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Copper-Mediated Direct C2-Cyanation of Indoles Using Acetonitrile as the Cyanide Source

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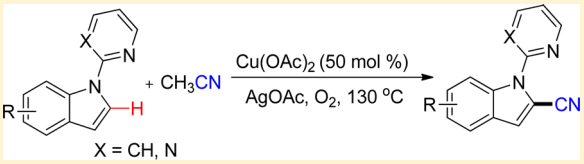
Supporting Information

ABSTRACT: A copper-mediated C2-cyanation of indoles using cheap and commercially available acetonitrile as the "nonmetallic" cyanide source was achieved through sequential C−C and C−H bond cleavages. The installation of a removable pyrimidyl group on the indole nitrogen atom is the key for this C2 selectivity. This approach provides a novel and alternative route leading to indole-2-carbonitrile.



Indoles are common structural motifs in a series of natural products and drugs.[1] Therefore, the selective and efficient functionalizations of such framework are highly desired in synthesis. In the past few years, direct transformation of the indole C−H bond has become the most straightforward method leading to functionalized indoles.[2] The C3-selective C−H functionalizations of indole, such as formylation, alkynylation, and alkenylation, were widely studied owning to its inherent property.[2] In order to alter the regioselectivity of C3 toward C2 C−H bonds, some easily removable directing groups are usually required to install to the indole nitrogen atom.[3−9]

The nitrile unit is widely present in dyes, herbicides, drugs, and natural products.[10] Traditional Sandmeyer reaction, Rosenmund−von Braun reactions,[11] and transition-metal-catalyzed cyanation of aryl halides were developed to access nitrile.[12] Recently, the direct cyanation of C−H bonds has emerged as an alternatively attractive method.[13−15,32−38] With regards to cyano source,[16] one is metallic cyano-group sources, such as CuCN, KCN, NaCN, $Zn(CN)_2$. The other is "nonmetallic" organic cyano-group sources, such as acetone cyanohydrin, BnSCN, *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide, DDQ, *tert*-butyl isocyanide, ethyl cyanoacetate, benzyl cyanide, malononitrile, DMF, or combined cyanide source.[17−29] The metallic cyano-group sources employed are generally toxic and not environmentally benign. Thus, the nonmetallic cyano-group sources becomes a promising alternative. As far as this is concerned, acetonitrile is a very ideal choice since it is cheap and commercially produced. In 1998, Cheng developed a palladium and zinc species-mediated cyanation of aryl halides with acetonitrile.[30] Recently, Li reported a copper-catalyzed oxidative cyanation of aryl halides using acetonitrile as the cyanide source.[31] However, to our knowledge, direct cyanation of the aromatic C−H bond with acetonitrile is not disclosed in the literature. Although direct C3-cyanations of indole with different cyanide sources have been well developed,[32−38] only one example on the direct C2-cyanation of indole was reported by Xu, using *tert*-butyl isocyanide as the cyano-group source.[39] Our interest in the cyanation[40] and C2-functionalization of indole[41] spurred us to test the feasibility of chelation effect of a pyrimidyl group in the cyanation of the C−H bond. Herein, we disclosed a copper-mediated C2-cyanation of indole with commercially available acetonitrile as the nonmetallic cyano-group source.

Initially, we examined the reaction of 1-(pyrimidin-2-yl)-1*H*-indole (**1a**) with acetonitrile (**2**) using $Cu(OAc)_2$ as the catalyst under O_2. To our delight, a 32% yield of the cyanated product **3a** was obtained (Table 1, entry 1). After surveying a series of oxidants, such as $AgNO_3$, AgOAc, Ag_2O, $K_2S_2O_8$, $PhI(OAc)_2$, and DDQ, AgOAc was found to be most efficient (Table 1, entry 2). $Cu(OAc)_2$ was the best among the screened copper sources, while $CuBr_2$ showed very poor activity for this transformation. The yield decreased to 25% under air. No product was obtained without a copper source (Table 1, entry 12).

