Supporting Information

Development of an imidazole-based N,N-bidentate ligand for the manganese catalyzed direct coupling of nitriles with alcohols

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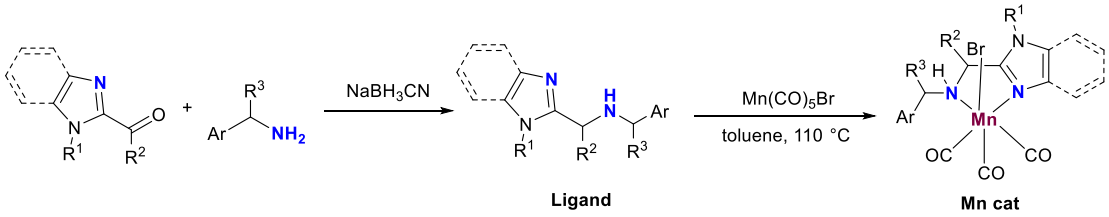
1. General information

NMR spectra were recorded with tetramethylsilane (TMS) as the internal standard. ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were recorded at 100 MHz and ^{19}F NMR (376 MHz) spectra were recorded at 376 MHz on Bruker AV ANCE II instruments. ^{1}H NMR chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS) with the solvent signal as the internal standard ($CDCl_3$ at 7.26 ppm). ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ at 77.16 ppm). Data are given as: s (singlet), d (doublet), t (triplet), q (quartet), dd (double of doublet) or m (multiplets), coupling constants (Hz) and integration. High resolution mass spectra were obtained with the Q-TOF-Premier mass spectrometer (Agilent 1200HPLC-6210TOFMS). Reactions were monitored by TLC and visualized with ultraviolet light. All the solvents were used directly without any purification.

2. General procedure for the synthesis of Mn catalyst



General procedure for the synthesis of ligands[1]

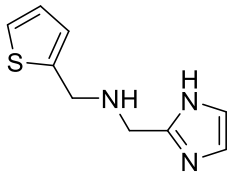
Under N_2 atmosphere, a solution of amine (1 mmol) and aldehyde (1.1 mmol) in dry MeOH (10 mL) was stirred at room temperature for 10-12 h. Then $NaBH_3CN$ (3 mmol) was added and the mixture was stirred at room temperature for 4 h. The solvent was removed under vacuum, and the crude product was purified by column chromatography on silica gel to get **L1**-**L4**, 59-64% yield.

General procedure for the synthesis of Mn catalyst

Under N_2 atmosphere, a solution of **L** (1.0 mmol, 1.0 eq) and $Mn(CO)_5Br$ (1.02 mmol, 1.02 eq) in dry THF (2.0 mL) was stirred at 90 °C for 10-12 h. The mixture was cooled to ambient temperature and concentrated to dryness. The crude material was dissolved in methylene chloride, filtered to remove insoluble material and the product precipitated by addition of n-hexane, collected by filtration, and washed with n-hexane and to give the desired Mn catalyst.

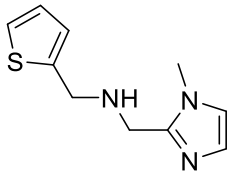
3. Spectra data of ligands

***N*-((1*H*-imidazol-2-yl)methyl)-1-(thiophen-2-yl)methanamine (L1):**



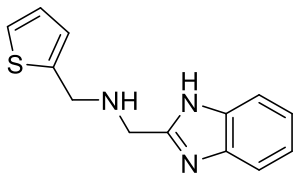
Colorless oil; 65% yield, ^{1}H NMR (400 MHz, Chloroform-d) δ 7.21 (dd, J = 5.2, 1.2 Hz, 1H), 6.98 (s, 2H), 6.94 (dd, *J* = 5.2, 3.2 Hz, 1H), 6.92 – 6.89 (m, 1H), 5.50 (s, 2H), 3.98 (d, J = 0.8 Hz, 2H), 3.93 (s, 2H); ^{13}C NMR (100 MHz, Chloroform-d) δ 146.8, 142.9, 126.9, 125.5, 124.8, 47.8, 46.0; HRMS-ESI (m/z): calcd for $C_9H_{12}N_3S^+$ $[M+H]^+$ 194.0749, found 194.0747.

1-(1-Methyl-1H-imidazol-2-yl)-*N*-(thiophen-2-ylmethyl)methanamine (L2):



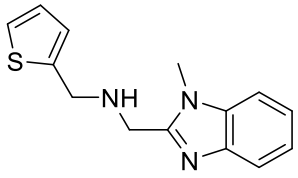
Colorless oil; 70% yield, ^{1}H NMR (400 MHz, Chloroform-d) δ 7.20 – 7.08 (m, 1H), 6.98 – 6.82 (m, 3H), 6.75 (d, *J* = 1.2 Hz, 1H), 3.95 (s, 2H), 3.79 (s, 2H), 3.57 (s, 3H), 2.63 (s, 1H).; ^{13}C NMR (100 MHz, Chloroform-d) δ 146.1, 143.6, 127.0, 126.6, 125.1, 124.5, 121.3, 47.8, 44.6, 32.7; HRMS-ESI (m/z): calcd for $C_{10}H_{14}N_3S^+$ $[M+H]^+$ 208.0903, found 208.0909.

***N*-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-1-(thiophen-2-yl)methanamine (L3):**



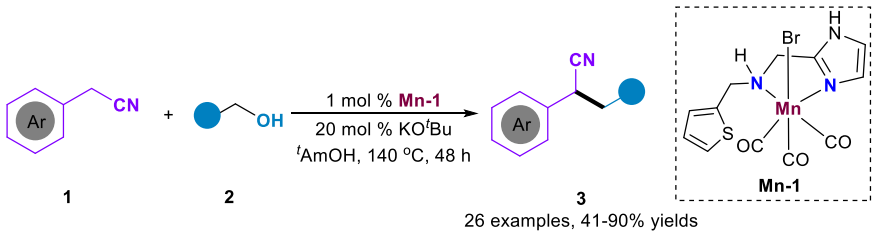
Colorless oil; 72% yield, ^{1}H NMR (400 MHz, Chloroform-d) δ 7.59 (dd, *J* = 6.1, 3.3 Hz, 2H), 7.29 – 7.23 (m, 3H), 6.99 – 6.93 (m, 2H), 4.16 (s, 2H), 4.07 (d, *J* = 0.8 Hz, 2H).; ^{13}C NMR (100 MHz, Chloroform-d) δ 152.4, 143.0, 141.9, 136.0, 126.8, 125.6, 124.8, 122.7, 122.7, 122.2, 119.3, 109.2, 48.0, 45.2, 30.0; HRMS-ESI (m/z): calcd for $C_{13}H_{14}N_3S$ $[M+H]^+$ 244.0903, found 244.0906.

1-(1-Methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiophen-2-ylmethyl)methanamine(L4):



Colorless oil; 66% yield, ^{1}H NMR (400 MHz, Chloroform-d) δ 7.74 – 7.70 (m, 1H), 7.36 – 7.26 (m, 3H), 7.26 – 7.21 (m, 2H), 6.99 – 6.94 (m, 2H), 4.12 (d, J = 3.2 Hz, 4H), 3.80 (s, 3H).; ^{13}C NMR (100 MHz, Chloroform-d) δ 180.8, 141.9, 129.6, 127.8, 124.1, 122.2, 109.8, 47.2, 23.6, 10.0; HRMS-ESI (m/z): calcd for $C_{14}H_{16}N_3S$ $[M+H]^+$ 258.1060, found 258.1062.

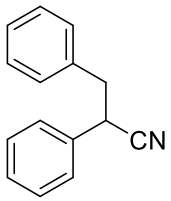
4. General procedure for the synthesis of *α*-alkylated nitriles



To a mixture of **Mn-1** catalyst (1 mol %), KO^{t}Bu (0.2 eq.), nitrile (1.0 mmol) and primary alcohol (0.5 mmol), 1.5 mL of ^{t}AmOH was added. Then, the reaction was stirred under Ar in a pressure tube (ACE pressure tube, 15 mL). The reaction was stirred at 140 °C for 48 hours. After the reaction is complete, dilute the reactant with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (10 mL) for three times. The combined organic layers were washed by brine and dried over magnesium sulfate and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:10 - 1:20 (v/v)) to give the desired product.

5. Spectra data of products

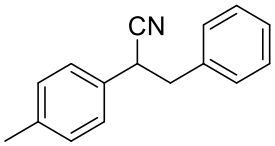
2,3-Diphenylpropanenitrile (3a):



Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 88 mg, 83% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.41 – 7.31

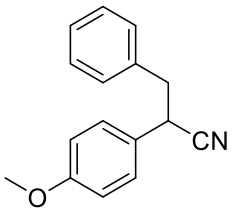
(m, 3H), 7.32 – 7.22 (m, 5H), 7.16 – 7.12 (1m, 2H), 3.99 (dd, *J* = 8.5, 6.4 Hz, 1H), 3.26 – 3.07 (m, 2H). The substrate data is consistent with the reference 2.

3-Phenyl-2-(*p*-tolyl) propanenitrile (3b):



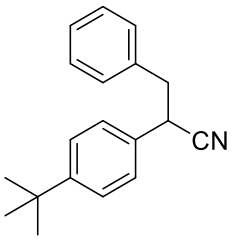
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 92 mg, 86% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.31 – 7.23 (m, 3H), 7.18 – 7.11 (m, 6H), 3.94 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.15 - 3.09 (m, 2H), 2.33 (s, 3H). The substrate data is consistent with the reference 2.

2-(4-Methoxyphenyl)-3-phenylpropanenitrile (3c):



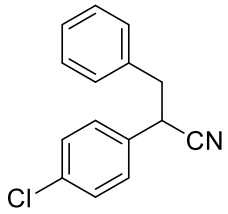
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 104 mg, 89% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.33 – 7.21 (m, 3H), 7.19 – 7.09 (m, 4H), 6.88 – 6.85 (m, 2H), 3.94 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.79 (s, 3H), 3.12 (qd, *J* = 13.6, 7.2 Hz, 2H). The substrate data is consistent with the reference 2.

2-(4-(Tert-butyl) phenyl)-3-phenylpropanenitrile (3d):



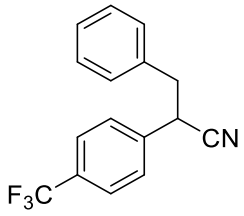
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 105 mg, 83% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.41 – 7.36 (m, 2H), 7.34 - 7.26(m, 3H), 7.25 – 7.17 (m, 4H), 3.97 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.21 – 3.07 (m, 2H), 1.32 (s, 9H). The substrate data is consistent with the reference 2.

2-(4-Chlorophenyl)-3-phenylpropanenitrile (3e):



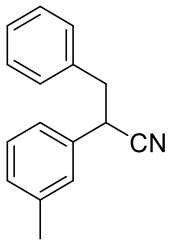
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 100 mg, 71% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.40 – 7.22 (m, 5H), 7.19 – 7.14 (m, 2H), 7.10 (dd, *J* = 7.6, 2.4 Hz, 2H), 4.02 – 3.94 (m, 1H), 3.23 – 3.05 (m, 2H). The substrate data is consistent with the reference 2.

3-Phenyl-2-(4-(trifluoromethyl) phenyl) propanenitrile (3f):



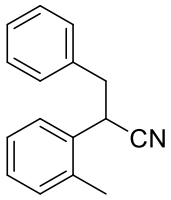
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 28 mg, 41% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.61 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.35 – 7.23 (m, 3H), 7.17 – 7.08 (m, 2H), 4.08 (dd, *J* = 8.0, 6.4 Hz, 1H), 3.26 – 3.09 (m, 2H). The substrate data is consistent with the reference 2.

3-Phenyl-2-(*m*-tolyl) propanenitrile (3g):



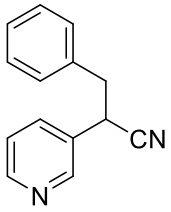
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 88 mg, 76% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.32 – 7.19 (m, 4H), 7.15 – 7.06 (m, 4H), 7.02 (dt, *J* = 7.6, 1.6 Hz, 1H), 3.91 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.09 (t, *J* = 7.2 Hz, 2H), 2.31 (s, 3H). The substrate data is consistent with the reference 2.

3-Phenyl-2-(*o*-tolyl) propanenitrile (3h):



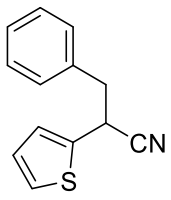
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 83 mg, 74% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.45 – 7.38 (m, 1H), 7.33 – 7.24 (m, 3H), 7.24 – 7.19 (m, 2H), 7.18 – 7.10 (m, 3H), 4.12 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.16 – 3.00 (m, 2H), 2.22 (s, 3H). The substrate data is consistent with the reference 2.

3-Phenyl-2-(pyridin-3-yl) propanenitrile (3i):



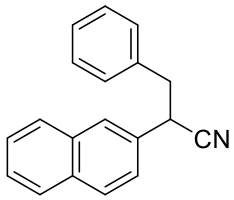
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:10) mixture as eluent. Colorless oil; 68 mg, 75% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.58 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.46 (d, *J* = 2.4 Hz, 1H), 7.57 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.28 (dqt, *J* = 4.0, 2.8, 1.6 Hz, 4H), 7.15 – 7.07 (m, 2H), 4.06 (dd, *J* = 8.0, 6.8 Hz, 1H), 3.26 – 3.09 (m, 2H). The substrate data is consistent with the reference 2.

3-Phenyl-2-(thiophen-2-yl) propanenitrile (3j):



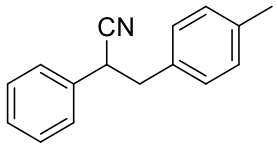
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:10) mixture as eluent. Colorless oil; 64 mg, 69% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.34 – 7.25 (m, 4H), 7.17 – 7.11 (m, 3H), 6.98 (dd, *J* = 5.2, 1.2 Hz, 1H), 4.11 (t, *J* = 7.2 Hz, 1H), 3.16 (dd, *J* = 7.2, 2.0 Hz, 2H). The substrate data is consistent with the reference 2.

2-(Naphthalen-2-yl)-3-phenylpropanenitrile (3k):



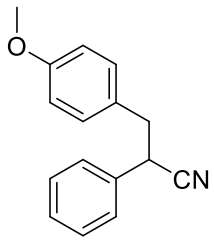
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 100 mg, 84% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.89 – 7.77 (m, 3H), 7.74 (d, *J* = 1.8 Hz, 1H), 7.52 (dt, *J* = 6.4, 3.6 Hz, 2H), 7.36 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.33 – 7.24 (m, 3H), 7.20 – 7.14 (m, 2H), 4.17 (dd, *J* = 8.0, 6.4 Hz, 1H), 3.34 – 3.16 (m, 2H). The substrate data is consistent with the reference 2.

2-Phenyl-3-(*p*-tolyl) propanenitrile (3l):



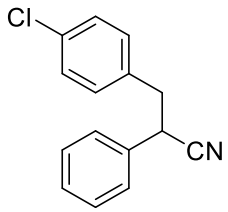
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 83 mg, 75% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.32 – 7.25 (m, 2H), 7.29 – 7.19 (m, 3H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 3.92 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.16 – 2.98 (m, 2H), 2.28 (s, 3H). The substrate data is consistent with the reference 2.

3-(4-Methoxyphenyl)-2-phenylpropanenitrile (3m):



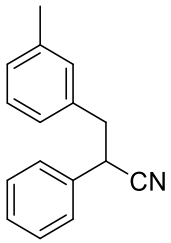
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 97 mg, 90% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.39 – 7.29 (m, 3H), 7.27 – 7.23 (m, 2H), 7.08 – 6.97 (m, 2H), 6.86 – 6.78 (m, 2H), 3.96 (dd, *J* = 8.0, 6.4 Hz, 1H), 3.79 (s, 3H), 3.18 – 3.03 (m, 2H). The substrate data is consistent with the reference 2.

3-(4-Chlorophenyl)-2-phenylpropanenitrile (3n):



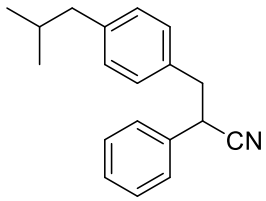
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 88 mg, 73% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.42 – 7.32 (m, 3H), 7.28 – 7.22 (m, 4H), 7.07 – 7.01 (m, 2H), 3.99 (dd, *J* = 8.0, 6.4 Hz, 1H), 3.20 – 3.08 (m, 2H). The substrate data is consistent with the reference 2.

2-Phenyl-3-(*m*-tolyl) propanenitrile (3o):



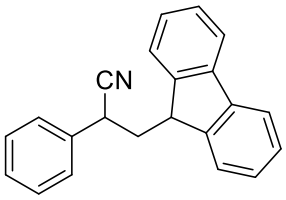
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 89 mg, 80% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.43 – 7.30 (m, 3H), 7.29 – 7.22 (m, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.99 – 6.90 (m, 2H), 3.96 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.10 (qd, *J* = 13.6, 7.6 Hz, 2H), 2.30 (s, 3H). The substrate data is consistent with the reference 2.

3-(4-Isobutylphenyl)-2-phenylpropanenitrile (3p):



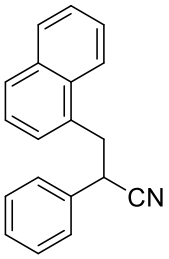
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 103 mg, 87% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.37 – 7.30 (m, 3H), 7.27 – 7.23 (m, 2H), 7.08 – 7.02 (m, 4H), 3.96 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.12 (qd, *J* = 13.6, 7.2 Hz, 2H), 2.44 (d, *J* = 7.2 Hz, 2H), 1.84 (dq, *J* = 13.6, 6.8 Hz, 1H), 0.88 (d, *J* = 6.4 Hz, 6H). The substrate data is consistent with the reference 2.

3-(9H-fluoren-9-yl)-2-phenylpropanenitrile (3p):



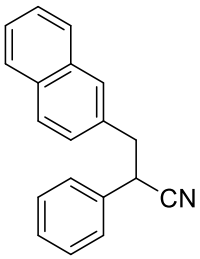
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 109 mg, 74% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.79 – 7.86 (m, 2H), 7.69 – 7.71 (d, *J* = 8.0Hz, 1H), 7.48 – 7.52 (t, *J* = 7.6Hz, 1H), 7.37 – 7.45 (m, 5H), 7.26 – 7.34 (m, 4H), 4.26 (dd, *J* = 6.4, 6.4Hz, 1H), 3.88 – 3.92 (m, 1H), 2.76 – 2.83 (m, 1H), 2.21 – 2.28 (m, 1H). The substrate data is consistent with the reference 2.

3-(Naphthalen-1-yl)-2-phenylpropanenitrile (3r):



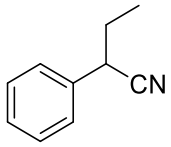
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 96 mg, 71% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.96 – 7.85 (m, 2H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.53 (dddd, *J* = 17.2, 8.0, 6.8, 1.2 Hz, 2H), 7.43 – 7.26 (m, 7H), 4.15 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.68 – 3.53 (m, 2H). The substrate data is consistent with the reference 2.

