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Iridium (III)-Catalyzed Regioselective C7-Amination of *N*-Pivaloylindoles with Sulfonoazides

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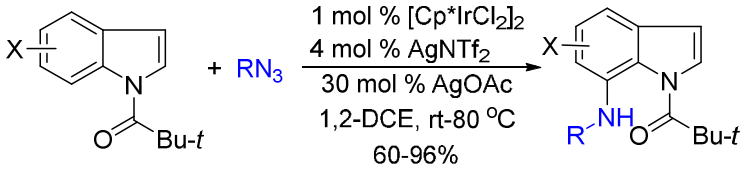
Abstract



R = Aryl, alkyl; X = 3, 4, 5, or 6-substituent, 34 examples

Direct C7-amination of *N*-pivaloylindoles has been achieved using a combination of $[Cp^*IrCl_2]_2$, $AgNTf_2$, and AgOAc as the catalyst and sulfonoazides as the nitrogen source. The reaction proceeded at room temperature to 80 °C to afford 7-sulfonamidoindoles in good to excellent yields. The reaction is broadly applicable to the C7-amination of a wide variety of 3-, 4-, 5- and 6-substituted *N*-pivaloyl indoles

[#] ISHC Member

with either alkyl or aryl sulfonoazides.

Introduction

7-Sulfonamidoindole moiety is a key substructure found in numerous biologically important compounds such as the tubulin polymerization and cell proliferation inhibitors ER-68394 (**1**)[1], E-7070 (**2**)[2], and compound **3**[3], and the glucocorticoid receptor antagonist compound **4**[4]. Indoles **1**, **2**, and **3** have potential for treatment of congestive heart diseases, and **4** lowers LDL while raises HDL in a hamster model of dyslipidemia (Figure 1). Traditionally, these molecules were synthesized from substituted 7-nitroindoles.[3c,5] Since these special heterocycles are not conveniently available, development of straightforward and general methods for assembling 7-sulfonamidoindoles are highly desired.[6,7] Recently, we discovered that regioselective C7-functionalization of indoles could be achieved by simply using *N*-pivaloyl as a directing group.[8,9] As an extension of this work, we explored the possibility if our substrates are applicable for other C7-functionalization reactions, and discovered that Ir-catalyzed direct functionalization of N-pivaloyl indoles with sulfonazides could proceed smoothly to afford 7-sulfonamidoindoles.[10-15] During the preparation of this manuscript, similar reactions with different conditions were disclosed by Chang[10a] and Antonchick[10b] groups. Chang and coworkers described that they could carry out the reaction at room temperature, but needed to use 5 mol % $Cp^*Ir(OAc)_2$ as the catalyst and 10 mol% $AgNTf_2$ as the additive;[10a] while Antonchick found that the reaction completed at 120 ^oC even using 4 mol %

$[Cp^*IrCl]_2$ as the catalyst and 16 mol % $AgNTf_2$ and 40 mol % LiOAc as the additives.[10b] In our hand, we discovered that only 1 mol % $[Cp^*IrCl]_2$ was required to complete the reaction at rt to 80 °C if 4 mol % $AgNTf_2$ and 30 mol % AgOAc were employed as the additives. These relatively practical reaction conditions and expanded substrate scope, together with preliminary mechanism study, are disclosed here.

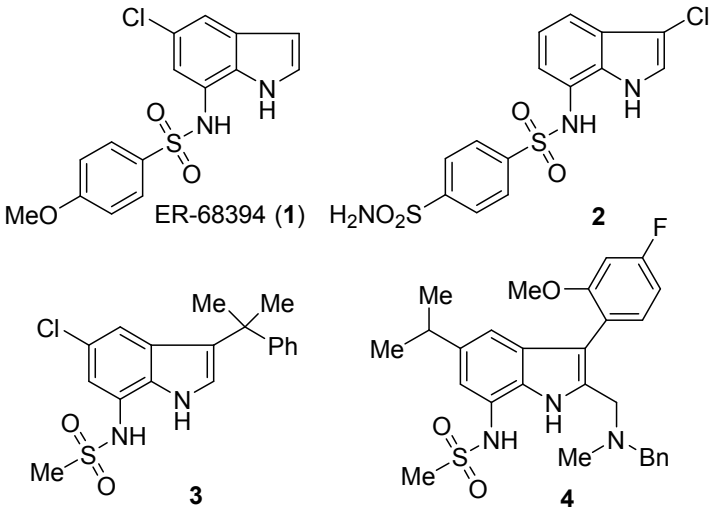


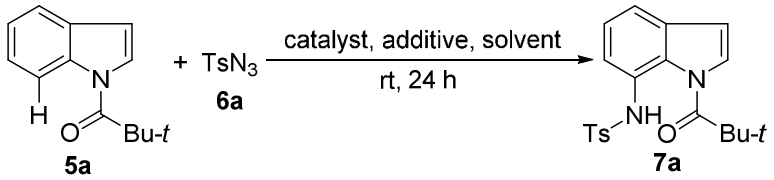
Figure 1. Biologically important compounds that contain the 7-sulfonamidoindole moiety

Results and Discussion

We commenced our amination research by employing our standard olefination conditions of *N*-pivaloylindoles by treatment of **5a** with tosyl azide **6a** in the presence of $[Cp^*RhCl_2]_2$, $AgNTf_2$ and $Cu(OAc)_2$ in DCE at 80 °C.[8] However, no desired product was obtained and **5a** was recovered completely. We then turned our attention to Ir catalysts.[13g] As indicated in Table 1, In the presence of $[Cp^*IrCl_2]_2$, $AgNTf_2$, and NaOAc, the reaction of N-pivaloylindole **5a** with tosyl azide **6a** took place at room

temperature but with only trace amount of the desired product **7a** owing to poor conversion (entry 1). Changing one of the additives from NaOAc to pivalic acid or CsOAc gave similar results (entries 2 and 3). However, when AgOAc was used, complete conversion was observed, and **7a** was obtained in 95% yield (entry 4). If AgOAc was switched to $Cu(OAc)_2 \cdot H_2O$ or Ag_2CO_3, the reaction yields were greatly decreased (entries 5 and 6). Further investigations revealed that the use of $AgNTf_2$ is critical to the reaction efficiency. No desired product was obtained without $AgNTf_2$ or replacing it with AgO_2CCF_3 and AgOTs even at 80 ^oC (entries 9-11). Interestingly, when $AgNTf_2$ was replaced with either $AgSbF_6$ or AgOTf, poor yields were obtained at room temperature but acceptable yields were realized at 80 ^oC (entries 7 and 8). Using the combination of $[Cp^*IrCl_2]_2$, $AgNTf_2$ and AgOAc, we examined several polar solvents, and found that trifluoromethylbenzene and methylene chloride afforded **7a** in 88-93% yields (entries 12 and 13), while *t*-AmylOH, MeCN, and dioxane gave poor yields or no conversion (entries 14-16). Additionally, we discovered that Ir catalyst was also essential for this reaction and little conversion was observed when $[Cp^*RhCl_2]_2$,[12] $[Ru(p\text{-cymene})Cl_2]_2$[14] and $Cp^*Co(CO)I_2$[15] were used as the catalyst (entries 17-19). We were pleased that the catalyst loading could be reduced to 1 mol % without decreasing the reaction yield with the optimized reaction conditions (entry 4 vs. 20). Noteworthy is that the combination of two silver salts was essential to ensure complete conversion because using $AgNTf_2$ or AgOAc alone gave a poor yield or no conversion (entries 21 and 22).

