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ARTICLE

Stereoselective α-Indolylation of Enals *via* an Organocatalytic Formal Cross-Coupling with Indoles†

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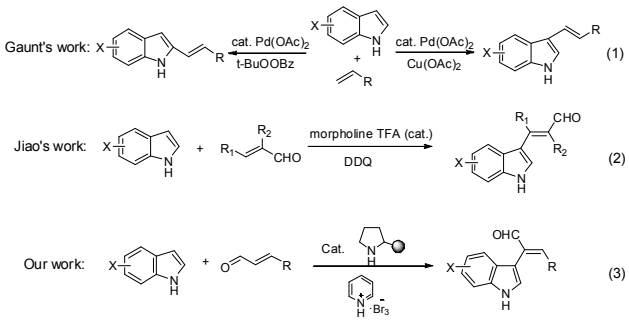
We report a novel organocatalytic one-pot cascade bromination-Michael-type Friedel-Crafts alkylation dearomatization-nucleophilic rearrangement aromatization cascade process for the direct α-indolylation of unfunctionalized enals from readily available indoles with good yields and high E selectivity. Simplicity and practicality of its high efficiency of formation of a new C(sp^2)-C(sp^2) bond constitute the most attractive advantage of this reaction.

Introduction

The functionalized indoles are important building blocks in organic synthesis and "privileged" structures in drug discovery.[1] The state-of-the-art synthetic technologies for the installation of the structure rely on the transition metal catalysed C-C cross-couplings[2] and C-H activation[3] reactions. Direct indolylation of alkenes with indoles represents an appealing approach because of their ready availability, but has been much less developed.[4] In this context, Gaunt and colleagues discovered an elegant Pd(II) catalyzed the C2 and C3 alkenylation of indoles by solvent-controlled regioselective C-H functionalization (Scheme 1, eqn 1).[5] In spite of these approaches, the development of efficient and transition-metal-free organocatalytic formal cross-coupling strategy is attracting attention.[6] Recently, functionalized enals have aroused great interest owing to their wide utility in pharmaceutical field and organocatalytic reactions.[7,8] In 2011, Jiao and co-workers described an impressive, morpholine trifluoroacetic acid salt catalyzed oxidative dehydrogenative C3 alkenylation of indoles with α, β-unsaturated aldehydes to generate highly stereoselective β-indolylenals (Scheme 1,eqn 2).[9]

Despite these great advances, to the best of our knowledge, in contrast to the developed direct β-indolylation of enals, the investigation of efficient metal-free organocatalysed C-H α-arylation reaction of enals remains highly challenging. In 2011, Wang and co-workers have carried out investigations leading to the development of new organocatalysed cross-coupling of prefunctionalized 3-bromoindoles and enals for α-indolylation of simple α,β-unsaturated aldehydes,[10] where 3-bromoindoles are used as essential substrates. Very recently, we reported a direct metal-free cross-coupling approach to highly regioselective α-naphtholylenals from simple unfunctionalized naphthols and enals.[11] Based on our previous works, herein we wish to reveal the investigation of organocatalytic direct C3 alkenylation of unfunctionalized indoles with simple enals for the construction of C(sp^2)-C(sp^2) coupling indole core skeleton in one-pot cascade process in the presence of pyridine hydrobromide perbromid[12] in good yields and with high *E* stereoselectivity (Scheme 1, eqn 3) To the best of our knowledge, there is no report about metal free approach for the direct C(sp^2)-C(sp^2) cross-coupling α-indolylation of enals from unfunctionalized indoles and enals.



Scheme 1 Direct indolation of enals.

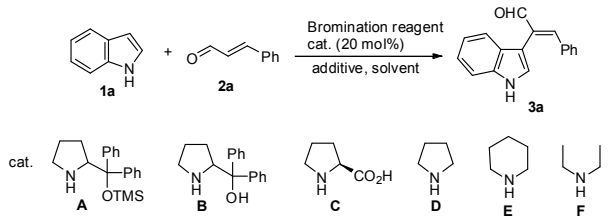
We envisioned that, in this one-pot operation, the perquisite 3-bromoindoles could be *in situ* produced from an electrophilic bromination reaction of indoles with pyridine hydrobromide perbromid, thereby creating an ambiphilic nucleophilic /electrophilic center for the subsequent Michael addition initial cascade process.