To evaluate the substrate scope of this protocol, the optimized reaction conditions were applied to a range of indoles. As illustrated in Scheme 1, *N*-pyrimidyl indoles bearing a series of substitutions at the C3-, C4-, C5- C6-, or C7-positions were compatible in this reaction with good yields. The indoles possessing electron-donating groups (**3b**−**3f**, Scheme 1) gave higher yields than those with electron-withdrawing groups (**3g**−**3j**, Scheme 1). Steric hindrance on the indole had obvious effect on the reaction. For example, methyl at C3 of indole could inhibit the efficiency and afforded lower yield (**3b** vs **3d**, Scheme 1). Furthermore, for those substrates with an ethyl or fluoro group at the pyrimidine ring, indole-2-carbonitriles could be isolated with good yields (**3k**

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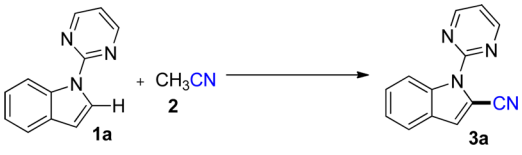
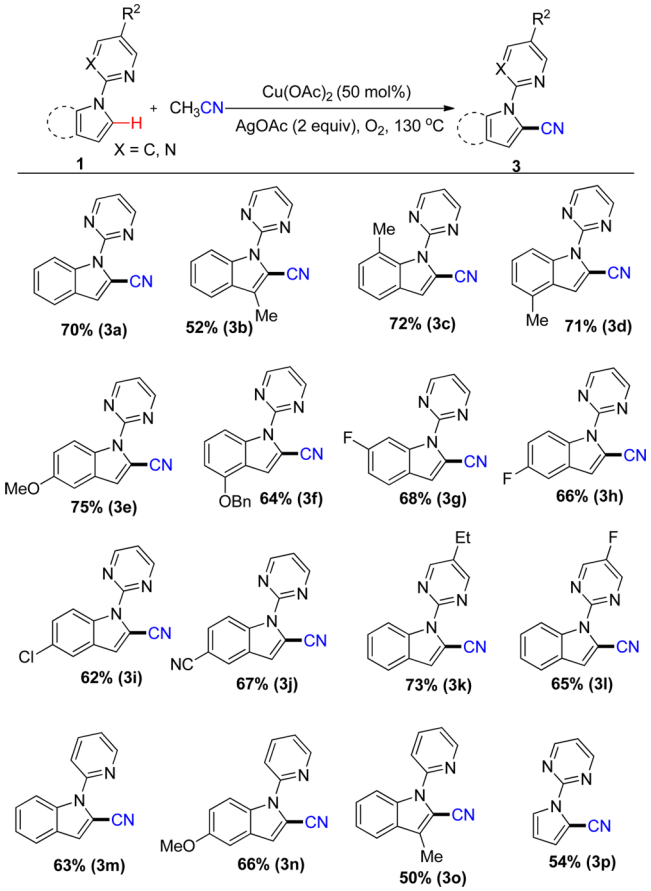
Table 1. Screening the Optimized Reaction Conditions[a]



entry	Cu	oxidant	yield (%)
1	$Cu(OAc)_2$	$AgNO_3$	32
2	$Cu(OAc)_2$	AgOAc	70(25)[b] (40)[c]
3	$Cu(OAc)_2$	AgF	10
4	$Cu(OAc)_2$	Ag_2CO_3	25
5	$Cu(OAc)_2$	Ag_2O	57
6	$Cu(OAc)_2$	$K_2S_2O_8$	23
7	$Cu(OAc)_2$	$PhI(OAc)_2$	12
8	$Cu(OAc)_2$	DDQ	0
9	CuI	AgOAc	50
10	$CuBr_2$	AgOAc	trace
11	$CuCl_2$	AgOAc	36
12		AgOAc	0
13	$Cu(OAc)_2$		41

[a]Reaction conditions: **1a** (0.2 mmol), Cu (50 mol %), oxidant (0.4 mmol), CH_3CN (2 mL), O_2, 130 °C in a sealed tube. [b]Air. [c]20 mol % of $Cu(OAc)_2$.

Scheme 1. Substrate Scope[a]



[a]Reaction conditions: **1** (0.2 mmol), $Cu(OAc)_2$ (50 mol %), AgOAc (0.4 mmol), CH_3CN (2 mL), O_2, 130 °C.

and **3l**, Scheme 1). Notably, *N*-pyridyl indoles also worked well in this cyanation reaction (**3m**−**3o**, Scheme 1).

