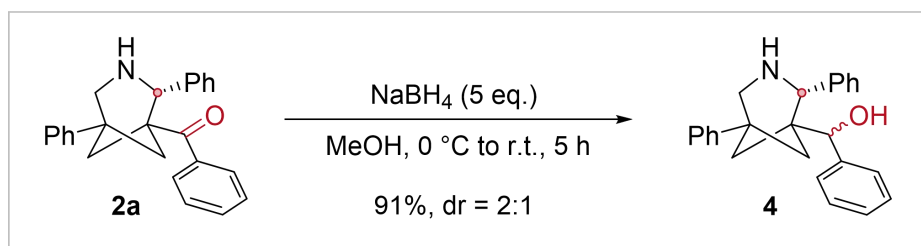
Chiral HPLC spectrum of (*rac*)-**3d**



Chiral HPLC spectrum of (*R*)-**3d**



c) Synthetic transformation



A 10 mL round bottom flask equipped with a magnetic stir bar was charged with **2a** (0.1 mmol, 1.0 equiv.) and MeOH (1 mL). Then, NaBH₄ (0.5 mmol, 5 equiv.) was added at 0 °C and the reaction was stirred at room temperature for 5 h before quenched with saturated aq. NH₄Cl (2 mL), and extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and filtered. The residue was purified by preparative TLC (petroleum ether/EtOAc = 1/2) to afford the product **4** as a white foam (32.3 mg, 91%, dr = 2:1).

(2,5-Diphenyl-3-azabicyclo[3.1.1]heptan-1-yl)(phenyl)methanol (**4 major**)

A white foam, 92% ee, [α]_D²⁵ -20.0 (c 0.5, CH₂Cl₂).

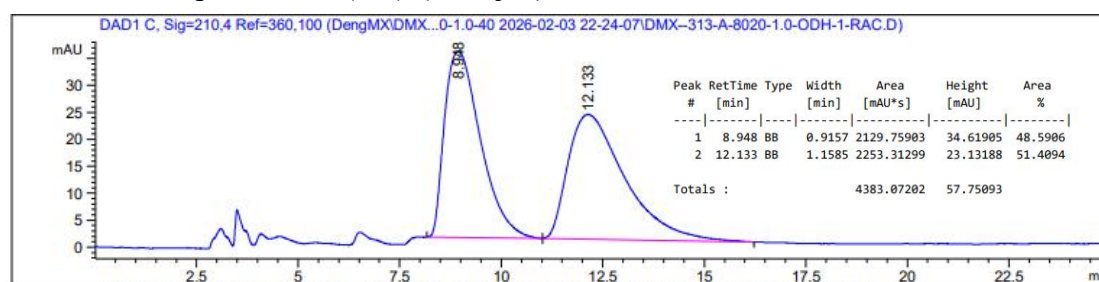
¹H NMR (400 MHz, CDCl₃): δ 7.35 – 7.27 (m, 6H), 7.24 – 7.16 (m, 7H), 6.86 (d, J = 6.4 Hz, 2H), 4.39 (s, 1H), 3.79 (s, 1H), 3.16 (s, 2H), 2.79 (d, J = 8.7 Hz, 1H), 2.72 – 2.67 (m, 1H), 2.52 (d, J = 9.1 Hz, 1H), 1.88 – 1.84 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 147.26, 141.24, 128.79, 128.53, 128.41, 128.12, 128.02, 127.89, 127.75, 126.15, 125.38, 64.59, 56.99, 47.42, 41.98, 40.79, 29.97.

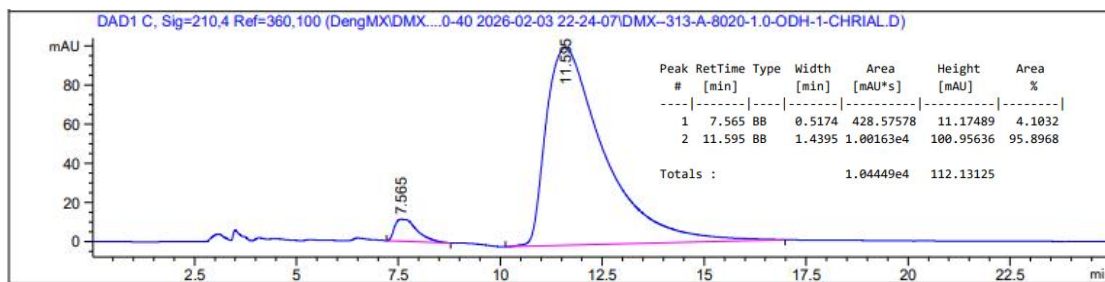
HRMS (ESI) m/z : [M+H]⁺ calcd. for C₂₅H₂₆NO, 356.2009; found, 356.2010.

HPLC analysis: DAICEL CHIRALPAK OD-H, *n*-hexane/isopropanol = 80/20, 1.0 mL/min, λ = 210 nm, t_R (minor) = 7.6 min, t_R (major) = 11.6 min, ee = 92%.

Chiral HPLC spectrum of (*rac*)-(**4 major**)



Chiral HPLC spectrum of (*R*)-(**4 major**)



(2,5-Diphenyl-3-azabicyclo[3.1.1]heptan-1-yl)(phenyl)methanol (4 minor)

A white foam, 98% ee, $[\alpha]_D^{25}$ -52.0 (*c* 0.5, CH₂Cl₂).

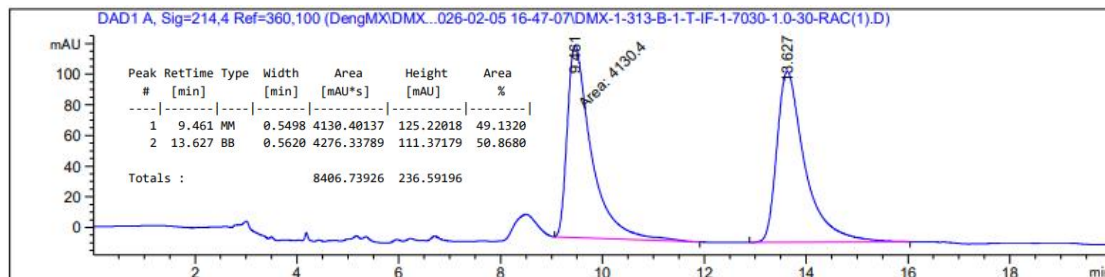
¹H NMR (400 MHz, CDCl₃): δ 7.59 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.34 – 7.29 (m, 1H), 7.25 – 7.22 (m, 4H), 7.19 – 7.12 (m, 2H), 7.11 – 7.08 (m, 2H), 7.00 (d, *J* = 7.1 Hz, 2H), 4.61 (s, 1H), 4.31 (s, 1H), 3.23 – 3.17 (m, 2H), 2.53 – 2.47 (m, 1H), 2.19 (d, *J* = 9.0 Hz, 1H), 2.06 – 1.96 (m, 3H), 1.36 (d, *J* = 9.2 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 147.45, 143.72, 141.55, 128.52, 128.45, 128.28, 128.00, 127.63, 127.47, 127.32, 125.97, 125.18, 63.95, 57.28, 46.77, 43.63, 38.70, 31.83.

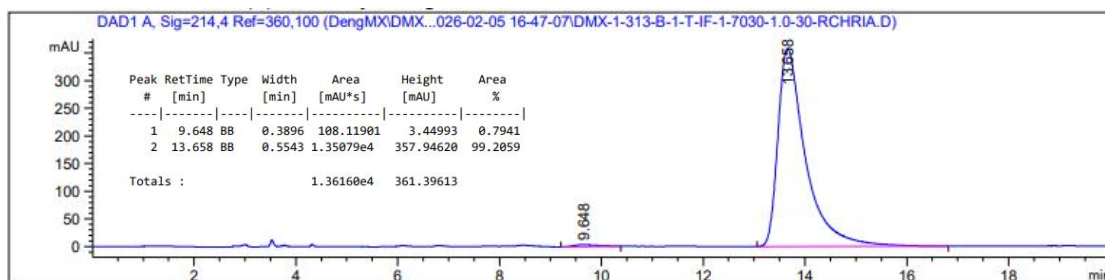
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₅H₂₆NO, 356.2009; found, 356.2011.

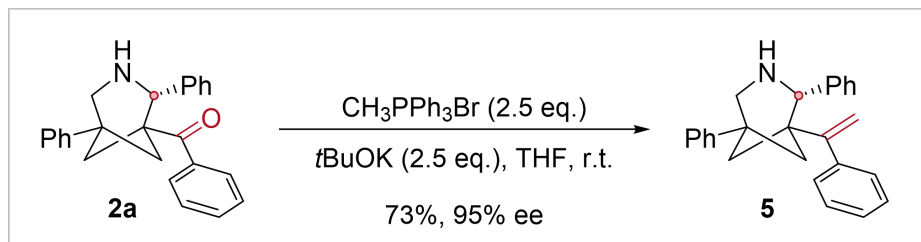
HPLC analysis: DAICEL CHIRALPAK IF, *n*-hexane/isopropanol = 70/30, 1.0 mL/min, λ = 214 nm, *t_R* (minor) = 9.4 min, *t_R* (major) = 13.6 min, ee = 98%.

Chiral HPLC spectrum of (*rac*)-(4 minor)



Chiral HPLC spectrum of (*R*)-(4 minor)





An oven-dried Schlenk tube equipped with a magnetic stir bar was charged with the methyltriphenylphosphonium bromide (0.25 mmol, 2.5 equiv.) and THF (1.0 mL), add solution of *t*BuOK (0.25 mL, 2.5 equiv.) in THF (1.0 M) dropwise at room temperature. The resultant mixture was stirred at room temperature for 2 h. Then, add solution of **2a** (0.1 mmol, 1.0 equiv.) in THF (1 mL) dropwise and stir for 12 h at room temperature. After the reaction was complete, dilute with saturated aqueous NH_4Cl and CH_2Cl_2 . Extract the aqueous layer with CH_2Cl_2 (3×5 mL). The combined organic layers were dried with Na_2SO_4 , concentrate the combined organic extracts in vacuo. The residue was purified by preparative TLC (petroleum ether/EtOAc = 2/1) to afford the product **5** as a colorless oil (25.8 mg, 73% yield, with 95% ee), $[\alpha]_{\text{D}}^{25} -38.0$ (*c* 0.5, CH_2Cl_2).

(*R*)-2,5-Diphenyl-1-(1-phenylvinyl)-3-azabicyclo[3.1.1]heptane (5**)**

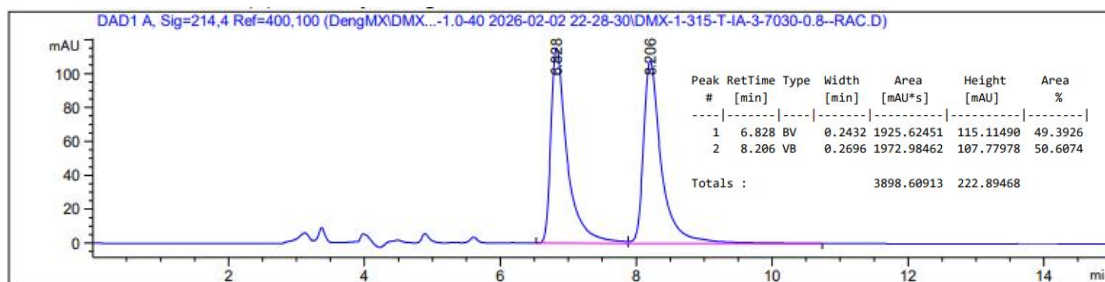
^1H NMR (400 MHz, CDCl_3): δ 7.34 (t, $J = 7.5$ Hz, 2H), 7.26 – 7.18 (m, 11H), 7.05 – 7.03 (m, 2H), 5.03 (s, 1H), 4.78 (s, 1H), 4.40 (s, 1H), 3.36 (d, $J = 11.6$ Hz, 1H), 3.28 (d, $J = 11.4$ Hz, 1H), 2.83 – 2.79 (m, 1H), 2.68 (t, $J = 8.0$ Hz, 1H), 2.63 – 2.57 (m, 1H), 2.33 (d, $J = 9.2$ Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 152.72, 146.92, 141.04, 128.50, 128.28, 128.01, 127.75, 127.63, 127.25, 126.30, 125.37, 114.95, 64.63, 56.68, 48.46, 47.27, 42.50, 35.41.

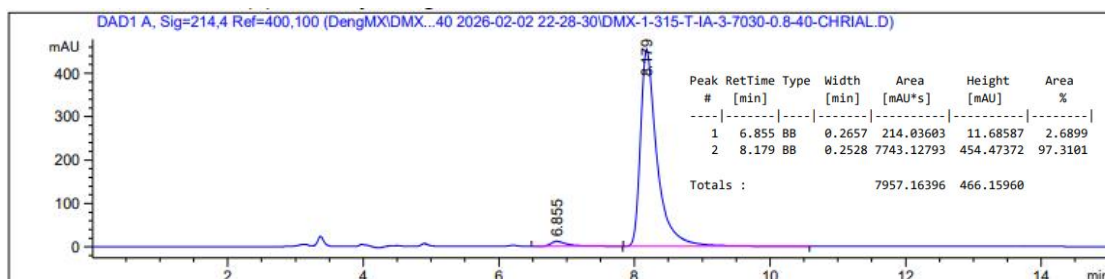
HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{26}\text{N}$, 352.2060; found, 352.2060.

HPLC analysis: DAICEL CHIRALPAK IA, *n*-hexane/isopropanol = 70/30, 0.8 mL/min, $\lambda = 214$ nm, t_{R} (minor) = 6.9 min, t_{R} (major) = 8.2 min, ee = 95%.

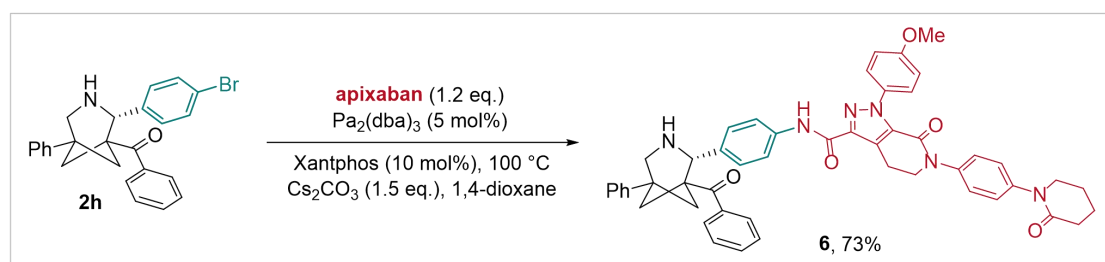
Chiral HPLC spectrum of (*rac*)-**5**



Chiral HPLC spectrum of (*R*)-**5**



d) Late-stage modification of apixaban via coupling with 3-aza-BCHeP



2h (0.06 mmol, 1.0 equiv.), apixaban (0.072 mmol, 1.2 equiv.), Cs_2CO_3 (0.09 mmol, 1.5 equiv.), xantphos (0.006 mmol, 0.1 equiv.) and $\text{Pd}_2(\text{dba})_3$ (5 mol%) were sequentially added to dried 10 mL Schlenk tube. And then the tube was evacuated and filled with argon (repeated for three times). Anhydrous dioxane (1 mL) was added under argon flow. The tube was sealed and the reaction was heated at 100 °C. After 36 h, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 20/1$) to afford the product **6** (35.6 mg, 73% yield) as a white solid.

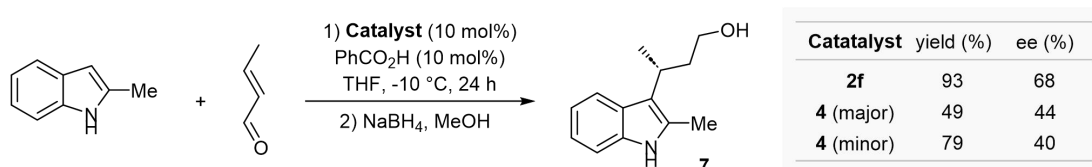
^1H NMR (400 MHz, CDCl_3): δ 8.68 (s, 1H), 7.59 (d, $J = 7.6$ Hz, 2H), 7.49 – 7.43 (m, 5H), 7.35 – 7.31 (m, 6H), 7.26 – 7.21 (m, 3H), 7.18 (d, $J = 6.7$ Hz, 4H), 6.95 (d, $J = 8.7$ Hz, 2H), 4.83 (s, 1H), 4.11 (t, $J = 6.4$ Hz, 2H), 3.82 (s, 3H), 3.60 – 3.58 (m, 2H), 3.41

– 3.25 (m, 4H), 2.86 – 2.82 (m, 1H), 2.73 – 2.66 (m, 2H), 2.54 – 2.50 (m, 3H), 2.16 (brs, 1H), 1.94 – 1.90 (m, 4H).

¹³C NMR (101 MHz, CDCl₃): δ 202.33, 170.21, 160.01, 159.56, 157.34, 146.19, 141.50, 141.28, 139.95, 137.39, 137.11, 136.47, 133.71, 132.55, 132.45, 128.65, 128.51, 128.38, 128.11, 126.91, 126.85, 126.41, 126.25, 125.88, 125.17, 119.44, 113.87, 63.99, 56.75, 55.66, 54.16, 51.68, 51.25, 46.67, 42.53, 33.02, 32.93, 23.59, 21.50, 21.37.

HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₅₀H₄₇N₆O₅, 811.3602; found, 811.3605.

e) 3-aza-BCHePs as chiral secondary amine catalyst



A mixture of α,β -unsaturated aldehydes (0.3 mmol, 3 equiv.), **Catalyst** (10 mol%) and PhCO₂H (0.01 mmol) as a cocatalyst which could promote the formation of iminium in THF (0.2 mL) was stirred for 30 min at room temperature. Then, the indole (0.1 mmol, 1 equiv.) was added and the reaction mixture was stirred for 24 h (monitored by TLC) at -10 °C. The resulting mixture was stirred for 30 min after MeOH (0.2 mL) and NaBH₄ (0.3 mmol, 3 equiv.) was added. The reaction mixture was quenched with saturated aqueous NH₄Cl, extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were then saturated with brine, dried over Na₂SO₄ and concentrated by evaporation. The residue was purified by preparative TLC to afford the product **7** as a light yellow oil. The spectroscopic data were consistent with those reported in the literature^[9].

(*R*)-(3-(2-Methyl-1*H*-indol-3-yl)butan-1-ol) (**7**)

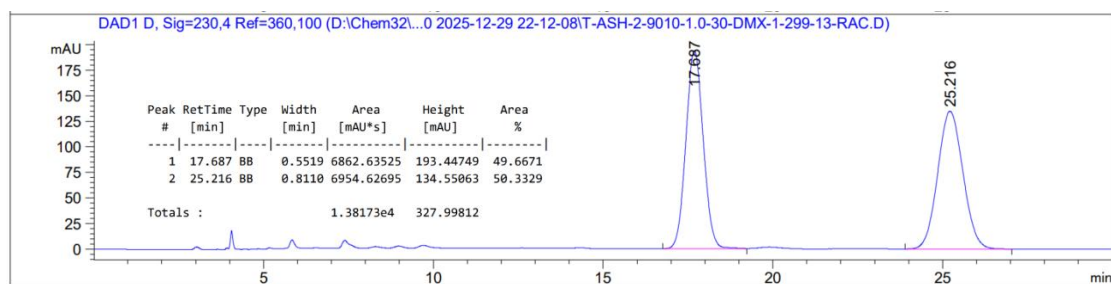
¹H NMR (400 MHz, CDCl₃): δ 7.74 (brs, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.10 – 7.01 (m, 2H), 3.58 – 3.45 (m, 2H), 3.20 – 3.10 (m, 1H), 2.35 (s, 3H), 2.16 – 2.07 (m, 1H), 1.97 (dt, *J* = 13.5, 6.7 Hz, 1H), 1.42 (d, *J* = 7.2 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 135.65, 130.50, 127.34, 120.82, 119.37, 118.95, 115.37, 110.52, 62.07, 39.55, 27.96, 21.53, 12.18.

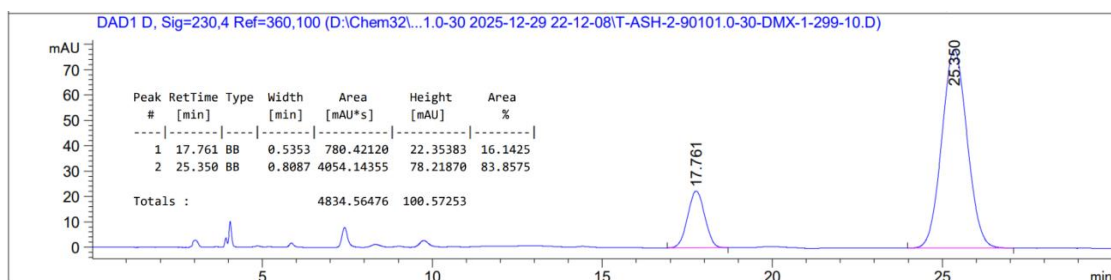
HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₁₃H₁₈NO, 204.1383; found, 204.1389.

HPLC analysis: DAICEL CHIRALPAK AS-H, *n*-hexane/isopropanol = 90/10, 1.0 mL/min, λ = 230 nm, *t_R* (minor) = 17.8 min, *t_R* (major) = 25.3 min, ee = 68%.

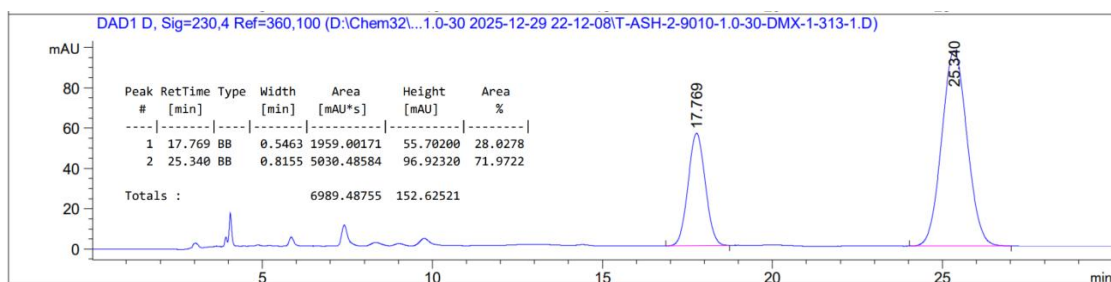
Chiral HPLC spectrum of (*rac*)-**7**



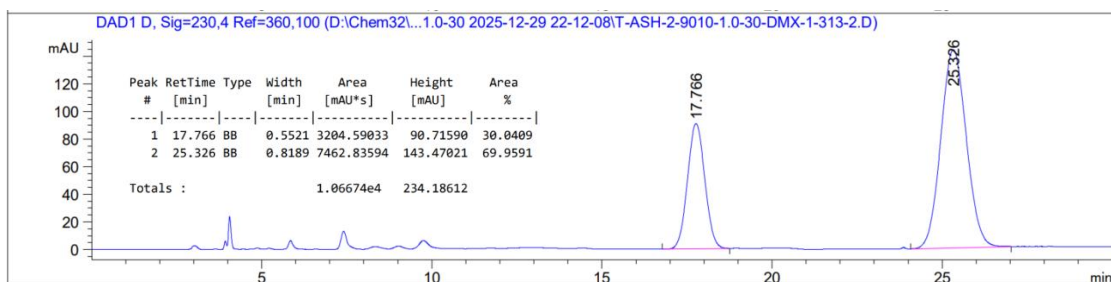
Chiral HPLC spectrum of (*R*)-**7** (entry 1)



Chiral HPLC spectrum of (*R*)-**7** (entry 2)



Chiral HPLC spectrum of (*R*)-**7** (entry 3)



8. Crystal data and structure refinement for 2a and 3a

The crystal structure of **2a** has been deposited at the Cambridge Crystallographic Data Centre (CCDC: 2544558).

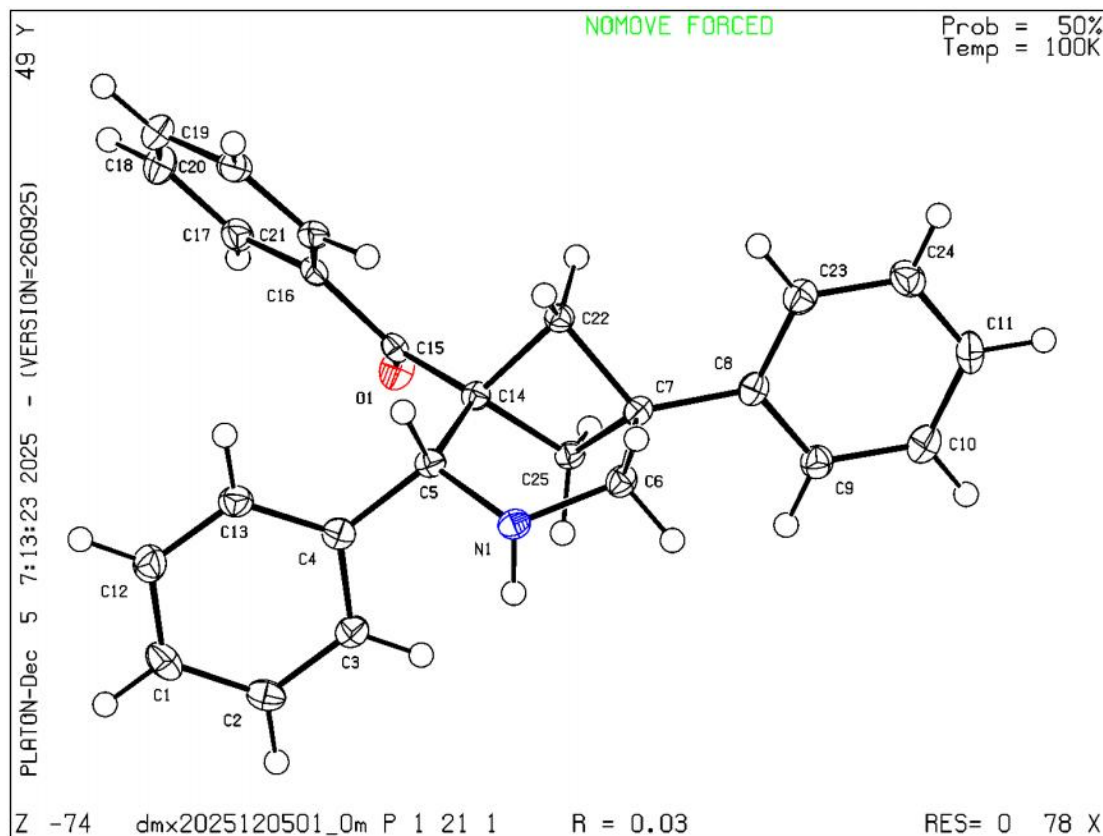


Table 1 Crystal data and structure refinement for **2a**.

Identification code	2a
Empirical formula	C ₂₅ H ₂₃ NO
Formula weight	353.44
Temperature/K	100.0(2)
Crystal system	monoclinic
Space group	P2 ₁
a/Å	5.94400(10)
b/Å	12.2599(3)
c/Å	12.9284(3)
α/°	90
β/°	102.0390(10)
γ/°	90
Volume/Å ³	921.41(3)
Z	2
ρ _{calc} /cm ³	1.274

μ/mm^{-1}	0.595
F(000)	376.0
Crystal size/ mm^3	$0.31 \times 0.3 \times 0.25$
Radiation	$\text{CuK}\alpha$ ($\lambda = 1.54178$)
2θ range for data collection/ $^\circ$	6.99 to 136.434
Index ranges	$-7 \leq h \leq 7, -14 \leq k \leq 14, -15 \leq l \leq 15$
Reflections collected	28238
Independent reflections	3371 [$R_{\text{int}} = 0.0310, R_{\text{sigma}} = 0.0160$]
Data/restraints/parameters	3371/1/247
Goodness-of-fit on F^2	1.048
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0276, wR_2 = 0.0696$
Final R indexes [all data]	$R_1 = 0.0279, wR_2 = 0.0697$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.16/-0.15
Flack parameter	0.03(17)

The crystal structure of **3a** has been deposited at the Cambridge Crystallographic Data Centre (CCDC: 2544448).

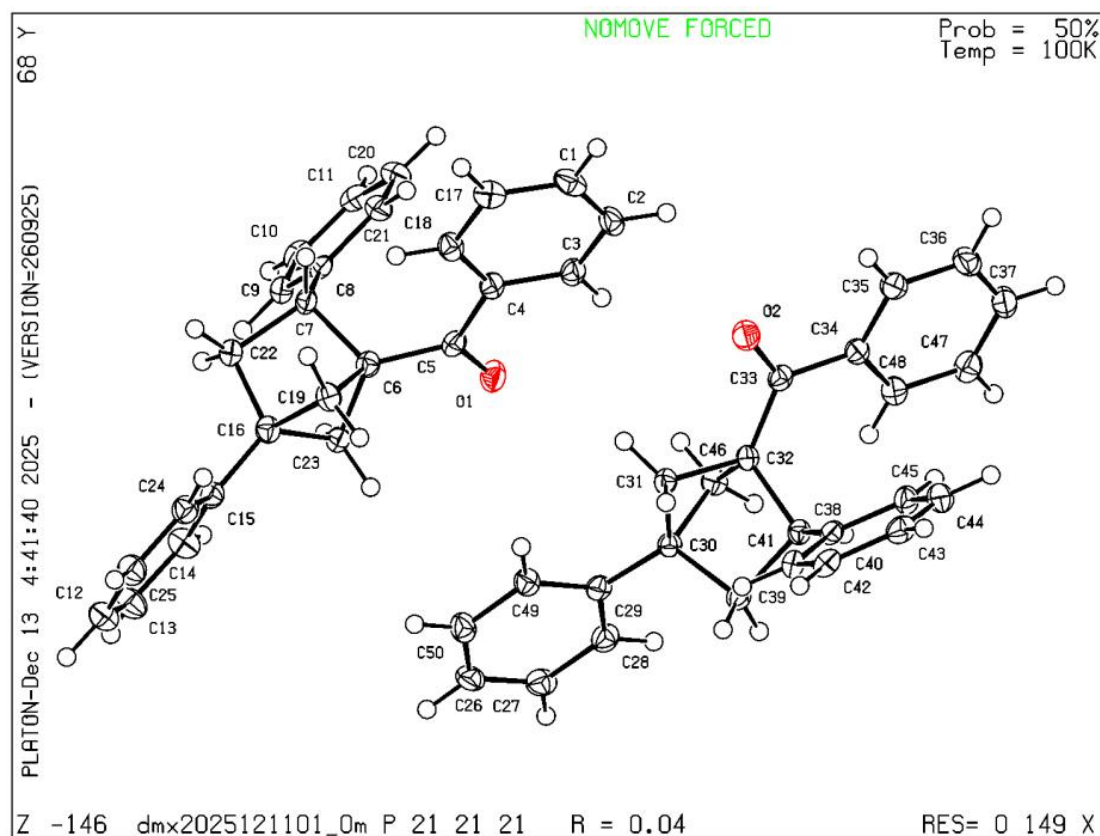


Table 1 Crystal data and structure refinement for **3a**.

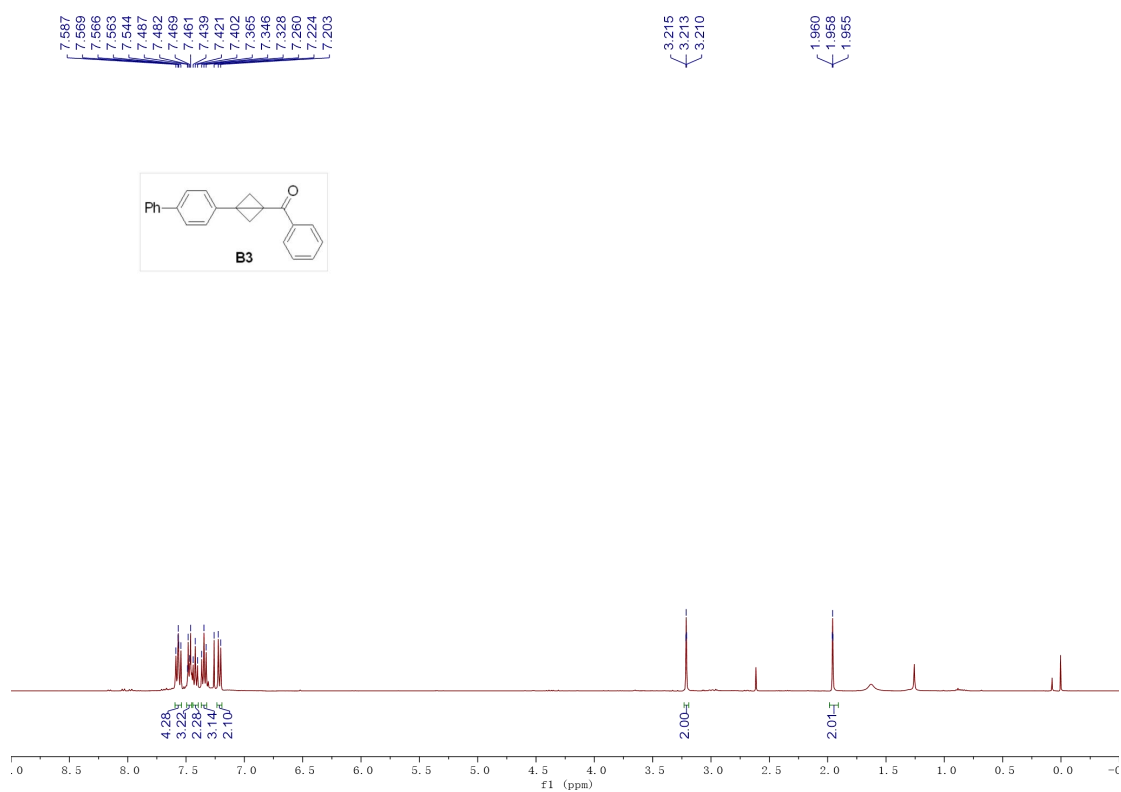
Identification code **3a**

Empirical formula	C ₂₅ H ₂₂ O
Formula weight	338.42
Temperature/K	100.0(2)
Crystal system	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	6.1895(2)
b/Å	19.8168(6)
c/Å	29.5819(8)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	3628.40(19)
Z	8
ρ _{calc} /g/cm ³	1.239
μ/mm ⁻¹	0.566
F(000)	1440.0
Crystal size/mm ³	0.26 × 0.21 × 0.2
Radiation	CuKα (λ = 1.54178)
2θ range for data collection/°	5.368 to 136.976
Index ranges	-7 ≤ h ≤ 7, -23 ≤ k ≤ 23, -35 ≤ l ≤ 35
Reflections collected	60379
Independent reflections	6686 [R _{int} = 0.0869, R _{sigma} = 0.0401]
Data/restraints/parameters	6686/0/469
Goodness-of-fit on F ²	1.068
Final R indexes [I > 2σ (I)]	R ₁ = 0.0367, wR ₂ = 0.0817
Final R indexes [all data]	R ₁ = 0.0437, wR ₂ = 0.0849
Largest diff. peak/hole / e Å ⁻³	0.14/-0.20
Flack parameter	-0.06(16)

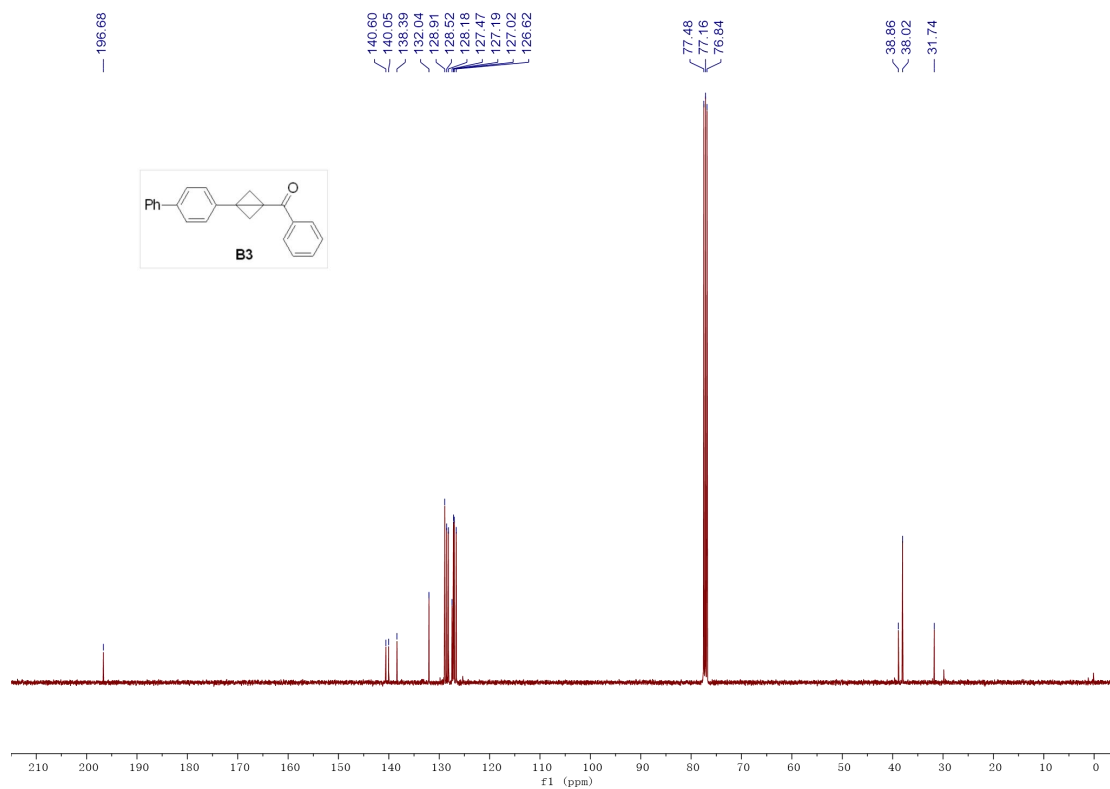
9. References

- 1.(a) Cao S, Ji Q, Li H, Pang M, Yuan H, Zhang J, et al. AgN₃-catalyzed hydroazidation of terminal alkynes and mechanistic studies. *J Am Chem Soc.* 2020;142(15):7083-7091. [DOI:10.1021/jacs.0c00836]; (b) Liu Z, Liao P, Bi X. General silver-catalyzed hydroazidation of terminal alkynes by combining TMS-N₃ and H₂O: Synthesis of vinyl azides. *Org Lett.* 2014;16(14):3668-3671. [DOI:10.1021/ol501661k]
- 2.Hu S, Gao Y, Pan Y, Ni D, Deng L. Modular synthesis of azidobicyclo[2.1.1]hexanes via (3 + 2) annulation of α -substituted vinyl azides and bicyclo[1.1.0]butanes. *J Org Chem.* 2024;89(20):15151-15157. [DOI:10.1021/acs.joc.4c01920]
- 3.Zhou X, Dong J, Liao H, Jiang Q, Zhang B, Li T, et al. Synthesis of 2,5-dithia-bicyclo[4.1.1]octanes by silver-catalyzed formal (4+3) cycloadditions of bicyclobutanes with benzodithioloimines. *Org Lett.* 2025;27(14):3571-3577. [DOI:10.1021/acs.orglett.5c00585]
- 4.Liu Y, Wu Z, Shan JR, Yan H, Hao EJ, Shi L. Titanium catalyzed $[2\sigma + 2\pi]$ cycloaddition of bicyclo[1.1.0]-butanes with 1,3-dienes for efficient synthesis of stilbene bioisosteres. *Nat Commun.* 2024;15: 4374. [DOI:10.1038/s41467-024-48494-9]
- 5.Lin Z, Ren H, Lin X, Yu X, Zheng J. Synthesis of azabicyclo[3.1.1]heptenes enabled by catalyst-controlled annulations of bicyclo[1.1.0]butanes with vinyl azides. *J Am Chem Soc.* 2024;146(27):18565-18575. [DOI:10.1021/jacs.4c04485]
- 6.Guo R, Chang YC, Herter L, Salome C, Braley SE, Fessard TC, et al. Strain-release $[2\pi + 2\sigma]$ cycloadditions for the synthesis of bicyclo[2.1.1]hexanes initiated by energy transfer. *J Am Chem Soc.* 2022;144(18):7988-7994. [DOI:10.1021/jacs.2c02976]
- 7.Yi L, Makarov AS, Maity B, Kong Deshen, Alshehri R, Cavallo L, et al. Modular access to sp³-rich bicyclo[1.1.1]pentane bioisosteres via energy-transfer-mediated carbene insertion. *Angew Chem Int Ed.* 2026;65(1):e18508. [DOI:10.1002/anie.202518508]
- 8.Wei J, Zhang J, Cheng JK, Xiang SH, Tan B. Modular enantioselective access to β -amino amides by Brønsted acid-catalysed multicomponent reactions. *Nat Chem.* 2023;15(5):647-657. [DOI:10.1038/s41557-023-01179-0]
- 9.Brouwer B, Della-Felice F, Thunnissen AM, Roelfes G. Genetically encoded 3-aminotyrosine as catalytic residue in a designer friedel–crafts alkylase. *Chem Sci.* 2025;16(20):8721-8728. [DOI:10.1039/D5SC01055A]

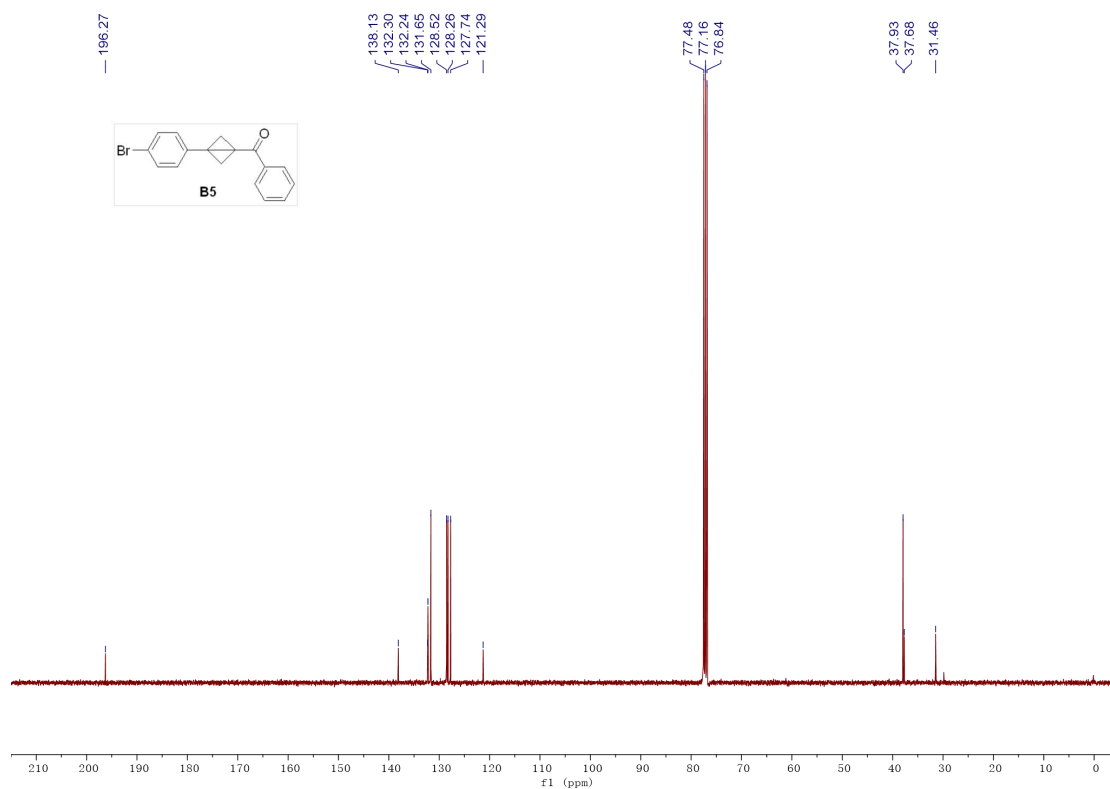
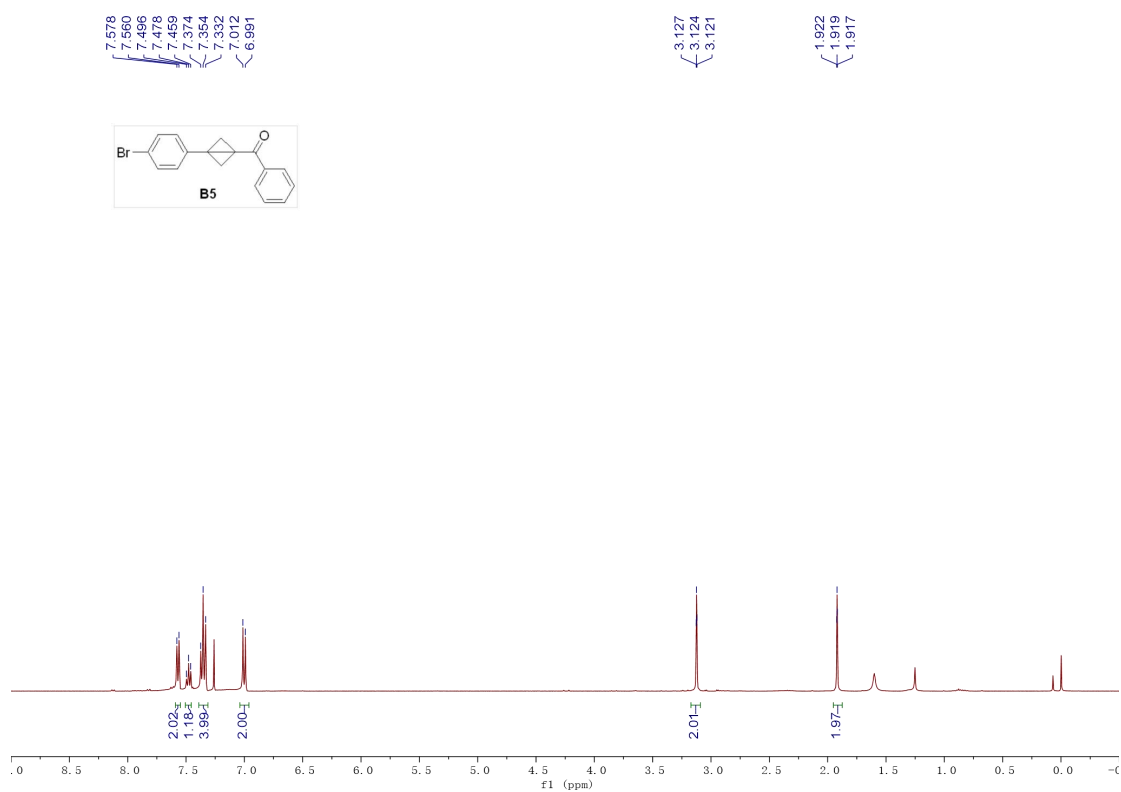
10. Copies of NMR spectra

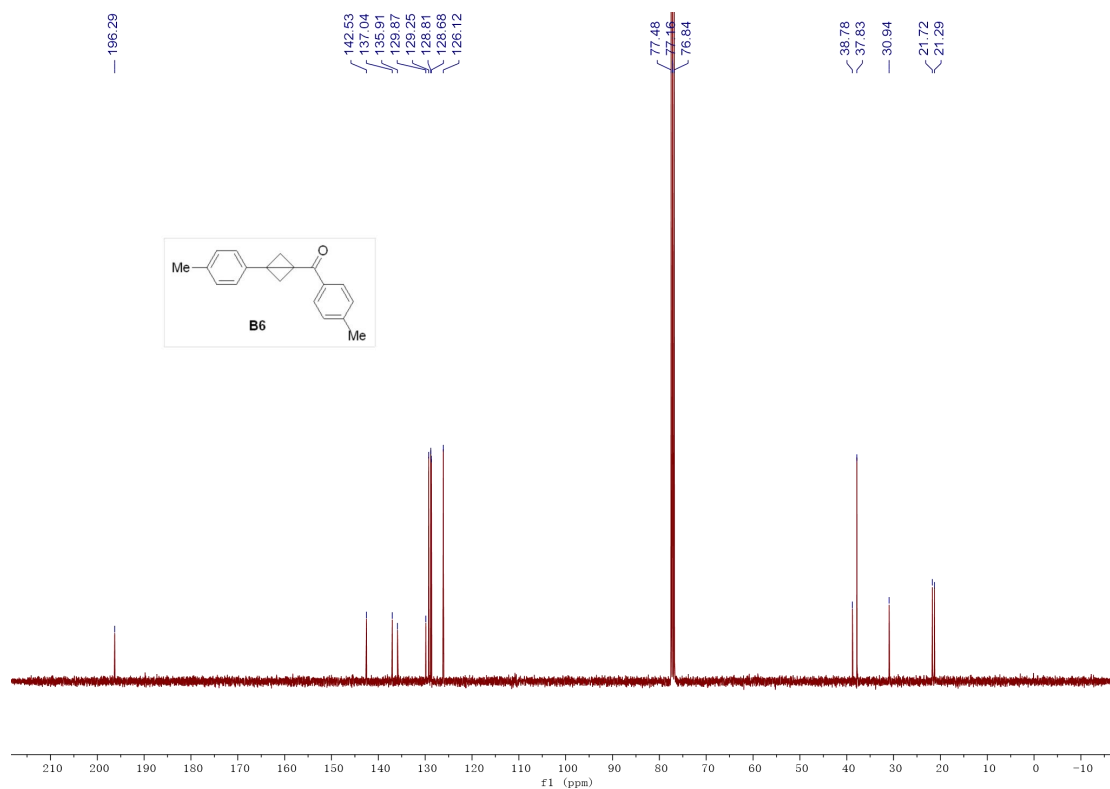
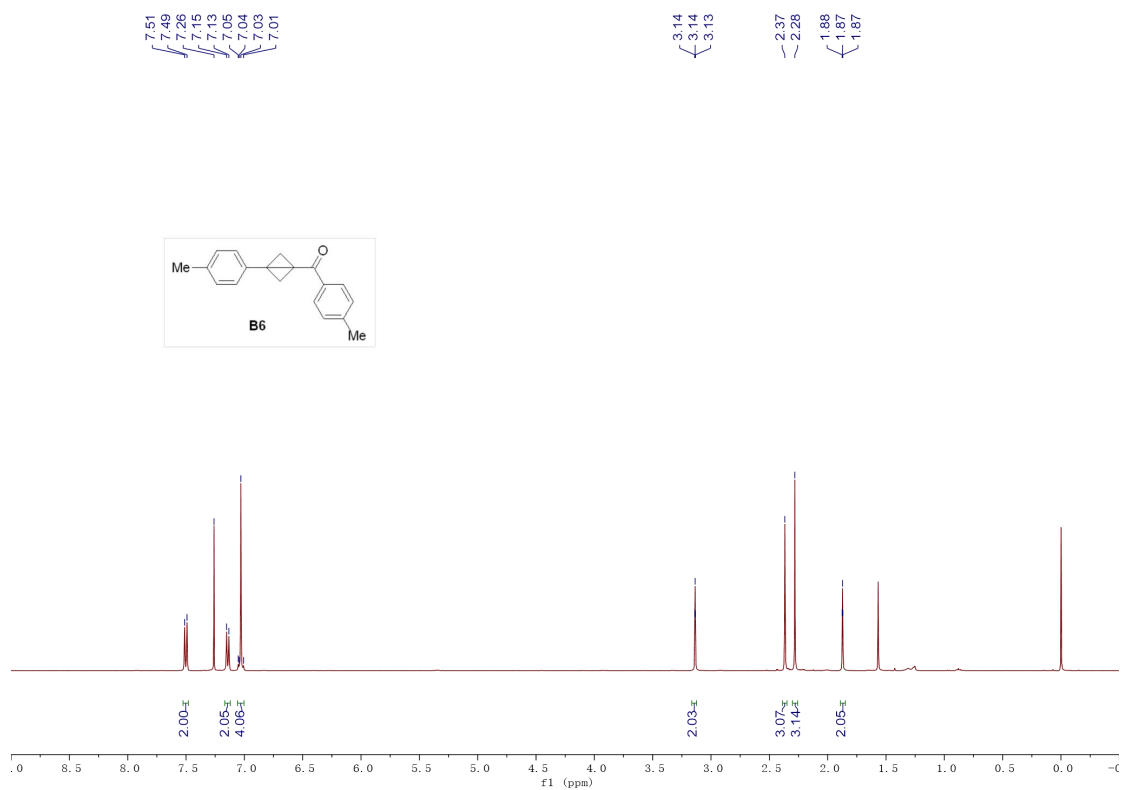


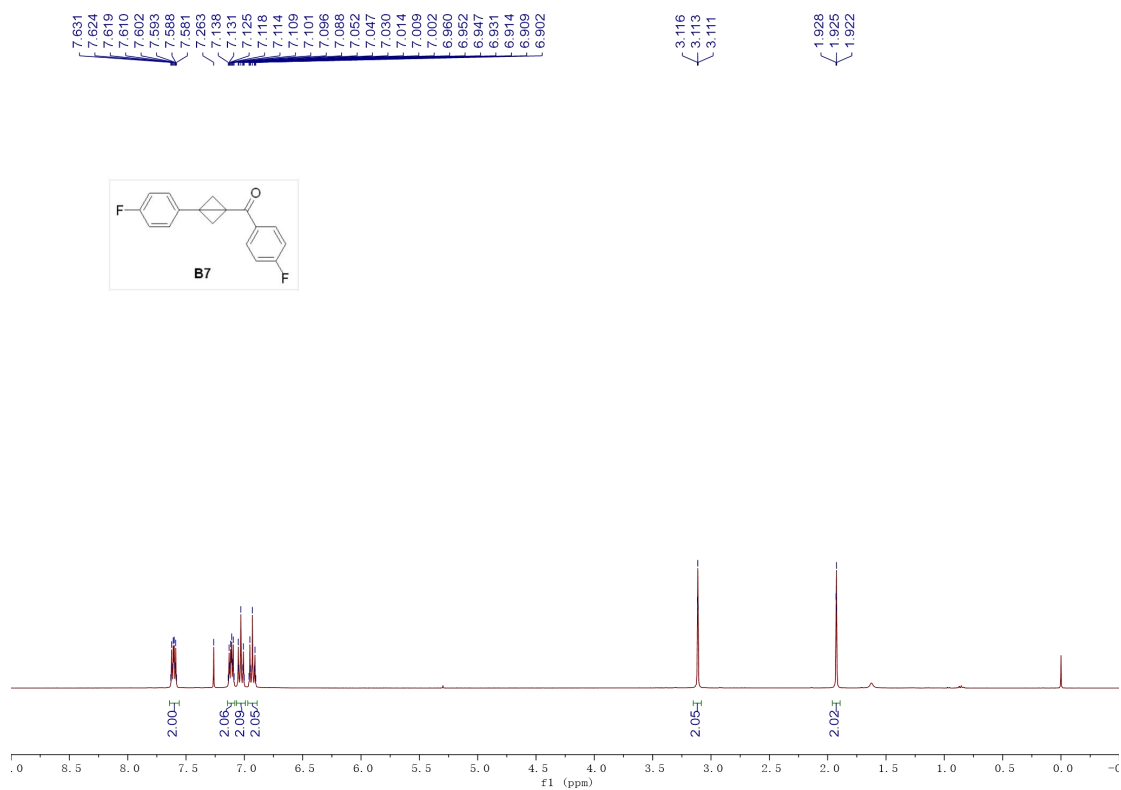
¹H NMR spectrum of B3



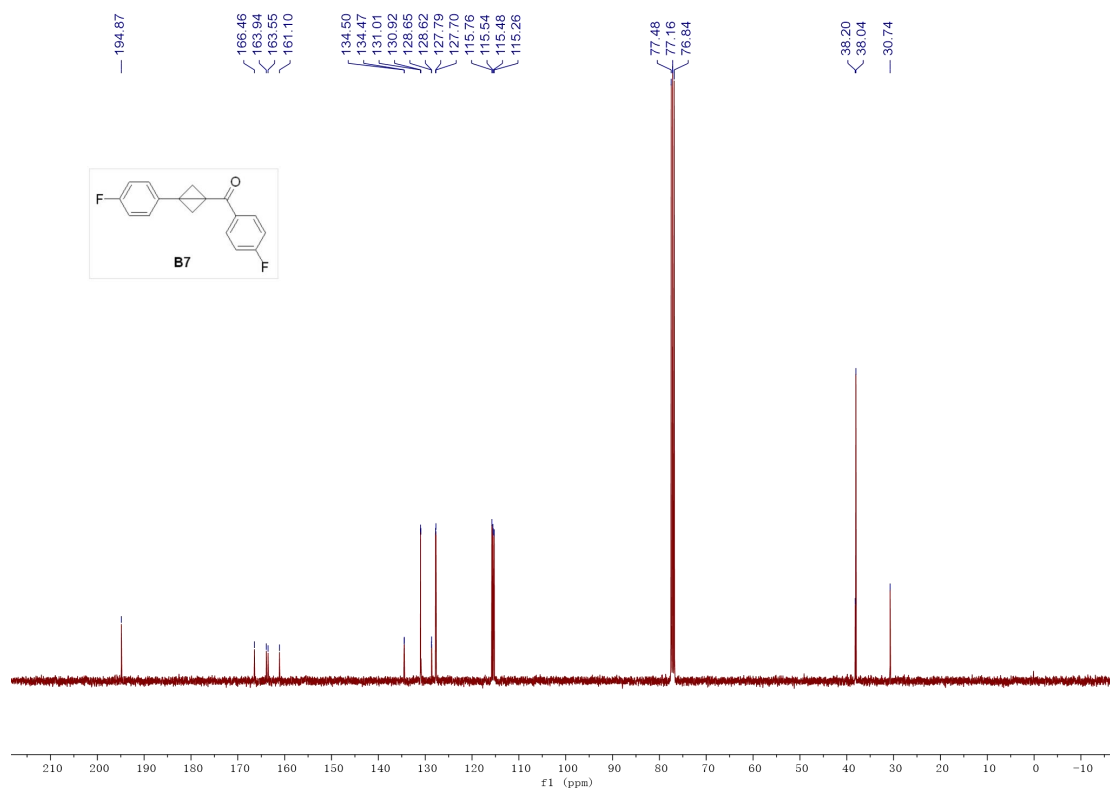
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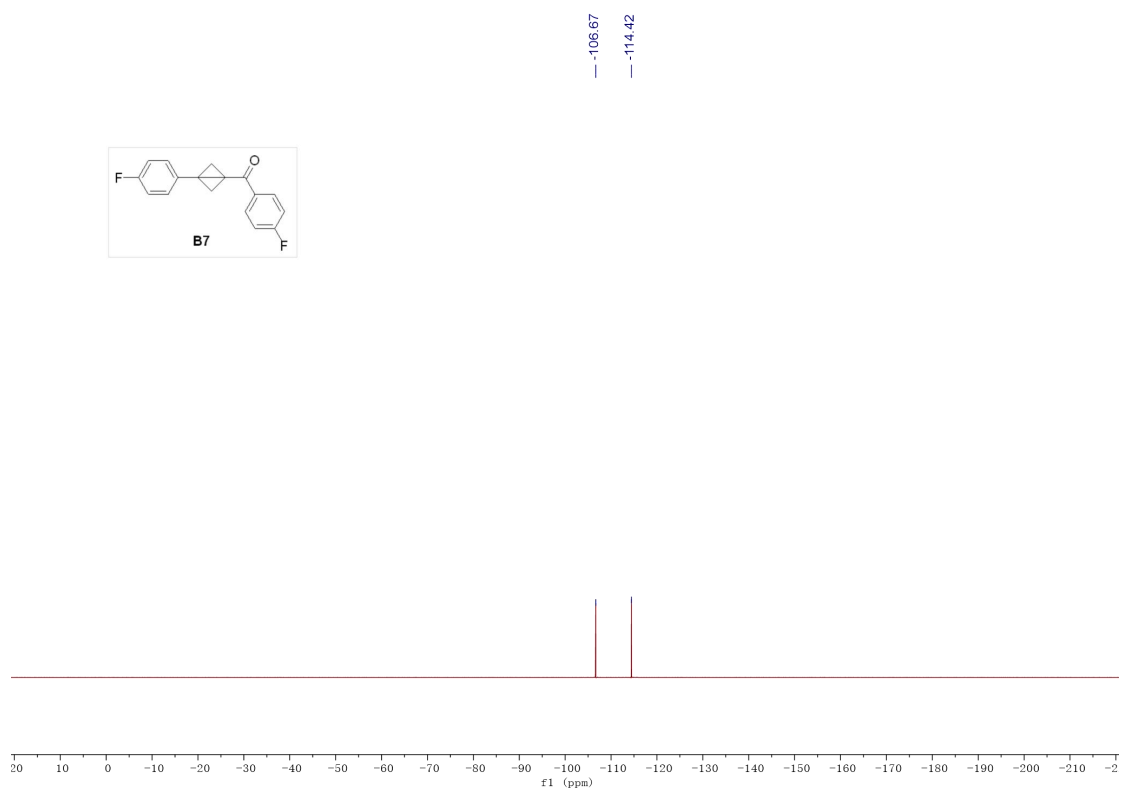




