Supporting Information for

Visible Light-Driven Copper-Catalyzed C(sp^3)-O Cross-Coupling of Benzylic Radicals with Phenols

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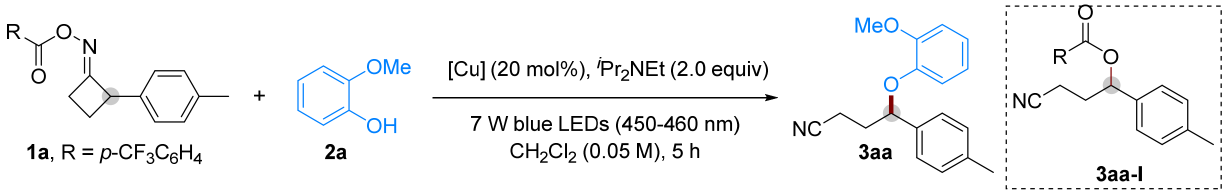
1. General Information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. All the solvents were treated according to general methods. Flash column chromatography was performed using 200-300 mesh silica gel. ^{1}H NMR spectra were recorded on 400 MHz spectrophotometers. Chemical shifts (δ) are reported in ppm from the resonance of tetramethyl silane as the internal standard (TMS: 0.00 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on 100 or 150 MHz with complete proton decoupling spectrophotometers. The high resolution mass spectra (HRMS) were measured on a Shimadzu LCMS-IT-TOF mass spectrometer or DIONEX UltiMate 3000 & Bruker Compact TOF mass spectrometer by ESI. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. And oxime esters were prepared according to literature.[1]

2. Detailed Optimization of Reaction Conditions and Control Experiments

2.1 Optimization of Reaction of Oxime Ester 1a with *o*-Methoxyphenol 2a

Table S1. Screening of the copper catalysts

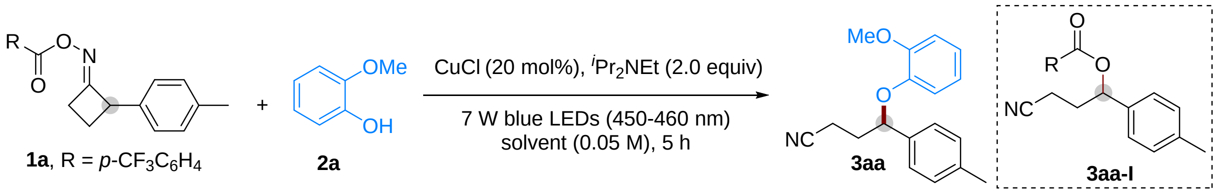


Entry[a]	[Cu]	Yield/3aa[b][%]	Yield/3aa-I[b][%]
1	CuCl	70	N.D.
2	CuTc	44	12
3	$Cu(CH_3CN)_4PF_6$	N.D.	52
4	Cu(OTf)(Toluene)/(2:1)	22	32
5	$Cu(OTf)_2$	43	39

[a] Unless otherwise noted, reactions were carried out with **1a** (34.7 mg, 0.1 mmol), **2a** (24.8 mg, 0.2 mmol), [Cu] (20 mol%) and ^{i}Pr$_2$NEt (25.8 mg, 2.0 equiv) in CH_2Cl_2 (2.0 mL) at rt under 7 W blue LEDs (450-460 nm). [b] Yields were determined by GC analysis using 1,1'-biphenyl as an internal standard.. CuTc = ((thiophene-2-carbonyl)oxy)copper(I); N.D. = not detected.

As shown in Table *S1*, among all the copper catalysts tested, CuCl gave the best results in terms of yield (70% yield), and was thus selected for further optimization studies.

Table *S2*. Screening of the solvents

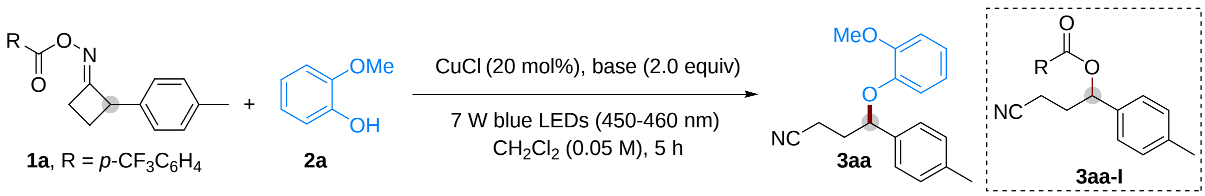


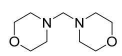
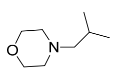
Entry[a]	Solvent	Yield/3aa[b][%]	Yield/3aa-I[b][%]
1	CH_2Cl_2	70	N.D.
2	CH_3CN	15	1
3	DCE	22	2
4	Toluene	27	13
5	THF	15	6
6	1,4-dioxane	18	9

[a] Unless otherwise noted, reactions were carried out with **1a** (34.7 mg, 0.1 mmol), **2a** (24.8 mg, 0.2 mmol), CuCl (1.98 mg, 20 mol%) and ^{i}Pr$_2$NEt (25.8 mg, 2.0 equiv) in solvent (2.0 mL) at rt under 7 W blue LEDs (450-460 nm). [b] Yields were determined by GC analysis using 1,1'-biphenyl as an internal standard. DCE = 1,2-dichloroethane; THF = Tetrahydrofuran; N.D. = not detected.

As show in Table ***S2***, among all the solvent tested, CH_2Cl_2 gave the best results in terms of yield (70% yield), and was thus selected for further optimization studies.

***Table S3*. Screening of bases**



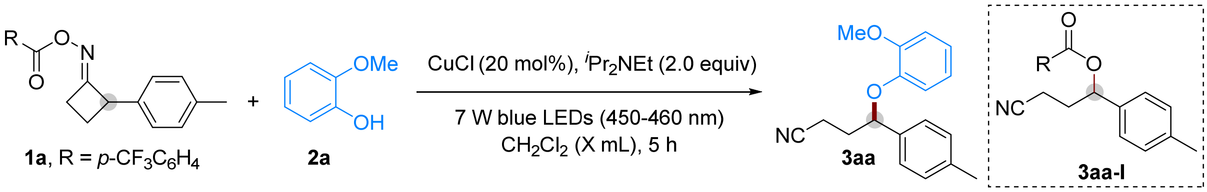
Entry[a]	Base	Yield/3aa[b][%]	Yield/3aa-I[b][%]
1	^{i}Pr$_2$NEt	70	N.D.
2		18	12
3		32	26
4	DABCO	10	9
5	NEt_3	35	7
6	TMEDA	7	8
7	Na_2CO_3	14	18

8	K_2CO_3	37	6

[a] Unless otherwise noted, reactions were carried out with **1a** (34.7 mg, 0.1 mmol), **2a** (24.8 mg, 0.2 mmol), CuCl (1.98 mg, 20 mol%) and base (2.0 equiv) in CH_2Cl_2 (2.0 mL) at rt under 7 W blue LEDs (450-460 nm, distance ca. 3 cm.). [b] Yields were determined by GC analysis using 1,1'-biphenyl as an internal standard. DABCO = 1,4-Diazabicyclo[2.2.2]octane; TMEDA = N,N,N',N'-Tetramethylethylenediamine; N.D. = not detected.

As shown in Table *S3*, among the base tested, ^{i}Pr$_2$NEt gave the best results (70% yield), and was thus selected for further studies.

Table S4. **Screening of concentration**



Entry[a]	Concentration (X mL)	Yield/3aa[b][%]	Yield/3aa-I[b][%]
1	0.1 M (1)	64	5
2	0.05 M (2)	71	N.D.
3	0.025 M (4)	60	3

[a] Unless otherwise noted, reactions were carried out with **1a** (34.7 mg, 0.1 mmol), **2a** (24.8 mg, 0.2 mmol), CuCl (1.98 mg, 20 mol%) and ^{i}Pr$_2$NEt (25.8 mg, 2.0 equiv) in CH_2Cl_2 (X mL) at rt under 7 W blue LEDs (450-460 nm, distance ca. 3 cm.). [b] Yields were determined by GC analysis using 1,1'-biphenyl as an internal standard. N.D. = not detected.

As shown in Table *S4*, among the concentration tested, 0.05 M gave the best result in terms of yield and the optimal condition was confirmed.

2.2 Control Experiments

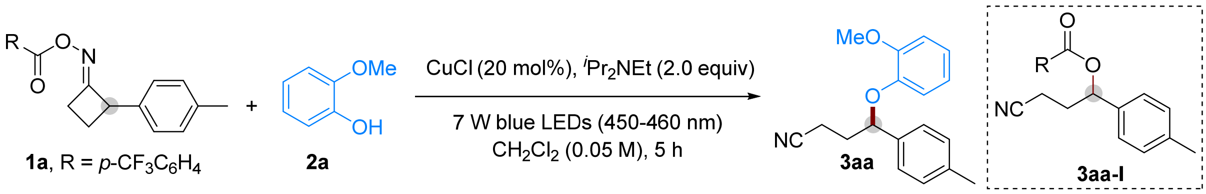


Table *S5*. Control experiments

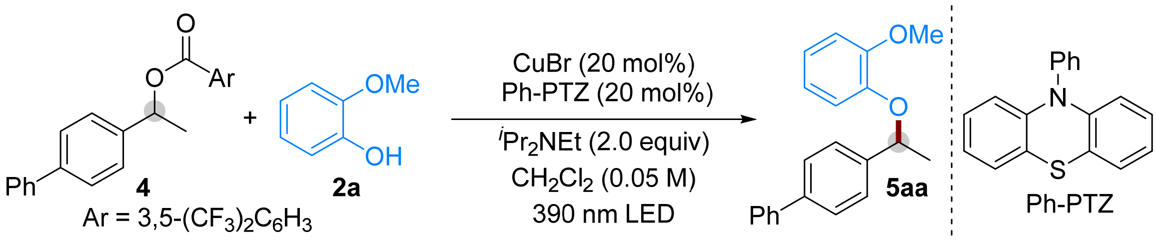
Entry[a]	[Cu]	hv	base	Yield/3aa[b] [%]	Yield/3aa-I[b] [%]
1[c]	-	+	+	No reaction	38
2[d]	+	-	+	57	N.D.
3[e]	+	+	-	18	20
4	+	+	+	71	N.D.

[a] Unless otherwise noted, reactions were carried out with **1a** (34.7 mg, 0.1 mmol), **2a** (24.8 mg, 0.2 mmol), CuCl (1.98 mg, 20 mol%) and $^{i}Pr_2NEt$ (25.8 mg, 2.0 equiv) in CH_2Cl_2 (2.0 mL) at rt under 7 W blue LEDs (450-460 nm, distance ca. 3 cm.). [b] Yields were determined by GC analysis using 1,1'-biphenyl as an internal standard. [c] Without Cu. [d] No visible light irradiation. [e] Without base. N.D. = not detected.

The results of Table S5 reveal that Copper is necessary, and lighting can improve the yield.

2.3 Optimization of Reaction of Benzylic Ester with *o*-Methoxyphenol

Table S6. Condition optimization[a]



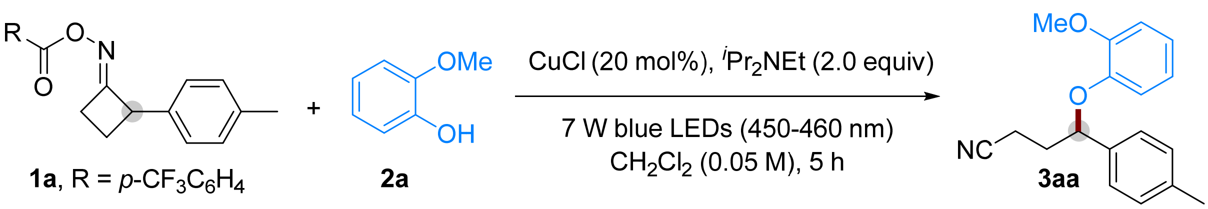
Entry[a]	Variation from the standard conditions	Yield[b][%]
1	none	50
2	CuCl instead of CuBr	40
	$Cu(OTf)_2$ instead of CuBr	35
	no CuBr	0
3	no Ph-PTZ	0

[a] Unless otherwise noted, reactions were carried out with **4a** (0.2 mmol,87.7 mg), **2a** (0.4 mmol, 49.6 mg), CuBr (3.96 mg, 20 mol%), Ph-PTZ (4.74 mg, 20 mol%) and $^{i}Pr_2NEt$ (51.6 mg, 2.0 equiv) in CH_2Cl_2 (4.0 mL) at rt under 390 nm LED. [b] Isolated yield.

The results of Table S6 reveal that both copper catalyst and photocatalyst are essential for this reaction.

3. General Procedure and Spectral Data of Products

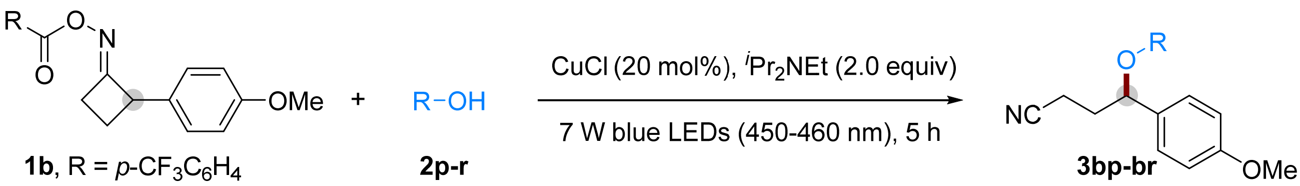
3.1 General Procedure for Synthesis of 3



To a stirred solution of CuCl (3.96 mg, 20 mol%) in CH_2Cl_2 (4.0 mL) under nitrogen was added **2a** (49.6 mg, 0.4 mmol) and $^{i}Pr_2NEt$ (51.6 mg, 2.0 equiv). And **1a** (69.4 mg, 0.2 mmol) were added subsequently. After that, the solution was stirred at a distance of

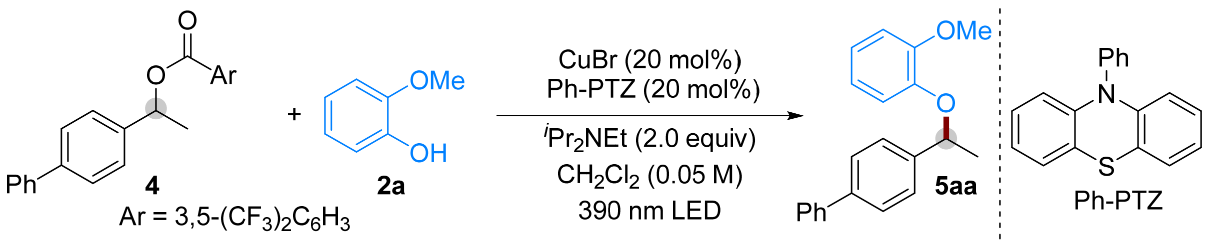
~5 cm from a 7 W blue LEDs (450-460 nm) at room temperature about 5 h until the reaction was completed as monitored by TLC analysis. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethylacetate 20:1~10:1) directly to give the desired product **3aa** in 70% yield as a colorless oil.

3.2 General Procedure for Synthesis of 3bp-br



To a stirred solution of CuCl (3.96 mg, 20 mol%) in alcohol **2p-r** (4.0 mL) under nitrogen was added $^{i}Pr_2NEt$ (51.6 mg, 2.0 equiv). And **1**b (72.6 mg, 0.2 mmol) were added subsequently. After that, the solution was stirred at a distance of ~5 cm from a 7 W blue LEDs (450-460 nm, distance ca. 3 cm.) at room temperature about 5 h until the reaction was completed as monitored by TLC analysis. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethylacetate 20:1~10:1) directly to give the desired product **3bp-br** as a colorless oil.

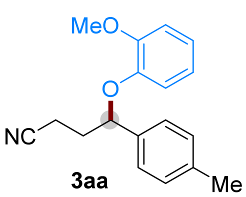
3.3 General Procedure for Synthesis of 5



To a stirred solution of CuBr (5.74 mg, 20 mol%) in CH_2Cl_2 (2.0 mL) under nitrogen was added **2a** (49.6 mg, 0.4 mmol) and $^{i}Pr_2NEt$ (51.6 mg, 2.0 equiv). And **4a** (87.7 mg, 0.2 mmol) and Ph-PTZ (4.74 mg, 20 mol%) were added subsequently. After that, the solution was stirred at 390 nm LEDs at room temperature about 24 h until the reaction was completed as monitored by TLC analysis. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethylacetate 30:1~20:1) directly to give the desired product **5aa** in 50% yield as a colorless oil.

3.4 Spectral Data of Products

4-(2-methoxyphenoxy)-4-(p-tolyl)butanenitrile 3aa

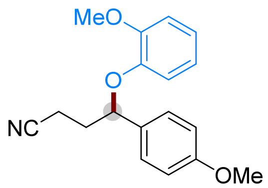


3aa

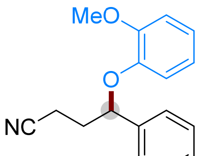
39 mg, colorless liquid, yield: 70%. R_f = 0.3 (petroleum ether/ethylacetate 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.24 (d, *J*=7.9, 2H), 7.13 (d, *J*=7.8, 2H), 6.90 – 6.85 (m, 2H), 6.68 (d, *J*=7.3, 2H), 5.15 – 5.11 (m, 1H), 3.87 (s, 3H), 2.77 – 2.69 (m, 1H), 2.16 – 2.08 (m, 1H), 2.56 – 2.49 (m, 1H), 2.31 (s, 3H), 2.16 – 2.08 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.3, 146.9, 137.8, 137.2, 129.3, 125.9, 122.3, 120.5, 119.6, 117.5, 111.9, 79.7, 55.6, 34.1, 21.0, 13.8. HRMS (EI): m/z $[M + Na]^+$ calcd for$C_{18}H_{19}N$ NaO_2 304.1308, found: 304.1309.

4-(2-methoxyphenoxy)-4-(4-methoxyphenyl)butanenitrile 3ba

52.3 mg, colorless liquid, yield: 88%. R_f = 0.4 (petroleum ether/ethylacetate 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27 (d, *J* = 8.8 Hz, 2H), 6.93 – 6.86 (m, 4H), 6.73 – 6.66 (m, 2H), 5.14 – 5.10 (m, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 2.80 – 2.72 (m, 1H), 2.59 – 2.53 (m, 1H), 2.40 – 2.31 (m, 1H), 2.17 – 2.05 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.4, 150.4, 146.8, 132.2, 127.4, 122.5, 120.6, 119.7, 117.8, 114.0, 111.9, 79.6, 55.7, 55.2, 34.1, 13.9. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{18}H_{19}NNaO_3$: 320.1257, found: 320.1260.



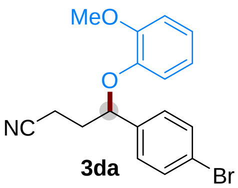
4-(2-methoxyphenoxy)-4-phenylbutanenitrile 3ca



3ca

21.9 mg, colorless liquid, yield: 41%. R_f = 0.4 (petroleum ether/ethylacetate 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.28 (q, *J* = 7.9 Hz, 4H), 7.22 (d, *J* = 6.8 Hz, 1H), 6.86 – 6.80 (m, 2H), 6.65 – 6.59 (m, 2H), 5.12 – 5.08 (m, 1H), 3.82 (s, 3H), 2.75 – 2.67 (m, 1H), 2.53 – 2.45 (m, 1H), 2.33 – 2.24 (m, 1H), 2.14 – 2.05 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.4, 146.9, 140.3, 128.7, 128.1, 126.1, 122.5, 120.7, 119.6, 117.7, 112.0, 80.0, 55.8, 34.2, 13.9. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{17}H_{17}NNaO_2$: 290.1151, found: 290.1148.

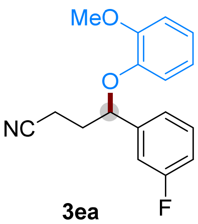
4-(4-bromophenyl)-4-(2-methoxyphenoxy)butanenitrile 3da



3da

20.8 mg, white solid, yield: 30%. R_f = 0.5 (petroleum ether/ethylacetate 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.48 (d, *J* = 8.4 Hz, 2H), 7.27 – 7.24 (m, 2H), 6.95 – 6.87 (m, 2H), 6.72 (t, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.16 – 5.13 (m, 1H), 3.88 (s, 3H), 2.84 – 2.76 (m, 1H), 2.60 – 2.53 (m, 1H), 2.37 – 2.28 (m, 1H), 2.16 – 2.08 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.5, 146.5, 139.4, 131.9, 127.8, 122.9, 122.1, 120.7, 119.5, 117.9, 112.0, 79.4, 55.7, 34.0, 13.9. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{17}H_{16}BrNNaO_2$: 368.0257, found: 368.0270.

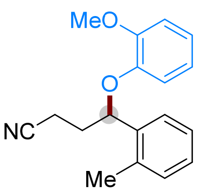
4-(3-fluorophenyl)-4-(2-methoxyphenoxy)butanenitrile 3ea



3ea

13.1 mg, colorless liquid, yield: 23%. R_f = 0.4 (petroleum ether/ethylacetate 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34 – 7.29 (m, 1H), 7.15 – 7.11 (m, 2H), 7.01 – 6.88 (m, 3H), 6.75 – 6.67 (m, 2H), 5.19 – 5.16 (m, 3H), 3.89 (s, 3H), 2.84 – 2.76 (m, 1H), 2.61 – 2.54 (m, 1H), 2.38 – 2.29 (m, 1H), 2.20 – 2.11 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.0 (*J* = 245.4 Hz), 150.4, 146.6, 143.0 (*J* = 6.8 Hz), 130.3 (*J* = 8.2 Hz), 122.9, 121.7 (*J* = 2.9 Hz), 120.6, 119.5, 117.7, 115.1 (*J* = 21.1 Hz), 113.0 (*J* = 22.1 Hz), 112.0, 79.3, 55.7, 34.0, 13.9. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{17}H_{16}FNNaO_2$: 308.1057, found: 308.1056.

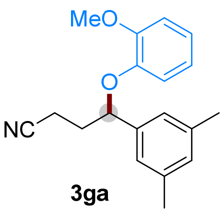
4-(2-methoxyphenoxy)-4-(o-tolyl)butanenitrile 3fa



3fa

28.1 mg, colorless liquid, yield: 50%. R_f = 0.4 (petroleum ether/ethylacetate 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.49 – 7.47 (m, 1H), 7.21 – 7.14 (m, 3H), 6.92 – 6.85 (m, 2H), 6.72 – 6.67 (m, 1H), 6.56 (d, *J* = 7.6 Hz, 1H), 5.41 – 5.38 (m, 1H), 3.90 (s, 3H), 2.89 – 2.81 (m, 1H), 2.67 – 2.60 (m, 1H), 2.37 (s, 3H), 2.32 – 2.23 (m, 1H), 2.15 – 2.07 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.2, 147.0, 138.4, 134.0, 130.7, 127.8, 126.5, 125.6, 122.2, 120.7, 119.7, 116.8, 111.9, 76.6, 55.7, 32.9, 18.9, 14.2. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{18}H_{19}NNaO_2$: 304.1308, found: 304.1309.

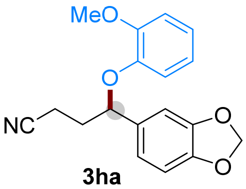
4-(3,5-dimethylphenyl)-4-(2-methoxyphenoxy)butanenitrile 3ga



3ga

40.2 mg, colorless liquid, yield: 68%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.98 (s, 2H), 6.93 – 6.87 (m, 3H), 6.75 – 6.69 (m, 2H), 5.09 – 5.06 (m, 1H), 3.89 (s, 3H), 2.79 – 2.71 (m, 1H), 2.59 – 2.51 (m, 1H), 2.37 – 2.32 (m, 1H), 2.29 (s, 6H), 2.18 – 2.09 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.3, 147.2, 140.3, 138.3, 129.8, 123.7, 122.3, 120.7, 119.7, 117.3, 111.9, 80.1, 55.8, 34.3, 21.3, 13.9. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{19}H_{21}NNaO_2$: 318.1465, found: 318.1455.

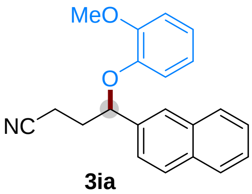
4-(benzo[d][1,3]dioxol-5-yl)-4-(2-methoxyphenoxy)butanenitrile 3ha



3ha

47.9 mg, colorless liquid, yield: 77%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.94 – 6.86 (m, 3H), 6.81 – 6.69 (m, 4H), 5.95 (s, 2H), 5.10 – 5.07 (m, 1H), 3.88 (s, 3H), 2.79 – 2.71 (m, 1H), 2.59 – 2.51 (m, 1H), 2.38 – 2.29 (m, 1H), 2.16 – 2.07 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5, 148.1, 147.5, 146.8, 134.2, 122.6, 120.7, 119.8, 119.6, 117.9, 112.0, 108.3, 106.4, 101.1, 79.8, 55.7, 34.2, 14.0. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{18}H_{17}NNaO_4$: 334.1050, found: 334.1040.

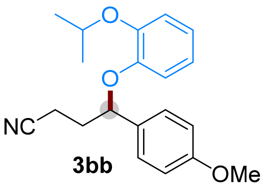
4-(2-methoxyphenoxy)-4-(naphthalen-2-yl)butanenitrile 3ia



3ia

32.4 mg, colorless liquid, yield: 51%. R_f = 0.4 (petroleum ether/ethylacetate 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.86 – 7.79 (m, 4H), 7.54 – 7.45 (m, 3H), 6.92 – 6.87 (m, 2H), 6.73 – 6.64 (m, 2H), 5.34 – 5.31 (m, 1H), 3.91 (s, 3H), 2.87 – 2.79 (m, 1H), 2.63 – 2.55 (m, 1H), 2.49 – 2.40 (m, 1H), 2.27 – 2.19 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.4, 146.9, 137.7, 133.1, 128.7, 127.9, 127.7, 126.3, 126.2, 125.3, 123.6, 122.6, 120.6, 119.6, 117.7, 111.9, 80.2, 55.7, 34.1, 14.0. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{21}H_{19}NNaO_2$: 340.1308, found: 340.1304.

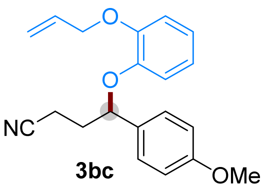
4-(2-isopropoxyphenoxy)-4-(4-methoxyphenyl)butanenitrile 3bb



3bb

39.7 mg, colorless liquid, yield: 61%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27 (d, J = 9.3 Hz, 3H), 6.90 – 6.85 (m, 3H), 6.74 – 6.66 (m, 2H), 5.12 – 5.09 (m, 1H), 4.53 (p, J = 6.1 Hz, 1H), 3.79 (s, 3H), 2.76 – 2.67 (m, 1H), 2.59 – 2.51 (m, 1H), 2.39 – 2.30 (m, 1H), 2.19 – 2.10 (m, 1H), 1.38 (t, J = 5.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.4, 148.9, 148.2, 132.3, 127.5, 122.6, 121.1, 119.7, 118.9, 116.3, 114.0, 79.9, 71.3, 55.2, 34.1, 22.3, 22.2, 13.8. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{20}H_{23}NNaO_3$: 348.1570, found: 348.1571.

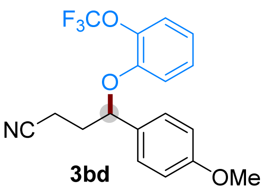
4-(2-(allyloxy)phenoxy)-4-(4-methoxyphenyl)butanenitrile 3bc



3bc

32.3 mg, colorless liquid, yield: 50%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.28 (d, J = 8.5 Hz, 2H), 6.88 – 6.85 (m, 4H), 6.74 – 6.68 (m, 2H), 6.15 – 6.06 (m, 1H), 5.46 – 5.30 (m, 2H), 5.14 – 5.11 (m, 1H), 4.60 (d, J = 5.4 Hz, 2H), 3.79 (s, 3H), 2.76 – 2.68 (m, 1H), 2.59 – 2.51 (m, 1H), 2.39 – 2.30 (m, 1H), 2.18 – 2.10 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.4, 149.5, 147.3, 133.4, 132.2, 127.4, 122.5, 121.1, 119.7, 118.3, 117.7, 114.1, 79.8, 76.7, 69.7, 55.2, 34.1, 13.9. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{20}H_{21}NNaO_3$: 346.1414, found: 346.1411.

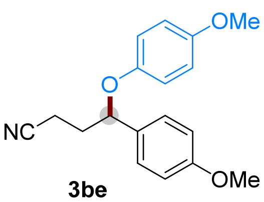
4-(4-methoxyphenyl)-4-(2-(trifluoromethoxy)phenoxy)butanenitrile 3bd



3bd

30.2 mg, colorless liquid, yield: 43%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27 – 7.25 (m, 2H), 7.21 (d, J = 8.1Hz, 1H), 7.08 – 7.03 (m, 1H), 6.91 – 6.87 (m, 3H), 6.78 – 6.75 (m, 1H), 5.25 – 5.21 (m, 1H), 3.79 (s, 3H), 2.69 – 2.61 (m, 1H), 2.53 – 2.45 (m, 1H), 2.38 – 2.29 (m, 1H), 2.22 – 2.13 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.6, 149.7, 138.5, 131.0, 127.7, 127.1, 123.2, 121.3, 120.7 (q, J = 255.4 Hz), 119.2, 116.0, 114.1, 78.4, 55.2, 34.1, 13.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.9. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{18}H_{16}F_3NNaO_3$: 374.0974, found: 374.0976.

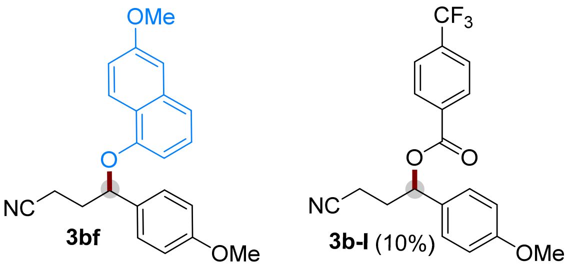
4-(4-methoxyphenoxy)-4-(4-methoxyphenyl)butanenitrile 3be



3be

19.0 mg, colorless liquid, yield: 32%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.25 (d, J = 8.3 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.77 – 6.71 (m, 4H), 5.09 – 5.06 (m, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 2.65 – 2.57 (m, 1H), 2.50 – 2.42 (m, 1H), 2.30 – 2.21 (m, 1H), 2.17 – 2.08 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.4, 154.2, 151.6, 132.1, 127.2, 119.4, 117.2, 114.5, 114.2, 78.5, 55.6, 55.2, 34.1, 13.9. HRMS (EI): m/z $[M + Na]^+$ calcd for $C_{18}H_{19}NNaO_3$: 320.1257, found: 320.1271.

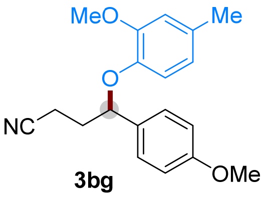
4-((6-methoxynaphthalen-1-yl)oxy)-4-(4-methoxyphenyl)butanenitrile 3bf



3bf 3b-I (10%)

13.9 mg, colorless liquid, yield: 20%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$, **3bg**) δ (ppm) 8.27 (d, J = 9.2 Hz, 1H), 7.37 – 7.35 (m, 2H), 7.26 (s, 1H), 7.18 – 7.14 (m, 2H), 7.09 (d, J = 2.5 Hz, 1H), 6.94 – 6.90 (m, 2H), 6.51 (dd, J = 7.8, 0.9 Hz, 1H), 5.42 (dd, J = 8.1, 4.4 Hz, 1H), 3.92 (s, 3H), 3.81 (s, 3H), 2.71 – 2.63 (m, 1H), 2.58 – 2.51 (m, 1H), 2.48 – 2.37 (m, 1H), 2.35 – 2.26 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, **3bg**) δ (ppm) δ 159.9, 158.1, 153.0, 135.9, 133.0, 127.7, 126.9, 124.9, 123.4, 120.9, 119.4 117.8, 114.3, 105.8, 105.2, 75.2, 55.3, 55.2, 31.8, 13.9. HRMS (EI): m/z $[M + Na]^+$ calcd for $C_{22}H_{21}NNaO_3$: 370.1414, found: 370.1409.

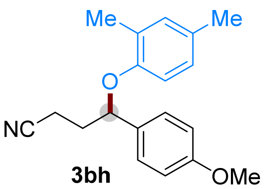
4-(2-methoxy-4-methylphenoxy)-4-(4-methoxyphenyl)butanenitrile 3bg



3bg

40.4 mg, colorless liquid, yield: 65%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27 (d, J = 8.6Hz, 2H), 6.86 (d, J = 8.6Hz, 2H), 6.68 (d, J = 1.8 Hz, 1H), 6.56 – 6.48 (m, 2H), 5.07 – 5.04 (m, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 2.79 – 2.71 (m, 1H), 2.58 – 2.50 (m, 1H), 2.39 – 2.29 (m, 1H), 2.24 (s, 3H), 2.13 – 2.06 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.3, 150.2, 144.5, 132.4, 132.3, 127.4, 120.7, 119.7, 118.1, 114.0, 112.9, 79.9, 55.7, 55.2, 34.1, 21.1, 13.9. HRMS (EI): m/z $[M + Na]^+$ calcd for $C_{19}H_{21}NNaO_3$: 334.1414, found: 334.1416.

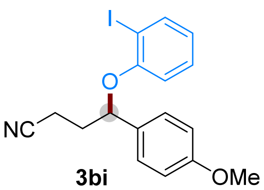
4-(2,4-dimethylphenoxy)-4-(4-methoxyphenyl)butanenitrile 3bh



3bh

16.0 mg, colorless liquid, yield: 27%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.26 – 7.23 (m, 2H), 6.93 (d, J = 2.2 Hz, 1H), 6.88 – 6.85 (m, 2H), 6.77 – 6.75 (m, 1H), 6.50 (d, J = 8.3 Hz, 1H), 5.19 – 5.16 (m, 1H), 3.78 (s, 3H), 2.63 – 2.55 (m, 1H), 2.51 – 2.43 (m, 1H), 2.33 – 2.25 (m, 4H), 2.22 – 2.14 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.3, 153.2, 132.1, 131.6, 130.0, 127.0, 126.8, 126.7, 119.4, 114.2, 112.8, 76.7, 55.2, 34.2, 20.4, 16.4, 13.8. HRMS (EI): m/z $[M + Na]^+$ calcd for $C_{19}H_{21}NNaO_2$: 318.1465, found: 318.1458.

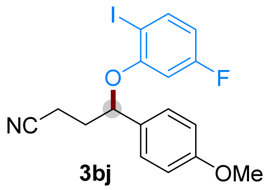
4-(2-iodophenoxy)-4-(4-methoxyphenyl)butanenitrile 3bi



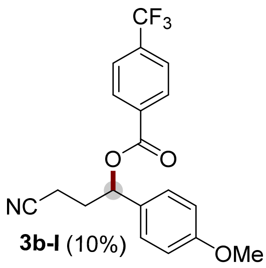
3bi

57.4 mg, colorless liquid, yield: 73%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.74 (d, J = 7.8 Hz, 1H), 7.26 (d, J = 8.3 Hz, 2H), 7.10 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 8.6 Hz, 2H), 6.65 (t, J = 7.6 Hz, 1H), 6.59 (d, J = 8.2 Hz, 1H), 5.29 – 5.25 (m, 1H), 3.78 (s, 3H), 2.81 – 2.73 (m, 1H), 2.60 – 2.53 (m, 1H), 2.38 – 2.29 (m, 1H), 2.25 – 2.16 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.5, 155.6, 139.4, 131.0, 129.3, 127.0, 122.9, 119.3, 114.3, 113.8, 87.0, 78.3, 55.2, 34.3, 13.9. HRMS (EI): m/z $[M + Na]^+$ calcd for $C_{17}H_{16}INNaO_2$: 416.0118, found: 416.0118.

4-(5-fluoro-2-iodophenoxy)-4-(4-methoxyphenyl)butanenitrile 3bj



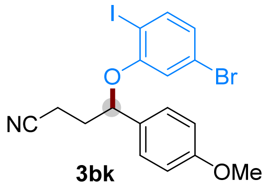
3bj



3b-l (10%)

42.8 mg, colorless liquid, yield: 52%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$, **3bj**) δ (ppm) 7.48 – 7.45 (m, 1H), 7.27 – 7.23 (m, 2H), 6.93 – 6.80 (m, 3H), 6.53 – 6.49 (m, 1H), 5.21 – 5.18 (m, 1H), 3.80 (s, 1H), 2.80 – 2.72 (m, 1H), 2.59 – 2.51 (m, 1H), 2.48 – 2.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, **3bj**) δ (ppm) 159.6, 158.0, 155.6, 152.3, 130.7, 130.1, 119.2, 115.6, 114.4, 114.0, 86.5, 79.1, 55.3, 34.1, 13.9. HRMS (EI): m/z $[M + Na]^+$ calcd for $C_{17}H_{15}FINNaO_2$: 434.0024, found: 434.0030.

