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Synthesis of 3-Cyanoindole Derivatives Mediated by Copper(I) Iodide Using Benzyl Cyanide

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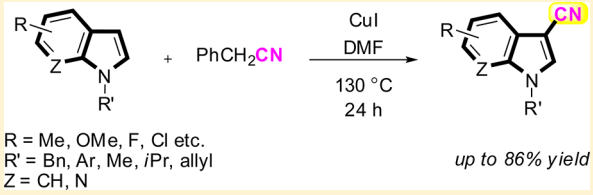
Supporting Information

ABSTRACT: Copper-mediated direct and regioselective C3-cyanation of indoles using benzyl cyanide as the cyanide anion source is presented. A wide range of indoles undergo cyanation smoothly by employing a reaction system of copper(I) iodide under open-to-air vessels.

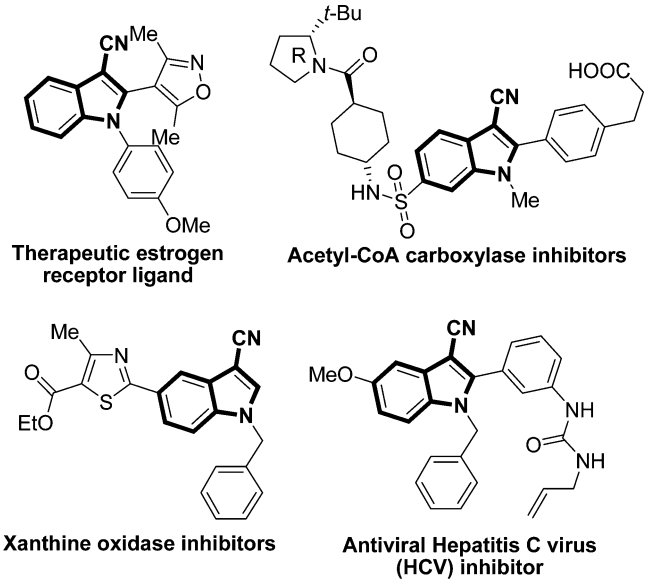


The indole scaffold is exemplified as an important subunit not only in pharmaceutical and agrochemical products but also basic constituents of dyes and herbicides.[1] In particular, 3-cyanoindole is a key building block in pharmaceutical syntheses that can be applied in medicinal chemistry and drug discovery. With the nitrile moiety, further transformations of this group into a broad range of functional groups, such as amines, aldehydes, acids, amides, ketones, and heterocycles, can be made.[2] In fact, 3-cyanoindole scaffold containing structures have been well-known for their use as therapeutic estrogen receptor ligands,[3] acetyl-CoA carboxylase inhibitors for type 2 diabetes,[4] xanthine−oxidase inhibitors,[5] antiviral hepatitis C virus inhibitors,[6] aldosterone synthase modulator for cardiovascular diseases,[7] anticancer agents,[8] and antithrombotics factor Xa inhibitors (Scheme 1).[9]

Aryl nitriles are generally prepared from classical organic transformations, such as Sandmeyer[10] and Rosenmund−von Braun reaction,[11] in which prefunctionalized starting materials are often required. Palladium- and copper-catalyzed cyanations of aryl halides and sulfonates are also well-documented methods.[12] Yet, there has been no example reported for the conversion of 3-bromoindole to 3-cyanoindole. In fact, organic transformations from a modified Madelung reaction,[13] metal-free oxidative synthesis from *N*-aryl enamines[14] (Scheme 2A), palladium-catalyzed *N*-heterocyclization,[15] and propylphosphonic anhydride-promoted conversion of aldehydes[16] are alternative approaches to afford 3-cyanoindoles. Indeed, emerging methods for facile synthesis of 3-cyanoindoles using a direct C−H functionalization protocol are highly desirable. Lewis acid, Fe, Cu, and Pd salts are usually employed as the catalyst for accessing 3-cyanoindole using various metal cyanides and other cyanide anion (CN^-) surrogates (Scheme 2B).[17]

Nevertheless, most commonly available metal cyanides are extremely toxic. Although $K_4[Fe(CN)_6]$ is exceptionally nontoxic, its low solubility in organic solvent limited its applicability. Despite these limited CN^- sources, an exploration of other user-friendly organic CN^- sources for direct cyanation of indole would be highly favorable. In 2012, Wang and co-workers first reported palladium-catalyzed cyanation of aryl halides and CuBr-mediated cyanation of arenes using benzyl cyanide as a CN^- surrogate.[18] This notable reagent is commercially available, hazardless, inexpensive, and highly soluble in common organic solvents. In view of the beneficial features associated with this CN^- source as well as our current interest in cyanation reactions,[19] herein we disclose our efforts on copper-mediated direct cyanation of indole using benzyl cyanide in a highly regioselective manner.

