Organic & Biomolecular Chemistry

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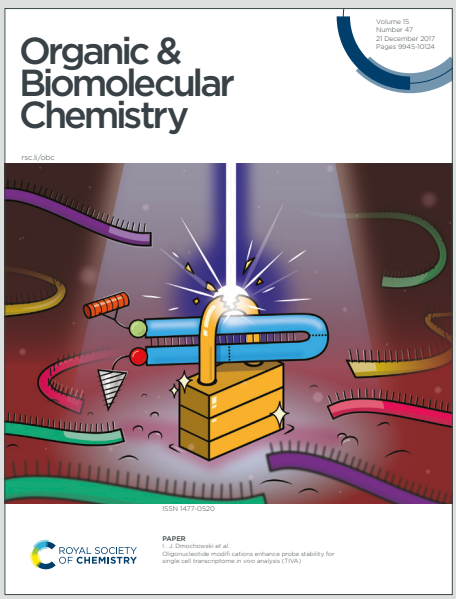

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DOI: 10.1039/D0OB00485E

ARTICLE

Palladium Catalyzed Direct C3-Cyanation of Indoles Using Acetonitrile as the Cyanide Source

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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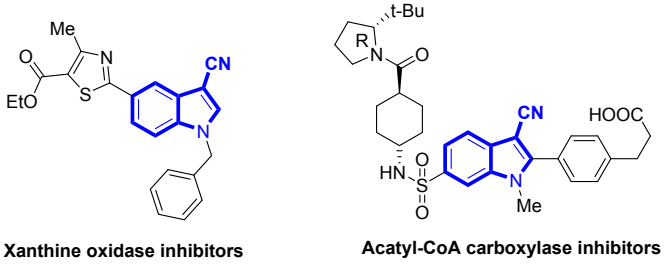
A ligand free palladium catalyzed C3-cyanation of indole via direct C-H functionalization was achieved. This protocol utilizing CH_3CN as green and readily available cyanide source obtaining the desired product in moderate to good yield through transition metal catalyzed C-CN bond cleavage.

Introduction

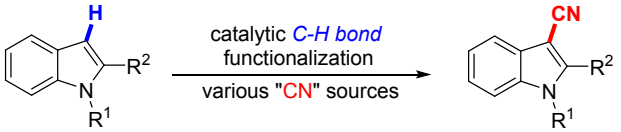
Indole nitrile especially 3-cyanoindole moiety is a value-added basic unit in organic synthesis, pharmaceutic science, material preparation and anti-virus/bacteria natural products (**Figure 1**).[1] In which, the versatile cyano group can realize its late-stage functionalization in suitable conditions transformed to carboxyl derivatives, amides, aldehydes and so on.[2]



Xanthine oxidase inhibitors **Acatyl-CoA carboxylase inhibitors**

Figure 1. Representatives containing 3-cyanoindole block

A comprehensive research has been conducted for the preparation of 3-cyanoindole.[3,6-9] The Sandmeyer and Rosenmund-von Braun reactions represents the most typically conventional method.[4] Significant efforts have been devoted to develop a more efficient and greener cyanation protocol to meet the modern organic synthesis demands.[5] Various cyano sources have been evolved (**Scheme 1**), which could be classified as nucleophilic CN^- sources,[6] electrophilic CN^+ sources,[7] combined cyano group[8] and organic R-CN units.[9] Among then, cyano anions like the metallic cyanides used to be frequently applied representatives. Nevertheless, the metallic cyanides like CuCN, NaCN or KCN are highly toxic to human and environment, and TMSCN suffers the same drawback. However, in which, the relatively environment-benign $K_4[Fe(CN)_6]$ shows weak solubility in organic solvent thus suppressed its further applications.[9b] Elegant progresses have been developed with the versatile combined cyanide sources exhibiting good feasibility constructing 3-cyanoindole.[8]



nucleophilic CN^- sources:	CuCN; NaCN; $K_4[Fe(CN)_6]$; TMSCN
electrophilic CN^+ sources:	NCTs; BrCN
combined [CN] group:	DMF/NH_4I; TMEDA/$(NH_4)_2CO_3$; DMF; NH_4HCO_3/DMSO
organic R-CN units:	t-BuNC; BnCN; CH_3CN

Scheme 1. Catalytic synthesis of 3-cyano indoles with various "CN" sources

Concerning the economic and environmentally friendly properties, acetonitrile would be an ideal alternative. While the C-CN bond activation in acetonitrile is of particularly difficult because it has a higher bond energy (133 Kcal mol-1) than the average alkane C-C bond energy (approximate 83 Kcal mol-1).[10] Few examples have been reported realizing the cyanation of aromatic compounds using CH_3CN as the sole cyano source.[9a,11] In which, Shen group reported an indole C3-cyanation protocol via the C-H bond activation catalysed by Cu/Si/TEMPO activation system gaining the target product in moderate to good yields with broad substrate scope application (**Scheme 2a**).[9a] Nevertheless, a ligand assistance and NIS promoted pre-iodination of indole C-H bond are essential to furnish the further cyanation consuming a lengthy reaction time (2-5 days). Herein,