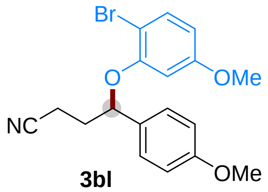
4-(5-bromo-2-iodophenoxy)-4-(4-methoxyphenyl)butanenitrile 3bk



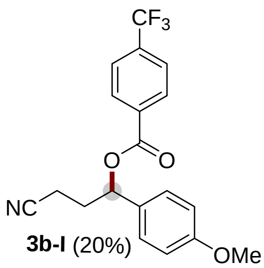
3bk

66.1 mg, colorless liquid, yield: 70%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.85 (d, *J* = 2.3 Hz, 1H), 7.26 – 7.19 (m, 3H), 6.90 – 6.86 (m, 2H), 6.45 (d, *J* = 8.8 Hz, 1H), 5.24 – 5.21 (m, 1H), 3.79 (s, 3H), 2.79 – 2.71 (m, 1H), 2.58 – 2.51 (m, 1H), 2.39 – 2.30 (m, 1H), 2.25 – 2.16 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.6, 155.0, 141.1, 132.0, 130.4, 127.1, 119.1, 114.9, 114.4, 114.0, 87.8, 78.8, 55.3, 34.1, 13.9. HRMS (EI): m/z $[M + Na]^+$ calcd for $C_{17}H_{15}BrINNaO_2$: 493.9223, found: 493.9218.

4-(2-bromo-5-methoxyphenoxy)-4-(4-methoxyphenyl)butanenitrile 3bl



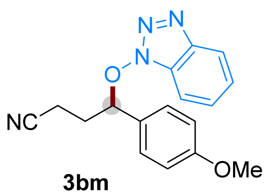
3bl



3b-l (20%)

22.6 mg, colorless liquid, yield: 30%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$, **3bl**) δ (ppm) 7.28 – 7.24 (m, 3H), 7.08 – 7.07 (m, 1H), 6.90 – 6.86 (m, 2H), 6.63 – 6.57 (m, 2H), 5.15 – 5.12 (m, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 2.78 – 2.70 (m, 1H), 2.58 – 2.51 (m, 1H), 2.49 – 2.13 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, **3bl**) δ (ppm) 159.5, 154.4, 147.9, 134.9, 130.1, 127.7, 127.3, 119.4, 118.6, 116.7, 114.2, 79.4, 55.8, 55.3, 34.0, 13.8. HRMS (EI): m/z $[M + Na]^+$ calcd for $C_{18}H_{18}BrNNaO_3$: 398.0362, found: 398.0349.

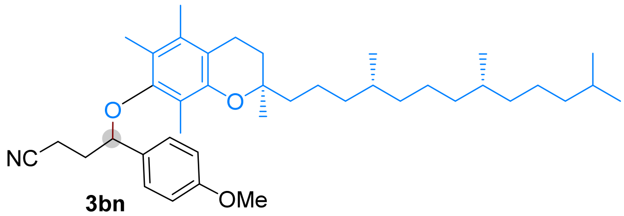
4-((1H-benzo[d][1,2,3]triazol-1-yl)oxy)-4-(4-methoxyphenyl)butanenitrile 3bm



3bm

30.8 mg, colorless liquid, yield: 50%. R_f = 0.2 (petroleum ether/ethylacetate 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.32 – 7.20 (m, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 7.04 – 7.02 (m, 1H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.59 – 5.56 (m, 1H), 3.74 (s, 3H), 2.86 – 2.67 (m, 3H), 2.42 – 2.32 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.9, 143.1, 129.2, 128.1, 127.8, 127.3, 124.3, 119.9, 118.6, 114.3, 108.7, 90.3, 55.3, 29.9, 14.4. HRMS (EI): m/z $[M + Na]^+$ calcd for $C_{17}H_{16}N_4NaO_2$: 331.1165, found: 331.1176.

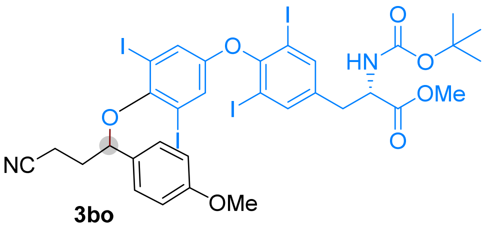
4-(4-methoxyphenyl)-4-(((R)-2,5,6,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-7-yl)oxy)butanenitrile 3bn



3bn

48.3 mg, colorless liquid, yield: 40%. d.r. = 1 : 1. R_f = 0.5 (petroleum ether/ethylacetate 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.23 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.65 – 4.61 (m, 1H), 3.81 (s, 3H), 2.54 – 2.41 (m, 3H), 2.38 – 2.20 (m, 2H), 2.16 – 2.08 (m, 1H), 2.04 (s, 3H), 2.02 (d, *J* = 3.1 Hz, 3H), 1.96 (d, *J* = 4.0 Hz, 3H), 1.82 – 1.72 (m, 2H), 1.56 – 1.47 (m, 3H), 1.45 – 1.34 (m, 4H), 1.29 – 1.19 (m, 11H), 1.16 – 1.00 (m, 6H), 0.87 – 0.83 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.7, 147.7, 146.8, 131.0, 128.8, 127.9, 126.0, 122.9, 119.2, 117.6, 113.8, 82.5, 74.8, 55.3, 39.9, 39.9, 39.4, 37.5, 37.4, 37.4, 37.3, 32.8, 32.7, 31.4, 30.9, 28.0, 24.8, 24.4, 23.8, 23.8, 22.7, 22.6, 21.0, 21.0, 20.7, 19.7, 19.6, 13.9, 13.9, 13.0, 11.9. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{40}H_{61}NNaO_3$: 626.4544, found: 626.4522.

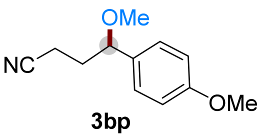
methyl(2S)-2-((tert-butoxycarbonyl)amino)-3-(4-(4-(3-cyano-1-(4-methoxyphenyl)propoxy)-3,5-diiodophenoxy)-3,5-diiodophenyl)propanoate 3bo



3bo

129.8 mg, white solid, yield: 61%. d.r. = 1 : 1. R_f = 0.2 (petroleum ether/ethylacetate 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 (s, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.09 (s, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 5.59 (t, *J* = 6.4 Hz, 1H), 5.12 (d, *J* = 8.1 Hz, 1H), 4.54 (d, *J* = 7.4 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.12 – 3.07 (m, 1H), 2.96 – 2.91 (m, 1H), 2.73 – 2.55 (m, 1H), 2.46 – 2.37 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.6, 160.1, 152.2, 151.4, 141.1, 137.9, 130.1, 128.3, 126.7, 119.3, 113.6, 91.5, 90.4, 82.3, 80.4, 55.2, 54.2, 52.5, 37.0, 31.1, 28.3, 14.3. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{32}H_{32}I_4N_2NaO_7$: 1086.8280, found: 1086.8276.

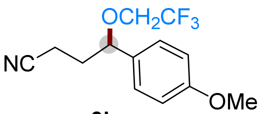
4-methoxy-4-(4-methoxyphenyl)butanenitrile 3bp



3bp

15 mg, colorless oil, yield: 70%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.21 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 4.20 (dd, *J* = 8.7, 4.8 Hz, 1H), 3.82 (s, 3H), 3.21 (s, 3H), 2.56 – 2.47 (m, 1H), 2.39 – 2.32 (m, 1H), 2.10 – 2.01 (m, 1H), 1.96 – 1.88 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.5, 132.2, 127.7, 118.3, 114.1, 81.0, 56.6, 55.3, 33.5, 13.9. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{12}H_{15}NNaO_2$: 228.0995, found: 228.0990.

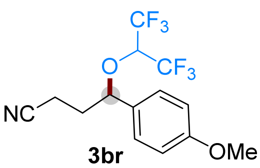
4-(4-methoxyphenyl)-4-(2,2,2-trifluoroethoxy)butanenitrile 3bq



3bq

13.7 mg, colorless oil, yield: 50%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.23 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 4.48 (dd, *J* = 9.1, 4.5 Hz, 1H), 3.82 (s, 3H), 3.74 – 3.56 (m, 2H), 2.59 – 2.51 (m, 1H), 2.46 – 2.39 (m, 1H), 2.20 – 2.11 (m, 1H), 2.02 – 1.93 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.1, 130.4, 127.9, 123.9 (q, *J* = 276.9 Hz), 119.1, 114.4, 80.9, 65.7 (q, *J* = 34.2 Hz), 55.3, 33.5, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -74.0. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{13}H_{14}F_3NNaO_3$: 296.0869, found: 296.0873.

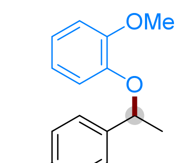
4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-4-(4-methoxyphenyl)butanenitrile 3br



3br

10 mg, colorless oil, yield: 30%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.26 (d, *J* = 8.6 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 4.74 (dd, *J* = 9.1, 4.6 Hz, 1H), 3.98 (p, *J* = 5.9 Hz, 1H), 3.84 (s, 3H), 2.58 – 2.41 (m, 2H), 2.37 – 2.28 (m, 1H), 2.07 – 1.99 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.8, 129.1, 127.9, 123.8 – 119.2 (m), 118.7, 114.6, 82.5, 72.2 (dt, *J* = 64.5, 32.4 Hz), 55.4, 33.0, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -72.4 (q, *J* = 9.3 Hz), -73.6 (q, *J* = 9.3 Hz). HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{14}H_{13}F_6NNaO_2$: 364.0743, found: 364.0744.

4-(1-(2-methoxyphenoxy)ethyl)-1,1'-biphenyl 5aa

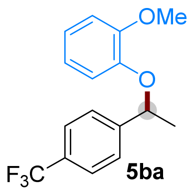


5aa

30 mg, colorless oil, yield: 50%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58 – 7.54 (m, 4H), 7.48 – 7.40 (m, 4H), 7.33 (q, *J* = 7.6 Hz, 1H), 6.90 – 6.85 (m, 2H), 6.83 – 6.73 (m, 2H), 5.35 (q, *J* = 6.5 Hz, 1H), 3.90 (s, 3H), 1.72 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.2, 147.5, 142.3, 140.9, 140.3, 128.7, 127.3, 127.2, 127.0, 126.1, 121.5, 120.7, 116.4, 112.2, 77.1, 56.0, 24.2. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{21}H_{20}NNaO_2$: 327.1356,

found: 327.1357.

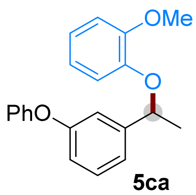
1-methoxy-2-(1-(4-(trifluoromethyl)phenyl)ethoxy)benzene 5ba



5ba

30 mg, colorless oil, yield: 34%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59 (d, J = 8.1 Hz, 2H), 7.52 (d, J = 8.1 Hz, 2H), 6.90 (d, J = 3.9 Hz, 2H), 6.77 – 6.69 (m, 2H), 5.36 (q, J = 6.5 Hz, 1H), 3.89 (s, 3H), 1.68 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.2, 147.3, 147.0, 127.9, 126.0, 125.5 (q, J = 3.8 Hz), 123.4 (q, J = 138.9 Hz), 121.9, 120.7, 116.5, 112.2, 76.8, 56.0, 24.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -62.5. HRMS (EI): m/z $[M + Na]^+$ calcd for $C_{16}H_{15}F_3NaO_2$: 319.0916, found: 319.0894.

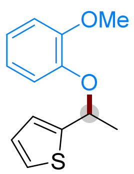
1-methoxy-2-(1-(3-methoxyphenyl)ethoxy)benzene 5ca



5ca

38 mg, colorless oil, yield: 59%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37 – 7.30 (m, 4H), 7.09 (t, J = 7.3 Hz, 1H), 7.00 – 6.94 (m, 4H), 6.89 – 6.88 (m, 2H), 6.78 – 6.77 (m, 2H), 5.30 (q, J = 6.4 Hz, 1H), 3.88 (s, 3H), 1.67 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.1, 156.5, 150.3, 147.4, 138.0, 129.7, 127.2, 123.2, 121.6, 120.7, 118.9, 118.7, 116.7, 112.1, 76.9, 56.0, 24.1. HRMS (EI): m/z $[M + Na]^+$ calcd for $C_{21}H_{20}NaO_3$: 343.1305, found: 343.1316.

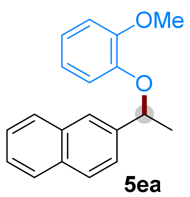
2-(1-(2-methoxyphenoxy)ethyl)thiophene 5da



5da

23 mg, colorless oil, yield: 50%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.22 (d, J = 5.0 Hz, 1H), 6.97 (d, J = 3.3 Hz, 1H), 6.94 – 6.87 (m, 4H), 6.80 (t, J = 7.5 Hz, 1H), 5.55 (q, J = 6.4 Hz, 1H), 3.87 (s, 3H), 1.76 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 151.0, 147.0, 146.5, 126.4, 124.7, 124.4, 122.6, 120.7, 118.5, 112.4, 73.9, 56.0, 23.7. HRMS (EI): m/z $[M + Na]^+$ calcd for $C_{13}H_{14}SNaO_2$: 257.0607, found: 257.0605.

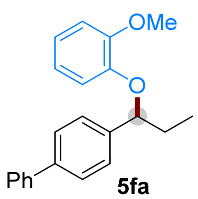
2-(1-(2-methoxyphenoxy)ethyl)naphthalene 5ea



5ea

34.5 mg, colorless oil, yield: 62%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.83 – 7.79 (m, 4H), 7.56 – 7.54 (m, 1H), 7.47 – 7.41 (m, 2H), 6.89 – 6.82 (m, 2H), 6.79 – 6.76 (m, 1H), 6.71 – 6.67 (m, 1H), 5.46 (q, J = 6.5 Hz, 1H), 3.91 (s, 3H), 1.76 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.2, 147.5, 140.7, 133.3, 132.9, 128.4, 127.9, 127.7, 126.0, 125.7, 124.4, 123.8, 121.5, 120.7, 116.5, 112.1, 77.5, 56.0, 24.4. HRMS (EI): m/z $[M + Na]^+$ calcd for $C_{19}H_{18}NaO_2$: 301.1199, found: 301.1215.

4-(1-(2-methoxyphenoxy)propyl)-1,1'-biphenyl 5fa

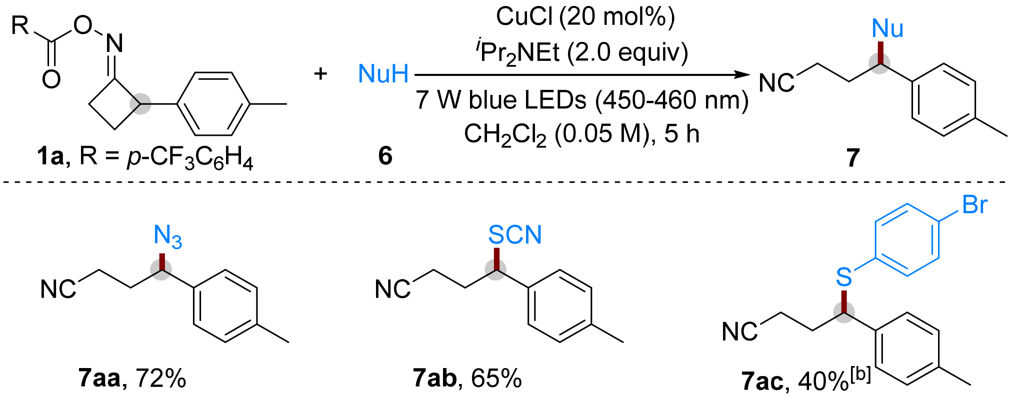


5fa

12.7 mg, colorless oil, yield: 20%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.56 (t, J = 8.3 Hz, 4H), 7.45 – 7.40 (m, 4H), 7.32 (t, J = 7.4 Hz, 1H), 6.89 – 6.83 (m, 2H), 6.77 – 6.71 (m, 2H), 5.06 (t, J = 6.6 Hz, 1H), 3.90 (s, 3H), 2.18 – 2.09 (m, 1H), 2.00 – 1.89 (m, 1H), 1.05 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.1, 148.0, 141.1, 140.8, 140.2, 128.7, 127.2, 127.1, 127.0, 126.6, 121.2, 120.7, 116.1, 112.3, 82.8, 56.1, 31.4, 10.3. HRMS (EI): m/z $[M + Na]^+$ calcd for $C_{19}H_{18}NaO_2$: 301.1199, found: 301.1215.

4. Examination of Other Nucleophiles

4.1 General Procedure for Synthesis of 7

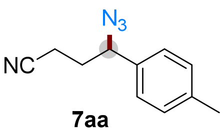


To a stirred solution of CuCl (3.96 mg, 20 mol%) in CH_2Cl_2 (4.0 mL) under nitrogen was added **6** (0.8 mmol) and ^{i}Pr$_2$NEt (51.6 mg, 2.0 equiv). And **1a** (69.4 mg, 0.2 mmol) were added subsequently. After that, the solution was stirred at a distance of ~5 cm from a 7 W blue LEDs (450-460 nm) at room temperature about 5 h until the reaction was completed as monitored by TLC analysis. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethylacetate 20:1~10:1) directly to give the desired product **7** as a colorless oil.

In the case of **6c**, 2.0 equiv of **6c** was used.

4.2 Spectral Data of Products

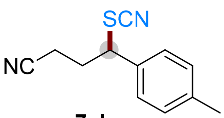
4-azido-4-(p-tolyl)butanenitrile 7aa



7aa

29 mg, colorless oil, yield: 72%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.28 – 7.19 (m, 4H), 4.60 – 4.57 (m, 1H), 2.55 – 2.42 (m, 1H), 2.39 – 2.31 (m, 4H), 2.14 – 1.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 138.9, 134.6, 129.8, 126.7, 118.7, 764.1, 31.9, 21.1, 14.3. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{11}H_{12}N_4Na$: 223.0954, found: 223.0941.

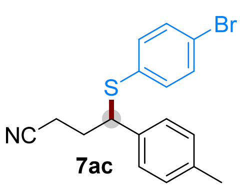
4-thiocyanato-4-(p-tolyl)butanenitrile 7ab



7ab

28 mg, colorless oil, yield: 65%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.26 – 7.18 (m, 4H), 4.46 – 4.42 (m, 1H), 2.64 – 2.53 (m, 1H), 2.51 – 2.45 (m, 2H), 2.37 – 2.28 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 140.0, 132.7, 130.3, 127.2, 117.7, 110.5, 50.9, 31.2, 21.2, 15.5. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{12}H_{12}N_2NaS$: 239.0613, found: 239.0612.

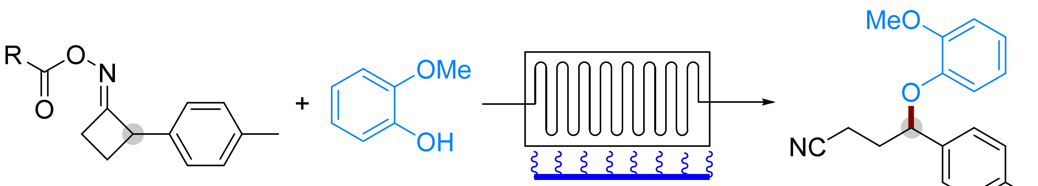
4-((4-bromophenyl)thio)-4-(p-tolyl)butanenitrile 7ac



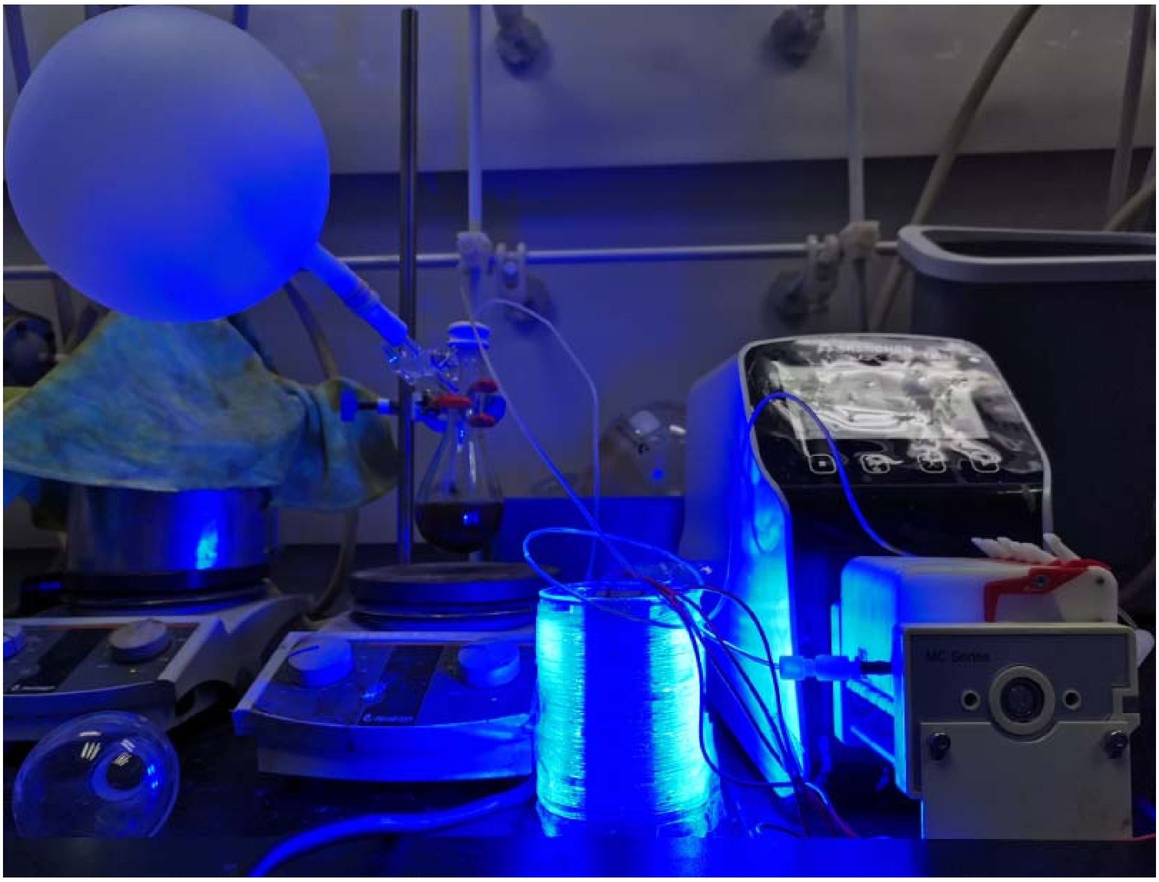
7ac

28 mg, colorless oil, yield: 40%. R_f = 0.4 (petroleum ether/ethylacetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36 – 7.34 (m, 2H), 7.16 – 7.07 (m, 4H), 4.20 – 4.16 (m, 1H), 2.48 – 2.35 (m, 1H), 2.33 (s, 3H), 2.30 – 2.12 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.9, 136.2, 134.3, 132.7, 132.0, 129.6, 127.5, 122.0, 118.8, 51.8, 31.5, 21.1, 15.5. HRMS (EI): m/z [M + Na]$^+$ calcd for $C_{17}H_{16}BrNNaS$: 368.0079, found: 368.0085.

5. Preparative Utility of the Methodology-Gram-Scale Continuous Flow Reaction



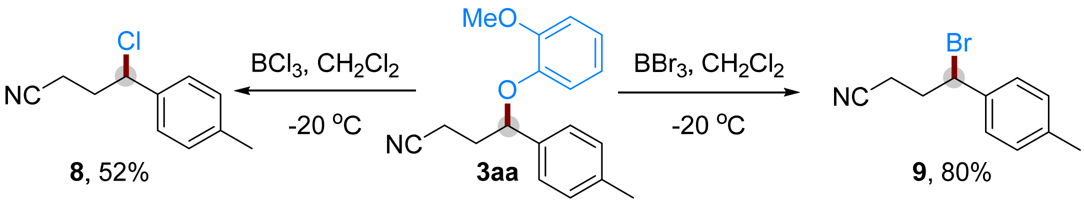
1a, R = *p*-$CF_3C_6H_4$ 5 mmol, 1.7 g; **2a** 10 mmol, 1.24 g; visible light only 2 h 35 min; **3aa** 956 mg, 65% yield



To a stirred solution of CuCl (99 mg, 20 mol%) in CH_2Cl_2 (50 mL) under nitrogen was added **2a** (1.24 g, 10.0 mmol) and $^{i}Pr_2NEt$ (1.29 g, 2.0 equiv). And **1a** (1.7 g, 5.0 mmol) were added subsequently. After that, the solution was stirred at a distance of ~5 cm from a 7 W blue LEDs (450-460 nm) at room temperature about 2.6 h until the reaction was completed as monitored by TLC analysis. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethylacetate 20:1~10:1) directly to give the desired product **3aa** (956 mg) in 65% yield as a colorless oil.

6. Derivatization of Product 3aa

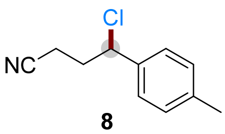
6.1 General Procedure for Synthesis of 8 and 9



BCl_3 (0.3 mL, 0.3 mmol, 1M) or BBr_3 (28 μL, 0.3 mmol) was added dropwise to a solution of compound **3aa** (56.3 mg, 0.2 mmol) in CH_2Cl_2 (8.0 mL) under nitrogen at -20 °C. The reaction mixture was stirred at -20 °C until the reaction was completed as monitored by TLC analysis. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethylacetate 20:1~10:1) directly to give the desired product **8** or **9** as a colorless oil.

6.2 Spectral Data of Products of 8 and 9

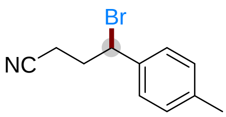
4-chloro-4-(p-tolyl)butanenitrile 8



8

20 mg, colorless oil, yield: 52%. R_f = 0.5 (petroleum ether/ethylacetate 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 4.97 – 4.94 (m, 1H), 2.61 – 2.53 (m, 1H), 2.51 – 2.47 (m, 1H), 2.45 – 2.39 (m, 1H), 2.38 – 2.28 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 138.9, 136.7, 129.6, 126.7, 118.5, 61.1, 35.3, 21.1, 15.2. HRMS (EI): m/z $[M + Na]^+$ calcd for $C_{11}H_{12}ClNNa$: 216.0550, found: 216.0547.

4-bromo-4-(p-tolyl)butanenitrile 9



9

38 mg, colorless oil, yield: 80%. R_f = 0.5 (petroleum ether/ethylacetate 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.29 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 5.06 – 4.95 (m, 1H), 2.60 – 2.44 (m, 4H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 139.1, 137.2, 129.7, 127.0, 118.3, 52.3, 35.3, 21.2, 16.4. HRMS (EI): m/z $[M + Na]^+$ calcd for $C_{11}H_{12}BrNNa$: 260.0045, found: 260.0032.

7. Mechanism Study and Possible Mechanisms

a) UV-Vis absorption spectra data

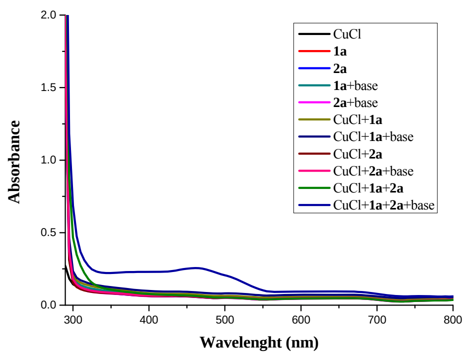
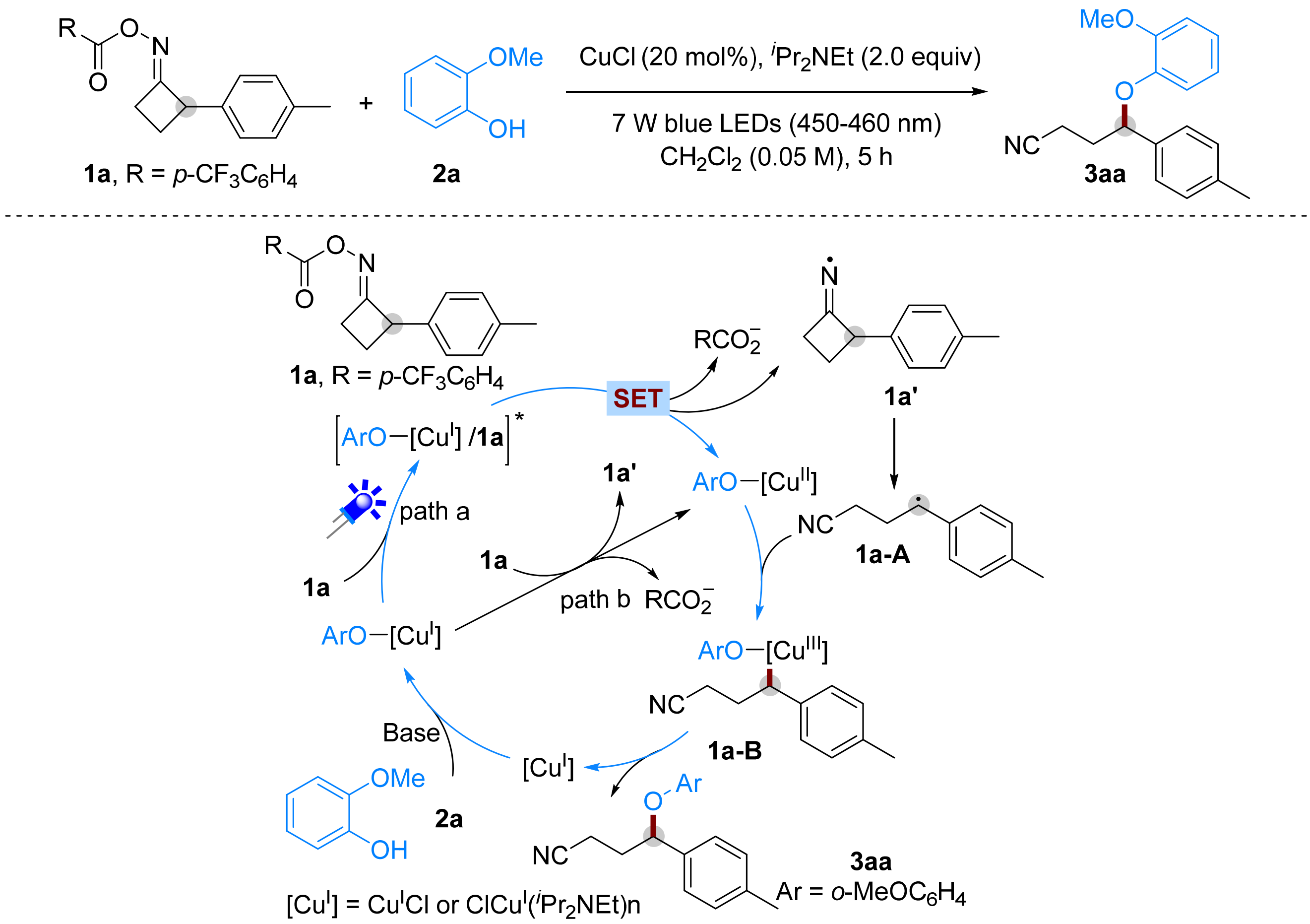


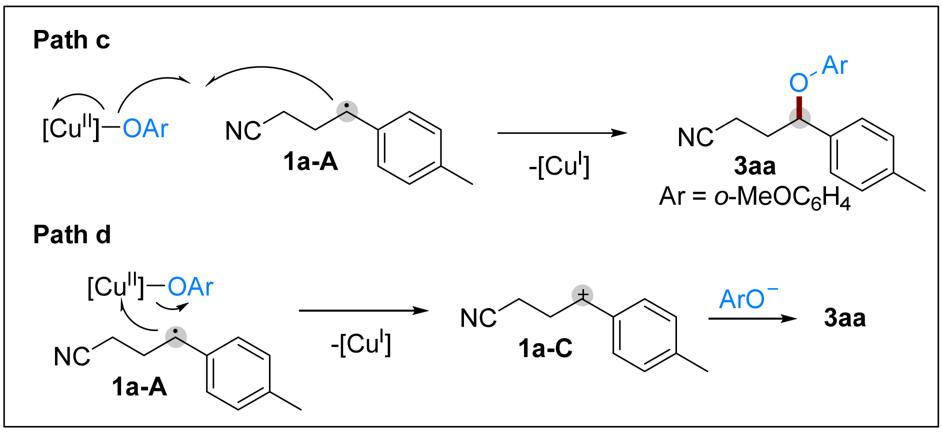
Figure S1. UV-Vis absorption Spectra of reaction component and their mixtures

UV-Vis Spectra: the reagents of model reaction and comparison of the mixture of CuCl with other components in CH_2Cl_2 (1/10 of the concentration as in the reaction conditions), respectively. As showed in the **Figure S1**, for the mixture of CuCl+**1a**+**2a**+base, the visible light absorption range is from 350-550 nm. Base = $^{i}Pr_2NEt$

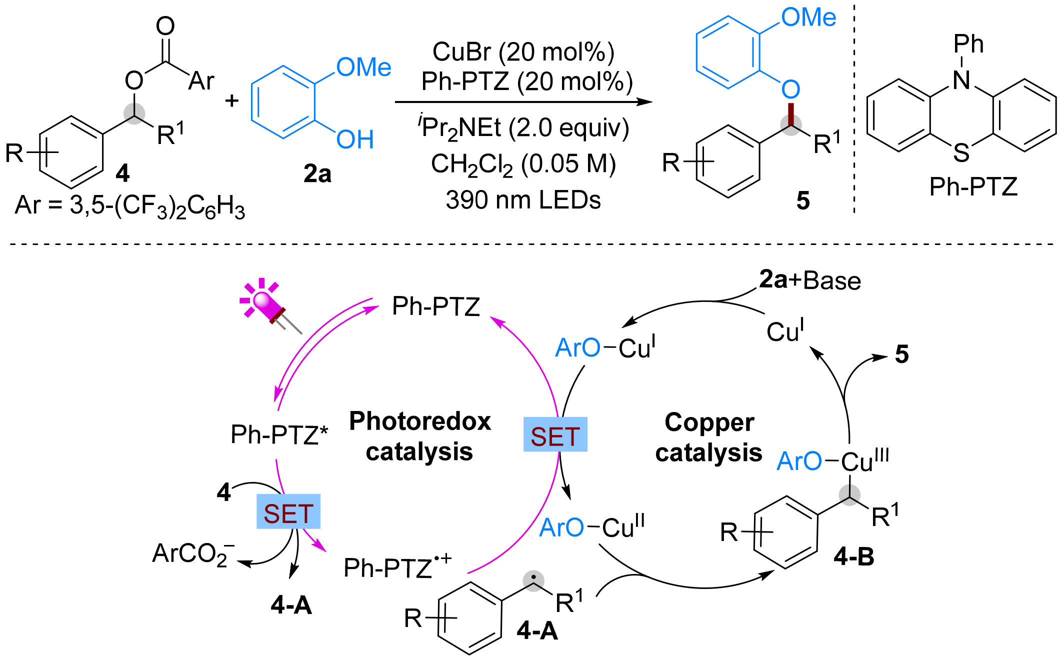
b) The proposed mechanisms



c) Alternative pathway of the reaction between Cu(II) complex and 1a-A



d) The Proposed mechanism for C(sp^3)-O cross-coupling of benzylic alcohol-derived esters

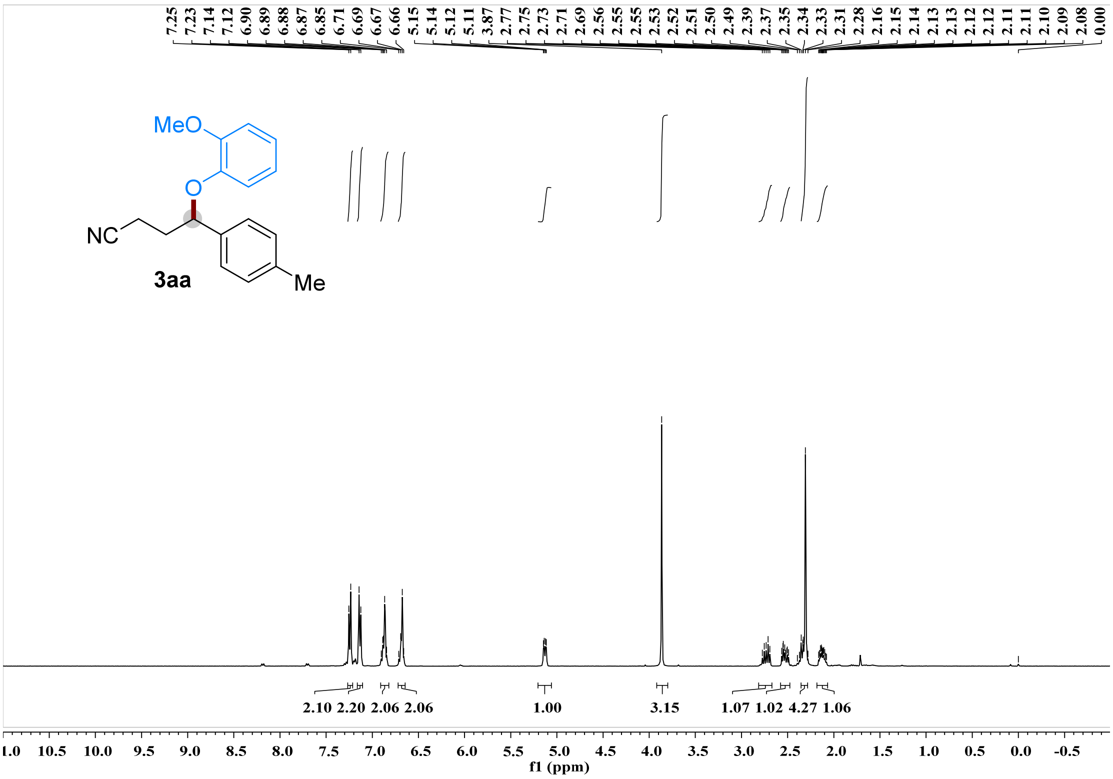


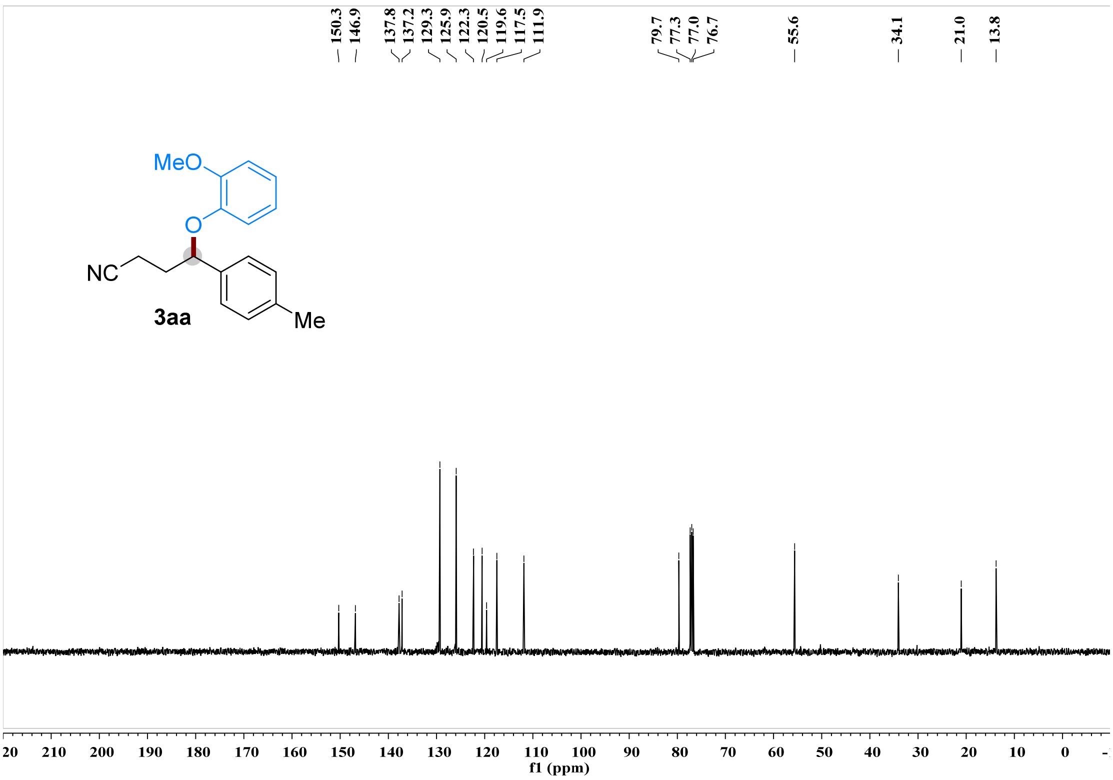
References:

[1] a) W. Ai, Y. Liu, Q. Wang, Z. Lu, Q. Liu, *Org. Lett.* 2018, *20*, 409-412; b) B. Zhao, C. Chen, J. Lv, Z. Li, Y. Yuan, Z. Shi, *Org. Chem. Front.* **2018**, *5*, 2719-2722; c) B. Zhao, H. Tan, C. Chen, N. Jiao, Z. Shi, *Chin. J. Chem.* **2018**, *36*, 995−999.

