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Metal-Free Activation of DMF by Dioxygen: A Cascade Multiple-Bond-Formation Reaction to Synthesize 3-Acylindoles from 2-Alkenylanilines

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Abstract: A cascade C-N, C-C and C-O multiple-bond-formation reaction to synthesize 3-acylindoles from 2-alkenylanilines with DMF (*N*,*N*-dimethylformamide) as a one-carbon synthon is described. This approach employed dioxygen as a terminal oxidant and oxygen donor, generally provided the 3-acylindoles in moderate to good yields. Moreover, the mechanistic investigation unambiguously revealed that the 2-carbon of 3-acylindole was derived from the *N*-methyl group of DMF.

Keywords: Dioxygen; 3-Acylindoles; DMF; Multiple-bond-formation reaction

The development of novel methods to synthesize complex compounds by employing simple and readily available starting materials remains a top goal in synthetic organic chemistry. As a common organic polar solvent, DMF (*N*,*N*-dimethylformamide) has attracted considerable attention as a multipurpose reagent in organic reactions.[1] For example, DMF can be used as a reaction precursor for cyanation,[2] amination,[3] formylation,[4] cycloaddition,[5] and other related reactions.[6] The utilization of DMF as a carbon source to realize cyclization reactions also has been investigated, especially mediated processes with transition-metal catalysts such as Pd, Cu, Ni, or Ru for the synthesis of nitrogen-containing heterocycles (Figure 1).[7] Although this is a powerful strategy and some successes have been achieved in this area, the activation of DMF under transition-metal-free conditions has rarely been documented.[5f, 8] Therefore, the development of new chemical transformations to replace these transition metals with more ecologically and economically favorable reagents is highly desirable. Additionally, as a highly atom-economical, low-cost and "green" oxidant, dioxygen combined with a metal (e.g., Pd and Cu) has been widely explored for versatile oxidative C-C, C-N and

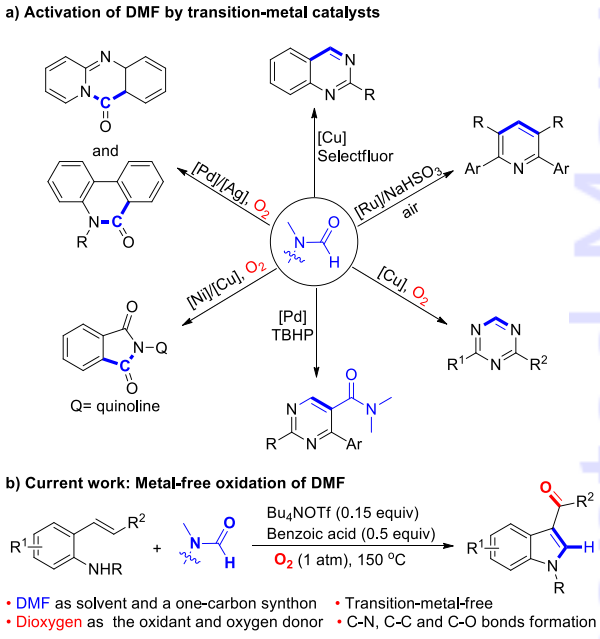
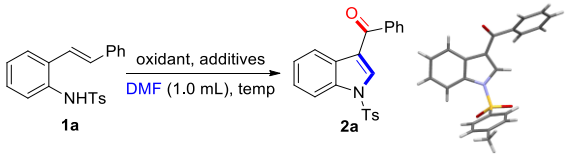


Figure 1. CH_3 group of DMF as a one-carbon synthon in cyclization reactions.

C-O bond formations in various aerobic reactions.[9] Consequently, designing a cascade reaction employing the activation of DMF by dioxygen under metal-free conditions for the synthesis of bioactive compounds has captured our interest. Herein, we report our success in achieving a cascade C-C, C-N and C-O bond-formation reaction to synthesize 3-acylindoles from 2-alkenylanilines through the activation of DMF using dioxygen as the sole oxidant.

Our optimization studies were initiated with (*E*)-4-methyl-*N*-(2-styrylphenyl) benzenesulfonamide (**1a**) as a model substrate for the cyclization reaction.

Table 1. Optimization of reaction conditions.[a]

