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Note

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Metal-Free Aerobic Oxidative Cyanation of Tertiary Amines: Azobisisobutyronitrile (AIBN) as a Sole Cyanide Source

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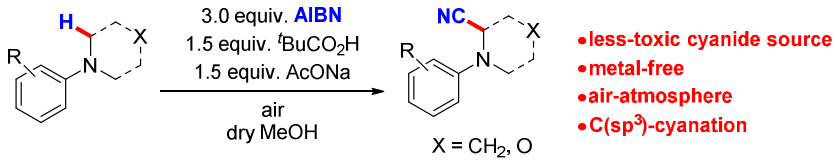


ABSTRACT: An aerobic oxidative cyanation for the synthesis of α-aminonitriles was reported. The formation of C(sp^3)-CN bonds was achieved under a metal-free condition by utilizing azobisisobutyronitrile as a sole organic-cyanide source with the combination of pivalic acid and sodium acetate as additives.

α-Aminonitriles are highly useful precursors for constructing nitrogen-containing bioactive compounds, such as α-amino acids and alkaloids.[1-4] These bifunctional compounds show versatile reactivity by generating both iminium ions (electrophilic reagents) and carbon anions (nucleophilic reagents),[5] which have been utilized to synthesize various valuable functionalities, including α-amino aldehydes, ketones and α-amino alcohols.[6,7] Therefore, the development of clean and efficient methods for the synthesis of α-aminonitriles has gained much interest.

Compared to the well-documented Strecker reaction,[6,8,9,10] transition-metal-catalyzed direct C-CN bond-forming reactions *via* the C-H bond functionalization of tertiary amines are presently the most straightforward strategies to assemble α-aminonitriles, including utilizing Ru,[11-17] Cu,[18-20] V,[21] Au,[22,23] Mo,[24] Re,[25] Fe,[26-33] and Ir[34] catalysts and stoichiometric amounts of oxidants. Regarding the existed CN sources, widely used metal cyanide (CN) sources (KCN, NaCN, etc.)[11-15,21,24,27,34-38] have been shown to be efficient for C-CN bonds formation. Alternatively, multiple organic CN sources,[39-54] such as cyanohydrin,[39,40,41] malononitrile,[42] ethylcyanoformate,[43,44] phenylacetonitrile,[45] acetonitrile,[13,46,47] trimethylsilyl cyanide,[23,48,49,50] cyanoacetic acid[51] as well as combined CN sources[52-55] have been intensively investigated. However, most of these protocols employ transition-metal catalytic systems and produce hazardous metal-CN waste. It is, therefore, highly demanding to develop an easily available less-toxic CN source that can be used for a metal-free cyanation of tertiary amines.

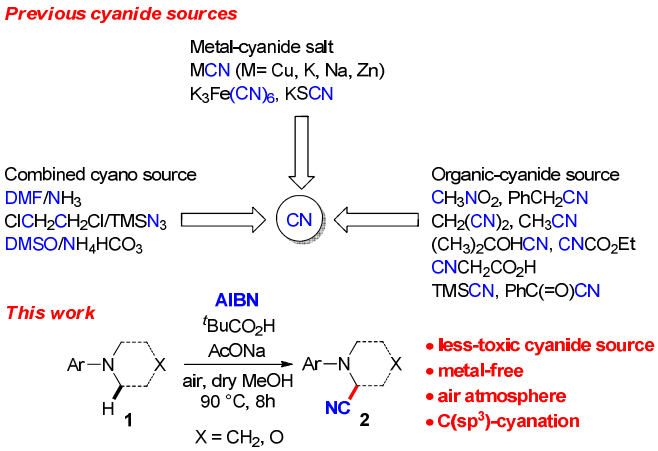
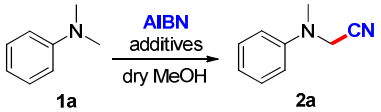


Figure 1. CN sources in cyanation reactions.

