JOC The Journal of Organic Chemistry

UNIVERSITY OF EXETER

Subscriber access provided by the University of Exeter

Article

# Visible-light-induced decarboxylative cyclization of 2-alkenylarylisocyanides with #-oxocarboxylic acids: direct access to 2-acylindoles

Xiaofei ZHANG, Peiyuan ZHU, Ruihong ZHANG, Xiang Li, and Tuanli Yao

*J. Org. Chem.*, **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c00039 • Publication Date (Web): 29 Jun 2020



## Just Accepted



is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

# Visible-light-induced decarboxylative cyclization of 2-alkenylarylisocyanides with *α*-oxocarboxylic acids: direct access to 2-acylindoles

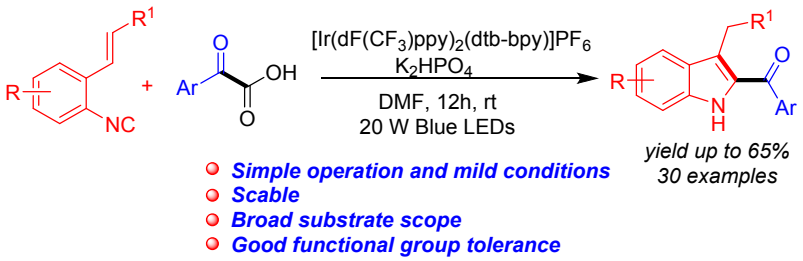
Xiaofei Zhang,*[a,b] Peiyuan Zhu,[a] Ruihong Zhang,[a] Xiang Li,*[a,b] Tuanli Yao*[a,b]

[a] College of Chemistry and Chemical Engineering, Shaanxi University of Science and Technology, Xi'an, Shaanxi 710021, China

Email: zhangxiaofei@sust.edu.cn; lix@sust.edu.cn; yaotuanli@sust.edu.cn

[b] Shaanxi Key Laboratory of Chemical Additives for Industry, Shaanxi University of Science and Technology, Xi'an 710021, China

**ABSTRACT:** An efficient and practical protocol for visible-light-induced decarboxylative cyclization of 2-alkenylarylisocyanides with α-oxocarboxylic acids has been developed, which afforded a broad range of 2-acylindoles in moderate to good yields. The reaction proceeds through a cascade of acyl radical addition/cyclization under irradiation of $Ir^{3+}$ photoredox catalyst without external oxidants, and features with simple operation, scalability, broad substrate scope and good functional group tolerance.




## INTRODUCTION

Functionalized indoles are widely found in pharmaceuticals and nature products.[1] In the past decades, considerable efforts have been devoted to the development of

efficient methods for the synthesis of functionalized indoles.[2] Traditionally, the indole scaffolds are constructed by cyclization reactions such as Hemetsberger or Cadogan−Sundberg indole synthesis, intramolecular Ullmann or Heck coupling reactions.[3] Although these cyclization reactions are effective, preparation of required starting materials through multistep reactions dramatically limits their application. Recently, transition-metal-catalyzed site-selective C-H bond activation of indoles has become one of the most powerful and straightforward methods for the synthesis of functionalized indoles,[4] C2, C3 or C7-substituted indoles were synthesized by arylation,[5] cyanation,[6] alkylation[7] and alkenylation reactions.[8] Among various functionalized indoles, 2-acylindoles are extremely important structural components that present in many natural products, pharmaceuticals, and biological active compounds (Figure 1).[9] Therefore, the development of mild and practical protocols for the synthesis of 2-acylindoles is of great value.

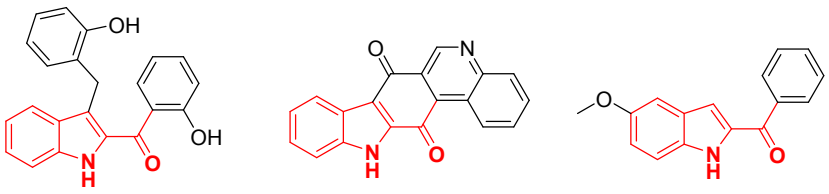
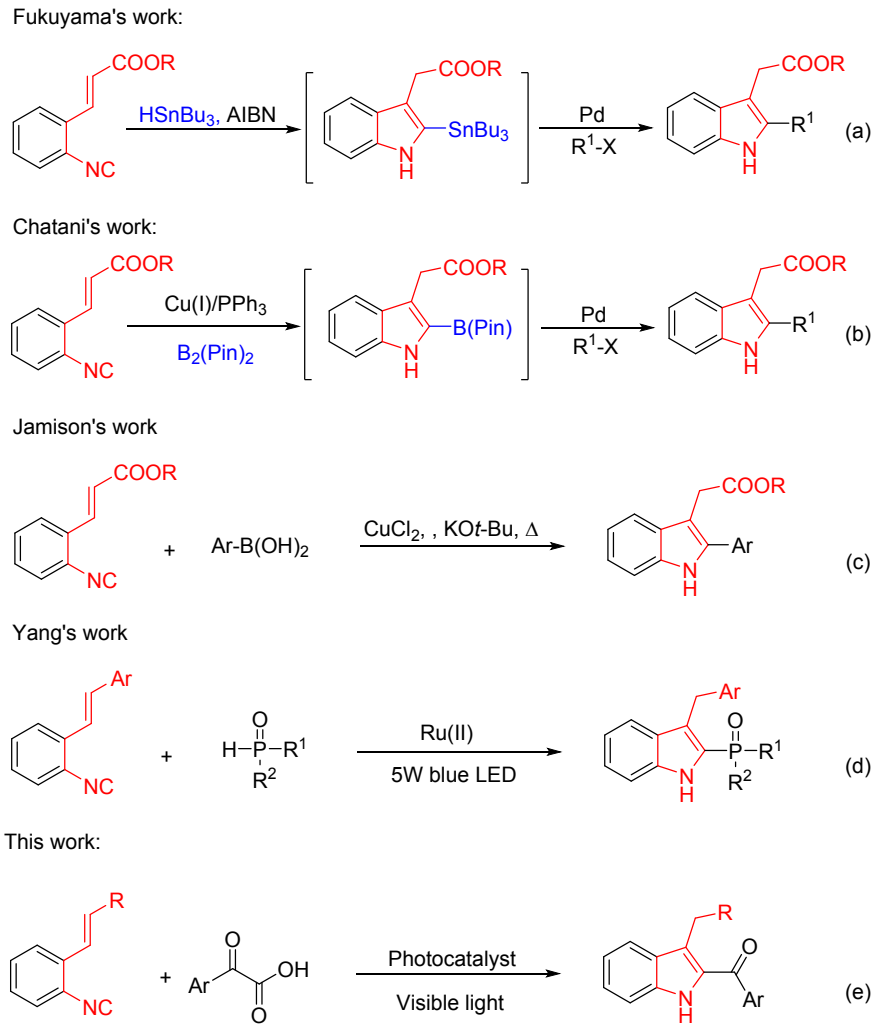



**Figure 1**. Representative compounds containing 2-acylindole scaffolds

Generally, 2-acylindoles are synthesized through nucleophilic addition of 2-lithioindoles,[10] palladium-catalyzed cross-couplings[11] or cyclization reactions.[12] Transition-metal-catalyzed, ligand directed C2-H acylation of indoles has been reported in the past decades.[13] However, these methods suffered from requirement of prefunctionalization, harsh reaction conditions and excess oxidants. Aryl isocyanides

have been widely applied for the construction of N-containing heterocycles involving a radical cyclization process.[14] In the cases of 2-alkenylarylisocyanides, Fukuyama and coworkers reported AIBN/$Bu_3SnH$-mediated cyclization of 2-alkenylarylisocyanides to synthesize 2-stannyl-3-substituted indole compounds (Scheme 1a).[15a] Chatani et al. developed a method for the synthesis of 2-boryl-3-substituted indoles via the copper(I)-catalyzed borylative cyclization of 2-alkenylphenyl isocyanides using diboronates (Scheme 1b).[15c] Jamison and co-workers developed a copper-catalyzed method to prepare 2-aryl-3-substituted indole derivatives using arylboronic acids (Scheme 1c).[15d]

Visible-light-induced photocatalysts have emerged as a powerful tool for the radical transformations.[16] The application of this strategy to the cyclization of 2-alkenylarylisocyanides with P-radicals was demonstrated by Yang and coworkers recently, a variety of 2-phosphinoylindoles was obtained in good yields (Scheme 1d).[17] On the other hand, $\alpha$-oxocarboxylic acids have been recognized as a good acyl radical precursor that could undergo decarboxylation under photocatalyst to generate the acyl radicals.[18] Inspired by these previous works, we envisioned that reaction of acyl radicals generated form $\alpha$-oxocarboxylic acids with 2-alkenylarylisocyanides would be a versatile process for the synthesis of 2-acylindoles. Herein, we report synthesis of 2-acylindoles through visible-light-induced decarboxylative cyclization of 2-alkenylarylisocyanides with $\alpha$-oxocarboxylic acids under mild conditions.



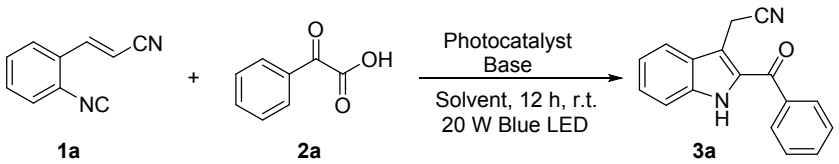

**Scheme 1** Cyclization of 2-alkenylarylisocyanides

## RESULTS AND DISCUSSION

Initially, the reaction of 2-alkenylarylisocyanide **1a** and 2-oxo-2-phenylacetic acid **2a** was first examined under 20 W blue LEDs. The desired product **3a** was isolated in a 12% yield in the presence of PC-A ($[Ir(dF(CF_3)ppy)_2(dtb\text{-}bpy)]PF_6$) and $K_2CO_3$ in $CH_3CN$ (Table 1, entry 1). Encouraged by this result, we next screened different solvents including DMA, DMF, DMSO, THF, DCM (Table 1, entries 2-7) and DMF was proved to be the best solvent which provided the desired product **3a** in a 55% yield(Table 1, entry 4). Then bases ($K_3PO_4$, $K_2HPO_4$, $Cs_2CO_3$, KOAc, NaOAc, DIPEA, $Et_3N$) were screened (Table 1, entries 8-14). When $K_2HPO_4$ was used, the

yield was improved to 61% (Table 1, entry 9). Photocatalysts were also essential to this decarboxylative cyclization. PC-B ($[Ir(dtb\text{-}bpy)(ppy)_2]PF_6$), PC-C ($[Ir(dF(CF_3)ppy)_2(1,10\text{-}Phen)]PF_6$), PC-D $Ir(ppy)_3$, PC-E ($Ru(bpy)_3Cl_2$) and PC-F (Eosin Y) did not give better results, and the reaction did not take place in the absence of photocatalyst (Table 1, entries 15-20). When the reaction was performed in dark, the reaction did not take place (Table 1, entry 21). When the reaction was performed in the absence of base, the yield decreased dramatically, which indicated that base was also essential to this reaction (Table 1, entry 22).