Scheme 1. Examples of Useful Substituted 3-Cyanoindole-Containing Molecules



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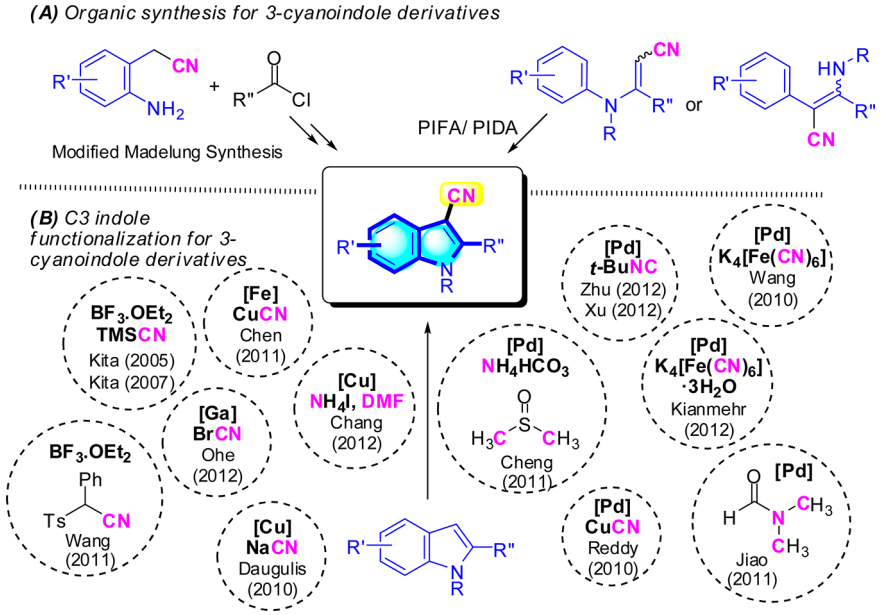
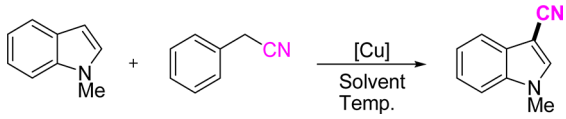
Scheme 2. Selected Synthetic Methods for 3-Cyanoindole Preparation Using Different Cyanide Sources



In order to achieve the C-3 indole functionalization for cyanation, a series of reaction parameter optimizations were deployed (Table 1). *N*-Methylindole was chosen as the benchmark substrate. Commercially available copper salts were investigated (entries 2–8). CuI showed successful cyanation of indole while other Cu complexes did not. A screening of solvent revealed that DMF was the solvent of choice (entries 6 and 9–12). When the reaction temperature was increased from 110 to 130 °C and the reaction time was extended to 24 h, the product yield was improved (entries 1 and 2, 2 and 6).

Table 1. Initial Optimization of Direct C3-Cyanation of *N*-Methylindole[a]