2,2'-Azobisisobutyronitrile (AIBN) is generally used as a radical initiator. In 2012, Fu and co-workers reported an elegant approach for the AIBN-initiated cyanation of tertiary amines.[56] In 2013, for the first time, the Han group published a pioneering work on the copper-mediated direct C(sp^2)-cyanation of 2-arylpyridine using AIBN as the CN source.[57] Recently, the Cheng group successfully developed the copper-catalyzed *S*-cyanation and *N*-cyanation using AIBN as an organic CN source.[58,59] To the best of our knowledge, no report

on the direct cyanation of C(sp^3)-H bond of tertiary amines adopting AIBN as a CN source has been disclosed. Herein, we report for the first time on the generation "CN" unit from AIBN without adding either transition-metal catalysts or an additional cyanide source, while efficiently delivering α-aminonitriles from tertiary amines in the presence of air as an oxidant under mild conditions. (Figure 1)

Table 1. Optimization of the oxidative cyanation of aniline **1a**[a]



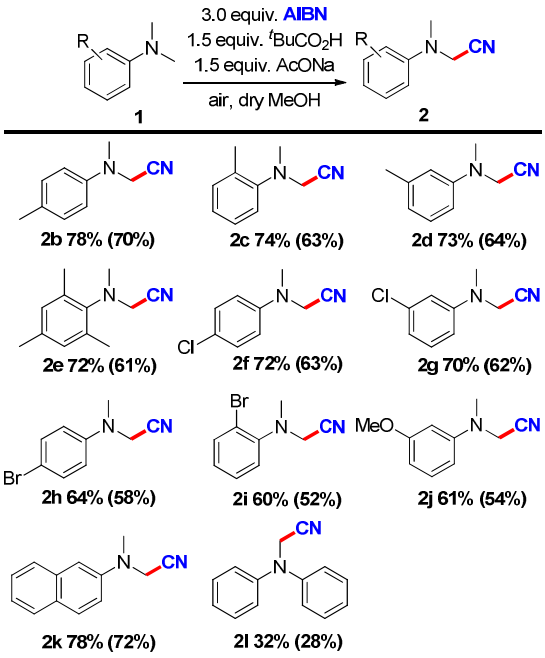
1a **2a**

Entry	AIBN (equiv.)	Acid (1.5 equiv.)	Base (1.5 equiv.)	Atm.	Temp. (°C)	Time (h)	Yield[b] (%)
1	3	-	-	air	90	8	46
2	3	-	-	air	90	12	45
3	5	-	-	air	90	8	48
4	3	AcOH	-	air	90	8	70
5	3	$PhCO_2H$	-	air	90	8	68
6	3	TFA	-	air	90	8	65
7	3	$^tBuCO_2H$	-	air	90	8	72
8	3	-	AcONa	air	90	8	52
9	3	-	AcOK	air	90	8	48
10	3	$^tBuCO_2H$	AcONa	air	90	8	**84(72)**[c]
11	3	$^tBuCO_2H$	AcONa	O_2	90	8	46
12	3	$^tBuCO_2H$	AcONa	Ar	90	8	<5[d]
13	2	$^tBuCO_2H$	AcONa	air	90	8	80
14	5	$^tBuCO_2H$	AcONa	air	90	8	83
15	3	$^tBuCO_2H$	AcONa	air	70	8	72
16	3	$^tBuCO_2H$	AcONa	air	110	8	68
17	3	$^tBuCO_2H$	AcONa	air	90	4	80
18	3	$^tBuCO_2H$	AcONa	air	90	12	82
19[e]	3	$^tBuCO_2H$	AcONa	air	90	8	32

[a]Reaction conditions: AIBN as the CN source, additive, and dry methanol (MeOH, 1.2 mL). [b]Yields are based on ^1H NMR analysis of the reaction mixture using 1,3,5-trimethoxybenzene as an internal standard on a 0.2 mmol scale. [c]Isolated yield is shown in parentheses. [d]The starting material was recovered in a 82% yield. [e]Using regular methanol from the standard supplier as the solvent.

