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Synthesis of Sulfonated Oxindoles by Potassium Iodide Catalyzed Arylsulfonylation of Activated Alkenes with Sulfonylhydrazides in Water

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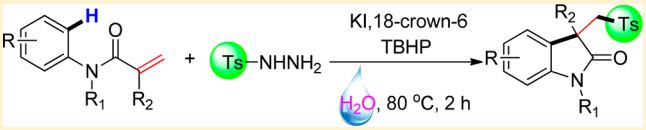
Supporting Information

ABSTRACT: A catalytic system consisting of KI, 18-crown-6, and TBHP for arylsulfonylation of activated alkenes with sulfonylhydrazides as sulfonyl precursor is described. This protocol provides a practical and environmentally benign method for the construction of sulfonated oxindoles in water.

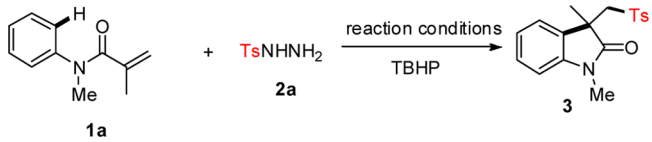


Sulfone-containing molecules are an omnipresent component of many classes of biologically active compounds and marketed drugs.[1] The sulfone moiety also serves as a versatile building block, especially as a carbon nucleophile as a consequence of its electron-withdrawing character.[2] The addition of sulfonyl radicals to carbon−carbon multiple bonds represents a particularly useful contribution to sulfone synthesis.[3] In a recent report, Taniguchi demonstrated iron-catalyzed synthesis of β-hydroxysulfone by mild oxidative additions of sulfonyl radicals to alkenes using readily accessible sulfonylhydrazides as a sulfonyl precursor.[4] Investigations by our group found that the generation of sulfonyl radicals from sulfonyl hydrazide could also be achieved by using TBAI as catalyst and TBHP as oxidant.[5] These processes are distinguished by using readily available reagents, environmentally benign byproducts, and an easy experimental operation. Thus, there still exists a great demand to develop new approaches toward sulfone-containing molecules using sulfonylhydrazides as sulfonyl precursor.

Recently, Pd-catalyzed oxidative difunctionalization of alkenes in *N*-arylacrylamides involving the direct aryl C(sp^2)-H functionalization has attracted considerable attention.[6] Various functionalized oxindoles could be constructed by this efficient protocol. Alternative palladium-free methods using more practical catalysts are also investigated.[7−9] Yang and coworkers reported $AgNO_3$-catalyzed carbon phosphorylation to form phosphorylated oxindoles.[8] The Li group described $FeCl_3$-catalyzed oxidative coupling of C(sp^3)-H bond adjacent to a heteroatom to form oxindoles using TBHP as oxidant.[9a] Very recently, they developed a method for the oxidative coupling of aldehyde C(sp^2)-H bond under metal-free conditions using TBHP.[9b] Mechanism studies demonstrated that both Yang and Li's works proceed by a radical pathway. We envisaged that the sulfonyl radicals generated from sulfonylhydrazides using our recently reported method[5] might be utilized to allow similar aryl C(sp^2)-H functionalization/cyclization reactions of *N*-arylacrylamides. Herein, we report readily accessible potassium iodide catalyzed intramolecular oxidative arylsulfonylation of *N*-arylacrylamides with sulfonylhydrazides in water to afford sulfonated oxindoles.

We commenced our reaction with *N*-arylacrylamide **1a** and *p*-toluenesulfonylhydrazide ($TsNHNH_2$) **2a** as model substrates (Table 1). As expected, sulfonated oxindole **3** was formed when the standard conditions established in our recently work were applied (TBAI as catalyst, TBHP as oxidant and water as solvent),[5b] albeit in a modest yield of 45% (Table 1, entry 1). The use of KI and NaI as the catalyst improved the yield of **3** to 55% and 52% (Table 1, entries 2 and

Table 1. Optimization of Reaction Conditions[a]



1a + **2a** → **3**

entry	cat. (mol %)	solvent	yield[b] (%)
1	TBAI (20)	H_2O	45
2	KI (20)	H_2O	55
3	NaI (20)	H_2O	52
4	KI (50)	H_2O	60
5	KI (20)	MeCN	51[c]
6	KI (20) + 18-crown-6 (20)	H_2O	81
7	CuBr (20)	H_2O	39
8	$CuCl_2$ (20)	H_2O	41
9	$Cu(OAc)_2·H_2O$ (20)	H_2O	45
10	*d*	H_2O	39

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), catalyst, and TBHP (70% aqueous solution) (3 equiv) in 2.0 mL of solvent at 80 °C for 2 h. [b]isolated yield. [c]5 h. [d]Without catalyst.