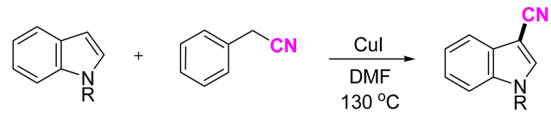


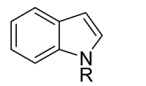
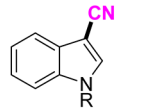
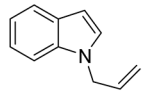
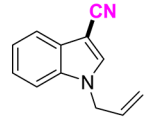
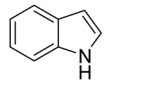
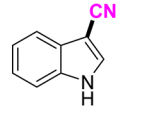
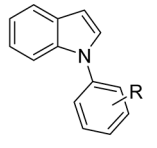
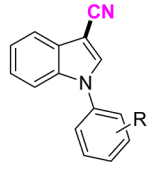
entry	[Cu] (equiv)	solvent	time (h)	% yield[b]
1[c]	CuI (1)	DMF	20	trace
2	CuI (1)	DMF	20	51
3	Cu_2O (1)	DMF	20	0
4	Cu(OAc) (1)	DMF	20	trace
5	$Cu(OAc)_2$ (1)	DMF	20	trace
6	CuI (1)	DMF	24	89
7	CuBr (1)	DMF	24	trace
8	CuCl (1)	DMF	24	0
9	CuI (1)	CH_3CN	24	0
10	CuI (1)	dioxane	24	0
11	CuI (1)	toluene	24	0
12	CuI (1)	DMSO	24	trace
13[d]	CuI (1)	DMF	24	79
14	CuI (1.5)	DMF	24	91

[a]Reaction conditions: copper source (0.5 mmol, 1 equiv), *N*-methylindole (0.5 mmol), $PhCH_2CN$ (0.75 mmol), and solvent (2.0 mL) were stirred under air at 130 °C for the indicated period of time. [b]Calibrated GC yields were reported using pentadecane as the internal standard. [c]110 °C was used. [d]140 °C was used.

Having the optimized reaction conditions in hand, we next examined the substrate scope of this cyanation reaction (Table 2). *N*-Alkylated indoles proceeded smoothly to give the corresponding products in good yields (entries 1 and 2). The allyl group remained intact during the course of the reaction (entry 3). Disappointingly, unprotected NH indole showed poor conversion under these reaction conditions (entry 4). It is possibly due to the decomposition of unprotected indole. *N*-

Table 2. Copper-Mediated Direct C3-Cyanation of Indoles[a]



entry	indole	product		time(h)	% yield[b]
1			R = Me	24	86
2			R = *i*-Pr	24	70
3				24	73
4				24	17
5[c]			R = H	48	60
6[c]			R = *p*-OMe	46	66
7[c]			R = 3,5-di-Me	48	57

[a]Reaction conditions: CuI (0.5 mmol), *N*-substituted indole (0.5 mmol), $PhCH_2CN$ (0.75 mmol), and DMF (2.0 mL) were stirred under air at 130 °C for indicated time. [b]Isolated yield. [c]1.5 equiv of CuI was used.

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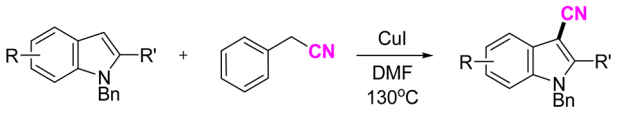
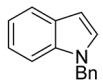
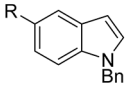
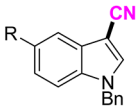
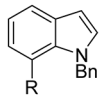
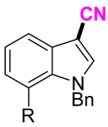
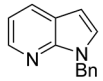
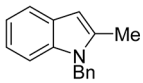
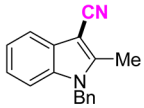
Arylindoles were also tested (entries 5–7). Moderate yields were generally obtained.

To further test the generality of the reaction system, a series of substituted *N*-benzylindoles was probed in this cyanation system (Table 3). Functional groups such as fluoro, chloro, and

Table 3. Copper-Mediated Direct C3-Cyanation of Benzylindoles[a]



entry	indole	product		time(h)	% yield[b]
1				24	82
2			R = OMe	24	78
3			R = F	28	62
4			R = Cl	28	73
5			R = Me	49	77
6			R = OMe	46	69
7			R = Me	46	58
8				46	65
9[c]				48	56

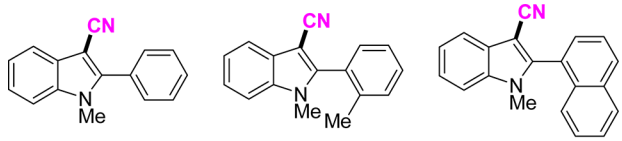
[a]Reaction conditions: CuI (0.5 mmol), substituted benzylindole (0.5 mmol), $PhCH_2CN$ (0.75 mmol), and DMF (2.0 mL) were stirred under air at 130 °C for the indicated time. [b]Isolated yield. [c]1.5 equiv of CuI was used.

methoxy were compatible under these reaction conditions (entries 2–4). The intact chloro group is beneficial for later functionalization using other coupling protocols.[20] In fact, these nitrile-containing products can undergo further organic transformations to afford a variety of potential xanthine oxidase inhibitors, HCV inhibitors, and therapeutic estrogen receptor ligands.[3,5,6] *N*-Benzylindoles with 5- and 7-substitutents furnished the desired product smoothly with extended reaction times (entries 5–7). Azaindole and sterically hindered 2-methyl-*N*-benzylindole were found to be feasible substrates for the cyanation (entries 8 and 9).