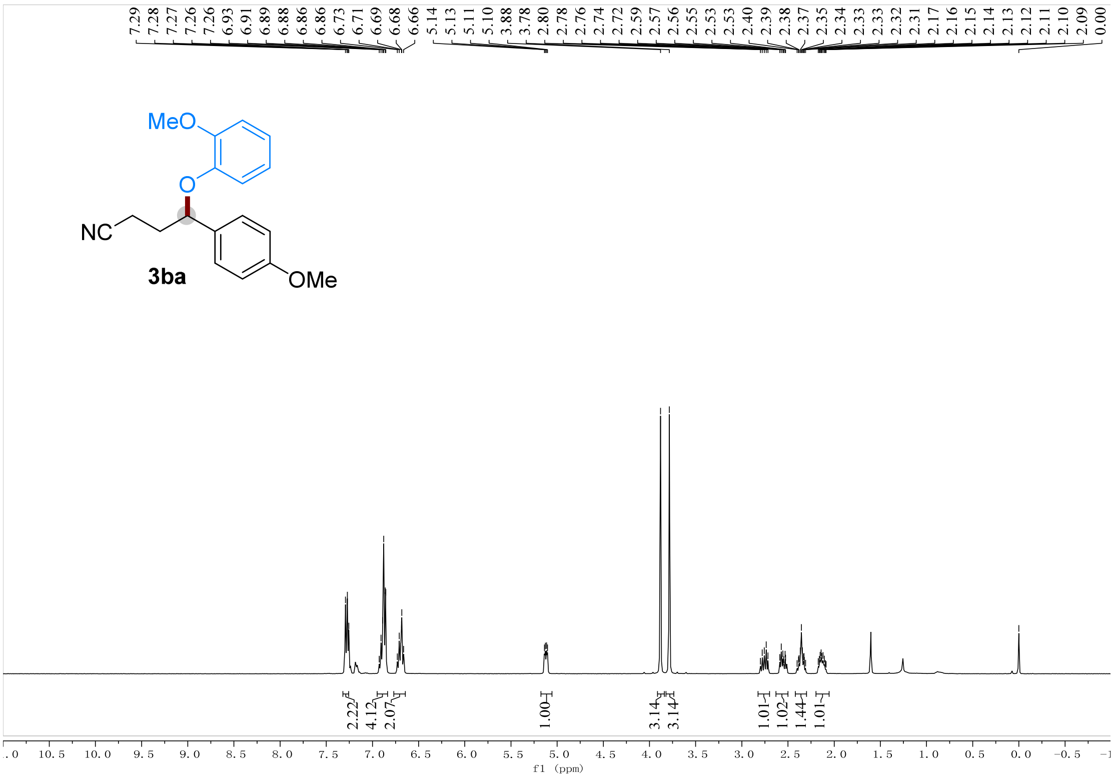
8. The Spectra of Products

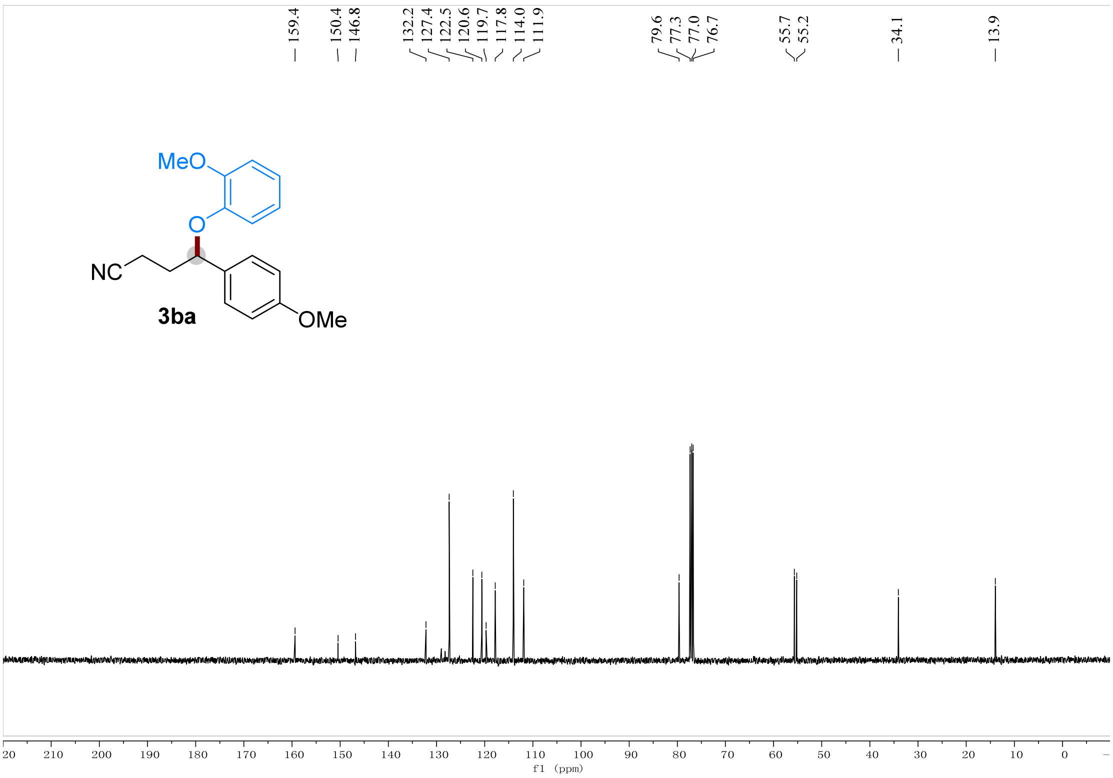
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 3aa



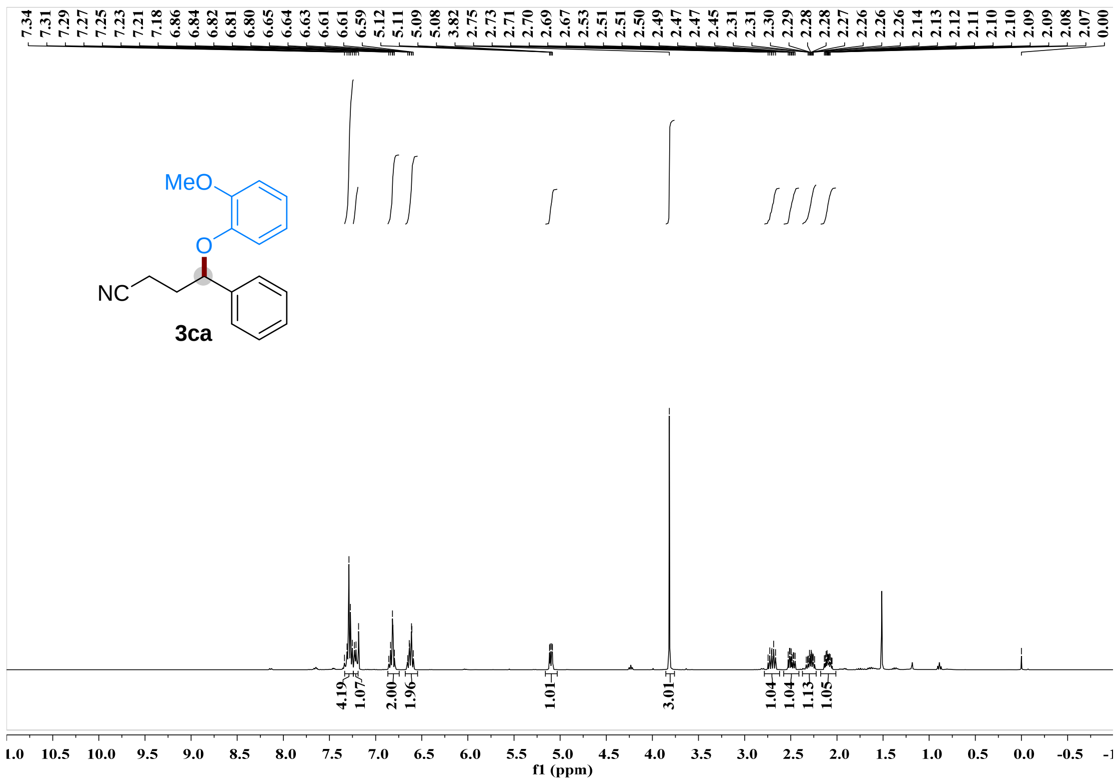


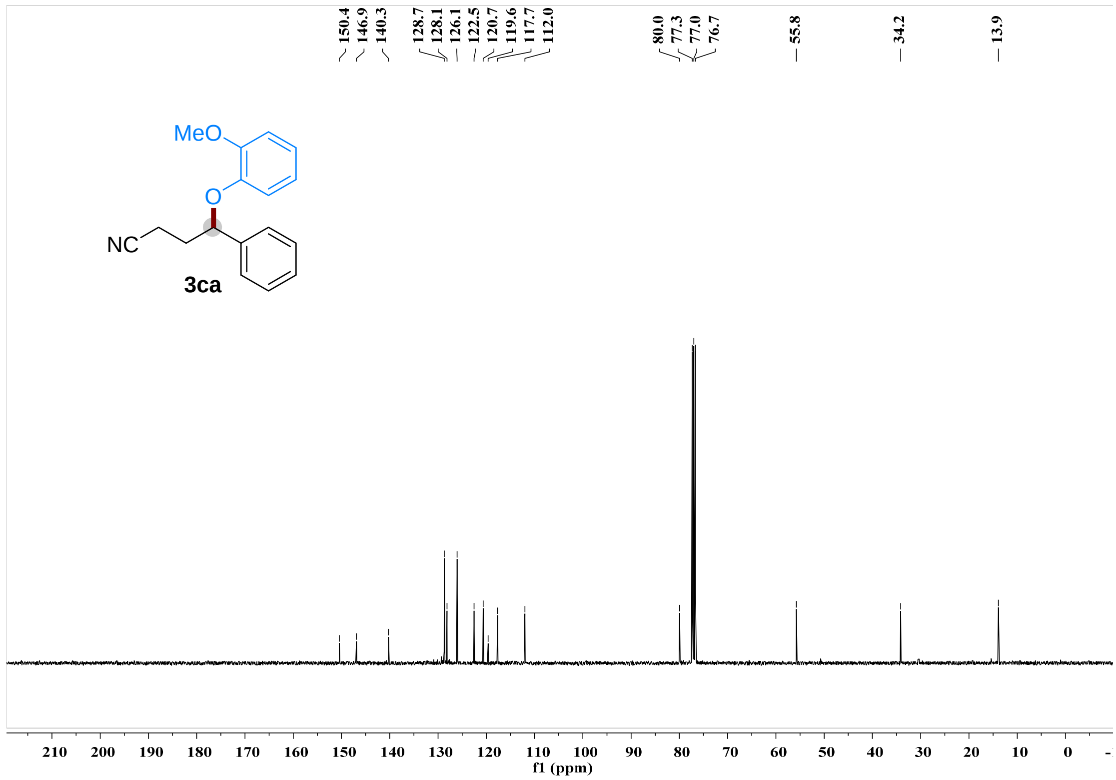
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 3ba



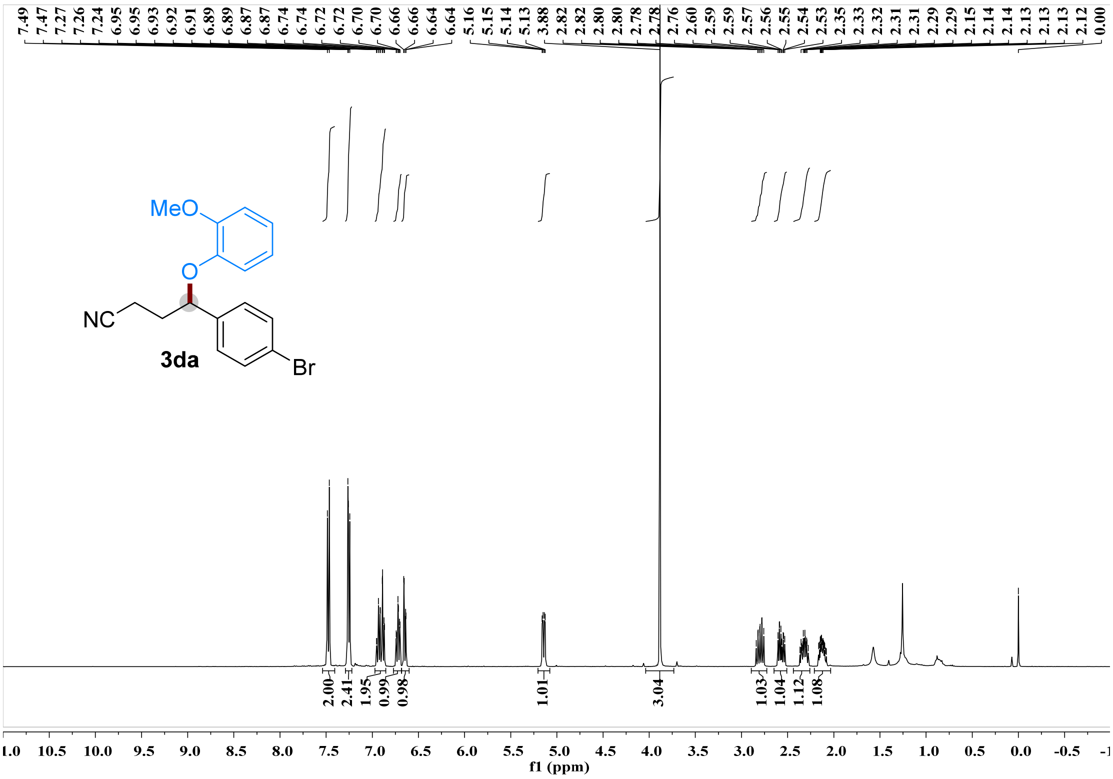


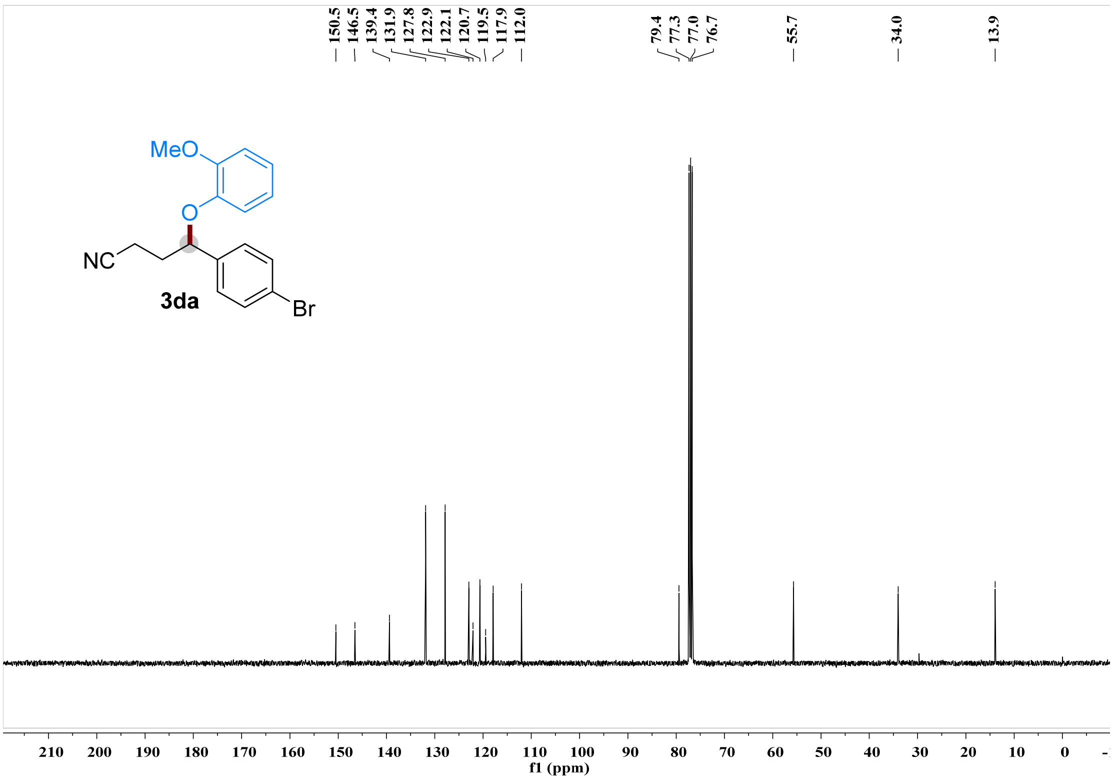
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 3ca



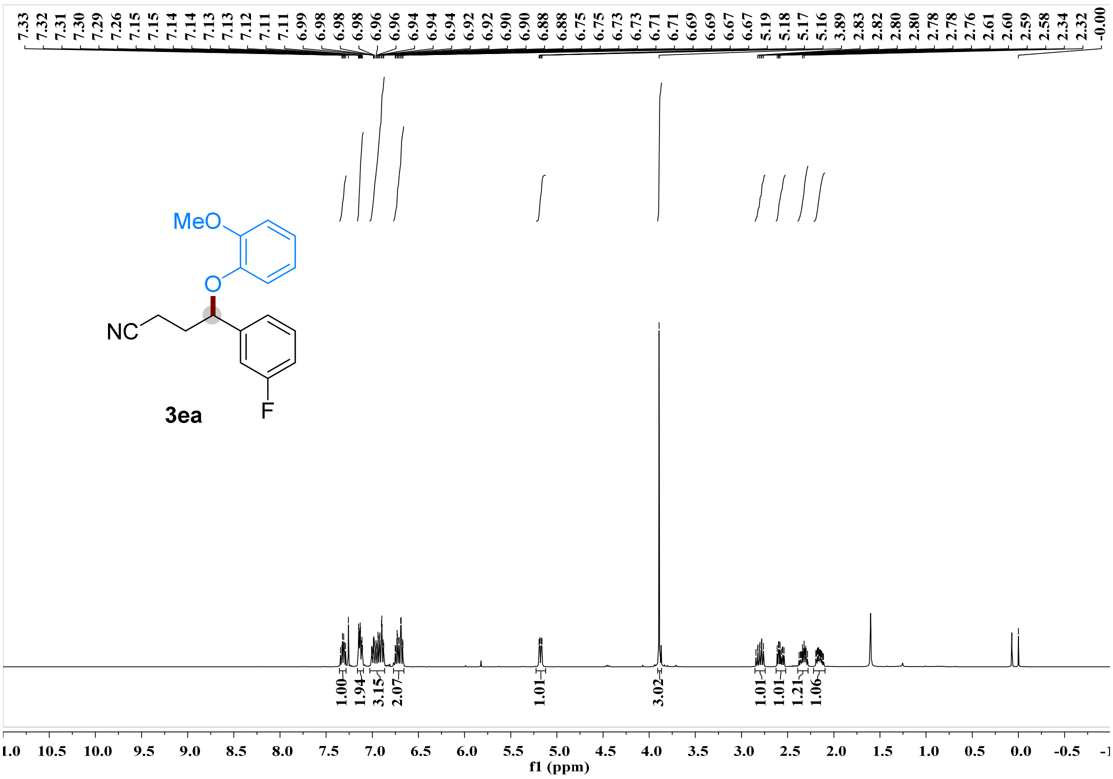


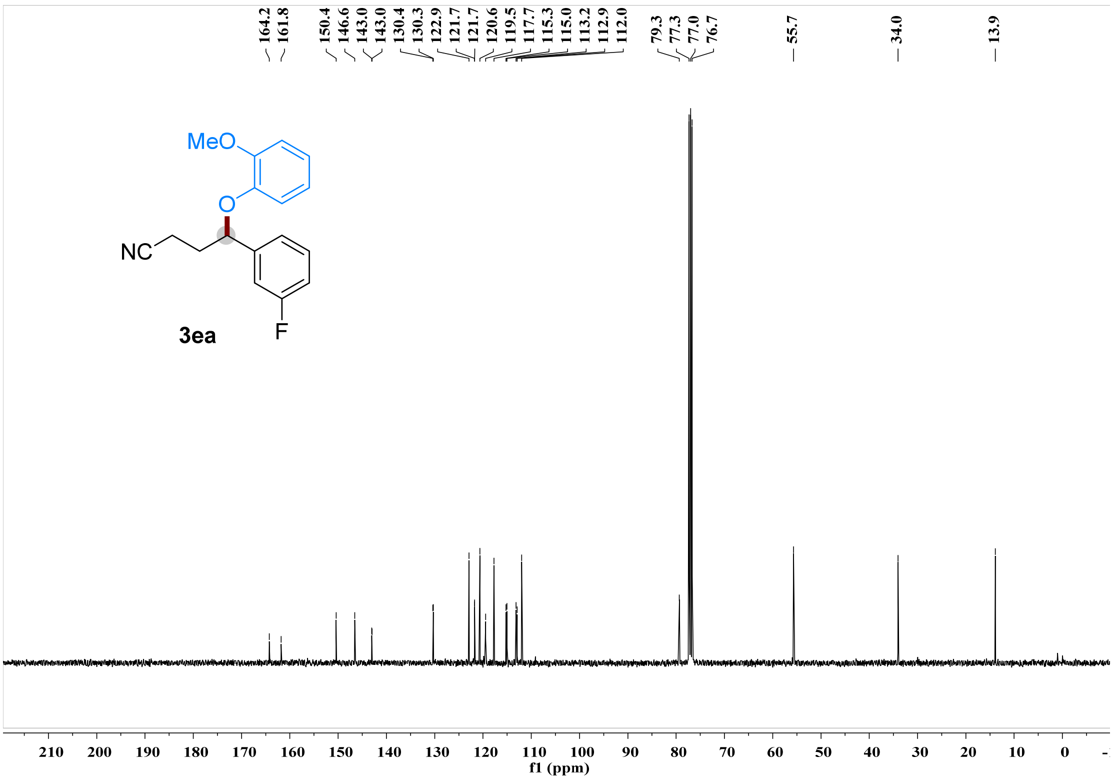
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 3da



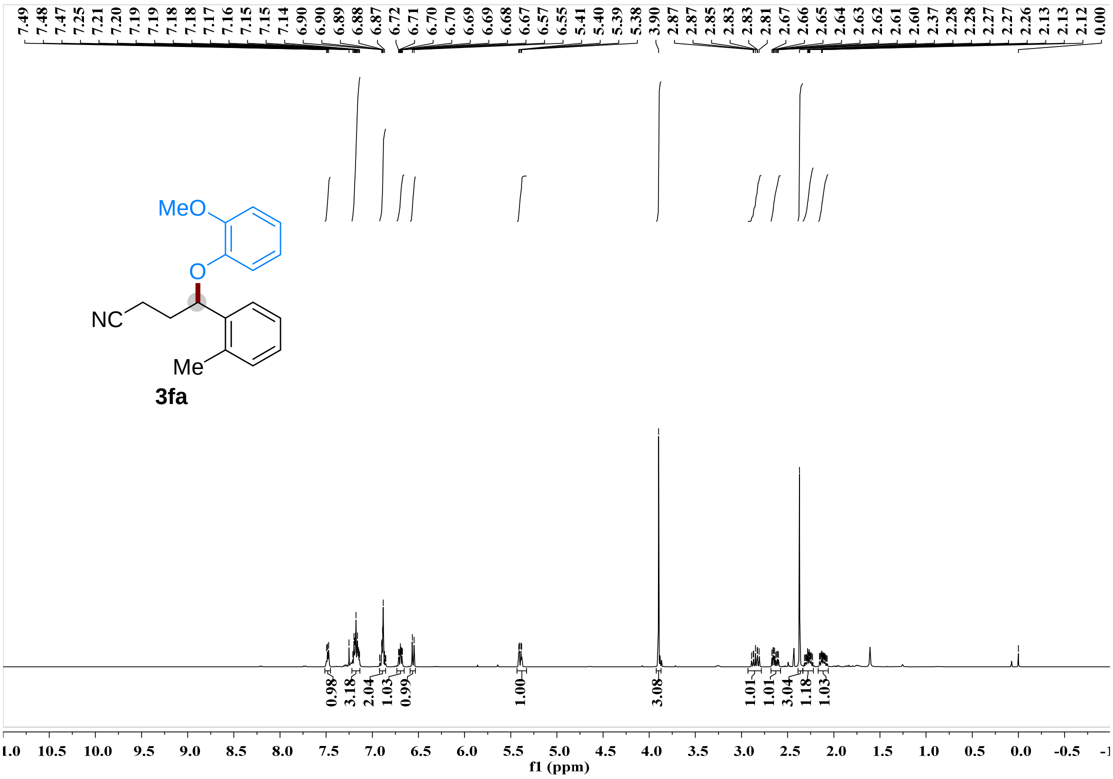


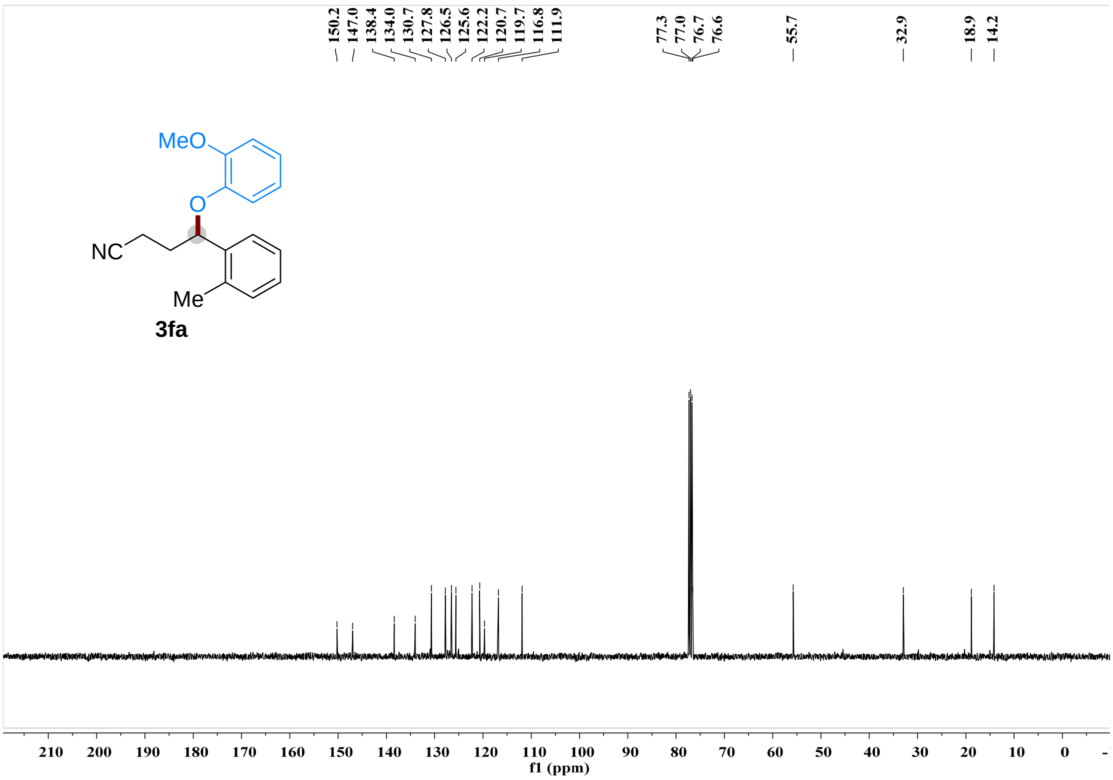
[1]H NMR (400 MHz, $CDCl_3$) and [13]C NMR (100 MHz, $CDCl_3$) spectra of product 3ea



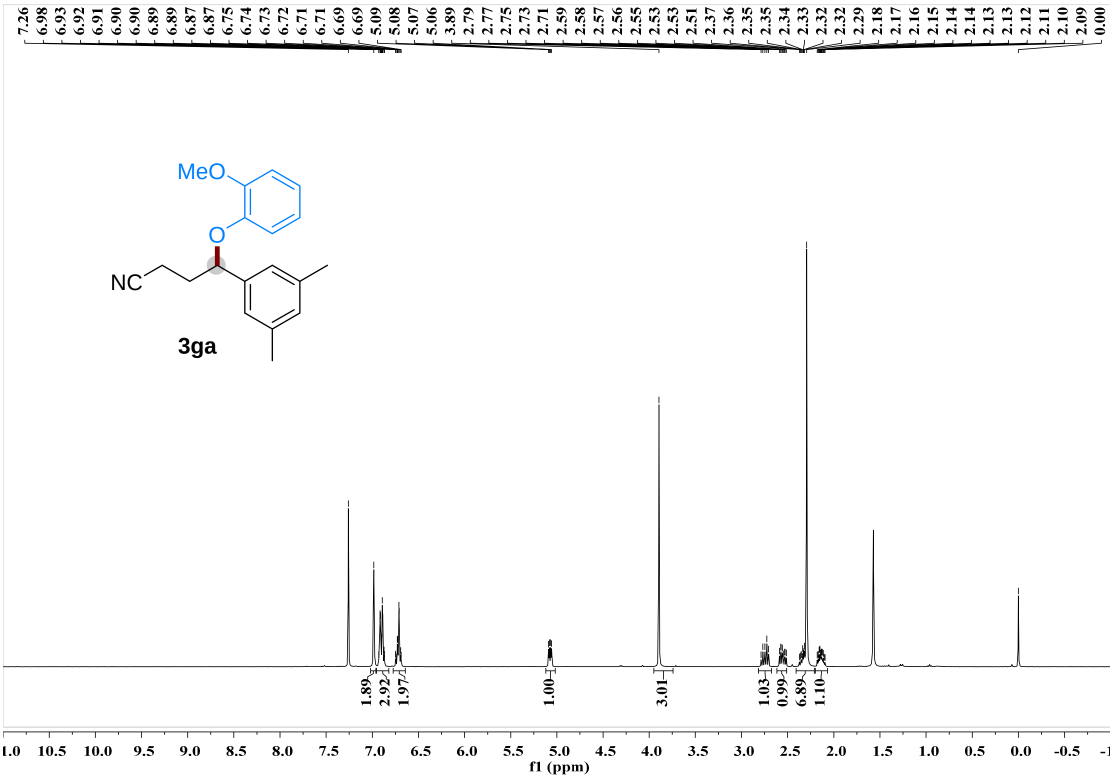


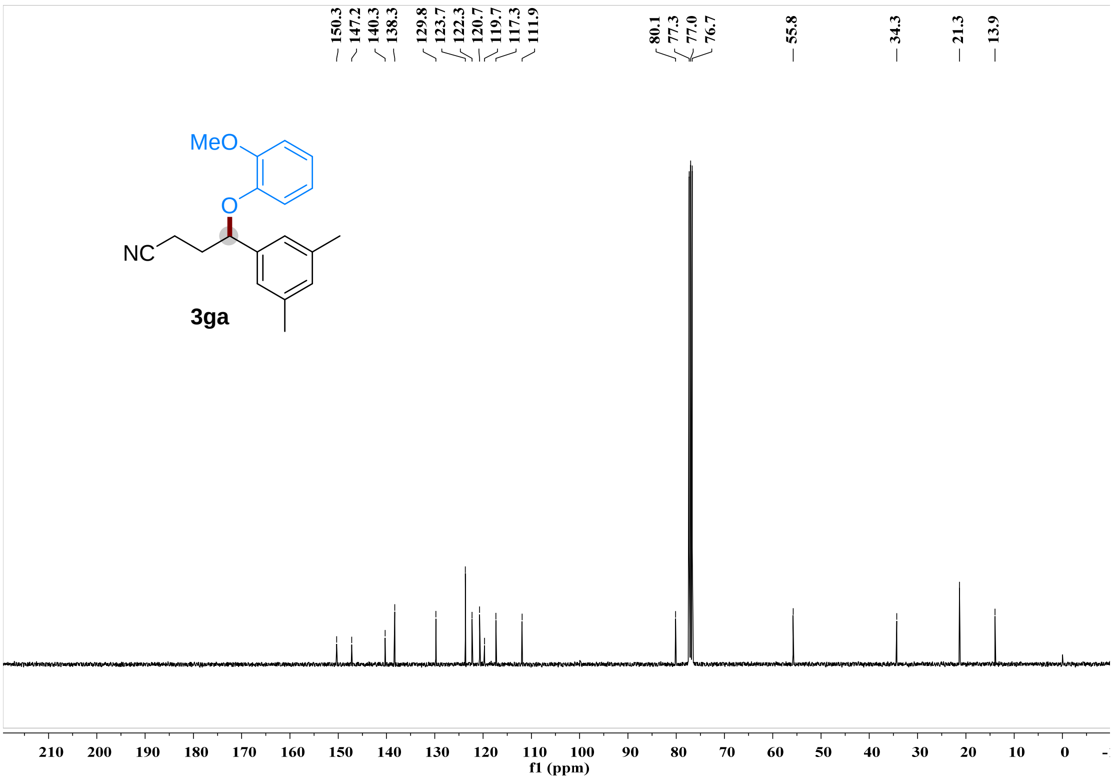
[1]H NMR (400 MHz, $CDCl_3$) and [13]C NMR (100 MHz, $CDCl_3$) spectra of product 3fa