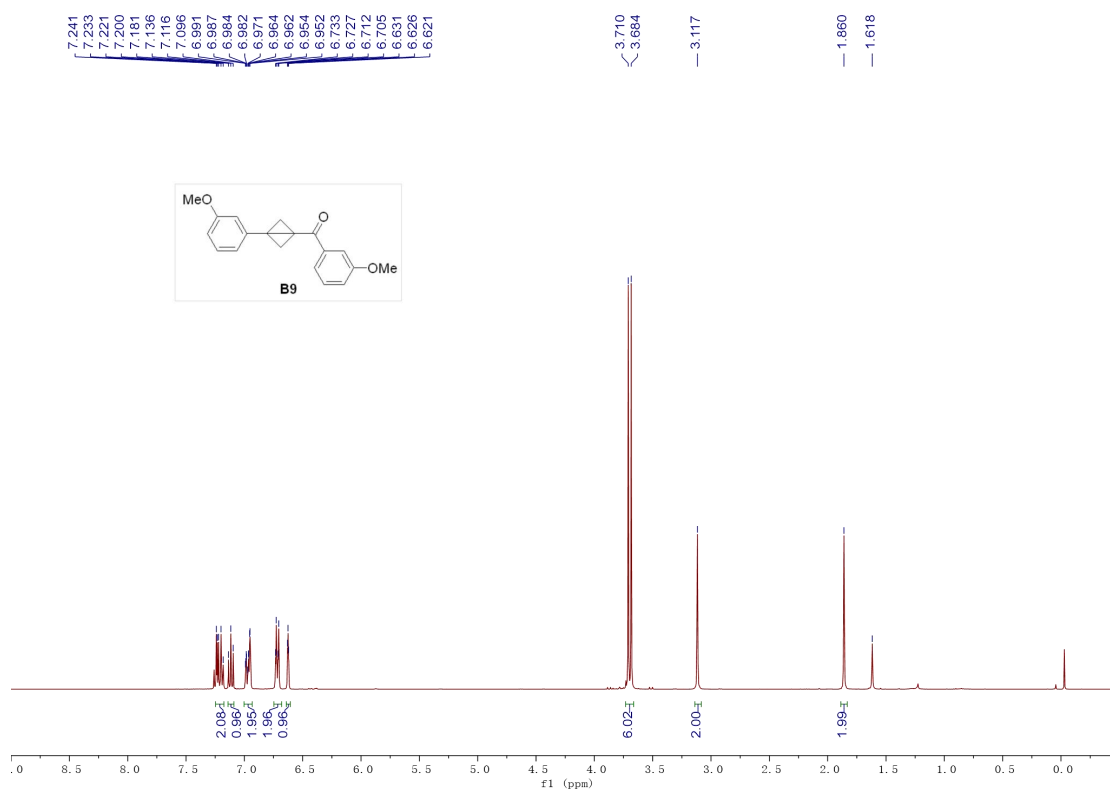
¹H NMR spectrum of B7



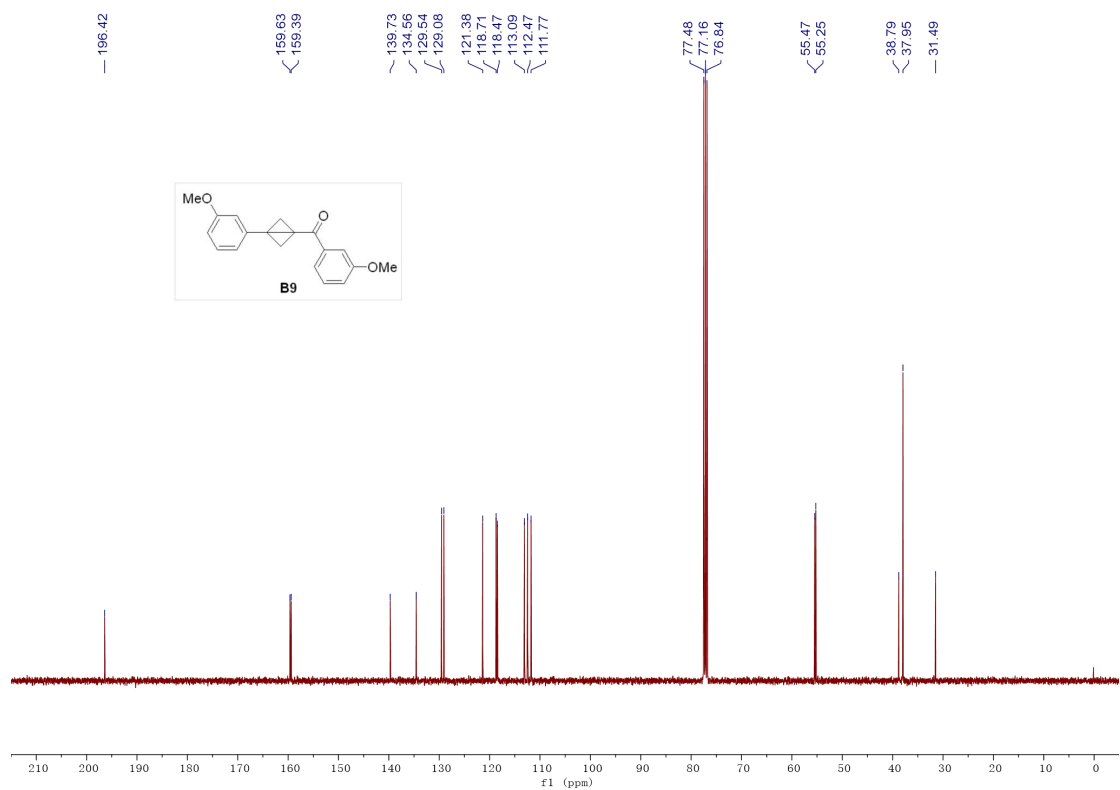
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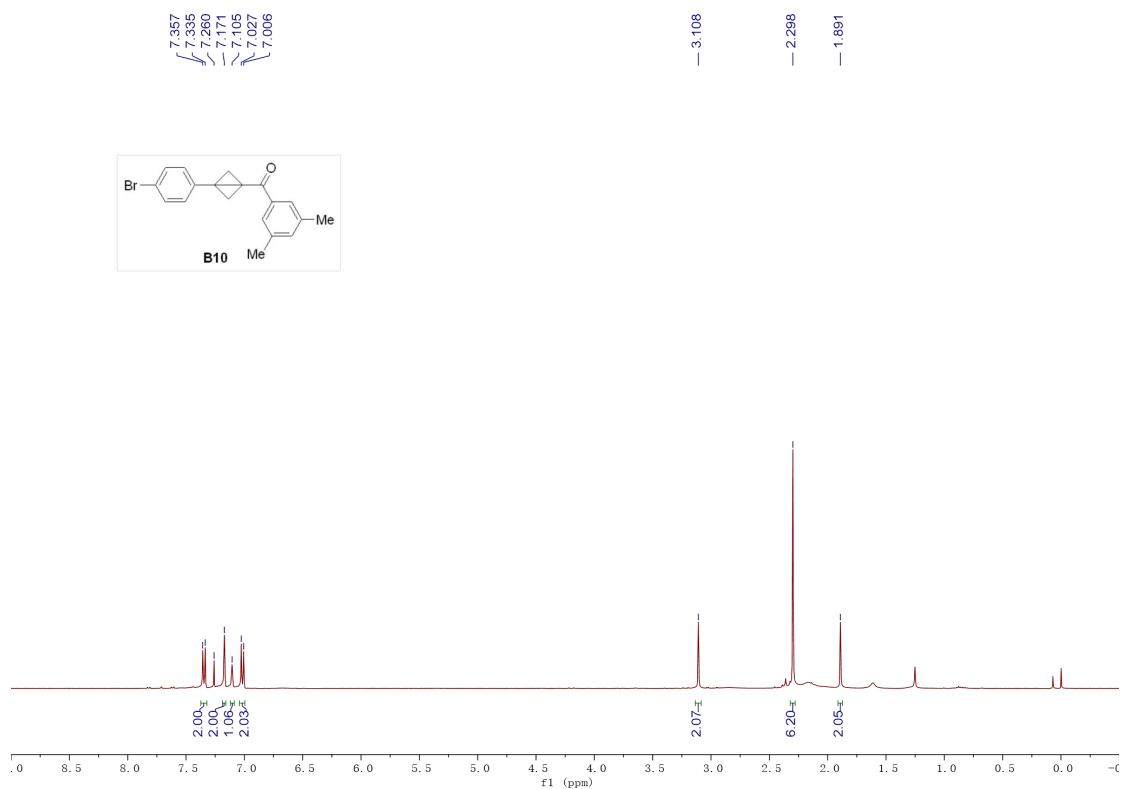
^{19}F NMR spectrum of **B7**



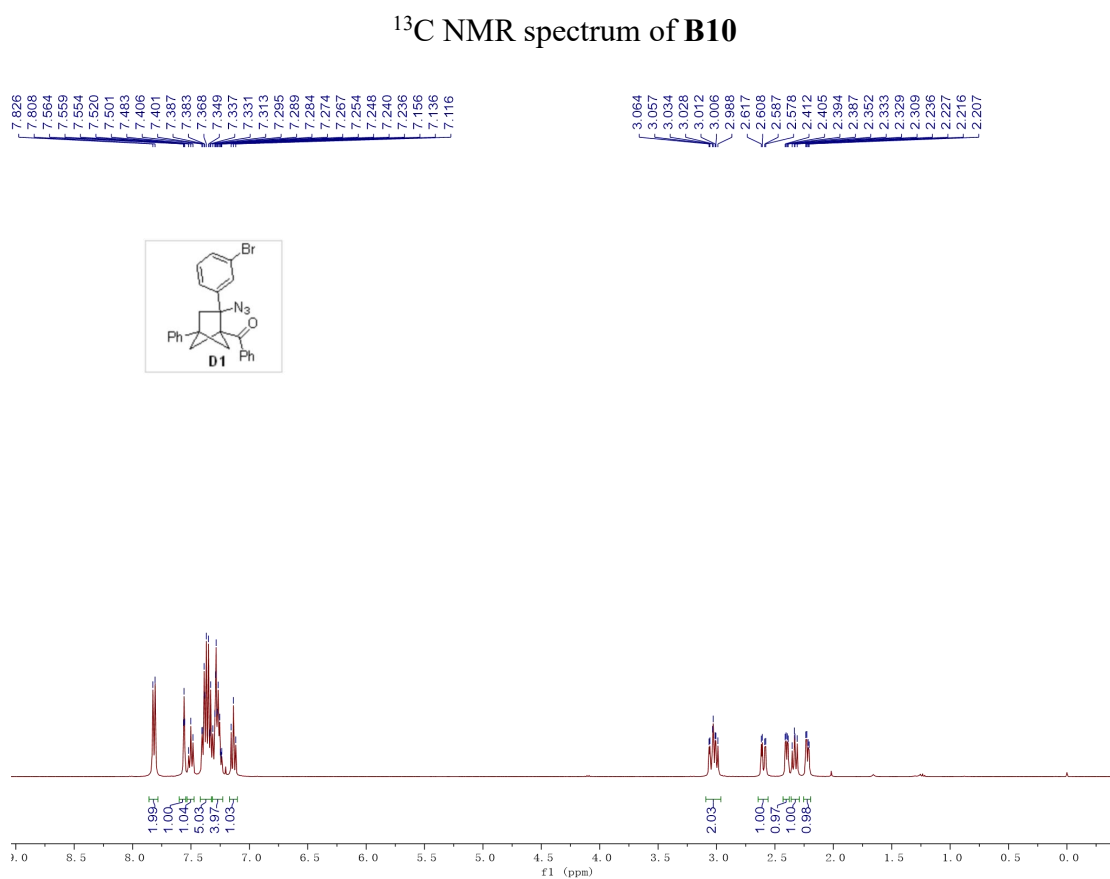
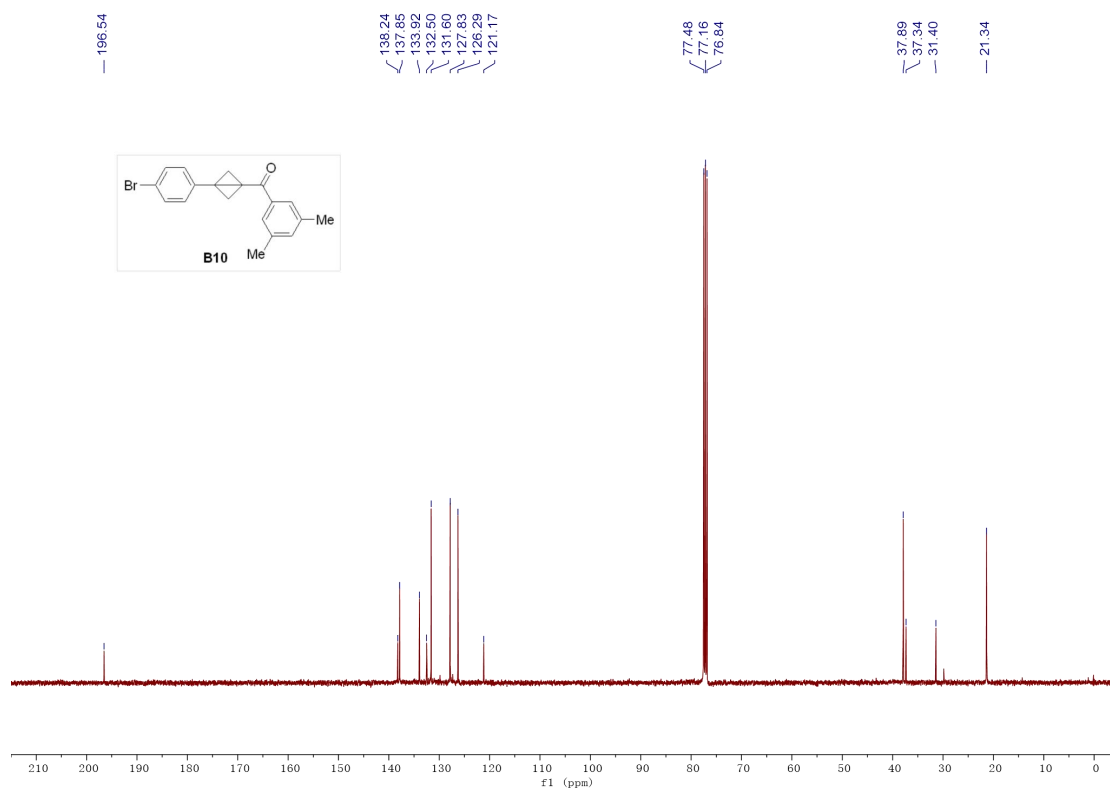
^1H NMR spectrum of **B9**

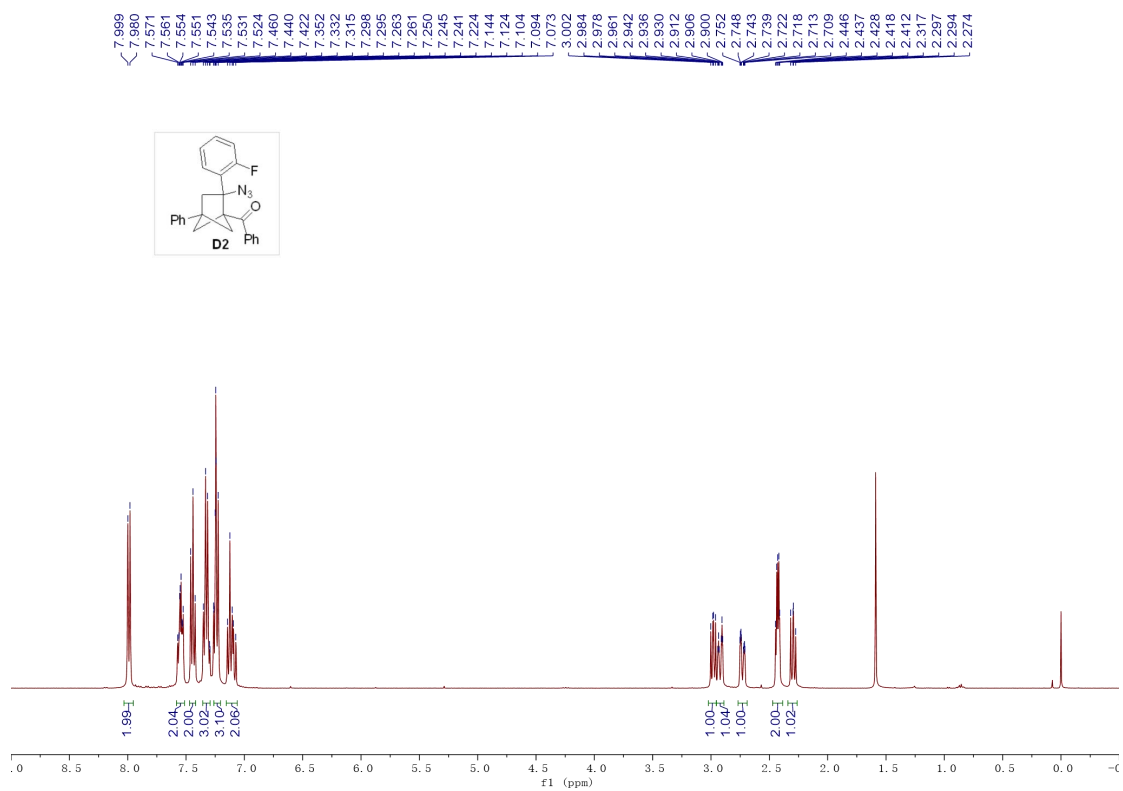
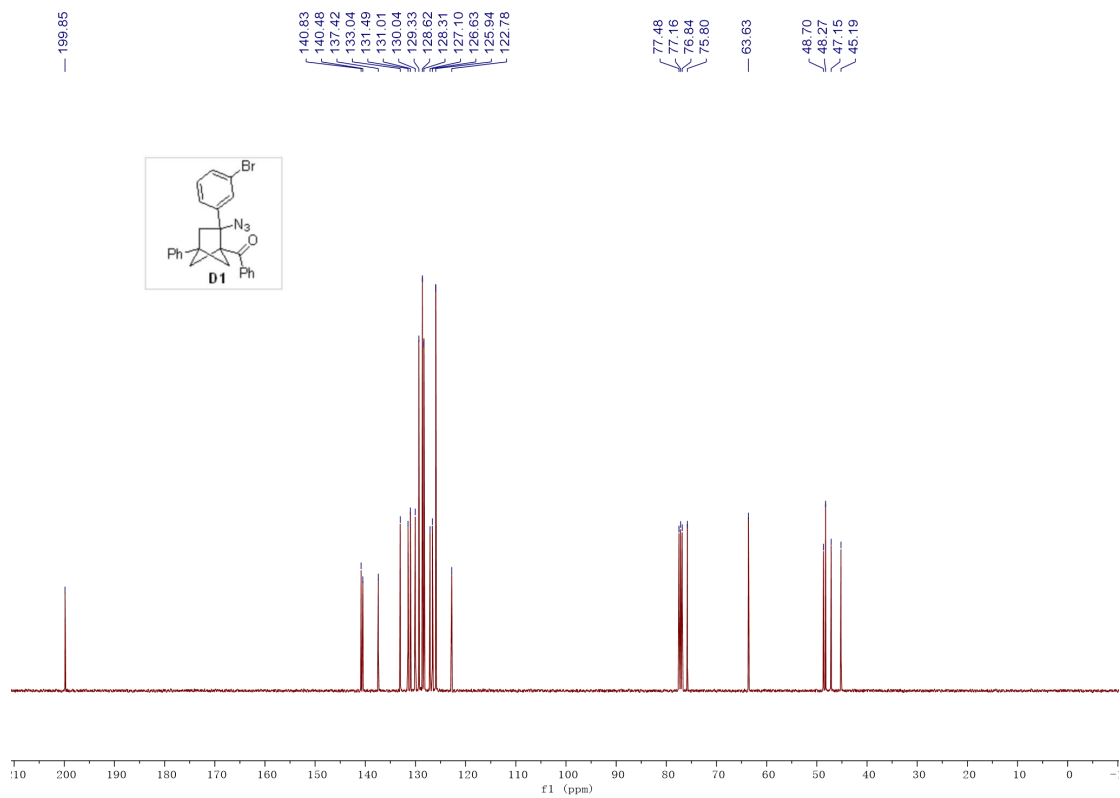


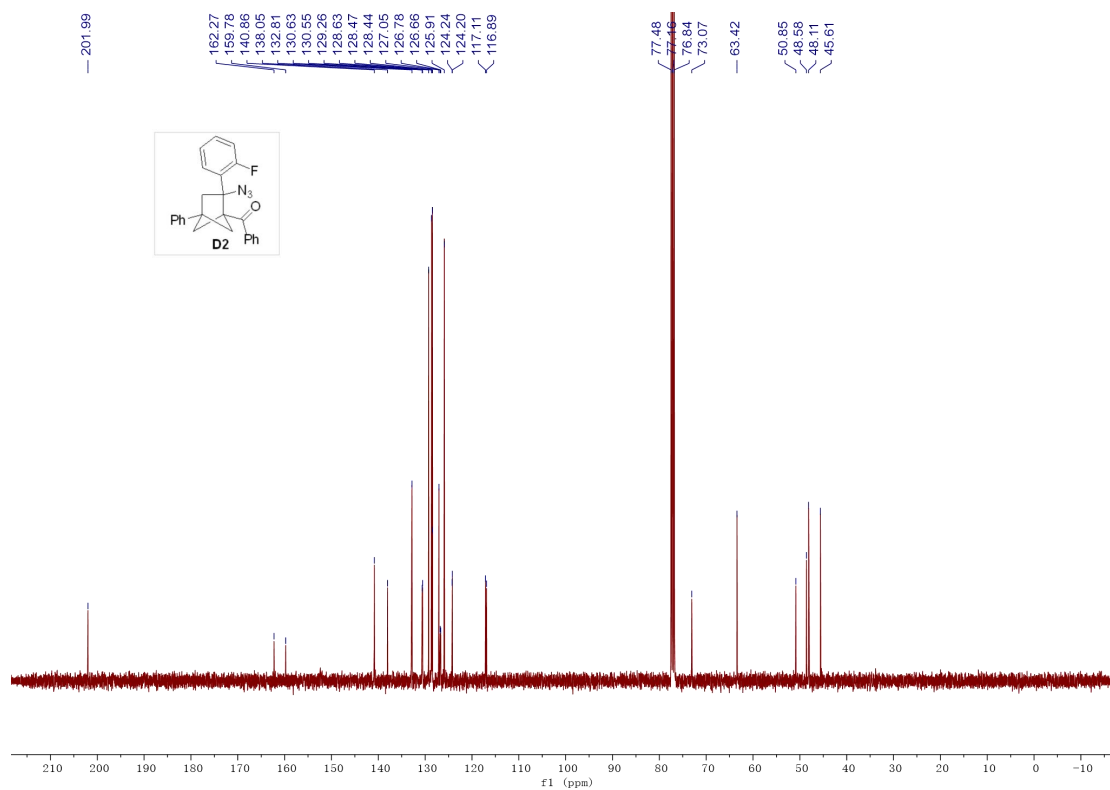
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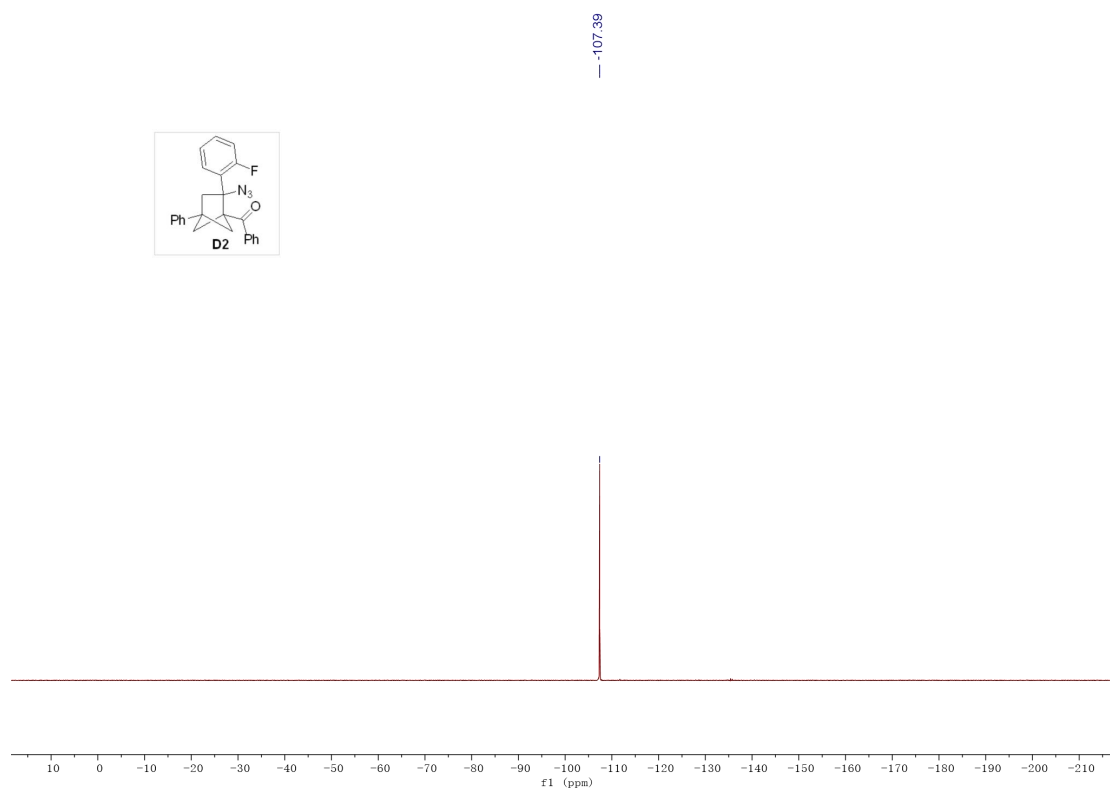
¹H NMR spectrum of B10



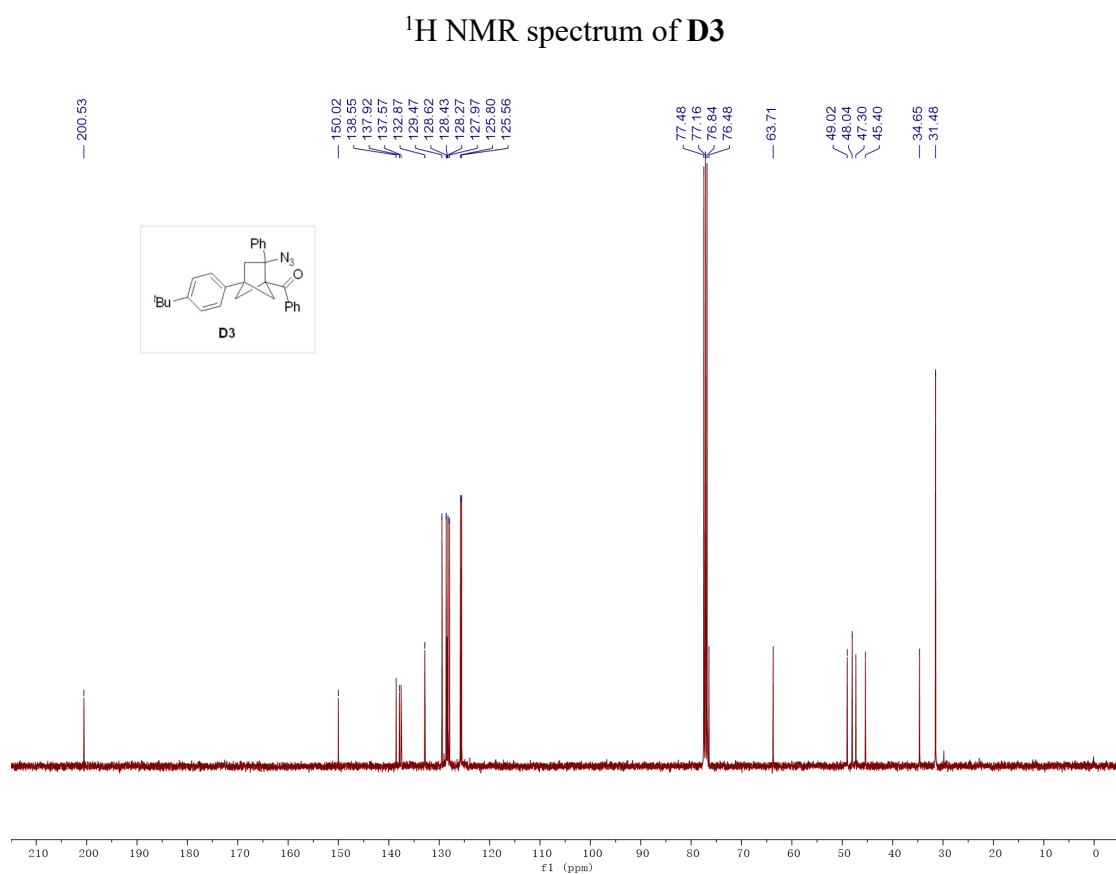
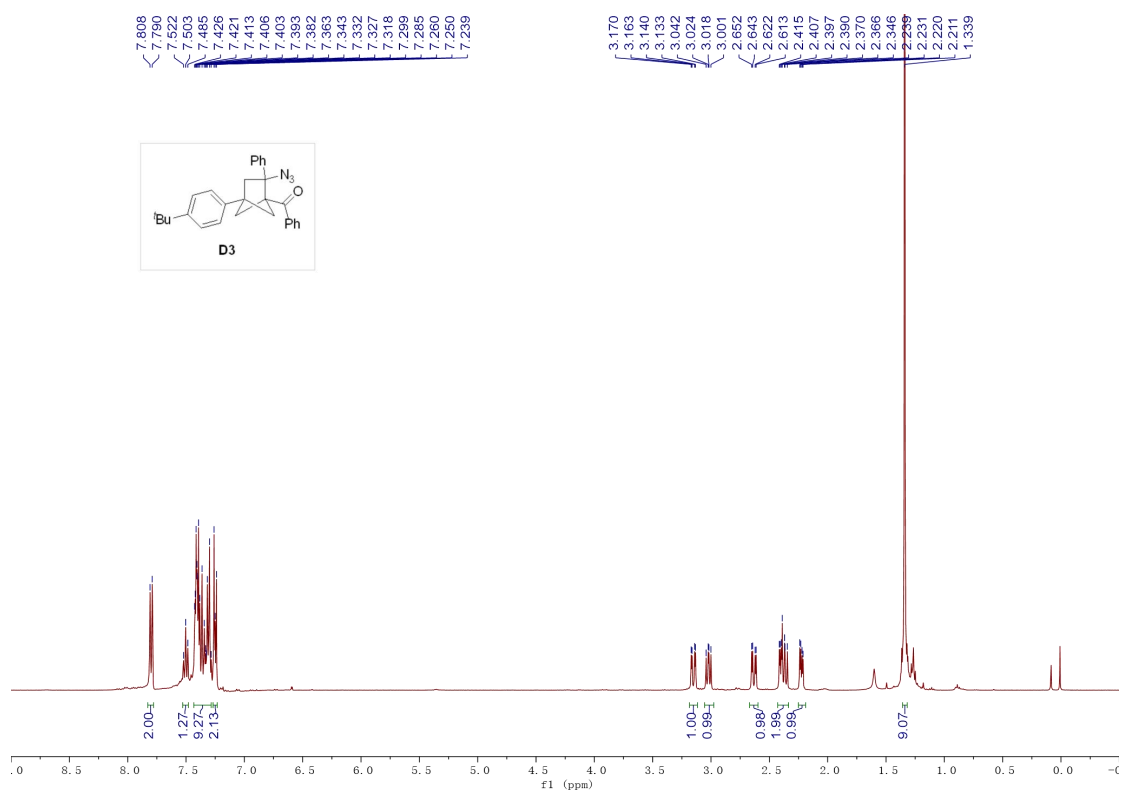


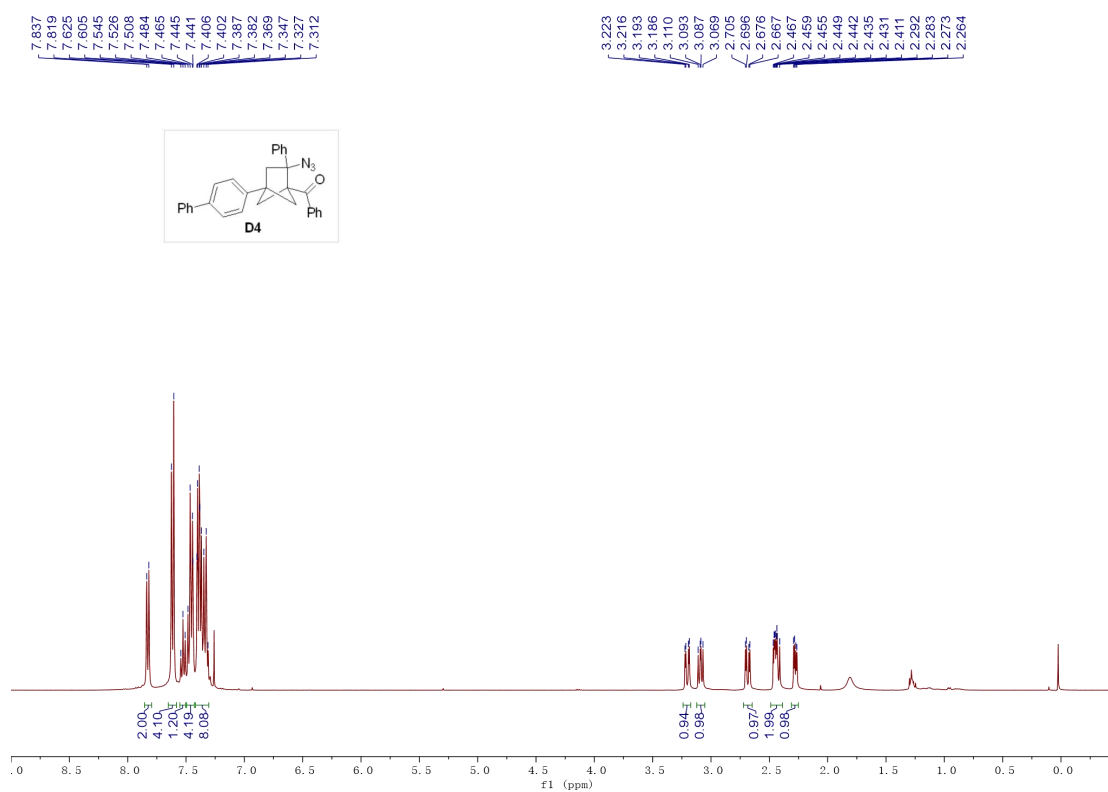


¹³C NMR spectrum of **D2**

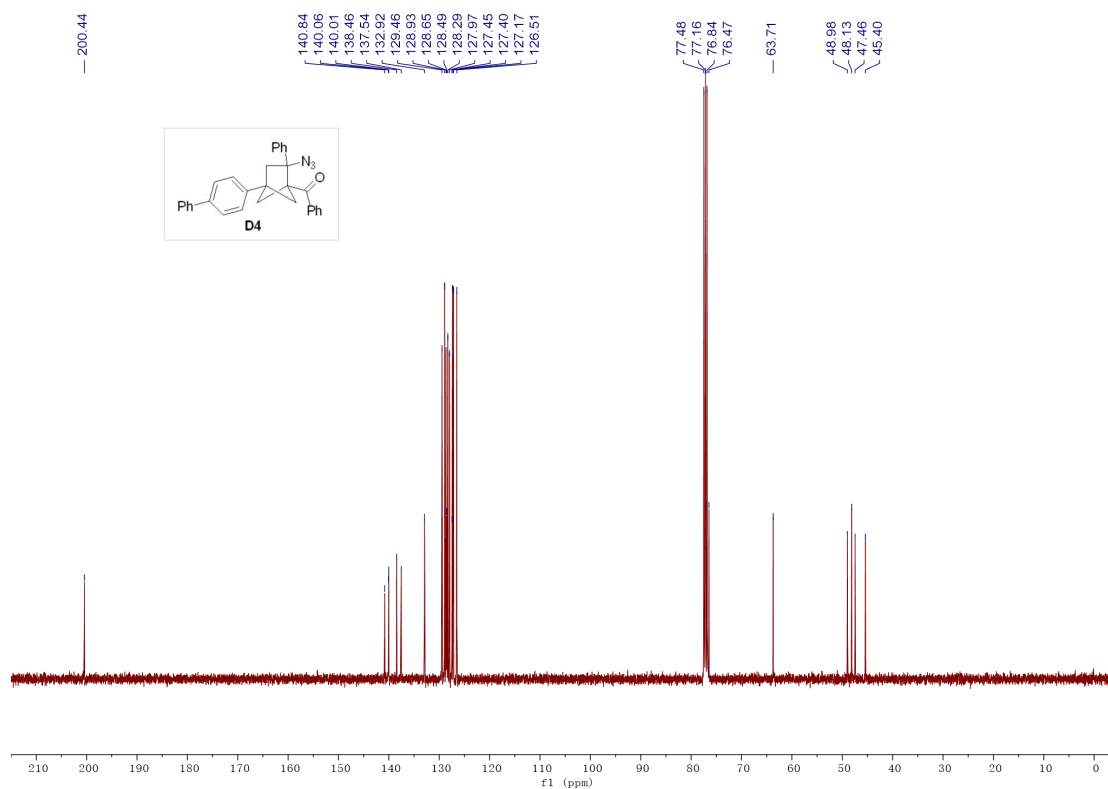


¹⁹F NMR spectrum of **D2**

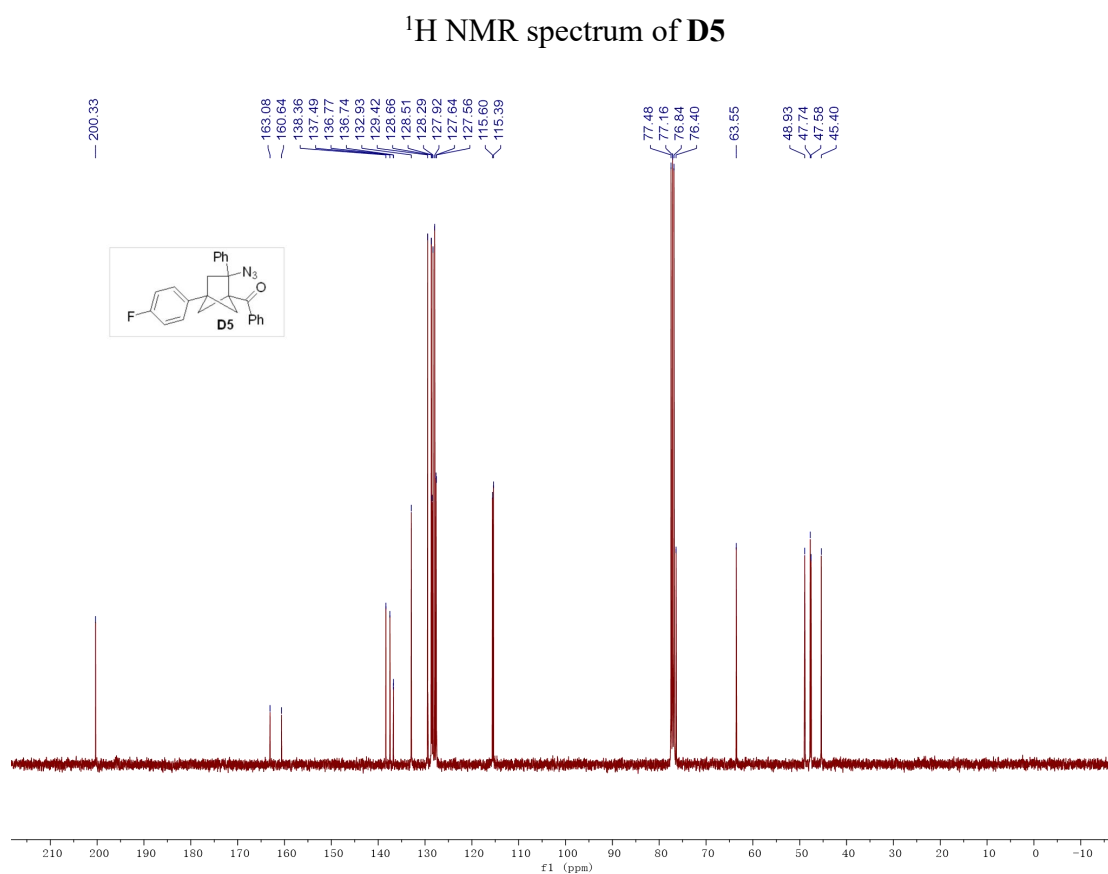
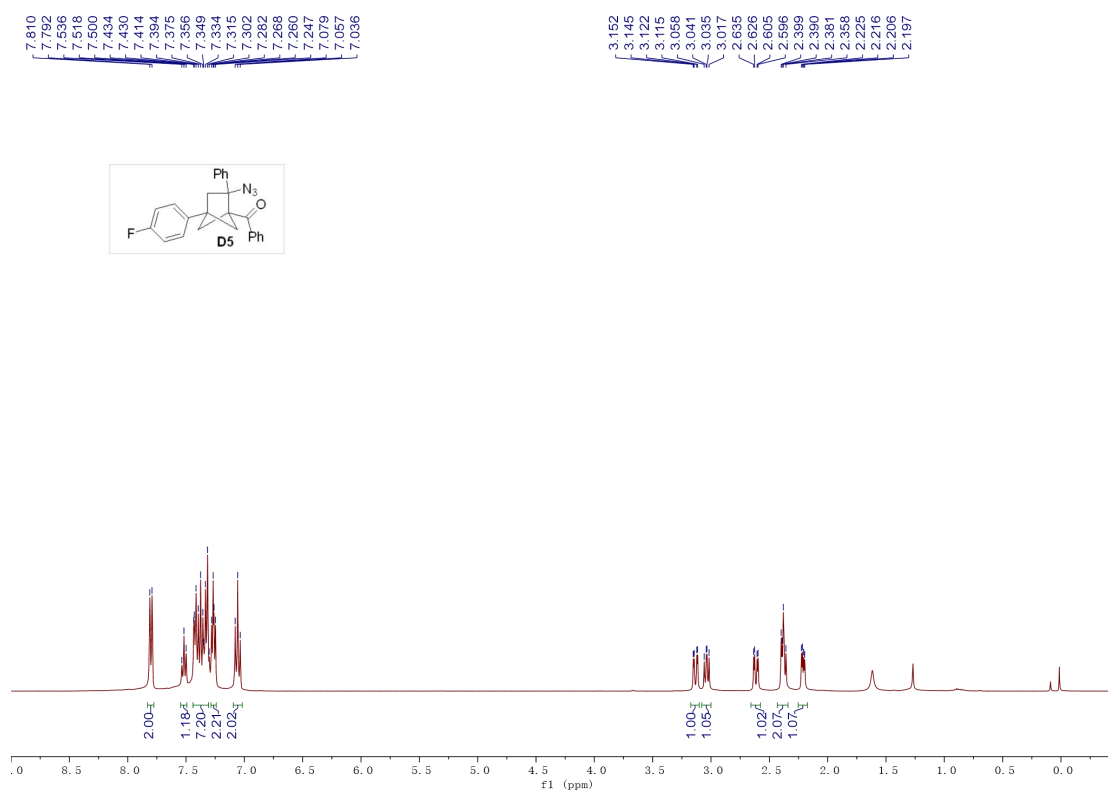


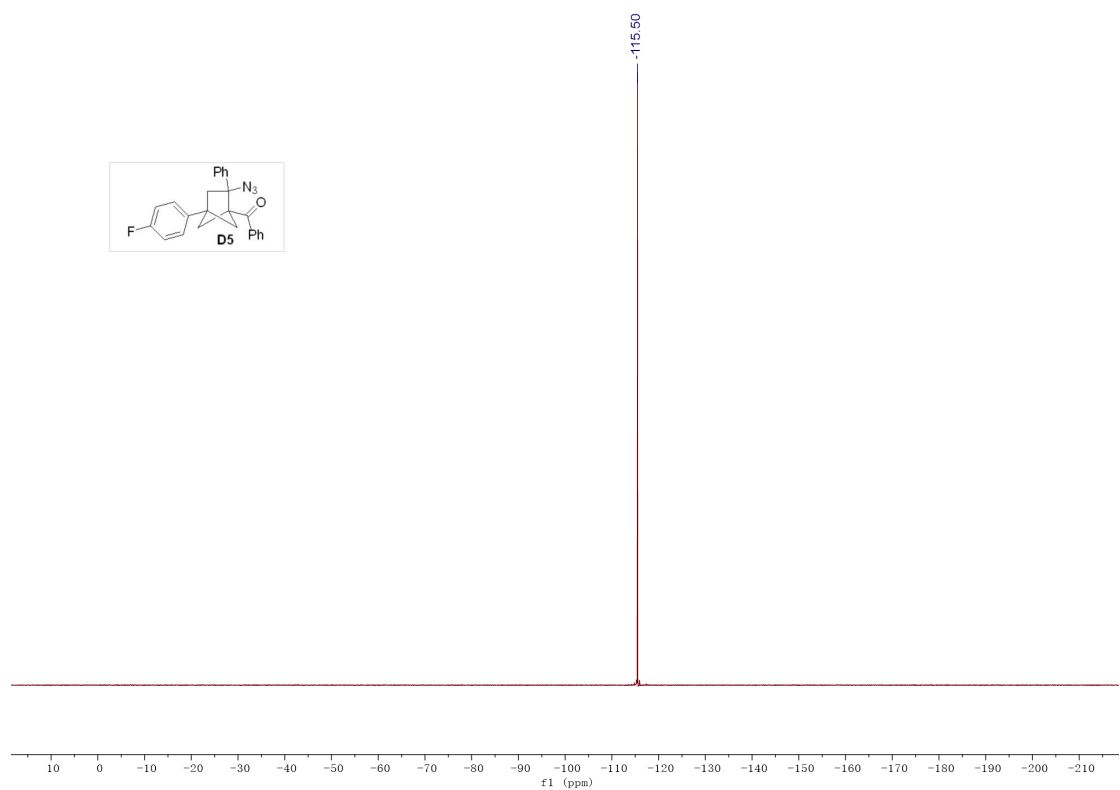


¹H NMR spectrum of D4

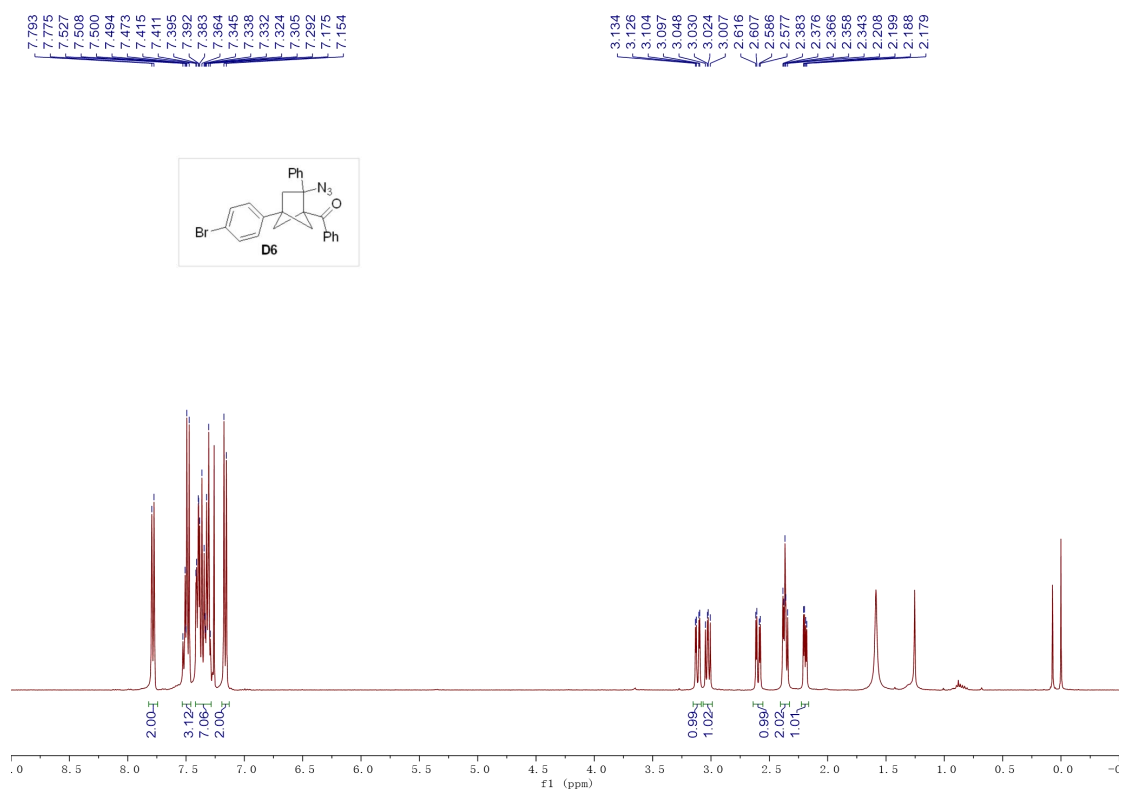


¹³C NMR spectrum of D4

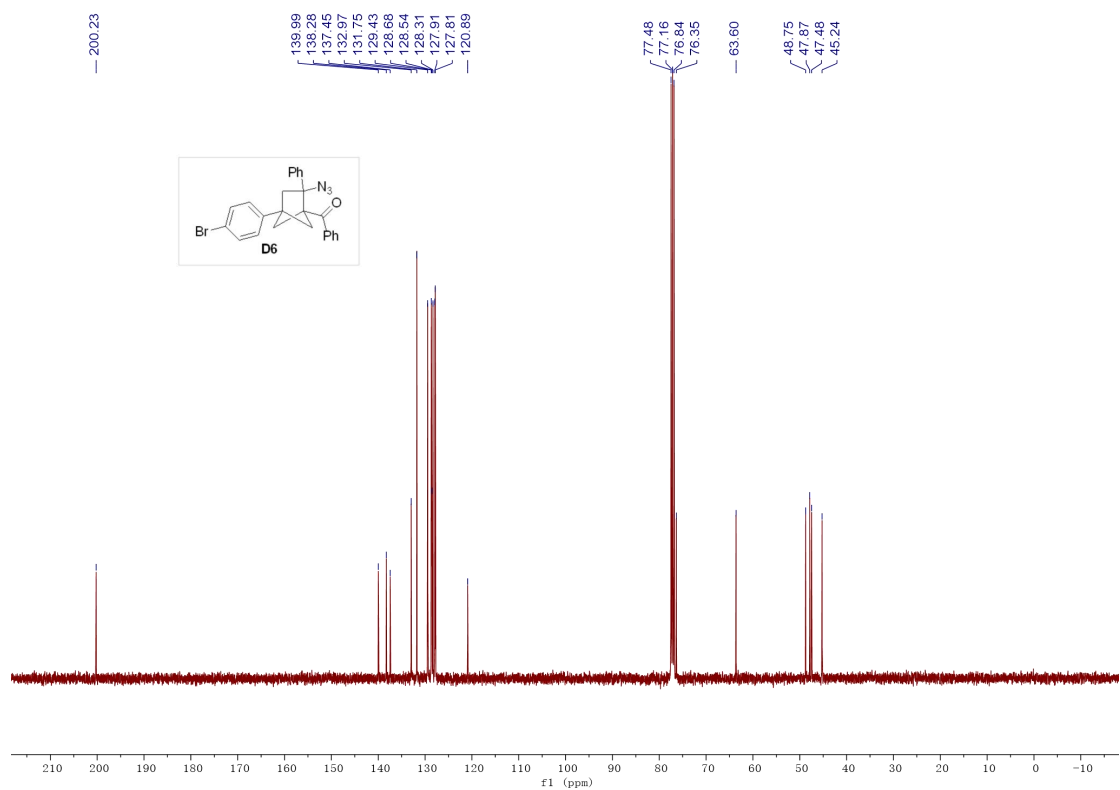




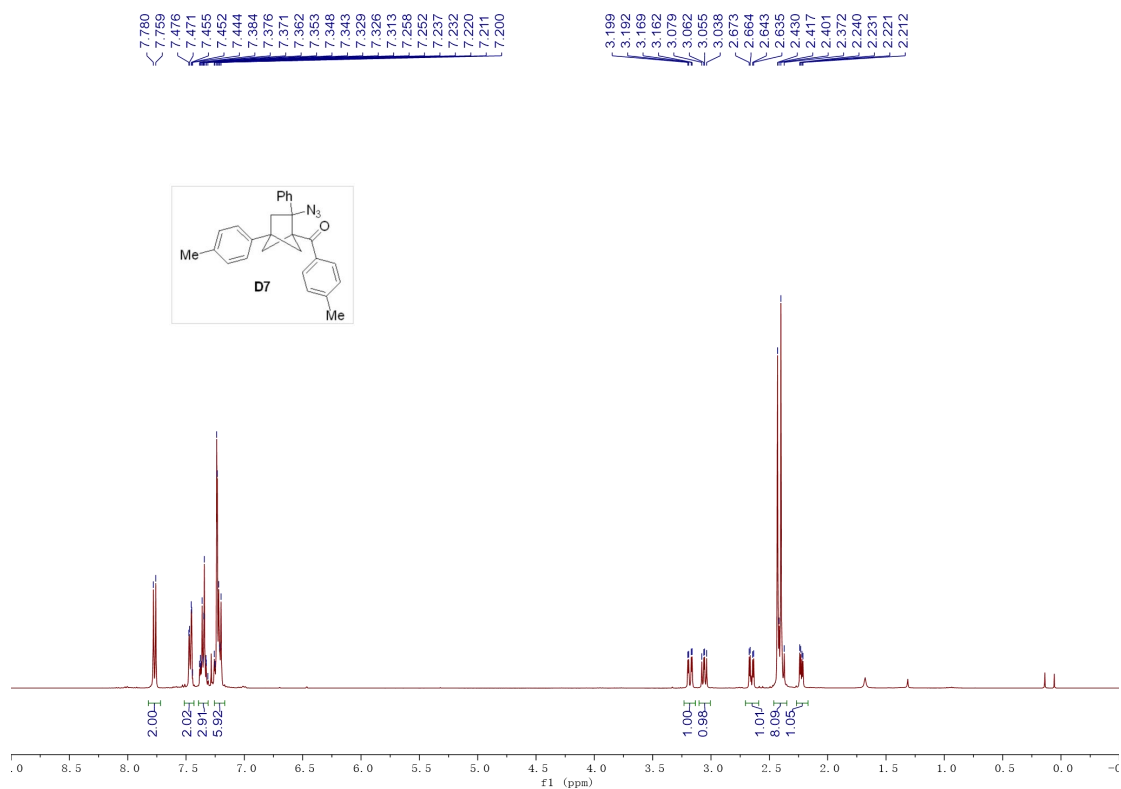
^{19}F NMR spectrum of **D5**



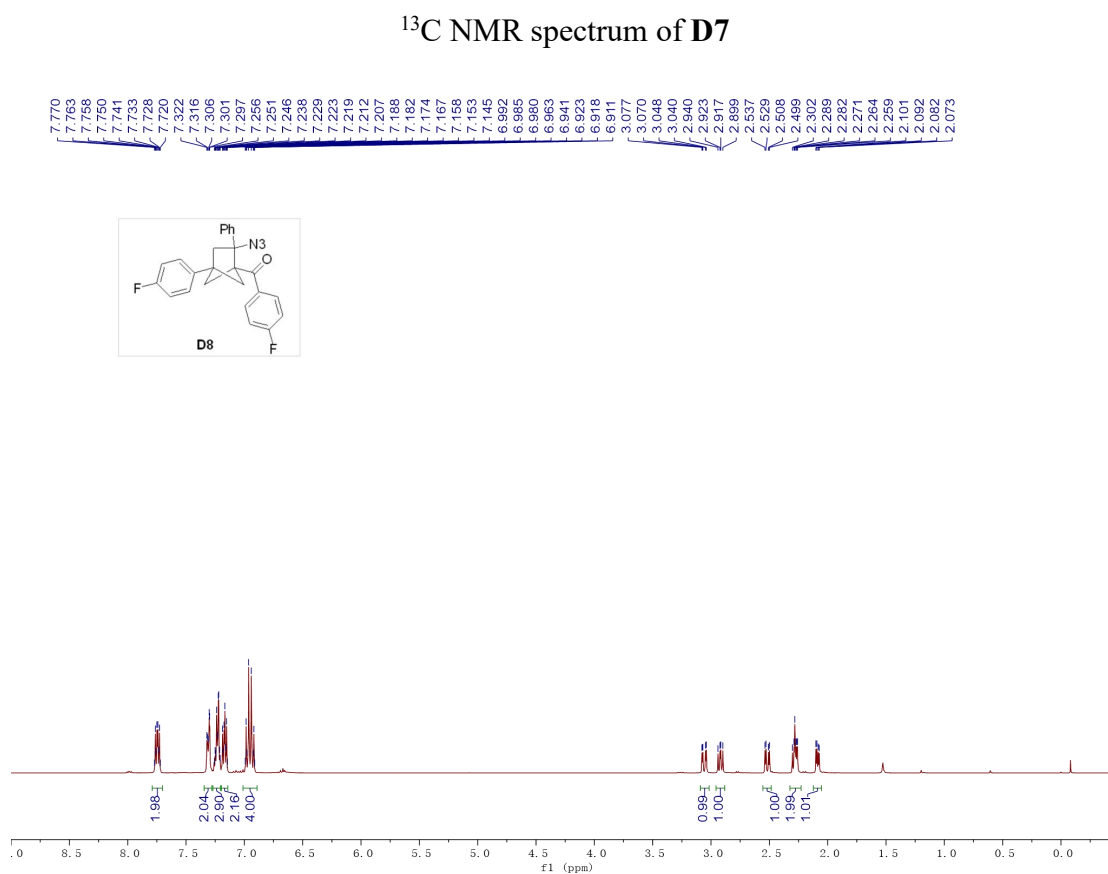
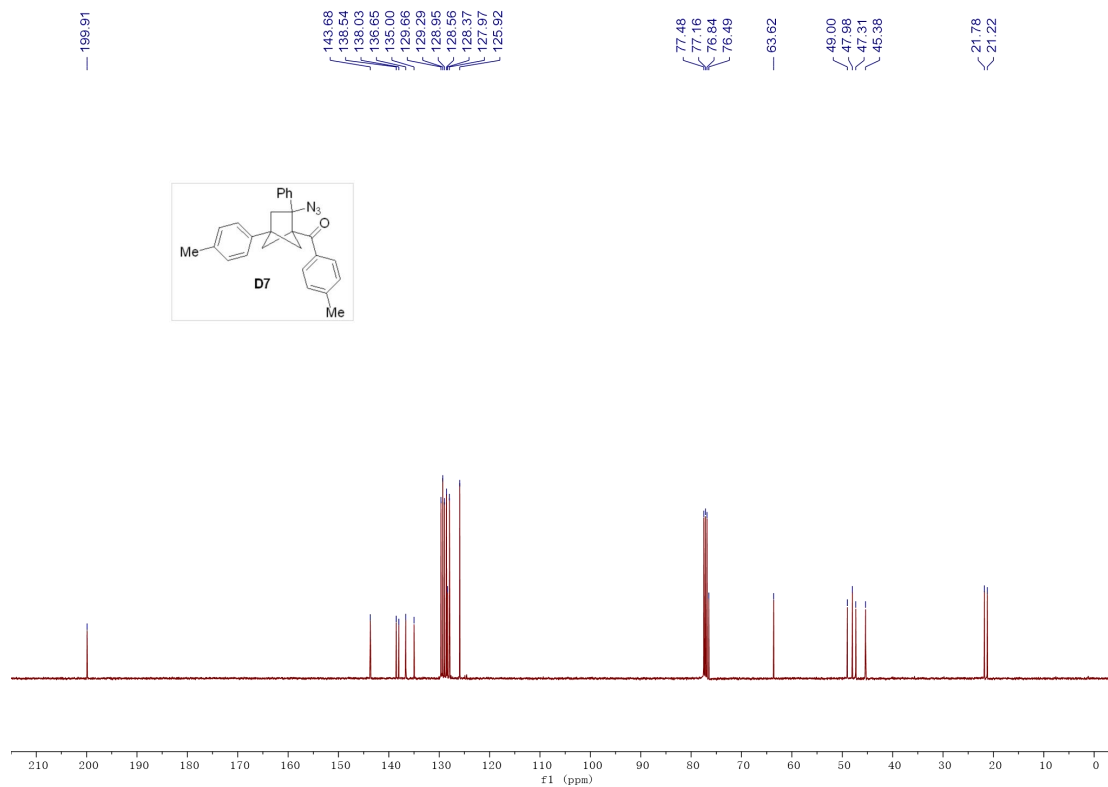
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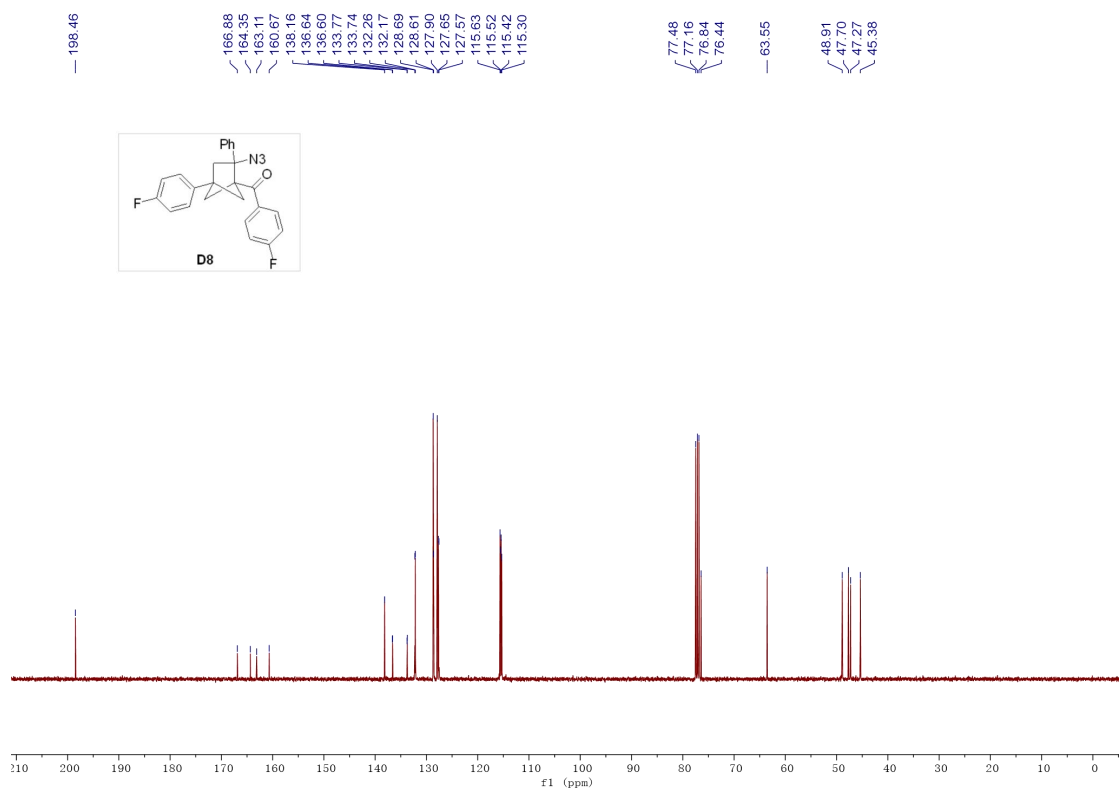