Highly sterically congested 2-aryl-*N*-methylindoles were applicable substrates for direct cyanation (Scheme 3). 2-(1-Naphthyl)-*N*-methylindole afforded the desired product in lower yield presumably due to the large steric hindrance of the *o*-naphthyl moiety.

In summary, we have developed a simple protocol for facile preparation of 3-cyanoindoles. This inexpensive reaction system, copper(I) iodide and benzyl cyanide, is found to effectively promote regioselective cyanation of indoles in open-to-air vessels. This protocol potentially provides a more direct and complementary access to pharmaceutically useful intermediates.

Scheme 3. Copper-Mediated Direct C3-Cyanation of *N*-Methylindoles (Reaction Conditions Were the Same as in Table 2, Entry 5)[a]



1: 76%, 48 h **2:** 60%[a], 48 h **3:** 50%, 46 h

[a]1.0 mmol of $PhCH_2CN$ was used.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All cyanations were performed in an open vessel, a vial (approximately 60 mL volume), fitted with an air condenser, and equipped with Teflon coated magnetic stir bar (4 mm × 10 mm). All indole derivatives except indole, *N*-methylindole, and *N*-methyl-2-phenylindole were synthesized according to the literature methods.[21] Silica gel (230–400 mesh) was used for column chromatography. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer. Spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm) or with TMS (δ 0.00 ppm) as the internal standard. Chemical shifts (δ) were reported as parts per million (ppm) on the δ scale downfield from TMS. ^{13}C NMR spectra were recorded on a 100 MHz spectrometer, and the spectra were referenced to $CDCl_3$ (δ 77.0 ppm, the middle peak). Coupling constants (J) are reported in hertz (Hz). Mass spectra (EI-MS and ES-MS) were recorded on a mass spectrometer. High-resolution mass spectra (HRMS) were obtained on an ESIMS mass spectrometer. GC–MS analysis was conducted on a GCD system. Products described in GC yield were accorded to the authentic samples/pentadecane calibration standard from GC-FID system.

General Procedure for Reaction Condition Screenings. All reagents were weighed in air, and the reactions were performed in an open-to-air vessel. Copper salt (0.5–0.75 mmol), *N*-methylindole (0.5 mmol), and $PhCH_2CN$ (0.75 mmol) were loaded into a 60 mL vial equipped with a Teflon-coated magnetic stir bar. The solvent (2 mL) was added at room temperature. The vial was fitted with an air condenser and then placed into a preheated oil bath with vigorous stirring for the indicated time. After the completion of reaction, the vial was allowed to cool at room temperature. Ethyl acetate (~20 mL) and pentadecane (internal standard) were added. The organic layer was subjected to GC analysis.

General Procedure for Cyanation of Indoles with Benzyl Cyanide. Copper(I) iodide (0.5–0.75 mmol), $PhCH_2CN$ (0.75–1.0 mmol), indole derivatives (0.5 mmol), and DMF (2.0 mL) were loaded into a 60 mL vial equipped with an air condenser and Teflon-coated magnetic stir bar under air. The vial was then placed into a preheated oil bath at the temperature indicated in Table 2 and vigorously stirred in an open system for the indicated time. After completion of reaction, the reaction vial was allowed to cool at room temperature. Ethyl acetate (~20 mL) was added for dilution. The organic layer was subjected to GC analysis. After analysis of the GC spectra, the crude product was further extracted with ethyl acetate (2 × 10 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to afford the desired product.

