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Copper-Catalyzed Cyanation of *N*-Tosylhydrazones with Thiocyanate Salt as the "CN" Source

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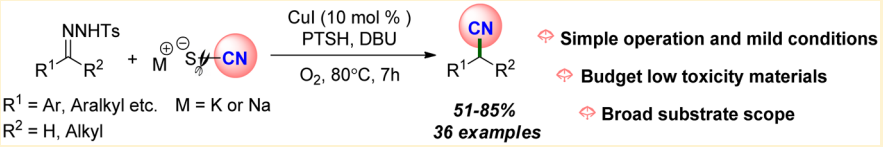
Supporting Information



ABSTRACT: A novel protocol for the synthesis of α-aryl nitriles has been successfully achieved via a copper-catalyzed cyanation of *N*-tosylhydrazones employing thiocyanate as the source of cyanide. The features of this method include a convenient operation, readily available substrates, low-toxicity thiocyanate salts, and a broad substrate scope.

α-Aryl nitriles are important compounds with extensive biological activities[1] and versatile synthetic intermediates[2] for transformations into ketones, esters, α-aryl amides, carboxylic acids, heterocycles compounds, etc. As potentially valuable structural motifs and versatile precursors, α-aryl nitriles also play an important role in the construction of drugs, for instance, ariflo,[3] verapamil, indoprofen,[4] anastrozole, and naproxen,[5] which has prompted the development of efficient strategies for their preparation. Commonly known α-aryl nitrile motifs are usually constructed by (i) nucleophilic substitution reactions involving cyanide and benzyl halides or alcohols,[5,6] (ii) photolytic reactions,[7] (iii) dehydrations,[8] etc. Recently, many other proposals for synthesizing α-aryl nitriles have been reported, among them transition metal-catalyzed synthetic strategies mainly consisting of hydrocyanation of olefins,[9] cyanations of alkynes,[10] coupling reactions of nitriles with aryl halides or arylboronic acids,[11] and acylations of silyl ketene imines.[12] Among them, expensive and complex metal catalysts (Co, Ni, Ru, Pd, etc.), toxic cyanides, and harsh reaction conditions are always thorny problems to be solved. Lately, Liu[13] has also reported a novel conversion of benzylic C−H bonds into benzylic nitriles via a copper-catalyzed radical relay pathway with TMSCN as the "CN" source.

Thiocyanate salts have been proved to be attractive and versatile reagents in organic transformations,[14] owing to their easy availability, low cost, and low toxicity. As an ambident nucleophilic unit (S or N nucleophilic unit), thiocyanate salts can introduce the "SCN" source, mainly via a nucleophilic substitution or a radical pathway, to afford thiocyanate products.[14,15] Meanwhile, in recent years, people gradually recognized that thiocyanate salts can also be used as a sulfur transfer reagent[16] or a stable "CN" source in organic transformations (Scheme 1).[17,18] In general, the reclamation of the "CN" source from thiocyanate is through an oxidation process[19] and peroxidases are sometimes required in these thiocyanate oxidations. In early 1989, Saito[20c] reported the synthesis of diarylacetonitrile from diaryl ketones and trimethylsilyl cyanide in the presence of a base, in which $TsNHNH_2$ promoted diaryl ketone conversion into hydrazone. On the basis of previous studies[20c,d] and our interest in the cyanation of *N*-tosylhydrazones, herein, we report a copper-catalyzed cyanation to construct racemic α-aryl nitriles from *N*-tosylhydrazones. Different from the case with *N*,*N*-dialkylhydrazones derived from aldehydes that underwent oxidative cleavage to nitriles,[20a,b] this novel cyanation reaction employs KSCN as the "CN" source to access diverse α-aryl nitriles.

In the preliminary experiment, we chose *N*-tosylhydrazone of benzaldehyde (**1aa**) as a model substrate to react with potassium thiocyanate (**2**) in the presence of CuI (10 mol %), PTSH (1.0 equiv), and DBU (2.0 equiv) in 1.0 mL of a mixed solvent at 80 °C under 1 atm of O_2. After investigating different proportions and types of solvent mixtures (Table 1, entries 1−7), we found that mixed solvents could promote the reaction more than the monosolvents could and that the solvent mixture MeCN/NMP (2:1) was effective in this catalytic system (entry 2). Through the examination of various copper catalysts (entries 2 and 8−10), we considered that the safer CuI was the optimal choice although CuI and CuCN were indicated to reach similar catalytic activities (entries 2 and 8). The yield was slightly increased to 72% when the amount of KSCN decreased to 2.5 equiv (entries 2, 11, and 12). When MeCN and NMP were used alone as a solvent, only 48% and 31% yields were achieved separately (entries 13 and 14). With the addition of 4 Å molecular sieves, the yield reached 79% (entry 15). When the reaction was carried out under a nitrogen atmosphere, the yield was reduced to 58% (entry 16). In

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Scheme 1. Organic Transformation of Thiocyanate Salts

