Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Alkylcarbene mediated intramolecular alkene cyclopropanation to construct aza[3.1.0] bicycles

Zhen Fu, Chengming Wang,* and Cong-Ying Zhou *

College of Chemistry and Materials Science, Guangdong Provincial Key Laboratory of Functional Supramolecular Coordination Materials and Applications, Jinan University, Guangzhou 510632, People's Republic of China. Email: cmwang2019@jnu.edu.cn, zhoucy2018@jnu.edu.cn

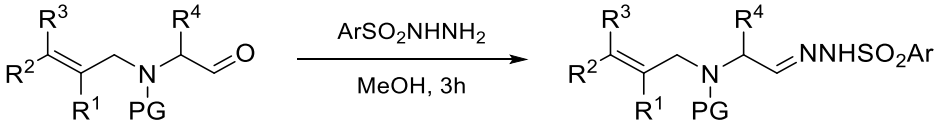
Contents

1. Experimental Section

1.1 General Information

All reactions were performed using the standard Schlenk technique under Ar atmosphere. Reagents were obtained commercially and used without further purification unless indicated otherwise. Arenesulfonylhydrazones were prepared according to the literature. [1-2] All solvents used in the reaction were dried and freshly distilled. Flash column chromatography were performed using silica gel (200-300 mesh, Branch of Qingdao Haiyang Chemical plant) and a gradient solvent system (EtOAc/n-hexane as eluent). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer. Chemical shifts (δ) were measured with tetramethylsilane (TMS) as internal reference. High Resolution Mass Spectrometry (HR-MS) data were obtained on AB SCIEX TripleTOF 5600+ mass spectrometer. Enantiomeric excess (ee) was determined using Agilent 1260 Infinity II high-performance liquid chromatography (HPLC) with a UV detector (at appropriate wavelength).

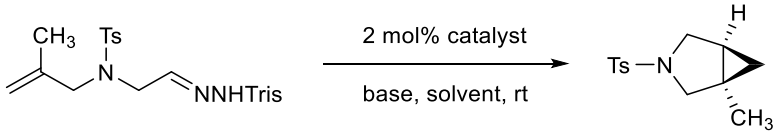
1.2 General procedure for the preparation of arenesulfonylhydrazones



A 25 mL round-bottom flask was charged with arenesulfonyl hydrazide (1 mmol) followed by addition of 5.0 mL of MeOH. Once the solid was dissolved, the aldehyde (1 mmol) was added. After the reaction was stirred for 3h, the solvent was removed directly under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the corresponding product in 80-95% yields.

1.3 General procedure for the intramolecular alkene cyclopropanation of alkyl diazomethanes *in situ* generated from arenesulfonylhydrazones

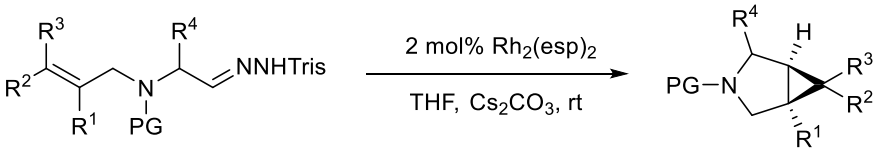
(1) General procedure for reaction condition screening



3a **4a**

A reaction vessel was charged with 2,4,6-triisopropylbenzenesulfonylhydrazone (164 mg, 0.3 mmol), base (3 equiv.), catalyst (2 mol%) and dry solvent (3.0 mL). The mixture was stirred at room temperature until the reaction was completed. The reaction mixture was filtered, the filtrate was concentrated, and the residue was purified by silica gel column chromatography to give corresponding product.

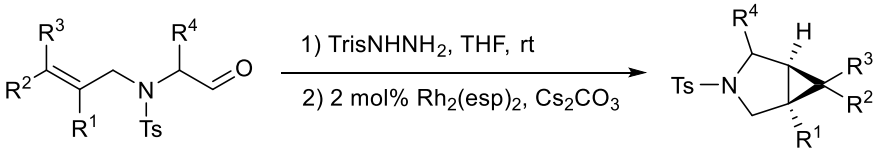
(2) General procedure for $Rh_2(esp)_2$-catalyzed intramolecular alkene cyclopropanation of alkyl diazomethanes *in situ* generated from arenesulfonylhydrazones



3 **4**

A reaction vessel was charged with substrate **3** (0.3 mmol), Cs_2CO_3 (292 mg, 3 equiv.), $Rh_2(esp)_2$ (4.55 mg, 2 mol%) and dry THF (3.0 mL). The mixture was stirred under room temperature until the reaction was completed. The reaction mixture was filtered, the filtrate was concentrated, and the residue was purified by silica gel column chromatography to give corresponding product.

1.4 General procedure for the one-pot $Rh_2(esp)_2$-catalyzed intramolecular alkene cyclopropanation of aldehydes

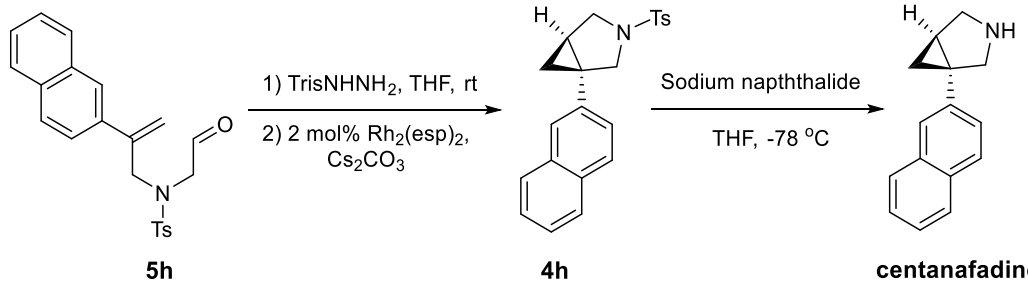


5 **4**

Under argon atmosphere, a solution of the aldehyde **5** (0.3 mmol) and 2,4,6-triisopropylbenzenesulfonyl hydrazide (93 mg, 1.05 equiv.) in 3.0 mL of dry THF was stirred at room temperature for 3 h in a Schlenk-type tube. Cs_2CO_3 (292 mg, 3 equiv.) and $Rh_2(esp)_2$ (4.55 mg, 2 mol%) were added to the reaction mixture. The mixture was stirred at room temperature for 10 h. The reaction mixture was filtered, the filtrate was concentrated, and the residue was purified by silica gel column chromatography to give corresponding product.

1.5 Procedure for the synthesis of Centanafadine and Bicifadine

Centanafadine

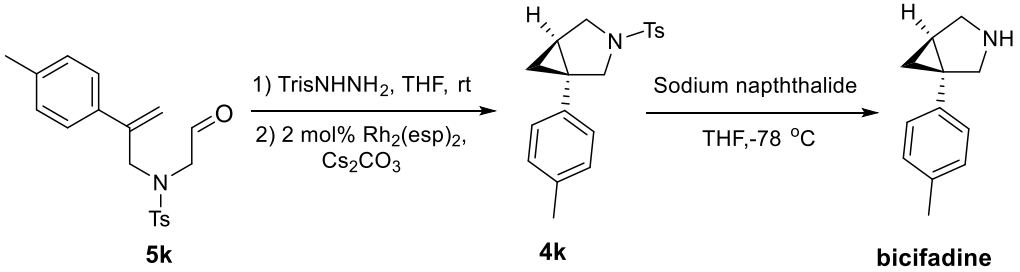


Under argon atmosphere, a solution of the aldehyde **5h** (113 mg, 0.3 mmol) and 2,4,6-triisopropylbenzenesulfonyl hydrazide (93 mg, 1.05 equiv.) in 3.0 mL of dry THF was stirred at room temperature for 3 h in a Schlenk-type tube. Cs_2CO_3 (292 mg, 3 equiv.) and $Rh_2(esp)_2$ (4.55 mg, 2 mol%) were added to the reaction mixture. The mixture was stirred at room temperature for 10h. The reaction mixture was filtered, the filtrate was concentrated, and the residue was purified by silica gel column chromatography to give product **4h** (87 mg, 80%).

Compound **4h** (43 mg, 0.12 mmol) was dissolved in THF (1.0 mL) and cooled to -78 °C. Sodium napththalide solution (~0.25 mL of a 1 M solution in DME) was added dropwise to the sulfonamide solution until a dark green color persisted. The reaction was warmed to room temperature and stirred for 5 minutes. The reaction was quenched with ethanol (until dark green color disappeared) and concentrated in vacuo. Ether and water were added (5 mL each), the layers shaken, and separated. The aqueous phase was washed twice with ether (5 mL each) and the combined organics were dried over sodium sulfate, filtered, and concentrated. Purification

via neutral alumina column (CH_2Cl_2: MeOH = 20:1) to furnish the desired compound Centanafadine (22 mg, 91%).

Bicifadine



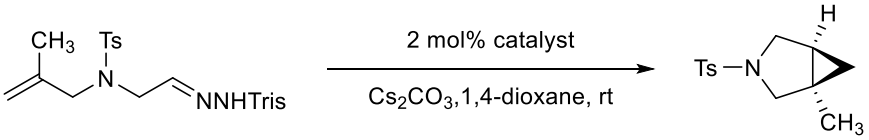
Under argon atmosphere, a solution of the aldehyde **5k** (102 mg, 0.3 mmol) and 2,4,6-triisopropylbenzenesulfonyl hydrazide (93 mg, 1.05 equiv.) in 3.0 mL of dry THF was stirred at room temperature for 3 h in a Schlenk-type tube. Cs_2CO_3 (292 mg, 3 equiv.) and $Rh_2(esp)_2$ (4.55 mg, 2 mol%) were added to the reaction mixture. The mixture was stirred at room temperature for 10h. The reaction mixture was filtered, the filtrate was concentrated, and the residue was purified by silica gel column chromatography to give products **4k** (79 mg, 81%). Compound **4k** (39 mg, 0.12 mmol) was dissolved in THF (1.0 mL) and cooled to -78 ℃. Sodium napththalide solution (~0.25 mL of a 1 M solution in DME) was added dropwise to the sulfonamide solution until a dark green color persisted. The reaction was warmed to room temperature and stirred for 5 minutes. The reaction was quenched with ethanol (until dark green color disappeared) and concentrated in vacuo. Ether and water were added (5 mL each), the layers shaken, and separated. The aqueous phase was washed twice with ether (5 mL each) and the combined organics were dried over sodium sulfate, filtered, and concentrated. Purification via neutral alumina column (CH_2Cl_2: MeOH = 20:1) to furnish the desired compound Bicifadine (18 mg, 92%).

1.6 General procedure for the asymmetric intramolecular cyclopropanation catalyzed by chiral dirhodium catalyst

A reaction vessel was charged with 2,4,6-triisopropylbenzenesulfonylhydrazone **3a** (164 mg, 0.3 mmol), Cs_2CO_3 (3 equiv.), chiral dirhodium catalyst (2 mol%) and dry 1,4-dioxane (3.0 mL). The mixture was stirred at room temperature until the reaction was completed. The

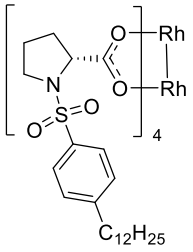
reaction mixture was filtered, the filtrate was concentrated, and the residue was purified by silica gel column chromatography to give corresponding product.

Table S1. Asymmetric intramolecular cyclopropanation of **3a** catalyzed by chiral dirhodium catalyst

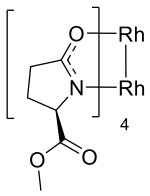


3a **4a**

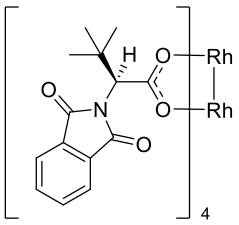
Entry	Catalyst	ee%	%Yield
1	Rh_2(*R*-DOSP)$_4$	42	61
2	Rh_2(*R*-MEPY)$_4$	12	67
3	Rh_2(*S*-PTTL)$_4$	-16	66



Rh_2(*R*-DOSP)$_4$



Rh_2(*R*-MPEY)$_4$



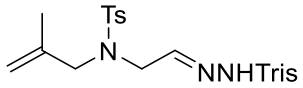
Rh_2(*S*-PTTL)$_4$

[a] Reactions were conducted with **3a** (0.3 mmol) and catalyst (2 mol%), base (0.9 mmol) in 2 mL solvent under Ar. [b] Isolated yields. [c] Determined by HPLC analysis.

2. Characterization Data of Compounds

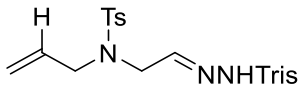
2.1 Characterization data of arenesulfonylhydrazones

4-methyl-N-(2-methylallyl)-N-(2-(2-((2,4,6-triisopropylphenyl)sulfonyl)hydrazineylidene)ethyl)benzenesulfonamide (3a)



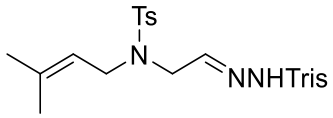
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.76 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 7.9 Hz, 2H), 7.17 (s, 2H), 6.95 (t, *J* = 5.4 Hz, 1H), 4.70 (d, *J* = 1.9 Hz, 1H), 4.53 (s, 1H), 4.13 (p, *J* = 6.7 Hz, 2H), 3.70 (d, *J* = 5.3 Hz, 2H), 3.51 (s, 2H), 2.42 (s, 3H), 1.52 (s, 3H), 1.24 (dd, *J* = 6.8, 1.6 Hz, 18H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 153.55, 151.31, 144.10, 143.90 – 135.71 (m), 130.37 (d, *J* = 80.1 Hz), 127.27, 123.30 (d, *J* = 82.0 Hz), 115.45, 54.16, 48.19, 34.22, 29.85, 24.79, 23.55, 21.53, 19.66; HR-MS (ESI): Calcd for $C_{28}H_{41}N_3O_4S_2Na^+$ $[M+Na]^+$: 570.2430; found: 570.2427.

N-allyl-4-methyl-N-(2-(2-((2,4,6-triisopropylphenyl)sulfonyl)hydrazineylidene)ethyl)benzenesulfonamide (3b)



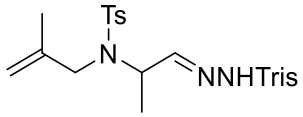
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.81 (s, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.19 (s, 2H), 7.07 (t, *J* = 5.4 Hz, 1H), 5.47 – 5.35 (m, 1H), 4.93 (dd, *J* = 10.1, 1.3 Hz, 1H), 4.80 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.17 (td, *J* = 12.8, 12.1, 6.9 Hz, 2H), 3.79 (d, *J* = 5.5 Hz, 2H), 3.60 (d, *J* = 6.5 Hz, 2H), 2.91 (p, *J* = 7.0 Hz, 1H), 2.37 (s, 3H), 1.24 (dd, *J* = 6.9, 1.8 Hz, 18H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 153.44, 151.30, 143.87, 143.76, 136.23, 131.53, 131.14, 129.90, 127.16, 123.80, 120.00, 50.28, 48.05, 34.19, 29.79, 24.81, 23.56, 21.46; HR-MS (ESI): Calcd for $C_{27}H_{39}N_3O_4S_2Na^+$ $[M+Na]^+$: 556.2274; found: 556.2276.

4-methyl-N-(3-methylbut-2-en-1-yl)-N-(2-(2-((2,4,6-triisopropylphenyl)sulfonyl)hydrazineylidene)ethyl)benzenesulfonamide (3c)



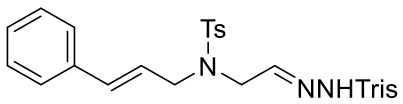
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.52 (s, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.18 (s, 2H), 7.09 (t, *J* = 5.3 Hz, 1H), 4.85 (tdd, *J* = 7.3, 3.0, 1.5 Hz, 1H), 4.18 (p, *J* = 6.7 Hz, 2H), 3.76 (d, *J* = 5.4 Hz, 3H), 3.66 (d, *J* = 7.3 Hz, 2H), 2.91 (p, *J* = 6.5 Hz, 1H), 2.39 (s, 3H), 1.55 (s, 3H), 1.34 (s, 3H), 1.29 – 1.20 (m, 18H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 153.38, 151.36, 144.78, 143.55, 138.43, 136.42, 131.13, 129.78, 127.21, 123.80, 117.69, 47.93, 45.42, 34.19, 29.83, 25.69, 24.79, 23.55, 21.47, 17.55; HR-MS (ESI): Calcd for $C_{29}H_{43}N_3O_4S_2Na^+$ $[M+Na]^+$: 584.2587; found: 584.2590.

4-methyl-N-(2-methylallyl)-N-(1-(2-((2,4,6-triisopropylphenyl)sulfonyl)hydrazineylidene)propan-2-yl)benzenesulfonamide (3d)



^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.48 (s, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.18 (s, 2H), 7.03 (d, *J* = 3.5 Hz, 1H), 4.73 – 4.63 (m, 2H), 4.51 (qd, *J* = 6.9, 3.5 Hz, 1H), 4.14 (p, *J* = 6.7 Hz, 2H), 3.56 (d, *J* = 2.2 Hz, 2H), 2.91 (hept, *J* = 7.0 Hz, 1H), 2.35 (s, 3H), 1.56 (s, 3H), 1.25 (dd, *J* = 6.9, 3.9 Hz, 18H), 1.12 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 153.43, 151.30, 147.55, 143.59, 141.18, 137.42, 131.22, 129.81, 127.11, 123.75, 114.03, 54.59, 50.42, 34.19, 29.88, 24.87, 24.84, 23.57, 23.55, 21.44, 19.78, 14.55; HR-MS (ESI): Calcd for $C_{29}H_{43}N_3O_4S_2Na^+$ $[M+Na]^+$: 584.2587; found: 584.2585.

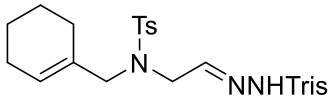
N-cinnamyl-4-methyl-N-(2-(2-((2,4,6-triisopropylphenyl)sulfonyl)hydrazineylidene)ethyl)benzenesulfonamide (3e)



^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.44 (s, 1H), 7.70 – 7.64 (m, 2H), 7.31 – 7.25 (m, 5H), 7.23 (t, *J* = 5.0 Hz, 2H), 7.20 (s, 2H), 7.09 (t, *J* = 5.3 Hz, 1H), 6.33 (d, *J* = 15.8 Hz, 1H), 5.86 (dd, *J* = 15.8, 6.8 Hz, 1H), 4.18 (dt, *J* = 13.5, 6.7 Hz, 2H), 3.83 (dd, *J* = 10.1, 6.1 Hz, 4H), 3.00

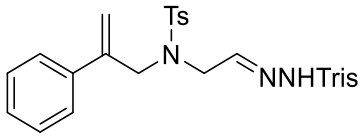
– 2.84 (m, 1H), 2.41 (s, 3H), 1.26 (q, *J* = 6.8 Hz, 18H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 153.48, 151.35, 144.03, 143.78, 136.40, 136.00, 135.03, 131.00, 129.89, 128.53, 128.01, 127.29, 126.54, 123.84, 122.54, 49.65, 47.99, 34.19, 29.86, 24.88, 24.80, 23.55, 21.50; HR-MS (ESI): Calcd for $C_{33}H_{43}N_3O_4S_2Na^+$ $[M+Na]^+$: 632.2587; found: 632.2585.

N-(cyclohex-1-en-1-ylmethyl)-4-methyl-N-(2-(2-((2,4,6-triisopropylphenyl)sulfonyl)hydrazineylidene)ethyl)benzenesulfonamide (3f)



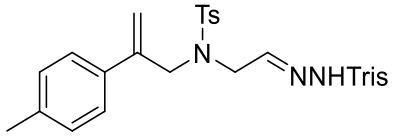
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.48 (s, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.19 (s, 2H), 7.01 (t, *J* = 5.3 Hz, 1H), 5.27 (d, *J* = 3.5 Hz, 1H), 4.16 (p, *J* = 6.8 Hz, 2H), 3.71 (d, *J* = 5.3 Hz, 2H), 3.48 (s, 2H), 2.91 (p, *J* = 7.0 Hz, 1H), 2.38 (s, 3H), 1.87 – 1.73 (m, 4H), 1.52 – 1.37 (m, 4H), 1.29 – 1.19 (m, 18H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 153.38, 151.33, 144.51, 143.58, 136.06, 131.43, 131.06, 129.78, 127.89, 127.25, 123.78, 54.62, 47.73, 34.18, 29.84, 25.89, 25.07, 24.78, 23.53, 22.28, 22.06, 21.46; HR-MS (ESI): Calcd for $C_{31}H_{45}N_3O_4S_2Na^+$ $[M+Na]^+$: 610.2743; found: 610.2741.

4-methyl-N-(2-phenylallyl)-N-(2-(2-((2,4,6-triisopropylphenyl)sulfonyl)hydrazineylidene)ethyl)benzenesulfonamide (3g)



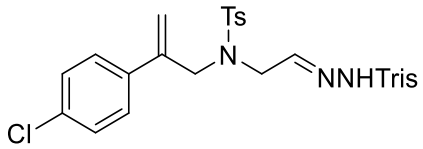
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.95 (s, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.31 – 7.25 (m, 5H), 7.21 (d, *J* = 8.2 Hz, 3H), 7.18 (s, 2H), 6.79 (t, *J* = 5.3 Hz, 1H), 5.28 (s, 1H), 4.88 (d, *J* = 1.2 Hz, 1H), 4.21 – 4.11 (m, 2H), 4.11 (s, 2H), 3.65 (d, *J* = 5.3 Hz, 2H), 2.96 – 2.83 (m, 1H), 2.39 (s, 3H), 1.24 (dd, *J* = 6.9, 2.3 Hz, 18H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 153.54, 151.39, 144.33, 143.79, 141.87, 137.91, 135.43, 130.98, 129.79, 128.44, 128.07, 127.42, 126.65, 123.85, 117.65, 51.85, 47.88, 34.22, 29.87, 24.82, 23.57, 21.51; HR-MS (ESI): Calcd for $C_{33}H_{43}N_3O_4S_2Na^+$ $[M+Na]^+$: 632.2587; found: 632.2589.

4-methyl-N-(2-(p-tolyl)allyl)-N-(2-(2-((2,4,6-triisopropylphenyl)sulfonyl)hydrazineylidene)ethyl)benzenesulfonamide (3h)



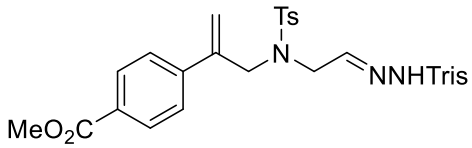
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.24 (dd, *J* = 8.4, 2.7 Hz, 4H), 7.21 (s, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.80 (t, *J* = 5.3 Hz, 1H), 5.26 (s, 1H), 4.84 (d, *J* = 1.2 Hz, 1H), 4.18 (q, *J* = 6.7 Hz, 2H), 4.10 (s, 2H), 3.67 (d, *J* = 5.2 Hz, 2H), 3.03 – 2.83 (m, 1H), 2.42 (s, 3H), 2.36 (s, 3H), 1.26 (dd, *J* = 6.8, 1.8 Hz, 18H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 153.53, 151.38, 144.44, 143.76, 141.60, 137.93, 135.41, 134.93, 130.97, 129.78, 129.13, 127.42, 126.51, 123.85, 116.93, 51.98, 47.87, 34.22, 29.87, 24.82, 23.57, 21.52, 21.16; HR-MS (ESI): Calcd for $C_{34}H_{45}N_3O_4S_2Na^+$ $[M+Na]^+$: 646.2743; found: 646.2744.

N-(2-(4-chlorophenyl)allyl)-4-methyl-N-(2-(2-((2,4,6-triisopropylphenyl)sulfonyl)hydrazineylidene)ethyl)benzenesulfonamide (3i)



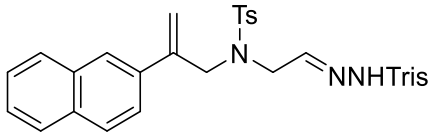
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.12 (s, 1H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.31 – 7.21 (m, 6H), 7.21 (s, 2H), 6.82 (dd, *J* = 6.1, 4.5 Hz, 1H), 5.29 (s, 1H), 4.90 (s, 1H), 4.19 – 4.11 (m, 2H), 4.08 (s, 2H), 3.67 (d, *J* = 5.4 Hz, 2H), 2.93 (p, *J* = 6.9 Hz, 1H), 2.42 (s, 3H), 1.26 (dd, *J* = 6.9, 4.1 Hz, 18H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 153.59, 151.37, 143.96, 143.86, 140.82, 136.28, 135.36, 133.96, 130.93, 129.85, 128.58, 127.99, 127.32, 123.87, 118.27, 51.80, 47.91, 34.21, 29.86, 24.82, 23.58, 21.53; HR-MS (ESI): Calcd for $C_{33}H_{42}ClN_3O_4S_2Na^+$ $[M+Na]^+$: 666.2197; found: 666.2185.

Methyl-4-(3-((4-methyl-N-(2-(2-((2,4,6-triisopropylphenyl)sulfonyl)hydrazineylidene)ethyl)phenyl)sulfonamido)prop-1-en-2-yl)benzoate (3j)



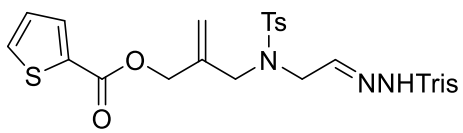
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.43 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 4H), 6.86 (t, *J* = 5.3 Hz, 1H), 5.34 (s, 1H), 4.95 (s, 1H), 4.21 – 4.09 (m, 2H), 4.11 (s, 2H), 3.90 (s, 3H), 3.67 (d, *J* = 5.3 Hz, 2H), 2.90 (p, *J* = 6.9 Hz, 1H), 2.36 (s, 3H), 1.23 (dd, *J* = 6.9, 4.3 Hz, 18H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 166.83, 153.53, 151.35, 143.96, 143.67, 142.49, 141.15, 135.42, 131.04, 129.85, 129.72, 129.50, 127.33, 126.61, 123.84, 119.48, 52.17, 51.53, 47.97, 34.20, 29.84, 24.82, 23.57, 21.47; HR-MS (ESI): Calcd for $C_{35}H_{45}N_3O_6S_2Na^+$ [M+Na]$^+$: 690.2642; found: 690.2642.

4-methyl-N-(2-(naphthalen-2-yl)allyl)-N-(2-(2-((2,4,6-triisopropylphenyl)sulfonyl)hydrazineylidene)ethyl)benzenesulfonamide (3k)



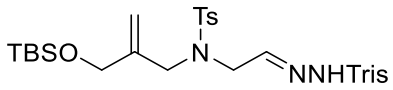
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.11 (s, 1H), 7.85 – 7.71 (m, 5H), 7.47 (qd, *J* = 6.7, 5.4, 3.1 Hz, 6H), 7.19 (s, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.81 (t, *J* = 5.2 Hz, 1H), 5.42 (s, 1H), 4.96 (s, 1H), 4.22 (s, 2H), 4.22 – 4.07 (m, 2H), 3.70 (d, *J* = 5.4 Hz, 2H), 2.98 – 2.82 (m, 1H), 2.34 (s, 3H), 1.29 – 1.21 (m, 18H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 153.53, 151.39, 144.21, 143.75, 141.67, 135.45, 135.18, 133.20, 133.01, 130.99, 129.74, 128.43, 128.03, 127.48, 127.32, 126.24, 125.83, 124.64, 123.86, 122.74, 118.33, 51.95, 47.92, 34.22, 29.87, 24.84, 23.58, 21.49; HR-MS (ESI): Calcd for $C_{37}H_{45}N_3O_4S_2Na^+$ [M+Na]$^+$: 682.2743; found: 682.2740.

2-(((4-methyl-N-(2-(2-((2,4,6-triisopropylphenyl)sulfonyl)hydrazineylidene)ethyl)phenyl)sulfonamido)methyl)allyl thiophene-2-carboxylate (3l)



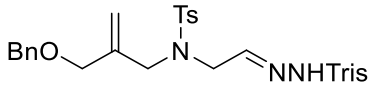
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 7.82 (dd, *J* = 3.8, 1.3 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.58 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.19 (s, 2H), 7.12 (dd, *J* = 5.0, 3.9 Hz, 2H), 5.12 (s, 1H), 4.81 (s, 1H), 4.59 (s, 2H), 4.17 (p, *J* = 6.7 Hz, 2H), 3.82 (d, *J* = 5.4 Hz, 2H), 3.73 (s, 2H), 2.92 (dq, *J* = 13.8, 6.9 Hz, 1H), 2.35 (s, 3H), 1.24 (dd, *J* = 6.9, 2.3 Hz, 18H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 161.65, 153.47, 151.32, 144.01, 143.76, 137.24, 135.60, 133.87, 133.18, 132.81, 131.12, 129.93, 127.92, 127.25, 123.83, 118.73, 64.69, 50.41, 48.36, 34.19, 29.83, 24.84, 23.57, 21.49; HR-MS (ESI): Calcd for $C_{33}H_{43}N_3O_6S_3Na^+$ $[M+Na]^+$: 696.2206; found: 696.2202.

