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Organocatalysis

Flavin/I_2-Catalyzed Aerobic Oxidative C–H Sulfenylation of Aryl-Fused Cyclic Amines

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Abstract: We report an aerobic oxidative C–H sulfenylation of aryl-fused cyclic amines with various thiols catalyzed by flavin/I_2 for the first time. While flavin **I** catalyzed the C–H sulfenylation of indolines to afford 3-sulfenylindoles, flavin **II** enabled transformations resulted in substitution at the position *para* to the *N* atom on the aryl ring to obtain 6-sulfenylquinolines. The advantages of this metal-free oxidative C–S coupling approach utilizing ambient oxygen as the terminal oxidant were that it was conducted under mild conditions with good atom-efficiency and excellent functional compatibility.

Introduction

Sulfur-containing heterocyclics are important scaffolds, widely applied in the field of materials science[1] and pharmaceuticals.[2] In particular, 3-sulfenylindoles and 6-sulfenylquinolines possess diverse biological activities. Selected examples include tubulin polymerization inhibitors (compound A and C),[3] anti-HIV reagent (compound B),[4] and PDE4 inhibitor (compound D, GSK-256066) that can be used to treat chronic obstructive pulmonary disease[5] and African trypanosomiasis[6] (Figure 1).

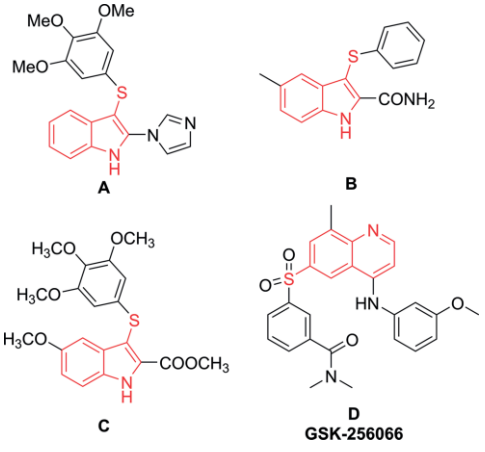
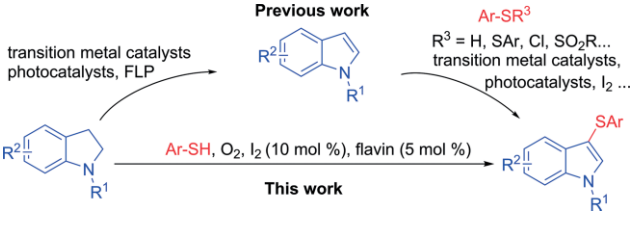


Figure 1. Selected bioactive 3-sulfenylindoles and 6-sulfenylquinolines.

In the past decades, many efforts were made to construct scaffolds related to these compounds, due to their interesting biological activities. Generally, the synthesis of 3-sulfenylindoles from indolines requires two steps: 1) dehydrogenation of indolines and 2) regioselective C–S coupling reaction of indoles. The dehydrogenation is mediated by stoichiometric amounts of oxidant (2-iodocybenzoic acid,[7] sulfur,[8] DEAD,[9] or SeO_2[10]), transition metal catalysts(Au,[11] Co,[12] Cu,[13] Fe,[14] Ir,[15] Pd,[16] Ru,[17] Rh,[18] or Zn[19]), or by using a photocatalyst[20] in the presence of oxygen. These methodologies have a good atomic economy, but require either expensive/environmentally unfriendly catalysts or harsh reaction conditions. In 2016, Paradies group[21] and Kanai group[22] used tris(pentafluorophenyl)-borane as a metal-free alternative to catalyze the dehydrogenation of N-heterocycles. However, this frustrated lewis pair (FLP) catalyzed dehydrogenative oxidation required high reaction temperature. Similarly, many different synthetic methods have been established for constructing 3-sulfenylindoles.[23] Nevertheless, most of them require acids,[24] bases,[25] transition-metals,[26] iodine,[27] or complex ligands,[28] and additionally harsh conditions. Moreover, thiolating agents, such as benzenesulfonyl chlorides,[29] disulfides,[25a,30] *N*-(thiophenyl)succinimide,[24,28b] and benzene sulfonhydrazide[31] generate stoichiometric amounts of by-products. Inspired by Murahashi[32] and Iida's[33] pioneering work on flavin catalysts as well as our ongoing research on C–H functionalization and heterocyclic chemistry,[34] herein, we demonstrate a single-step flavin/I_2 catalyzed



Scheme 1. General strategies for the synthesis of sulfenylindoles.

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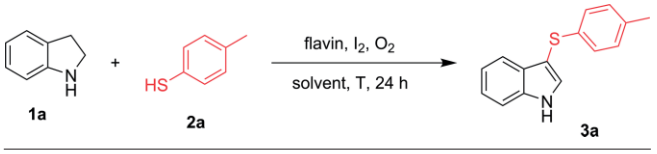
direct oxidation and sulfenylation of indolines using molecular oxygen as the only sacrificial reagent to synthesize 3-sulfenylindoles in one step. To the best of our knowledge, this environment friendly transformation is the first example to achieve dehydrogenation of indolines and their sulfenylation with thiophenols in a single step (Scheme 1).

