Electronic Supplementary Information

Chemoselective Reductive Alkynylation of Tertiary Amides by Ir and Cu(I) Bis-metal Sequential Catalysis

Pei-Qiang Huang, Wei Ou, and Feng Han*

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Table 1. The structures of the amides used

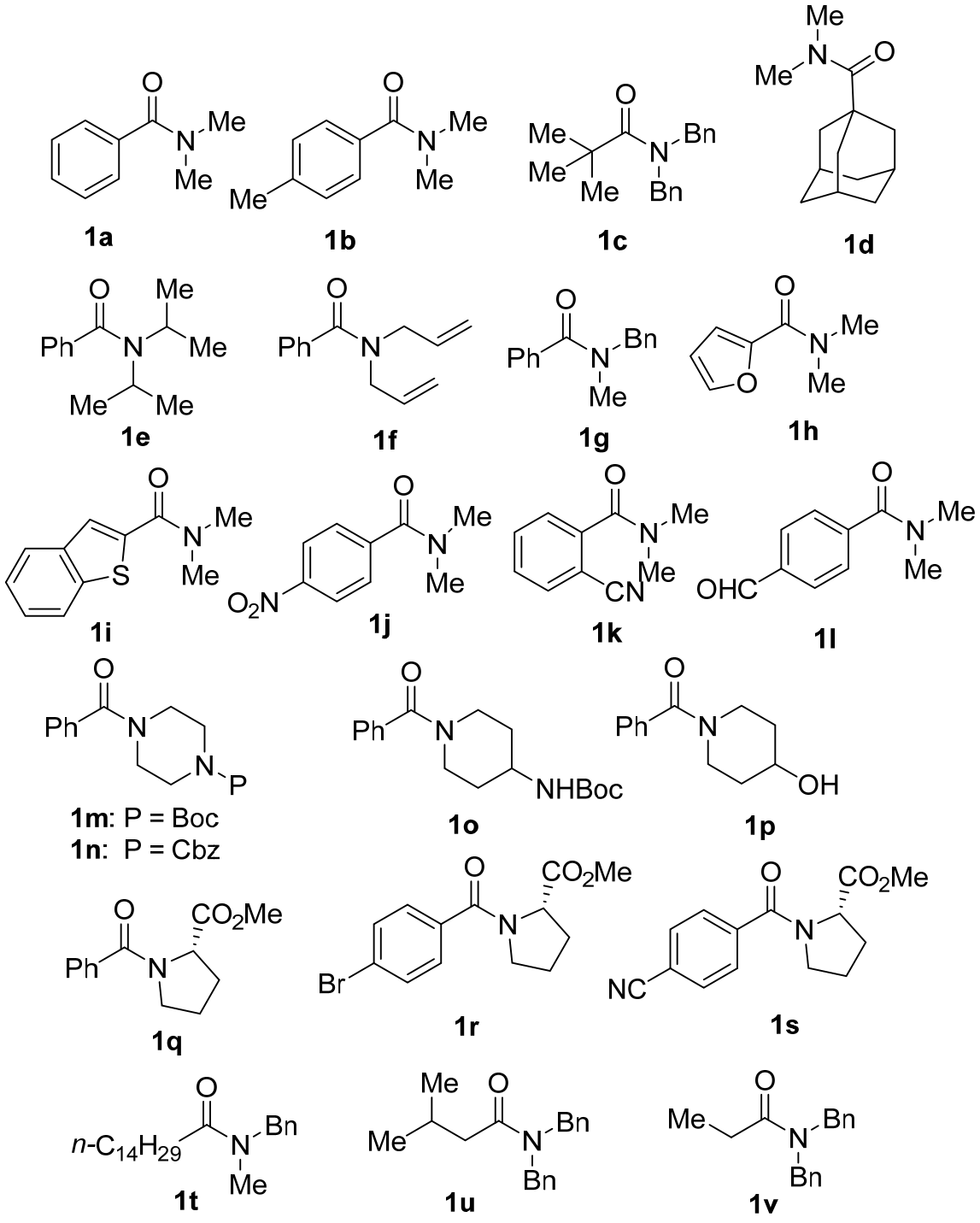
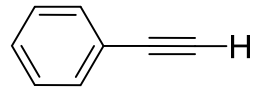
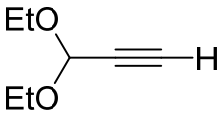


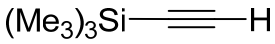
Table 2. The structures of the alkynes used



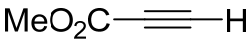
2a



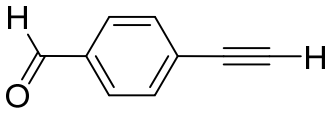
2b



2c

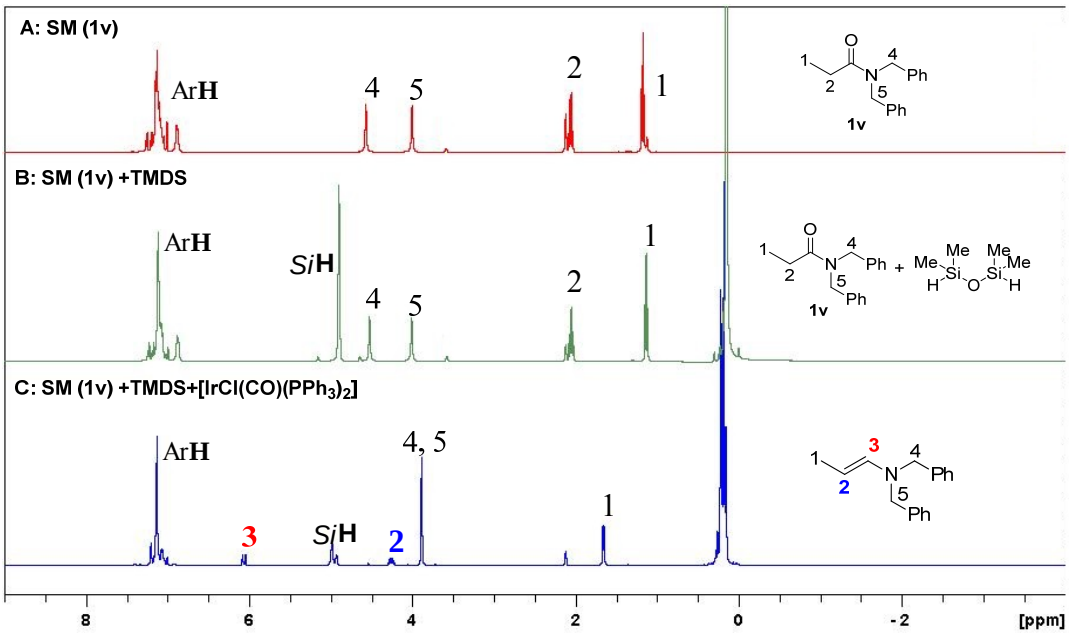


2d

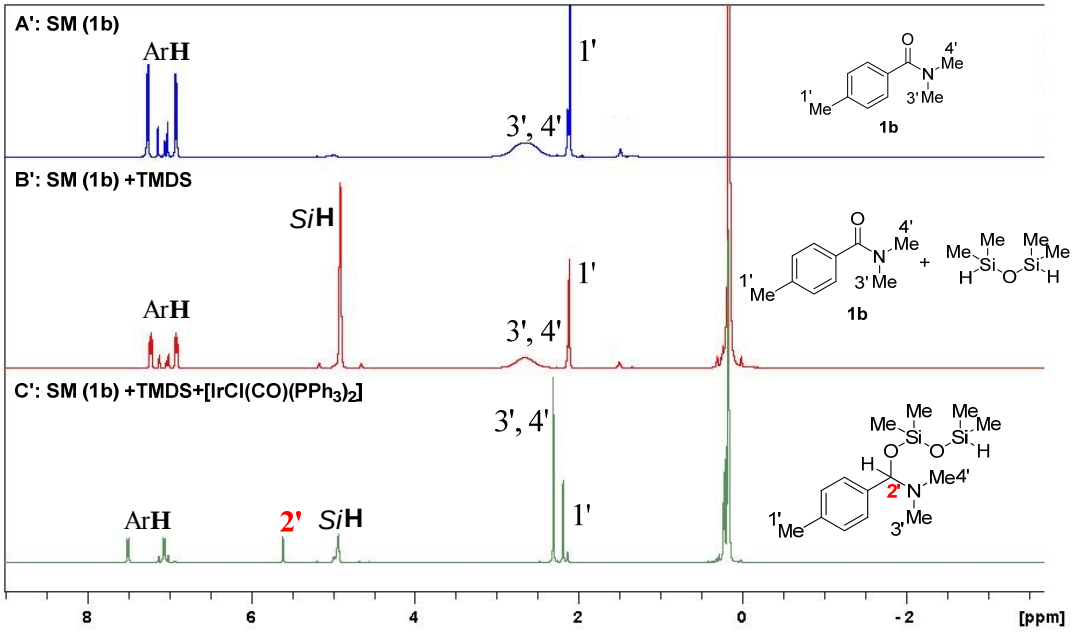


2e

In situ ^{1}H NMR Spectra of the reaction



^{1}H NMR spectra (400 MHz) of starting material, intermediates in D_8-toluene. (A) **1v** in D_8-toluene; (B) **1v** and $(Me_2HSi)_2O$ in D_8-toluene; (C) **1v**, $(Me_2HSi)_2O$ (2.0 equiv), and $[IrCl(CO)(PPh_3)_2]$ (1 mol %) in D_8-toluene, 10 min.

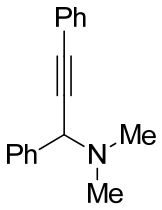


^{1}H NMR spectra (400 MHz) of starting material, intermediates in D_8-toluene. (A') **1b** in D_8-toluene; (B') **1b** and $(Me_2HSi)_2O$ in D_8-toluene; (C') **1b**, $(Me_2HSi)_2O$ (1.2 equiv), and $[IrCl(CO)(PPh_3)_2]$ (1 mol %) in D_8-toluene, 30 min.

Experimental Procedures

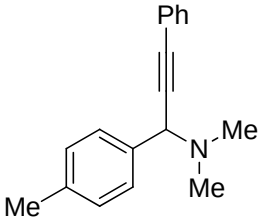
General Methods. Melting points were determined on a Büchi M560 Automatic Melting Point apparatus and are uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. NMRSpectra were recorded on a Bruker AV 400 or AC 500 spectrometer at 25 ºC in the solvents indicated. Chemical shifts (δ) are reported in ppm and respectively referenced to internal standard Me_4Si and solvent signals (Me_4Si, 0 ppm for ^1H NMR and $CDCl_3$, 77.0 ppm for ^{13}C NMR). Mass spectra were recorded on a Bruker Dalton ESquire 3000 plus LC-MS apparatus (ESI direct injection). HRMS spectra were recorded on a 7.0T FT-MS apparatus. Silica gel (300-400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with EtOAc/ *n*-hexane mixture. Toluene were distilled over sodium benzophenone ketyl under N_2.

***N,N*-Dimethyl-1,3-diphenylprop-2-yn-1-amine (3a)**[1]



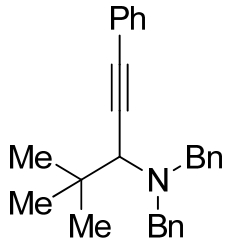
Following the general procedure, the reaction of *tert*-amide **1a** (149 mg, 1.0 mmol) with phenylacetylene **2a** (0.13 mL, 1.2 mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 100), the known propargylic amine **3a**[1] (209 mg, yield: 89%) as a pale yellow oil; IR (film) ν_{max}: 2939, 1597, 1488, 1450, 1325, 1021, 755, 694cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 6H), 4.82 (s, 1H), 7.27-7.38 (m, 6H), 7.51-7.53 (m, 2H), 7.60-7.62 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.6 (2C), 62.2, 84.8, 88.3, 123.2, 127.6, 128.1 (2C), 128.2 (2C), 128.3 (2C), 128.3 (2C), 128.4, 131.8, 138.7 ppm; MS (ESI) *m/z* 236 ($M+H^+$).

***N,N*-Dimethyl-3-phenyl-1-(p-tolyl)prop-2-yn-1-amine (3b)**



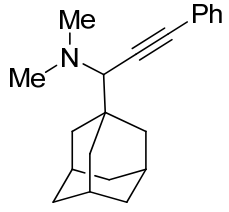
Following the general procedure, the reaction of *tert*-amide **1b** (163 mg, 1.0 mmol) with phenylacetylene **2a** (0.13 mL, 1.2 mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 100), the propargylic amine **3b** (224 mg, yield: 90%) as a pale yellow oil; IR (film) ν_{max}: 2939, 1597, 1488, 1450, 1325, 1021, 755, 694cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 6H), 2.35 (s, 3H), 4.78 (s, 1H), 7.17 (d, J = 7.8 Hz, 2H), 7.31-7.33 (m, 3H), 7.47-7.53 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 41.6 (2C), 61.9, 85.1, 88.1, 123.2, 128.1, 128.2 (2C), 128.3 (2C), 128.9 (2C), 131.8 (2C), 135.7, 137.3 ppm; MS (ESI) *m/z* 250 (M+H$^+$); HRMS (ESI) *m/z* calcd for $[C_{18}H_{20}N]^+$(M + H$^+$): 250.1590; found: 250.1591.

_N,N_-Dibenzyl-4,4-dimethyl-1-phenylpent-1-yn-3-amine (3c)



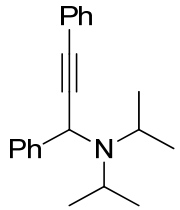
Following the general procedure, the reaction of tertiary amide **1c** (281 mg, 1.0 mmol) with phenylacetylene **2b** (0.13 mL, 1.2 mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 100), propargylic amine **3c** (220 mg, yield: 60%) as a pale yellow oil; IR (film) ν_{max}: 2955, 1601, 1495, 1453, 1357, 1258, 1030, 800, 749, 691 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H), 3.37 (s, 1H), 3.45 (d, J = 14.0 Hz, 2H), 3.95 (d, J = 14.0 Hz, 2H), 7.22-7.25 (m, 2H), 7.30-7.35 (m, 7H), 7.42-7.44 (m, 4H), 7.50-7.52 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9 (3C), 36.2, 57.9 (2C), 62.2, 86.6, 86.7, 123.8, 126.9, 127.8 (2C), 128.0 (2C), 128.1 (4C), 128.3 (4C), 129.1 (2C), 131.8, 140.0 ppm; MS (ESI) *m/z*368 (M+H$^+$); HRMS (ESI) *m/z* calcd for $[C_{27}H_{30}N]^+$(M + H$^+$): 368.2373; found: 368.2376.

1-((3*r*,5*r*,7*r*)-Adamantan-1-yl)-*N*,*N*-dimethyl-3-phenylprop-2-yn-1-amine (3d)



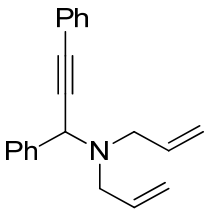
Following the general procedure, the reaction of *tert*-amide **1d** (207 mg, 1.0 mmol) with phenylacetylene **2a** (0.13 mL, 1.2 mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 80), propargylic amine **3d** (234 mg, yield: 80%) as a pale yellow oil; IR (film) ν_{max}: 2901, 1492, 1447, 1341, 1021, 752, 688 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.63-1.78 (m, 12H), 2.00 (s, 3H), 2.36 (s, 6H), 3.04 (s, 1H), 7.28-7.33 (m, 3H), 7.45-7.47 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.7, 37.2 (2C), 38.2 (3C), 39.9 (3C), 45.2(3C), 69.3, 85.1, 88.1, 123.8, 127.7 (2C), 128.2 (2C), 131.7 ppm; MS (ESI) *m/z* 294 ($M+H^+$); HRMS (ESI) *m/z* calcd for $[C_{21}H_{28}N]^+(M + H^+)$: 294.2216; found: 294.2216.

***N,N*-Diisopropyl-1,3-diphenylprop-2-yn-1-amine (3e)**[2]



Following the general procedure, the reaction of *tert*-amide **1e** (205 mg, 1.0 mmol) with phenylacetylene **2a** (0.13 mL, 1.2mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 100), the known propargylic amine **3e**[2] (195 mg, yield: 67%) as a pale yellow oil; IR (film) ν_{max}: 2952, 1601, 1492, 1447, 1380, 1181, 758, 710, 685 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.05 (d, J = 6.7 Hz, 3H), 1.29 (d, J = 6.7 Hz, 3H), 3.16-3.26 (m, 2H), 5.02 (s, 1H), 7.22-7.35 (m, 6H), 7.46-7.49 (m, 2H), 7.73-7.75 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7 (2C), 23.8 (2C), 46.6 (2C), 50.5, 85.9, 91.6, 123.9, 126.8, 127.8 (2C), 127.9 (4C), 128.3 (2C), 131.3, 142.2 ppm; MS (ESI) *m/z* 292 ($M+H^+$).

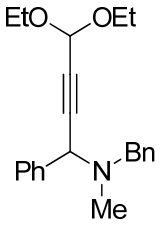
***N*-Allyl-*N*-(1,3-diphenylprop-2-yn-1-yl)prop-2-en-1-amine (3f)**[3]



Following the general procedure, the reaction of *tert*-amide **1f** (201 mg, 1.0 mmol) with phenylacetylene **2a** (0.13 mL, 1.2 mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 100), the known propargylic amine **3f**[3] (244 mg, yield: 85%) as a pale yellow oil; IR (film) ν_{max}: 3077, 2923, 2814, 1642, 1594, 1485, 1444, 1267, 1114,

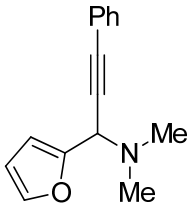
992, 970, 922, 755, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.02-3.08 (m, 2H), 3.26-3.29 (m, 2H), 5.10-5.14 (m, 3H), 5.25-5.29 (m, 2H), 5.81-5.91 (m, 2H), 7.24-7.37 (m, 6H), 7.52-7.53 (m, 2H), 7.67-7.70 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.5 (2C), 56.6, 117.3 (2C), 123.3, 127.3 (2C), 127.4 (4C), 128.1 (2C), 128.3 (2C), 131.8 (2C), 136.5 (2C), 139.3 ppm; MS (ESI) *m/z* 288 ($M+H^+$).

_N_-Benzyl-4,4-diethoxy-_N_-methyl-1-phenylbut-2-yn-1-amine (3g)



Following the general procedure, the reaction of *tert*-amide **1g** (225 mg, 1.0 mmol) with 3,3-diethoxyprop-1-yne **2b** (0.17 mL, 1.2 mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 100), propargylic amine **3g** (307 mg, yield: 91%) as a pale yellow oil; IR (film) ν_{max}: 2978, 1450, 1328, 1053, 1011, 736, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, J = 7.0 Hz, 6H), 2.18 (s, 3H), 3.55 (d, J = 13.2 Hz, 1H), 3.65-3.73 (m, 3H), 3.81-3.90 (m, 2H), 4.78 (s, 1H), 5.48 (d, J = 1.1 Hz, 1H), 7.24-7.38 (m, 8H), 7.59-7.61 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ15.2 (2C),38.0,58.7, 59.1, 60.8, 60.9, 80.6, 84.0, 91.5, 127.1, 127.5, 128.1 (2C), 128.2 (2C), 128.3 (2C), 128.9 (2C), 138.4, 139.1 ppm; MS (ESI) *m/z* 338 ($M+H^+$); HRMS (ESI) *m/z* calcd for $[C_{22}H_{28}NO_2]^+$($M + H^+$): 338.2115; found: 338.2115.

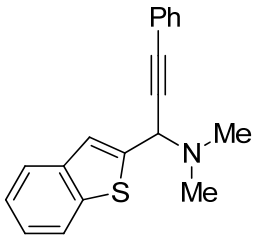
1-(Furan-2-yl)-_N,N_-dimethyl-3-phenylprop-2-yn-1-amine (3h)



Following the general procedure, the reaction of *tert*-amide **1h** (139 mg, 1.0 mmol) with phenylacetylene **2a** (0.13 mL, 1.2 mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 90), propargylic amine **3h** (180 mg, yield: 80%) as a pale yellow oil; IR (film) ν_{max}: 2936, 1700, 1594, 1485, 1181, 1072, 758, 691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 6H), 4.89 (s, 1H), 6.35 (dd, J = 1.9, 3.2 Hz, 1H), 6.49-6.50 (m, 1H), 7.31-7.34 (m, 3H), 7.42-7.43 (m, 1H), 7.49-7.51 (m, 2H) ppm; ^{13}C NMR (100

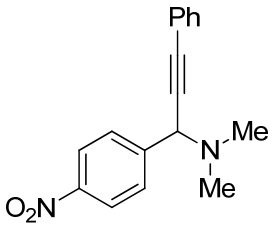
MHz, $CDCl_3$): δ 41.3 (2C), 56.2, 82.6, 86.2, 108.9, 109.9, 122.7, 128.2 (2C), 128.3 (2C), 131.8, 142.6, 151.9 ppm; MS (ESI) *m/z*226 ($M+H^+$); HRMS (ESI) *m/z* calcd for $[C_{15}H_{16}NO]^+$($M + H^+$): 226.1226; found: 226.1228.