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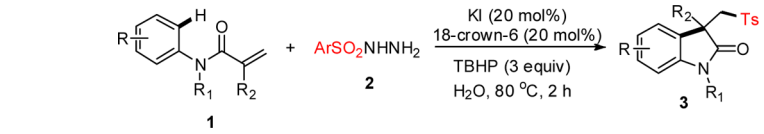
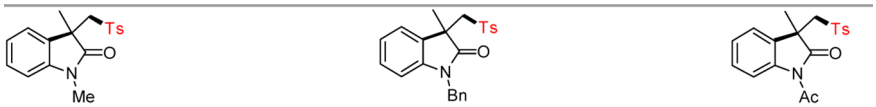
Table 2. Synthesis of Sulfonated Oxindoles

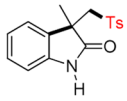




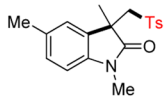
3: 81%

4: 51%

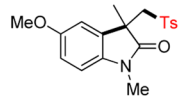
5: 0%



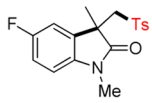
6: 0%



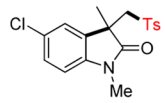
7: 69%



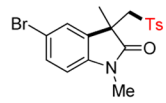
8: 64%



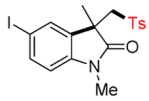
9: 65%[c]



10: 62%



11: 52%



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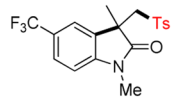
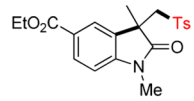


13: 40%[c]



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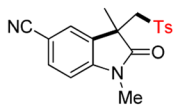
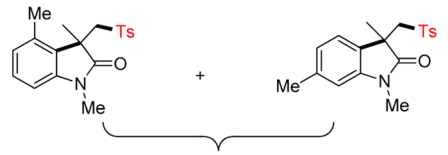
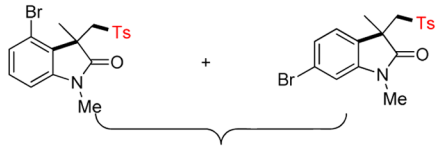


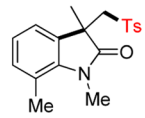
15: 76%[c]



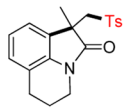
16+**16'**: 82% (2:1)



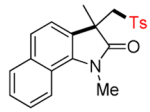
17 + **17'** 72%[c] (3:1), 41%[d]



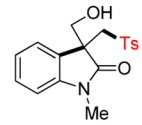
18: trace



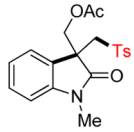
19: 52%



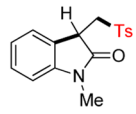
20: 51% [c]



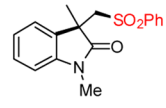
21: 51%



22: 54%



23: 0%



24: 53%

[a]Reaction conditions: *N*-arylacrylamides **1** (0.25 mmol), sulfonylhydrazides **2** (0.5 mmol), KI (20 mol %), 18-crown-6 (20 mol %), TBHP (70% aqueous solution) (3 equiv) in H_2O (2.0 mL) at 80 °C for 2 h. [b]Isolated yield. [c]KI (50 mol %), 18-crown-6 (50 mol %). [d]Yield of **17** after recrystallization.

3). The yield was slightly improved to 60% when the loading of KI was increased from 20 mol % to 50 mol % (Table 1, entry 4). However, the use of MeCN as solvent reduced the reaction efficiency, and only 51% of **3** was obtained after 5 h (Table 1,

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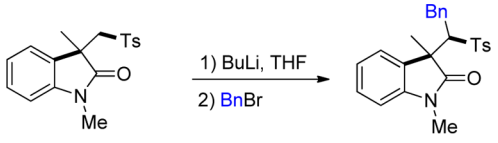
entry 5). To our delight, the addition of 18-crown-6 as a phase transfer catalyst significantly improved the yield of **3** to 81% (Table 1, entry 6). Copper salts, which were reported to assist the decomposition of TBHP,[10] exhibited much lower activity (Table 1, entries 7−9). Notably, the reaction could occur smoothly under catalyst-free condition, albeit in lower yield (Table 1, entry 10).

With the optimized conditions in hand, we then explored the scope and limitations of the above reaction, and the results are summarized in Table 2. The effect of N-protecting groups was first examined. The reaction underwent only for methyl and benzyl group (products **3** and **4**), whereas acetyl and N-free *N*-arylacrylamides does not work at all (products **5** and **6**). Next, substrates with various substitution patterns at the *N*-aryl moiety were screened. The reaction proceeded smoothly not only for the *N*-arylacrylamides bearing an electron-donating group (products **7** and **8**) but also for those substrates having halides (products **9**−**12**) or strong electron-withdrawing substituents such as CF_3, CO_2Et, or CN (products **13**−**15**) on the *para*-position, although 50 mol % of the catalyst loading was required for some substrates to furnish the products. As expected, *meta*-substituted substrates gave a mixture of two regioselective products (products **16**/**16′** and **17**/**17′**). We were pleased to discover that pure **17** could be isolated by recrystallization from DCM/petroleum in 41% yield, thereby facilitating possible modifications at the *meta*-positions. *Ortho*-substituted substrate failed in the reaction to give the desired oxindole **18** due to the steric effect. In addition, naphthalene and tetrahydroquinoline derivative were also viable substrates to provide the corresponding oxindoles **19** and **20**. Next, the substituent effect at R_2 position was evaluated. Both CH_2OH and CH_2OAc substituents were compatible with the optimal conditions (products **21** and **22**), whereas monosubstituented olefin (R_2 = H) did not undergo the cyclization (product **23**). Finally, readily accessible phenylsulfonylhydrazide was also utilized as a sulfonyl precursor to afford the corresponding oxindole **24**.