Results and Discussion

First, the reaction conditions for oxidative C–H sulfenylation of indoline **1a** with 4-methylbenzenethiol **2a** were screened (Table 1). The reactions were performed using **1a** (0.5 mmol), **2a** (0.5 mmol), iodine (10 mol-%), and different flavins (5 mol-%), under oxygen atmosphere at 60 °C for 24 h (entries 1–6). Among these flavin derivatives, flavin **I** (Figure 2) showed the best results of 71 % yield for the synthesis of 3-(*p*-tolylthio)-1*H*-indole **3a** (entry 1). Next, different solvents were screened, in which solvents such as MeCN, DMF, DCE, and DMA gave **3a** in low yields (entries 7–10). Changes in reaction temperature to 80 °C and 40 °C decreased the yield of **3a** to 38 % and 40 %, respectively (entries 11–12). Furthermore, the reaction in aerobic environment (entry 13) or with lower catalyst loading (entry 14) also resulted in low efficiency. Remarkably, when 1.2 equiv. of **1a** was used, the yield could be successfully increased to 91 %, due to the improved conversion rate of **2a** (entry 15). In the absence of iodine or oxygen, this oxidative sulfenylation hardly occurred (entries 16 and 17). Thus, the optimized reaction conditions were found to be **1a** (0.6 mmol), **2a** (0.5 mmol), flavin **I** (5 mol-%), I_2 (10 mol-%), and DMSO (1 mL) under O_2 (1 atm) at 60 °C for 24 h.

Table 1. Optimization of reaction conditions.[a]



Entry	solvent	flavin	temperature [°C]	yield [%]
1	DMSO	I	60	71
2	DMSO	II	60	/
3	DMSO	III	60	trace
4	DMSO	IV	60	trace
5	DMSO	V	60	trace
6	DMSO	VI	60	63
7	MeCN	I	60	50
8	DMF	I	60	55
9	DCE	I	60	6
10	DMA	I	60	39
11[b]	DMSO	I	40	38
12[b]	DMSO	I	80	40
13[b,c]	DMSO	I	60	68
14[b,d]	DMSO	I	60	21
15[e]	**DMSO**	**I**	**60**	**91**
16[e,f]	DMSO	I	60	trace
17[e,g]	DMSO	I	60	trace

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), flavin (5 mol-%), I_2 (10 mol-%), and DMSO (1 mL) under O_2 (1 atm) at 60 °C for 24 h. [b] **1a** (0.5 mmol), **2a** (0.75 mmol). [c] Open air. [d] Flavin (3 mol-%), I_2 (5 mol-%). [e] **1a** (0.6 mmol), **2a** (0.5 mmol). [f] No I_2. [g] Under N_2 protection.

With optimal reaction conditions in hand, the scope of thiophenols with indoline **1a** was investigated (Table 2). To our delight, different electron-donating (Me, OMe, and Ph) and electron-withdrawing groups (F, Cl, Br, and CF_3) at different positions of thiophenol were all well tolerated, giving desired products in 77–92 % yields (**3a**–**3f** and **3h**–**3l**). Bulky substrate like naphthalene-2-thiol could also form the corresponding

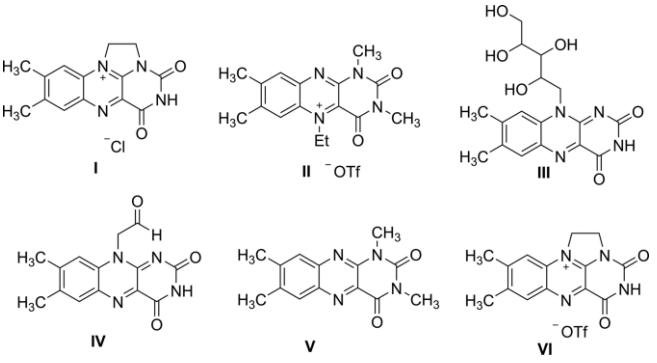
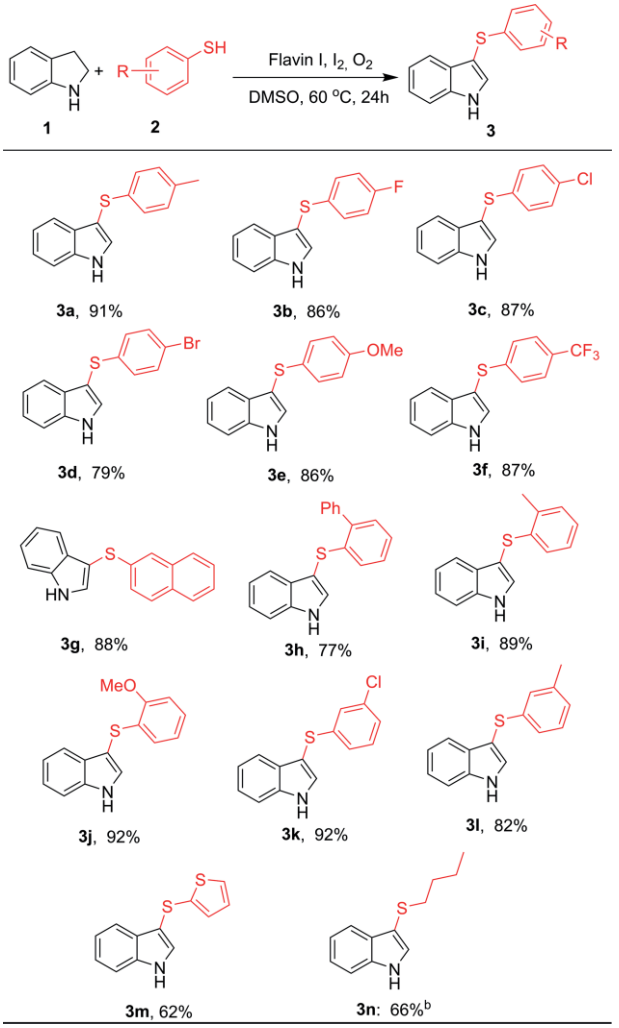


Figure 2. Structures of flavins and flavinium salts.