1-(Benzo[*b*]thiophen-2-yl)-*N, N*-dimethyl-3-phenylprop-2-yn-1-amine (3i)



Following the general procedure, the reaction of *tert*-amide **1i** (205 mg, 1.0 mmol) with phenylacetylene **2a** (0.13 mL, 1.2 mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 80), propargylic amine **3i** (236 mg, yield: 81%) as a white solid; Mp70-72 ^oC; IR (film) ν_{max}: 2938, 1715, 1590, 1491, 1180, 1135, 1052, 768, 698 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 6H), 5.08 (d, J = 1.1Hz, 1H), 7.27-7.36 (m, 5H), 7.49 (s, 1H), 7.55-7.57 (m, 2H), 7.71-7.80 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.6 (2C), 58.7, 83.4, 87.9, 122.3, 122.6, 122.8, 123.5 (2C), 124.1 (2C), 128.3, 128.4, 131.9, 139.3, 140.3, 145.1 ppm;MS (ESI) *m/z*292 ($M+H^+$); HRMS (ESI) *m/z* calcd for $[C_{19}H_{18}NS]^+$($M + H^+$): 292.1154; found: 292.1156.

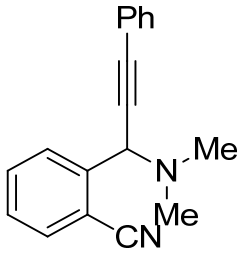
***N, N*-Dimethyl-1-(4-nitrophenyl)-3-phenylprop-2-yn-1-amine (3j)**



Following the general procedure, the reaction of *tert*-amide **1j** (194 mg, 1.0 mmol) with phenylacetylene **2a** (0.13 mL, 1.2 mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 20), propargylic amine **3j** (216 mg, yield: 77%) as a pale yellow oil; IR (film) ν_{max}: 2952, 1745, 1488, 1203, 758, 691cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 6H), 4.90 (s, 1H), 7.34-7.38 (m, 3H), 7.51-7.56 (m, 2H), 7.81-7.85 (m, 2H), 8.21-8.24 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.7 (2C), 61.7, 83.0, 89.5, 122.5, 123.4, 128.4 (2C), 128.6 (2C), 129.2 (2C), 131.8 (2C), 146.3, 147.5 ppm; MS

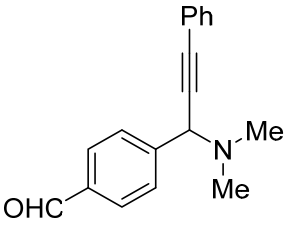
(ESI) *m/z* 281 ($M+H^+$); HRMS (ESI) *m/z* calcd for $[C_{17}H_{17}N_2O_2]^+(M + H^+)$: 281.1285; found: 281.1280.

2-(1-(Dimethylamino)-3-phenylprop-2-yn-1-yl)benzonitrile (3k)

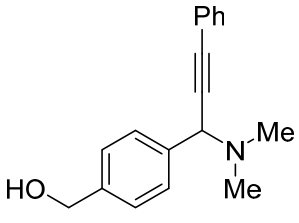


Following the general procedure, the reaction of *tert*-amide **1k** (174 mg, 1.0 mmol) with phenylacetylene **2a** (0.13 mL, 1.2 mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 40), propargylic amine **3k** (208 mg, yield: 80%) as a pale yellow oil; IR (film) ν_{max}: 2944, 2224, 1705, 1597, 1320, 1017, 758, 691cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 6H), 5.09 (s, 1H), 7.35-7.42 (m, 4H), 7.53-7.61 (m, 3H), 7.69-7.71 (m, 1H), 7.84-7.86 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.5 (2C), 60.5, 82.7, 89.4, 113.3, 117.6, 122.6, 128.1, 128.4 (2C), 128.5 (2C), 129.1, 131.8, 132.1, 133.4, 143.0 ppm; MS (ESI) *m/z* 261 ($M+H^+$).

4-(1-(Dimethylamino)-3-phenylprop-2-yn-1-yl)benzaldehyde (3l)



(3l)



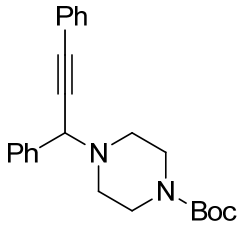
(3l')

Following the general procedure, the reaction of *tert*-amide **1l** (354 mg, 2.0 mmol) with phenylacetylene **2a** (0.26 mL, 2.4 mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 70; 1: 5), propargylic amine **3l** (336 mg, yield: 64%), and propargylic amine **3l'** (42 mg, yield: 8%).

3l: pale yellow oil; IR (film) ν_{max}: 2943, 2824, 1703, 1607, 1492, 1021, 790, 758, 688, 598 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 6H), 4.88 (s, 1H), 7.34-7.36 (m, 3H), 7.52-7.55 (m, 2H), 7.80-7.90 (m, 4H), 10.0 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.6 (2C), 62.0, 83.6, 89.1, 122.7, 128.3, 128.4 (2C), 129.0 (2C), 129.6 (2C), 131.8 (2C), 135.8, 145.7, 191.9 ppm; MS (ESI) *m/z* 264 ($M+H^+$); HRMS (ESI) *m/z* calcd for $[C_{18}H_{18}NO]^+(M + H^+)$: 264.1383; found: 264.1384.

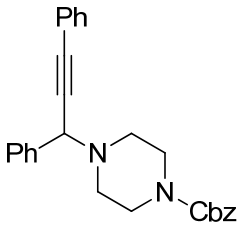
(4-(1-(Dimethylamino)-3-phenylprop-2-yn-1-yl)phenyl)methanol (3l'): pale yellow oil; IR (film) ν_{max}: 3240, 2936, 2858, 2773, 1485, 752, 688 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 1H), 2.30 (s, 6H), 4.68 (s, 2H), 4.80 (s, 1H), 7.32-7.36 (m, 5H), 7.50-7.51 (m, 2H), 7.58-7.60 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.5 (2C), 62.0, 65.0, 84.7, 88.4, 123.1, 126.8, 128.2 (2C), 128.3 (2C), 128.7 (2C), 131.8 (2C), 138.0, 140.5 ppm; MS (ESI) *m/z* 266 ($M+H^+$). The structure of this side-product was confirmed by HMBC spectrum (cf. ESI p.44).

***tert*-Butyl 4-(1,3-diphenylprop-2-yn-1-yl)piperazine-1-carboxylate (3m)**



Following the general procedure, the reaction of *tert*-amide **1m** (290 mg, 1.0 mmol) with phenylacetylene **2a** (0.13 mL, 1.2 mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 100), propargylic amine **3m** (346 mg, yield: 92%) as a white solid; Mp 86-87 °C; IR (film) ν_{max}: 2935, 2807, 1702, 1496, 1363, 1167, 1044, 756, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.56-2.58 (m, 4H), 3.40-3.49 (m, 4H), 4.84 (s, 1H), 7.29-7.39 (m, 6H), 7.49-7.51 (m, 2H), 7.62-7.64 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.4 (3C), 43.6 (2C), 49.2 (2C), 61.8, 79.5, 84.9, 88.5, 122.9, 127.7 (2C), 128.2 (2C), 128.3 (2C), 128.5 (2C), 131.8 (2C), 137.9, 154.8 ppm; MS (ESI) *m/z*377 ($M+H^+$); HRMS (ESI) *m/z* calcd for $[C_{24}H_{29}N_2O_2]^+$($M + H^+$): 377.2224; found: 377.2226.

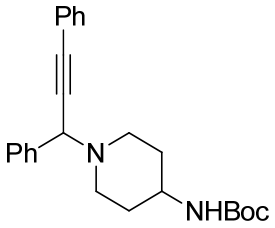
Benzyl 4-(1,3-diphenylprop-2-yn-1-yl)piperazine-1-carboxylate (3n)



Following the general procedure, the reaction of *tert*-amide **1n** (324mg, 1.0 mmol) with phenylacetylene **2a** (0.13 mL, 1.2 mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 100), propargylic amine **3n** (390 mg, yield: 95%) as a white solid; Mp

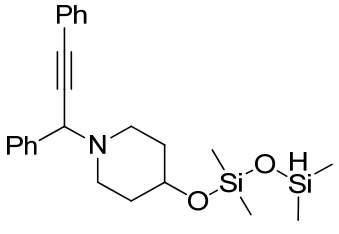
111-113 ºC; IR (film) ν_{max}: 2933, 1703, 1597, 1239, 1178, 1072, 1021, 755, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.59 (br s, 4H), 3.48-3.58 (m, 4H), 4.85 (s, 1H), 5.12 (s, 2H), 7.28-7.39 (m, 11H), 7.48-7.51 (m, 2H), 7.62-7.63 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.9 (2C), 49.1 (2C), 61.7, 67.0, 84.6, 88.6, 122.8, 127.8, 127.9 (2C), 128.2 (4C), 128.3 (4C), 128.4 (2C), 131.8 (2C), 136.7, 137.7, 155.2 ppm; MS (ESI) *m/z* 411 ($M+H^+$); HRMS (ESI) *m/z* calcd for $[C_{27}H_{27}N_2O_2]^+$($M + H^+$): 411.2067; found: 411.2070.

tert-Butyl (1-(1,3-diphenylprop-2-yn-1-yl)piperidin-4-yl)carbamate (3o)



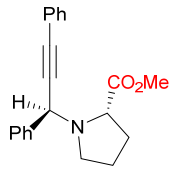
Following the general procedure, the reaction of *tert*-amide **1o** (304 mg, 1.0 mmol) with phenylacetylene **2a** (0.13 mL, 1.2 mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 100), propargylic amine **3o** (347 mg, yield: 89%) as a white solid; Mp 132-134 ºC; IR (film) ν_{max}: 3401, 2954, 1697, 1418, 1248, 1181, 1130, 1072, 758, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.32-1.56 (m, 11H), 1.86-2.00 (m, 2H), 2.30-2.35 (m, 1H), 2.59-2.66 (m, 2H), 2.89-2.92 (m, 1H), 3.48 (br s, 1H), 4.43 (s, 1H), 4.82 (s, 1H), 7.27-7.37 (m, 6H), 7.48-7.51 (m, 2H), 7.60-7.62 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.4 (3C), 32.6, 33.0, 46.2, 47.9, 50.8, 61.7, 79.1, 85.3, 88.2, 123.0, 127.6 (2C), 128.1 (2C), 128.3 (2C), 128.4 (2C), 131.7 (2C), 138.4, 155.1 ppm; MS (ESI) *m/z*391 ($M+H^+$); HRMS (ESI) *m/z* calcd for $[C_{25}H_{31}N_2O_2]^+$($M + H^+$): 391.2380; found: 391.2383.

1-(1,3-Diphenylprop-2-yn-1-yl)-4-((1,1,3,3-tetramethyldisiloxanyl)oxy)piperidine (3p)



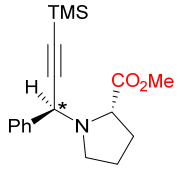
Following the general procedure, the reaction of *tert*-amide **1p** (205mg, 1.0 mmol) with phenylacetylene **2a** (0.13 mL, 1.2 mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 40), propargylic amine **3p** (215 mg, yield: 52%) as a pale yellow oil; IR (film) ν_{max}: 2952, 1097, 1485, 1258, 1069, 909, 797, 758, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.17 (s, 3H), 0.18 (s, 3H), 1.54-1.86 (m, 4H), 2.28-2.33 (m, 1H), 2.52-2.58 (m, 1H), 2.68-2.70 (m, 1H), 2.89-2.92 (m, 1H), 3.75-3.80 (m, 1H), 4.68-4.72 (m, 1H), 4.83 (s, 1H), 7.29-7.37 (m, 6H), 7.49-7.53 (m, 2H), 7.63-7.64 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.5 (2C), 0.7 (2C), 34.8, 35.2, 45.9 (2C), 61.7, 68.6, 85.8, 88.0, 123.3, 127.5 (2C), 128.1 (2C), 128.3 (2C), 128.4 (2C), 131.8 (2C), 138.7 ppm; MS (ESI) *m/z*414 ($M+H^+$); HRMS (ESI) *m/z* calcd for $[C_{24}H_{34}NO_2Si_2]^+$($M + H^+$): 414.2123; found: 414.2124.

Methyl (*S,S*)- 1-(1, 3-diphenylprop-2-yn-1-yl)pyrrolidine-2-carboxylate (3q) [4]



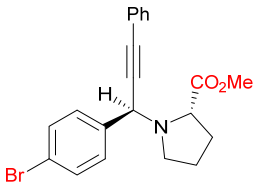
Following the general procedure, the reaction of *tert*-amide **1q** (233 mg, 1.0 mmol) with phenylacetylene **2a** (0.13 mL, 1.2 mmol) gave a diastereomeric mixture (*dr* = 20:1, determined by ^1H NMR of the crude product), after FC (eluent: EtOAc/*n*-hexane = 1: 80), the major diastereomeric propargylic amine **3q**[4] (239 mg, yield: 75%) as a pale yellow oil; $[\alpha]_D^{26}$ –107.8 (*c* 1.8, $CHCl_3$); IR (film) ν_{max}: 2949, 1745, 1488, 1447, 1271, 1200, 758, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.76-1.85 (m, 2H), 2.01-2.03 (m, 2H), 2.67-2.77 (m, 2H), 3.77 (dd, *J* = 8.9, 7.1 Hz, 1H) superposed with 3.77 (s, 3H), 5.24 (s, 1H), 7.27-7.38 (m, 6H), 7.50-7.52 (m, 2H), 7.67-7.69 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.2, 29.3, 47.4, 51.9, 57.3, 63.1, 85.2, 87.9, 123.0, 127.6 (2C), 128.2 (3C), 128.3 (3C), 131.8 (2C), 138.9, 174.5 ppm; MS (ESI) *m/z* 320 ($M+H^+$).

Methyl (*S,S*)-1-(1'-phenyl-3'-(trimethylsilyl)prop-2-yn-1'-yl)pyrrolidine-2-carboxylate (3r)



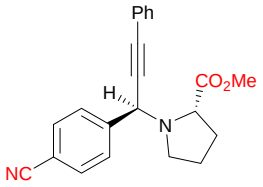
Following the general procedure, the reaction of *tert*-amide **1q** (233 mg, 1.0 mmol) with ethynyltrimethylsilane **2c** (0.17 mL, 1.2 mmol) gave a diastereomeric mixture (*dr* = 17:1, determined by ^{1}H NMR of the crude product), after FC (eluent: EtOAc/*n*-hexane = 1: 100), the major diastereomeric propargylic amine **3r** (246 mg, yield: 78%) as a pale yellow oil; $[\alpha]_D^{26}$ –101.3 (*c* 1.6, $CHCl_3$); IR (film) ν_{max}: 2955, 1745, 1450, 1197, 1127, 995, 851, 758cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.23 (s, 9H), 1.72-1.82 (m, 2H), 1.98-2.19 (m, 2H), 2.59-2.64 (m, 2H), 3.67 (dd, *J* = 9.0, 6.8 Hz, 1H) superposed with 3.76 (s, 3H), 5.01 (s, 1H), 7.24-7.35 (m, 3H), 7.59-7.61 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.2 (3C), 23.2, 29.3, 47.1, 51.8, 57.4, 63.0, 92.4, 101.5, 127.5, 128.1 (2C), 128.2 (2C), 138.6, 174.5 ppm; MS (ESI) *m/z* 316 ($M+H^+$); HRMS (ESI) *m/z* calcd for $[C_{18}H_{26}NO_2Si]^+$($M + H^+$): 316.1727; found: 316.1726.

Methyl (*S*,*S*)-1-(1'-(4''-bromophenyl)-3'-phenylprop-2-yn-1'-yl)pyrrolidine-2-carboxylate (3s)



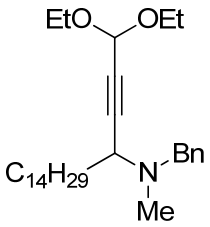
Following the general procedure, the reaction of *tert*-amide **1r** (311 mg, 1.0 mmol) with phenylacetylene **2a** (0.13 mL, 1.2 mmol) gave a mixture (*dr* = 15:1, determined by ^{1}H NMR of the crude product), after FC (eluent: EtOAc/*n*-hexane = 1: 100), the major diastereomeric propargylic amine **3s** (314 mg, yield: 79%) as a pale yellow oil; $[\alpha]_D^{26}$ –85.5 (*c* 2, $CHCl_3$); IR (film) ν_{max}: 2949, 1738, 1488, 1264, 1203, 761, 691 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76-1.85 (m, 2H), 2.00-2.24 (m, 2H), 2.63-2.73 (m, 2H), 3.75 (dd, *J* = 9.0, 7.1 Hz, 1H) superposed with 3.77 (s, 3H), 5.20 (s, 1H), 7.33-7.35 (m, 3H), 7.47-7.58 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.2, 29.3, 47.2, 51.9, 56.6, 63.0, 84.5, 88.3, 121.5, 122.7, 128.3 (2C), 128.4 (2C), 129.9 (2C), 131.3 (2C), 131.8, 138.1, 174.4 ppm; MS (ESI) *m/z* 398 ($M+H^+$); HRMS (ESI) *m/z* calcd for $[C_{21}H_{21}BrNO_2]^+$($M + H^+$): 398.0750; found: 398.0751.

Methyl (*S*,*S*)-1-(1'-(4''-cyanophenyl)-3'-phenylprop-2-yn-1'-yl)pyrrolidine-2-carboxylate (3t)



Following the general procedure, the reaction of *tert*-amide **1s** (258 mg, 1.0 mmol) with phenylacetylene **2a** (0.13 mL, 1.2 mmol) gave a diastereomeric mixture (*dr* = 17:1, determined by ^{1}H NMR from crude product), after FC (eluent: EtOAc/*n*-hexane = 1: 50), the major diastereomeric propargylic amine **3t** (293 mg, yield: 85%) as a pale yellow oil; $[\alpha]_D^{26}$ –103.3 (*c* = 2, $CHCl_3$); IR (film) ν_{max}: 2949, 2215, 1741, 1607, 1457, 1200, 1133, 758, 691 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78-1.85 (m, 2H), 2.00-2.26 (m, 2H), 2.57-2.75 (m, 2H), 3.77 (dd, *J* = 9.1, 7.1 Hz, 1H) superposed with 3.79 (s, 3H), 5.30 (s, 1H), 7.35-7.37 (m, 3H), 7.50-7.53 (m, 2H), 7.65-7.67 (m, 2H), 7.83-7.85 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.2, 29.2, 47.1, 51.9, 56.8, 63.0, 83.5, 88.9, 111.4, 118.8, 122.3, 128.4 (2C), 128.6 (2C), 128.9 (2C), 131.8 (2C), 132.0, 144.5, 174.2 ppm; MS (ESI) *m/z* 345 (M+H$^+$); HRMS (ESI) *m/z* calcd for $[C_{22}H_{21}N_2O_2]^+$(M + H$^+$): 345.1598; found: 345.1597.