The synthetic utility of the sulfonated oxindoles was exemplified by the alkylation of oxindole **3** to oxindole **25** (Scheme 1). Treatment of **3** with 1.1 equiv of *n*-butyllithium at

Scheme 1. Alkylation of Oxindole 3



3 **25**: 64%

−78 °C led to smooth deprotonation, and the corresponding carbanion reacted with benzyl bromide to give oxindole **25** in 64% yield.

Several control experiments were conducted to elucidate the mechanism of this C(sp^2)-H functionalization/cyclization reaction (Scheme 2). First, the inter- and intramolecular kinetic isotope experiments were performed, and no kinetic isotope effect (k_H/k_D = 1.0) was observed. Then, a stoichiometric amount of TEMPO (2.5 equiv), a well-known radical inhibitor, was introduced to the reaction mixture and the formation of the desired oxindole was completely suppressed. All this results indicated that the reaction underwent by a radical pathway.[8,9,11]

According to the above experimental results and previous reports,[5,8,9,12] a plausible mechanism is proposed (Scheme 3). Initially, the *tert*-butoxyl and *tert*-butylperoxy radicals were generated in iodine anion-TBHP catalytic system.[12] The addition of 18-crown-6 as phase-transfer catalyst might accelerate the rate of transfer of water-soluble KI across the interface to the organic phase and thus enhance the efficiency of iodine anion catalyzed TBHP decomposion.[12c] Then, the resultant radicals abstract hydrogen atoms from sulfonylhydrazides to generate sulfonyl radicals with the release of molecular nitrogen.[5] The addition of sulfonyl radicals to *N*-arylacrylamides and subsequent intramolecular radical substitution reaction of alkyl radical I gives intermediate II. Finally, radical intermediate II undergoes hydrogen abstraction by TBHP to give sulfonated oxindoles.[9b]

In summary, we have developed a novel protocol for the synthesis of sulfonated oxindoles by transition-metal-free intramolecular oxidative arylsulfonylation of activated alkenes through direct aryl C(sp^2)-H functionalization. The reaction is environmentally benign in adoption of readily available sulfonylhydrazides as sulfonyl precursor, nontoxic KI as catalyst, and water as solvent.

EXPERIMENTAL SECTION

General Procedures. All reagents and solvents were purchased from commercial suppliers and used without purification. Melting points are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ at 500 or 400 and 125 or 100 MHz, respectively, with TMS as the internal standard. Chemical shifts (δ) are expressed in ppm, and coupling constants J are given in hertz. High-resolution mass spectra (HRMS) were obtained on a TOF MS instrument with ESI source. The *N*-arylacrylamides were synthesized according to the literature method.[13]

Typical Procedure for the Synthesis of Sulfonated Oxindoles. To a suspension of *N*-arylacrylamides (0.25 mmol), sulfonylhydrazides (0.50 mol), KI (0.05 mol), and 18-crown-6 (0.05 mmol) in water (2 mL) was added TBHP (0.75 mmol) at room temperature, and the mixture was heated at 80 °C for 2 h. After the mixture was cooled to room temperature, the crude product changed from an oil to a viscous solid. The residue was separated by decantation and purified by silica gel chromatography (petroleum/ethyl acetate = 3:2) to give sulfonated oxindoles.

*1,3-Dimethyl-3-(tosylmethyl)indolin-2-one (**3**):* white solid (66.6 mg, 81%); mp 135−137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 8.3 Hz, 2H), 7.31−7.26 (m, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 7.0 Hz, 1H), 6.91 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 3.85 (d, J = 14.6 Hz, 1H), 3.67 (d, J = 14.6 Hz, 1H), 3.16 (s, 3H), 2.39 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 144.3, 143.2, 137.1, 129.6, 129.5, 128.5, 127.8, 124.1, 122.4, 108.3, 61.9, 45.6, 26.5, 25.4, 21.5; HRMS (ESI) calcd for $C_{18}H_{20}NO_3S$ $(M + H)^+$ 330.1164, found 330.1160.

*1-Benzyl-3-methyl-3-(tosylmethyl)indolin-2-one (**4**):* colorless oil (51.6 mg, 51%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 8.3 Hz, 2H), 7.39−7.23 (m, 5H), 7.18−7.10 (m, 3H), 7.05 (dd, J = 7.4, 0.6 Hz, 1H), 6.85 (td, J = 7.6, 0.8 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 4.99 (d, J = 15.8 Hz, 1H), 4.78 (d, J = 15.8 Hz, 1H), 3.90 (d, J = 14.5 Hz, 1H), 3.71 (d, J = 14.5 Hz, 1H), 2.39 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 144.3, 142.4, 137.3, 135.8, 129.8, 129.6, 128.8, 128.4, 127.8, 127.6, 127.3, 124.1, 122.5, 109.5, 61.7, 45.8, 44.2, 26.0, 21.6; HRMS (ESI) calcd for $C_{24}H_{24}NO_3S$ $(M + H)^+$ 406.1477, found 406.1472.