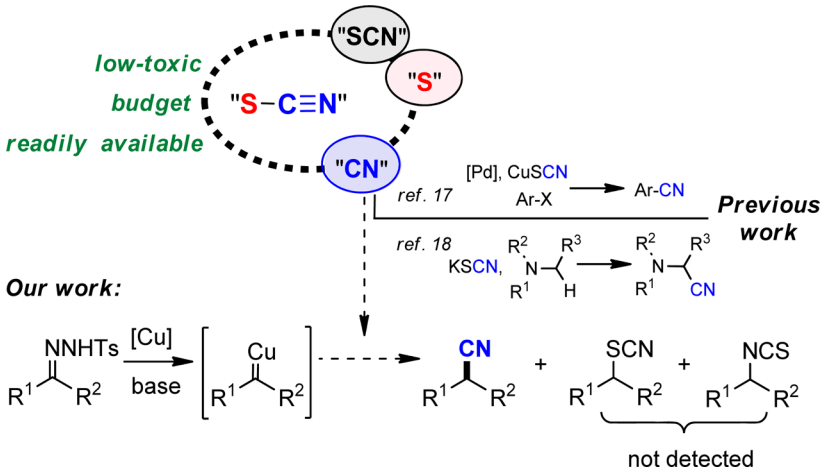
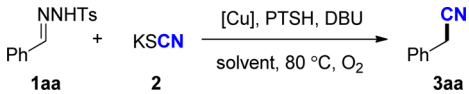


Table 1. Optimization of Reaction Conditions[a]



1aa 2 3aa

entry	[Cu]	2 (equiv)	solvent	yield (%)[b]
1	CuI	3.0	MeCN/NMP (1:1)	39
2	CuI	3.0	MeCN/NMP (2:1)	71
3	CuI	3.0	MeCN/NMP (3:1)	66
4	CuI	3.0	MeCN/NMP (5:1)	47
5	CuI	3.0	MeCN/DCE (2:1)	64
6	CuI	3.0	MeCN/DMF (2:1)	32
7	CuI	3.0	MeCN/H_2O (2:1)	trace
8	CuCN	3.0	MeCN/NMP (2:1)	70
9	CuSCN	3.0	MeCN/NMP (2:1)	61
10	CuBr	3.0	MeCN/NMP (2:1)	34
11	CuI	2.5	MeCN/NMP (2:1)	72
12	CuI	2.0	MeCN/NMP (2:1)	60
13	CuI	2.5	MeCN	48
14	CuI	2.5	NMP	31
15[c]	CuI	2.5	MeCN/NMP (2:1)	79 (71)[f]
16[d]	CuI	2.5	MeCN/NMP (2:1)	58
17[c,e]	CuI		MeCN/NMP (2:1)	82

[a]Reaction conditions: All reactions were performed with **1aa** (0.2 mmol), **2** catalyst (0.02 mmol), PTSH (0.2 mmol), and DBU (0.4 mmol) in 1.0 mL of solvent at 80 °C under 1 atm O_2 for 7 h unless otherwise noted. [b]GC−MS yield using *n*-dodecane as an internal standard. [c]4 Å molecular sieves was added. [d]Under N_2. [e]2.5 equiv of NaSCN was added instead of KSCN. [f]Isolated yield. PTSH = *p*-toluenesulfonyl hydrazide.

addition, the 82% yield confirmed that NaSCN could be also used as a "CN" source in this reaction system (entry 17). In light of the low cost and similar yields (entries 15 and 17), KSCN was believed to be more suitable as a "CN" source.

With the optimal reaction conditions in hand, we subsequently explored the substrate scopes of *N*-tosylhydrazones (R^2 = H) in this copper-catalyzed cyanation reaction (Table 2). H-, methyl-, and methoxy-substituted substrates could be tolerated and converted to the desired phenylacetonitriles in good yields, whereas halogen substituted products were delivered in lower yields (**3ac**, **3ad**, and **3af**). Moreover, a good isolated yield was obtained when heterocyclic (**3ak**−**3am**) and naphthaldehyde (**3an**) derived *N*-tosylhydrazones were used as substrates, respectively. However, phenylacetaldehyde derived *N*-tosylhydrazone could only generate the corresponding nitrile **3am** in 51% yield.

A series of substrate scopes of *N*-tosylhydrazones (R^2 = alkyl) was then explored in this copper-catalyzed cyanation reaction (Table 3). When R^2 was methyl, *N*-tosylhydrazones bearing electron-withdrawing and electron-donating substituents afforded the products (**3ba**−**3bl**) in moderate to good yields. Notably, acylnaphthalene derived *N*-tosylhydrazones are good substrates to deliver the corresponding nitriles in 82% (**3bm**) and 80% (**3bn**) yields, respectively. When R^2 was ethyl (**3bo**), isopropyl (**3bp**), or *n*-propyl (**3br**), the desired products were obtained in good yields; however, only 57% yield could be obtained when R^2 was cyclopropyl. To our delight, the reaction could afford the corresponding benzocyclic nitriles (**3bs**−**3bu**) in excellent yields. Meanwhile, 2-methyl-4-phenylbutanenitrile (**3bv**) was also obtained in 76% isolated yield. In addition, when using 4,4-dimethylcyclohex-2-enone derived *N*-tosylhydrazone as a substrate, an unexpected double-bond migration product (**3bw**) was isolated in 62% yield in this reaction system.

To gain more mechanistic insights into this copper-catalyzed cyanation reaction, we conducted a series of control experiments (Scheme 2). Taking the synthetic materials of *N*-tosylhydrazones into account, we suspected that the role of sulfohydrazide was to regenerate *N*-tosylhydrazones by reacting with aldehyde or ketone byproducts. However, no desired nitrile product was detected when benzaldehyde was switched as a substrate in the reaction (Scheme 2a). When 1.5 equiv of TEMPO was introduced, the desired product was not significantly inhibited (Scheme 2b). The results of changes c and d demonstrated further that KSCN provides a direct nitrile source for the transformation, and PTSH can facilitate this transformation. Subsequently, we changed PTSH to equivalent BZH and found that benzoylhydrazine can promote the reaction as well (Scheme 2e).