**Table 1** Optimization of Reaction Conditions[a]




| Entry | Photocatalyst | Base | Solvent | Yield[b] (%) |
|---|---|---|---|---|
| 1 | PC-A | $K_2CO_3$ | $CH_3CN$ | 12 |
| 2 | PC-A | $K_2CO_3$ | DMA | 50 |
| 3 | PC-A | $K_2CO_3$ | DMSO | 49 |
| 4 | PC-A | $K_2CO_3$ | DMF | 55 |
| 5 | PC-A | $K_2CO_3$ | DCM | 32 |
| 6 | PC-A | $K_2CO_3$ | THF | 41 |
| 7 | PC-A | $K_2CO_3$ | MeOH | NR |
| 8 | PC-A | $K_3PO_4$ | DMF | 48 |
| **9** | PC-**A** | **$K_2HPO_4$** | **DMF** | **61** |

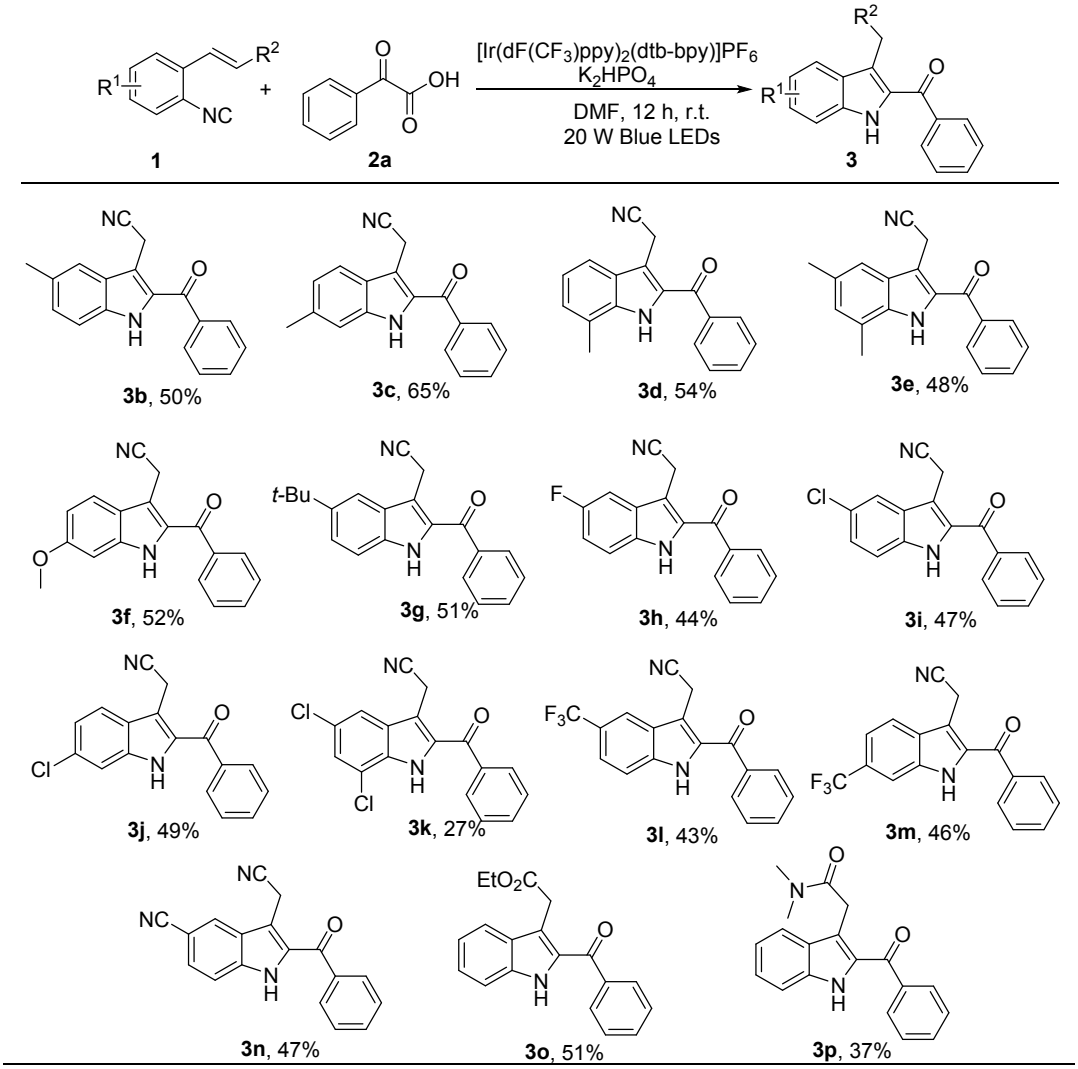
| | | | | |
|---|---|---|---|---|
| 10 | PC-A | $Cs_2CO_3$ | DMF | 44 |
| 11 | PC-A | KOAc | DMF | 16 |
| 12 | PC-A | NaOAc | DMF | 21 |
| 13 | PC-A | DIPEA | DMF | 32 |
| 14 | PC-A | $Et_3N$ | DMF | 41 |
| 15 | PC-B | $K_2HPO_4$ | DMF | 17 |
| 16 | PC-C | $K_2HPO_4$ | DMF | 41 |
| 17 | PC-D | $K_2HPO_4$ | DMF | 20 |
| 18 | PC-E | $K_2HPO_4$ | DMF | NR |
| 19 | PC-F | $K_2HPO_4$ | DMF | NR |
| 20 | - | $K_2HPO_4$ | DMF | NR |
| 21[c] | PC-A | $K_2HPO_4$ | DMF | NR |
| 22 | PC-A | - | DMF | 21 |

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.4 mmol, 2.0 equiv.), catalyst (2.0 mol%) and base (0.4 mmol, 2 equiv.) in solvent (2 mL), irradiated with 20 W blue LEDs for 12 h at room temperature. [b] Isolated yields. NR = no reaction. [c] Reaction was conducted in dark.

With the optimized conditions in hand, we next evaluated the substrate scope with respect to 2-alkenylarylisocyanides, and the results was summarized in Table 2. It was found that the electronic effect had no obvious influence on this transformation. Both electron-donating and electron–withdrawing groups on 2-alkenylarylisocyanide were tolerated, affording the corresponding product **3b-3o** in moderate to good yields. Halogenes such as F, Cl, $CF_3$ were also compatible. Unfortunately,

dichloro-substituted isocyanide only gave product **3k** in a low 27% yield. Notably, 2-alkenylarylisocyanide bearing synthetic valuable -CN could be smoothly converted into the corresponding product **3n** in 47% yield. The functional groups on the alkenyl were finally checked. Both COOEt and $CONMe_2$ were tolerated and afforded the desired products **3o** and **3p** in 51%, 37% yields, respectively. The structure of **3o** was confirmed by X-ray crystallography (CCDC, No. 1977763).

**Table 2** Scope of 2-alkenylarylisocyanides

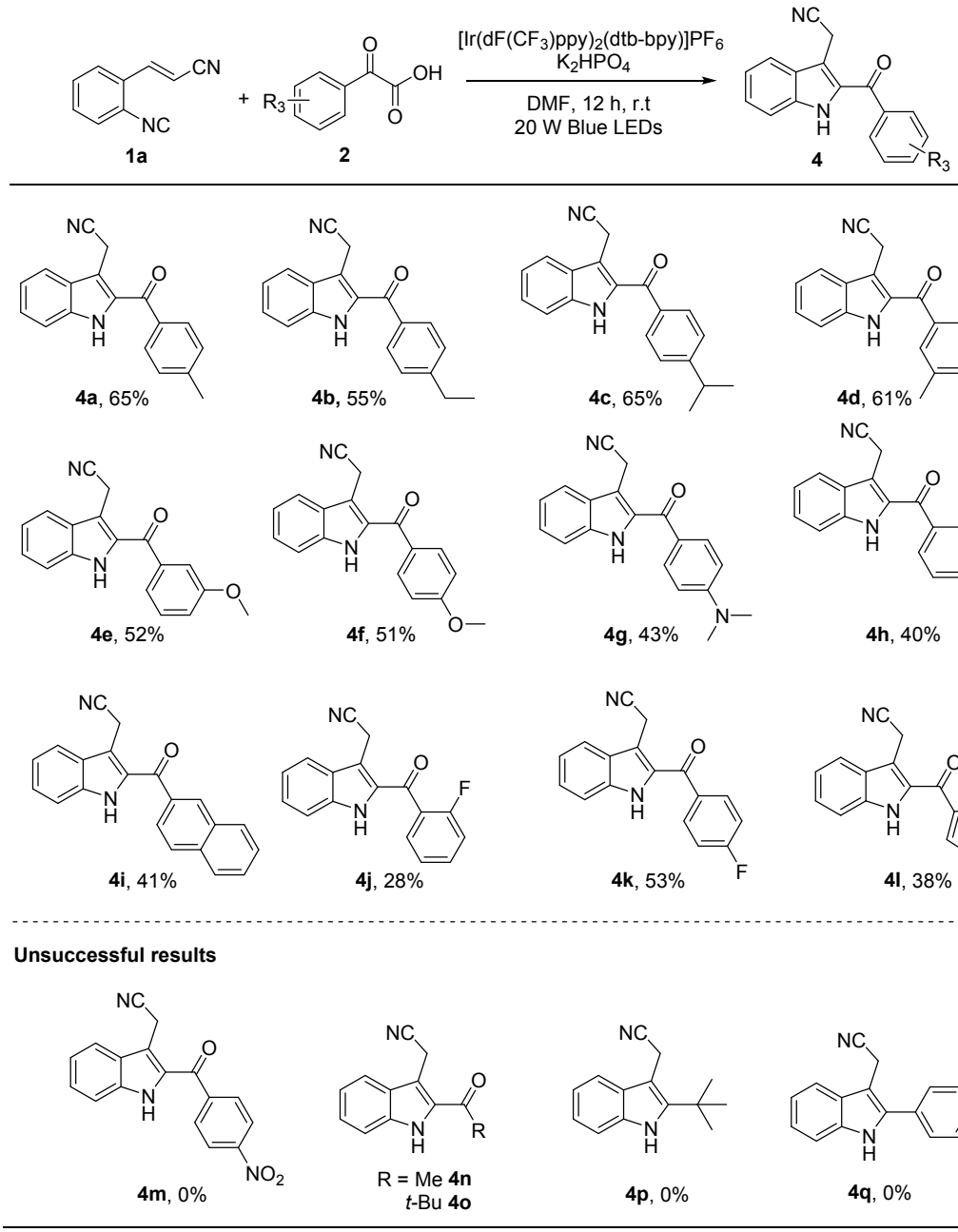



Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.4 mmol, 2.0 equiv.), $K_2HPO_4$ (0.4mmol, 2.0 equiv.) and $[Ir(dF(CF_3)ppy)_2(dtb\text{-}bpy)]PF_6$ (2.0 mol%) in DMF (2 mL) with 20W blue LEDs for

12 h.

The scope of $\alpha$-oxocarboxylic acids was next explored. As shown in Table 3, various acids bearing the electron-donating groups (e.g., $CH_3$, $C_2H_5$, $OCH_3$ and $NMe_2$) could successfully be converted to the corresponding products **4a-4i** in 40-65% yields. Furthermore, substituents at *meta* or *para* position of 2-oxo-2-phenylacetic acid did not affect the efficiency of reactions. Acids with a fluorine also reacted with isocyanide **1a** to generate the corresponding products **4j** and **4k**. However, *ortho*-fluoro-substituted acid gave the desired product **4j** in a low yield. Pleasingly, heterocyclic $\alpha$-oxocarboxylic acid afforded the cyclization product **4l** in a 38% yield. Unfortunately, $NO_2$-substituted 2-oxo-2-phenylacetic acid, alkyl substituted (e.g., $CH_3$ and *t*-Bu) $\alpha$-oxocarboxylic acids, pivalic acid and benzoic acid failed to give the desired product **4m-4q**.

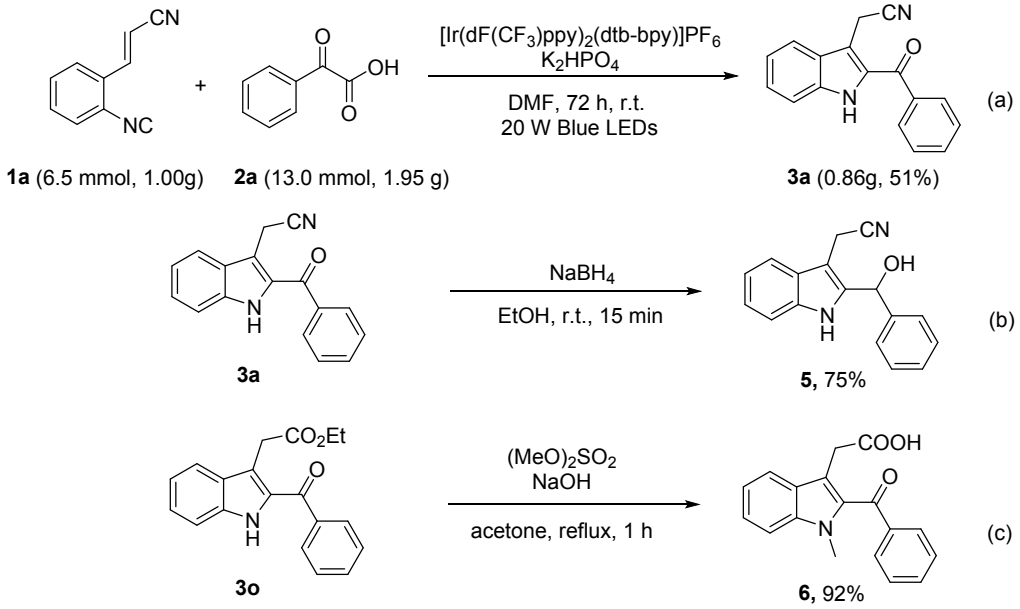
**Table 3** Scope of $\alpha$-oxocarboxylic acids




Reaction condition: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.4 mmol, 2.0 equiv.), $K_2HPO_4$ (0.4 mmol, 2.0 equiv.) and $[Ir(dF(CF_3)ppy)_2(dtb\text{-}bpy)]PF_6$ (2.0 mol%) in DMF (2 mL) with 20W blue LEDs for 12 h.