*1,3,5-Trimethyl-3-(tosylmethyl)indolin-2-one (**7**):* colorless oil (59.5 mg, 69%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.24 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 7.03 (dd, J = 7.9, 0.7 Hz, 1H), 6.73 (d, J = 7.9 Hz, 1H), 6.63 (s, 1H), 3.88 (d, J = 14.7 Hz, 1H), 3.66 (d, J = 14.7 Hz, 1H), 3.17 (s, 3H), 2.38 (s, 3H), 2.12 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 144.0, 141.0, 137.0,

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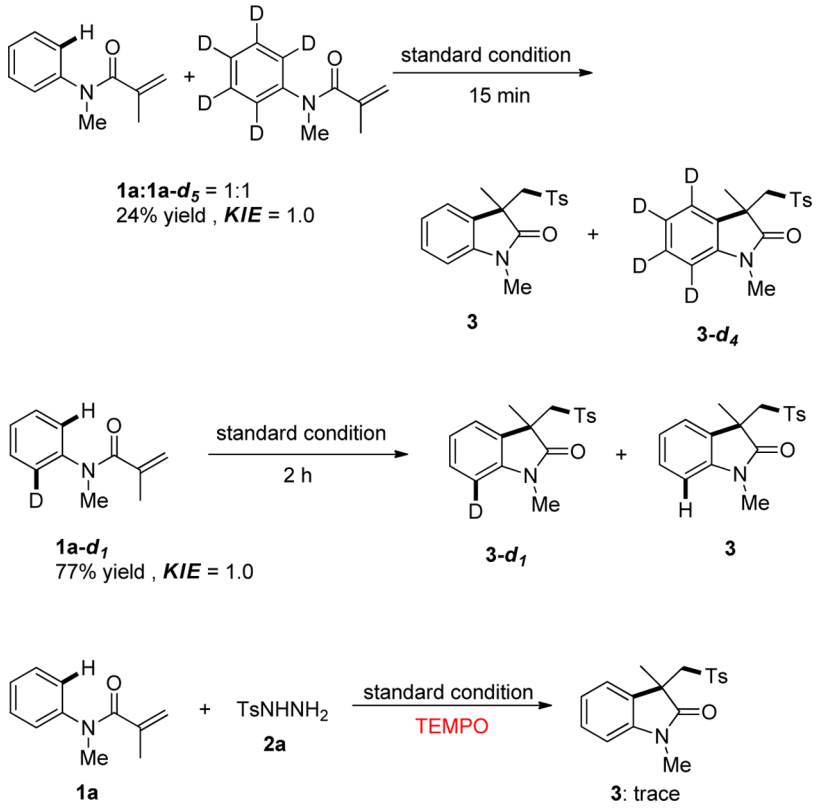
Scheme 2. Control Experiments



131.8, 129.3, 128.7, 127.7, 124.7, 108.0, 61.9, 45.5, 26.5, 25.4, 21.4, 20.8; HRMS (ESI) calcd for $C_{19}H_{22}NO_3S$ $(M + H)^+$ 344.1320, found 344.1314.

5-Methoxy-1,3-dimethyl-3-(tosylmethyl)indolin-2-one ***(8):*** colorless oil (57.8 mg, 64%); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.29 (m, 2H), 7.13 (d, J = 8.0 Hz, 2H), 6.77 (m,, 2H), 6.47 (d, J = 2.3 Hz, 1H), 3.86 (d, J = 14.7 Hz, 1H), 3.70−3.60 (m, 4H), 3.16 (s, 3H), 2.38 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 155.7, 144.2, 137.0, 136.7, 130.5, 129.3, 127.7, 113.1, 110.8, 108.6, 61.8, 55.3, 46.0, 26.6, 25.3, 21.4; HRMS (ESI) calcd for $C_{19}H_{22}NO_4S$ $(M + H)^+$ 360.1270, found 360.1264.

5-Fluoro-1,3-dimethyl-3-(tosylmethyl)indolin-2-one ***(9):*** white solid (56.3 mg, 65%); mp 145−147 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.97 (td, J = 8.9, 2.6 Hz, 1H), 6.77 (dd, J = 8.5, 4.1 Hz, 1H), 6.70 (dd, J = 7.9, 2.6 Hz, 1H), 3.85 (d, J = 14.7 Hz, 1H), 3.65 (d, J = 14.7 Hz, 1H), 3.18 (s, 3H), 2.40 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 159.0 (d, J = 239.5 Hz), 144.6, 139.2 (d, J = 1.7 Hz), 136.9, 131.1 (d, J = 8.1 Hz), 129.5, 127.7, 114.8 (d, J = 23.8 Hz), 112.2 (d, J = 24.9 Hz), 108.8 (d, J = 8.1 Hz), 61.7, 46.0 (d, J = 1.6 Hz), 26.7, 25.2, 21.5; HRMS (ESI) calcd for $C_{18}H_{19}FNO_3S$ $(M + H)^+$ 348.1070, found 348.1065.