Table 1. Condition screening for reaction of N-pivaloylindole with tosyl azide[a]



entry	catalyst (mol %)	additives (mol %)	solvent	yield (%)[b]
1	$[Cp^*IrCl_2]_2$	$AgNTf_2$ (16)/NaOAc (30)	1,2-DCE	2
2	$[Cp^*IrCl_2]_2$	$AgNTf_2$ (16)/PivOH (30)	1,2-DCE	0
3	$[Cp^*IrCl_2]_2$	$AgNTf_2$ (16)/CsOAc (30)	1,2-DCE	0
4	$[Cp^*IrCl_2]_2$	$AgNTf_2$ (16)/AgOAc (30)	1,2-DCE	95
5	$[Cp^*IrCl_2]_2$	$AgNTf_2$ (16)/$Cu(OAc)_2 \cdot H_2O$ (30)	1,2-DCE	55
6	$[Cp^*IrCl_2]_2$	$AgNTf_2$ (16)/Ag_2CO_3 (30)	1,2-DCE	25
7	$[Cp^*IrCl_2]_2$	$AgSbF_6$ (16)/AgOAc (30)	1,2-DCE	30 (73)[c]
8	$[Cp^*IrCl_2]_2$	AgOTf (16)/AgOAc (30)	1,2-DCE	45 (81)[c]
9	$[Cp^*IrCl_2]_2$	AgO_2CCF_3 (16)/AgOAc (30)	1,2-DCE	0 (0)[c]
10	$[Cp^*IrCl_2]_2$	AgOTs (16)/AgOAc (30)	1,2-DCE	0 (0)[c]
11	$[Cp^*IrCl_2]_2$	$AgNTf_2$ (0)/AgOAc (30)	1,2-DCE	0 (0)[c]
12	$[Cp^*IrCl_2]_2$	$AgNTf_2$ (16)/AgOAc (30)	$C_6H_5CF_3$	88
13	$[Cp^*IrCl_2]_2$	$AgNTf_2$ (16)/AgOAc (30)	CH_2Cl_2	93

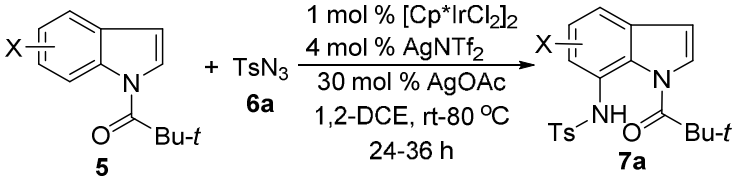
14	$[Cp^*IrCl_2]_2$	$AgNTf_2$ (16)/AgOAc (30)	*t*-AmOH	15
15	$[Cp^*IrCl_2]_2$	$AgNTf_2$ (16)/AgOAc (30)	MeCN	0
16	$[Cp^*IrCl_2]_2$	$AgNTf_2$ (16)/AgOAc (30)	dioxane	5
17	$[Cp^*RhCl_2]_2$	$AgNTf_2$ (16)/AgOAc (30)	1,2-DCE	0
18	[Ru(*p*-cymene)Cl_2]$_2$	$AgNTf_2$ (16)/AgOAc (30)	1,2-DCE	9
19	$Cp^*Co(CO)I_2$	$AgNTf_2$ (16)/AgOAc (30)	1,2-DCE	0
20	$[Cp^*IrCl_2]_2$	$AgNTf_2$ (4)/AgOAc (30)	1,2-DCE	93[d]
21	$[Cp^*IrCl_2]_2$	$AgNTf_2$ (4)/ AgOAc (0)	1,2-DCE	5[d]
22	$[Cp^*IrCl_2]_2$	$AgNTf_2$ (0)/ AgOAc (30)	1,2-DCE	0[d]

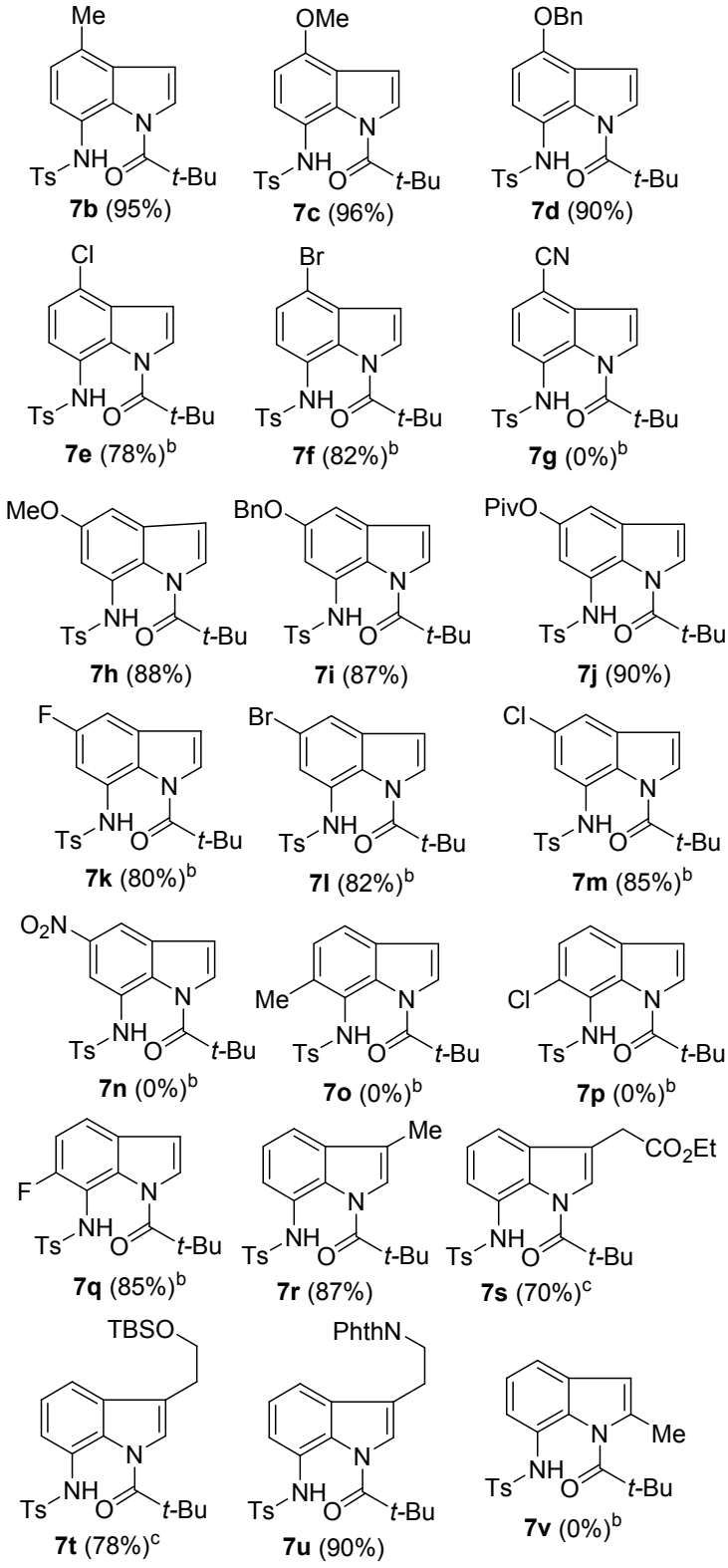
[a]**5a** (0.2 mmol), **6a** (0.3 mmol), catalyst (4.0 mol%), and DCE (1.0 mL) at room temperature for 24 h. [b]Yields based on ^{1}H NMR analysis of the crude mixture (1,3,5-trimethoxybenzene; internal standard). [c]Reaction temperature was 80 ^{o}C. [d]$[Cp^*IrCl_2]_2$ (1.0 mol%) and DCE (0.2 mL) was used.

With the optimized conditions in hand, we next explored the substrate scope using different substituted indoles. As summarized in Table 2, indoles bearing an electron-donating group at the 4-, or 5- position worked well at room temperature, leading to the formation of **7b**-**7d** and **7h**-**7j** in 87-95% yields. Halogen-substituted indoles were less reactive, and required increased reaction temperature (80 ^{o}C) to afford **7e**, **7f** and **7k**-**7m** in good yields. However, more electron-deficient substrates like 4-cyano-*N*-pivaloylindole and 5-nitro-*N*-pivaloylindole gave no conversion even

at 80 °C. The present reaction is very sensitive to the steric hindrance of the 6-position in *N*-pivaloylindoles. No product was obtained when 6-methyl-*N*-pivaloylindole or 6-chloro-*N*-pivaloylindole was utilized as the substrates. In contrast, 6-fluoro-*N*-pivaloylindole that possesses a small F at the 6-position delivered the amination product **7q** in 85% yield.