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

we report a palladium catalysed ligand-free direct C3-cyanation protocol of indoles using acetonitrile as the green cyanide

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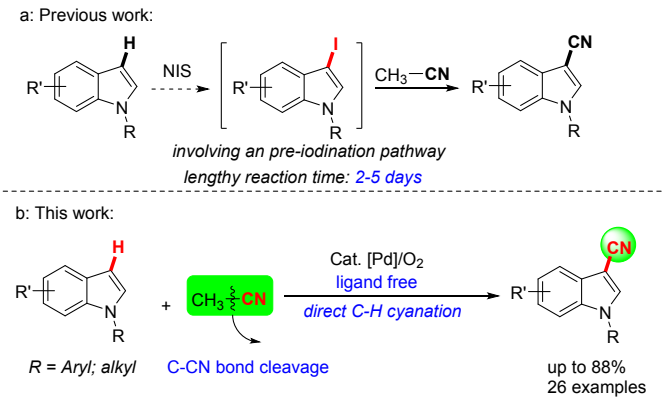
source via C-H bond activation and C-CN bond cleavage (**Scheme 2b**).

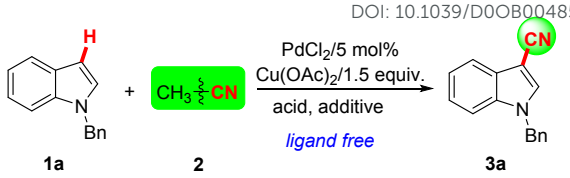


Scheme 2. Pd-catalysed preparation of 3-cyanoindole with acetonitrile

Results and discussion

We initiated our study from utilizing *N*-Benzyl indole (**1a**) as the model substrate, acetonitrile as both the cyanide source and solvent in the presence of $PdCl_2$ (5 mol %) and $Cu(OAc)_2$ (1.5 equiv.) under O_2 atmosphere at 135°C for 24 h, the desired product 3-cyanoindole (**3a**) was obtained in 16% yield (**Table 1**, run 1). And screening of other Pd-catalyst showed inferior efficiency in this transformation (run 2-5). Then we optimized the copper species, the results contained indicated that cupric halide or Cu_2O showed no reactivity (run 6-9) while $Cu(TFA)_2$ exhibited almost the same reactivity to $Cu(OAc)_2$ (Run 10). With a screening of acids (run 11-15), a slight promotion was observed and 4-nitrobenzoic acid showed better performance gaining the desired product in 26% yield (run 13). When we further introduced the AgOAc as additive, which might be a role of co-oxidant, yield of the desired product was increased to 45% (run 16). While trace amount of product was observed without the loading of acid (run 17). Encouraged by the effect of AgOAc, we further optimized a serial of Ag salts (run 18-21), and AgOTf contributed the best reactivity promotion producing the desired product in 58% yield (run 21). Either further elevating the temperature to 150 °C or down to 100 °C showed no promotion (run 22-23). As we screening the solvent effect, we found that $Cu(OAc)_2$ showed good solubility in DMF. Gratifyingly, the mixed solvent (CH_3CN/DMF = 3.5 mL/1.5 mL) indeed exhibited good preference obtaining the desired product in 73% yield (run 24). Further considering that DMF could also act as an internal combined cyanide source,[8a] we applied DMF as the sole solvent but only trace amount of the desired product was observed (run 25) that indicated the cyanide source mainly formed from acetonitrile. Selected control experiments conducted showed that catalytic loading of palladium and the O_2 atmosphere were essential to this oxidative cross-coupling system (run 26-27). Meanwhile, once we decreased the $Cu(OAc)_2$ or AgOTf to catalytic amount of 20%, the reactivity were dramatically depressed (run 28-29).

Table 1 Oxidative C-3 cyanation of *N*-benzyl indole with CH_3CN [a]



