JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

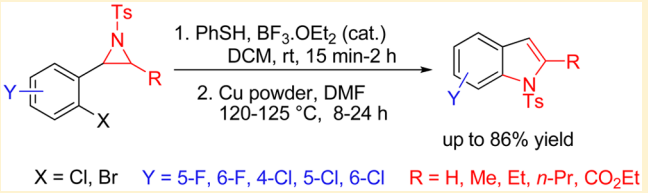
A Synthetic Route to 2-Alkyl Indoles via Thiophenol-Mediated Ring-Opening of *N*-Tosylaziridines Followed by Copper Powder-Mediated C−N Cyclization/Aromatization

Masthanvali Sayyad, Yerramsetti Nanaji, and Manas K. Ghorai*

Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India

Supporting Information

ABSTRACT: A simple strategy for the syntheses of 2-alkyl indoles via regioselective ring-opening of 2-(2-haloaryl)-3-alkyl-*N*-tosylaziridines with thiophenol, followed by copper powder-mediated intramolecular C−N cyclization and subsequent aromatization by the elimination of thiophenol, with good yields is described. Utilizing this protocol, 2-carboxyindole has been synthesized easily.



Indoles are one of the most valuable and hence desired heterocyclic scaffolds in organic and medicinal chemistry. To date, more than 4000 indole alkaloids have been isolated from different natural sources; many of them are of immense biological, pharmacological, and synthetic importance.[1] Some of the natural products and other commercial drug molecules containing an indole skeleton as the key molecular framework, e.g., Birnbaumin A, Meridianin C, Apaziquone, Indomethacin, Fluvastatin, etc., are shown in Figure 1. Because of the biological relevance and chemical versatility of indole heterocycles, development of their practical synthetic routes has been extensively explored over the years.[2] Although the classical "Fischer indole synthesis" is a unique method for the large-scale production of a variety of indoles,[3] a number of other interesting protocols based on metal catalysis were introduced in the literature.[4,5] Although 2-alkyl indoles can be easily obtained via alpha lithiation of indoles,[5e] it is difficult to make halogenated 2-alkyl indoles via the same route. In this context, an interesting protocol to 2-alkyl indoles via Pd-catalyzed C−H activation of indole has recently been developed by Bach et al.[5f] Although the synthesis of indoles from azirines is well-known,[6] to the best of our knowledge, no such synthetic route to indoles from aziridines has been reported in the literature so far. Recently, we have developed a simple route for the synthesis of 3-heteroatom substituted-indolines via ring-opening of 2-(2-haloaryl)-*N*-tosylaziridines with various heteroatomic nucleophiles including thiophenol, followed by C−N cyclization.[7] Inspired by our results, we envisioned that 2-substituted indoles can easily be synthesized from the ring-opening of 2-(2-haloaryl)-*N*-activated aziridines with thiophenol, followed by metal-catalyzed C−N cyclization and simultaneous aromatization via elimination of thiophenol. Several interesting strategies are known for the ring-opening of aziridines with sulfur atomic nucleophiles[8] and other nucleophiles.[9] In recent time, copper-catalyzed C−N cyclization has become a powerful tool in organic synthesis.[8h,10,11] In continuation of our research activities in this area, we have developed a simple and straightforward strategy for the synthesis of 2-substituted indoles via S_N2-type ring-opening of 2-(2-haloaryl)-*N*-activated aziridines with thiophenol, followed by Cu-mediated C−N cyclization/aromatization (Scheme 1). Herein, we report our results as a Note.

To realize our idea, initially, we studied the reaction of 2-(2-bromophenyl)-1-tosylaziridine **3a** with thiophenol in the presence of K_2CO_3 in toluene at 90 °C, and the ring-opening product **4a** was obtained in 95% yield as a single regioisomer (Scheme 2).[8h]

The compound **4a** was subjected to C−N cyclization with copper powder (1.0 equiv) in DMF at 120 °C for 8 h, and indole **5a** was obtained in 65% yield along with indoline **6a** in 25% yield (Table 1, entry 1). To find out the optimized reaction conditions for the exclusive formation of **5a**, the ring-opening product **4a** was subjected to C−N cyclization and subsequent aromatization with different Cu catalysts and ligands. The optimization results are summarized in Table 1. The best result was obtained with a super stoichiometric amount of copper powder (2.0 equiv) in DMF at 120 °C (Table 1, entry 4), where the expected product **5a** was obtained in 85% yield as the only product. It is worth mentioning that thiophenol was recovered back completely during column chromatographic purification of the indole product **5a**.