5-Chloro-1,3-dimethyl-3-(tosylmethyl)indolin-2-one ***(10):*** white solid (56.3 mg, 62%); mp 186−188 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 8.3 Hz, 2H), 7.21 (dd, J = 8.3, 2.1 Hz, 1H), 7.16 (d, J = 8.0 Hz, 2H), 6.77 (d, J = 8.3 Hz, 1H), 6.72 (d, J = 2.1 Hz, 1H), 3.88 (d, J = 14.8 Hz, 1H), 3.65 (d, J = 14.8 Hz, 1H), 3.21 (s, 3H), 2.41 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 144.7, 142.0, 136.8, 131.0, 129.6, 128.4, 127.9, 127.5, 124.4, 109.3, 61.7, 45.7, 26.7, 25.2, 21.6; HRMS (ESI) calcd for $C_{18}H_{19}ClNO_3S$ $(M + H)^+$ 364.0774, found 364.0770.

5-Bromo-1,3-dimethyl-3-(tosylmethyl)indolin-2-one ***(11):*** white solid (53.2 mg, 52%); mp 175−177 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (dd, J = 8.3, 2.0 Hz, 1H), 7.30−7.26 (m, 2H), 7.16 (d, J = 7.9 Hz, 2H), 6.80 (d, J = 1.9 Hz, 1H), 6.74 (d, J = 8.3 Hz, 1H), 3.88 (d, J = 14.8 Hz, 1H), 3.67 (d, J = 14.8 Hz, 1H), 3.22 (s, 3H), 2.43 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 144.7, 142.5, 136.7, 131.3, 131.3, 129.6, 127.4, 127.0, 115.2, 109.8, 61.7, 45.6, 26.7, 25.2, 21.7; HRMS (ESI) calcd for $C_{18}H_{19}BrNO_3S$ $(M + H)^+$ 408.0269, found 408.0265.

5-Iodo-1,3-dimethyl-3-(tosylmethyl)indolin-2-one ***(12):*** white solid (88.2 mg, 77%); mp 195−197 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, J = 8.2, 1.7 Hz, 1H), 7.27−7.24 (m, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 1.7 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 3.88 (d, J = 14.9 Hz, 1H), 3.66 (d, J = 14.9 Hz, 1H), 3.22 (s, 3H), 2.46 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 144.7, 143.3, 137.3, 136.8, 132.6, 131.8, 129.8, 127.5, 110.4, 85.1, 61.8, 45.5, 26.7, 25.2, 21.9; HRMS (ESI) calcd for $C_{18}H_{19}INO_3S$ $(M + H)^+$ 456.0130, found 456.0125.

1,3-Dimethyl-3-(tosylmethyl)-5-(trifluoromethyl)indolin-2-one ***(13):*** white solid (40.0 mg, 40%); mp 132−134 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, J = 8.2, 0.9 Hz, 1H), 7.28 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.02 (d, J = 0.9 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 3.92 (d, J = 14.8 Hz, 1H), 3.73 (d, J = 14.8 Hz, 1H), 3.28 (s, 3H), 2.37 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 146.5, 144.8, 136.9, 130.0, 129.6, 127.4, 126.4 (q, J = 3.5 Hz), 124.5 (q, J = 32.6 Hz), 124.0 (q, J = 269.8), 120.8(q, J = 3.7 Hz), 108.2, 61.9, 45.5, 26.8, 25.2, 21.4; HRMS (ESI) calcd for $C_{19}H_{19}F_3NO_3S$ $(M + H)^+$ 398.1038, found 398.1034.

Ethyl 1,3-dimethyl-2-oxo-3-(tosylmethyl)indoline-5-carboxylate ***(14):*** white solid (61.4 mg, 61%); mp 174−176 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (dd, J = 8.2, 1.7 Hz, 1H), 7.40 (d, J = 1.5 Hz, 1H), 7.30−7.24 (m, 2H), 7.10 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.2 Hz, 1H), 4.32 (qd, J = 7.1, 1.7 Hz, 2H), 3.93 (d, J = 14.8 Hz, 1H), 3.74 (d, J = 14.8 Hz, 1H), 3.27 (s, 3H), 2.34 (s, 3H), 1.38 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 165.8, 147.5, 144.3, 136.9, 131.1, 129.5, 129.2, 127.5, 124.9, 124.7, 107.9, 61.9, 60.8, 45.3, 26.8, 25.3, 21.4, 14.4; HRMS (ESI) calcd for $C_{21}H_{24}NO_5S$ $(M + H)^+$ 402.1375, found 402.1371.

1,3-Dimethyl-2-oxo-3-(tosylmethyl)indoline-5-carbonitrile ***(15):*** white solid (67.5 mg, 76%); mp 207−209 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.2, 1.6 Hz, 1H), 7.33 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 7.02 (d, J = 1.5 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 3.90 (d, J = 14.8 Hz, 1H), 3.72 (d, J = 14.8 Hz, 1H), 3.28 (s, 3H), 2.46