Table 2. Scope of thiophenols.[a]

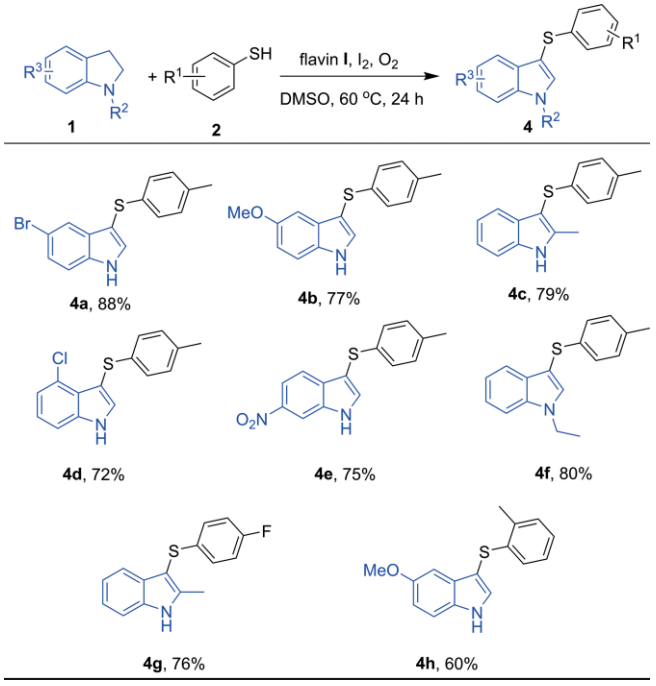


[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), flavin **I** (5 mol-%), I_2 (10 mol-%), and DMSO (1 mL) under O_2 (1 atm) at 60 °C for 24 h. [b] **1a** (0.5 mmol), **2a** (0.75 mmol). Isolated yields.

product **3g** in 88 % yield under standard conditions. Furthermore, heteroaryl thiol and aliphatic thiol underwent oxidative coupling to give products **3m** and **3n** in 62 % and 66 % yields, respectively.

Next, a wide range of indolines and thiophenols were explored (Table 3). First, differently substituted indolines with various electron-donating groups (Me and OMe) and electron-withdrawing groups (Cl, Br, and NO_2) at C-2, C-4, C-5, and C-6 positions of the indoline ring in combination with 4-methylbenzenethiol **2a** were tested. Gratifyingly, all the reactions afforded the desired products **4a**–**4e** in 72–88 % yields. It is noteworthy that *N*-ethyl protected indoline also afforded the corresponding product **4f** in 80 % yield. Moreover, methyl and methoxyl group substituted indolines underwent smooth oxidative dehydrogenative coupling reactions with *p*-fluoro and *o*-methyl-substituted thiophenols to form **4g** and **4h** in 76 % and 60 % yields, respectively.

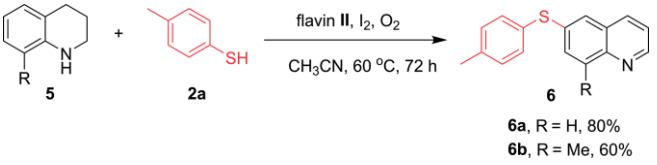
Table 3. Scope of thiophenols and indolines.[a]



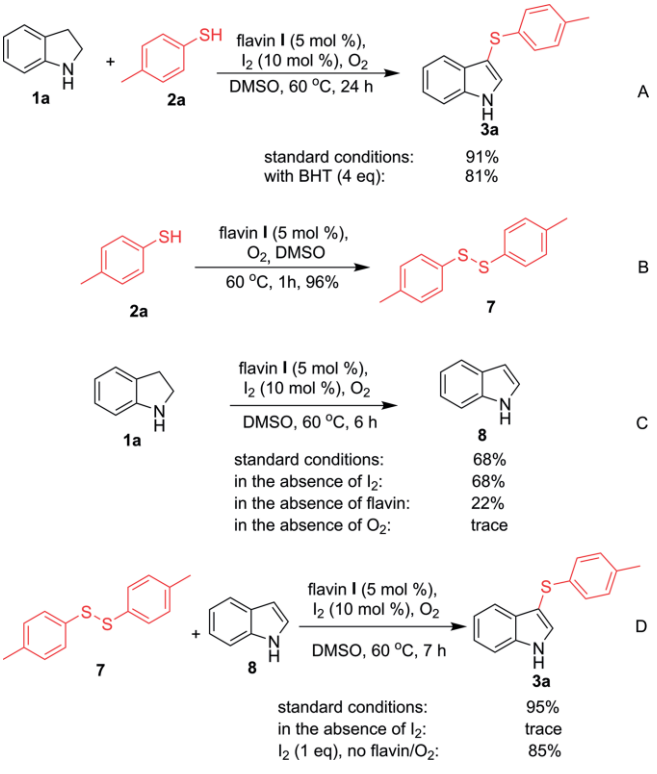
[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), flavin **I** (5 mol-%), I_2 (10 mol-%), and DMSO (1 mL) under O_2 (1 atm) at 60 °C for 24 h. Isolated yields.

