Copper-Catalyzed Transnitrilation of Arylborons with Dimethylmalononitrile via a Radical Pathway

Xiaofu Jian,[†,§] Xibao Zhang,[†,§] and Weilong Xie[†,‡*]

[†]College of Chemistry and Chemical Engineering, Donghua University, Shanghai 201620, China
[‡]State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

[§]X. J. and X. Z. contributed equally

*Corresponding Author E-mail: weilongxie@dhu.edu.cn

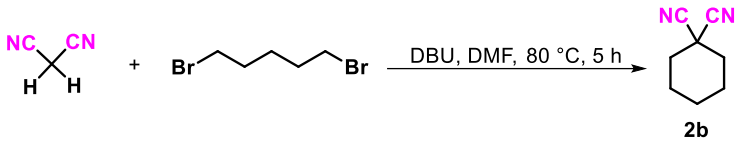
Table of Contents

I. General Methods

Unless otherwise stated, all commercial reagents were purchased from Adamas, Aldrich, TCI, Bide, and J&K chemical, and used without additional purification. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F254 plate. Visualization on TLC was achieved by the use of UV light (254 nm). Column chromatography was undertaken on silica gel (300-500 mesh) using proper eluents. ^{1}H, ^{13}C and ^{19}F NMR spectroscopic data were recorded on Bruker Avance (400 or 600 MHz), and chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak [$CHCl_3$ in $CDCl_3$: 7.26 ppm, C_6H_6 in C_6D_6: 7.15 ppm]. Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are in Hertz (Hz). The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

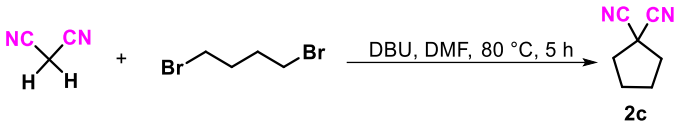
II. Procedures for the Preparation of Starting Materials

a) Preparation of Various Substituted Malononitriles



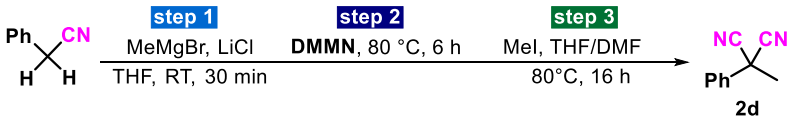
2b

Following the reported procedures,[1] an oven-dried flask equipped with a stir bar were charged with malononitrile (0.66 g, 10 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 3.35 g, 22 mmol, 2.2 equiv) and 1,4-dibromobutane (2.53 g, 11 mmol 1.1 equiv). *N*,*N*-Dimethylformamide (DMF, 25 mL) was added to the flask, and the mixture was heated to 80 °C for 5 h. After the reaction was completed, the mixture was cooled to room temperature. The above solution was quenched with water (50 mL) and extracted with dichloromethane (DCM, 3 x 15 mL). Then, the combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel chromatography to afford the dialkylated malononitrile **2b** (1.21 g, 90%).



2c

Following the reported procedures,[1] an oven-dried flask equipped with a stir bar were charged with malononitrile (0.66 g, 10 mmol), DBU (3.35 g, 22 mmol, 2.2 equiv) and 1,4-dibromobutane (2.38 g, 11 mmol 1.1 equiv). DMF (25 mL) was added to the flask, and the mixture was heated to 80 °C for 5 h. After the reaction was completed, the mixture was cooled to room temperature. The above solution was quenched with water (50 mL) and extracted with dichloromethane (DCM, 3 x 15 mL). Then, the combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel chromatography to afford the dialkylated malononitrile **2c** (1.04 g, 87%).

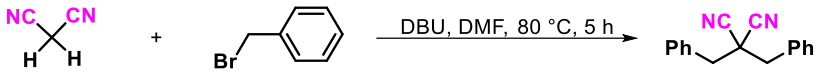


2d

Step 1: Following the reported procedures,[2] to a Schlenk flask with a stir bar was added lithium chloride (LiCl, 0.47 g, 11 mmol, 1.1 equiv). The flask was flame-dried under vacuum, and then cooled under a nitrogen atmosphere. Anhydrous THF solvent (10 mL) was added, followed by phenylacetonitrile (1.17 g, 10 mmol). Subsequently, methylmagnesium bromide (4.0 mL, 2.5 M in THF, 11 mmol) was added dropwise at room temperature, and the solution was stirred at room temperature for 30 min under the nitrogen atmosphere.

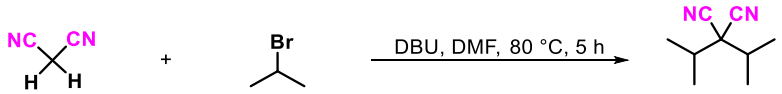
Step 2: Dimethylmanononitrile (**DMMN**, 1.07 g, 11 mmol, 1.1 equiv) in THF solvent (10 mL) was prepared, and then added to the above solution at room temperature. The reaction was stirred at 80 °C for 6 h under nitrogen atmosphere.

Step 3: The above reaction solution was cooled to room temperature, and DMF solvent was added to bring the mixed solvent ratio to 1:1 (THF/DMF). Iodomethane (1.70 g, 12 mmol, 1.2 equiv) was added in one portion, and the reaction mixture was stirred at 80 ˚C for 16 h. After the reaction was completed, the solution was cooled to room temperature. Then, the reaction solution was quenched with HCl (1 N aqueous solution), and extracted with ethyl acetate (EtOAc, 3 x 15 mL). The combined organic layer was dried over $MgSO_4$, and then concentrated. The crude residue was purified by flash column chromatography to yield the product of 2-methyl-2-phenylpropanedinitrile. The crude residue was purified by flash column chromatography (gradient of 0-30% EtOAc/hexanes) to yield as a colorless oil **2d** (1.33 g, 85%).



2e

Following the reported procedures,[1] an oven-dried flask equipped with a stir bar were charged with malononitrile (0.66 g, 10 mmol), DBU (3.35 g, 22 mmol, 2.2 equiv) and benzyl bromide (3.35 g, 22 mmol, 2.2 equiv). DMF (25 mL) was added to the flask, and the mixture was heated to 80 °C for 5 h. After the reaction was completed, the mixture was cooled to room temperature. The above solution was quenched with water (50 mL) and extracted with dichloromethane (DCM, 3 x 15 mL). Then, the combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel chromatography to afford the dialkylated malononitrile **2e** (2.04g, 83%).



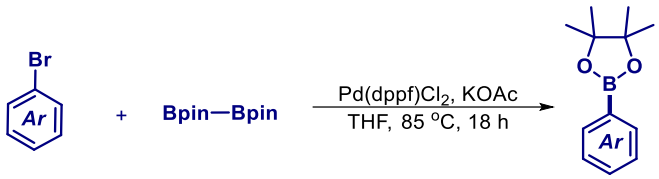
2f

Following the reported procedures,[1] an oven-dried flask equipped with a stir bar were charged with malononitrile (0.66 g, 10 mmol), DBU (3.35 g, 22 mmol, 2.2 equiv) and 2-bromopropane (2.71 g, 22 mmol 2.2 equiv). DMF (25 mL) was added to the flask, and the mixture was heated to 80 °C for 5 h. After the reaction was completed, the mixture was cooled to room temperature. The above solution was quenched with water (50 mL) and extracted with dichloromethane (DCM, 3 x 15 mL). Then, the combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel chromatography to afford the dialkylated malononitrile **2f** (1.20 g, 80%).

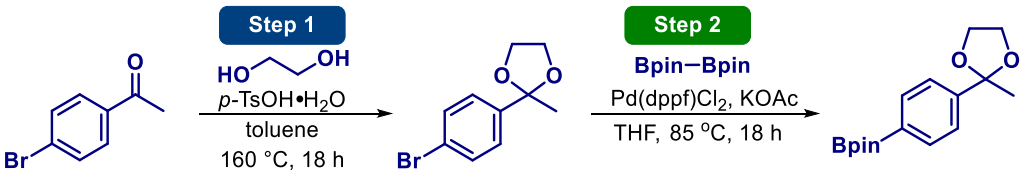
b) Preparation of Arylboronic Esters

Arylboronic esters were prepared following the reported procedures,[3] and the reported compounds and related references were list below.

General procedure

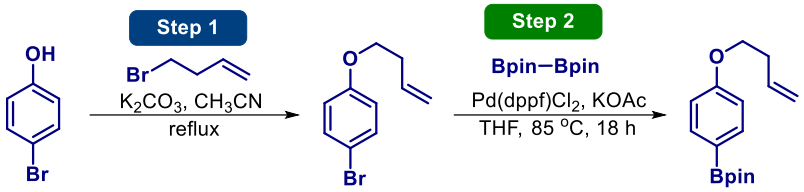


To an oven-dried Schlenk flask equipped with a stir bar were added $B_2(pin)_2$ (1.52 g, 6.0 mmol, 1.2 equiv), $Pd(dppf)Cl_2$ (183 mg, 0.25 mmol, 0.05 equiv) and KOAc (589 mg, 6.0 mmol, 1.2 equiv) under a nitrogen atmosphere. Next, THF solvent (10 mL) was added to the above mixture, followed by the addition of aryl bromide. The reaction mixture was heated to 85 °C and stirred at this temperature for 18 h. After cooling down to room temperature, the mixture was quenched with saturated $NaHCO_3$ solution and extracted with DCM (3 x 10 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate) to obtain the product.



Step 1: According to a reported procedure,[4] to a round-bottom flask equipped with a Dean-Stark apparatus were added 4-bromoacetophenone (1.0 g, 5.0 mmol), ethylene glycol (465 mg, 7.5 mmol, 1.50 equiv) and *para*-toluenesulfonic acid monohydrate (48 mg, 0.25 mmol, 0.05 equiv) in toluene (30 mL). The reaction mixture was stirred at 160° C for 16 h. Then, the reaction was quenched with the saturated aqueous $NaHCO_3$ (20 mL), and extracted with DCM (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, and concentrated under reduced pressure. 2-(4-Bromophenyl)-2-methyl-1,3-dioxolane (80%) was obtained as colorless solid and used for the next step without further purification.

Step 2: The procedure was similar as described in the **General procedure**, and the product was obtained as colorless solid (754 mg, 65%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 4.06 – 4.00 (m, 2H), 3.79 – 3.72 (m, 2H), 1.65 (s, 3H), 1.34 (s, 12H). The spectral data is similar to that previously reported in the literature.[5]



Step 1: Following the reported procedures,[5] an oven-dried flask equipped with a stir bar were charged with 4-bromophenol (1.73 g, 10 mmol), 4-bromobutene (2.70 g, 20 mmol, 2.0 equiv) and potassium carbonate (3.46 g, 25 mmol, 2.5 equiv). The mixture was dissolved in 40 mL acetonitrile, and then heated to reflux for 48 h. After completion, the reaction solution was quenched with saturated $NaHCO_3$ and extracted with DCM (3 x 15 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 10:1) to obtain as colorless liquid (2.04 g, 90%). R_f = 0.32 (petroleum ether/ethyl acetate = 30:1).

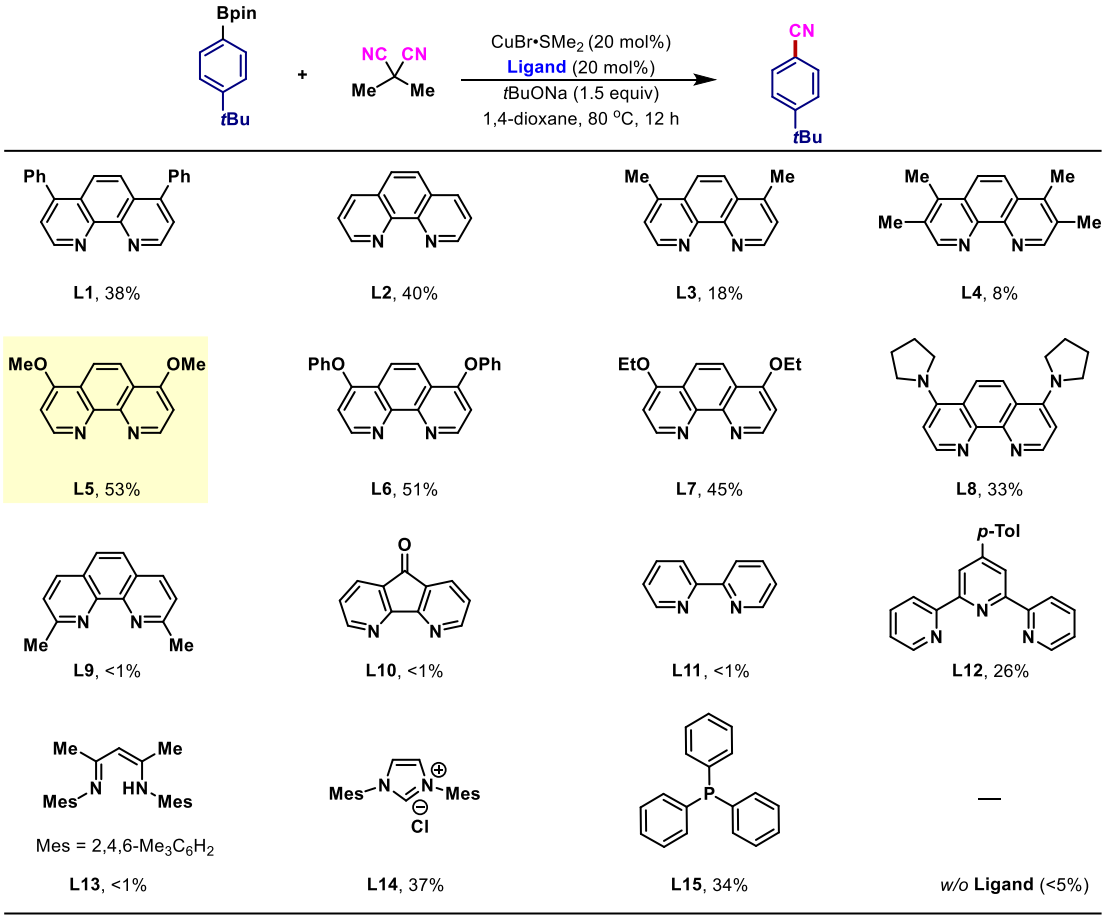
Step 2: The procedure was similar as described in the **General procedure**, and the product was obtained as colorless solid (1.23 g, 50%). The product was confirmed by GC-MS analyses.

III. Optimization of Reaction Conditions

a) Evaluation of Ligand Effect for the Cyanation Reactions

In a glovebox, to an oven-dried screw capped vial equipped with a Teflon stir bar were added dimethylmalononitrile (**DMMN**, 57 mg, 0.60 mmol), CuBr•SMe_2 (17 mg, 0.08 mmol), the corresponding ligand (0.08 mmol), *t*BuONa (58 mg, 0.60 mmol) and 4-*tert*-butyl phenylboronic acid pinacol ester (104 mg, 0.40 mmol) in anhydrous cyclohexane (0.50 mL). The reaction vial was capped, removed from the glovebox and stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature, and passed through a pad of silica gel with EtOAc. The yields of the desired product were determined by GC analyses against *n*-hexadecane as a calibrated internal standard.

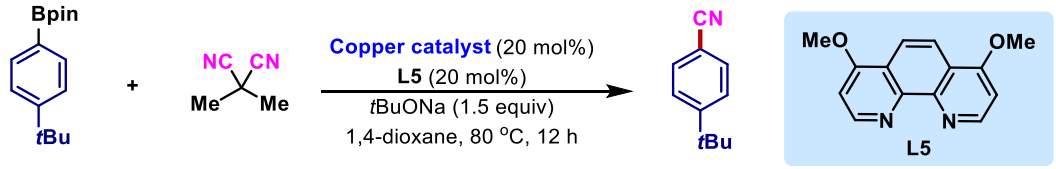
Table S1. Evaluation of the Ligand Effect.



b) Evaluation of the Copper Catalyst Effect for the Cyanation Reactions

In a glovebox, to an oven-dried screw capped vial equipped with a Teflon stir bar were added dimethylmalononitrile (**DMMN**, 57 mg, 0.60 mmol), corresponding copper salt (0.08 mmol), the ligand **L5** (19 mg, 0.08 mmol), *t*BuONa (58 mg, 0.60 mmol) and 4-*tert*-butylphenylboronic acid pinacol ester (104 mg, 0.40 mmol) in anhydrous 1,4-dioxane (0.50 mL). The reaction vial was capped, removed from the glovebox and stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature, and passed through a pad of silica gel with EtOAc. The yields were determined by GC analyses against *n*-hexadecane as a calibrated internal standard.

Table S2. Evaluation of the copper catalyst effect

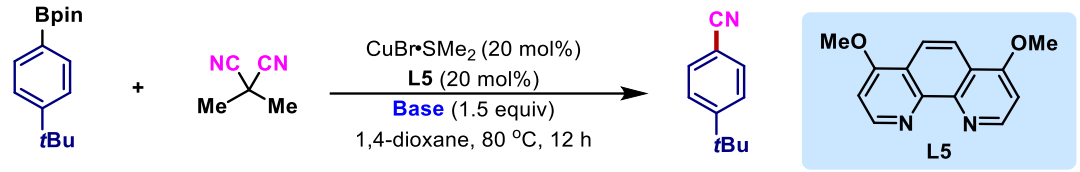


Entry	Copper catalyst	Yield (%)
1	$CuBr•SMe_2$	53
2	CuOTf	38
3	CuBr	20
4	CuI	13
5	CuCl	32
5	$CuBr_2$	<1
7	CuTc	45
8	CuSCN	19
9	CuCN	16
10	*w/o* Cu	<1

c) Evaluation of the Base Effect for the Cyanation Reactions

In a glovebox, to an oven-dried screw capped vial equipped with a Teflon stir bar were added dimethylmalononitrile (**DMMN**, 57 mg, 0.60 mmol), CuBr•SMe_2 (17 mg, 0.08 mmol) and the ligand **L5** (19 mg, 0.08 mmol), base (0.60 mmol), 4-*tert*-butyl phenylboronic acid pinacol ester (104 mg, 0.40 mmol) in anhydrous 1,4-dioxane (0.50 mL). The reaction vial was capped, removed from the glovebox and stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature, and passed through a pad of silica gel with EtOAc. The yields were determined by GC analyses against *n*-hexadecane as a calibrated internal standard.

Table S3. Evaluation of the Base effect

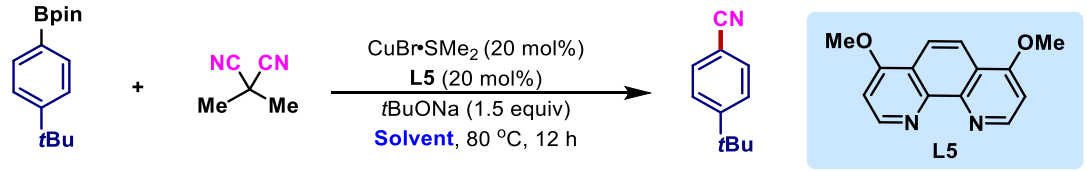


Entry	Base	Yield (%)
1	*t*BuONa	53
2	*t*BuOLi	38
3	*t*BuOK	51
4	EtONa	43
5	MeONa	<1
6	Na_2CO_3	<1
7	Cs_2CO_3	<1
8	KF	<1
9	*w/o* Base	<1

d) Evaluation of the Solvent Effect for the Cyanation Reactions

In a glovebox, to an oven-dried screw capped vial equipped with a Teflon stir bar were added dimethylmalononitrile (**DMMN**, 57 mg, 0.60 mmol), CuBr•SMe_2 (17 mg, 0.08 mmol), the ligand **L5** (19 mg, 0.08 mmol), *t*BuONa (58 mg, 0.60 mmol) and 4-*tert*-butyl phenylboronic acid pinacol ester (104 mg, 0.40 mmol) in anhydrous solvent (0.50 mL). The reaction vial was capped, removed from the glovebox and stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature, and passed through a pad of silica gel with EtOAc. The yields were determined by GC analyses against *n*-hexadecane as a calibrated internal standard.

Table S4. Evaluation of the Solvent Effect



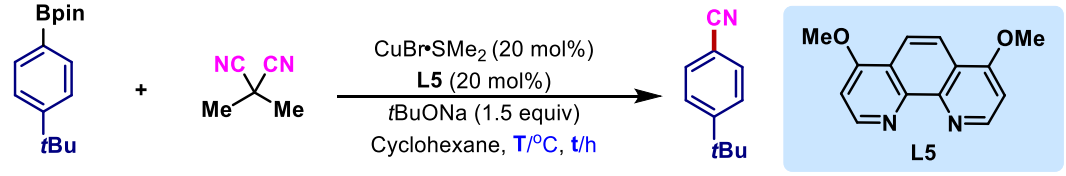
Entry	Solvent	Yield (%)
1	1,4-Dioxane	53
2	THF	55
3	MTBE (Methyl *tert*-butyl ether)	53
4	*n*-Hexane	74
5	Cyclohexane	78
6	PhH	65
7	$PhCH_3$	72
8	CH_3CN	<1
9	EtOAc	<1
10	DMA (Dimethylacetamide)	<1
11[a]	Cyclohexane	10
12[b]	Cyclohexane	59

[a] *t*BuONa (19 mg, 0.20 mmol, 0.50 equiv). [b] *t*BuONa (39 mg, 0.40 mmol, 1.0 equiv).

e) Evaluation of Reaction Temperature and Reaction Time Effect

In a glovebox, to an oven-dried screw capped vial equipped with a Teflon stir bar were added dimethylmalononitrile (**DMMN**, 57 mg, 0.60 mmol), CuBr•SMe_2 (17 mg, 0.08 mmol), the ligand **L5** (19 mg, 0.08 mmol), *t*BuONa (58 mg, 0.60 mmol) and 4-*tert*-butyl phenylboronic acid pinacol ester (104 mg, 0.40 mmol) in anhydrous cyclohexane (0.50 mL). The reaction vial was capped, removed from the glovebox and stirred at the indicated temperature and time. The reaction mixture was cooled to room temperature, and passed through a pad of silica gel with EtOAc. The yields were determined by GC analyses against *n*-hexadecane as a calibrated internal standard.

Table S5. Evaluation of the Reaction Temperature and Reaction Time effect.

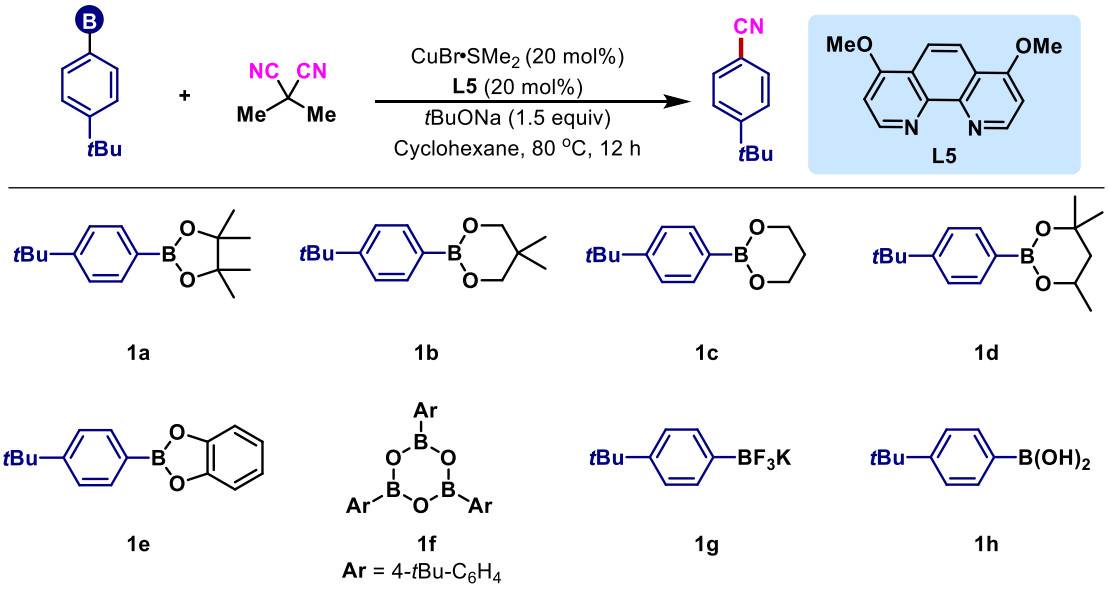


Entry	T/°C	t/h	Yield (%)
1	80	12	78
2	70	12	73
3	60	12	25
5	90	12	64
6	100	12	54
7	80	6	78
8	80	3	14

f) Evaluation of Arylboron Effect

In a glovebox, to an oven-dried screw capped vial equipped with a Teflon stir bar were added dimethylmalononitrile (**DMMN**, 57 mg, 0.60 mmol), CuBr•SMe_2 (17 mg, 0.08 mmol), the ligand **L5** (19 mg, 0.08 mmol), *t*BuONa (58 mg, 0.60 mmol) and the corresponding arylboron (0.40 mmol) in anhydrous cyclohexane (0.50 mL). The reaction vial was capped, removed from the glovebox and stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature, and passed through a pad of silica gel with EtOAc. The yields were determined by GC analyses against *n*-hexadecane as a calibrated internal standard.

Table S6. Evaluation of Arylboron effect.

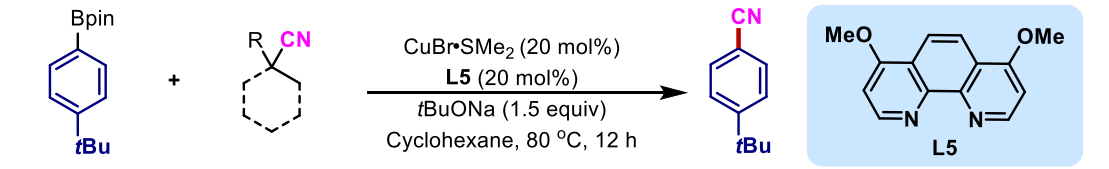


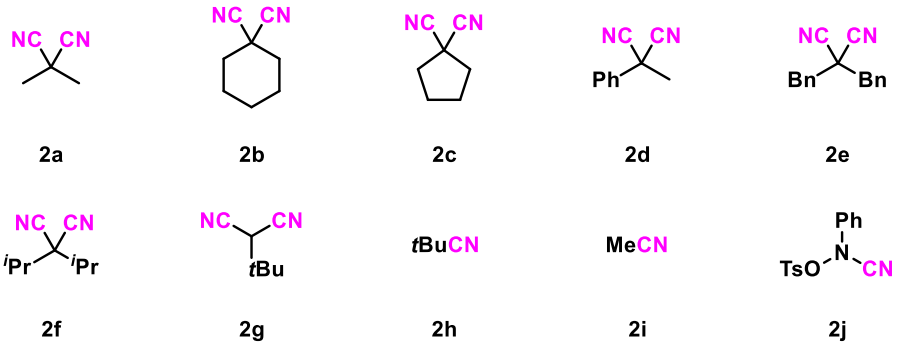
Entry	Arylboron	Yield (%)
1	**1a**	78
2	**1b**	24
3	**1c**	40
4	**1d**	41
5	**1e**	<1
6	**1f**	56
7	**1g**	7
8	**1h**	<1

g) Evaluation of Transnitrilation Reagent Effect

In a glovebox, to an oven-dried screw capped vial equipped with a Teflon stir bar were added transnitrilation reagents (0.6 mmol), CuBr•SMe_2 (17 mg, 0.08 mmol), the ligand **L5** (19 mg, 0.08 mmol), *t*BuONa (58 mg, 0.6 mmol) and 4-*tert*-butylphenylboronic acid pinacol ester (104 mg, 0.4 mmol) in anhydrous cyclohexane (0.50 mL). The reaction vial was capped, removed from the glovebox and stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature, and passed through a pad of silica gel with EtOAc. The yields were determined by GC analyses against *n*-hexadecane as a calibrated internal standard.

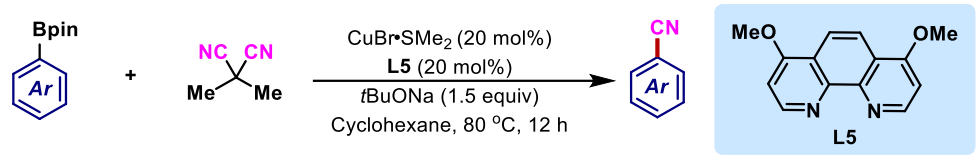
Table S7. Evaluation of transnitrilation reagent effect.





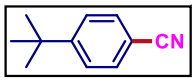
Entry	Transnitrilation Reagents	Yield (%)
1	**2a**	78
2	**2b**	67
3	**2c**	69
4	**2d**	10
5	**2e**	16
6	**2f**	<1
7	**2g**	<1
8	**2h**	<1
9	**2i**	<1
10	**2j**	<1

IV. Reaction Scope for Arylboronic Esters



In a glovebox, to an oven-dried screw capped vial equipped with a Teflon stir bar were added dimethylmalononitrile (**DMMN**, 57 mg, 0.60 mmol), CuBr•SMe_2 (17 mg, 0.08 mmol), the ligand **L5** (19 mg, 0.08 mmol), *t*BuONa (58 mg, 0.60 mmol) and arylboronic acid pinacol ester (0.40 mmol) in anhydrous cyclohexane (0.50 mL). The reaction vial was capped, removed from the glovebox and stirred at 80 °C for 12 h. The reaction mixture was then cooled to room temperature. The solution was passed through a pad of silica gel and $MgSO_4$ with dichloromethane, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to yield the desired products.

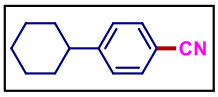
4-*tert*-Butyl benzonitrile (Table 3, 3)



Column chromatography (petroleum ether/ethyl acetate = 100:0 to 20:1) afforded yellow oil (76%). R_f = 0.30 (petroleum ether/ethyl acetate = 20:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7. 58 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 1.32 (s, 9H). The spectral data is similar to that previously reported in the literature.[6]

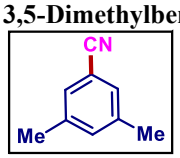
4-Cyclohexylbenzonitrile (Table 3, 4)



Column chromatography (petroleum ether/ethyl acetate = 100:0 to 10:1) afforded yellow oil (73%). R_f = 0.35 (petroleum ether/ethyl acetate = 10:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 2H), δ 7.29 (d, *J* = 8.1 Hz, 2H), 2.56 – 2.53 (m, 1H), 1.85 – 1.83 (m, 4H), 1.76 – 1.74 (m, 1H), 1.44 – 1.37 (m, 4H), 1.27 – 1.23 (m, 1H). The spectral data is similar to that previously reported in the literature.[7]

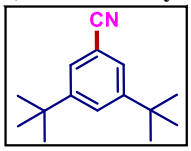
3,5-Dimethylbenzonitrile (Table 3, 5)



Column chromatography (petroleum ether/ethyl acetate = 100:0 to 20:1) afforded white solid (80%). R_f = 0.30 (petroleum ether/ethyl acetate = 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 1.8 Hz, 2H), 7.16 – 7.13 (m, 1H), 2.28 (s, 6H). The spectral data is similar to that previously reported in the literature.[8]

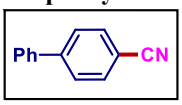
3,5-Di-*tert*-butyl benzonitrile (Table 3, 6)



Column chromatography (petroleum ether/ethyl acetate = 100:0 to 20:1) afforded white solid (72%). R_f = 0.30 (petroleum ether/ethyl acetate = 20:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 1.9 Hz, 1H), 7.48 (d, *J* = 1.9 Hz, 2H), 1.32 (s, 18H). The spectral data is similar to that previously reported in the literature.[9]

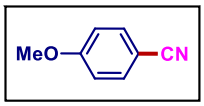
4-Biphenylcarbonitrile (Table 3, 7)



Using a modified method by performing the reaction at 100 °C. Column chromatography (petroleum ether/ethyl acetate = 100:1 to 10:1) afforded white solid (78%). R_f = 0.28 (petroleum ether/ethyl acetate = 10:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 1H). The spectral data is similar to that previously reported in the literature.[8]

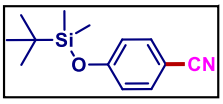
4-Methoxybenzonitrile (Table 3, 8)



Column chromatography (petroleum ether/ethyl acetate = 50:1 to 5:1) afforded white solid (80%). R_f = 0.27 (petroleum ether/ethyl acetate = 5:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H). The spectral data is similar to that previously reported in the literature.[8]

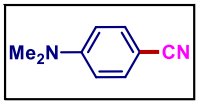
4-(*tert*-Butyldimethylsilyloxy)benzonitrile (Table 3, 9)



Using a modified method by performing the reaction at 100 °C. Column chromatography (petroleum ether/ethyl acetate =20:1) afforded colorless solid (80%). R_f = 0.32 (petroleum ether/ethyl acetate = 20:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 0.98 (s, 9H), 0.23 (s, 6H). The spectral data is similar to that previously reported in the literature.[10]

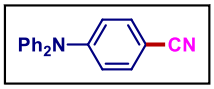
4-(Dimethylamino)benzonitrile (Table 3, 10)



Column chromatography (petroleum ether/ethyl acetate = 30:1 to 8:1) afforded white solid (90%). R_f = 0.25 (petroleum ether/ethyl acetate = 8:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 8.7 Hz, 2H), 3.04 (s, 6H). The spectral data is similar to that previously reported in the literature.[11]

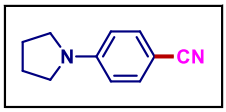
4-(Diphenylamino)benzonitrile (Table 3, 11)



Column chromatography (petroleum ether/ethyl acetate =15:1) afforded white solid (83%). R_f = 0.25 (petroleum ether/ethyl acetate = 15:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 4H), 7.18 – 7.14 (m, 6H), 6.96 (d, *J* = 8.4 Hz, 2H). The spectral data is similar to that previously reported in the literature.[12]

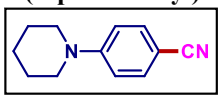
4-(Pyrrolidin-1-yl)benzonitrile (Table 3, 12)



Column chromatography (petroleum ether/ethyl acetate = 10:1) afforded white solid (91%). R_f = 0.30 (petroleum ether/ethyl acetate = 10:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.43 (m, 2H), 6.50 (d, *J* = 8.8 Hz, 2H), 3.35 – 3.30 (m, 4H), 2.06 – 2.02 (m, 4H). The spectral data is similar to that previously reported in the literature.[13]

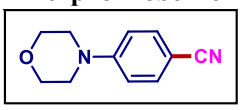
4-(Piperidin-1-yl)benzonitrile (Table 3, 13)



Column chromatography (petroleum ether/ethyl acetate =30:1) afforded yellow solid (83%). R_f = 0.28 (petroleum ether/ethyl acetate = 30:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.43 (m, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 3.33 (d, *J* = 3.2 Hz, 4H), 1.66 (t, *J* = 2.1 Hz, 6H). The spectral data is similar to that previously reported in the literature.[14]

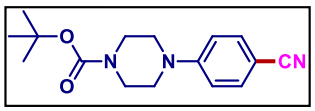
4-Morpholinobenzonitrile (Table 3, 14)



Column chromatography (petroleum ether/ethyl acetate = 9:1) afforded white solid (94%). R_f = 0.30 (petroleum ether/ethyl acetate = 9:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 – 7.50 (m, 2H), 6.89 – 6.83 (m, 2H), 3.87 – 3.83 (t, *J* = 5.3 Hz, 4H), 3.28 (t, *J* = 5.9 Hz, 4H). The spectral data is similar to that previously reported in the literature.[8]

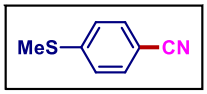
***tert*-Butyl 4-(4-cyanophenyl)piperazine-1-carboxylate (Table 3, 15)**



Using a modified method by performing the reaction at 100 °C. Column chromatography (petroleum ether/ethyl acetate =5:1) afforded white solid (80%). R_f = 0.30 (petroleum ether/ethyl acetate = 5:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 3.59 – 3.56 (m, 4H), 3.32 – 3.28 (m, 4H), 1.48 (s, 9H). The spectral data is similar to that previously reported in the literature.[15]

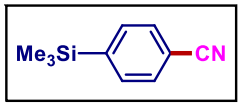
4-(Methylthio)benzonitrile (Table 3, 16)



Column chromatography (petroleum ether/ethyl acetate = 30:1 to 15:1) afforded white solid (69%). R_f = 0.32 (petroleum ether/ethyl acetate = 15:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.45 (m, 2H), 7.21 – 7.18 (m, 2H), 2.44 (s, 3H). The spectral data is similar to that previously reported in the literature.[16]

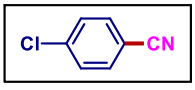
4-(Trimethylsilyl)benzonitrile (Table 3, 17)



Column chromatography (petroleum ether/ethyl acetate =100:1) afforded yellow oil (87%). R_f = 0.27 (petroleum ether/ethyl acetate = 100:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 – 7.55 (m, 4H), 0.30 (s, 9H). The spectral data is similar to that previously reported in the literature.[17]

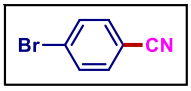
4-Chlorobenzonitrile (Table 3, 18)



Using a modified method with 30 mol% CuBr•SMe_2 and 30 mol% **L5** at 100 °C. Column chromatography (petroleum ether/ethyl acetate = 30:1 to 15:1) afforded white solid (85%). R_f = 0.32 (petroleum ether/ethyl acetate = 15:1).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 (d, *J* = 10.1 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H). The spectral data is similar to that previously reported in the literature.[18]

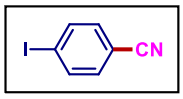
4-Bromobenzonitrile (Table 3, 19)



Using a modified method with 30 mol% CuBr•SMe_2 and 30 mol% **L5** at 100 °C Column chromatography (petroleum ether/ethyl acetate = 95:5 to 9:1) afforded white solid (66%). R_f = 0.32 (petroleum ether/ethyl acetate = 9:1).

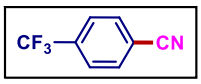
^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H). The spectral data is similar to that previously reported in the literature.[6]

4-Iodobenzonitrile (Table 3, 20)



The yield of the 4-iodobenzonitrile was measured to be <1% by using NMR spectroscopy with 1,4-dioxane as an internal standard.

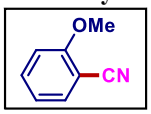
4-(Trifluoromethyl)benzonitrile (Table 3, 21)



Using a modified method with 30 mol% CuBr•SMe_2 and 30 mol% **L5** at 100 °C Column chromatography (petroleum ether/ethyl acetate =20:1) afforded white solid (46%). R_f = 0.29 (petroleum ether/ethyl acetate = 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H). The spectral data is similar to that previously reported in the literature.[6]

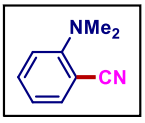
2-Methoxybenzonitrile (Table 3, 22)



Using a modified method by performing the reaction at 100 °C. Column chromatography (petroleum ether/ethyl acetate =20:1) afforded colorless oil (65%). R_f = 0.29 (petroleum ether/ethyl acetate = 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.50 (m, 2H), 7.04 – 6.93 (m, 2H), 3.93 (s, 3H). The spectral data is similar to that previously reported in the literature.[8]

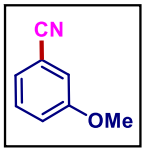
2-(Dimethylamino)benzonitrile (Table 3, 23)



Column chromatography (petroleum ether/ethyl acetate =20:1) afforded colorless oil (45%). R_f = 0.29 (petroleum ether/ethyl acetate = 20:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.7 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 3.04 (s, 6H). The spectral data is similar to that previously reported in the literature.[19]

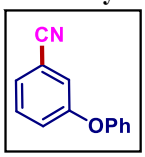
3-Methoxybenzonitrile (Table 3, 24)



Using a modified method by performing the reaction at 100 °C. Column chromatography (petroleum ether/ethyl acetate =20:1) afforded colorless oil (73%). R_f = 0.29 (petroleum ether/ethyl acetate = 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 1H), 7.20 – 7.16 (m, 1H), 7.06 (dd, *J* = 7.0, 1.2 Hz, 2H), 3.76 (s, 3H). The spectral data is similar to that previously reported in the literature.[6]

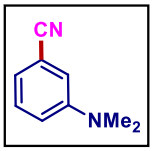
3-Phenoxybenzonitrile (Table 3, 25)



Using a modified method by performing the reaction at 100 °C. Column chromatography (petroleum ether/ethyl acetate =20:1) afforded white solid (72%). R_f = 0.29 (petroleum ether/ethyl acetate = 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 4H), 7.22 – 7.03 (m, 3H), 7.01 – 6.94 (m, 2H). The spectral data is similar to that previously reported in the literature.[20]

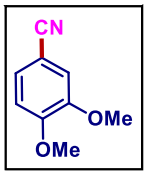
3-(Dimethylamino)benzonitrile (Table 3, 26)



Column chromatography (petroleum ether/ethyl acetate =20:1) afforded colorless oil (64%). R_f = 0.29 (petroleum ether/ethyl acetate = 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.90 – 6.84 (m, 2H), 2.98 (s, 6H). The spectral data is similar to that previously reported in the literature.[18]

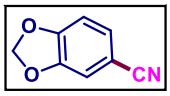
3,4-Dimethoxybenzonitrile (Table 3, 27)



Column chromatography (petroleum ether/ethyl acetate =9:1) afforded white solid (62%). R_f = 0.23 (petroleum ether/ethyl acetate = 9:1).

^{1}H NMR (600 MHz, CDCl3) δ 7.29 (d, *J* = 8.3 Hz, 1H), 7.08 (d, *J* = 2.1 Hz, 1H), 6.90 (dd, *J* = 8.4, 1.5 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H). The spectral data is similar to that previously reported in the literature.[8]

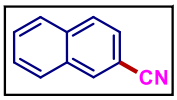
1,3-Benzodioxole-5-carbonitrile (Table 3, 28)



Using a modified method with 100 °C as the reaction temperature. Column chromatography (petroleum ether/ethyl acetate = 30:1 to 15:1) afforded white solid (49%). R_f = 0.32 (petroleum ether/ethyl acetate = 15:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.03 (d, *J* = 1.8 Hz, 1H), 6.86 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.07 (s, 2H). The spectral data is similar to that previously reported in the literature.[6]

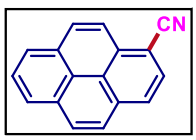
2-Naphthonitrile (Table 3, 29)



Column chromatography (petroleum ether/ethyl acetate = 100:1 to 20:1) afforded white solid (82%). R_f = 0.35 (petroleum ether/ethyl acetate = 20:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.97 – 7.83 (m, 3H), 7.72 – 7.55 (m, 3H). The spectral data is similar to that previously reported in the literature.[8]

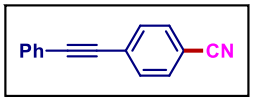
Pyrene-1-carbonitrile (Table 3, 30)



Column chromatography (petroleum ether/ethyl acetate =20:1) afforded white solid (67%). R_f = 0.32 (petroleum ether/ethyl acetate = 20:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41 (d, *J* = 9.0 Hz, 1H), 8.29 (t, *J* = 7.5 Hz, 2H), 8.27 – 8.20 (m, 3H), 8.15 – 8.09 (m, 2H), 8.06 (d, *J* = 8.9 Hz, 1H). The spectral data is similar to that previously reported in the literature.[21]

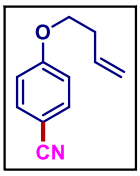
1-(4-Cyanophenyl)-2-phenylacetylene (Table 3, 31)



Column chromatography (petroleum ether/ethyl acetate =100:0) afforded white solid (73%). R_f = 0.28 (petroleum ether/ethyl acetate = 100:0).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.59 (m, 4H), 7.57 – 7.53 (m, 2H), 7.41 – 7.37 (m, 3H). The spectral data is similar to that previously reported in the literature.[22]

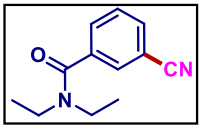
But-3-enyl 4-cyanophenyl ether (Table 3, 32)



Column chromatography (petroleum ether/ethyl acetate =100:0 to 50:1) afforded white solid (73%). R_f = 0.25 (petroleum ether/ethyl acetate = 50:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 5.88 (m, 1H), 5.20 – 5.08 (m, 2H), 4.05 (t, *J* = 6.7 Hz, 2H), 2.60 – 2.53 (m, 2H). The spectral data is similar to that previously reported in the literature.[23]

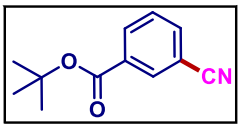
***N, N*-diethyl-3-ethynyl benzamide (Table 3, 33)**



Using a modified method by performing the reaction in fluorobenzene at 100 °C. Column chromatography (petroleum ether/ethyl acetate = 4:1) afforded colorless solid (87%). R_f = 0.25 (petroleum ether/ethyl acetate = 4:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.7 Hz, 1H), 7.66 (s, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 3.54 (br s, 2H), 3.22 (br s, 2H), 1.23 (br s, 3H), 1.12 (br s, 3H). The spectral data is similar to that previously reported in the literature.[24]

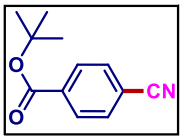
***tert*-Butyl 3-cyanobenzoate (Table 3, 34)**



Using a modified method by performing the reaction at 100 °C. Column chromatography (petroleum ether/ethyl acetate =20:1) afforded white solid (55%). R_f = 0.29 (petroleum ether/ethyl acetate = 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 1.8 Hz, 1H), 8.21 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.79 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 1.60 (s, 9H). The spectral data is similar to that previously reported in the literature.[25]

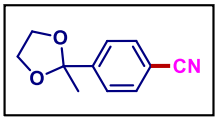
***tert*-Butyl 4-cyanobenzoate (Table 3, 35)**



Using a modified method by performing the reaction at 100 °C. Column chromatography (petroleum ether/ethyl acetate = 10:1) afforded colorless solid (59%). R_f = 0.26 (petroleum ether/ethyl acetate = 10:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 1.59 (s, 9H). The spectral data is similar to that previously reported in the literature.[26]

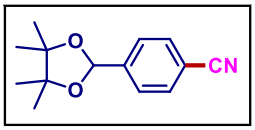
4-(2-Methyl-1,3-dioxolan-2-yl)benzonitrile (Table 3, 36)



Using a modified method by performing the reaction at 100 °C. Column chromatography (petroleum ether/ethyl acetate = 15:1 to 8:1) afforded white solid (72%). R_f = 0.28 (petroleum ether/ethyl acetate = 15:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.57 (m, 4H), 4.09 – 4.04 (m, 2H), 3.78 – 3.72 (m, 2H), 1.63 (s, 3H). The spectral data is similar to that previously reported in the literature.[27]

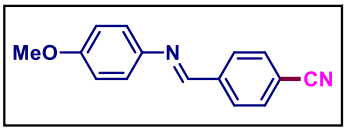
4-(4,4,5,5-Tetramethyl-1,3-dioxolan-2-yl)benzonitrile (Table 3, 37)



Using a modified method by performing the reaction at 100 °C. Column chromatography (petroleum ether/ethyl acetate = 50:1 to 10:1) afforded white solid (65%). R_f = 0.26 (petroleum ether/ethyl acetate = 10:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 5.97 (s, 1H), 1.32 (s, 6H), 1.22 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.3, 132.1, 126.9, 118.8, 112.3, 98.7, 83.2, 24.1, 22.1. HRMS (ESI) calcd. for $C_{14}H_{18}NO_2$ $[M+H]^+$: 232.1333, found: 232.1331.

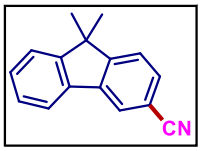
4-{(*E*)-[(4-Methoxyphenyl)imino]methyl}benzonitrile(Table 3, 38)



Column chromatography (petroleum ether/ethyl acetate =100:0 to 3:1) afforded yellow solid (32%). R_f = 0.27 (petroleum ether/ethyl acetate = 3:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.98 (d, *J* = 7.9 Hz, 2H), 7.74 (d, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 155.4, 143.7, 140.3, 132.5, 128.9, 122.6, 118.6, 114.5, 113.9, 55.5. HRMS (ESI) calcd. for $C_{15}H_{13}N_2O$ $[M+H]^+$: 237.1023, found: 237.1023.