3-(Naphthalen-2-yl)-2-phenylpropanenitrile (3s):



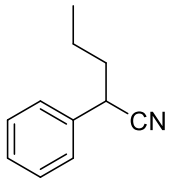
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 96 mg, 67% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.80 (dddd, *J* = 15.2, 6.8, 4.8, 2.4 Hz, 3H), 7.60 (s, 1H), 7.47 (dt, *J* = 7.2, 2.4 Hz, 2H), 7.38 – 7.33 (m, 3H), 7.31 – 7.27 (m, 2H), 7.25 – 7.23 (m, 1H), 4.13 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.33 (qd, *J* = 13.6, 7.6 Hz, 2H). The substrate data is consistent with the reference 2.

2-Phenylbutanenitrile (3t):



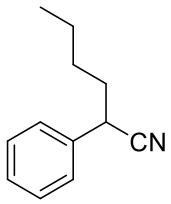
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 61 mg, 65% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.41 – 7.35 (m, 2H), 7.35 – 7.29 (m, 3H), 3.74 (t, *J* = 7.2 Hz, 1H), 2.02 – 1.87 (m, 2H), 1.08 (t, *J* = 7.2 Hz, 3H). The substrate data is consistent with the reference 2.

2-Phenylpentanenitrile (3u):



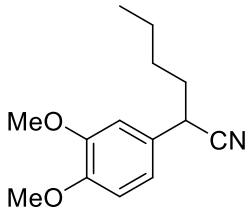
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 63 mg, 66% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.41 – 7.35 (m, 2H), 7.35 – 7.29 (m, 3H), 3.79 (dd, *J* = 8.8, 6.4 Hz, 1H), 2.01 – 1.75 (m, 2H), 1.63 – 1.40 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H). The substrate data is consistent with the reference 2.

2-Phenylhexanenitrile (3v):



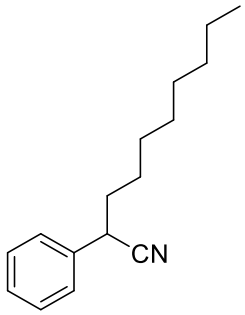
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 71 mg, 56% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.43 – 7.38 (m, 2H), 7.37 – 7.33 (m, 3H), 3.79 (dd, *J* = 8.4, 6.4 Hz, 1H), 2.01 – 1.85 (m, 2H), 1.52 – 1.33 (m, 4H), 0.93 (t, *J* = 7.2 Hz, 3H). The substrate data is consistent with the reference 2.

2-(3,4-Dimethoxyphenyl) hexanenitrile (3w):



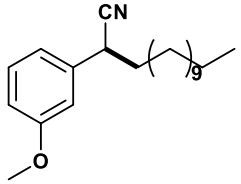
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 88 mg, 71% yield, ^{1}H NMR (400 MHz, CDCl3, ppm) δ 6.83 (d, *J* = 2.0 Hz, 2H), 6.80 (d, *J* = 1.6 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.69 (dd, *J* = 8.4, 6.4 Hz, 1H), 1.97 – 1.75 (m, 2H), 1.52 – 1.28 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H). The substrate data is consistent with the reference 2.

2-Phenyldecanenitrile (3x):



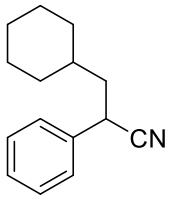
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 85 mg, 74% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.42 – 7.34 (m, 2H), 7.36 – 7.28 (m, 3H), 3.77 (dd, *J* = 8.6, 6.4 Hz, 1H), 2.00 – 1.79 (m, 2H), 1.58 – 1.37 (m, 2H), 1.31 – 1.23 (m, 10H), 0.88 (t, *J* = 6.8 Hz, 3H). The substrate data is consistent with the reference 2.

2-(3-Methoxyphenyl) tetradecanenitrile (3y):



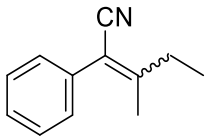
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless liquid; 118 mg, 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.34 – 7.25 (m, 1H), 6.94 – 6.80 (m, 3H), 3.82 (s, 3H), 3.73 (dd, *J* = 8.8, 6.4 Hz, 1H), 1.99 – 1.78 (m, 2H), 1.61 – 1.36 (m, 2H), 1.34 – 1.23 (m, 18H), 0.88 (t, *J* = 6.4 Hz, 3H). The substrate data is consistent with the reference 2.

2-Cyclohexyl-2-phenylacetonitrile (3z):



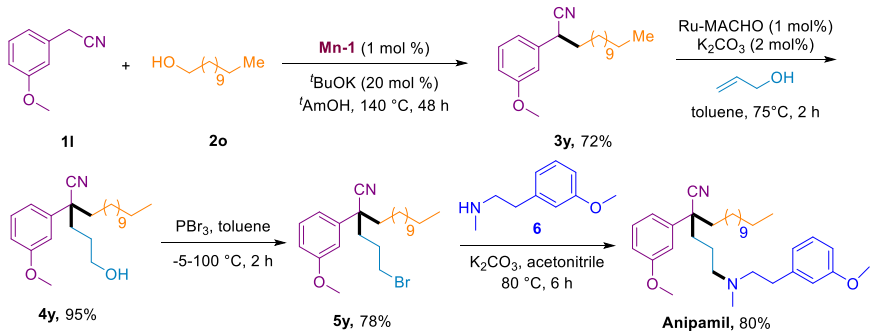
Purified by silica-gel column chromatography using ethyl acetate/hexane (1:20) mixture as eluent. Colorless oil; 74 mg, 62% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.40 – 7.35 (m, 2H), 7.35 – 7.27 (m, 3H), 3.84 (dd, *J* = 10.0, 6.0 Hz, 1H), 1.94 – 1.79 (m, 2H), 1.79 – 1.64 (m, 5H), 1.67 – 1.45 (m, 1H), 1.35 – 1.13 (m, 3H), 1.04 – 0.86 (m, 2H). The substrate data is consistent with the reference 2.

3-Methyl-2-phenylpent-2-enenitrile (3za):



Purified by silica-gel column chromatography using ethyl acetate/hexane (1:40) mixture as eluent. Colorless liquid. Yield: 75 mg, 88%. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.42 – 7.28 (m, 5H), 2.62 (q, *J* = 7.6 Hz, 1H), 2.23 (d, *J* = 7.6 Hz, 2H), 1.91 (s, 1H), 1.22 (d, *J* = 7.6 Hz, 1H), 1.07 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 159.9, 134.2, 134.1, 129.1, 128.9, 128.7, 128.6, 128.3, 128.2, 118.9, 118.6, 110.7, 110.2, 31.8, 27.5, 21.8, 19.1, 12.6, 12.4. HRMS-ESI (m/z): calcd for $C_{12}H_{13}N$ $[M+H]^+$: 172.1048, found: 172.1053.

6. Experimental for the synthesis of anipamil



Experimental procedure for 2-(3-Methoxyphenyl) tetradecanenitrile (3y):

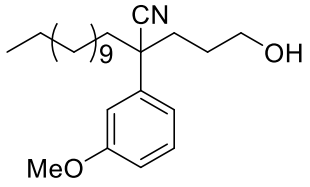
To a mixture of **Mn-1** catalyst (0.03 mmol), ^{t}BuOK (0.6 mmol), 3-methoxy phenyl acetonitrile (6 mmol) and 1-dodecanol (3 mmol), 9 mL of ^{t}AmOH was added. Then, the reaction was stirred under Ar in a pressure tube (ACE pressure tube, 15 mL). The reaction was stirred at 140 °C for 48

hours. After cooling to room temperature, the reaction was diluted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (10 mL) for three times. The combined organic layers were washed by brine and dried over magnesium sulfate and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1-10:1(v/v)) to give the desired product **3y** (682 mg, 72% yield).

Experimental procedure for 2-(3-Hydroxypropyl)-2-(3-methoxyphenyl) tetradecanenitrile (4y):

A Schlenk flask (10 mL) was equipped with a stir bar, **Ru-MACHO** (0.02 mmol), K_2CO_3 (0.4 mmol), 2-(3-methoxyphenyl) tetradecanenitrile (**3y**, 2 mmol), allyl alcohol (3 mmol) and toluene (3 mL) were added under nitrogen atmosphere. The solution was heated at 75 °C (oil bath temperature) with stirring under N_2 for 2 h. Then, the solvent was evaporated, and the resulted residue was purified by silica-gel (100-200 mesh) column chromatography using ethyl acetate/hexane (20:80(v/v))) mixture as eluent. **4y** was isolated in 709 mg, 95 %.

2-(3-Hydroxypropyl)-2-(3-methoxyphenyl) tetradecanenitrile (4y):



Colorless oil;709 mg, 95% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.26 – 7.16 (m, 1H), 6.93 – 6.83 (m, 2H), 6.77 – 6.73 (m, 1H), 3.74 (s, 3H), 3.48 (t, J = 6.4 Hz, 2H), 2.09 – 1.71 (m, 6H), 1.67 – 1.51 (m, 1H), 1.43 – 1.24 (m, 2H), 1.27 – 1.11 (m, 10H), 0.79 (t, J = 6.8 Hz, 3H). The substrate data is consistent with the literature I have published[2].

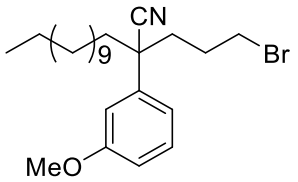
Experimental procedure for anipamil (6y)[4]:

Step 1: To a round bottom flask, a magnetic stir bar, 2-(3-hydroxypropyl)-2-(3-methoxyphenyl) tetradecanenitrile (**4y**, 0.5 mmol, 1 equiv) and toluene (1 mL) were added under nitrogen atmosphere and cooled to -5 °C. To this solution, PBr_3 (0.6 mmol, 1.1 equiv) was added dropwise and stirred for 30 minutes. The reaction mixture was allowed to warm to room temperature and then heated at

100 °C for 2 h. Upon completion, reaction mixture was cooled to room temperature, poured into ice, and the resulted aqueous solution was extracted using diethyl ether (2 × 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure using a rotavapor, and the residue was used directly in next step.

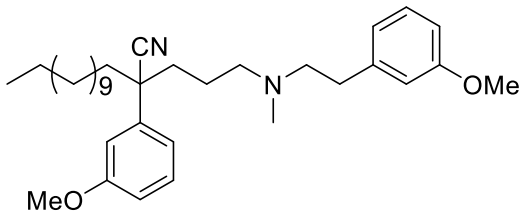
Step two: Residue (above), 2-(3-methoxyphenyl)-*N*-methylethan-1-amine[3] (**5y**, 0.3 mmol, 1 equiv.) and acetonitrile (1 mL) were charged in a round bottom flask. Freshly ground anhydrous Na_2CO_3 (0.9 mmol, 3 equiv.) was added as one portion, and the solution was heated at 80 °C for 6 h. Upon completion of the reaction, the solvent was removed under reduced pressure using a rotavapor, and the residue obtained was dissolved in water (2 mL). The aqueous solution was extracted using ethyl acetate (3 × 10 mL), the combined organic layer washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed, and resulted residue purified by silica gel column chromatography using DCM/MeOH (95:5) mixture as eluent. Yields were calculated for pure isolated products. The aqueous solution was extracted using ethyl acetate (3 × 10 mL), the combined organic layer washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed, and the resulted residue was purified by silica gel column chromatography using DCM/MeOH (90:10(v/v))) mixture as eluent. Anipamil (**6y**) was isolated in 151 mg, 58% yield.

2-(3-Bromopropyl)-2-(3-methoxyphenyl) hexanenitrile (5y):



Colorless oil,170 mg, 78% yield ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.30 (t, *J* = 8.0 Hz, 1H), 7.00 – 6.90 (m, 2H), 6.84 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.83 (s, 3H), 3.37 – 3.30 (m, 2H), 2.21 – 1.80 (m, 5H), 1.75 – 1.60 (m, 1H), 1.51 – 1.09 (m, 20H), 0.87 (t, *J* = 6.8 Hz, 3H). The substrate data is consistent with the literature I have published[2].

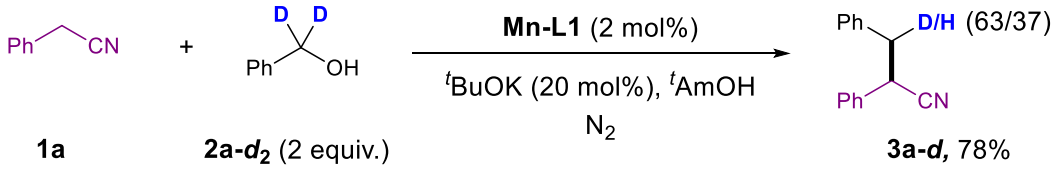
Anipamil (6y):



Colorless oil;151mg 80% yield, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.25 – 7.16 (m, 1H), 7.15 – 7.07 (m, 1H), 6.91 – 6.84 (m, 2H), 6.78 – 6.62 (m, 4H), 3.73 (d, J = 10.8 Hz, 6H), 2.71 – 2.58 (m, 2H), 2.50 – 2.39 (m, 2H), 2.35 – 2.18 (m, 2H), 2.13 (s, 3H), 1.95 – 1.69 (m, 4H), 1.63 – 1.47 (m, 2H), 1.15 (dd, J = 11.6, 4.8 Hz, 21H), 0.80 (t, J = 6.8 Hz, 3H). The substrate data is consistent with the literature I have published[2].

7. Mechanism studies

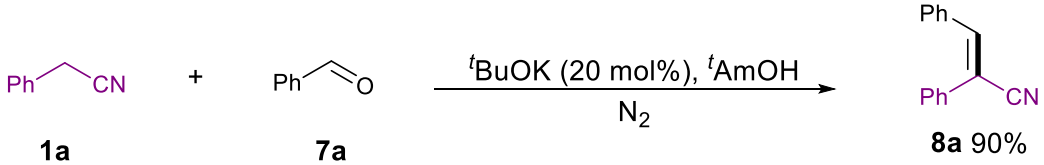
Isotopic labeling experiments



1a **2a-d_2** (2 equiv.) **3a-*d*,** 78%

To a mixture of **Mn-1** catalyst (1 mol %), KO^{t}Bu (0.2 eq.), nitriles (1.0 mmol) and alcohol **2a-d$_2$** (0.5 mmol), 1.5 mL of ^{t}AmOH was added. Then, the reaction was stirred under Ar in a pressure tube (ACE pressure tube, 15 mL). The reaction was stirred at 140 ºC for 48 hours.After cooling to room temperature, the reaction was diluted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (10 mL) for three times. The combined organic layers were washed by brine and dried over magnesium sulfate and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1-10:1(v/v))) to give the desired product **3a-D** (100 mg, 78%).

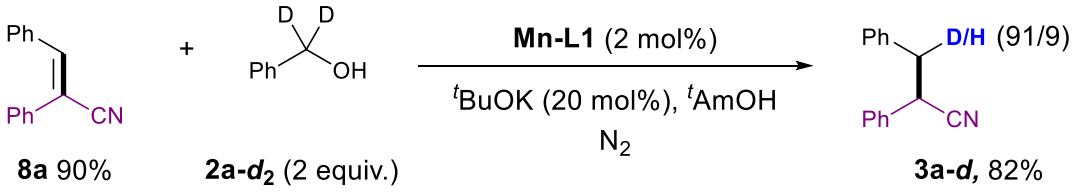
Synthesis of products 8a



1a **7a** **8a** 90%

To a mixture of **Mn-1** catalyst (1 mol %), KO^{t}Bu (0.2 eq.), nitriles (1.0 mmol) and benzaldehyde (0.5 mmol), 1.5 mL of ^{t}AmOH was added. Then, the reaction was stirred under Ar in a pressure tube (ACE pressure tube, 15 mL). The reaction was stirred at 140 °C for 48 hours.After cooling to room temperature, the reaction was diluted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (10 mL) for three times. The combined organic layers were washed by brine and dried over magnesium sulfate and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1-10:1(v/v))) to give the desired product **8a'** (116 mg, 90%).

Synthesis of products 3a-d



To a mixture of **Mn-1** catalyst (1 mol %), KO^{t}Bu (0.2 eq.), **8a** (1.0 mmol) and alcohol **2a-d$_2$** (0.5 mmol), 1.5 mL of ^{t}AmOH was added. Then, the reaction was stirred under Ar in a pressure tube (ACE pressure tube, 15 mL). The reaction was stirred at 140 °C for 48 hours.After cooling to room temperature, the reaction was diluted with ethyl acetate (10 mL) and water (10 mL).. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (10 mL) for three times. The combined organic layers were washed by brine and dried over magnesium sulfate and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1-10:1(v/v))) to give the desired product **3a-D** (115 mg, 90%).

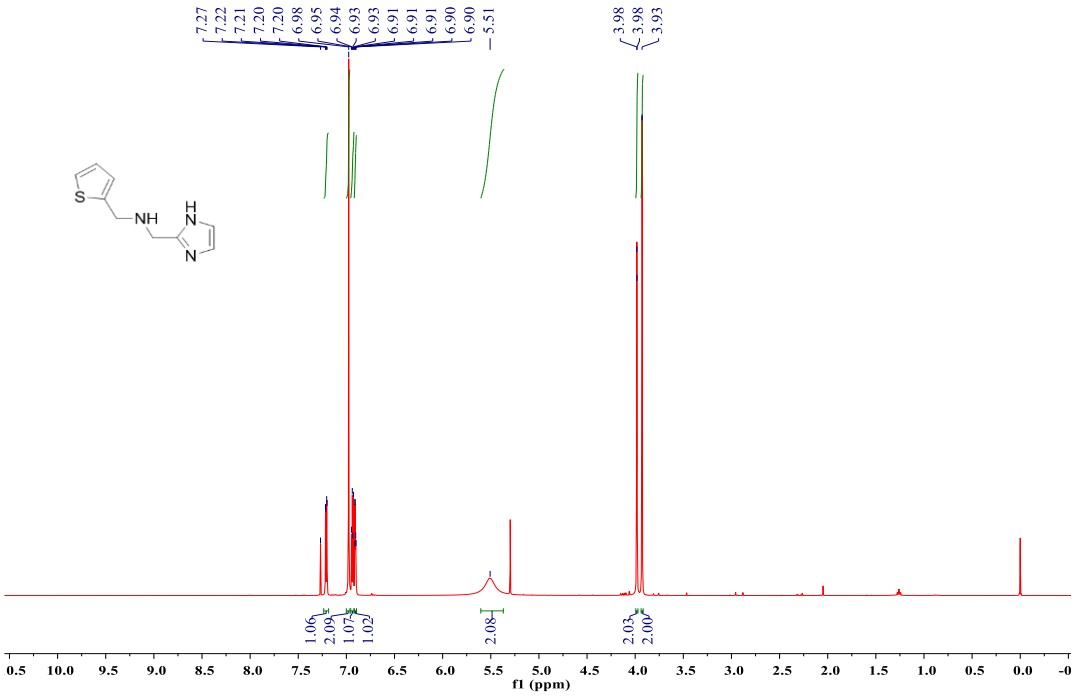
8. Reference

1. S. Rajalakshmi, M. S. Kiran, V. G. Vaidyanathan, E. R. A. Singam, V. Subramaniam and B. U. Nair, *Eur. J. Med. Chem.*, 2011, **70**, 280-293.