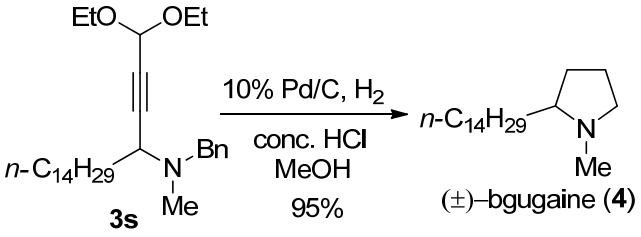
***N*-Benzyl-1,1-diethoxy-N-methyloctadec-2-yn-4-amine (3u)**



Following the general procedure(except the 2.0 equiv TMDS was used), the reaction of *tert*-amide **1t** (1380 mg, 4 mmol) with 3,3-diethoxyprop-1-yne **2b** (0.68 mL, 4.8mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 100), propargylic amine **3s** (1716mg, yield: 94%) as a colourless oil; IR (film) ν_{max}: 2930, 2856, 1604, 1460, 1325, 1133, 1053, 701cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.24-1.28 (m, 28H), 1.37-1.45 (m, 2H), 1.63-1.70 (m, 2H), 2.20 (s, 3H), 3.42-3.46 (m, 2H),

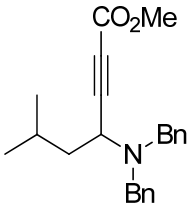
3.59-3.68 (m, 3H), 3.75-3.83 (m, 2H), 3.61 (d, J = 1.2 Hz, 1H), 7.21-7.34 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, some peaks overlapped): δ 14.1, 15.1, 22.7, 26.4, 29.2, 29.3, 29.5, 29.6, 29.7, 31.9, 33.6, 37.7, 55.4, 59.1, 60.7, 80.9, 83.5, 91.5, 126.9, 128.2, 128.9, 139.3 ppm; MS (ESI) *m/z*458 ($M+H^+$); HRMS (ESI) *m/z* calcd for $[C_{30}H_{52}NO_2]^+$($M + H^+$): 458.3993; found: 458.3996.

1-Methyl-2-tetradecylpyrrolidine (4)[5]



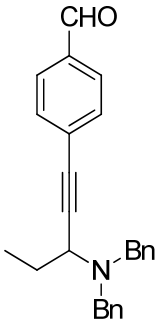
A suspension of **3u** (457 mg, 1.0 mmol) and 10% Pd/C (45 mg) in MeOH (10 mL) containing concentrated HCl (0.3 mL) was stirred under a hydrogen atmosphere (1 atm, ballon) at RT for 24 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (FC) on silica gel (eluent: DCM/MeOH = 20: 1). The fractions were collected, and concentrated. To the residue were added CH_2Cl_2 (5 mL) and Et_3N (1 mL), and the mixture was stirred for 2 h at RT before treating with a saturated aqueous Na_2CO_3 solution. The resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford (±)-bgugaine (**4**)[4] (267 mg, yield: 95%) as a pale yellow oil. IR (film) ν_{max}: 2901, 2843, 2360, 1488, 1447, 1027, 749, 688 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 7.0 Hz, 3H), 1.18-1.33 (m, 25H), 1.38-1.48 (m, H), 1.64-1.70 (m, 2H), 1.71-1.81 (m, 1H), 1.88-1.99 (m, 2H), 2.11 (dd, J = 17.8, 9.4 Hz, 1H), 2.30 (s, 3H), 3.03-3.08 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,some peaks overlapped): δ 14.1, 21.8, 22.6, 26.7, 29.3, 29.6, 29.7, 30.0, 31.9, 33.8, 40.4, 57.3, 66.4 ppm; MS (ESI) *m/z* 282 ($M+H^+$).

Methyl 4-(dibenzylamino)-6-methylhept-2-ynoate (3v)



Following the general procedure(except the 2.0 equiv TMDS was used), the reaction of *tert*-amide **1u** (1405 mg, 5 mmol) with methyl propiolate **2d** (0.55 mL, 6.0 mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 100), propargylic amine **3v** (1535 mg, yield: 88%) as a pale yellow oil; IR (film) ν_{max}: 2955, 2222, 1716, 1450, 1245, 1072, 749, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.63 (d, J = 6.6 Hz, 3H), 0.78 (d, J = 6.6 Hz, 3H), 1.45-1.52 (m, 1H), 1.66-1.73 (m, 1H), 1.80-1.90 (m, 1H), 3.39 (d, J = 13.7 Hz, 2H), 3.60 (t, J = 7.6 Hz, 1H), 3.81 (s, 3H), 3.85 (d, J = 13.7 Hz, 2H), 7.21-7.37 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6 (2C), 22.7, 24.4, 41.9, 49.6, 52.7, 54.9, 76.9, 87.5, 127.1, 128.2 (2C), 128.3 (4C), 128.8 (4C), 139.0, 154.1 ppm;MS (ESI) *m/z* 350 ($M+H^+$); HRMS (ESI) *m/z* calcd for $[C_{23}H_{28}NO_2]^+$($M + H^+$): 350.2115; found: 350.2112.

4-(3-(Dibenzylamino)pent-1-yn-1-yl)benzaldehyde (3w)



Following the general procedure (except the 2.0 equiv TMDS was used), the reaction of *tert*-amide **1v** (253 mg, 1.0 mmol) with 4-ethynylbenzaldehyde **2e** (157 mg, 1.2 mmol) gave, after FC (eluent: EtOAc/*n*-hexane = 1: 100), propargylic amine **3w** (246 mg, yield: 67%) as a white solid. Mp 79-81°C; IR (film) ν_{max}: 3439, 2885,1697, 1639, 1450, 1136, 1075, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.01 (t, J = 7.3 Hz, 3H),1.73-1.89 (m,2H), 3.48 (d, J = 13.7 Hz, 2H), 3.05 (t, J = 7.6 Hz, 1H), 3.90 (d, J = 13.7 Hz, 2H), 7.20-7.25 (m, 2H), 7.31-7.34 (m, 4H), 7.41-7.43 (m, 4H), 7.63 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 2H), 10.0 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.2, 26.8, 54.1, 55.0 (2C), 84.7, 92.7, 126.9, 128.3 (2C), 128.8 (2C), 129.5 (2C),

129.9 (4C), 132.4 (4C), 135.2 (2C), 139.6, 191.5 ppm; MS (ESI) *m/z* 368 ($M+H^+$); HRMS (ESI) *m/z* calcd for $[C_{26}H_{26}NO]^+(M+H^+)$: 368.2009; found: 368.2010.

Reference

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[2] J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* 2005, **105**, 1001−1020.

[3] X. Zhang, A. Corma, *Angew. Chem. Int. Ed.* **2003**, *42*, 4358-4361.

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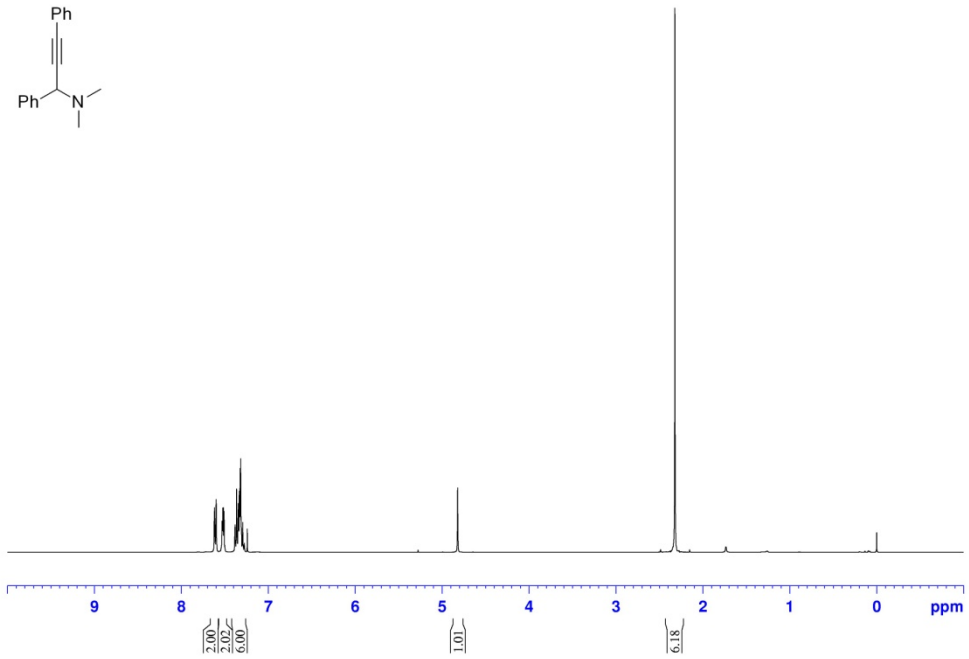
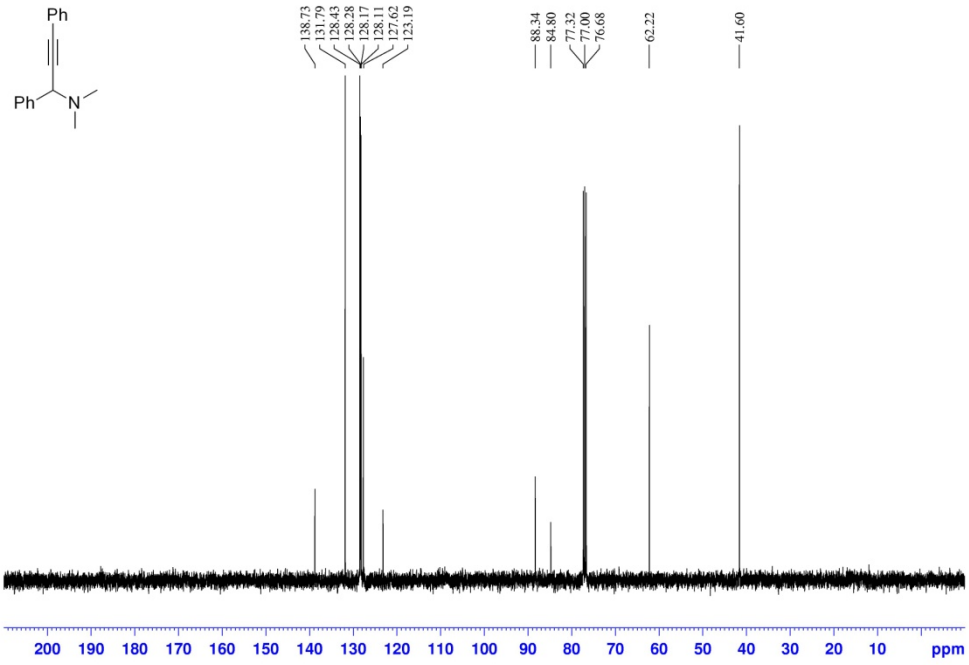
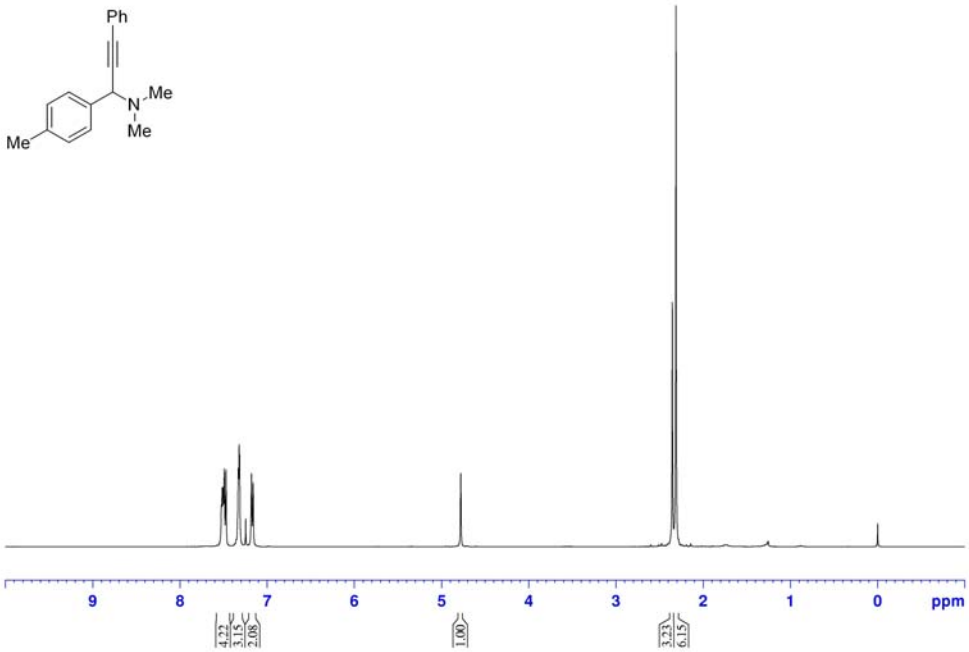
[5] C. Shu, M.-Q. Liu, S.-S. Wang, L. Li, L.-W. Ye, *J. Org. Chem.* 2013, **78**, 3292−3299.

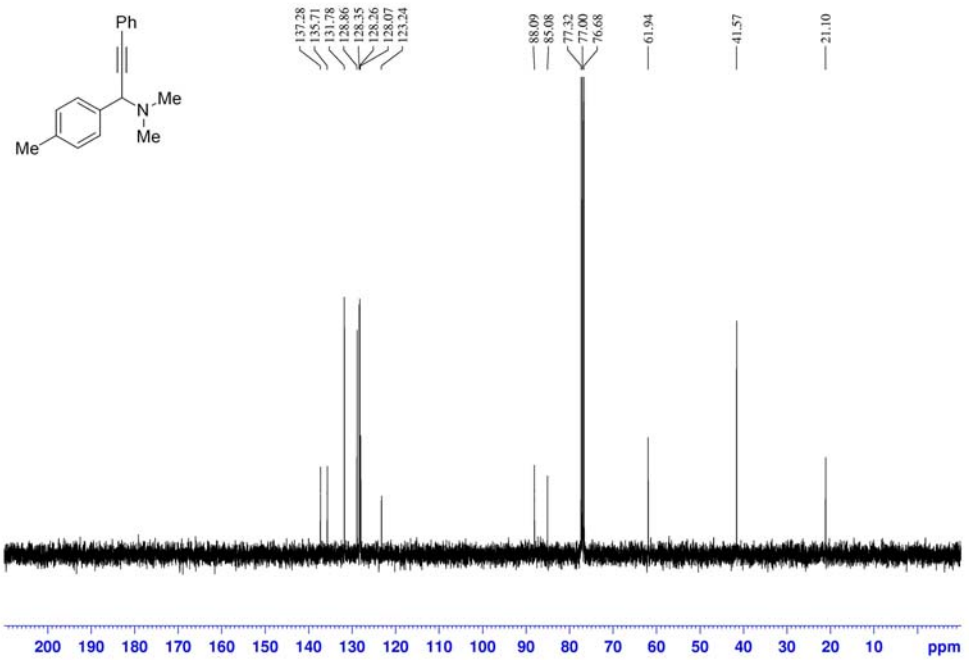
The ^{1}H NMR and ^{13}C NMR spectra of compound **3a**



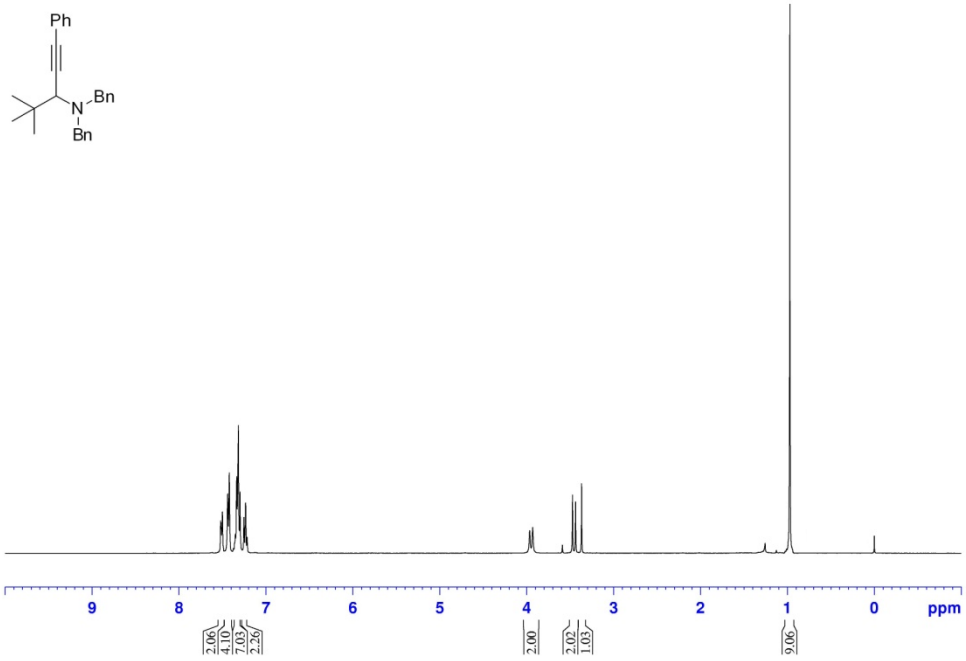


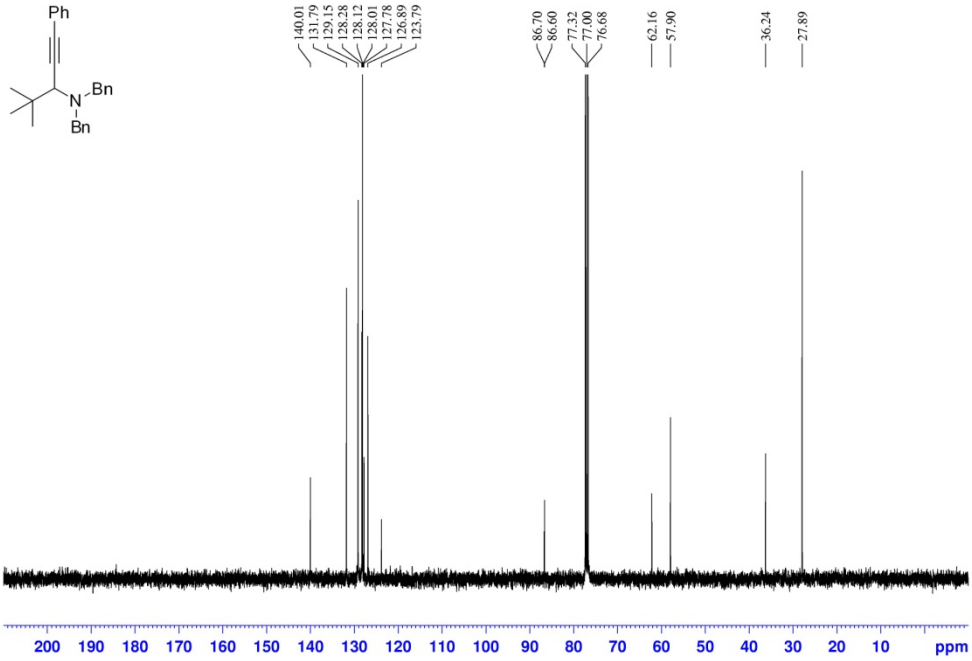
The ^{1}H NMR and ^{13}C NMR spectra of compound **3b**



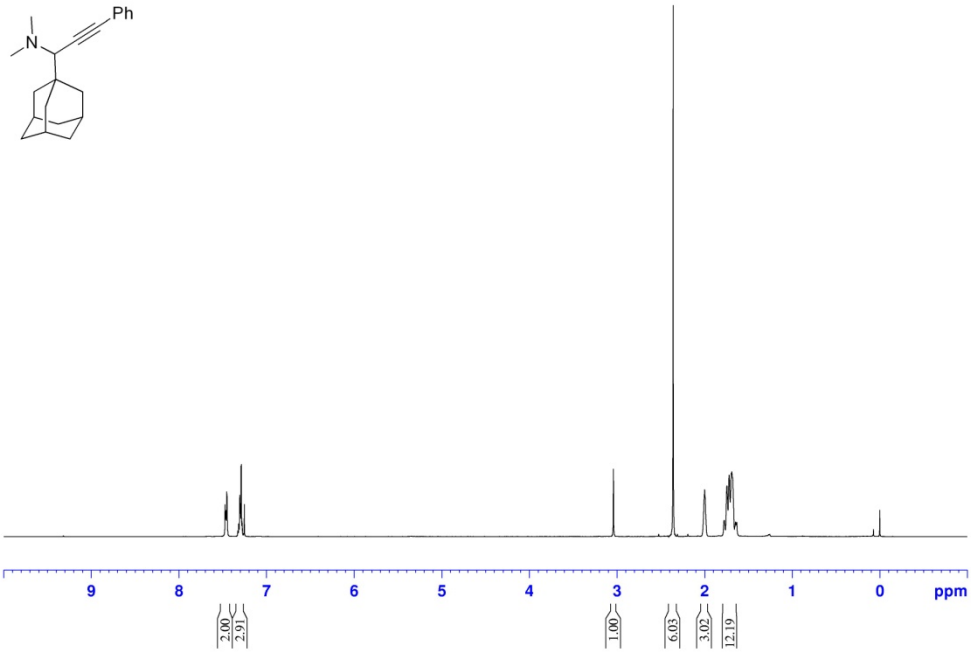


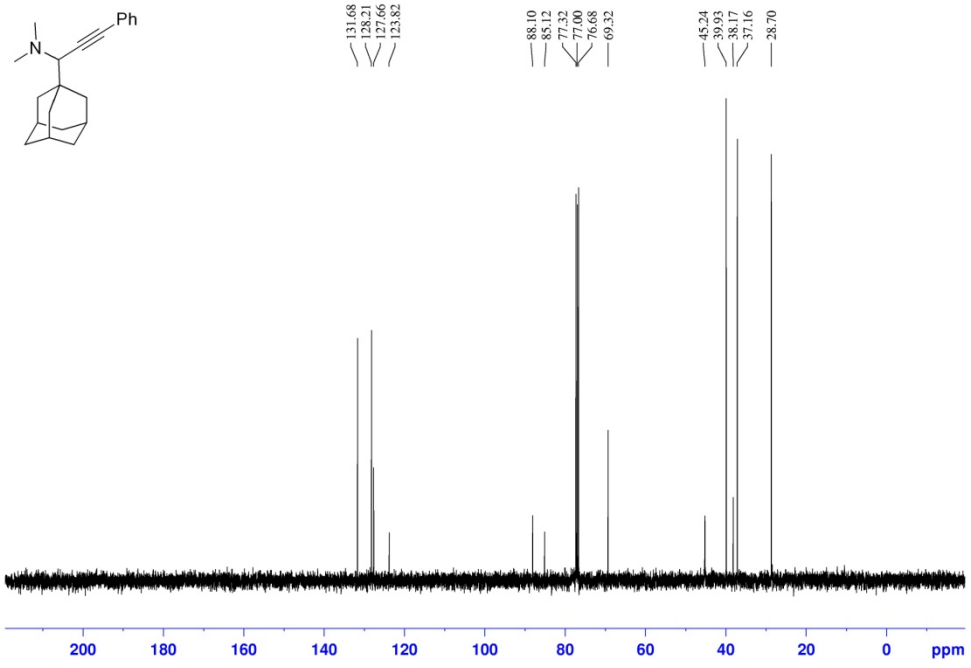
The ^{1}H NMR and ^{13}C NMR spectra of compound **3c**