N-(2-(((tert-butyldimethylsilyl)oxy)methyl)allyl)-4-methyl-N-(2-(2-((2,4,6-triisopropylphenyl)sulfonyl)hydrazineylidene)ethyl)benzenesulfonamide (3m)



^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.72 (d, *J* = 2.8 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.20 (s, 2H), 6.99 (t, *J* = 5.3 Hz, 1H), 5.07 (d, *J* = 1.8 Hz, 1H), 4.58 (d, *J* = 1.8 Hz, 1H), 4.17 (p, *J* = 6.6 Hz, 2H), 3.89 (s, 2H), 3.76 (d, *J* = 5.3 Hz, 2H), 3.61 (s, 2H), 2.91 (p, *J* = 6.9 Hz, 1H), 2.35 (s, 3H), 1.25 (dd, *J* = 6.9, 3.2 Hz, 18H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 153.48, 151.34, 143.81, 143.56, 141.61, 135.98, 131.01, 129.89, 127.23, 123.82, 114.70, 63.33, 49.82, 47.67, 34.20, 29.82, 25.85, 24.82, 23.58, 21.44, 18.28, -5.46; HR-MS (ESI): Calcd for $C_{34}H_{55}N_3O_5S_2SiNa^+$ $[M+Na]^+$: 700.3244; found: 700.3244.

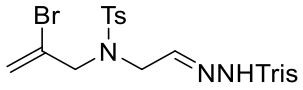
N-(2-((benzyloxy)methyl)allyl)-4-methyl-N-(2-(2-((2,4,6-triisopropylphenyl)sulfonyl)hydrazineylidene)ethyl)benzenesulfonamide (3n)



^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.80 (t, *J* = 3.8 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.25 (m, 5H), 7.22 (d, *J* = 8.5 Hz, 4H), 7.01 (t, *J* = 5.3 Hz, 1H), 5.09 (s, 1H), 4.79 (s, 1H), 4.43 (s, 2H), 4.20 (p, *J* = 6.6 Hz, 2H), 3.84 (s, 2H), 3.77 (d, *J* = 5.4 Hz, 2H), 3.68 (s, 2H), 2.91 (p, *J*

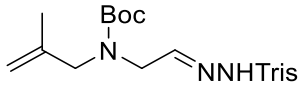
= 6.9 Hz, 1H), 2.34 (s, 3H), 1.33 – 1.19 (m, 18H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 153.48, 151.37, 143.85, 143.77, 139.54, 138.14, 135.77, 131.19, 129.93, 128.40, 127.75, 127.65, 127.32, 123.86, 117.29, 72.27, 70.44, 50.32, 48.40, 34.23, 29.85, 26.95, 24.88, 23.63, 21.48; HR-MS (ESI): Calcd for $C_{35}H_{47}N_3O_5S_2Na^+$ $[M+Na]^+$: 676.2849; found:676.2851.

N-(2-bromoallyl)-4-methyl-N-(2-(2-((2,4,6-triisopropylphenyl)sulfonyl)hydrazineylidene)ethyl)benzenesulfonamide (3o)



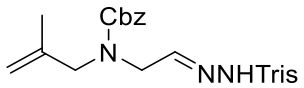
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.50 (s, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.20 (s, 2H), 7.08 (t, *J* = 5.4 Hz, 1H), 5.48 (d, *J* = 1.9 Hz, 1H), 5.39 (d, *J* = 2.1 Hz, 1H), 4.16 (p, *J* = 6.7 Hz, 2H), 3.89 (s, 2H), 3.81 (d, *J* = 5.4 Hz, 2H), 2.92 (p, *J* = 6.9 Hz, 1H), 2.40 (s, 3H), 1.26 (dd, *J* = 6.9, 2.6 Hz, 18H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 153.59, 151.34, 144.07, 143.16, 135.96, 130.94, 129.86, 127.42, 126.92, 123.87, 120.98, 54.99, 48.20, 34.21, 29.85, 24.83, 23.57, 21.52; HR-MS (ESI): Calcd for $C_{27}H_{38}BrN_3O_4S_2Na^+$ $[M+Na]^+$: 612.1559; found: 612.1555.

tert-butyl-(2-methylallyl)(2-(2-((2,4,6-triisopropylphenyl)sulfonyl)hydrazineylidene)ethyl)carbamate (3p)



^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.50 (s, 1H), 7.16 (s, 2H), 7.13 – 7.04 (m, 1H), 4.70 (s, 1H), 4.52 (d, *J* = 11.1 Hz, 1H), 4.18 (p, *J* = 6.7 Hz, 2H), 3.80 (td, *J* = 12.4, 11.4, 5.9 Hz, 3H), 3.56 (d, *J* = 23.1 Hz, 2H), 2.88 (p, *J* = 6.9 Hz, 1H), 1.53 (s, 3H), 1.49 – 1.28 (m, 11H), 1.24 (dt, *J* = 6.9, 2.7 Hz, 18H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 153.35, 151.30, 151.27, 144.88, 140.38, 131.10, 123.78, 113.23, 112.22, 80.28, 52.06, 47.45, 46.84, 34.19, 34.16, 29.82, 28.22, 24.85, 24.81, 23.56, 19.77; HR-MS (ESI): Calcd for $C_{26}H_{43}N_3O_4SNa^+$ $[M+Na]^+$: 516.2866; found: 516.2872.

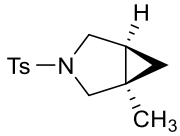
benzyl-(2-methylallyl)(2-(2-((2,4,6-triisopropylphenyl)sulfonyl)hydrazineylidene)ethyl)carbamate (3q)



^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.33 (t, *J* = 6.9 Hz, 5H), 7.21 (s, 2H), 7.11 (d, *J* = 25.2 Hz, 1H), 5.11 (d, *J* = 11.4 Hz, 2H), 4.75 (s, 1H), 4.56 (s, 1H), 4.22 (p, *J* = 6.7 Hz, 2H), 4.00 – 3.83 (m, 2H), 3.66 (d, *J* = 7.8 Hz, 2H), 3.00 – 2.85 (m, 1H), 1.55 (d, *J* = 7.7 Hz, 3H), 1.27 (dd, *J* = 6.9, 1.3 Hz, 18H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 156.38, 153.36, 151.32, 144.11, 139.80, 136.32, 128.57, 128.50, 128.07, 128.02, 127.80, 123.81, 112.63, 67.63, 54.03, 52.37, 51.88, 47.39, 47.03, 34.21, 29.85, 24.83, 23.58, 19.81; HR-MS (ESI): Calcd for $C_{29}H_{41}N_3O_4SNa^+$ $[M+Na]^+$: 550.2710; found: 550.2713.

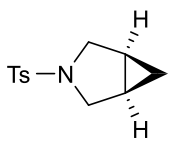
2.2 Characterization data of products

1-methyl-3-tosyl-3-azabicyclo[3.1.0]hexane (4a)



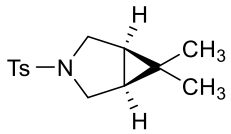
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 3.49 (dd, *J* = 9.1, 3.4 Hz, 2H), 3.10 (dd, *J* = 9.1, 3.9 Hz, 1H), 2.84 (d, *J* = 9.0 Hz, 1H), 2.45 (s, 3H), 1.16 (s, 3H), 1.14 – 1.08 (m, 1H), 0.56 (t, *J* = 4.5 Hz, 1H), 0.46 (dd, *J* = 7.8, 5.0 Hz, 1H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 143.35, 133.61, 129.58, 127.55, 54.39, 50.37, 23.09, 22.19, 21.54, 18.24, 14.37; HR-MS (ESI): Calcd for $C_{13}H_{17}NO_2SNa^+$ $[M+Na]^+$: 274.0872; found: 274.0875.

3-tosyl-3-azabicyclo[3.1.0]hexane (4b)



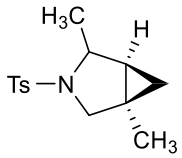
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.50 (d, *J* = 9.1 Hz, 2H), 3.04 (d, *J* = 9.3 Hz, 1H), 2.42 (s, 3H), 1.39 (dddd, *J* = 7.7, 3.9, 2.4, 1.3 Hz, 2H), 0.54 (td, *J* = 7.8, 5.1 Hz, 1H), 0.35 (q, *J* = 4.3 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 143.36, 133.60, 129.56, 127.54, 49.81, 21.51, 15.59, 7.56; HR-MS (ESI): Calcd for $C_{12}H_{15}NO_2SNa^+$ $[M+Na]^+$: 260.0715; found: 260.0720.

6,6-dimethyl-3-tosyl-3-azabicyclo[3.1.0]hexane (4c)



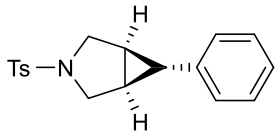
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.39 – 3.23 (m, 4H), 2.42 (s, 3H), 1.66 (s, 1H), 1.25 (dd, *J* = 3.1, 1.5 Hz, 2H), 0.96 (d, *J* = 1.5 Hz, 6H).^{13}C NMR (75 MHz, Chloroform-*d*) δ 143.23, 134.07, 129.55, 127.41, 47.75, 28.09, 26.54, 21.51, 19.84, 12.65; HR-MS (ESI): Calcd for $C_{14}H_{19}NO_2SNa^+$ $[M+Na]^+$: 288.1028; found: 288.1032.

1,4-dimethyl-3-tosyl-3-azabicyclo[3.1.0]hexane (4d)



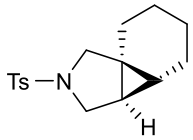
A mixture of diastereoisomers in dr = 1:1. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 3.4 Hz, 2H), 7.66 (d, *J* = 3.4 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 3.87 (q, *J* = 6.4 Hz, 1H), 3.55 (d, *J* = 9.0 Hz, 1H), 3.43 (d, *J* = 10.3 Hz, 1H), 3.37 (td, *J* = 6.0, 4.0 Hz, 1H), 3.30 (dd, *J* = 10.3, 1.2 Hz, 1H), 2.91 (d, *J* = 9.0 Hz, 1H), 2.45 (s, 3H), 2.42 (s, 3H), 1.40 (d, *J* = 6.0 Hz, 3H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.18 (s, 3H), 1.10 (s, 3H), 0.91 (dd, *J* = 7.8, 4.1 Hz, 1H), 0.79 (t, *J* = 4.4 Hz, 1H), 0.35 (dd, *J* = 7.9, 4.9 Hz, 1H), 0.29 (ddd, *J* = 7.8, 5.1, 1.2 Hz, 1H), -0.30 (t, *J* = 4.6 Hz, 1H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 143.41, 142.98, 137.33, 132.98, 129.61, 129.51, 127.84, 126.85, 59.11, 57.53, 57.18, 53.00, 30.17, 29.26, 23.21, 22.03, 21.54, 21.49, 19.96, 18.79, 18.53, 18.49, 14.41, 12.12; HR-MS (ESI): Calcd for $C_{14}H_{19}NO_2SNa^+$ $[M+Na]^+$: 288.1028; found: 288.1030.

6-phenyl-3-tosyl-3-azabicyclo[3.1.0]hexane (4e)



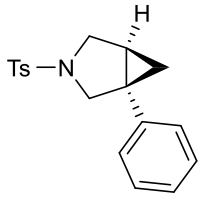
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.27 – 7.09 (m, 3H), 6.97 – 6.91 (m, 2H), 3.71 (d, *J* = 9.5 Hz, 2H), 3.18 (dt, *J* = 9.4, 1.7 Hz, 2H), 2.46 (s, 3H), 1.88 (t, *J* = 3.6 Hz, 1H), 1.76 – 1.68 (m, 2H);^{13}C NMR (75 MHz, Chloroform-*d*) δ 143.61, 140.41, 133.33, 129.70, 128.43, 127.63, 125.96, 125.65, 50.29, 26.57, 25.04, 21.57; HR-MS (ESI): Calcd for $C_{18}H_{19}NO_2SNa^+$ $[M+Na]^+$: 336.1028; found: 336.1032.

2-tosyloctahydro-1H-benzo[1,3]cyclopropa[1,2-c]pyrrole (4f)



^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.70 – 7.61 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 3.47 (dd, *J* = 14.9, 9.0 Hz, 2H), 3.05 (dd, *J* = 9.0, 3.9 Hz, 1H), 2.85 (d, *J* = 9.0 Hz, 1H), 2.42 (s, 3H), 1.86 (ddt, *J* = 13.6, 7.9, 5.8 Hz, 1H), 1.76 – 1.57 (m, 3H), 1.48 – 1.31 (m, 2H), 1.31 – 1.02 (m, 2H), 1.01 – 0.89 (m, 2H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 143.23, 133.75, 129.52, 127.55, 55.04, 50.76, 27.10, 26.46, 24.19, 23.17, 21.98, 21.79, 21.51, 18.86; HR-MS (ESI): Calcd for $C_{16}H_{22}NO_2S^+$ $[M+H]^+$: 292.1365; found: 292.1364.

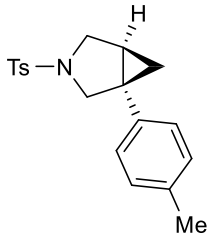
1-phenyl-3-tosyl-3-azabicyclo[3.1.0]hexane (4g)



^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.16 (m, 5H), 7.09 – 7.02 (m, 2H), 3.89 (d, *J* = 8.9 Hz, 1H), 3.66 (d, *J* = 9.1 Hz, 1H), 3.27 – 3.17 (m, 2H), 2.43 (s, 3H), 1.79 (dt, *J* = 8.1, 4.1 Hz, 1H), 1.14 (t, *J* = 4.7 Hz, 1H), 0.97 (dd, *J* = 8.1, 5.1 Hz, 1H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 143.59, 140.34, 133.26, 129.69, 128.53, 127.61, 126.52, 126.45,

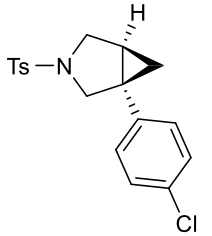
53.26, 50.14, 31.10, 23.77, 21.54, 17.34; HR-MS (ESI): Calcd for $C_{18}H_{19}NO_2SNa^+$ $[M+Na]^+$: 336.1028; found: 336.1027.

1-(p-tolyl)-3-tosyl-3-azabicyclo[3.1.0]hexane (4h)



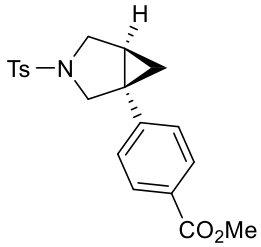
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.2 Hz, 1H), 3.81 (d, *J* = 8.9 Hz, 1H), 3.60 (d, *J* = 9.1 Hz, 1H), 3.19 – 3.10 (m, 2H), 2.38 (s, 3H), 2.25 (s, 3H), 1.70 (dt, *J* = 8.0, 4.1 Hz, 1H), 1.05 (t, *J* = 4.7 Hz, 1H), 0.88 (dd, *J* = 8.1, 5.0 Hz, 1H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 143.57, 137.23, 136.25, 133.27, 129.68, 129.20, 127.61, 126.51, 53.50, 50.20, 30.87, 23.58, 21.54, 20.97, 17.02; HR-MS (ESI): Calcd for $C_{19}H_{21}NO_2SNa^+$ $[M+Na]^+$: 350.1185; found: 350.1186.

1-(4-chlorophenyl)-3-tosyl-3-azabicyclo[3.1.0]hexane (4i)



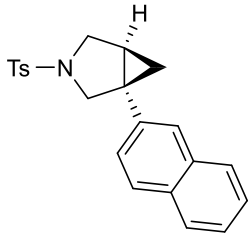
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 3.85 (d, *J* = 9.0 Hz, 1H), 3.64 (d, *J* = 9.2 Hz, 1H), 3.23 – 3.14 (m, 2H), 2.42 (s, 3H), 1.76 (dt, *J* = 7.9, 3.9 Hz, 1H), 1.12 (t, *J* = 4.8 Hz, 1H), 0.93 (dd, *J* = 8.0, 5.2 Hz, 1H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 143.71, 138.81, 133.22, 132.30, 129.75, 128.63, 127.99, 127.58, 53.20, 50.06, 30.68, 23.89, 21.57, 17.20. HR-MS (ESI): Calcd for $C_{18}H_{18}ClNO_2SNa^+$ $[M+Na]^+$: 370.0639; found: 370.0647.

methyl 4-(3-tosyl-3-azabicyclo[3.1.0]hexan-1-yl)benzoate (4j)



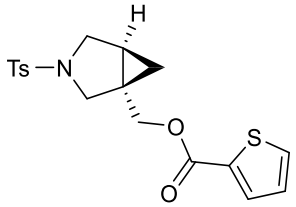
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.90 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 3.89 (d, *J* = 9.3 Hz, 2H), 3.87 (s, 3H), 3.65 (d, *J* = 9.2 Hz, 1H), 3.25 (d, *J* = 9.0 Hz, 1H), 3.19 (dd, *J* = 9.2, 3.7 Hz, 1H), 2.41 (s, 3H), 1.86 (dt, *J* = 8.1, 4.0 Hz, 1H), 1.21 (dd, *J* = 10.0, 5.2 Hz, 1H), 1.00 (dd, *J* = 8.1, 5.2 Hz, 1H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 166.72, 145.88, 143.75, 133.13, 129.80, 129.76, 128.21, 127.59, 126.00, 52.52, 52.12, 49.93, 31.04, 24.72, 21.55, 18.36; HR-MS (ESI): Calcd for $C_{20}H_{21}NO_4SNa^+$ $[M+Na]^+$: 394.1083; found: 394.1078.

1-(naphthalen-2-yl)-3-tosyl-3-azabicyclo[3.1.0]hexane (4k)



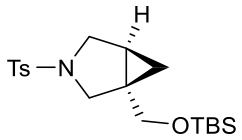
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.83 – 7.74 (m, 5H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.47 (tt, *J* = 6.9, 5.1 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.16 (dd, *J* = 8.6, 1.9 Hz, 1H), 4.01 (d, *J* = 9.0 Hz, 1H), 3.74 (d, *J* = 9.1 Hz, 1H), 3.39 (d, *J* = 9.0 Hz, 1H), 3.30 (dd, *J* = 9.1, 3.7 Hz, 1H), 2.45 (s, 3H), 1.93 (dt, *J* = 8.1, 4.1 Hz, 1H), 1.23 (t, *J* = 4.7 Hz, 1H), 1.10 (dd, *J* = 8.0, 5.1 Hz, 1H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 143.64, 137.65, 133.33, 133.25, 132.11, 129.75, 128.31, 127.63, 127.43, 126.42, 125.76, 125.20, 124.64, 53.38, 50.22, 31.42, 23.82, 21.57, 17.26; HR-MS (ESI): Calcd for $C_{22}H_{21}NO_2SNa^+$ $[M+Na]^+$: 386.1185; found: 386.1186.

3-tosyl-3-azabicyclo[3.1.0]hexan-1-yl)methyl thiophene-2-carboxylate (4l)



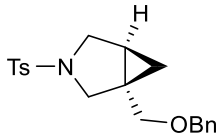
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.72 (dd, *J* = 3.8, 1.3 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.56 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.36 – 4.15 (m, 2H), 3.66 (d, *J* = 9.2 Hz, 1H), 3.54 (d, *J* = 9.3 Hz, 1H), 3.14 – 3.06 (m, 2H), 2.43 (s, 3H), 1.52 – 1.40 (m, 1H), 0.82 (d, *J* = 6.2 Hz, 2H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 161.95, 143.54, 133.61, 133.15, 132.66, 129.66, 127.81, 127.60, 66.90, 51.54, 49.80, 27.26, 21.56, 20.96, 13.16; HR-MS (ESI): Calcd for $C_{18}H_{19}NO_4S_2Na^+$ $[M+Na]^+$: 400.0647; found: 400.0647.

1-(((tert-butyldimethylsilyl)oxy)methyl)-3-tosyl-3-azabicyclo[3.1.0]hexane (4m)



^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.71 – 7.64 (m, 2H), 7.37 – 7.27 (m, 2H), 3.65 (d, *J* = 10.9 Hz, 1H), 3.48 (d, *J* = 9.1 Hz, 2H), 3.44 (d, *J* = 11.1 Hz, 1H), 3.11 – 2.98 (m, 2H), 2.42 (s, 3H), 1.30 – 1.20 (m, 1H), 0.77 (s, 8H), 0.69 – 0.53 (m, 2H), -0.05 (d, *J* = 7.5 Hz, 5H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 143.40, 133.01, 129.57, 127.61, 64.32, 51.03, 50.30, 30.05, 25.74, 21.52, 20.06, 18.11, 12.22, -5.36, -5.44; HR-MS (ESI): Calcd for $C_{19}H_{31}NO_3SSiNa^+$ $[M+Na]^+$: 404.1686; found: 404.1689.

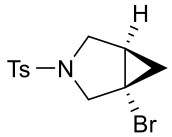
1-((benzyloxy)methyl)-3-tosyl-3-azabicyclo[3.1.0]hexane (4n)



^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.30 (t, *J* = 7.9 Hz, 5H), 7.26 – 7.20 (m, 2H), 4.44 (d, *J* = 3.1 Hz, 2H), 3.59 (d, *J* = 9.1 Hz, 1H), 3.51 (d, *J* = 9.3 Hz, 1H), 3.49 – 3.37 (m, 2H), 3.11 (dd, *J* = 9.2, 4.8 Hz, 2H), 2.43 (s, 3H), 1.30 (dt, *J* = 8.1, 4.1 Hz, 1H), 0.66 (dd, *J* = 9.2, 3.5 Hz, 2H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 143.43, 137.99, 133.55, 129.62,

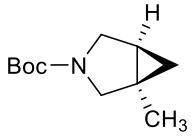
128.42, 127.73, 127.57, 127.55, 72.70, 72.02, 51.61, 49.91, 27.86, 21.56, 20.13, 12.92; HR-MS (ESI): Calcd for $C_{20}H_{23}NO_3SNa^+$ $[M+Na]^+$: 380.1291; found: 380.1292.

1-bromo-3-tosyl-3-azabicyclo[3.1.0]hexane (4o)



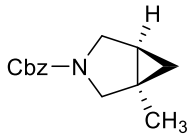
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 3.87 (d, *J* = 9.2 Hz, 1H), 3.47 (d, *J* = 9.5 Hz, 1H), 3.24 – 3.16 (m, 2H), 2.44 (s, 3H), 1.76 (ddd, *J* = 8.6, 4.7, 3.7 Hz, 1H), 1.28 – 1.15 (m, 1H), 1.15 – 1.05 (m, 1H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 143.97, 133.11, 129.85, 127.53, 55.89, 49.20, 29.58, 25.03, 21.58, 17.60; HR-MS (ESI): Calcd for $C_{12}H_{15}BrNO_2S^+$ $[M+H]^+$: 316.0001; found: 316.0002.

tert-butyl-1-methyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (4p)



^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.52 (dt, *J* = 18.7, 9.7 Hz, 2H), 3.43 – 3.29 (m, 1H), 3.10 (d, *J* = 10.4 Hz, 1H), 1.41 (s, 9H), 1.21 (s, 3H), 1.16 – 1.07 (m, 1H), 0.53 (dd, *J* = 7.8, 4.8 Hz, 1H), 0.31 (t, *J* = 4.4 Hz, 1H);^{13}C NMR (75 MHz, Chloroform-*d*) δ 155.03, 79.07, 53.34, 52.92, 49.81, 48.98, 48.62, 28.48, 23.23, 22.65, 22.48, 21.98, 18.65, 16.02; HR-MS (ESI): Calcd for $C_{11}H_{19}NO_2Na^+$ $[M+Na]^+$: 220.1308; found: 220.1306.

benzyl-1-methyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (4q)

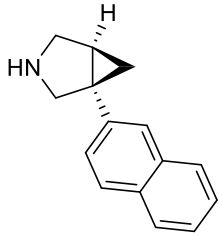


^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.41 – 7.29 (m, 5H), 5.10 (d, *J* = 2.4 Hz, 2H), 3.61 (ddd, *J* = 17.7, 13.5, 10.5 Hz, 2H), 3.45 (dt, *J* = 10.1, 4.4 Hz, 1H), 3.25 – 3.16 (m, 1H), 1.24 (d, *J* = 6.1 Hz, 3H), 1.25 – 1.13 (m, 1H), 0.58 (dd, *J* = 7.9, 4.9 Hz, 1H), 0.35 (t, *J* = 4.4 Hz,

1H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 155.29, 136.95, 128.44, 127.88, 127.79, 127.76, 66.66, 53.52, 53.14, 49.28, 48.87, 23.38, 22.66, 21.96, 18.63, 16.12; HR-MS (ESI): Calcd for $C_{14}H_{17}NO_2Na^+$ $[M+Na]^+$: 254.1151; found: 254.1155.

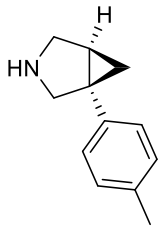
2.3 Characterization data of products centanafadine and bicifadine

Centanafadine



^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.81 (t, *J* = 7.7 Hz, 3H), 7.73 – 7.64 (m, 1H), 7.52 – 7.36 (m, 2H), 7.36 – 7.26 (m, 1H), 3.39 (q, *J* = 11.2 Hz, 2H), 3.28 – 3.11 (m, 2H), 1.86 (dt, *J* = 7.8, 3.8 Hz, 1H), 1.12 (dd, *J* = 8.0, 5.2 Hz, 1H), 1.02 (t, *J* = 4.9 Hz, 1H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 139.42, 133.42, 132.02, 128.02, 127.59, 127.42, 126.17, 125.54, 125.50, 125.40, 53.17, 49.28, 33.03, 25.91, 14.83; HR-MS (ESI): Calcd for $C_{15}H_{16}N^+$ $[M+H]^+$: 210.1276; found: 210.1283.

Bicifadine



^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.13 (s, 4H), 3.36 – 3.19 (m, 2H), 3.17 – 3.04 (m, 2H), 3.01 (s, 2H), 2.35 (s, 3H), 1.70 (ddd, *J* = 7.8, 4.4, 3.2 Hz, 1H), 0.97 (dd, *J* = 8.1, 5.1 Hz, 1H), 0.89 (q, *J* = 4.6 Hz, 1H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 139.04, 135.60, 129.04, 127.05, 53.36, 49.27, 32.48, 25.70, 20.98, 14.54; HR-MS (ESI): Calcd for $C_{12}H_{16}N^+$ $[M+H]^+$: 174.1276; found: 174.1287.

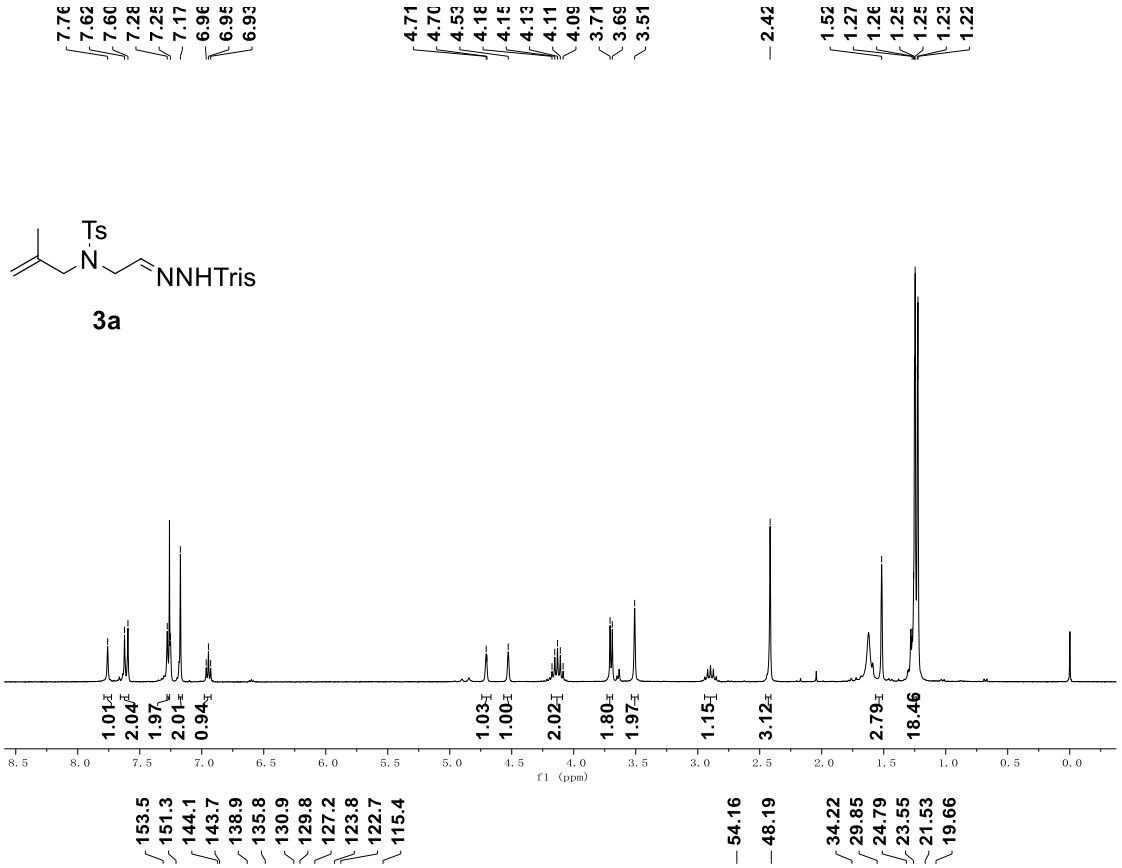
3. Reference

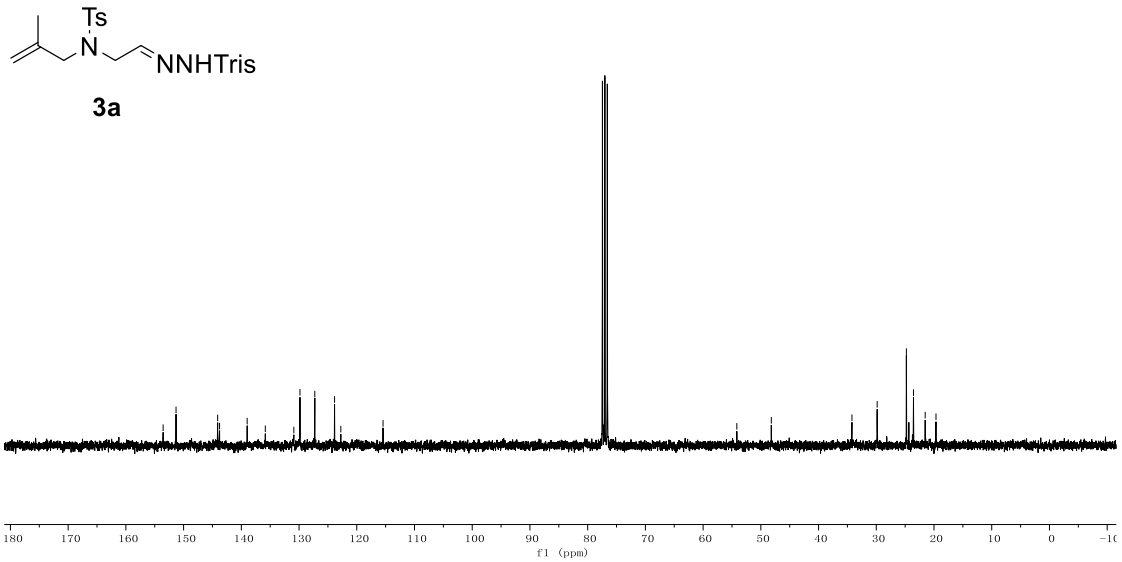
[1] P. Zhou, X. X. Li, D. Wang and T. Xu, Dual Nickel- and Photoredox-Catalyzed Reductive Cross-Coupling to Access Chiral Trifluoromethylated Alkanes, *Org. Lett.,* 2021, **23**, 4683.