¹³C NMR spectrum of D6

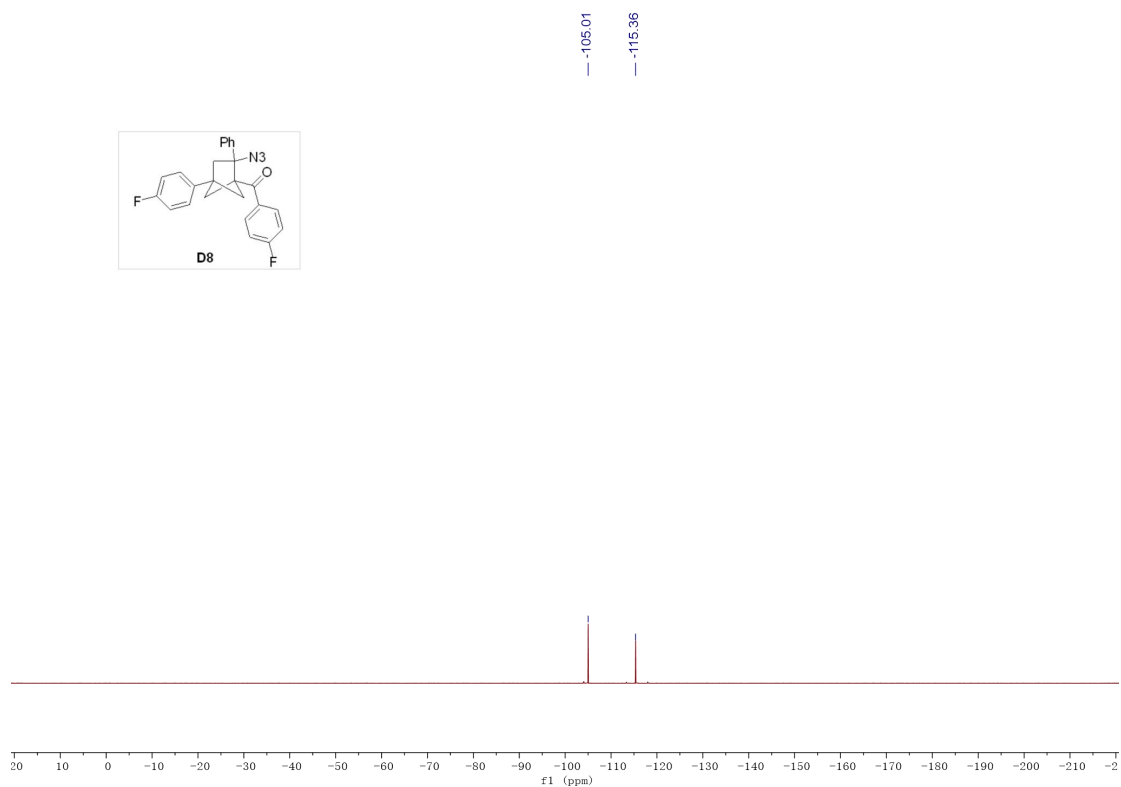


¹H NMR spectrum of D7

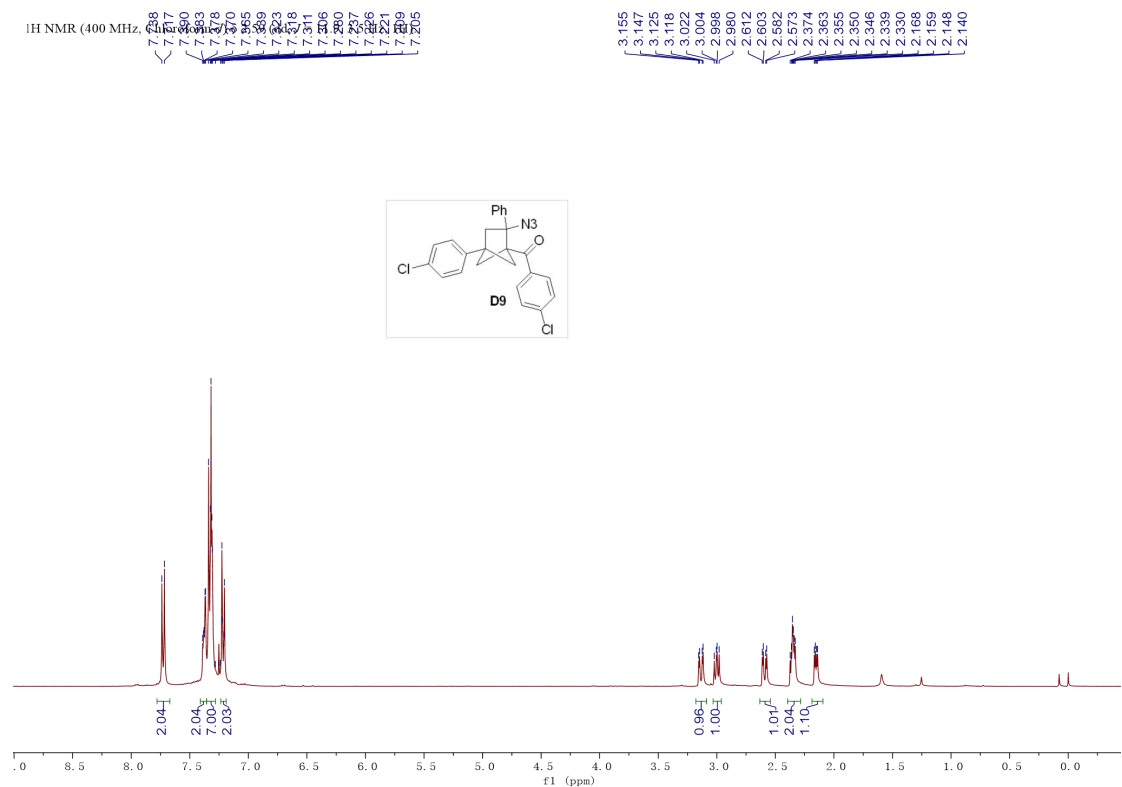




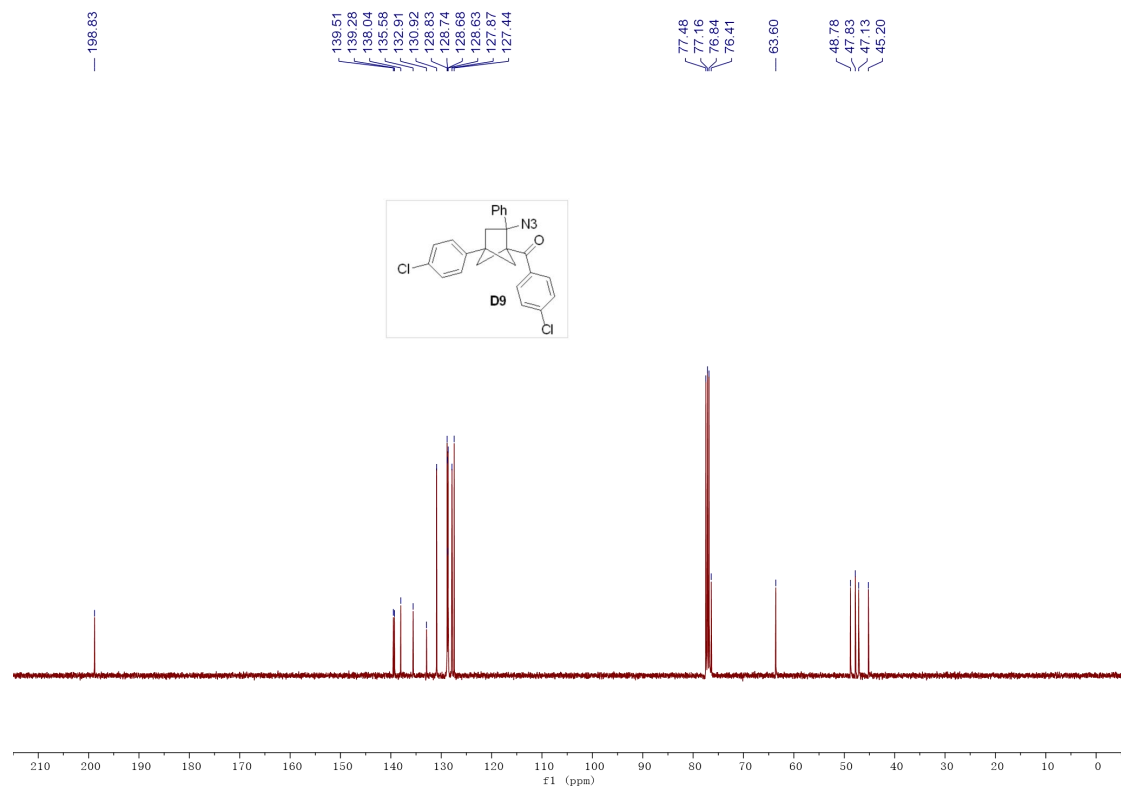
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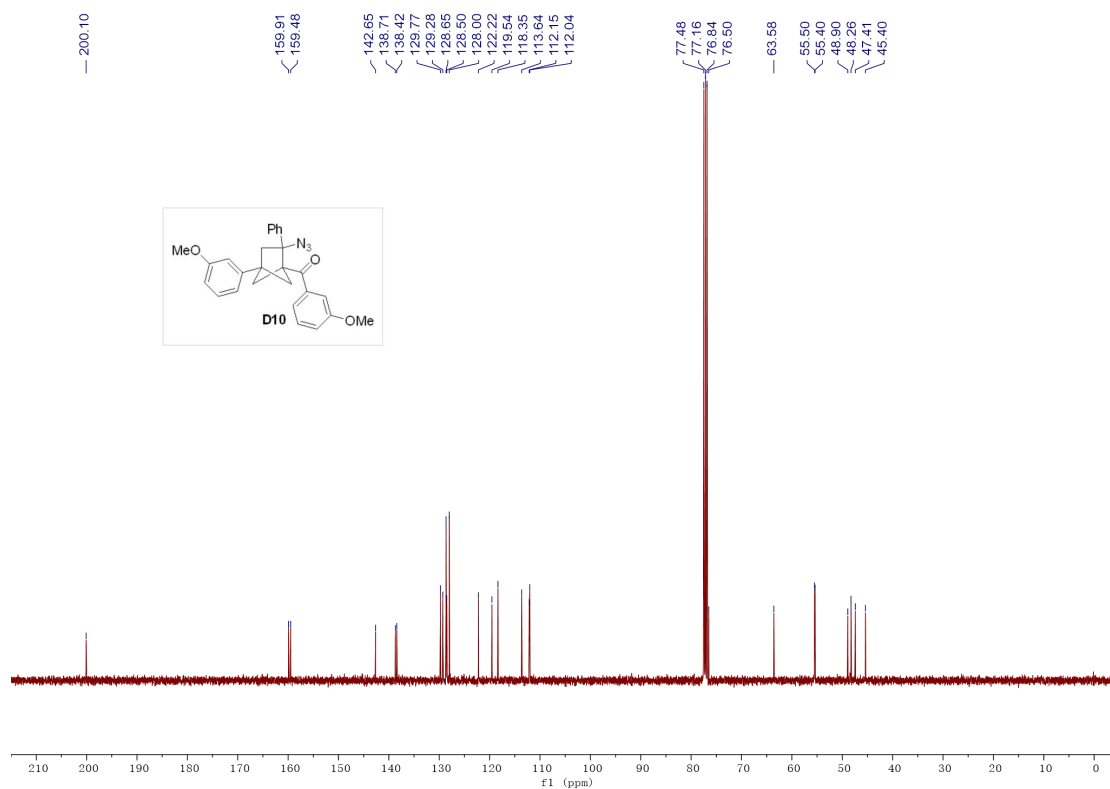
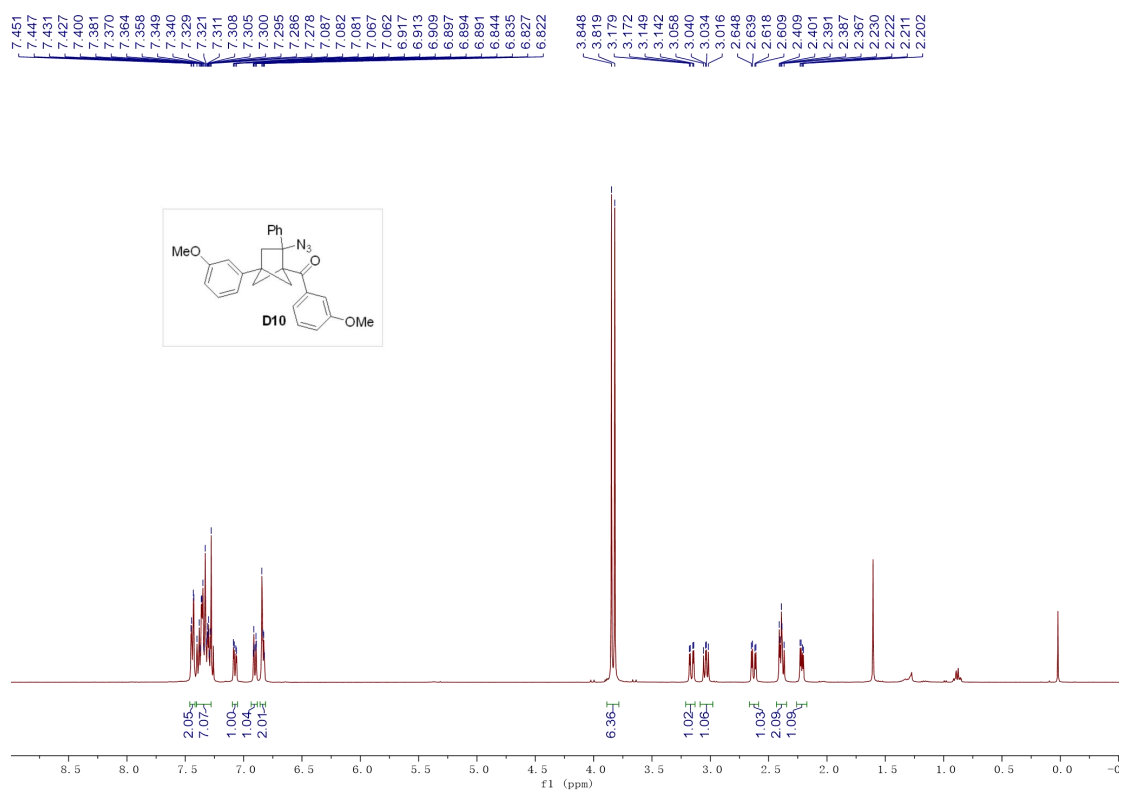
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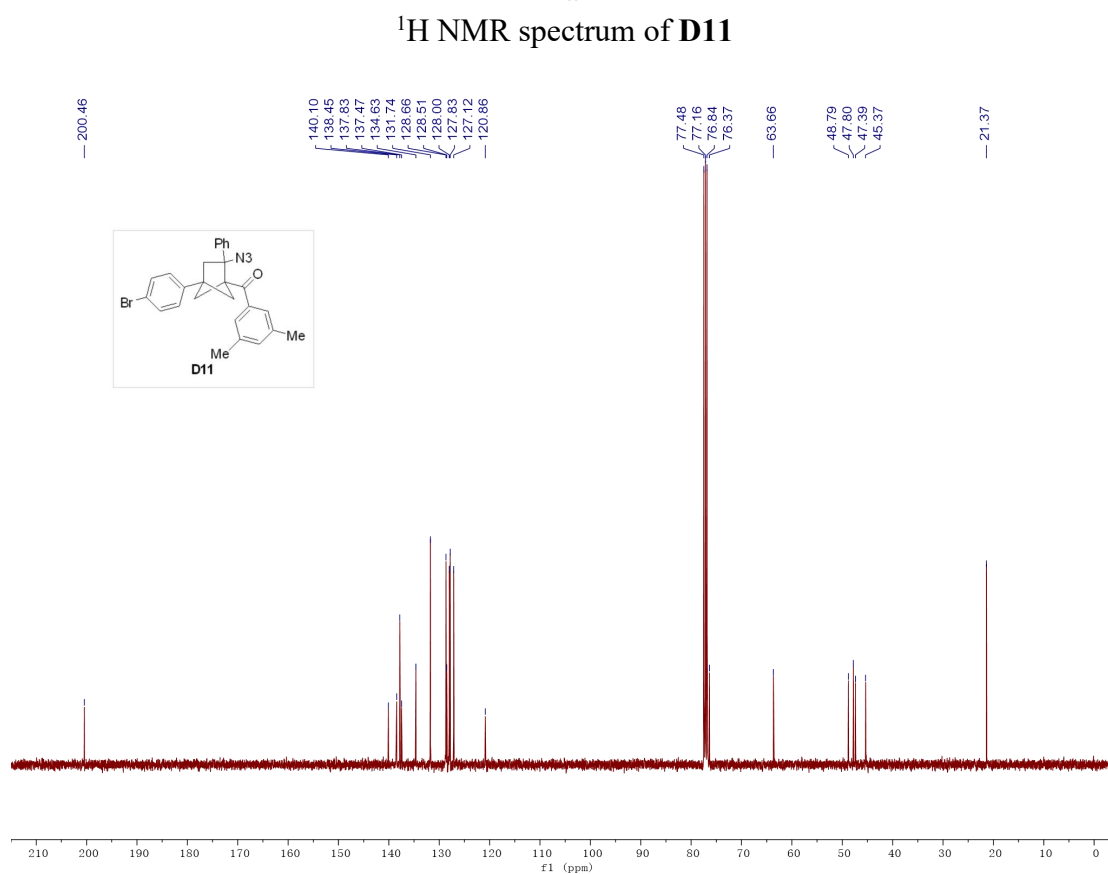
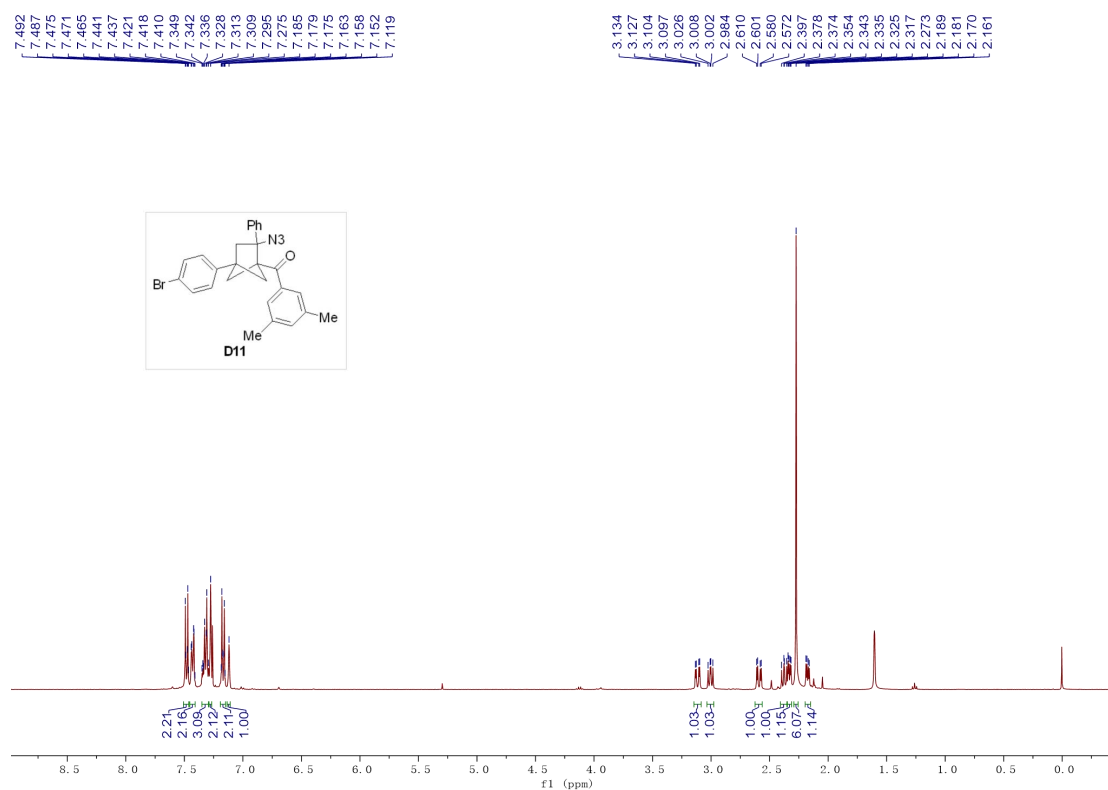


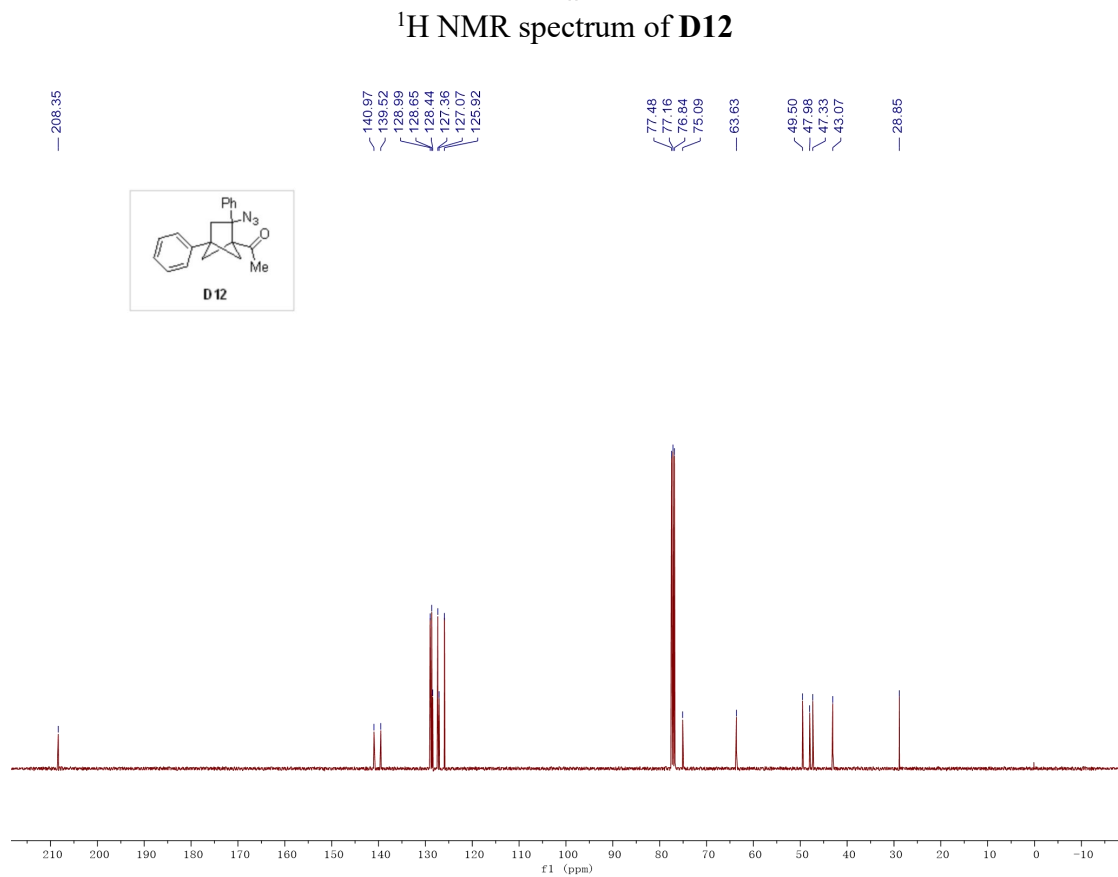
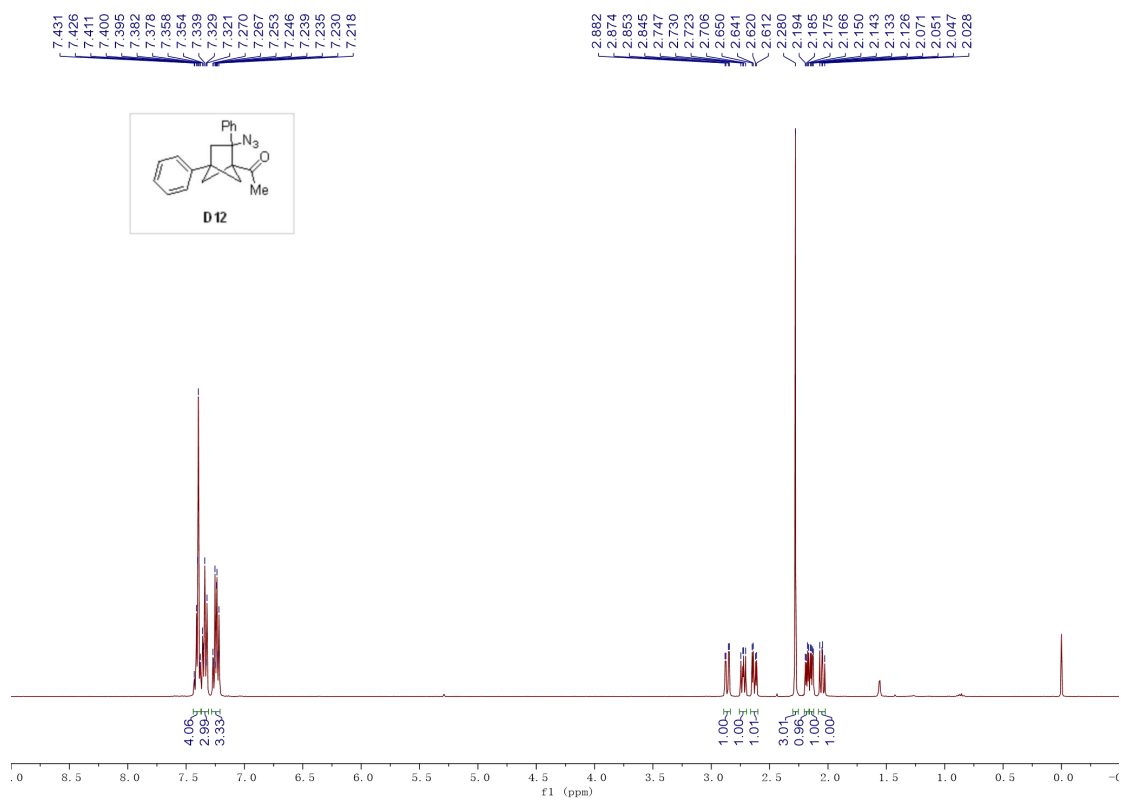
¹H NMR spectrum of D9

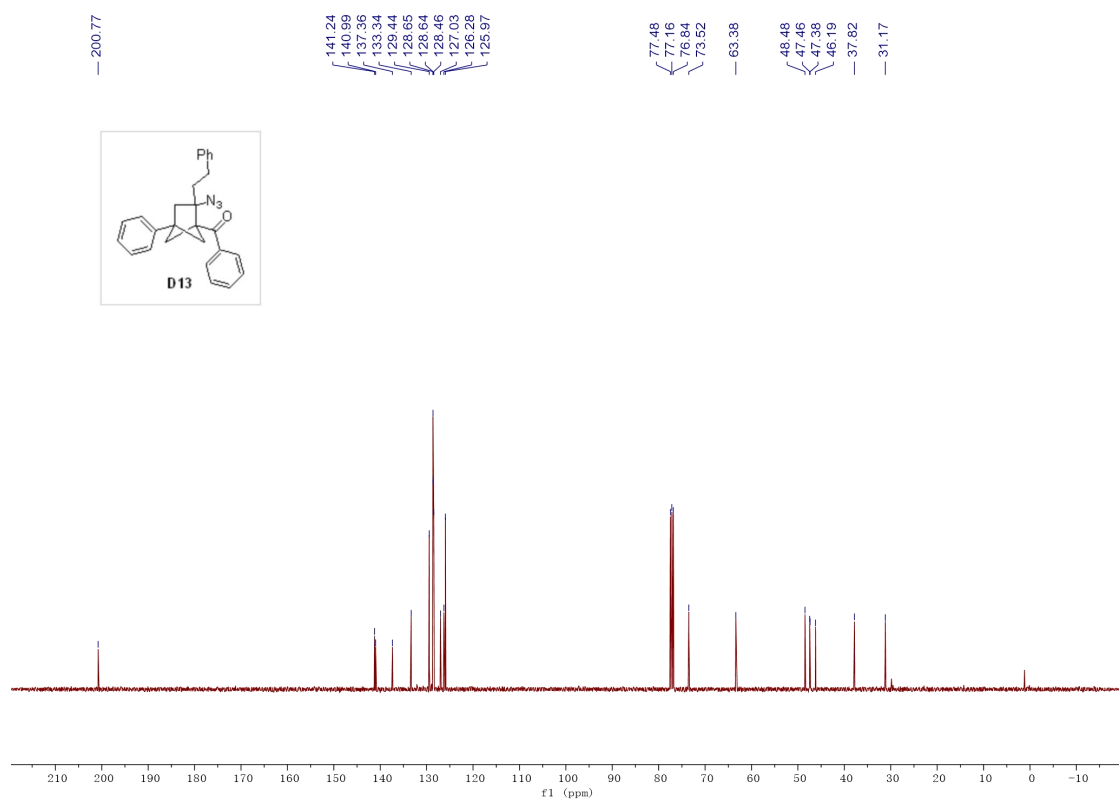
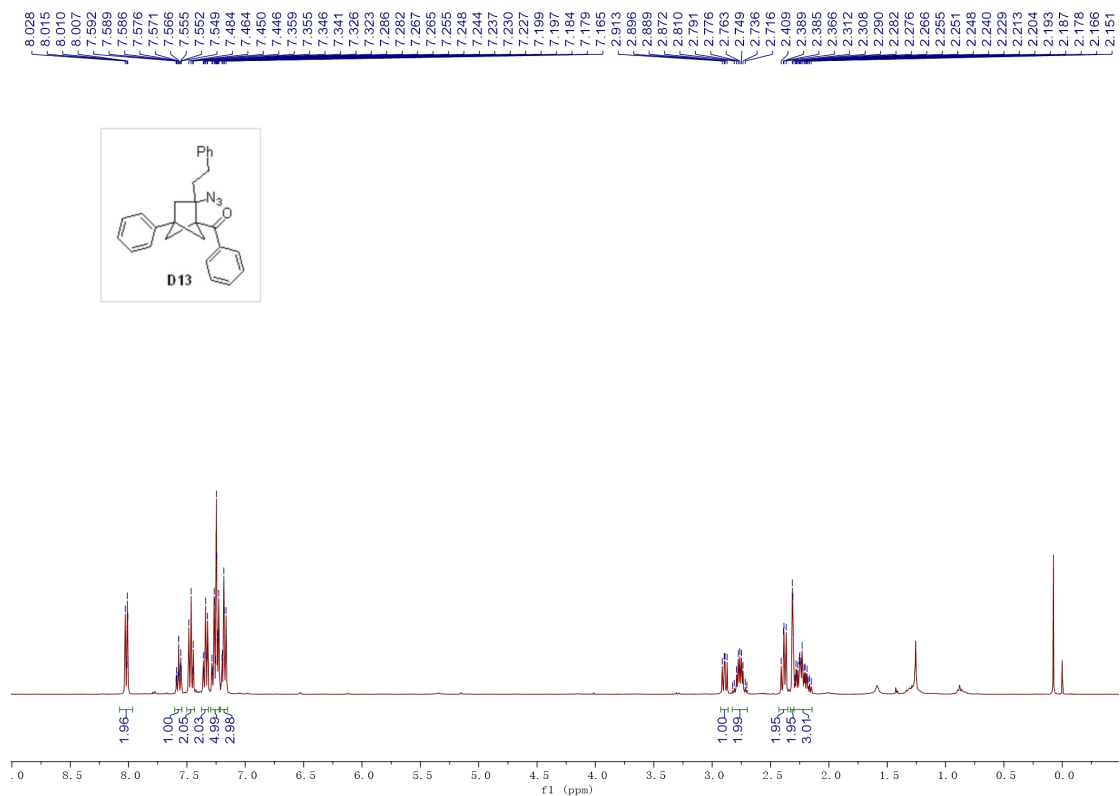


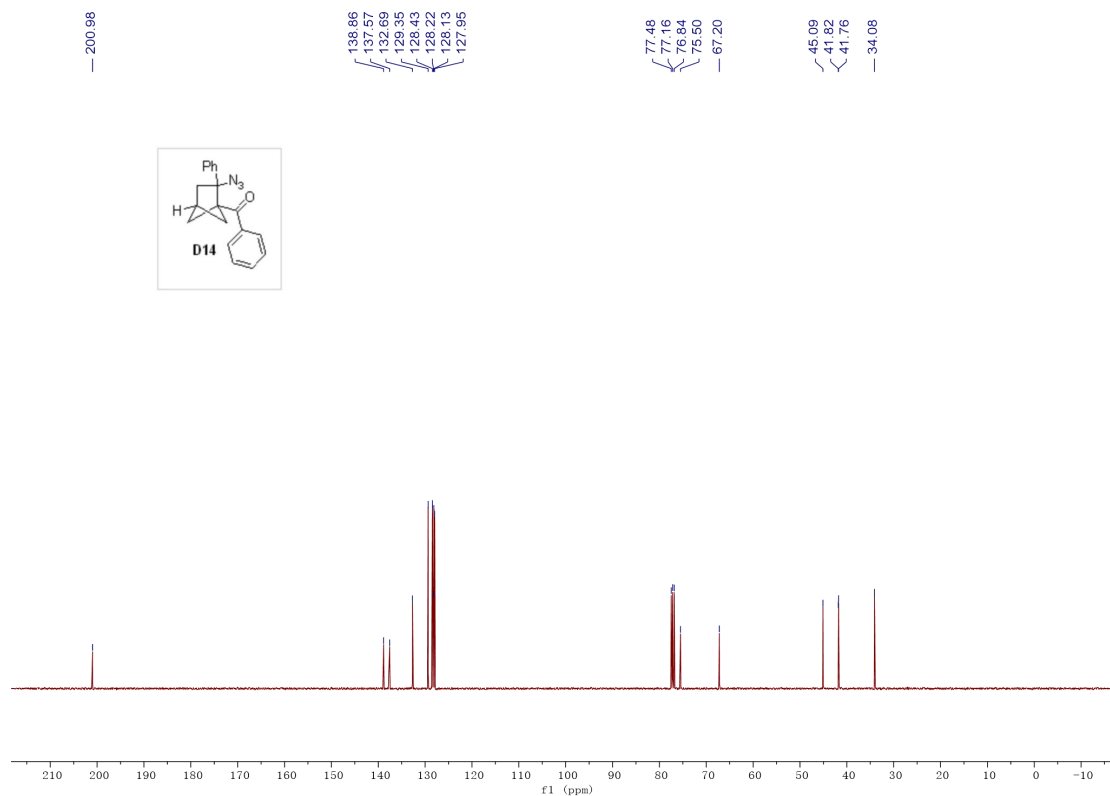
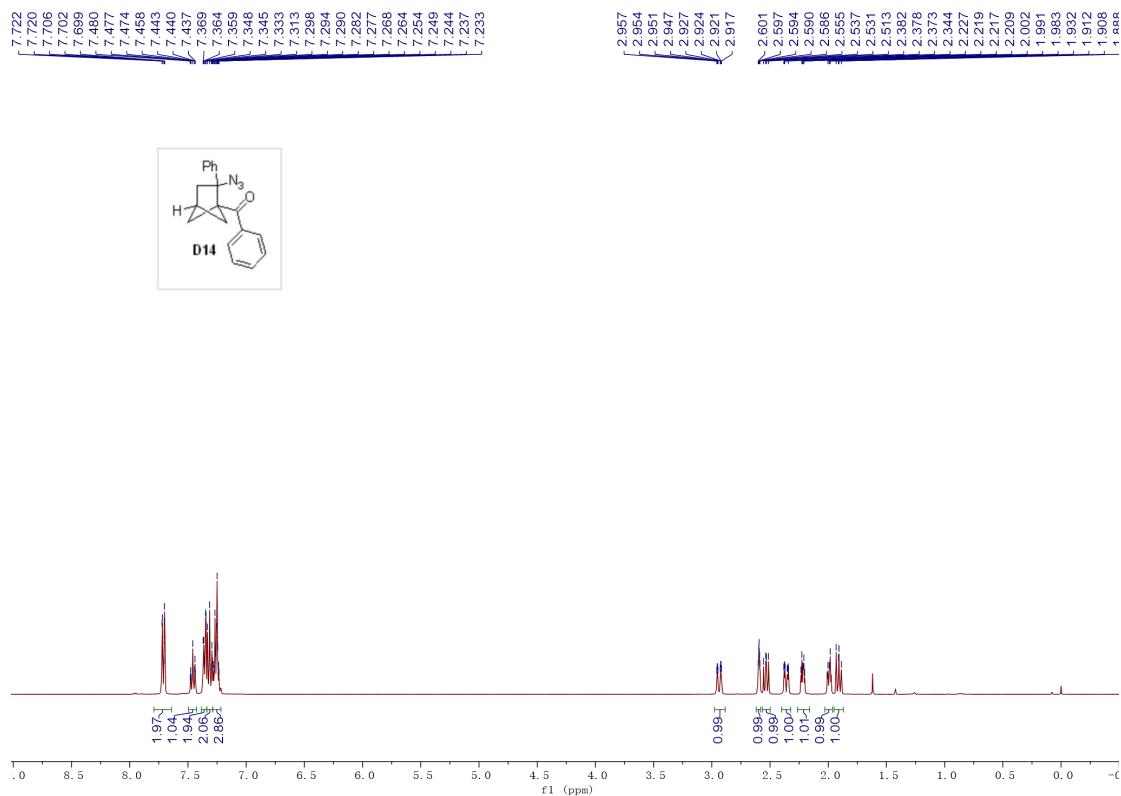
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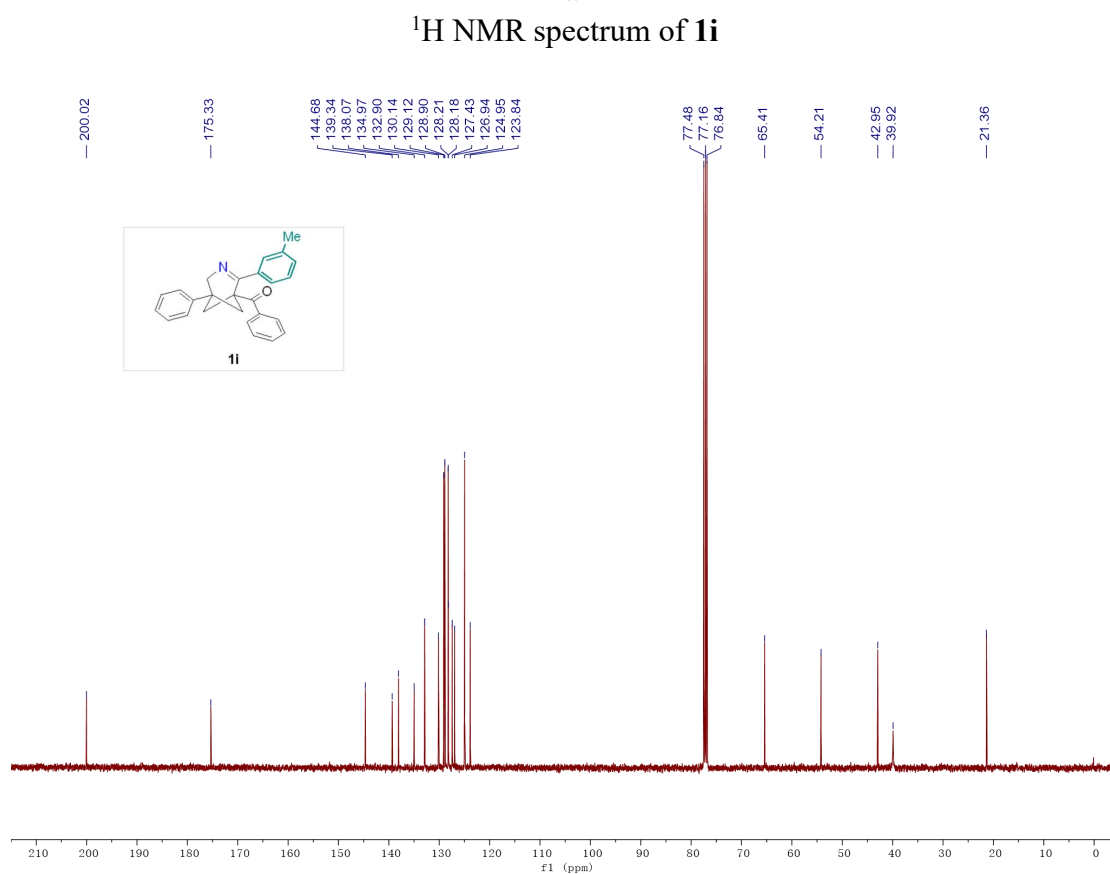
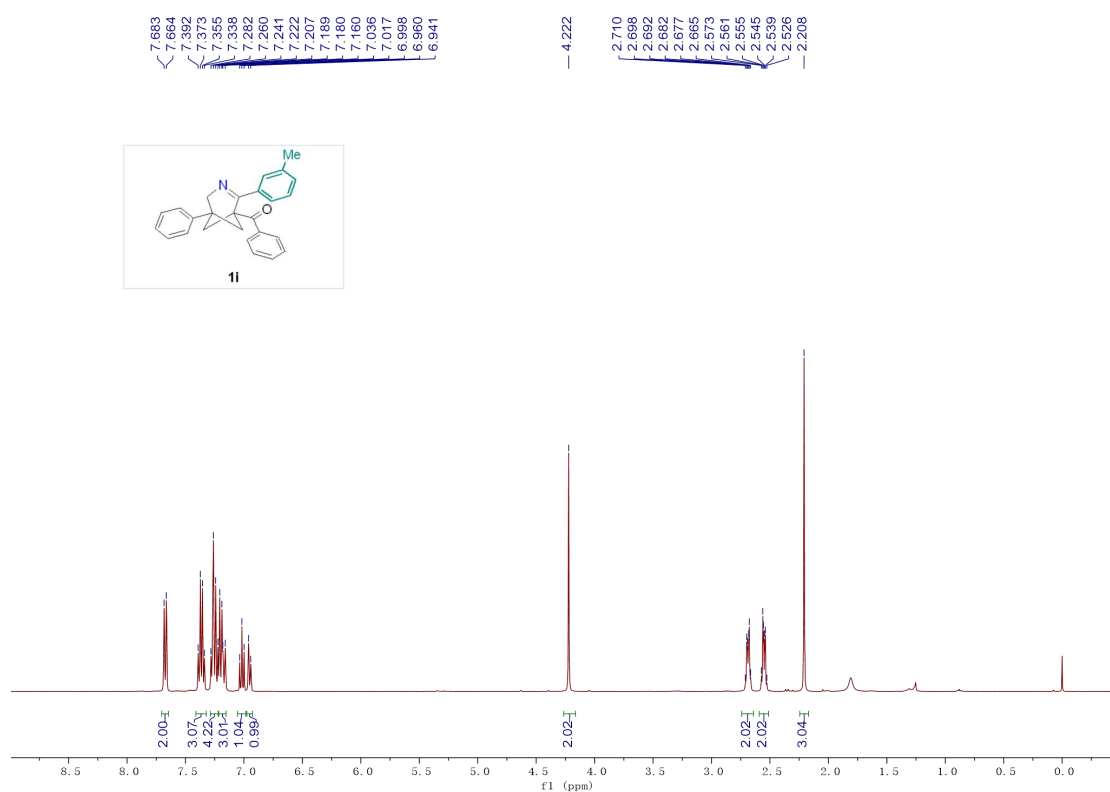


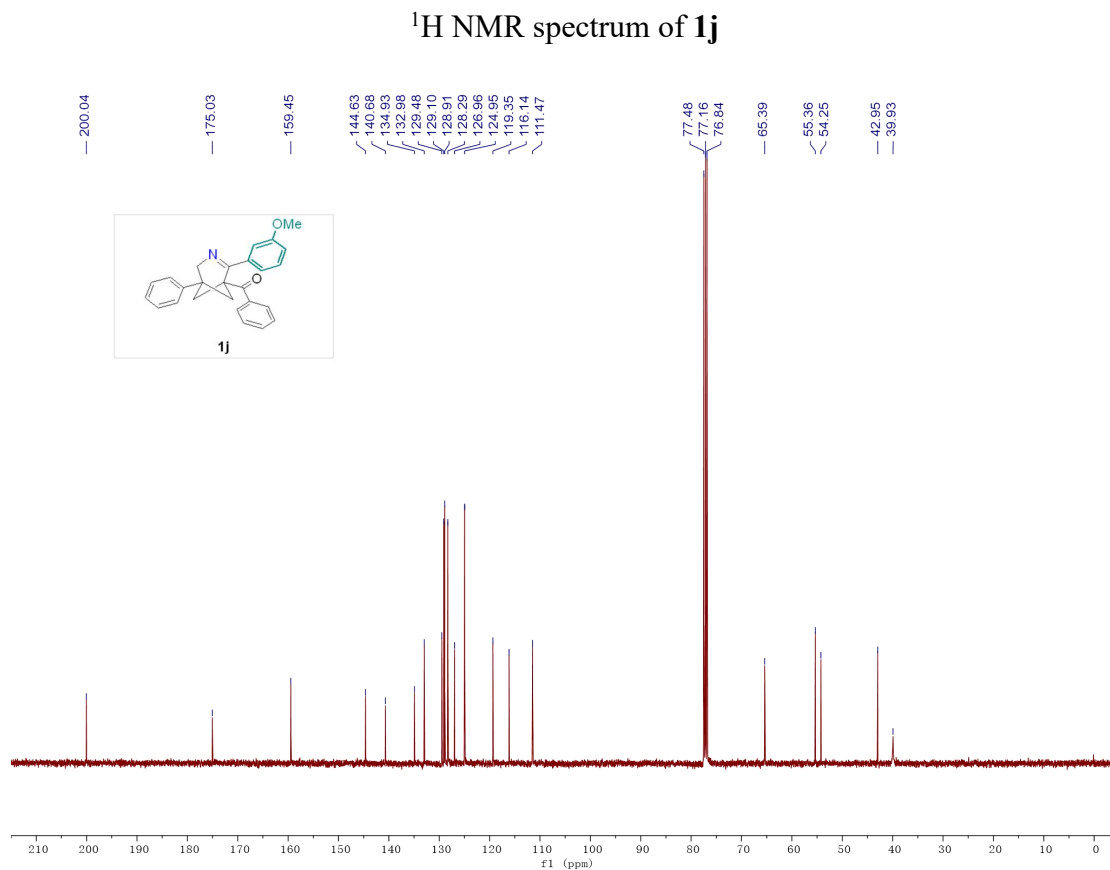
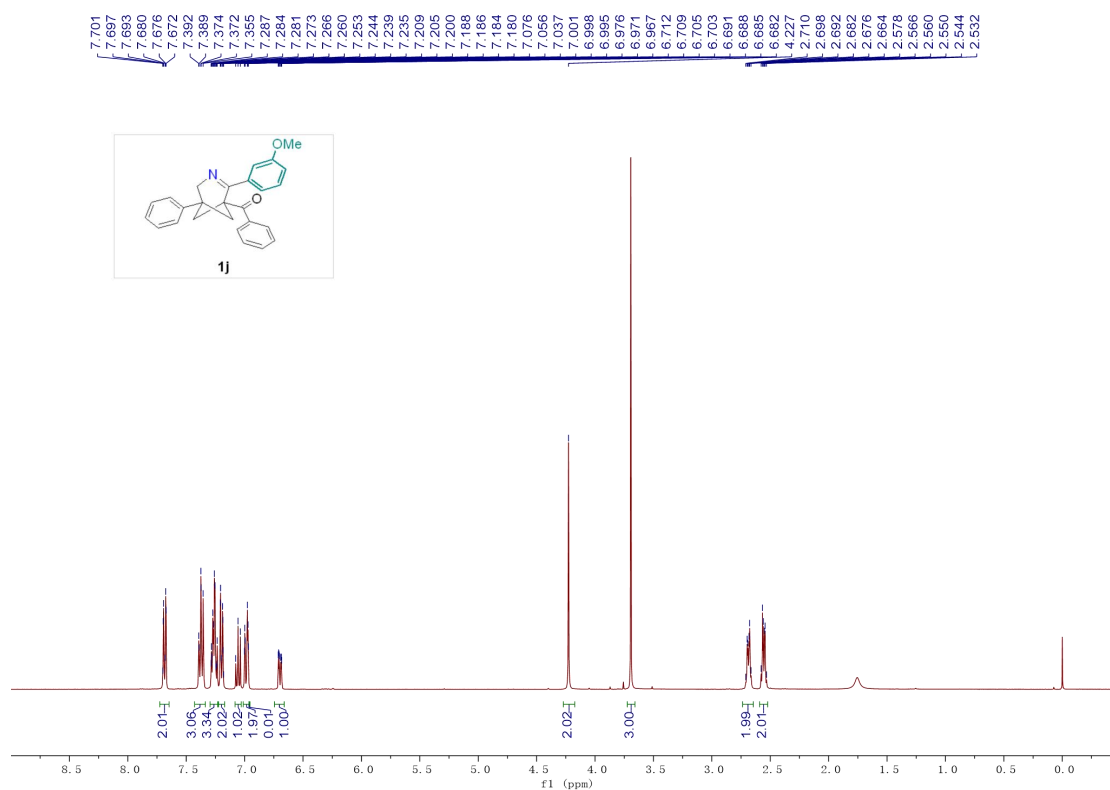


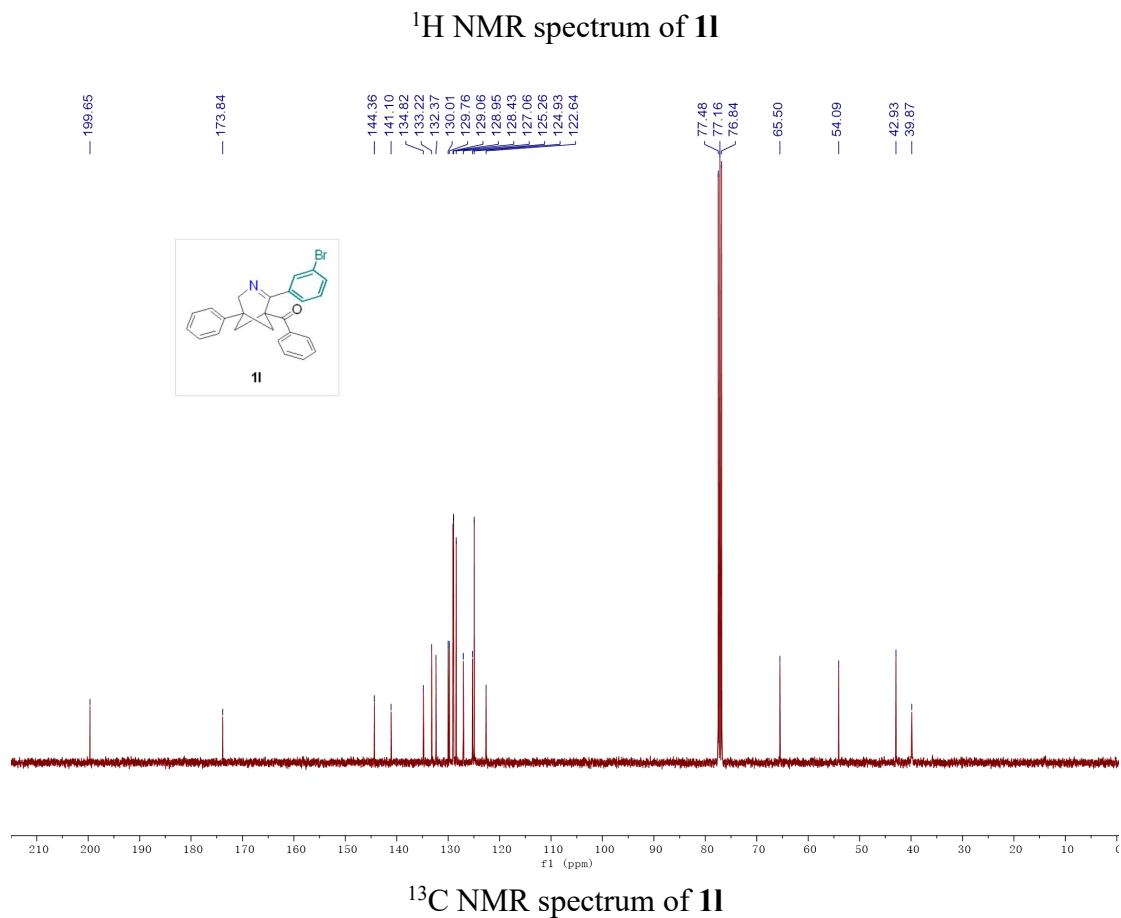
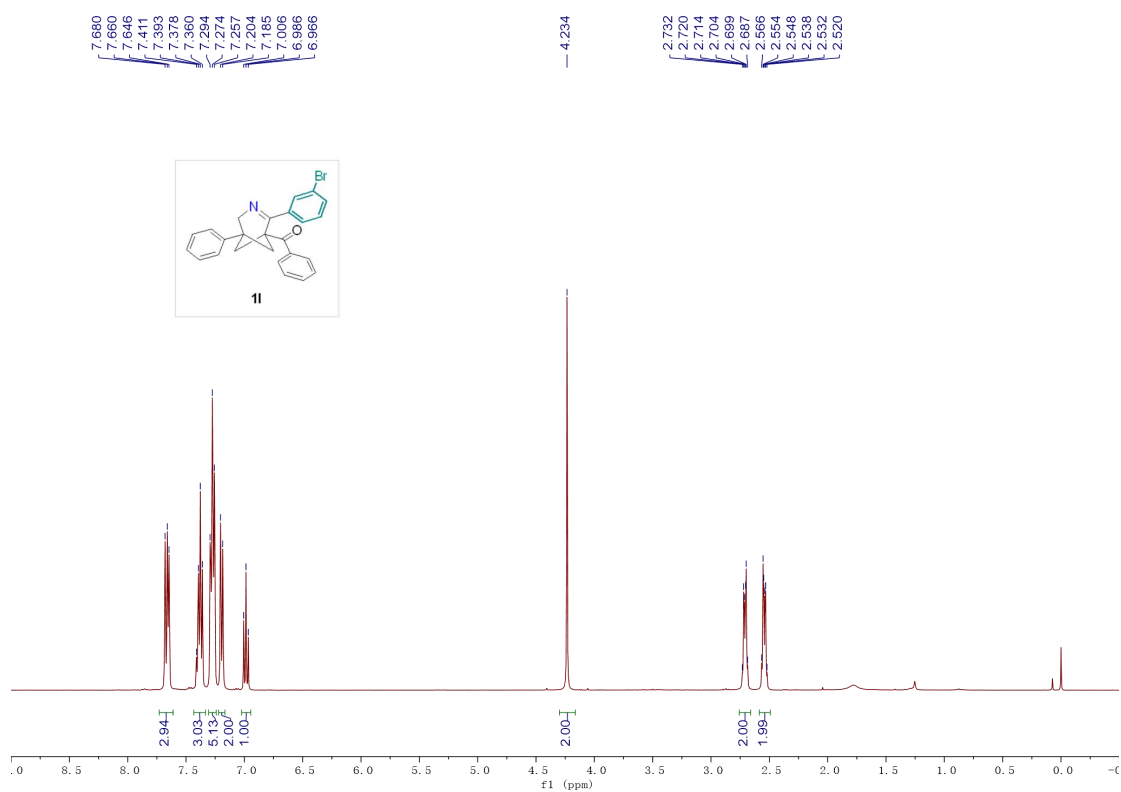