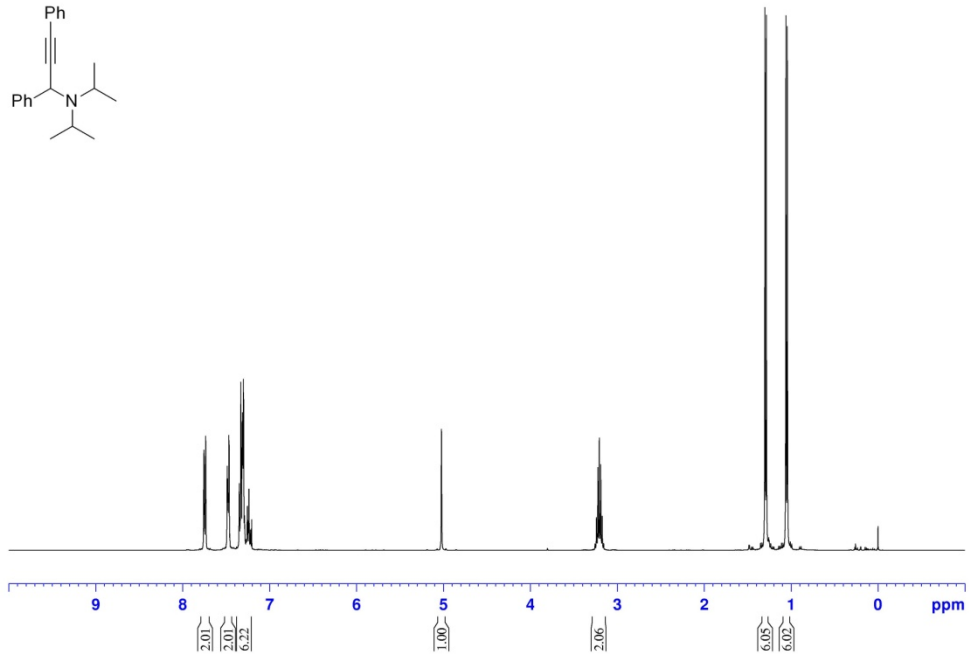


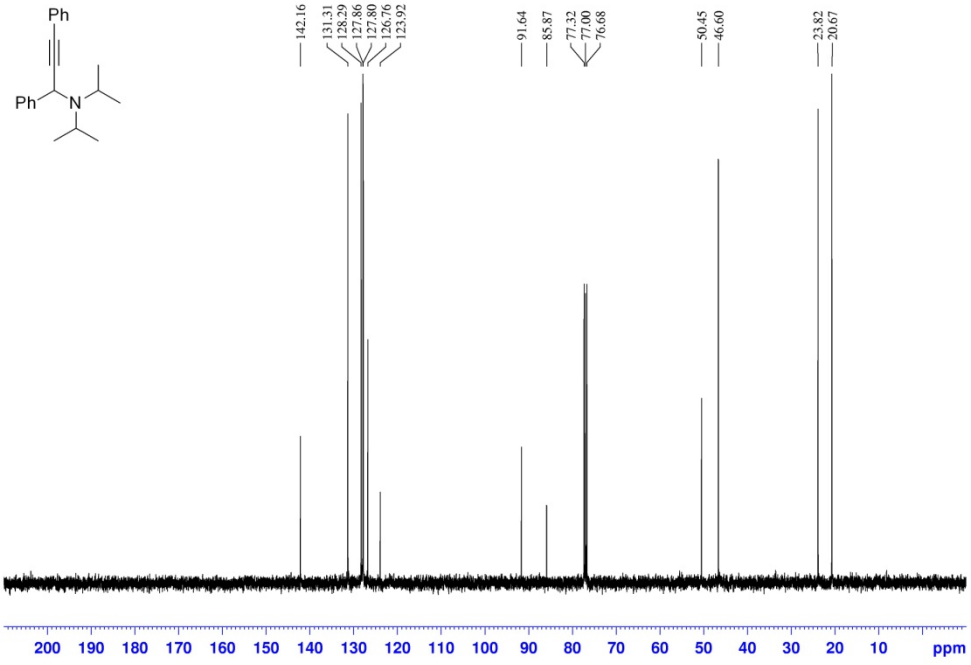
The ^{1}H NMR and ^{13}C NMR spectra of compound **3d**



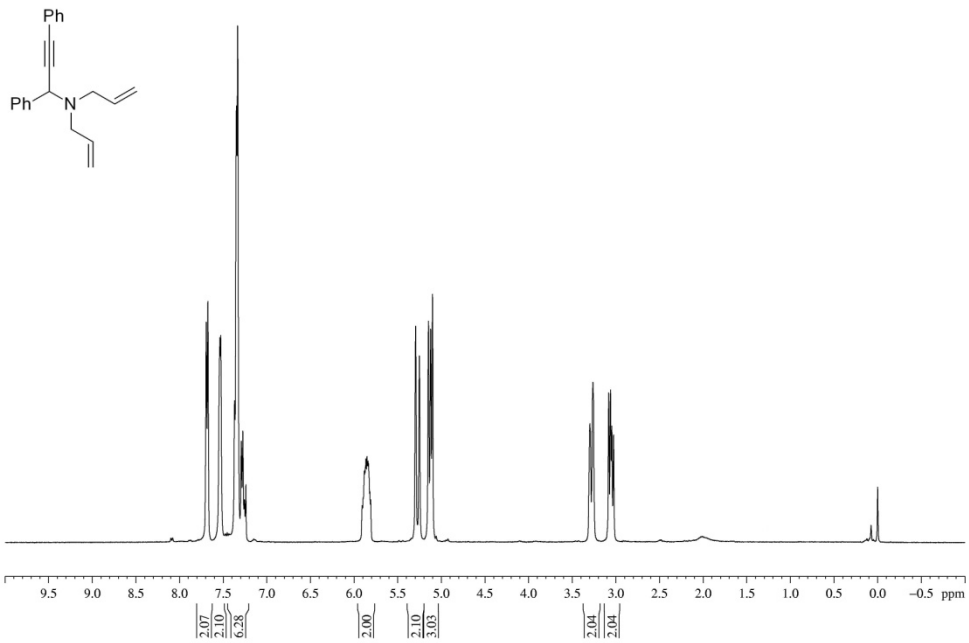


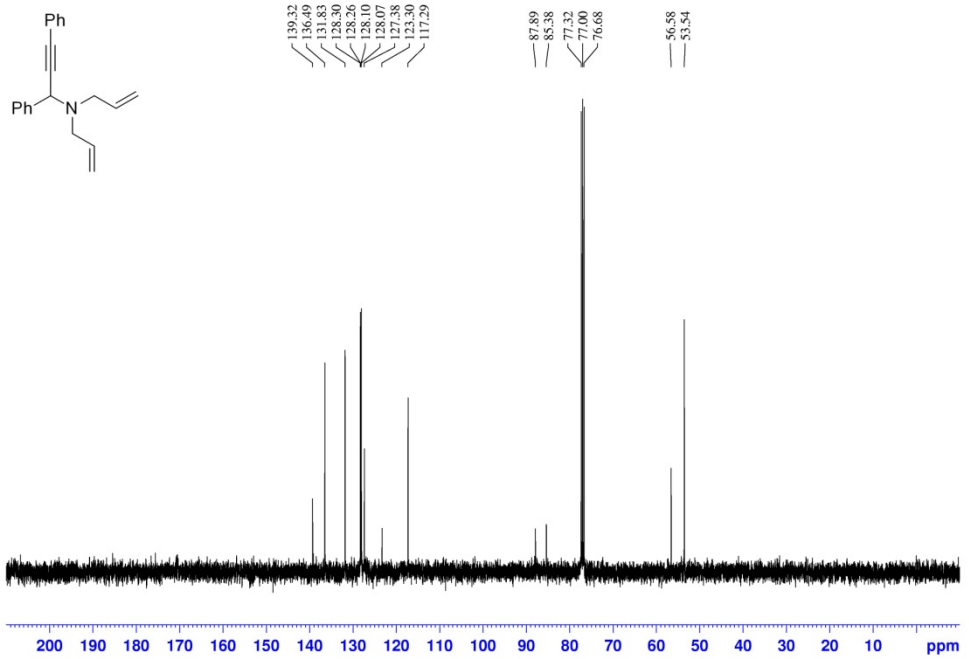
The ^{1}H NMR and ^{13}C NMR spectra of compound **3e**



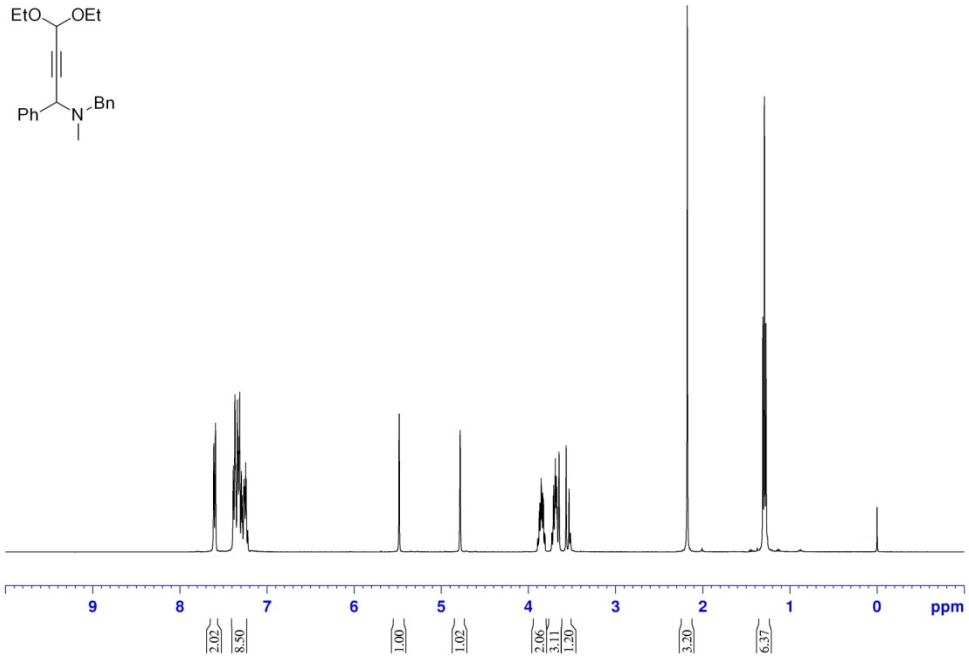


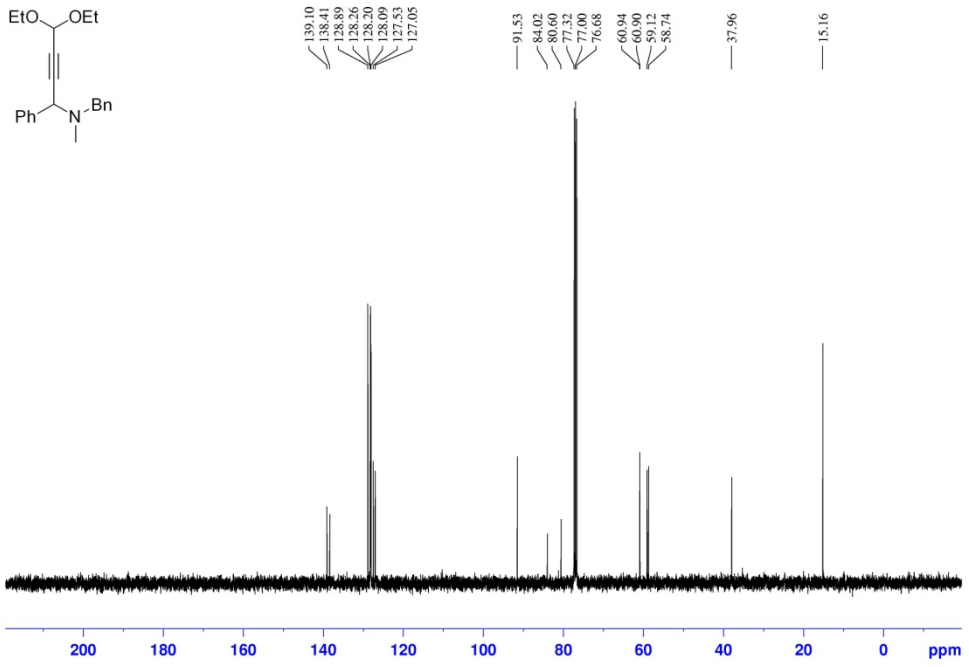
The ^{1}H NMR and ^{13}C NMR spectra of compound **3f**



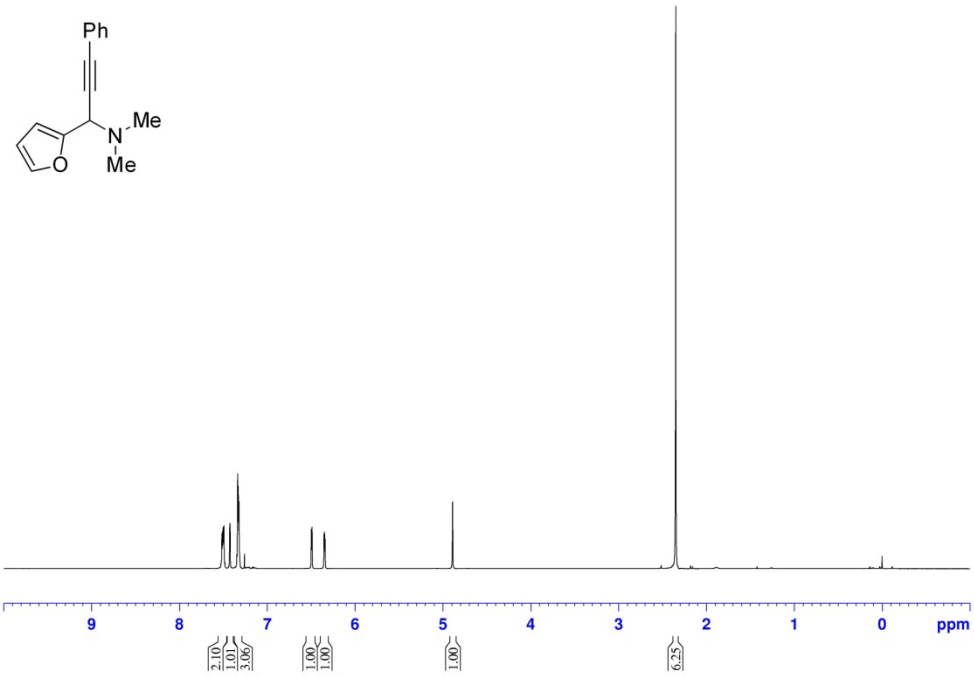


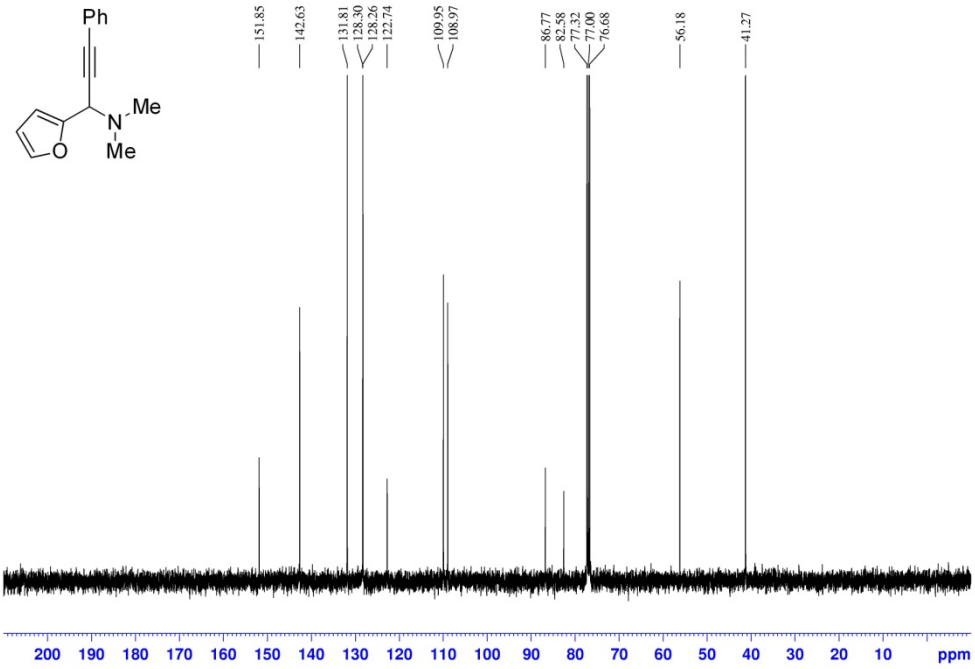
The ^{1}H NMR and ^{13}C NMR spectra of compound **3g**