To increase the reaction practicability, we attempted to remove the pyrimidinyl group (Scheme 2). Upon treatment of **3a** with NaOEt in DMSO at 110 °C,[42] 1*H*-indole-2-carbonitrile **4a** was isolated in 95% yield, which is the key intermediate for pharmaceutical products.[43−45]

In order to confirm the origin of the cyano group in this cyanation procedure, an array of experiments were performed. CuI or $CuCl_2$ instead of $Cu(OAc)_2$ provided the cyanide product (Table 1, entries 9 and 11), and replacing AgOAc with $AgNO_3$, Ag_2O, or $K_2S_2O_8$ also provided the desired product (Table 1, entries 1−6). These results ruled out the possibility of the carbon atom in the cyano group deriving from $Cu(OAc)_2$ or AgOAc. According to these results, the unique possibility of the CN unit comes from CH_3CN.

Moreover, when 1-methyl-1*H*-indole or 1-phenyl-1*H*-indole instead of 1-(pyrimidin-2-yl)-1*H*-indole (**1a**) was submitted to the procedure, only a trace of cyanated product was detected by GC−MS. These results revealed that the directing group was crucial for this selectivity.

Although the detailed mechanism remained unclear at the current stage, a possible mechanism based on the above results is outlined in Scheme 3. First, coordination of the N atom of **1a** to Cu(II) and directed cyclometalation affords a Cu(II) intermediate **A**. The intermediate **A** chelates with the C−N triple bond in MeCN to form intermediate **B**. Then, the carbon−cyano σ-bond is cleaved to form intermediate **C**,[46−48] and intermediate **C** is oxidized to the Cu(III) intermediate **D** in the presence of oxidant.[49,50] Finally, the reductive elimination of intermediate **C** gives the product **3a** along with Cu(I), which is oxidized to regenerate Cu(II).

In conclusion, we have developed a copper-mediated C2-cyanation of indoles using cheap and commercially available acetonitrile as the nonmetallic cyano-group source through sequential C−C bond and C−H bond cleavage. The key to this C2-cyanation is the installation of a pyrimidyl group on the indole nitrogen atom. This approach provides a novel and alternative route for preparation of indole-2-carbonitrile.

EXPERIMENTAL SECTION

General Information. ^1H NMR and ^{13}C NMR spectra were measured on 300, 400, or 600 MHz NMR spectrometers using $CDCl_3$ or DMSO-d^6 as the solvent with tetramethylsilane (TMS) as the internal standard. Chemical shifts are given in δ relative to TMS, the coupling constants *J* are given in Hz. HRMS were recorded on a TOF LC/MS equipped with electrospray ionization (ESI) probe operating in positive or negative ion mode.

All the 2-pyrimidylindoles were prepared according to the literature.[42] The 2-pyrimidylindoles **1f**, **1k**, **1l** are unknown.

4-(Benzyloxy)-1-(pyrimidin-2-yl)-1*H*-indole (1f). White solid; mp 98−100 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.68 (d, *J* = 4.8 Hz, 2H), 8.42 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 3.6 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.42−7.38 (m, 2H), 7.35−7.32 (m, 1H), 7.25−7.22 (m, 1H), 7.02 (t, *J* = 4.8 Hz, 1H), 6.89 (dd, *J* = 3.6 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 5.24 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 157.9, 152.1, 137.5, 136.8, 128.5, 127.8, 127.4, 124.4, 122.0, 116.2, 109.8, 104.2, 104.1, 70.1. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{16}N_3O$ $(M + H)^+$ 302.1288, found 302.1290.

1-(5-Ethylpyrimidin-2-yl)-1*H*-indole (1k). White solid; mp 44−46 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.78 (d, *J* = 8.8 Hz 1H), 8.53 (s, 2H), 8.25 (d, *J* = 3.6 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.33−7.31 (m, 1H), 7.24−7.22 (m, 1H), 6.68 (d, *J* = 3.3 Hz, 1H), 2.64 (q, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.4, 156.4, 135.3, 131.2, 131.1, 125.8, 123.4, 121.8, 120.7, 116.0, 106.4, 23.0, 15.1. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{14}N_3$ $(M + H)^+$ 224.1182, found 224.1179.