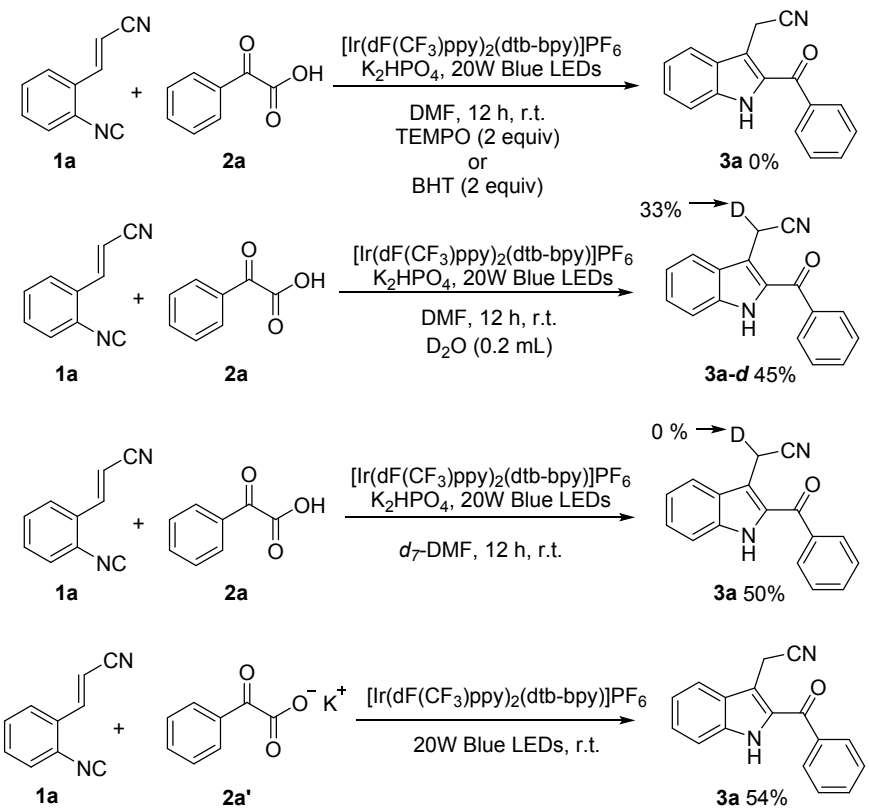
To highlight the synthetic utility of this reaction, a gram-scale experiment was performed and product **3a** was obtained in a 51% yield (Scheme 2a). Product **3a** was then subjected to the reduction reaction, and the corresponding product **5** was isolated in a 75% yield (Scheme 2b). Moreover, the product **5o** can be easily hydrolyzed and

*N*-methylated in the presence of $(MeO)_2SO_2$ and NaOH, and the desired product **6** was obtained in 92% yield.[19]



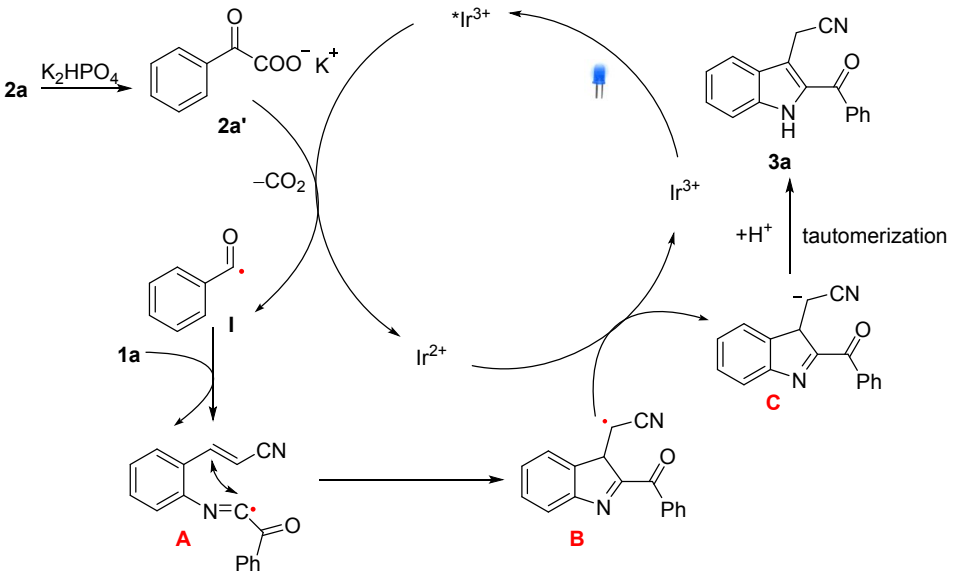

**Scheme 2** Scale-up experiment and transformations of product **3a**, **3o**

To gain insight of the reaction mechanism, the radical trapping experiments were performed by adding TEMPO or BHT as the radical scavenger. When 2.0 equivalents of TEMPO or BHT were added, the reaction did not take place, which suggested a radical process might involve in this reaction. Furthermore, when using $D_2O$ as the cosolvent, deuterated product **3a** was obtained in a 45% yield, and 33% of deuteration was detected at benzyl position. When DMF-$d_7$ was used as the solvent, the deuterated product [D]-**3a** was not detected. These results indicate that the proton of benzyl position might come from the water existed in DMF (Scheme 3). The reaction of potassium 2-oxo-2-phenylacetate **2a'** and **1a** also works with a competitive yield of 54%, which demonstrates that the base could facilitate the elimination of $CO_2$.




**Scheme 3** Mechanistic Studies

On the basis of our own studies and the previous reports, a plausible catalytic cycle was proposed in Scheme 4. First, the irritation of the photocatalyst $Ir^{3+}$ with visible light affords the excited-state $Ir^{3+}$*. The potassium 2-oxo-2-phenylacetate **2a'** generated from phenylglyoxylic acid **2a** was oxidized by excited-state $Ir^{3+}$* affords benzoyl radical **I**, along with the formation of $Ir^{2+}$. Then the benzoyl radical **I** was trapped by 2-alkenylarylisocyanide (**1a**) to produce A, which was followed by 5-exo-trig cyclization to afford benzyl radical B. The reduction of benzyl radical B with $Ir^{2+}$ specie through a SET pathway produces benzyl anion C and $Ir^{3+}$ specie was formed at the same time to fulfill1g the catalytic cycle. Finally, benzyl anion C underwent protonation and isomerization to yield the desired product **3a**.




**Scheme 4** Proposed Mechanism

## CONCLUSION

In summary, we have developed a mild approach for the synthesis of 2-acylindoles via visible-light-induced decarboxylative cyclization of 2-alkenylarylisocyanides with *α*-oxocarboxylic acids. This reaction is performed under air at room temperature, which features simple operation, scalability, broad substrate scope and good functional group tolerance. The primary mechanism investigations suggested a radical process in this reaction.

## EXPERIMENTAL SECTION

**General Information.** All reagents and all solvents were used directly as obtained commercially unless otherwise noted. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker AM 400 spectrometer (operating at 400 and 101 MHz, respectively) in $CDCl_3$ (with tetramethylsilane as internal standard, δ = 7.26 ppm for $^{1}H$ NMR; 77.16 ppm for $^{13}C$ NMR), DMSO-$d_6$ (with tetramethylsilane as internal standard, δ = 2.50 ppm for $^{1}H$ NMR; 39.52 ppm for $^{13}C$ NMR). HPLC/MS analysis was carried out with gradient elution (5% $CH_3CN$ to 100% $CH_3C$

N) on an Agilent 1200 RRLC with a photodiode array UV detector and an Agilent 62 24 TOF mass spectrometer (also used to produce high resolution mass spectra). The infrared (IR) spectra were acquired as thin films using a universal ATR sampling accessory on a Bruker Vertex 80 FT-IR spectrometer and the absorption frequencies are reported in $cm^{-1}$ using KBr plates. Melting points were determined on a Stanford Research Systems OptiMelt apparatus. 20W blue LEDs (LDL04-20W, $\lambda$ = 455 nm) were purchased from Qianfang Lighting Technology Co., Ltd. The material of the irradiation vessel is borosilicate glass and the distance between the light source to the irradiation vessel is about 3 cm. α-keto acids[20], arylisocyanides **1b-1p**[21], and photocatalyst **A-C**[22] were synthesized according the reported literature. The arylisocyanides **1a**[23], **1o**[24], **1p**[23], **6**[19] and all the α-keto acids[25] are compounds known.

**General Procedure for the Synthesis of Arylisocyanides.** Aniline (2.5 mmol, 1.0 equiv), palladium acetate (10 mol%), tri-orthotolyl phosphine (20 mol%) were added to a screw-cap pressure vial containing a stir bar. The vial was equipped with a rubber septum and the vessel was evacuated and back-filled with argon three times. DMF (degassed, 5mL), triethylamine (3.0 equiv) and alkenyl coupling partner (1.2 equiv) were added through a needle. The pressure vial was sealed and stirred at 130 ºC for 8 hours. After cooling to room temperature, the mixture was quenched with saturated aqueous solution of NaCl (30 mL) and extracted with ethyl acetate (3×30 mL), the combined organic layer was dried over $Na_2SO_4$. The filtrate was concentrated in vacuo and the resulting mixture was purified by flash column chromatography on silica gel to afford the corresponding 2-alkenylarylaniline.

Acetic anhydride (1.5 equiv) and formic acid (1.6 equiv) were stirred at 50 ºC in a sealed tube for 1.5 hours. The resulting anhydride was cooled to room temperature and was added dropwise over 10 min to a stirred solution of 2-alkenyl aniline (2.0 mmol, 1.0 equiv) in THF (8mL) at 0 ºC. The solution was warmed to room temperature and stirred for 1 hour. A saturated aqueous solution of sodium bicarbonate (30 mL) was added slowly to the mixture and then the organic layer was extracted with ethyl acetate (3×30 mL). The combined organic layer was dried over $Na_2SO_4$, filtered and concentrated in vacuo. The crude product was used directly in the next step without further purification.

A solution (12 mL) of the crude formamide (2.0 mmol, 1.0 equiv) and triethylamine (3.0 equiv) in THF was cooled to 0 ºC and phosphoryl chloride (1.5 equiv) was added dropwise while maintaining the reaction temperature at 0 ºC. After reacted for an additional 1 hour at 0 ºC, the mixture was warmed to room temperature and quenched with saturated aqueous solution of sodium bicarbonate (30 mL). The mixture was extracted with ethyl acetate (3×30 mL) and the combined organic layer was dried over $Na_2SO_4$, filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography on silica gel to afford the corresponding arylisocyanides.

**General Procedure for the Synthesis of Indole Products.** To a 10 mL vial equipped with a magnetic stirrer bar, arylisocyanides **1** (0.2 mmol), α-keto acids **2** (0.4 mmol), $[Ir(dF(CF_3)ppy)_2(dtb\text{-}bpy)]PF_6$ (2 mol%), $K_2HPO_4$ (0.4 mmol) and DMF (2 mL) were added in sequence. Two 20W blue LEDs was placed at a distance of about 3cm from

the reaction vessel. After the reaction was complete (as monitored by TLC), the mixture was quenched with $H_2O$ (10 mL) and extracted with ethyl acetate (3×10 mL), the combined organic layer was dried over $Na_2SO_4$, filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography on silica gel to afford the corresponding indole products.

**General Procedure for Gram-scale Experiment.** To a 250 mL round bottom flask equipped with a magnetic stirrer bar, arylisocyanides **1a** (6.5 mmol, 1.00 g), α-keto acids **2a** (13.00 mmol, 1.95 g), $[Ir(dF(CF_3)ppy)_2(dtb\text{-}bpy)]PF_6$ (0.065 mmol, 75 mg), $K_2HPO_4$ (13.00 mmol, 2.26 g) and DMF (65 mL) were added in sequence. Two 20W blue LEDs was placed at a distance of about 3cm from the reaction vessel. After the reaction was complete (as monitored by TLC, 3 days), the mixture was quenched with $H_2O$ (100 mL) and extracted with ethyl acetate (3×150 mL), the combined organic layer was dried over $Na_2SO_4$, filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography on silica gel to afford the corresponding indole products (0.86 g, 51%).

**3-(2-Isocyano-5-methylphenyl)acrylonitrile (1b).** This product was obtained as a yellow solid (238 mg, 71% yield). Eluent: petroleum ether/ethyl acetate 6:1 (v/v). m.p.: 138-139℃; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.78 (s, 1H), 7.68 (d, $J$ = 16.6 Hz, 1H), 7.57 (d, $J$ = 8.1 Hz, 1H), 7.41 (d, $J$ = 8.1 Hz, 1H), 6.66 (d, $J$ = 16.6 Hz, 1H), 2.37 (s, 3H). $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 168.1, 143.6, 140.5, 132.7, 129.3, 127.5, 127.0, 122.3, 118.1, 101.3, 20.8. IR (neat): 2216, 2117, 1619, 1482 cm$^{-1}$; HRMS (ESI) calculated for $C_{11}H_8N_2$ $[M+H]^+$: 169.0760, found: 169.0762.

**3-(2-Isocyano-4-methylphenyl)acrylonitrile (1c).** This product was obtained as a yellow solid (229 mg, 68% yield). Eluent: petroleum ether/ethyl acetate 6:1 (v/v). m.p.: 137-138℃; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.82 (d, $J$ = 8.1 Hz, 1H), 7.63 (d, $J$ = 16.6 Hz, 1H), 7.50 (s, 1H), 7.40 (d, $J$ = 8.1 Hz, 1H), 6.62 (d, $J$ = 16.6 Hz, 1H), 2.35 (s, 3H). $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 168.3, 143.3, 143.0, 131.1, 127.8, 126.8, 126.6, 124.5, 118.2, 100.4, 20.5. IR (neat): 2210, 2113, 1604, 1496 cm$^{-1}$; HRMS (ESI) calculated for $C_{11}H_8N_2$ [M+H]$^{+}$: 169.0760, found: 169.0763.

