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Synthesis of aryl nitriles by palladium-assisted cyanation of aryl iodides using *tert*-butyl isocyanide as cyano source

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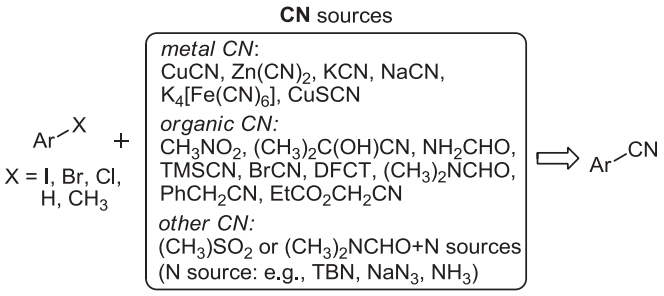
ABSTRACT

A palladium-catalyzed synthesis of aryl nitriles by the cyanation of aryl iodides with *tert*-butyl isocyanide as cyano source has been developed. This novel and efficient method avoids the use of toxic cyanides. The reaction is easy-to-handle and shows good functional group compatibility.

1. Introduction

Aryl nitriles are an integral part of many natural products, pharmaceuticals, agrochemicals, herbicides, pigments, and dyes.[1] In addition, they are easily transformed into other functional groups, such as amines, acids, amides, aldehydes, and heterocycles.[2] As a result, a number of methods to introduce cyano group to aromatic ring have been developed. Of these transformations, transition-metal-catalyzed cyanation of aryl halides[2e] or aromatic C–H bond activation was an elegant route to benzonitriles (Scheme 1). However, typical protocols utilized toxic cyanides (e.g., $Cu(CN)_2$,[3] $Zn(CN)_2$,[4] NaCN, and KCN[5]), CH_3NO_2,[6] acetone cyanohydrin,[7] cyanogen halides,[8] TMSCN,[9] *N*-cyano-*N*-phenyl-*para*-toluenesulfonamide (NCTS),[10] and aryl(cyano)iodonium triflates (DFCT)[11] as cyanating agents. Low toxic CN source was thus highly desired. $K_4[Fe(CN)_6]$ was first used by Beller and co-workers to introduce CN into organic molecules.[12] Recently, other CN sources such as ammonium salts or organic amine/DMSO,[13] DMF,[14] formamide,[14f,g] ethyl cyanoacetate,[15a] benzyl cyanide,[15b–d] CuSCN,[16] NaN_3,[17] NH_3, and *tert*-butyl nitrite (TBN)[18] have been demonstrated to deliver nitriles. However, poor functional group tolerance and maneuverability restricted their application.



Scheme 1. Approaches to aryl nitriles.

Isocyanides, which are well known as isoelectronic equivalent of CO, are powerful C_1 building blocks in organic synthesis since the pioneer work of Passerini and Ugi.[19] Palladium-catalyzed isocyanide insertion has been widely applied in the synthesis of nitrogenous compounds.[20] Our group has successfully constructed C–O, C–C, C–N and aldehydes via metal-catalyzed isocyanide insertion into C-X bonds.[21] Nevertheless, the use of isocyanides as a cyano source has been less explored.[22] Palladium-catalyzed direction C–H cyanation of phenylindole and phenylpyridine was only reported by Xu and Zhu.[22e–g] However, those reactions limit the scope to electron-rich and regioselective nitrogen-containing indoles or 2-phenylpyridine derivatives. Herein, for further broadening the application of isocyanides as CN source in the

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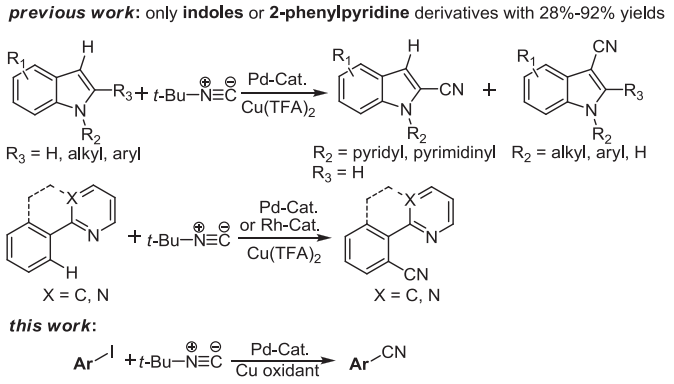
synthesis of aromatic and heteroaromatic nitriles, we describe an efficient palladium-catalyzed cyanation of aryl iodides using *tert*-butyl isocyanide as CN source (Scheme 2).