Table 2. Substrate Scope of Indoles[a]

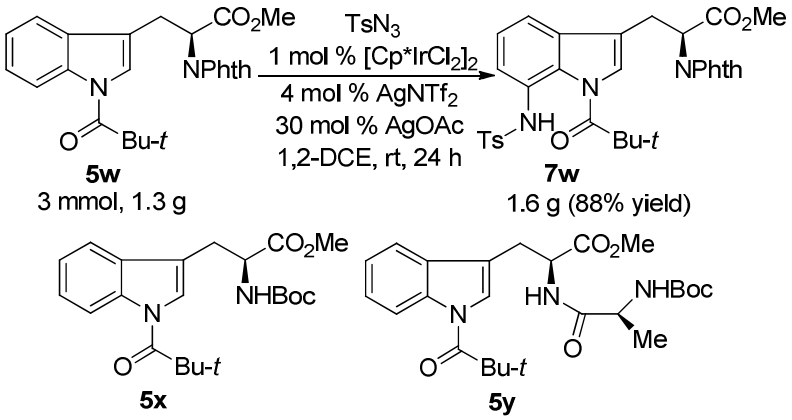




[a]**5** (0.2 mmol), **6a** (0.3 mmol), DCE (0.2 mL) at room temperature for 24-36 h. [b]At 80 °C. [c]At 50 °C.

In addition, substrates with both simple and functionalized alkyl substituents at the 3-position of *N*-pivaloylindoles underwent the amination smoothly, producing **7r**-**7u** in 70-90% yields. The additional functional groups in the side chain of these products should be useful for further conversion to pharmaceutically important molecules. However, 2-methyl-*N*-pivaloylindole was inert under the present reaction conditions, presumably because the steric hindrance at this position could inhibit the formation of the active metal complex intermediates.

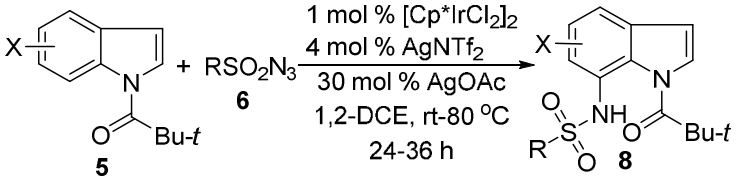
The reaction was successfully conducted on gram scale without any difficulty. Thus 1.6 g of the desired amination product **7w** was obtained in 88% yield from the tryptophan derivative **5w** (Scheme 1). Interestingly, the phthoyl protecting group in **5w** was essential for this transformation, as Boc-protected tryptophan derivative **5x** and dipeptide **5y** were inert under the same reaction conditions. This phenomenon indicated that the free NH moiety in the substrates might bond to the metal in a way that blocked the catalytic reaction.



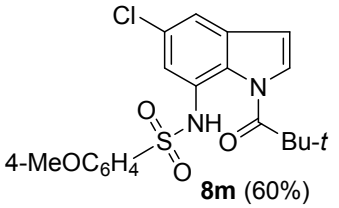
Scheme 1. Gram-scale reaction of a tryptophan derivative

We also evaluated the reaction scope using different sulfonyl azides and the results were summarized in Table 3. Aryl sulfonyl azides with electron-donating groups, in general, were more reactive, giving complete conversion and excellent yields at room temperature, while aryl sulfonyl azides with electron-withdrawing groups required elevated temperature to reach complete conversion. Alkyl sulfonyl azides also worked well, and **8k** and **8l** were obtained in 88% and 81% yields, respectively. Using methylsulfonyl azide as the reagent, we examined several substituted *N*-pivaloylindoles, and were pleased that all of them proceeded smoothly to afford the desired products **8o**-**8s** in good to excellent yields.

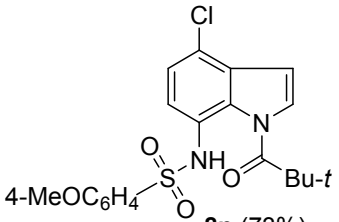
Table 3. Scope of Sulfonyl Azides[a]



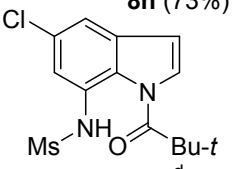
8a: R = Ph, 89%[b]
8b: R = 4-FC_6H_4, 88%[c]
8c: R = 4-ClC_6H_4, 90%[c]
8d: R = 4-BrC_6H_4, 78%[c]
8e: R = 4-NCC_6H_4, 70%
8f: R = 4-AcC_6H_4, 79%
8g: R = 3,5-$Cl_2C_6H_3$, 79%[c]
8h: R = 2,4-$F_2C_6H_3$, 83%
8i: R = 4-$MeOC_6H_4$, 88%[b]
8j: R = 2-Naphth, 85%[c]
8k: R = Me, 88%[d]
8l: R = *n*-C_8H_{17}, 81%[d]



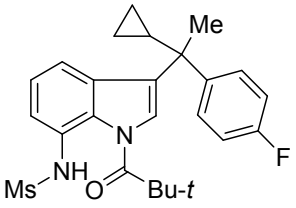
8m (60%)



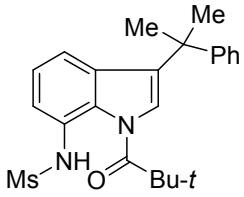
8n (73%)



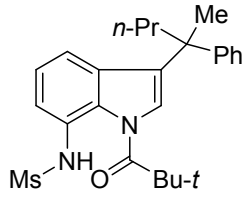
8o (63%)[d]



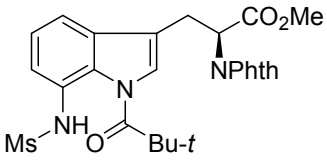
8p (91%)[d]



8q (77%)[d]



8r (83%)[d]

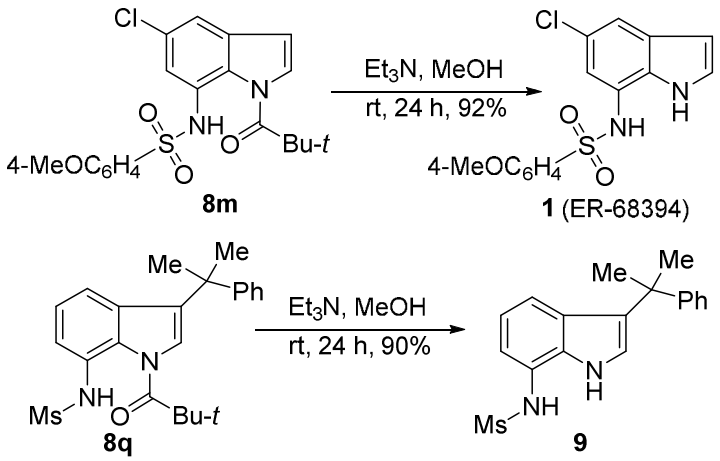


8s (77%)[d]

[a]**5** (0.2 mmol), **6** (0.3 mmol), DCE (0.2 mL) at 80 °C for 24-36 h in pressure tubes. [b]At room temperature. [c]At 50 °C. [d]$[IrCp^*Cl_2]_2$ (4 mol %), $AgNTf_2$ (16 mol %), DCE (1.0 mL) were used at 80 °C.

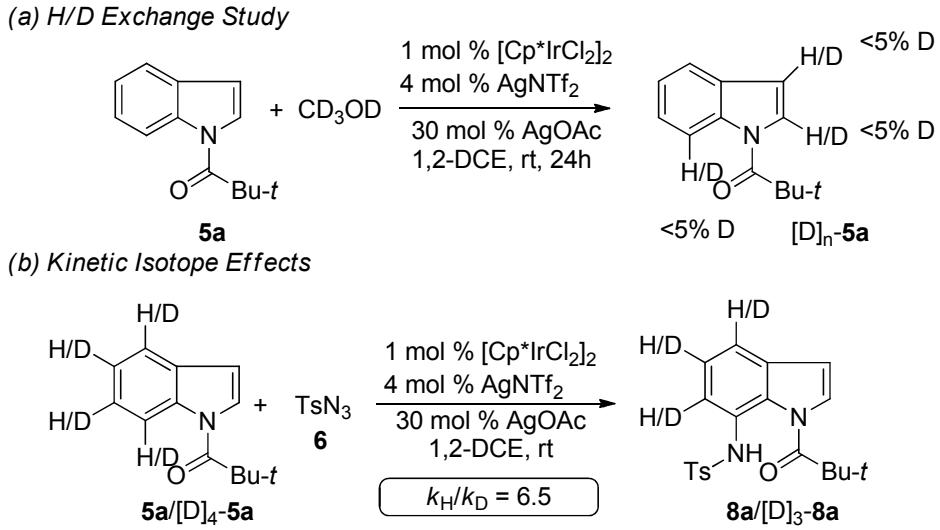
The application of the current methodology is demonstrated by the successful preparation of a known tubulin polymerization and cell proliferation inhibitor **1** (ER-68394)[1] and **9**, a compound with interesting activity against congestive heart diseases.[3] Thus, treatment of **8m** and **8q**, prepared as discussed above, with our

standard mild deprotection condition (Et_3N in MeOH, room temperature)[8] afforded **1** and **9** in 92% and 90% yield respectively (Scheme 2).