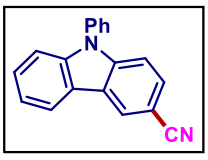
9,9-Dimethyl-9*H*-fluorene-3-carbonitrile (Table 3, 39)



Column chromatography (petroleum ether/ethyl acetate = 100:1 to 10:1) afforded yellow liquid (75%). R_f = 0.26 (petroleum ether/ethyl acetate = 10:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 – 7.76 (m, 2H), 7.70 (s, 1H), 7.64 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.49 – 7.47 (m, 1H), 7.40 (m, 2H), 1.50 (s, 6H). The spectral data is similar to that previously reported in the literature.[28]

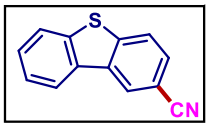
9-Phenyl-9*H*-carbazole-2-carbonitrile (Table 3, 40)



Column chromatography (petroleum ether/ethyl acetate = 3:1) afforded yellow solid (72%). R_f = 0.28 (petroleum ether/ethyl acetate = 3:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (d, *J* = 1.5 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.66 – 7.63 (m, 3H), 7.56 – 7.48 (m, 4H), 7.42 – 7.36 (m, 3H). The spectral data is similar to that previously reported in the literature.[25]

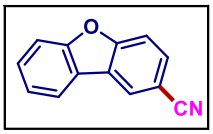
2-Dibenzothiophenecarbonitrile (Table 3, 41)



Using a modified method by performing the reaction at 70 °C. Column chromatography (petroleum ether/ethyl acetate = 20:1) afforded white solid (63%). R_f = 0.29 (petroleum ether/ethyl acetate = 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 – 8.43 (m, 1H), 8.21 – 8.17 (m, 1H), 7.95 (dd, *J* = 8.3, 0.7 Hz, 1H), 7.92 – 7.88 (m, 1H), 7.69 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.58 – 7.53 (m, 2H). The spectral data is similar to that previously reported in the literature.[29]

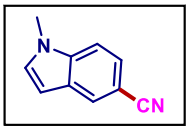
2-Dibenzofurancarbonitrile (Table 3, 42)



Using a modified method by performing the reaction at 70 °C. Column chromatography (petroleum ether/ethyl acetate = 20:1) afforded white solid (54%). R_f = 0.27 (petroleum ether/ethyl acetate = 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 1.7 Hz, 1H), 8.01 – 7.93 (m, 1H), 7.74 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.67 – 7.60 (m, 2H), 7.55 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.42 (td, *J* = 7.5, 1.1 Hz, 1H). The spectral data is similar to that previously reported in the literature.[29]

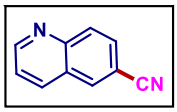
1-Methyl-1*H*-indole-5-carbonitrile (Table 3, 43)



Column chromatography (petroleum ether/ethyl acetate = 3:2) afforded yellow solid (85%). R_f = 0.30 (petroleum ether/ethyl acetate = 3:2).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.17 (d, *J* = 3.2 Hz, 1H), 6.57 (d, *J* = 3.0 Hz, 1H). 3.84 (s, 3H). The spectral data is similar to that previously reported in the literature.[8]

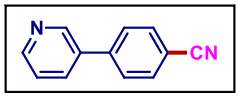
Quinoline-6-carbonitrile (Table 3, 44)



Using a modified method by performing the reaction at 100 °C. Column chromatography (petroleum ether/ethyl acetate = 3:2) afforded white solid (48%). R_f = 0.30 (petroleum ether/ethyl acetate = 3:2).

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.07 (d, *J* = 2.9 Hz, 1H), 8.26 – 8.21 (m, 3H), 7.88 (d, *J* = 8.7 Hz, 1H), 7.56 (dd, *J* = 8.3, 4.2 Hz, 1H). The spectral data is similar to that previously reported in the literature.[17]

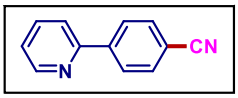
3-(4-(Trifluoromethyl)phenyl)pyridine (Table 3, 45)



Using a modified method by performing the reaction at 100 °C. Column chromatography (petroleum ether/ethyl acetate =5:1) afforded white solid (82%). R_f = 0.27 (petroleum ether/ethyl acetate = 5:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.70 – 8.66 (m, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.78 (d, *J* = 8.2, 2.3 Hz, 2H), 7.70 (dd, *J* = 8.3, 2.3 Hz, 2H), 7.44 (t, *J* = 6.4 Hz, 1H). The spectral data is similar to that previously reported in the literature.[30]

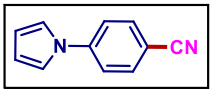
4-(2-Pyridinyl)benzonitrile (Table 3, 46)



Column chromatography (petroleum ether/ethyl acetate =10:1) afforded white solid (58%). R_f = 0.25 (petroleum ether/ethyl acetate = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dt, *J* = 4.9, 1.4 Hz, 1H), 8.15 – 8.08 (m, 2H), 7.84 – 7.72 (m, 4H), 7.32 (ddd, *J* = 7.3, 4.8, 1.4 Hz, 1H). The spectral data is similar to that previously reported in the literature.[30]

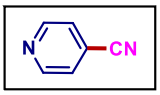
4-(1*H*-Pyrrol-1-yl)benzonitrile (Table 3, 47)



Column chromatography (petroleum ether/ethyl acetate =20:1) afforded white solid (69%). R_f = 0.27 (petroleum ether/ethyl acetate = 20:1).

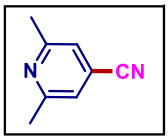
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.14 (t, *J* = 2.2 Hz, 2H), 6.41 (t, *J* = 2.2 Hz, 2H). The spectral data is similar to that previously reported in the literature.[28]

4-Cyanopyridine (Table 3, 48)



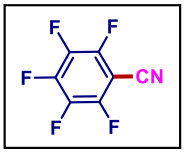
The yield of the isonicotinonitrile was measured to be <1% by using NMR spectroscopy with 1,4-dioxane as an internal standard.

4-cyano-2,6-lutidine (Table 3, 49)



The yield of the isonicotinonitrile was measured to be <1% by using NMR spectroscopy with 1,4-dioxane as an internal standard.

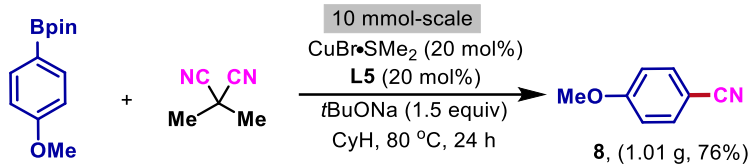
Pentafluorobenzonitrile (Table 3, 50)



The yield of the 2,3,4,5,6-pentafluorobenzonitrile was measured to be <1% by using NMR spectroscopy with 1,4-dioxane as an internal standard.

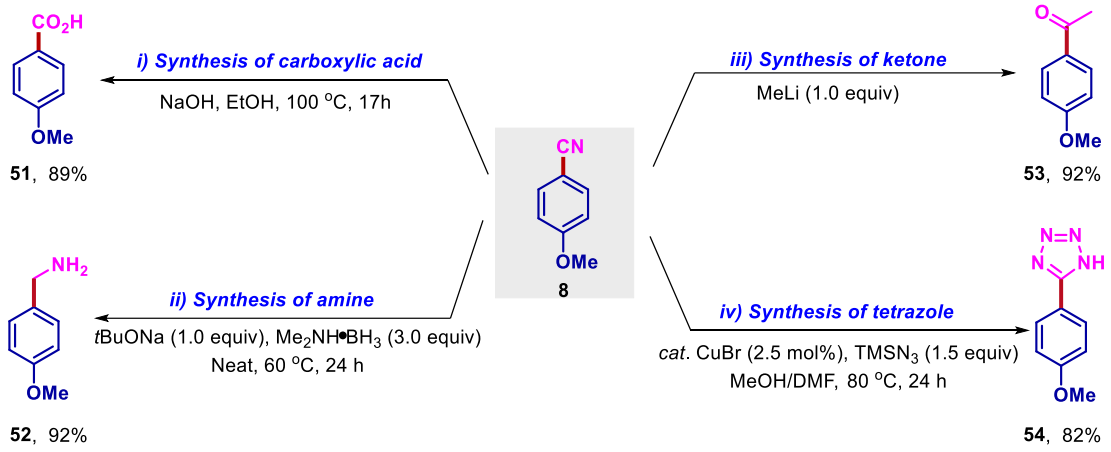
V. Synthetic Applications

a) Scale-up Reaction



To an oven-dried Schlenk flask equipped with a stir bar were added CuBr•SMe_2 (165 mg, 0.80 mmol), the ligand **L5** (193 mg, 0.80 mmol), dimethylmalononitrile (**DMMN**, 1.46 g, 15.0 mmol, 1.5 equiv), *t*BuONa (1.44 g, 15.0 mmol, 1.5 equiv) and 4-methoxyphenylboronic acid pinacol ester (2.34 g, 10.0 mmol) in anhydrous cyclohexane (5.0 mL). The reaction flask was capped, removed from the glovebox and stirred at 80 °C for 12 h. The reaction mixture was then cooled to room temperature. The reaction solution was passed through a pad of silica gel and $MgSO_4$ with dichloromethane, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to yield the desired product (1.01 g, 76%).

Diversification of product 8



i) Synthesis of carboxylic acid

To an oven-dried round flask equipped with a stir bar were added product **8** (133 mg, 1.0 mmol), EtOH (8.0 mL) and an aqueous NaOH solution (6.0 mL, 6N). The reaction mixture was refluxed for 17 h at 100 °C. After completion, the reaction was cooled down to room temperature. The volatiles were removed under reduced pressure, and the residue was diluted with H_2O (20 mL), followed by acidification with conc. HCl solution (4.0 mL) at 0 °C. The mixture was then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to obtain the product **51** as white solid (135 mg, 89%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.59 (s, 1H), 7.89 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.9 Hz, 2H), 3.82 (s, 3H). The spectral data is similar to that previously reported in the literature.[31]

ii) Synthesis of amine

To an oven-dried heavy-walled pressure vessel equipped with a stir bar were added product **8** (133 mg, 1.0 mmol), *t*BuONa (96 mg, 1.0 mmol) and $Me_2NH{\bullet}BH_3$ (3.0 mmol) under a nitrogen atmosphere. The reaction mixture was heated to 60 ºC and stirred at this temperature for 24 h. After completion, the mixture was cooled down, quenched with the addition of methanol. The methanol solution of the reaction mixture was evaporated, and the residue was dissolved in diethyl ether. The ether solution was washed three times with water, the combined organic layer was dried with anhydrous $MgSO_4$. The residue was purified by column chromatography to obtain product **52** as yellow solid (126 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 8.7, 1.9 Hz, 2H), 6.84 (dd, *J* = 8.5, 1.8 Hz, 2H), 3.86 – 3.36 (m, 5H), 1.56 (br s, 2H). The spectral data is similar to that previously reported in the literature.[32]

iii) Synthesis of ketone

To an oven-dried Schlenk flask equipped with a stir bar was added product **8** (133 mg, 1.0 mmol). MeLi (0.7 mL, 1.6 M in diethyl ether) was added with a vigorous stirring. After 3 seconds of stirring, the reaction was quenched with a saturated solution of NH_4Cl and then heated to 100 ºC for 3 h. Saturated $NaHCO_3$ solution was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to obtain the product **53** as white solid (138 mg, 92%).

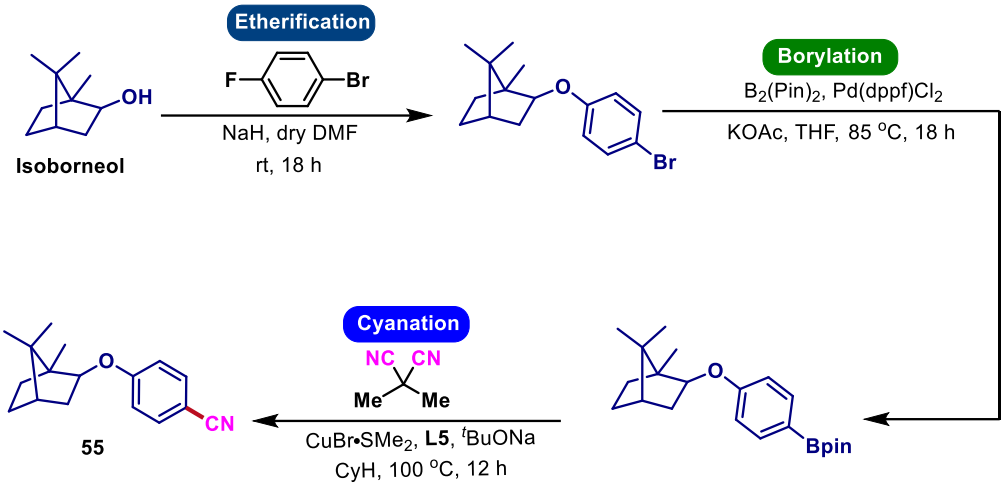
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H), 2.54 (s, 3H). The spectral data is similar to that previously reported in the literature.[33]

iv) Synthesis of tetrazole

To an oven-dried heavy-walled pressure vessel equipped with a stir bar were added trimethylsilyl azide ($TMSN_3$, 0.20 mL, 1.5 mmol), CuBr (3.6 mg, 0.025 mmol) and product **8** (133 mg,1.0 mmol) with a DMF-MeOH mixed solvent (9:1, 2.0 mL). The reaction mixture was stirred at room temperature for 10 min and then heated at 80 ºC for 12 h. After consumption of compound **8**, the reaction mixture was cooled to room temperature. The organic layer was washed with HCl (1 N), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. Aqueous NaOH solution (0.25 N) was added to the residue, and the resulting mixture was stirred for 30 min at room temperature. The mixture was washed with EtOAc, and then concentrated HCl was added until the pH = 1. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with HCl (1 N). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography to obtain the product **54** as white solid (144 mg, 82%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 8.9 Hz, 2H), 3.84 (s, 3H). The spectral data is similar to that previously reported in the literature.[34]

b) Functionalization of Complex Molecules



Etherification: To an oven-dried round-bottom flask equipped with a stir bar were added isoborneol (2.55 g, 16.5 mmol, 1.1 equiv) and anhydrous DMF (20 mL) and sodium hydride (0.72 g of a 60% *w/w* dispersion in mineral oil, 18 mmol, 1.2 equiv). The reaction solution was stirred at room temperature for 30 min. Then, 1-bromo-4-fluorobenzene (1.7 mL, 15 mmol) was added and the mixture was stirred at room temperature for 18 h. The mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3 x 20 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether) to obtain the product as colorless oil (1.35 g, 29% yield). R_f = 0.68 (petroleum ether). This compound was confirmed by ^{1}H NMR spectrum analyses.

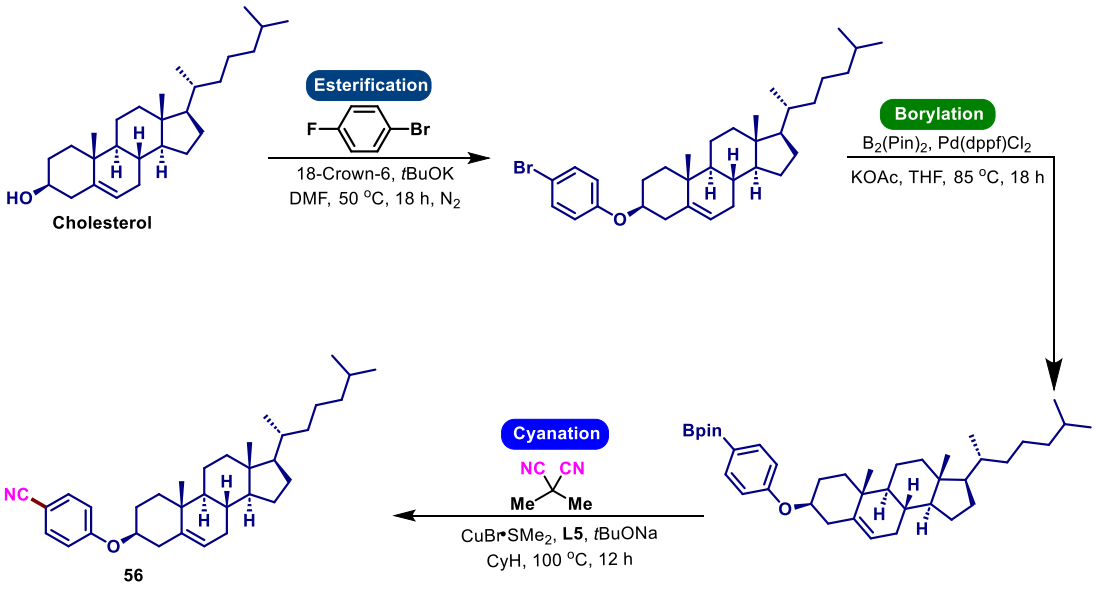
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 2H), 6.75 – 6.70 (m, 2H), 3.99 (t, *J* = 5.4 Hz, 1H), 1.80 (dt, *J* = 5.5, 1.9 Hz, 2H), 1.78 – 1.71 (m, 2H), 1.63 – 1.58 (m, 1H), 1.16 – 1.06 (m, 2H), 1.03 (s, 3H), 0.97 (s, 3H), 0.87 (s, 3H). The spectral data is similar to that previously reported in the literature.[35]

Borylation: To an oven-dried Schlenk flask equipped with a stir bar were added $B_2(pin)_2$ (0.92 g, 3.6 mmol, 1.2 equiv), $Pd(dppf)Cl_2$ (110 mg, 0.15 mmol, 0.05 equiv), KOAc (0.88 g, 9.0 mmol, 3.0 equiv) and the obtained aryl bromide (0.93 g, 3.0 mmol) under a nitrogen atmosphere. Then, anhydrous THF (4.5 mL) was added. The mixture was heated to 85 °C and stirred at this temperature for 18 h. After cooling to room temperature, the mixture was quenched with saturated $NaHCO_3$ and extracted with DCM (3 x 5 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 100:1 to 25:1) to obtain the product as white solid (0.73 g, 68% yield). R_f = 0.25 (petroleum ether/ethyl acetate = 100:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 – 7.70 (m, 2H), 6.86 – 6.82 (m, 2H), 4.08 (dd, *J* = 6.4, 4.5 Hz, 1H), 1.86 – 1.81 (m, 2H), 1.77 – 1.71 (m, 2H), 1.64 – 1.56 (m, 1H), 1.33 (s, 12H), 1.17 – 1.08 (m, 2H), 1.05 (s, 3H), 0.98 (s, 3H), 0.87 (s, 3H).

Cyanation: The reaction was performed under the modified conditions at 100 °C. Column chromatography (petroleum ether/ ethyl acetate = 20:1) afforded product **55** as white solid (90%). R_f =0.29 (petroleum ether/ ethyl acetate = 20:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 4.08 (dd, *J* = 7.2, 3.0 Hz, 1H), 1.93 – 1.73 (m, 2H), 1.68 – 1.60 (m, 2H), 1.17 – 1.11 (m, 3H), 1.02 (s, 3H), 0.98 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.2, 133.9, 119.5, 116.0, 103.1, 85.1, 49.3, 47.1, 45.2, 39.3, 34.1, 27.3, 20.3, 20.0, 11.7. The spectral data is similar to that previously reported in the literature.[35]



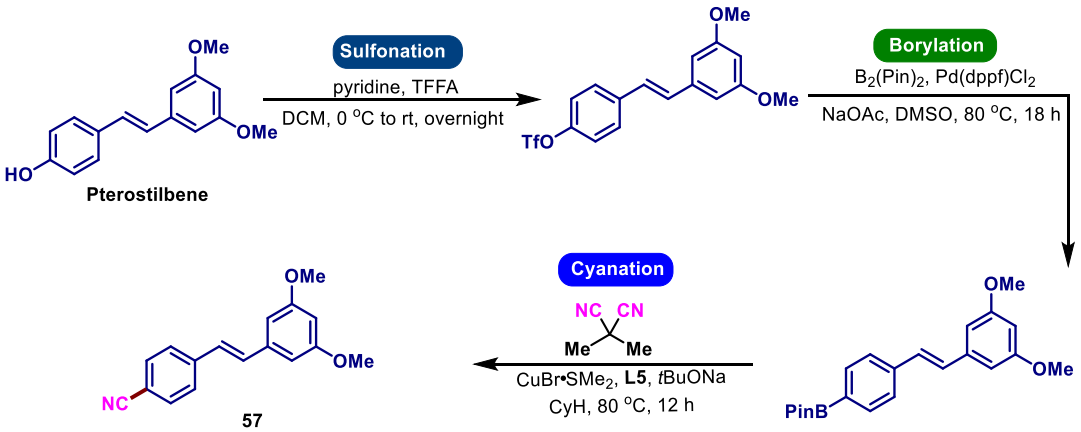
Etherification: Following a literature report,[36] to an oven-dried Schlenk flask equipped with a stir bar were added 1-bromo-4-fluorobenzene (1.75 g, 10 mmol), 18-crown-6 (3.97 g, 15 mmol, 1.5 equiv) and DMF (50 mL) under a nitrogen atmosphere. Cholesterol (5.45 g, 15 mmol, 1.5 equiv, dissolved in 15 mL THF) is then added through a syringe, and the resulting solution is cooled to 0 °C. *t*BuOK (1.68 g, 15 mol, 1.5 equiv, dissolved in 15 mL THF) was then added through a syringe. The mixture was heated to 50 °C and stirred at this temperature for 18 h. The mixture was quenched with saturated NH_4Cl and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 30:1) to obtain the product as white solid (4.1 g, 70%). R_f = 0.27 (petroleum ether/ethyl acetate = 30:1). The product was directly used for the next step.

Borylation: Following a literature report,[3] to an oven-dried sealed tube equipped with a stir bar were added the above cholesterol derivative (1.08 g, 2.0 mmol), $B_2(pin)_2$ (622 mg, 2.4 mmol, 1.2 equiv), $Pd(dppf)Cl_2$ (88 mg, 0.12 mmol, 0.06 equiv) and KOAc (589 mg, 6.0 mmol, 3.0 equiv) under a nitrogen atmosphere. Then, anhydrous THF (4.0 mL) was added to the mixture. The reaction solution was heated to 85 °C, and stirred at this temperature for 18 h. After cooling down to room temperature, saturated $NaHCO_3$ solution was added, and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 20:1 to 15:1) to obtain the product as white solid (942 mg, 80% yield). R_f = 0.22 (petroleum ether/ethyl acetate = 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.39 (d, *J* = 5.4 Hz, 1H), 4.18 (ddd, *J* = 15.6, 11.1, 4.5 Hz, 1H), 2.57 – 2.31 (m, 2H), 2.01 (dt, *J* = 14.7, 6.8 Hz, 3H), 1.92 (dt, *J* = 13.4, 3.5 Hz, 1H), 1.88 – 1.77 (m, 1H), 1.75 – 1.64 (m, 1H), 1.54 (d, *J* = 13.3 Hz, 3H), 1.51 – 1.39 (m, 4H), 1.33 (s, 16H), 1.19 – 1.08 (m, 6H), 1.05 (s, 3H), 1.03 – 0.95 (m, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (dd, *J* = 6.6, 1.8 Hz, 6H), 0.69 (s, 3H).

Cyanation: The reaction was performed at 100 °C as the reaction temperature. Column chromatography (petroleum ether/ ethyl acetate = 10:1 to 8:1) afforded product **56** as white solid (70%). R_f =0.25 (petroleum ether/ ethyl acetate = 8:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 5.41 (dd, *J* = 5.1, 2.6 Hz, 1H), 4.23 – 4.16 (m, 1H), 2.49 – 2.38 (m, 2H), 2.01 (ddt, *J* = 19.2, 9.7, 3.6 Hz, 3H), 1.93 (dt, *J* = 13.5, 3.6 Hz, 1H), 1.87 – 1.79 (m, 1H), 1.75 – 1.65 (m, 1H), 1.64 – 1.55 (m, 3H), 1.52 – 1.43 (m, 4H), 1.41 – 1.31 (m, 4H), 1.22 – 1.09 (m, 6H), 1.06 (s, 3H), 0.99 (ddt, *J* = 24.0, 11.4, 5.9 Hz, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.86 (dd, *J* = 6.6, 2.7 Hz, 6H), 0.69 (s, 3H). The spectral data is similar to that previously reported in the literature.[37] X-Ray crystallographic data are in ***Appendix I***.



Sulfonation: Following a literature report,[38] to an oven-dried Schlenk flask equipped with a stir bar were added pterostilbene (1.28 g, 5.0 mmol) and anhydrous DCM (15 mL) as the solvent under a nitrogen atmosphere. Then, pyridine (0.8 mL, 10 mmol, 2.0 equiv) was slowly added to the mixture at 0 °C. The reaction was stirred at this temperature for 10 minutes, and then trifluoromethanesulfonic anhydride (TFFA, 1.0 mL, 6.0 mmol, 1.2 equiv) was added dropwise. The reaction mixture was warmed up to room temperature and stirred overnight. Saturated $NaHCO_3$ solution was added, and the mixture was extracted with EtOAc (3 x 10 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 5:1) to obtain the product as white solid (1.67 g, 86% yield). R_f = 0.32 (petroleum ether/ethyl acetate = 5:1). The product was directly used for the next step.

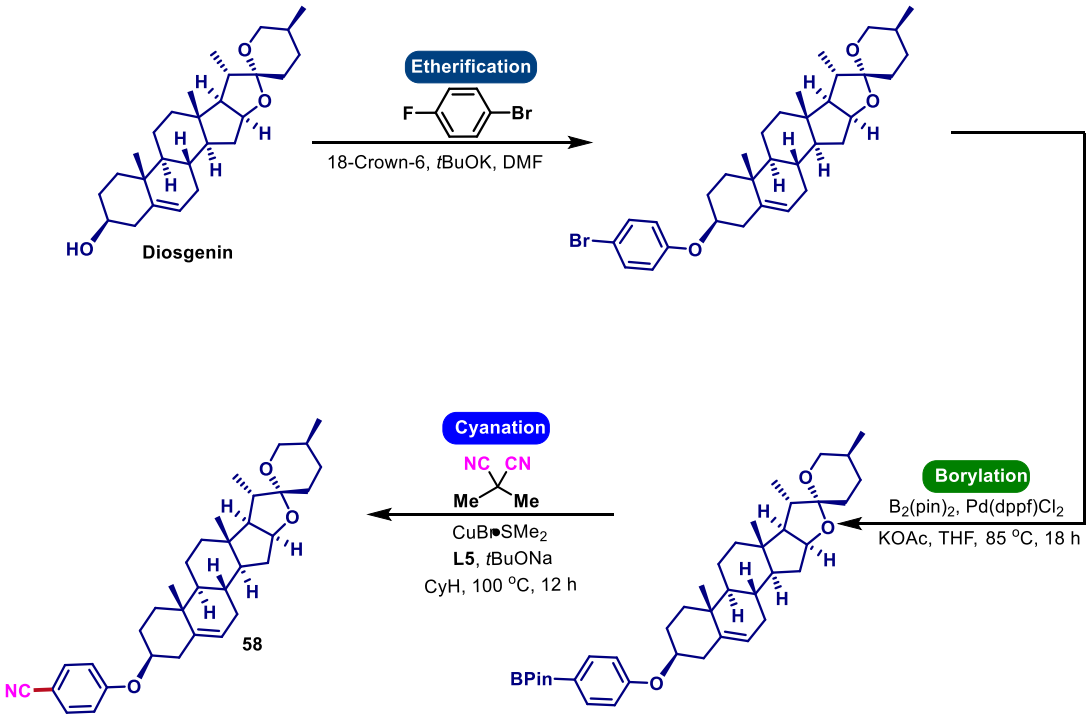
Borylation: Following a literature report,[3] to an oven-dried heavy-walled pressure vessel equipped with a stir bar were added the above pterostilbene derivative (776 mg, 2.0 mmol), $B_2(pin)_2$ (632 mg, 2.44 mmol, 1.22 equiv), $Pd(dppf)Cl_2$ (73 mg, 0.10 mmol, 0.05 equiv), NaOAc (493 mg, 6.0 mmol, 3.0 equiv) in anhydrous DMSO (6.0 mL) under nitrogen. The mixture was heated to 80 °C, and stirred at this

temperature for 18 h. After cooling down to room temperature, saturated $NaHCO_3$ solution was added to the mixture, and followed by the extraction with DCM (3 x 10 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 10:1) to obtain the product as white solid (549 mg, 75% yield). R_f = 0.26 (petroleum ether/ethyl acetate = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.9 Hz, 2H), 7.52 (d, *J* = 7.9 Hz, 2H), 7.11 (s, 2H), 6.69 (d, *J* = 2.3 Hz, 2H), 6.41 (s, 1H), 3.83 (s, 6H), 1.36 (s, 12H).

Cyanation: The reaction was performed under the standard conditions. Column chromatography (petroleum ether/ ethyl acetate = 10:1 to 8:1) afforded the product **57** as white solid (63%). R_f =0.25 (petroleum ether/ ethyl acetate = 8:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 16.2 Hz, 1H), 7.06 (d, *J* = 16.3 Hz, 1H), 6.68 (d, *J* = 2.2 Hz, 2H), 6.44 (s, 1H), 3.84 (s, 6H). The spectral data is similar to that previously reported in the literature.[39]



Etherification: Following a literature report,[36] to an oven-dried Schlenk flask equipped with a stir bar were added 1-bromo-4-fluorobenzene (875 mg, 5.0 mmol), 18-crown-6 (1.99 g, 7.5 mmol, 1.5 equiv) and DMF (25 mL) under nitrogen. Diosgenin (3.17 g, 7.5 mmol, 1.5 equiv, dissolved in 7.5 mL THF) is then added through a syringe, and the resulting solution is cooled to 0 °C, followed by the addition of *t*BuOK (840 mg, 7.5 mol, 1.5 equiv, dissolved in 7.5 mL THF) through a syringe. The reaction mixture was heated to 50 °C, and stirred at this temperature for 5 h. The mixture was quenched with saturated NH_4Cl and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 20:1) to obtain the product as white solid

(852 mg, 30%). R_f = 0.25 (petroleum ether/ethyl acetate = 20:1). The product was directly used for the next step.

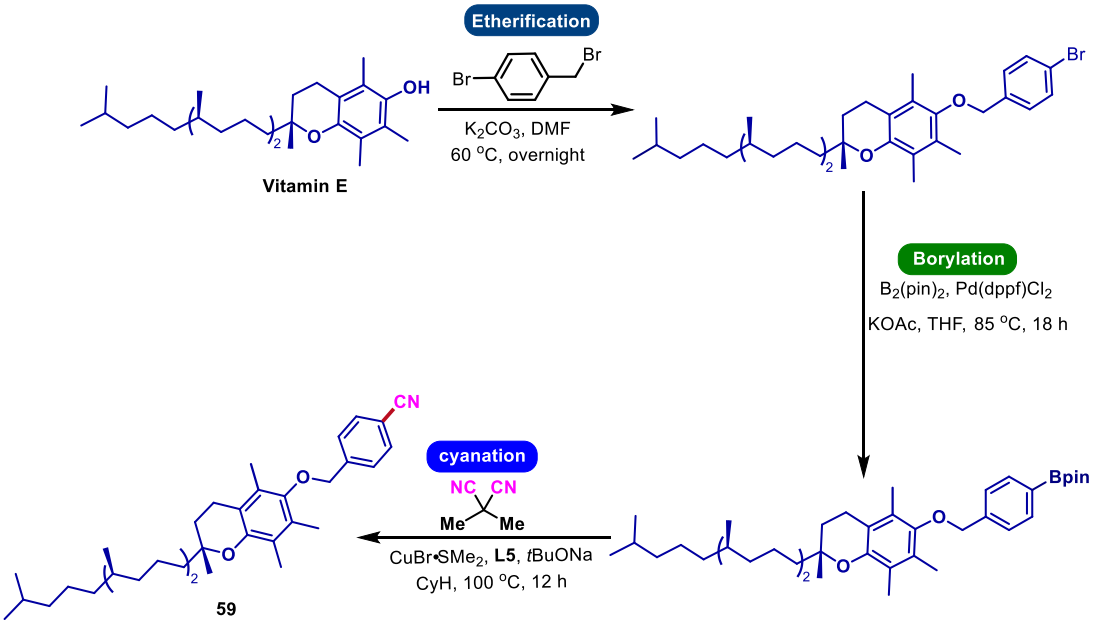
Borylation: Following a literature report,[3] to an oven-dried heavy-walled pressure vessel equipped with a stir bar were added the above diosgenin derivative (852 mg, 1.5 mmol), $B_2(pin)_2$ (467 mg, 1.8 mmol, 1.2 equiv), $Pd(dppf)Cl_2$ (67 mg, 0.09 mmol, 0.06 equiv) and KOAc (442 mg, 4.5 mmol, 3.0 equiv) under a nitrogen atmosphere. Then, anhydrous THF was added. The mixture was heated to 85 °C and stirred at this temperature for 18 h. After cooling down to room temperature, saturated $NaHCO_3$ solution was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 15:1) to obtain the product as white solid (462 mg, 50 % yield). R_f = 0.24 (petroleum ether/ethyl acetate = 15:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 5.39 (s, 1H), 4.42 (q, *J* = 7.4 Hz, 1H), 4.18 (td, *J* = 11.0, 5.5 Hz, 1H), 3.47 (d, *J* = 9.0 Hz, 1H), 3.38 (t, *J* = 10.9 Hz, 1H), 2.49 (d, *J* = 13.3 Hz, 1H), 2.38 (t, *J* = 12.4 Hz, 1H), 2.05 – 1.98 (m, 3H), 1.93 – 1.86 (m, 2H), 1.81 – 1.73 (m, 2H), 1.69 – 1.53 (m, 8H), 1.51 – 1.42 (m, 3H), 1.32 (s, 12H), 1.28 – 1.24 (m, 1H), 1.22 – 1.13 (m, 3H), 1.07 (s, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 6H).

Cyanation: The reaction was performed at 100 °C as the reaction conditions. Column chromatography (petroleum ether/ ethyl acetate = 15:1 to 10:1) afforded the product **58** as white solid (45%). R_f =0.28 (petroleum ether/ ethyl acetate = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 5.41 (dd, *J* = 4.9, 2.4 Hz, 1H), 4.42 (td, *J* = 7.7, 6.3 Hz, 1H), 4.17 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.48 (ddd, *J* = 10.9, 4.5, 1.9 Hz, 1H), 3.38 (t, *J* = 10.9 Hz, 1H), 2.52 – 2.35 (m, 2H), 2.09 – 1.84 (m, 6H), 1.81 – 1.58 (m, 8H), 1.53 (t, *J* = 2.5 Hz, 3H), 1.28 (s, 1H), 1.16 (ddd, *J* = 14.1, 10.7, 3.9 Hz, 3H), 1.08 (s, 3H), 0.98 (d, *J* = 6.9 Hz, 4H), 0.79 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 161.2, 139.7, 134.1, 122.7, 119.4, 116.1, 109.3, 103.5, 80.8, 77.0, 66.9, 62.1, 56.5, 50.1, 41.6, 40.3, 39.7, 38.3, 37.0, 36.9, 32.1, 31.9, 31.41, 31.39, 30.3, 28.8, 27.9, 20.9, 19.4, 17.2, 16.3, 14.6. HRMS (ESI) calcd. for $C_{34}H_{46}NO_3[M+H]^+$: 516.3473, found: 516.3472.



Etherification: Following a literature report,[40] to an oven-dried Schlenk flask equipped with a stir bar were added 1-bromo-4-(bromomethyl)benzene (1.28 g, 5.0 mmol), vitamin E (2.56 g, 6.0 mmol, 1.2 equiv), K_2CO_3 (2.1 g, 15 mmol, 3.0 equiv) and DMF (10 mL) under nitrogen at room temperature overnight. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 x 10 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 30:1) to obtain the product as clear oil (2.1 g, 70%). R_f = 0.27 (petroleum ether/ethyl acetate = 30:1). The product was directly used for the next step.

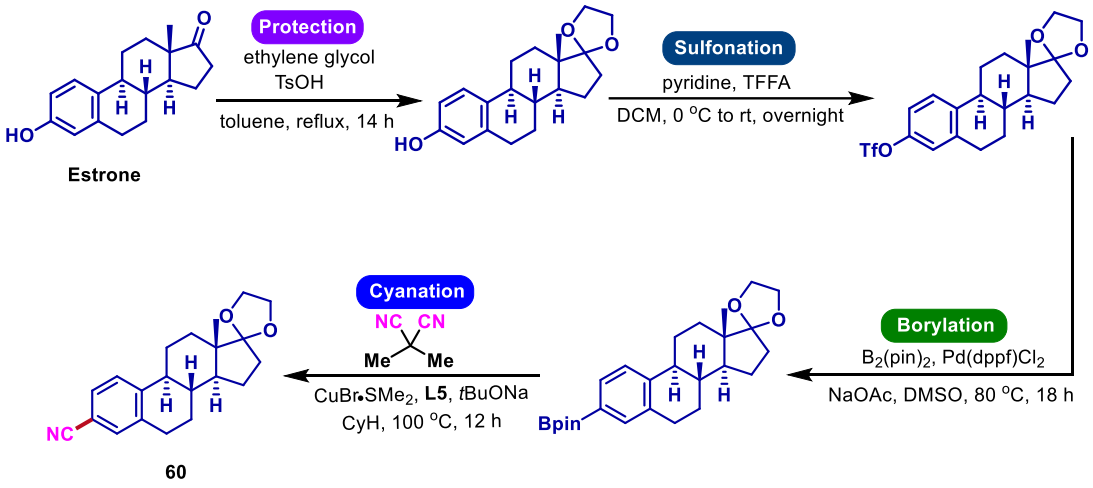
Borylation: Following a literature report,[3] to an oven-dried heavy-walled pressure vessel equipped with a stir bar were added the above vitamin E derivative (1.2 g, 2.0 mmol), $B_2(pin)_2$ (622 mg, 2.4 mmol, 1.2 equiv), $Pd(dppf)Cl_2$ (88 mg, 0.12 mmol, 0.06 equiv) and KOAc (589 mg, 6.0 mmol, 3.0 equiv) under nitrogen atmosphere. Then, anhydrous THF (4.0 mL) was added. The mixture was heated to 85 °C, and stirred at this temperature for 18 h. After cooling down to room temperature, saturated aqueous $NaHCO_3$ solution was added, followed by the extraction with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 20:1 to 15:1) to obtain the product as clear oil (776 mg, 60% yield). R_f = 0.26 (petroleum ether/ethyl acetate = 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 4.72 (s, 2H), 2.59 (t, *J* = 6.8 Hz, 2H), 2.25 – 2.02 (m, 6H), 1.80 (ddq, *J* = 20.0, 13.3, 6.8 Hz, 2H), 1.57 – 1.49 (m, 3H), 1.45 – 1.37 (m, 3H), 1.36 (s, 12H), 1.27 (m, 10H), 1.21 – 0.99 (m, 8H), 0.89 – 0.83 (m, 12H).

Cyanation: The reaction was performed at 100 °C as the reaction temperature. Column chromatography (petroleum ether/ ethyl acetate = 20:1 to 10:1) afforded the product **59** as yellow liquid (56%). R_f = 0.29 (petroleum ether/ ethyl acetate = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 4.76 (s, 2H), 2.59 (t, *J* = 6.8 Hz, 2H), 2.18 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H), δ 1.85 – 1.74 (m, 2H), 1.53 (ddt, *J* = 19.6, 13.2, 5.8 Hz, 3H), 1.45 (d, *J* = 8.9 Hz, 3H), 1.28 (m, 10H), 1.09 (m, 8H), 0.85 (m, 12H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 148.2, 147.7, 143.5, 132.3, 127.7, 127.6, 125.8, 123.2, 118.9, 117.8, 111.4, 75.0, 73.4, 40.0, 39.4, 37.5, 37.3, 32.9, 32.7, 31.5, 31.3, 30.2, 29.8, 28.0, 24.8, 24.5, 23.90, 22.8, 22.7, 21.0, 20.7, 19.8, 12.8, 12.0, 11.8. HRMS (ESI) calcd. for $C_{37}H_{56}NO_2[M+H]^+$: 546.4306, found: 546.4312.



Protection: To an oven-dried sealed tube equipped with a stir bar were added estrone (2.7 g, 10 mmol), *p*-toluenesulfonic acid monohydrate ($TsOH•H_2O$, 170 mg, 3 mol%), ethylene glycol (2.83 mL, 50 mmol), and toluene (60 mL). The mixture was heated to 135 °C and stirred at this temperature for 14 h. After cooling the reaction mixture to room temperature, the reaction solution was extracted with DCM (3 x 10 mL) and concentrated under reduced pressure. The resulting product was directly used for the next step without further purification.

Sulfonation: Following a literature report,[41] to an oven-dried Schlenk flask equipped with a stir bar were added the above estrone derivative (1.60 g, 5.0 mmol) and anhydrous DCM (15 mL) under nitrogen atmosphere. Then, pyridine (0.8 mL, 10 mmol, 2.0 equiv) was slowly added to the mixture at 0 °C. The reaction mixture was stirred at this temperature for 10 minutes, and trifluoromethanesulfonic anhydride (TFFA, 1.0 mL, 6 mmol, 1.2 equiv) was subsequently added dropwisely to the solution. The reaction mixture was warmed up to room temperature and stirred overnight. Saturated aqueous $NaHCO_3$ solution was added, and the mixture was extracted with EtOAc (3 x 10 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 5:1) to obtain the product as white solid (1.9 g, 85% yield). R_f = 0.30 (petroleum ether/ethyl acetate = 5:1). The product was directly used for the next step.

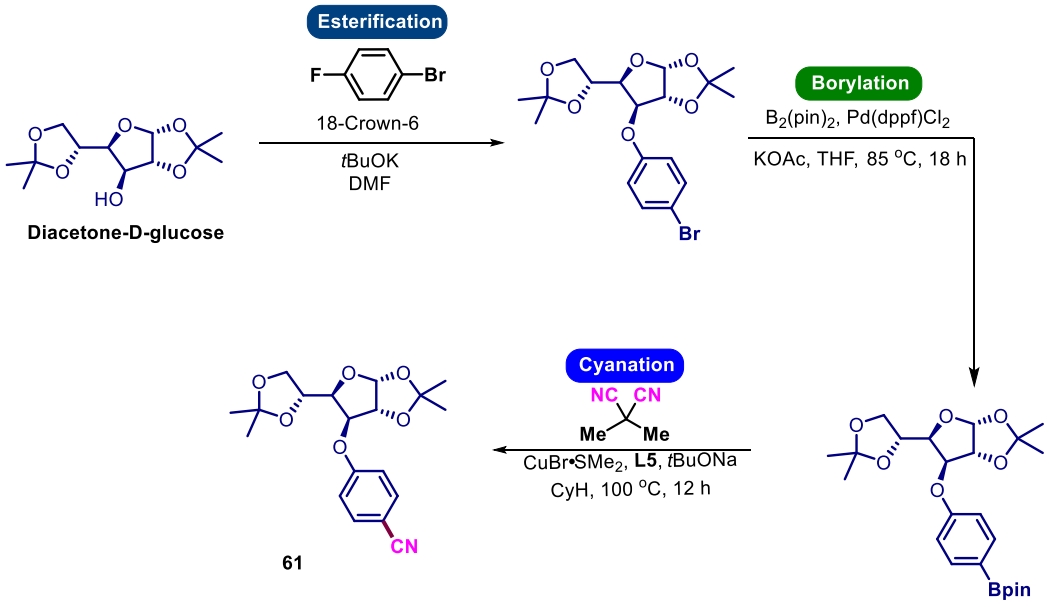
Borylation: Following a literature report,[3] to an oven-dried Sealed tube equipped with a stir bar were added the above obtained estrone derivative (893 mg, 2.0 mmol), $B_2(pin)_2$ (632 mg, 2.44 mmol, 1.22 equiv), $Pd(dppf)Cl_2$ (73 mg, 0.1 mmol, 0.05 equiv), NaOAc (493 mg, 6.0 mmol, 3.0 equiv) and

anhydrous DMSO (6.0 mL) under an nitrogen atmosphere. The mixture was heated to 80 °C and stirred at this temperature for 18 h. After cooling down to room temperature, a saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with DCM (3 x 10 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 10:1 to 8:1) to obtain the product as white solid (661 mg, 78% yield). R_f = 0.26 (petroleum ether/ethyl acetate = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.51 (m, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 4.01 – 3.84 (m, 4H), 2.96 – 2.83 (m, 2H), 2.42 – 2.26 (m, 2H), 2.05 – 1.72 (m, 5H), 1.69 – 1.59 (m, 2H), 1.56 – 1.42 (m, 4H), 1.33 (s, 12H), 0.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 136.2, 135.7, 132.1, 124.9, 119.5, 83.7, 65.4, 64.7, 49.6, 46.2, 44.5, 38.8, 34.3, 30.9, 29.4, 27.0, 25.9, 25.0, 24.9, 22.5, 14.4.

Cyanation: The reaction was performed at 100 °C as the reaction temperature. Column chromatography (petroleum ether/ ethyl acetate = 20:1 to 10:1) afforded product **60** as white solid (71%). R_f = 0.29 (petroleum ether/ ethyl acetate = 10:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 3H), 3.99 – 3.87 (m, 4H), 2.87 (t, *J* = 5.1 Hz, 2H), 2.36 – 2.24 (m, 2H), 2.03 (ddd, *J* = 14.3, 11.8, 3.0 Hz, 1H), 1.96 – 1.91 (m, 1H), 1.88 – 1.74 (m, 3H), 1.70 – 1.61 (m, 2H), 1.59 – 1.38 (m, 4H), 0.88 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.1, 138.2, 132.5, 129.1, 126.2, 119.2, 109.2, 65.3, 64.6, 49.4, 46.0, 44.3, 38.2, 34.2, 30.5, 29.1, 26.4, 25.7, 22.3, 14.3. The spectral data is similar to that previously reported in the literature.[42]



Etherification: To an oven-dried Schlenk flask equipped with a stir bar were added 1-bromo-4-fluorobenzene (875 mg, 5.0 mmol), 18-crown-6 (1.99 g, 7.5 mmol, 1.5 equiv) and DMF (25 mL) under a nitrogen atmosphere. diacetone-D-glucose (1.99 g, 7.5 mol, 1.5 equiv, dissolved in 7.5 mL THF) is then added through a syringe, and the resulting solution was cooled to 0 °C. *t*BuOK (840 mg, 7.5 mmol, 1.5 equiv, dissolved in 7.5 mL THF) was added through a syringe, and stirred at this temperature for 4 h. The mixture was quenched with saturated NH_4Cl solution and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum

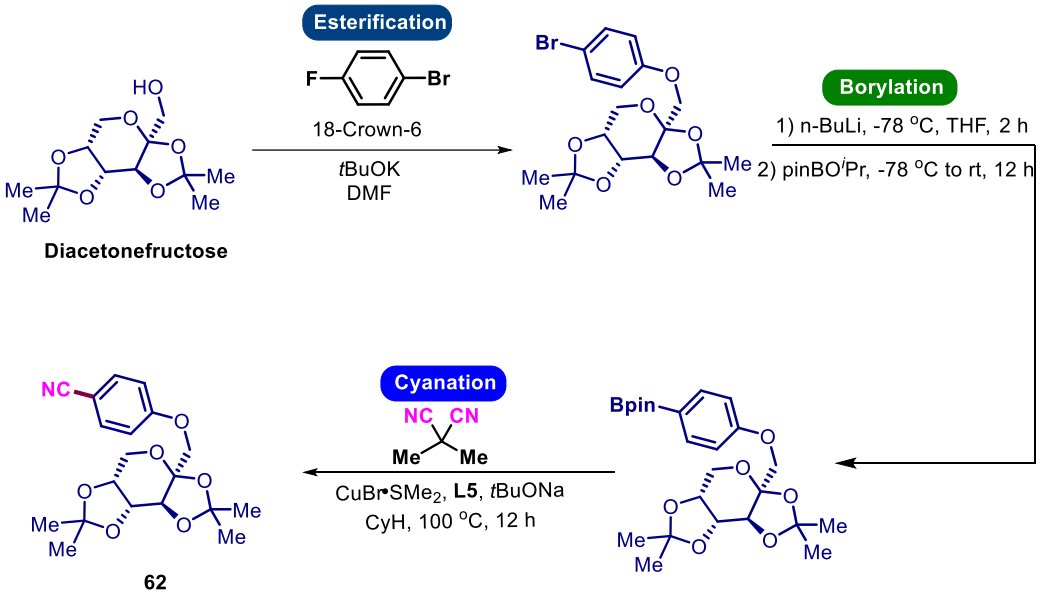
ether/ethyl acetate = 20:1) to obtain the product as clear oil (1.46 g, 70%). R_f = 0.27 (petroleum ether/ethyl acetate = 20:1). The product was directly used for the next step.