1-Methyl-1*H*-indole-3-carbonitrile (Example from Table 2, Entry 1).[17f] Eluents (DCM/hexane = 1:1, R_f = 0.5) were used for flash column chromatography: 67.1 mg, 86% yield, brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 7.29–7.42 (m, 3H), 7.55 (s, 1H), 7.76 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.6, 85.3, 110.3, 115.9, 122.1, 123.8, 127.7, 135.5, 136.0. (See the Supporting Information for copies of the spectra.)

1-Isopropyl-1*H*-indole-3-carbonitrile (Table 2, Entry 2). Eluents (DCM/hexane = 1:1, R_f = 0.35) were used for flash column chromatography: 64.4 mg, 70% yield, brown liquid; ^{1}H NMR (400

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MHz, $CDCl_3$) δ 1.59 (d, J = 6.8 Hz, 6H), 4.70−4.77 (m, 1H), 7.29−7.38 (m, 2H), 7.48 (d, J = 8.0 Hz, 1H), 7.74 (s, 1H), 7.78 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 48.4, 85.6, 110.7, 116.2, 119.9, 122.1, 123.6, 128.0, 131.2, 135.0; HRMS (ESI) calcd. for $C_{12}H_{13}N_2$ [M + H$^+$] 185.1079, found 185.1083.

1-Allyl-1*H*-indole-3-carbonitrile (Table 2, Entry 3).[17i] Eluents (DCM/hexane = 1:1, R_f = 0.35) were used for flash column chromatography: 64.4 mg, 73% yield, brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (d, J = 5.6 Hz, 2H), 5.18 (d, J = 17.2 Hz, 1H), 5.33 (d, J = 10.4 Hz, 1H), 5.96−6.06 (m, 1H), 7.30−7.39 (m, 2H), 7.42 (d, J = 7.4 Hz, 1H), 7.63 (s, 1H), 7.79 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.4, 86.0, 110.7, 115.8, 119.0, 119.9, 122.2, 123.8, 127.9, 131.6, 134.6, 135.4.

1*H*-Indole-3-carbonitrile (Table 2, Entry 4).[17f] Eluents (DCM/hexane = 6:1, R_f = 0.20) were used for flash column chromatography: 12.1 mg, 17% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.42 (m, 2H), 7.51 (d, J = 8.4 Hz, 1H), 7.76 (s, 1H), 7.81 (d, J = 6.4 Hz, 1H), 8.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 87.5, 112.0, 115.7, 119.6, 122.3, 124.3, 126.9, 131.7, 134.8.

1-Phenyl-1*H*-indole-3-carbonitrile (Table 2, Entry 5).[17i] Eluents (DCM/hexane = 1:1, R_f = 0.5) were used for flash column chromatography: 65.4 mg, 60% yield, light orange solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.39 (m, 2H), 7.49−7.56 (m, 4H), 7.59−7.63 (m, 2H), 7.82 (s, 1H), 7.84−7.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.0, 111.5, 115.4, 119.9, 122.7, 124.5, 124.8, 127.9, 128.3, 130.0, 134.6, 135.5, 137.2.

1-(4-Methoxyphenyl)-1*H*-indole-3-carbonitrile (Table 2, Entry 6).[17i] Eluents (DCM/hexane = 1:1, R_f = 0.25) were used for flash column chromatography: 81.8 mg, 66% yield, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.09 (d, J = 8.8 Hz, 2H), 7.34−7.36 (m, 2H), 7.40 (d, J = 8.8 Hz, 2H), 7.43−7.46 (m, 1H), 7.76 (s, 1H), 7.82−7.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 87.4, 111.4, 115.0, 115.6, 119.8, 122.5, 124.3, 126.3, 127.7, 130.5, 134.9, 136.0, 159.4.

1-(3,5-Dimethylphenyl)-5-methoxy-1*H*-indole-3-carbonitrile (Table 2, Entry 7). Eluents (DCM/hexane = 1:1, R_f = 0.25) were used for flash column chromatography: 78.7 mg, 57% yield, light orange solid; mp 140.7−141.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 6H), 3.91 (s, 3H), 6.97 (d, J = 8.8 Hz, 1H), 7.08 (s, 2H), 7.11 (s, 1H), 7.23 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 55.8, 87.2, 100.8, 112.7, 115.1, 122.3, 128.9, 129.9, 130.5, 134.5, 137.8, 139.9, 156.3; HRMS (ESI) calcd. for $C_{18}H_{17}N_2O$ [M + H$^+$] 277.1341, found 277.1332.