A plausible reaction mechanism is proposed as shown in Scheme 3. Initially, the Cu species **A** is generated from the Cu(I) catalyst and SCN^-,[21] followed by the reaction with the diazo substrate **B**, generated in situ from *N*-tosylhydrazone in the presence of a base,[22] to form the copper(I) carbene species **D**. Subsequent to the generation of the thiocarbonyl compound **E**, which could regenerate *N*-tosylhydrazone with $TsNHNH_2$ while releasing H_2S, the species Cu^ICN (**F**)[23] is formed. On the one hand, the cyanide ion could directly attack *N*-

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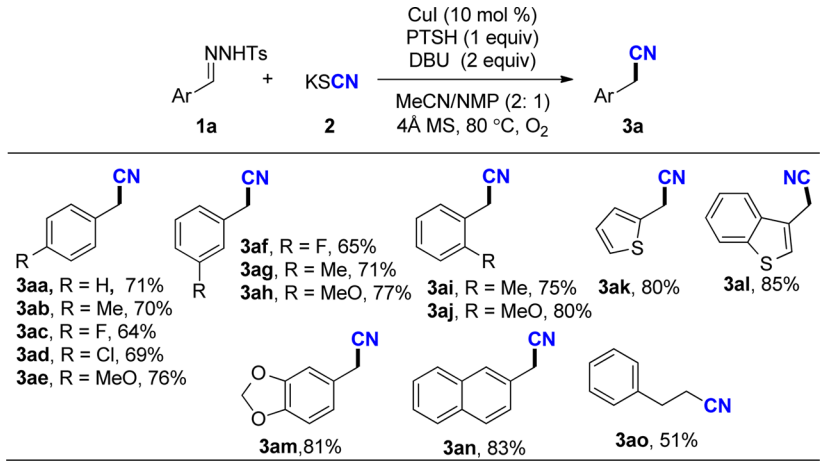
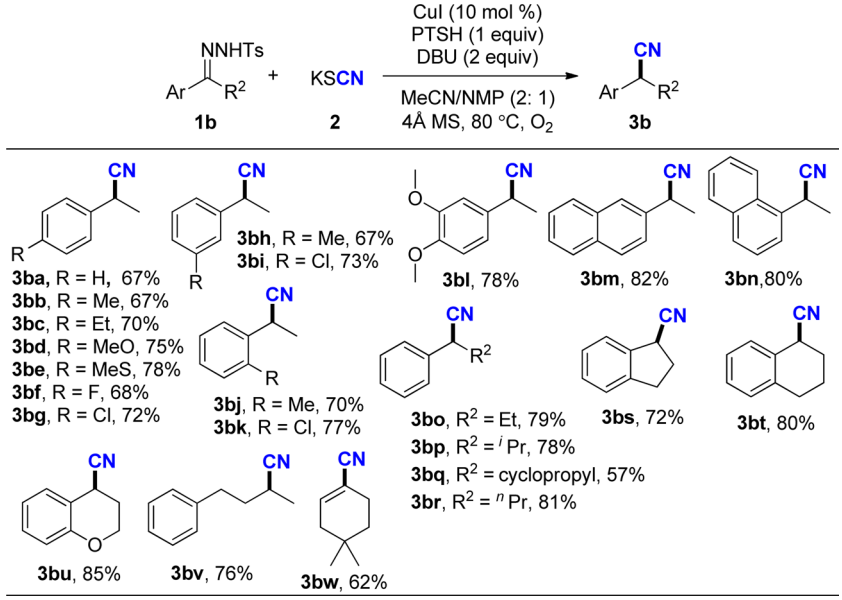
Table 2. Substrate Scope of *N*-Tosylhydrazones[a]



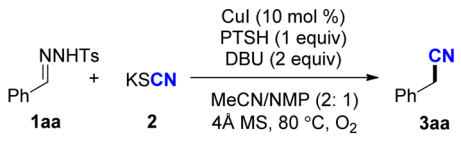
[a]Reaction conditions: All reactions were performed with **1a** (0.5 mmol), **2** (1.25 mmol), CuI (0.05 mmol), PTSH (0.5 mmol), and DBU (1.0 mmol) in 2 mL of MeCN/NMP (2:1) at 80 °C under 1 atm O_2 for 7 h unless otherwise noted. Yields refer to the isolated yields.

Table 3. Substrate Scope of *N*-Tosylhydrazones (R^2 = alkyl)[a]



[a]Reaction conditions: All reactions were performed with **1b** (0.5 mmol), **2** (1.25 mmol), CuI (0.05 mmol), PTSH (0.5 mmol), and DBU (1.0 mmol) in 2 mL of MeCN/NMP (2:1) at 80 °C under 1 atm O_2 for 7 h unless otherwise noted. Yields refer to the isolated yields.

Scheme 2. Control Experiments



changes	yield (%)[a]
a. Switch benzaldehyde as **1a**	n.r.
b. Add 1.5 equiv of TEMPO;	67
c. Remove KSCN;	n.d
d. Remove PTSH;	30
e. Replace PTSH with 1 equiv BZH.	54

tosylhydrazone **1** to form the nitrile product **3**,[20c,d] and on the other hand, the reaction of the species $Cu^{I}CN$ (**F**) and the diazo substrate **B** leads to the formation of the copper(I) carbene species **G**, followed by the migratory insertion[21,24] to generate the intermediate **H**. The protonation of **H** releases the nitrile product **3** and regenerates the copper(I) catalyst.

In conclusion, a copper-catalyzed cyanation to construct racemic α-aryl nitriles employing KSCN as a "CN" source has been developed. The use of the inexpensive copper catalyst, eco-friendly oxygen, and readily available starting materials, simple operation conditions, and regeneration of "CN" sources from low-toxicity thiocyanate salts has presented a novel and safe protocol for the synthesis of α-aryl nitriles.