Borylation: To an oven-dried Sealed tube equipped with a stir bar were added the above diacetone-D-glucose derivative (832 mg, 2.0 mmol), $B_2(pin)_2$ (622 mg, 2.4 mmol, 1.2 equiv), $Pd(dppf)Cl_2$ (88 mg, 0.12 mmol, 0.06 equiv) and KOAc (589 mg, 6.0 mmol, 3.0 equiv) under a nitrogen atmosphere. Then, anhydrous THF (4 mL) was added, and the mixture was heated to 85 °C and stirred at this temperature for 18 h. After cooling down to room temperature, saturated $NaHCO_3$ solution was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 15:1) to obtain the product as clear oil (629 mg, 68 % yield). R_f = 0.24 (petroleum ether/ethyl acetate = 15:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 5.92 (d, *J* = 3.8 Hz, 1H), 4.77 (d, *J* = 3.1 Hz, 1H), 4.58 (d, *J* = 3.8 Hz, 1H), 4.50 – 4.42 (m, 1H), 4.33 (dd, *J* = 7.4, 3.1 Hz, 1H), 4.13 (qd, *J* = 8.6, 5.8 Hz, 2H), 1.56 (d, *J* = 9.7 Hz, 6H), 1.43 (s, 3H), 1.33 (s, 12H), 1.31 (s, 3H).

Cyanation: The reaction was performed at 100 °C as the reaction temperature. Column chromatography (petroleum ether/ ethyl acetate = 20:1 to 10:1) afforded product **61** as white solid (80%). R_f = 0.30 (petroleum ether/ ethyl acetate = 10:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 5.93 (d, *J* = 3.2 Hz, 1H), 4.77 (d, *J* = 3.0 Hz, 1H), 4.55 (d, *J* = 3.3 Hz, 1H), 4.44 – 4.37 (m, 1H), 4.28 (dd, *J* = 8.1, 2.9 Hz, 1H), 4.17 – 4.04 (m, 2H), 1.55 (s, 3H), 1.43 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H). The spectral data is similar to that previously reported in the literature.[43]

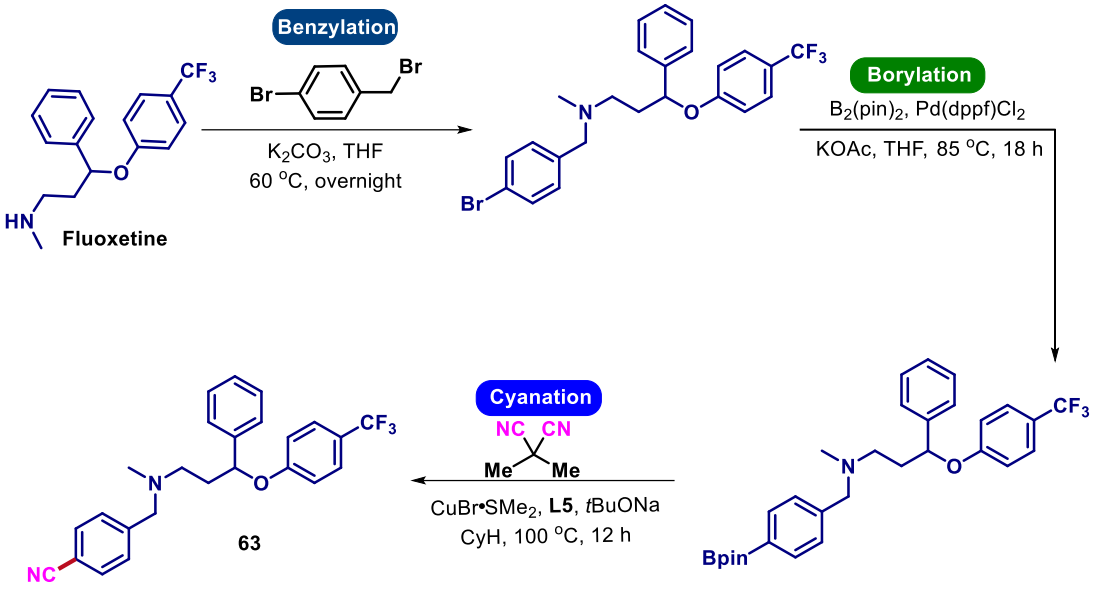


Etherification: To an oven-dried Schlenk flask equipped with a stir bar were added 1-bromo-4-fluorobenzene (875 mg, 5.0 mmol), 18-crown-6 (1.99 g, 7.5 mmol, 1.5 equiv) and DMF (25 mL) under nitrogen atmosphere. Diacetonefructose (1.99 g, 7.5 mmol, 1.5 equiv, dissolved in 7.5 mL THF) is then

added through a syringe, and the resulting solution was cooled to 0 °C, *t*BuOK (840 mg, 7.5 mmol, 1.5 equiv, dissolved in 7.5 mL THF) was added to the above solution through the syringe. The reaction mixture was heated to 50 °C and stirred at this temperature for 5 h. The mixture was quenched with saturated NH_4Cl solution and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 15:1) to obtain the product as white solid (1.62 g, 75%). R_f = 0.25 (petroleum ether/ethyl acetate = 15:1). The product was directly used for the next step.

Borylation: To an oven-dried Schlenk flask equipped with a stir bar were added the above diacetonefructose derivative (832 mg, 2.0 mmol) and anhydrous THF (8.0 mL). The resulting solution was cooled to -78 °C. Then, *n*-BuLi (0.93 mL, 2.5 M in *n*-hexane, 2.3 mmol) was added dropwise, and the solution was stirred for 2 h at -78 °C. Isopropoxyboronic acid pinacol ester (0.43 g, 2.3 mmol, 1.15 equiv) was added to the above solution. The reaction mixture suspension was allowed to warm to room temperature and stirred for 12 h. After cooling down to room temperature, saturated $NaHCO_3$ solution was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ ethyl acetate = 10:1) to obtain the product as white solid (833 mg, 90%). R_f = 0.26 (petroleum ether/ethyl acetate = 10:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 4.63 (dd, *J* = 7.9, 2.6 Hz, 1H), 4.54 (d, *J* = 2.6 Hz, 1H), 4.26 (dd, *J* = 8.0, 1.7 Hz, 1H), 4.19 (d, *J* = 10.3 Hz, 1H), 4.06 (d, *J* = 10.3 Hz, 1H), 3.96 (dd, *J* = 12.9, 1.9 Hz, 1H), 3.78 (d, *J* = 13.0 Hz, 1H), 1.55 (s, 3H), 1.47 (s, 6H), 1.33 (s, 3H), 1.32 (s, 12H).

Cyanation: The reaction was performed at 100 °C as the reaction temperature. The reaction was performed under the standard conditions. Column chromatography (petroleum ether/ ethyl acetate = 15:1 to 5:1) afforded product **62** as white solid (65%). R_f = 0.24 (petroleum ether/ ethyl acetate = 5:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 4.64 (dd, *J* = 7.9, 2.7 Hz, 1H), 4.49 (d, *J* = 2.6 Hz, 1H), 4.27 (d, *J* = 7.9 Hz, 1H), 4.20 (d, *J* = 10.3 Hz, 1H), 4.08 (d, *J* = 10.3 Hz, 1H), 3.96 (d, *J* = 14.8 Hz, 1H), 3.79 (d, *J* = 13.0 Hz, 1H), 1.55 (s, 3H), 1.48 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.7, 134.0, 119.1, 115.5, 109.2, 109.1, 104.6, 101.8, 70.9, 70.07, 70.05, 69.0, 61.3, 26.6, 26.0, 25.3, 24.0. HRMS (ESI) calcd. for $C_{19}H_{24}NO_6$ $[M+H]^+$: 362.1599, found: 362.1600.



Benzylation: To an oven-dried sealed tube equipped with a stir bar were added 1-bromo-4-(bromomethyl)benzene (1.28 g, 5.0 mmol), fluoxetine (1.91 g, 6.0 mmol, 1.2 equiv), K_2CO_3 (2.1 g, 15 mmol, 3.0 equiv) and THF (10 mL) under a nitrogen atmosphere. The reaction mixture was heated to 60 °C and stirred at this temperature overnight. The mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3 x 10 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 20:1) to obtain the product as yellow oil (1.36 g, 57%). R_f = 0.28 (petroleum ether/ethyl acetate = 20:1). The product was directly used for the next step.

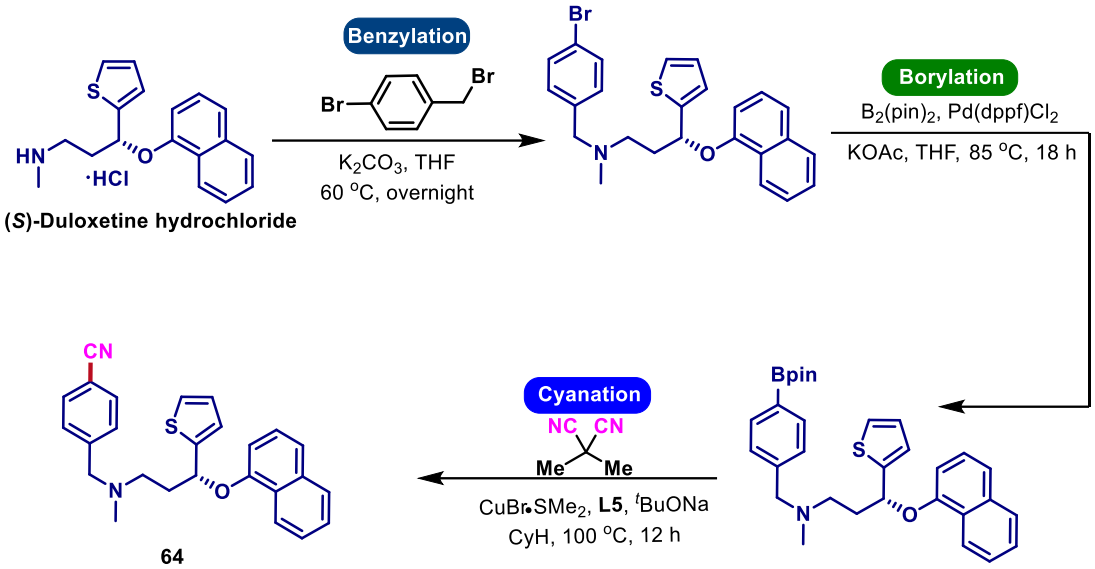
Borylation: To an oven-dried sealed tube equipped with a stir bar were added the above fluoxetine derivative (0.94 g, 2.0 mmol), $B_2(pin)_2$ (622 mg, 2.4 mmol, 1.2 equiv), $Pd(dppf)Cl_2$ (88 mg, 0.12 mmol, 0.06 equiv) and KOAc (589 mg, 6.0 mmol, 3.0 equiv) under a nitrogen atmosphere. Then, anhydrous THF (4.0 mL) was added. The mixture was heated to 85 °C and stirred at this temperature for 18 h. After cooling down to room temperature, saturated $NaHCO_3$ solution was added to the above mixture and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 10:1) to obtain the product as clear oil (567 mg, 54% yield). R_f = 0.26 (petroleum ether/ethyl acetate = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.9 Hz, 2H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.32 – 7.23 (m, 7H), 6.86 (d, *J* = 8.9 Hz, 2H), 5.32 (dd, *J* = 8.3, 4.8 Hz, 1H), 3.50 (q, *J* = 13.3 Hz, 2H), 2.65 – 2.54 (m, 1H), 2.46 (ddd, *J* = 12.6, 7.4, 5.5 Hz, 1H), 2.21 (s, 3H), 2.19 – 2.11 (m, 1H), 2.04 – 1.98 (m, 1H), 1.34 (s, 12H).

Cyanation: The reaction was performed at 100 °C as the reaction conditions. The reaction was performed under the standard conditions. Column chromatography (petroleum ether/ ethyl acetate = 15:1 to 5:1) afforded the product **63** as white solid (49%). R_f = 0.24 (petroleum ether/ ethyl acetate = 5:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.32 (dd, *J* = 13.8, 6.6 Hz, 7H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.31 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.57 (d, *J* = 13.8 Hz, 1H), 3.48 (d, *J* =

16.4 Hz, 1H)., 2.63 (s, 1H), 2.44 (s, 1H), 2.23 (s, 3H), 2.17 (d, *J* = 7.3 Hz, 1H), 2.02 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.5, 145.3, 134.6, 129.2, 128.3, 127.5, 126.6, 126.3, 125.8, 125.2, 124.7, 122.2, 120.6, 106.9, 74.4, 62.3, 53.2, 42.1, 36.6. ^{19}F NMR (565 MHz, $CDCl_3$) δ -61.51.
HRMS (ESI) calcd. for $C_{25}H_{24}F_3N_2O$ $[M+H]^+$: 425.1835, found: 425.1828.



Benzylation: Following a literature report,[31] to an oven-dried Schlenk flask equipped with a stir bar were added 1-bromo-4-(bromomethyl)benzene (3.13 g, 12.5 mmol), (*S*)-duloxetine hydrochloride (4.46 g, 15 mmol, 1.2 equiv), K_2CO_3 (4.15 g, 30 mmol, 2.4 equiv) and THF (25 mL) under a nitrogen atmosphere. The reaction mixture was heated to 60 °C and stirred at this temperature overnight. Then, the mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3 x 15 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 3:1) to obtain the product as colorless liquid (3.50 g, 60%). R_f = 0.30 (petroleum ether/ethyl acetate = 3:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.78 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.47 (dddd, *J* = 16.8, 8.2, 6.8, 1.4 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.30 – 7.24 (m, 3H), 7.21 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.11 – 7.07 (m, 2H), 7.02 – 6.99 (m, 1H), 6.93 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 5.79 (dd, *J* = 7.9, 5.1 Hz, 1H), 3.42 (q, *J* = 13.3 Hz, 2H), 2.67 (dt, *J* = 12.3, 7.1 Hz, 1H), 2.55 (ddd, *J* = 12.6, 7.4, 5.6 Hz, 1H), 2.45 (dtd, *J* = 13.4, 7.5, 5.6 Hz, 1H), 2.25 – 2.20 (m, 4H). The spectral data is similar to that previously reported in the literature.[31]

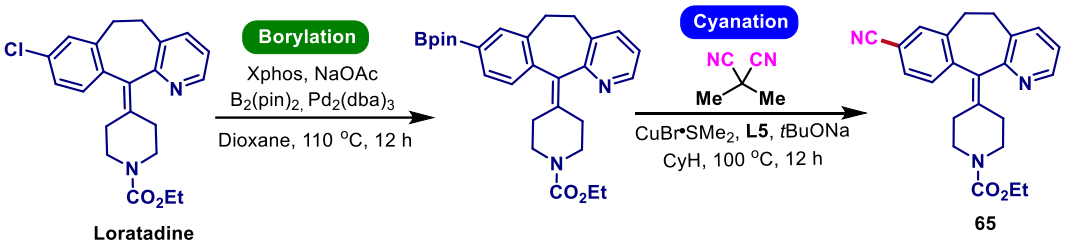
Borylation: To an oven-dried Schlenk flask equipped with a stir bar were added $B_2(pin)_2$ (2.14 g, 8.4 mmol, 1.2 equiv), $Pd(dppf)Cl_2$ (256 mg, 0.25 mmol, 0.05 equiv), KOAc (825 mg, 8.4 mmol, 1.2 equiv) and the obtained aryl bromide (3.27 g, 7.0 mmol) under nitrogen atmosphere. Then, anhydrous THF (10 mL) was added. The mixture was heated to 85 °C and stirred at this temperature for 18 h. After cooling down to room temperature, the mixture was quenched with saturated $NaHCO_3$ solution and extracted with DCM (3 x 20 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl

acetate = 3:1) to obtain the product as viscous liquid (1.87 g, 52% yield). R_f = 0.27 (petroleum ether/ethyl acetate = 3:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 – 8.26 (m, 1H), 7.78 – 7.75 (m, 1H), 7.71 (d, *J* = 7.6 Hz, 2H), 7.48 – 7.44 (m, 2H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.28 (dd, *J* = 7.8, 4.2 Hz, 3H), 7.19 (dd, *J* = 4.9, 1.2 Hz, 1H), 6.98 (d, *J* = 3.5 Hz, 1H), 6.91 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 5.80 (dd, *J* = 7.6, 5.4 Hz, 1H), 3.51 (s, 2H), 2.64 (qt, *J* = 12.8, 7.0 Hz, 2H), 2.48 (dq, *J* = 13.9, 7.2 Hz, 1H), 2.25 – 2.18 (m, 4H), 1.35 (s, 12H).

Cyanation: The reaction was performed at 100 °C. The reaction was performed under the standard conditions. Column chromatography (petroleum ether/ ethyl acetate = 10:1 to 3:1) afforded product **64** as yellow liquid (35%). R_f = 0.29 (petroleum ether/ ethyl acetate = 3:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.0 Hz, 1H), 7.79 – 7.76 (m, 1H), 7.49 – 7.42 (m, 2H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.23 – 7.15 (m, 4H), 6.99 (d, *J* = 3.5 Hz, 1H), 6.92 – 6.90 (m, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 5.81 (dd, *J* = 7.7, 5.3 Hz, 1H), 3.51 (s, 2H), 2.66 (d, *J* = 43.8 Hz, 2H), 2.49 (dq, *J* = 14.0, 7.1 Hz, 1H), 2.25 (s, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.5, 145.4, 138.3, 134.6, 129.2, 128.3, 127.5, 127.1, 126.6, 126.3, 126.2, 125.8, 125.2, 124.7, 124.6, 122.2, 120.5, 106.9, 74.4, 62.4, 53.3, 42.1, 36.6. HRMS (ESI) calcd. for $C_{26}H_{25}NO_2S$ $[M+H]^+$: 413.1683, found: 413.1672.



Borylation: Following a literature report,[3] to an oven-dried sealed tube equipped with a stir bar were added loratadine (766 mg, 2.0 mmol), $B_2(pin)_2$ (622 mg, 2.4 mmol, 1.2 equiv), $Pd_2(dpa)_3$ (38 mg, 0.04 mmol, 2.0 mol%), Xphos (2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 39 mg, 0.08 mmol, 4.0 mol%) and NaOAc (492 mg, 6.0 mmol, 3.0 equiv) under a nitrogen atmosphere. Then, anhydrous 1,4-dioxane (4.0 mL) was added. The mixture was heated to 110 °C and stirred at this temperature for 12 h. After cooling down to room temperature, saturated $NaHCO_3$ solution was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to 2:1) to obtain the product as white solid (854 mg, 90%). R_f = 0.21 (petroleum ether/ethyl acetate = 5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 6.5 Hz, 1H), 7.61 (d, *J* = 9.2 Hz, 2H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.04 (dd, *J* = 7.7, 4.7 Hz, 1H), 4.10 (t, *J* = 7.0 Hz, 2H), 3.78 (s, 2H), 3.47 – 3.23 (m, 2H), 3.12 (ddd, *J* = 13.0, 9.2, 5.6 Hz, 2H), 2.89 – 2.76 (m, 2H), 2.47 (ddd, *J* = 14.0, 9.4, 4.6 Hz, 1H), 2.37 – 2.26 (m, 3H), 1.30 (s, 12H), 1.23 (d, *J* = 7.1 Hz, 3H).

Cyanation: The reaction was performed at 100 °C as the reaction temperature. The reaction was performed under the standard conditions. Column chromatography (petroleum ether/ ethyl acetate = 10:1 to 2:1) afforded colorless liquid (37%). R_f = 0.22 (petroleum ether/ ethyl acetate = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 6.0 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.22 – 7.16 (m, 3H), 7.08 (d, *J* = 2.9 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.89 – 3.76 (m, 2H), 3.47 – 3.26 (m, 2H), 3.19 – 3.06 (m, 2H), 2.89 – 2.75 (m, 2H), 2.56 – 2.44 (m, 1H), 2.41 – 2.27 (m, 3H), 1.24 (t, *J* = 3.6 Hz, 3H). The spectral data is similar to that previously reported in the literature.[44]

VI. Mechanistic Investigations

a) Influence of the Radical Scavenger and EPR experiments

i) Reaction in the presence of 1,1-diphenylethene

In a glovebox, to an oven-dried screw capped vial equipped with a Teflon stir bar were added **DMMN** (**2a**, 57 mg, 0.6 mmol), CuBr•SMe_2 (17 mg, 0.08 mmol), the ligand **L5** (19 mg, 0.08 mmol), *t*BuONa (58 mg, 0.6 mmol), 4-*tert*-butylphenylboronic acid pinacol ester (**1a**, 0.40 mmol) and **1,1-diphenylethene** (216 mg, 1.2 mmol) in anhydrous cyclohexane (0.50 mL). The reaction vial was capped, removed from the glovebox and stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature and diluted with EtOAc. The crude yield of **3** was measured to be 51% by using GC spectroscopy with *n*-hexadecane as an internal standard, and the scavenger was observed to couple with β-cyano-β-propanyl radical, forming the adduct of 2,2-dimethyl-4,4-diphenylbutanenitrile (**66**), albeit in a low yield.

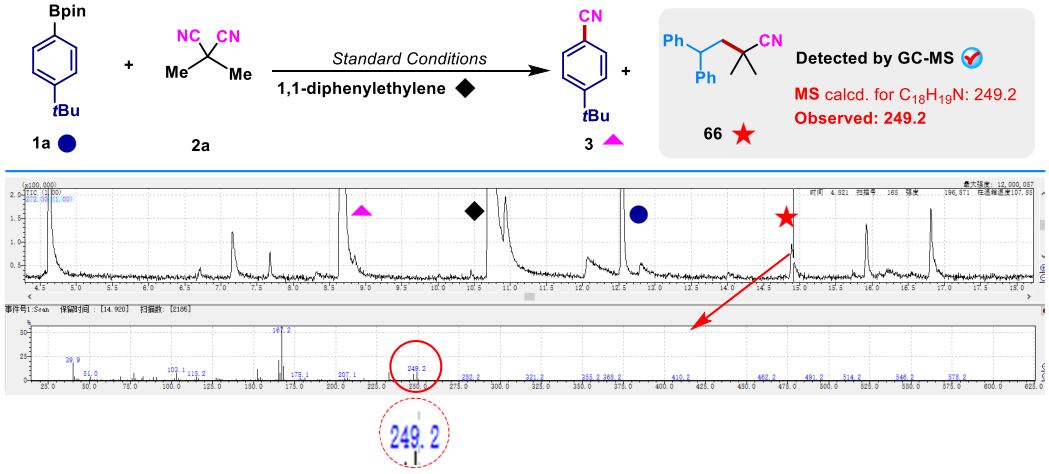


Fig. S1. GC-MS Spectrum of detection of **66** in the radical scavenger experiment.

ii) Reaction in the presence of PBN

In a glovebox, to an oven-dried screw capped vial equipped with a Teflon stir bar were added **DMMN** (**2a**, 57 mg, 0.6 mmol), CuBr•SMe_2 (17 mg, 0.08 mmol), the ligand **L5** (19 mg, 0.08 mmol), *t*BuONa (58 mg, 0.6 mmol), 4-*tert*-butylphenylboronic acid pinacol ester (**1a**, 0.40 mmol) and **PBN** (214 mg, 1.2 mmol) in anhydrous cyclohexane (0.50 mL). The reaction vial was capped, removed from the glovebox and stirred at 80 ºC for 12 h. The reaction mixture was cooled to room temperature and diluted with EtOAc. The crude yield of **3** was measured to be 32% by using GC spectroscopy with *n*-hexadecane as an internal standard. In addition, GC-MS analyses disclosed that the scavenger was observed to couple with carbon centered radical and nitrogen centered radical, forming the adducts **67** and **68**, albeit the adduct **68** was only detected in a trace quantality, which might due to its instability.

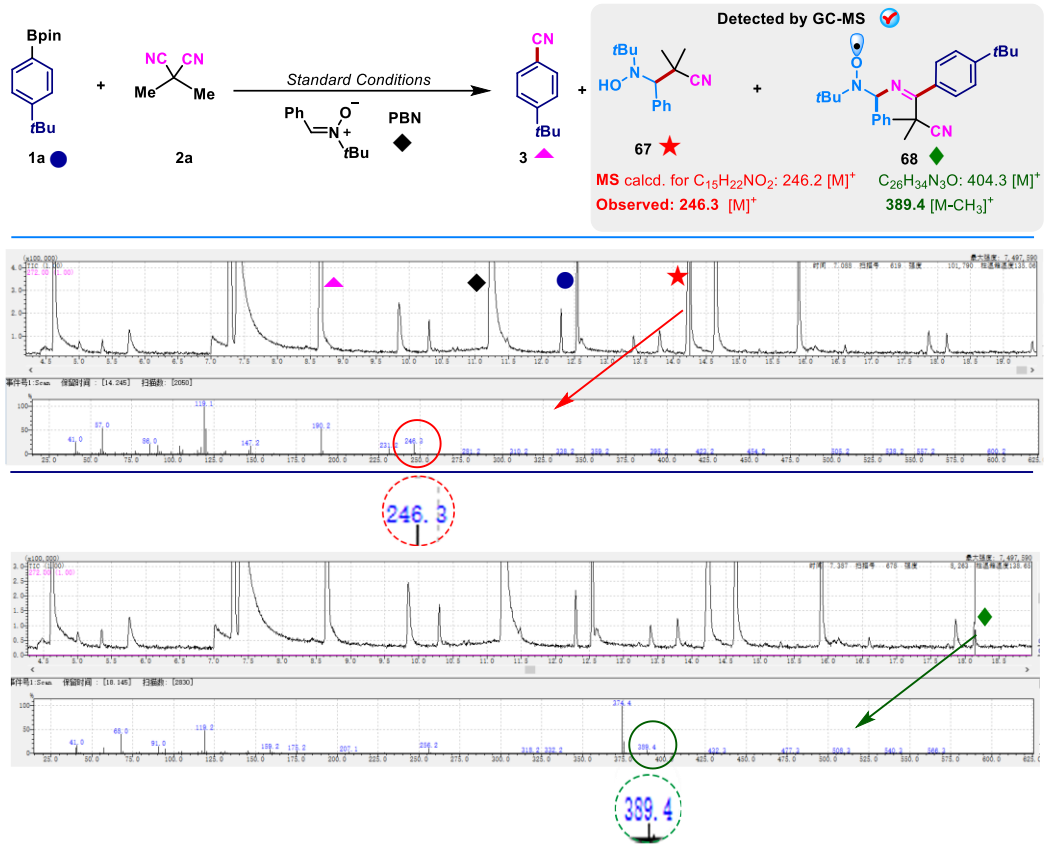
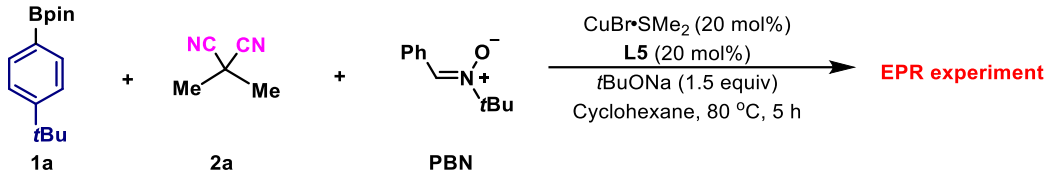


Fig. S2. GC-MS Spectra of detection of **67** and **68** in the radical scavenger experiment.

iii) EPR Experiments of the standard reaction in the presence of PBN



In a glovebox, to an oven-dried screw capped vial equipped with a Teflon stir bar were added dimethylmalononitrile (**DMMN**, 57 mg, 0.60 mmol), CuBr•SMe_2 (17 mg, 0.08 mmol), the ligand **L5** (19 mg, 0.08 mmol), *t*BuONa (58 mg, 0.60 mmol), arylboron **1a** (104 mg, 0.40 mmol) and **PBN** (214 mg, 1.2 mmol) in anhydrous cyclohexane (0.50 mL). The reaction vial was capped, removed from the glovebox and stirred at 80 °C for 5 h. The reaction vial was again taken into the glovebox, and a portion of the reaction mixture was transferred into an EPR cell. X-Band (9.37 GHz) EPR spectroscopy was performed at 298 K with the following experimental parameters: power attenuation = 20.0 dB, power = 2.000 mW, modulation amplitude = 1.000 G, and modulation frequency = 100.0 kHz. The EPR spectrum simulation was done by easyspin software imported in MATLAB. The strong organic radical signal (g_{iso} = 2.00612) with significant hyperfine interactions (A_N = 40.29 MHz, A_H = 9.43 MHz) being assignable to the captured radical **68**.

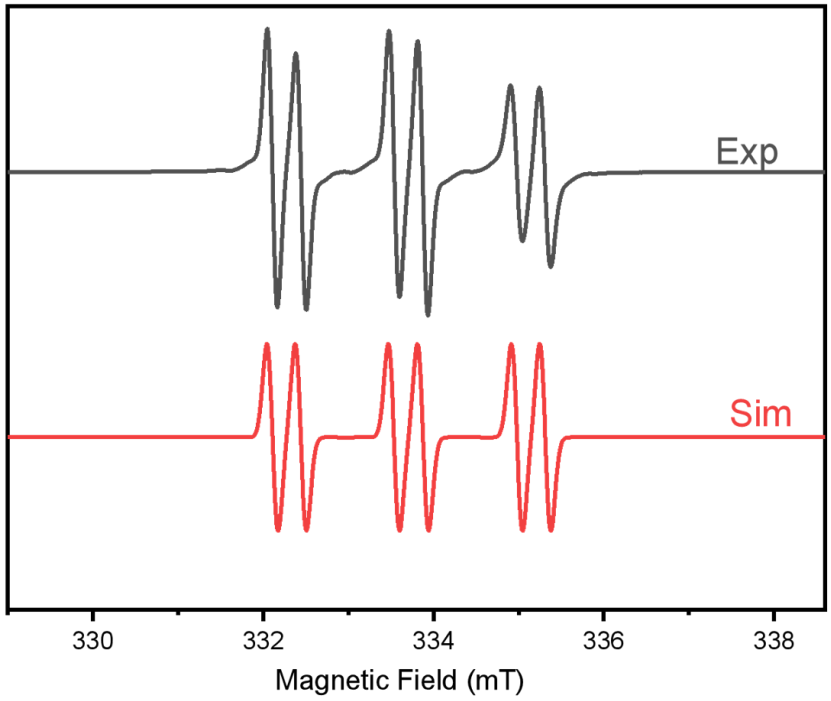
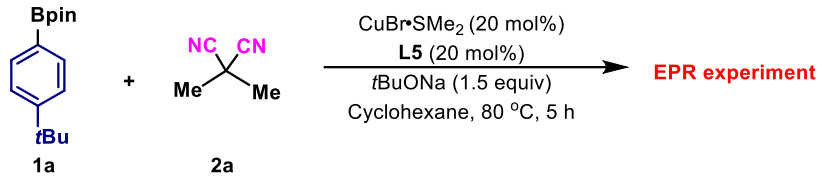


Fig. S3. EPR spectrum simulation using easyspin software. (red) Experimental EPR spectrum of the reaction mixture as described above (black).

iv) EPR Experiments of the standard reaction



In a glovebox, to an oven-dried screw capped vial equipped with a Teflon stir bar were added dimethylmalononitrile (**DMMN**, 57 mg, 0.60 mmol), CuBr•SMe_2 (17 mg, 0.08 mmol), the ligand **L5** (19 mg, 0.08 mmol), *t*BuONa (58 mg, 0.60 mmol) and arylboron **1a** (104 mg, 0.40 mmol) in anhydrous cyclohexane (0.50 mL). The reaction vial was capped, removed from the glovebox and stirred at 80 °C for 5 h. The reaction vial was again taken into the glovebox, and a portion of the reaction mixture was transferred into an EPR cell. The EPR spectroscopy was performed under otherwise identical conditions. However, no signal was observed during the process, suggesting that Cu^{II} species was not likely to be involved in the reaction system.

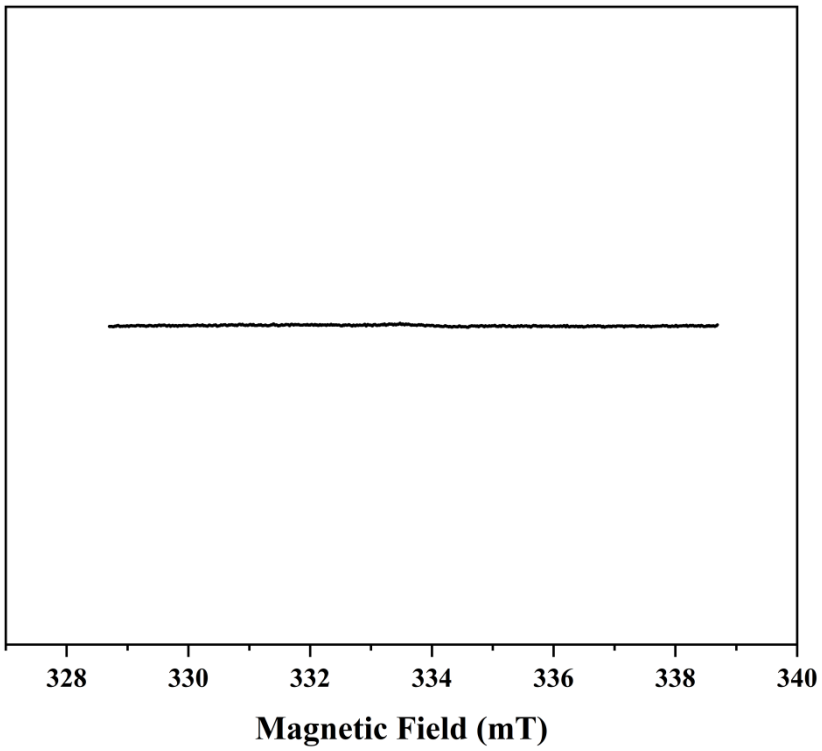


Fig. S4. Experimental EPR spectrum of the standard reaction mixture.

v) Reaction of other arylboron in the presence of PBN

In a glovebox, to an oven-dried screw capped vial equipped with a Teflon stir bar were added **DMMN** (**2a**, 57 mg, 0.6 mmol), CuBr•SMe_2 (17 mg, 0.08 mmol), the ligand **L5** (19 mg, 0.08 mmol), *t*BuONa (58 mg, 0.6 mmol), 4-dimethylaminophenylboronic acid pinacol ester (99 mg, 0.40 mmol) and **PBN** (214 mg, 1.2 mmol) in anhydrous cyclohexane (0.50 mL). The reaction vial was capped, removed from the glovebox and stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature and diluted with EtOAc. The crude yield of **3** was measured to be 24% by using GC spectroscopy with *n*-hexadecane as an internal standard. In addition, GC-MS analyses disclosed that the scavenger was observed to couple with carbon centered radical and nitrogen centered radical, forming the adducts **67** and **69**, albeit the adduct **69** was only detected in a trace quantality, which might due to its instability.

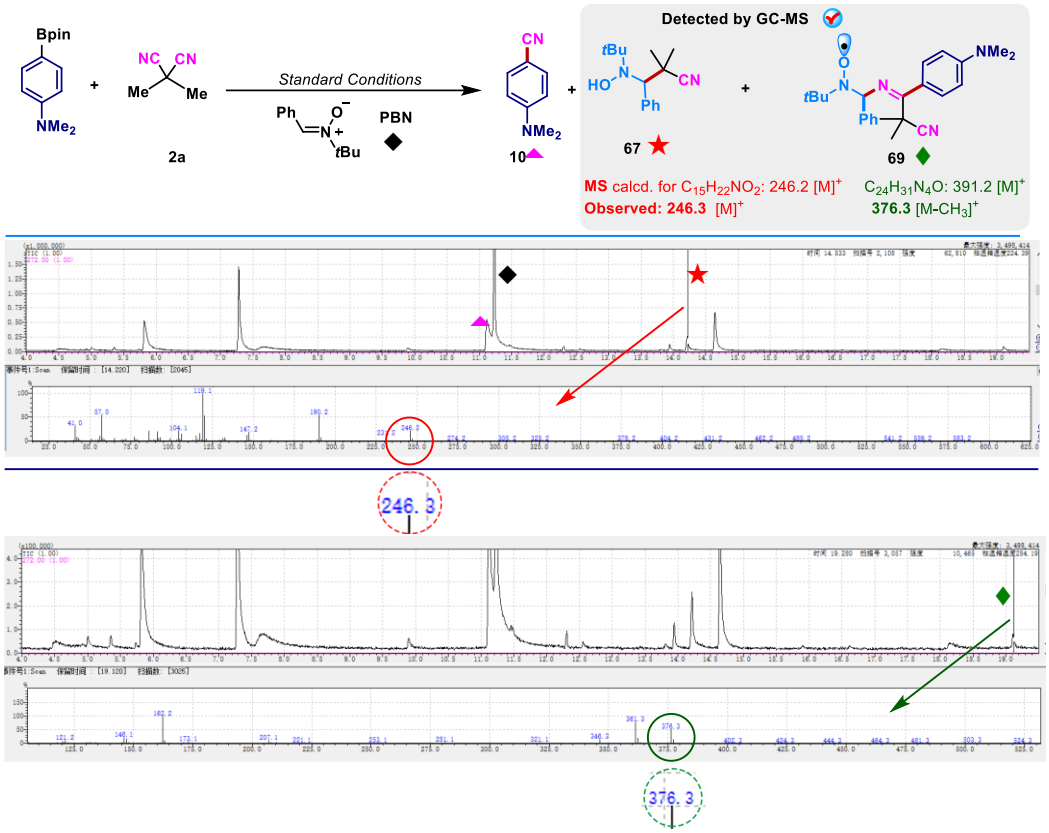


Fig. S5.GC-MS Spectra of detection of **67** and **69** in the radical scavenger experiment.

vi) Detection other fragment of the cynation agent after reation course

In a glovebox, to an oven-dried screw capped vial equipped with a Teflon stir bar were added Cyclohexanedicarbonitrile (82 mg, 0.6 mmol), CuBr•SMe_2 (17 mg, 0.08 mmol), the ligand **L5** (19 mg, 0.08 mmol), *t*BuONa (58 mg, 0.6 mmol), 4-*tert*-butylphenylboronic acid pinacol ester (104 mg, 0.4 mmol) and in anhydrous cyclohexane (0.50 mL). The reaction vial was capped, removed from the glovebox and stirred at 80 ºC for 12 h. The reaction mixture was cooled to room temperature, worked-up with water, diluted with EtOAc, filtered through silica gel with EtOAc, and the solvent was removed under the reduced pressure. The crude yield of **3** was measured to be 67% by using GC spectroscopy with *n*-hexadecane as an internal standard, and cyclohexanecarbonitrile (**70**) was also detected by GC-MS analyses.

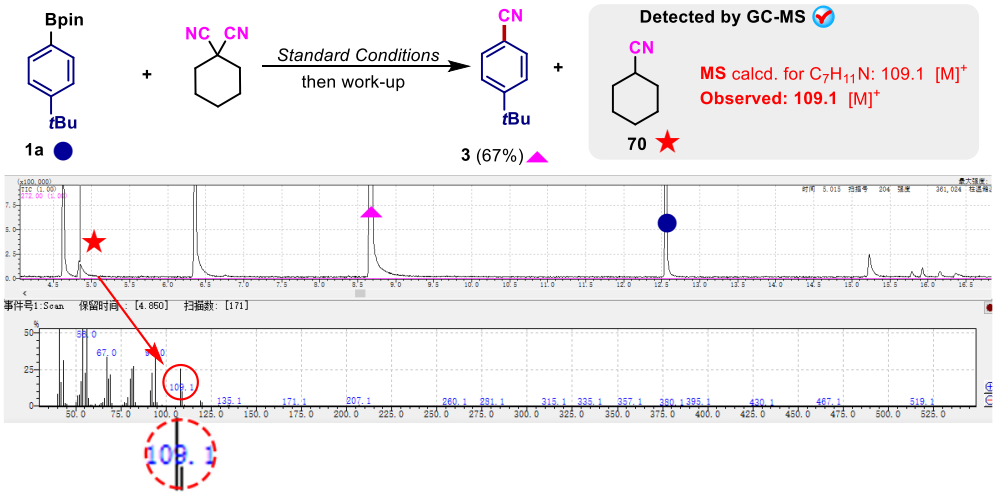
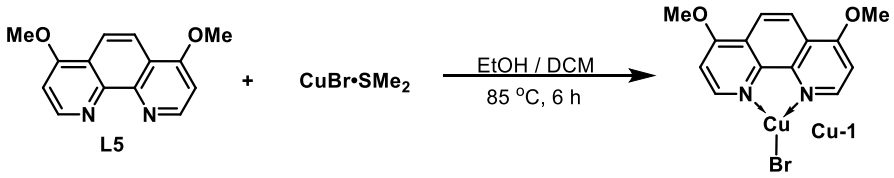


Fig. S6.GC-MS Spectra detection for the other fragment of the cyanation source.

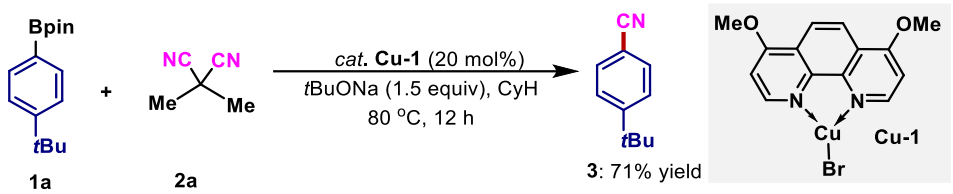
b) Catalytic Reaction with Copper Complexe

1) Preparation of Copper Complexes Cu-1



Following a similar procedure,[35] to an oven-dried flask equipped with a stir bar were added CuBr•SMe_2 (824 mg, 4.0 mmol) and ethanol (20 mL) under nitrogen. Next, ligand **L5** (960 mg, 4.0 mmol) in DCM (20 mL) was added to the above solution. The mixture was at 85 °C for 6 h and then cooled to room temperature. The solution was concentrated under reduced pressure, and then washed with a mixed solvent of DCM and diethyl ether (v/v = 2:1) to afford red brown solid (1.22 g, 80%).

2) Procedure of the catalytic Reaction with Copper Complexes Cu-1



In a glovebox, to an oven-dried screw capped vial equipped with a Teflon stir bar were added **DMMN** (**2a**, 57 mg, 0.6 mmol), copper complex **Cu-1** (31 mg, 0.08 mmol), *t*BuONa (58 mg, 0.6 mmol), 4-*tert*-butylphenylboronic acid pinacol ester (**1a**, 104 mg, 0.4 mmol) in anhydrous cyclohexane (0.50 mL). The reaction vial was capped, removed from the glovebox and stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature and diluted with EtOAc, filtered through silica gel with EtOAc, and the solvent was removed under the reduced pressure. The crude yield of **3** was measured to be 71% by GC analyses with *n*-hexadecane as an internal standard.

c) XPS analysis

In a glovebox, to an oven-dried screw capped vial equipped with a Teflon stir bar were added **DMMN** (**2a**, 57 mg, 0.6 mmol), CuBr•SMe_2 (16.5 mg, 0.08 mmol), the ligand **L5** (20 mg, 0.08 mmol), *t*BuONa (58 mg, 0.6 mmol), 4-*tert*-butylphenylboronic acid pinacol ester (**1a**, 104 mg, 0.4 mmol) in anhydrous cyclohexane (0.50 mL). The reaction vial was capped, removed from the glovebox and stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature, and the volatiles were removed in vacuum oven at 100 °C, and then the sample was analyzed by XPS spectra.

The main peak of Cu $2p_{3/2}$ indicates the presence of at least two phases that are correlated with double peaks in Auger line. The Cu LMM Auger line position at a kinetic energy of 918.60 eV and obtained Auger parameter ~ 1851.1 eV corroborated the presence of Cu(0). The Cu LMM Auger line position at a kinetic energy of 916.90 eV and obtained Auger parameter ~ 1848.4 eV corroborated the presence of Cu(I).

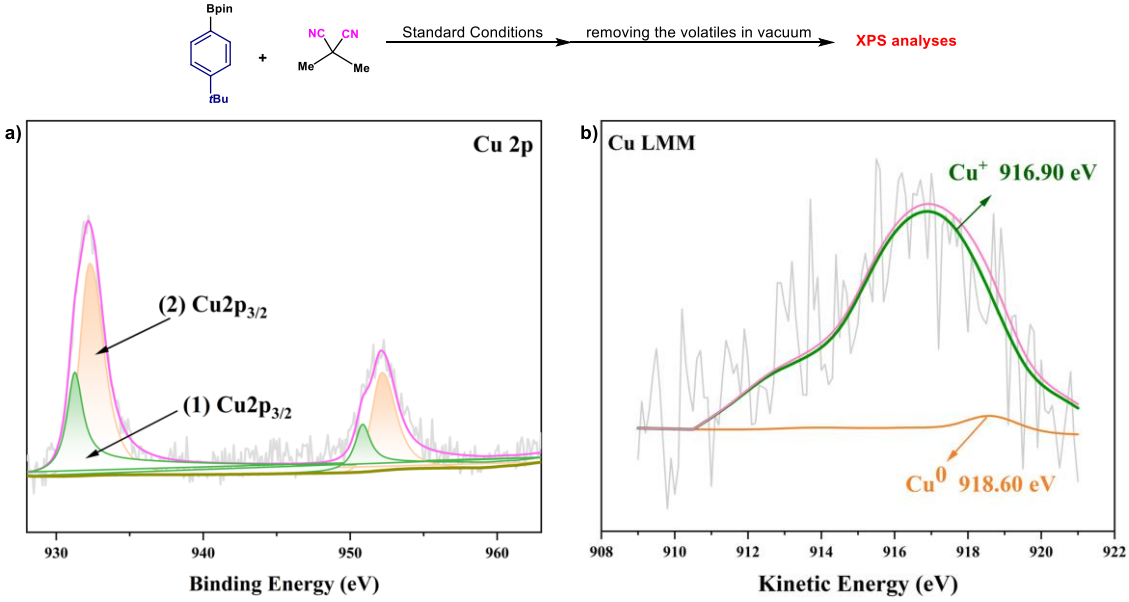


Fig. S7. XPS Spectrum analyses for the copper species for the cyanation system.

VII. Reference

[1] Takashi, S.; Masahisa, N. Preparation of New Chiral Bisoxazoline Ligands for the Catalytic Asymmetric Intramolecular Cyclopropanation of *α*-diazo-*β*-keto Phenyl Sulfone to Afford a Useful Bicyclo[3.1.0]hexane derivative. *Tetrahedron: Asymmetry.* **2012**, *23*, 350–356.

[2] Mills, L.R., Rousseaux, S. A. L. A. One-pot Electrophilic Cyanation-functionalization Strategy for the Synthesis of Disubstituted malononitriles. *Tetrahedron*. **2019**, *75*, 4298-4306.