Results and discussion

Firstly, we carried out a model reaction between indole **1a**, *trans*-cinnamaldehye **2a** and pyridine hydrobromide perbromid in the presence of racemic diphenylprolinol trimethylsilyl ether[13] (**A**, 20mol%) and base NaOAc in toluene (Table 1, entry 1). To our delight, the reaction occurred to give

the desired product **3a** despite of low yield (32%). Solvents have meaningful impact on the yield of this process. Although the reactions were not satisfactory in less polar solvents such as toluene and $CHCl_3$, the product was obtained in polar CH_3CN in even lower yield (entries 1-3). It was found that process performed in a mixture of toluene:$CHCl_3$ (1:1) generally afford the better efficiency (entry 4). The effect and amount of base on this process were evaluated next. The study revealed NaOAc as choice. In addition, screening of bromination reagents led to the selection of pyridine hydrobromide perbromid (entry 4 *vs* 6). Other aminocatalyst diphenylprolinol (**B**) and simple secondary amines such as L-proline (**C**), pyrrolidine (**D**), piperidine (**E**) and diethylamine (**F**) were sluggish with poor yields in 0~10% (entries 7-11).

Table 1 Optimization of the reaction conditions[a]

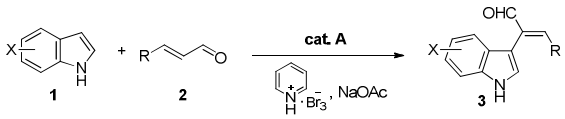


Entry	Cat.	Bromination Reagent	Solvent	Additive	Yield(%)[b]
1	**A**		toluene (tol)	NaOAc	32
2	**A**		MeCN	NaOAc	35
3	**A**		$CHCl_3$	NaOAc	30
4	**A**		tol:$CHCl_3$(1:1)	NaOAc	62
5	**A**		tol:$CHCl_3$(1:1)	TEA	42
6	**A**	NBS	tol:$CHCl_3$(1:1)	NaOAc	50
7	**B**		tol:$CHCl_3$(1:1)	NaOAc	—[c]
8	**C**		tol:$CHCl_3$(1:1)	NaOAc	—[c]
9	**D**		tol:$CHCl_3$(1:1)	NaOAc	—[c]
10	**E**		tol:$CHCl_3$(1:1)	NaOAc	10
11	**F**		tol:$CHCl_3$(1:1)	NaOAc	—[c]

[a] Unless otherwise specified, all reactions were carried out using a solution of **1a** (1.0mmol, 1.0 equiv.) was added a pyridine hydrobromide perbromid (1.0mmol, 1.0 equiv.) at 0 °C, followed by addition of **2a** (1.5mmol, 1.5 equiv.), catalyst (0.02mmol, 0.2 equiv.) and NaOAc(12.0mmol, 12.0 equiv.), the reaction mixture was stirred for 24h at 65 °C. [b] Isolatedyields. [c] No desired products were obtained.

The optimization reaction conditions allowed us to select **A** as catalyst, NaOAc as base, toluene:$CHCl_3$ (1:1) as solvents to evaluate the generality of one-pot cascade α-indolylation of enals process (Table 2). As revealed in Table 2, the one-pot cascade protocol serves as a general method for the preparation of α-indolylenals from a variety of indoles and enals. Remarkably, in this process, a new sp^2-sp^2 C-C bond (C3 of indole and α-C of enal) is directly and efficiently assembled in a single operation with good yield. Structural variation of enals can be applicable to the powerful processes to obtain the structurally diverse products **3** (entries 1-9). The electronic nature of the substituents of aromatic systems of enals **2** apparently has limited influence on the reaction yield. Electron-neutral (entry 1), -withdrawing (entries 2-5), -donating (entries 6 and 7) and heterocyclic groups (entry 8) can be tolerated. Their steric effects on stereoselectivity were more pronounced than that of electronic effects. Relatively poorer E/Z ratios attended reactions of cinnamaldehydes containing *ortho*- versus *para*- aromatic substituents (entries 4,5 *vs* entries 1-3 and 6,7). Furthermore, it is also viable to unactive α-C-H activation of conjugated dienals (entry 9) although a relatively longer reaction time is required. Probe of the structural effect of indoles reveals that the efficiency is somewhat dependent on its electronic properties. Electron-withdrawing groups on indoles slow down the reaction and give the product in lower yield (entries 19-21). When 2-phenylindole was employed, the lower yield was obtained presumably due to the steric hindrance induced by the phenyl group (entry 23).