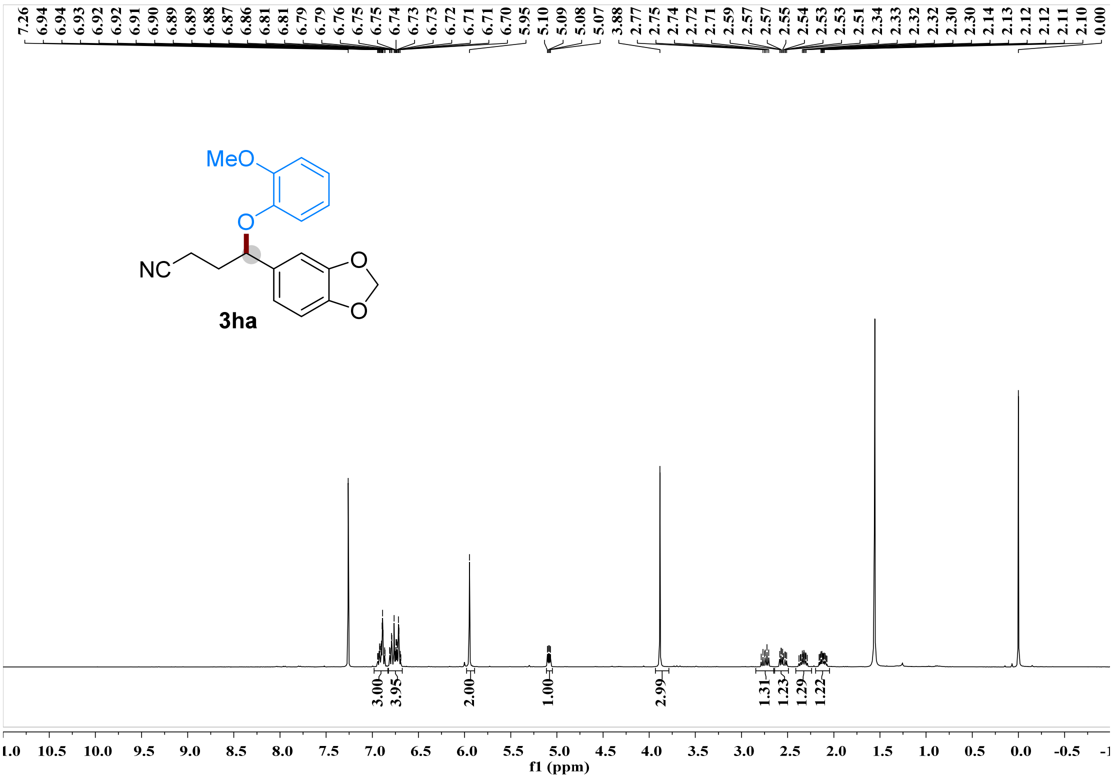


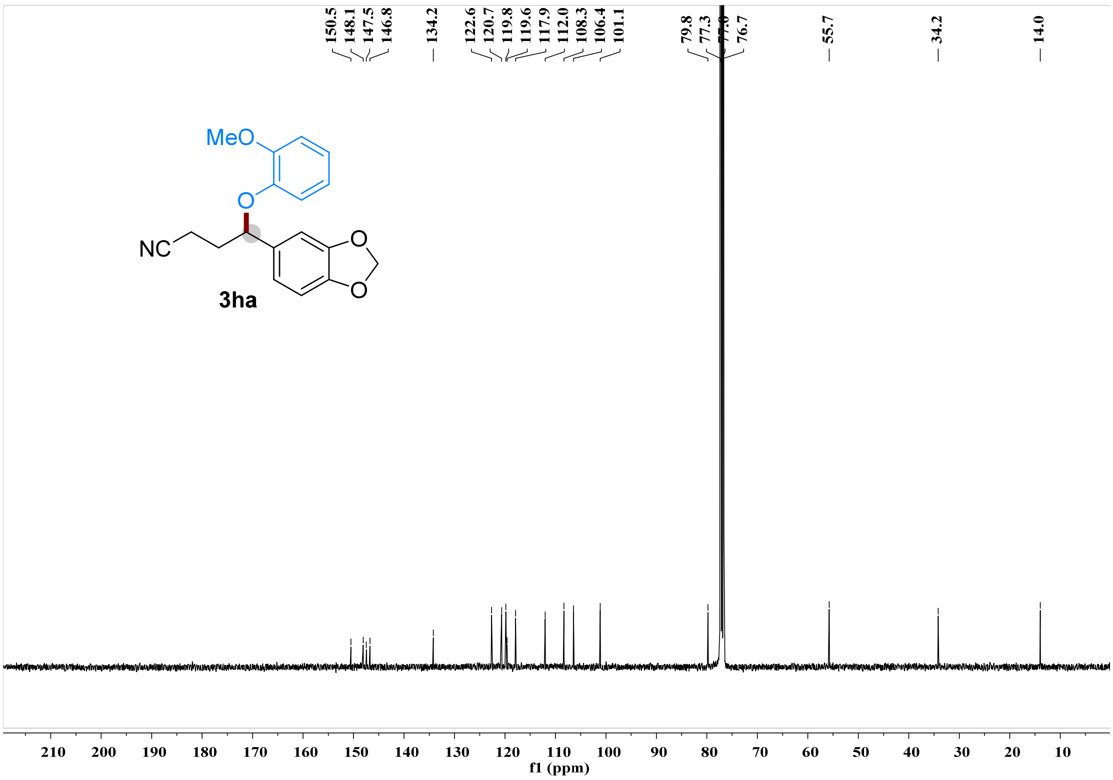
[1]H NMR (400 MHz, $CDCl_3$) and [13]C NMR (100 MHz, $CDCl_3$) spectra of product 3ga



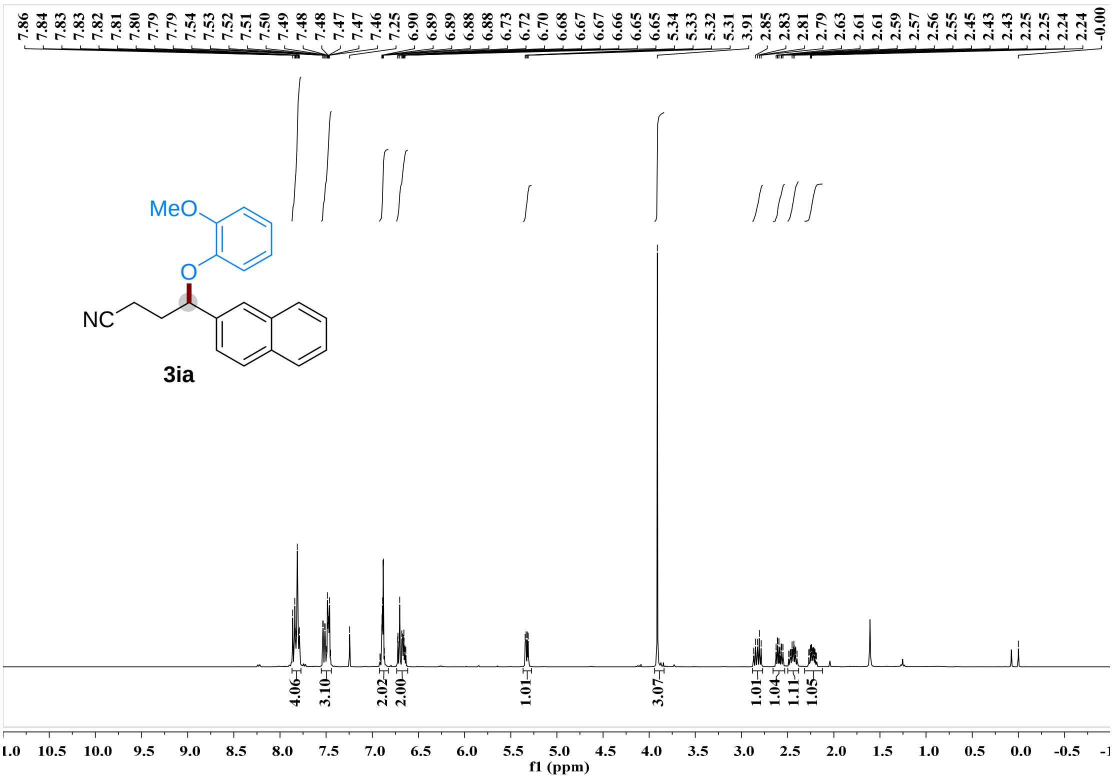


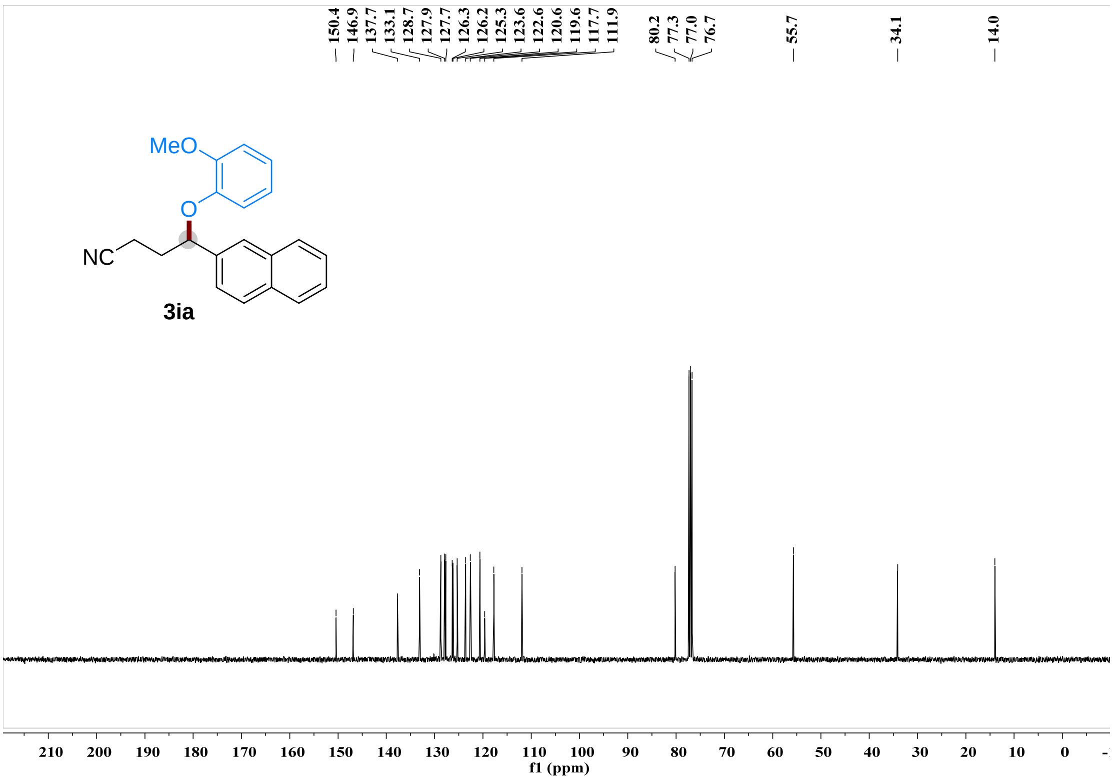
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 3ha



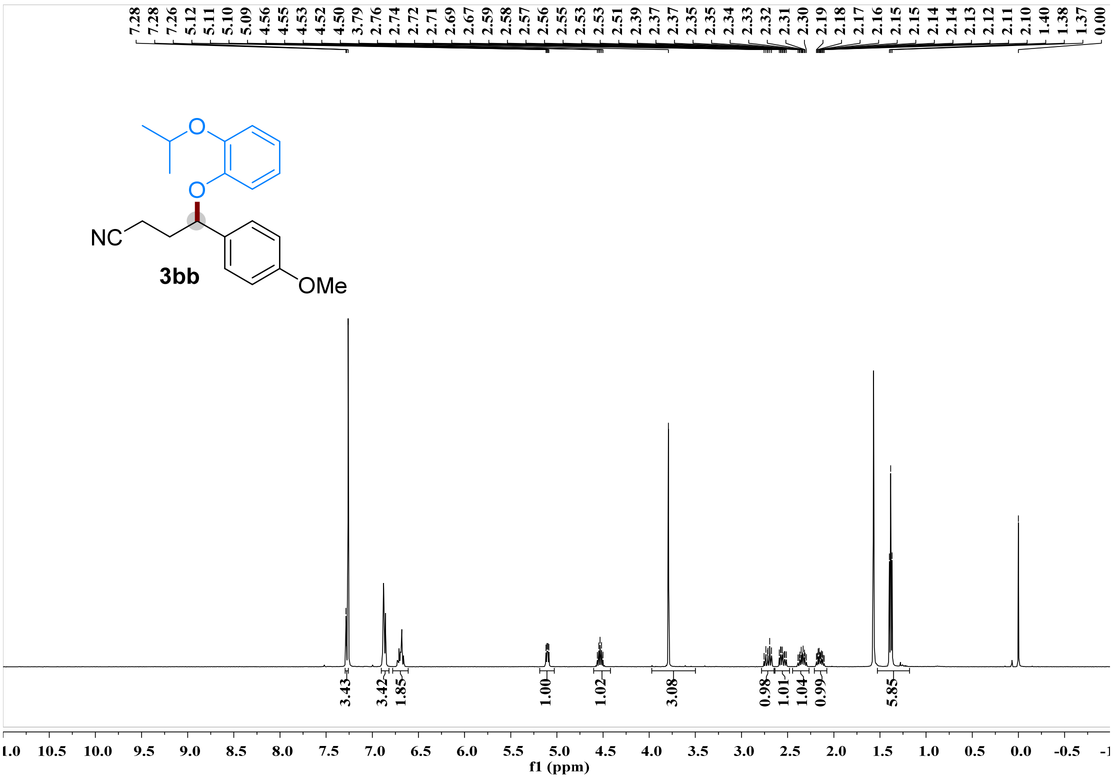


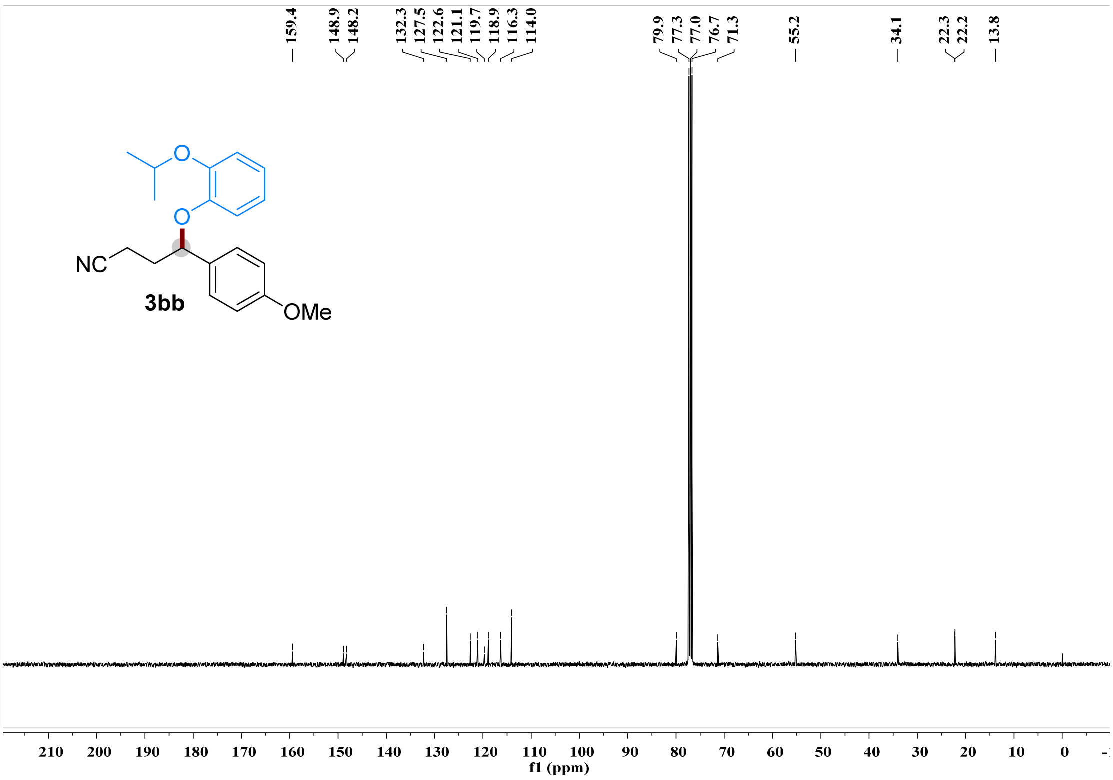
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 3ia



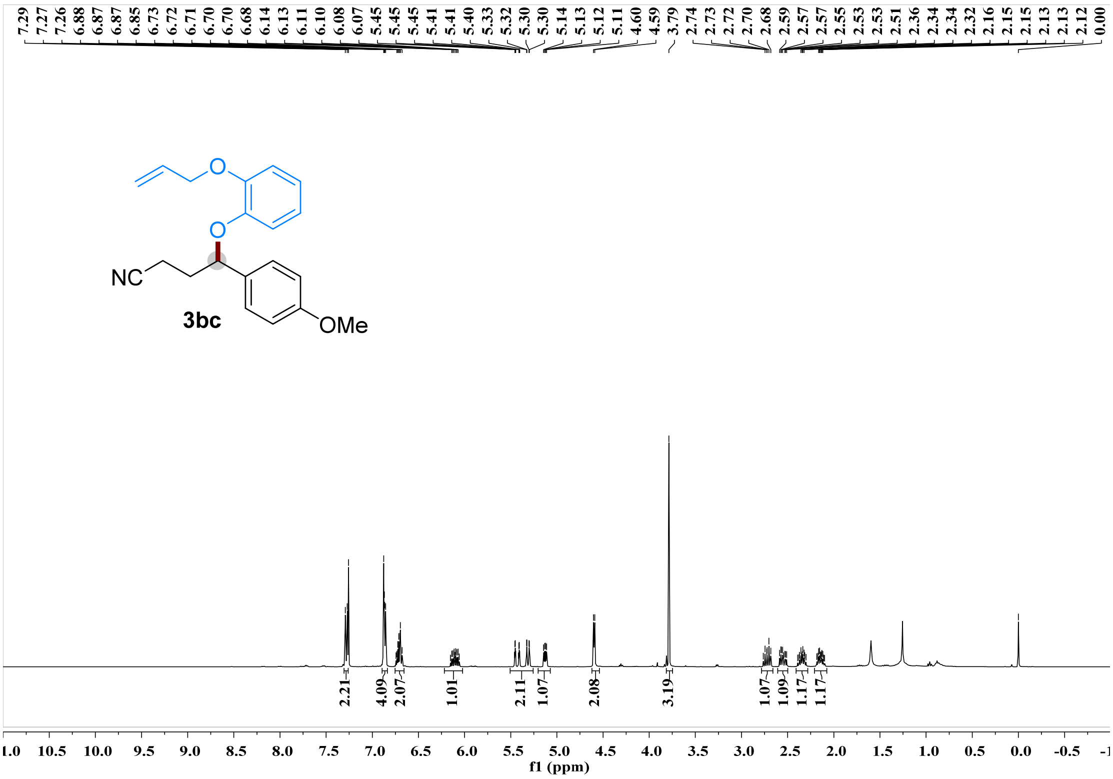


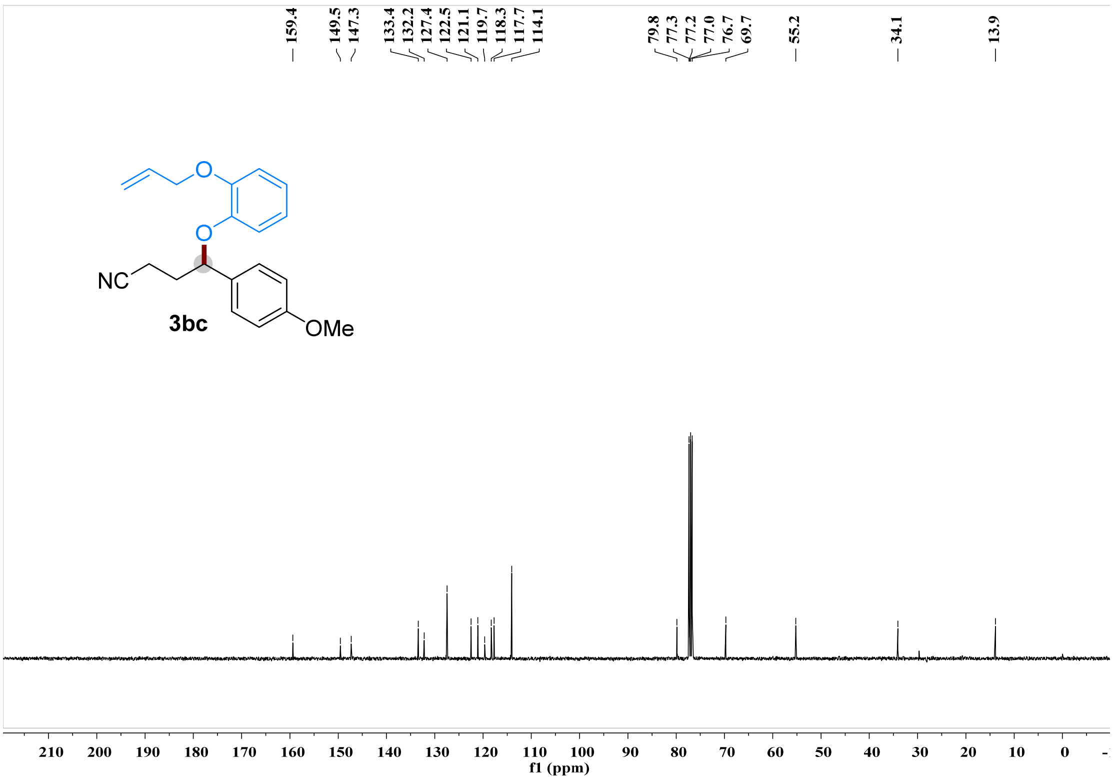
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 3bb



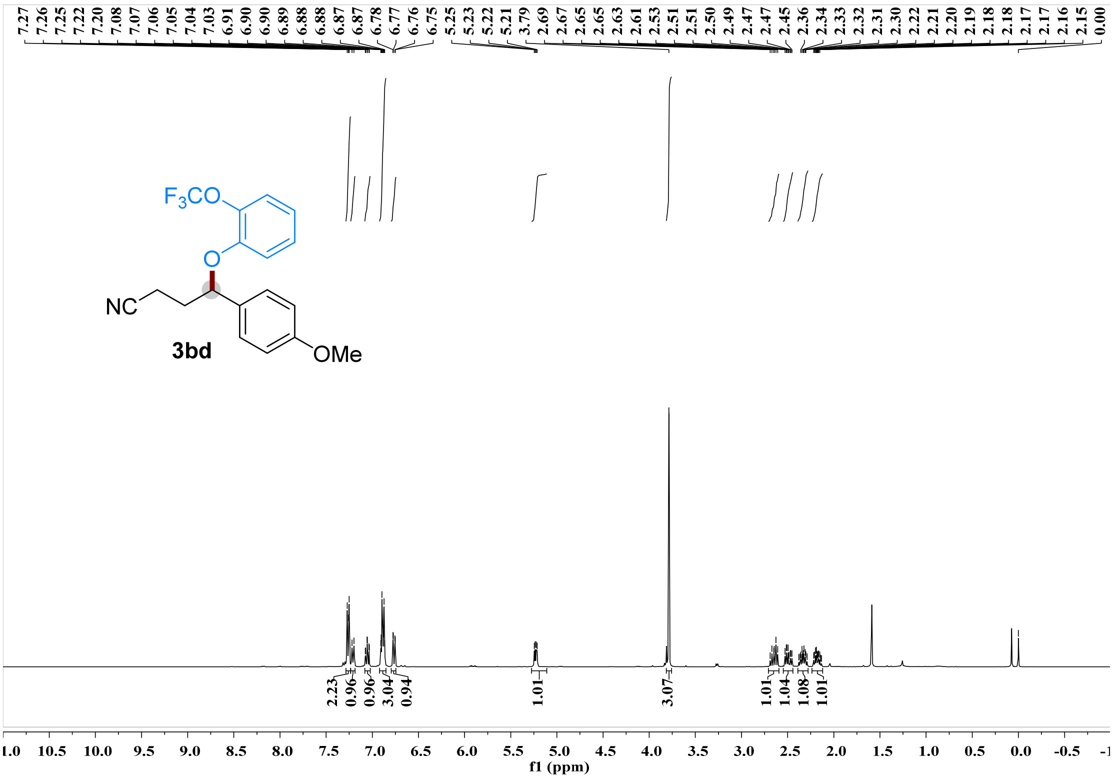


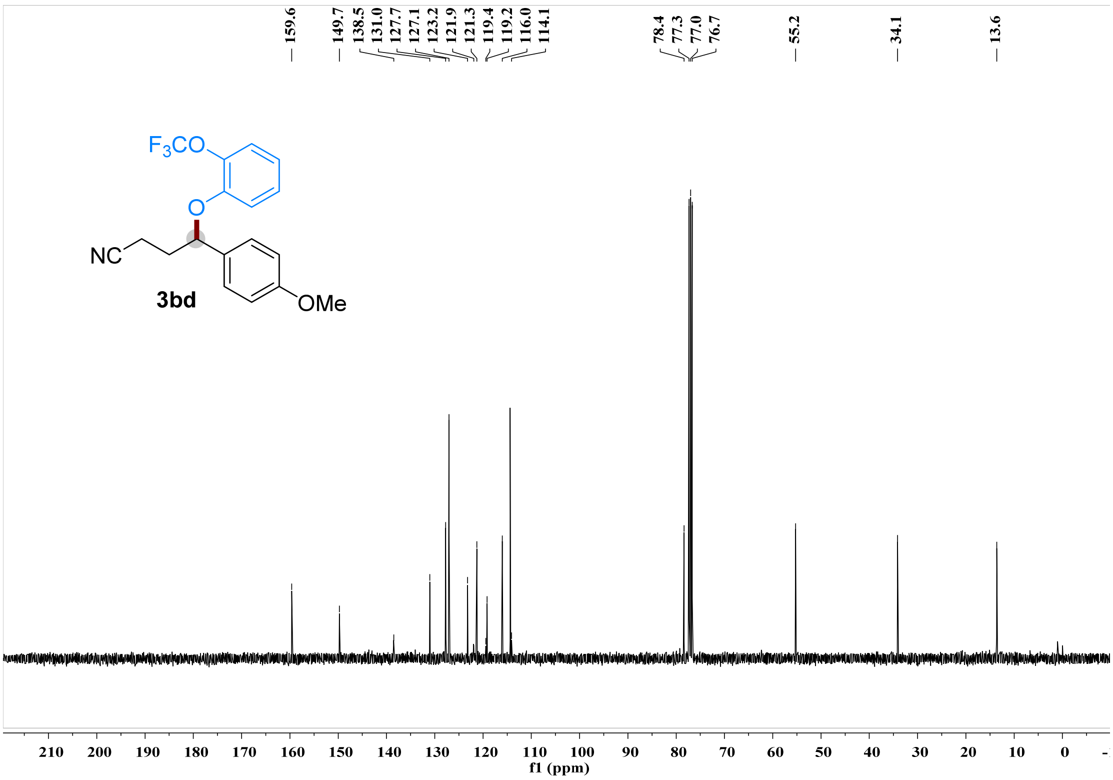
[1]H NMR (400 MHz, $CDCl_3$) and [13]C NMR (100 MHz, $CDCl_3$) spectra of product 3bc

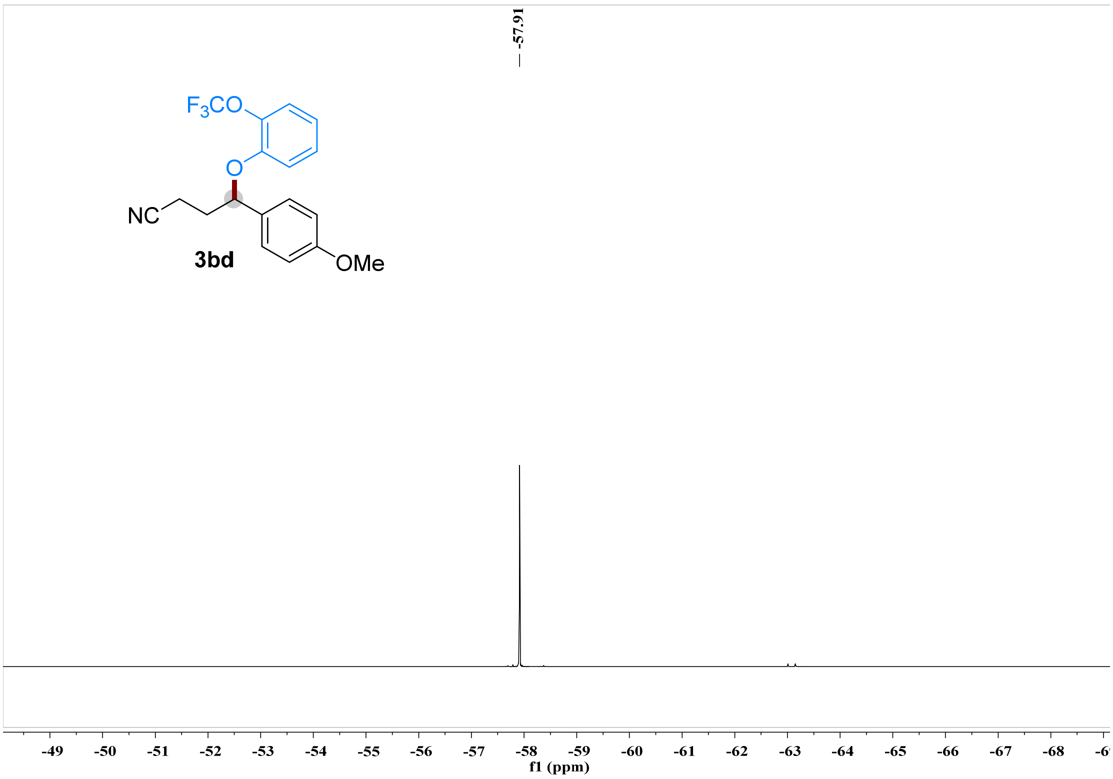




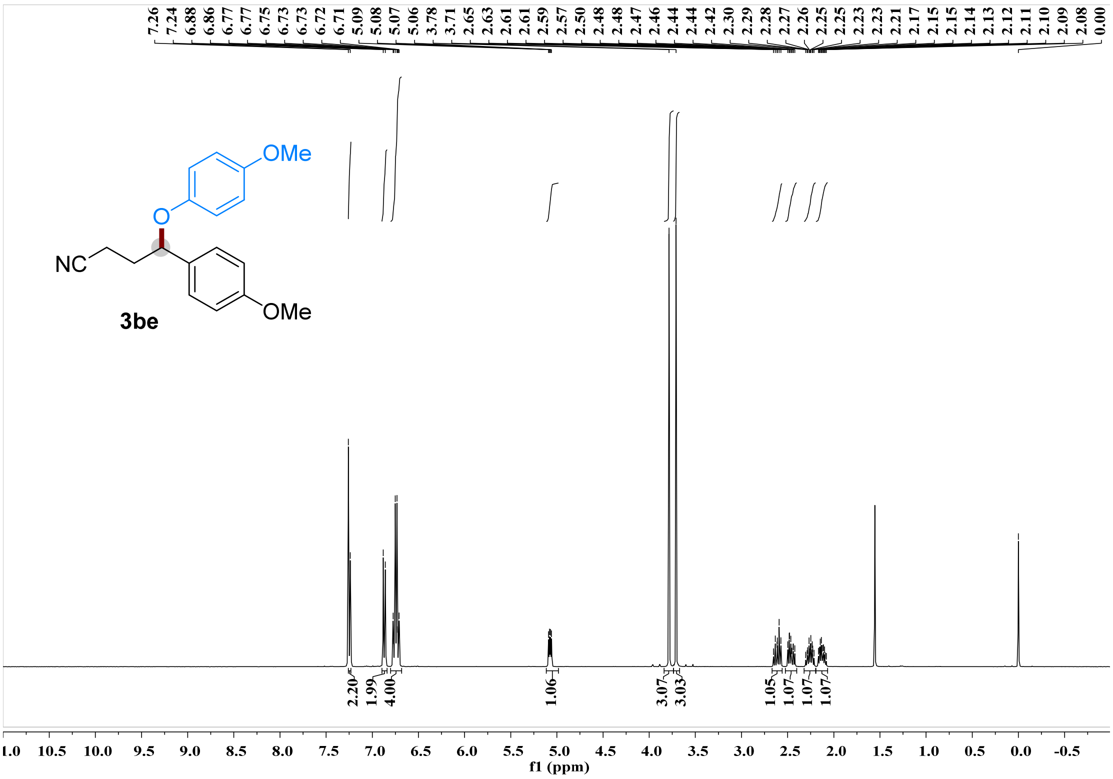
[1]H NMR (400 MHz, $CDCl_3$), [13]C NMR (100 MHz, $CDCl_3$) and [19]F NMR (376 Hz, $CDCl_3$) spectra of product 3bd

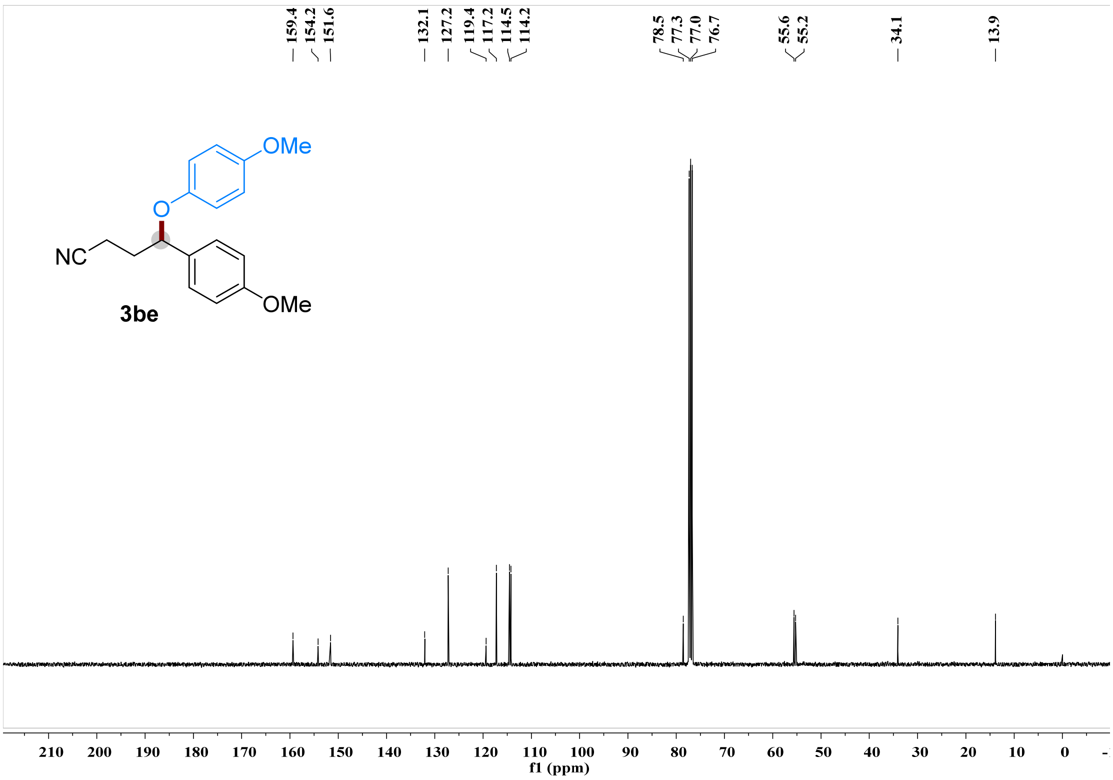




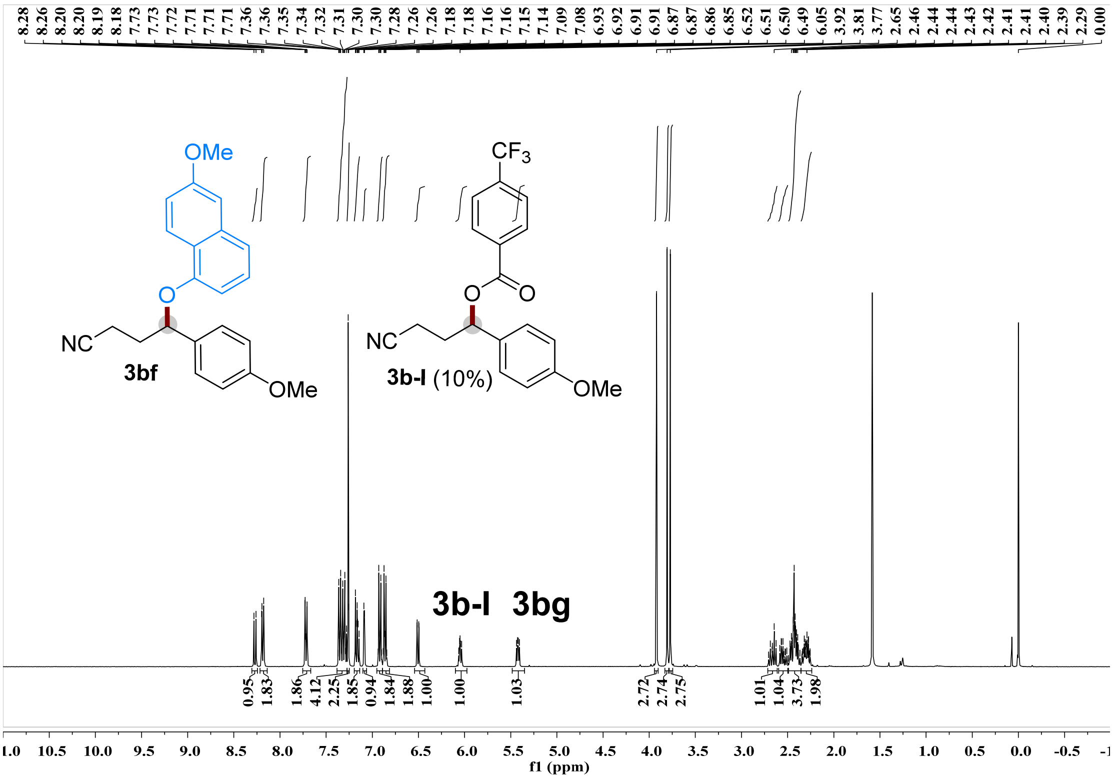

-57.91
F3CO
O
NC
3bd
OMe
-49
-50
-51
-52
-53
-54
-55
-56
-57
-58
-59
-60
-61
-62
-63
-64
-65
-66
-67
-68
f1 (ppm)