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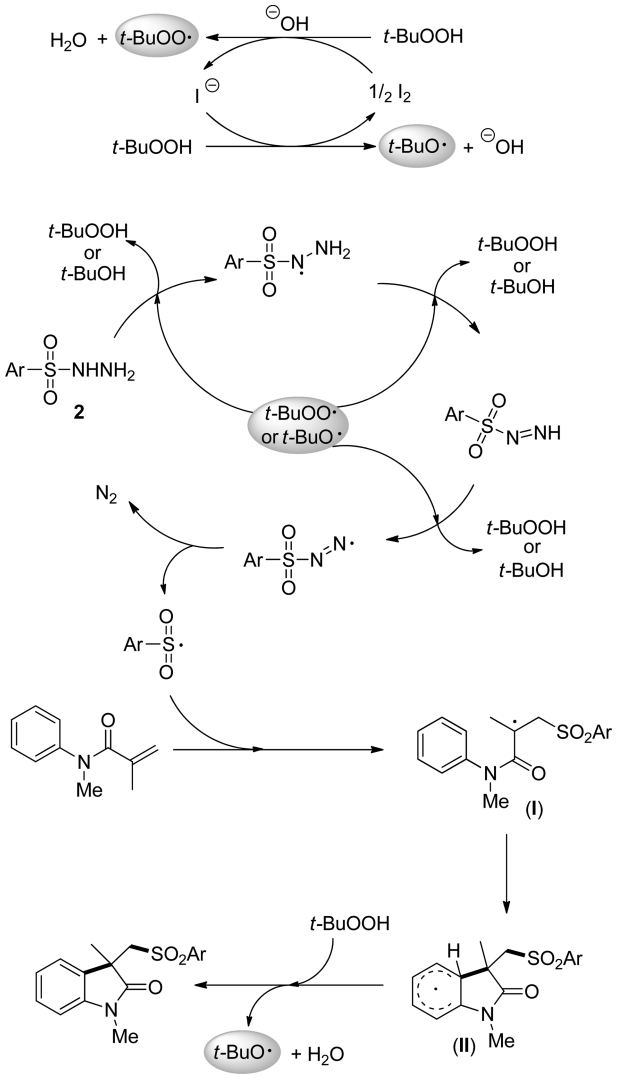
Scheme 3. Proposed Preliminary Mechanisms



(s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 147.3, 145.1, 136.8, 133.7, 130.4, 129.8, 127.4, 127.1, 118.7, 108.9, 105.6, 61.6, 45.3, 26.9, 25.0, 21.6; HRMS (ESI) calcd for $C_{19}H_{19}N_2O_3S$ (M + H)$^+$ 355.1116, found 355.1112.

*1,3,4-Trimethyl-3-(tosylmethyl)indolin-2-one (**16**) and 1,3,6-trimethyl-3-(tosylmethyl)indolin-2-one (**16′**):* colorless oil (70.5 mg, 82%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.40 (m, 1H), 7.36–7.31 (m, 2H), 7.25–7.14 (m, 4H), 7.01 (d, J = 7.6 Hz, 0.5H), 6.78–6.65 (m, 3H), 3.98 (d, J = 14.7 Hz, 1H), 3.84–3.80 (m, 1.5H), 3.64 (d, J = 14.5 Hz, 0.5H), 3.16 (s, 1.5H), 3.13 (s, 3H), 2.41 (s + s, 6H), 2.14 (s, 3H), 1.41 (s, 3H), 1.38 (s, 1.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 177.7, 144.4, 144.3, 143.7, 143.3, 138.8, 137.2, 136.6, 135.5, 129.4, 129.4, 128.6, 128.2, 127.9, 126.8, 125.0, 123.9, 123.0, 109.3, 106.1, 62.1, 61.0, 45.9, 45.5, 26.6, 26.5, 25.5, 23.3, 21.9, 21.6, 18.3; HRMS (ESI) calcd for $C_{19}H_{22}NO_3S$ (M + H)$^+$ 344.1320, found 344.1313.

*4-Bromo-1,3-dimethyl-3-(tosylmethyl)indolin-2-one (**17**) and 6-bromo-1,3-dimethyl-3-(tosylmethyl)indolin-2-one (**17′**):* colorless oil (73.3 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–6.83 (m, 8.75H), 4.25 (d, J = 14.5 Hz, 1H), 3.80 (t, J = 14.5 Hz, 1.33H), 3.64 (d, J = 14.5 Hz, 0.33H), 3.23 (s, 3H), 3.16 (s, 1H), 2.41 (s + s, 4H), 1.48 (s, 3H), 1.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 145.7, 144.4, 136.7, 130.2, 129.6, 129.5, 128.0, 127.7, 126.4, 125.3, 120.2, 107.5, 61.8, 59.6, 47.3, 45.4, 26.8, 25.2, 22.0, 21.6; HRMS (ESI) calcd for $C_{18}H_{19}BrNO_3S$ (M + H)$^+$ 408.0269, found 408.0264.

*4-Bromo-1,3-dimethyl-3-(tosylmethyl)indolin-2-one (**17**):* white solid (41.8 mg, 41%); mp 175–177 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (m, 2H), 7.16 (m, 3H), 6.96 (dd, J = 8.2, 0.7 Hz, 1H), 6.84 (dd, J = 7.8, 0.6 Hz, 1H), 4.25 (d, J = 14.6 Hz, 1H), 3.78 (d, J = 14.6 Hz, 1H), 3.23 (s, 3H), 2.40 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 145.7, 144.4, 136.7, 130.1, 129.4, 128.0, 127.8, 126.4, 120.2, 107.5, 59.6, 47.2, 26.8, 22.0, 21.6; HRMS (ESI) calcd for $C_{18}H_{19}BrNO_3S$ (M + H)$^+$ 408.0269, found 408.0264.