[3] Kusukawa, T.; Kojima, Y.; Kannen, F. Mechanofluorochromic Properties of 1,8-Diphenylanthracene Derivatives. *Chem. Lett*. **2019**, *48*, 1213-1216.

[4] Shaykhutdinova, P.; Oestreich, M. Achieving Enantioselectivity in Difficult Cyclohexa-1,3-diene Diels−Alder Reactions with Sulfur-Stabilized Silicon Cations as Lewis Acid Catalysts. Org. Lett. 2018, 20, 7029−7033.

[5] Ma, X.; Xu, C.; Wang, J.; Tian, H. Amorphous Pure Organic Polymers for Heavy-Atom-Free Efficient Room-Temperature Phosphorescence Emission. *Angew. Chem. Int. Ed.* **2018,** *57*, 10854-10858.

[6] Kelly, C. B.; Lambert, K. M.; Mercadante, M. A.; Ovian, J. M.; Bailey, W. F.; Leadbeater, N. E. Access to Nitriles from Aldehydes Mediated by an Oxoammonium Salt. *Angew. Chem. Int. Ed.* **2015**, *54*, 4241 –4245.

[7] Keaveney, S. T.; Kundu, G.; Schoenebeck, F. Modular Functionalization of Arenes in a Triply Selective Sequence:Rapid C(sp^2) and C(sp^3) Coupling of C-Br, C-OTf, and C-Cl BondsEnabled by a Single Palladium(I) Dimer. *Angew. Chem. Int. Ed.* **2018**, *57*, 12573 –12577.

[8] Ahmad, M. S.; Zeng, B.; Qsaim, R.; Zheng, D.; Zhang, Q.; Jin, Y.; Wang, Q.; Meguellati, K. Ni-Catalyzed Cyanation of (Hetero)aryl Halides with Acetonitrile as Cyano Source. *ACS Catal.* **2024**, *14*, 2350−2357.

[9] Verheyde, B.; Dehaen, W. Synthesis of Dendrimers Containing 1,3,4-Oxadiazoles. *J. Org. Chem*. **2001**, *66*, 4062-4064.

[10] Dorval, C.; Tricoire, M.; Begouin, J.; Gandon, V.; Gosmini, C. Cobalt-Catalyzed C(sp^2)–CN Bond Activation: Cross-Electrophile Coupling for Biaryl Formation and Mechanistic Insight. *ACS Catal.* **2020**, *10*, 12819−12827.

[11] Zhang, Y.; Zhang, H.; Gao, K. Borane–Trimethylamine Complex as a Reducing Agent for Selective Methylation and Formylation of Amines with CO_2. *Org. Lett.* **2021**, *23*, 8282−8286.

[12] Yan, M. –Q.; Yuan, J.; Pi, Y. –X.; Liang, J. –H.; Liu, Y.; Luo, X.; Liu, S. –H.; Chen, J.; Zhu, X. –L.; Yu, G. –A. Pd-indenyl-diphosphine: An Effective Catalyst for the Preparation of Triarylamines. *Org. Biomol. Chem.*, **2016**, *14*, 451–454.

[13] Hu, S.; Radosevich, A. T. Electrophilic C(sp^2)−H Cyanation with Inorganic Cyanate (OCN^-) by P^{III}/PV=O-Catalyzed Phase Transfer Activation. *Angew. Chem. Int. Ed.* **2024**, *63*, e202409854.

[14] Nanni, A.; Kong, D.; Zhu, C.; Rueping, M. Nickel-catalyzed Cross-Coupling Aminations via High-throughput Mechanochemistry Enabled byResonant Acoustic Mixing. *Green Chem*., **2024**, *26*, 8341–8347.

[15] Maiti, Debarata.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. Palladium-catalyzed Coupling of Functionalized Primary and Secondary Amines with Aryl and Heteroaryl Halides: Two Ligands Suffice in Most Cases. *Chem. Sci.*, **2011**, *2*, 57–68.

[16] Wang, G.; Zhang, H.; Zhao, J.; Li, W.; Cao, J.; Zhu, C.; Li, S. Homolytic Cleavage of a B−B Bond by the Cooperative Catalysis of Two Lewis Bases: Computational Design and Experimental Verification. *Angew. Chem. Int. Ed.* **2016**, *55*, 5985 –5989.

[17] Zhang, X., Xia, A., Chen, H., Liu, Y. General and Mild Nickel-Catalyzed Cyanation of Aryl/HeteroarylChlorides with $Zn(CN)_2$: Key Roles of DMAP. *Org. Lett.* **2017**, *19*, 2118−2121.

[18] Zhao, C.; Fang, W. –Y.; Pakesh, K. P.; Qin, H. –L. Pd-Catalyzed One-pot Dehydroxylative Coupling of Phenols with $K_4[Fe(CN)_6]$ Mediated by SO_2F_2: A Practical Method for the Direct Conversion of Phenols to Aryl nitriles. *Org. Chem. Front*.,**2018**, *5*, 1835–1839.

[19]Torigoe, T.; Ohmura, T.; Suginome, M. Asymmetric Cycloisomerization of *o*-Alkenyl-N-Methylanilines to Indolines by Iridium-Catalyzed C(sp3)−H Addition to Carbon–Carbon Double Bonds. *Angew. Chem. Int. Ed*. **2017**, *56*, 14272 –14276.

[20] Wang, H.; Xu, D.; Guan, E.; Wang, L.; Zhang, J.; Wang, C.; Wang, S.; Xu, H.; Meng, X.; Yang, B.; Gates, B. C.; Xiao, F. –S. Atomically Dispersed Ru on Manganese Oxide Catalyst Boosts Oxidative Cyanation. *ACS Catal*. **2020**, *10*, 6299−6308.

[21] Lizumi, K.; Tanaka, H.; Muto, K.; Yamaguchi, J. Palladium-Catalyzed Denitrative Synthesis of Aryl Nitriles from Nitroarenes and Organocyanides. *Org. Lett*. **2024**, *26*, 3977−3981.

[22] Pal, D.; Sarmah, R.; Srimani, D. Designing Cobalt(II) Complexes for Tandem Dehydrogenative Synthesis of Quinoline and Quinazoline Derivatives. *Org. Lett.* **2024**, *26*, 514−518.

[23] Tang, J.; Zhao, X.; Ni, J.; Huo, Y.; Cao, Y.; Li, X.; Liu, Y.; Maruoka, K.; Chen, Q. Visible Light-induced Aerobic Photooxidative Cleavage of C(sp^3)–C(sp^2) σ-bonds of Allylarenes. *Org. Chem. Front*., **2024**, *11*, 6385–6392.

[24] Zhao, Y.; Snieckus, V. A Practical in situ Generation of the Schwartz Reagent. Reduction of Tertiary Amides to Aldehydes and Hydrozirconation. *Org. Lett*. **2014**, *16*, 390−393.

[25] Delcaillau, T.; Woenckhaus-Alvarez, A.; Morandi, B. Nickel-Catalyzed Cyanation of Aryl Thioethers. *Org. Lett.* **2021**, *23*, 7018−7022.

[26] Yang, H. S.; Macha, L.; Ha, H. –J.; Yang, J. W. Functionalisation of Esters via 1,3-Chelation Using NaO*t*Bu: Mechanistic Investigations and Synthetic Applications. *Org. Chem. Front.*, **2021**, *8,* 53–60.

[27] Radomkit, S; White, J. A. H.; Chong, E.; Zhng, Y. MSTFA as an Effective TMS Source for the TMSOTf-Catalzyed Synthesis of Cyclic Acetals. *J. Org. Chem*. **2024**, 89, 5555−5559.

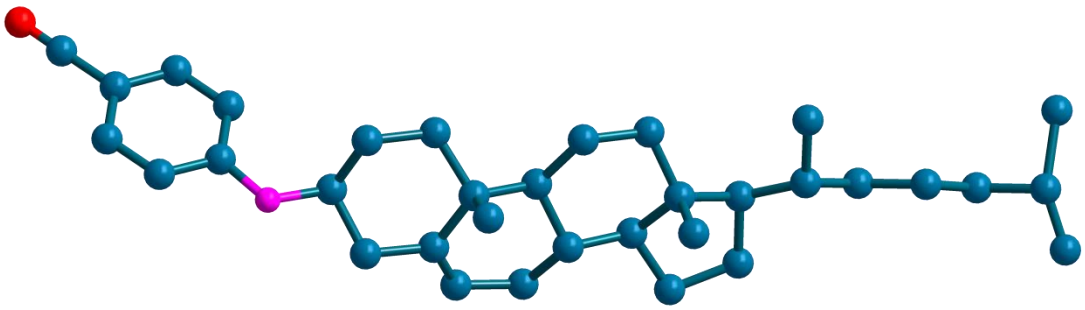
[28] Chen, H.; Sun, S.; Liu, Y. A.; Liao, X. Nickel-Catalyzed Cyanation of Aryl Halides and Hydrocyanation of Alkynes via C–CN Bond Cleavage and Cyano Transfer. *ACS Catal.* **2020**, *10*, 1397−1405.

[29] Lee, S.; Zhu, C.; Huang, K.; Bau, J. A.; Yue, H.; Rueping, M. Photoinduced Nickel-Catalyzed Demethylative Cyanation and Decarboxylative Cyanomethylation of Aryl Halides. *ACS Catal*. **2023**, *13*, 16279−16285.
[30] Liu, H.; Ren, J.; Lin, Y.; Huang, S.; Lu, G. –P. The Substituent Effects of Suzuki Coupling in Aqueous Micelles. *J. Org. Chem*. **2024**, *89*, 11930−11938.
[31] Ghosh, R., Lindstedt, E., Jalalian, N., Olofsson, B. Room Temperature, Metal-Free Arylation of Aliphatic Alcohols. *ChemistryOpen*. **2014**, *3*, 54 – 57.
[32] Chowdhury, D., Sutradhar, R., Paul, A., Mukherjee, A. Insight into the MOtBu (M=Na, K)-Mediated Dehydrogenation of Dimethylamine-Borane and Transfer Hydrogenation of Nitriles to Primary Amines. *Chem. Eur. J.* **2024**, *30*, e202400942.
[33] Elorriaga, D., Carrillo-Hermosilla, F., Parra-Cadenas, B., Antiñolo, A., García-Álvarez, J. Aerobic/Room-Temperature-Compatible *s*-Block Organometallic Chemistry in Neat Conditions: A Missing Synthetic Tool for the Selective Conversion of Nitriles into Asymmetric Alcohols. *ChemSusChem*. **2022**, *15*, e202201348.
[34] Jin, T., Kitahara, F., Kamijo, S., Yamamoto, Y. Synthesis of 5-Substituted 1*H*-Tetrazoles by the Copper-Catalyzed [3+2] Cycloaddition of Nitriles and Trimethylsilyl Azide. *Chem. Asian J.* **2008**, *3*, 1575 – 1580
[35] Zhou Y., Qiu, L., Li, J.,Xie, W. A General Copper Catalytic System for Suzuki–Miyaura Cross-Coupling of Unactivated Secondary and Primary Alkyl Halides with Arylborons. *J. Am. Chem. Soc*. **2023**, *145*,28146–28155.
[36] Tsuzaki, M., Ando, S., Ishizuka, T. Etherification via Aromatic Substitution on 1,3-DisubstitutedBenzene Derivatives. *J. Org. Chem*. **2022**, *87*, 1357−1365.
[37] Ando, S.; Tsuzaki, M.; Ishizuka, T. Aryl Ether Syntheses via Aromatic Substitution Proceeding under Mild Conditions. *J. Org. Chem*. **2020**, *85*, 11181−11189.
[38] Chen, H.; Yang, W.; Zhang, J.; Lu, B.; Wang, X. Divergent Geminal Alkynylation–Allylation and Acylation–Allylation of Carbenes: Evolution and Roles of Two Transition-Metal Catalysts. *J. Am. Chem. Soc.* **2024**, *146*, 4727−4740.
[39] Chen, G. –G.; Wei, J. –Q.; Yang, X.; Yao, Z. –J. Convenient One-Step Synthesis of Benzo[*c*]phenanthridines by Three-Component Reactions of Isochromenylium Tetrafluoroborates and Stilbenes in Acetonitrile. *Org. Lett.* **2016**, *18*, 1502−1505.
[40] Cheng, L., Tang Q., Dai, Y. –M., Wang, B. –Q., Hu, P., Cao, P., Song, F. Rh-Catalyzed Intramolecular Hydroarylation of Unactivated Alkenes via C–C Bond Activation. *ACS Catal.* **2023**, *13*, 4362−4368.
[41] Cheng, L.; Tang, Q.; Dai, Y.-M.; Wang, B.-Q.; Hu, P.; Cao, P.; Song, F. Rh-Catalyzed Intramolecular Hydroarylation of Unactivated Alkenes via C–C Bond Activation. *ACS Catal.* **2023,** *13*, 4362−4368.
[42] Zhou, M.; Li, K.; Chen, D.; Xu, R.; Xu, G.; Tang, W. Enantioselective Reductive Coupling of Imines Templated by Chiral Diboron. *J. Am. Chem. Soc*. **2020**, *142*, 10337−10342.
[43] Yan, Y.; Sun, J.; Li, G.; Yang, L.; Zhng, W.; Cao, R.; Wang, C.; Xiao, J.; Xue, D. Photochemically Enabled, Ni-Catalyzed Cyanation of Aryl Halides. *Org. Lett*. **2022**, *24*, 2271−2275.
[44] Dong, Y., Yang, P., Zhao, S., Li, Y. Reductive cyanation of organic chlorides using CO2 and NH3 via Triphos–Ni(I) species. Nat Commun. **2020**, *11*, 4069.

Appendix I

Crystallographic Data

Table S8. Crystal data and structure refinement for **56**.



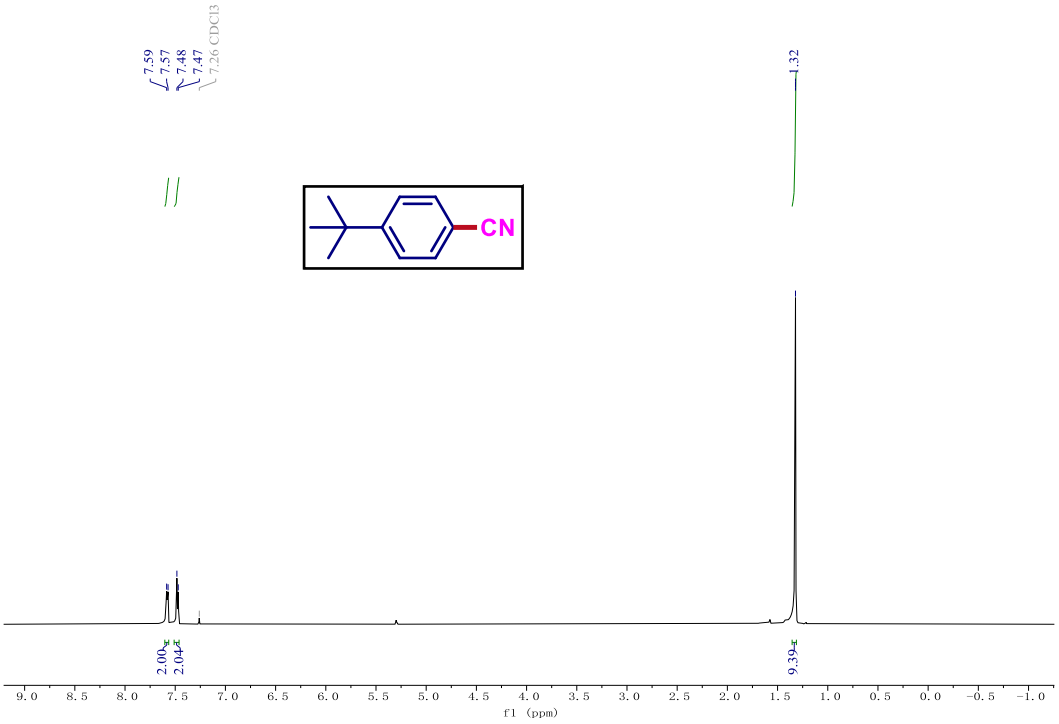
Empirical formula	$C_{34}H_{49}NO$	
Formula weight	487.74	
Temperature	220 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 8.8680 (7) Å	α = 90°
	b = 6.0061 (4) Å	β = 96.301(3)°
	c = 27.860 (2) Å	γ = 90°
Volume	1474.92 (19) $Å^3$	
Z	2	
Density (calculated)	1.098 Mg/m^3	
Absorption coefficient	0.064 mm^{-1}	
F(000)	536	
Crystal size	0.2 x 0.19 x 0.18 mm^3	
Theta range for data collection	4.474 to 49.472°.	
Index ranges	–11<=h<=11, –7<=k<=7, –36<=l<=36	
Data / restraints / parameters	6726 / 73 / 351	
Goodness-of-fit on F^2	1.046	
Final R indices [I>2sigma(I)]	R1 = 0.0472, wR2 = 0.1134	
R indices (all data)	R1 =0.0556, wR2 = 0.1207	

Appendix II

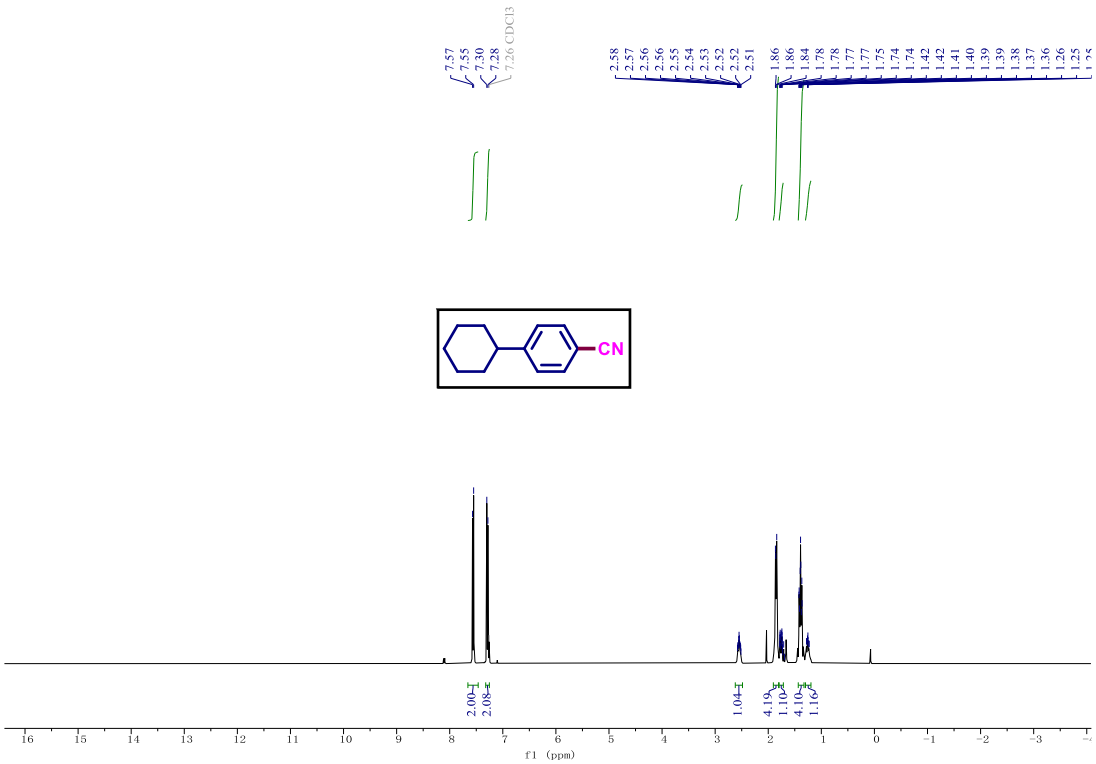
Spectral Copies of NMR of Newly Obtained Compounds

Note: only ^{1}H NMR Spectra are provided for the reported compounds

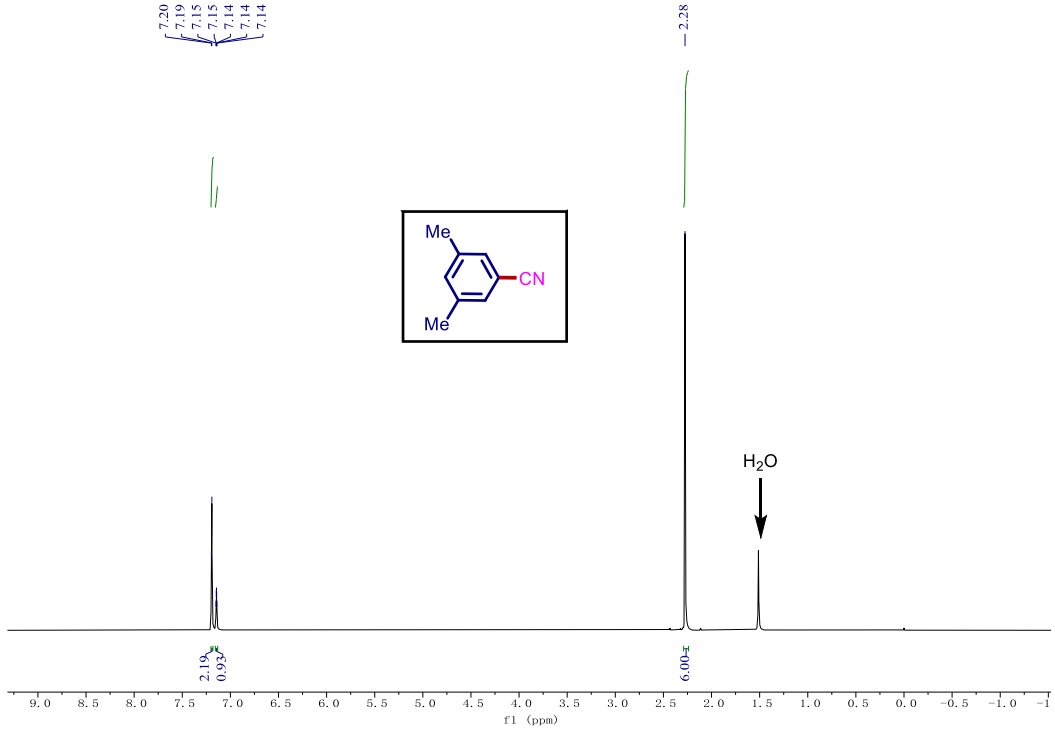
4-*tert*-Butyl benzonitrile (Table 3, 3)



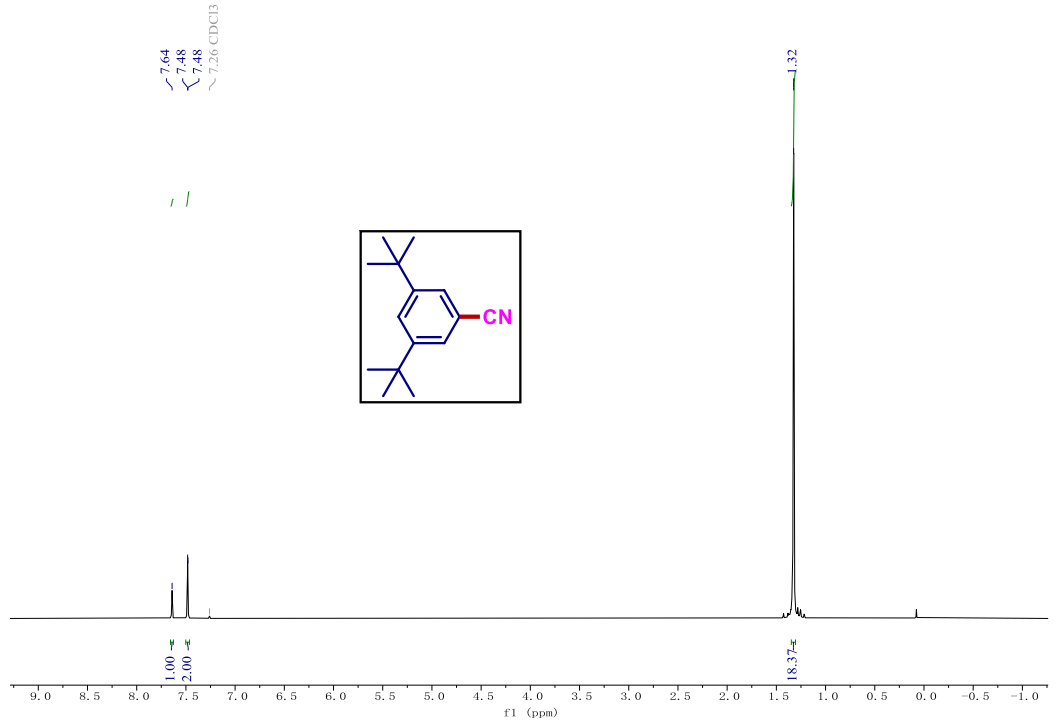
4-Cyclohexylbenzonitrile (Table 3, 4)



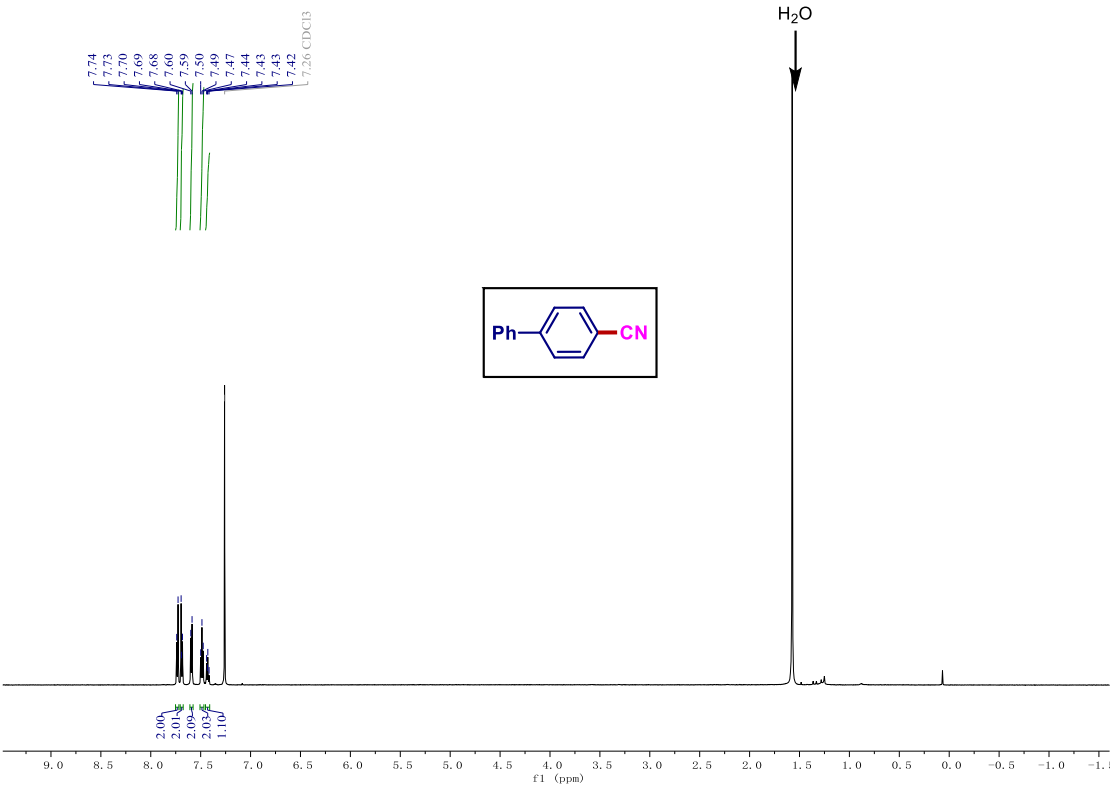
3,5-Dimethylbenzonitrile (Table 3, 5)



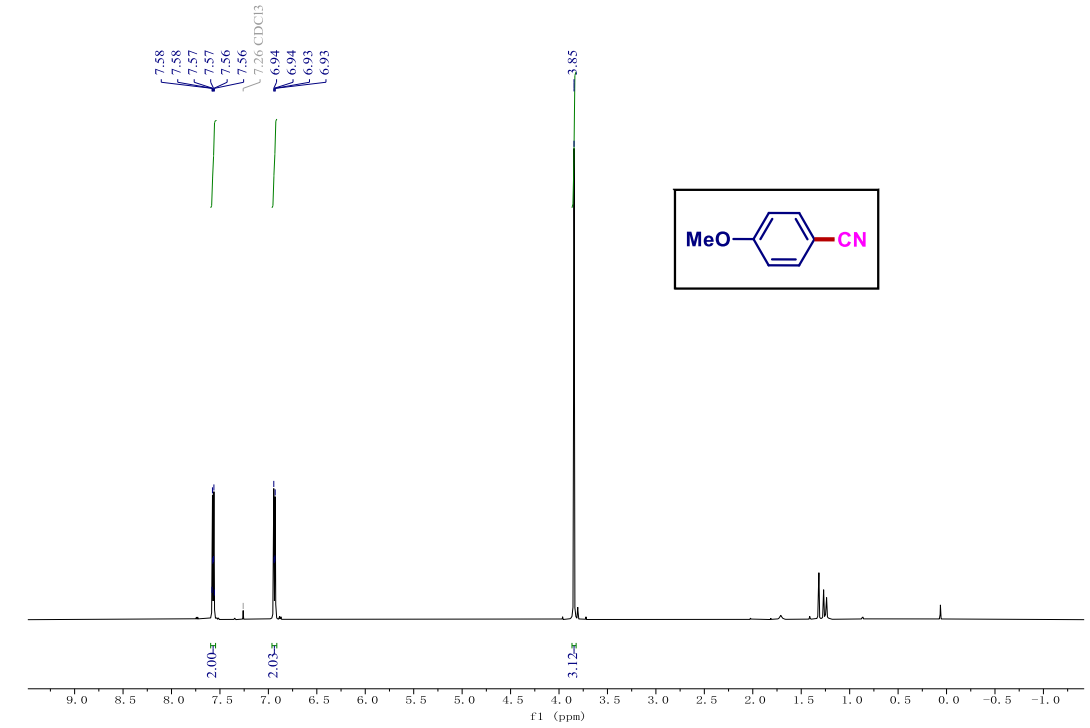
3,5-Di-*tert*-butyl benzonitrile (Table 3, 6)



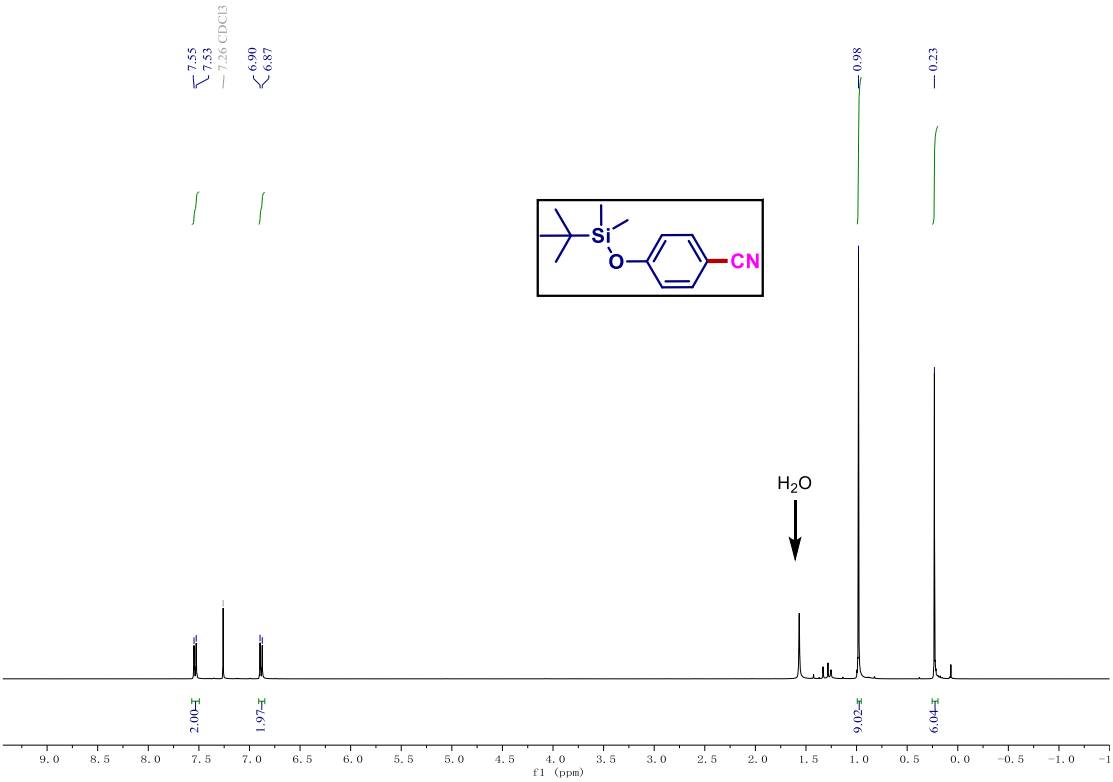
4-Biphenylcarbonitrile (Table 3, 7)



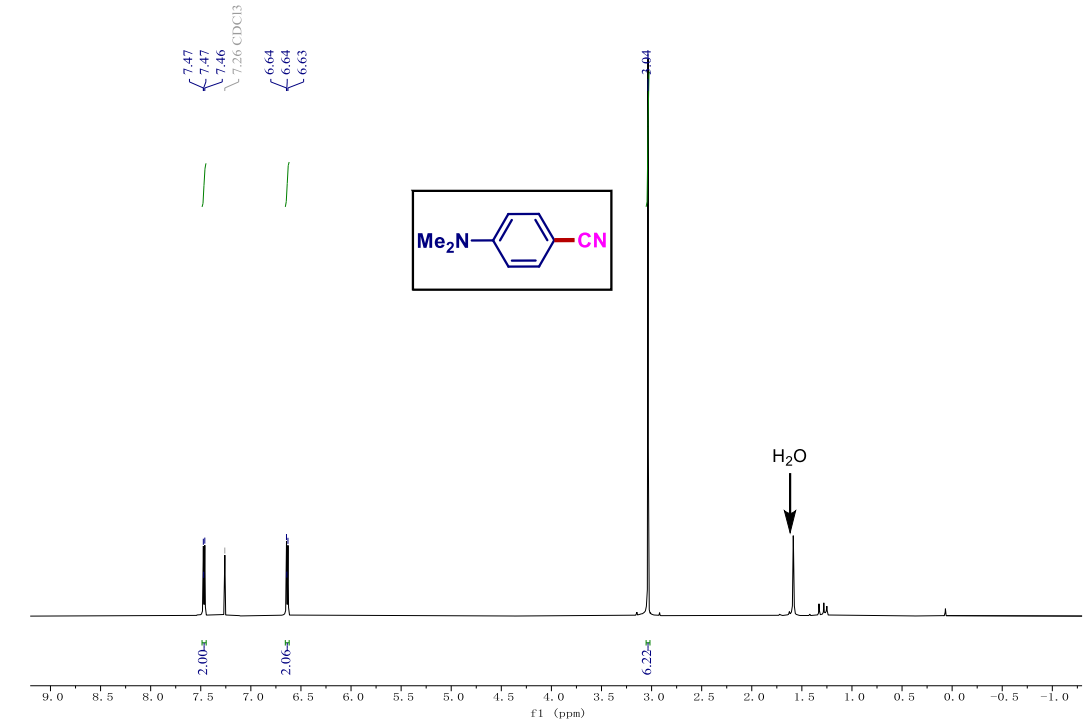
4-Methoxybenzonitrile (Table 3, 8)



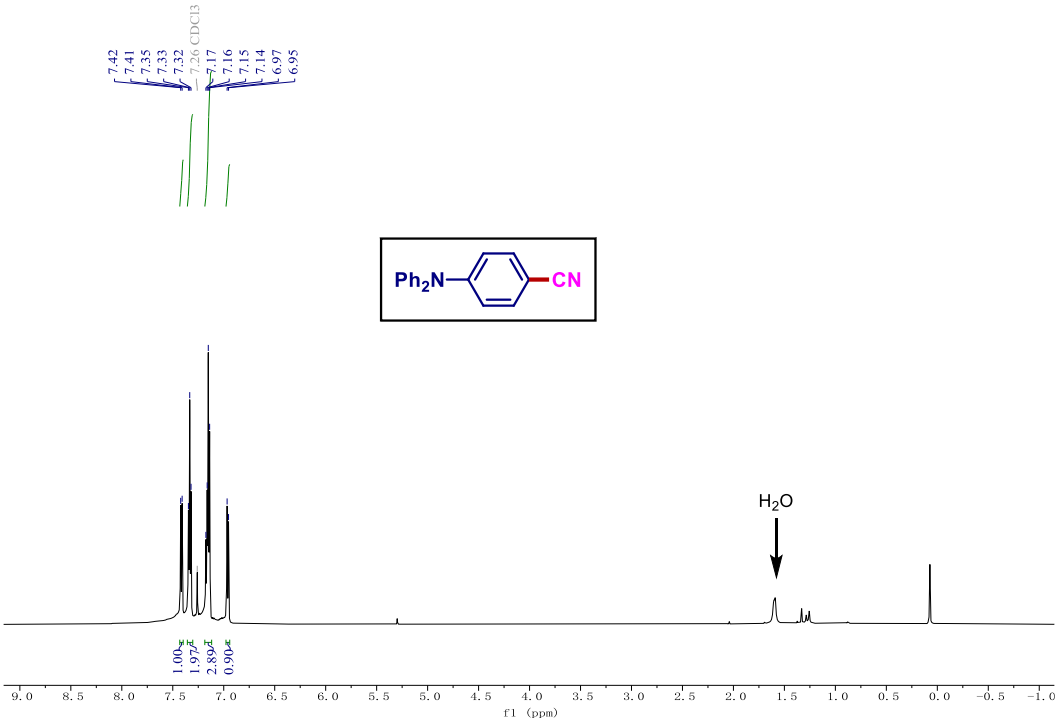
4-(*tert*-Butyldimethylsilyloxy)benzonitrile (Table 3, 9)



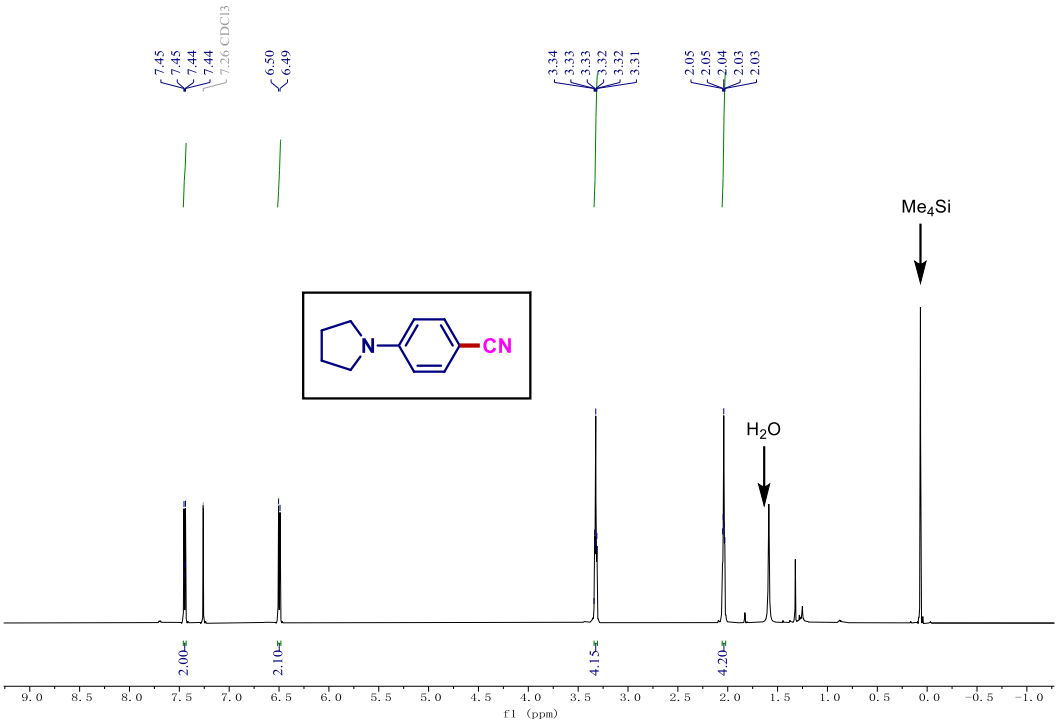
4-(Dimethylamino)benzonitrile (Table 3, 10)



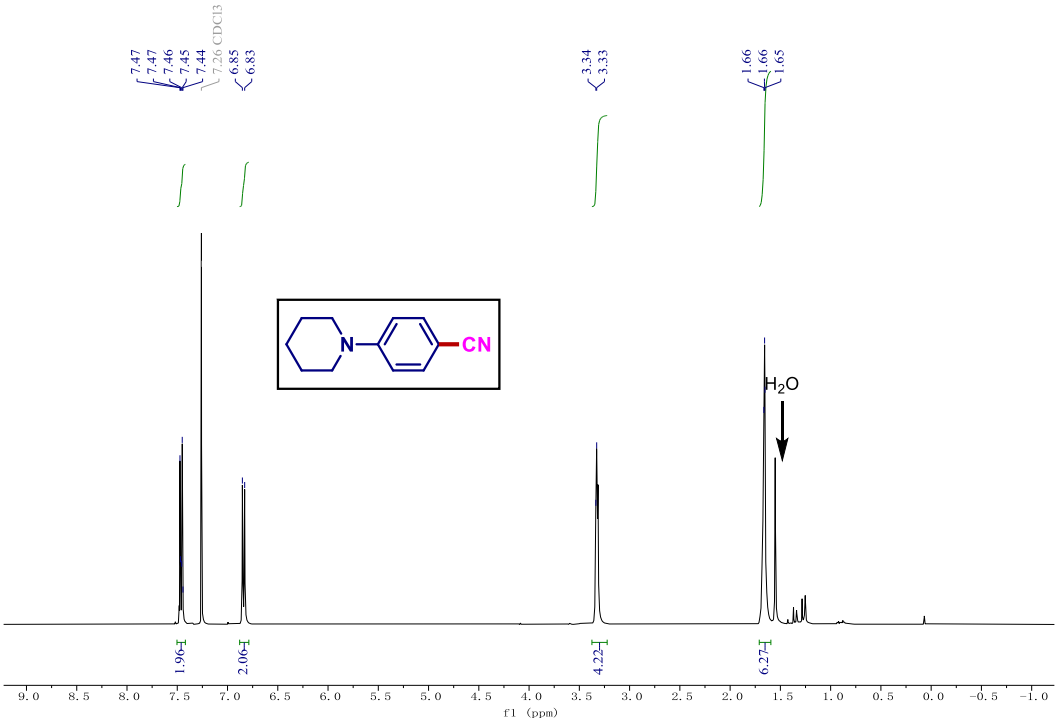
4-(Diphenylamino) benzonitrile (Table 3, 11)



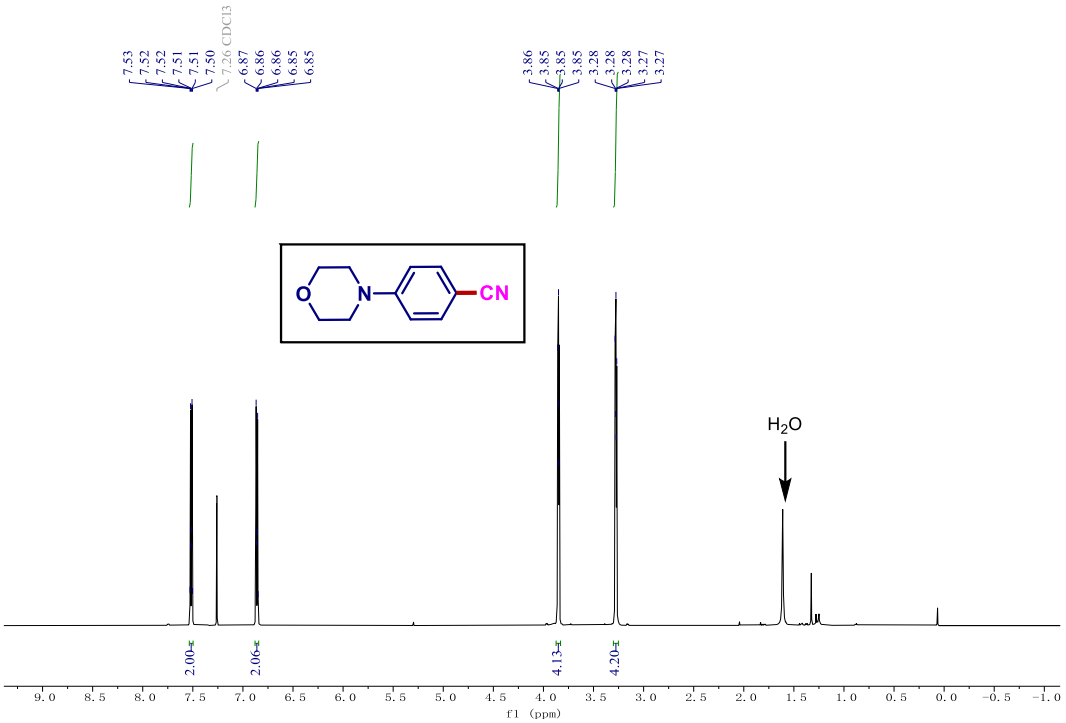
4-(Pyrrolidin-1-yl)benzonitrile (Table 3, 12)



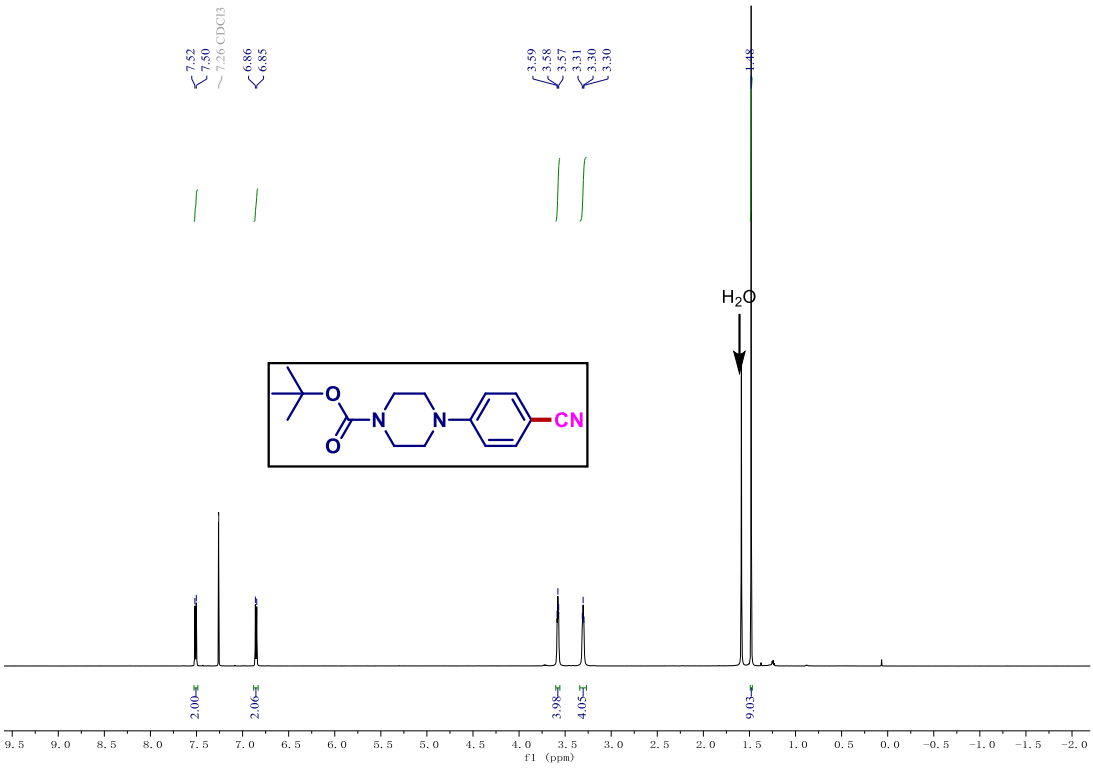
4-(Piperidin-1-yl)benzonitrile (Table 3, 13)