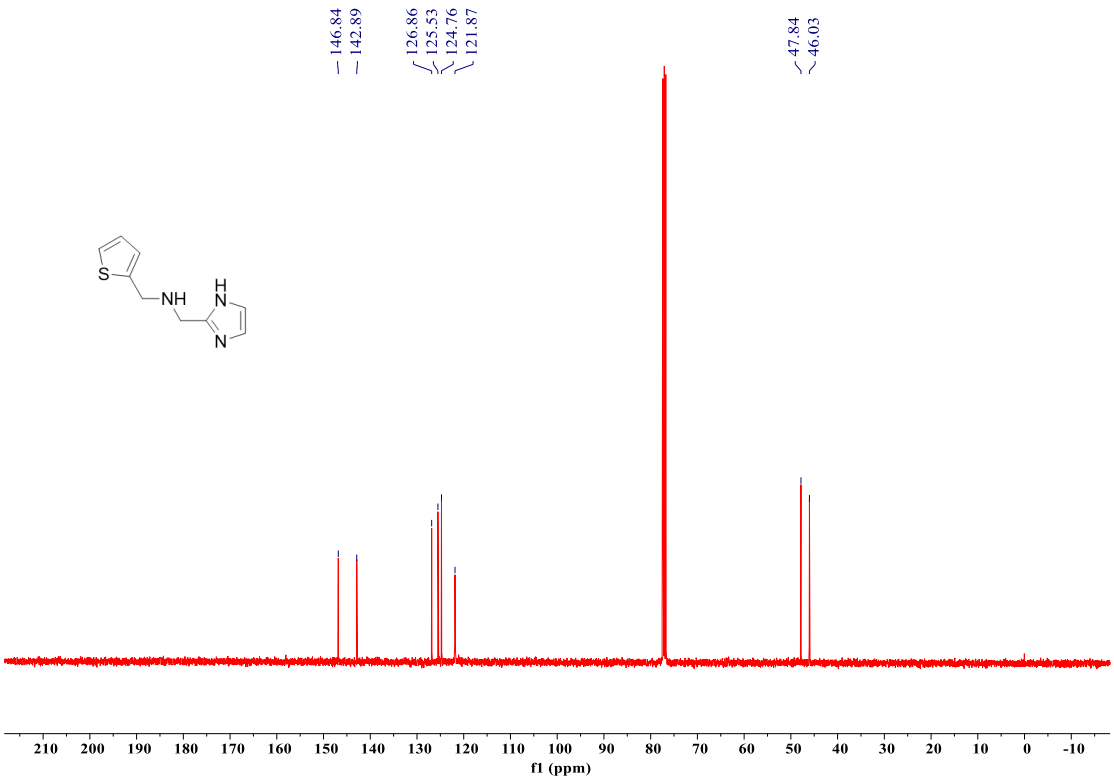
2. D. Song, S. Wang, W. Huang, R. Chen, F. Hu, L. Cheng, X. Zhao, F. Ling, and W. Zhong, *Org. Chem. Front*., 2023, **10**, 5908-5915
3. J. H. Schrittwieser, V. Resch, J. H. Sattler, W. D. Lienhart, K. Durchschein, A. Winkler, K. Gruber, P. Macheroux and W. Kroutil, *Angew. Chem., Int. Ed.*, 2011, **50**, 1068-1071.
4. S. Thiyagarajan, R. V. Sankar, P. K. Anjalikrishna, C. H. Suresh and C. Gunanathan, *ACS Catalysis*, 2022, **12**, 2191-2204.

9. NMR spectra

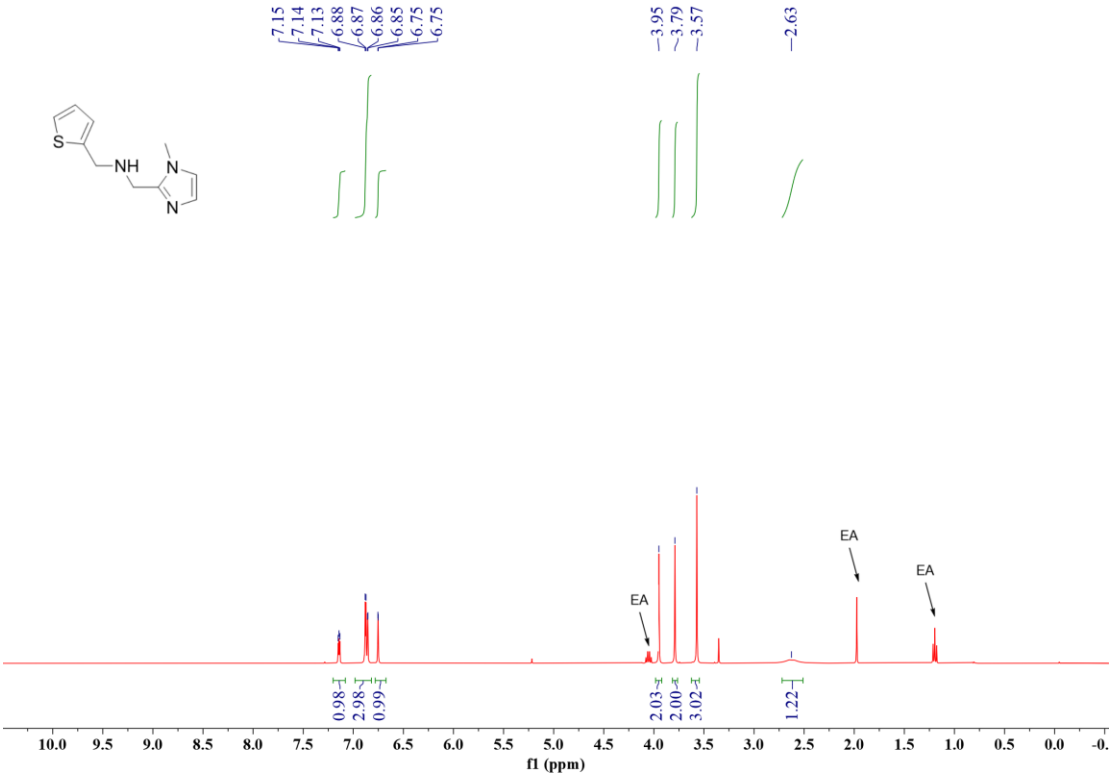
^{1}H NMR spectrum of *N*-((1H-imidazol-2-yl)methyl)-1-(thiophen-2yl)methanamine (**L 1**, 400 MHz, $CDCl_3$):



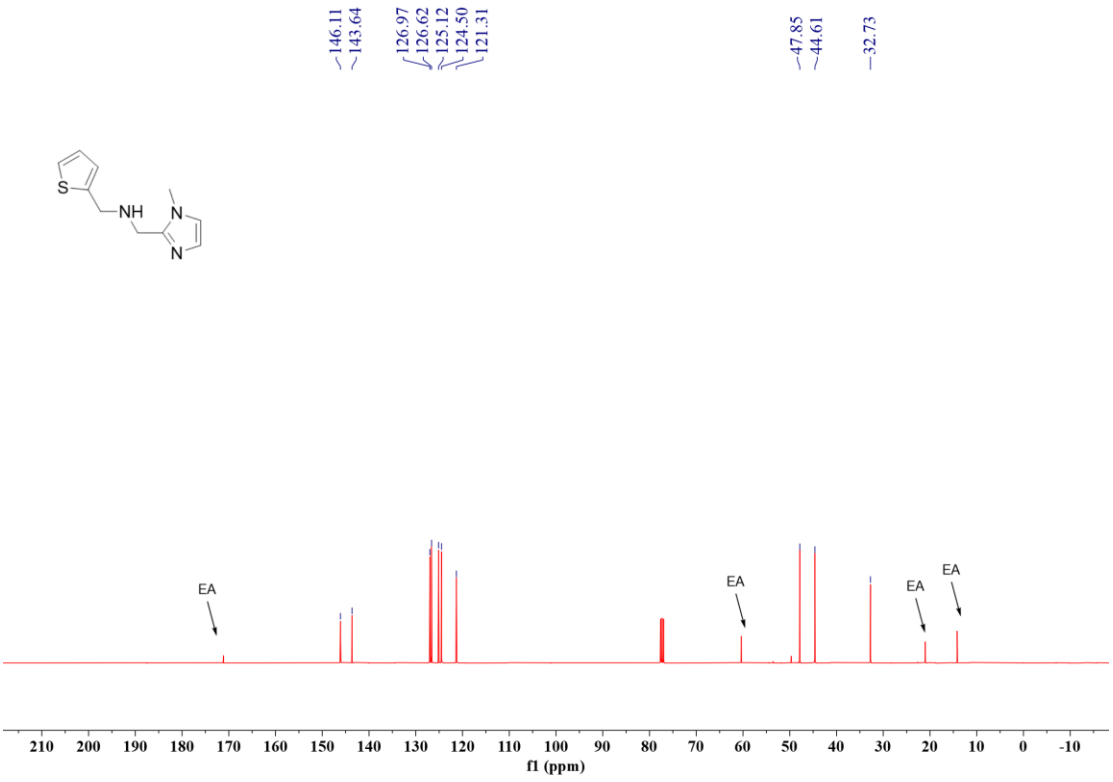
^{13}C NMR spectrum of *N*-((1H-imidazol-2-yl)methyl)-1-(thiophen-2yl)methanamine (**L1**, 100 MHz, $CDCl_3$):



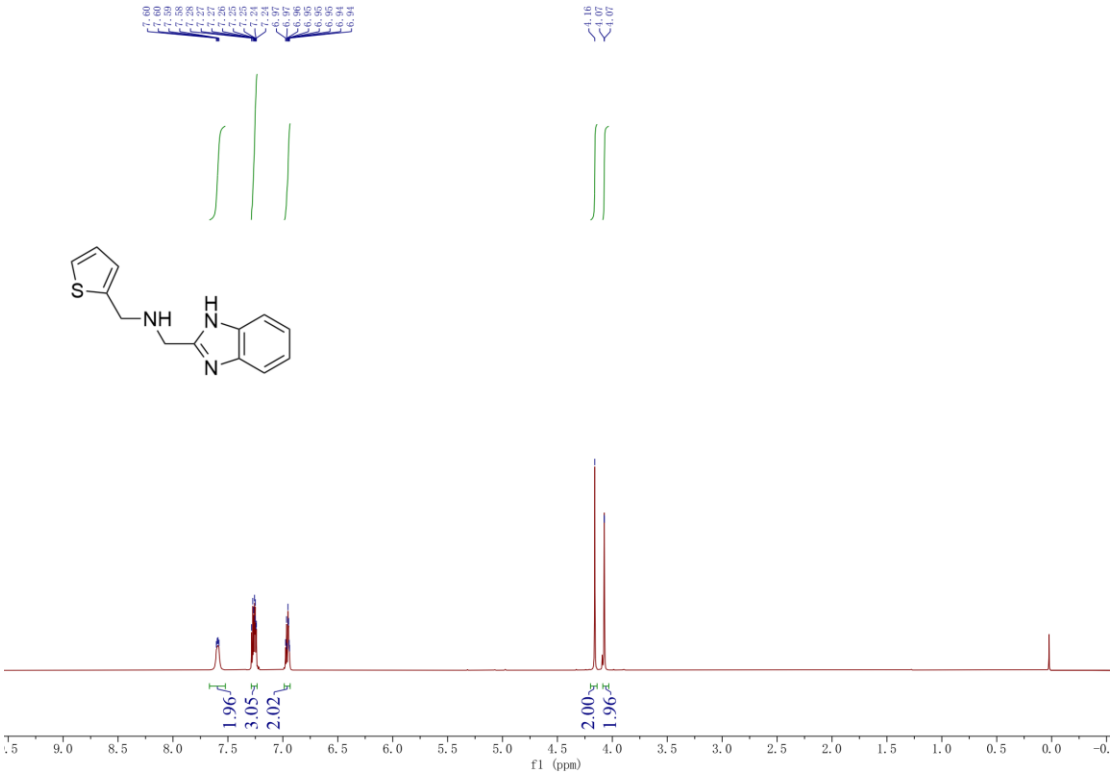
^{1}H NMR spectrum of 1-(1-Methyl-1H-imidazol-2-yl)-N-(thiophen-2-ylmethyl)methanamine (**L2**, 400 MHz, $CDCl_3$):



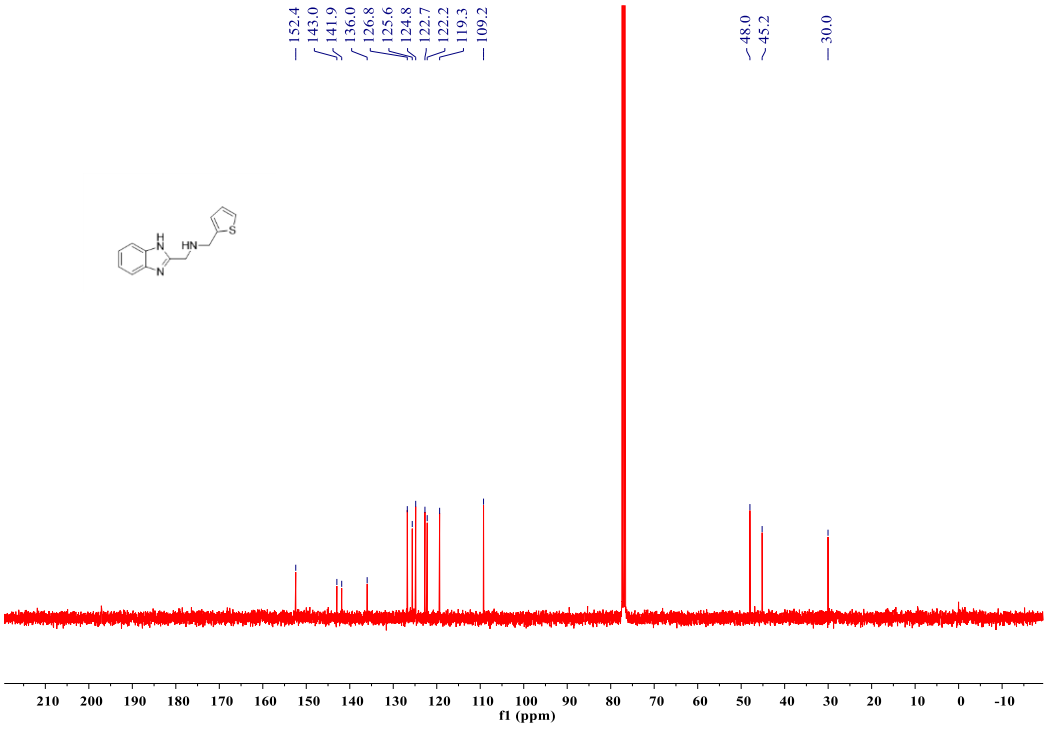
^{13}C NMR spectrum of 1-(1-Methyl-1H-imidazol-2-yl)-N-(thiophen-2-ylmethyl)methanamine (**L2**, 100 MHz, $CDCl_3$):



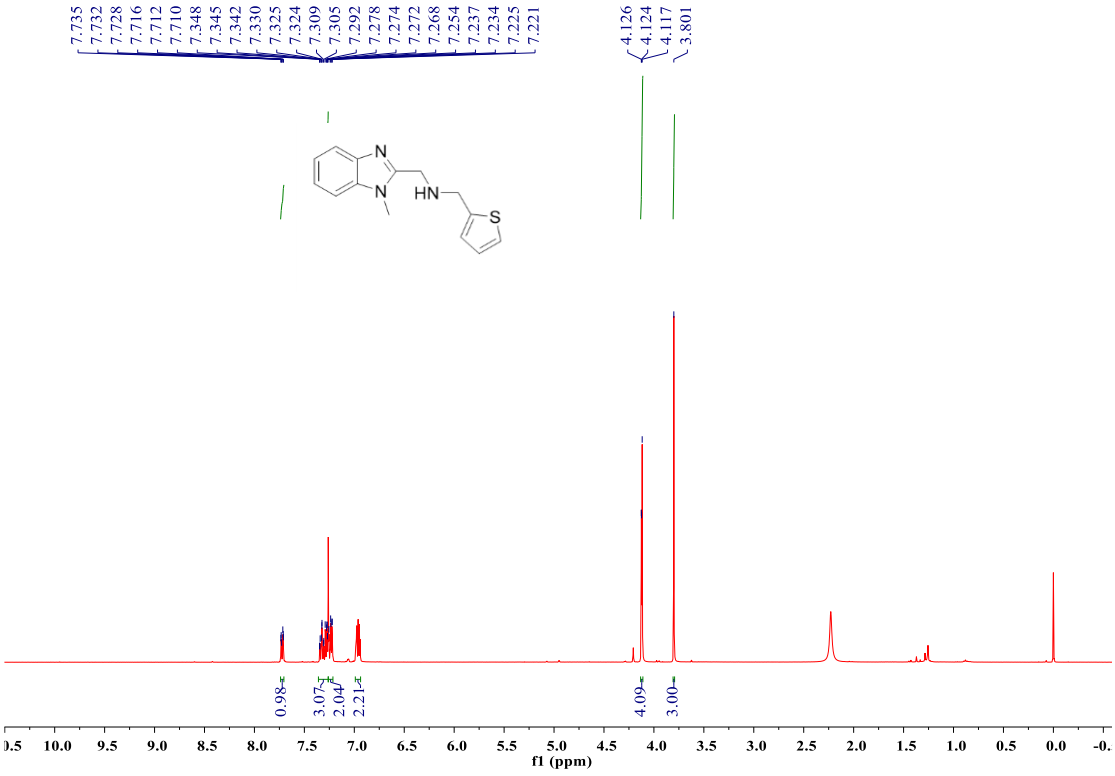
^{1}H NMR spectrum of N-((1H-benzo[d]imidazol-2-yl)methyl)-1-(thiophen-2-yl)methanamine (**L3**, 400 MHz, $CDCl_3$):



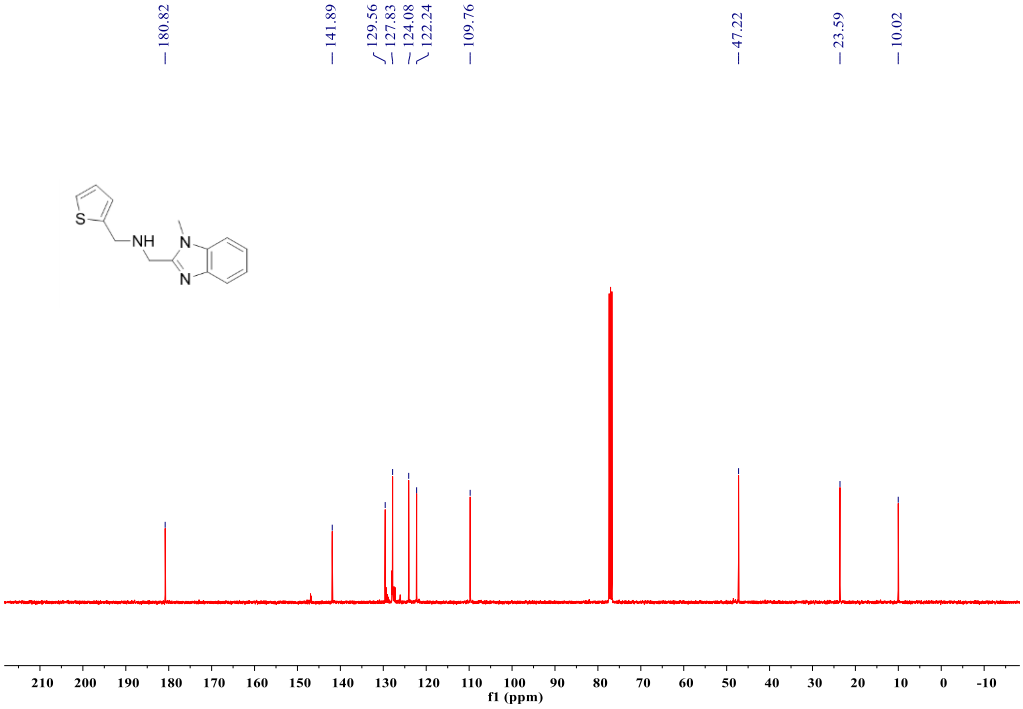
^{13}C NMR spectrum of N-((1H-benzo[d]imidazol-2-yl)methyl)-1-(thiophen-2-yl)methanamine (**L3**, 100 MHz, $CDCl_3$):