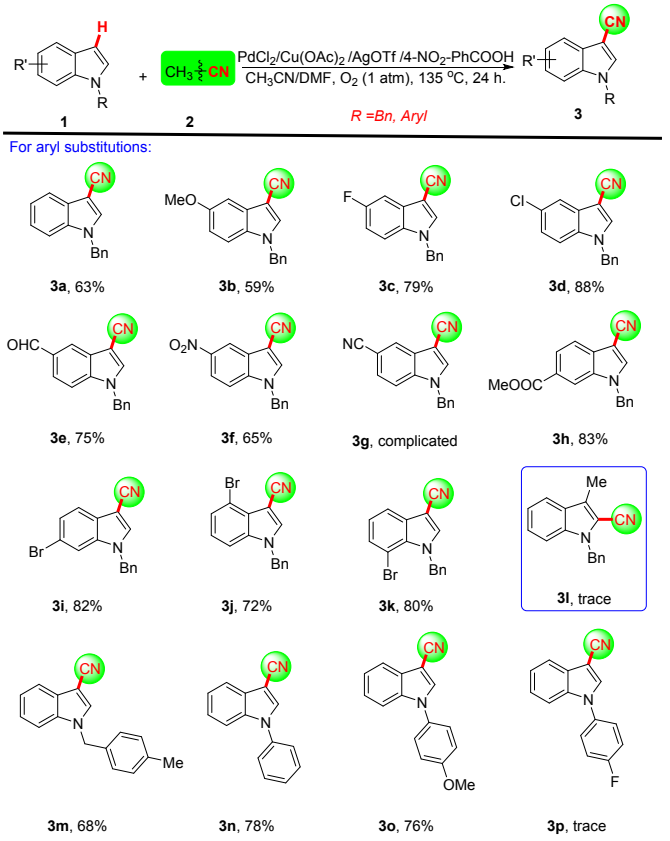
Run	Cat. [Pd]	Cu salt	Acid	Additive	**3aa**
	mol %	1.5 eq.	(1 eq.)	(1 eq.)	Yield %[b]
1	$PdCl_2$/5	$Cu(OAc)_2$	/	/	16
2	$PdCl_2(PPh)_3$/5	$Cu(OAc)_2$	/	/	11
3	$Pd(OAc)_2$/5	$Cu(OAc)_2$	/	/	13
4	$PdBr_2$/5	$Cu(OAc)_2$	/	/	9
5	$Pd(PPh_3)_4$/5	$Cu(OAc)_2$	/	/	trace
6	$PdCl_2$/5	$CuBr_2$	/	/	trace
7	$PdCl_2$/5	CuBr	/	/	trace
8	$PdCl_2$/5	CuI	/	/	trace
9	$PdCl_2$/5	Cu_2O	/	/	N.D
10	$PdCl_2$/5	$Cu(TFA)_2$	/	/	15
11	$PdCl_2$/5	$Cu(OAc)_2$	Ph_2POOH	/	20
12	$PdCl_2$/5	$Cu(OAc)_2$	PhCOOH	/	15
13	$PdCl_2$/5	$Cu(OAc)_2$	4-NO_2-PhCOOH	/	26
14	$PdCl_2$/5	$Cu(OAc)_2$	4-MeO-PhCOOH	/	16
15	$PdCl_2$/5	$Cu(OAc)_2$	$(CH_3)_3CCOOH$	/	10
16	$PdCl_2$/5	$Cu(OAc)_2$	4-NO_2-PhCOOH	AgOAc	45
17	$PdCl_2$/5	$Cu(OAc)_2$	/	AgOAc	trace
18	$PdCl_2$/5	$Cu(OAc)_2$	4-NO_2-PhCOOH	$AgClO_4$	45
19	$PdCl_2$/5	$Cu(OAc)_2$	4-NO_2-PhCOOH	Ag_2CO_3	47
20	$PdCl_2$/5	$Cu(OAc)_2$	4-NO_2-PhCOOH	$AgNO_3$	17
21	$PdCl_2$/5	$Cu(OAc)_2$	4-NO_2-PhCOOH	AgOTf	58
22	$PdCl_2$/5	$Cu(OAc)_2$	4-NO_2-PhCOOH	AgOTf	38[c]
23	$PdCl_2$/5	$Cu(OAc)_2$	4-NO_2-PhCOOH	AgOTf	trace[d]
24	$PdCl_2$/5	$Cu(OAc)_2$	4-NO_2-PhCOOH	AgOTf	73[e]
25	$PdCl_2$/5	$Cu(OAc)_2$	4-NO_2-PhCOOH	AgOTf	trace[f]
26	$PdCl_2$/5	$Cu(OAc)_2$	4-NO_2-PhCOOH	AgOTf	N.D[g]
27	/	$Cu(OAc)_2$	4-NO_2-PhCOOH	AgOTf	N.D[e]
28	$PdCl_2$/5	$Cu(OAc)_2$	4-NO_2-PhCOOH	AgOTf	N.D[e,h]
29	$PdCl_2$/5	$Cu(OAc)_2$	4-NO_2-PhCOOH	AgOTf	N.D[e,i]

Reaction condition: *N*-benzyl indole (0.2 mmol, 41.4 mg), $PdCl_2$ (0.01 mmol, 1.8 mg), $Cu(OAc)_2$ (0.3 mmol, 54.3 mg), $AgSO_3CF_3$ (0.2 mmol, 51.4 mg), 4-NO_2-PhCOOH (0.2 mmol, 33.4 mg) in CH_3CN/5 mL, O_2 (1 atm, 25 mL), 135°C, 24 h. [b] GC yields using dodecane as the internal stander. [c] 150 °C was used; [d] 100 °C was used; [e] Solvent (CH_3CN/3.5 mL, DMF/1.5 mL) was used. [f] Solvent (DMF/5 mL) was used. [g] Under the atmosphere of N_2 or air. [h] 20 mol % $Cu(OAc)_2$ was used. [i] 20 mol % AgOTf was used.