**3-(2-Isocyano-3-methylphenyl)acrylonitrile (1d).** This product was obtained as a yellow solid (161 mg, 48% yield). Eluent: petroleum ether/ethyl acetate 6:1 (v/v). m.p.: 118-119℃; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.75 (d, $J$ = 7.7 Hz, 1H), 7.69 (d, $J$ = 16.6 Hz, 1H), 7.53 – 7.45 (m, 2H), 6.65 (d, $J$ = 16.6 Hz, 1H), 2.38 (s, 3H). $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 170.9, 143.9, 135.7, 132.9, 129.6, 129.6, 124.6, 124.2, 118.1, 101.4, 18.4. IR (neat): 2217, 2113, 1619, 1447 cm$^{-1}$; HRMS (ESI) calculated for $C_{11}H_8N_2$ [M+H]$^{+}$: 169.0760, found: 169.0762.

**3-(2-Isocyano-3,5-dimethylphenyl)acrylonitrile (1e).** This product was obtained as a white solid (273 mg, 75% yield). Eluent: petroleum ether/ethyl acetate 6:1 (v/v). m.p.: 134-135℃; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.64 – 7.57 (m, 2H), 7.33 (s, 1H), 6.60 (d, $J$ = 16.4 Hz, 1H), 2.32 (s, 6H). $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 170.3, 144.0, 139.6, 135.4, 133.6, 129.3, 124.5, 122.4, 118.2, 101.1, 20.7, 18.3. IR (neat): 2216, 2109, 1610, 1461 cm$^{-1}$; HRMS (ESI) calculated for $C_{12}H_{10}N_2$ [M+H]$^{+}$: 183.0917, found: 183.0913.

**3-(2-Isocyano-4-methoxyphenyl)acrylonitrile (1f).** This product was obtained as a

yellow solid (250 mg, 68% yield). Eluent: petroleum ether/ethyl acetate 6:1 (v/v). m.p.: 131-132℃; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.89 (d, $J$ = 8.9 Hz, 1H), 7.60 (d, $J$ = 16.6 Hz, 1H), 7.31 (s, 1H), 7.17 (d, $J$ = 8.8 Hz, 1H), 6.54 (d, $J$ = 16.6 Hz, 1H), 3.85 (s, 3H). $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 168.5, 161.8, 143.0, 128.1, 126.0, 122.0, 118.5, 117.3, 112.3, 98.5, 56.2. IR (neat): 2210, 2121, 1602, 1453 cm$^{-1}$; HRMS (ESI) calculated for $C_{11}H_8N_2O$ $[M+H]^+$: 185.0709, found: 185.0706.

**3-(5-(Tert-butyl)-2-isocyanophenyl)acrylonitrile (1g).** This product was obtained as a green solid (294 mg, 70% yield). Eluent: petroleum ether/ethyl acetate 6:1 (v/v). m.p.: 94-95℃; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.89 (s, 1H), 7.67 (d, $J$ = 16.6 Hz, 1H), 7.59 (s, 2H), 6.80 (d, $J$ = 16.6 Hz, 1H), 1.29 (s, 9H). $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 168.2, 153.3, 143.7, 129.2, 129.1, 127.3, 123.7, 122.3, 118.2, 101.5, 35.0, 30.6. IR (neat): 2218, 2117, 1612, 1478 cm$^{-1}$; HRMS (ESI) calculated for $C_{14}H_{14}N_2$ $[M+H]^+$: 211.1230, found: 211.1229.

**3-(5-Fluoro-2-isocyanophenyl)acrylonitrile (1h).** This product was obtained as a yellow solid (210 mg, 61% yield). Eluent: petroleum ether/ethyl acetate 6:1 (v/v). m.p.: 128-129℃; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.89 (d, $J$ = 9.5 Hz, 1H), 7.84 – 7.74 (m, 1H), 7.69 (d, $J$ = 16.5 Hz, 1H), 7.54 – 7.44 (m, 1H), 6.76 (d, $J$ = 16.5 Hz, 1H). $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 168.8, 161.8 (d, $J$ = 250.5 Hz), 142.6 (d, $J$ = 2.0 Hz), 132.2 (d, $J$ = 9.1 Hz), 130.3 (d, $J$ = 9.1 Hz), 121.2, 119.3 (d, $J$ = 24.2 Hz), 117.7, 113.6 (d, $J$ = 26.3 Hz), 103.1. $^{19}$F NMR (377 MHz, $CDCl_3$) δ -106.8. IR (neat): 2225, 2121, 1609, 1480 cm$^{-1}$; HRMS (ESI) calculated for $C_{10}H_5FN_2$ $[M+Na]^+$: 195.0329, found: 195.0328.

**3-(5-Chloro-2-isocyanophenyl)acrylonitrile (1i).** This product was obtained as a yellow solid (244 mg, 65% yield). Eluent: petroleum ether/ethyl acetate 6:1 (v/v). m.p.: 132-133℃; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.09 (s, 1H), 7.75 (d, $J$ = 8.5 Hz, 1H), 7.72 – 7.63 (m, 2H), 6.80 (d, $J$ = 16.5 Hz, 1H). $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 169.8, 142.4, 135.0, 131.8, 131.5, 129.5, 126.7, 123.4, 117.8, 103.2. IR (neat): 2219, 2117, 1622, 1472 cm$^{-1}$; HRMS (ESI) calculated for $C_{10}H_5ClN_2$ [M+H]$^{+}$: 189.0214, found: 189.0226.

**3-(4-Chloro-2-isocyanophenyl)acrylonitrile (1j).** This product was obtained as a yellow solid (263 mg, 70% yield). Eluent: petroleum ether/ethyl acetate 6:1 (v/v). m.p.: 161-162℃; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.99 – 7.84 (m, 2H), 7.69 – 7.63 (m, 2H), 6.71 (d, $J$ = 16.6 Hz, 1H). $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 170.0, 142.5, 136.1, 130.6, 128.6, 128.3, 127.5, 125.5, 117.9, 102.2. IR (neat): 2215, 2120, 1622, 1478 cm$^{-1}$; HRMS (ESI) calculated for $C_{10}H_5ClN_2$ [M+H]$^{+}$: 189.0214, found: 189.0222.

**3-(3,5-Dichloro-2-isocyanophenyl)acrylonitrile (1k).** This product was obtained as a green solid (320 mg, 72% yield). Eluent: petroleum ether/ethyl acetate 6:1 (v/v). m.p.: 135-136℃; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.10 – 8.02 (m, 2H), 7.67 (d, $J$ = 16.4 Hz, 1H), 6.82 (d, $J$ = 16.5 Hz, 1H). $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 174.6, 142.1, 135.2, 133.1, 131.8, 131.3, 125.6, 122.3, 117.5, 104.4. IR (neat): 2222, 2113, 1622, 1461 cm$^{-1}$; HRMS (ESI) calculated for $C_{10}H_4Cl_2N_2$ [M+H]$^{+}$: 222.9824, found: 222.9827.

**3-(2-Isocyano-5-(trifluoromethyl)phenyl)acrylonitrile (1l).** This product was

obtained as a yellow solid (222 mg, 50% yield). Eluent: petroleum ether/ethyl acetate 6:1 (v/v). m.p.: 118-119℃; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.34 (s, 1H), 7.97 – 7.90 (m, 2H), 7.73 (d, $J$ = 16.6 Hz, 1H), 6.92 (d, $J$ = 16.6 Hz, 1H). $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 171.2, 142.3, 130.8, 130.4 (q, $J$ = 33.3 Hz), 129.0, 128.6 (q, $J$ = 4.0 Hz), 127.5, 124.2 (q, $J$ = 4.0 Hz), 123.1 (q, $J$ = 273.7 Hz), 117.7, 103.8. $^{19}$F NMR (377 MHz, $CDCl_3$) δ -63.1. IR (neat): 2219, 2119, 1612, 1482 cm$^{-1}$; HRMS (ESI) calculated for $C_{11}H_5F_3N_2$ [M+Na]$^{+}$: 245.0297, found: 245.0305.

**3-(2-Isocyano-4-(trifluoromethyl)phenyl)acrylonitrile (1m).** This product was obtained as a yellow solid (235 mg, 53% yield). Eluent: petroleum ether/ethyl acetate 6:1 (v/v). m.p.: 118-119℃; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.20 (s, 1H), 8.14 (d, $J$ = 8.3 Hz, 1H), 7.97 (d, $J$ = 8.4 Hz, 1H), 7.76 (d, $J$ = 16.6 Hz, 1H), 6.84 (d, $J$ = 16.6 Hz, 1H). $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 170.4, 142.4, 133.5, 131.8 (q, $J$ = 33.3 Hz), 128.2, 126.9 (q, $J$ = 4.0 Hz), 125.0 (q, $J$ = 4.0 Hz), 122.9 (q, $J$ = 273.7 Hz), 117.6, 104.4 (one carbon missing due to overlap). $^{19}$F NMR (377 MHz, $CDCl_3$) δ -63.3. IR (neat): 2221, 2120, 1620 cm$^{-1}$; HRMS (ESI) calculated for $C_{11}H_5F_3N_2$ [M+Na]$^{+}$: 245.0297, found: 245.0296.

**3-(2-Cyanovinyl)-4-isocyanobenzonitrile (1n).** This product was obtained as a yellow solid (100 mg, 28% yield). Eluent: petroleum ether/ethyl acetate 4:1 (v/v). m.p.: 147-148℃; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.51 (s, 1H), 8.09 (d, $J$ = 8.3 Hz, 1H), 7.92 (d, $J$ = 8.3 Hz, 1H), 7.73 (d, $J$ = 16.5 Hz, 1H), 6.82 (d, $J$ = 16.5 Hz, 1H). $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 172.0, 142.1, 135.2, 131.3, 130.9, 128.9, 127.6, 117.6, 117.2, 113.1, 103.7. IR (neat): 2233, 2222, 2123, 1484 cm$^{-1}$; HRMS

(ESI) calculated for $C_{11}H_5N_3$ $[M+H]^+$: 180.0556, found: 180.0559.

**2-(2-Benzoyl-1*H*-indol-3-yl)acetonitrile (3a).** This product was obtained as a yellow solid (31.7 mg, 61% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 154-155℃; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.90 (s, 1H), 7.87 (d, $J$ = 8.1 Hz, 1H), 7.83 (d, $J$ = 7.7 Hz, 2H), 7.77 – 7.69 (m, 1H), 7.66 – 7.58 (m, 2H), 7.52 (d, $J$ = 8.3 Hz, 1H), 7.37 (t, $J$ = 7.6 Hz, 1H), 7.21 (t, $J$ = 7.5 Hz, 1H), 4.21 (s, 2H). $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 188.0, 138.1, 136.5, 132.8, 131.4, 129.1, 128.8, 126.3, 125.8, 120.8, 120.2, 118.6, 113.2, 111.2, 13.5. IR (neat): 3325, 2253, 1633, 1534, 1442 cm$^{-1}$; HRMS (ESI) calculated for $C_{17}H_{12}N_2O$ $[M+H]^+$: 261.1022, found: 261.1023.

**2-(2-Benzoyl-5-methyl-1*H*-indol-3-yl)acetonitrile (3b).** This product was obtained as a yellow solid (27.4 mg, 50% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 159-160℃; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.77 (s, 1H), 7.81 (d, $J$ = 7.6 Hz, 2H), 7.74 – 7.79 (m, 1H), 7.66 – 7.56 (m, 3H), 7.41 (d, $J$ = 8.4 Hz, 1H), 7.21 (d, $J$ = 8.5 Hz, 1H), 4.16 (s, 2H), 2.43 (s, 3H). $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 187.9, 138.2, 135.0, 132.7, 131.4, 129.6, 129.1, 128.8, 127.9, 126.6, 119.1, 118.6, 113.0, 110.7, 21.3, 13.4. IR (neat): 3323, 2251, 1632, 1534 cm$^{-1}$; HRMS (ESI) calculated for $C_{18}H_{14}N_2O$ $[M+H]^+$: 275.1179, found: 275.1175.

**2-(2-Benzoyl-6-methyl-1*H*-indol-3-yl)acetonitrile (3c).** This product was obtained as a yellow solid (35.6 mg, 65%). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 121-122℃; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.74 (s, 1H), 7.81 (d, $J$ = 7.8 Hz, 2H), 7.78 – 7.69 (m, 2H), 7.64 – 7.59 (m, 2H), 7.29 (s, 1H), 7.05 (d, $J$ = 8.3 Hz, 1H), 4.16 (s, 2H), 2.44 (s, 3H); $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 187.8, 138.3, 137.0,

135.7, 132.6, 131.0, 129.1, 128.8, 124.4, 122.9, 119.9, 118.6, 112.5, 111.4, 21.7, 13.6; IR (neat): 3325, 2252, 1630, 1532 $cm^{-1}$; HRMS (ESI) calculated for $C_{18}H_{14}N_2O$ $[M+H]^+$: 275.1179, found: 275.1177.