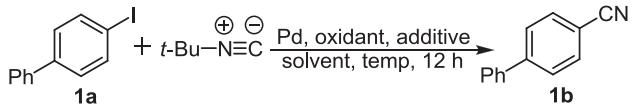
Scheme 2. Cyanation using isocyanide as CN source.

2. Results and discussion

Our investigation began with examining the reaction of 4-phenyliodobenzene and *t*-BuNC (1.2 equiv) utilizing $Pd(OAc)_2$ (5 mol %) as catalyst, copper(II) trifluoroacetate hydrate (3 equiv) as oxidant and Na_2CO_3 (1 equiv) as base at 130 °C. To our delight, 4-phenylbenzonitrile was produced in 46% yield in DMF under N_2 for 12 h (Table 1, entry 1). In the presence of 3 equiv of *t*-BuNC, completed conversion was achieved under 2 equiv of $Cu(TFA)_2 \cdot xH_2O$ and the yield was increased to 83% (Table 1, entry 2). Base had no significant effect on this reaction (Table 1, entry 3 and 4). Both of 76% yield of the corresponding benzonitrile and 4-phenylbenzaldehyde were obtained in absence of base, which might be attributed to the solvent DMF (Table 1, entry 5). Solvent screening showed that DMSO was better than other non-polar solvents in the reaction (Table 1, entries 6–8). Lower temperature led to decrease in the yield of desired product (Table 1, entry 9). Compared to other palladium catalysts such as $PdCl_2$, $Pd(TFA)_2$, and $Pd_2(dba)_3$, $Pd(OAc)_2$ gave better result (Table 1, entries 10–12). The absence of $Pd(OAc)_2$ decreased the yield of the product (Table 1, entry 13), and trace amounts of the desired product was produced without $Cu(TFA)_2 \cdot xH_2O$ (Table 1, entry 14). With using CF_3COOAg as oxidant, only 23% yield was got (Table 1, entry 15). Different Cu(II) oxidants were tested (Table 1, entries 16–20). And we observed that the presence of H_2O promoted this reaction (Table 1, entries 16, 19, and 20–22). When the reaction was run with 10% of $Cu(TFA)_2 \cdot xH_2O$ under O_2, no desired product was detected (Table 1, entry 23). However, attempt to utilize other isocyanides such as cyclohexyl isocyanide was not successful (Table 1, entry 24). Thus, the optimized reaction conditions was aryl halide (1 equiv), *tert*-butyl isocyanide (3 equiv), $Pd(OAc)_2$ (5 mol %), and $Cu(TFA)_2 \cdot xH_2O$ (2 equiv) in DMSO at 130 °C under N_2 atmosphere.

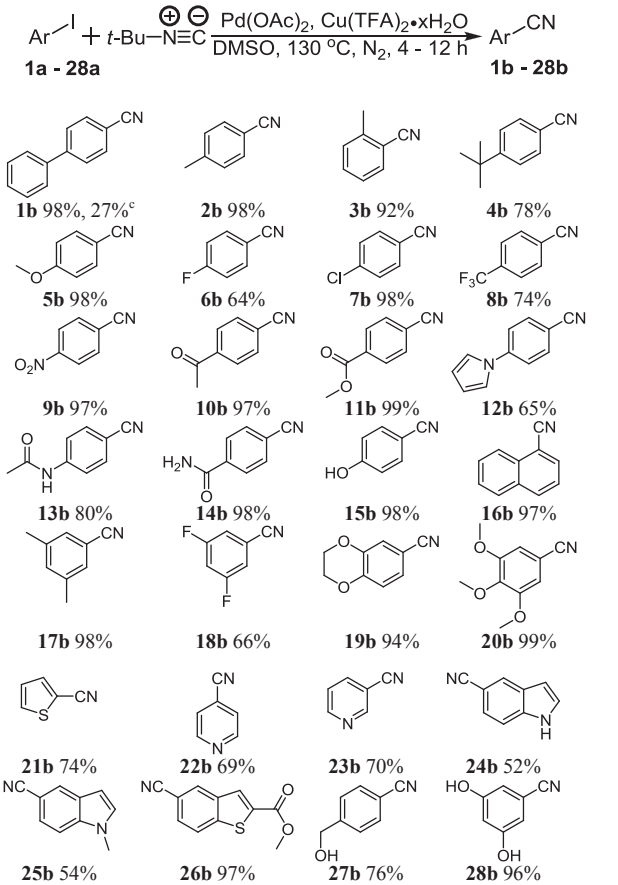
Next we explored the scope and limitation of the new protocol (Scheme 3). Only 27% yield of nitrile was obtained when using 4-bromobiphenyl (Scheme 3, **1b**). Both electron neutral (Scheme 3, **1b**–**5b**, **15b**, **16b**, **17b**, **19b**, and **20b**) and electron deficient (Scheme 3, **6b**–**14b**, and **18b**) aryl iodides were transformed to the desired aryl nitriles smoothly with 64%–99% yields. Steric hindrance has a slight effect on the reaction (Scheme 3, **2b** and **3b**). Various of