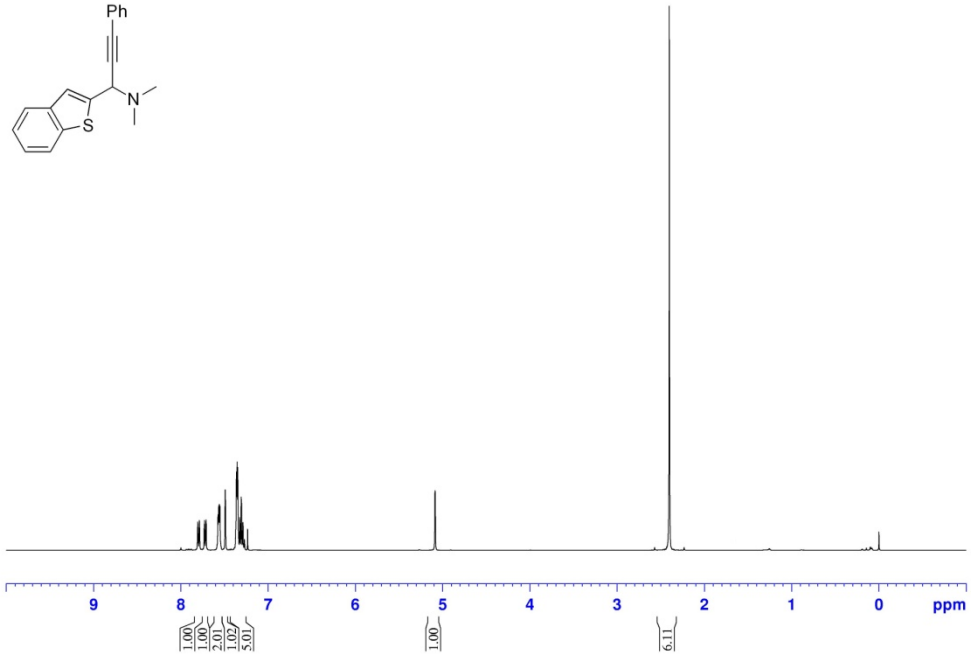


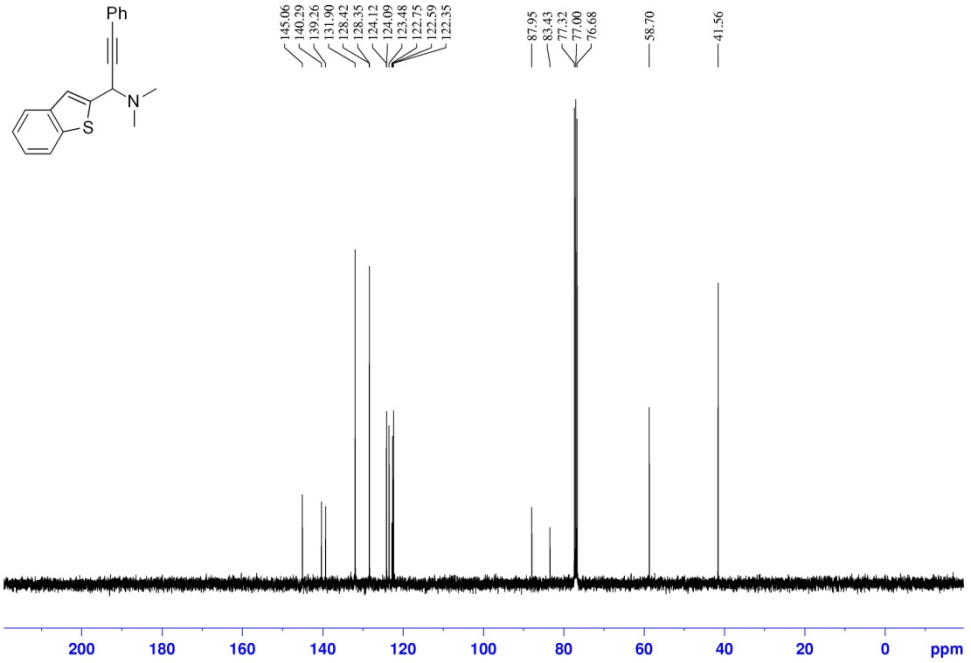
The ^{1}H NMR and ^{13}C NMR spectra of compound **3h**



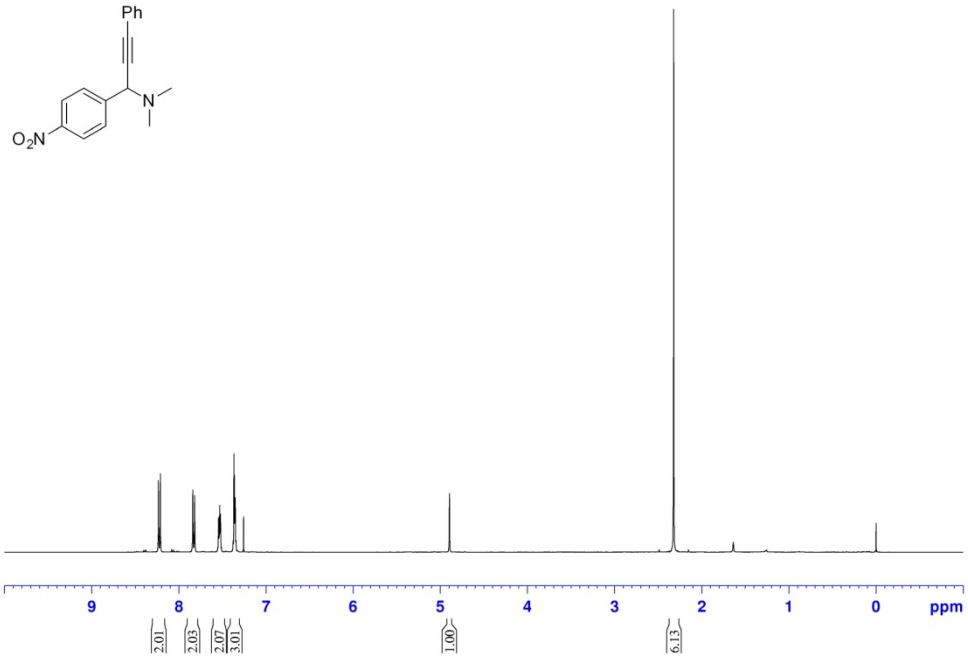


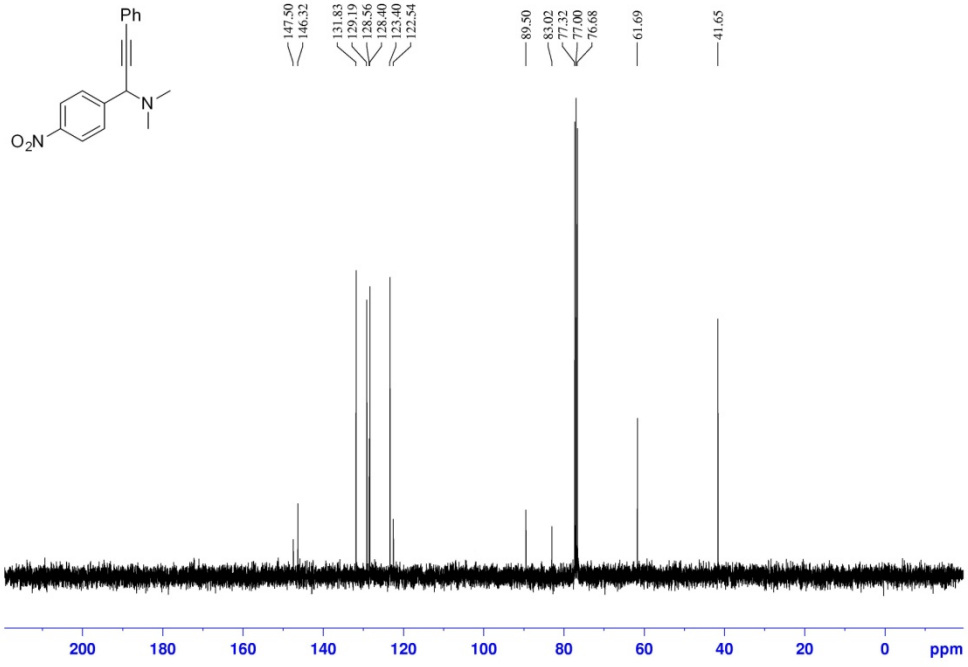
The ^{1}H NMR and ^{13}C NMR spectra of compound **3i**



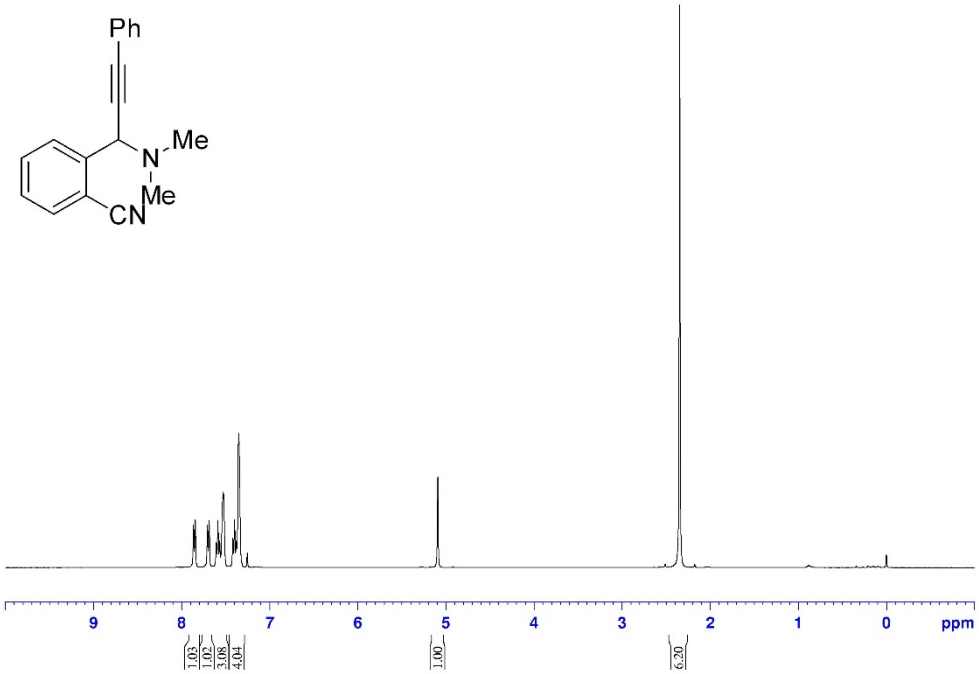


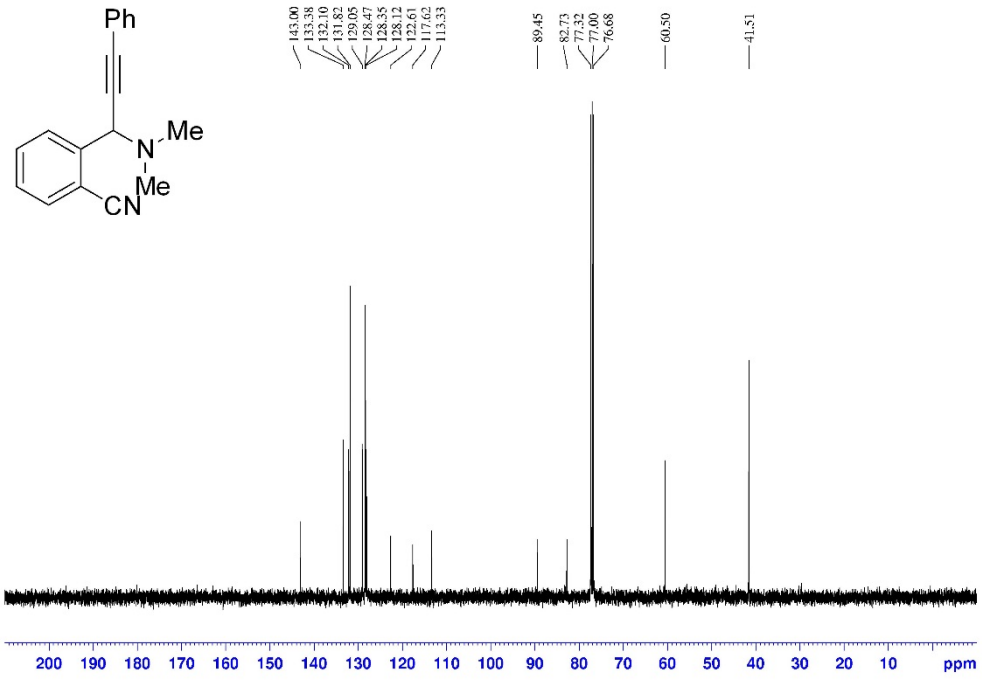
The ^{1}H NMR and ^{13}C NMR spectra of compound **3j**



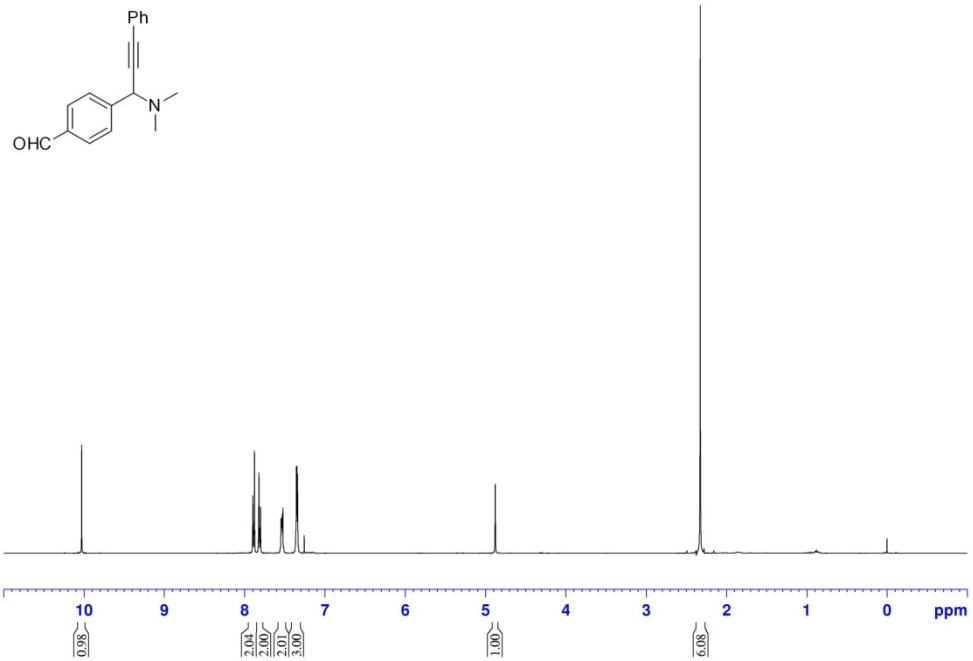


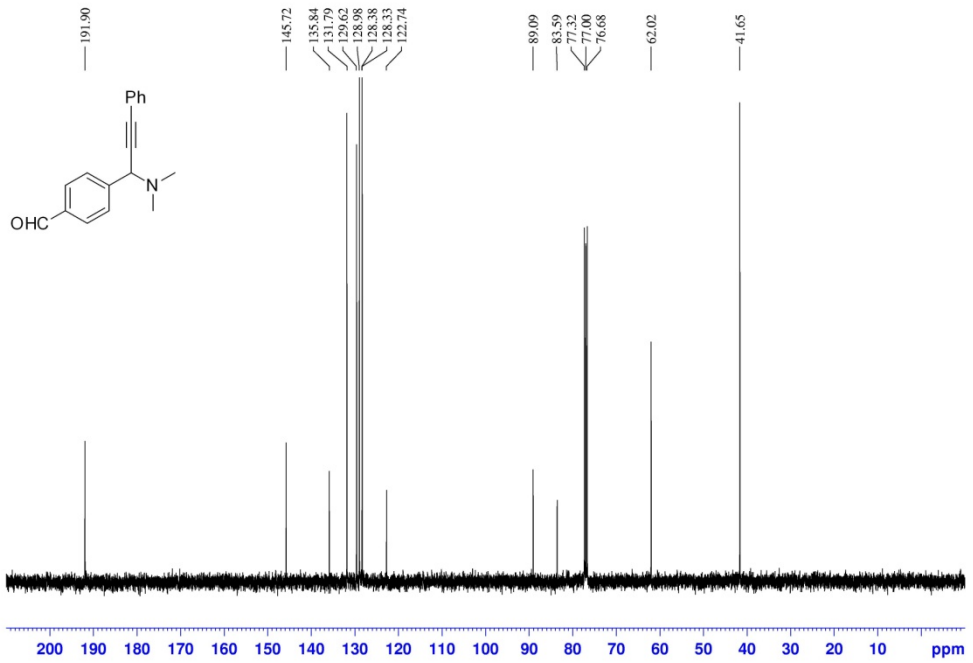
The ^{1}H NMR and ^{13}C NMR spectra of compound **3k**



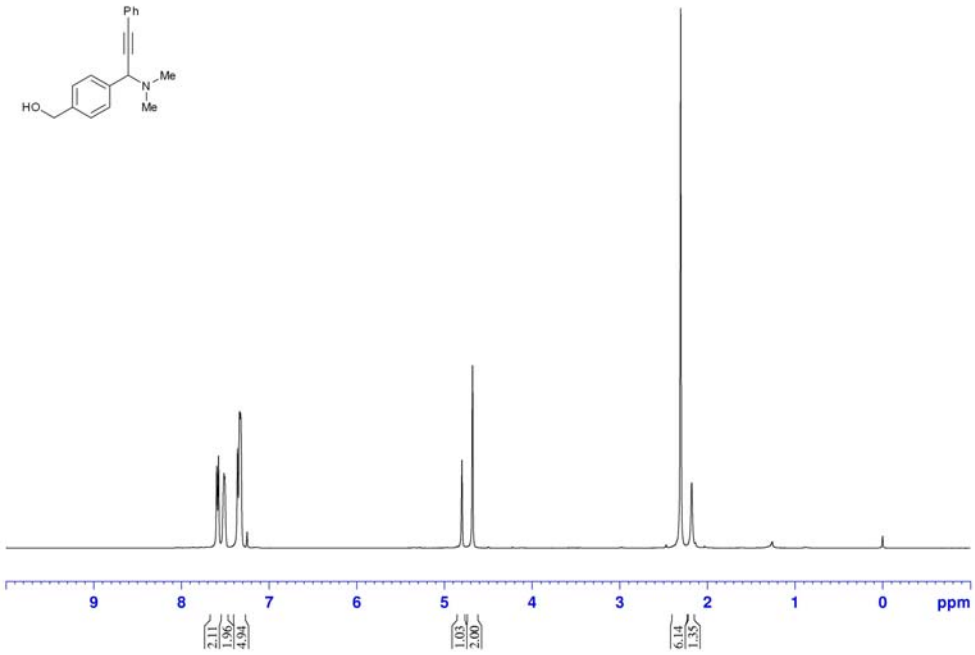


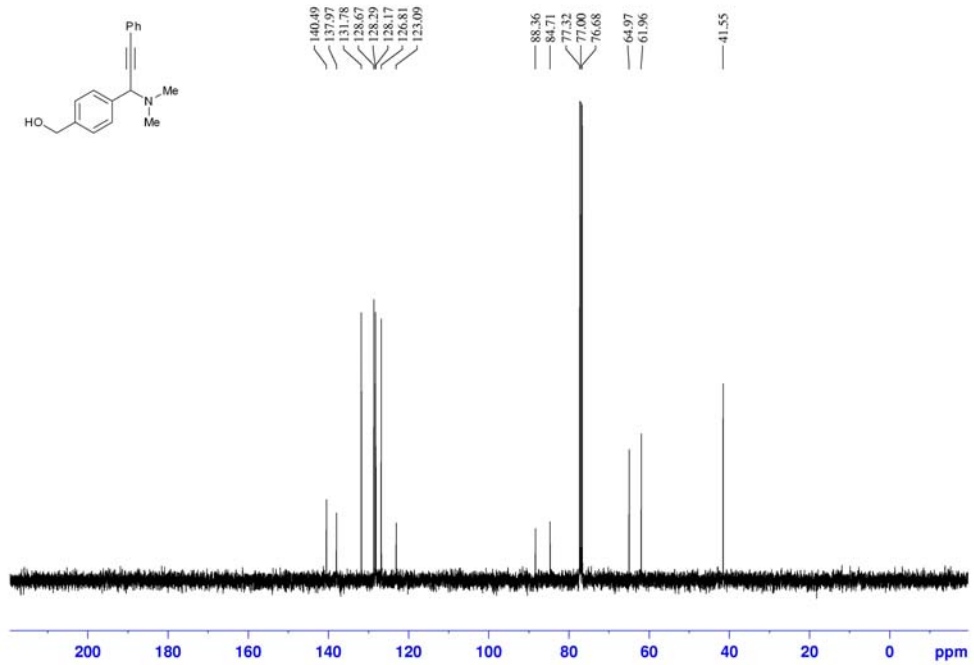
The ^{1}H NMR and ^{13}C NMR spectra of compound **3l**