Table 2 The substrate scope of the organocatalytic one-pot operation[a]

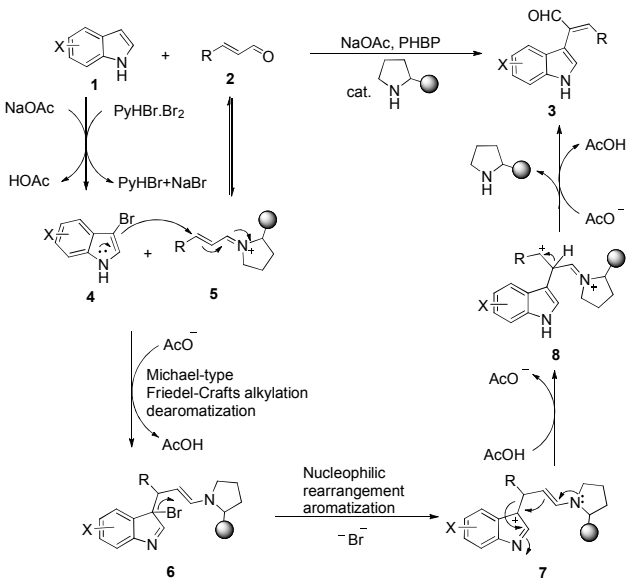


Entry	X	R	**3**	Yield(%)[b]	E/Z[c]
1	H	Ph	**3a**	62	96:4
2	H	4-Cl-Ph	**3b**	67	92:8
3	H	4-F-Ph	**3c**	65	>99:1
4	H	2-Br-Ph	**3d**	68	90:10
5	H	2-NO_2-Ph	**3e**	70	84:16
6	H	4-Me-Ph	**3f**	56	91:9
7	H	4-OMe-Ph	**3g**	51	>99:1
8	H	2-furanyl	**3h**	55	87:13
9[d]	H	(E)-Ph-(CH=CH)-	**3i**	57	>99:1
10	2-Me	Ph	**3j**	68	93:7
11	2-Me	4-Cl-Ph	**3k**	68	97:3
12	2-Me	4-OMe-Ph	**3l**	59	88:12
13	2-Et	Ph	**3m**	65	93:7
14	6-OMe	Ph	**3n**	51	88:12
15	7-Me	Ph	**3o**	60	94:6
16	7-MeO	Ph	**3p**	66	92:8
17	5-MeO	4-F-Ph	**3q**	66	92:8
18	5-MeO	4-MeO-Ph	**3r**	52	90:10
19	5-Br	Ph	**3s**	45	>99:1
20	5-Br	4-Cl-Ph	**3t**	47	>99:1
21[d]	5-NO_2	4-Cl-Ph	**3u**	40	>99:1
22	5-MeO-2-Me	2-NO_2-Ph	**3v**	68	72:28
23[d]	2-Ph	Ph	**3w**	36	95:5

[a] Reation conditions: unless specified, at 0 °C, to a solution of **1** (1.0mmol, 1.0equiv.) was added a pyridinium bromideper bromide (1.0mmol, 1.0equiv.), followed by addition of **2** (1.5mmol, 1.5equiv.), catalyst **A** (0.02mmol, 0.2equiv.) and NaOAc (12.0mmol, 12.0 equiv.), the reaction mixture was stirred for 24h at 65℃. [b] Isolated yields. [c] Determined by NMR. [d] Reaction was performed for 48h.

On the basis of above results, a catalytic cycle is proposed for the process (Scheme 2). The pathway involves an *in situ*

bromination-Friedel-Crafts alkylation dearomatization-nucleophilic rearrangement aromatization cascade by iminium-enamine catalysis in a single-pot. It is reasonably believed that bromination at the 3-position of indoles with pyridine hydrobromide perbromid create ambiphilic nucleophilic/ electrophilic center *in situ*. Then it is served as nucleophile for the Michael-type Friedel-Crafts alkylation with iminium ion **5** with the assistance of NaOAc to form the dearomatized enamine **6**. Subsequently, an intramolecular nucleophilic rearrangement aromatization occurs in the presence of NaOAc *via* the cleavage of benzyl Br following deprotonation to generate iminium ion intermediate 8. Finally, product **3** is generated directly from **8** with the regeneration of catalyst **A**.



Scheme 2 Proposed catalytic cycle.

Conclusions

In summary, we have developed an organocatalytic 'one-pot' cascade process for the direct functionalization of indoles with enals in good yields and with high *E* stereoselectivity. The noteworthy features of the one-pot process is highlighted by its high efficiency of formation of a new $C(sp^2)$-$C(sp^2)$ bond under a metal free mild reaction conditions. The exploration of the powerful strategy in the preparation of structurally diverse heterocyclics for biological studies is under investigation in our laboratories.