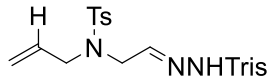
[2] A. R. Reddy, C.-Y. Zhou, Z. Guo, J. Wei and C.-M. Che, Ruthenium-Porphyrin-Catalyzed Diastereoselective Intramolecular Alkyl Carbene Insertion into C-H Bonds of Alkyl Diazomethanes Generated In Situ from N-Tosylhydrazones, *Angew. Chem., Int. Ed.,* 2014, **53**, 14175.

4. NMR Spectra of Compunds

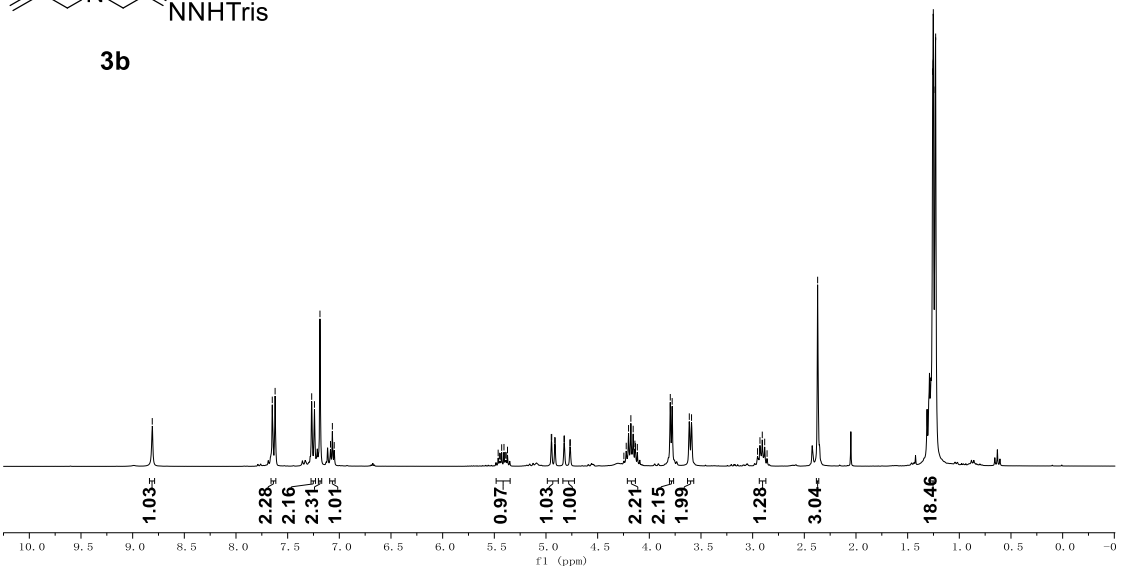
NMR Spectra of arenesulfonylhydrazones






H
Ts
N
NNHTris

3b


1.03
2.28
2.16
2.31
1.01
0.97
1.03
1.00
2.21
2.15
1.99
1.28
3.04
18.46
f1 (ppm)


153.4
151.3
143.8
143.7
136.2
131.5
131.1
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127.1
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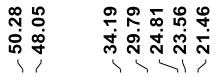
120.0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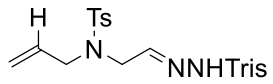
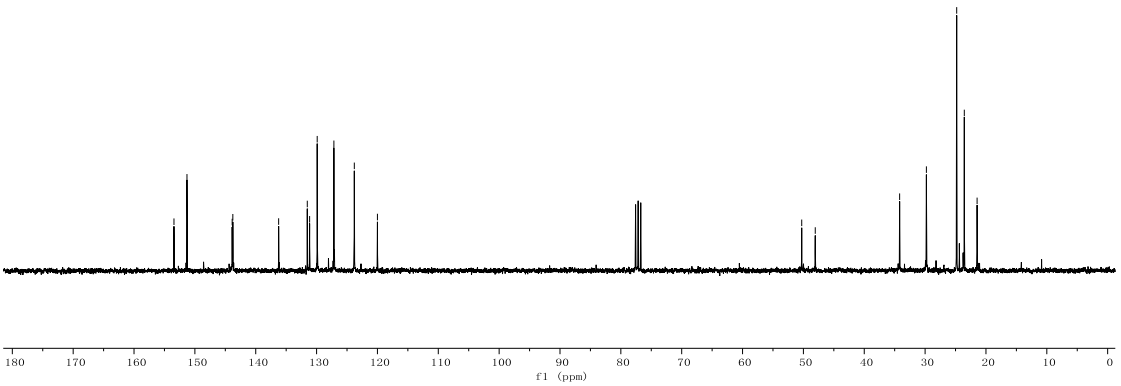
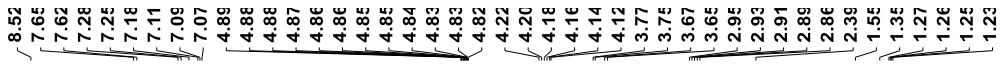
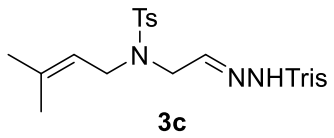
21.46


H
Ts
N
NNHTris

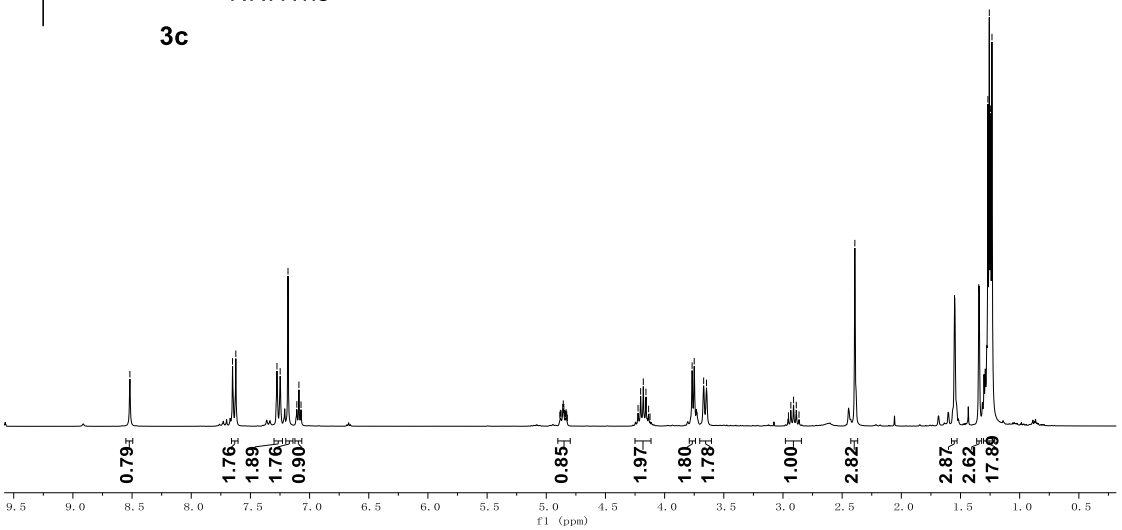
3b


f1 (ppm)




Ts
N
NNHTris

3c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1.76
1.89
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0.90
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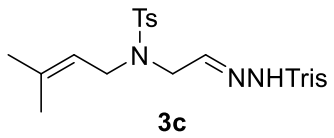
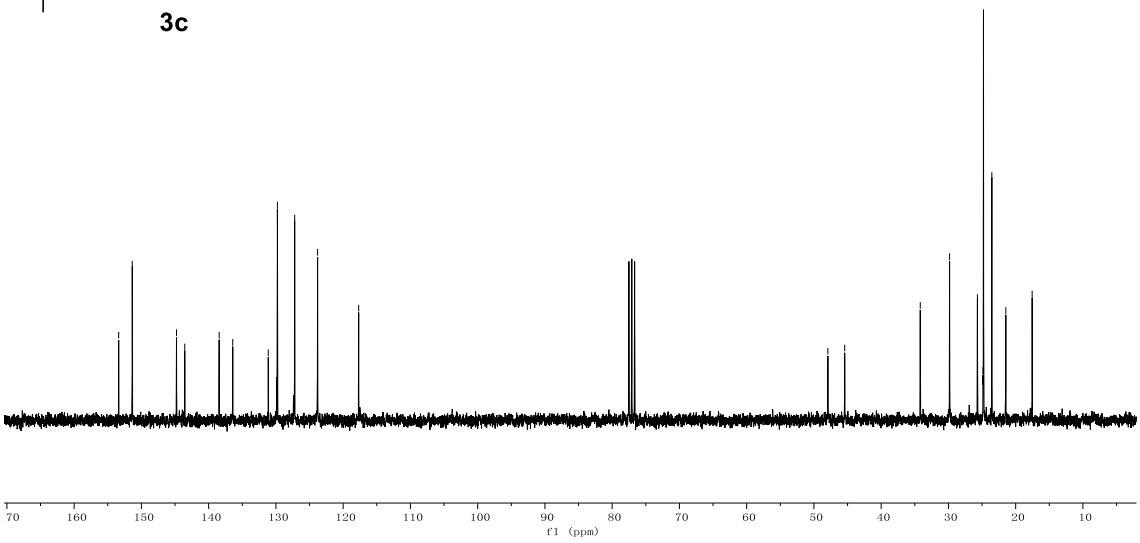
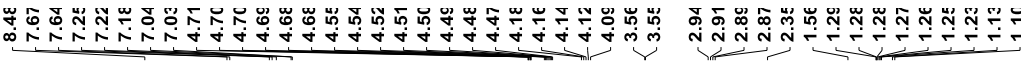
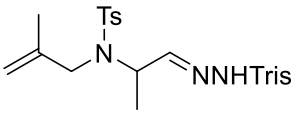
1.97
1.80
1.78
1.00
2.82
2.87
2.62
17.80
f1 (ppm)


Ts
N
NNHTris

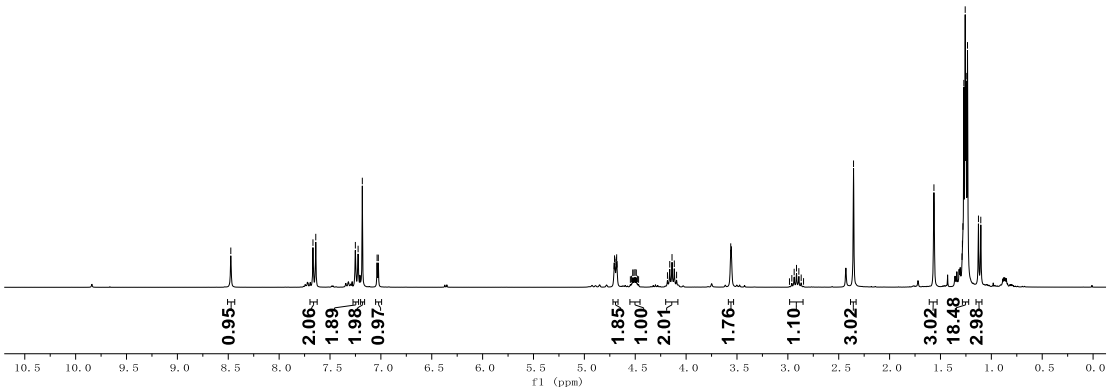
3c


f1 (ppm)




Ts
N
NNHTris

3d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1.98
0.97
1.85
1.00
2.01
1.76
1.10
3.02
3.02
18.48
2.98
f1 (ppm)


153.4
151.3
147.5
143.5
141.1
137.4
136.0
131.2
129.8
127.1
123.7
114.0
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23.57
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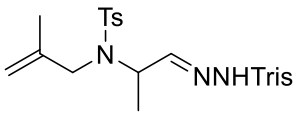
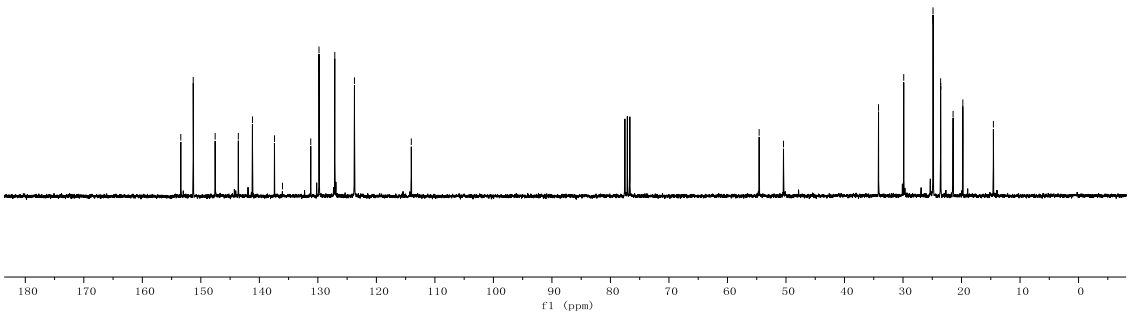
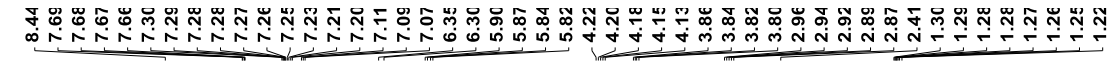
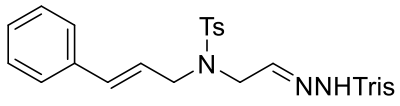
14.55


Ts
N
NNHTris

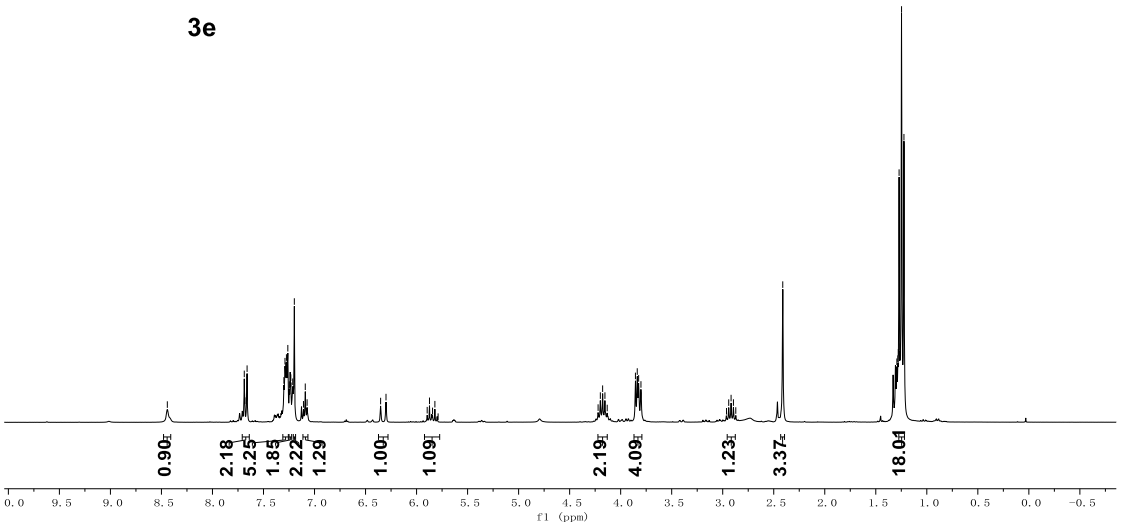
3d

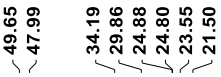

f1 (ppm)

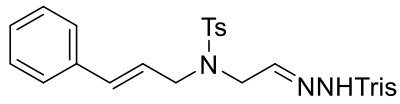



Ts
N
NNHTris

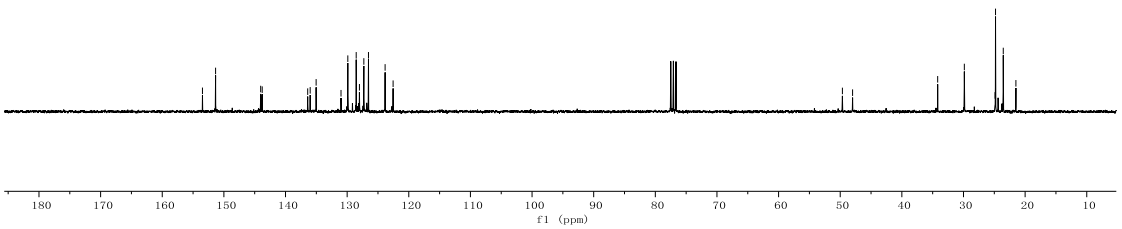
3e

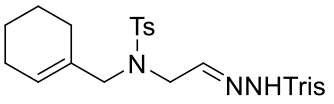

0.90
2.18
5.25
1.85
2.22
1.29
1.00
1.09
2.19
4.09
1.23
3.37
18.04
f1 (ppm)



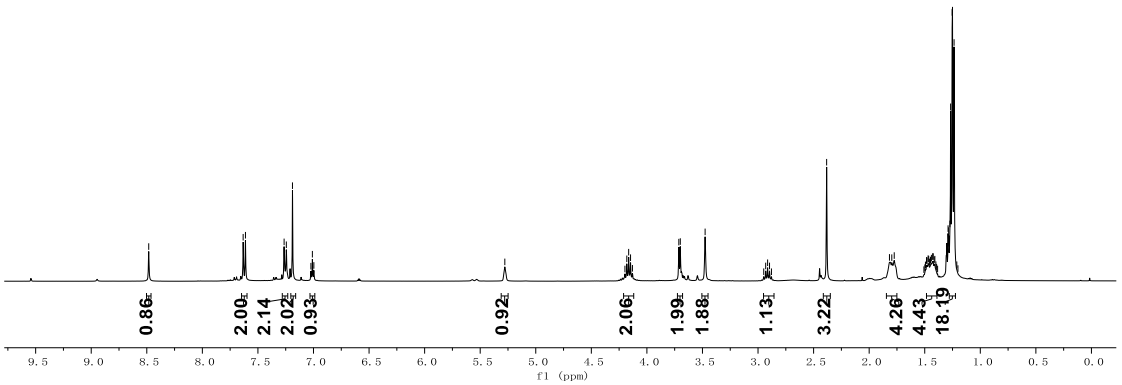

Ts
N
NNHTris

3e


f1 (ppm)


Ts
N
NNHTris

3f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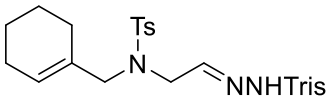
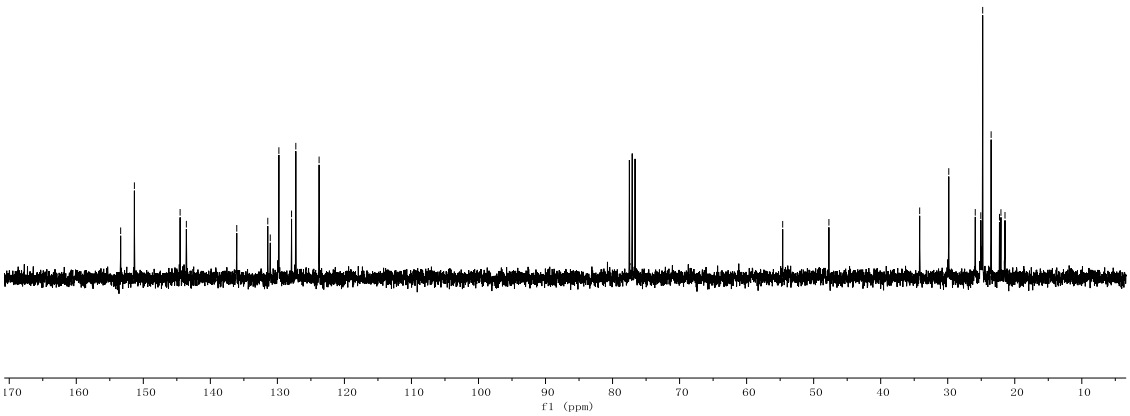
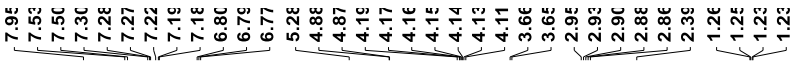
0.93
0.92
2.06
1.99
1.88
1.13
3.22
4.26
4.43
18.19
f1 (ppm)

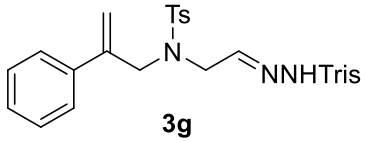

153.3
151.3
144.5
143.5
136.0
131.4
131.0
129.7
127.8
127.2
123.7
54.62
47.73
34.18
29.84
25.89
25.07
24.78
23.53
22.28
22.06
21.46


Ts
N
NNHTris

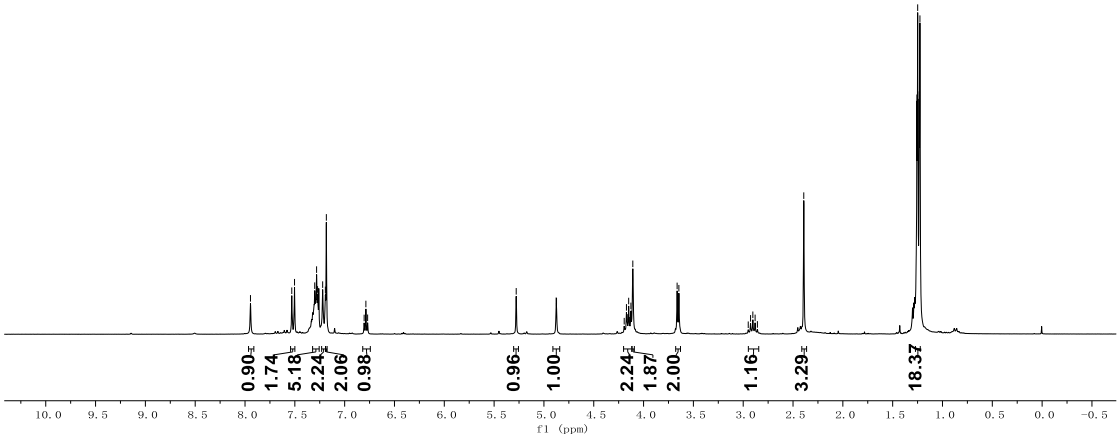
3f


f1 (ppm)




Ts
N
NNHTris

3g


0.90
1.74
5.18
2.24
2.06
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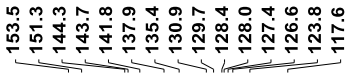
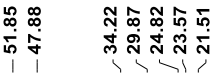
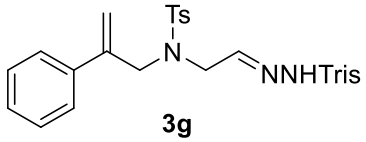
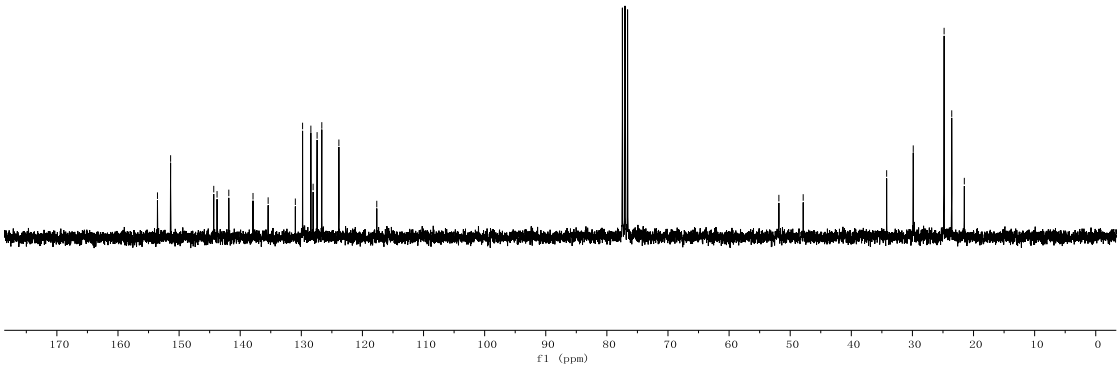
0.96
1.00
2.24
1.87
2.00
1.16
3.29
18.37
f1 (ppm)

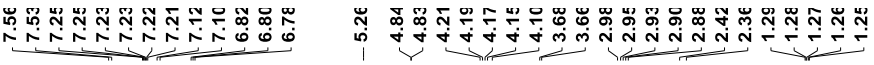


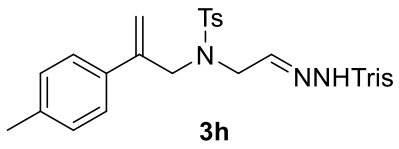



Ts
N
NNHTris

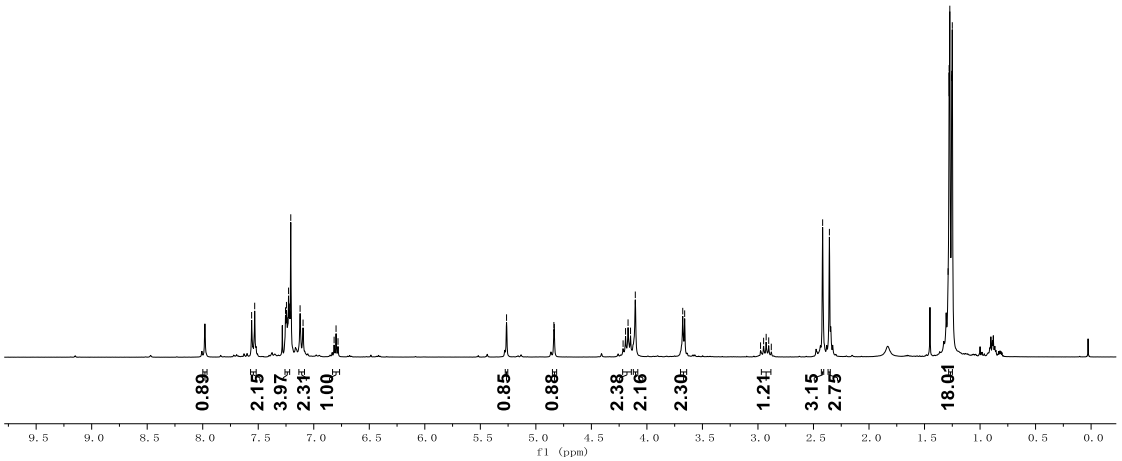
3g


f1 (ppm)




Ts
N
NNHTris

3h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2.19
3.97
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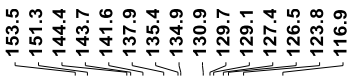
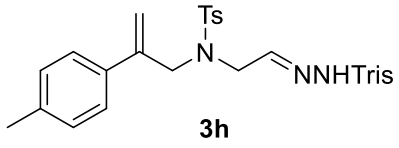
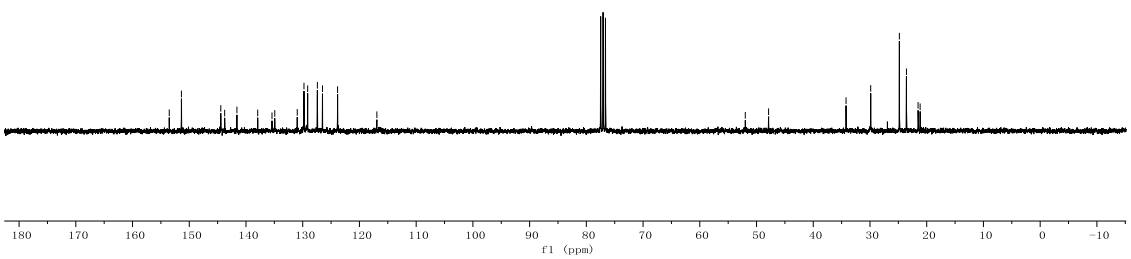
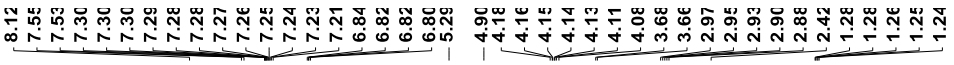
0.88
2.38
2.16
2.30
1.21
3.15
2.75
18.04
f1 (ppm)