Table 1
Optimization of reaction conditions[a]



Entry	Catalyst	Oxidant	Additive	Solvent	Temp (°C)	Yield[b] (%)
1	$Pd(OAc)_2$	$Cu(TFA)_2 \cdot xH_2O$	Na_2CO_3	DMF	130	46[c]
2	$Pd(OAc)_2$	$Cu(TFA)_2 \cdot xH_2O$	Na_2CO_3	DMF	130	83
3	$Pd(OAc)_2$	$Cu(TFA)_2 \cdot xH_2O$	Cs_2CO_3	DMF	130	82
4	$Pd(OAc)_2$	$Cu(TFA)_2 \cdot xH_2O$	$NaHCO_3$	DMF	130	84
5	$Pd(OAc)_2$	$Cu(TFA)_2 \cdot xH_2O$	—	DMF	130	76
6	$Pd(OAc)_2$	$Cu(TFA)_2 \cdot xH_2O$	—	DMSO	130	98
7	$Pd(OAc)_2$	$Cu(TFA)_2 \cdot xH_2O$	—	toluene	130	35
8	$Pd(OAc)_2$	$Cu(TFA)_2 \cdot xH_2O$	—	dioxane	120	28
9	$Pd(OAc)_2$	$Cu(TFA)_2 \cdot xH_2O$	—	DMSO	110	59
10	$PdCl_2$	$Cu(TFA)_2 \cdot xH_2O$	—	DMSO	130	93
11	$Pd(TFA)_2$	$Cu(TFA)_2 \cdot xH_2O$	—	DMSO	130	95
12	$Pd_2(dba)_3$	$Cu(TFA)_2 \cdot xH_2O$	—	DMSO	130	92
13	—	$Cu(TFA)_2 \cdot xH_2O$	—	DMSO	130	86
14	$Pd(OAc)_2$	—	—	DMSO	130	trace[d]
15	$Pd(OAc)_2$	AgTFA	—	DMSO	130	23
16	$Pd(OAc)_2$	$CuCl_2$	—	DMSO	130	45
17	$Pd(OAc)_2$	$Cu(OAc)_2$	—	DMSO	130	38
18	$Pd(OAc)_2$	$Cu(NO_3)_2 \cdot 2.5H_2O$	—	DMSO	130	87
19	$Pd(OAc)_2$	$CuSO_4$	—	DMSO	130	59
20	$Pd(OAc)_2$	$CuSO_4 \cdot 5H_2O$	—	DMSO	130	76
21	$Pd(OAc)_2$	$Cu(TFA)_2 \cdot xH_2O$	$CaCl_2$	DMSO	130	51
22	$Pd(OAc)_2$	$CuCl_2$	H_2O	DMSO	130	52
23	$Pd(OAc)_2$	$Cu(TFA)_2 \cdot xH_2O/O_2$	—	DMSO	130	trace[e]
24	$Pd(OAc)_2$	$Cu(TFA)_2 \cdot xH_2O$	—	DMSO	130	18[f]

[a] Conditions: All reactions were performed with **1a** (0.7 mmol), *tert*-butyl isocyanide (3 equiv), catalyst (5 mol %), oxidant (2 equiv), and additive (1 equiv) in 2.5 mL of solvent under nitrogen for 12 h in a sealed tube unless otherwise noted.
[b] Isolated yield.
[c] *tert*-Butyl isocyanide (1.2 equiv), oxidant (3 equiv).
[d] With DPPP (10 mol %).
[e] Performed with 10 mol % of oxidant under O_2.
[f] Cyclohexyl isocyanide (3 equiv).