**2-(2-Benzoyl-7-methyl-1*H*-indol-3-yl)acetonitrile (3d).** This product was obtained as a white solid (29.6 mg, 54% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 202-203℃; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 11.77 (s, 1H), 7.85 (d, $J$ = 7.7 Hz, 2H), 7.76 – 7.70 (m, 1H), 7.67 (d, $J$ = 7.8 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.20 – 7.08 (m, 2H), 4.08 (s, 2H), 2.52 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-$d_6$) δ 188.0, 138.2, 136.1, 133.0, 132.1, 129.4, 128.8, 126.2, 126.0, 122.7, 121.0, 118.6, 117.6, 111.3, 17.0, 13.6. IR (neat): 3317, 2250, 1626, 1535 $cm^{-1}$; HRMS (ESI) calculated for $C_{18}H_{14}N_2O$ $[M+H]^+$: 275.1179, found: 275.1176.

**2-(2-Benzoyl-5,7-dimethyl-1*H*-indol-3-yl)acetonitrile (3e).** This product was obtained as a yellow solid (27.6 mg, 48% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 175-176℃; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 11.66 (s, 1H), 7.83 (d, $J$ = 7.4 Hz, 2H), 7.76 – 7.68 (m, 1H), 7.65 – 7.57 (m, 2H), 7.43 (s, 1H), 7.01 (s, 1H), 4.04 (s, 2H), 2.48 (s, 3H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-$d_6$) δ 188.0, 138.3, 134.7, 132.9, 132.1, 129.8, 129.4, 128.8, 128.2, 126.5, 122.4, 118.6, 116.6, 110.8, 21.2, 16.9, 13.5. IR (neat): 3309, 2251, 1627, 1536 $cm^{-1}$; HRMS (ESI) calculated for $C_{19}H_{16}N_2O$ $[M+H]^+$: 289.1335, found: 289.1336.

**2-(2-Benzoyl-6-methoxy-1*H*-indol-3-yl)acetonitrile (3f).** This product was obtained as a yellow solid (30.2 mg, 52% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 121-122℃; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 11.70 (s, 1H), 7.83 – 7.73

(m, 3H), 7.73 – 7.67 (m, 1H), 7.65 – 7.57 (m, 2H), 6.94 (s, 1H), 6.87 (d, $J$ = 8.9 Hz, 1H), 4.17 (s, 2H), 3.81 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-$d_6$) δ 187.2, 158.9, 138.5, 137.9, 132.4, 130.5, 128.9, 128.8, 121.2, 120.9, 118.6, 112.8, 112.2, 94.2, 55.2, 13.6. IR (neat): 3325, 2252, 1627, 1529 $cm^{-1}$; HRMS (ESI) calculated for $C_{18}H_{14}N_2O_2$ $[M+H]^+$: 291.1128, found: 291.1129.

**2-(2-Benzoyl-5-(tert-butyl)-1*H*-indol-3-yl)acetonitrile (3g).** This product was obtained as a yellow solid (32.2 mg, 51% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 55-56℃; $^{1}H$ NMR (400 MHz, DMSO-$d_6$) δ 11.77 (s, 1H), 7.85 – 7.79 (m, 3H), 7.74 – 7.68 (m, 1H), 7.65 – 7.58 (m, 2H), 7.51 – 7.44 (m, 2H), 4.23 (s, 2H), 1.37 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-$d_6$) δ 187.9, 143.3, 138.3, 134.9, 132.6, 131.5, 129.1, 128.8, 126.1, 124.7, 118.7, 115.2, 112.9, 111.4, 34.6, 31.5, 13.5. IR (neat): 3328, 2253, 1633, 1535 $cm^{-1}$; HRMS (ESI) calculated for $C_{21}H_{20}N_2O$ $[M+H]^+$: 317.1648, found: 317.1648.

**2-(2-Benzoyl-5-fluoro-1*H*-indol-3-yl)acetonitrile (3h).** This product was obtained as a yellow solid (24.5 mg, 44% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 176-178℃; $^{1}H$ NMR (400 MHz, DMSO-$d_6$) δ 12.00 (s, 1H), 7.83 (d, $J$ = 7.5 Hz, 2H), 7.77 – 7.59 (m, 4H), 7.57 – 7.49 (m, 1H), 7.29 – 7.20 (m, 1H), 4.20 (s, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-$d_6$) δ 187.8, 157.5 (d, $J$ = 236.3 Hz), 137.9, 133.1, 132.9, 129.2, 128.9, 126.5 (d, $J$ = 10.1 Hz), 118.5, 114.9 (d, $J$ = 26.3 Hz), 114.8 (d, $J$ = 10.1 Hz), 111.2 (d, $J$ = 6.1 Hz), 104.4 (d, $J$ = 24.2 Hz), 13.5 (one carbon missing due to overlap). $^{19}F$ NMR (377 MHz, DMSO-$d_6$) δ -20.6. IR (neat): 3317, 2253, 1636,

1533 $cm^{-1}$; HRMS (ESI) calculated for $C_{17}H_{11}FN_2O$ $[M+Na]^+$: 301.0748, found: 301.0749.

**2-(2-Benzoyl-5-chloro-1*H*-indol-3-yl)acetonitrile (3i).** This product was obtained as a white solid (27.6 mg, 47% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 181-182℃; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 12.09 (s, 1H), 7.99 (s, 1H), 7.83 (d, $J$ = 7.4 Hz, 2H), 7.78 – 7.70 (m, 1H), 7.66 – 7.59 (m, 2H), 7.53 (d, $J$ = 8.8 Hz, 1H), 7.37 (d, $J$ = 8.8 Hz, 1H), 4.21 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-$d_6$) δ 187.9, 137.8, 134.8, 133.0, 132.7, 129.2, 128.9, 127.3, 125.9, 125.3, 119.4, 118.5, 115.0, 110.7, 13.4. IR (neat): 3317, 2253, 1637, 1532 $cm^{-1}$; HRMS (ESI) calculated for $C_{17}H_{11}ClN_2O$ $[M+H]^+$: 295.0633, found: 295.0633.

**2-(2-Benzoyl-6-chloro-1*H*-indol-3-yl)acetonitrile (3j).** This product was obtained as a yellow solid (28.8 mg, 49% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 198-199℃; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 12.03 (s, 1H), 7.91 (d, $J$ = 8.7 Hz, 1H), 7.86 – 7.80 (m, 2H), 7.77 – 7.70 (m, 1H), 7.66 – 7.59 (m, 2H), 7.54 (s, 1H), 7.24 (d, $J$ = 8.7 Hz, 1H), 4.21 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-$d_6$) δ 187.8, 137.9, 136.6, 132.9, 132.3, 130.4, 129.2, 128.9, 125.1, 121.9, 121.4, 118.4, 112.6, 111.4, 13.5. IR (neat): 3317, 2253, 1634, 1531 $cm^{-1}$; HRMS (ESI) calculated for $C_{17}H_{11}ClN_2O$ $[M+H]^+$: 295.0633, found: 295.0629.

**2-(2-Benzoyl-5,7-dichloro-1*H*-indol-3-yl)acetonitrile (3k).** This product was obtained as a yellow solid (17.7 mg, 27% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 70-71℃; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 12.49 (s, 1H), 8.00 (s, 1H), 7.87 – 7.81 (m, 2H), 7.78 – 7.70 (m, 1H), 7.65 – 7.55 (m, 3H), 4.14 (s, 2H). $^{13}C\{^1H\}$

NMR (101 MHz, DMSO-$d_6$) δ 187.9, 137.5, 134.8, 133.6, 132.0, 129.7, 128.9, 128.4, 125.2, 124.6, 118.6, 118.3, 111.0, 13.3 (one carbon missing due to overlap). IR (neat): 3278, 2204, 1644, 1568 $cm^{-1}$; HRMS (ESI) calculated for $C_{17}H_{10}Cl_2N_2O$ $[M+H]^+$: 329.0243, found: 329.0244.

**2-(2-Benzoyl-5-(trifluoromethyl)-1*H*-indol-3-yl)acetonitrile (3l).** This product was obtained as a yellow solid (28.2 mg, 43% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 149-150℃; $^1H$ NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.11 (s, 1H), 7.83 – 7.77 (m, 2H), 7.69 – 7.52 (m, 5H), 3.94 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 188.2, 138.0, 137.3, 133.6, 133.1, 129.4, 129.0, 126.4, 124.7 (q, $J$ = 272.7 Hz), 124.4 (q, $J$ = 33.3 Hz), 123.6 (q, $J$ = 3.0 Hz), 118.6 (q, $J$ = 4.0 Hz), 117.1, 113.3, 112.2, 14.5. $^{19}F$ NMR (377 MHz, $CDCl_3$) δ -60.9. IR (neat): 3312, 2256, 1640, 1541 $cm^{-1}$; HRMS (ESI) calculated for $C_{18}H_{11}F_3N_2O$ $[M+Na]^+$: 351.0716, found: 351.0725.

**2-(2-Benzoyl-6-(trifluoromethyl)-1*H*-indol-3-yl)acetonitrile (3m).** This product was obtained as a white solid (30.1 mg, 46% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 146-147℃; $^1H$ NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.94 (d, $J$ = 8.5 Hz, 1H), 7.84 – 7.78 (m, 2H), 7.75 (s, 1H), 7.71 – 7.64 (m, 1H), 7.61 – 7.54 (m, 2H), 7.48 (d, $J$ = 8.5 Hz, 1H), 3.96 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 188.2, 138.0, 135.1, 133.6, 129.5, 129.2, 129.1, 129.0 (q, $J$ = 31.3 Hz), 124.6 (q, $J$ = 272.7 Hz), 121.6, 118.4 (q, $J$ = 3.0 Hz), 117.2, 111.3, 110.4 (q, $J$ = 4.0 Hz), 14.5 (one carbon missing due to overlap). $^{19}F$ NMR (377 MHz, $CDCl_3$) δ -61.6. IR (neat): 3313, 2255, 1640, 1513 $cm^{-1}$; HRMS (ESI) calculated for $C_{18}H_{11}F_3N_2O$ $[M+Na]^+$: 351.0716, found: 351.0722.

**2-Benzoyl-3-(cyanomethyl)-1*H*-indole-5-carbonitrile (3n).** This product was obtained as a white solid (26.8 mg, 47% yield). Eluent: petroleum ether/ethyl acetate 1:1 (v/v). m.p.: 226-227℃; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.45 (s, 1H), 8.53 (s, 1H), 7.87 – 7.81 (m, 2H), 7.79 – 7.72 (m, 1H), 7.72 – 7.60 (m, 4H), 4.24 (s, 2H). $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 187.8, 137.6, 137.5, 133.6, 133.3, 129.3, 129.0, 127.5, 126.7, 126.0, 120.0, 118.3, 114.6, 111.8, 102.9, 13.4. IR (neat): 3299, 2223, 1645, 1538 cm$^{-1}$; HRMS (ESI) calculated for $C_{18}H_{11}N_3O$ $[M+H]^+$: 286.0975, found: 286.0977.

**Ethyl 2-(2-benzoyl-1*H*-indol-3-yl)acetate (3o).** This product was obtained as a yellow solid (31.3 mg, 51% yield). Eluent: petroleum ether/ethyl acetate 6:1 (v/v). m.p.: 138-139℃; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.82 – 7.74 (m, 2H), 7.64 (d, $J$ = 8.2 Hz, 1H), 7.62 – 7.54 (m, 1H), 7.52 – 7.44 (m, 2H), 7.42 – 7.30 (m, 2H), 7.19 – 7.13 (m, 1H), 4.09 (q, $J$ = 7.1 Hz, 2H), 3.81 (s, 2H), 1.20 (t, $J$ = 7.1 Hz, 3H). $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 189.0, 171.1, 139.2, 136.6, 132.5, 132.3, 129.0, 128.8, 128.5, 126.7, 121.3, 121.1, 116.5, 112.3, 61.1, 31.5, 14.4. IR (neat): 3345, 1728, 1631, 1534, 1443 cm$^{-1}$; HRMS (ESI) calculated for $C_{19}H_{17}NO_3$ $[M+H]^+$: 308.1281, found 308.1290.

**2-(2-Benzoyl-1*H*-indol-3-yl)-*N*,*N*-dimethylacetamide (3p).** This product was obtained as a yellow solid (22.6 mg, 37% yield). Eluent: petroleum ether/ethyl acetate 6:1 (v/v). m.p.: 159-160℃; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.79 – 7.70 (m, 3H), 7.62 – 7.54 (m, 1H), 7.52 – 7.43 (m, 2H), 7.36 – 7.27 (m, 2H), 7.17 – 7.09 (m, 1H), 3.86 (s, 2H), 2.90 (s, 3H), 2.83 (s, 3H). $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ

189.0, 170.4, 139.6, 136.8, 132.2, 131.8, 129.0, 128.9, 128.7, 126.6, 122.0, 121.0, 118.5, 112.2, 37.4, 35.9, 31.3. IR (neat): 3256, 1634, 1530, 1444 $cm^{-1}$; HRMS (ESI) calculated for $C_{19}H_{18}N_2O_2$ $[M+H]^+$: 307.1441, found 307.1445.