To establish our strategy as a practical and useful general synthetic methodology for this purpose, a one-pot (stepwise) protocol for the synthesis of indole **5a** from **3a** was explored. When aziridine **3a** was treated with PhSH, followed by Cu powder under the reaction conditions as shown in Scheme 3, the expected indole **5a** was obtained in 82% yield.

To demonstrate the scope of our strategy, it was further extended for the synthesis of 2-methyl indole **5b** from the ring-opening of an inseparable mixture (1:1) of *cis* and *trans* isomers of 2-(2-bromophenyl)-3-methyl-1-tosylaziridine **3b** with thio-

Received: September 26, 2015
Published: December 3, 2015

DOI: 10.1021/acs.joc.5b02251
J. Org. Chem. 2015, 80, 12659−12667

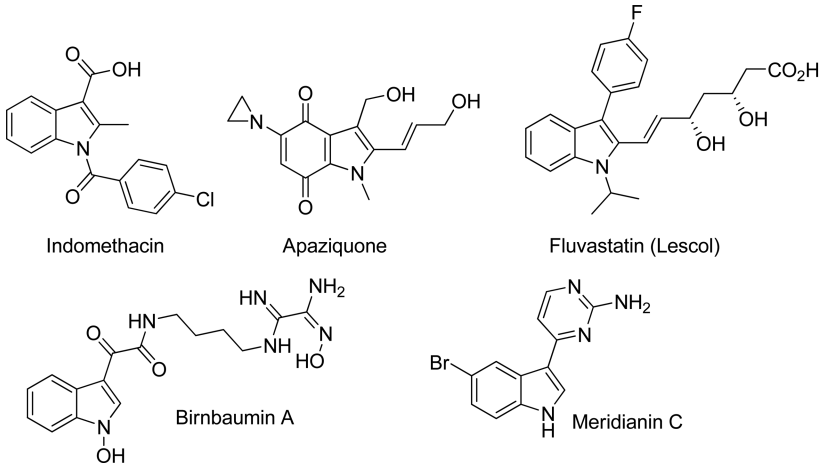
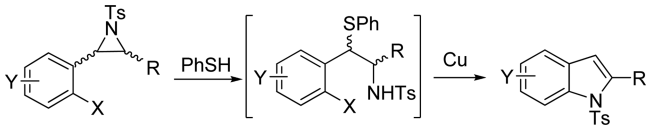


Figure 1. Indole core structure containing commercial drugs and natural products.

Scheme 1. Proposed Reaction Pathway



Scheme 2. Regioselective Ring-Opening of 3a

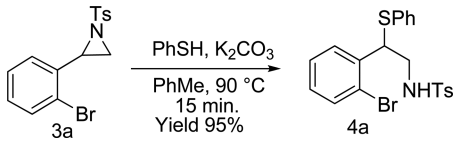
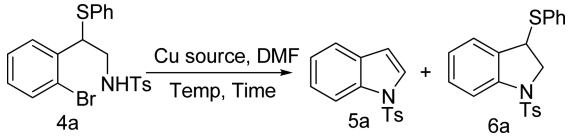


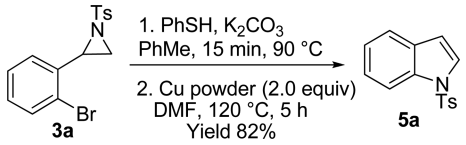
Table 1. Optimization Study



entry	reaction conditions[a]	**5a** yield (%)	**6a** yield (%)
1	Cu powder (1.0 equiv), DMF, 120 °C, 8 h	65	25
2	Cu powder (1.0 equiv), DMF, 90 °C, 7 h	0	87
3	CuI (1.0 equiv), DMF, 120 °C, 1 h	0	90
4	**Cu powder (2.0 equiv), DMF, 120 °C, 4 h**	**85**	**0**
5[b]	CuI, ligand L_1, K_2CO_3, DMF, 120 °C, 5 h	0	80
6[b]	CuI, ligand L_2, K_2CO_3, DMF, 120 °C, 5 h	0	85
7[b]	CuI, ligand L_3, K_2CO_3, DMF, 120 °C, 5 h	0	84