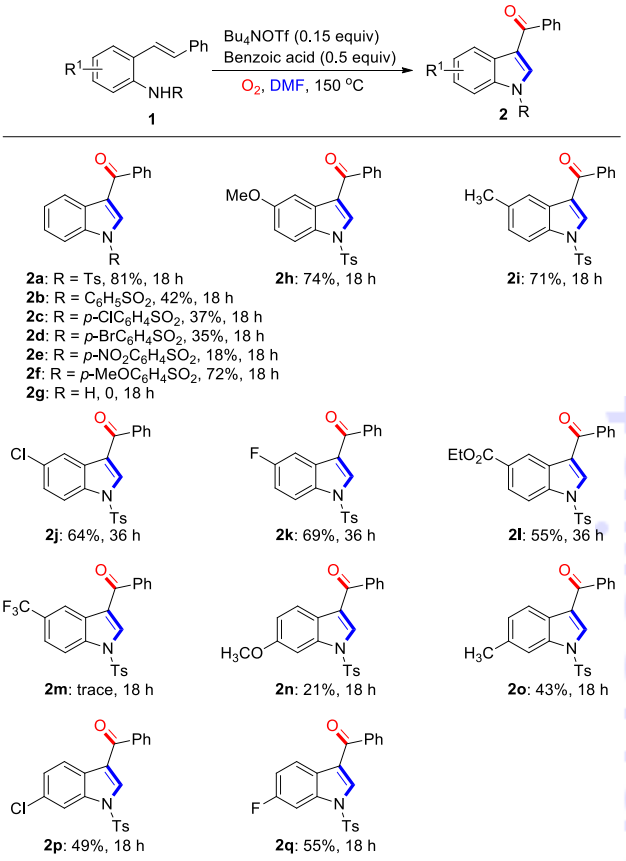


Entry	Oxidants	Temp. (°C)	Additives (equiv.)	Yield (%)[b]
1	O_2	125	---	43
2[c]	H_2O_2	125	---	Trace
3[d]	TBHP	125	---	N.D.[e]
4	Air	125	---	7
5[f]	-	125	---	0
6	O_2	150	---	57
7	O_2	170	---	23
8[g]	O_2	150	---	48
9[h]	O_2	150	---	42
10	O_2	150	Benzoic acid (0.5)	62
11	O_2	150	Bu_4NOTf (0.15)[i]	60
12	O_2	150	Bu_4NOTf (0.15)[j]	81
13	O_2	150	Bu_4NOTf (0.15)[k]	58
14	O_2	150	Bu_4NOTf (0.30)[j]	75
15	O_2	150	Bu_4NOAc (0.15)[j]	39
16	O_2	150	Bu_4NBr (0.15)[j]	37
17	O_2	150	Bu_4NOTf (0.15)[l]	13
18	O_2	150	Bu_4NOTf (0.15)[m]	Trace

[a] Reaction conditions: **1a** (0.20 mmol), 1 atm O_2 in DMF (1.0 mL) under heating conditions.
[b] Isolated yields.
[c] H_2O_2: 10.0 equiv.
[d] TBHP: 10.0 equiv.
[e] N.D. = Not detected.
[f] Reaction under 1 atm N_2.
[g] DMF: 2.0 mL.
[h] DMF: 0.5 mL.
[i] Bu_4NOTf = tetrabutylammonium trifluoromethanesulfonate.
[j] Benzoic acid (0.5 equiv).
[k] Benzoic acid (1.0 equiv).
[l] Pyromellitic acid (0.5 equiv).
[m] Citric acid (0.5 equiv).

When the reaction was performed in DMF (1.0 mL) at 125 °C under O_2 (1 atm), the annulation product **2a** was obtained in 43% yield (entry 1). The structure of **2a** was confirmed by X-ray crystallography.[10] However, other oxidants, including H_2O_2 and *t*-BuOOH, did not work well in this transformation (Table 1, entries 2 and 3). When the reaction was conducted in ambient air, the yield decreased significantly to 7% (Table 1, entry 4). In addition, no product was obtained after 36 h under N_2 atmosphere (Table 1, entry 5). The yield of **2a** increased to 57% while increasing the reaction temperature to 150 °C but sharply decreased to 23% when the temperature was further raised to 170 °C (Table 1, entries 6 and 7). Furthermore, increasing or decreasing the

Table 2. Scope of 2-alkenylanilines.[a]



[a] Reaction conditions: **1** (0.2 mmol), benzoic acid (0.1 mmol), Bu_4NOTf (0.03 mmol), O_2 (1 atm), DMF (1.0 mL, 0.2 M), isolated yields.

concentration did not provide any benefit to this reaction (Table 1, entries 8 and 9). Based on our previous report,[11] the addition of benzoic acid (0.5 equiv) or Bu_4NOTf (0.15 equiv) slightly promoted the reaction, approximately 60% yields of **2a** were provided (entries 10 and 11). The good yield was obtained by adding Bu_4NOTf possibly attributed to the solubility enhancement of the dioxygen during the reaction process.[12a] With our continuous efforts, the yield of **2a** finally reached to 81%, and the reaction could be completed within 18 h (Table 1, entry 12). Notably, the combination of 0.5 equiv. of benzoic acid and 0.15 equiv. of Bu_4NOTf was crucial for the transformation and afforded higher yields (Table 1, entries 12-14). The effects of other carboxylic acids and quaternary ammonium salts were also explored (Table 1, entries 15-18). However, none of them provided favorable results.

Under the optimized conditions, the scope of the substrates was explored (Table 2). Initially, the effect of different *N*-protecting groups on the 2-alkenylanilines was investigated. The 2-alkenylanilines containing tosyl groups and other sulfonamides with different substituents afforded the desired 3-acylindoles in 18-72% yields (Table 2, **2b-2f**). Unfortunately, the substrate with a primary amine group did not provide the target compound (Table 2, **2g**). The substrates with other substituent groups on

Table 3. Scope of 2-alkenylanilines.[a]