Experimental section

General information

All reagents were purchased from commercial suppliers and used without further purification. Nuclear Magnetic Resonance (NMR) spectra were acquired on a Bruker Avance spectrometer, running at 400 MHz for ^{1}H and 100 MHz for ^{13}C, respectively, and chemical shifts are reported in parts permillion (ppm) downfield from TMS, using residual $CDCl_3$ or DMSO-d_6 as an internal standard. Mass Spectra were obtained from East China University of Science & Technology mass spectral facility. Reactions were run under an atmosphere of nitrogen unless mentioned otherwise. Purification of the reaction products was carried out column chromatography using silica gel (200-300 mesh). Analytical thin layer chromatography was performed on glass-backed silica gel plates containing ultraviolet-active phosphor and the compounds were visualized either by UV illumination (254 nm), or by means of lime or ink powder. Toluene was dried by sodium metal.

General experimental procedures for the preparation of (*E*)-2-(1H-indole-3-yl)-3-arylacrylaldehyde 3

A solution of indole **1** (1.0 mmol) in 10 mL of Tol:$CHCl_3$ (1:1) was added dropwise pyridinium bromide perbromide (1.0 mmol) which was dissolved in 0.5mL of CH_3OH, followed by addition of enals **2** (1.5 mmol), NaOAc (12.0 mmol) and catalyst **A** (0.2 mmol). Then the reaction mixture was stirred at 65℃ for 24 h. The mixture was filtered and the filtrate was removed by vacuum distillation. The crude product was purified by column chromatography on silica gel.

(*E*)-2-(1*H*-indole-3-yl)-3-phenylacrylaldehyde (3a). Flash column chromatography eluent: petroleum ether/ethylacetate = 5/1, yellow solid, 62% yield (152 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): 9.89 (s, 1H), 8.59 (br, 1H), 7.51(s, 1H), 7.41-7.37 (m, 4H), 7.27-7.25 (m, 1H), 7.22-7.15 (m, 3H), 6.98-6.93 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): 195.1, 149.7, 136.2, 135.0, 134.4, 130.5, 129.9, 128.4, 125.8, 125.1, 122.1, 120.7, 119.9, 111.5, 107.3. HRMS (EI+) m/z calcd. for $C_{17}H_{13}NO$: 247.0997; found: 247.0999. Collected NMR spectra are consistent with the literature.[14]

(*E*)-2-(1*H*-indole-3-yl)-3-(4-chlorophenyl)acrylaldehyde (3b). Flash column chromatography eluent: petroleum ether/ ethylacetate = 5/1, yellow solid, 67% yield (188 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): 9.87 (s, 1H), 8.59 (br, 1H), 7.44-7.41 (m, 3H), 7.32-7.29 (m, 2H), 7.21-7.16 (m, 3H), 6.70-6.91 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): 194.6, 147.5, 136.1, 135.7, 134.6, 133.4, 131.6, 128.7, 125.8, 124.8, 122.4, 120.7, 120.1, 111.5, 107.2. HRMS (EI+) m/z calcd. for $C_{17}H_{12}ClNO$: 281.0607; found: 281.0603.

(*E*)-2-(1*H*-indole-3-yl)-3-(4-fluorophenyl)acrylaldehyde (3c). Flash column chromatography eluent: petroleum ether/ ethylacetate = 6/1, yellow solid, 65% yield (171 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): 9.88 (s, 1H), 8.69 (br, 1H), 7.47 (s, 1H), 7.38-7.36 (m, 3H), 7.31-7.30 (m, 1H), 7.19-7.16 (m, 1H), 7.98-7.96 (m, 2H), 6.91-6.86 (t, *J* = 8.58 Hz, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): 194.9, 162.1, 148.3, 136.2, 134.0, 132.6, 131.2, 125.8, 124.9, 122.3, 120.6, 120.0, 115.7, 115.5, 111.6. HRMS (EI+) m/z calcd. for $C_{17}H_{12}FNO$: 265.0903; found: 265.0901.