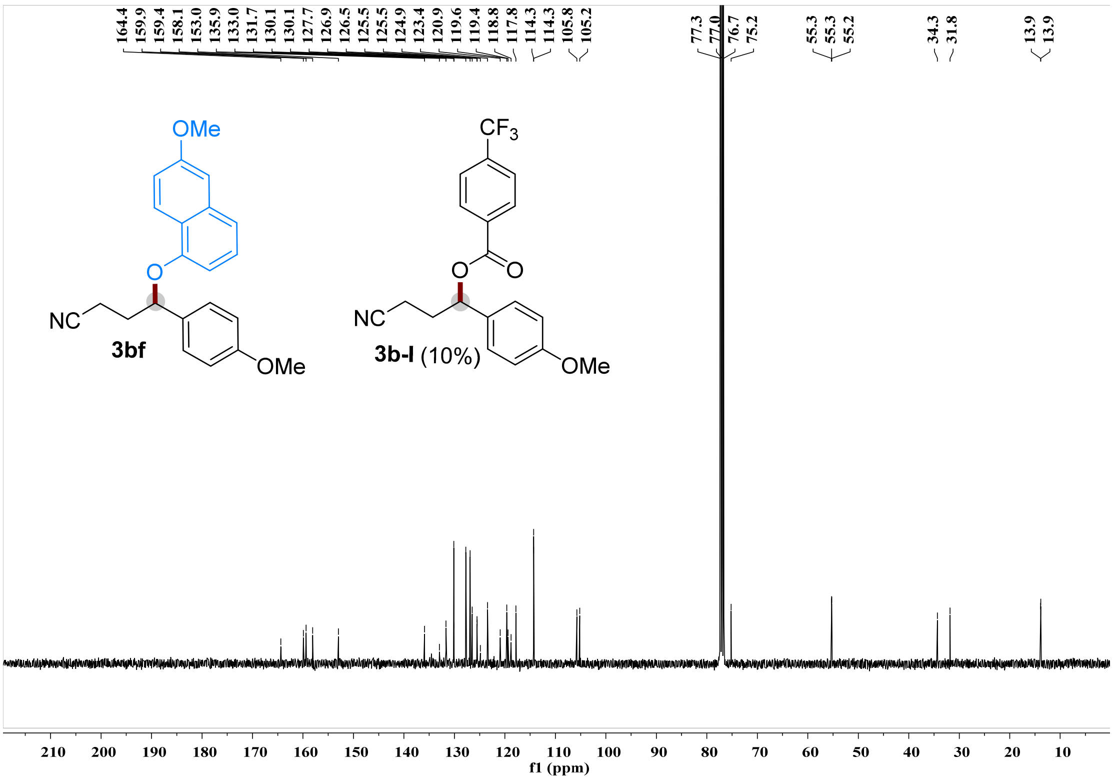
[1]H NMR (400 MHz, $CDCl_3$) and [13]C NMR (100 MHz, $CDCl_3$) spectra of product 3be

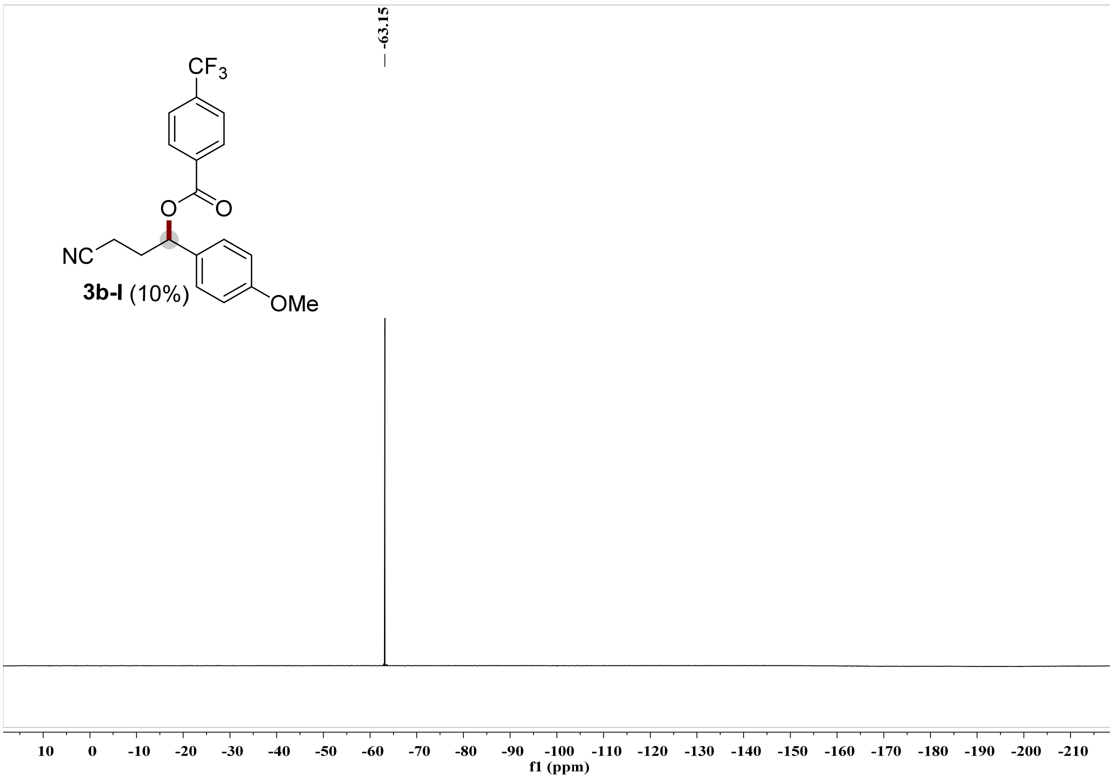




^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 3bf

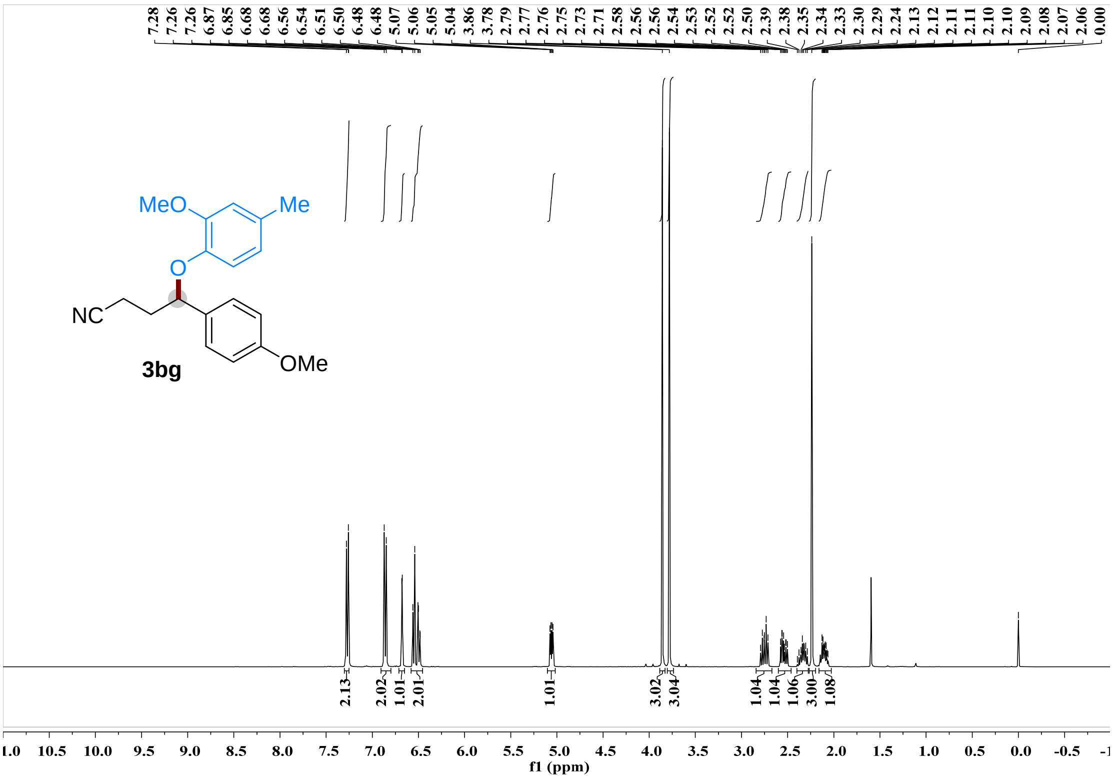


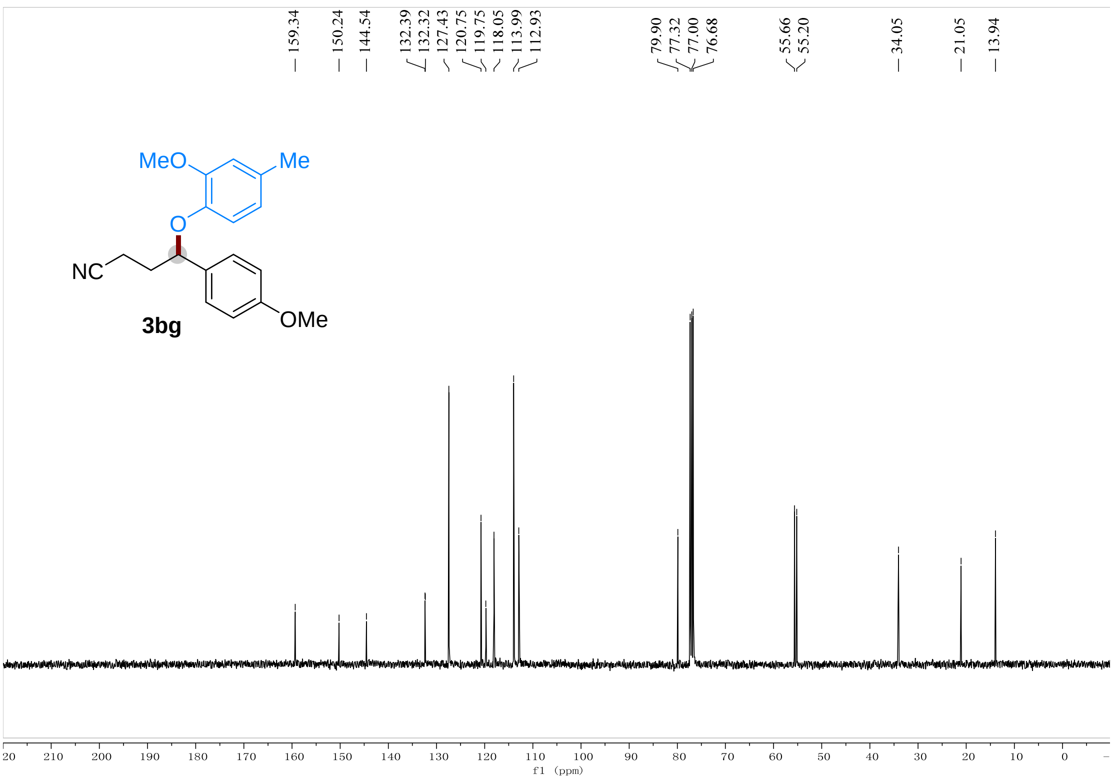




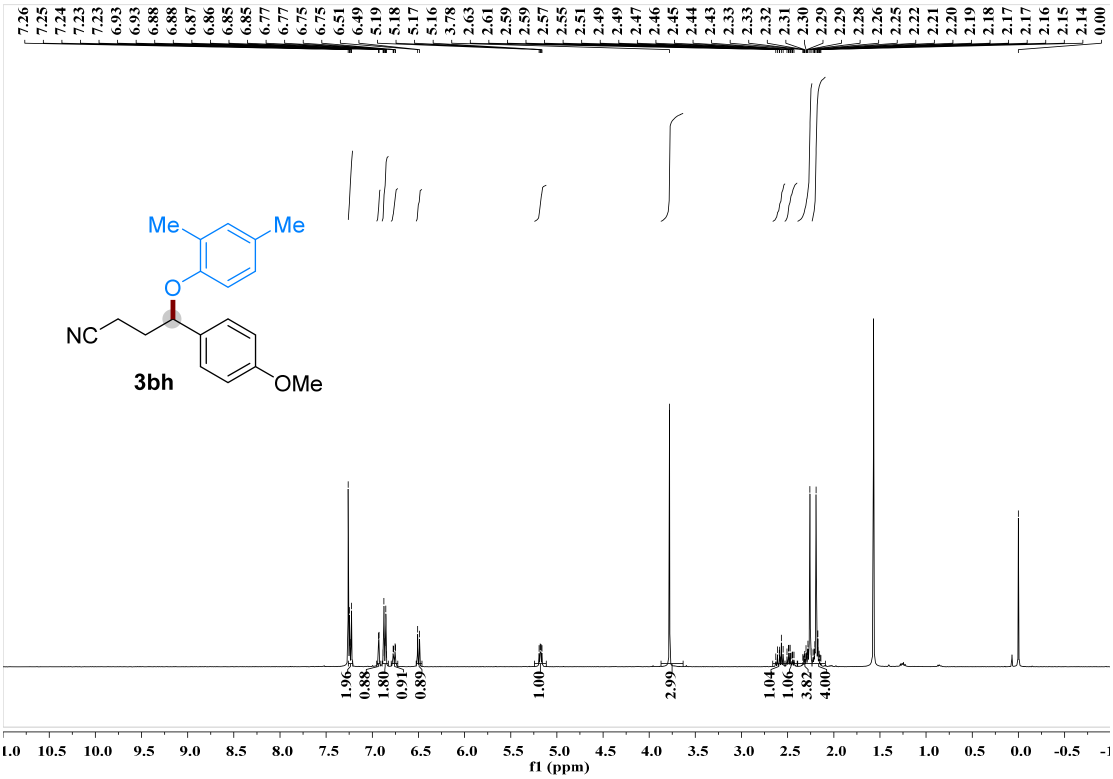
-63.15
CF3
O
O
NC
OMe
3b-I (10%)
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

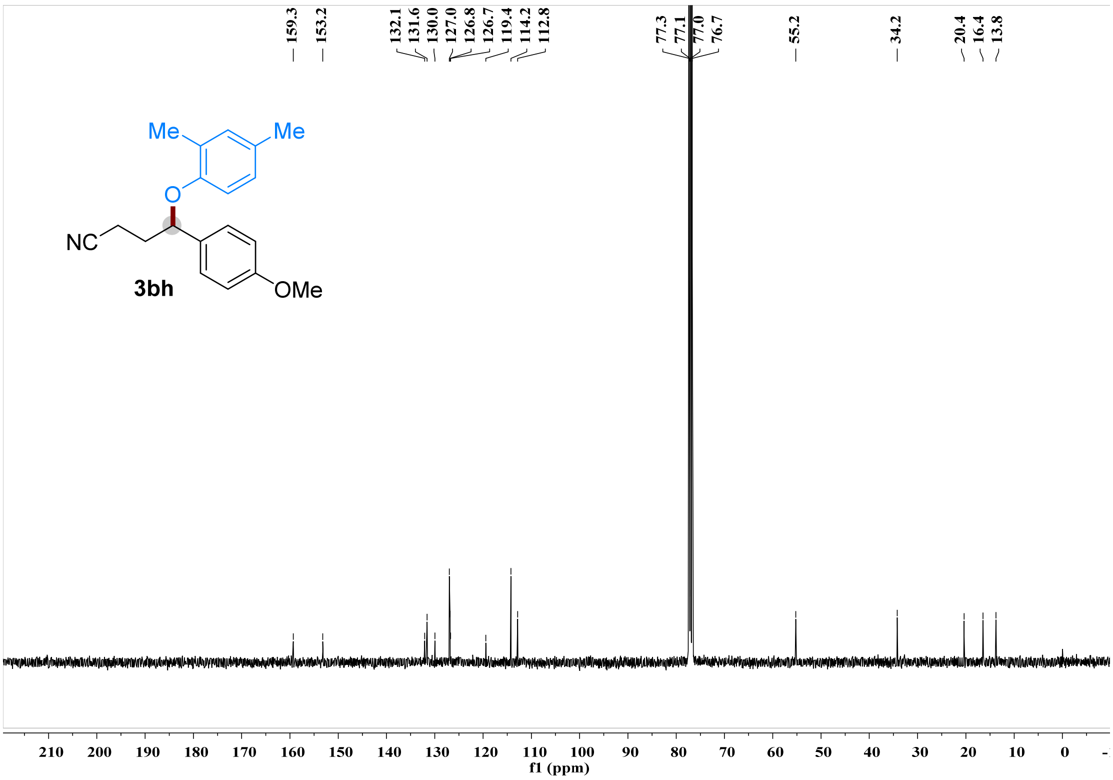
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 3bg



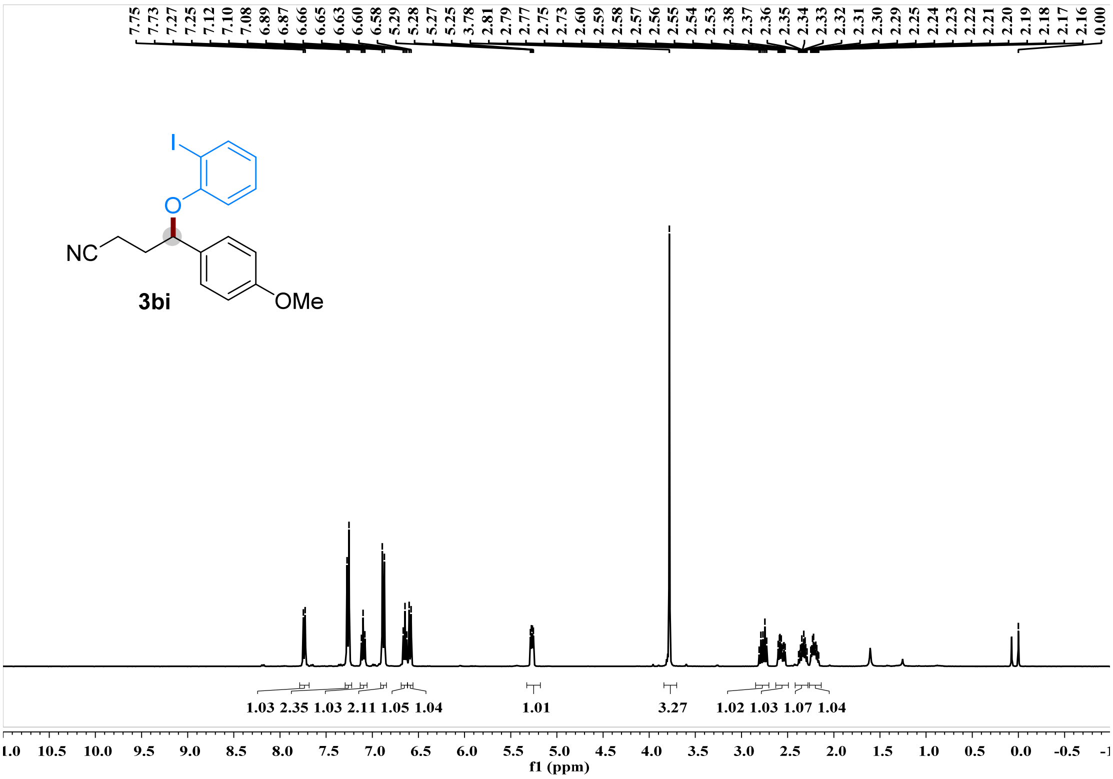


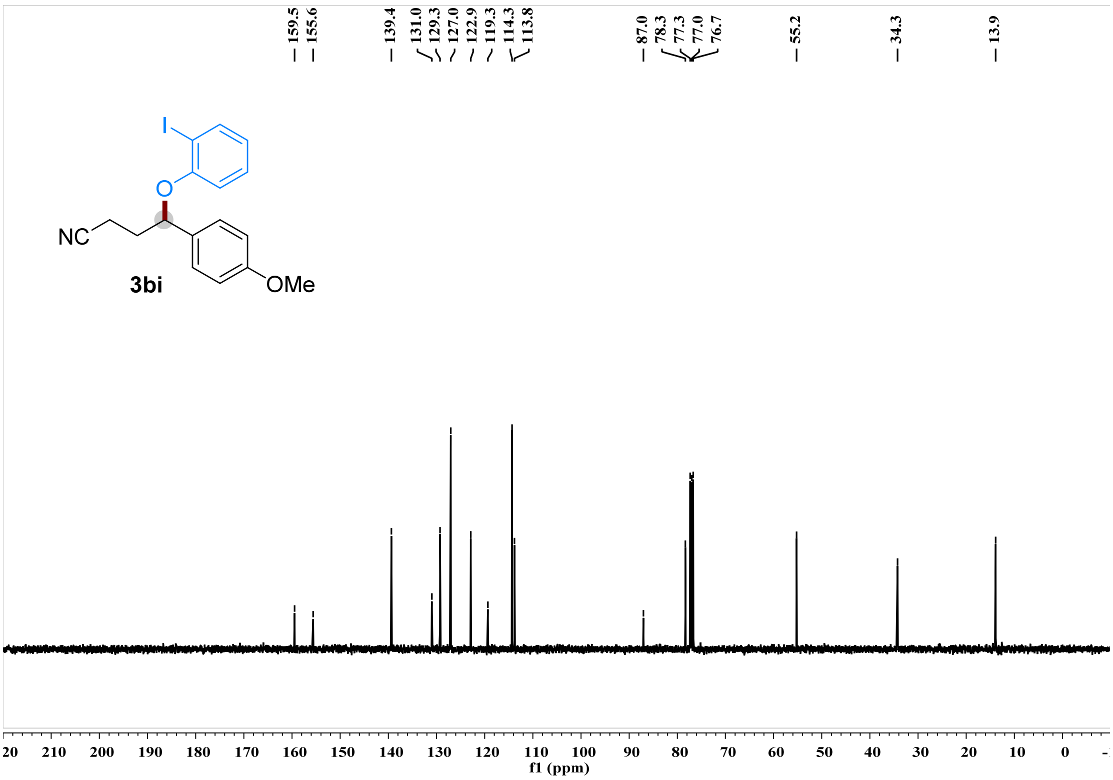
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 3bh



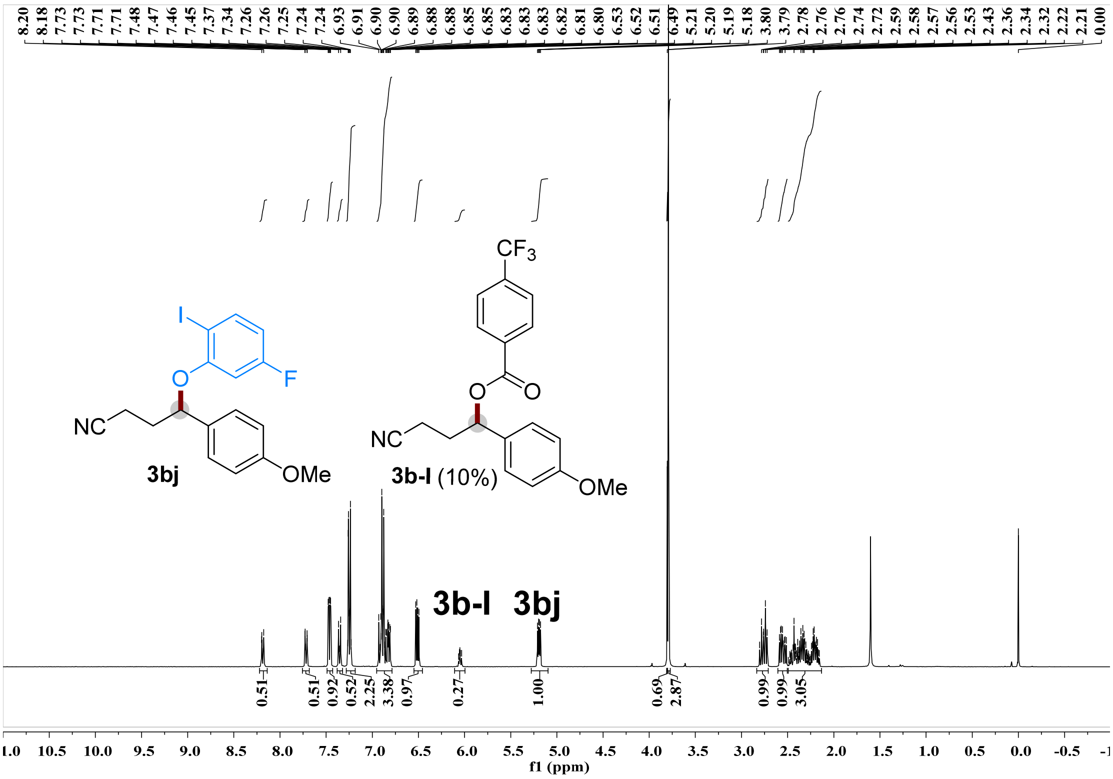


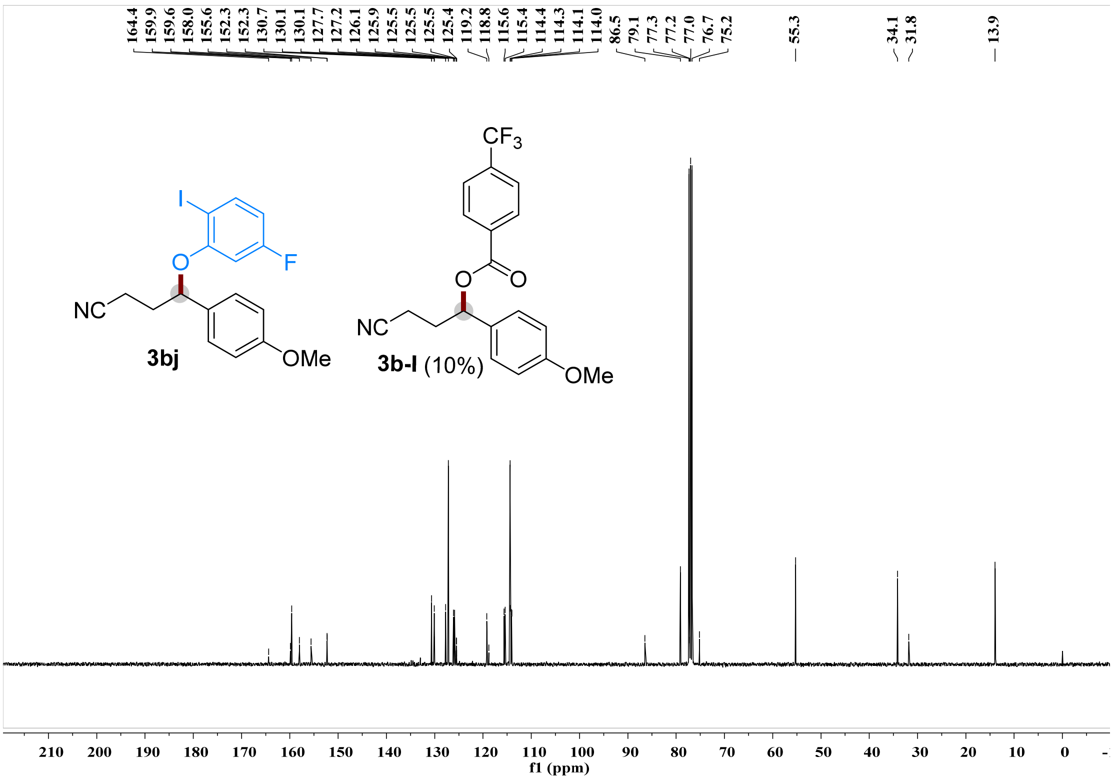
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 3bi

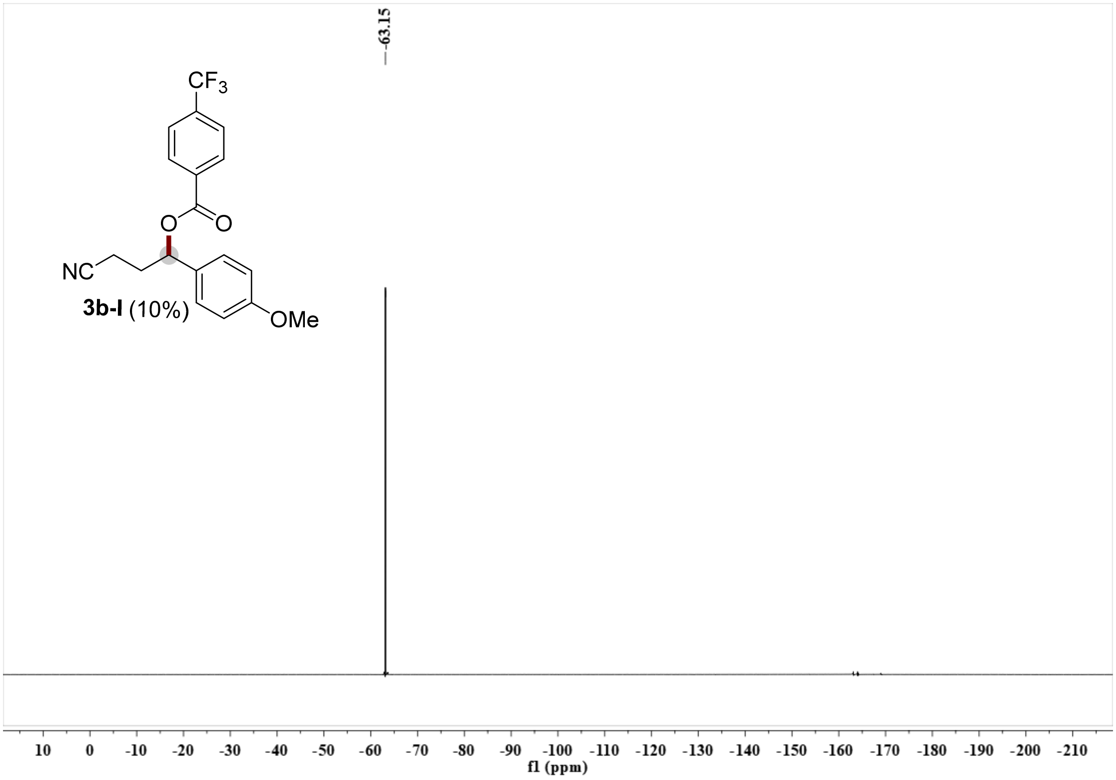




^1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 3bj

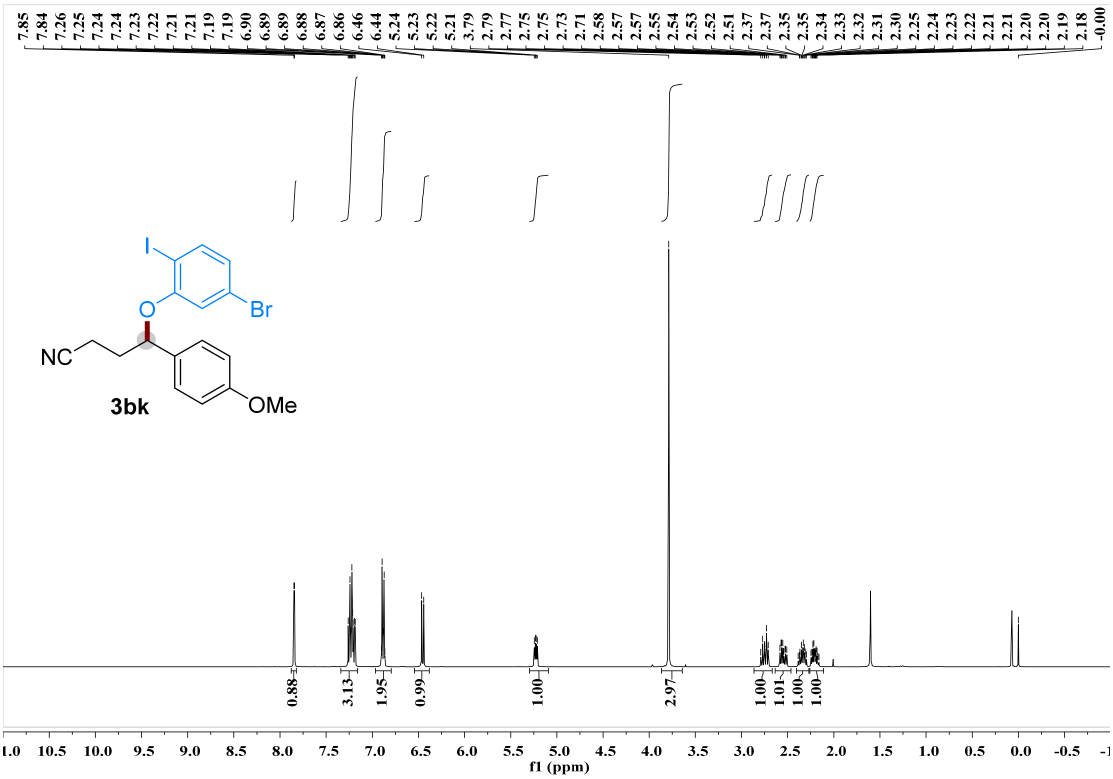


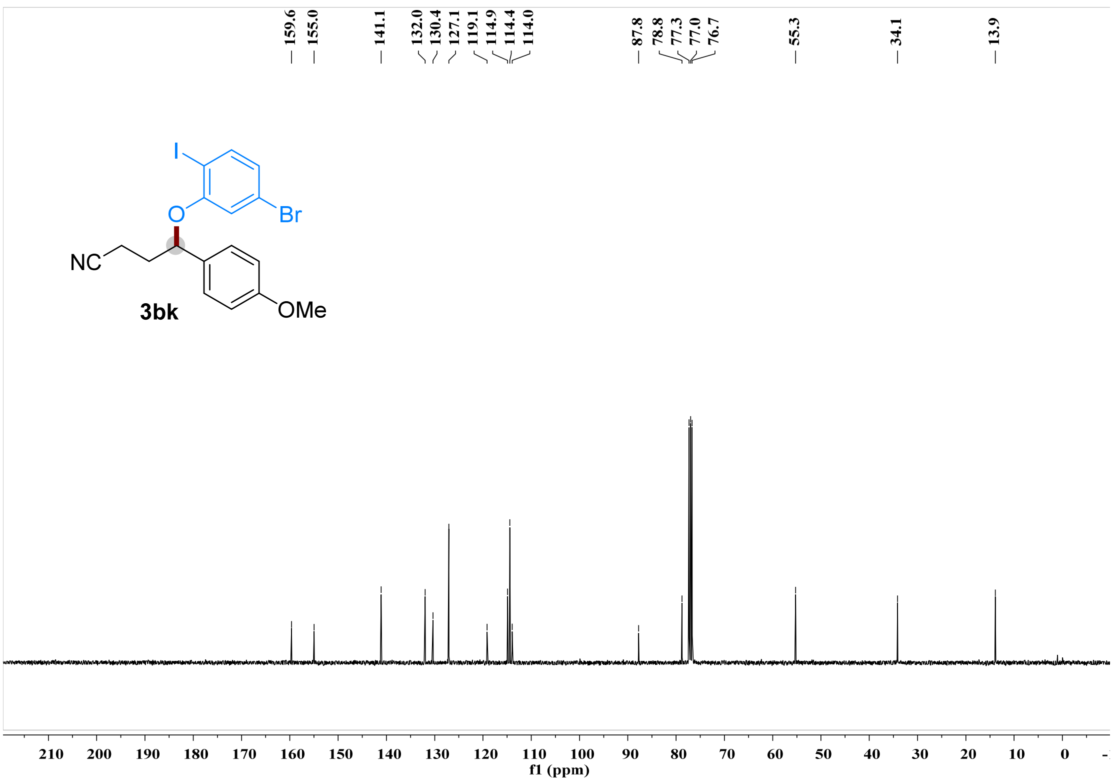




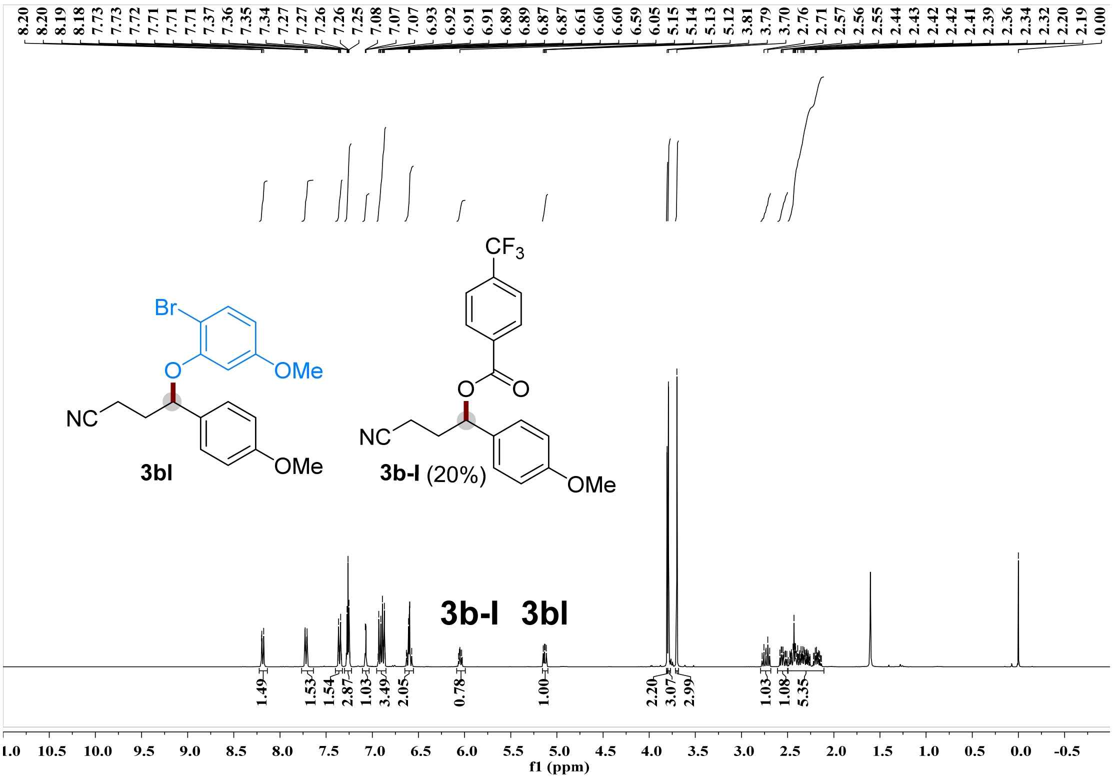
-63.15
CF3
O
O
NC
3b-l (10%)
OMe
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