To further demonstrate the synthetic diversity, coupling reactions of tetrahydroquinolines **5** with 4-methylbenzenethiol **2a** were then tested. The reaction using flavin **II** under mild conditions was regioselective, affording desired products **6a** and **6b**, with substitution at the position *para* to the *N* atom in 80 % and 60 % yields, respectively (Scheme 2).

To gain insight into the mechanism of this reaction, several control experiments were conducted (Scheme 3). First, a radical scavenger butylated hydroxytoluene (BHT) was added to the reaction under standard conditions. Only a slight decrease in yield ruled out the possibility of a radical mechanism (Scheme 3A). Secondly, 4-methylbenzenethiol **2a** could be easily oxidized by oxygen to 1,2-di-*p*-tolyldisulfane **7** in the absence of iodine (Scheme 3B). Thirdly, indoline **1a** could be oxidized to indole **8** in 68 % yield under standard conditions regardless of the presence or absence of iodine. But when there is no flavin or oxygen, only low amounts of **8** were produced. These results indicated that the flavin-catalyzed system played a significant role in the dehydrogenation of indoline (Scheme 3C). Finally, the reaction of disulfide **7** and indole **8** produced **3a** in 95 % yield under standard conditions. However, only trace amounts of **3a** were obtained in the absence of iodine. In addition, 85 % of **3a** formed using 1 equivalent of iodine without flavin and oxygen (Scheme 3D). Therefore, we speculated that in situ generated sulfenyl iodide could be the key intermediate in this reaction.



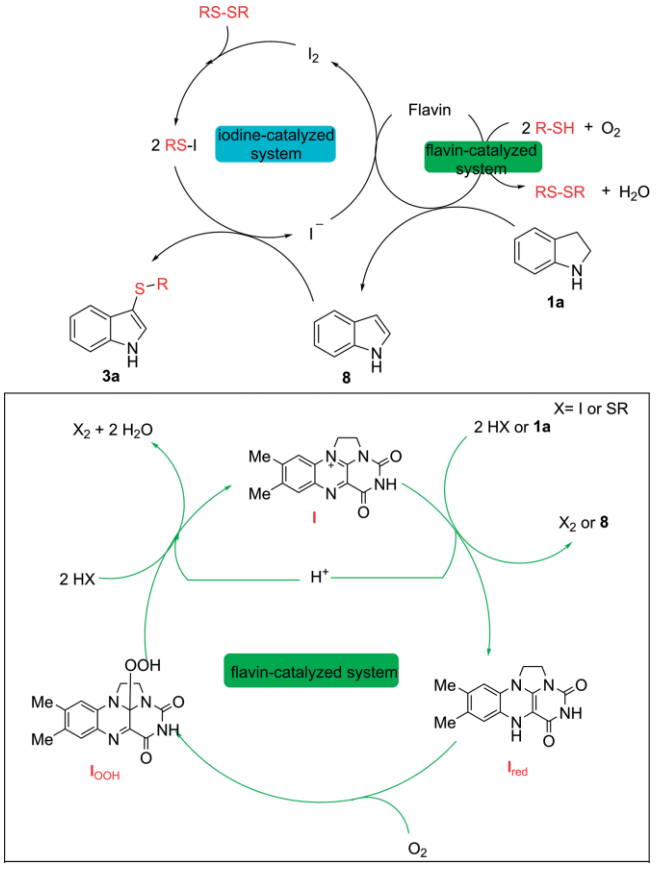
Scheme 2. Variations of tetrahydroquinolines. Reaction conditions: **5a** (0.5 mmol), **2a** (0.5 mmol), flavin **II** (5 mol-%), I_2 (10 mol-%), and MeCN (0.5 mL) under O_2 (1 atm) at 60 °C for 72 h. Isolated yields.



Scheme 3. Control experiments.

Based on previous reports[33c] and our control experiments, a mechanism for the flavin/I_2-catalyzed oxidative sulfenylation is proposed in Scheme 4. This tandem reaction proceeds in two consecutive steps: 1) flavin-catalyzed disulfide formation and dehydrogenation of indoline **1a** to form indole **8**;[35] 2) reaction of in situ generated disulfide with I_2 to form sulfenyl iodide,[27a] which is then nucleophilically attacked by the newly formed indole to obtain **3a** and I^-.[33] Iodide anion is oxidized by flavin-

catalyzed system, which then enters the next catalytic cycle. In flavin-catalyzed system, HI and indolines could be oxidized to I_2 and indoles respectively.[35] The catalyst itself undergoes reduction to form flavin $\mathbf{I_{red}}$, which reacts with oxygen to form hydroperoxy flavin $\mathbf{I_{OOH}}$. Oxidatively active $\mathbf{I_{OOH}}$ promotes the conversion of HI to I_2, while producing flavin **I** and water.[32,36] Similarly, thiol can also be converted to disulfide by this flavin-catalyzed aerobic oxidation.[8]



Scheme 4. Proposed mechanism for the reaction.