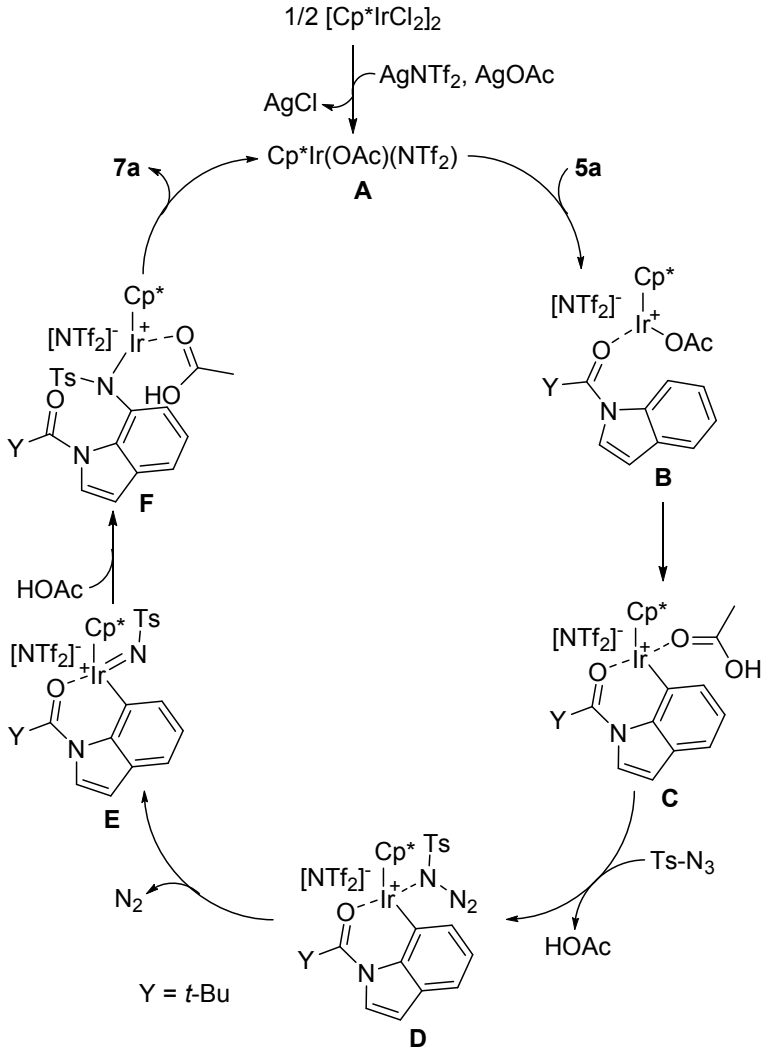
Scheme 2. Deprotection of the amidation products

To obtain mechanistic insights into the present Ir-catalyzed direct C-H amination, we conducted some deuteration experiments as depicted in Scheme 3. No significant H/D exchange was observed when **5a** was treated with CD_3OD in the presence of $[IrCp^*Cl_2]_2$, $AgNTf_2$ and AgOAc, indicating that the C-H activation step might be irreversible. Additionally, kinetic isotope effect (KIE) experiments on parallel reactions of **6a** with **5a** and $[D]_4$-**5a** in separate vessels were carried out under the standard reaction conditions, giving the KIE value of k_H/k_D = 6.5. This result implied that the C-H bond cleavage might occur in the rate-limiting stage.



Scheme 3. Preliminary Mechanistic Studies.

On the basis of the above mechanistic studies and known reports on metal-catalyzed directing group assisted C-H amidation,[11-15] a plausible mechanism is proposed as shown in Scheme 4. First, treatment of the dimeric precursor $[IrCp^*Cl_2]_2$ with $AgNTf_2$ and AgOAc generates the cationic Ir(III) catalyst **A**. The coordination of **A** to the *N*-pivaloyl group of **5a** forms **B**, which accordingly undergoes an irreversible C-H activation at the C7 position of indole substrate to result the six-membered iridacycle **C**. The latter step may be the rate-limiting step based on KIE studies. Next, coordination of sulfonoazide gives the complex **D**, which may undergo release of N_2 to provide a metal-nitrenoid intermediate **E**. The subsequent intramolecular insertion of nitrenoid moiety into iridacycle forms a new C-N bond to deliver complex **F**, upon coordination with acetic acid. Finally, protonolysis of **F** affords the desired product **7a** and regenerate the catalyst **A**. Further efforts to explore the detailed mechanistic insights of the present regioselective amination reaction are ongoing in our group.



Scheme 4. Proposed mechanistic pathway

In summary, we have developed a straightforward and general method for preparing 7-sulfonamidoindoles from conveniently available starting materials through Ir-catalyzed C-H activation. The key is an iridium(III)-catalyzed, C7-selective amidation of *N*-pivaloyindole derivatives. High efficiency and regioselectivity are achieved even at room temperature with considerably low catalyst loading. A number

of functional groups are tolerated under these reaction conditions, and thus allows synthesizing 7-sulfonamidoindoles in a diverse manner. The usage of this method has been illustrated by quick access to some pharmaceutically important molecules.

Experimental

General Information. All the reactions were carried out under inert atmosphere. All the solvents used for the reactions were dried according to standard procedures. All commercial materials were used as received unless otherwise noted. All the *N*-pivalyl indoles were synthesized according to the literature procedure.[16,17] All the sulfonoazides were synthesized according to the literature procedure.[18] All the reactions were monitored by thin layer chromatography (TLC, Silica gel Merck 60 F_{254}); The spots were visualized by UV light. Purification of products was conducted by flash chromatography on silica gel (particle size 40-63 μm, 230-400 mesh SiliaFlash® P60 (Silicycle Inc.)). Optical rotations were measured at room temperature with a digital polarimeter. $CDCl_3$ was used as NMR solvents. Chemical shifts were given relative to $CDCl_3$ (7.24 ppm for ^{1}H NMR, 77.23 ppm for ^{13}C NMR); For the characterization of the observed signal multiplicities, the following abbreviations were applied: s (singlet), d (doublet), dd (double doublet), t (triplet), td (triple doublet), q (quartet), m (multiplet), as well as br (broad). High-resolution mass spectra were acquired using ESI-FTMS method. Melting point was measured with X-4 Melting-point apparatus with microscope.

General procedure for the Ir-catalyzed amidation with sulfonoazides: A sealed

tube was charged with indole substrates (0.2 mmol), $[IrCp^*Cl_2]_2$ (1.6 mg, 0.002 mmol), AgOAc (10.0 mg, 0.06 mmol), $AgNTf_2$ (2.0 mg, 0.008 mmol), sulfonoazides (0.3 mmol). The tube was evacuated and backfilled with argon before 0.2 mL 1,2-DCE was added. The reaction mixture was stirred for 24-36 h at indicated temperatures. After cooling to room temperature, the mixture was diluted with dichloromethane, filtered through a plug of diatomite, concentrated under vacuum and the residue was purified by chromatography on silica with a gradient eluent of petroleum ether and ethyl acetate to give the corresponding products.

Large scale preparation of 7w: A sealed tube was charged with indole **5e** (1.3 g, 3.0 mmol), $[IrCp^*Cl_2]_2$ (23.9 mg, 0.03 mmol), AgOAc (150 mg, 0.9 mmol), $AgNTf_2$ (30.7 mg, 0.12 mmol), *p*-toluenesulfonyl azide (887 mg, 4.5 mmol). The tube was evacuated and backfilled with argon before 3.0 mL 1,2-DCE was added. The reaction mixture was stirred at room temperature for 40 h. Then the mixture was diluted with dichloromethane, filtered through a plug of diatomite, concentrated under vacuum and the residue was purified by chromatography on silica with a gradient eluent of petroleum ether and ethyl acetate to give 1.6 g (88%) of **7w**.