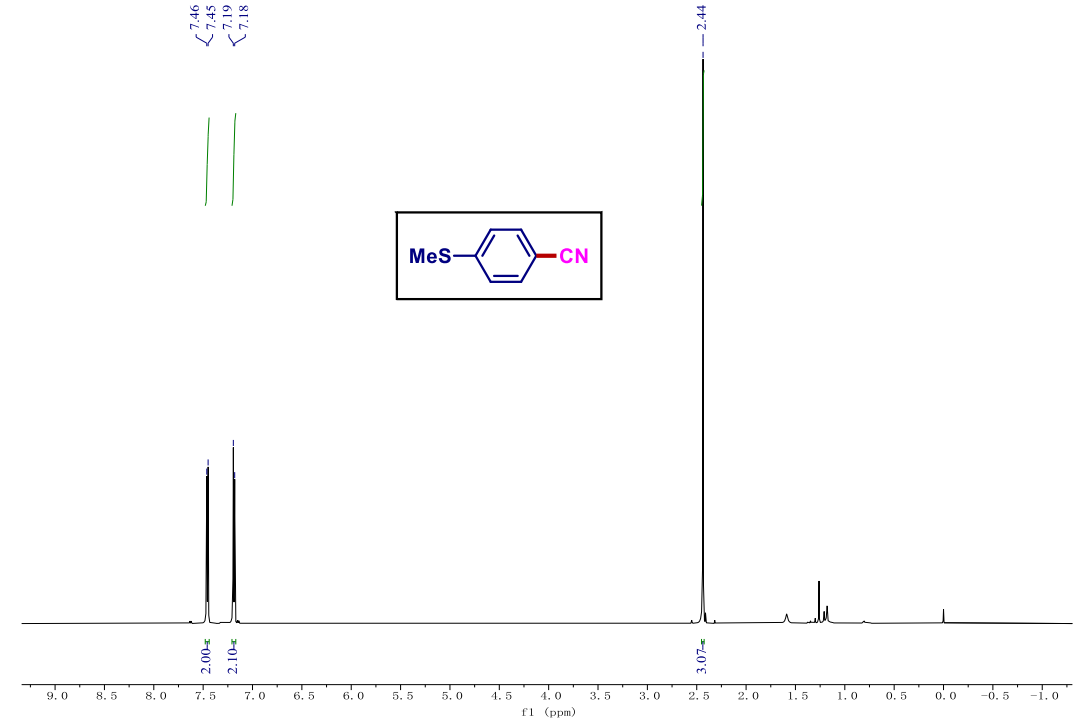
4-Morpholinobenzonitrile (Table 3, 14)



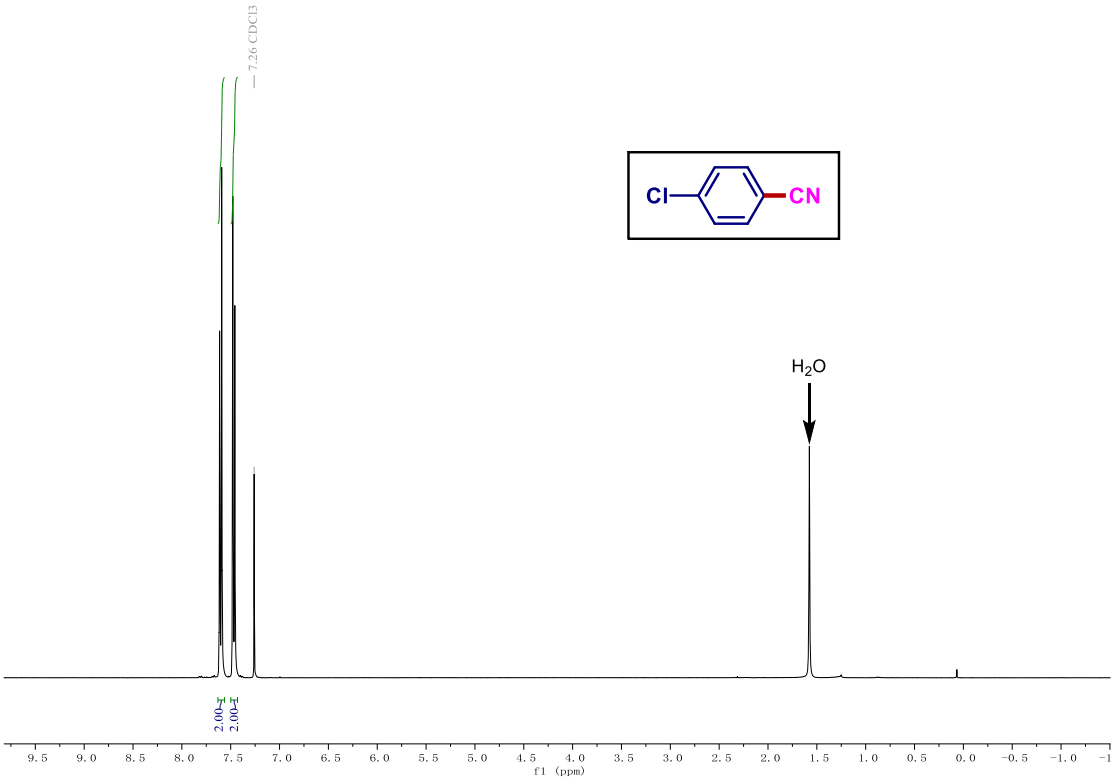
***tert*-Butyl 4-(4-cyanophenyl)piperazine-1-carboxylate (Table 3, 15)**



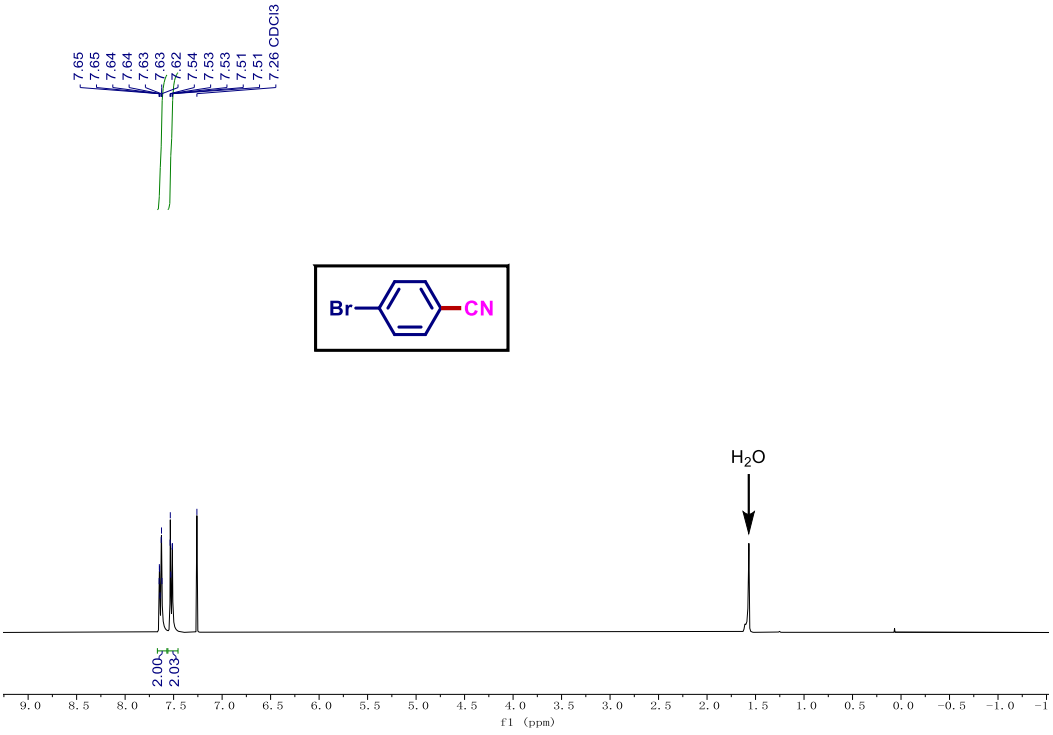
4-(Methylthio)benzonitrile (Table 3, 16)



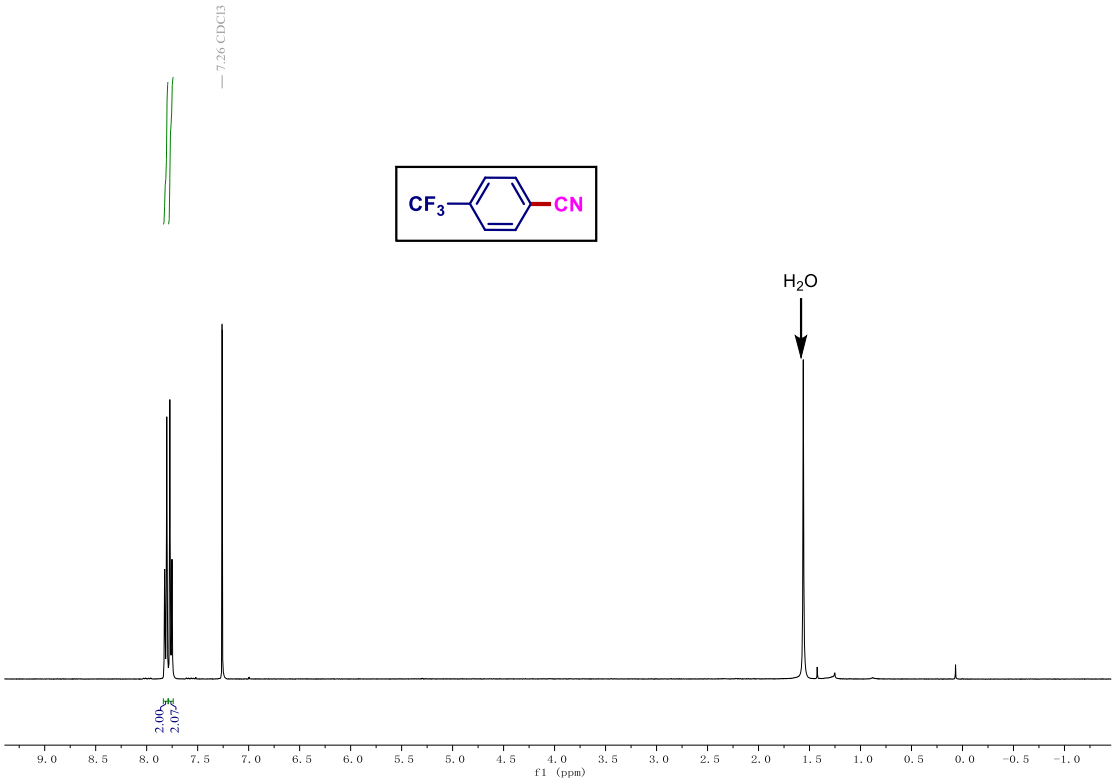
4-Chlorobenzonitrile (Table 3, 18)



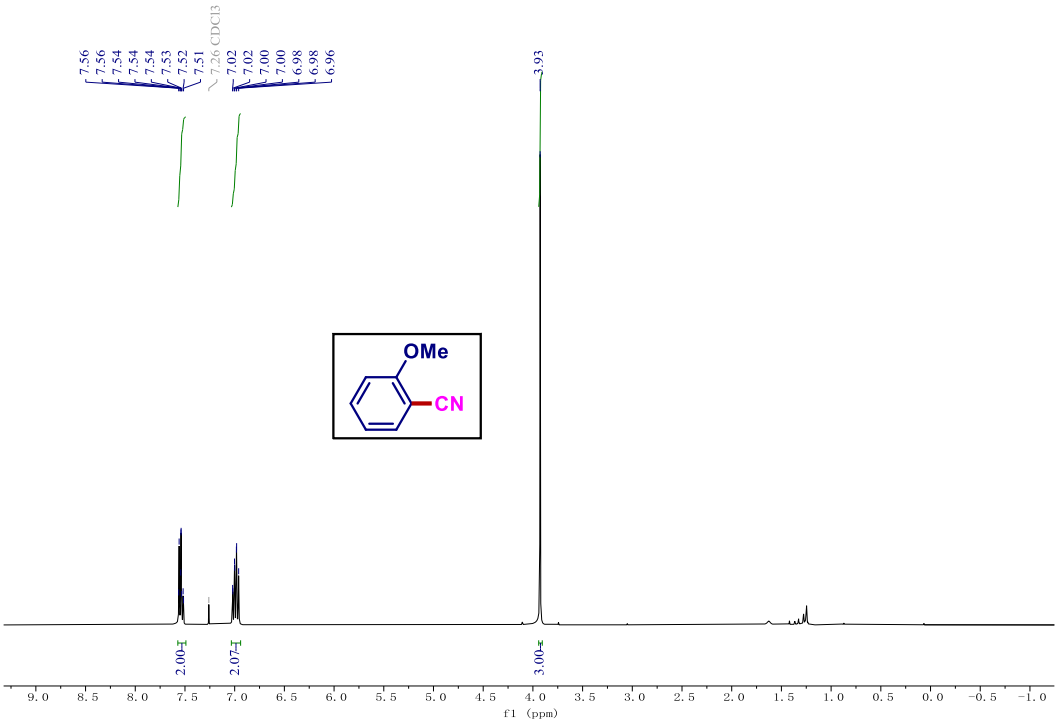
4-Bromobenzonitrile (Table 3, 19)



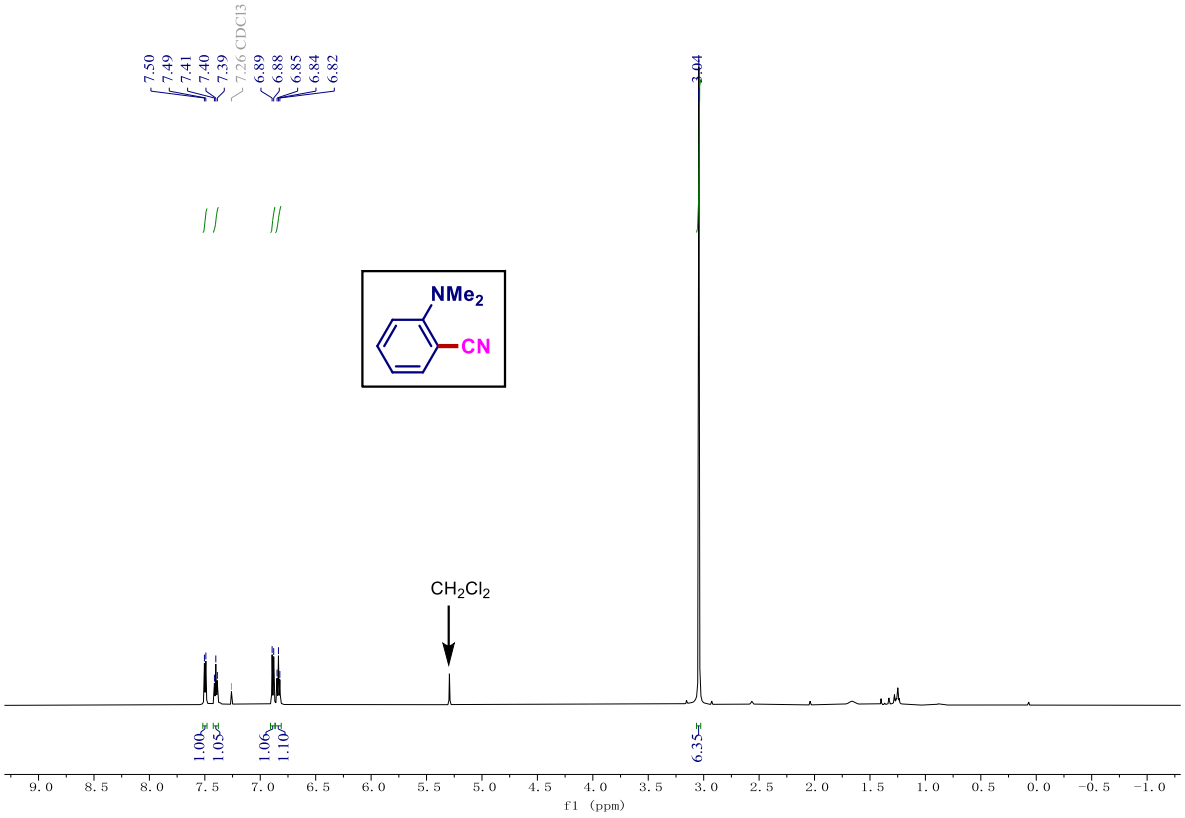
4-(Trifluoromethyl)benzonitrile (Table 3, 21)



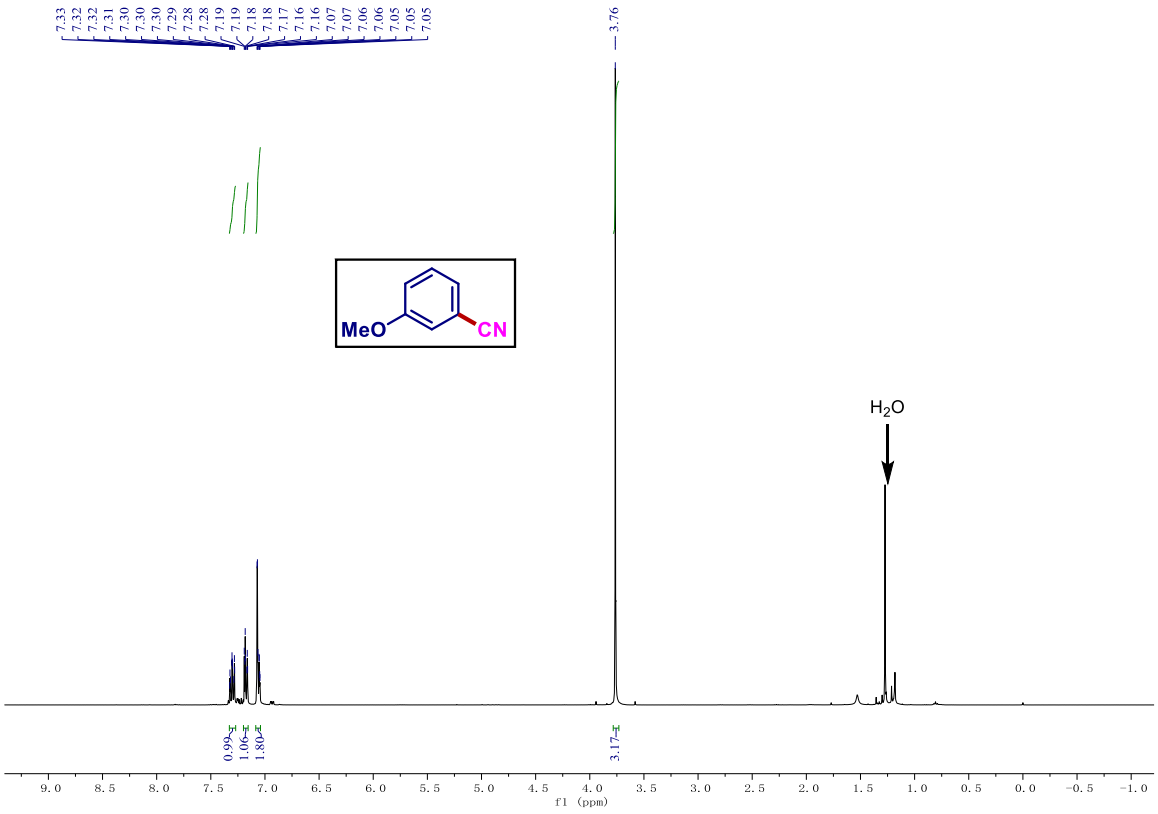
2-Methoxybenzonitrile (Table 3, 22)



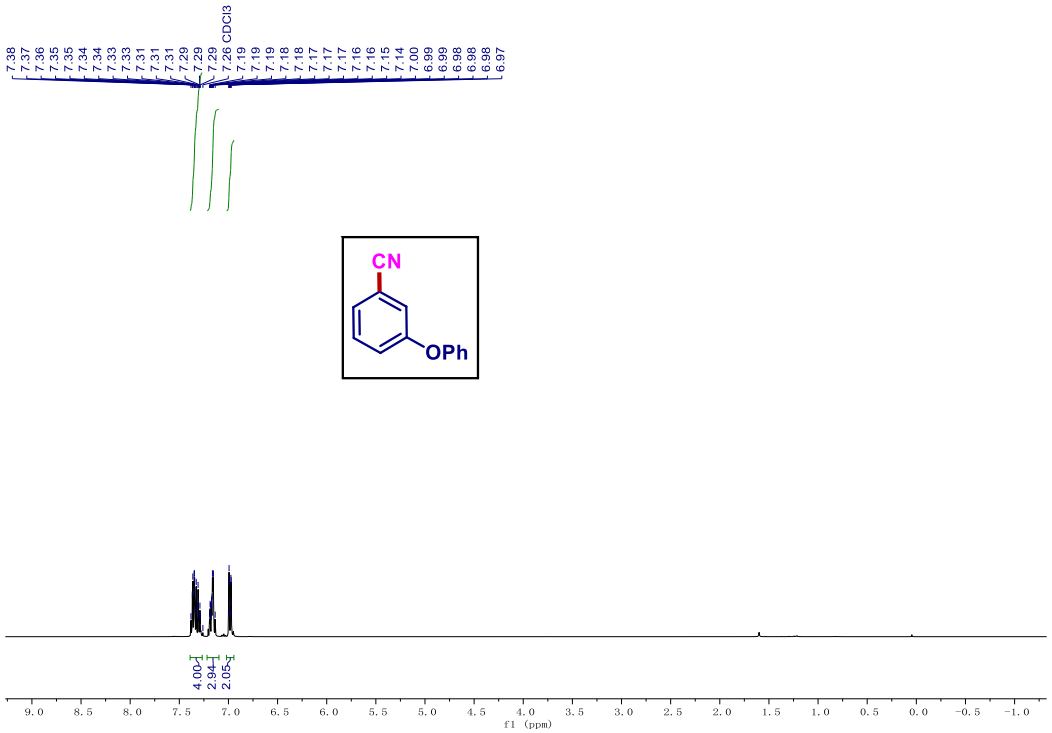
2-(Dimethylamino)benzonitrile (Table 3, 23)



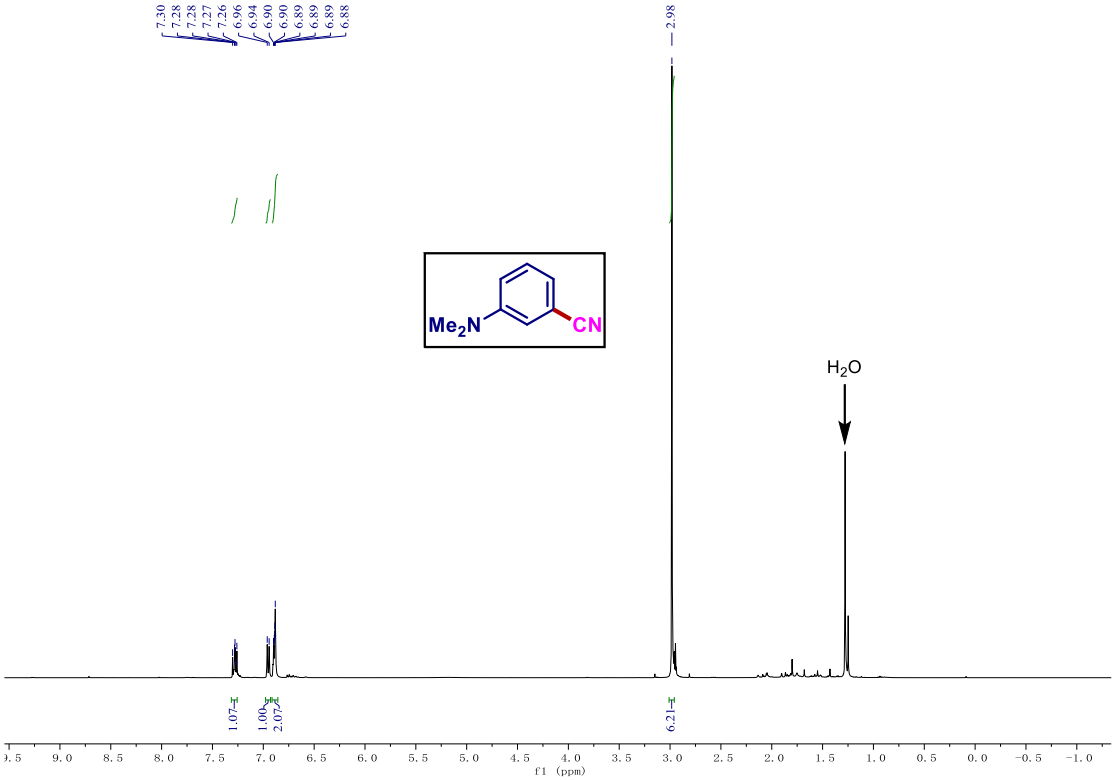
3-Methoxybenzonitrile (Table 3, 24)



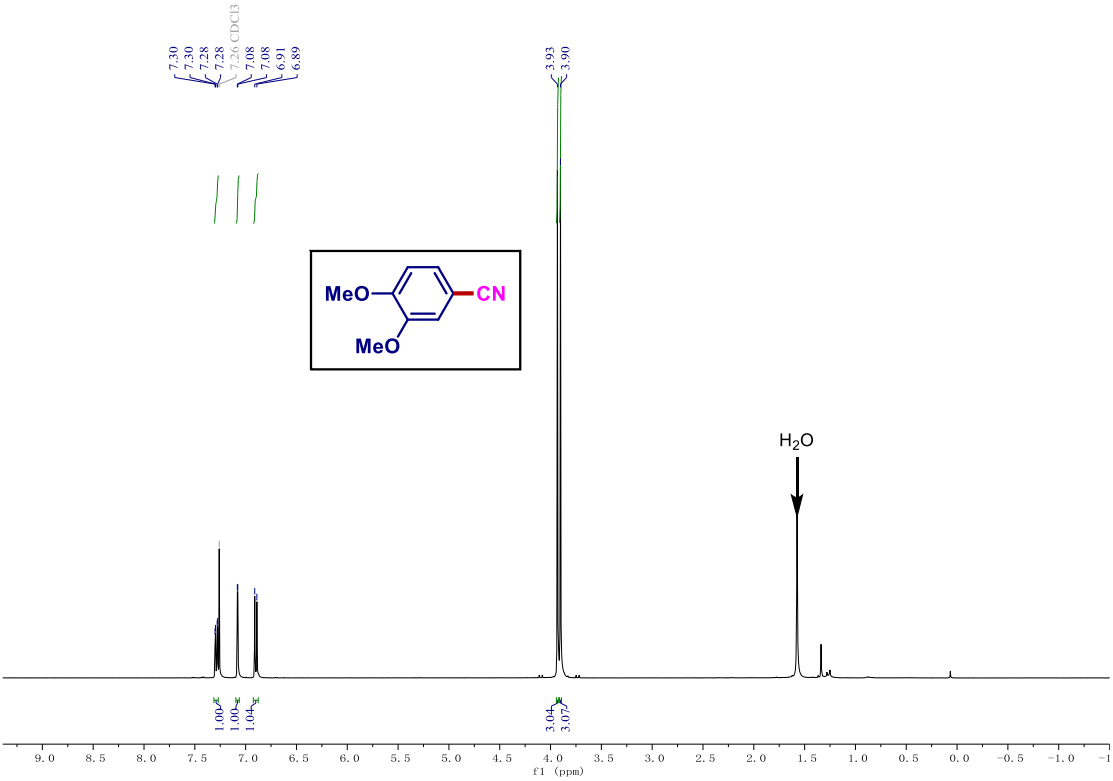
3-Phenoxybenzonitrile (Table 3, 25)



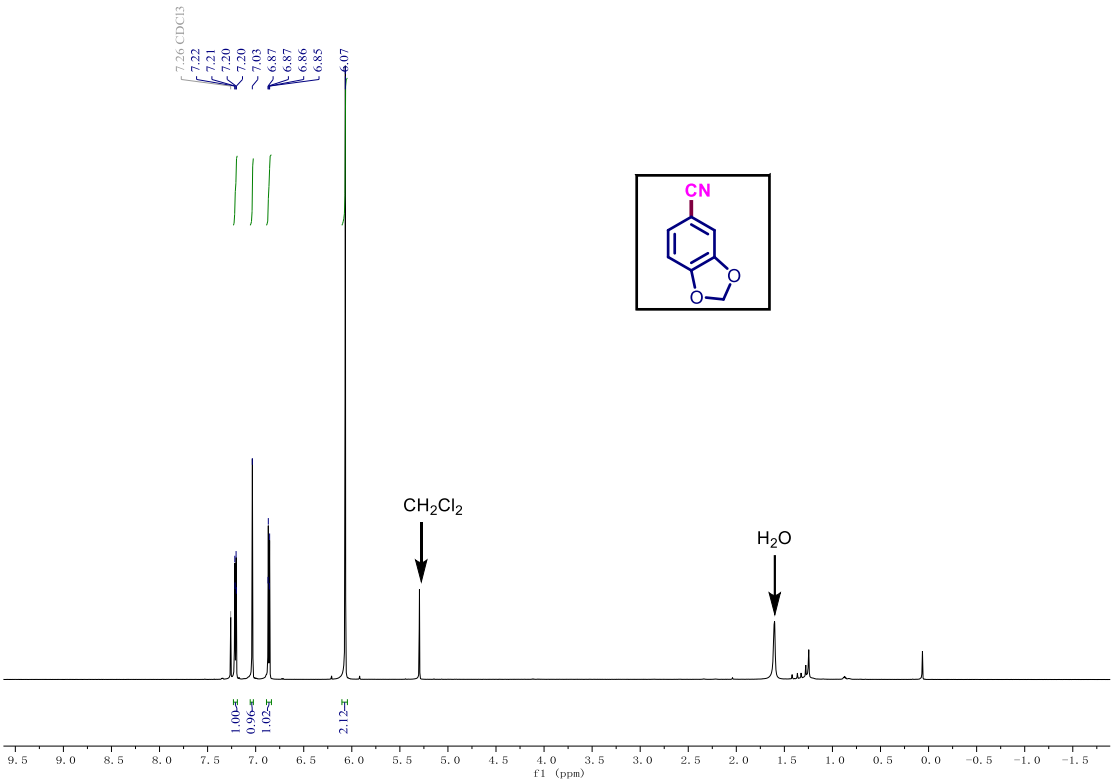
3-(Dimethylamino)benzonitrile (Table 3, 26)



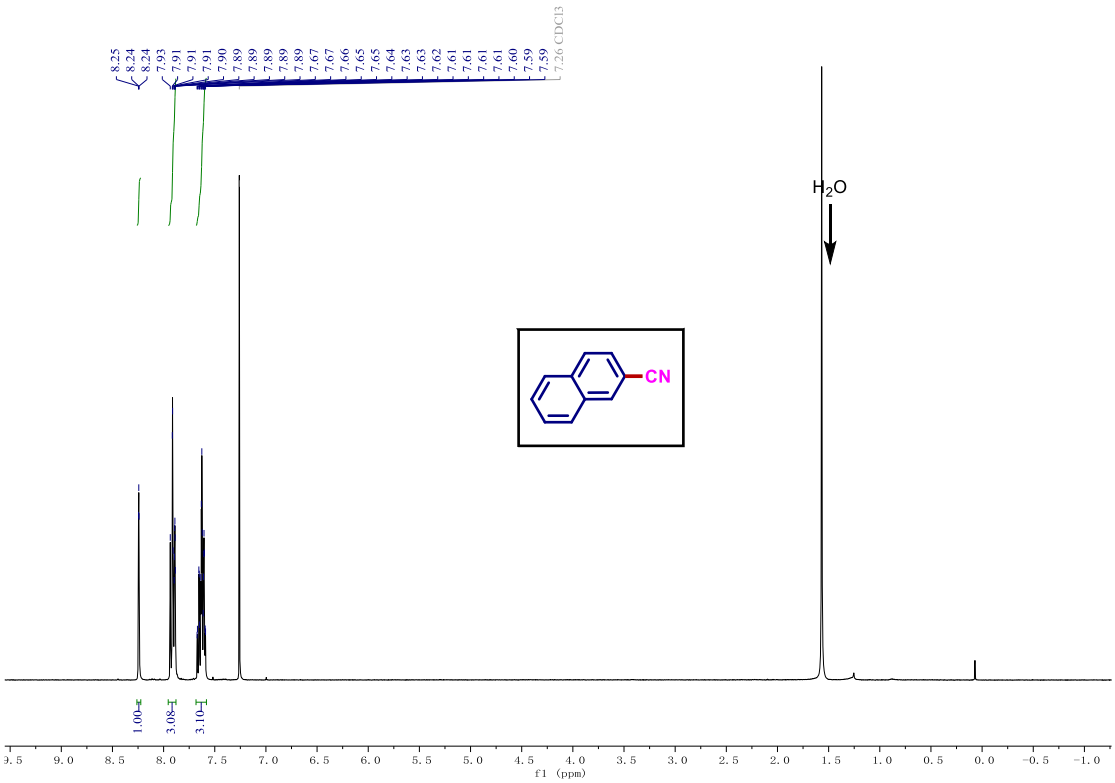
3,4-Dimethoxybenzonitrile (Table 3, 27)



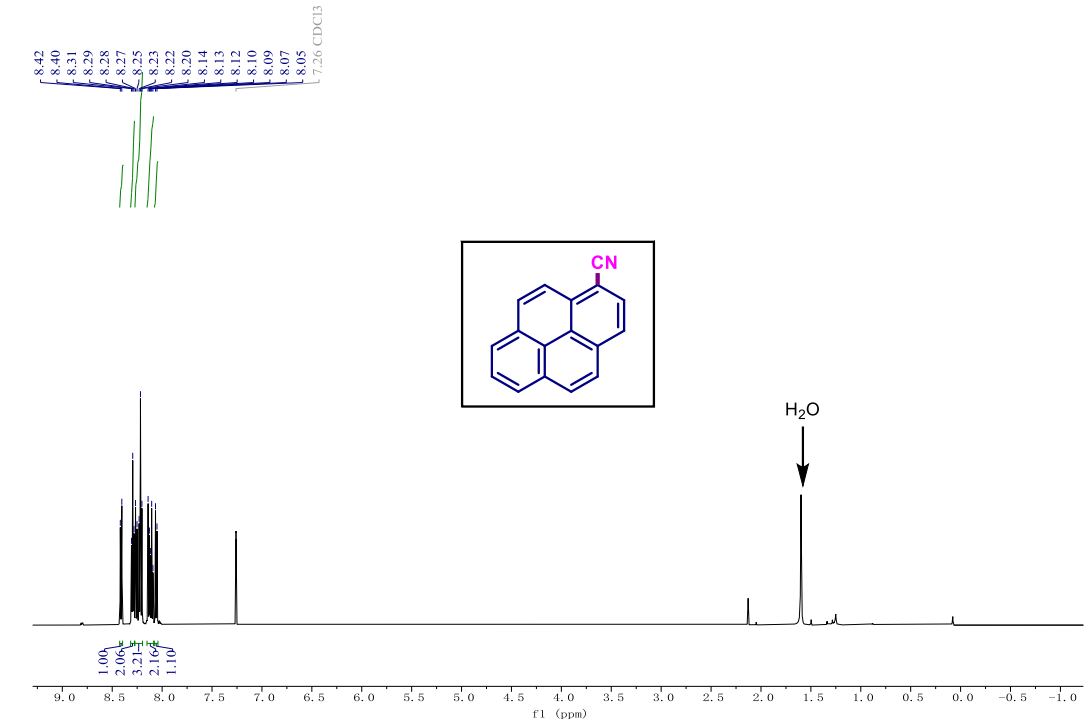
2-(Dimethylamino)benzonitrile (Table 3, 28)



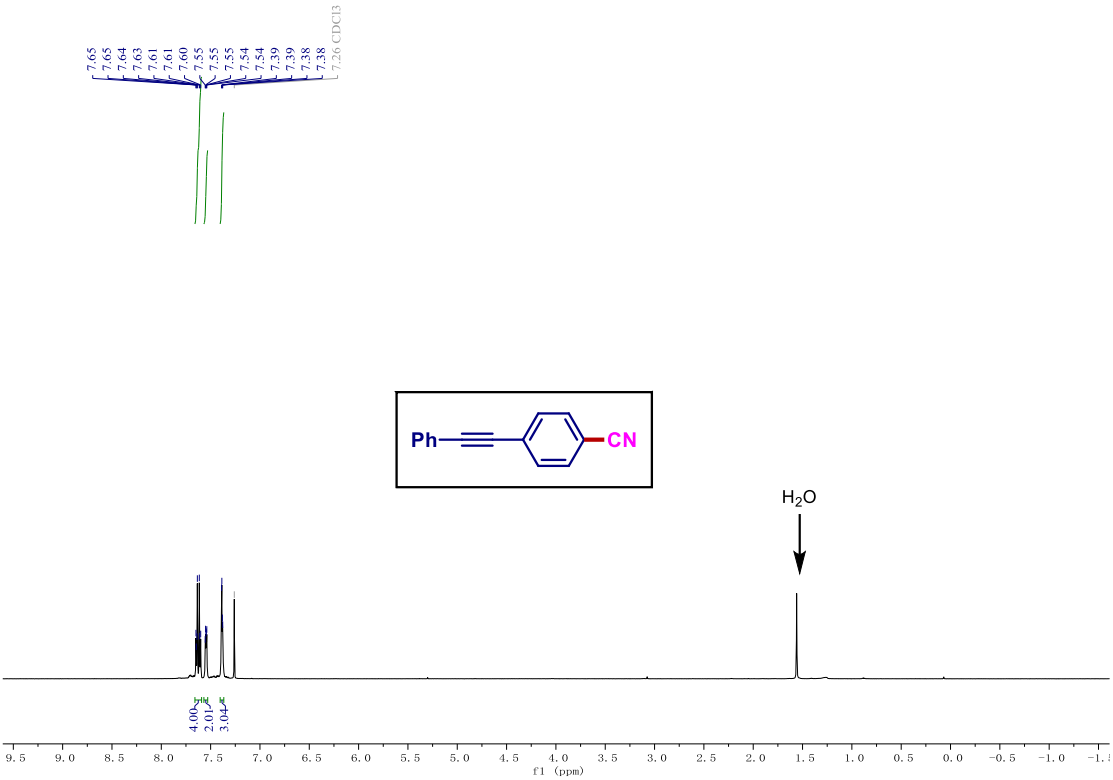
2-Naphthonitrile (Table 3, 29)



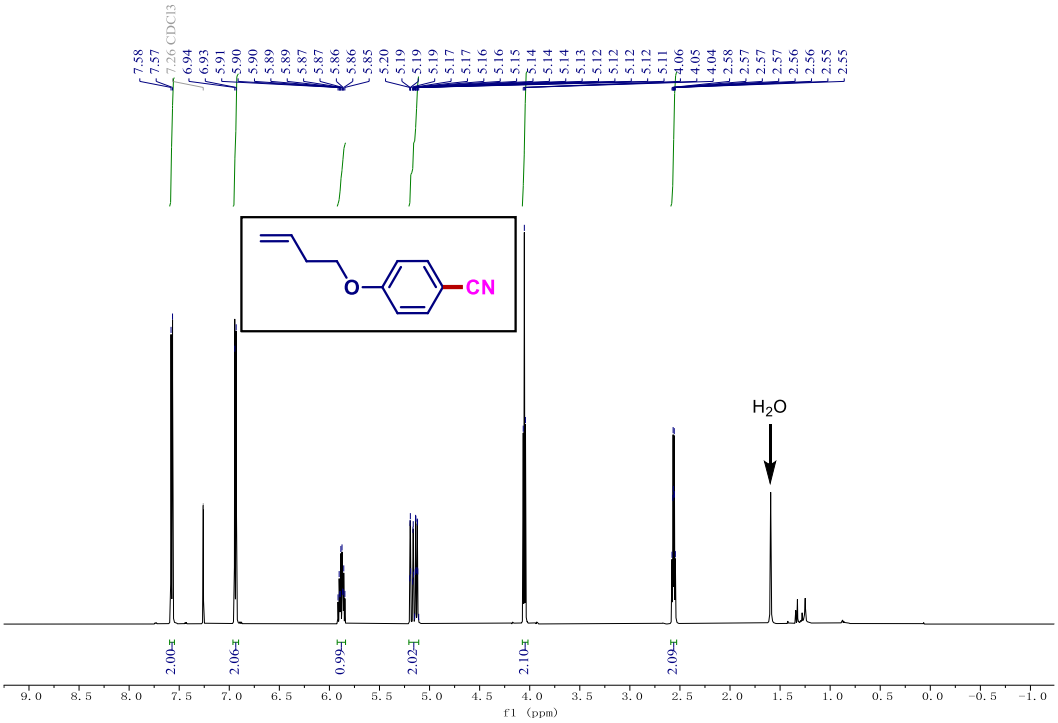
Pyrene-1-carbonitrile (Table 3, 30)



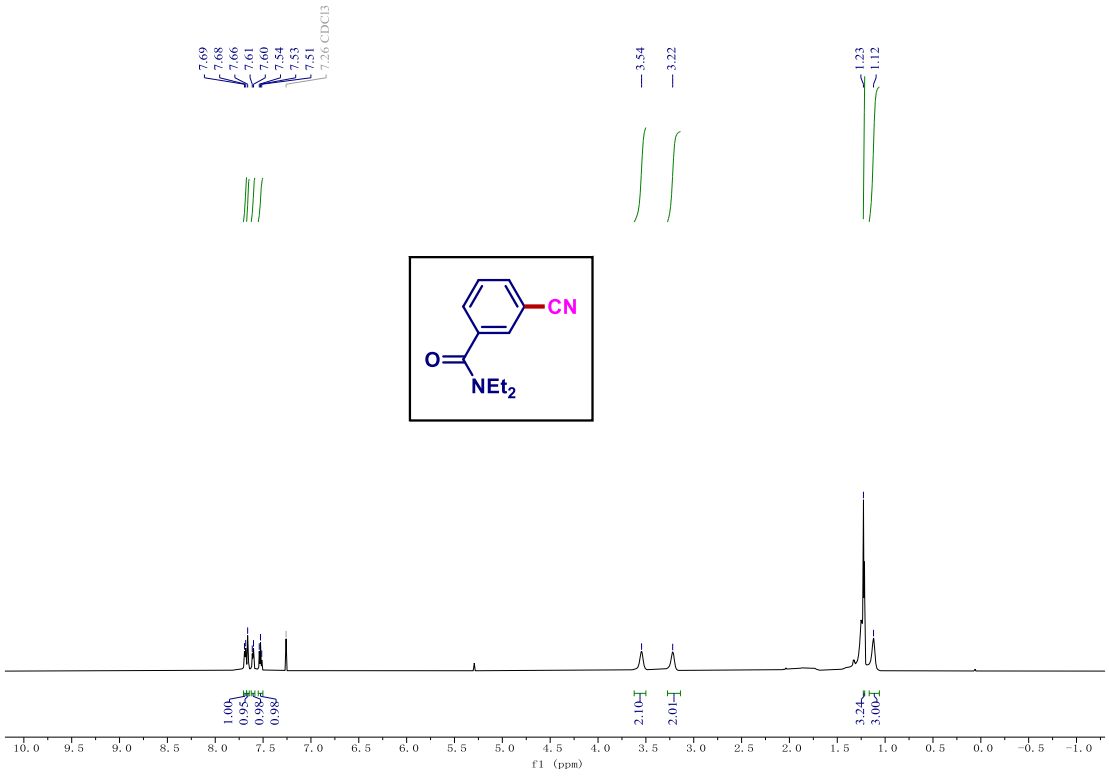
1-(4-Cyanophenyl)-2-phenylacetylene (Table 3, 31)



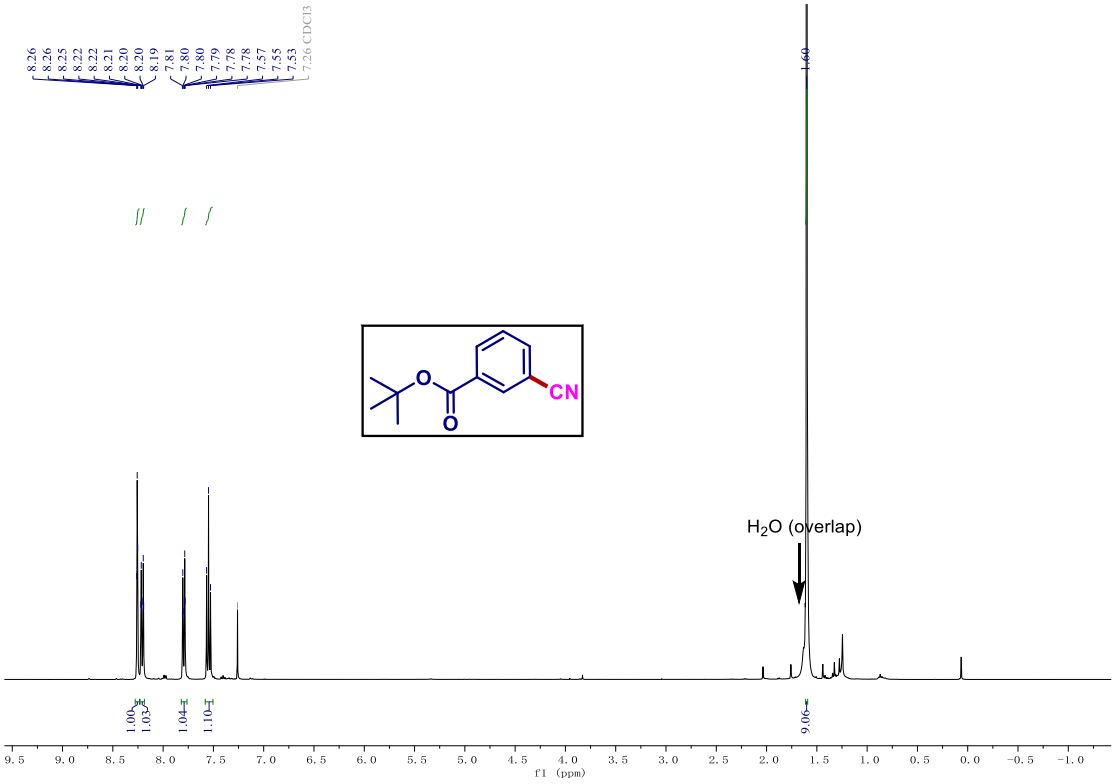
But-3-enyl 4-cyanophenyl ether (Table 3, 32)