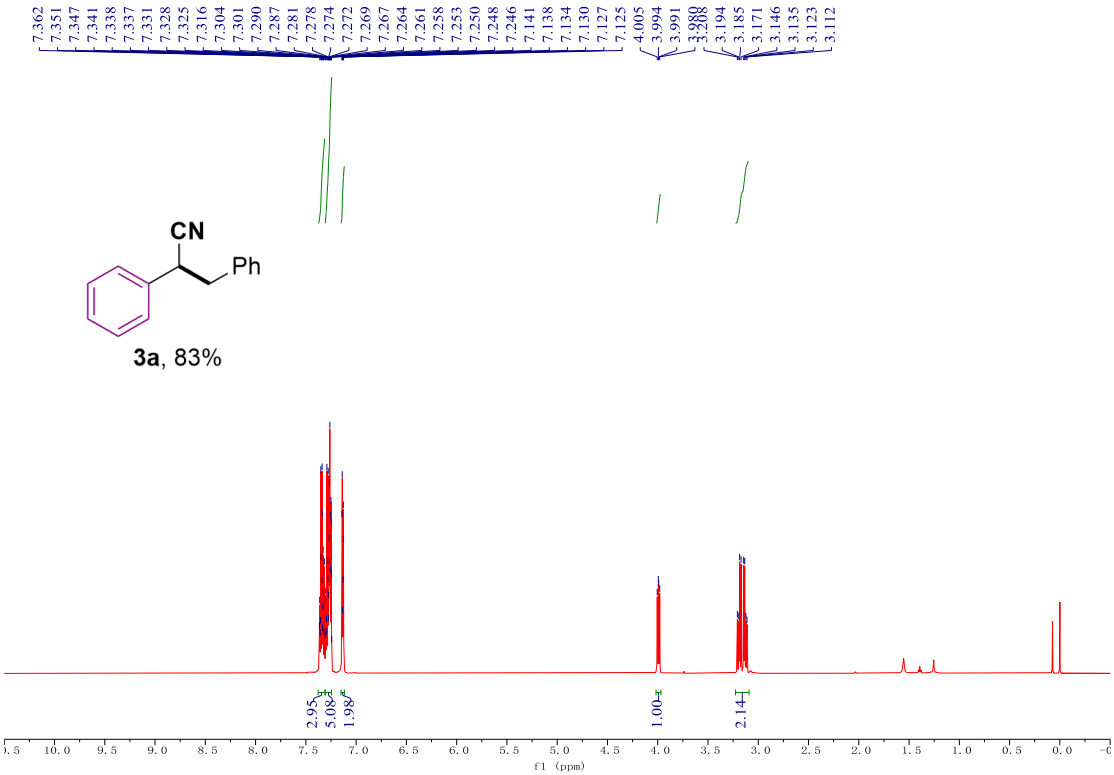
^{1}H NMR spectrum of 1-(1-Methyl-1H-benzo[d]imidazol-2-yl)-N-(thiophen-2-ylmethyl)methanamine (**L4**, 400 MHz, $CDCl_3$):



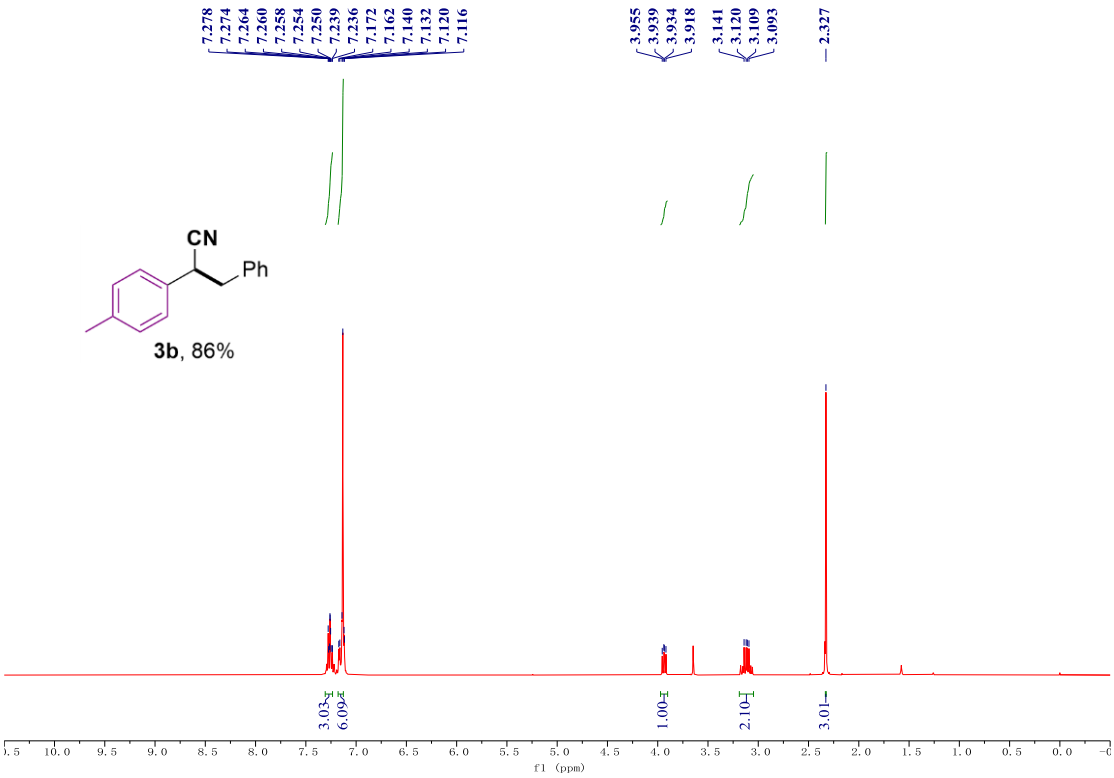
^{13}C NMR spectrum of 1-(1-Methyl-1H-benzo[d]imidazol-2-yl)-N-(thiophen-2-ylmethyl)metha -amine (**L4**, 100 MHz, $CDCl_3$):



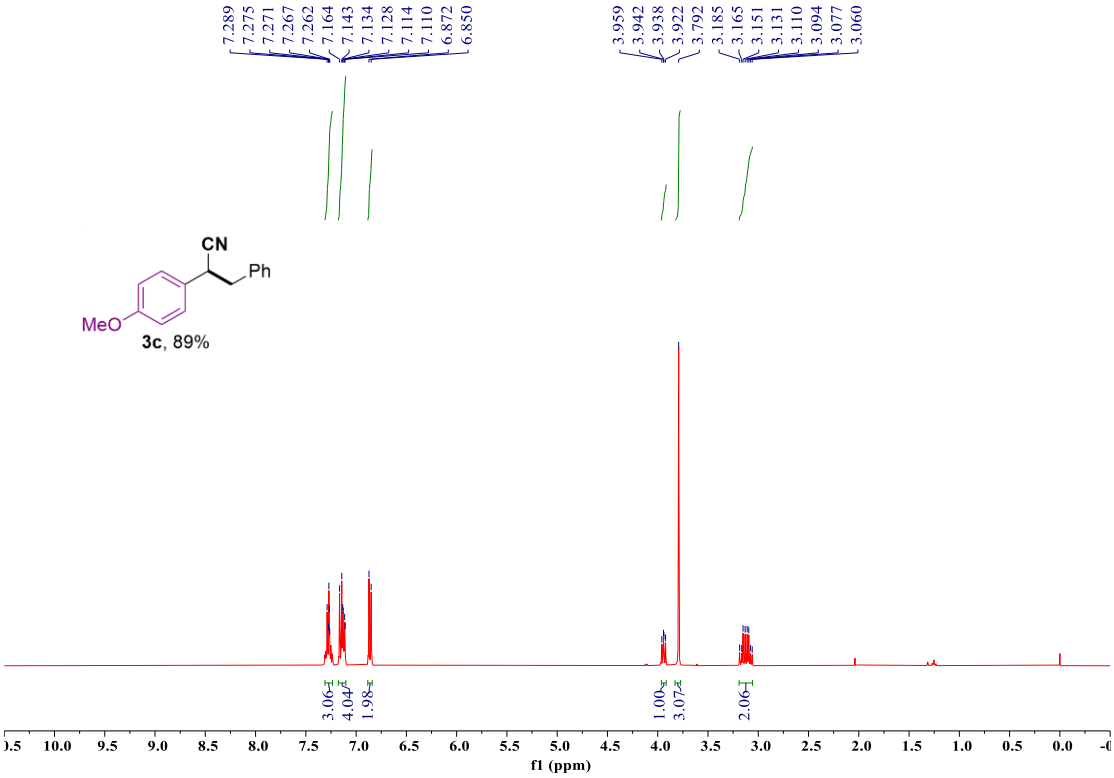
^{1}H NMR spectrum of 2,3-diphenylpropanenitrile (**3a**, 400 MHz, $CDCl_3$):



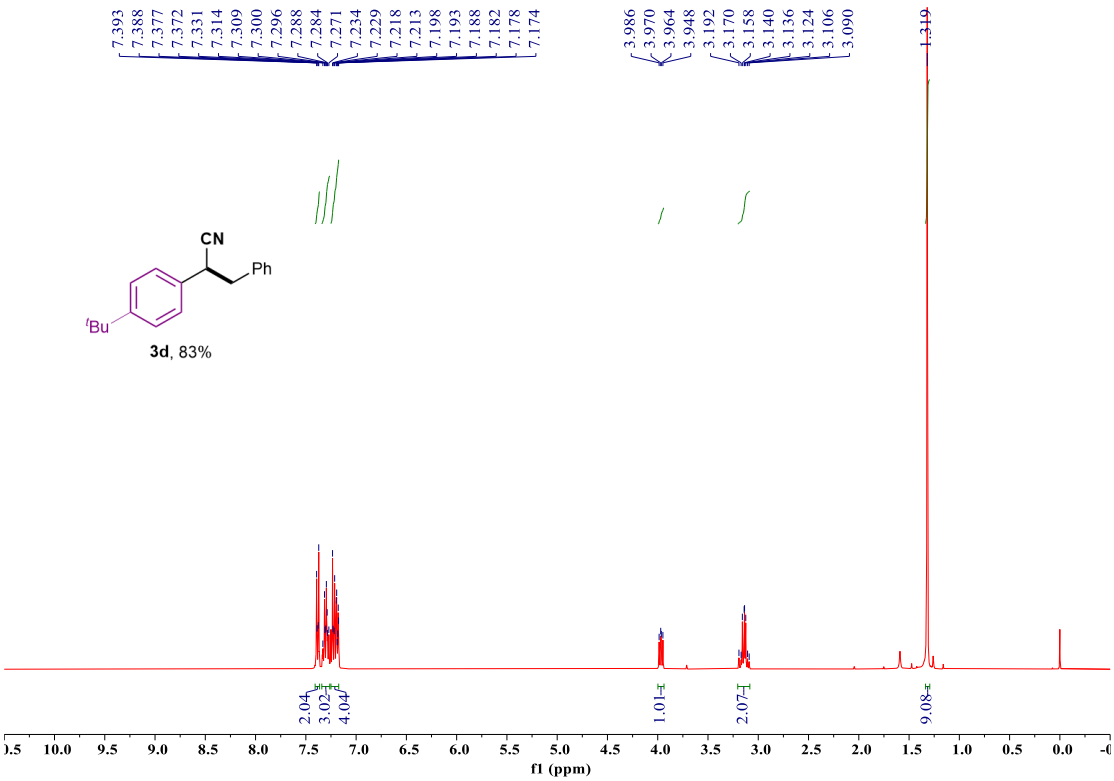
^{1}H NMR spectrum of 3-phenyl-2-(p-tolyl) propanenitrile (**3b**, 400 MHz, $CDCl_3$):



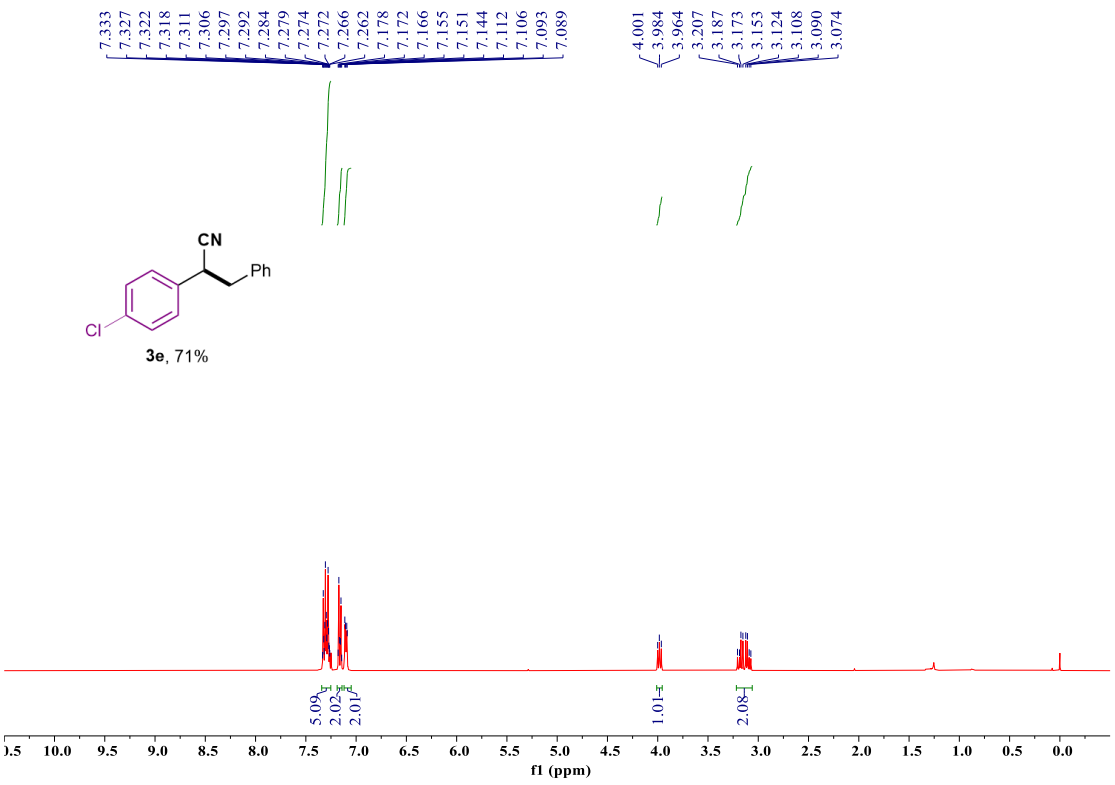
^{1}H NMR spectrum of 2-(4-methoxyphenyl)-3-phenylpropanenitrile (**3c**, 400 MHz, $CDCl_3$):



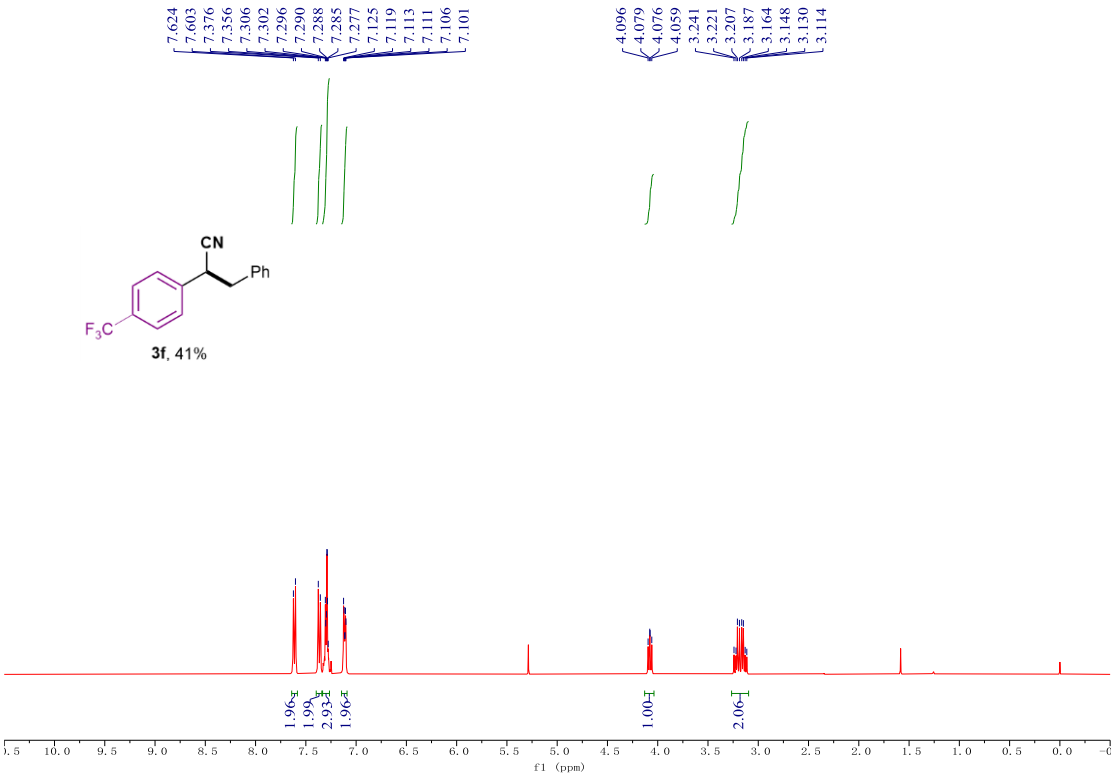
^{1}H NMR spectrum of 2-(4-(tert-butyl) phenyl)-3-phenylpropanenitrile (**3d**, 400 MHz, $CDCl_3$):