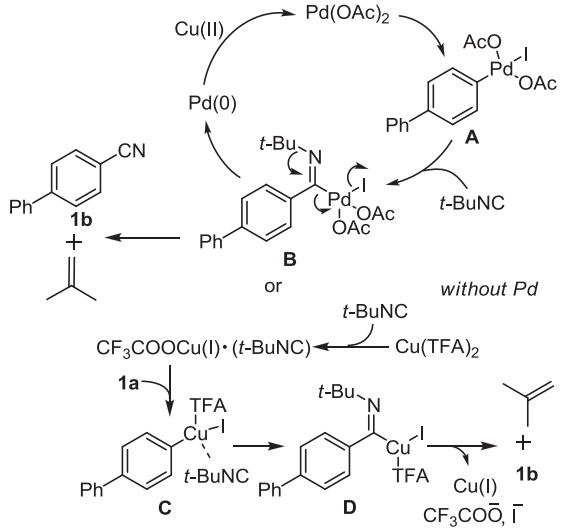


[a] Conditions: All reactions were performed with **1** (0.7 mmol), *tert*-butyl isocyanide (3 equiv), $Pd(OAc)_2$ (5 mol %), $Cu(TFA)_2 \cdot xH_2O$ (2 equiv) and DMSO (2.5 mL) under nitrogen at 130 °C for 4-12 h in a sealed tube unless otherwise noted. [b] Isolated yield. [c] 4-Bromobiphenyl.

Scheme 3. Synthesis of aryl nitriles.[a,b]

functional groups including ether, halogen, nitryl, ketone, ester and pyrrolyl are well tolerated, affording the desired products with good to excellent yields (Scheme 3, **5b**–**12b**). Intriguingly, compounds containing active hydrogen, such as acetamide, amide, phenol and alcohol, were well tolerated (Scheme 3, **13b**–**15b** and **27b**). And the product of disubstituted and trisubstituted iodobenzenes gave the nitriles in 66%–99% yields (Scheme 3, **17b**–**20b** and **28b**). Notably, moderate to good yields were obtained with some heteroaromatic substrates (Scheme 3, **21b**–**25b**). Besides, **26b** was achieved in 97% yield.

When the reaction was performed with *N*-*tert*-butylbiphenyl-4-carboxamide[20d] under the standard reaction conditions, no desired **1b** was observed, which indicated nitrile can not be converted from amide in this reaction conditions. As shown in Table 1, entries 13, 14 and 15, both of $Pd(OAc)_2$ and $Cu(TFA)_2$ can catalyze this transformation. Based on the reports of Xu and Zhu,[22e–g] we preliminarily speculate the following possible mechanism (Scheme 4). Electrophilic palladation of Pd(II) with **1a** leads to the intermediate **A**. The key imidoyl Pd intermediate **B** is generated via migratory insertion of isocyanide. Then the product of **1b** was obtained with the elimination of Isobutene from **B**. And palladium(II) species can be regenerated by the oxidation of Cu(II). In absence of Pd, Cu(I) carboxylate-isonitrile complex can also provide *tert*-butyl isocyanide for migratory insertion.[22] And with the formation of Cu(I) carboxylate-isonitrile,[23] product **1b** can be achieved through intermediate **C** and **D** followed by reductive elimination of Cu(I) in the absence of palladium.



Scheme 4. Plausible mechanism.

3. Conclusion

In summary, we have developed a novel and efficient protocol for palladium-catalyzed cyanation of aryl iodides using *tert*-butyl isocyanide as cyano source. This method features a new mode of application of isocyanide insertion. And it provides a convenient cyanation approach with wide scope of both aromatic and heteroaromatic compounds in good to excellent yields, even for aromatics having activated hydrogen and electron-withdrawing substituents. Further investigation into detailed mechanisms and synthetic applications are underway.