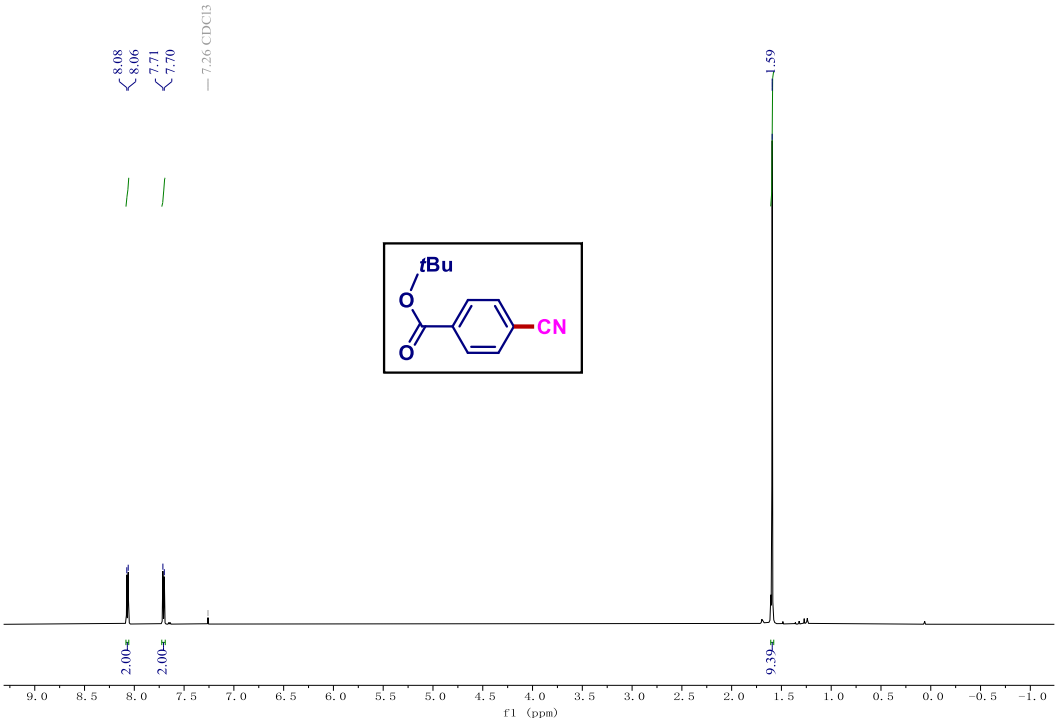
***N*, *N*-diethyl-3-ethynyl benzamide (Table 3, 33)**



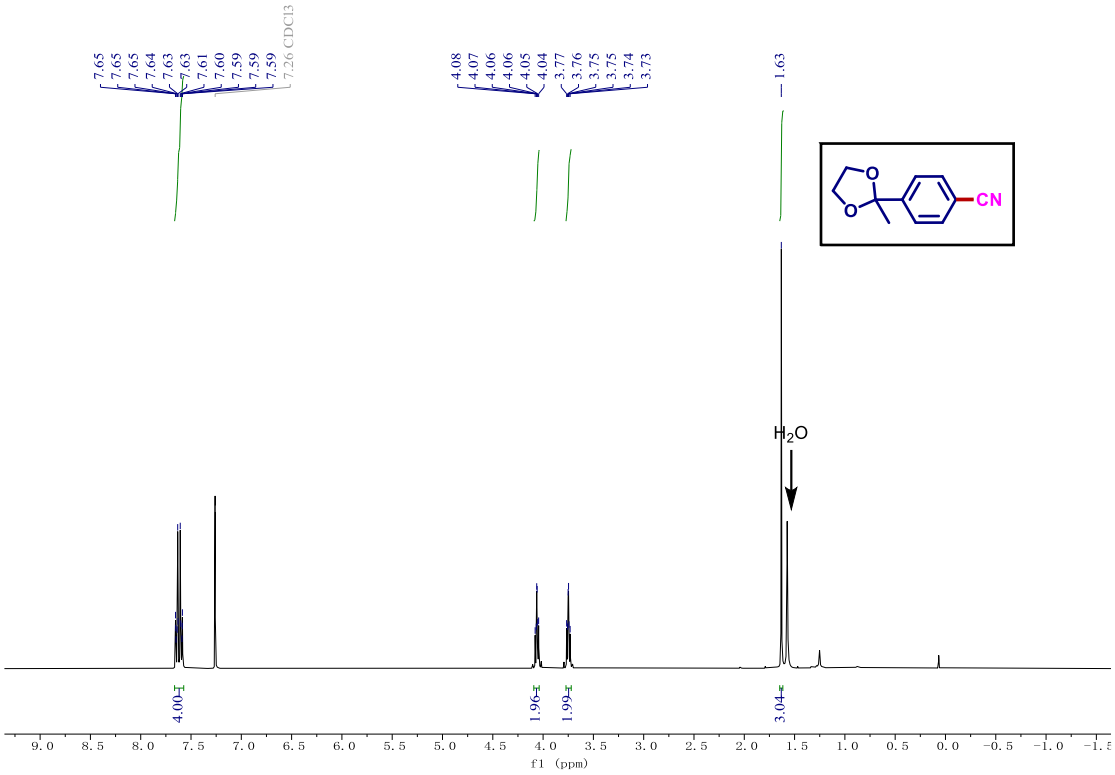
1,1-Dimethylethyl 3-cyanobenzoate (Table 3, 34)



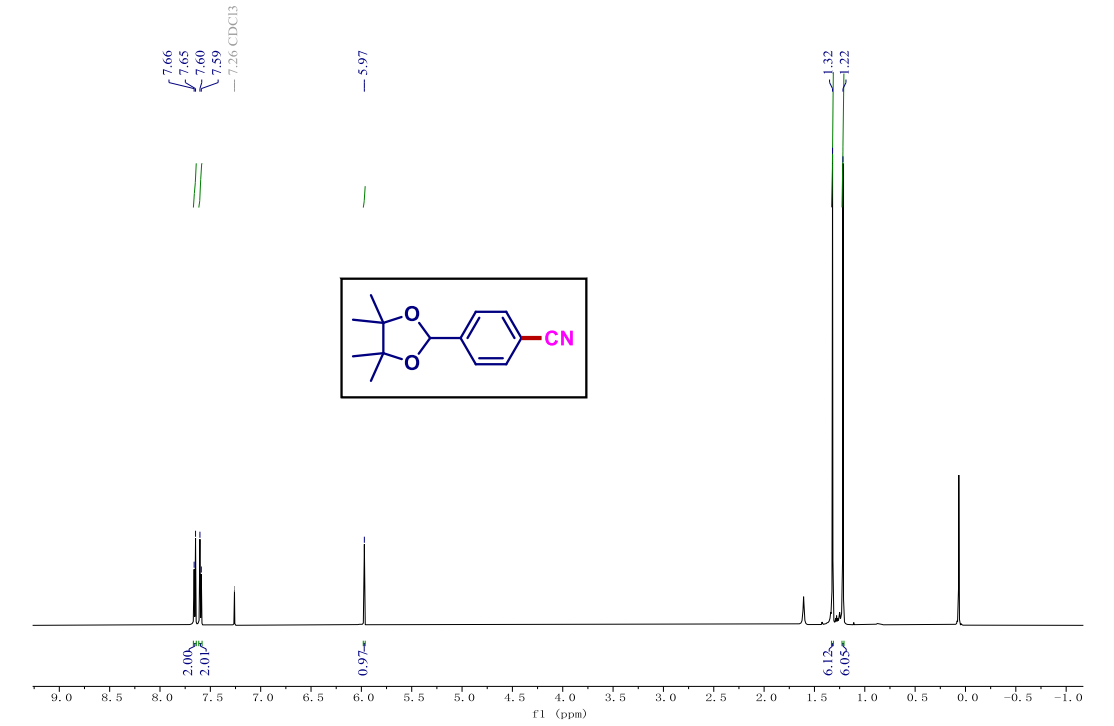
***tert*-Butyl 4-cyanobenzoate (Table 3, 35)**

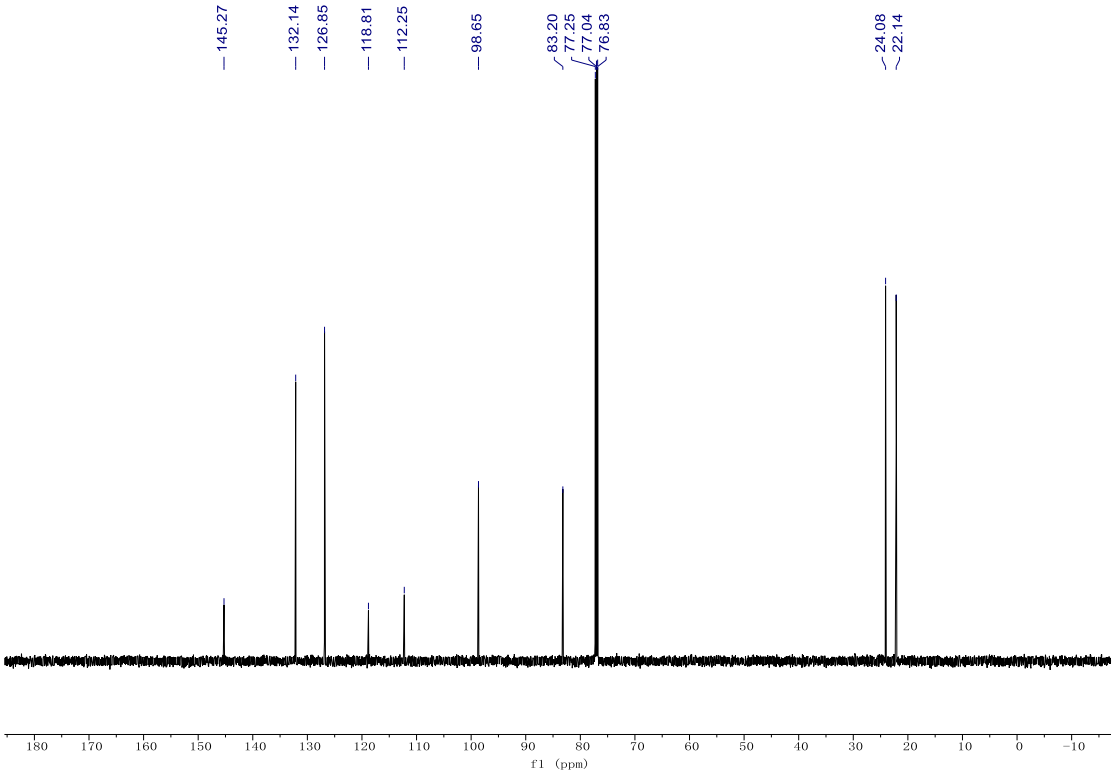


4-(4,4,5,5-Tetramethyl-1,3-dioxolan-2-yl)benzonitrile (Table 3, 36)

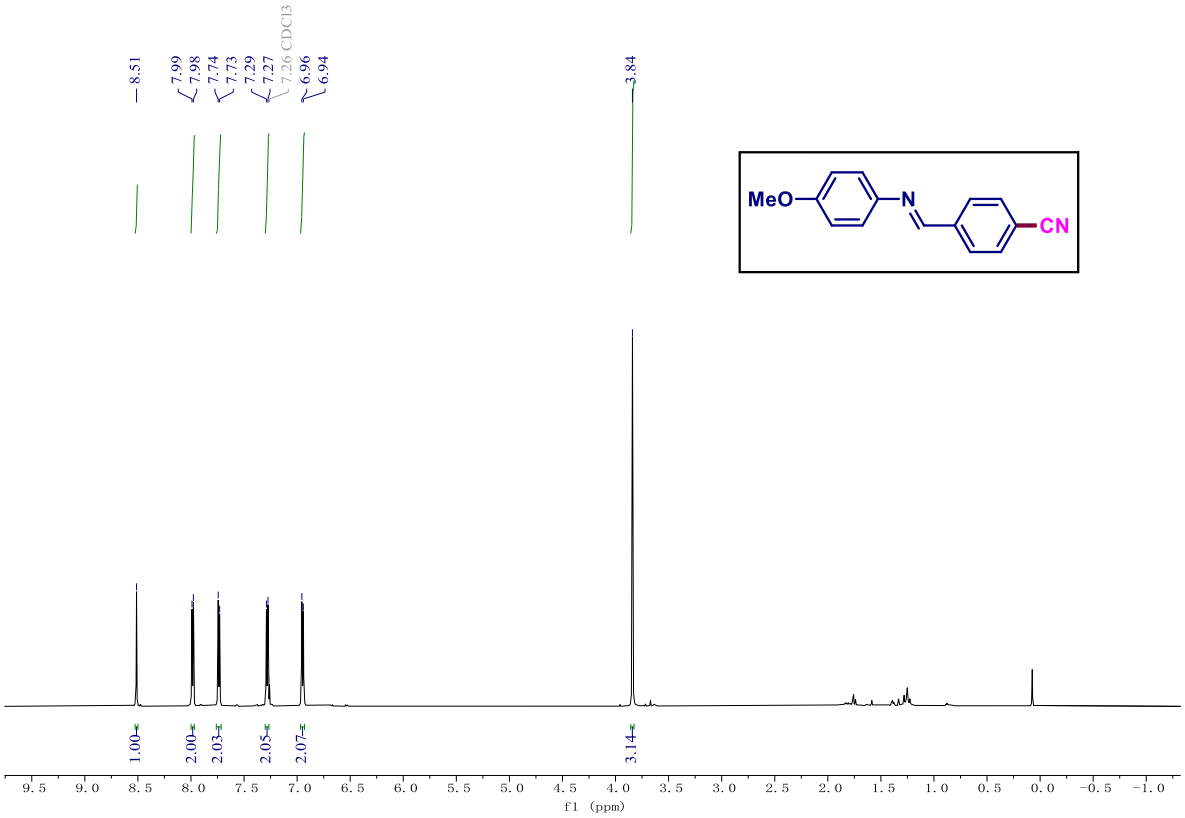


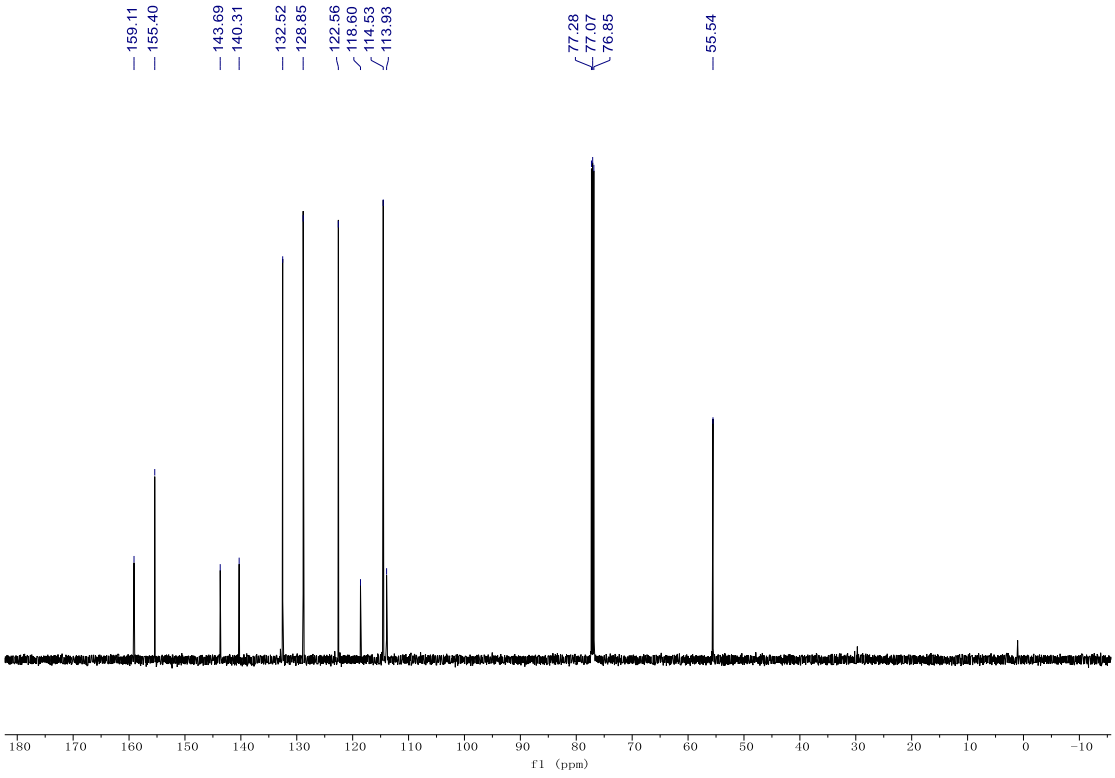
4-(4,4,5,5-Tetramethyl-1,3-dioxolan-2-yl)benzonitrile (Table 3, 37)



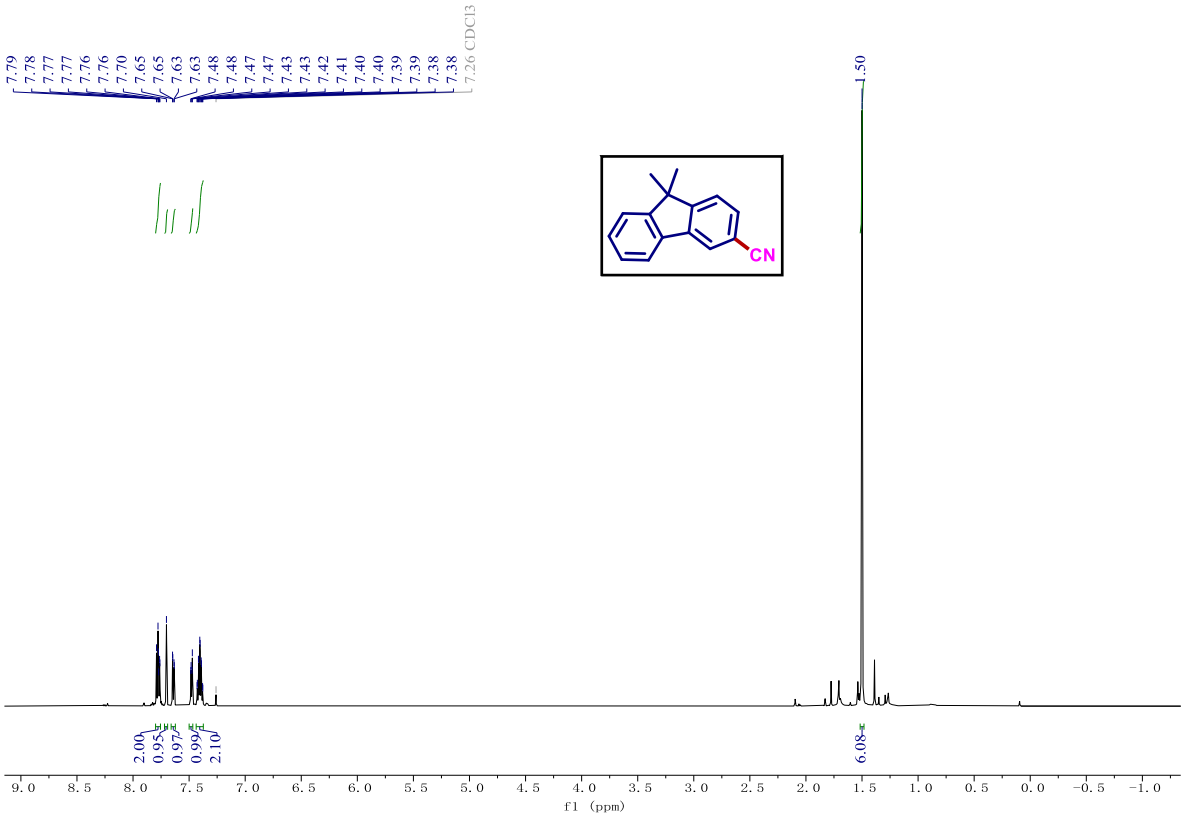


4-[(*E*)-[(4-Methoxyphenyl)imino]methyl]benzonitrile(Table 3, 38)

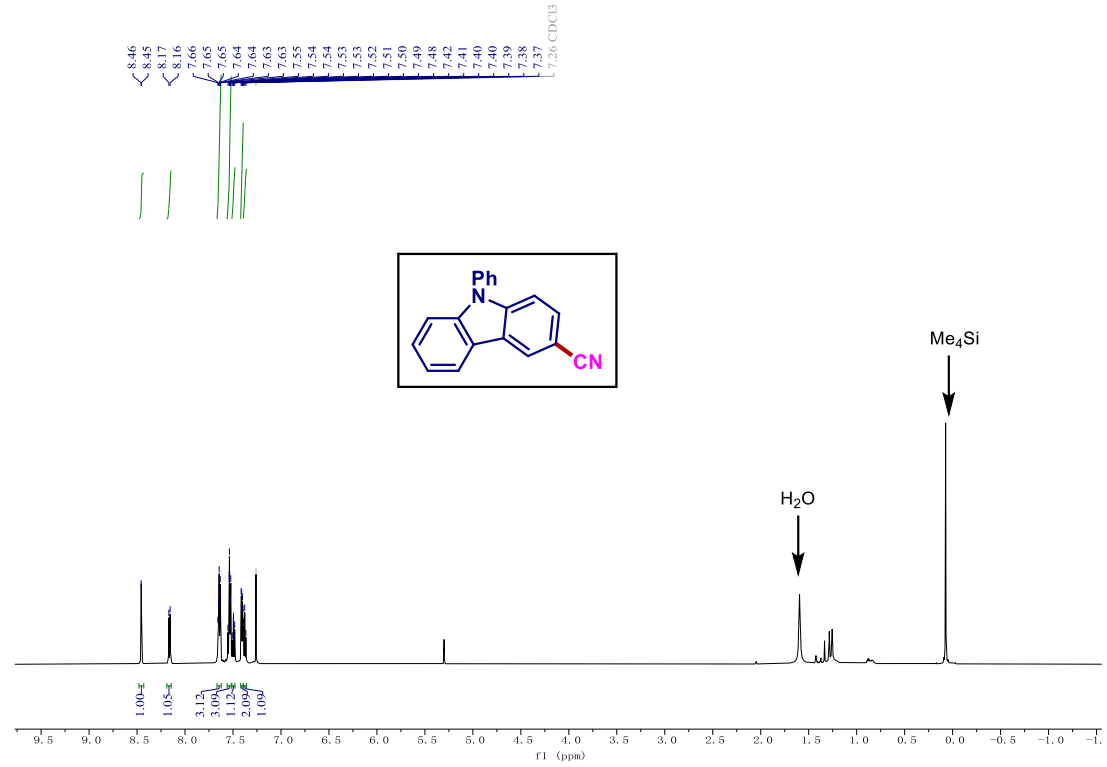




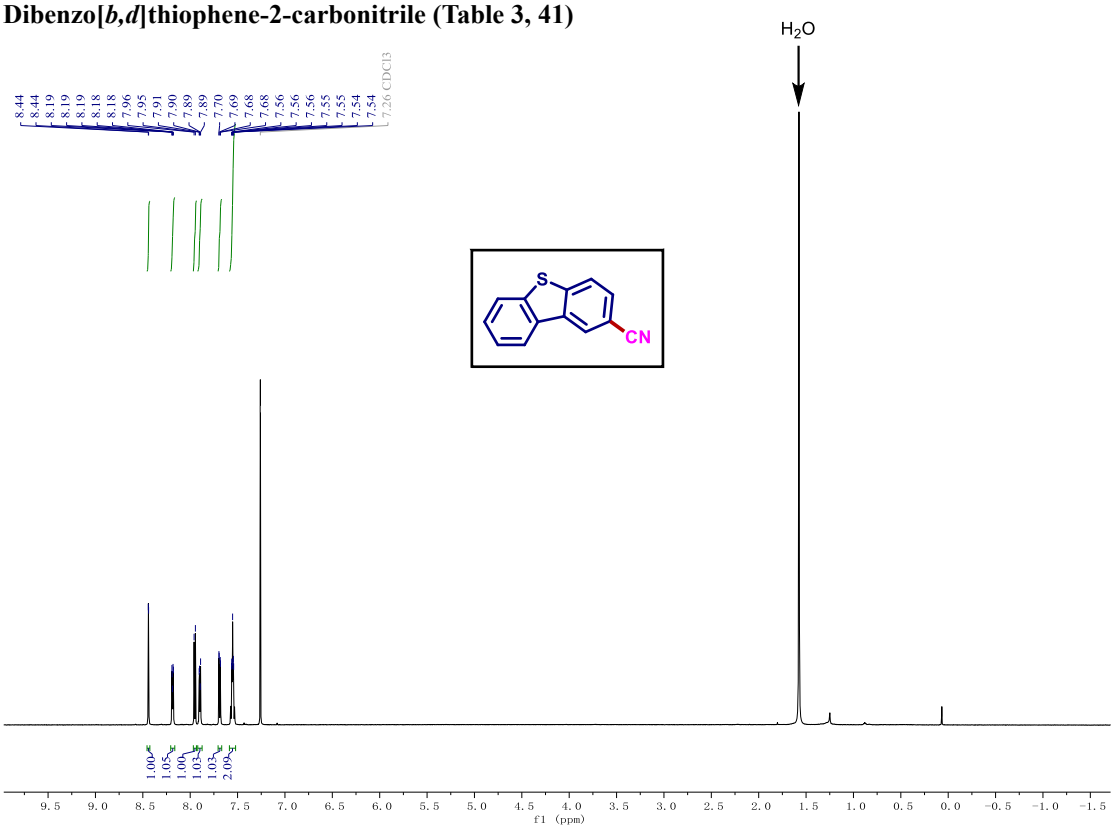
9,9-Dimethyl-9*H*-fluorene-3-carbonitrile (Table 3, 39)



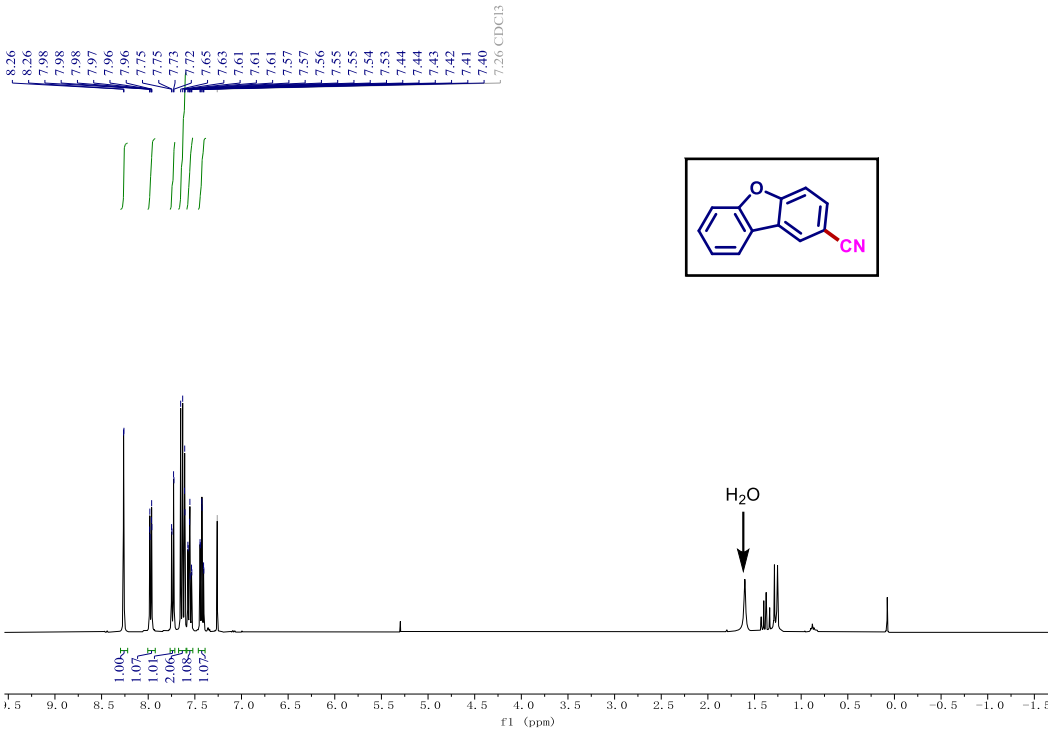
9-Phenyl-9*H*-carbazole-2-carbonitrile (Table 3, 40)



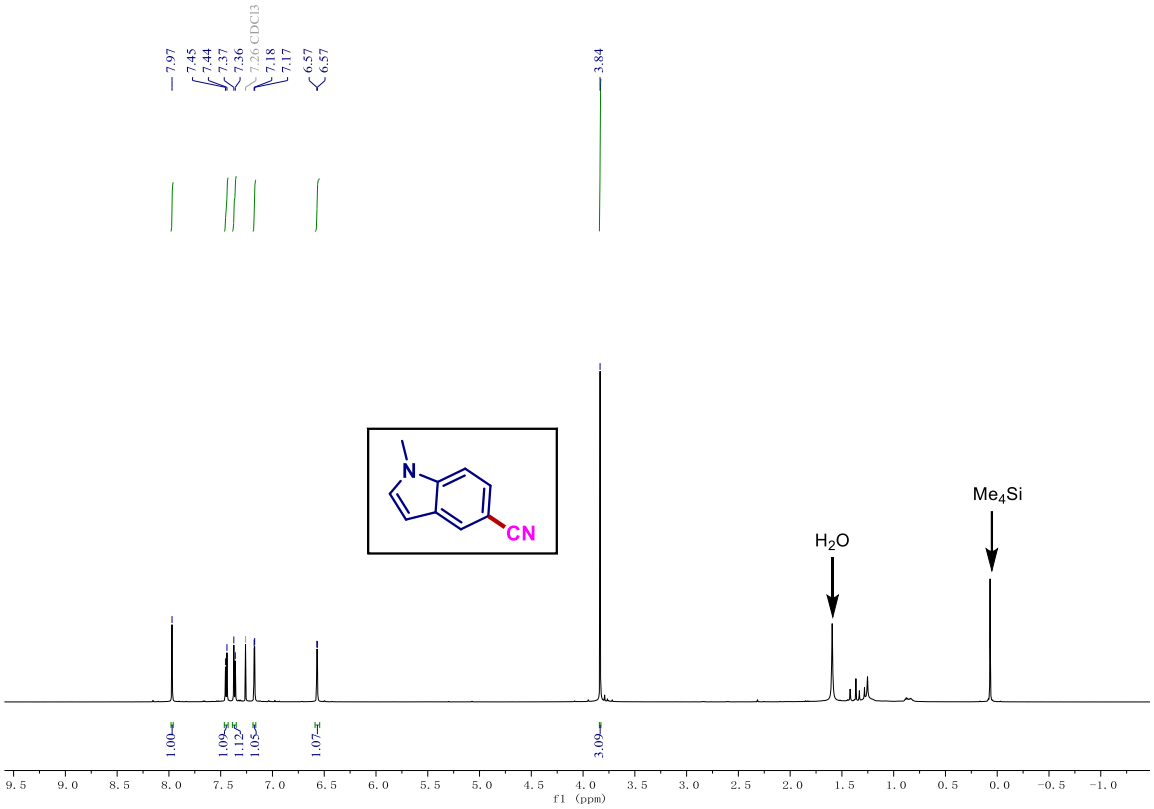
Dibenzo[*b*,*d*]thiophene-2-carbonitrile (Table 3, 41)



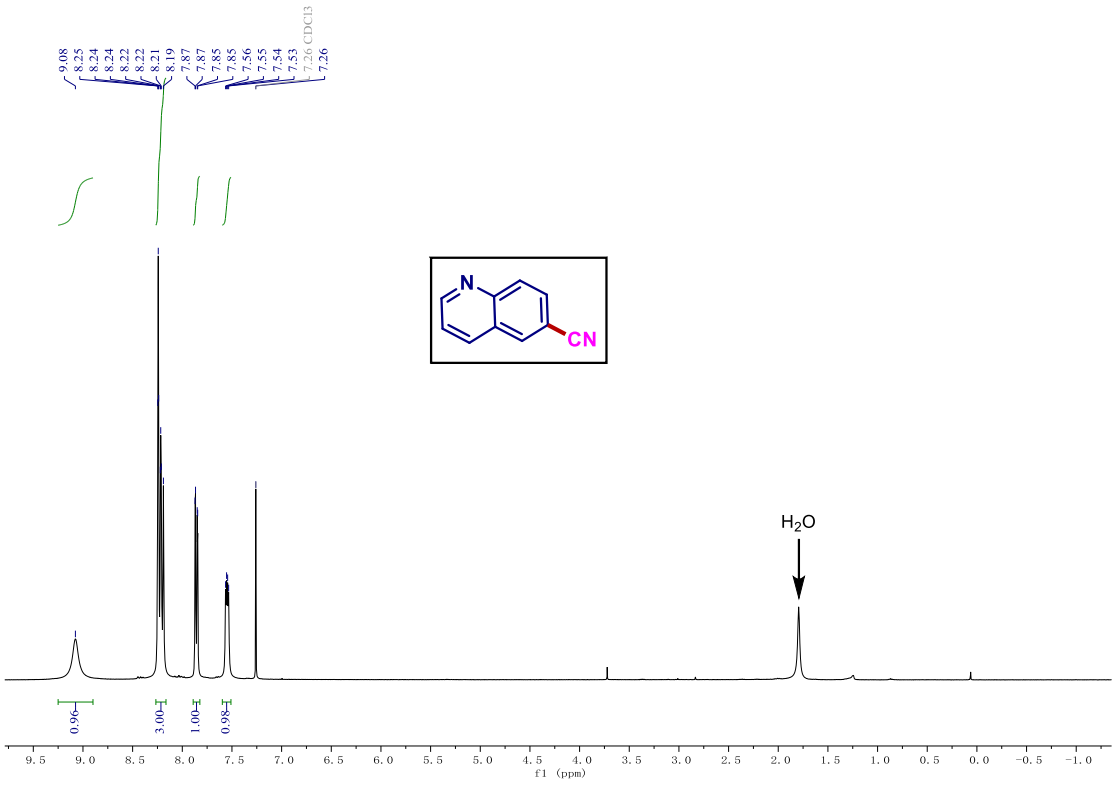
Dibenzo[*b*,*d*]furan-2-carbonitrile (Table 3, 42)



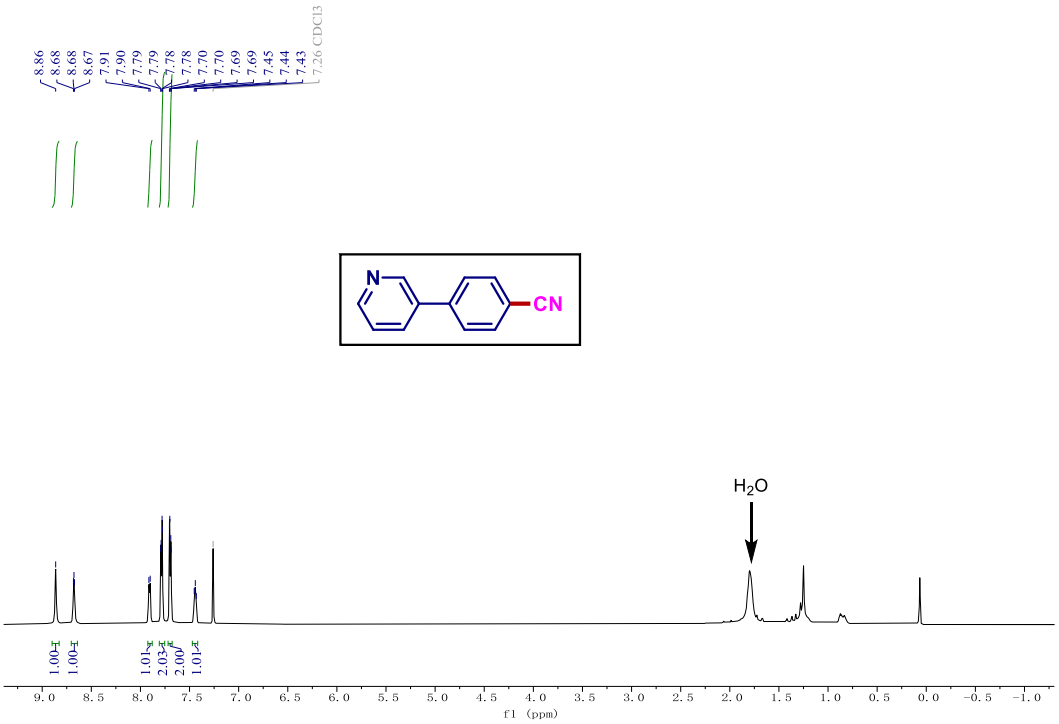
1-Methyl-1*H*-indole-5-carbonitrile (Table 3, 43)



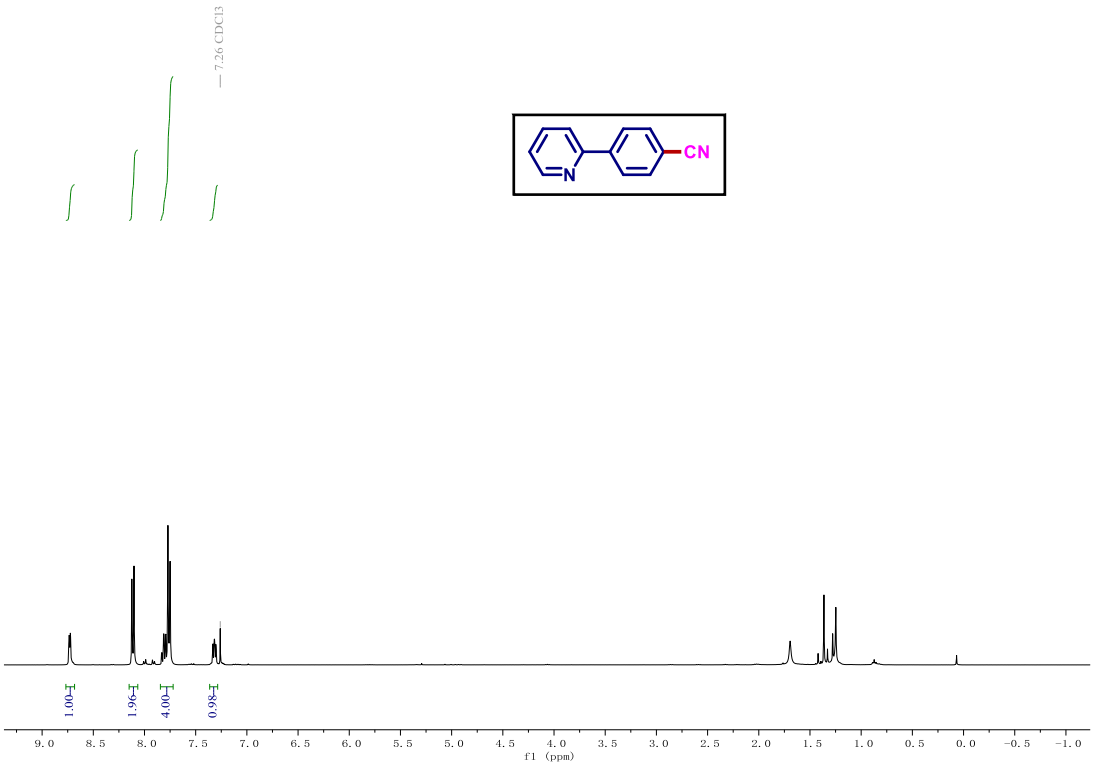
Quinoline-6-carbonitrile (Table 3, 44)



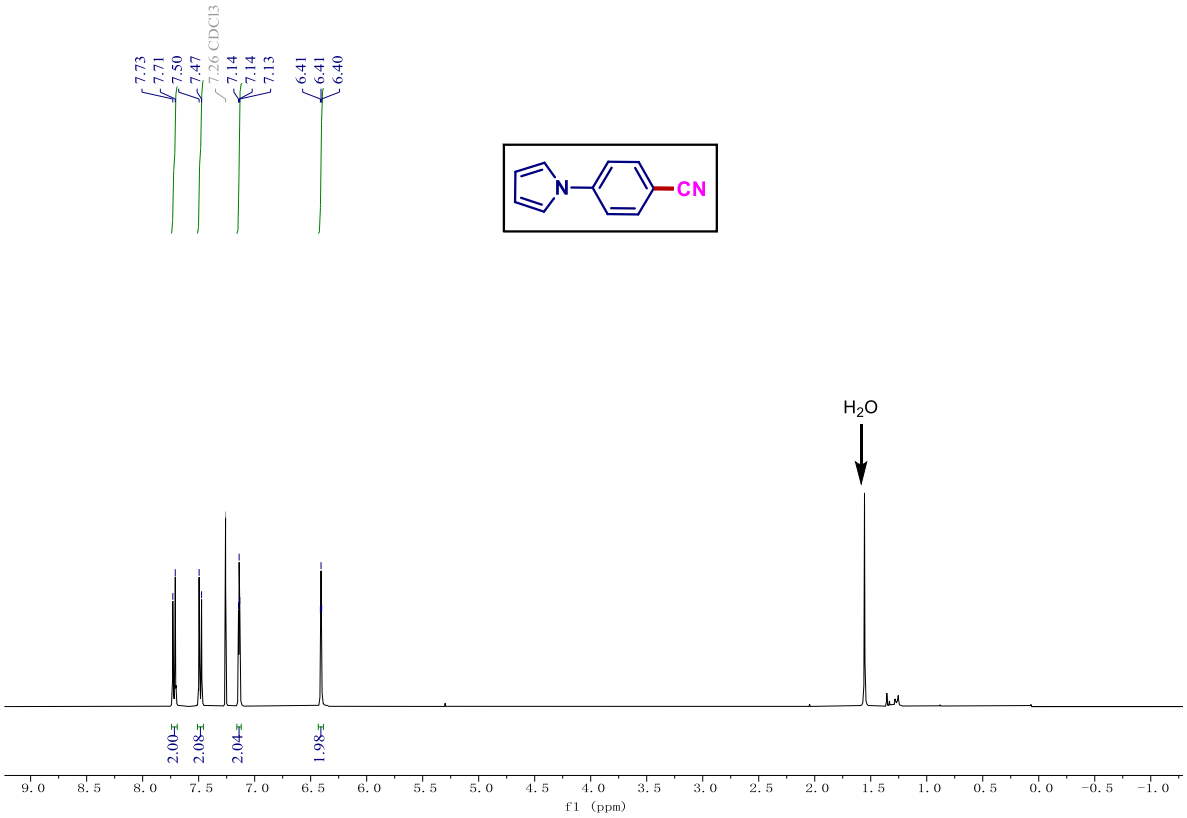
3-[4-(Trifluoromethyl)phenyl]pyridine (Table 3, 45)



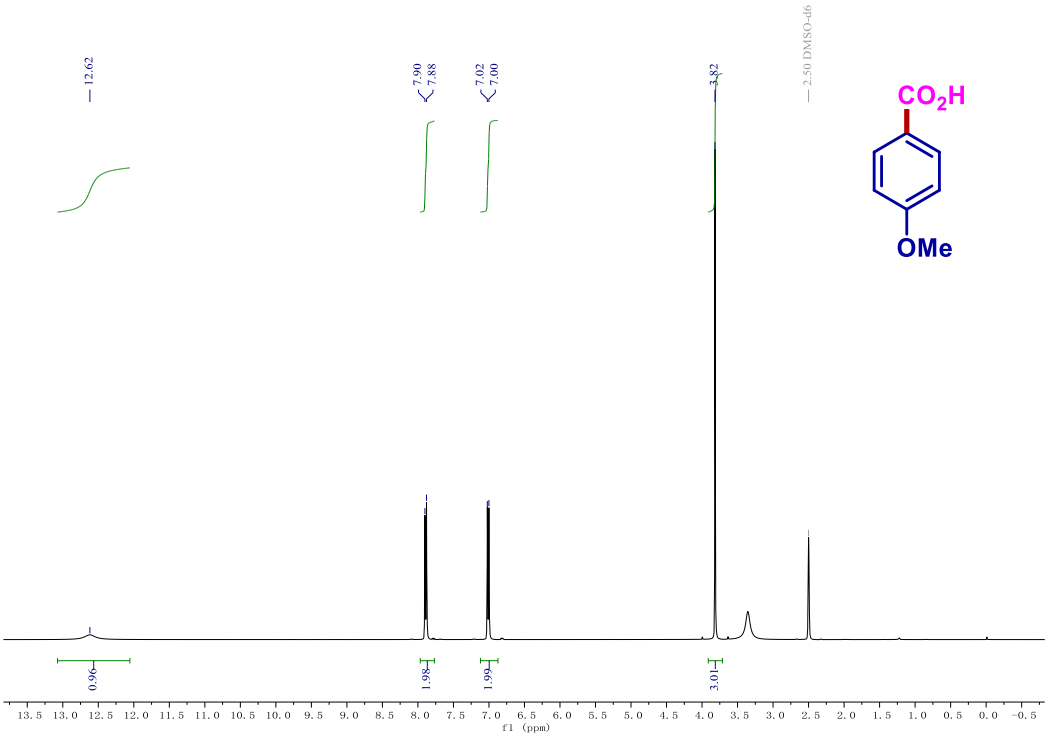
4-(Pyridin-2-yl)benzonitrile (Table 3, 46)



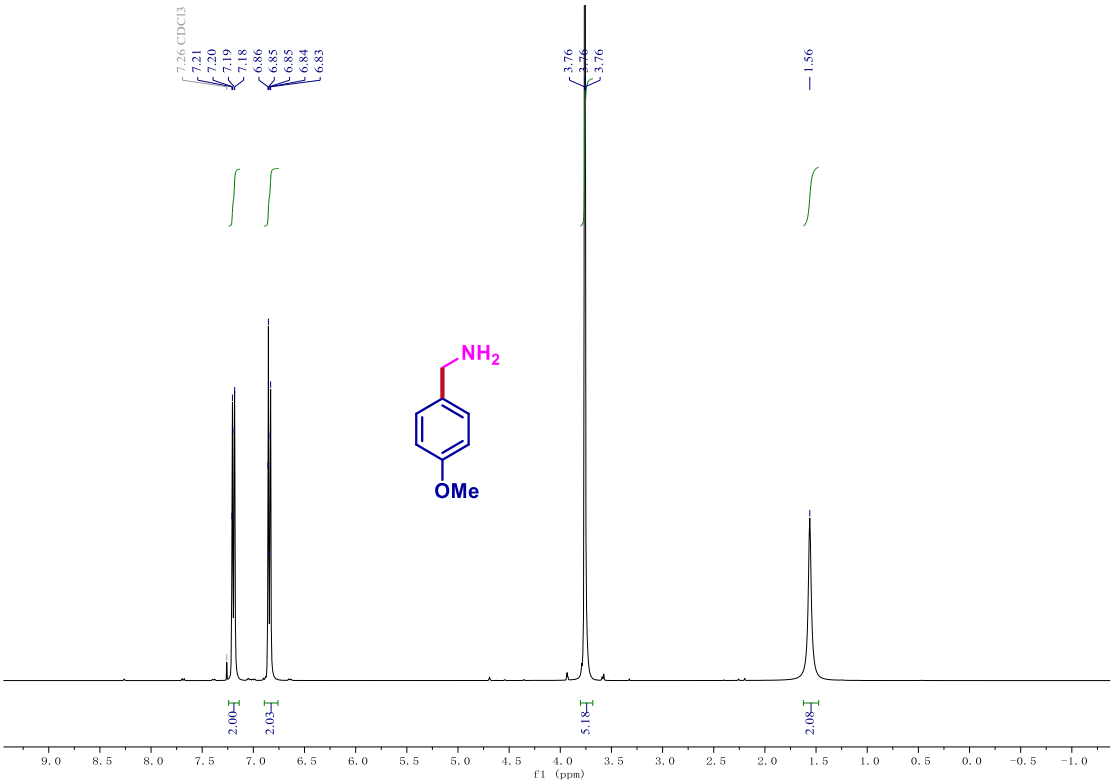
4-(1*H*-pyrrol-1-yl)benzonitrile (Table 3, 47)