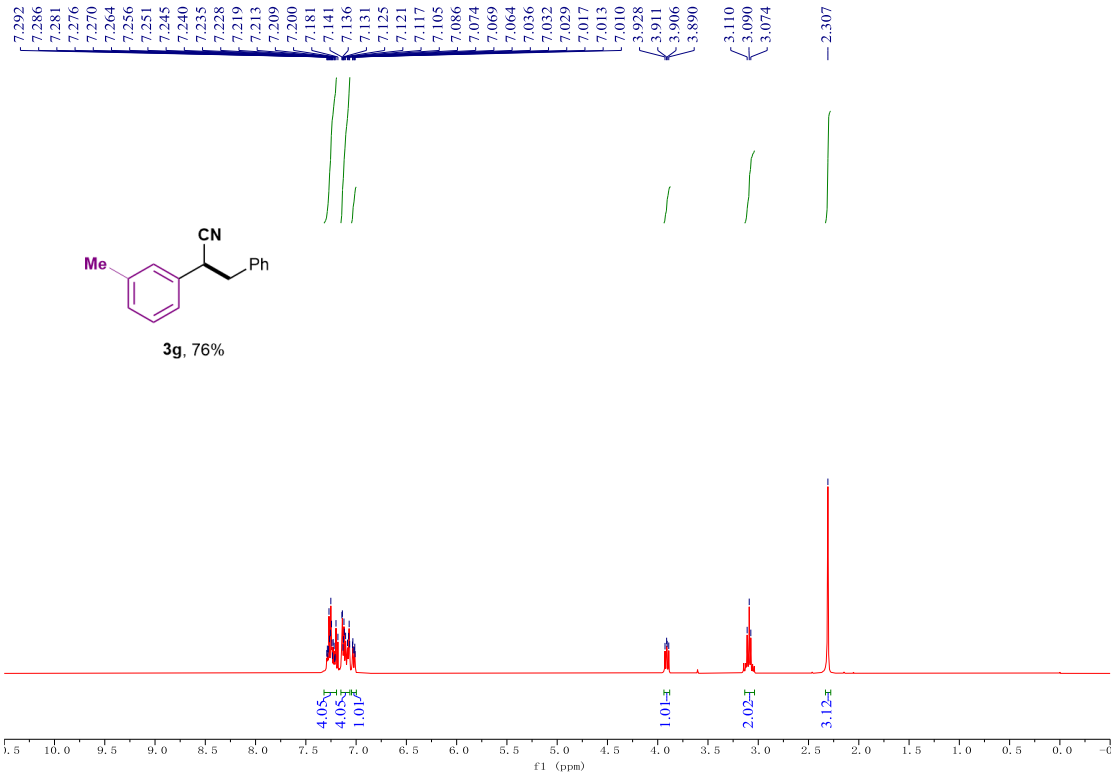
^{1}H NMR spectrum of 2-(4-chlorophenyl)-3-phenylpropanenitrile (**3e**, 400 MHz, $CDCl_3$):



^{1}H NMR spectrum of 3-phenyl-2-(4-(trifluoromethyl) phenyl) propanenitrile (**3f**, 400 MHz, $CDCl_3$):

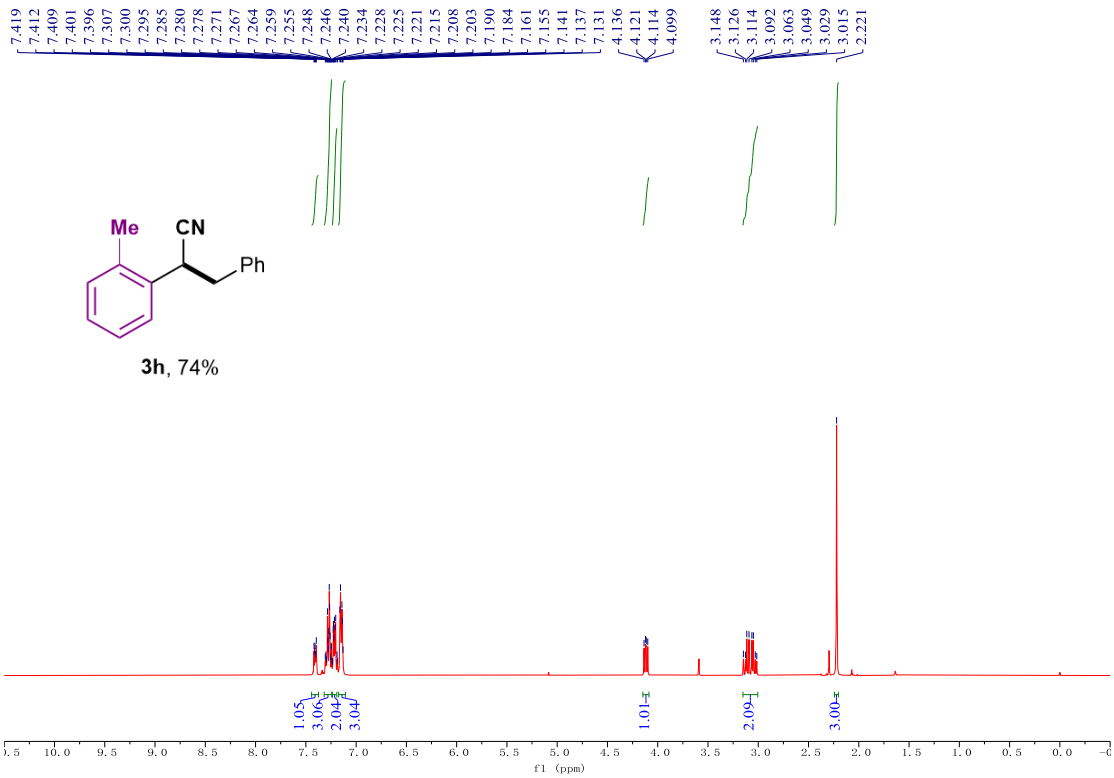


^{1}H NMR spectrum of 3-phenyl-2-(m-tolyl) propanenitrile (**3g**, 400 MHz, $CDCl_3$):



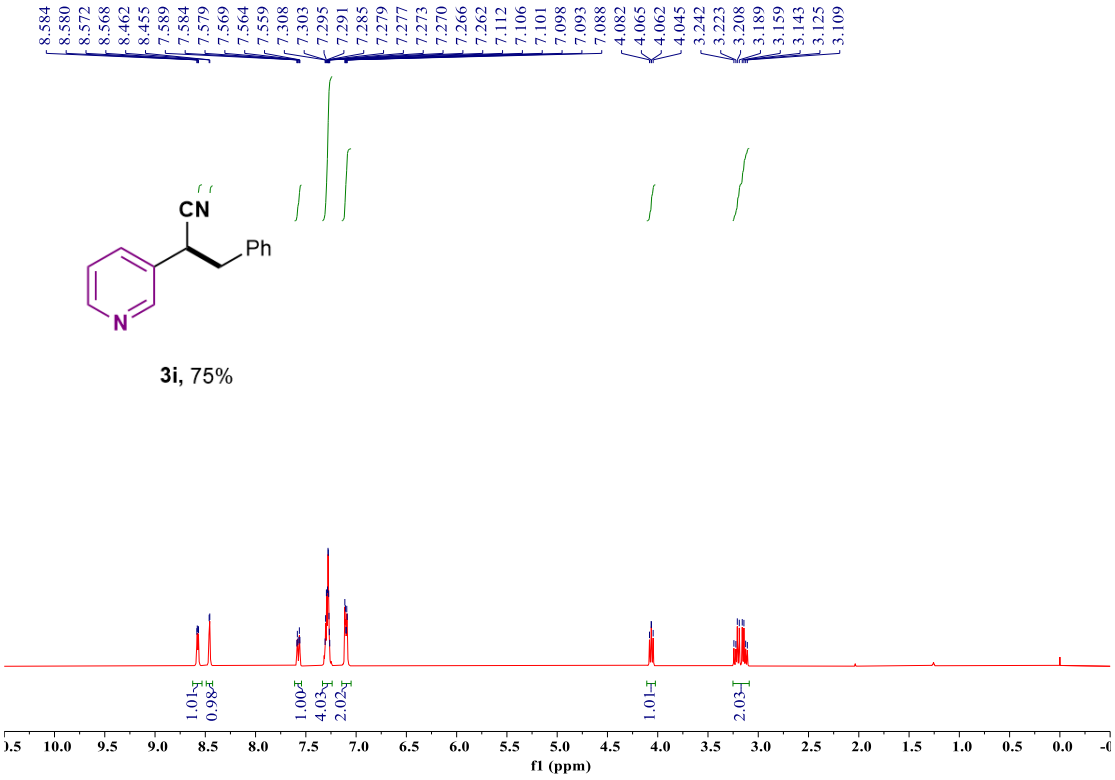
3g, 76%

^{1}H NMR spectrum of 3-phenyl-2-(p-tolyl) propanenitrile (**3h**, 400 MHz, $CDCl_3$) :



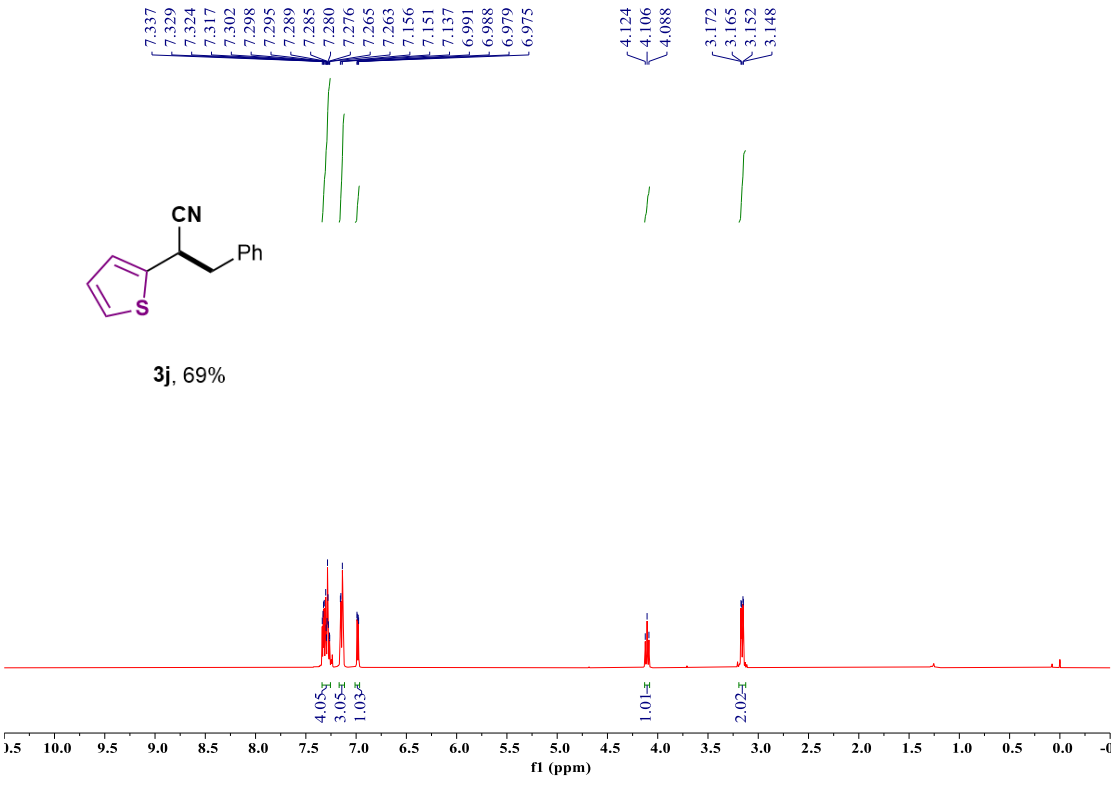
3h, 74%

^{1}H NMR spectrum of 3-phenyl-2-(pyridin-3-yl) propanenitrile (**3i**, 400 MHz, $CDCl_3$):



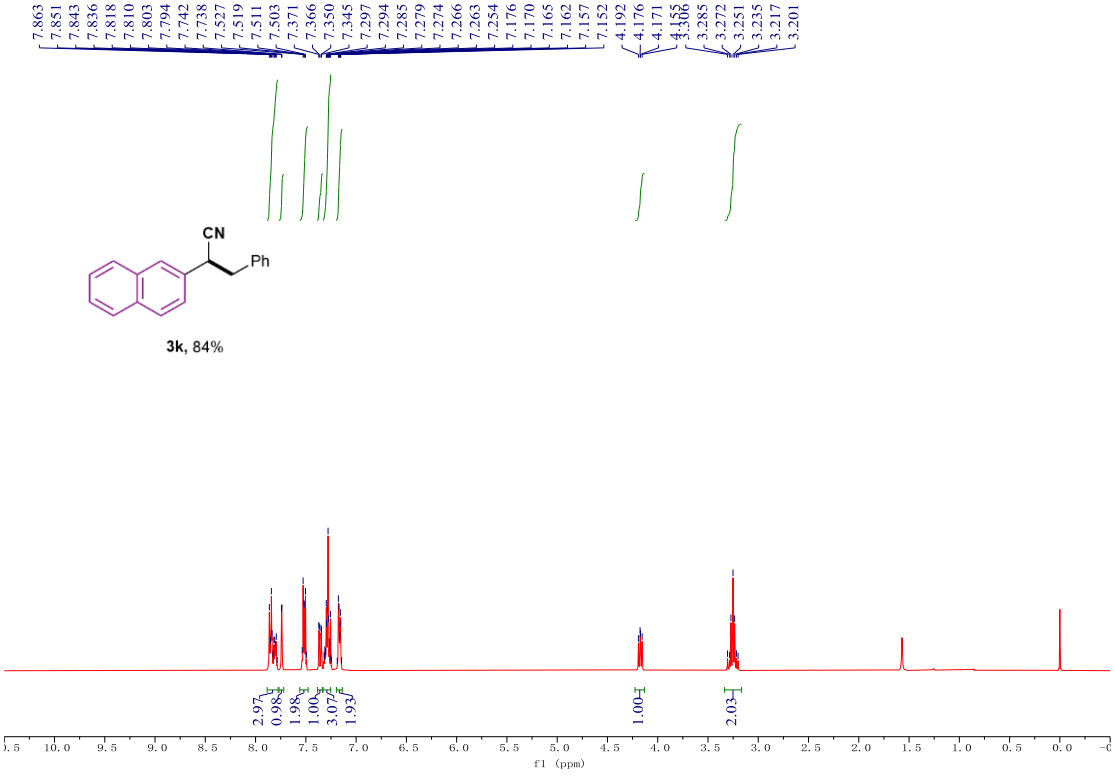
3i, 75%

^{1}H NMR spectrum of 3-phenyl-2-(thiophen-2-yl) propanenitrile (**3j**, 400 MHz, $CDCl_3$):

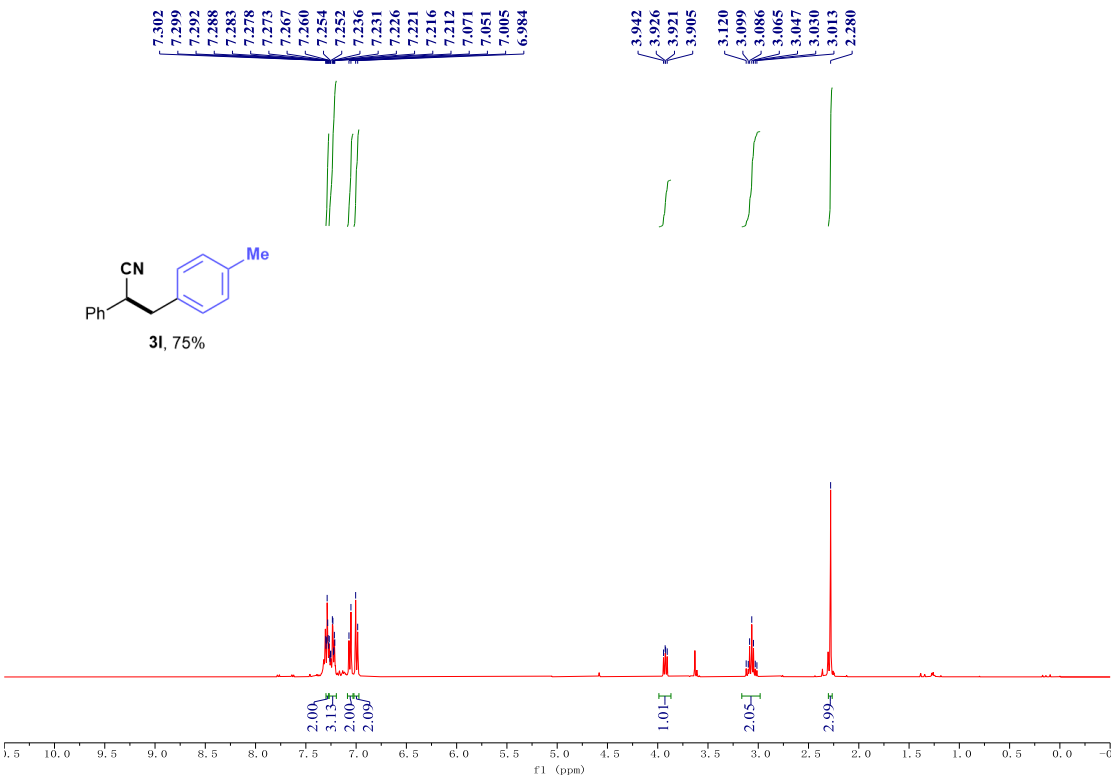


3j, 69%

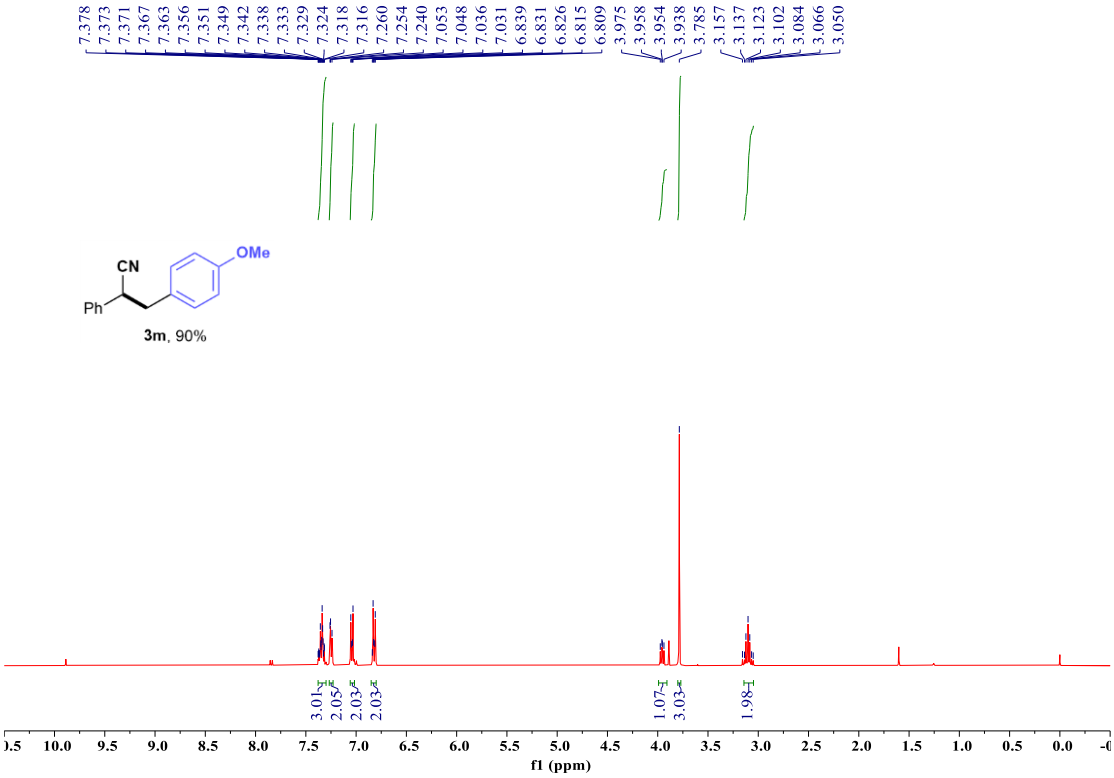
^{1}H NMR spectrum of 2-(naphthalen-2-yl)-3-phenylpropanenitrile (**3k**, 400 MHz, $CDCl_3$) :