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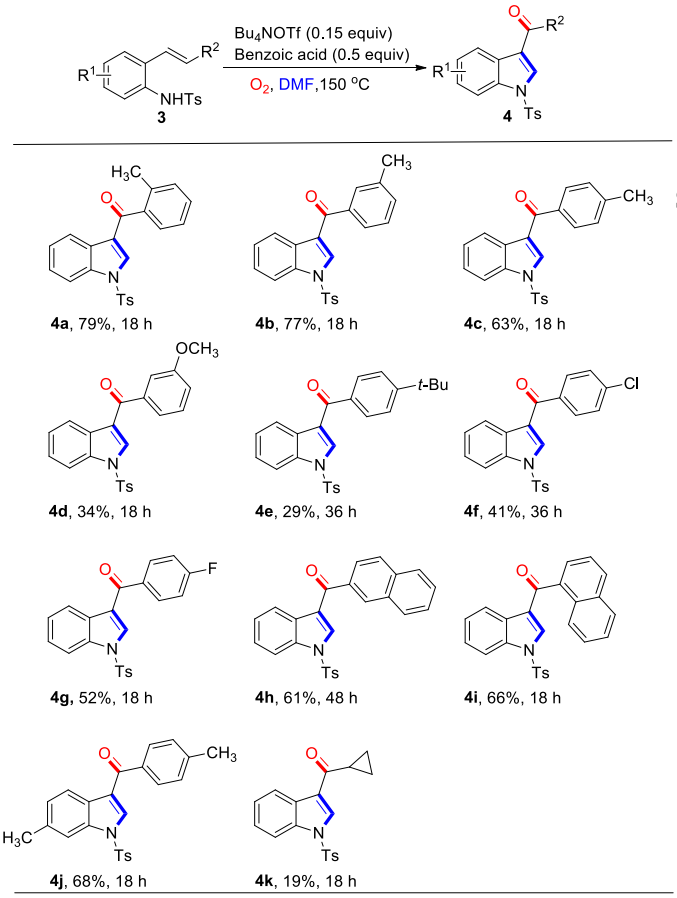
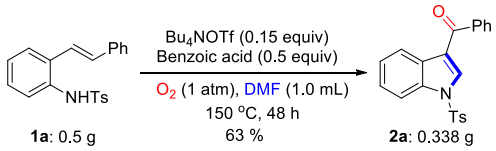
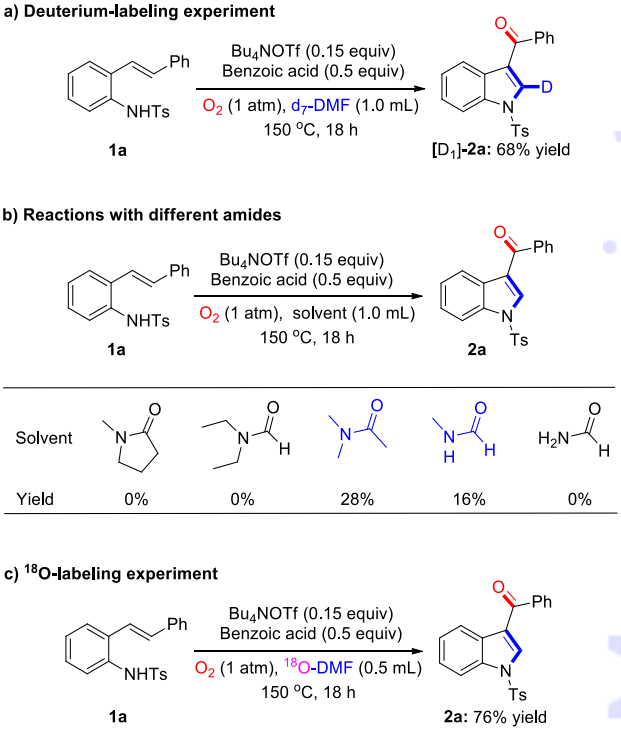


[a] Reaction conditions: **3** (0.2 mmol), benzoic acid (0.1 mmol), Bu_4NOTf (0.03 mmol), O_2 (1 atm), DMF (1.0 mL, 0.2 M), isolated yields.



Scheme 1. Gram-scale reaction.



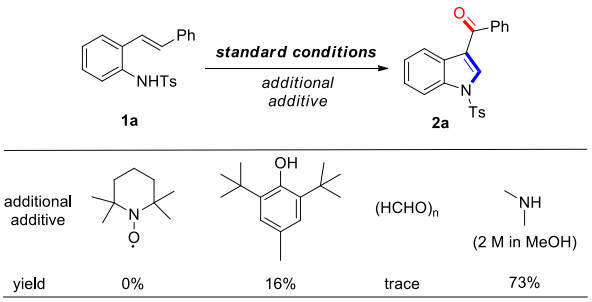
Scheme 2. Investigation of the mechanism.

the nitrogen atom such as acetyl, Cbz, phenyl and methyl were subjected to this optimal reaction conditions, no desired products could be obtained. On the other hand, the reaction exhibited good tolerance to various substituents on the aniline ring as described in Table 2. The anilines bearing electron-donating groups (*p*-OMe and *p*-Me) provided the corresponding products (**2h** and **2i**) in 74% and 71% yields. Not surprisingly, the yields decreased when the substrates were appended with electron-withdrawing groups (*p*-Cl and *p*-F), products **2j** and **2k** were isolated in 64% and 69% yields, respectively. A closer investigation revealed that a strong electron-withdrawing group (*p*-COOEt) could lead to a lower yield of **2l** in 55% yield. However, a CF_3 group appeared to retard the reaction, and only a trace amount of product was detected. In addition, the substrates bearing either electron-donating or electron-withdrawing groups at the *meta* position of the anilines were compatible with these reaction conditions. The corresponding products were formed in slightly lower yields (21-55%).

To further demonstrate the flexibility of this methodology, the effect of the substituent on the alkene moiety (Table 3) was investigated. Gratifyingly, the introduction of methyl, methoxy, *tert*-butyl and halogen groups on the phenyl ring of the 2-alkenylanilines was also tolerated. The reaction occurred smoothly to give the desired indoles (**4a**-**4g**) in 29-79% yields. Moreover, good yields (61% and 66%, Table 3, **4h** and **4i**) were obtained when 1-naphthyl and 2-naphthyl-substituted substrates were applied under the optimized conditions. Meanwhile, a substrate with two substituents was found to be suitable for this reaction and delivered the desired 3-acylindole in 68% yield (Table 3, **4j**). It should be noted that the cyclopropyl-substituted substrate was also successful. The product **4k** was uneventfully produced in 19% yield, and no ring-opening product was isolated.

In addition, to demonstrate the potential synthetic utility of this method, a gram scale reaction has been carried out using **1a** as the substrate under the developed conditions. The yield of the desired product was slightly decreased to 63% (Scheme 1).