As indicated in Table 1, we chose *N,N*-dimethylaniline **1a** as a model substrate to explore the suitable conditions for the aerobic oxidative cyanation. Initial trials showed that the reaction proceeded to give the desired product **2a** in moderate yields when AIBN was used as the cyanation reagent at 90 °C for 8-12 h in the absence of an additive (entries 1-3). The yield of **2a** was improved to 65-72%, and the starting material was almost completely consumed with 1.5 equiv. of Brønsted acid used as an additive (entries 4-7), indicating that the addition of a Brønsted acid was crucial to ensure good conversion. A brief comparison of acids showed that pivalic acid ($^tBuCO_2H$) was slightly better than the others (entries 4-7). The use of basic additives, such as sodium acetate (AcONa) and potassium acetate (AcOK), resulted in lower yields (entries 8 and 9). However, surprisingly, the combination of $^tBuCO_2H$ and AcONa was found to be most effective for the cyanation reaction (entry 10, 84% yield). The optimized yield of **2a** was achieved in an air atmosphere, while the cyanation produced a complex mixture with only 46% yield under a pure O_2 atmosphere (entry 11). The reaction hardly proceeded in an argon atmosphere, which agrees with the isotopic labeling experiment conducted by Han and co-workers (entry 12). Further investigation of the reaction conditions revealed that changing the amount of AIBN, the reaction time, and temperature did not improve the transformation (entries 13-18). CAUTION: The entire reaction process including the work-up must be carried out in a well-ventilated fume hood and the lid of the high pressure flask should be tight throughout the reaction process.

Table 2. Synthesis of substituted anilines via oxidative cyanation[a,b]



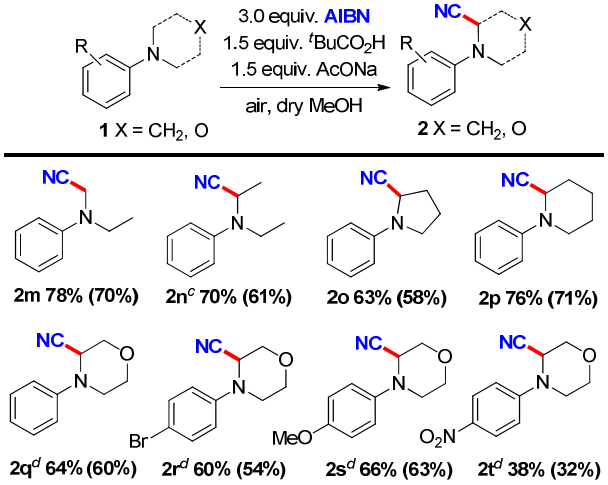
[a]Reaction conditions: 0.2 mmol of the starting materials. Yields are based on ^1H NMR analysis of the reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yields are shown in parentheses.

With the optimal reaction conditions in hand, we next examined the reaction scope by varying the substituents on the aromatic ring of *N,N*-dimethylaniline (Table 2). The results are summarized in Table 2. Methyl and trimethyl substitutions on the aniline aromatic ring worked well, leading to the formation of **2b-e** in 72-78% yields. Notably, substrates decorated by halogen groups, including chloro and bromo groups (**2f-i**), were also viable under these reaction conditions, providing handles for further derivatization. However, no reaction was observed utilizing substrates containing strong electron-withdrawing groups, such as nitro or CN on the phenyl ring of *N,N*-dimethylaniline, while the substrate with *m*-methoxy group smoothly underwent the cyanation to yield **2j**. This pro-

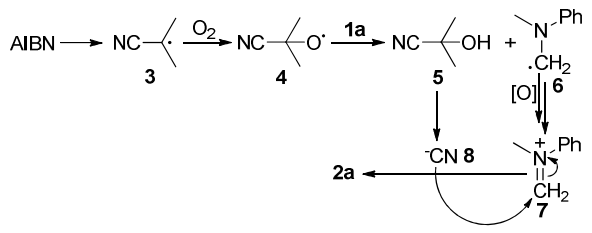
cess can also be applied to *N*,*N*-dimethylnaphthalen-2-amine, delivering **2k** in a 78% yield. Notably, cyanation of *N*-methyl-*N*-phenylaniline was observed under the standard condition (**2l**, 32%).