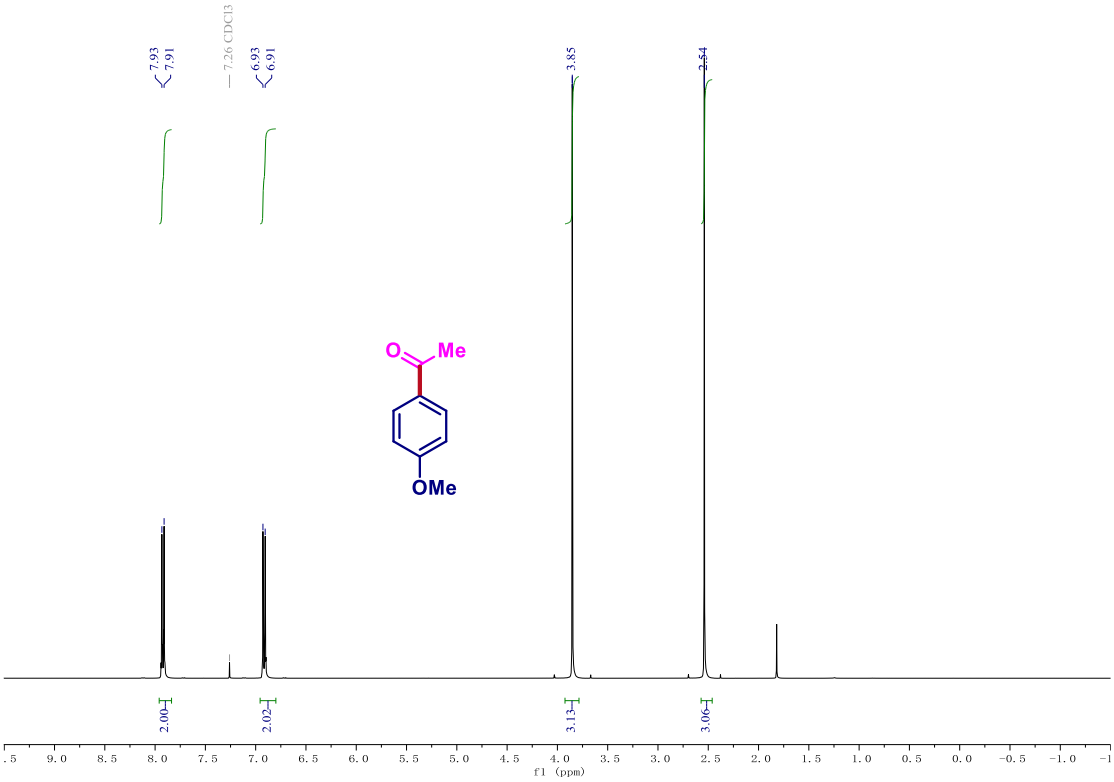
4-Methoxybenzoic acid (Scheme 2, 51)



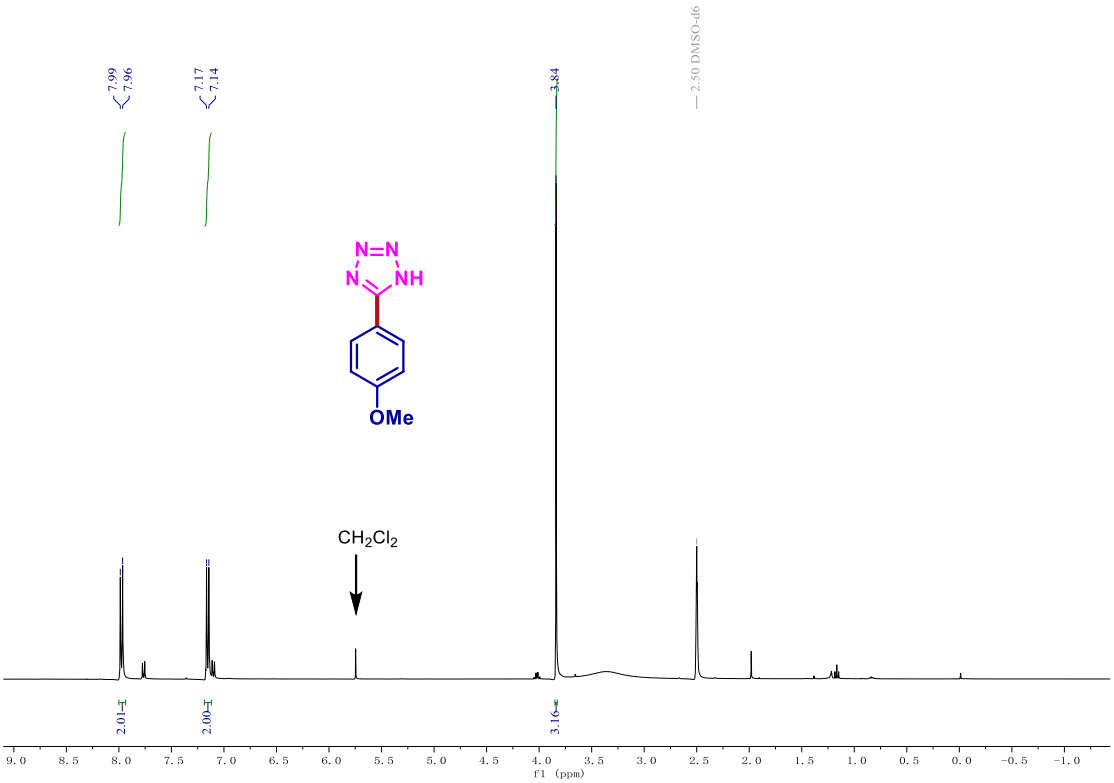
4-Methoxybenzylamine (Scheme 2, 52)



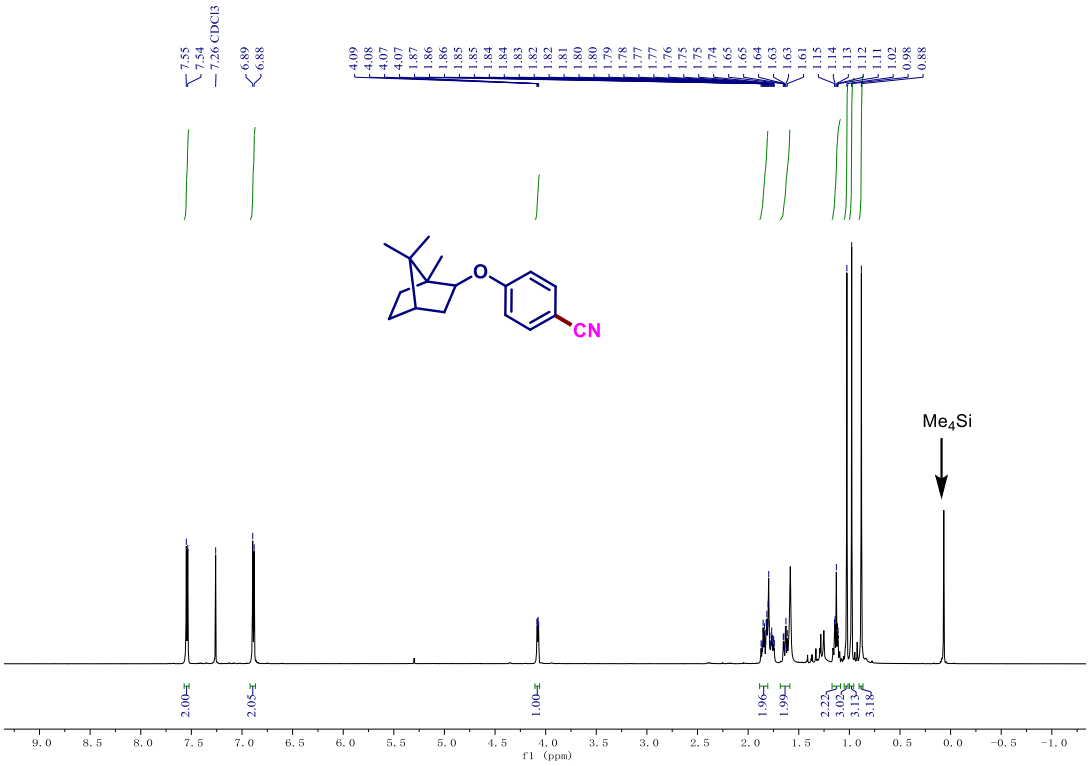
4'-Methoxyacetophenone (Scheme 2, 53)

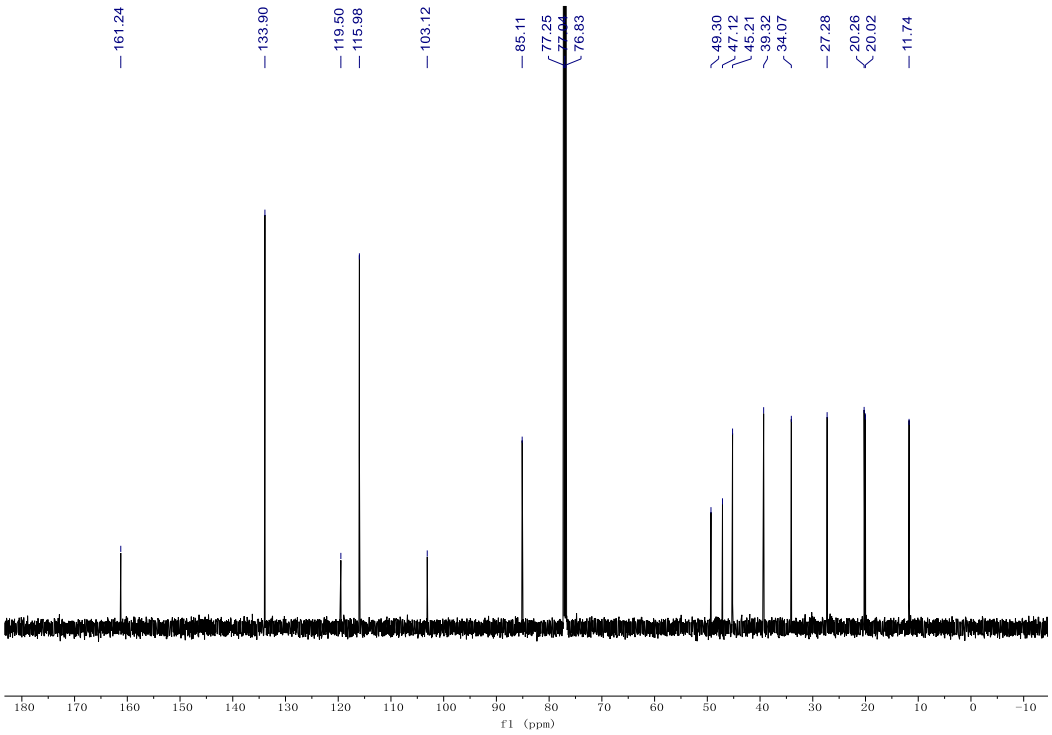


5-(4-Methoxyphenyl)-2*H*-Tetrazole (Scheme 2, 54, containing small amount of impurity)

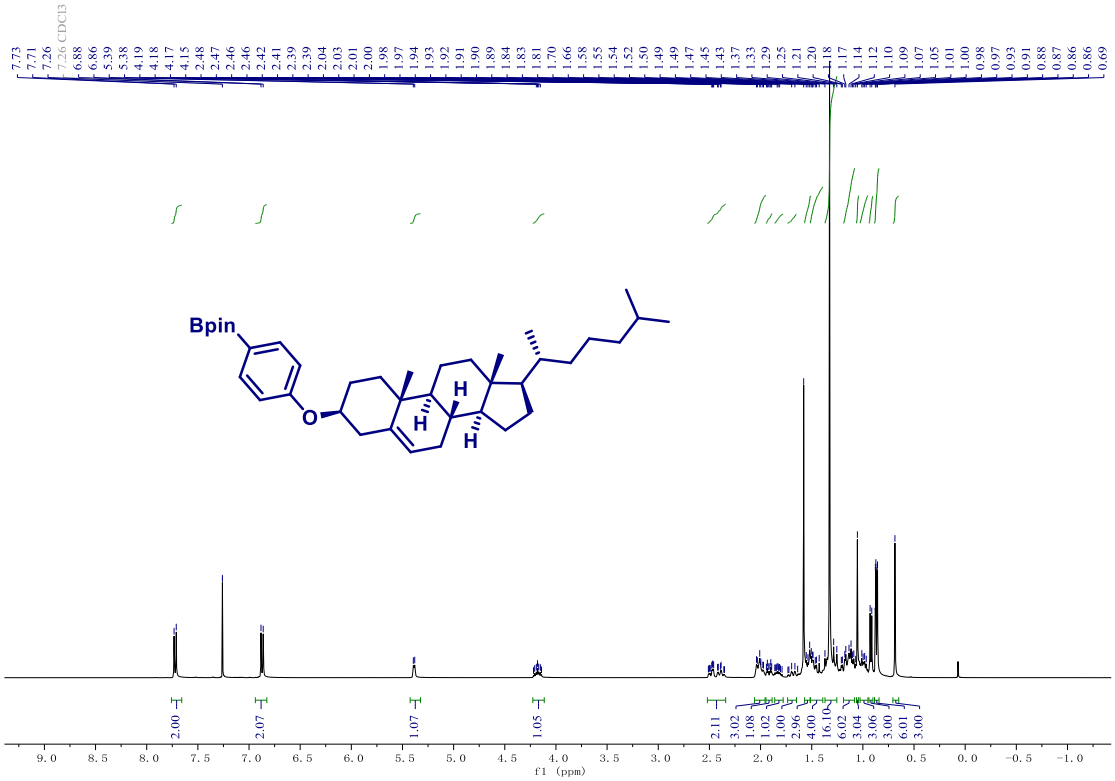


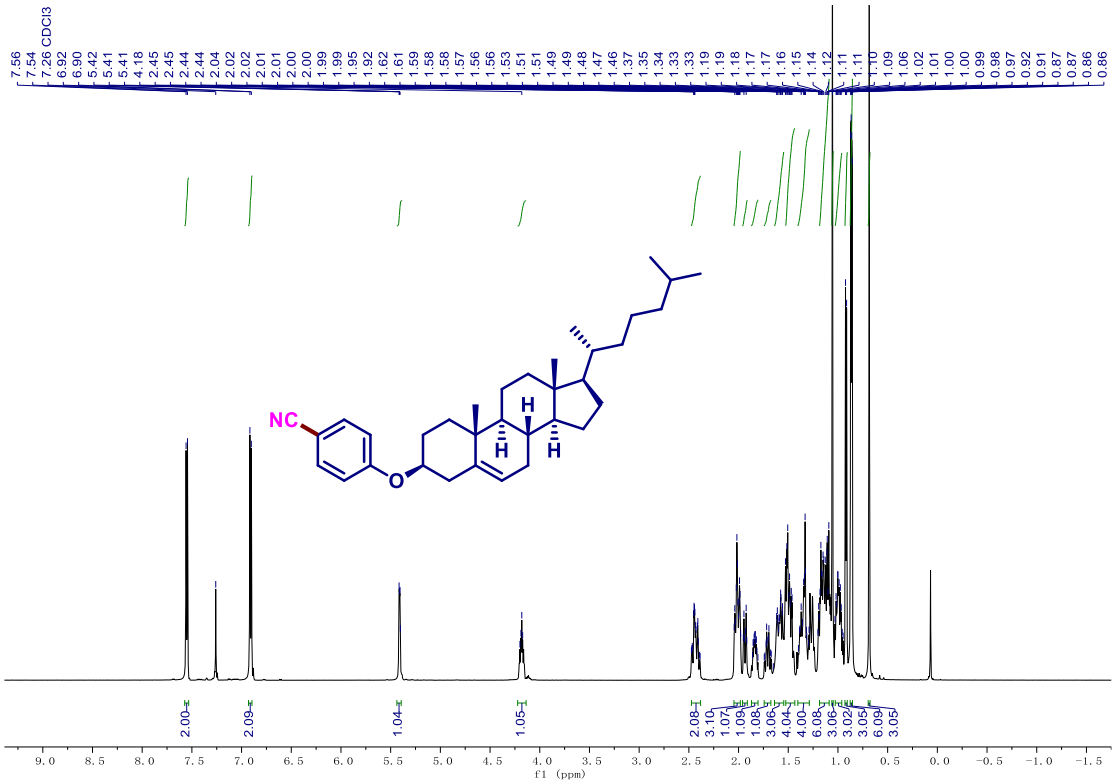
Functionalization of isoborneol (Scheme 2, 55)

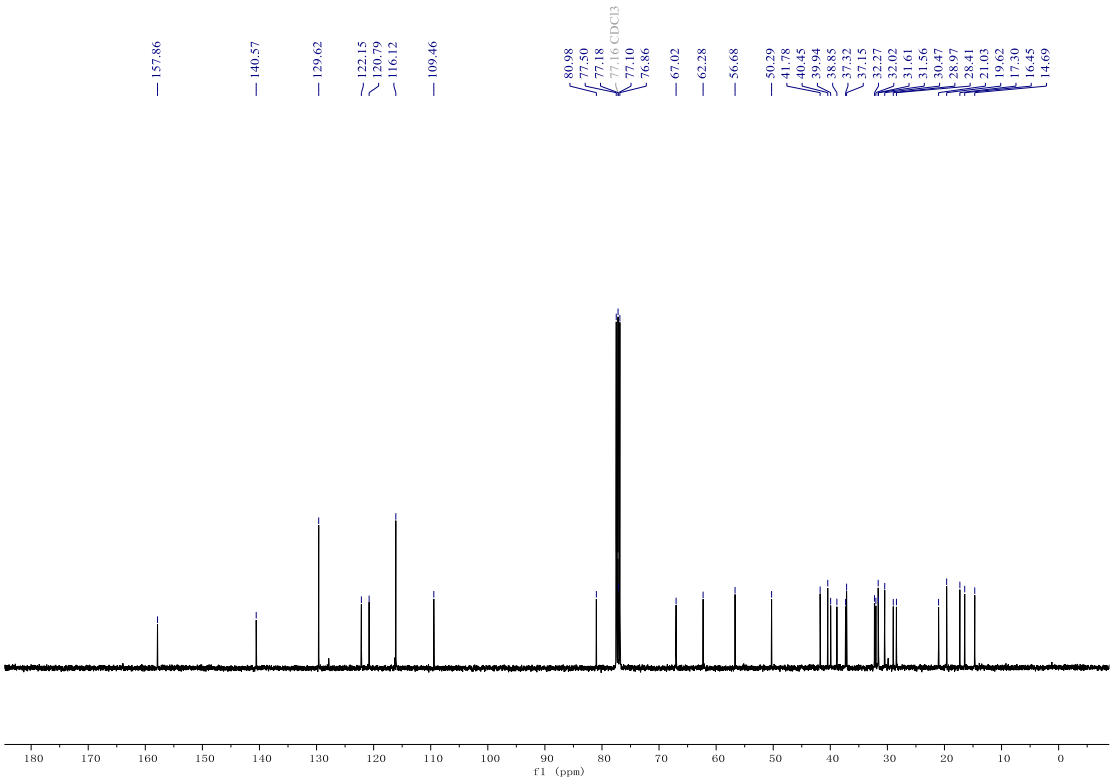




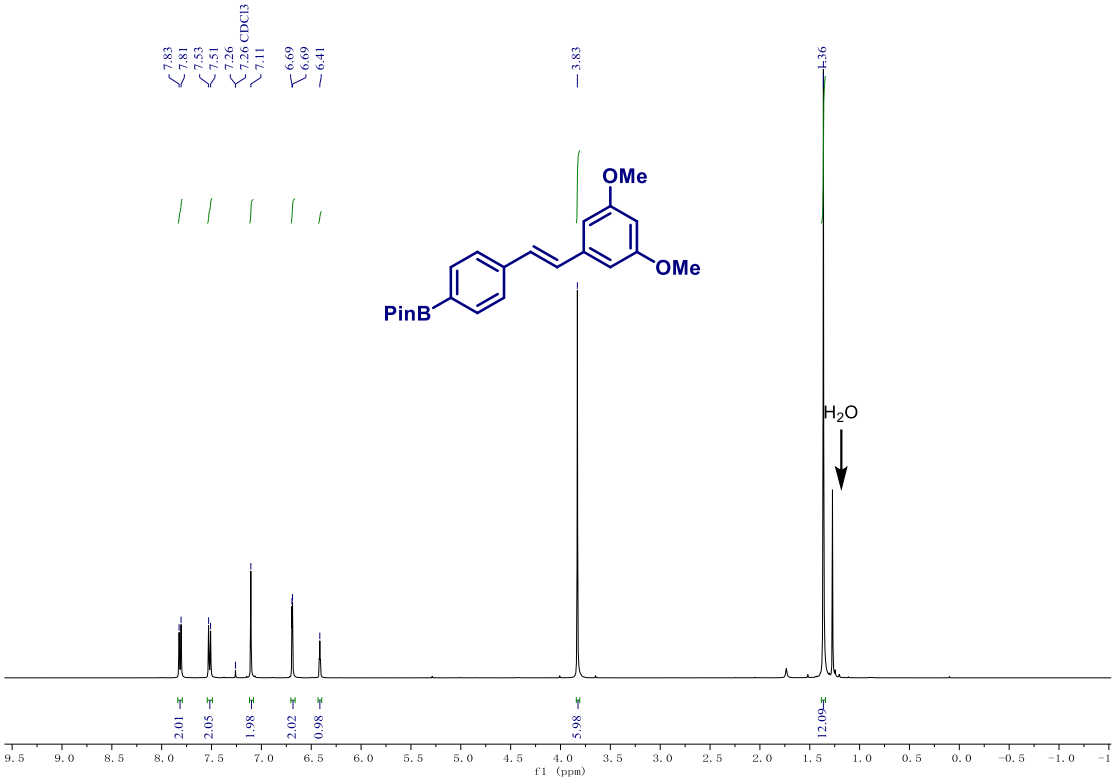
Functionalization of cholesterol (Scheme 2, 56)

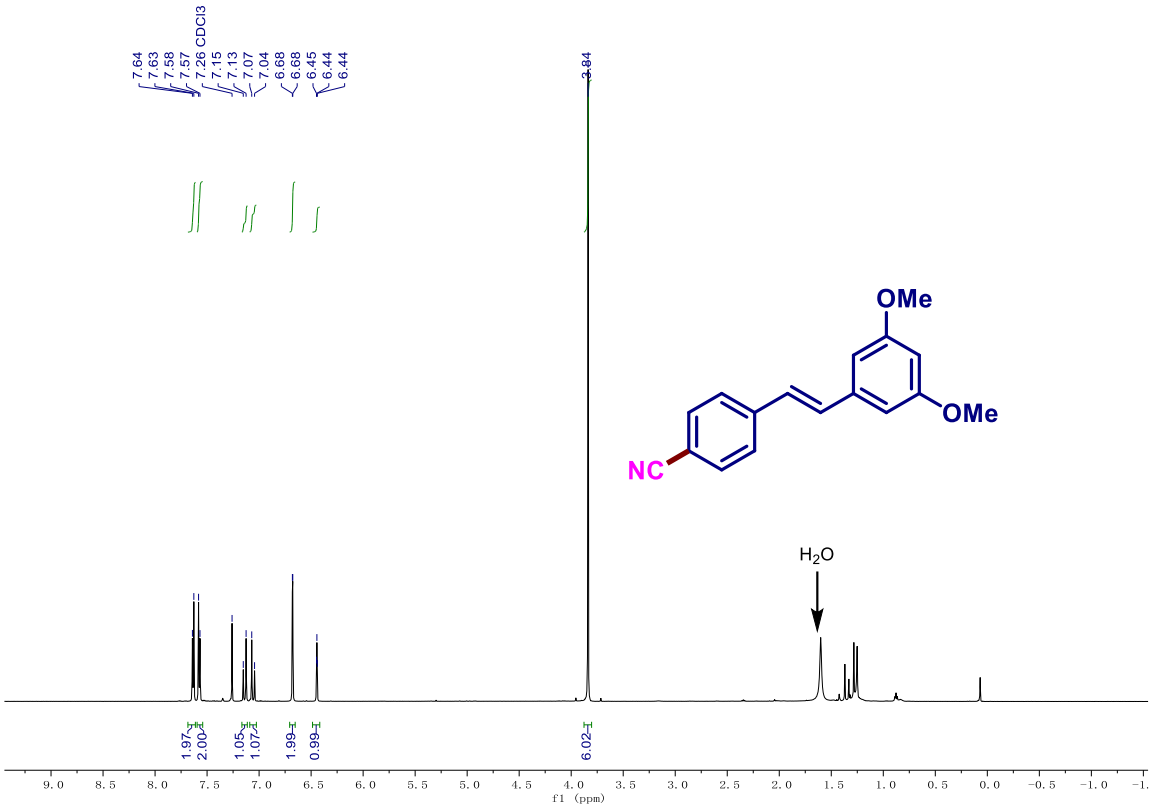




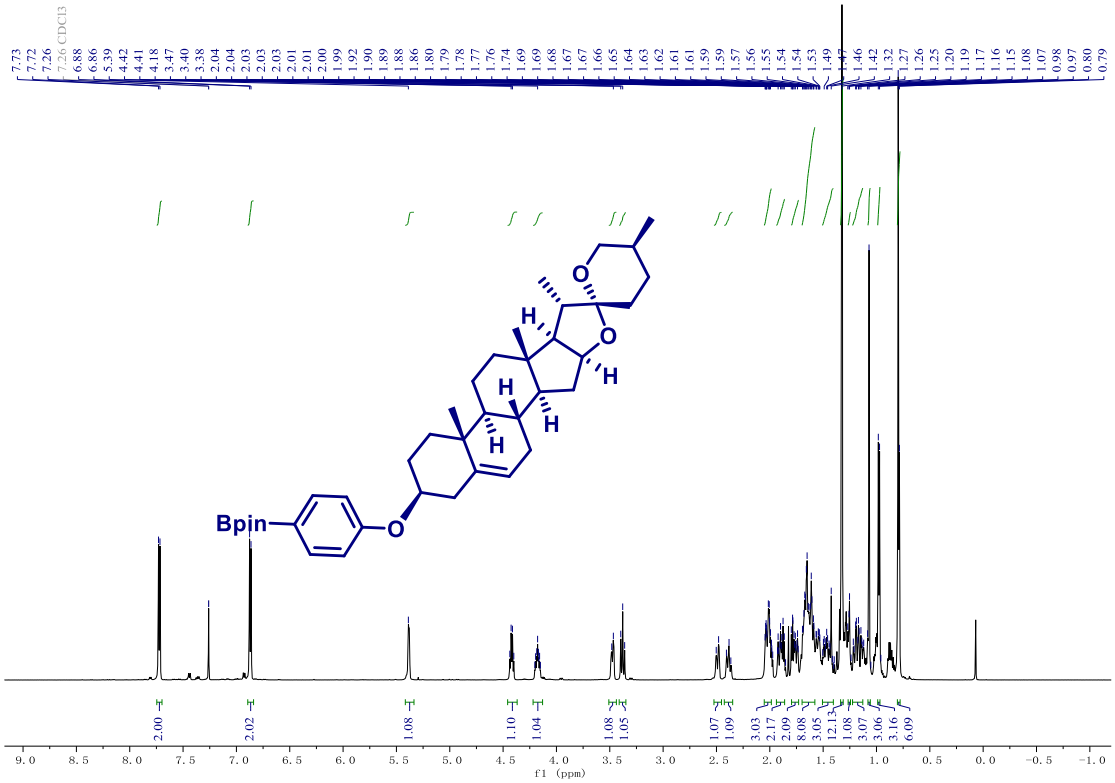

157.86
140.57
129.62
122.15
120.79
116.12
109.46
80.98
77.50
77.18
77.16 CDCl3
77.10
76.86
67.02
62.28
56.68
50.29
41.78
40.45
39.94
38.85
37.32
37.15
32.27
32.02
31.61
31.56
30.47
28.97
28.41
21.03
19.62
17.30
16.45
14.69
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

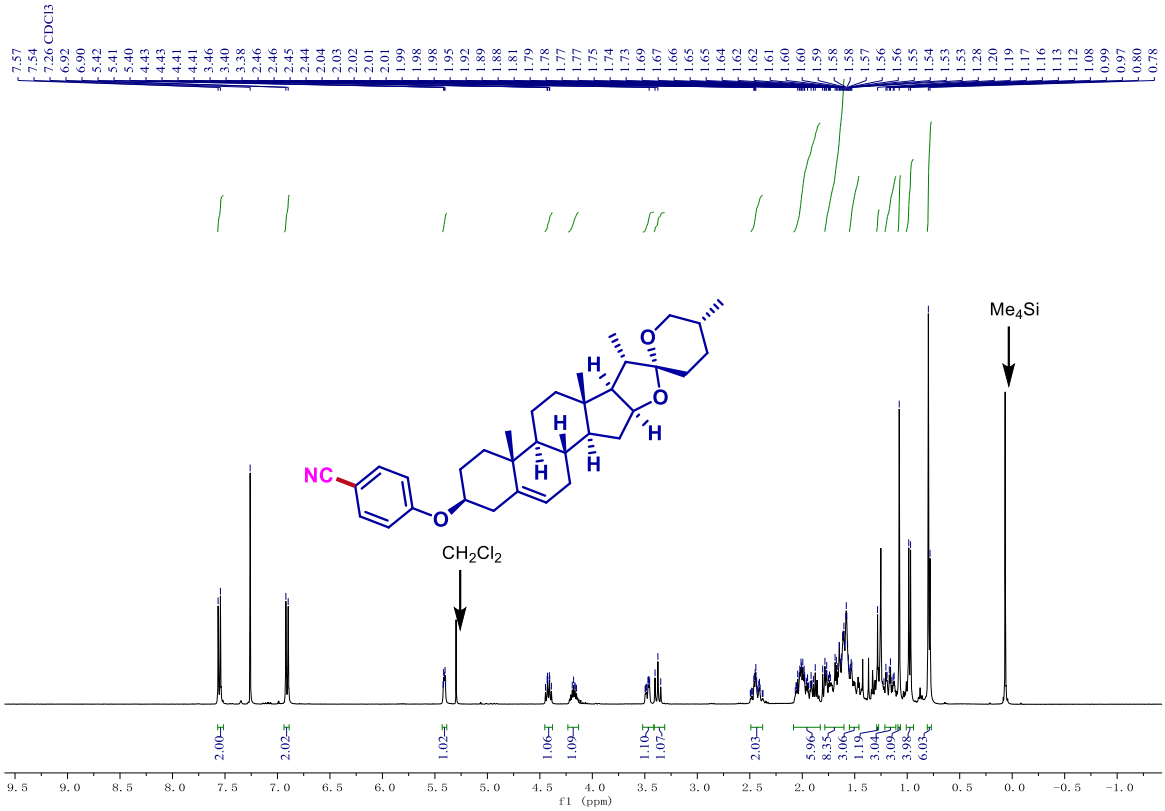
Functionalization of pterostilbene (Scheme 2, 57)

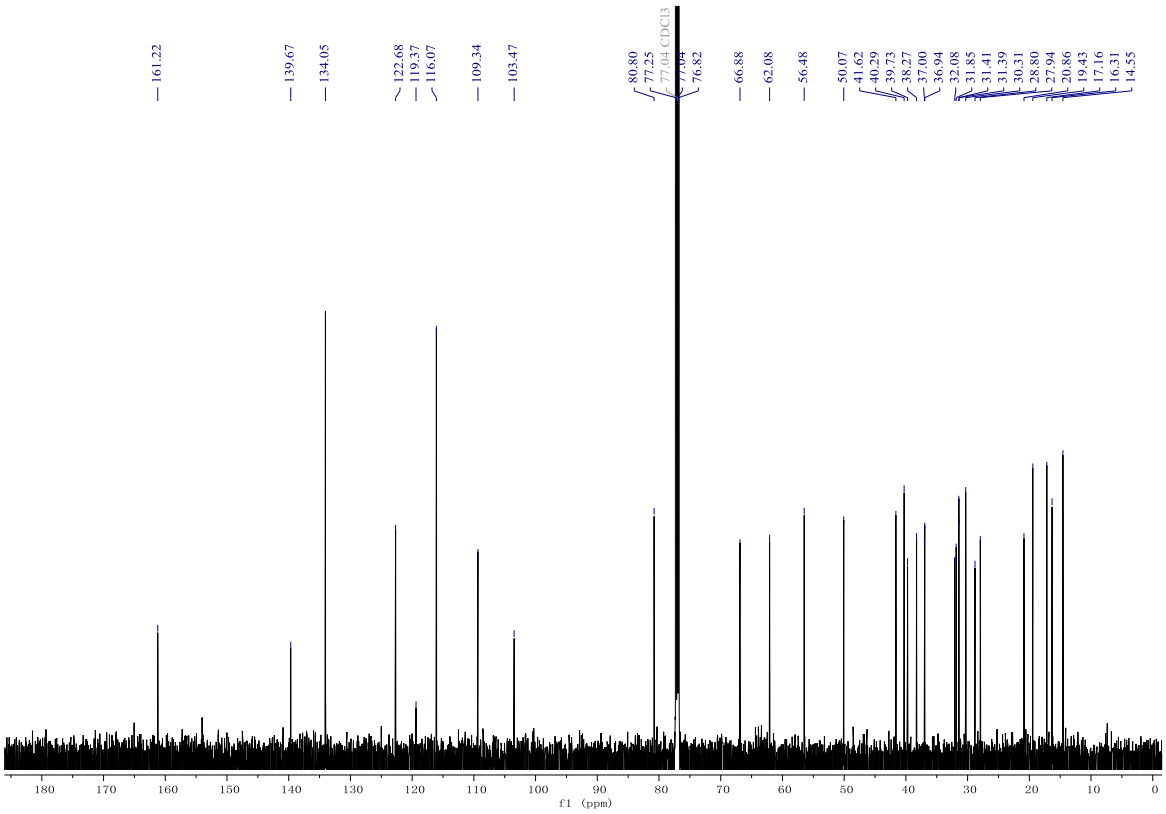




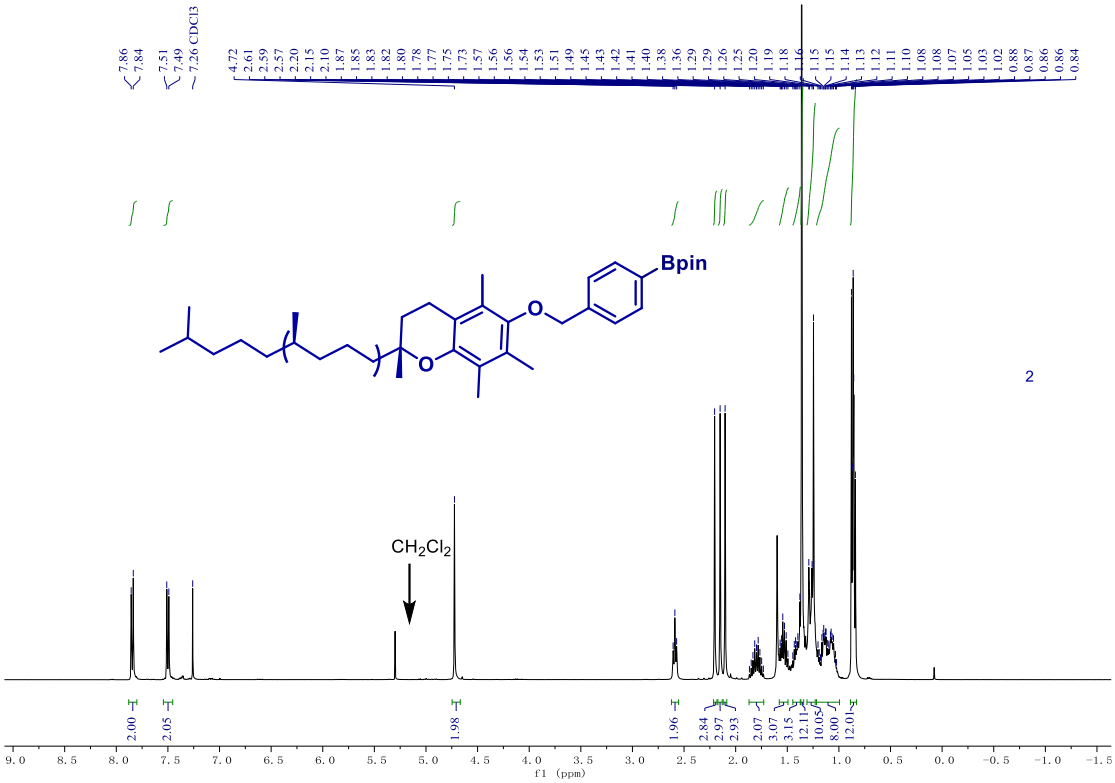
Functionalization of diosgenin (Scheme 2, 58)

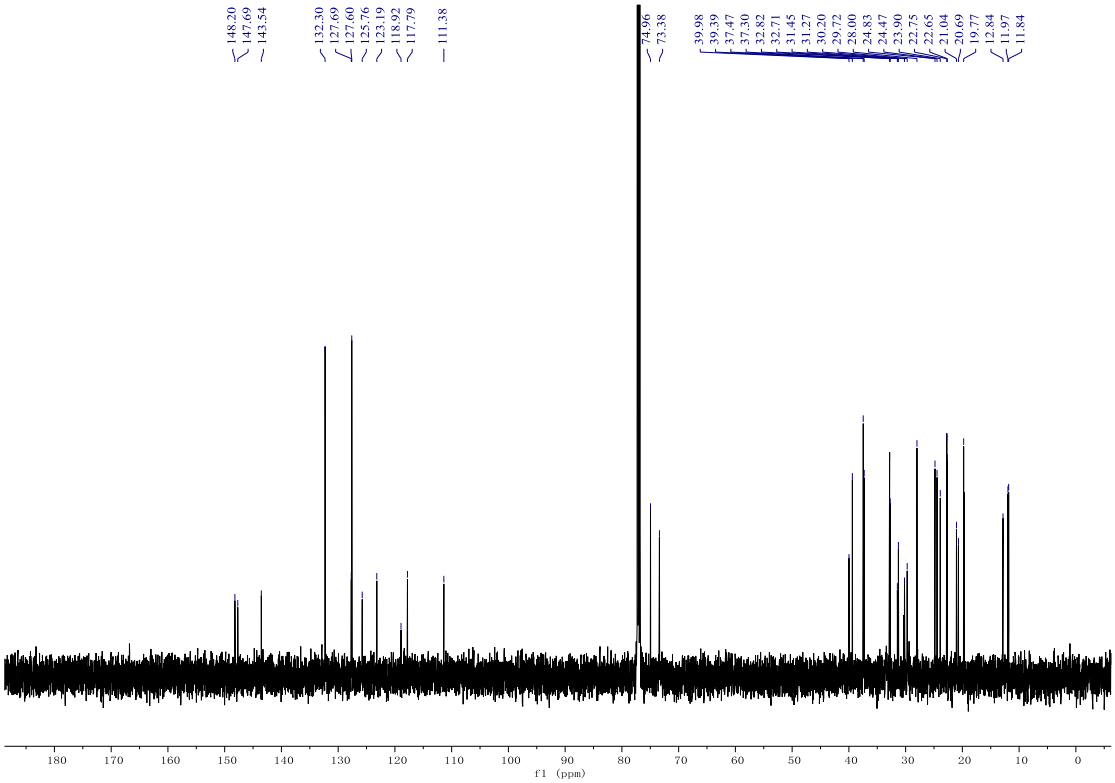


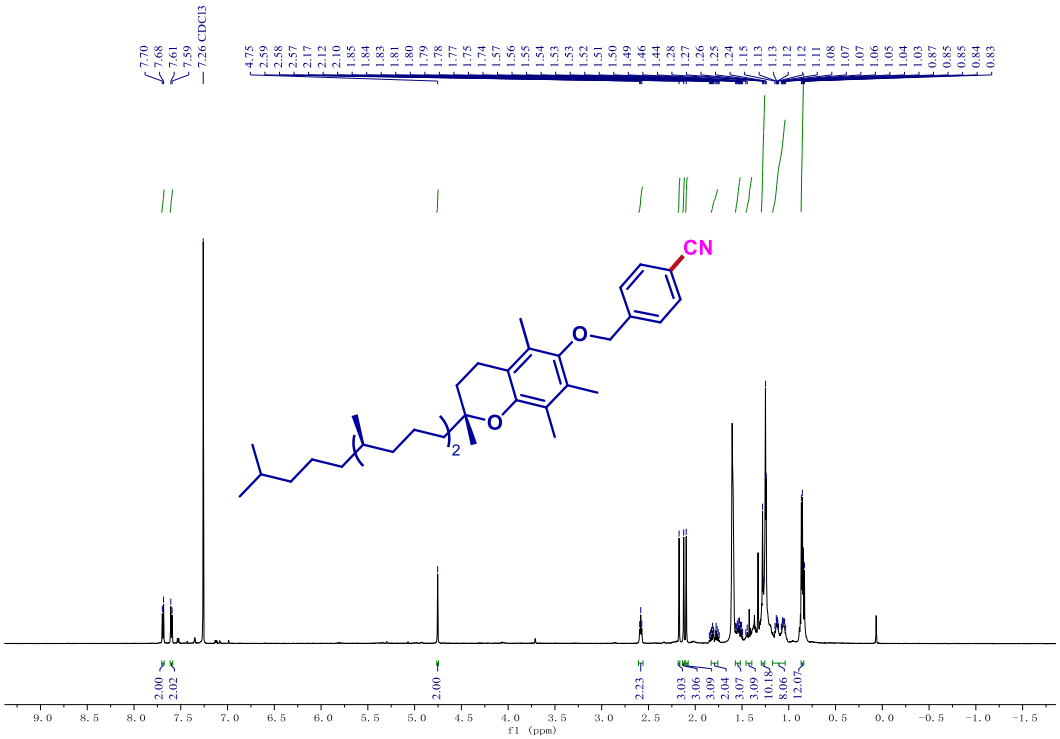


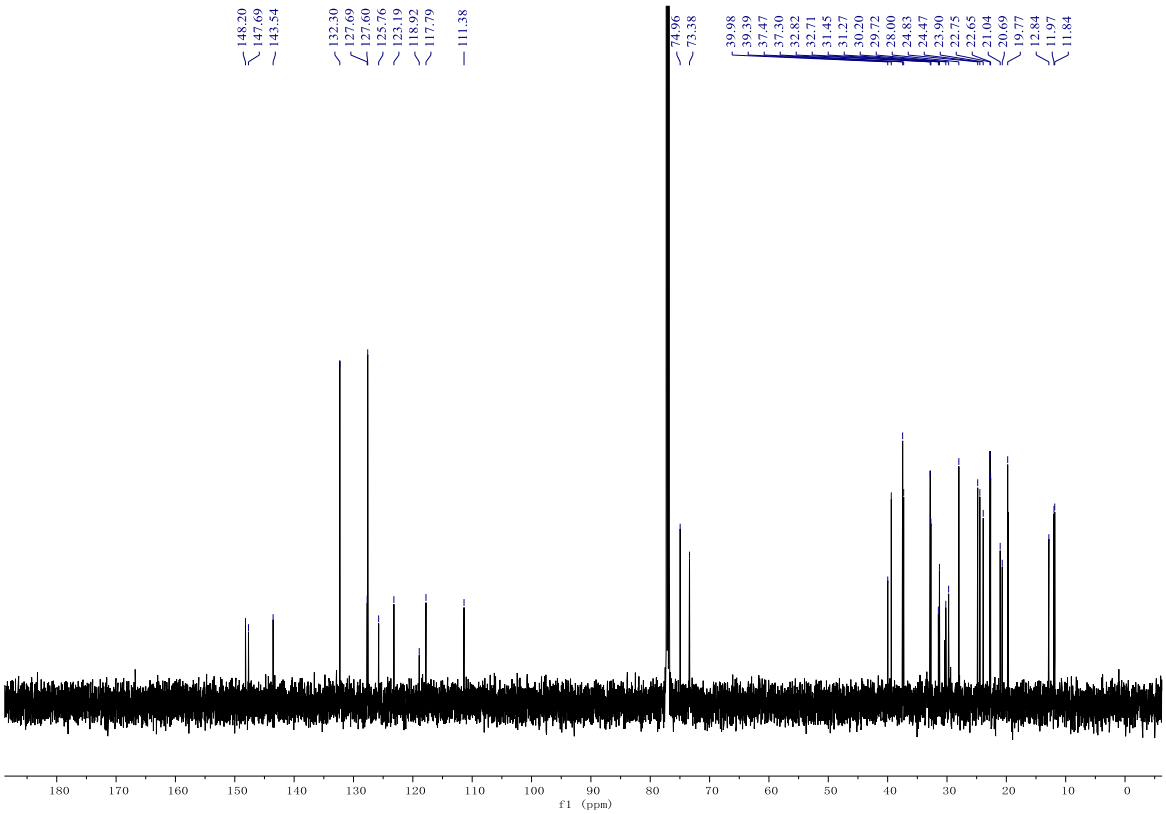

161.22
139.67
134.05
122.68
119.37
116.07
109.34
103.47
80.80
77.25
77.04 CDCl3
76.82
66.88
62.08
56.48
50.07
41.62
40.29
39.73
38.27
37.00
36.94
32.08
31.85
31.41
31.39
30.31
28.80
27.94
20.86
19.43
17.16
16.31
14.55
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Functionalization of vitamin E (Scheme 2, 59)