EXPERIMENTAL SECTION

General Information. Melting points were determined with a Buchi Melting Point B-545 instrument. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker DRX-400 spectrometer using $CDCl_3$ as

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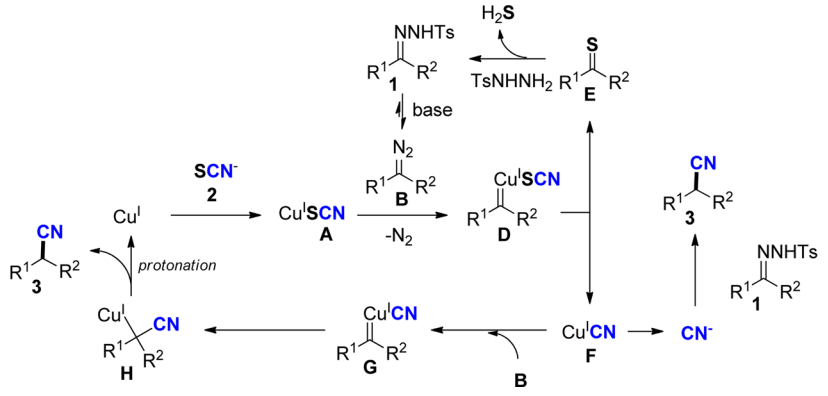
Scheme 3. Proposed Mechanism



solvent. The chemical shifts are referenced to signals at 7.26 and 77.0 ppm, respectively, and chloroform was used as the solvent with TMS as the internal standard. IR spectra were obtained either as potassium bromide pellets or as liquid films between two potassium bromide pellets with a Bruker TENSOR 27 spectrometer. Mass spectra were recorded on a Thermo Scientific ISQ gas chromatograph−mass spectrometer. The data of HRMS were collected on a high-resolution mass spectrometer (LCMS-IT-TOF). TLC was performed by using commercially prepared 100−400 mesh silica gel plates, and visualization was effected at 254 nm. Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification.

General Procedure for *N*-Tosylhydrazones. A mixture of ketone compounds (5.0 mmol) and *p*-toluenesulfonyl hydrazide (5.0 mmol) in 7.5 mL of MeOH was stirred at 70 °C for 0.5−3 h to afford the corresponding *N*-tosylhydrazone **1** as a white precipitate. After that, the precipitate was washed and filtered with petroleum ether twice and dried under vacuum to provide the pure compounds.

General Procedure for the Synthesis of α-Aryl Nitriles. A mixture of *N*-tosylhydrazone (0.5 mmol), KSCN (1.25 mmol), CuI (0.05 mmol), PTSH (0.5 mmol), DBU (1.0 mmol), 4 Å MS, and 2.0 mL of MeCN/NMP (2:1) was added to a test tube. The mixture was stirred at 80 °C under 1 atm O_2 for 7 h. After that, water was added and extracted with ethyl acetate twice. The combined organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (PE/EA = 10:1−20:1) as the eluent to afford the corresponding α-aryl nitriles.

*2-Phenylacetonitrile (**3aa**).* Yield: 41 mg (71%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.38 (m, 2H), 7.32 (dd, *J* = 7.3, 3.9 Hz, 3H), 3.75 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 129.9, 129.2, 128.1, 127.9, 117.8, 23.6. IR (KBr, cm^{-1}): ν = 3039, 2929, 2251, 1681, 1599, 1496, 1415, 670. HRMS (ESI) C_8H_7NNa [M + Na]$^+$: calcd, 140.0471; found, 140.0469.

*2-(p-Tolyl)acetonitrile (**3ab**).* Yield: 46 mg (70%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.20 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 3.69 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 137.9, 129.8, 127.8, 126.9, 118.1, 23.2, 21.1. IR (KBr, cm^{-1}): ν = 2930, 2928, 2251, 1726, 1526, 1456, 1276, 670. HRMS (ESI) C_9H_9NNa [M + Na]$^+$: calcd, 154.0627; found, 154.0626.

*2-(p-Fluorophenyl)acetonitrile (**3ac**).* Yield: 43 mg (64%), pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.30 (t, *J* = 7.4 Hz, 2H), 7.06 (t, *J* = 8.3 Hz, 2H), 3.72 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 162.4 (d, *J* = 247.1 H), 129.7 (d, *J* = 8.3 Hz), 125.7 (d, *J* = 3.1 Hz), 117.8, 116.1 (d, *J* = 21.9 Hz), 22.9. IR (KBr, cm^{-1}): ν = 3071, 2349, 2252, 1728, 1511, 1420, 1228, 826. HRMS (ESI) C_8H_6FNNa [M + Na]$^+$: calcd, 158.0376; found, 158.0375.

*2-(p-Chlorophenyl)acetonitrile (**3ad**).* Yield: 52 mg (69%), pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.38 (d, *J* = 7.9 Hz, 2H), 7.29 (d, *J* = 7.7 Hz, 2H), 3.75 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 134.2, 129.3, 129.3, 128.4, 117.4, 23.1. IR (KBr, cm^{-1}): ν = 3064, 2931, 2253, 1491, 1414, 1095, 805. HRMS (ESI) C_8H_6ClNNa [M + Na]$^+$: calcd, 174.0081; found, 174.0080.

*2-(p-Methoxyphenyl)acetonitrile (**3ae**).* Yield: 56 mg (76%), yellowish-green oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.22 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 3.80 (s, 3H), 3.67 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 159.4, 129.1, 121.8, 118.3, 114.5, 55.4, 22.8. IR (KBr, cm^{-1}): ν = 2943, 2840, 2250, 1607, 1512, 1447, 1249, 1181, 1028, 823. HRMS (ESI) C_9H_9NNaO [M + Na]$^+$: calcd, 170.0575; found, 170.0576.