With the optimizing condition in hand, the palladium catalysed direct indole C3-cyanation strategy was applied to other indole substrates. The *N*-aryl substituted and *N*-alkyl substituted indoles both exhibited good feasibility in this catalytic transformation. As displayed in **Table 2**, the *N*- aryl substituted indoles with electronic donating group like MeO- substitution could be well fitted gaining the yield of 59% (**Table 2**, **3b**). Meanwhile, the electronic withdrawing group substitutions also exhibited good compatibility in this catalytic system. Such as the simple halogen substitutions (F-, Cl-) at 5-position of indole ring, ideal yields could be obtained in 79% (**3c**) and 88% (**3d**), respectively. Besides, the strong electronic withdrawing groups like -CHO and -NO_2, could also well featured in this protocol generating the desired cyanation products in good yields (**3e**

and **3f**, 75% and 65%, respectively). However, complicated target product was produced when the 5- position of indole ring was occupied by -CN group. Furthermore, not only for the 5-position substitutions could be adapted to this transformation, functionalization of other positions could also be well accommodated. In which, the selected simple bromide and the strong electronic withdrawing ester group substitutions distributed at 4-, 6-, 7- positions all exhibited good reactivity obtaining the desired products in 72%-83% yields (**3h**-**3k**). Meantime, a brief control experiment was conducted indicated that the reactivity of 3- position was far more active than 2-position. For which, trace amount of the 2-cyanation product was obtained (GC-MS detected) when the 3- position was occupied by methyl group (**3l**).

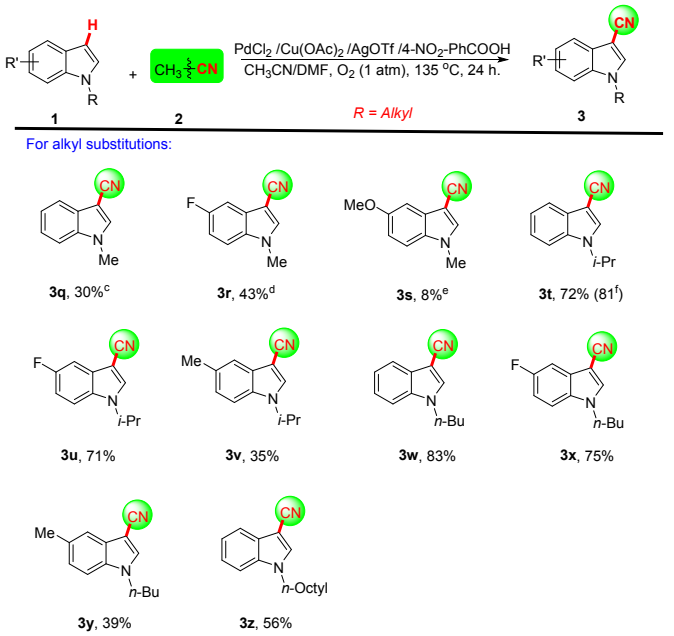
Table 2 C-3 cyanation of *N*-aryl indoles with acetonitrile [a]



[a] Reaction condition: indoles (0.2 mmol), $PdCl_2$ (0.01 mmol), $Cu(OAc)_2$ (0.3 mmol), AgOTf (0.2 mmol), 4-nitrobenzoic acid (0.2 mmol) in CH_3CN (3.5 mL) and DMF (1.5 mL) were stirred under O_2 atmosphere (1 atm) at 135°C in the Schlenk tube (25 mL) for the indicated time. [b] Isolated yield.

Furthermore, benzyl (Me- functionalization on the phenyl group of benzyl unit) substitutions could also well promote this catalytic transformation gaining the desired product in 68% yield (**3m**). Given that serials of indole C-H functionalization has been performed mainly focused on the substitution effect to the phenyl ring of indole. We tended to consider the influence of various *N*-protection concerning to the reactivity of cyanation. Except for the benzyl substitution, other aryl group like phenyl block could also be served in this system (**3n**-**3p**). Interestingly, when the phenyl group was substituted with an electron-deficient group like F- at its 4- position, trace amount of cyanation product was observed (**3p**), while the electron-rich substitution (MeO-) showed no influence to the reactivity (**3o**, 76% yield).

Table 3 C-3 cyanation of *N*-alkyl indoles with acetonitrile [a]



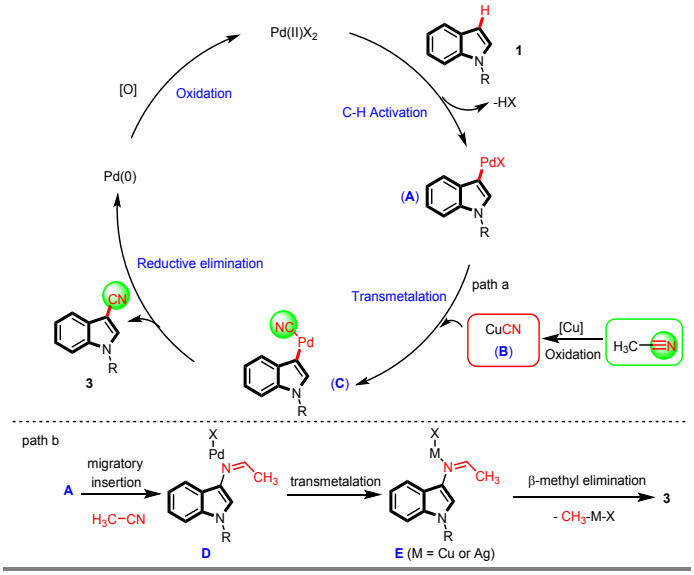
[a] Reaction condition: indoles (0.2 mmol), $PdCl_2$ (0.01 mmol), $Cu(OAc)_2$ (0.3 mmol), AgOTf (0.2 mmol), 4-nitrobenzoic acid (0.2 mmol) in CH_3CN (3.5 mL) and DMF (1.5 mL) were stirred under O_2 atmosphere (1 atm) at 135°C in the Schlenk tube (25 mL) for the indicated time. [b] Isolated yield. [c] $AgSO_3C_8F_{17}$ was used. [d] $PdCl_2$ (0.02 mmol), $Cu(OAc)_2$ (0.04 mmol) was used. [e] GC yield using dodecane as the internal standard, no further purification. [f] 3,5-dinitrobenzoic acid was used.