Next, we evaluated the substrate scope by changing the *N*-alkyl group (Table 3). Interestingly, oxidative cyanation of *N*-ethyl-*N*-methylaniline produced corresponding methyl cyanated α-aminonitrile **2m** as the only observed product in good yield (78%), and no observation of the ethyl cyanate showed a high chemoselectivity. When *N*,*N*-diethylaniline was treated under the optimized reaction condition, **2m** was obtained as a major product associated with a small amount of **2n**.[30] However, when ethanol was utilized as the solvent instead of the regular methanol, **2n** was obtained in 70% yield without formation of **2m** as the byproduct. *N*-arylated cyclic amines, such as pyrrolidine **2o** and piperidine **2p**, were well tolerated in this transformation, giving the cyanation products in good yields. Further study of the reaction scope indicated that the reactivity of *N*-phenylmorpholines was relatively lower, satisfactory yields of **2q-t** could be obtained by adding another 1.5 equiv. of AIBN after 4 h.

Table 3. Synthesis of substituted tertiary amines via oxidative cyanation[a,b]



[a]Reaction conditions: 0.2 mmol of the starting materials. Yields are based on ^{1}H NMR analysis of the reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yields are shown in parentheses. [c]Dry ethanol (EtOH) was used as the solvent. [d]Another 1.5 equiv. of AIBN was added after 4 h.



Scheme 1. Possible reaction mechanism

On the basis of our results and works published by the Fu,[56] Han[57] and Ofial[30] groups, iminium intermediate **7** and CN^- ion **8** are thought to be present during the oxidative cyanation.(Scheme 1) Initially, AIBN is decomposed under heating to form radical intermediate **3** which then is converted to the active species 2-cyano-2-propyloxyl radical **4** with the aid of oxygen. Abstraction of a hydrogen atom from **1a** by radical **4** generates acetone cyanohydrin **5** and the crucial radical intermediate **6**.[56] Then, acetone cyanohydrin **5** eliminates CN^- ion **8**[56] and the radical intermediate **6** is oxidized to iminium cation **7** under oxidative condition.[30,56] Finally the iminium **7** is attacked by CN^- ion **8** to deliver the product **2a**.

In summary, a metal-free process for constructing C(sp^3)-CN bonds was developed utilizing AIBN as a sole CN source and air as a clean oxidant for the aerobic oxidative cyanation of tertiary amines. This novel protocol may provide α-aminonitriles as precursors particularly useful for the synthesis of biologically important compounds. Applications of this metal-free oxidative cyanation to other coupling reactions, together with detailed mechanistic studies, are currently under exploration in our laboratory.

Experiment Section

General information.

1. All commercial materials were used as received unless otherwise noted. AIBN (98%, Aldrich) was used in the aerobic oxidative cyanation. Flash chromatography was performed using 230-400 mesh SiliaFlash® P60 (Silicycle Inc.).

2. Instruments: All products were characterized by their ^{1}H NMR, ^{13}C NMR on a Bruker AV-400 and 500 MHz spectrometer. Data for ^{1}H NMR are reported as follows chemical shift, integration, multiplicity (s = singlet, d = doublet, dd = doublet doublet, t = triplet, q = quarte, m = multiplet) and coupling constants are reported as values in hertz (Hz). Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$: 7.26 ppm for 1H and 77.16 ppm for 13C; Acetone-d6: 2.05 ppm for 1H and 206.26, 29.84 ppm for 13C). High resolution ESI mass experiments were operated on a Bruker Daltonics, Inc. APEXIII 7.0 TESLA FTMS instrument using FT-ICR analyzer type for HRMS measurements.