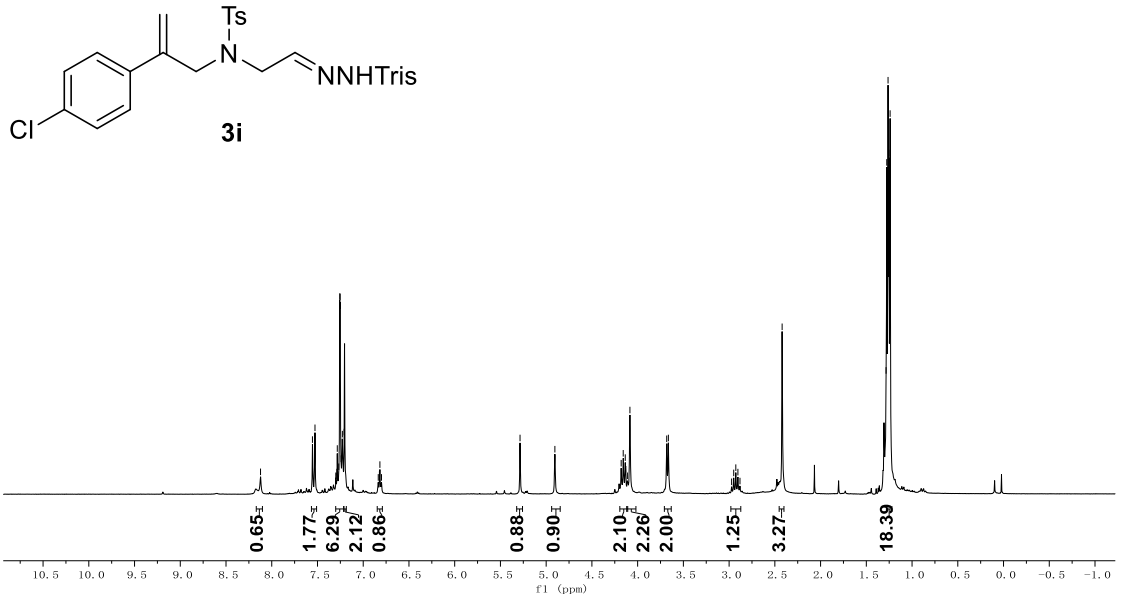


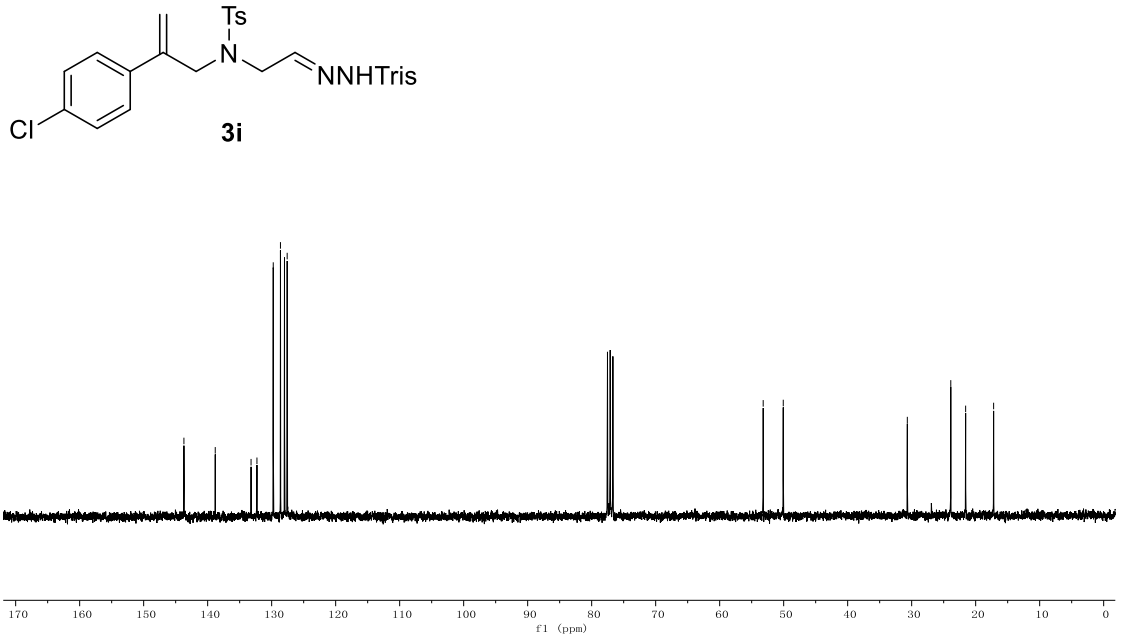

Ts
N
NNHTris

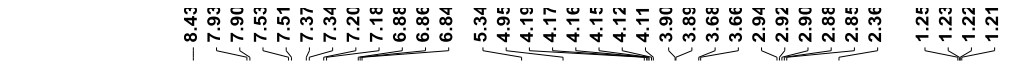
3h


f1 (ppm)




Ts
N
NNHTris
Cl
3i
0.65
1.77
6.29
2.12
0.86
0.88
0.90
2.10
2.26
2.00
1.25
3.27
18.39
f1 (ppm)


Ts
N
NNHTris
Cl
3i
f1 (ppm)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7.90
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7.51
7.37
7.34
7.20
7.18
6.88
6.86
6.84
5.34
4.95
4.19
4.17
4.16
4.15
4.12
4.11
3.90
3.89
3.68
3.66
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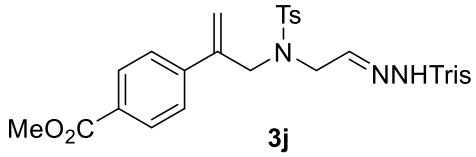
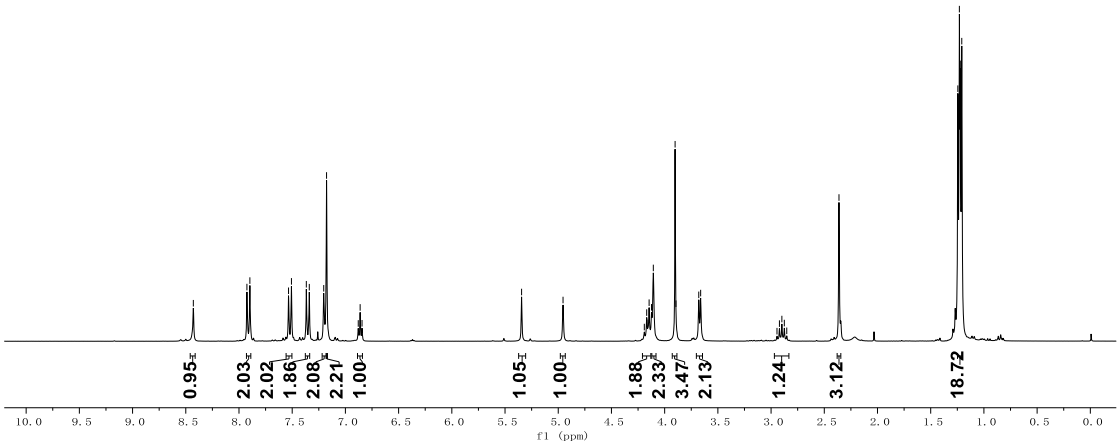
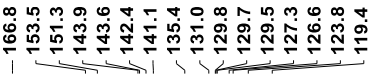
2.92
2.90
2.88
2.85
2.36
1.25
1.23
1.22
1.21


Ts
N
NNHTris
MeO2C

3j


0.95
2.03
2.02
1.86
2.08
2.21
1.00
1.05
1.00
1.88
2.33
3.47
2.13
1.24
3.12
18.72
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


166.8
153.5
151.3
143.9
143.6
142.4
141.1
135.4
131.0
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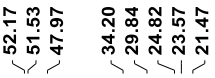
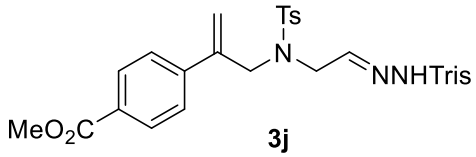
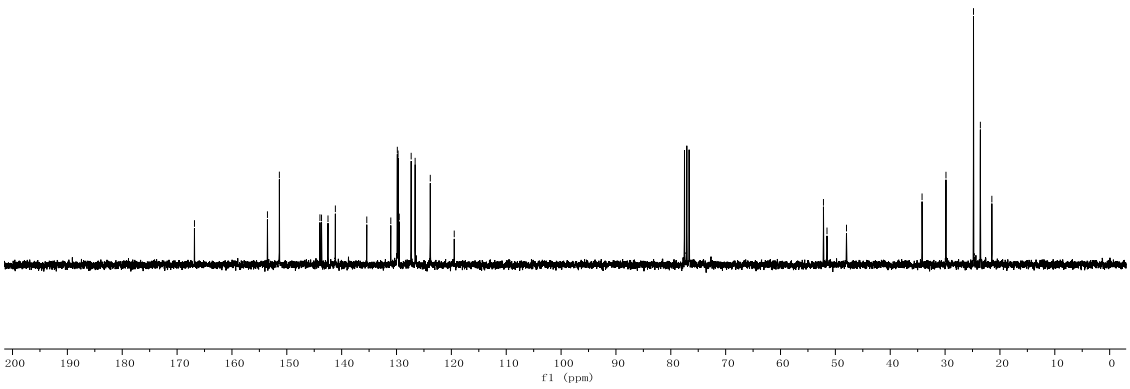
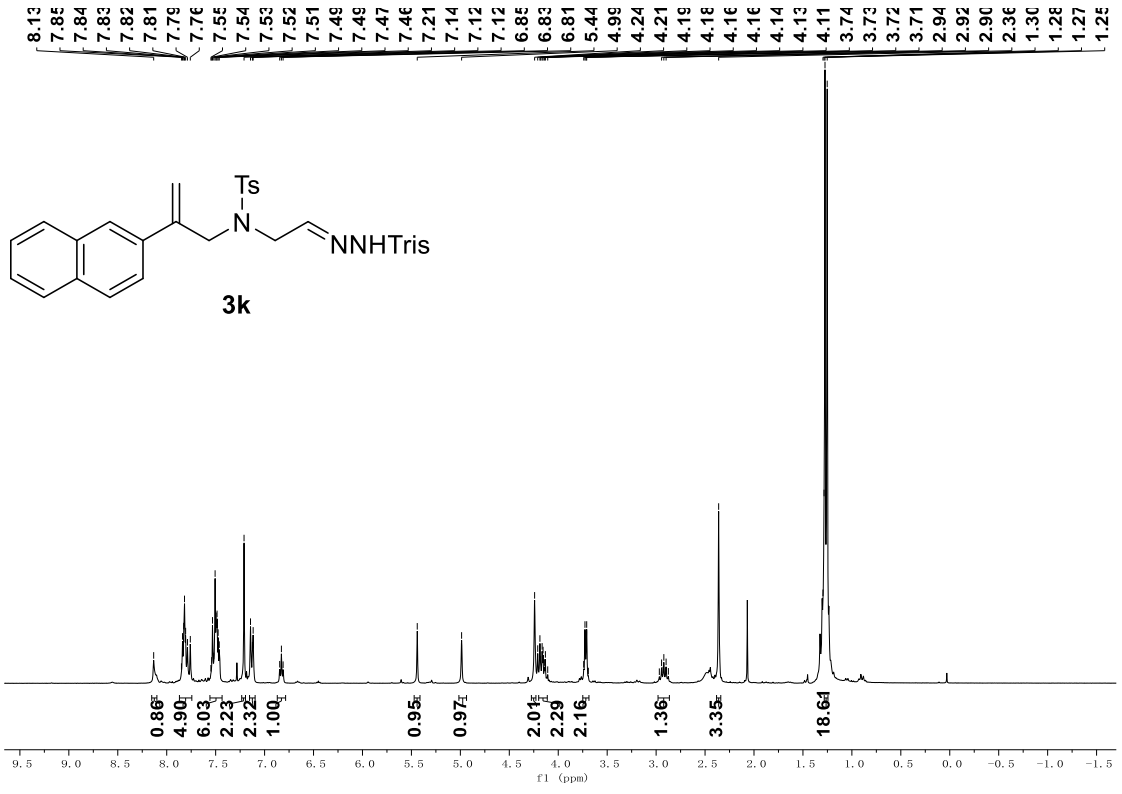
129.7
129.5
127.3
126.6
123.8
119.4

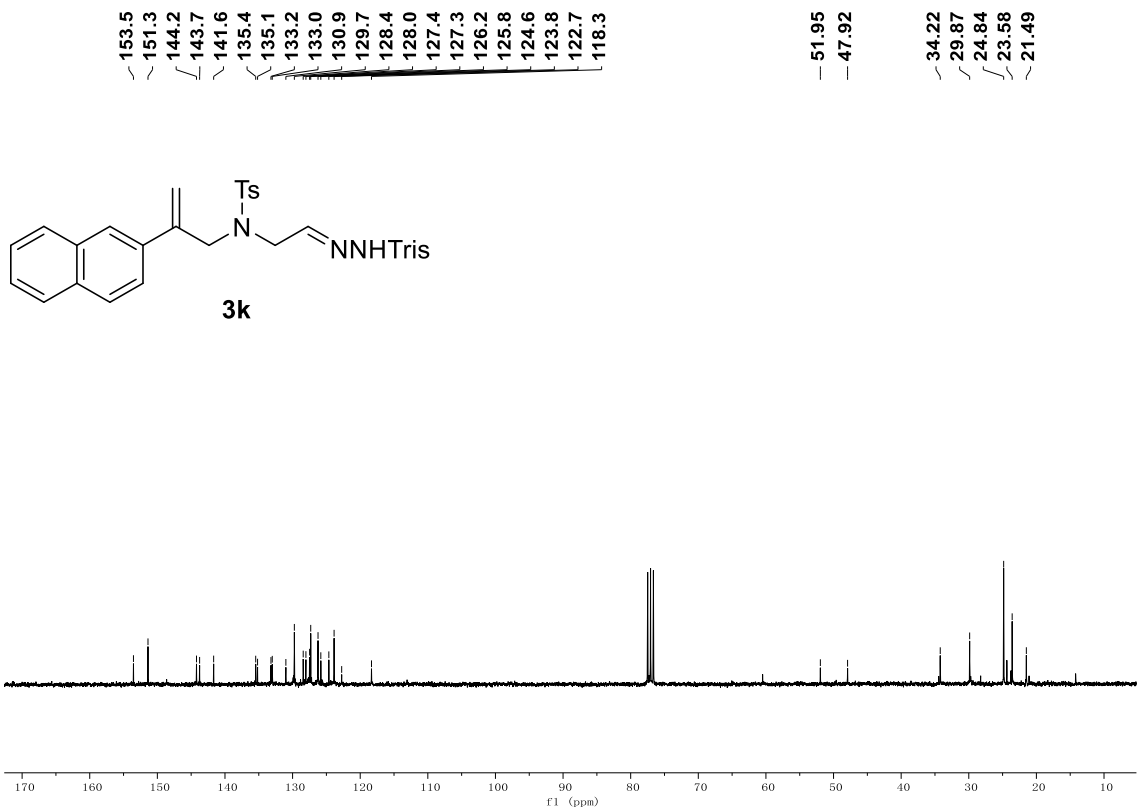

52.17
51.53
47.97
34.20
29.84
24.82
23.57
21.47

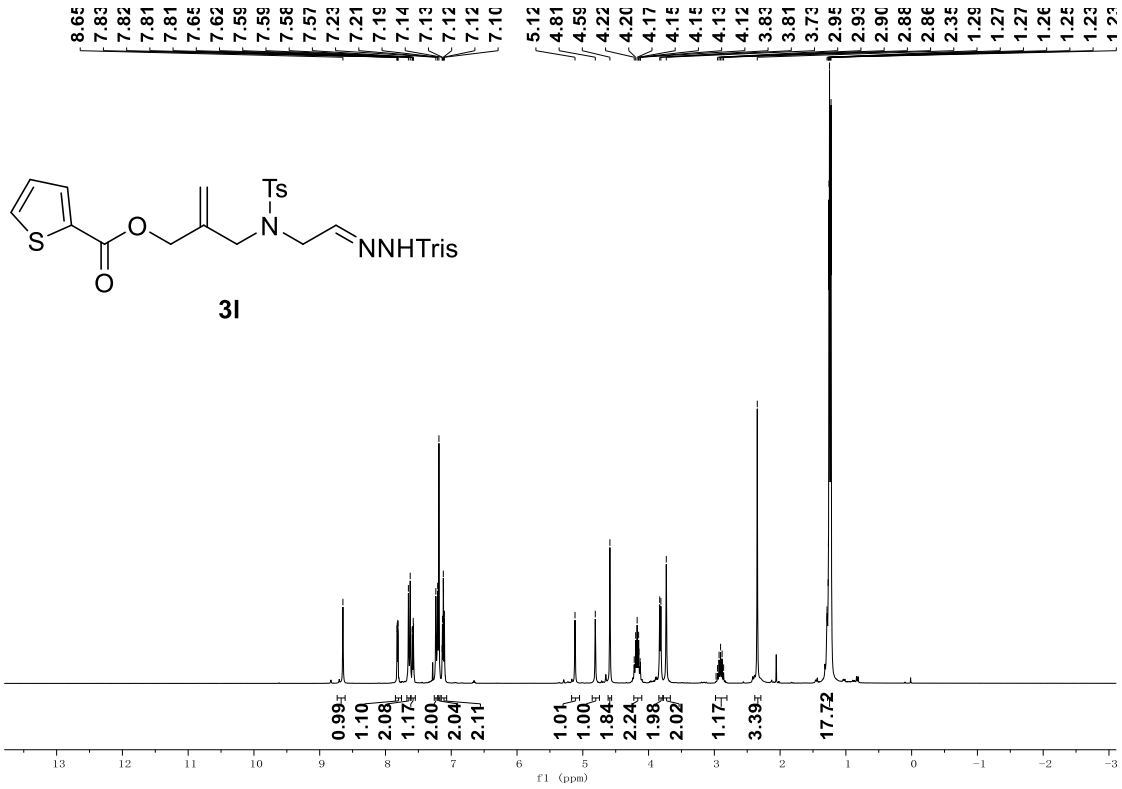

Ts
N
NNHTris
MeO2C

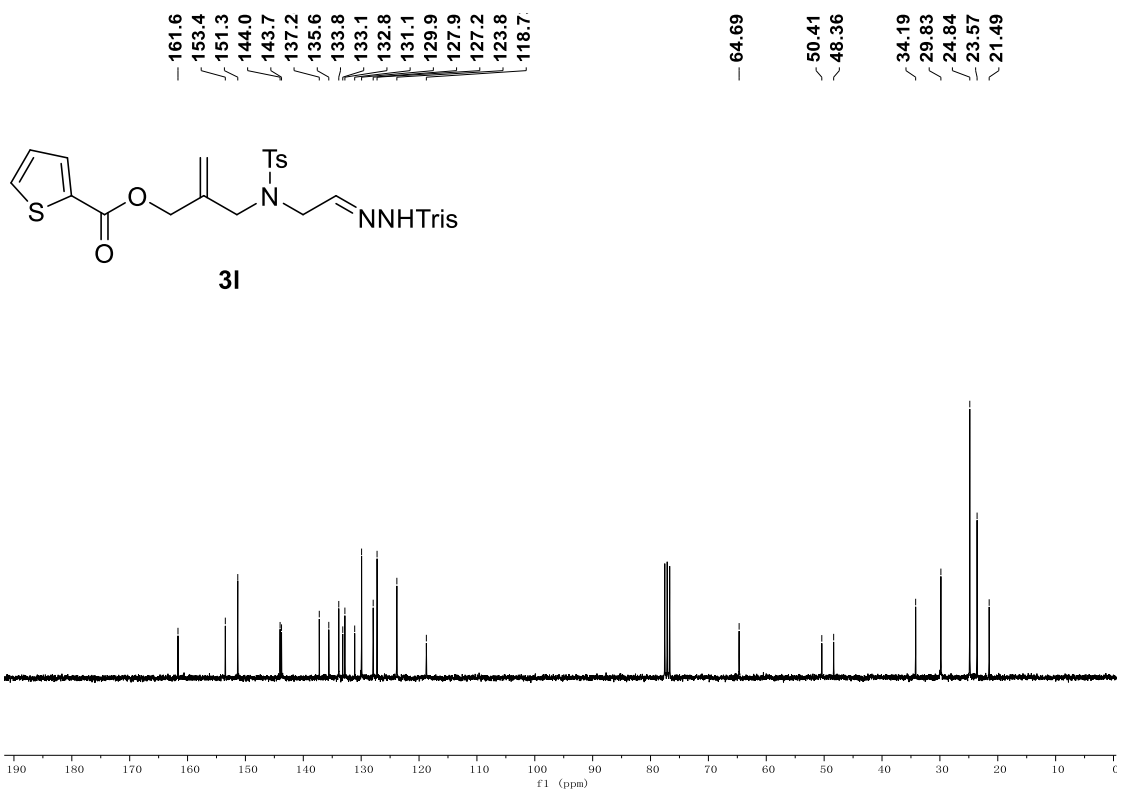
3j

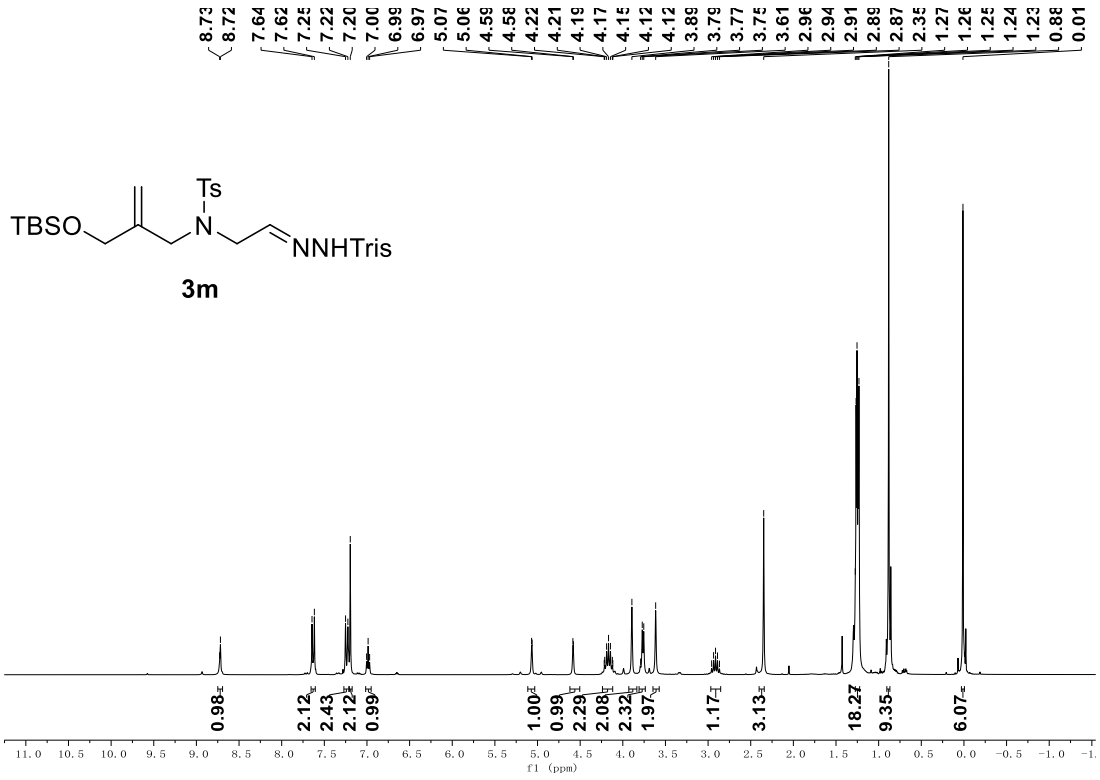

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

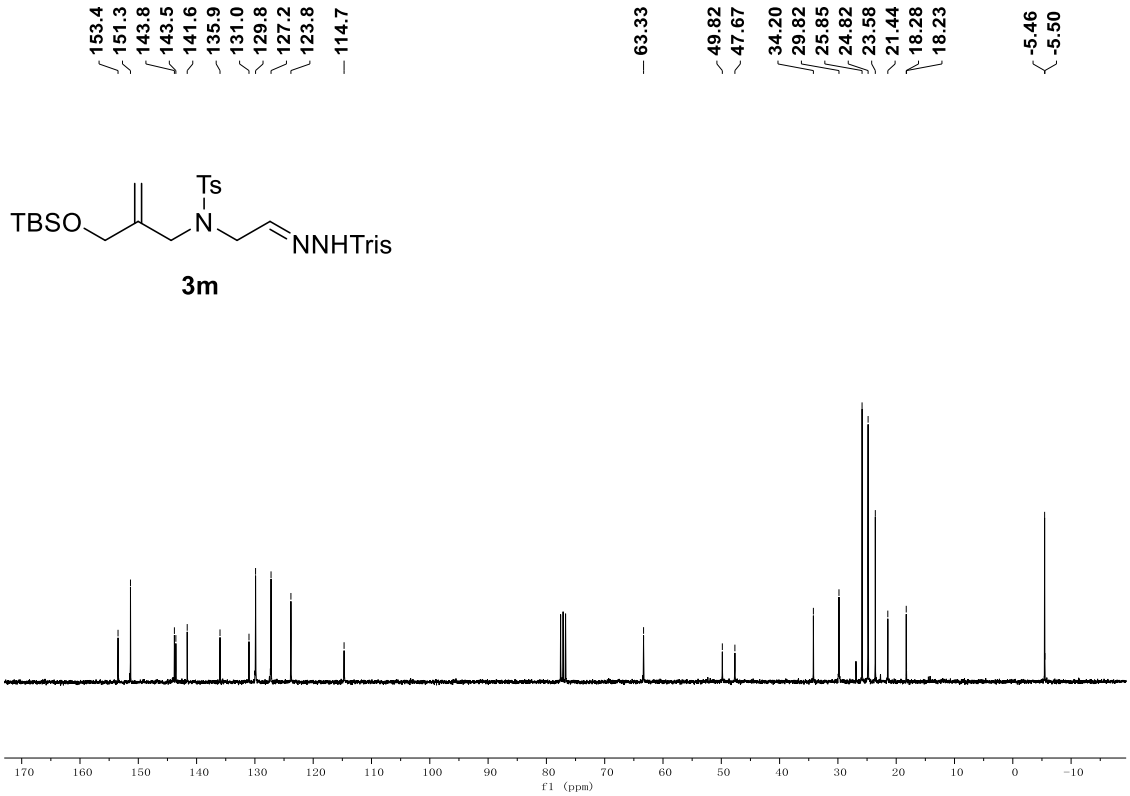

Ts
N
NNHTris
3k
f1 (ppm)

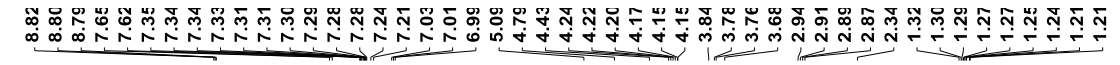

Ts
N
NNHTris
3k
f1 (ppm)

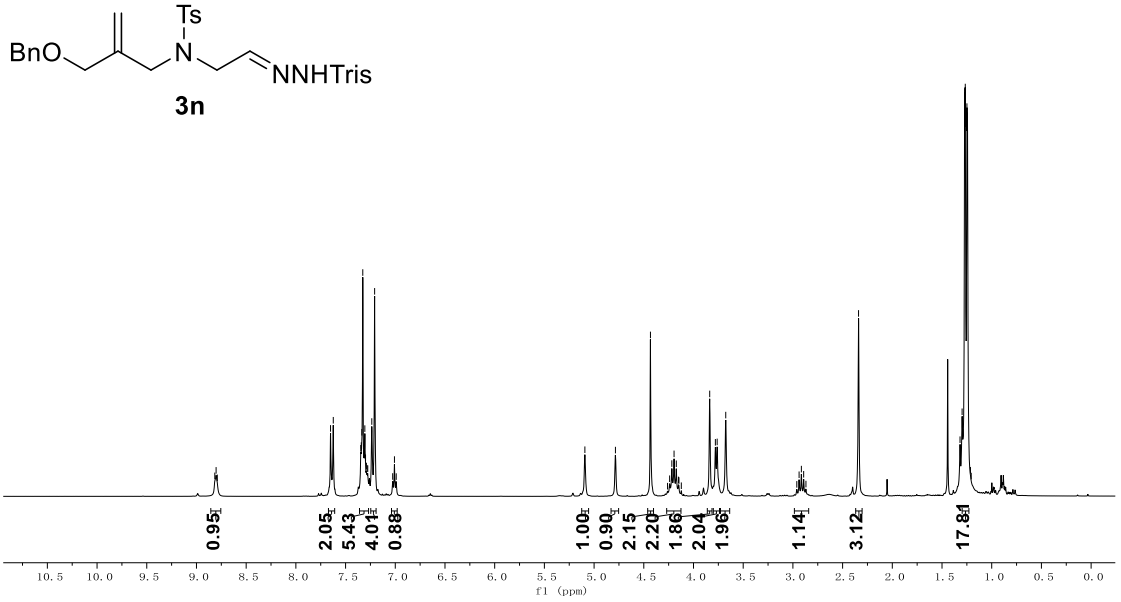

Ts
N
O
S
O
NNHTris
3l
f1 (ppm)

