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Copper-Catalyzed Three-Component Formal [3+1+2] Benzannulation for Carbazoles and Indoles Synthesis

Tenglong Guo,[†,§] Li Han,[‡,§] Tingpeng Wang,[†] Lan Lei,[‡] Jian Zhang*[,†] and Dezhu Xu*[,†]

[†] Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, People's Republic of China

[‡]Dalian University of Technology, Dalian 116024 (China)

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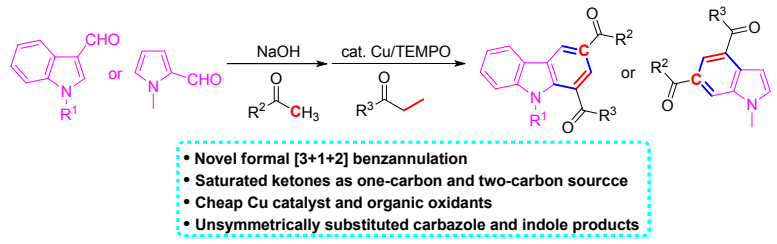


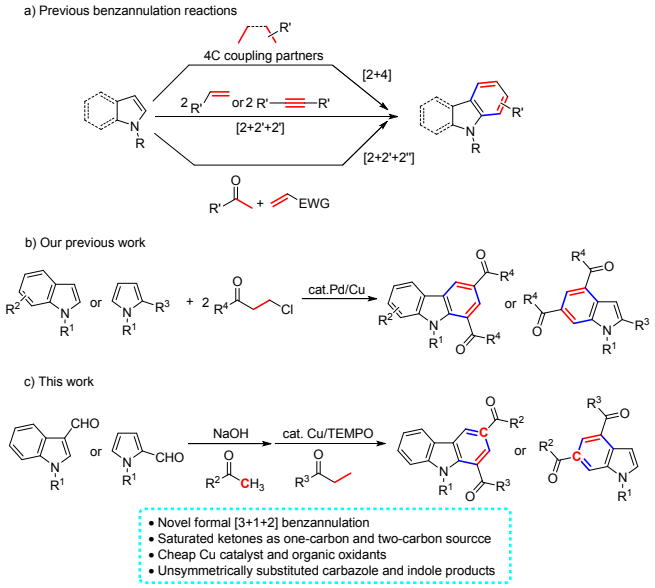
ABSTRACT: Three-component formal [3+1+2] benzannulation reactions of indole-3-carbaldehydes or 1-methyl-pyrrole-2-carbaldehydes with two different molecules of saturated ketones have been successfully developed under Cu-catalyzed and TEMPO-mediated conditions. Various unsymmetrically substituted carbazoles and indoles were obtained up to 95% yield. Furthermore, the resulting products exhibit unusual AIE properties in the solid state. This method features high atom-economy, cheap catalyst and oxidants, wide substrate scope and saturated ketones as one-carbon and two-carbon source, thus providing an efficient approach to polycyclic carbazole and indole compounds.

INTRODUCTION

Carbazoles and indoles are important nitrogen containing heterocycles because their structural core is omnipresent in natural products and biologically active compounds.[1] The recently known carbazole and indole syntheses are predominantly directed towards construction of a heterocyclic ring onto a prefunctionalized benzene precursor.[2] On the other hand, the alternative method which uses a heterocyclic ring as the "template"-like structure to establish a benzene ring onto it may provide a complementary and valuable strategy. In this aspect, indoles or pyrroles reacted with highly reactive coupling partners such as 1,4-dicarbonyl compounds[3] and their derivatives,[4] α-diazocarbonyl compounds,[5] biaryl compounds[6] through [2+4] annulation to afford the carbazole or indole products; [2+2′+2′] annulations of indoles or pyrroles with two molecules of alkene[7] or alkyne[8] in the presence of a transition-metal catalyst were also well established, allowing efficient synthesis of highly symmetric carbazoles and indoles; Meanwhile, [2+2′+2″] annulation, in which indoles coupled with two different molecules provide a concise method for the preparation of unsymmetrically substituted carbazoles derivatives (Scheme 1a).[9] Among these strategies, the [2+2′+2″] annulation was the most attractive method for carbazole synthesis since different substituents can be introduced in one-pot. However, to date, the productivity for creating molecular diversity has not yet to be fully displayed, very limited annulation reactions of pyrroles have been reported to synthesize unsymmetrically substituted indoles due to the poor regioselectivity and significant polymerization of the pyrrole substrates. Therefore, the development of

novel three-component synthetic methods for the unsymmetrically substituted carbazoles and indoles synthesis in green and efficient fashion is highly desirable.

Scheme 1. Indole-to-Carbazole and Pyrrole-to-Indole Transformation



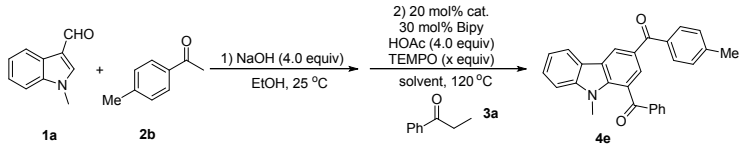
α,β-Unsaturated ketones are ubiquitous in bioactive compounds and regarded as versatile synthetic intermediates in the syntheses of fine chemicals, pharmaceuticals and materials.[10] Traditionally, approaches to access α,β-unsaturated ketones required multiple steps[11] or use of stoichiometric oxidants[12] and some substrates such as aryl vinyl ketones (enones) are hardly to prepare and isolate due to their poor stability and high reactivity. To overcome these problem, the one-pot reactions of in situ generated enones through catalytic dehydrogenation[13] or transition-metal-free α-Csp^3-H methylenation[14] of saturated ketones have been well developed in the recent years and provided efficient methods for the application of unstable enones. As an alternative route, our group utilized β-chloroalkyl aryl ketones as the precursors of enones to

realize the one-shot synthesis of carbazoles and indoles through [2+2′+2′] benzannulation of simple indoles[15a] and pyrroles[15b] (Scheme 1b). However, these reactions suffer from several shortcomings: 1) the requirements of expensive metal catalyst and excess metal oxidants; 2) the limited product structures, only highly symmetric carbazoles and 2-substituted indoles were obtained; 3) the poor atom-economy due to the dehydrochlorination of β-chloroalkyl aryl ketones. Intrigued by the advantages of utilizing in situ generated enones as olefin sources for the heterocycles synthesis, herein, we report a three-component formal [3+1+2] benzannulation reaction[16] for the synthesis of unsymmetrically substituted carbazoles and 1,2-unsubstituted indoles by using saturated ketones as one-carbon and two-carbon source (Scheme 1c).

RESULTS AND DISCUSSION

Initially, the adol reaction of 1-methyl-1H-indole-3-carbaldehyde (**1a**) with 4-methylacetophenone (**2b**) was conducted in EtOH at ambient temperature in the presence of NaOH (4.0 equiv), then the further one-pot, two-step reaction with propiophenone (**3a**) in chlorobenzene at 120 ^{o}C was chosen as a model system for the optimization studies by using 20 mol% $Cu(OAc)_2$ as catalyst, 30 mol% Bipy as ligand, TEMPO (3.0 equiv) as oxidant and HOAc as additives (Table 1, entry 1). The desired carbazole product **4e** was isolated in 87% yield. Encouraged by this exciting result we investigated several solvents i.e., DMF, DMSO, Toluene, EtOH (Table 1, entries 1-5). Chlorobenzene proved to facilitate the reaction. The reaction hardly occurred without

Table 1. Screening of Conditions[a]



entry	cat.	solvent	TEMPO (x equiv)	yield[b] (%)
1	$Cu(OAc)_2·H_2O$	chlorobenzene	3.0	87
2	$Cu(OAc)_2·H_2O$	DMF	3.0	80
3	$Cu(OAc)_2·H_2O$	DMSO	3.0	62
4	$Cu(OAc)_2·H_2O$	Toluene	3.0	57
5	$Cu(OAc)_2·H_2O$	EtOH	3.0	trace
6	-	chlorobenzene	3.0	NR
7	$CuCl_2·2H_2O$	chlorobenzene	3.0	93
8	CuCl	chlorobenzene	3.0	85
9	CuI	chlorobenzene	3.0	77
10	$FeCl_3$	chlorobenzene	3.0	NR
11	$CoCl_2$	chlorobenzene	3.0	NR
12[c]	$CuCl_2·2H_2O$	chlorobenzene	3.0	80
13	$CuCl_2·2H_2O$	chlorobenzene	-	NR
14	$CuCl_2·2H_2O$	chlorobenzene	2.0	77
15[d]	$CuCl_2·2H_2O$	chlorobenzene	3.0	67
16[e]	$CuCl_2·2H_2O$	chlorobenzene	3.0	10
17[f]	$CuCl_2·2H_2O$	chlorobenzene	3.0	95

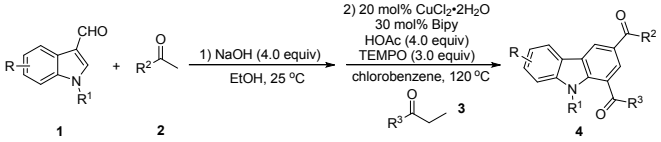
[a] Conditions: 1) **1a** (0.2 mmol), **2b** (0.4 mmol), NaOH (0.8 mmol), EtOH (2.0 mL), 24 h. 2) catalyst (0.04 mmol), Bipy (0.06 mmol), HOAc (0.8 mmol), TEMPO (0.6 mmol), **3a** (0.6 mmol), solvent (2.5 mL), air, 16 h, in oil bath. [b] Isolated yields. [c] $CuCl_2·2H_2O$ (0.02 mmol). [d] Without Bipy. [e] Without HOAc. [f] **3a** (0.4 mmol).