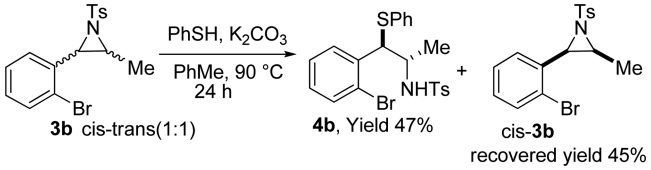
[a]All reactions were carried out with **4a** (0.2 mmol), *N*,*N*-dimethylformamide (DMF) (1.0 mL), in solvent under an argon atmosphere. [b]CuI (10 mol %), L_1, L_2, and L_3 (20 mol %), K_2CO_3 (1.0 equiv). L_1 = (±)-*trans*-1,2-diaminocyclohexane, L_2 = L-proline, L_3 = ethylenediamine.

Scheme 3. Synthesis of Indole 5a



phenol at 90 °C in toluene. Under the optimized conditions, when aziridine **3b** was reacted, only 50% of the starting material was found to be consumed after 12 h. The reaction was continued for another 12 h; however, no further progress of the reaction could be noted. We could isolate the ring-opening product **4b** along with the unreacted aziridine **3b** as a pure *cis* isomer[12] (Scheme 4). *Trans* disubstituted aziridines are more

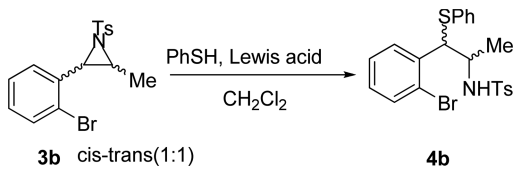
Scheme 4. Regioselective Ring-Opening of 3b



reactive than the *cis* isomer due to steric reasons, and under basic conditions, only the *trans* isomer reacted and the *cis* isomer was recovered completely.

To overcome this problem, we explored the LA (Lewis acid)-catalyzed ring-opening of aziridines (as a mixture of both *cis* and *trans* isomers) with thiophenol. Various Lewis acids were screened for the ring-opening of aziridine **3b** (1:1 mixture of *cis* and *trans* isomers) with thiophenol, and the results are shown in Table 2. The best result was obtained with $BF_3{\cdot}OEt_2$ (15 mol %) in CH_2Cl_2 for 2 h, and the ring-opening product **4b** was obtained in 94% yield with dr 4:1 (Table 2, entry 2). LA-catalyzed ring-opening of disubstituted aziridines by thiophenol follows an S_N2-pathway. Under acidic conditions, starting from aziridine **3b** (trans/*cis* 1:1), the ring-opening product **4b** was obtained with enhanced dr (*trans*/*cis* 4:1) in 94% yield. The

Table 2. Optimization Study of Ring-Opening Product 4b



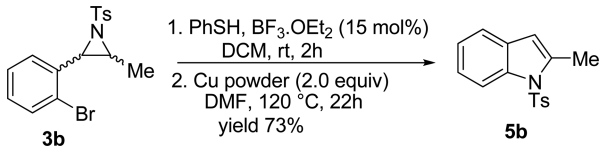
entry	Lewis acids	time (h)	yield (%)
1	$BF_3{\cdot}OEt_2$ (10 mol %)	3	90
2	**$BF_3{\cdot}OEt_2$ (15 mol %)**	**2**	**94**
3	$Cu(OTf)_2$ (15 mol %)	24	65
4	$Sc(OTf)_3$ (15 mol %)	24	67
5	$Zn(OTf)_2$ (15 mol %)	24	55

DOI: 10.1021/acs.joc.5b02251
J. Org. Chem. 2015, 80, 12659−12667

observed enhanced diastereoselectivity of **4b** is probably due to epimerization of the benzylic carbon center from the unreacted *cis* isomer of **3b** during the reaction. This could be possible as the epimerization would lead to the formation of the more stable *trans* isomer of **3b**.

Next, we intended to apply both the optimization conditions (Tables 1 and 2) for the one-pot synthesis of 2-methyl indole **5b** from aziridine **3b**. To our great pleasure, the strategy worked well and the expected product **5b** was obtained in 73% yield (Scheme 5).