*1-Methyl-1-(tosylmethyl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]-quinolin-2(4H)-one (**19**):* yellow oil (46.2 mg, 52%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 7.03 (d, J = 7.7 Hz, 1H), 6.95 (d, J = 7.4 Hz, 1H), 6.82 (t, J = 7.6 Hz, 1H), 3.82 (d, J = 14.5 Hz, 1H), 3.73–3.57 (m, 3H), 2.78 (t, J = 7.6 Hz, 2H), 2.39 (s, 3H), 2.03–1.95 (m, 2H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 144.2, 139.0, 137.2, 129.4, 128.2, 127.8, 127.2, 122.0, 121.9, 120.3, 61.8, 46.8, 39.0, 25.0, 24.5, 21.5, 20.9; HRMS (ESI) calcd for $C_{20}H_{22}NO_3S$ (M + H)$^+$ 356.1320, found 356.1315.

*1,3-Dimethyl-3-(tosylmethyl)-1H-benzo[g]indol-2(3H)-one (**20**):* white solid (48.4 mg, 51%); mp 207–208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.23 (q, J = 6.7 Hz, 3H), 7.02 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 7.3 Hz, 1H), 4.60 (d, J = 14.4 Hz, 1H), 3.88 (d, J = 14.4 Hz, 1H), 3.50 (s, 3H), 2.33 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 143.9, 137.6, 136.4, 133.7, 133.4, 129.2, 127.8, 126.7, 126.6, 123.5, 123.7, 122.7, 119.3, 108.9, 66.0, 45.6, 33.8, 30.0, 21.5; HRMS (ESI) calcd for $C_{22}H_{22}NO_3S$ (M + H)$^+$ 380.1320, found 380.1316.

*3-(Hydroxymethyl)-1-methyl-3-(tosylmethyl)indolin-2-one (**21**):* white solid (44.0 mg, 51%); mp 147–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.36 (m, 2H), 7.32 (dd, J = 10.9, 4.5 Hz, 1H), 7.17 (d, J = 7.4 Hz, 2H), 7.10 (d, J = 7.2 Hz, 1H), 7.00–6.90 (m, 1H), 6.86 (d, J = 7.8 Hz, 1H), 4.01 (d, J = 14.7 Hz, 1H), 3.84 (d, J = 14.7 Hz, 1H), 3.74–3.58 (m, 2H), 3.16 (d, J = 1.0 Hz, 3H), 2.73 (dd, J = 9.0, 4.3 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 144.5, 143.9, 137.1, 129.6, 129.2, 127.8, 125.8, 124.8, 122.7, 108.6, 67.5, 58.3, 51.0, 26.5, 21.6; HRMS (ESI) calcd for $C_{18}H_{20}NO_4S$ (M + H)$^+$ 346.1113, found 346.1109.

*(1-Methyl-2-oxo-3-(tosylmethyl)indolin-3-yl)methyl acetate (**22**):* colorless oil (52.3 mg, 54%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.0 Hz, 2H), 7.33 (t, J = 7.7 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 7.4 Hz, 1H), 6.94 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H), 4.31 (d, J = 10.9 Hz, 1H), 4.02 (d, J = 10.9 Hz, 1H), 3.88 (q, J = 14.5 Hz, 2H), 3.16 (s, 3H), 2.40 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 169.9, 144.6, 144.0, 136.9, 129.6, 129.4, 127.9, 125.4, 122.5, 108.5, 67.2, 58.2, 49.3, 26.7, 21.6, 20.5; HRMS (ESI) calcd for $C_{20}H_{22}NO_5S$ (M + H)$^+$ 388.1219, found 388.1214.

*1,3-Dimethyl-3-((phenylsulfonyl)methyl)indolin-2-one (**24**):* white solid (42.1 mg, 53%); mp 158–160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.46 (m, 3H), 7.40–7.35 (m, 2H), 7.27 (m, 1H), 7.03 (dd, J = 7.4, 0.6 Hz, 1H), 6.88 (m, 2H), 3.88 (d, J = 14.6 Hz, 1H), 3.70 (d, J = 14.6 Hz, 1H), 3.17 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 143.2, 139.9, 133.3, 129.4, 128.9, 128.6, 127.7, 124.0, 122.5, 108.4, 61.8, 45.6, 26.5, 25.4; HRMS (ESI) calcd for $C_{17}H_{18}NO_3S$ (M + H)$^+$ 316.1007, found 316.1002.

Synthesis of 1,3-Dimethyl-3-((*R*)-2-phenyl-1-tosylethyl)-indolin-2-one (25). Oxindole **3** (200 mg, 0.607 mmol) in THF (10 mL) was cooled to −78 °C and treated with 1.6 M *n*-butyllithium in hexanes (1.05 equiv). After the mixture was stirred for 15 min at −78 °C, benzyl bromide (1.05 equiv) was added dropwise. The mixture was stirred for 5 min at −78 °C, warmed to room temperature, and stirred for another 12 h. Saturated aqueous ammonium chloride (3 mL) was added, and the THF was removed in vacuo. The residue was dissolved in dichloromethane (20 mL) and washed with water (50 mL). The aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic portions were dried over sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum/ethyl acetate = 3:1) to afford the desired product **25** as white solid (163 mg, 64%): mp 213–215 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.3 Hz, 1H), 7.35 (m, 3H), 7.09 (m, 8H), 6.92 (d, J = 7.8 Hz, 1H),

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4.36 (dd, J = 7.4, 5.6 Hz, 1H), 3.56 (m, 2H), 3.27 (s, 3H), 2.31 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 143.7, 143.7, 137.5, 137.2, 129.2, 128.8, 128.7, 128.4, 128.2, 126.6, 124.1, 122.3, 108.8, 71.0, 49.0, 32.4, 26.8, 25.7, 21.5; HRMS (ESI) calcd for $C_{25}H_{26}NO_3S$ $(M + H)^+$ 420.1633, found 420.1628.