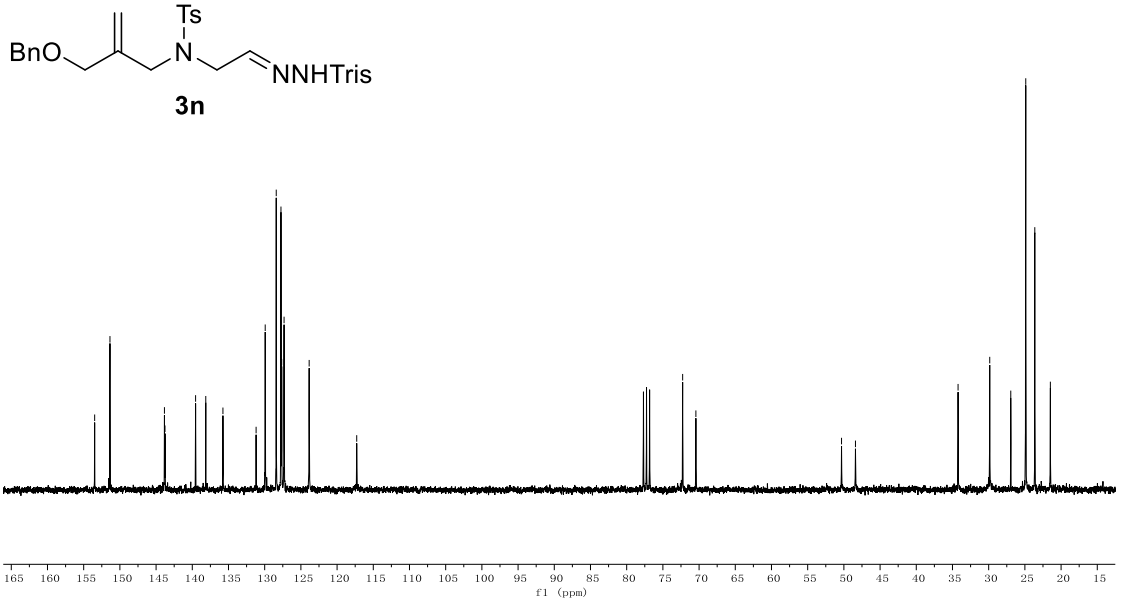

Ts
N
O
S
O
NNHTris
3l
f1 (ppm)

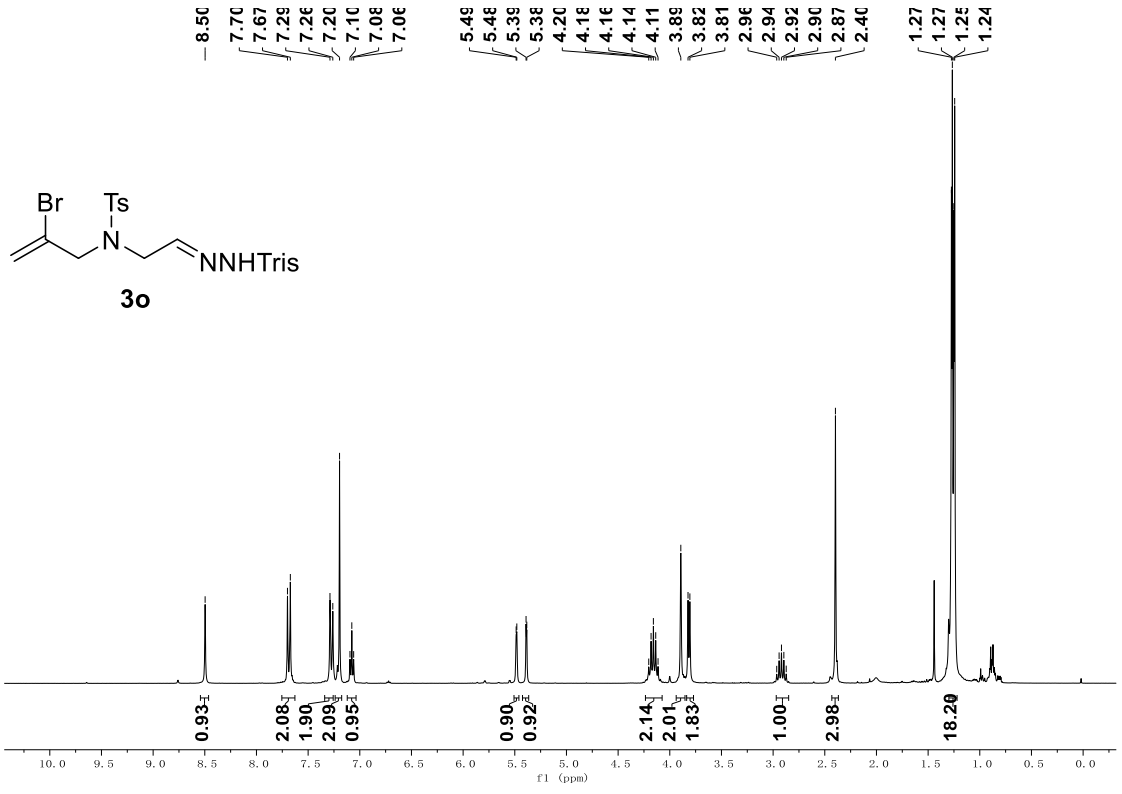

TBSO
Ts
N
NNHTris
3m
8.73
8.72
7.64
7.62
7.25
7.22
7.20
7.00
6.99
6.97
5.07
5.06
4.59
4.58
4.22
4.21
4.19
4.17
4.15
4.12
4.12
3.89
3.79
3.77
3.75
3.61
2.96
2.94
2.91
2.89
2.87
2.35
1.27
1.26
1.25
1.24
1.23
0.88
0.01
0.98
2.12
2.43
2.12
0.99
1.00
0.99
2.29
2.05
2.32
1.97
1.17
3.13
18.27
9.35
6.07
f1 (ppm)

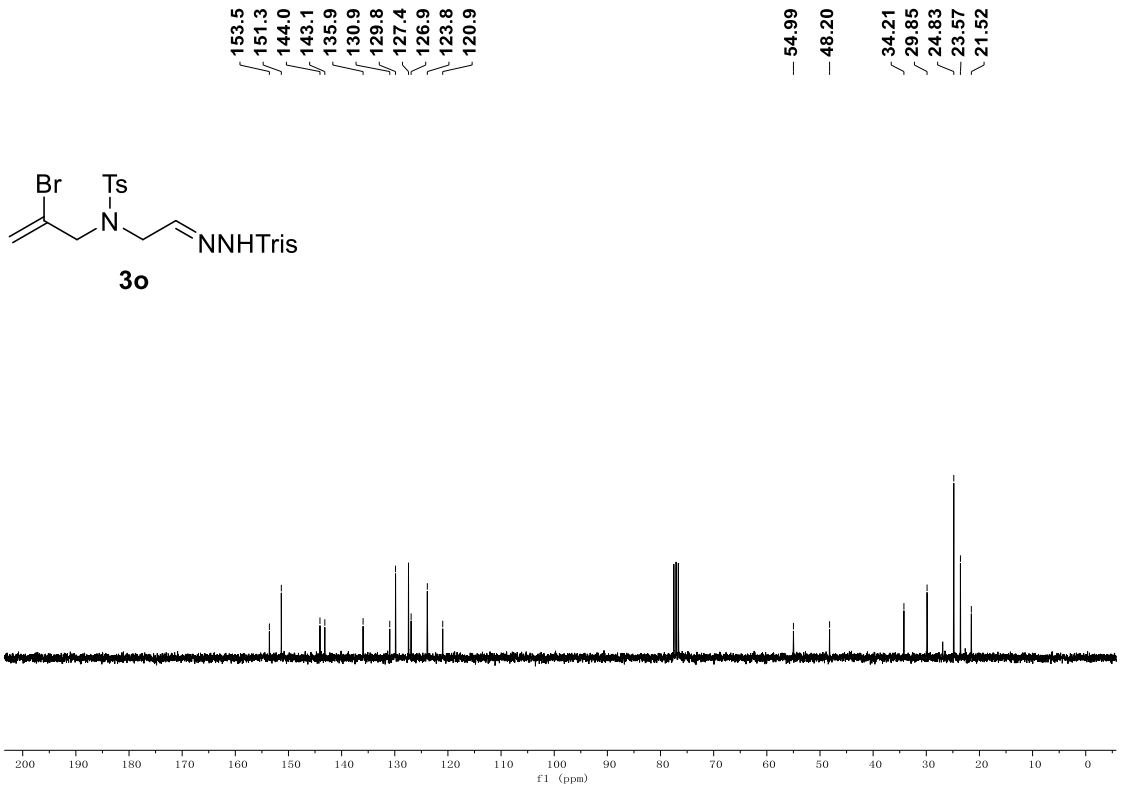

153.4
151.3
143.8
143.5
141.6
135.9
131.0
129.8
127.2
123.8
114.7
63.33
49.82
47.67
34.20
29.82
25.85
24.82
23.58
21.44
18.28
18.23
-5.46
-5.50
TBSO
Ts
N
NNHTris
3m
f1 (ppm)

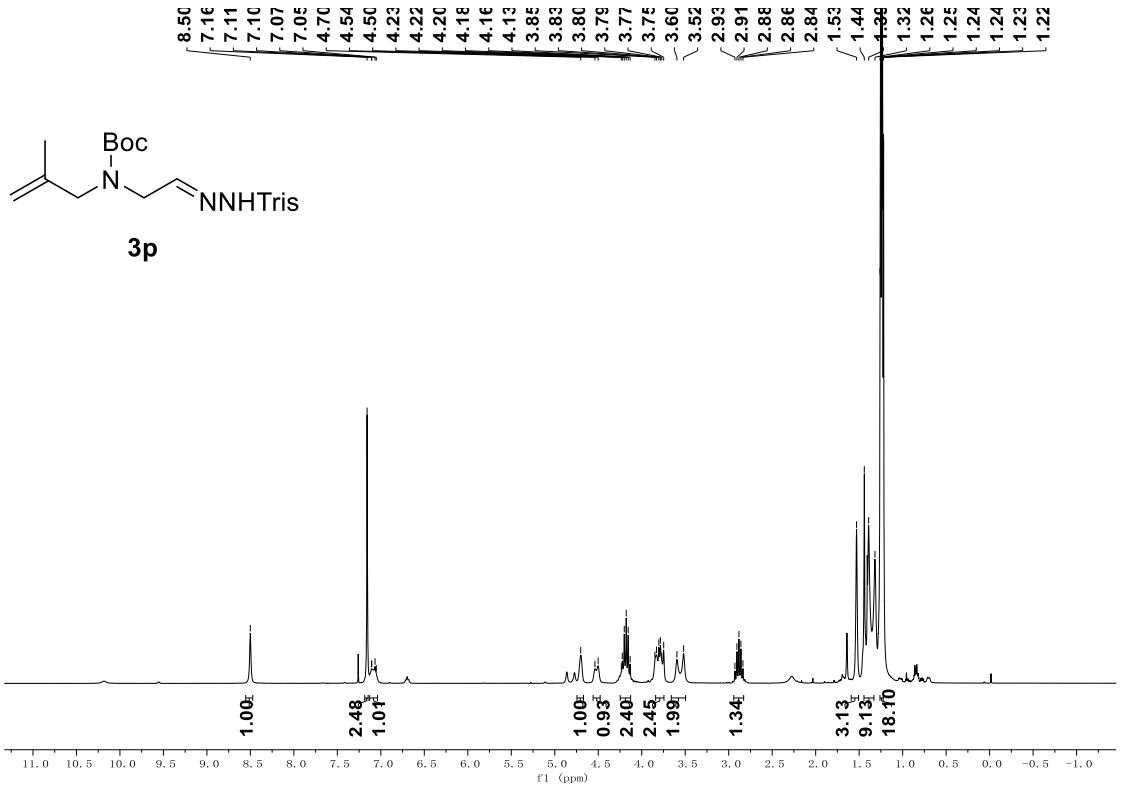


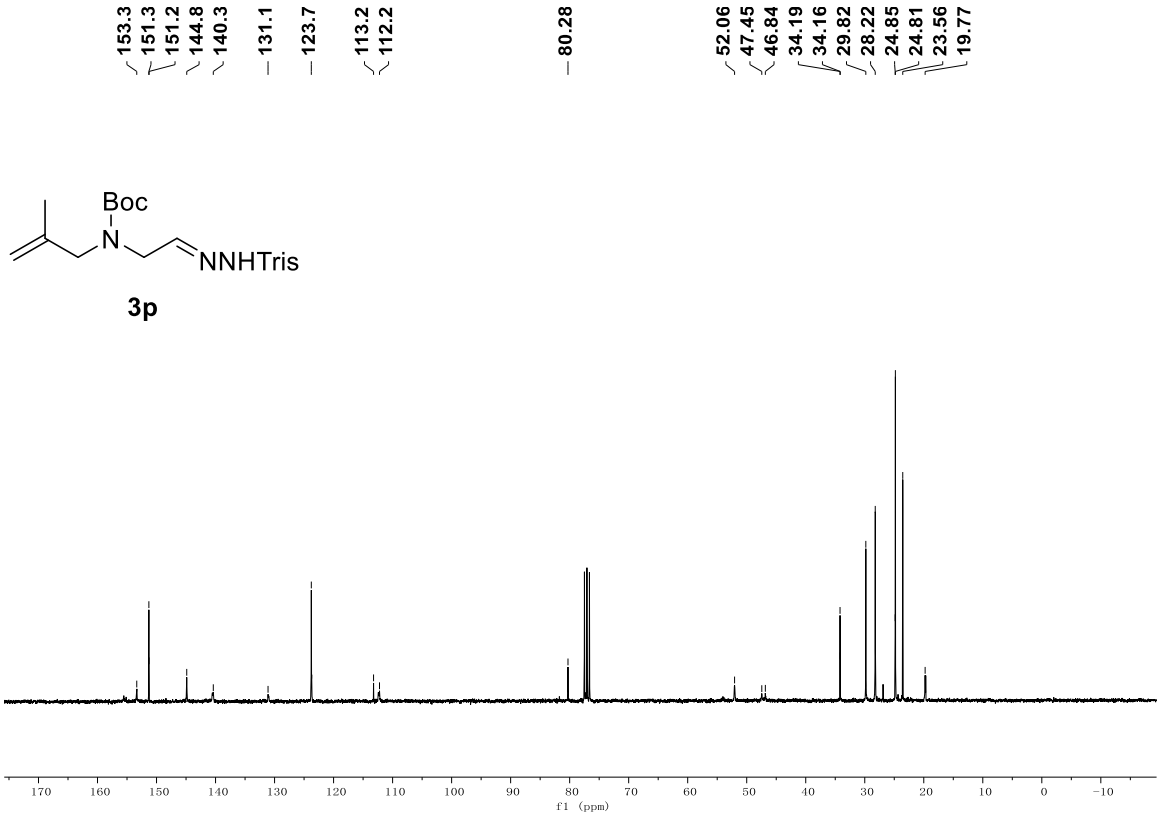

Ts
BnO
N
NNHTris
3n
0.95
2.05
5.43
4.01
0.88
1.00
0.90
2.15
2.20
1.86
2.04
1.96
1.14
3.12
17.84
f1 (ppm)

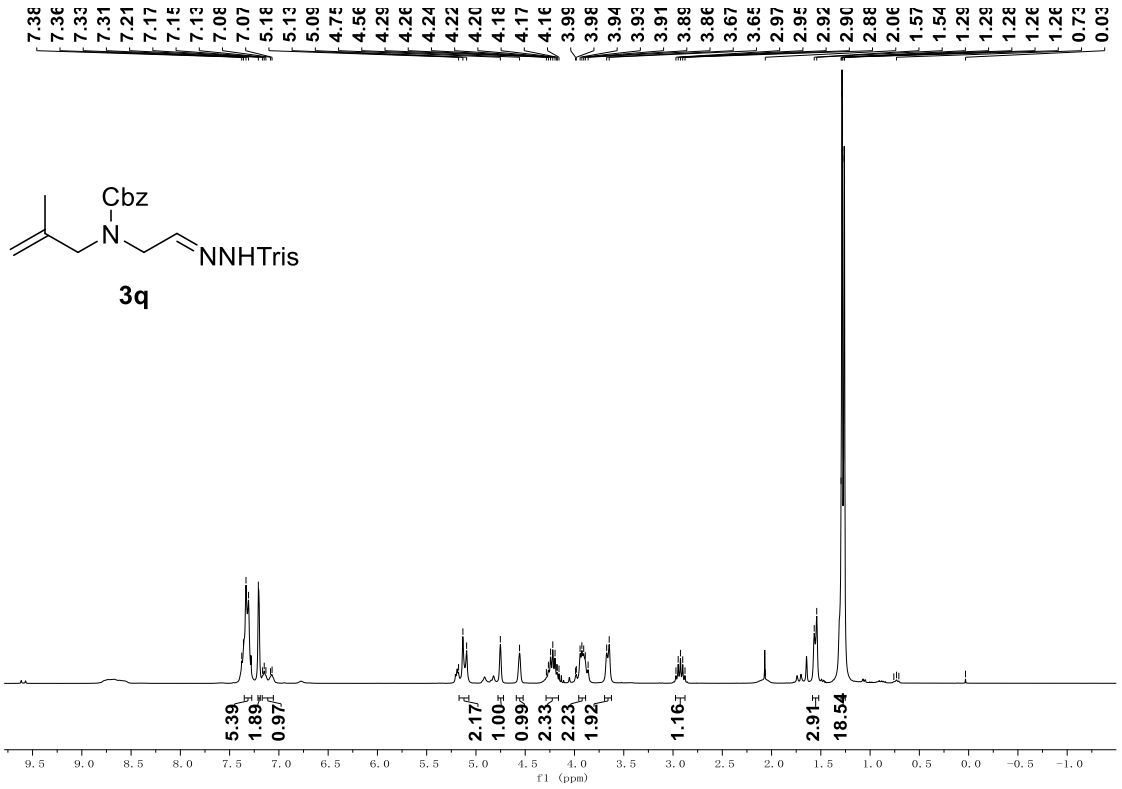

Ts
BnO
N
NNHTris
3n
f1 (ppm)

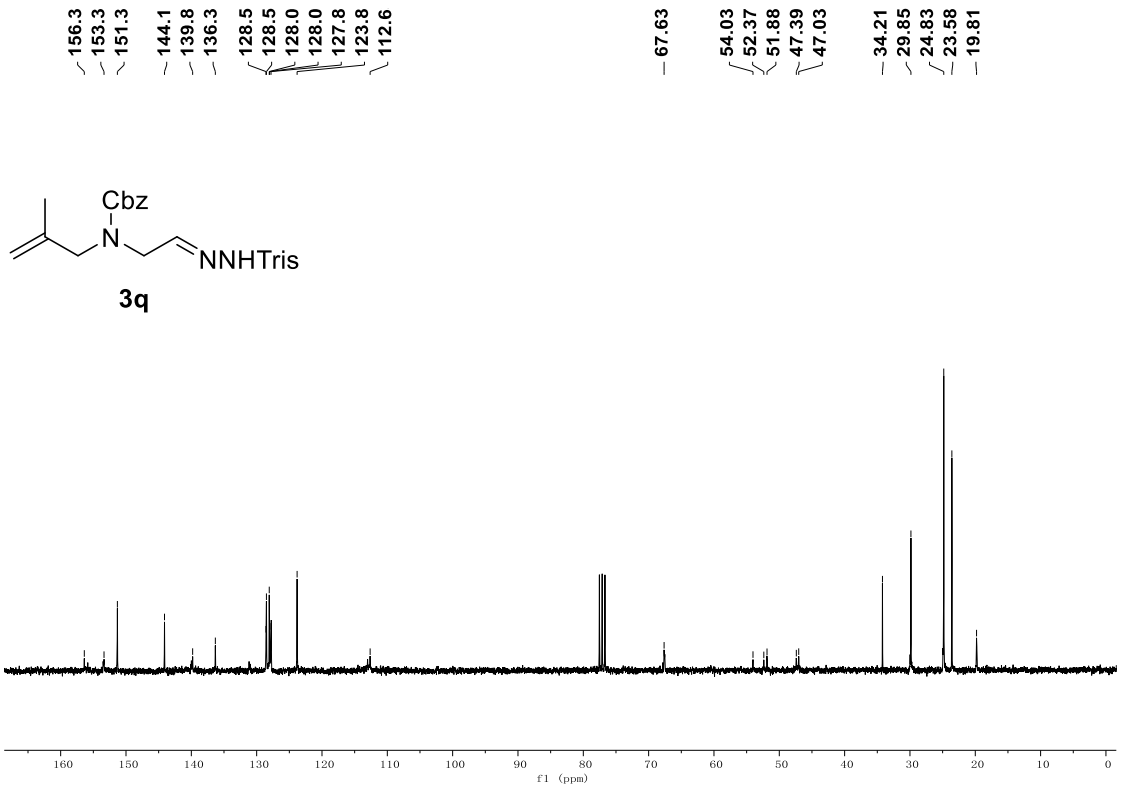

8.50
7.70
7.67
7.29
7.26
7.20
7.10
7.08
7.06
5.49
5.48
5.39
5.38
4.20
4.18
4.16
4.14
4.11
3.89
3.82
3.81
2.96
2.94
2.92
2.90
2.87
2.40
1.27
1.27
1.25
1.24
Br
Ts
N
NNHTris
3o
0.93
2.08
1.90
2.09
0.95
0.90
0.92
2.14
2.01
1.83
1.00
2.98
18.20
f1 (ppm)


153.5
151.3
144.0
143.1
135.9
130.9
129.8
127.4
126.9
123.8
120.9
54.99
48.20
34.21
29.85
24.83
23.57
21.52
Br
Ts
N
NNHTris
3o
f1 (ppm)


Boc
N
NNHTris
3p
8.50
7.16
7.11
7.10
7.07
7.05
4.70
4.54
4.50
4.23
4.22
4.20
4.18
4.16
4.13
3.85
3.83
3.80
3.79
3.77
3.75
3.60
3.52
2.93
2.91
2.88
2.86
2.84
1.53
1.44
1.39
1.32
1.26
1.25
1.24
1.24
1.23
1.22
1.00
2.48
1.01
1.00
0.93
2.40
2.45
1.99
1.34
3.13
9.13
18.10
f1 (ppm)


153.3
151.3
151.2
144.8
140.3
131.1
123.7
113.2
112.2
80.28
52.06
47.45
46.84
34.19
34.16
29.82
28.22
24.85
24.81
23.56
19.77
Boc
N
NNHTris
3p
f1 (ppm)


Cbz
N
NNHTris
3q
5.39
1.89
0.97
2.17
1.00
0.99
2.33
2.23
1.92
1.16
2.91
18.54
f1 (ppm)


Cbz
N
NNHTris
3q
156.3
153.3
151.3
144.1
139.8
136.3
128.5
128.5
128.0
128.0
127.8
123.8
112.6
67.63
54.03
52.37
51.88
47.39
47.03
34.21
29.85
24.83
23.58
19.81
f1 (ppm)

NMR Spectra of products

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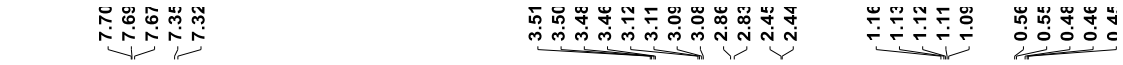
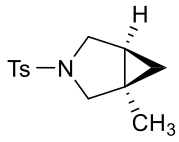
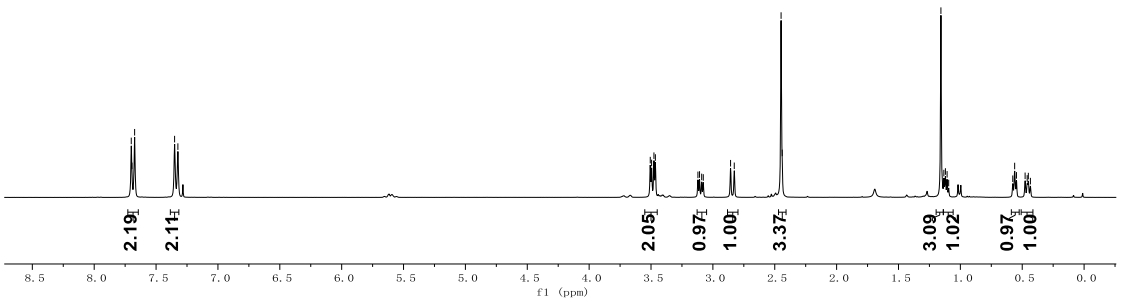
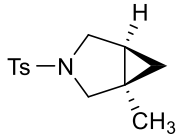


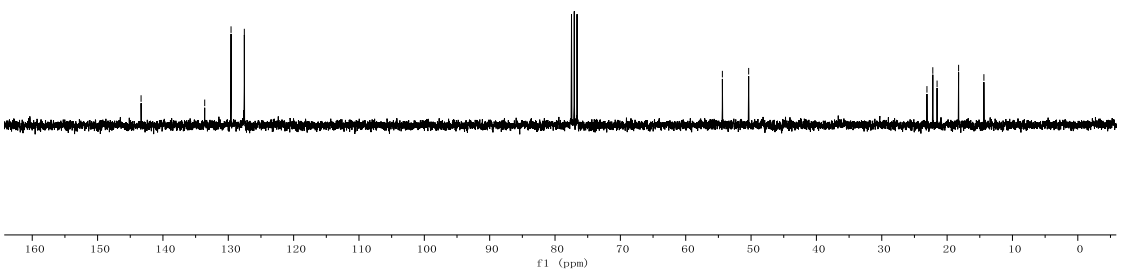


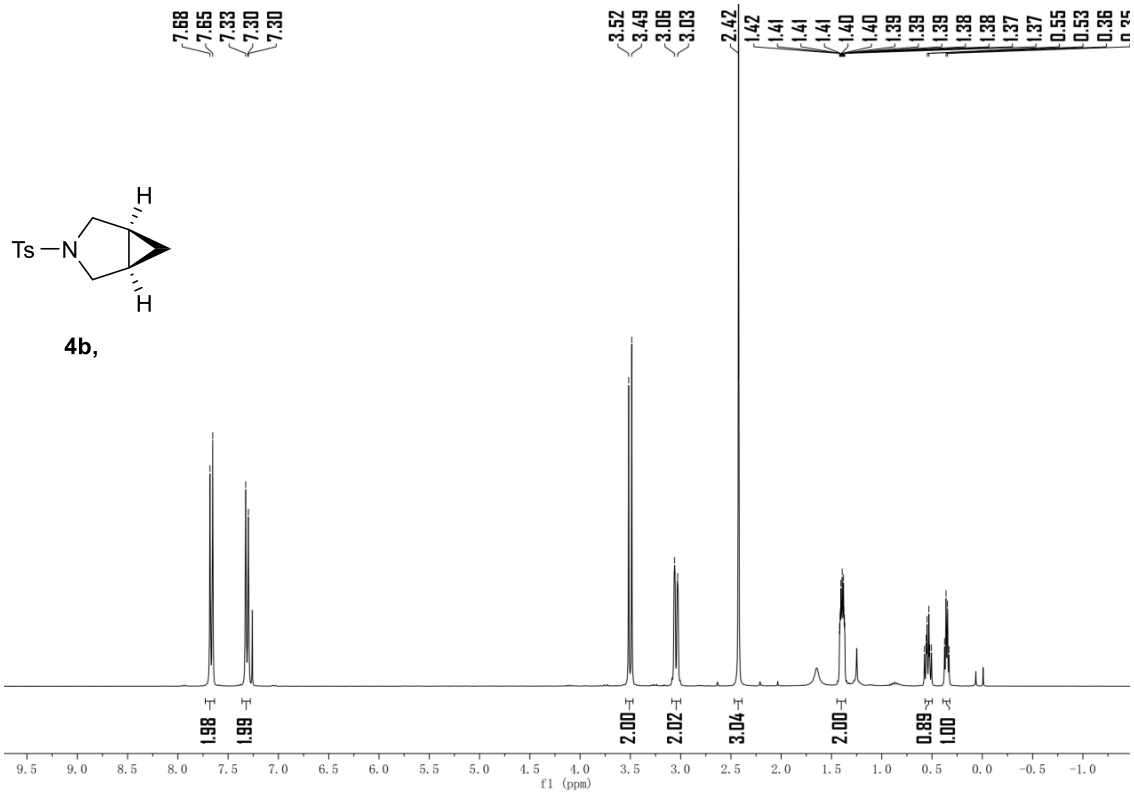
4a



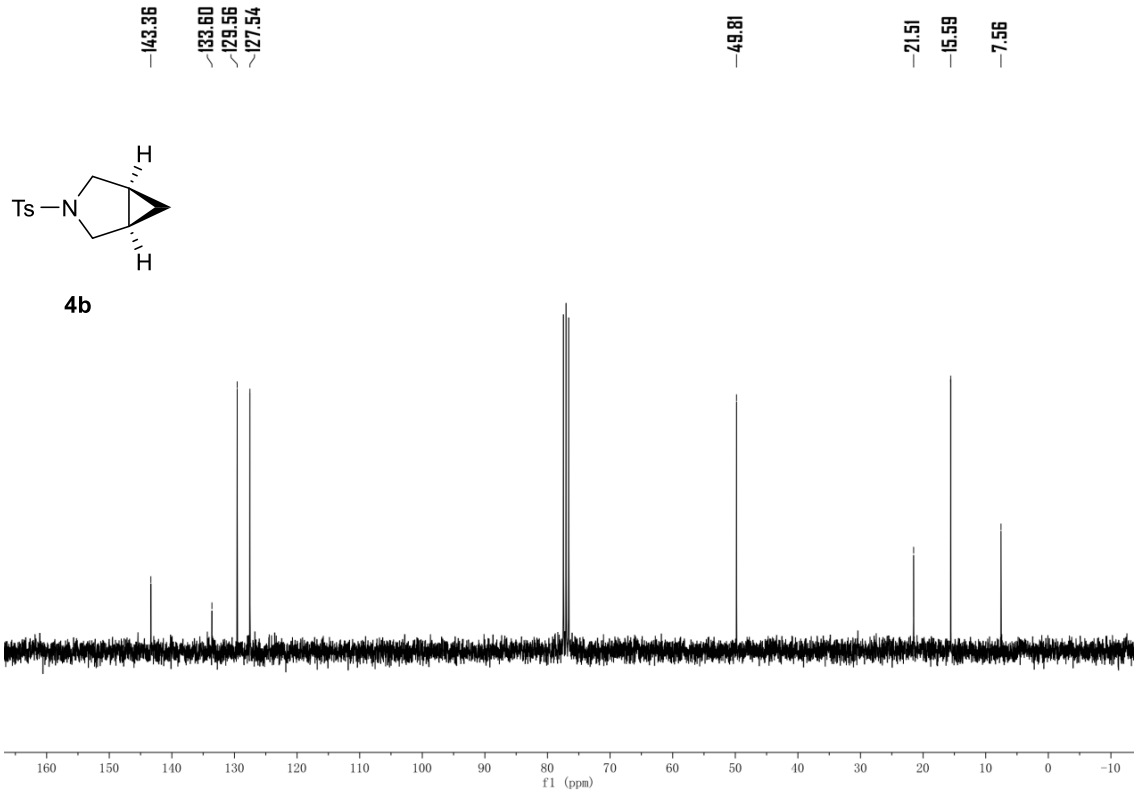


4a

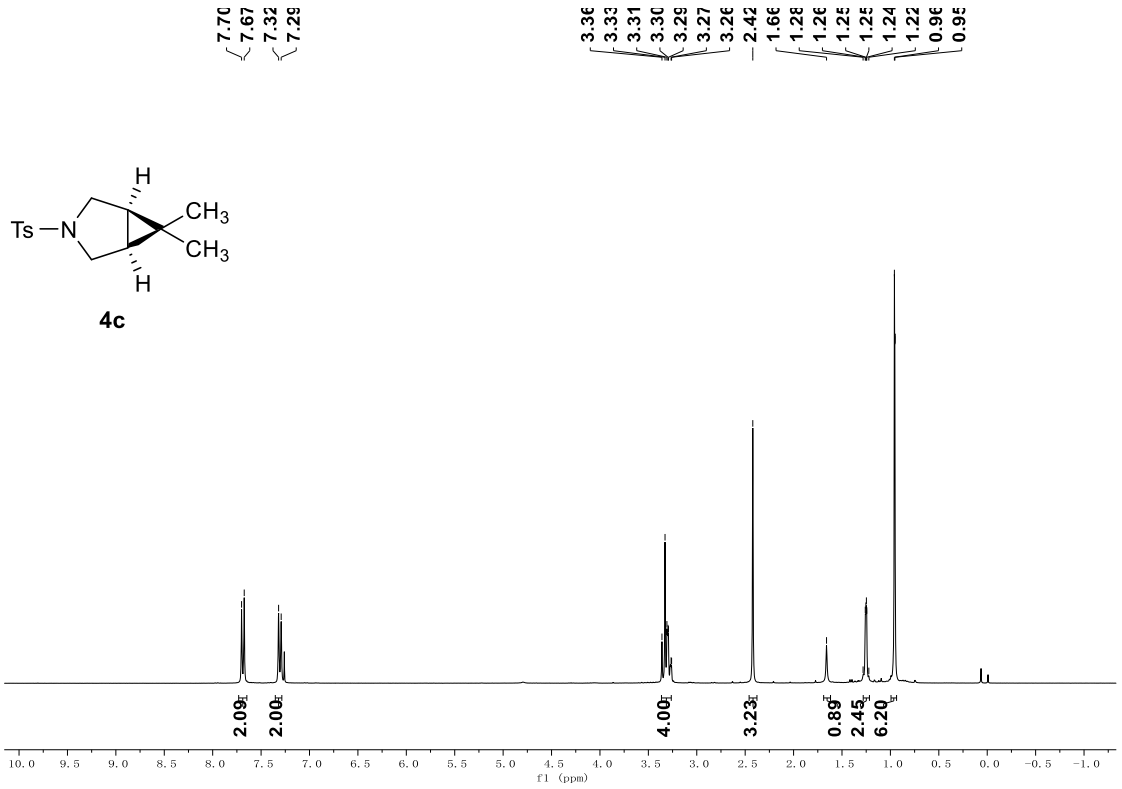



7.68
7.65
7.33
7.30
7.30
3.52
3.49
3.06
3.03
2.42
1.42
1.41
1.41
1.41
1.40
1.40
1.39
1.39
1.39
1.38
1.38
1.37
1.37
0.55
0.53
0.36
Ts—N
H
H
1.98
1.99
2.00
2.02
3.04
2.00
0.89
1.00
f1 (ppm)