To obtain insight into the mechanism of this transformation, several control experiments have been conducted. First, a deuterium-labeling experiment with d_7-DMF as the solvent was carried out. The deuterated product was obtained in 68% yield



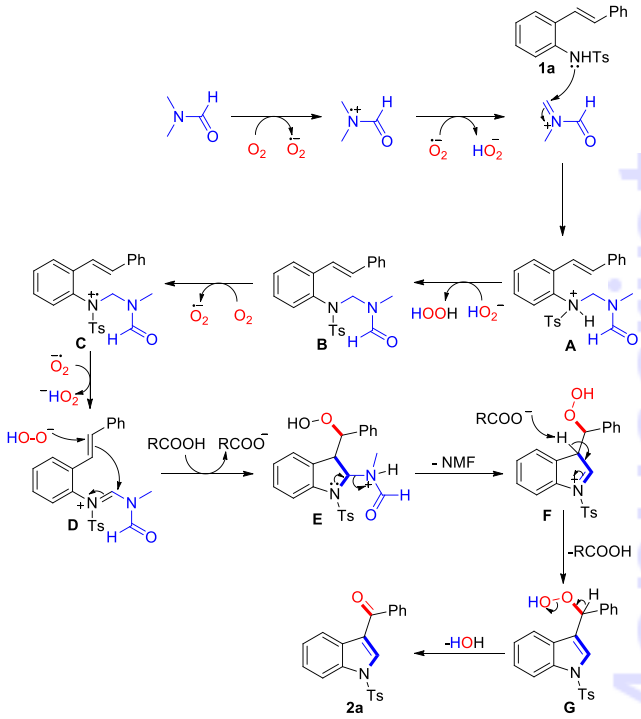
Scheme 3. Further exploration of the reaction mechanism.

(Scheme 2, a). Furthermore, five other amides were employed, the reaction could only proceed in *N*,*N*-dimethylacetamide and *N*-methylformamide (NMF) (Scheme 2, b). The results implied that the *N*-methyl group of DMF is the carbon source of the C-2 in the 3-acylindoles. Meanwhile, to explore the source of the oxygen atom in the resulting product, a reaction of **1a** has been carried out in ^{18}O-DMF under the optimized conditions (Scheme 2, c). Only 76% of ^{16}O-product **2a** was generated and the result has been confirmed by the HRMS spectra. (See Supporting Information for the details). Therefore, we reasoned that the dioxygen instead of DMF is the source of the oxygen atom in the product.

Further control experiments have been carried out to probe the mechanism (Scheme 3). There was no reaction in the presence of 1.0 equiv. of TEMPO. While using 1.0 equiv. of BHT (2,6-di-*tert*-butyl-4-methylphenol), 16% yield of the product could be obtained. In addition, no improvement of the yields was observed by using paraformaldehyde or dimethylamine as the additives. These results possibly suggest that the oxidation of DMF to the corresponding iminium ion is a two-step process. DMF is first oxidized to the nitrogen radical cation through single-electron transfer then further oxidized to the iminium ion.[12b,c]

Based on the above results and previous reports,[12] a possible mechanism is proposed as illustrated in Scheme 4. Initially, DMF is oxidized to the iminium ion, which is attacked by the electron pair of the nitrogen atom of **1a** to form intermediate **A**, and the peroxide anion is formed simultaneously. Then, the iminium ion is generated again under the oxygen atmosphere to form intermediate **D**. Subsequently, the addition of the peroxide anion to the alkene and intramolecular nucleophilic addition of the iminium ion occurred and formed intermediate **E**. With the aid of the carboxylic acid, the *N*-methyl formamide could be eliminated through C-N bond cleavage to form the iminium-cation intermediate **F**.[13] Finally, the desired product **2a** is generated through aromatization and oxidation.

In summary, we developed a cascade C-N, C-C and C-O multiple-bond-formation reaction to synthesize 3-acylindoles from 2-alkenylanilines with DMF as a one-carbon synthon through C-N bond cleavage, and a series of 3-acylindoles were afforded in moderate to good yields. Additionally, dioxygen played two functional roles as the terminal oxidant and oxygen supplier in the process. Furthermore, a series of verification experiments unambiguously revealed that the 2-carbon of the 3-acylindole was derived from the methyl group of DMF. A detailed mechanistic investigation and further application of this method are currently underway in our laboratory.



Scheme 4. A proposed mechanistic pathway.

Experimental Section

General Information

All reactions were performed in standard glassware. Solvents were distilled prior to use. All commercially available reagents were used as purchased without further purification. Flash column chromatography was performed over silica gel 200-300 mesh. Infrared spectra were measured on a FT/IR instrument. Melting points were determined with a micromelting point apparatus without corrections. High-resolution mass spectrometry (HRMS) was obtained on a Q-TOF microspectrometer. ^{1}H and ^{13}C NMR spectra were obtained on 600 MHz spectrometer (151 MHz for ^{13}C NMR) or 400 MHz spectrometer (100 MHz for ^{13}C NMR) at 25 °C, using $CDCl_3$ with TMS or residual solvent as standard unless otherwise noted. Chemical-shift values were given in ppm and referenced to the internal standard TMS (tetramethylsilane). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; dd, doublet of doublets, and br s, broad singlet. The coupling constants (*J*) are reported in hertz (Hz).

General procedure for synthesis of 3-acylindoles

To a 10 mL Schlenk tube with a stirring bar was added successively 2-alkeneanilines (**1** or **3**) (0.2 mmol, 1.0 equiv), benzoic acid (12.2 mg, 0.1 mmol, 0.5 equiv), tetrabutylammonium trifluoromethanesulfonate (11.7 mg,

0.03 mmol, 0.15 equiv) and DMF (1.0 mL). The tube was capped with a rubber septum, evacuated and backfilled with O_2 (1 atm), then the reaction mixture was stirred at 150 °C for the reported time. The resulting mixture was allowed to cool to room temperature and then directly purified by flash column chromatography on silica gel, eluting with EtOAc/petroleum ether (1:100 ~ 5:100, v/v) to afford the corresponding products **2** or **4**.

Phenyl(1-tosyl-1*H*-indol-3-yl)methanone (2a).[14] Reaction time: 18 h; 61 mg, 81% yield, white solid, mp 119-121 °C; R_f = 0.55 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.36 (s, 3H), 7.27 (d, J = 7.6 Hz, 2H), 7.43 (m, 2H), 7.56 (t, J = 7.4 Hz, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 7.0 Hz, 2H), 7.99 (d, J = 8.0 Hz, 1H), 8.02 (s, 1H), 8.31 (d, J = 8.1 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.6, 113.2, 120.4, 123.0, 124.9, 126.0, 127.2, 128.5, 128.7, 129.0, 130.2, 132.4, 133.6, 134.5, 135.0, 139.2, 145.9, 190.8; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}NNaO_3S$ $(M+Na)^+$ 398.0827, found 398.0828.