Conclusion

In summary, an oxidative C-H sulfenylation of aryl-fused cyclic amines with various thiols catalyzed by flavin/I_2 system with high atom-efficiency and excellent functional compatibility is reported for the first time. Different flavin derivatives could catalyze the C-H sulfenylation of aryl-fused cyclic amines to form corresponding 3-sulfenylindoles and 6-sulfenylquinolines, respectively. This metal-free reaction uses molecular oxygen as the only terminal oxidant and produces environmental-friendly H_2O as the only by-product.

Experimental Section

Unless otherwise stated, all substrates, reagents, and solvents were obtained from commercial sources and without further purification. NMR spectra were recorded using Varian Mercury Plus 400 MHz or Bruker Avance III 600 MHz spectrometers. Chemical shifts of ^{1}H-NMR were reported relative to the solvent signal ($CDCl_3$: δ = 7.26 ppm; $[D_6]$DMSO: δ = 2.50 ppm). Chemical shifts of ^{13}C NMR were reported relative to the solvent signal ($CDCl_3$: δ = 77.00 ppm; $[D_6]$DMSO: δ = 39.50 ppm). HRMS spectra were recorded on an electrospray ionization quadrupole time-of-flight (ESI-Q-TOF) mass spectrometer. The reactions were monitored by TLC visualized by UV (254 nm). Column chromatography was performed on silica gel (300–400 mesh). The substrates **2**, **1a**, **1c**, **1e**, and **5a** were purchased from Energy Chemical, substrate **1d** was purchased from Aladdin. Substrates **1b**,[37] **1f**,[38] **5b**,[39] flavin **I** (**8·Cl**),[32c,33a] and flavin **II** (**8·TfO**)[33c] were prepared according to the literature reports.

General Procedure for the Synthesis of 3 and 4: A mixture of indoline **1** (0.6 mmol), thiol **2** (0.5 mmol), I_2 (0.05 mmol), and flavin **I** (0.025 mmol) in DMSO (1 mL) was stirred at 60 °CC for 24 h under oxygen atmosphere (1 atm). After the completion of the reaction as indicated by TLC, it was quenched by adding brine (15 mL) at room temperature and then extracted with ethyl acetate (10 mL × 3). The combined organic phase was washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to give the final product.

1,2-Di-*p*-tolyldisulfane (7): The product **7** was obtained as a white solid (59 mg, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 (d, J = 8.2 Hz, 4H), 7.12 (d, J = 8.0 Hz, 4H), 2.34 (s, 6H).

1*H*-Indole (8): The product **8** was obtained as a white solid (40 mg, 68 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (br, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.23–7.15 (m, 1H), 7.07–7.15 (m, 2H), 6.52–6.55 (m, 1H).

3-(*p*-Tolylthio)-1*H*-indole (3a): The product **3a** was obtained as a white solid (109 mg, 91 % yield). M.p. 119–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.36 (br, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 2.5 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.32–7.24 (m, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.05 (d, J = 8.3 Hz, 2H), 6.99 (d, J = 8.2 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.42, 135.43, 134.61, 130.40, 129.45, 129.06, 126.20, 122.94, 120.79, 119.65, 111.50, 103.42, 20.84; ESI-MS *m/z*: 238.12 $[M - H]^-$, the spectra data matched those previously reported.[33c]

3-[(4-Fluorophenyl)thio]-1*H*-indole (3b): The product **3b** was obtained as a white solid (122 mg, 86 %). M.p. 137–141 °C. ^{1}H NMR (400 MHz, $[D_6]$DMSO) δ = 11.70 (br, 1H), 7.77 (d, J = 2.6 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.03–7.09 (m, 5H); ^{13}C NMR (101 MHz, $[D_6]$DMSO) δ = 160.14 (d, J = 241.6 Hz), 136.71, 134.57 (d, J = 3.0 Hz), 132.43, 128.46, 127.47 (d, J = 7.9 Hz), 122.17, 119.18 (d, J = 199.2 Hz), 115.98, 115.76, 112.38, 99.65; ^{19}F NMR (376 MHz, $[D_6]$DMSO) δ = −118.29; ESI-MS *m/z*: 242.22 $[M - H]^-$, the spectra data matched those previously reported.[40]

3-[(4-Chlorophenyl)thio]-1*H*-indole (3c): The product **3c** was obtained as a white solid (113 mg, 87 %). M.p. 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.43 (br, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 2.6 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.30 (t, J = 8.6 Hz, 1H), 7.18 (t, J = 7.3 Hz, 1H), 7.12 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 8.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.80, 136.49, 130.67, 130.53, 128.79, 128.73, 127.09, 123.19, 121.04, 119.49, 111.64, 102.45; ESI-MS *m/z*: 258.18 $[M - H]^-$, the spectra data matched those previously reported.[31c]

3-[(4-Bromophenyl)thio]-1*H*-indole (3d): The product **3d** was obtained as a white solid (120 mg, 79 %). M.p. 145–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.43 (br, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 2.5 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.32–7.22 (m, 3H), 7.18 (t,