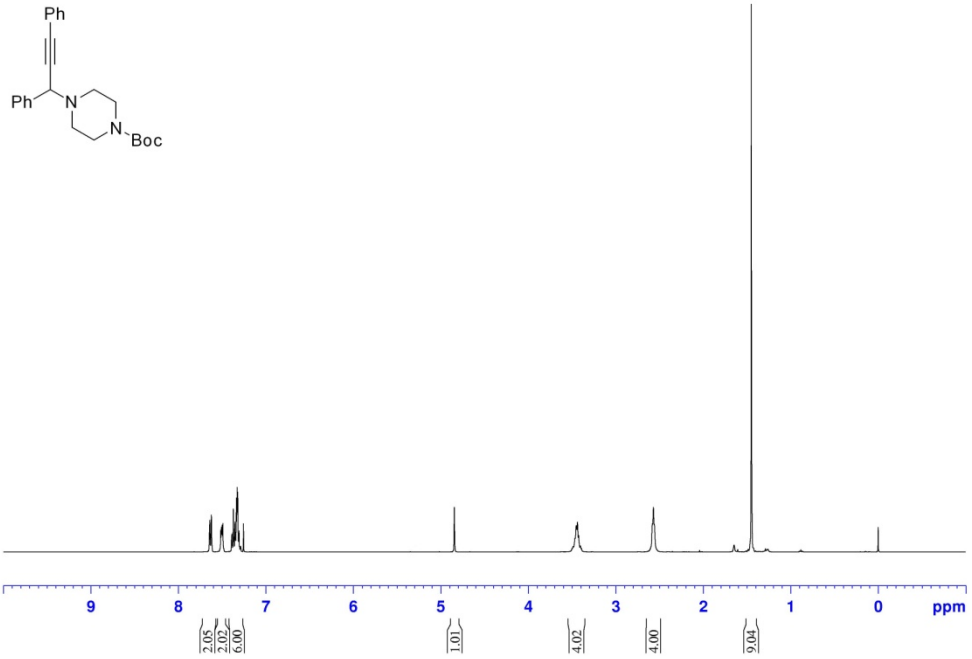


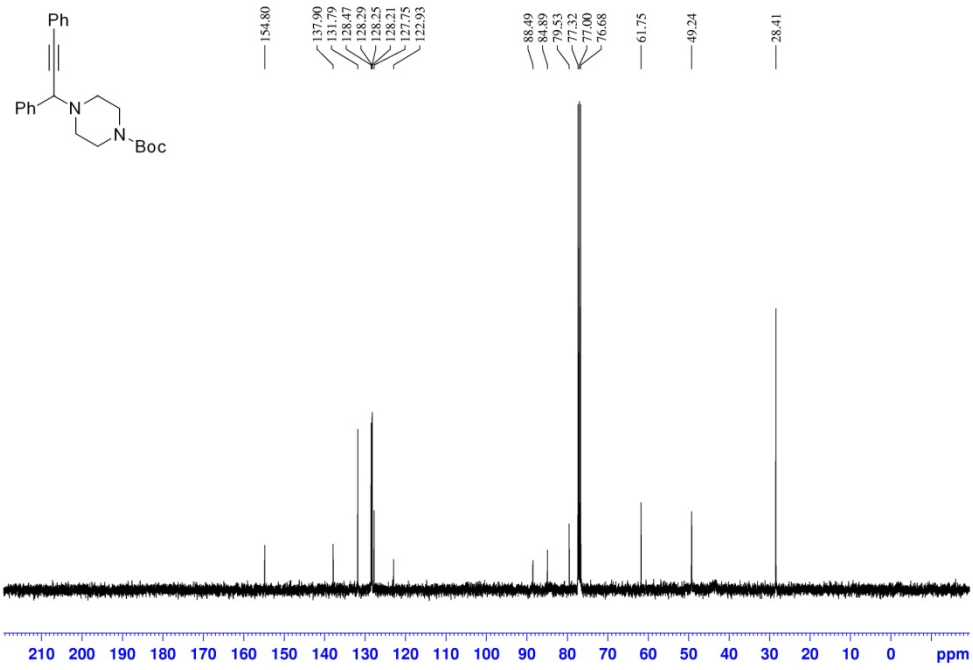
The ^{1}H NMR and ^{13}C NMR spectra of compound **3l'**



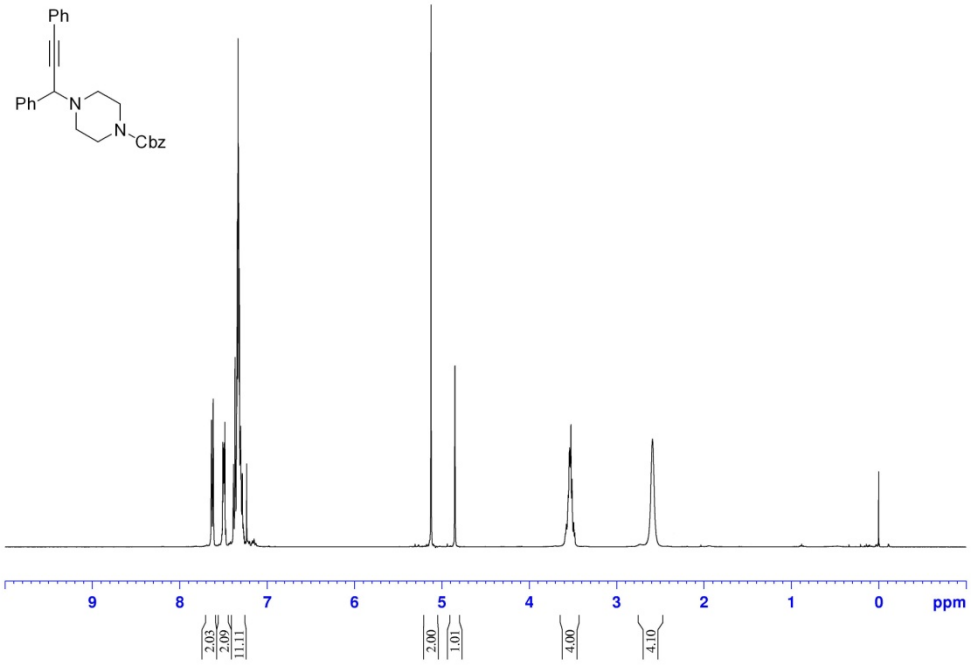


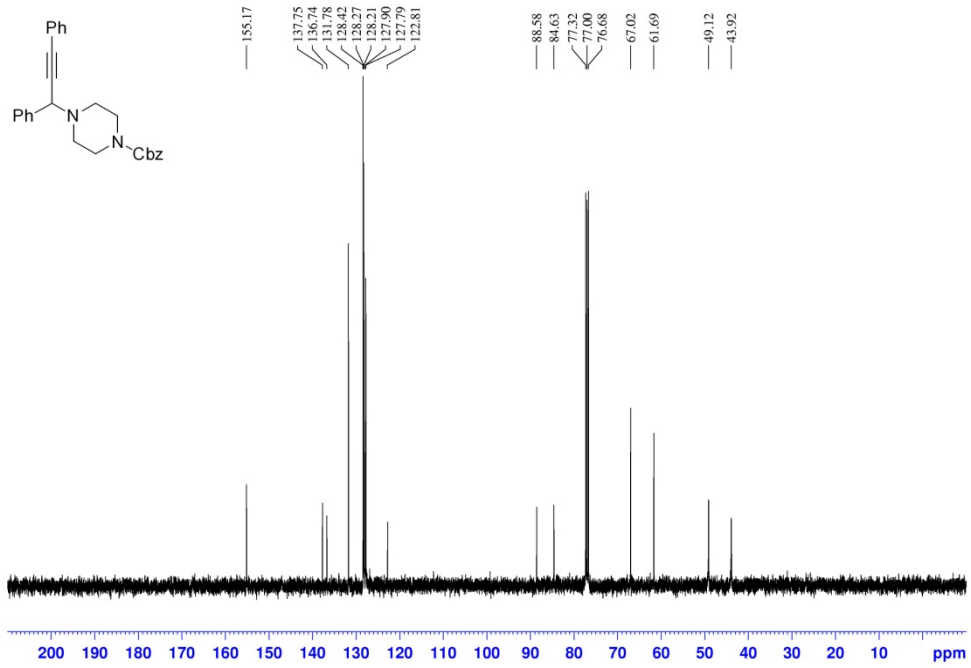
The ^{1}H NMR and ^{13}C NMR spectra of compound **3m**



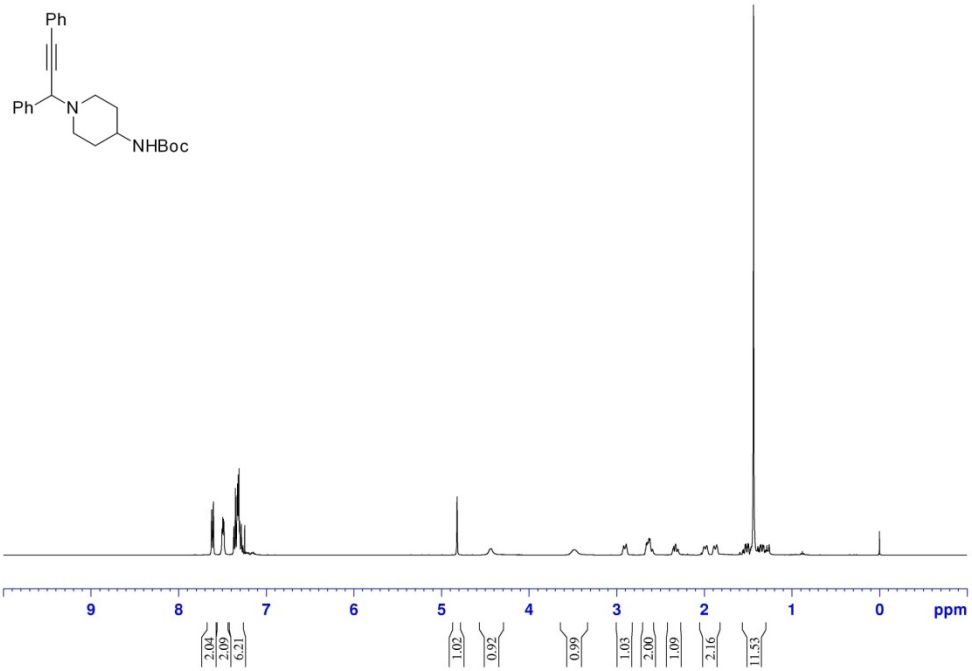


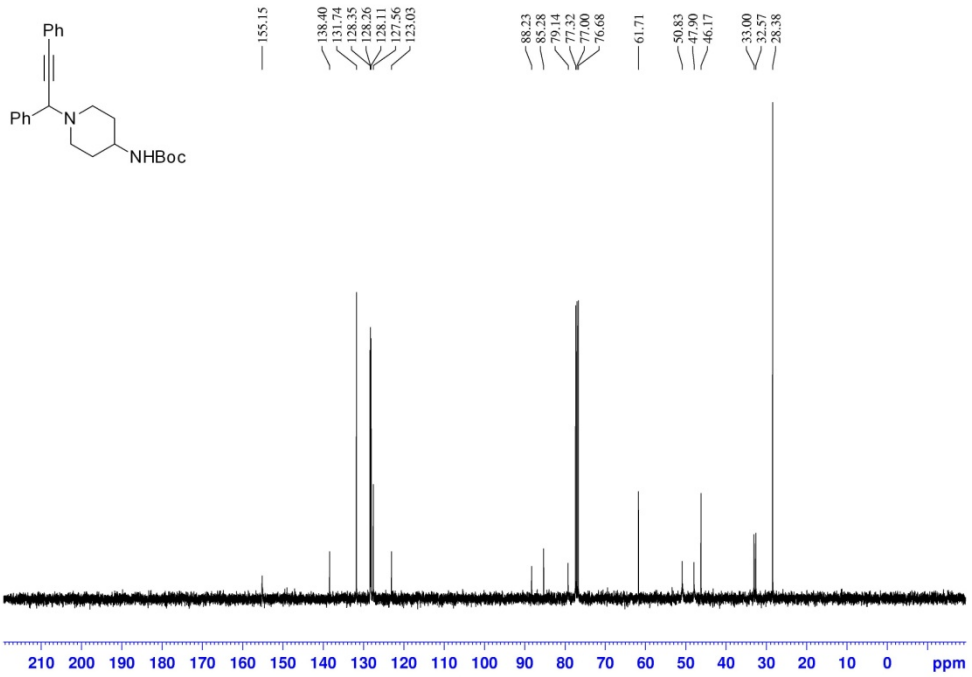
The ^{1}H NMR and ^{13}C NMR spectra of compound **3n**



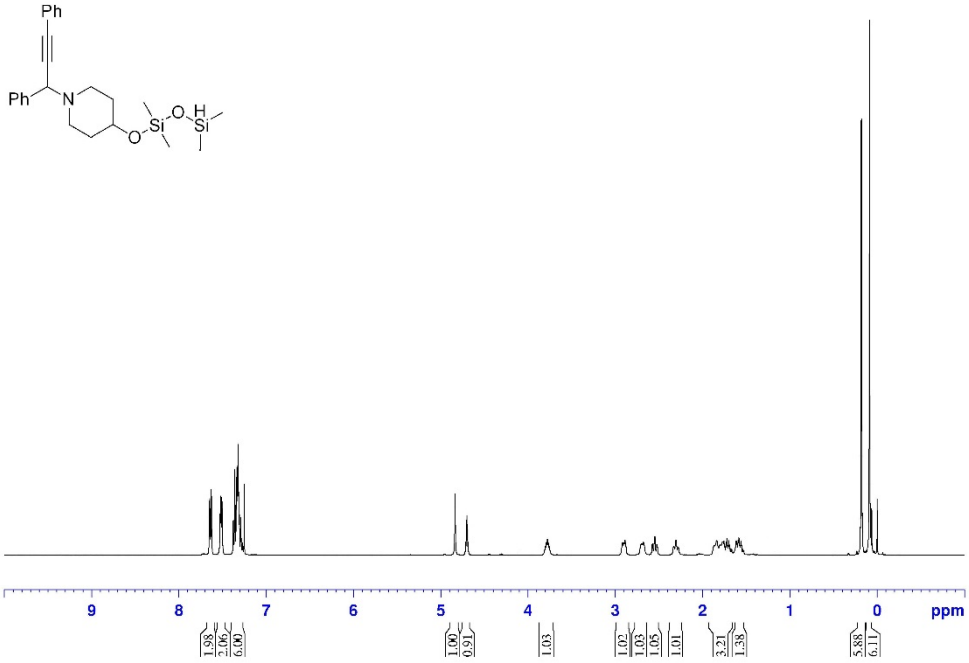


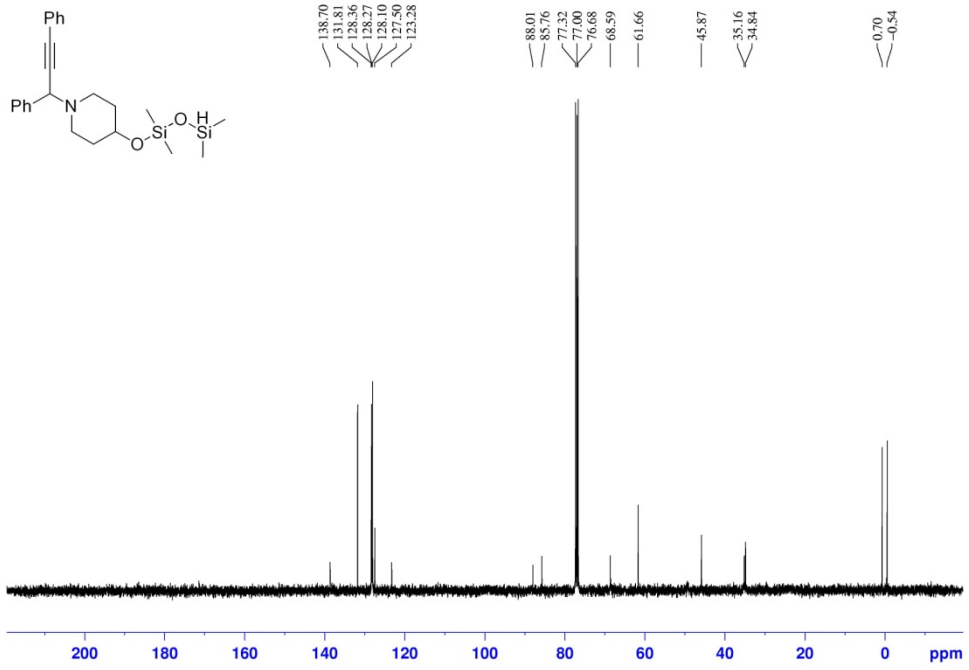
The ^{1}H NMR and ^{13}C NMR spectra of compound **3o**



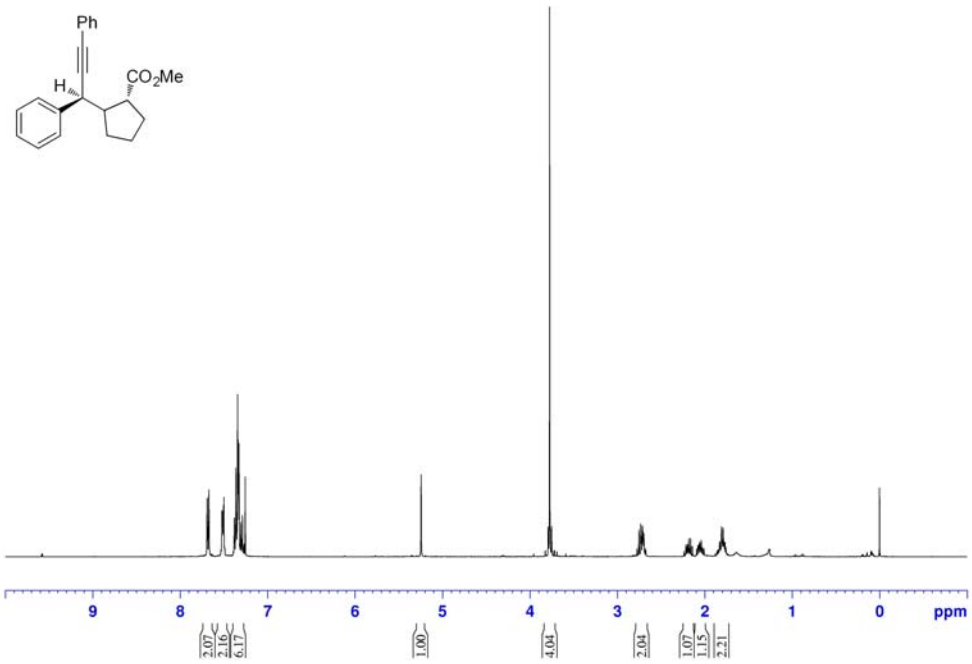


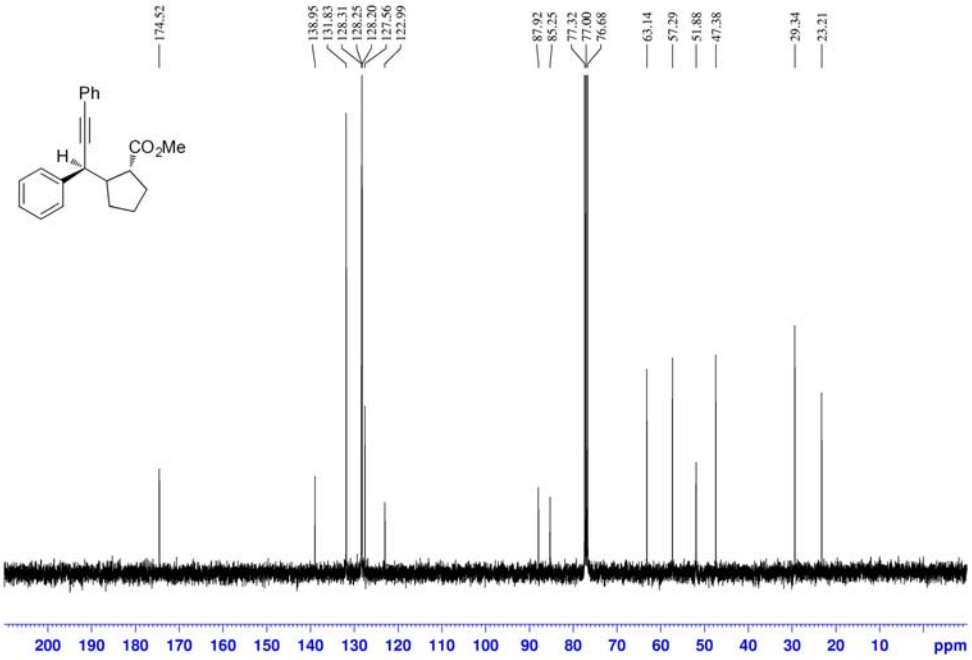
The ^{1}H NMR and ^{13}C NMR spectra of compound **3p**