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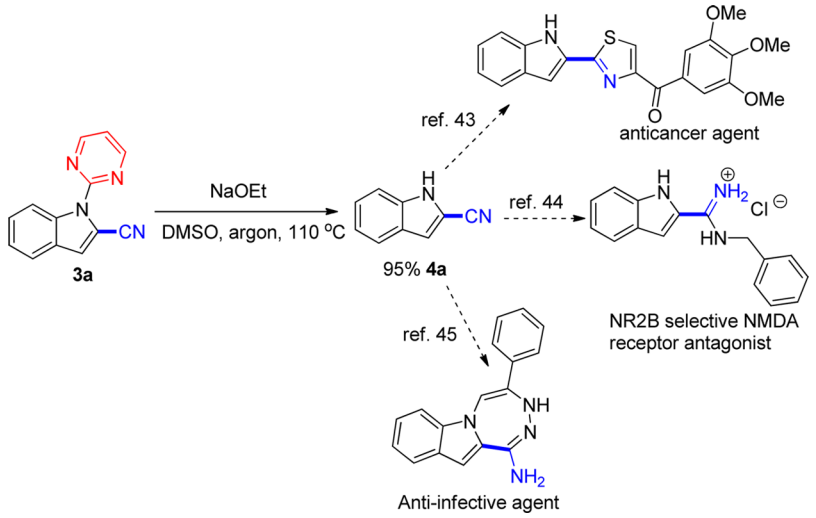
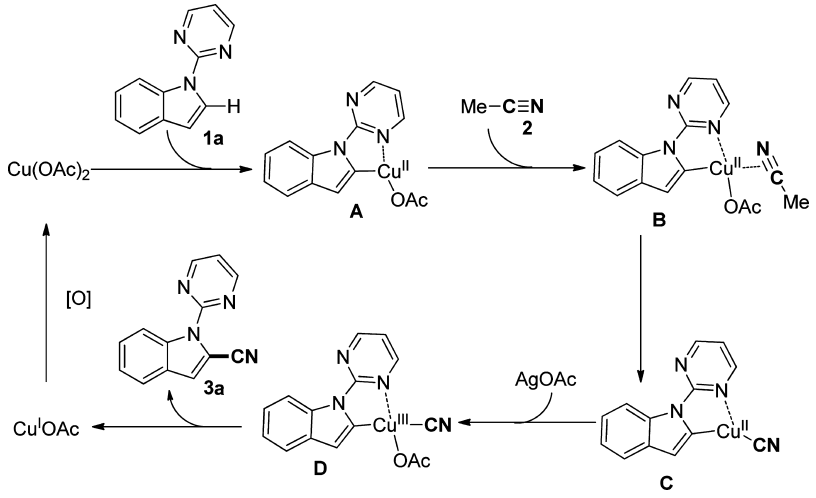
Scheme 2. Removal of Directing Group to 1*H*-Indole-2-carbonitrile[a] and Its Application



[a]Reaction conditions: **3a** (0.15 mmol), NaOEt (0.6 mmol), DMSO (1.5 mL), argon, 110 °C.

Scheme 3. Proposed Mechanism



1-(5-Fluoropyrimidin-2-yl)-1*H*-indole (1l). White solid; mp 113−115 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.71 (d, J = 8.4 Hz, 1H), 8.57 (s, 2H), 8.19 (d, J = 3.6 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.34−7.32 (m, 1H), 7.25−7.22 (m, 1H), 6.70 (d, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5 (d, J_{C-F} = 256.2 Hz), 154.1 (d, J_{C-F} = 2.2 Hz), 145.7 (d, J_{C-F} = 21.9 Hz), 135.2, 131.1, 126.0, 123.7, 122.2, 120.9, 115.7, 107.0. HRMS (ESI) m/z calcd for $C_{12}H_9FN_3$ (M + H)$^+$ 214.0775, found 214.0772.

General Procedure for the Direct C2-Cyanation of Indole with Acetonitrile as Cyanide Source. A sealed reaction tube was charged with **1** (0.2 mmol), $Cu(OAc)_2$ (18 mg, 50 mol %), AgOAc (66.8 mg, 0.4 mmol), and dry CH_3CN (2 mL). After stirring at 130 °C for 48 h under an O_2 atmosphere, the reaction mixture was concentrated and purified by flash column chromatography on silica gel to give the desired products **3m**−**3p**.