General procedure. A mixture of tertiary amine derivatives **1** (0.2 mmol, 1.0 eq), AIBN (98.5 mg, 0.6 mmol, 3.0 eq), ^{t}BuCO$_2$H (30.6 mg, 0.3 mmol, 1.5 eq), AcONa (24.6 mg, 0.3 mol, 1.5 eq) and dry methanol (1.0 ml, dried with magnesium and iodine) in 15 mL high pressure flask vial under an air atmosphere was heated at 90 ºC for 8 hours (slowly heated up, from rt. to 90 ºC over 40 min.). The reaction mixture was cooled to room temperature, and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography using 3-20% ethyl acetate in petroleum ether to give the cyanation product. (For **2q-t**, another 1.5 equiv. of AIBN was added after 4 h.)

CAUTION: Although we have not observed any issue during our extensive work with AIBN, extra caution should be taken when working with AIBN and air under heating conditions due to the potential production of cyanide ion which produces HCN gas in the presence of a Brønsted acid. It should be particularly stressed that the entire reaction process including the work-up must be carried out in a well-ventilated fume hood. Moreover, the lid of the high pressure flask should be tight throughout the reaction process, and it should be carefully

opened after the reaction mixture is cooled to room temperature. When the lid was opened at room temperature during our experiment, no pressure was observed.

2-(methyl(phenyl)amino)acetonitrile (2a).[11] 21.0 mg, 72%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33 (t, *J* = 8.0 Hz, 2H), 6.94 (t, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 4.17 (s, 1H), 3.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.9, 129.6, 120.3, 115.6, 115.0, 42.4, 39.3.

2-(methyl(*p*-tolyl)amino)acetonitrile (2b).[11] 22.4 mg, 70%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.13 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 4.14 (s, 2H), 2.97 (s, 3H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 145.8, 130.1, 115.6, 43.0, 39.6, 20.5.

2-(methyl(*o*-tolyl)amino)acetonitrile (2c).[13] 20.2 mg, 63%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.23-7.19 (m, 3H), 7.10-7.06 (m, 1H), 3.86 (s, 2H), 2.87 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz): δ = 148.6, 133.0, 131.5, 127.0, 125.1, 120.8, 115.8, 45.2, 41.1, 17.9.

2-(methyl(*m*-tolyl)amino)acetonitrile (2d).[11] 20.5 mg, 64%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.22-7.18 (m, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.69-6.68 (m, 2H), 4.17 (s, 2H), 3.00 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.0, 139.4, 129.4, 121.3, 115.9, 115.7, 112.3, 39.4, 42.5, 21.9.

2-(mesityl(methyl)amino)acetonitrile (2e).[30] 23.0 mg, 61%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.84 (s, 2H), 3.92 (s, 2H), 2.94 (s, 3H), 2.27 (s, 6H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 144.3, 137.0, 136.0, 129.8, 117.8, 44.2, 40.5, 29.9, 20.9, 19.1.

2-((4-chlorophenyl)(methyl)amino)acetonitrile (2f).[25] 22.8 mg, 63%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.28-7.25 (m, 2H), 6.79 (d, *J* = 8.0 Hz, 2H), 4.15 (s, 2H), 3.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 146.5, 129.5, 125.6, 116.3, 115.3, 42.5, 39.6.

2-((3-chlorophenyl)(methyl)amino)acetonitrile (2g).[23] 22.4 mg, 62%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.22 (t, *J* = 8.0 Hz, 1H), 6.90-6.87 (m, 1H), 6.82 (t, *J* = 2.0 Hz, 1H), 6.73-6.70 (m, 1H), 4.16 (s, 2H), 3.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.9, 135.5, 130.6, 120.1, 115.3, 114.8, 112.7, 42.0, 39.3.