(*E*)-2-(1*H*-indole-3-yl)-3-(2-bromophenyl)acrylaldehyde (3d). Flash column chromatography eluent: petroleum ether/ ethylacetate = 4/1, orange solid, 68% yield (221 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): 9.98 (s, 1H), 8.61 (br, 1H), 7.69-7.68 (m, 2H), 7.42 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.16-7.14 (m, 2H), 7.08 (t, *J* = 7.7 Hz, 1H), 6.94-6.85 (m, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): 194.8, 146.9, 136.1, 135.7, 135.6, 132.9, 130.8, 130.5, 126.9, 126.5, 125.2, 124.8, 122.2, 120.6, 120.1, 111.4, 106.7. HRMS (EI+) m/z calcd. for $C_{17}H_{12}BrNO$: 325.0102; found: 325.0097.

(*E*)-2-(1*H*-indole-3-yl)-3-(2-nitrophenyl)acrylaldehyde (3e). Flash column chromatography eluent: petroleum ether/ ethylacetate = 3/1, orange solid, 70% yield (204 mg). ^{1}H NMR (DMSO-d_6, 400 MHz): 11.69 (s, 1H), 10.14 (s, 1H), 8.35 (d, *J* = 8.1 Hz, 1H), 8.08 (s, 1H), 7.70-7.67 (m, 2H), 7.60- 7.57 (m, 2H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.23-7.19 (m, 1H), 6.99-6.96 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): 195.1, 147.9, 143.7, 136.6, 136.5, 133.8, 132.2, 130.9, 130.2, 128.0, 125.4, 125.1, 121.7, 119.6, 119.5, 112.2, 105.6. HRMS (EI+) m/z calcd. for C17H12N2O3: 292.0848; found: 292.0846.

(*E*)-2-(1*H*-indole-3-yl)-3-(p-tolyl)acrylaldehyde (3f). Flash column chromatography eluent: petroleum ether/ethylacetate = 6/1, yellow solid, 56% yield (147 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): 9.86 (s, 1H), 8.49 (br, 1H), 7.49 (s, 1H), 7.44-7.39 (m, 2H), 7.28 (s, 2H), 7.21-7.17 (m, 1H), 7.02-6.97 (m, 4H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): 194.8, 150.0, 149.5, 140.4, 136.1, 133.4, 132.2, 130.6, 129.1, 125.4, 122.2, 120.8, 119.9, 112.3, 21.2. HRMS (EI+) m/z calcd. for $C_{18}H_{15}NO$: 261.1154; found: 261.1159.

(*E*)-2-(1*H*-indole-3-yl)-3-(4-methoxyphenyl)acrylaldehyde (3g). Flash column chromatography eluent: petroleum ether/ ethylacetate = 6/1, yellow solid, 51% yield (140 mg). ^{1}H NMR (DMSO-d_6, 400 MHz): 11.41 (s, 1H), 9.77 (s, 1H), 7.63 (s, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 2.5 Hz, 1H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.10-7.06 (m, 1H), 6.86-6.85 (m, 2H), 6.78 (d, *J* = 8.9 Hz, 2H), 3.70 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): 194.7, 160.5, 149.3, 136.2, 132.4, 132.1, 127.5, 125.9, 125.2, 121.2, 119.7, 118.9, 113.9, 111.8, 106.4, 55.2. HRMS (EI+) m/z calcd. for $C_{18}H_{15}NO_2$: 277.1103; found: 277.1104.

(E)-2-(1*H*-indole-3-yl)-3-(furan-2-yl)acrylaldehyde (3h). Flash column chromatography eluent: petroleum ether/ethylacetate = 5/1, yellow solid, 55% yield (132 mg). ^{1}H NMR (DMSO-d_6, 400 MHz): 11.70 (s, 1H), 10.01 (s, 1H), 8.04 (s, 1H), 7.82 (s, 1H), 7.71-7.68 (m, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.24-7.17 (m, 2H), 6.75 (s, 1H), 6.50 (d, *J* = 3.3 Hz, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz): 194.4, 151.3, 136.4, 136.5, 135.5, 131.9, 126.7, 125.8, 121.6, 120.2, 119.4, 116.7, 113.4, 112.3, 106.6. HRMS (EI+) m/z calcd. for $C_{15}H_{11}NO_2$: 237.0790; found: 237.0791.

(2*E*,4*E*)-2-(1*H*-indol-3-yl)-5-phenylpenta-2,4-dienal (3i). Flash column chromatography eluent: petroleum ether/ethylacetate = 3/1, yellow solid, 57% yield (154 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): 9.77 (s, 1H), 8.82 (br, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.34-7.32 (m, 3H), 7.24-7.17 (m, 7H), 7.13-7.11 (m, 1H), 7.04 (d, *J* = 14.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): 194.0, 148.4, 141.1, 136.3, 136.1, 135.0, 129.3, 128.9, 127.5, 126.7, 126.1, 122.3, 120.3, 120.2, 111.6, 107.5, 107.4. HRMS (EI+) m/z calcd. for $C_{19}H_{15}NO$: 273.1154; found: 273.1153.