J = 7.4 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.52, 136.49, 131.62, 130.70, 128.76, 127.37, 123.21, 121.06, 119.49, 118.28, 111.65, 102.27; ESI-MS *m/z*: 302.13 [M – H]$^-$, the spectra data matched those previously reported.[31c]

3-[(4-Methoxyphenyl)thio]-1*H*-indole (3e): The product **3e** was obtained as a white solid (110 mg, 86 %). M.p. 109–112 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.33 (br, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 2.5 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.27–7.23 (m, 1H), 7.18–7.15 (m, 1H), 7.16–7.12 (m, 2H), 6.76–6.73 (m, 2H), 3.73 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 157.79, 136.45, 129.95, 129.51, 129.01, 128.59, 122.92, 120.75, 119.64, 114.49, 111.48, 104.70, 55.31; ESI-MS *m/z*: 254.21 [M – H]$^-$, the spectra data matched those previously reported.[31c]

3-{[4-(Trifluoromethyl)phenyl]thio}-1*H*-indole (3f): The product **3f** was obtained as a white solid (128 mg, 87 %). M.p. 116–121 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.49 (br, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 2.6 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.33–7.29 (m, 1H), 7.21–7.18 (m, 1H), 7.14 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.68, 136.53, 131.01, 128.71, 126.70 (q, *J* = 32.6 Hz), 125.46 (q, *J* = 3.7 Hz), 124.41 (q, *J* = 272.7 Hz), 125.23, 123.33, 121.19, 119.40, 111.75, 101.19; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –62.23; ESI-MS *m/z*: 292.23 [M – H]$^-$, the spectra data matched those previously reported.[41]

3-(Naphthalen-2-ylthio)-1*H*-indole (3g): The product **3g** was obtained as a white solid (121 mg, 88 %). M.p. 173–176 °C. ^{1}H NMR (400 MHz, [D_6]DMSO) δ = 11.74 (br, 1H), 7.84 (d, *J* = 2.6 Hz, 1H), 7.81–7.72 (m, 2H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.54–7.49 (m, 2H), 7.44–7.34 (m, 3H), 7.24–7.16 (m, 2H), 7.04 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR (101 MHz, [D_6]DMSO) δ = 136.78, 136.76, 133.23, 132.52, 130.83, 128.62, 128.33, 127.58, 126.64, 126.60, 125.19, 124.35, 122.77, 122.14, 120.12, 118.26, 112.39, 99.16; ESI-MS *m/z*: 274.25 [M – H]$^-$, the spectra data matched those previously reported.[42]

3-([1,1′-Biphenyl]-2-ylthio)-1*H*-indole (3h): The product **3h** was obtained as a white solid (116 mg, 77 %). M.p. 155–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.37 (br, 1H), 7.60 (t, *J* = 8.5 Hz, 3H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.45–7.41 (m, 2H), 7.39–7.36 (m, 1H), 7.30–7.20 (m, 2H), 7.20–7.10 (m, 2H), 7.04 (td, *J* = 7.7, 1.5 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.53, 139.51, 137.79, 136.49, 130.81, 129.98, 129.48, 129.13, 128.18, 127.66, 127.53, 125.80, 124.53, 122.98, 120.82, 119.72, 111.53, 102.84; HRMS (ESI) *m/z*: calcd. for $C_{20}H_{15}NNaS$ [M + Na]$^+$ 324.0817, found 324.0820.

3-(*o*-Tolylthio)-1*H*-indole (3i): The product **3i** was obtained as a white solid (116 mg, 89 %). M.p. 108–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.43 (br, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.50–7.43 (m, 2H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.20–7.12 (m, 2H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.91 (t, *J* = 7.3 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.24, 136.51, 134.28, 130.76, 129.78, 129.19, 126.22, 125.17, 124.40, 123.01, 120.84, 119.66, 111.57, 102.23, 19.88; ESI-MS *m/z*: 238.17 [M – H]$^-$, the spectra data matched those previously reported.[27e]

3-[(2-Methoxyphenyl)thio]-1*H*-indole (3j): The product **3j** was obtained as a white solid (116 mg, 92 %). M.p. 147–149 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.45 (br, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 2.6 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.30–7.26 (m, 1H), 7.20–7.14 (m, 1H), 7.07–7.03 (m, 1H), 6.86 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.71–6.66 (m, 1H), 6.63 (dd, *J* = 7.8, 1.7 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 155.11, 136.59, 131.07, 129.36, 127.90, 125.94, 125.37, 122.98, 121.11, 120.84, 119.75, 111.57, 110.11, 101.43, 55.86; ESI-MS *m/z*: 254.22 [M – H]$^-$, the spectra data matched those previously reported.[42]

3-[(3-Chlorophenyl)thio]-1*H*-indole (3k): The product **3k** was obtained as a white solid (116 mg, 92 %). M.p. 90–92 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.45 (br, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 2.6 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.32–7.27 (m, 1H), 7.23–7.17 (m, 1H), 7.10–7.05 (m, 2H), 7.04–7.01 (m, 1H), 7.00–6.96 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 141.60, 136.51, 134.66, 130.93, 129.65, 128.86, 125.44, 124.92, 123.87, 123.22, 121.11, 119.46, 111.66, 101.89; ESI-MS *m/z*: 258.20 [M – H]$^-$, the spectra data matched those previously reported.[27e]