■ ASSOCIATED CONTENT

Supporting Information

Kinetic isotopic effect (KIE) studies and copies of ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected examples, see: (a) Napier, C.; Stewart, M.; Melrose, H.; Hopkins, B.; McHarg, A.; Wallis, R. *Eur. J. Pharmacol.* **1999**, *375*, 61. (b) Petrov, K. G.; Zhang, Y.; Carter, M.; Cockerill, G. S.; Dickerson, S.; Gauthier, C. A.; Guo, Y.; Mook, R. A.; Rusnak, D. W.; Walker, A. L.; Wood, E. R.; Lackey, K. E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4686.

(2) For selected examples, see: (a) Sikervar, V.; Fleet, J. C.; Fuchs, P. L. *Chem. Commun.* **2012**, *48*, 9077. (b) Cassani, C.; Bernardi, L.; Fini, F.; Ricci, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 5694. (c) Sikervar, V.; Fleet, J. C.; Fuchs, P. L. *J. Org. Chem.* **2012**, *77*, 5132.

(3) Bertrand, M. P.; Ferreri, C. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 485−504.

(4) Taniguchi, T.; Idota, A.; Ishibashi, H. *Org. Biomol. Chem.* **2011**, *9*, 3151.

(5) (a) Li, X.; Xu, X.; Zhou, C. *Chem. Commun.* **2012**, *48*, 12240. (b) Li, X.; Xu, X.; Tang, Y. *Org. Biomol. Chem.* **2013**, *11*, 1739. (c) Li, X.; Xu, X.; Shi, X. *Tetrahedron Lett.* **2013**, *54*, 3071.

(6) (a) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084. (b) Jia, Y.-K.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1636. (c) Perry, A.; Taylor, J. K. *Chem. Commun.* **2009**, 3249. (d) Jaegli, S.; Dufour, J.; Wei, H.-l.; Piou, T.; Duan, X.-H.; Vors, J.-P.; Neuville, L.; Zhu, J. *Org. Lett.* **2010**, *12*, 4498. (e) Wu, T.; Mu, X.; Liu, G.-S. *Angew. Chem., Int. Ed.* **2011**, *50*, 12578. (f) Mu, X.; Wu, T.; Wang, H.-Y.; Guo, Y.-L.; Liu, G.-S. *J. Am. Chem. Soc.* **2012**, *134*, 878. (g) Zhang, H.; Chen, P.; Liu, G. *Synlett.* **2012**, 2749.

(7) (a) Fabry, D. C.; Stodulski, M.; Hoerner, S.; Gulder, T. *Chem.—Eur. J.* **2012**, *18*, 10834. (b) Xie, J.; Xu, P.; Li, H.; Xue, Q.; Jin, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2013**, *49*, 5672.

(8) Li, Y.-M.; Sun, M.; Wang, H.-L.; Tian, Q.-P.; Yang, S.-D. *Angew. Chem., Int. Ed.* **2013**, *52*, 3972.

(9) (a) Wei, W.-T.; Zhou, M.-B.; Fan, J.-H.; Liu, W.; Song, R.-J.; Liu, Y.; Hu, M.; Xie, P.; Li, J.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 3638. (b) Zhou, M.-B.; Song, R.-J.; Ouyang, X.-H.; Liu, Y.; Wei, W.-T.; Deng, G.-B.; Li, J.-H. *Chem. Sci.* **2013**, *4*, 2690.

(10) (a) Wang, J.; Liu, C.; Yuan, J.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 2256. (b) Cadoni, R.; Porcheddu, A.; Giacomelli, G.; Luca, L. D. *Org. Lett.* **2012**, *14*, 5014. (c) Jiang, H.; Lin, A.; Zhu, C.; Cheng, Y. *Chem. Commun.* **2013**, *49*, 819.

(11) (a) Jones, W. D. *Acc. Chem. Res.* **2003**, *36*, 140. (b) Pinto, A.; Neuville, L.; Retailleau, P.; Zhu, J. *Org. Lett.* **2006**, *8*, 4927. (c) Jones, W. D.; Feher, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 4814. (d) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790.

(12) (a) Liu, Z. J.; Zhang, J.; Chen, S. L.; Shi, E.; Xu, Y.; Wan, X. B. *Angew. Chem., Int. Ed.* **2012**, *51*, 3231. (b) Uyanik, M.; Ishihara, K. *ChemCatChem* **2012**, *4*, 177. (c) Wei, W.; Zhang, C.; Xu, Y.; Wan, X. *Chem. Commun.* **2011**, *47*, 10827.

(13) Fabry, D. C.; Stodulski, M.; Hoerner, S.; Gulder, T. *Chem.—Eur. J.* **2012**, *18*, 10834.