1-Benzyl-1*H*-indole-3-carbonitrile (Table 3, Entry 1).[17i] Eluents (DCM/hexane = 1:1, R_f = 0.5) were used for flash column chromatography: 95.1 mg, 82% yield, brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 2H), 7.16−7.19 (m, 2H), 7.32−7.41 (m, 6H), 7.62 (s, 1H), 7.80−7.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.8, 86.1, 110.7, 119.9, 122.2, 123.9, 127.0, 127.9, 128.3, 129.0, 134.9, 135.1, 135.5.

1-Benzyl-5-methoxy-1*H*-indole-3-carbonitrile (Table 3, Entry 2).[22] Eluents (DCM/hexane = 1:1, R_f = 0.2) were used for flash column chromatography: 102.2 mg, 78% yield, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 5.30 (m, 2H), 6.95 (dd, J = 2.4, 9.2 Hz, 1H), 7.14−7.17 (m, 2H), 7.19 (s, 1H), 7.24 (d, J = 9.2 Hz, 1H), 7.34−7.37 (m, 3H), 7.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.9, 55.6, 85.5, 100.8, 111.7, 114.6, 126.9, 128.3, 128.8, 129.0, 130.4, 134.8, 135.2, 156.0.

1-Benzyl-5-fluoro-1*H*-indole-3-carbonitrile (Table 3, Entry 3). Eluents (DCM/hexane = 1:1, R_f = 0.25) were used for flash column chromatography: 77.5 mg, 62% yield, orange solid; mp 93.4−95.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, 2H), 7.05 (td, J = 2.4, 8.8 Hz, 1H), 7.17 (d, J = 6.8 Hz, 2H), 7.29−7.34 (m, 1H), 7.36−7.42 (m, 4H), 7.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.1, 86.1, 104.9, 105.2, 111.9, 112.5, 112.8, 115.2, 127.0, 128.5, 129.1, 132.0, 134.8, 136.1, 157.9, 160.3; ^{19}F NMR (400 MHz, $CDCl_3$) δ −120.3; HRMS (ESI) calcd for $C_{16}H_{11}N_2F$ [M + Na$^+$] 273.0804, found 273.0810.

1-Benzyl-5-chloro-1*H*-indole-3-carbonitrile (Table 3, Entry 4). Eluents (DCM/hexane = 1:1, R_f = 0.4) were used for flash column chromatography: 97.3 mg, 73% yield, orange solid; mp 117.9−120.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, 2H), 7.15 (d, J = 6.0 H, 2H), 7.25−7.31 (m, 2H), 7.36−7.41 (m, 3H), 7.63 (s, 1H), 7.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.0, 85.7, 112.0, 115.0, 119.2, 124.4, 127.0, 128.2, 128.5, 128.8, 129.1, 133.8, 134.7, 135.9; HRMS (ESI) calcd for $C_{16}H_{12}N_2Cl$ [M + H$^+$] 267.0689, found 267.0684.

1-Benzyl-5-methyl-1*H*-indole-3-carbonitrile (Table 3, Entry 5).[17d] Eluents (DCM/hexane = 1:1, R_f = 0.45) were used for flash column chromatography: 94.5 mg, 77% yield, light orange solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H), 5.33 (s, 2H), 7.14−7.17 (m, 3H), 7.26 (d, J = 8.4 Hz, 1H), 7.34−7.39 (m, 3H), 7.58 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 50.9, 85.6, 110.5, 116.0, 119.6, 125.7, 127.1, 128.3, 128.4, 129.1, 132.1, 134.0, 134.9, 135.4.

1-Benzyl-7-methoxy-1*H*-indole-3-carbonitrile (Table 3, Entry 6). Eluents (DCM/hexane = 1:1, R_f = 0.2) were used for flash column chromatography: 90.4 mg, 69% yield, light orange solid; mp 142.8−146.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 5.66 (s, 2H), 6.75 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 7.2 Hz, 2H), 7.21 (t, J = 8.0 Hz, 1H), 7.31−7.38 (m, 4H), 7.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.4, 55.4, 86.4, 104.7, 112.3, 115.8, 122.9, 125.4, 126.9, 127.9, 128.8, 130.2, 135.4, 137.2, 147.9; HRMS (ESI) calcd. for $C_{17}H_{15}N_2O$ [M + H$^+$] 263.1184, found 263.1191.