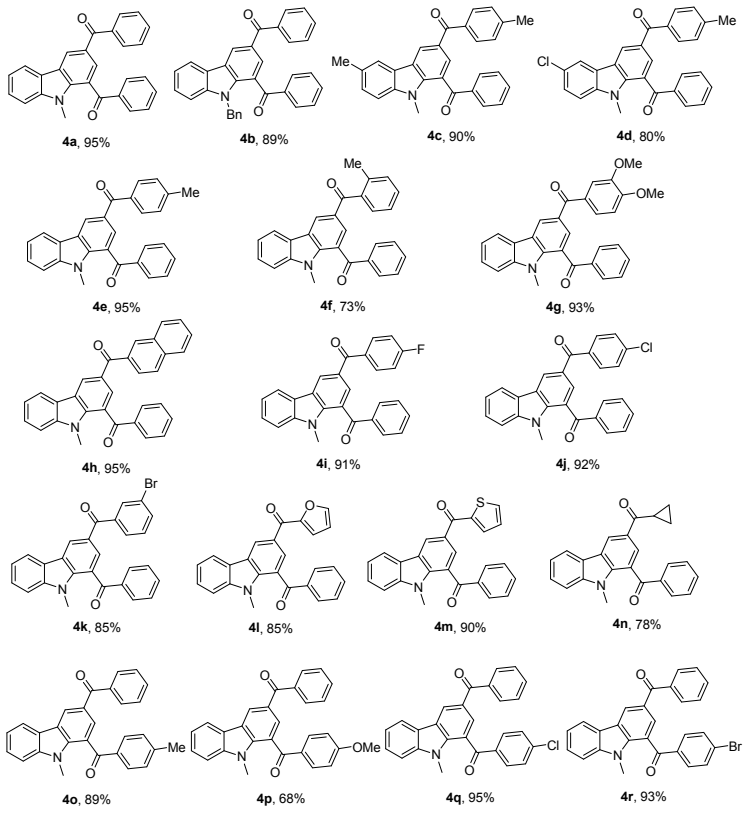
a catalyst (Table 1, entry 6). Among the screened copper catalysts, i.e., $Cu(OAc)_2$, CuCl, CuI, $CuCl_2 \cdot 2H_2O$ was found to be the most efficientive and 93% yield of the desired product was obtained (Table 1, entries 7-9). Other transition metals i.e., $FeCl_3$, $CoCl_2$ did not exhibited any catalytic activity (Table 1, entries 10 and 11). Decreasing the amount of catalyst to 0.1 equiv. led to 80% yield (Table 1, entry 12). No reaction occurred in the absence of TEMPO and the yield of **4e** decreased to 77% when TEMPO amount was reduced (Table 1, entries 13 and 14). Low yield (67%) was obtained without ligand (Table 1, entry 15). HOAc was acquired to neutralized NaOH to ensure the high yield of **4e** (Table 1, entry 16). To our delight, reducing the amount of **3a** had little impact on the reaction, the target product **4e** was achieved up to 95% yield (Table 1, entry 17).

Next, the protocol generality was investigated by reacting indole-3-carbaldehydes with various saturated ketones **2** and **3** (Table 2). The highly symmetric carbazole **4a** was obtained in 95% yield through the reaction of **1a** with acetophenone **2a** and propiophenone **3a**, which was more effective than our previous work (82% yield).[15a] Changing the *N*-R moiety in indoles from methyl to benzyl had a slight influence on the yield of **4b** (89%). The electron-donating methyl substituent on the aryl ring of the indole did not obviously affect the reaction efficiency as **4c** was obtained in 90% yield, whereas the electron-withdrawing chloro group lessened the formation of the desired products **4d** (80%). Aryl methyl ketones **2** bearing electron-donating methyl or methoxy substituent reacted with **1a** and **3a** to form the desired products **4e-g** in 73-93% yields, and the steric hindrance from a 2-methyl group on the aryl ring of **2c**

lessened the reaction efficiency, producing **4f** in 73% yield. The reaction of naphthyl or electron-withdrawing group substituted aryl methyl ketones also efficiently gave the desired products **4h-k** (85-95%). Heteroaryl methyl ketones underwent the same reactions to generate carbazoles **4l** (85%) and **4m** (90%), respectively. However, cyclopropyl methyl ketone exhibited a low reactivity, and its reaction with **1a** and **3a**

Table 2. One-pot three-component synthesis of carbazoles (4) [a,b]



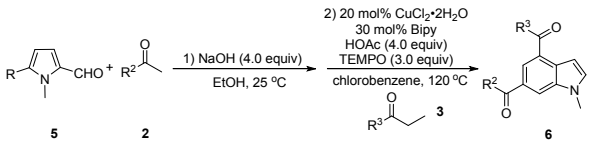


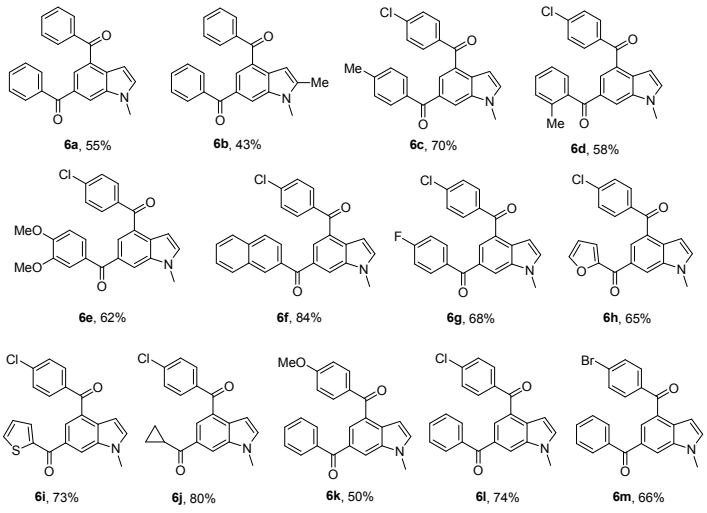
[a] Conditions: 1) **1** (0.2 mmol), **2** (0.4 mmol), NaOH (0.8 mmol), EtOH (2.0 mL), 25 °C. 2) $CuCl_2 \cdot 2H_2O$ (0.04 mmol), Bipy (0.06 mmol), HOAc (0.8 mmol), TEMPO (0.6 mmol), **3** (0.4 mmol), chlorobenzene (2.5 mL), 120 °C, air, 16 h, in oil bath. [b] Yields refer to the isolated products.

gave **4n** in 78% yield. Then different substituted aryl ethyl ketones **3** were also investigated. **1a** and **2a** reacted with aryl ethyl ketones bearing a substituent on the aryl moiety proceeded to form the target products **4o-r** in 68-95% yields. Strong electron-donating methoxy was detrimental to the reaction efficiency, giving the product **4p** only in 68% yield.

The substrate scope was further investigated by reacting 1-methyl-1H-pyrrole-2-carbaldehydes **5** with a variety of saturated ketone substrates **2** and **3** to synthesize 1,2-unsubstituted indoles (Table 3). Treatment of **5a** with acetophenone **2a** and propiophenone **3a** gave the desired highly symmetric indole **6a** in 55% yield which

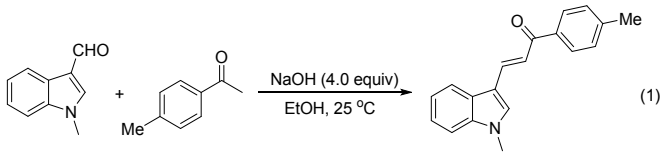
Table 3. One-pot three-component synthesis of indoles (6) [a,b]

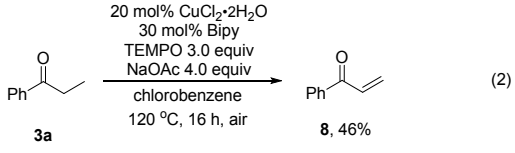




[a] Conditions: 1) **5** (0.2 mmol), **2** (0.4 mmol), NaOH (0.8 mmol), EtOH (2.0 mL), 25 °C. 2) $CuCl_2 \cdot 2H_2O$ (0.04 mmol), Bipy (0.06 mmol), HOAc (0.8 mmol), TEMPO (0.6 mmol), **3** (0.4 mmol), chlorobenzene (2.5 mL), 120 °C, air, 16 h, in oil bath. [b] Yields refer to the isolated products.

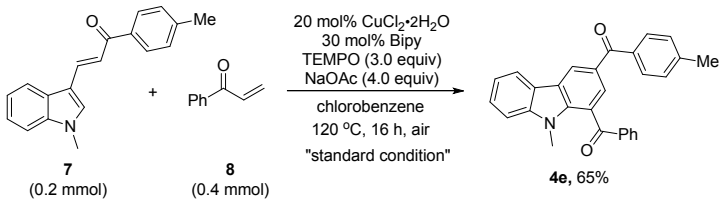
was much higher than that in our previous work (17% yield).[15b] The reaction of 1,5-dimethyl-1*H*-pyrrole-2-carbaldehyde (**5b**) only formed **6b** in 43% yield, exhibiting a negative electronic effect from the 2-substituent of the pyrrole backbone. The electron-donating substituents i.e., methyl and methoxy or electron-withdrawing substituents i.e., naphthyl, -F, -Br on the aryl rings of the aryl methyl ketone substrates **2** did not obviously affect the reaction efficiency and target products **6c**, **6e-g** were obtained in 62-84% yields. Increasing the steric hindrance of the aryl moiety in **2** by introducing methyl led to 58% yield of the corresponding products **6d**, which is attributed to the steric effect of the aryl moiety of **2**. The reaction also tolerated furyl and thienyl, yielding indole products **6h** (65%) and **6i** (73%), respectively. To our delight, cyclopropyl methyl ketone exhibited a high reactivity, giving **6j** in 80% yield. Methoxy, -Cl, -Br substituted propiophenones also smoothly reacted with **1a** and **2a** to afford products **6k** (50%), **6l** (74%) and **6m** (66%), respectively.