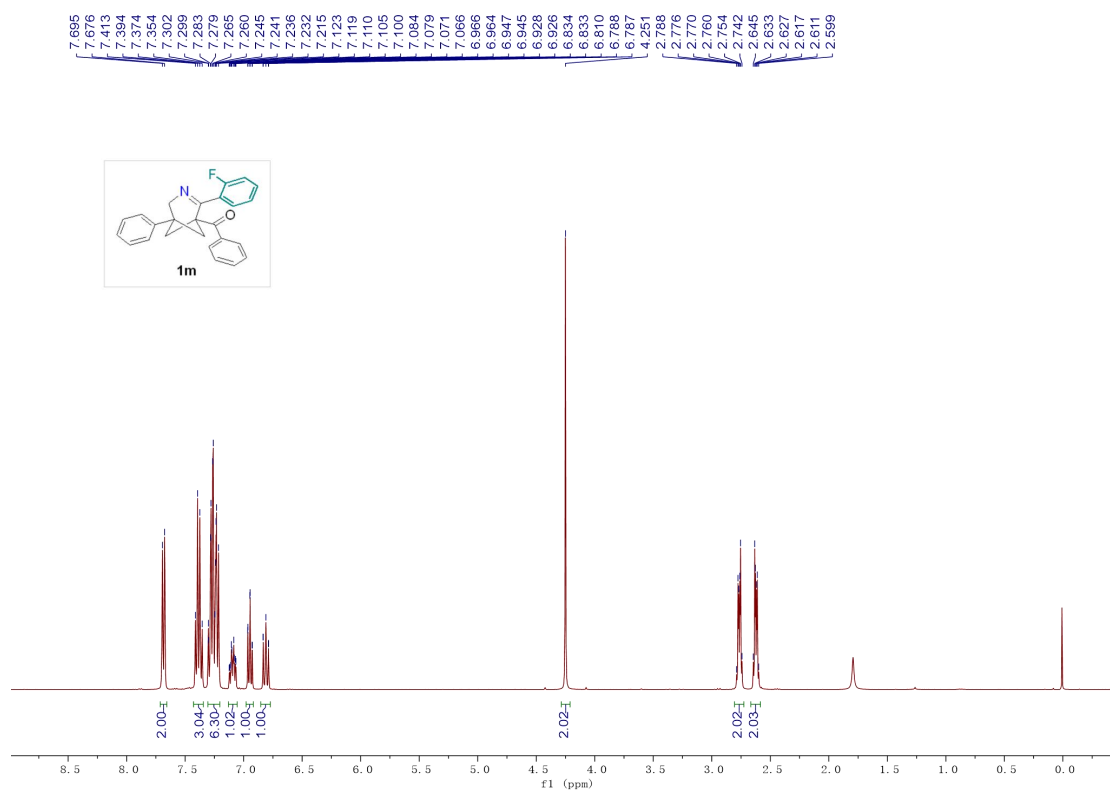




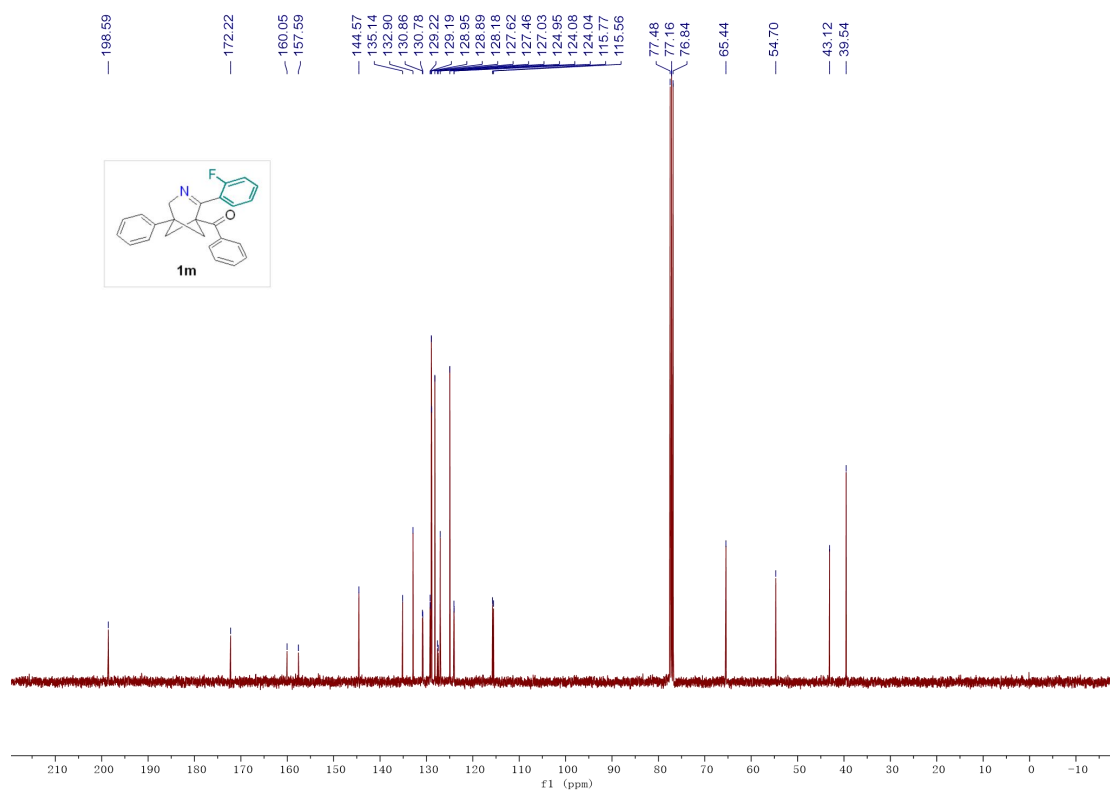




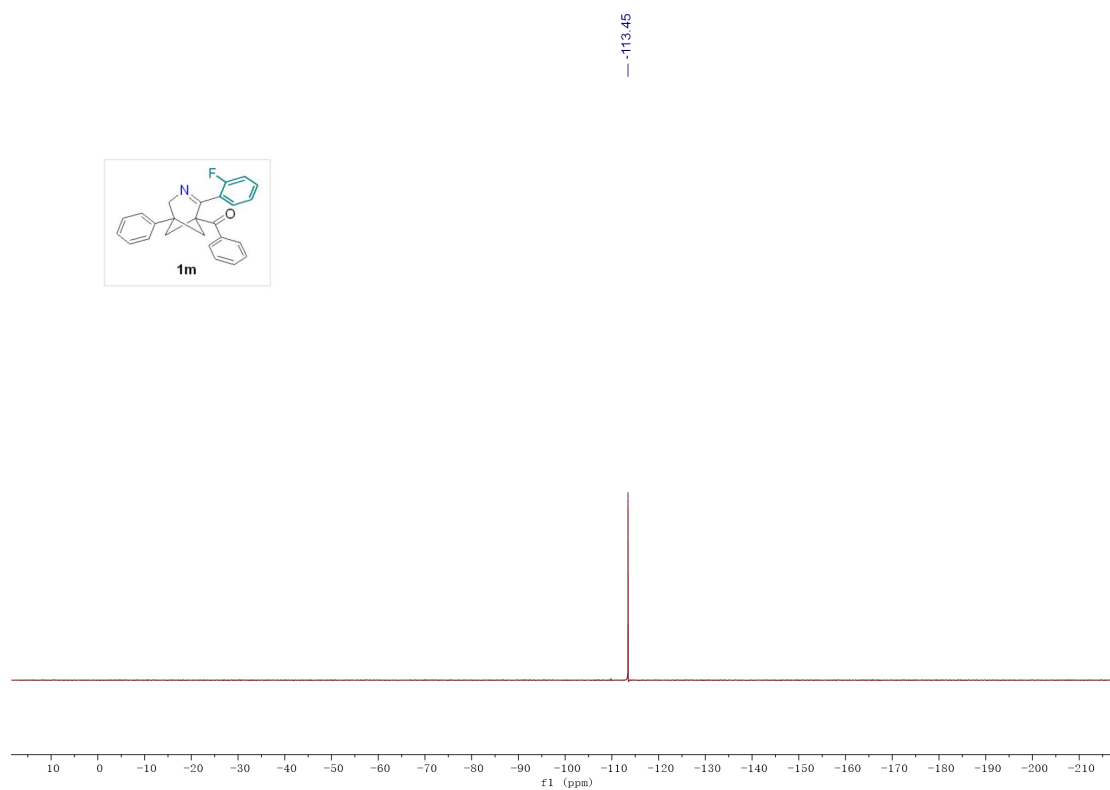




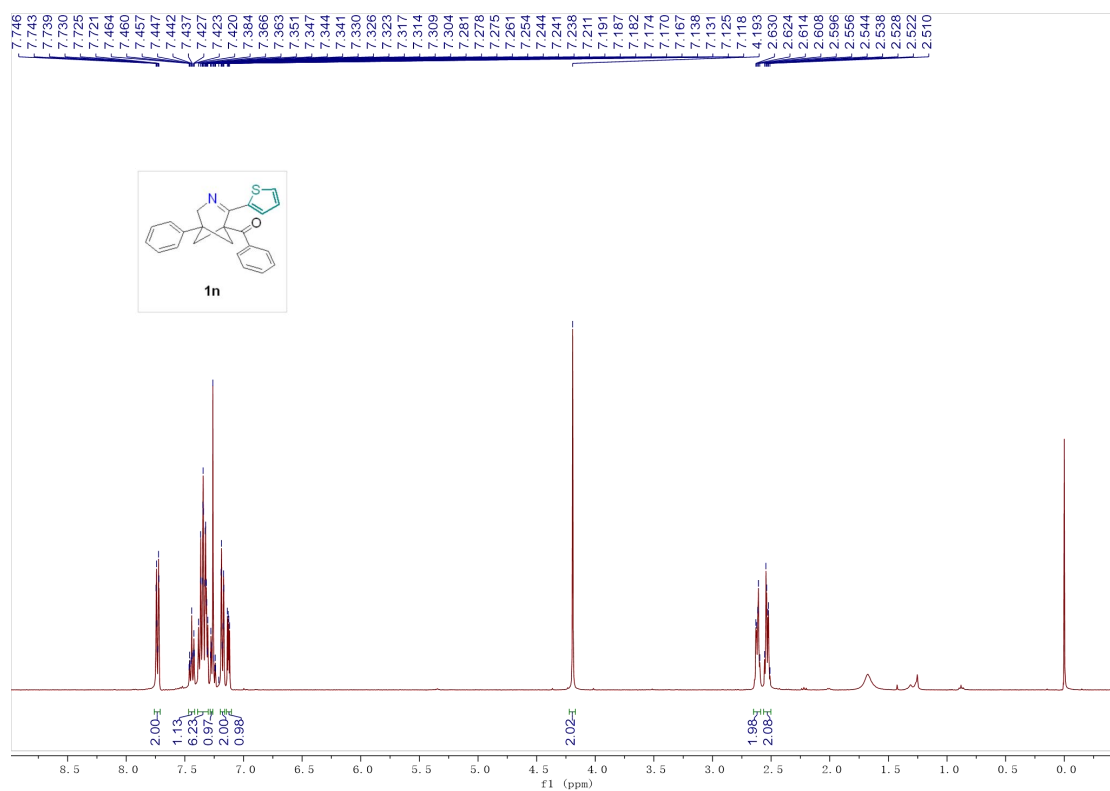
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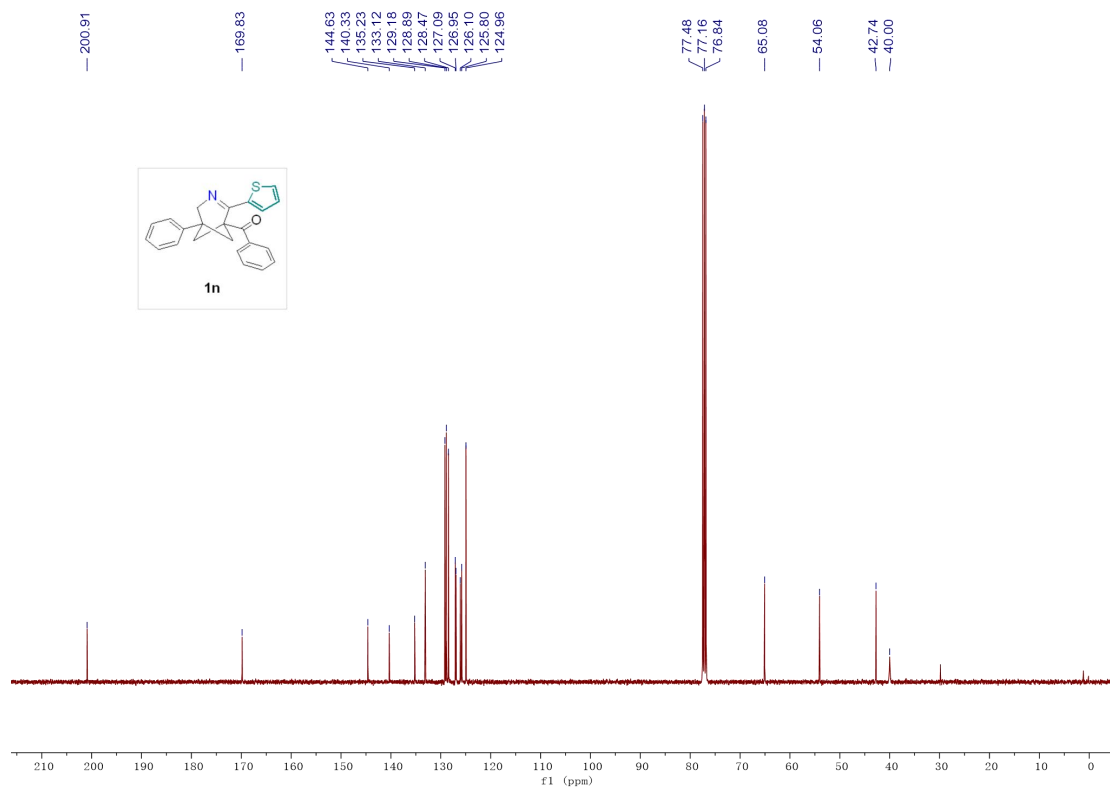
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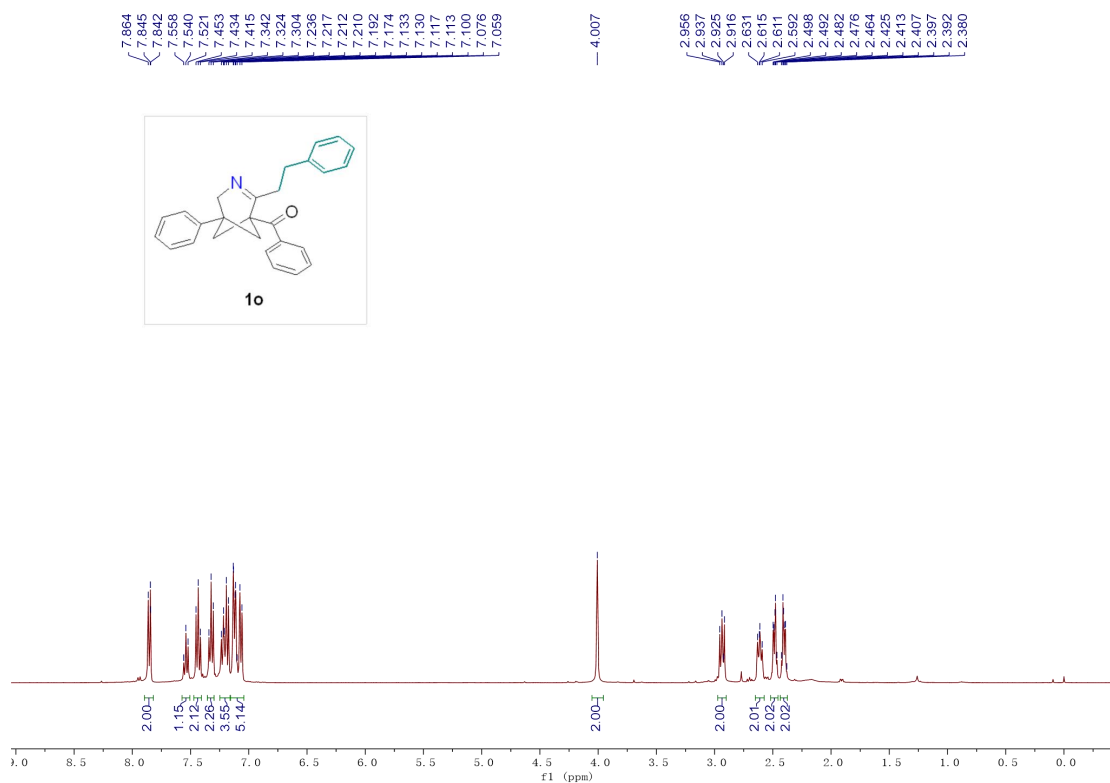
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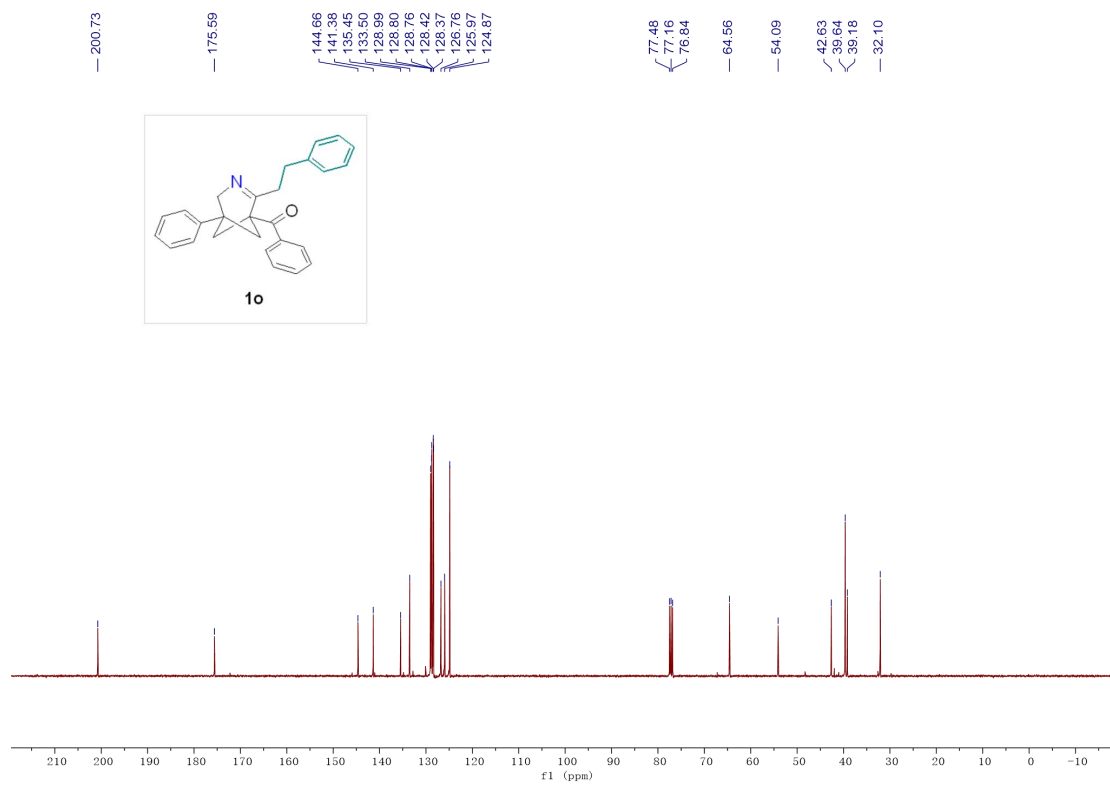
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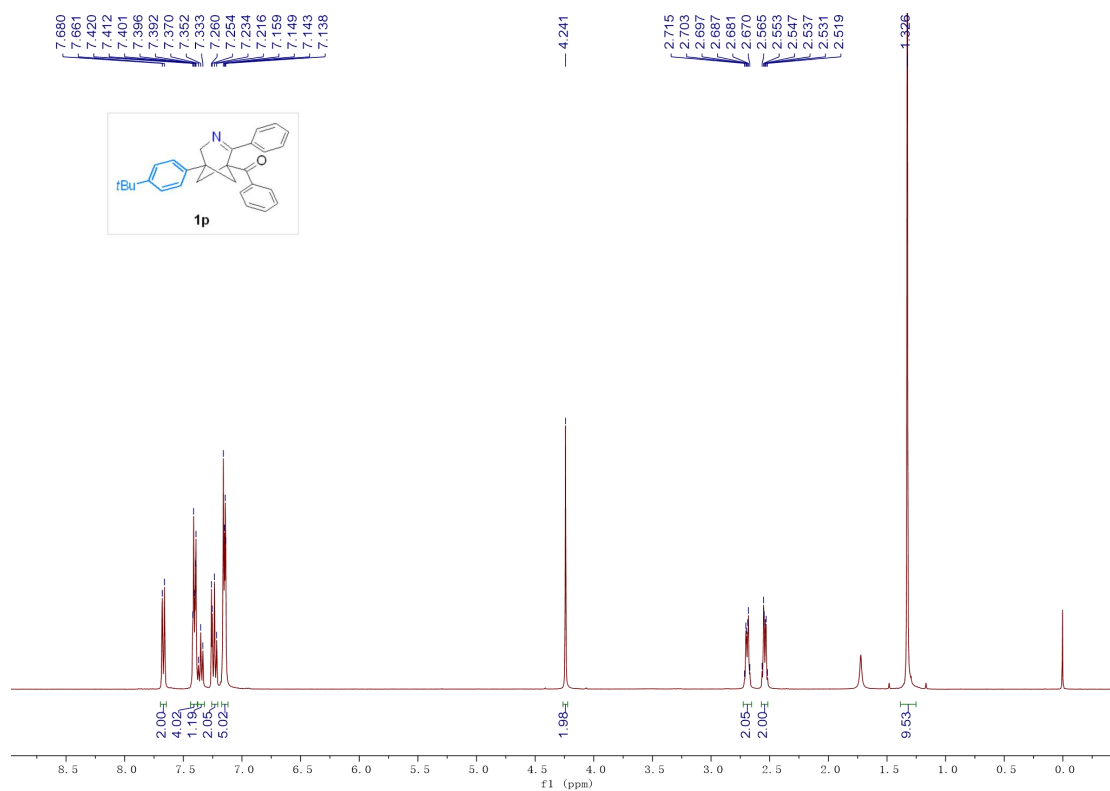
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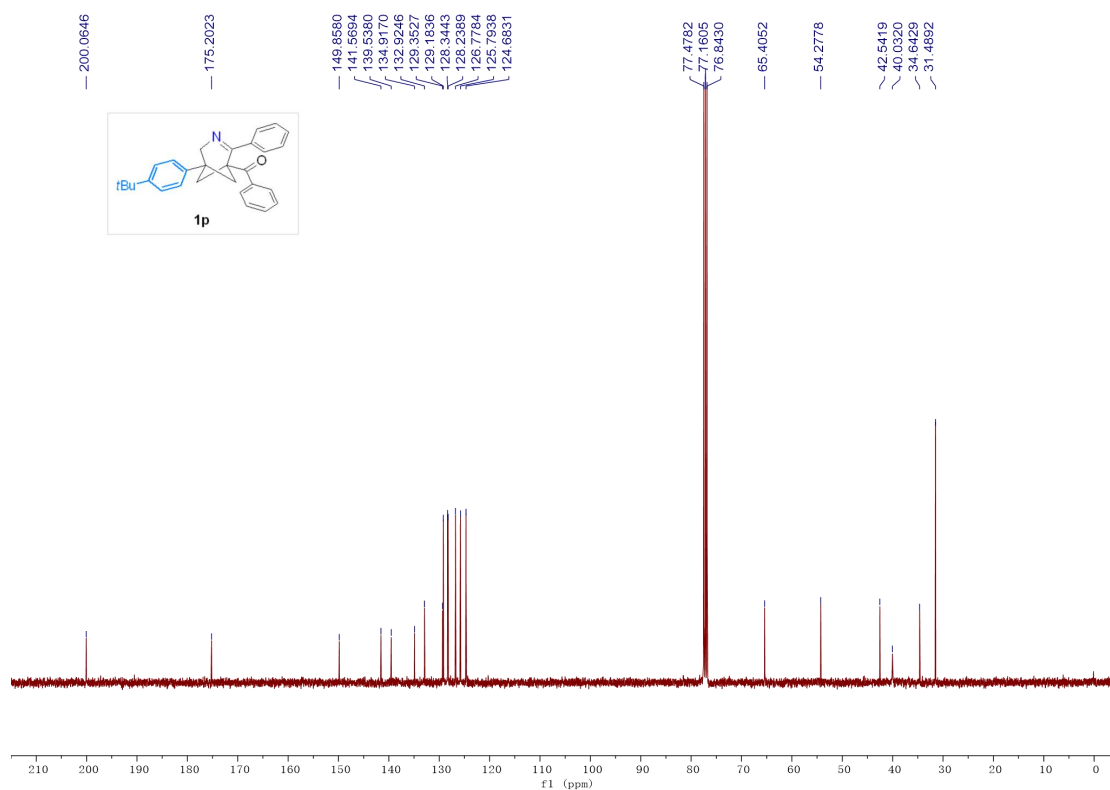
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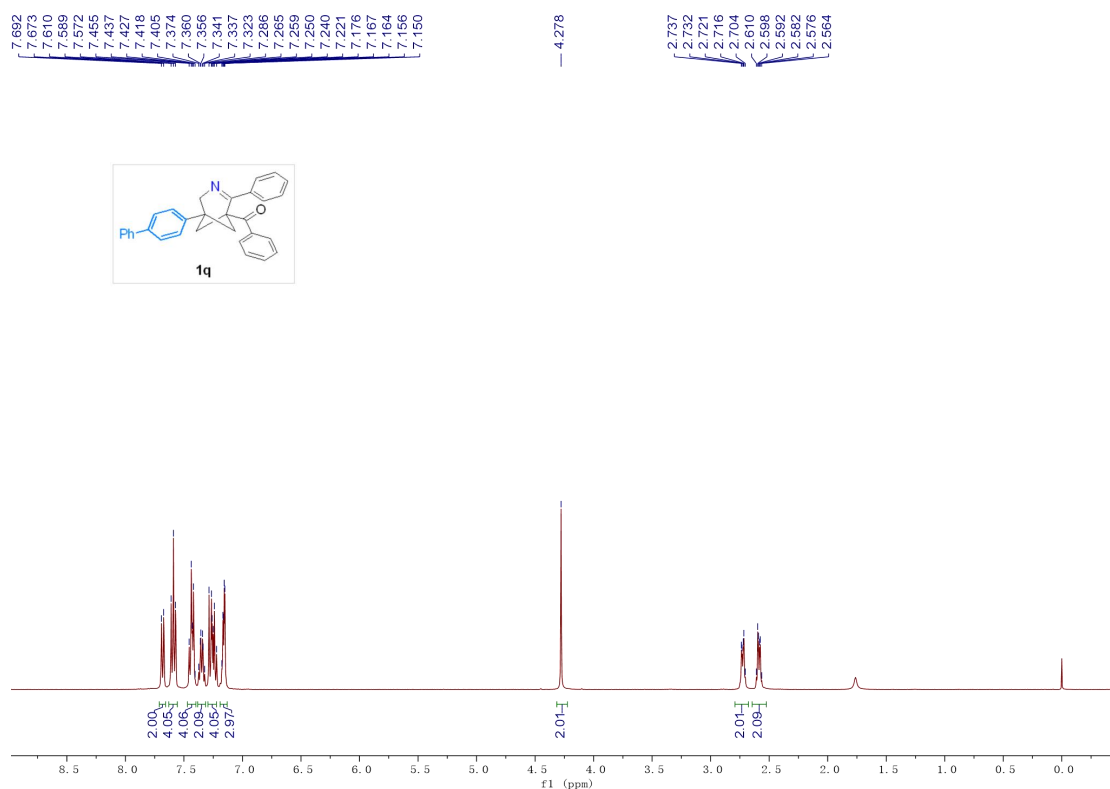
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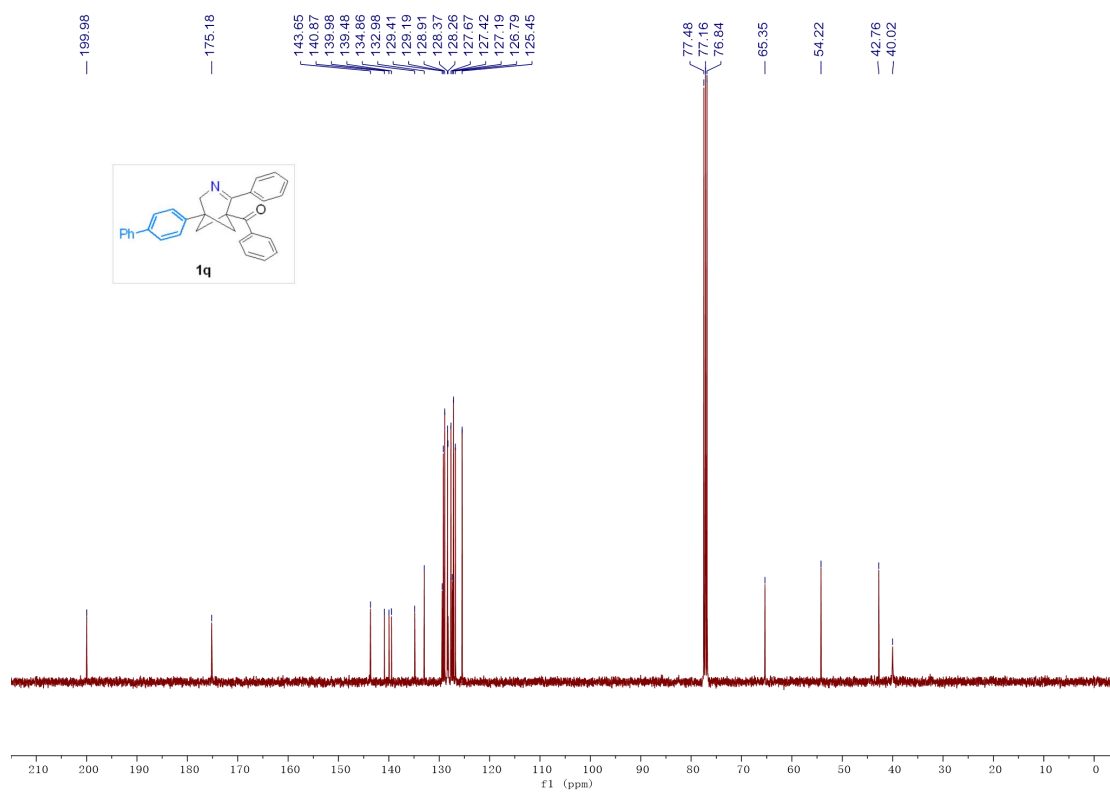
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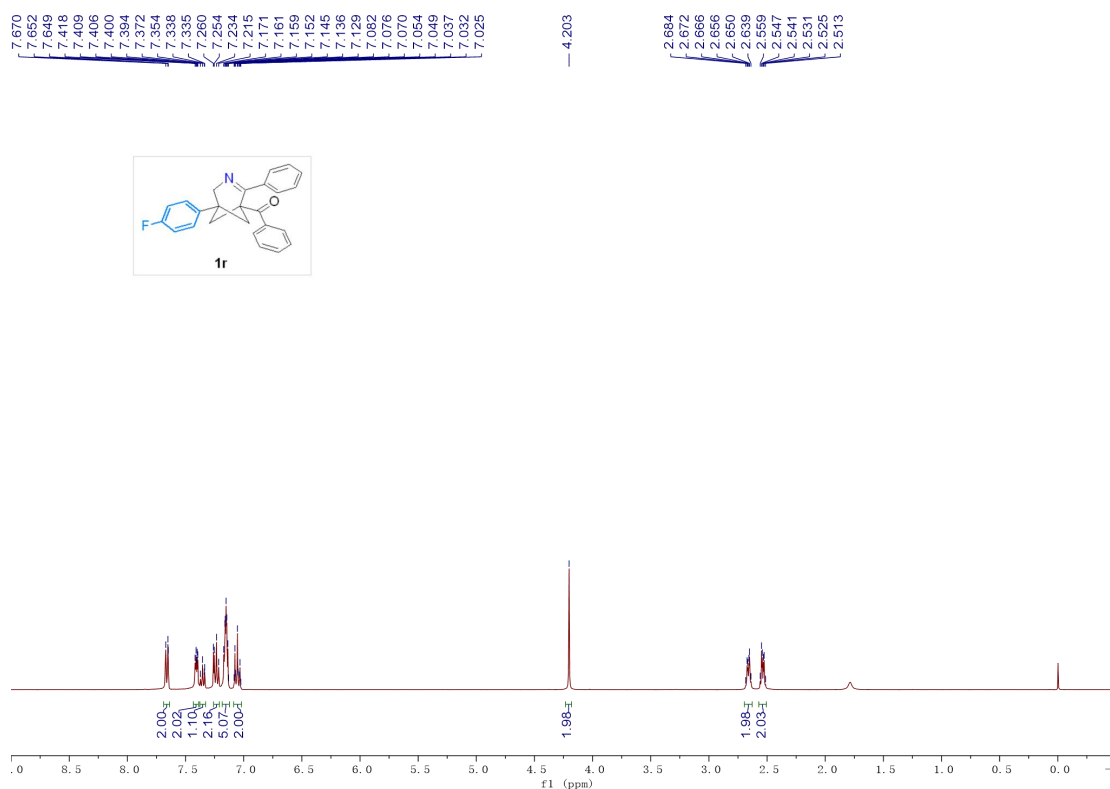
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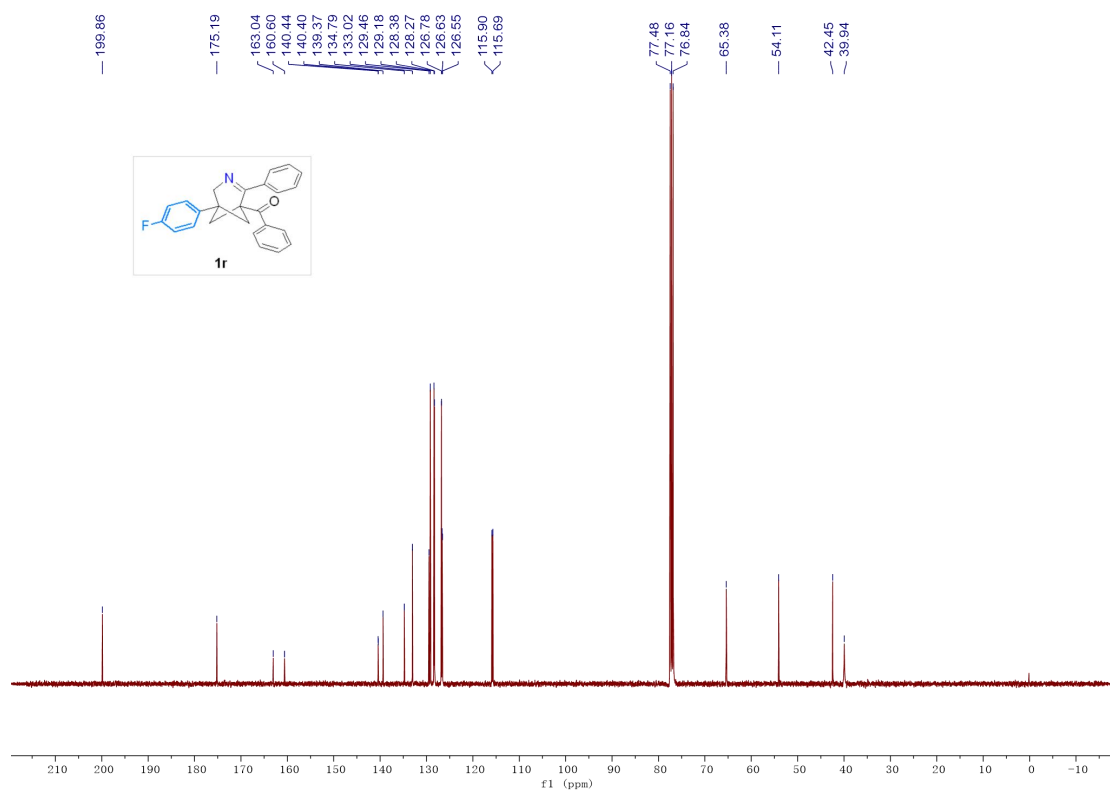
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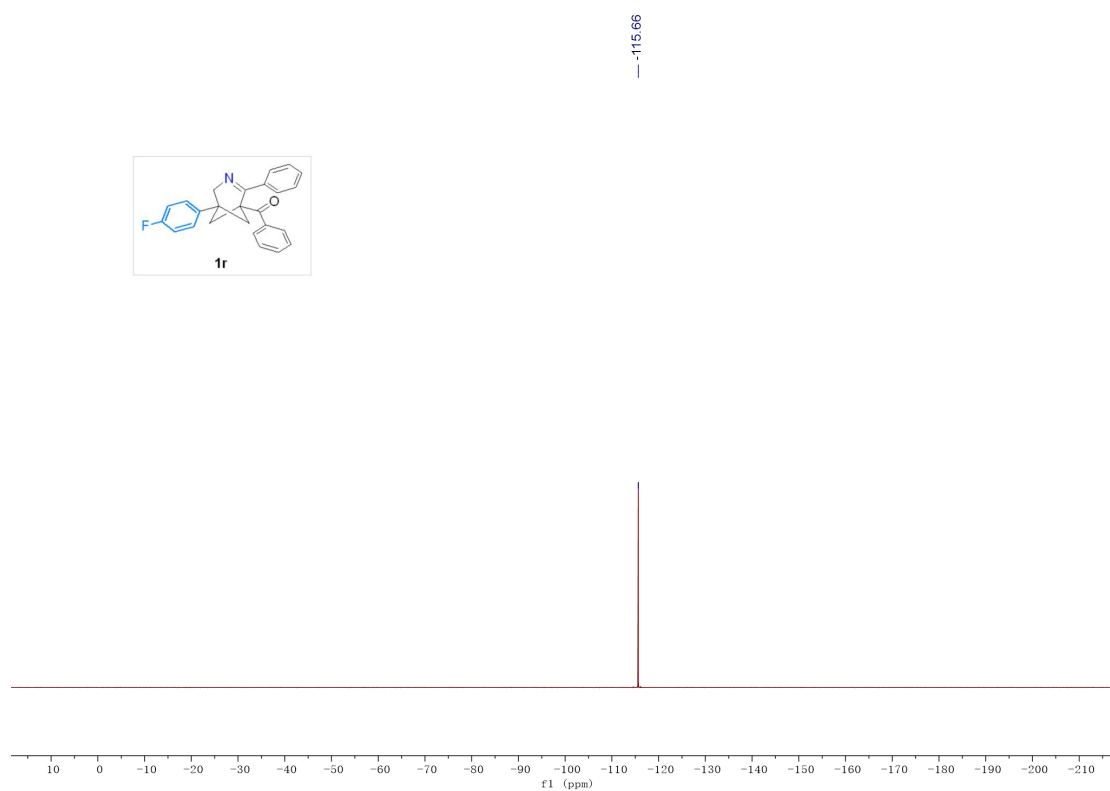
¹³C NMR spectrum of 1q



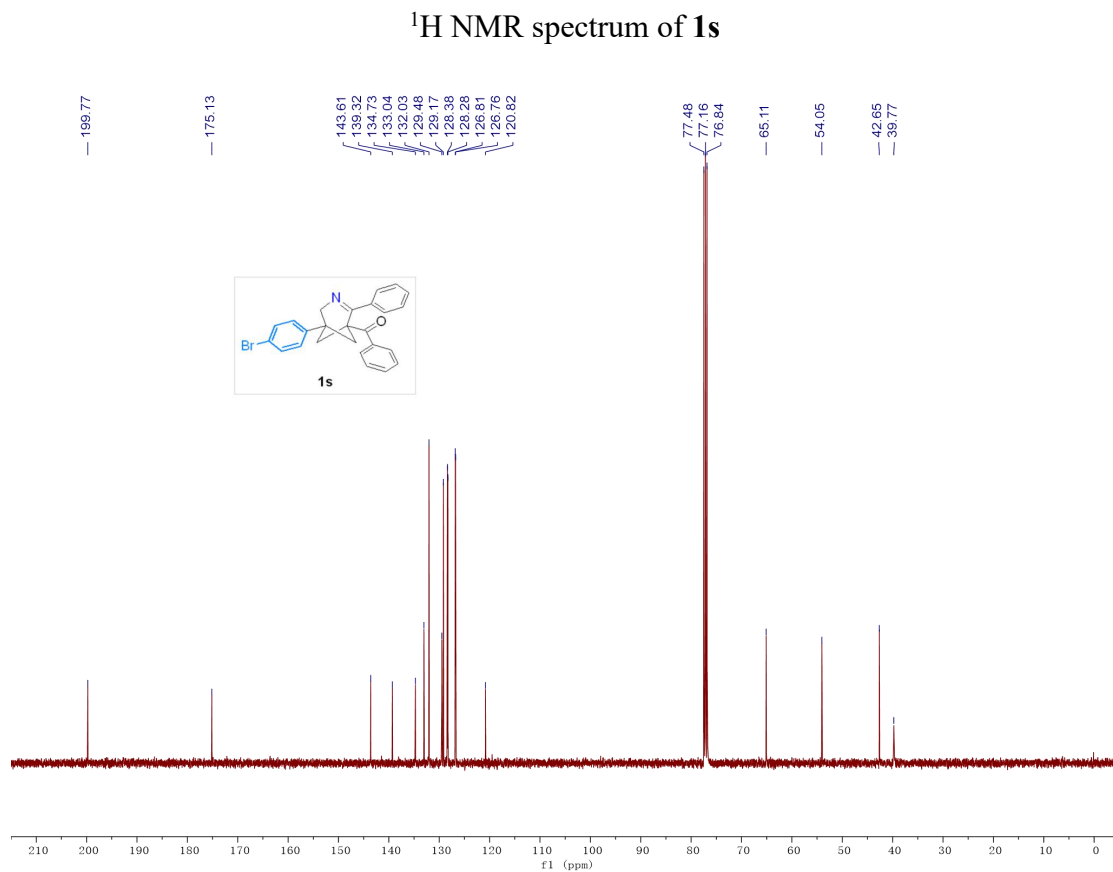
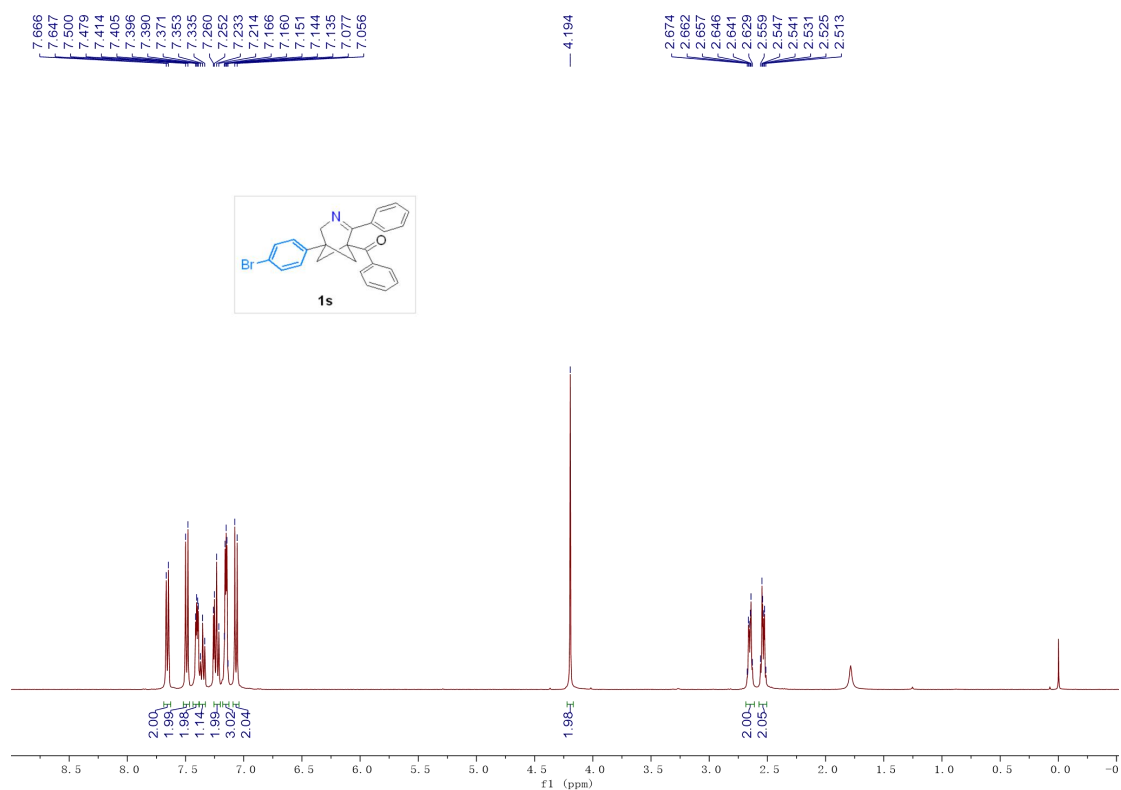
¹H NMR spectrum of 1r

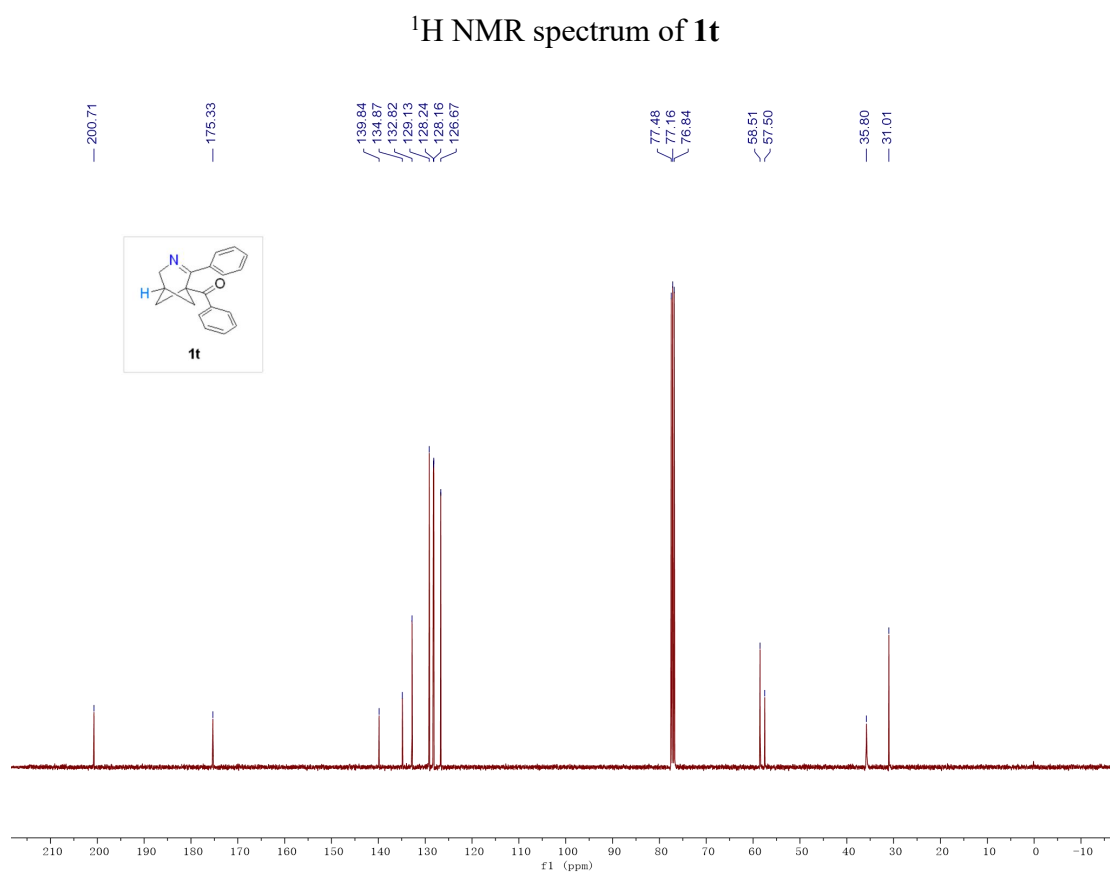
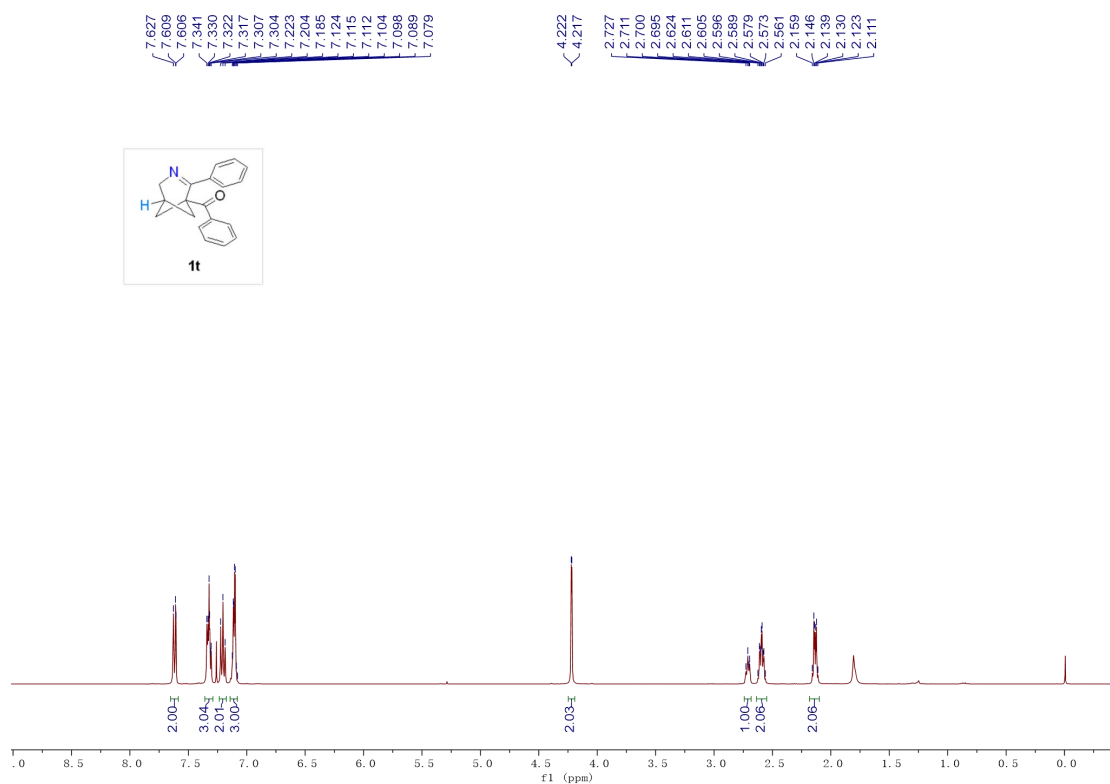


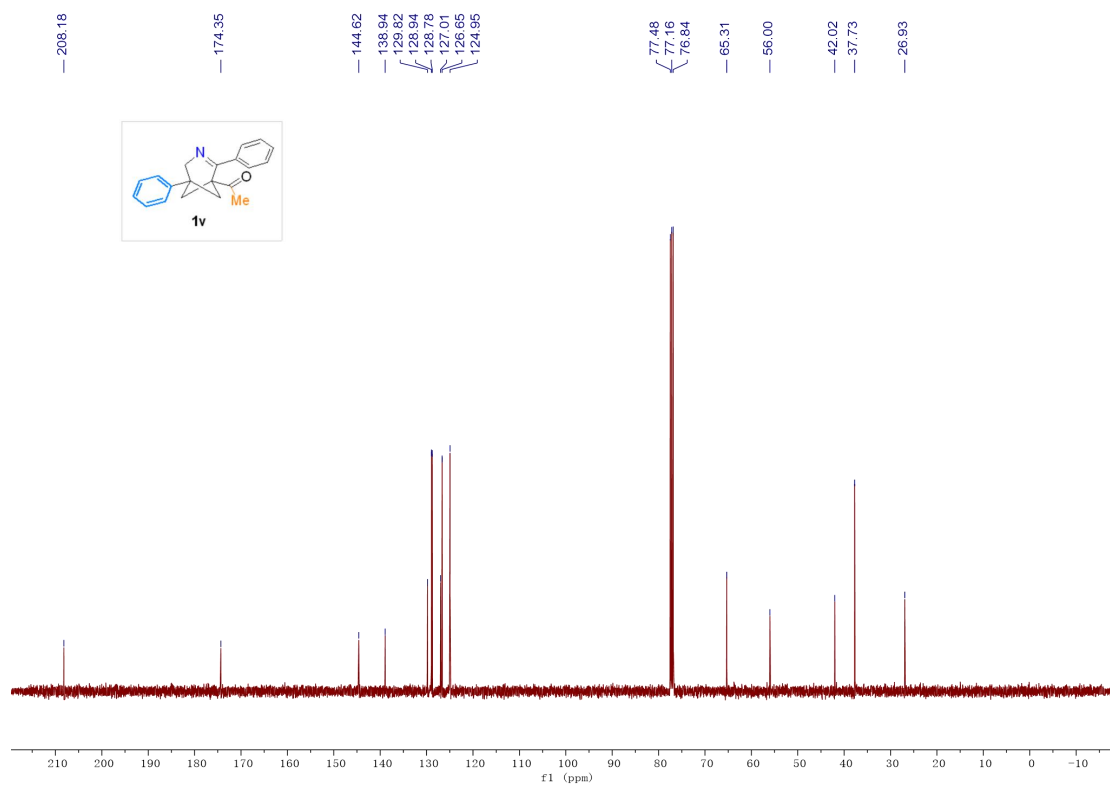
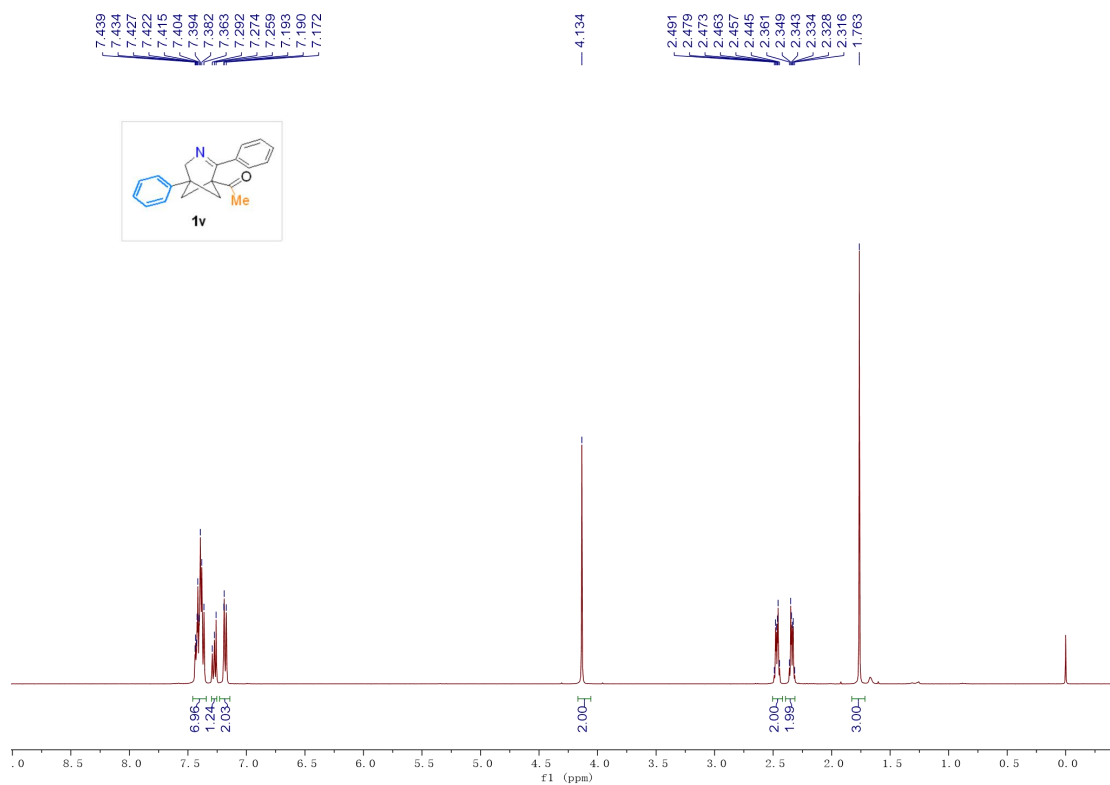
¹³C NMR spectrum of **1r**

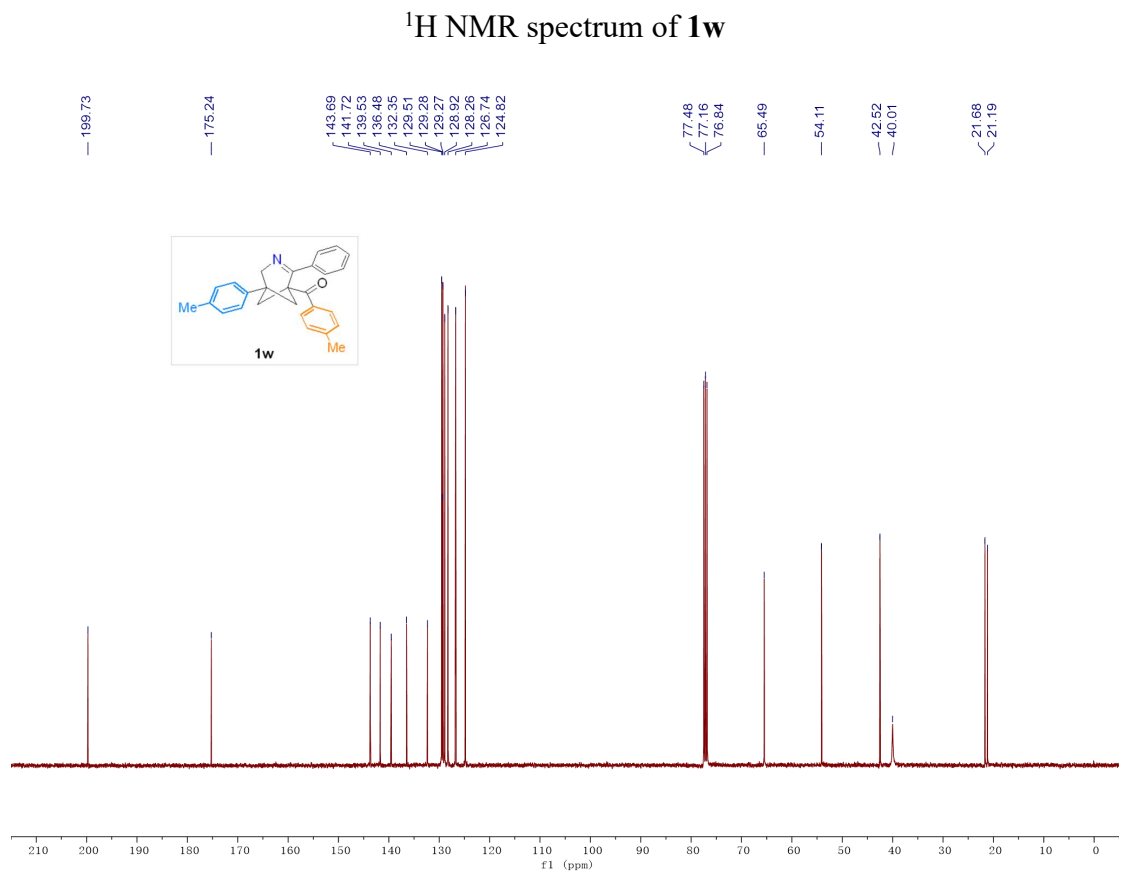
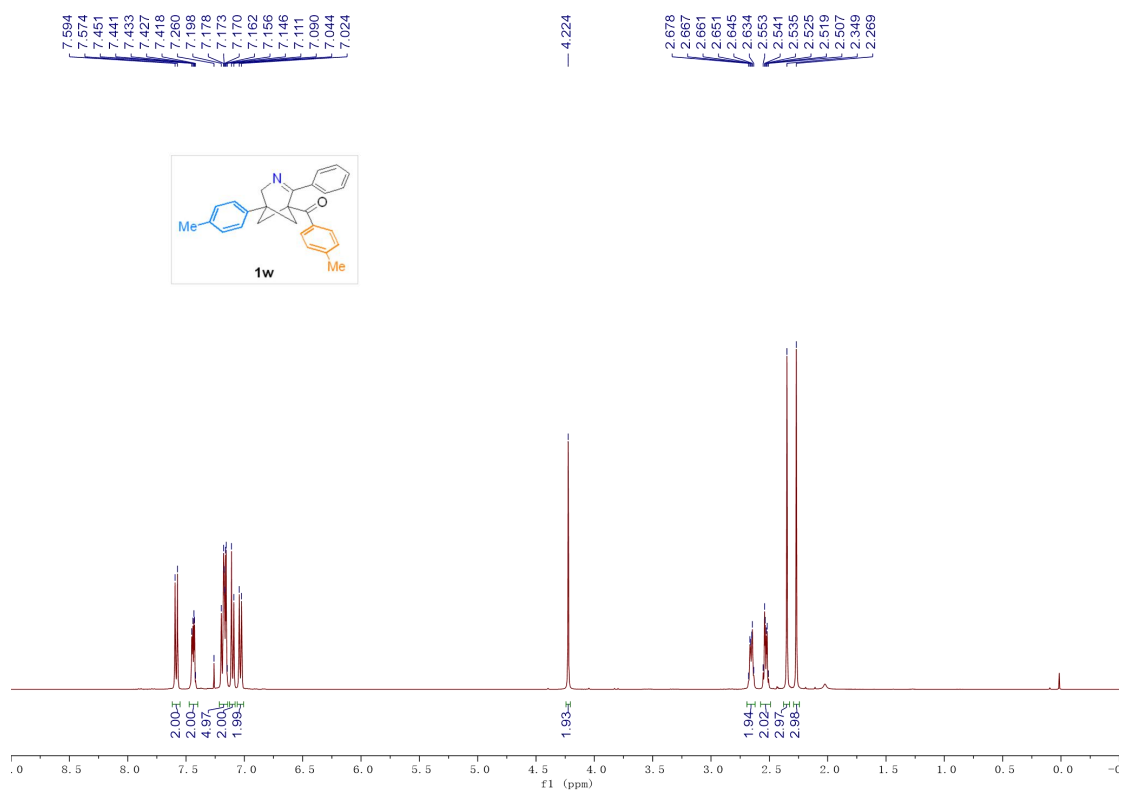