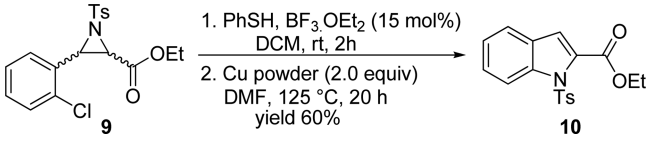
Scheme 5. Synthesis of 2-Methyl Indole 5b



Encouraged by this result, the reactions of several disubstituted aziridines (as a mixture of *cis* and *trans* isomers) and several monosubstituted aziridines with thiophenol, followed by copper powder-mediated C−N cyclization/aromatization, were studied, and the corresponding 2-alkyl indoles **5a,c−p** were obtained with good yields (Table 3). It is needless to mention that, in all the cases, thiophenol was recovered back completely.

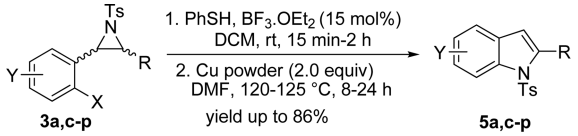
For wider applicability of our protocol in terms of substrate scope, indole functionalized with a carbethoxy group at the 2-position (**10**) was synthesized from ethyl 3-(2-chlorophenyl)-1-tosylaziridine-2-carboxylate in good yield (Scheme 6).

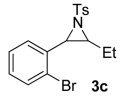
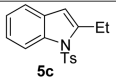
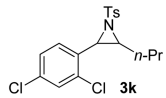
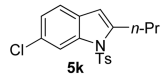
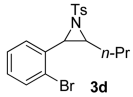
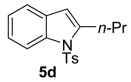
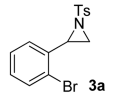
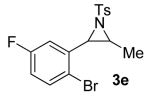
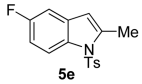
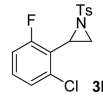
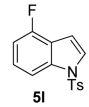
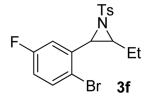
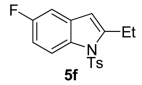
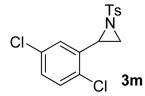
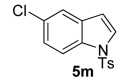
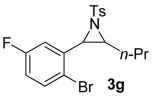
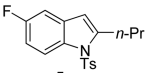
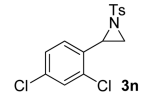
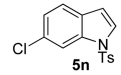
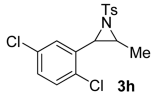
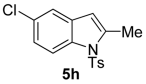
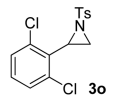
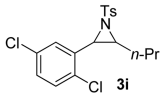
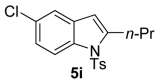
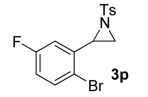
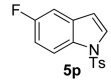
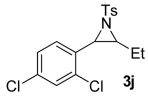
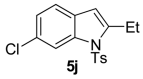
Scheme 6. Synthesis of 2-Ethyl Carboxylate Indole 10



We believe that the copper powder-mediated C−N cyclization follows our earlier proposed mechanism.[8h] Most probably, the final aromatization step follows Cu(I)-mediated

Table 3. Synthesis of 2-Alkyl Indoles and Indoles Derivatives

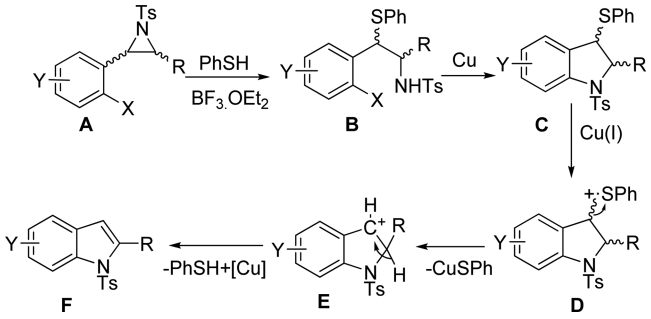


entry	2-halo-aziridines **3** (mixture of *cis* and *trans*)	Product **5**	Time (h)	Yield (%)	entry	2-halo-aziridines **3** (mixture of *cis* and *trans*)	Product **5**	Time (h)	Yield (%)
1	 **3c**	 **5c**	22	70	9	 **3k**	 **5k**	24	64
2	 **3d**	 **5d**	20	67	10	 **3a**	 **5a**	5	86
3	 **3e**	 **5e**	16	65	11	 **3l**	 **5l**	16	80
4	 **3f**	 **5f**	17	65	12	 **3m**	 **5m**	16	85
5	 **3g**	 **5g**	16	65	13	 **3n**	 **5n**	16	82
6	 **3h**	 **5h**	21	70	14	 **3o**	 **5o**	16	80
7	 **3i**	 **5i**	24	65	15	 **3p**	 **5p**	8	81
8	 **3j**	 **5j**	20	67					