Encouraged by the good performance of this catalytic cyanation protocol of *N*-aryl indoles, we further explored the feasibility of *N*-alkyl indoles. However, *N*-alkyl substitutions of indole exhibited relatively defective reactivity furnishing this catalytic system obtaining the desired product in moderate to good yield. In which, methyl, iso-propyl (for **3t**, **3u** and **3v**, in 81%, 71% and 35% yield, respectively), butyl (for **3w**, **3x** and **3y**, in 83%, 75% and 39% yield, respectively) and even octyl group (**3z**, 56%) substitution could be applied in this palladium catalysed direct C3-cyanation of indole. Meanwhile, it compiled to the regularity of electrophilic attack, that is, the electronic donating substitution on the phenyl ring of indole showed poorer reactivity (**3s** in 8% yield, **3v** in 35% yield, **3y** in 42% yield). Among then, *N*-methyl protection derivatives (for **3q**, **3r** and **3s** in 30%, 43% and 8% yield, respectively) displayed inferior performance for the reason of the probably easier decomposition compared thus suppressed the reactivity. We also applied our catalytic system to other heteroaromatic substrates for cyanation, however, benzofuran, benzothiophene, benzoxazole, and benzothiazole exhibited low efficiency in this transformation and no corresponding products were detected.

According to the precedent literature[6b,10a,11a], and experimental observation, a tentative mechanism for this C3-cyanylation of

indoles is depicted in Scheme 3. Initially, C3-H activation of indole substrates took place with Pd(II) catalyst to afford aryl-Pd(II)-X species **A**. On the other hand (path a), oxidation of acetonitrile gave cyanide anion, which further reacted to copper salt to give cuprous cyanide **B**. Subsequent transmetalation followed by reductive elimination to release the desired C3-cyanylation indole products **3** and Pd(0), which underwent further oxidation to generate reactive Pd(II) catalyst and restart the catalytic cycle.

Alternatively (path b), migratory insertion of C-N triple bond of acetonitrile into the aryl-Pd(II)-X species A might take place to give iminyl palladium complex D. Upon transmetalation to copper or silver salt, which followed by β-methyl elimination, the desired nitrile products **3** were obtained, with the release of CH_3-M-X byproduct.



Scheme 3. Proposed mechanism for the C3-H cyanylation of indoles

Conclusions

In summary, we have explored a ligand free direct C3-cyanation methodology of indole via palladium catalysed applying acetonitrile as the green and readily available cyanide source obtaining the desired product in moderate to good yields. In which, the pre-functionalization of indole C-H bond wasn't essential and a transition catalysed C-CN bond cleavage was involved in this protocol.

Experimental

General information

All reactions were carried out under O_2 atmosphere (1 atm) using standard Schlenk technique in the parallel synthesizer. All reagent/reactant were commercially available except other noted. The substituted indole substrates were prepared according to the known methods. DMF and CH_3CN were purified according to the <Purification of Laboratory Chemicals: The Six Edition > before being used. Column chromatography was performed using Silica Gel 60 (particle size 37-54 μm). The pure products were obtained by column chromatography using ethyl acetate/petroleum ether as an eluent and detected by NMR using $CDCl_3$ as the deuterium reagent. GC analysis was performed on GC 7820A (Shimadzu). GC-MS results were recorded on GC-MS QP2010 (Shimadzu). The ^1H NMR and ^{13}C NMR data were data were acquired on a Brucker ADVANCE III spectrometer (400 MHz for ^1H NMR spectroscopy and 100 MHz for ^{13}C NMR spectroscopy). Exact mass was conducted by the College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, 325000, China

General Procedure for the preparation of 1-Benzyl-1H-indole-3-carbonitrile (3a):

A mixture of *N*-benzyl indole (0.2 mmol, 41.4 mg), $PdCl_2$ (0.01 mmol, 1.8 mg), $Cu(OAc)_2$ (0.3 mmol, 54.3 mg), $AgSO_3CF_3$ (0.2 mmol, 51.4 mg) and 4-NO_2-PhCOOH (0.2 mmol, 33.4 mg) was added to a 25 mL Schleck tube with a combined solvent (CH_3CN/DMF = 3.5 mL/1.5 mL), the solution was then vigorously stirred at 135 °C under O_2 atmosphere (1 atm) for 24 h. After cooling the mixture to ambient temperature, the reaction mixture was filtrated and evaporated to remove the solvent and the crude product was purified by column chromatography on silica gel (DCM/hexane = 1:1, Rf = 0.5) to afforded the desired product **3a** (63%, 29.2 mg) in white solid.