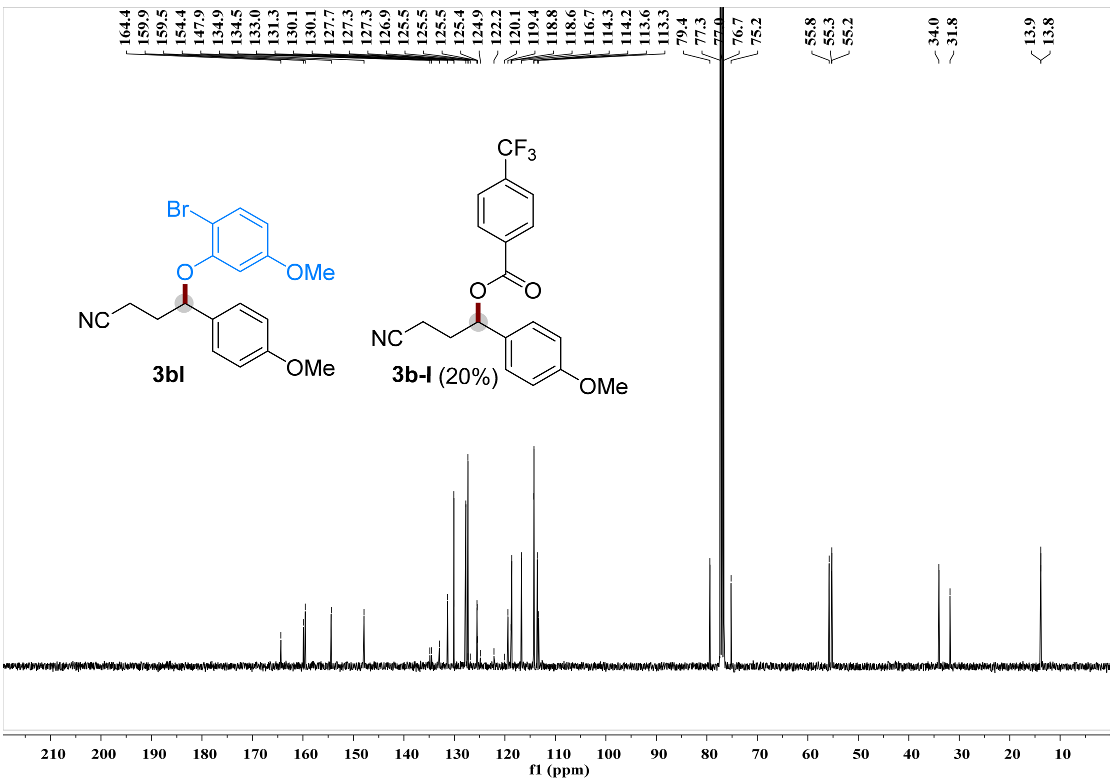
[1]H NMR (400 MHz, $CDCl_3$) and [13]C NMR (100 MHz, $CDCl_3$) spectra of product 3bk

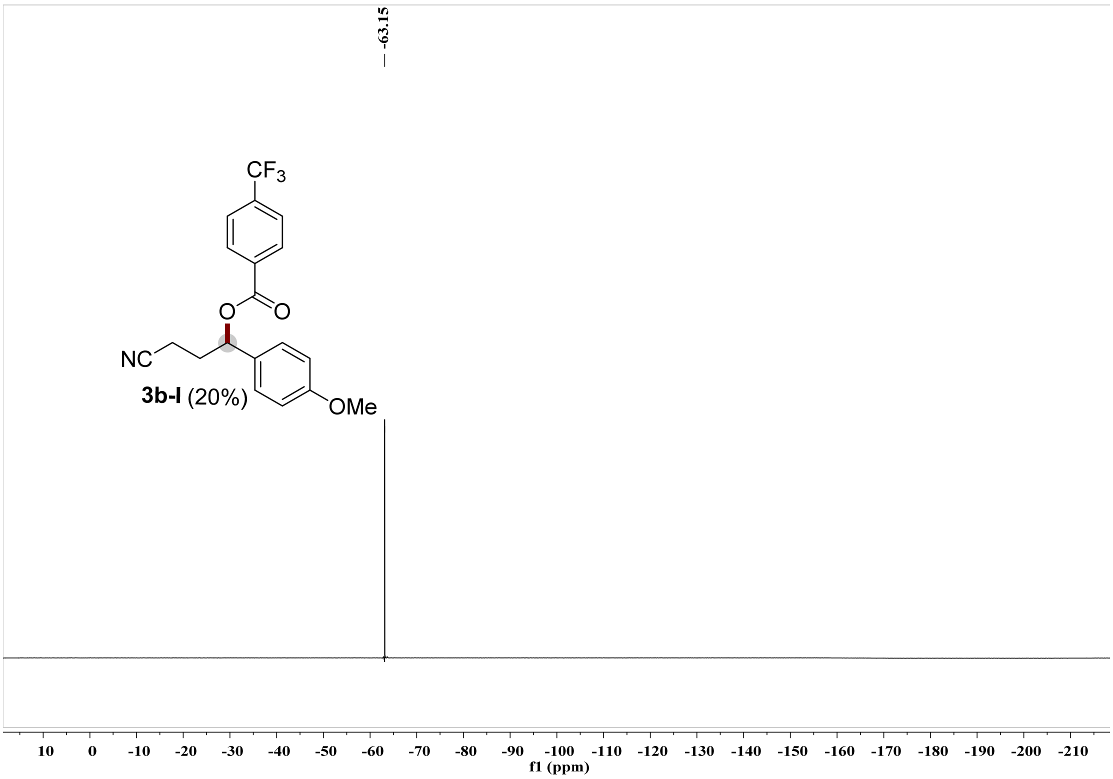




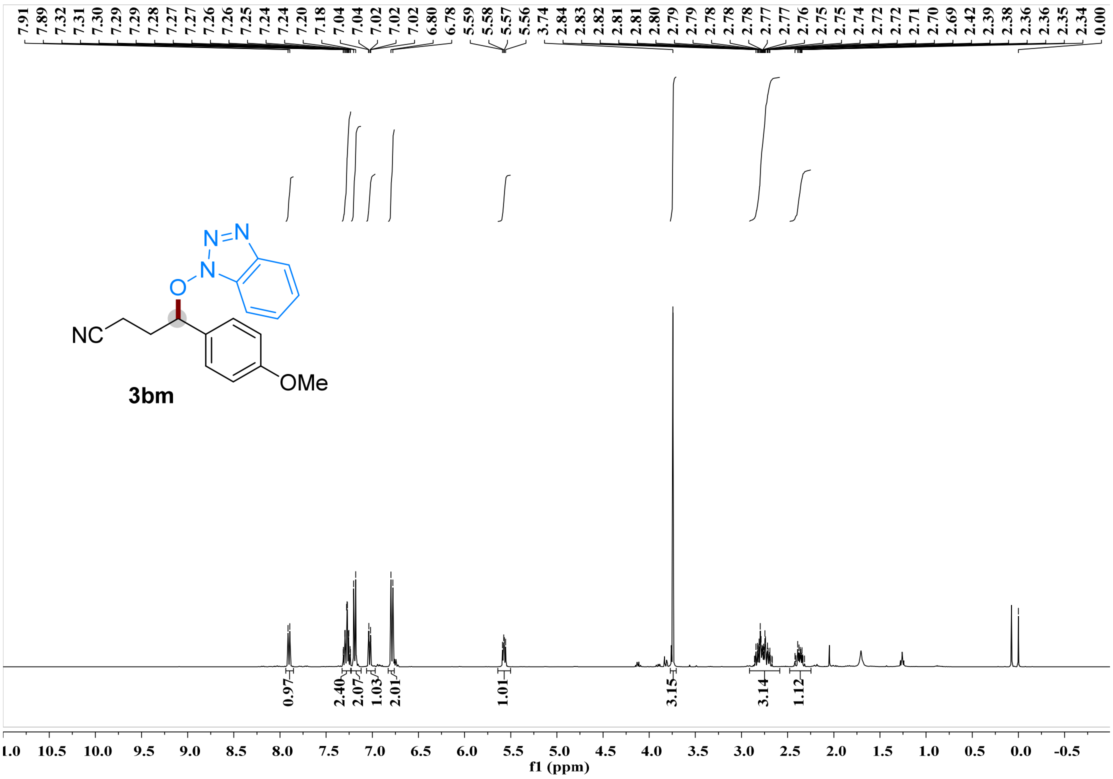
^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (100 MHz, CDCl$_3$) spectra of product 3bl

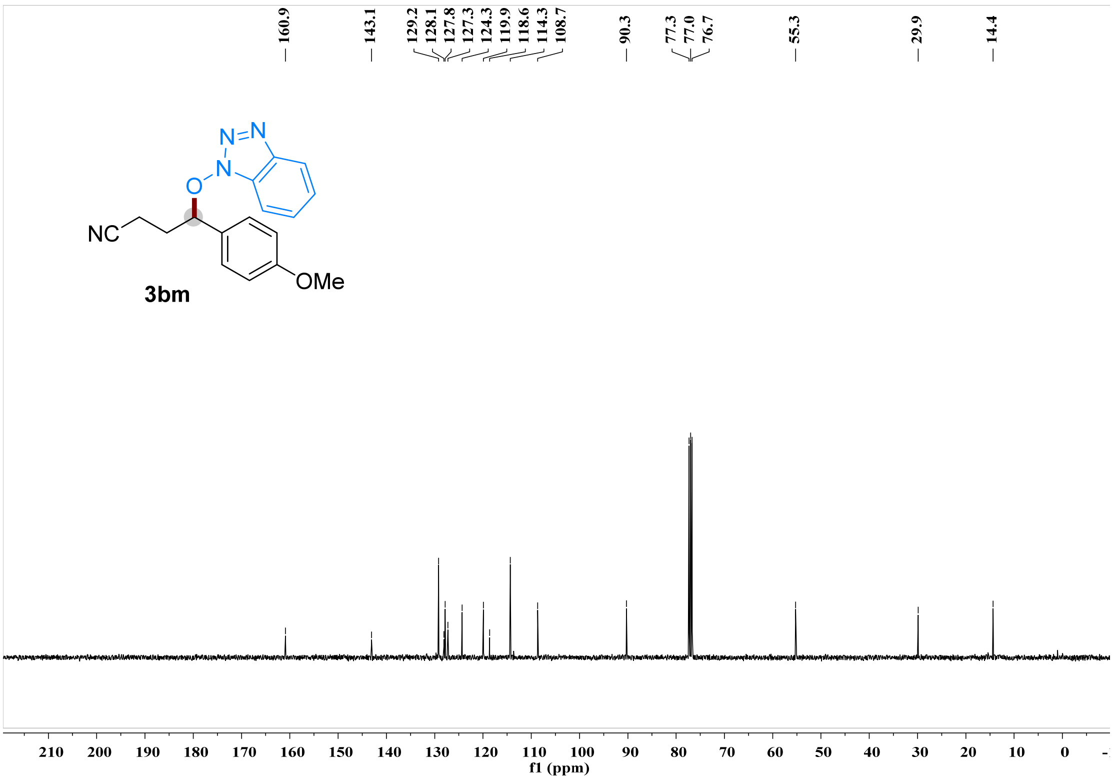




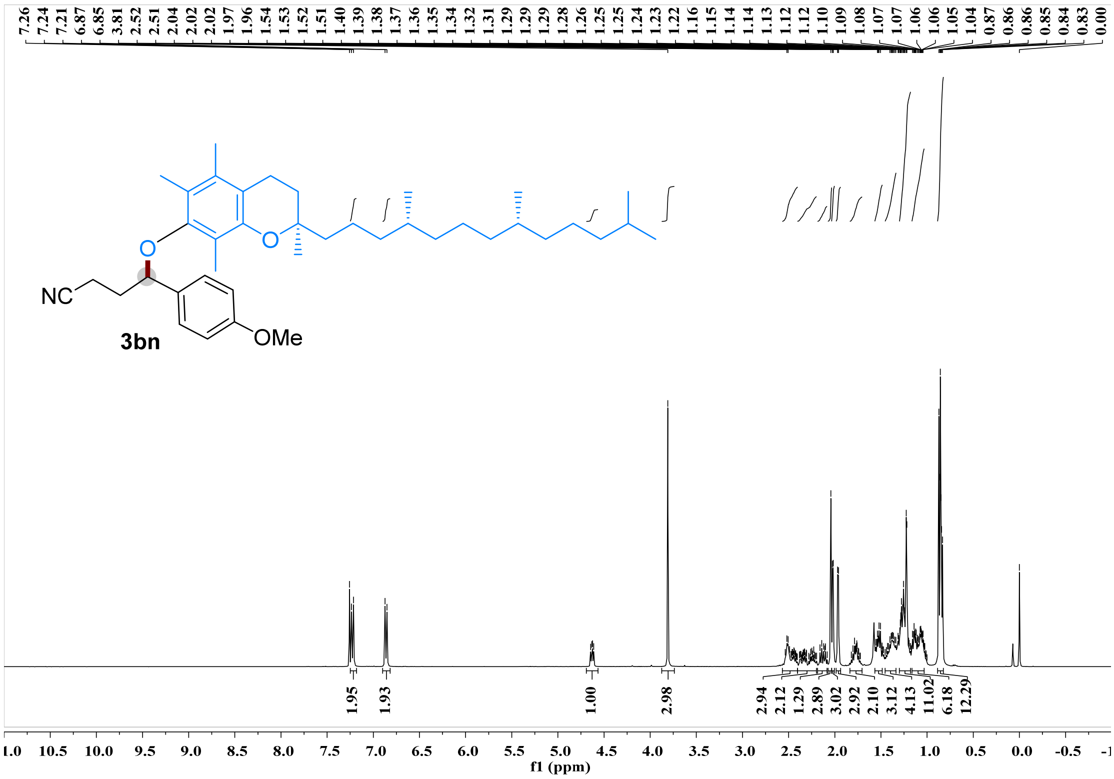

-63.15
CF3
O
O
NC
3b-I (20%)
OMe
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

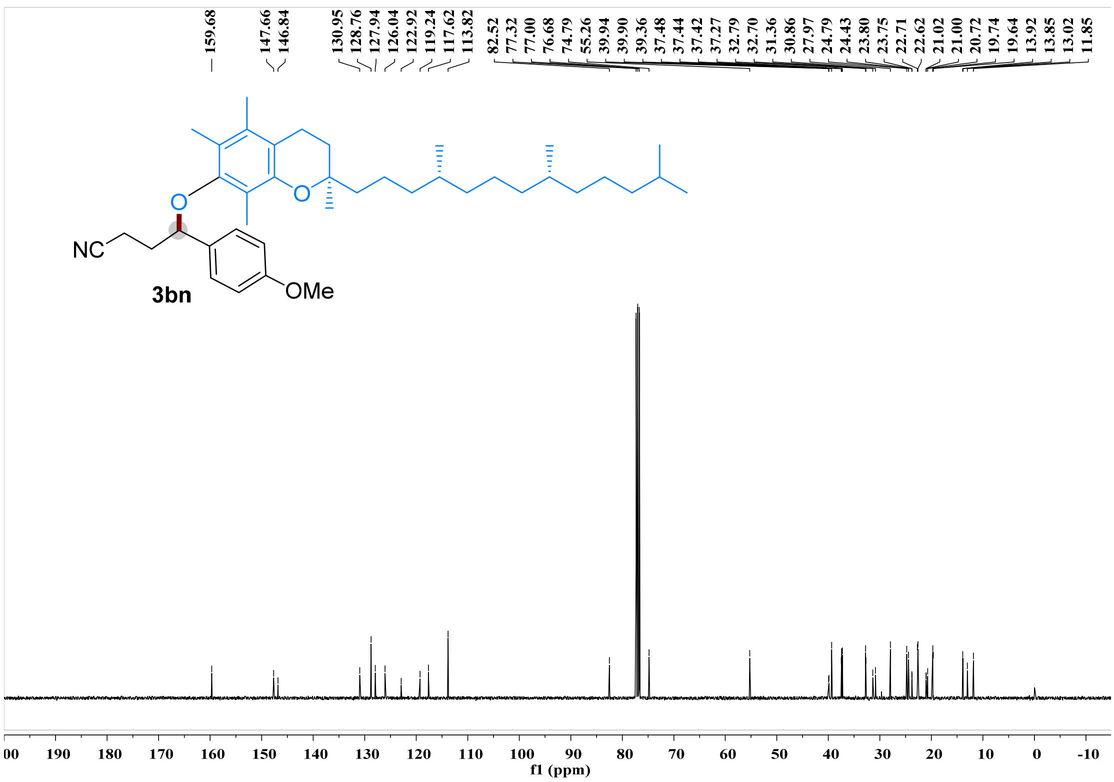
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 3bm

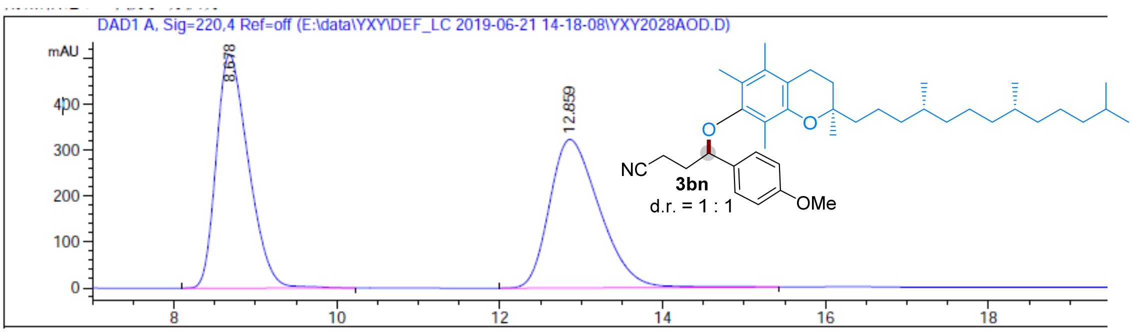




^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$) and HPLC spectra of product 3bn







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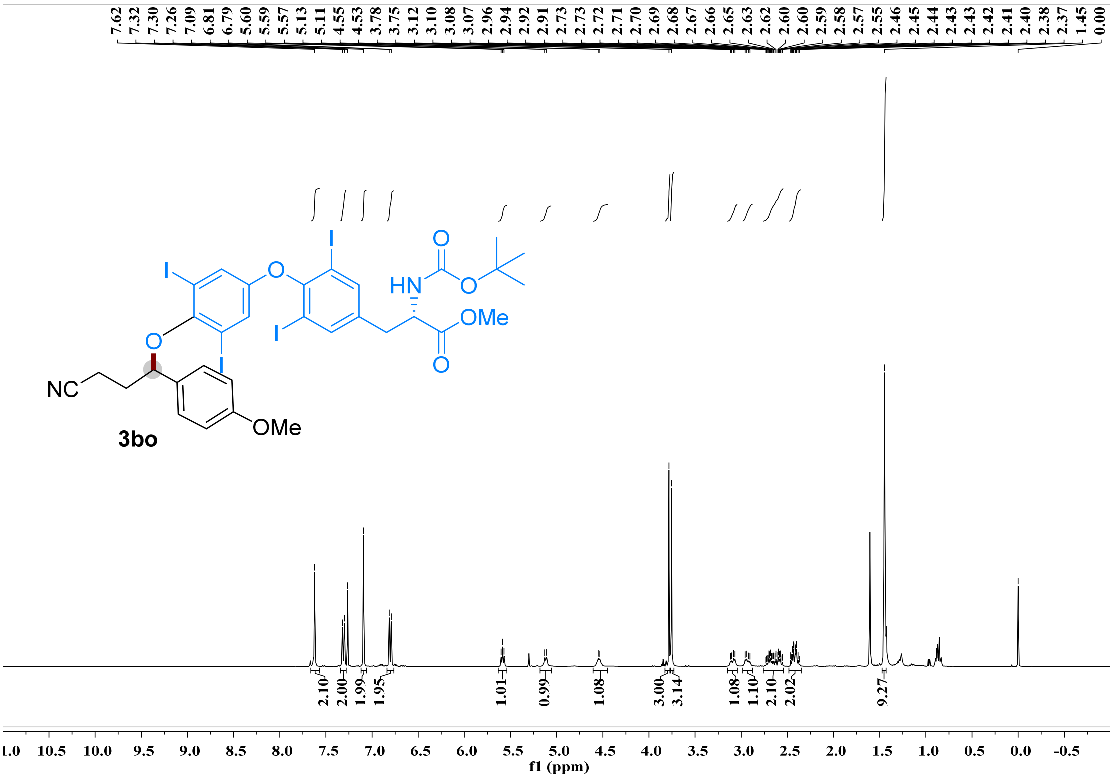
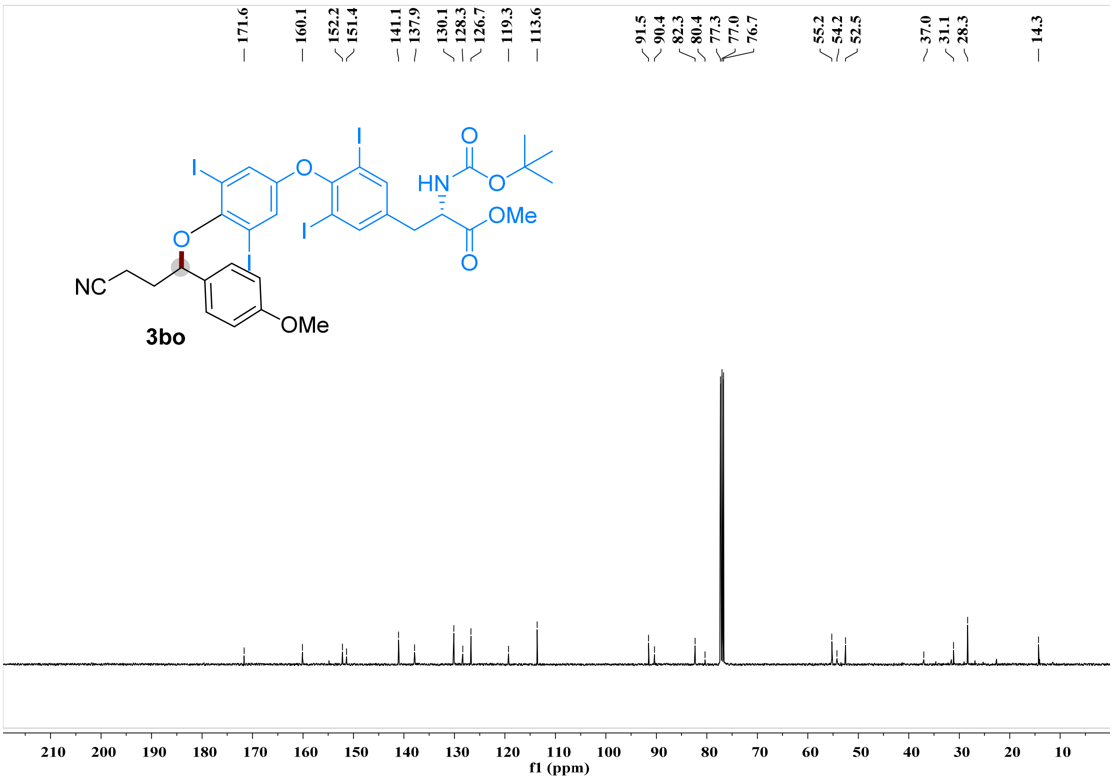
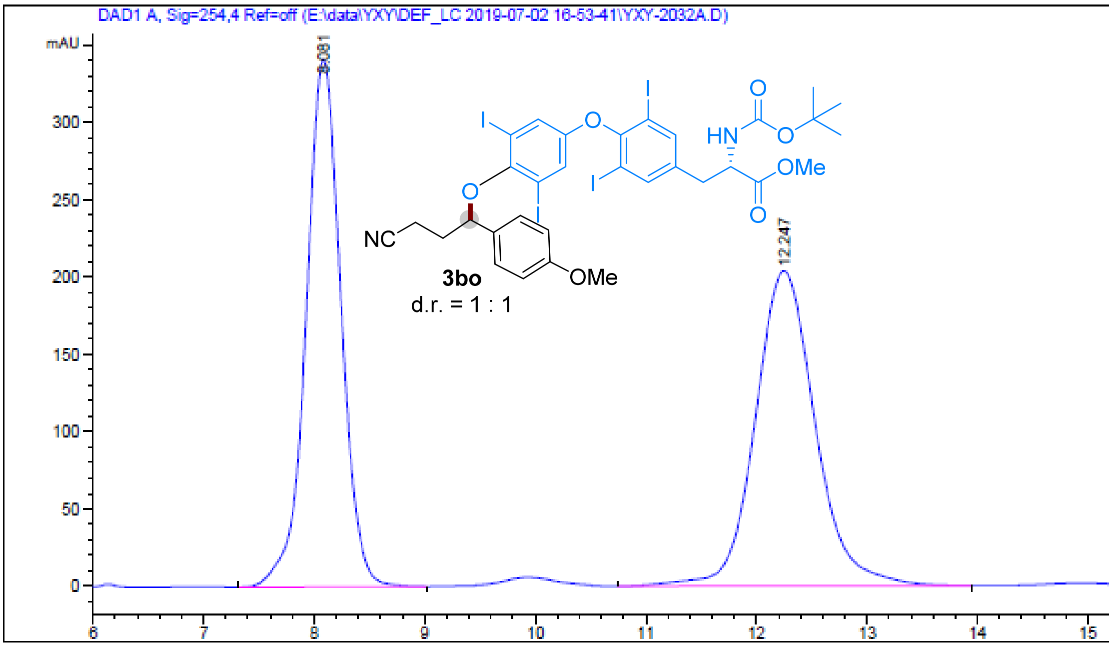
2	12.859	BB	0.6571	1.37751e4	323.30698	49.6380

Totals : 2.77512e4 831.70560

[1]H NMR (400 MHz, $CDCl_3$), [13]C NMR (100 MHz, $CDCl_3$) and HPLC spectra of product 3bo







Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
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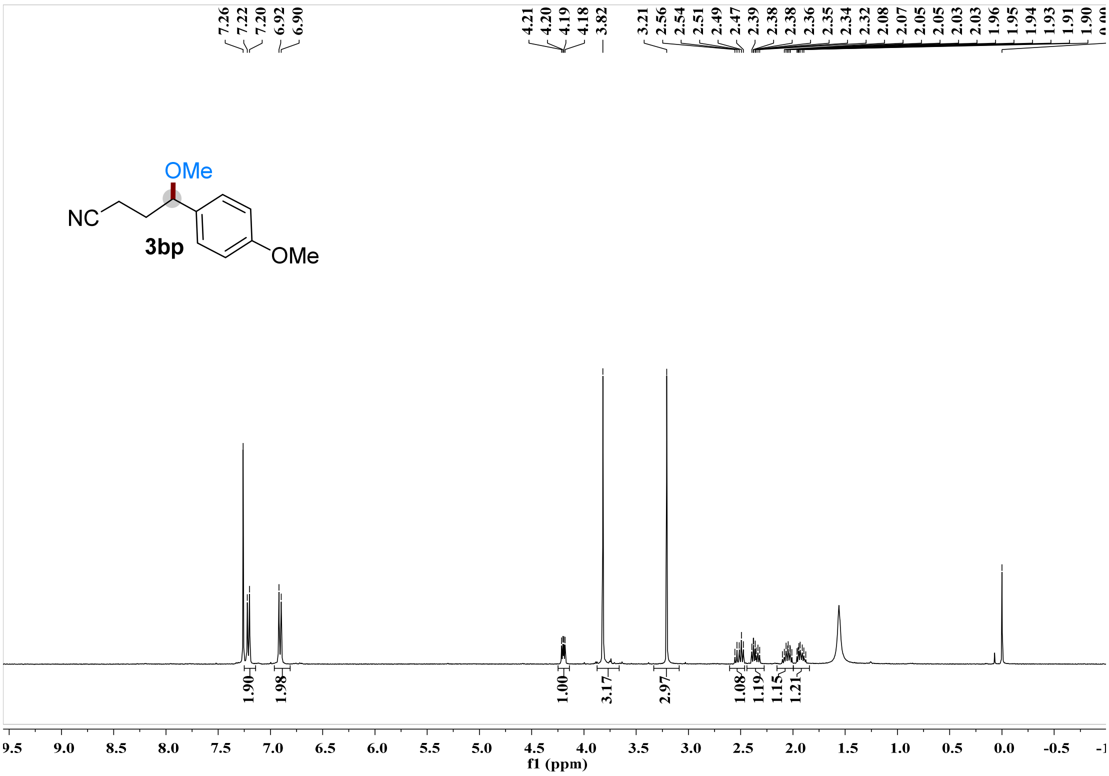
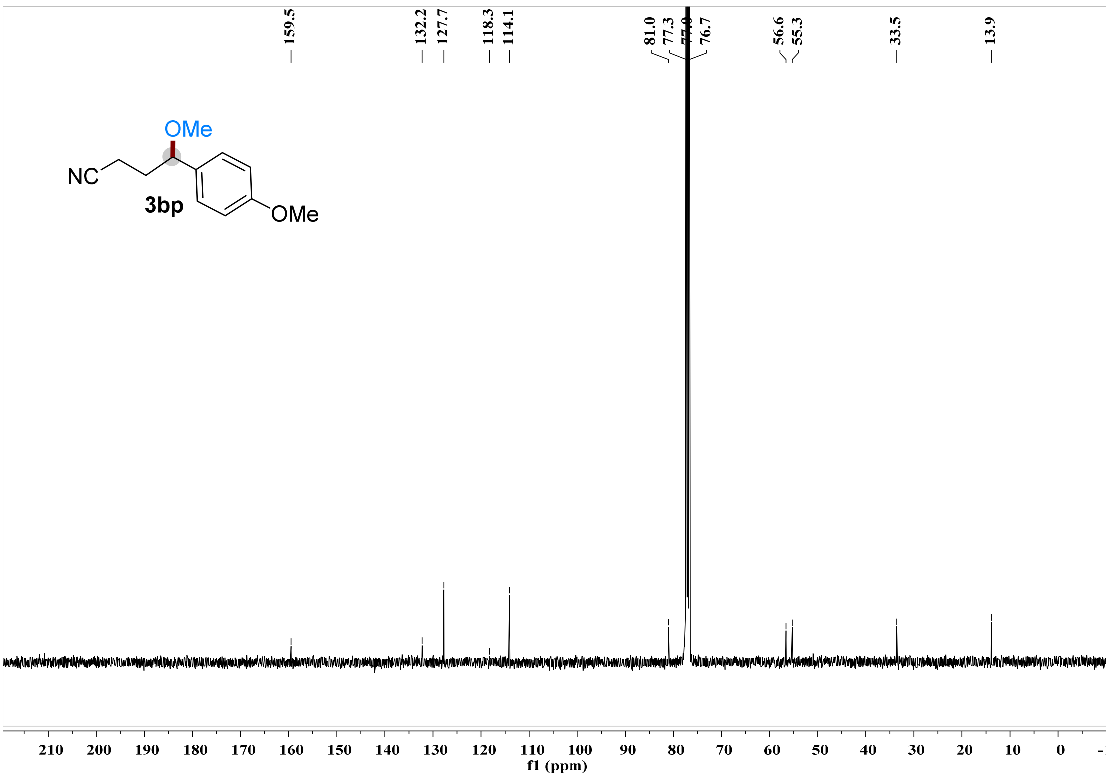
2	12.247	BB	0.5801	7686.49561	203.77031	50.7364