**2-(2-(4-Methylbenzoyl)-1*H*-indol-3-yl)acetonitrile (4a).** This product was obtained as a yellow solid (35.6 mg, 65% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 175-176℃; $^1H$ NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.82 (d, $J$ = 8.2 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.46 – 7.35 (m, 2H), 7.34 (d, $J$ = 7.9 Hz, 2H), 7.28 – 7.20 (m, 1H), 3.93 (s, 2H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 188.2, 144.1, 136.2, 135.8, 131.8, 129.9, 129.2, 127.2, 127.0, 121.8, 120.6, 117.6, 112.6, 111.1, 21.9, 14.6. IR (neat): 3325, 2252, 1633, 1534 $cm^{-1}$; HRMS (ESI) calculated for $C_{18}H_{14}N_2O$ $[M+H]^+$: 275.1179, found: 275.1177.

**2-(2-(4-Ethylbenzoyl)-1*H*-indol-3-yl)acetonitrile (4b).** This product was obtained as a yellow solid (31.7 mg, 55% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 126-127℃; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.83 (d, $J$ = 8.2 Hz, 1H), 7.77 – 7.71 (m, 2H), 7.46 – 7.35 (m, 4H), 7.27 – 7.23 (m, 1H), 3.96 (s, 2H), 2.75 (q, $J$ = 7.6 Hz, 2H), 1.29 (t, $J$ = 7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 188.2, 150.3, 136.2, 136.0, 131.8, 129.3, 128.8, 127.2, 127.0, 121.8, 120.7, 117.7, 112.6, 111.2, 29.2, 15.4, 14.6. IR (neat): 3323, 2252, 1632, 1534 $cm^{-1}$; HRMS (ESI) calculated for $C_{19}H_{16}N_2O$ $[M+H]^+$: 289.1335, found: 289.1337.

**2-(2-(4-Isopropylbenzoyl)-1*H*-indol-3-yl)acetonitrile (4c).** This product was obtained as a yellow solid (39.3 mg, 65% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 105-106℃; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 11.85 (s, 1H), 7.86 (d, $J$

= 8.1 Hz, 1H), 7.81 – 7.75 (m, 2H), 7.55 – 7.45 (m, 3H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.24 – 7.17 (m, 1H), 4.23 (s, 2H), 3.03 (dt, *J* = 13.6, 6.8 Hz, 1H), 1.32 – 1.20 (m, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-$d_6$) δ 187.5, 153.7, 136.4, 135.8, 131.6, 129.5, 126.8, 126.2, 125.6, 120.7, 120.0, 118.6, 113.2, 110.9, 33.6, 23.5, 13.4. IR (neat): 3325, 2253, 1633, 1534 $cm^{-1}$; HRMS (ESI) calculated for $C_{20}H_{18}N_2O$ $[M+H]^+$: 303.1492, found: 303.1491.

**2-(2-(3,5-Dimethylbenzoyl)-1*H*-indol-3-yl)acetonitrile (4d).** This product was obtained as a white solid (35.2 mg, 61% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 161-162℃; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.50 – 7.42 (m, 4H), 7.32 – 7.27 (m, 2H), 3.90 (s, 2H), 2.44 (s, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 188.8, 139.2, 138.7, 136.3, 134.9, 132.0, 127.4, 127.1, 126.6, 121.9, 120.7, 117.6, 112.6, 111.2, 21.4, 14.7. IR (neat): 3322, 2252, 1633, 1534 $cm^{-1}$; HRMS (ESI) calculated for $C_{19}H_{16}N_2O$ $[M+H]^+$: 289.1335, found: 289.1337.

**2-(2-(3-Methoxybenzoyl)-1*H*-indol-3-yl)acetonitrile (4e).** This product was obtained as a yellow solid (30.2 mg, 52% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 152-153℃; $^{1}H$ NMR (400 MHz, DMSO-$d_6$) δ 11.89 (s, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.41 – 7.26 (m, 4H), 7.24 – 7.17 (m, 1H), 4.19 (s, 2H), 3.85 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-$d_6$) δ 187.7, 159.3, 139.5, 136.5, 131.3, 130.1, 126.3, 125.9, 121.4, 120.8, 120.2, 118.9, 118.6, 113.5, 113.2, 111.3, 55.4, 13.5. IR (neat): 3326, 2252, 1634, 1586, 1533 $cm^{-1}$; HRMS (ESI) calculated for $C_{18}H_{14}N_2O_2$ $[M+H]^+$: 291.1128, found: 291.1127.

**2-(2-(4-Methoxybenzoyl)-1*H*-indol-3-yl)acetonitrile (4f).** This product was obtained as a yellow solid (29.7 mg, 51% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 171-172℃;$^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 11.86 (s, 1H), 7.89 – 7.80 (m, 3H), 7.54 – 7.49 (m, 1H), 7.36 (t, $J$ = 7.6 Hz, 1H), 7.20 (t, $J$ = 7.5 Hz, 1H), 7.16 (d, $J$ = 8.1 Hz, 2H), 4.20 (s, 2H), 3.89 (s, 3H). $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 186.5, 163.1, 136.2, 131.8, 131.7, 130.5, 126.2, 125.4, 120.6, 119.9, 118.6, 114.1, 113.0, 110.2, 55.6, 13.4. IR (neat): 3346, 1719, 1597, 1540, 1439, 1266 cm$^{-1}$; HRMS (ESI) calculated for $C_{18}H_{14}N_2O_2$ [M+H]$^{+}$: 291.1128, found: 291.1127.

**2-(2-(4-(Dimethylamino)benzoyl)-1*H*-indol-3-yl)acetonitrile (4g).** This product was obtained as a yellow solid (26.1 mg, 43% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 228-229℃; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 11.79 (s, 1H), 7.81 (d, $J$ = 8.1 Hz, 1H), 7.74 (d, $J$ = 8.3 Hz, 2H), 7.52 – 7.46 (m, 1H), 7.32 (t, $J$ = 7.6 Hz, 1H), 7.18 (t, $J$ = 7.5 Hz, 1H), 6.83 (d, $J$ = 8.3 Hz, 2H), 4.16 (s, 2H), 3.07 (s, 6H). $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 185.5, 153.4, 135.9, 132.8, 131.8, 126.3, 124.8, 124.7, 120.3, 119.7, 118.8, 112.9, 111.0, 108.7, 39.7, 13.4. IR (neat): 3299, 1676, 1586, 1533 cm$^{-1}$; HRMS (ESI) calculated for $C_{19}H_{17}N_3O$ [M+H]$^{+}$: 304.1444, found: 304.1446.

**2-(2-([1,1'-Biphenyl]-4-carbonyl)-1*H*-indol-3-yl)acetonitrile (4h).** This product was obtained as a yellow solid (26.9 mg, 40% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 178-179℃; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 11.94 (s, 1H), 7.97 – 7.87 (m, 5H), 7.84 – 7.77 (m, 2H), 7.58 – 7.49 (m, 3H), 7.49 – 7.42 (m, 1H), 7.38 (t, $J$ = 7.6 Hz, 1H), 7.22 (t, $J$ = 7.5 Hz, 1H), 4.26 (s, 2H). $^{13}$C{$^{1}$H} NMR (101 MHz,

DMSO-$d_6$) δ 187.5, 144.2, 138.9, 136.9, 136.5, 131.5, 130.0, 129.2, 128.5, 127.0, 126.9, 126.3, 125.8, 120.8, 120.2, 118.7, 113.2, 111.2, 13.5. IR (neat): 3317, 2252, 1632, 1609, 1534 $cm^{-1}$; HRMS (ESI) calculated for $C_{23}H_{16}N_2O$ $[M+H]^+$: 337.1335, found: 337.1334.

**2-(2-(2-Naphthoyl)-1*H*-indol-3-yl)acetonitrile (4i).** This product was obtained as a yellow solid (25.5 mg, 41% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 197-198℃; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 11.99 (s, 1H), 8.46 (s, 1H), 8.19 – 8.10 (m, 2H), 8.11 – 8.05 (m, 1H), 7.95 – 7.87 (m, 2H), 7.77 – 7.61 (m, 2H), 7.57 – 7.50 (m, 1H), 7.39 (t, $J$ = 7.6 Hz, 1H), 7.23 (t, $J$ = 7.5 Hz, 1H), 4.26 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-$d_6$) δ 188.0, 136.5, 135.3, 134.9, 132.0, 131.6, 131.0, 129.7, 128.7, 128.6, 127.7, 127.1, 126.4, 125.8, 124.9, 120.8, 120.2, 118.6, 113.2, 111.1, 13.6. IR (neat): 3314, 2251, 1626, 1533 $cm^{-1}$; HRMS (ESI) calculated for $C_{21}H_{14}N_2O$ $[M+H]^+$: 311.1179, found: 311.1171.

**2-(2-(2-Fluorobenzoyl)-1*H*-indol-3-yl)acetonitrile (4j).** This product was obtained as a yellow solid (15.6 mg, 28% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 157-158℃; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.82 (d, $J$ = 8.2 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.45 – 7.39 (m, 2H), 7.37 – 7.30 (m, 1H), 7.27 – 7.22 (m, 2H), 3.92 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 184.2, 159.6 (d, $J$ = 253.5 Hz), 136.5, 134.0 (d, $J$ = 8.1 Hz), 131.7, 130.2 (d, $J$ = 2.0 Hz), 127.8, 127.2, 127.1, 125.3 (d, $J$ = 4.0 Hz), 122.0, 121.0, 117.2 (d, $J$ = 9.1 Hz), 116.9, 112.7, 112.3, 14.1. $^{19}F$ NMR (377 MHz, $CDCl_3$) δ -12.4. IR (neat): 3326, 2253, 1639, 1533 $cm^{-1}$; HRMS (ESI) calculated for $C_{17}H_{11}FN_2O$ $[M+Na]^+$: 301.0748, found: 301.0752.

**2-(2-(4-Fluorobenzoyl)-1*H*-indol-3-yl)acetonitrile (4k).** This product was obtained as a yellow solid (29.5 mg, 53% yield). Eluent: petroleum ether/ethyl acetate 3:1 (v/v). m.p.: 188-189℃; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 11.90 (s, 1H), 7.95 – 7.86 (m, 3H), 7.56 – 7.48 (m, 1H), 7.49 – 7.41 (m, 2H), 7.38 (dd, $J$ = 7.6 Hz, $J$ = 7.6 Hz, 1H), 7.21 (dd, $J$ = 7.6 Hz, $J$ = 7.6 Hz, 1H), 4.23 (s, 2H). $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 186.6, 164.8 (d, $J$ = 252.5 Hz), 134.7 (d, $J$ = 2.0 Hz), 136.5, 132.1 (d, $J$ = 9.1 Hz), 131.3, 126.3, 125.9, 120.8, 120.2, 118.6, 115.9 (d, $J$ = 22.2 Hz), 113.2, 111.4, 13.5. $^{19}$F NMR (377 MHz, $CDCl_3$) δ -104.5. IR (neat): 3326, 2253, 1634, 1598, 1535 cm$^{-1}$; HRMS (ESI) calculated for $C_{17}H_{11}FN_2O$ [M+Na]$^{+}$: 301.0748, found: 301.0747.

**2-(2-(Thiophene-3-carbonyl)-1*H*-indol-3-yl)acetonitrile (4l).** This product was obtained as a yellow solid (20.2 mg, 38% yield). Eluent: petroleum ether/ethyl acetate3:1 (v/v). m.p.: 155-156℃; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 11.92 (s, 1H), 8.40 (s, 1H), 7.87 (d, $J$ = 8.1 Hz, 1H), 7.81 – 7.73 (m, 1H), 7.62 – 7.51 (m, 2H), 7.37 (t, $J$ = 7.6 Hz, 1H), 7.21 (t, $J$ = 7.5 Hz, 1H), 4.28 (s, 2H). $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 181.2, 141.0, 136.4, 134.9, 132.0, 127.8, 127.7, 126.3, 125.6, 120.7, 120.0, 118.7, 113.3, 110.8, 13.3. IR (neat): 3318, 2252, 1624, 1536 cm$^{-1}$; HRMS (ESI) calculated for $C_{15}H_{10}N_2OS$ [M+H]$^{+}$: 267.0587, found: 267.0587.