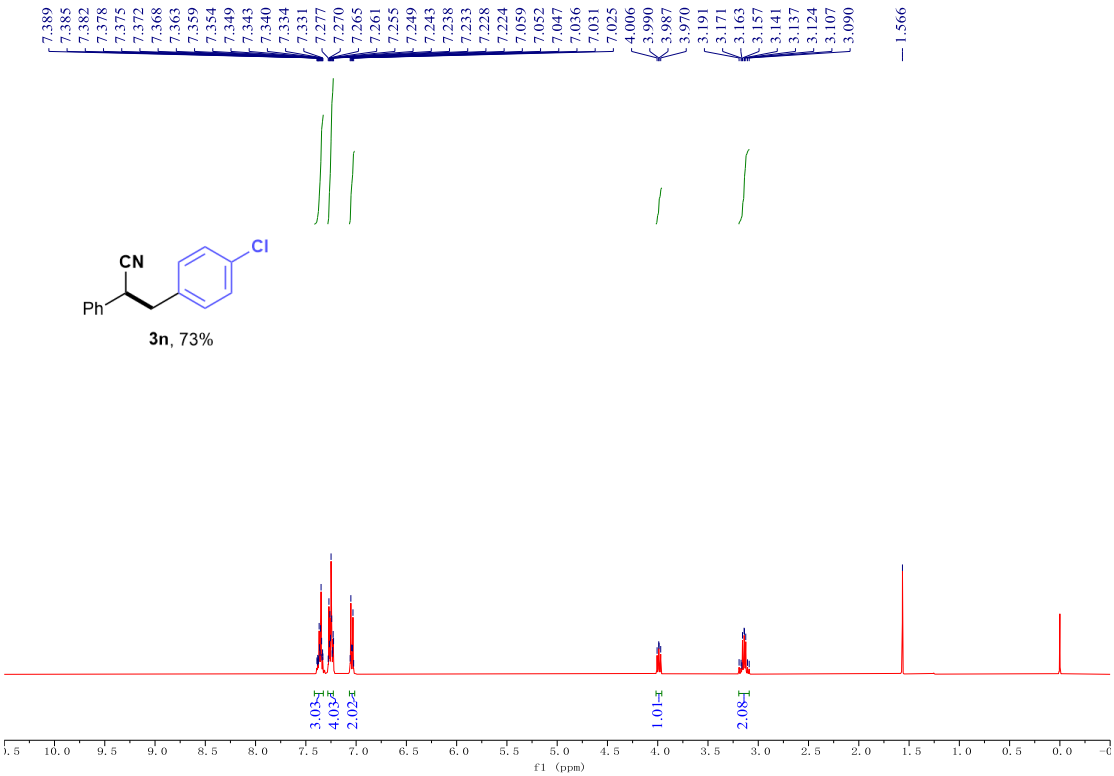
^{1}H NMR spectrum of 2-phenyl-3-(p-tolyl) propanenitrile (**3l**, 400 MHz, $CDCl_3$) :



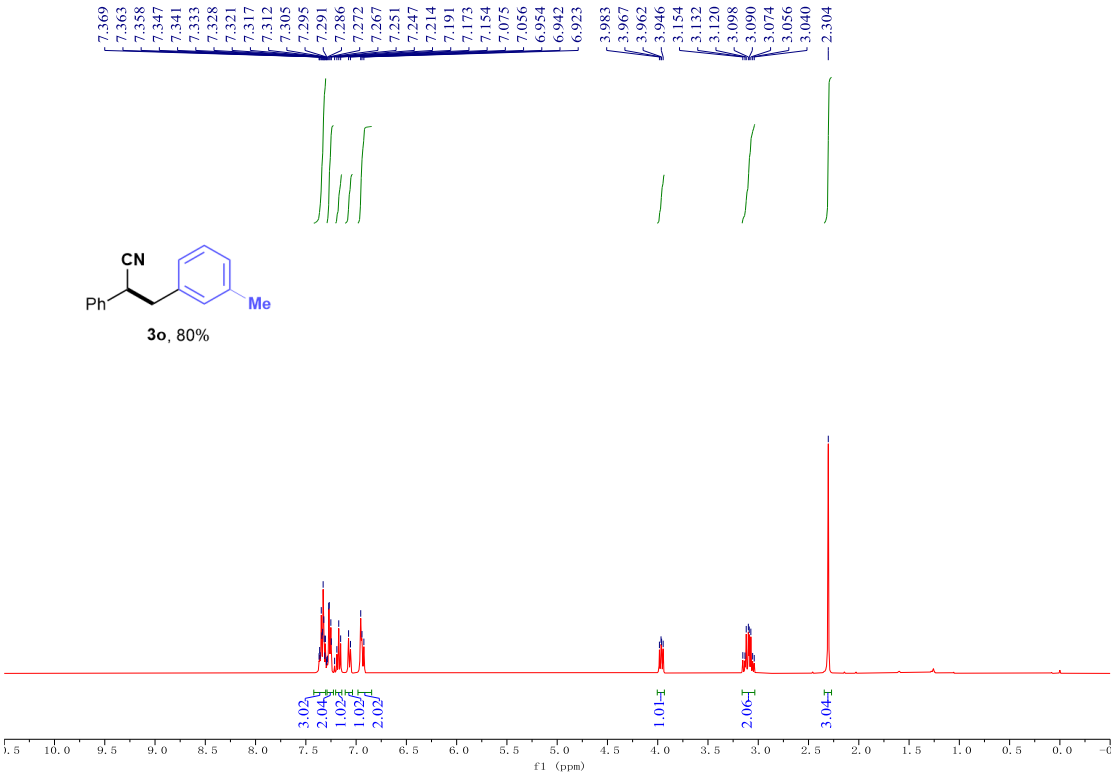
^{1}H NMR spectrum of 3-(4-methoxyphenyl)-2-phenylpropanenitrile (**3m**, 400 MHz, $CDCl_3$):



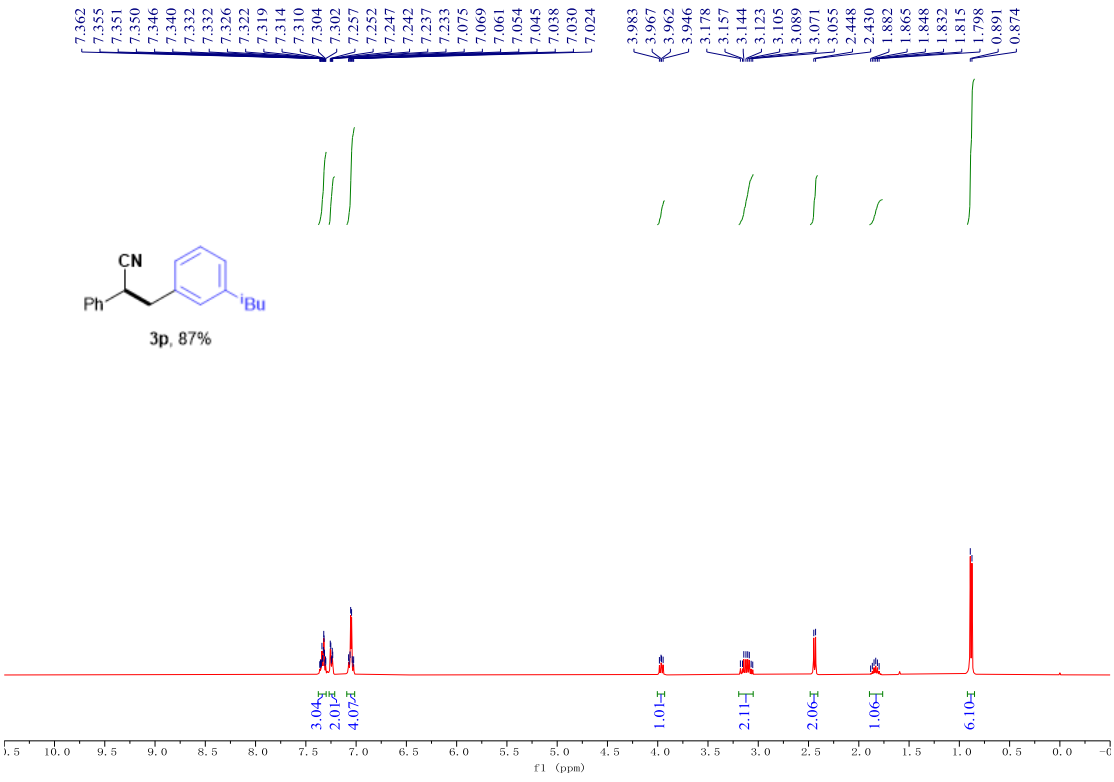
^{1}H NMR spectrum of 3-(4-chlorophenyl)-2-phenylpropanenitrile (**3n**, 400 MHz, $CDCl_3$) :



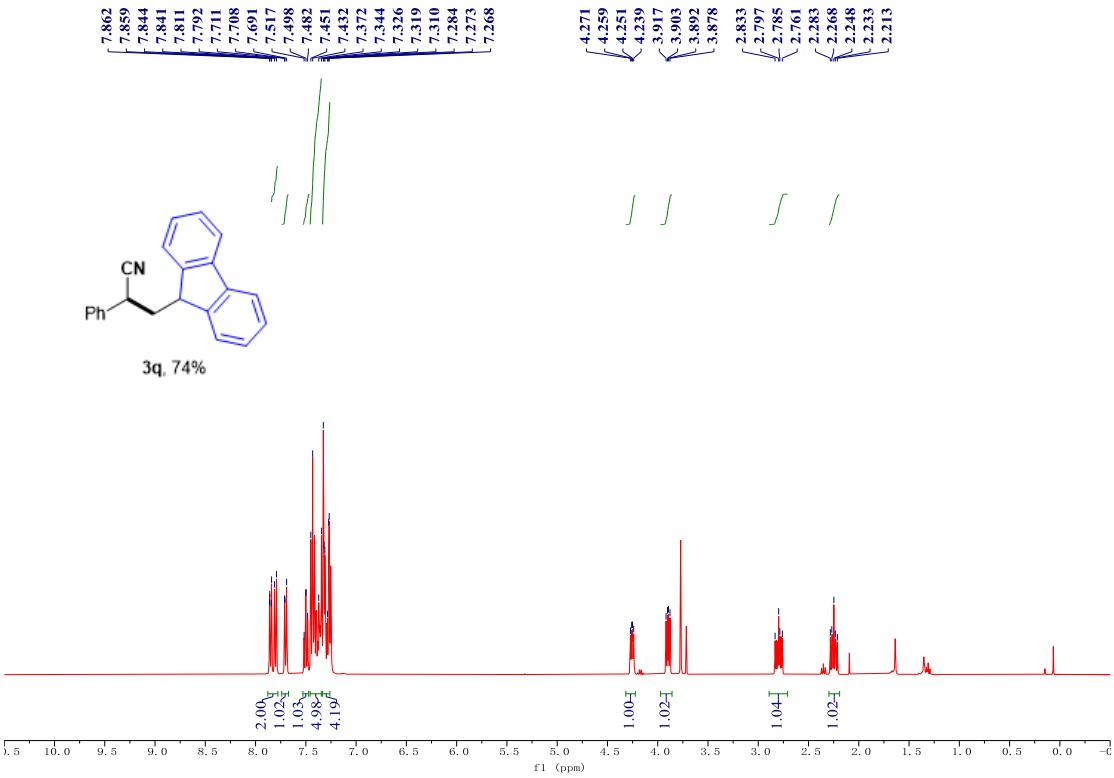
^{1}H NMR spectrum of 2-phenyl-3-(m-tolyl) propanenitrile (**3o**, 400 MHz, $CDCl_3$) :



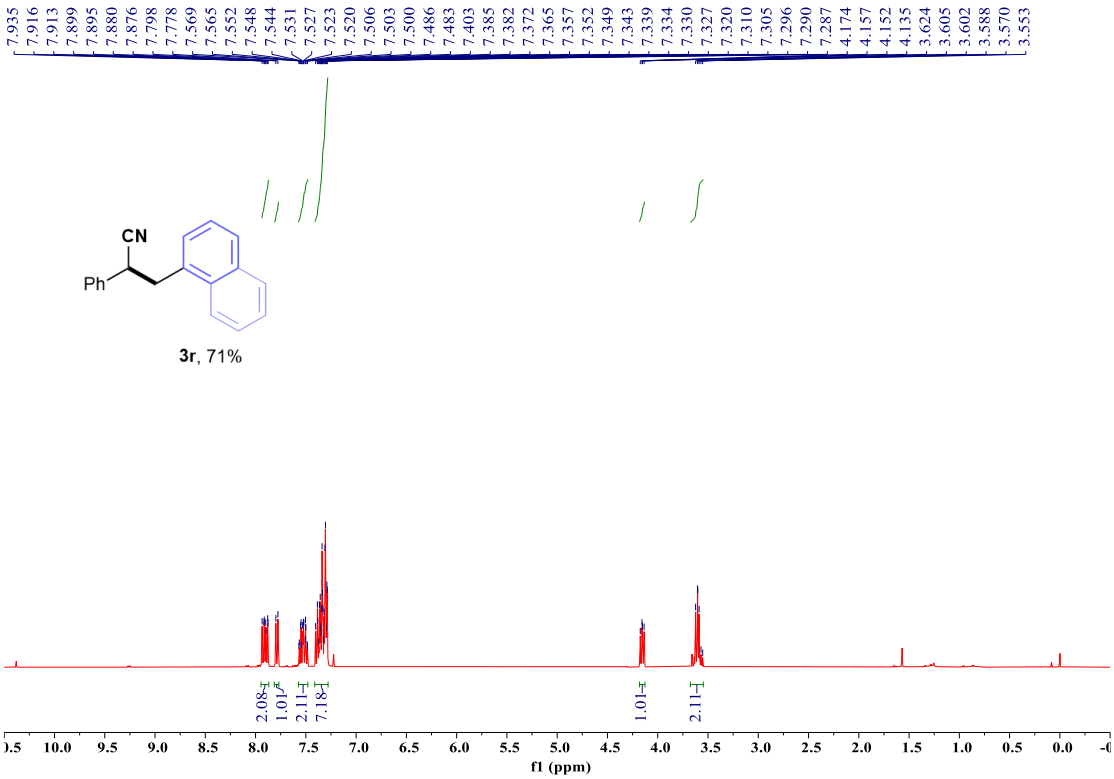
^{1}H NMR spectrum of 3-(4-isobutylphenyl)-2-phenylpropanenitrile (**3p**, 400 MHz, $CDCl_3$) :



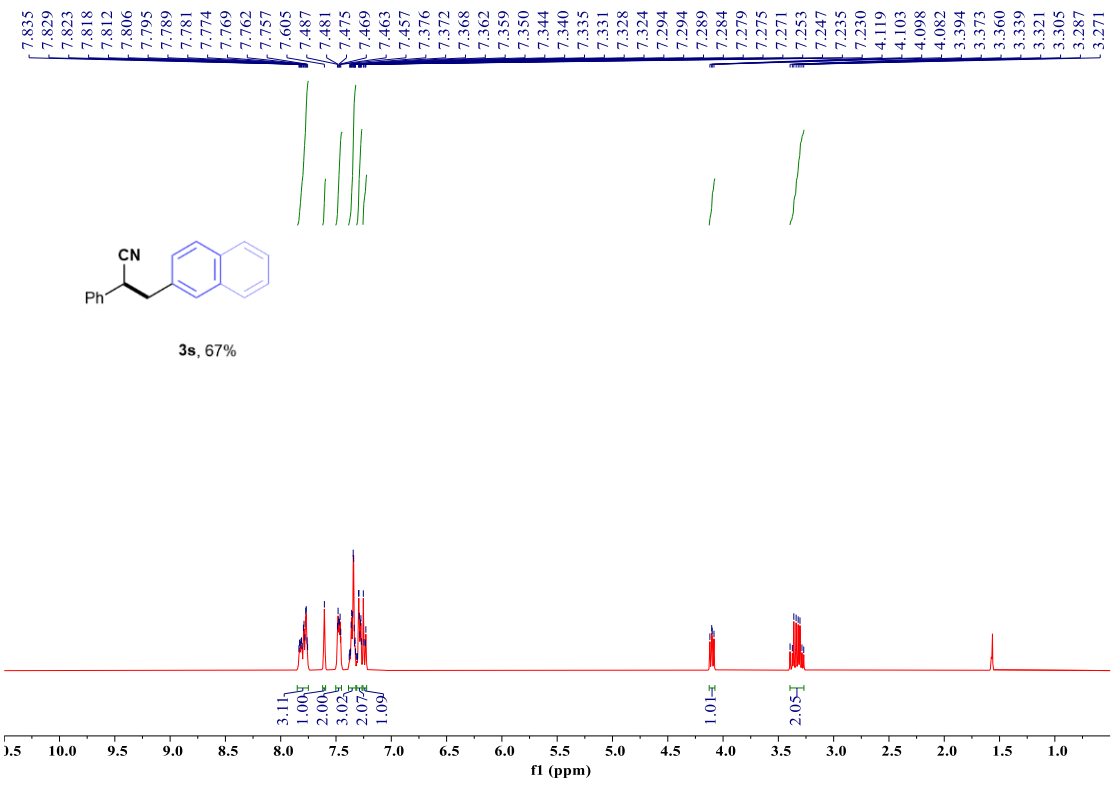
^{1}H NMR spectrum of 3-(9h-fluoren-9-yl)-2-phenylpropanenitrile (**3q**, 400 MHz, $CDCl_3$):



^{1}H NMR spectrum of 3-(naphthalen-1-yl)-2-phenylpropanenitrile (**3r**, 400 MHz, $CDCl_3$) :

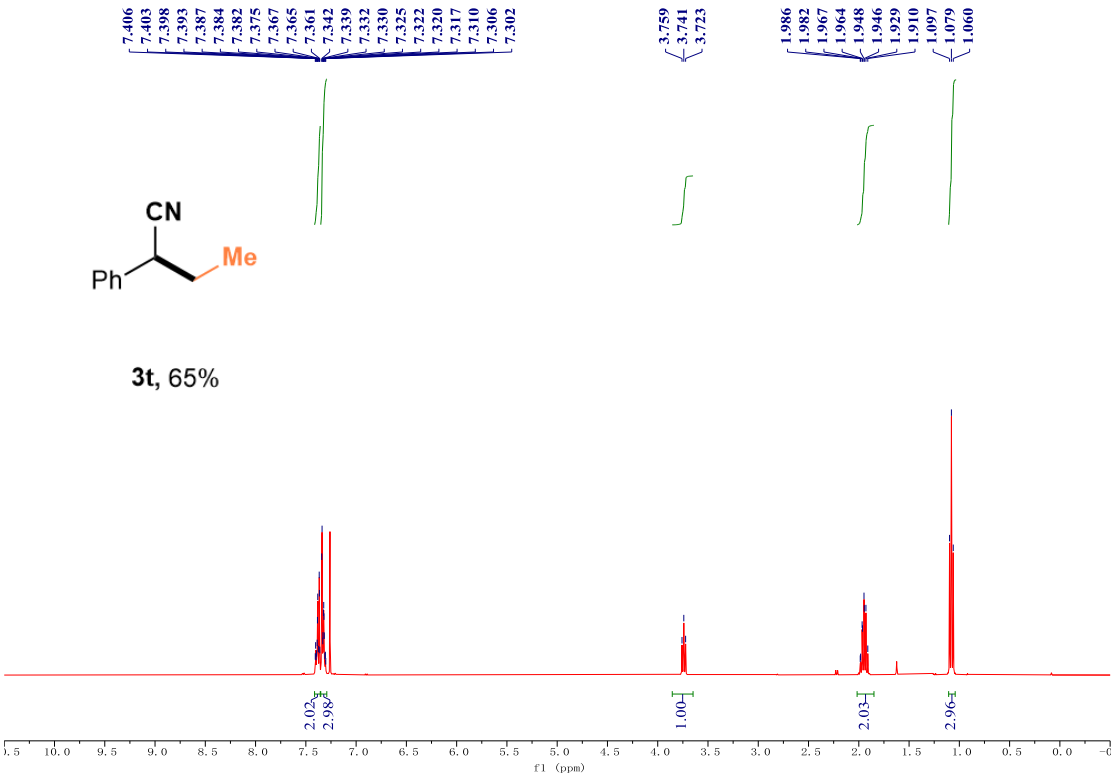


^{1}H NMR spectrum of 3-(naphthalen-2-yl)-2-phenylpropanenitrile (**3s**, 400 MHz, $CDCl_3$) :