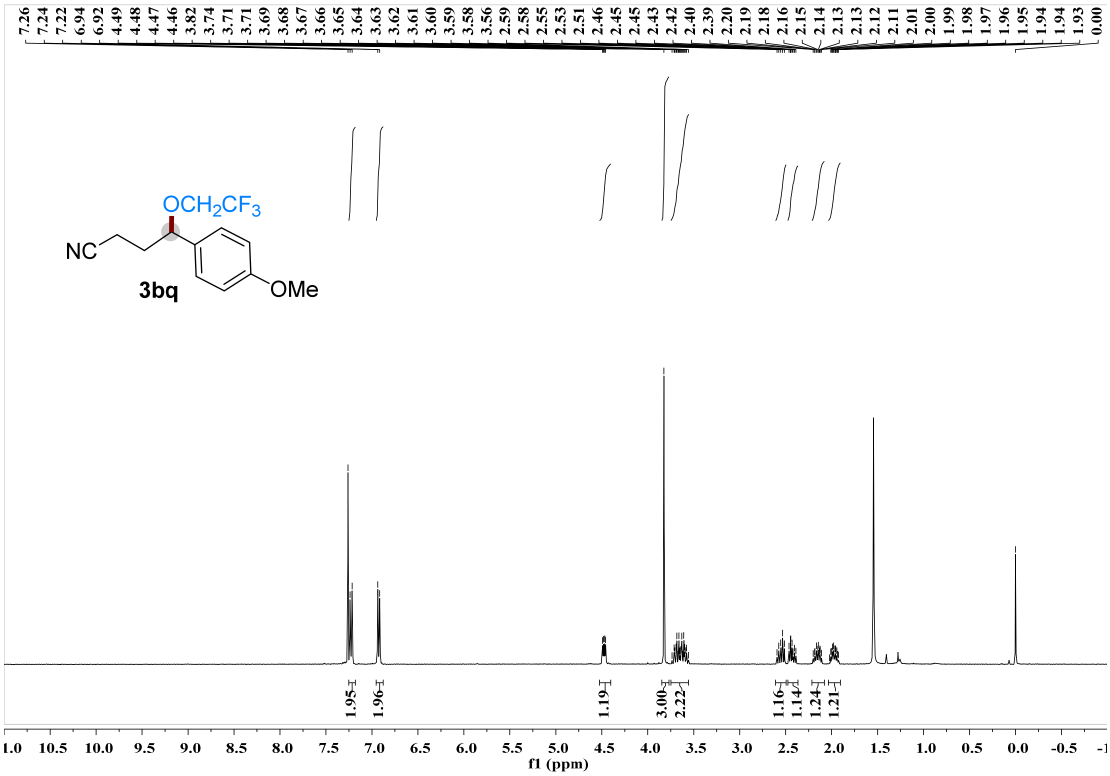
Totals : 1.51499e4 544.50417

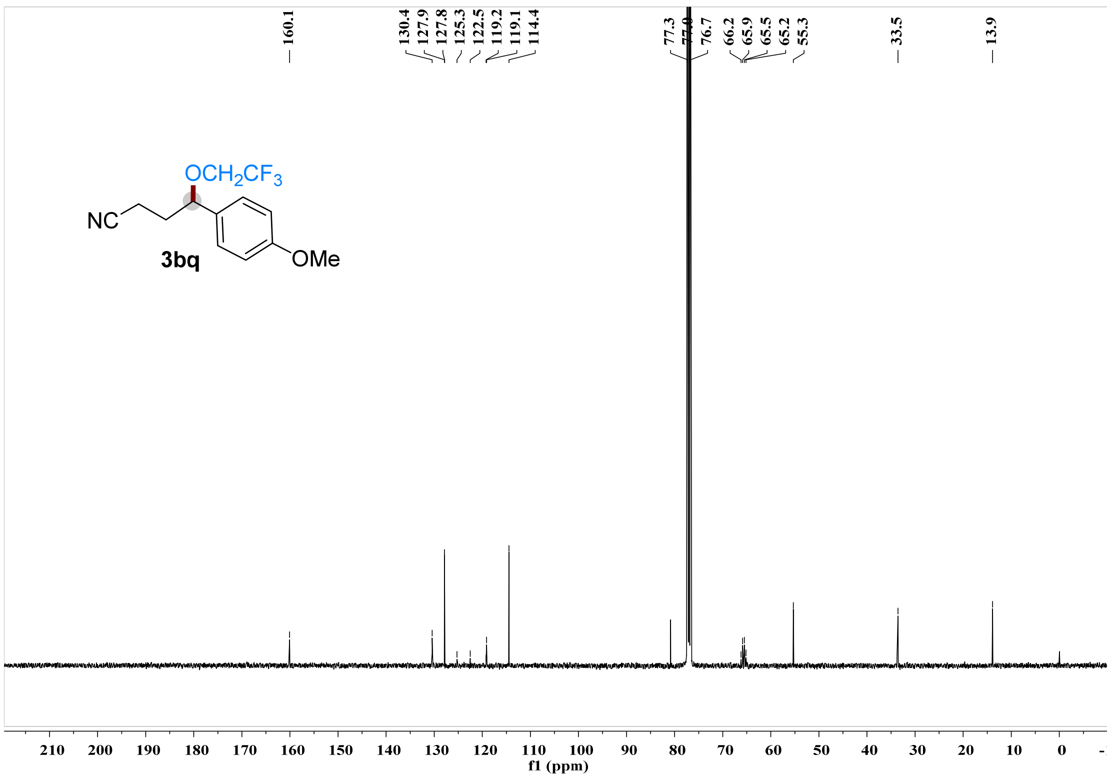
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 3bp

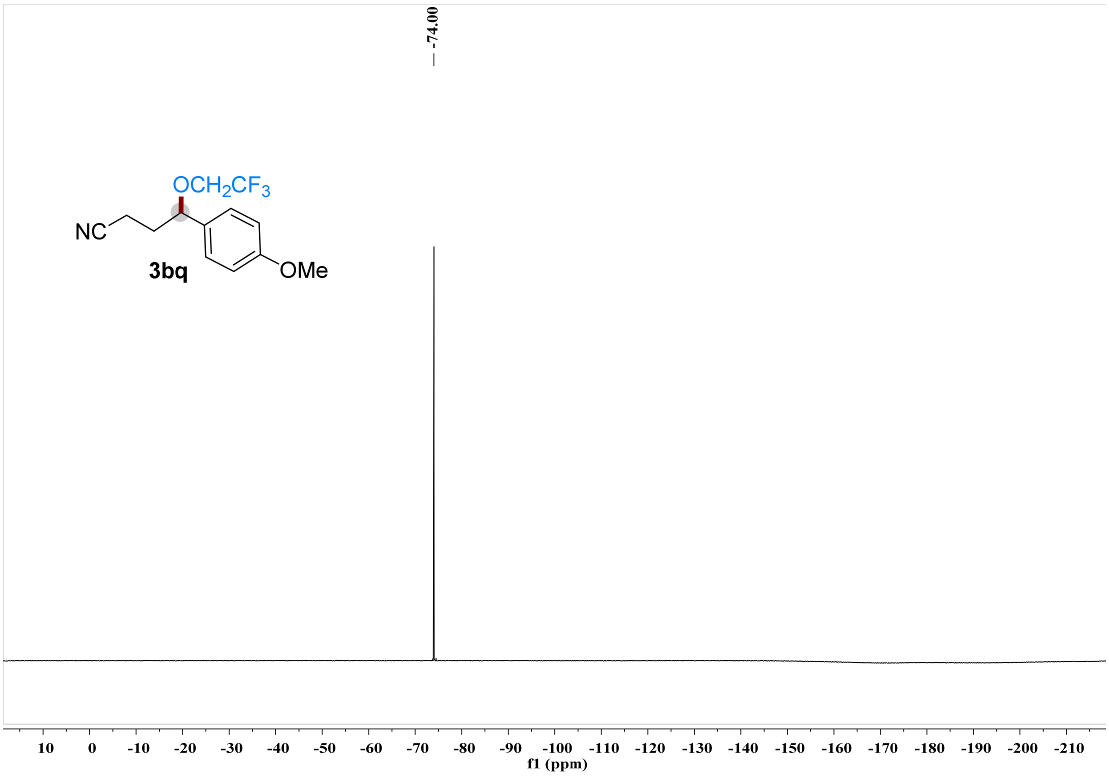




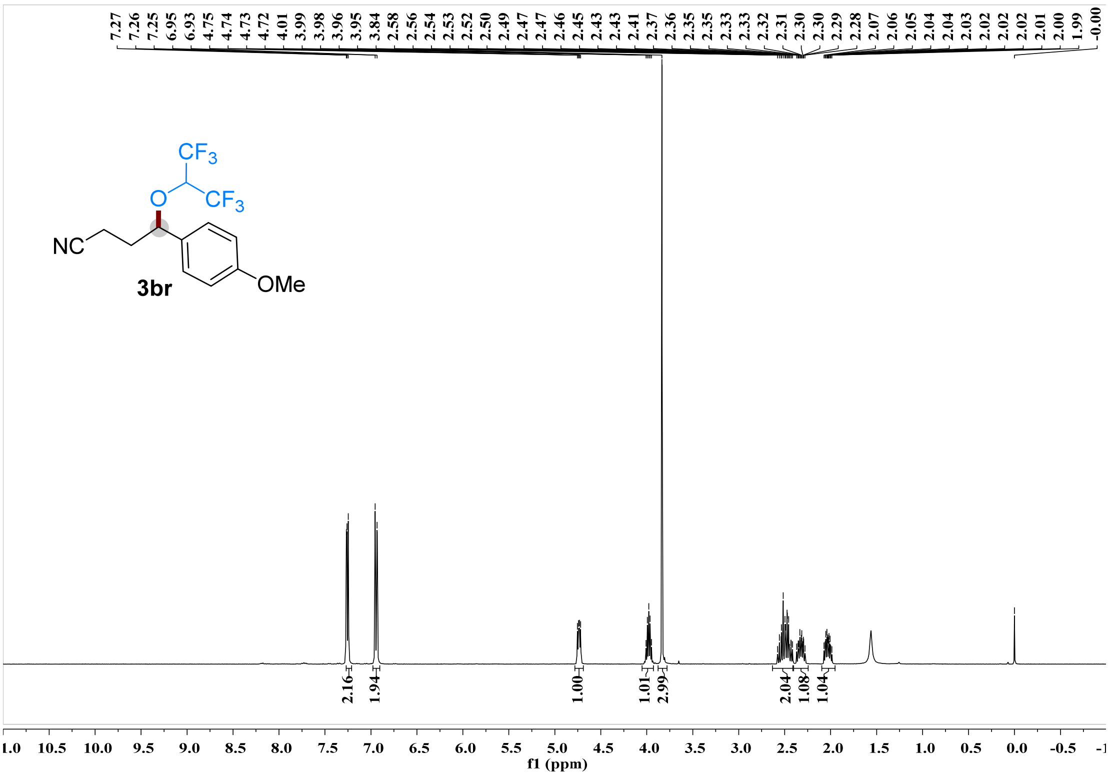
[1]H NMR (400 MHz, $CDCl_3$), [13]C NMR (100 MHz, $CDCl_3$) and [19]F NMR (376 Hz, $CDCl_3$) spectra of product 3bq

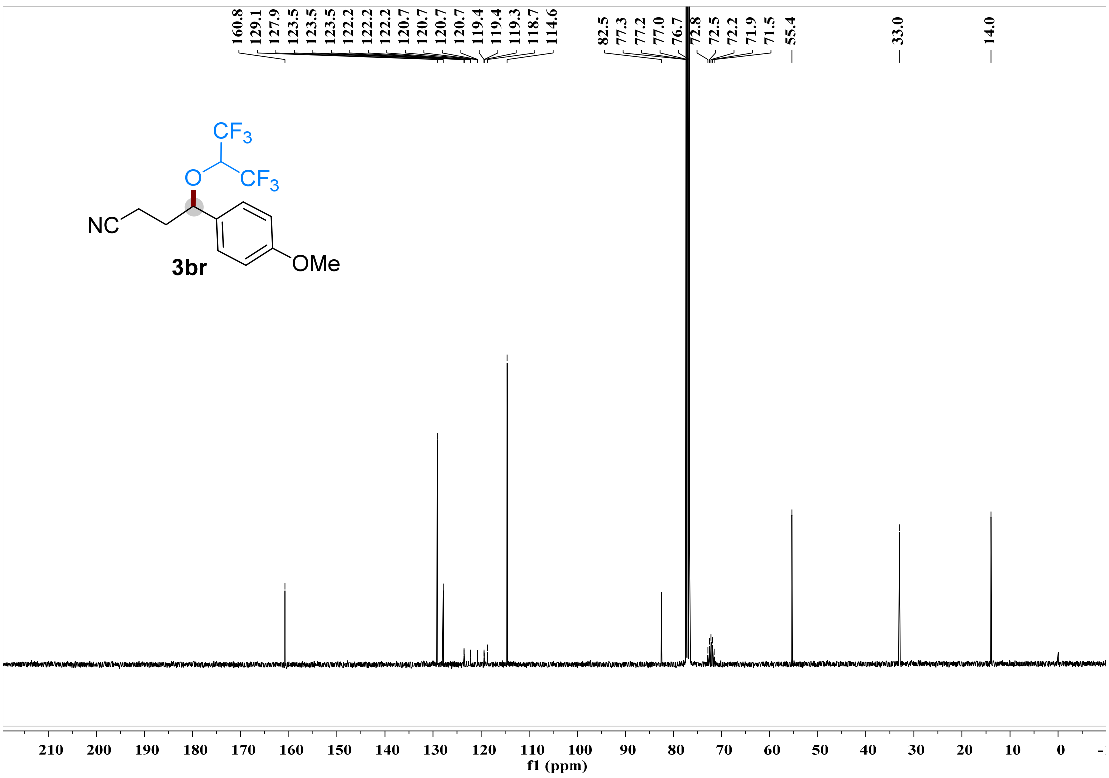


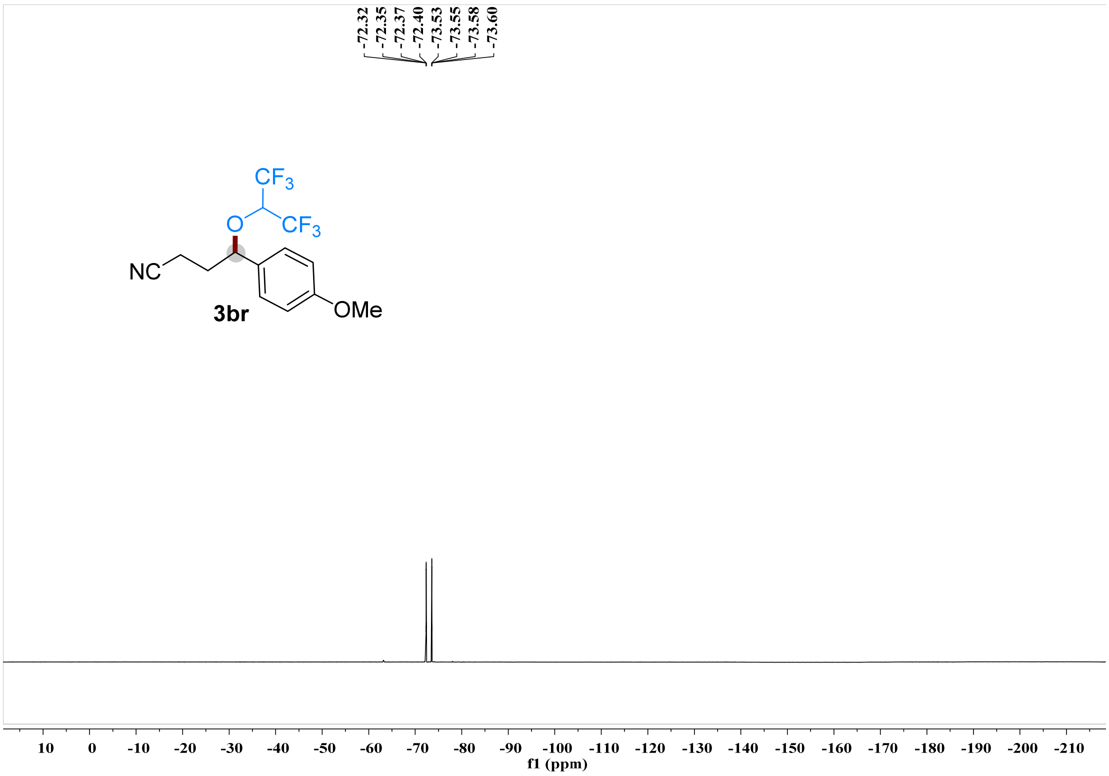



-74.00
OCH2CF3
NC
3bq
OMe
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

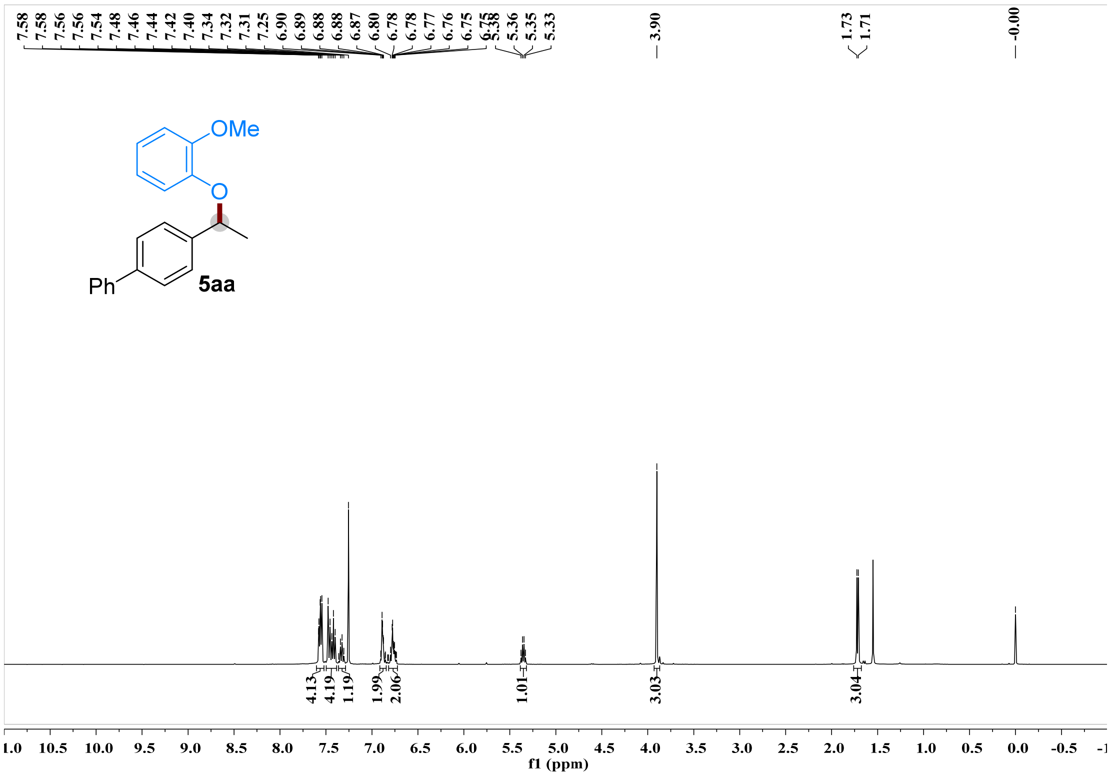
[1]H NMR (400 MHz, $CDCl_3$), [13]C NMR (100 MHz, $CDCl_3$) and [19]F NMR (376 Hz, $CDCl_3$) spectra of product 3br

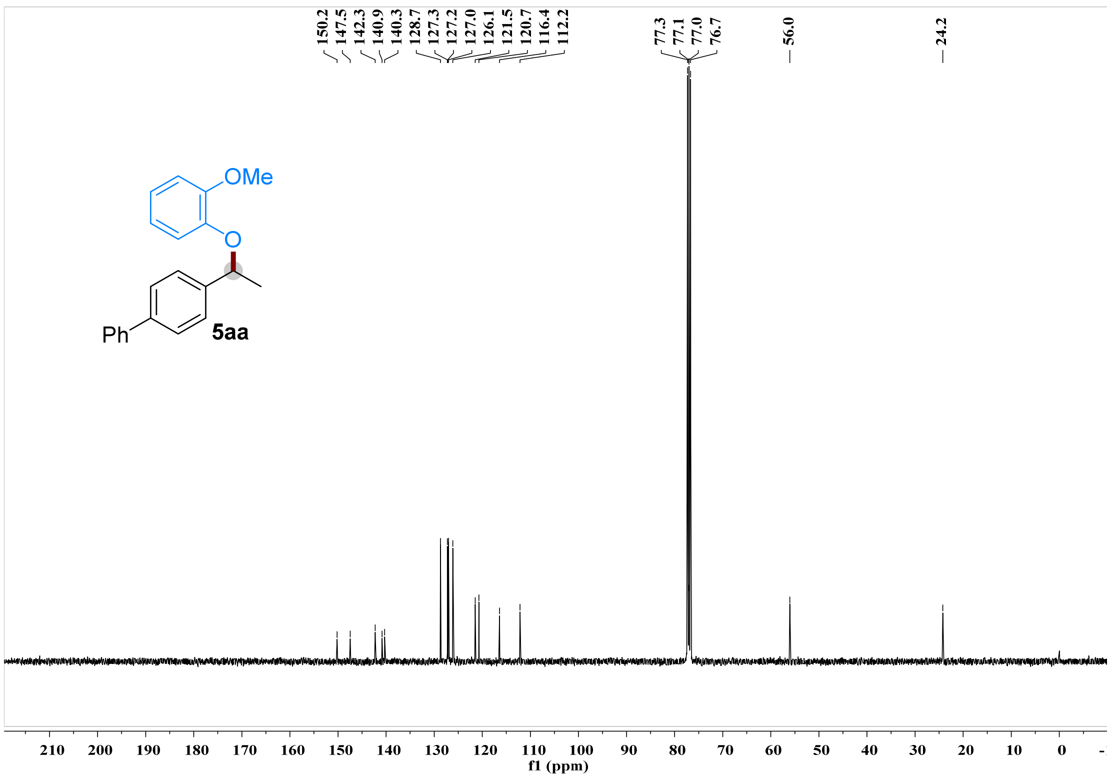




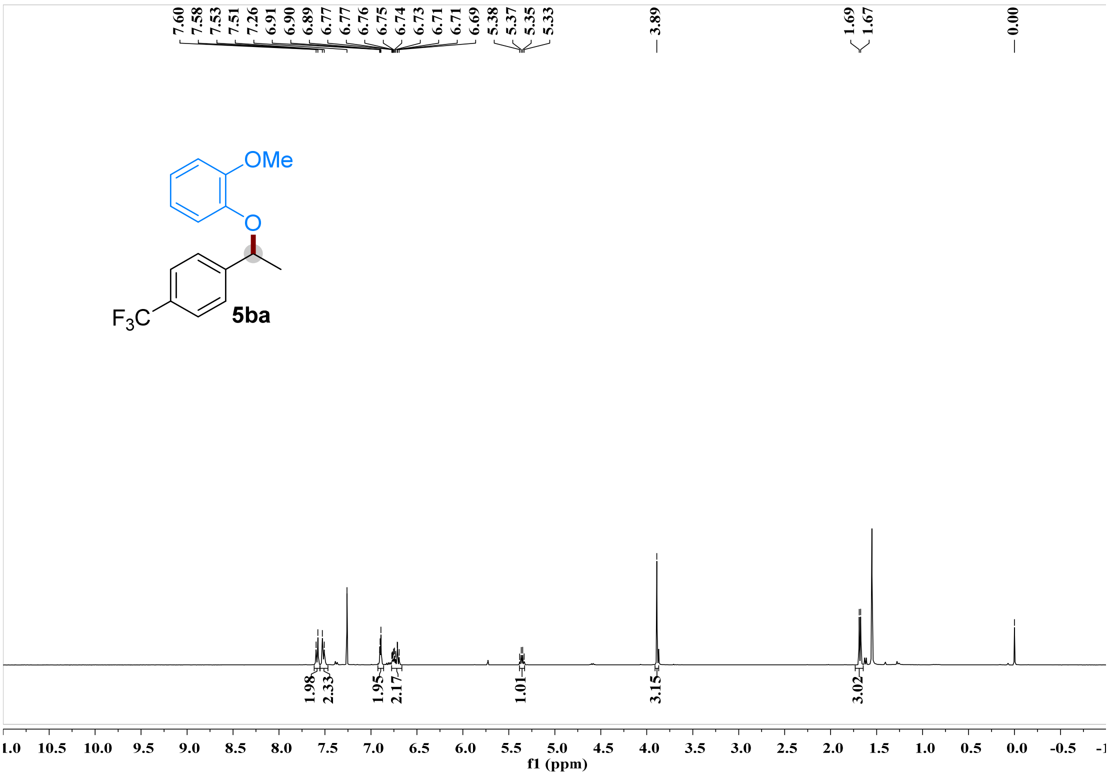

-72.32
-72.35
-72.37
-72.40
-73.53
-73.55
-73.58
-73.60
CF3
O
CF3
NC
3br
OMe
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

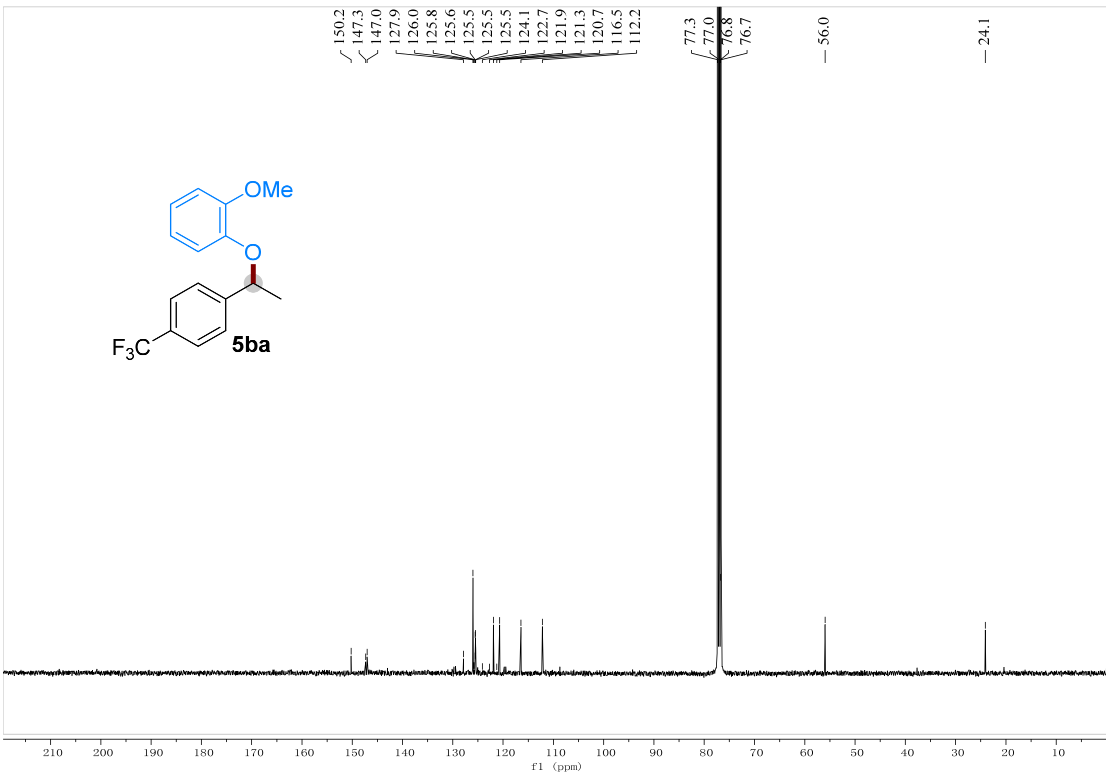
[1]H NMR (400 MHz, $CDCl_3$) and [13]C NMR (100 MHz, $CDCl_3$) spectra of product 5aa

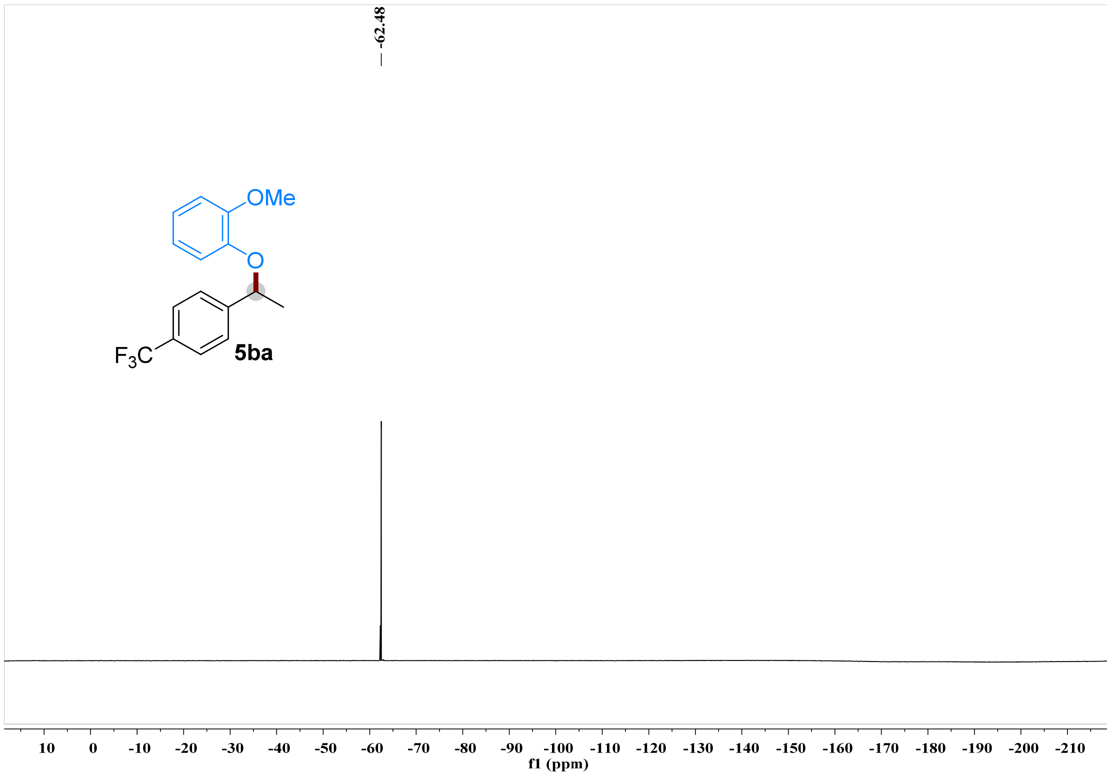




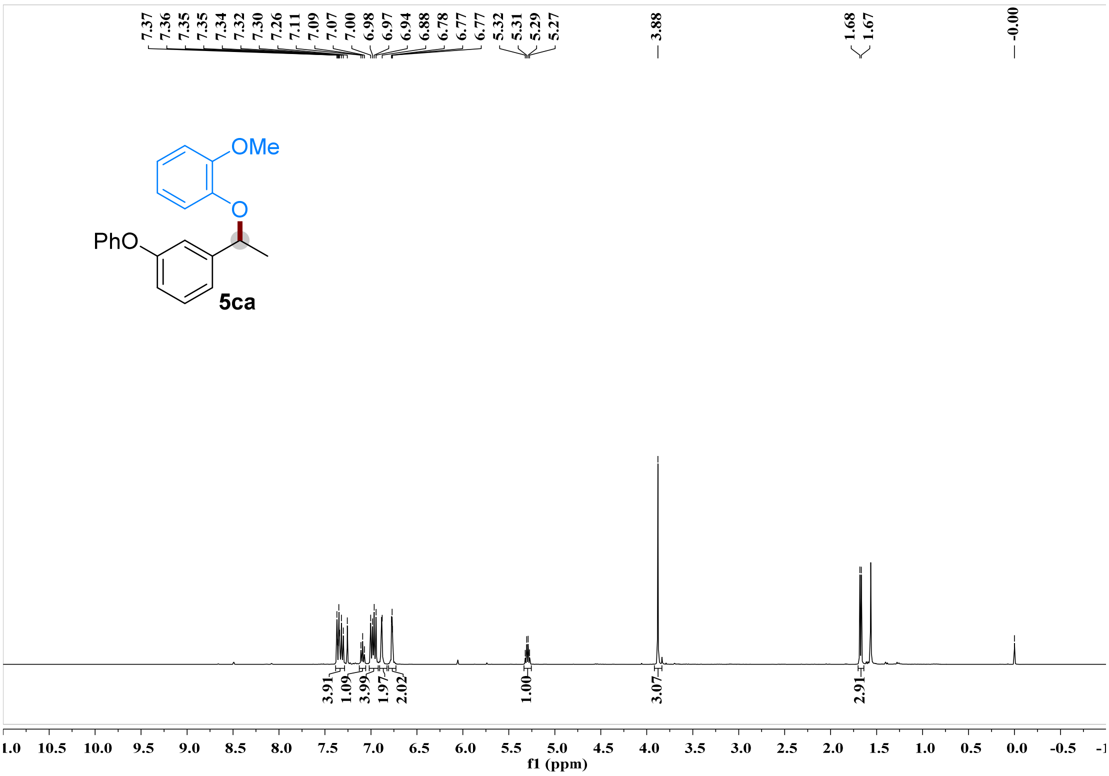
[1]H NMR (400 MHz, $CDCl_3$), [13]C NMR (100 MHz, $CDCl_3$) and [19]F NMR (376 Hz, $CDCl_3$) spectra of product 5ba

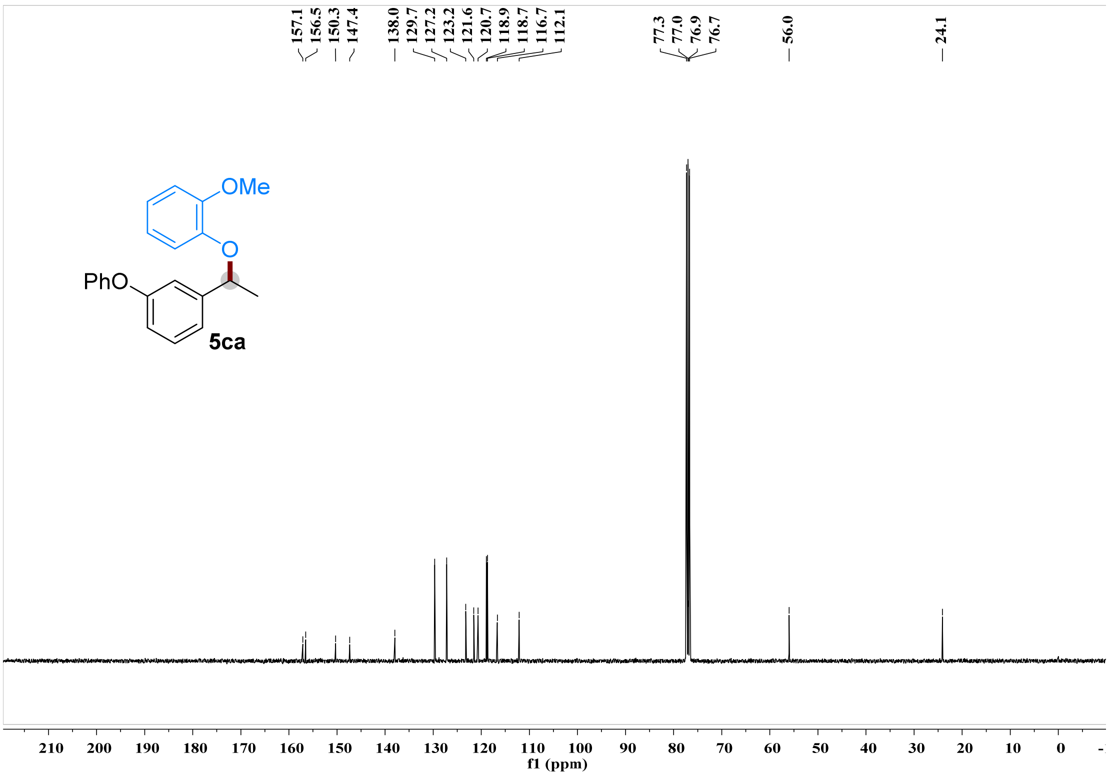




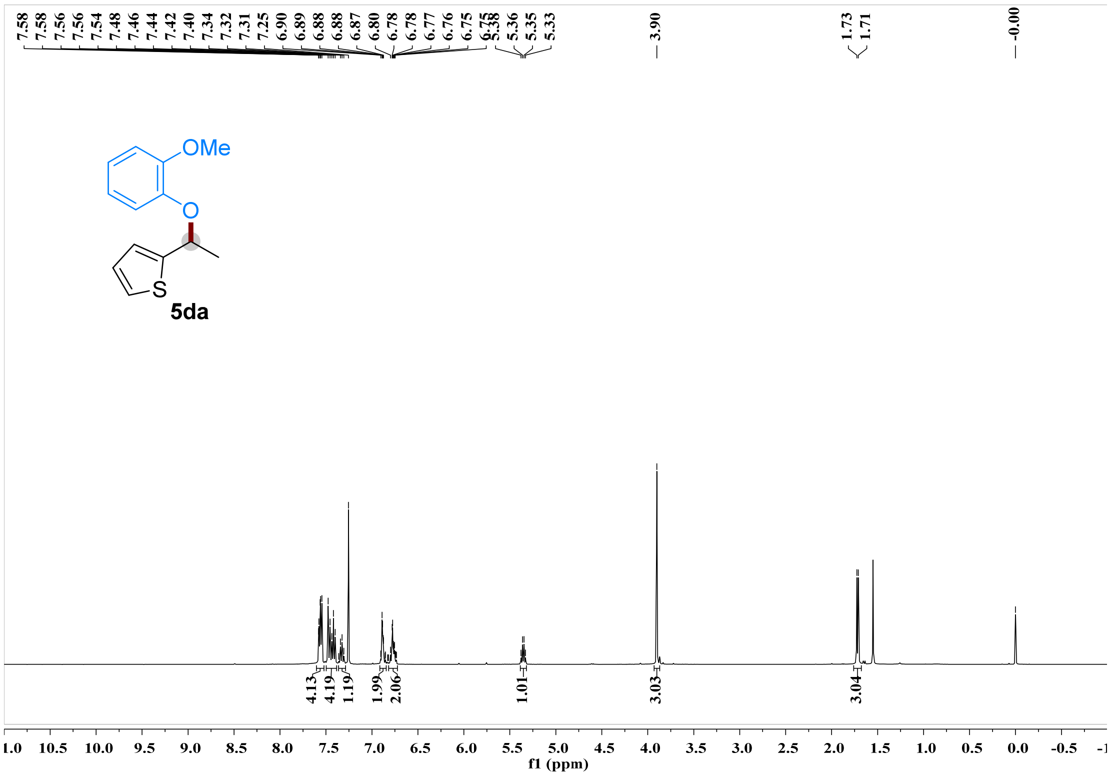

-62.48
OMe
O
F3C
5ba
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

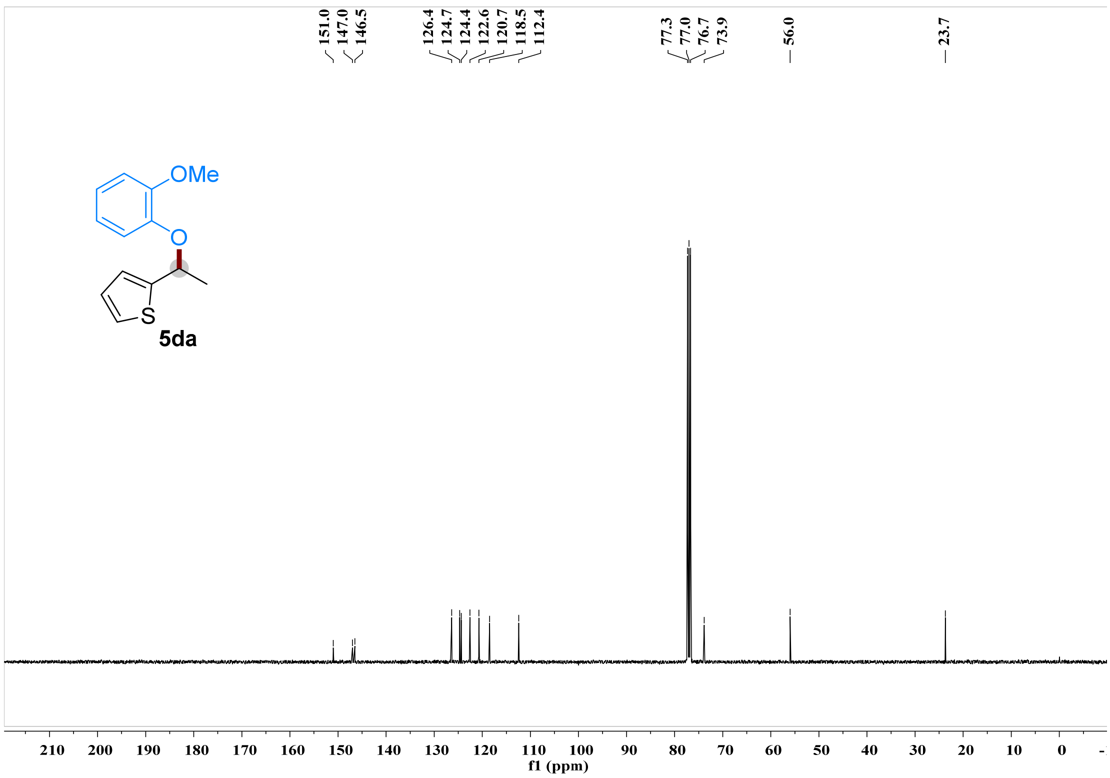
[1]H NMR (400 MHz, $CDCl_3$) and [13]C NMR (100 MHz, $CDCl_3$) spectra of product 5ca