4. Experimental section

4.1. General

Chemicals and reagents were purchased from commercial suppliers and used without special instructions. All anhydrous solvents used in the reactions were dried and freshly distilled. TLC was performed on silica HSGF254 plates. Melting points were determined with a digital melting-point apparatus. ^1H and ^{13}C NMR spectra were obtained from a solution in $CDCl_3$ or DMSO-d_6 with TMS as internal standard using a 400/101 or 151 MHz ($^1H/^{13}C$) spectrometer.

4.2. General procedure for the synthesis of aryl nitriles 1b–28b

Aryl iodide (0.7 mmol, 1 equiv), *tert*-butyl isocyanide (2.1 mmol, 237 μL, 3 equiv), $Pd(OAc)_2$ (0.035 mmol, 8 mg, 5 mol %), $Cu(TFA)_2 \cdot xH_2O$ (1.4 mmol, 405 mg, 2 equiv) and DMSO (2.5 mL) were added to a 15 mL sealed tube, and stirred at 130 °C for 4–12 h under nitrogen. After completion of the reaction indicated by TLC, the mixture was extracted with Et_2O (5×10 mL). The combined organic phases was dried over Na_2SO_4, and concentrated under vacuum. Then the residue was purified by column chromatography on silica gel using petroleum ether (30–60 °C)/Et_2O as eluant to provide the pure target product.

*4.2.1. Biphenyl-4-carbonitrile (**1b**).*[18d] **1b** was obtained as a white solid (123 mg, 98%) following the general procedure for 12 h. Mp. 86–87 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (q, *J*=8.3 Hz, 4H), 7.61–7.56 (m, 2H), 7.49 (t, *J*=7.3 Hz, 2H), 7.44 (dd, *J*=8.3, 6.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5, 139.0, 132.5, 129.1, 128.6, 127.6, 127.2, 118.9, 110.8.

*4.2.2. 4-Methylbenzonitrile (**2b**).*[18d] **2b** was obtained as a colorless oil (80 mg, 98%) following the general procedure for 4 h. ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J*=8.1 Hz, 2H), 7.24 (d, *J*=7.9 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 132.0, 129.8, 119.1, 109.2, 21.8.

*4.2.3. 2-Methylbenzonitrile (**3b**).*[18d] **3b** was obtained as a colorless oil (75 mg, 92%) following the general procedure for 5 h. ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J*=7.7 Hz, 1H), 7.49 (t, *J*=7.6 Hz, 1H), 7.38–7.24 (m, 2H), 2.56 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0, 132.7, 132.6, 130.3, 126.3, 118.3, 112.8, 20.6.

*4.2.4. 4-tert-Butylbenzonitrile (**4b**).*[24a] **4b** was obtained as a colorless oil (87 mg, 78%) following the general procedure for 8 h. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J*=8.6 Hz, 2H), 7.47 (d, *J*=8.5 Hz, 2H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 132.0, 126.2, 119.2, 109.3, 35.3, 31.0.

*4.2.5. 4-Methoxybenzonitrile (**5b**).*[18d] **5b** was obtained as a white solid (91 mg, 98%) following the general procedure for 6 h. Mp. 62–63 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J*=9.0 Hz, 2H), 6.93 (d, *J*=8.9 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 134.09, 119.3, 114.8, 103.9, 55.6.

*4.2.6. 4-Fuorobenzonitrile (**6b**).*[18d] **6b** was obtained as a colorless oil (54 mg, 64%) following the general procedure for 5 h. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73–7.61 (m, 2H), 7.18 (t, *J*=8.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2 (d, *J*=256.6 Hz), 134.8 (d, *J*=9.4 Hz), 118.2, 117.0 (d, *J*=22.7 Hz), 108.7 (d, *J*=3.7 Hz).

*4.2.7. 4-Chlorobenzonitrile (**7b**).*[18d] **7b** was obtained as a white solid (94 mg, 98%) following the general procedure for 6 h. Mp. 92–93 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J*=8.6 Hz, 2H), 7.45 (d, *J*=8.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 133.4, 129.7, 118.0, 110.8.