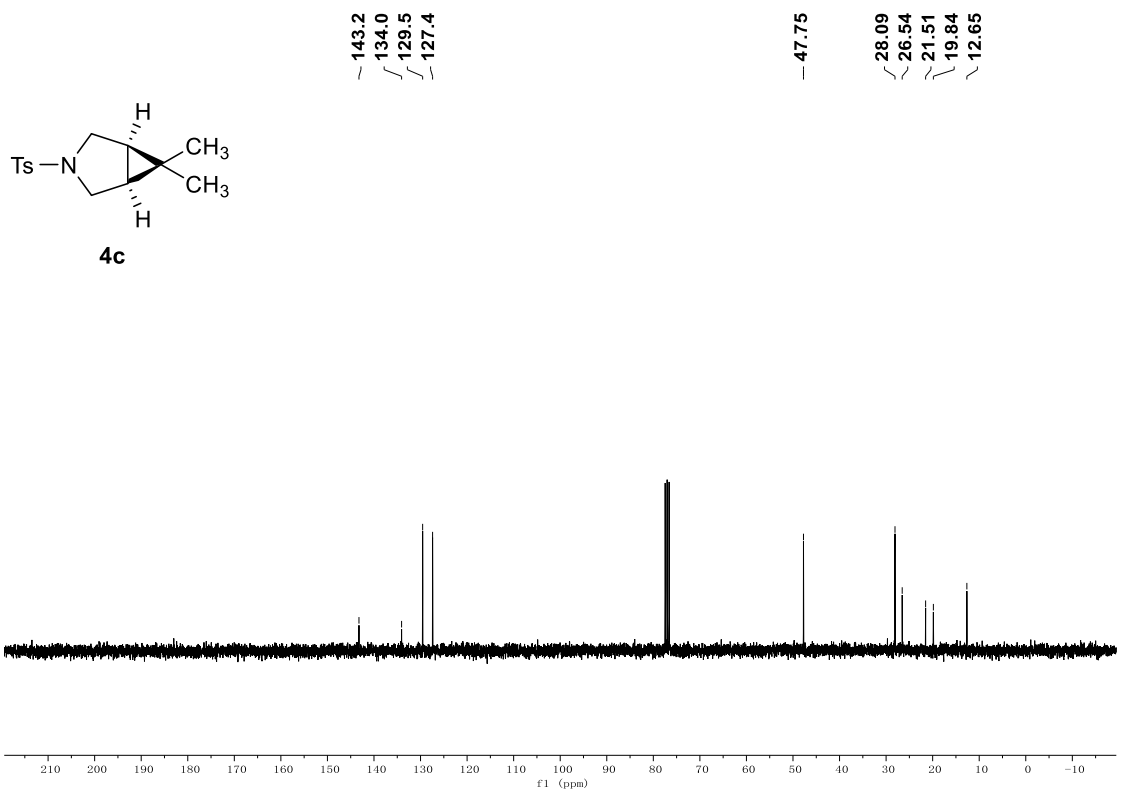
4b,


143.36
133.60
129.56
127.54
49.81
21.51
15.59
7.56
Ts—N
H
H
f1 (ppm)

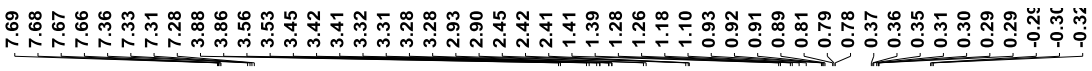
4b

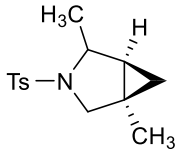

7.70
7.67
7.32
7.29
3.36
3.33
3.31
3.30
3.29
3.27
3.26
2.42
1.66
1.28
1.26
1.25
1.25
1.24
1.22
0.96
0.95
H
CH3
Ts—N
CH3
H
2.09
2.00
4.00
3.23
0.89
2.45
6.20
f1 (ppm)

4c


143.2
134.0
129.5
127.4
47.75
28.09
26.54
21.51
19.84
12.65
H
CH3
Ts—N
CH3
H
f1 (ppm)

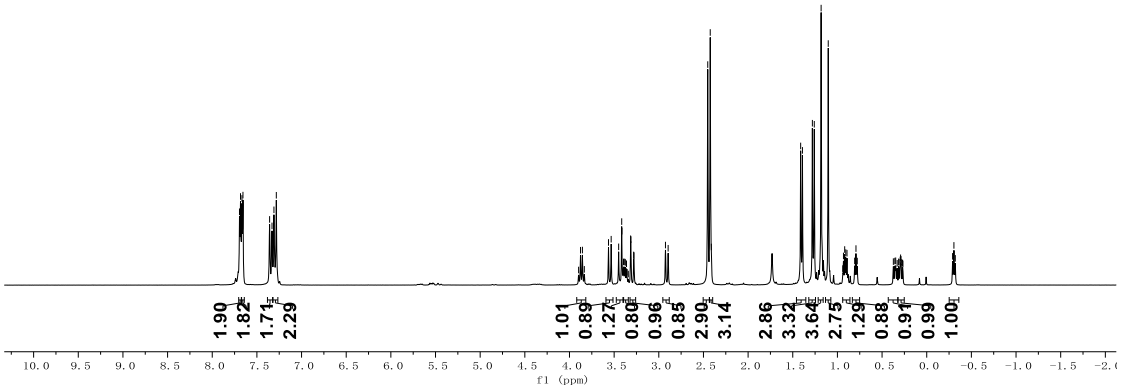
4c

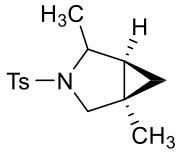




4d

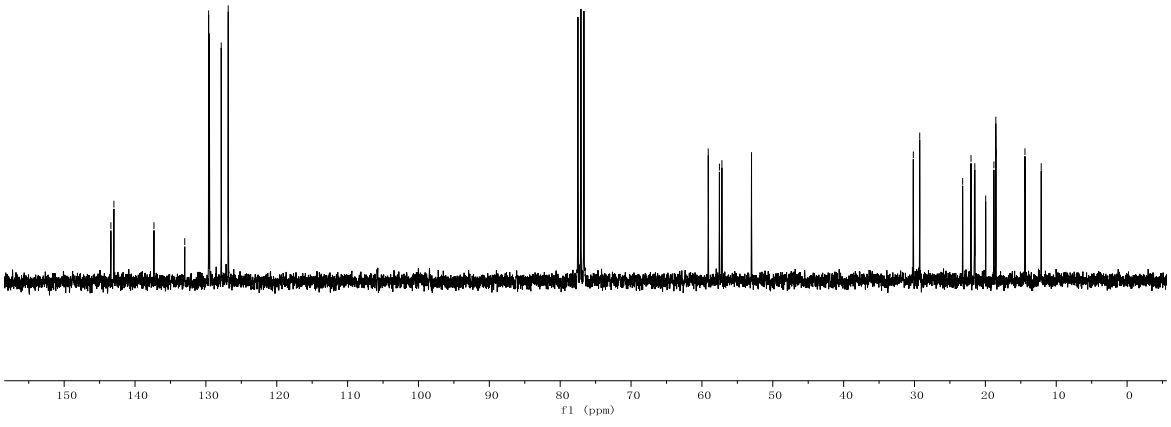
a mixture of diastereoisomers in dr = 1:1

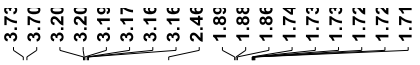


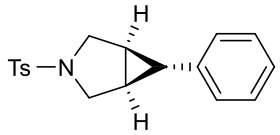


4d

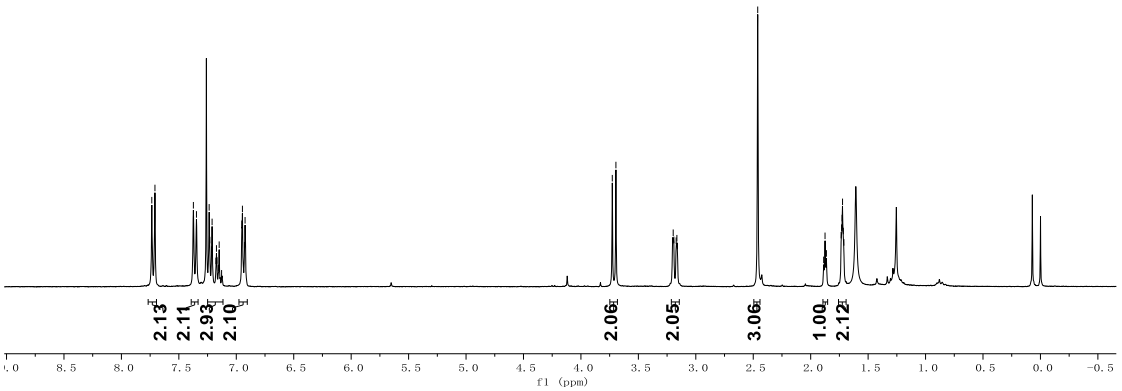
a mixture of diastereoisomers in dr = 1:1

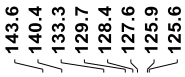


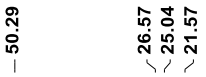


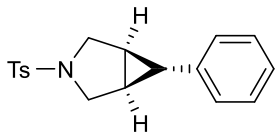

H
Ts—N
H

4e


2.13
2.11
2.93
2.10
2.06
2.05
3.06
1.00
2.12
f1 (ppm)

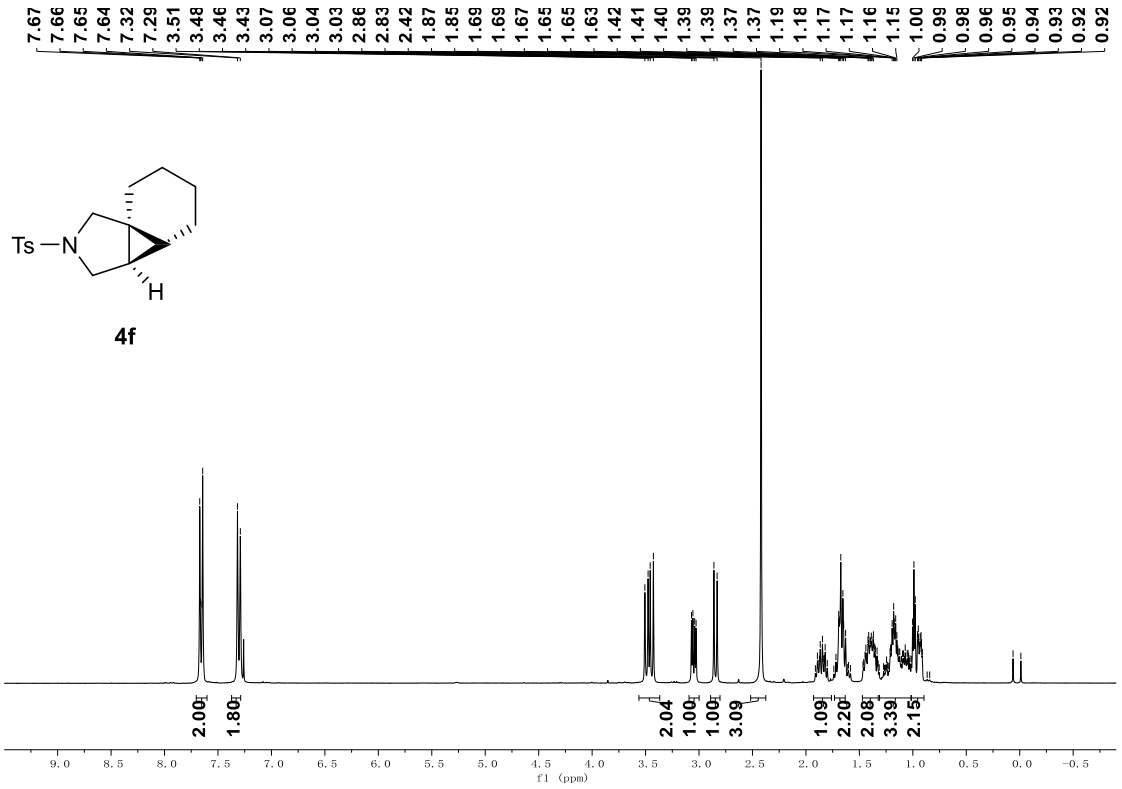

143.6
140.4
133.3
129.7
128.4
127.6
125.9
125.6


50.29
26.57
25.04
21.57

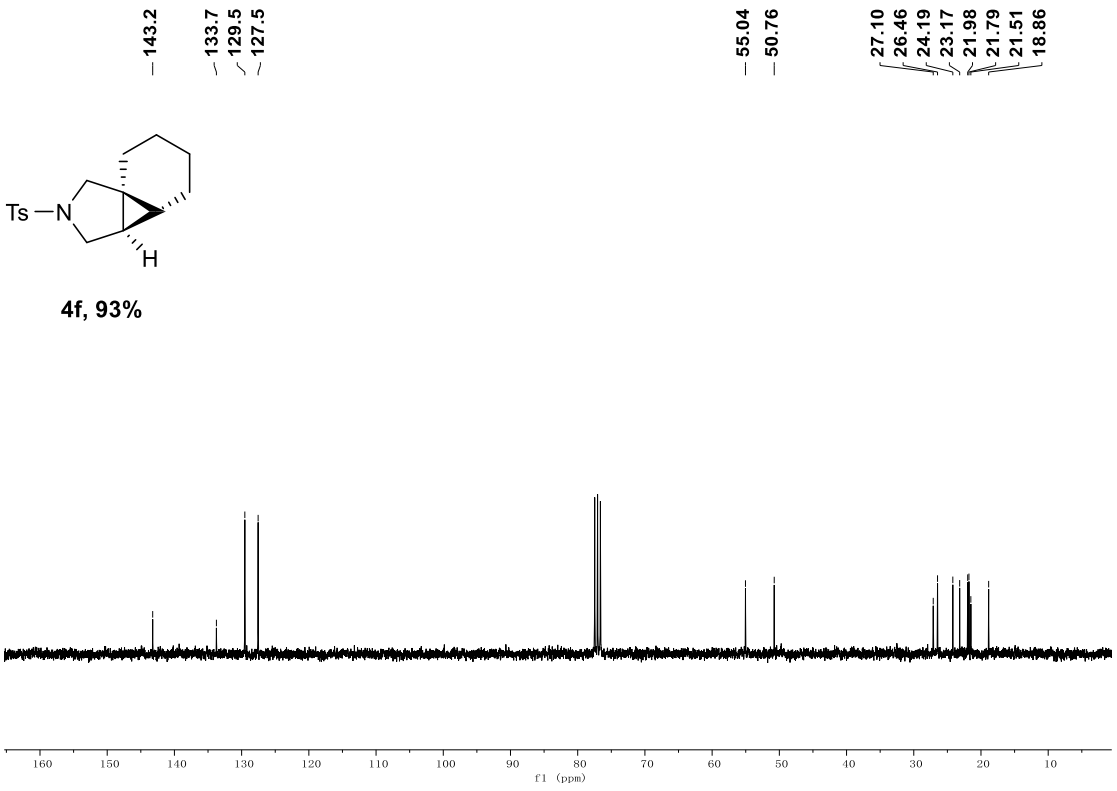

H
Ts—N
H

4e

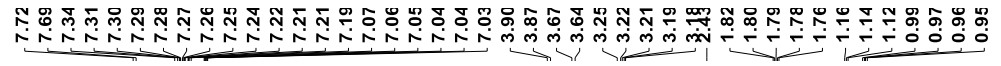
f1 (ppm)

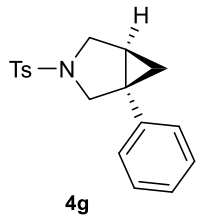

7.67
7.66
7.65
7.64
7.32
7.29
3.51
3.48
3.46
3.43
3.07
3.06
3.04
3.03
2.86
2.83
2.42
1.87
1.85
1.69
1.69
1.67
1.65
1.65
1.63
1.42
1.41
1.40
1.39
1.39
1.37
1.37
1.19
1.18
1.17
1.17
1.16
1.15
1.00
0.99
0.98
0.96
0.95
0.94
0.93
0.92
0.92
Ts—N
H
2.00
1.80
2.04
1.00
1.00
3.09
1.09
2.20
2.08
3.39
2.15
f1 (ppm)

4f

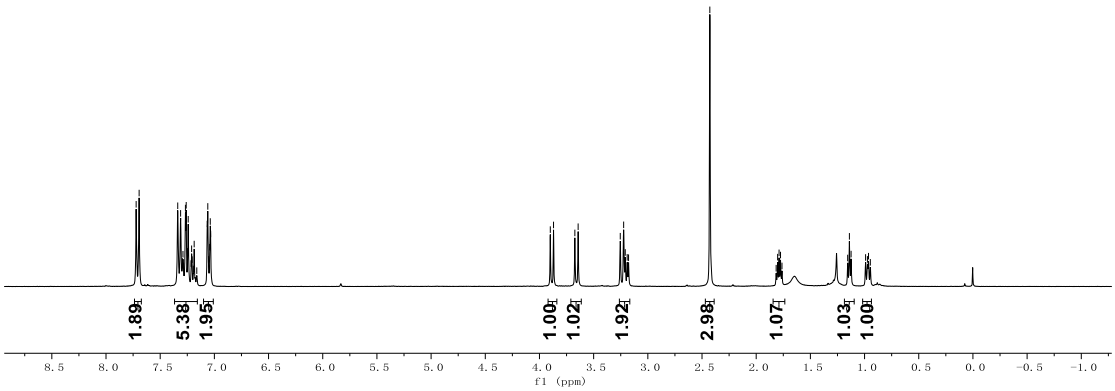

143.2
133.7
129.5
127.5
55.04
50.76
27.10
26.46
24.19
23.17
21.98
21.79
21.51
18.86
Ts—N
H
f1 (ppm)

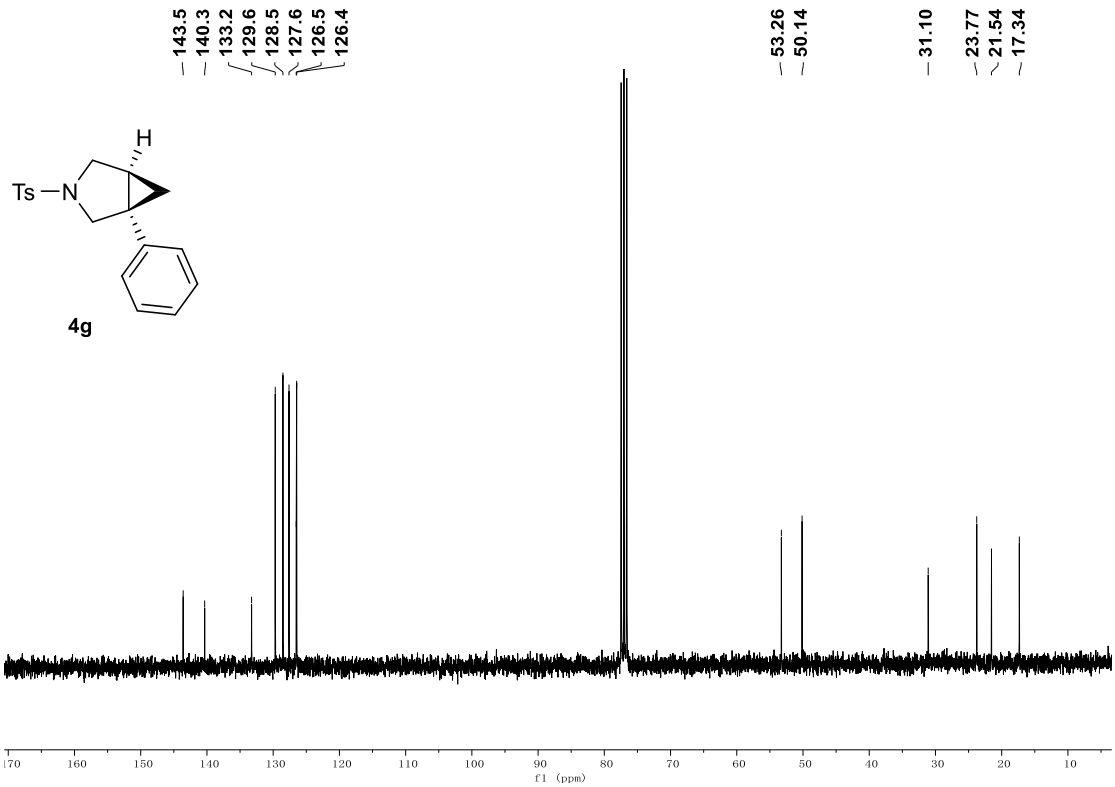
4f, 93%


7.72
7.69
7.34
7.31
7.30
7.29
7.28
7.27
7.26
7.25
7.24
7.22
7.21
7.21
7.19
7.07
7.06
7.05
7.04
7.04
7.03
3.90
3.87
3.67
3.64
3.25
3.22
3.21
3.19
2.43
1.82
1.80
1.79
1.78
1.76
1.16
1.14
1.12
0.99
0.97
0.96
0.95


H
Ts—N

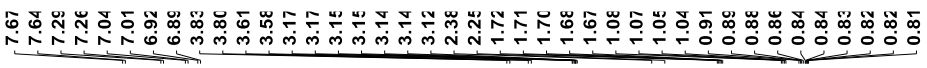
4g

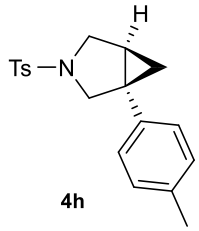

1.89
5.38
1.95
1.00
1.02
1.92
2.98
1.07
1.03
1.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1.0
f1 (ppm)


143.5
140.3
133.2
129.6
128.5
127.6
126.5
126.4
53.26
50.14
31.10
23.77
21.54
17.34
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

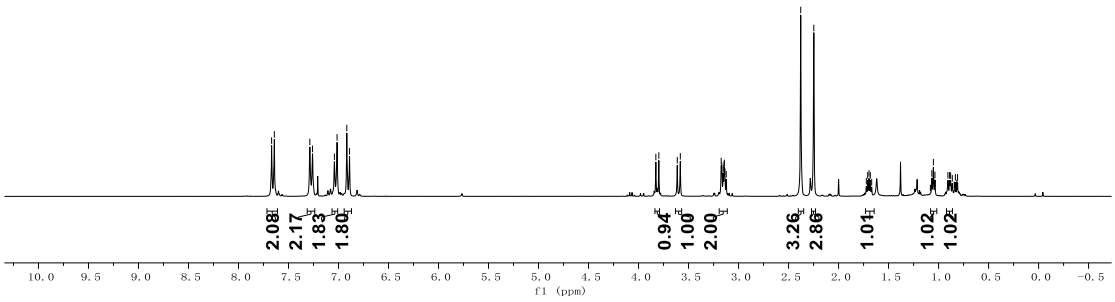
H
Ts—N

4g

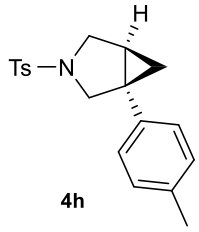

7.67
7.64
7.29
7.26
7.04
7.01
6.92
6.89
3.83
3.80
3.61
3.58
3.17
3.17
3.15
3.15
3.14
3.14
3.12
2.38
2.25
1.72
1.71
1.70
1.68
1.67
1.08
1.07
1.05
1.04
0.91
0.89
0.88
0.86
0.84
0.84
0.83
0.82
0.82
0.81