3-(*m*-Tolylthio)-1*H*-indole (3l): The product **3l** was obtained as a white solid (93 mg, 82 %). M.p. 117–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.41 (br, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 2.5 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.7 Hz, 1H), 6.99 (s, 1H), 6.91–6.86 (m, 2H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.92, 138.43, 136.42, 130.63, 129.13, 128.55, 126.41, 125.72, 122.95, 122.94, 120.82, 119.66, 111.51, 102.87, 21.35; ESI-MS *m/z*: 238.17 [M – H]$^-$, the spectra data matched those previously reported.[27e]

3-(Thiophen-2-ylthio)-1*H*-indole (3m): The product **3m** was obtained as a white solid (116 mg, 62 %). M.p. 98–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26 (br, 1H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 2.5 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.27–7.18 (m, 2H), 7.17 (dd, *J* = 5.3, 1.2 Hz, 1H), 7.11 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.88 (dd, *J* = 5.3, 3.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.90, 136.11, 129.80, 129.20, 128.48, 127.28, 127.20, 122.95, 120.79, 119.41, 111.49, 106.72; ESI-MS *m/z*: 230.15 [M – H]$^-$, the spectra data matched those previously reported.[43]

3-(Butylthio)-1*H*-indole (3n): The product **3n** was obtained as an oil (67 mg, 66 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.19 (br, 1H), 7.78 (d, *J* = 6.8 Hz, 1H), 7.37–7.31 (m, 1H), 7.26 (d, *J* = 2.5 Hz, 1H), 7.24–7.17 (m, 2H), 2.69 (t, *J* = 8.0 Hz,2H), 1.59–1.45 (m, 2H), 1.44–1.33 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.18, 129.39, 129.21, 122.54, 120.28, 119.31, 111.41, 106.01, 36.05, 31.93, 21.61, 13.65; ESI-MS *m/z*: 204.21 [M – H]$^-$, the spectra data matched those previously reported.[27d]

5-Bromo-3-(*p*-tolylthio)-1*H*-indole (4a): The product **4a** was obtained as a white solid (140 mg, 88 %). M.p. 121–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.43 (br, 1H), 7.77–7.75 (m, 1H), 7.47 (d, *J* = 2.5 Hz, 1H), 7.33 (dd, *J* = 1.8 Hz, 1H), 7.31–7.27 (m, 1H), 7.04–6.97 (m, 4H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 135.05, 134.94, 134.90, 131.58, 130.95, 129.58, 126.28, 126.01, 122.23, 114.37, 112.99, 103.42, 20.85; ESI-MS *m/z*: 316.18 [M – H]$^-$, the spectra data matched those previously reported.[33c]

5-Methoxy-3-(*p*-tolylthio)-1*H*-indole (4b): The product **4b** was obtained as an oil (104 mg, 77 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.35 (br, 1H), 7.44–7.41 (m, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.08–6.96 (m, 5H), 6.91 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.80 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.03, 135.59, 134.52, 131.29, 131.12, 129.95, 129.46, 125.97, 113.47, 112.35, 102.73, 100.77, 55.75, 20.82; ESI-MS *m/z*: 270.12 [M + H]$^+$, the spectra data matched those previously reported.[33c]

2-Methyl-3-(*p*-tolylthio)-1*H*-indole (4c): The product **4c** was obtained as a white solid (101 mg, 79 %). M.p. 91–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.19 (br, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.01–6.94 (m, 4H), 2.51 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.87, 135.65, 135.39, 134.27, 130.32, 129.44, 125.76, 122.07, 120.60, 118.97, 110.56, 99.87, 20.80, 12.11; ESI-MS *m/z*: 252.19 [M – H]$^-$, the spectra data matched those previously reported.[33c]

4-Chloro-3-(*p*-tolylthio)-1*H*-indole (4d): The product **4d** was obtained as a white solid (98 mg, 72 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ =

8.48 (br, 1H), 7.43 (d, *J* = 2.5 Hz, 1H), 7.31 (dd, *J* = 6.5, 2.5 Hz, 1H), 7.15–7.11 (m, 2H), 7.08–6.99 (m, 4H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.92, 136.97, 134.61, 132.38, 129.46, 126.84, 126.27, 125.12, 123.50, 122.14, 110.42, 103.52, 20.85; ESI-MS *m/z*: 272.17 [M – H]$^-$, the spectra data matched those previously reported.[26d]

6-Nitro-3-(*p*-tolylthio)-1*H*-indole (4e): The product **4e** was obtained as a yellow solid (106 mg, 75 %). M.p. 154–157 °C. ^{1}H NMR (600 MHz, [D_6]DMSO) δ = 12.35 (br, 1H), 8.41 (d, *J* = 2.1 Hz, 1H), 8.17 (d, *J* = 2.8 Hz, 1H), 7.95 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.3 Hz, 2H), 2.19 (s, 3H); ^{13}C NMR (151 MHz, [D_6]DMSO) δ = 142.78, 138.39, 135.13, 134.74, 134.32, 133.56, 129.65, 126.17, 118.74, 115.23, 109.08, 102.02, 20.37; HRMS (ESI) *m/z*: calcd. for $C_{15}H_{13}N_2O_2S$ [M + H]$^+$ 285.0692, found 285.0703.