To investigate the mechanism of this reaction, adol reaction of **1a** and **2b** was conducted and suspended prior to the next step (eq 1). 3-Alkenylated indole **7** was isolated and characterized. Propiophenone **3a** was treated under the standard reaction conditions of the second step without other substrates, enone **8** was obtained in 46% yield (eq 2). To probe further into the reaction pathway of **7** with the in situ generated enone **8**, the controlled reaction of **7** with **8** was investigated (Scheme 2). Under the standard conditions as shown in Scheme 2, **4e** was formed in 65% yield lower than one-pot two-steps reaction, revealing that enone **8** was a key reaction intermediate and in situ generated enone was more efficient for carbazole synthesis. Without $CuCl_2 \cdot 2H_2O$ or TEMPO, the yield of **4e** slightly decreased to 57% and 58%, respectively. In the absence of $CuCl_2 \cdot 2H_2O$ and TEMPO, **4e** was still obtained in 45% yield. These results suggested that $CuCl_2 \cdot 2H_2O$ and TEMPO as added oxidants could promote the reaction.

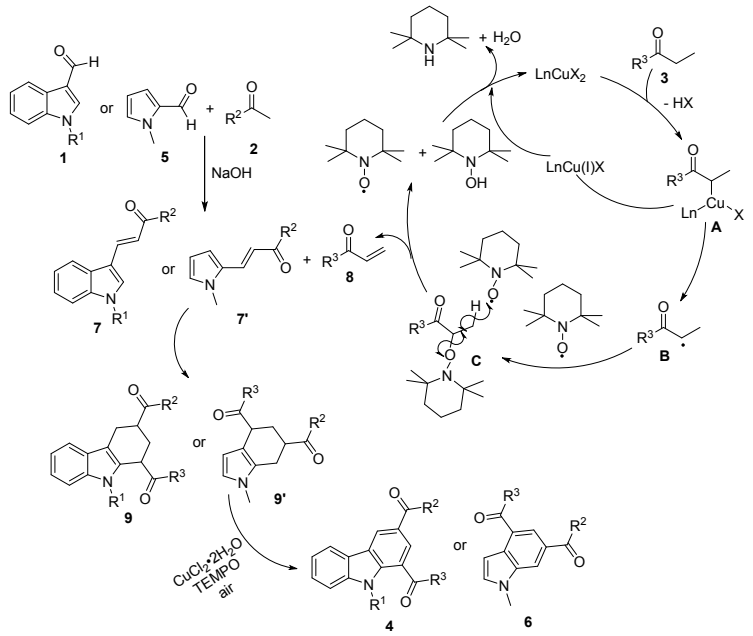
Scheme 2. Controlled reactions of 7 with 8



Based on the experimental results and aforementioned control experiments, a proposed mechanism for this transformation is illustrated in Scheme 3.[13b] Initially,

$CuCl_2 \cdot 2H_2O$ enolizes saturated ketone **3** to give complex **A** which undergoes homolytic bond cleavage to generate Cu(I) species and intermediate **B** which upon reaction with TEMPO produced α-TEMPO-substituted ketone, another molecule of TEMPO then abstracted β-hydrogen of α-TEMPO-substituted ketone to generate intermediate **C**, resulting in elimination of TEMPOH from **C** to form the desired enone **8**. Cu(I) species gets oxidized by TEMPO or TEMPOH to regenerate Cu(II) species. 3-Alkenylated indoles **7** or 2-alkenylated pyrroles **7'** are generated through the adol reactions of **1** or **5** with saturated ketones **2**. A Diels-Alder cycloaddition of enone **8** to **7** or **7'** forms tetrahydrocarbazole **9** or tetrahydroindole **9'**, which is subsequently oxidized to carbazoles **4** or indoles **6** by the Cu(II), TEMPO and air. In the reaction sequence, $CuCl_2 \cdot 2H_2O$ acts as a disfunctional agent: catalyst of in situ generated enone reaction and oxidant of benzannulation reaction.

Scheme 3. Proposed Mechanism



With the carbazoles **4** and indoles **6** in hand, a preliminary survey of their optical properties was carried out. To our delight, both products **4** and **6** displayed unusual aggregation-induced emission (AIE)[17] phenomenon in solid state, which were very different from the reported solvent fluorescence emission.[18,6c] The fluorescence spectra of **4g** and **6e** in solid state (as the representative examples) were outlined in Figure 1. The emission maximum of carbazoles **4** range from 425 to 440 nm. Otherwise indoles **6** displayed broader emissions with emission maximum from 425 to 535 nm, depending on the electronic properties of the substituent groups (see the Supporting Information for details). Owing to the unique AIE property, products **4** and **6** could be applied as promising materials in various fields such as fluorescence sensing and one- and two-photon bioimaging.[19]

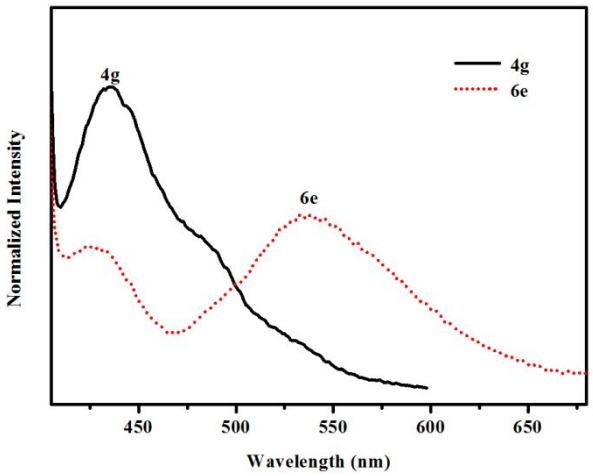


Figure 1. Fluorescence spectra of 4g and 6e in solid state.

In conclusion, a copper-catalyzed, TEMPO-mediated three-component formal [3+1+2] benzannulation reaction has been successfully developed for the synthesis of unsymmetrically substituted carbazoles and indoles by using saturated ketones as

one-carbon and two-carbon source. A one-pot two-step adol reaction/ dehydrogenation/Diels-Alder cycloaddition/aromatization sequence was established as the reaction pathway. Considering the wide availability of the starting materials, broad substrate scopes and high atom economy, the present method provides an attractive and novel route to unsymmetrically substituted carbazoles and indoles which are regarded as promising solid fluorescence materials for optoelectronics.

EXPERIMENTAL SECTION

General Considerations. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a Bruker DRX-400 spectrometer and all chemical shift values refer to $\delta_{TMS} = 0.00$ ppm or $CDCl_3$ ($\delta(^{1}H)$, 7.26 ppm; $\delta(^{13}C)$, 77.16 ppm). The HRMS analysis was obtained on a Waters GC-TOF CA156 mass spectrometer. Fluorescence emission spectra were measured on Agilent Cary Eclipse Fluorescence Spectrophotometer (MY16500004) in solid state at room temperature with excitation at 370 nm for all of the products. All the melting points were uncorrected. Analytical TLC plates, Sigma-Aldrich silica gel 60_{F200} were viewed by UV light (254 nm). Column chromatographic purifications were performed on SDZF silica gel 160. The starting substrates **1b**,[20a] **1c**,[20b] **1d**[20b] and **5b**[20c] were known compounds and prepared by the literature procedures. Products **4a**,[15a] **4b**,[15a] **4o**,[15a] **4q**,[15a] **6a**,[15b] **6b**,[15b] **7**[21a] and **8**[21b] were also known compounds and their spectroscopic features are in good agreement with those reported in the literatures. All of the other chemical reagents were purchased from commercial sources and used as received unless otherwise indicated.

Synthesis of 1-benzyl-1H-indole-3-carbaldehyde 1b: A mixture of 1H-indole-3-carbaldehyde (145 mg, 1.0 mmol) and KOH (168 mg, 3.0 mmol) in 5.0 mL DMSO was stirred at ambient temperature under an air atmosphere. Then (bromomethyl)benzene (340 mg, 2.0 mmol) was added. The reaction mixture was further stirred at room temperature and monitored by TLC. When 1H-indole-3-carbaldehyde was consumed completely, the reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60-90 ^oC) /EtOAc/CH_2Cl_2 = 10:1:2, v/v/v) to afford **1b** as a white solid (211 mg, 90%).

1-Benzyl-1H-indole-3-carbaldehyde (**1b**): 211 mg, 90% yield; white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1 H), 8.37-8.28 (m, 1 H), 7.72 (s, 1 H), 7.38 – 7.29 (m, 6 H), 7.19 (m, 2 H), 5.37 (s, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.8 (Cq, C=O), 137.6, 135.4, 125.64 and 118.64 (Cq each), 138.6, 129.3, 128.5, 127.4, 124.3, 123.2, 122.3, 110.5, 51.1.