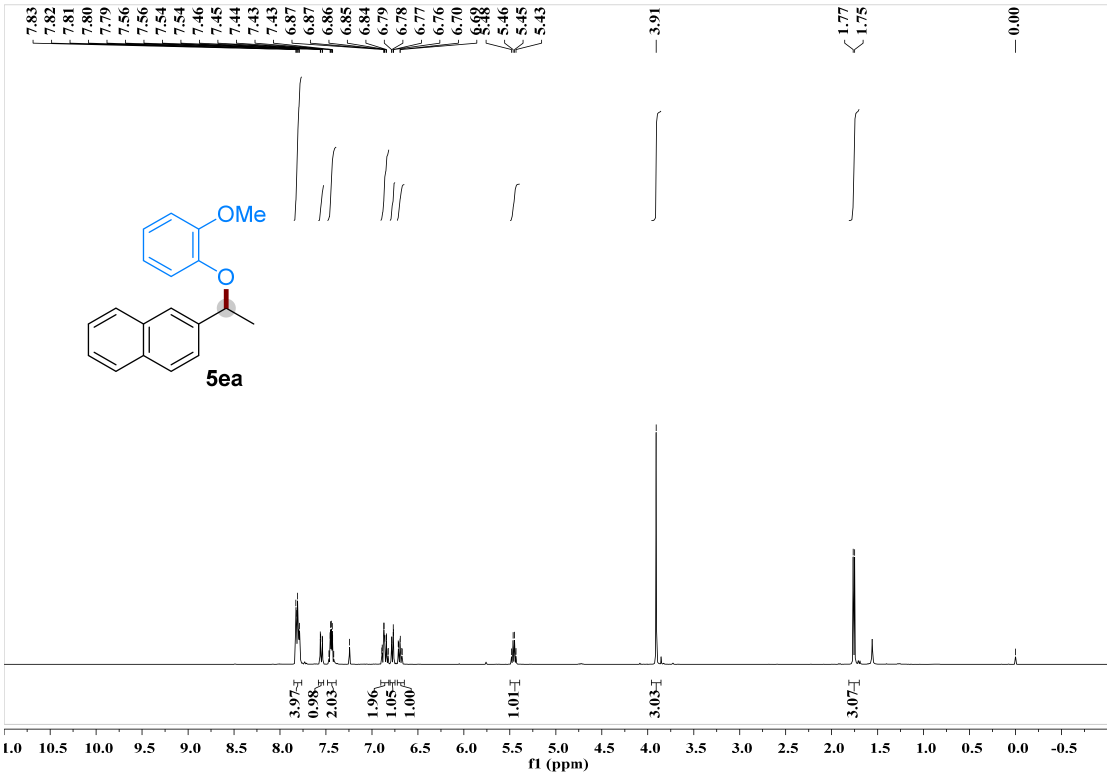


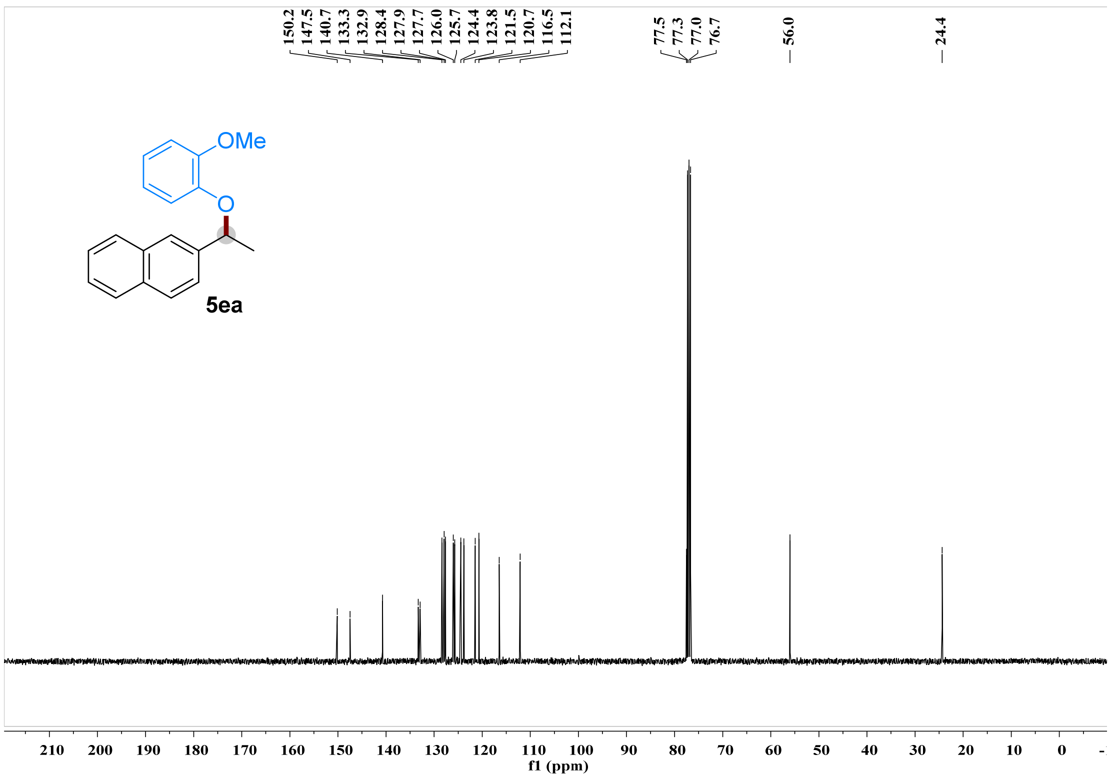
[1]H NMR (400 MHz, $CDCl_3$) and [13]C NMR (100 MHz, $CDCl_3$) spectra of product 5da



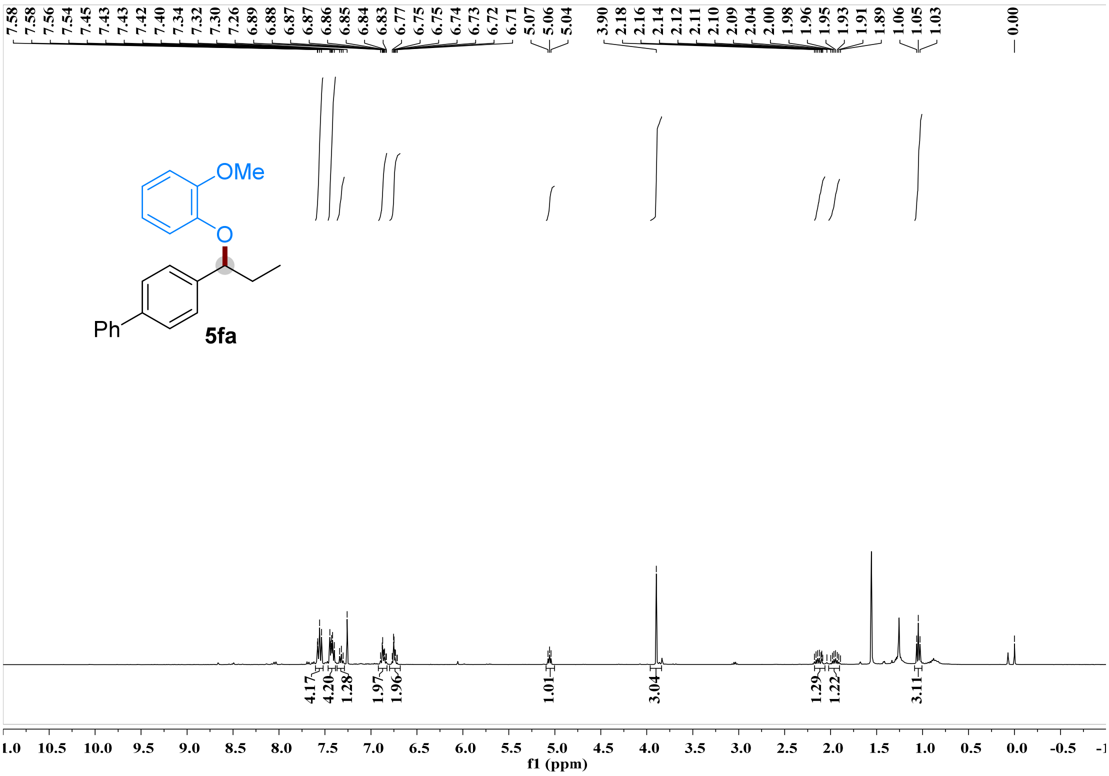


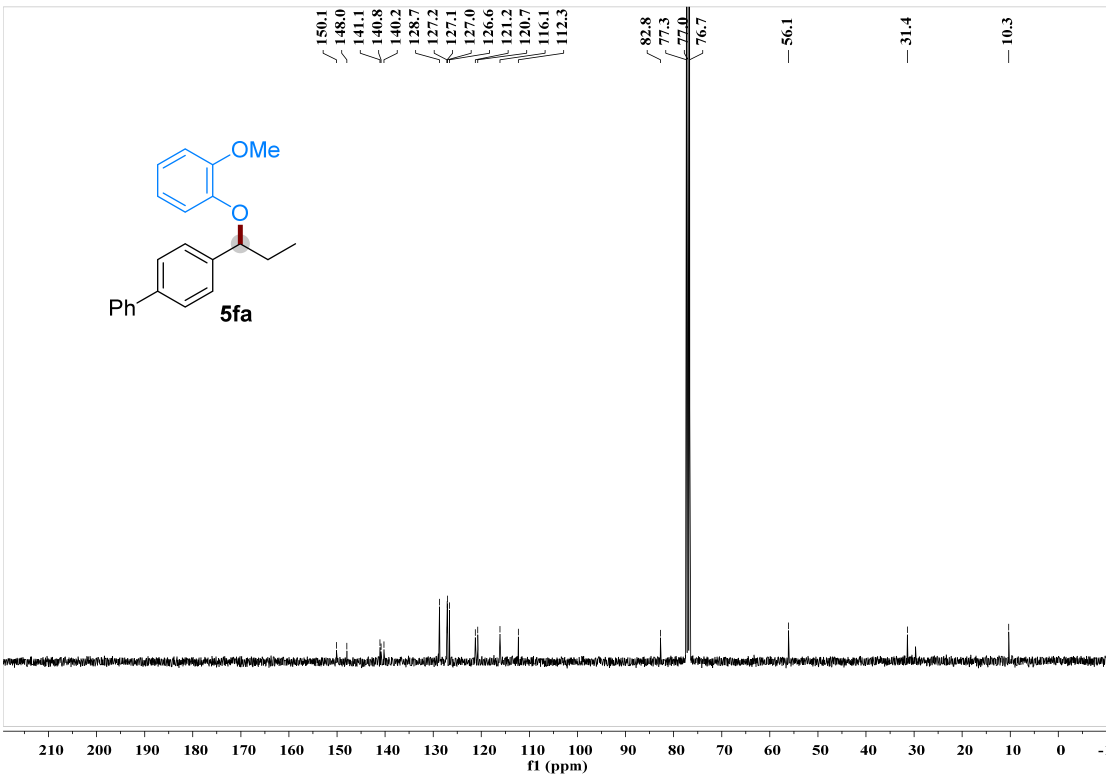
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 5ea



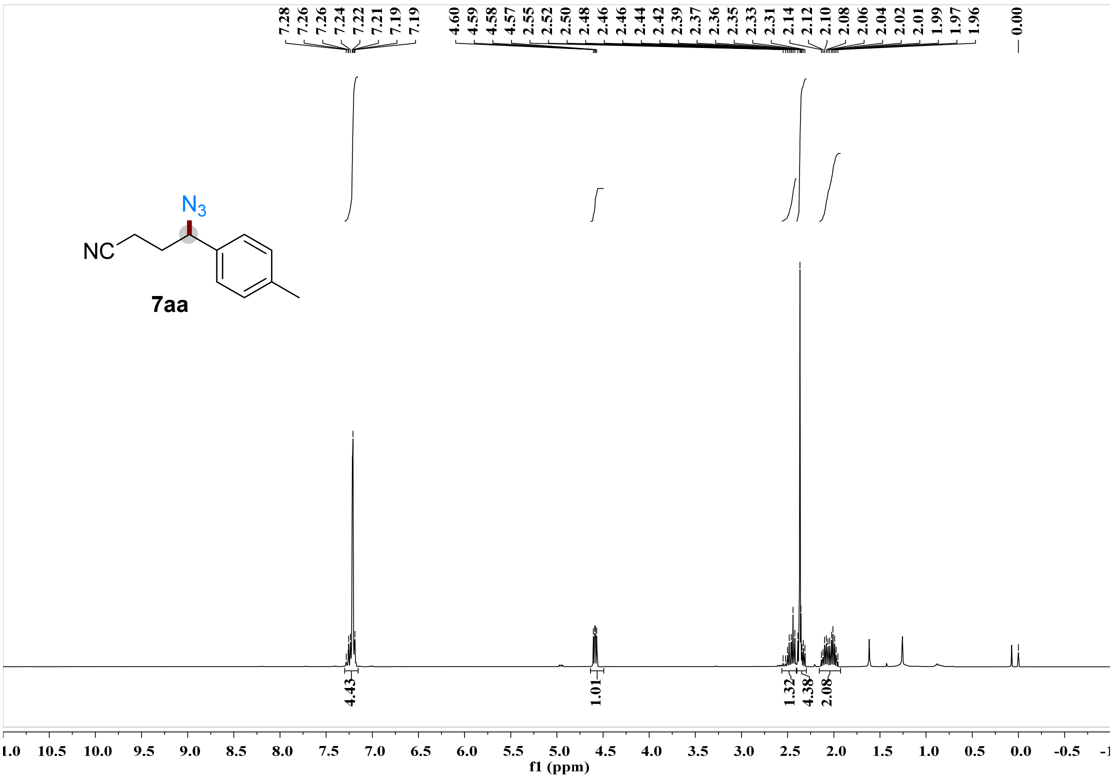


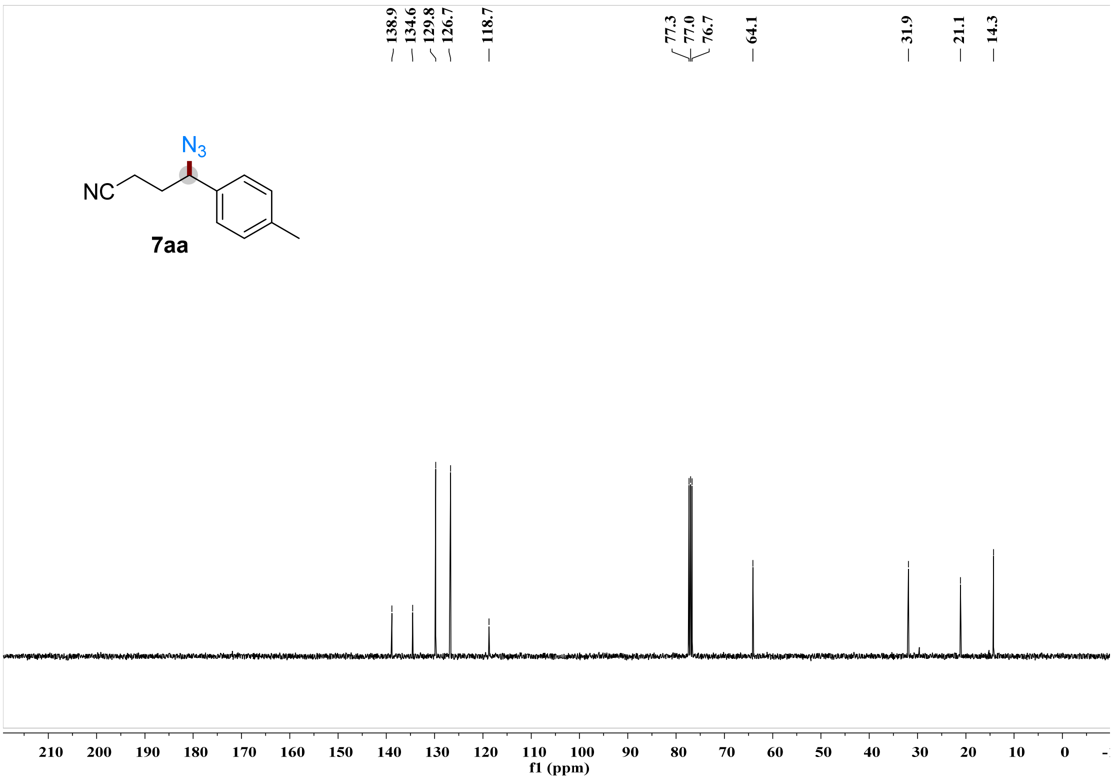
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 5fa



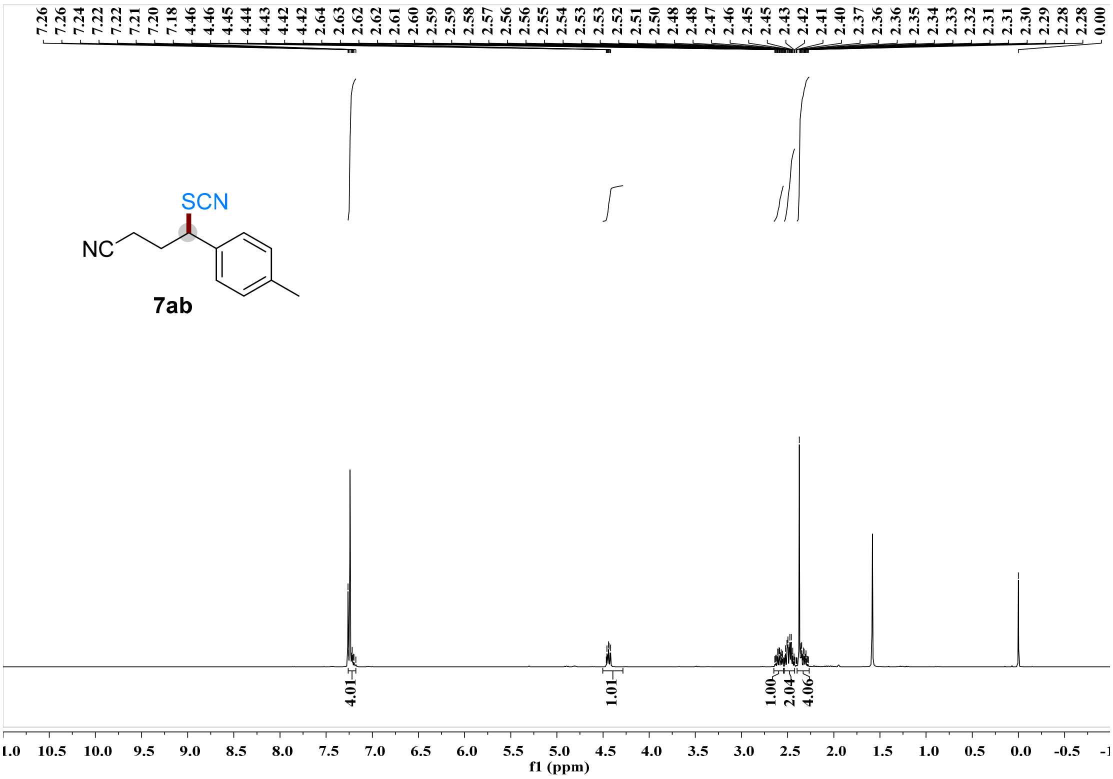


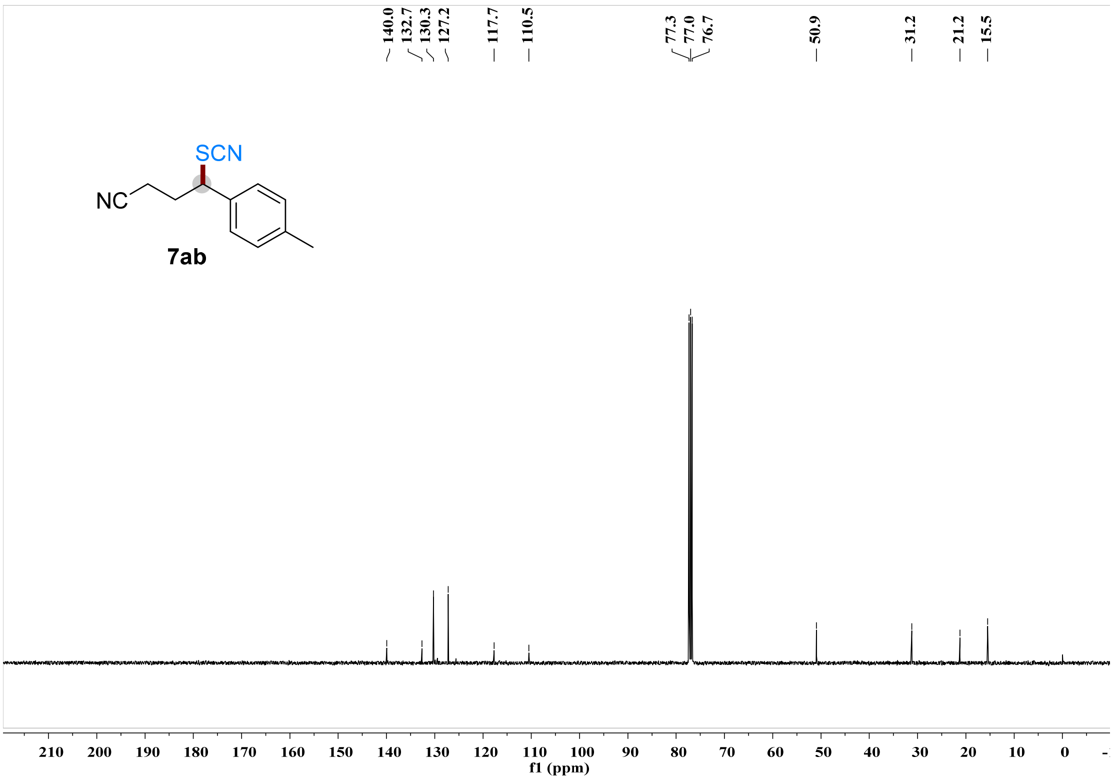
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 7aa



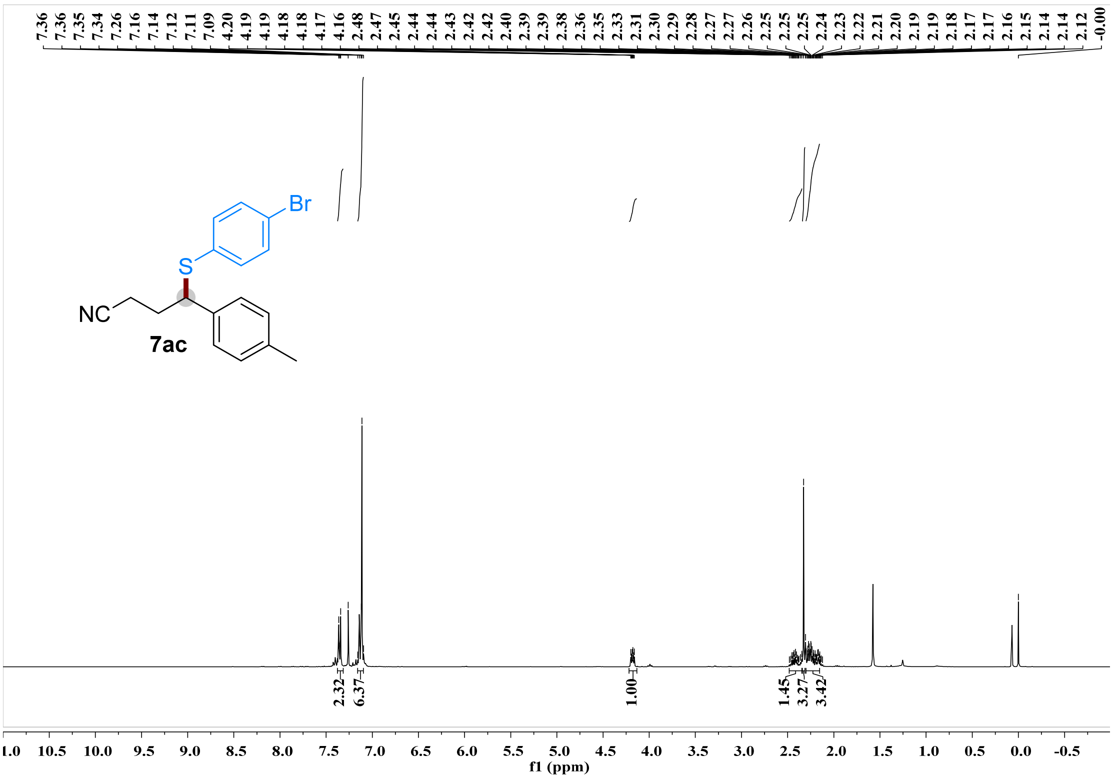


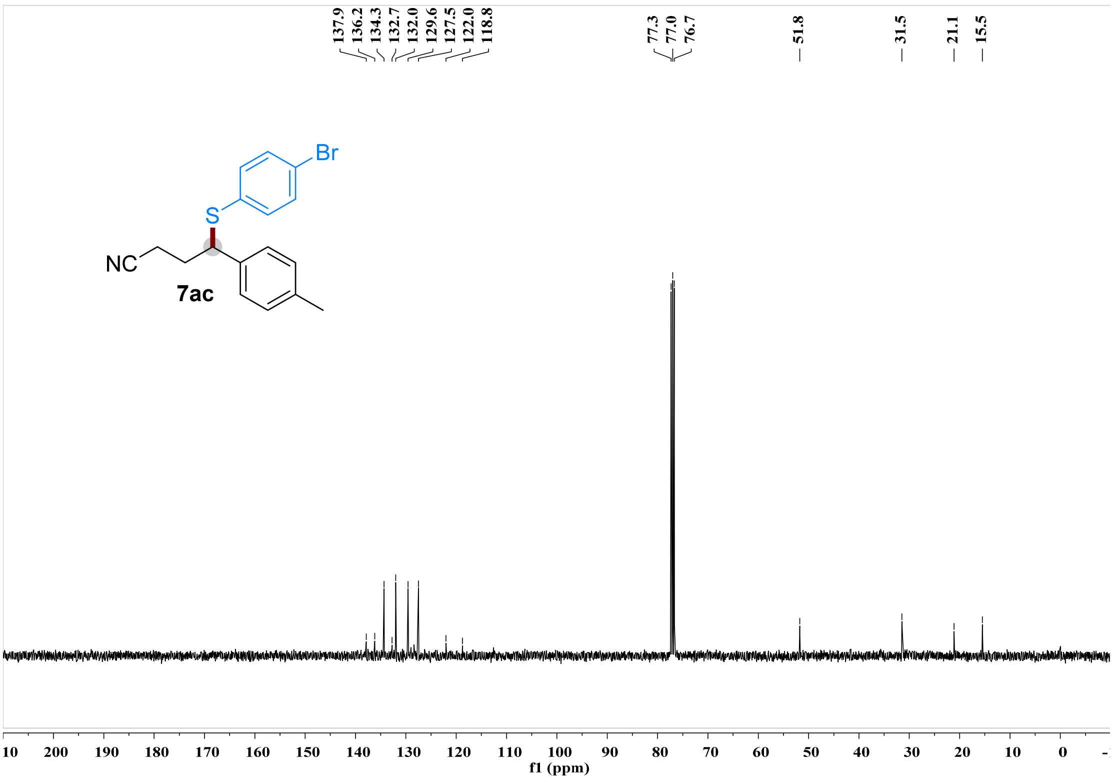
[1]H NMR (400 MHz, $CDCl_3$) and [13]C NMR (100 MHz, $CDCl_3$) spectra of product 7ab



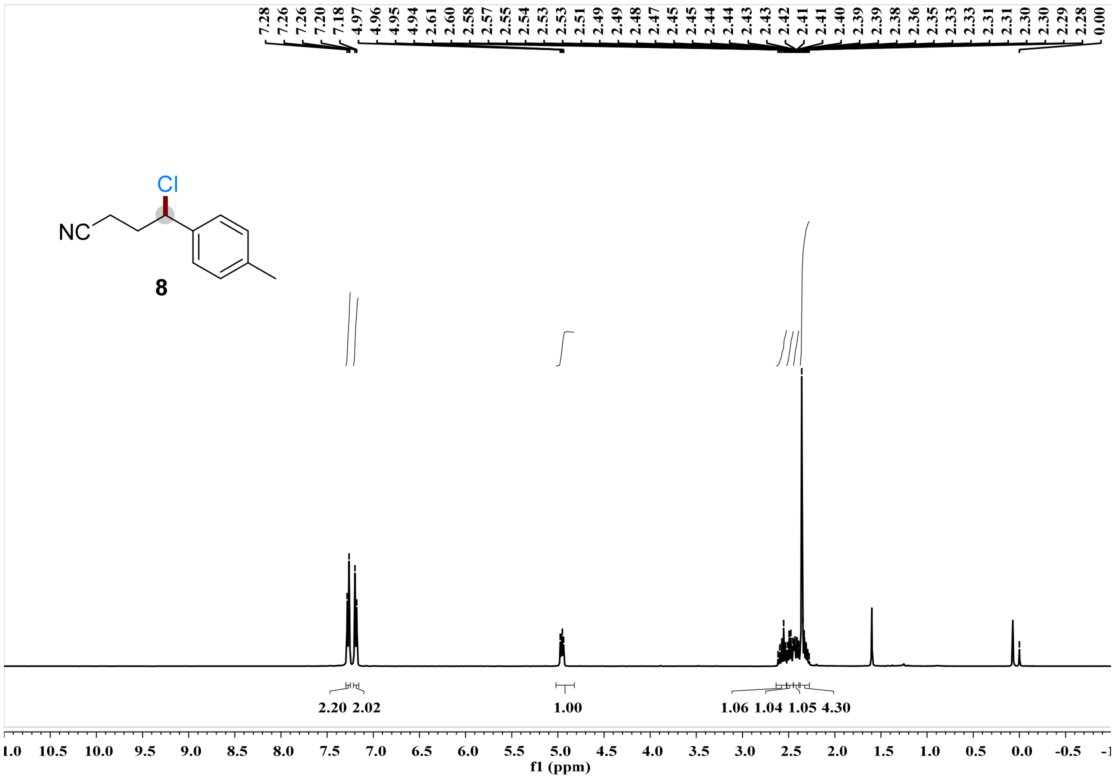


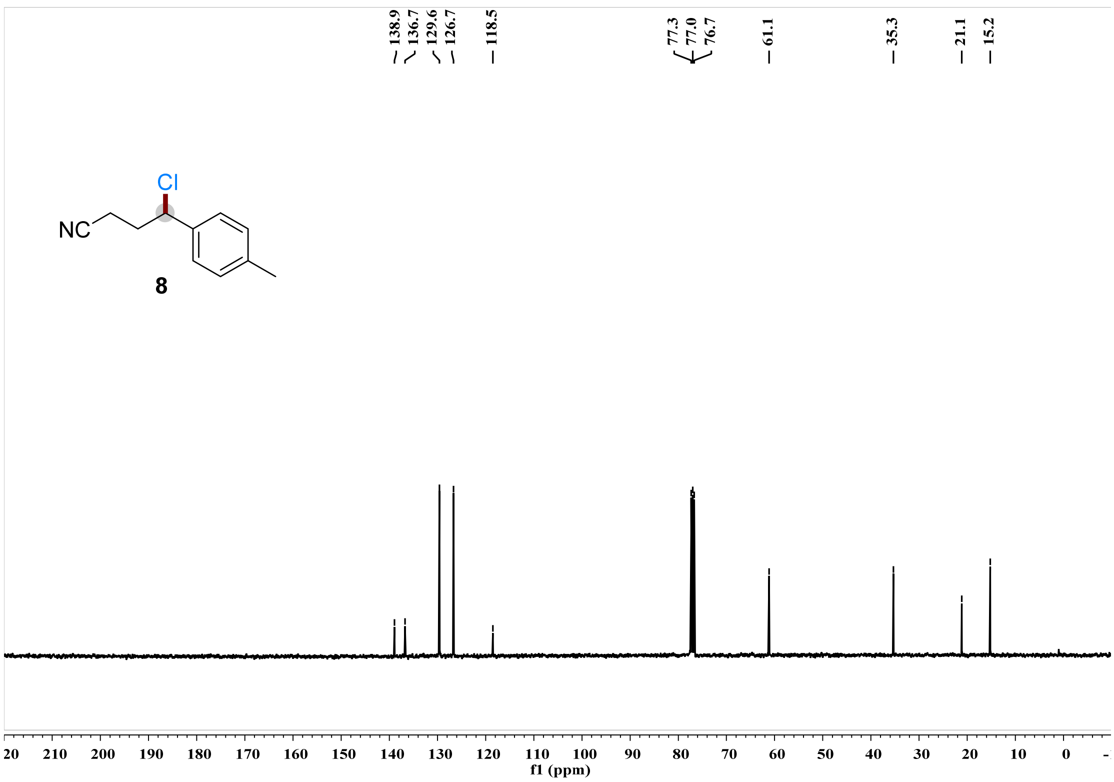
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 7ac





^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 8





^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of product 9