*4.2.8. 4-(Trifluoromethyl)benzonitrile (**8b**).*[24b] **8b** was obtained as a colorless oil (88 mg, 74%) following the general procedure for 8 h. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J*=8.2 Hz, 2H), 7.76 (d, *J*=8.2 Hz,

2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7 (q, J=33.4 Hz), 132.8, 126.32 (q, J=3.7 Hz), 123.2 (q, J=273.0 Hz), 117.6, 116.18 (d, J=1.2 Hz).

*4.2.9. 4-Nitrobenzonitrile (**9b**).*[18d] **9b** was obtained as a white solid (100 mg, 97%) following the general procedure for 6 h. Mp. 147–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J=8.3 Hz, 2H), 7.89 (d, J=8.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1, 133.6, 124.3, 118.4, 116.9.

*4.2.10. 4-Acetylbenzonitrile (**10b**).*[18d] **10b** was obtained as a white solid (98 mg, 97%) following the general procedure for 6 h. Mp. 52–54 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J=8.2 Hz, 2H), 7.77 (d, J=8.2 Hz, 2H), 2.64 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.7, 140.0, 132.6, 128.8, 118.0, 116.5, 26.9.

*4.2.11. Methyl 4-cyanobenzoate (**11b**).*[18d] **11b** was obtained as a white solid (112 mg, 99%) following the general procedure for 6 h. Mp. 65–67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J=8.1 Hz, 2H), 7.69 (d, J=8.6 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 133.9, 132.2, 130.0, 117.9, 116.3, 52.7.

*4.2.12. 4-(1H-Pyrrol-1-yl)benzonitrile (**12b**).*[5b] **12b** was obtained as a white solid (76 mg, 65%) following the general procedure for 5 h. Mp. 101–103 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J=7.9 Hz, 2H), 7.47 (d, J=8.2 Hz, 2H), 7.14 (s, 2H), 6.41 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 133.8, 119.9, 118.9, 118.6, 112.2, 108.6.

*4.2.13. N-(4-Cyanophenyl)acetamide (**13b**).*[13b] **13b** was obtained as a white solid (90 mg, 80%) following the general procedure for 7 h. Mp. 205–206 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 7.74 (s, 4H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.2, 143.5, 133.3, 119.1, 118.9, 104.7, 24.2.

*4.2.14. 4-Cyanobenzamide (**14b**).*[18e] **14b** was obtained as a white solid (100 mg, 98%) following the general procedure for 10 h. Mp. 222–224 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 (s, 1H), 7.07 (d, J=8.3 Hz, 2H), 6.97 (d, J=8.2 Hz, 2H), 6.75 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.6, 138.3, 132.4, 128.3, 118.4, 113.8.

*4.2.15. 4-Hydroxybenzonitrile (**15b**).*[5e] **15b** was obtained as a white solid (82 mg, 98%) following the general procedure for 6 h. Mp. 112–113 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.6 (s, 1H), 7.61 (d, J=6.7 Hz, 2H), 6.89 (d, J=6.1 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.7, 134.3, 119.6, 116.5, 101.1.

*4.2.16. 1-Naphthonitrile (**16b**).*[18d] **16b** was obtained as a yellow oil (104 mg, 97%) following the general procedure for 6 h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J=8.3 Hz, 1H), 8.00 (d, J=8.3 Hz, 1H), 7.84 (t, J=7.3 Hz, 2H), 7.62 (t, J=7.6 Hz, 1H), 7.55 (t, J=7.5 Hz, 1H), 7.48–7.40 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.3, 132.9, 132.7, 132.4, 128.7, 128.6, 127.6, 125.1, 125.0, 117.9, 110.2.

*4.2.17. 3,5-Dimethylbenzonitrile (**17b**).*[18d] **17b** was obtained as a yellow solid (90 mg, 98%) following the general procedure for 6 h. Mp. 44–45 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 2H), 7.12 (s, 1H), 2.24 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.0, 134.6, 129.6, 119.2, 111.9, 21.0.

*4.2.18. 3,5-Difluorobenzonitrile (**18b**).*[24d] **18b** was obtained as a yellow oil (64 mg, 66%) following the general procedure for 8 h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.19 (m, 2H), 7.10 (tt, J=8.6, 2.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0 (dd, J=253.3, 12.6 Hz), 116.6 (t, J=3.7 Hz), 115.98–115.54 (m), 114.74 (t, J=11.5 Hz), 109.57 (t, J=24.9 Hz).