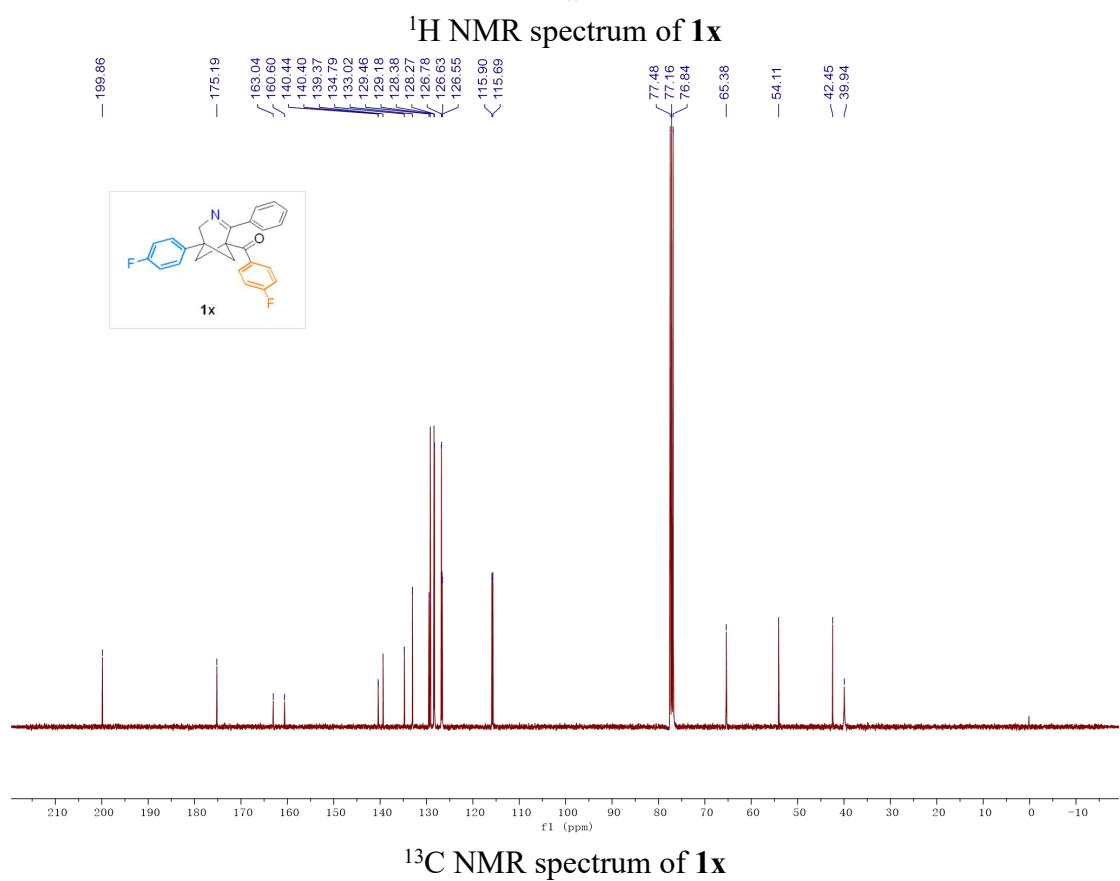
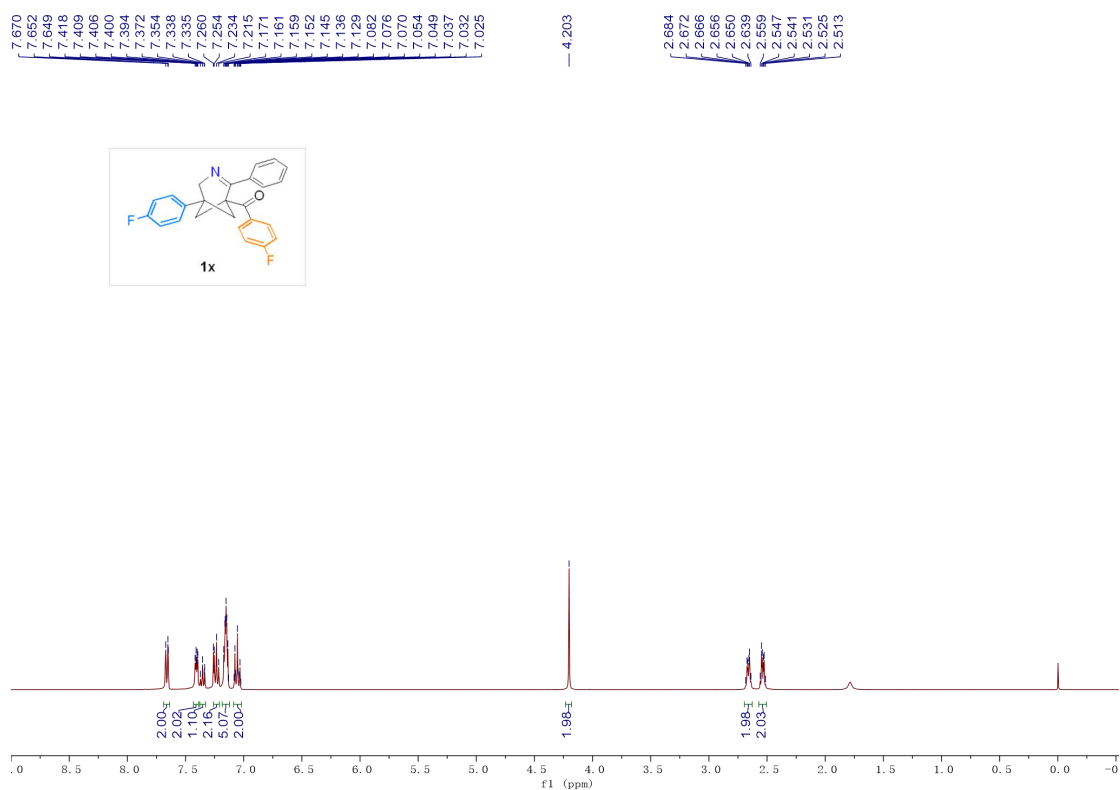
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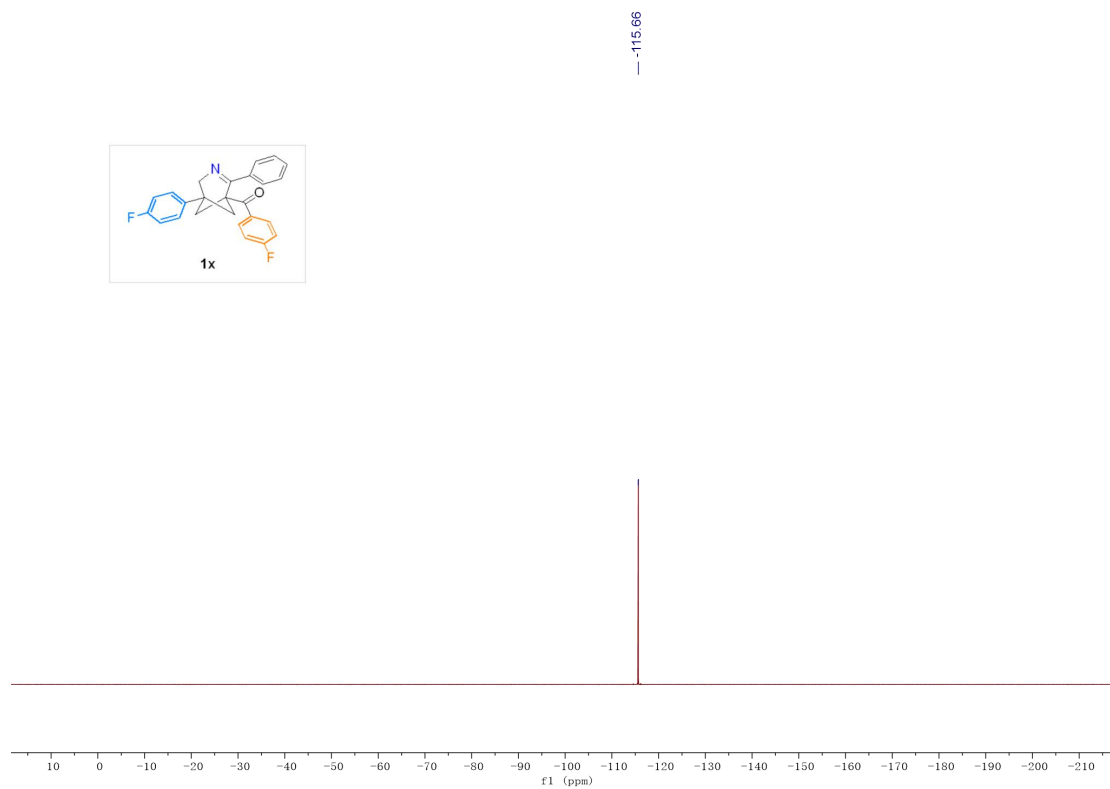




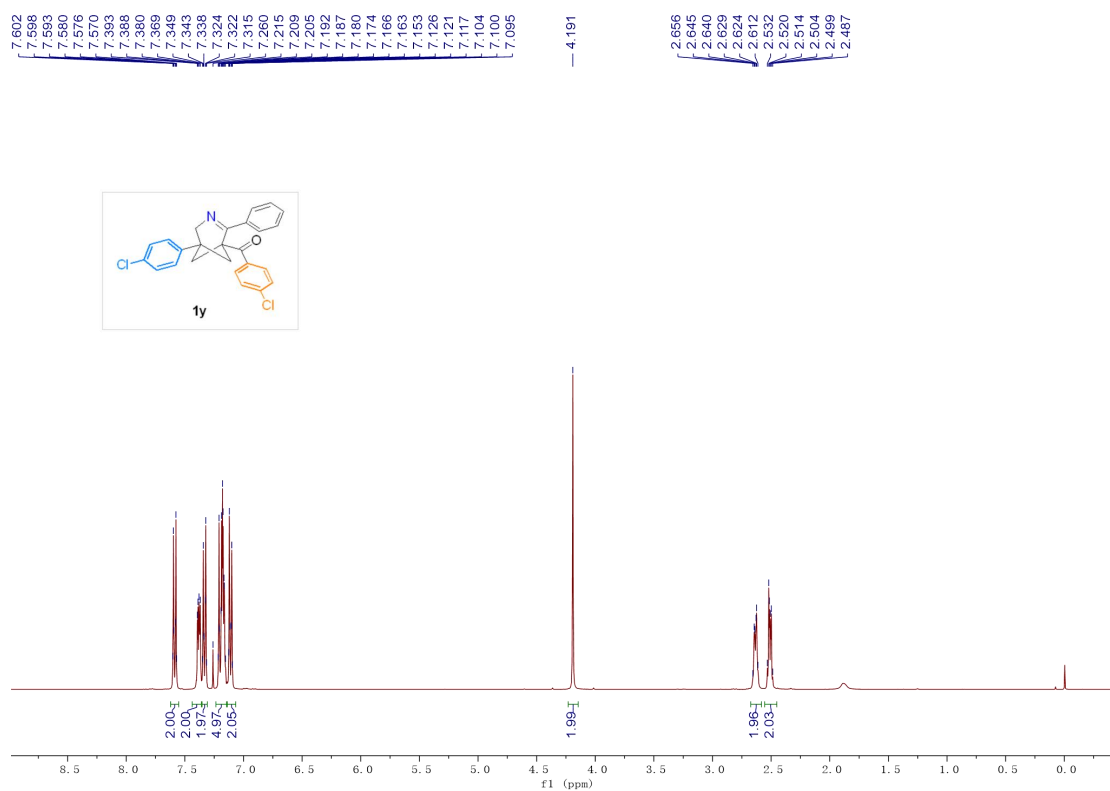




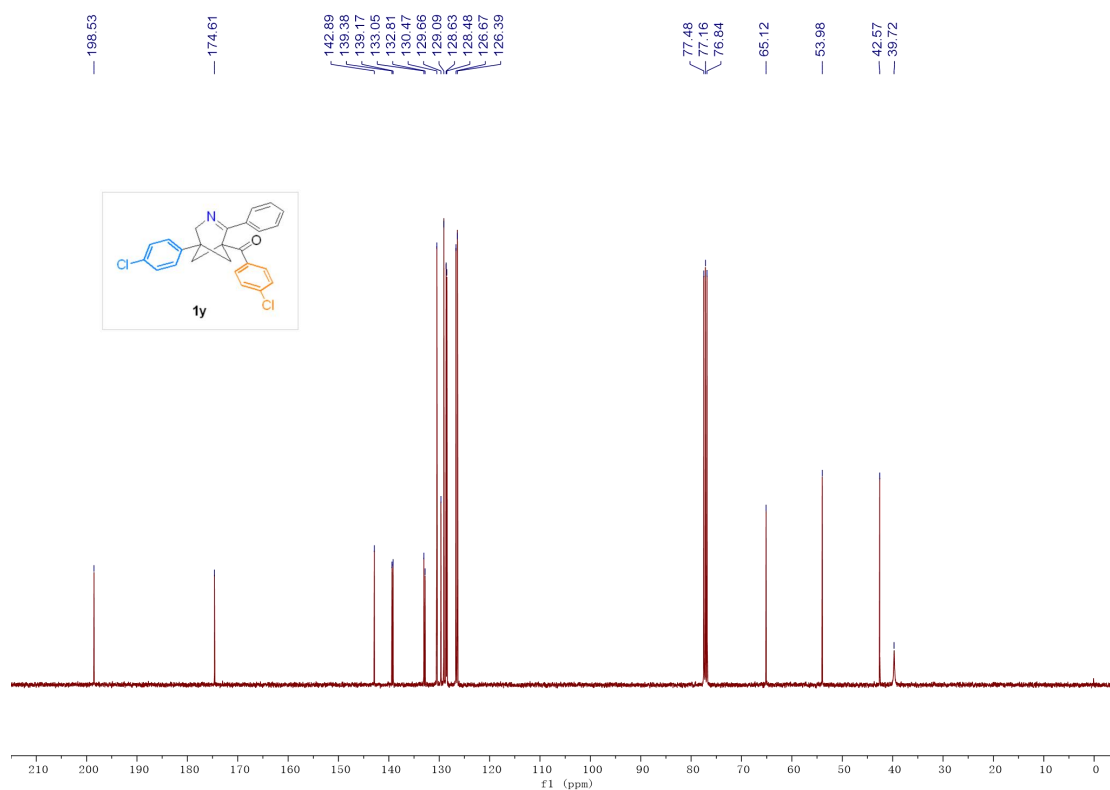




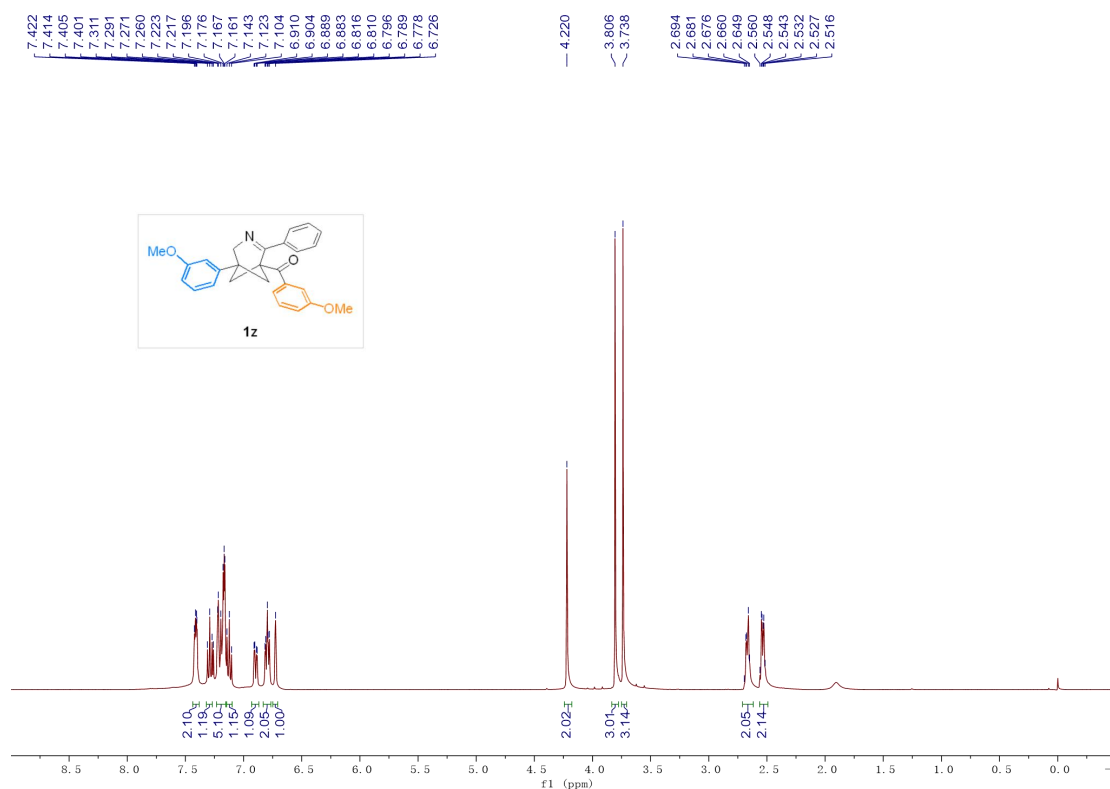
¹⁹F NMR spectrum of **1x**



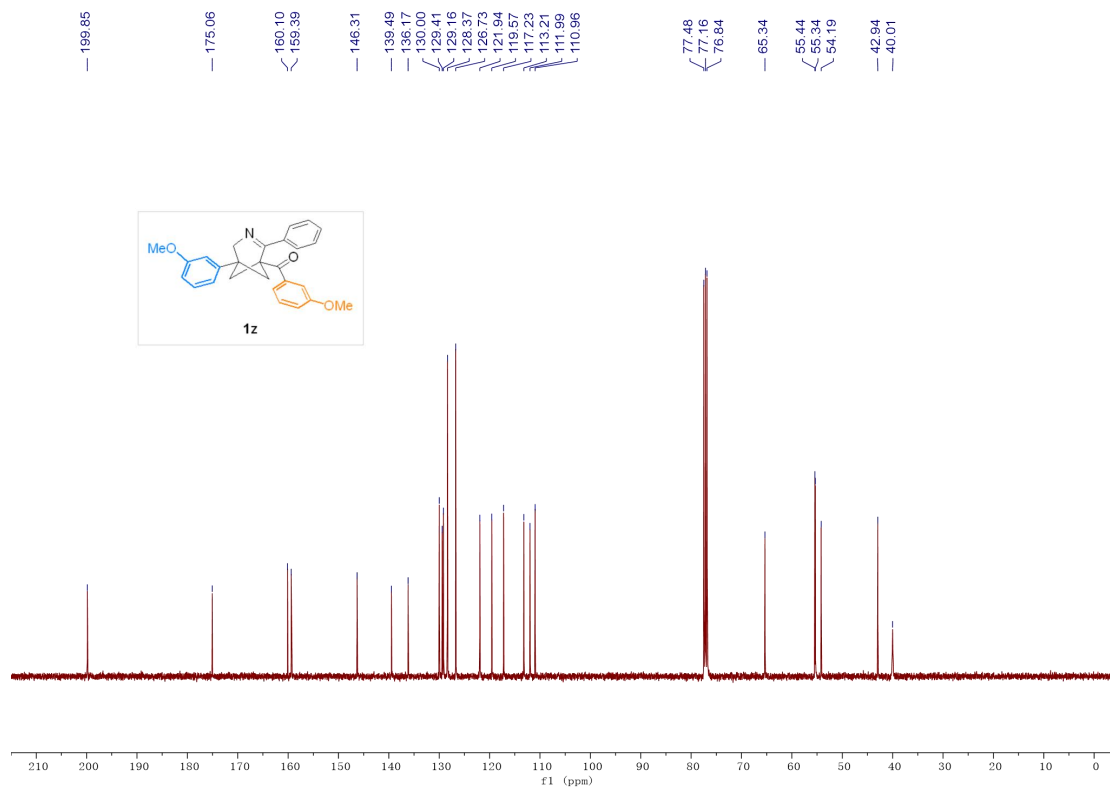
¹H NMR spectrum of **1y**



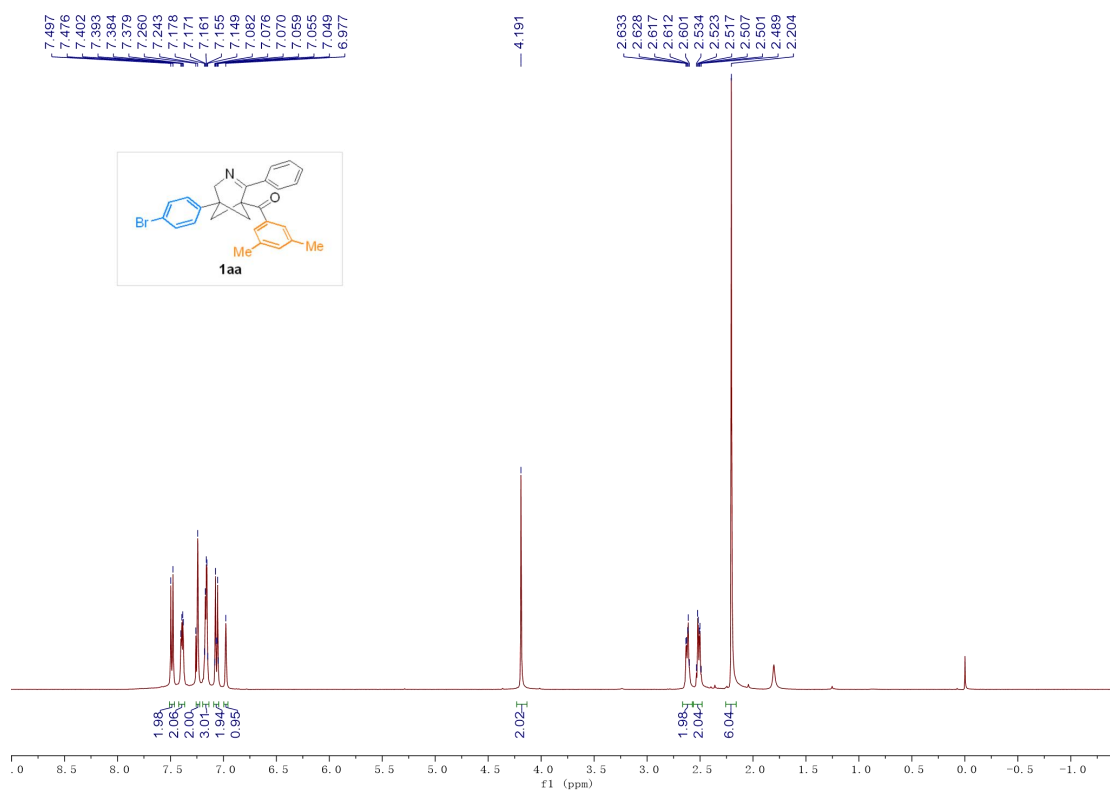
¹³C NMR spectrum of 1y



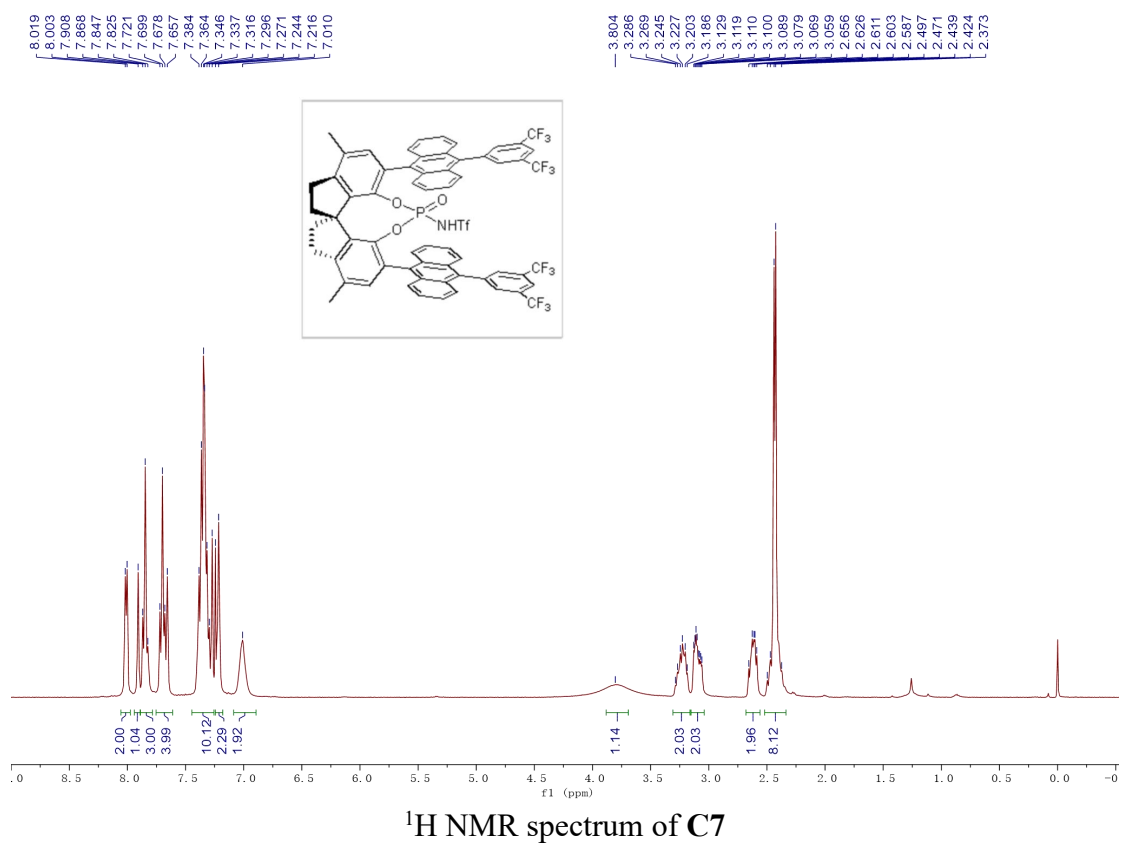
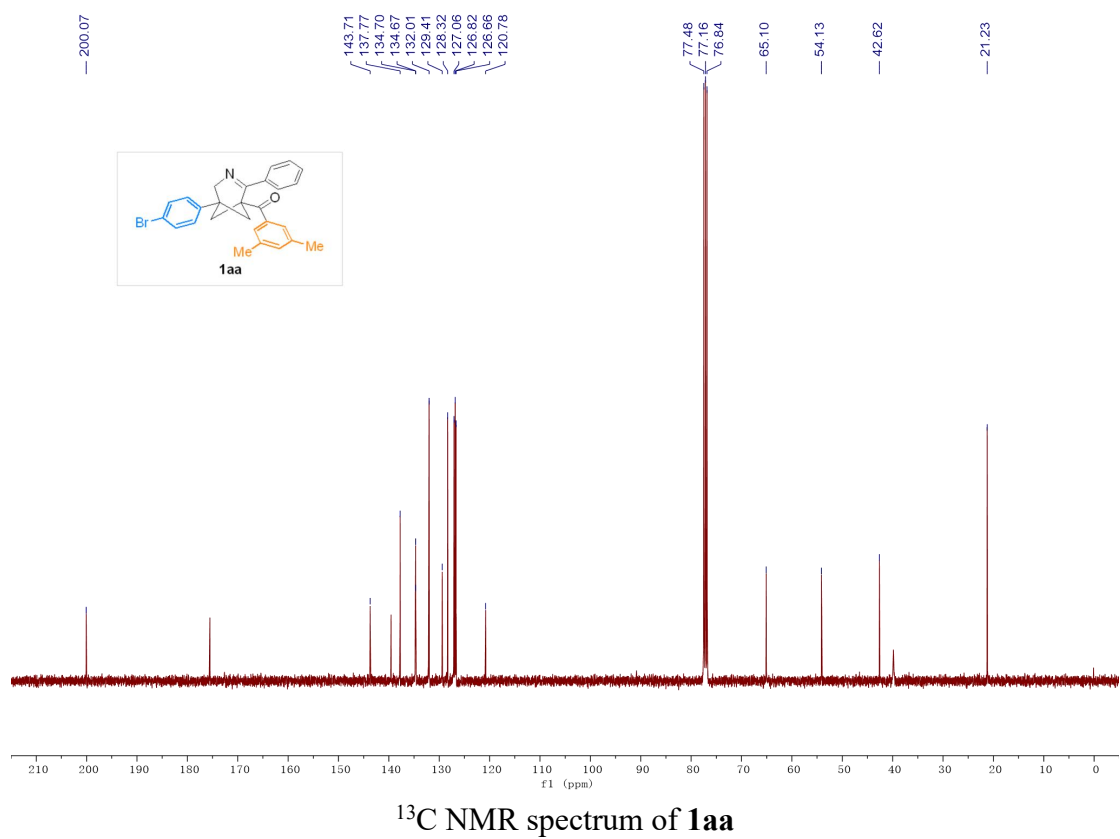
¹H NMR spectrum of 1z

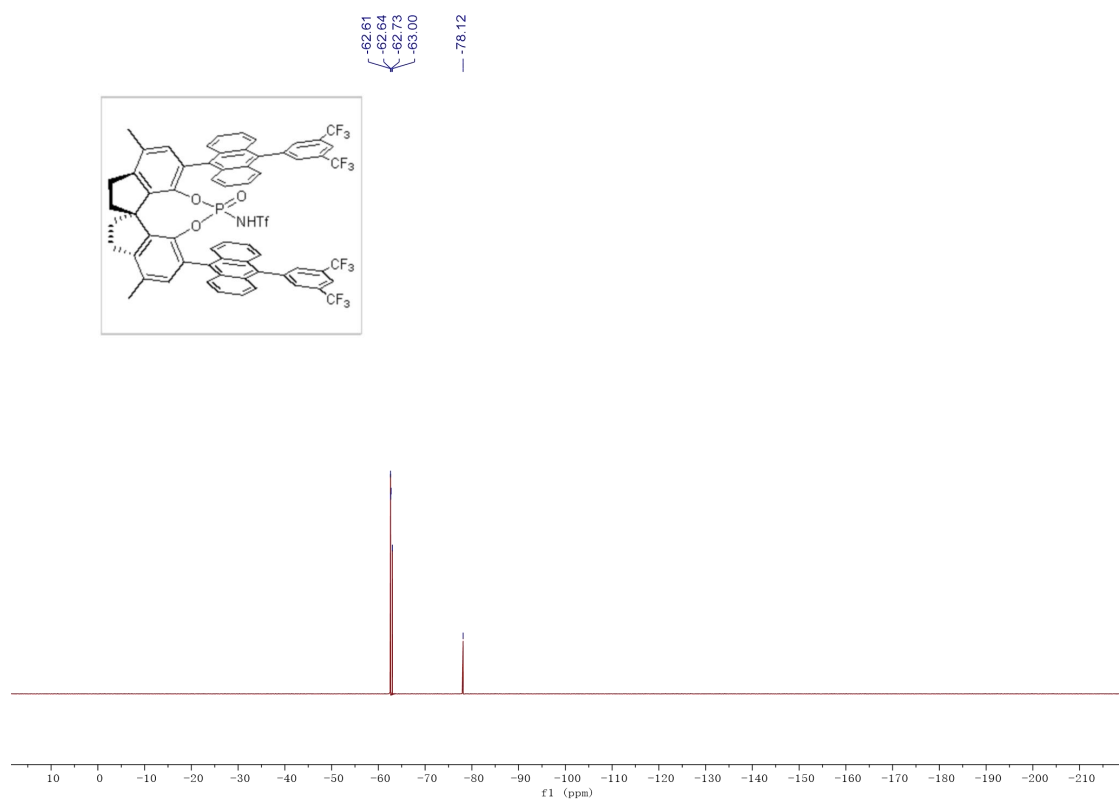
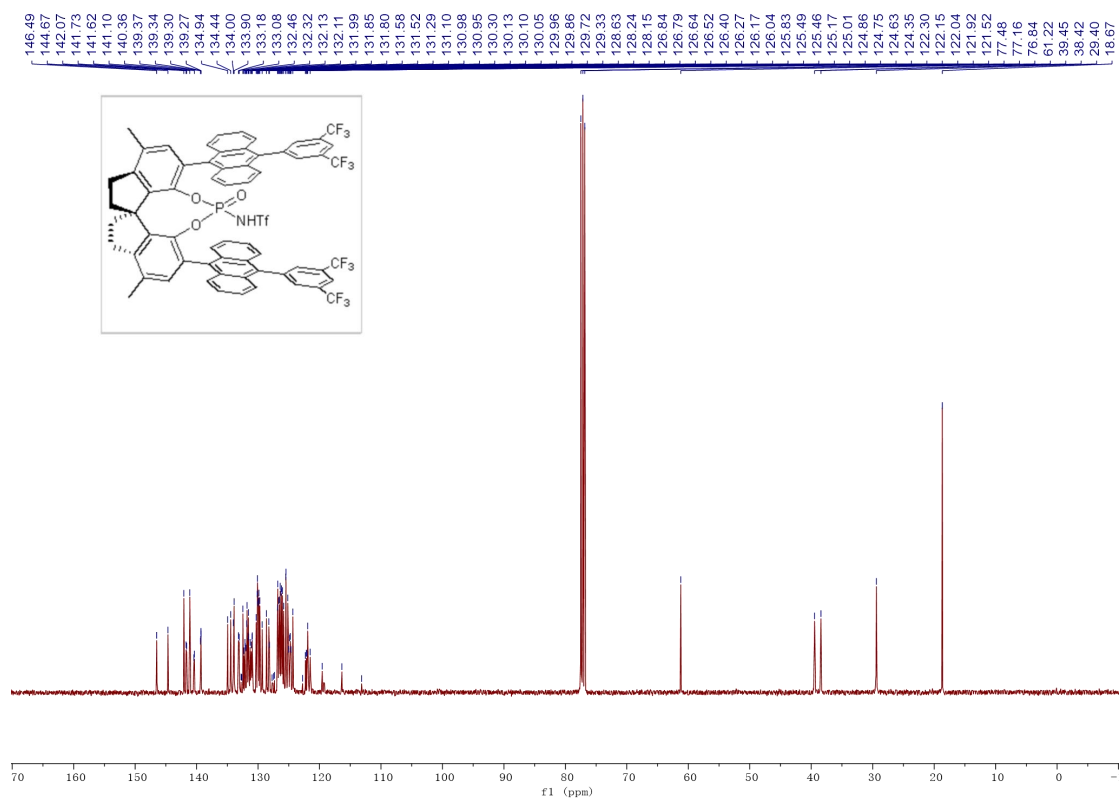