2-((4-bromophenyl)(methyl)amino)acetonitrile (2h).[11] 26.1 mg, 58%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.40 (d, *J* = 8.0 Hz, 2H), 6.74 (d, *J* = 8.0 Hz, 2H), 4.15 (s, 2H), 3.0 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 146.9, 132.4, 116.6, 115.2, 112.8, 42.4, 39.5.

2-((2-bromophenyl)(methyl)amino)acetonitrile (2i).[26] 23.4 mg, 52%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.59 (dd, *J* = 1.6, 9.2 Hz, 1H), 7.36-7.32 (m, 1H), 7.28 (dd, *J* = 2.0, 10.0 Hz, 1H), 7.05-7.01 (m, 1H), 4.09 (s, 2H), 2.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.5, 134.1, 128.7, 126.5, 122.9, 119.9, 115.3, 45.0, 40.7.

2-((3-methoxyphenyl)(methyl)amino)acetonitrile (2j).[45] 19.0 mg, 54%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.22 (t, *J* = 8.25 Hz, 1H), 6.49-6.46 (m, 2H), 6.40 (t, *J* = 2.25 Hz, 1H), 4.16 (s, 3H), 3.81 (s, 3H), 3.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 160.9, 149.3, 130.4, 115.6, 107.7, 104.9, 101.9, 55.4, 42.4, 39.4.

2-(methyl(naphthalen-2-yl)amino)acetonitrile (2k). 28.3 mg, 72%. Light yellow liquid; R_f = 0.50, PE/EA = 2:1; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.80-7.73 (m, 3H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.19-7.14 (m, 2H), 4.26 (s, 2H), 3.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 145.7, 134.5, 129.5, 128.6, 127.6, 126.9, 126.8, 123.9, 117.3, 115.5, 110.4, 42.7, 39.6; IR: 2958.0, 2236.4 (CN), 1674.5, 1600.2 cm^{-1}; HRMS Calcd for $C_{13}H_{13}N_2^+$ $[M+H]^+$: 197.1073; Found: 197.1072.

2-(diphenylamino)acetonitrile (2l).[60] 11.7 mg, 28%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35 (t, *J* = 8.0 Hz, 2H), 7.11 (t, *J* = 8.0 Hz, 2H), 7.06 (t, *J* = 8.0 Hz, 4H), 4.52 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 146.5, 129.9, 123.6, 121.4, 116.2, 41.4.

2-(ethyl(phenyl)amino)acetonitrile (2m).[12] 22.4 mg, 70%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33-7.29 (m, 2H), 6.92-6.86 (m, 3H), 4.15 (s, 2H), 3.44 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 146.9, 129.6, 119.9, 116.5, 115.1, 46.4, 39.7, 12.4.

2-(ethyl(phenyl)amino)propanenitrile (2n).[22] 21.3 mg, 61%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.31 (t, *J* = 7.5 Hz, 2H), 6.99 (t, *J* = 7.5 Hz, 3H), 4.48 (q, *J* = 5.0 Hz, 1H), 3.40-3.31 (m, 2H), 1.57 (d, *J* = 5.0 Hz, 3H), 1.19 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 146.9, 129.5, 121.8, 119.6, 119.1, 48.3, 43.7, 18.6, 13.9.

1-phenylpyrrolidine-2-carbonitrile (2o).[14] 20.0 mg, 58%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33-7.29 (m, 2H), 6.85 (t, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 2H), 4.43 (d, *J* = 8.0 Hz, 1H), 3.48-3.33 (m, 2H), 2.42-2.41 (m, 1H), 2.29-2.18 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 145.3, 129.6 ,119.4, 118.4, 112.8, 49.2, 47.6, 31.7, 24.1.