1-Ethyl-3-(*p*-tolylthio)-1*H*-indole (4f): The product **4f** was obtained as an oil (107 mg, 80 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 7.9 Hz, 1H), 7.44–7.39 (m, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 8.3 Hz, 2H), 4.22 (q, *J* = 7.3 Hz, 2H), 2.26 (s, 3H), 1.53 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.55, 135.96, 134.41, 133.11, 129.95, 129.40, 125.99, 122.31, 120.33, 119.84, 109.72, 101.10, 41.28, 20.82, 15.35; HRMS (ESI) *m/z*: calcd. for $C_{17}H_{17}NNaS$ [M + Na]$^+$ 290.0974, found 290.0967.

3-[(4-Fluorophenyl)thio]-2-methyl-1*H*-indole (4g): The product **4g** was obtained as a white solid (98 mg, 76 %). M.p. 95–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23 (br, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.06–6.99 (m, 2H), 6.86 (t, *J* = 8.7 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.71 (d, *J* = 243.5 Hz), 140.96, 135.39, 134.18 (d, *J* = 3.1 Hz), 130.06, 127.33 (d, *J* = 7.7 Hz), 122.25, 120.75, 118.83, 115.68 (d, *J* = 22.0 Hz), 110.66, 99.86, 12.12; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –118.73; ESI-MS *m/z*: 258.07 [M + H]$^+$, the spectra data matched those previously reported.[44]

5-Methoxy-3-(*o*-tolylthio)-1*H*-indole (4h): The product **4h** was obtained as a white solid (81 mg, 60 %). M.p. 90–92 °C. ^{1}H NMR (400 MHz, [D_6]DMSO) δ = 11.58 (br, 1H), 7.68 (d, *J* = 2.7 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 7.19–7.11 (m, 1H), 6.99–6.90 (m, 2H), 6.88–6.79 (m, 2H), 6.58 (dd, *J* = 7.4, 1.6 Hz, 1H), 3.67 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, [D_6]DMSO) δ = 154.28, 138.31, 133.43, 132.97, 131.69, 129.79, 129.61, 126.28, 124.44, 124.31, 113.21, 112.28, 99.69, 98.05, 55.25, 19.38; HRMS (ESI) *m/z*: calcd. for $C_{16}H_{15}NOSNa$ [M + Na]$^+$ 292.0767, found 292.0757.

6-(*p*-Tolylthio)quinoline (6a): The mixture of 1,2,3,4-tetrahydroquinoline **5a** (67 mg, 0.5 mmol), 4-methylbenzenethiol **2a** (62 mg, 0.5 mmol), I_2 (13 mg, 0.5 mmol), and flavin **II** (11 mg, 0.025 mmol), in CH_3CN (0.5 mL) was stirred at 60 °CC for 72 h under oxygen. After the completion of reaction as indicated by TLC, the solution was then quenched by adding brine (15 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic phase was washed with water and brine, dried with Na_2SO_4, filtered, and then concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate = 30:1 to 20:1) to give **6a** as a yellow oil (100 mg, 80 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.84 (d, *J* = 2.9 Hz, 1H), 7.98 (d, *J* = 8.6 Hz, 2H), 7.61- 7.58 (m, 1H), 7.54 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.41–7.32 (m, 3H), 7.19 (d, *J* = 7.9 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.95, 146.84, 138.39, 136.49, 135.17, 133.09, 130.62, 130.30, 129.96, 128.61, 126.45, 121.56, 21.17; ESI-MS *m/z*: 252.1 [M + H]$^+$, the spectra data matched those previously reported.[45]

8-Methyl-6-(*p*-tolylthio)quinoline (6b): Following the procedure of preparation of **6a**, the product **6b** was obtained as a yellow oil (79 mg, 60 %). ^{1}H NMR (400 MHz, [D_6]DMSO) δ = 8.87 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.22 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.63 (d, *J* = 1.8 Hz, 1H), 7.53–7.48 (m, 1H), 7.45 (s, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 2.64 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, [D_6]DMSO) δ = 149.50, 145.54, 137.87, 137.81, 135.59, 134.16, 132.18, 130.43, 130.29, 129.82, 128.28, 125.47, 121.98, 20.69, 17.55; HRMS (ESI) *m/z*: calcd. for $C_{17}H_{16}NS$ [M + H]$^+$ 266.0998, found 266.0996.

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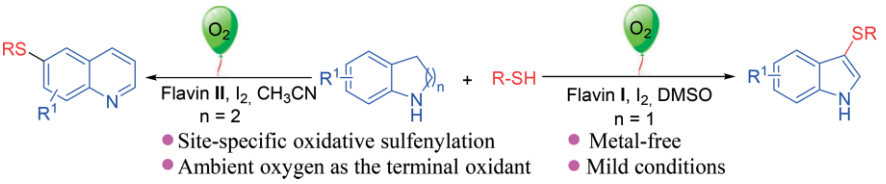

A metal-free aerobic oxidative C–H sulfenylation of aryl-fused cyclic amines with various thiols was developed with excellent functional compatibility. While flavin **I** catalyzed the C–H sulfenylation of indolines to afford 3-sulfenylindoles, flavin **II** enabled transformations resulting in substitution at the position *para* to the *N* atom on the aryl ring to obtain 6-sulfenylquinolines.

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