(*E*)-2-(2-methyl-1*H*-indole-3-yl)-3-phenylacrylaldehyde (3j). Flash column chromatography eluent: petroleum ether/ ethylacetate = 3/1, yellow solid, 68% yield (178 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): 9.86 (s, 1H), 8.26 (br, 1H), 8.02 (s, 1H), 7.59 (s, 1H), 7.31 (d, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 1H), 7.19-7.15 (m, 2H), 7.11-7.08 (m, 2H), 6.97 (t, *J* = 7.4 Hz, 1H), 2.03 (s, 3H). ^{13}C NMR($CDCl_3$, 101 MHz): 194.9, 150.9, 135.9, 135.1, 134.9, 133.6, 130.4, 130.0, 128.5, 127.3, 121.4, 119.8, 119.3, 110.6, 105.3, 12.7. HRMS (EI+) m/z calcd. for $C_{18}H_{15}NO$: 261.1154; found: 261.1153.

(*E*)-2-(2-methyl-1*H*-indole-3-yl)-3-(4-hlorophenyl) acrylaldehyde (3k). Flash column chromatography eluent: petroleum ether/ ethylacetate = 4/1, yellow solid, 68% yield (200 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): 9.88 (s, 1H), 8.52 (br, 1H), 7.56 (s, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.20-7.10 (m, 5H), 7.02 (t, *J* = 7.3 Hz, 1H), 2.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): 195.0, 149.3, 136.0, 135.9, 135.5, 134.0, 133.4, 131.6, 128.8, 126.9, 121.5, 119.9, 119.1, 110.9, 104.6, 12.6. HRMS (EI+) m/z calcd. for $C_{18}H_{14}ClNO$: 295.0764; found: 295.0761.

(*E*)-2-(2-methyl-1*H*-indole-3-yl)-3-(4-methoxyphenyl) acrylaldehyde (3l). Flash column chromatography eluent: petroleum ether/ ethylacetate = 3/1, yellow solid, 59% yield (170 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): 9.84 (s, 1H), 8.42 (br, 1H), 7.58 (s, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 1H), 7.14-7.10 (m, 2H), 7.01 (t, *J* = 7.2 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 2H), 3.76 (s, 3H), 2.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): 195.0, 161.1, 151.3, 136.0, 133.7, 132.9, 132.5, 127.6, 127.3, 121.3, 119.7, 119.2, 114.0, 110.7, 105.3, 55.3, 12.6. HRMS (EI+) m/z calcd. for $C_{19}H_{17}NO_2$: 291.1259; found: 291.1260.

(*E*)-2-(2-ethyl-1*H*-indole-3-yl)-3-phenylacrylaldehyde (3m). Flash column chromatography eluent: petroleum ether/ ethylacetate = 4/1, yellow solid, 65% yield (180 mg). ^{1}H NMR (DMSO-d_6, 400 MHz): 10.96 (s, 1H), 9.57 (s, 1H), 7.56 (s, 1H), 7.10-7.05 (m, 3H), 7.01 (d, *J* = 6.91 Hz, 1H), 6.98- 6.94 (m, 2H), 6.76 (t, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 7.7 Hz, 1H), 6.57 (t, *J* = 7.3 Hz, 1H), 2.19-2.12 (m, 2H), 0.80 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): 195.6, 151.4, 139.7, 136.4, 135.8, 135.4, 130.5, 130.4, 128.9, 127.1, 121.0, 119.2, 118.9, 111.4, 103.7, 20.4, 13.8. HRMS (EI+) m/z calcd. for $C_{19}H_{17}NO$: 275.1310; found: 275.1309.

(*E*)-2-(6-methoxy-1*H*-indol-3-yl)-3-phenylacrylaldehyde (3n). Flash column chromatography eluent: petroleum ether/ ethylacetate = 3/1, orange solid, 51% yield (140 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): 9.83 (s, 1H), 8.81 (br, 1H), 7.66 (s, 1H), 7.32-7.30 (m, 3H), 7.26 (d, *J* = 7.1 Hz, 1H), 7.21-7.17 (m, 2H), 6.96 (d, *J* = 8.5 Hz, 1H), 6.66-6.63 (m, 2H), 3.75 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): 194.0, 156.6, 152.2, 137.3, 134.3, 133.3, 130.6, 128.6, 128.6, 121.0, 119.7, 110.5, 108.8, 107.4, 94.5, 55.6. HRMS (EI+) m/z calcd. for $C_{18}H_{15}NO_2$: 277.1103; found: 277.1110.