**2-(2-(Hydroxy(phenyl)methyl)-1*H*-indol-3-yl)acetonitrile (5).** Compound **3a** (131 mg, 0.5 mmol) was dissolved in ethanol (EtOH) (10 mL) and was cooled to 0 ºC. It was then treated with sodium borohydride ($NaBH_4$) (21 mg, 0.51 mmol). The reaction was stirred at this temperature and was monitored by TLC. After about fifteen minutes the starting material was consumed. The reaction was quenched with brine

and was extracted to DCM. The organic layer dried over $Na_2SO_4$ and was evaporated to afford the crude compound, which was purified by column chromatography to afford the desired alcohol as a yellow oil (98.3 mg, 75%). Eluent: petroleum ether/ethyl acetate 1:1 (v/v). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.12 (s, 1H), 7.55 (d, $J$ = 7.8 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.36 – 7.28 (m, 3H), 7.26 – 7.20 (m, 1H), 7.09 (t, $J$ = 7.5 Hz, 1H), 7.02 (t, $J$ = 7.4 Hz, 1H), 6.24 (s, 1H), 6.08 (s, 1H), 4.12 (s, 2H). $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 143.6, 139.4, 135.4, 128.2, 127.1, 126.8, 126.1, 121.4, 119.3, 118.9, 117.8, 111.5, 98.8, 67.3, 12.2. IR (neat): 3409, 2923, 2854, 2252, 1532, 1493, 1410, 1026 cm$^{-1}$; HRMS (ESI) calculated for $C_{17}H_{14}N_2O$ $[M+H]^+$: 263.1179, found: 263.1178.

**2-(2-(hydroxy(phenyl)methyl)-1-methyl-1H-indol-3-yl)acetic acid (6).**[19] To the solution of ethyl 2-(2-benzoyl-1H-indol-3-yl)acetate **3o** (0.50 g, 1.63 mmol) in 4 mL of acetone, dimethyl sulfate (0.23 mL, 2.44 mmol) and finely powdered sodium hydroxide (0.34 g, 8.31 mmol) were added. Then the mixture was stirred and refluxed for 1 h. After cooling to room temperature, the precipitate was filtered off and dissolved in 10 mL of water, the water solution was then acidified with acetic acid to pH ~5 to afford the precipitate. The product was obtained as fine yellowish crystals after filtration and washing with water. Yield (0.44 g, 92%). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 3.48 (s, 2H), 3.75 (s, 3H), 7.12-7.16 (m, 1H), 7.35-7.39 (m, 1H), 7.54–7.57 (m, 3H), 7.64–7.69 (m, 2H), 7.76–7.77 (m, 2H). 13C{1H} NMR (101 MHz, DMSO-$d_6$) δ 189.2, 171.8, 138.9, 138.1, 134.2, 133.1, 129.2, 128.7, 126.5, 124.9, 120.7, 120.0, 114.8, 110.5, 31.6, 30.8.

**Associated content**

Supporting information

The supporting information is available free of charge on the ACS publication website.

Copies of 1H and $^{13}C\{^{1}H\}$ NMR data (PDF)

X-ray crystal data for **3o**

## AUTHOR INFORMATION

### Corresponding Author

***E-mail:** zhangxiaofei@sust.edu.cn;

lix@sust.edu.cn;

yaotuanli@sust.edu.cn

## ACKNOWLEDGMENT

We thank the Education Department of Shaanxi Province (19JK0148) and Shaanxi University of Science and Technology for financial support of this research (2017GBJ-05 and 2016BJ-67).

## REFERENCES:

1. (a) Van Order, R. B.; Lindwall, H. G. Indole. *Chem. Rev.* **1942**, *30*, 69-96. (b) Benincori, T.; Piccolo, O.; Rizzo, S.; Sannicolo, F. 3, 3'-Bis (diphenylphosphino)-1, 1'-disubstituted-2, 2'-biindoles: easily accessible, electron-rich, chiral diphosphine ligands for homogeneous enantioselective hydrogenation of oxoesters. *J. Org. Chem.* **2000**, *65*, 8340-8347. (c) Van Zandt,

M. C.; Jones, M. L.; Gunn, D. E.; Geraci, L. S.; Jones, J. H.; Sawicki, D. R.; Sredy, J.; Jacot, J. L.; DiCioccio, A. T.; Petrova, T.; Mitschler, A.; Podjarny, A. D. Discovery of 3-[(4, 5, 7-trifluorobenzothiazol-2-yl) methyl] indole-*N*-acetic acid (lidorestat) and congeners as highly potent and selective inhibitors of aldose reductase for treatment of chronic diabetic complications. *J. Med. Chem.* **2005**, *48*, 3141-3152. (d) Bisseret, P.; Thielges, S.; Bourg, S.; Miethke, M.; Marahiel, M. A.; Eustache, J. Synthesis of a 2-indolylphosphonamide derivative with inhibitory activity against yersiniabactin biosynthesis. *Tetrahedron Lett.* **2007**, *48*, 6080-6083. (e) Wang, Y.; Vaismaa, M. J. P.; Rissanen, K.; Franzen, R. *N*1-Functionalized indole‐phosphane oxazoline ligands in asymmetric allylic substitution reactions. *Eur. J. Org. Chem.* **2012**, 8, 1569-1576. (f) Zhang, M.-Z.; Chen, Q.; Yang, G.-F. A review on recent developments of indole-containing antiviral agents. *Eur. J. Med. Chem.* **2015**, *89*, 421-441. (g) Wang, X.; Zhang, J.; Chen, D.; Wang, B.; Yang, X.; Ma, Y.; Szostak, M. Rh(III)-Catalyzed C-H amidation of 2-arylindoles with dioxazolones: a route to indolo [1, 2-c] quinazolines. *Org. Lett.* **2019**, *21*, 7038-7043. (h) Higuchi, K.; Kawasaki, T. Simple indole alkaloids and those with a nonrearranged monoterpenoid unit. Natural product reports. *Nat. Prod. Rep.* **2007**, *24*, 843-868.

2. (a) Nakamura I, Yamamoto Y. Transition-metal-catalyzed reactions in heterocyclic synthesis. *Chem. Rev.* **2004**, *104*, 2127-2198. (b) Cacchi, S.; Fabrizi, G. Synthesis and functionalization of indoles through palladium-catalyzed reactions. *Chem. Rev.* **2005**, *105*, 2873-2920. (c) Shiri, M. Indoles in

multicomponent processes (MCPs). *Chem. Rev.* **2012**, *112*, 3508-3549. (d) Vicente, R. Recent advances in indole syntheses: new routes for a classic target. *Org. Biomol. Chem.* **2011**, *9*, 6469-6480.

3. (a) Sundberg, R. J.; Yamazaki, T. Rearrangements and ring expansions during the deoxygenation of β, β-disubstituted o-nitrostyrenes. *J. Org. Chem.* **1967**, *32*, 290-294. (b) Cadogan, J. I. G. New series of nitrene-induced aromatic rearrangements. *Acc. Chem. Res.* **1972**, *5*, 303-310. (c) Creencia, E. C.; Kosaka, M.; Muramatsu, T.; Kobayashi, M.; Iizuka, T.; Horaguchi, T. Microwave - assisted cadogan reaction for the synthesis of 2-aryl-2H-indazoles, 2-aryl-1H-benzimidazoles, 2-carbonylindoles, carbazole, and phenazine. *J. Heterocycl. Chem.* **2009**, *46*, 1309-1317. (d) Cai, Q.; Li, Z.; Wei, J.; Ha, C.; Pei, D.; Ding, K. Assembly of indole-2-carboxylic acid esters through a ligand-free copper-catalysed cascade process. *Chem. Commun.* **2009**, 48, 7581-7583. (e) Yamazaki, K.; Nakamura, Y.; Kondo, Y. Solid-phase synthesis of indolecarboxylates using palladium-catalyzed reactions. *J. Org. Chem.* **2003**, *68*, 6011-6019. (f) Ji, X.; Huang, H.; Wu, W.; Li, X.; Jiang, H. Palladium-catalyzed oxidative coupling of aromatic primary amines and alkenes under molecular oxygen: stereoselective assembly of (Z)-enamines. *J. Org. Chem.* **2013**, *78*, 11155-11162. (g) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. Intramolecular C-H amination reactions: exploitation of the Rh(II)-catalyzed decomposition of azidoacrylates. *J. Am. Chem. Soc.* **2007**, *129*, 7500-7501. (h) Bonnamour, J.; Bolm, C. Iron (II) triflate as a catalyst for the synthesis of indoles

by intramolecular C-H amination. *Org. Lett.* **2011**, *13*, 2012-2014.

4. (a) Sandtorv, A. H. Transition metal catalyzed C-H activation of indoles. *Adv. Synth. Catal.* **2015**, *357*, 2403-2435. (b) Leitch, J. A.; Bhonoah, Y.; Frost, C. G. Beyond C2 and C3: transition-metal-catalyzed C–H functionalization of indole. *ACS Catal.* **2017**, *7*, 5618-5627.
5. (a) Qiu, X.; Wang, P.; Wang, D.; Wang, M.; Yuan, Y.; Shi, Z. PIII-Chelation-assisted indole C7-arylation, olefination, methylation, and acylation with carboxylic acids/anhydrides by rhodium catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 1504-1508. (b) Wang, L.; Qu, X.; Li, Z.; Peng, W. M. Rhodium-catalyzed regioselective direct C-H arylation of indoles with aryl boronic acids. *Tetrahedron Lett.* **2015**, *56*, 3754-3757. (c) Nareddy, P.; Jordan, F.; Szostak, M. Ruthenium(II)-Catalyzed direct C-H arylation of indoles with arylsilanes in water. *Org. Lett.* **2018**, *20*, 341-344. (d) Sollert, C.; Devaraj, K.; Orthaber, A.; Gates, P. J.; Pilarski, L. T. Ru-Catalysed C-H arylation of indoles and pyrroles with boronic acids: scope and mechanistic studies. *Chem-Eur. J.* **2015**, *21*, 5380-5386. (e) Devaraj, K.; Sollert, C.; Juds, C.; Gates, P. J.; Pilarski, L. Ru-Catalysed C-H silylation of unprotected gramines, tryptamines and their congeners. *Chem. Commun.* **2016**, *52*, 5868-5871. (f) Tiwari, V. K.; Kamal, N.; Kapur, M. Ruthenium-Catalyzed heteroatom-directed regioselective C-H arylation of Indoles using a removable tether. *Org. Lett.* **2015**, *17*, 1766-1769. (g) Kumar, G. S.; Kapur, M. Ruthenium-Catalyzed, site-selective C-H allylation of indoles with allyl alcohols as coupling partners. *Org. Lett.* **2016**, *18*, 1112-1115. (h) Lu,

M. Z.; Wang, C. Q.; Song, S. J.; Loh, T. P. Rhodium (Ⅲ)-catalyzed directed C-H benzylation and allylation of indoles with organosilicon reagents. *Org. Chem. Front.* **2017**, *4*, 303-307.

6. (a) Li, J.; Ackermann, L. Cobalt-Catalyzed C-H cyanation of Aarenes and heteroarenes. *Angew. Chem., Int. Ed.* **2015**, *54*, 3635-3638. (b) Lv, S.; Li, Y.; Yao, T.; Yu, X.; Zhang, C.; Hai, L.; Wu, Y. Rhodium-Catalyzed direct CH bond cyanation in ionic liquids. *Org. Lett.* **2018**, *20*, 16, 4994-4997. (c) Qi, C.; Hua, X.; Jiang, H. Copper-mediated C-H cyanation of (hetero) arenes with ethyl (ethoxymethylene) cyanoacetate as a cyanating agent. *Chem. Commun.* **2017**, *53*, 7994-7997. (d) Ding S.; Jiao, N. Direct transformation of *N, N*-dimethylformamide to - CN: Pd-catalyzed cyanation of heteroarenes via C-H functionalization. *J. Am. Chem. Soc.* **2011**, *133*, 12374-12377. (e) Xu, S.; Huang, X.; Hong, X.; Xu, B. Palladium-assisted regioselective C-H cyanation of heteroarenes using isonitrile as cyanide source. *Org. Lett.* **2012**, *14*, 4614-4617.
7. (a) Xu, Y.; Zhou, X.; Zheng, G.; Li, X. Sulfoxonium ylides as a carbene precursor in Rh (III)-catalyzed C-H acylmethylation of arenes. *Org. Lett.* **2017**, *19*, 19, 5256-5259. (b) Borah, A. J.; Shi, Z. Rhodium-catalyzed, remote terminal hydroarylation of activated olefins through a long-range deconjugative isomerization. *J. Am. Chem. Soc.* **2018**, *140*, 6062-6066. (c) Wang, C.; Maity, B.; Cavallo, L.; Rueping, M. Manganese catalyzed regioselective C-H alkylation: experiment and computation. *Org. Lett.* **2018**, *20*, 3105-3108. (d) Li, X.; Zhang, F.; Wu, D.; Liu, Y.; Xu, G.; Peng, Y.; Liu, Z.; Huang, Y. Rhodium (III)-catalyzed

C-H alkylation of heterocycles with allylic alcohols in water: a reusable catalytic system for the synthesis of β-aryl ketones. *Tetrahedron* **2018**, *74*, 7364-7371.