Characterization and analytical data of products

1-Benzyl-1H-indole-3-carbonitrile (**3a**). Following the general procedure, **3a** was obtained in 63% yield as a white solid (reacting for 24 h). ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.80-7.76 (m, 1H), 7.61 (s, 1H), 7.38-7.29 (m, 6H), 7.15 (d, J = 8.0 Hz, 2H), 5.34 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 135.6, 135.2, 135.0, 129.2, 128.5, 128.0, 127.1, 124.0, 122.3, 120.0, 115.8, 110.9, 86.3, 50.9.

1-Benzyl-5-methoxy-1H-indole-3-carbonitrile (**3b**). Following the general procedure, **3b** was obtained in 59% yield as a white solid (reacting for 36 h). ^1H NMR($CDCl_3$, 400 MHz, TMS) δ 7.55 (s, 1H), 7.37-7.32 (m, 3H), 7.22 (d, J = 8.8 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 6.94-6.91 (m, 1H), 5.29 (s, 2H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 156.1, 135.3, 134.9, 130.6, 129.1, 128.9, 128.4, 127.1, 116.1, 114.8, 111.8, 100.9, 85.7, 55.8, 51.1.

1-benzyl-5-fluoro-1H-indole-3-carbonitrile (**3c**). Following the general procedure, **3c** was obtained in 79% yield as a white solid (reacting for 36 h). ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.64 (s, 1H), 7.44-7.41 (m, 1H), 7.38-7.34 (m, 3H), 7.29-7.26 (m, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.07-7.02 (m, 1H), 5.33 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 160.5 (d, J_{F-C} = 240.5 Hz), 136.2, 134.8, 132.1, 129.2, 128.6, 127.1, 115.3, 113.0, 112.7, 112.0 (d, J_{F-C} = 9.6 Hz), 105.5 (d, J_{F-C} = 24.8 Hz), 86.4 (d, J_{F-C} = 4.5 Hz), 51.3

1-benzyl-5-chloro-1H-indole-3-carbonitrile (**3d**). Following the general procedure, **3d** was obtained in 88% yield as a yellow solid (reacting for 36 h). ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.74 (s, 1H), 7.64 (s, 1H), 7.42-7.38 (m, 3H), 7.32-7.25 (m, 2H), 7.18-7.16 (m, 2H), 5.36 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ

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DOI: 10.1039/D0OB00485E

136.1, 134.8, 134.0, 129.3, 129.0, 128.7, 128.5, 127.1, 124.6, 119.5, 115.2, 112.1, 86.0, 51.2.

1-benzyl-5-formyl-1H-indole-3-carbonitrile (**3e**). Following the general procedure, **3e** was obtained in 88% yield as a light yellow solid (reacting for 36 h). ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 10.44 (s, 1H), 8.63 (s, 1H), 8.23 (d, J = 7.2 Hz, 1H), 8.11 (s, 1H), 7.88-7.65 (m, 4H), 7.56 (s, 2H), 5.78 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 192.0, 139.1, 137.2, 134.9, 131.9, 129.7, 129.2, 128.2, 127.6, 125.1, 124.2, 115.1, 112.1, 88.7, 51.7

1-benzyl-5-nitro-1H-indole-3-carbonitrile. (**3f**) Following the general procedure, **3f** was obtained in 88% yield as a yellow solid (reacting for 36 h). ^{1}H NMR (DMSO, 400 MHz, TMS) δ 8.79 (s, 1H), 8.54 (s, 1H), 8.19 (s, 1H), 7.95 (s, 1H), 7.36 (m, 5H), 5.66 (s, 2H); ^{13}C NMR (DMSO, 100 MHz, TMS) δ 143.4, 141.6, 138.5, 136.6, 129.3, 128.6, 127.9, 127.0, 119.3, 116.0, 113.3, 100.0, 87.2, 50.8

1-benzyl-3-cyano-1H-indole-6-carboxylate. (**3h**) Following the general procedure, **3h** was obtained in 88% yield as a yellow solid (reacting for 36 h). ^{1}H NMR (DMSO, 400 MHz, TMS) δ 8.66 (s, 1H), 8.25 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.37-7.27 (m, 5H), 5.65 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (DMSO, 100 MHz, TMS) δ 166.8, 140.7, 136.9, 135.1, 131.4, 129.3, 128.4, 127.5, 125.4, 123.0, 119.5, 115.7, 114.0, 85.2, 52.6, 50.5

1-benzyl-6-bromo-1H-indole-3-carbonitrile. (**3i**) Following the general procedure, **3i** was obtained in 88% yield as a yellow solid (reacting for 36 h). ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.68 (d, 3H), 7.39 (m, 4H), 7.2 (m 2H), 5.30 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 136.4, 135.8, 134.9, 129.3, 128.7, 127.3, 126.8, 125.7, 121.2, 117,7, 115.4, 114.0, 86.6, 51.0