1-(Pyrimidin-2-yl)-1*H*-indole-2-carbonitrile (3a).[39] White solid (30.8 mg, 70%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.83 (d, J = 4.6 Hz, 2H), 8.69 (d, J = 8.6 Hz, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.53−7.47 (m, 2H), 7.35−7.30 (m, 1H), 7.25−7.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 156.5, 136.6, 127.7, 127.5, 123.5, 122.0, 121.0, 118.0, 116.2, 114.2, 108.9.

3-Methyl-1-(pyrimidin-2-yl)-1*H*-indole-2-carbonitrile (3b).[39] White solid (24.3 mg, 52%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.81 (d, J = 4.8 Hz, 2H), 8.70 (d, J = 8.6 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.54−7.48 (m, 1H), 7.37−7.27 (m, 1H), 7.19 (t, J = 4.8 HZ, 1H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 156.6, 136.5, 131.6, 128.7, 127.7, 123.0, 120.1, 117.4, 116.3, 114.0, 107.2, 9.9.

7-Methyl-1-(pyrimidin-2-yl)-1*H*-indole-2-carbonitrile (3c). White solid (33.7 mg, 72%); mp 128−129 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.92 (d, J = 4.8 Hz, 2H), 7.59−7.56 (m, 1H), 7.43−7.39 (m, 2H), 7.24−7.23 (m, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 156.6, 136.5, 129.8, 127.8, 123.6, 123.2, 120.2, 120.0, 118.5, 113.4, 111.1, 20.7. HRMS (ESI) m/z calcd for $C_{14}H_{11}N_4$ (M + H)$^+$ 235.0978, found 235.0977.

4-Methyl-1-(pyrimidin-2-yl)-1*H*-indole-2-carbonitrile (3d). White solid (33.2 mg, 71%); mp 158−160 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.83 (d, J = 4.8 Hz, 2H), 8.60 (d, J = 8.6 Hz, 1H), 7.51 (s, 1H), 7.43−7.37 (m, 1H), 7.24 (d, J = 4.8 Hz, 1H), 7.22−7.10 (m, 1H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 156.6, 136.5, 131.6, 127.7, 127.7, 123.7, 119.5, 117.9, 114.3, 113.6, 108.3, 18.4. HRMS (ESI) m/z calcd for $C_{14}H_{11}N_4$ (M + H)$^+$ 235.0978, found 235.0978.

5-Methoxy-1-(pyrimidin-2-yl)-1*H*-indole-2-carbonitrile (3e).[39] White solid (37.5 mg, 75%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.80 (d, J = 4.8 Hz, 2H), 8.60 (d, J = 9.2 Hz, 1H), 7.37 (s, 1H), 7.21 (t, J = 4.8 Hz, 1H), 7.14−7.05 (m, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 156.5, 156.3, 131.6, 128.5, 120.5, 117.9, 117.8, 117.3, 114.3, 109.0, 102.5, 55.6.

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4-(Benzyloxy)-1-(pyrimidin-2-yl)-1*H*-indole-2-carbonitrile (3f). White solid (41.7 mg, 64%); mp 169−171 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.84 (d, J = 4.8 Hz, 2H), 8.26 (d, J = 8.6 Hz, 1H), 7.66 (s, 1H), 7.51−7.38 (m, 6H), 7.26 (d, J = 9.2 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 5.25 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 156.7, 152.6, 137.9, 136.6, 128.7, 128.7, 128.1, 127.4, 119.3, 118.6, 118.0, 114.3, 109.0, 107.5, 104.3, 70.2. HRMS (ESI) m/z calcd for $C_{20}H_{14}N_4NaO$ $(M + Na)^+$ 349.1060, found 349.1061.

6-Fluoro-1-(pyrimidin-2-yl)-1*H*-indole-2-carbonitrile (3g). White solid (32.4 mg, 68%); mp 178−180 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.85 (d, J = 4.8 Hz, 2H), 8.47 (dd, J = 10.7 Hz, 2.1 Hz, 1H), 7.62 (dd, J = 8.7 Hz, 5.5 Hz, 1H), 7.45 (s, 1H), 7.28−7.25 (m, 1H), 7.14−7.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (d, J_{C-F} = 182.1 Hz), 158.3, 156.4, 136.8 (d, J_{C-F} = 10.1 Hz), 124.2, 123.0 (d, J_{C-F} = 7.6 Hz), 120.8 (d, J_{C-F} = 1.0 Hz), 118.2, 113.9, 112.7 (d, J_{C-F} = 18.7 Hz), 109.4, 103.3 (d, J_{C-F} = 22.0 Hz). HRMS (ESI) m/z calcd for $C_{13}H_8FN_4$ $(M + H)^+$ 239.0728, found 239.0726.