DOI: 10.1021/acs.joc.5b02251
J. Org. Chem. 2015, 80, 12659−12667

desulfonylation via the formation of an intermediate cationic thioether species **D** (Scheme 7).[13]

Scheme 7. Plausible Mechanism



To conclude, we have developed a simple route to 2-alkyl indoles via regioselective ring-opening of 2,3-disubstituted aziridines with thiophenol, followed by copper powder-mediated C−N cyclization and aromatization with good yields. It is needless to mention that our strategy is very simple, based on a C−N coupling step involving environmentally benign Cu powder without using any ligand or a base. We strongly believe that our described strategy can be used as an alternate general methodology for the synthesis of 2-alkyl indoles.

EXPERIMENTAL SECTION

General Experimental. Analytical thin-layer chromatography (TLC) was carried out using silica gel 60 F_{254} precoated plates. Visualization was accomplished with a UV lamp or I_2 stain. Silica gel 230−400 mesh size was used for column chromatography using the combination of ethyl acetate and petroleum ether as an eluent. Unless noted, all reactions were carried out in oven-dried glassware under an atmosphere of nitrogen using anhydrous solvents. Where appropriate, solvents and all reagents were purified prior to use following the guidelines of Perrin and Armarego[14] and Vogel.[15] Monosubstituted *N*-Ts aziridines and disubstituted *N*-Ts aziridines were prepared by following earlier reports.[16] All styrenes were prepared by following earlier reports.[17] All commercial reagents were used as received. IR spectra were recorded in potassium bromide (KBr) pellets. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 and 500 MHz. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethyl silane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q), or multiplet (m). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 and 125 MHz. Mass spectra (MS) were obtained using FAB and ESI mass spectrometer (TOF). Melting points were determined using a hot stage apparatus and are reported as uncorrected.

***N*-(2-(2-Bromophenyl)-2-(phenylthio)ethyl)-4-methylbenzenesulfonamide (4a).**[8h] A solution of thiophenol (23 μL, 0.22 mmol) in dry toluene (1.0 mL) was added dropwise at 90 °C to a stirred suspension of K_2CO_3 (1.1 equiv) in dry toluene (1.0 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 90 °C for 5 min, and a solution of 2-(2-bromophenyl)-1-tosylaziridine **3a** (71 mg, 0.2 mmol) in dry toluene (1.0 mL) was added dropwise over a period of 1 min at 90 °C. The reaction mixture was further stirred for 15 min at the same temperature. The reaction was monitored by TLC. It was cooled to room temperature, quenched with water, and extracted with ethyl acetate (3 × 5.0 mL). The combined organic extract was washed with H_2O (3 × 5.0 mL) and brine (15.0 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel (230−400 mesh) by using ethyl acetate in petroleum ether to afford the pure products as a thick liquid in 95% yield. R_f 0.52 (30% ethyl acetate in petroleum ether); IR ν_{max} (neat, cm^{-1}): 3281, 3059, 2923, 2854, 1597, 1470, 1438, 1329, 1159, 1092, 1024, 813, 691, 663, 551; ^{1}H NMR (500 MHz, CDCl3) δ 2.42 (s, 3H) 3.30−3.36 (m, 1H), 3.42−3.47 (m, 1H), 4.65 (t, J = 7.4 Hz, 1H), 4.82 (t, J = 6.4 Hz, 1H), 7.08−7.15 (m, 2H), 7.18−7.25 (m, 5H), 7.52 (dd, J = 8.0, 1.3 Hz, 1H), 7.64 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 46.1, 51.2, 124.8, 127.2, 127.9, 128.1, 128.7, 129.1, 129.5, 129.9, 132.5, 132.9, 133.4, 136.8, 137.4, 143.6; HRMS (ESI) calcd for $C_{21}H_{21}BrNO_2S_2$ $(M + H)^+$ 462.0197, found 462.0199.