*2-(m-Fluorophenyl)acetonitrile (**3af**).* Yield: 44 mg (65%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.35 (dd, *J* = 14.4, 7.0 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.04 (t, *J* = 10.0 Hz, 2H), 3.75 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 163.0 (d, *J* = 247.8 Hz), 132.2 (d, *J* = 7.9 Hz), 130.8 (d, *J* = 8.3 Hz), 123.7 (d, *J* = 3.0 Hz), 117.3, 115.3, 115.1, 23.4. IR (KBr, cm^{-1}): ν = 3088, 2938, 2253, 1600, 1489, 1252, 1078, 784. HRMS (ESI) C_8H_6FNNa [M + Na]$^+$: calcd, 158.0376; found, 158.0381.

*2-(m-Tolyl)acetonitrile (**3ag**).* Yield: 46 mg (71%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.25 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 8.6 Hz, 3H), 3.69 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 139.0, 129.8, 129.0, 128.8, 128.6, 125.0, 118.0, 23.5, 21.3. IR (KBr, cm^{-1}): ν = 3031, 2927, 2251, 1606, 1485, 777, 694. HRMS (ESI) C_9H_9NNa [M + Na]$^+$: calcd, 154.0627; found, 154.0625.

*2-(m-Methoxyphenyl)acetonitrile (**3ah**).* Yield: 56 mg (77%), pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.27 (t, *J* = 8.1 Hz, 1H), 6.87 (m, 3H), 3.80 (s, 3H), 3.70 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 160.1, 131.4, 130.2, 120.2, 117.9, 113.7, 113.6, 55.3, 23.6. IR (KBr, cm^{-1}): ν = 2949, 2840, 2251, 1600, 1479, 1263, 1158, 1044, 779. HRMS (ESI) $C_9H_{10}NO$ [M + H]$^+$: calcd, 148.0762; found, 148.0761.

*2-(o-Tolyl)acetonitrile (**3ai**).* Yield: 49 mg (75%), pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.34 (d, *J* = 6.9 Hz, 1H), 7.22 (q, *J* = 6.9 Hz, 3H), 3.64 (s, 2H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 136.1, 130.7, 128.6, 128.5, 128.4, 126.75, 117.6, 21.9, 19.3. IR (KBr, cm^{-1}): ν = 2934, 2250, 1604, 1469, 750. HRMS (ESI) C_9H_9NNa [M + Na]$^+$: calcd, 154.0627; found, 154.0628.

*2-(o-Methoxyphenyl)acetonitrile (**3aj**).* Yield: 59 mg (80%), pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.32 (m, 2H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 3.86 (s, 3H), 3.67 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 156.8, 129.6, 129.2, 120.8, 118.6, 118.1, 110.5, 55.5, 18.7. IR (KBr, cm^{-1}): ν = 2946, 2841, 2251, 1597, 1492, 1252, 1110, 1029, 751. HRMS (ESI) $C_9H_{10}NO$ [M + H]$^+$: calcd, 148.0764; found, 148.0762.

*2-(Thiophen-2-yl)acetonitrile (**3ak**).* Yield: 49 mg (80%), tan oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.26 (d, *J* = 5.3 Hz, 1H), 7.05 (s, 1H), 6.98 (d, *J* = 3.0 Hz, 1H), 3.91 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 131.0, 127.4, 127.2, 126.0, 117.0, 18.6. IR (KBr, cm^{-1}): ν = 2926, 2253, 1418, 1246, 840, 707. HRMS (ESI) C_6H_5NNaS [M + Na]$^+$: calcd, 146.0035; found, 146.0037.

*2-(Benzo[b]thiophen-3-yl)acetonitrile (**3al**).* Yield: 74 mg (85%), white solid, mp 65−67 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.92 (d, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.51 (s, 1H), 7.46

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(dd, J = 14.6, 7.3 Hz, 2H), 3.92 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 140.5, 137.0, 125.1, 125.0, 124.7, 123.9, 123.2, 120.8, 117.0, 17.8. IR (KBr, cm^{-1}): ν = 3076, 2922, 2247, 1643, 1426, 1263, 75. HRMS (ESI) $C_{10}H_7NNaS$ [M + Na]$^+$: calcd, 196.0191; found, 196.0194.

*2-(Benzo[d][1,3]dioxol-5-yl)acetonitrile (**3am**).* Yield: 78 mg (81%), white solid, mp 43−45 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 6.78 (m, 3H), 5.97 (s, 2H), 3.65 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 148.3, 147.5, 123.4, 121.3, 118.0, 108.7, 108.4, 101.4, 23.3. IR (KBr, cm^{-1}): ν = 2904, 2249, 1500, 1439, 1248, 1112, 1038, 92. HRMS (ESI) $C_9H_7NNaO_2$ [M + Na]$^+$: calcd, 184.0369; found, 184.0372.

*2-(Naphthalen-2-yl)acetonitrile (**3an**).* Yield: 69 mg (83%), white solid, mp 84−85 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.84 (m, 4H), 7.52 (m, 2H), 7.38 (d, J = 8.4 Hz, 1H), 3.90 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 133.4, 132.7, 129.1, 127.8, 127.7, 127.2, 126.9, 126.8, 126.5, 125.5, 117.9, 23.8. IR (KBr, cm^{-1}): ν = 3056, 2947, 2251, 1603, 1363, 1265, 954, 827, 753. HRMS (ESI) $C_{12}H_{10}N$ [M + H]$^+$: calcd, 168.0813; found, 168.0817.