(*E*)-2-(7-methyl-1*H*-indol-3-yl)-3-phenylacrylaldehyde (3o). Flash column chromatography eluent: petroleum ether/ ethylacetate = 2/1, yellow solid, 60% yield (157 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): 9.80 (s, 1H), 8.60 (br, 1H), 7.43 (s, 1H), 7.32 (d, *J* = 7.4 Hz, 2H), 7.25 (d, *J* = 2.5 Hz, 1H), 7.19 (t, *J* = 7.1 Hz, 1H), 7.14-7.10 (m, 2H), 6.87 (d, *J* = 6.8 Hz, 1H), 6.82-6.73 (m, 2H), 2.37 (s, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): 159.3, 149.9, 135.8, 135.0, 134.6, 130.6, 129.9, 128.4, 125.4, 124.7, 122.7, 120.7, 120.1, 118.4, 107.8, 16.6. HRMS (EI+) m/z calcd. for $C_{18}H_{15}NO$: 261.1154; found: 261.1153.

(*E*)-2-(7-methoxy-1*H*-indol-3-yl)-3-phenylacrylaldehyde (3p). Flash column chromatography eluent: petroleum ether/ ethylacetate = 3/1, yellow solid, 66% yield (182 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): 9.78 (s, 1H), 8.71 (br, 1H), 7.40 (s, 1H), 7.33-7.27 (m, 3H), 7.19 (t, *J* = 6.9 Hz, 1H), 7.15-7.09 (m, 2H), 6.79 (t, *J* = 7.9 Hz, 1H), 6.54 (d, *J* = 7.7 Hz, 1H), 6.49 (d, *J* = 8.1 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): 194.9, 149.4, 146.2, 135.0, 134.4, 130.5, 129.8, 128.4, 126.7, 126.6, 125.1, 120.3, 113.6, 108.0, 102.1, 55.4. HRMS (EI+) m/z calcd. for $C_{18}H_{15}NO_2$: 277.1103; found: 277.1111.

(*E*)-2-(5-methoxy-1*H*-indole-3-yl)-3-(4-fluorophenyl) acrylaldehyde (3q). Flash column chromatography eluent: petroleum ether/ ethylacetate = 2/1, yellow solid, 66% yield (194 mg). ^{1}H NMR (DMSO-d_6, 400 MHz): 11.36 (s, 1H), 9.81 (s, 1H), 7.64 (s, 1H), 7.48 (d, *J* = 2.5 Hz, 1H), 7.42 (dd, *J* = 8.5, 5.8 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.10 (t, *J* = 8.8 Hz, 2H), 6.71 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.12 (d, *J* = 2.1 Hz, 1H), 3.38 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): 195.4, 164.0, 161.5, 153.6, 146.9, 134.7, 132.7, 132.6, 132.4, 132.3, 131.6, 127.8, 125.4, 116.0, 115.7, 113.0, 112.0, 105.9, 102.0, 55.2. HRMS (EI+) m/z calcd. for $C_{18}H_{14}FNO_2$: 295.1009; found: 295.1010.

(*E*)-2-(5-methoxy-1*H*-indole-3-yl)-3-(4-methoxyphenyl) acrylaldehyde (3r). Flash column chromatography eluent: petroleum ether/ethylacetate = 2/1, yellow solid, 52% yield (159 mg). ^{1}H NMR (DMSO-d_6, 400 MHz): 11.29 (s, 1H), 9.76 (s, 1H), 7.60 (s, 1H), 7.42 (d, *J* = 2.5 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 3H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.72 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.24 (d, *J* = 2.2 Hz, 1H), 3.71 (s, 3H), 3.42 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): 195.3, 160.8, 153.5, 149.1, 133.0, 132.5, 131.7, 128.2, 127.3, 125.9, 114.3, 112.9, 111.8, 106.5, 102.2, 55.9, 55.3. HRMS (EI+) m/z calcd. for $C_{19}H_{17}NO_3$: 307.1208; found: 307.1209.