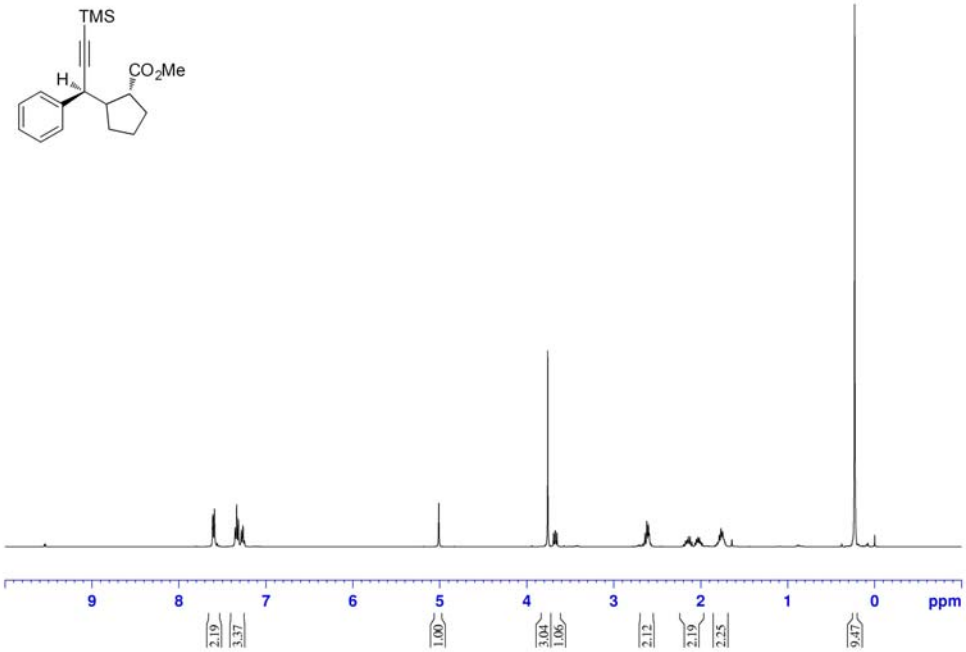


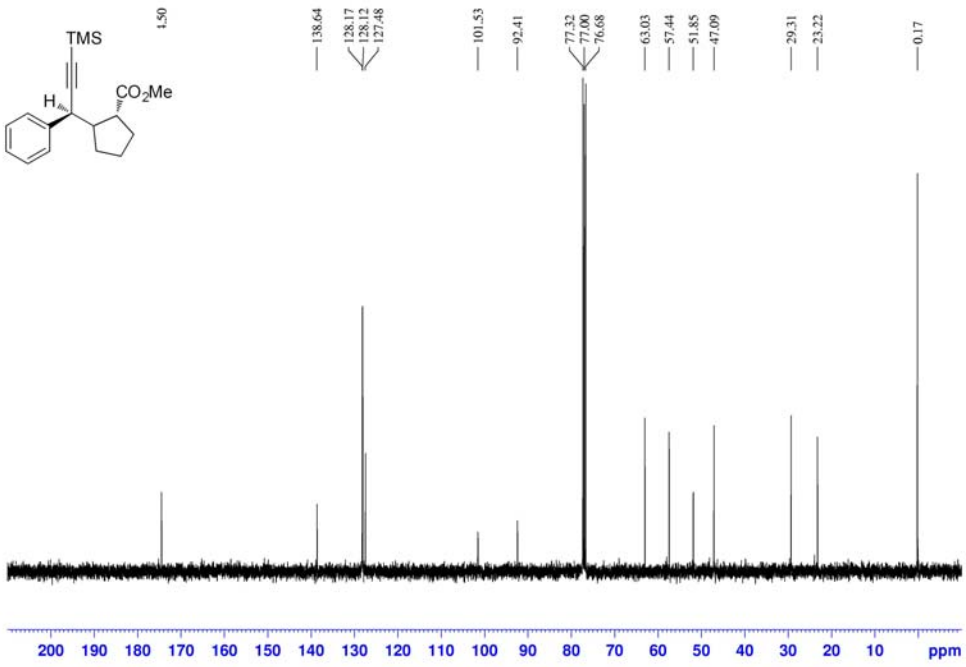
The ^{1}H NMR and ^{13}C NMR spectra of compound **3q**



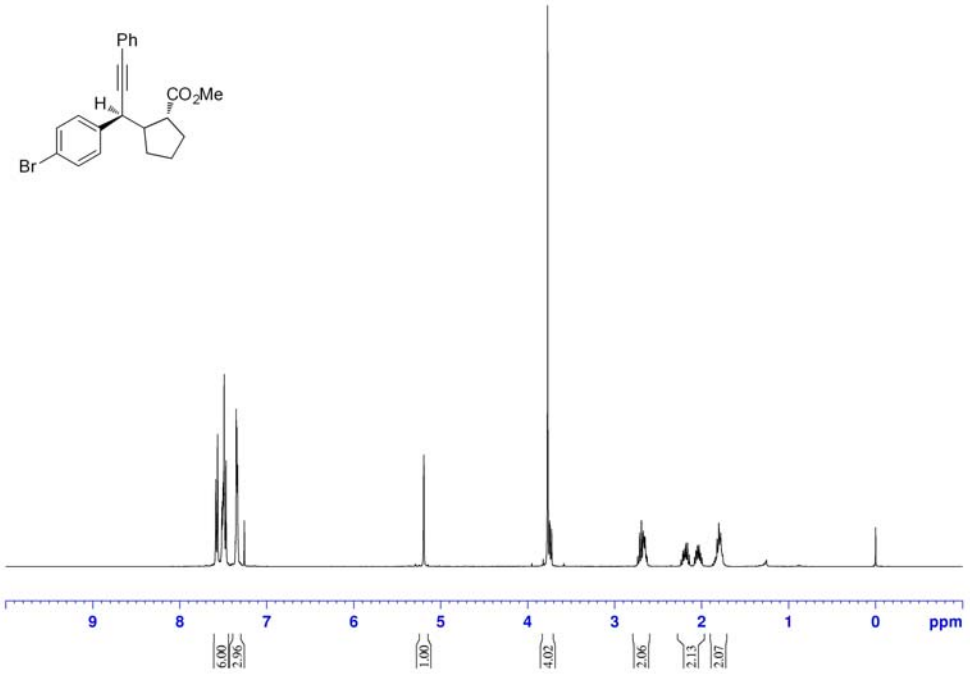


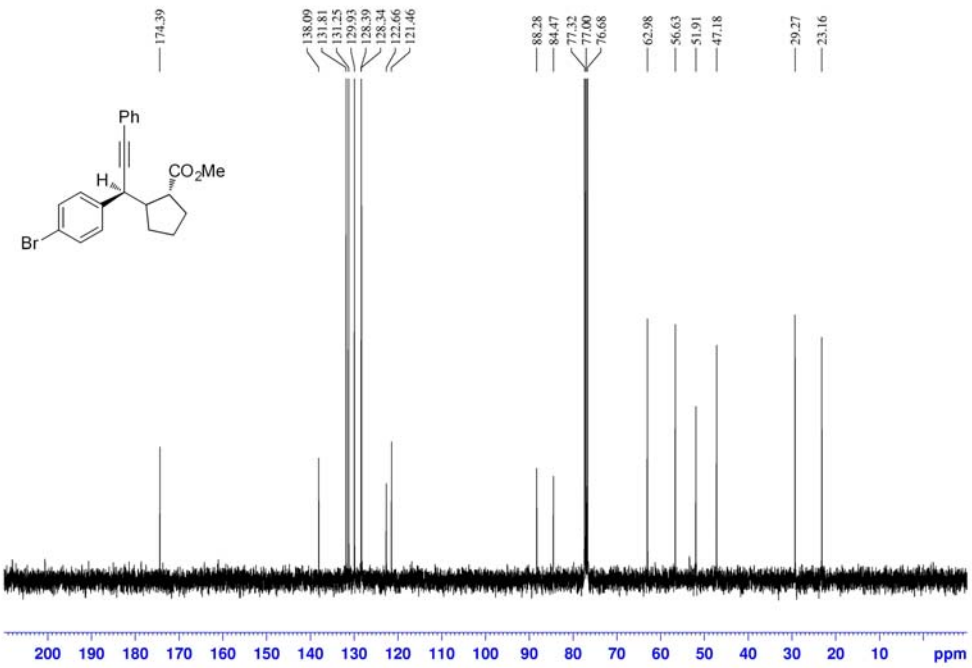
The ^{1}H NMR and ^{13}C NMR spectra of compound **3r**



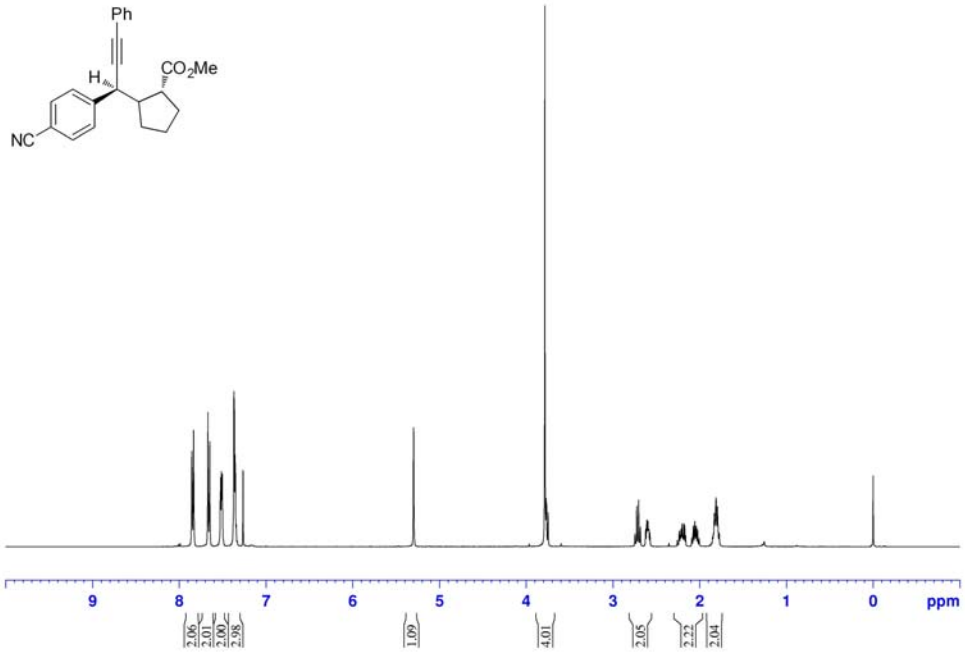


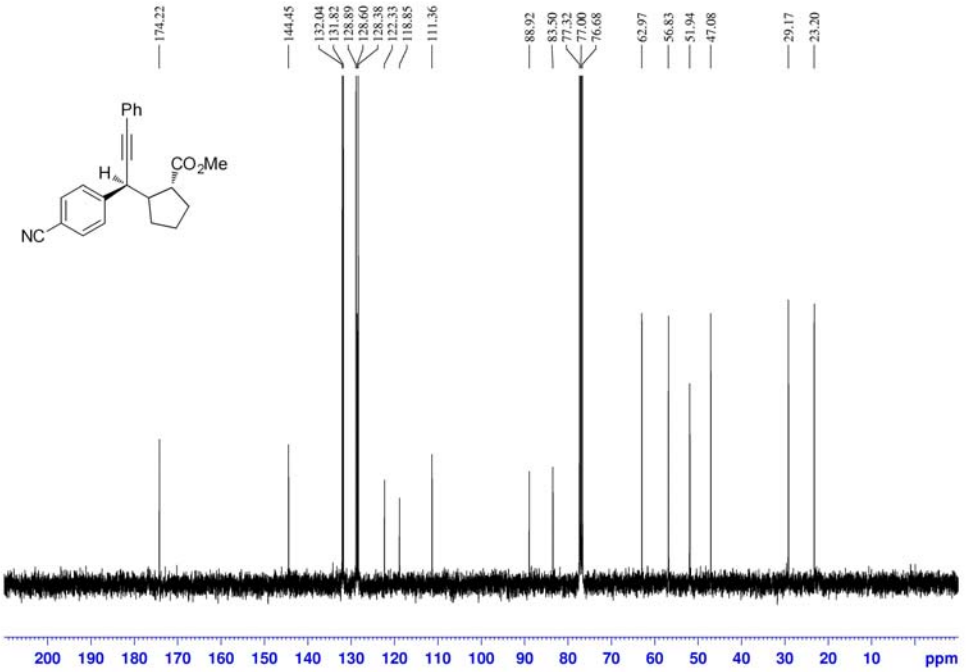
The ^{1}H NMR and ^{13}C NMR spectra of compound **3s**



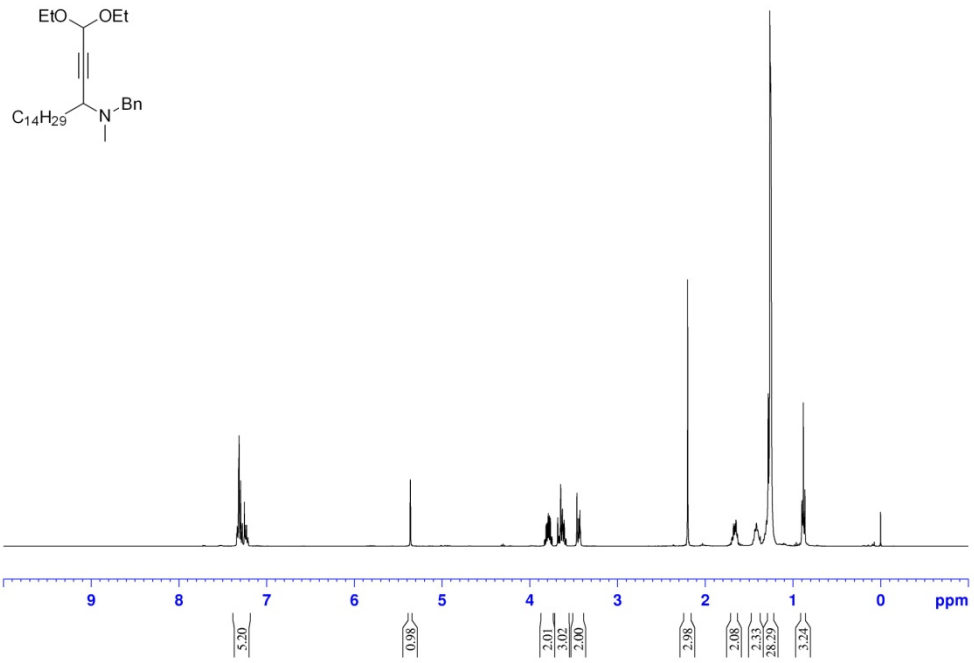


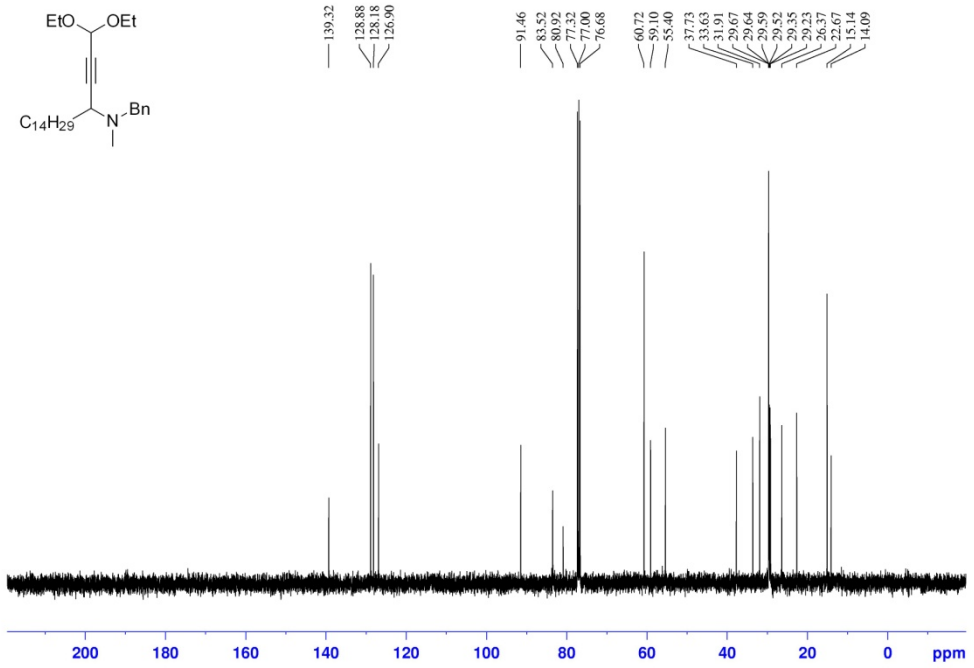
The ^{1}H NMR and ^{13}C NMR spectra of compound **3t**



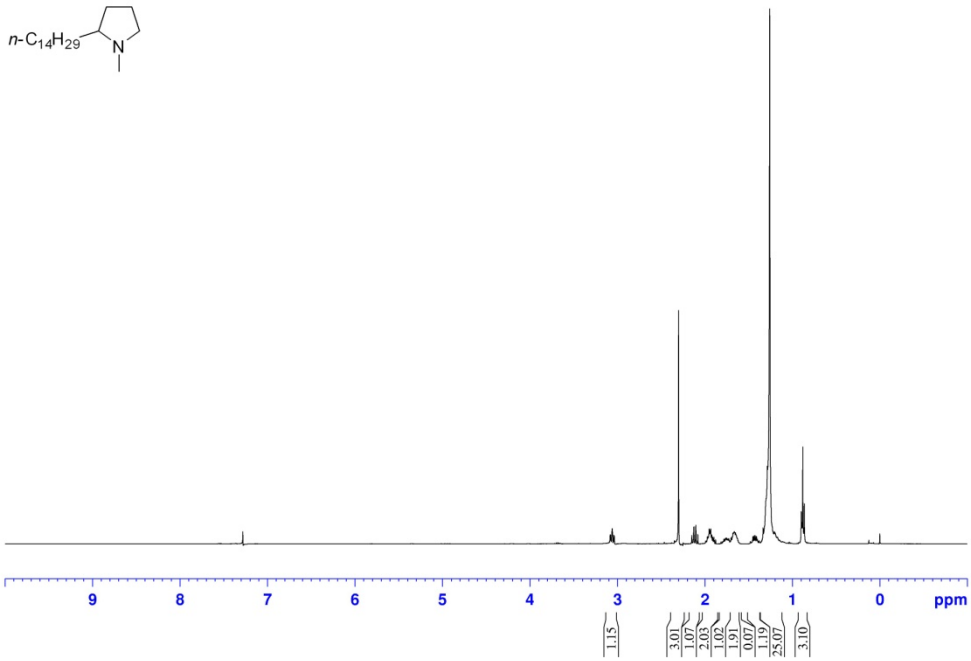


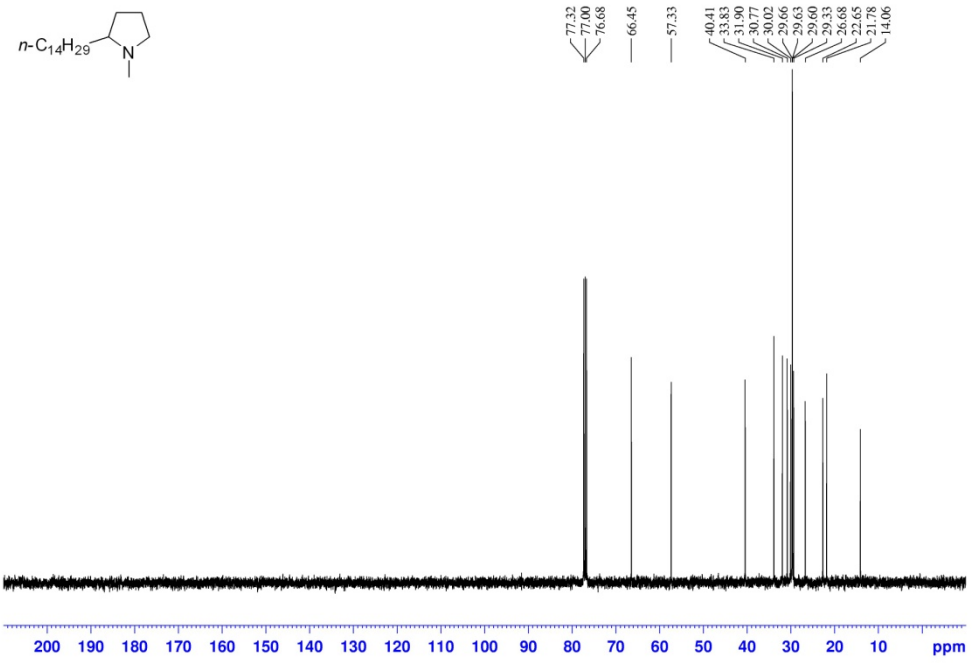
The ^{1}H NMR and ^{13}C NMR spectra of compound **3u**