5-Fluoro-1-(pyrimidin-2-yl)-1*H*-indole-2-carbonitrile (3h). White solid (31.4 mg, 66%); mp 218−219 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.84 (d, J = 4.8 Hz, 1H), 8.70 (dd, J = 9.3, 4.6 Hz, 1H), 7.42 (s, 1H), 7.33 (dd, J = 8.4, 2.5 Hz, 1H), 7.30−7.20 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4 (d, J_{C-F} = 240.1 Hz), 158.4, 156.4, 133.1, 128.4 (d, J_{C-F} = 10.4 Hz), 120.3 (d, J_{C-F} = 4.7 Hz), 118.2, 117.7 (d, J_{C-F} = 8.8 Hz), 116.0 (d, J_{C-F} = 25.2 Hz), 113.7, 110.4, 106.7 (d, J_{C-F} = 23.7 Hz). HRMS (ESI) m/z calcd for $C_{13}H_8FN_4$ $(M + H)^+$ 239.0728, found 239.0727.

5-Chloro-1-(pyrimidin-2-yl)-1*H*-indole-2-carbonitrile (3i). White solid (31.5 mg, 62%); mp 193−195 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.85 (d, J = 3.6 Hz, 2H), 8.77 (s, 1H), 7.60 (d, J = 6.4 Hz, 1H), 7.42−7.25 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 156.3, 136.7, 133.7, 126.2, 124.4, 122.7, 120.6, 118.3, 116.4, 113.8, 109.6. HRMS (ESI) m/z calcd for $C_{13}H_7ClN_4Na$ $(M + Na)^+$ 277.0251, found 277.0252.

1-(Pyrimidin-2-yl)-1*H*-indole-2,5-dicarbonitrile (3j). White solid (32.8 mg, 67%); mp 228−230 °C; ^{1}H NMR (d_6-DMSO, 400 MHz) δ 9.02 (d, J = 4.9 Hz, 2H), 8.72 (d, J = 8.9 Hz, 1H), 8.38 (s, 1H), 7.96−7.90 (m, 1H), 7.60 (t, J = 4.9 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 159.1, 155.1, 137.3, 129.6, 127.8, 127.1, 120.6, 119.7, 119.0, 116.8, 112.9, 110.5, 105.8. HRMS (ESI) m/z calcd for $C_{14}H_8N_5$ $(M + H)^+$ 246.0774, found 246.0776.

1-(5-Ethylpyrimidin-2-yl)-1*H*-indole-2-carbonitrile (3k). Yellowish liquid (36.2 mg, 73%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68−8.62 (m, 3H), 7.69 (d, J = 8.0 Hz, 1H), 7.52−7.45 (m, 2H), 7.34−7.26 (m, 1H), 2.73 (q, J = 8.0 Hz, 2H), 1.35 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 154.9, 136.6, 133.4, 127.6, 127.3, 123.3, 122.0, 120.3, 115.8, 114.3, 108.9, 23.1, 14.9. HRMS (ESI) m/z calcd for $C_{15}H_{13}N_4$ $(M + H)^+$ 249.1135, found 249.1134.

1-(5-Fluoropyrimidin-2-yl)-1*H*-indole-2-carbonitrile (3l). White solid (30.9 mg, 65%); mp 140−142 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.68 (s, 2H), 8.56−8.54 (m, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.52−7.47 (m, 1H), 7.45 (s, 1H), 7.34−7.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3 (d, J_{C-F} = 260.3 Hz), 152.5 (d, J_{C-F} = 2.8 Hz), 146.0 (d, J_{C-F} = 22.2 Hz), 136.4, 127.6, 127.6, 123.6, 122.1, 120.9, 115.5, 113.9, 109.0. HRMS (ESI) m/z calcd for $C_{13}H_8FN_4$ $(M + H)^+$ 239.0728, found 239.0726.