Phenyl(1-(phenylsulfonyl)-1*H*-indol-3-yl)methanone (2b).[15] Reaction time: 18 h; 26 mg, 36% yield, light yellow solid; mp 108-110 °C; R_f = 0.65 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.9 Hz, 2H), 7.55 (t, J = 7.8 Hz, 2H), 7.60 (t, J = 7.2 Hz, 1H), 7.65 (t, J = 7.2 Hz, 1H), 7.87 (d, J = 7.2 Hz, 2H), 7.92 (d, J = 7.8 Hz, 1H), 8.00 (d, J = 7.8 Hz), 8.03 (s, 1H), 8.31 (d, J = 7.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 113.2, 120.6, 123.0, 125.0, 126.1, 127.1, 128.5, 128.7, 129.1, 129.7, 132.5, 133.5, 134.6, 135.0, 137.5, 139.1, 190.9; HRMS (ESI) *m/z* calcd for $C_{21}H_{15}NNaO_3S$ $(M+Na)^+$ 361.0773, found 361.0769.

(1-((4-Chlorophenyl)sulfonyl)-1*H*-indol-3-yl)(phenyl)-methanone (2c). Reaction time: 18 h; 25 mg, 32% yield, white solid; mp 119-121 °C; R_f = 0.82 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (t, J = 9.0 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.56 (t, J = 7.8 Hz, 2H), 7.65 (t, J = 7.2 Hz, 1H), 7.86 (t, J = 8.4 Hz, 4H), 7.98 (d, J = 7.8 Hz, 1H), 8.00 (s, 1H), 8.31 (d, J = 7.8 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 113.1, 120.9, 123.2, 125.2, 126.2, 128.5, 128.6, 128.7, 129.0, 130.0, 132.5, 133.2, 134.9, 135.8, 139.0, 141.5, 190.7; HRMS (ESI) *m/z* calcd for $C_{21}H_{14}ClNNaO_3S$ $(M+Na)^+$ 418.0281, found 418.0289.

(1-((4-Bromophenyl)sulfonyl)-1*H*-indol-3-yl)(phenyl)-methanone (2d). Reaction time: 18 h; 34 mg, 39% yield, light yellow solid; mp 120-122 °C; R_f = 0.78 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.56 (t, J = 7.8 Hz, 2H), 7.62 (d, J = 9.0 Hz, 2H), 7.64 (t, J = 7.8 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 7.2 Hz, 2H), 7.97 (d, J = 8.4 Hz, 1H), 7.99 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 113.1, 121.0, 123.2, 125.2, 126.2, 126.6, 128.5, 128.6, 128.7, 129.0, 130.1, 132.5, 133.0, 133.2, 134.9, 136.4, 139.0, 190.7; HRMS (ESI) *m/z* calcd for $C_{21}H_{14}BrNNaO_3S$ $(M+Na)^+$ 461.9775, found 461.9779.

(1-((4-Nitrophenyl)sulfonyl)-1*H*-indol-3-yl)(phenyl)-methanone (2e). Reaction time: 18 h; 15 mg, 18% yield, white solid; mp 161-164 °C; R_f = 0.43 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.2 Hz, 1H), 7.57 (m, J = 7.2 Hz, 2H), 7.67 (t, J = 7.2 Hz, 1H), 7.87 (d, J = 7.2 Hz, 1H), 7.99 (s, 1H), 8.01 (d, J = 9.0 Hz, 1H), 8.10 (d, J = 7.8 Hz, 2H), 8.30 (d, J = 7.8 Hz, 1H), 8.32 (d, J = 9.0 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 113.0, 121.7, 123.4, 124.4, 124.9, 125.5, 126.6, 128.3, 128.4, 128.7, 128.8, 129.1, 132.7, 134.9, 138.8, 142.7, 151.0, 190.4; HRMS (ESI) *m/z* calcd for $C_{21}H_{14}N_2NaO_5S$ $(M+Na)^+$ 406.0623, found 406.0625.

(1-((4-Methoxyphenyl)sulfonyl)-1*H*-indol-3-yl)(phenyl)-methanone (2f). Reaction time: 18 h; 56 mg, 72% yield, white solid; mp 118-120 °C; R_f = 0.72 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.81 (s, 3H), 7.39 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.55 (t, J = 7.8 Hz, 2H), 7.64 (t, J = 7.2 Hz, 1H), 7.85 (d, J = 6.6 Hz, 2H), 7.87 (d, J = 4.8 Hz, 2H), 7.98 (d, J = 8.4 Hz, 1H), 8.03 (s, 1H), 8.31 (d, J = 7.8 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 55.8, 113.2, 114.8, 120.3, 123.0, 124.8, 125.9, 128.5, 128.68, 128.74, 129.0, 129.5, 132.4, 133.6, 134.9, 139.2, 164.4, 190.9; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}NNaO_4S$ $(M+Na)^+$ 414.0776, found 414.0779.

(5-Methoxy-1-tosyl-1*H*-indol-3-yl)(phenyl)methanone (2h). Reaction time: 18 h; 58 mg, 74% yield, white solid; mp 98-99 °C; R_f = 0.63 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.86 (s, 3H), 7.02 (dd, J = 2.4, 9.0 Hz, 1H), 7.55 (t, J = 7.8 Hz, 2H), 7.64 (t, J = 7.8 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 2.4 Hz, 1H), 7.86 (dd, J = 4.2, 7.2 Hz, 3H), 7.98 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.6, 55.7, 104.4, 114.1, 115.9, 120.2, 127.1, 128.7, 129.0, 129.55, 129.6, 130.2, 132.3, 134.1, 134.5, 139.2, 145.9, 157.7, 191.0; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}NNaO_4S$ $(M+Na)^+$ 428.0932, found 428.0925.