H
Ts—N

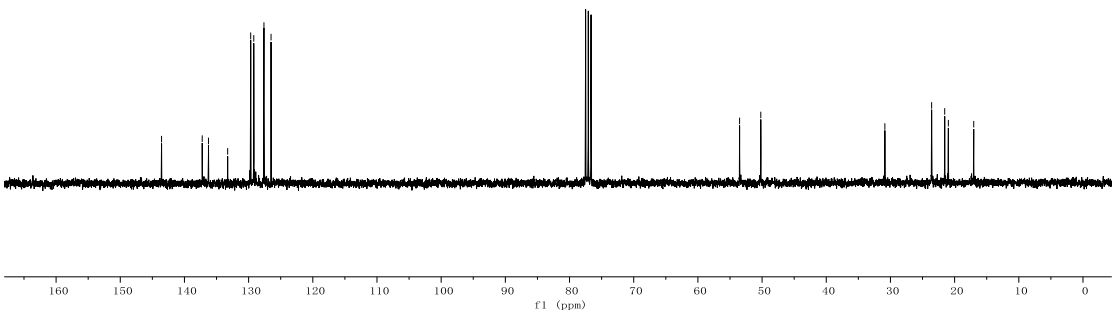
4h

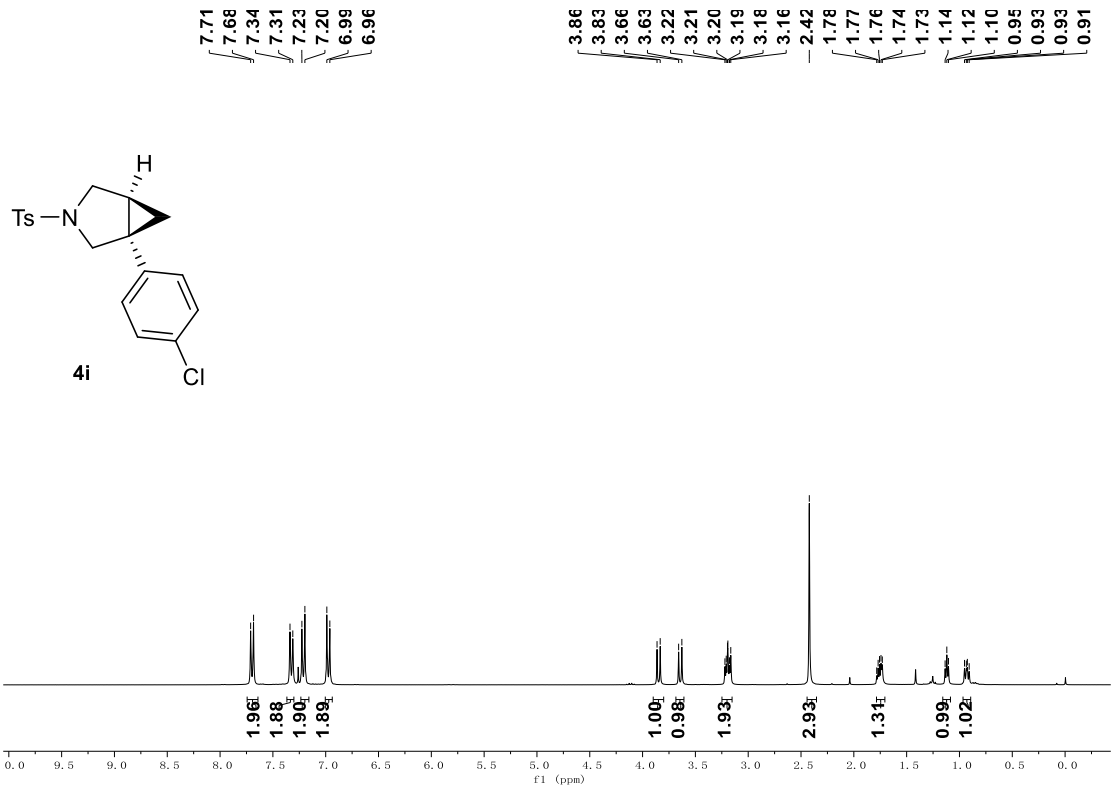

2.08
2.17
1.83
1.80
0.94
1.00
2.00
3.26
2.86
1.01
1.02
1.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

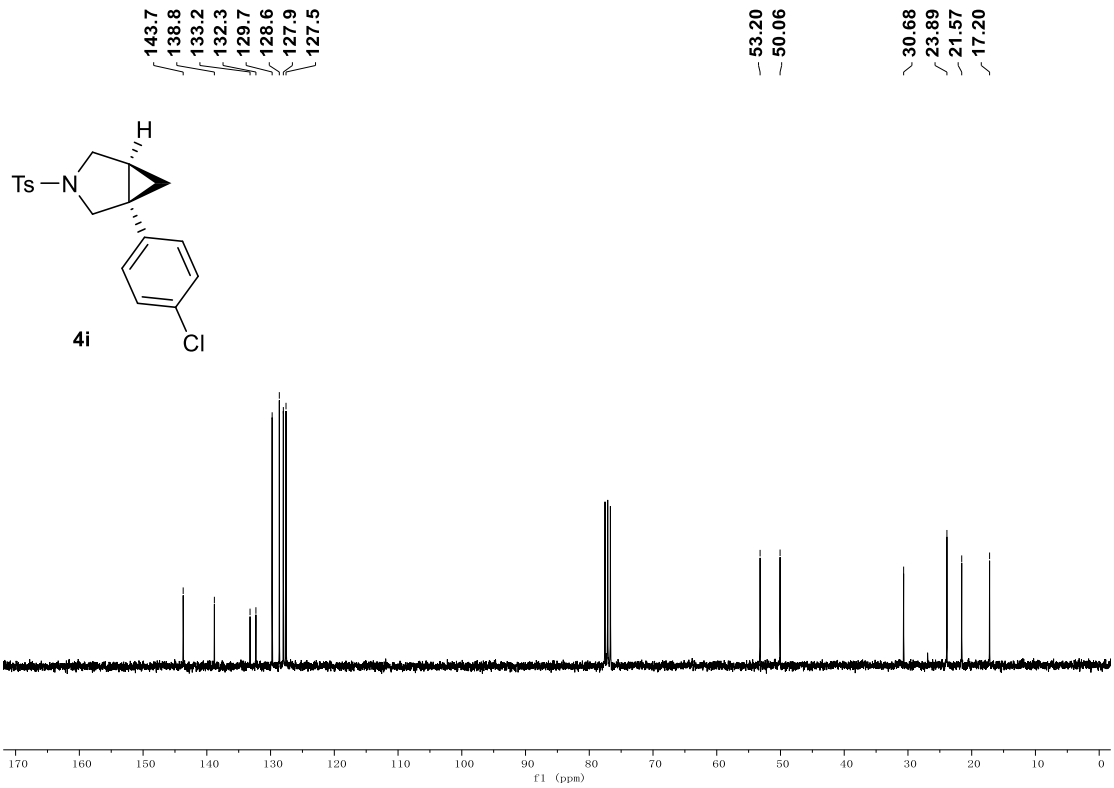

143.5
137.2
136.2
133.2
129.6
129.2
127.6
126.5
53.50
50.20
30.87
23.58
21.54
20.97
17.02

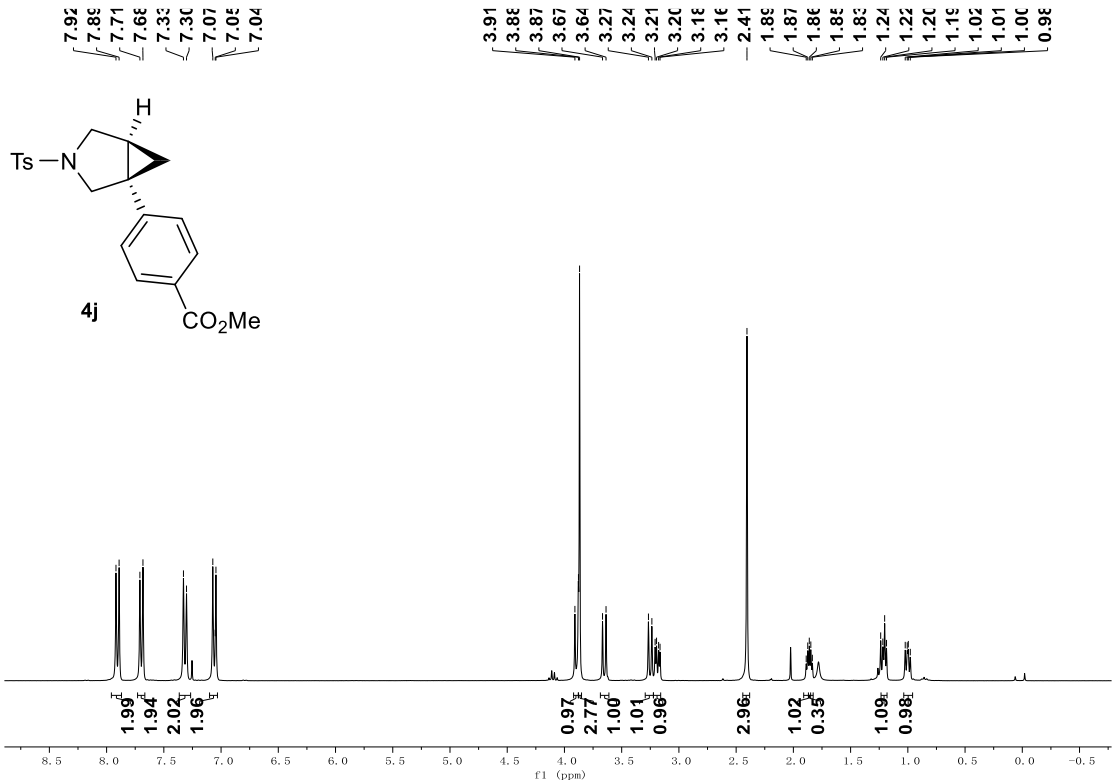

H
Ts—N

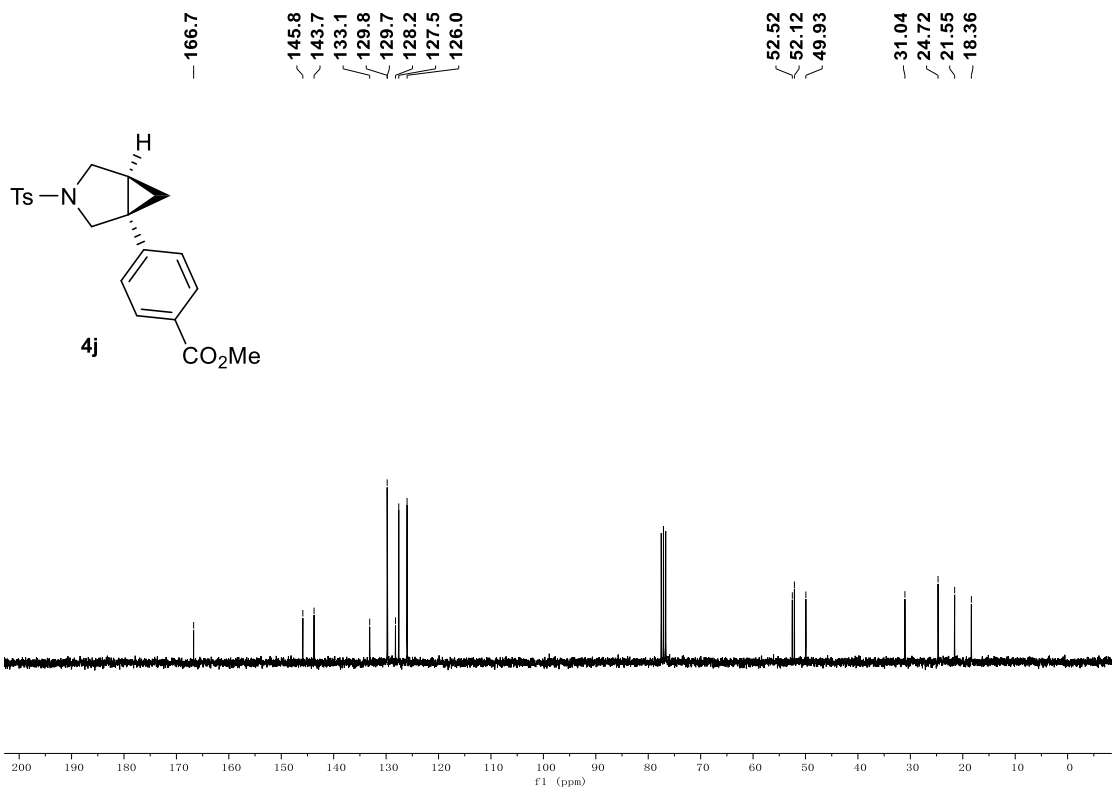
4h

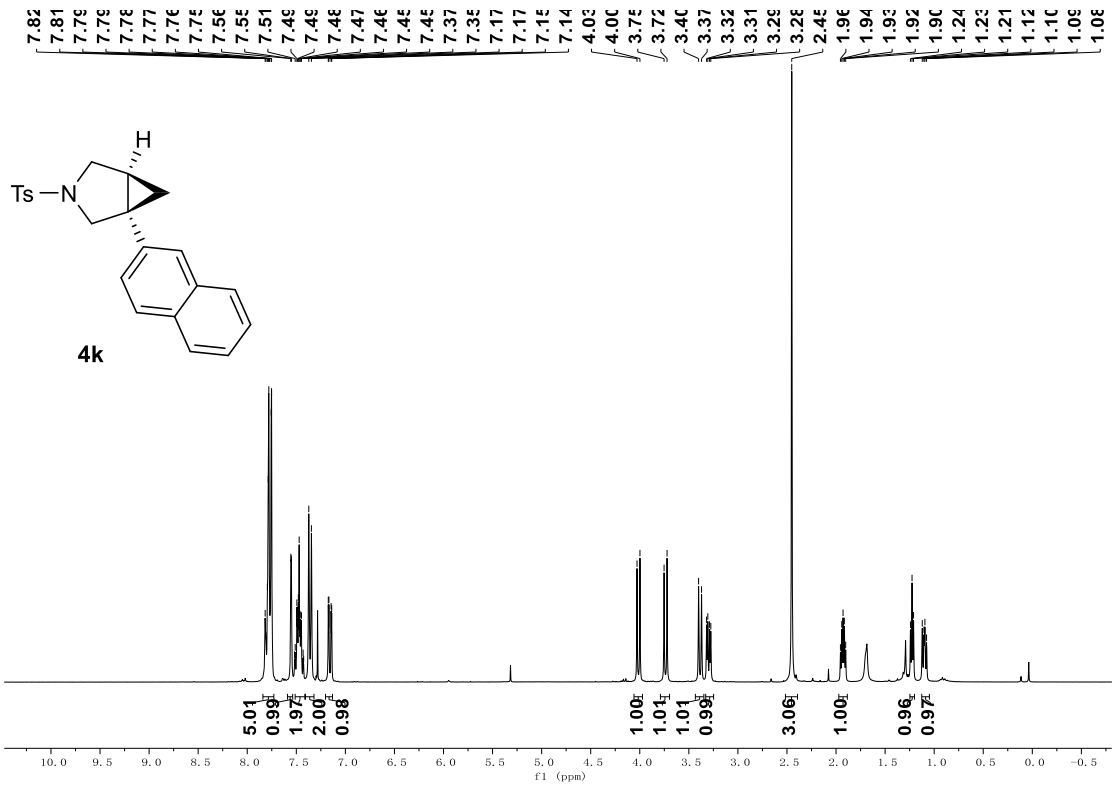

160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

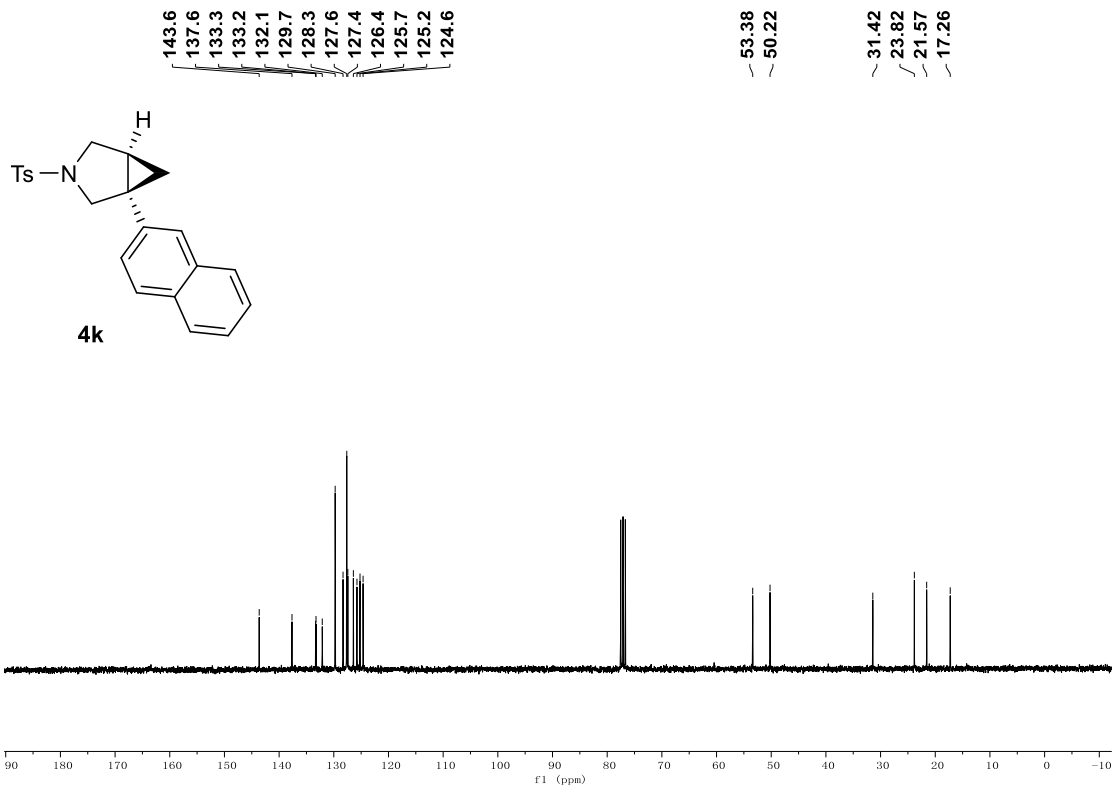

7.71
7.68
7.34
7.31
7.23
7.20
6.99
6.96
3.86
3.83
3.66
3.63
3.22
3.21
3.20
3.19
3.18
3.16
2.42
1.78
1.77
1.76
1.74
1.73
1.14
1.12
1.10
0.95
0.93
0.93
0.91
H
Ts—N
Cl
4i
1.96
1.88
1.90
1.89
1.00
0.98
1.93
2.93
1.31
0.99
1.02
f1 (ppm)

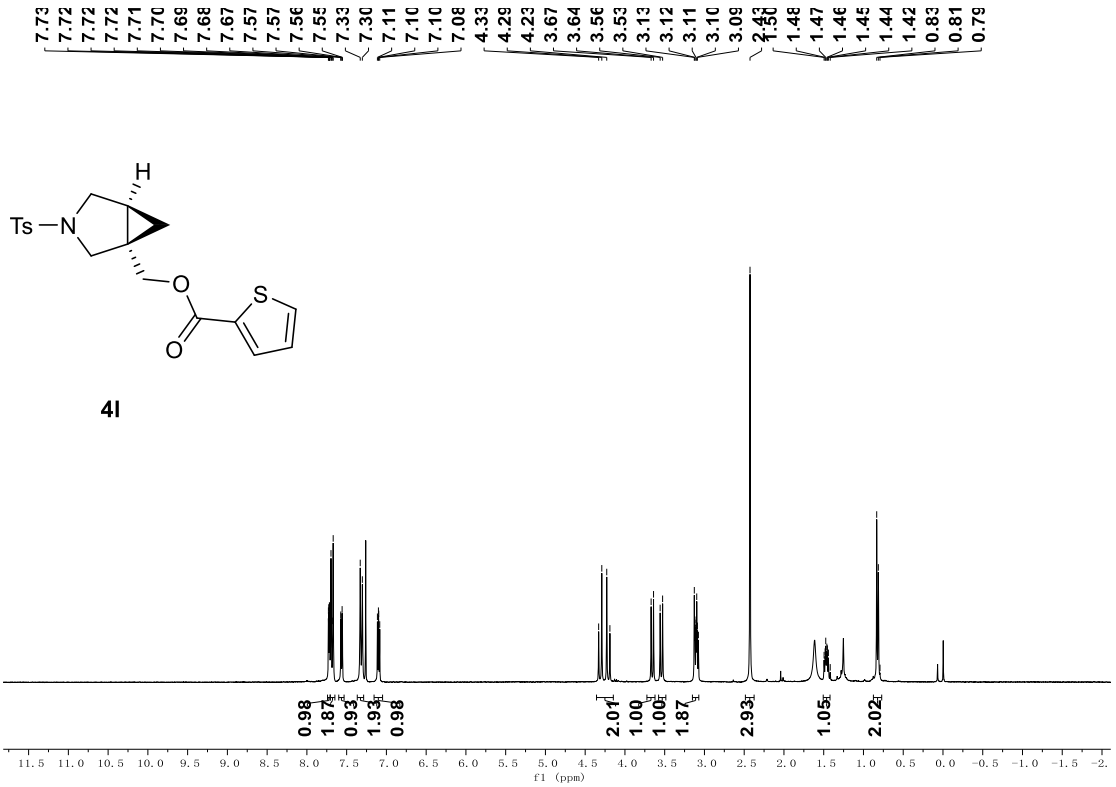

143.7
138.8
133.2
132.3
129.7
128.6
127.9
127.5
53.20
50.06
30.68
23.89
21.57
17.20
H
Ts—N
Cl
4i
f1 (ppm)

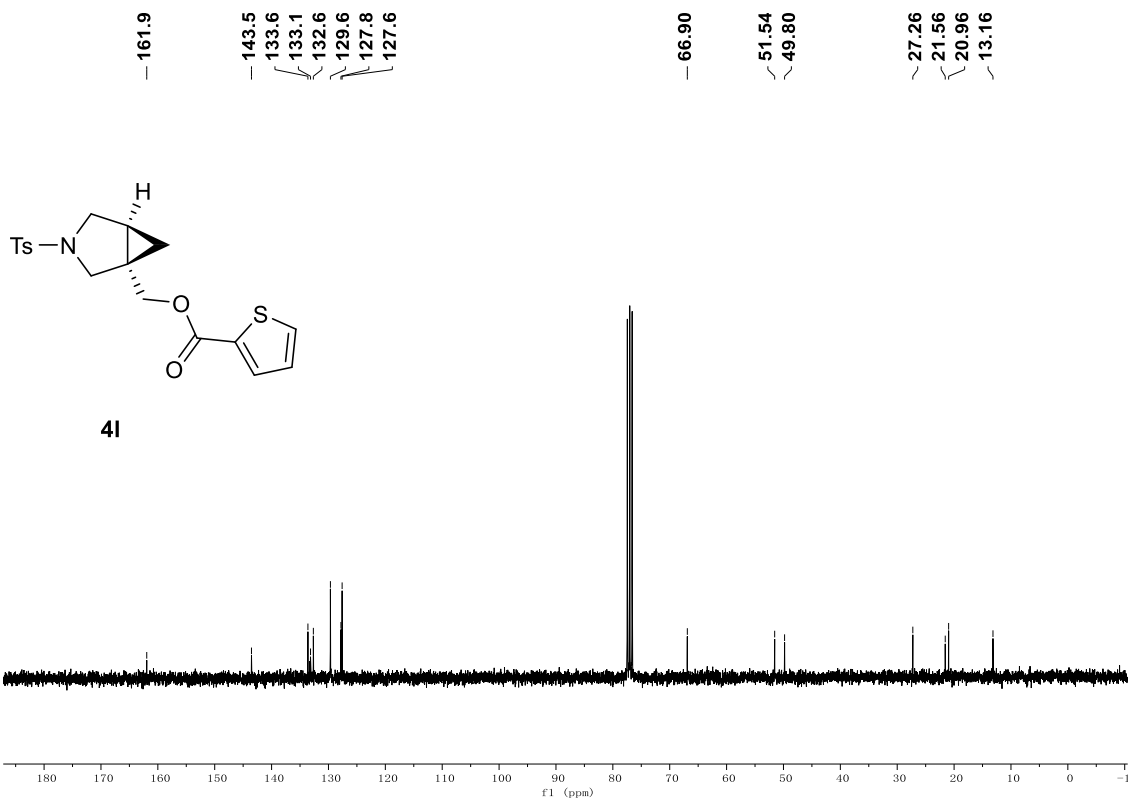

7.92
7.88
7.71
7.68
7.33
7.30
7.07
7.05
7.04
3.91
3.88
3.87
3.67
3.64
3.27
3.24
3.21
3.20
3.18
3.16
2.41
1.89
1.87
1.86
1.85
1.83
1.24
1.22
1.20
1.19
1.02
1.01
1.00
0.98
H
Ts—N
4j
CO2Me
1.99
1.94
2.02
1.96
0.97
2.77
1.00
1.01
0.98
2.96
1.02
0.35
1.09
0.98
f1 (ppm)

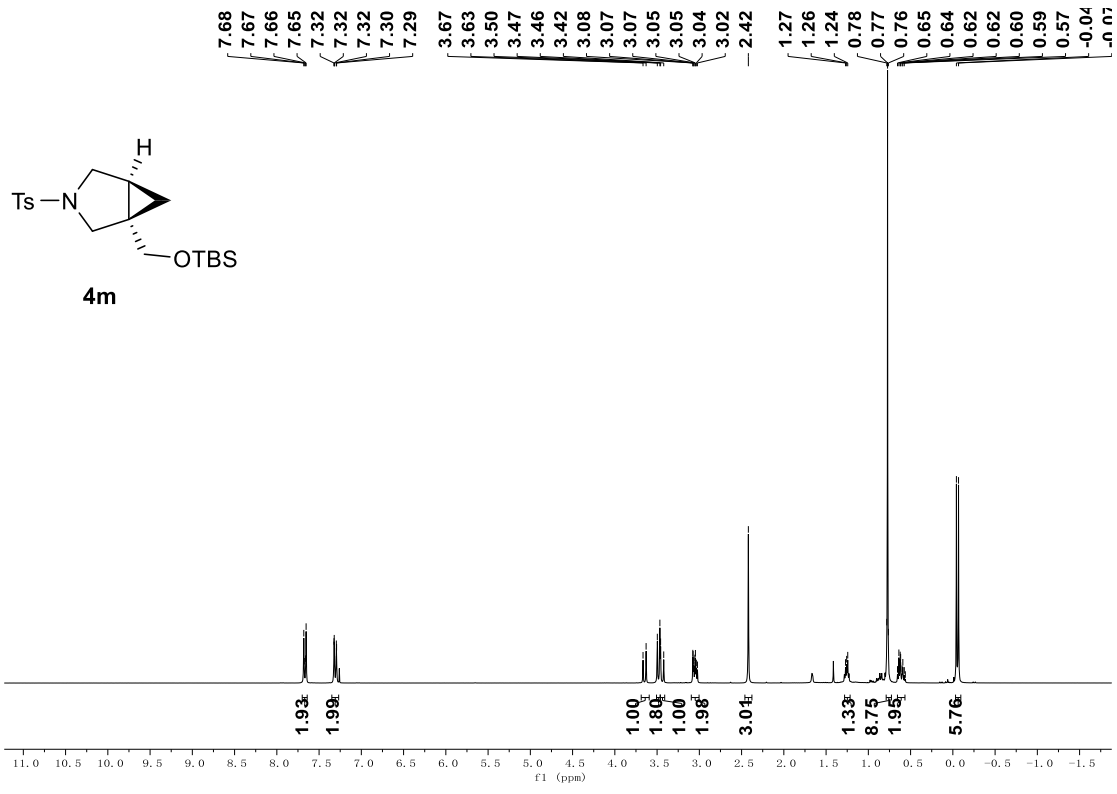

166.7
145.8
143.7
133.1
129.8
129.7
128.2
127.5
126.0
52.52
52.12
49.93
31.04
24.72
21.55
18.36
H
Ts—N
4j
CO2Me
f1 (ppm)


7.82
7.81
7.79
7.79
7.78
7.77
7.76
7.75
7.56
7.55
7.51
7.49
7.49
7.48
7.47
7.46
7.45
7.45
7.37
7.35
7.17
7.17
7.15
7.14
4.03
4.00
3.75
3.72
3.40
3.37
3.32
3.31
3.29
3.28
2.45
1.96
1.94
1.93
1.92
1.90
1.24
1.23
1.21
1.12
1.10
1.09
1.08
H
Ts—N
4k
5.01
0.99
1.97
2.00
0.98
1.00
1.01
1.01
0.99
3.06
1.00
0.96
0.97
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


143.6
137.6
133.3
133.2
132.1
129.7
128.3
127.6
127.4
126.4
125.7
125.2
124.6
53.38
50.22
31.42
23.82
21.57
17.26
H
Ts—N
4k
90 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

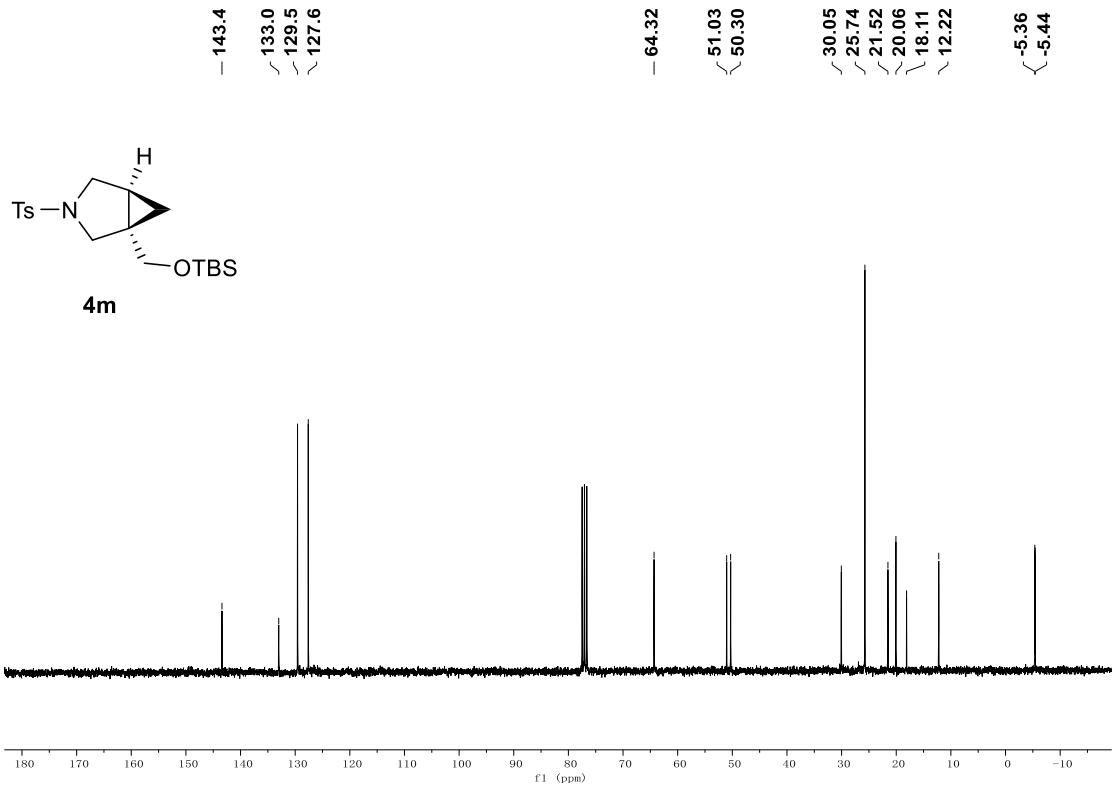

7.73
7.72
7.72
7.72
7.71
7.70
7.69
7.68
7.67
7.57
7.57
7.56
7.55
7.33
7.30
7.11
7.10
7.10
7.08
4.33
4.29
4.23
3.67
3.64
3.56
3.53
3.13
3.12
3.11
3.10
3.09
2.43
2.50
1.48
1.47
1.46
1.45
1.44
1.42
0.83
0.81
0.79
H
Ts—N
O
S
O
4l
0.98
1.87
0.93
1.93
0.98
2.01
1.00
1.00
1.87
2.93
1.05
2.02
f1 (ppm)