*3-Phenylpropanenitrile (**3ao**).* Yield: 33 mg (51%), pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.33 (t, J = 7.2 Hz, 2H), 7.27 (d, J = 6.6 Hz, 1H), 7.22 (d, J = 7.4 Hz, 2H), 2.93 (t, J = 7.4 Hz, 2H), 2.59 (t, J = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 138.1, 128.9, 128.3, 127.3, 119.2, 31.6, 19.3. IR (KBr, cm^{-1}): ν = 3034, 2937, 2247, 1600, 1339, 749. HRMS (ESI) $C_9H_{10}N$ [M + H]$^+$: calcd, 132.0813; found, 132.0811.

*2-Phenylpropanenitrile (**3ba**).* Yield: 44 mg (67%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.36 (m, 5H), 3.90 (q, J = 7.3 Hz, 1H), 1.65 (d, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 137.1, 129.2, 128.1, 126.7, 121.6, 31.3, 21.5. IR (KBr, cm^{-1}): ν = 2924, 2242, 1725, 1454, 1288, 990, 896, 752. HRMS (ESI) C_9H_9NNa [M + Na]$^+$: calcd, 154.0627; found, 154.0625.

*2-(p-Tolyl)propanenitrile (**3bb**).* Yield: 48 mg (67%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.24 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 3.86 (q, J = 7.3 Hz, 1H), 2.35 (s, 3H), 1.62 (d, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 137.9, 134.1, 129.8, 126.6, 121.8, 30.9, 21.5, 21.1. IR (KBr, cm^{-1}): ν = 2926, 2859, 2242, 1728, 1512, 1453, 1298, 994, 819, 734. HRMS (ESI) $C_{10}H_{11}NNa$ [M + Na]$^+$: calcd, 168.0784; found, 168.0778.

*2-(p-Ethylphenyl)propanenitrile (**3bc**).* Yield: 56 mg (70%), yellowish-green oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.27 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 7.8 Hz, 2H), 3.87 (q, J = 7.2 Hz, 1H), 2.65 (q, J = 7.6 Hz, 2H), 1.63 (d, J = 7.3 Hz, 3H), 1.23 (t, J = 7.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 144.2, 134.3, 128.6, 126.7, 121.8, 30.9, 28.4, 21.5, 15.5. IR (KBr, cm^{-1}): ν = 2924, 2848, 1727, 1458, 1282, 986, 834, 743. HRMS (ESI) $C_{11}H_{13}NNa$ [M + Na]$^+$: calcd, 182.0940; found, 182.0938.

*2-(p-Methoxyphenyl)propanenitrile (**3bd**).* Yield: 60 mg (75%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.26 (d, J = 8.2 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 3.85 (d, J = 7.5 Hz, 1H), 3.81 (s, 3H), 1.61 (d, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 159.3, 129.11, 127.8, 121.9, 114.5, 55.4, 30.5, 21.5. IR (KBr, cm^{-1}): ν = 2927, 2848, 2240, 1608, 1512, 1455, 1251, 1027, 827, 734. HRMS (ESI) $C_{10}H_{11}NNaO$ [M + Na]$^+$: calcd, 184.0733; found, 184.0732.

*2-(p-(Methylthio)phenyl)propanenitrile (**3be**).* Yield: 69 mg (78%), yellow solid, mp 65−67 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.28 (s, 4H), 3.88 (q, J = 7.3 Hz, 1H), 2.50 (s, 3H), 1.64 (d, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 138.7, 133.8, 127.2, 127.1, 121.5, 30.8, 21.38, 15.7. IR (KBr, cm^{-1}): ν = 2986, 2927, 2240, 1600, 1491, 1432, 1314, 1097, 963, 819. HRMS (ESI) $C_{10}H_{11}NNaS$ [M + Na]$^+$: calcd, 200.0504; found, 200.0509.

*2-(p-Fluorophenyl)propanenitrile (**3bf**).* Yield: 51 mg (68%), tan oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.33 (m, 2H), 7.08 (m, 2H), 3.89 (q, J = 7.3 Hz, 1H), 1.63 (d, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 162.4 (d, J = 247.3 Hz), 132.9 (d, J = 3.3 Hz), 128.4 (d, J = 8.3 Hz), 121.4, 116.1 (d, J = 21.8 Hz), 30.6, 21.5. IR (KBr, cm^{-1}): ν = 2921, 2853, 1648, 1462, 1305, 1231, 960. HRMS (ESI) C_9H_9FN [M + H]$^+$: calcd, 150.0714; found, 150.0712.

*2-(p-Chlorophenyl)propanenitrile (**3bg**).* Yield: 59 mg (72%), tan oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.36 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 3.88 (q, J = 7.2 Hz, 1H), 1.63 (d, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 135.6, 134.1, 129.3, 128.1, 121.1, 30.7, 21.4. IR (KBr, cm^{-1}): ν = 2930, 2243, 1658, 1489, 1290, 1094, 1010, 827, 736. HRMS (ESI) C_9H_8ClNNa [M + Na]$^+$: calcd, 188.0237; found, 188.0234.

*2-(m-Tolyl)propanenitrile (**3bh**).* Yield: 48 mg (67%), tan oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.30 (t, J = 6.7 Hz, 1H), 7.20 (s, 1H), 7.16 (d, J = 7.6 Hz, 2H), 3.88 (q, J = 7.2 Hz, 1H), 2.40 (s, 3H), 1.66 (d, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 139.0, 137.0, 129.0, 128.8, 127.4, 123.7, 121.7, 31.2, 21.5, 21.4. IR (KBr, cm^{-1}): ν = 2923, 2855, 1646, 1451, 1291, 990, 781, 701. HRMS (ESI) $C_{10}H_{11}NNa$ [M + Na]$^+$: calcd, 168.0784; found, 168.0783.