¹³C NMR spectrum of **1z**

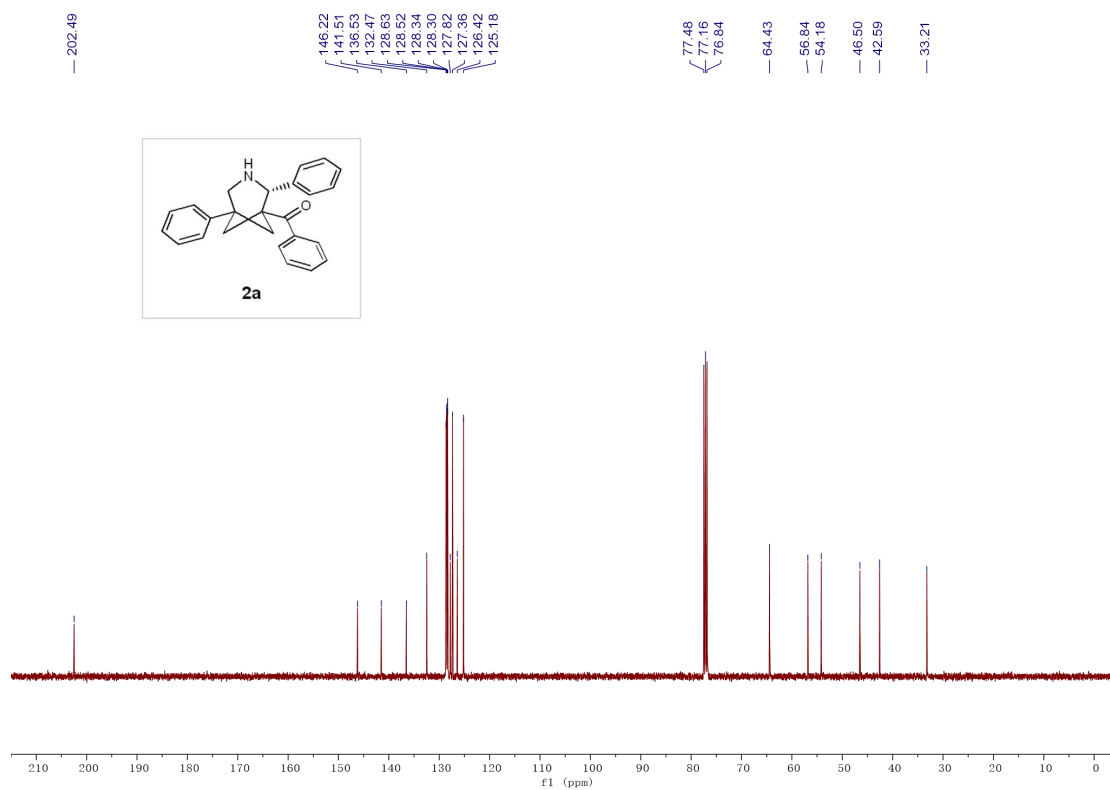


¹H NMR spectrum of **1aa**

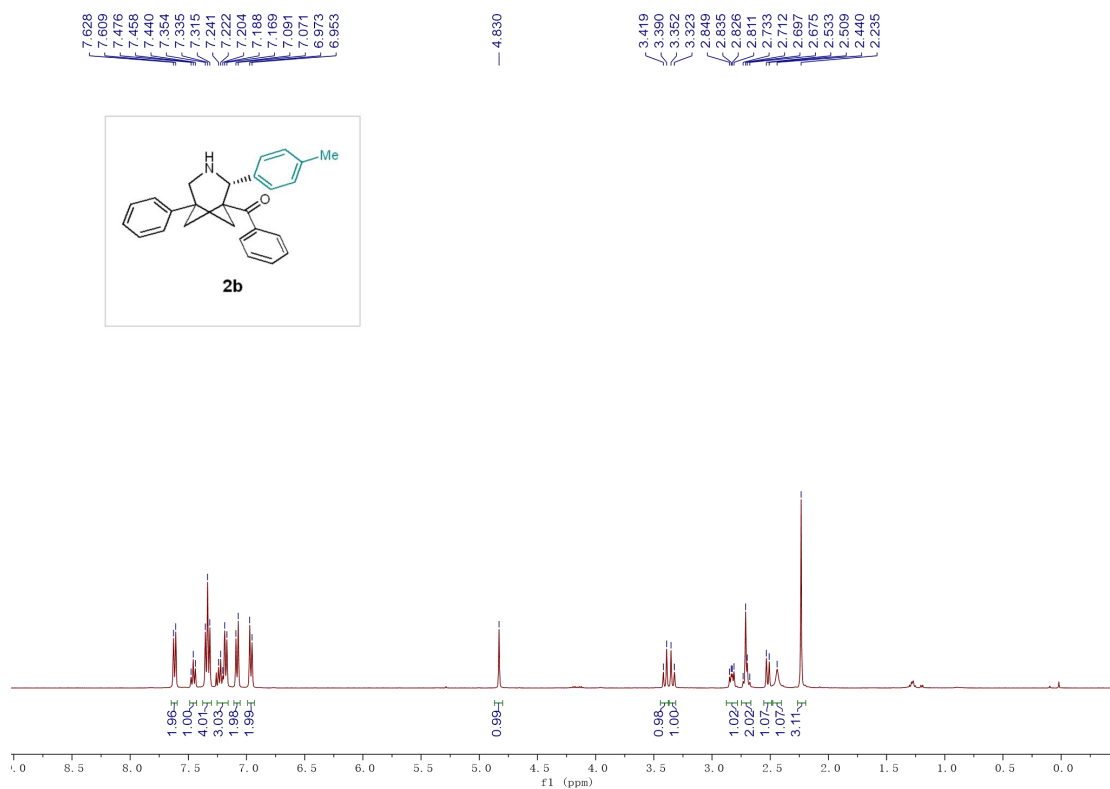




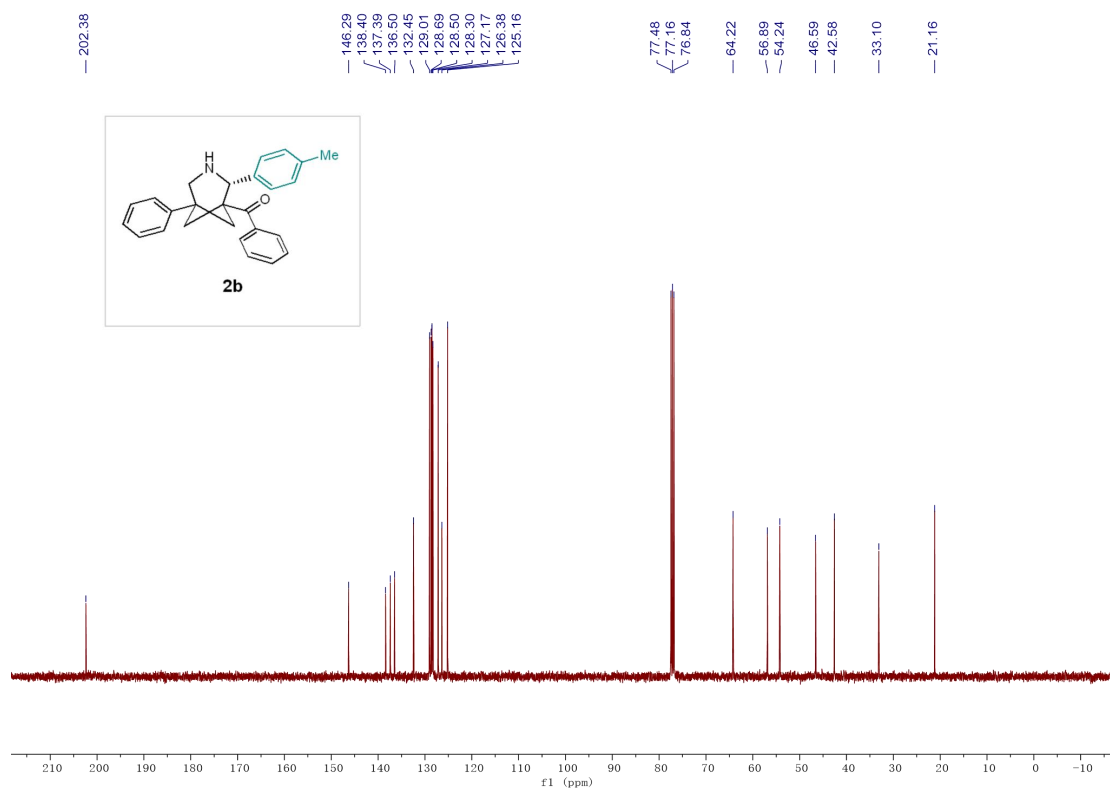




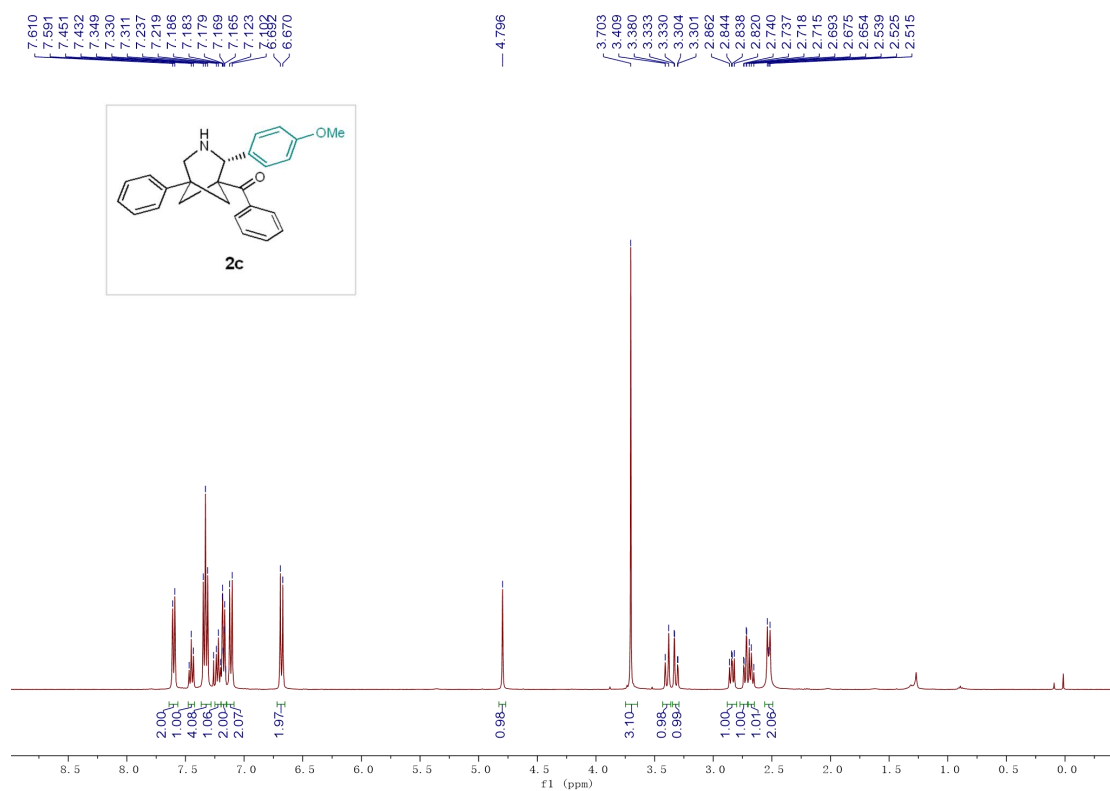
¹³C NMR spectrum of **2a**



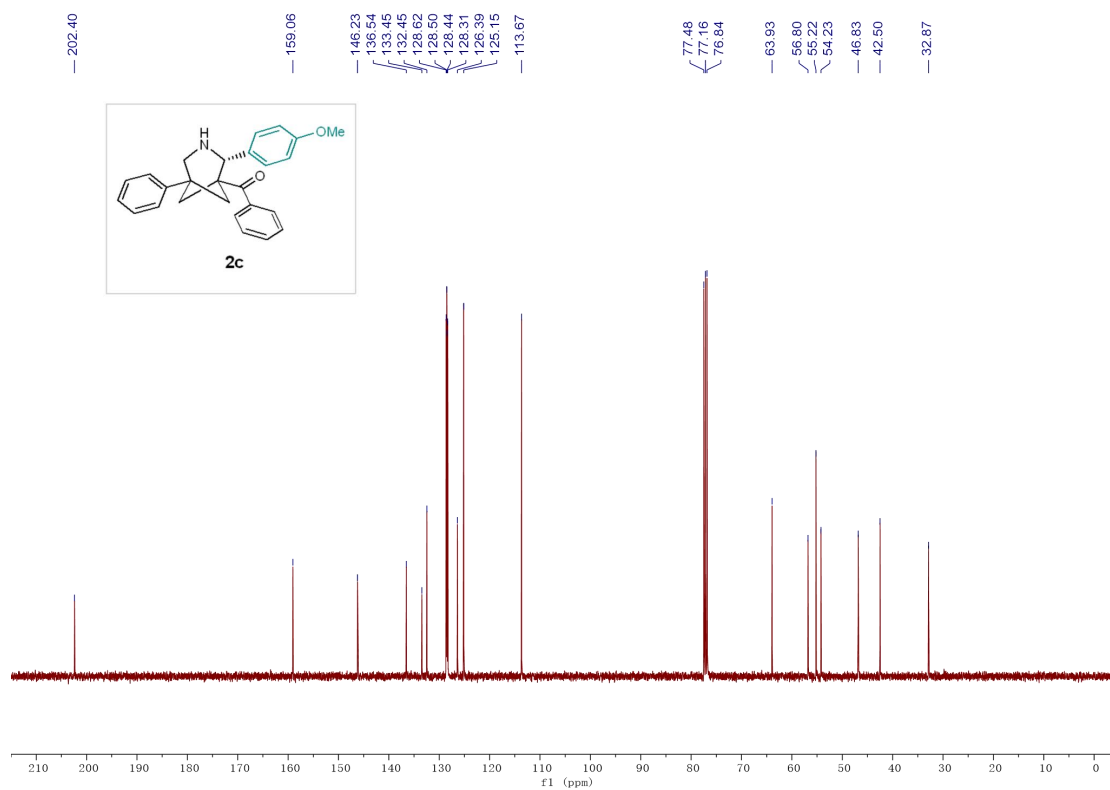
¹H NMR spectrum of **2b**



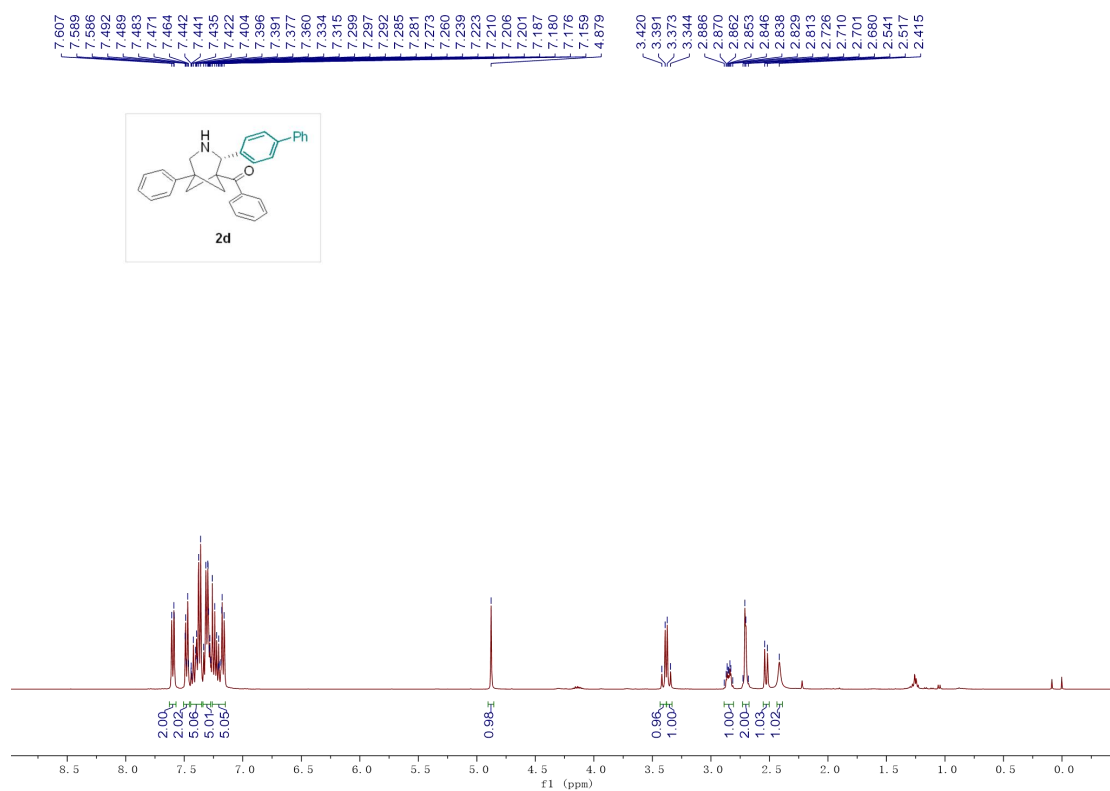
¹³C NMR spectrum of **2b**



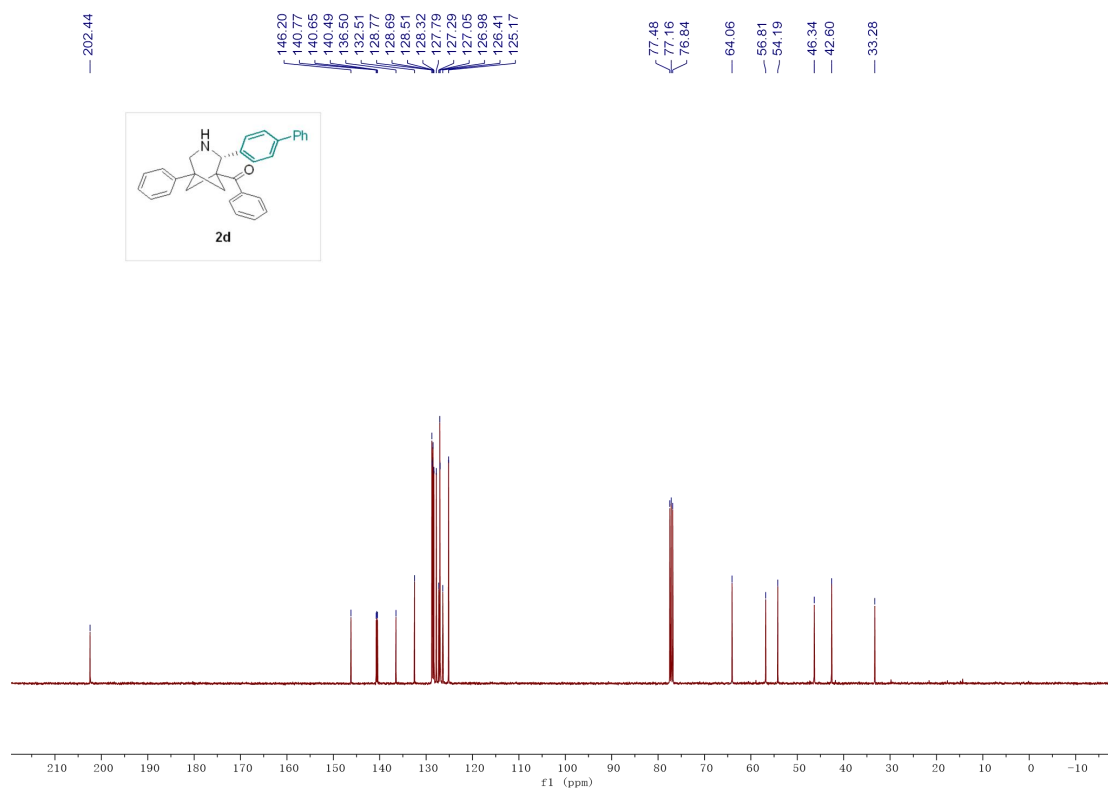
¹H NMR spectrum of **2c**



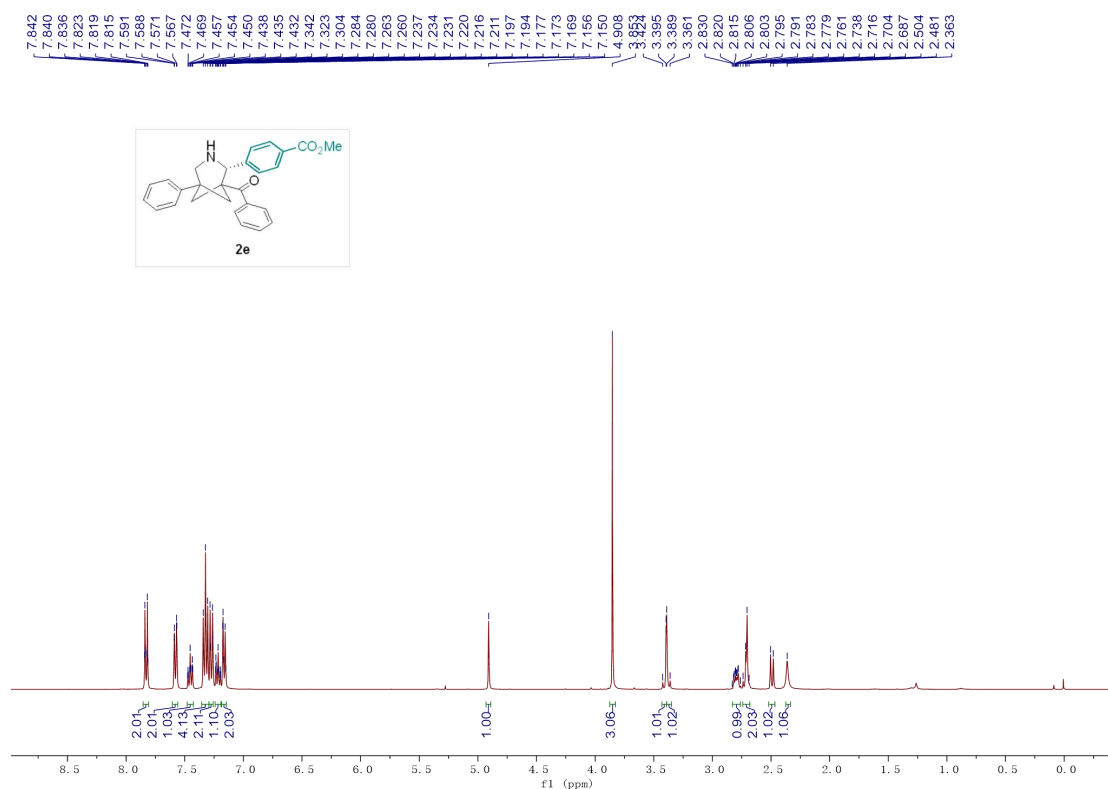
¹³C NMR spectrum of **2c**



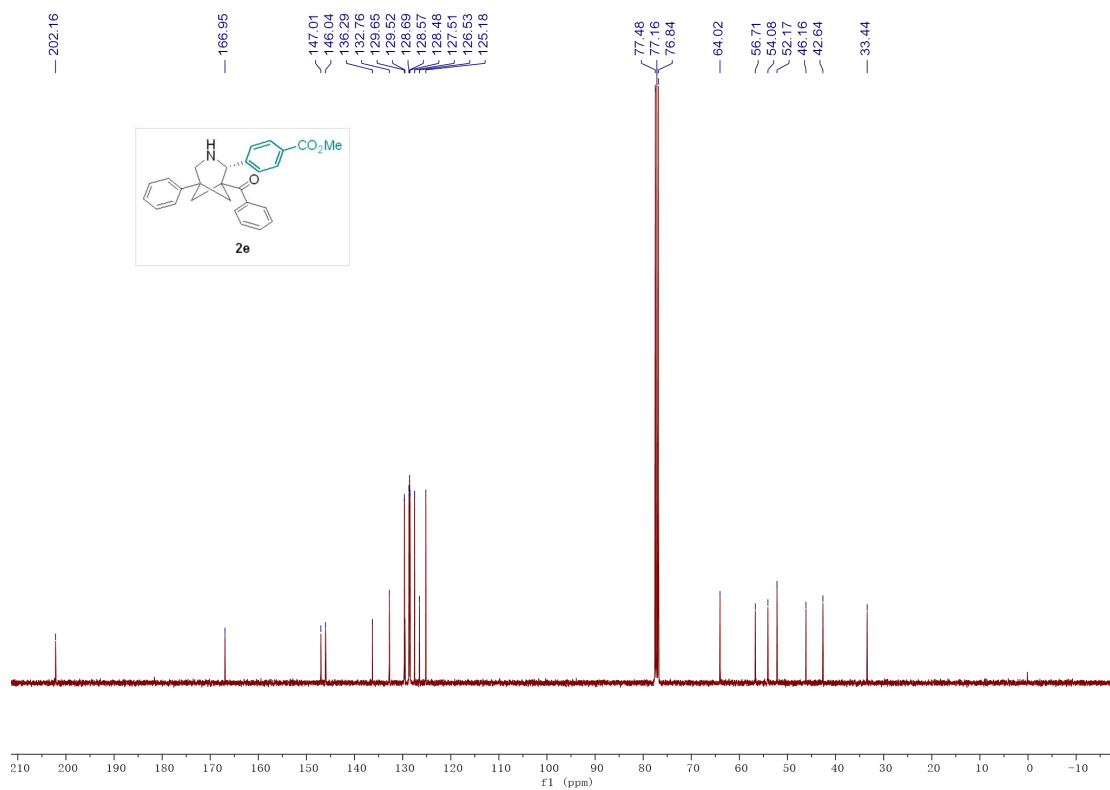
¹H NMR spectrum of **2d**



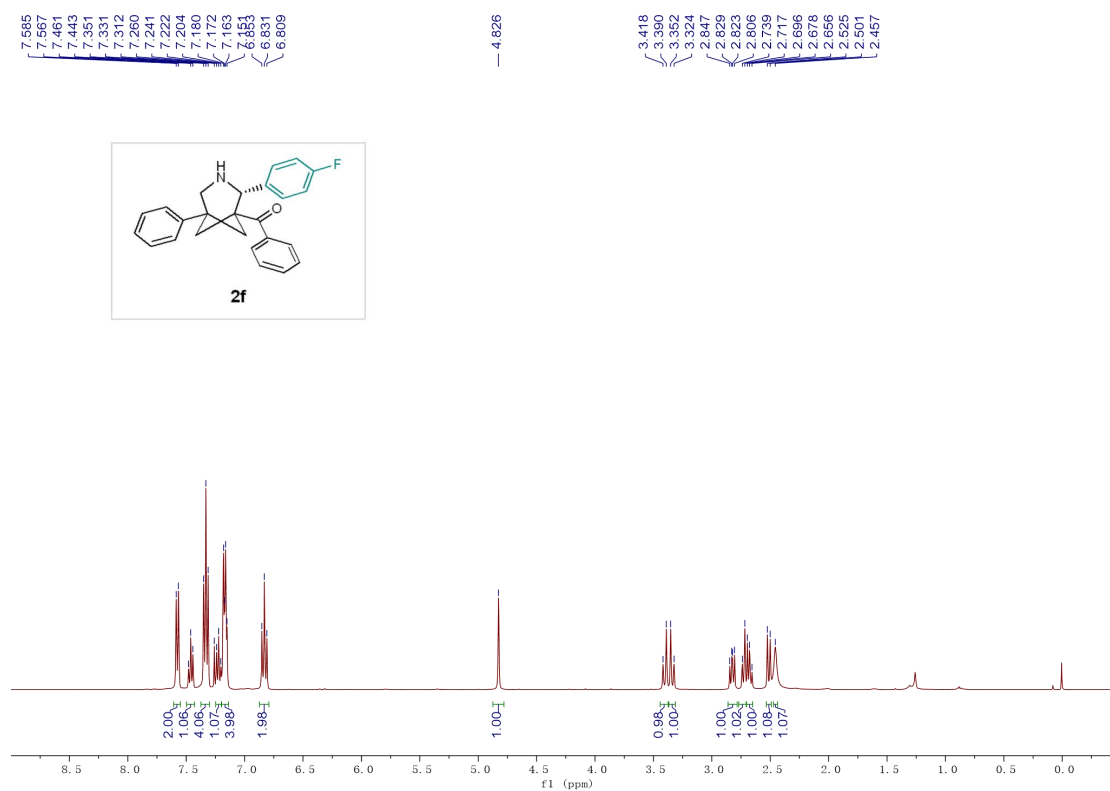
¹³C NMR spectrum of **2d**



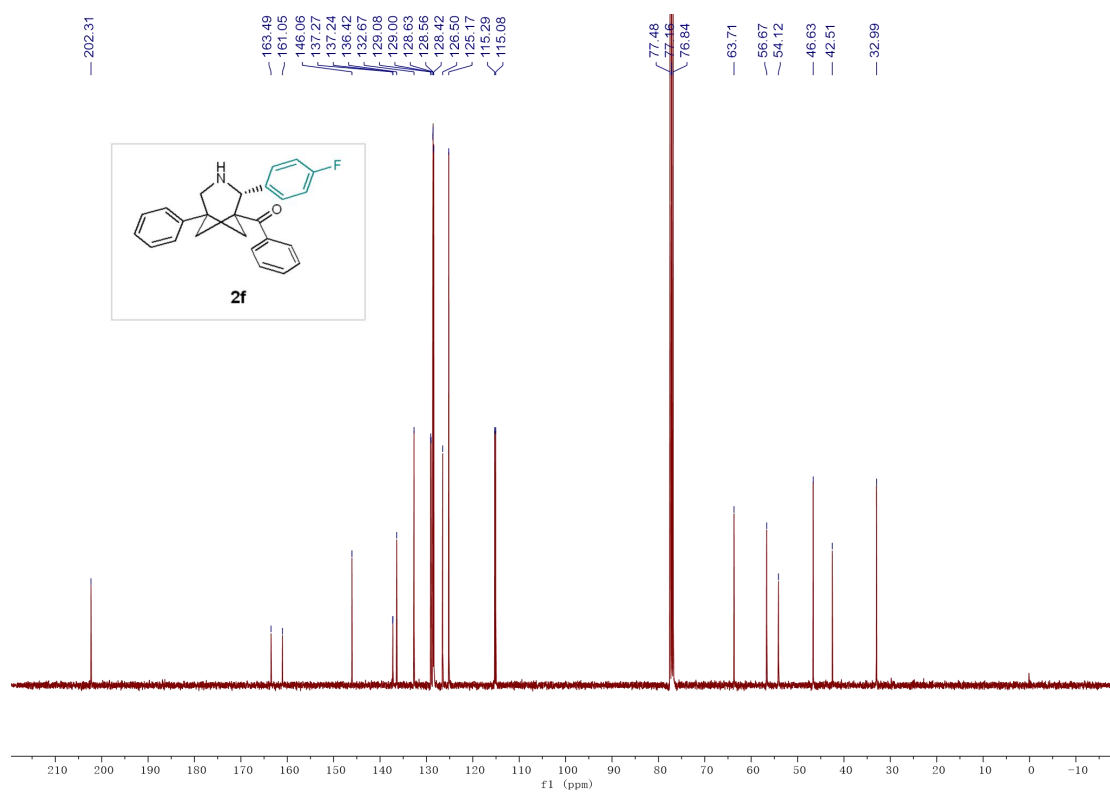
¹H NMR spectrum of **2e**



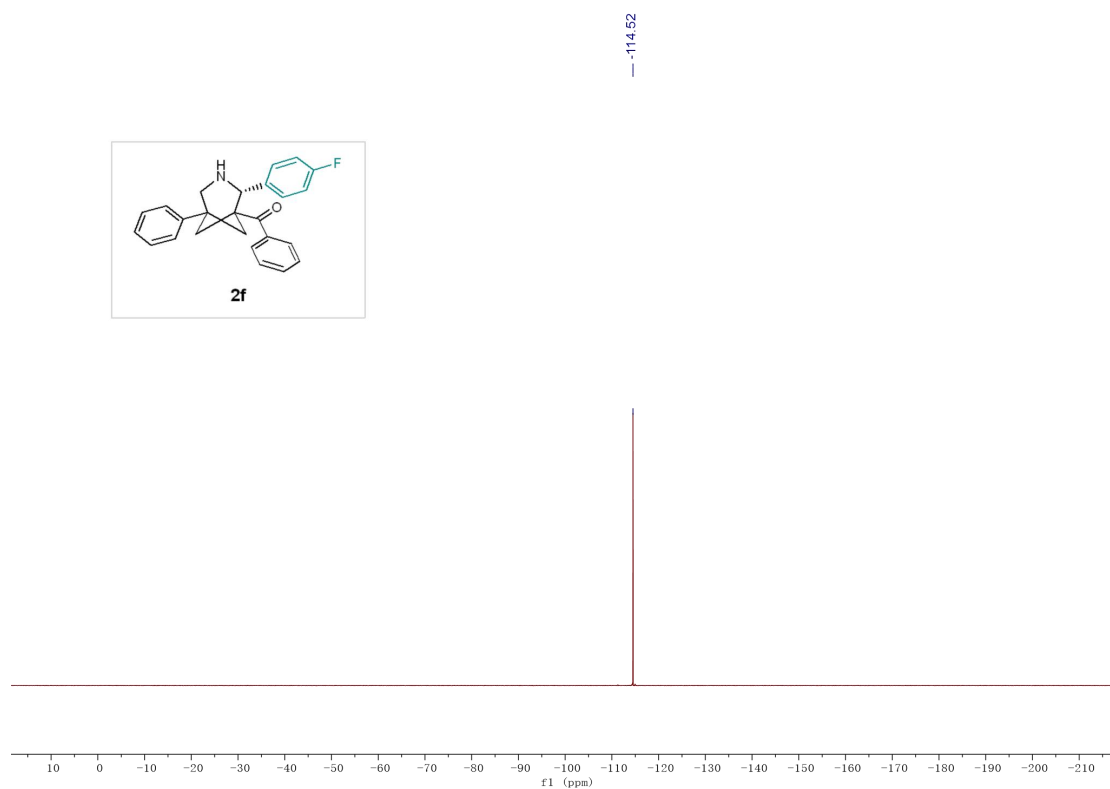
¹³C NMR spectrum of **2e**



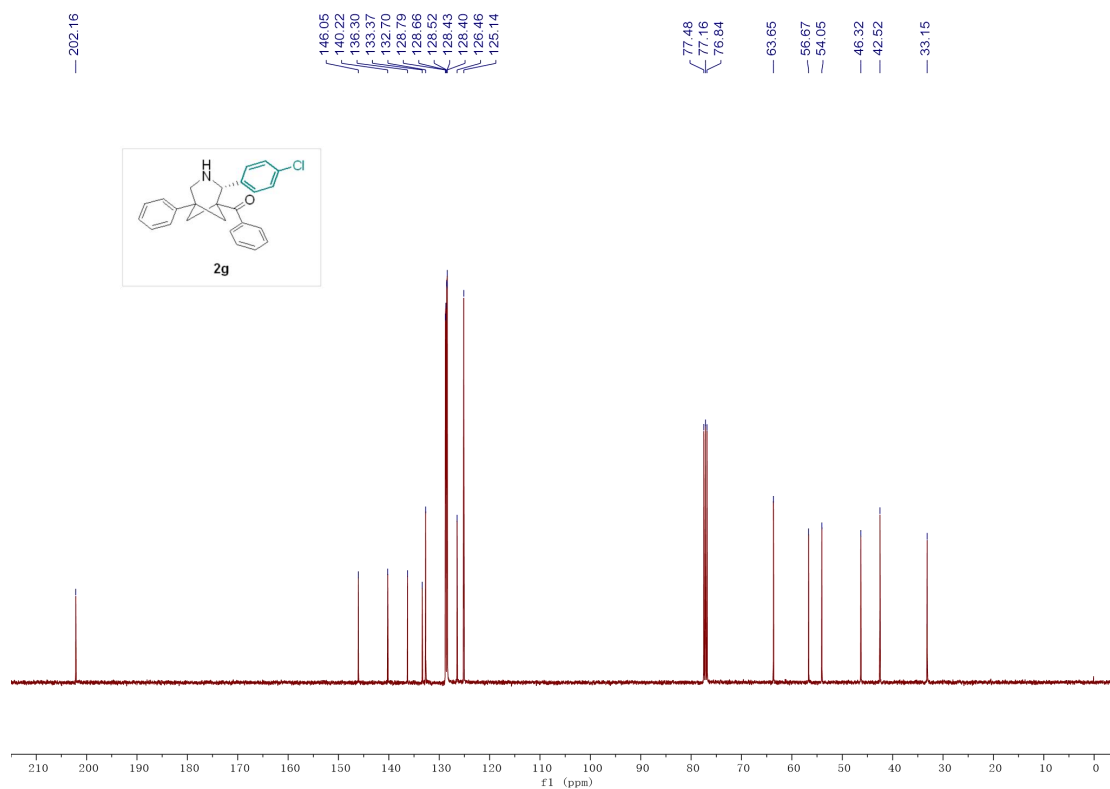
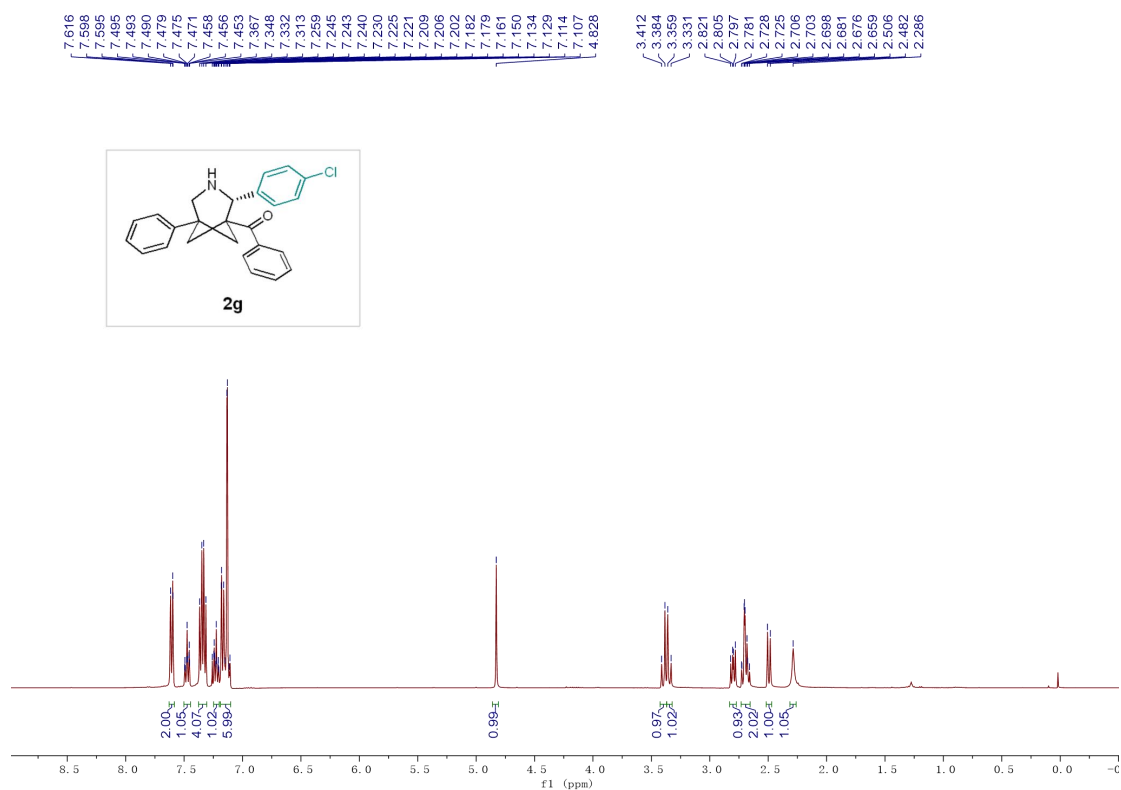
¹H NMR spectrum of **2f**

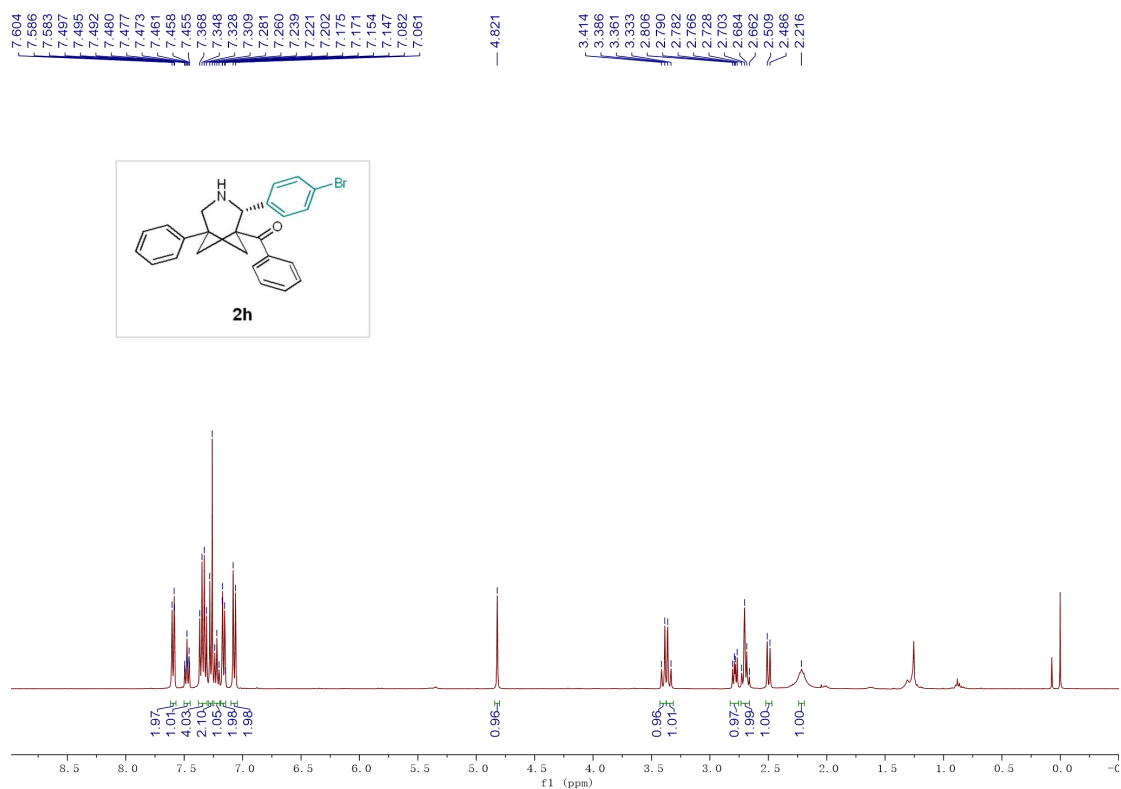


¹³C NMR spectrum of **2f**

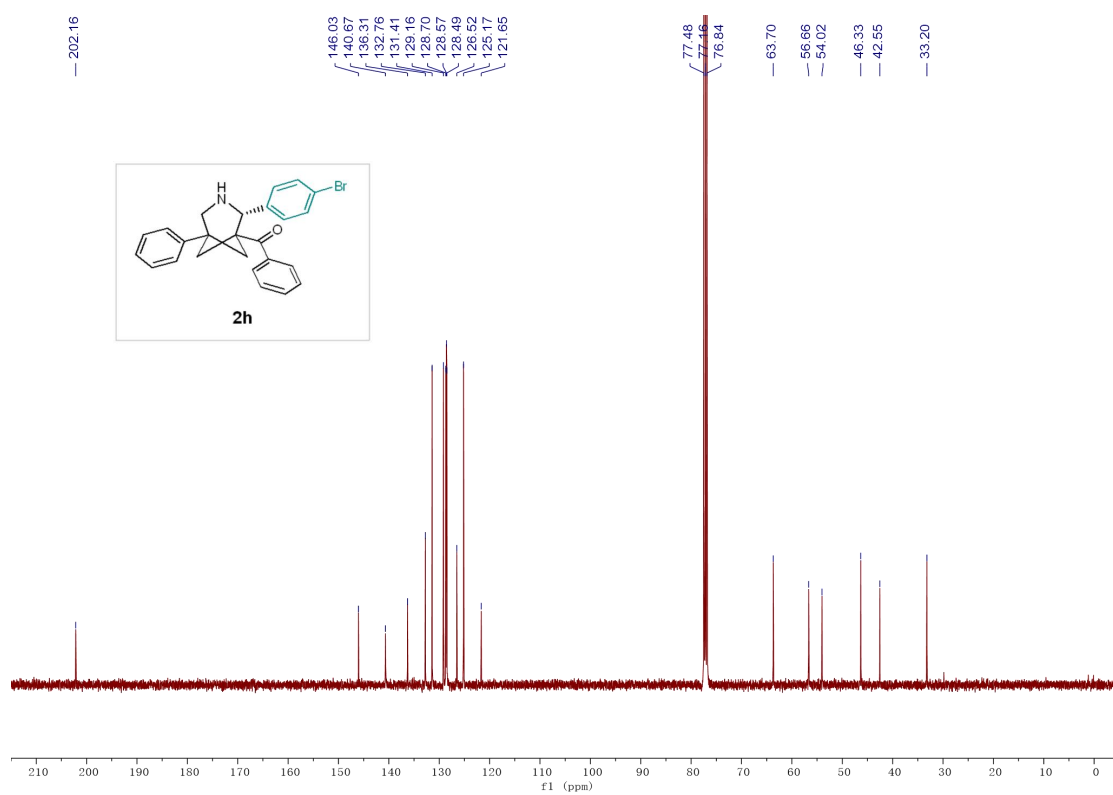


¹⁹F NMR spectrum of **2f**

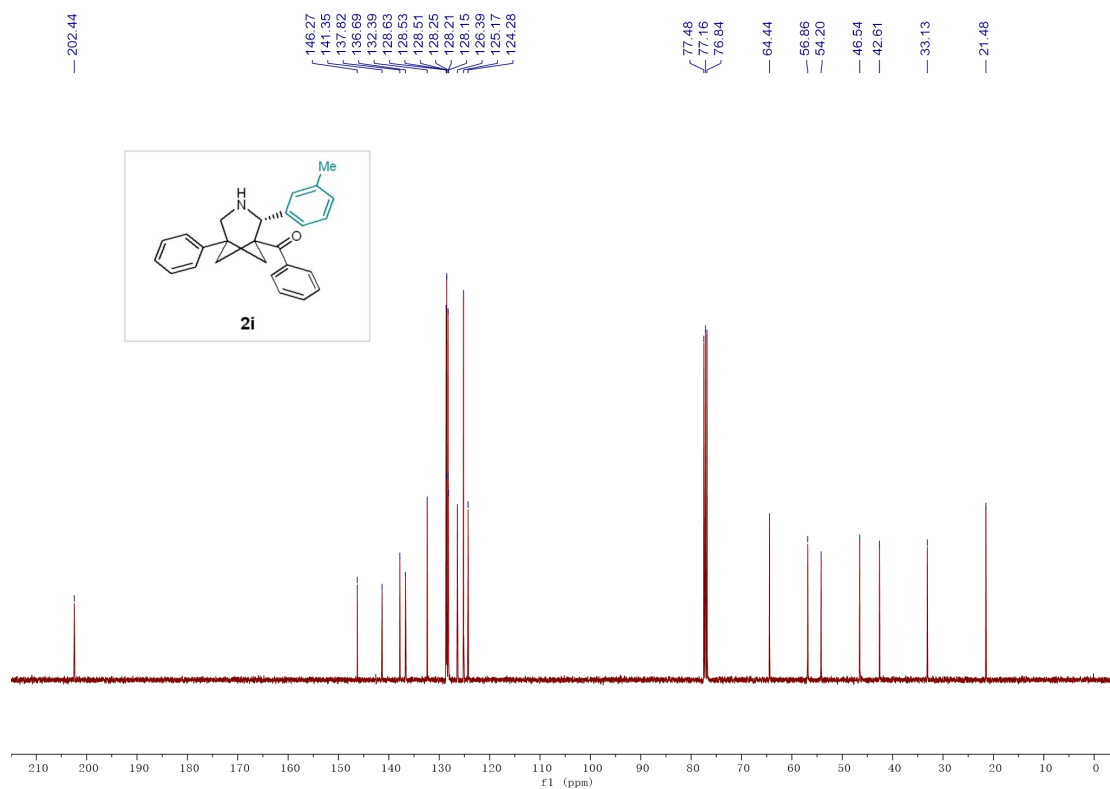
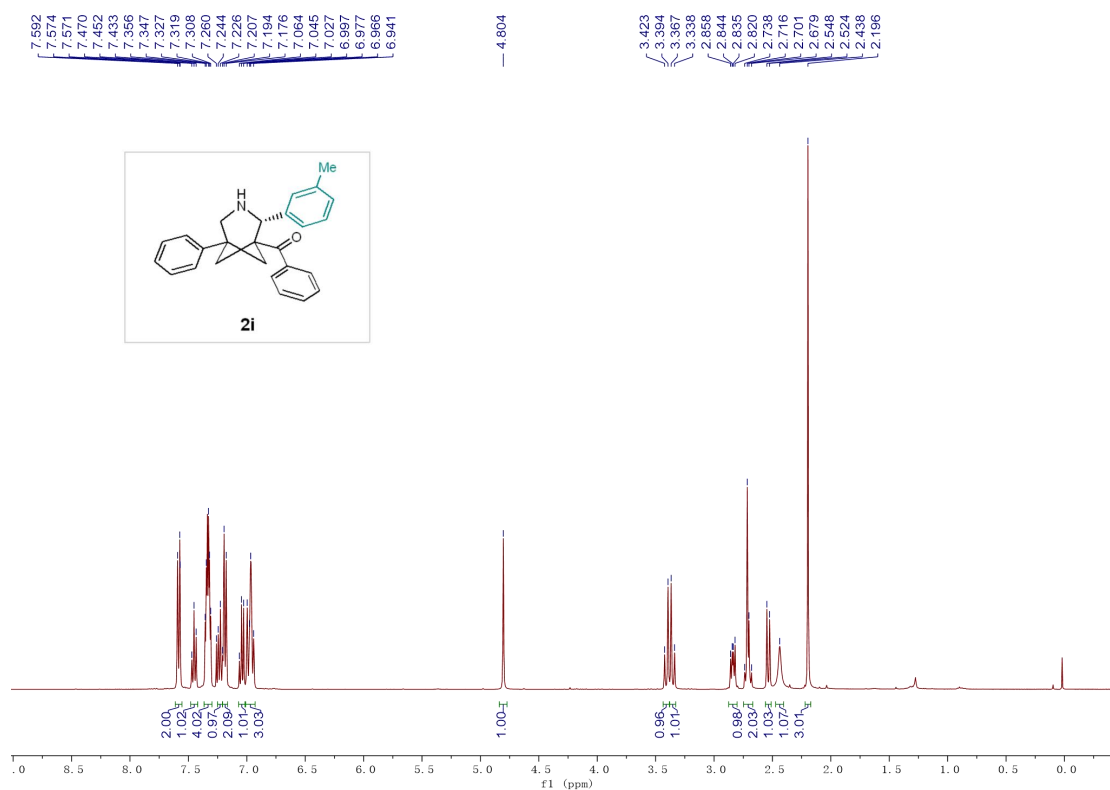


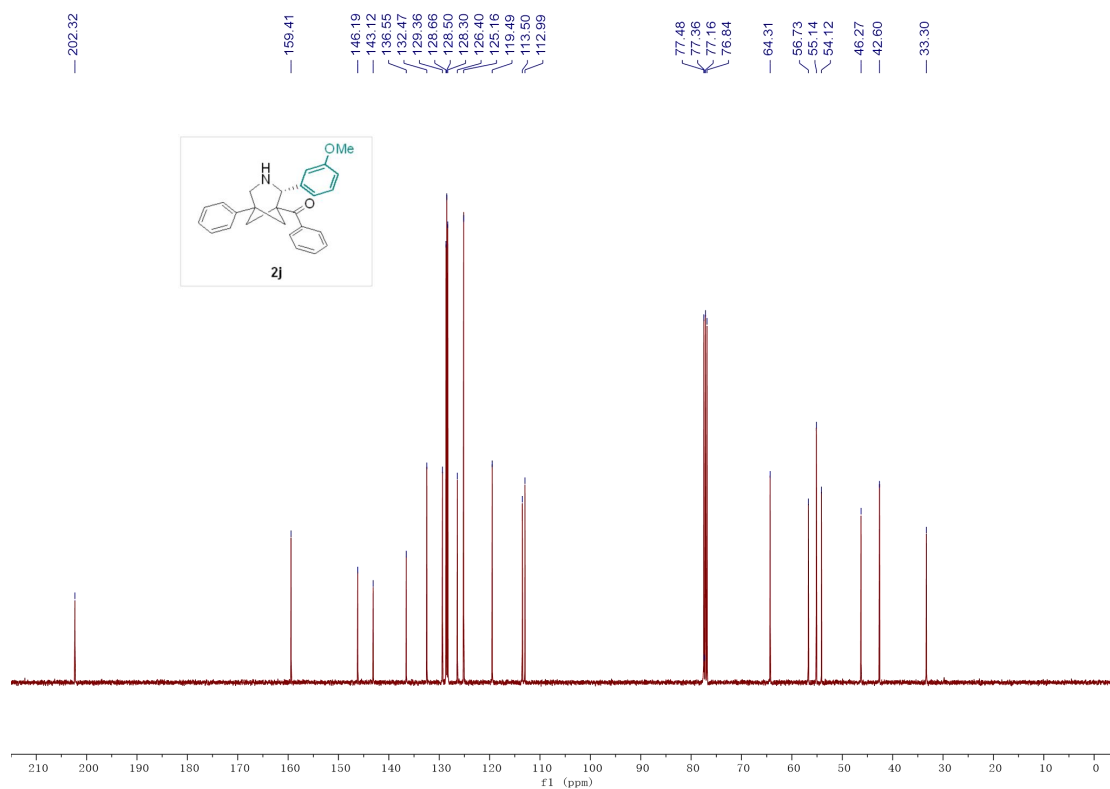
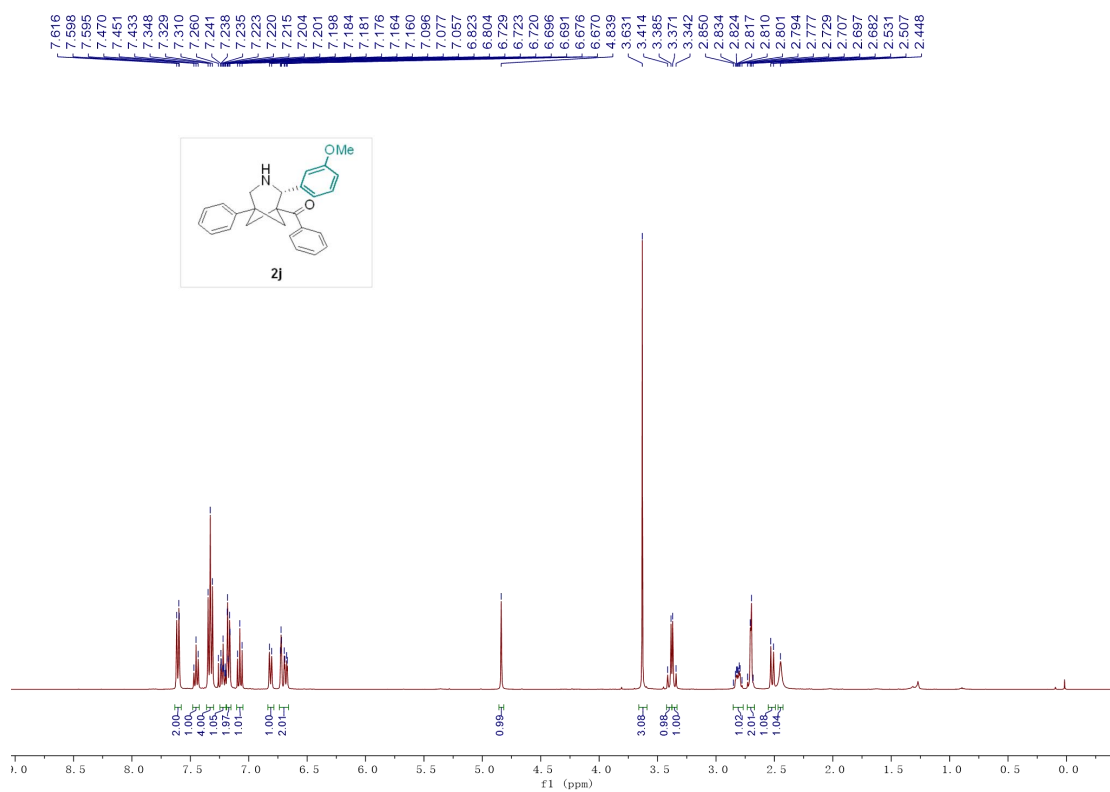


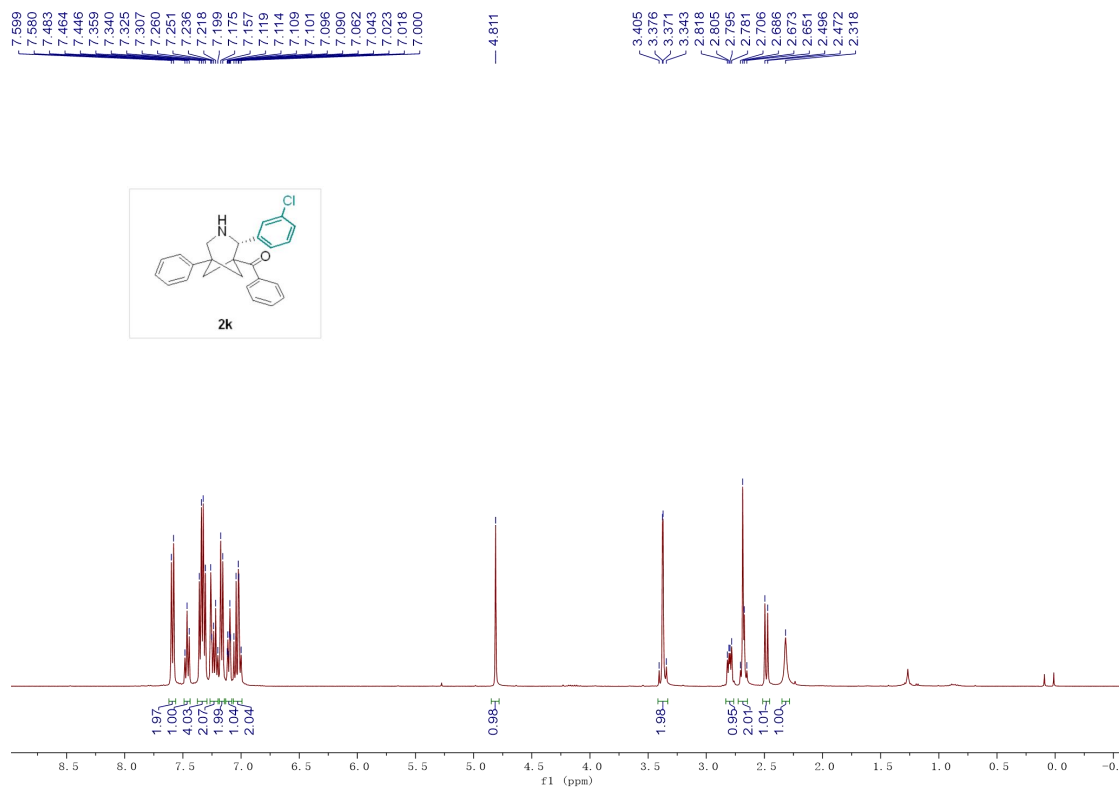
¹H NMR spectrum of 2h



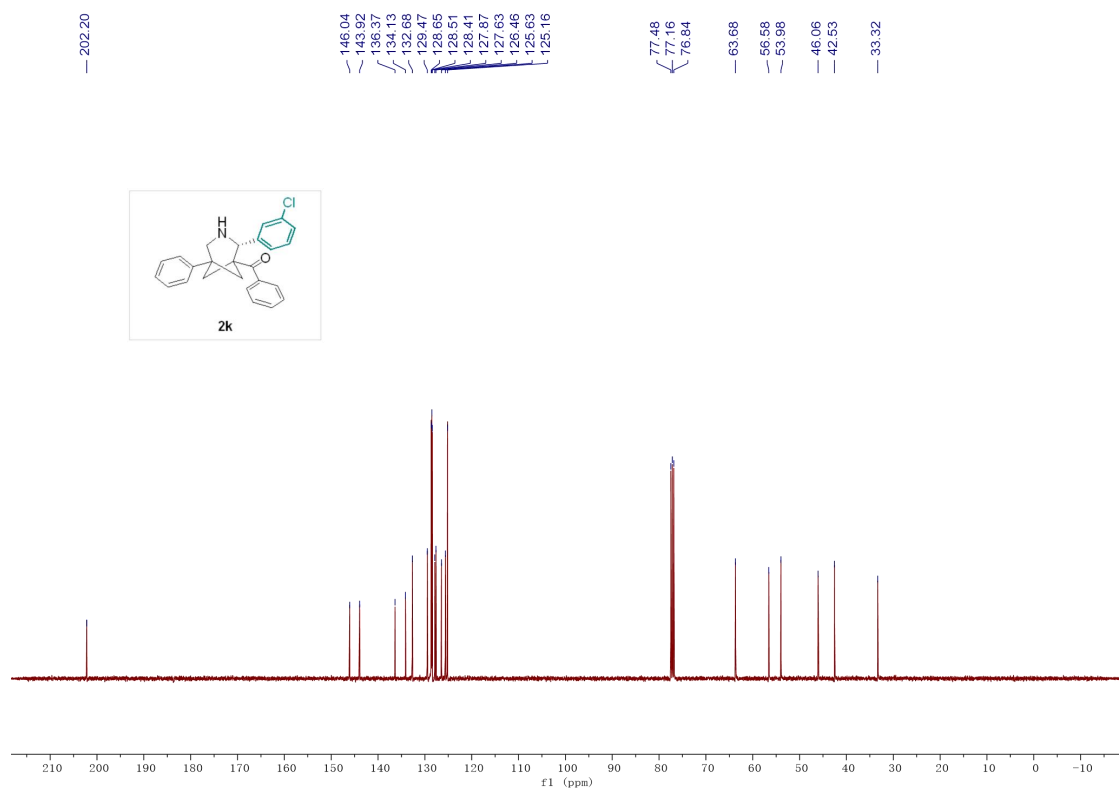
¹³C NMR spectrum of 2h



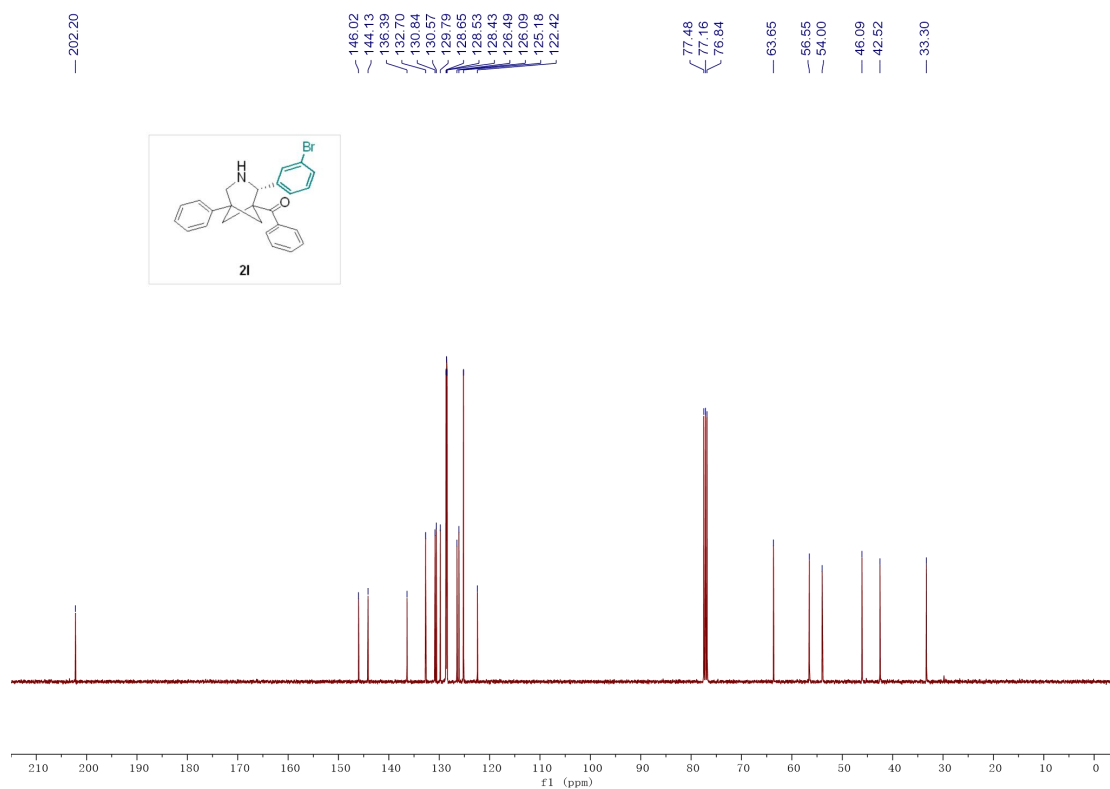
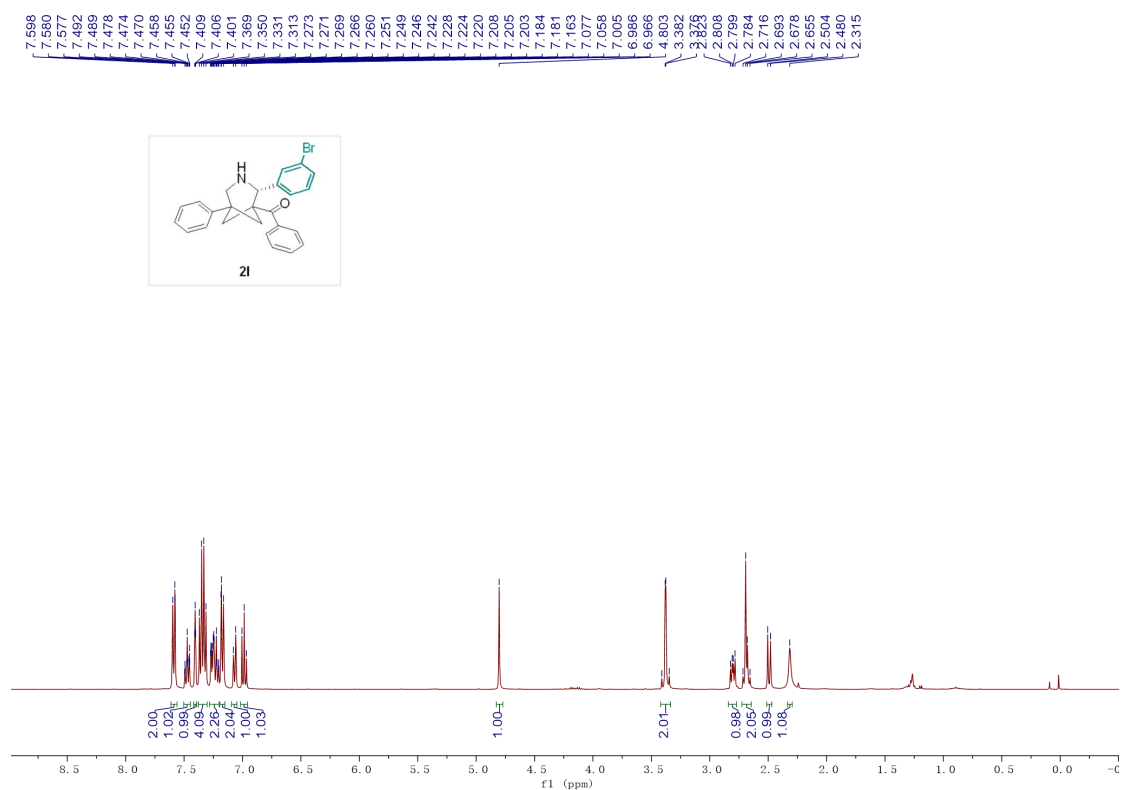


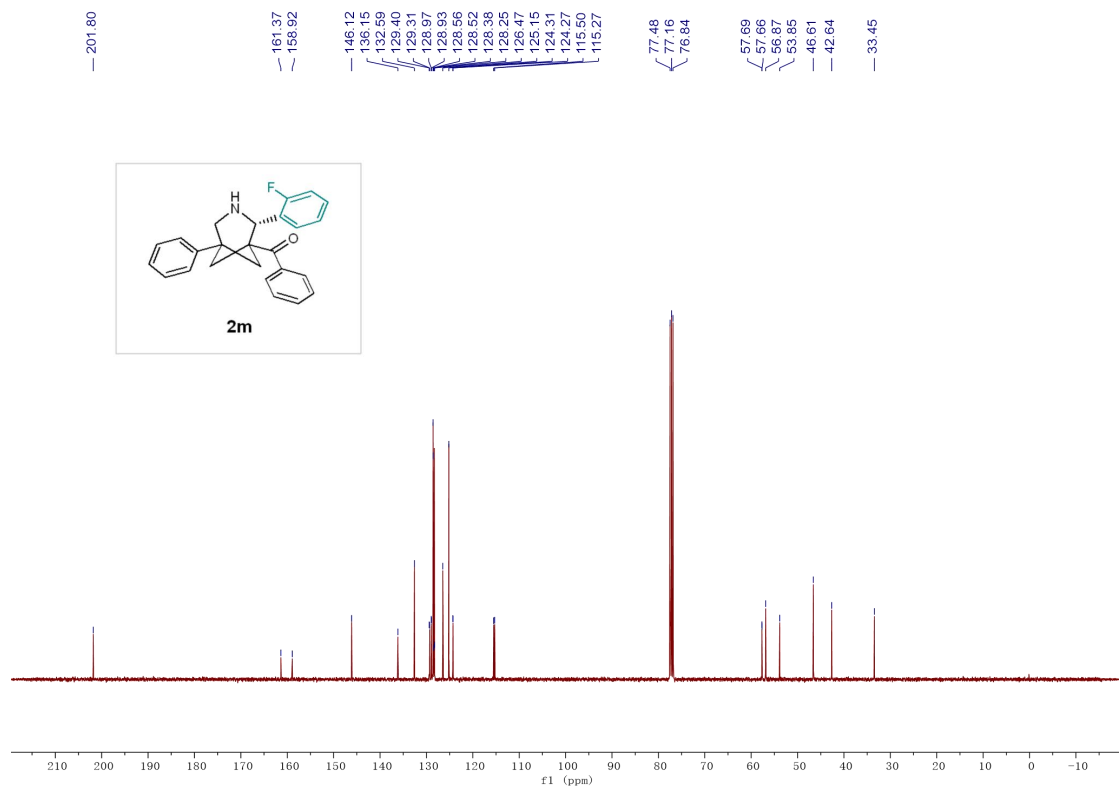
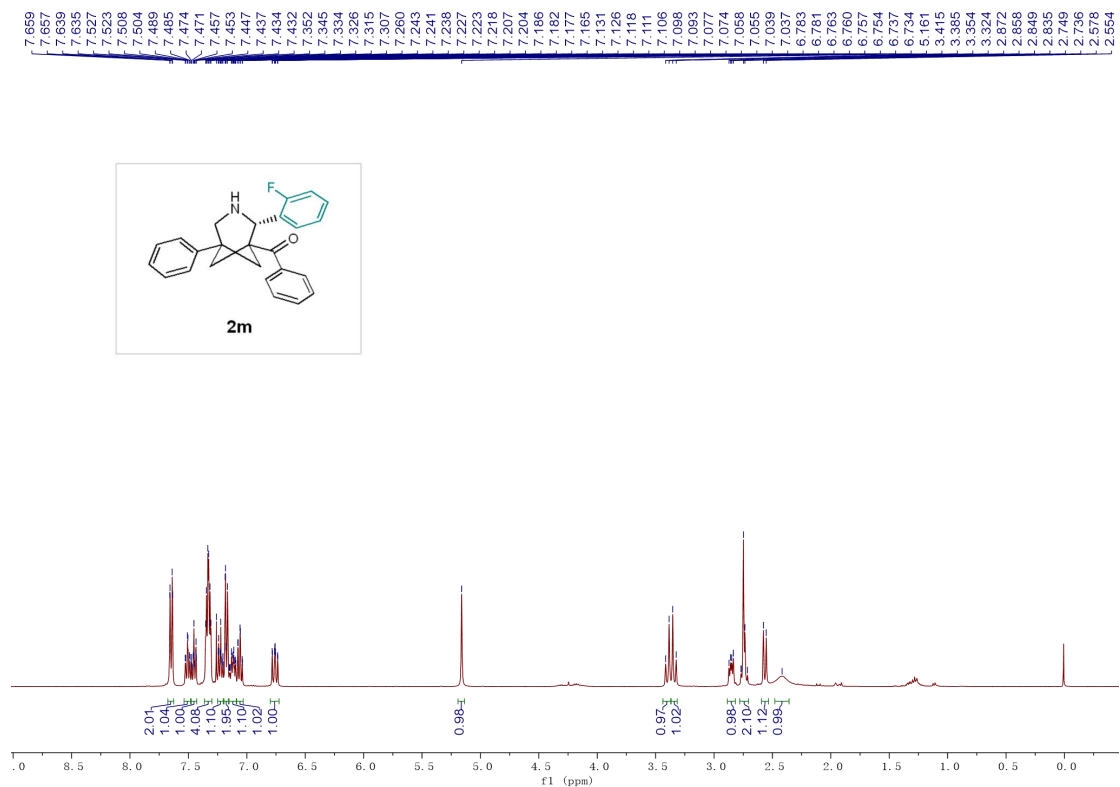