161.9
143.5
133.6
133.1
132.6
129.6
127.8
127.6
66.90
51.54
49.80
27.26
21.56
20.96
13.16
H
Ts—N
O
S
O
4l
f1 (ppm)


7.68
7.67
7.66
7.65
7.32
7.32
7.32
7.30
7.29
3.67
3.63
3.50
3.47
3.46
3.42
3.08
3.07
3.07
3.05
3.05
3.04
3.02
2.42
1.27
1.26
1.24
0.78
0.77
0.76
0.65
0.64
0.62
0.62
0.60
0.59
0.57
1.93
1.99
1.00
1.80
1.00
1.98
3.01
1.33
8.75
1.95
5.76
f1 (ppm)

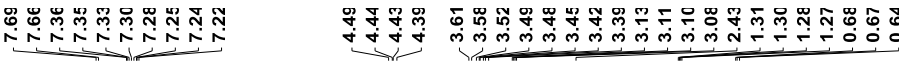
H
Ts
N
OTBS

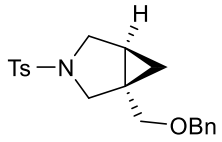
4m


143.4
133.0
129.5
127.6
64.32
51.03
50.30
30.05
25.74
21.52
20.06
18.11
12.22
-5.36
-5.44
f1 (ppm)

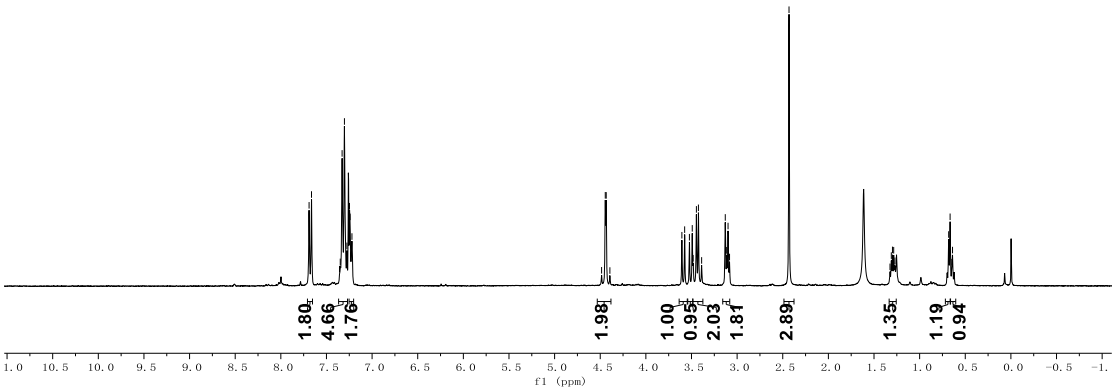
H
Ts
N
OTBS

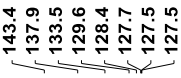
4m

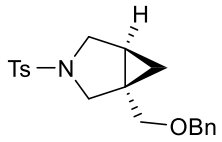

7.69
7.66
7.36
7.35
7.33
7.30
7.28
7.25
7.24
7.22
4.49
4.44
4.43
4.39
3.61
3.58
3.52
3.49
3.48
3.45
3.42
3.39
3.13
3.11
3.10
3.08
2.43
1.31
1.30
1.28
1.27
0.68
0.67


H
Ts—N
OBn

4n

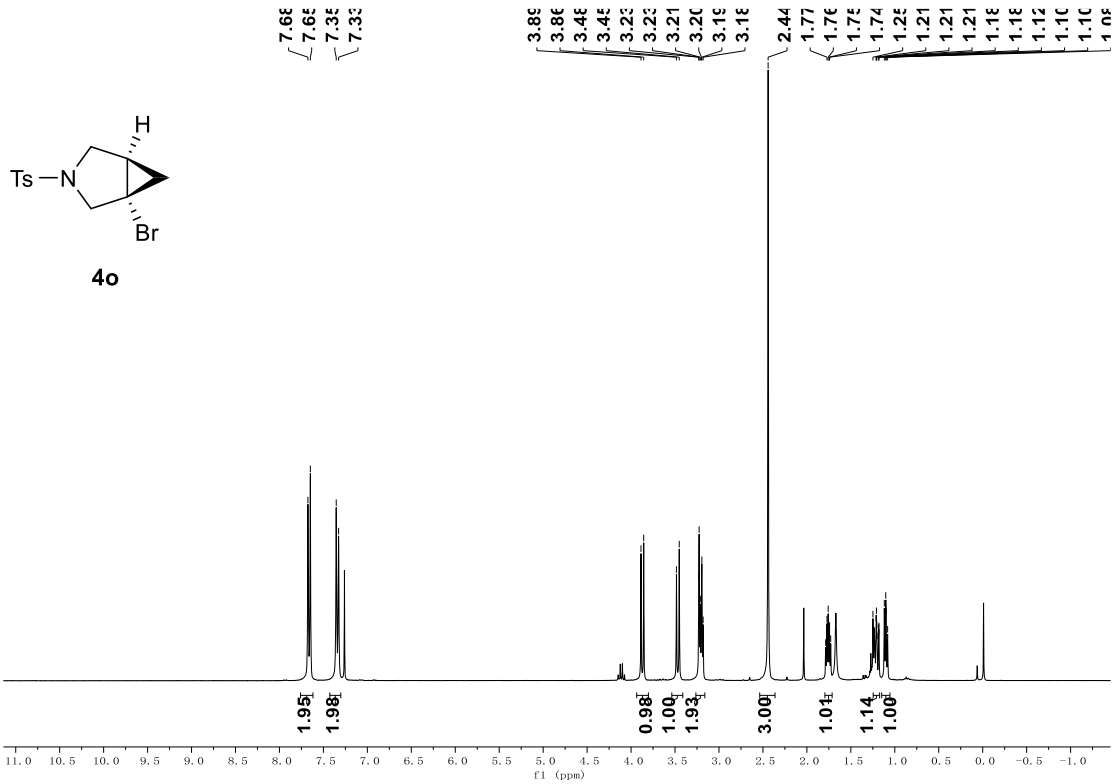

1.80
4.66
1.78
1.98
1.00
0.95
2.03
1.81
2.89
1.35
1.19
0.94
f1 (ppm)


143.4
137.9
133.5
129.6
128.4
127.7
127.5
127.5


H
Ts—N
OBn

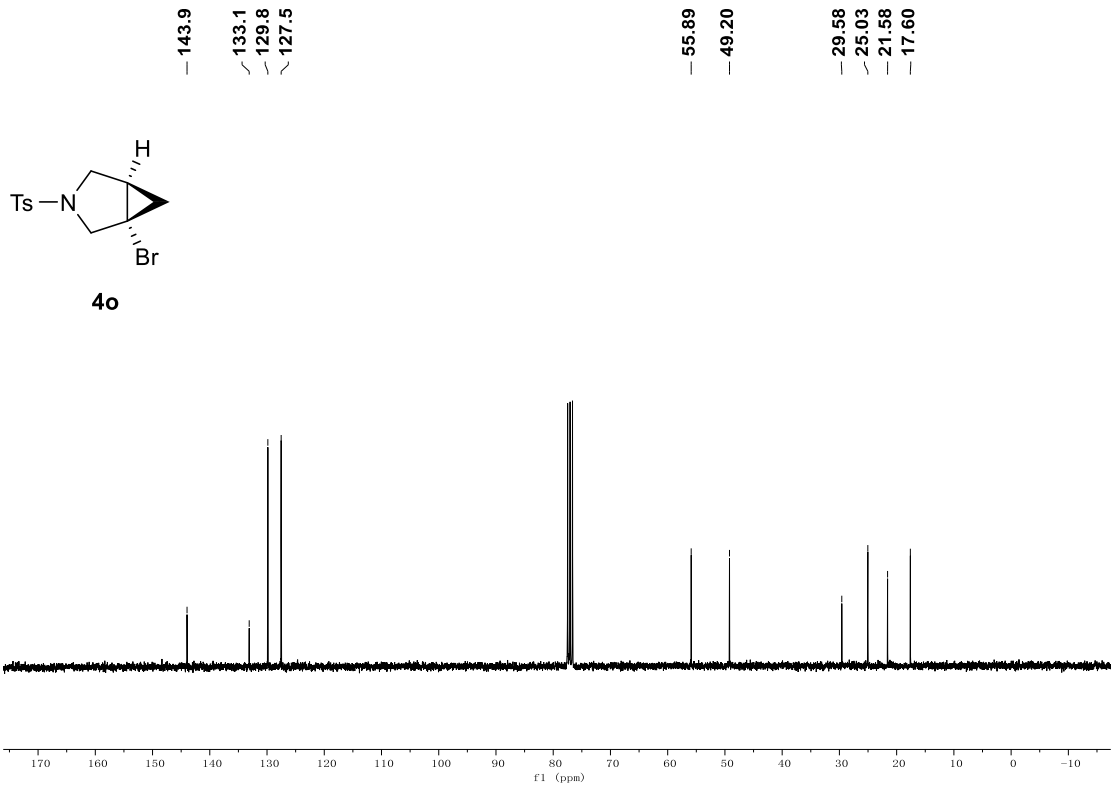
4n

72.70
72.02
51.61
49.91
27.86
21.56
20.13
12.92
f1 (ppm)


H
Ts—N
Br

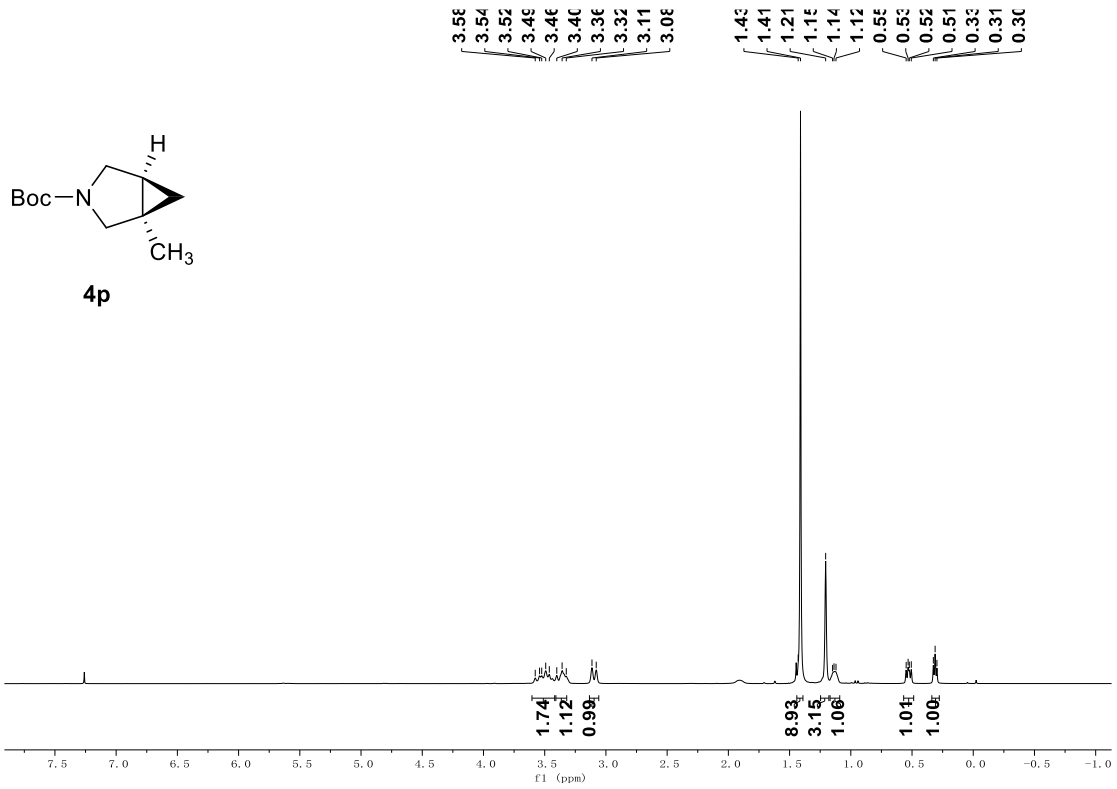
4o

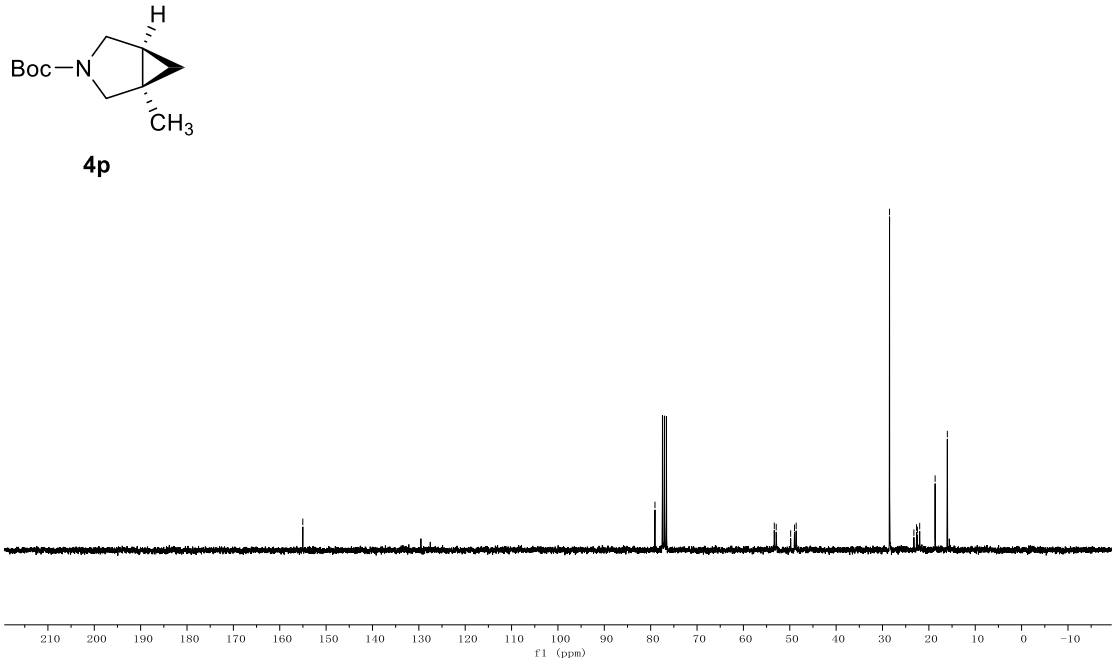
7.68
7.68
7.35
7.33
3.89
3.86
3.48
3.45
3.23
3.23
3.21
3.20
3.19
3.18
2.44
1.77
1.76
1.75
1.74
1.25
1.21
1.21
1.21
1.18
1.18
1.12
1.10
1.10
1.05
1.95
1.98
0.98
1.00
1.93
3.00
1.01
1.14
1.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

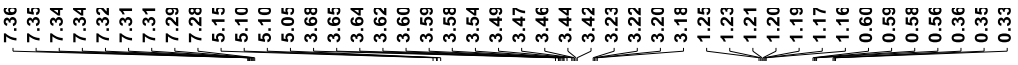

143.9
133.1
129.8
127.5
55.89
49.20
29.58
25.03
21.58
17.60
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

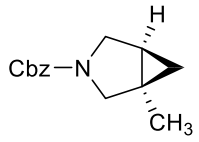
H
Ts—N
Br

4o

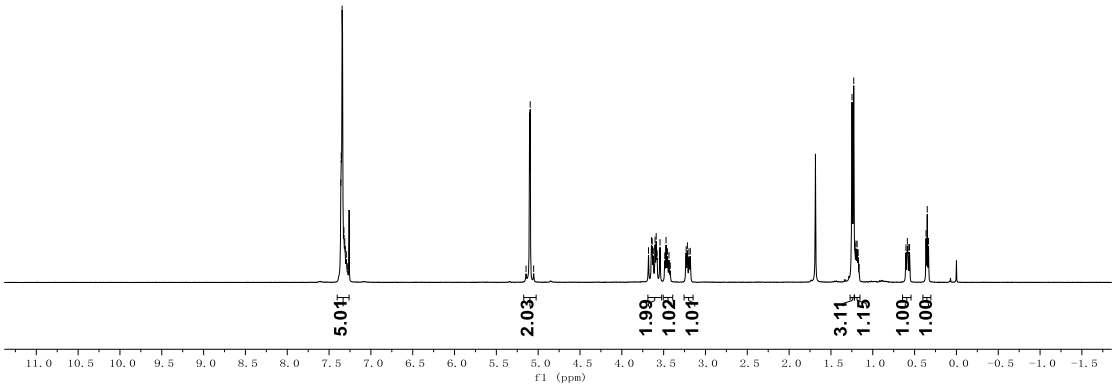

Boc—N
H
CH3
4p
f1 (ppm)


Boc—N
H
CH3
4p
f1 (ppm)

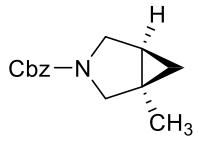

7.36
7.35
7.34
7.34
7.32
7.31
7.31
7.29
7.28
5.15
5.10
5.10
5.05
3.68
3.65
3.64
3.62
3.60
3.59
3.58
3.54
3.49
3.47
3.46
3.44
3.42
3.23
3.22
3.20
3.18
1.25
1.23
1.21
1.20
1.19
1.17
1.16
0.60
0.59
0.58
0.56
0.36
0.35
0.33


H
Cbz—N
CH3

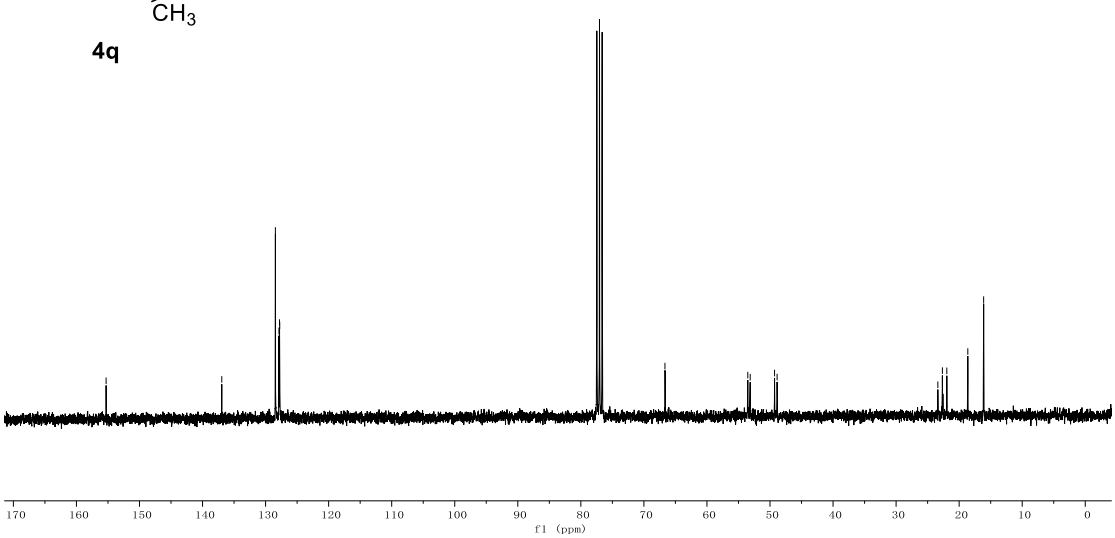
4q


5.01
2.03
1.99
1.02
1.04
3.11
1.15
1.00
1.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

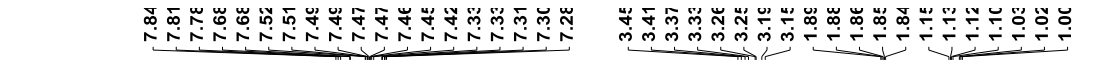

155.2
136.9
128.4
127.8
127.7
127.7
66.66
53.52
53.14
49.28
48.87
23.38
22.66
21.96
18.63
16.12

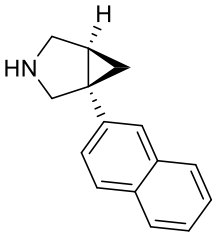

H
Cbz—N
CH3

4q

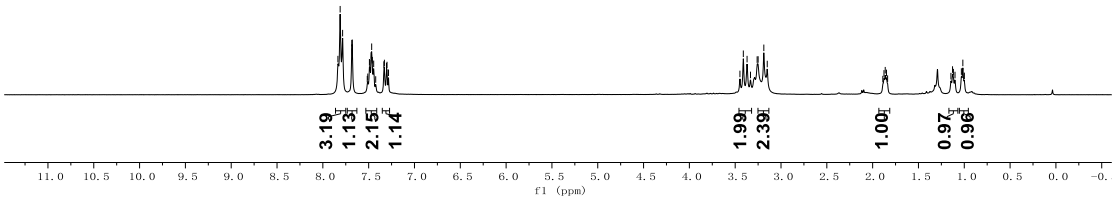

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

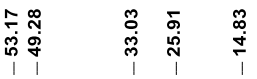
NMR spectrum for centanafadine and bicifadine

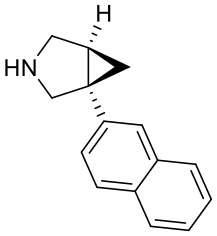




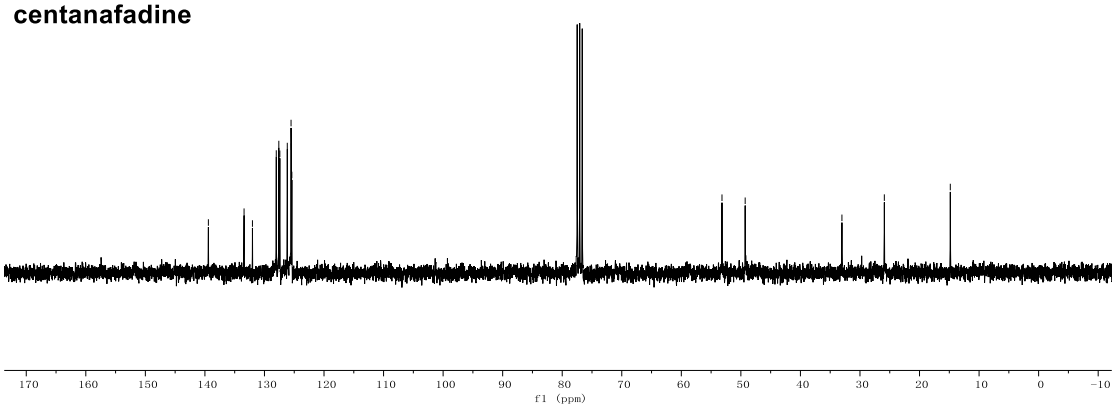
centanafadine

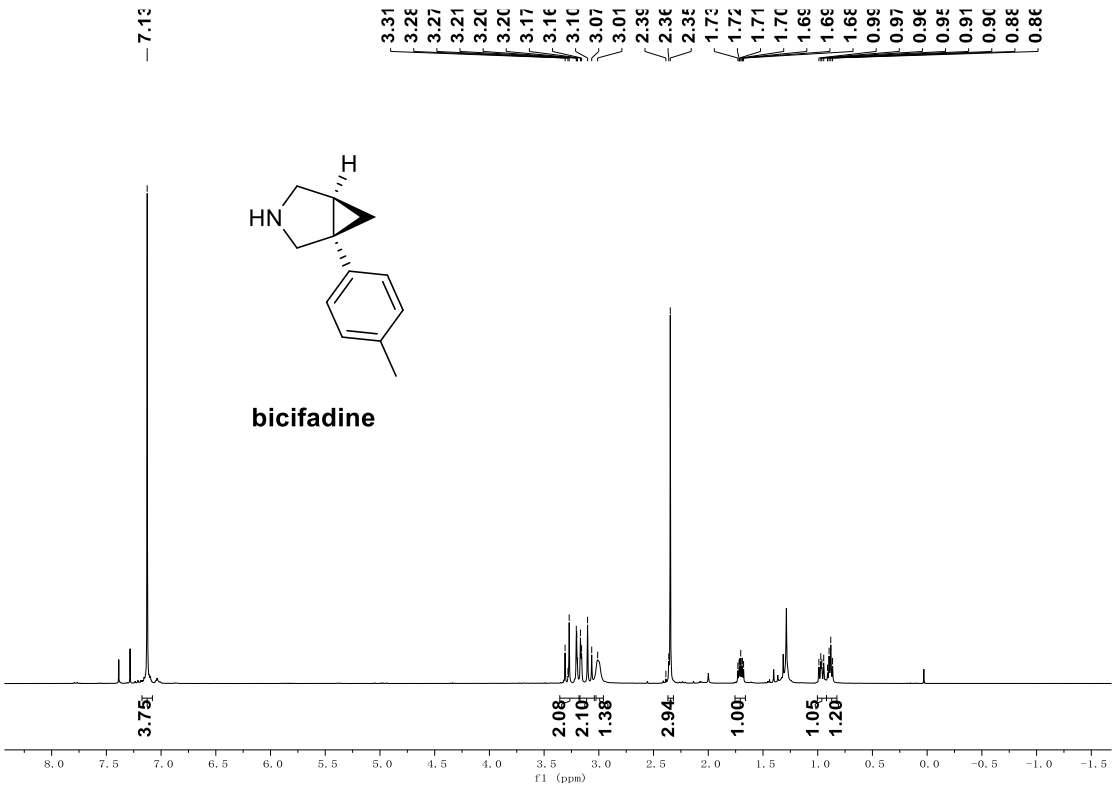


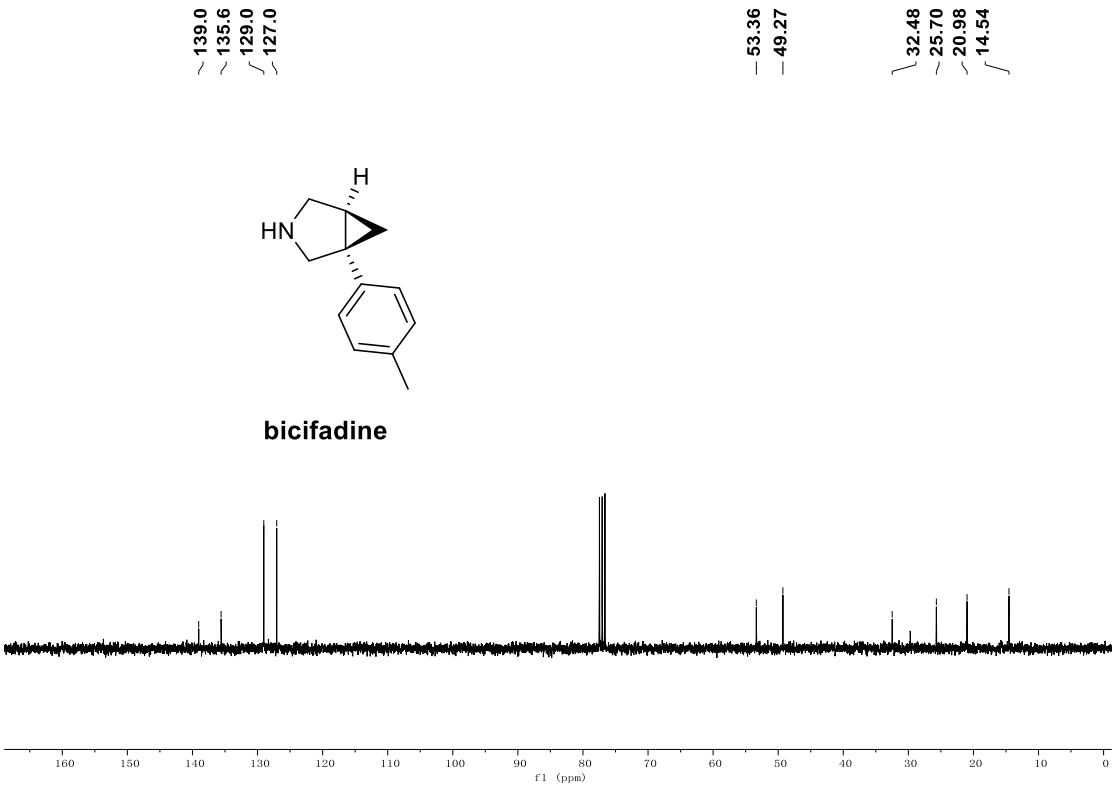




centanafadine




7.13
3.31
3.28
3.27
3.21
3.20
3.20
3.17
3.16
3.10
3.07
3.01
2.39
2.36
2.35
1.73
1.72
1.71
1.70
1.69
1.68
1.68
0.99
0.97
0.96
0.95
0.91
0.90
0.88
0.86
H
HN
bicifadine
3.75
2.08
2.10
1.38
2.94
1.00
1.05
1.20
f1 (ppm)


139.0
135.6
129.0
127.0
53.36
49.27
32.48
25.70
20.98
14.54
H
HN
bicifadine
f1 (ppm)

HPLC spectra of products 4a