1-Benzyl-7-methyl-1*H*-indole-3-carbonitrile (Table 3, Entry 7). Eluents (DCM/hexane = 1:1, R_f = 0.45) were used for flash column chromatography: 71.3 mg, 58% yield, yellow solid; mp 153.7−154.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (s, 3H), 5.63 (s, 2H), 6.97 (d, J = 7.2 Hz, 2H), 7.04 (d, J = 7.2 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.32−7.38 (m, 3H), 7.56 (s, 1H), 7.67 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 52.9, 86.4, 115.6, 117.9, 122.1, 122.4, 125.5, 126.8, 128.0, 128.9, 129.1, 130.7, 134.4, 136.4, 137.1; HRMS (ESI) calcd for $C_{17}H_{15}N_2$ [M + H$^+$] 247.1235, found 247.1226.

1-Benzyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (Table 3, Entry 8). Eluents (DCM/hexane = 1:1, R_f = 0.2) were used for flash column chromatography: 75.7 mg, 65% yield, yellow solid; mp 90.3−91.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (s, 2H), 7.28−7.38 (m, 6H), 7.71 (s, 1H), 8.12 (dd, J = 1.6, 6.4 Hz, 1H), 8.51 (dd, J = 1.6, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.7, 85.0, 118.3, 120.1, 127.9, 128.4, 128.5, 129.0, 134.9, 135.6, 145.2, 146.4; HRMS (ESI) calcd for $C_{15}H_{12}N_3$ [M + H$^+$] 234.1031, found 234.1041.

1-Benzyl-2-methyl-1*H*-indole-3-carbonitrile (Table 3, Entry 9).[17d] Eluents (DCM/hexane = 1:1, R_f = 0.45) were used for flash column chromatography: 68.9 mg, 56% yield, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (s, 3H), 5.35 (s, 2H), 7.00 (d, J = 6.4 Hz, 2H), 7.26−7.33(m, 6H), 7.73 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 47.3, 85.7, 110.3, 116.5, 119.1, 122.2, 123.4, 126.0, 127.2, 128.0, 129.1, 135.7, 136.2, 145.8.

1-Methyl-2-phenyl-1*H*-indole-3-carbonitrile (Scheme 3, Compound 1).[17h] Eluents (DCM/hexane = 1:1, R_f = 0.4) were used for flash column chromatography: 88.2 mg, 76% yield, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 7.37−7.44 (m, 3H), 7.58 (s, 5H), 7.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6, 85.2, 110.5, 119.2, 119.2, 122.2, 123.7, 127.4, 128.5, 128.8, 129.7, 136.7, 147.9.

1-Methyl-2-(*o*-tolyl)-1*H*-indole-3-carbonitrile (Scheme 3, Compound 2). Eluents (DCM/hexane = 1:1, R_f = 0.6) were used for flash column chromatography: 73.8 mg, 60% yield, yellow solid; mp 113.9−114.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 3.60 (s, 3H), 7.34−7.44 (m, 5H), 7.46−7.50 (m, 2H), 7.83 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 31.0, 86.2, 110.6, 116.3, 119.5, 122.4, 123.7, 126.2, 127.5, 128.4, 130.3, 130.6, 130.7, 136.4, 138.0, 148.1; HRMS (ESI) calcd for $C_{17}H_{15}N_2$ [M + H$^+$] 247.1235, found 247.1229.

1-Methyl-2-(naphthalen-1-yl)-1*H*-indole-3-carbonitrile (Scheme 3, Compound 3).[17k] Eluents (DCM/hexane = 1:1, R_f = 0.45) were used for flash column chromatography: 70.8 mg, 50% yield, orange liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (s, 3H), 7.39−7.44 (m, 1H), 7.46−7.55 (m, 4H), 7.59 (t, J = 7.6 Hz, 1H), 7.65−7.67 (m, 2H), 7.89 (d, J = 7.8 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5, 110.5, 119.7, 122.5, 123.9, 124.9, 125.4, 126.6, 127.5, 128.8, 129.6, 130.8, 133.6.

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■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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