A typical procedure for *N*-methylation of indoles and pyrrole– *Synthesis of **1c***: A mixture of 5-methyl-1H-indole-3-carbaldehyde (159 mg, 1.0 mmol) and KOH (168 mg, 3.0 mmol) in 4.0 mL DMF was stirred at ambient temperature under an air atmosphere. Then MeI (282 mg, 2.0 mmol) was added. The reaction mixture was further stirred at room temperature and monitored by TLC. When 5-methyl-1H-indole-3-carbaldehyde was consumed completely, the reaction mixture

was quenched with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60-90 ^oC) /EtOAc/CH_2Cl_2 = 10:3:2, v/v/v) to afford **1c** as a yellow solid (147 mg, 85%).

1,5-Dimethyl-1H-indole-3-carbaldehyde (**1c**): 147 mg, 85% yield; yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1 H), 8.22 (s, 1 H), 7.68 (s, 1 H), 7.30 (m, 2 H), 3.90 (s, 3 H), 2.59 (s, 3 H). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 184.50 (Cq, C=O), 139.5, 136.4, 132.8 and 117.7 (Cq each), 125.6, 125.5, 121.8, 109.6, 33.7, 21.5.

5-Chloro-1-methyl-1H-indole-3-carbaldehyde (**1d**): Following the general procedure, compound **1d** was obtained by column chromatography on silica gel (eluent: petroleum ether (60−90 °C)/EtOAc/CH_2Cl_2 = 10:3:2, v/v/v). 158 mg, 82% yield; white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.91 (d, J = 1.2 Hz, 1 H), 8.27 (s, 1 H), 7.65 (s, 1 H), 7.25 (m, 2 H), 3.85 (s, 3 H). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 184.3 (Cq, C=O), 136.3, 129.0, 126.2 and 117.5 (Cq each), 140.0, 124.5, 121.6, 111.0, 34.0.

1,5-Dimethyl-1H-pyrrole-2-carbaldehyde (**5b**): Following the general procedure, compound **5b** was obtained by column chromatography on silica gel (eluent: petroleum ether (60−90 °C)/EtOAc/CH_2Cl_2 = 10:3:2, v/v/v). 111 mg, 90% yield; yellow liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.37 (d, J = 3.0 Hz, 1 H), 6.78 (m, 1 H), 5.98 (d, J = 3.5 Hz, 1 H), 3.82 (s, 3 H), 2.22 (s, 3 H). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 178.5 (Cq, C=O), 140.6 and 131.8 (Cq each), 124.6, 109.6, 32.3, 12.1.

A typical procedure for the synthesis of carbazoles 4 – *Synthesis of **4e***: A mixture of 1-methyl-1H-indole-3-carbaldehyde (**1a**) (32 mg, 0.2 mmol), 4-methylacetophenone (**2b**) (54 mg, 0.4 mmol), and NaOH (32 mg, 0.8 mmol) in 2.0 mL EtOH was stirred at ambient temperature under an air atmosphere. When **1a** was consumed completely, HOAc (48 mg, 0.8 mmol) was added and EtOH was evaporated at 120 °C. $CuCl_2 \cdot 2H_2O$ (6.8 mg, 0.04 mmol), Bipy (9.4 mg, 0.06 mmol), TEMPO (94 mg, 0.6 mmol), propiophenone (**3a**) (54 mg, 0.4 mmol), and chlorobenzene (2.5 ml) was added to the mixture and stirred at 120 °C under an air atmosphere for 16 h. After cooled to ambient temperature, 10 mL CH_2Cl_2 was added and the resultant mixture was filtered through a short pad of celite, followed by rinsing with 20 mL CH_2Cl_2. The combined filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60-90 °C) /EtOAc/CH_2Cl_2 = 20:1:2, v/v/v) to afford **4e** as a white solid (76 mg, 95%).

(9-Methyl-9H-carbazole-1,3-diyl)bis(phenylmethanone) (**4a**): Following the general procedure, compound **4a** was obtained by column chromatography on silica gel (eluent: petroleum ether (60−90 °C)/EtOAc/CH_2Cl_2 = 20:1:2, v/v/v). 74 mg, 95% yield; pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$),. δ 8.76 (d, *J* = 1.6 Hz, 1 H), 8.16 (d, *J* = 7.8 Hz, 1 H), 8.04 (d, *J* = 1.6 Hz, 1 H), 7.98 (m, 2 H), 7.84 (m, 2 H), 7.64 (t, J = 7.4 Hz, 1 H), 7.58 (m, 2 H), 7.50 (m, 5 H), 7.35 (t, *J* = 7.4 Hz, 1 H), 3.69 (s, 3 H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.83 and 195.79 (Cq each, C=O), 142.6, 141.1, 138.4, 137.7, 127.5, 124.8, 122.7 and 122.4 (Cq each), 133.8, 132.1, 130.7,

129.9, 129.8, 128.8, 128.4, 127.3, 125.6, 120.8, 120.6, 109.6, 33.2.

(9-Benzyl-9H-carbazole-1,3-diyl)bis(phenylmethanone) (**4b**): Following the general procedure, compound **4b** was obtained by column chromatography on silica gel (eluent: petroleum ether (60−90 °C)/EtOAc/CH_2Cl_2 = 20:1:2, v/v/v). 81 mg, 89% yield; yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 0.9 Hz, 1 H), 8.22 (d, *J* = 7.8 Hz, 1 H), 7.86 (s, 1 H), 7.82 (d, *J* = 7.4 Hz, 2 H), 7.56 (m, 3 H), 7.48 (m, 5 H), 7.40 (m, 1 H), 7.29 (d, *J* = 7.7 Hz, 2 H), 6.91 (d, *J* = 7.1 Hz, 1 H), 6.86 (t, *J* = 7.3 Hz, 2 H), 6.65 (d, *J* = 7.4 Hz, 2 H), 5.61 (s, 2 H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.8 and 195.4 (Cq each, C=O), 143.0, 139.8, 138.2, 137.1, 135.7, 127.5, 125.4, 123.4 and 122.8 (Cq each), 133.0, 132.1, 130.4, 130.0, 129.8, 128.4, 128.3, 128.1, 127.5, 127.3, 126.9, 125.6, 121.1, 120.7, 109.9, 48.2.

(1-benzoyl-6,9-dimethyl-9H-carbazol-3-yl)(p-tolyl)methanone (**4c**): Following the general procedure, compound **4c** was obtained by column chromatography on silica gel (eluent: petroleum ether (60−90 °C)/EtOAc/CH_2Cl_2 = 20:1:2, v/v/v). 75 mg, 90% yield; white solid, m.p.: 168-170 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1 H), 8.02 (s, 1 H), 7.97 (m, 3 H), 7.76 (d, *J* = 7.8 Hz, 2 H), 7.63 (d, *J* = 7.4 Hz, 1 H), 7.51 (t, *J* = 7.6 Hz, 2 H), 7.36 (m, 2 H), 7.30 (d, *J* = 7.8 Hz, 2 H), 3.66 (s, 3 H), 2.55 (s, 3 H), 2.45 (s, 3 H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.0 and 195.7 (Cq each, C=O), 142.8, 141.3, 141.1, 137.9, 130.4, 135.8, 127.6, 124.6, 123.0 and 122.3 (Cq each), 133.8, 130.8, 130.3, 129.7, 129.1, 128.8, 128.7, 125.6, 120.6, 109.4, 33.3, 21.8, 21.5. HRMS Calcd for $C_{29}H_{24}NO_2$ $[M+H]^+$: 418.1807; Found: 418.1805.

(9-Benzyl-9H-carbazole-1,3-diyl)bis(phenylmethanone) (**4d**): Following the

general procedure, compound **4d** was obtained by column chromatography on silica gel (eluent: petroleum ether (60−90 °C)/EtOAc/CH_2Cl_2 = 20:1:10, v/v/v). 70 mg, 80% yield; white solid, m.p.: 256-259 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1 H), 8.13-8.04 (m, 2 H), 7.98 (d, *J* = 7.6 Hz, 2 H), 7.74 (d, *J* = 8.0 Hz, 2 H), 7.65 (t, *J* = 7.3 Hz, 1 H), 7.55-7.48 (m, 3 H), 7.38 (d, *J* = 8.7 Hz, 1 H), 7.30 (d, *J* = 7.9 Hz, 2 H), 3.68 (s, 3 H), 2.46 (s, 3 H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.7 and 195.4 (Cq each, C=O), 143.1, 141.4, 141.0, 137.6, 135.5, 128.2, 126.5, 123.9, 123.7 and 122.8 (Cq each), 134.0, 130.8, 130.2, 130.2, 129.2, 128.9, 127.4, 125.8, 120.4, 110.7, 33.4, 21.8. HRMS Calcd for $C_{28}H_{21}ClNO_2$ $[M+H]^+$: 438.1261; Found: 438.1265.

(1-Benzoyl-9-methyl-9H-carbazol-3-yl)(p-tolyl)methanone (**4e**): Following the general procedure, compound **4e** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/EtOAc/CH_2Cl_2 = 20:1:2, v/v/v). 76 mg, 95% yield; white solid, m.p.: 167-170 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1 H), 8.16 (d, *J* = 7.8 Hz, 1 H), 8.04 (s, 1 H), 7.99 (d, *J* = 7.7 Hz, 2 H), 7.77 (d, *J* = 7.9 Hz, 2 H), 7.64 (t, *J* = 7.4 Hz, 1 H), 7.54 (m, 3 H), 7.46 (d, *J* = 8.2 Hz, 1 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 7.30 (d, *J* = 7.9 Hz, 2 H), 3.68 (s, 3 H), 2.45 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.9 and 195.6 (Cq each, C=O), 142.9, 142.7, 141.1, 137.8, 135.7, 127.9, 124.8, 122.8 and 122.4 (Cq each), 133.8, 130.8, 130.3, 129.8, 129.1, 128.8, 127.3, 125.5, 120.8, 120.6, 109.6, 33.2, 21.7. HRMS Calcd for $C_{28}H_{22}NO_2$ $[M+H]^+$: 404.1651; Found: 404.1653.