1-(Pyridin-2-yl)-1*H*-indole-2-carbonitrile (3m).[39] White solid (27.6 mg, 63%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.71 (d, J = 3.2 Hz, 1H), 8.00−7.94 (m, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.0 Hz, 1H), 7.63−7.38 (m, 3H), 7.30 (d, J = 7.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.7, 149.7, 138.9, 137.1, 127.0, 126.9, 122.8, 122.7, 122.4, 118.8, 117.4, 113.7, 112.3, 109.1.

5-Methoxy-1-(pyridin-2-yl)-1*H*-indole-2-carbonitrile (3n).[39] White solid (32.9 mg, 66%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.69 (d, J = 4.8 Hz, 1H), 7.98−7.92 (m, 1H), 7.72 (d, J = 9.4 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.40−7.32 (m, 2H), 7.11−7.07 (m, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 149.8, 149.6, 138.9, 132.3, 127.5, 122.6, 118.5, 118.2, 116.9, 113.8, 113.5, 109.0, 102.3, 55.7.

3-Methyl-1-(pyridin-2-yl)-1*H*-indole-2-carbonitrile (3o).[39] White solid (23.3 mg, 50%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68 (dd, J = 4.9, 1.1 Hz, 1H), 7.94 (td, J = 8.0, 1.9 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.64 (dd, J = 26.3, 8.1 Hz, 2H), 7.49−7.40 (m, 1H), 7.38−7.28 (m, 2H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 149.5, 138.8, 137.0, 128.6, 127.5, 127.1, 122.2, 122.1, 120.5, 118.3, 113.7, 112.3, 107.6, 9.9.

1-(Pyrimidin-2-yl)-1*H*-pyrrole-2-carbonitrile (3p).[39] White solid (18.4 mg, 54%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.75 (d, J = 4.8 Hz, 2H), 8.0 (dd, J = 3.0 Hz, 1.7 Hz, 1H), 7.25 (t, J = 4.5 Hz, 1H), 7.10−7.08 (m, 1H), 6.38 (t, J = 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 155.2, 126.2, 125.0, 118.9, 114.1, 111.8, 102.9.

Procedure for Removal of 2-Pyrimidyl Director.[42] Under argon, a mixture of 1-(pyrimidin-2-yl)-1*H*-indole-2-carbonitrile **3a** (33 mg, 0.15 mmol), EtONa (40.8 mg, 0.6 mmol), and DMSO (1.5 mL) was stirred in a reaction tube at 110 °C for 24 h. The resulting mixture was then quenched with water. The mixture was extracted with ethyl acetate, and the combined organic layer was dried by sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel to give the product 1*H*-indole-2-carbonitrile **4a**.

1*H*-Indole-2-carbonitrile (4a).[39] White solid (20.2 mg, 95%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.78 (s, 1H), 8.67 (d, J = 8.1 Hz, 1H), 7.43−7.36 (m, 2H), 7.24−7.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 126.3, 126.2, 122.1, 121.8, 114.5, 114.2, 111.8, 106.2.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of compounds **3a**−**3p** and **4a**. 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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■ DEDICATION

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■ REFERENCES

(1) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489.

(2) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215.

(3) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 6993.

(4) Ding, Z.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4698.

(5) Zhou, B.; Yang, Y.; Li, Y. *Chem. Commun.* **2012**, *48*, 5163.

(6) Schipper, D.; Hutchinson, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6910.

(7) Garca-Rubia, A.; Arrays, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 6511.

(8) Pan, S.; Ryu, N.; Shibata, T. *J. Am. Chem. Soc.* **2012**, *134*, 17474.

(9) Qin, X.; Liu, H.; Qin, D.; Wu, Q.; You, J.; Zhao, D.; Guo, Q.; Huang, X.; Lan, J. *Chem. Sci.* **2013**, *4*, 1964.

(10) *The Chemisty of the Cyano Group*; Rappoport, Z., Ed.; Interscience: London, 1970.