1-benzyl-4-bromo-1H-indole-3-carbonitrile. (**3j**) Following the general procedure, **3j** was obtained in 88% yield as a yellow solid (reacting for 36 h). ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.68 (d, *J* = 7.2 Hz, 1H), 7.45-7.34 (m, 5H) 7.38-7.34 (m, 5H), 7.18-7.14 (m 3H), 5.37 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 137.1, 136.3, 134.7, 129.3, 128.7, 127.2, 126.4, 126.2, 124.9, 115.7, 114.7, 110.3, 87.1, 51.3

1-benzyl-7-bromo-1H-indole-3-carbonitrile. (**3k**) Following the general procedure, **3k** was obtained in 88% yield as a yellow solid (reacting for 36 h). ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.77-7.75 (m, 1H), 7.60-7.49 (m, 2H), 7.38-7.36 (m 3H), 7.19-7.11 (m, 3H), 5.86 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 137.7, 136.8, 132.2, 130.9, 129.5, 129.1, 128.2, 126.6, 123.5, 119.5, 115.0, 104.8, 87.0, 52.4

1-(4-methylbenzyl)-1H-indole-3-carbonitrile. (**3m**) Following the general procedure, **3m** was obtained in 68% yield as a yellow solid (reacting for 36 h). ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.70-7.68 (m, 1H), 7.50 (s, 1H), 7.31-7.28 (m, 1H), 7.24-7.21 (m, 2H), 7.07 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 5.21 (s, 2H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 138.4, 135.6, 134.9, 132.1, 129.8, 128.0, 127.2, 123.9, 122.3, 120.0, 115.8, 110.8, 86.1, 50.7, 21.1.

1-phenyl-1H-indole-3-carbonitrile. (**3n**) Following the general procedure, **3n** was obtained in 78% yield as a white solid (reacting for 24 h). ^{1}H NMR($CDCl_3$, 400 MHz, TMS) δ 7.85-7.81 (m, 2H), 7.60-7.56 (m, 2H), 7.53-7.48 (m, 4H), 7.38-7.33 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 137.8, 135.6, 134.7, 130.0, 128.4, 128.0, 124.9, 124.6, 122.8, 120.1, 115.6, 111.5, 88.1.

1-(4-methoxyphenyl)-1H-indole-3-carbonitrile. (**3o**) Following the general procedure, **3o** was obtained in 76% yield as a white solid (reacting for 36 h). ^{1}H NMR($CDCl_3$, 400 MHz, TMS) δ 7.83-7.81 (m, 1H), 7.75 (s, 1H), 7.44-7.41 (m, 1H), 7.38 (d, J = 8.8 Hz, 2H), 7.34-7.32 (m, 2H), 7.07 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 159.5, 136.1, 135.0, 130.6, 127.8, 126.4, 122.6, 120.0, 115.7, 115.1, 111.5, 87.4, 55.7.

1-Methyl-1H-indole-3-carbonitrile. (**3q**) Following the general procedure, **3q** was obtained with 30% in as a brown liquid (reacting for 24 h). ^{1}H NMR($CDCl_3$, 400 MHz, TMS) δ 7.76 (d, J = 8.0 Hz, 1H), 7.57 (s, 1H), 7.26-7.41 (m, 3H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 135.9, 135.6, 127.7, 123.8, 122.1, 119.9, 116.0, 110.3, 85.4, 33.7.

5-Fluoro-1-methyl-1H-indole-3-carbonitrile. (**3r**) Following the general procedure, **3r** was obtained in 43% yield as a yellow liquid (reacting for 24 h). ^{1}H NMR($CDCl_3$, 400 MHz, TMS) δ 7.57 (s, 1H), 7.41 (dd, J = 2.4, 2.4 Hz, 1H), 7.35-7.31 (m, 1H), 7.13-7.08 (m, 1H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 160.5 (d, J = 238.2 Hz), 136.6, 132.6, 128.5 (d, J = 10.7 Hz), 115.4, 112.8 (d, J = 26.4 Hz), 111.4 (d, J = 3.8 Hz), 105.3 (d, J = 24.8 Hz), 85.6 (d, J = 4.7 Hz), 33.9.

1-isopropyl-1H-indole-3-carbonitrile. (**3t**) Following the general procedure, **3t** was obtained in 81% yield as a yellow liquid (reacting for 24 h). ^{1}H NMR($CDCl_3$, 400 MHz, TMS) δ 7.76 (d, J = 7.2 Hz, 1H), 7.71 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.36-7.26 (m, 2H), 4.76-4.66 (m, 1H), 1.56 (d, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 134.9, 131.1, 128.0, 123.6, 122.1, 120.0, 116.2, 110.6, 85.7, 48.3, 22.6.

5-fluoro-1-isopropyl-1H-indole-3-carbonitrile. (**3u**) Following the general procedure, **3u** was obtained in 71% yield as a yellow liquid (reacting for 24 h). ^{1}H NMR($CDCl_3$, 400 MHz, TMS) δ 7.74 (s, 1H), 7.42-7.36 (m, 2H), 7.11-7.06 (m, 1H), 4.73-4.63 (m, 1H), 1.57 (d, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 160.3 (d, J_{F-C} = 238.2 Hz), 132.2, 131.5, 128.6 (d, J_{F-C} = 10.7 Hz), 115.6, 112.5 (d, J_{F-C} = 26.3 Hz), 111.7 (d, J_{F-C} = 11.5 Hz), 105.3 (d, J_{F-C} = 24.6 Hz), 85.8, 48.7, 22.6. HRMS-ESI (m/z) [M + H$^+$]: Calcd for $C_{12}H_{12}FN_2^+$, 202.0906; found, 202.0912.