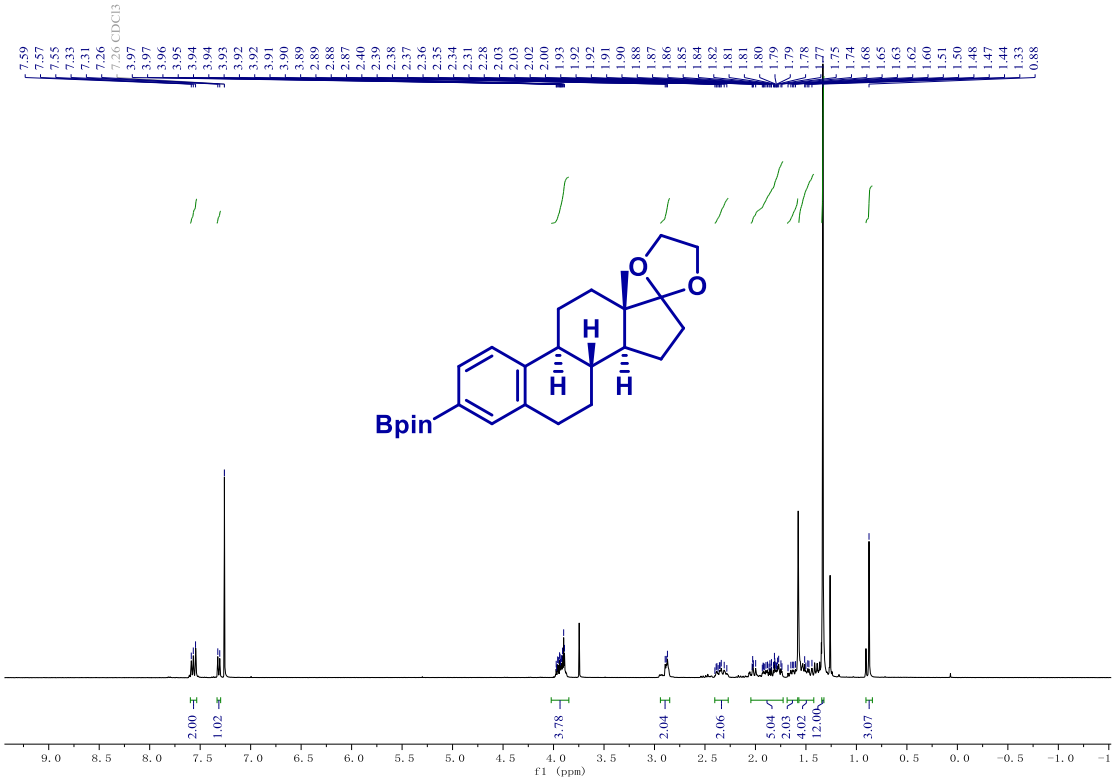


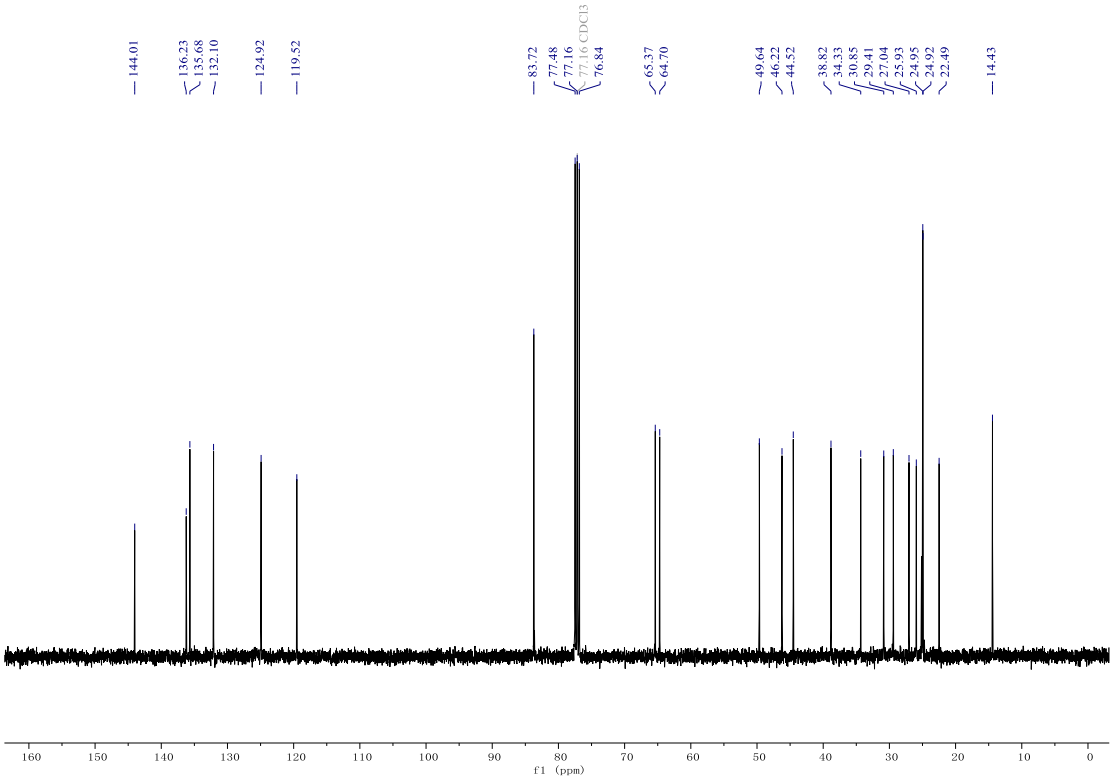


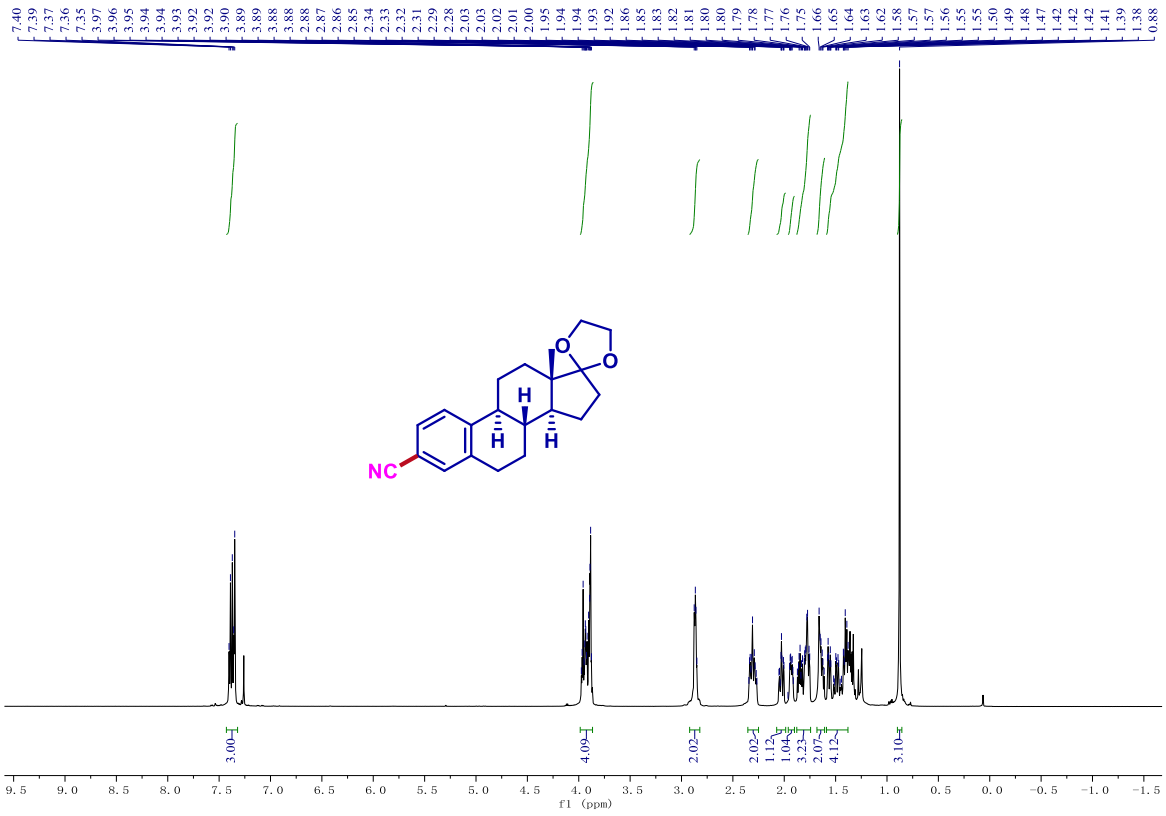

7.70
7.68
7.61
7.59
7.26 CDCl3
4.75
2.59
2.58
2.57
2.17
2.12
2.10
1.85
1.84
1.83
1.81
1.80
1.79
1.78
1.77
1.75
1.74
1.57
1.56
1.55
1.54
1.53
1.53
1.52
1.51
1.50
1.49
1.46
1.44
1.28
1.27
1.26
1.25
1.24
1.15
1.13
1.13
1.12
1.11
1.08
1.07
1.07
1.06
1.05
1.04
1.03
0.87
0.85
0.85
0.84
0.83
CN
O
O
2
2.00
2.02
2.00
2.23
3.03
3.06
3.09
2.04
3.07
3.09
10.18
8.06
12.07
f1 (ppm)

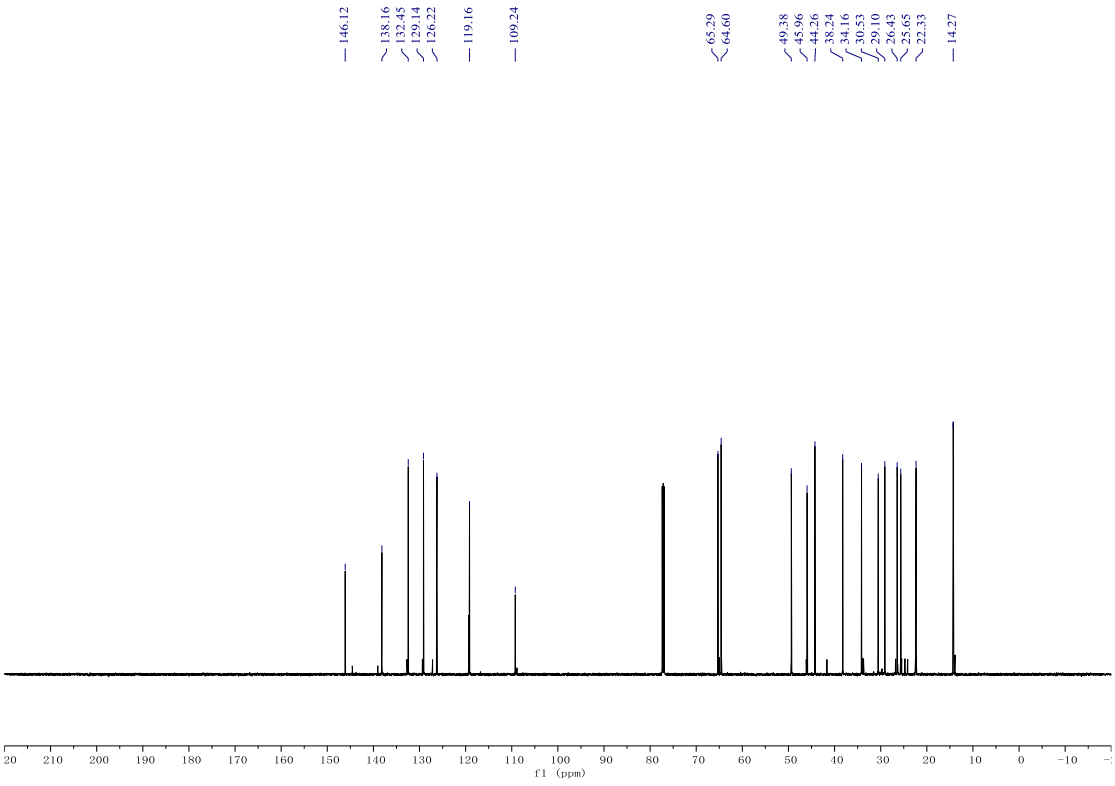

148.20
147.69
143.54
132.30
127.69
127.60
125.76
123.19
118.92
117.79
111.38
74.96
73.38
39.98
39.39
37.47
37.30
32.82
32.71
31.45
31.27
30.20
29.72
28.00
24.83
24.47
23.90
22.75
22.65
21.04
20.69
19.77
12.84
11.97
11.84
f1 (ppm)

Functionalization of estrone (Scheme 2, 60)

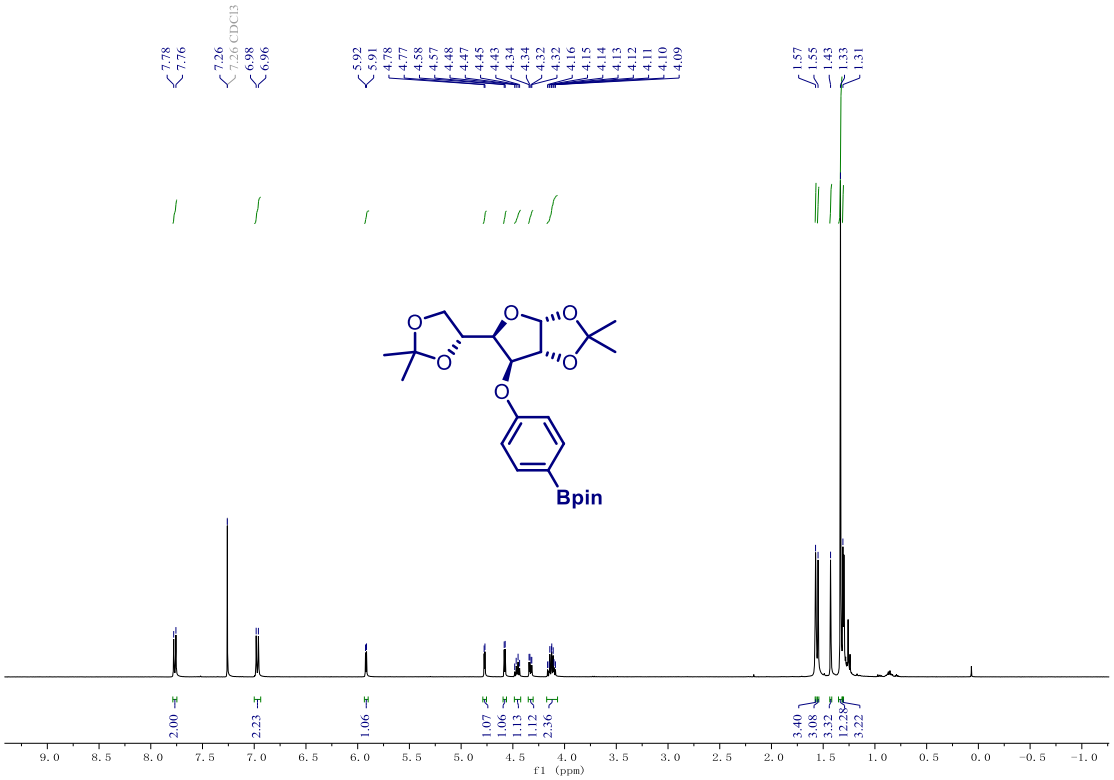


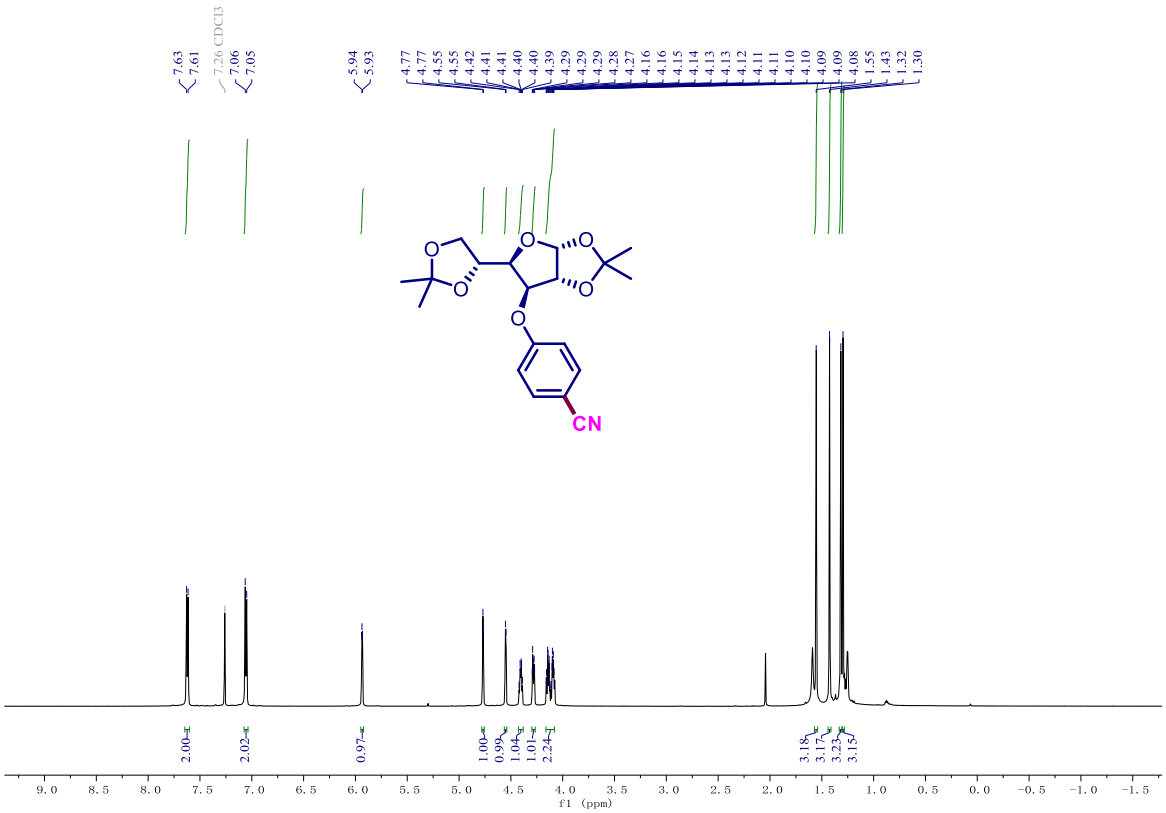



7.40 7.39 7.37 7.36 7.35 3.97 3.96 3.95 3.94 3.94 3.93 3.92 3.92 3.90 3.89 3.89 3.88 3.88 2.88 2.87 2.86 2.85 2.34 2.33 2.32 2.31 2.29 2.28 2.03 2.03 2.02 2.01 2.00 1.95 1.94 1.94 1.93 1.92 1.86 1.85 1.83 1.82 1.81 1.80 1.80 1.79 1.78 1.77 1.76 1.75 1.66 1.65 1.64 1.63 1.62 1.58 1.57 1.57 1.56 1.55 1.55 1.50 1.49 1.48 1.47 1.42 1.42 1.42 1.41 1.39 1.38 0.88
O
O
H
H
H
NC
3.00
4.09
2.02
2.02
1.12
1.04
3.23
2.07
4.12
3.10
f1 (ppm)

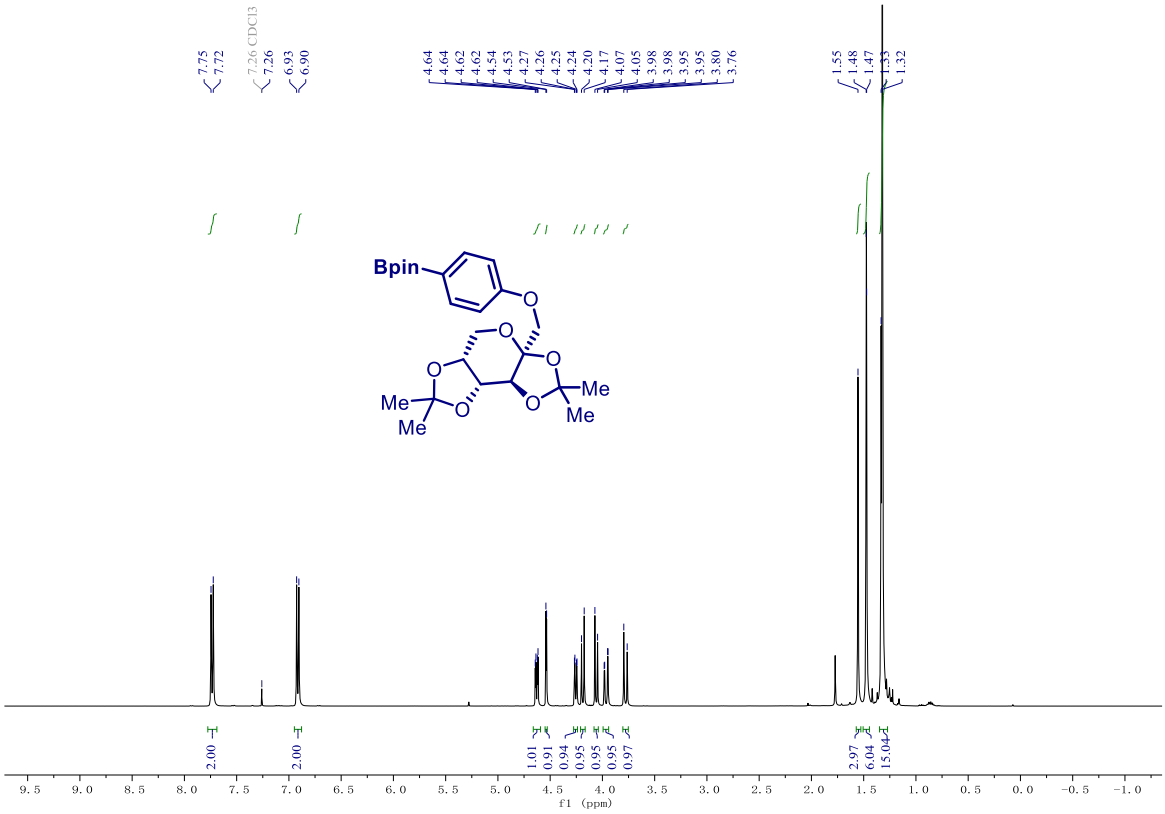

146.12
138.16
132.45
129.14
126.22
119.16
109.24
65.29
64.60
49.38
45.96
44.26
38.24
34.16
30.53
29.10
26.43
25.65
22.33
14.27
f1 (ppm)

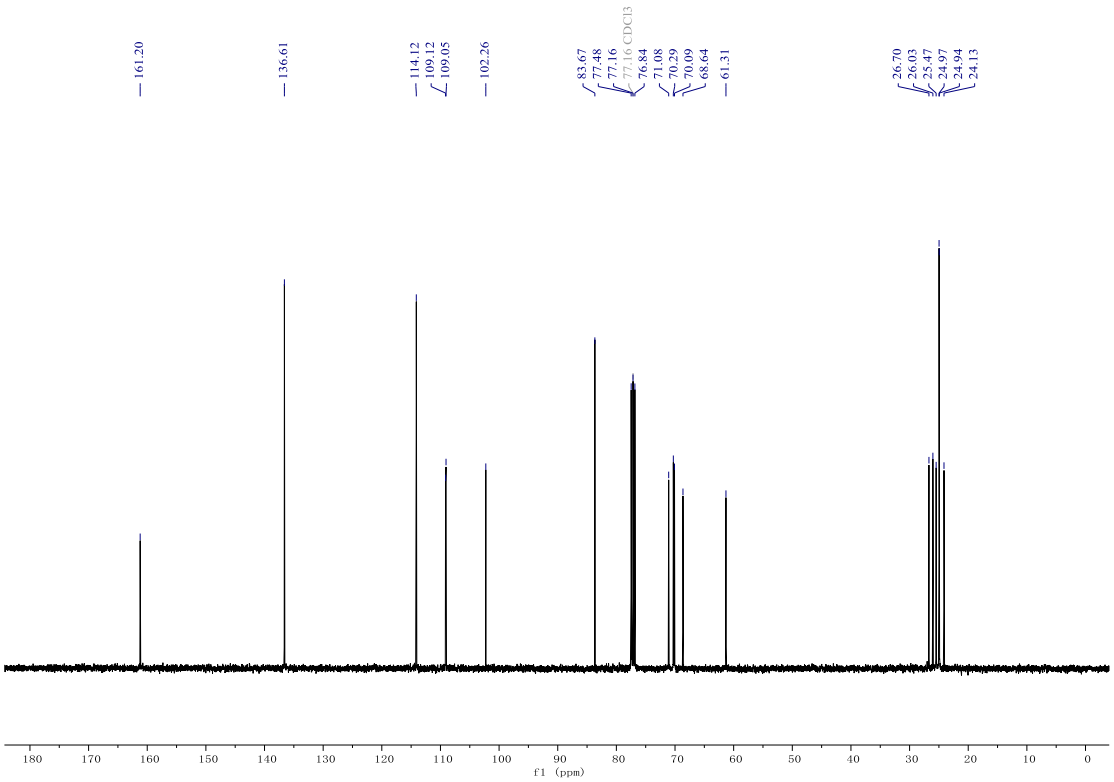
Functionalization of diacetone-D-glucose (Scheme 2, 61)

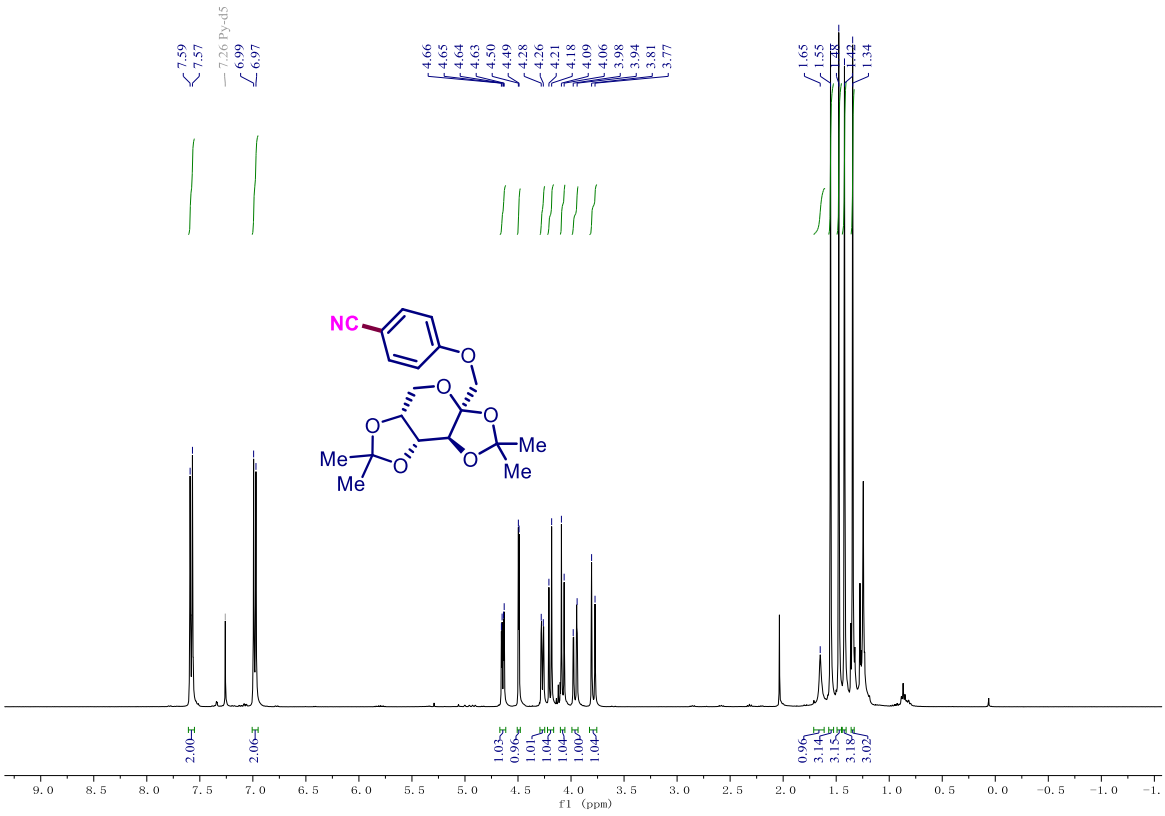


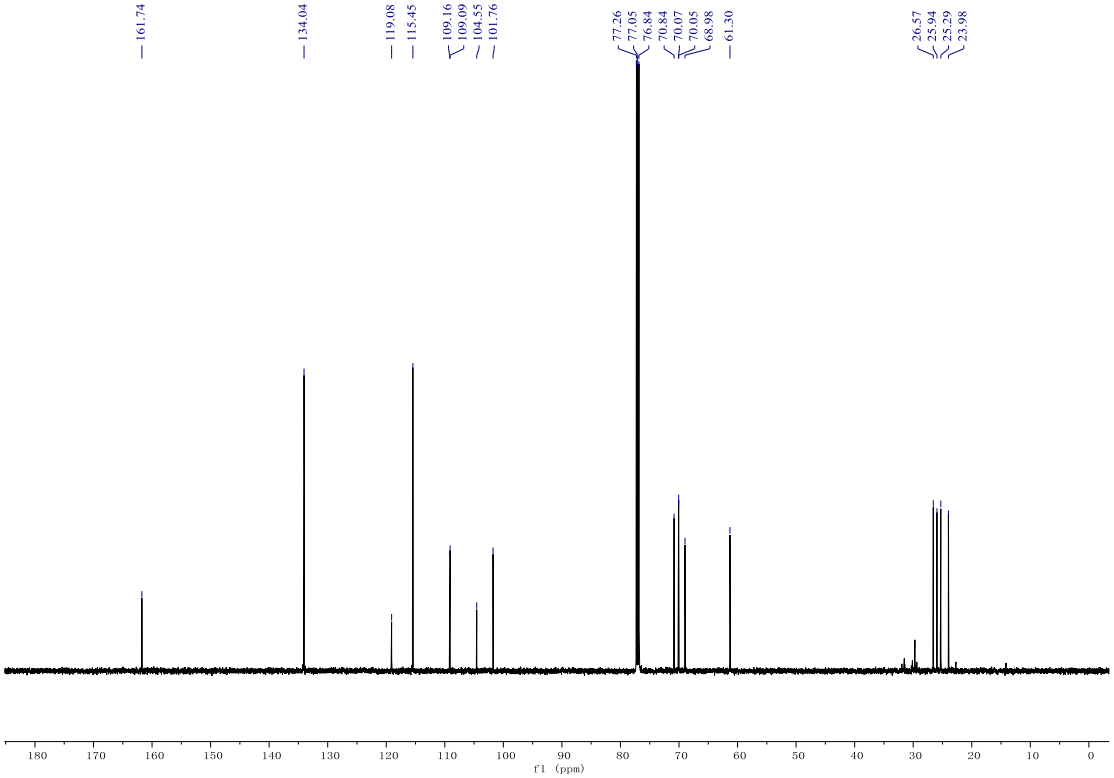


Functionalization of diacetonefructose (Scheme 2, 62)

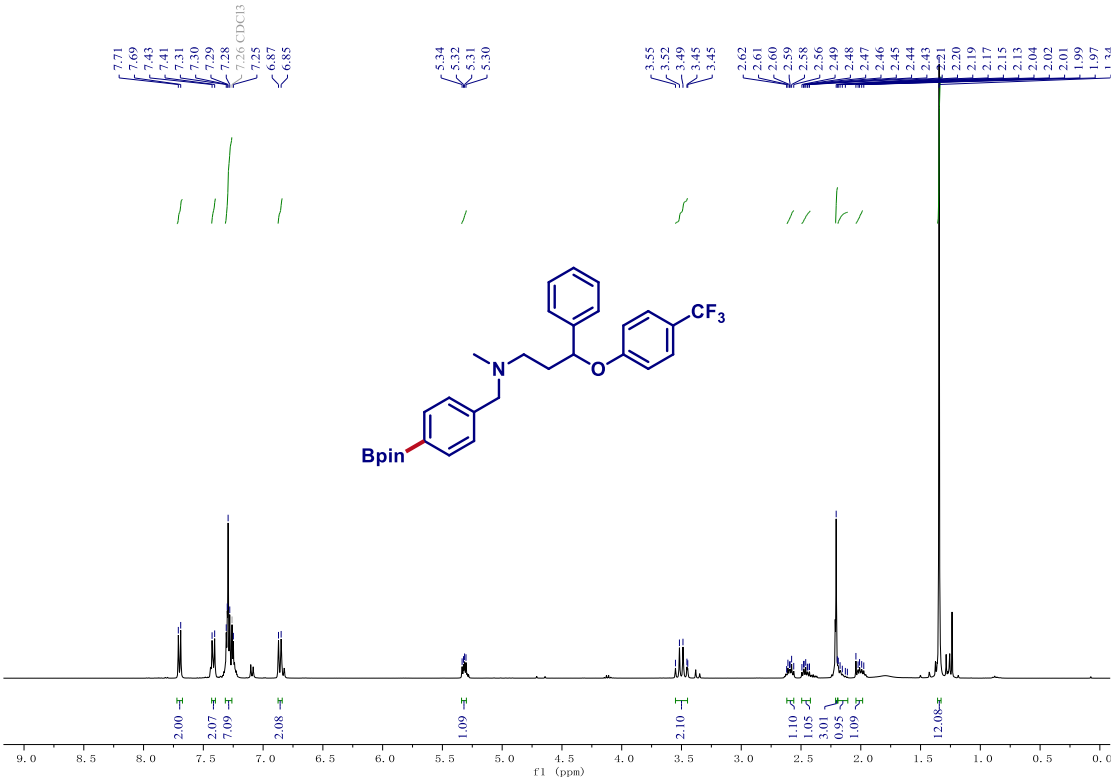


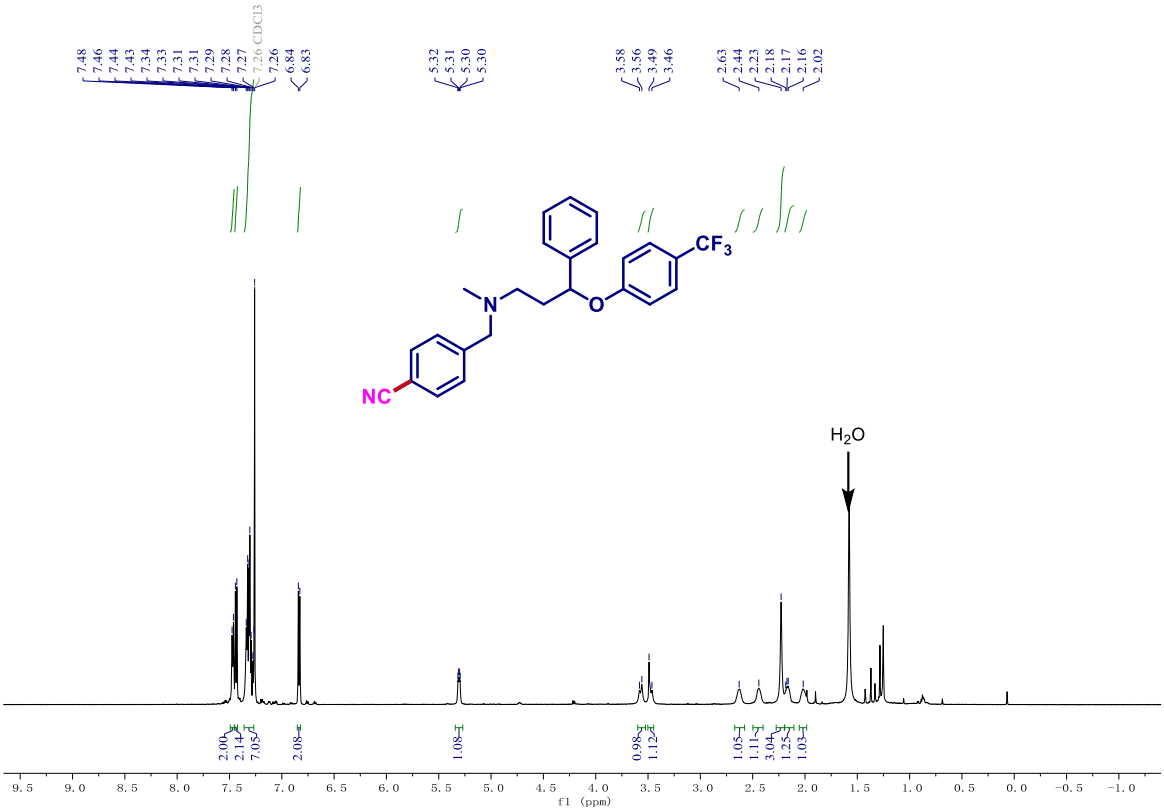


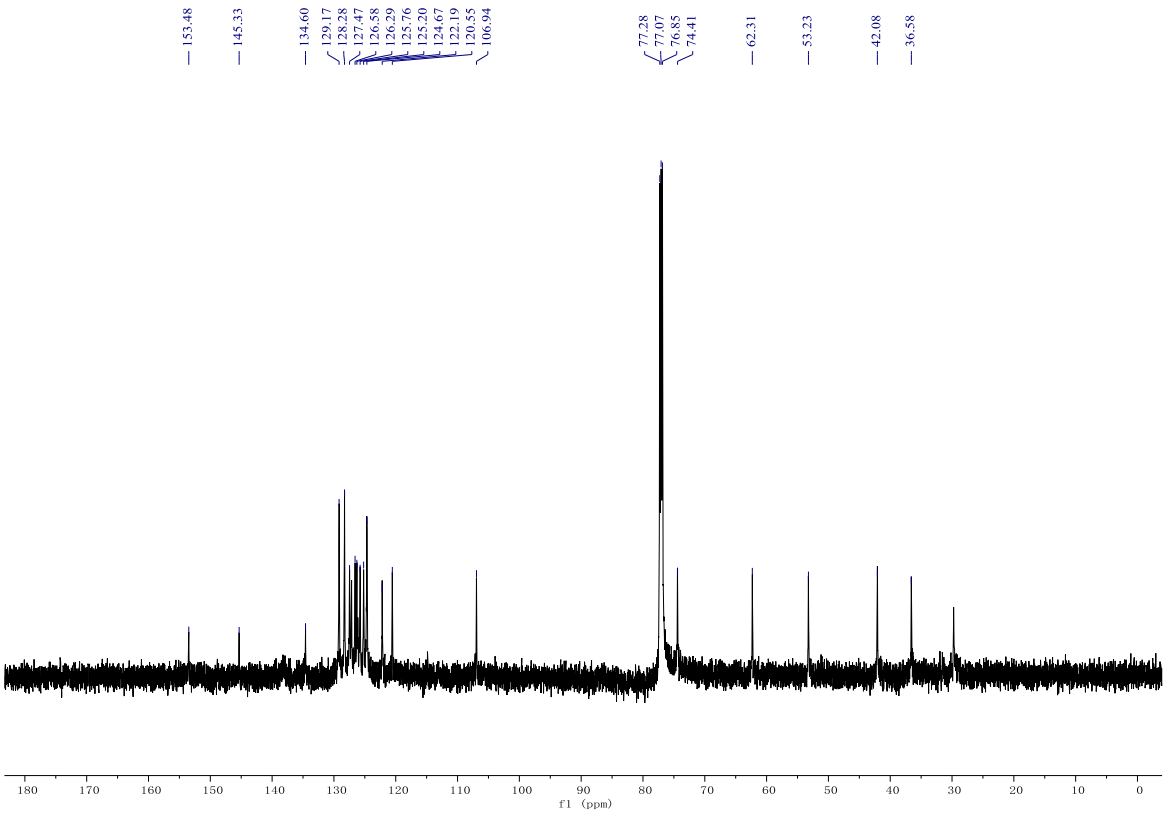

7.59
7.57
7.26 Py-d5
6.99
6.97
4.66
4.65
4.64
4.63
4.50
4.49
4.28
4.26
4.21
4.18
4.09
4.06
3.98
3.94
3.81
3.77
1.65
1.55
1.48
1.42
1.34
NC
O
O
O
O
O
O
Me
Me
Me
Me
2.00
2.06
1.03
0.96
1.01
1.04
1.04
1.00
1.04
0.96
3.14
3.15
3.18
3.02
f1 (ppm)

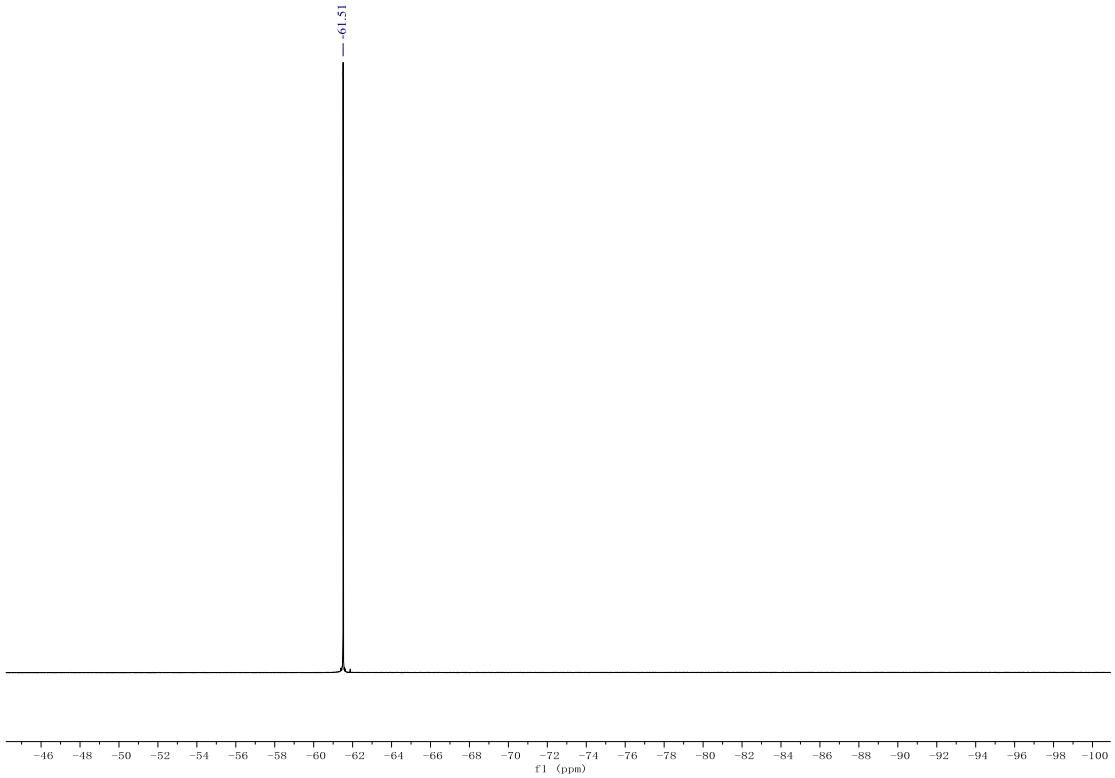

161.74
134.04
119.08
115.45
109.16
109.09
104.55
101.76
77.26
77.05
76.84
70.84
70.07
70.05
68.98
61.30
26.57
25.94
25.29
23.98
f1 (ppm)

Functionalization of fluoxetine (Scheme 2, 63)

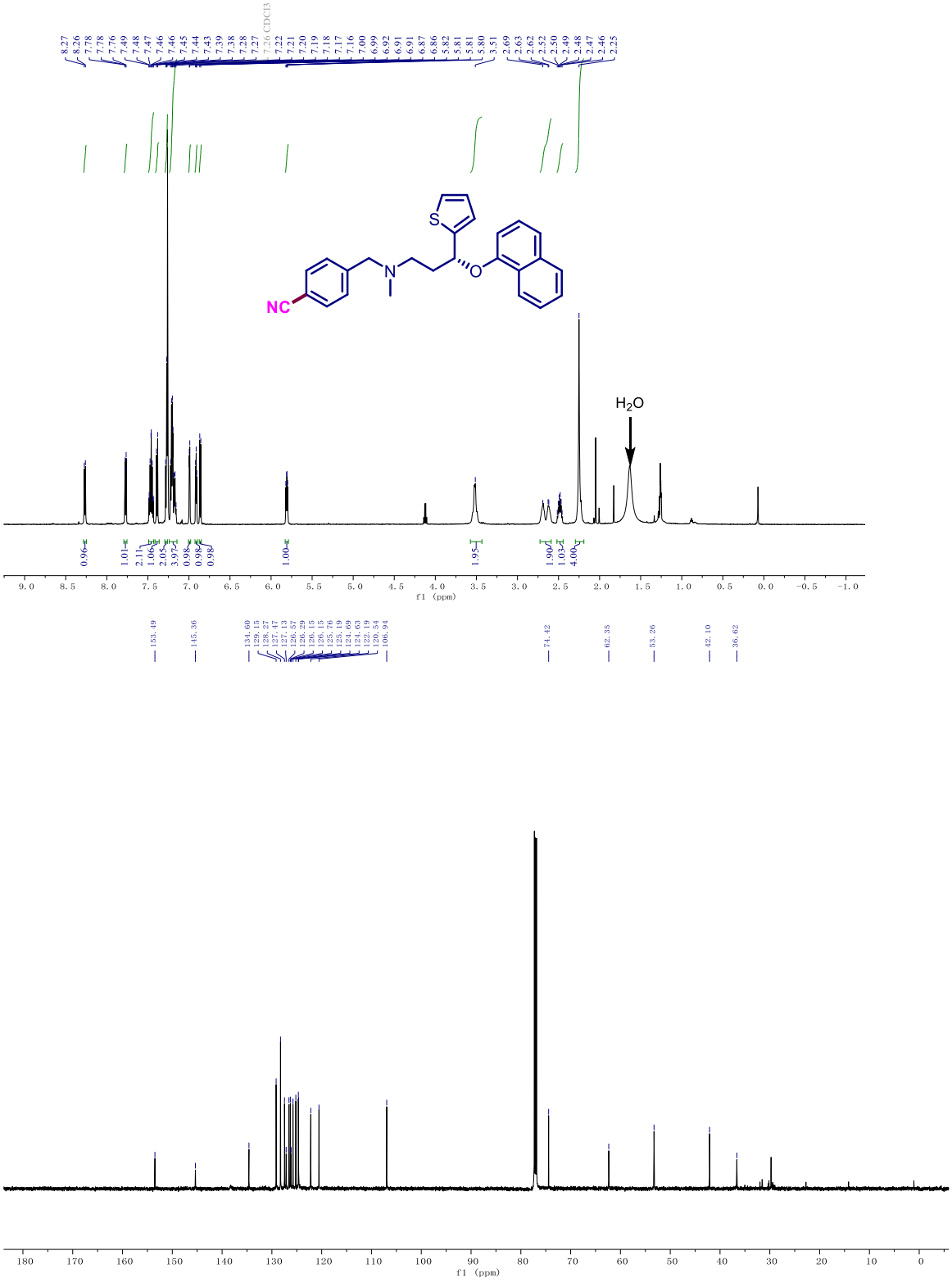




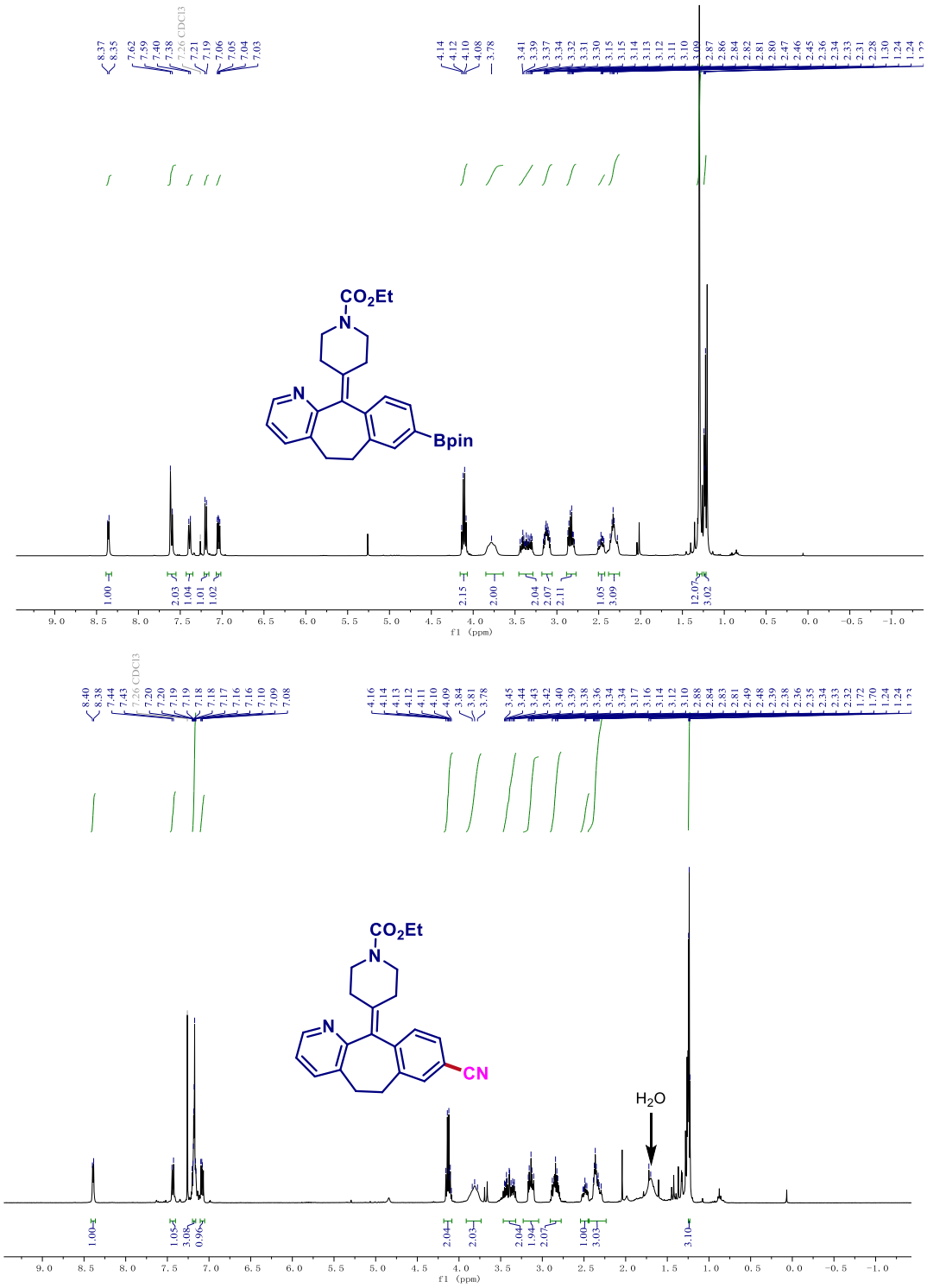

153.48
145.33
134.60
129.17
128.28
127.47
126.58
126.29
125.76
125.20
124.67
122.19
120.55
106.94
77.28
77.07
76.85
74.41
62.31
53.23
42.08
36.58
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

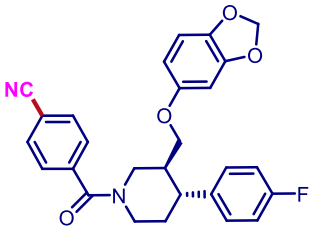

-61.51
-46 -48 -50 -52 -54 -56 -58 -60 -62 -64 -66 -68 -70 -72 -74 -76 -78 -80 -82 -84 -86 -88 -90 -92 -94 -96 -98 -100
f1 (ppm)

Functionalization of duloxetine (Scheme 2, 64)



Functionalization of loratadine (Scheme 2, 65)




NC
O
O
O
O
N
F