*2-(m-Chlorophenyl)propanenitrile (**3bi**).* Yield: 60 mg (73%), tan oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.35 (s, 1H), 7.32 (d, J = 5.4 Hz, 2H), 7.25 (d, J = 6.1 Hz, 1H), 3.88 (q, J = 7.2 Hz, 1H), 1.64 (d, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 138.9, 135.0, 130.5, 128.4, 127.0, 125.0, 120.9, 31.0, 21.3. IR (KBr, cm^{-1}): ν = 2927, 2856, 2243, 1583, 1469, 1245, 1082, 992, 881, 786. HRMS (ESI) C_9H_8ClNNa [M + Na]$^+$: calcd, 188.0237; found, 188.0234.

*2-(o-Tolyl)propanenitrile (**3bj**).* Yield: 51 mg (70%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.48 (d, J = 7.0 Hz, 1H), 7.28 (dd, J = 12.3, 7.1 Hz, 2H), 7.22 (t, J = 5.9 Hz, 1H), 4.07 (q, J = 7.2 Hz, 1H), 2.39 (s, 3H), 1.64 (d, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 135.3, 134.8, 131.0, 128.1, 127.0, 126.7, 121.8, 28.2, 20.0, 19.0. IR (KBr, cm^{-1}): ν = 2984, 2932, 2883, 2241, 1457, 1297, 1230, 985, 752. HRMS (ESI) $C_{10}H_{11}NNa$ [M + Na]$^+$: calcd, 168.0784; found, 168.0781.

*2-(o-Chlorophenyl)propanenitrile (**3bk**).* Yield: 64 mg (77%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.61 (d, J = 7.5 Hz, 1H), 7.42 (d, J = 7.7 Hz, 1H), 7.33 (dd, J = 15.4, 7.5 Hz, 2H), 4.38 (q, J = 6.7 Hz, 1H), 1.65 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 134.8, 132.5, 130.0, 129.5, 128.2, 127.8, 121.0, 28.9, 19.9. IR (KBr, cm^{-1}): ν = 2925, 2855, 2244, 1675, 1454, 1305, 1034, 752. HRMS (ESI) C_9H_8ClNNa [M + Na]$^+$: calcd, 188.0237; found, 188.0233.

*2-(3,4-Dimethoxyphenyl)propanenitrile (**3bl**).* Yield: 74 mg (78%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 6.89 (m, 3H), 3.89 (m, 7H), 1.65 (d, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 149.4, 148.9, 129.5, 121.8, 121.8, 118.9, 118.9, 111.5, 109.9, 56.0, 30.8, 21.5. IR (KBr, cm^{-1}): ν = 2932, 2846, 2241, 1709, 1515, 1258, 1150, 1024, 750. HRMS (ESI) $C_{11}H_{13}NNaO_2$ [M + Na]$^+$: calcd, 214.0838; found, 214.0843.

*2-(Naphthalen-2-yl)propanenitrile (**3bm**).* Yield: 74 mg (82%), white solid, mp 69−70 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.89 (m, 4H), 7.55 (m, 2H), 7.46 (d, J = 8.5 Hz, 1H), 4.09 (q, J = 7.2 Hz, 1H), 1.75 (d, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 134.4, 133.4, 132.8, 129.2, 127.9, 127.7, 126.8, 126.5, 125.6, 124.4, 121.6, 31.4, 21.4. IR (KBr, cm^{-1}): ν = 3055, 2988, 2932, 2241, 1601, 1509, 1453, 1372, 1148, 821, 750. HRMS (ESI) $C_{13}H_{12}N$ [M + H]$^+$: calcd, 182.0970; found, 182.0972.

*2-(Naphthalen-1-yl)propanenitrile (**3bn**).* Yield: 72 mg (80%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.91 (m, 2H), 7.83 (d, J = 8.3 Hz, 1H), 7.69 (d, J = 6.8 Hz, 1H), 7.54 (m, 3H), 4.61 (q, J = 7.2 Hz, 1H), 1.78 (d, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 134.1, 132.7, 129.8, 129.3, 129.0, 127.0, 126.2, 125.6, 124.7, 122.1, 121.8, 28.3, 20.6. IR (KBr, cm^{-1}): ν = 3057, 2987, 2928, 2240, 1762, 1595, 1452, 1249, 769. HRMS (ESI) $C_{13}H_{12}N$ [M + H]$^+$: calcd, 182.0970; found, 182.0967.

*2-Phenylbutanenitrile (**3bo**).* Yield: 57 mg (79%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.38 (t, J = 6.6 Hz, 2H), 7.32 (m, 3H), 3.74 (t, J = 7.1 Hz, 1H), 1.94 (p, J = 7.1 Hz, 2H), 1.08 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 135.8, 129.0, 128.0, 127.3, 120.8, 38.9, 29.2, 11.5. IR (KBr, cm^{-1}): ν = 3045, 2963, 2241, 1600, 1458, 1327, 753, 700. HRMS (ESI) $C_{10}H_{11}NNa$ [M + Na]$^+$: calcd, 168.0784; found, 168.0785.

*3-Ethyl-2-phenylbutanenitrile (**3bp**).* Yield: 62 mg (78%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.37 (d, J = 6.6 Hz, 2H), 7.30 (d, J = 6.9 Hz, 3H), 3.66 (d, J = 6.1 Hz, 1H), 2.14 (m, 1H), 1.05 (t, J = 7.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 135.0, 128.8, 128.0, 127.9, 119.8, 45.1, 33.8, 20.8, 18.8. IR (KBr, cm^{-1}): ν =

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2926, 2865, 2240, 1723, 1457, 1266, 976, 749, 700. HRMS (ESI) $C_{11}H_{13}NNa$ $[M + Na]^+$: calcd, 182.0940; found, 182.0936.