1-isopropyl-5-methyl-1H-indole-3-carbonitrile. (**3v**) Following the general procedure, **3v** was obtained in 35% yield as a yellow liquid (reacting for 24 h). ^{1}H NMR($CDCl_3$, 400 MHz, TMS) δ 7.66 (s, 1H), 7.55 (s, 1H), 7.33 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 4.72-4.61 (m, 1H), 2.48 (s, 3H), 1.55 (d, J = 7.2 Hz, 6H); ^{13}C

DOI: 10.1039/D0OB01485F

NMR ($CDCl_3$, 100 MHz, TMS) δ 133.3, 131.8, 131.0, 128.3, 125.2, 119.6, 116.4, 110.3, 85.0, 48.3, 22.6, 21.4.

1-butyl-1H-indole-3-carbonitrile. (**3w**) Following the general procedure, **3w** was obtained in 83% yield as a brown liquid (reacting for 24 h). ^{1}H NMR($CDCl_3$, 400 MHz, TMS) δ 7.76 (d, J = 7.6 Hz, 1H), 7.59 (s, 1H), 7.35-7.32 (m, 1H), 7.41 (d, J = 8.0 Hz), 7.36-7.26 (m, 2H), 4.15 (t, J = 7.2 Hz, 2H), 1.88-1.81 (m, 2H), 1.39-1.30 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 135.3, 134.7, 128.0, 123.7, 122.0, 120.0, 116.1, 110.5, 85.5, 47.0, 31.9, 20.0, 13.6.

1-Butyl-5-fluoro-1H-indole-3-carbonitrile. (**3x**) Following the general procedure, **3x** was obtained in 75% yield as a brown liquid (reacting for 24 h). ^{1}H NMR($CDCl_3$, 400 MHz, TMS) δ 7.62 (s, 1H), 7.40 (dd, J = 2.4, 2.4 Hz, 1H), 7.35-7.32 (m, 1H), 7.11-7.06 (m, 1H), 4.14 (t, J = 7.2 Hz, 2H), 1.88-1.80 (m, 2H), 1.39-1.30 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 160.3 (d, J = 231 Hz), 135.7, 131.94, 128.62 (d, J = 10.8 Hz), 115.4, 112.6 (d, J = 26.3 Hz), 111.5 (d, J = 9.6 Hz), 105.4 (d, J = 24.6 Hz), 85.6, 47.3, 31.8, 19.9, 13.5. HRMS-ESI (m/z) [M + H$^+$]: Calcd for $C_{13}H_{14}FN_2^+$, 216.1063; found, 216.1071.

1-butyl-5-methyl-1H-indole-3-carbonitrile. (3y) Following the general procedure, **3y** was obtained in 39% yield as a yellow liquid (reacting for 24 h). ^{1}H NMR($CDCl_3$, 400 MHz, TMS) δ 7.55 (s, 1H), 7.54 (s, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.16-7.14 (m, 1H), 4.12 (t, J = 6.0 Hz, 2H), 2.48 (s, 3H), 1.87-1.79 (m, 2H), 1.38-1.26 (m, 2H), 0.94 (t, J = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 134.5, 133.7, 131.8, 128.3, 125.3, 119.6, 116.2, 110.2, 84.8, 47.0, 31.9, 21.4, 20.0, 13.6.

1-octyl-1H-indole-3-carbonitrile. (**3z**) Following the general procedure, **3z** was obtained in 56% yield as a brown liquid (reacting for 24 h). ^{1}H NMR($CDCl_3$, 400 MHz, TMS) δ 7.76 (d, J = 7.6 Hz, 1H), 7.59 (s, 1H), 7.41 (d, J = 7.2 Hz, 1H), 7.35-3.26 (m, 2H), 4.14 (t, J = 7.2 Hz, 2H), 1.89-1.83 (m, 2H), 1.31-1.25 (m, 10H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 135.4, 134.6, 128.0, 123.7, 122.0, 120.0, 116.0, 110.5, 85.5, 47.3, 31.7, 29.8, 29.1, 29.1, 26.8, 22.6, 14.0. HRMS-ESI (m/z) [M + H$^+$]: Calcd for $C_{17}H_{23}FN_2^+$, 254.1783; found, 254.1791.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the financial support by the National Natural Science Foundation of China (21502066), the Natural Science Foundation of Guangdong Province (No. 2014a030310113), the Program for Innovative Research Team of Huizhou University (cxtd2019002), the Professorial and Doctoral Scientific Research Foundation of Huizhou University (2018JB011), Youth Innovative Talents Project in Colleges and Universities in Guangdong Province (2019KQNCX154), and the Open Fund of the Key Laboratory of Functional Molecular Engineering of Guangdong Province (No.2018kf02, South China University of Technology).

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