(1-Benzoyl-9-methyl-9H-carbazol-3-yl)(o-tolyl)methanone (**4f**): Following the general procedure, compound **4f** was obtained by column chromatography on silica

gel (eluent: petroleum ether (60-90 °C)/EtOAc/CH_2Cl_2 = 20:1:2, v/v/v). 59 mg, 73% yield; white solid, m.p.: 139-141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1 H), 8.12 (d, *J* = 7.8 Hz, 1 H), 8.07 (m, 1 H), 7.97 (d, *J* = 7.4 Hz, 2 H), 7.65 (t, *J* = 7.4 Hz, 1 H), 7.54 (m, 3 H), 7.45 (d, *J* = 8.2 Hz, 1 H), 7.40 (m, 2 H), 7.35 (d, *J* = 7.4 Hz, 1 H), 7.30 (m, 2 H), 3.67 (s, 3 H), 2.37 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.5 and 195.8 (Cq each, C=O), 142.6, 141.4, 139.1, 137.7, 136.5, 128.0, 124.9, 122.8 and 122.6 (Cq each), 133.8, 131.1, 130.7, 130.1, 129.4, 128.8, 128.3, 127.3, 125.6, 125.3, 120.9, 120.6, 109.6, 33.2, 20.0. HRMS Calcd for $C_{28}H_{22}NO_2$ $[M+H]^+$: 404.1651; Found: 404.1651.

(1-Benzoyl-9-methyl-9H-carbazol-3-yl)(3,4-dimethoxyphenyl)methanone (**4g**): Following the general procedure, compound **4g** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/EtOAc/CH_2Cl_2 = 20:5:2, v/v/v). 83 mg, 93% yield; white solid, m.p.: 132-134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 1.6 Hz, 1 H), 8.15 (d, *J* = 7.8 Hz, 1 H), 7.98 (m, 3 H), 7.63 (m, 1 H), 7.56 (m, 1 H), 7.52 (m, 1 H), 7.49 (m, 2 H), 7.44 (m, 2 H), 7.33 (m, 1 H), 6.91 (d, *J* = 8.3 Hz, 1 H), 3.95 and 3.93 (s each, 3:3 H), 3.67 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.9 and 194.7 (Cq each, C=O), 152.7, 149.0, 142.6, 140.9, 137.8, 130.9, 128.1, 124.7, 122.7 and 122.3 (Cq each), 133.8, 130.7, 129.6, 128.8, 127.2, 125.3, 125.1, 120.8, 120.6, 112.4, 109.9, 109.6, 56.2, 56.1, 33.2. HRMS Calcd for $C_{29}H_{24}NO_4$ $[M+H]^+$: 450.1705; Found: 450.1702.

(3-(2-Naphthoyl)-9-methyl-9H-carbazol-1-yl)(phenyl)methanone (**4h**): Following the general procedure, compound **4h** was obtained by column chromatography on

silica gel (eluent: petroleum ether (60-90 °C)/EtOAc/CH_2Cl_2 = 20:1:5, v/v/v). 83 mg, 95% yield; white solid, m.p.: 161-163 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 1.4 Hz, 1 H), 8.34 (s, 1 H), 8.14 (d, *J* = 7.4 Hz, 2 H), 8.00 (m, 4 H), 7.92 (m, 2 H), 7.63 (d, *J* = 7.5 Hz, 1 H), 7.57 (m, 3 H), 7.51 (t, *J* = 7.7 Hz, 2 H), 7.46 (d, *J* = 8.3 Hz, 1 H), 7.34 (t, *J* = 7.4 Hz, 1 H), 3.70 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.75 and 195.73 (Cq each, C=O), 142.7, 141.2, 137.7, 135.7, 135.1, 132.3, 127.7, 124.9, 122.7 and 122.4 (Cq each), 133.8, 131.4, 130.7, 129.9, 129.4, 128.8, 128.3, 128.2, 127.9, 127.3, 126.8, 126.0, 125.6, 120.8, 120.6, 109.6, 33.2. HRMS Calcd for $C_{31}H_{22}NO_2$ $[M+H]^+$: 440.1651; Found: 440.1651.

(1-Benzoyl-9-methyl-9H-carbazol-3-yl)(4-fluorophenyl)methanone (**4i**): Following the general procedure, compound **4i** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/EtOAc/CH_2Cl_2 = 20:1:5, v/v/v). 74 mg, 91% yield; white solid, m.p.: 189-192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 1.3 Hz, 1 H), 8.15 (d, *J* = 7.8 Hz, 1 H), 7.99 (m, 3 H), 7.87 (m, 2 H), 7.64 (t, *J* = 7.4 Hz, 1 H), 7.54 (m, 3 H), 7.46 (d, *J* = 8.2 Hz, 1 H), 7.35 (t, *J* = 7.4 Hz, 1 H), 7.17 (t, *J* = 8.6 Hz, 2 H), 3.68 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.7 and 194.3 (Cq each, C=O), 165.2 (Cq, d, *J* = 252.0 Hz, *i*-C of C_6H_4F), 142.7, 141.1, 137.7 and 134.6 (Cq, d, *J* = 3.0 Hz, *p*-C of C_6H_4F) (Cq), 127.3, 124.8, 122.7, 122.5, 132.5 (CH, d, *J* = 8.9 Hz, *m*-C of C_6H_4F), 133.9, 130.7, 129.6, 128.8, 127.4, 125.4, 120.9, 120.6, 115.5 (CH, d, *J* = 21.7 Hz, *o*-C of C_6H_4F), 109.7, 33.2. ^{19}F NMR (100 MHz, $CDCl_3$) δ 106.6. HRMS Calcd for $C_{27}H_{19}FNO_2$ $[M+H]^+$: 408.1400; Found: 408.1398.

(1-Benzoyl-9-methyl-9H-carbazol-3-yl)(4-chlorophenyl)methanone (**4j**):

Following the general procedure, compound **4j** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/EtOAc/CH_2Cl_2 = 20:1:5, v/v/v). 78 mg, 92% yield; white solid, m.p.: 190-193 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, 1 H), 8.16 (d, *J* = 7.7 Hz, 1 H), 7.97 (m, 3 H), 7.78 (d, *J* = 8.5 Hz, 2 H), 7.65 (t, *J* = 7.4 Hz, 1 H), 7.57 (m, 1 H), 7.52 (t, *J* = 7.7 Hz, 2 H), 7.47 (m, 3 H), 7.36 (m, 1 H), 3.68 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.8 and 194.6 (Cq each, C=O), 142.7, 141.2, 138.5, 137.7, 136.8, 127.2, 124.9, 122.7 and 122.6 (Cq each), 134.0, 131.4, 130.8, 129.6, 128.9, 128.8, 127.5, 125.5, 121.0, 120.7, 109.7, 33.3. HRMS Calcd for $C_{27}H_{19}ClNO_2$ $[M+H]^+$: 424.1104; Found: 424.1107.

(1-Benzoyl-9-methyl-9H-carbazol-3-yl)(3-bromophenyl)methanone (**4k**): Following the general procedure, compound **4k** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/EtOAc/CH_2Cl_2 = 20:1:5, v/v/v). 79 mg, 85% yield; white solid, m.p.: 172-174 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 1.5 Hz, 1 H), 8.16 (d, *J* = 7.8 Hz, 1 H), 7.98 (m, 4 H), 7.74 (d, *J* = 7.7 Hz, 1 H), 7.70 (d, *J* = 8.0 Hz, 1 H), 7.65 (t, *J* = 7.4 Hz, 1 H), 7.55 (m, 3 H), 7.47 (d, *J* = 8.2 Hz, 1 H), 7.36 (t, *J* = 7.7 Hz, 2 H), 3.69 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.6 and 194.2 (Cq each, C=O), 142.8, 141.4, 140.4, 137.7, 126.8, 125.1, 122.7, 122.7 and 122.5 (Cq each), 135.0, 133.9, 132.7, 130.8, 130.0, 129.8, 128.9, 128.4, 127.5, 125.6, 121.1, 120.7, 109.8, 33.3. HRMS Calcd for $C_{27}H_{19}BrNO_2$ $[M+H]^+$: 468.0599; Found: 468.0595.

(1-Benzoyl-9-methyl-9H-carbazol-3-yl)(furan-2-yl)methanone (**4l**): Following the general procedure, compound **4l** was obtained by column chromatography on silica

gel (eluent: petroleum ether (60-90 °C)/EtOAc/CH_2Cl_2 = 20:5:2, v/v/v). 79 mg, 85% yield; yellow solid, m.p.: 168-170 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (m, 1 H), 8.24 (d, *J* = 1.5 Hz, 1 H), 8.19 (d, *J* = 7.8 Hz, 1 H), 7.99 (d, *J* = 7.5 Hz, 2 H), 7.68 (s, 1 H), 7.63 (t, *J* = 7.4 Hz, 1 H), 7.53 (m, 3 H), 7.43 (d, *J* = 8.2 Hz, 1 H), 7.34 (t, *J* = 7.4 Hz, 1 H), 7.29 (d, *J* = 3.5 Hz, 1 H), 6.58 (d, *J* = 1.8 Hz, 1 H), 3.65 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.7 and 181.2 (Cq each, C=O), 152.8, 142.6, 141.2, 137.8, 127.0, 124.9, 122.7 and 122.4 (Cq each), 146.7, 133.8, 130.7, 129.2, 128.8, 127.3, 124.8, 120.8, 120.5, 119.9, 112.2, 109.6, 33.2. HRMS Calcd for $C_{25}H_{18}NO_3$ $[M+H]^+$: 380.1287; Found: 380.1286.