*2-Cyclopropyl-2-phenylacetonitrile (**3bq**).* Yield: 45 mg (57%), yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.39 (d, J = 4.1 Hz, 5H), 3.50 (d, J = 7.5 Hz, 1H), 1.28 (m, 1H), 0.70 (m, 2H), 0.52 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 135.6, 129.0, 128.2, 127.4, 119.8, 41.0, 15.5, 4.8, 3.9. IR (KBr, cm^{-1}): ν = 3017, 2923, 2241, 1725, 1454, 1280, 1021, 743, 698. HRMS (ESI) $C_{11}H_{11}NNa$ $[M + Na]^+$: calcd, 180.0784; found, 180.0782.

*2-Phenylpentanenitrile (**3br**).* Yield: 64 mg (81%), yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.36 (d, J = 6.7 Hz, 2H), 7.31 (t, J = 7.2 Hz, 3H), 3.78 (t, J = 7.4 Hz, 1H), 1.87 (m, 2H), 1.51 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 136.1, 129.0, 128.0, 127.2, 120.9, 37.9, 37.2, 20.3, 13.4. IR (KBr, cm^{-1}): ν = 3035, 2955, 2871, 2240, 1682, 1456, 1380, 753, 699. HRMS (ESI) $C_{11}H_{13}NNa$ $[M + Na]^+$: calcd, 182.0940; found, 182.0939.

*2,3-Dihydro-1H-indene-1-carbonitrile (**3bs**).* Yield: 51 mg (72%), yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.42 (d, J = 5.3 Hz, 1H), 7.26 (s, 3H), 4.09 (t, J = 8.1 Hz, 1H), 3.08 (m, 1H), 2.96 (m, 1H), 2.57 (ddd, J = 11.8, 8.2, 3.7 Hz, 1H), 2.36 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 142.9, 137.6, 128.6, 127.3, 125.0, 124.3, 121.1, 34.5, 31.4, 31.2. IR (KBr, cm^{-1}): ν = 3035, 2940, 2858, 2240, 1609, 1466, 1317, 1147, 753. HRMS (ESI) $C_{10}H_9NNa$ $[M + Na]^+$: calcd, 166.0627; found, 166.0623.

*1,2,3,4-Tetrahydronaphthalene-1-carbonitrile (**3bt**).* Yield: 63 mg (80%), yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.35 (d, J = 6.7 Hz, 1H), 7.20 (dd, J = 5.4, 3.1 Hz, 2H), 7.11 (d, J = 6.5 Hz, 1H), 3.96 (t, J = 6.2 Hz, 1H), 2.82 (dt, J = 14.1, 8.4 Hz, 2H), 2.13 (m, 2H), 2.03 (m, 1H), 1.84 (d, J = 5.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 136.4, 129.9, 129.8, 128.8, 128.0, 126.6, 121.8, 30.8, 28.4, 27.4, 20.8. IR (KBr, cm^{-1}): ν = 3024, 2938, 2238, 1688, 1448, 1283, 739. HRMS (ESI) $C_{11}H_{12}N$ $[M + H]^+$: calcd, 158.0970; found, 158.0962.

*Chroman-4-carbonitrile (**3bu**).* Yield: 67 mg (85%), yellowish-green oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.29 (d, J = 7.7 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 4.34 (m, 1H), 4.23 (m, 1H), 4.03 (t, J = 6.0 Hz, 1H), 2.34 (dd, J = 10.3, 5.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 154.0, 129.9, 129.4, 121.2, 120.5, 117.8, 115.2, 63.6, 26.9, 26.1. IR (KBr, cm^{-1}): ν = 3889, 3746, 3557, 3208, 2922, 2856, 1646, 1477, 1227, 754. HRMS (ESI) $C_{10}H_{10}NO$ $[M + H]^+$: calcd, 160.0762; found, 160.0766.

*2-Methyl-4-phenylbutanenitrile (**3bv**).* Yield: 60 mg (76%), yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.31 (m, 2H), 7.22 (m, 3H), 2.87 (ddd, J = 14.2, 9.0, 5.5 Hz, 1H), 2.75 (m, 1H), 2.58 (m, 1H), 1.95 (ddd, J = 14.5, 8.6, 4.5 Hz, 1H), 1.84 (m, 1H), 1.33 (d, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 140.2, 128.6, 128.4, 126.4, 122.8, 35.8, 33.2, 24.8, 18.0. IR (KBr, cm^{-1}): ν = 3337, 3190, 2922, 2856, 1730, 1464, 1272, 743. HRMS (ESI) $C_{11}H_{13}NNa$ $[M + Na]^+$: calcd, 182.0940; found, 182.0936.

*4,4-Dimethylcyclohex-2-enecarbonitrile (**3bw**).* Yield: 42 mg (62%), yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 6.56 (dq, J = 5.8, 1.8 Hz, 1H), 2.24 (ddd, J = 8.9, 3.8, 2.4 Hz, 2H), 1.96 (dd, J = 6.5, 2.8 Hz, 2H), 1.43 (t, J = 6.4 Hz, 2H), 0.93 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ = 144.3, 119.7, 111.3, 39.4, 34.1, 29.7, 28.0, 28.0, 24.5. IR (KBr, cm^{-1}): ν = 2930, 2661, 2222, 1762, 1454, 1249, 1035, 753. HRMS (ESI) $C_9H_{13}NNa$ $[M + Na]^+$: calcd, 158.0940; found, 158.0952.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00836.

NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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