(5-Methyl-1-tosyl-1*H*-indol-3-yl)(phenyl)methanone (2i).[14] Reaction time: 18 h; 50 mg, 71% yield, white solid; mp 143-145 °C; R_f = 0.58 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.46 (s, 3H), 7.24 (d, J = 9.0 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.55 (t, J = 7.8 Hz, 2H), 7.64 (t, J = 7.8 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 3H), 7.97 (s, 1H), 8.12 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.4, 21.6, 112.8, 120.2, 122.7, 127.1, 127.4, 128.7, 128.7, 129.0, 130.2, 132.3, 133.3, 133.7, 134.5, 134.8, 139.3, 145.8, 191.0; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}NNaO_3S$ $(M+Na)^+$ 412.0983, found 412.0988.

(5-Chloro-1-tosyl-1*H*-indol-3-yl)(phenyl)methanone (2j). Reaction time: 18 h; 58 mg, 64% yield, white solid; mp 98-99 °C; R_f = 0.26 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.38 (s, 3H), 7.29 (d, J = 8.4 Hz, 1H), 7.38 (dd, J = 1.8, 8.4 Hz, 1H), 7.56 (t, J = 7.8 Hz, 2H), 7.65 (t, J = 7.2 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 7.2 Hz, 2H), 7.92 (d, J = 9.0 Hz, 1H), 8.03 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.7, 114.2, 119.8, 122.8, 126.4, 127.1, 128.8, 129.0, 130.4, 131.0, 132.6, 133.3, 134.4, 138.9, 146.3, 191.0; HRMS (ESI) *m/z* calcd for $C_{22}H_{16}ClNNaO_3S$ $(M+Na)^+$ 432.0437, found 432.0431.

(5-Fluoro-1-tosyl-1*H*-indol-3-yl)(phenyl)methanone (2k). Reaction time: 18 h; 54 mg, 69% yield, white solid; mp 97-101 °C; R_f = 0.73 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.37 (s, 3H), 7.14 (td, J = 9.0, 2.4 Hz, 1H), 7.27 (d, J = 7.2 Hz, 2H), 7.64 (t, J = 7.8 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 7.2 Hz, 2H), 7.93 (dd, J = 4.2, 9.0 Hz, 1H), 8.00 (dd, J = 2.4, 9.0 Hz, 1H), 8.05 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.7, 108.9 (d, J = 25.5 Hz), 114.1 (d, J = 31.5 Hz), 114.3 (d, J = 3.0 Hz), 120.1 (d, J = 3.0 Hz), 127.1, 127.8, 128.8, 129.0, 129.7 (d, J = 10.5 Hz), 130.3, 131.3, 132.5, 134.3, 134.8, 138.9, 146.2, 159.8 (d, J = 241.5 Hz), 190.5; HRMS (ESI) *m/z* calcd for $C_{22}H_{16}FNNaO_3S$ $(M+Na)^+$ 416.0733, found 416.0733.

Ethyl-3-benzoyl-1-tosyl-1*H*-indole-5-carboxylate (2l). Reaction time: 18 h; 49 mg, 55% yield, white solid; mp 133-135 °C; R_f = 0.52 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.40 (t, J = 7.2Hz, 3H), 2.37 (s, 3H), 4.40 (dd, J = 7.2, 14.4 Hz, 2H), 7.29 (d, J = 7.8 Hz, 2H), 7.56 (t, J = 7.8 Hz, 2H), 7.66 (t, J = 7.2 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 7.8 Hz, 2H), 8.02 (d, J = 9.0 Hz, 1H), 8.07 (s, 1H), 8.13 (dd, J = 0.6, 8.4 Hz, 1H), 8.99 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.4, 21.7, 61.1, 113.0, 120.6, 125.1, 127.2, 127.3, 127.4, 128.4, 128.8, 129.1, 130.4, 132.6, 134.2, 134.3, 137.4, 138.9, 146.3, 166.5, 190.3; HRMS (ESI) *m/z* calcd for $C_{25}H_{21}NNaO_5S$ $(M+Na)^+$ 470.1083, found 470.1089.

(6-Methoxy-1-tosyl-1*H*-indol-3-yl)(phenyl)methanone (2n). Reaction time: 10 h; 17 mg, 21% yield, yellow solid; mp 49-51 °C; R_f = 0.62 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.90 (s, 3H), 7.01 (dd, *J* = 2.4, 9.0 Hz, 1H), 7.28 (d, *J* = 9.6 Hz, 2H), 7.50 (d, *J* = 1.8 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.63 (t, *J* = 7.2 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.90 (s, 1H), 8.18 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.6, 55.8, 97.5, 113.7, 120.5, 122.2, 123.6, 127.1, 128.6, 129.0, 130.2, 132.3, 132.5, 134.5, 136.1, 139.2, 145.9, 158.7, 190.9; HRMS (ESI) *m/z* calcd for $C_{21}H_{15}NNaO_3S$ $(M+Na)^+$ 361.0773, found 361.0769.

(6-Methyl-1-tosyl-1*H*-indol-3-yl)(phenyl)methanone (2o). Reaction time: 18 h; 34 mg, 43% yield, white solid; mp 102-104 °C; R_f = 0.49 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.50 (s, 3H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.79 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.96 (s, 1H), 8.17 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.6, 22.0, 113.2, 120.4, 122.5, 126.2, 126.4, 127.1, 128.6, 129.0, 130.2, 132.3, 133.1, 134.7, 135.4, 136.3, 139.3, 145.8, 190.8; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}NNaO_3S$ $(M+Na)^+$ 412.0983, found 412.0986.