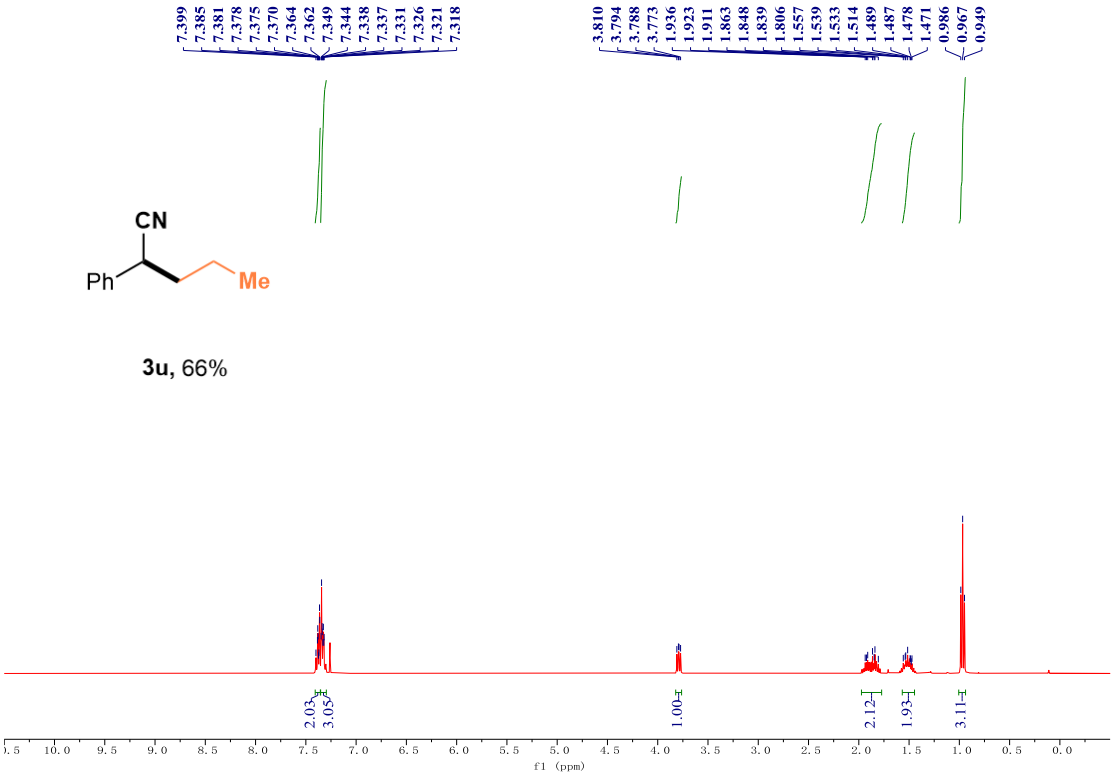
3s, 67%

^{1}H NMR spectrum of 2-phenylbutanenitrile (**3t**, 400 MHz, $CDCl_3$) :

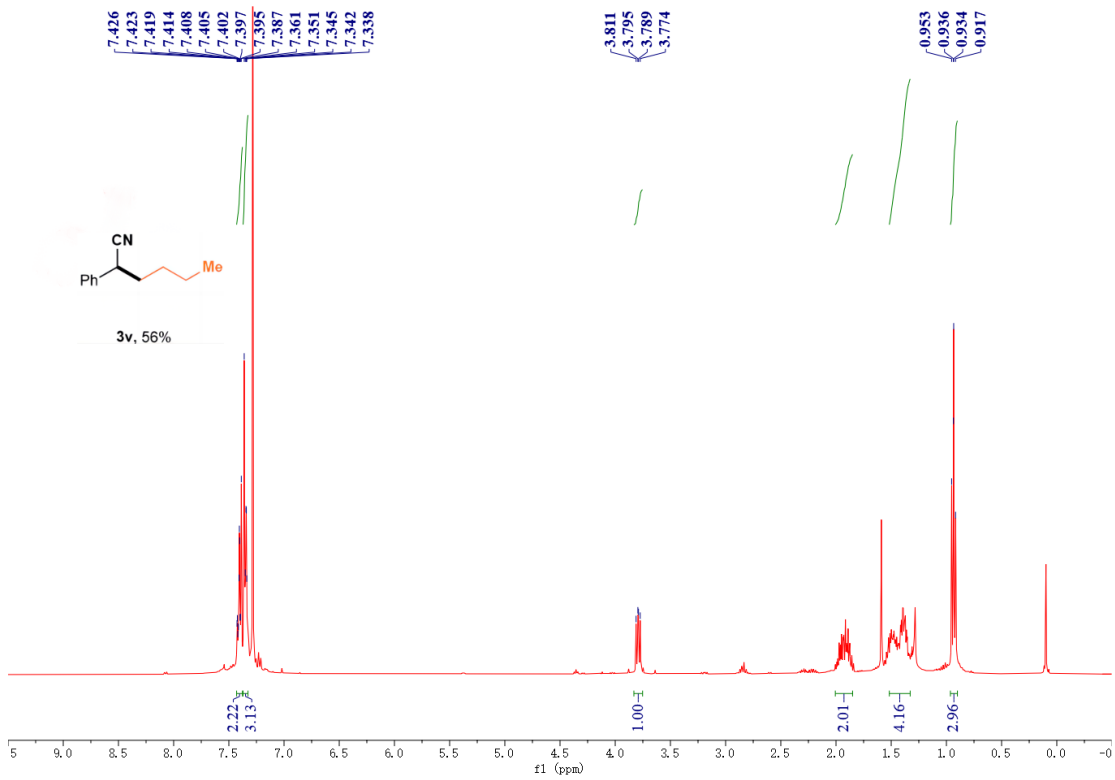


3t, 65%

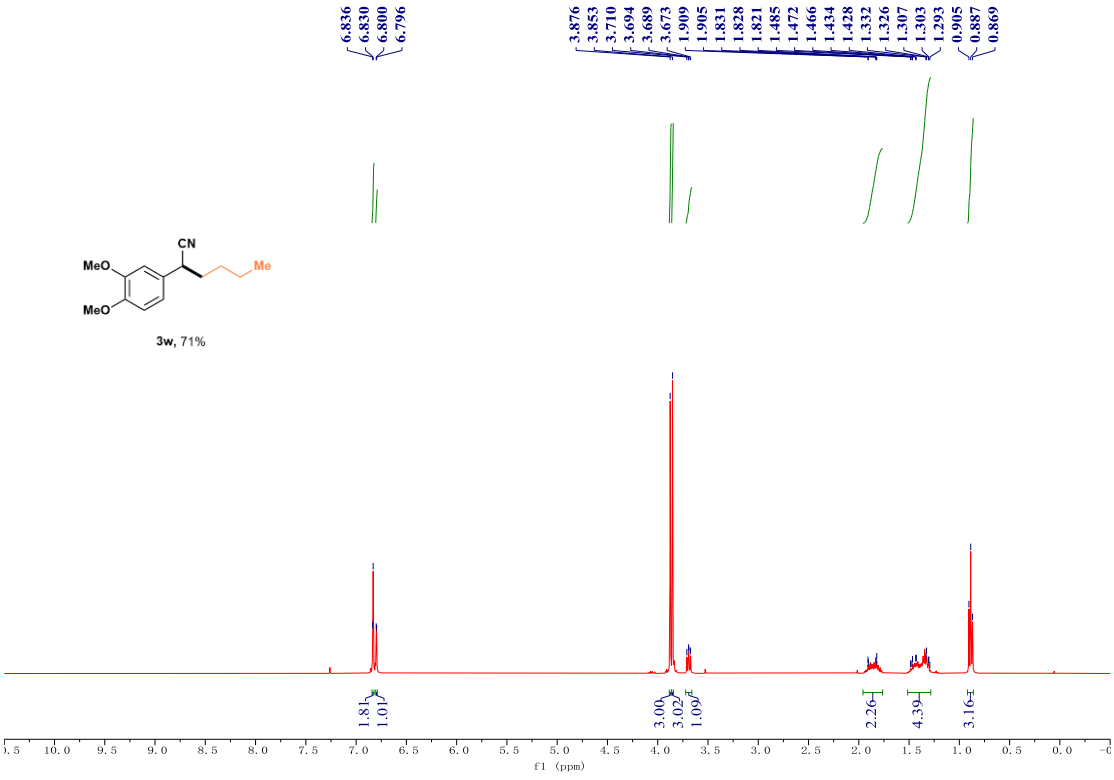
^{1}H NMR spectrum of 2-phenylpentanenitrile (**3u**, 400 MHz, $CDCl_3$) :



^{1}H NMR spectrum of 2-phenylhexanenitrile (**3v**, 400 MHz, $CDCl_3$) :

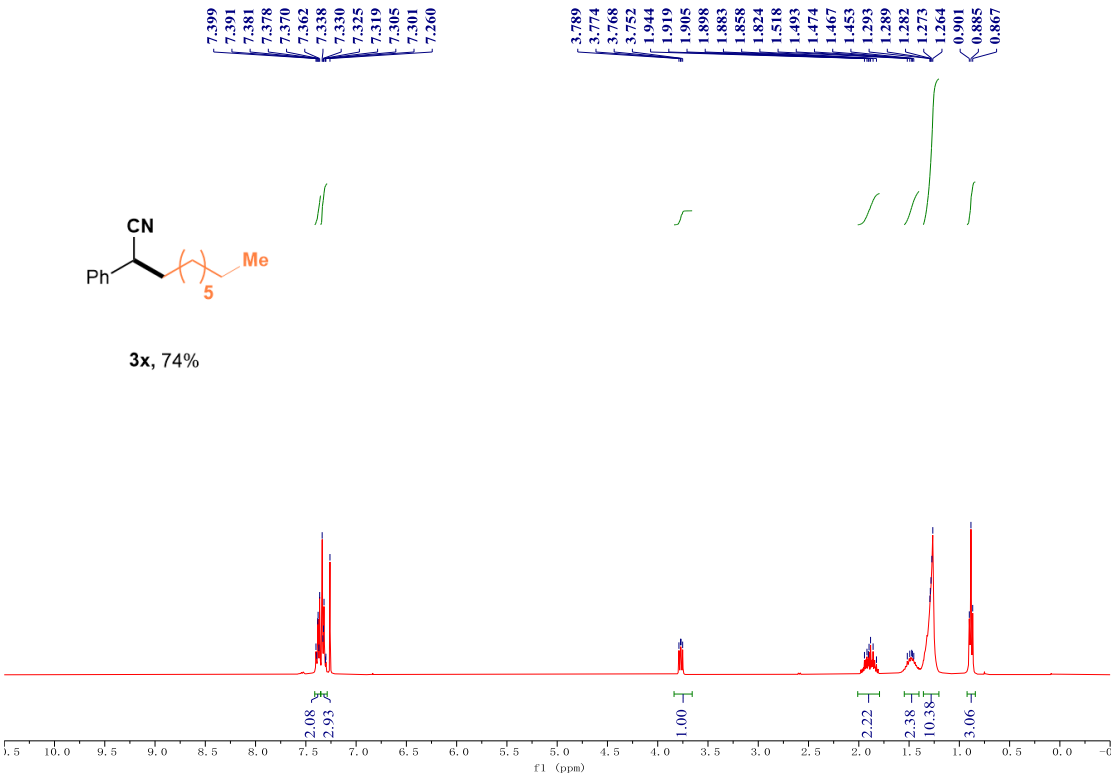


^{1}H NMR spectrum of 2-(3,4-dimethoxyphenyl) hexanenitrile (**3w**, 400 MHz, $CDCl_3$) :



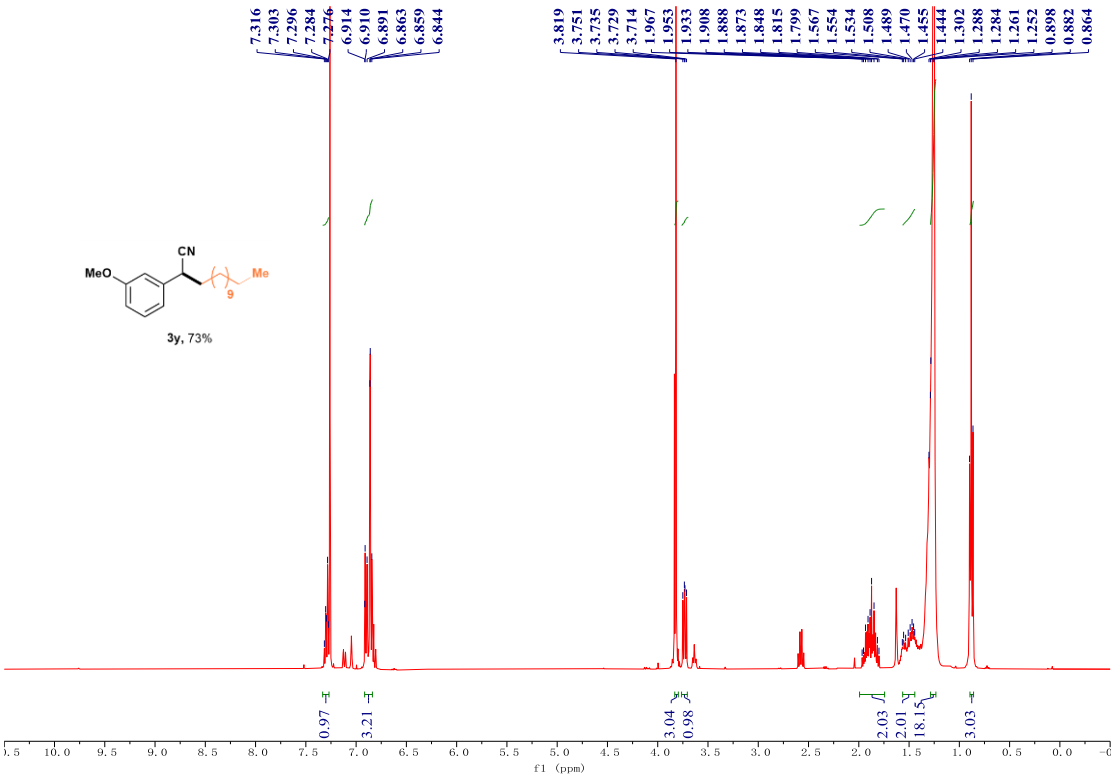
3w, 71%

^{1}H NMR spectrum of 2-phenyldecanenitrile (**3x**, 400 MHz, $CDCl_3$) :

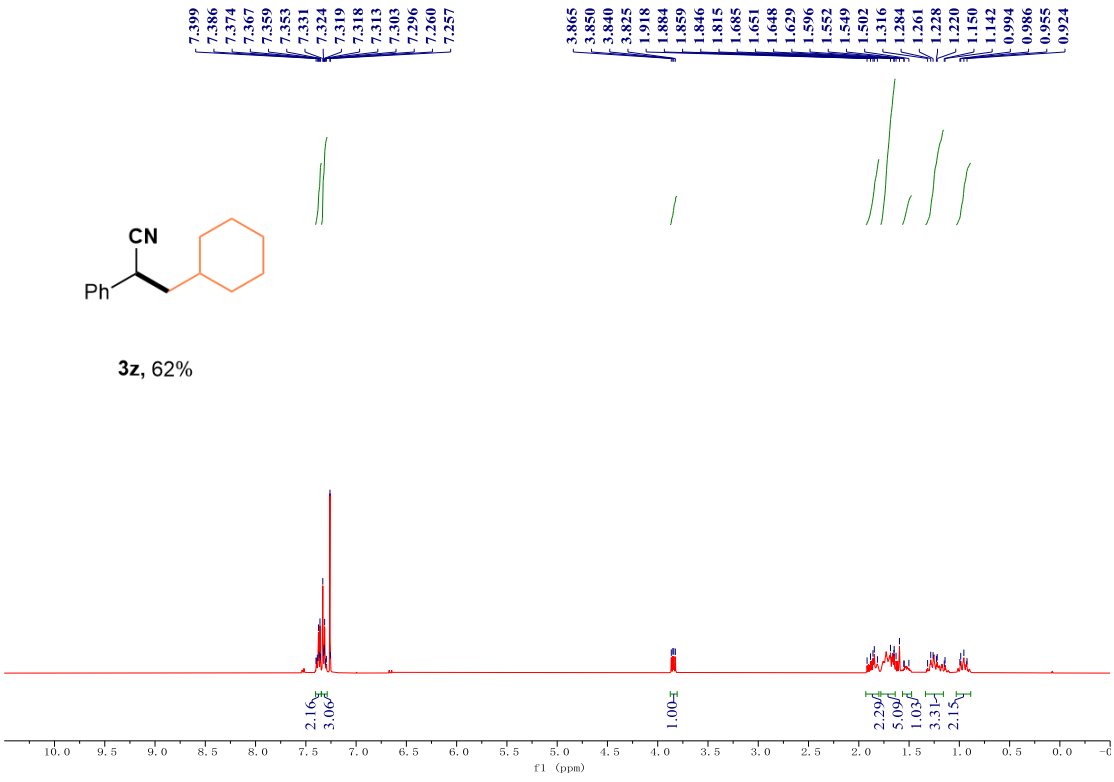


3x, 74%

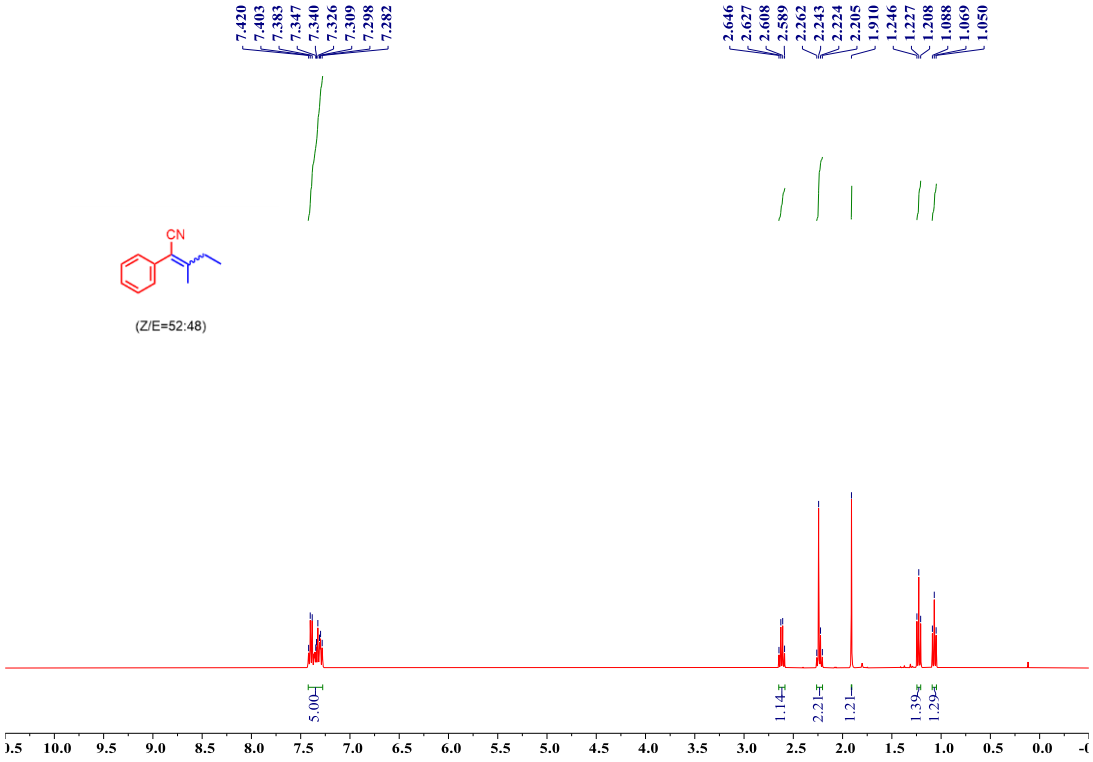
^{1}H NMR spectrum of 2-(3-methoxyphenyl) tetradecanenitrile (**3y**, 400 MHz, $CDCl_3$):