4-Methyl-*N*-(1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (7a): White solid (67 mg, 90%); m.p. 119-121 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.52-7.48 (m, 2H), 7.39-7.35 (m, 3H), 7.30 (t, J = 7.7 Hz, 1H), 7.07 (d, J = 8.0 Hz, 2H), 6.56 (d, J = 3.9 Hz, 1H), 2.28 (s, 3H), 1.35 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.5, 143.3, 137.7, 132.4, 129.6, 129.5, 127.0, 126.7, 125.4, 125.4, 123.0, 119.0, 109.5, 41.8, 29.2, 21.6; HRMS (ESI) *m/e* calcd for $C_{20}H_{23}N_2O_3S$ $(M + H)^+$ 371.1424, found

371.1426.

4-Methyl-*N*-(4-methyl-1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (7b): White solid (73 mg, 95%); m.p. 162-164 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.47 (d, *J* = 3.9 Hz, 1H), 7.40-7.35 (m, 3H), 7.10-7.04 (m, 3H), 6.58 (d, *J* = 3.9 Hz, 1H), 2.45 (s, 3H), 2.28 (s, 3H), 1.33 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.5, 143.2, 137.8, 131.6, 129.6, 129.5, 128.6, 127.0, 126.0, 125.8, 123.7, 122.9, 107.7, 41.8, 29.2, 21.6, 18.3; HRMS (ESI) *m/e* calcd for $C_{21}H_{25}N_2O_3S$ $(M + H)^+$ 385.1580, found 385.1586.

***N*-(4-Methoxy-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (7c):** White solid (77 mg, 96%); m.p. 155-157 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.35 (d, *J* = 3.9 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 1H), 6.68 (d, *J* = 3.9 Hz, 1H), 3.92 (s, 3H), 2.27 (s, 3H), 1.29 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.3, 151.7, 143.2, 137.7, 131.5, 129.5, 127.0, 125.8, 125.0, 122.0, 118.02, 106.2, 105.4, 55.9, 41.7, 29.1, 21.6. HRMS (ESI) *m/e* calcd for $C_{21}H_{25}N_2O_4S$ $(M + H)^+$ 401.1530, found 401.1532.

***N*-(4-(Benzyloxy)-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (7d)**: Br own solid (86 mg, 90%); m.p. 156-158 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.46-7.29 (m, 9H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 1H), 6.74 (d, *J* = 3.9 Hz, 1H), 5.18 (s, 2H), 2.27 (s, 3H), 1.30 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.3, 150.7, 143.2, 137.6, 136.9, 131.5, 129.5, 128.8, 128.3, 127.6, 127.0, 125.6, 125.1, 122.4, 118.2, 106.9, 106.3, 70.5, 41.7, 29.0, 21.5; HRMS (ESI) *m/e* calcd for $C_{27}H_{29}N_2O_4S$ $(M + H)^+$ 477.1843, found 477.1844.

***N*-(4-Chloro-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (7e):** White solid (63 mg, 78%); m.p. 144-146 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.54 (d, *J* = 3.9 Hz, 1H), 7.44-7.39 (m, 3H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.70 (dd, *J* = 3.9, 0.9 Hz, 1H), 2.29 (s, 3H), 1.35 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.7, 143.6, 137.4, 130.7, 130.2, 129.6, 127.2, 126.9, 124.9, 124.1, 124.0, 123.8, 107.5, 41.9, 29.0, 21.6; HRMS (ESI) *m/e* calcd for $C_{20}H_{22}N_2O_3SCl$ $(M + H)^+$ 405.1034, found 405.1038.

***N*-(4-Bromo-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (7f):** Brown solid (74 mg, 82%); m.p. 141-143 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.55 (d, *J* = 3.9 Hz, 1H), 7.44-7.35 (m, 4H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.66 (d, *J* = 3.9 Hz, 1H), 2.29 (s, 3H), 1.35 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.8, 143.6, 137.5, 132.6, 130.0, 129.7, 128.2, 127.2, 127.0, 124.7, 123.9, 112.4, 109.4, 42.0, 29.1, 21.6; HRMS (ESI) *m/e* calcd for $C_{20}H_{22}N_2O_3BrS$ $(M + H)^+$ 449.0529, found 449.0525.

***N*-(5-Methoxy-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (7h):** White solid (70 mg, 88%); m.p. 125-127 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.48-7.45 (m, 3H), 7.14 (d, *J* = 2.5 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.79 (d, *J* = 2.5 Hz, 1H), 6.47 (d, *J* = 3.9 Hz, 1H), 3.82 (s, 3H), 2.28 (s, 3H), 1.35 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.0, 157.6, 143.4, 137.5, 133.3, 129.5, 127.5, 127.0, 126.2, 123.8, 109.6, 109.5, 102.0, 55.9, 41.7, 29.2, 21.6; HRMS (ESI) *m/e* calcd for $C_{21}H_{25}N_2O_4S$ $(M + H)^+$ 401.1530, found 401.1534.

***N*-(5-(Benzyloxy)-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (7i):**

White solid (83 mg, 87%); m.p. 157-159 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.47-7.41 (m, 5H), 7.38-7.29 (m, 3H), 7.26 (d, *J* = 2.4 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 2.5 Hz, 1H), 5.10 (s, 2H), 2.28 (s, 3H), 1.35 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.0, 156.7, 143.4, 137.5, 137.0, 133.2, 129.5, 128.8, 128.2, 127.7, 127.5, 127.1, 126.3, 124.0, 110.2, 109.6, 103.5, 70.7, 41.7, 29.2, 21.6; HRMS (ESI) *m/e* calcd for $C_{27}H_{29}N_2O_4S$ $(M + H)^+$ 477.1843, found 477.1849.

7-(4-Methylphenylsulfonamido)-1-pivaloyl-1*H*-indol-5-yl pivalate (7j): White solid (85 mg, 90%); m.p. 145-147 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 7.51 (d, *J* = 3.9 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 2.3 Hz, 1H), 7.08-7.06 (m, 3H), 6.50 (d, *J* = 3.9 Hz, 1H), 2.27 (s, 3H), 1.36 (s, 9H), 1.34 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.3, 177.2, 148.5, 143.5, 137.2, 132.7, 129.5, 127.7, 127.1, 127.0, 126.0, 116.3, 111.4, 109.5, 41.8, 39.3, 29.1, 27.3, 21.6; HRMS (ESI) *m/e* calcd for $C_{25}H_{31}N_2O_5S$ $(M + H)^+$ 471.1948, found 471.1951.

***N*-(5-Fluoro-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (7k):** White solid (62 mg, 80%); m.p. 128-130 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.57 (d, *J* = 3.9 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.30 (dd, *J* = 10.6, 2.5 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.99 (dd, *J* = 7.5 Hz, 2.5 Hz, 1H), 6.52 (d, *J* = 3.9 Hz, 1H), 2.30 (s, 3H), 1.38 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.5, 161.5 ($J_{C\text{-}F}$ = 240.8 Hz), 143.7, 137.4, 133.2 ($J_{C\text{-}F}$ = 11.1 Hz), 129.7, 128.2, 127.1, 126.8 ($J_{C\text{-}F}$ = 11.9 Hz), 125.5 ($J_{C\text{-}F}$ = 1.8 Hz), 109.50 ($J_{C\text{-}F}$ = 32.2 Hz), 109.46, 104.1 ($J_{C\text{-}F}$ = 23.4 Hz), 42.0, 29.2, 21.6; HRMS (ESI) *m/e* calcd for $C_{20}H_{22}N_2O_3FS$ $(M + H)^+$ 389.1330, found 389.1334.

***N*-(5-Bromo-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (7l):** Brown solid (74 mg, 82%); m.p. 165-167 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.63 (d, J = 1.9 Hz, 1H), 7.52 (d, J = 3.9 Hz, 1H), 7.47-7.45 (m, 3H), 7.11 (d, J = 8.0 Hz, 2H), 6.50 (d, J = 3.9 Hz, 1H), 2.30 (s, 3H), 1.36 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 179.6, 143.7, 137.3, 133.7, 129.7, 128.3, 127.8, 127.0, 126.5, 124.7, 121.3, 118.2, 108.8, 42.0, 29.1, 21.6; HRMS (ESI) *m/e* calcd for $C_{20}H_{22}N_2O_3BrS$ $(M + H)^+$ 449.0529, found 449.0525.