(6-Chloro-1-tosyl-1*H*-indol-3-yl)(phenyl)methanone (2p). Reaction time: 18 h; 34 mg, 49% yield, colorless oil; R_f = 0.63 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.38 (s, 3H), 7.29 (d, *J* = 9.6 Hz, 2H), 7.36 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 7.2 Hz, 2H), 8.00 (s, 1H), 8.01 (d, *J* = 1.8 Hz, 1H), 8.22 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.7, 113.4, 120.1, 123.9, 125.6, 127.1, 127.2, 128.8, 129.0, 130.4, 132.0, 132.6, 133.8, 134.2, 135.3, 138.9, 146.3, 190.5; HRMS (ESI) *m/z* calcd for $C_{22}H_{16}ClNNaO_3S$ $(M+Na)^+$ 432.0437, found 432.0433.

(6-Fluoro-1-tosyl-1*H*-indol-3-yl)(phenyl)methanone (2q). Reaction time: 18 h; 43 mg, 55% yield, white solid; mp 99-101 °C; R_f = 0.78 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.39 (s, 3H), 7.14 (td, *J* = 9.0, 2.4 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.70 (dd, *J* = 1.8, 9.0 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.99 (s, 1H), 8.27 (dd, *J* = 4.8, 8.4 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.7, 100.5 (d, *J* = 28.5 Hz), 113.3 (d, *J* = 23.9 Hz), 120.2, 124.1 (d, *J* = 9.7 Hz), 124.8, 127.2, 128.7, 129.0, 130.4, 132.5, 133.6 (d, *J* = 3.2 Hz), 134.2, 135.2 (d, *J* = 12.4 Hz), 139.0, 146.3, 160.6 (d, *J* = 244.5 Hz), 190.6; HRMS (ESI) *m/z* calcd for $C_{22}H_{16}FNNaO_3S$ $(M+Na)^+$ 416.0733, found 416.0739.

***o*-Tolyl(1-tosyl-1*H*-indol-3-yl)methanone (4a).** Reaction time: 18 h; 61 mg, 79% yield, white solid; mp 104-107 °C; R_f = 0.73 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.39 (s, 3H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.37 – 7.45 (m, 4H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.82 (s, 1H), 7.97 (d, *J* = 7.2 Hz, 1H), 8.36 (d, 7.2 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 19.8, 21.7, 113.2, 121.8, 123.1, 125.0, 125.5, 125.9, 127.2, 128.0, 128.1, 130.3, 130.4, 131.3, 134.5, 134.7, 135.1, 136.5, 139.4, 146.0, 193.2; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}NNaO_3S$ $(M+Na)^+$ 412.0983, found 412.0986.

***m*-Tolyl(1-tosyl-1*H*-indol-3-yl)methanone (4b).** Reaction time: 18 h; 60 mg, 77% yield, white solid; mp 105-108 °C; R_f = 0.76 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.45 (s, 3H), 7.23 (d, *J* = 9.0 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 2H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 7.8 Hz, 3H), 7.97 (s, 1H), 8.12 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.4, 21.6, 112.8, 120.2, 122.7, 127.1, 127.3, 128.6, 128.7, 129.0, 130.2, 132.3, 133.3, 133.7, 134.6, 134.8, 139.3, 145.8, 190.9; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}NNaO_3S$ $(M+Na)^+$ 412.0983, found 412.0982.

***p*-Tolyl(1-tosyl-1*H*-indol-3-yl)methanone (4c).** Reaction time: 18 h; 49 mg, 63% yield, white solid; mp 105-108 °C; R_f = 0.57 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.47 (s, 3H), 7.24 (d, *J* = 9.0 Hz, 2H), 7.36 (td, *J* = 1.2, 7.2 Hz, 1H), 7.40 (td, *J* = 1.2, 8.4Hz, 1H), 7.79 (m, 4H), 7.98 (d, *J* = 8.4 Hz, 1H), 8.02 (s, 1H), 8.27 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.6, 21.7, 113.2, 120.6, 123.0, 124.8, 125.9, 127.1, 128.6, 129.2, 129.4, 130.2, 133.2, 134.6, 135.0, 136.5, 143.2, 145.9, 190.5; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}NNaO_3S$ $(M+Na)^+$ 412.0983, found 412.0985.

(3-Methoxyphenyl)(1-tosyl-1*H*-indol-3-yl)methanone (4d). Reaction time: 18 h; 28 mg, 34% yield, white solid; mp 149-154 °C; R_f = 0.65 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.90 (s, 3H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 2H), 7.38 – 7.47 (m, 5H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.98 (d, *J* = 7.8 Hz, 1H), 8.05 (s, 1H), 8.30 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.7, 55.5, 113.2, 113.5, 118.8, 120.4, 121.6, 123.0, 124.9, 126.0, 127.2, 128.5, 129.7, 130.3, 133.7, 134.5, 135.0, 140.5, 146.0, 159.8, 190.6; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}NNaO_4S$ $(M+Na)^+$ 428.0932, found 428.0939.

(4-(*tert*-Butyl)phenyl)(1-tosyl-1*H*-indol-3-yl)methanone (4e). **R**eaction time: 18 h; 25 mg, 29% yield, white solid; mp 190-194 °C; R_f = 0.51 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.36 (s, 3H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.81 (dd, *J* = 8.4, 16.2 Hz, 4H), 7.98 (d, *J* = 8.4 Hz, 1H), 8.05 (s, 1H), 8.30 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.6, 31.2, 35.2, 113.2, 120.5, 123.0, 124.8, 125.7, 125.9, 127.1, 128.7, 129.1, 130.2, 133.3, 134.5, 135.0, 136.4, 145.9, 156.2, 190.5; HRMS (ESI) *m/z* calcd for $C_{26}H_{19}NO_3S$ $(M+Na)^+$ 454.1453, found 454.1456.

(4-Chlorophenyl)(1-tosyl-1*H*-indol-3-yl)methanone (4f). Reaction time: 18 h; 34 mg, 41% yield, white solid; mp 134-136 °C; R_f = 0.73 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.37 (s, 3H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.80 – 7.82 (m, 4H), 7.98 (d, *J* = 7.2 Hz, 1H), 7.99 (s, 1H), 8.26 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.7, 113.2, 120.2, 122.9, 124.9, 126.1, 127.2, 128.3, 129.0, 130.3, 130.4, 133.3, 134.4, 135.0, 137.5, 138.8, 146.0, 189.5; HRMS (ESI) *m/z* calcd for $C_{22}H_{16}ClNNaO_3S$ $(M+Na)^+$ 432.0437, found 432.0429.