8. (a) Yang, D.; Mao, S.; Gao, Y.-R.; Guo, D.-D.; Guo, S.-H.; Lia, B.; Wang, Y.-Q. Palladium-catalyzed C-7 alkenylation of indolines using molecular oxygen as the sole oxidant. *RSC Adv.* **2015**, *5*, 23727-23736. (b) Jagtap, R. A.; Vinod, C. P.; Punji, B. Nickel-Catalyzed straightforward and regioselective C-H alkenylation of indoles with alkenyl bromides: scope and mechanistic aspect. *ACS Catal.* **2019**, *9*, 431-441. (c) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. Palladium-Catalyzed intermolecular alkenylation of indoles by solvent-controlled regioselective C-H functionalization. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125-3129. (d) Xiang, S.-K.; Zhang, B.; Zhang, L.-H.; Cui, Y.; Jiao, N. Morpholine catalyzed direct C3 alkenylation of indoles with α, β-unsaturated aldehydes. *Chem. Commun.* **2011**, *47*, 8097-8099. (e) Chen, W.-L.; Gao, Y.-R.; Mao, S.; Zhang, Y.-L.; Wang, Y.-F.; Wang, Y.-Q. Palladium-Catalyzed intermolecular C3 alkenylation of indoles using oxygen as the oxidant. *Org. Lett.* **2012**, *14*, 5920-5923. (f) Yu, H.; Yu, Z. Direct alkenylation of indoles with α-oxo ketene dithioacetals: efficient synthesis of indole alkaloids meridianin derivatives. *Angew. Chem., Int. Ed.* **2009**, *48*, 2929-2933.

9. (a) Shiri, M. Indoles in multicomponent processes (MCPs). *Chem. Rev.* **2012**, *112*, 3508-3549. (b) Kochanowska-Karamyan, A. J.; Hamann, M. T. Marine indole alkaloids: potential new drug leads for the control of depression and anxiety. *Chem. Rev.* **2010**, *110*, 4489-4497. (c) Somei, M.; Yamada, F. Simple indole

alkaloids and those with a non-rearranged monoterpenoid unit. *Nat. Prod. Rep.* **2005**, *22*, 73-103. (d) Kingston, D. G. I.; Ekundayo, O. 2-Acylindole alkaloids. *J. Nat. Prod.* **1981**, *44*, 509-525.

10. (a) Mahboobi, S.; Burgemeister, T.; Dove, S.; Kuhr, S.; Popp, A. Homoarcyriaflavin: synthesis of ring-expanded arcyriaflavin analogues. *J. Org. Chem.* **1999**, *64*, 8130-8137. (b) Katritzky, A. R.; Akutagawa, K. Carbon dioxide: A reagent for the protection of nucleophilic centres and the simultaneous activation of alternative locations to electrophilic attack: Part I. A new synthetic method for the 2-substitution of 1-unsubstituted indoles. *Tetrahedron Lett.* **1985**, *26*, 5935-5838.
11. Arthuis, M.; Pontikis, R.; Florent, J. C. Palladium-Catalyzed domino C, *N*-coupling/carbonylation/Suzuki coupling reaction: an efficient synthesis of 2-aroyl-/heteroaroylindoles. *Org. Lett.* **2009**, *11*, 4608-4611.
12. (a) Dhayalan, V.; Panchapakesan, G.; Mohanakrishnan, A. K. One-pot synthesis of 1-phenylsulfonyl-2-aroylindoles. *Synth. Commun.* **2012**, *42*, 402-411. (b) Zhao, Y.; Li, D.; Zhao, L.; Zhang, J. A practical synthesis of 2-aroylindoles from *N*-(2-formylphenyl) trifluoroacetamides in PEG-400. *Synthesis*. **2011**, 6, 873-880.
13. (a) Kumar, G.; Sekar, G. Pd-Catalyzed direct C2-acylation and C2, C7-diacylation of indoles: pyrimidine as an easily removable C–H directing group. *RSC Adv.* **2015**, *5*, 28292-28298. (b) Wang, W.; Liu, J.; Gui, Q.; Tan, Z. Synthesis of 2-acylated indoles through palladium-catalyzed dehydrogenative coupling of *N*-Pyrimidine-protected indoles with aldehydes and ethyl glyoxylate. *Synlett* **2015**,

*26*, 771-778. (c) Li, C.; Zhu, W.; Shu, S.; Wu, X.; Liu, H. Palladium‐Catalyzed C2‐acylation of indoles with α-diketones assisted by the removable *N*‐(2‐Pyrimidyl) Group. *Eur. J. Org. Chem.* **2015**, 17, 3743-3750. (d) Pan, C.; Jin, H.; Liu, X.; Cheng, Y.; Zhu, C. Palladium-Catalyzed decarboxylative C2-acylation of indoles with α-oxocarboxylic acids. *Chem. Commun.* **2013**, *49*, 2933-2935. (e) Zhou, B.; Yang, Y.; Li, Y. Rhodium-Catalyzed oxidative C2-acylation of indoles with aryl and alkyl aldehydes. *Chem. Commun.* **2012**, *48*, 5163-5165. (f) Wu, Y.; Li, B.; Mao, F.; Li, X.; Kwong, F.-Y. Palladium-Catalyzed oxidative C-H bond coupling of steered acetanilides and aldehydes: a facile access to ortho-acylacetanilides. *Org. Lett.* **2011**, *13*, 3258-3261. (g) Sharma, U. K.; Gemoets, H. P. L.; Schröder, F.; Noël, T.; Van der Eycken, E. V. Merger of visible-light photoredox catalysis and C-H activation for the room-temperature C-2 acylation of indoles in batch and flow. *ACS Catal.* **2017**, *7*, 3818-3823.

14. (a) Sadjadi, S.; Heravi, M. M.; Nazari, N. Isocyanide-based multicomponent reactions in the synthesis of heterocycles. *RSC Adv.* **2016**, *6*, 53203-53272. (b) Chakrabarty, S.; Choudhary, S.; Doshi, A.; Liu, F. Q.; Mohan, R.; Ravindra Manasa, P.; Shah, D.; Yang, X.; Fleming Fraser, F. Catalytic isonitrile insertions and condensations initiated by RNC-X complexation. *Adv. Synth. Catal.* **2014**, *356*, 2135-2196. (c) Lygin, A. V.; De Meijere, A. Isocyanides in the synthesis of nitrogen heterocycles. *Angew. Chem., Int. Ed.* **2010**, *49*, 9094-9124. (d) Liu, Y.; Li, S.; Chen, X.; Fan, L.; Li, X.; Zhu, S.; Qu, L.; Yu, B. Mn(III)-Mediated regioselective 6-endo-trig radical cyclization of *o*-vinylaryl isocyanides to access

2-functionalized quinolines. *Adv. Synth. Catal.* **2020**, *362*, 688-694.

15. (a) Fukuyama, T.; Chen, X.; Peng, G. A novel tin-mediated indole synthesis. *J. Am. Chem. Soc.* **1994**, *116*, 3127-3128. (b) Tokuyama, H.; Kaburagi, Y.; Chen, X.; Fukuyama, T. Synthesis of 2, 3-disubstituted indoles by palladium-mediated coupling of 2-iodoindoles. *Synthesis* **2000**, 3, 429-434. (c) Tobisu, M.; Fujihara, H.; Koh, K.; Chatani, N. Synthesis of 2-boryl-and silylindoles by copper-catalyzed borylative and silylative cyclization of 2-alkenylaryl isocyanides. *J. Org. Chem.* **2010**, *75*, 4841-4847. (d) Heckman, L. M.; He, Z.; Jamison, T. F. Synthesis of highly substituted 2-arylindoles via copper-catalyzed coupling of isocyanides and arylboronic acids. *Org. Lett.* **2018**, *20*, 3263-3267.
16. (a) Huang, L.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Photosensitizer‐Free visible-light nediated gold catalyzed 1, 2-difunctionalization of alkynes. *Angew. Chem., Int. Ed.* **2016**, *55*, 4808-4813. (b) Xuan, J.; Xiao, W.-J. Visible-light photoredox catalysis. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828-6838. (c) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible light photoredox catalysis with transition metal complexes: applications in organic synthesis. *Chem. Rev.* **2013**, *113*, 5322-5363. (d) Rong, J.; Deng, L.; Tan, P.; Ni, C.; Gu, Y.; Hu, J. Radical fluoroalkylation of isocyanides with fluorinated sulfones by visible-light photoredox catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 2743-2747. (e) Ravelli, D.; Protti, S.; Fagnoni, M. Carbon-carbon bond forming reactions via photogenerated intermediates. *Chem. Rev.* **2016**, *116*, 9850-9913. (f) Romero, N. A.; Nicewicz, D. A. Organic photoredox catalysis. *Chem. Rev.* **2016**, *116*,

10075-10166. (g) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox catalysis in organic chemistry. *J. Org. Chem.* **2016**, *81*, 6898-6926. (h) Liu, X.; Chen, X.; Liu, Y.; Sun, K.; Peng, Y.; Qu, L.; Yu, B. Visible-light-induced metal-free synthesis of 2-phosphorylated thioflavones in water. *ChemSusChem*. **2020**, *13*, 298-303. (i) Wang, L.; Zhang, M.; Zhang, Y.; Liu, Q.; Zhao, X.; Li, J.; Luo, Z.; Wei, W. Metal-free visible-light-induced oxidative cyclization reaction of 1,6-enynes and arylsulfinic acids leading to sulfonylated benzofurans. *Chin. Chem. Lett.* **2020**, *31*, 67-70. (j) Shang, T.; Lu, L.; Cao, Z.; Liu, Y.; He, W.; Yu, B. Recent advances of 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) in photocatalytic transformations. *Chem. Commun.* **2019**, *55*, 5408-5419.

17. Wang, C.-H.; Li, Y.-H.; Yang, S.-D. Autoxidation photoredox catalysis for the synthesis of 2-phosphinoylindoles. *Org. Lett.* **2018**, *20*, 2382-2385.

18. (a) Penteado, F.; Lopes, E. F.; Alves, D.; Perin, G.; Jacob, R. G.; Lenardao, E. J. α-Keto Acids: acylating agents in organic synthesis. *Chem. Rev.* **2019**, *119*, 7113-7278. (b) Xu, N.; Li, P.; Xie, Z.; Wang, L. Merging visible-light photocatalysis and palladium catalysis for C-H acylation of azo- and azoxybenzenes with α-keto acids. *Chem.-Eur. J.* **2016**, *22*, 2236-2242. (c) Zhou, C.; Li, P.; Zhu, X.; Wang, L. Merging photoredox with palladium catalysis: decarboxylative ortho-acylation of acetanilides with α-oxocarboxylic acids under mild reaction conditions. *Org. Lett.* **2015**, *17*, 6198-6201. (d) Meng, M.; Wang, G.; Yang, L.; Cheng, K.; Qi, C. Silver-Catalyzed double decarboxylative radical

alkynylation/annulation of arylpropiolic acids with α-keto Acids: access to ynones and flavones under mild conditions. *Adv. Synth. Catal.* **2018**, *360*, 1218-1231.

19. Kharaneko, A.O., Pekhtereva, T.M. & Kharaneko, O.I. Heterocyclizations of di- and tricarbonyl indole derivatives. synthesis of β-carbolines, 3H-[1,2,5]triazepino-[5,4-a]indol-4(5H)-one, and 5,10-dihydro[1,2]diazepino-[4,5-b]indol-4(3H)-one. *Russ. J. Org. Chem.* **2020**, *56*, 95–104.
20. Wadhwa, K.; Yang, C.; West, P. R.; Deming, K. C. Synthesis of arylglyoxylic acids and their collision-induced dissociation. *Synth. Commun.* **2008**, 38, 4434-4444.
21. Laurel M, Heckman.; Zhi He.; and Timothy F, Jamison. Synthesis of highly substituted 2-arylindoles via copper-catalyzed coupling of isocyanides and arylboronic acids. *Org. Lett.* **2018**, 20, 3263-3267.
22. (a) Peng, L.; Li, Z.; Yin, G. Photochemical nickel-catalyzed reductive migratory cross-coupling of alkyl bromides with aryl bromides. *Org. Lett.* **2018**, *20*, 1880-1883. (b) Lee, M.; Neukirchen, S.; Cabrele, C.; Reiser, O. Visible-light photoredox-catalyzed desulfurization of thiol- and disulfide-containing amino acids and small peptides. *J. Pept Sci.* **2017**, *23*, 556-562.
23. Tobisu, M.; Fujihara, H.; Koh, K. Synthesis of 2-boryl- and silylindoles by copper-catalyzed borylative and silylative cyclization of 2-alkenylaryl isocyanides. *J. Org. Chem*. **2010**, 75, 4841-4847.
24. Evoniuk, C. J.; Gomes, G. P.; Ly, M.; White, F. D. Coupling radical homoallylic

expansions with C-C fragmentations for the synthesis of heteroaromatics: quinolines from reactions of *o*-alkenylarylisonitriles with aryl, alkyl, and perfluoroalkyl radicals. *J. Org. Chem*. **2017**, 82, 4265-4278.

25. (a) Furukawa, K.; Inada, H.; Shibuya, M.; et al. Chemoselective conversion from α-hydroxy acids to *α*-keto acids enabled by nitroxyl-radical-catalyzed aerobic oxidation. *Org. Lett*, **2016**, 18, 4230-4233. (b) Crich, D.; Zou, Y. Catalytic oxidation adjacent to carbonyl groups and at benzylic positions with a fluorous seleninic acid in the presence of iodoxybenzene. *J. Org. Chem*. **2005**, 70, 3309-3311.