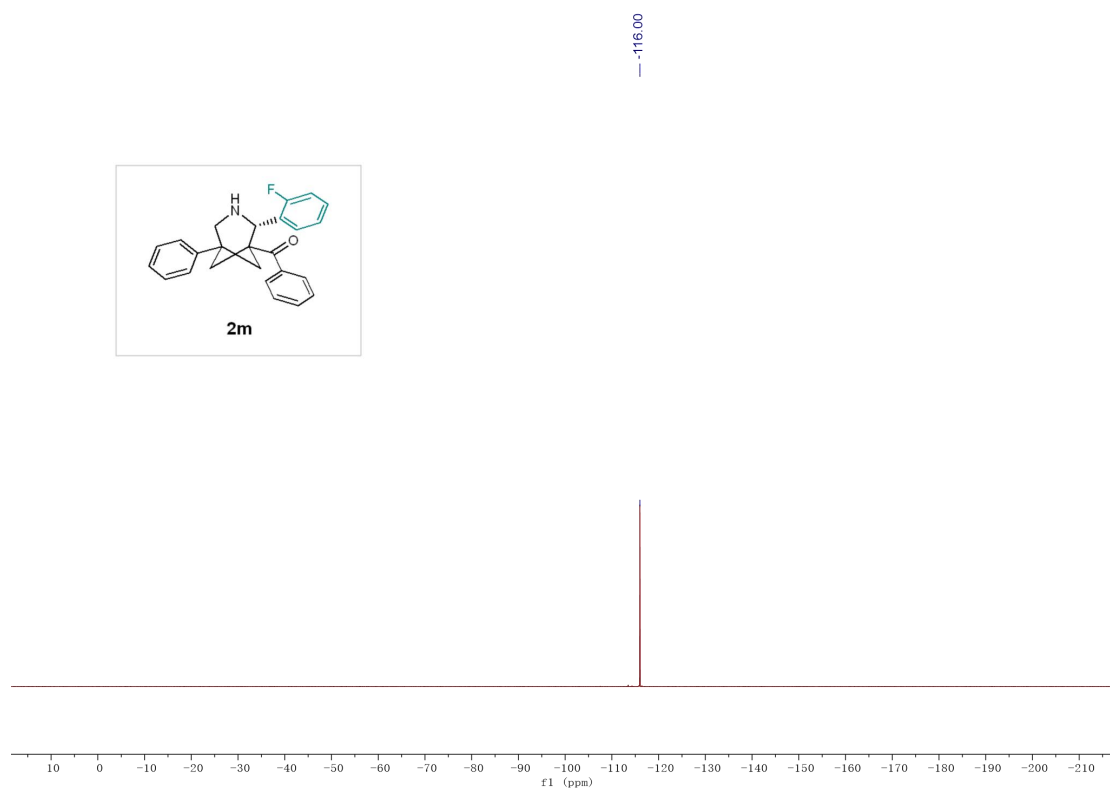
¹H NMR spectrum of **2k**



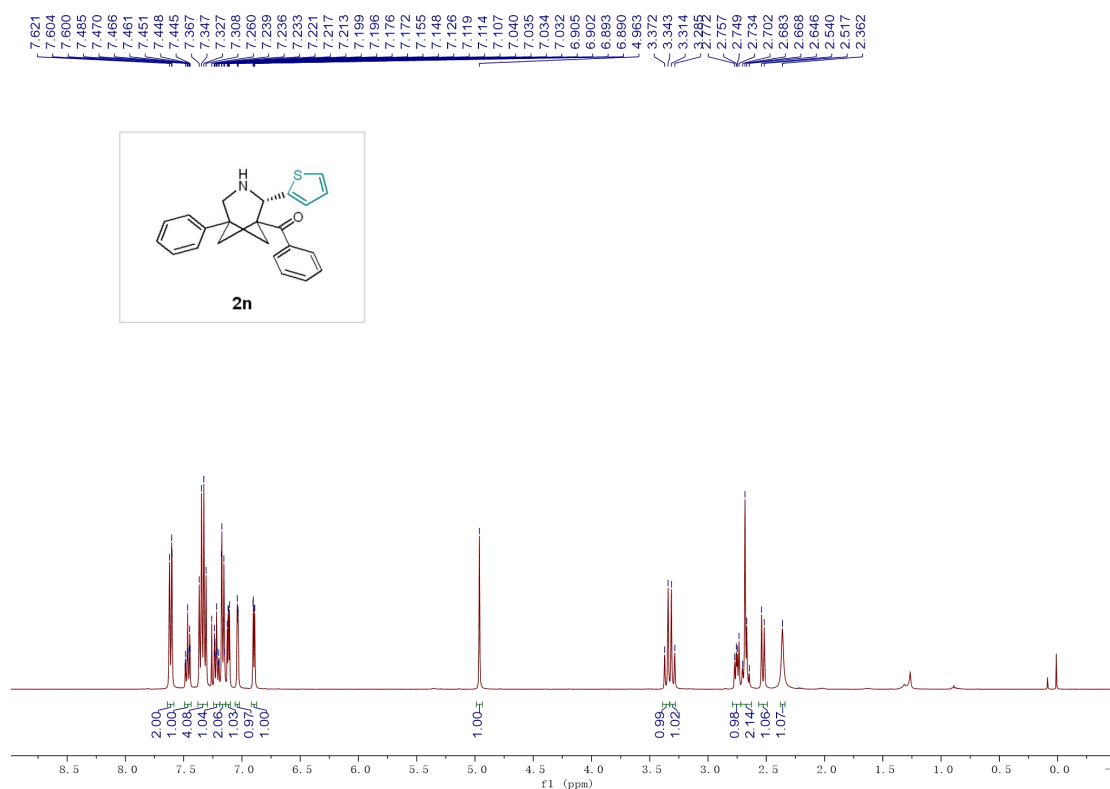
¹³C NMR spectrum of **2k**



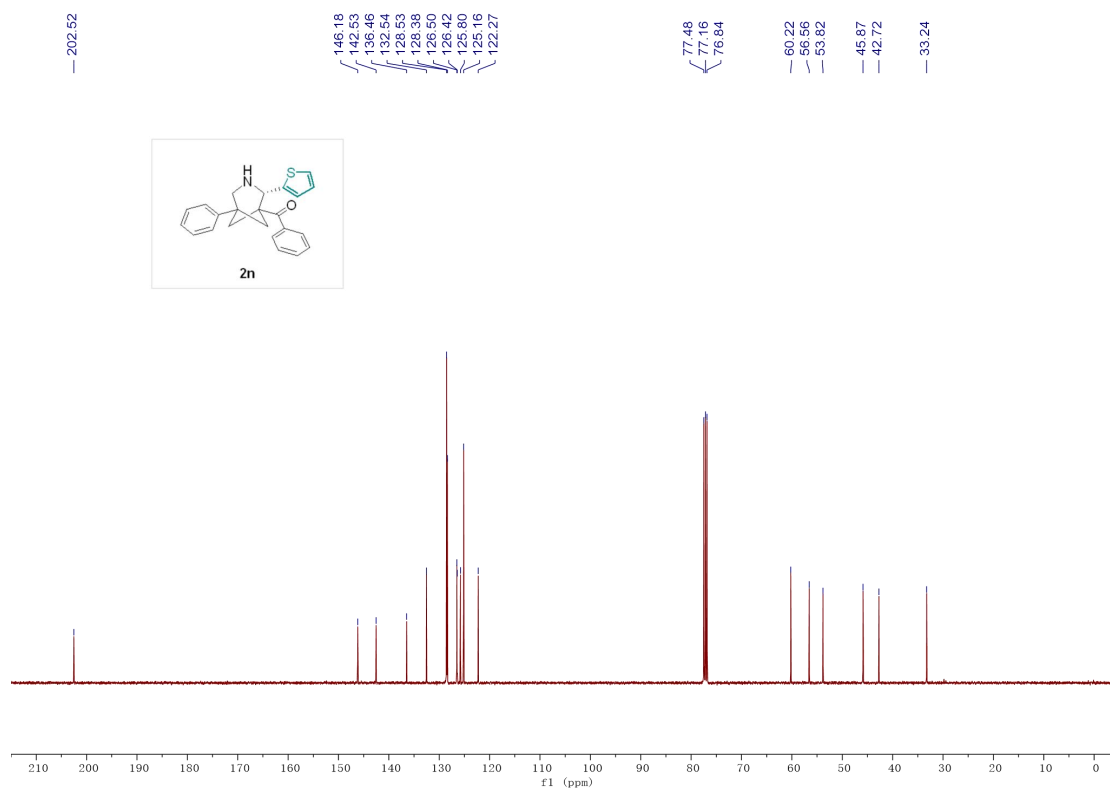




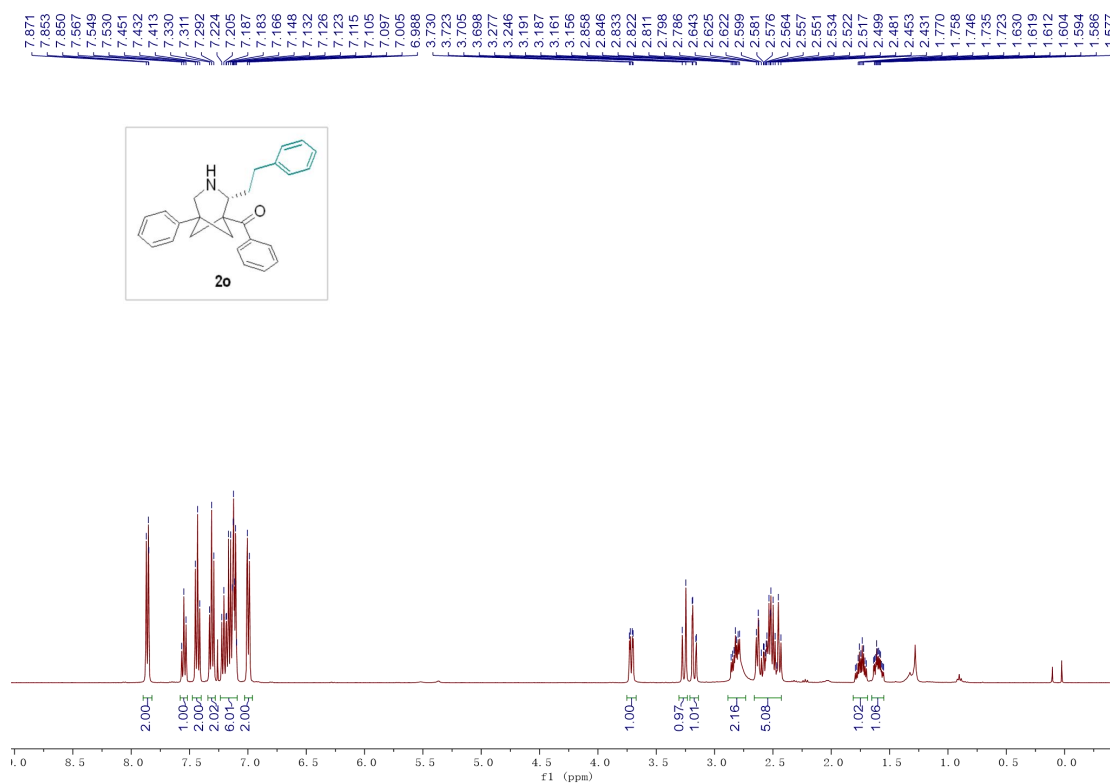
¹⁹F NMR spectrum of **2m**



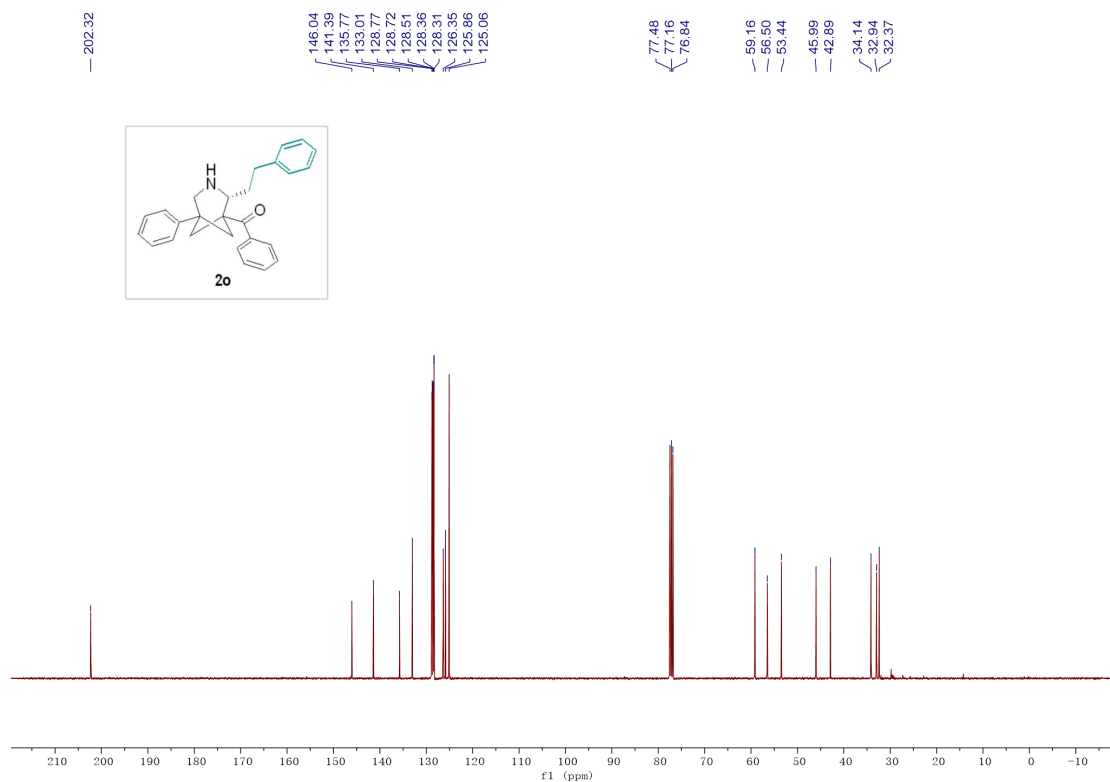
¹H NMR spectrum of **2n**



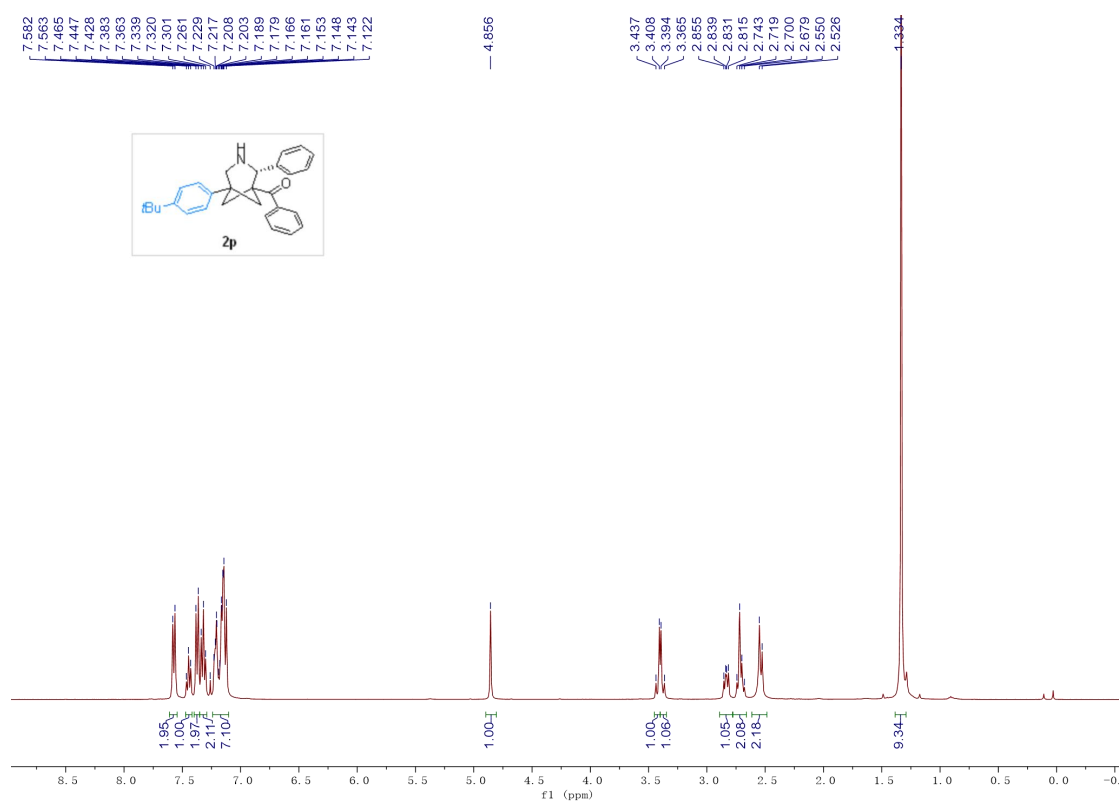
¹³C NMR spectrum of 2n



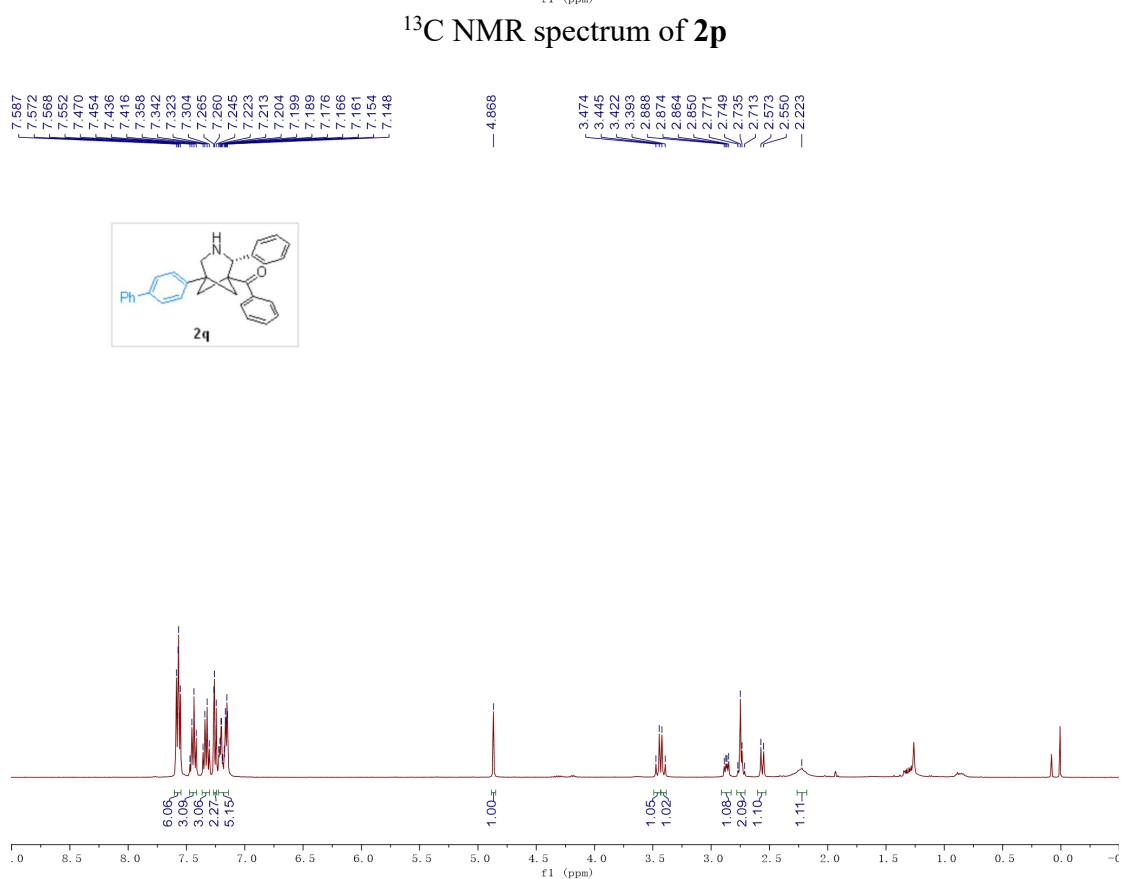
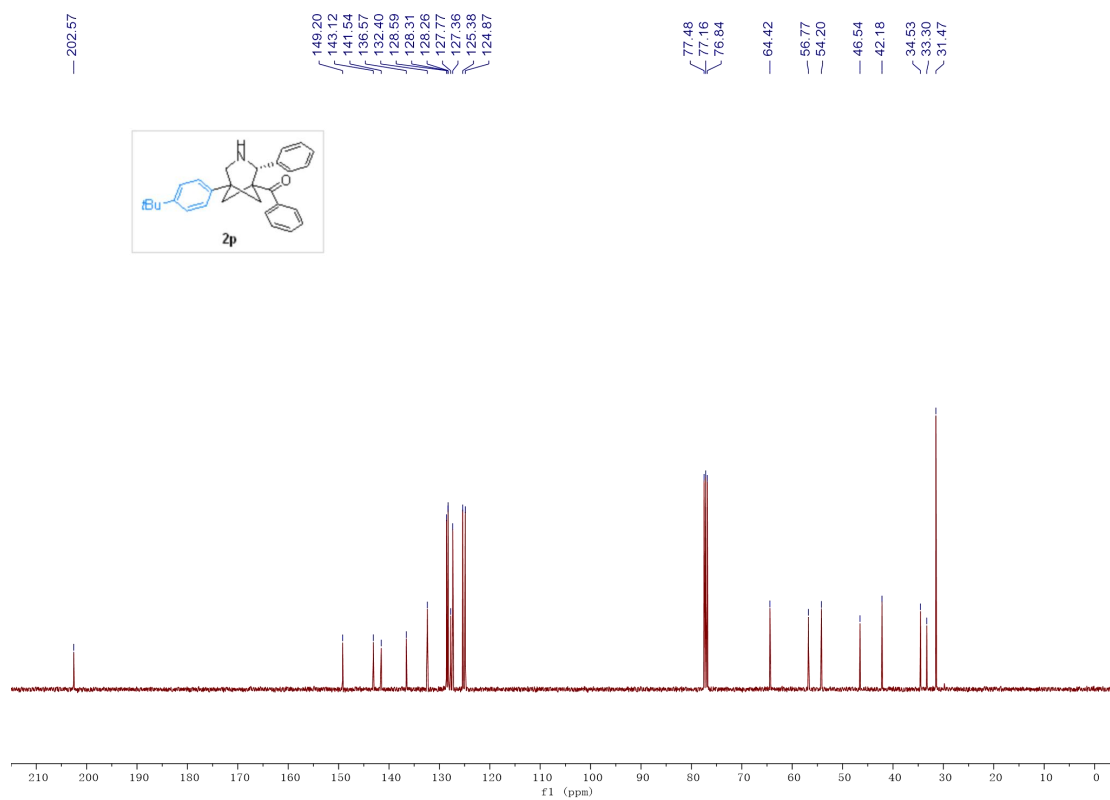
¹H NMR spectrum of 2o

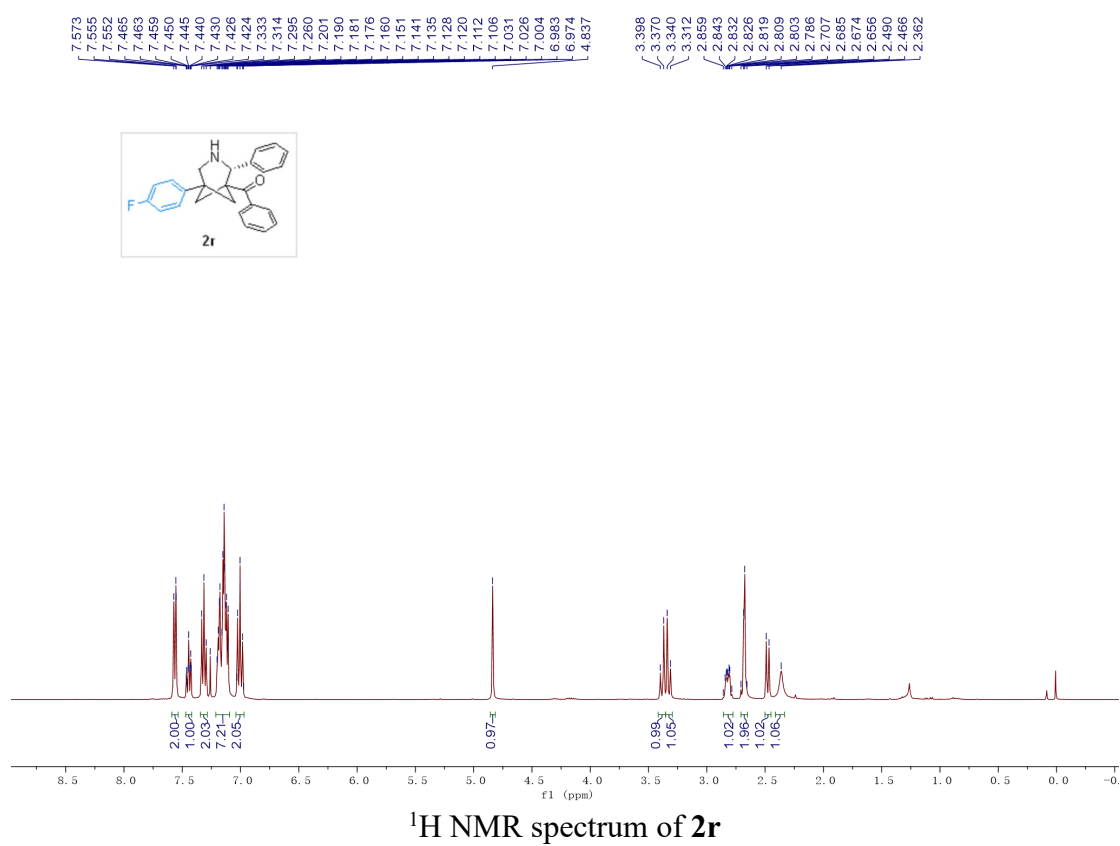
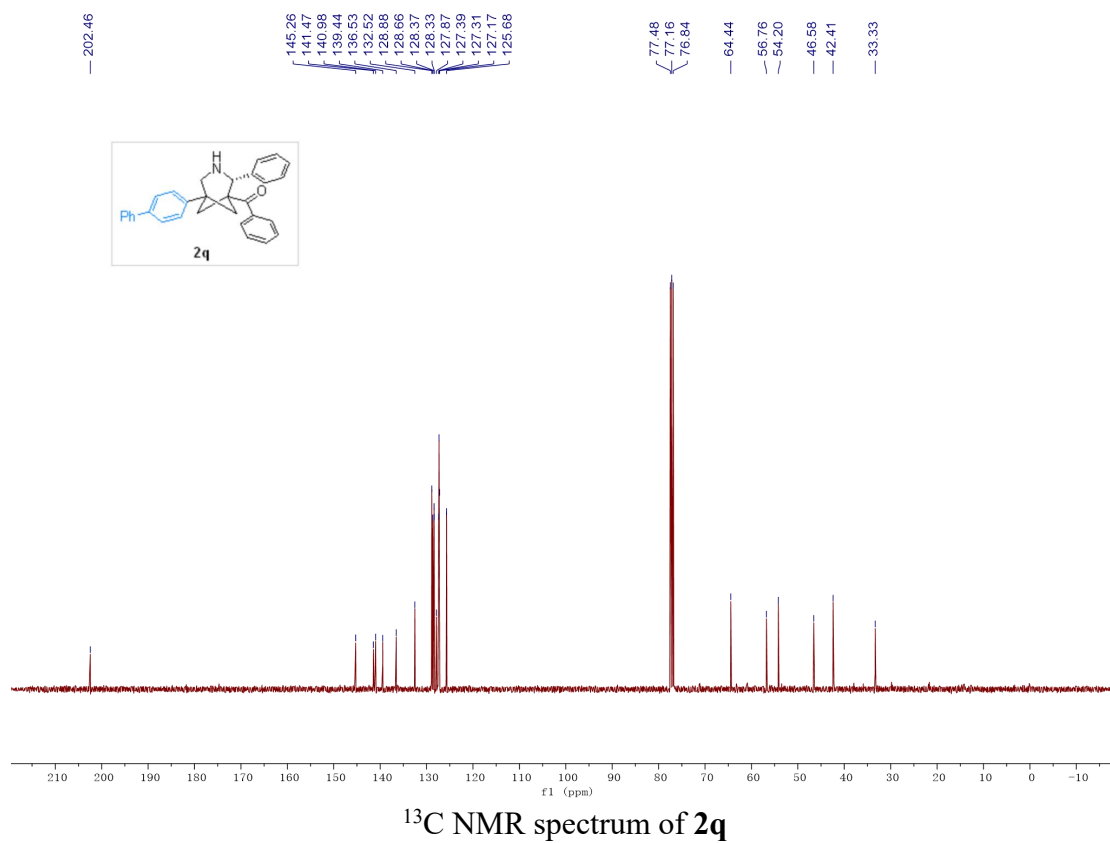


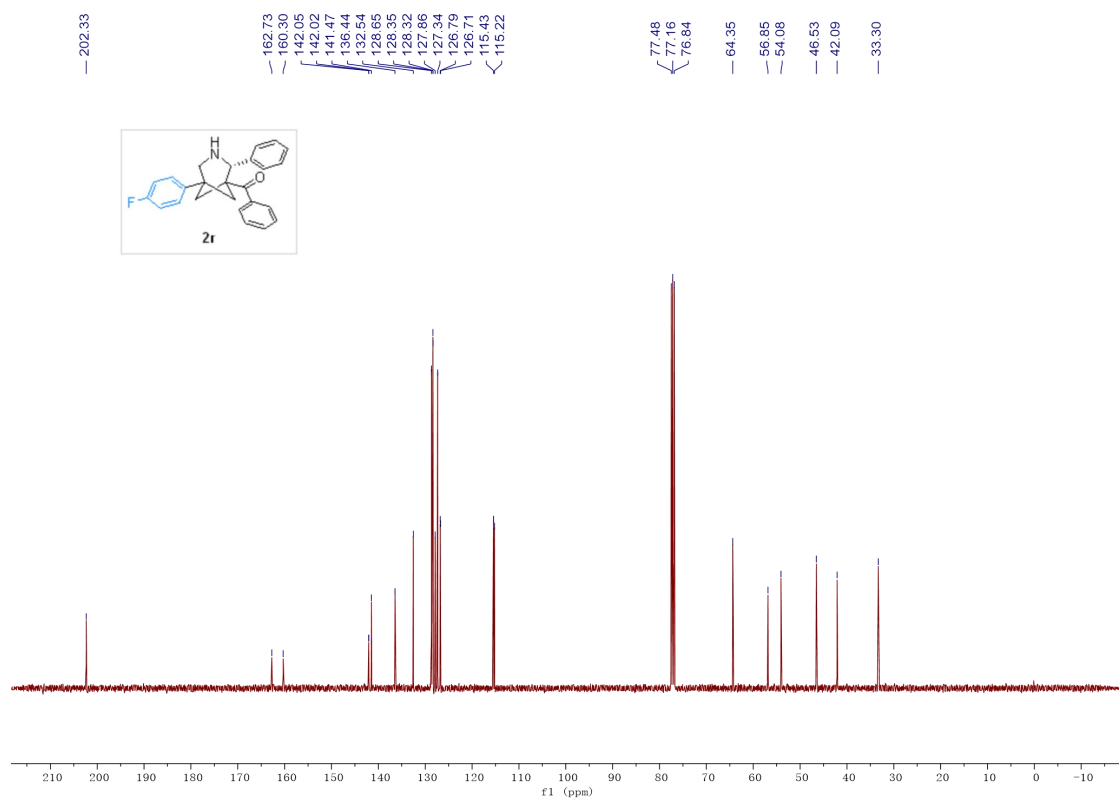
¹³C NMR spectrum of 2o



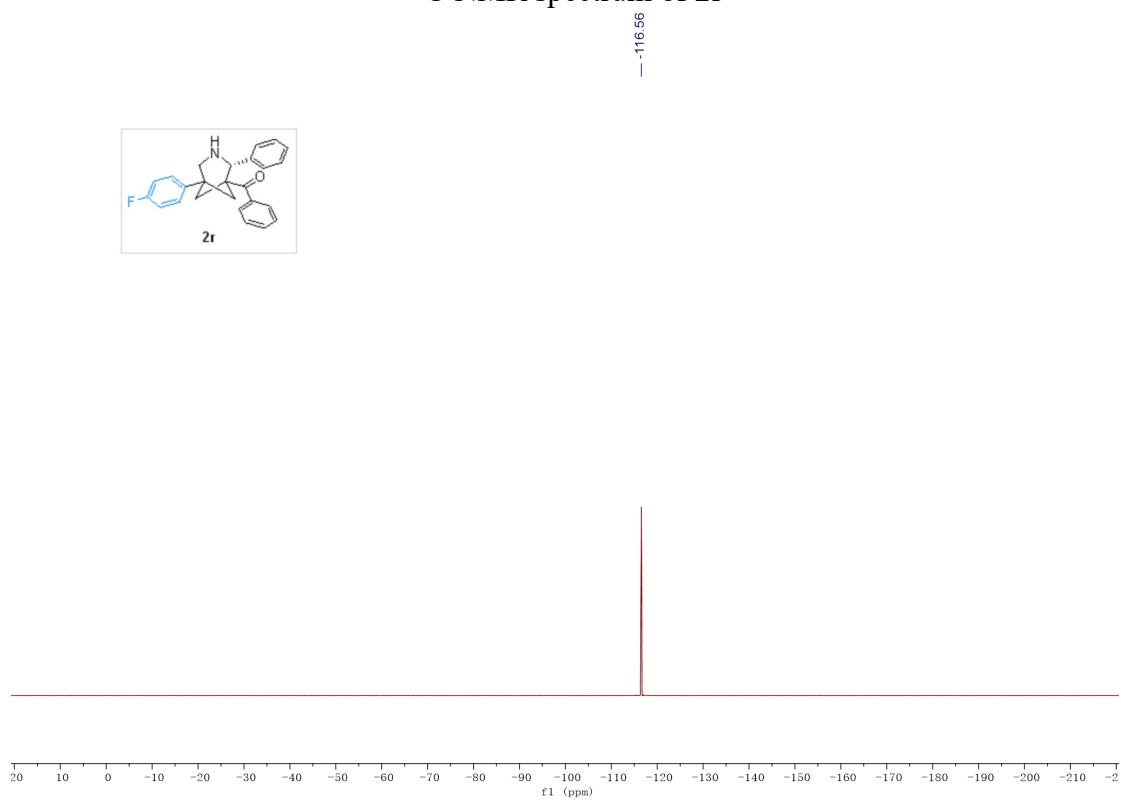
¹H NMR spectrum of 2p



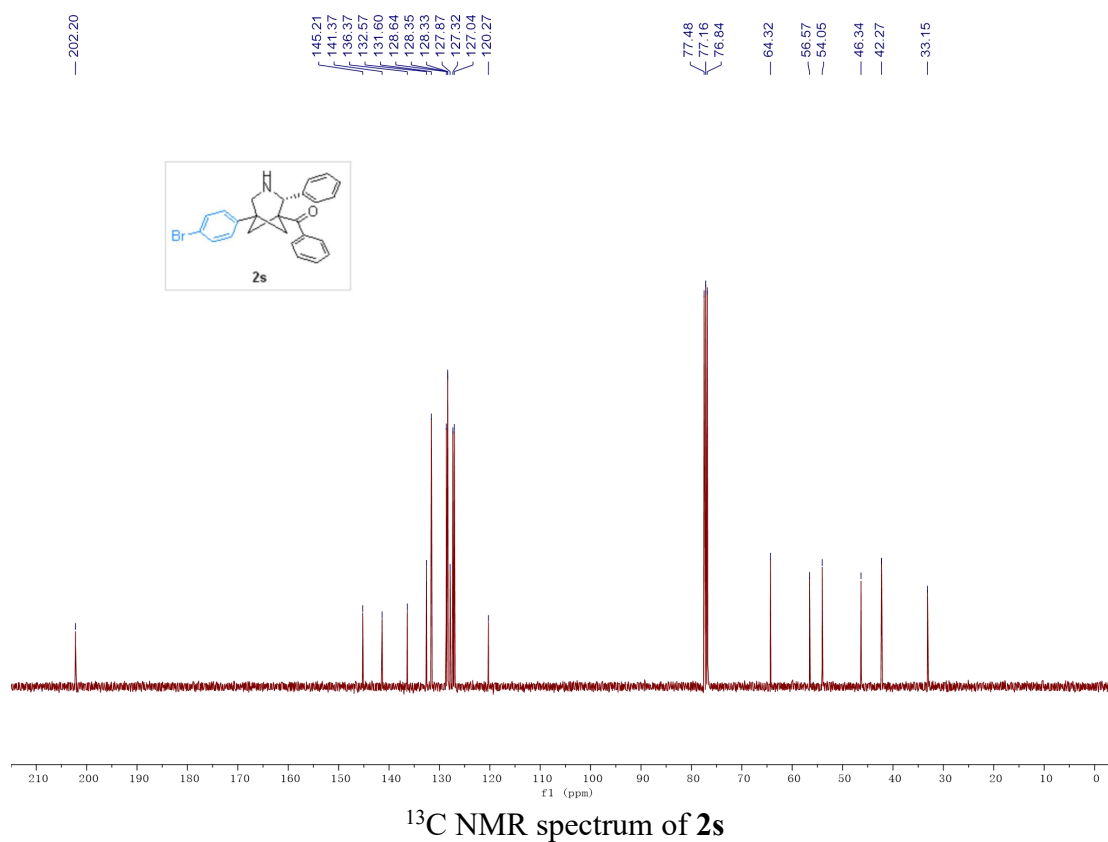
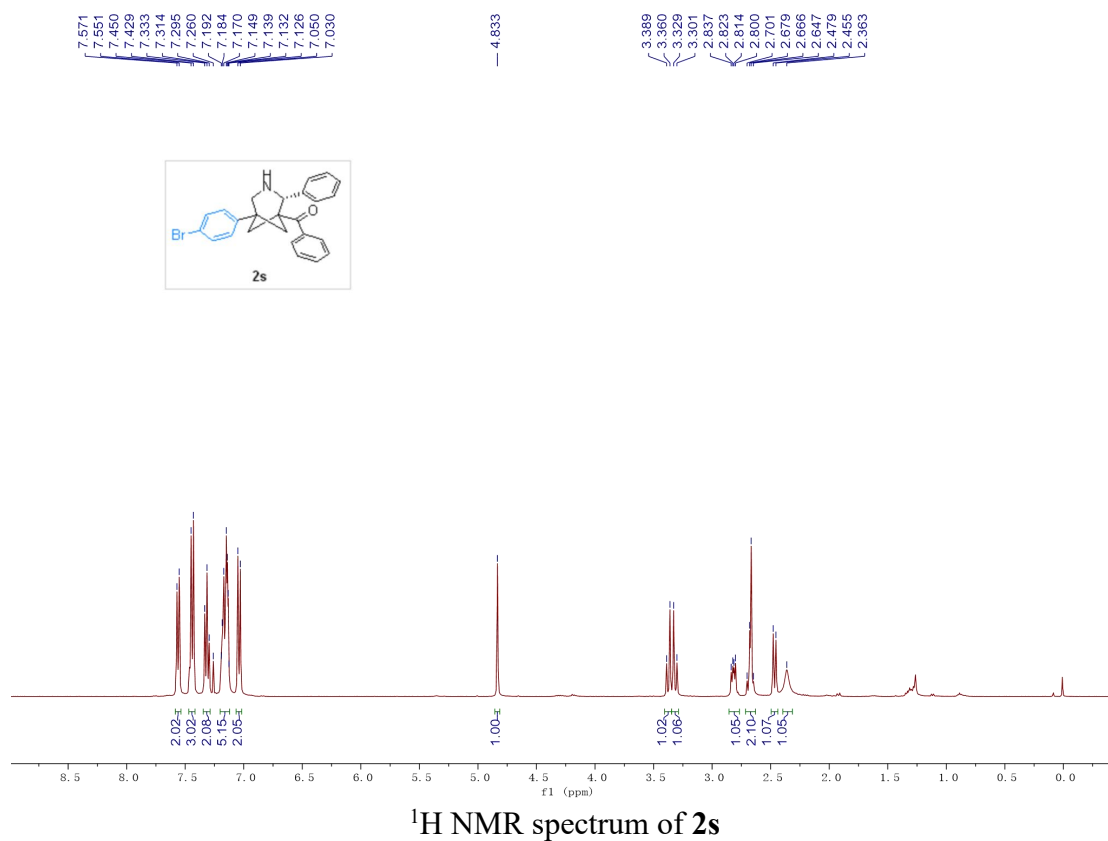


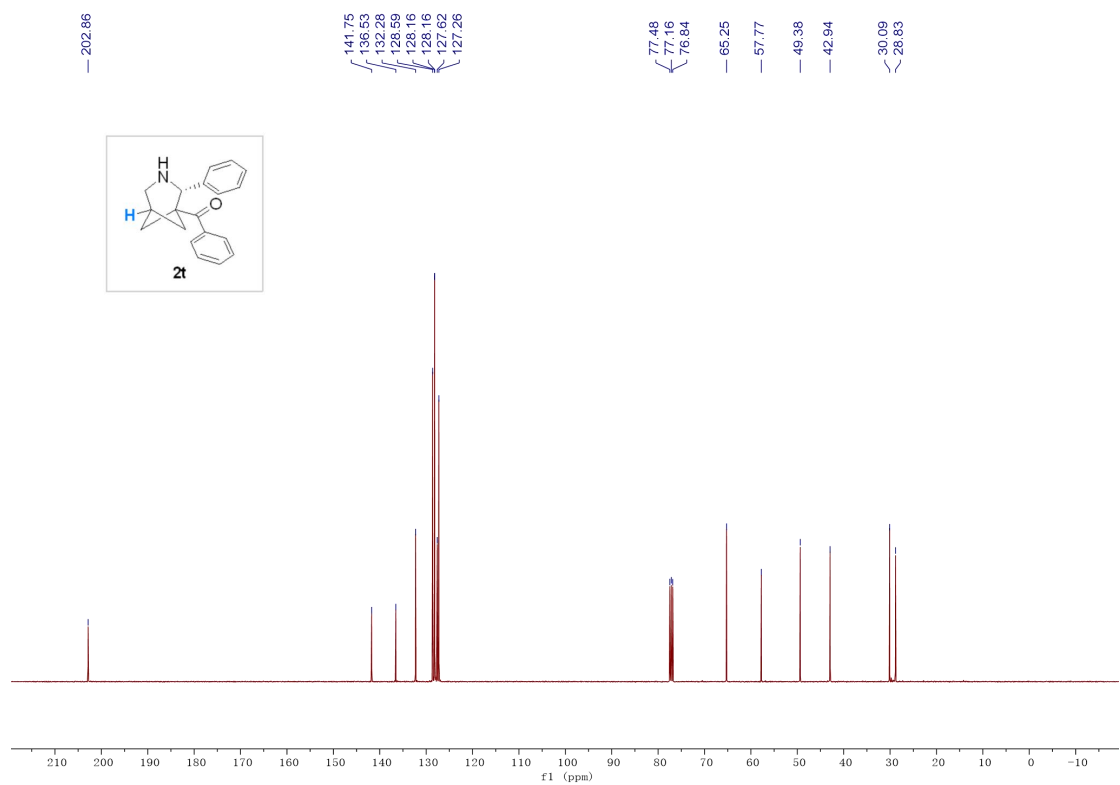
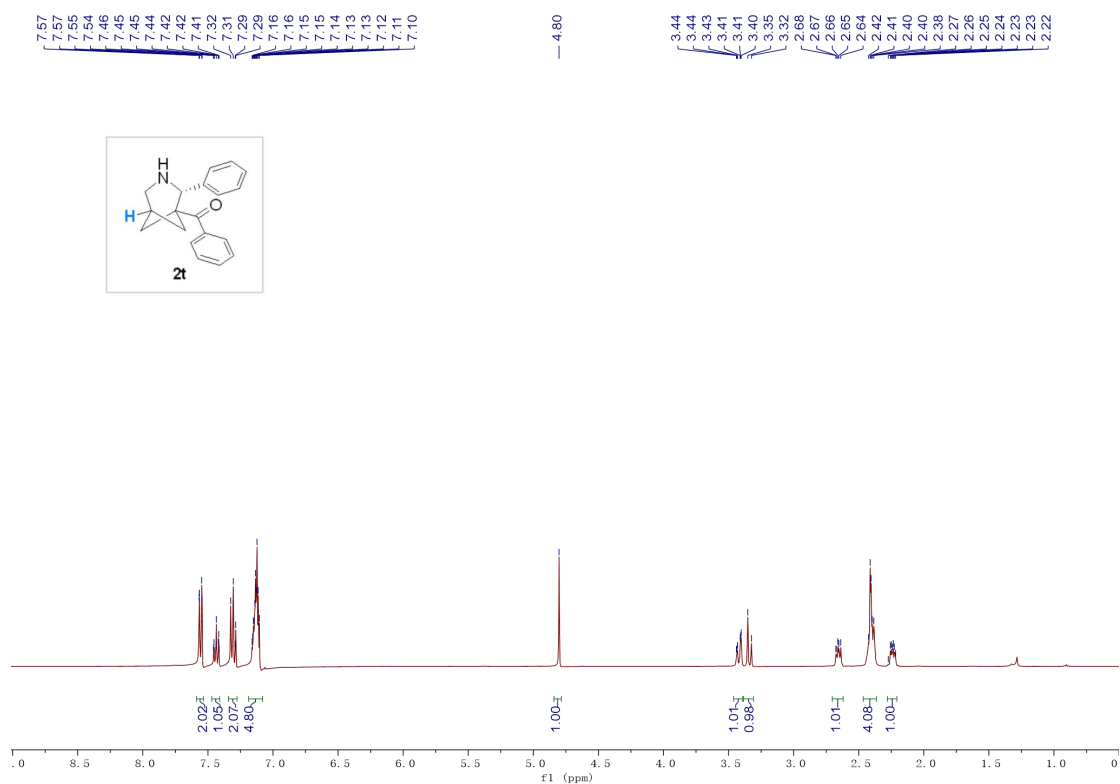


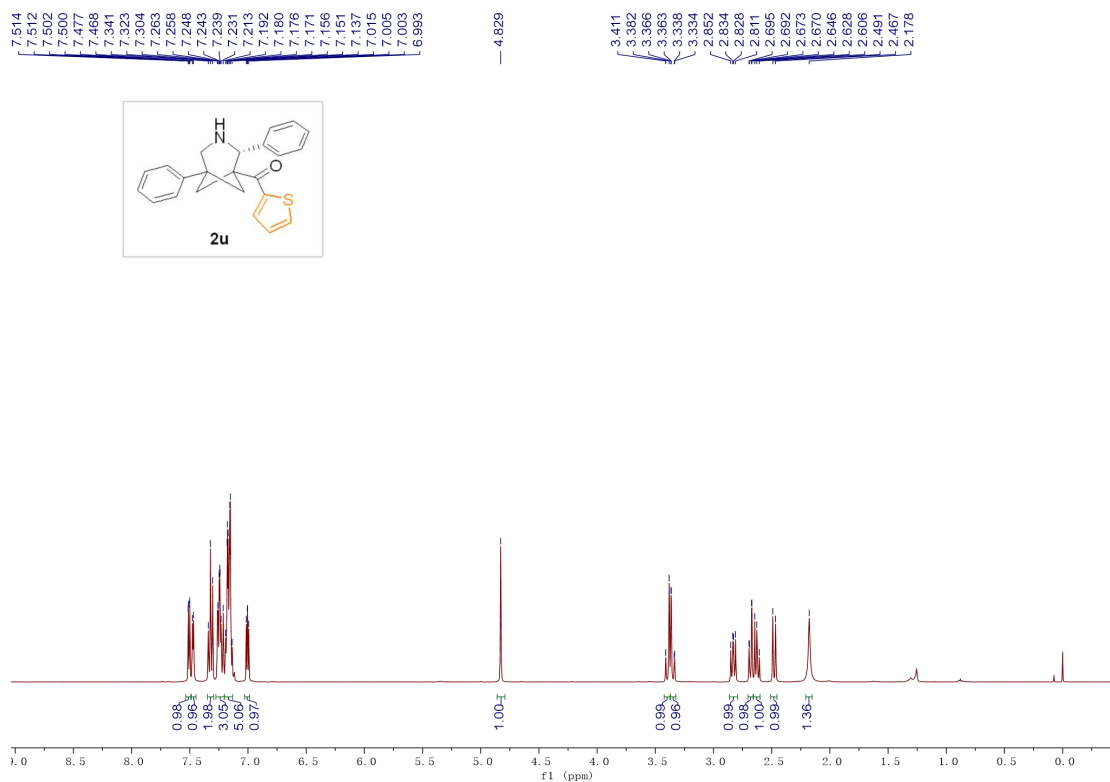
^{13}C NMR spectrum of **2r**



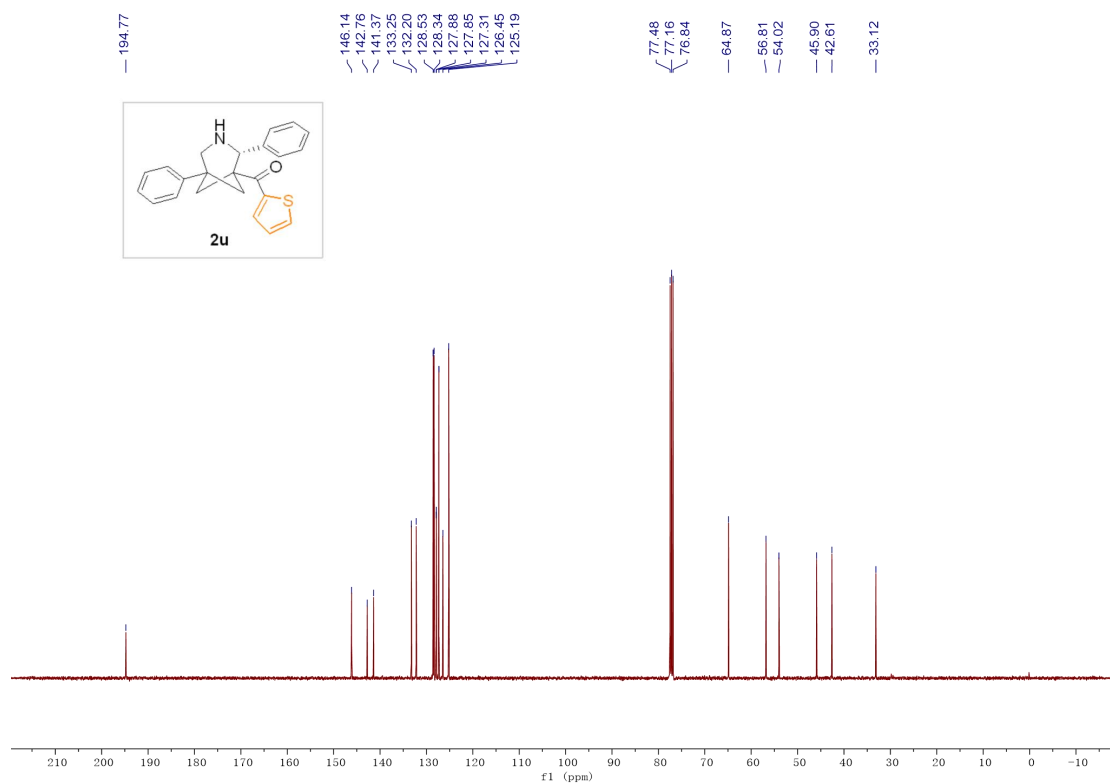
^{19}F NMR spectrum of **2r**



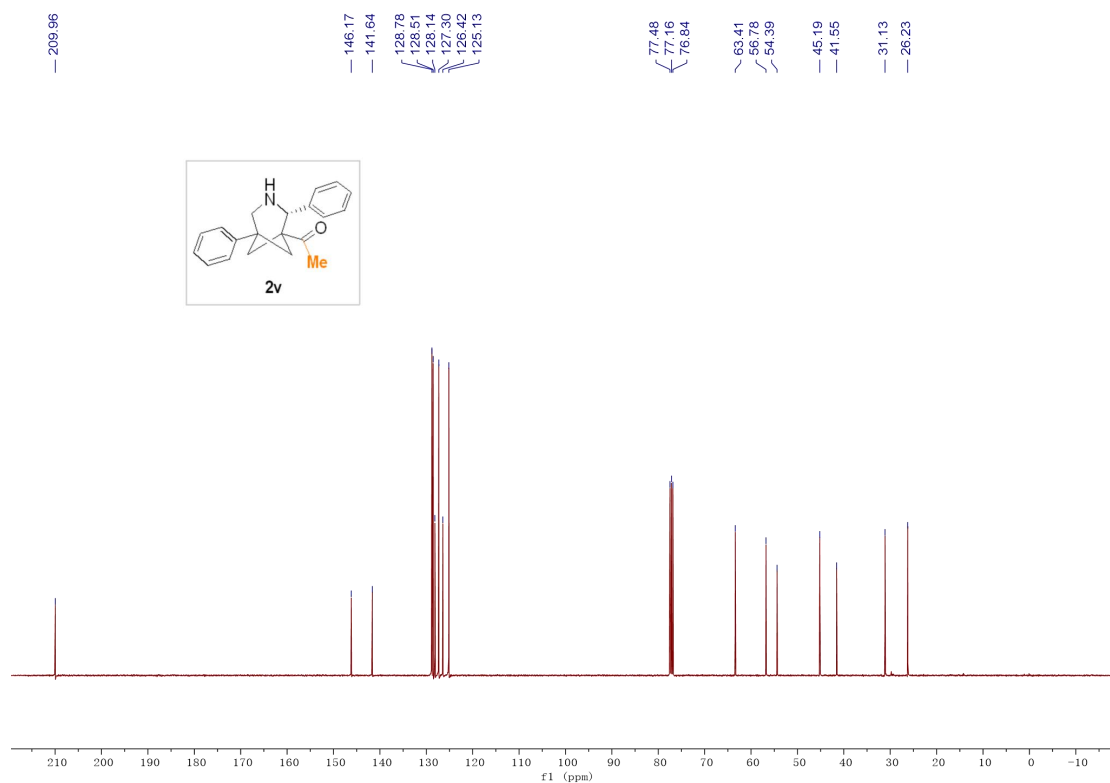
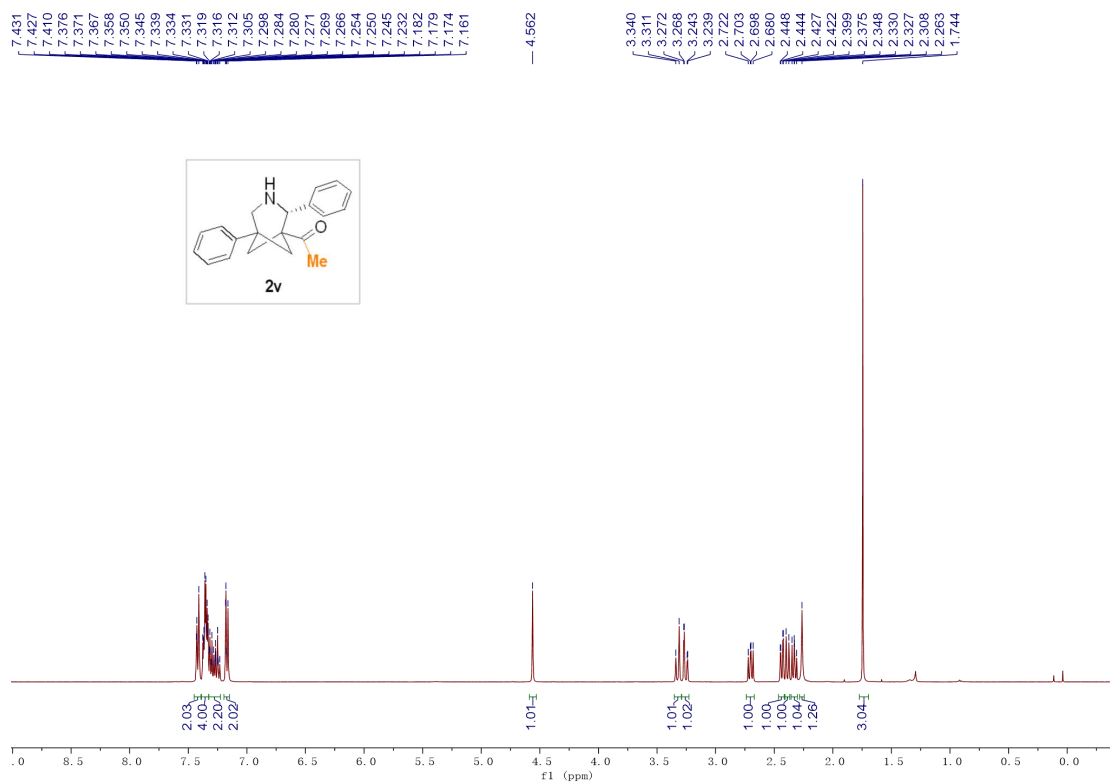


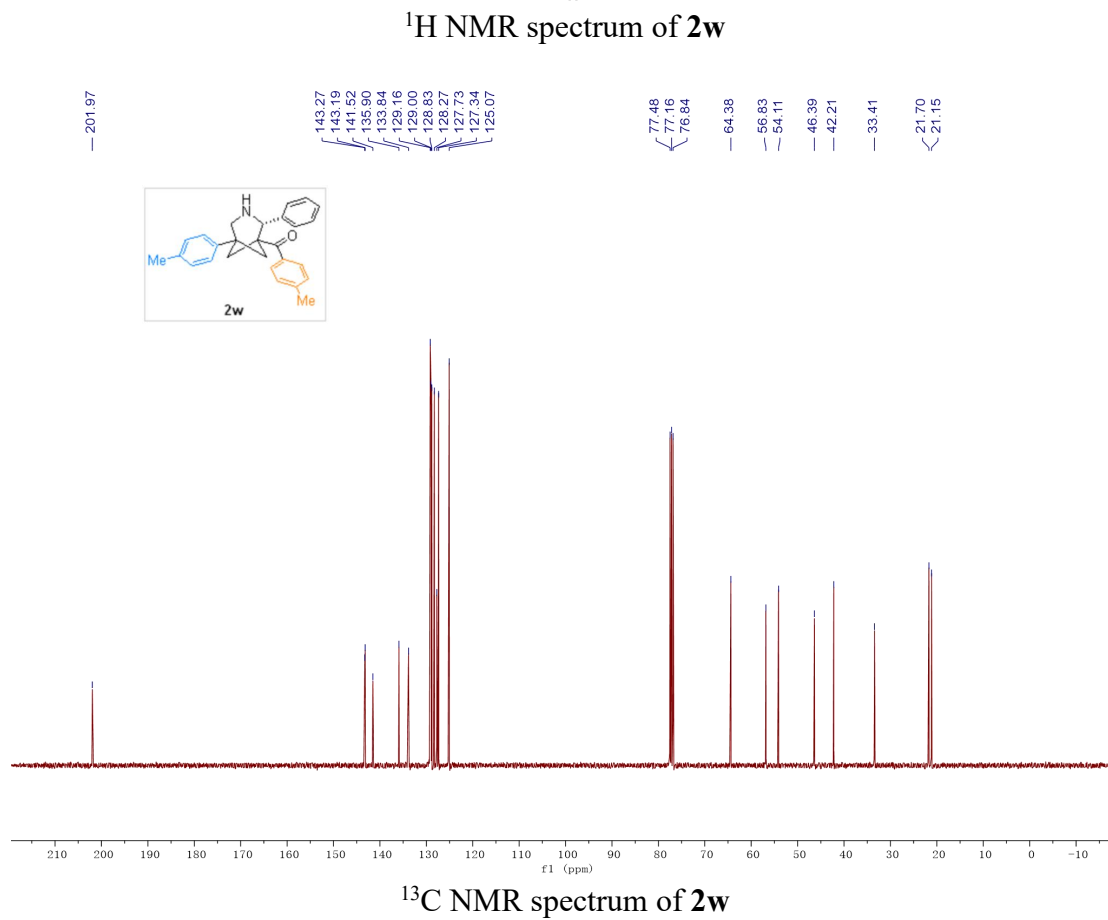
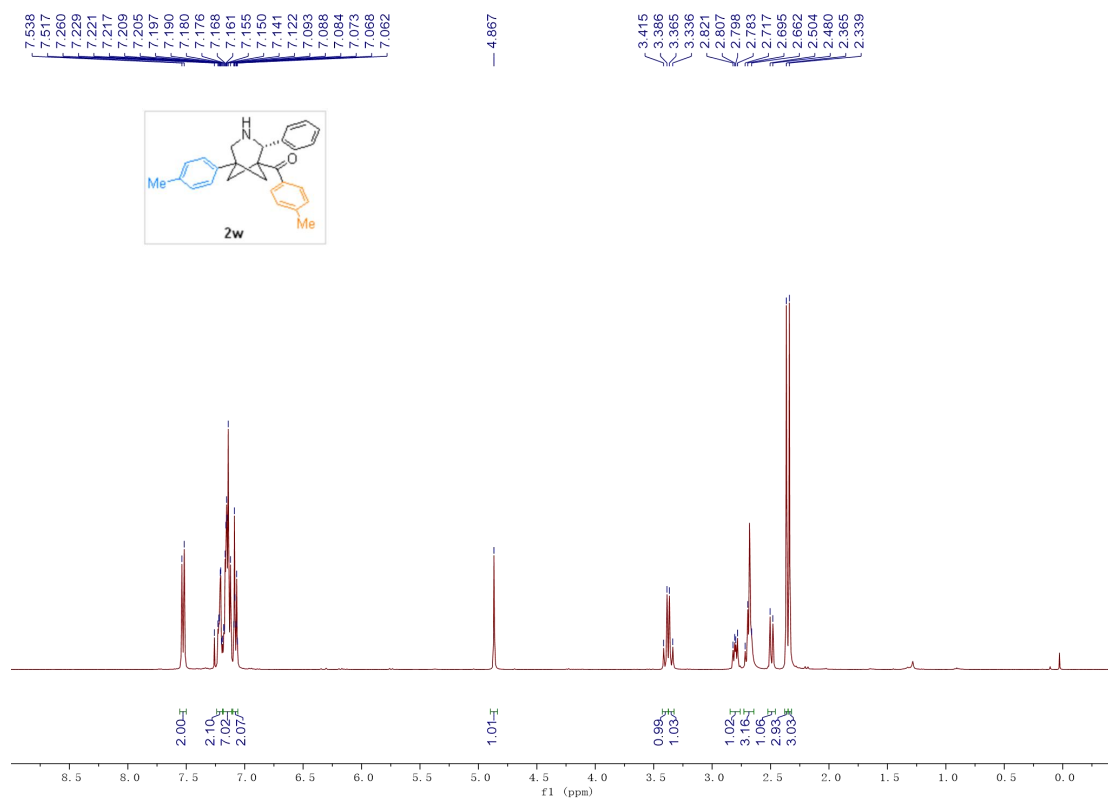


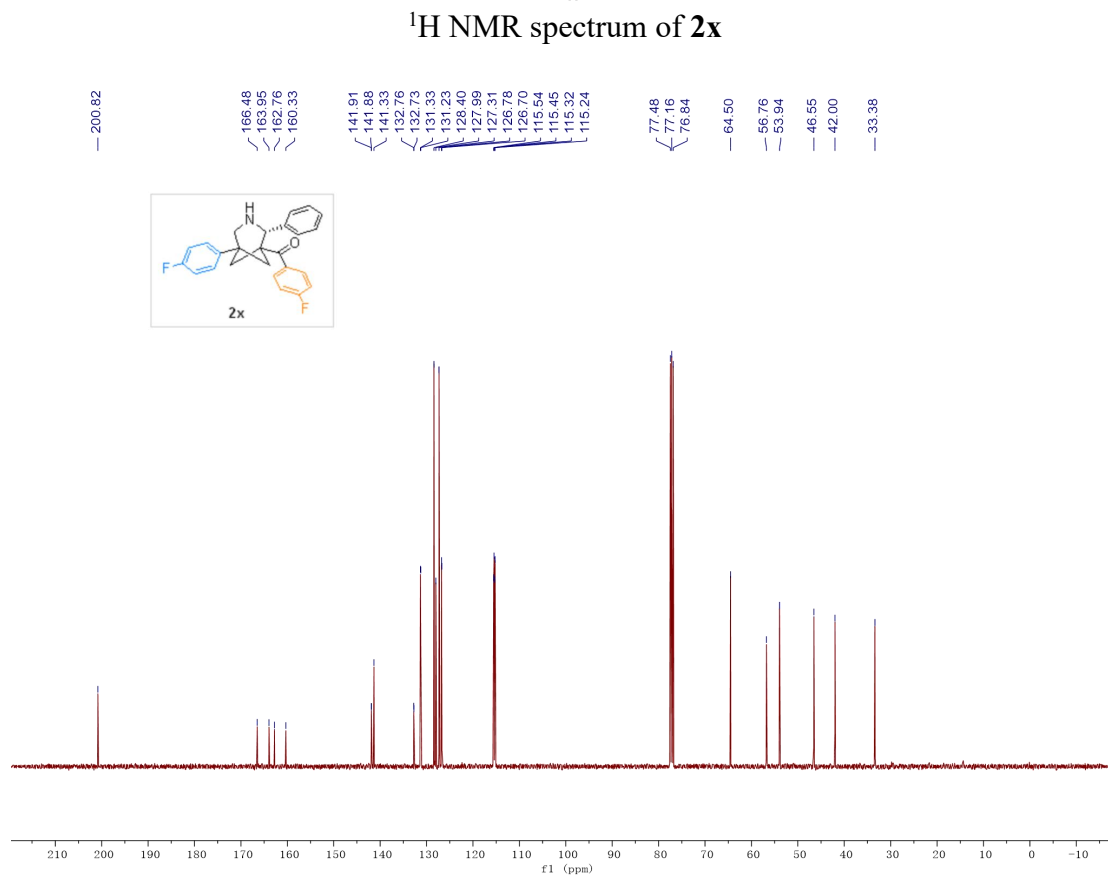
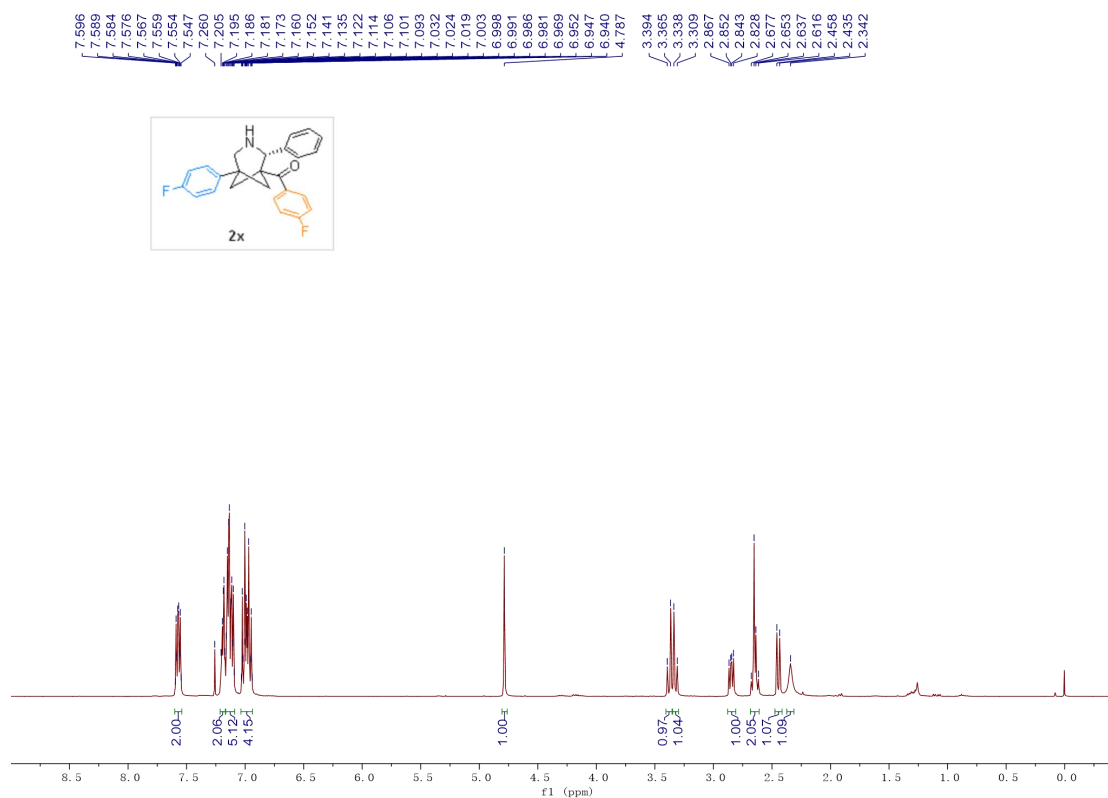
¹H NMR spectrum of 2u