(11) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.
(12) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 5049.
(13) Qin, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 15893.
(14) Jia, X.; Yang, D.; Wang, W.; Luo, F.; Cheng, J. *J. Org. Chem.* **2009**, *74*, 9470.
(15) Jia, X.; Yang, D.; Zhang, S.; Cheng, J. *Org. Lett.* **2009**, *11*, 4716.
(16) Kim, J.; Kim, H.; Chang, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 11948.
(17) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661.
(18) Zhang, Z.; Liebeskind, L. S. *Org. Lett.* **2006**, *8*, 4331.
(19) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 519.
(20) Peng, J.; Zhao, J.; Hu, Z.; Liang, D.; Huang, J.; Zhu, Q. *Org. Lett.* **2012**, *14*, 4966.
(21) Zhang, G.; Chen, S.; Fei, H.; Cheng, J.; Chen, F. *Synlett* **2012**, *23*, 2247.
(22) Zheng, S.; Yu, C.; Shen, Z. *Org. Lett.* **2012**, *14*, 3644.
(23) Jin, J.; Wen, Q.; Lu, P.; Wang, Y. *Chem. Commun.* **2012**, *48*, 9933.
(24) Okamoto, K.; Watanabe, M.; Murai, M.; Hatano, R.; Ohe, K. *Chem. Commun.* **2012**, *48*, 3127.
(25) Jiang, Z.; Huang, Q.; Chen, S.; Long, L.; Zhou, X. *Adv. Synth. Catal.* **2012**, *354*, 589.
(26) Ding, S.; Jiao, N. *J. Am. Chem. Soc.* **2011**, *133*, 12374.
(27) Kim, J.; Chang, S. *J. Am. Chem. Soc.* **2010**, *132*, 10272.
(28) Kim, J.; Choi, J.; Shin, K.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 2528.
(29) Zhang, G.; Ren, X.; Chen, J.; Hu, M.; Cheng, J. *Org. Lett.* **2011**, *13*, 5004.
(30) Luo, F.-H.; Chu, C.-I.; Cheng, C.-H. *Organometallics* **1998**, *17*, 1025.
(31) Song, R.-J.; Wu, J.-C.; Liu, Y.; Deng, G.-B.; Wu, C.-Y.; Wei, W.-T.; Li, J.-H. *Synlett* **2012**, *23*, 2491.
(32) Ren, X.; Chen, J.; Chen, F.; Cheng, J. *Chem. Commun.* **2011**, *47*, 6725.
(33) Do, H.-Q.; Daugulis, O. *Org. Lett.* **2010**, *12*, 2517.
(34) Yang, Y.; Zhang, Y.; Wang, J. *Org. Lett.* **2011**, *13*, 5608.
(35) Yan, G.; Kuang, C.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 1052.
(36) Kim, J.; Kim, H.; Chang, S. *Org. Lett.* **2012**, *14*, 3924.
(37) Zhang, G.; Lv, G.; Pan, C.; Cheng, J.; Chen, F. *Synlett* **2011**, 2991.
(38) Yuen, O. Y.; Choy, P. Y.; Chow, W. K.; Wong, W. T.; Kwong, F. Y. *J. Org. Chem.* **2013**, *78*, 3374.
(39) Xu, S.; Huang, X.; Hong, X.; Xu, B. *Org. Lett.* **2012**, *14*, 4614.
(40) Zhang, Y.; Peng, H.; Zhang, M.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2011**, *47*, 2354.
(41) Pan, C.; Jin, H.; Liu, X.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2013**, *49*, 2933.
(42) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2011**, *13*, 3332.
(43) Lu, Y.; Li, C.-M.; Wang, Z.; Chen, J.; Mohler, M. L.; Li, W.; Dalton, J. T.; Miller, D. D. *J. Med. Chem.* **2011**, *54*, 4678.
(44) Borza, I.; Kolok, S.; Ignácz-Szendrei, G.; Greiner, I.; Tárkányi, G.; Galgózy, K.; Horváth, C.; Farkas, S.; Domány, G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5439.
(45) Reddy, G.; Kumar, P.; Anand, R.; Mukkanti, K.; Reddy, P. *Synlett* **2009**, 1463.
(46) Lu, T.; Zhuang, X.; Li, Y.; Chen, S. *J. Am. Chem. Soc.* **2004**, *126*, 4760.
(47) Xu, F.; Tao, T.; Zhang, K.; Wang, X.-X.; Huang, W.; You, X.-Z. *Dalton Trans.* **2013**, *42*, 3631.
(48) Xu, F.; Huang, W.; You, X.-Z. *Dalton Trans.* **2010**, *39*, 10652.
(49) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068.
(50) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.