***N*-(5-Chloro-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (7m):** White solid (69 mg, 85%); m.p. 149-151 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.54 (d, J = 3.9 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 2.0 Hz, 1H), 7.11 (d, J = 8.1 Hz, 2H), 6.50 (d, J = 3.9 Hz, 1H), 2.30 (s, 3H), 1.36 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 179.6, 143.7, 137.4, 133.3, 130.8, 129.7, 127.9, 127.8, 127.1, 126.3, 121.9, 118.2, 108.9, 42.0, 29.2, 21.6; HRMS (ESI) *m/e* calcd for $C_{20}H_{22}N_2O_3ClS$ $(M + H)^+$ 405.1034, found 405.1032.

***N*-(6-Fluoro-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (7q):** White solid (66 mg, 85%); m.p. 129-131 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.56-7.53 (m, 3H), 7.40 (dd, J = 8.5, 4.9 Hz, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.13 (dd, J = 10.0, 8.6 Hz, 1H), 6.56 (d, J = 3.9 Hz, 1H), 2.35 (s, 3H), 1.40 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 179.5, 158.7 ($J_{C\text{-}F}$ = 245.6 Hz), 143.7, 137.7, 132.9 ($J_{C\text{-}F}$ = 3.7 Hz), 129.5, 128.2 ($J_{C\text{-}F}$ = 1.9 Hz), 127.4, 127.1 ($J_{C\text{-}F}$ = 3.8 Hz), 120.5 ($J_{C\text{-}F}$ = 9.8 Hz), 113.8 ($J_{C\text{-}F}$ = 24.1 Hz), 113.5 ($J_{C\text{-}F}$ = 17.3 Hz), 108.5 ($J_{C\text{-}F}$ = 1.4 Hz), 41.8, 29.0, 21.7; HRMS (ESI) *m/e* calcd for $C_{20}H_{22}N_2O_3FS$ $(M + H)^+$ 389.1330, found 389.1323.

4-Methyl-*N*-(3-methyl-1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (7r): Yellow solid (67 mg, 87%); m.p. 129-131 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.53 (dd, *J* = 7.0, 1.9 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.30-7.24 (m, 3H), 7.06 (d, *J* = 8.0 Hz, 2H), 2.28 (s, 3H), 2.19 (d, *J* = 1.1 Hz, 3H), 1.33 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.0, 143.3, 137.7, 133.4, 129.8, 129.5, 127.0, 125.4, 125.1, 123.5, 122.8, 118.3, 116.7, 41.7, 29.1, 21.6, 9.9; HRMS (ESI) *m/e* calcd for $C_{21}H_{25}N_2O_3S$ $(M + H)^+$ 385.1580, found 385.1585.

Ethyl 2-(7-(4-methylphenylsulfonamido)-1-pivaloyl-1*H*-indol-3-yl)acetate (7s): Yellow semisolid (64 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.62 (s, 1H), 7.53-7.51 (m, 1H), 7.40 (d, *J* = 7.0 Hz, 2H), 7.30-7.28 (m, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.64 (d, *J* = 1.0 Hz, 2H), 2.28 (s, 3H), 1.36 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 179.3, 170.7, 143.4, 137.6, 132.2, 129.5 (2C), 126.9 (2C), 125.5, 125.3, 122.9, 116.6, 114.9, 61.3, 41.8, 30.7, 29.1, 21.6, 14.4; HRMS (ESI) *m/e* calcd for $C_{24}H_{29}N_2O_5S$ $(M + H)^+$ 457.1792, found 457.1794.

***N*-(3-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-pivaloyl-1*H*-indol-7-yl)-4-methyl-benzenesulfonamide (7t):** Brown semisolid (82 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.52 (dd, *J* = 6.7, 2.0 Hz, 1H), 7.39-7.38 (m, 3H), 7.31-7.25 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 3.87 (t, *J* = 6.1 Hz, 2H), 2.81 (t, *J* = 6.0 Hz, 2H), 2.27 (s, 3H), 1.33 (s, 9H), 0.83 (s, 9H), -0.06 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.1, 143.2, 137.7, 132.9, 129.6, 129.5, 127.0, 125.4, 125.0, 124.3, 122.8, 120.1, 116.7, 62.4, 41.7, 29.1, 28.5, 26.1, 21.6, 18.4, -5.2; HRMS (ESI) *m/e* calcd for

$C_{28}H_{40}N_2O_4SSiNa$ $(M + Na)^+$ 551.2370, found 551.2365.

***N*-(3-(2-(1,3-Dioxoisoindolin-2-yl)ethyl)-1-pivaloyl-1*H*-indol-7-yl)-4-methyl-benzenesulfonamide (7u):** White solid (98 mg, 90%); m.p. 167-169 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.81-7.79 (m, 2H), 7.70-7.68 (m, 2H), 7.50-7.48 (m, 1H), 7.44-7.42 (m, 1H), 7.38-7.36 (m, 3H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 3.98 (t, *J* = 7.2, 2H), 3.06 (t, *J* = 7.2 Hz, 2H), 2.26 (s, 3H), 1.29 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.2, 168.4, 143.3, 137.7, 134.4, 132.3, 132.1, 129.8, 129.5, 126.9, 125.4, 125.3, 123.7, 123.5, 123.1, 118.8, 116.7, 41.7, 37.2, 29.0, 24.1, 21.6; HRMS (ESI) *m/e* calcd for $C_{30}H_{30}N_3O_5S$ $(M + H)^+$ 544.1901, found 544.1902.

(*S*)-Methyl 2-(1,3-dioxoisoindolin-2-yl)-3-(7-(4-methylphenylsulfonamido)-1-pivaloyl-1*H*-indol-3-yl)propanoate (7w): White semisolid (1.6 g, 88%); $[\alpha]_D$ -101.9 (c 0.2, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.77-7.75 (m, 2H), 7.70-7.68 (m, 2H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.34-7.23 (m, 5H), 7.01 (d, *J* = 8.0 Hz, 2H), 5.21-5.18 (m, 1H), 3.76 (s, 3H), 3.62-3.59 (m, 2H), 2.22 (s, 3H), 1.19 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 179.1, 169.2, 167.6, 143.2, 137.7, 134.6, 132.0, 131.7, 129.7, 129.5, 126.9, 125.5, 125.3, 124.5, 123.7, 123.1, 117.6, 116.3, 53.3, 51.3, 41.6, 28.9, 24.6, 21.5.; HRMS (ESI) *m/e* calcd for $C_{32}H_{32}N_3O_7S$ $(M + H)^+$ 602.1955, found 602.1945.

***N*-(1-Pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (8a):** White solid (63 mg, 89%); m.p. 125-127 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.54-7.48 (m, 4H), 7.42-7.36 (m, 2H), 7.31-7.25 (m, 3H), 6.55 (d, *J* = 3.9 Hz, 1H), 1.35 (s, 9H); $^{13}C\{^1H\}$

NMR (100 MHz, $CDCl_3$) δ 179.5, 140.5, 132.6, 132.4, 129.6, 128.9, 126.9, 126.7, 125.4, 125.2, 123.1, 119.1, 109.5, 41.8, 29.2; HRMS (ESI) *m/e* calcd for $C_{19}H_{21}N_2O_3S$ $(M + H)^+$ 357.1267, found 357.1269.

4-Fluoro-*N*-(1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (8b): White solid (66 mg, 88%); m.p. 116-118 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.54-7.49 (m, 4H), 7.39 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 6.97-6.93 (m, 2H), 6.57 (d, *J* = 3.9 Hz, 1H), 1.38 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.5, 166.4 ($J_{C\text{-}F}$ = 253.2 Hz), 136.6 ($J_{C\text{-}F}$ = 2.8 Hz), 132.5, 129.7 ($J_{C\text{-}F}$ = 9.2 Hz), 129.6, 126.9, 125.5, 125.0, 122.9, 119.2, 116.2 ($J_{C\text{-}F}$ = 22.3 Hz), 109.7, 41.9, 29.3; HRMS (ESI) *m/e* calcd for $C_{19}H_{20}FN_2O_3S$ $(M + H)^+$ 375.1173, found 375.1181.