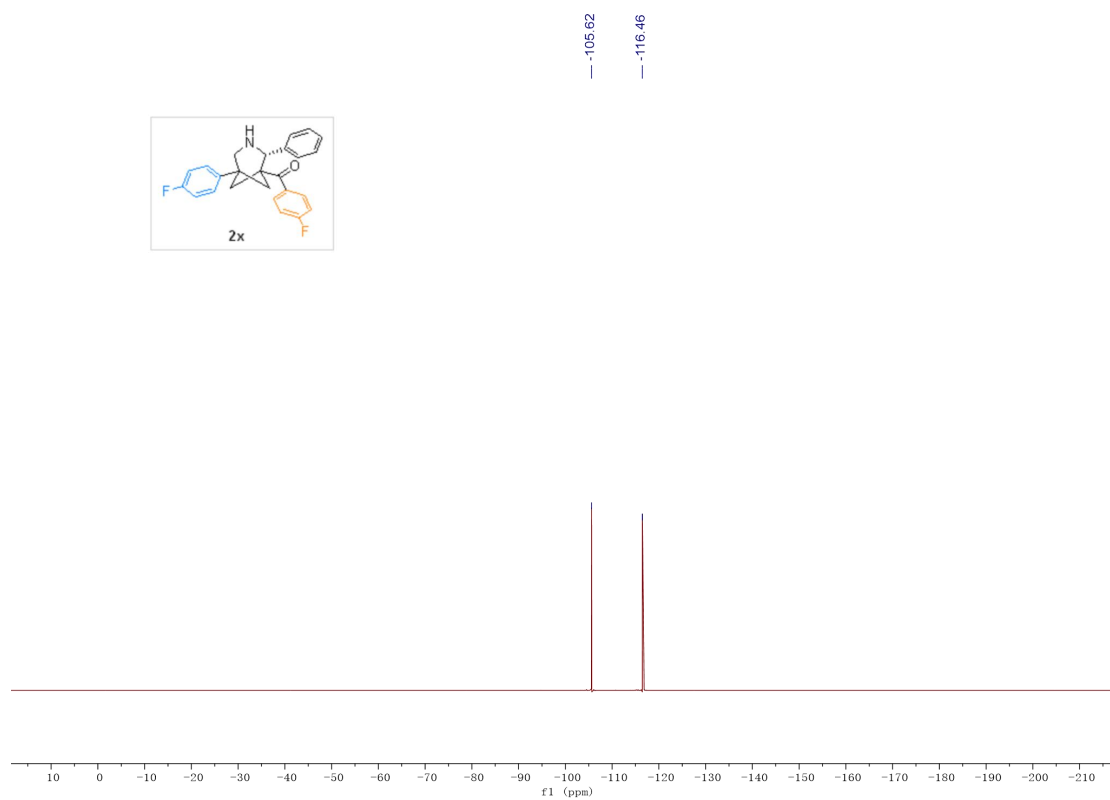


¹³C NMR spectrum of 2u

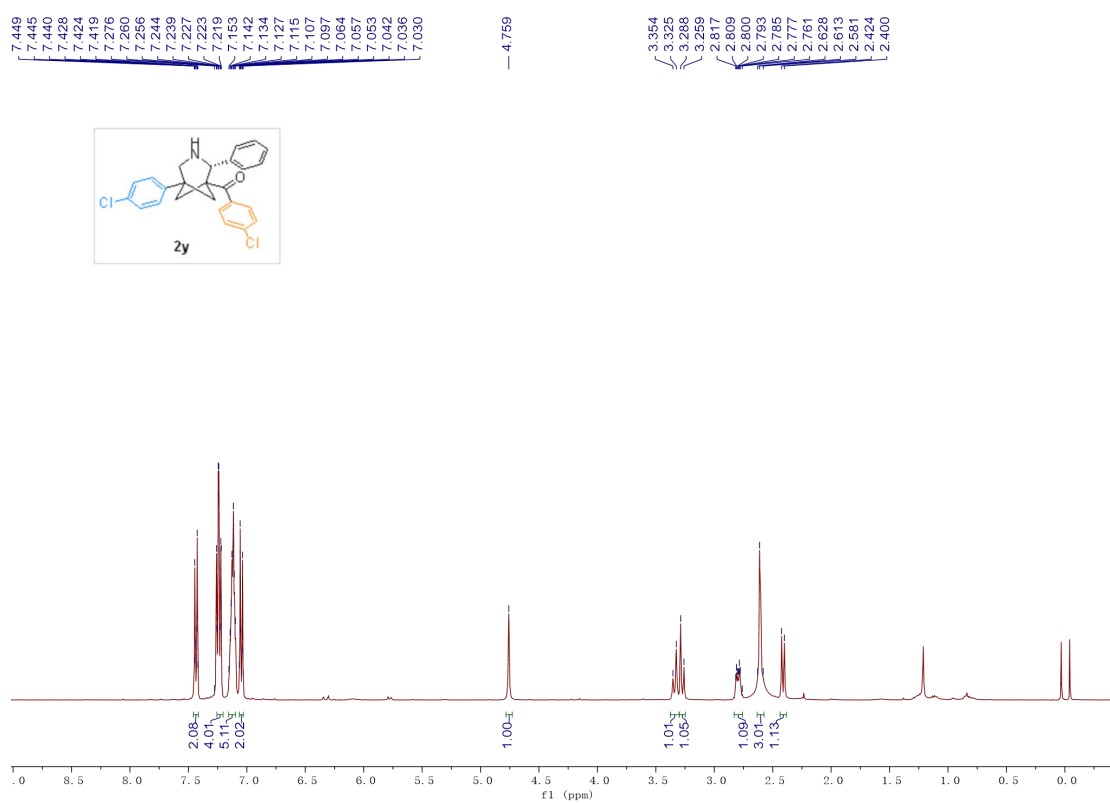




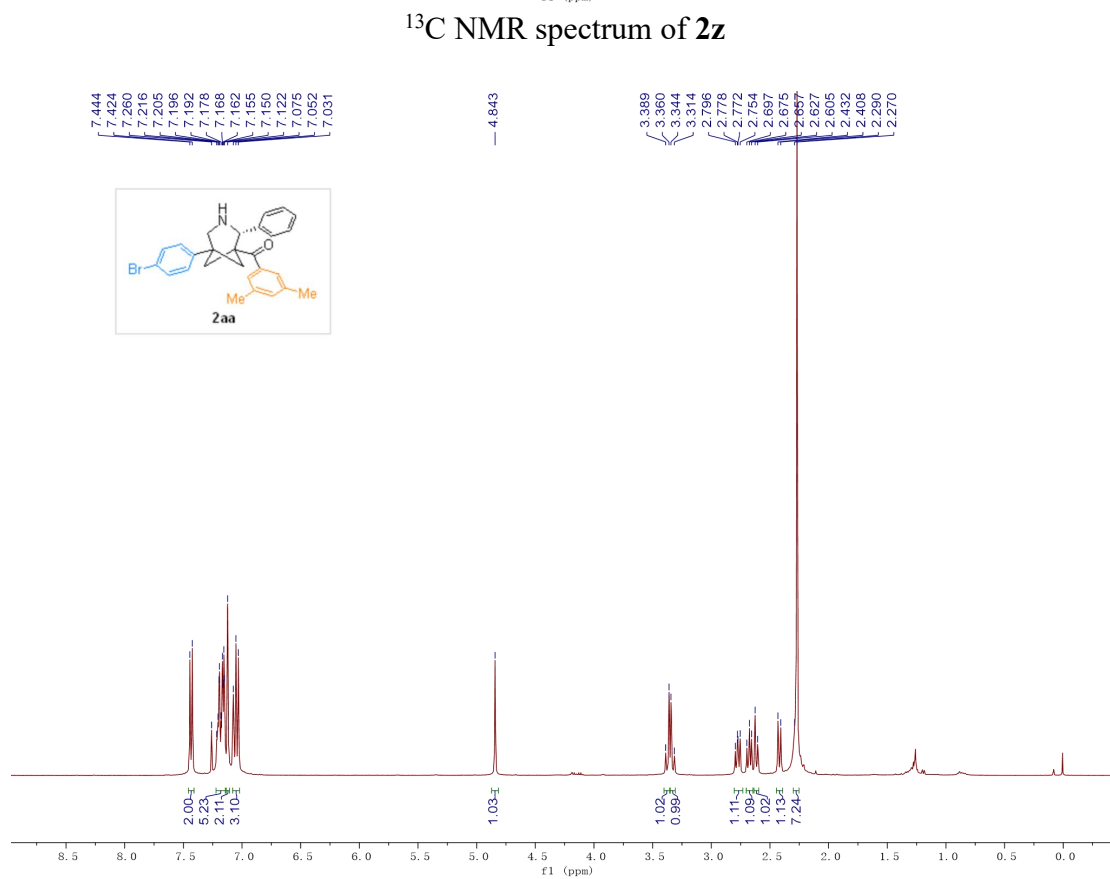
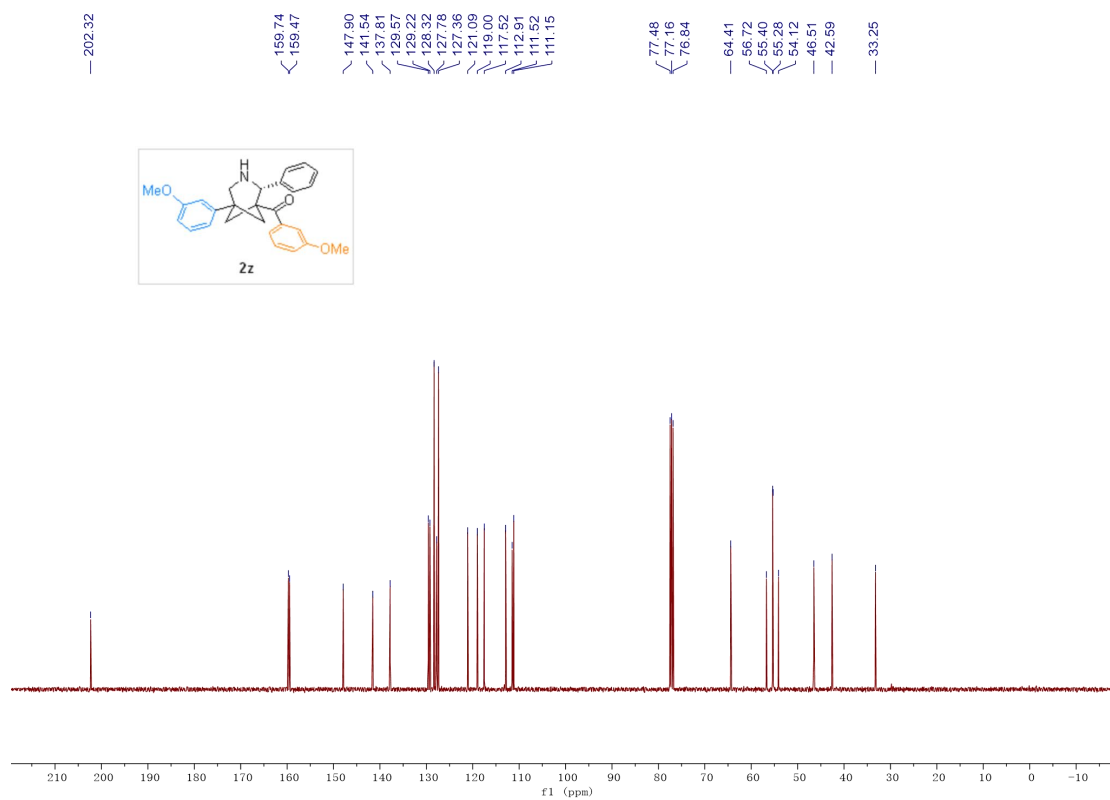


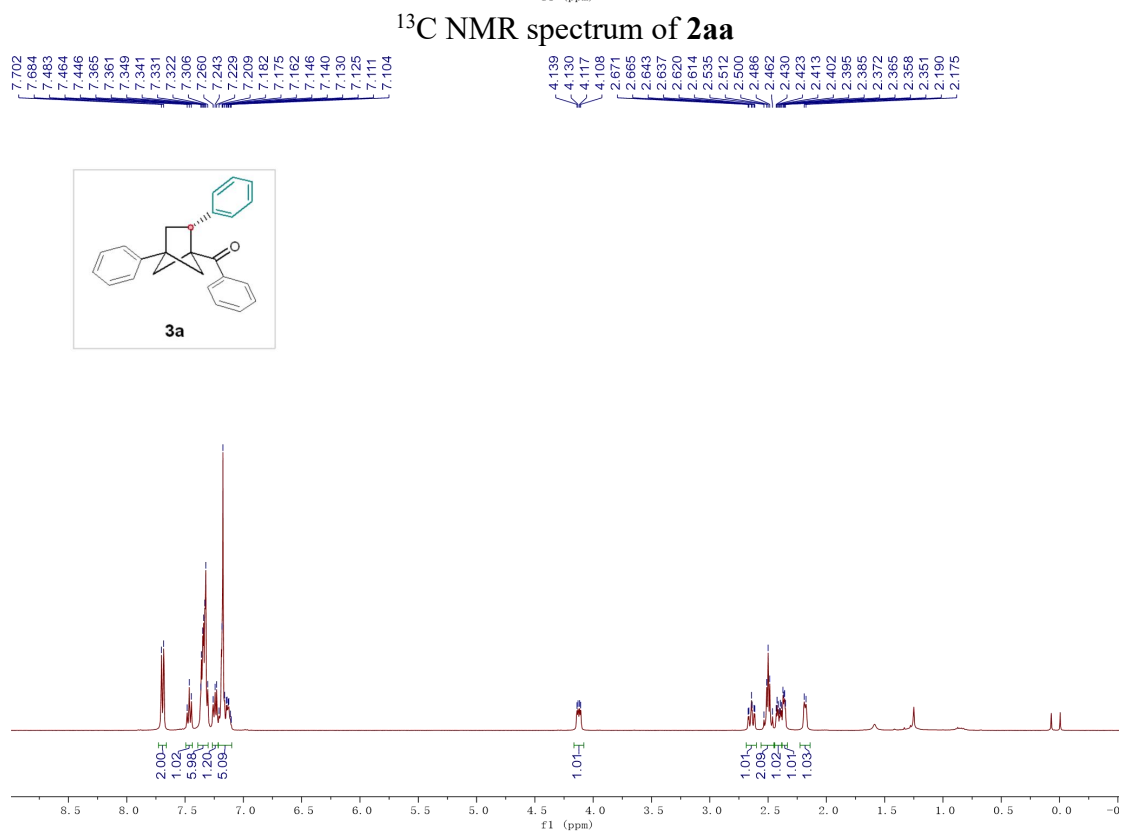
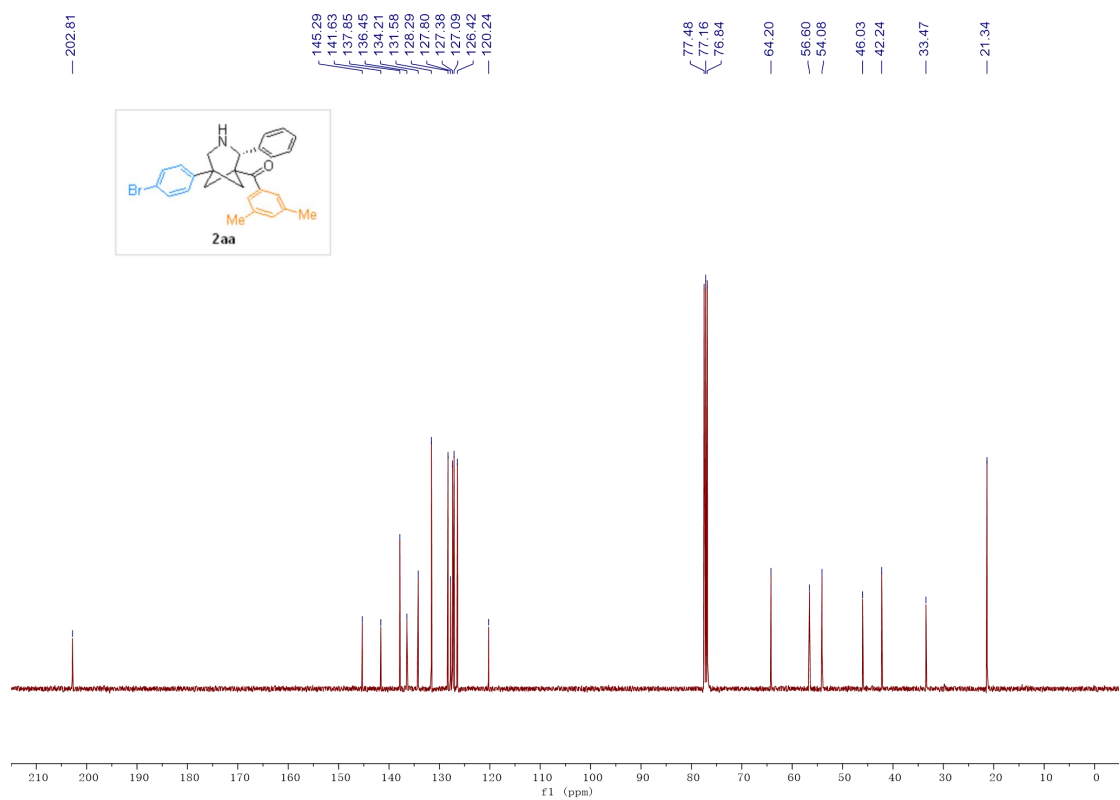


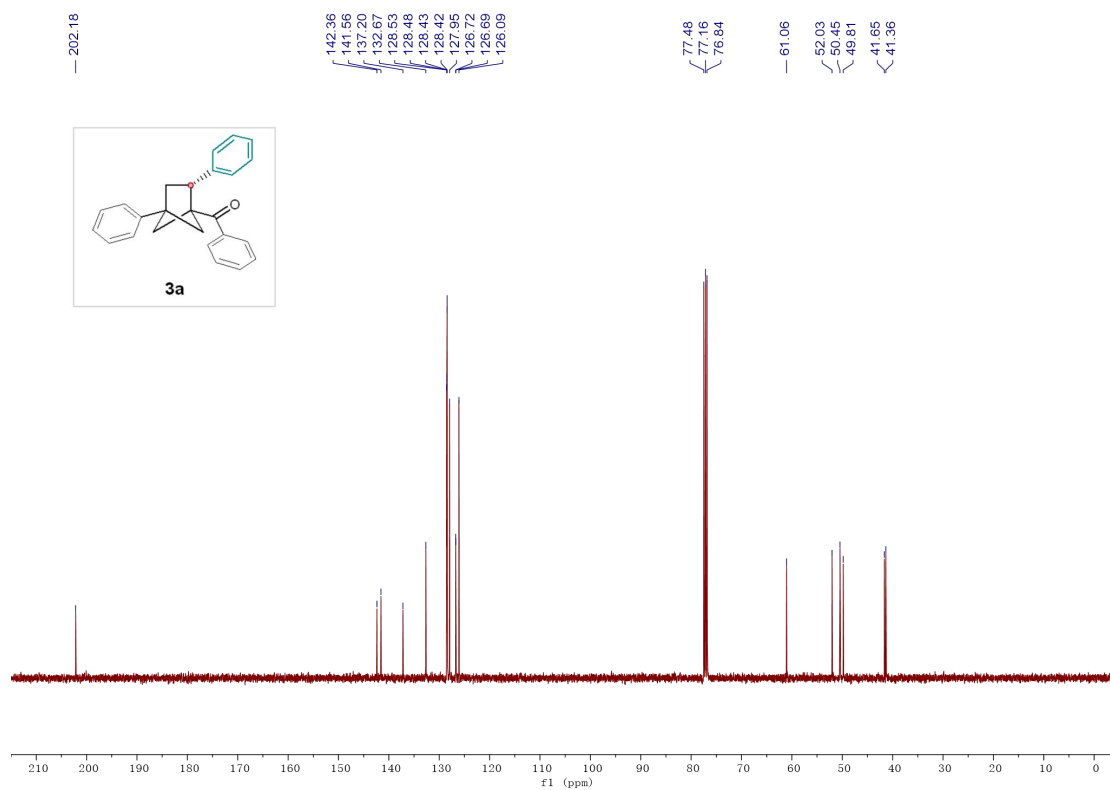
^{19}F NMR spectrum of **2x**



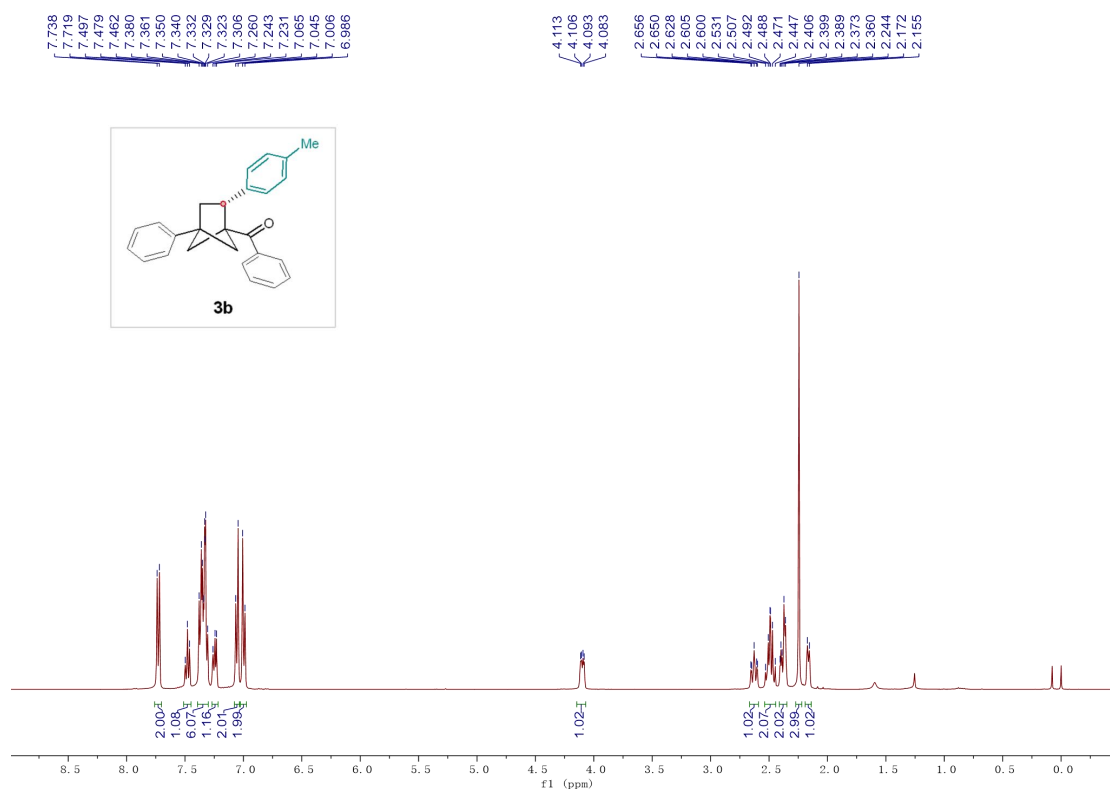
^1H NMR spectrum of **2y**



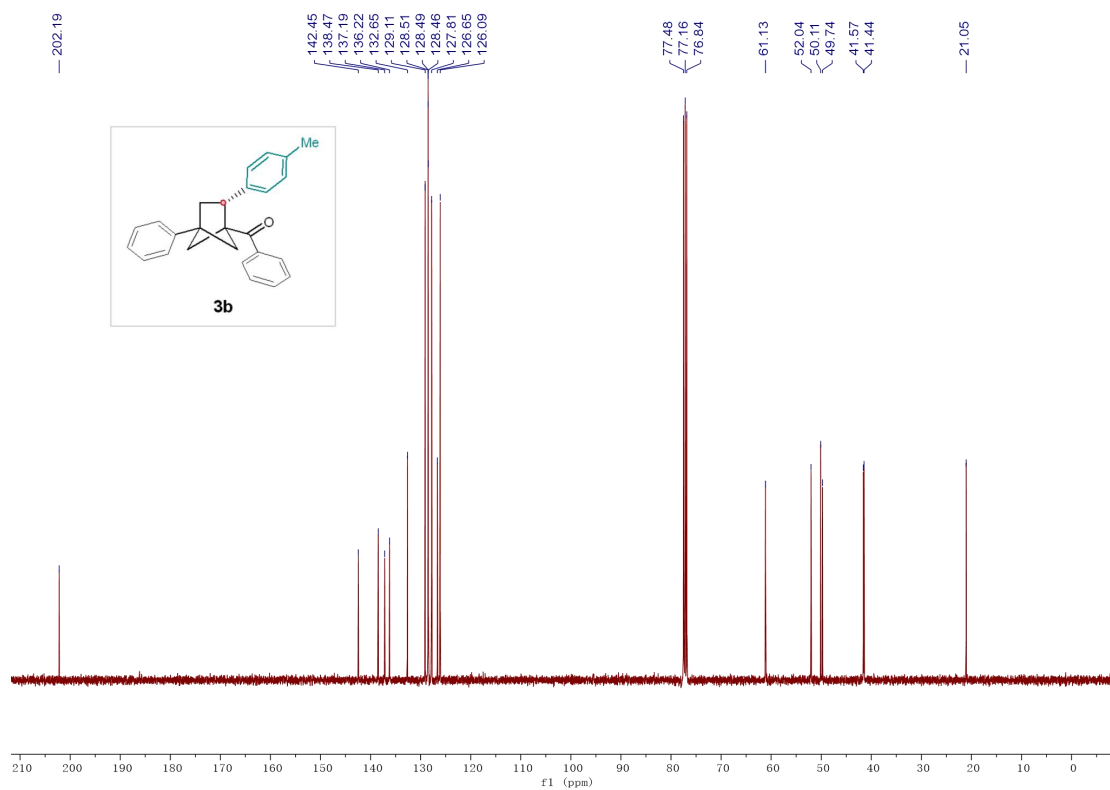




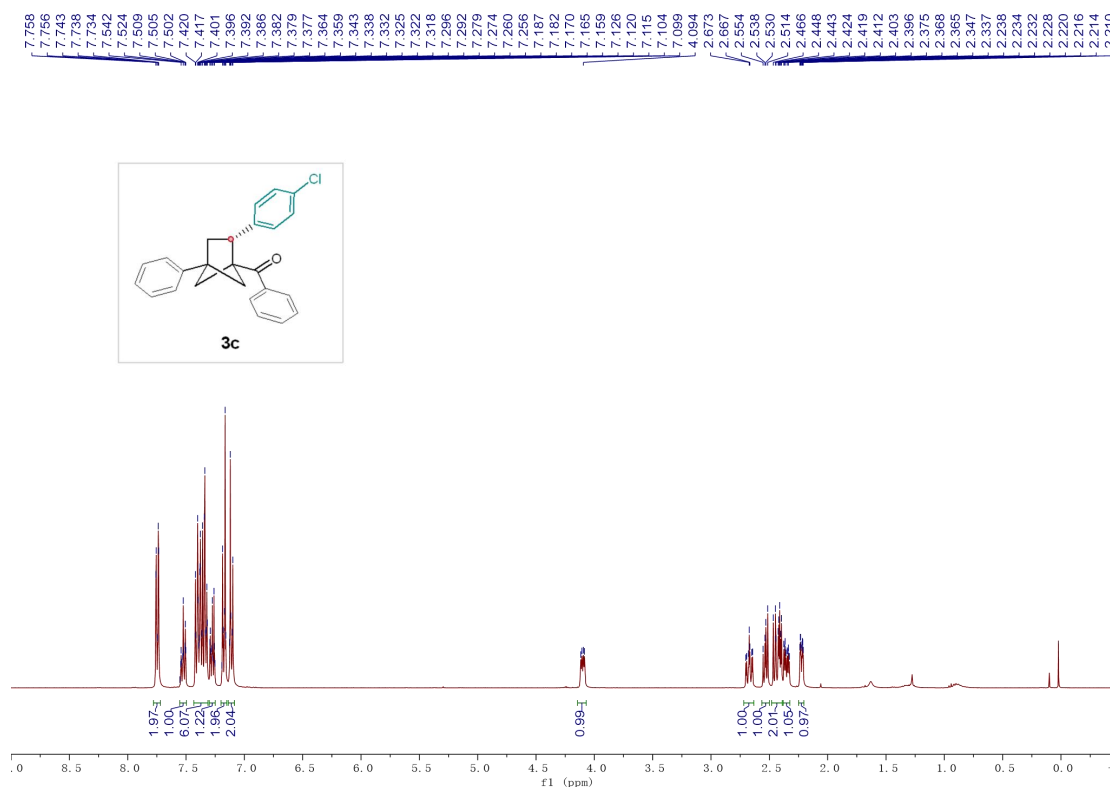
¹³C NMR spectrum of **3a**



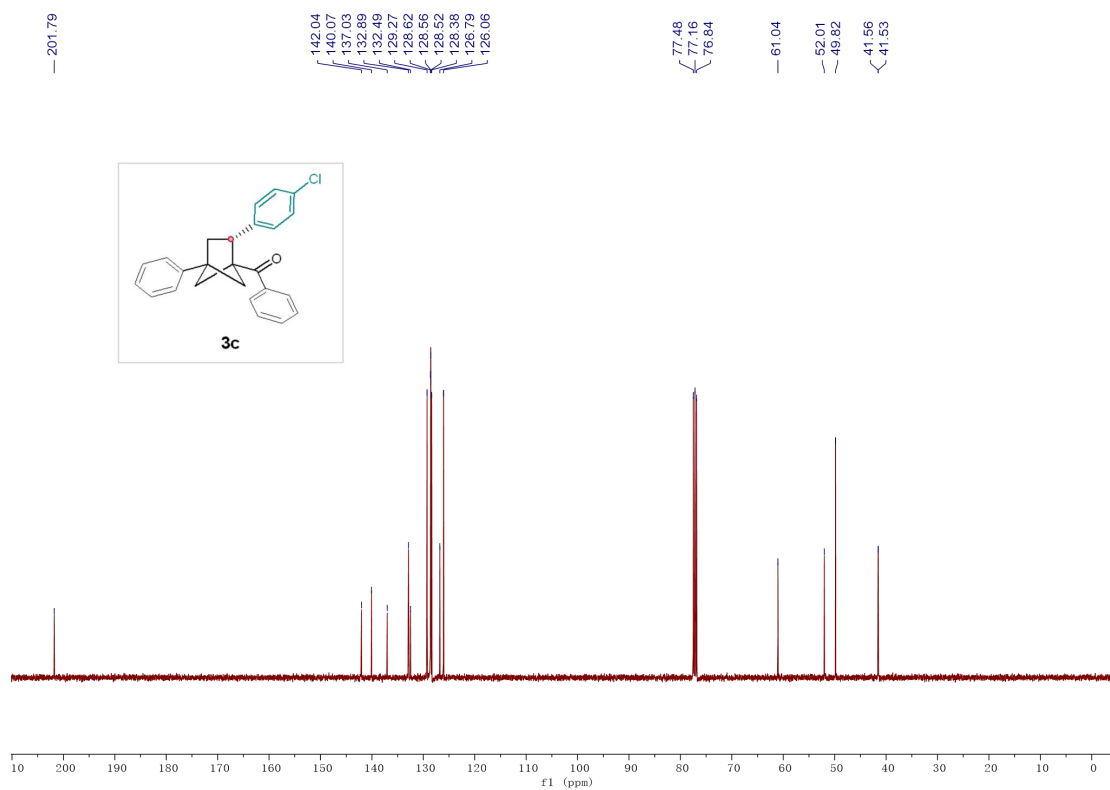
¹H NMR spectrum of **3b**



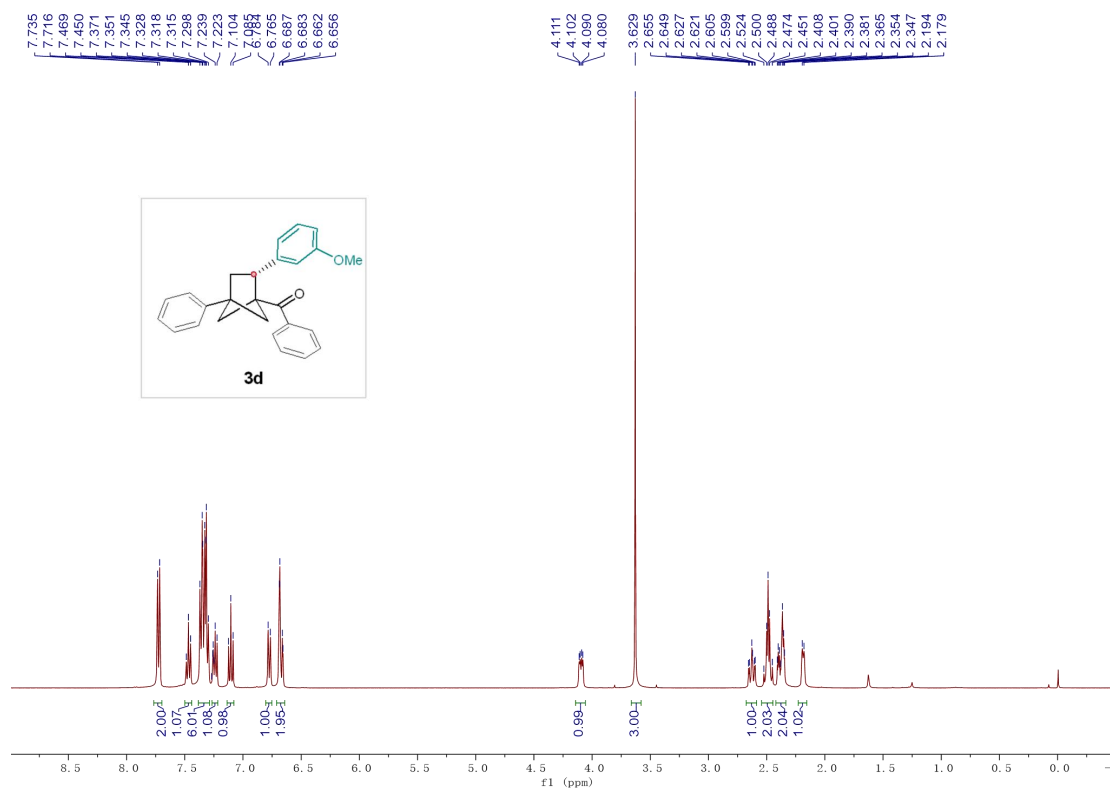
¹³C NMR spectrum of **3b**



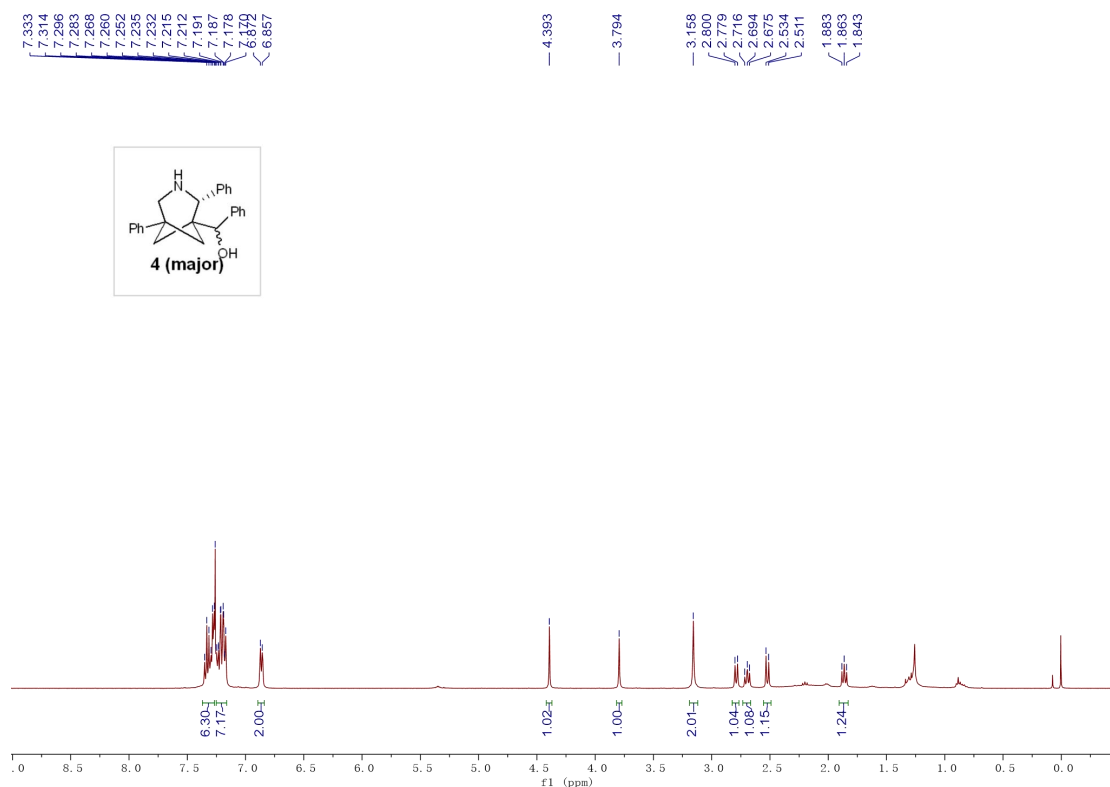
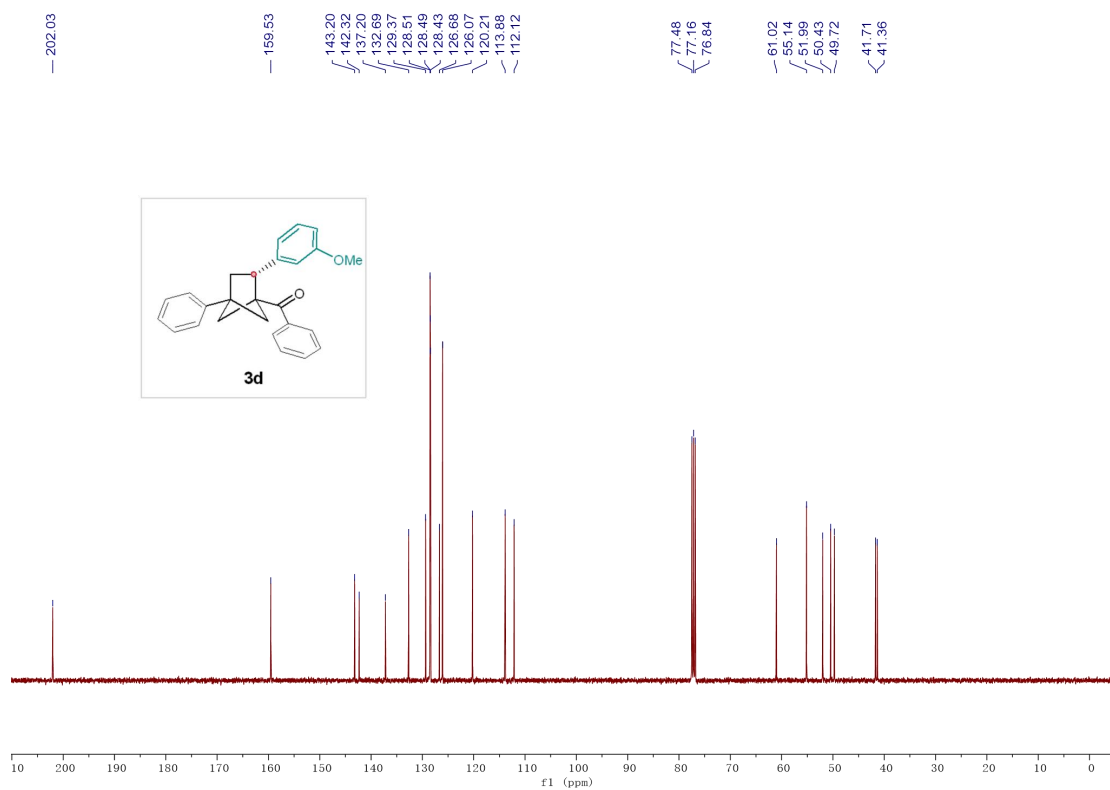
¹H NMR spectrum of **3c**



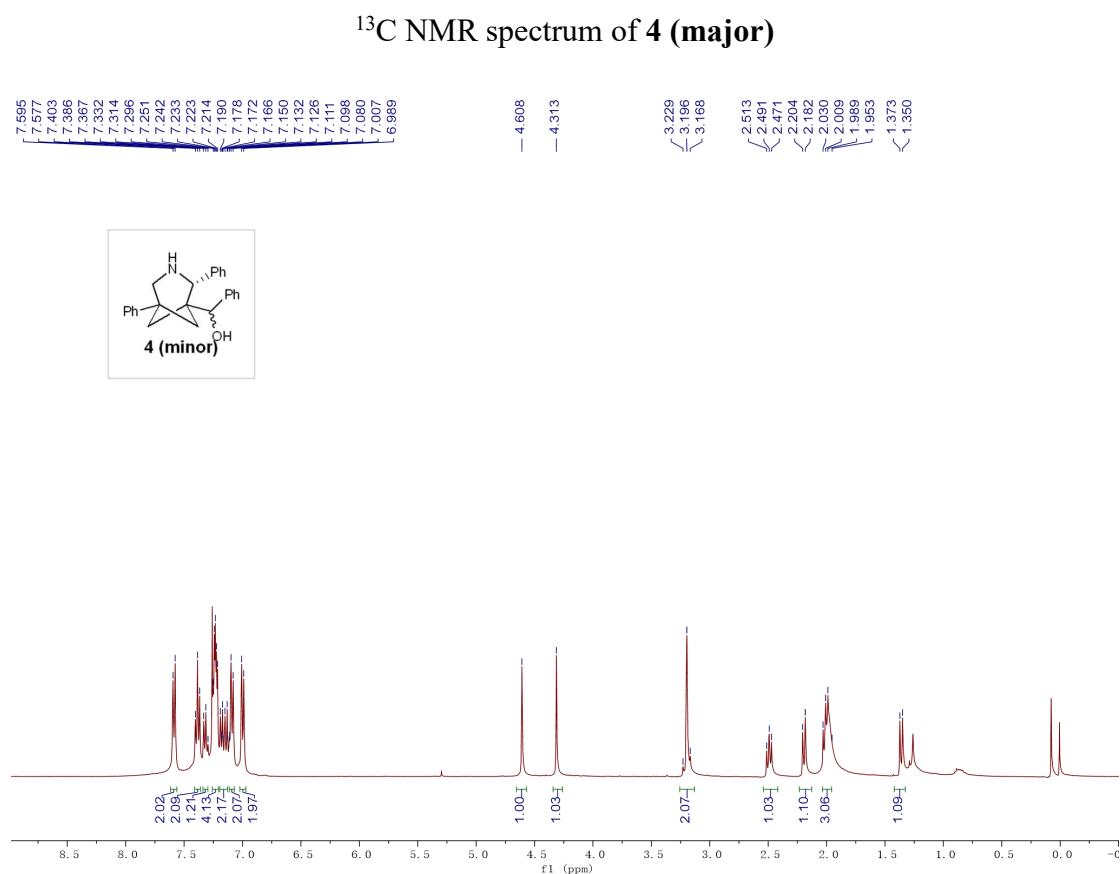
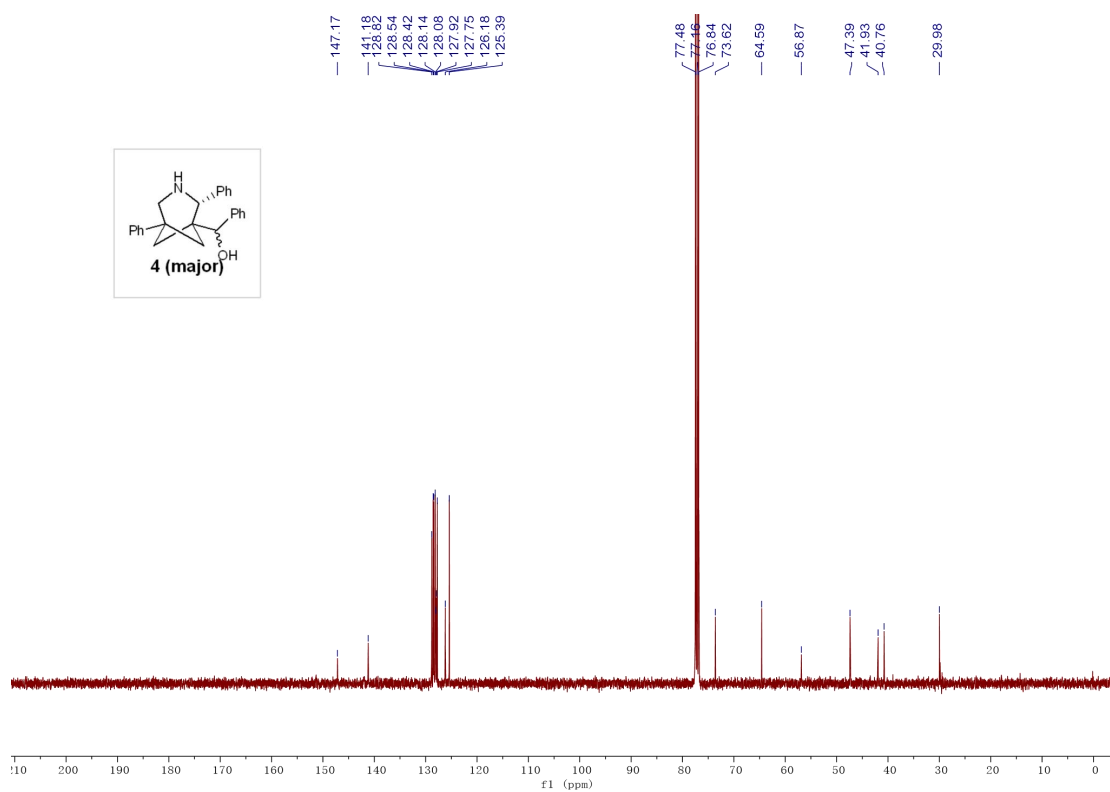
¹³C NMR spectrum of **3c**

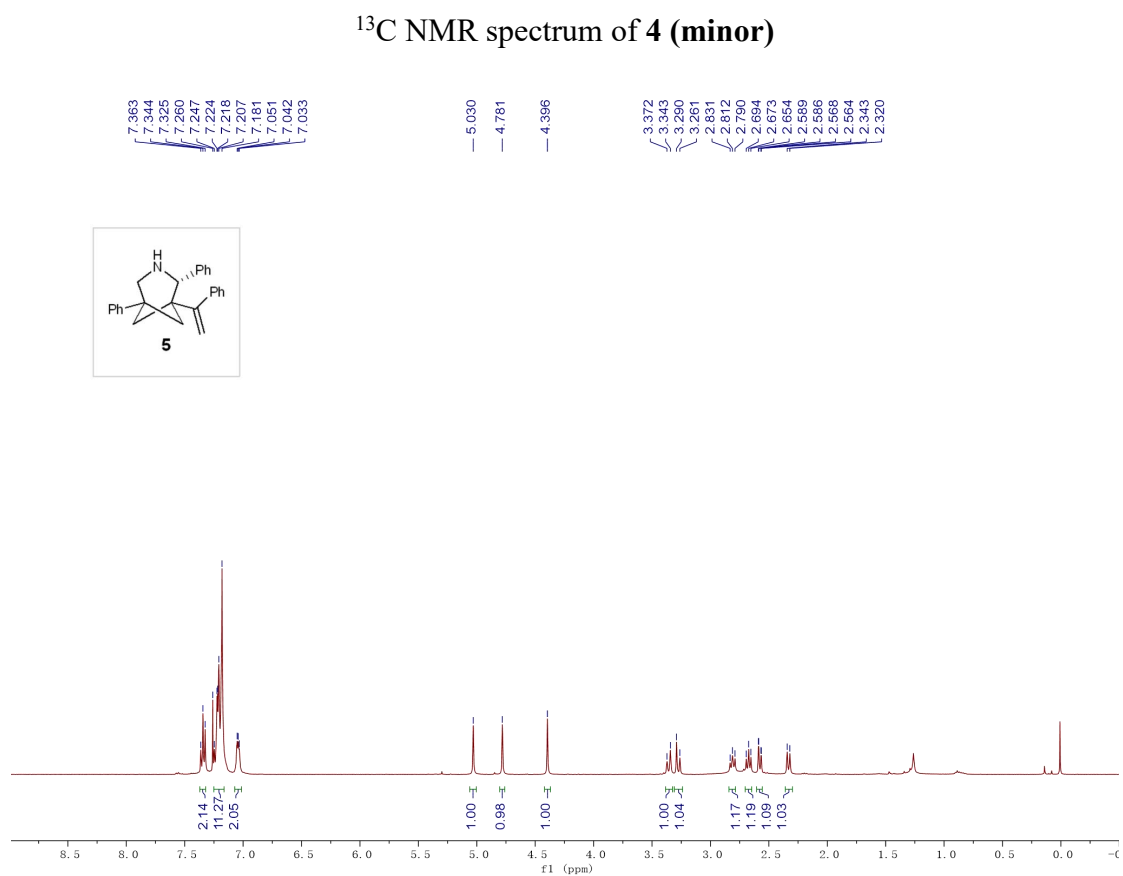
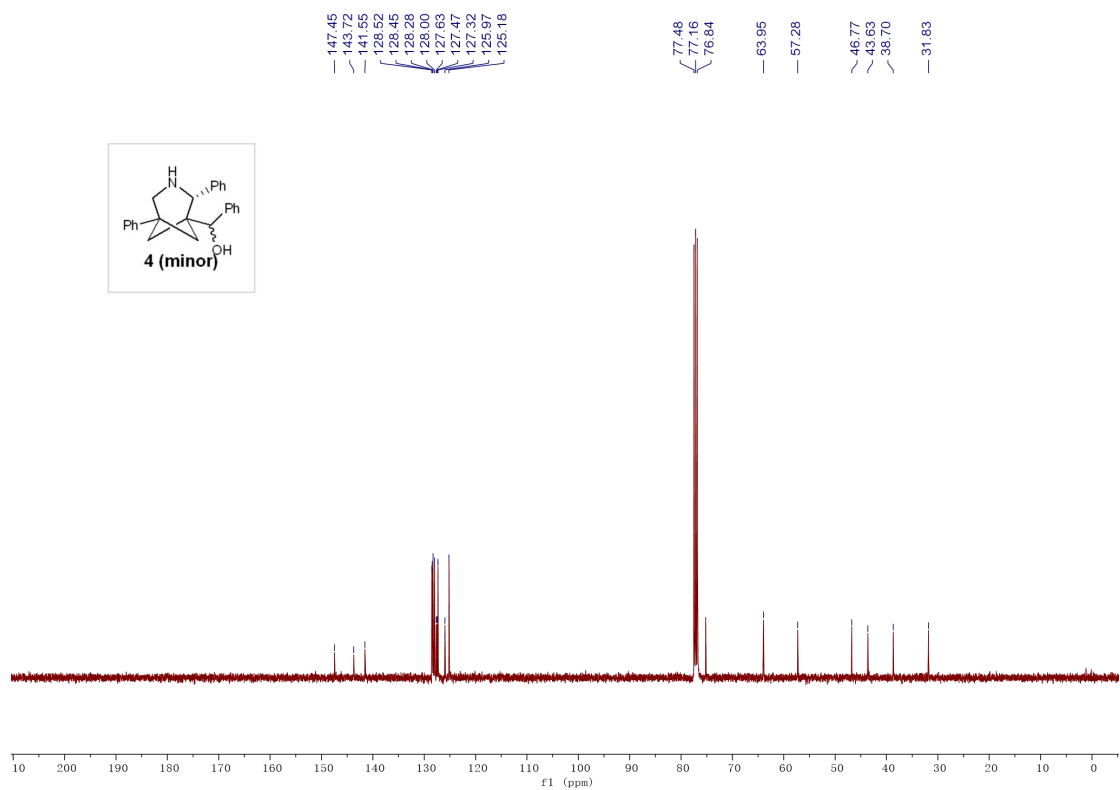


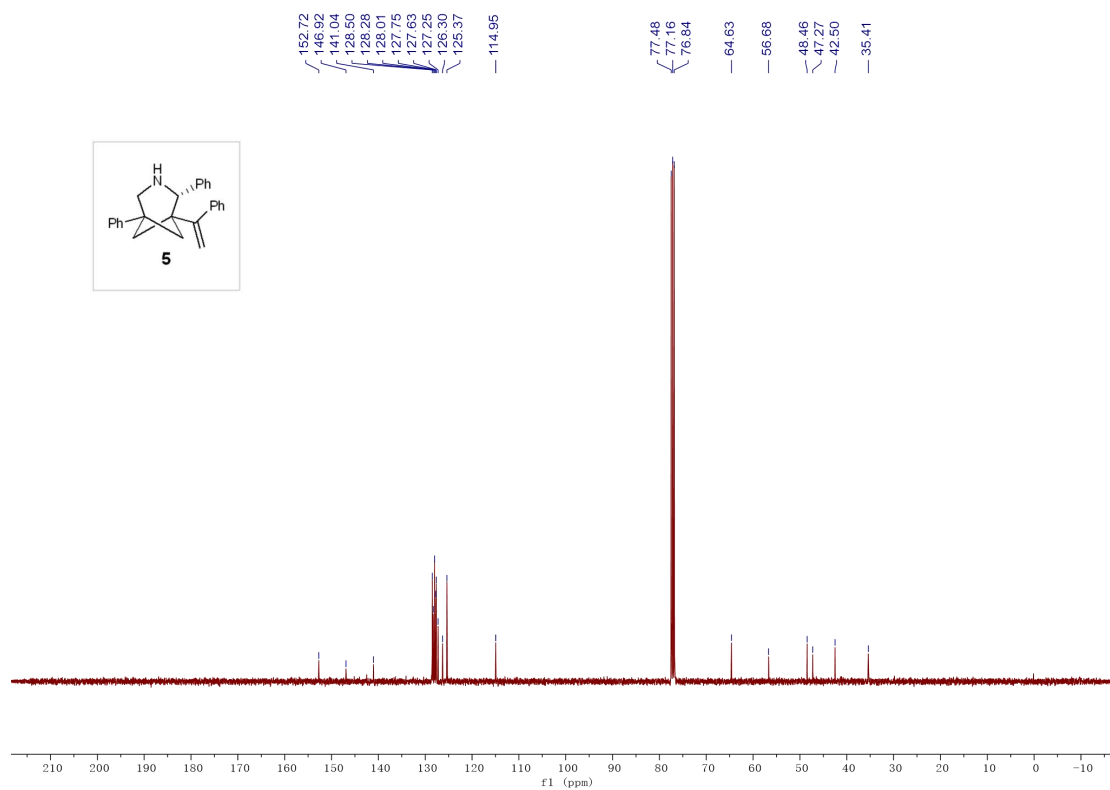
¹H NMR spectrum of **3d**



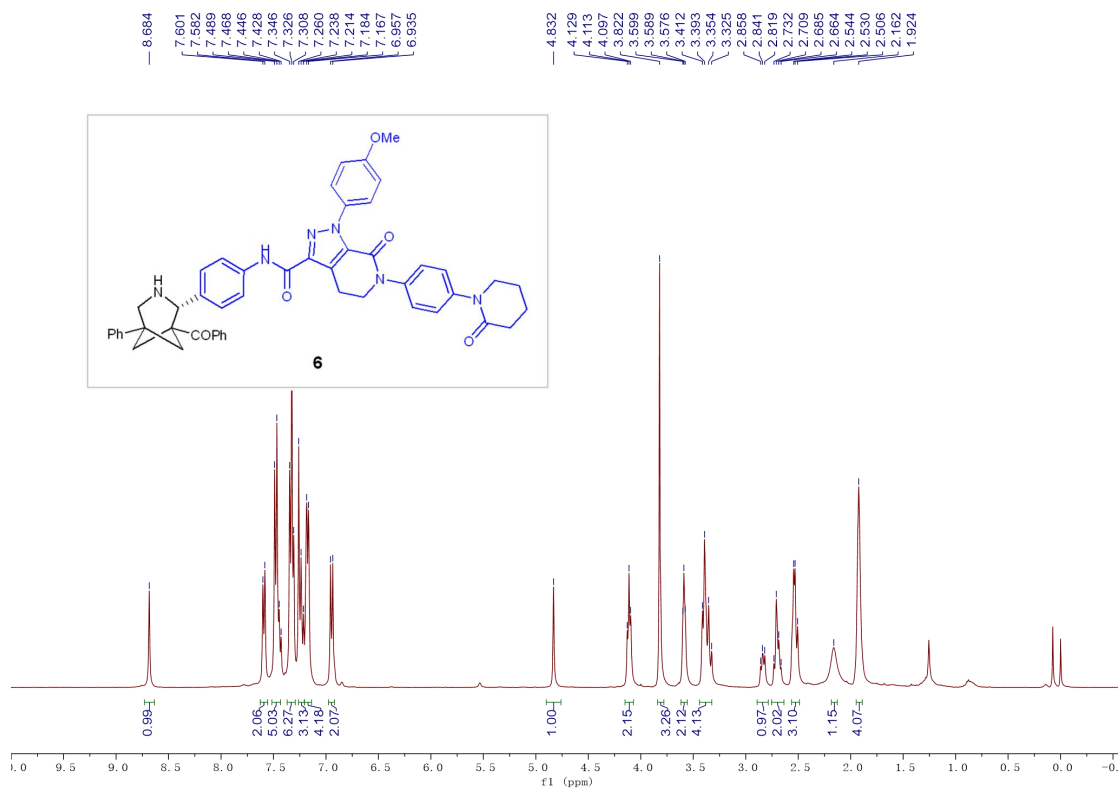
¹H NMR spectrum of **4 (major)**



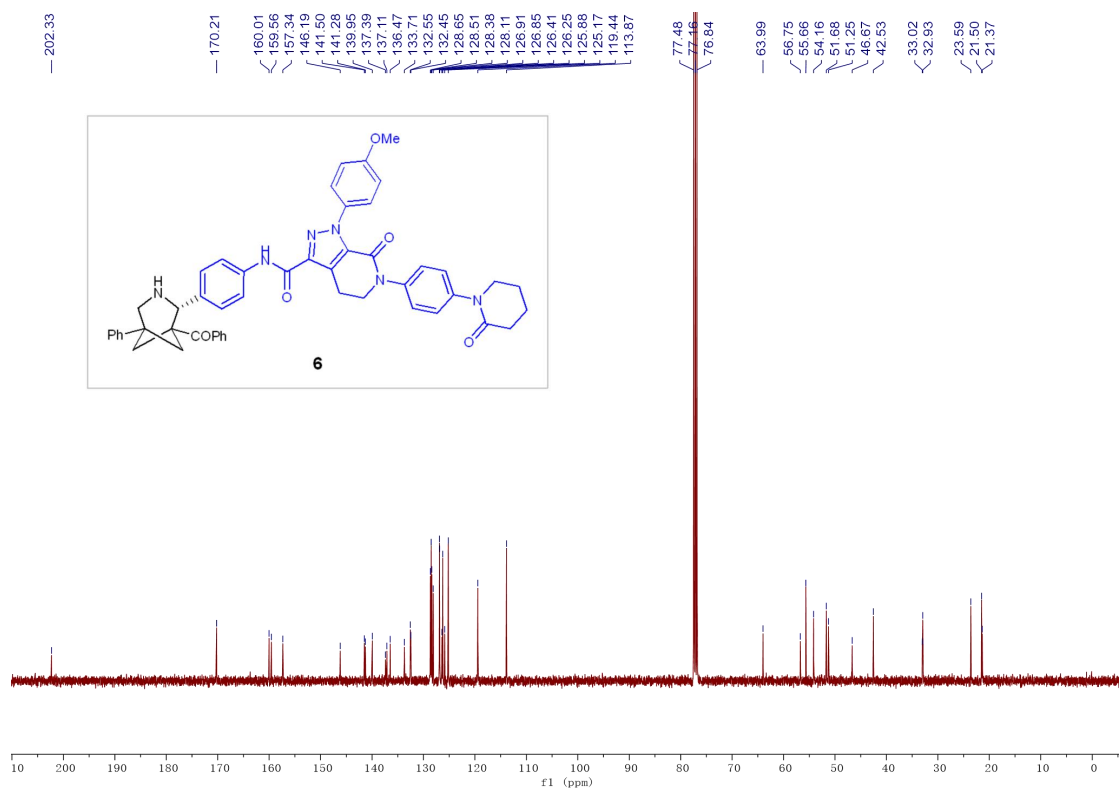




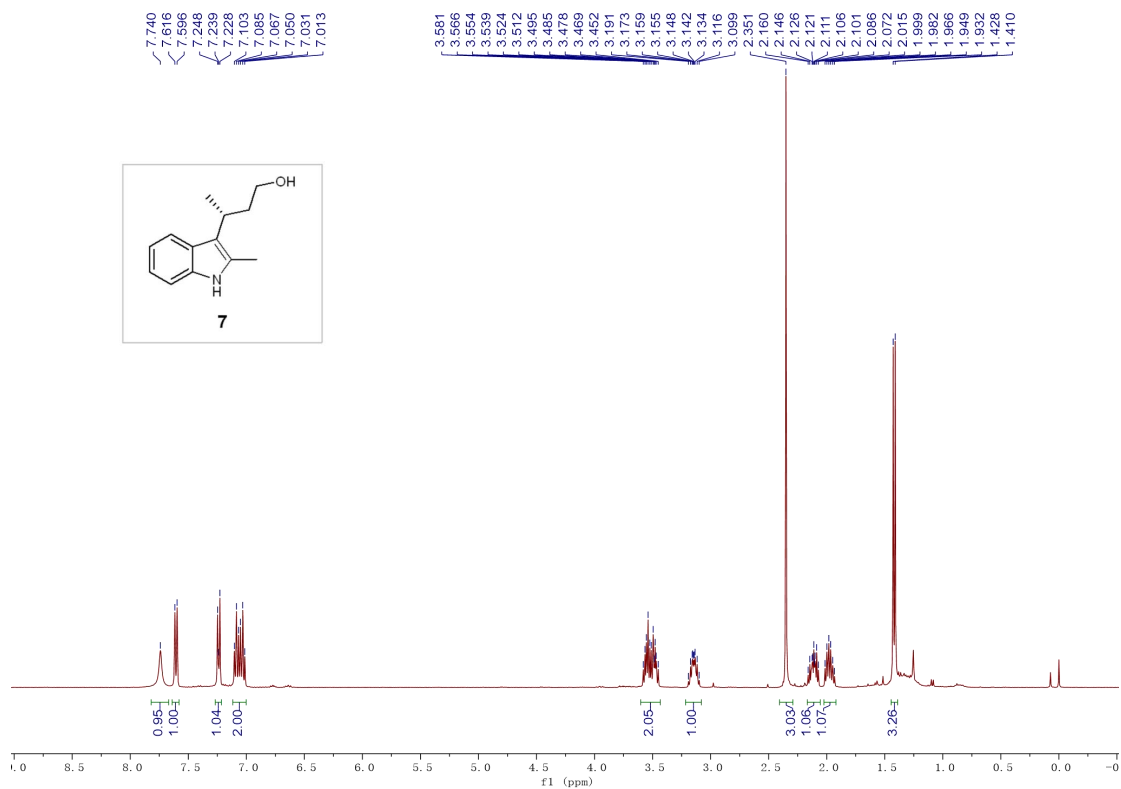
¹³C NMR spectrum of **5**



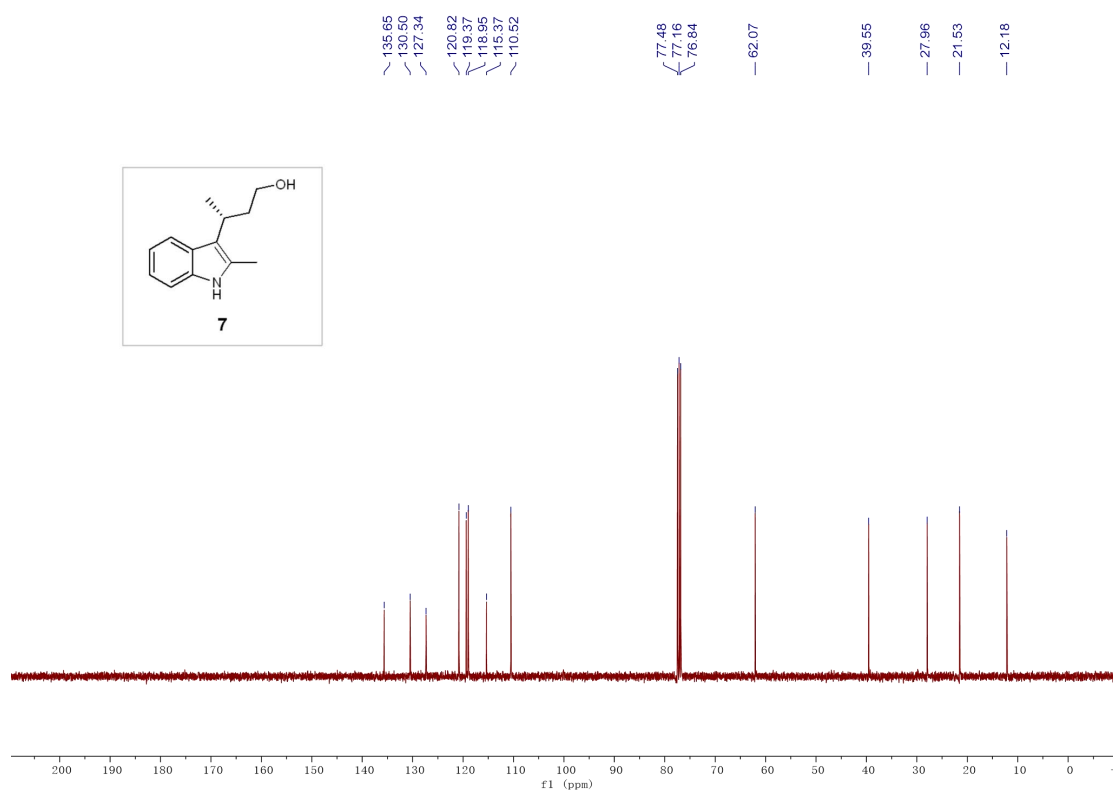
¹H NMR spectrum of **6**



^{13}C NMR spectrum of **6**



^1H NMR spectrum of **7**



^{13}C NMR spectrum of **7**