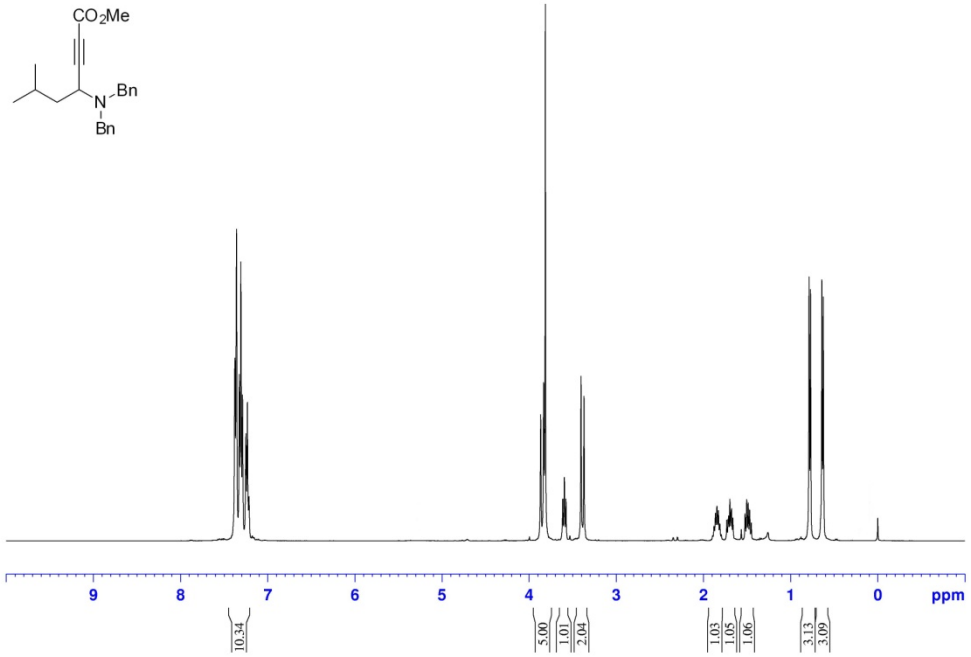


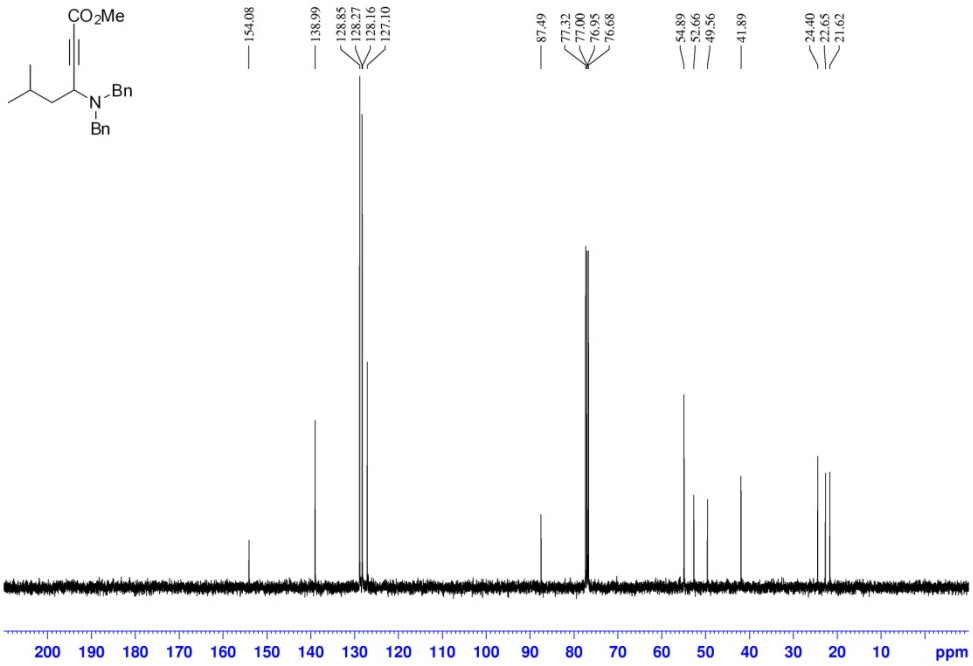
The ^{1}H NMR and ^{13}C NMR spectra of compound **4**



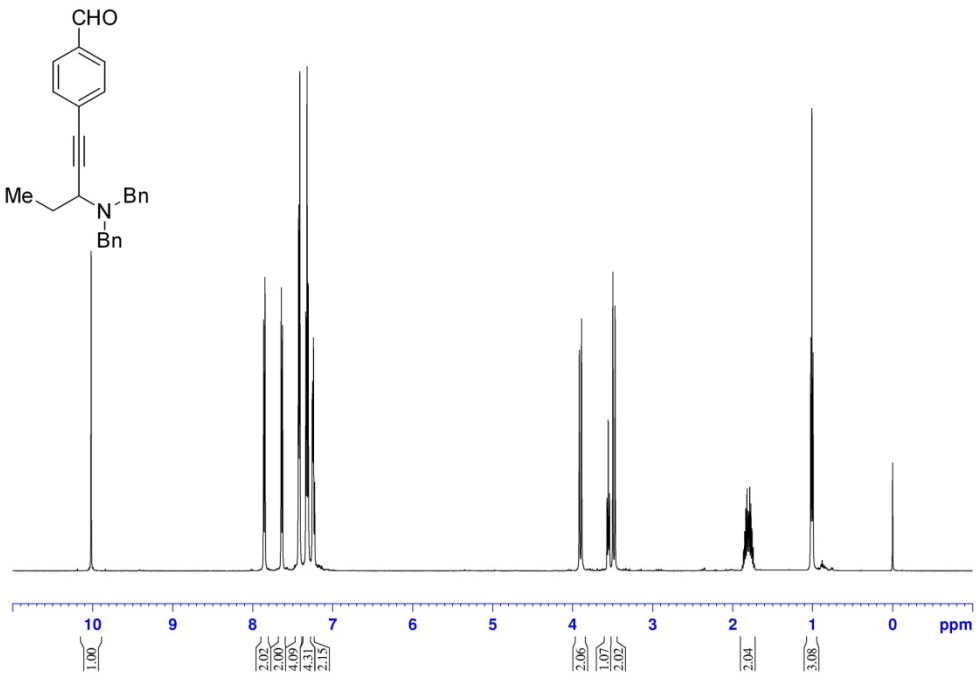


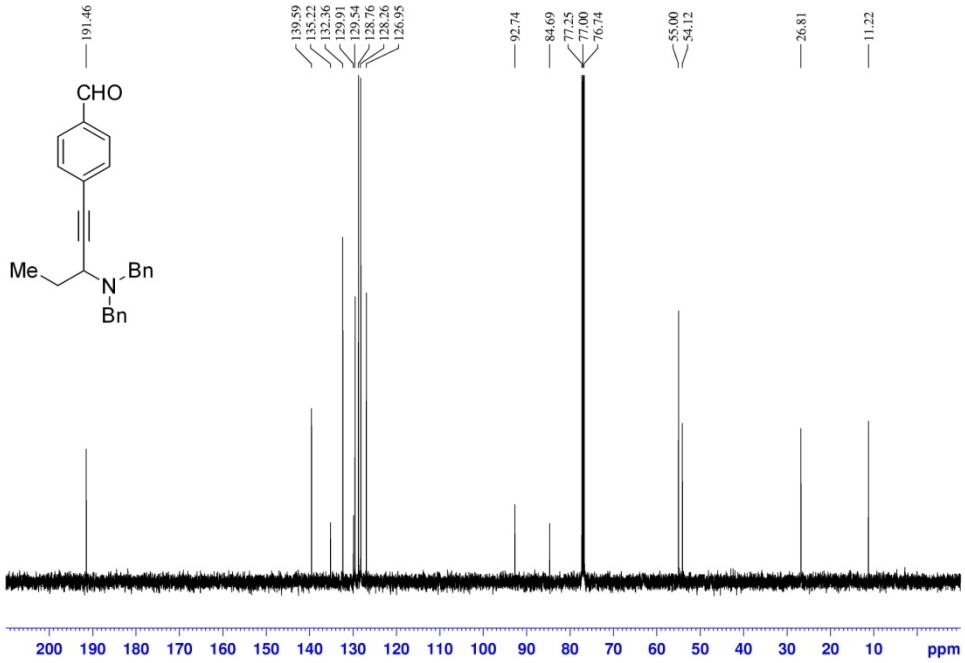
The ^{1}H NMR and ^{13}C NMR spectra of compound **3v**





The ^{1}H NMR and ^{13}C NMR spectra of compound **3w**





HMBC Spectrum of compound **3l'**

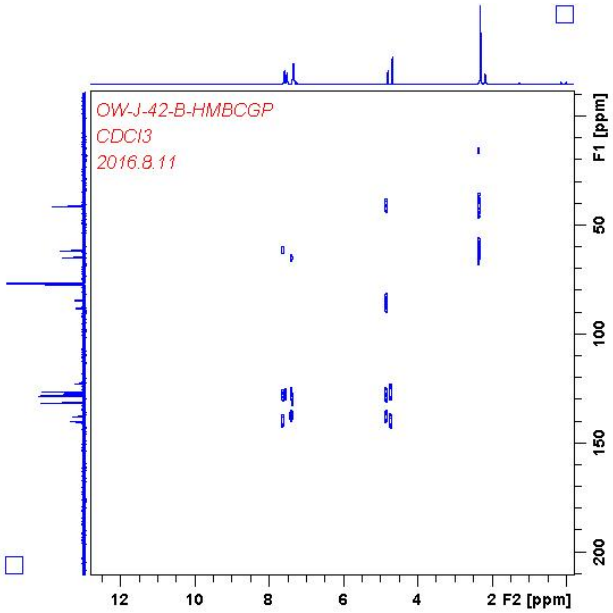
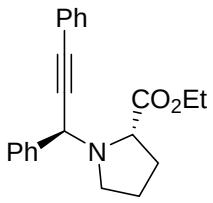
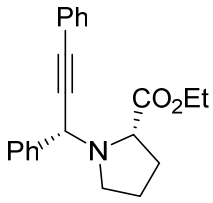
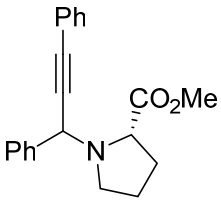
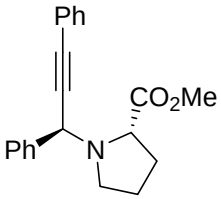
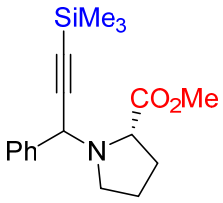
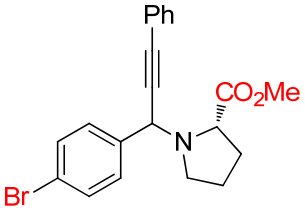
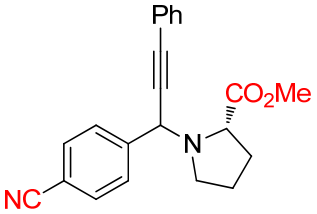


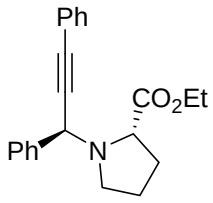
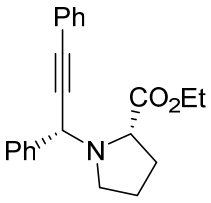
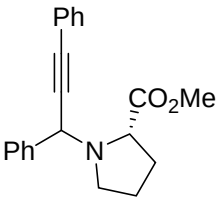
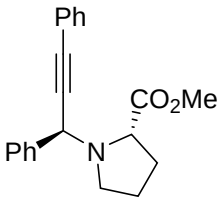
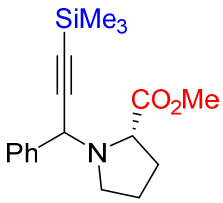
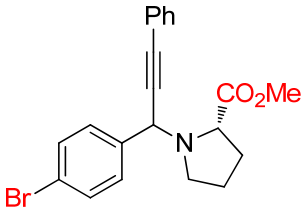
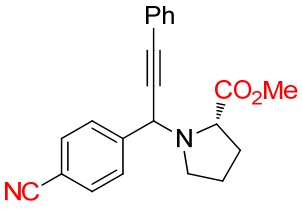
Table 1. Comparison of the data of the diagnostic protons at the stereogenic centres of the known diastereomers[1,2] **A**, **B**, and **C** with those of the major diastereomers **3q** – **3t** (^{1}H NMR, $CDCl_3$)

 **A** (300 MHz) 3.73-3.78 (dd, *J* = 9.0, 6.9 Hz, 1H) 5.27 (s, 1H)	 **B** (300 MHz) 3.57-3.61 (dd, *J* = 9.3, 4.5 Hz, 1H) 5.12 (s, 1H)	 **C** (300 MHz) 3.74-3.78 (m, 1H) 3.78 (s, 3H) 5.24 (s, 1H, CH)	 **3q** (400 MHz) 3.77 (dd, *J* = 8.9, 7.1 Hz, 1H) superposed with 3.77 (s, 3H) 5.24 (s, 1H, CH)
 **3r** 3.67 (dd, J = 9.0, 6.8 Hz, 1H) superposed with 3.76 (s, 3H) 5.01 (s, 1H, CH)	 **3s** 3.75 (dd, J = 9.0, 7.1 Hz, 1H) superposed with 3.77 (s, 3H) 5.20 (s, 1H, CH)	 **3t** 3.77 (dd, J = 9.1, 7.1 Hz, 1H) superposed with 3.79 (s, 3H) 5.30 (s, 1H, CH)	

Reference:

1. V. K.-Y. Lo, Y. Liu, M.-K. Wong and C.-M. Che, *Org. Lett.,* 2006, **8**, 1529-1532.
2. L. Shi, Y.-Q. Tu, M. Wang, F.-M. Zhang, C.-A. Fan, *Org. Lett.,* 2004, **6**, 1001-1003.

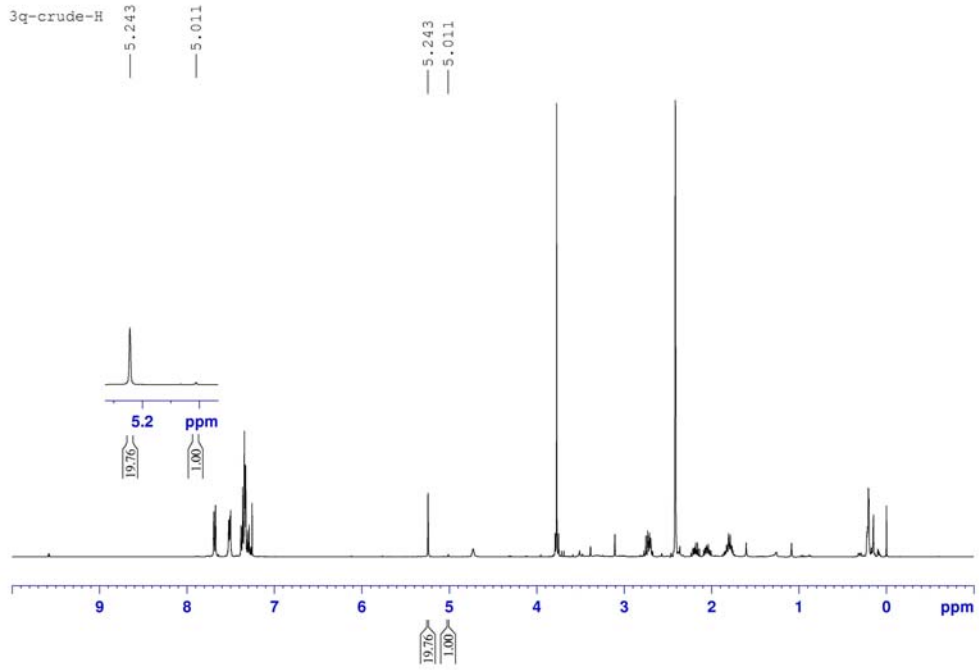
Table 2. Comparison of data of the diagnostic carbon at the stereogenic centre of the known diastereomers[1] **A**, **B**, and **C** with those of our major diastereomers **3q** – **3t** (^{13}C NMR, $CDCl_3$)

 **A** (125 MHz) 63.25	 **B** (125 MHz) 60.85	 **C** (75 MHz) 63.1	 **3q** (100 MHz) 63.1
 **3r** 63.0	 **3s** 63.0	 **3t** 63.0	

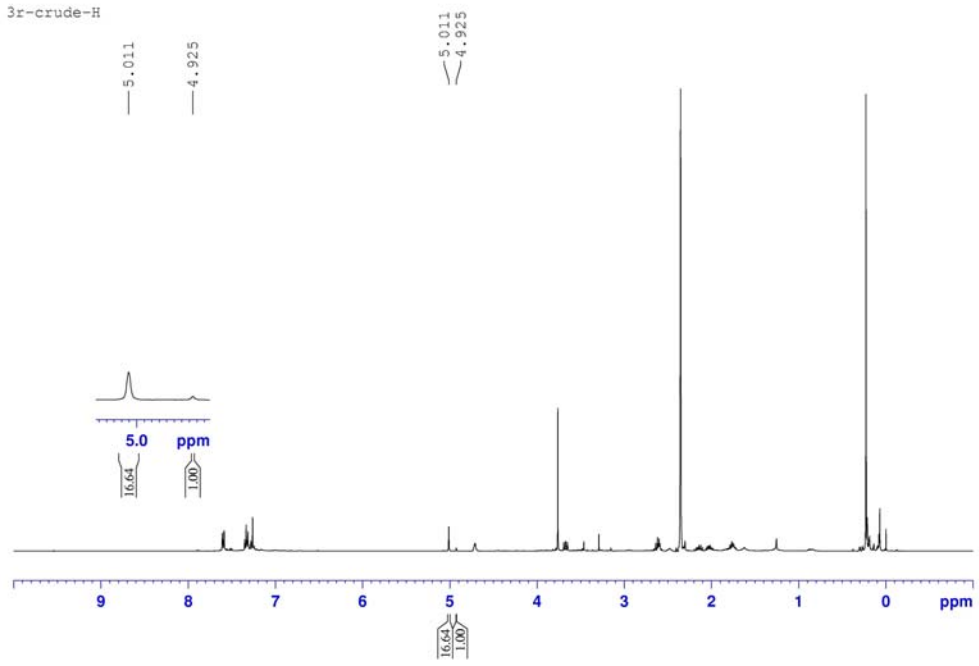
Reference:

1. V. K.-Y. Lo, Y. Liu, M.-K. Wong and C.-M. Che, *Org. Lett.,* 2006, **8**, 1529-1532.
2. L. Shi, Y.-Q. Tu, M. Wang, F.-M. Zhang, C.-A. Fan, *Org. Lett.,* 2004, **6**, 1001-1003.

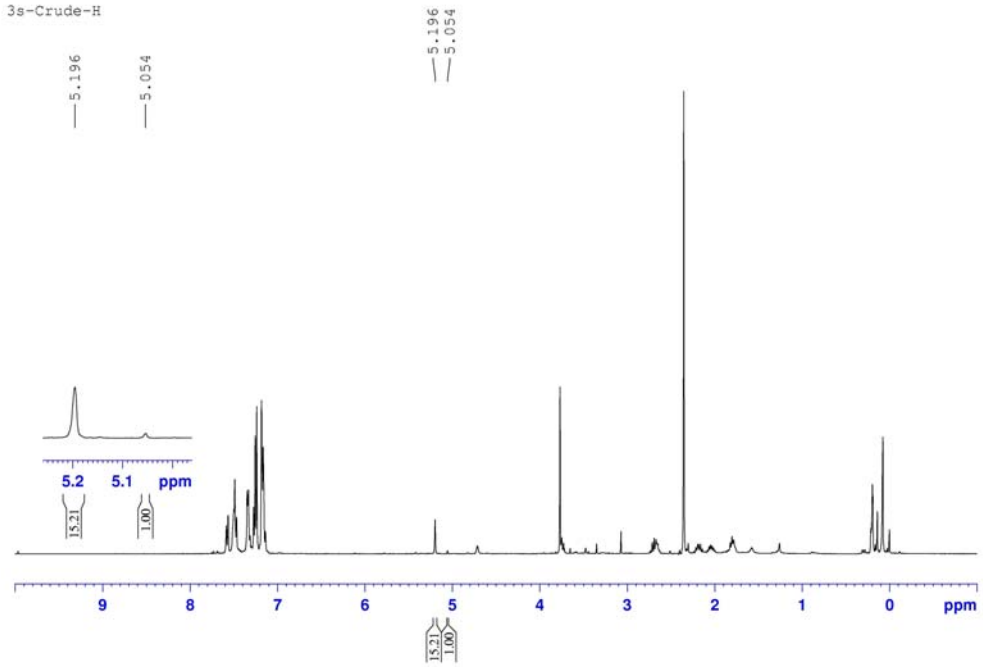
^{1}H NMR Spectrum of the crude **3q**



^{1}H NMR Spectrum of the crude **3r**



^{1}H NMR Spectrum of the crude **3s**



^{1}H NMR Spectrum of the crude **3t**