4-Chloro-*N*-(1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (8c): White solid (70 mg, 90%); m.p. 112-114 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.53 (d, *J* = 3.9 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.45-7.41 (m, 2H), 7.39 (dd, *J* = 7.7, 1.2 Hz, 1H),7.32 (t, *J* = 7.7 Hz, 1H), 7.25-7.23 (m, 2H), 6.58 (d, *J* = 3.9 Hz, 1H), 1.37 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.5, 139.1, 138.9, 132.5, 129.5, 129.1, 128.4, 126.8, 125.5, 124.9, 123.0, 119.3, 109.7, 41.9, 29.2; HRMS (ESI) *m/e* calcd for $C_{19}H_{20}N_2O_3ClS$ $(M + H)^+$ 391.0878, found 391.0884.

4-Bromo-*N*-(1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (8d): White solid (68 mg, 78%); m.p. 118-120 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.53 (d, *J* = 3.9 Hz, 1H), 7.51 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.42-7.37 (m, 3H), 7.36-7.33 (m, 2H), 7.32 (t, *J* = 7.7 Hz, 1H), 6.58 (d, *J* = 3.9 Hz, 1H), 1.37 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.5, 139.5, 132.5, 132.1, 129.5, 128.5, 127.6, 126.8, 125.5, 124.8,

123.0, 119.4, 109.7, 41.9, 29.2; HRMS (ESI) *m/e* calcd for $C_{19}H_{20}BrN_2O_3S$ $(M + H)^+$ 435.0372, found 435.0376.

4-Cyano-*N*-(1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (8e): Brown semisolid (53 mg, 70%); ^1H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.64-7.62 (m, 2H), 7.59-7.56 (m, 2H), 7.54 (d, *J* = 3.9 Hz, 1H), 7.49-7.47 (m, 1H), 7.40-7.38 (m, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 6.59 (d, *J* = 3.9 Hz, 1H), 1.38 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.7, 144.7, 132.69, 132.65, 129.4, 127.7, 126.9, 125.7, 124.5, 122.5, 119.6, 117.4, 116.3, 109.9, 42.0, 29.3; HRMS (ESI) *m/e* calcd for $C_{20}H_{20}N_3O_3S$ $(M + H)^+$ 382.1220, found 382.1220.

4-Acetyl-*N*-(1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (8f): Brown semisolid (63 mg, 79%); ^1H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.50-7.48 (m, 2H), 7.37 (d, *J* = 7.0 Hz, 1H), 7.30-7.26 (m, 1H), 6.55 (d, *J* = 3.9 Hz, 1H), 2.52 (s, 3H), 1.34 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.9, 179.6, 144.3, 139.9, 132.5, 129.4, 128.7, 127.3, 126.8, 125.5, 124.7, 122.5, 119.3, 109.7, 41.9, 29.2, 27.0; HRMS (ESI) *m/e* calcd for $C_{21}H_{23}N_2O_4S$ $(M + H)^+$ 399.1373, found 399.1378.

3,5-Dichloro-*N*-(1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (8g): Brown solid (67 mg, 79%); m.p. 108-110 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.56 (d, *J* = 3.9 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.43 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.36-7.31 (m, 4H), 6.61 (d, *J* = 3.9 Hz, 1H), 1.41 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.7, 143.1, 135.8, 132.7, 132.5, 129.6, 126.9, 125.7, 125.4, 124.4, 123.0, 119.8, 109.9, 41.9, 29.2; HRMS (ESI) *m/e* calcd for $C_{19}H_{19}N_2O_3Cl_2S$ $(M + H)^+$

425.0488, found 425.0487.

2,4-Difluoro-*N*-(1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (8h): White semisolid (65 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.77-7.72 (m, 1H), 7.64 (d, *J* = 3.9 Hz, 1H), 7.47-7.45 (m, 1H), 7.30-7.28 (m, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 6.82-6.77 (m, 1H), 6.74-6.69 (m, 1H), 6.57 (d, *J* = 3.9 Hz, 1H), 1.51 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.9, 167.2 ($J_{C\text{-}F}$ = 256.0, 11.3 Hz), 161.0 ($J_{C\text{-}F}$ = 256.7, 12.7 Hz), 133.0 ($J_{C\text{-}F}$ = 10.4, 1.4 Hz), 132.6, 128.8, 127.0, 125.4, 124.8, 124.5 ($J_{C\text{-}F}$ = 26.2, 14.0 Hz), 120.4, 118.7, 112.0 ($J_{C\text{-}F}$ = 21.7, 3.8 Hz), 109.6, 105.6 ($J_{C\text{-}F}$ = 25.7, 24.6 Hz), 42.1, 29.3; HRMS (ESI) *m/e* calcd for $C_{19}H_{19}N_2O_3SF_2$ $(M + H)^+$ 393.1079, found 393.1082.

4-Methoxy-*N*-(1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (8i): White solid (68 mg, 88%); m.p. 119-121 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.48-7.46 (m, 2H), 7.40 (d, *J* = 8.8 Hz, 2H),7.33 (d, *J* = 7.0 Hz, 1H), 7.26-7.21 (m, 1H), 6.70 (d, *J* = 8.9 Hz, 2H), 6.53 (d, *J* = 3.9 Hz, 1H), 3.70 (s, 3H), 1.34 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.5, 162.8, 132.4, 132.1, 129.5, 129.0, 126.7, 125.4, 125.3, 122.9, 118.9, 114.0, 109.5, 55.7, 41.8, 29.2; HRMS (ESI) *m/e* calcd for $C_{20}H_{23}N_2O_4S$ $(M + H)^+$ 387.1372, found 387.1376.

***N*-(1-Pivaloyl-1*H*-indol-7-yl)naphthalene-2-sulfonamide (8j):** Brown semisolid (69 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.14 (s, 1H), 7.77-7.74 (m, 2H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.58-7.48 (m, 3H), 7.37-7.28 (m, 4H), 6.50 (d, *J* = 3.9 Hz, 1H), 1.16 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.4, 137.4, 134.8, 132.4, 132.2, 129.6, 129.3, 129.0, 128.9, 128.1, 127.9, 127.6, 126.7, 125.4, 125.2, 123.2,

122.3, 119.2, 109.5, 41.6, 28.9; HRMS (ESI) *m/e* calcd for $C_{23}H_{22}N_2O_3SNa$ (M + Na)$^+$ 429.1243, found 429.1250.

***N*-(1-Pivaloyl-1*H*-indol-7-yl)methanesulfonamide (8k):** White solid (52 mg, 88%); m.p. 160-162 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.72 (d, *J* = 3.9 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.41-7.39 (m, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 3.9 Hz, 1H), 2.90 (s, 3H), 1.54 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 180.1, 132.9, 129.1, 127.0, 125.6, 125.5, 120.8, 118.8, 109.7, 42.2, 39.9, 29.4; HRMS (ESI) *m/e* calcd for $C_{14}H_{18}N_2O_3SNa$ (M + Na)$^+$ 317.0930, found 317.0928.

***N*-(1-Pivaloyl-1*H*-indol-7-yl)octane-1-sulfonamide (8l):** Brown semisolid (64 mg, 81%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.71 (d, *J* = 3.9 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.38 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 3.9 Hz, 1H), 3.00-2.96 (m, 2H), 1.78-1.71 (m, 2H), 1.54 (s, 9H), 1.32-1.18 (m, 10H), 0.85 (t, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 180.1, 132.9, 128.9, 127.0, 125.9, 125.5, 120.0, 118.4, 109.7, 52.2, 42.2, 31.8, 29.4, 29.1, 29.0, 28.3, 23.5, 22.7, 14.2; HRMS (ESI) *m/e* calcd for $C_{21}H_{33}N_2O_3S$ (M + H)$^+$ 393.2206, found 393.2209.

***N*-(5-Chloro-1-pivaloyl-1*H*-indol-7-yl)-4-methoxybenzenesulfonamide (8m):** White solid (51 mg, 60%); m.p. 151-153 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.56 (d, *J* = 4.0 Hz, 1H), 7.53 (d, *J* = 9.0 Hz, 2H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.29 (d, *J* = 2.0 Hz, 1H), 6.78 (d, *J* = 9.0 Hz, 2H), 6.5 (d, *J* = 4.0 Hz, 1H), 3.75 (s, 3H), 1.39 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 179.6, 163.1, 133.4, 131.9, 130.8, 129.2, 128.0, 127.8, 126.5, 121.7, 118.1, 114.2, 108.9, 55.8, 42.0, 29.3; HRMS (ESI)

m/e calcd for $C_{20}H_{22}N_2O_4ClS$ $(M + H)^+$ 421.0983, found 421.0981.