(*E*)-2-(5-bromo-1*H*-indole-3-yl)-3-phenylacrylaldehyde (3s). Flash column chromatography eluent: petroleum ether/ ethylacetate = 2/1, orange solid, 45% yield (159 mg). ^{1}H NMR (DMSO-d_6, 400 MHz): 11.66 (s, 1H), 9.82 (s, 1H), 7.72 (s, 1H), 7.51 (d, *J* = 2.5 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 7.36-7.24 (m, 5H), 7.18 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.92 (d, *J* = 1.5 Hz, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz): 195.3, 149.8, 135.4, 135.3, 134.5, 130.4, 130.3, 128.9, 128.4, 127.4, 124.2, 122.4, 114.3, 112.0, 106.3. HRMS (EI+) m/z calcd. for $C_{17}H_{12}BrNO$: 325.0102; found: 325.0098.

(*E*)-2-(5-bromo-1*H*-indole-3-yl)-3-(4-hlorophenyl) acrylaldehyde (3t). Flash column chromatography eluent: petroleum ether/ ethylacetate = 3/1, orange solid in 47% yield (169 mg). ^{1}H NMR (DMSO-d_6, 400 MHz): 11.69 (s, 1H), 9.81 (s, 1H), 7.70 (s, 1H), 7.52 (d, *J* = 2.5 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 7.34 (s, 4H), 7.19 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.91 (d, *J* = 1.6 Hz, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz): 195.1, 147.9, 135.4, 134.9, 134.7, 134.3, 132.0, 129.0, 128.6, 127.2, 124.3, 122.4, 114.3, 112.2, 105.9. HRMS (EI+) m/z calcd. for $C_{17}H_{11}BrClNO$: 358.9713; found: 358.9714.

(*E*)-2-(5-nitro-1*H*-indole-3-yl)-3-(4-chlorophenyl) acrylaldehyde (**3u**). Flash column chromatography eluent: petroleum ether/ ethylacetate = 2/1, orange solid, 40% yield (131 mg). ^{1}H NMR (DMSO-d_6, 400 MHz): 12.19 (s, 1H), 9.84 (s, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.82 (s, 1H), 7.76 (s, 1H), 7.72 (s, 1H), 7.62 (d, *J* = 8.9 Hz, 1H), 7.34-7.31(m, 4H). ^{13}C NMR (DMSO-d_6, 101 MHz): 194.9, 148.9, 141.1, 139.9, 134.9, 134.2, 134.0, 132.0, 130.9, 129.1, 124.8, 117.2, 117.0, 113.0, 108.8. HRMS (EI+) m/z calcd. for $C_{17}H_{11}ClN_2O_3$: 326.0458; found: 326.0456

(*E*)-2-(5-methoxy-2-methyl-1*H*-indole-3-yl)-3-(2-nitrophenyl) acrylaldehyde (3v). Flash column chromatography eluent: petroleum ether/ ethylacetate = 1/1, orange solid, 68% yield (227 mg). ^{1}H NMR (DMSO-d_6, 400 MHz): 11.04 (s, 1H), 9.90 (s, 1H), 8.09-8.05 (m, 1H), 8.00 (s, 1H), 7.48-7.42 (m, 2H), 7.15 (d, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 6.56 (dd, *J* = 8.6, 1.4 Hz, 1H), 6.35 (s, 1H), 3.45 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): 194.9, 153.6, 147.8, 146.3, 137.8, 136.4, 133.9, 132.1, 130.8, 130.8, 130.3, 127.9, 124.9, 111.7, 110.7, 100.4, 100.3, 55.3, 12.9. HRMS (EI+) m/z calcd. for $C_{19}H_{16}N_2O_4$: 336.1110; found: 336.1109.

(*E*)-2-(2-phenyl-1*H*-indole-3-yl)-3-phenylacrylaldehyde (3w). Flash column chromatography eluent: petroleum ether/ ethylacetate = 5/1, orange solid in 36% yield (116 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): 9.74 (s, 1H), 8.88 (br, 1H), 8.09-8.05 (m, 1H), 7.53-7.49 (m, 2H), 7.41-7.38 (m, 2H), 7.36-7.31 (m, 5H), 7.26-7.22 (m, 1H), 7.18-7.12 (m, 2H), 7.07-7.05 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): 194.5, 149.5, 136.6, 136.1, 135.5, 133.9, 132.4, 131.7, 131.6, 128.7, 127.6, 126.8, 126.5, 123.7, 122.1, 119.5, 118.7, 111.6, 104.1. HRMS (EI+) m/z calcd. for $C_{23}H_{17}NO$: 323.1310; found: 323.1308.

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