(1-Benzoyl-9-methyl-9H-carbazol-3-yl)(thiophen-2-yl)methanone (**4m**): Following the general procedure, compound **4m** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/EtOAc/CH_2Cl_2 = 20:5:2, v/v/v). 71 mg, 90% yield; white solid, m.p.: 110-113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 1.6 Hz, 1 H), 8.19 (d, *J* = 7.7 Hz, 1 H), 8.11 (d, *J* = 1.5 Hz, 1 H), 8.00 (d, *J* = 7.4 Hz, 2 H), 7.72 (m, 2 H), 7.65 (t, *J* = 7.4 Hz, 1 H), 7.55 (m, 3 H), 7.46 (d, *J* = 8.2 Hz, 1 H), 7.36 (t, *J* = 7.4 Hz, 1 H), 7.18 (m, 1 H), 3.69 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.7 and 186.9 (Cq each, C=O), 143.8, 142.5, 140.9, 137.6, 127.9, 124.8, 122.6 and 122.4 (Cq each), 134.2, 133.7, 133.5, 130.6, 128.9, 128.7, 127.9, 127.2, 124.5, 120.7, 120.5, 109.5, 33.1. HRMS Calcd for $C_{25}H_{17}SNO_2$ $[M+H]^+$: 396.1058; Found: 396.1061.

(1-Benzoyl-9-methyl-9H-carbazol-3-yl)(cyclopropyl)methanone (**4n**): Following the general procedure, compound **4n** was obtained by column chromatography on

silica gel (eluent: petroleum ether (60-90 °C)/EtOAc/CH_2Cl_2 = 20:2:3, v/v/v). 55 mg, 78% yield; white solid, m.p.: 170-173 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 1.5 Hz, 1 H), 8.20 (t, 2 H), 7.98 (m, 2 H), 7.64 (t, 1 H), 7.58-7.48 (m, 3 H), 7.43 (d, *J* = 8.2 Hz, 1 H), 7.35 (t, 1 H), 3.64 (s, 3 H), 2.84-2.74 (m, 1 H), 1.30 (m, 2 H), 1.06 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.2 and 196.0 (Cq each, C=O), 142.7, 141.2, 137.9, 128.5, 124.9, 122.9 and 122.5 (Cq each), 133.8, 130.7, 128.9, 127.8, 127.2, 123.3, 120.8, 120.5, 109.6, 33.2, 17.1, 11.6. HRMS Calcd for $C_{24}H_{19}NO_2$ $[M+H]^+$: 354.1494; Found: 354.1492.

(3-Benzoyl-9-methyl-9H-carbazol-1-yl)(p-tolyl)methanone (**4o**): Following the general procedure, compound **4o** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/EtOAc/CH_2Cl_2 = 20:1:2, v/v/v). 72 mg, 89% yield; yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 1.6 Hz, 1 H), 8.15 (d, *J* = 7.8 Hz, 1 H), 8.03 (d, *J* = 1.6 Hz, 1 H), 7.86 (m, 4 H), 7.57 (m, 2 H), 7.49 (t, *J* = 7.5 Hz, 2 H), 7.45 (d, *J* = 8.2 Hz, 1 H), 7.33 (m, 3 H), 3.68 (s, 3 H), 2.45 (s, 3 H). ^{13}C{^{1}H} (100 MHz, $CDCl_3$) δ 195.9 and 195.7 (Cq each, C=O), 145.0, 142.7, 141.1, 138.6, 135.4, 127.7, 124.8, 122.9 and 122.8 (Cq each), 132.1, 130.9, 130.0, 129.6, 128.4, 127.3, 125.4, 120.8, 120.6, 109.6, 33.1, 21.9.

(3-Benzoyl-9-methyl-9H-carbazol-1-yl)(4-methoxyphenyl)methanone (**4p**): Following the general procedure, compound **4p** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/EtOAc/CH_2Cl_2 = 20:5:2, v/v/v). 57 mg, 68% yield; yellow solid, m.p.: 209-210 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 1.1 Hz, 1 H), 8.15 (d, *J* = 7.8 Hz, 1 H), 8.02 (d, *J* = 1.1 Hz, 1 H),

7.95 (d, *J* = 8.8 Hz, 2 H), 7.85 (d, *J* = 7.3 Hz, 2 H), 7.57 (m, 2 H), 7.50 (t, *J* = 7.5 Hz, 2 H), 7.45 (d, *J* = 8.2 Hz, 1 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 6.97 (d, *J* = 8.8 Hz, 2 H), 3.89 (s, 3 H), 3.68 (s, 3 H). $^{13}C\{^{1}H\}$ (100 MHz, $CDCl_3$) δ 196.0 and 194.7 (Cq each, C=O), 164.3, 142.6, 141.0, 138.6, 130.7, 129.3, 127.6, 124.7 and 122.8 (Cq each), 133.2, 132.1, 130.0, 128.4, 127.2, 125.3, 120.8, 120.6, 114.1, 109.6, 55.7, 33.0. HRMS Calcd for $C_{28}H_{22}NO_3$ $[M+H]^+$: 420.1600; Found: 420.1602.

(3-Benzoyl-9-methyl-9H-carbazol-1-yl)(4-chlorophenyl)methanone (**4q**): Following the general procedure, compound **4q** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/EtOAc/CH_2Cl_2 = 20:1:5, v/v/v). 80 mg, 95% yield; yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 1.6 Hz, 1 H), 8.15 (d, *J* = 7.8 Hz, 1 H), 8.02 (d, *J* = 1.6 Hz, 1 H), 7.92 (m, 2 H), 7.83 (m, 2 H), 7.63-7.54 (m, 2 H), 7.53-7.45 (m, 5 H), 7.35 (t, *J* = 7.4 Hz, 1 H), 3.68 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 195.7 and 194.5 (Cq each, C=O), 142.7, 141.1, 140.5, 138.4, 136.1, 127.6, 125.0, 122.8 and 122.0 (Cq each), 132.2, 132.1, 130.0, 129.7, 129.2, 128.5, 127.5, 125.9, 121.0, 120.7, 109.7, 33.3.

(3-Benzoyl-9-methyl-9H-carbazol-1-yl)(4-bromophenyl)methanone (**4r**): Following the general procedure, compound **4r** was obtained by column chromatography on silica gel (eluent: petroleum ether (60−90 °C)/EtOAc/CH_2Cl_2 = 20:1:5, v/v/v). 87 mg, 93% yield; yellow solid, m.p.: 174-176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1 H), 8.15 (d, *J* = 7.7 Hz, 1 H), 8.02 (s, 1 H), 7.84 (m, 4 H), 7.65 (m, 2 H), 7.58 (m, 2 H), 7.49 (dd, *J* = 3 H), 7.35 (t, *J* = 7.4 Hz, 1 H), 3.68 (s, 3 H). $^{13}C\{^{1}H\}$ (100 MHz, $CDCl_3$) δ 195.7 and 194.7 (Cq each, C=O), 142.7, 141.1, 138.4, 136.5,

129.3, 127.6, 124.9, 122.7 and 121.9 (Cq each), 132.2, 132.2, 130.0, 129.7, 128.4, 127.4, 125.9, 121.0, 120.7, 109.7, 33.3. HRMS Calcd for $C_{27}H_{19}BrNO_2$ $[M+H]^+$: 468.0599; Found: 468.0595.

Gram-scale experiment– *Synthesis of **4e:*** A mixture of 1-methyl-1H-indole-3-carbaldehyde (**1a**) (480 mg, 3.0 mmol), 4-methylacetophenone (**2b**) (675 mg, 5.0 mmol), and NaOH (480 mg, 12.0 mmol) in 30.0 mL EtOH was stirred at ambient temperature under an air atmosphere. When **1a** was consumed completely, HOAc (720 mg, 12.0 mmol) was added and EtOH was evaporated at 120 ^oC. $CuCl_2 \cdot 2H_2O$ (102 mg, 0.6 mmol), Bipy (141 mg, 0.9 mmol), TEMPO (1410 mg, 9.0 mmol), propiophenone (**3a**) (810 mg, 6.0 mmol), and chlorobenzene (50 ml) was added to the mixture and stirred at 120 ^oC under an air atmosphere for 24 h. After cooled to ambient temperature, 30 mL CH_2Cl_2 was added and the resultant mixture was filtered through a short pad of celite, followed by rinsing with 50 mL CH_2Cl_2. The combined filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60-90 ^oC) /EtOAc/CH_2Cl_2 = 20:1:2, v/v/v) to afford **4e** as a white solid (1.01 g, 84%).

A typical procedure for the synthesis of indoles 6 – *Synthesis of **6a***: A mixture of 1-methyl-1H-pyrrole-2-carbaldehyde (**5a**) (22 mg, 0.2 mmol), acetophenone (**2a**) (48 mg, 0.4 mmol), and NaOH (32 mg, 0.8 mmol) in 2.0 mL EtOH was stirred at ambient temperature under an air atmosphere. When **5** was consumed completely, HOAc (48 mg, 0.8 mmol) was added and EtOH was evaporated at 120 ^oC. $CuCl_2 \cdot 2H_2O$ (6.8 mg, 0.04 mmol), Bipy (9.4 mg, 0.06 mmol), TEMPO (94 mg, 0.6

mmol), propiophenone (**3a**) (54 mg, 0.4 mmol), and chlorobenzene (2.5 ml) was added to the mixture and stirred at 120 °C under an air atmosphere for 16 h. After cooled to ambient temperature, 10 mL CH_2Cl_2 was added and the resultant mixture was filtered through a short pad of celite, followed by rinsing with 20 mL CH_2Cl_2. The combined filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60-90 °C)/Et_2O/CH_2Cl_2 = 20:5:2, v/v/v) to afford **6a** as a yellow liquid (37 mg, 55%).