(4-Fluorophenyl)(1-tosyl-1*H*-indol-3-yl)methanone (4g). Reaction time: 18 h; 41 mg, 52% yield, white solid; mp 139-141 °C; R_f = 0.76 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.36 (s, 3H), 7.22 (t, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.89 – 7.91 (m, 2H), 8.01 (s, 1H), 8.26 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.6, 113.2, 115.8 (d, *J* = 21.5 Hz), 120.3, 122.9, 124.9, 126.0, 127.2, 128.5, 130.3, 131.5 (d, *J* = 9.0 Hz), 133.2, 134.4, 135.0, 135.4 (d, *J* = 1.8 Hz), 146.0, 164.5 (d, *J* = 254.3 Hz), 189.2; HRMS (ESI) *m/z* calcd for $C_{22}H_{16}FNNaO_3S$ $(M+Na)^+$ 416.0733, found 416.0737.

Naphthalen-2-yl(1-tosyl-1*H*-indol-3-yl)methanone (4h). Reaction time: 36 h; 52 mg, 61% yield, light yellow solid; mp 83-85 °C; R_f = 0.56 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.37 (s, 3H), 7.25 (d, *J* = 6.0 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.40 – 7.45 (m, 2H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.57 (dd, *J* = 6.6, 14.4 Hz, 2H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.75 (d, 8.4 Hz, 2H), 8.85 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.98 – 7.99 (m, 1H), 8.05 (d, *J* = 8.4 Hz, 1H,), 8.18 (d, *J* = 8.4 Hz, 1H), 8.46 (dd, *J* = 2.4, 5.4 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.7, 113.2, 122.2, 123.2, 124.6, 125.0, 125.5, 126.0, 126.6, 127.16, 127.23, 127.26, 128.1, 128.5, 130.3, 130.6, 131.4, 134.3, 134.9, 135.1, 137.2, 146.0, 192.4; HRMS (ESI) *m/z* calcd for $C_{26}H_{19}NNaO_3S$ $(M+Na)^+$ 448.0983, found 448.0980.

Naphthalen-1-yl(1-tosyl-1*H*-indol-3-yl)methanone (4i). Reaction time: 70 h; 56 mg, 66% yield, light yellow solid; mp 74-76 °C; R_f = 0.55 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.37 (s, 3H), 7.25 (d, J = 7.2 Hz, 2H), 7.41 – 7.45 (m, 2H), 7.52 (t, J = 7.8 Hz, 1H), 7.57 (dd, J = 7.2, 14.4 Hz, 2H), 7.71 (d, J = 6.6 Hz, 1H), 7.75 (d, 8.4 Hz, 2H), 7.84 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.98 – 7.99 (m, 1H), 8.05 (d, J = 8.4 Hz, 1H,), 8.18 (d, J = 8.4 Hz, 1H), 8.46 (dd, J = 2.4, 5.4 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.7, 113.2, 122.3, 123.2, 124.6, 125.0, 125.5, 126.0, 126.6, 127.1, 127.22, 127.25, 128.2, 128.5, 130.2, 130.6, 131.4, 133.9, 134.4, 134.9, 135.1, 137.2, 146.0, 192.4; HRMS (ESI) *m/z* calcd for $C_{26}H_{19}NNaO_3S$ $(M+Na)^+$ 448.0983, found 448.0978.

(6-Methyl-1-tosyl-1*H*-indol-3-yl)(p-tolyl)methanone (4j). Reaction time: 18 h; 55 mg, 68% yield, white solid; mp 122-124 °C; R_f = 0.63 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.45 (s, 3H), 2.48 (s, 3H), 7.21 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 7.8 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 7.77 (dd, J = 4.8, 8.4 Hz, 4H), 7.85 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 8.09 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.4, 21.61, 21.64, 112.8, 120.4, 122.7, 127.1, 127.3, 128.8, 129.2, 129.3, 130.2, 133.25, 133.34, 134.6, 134.7, 136.6, 143.1, 145.8, 190.6; HRMS (ESI) *m/z* calcd for $C_{24}H_{21}NNaO_3S$ $(M+Na)^+$ 426.1140, found 426.1133.

Cyclopropyl(1-tosyl-1*H*-indol-3-yl)methanone (4k). Reaction time: 48 h; 13 mg, 19% yield, white solid; mp 159-161 °C; R_f = 0.75 (20% EtOAc/petroleum ether). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.03 (m, 2H), 1.25 (m, 2H), 2.36 (s, 1H), 2.50 (m, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.33 (m, 1H), 7.38 (m, 1H), 7.84 (d, J = 7.8 Hz, 2H), 7.93 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 7.2 Hz, 1H), 8.36 (s, 1H); ^{13}C NMRpp (151 MHz, $CDCl_3$) δ 11.0, 18.6, 21.7, 113.0, 122.1, 123.2, 124.8, 125.7, 127.2, 127.7, 130.2, 131.6, 134.6, 134.9, 145.9, 195.7; HRMS (ESI) *m/z* calcd for $C_{19}H_{17}NNaO_3S$ $(M+Na)^+$ 362.0287, found 362.0289.

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Metal-Free Activation of DMF by Dioxygen: A Cascade Multiple-Bond-Formation Reaction to Synthesize 3-Acylindoles from 2-Alkenylanilines

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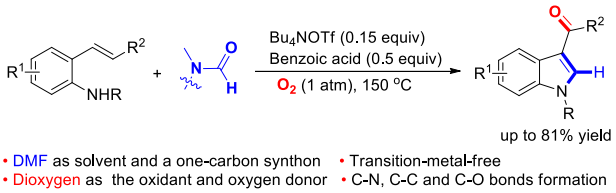

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