1-phenylpiperidine-2-carbonitrile (2p).[12] 26.4 mg, 71%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.32 (t, *J* = 8.0 Hz, 2H), 7.02-6.98 (t, *J* = 8.0 Hz, 3H), 4.63 (s, 1H), 3.46 (d, *J* = 12.0 Hz, 1H), 3.04 (t, *J* = 12.0 Hz, 1H), 2.04-2.01 (m, 2H), 1.87-1.85 (m, 2H), 1.70-1.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 149.9, 129.5, 122.3, 118.4, 117.3, 52.1, 46.7, 29.4, 25.3, 20.3.

4-phenylmorpholine-3-carbonitrile (2q).[30] 22.6 mg, 60%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.38-7.34 (t, *J* = 8.0 Hz, 2H), 7.05 (t, *J* = 6.0 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 4.42 (t, *J* = 2.0 Hz, 1H), 4.16-4.07 (m, 2H), 3.89 (dd, *J* = 1.6 Hz, 14.4 Hz, 1H), 3.77-3.71 (m, 1H), 3.29-3.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.4, 129.7, 122.6, 117.3, 116.1, 68.1, 66.9, 51.0, 45.5.

4-(4-bromophenyl)morpholine-3-carbonitrile (2r). 28.8 mg, 54%. Light yellow liquid; R_f = 0.5, PE/EA = 2:1; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.45 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 2H), 4.37 (s, 1H), 4.18-4.08 (m, 2H), 3.90 (dd, *J* = 4.0 Hz, 16.0 Hz, 1H), 3.77-3.70 (m, 1H), 3.26-3.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.6, 132.6, 119.1, 115.8 ,115.5, 68.1, 66.9, 60.0, 45.6; IR: 2919, 2237 (CN), 1724, 1592 cm^{-1}; HRMS Calcd for $C_{11}H_{12}BrON_2^+$ $[M+H]^+$: 267.0128; Found: 267.0124.

4-(4-methoxyphenyl)morpholine-3-carbonitrile (2s). 27.5 mg, 63%. Yellow viscous liquid; R_f = 0.47, PE/EA = 2:1; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.97 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 4.25 (s, 1H), 4.14-4.05 (m, 2H), 3.93 (dd, *J* = 2.8 Hz, 14.0 Hz, 1H), 3.79 (s, 3H), 3.73 (dd, *J* = 4.0 Hz, 14.0 Hz, 1H), 3.33-3.26 (m, 1H), 3.09 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.9, 142.4, 120.1,116.2, 115.0, 68.3, 67.2, 55.7, 53.0, 46.5; IR: 3009, 2229 (CN), 1514, 1447 cm^{-1}; HRMS Calcd for $C_{12}H_{15}O_2N_2^+$ $[M+H]^+$: 219.1128; Found: 219.1127.

4-(4-nitrophenyl)morpholine-3-carbonitrile (2t). 14.9 mg, 32%. A light yellow solid; mp: 123-124 ºC; R_f = 0.33, PE/EA = 2:1; ^{1}H NMR (acetone-d_6, 400 MHz): δ = 8.23 (d, *J* = 9.6 Hz, 2H), 7.28 (d, *J* = 9.2 Hz, 2H), 5.23 (s, 1H), 4.25 (d, *J* =

12.0 Hz, 1H), 4.13 (dd, J = 3.2 Hz, 11.6 Hz, 1H), 3.94 (dd, J = 2.8 Hz, 14.8 Hz, 1H), 3.84 (d, J = 8.0 Hz, 1H), 3.75 (dt, J = 1.2 Hz, 11.6 Hz, 1H), 3.20 (dt, J = 3.6 Hz, 15.6 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz): δ = 154.3, 141.8, 126.2, 117.0, 115.6, 68.5, 67.0, 48.8, 45.0; IR: 3262, 2976, 2241 (CN), 1652, 1548 cm^{-1}; HRMS Calcd for $C_{11}H_{12}O_3N_3^+$ $[M+H]^+$: 234.0873; Found: 234.0868.

ASSOCIATED CONTENT

Supporting Information

Supporting Information ^{1}H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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