(1-Methyl-1H-indole-4,6-diyl)bis(phenylmethanone) (**6a**): Following the general procedure, compound **6a** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/Et_2O/CH_2Cl_2 = 20:5:2, v/v/v). 37 mg, 55% yield; yellow oil liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 and 7.91 (s each, 1:1 H), 7.83 (m, 4 H), 7.56 (m, 2 H), 7.47 (m, 4 H), 7.38 (d, J = 3.0 Hz, 1 H), 6.93 (d, J = 2.6 Hz, 1 H), 3.92 (s, 3 H). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 196.9 and 196.5 (Cq, C=O), 138.6, 138.4, 137.2, 131.2, 130.1 and 129.0 (Cq), 134.8, 132.5, 132.2, 130.2, 130.1, 128.4, 126.1, 115.9, 102.9, 33.4.

(1,2-dimethyl-1H-indole-4,6-diyl)bis(phenylmethanone) (**6b**): Following the general procedure, compound **6b** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/Et_2O/CH_2Cl_2 = 20:5:2, v/v/v). 30 mg, 43% yield; yellow oil liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1 H), 7.87 (s, 1 H), 7.81 (m, 4 H), 7.55 (t, J = 7.4 Hz, 2 H), 7.46 (m, 4 H), 6.76 (s, 1 H), 3.78 (s, 3 H), 2.50 (s, 3 H). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 197.0 and 196.5 (Cq, C=O), 144.2, 138.8, 138.6, 138.0, 131.1, 128.8 and 127.4 (Cq each), 132.3, 132.0, 130.1, 130.0,

128.3, 128.3, 126.6, 115.2, 102.2, 30.0, 13.3.

(4-(4-Chlorobenzoyl)-1-methyl-1H-indol-6-yl)(p-tolyl)methanone (**6c**): Following the general procedure, compound **6c** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/Et_2O/CH_2Cl_2 = 20:5:2, v/v/v). 54 mg, 70% yield; yellow oil liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 7.86 (d, *J* = 1.3 Hz, 1 H), 7.78 (m, 2 H), 7.73 (d, *J* = 8.1 Hz, 2 H), 7.43 (m, 2 H), 7.37 (d, *J* = 3.0 Hz, 1 H), 7.28 (d, *J* = 7.9 Hz, 2 H), 6.89 (m, 1 H), 3.91 (s, 3 H), 2.44 (s, 3 H). ^{13}C{^{1}H} (100 MHz, $CDCl_3$) δ 196.2 and 195.6 (Cq, C=O), 143.1, 138.9, 137.1, 136.9, 135.5, 130.8, 130.5 and 128.5 (Cq), 134.7, 131.6, 130.3, 129.1, 128.7, 125.7, 116.1, 102.7, 33.4, 21.8. HRMS Calcd for $C_{24}H_{19}ClNO_2$ $[M+H]^+$: 388.1104; Found: 388.1101.

(4-(4-Chlorobenzoyl)-1-methyl-1H-indol-6-yl)(o-tolyl)methanone (**6d**): Following the general procedure, compound **6d** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/Et_2O/CH_2Cl_2 = 20:5:2, v/v/v). 45 mg, 58% yield; yellow oil liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1 H), 7.86 (d, *J* = 1.1 Hz, 1 H), 7.76 (d, *J* = 8.5 Hz, 2 H), 7.43 (s, 1 H), 7.41 (s, 1 H), 7.36 (m, 3 H), 7.29 (d, *J* = 7.6 Hz, 1 H), 7.24 (m, 1 H), 6.88 (d, *J* = 2.9 Hz, 1 H), 3.89 (s, 3 H), 2.35 (s, 3 H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.2 and 195.5 (Cq, C=O), 139.1, 138.9, 137.2, 136.8, 136.7, 131.4, 130.5 and 128.8 (Cq), 135.2, 131.5, 131.2, 130.3, 128.7, 128.3, 125.7, 125.3, 116.0, 102.9, 33.5, 20.1. HRMS Calcd for $C_{24}H_{19}ClNO_2$ $[M+H]^+$: 388.1104; Found: 388.1110.

(4-(4-Chlorobenzoyl)-1-methyl-1H-indol-6-yl)(3,4-dimethoxyphenyl)methanone (**6e**): Following the general procedure, compound **6e** was obtained by column

chromatography on silica gel (eluent: petroleum ether (60-90 °C)/Et_2O/CH_2Cl_2 = 20:10:2, v/v/v). 54 mg, 62% yield; yellow solid, m.p.: 68-70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1 H), 7.83 (s, 1 H), 7.78 (d, *J* = 8.2 Hz, 2 H), 7.47 (s, 1 H), 7.42 (d, *J* = 8.3 Hz, 2 H), 7.37 (m, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 3.95 and 3.93 (s each, 3:3 H), 3.91 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.6 and 195.2 (Cq each, C=O), 152.9, 149.1, 138.9, 137.1, 136.9, 134.5, 130.6 and 128.5 (Cq each), 131.5, 130.8, 128.7, 125.6, 125.2, 115.9, 112.4, 109.9, 102.6, 56.20, 56.18, 33.4. HRMS Calcd for $C_{25}H_{21}ClNO_4$ $[M+H]^+$: 434.1159; Found: 434.1158.

(6-(2-Naphthoyl)-1-methyl-1H-indol-4-yl)(4-chlorophenyl)methanone (**6f**): Following the general procedure, compound **6f** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/Et_2O/CH_2Cl_2 = 20:5:5, v/v/v).71 mg, 84% yield; yellow solid, m.p.: 159-162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1 H), 8.17 (s, 1 H), 7.93 (m, 5 H), 7.80 (m, 2 H), 7.60 (m, 2 H), 7.40 (m, 3 H), 6.95 (m, 1 H), 3.92 (s, 3 H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.5 and 195.6 (Cq, C=O), 138.9, 137.2, 136.9, 135.6, 135.3, 132.4, 131.1, 130.5 and 128.6 (Cq), 134.9, 131.6, 131.6, 129.4, 128.8, 128.4, 128.4, 128.0, 127.0, 126.0, 125.8, 116.2, 102.8, 33.5. HRMS Calcd for $C_{27}H_{19}ClNO_2$ $[M+H]^+$: 424.1104; Found: 424.1101.

(4-(4-Chlorobenzoyl)-1-methyl-1H-indol-6-yl)(4-fluorophenyl)methanone (**6g**): Following the general procedure, compound **6g** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/Et_2O/CH_2Cl_2 = 20:5:2, v/v/v). 53 mg, 68% yield; yellow solid, m.p.: 56-58 °C. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.08 (s, 1 H), 7.85 (m, 3 H), 7.78 (d, *J* = 8.4 Hz, 2 H), 7.44 (d, *J* = 8.4 Hz, 2 H), 7.39 (d, *J* = 3.0 Hz, 1 H), 7.16 (t, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 3.0 Hz, 1 H), 3.92 (s, 3 H).^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.5 and 195.0 (Cq each, C=O), 165.4 (Cq, d, *J* = 252.3 Hz, *i*-C of C_6H_4F), 139.1, 137.1, 136.8, 134.5 (Cq, d, *J* = 3.1 Hz, *p*-C of C_6H_4F), 131.1, 130.1 and 100.1 (Cq), 134.9, 132.6 (CH, d, *J* = 9.0 Hz, *m*-C of C_6H_4F), 131.6, 128.8, 125.4, 115.8 (CH, d, *J* = 22.7 Hz, *o*-C of C_6H_4F), 115.5, 102.8, 33.5. ^{19}F NMR (100 MHz, $CDCl_3$) δ 106.2. HRMS Calcd for $C_{23}H_{16}ClFNO_2$ $[M+H]^+$: 392.0854; Found: 392.0855.

(4-(4-Chlorobenzoyl)-1-methyl-1H-indol-6-yl)(furan-2-yl)methanone (**6h**): Following the general procedure, compound **6h** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/Et_2O/CH_2Cl_2 = 20:10:2, v/v/v). 47 mg, 65% yield; yellow solid, m.p.: 170-173 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1 H), 8.14 (d, *J* = 1.3 Hz, 1 H), 7.80 (m, 2 H), 7.68 (d, *J* = 1.5 Hz, 1 H), 7.46 (m, 2 H), 7.38 (d, *J* = 3.0 Hz, 1 H), 7.27 (d, *J* = 3.5 Hz, 1 H), 6.89 (d, *J* = 3.0 Hz, 1 H), 6.60 (m, 1 H, furyl CH), 3.95 (s, 3 H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.6 and 181.8 (Cq, C=O), 152.9, 138.9, 137.2, 137.0, 131.1, 129.7 and 128.7 (Cq), 146.9, 134.9, 131.6, 128.7, 125.2, 120.2, 115.6, 112.4, 102.8, 33.5. HRMS Calcd for $C_{21}H_{15}ClNO_3$ $[M+H]^+$: 364.0740; Found: 364.0743.