*4.2.19. 2,3-Dihydrobenzo[b][1,4]dioxine-6-carbonitrile (**19b**).*[24e] **19b** was obtained as a white solid (106 mg, 94%) following the general procedure for 6 h. Mp. 105–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–7.01 (m, 2H), 6.88 (d, J=8.9 Hz, 1H), 4.35–4.13 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8, 143.8, 125.9, 121.2, 118.9, 118.3, 104.4, 64.6, 64.1.

*4.2.20. 3,4,5-Trimethoxybenzonitrile (**20b**).*[24a] **20b** was obtained as a white solid (134 mg, 99%) following the general procedure for 6 h. Mp. 95–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 2H), 3.84 (s, 3H), 3.82 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5, 142.2, 118.9, 109.4, 106.6, 61.0, 56.3.

*4.2.21. Thiophene-2-carbonitrile (**21b**).*[5e] **21b** was obtained as a yellow oil (56 mg, 74%) following the general procedure for 8 h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (ddd, J=6.2, 4.4, 1.1 Hz, 2H), 7.13 (dd, J=5.0, 3.8 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.4, 132.6, 127.6, 114.2, 109.9.

*4.2.22. Isonicotinonitrile (**22b**).*[12c] **22b** was obtained as a yellow solid (50 mg, 69%) following the general procedure for 6 h. Mp. 79–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, J=3.5 Hz, 2H), 7.51 (d, J=4.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8, 125.3, 120.4, 116.4.

*4.2.23. Nicotinonitrile (**23b**).*[7a] **23b** was obtained as a yellow oil (51 mg, 70%) following the general procedure for 8 h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.78 (d, J=4.9 Hz, 1H), 7.94 (d, J=8.0 Hz, 1H), 7.41 (dd, J=6.9, 5.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0, 152.4, 139.3, 123.7, 116.5, 110.1.

*4.2.24. 1H-Indole-5-carbonitrile (**24b**).*[5b] **24b** was obtained as a white solid (52 mg, 52%) following the general procedure for 6 h. Mp. 107–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.99 (s, 1H), 7.48 (d, J=8.5 Hz, 1H), 7.41 (dd, J=8.5, 1.3 Hz, 1H), 7.37–7.33 (m, 1H), 6.63 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 127.7, 126.7, 126.5, 124.8, 121.1, 112.2, 103.4, 102.6.

*4.2.25. 1-Methyl-1H-indole-5-carbonitrile (**25b**).*[15a] **25b** was obtained as a white solid (59 mg, 54%) following the general procedure for 6 h. Mp. 69–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.44 (dd, J=8.5, 1.3 Hz, 1H), 7.36 (d, J=8.5 Hz, 1H), 7.17 (d, J=3.1 Hz, 1H), 6.56 (d, J=3.1 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.3, 131.2, 128.3, 126.6, 124.6, 121.0, 110.2, 102.5, 102.3, 33.2.

*4.2.26. Methyl 5-cyanobenzo[b]thiophene-2-carboxylate (**26b**).*[24c] **26b** was obtained as a white solid (147 mg, 97%) following the general procedure for 12 h. Mp. 161–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.07 (s, 1H), 7.95 (d, J=7.8 Hz, 1H), 7.64 (d, J=8.4 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 145.8, 138.5, 136.3, 130.2, 129.9, 128.5, 124.0, 118.8, 109.0, 53.0.

*4.2.27. 4-(Hydroxymethyl)benzonitrile (**27b**).*[15e] **27b** was obtained as a yellow oil (71 mg, 76%) following the general procedure for 6 h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J=8.1 Hz, 2H), 7.42 (d, J=8.0 Hz, 2H), 4.70 (s, 1H), 3.28 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6, 132.2, 127.0, 118.9, 110.6, 63.8.

*4.2.28. 3,5-Dihydroxybenzonitrile (**28b**).*[24f] **28b** was obtained as a white solid (91 mg, 96%) following the general procedure for 6 h. Mp. 154–156 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 2H), 6.56 (d, J=2.2 Hz, 2H), 6.53 (t, J=2.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.3, 119.1, 112.3, 109.9, 107.9.

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