***N*-(4-Chloro-1-pivaloyl-1*H*-indol-7-yl)-4-methoxybenzenesulfonamide (8n):** Brown semisolid (61 mg, 73%); ^1H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.56 (d, *J* = 4.0 Hz, 1H), 7.46 (d, *J* = 9.0 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 9.0 Hz, 2H), 6.70 (d, *J* = 4.0 Hz, 1H), 3.75 (s, 3H), 1.38 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 179.7, 163.0, 132.0, 130.8, 130.3, 129.1, 127.2, 124.9, 124.1, 124.0, 123.7, 114.2, 107.5, 55.8, 42.0, 29.2; HRMS (ESI) *m/e* calcd for $C_{20}H_{22}N_2O_4ClS$ $(M + H)^+$ 421.0983, found 421.0985.

***N*-(5-Chloro-1-pivaloyl-1*H*-indol-7-yl)methanesulfonamide (8o):** White semisolid (41 mg, 63%); ^1H NMR (500 MHz, $CDCl_3$) δ 9.24 (s, 1H), 7.74 (d, *J* = 4.0 Hz, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.34 (d, *J* = 2.0 Hz, 1H), 6.60 (d, *J* = 4.0 Hz, 1H), 2.96 (s, 3H), 1.53 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 180.2, 133.8, 131.0, 128.3, 127.2, 126.7, 119.5, 117.9, 109.1, 42.3, 40.2, 29.4. HRMS (ESI) *m/e* calcd for $C_{14}H_{17}ClN_2O_3SNa$ $(M + Na)^+$ 351.0541, found 351.0543.

***N*-(3-(1-Cyclopropyl-1-(4-fluorophenyl)ethyl)-1-pivaloyl-1*H*-indol-7-yl)methane-sulfonamide (8p):** Brown semisolid (83 mg, 91%); ^1H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.86 (s, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.20-7.17 (m, 2H), 7.05 (t, *J* = 7.9 Hz, 1H), 6.94 (t, *J* = 8.7 Hz, 2H), 6.63 (d, *J* = 7.8 Hz, 1H), 2.93 (s, 3H), 1.58 (s, 12H), 1.49-1.45 (m, 1H), 0.57-048 (m, 2H), 0.31-0.27 (m, 1H), 0.14-0.11 (m, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 179.9, 162.6 ($J_{C\text{-}F}$ = 243.8 Hz), 140.7 ($J_{C\text{-}F}$ = 3.2 Hz), 131.5 ($J_{C\text{-}F}$ = 89.3 Hz), 130.3, 129.3, 129.2, 125.8, 124.8, 124.3, 120.1, 119.2, 115.1 ($J_{C\text{-}F}$ = 20.9 Hz), 42.3, 41.8, 40.2, 29.5, 25.1, 22.1, 1.8, 1.5; HRMS (ESI) *m/e* calcd for

$C_{25}H_{29}FN_2O_3SNa$ $(M + Na)^+$ 479.1775, found 479.1774.

***N*-(3-(2-Phenylpropan-2-yl)-1-pivaloyl-1*H*-indol-7-yl)methanesulfonamide (8q):** Brown semisolid (64 mg, 77%); ^1H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.59 (s, 1H), 7.38 (dd, *J* = 0.9, 7.8 Hz, 1H), 7.28-7.27 (m, 4H), 7.20-7.18 (m, 1H), 7.07 (t, *J* = 7.9 Hz, 1H), 6.78 (dd, *J* = 1.1, 7.9 Hz, 1H), 2.92 (s, 3H), 1.74 (s, 6H), 1.57 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.9, 147.7, 131.7, 131.6, 130.5, 128.6, 126.5, 126.3, 125.7, 124.9, 123.1, 120.3, 119.3, 42.2, 40.2, 39.1, 30.1, 29.5. HRMS (ESI) *m/e* calcd for $C_{23}H_{29}N_2O_3S$ $(M + H)^+$ 413.1893, found 413.1894.

***N*-(3-(2-Phenylpentan-2-yl)-1-pivaloyl-1*H*-indol-7-yl)methanesulfonamide (8r):** Brown semisolid (73 mg, 83%); ^1H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.59 (s, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.29-7.26 (m, 4H), 7.21-7.18 (m, 1H), 7.06 (t, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 2.94 (s, 3H), 2.14-2.02 (m, 2H), 1.70 (s, 3H), 1.59 (s, 9H), 1.13-1.10 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.9, 146.9, 131.7, 130.7, 130.2, 128.5, 126.9, 126.4, 125.6, 124.9, 123.8, 120.1, 119.3, 43.4, 42.5, 42.2, 40.2, 29.5, 27.0, 17.9, 14.9. HRMS (ESI) *m/e* calcd for $C_{25}H_{32}N_2O_3SNa$ $(M + Na)^+$ 463.2026, found 463.2018.

(*S*)-Methyl 2-(1,3-dioxoisoindolin-2-yl)-3-(7-(methylsulfonamido)-1-pivaloyl-1*H*-indol-3-yl) propanoate (8s): White semisolid (81 mg, 77%); $[\alpha]_D$ -140.3 (c 0.2, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ 9.09 (s, 1H), 7.78-7.75 (m, 2H), 7.70-7.68 (m, 2H), 7.54 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.38 (dd, *J* = 1.0, 7.8 Hz. 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 5.27-5.23 (m, 1H), 3.79 (s, 3H), 3.67-3.65 (m, 2H), 2.83 (s, 3H), 1.38 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 179.7, 169.2, 167.7, 134.7, 132.5, 131.7,

129.2, 125.9, 125.6, 124.8, 123.8, 120.9, 117.9, 116.2, 53.4, 51.1, 42.0, 39.9, 29.1, 24.8. HRMS (ESI) *m/e* calcd for $C_{26}H_{27}N_3O_7SNa$ $(M + Na)^+$ 548.1462, found 548.1452.

***N*-(5-Chloro-1*H*-indol-7-yl)-4-methoxybenzenesulfonamide (1):** To a solution of **8m (**84 mg, 0.2 mmol) in 1.0 mL of methanol was added Et_3N (1.0 mL) dropwise at room temperature. The reaction mixture was stirred for 24 h before it was concentrated under vacuum. The residue was purified by chromatography on silica with a gradient eluent of petroleum ether and ethyl acetate to give 62 mg (92%) of **1** as white solid. m.p. 142-144 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.63 (d, *J* = 9.0 Hz, 2H), 7.42 (d, *J* = 1.3 Hz, 1H), 7.26-7.25 (m, 1H), 7.15 (s, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 6.54 (d, *J* = 1.6 Hz, 1H), 6.46-6.44 (m, 1H), 3.79 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.7, 130.8, 130.0, 129.7, 129.0, 126.8, 124.8, 121.0, 119.1, 117.5, 114.6, 102.7, 55.8. HRMS (ESI) *m/e* calcd for $C_{15}H_{14}ClN_2O_3S$ $(M + H)^+$ 337.0408, found 337.0402.

***N*-(3-(2-Phenylpropan-2-yl)-1*H*-indol-7-yl)methanesulfonamide (9):** Following the same procedure for preparing **1** from **8m**, **9** was obtained in 90% yield (yellow solid，59 mg) from **8q**. m.p. 161-163 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.33-7.31 (m, 2H), 7.25-7.21 (m, 2H), 7.18-7.13 (m, 2H), 6.98 (s, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.3 Hz, 1H), 6.82 (t, *J* = 7.8 Hz, 1H), 3.00 (s, 3H), 1.75 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.8, 133.1, 128.6, 128.2, 126.54, 126.53, 125.8, 122.1, 120.9, 119.9, 119.2, 117.5, 39.0, 38.8, 30.8. HRMS (ESI) *m/e* calcd for $C_{18}H_{21}N_2O_2S$ $(M + H)^+$ 329.1318, found 329.1314.

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Supporting Information: The copies of ^{1}H and ^{13}C NMR spectrum of products, X-ray diffraction parameters and data of **7a**, and detailed deuteration experiments. This material is available free of charge via the Internet at http://pubs.acs.org

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