(4-(4-Chlorobenzoyl)-1-methyl-1H-indol-6-yl)(thiophen-2-yl)methanone (**6i**): Following the general procedure, compound **6i** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/Et_2O/CH_2Cl_2 = 20:10:2, v/v/v). 55 mg, 73% yield; yellow solid, m.p.: 184-187 °C. ^{1}H NMR (400

MHz, $CDCl_3$) δ 8.16 (s, 1 H), 7.97 (s, 1 H), 7.80 (d, *J* = 8.3 Hz, 2 H), 7.69 (m, 2 H), 7.45 (d, *J* = 8.2 Hz, 2 H), 7.38 (d, *J* = 2.9 Hz, 1 H), 7.16 (t, *J* = 4.3 Hz, 1 H), 6.89 (d, *J* = 3.0 Hz, 1 H), 3.94 (s, 3 H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 195.6 and 187.6 (Cq, C=O), 143.8, 138.9, 137.2, 136.9, 130.9 and 130.7 (Cq), 134.7, 134.5, 134.0, 131.5, 128.8, 128.1, 124.8, 115.3, 102.7, 33.5. HRMS Calcd for $C_{21}H_{15}ClNO_2S$ $[M+H]^+$: 380.0512; Found: 380.0514.

(4-(4-Chlorobenzoyl)-1-methyl-1H-indol-6-yl)(cyclopropyl)methanone (**6j**): Following the general procedure, compound **6j** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/Et_2O/CH_2Cl_2 = 20:7:5, v/v/v). 54 mg, 80% yield; yellow solid, m.p.: 165-168 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1 H), 8.13 (s, 1 H), 7.78 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 8.3 Hz, 2 H), 7.34 (d, *J* = 2.9 Hz, 1 H), 6.82 (d, *J* = 2.9 Hz, 1 H), 3.92 (s, 3 H), 2.76-2.65 (m, 1 H), 1.27 (m, 2 H), 1.04 (m, 2 H). ^{13}C{^1H} NMR (100 MHz, $CDCl_3$) δ 199.8 and 195.7 (Cq each, C=O), 138.8, 137.3, 137.1, 131.1, 130.9 and 128.7 (Cq each), 134.8, 131.5, 128.7, 123.8, 113.9, 102.6, 33.4, 17.3, 11.8. HRMS Calcd for $C_{20}H_{17}ClNO_2$ $[M+H]^+$: 338.0948; Found: 338.0948.

(6-Benzoyl-1-methyl-1H-indol-4-yl)(4-methoxyphenyl)methanone (**6k**): Following the general procedure, compound **6k** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/Et_2O/CH_2Cl_2 = 20:10:2, v/v/v). 37 mg, 50% yield; yellow oil liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 7.84 (m, 5 H), 7.57 (t, 1 H), 7.48 (t, 2 H), 7.35 (d, *J* = 2.8 Hz, 1 H), 6.94 (d, *J* = 8.7 Hz, 2 H), 6.83 (d, *J* = 2.6 Hz, 1 H), 3.91 (s, 3 H), 3.87 (s, 3 H). ^{13}C{^1H}NMR (100 MHz, $CDCl_3$)

δ 196.7 and 195.5 (Cq, C=O), 163.4, 138.5, 137.1, 131.1, 130.2 and 129.8 (Cq), 134.4, 132.7, 132.2, 130.1, 128.4, 125.0, 115.4, 113.7, 102.7, 55.6, 33.4. HRMS Calcd for $C_{24}H_{19}NO_3$ $[M+H]^+$: 370.1443; Found: 370.1446.

(6-Benzoyl-1-methyl-1H-indol-4-yl)(4-chlorophenyl)methanone (**6l**): Following the general procedure, compound **6l** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/Et_2O/CH_2Cl_2 = 20:5:2, v/v/v). 55 mg, 74% yield; yellow oil liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 and 7.88 (s each, 1:1 H), 7.80 (m, 4 H), 7.59 (t, 1 H), 7.49 (t, 2 H), 7.43 (d, *J* = 8.2 Hz, 2 H), 7.39 (d, *J* = 2.9 Hz, 1 H), 6.90 (d, *J* = 2.9 Hz, 1 H), 3.92 (s, 3 H). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 196.4 and 195.6 (Cq, C=O), 139.0, 138.3, 137.2, 136.9, 131.0 and 130.2 (Cq), 134.9, 132.4, 131.6, 130.1, 128.7, 128.4, 125.8, 116.2, 102.8, 33.5. HRMS Calcd for $C_{23}H_{16}ClNO_2$ $[M+H]^+$: 374.0948; Found: 374.0943.

(6-Benzoyl-1-methyl-1H-indol-4-yl)(4-bromophenyl)methanone (**6m**): Following the general procedure, compound **6m** was obtained by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/Et_2O/CH_2Cl_2 = 20:5:5, v/v/v). 55 mg, 66% yield; yellow solid, m.p.: 141-144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1 H), 7.88 (d, *J* = 1.3 Hz, 1 H), 7.81 (m, 2 H), 7.71 (m, 2 H), 7.59 (m, 3 H), 7.49 (t, *J* = 7.5 Hz, 2 H), 7.39 (d, *J* = 3.1 Hz, 1 H), 6.90 (m, 1 H), 3.92 (s, 3 H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.5 and 195.8 (Cq, C=O), 138.4, 137.4, 137.2, 131.7, 131.1, 128.8 and 127.7 (Cq), 135.0, 132.5, 131.9, 131.8, 130.2, 128.5, 125.9, 116.3, 102.9, 33.6. HRMS Calcd for $C_{23}H_{17}BrNO_2$ $[M+H]^+$: 418.0443; Found: 418.0445.

Preparation of 3-alkenylated indole 7: A mixture of 1-methyl-1H-indole-3-

carbaldehyde (**1a**) (32 mg, 0.2 mmol), 4-methylacetophenone (**2b**) (54 mg, 0.4 mmol), and NaOH (32 mg, 0.8 mmol) in 2.0 mL EtOH was stirred at ambient temperature under an air atmosphere. When **1a** was consumed completely, the mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60-90 ^{o}C) /EtOAc/CH_2Cl_2 = 5:1:2, v/v/v) to afford **7** as a yellow solid (53 mg, 96%).

(E)-3-(1-Methyl-1H-indol-3-yl)-1-(p-tolyl)prop-2-en-1-one (**7**): 53 mg, 96% yield; yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 15.5 Hz, 1 H), 8.02 (m, 1 H), 7.98 (m, 2 H), 7.56 (d, *J* = 15.5 Hz, 1 H), 7.45 (s, 1 H), 7.39-7.28 (m, 5 H), 3.82 (s, 3 H), 2.44 (s, 3 H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.4 (Cq, C=O), 142.9, 138.4, 136.6, 126.3 and 113.2 (Cq), 138.3, 134.5, 129.3, 128.5, 123.2, 121.6, 120.9, 117.2, 110.2, 33.4, 21.8.

Preparation of enone intermediate 8: A mixture of $CuCl_2 \cdot 2H_2O$ (6.8 mg, 0.04 mmol), Bipy (9.4 mg, 0.06 mmol), TEMPO (94 mg, 0.6 mmol), NaOAc (66 mg, 0.8 mmol), and propiophenone (**3a**) (54 mg, 0.4 mmol) was stirred at 120 ^{o}C in 2.5 ml chlorobenzene under an air atmosphere for 16 h. After cooled to ambient temperature, 10 mL CH_2Cl_2 was added and the resultant mixture was filtered through a short pad of celite, followed by rinsing with 20 mL CH_2Cl_2. The combined filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60-90 ^{o}C) /EtOAc/CH_2Cl_2 = 30:1:2, v/v/v) to afford **8** as a yellow liquid (13 mg, 46%).

1-Phenylprop-2-en-1-one (**8**): 13 mg, 46% yield; yellow liquid. ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.95 (dt, *J* = 8.5, 1.7 Hz, 2 H), 7.62-7.53 (m, 1 H), 7.48 (m, 2 H), 7.16 (dd, *J* = 17.1, 10.6 Hz, 1 H), 6.44 (dd, *J* = 17.1, 1.7 Hz, 1 H), 5.93 (dd, *J* = 10.6, 1.7 Hz, 1 H).

A typical procedure for the reaction of 7 with 8 under the standard conditions: A mixture of **7** (56 mg, 0.2 mmol), **8** (53 mg, 0.4 mmol), $CuCl_2 \cdot 2H_2O$ (6.8 mg, 0.04 mmol), Bipy (9.4 mg, 0.06 mmol), TEMPO (94 mg, 0.6 mmol), NaOAc (66 mg, 0.8 mmol), and propiophenone (**3a**) (54 mg, 0.4 mmol) was stirred at 120 °C in 2.5 ml chlorobenzene under an air atmosphere for 16 h. After cooled to ambient temperature, 10 mL CH_2Cl_2 was added and the resultant mixture was filtered through a short pad of celite, followed by rinsing with 20 mL CH_2Cl_2. The combined filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60-90 °C) /EtOAc/CH_2Cl_2 = 20:1:2, v/v/v) to afford **4e** as a white solid (53 mg, 65%).

ASSOCIATED CONTENT

Supporting Information Available

NMR spectra of the products and fluorescence spectra of representative products. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: zhangjian@dicp.ac.cn (J. Z.)

dzxu@dicp.ac.cn (D. Z. X.)

Author Contributions

§These authors contributed equally (T. L. G. and L. H.)

ORCID

Tenglong Guo: 0000-0001-9117-0969

Li Han: 0000-0002-9304-551x

Jian Zhang: 0000-0002-5606-616x

Notes

The authors declare no competing financial interest.

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