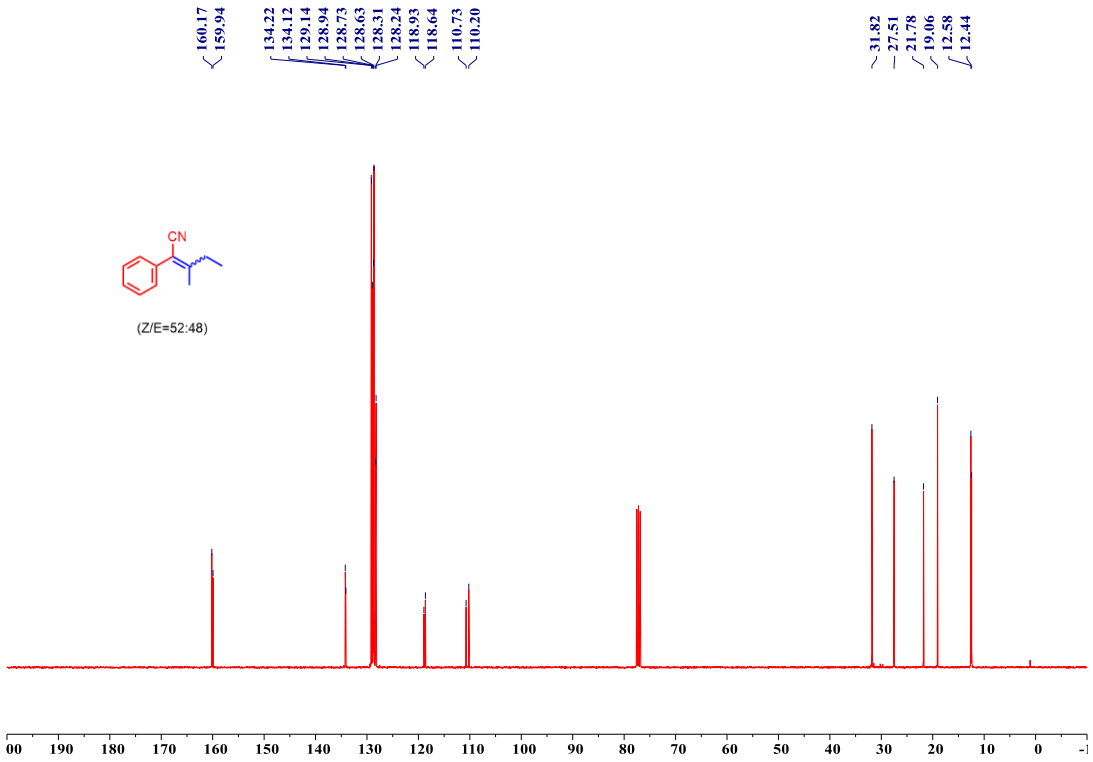
^{1}H NMR spectrum of 2-cyclohexyl-2-phenylacetonitrile (**3z**, 400 MHz, $CDCl_3$) :



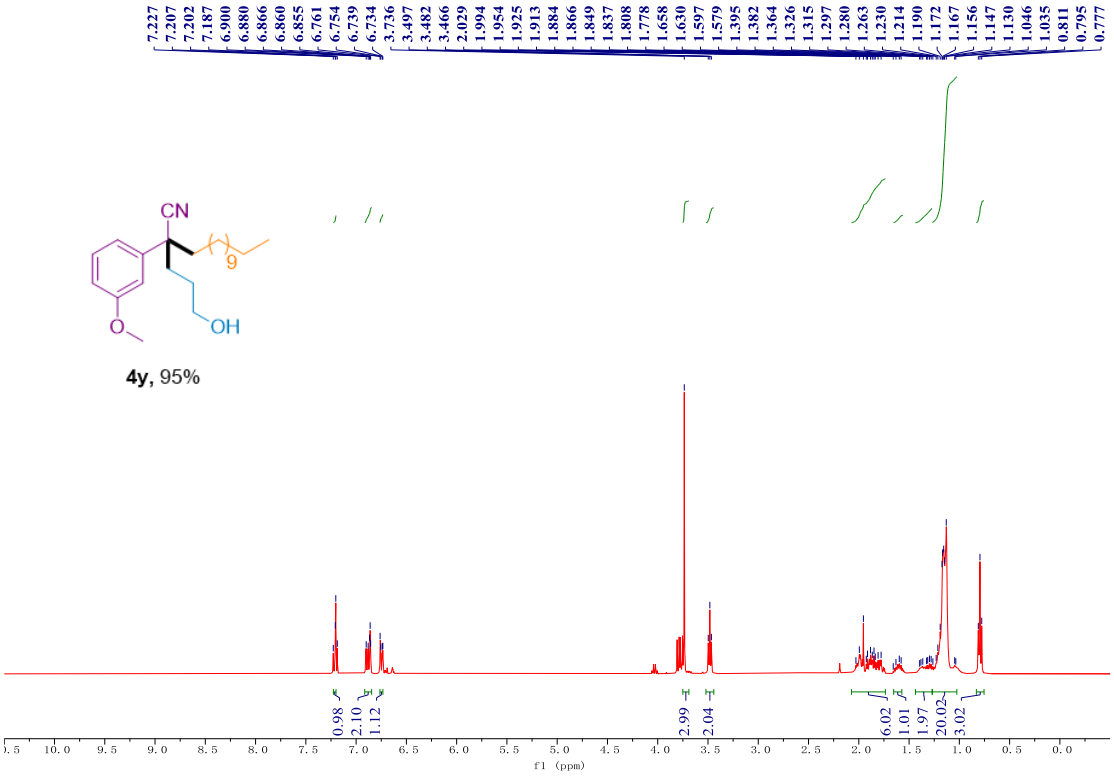
^{1}H NMR spectrum of 3-methyl-2-phenylpent-2-enenitrile (**3za**, 400 MHz, $CDCl_3$):



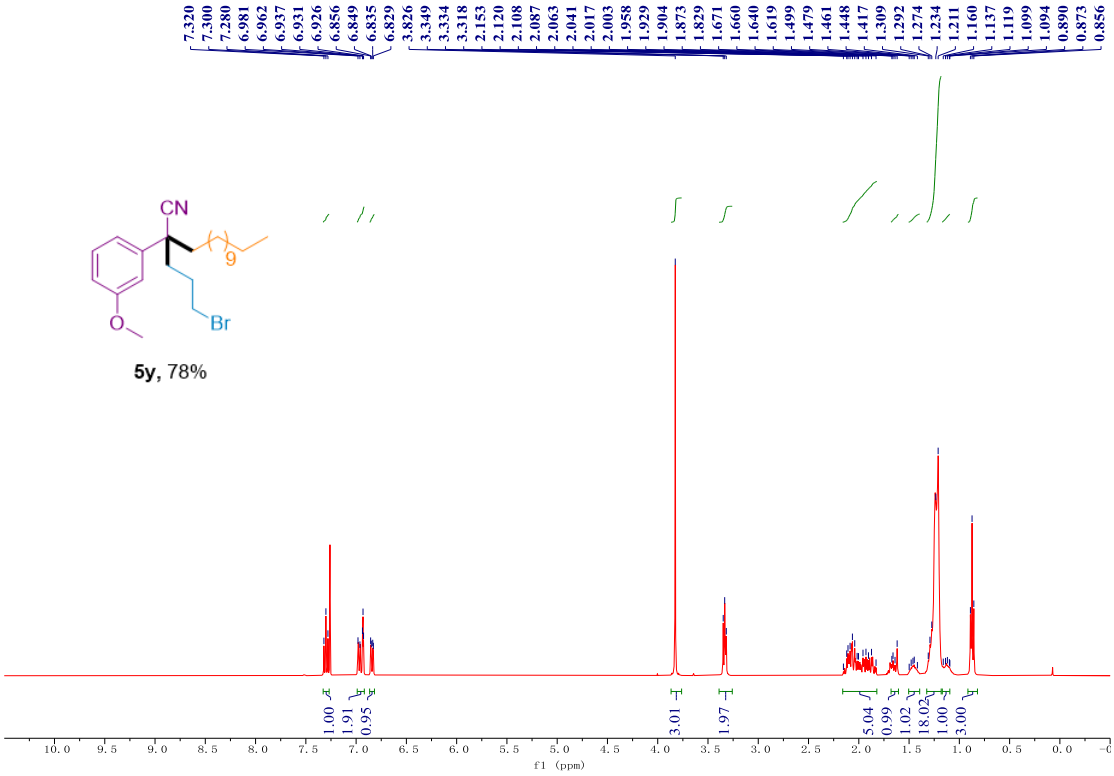
^{13}C NMR spectrum of 3-methyl-2-phenylpent-2-enenitrile (**3za**, 100 MHz, $CDCl_3$):



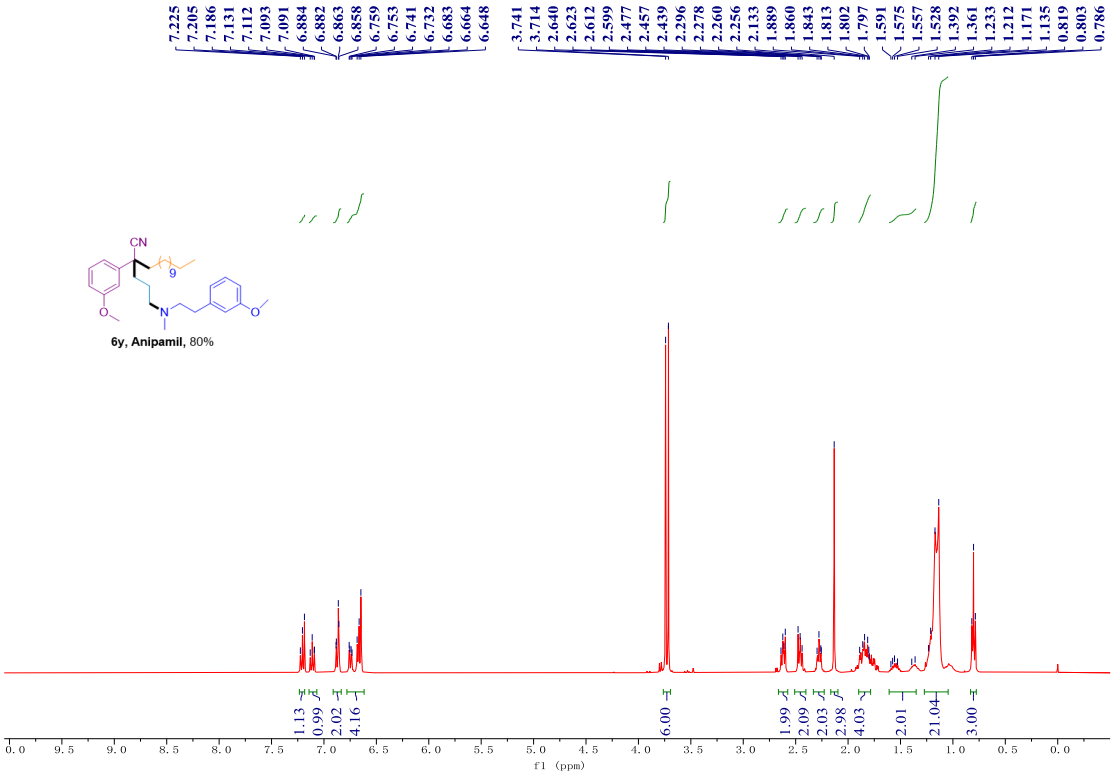
^{1}H NMR spectrum of 2-(3-hydroxypropyl)-2-(3-methoxyphenyl) tetradecanenitrile (**4y**, 400 MHz, $CDCl_3$):



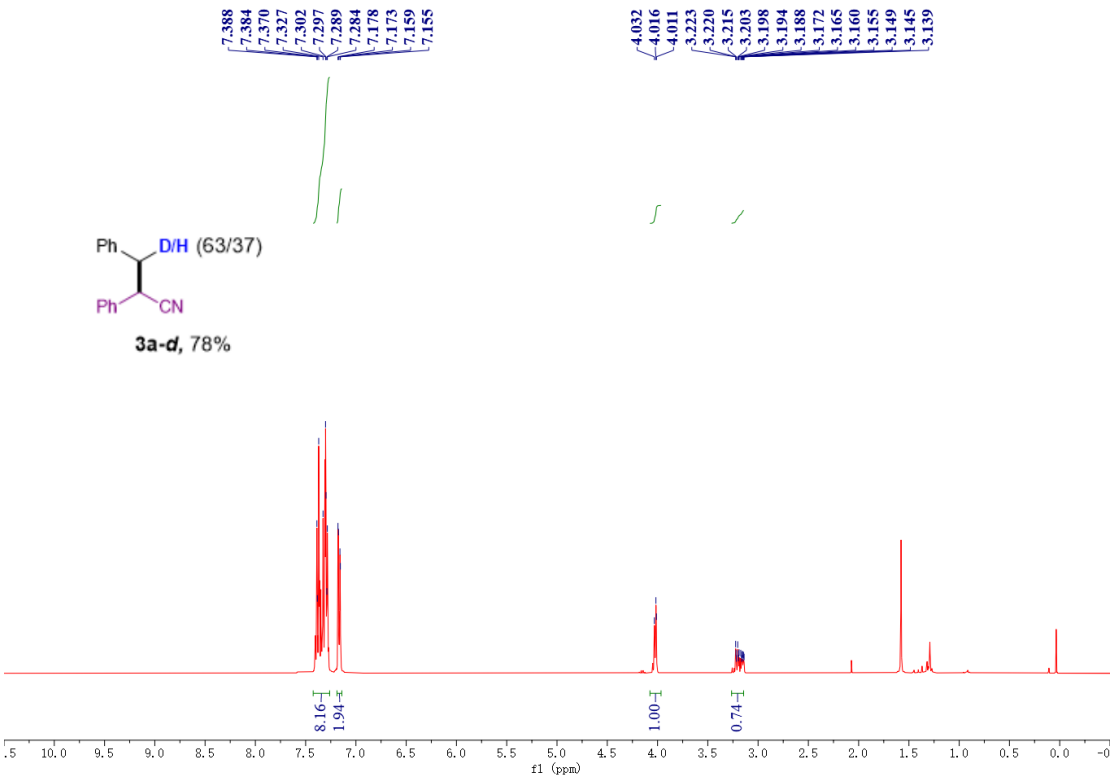
^{1}H NMR spectrum of 2-(3-bromopropyl)-2-(3-methoxyphenyl) tetradecanenitrile (**5y**, 400 MHz, $CDCl_3$):



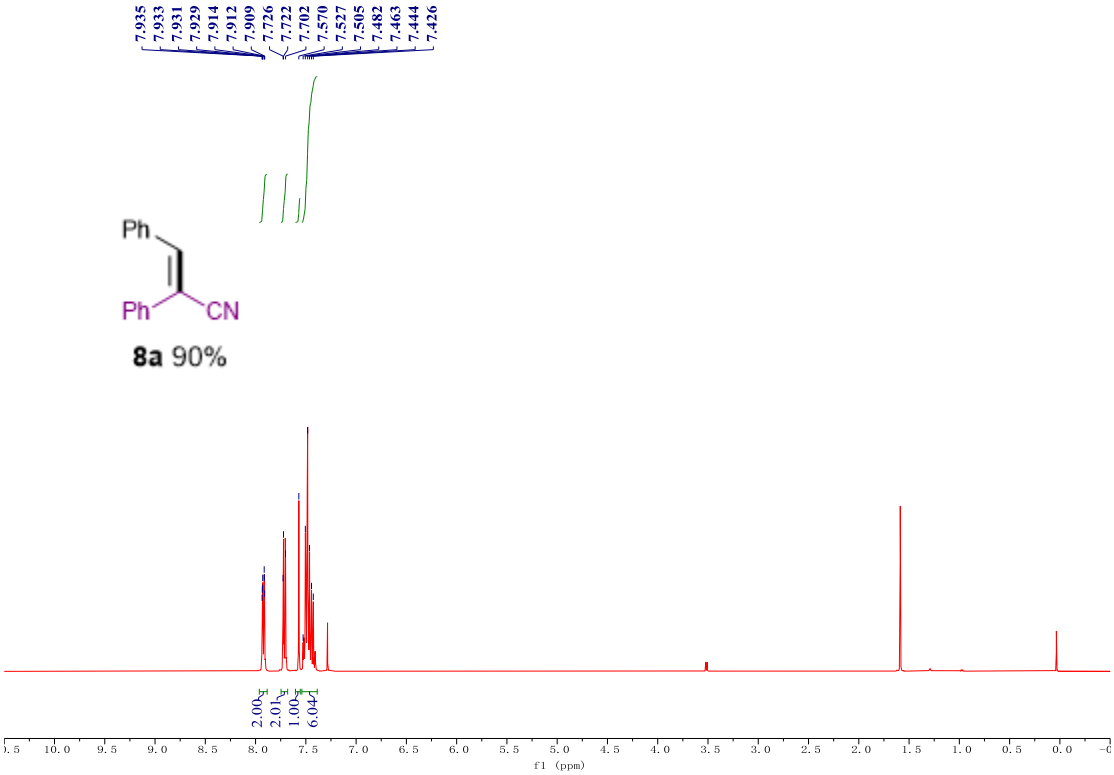
^{1}H NMR spectrum of 2-(3-((3-methoxyphenethyl) (methyl)amino) propyl)-2-(3-methoxyphenyl) tetradecanenitrile (**6y**, 400 MHz, $CDCl_3$):



^{1}H NMR spectrum of product (**3a-d**, 400 MHz, $CDCl_3$):



^{1}H NMR spectrum of product (**8a**, 400 MHz, $CDCl_3$):



^{1}H NMR spectrum of product (**3a-D**, 400 MHz, $CDCl_3$):