***N*-(1-(2-Bromophenyl)-1-(phenylthio)propan-2-yl)-4-methylbenzenesulfonamide (4b).** Obtained only *trans* isomer **4b** in 47% yield under basic conditions: IR ν_{max} (neat, cm^{-1}): 3210, 3015 2923, 1594, 1560, 1478, 1376, 1228, 1185, 1163, 1093, 1051, 982, 910, 865, 815, 731, 690, 664, 576, 557; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 (d, J = 6.9 Hz, 3H), 2.36 (s, 3H), 3.83−3.90 (m, 1H), 4.75 (d, J = 4.6 Hz, 1H), 5.02 (d, J = 9.2 Hz, 1H), 7.04 (dd, J = 7.5, 1.6 Hz, 1H), 7.07−7.09 (m, 2H), 7.13−7.18 (m, 5H), 7.20 (td, J = 7.5, 1.7 Hz, 1H), 7.45 (dd, J = 8.0, 1.2 Hz, 1H), 7.64 (dd, J = 7.5, 1.7 Hz, 1H), 7.69 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz,$CDCl_3$): δ 18.4, 21.6, 52.3, 58.4, 124.4, 126.9, 127.3, 127.7, 129.0, 129.2, 129.6, 130.2, 131.0, 133.0, 134.4, 138.0, 138.1, 143.3; HRMS (ESI) calcd for $C_{22}H_{26}BrN_2O_2S_2$ $(M + NH_4)^+$ 493.0619, found 493.0618.

2-(2-Bromophenyl)-3-methyl-1-tosylaziridine (*cis*-3b). Recovered *cis* aziridine **3b** obtained in 45% yield: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (d, J = 5.7 Hz, 3H), 2.44 (s, 3H), 3.26−3.31 (m, 1H), 3.96 (d, J = 7.5 Hz, 1H), 7.13 (td, J = 7.5, 2.3 Hz, 1H), 7.15−7.20 (m, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 7.5 Hz, 1H), 7.89 (d, J = 8.0 Hz, 2H); ^{1}3C NMR (125 MHz,$CDCl_3$): δ 12.1, 21.7, 41.9, 47.1, 123.1, 127.3, 128.0, 129.4, 129.9, 130.1, 132.3, 133.0, 135.3, 144.7; HRMS (ESI) calcd for $C_{16}H_{17}BrNO_2S$ $(M + H)^+$ 366.0163, found 366.0164.

General Procedure for the C−N Cyclization. ***Method A.*** To *N*-(2-(2-bromophenylthio)-2-phenylethyl)-4methylbenzenesulfonamide **4a** (1.0 equiv) in dry DMF (2.0 mL) was added Cu powder (2.0 equiv). The reaction mixture was heated at 120 °C for 4 h, and the progress of the reaction was monitored by TLC. It was cooled to room temperature and quenched with water and extracted with ethyl acetate (3 × 5.0 mL). The combined organic extract was washed with H_2O (3 × 5.0 mL) and brine (30.0 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography on silica gel (230−400 mesh) using ethyl acetate in petroleum ether to afford the pure product **5a** as a white solid.

*1-Tosyl-1H-indole (**5a**).* The general method **A** described above was followed when **4a** (92.5 mg, 0.2 mmol) was reacted with Cu powder (25.4 mg 0.4 mmol). The reaction mixture was heated 120 °C for 4 h to afford **5a** (46.1 mg, 0.170 mmol) as a white solid in 85% yield: mp 80−82 °C; R_f 0.46 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 3143, 2924, 2853, 1735, 1597, 1527, 1493, 1445, 1371, 1306, 1290, 1262, 1204, 1187, 1174, 1130, 1091, 1018, 992, 879, 812, 769, 747, 723, 703, 678, 644, 537; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 6.63 (d, J = 3.6 Hz, 1H), 7.18−7.31 (m, 4H), 7.51(d, J = 7.8 Hz, 1H), 7.55 (d, J = 3.6 Hz, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.98 (d, J = 9.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.6, 109.1, 113.6, 121.4, 123.3, 124.6, 126.4, 126.9, 129.9, 130.8, 134.9, 135.4, 145.0; HRMS (ESI) calcd for $C_{15}H_{13}$ $NNaO_2S$ $(M + Na)^+$ 294.0565, found 294.0569.

General Procedure for Regioselective the Ring-Opening of 2-(2-Bromophenyl)-3-methyl-1-tosylaziridine with Thiophenols. ***Method B.*** To a stirred solution of **3b** (1.0 equiv) under a N_2 atmosphere in dry DCM (0.5 mL) was added thiophenol (1.0 equiv), followed by $BF_3{\cdot}OEt_2$ (15 mol %). The reaction mixture was stirred at rt for 15 min-2 h. The reaction was monitored by TLC. After completion of the reaction mixture, it was quenched with water and extracted with ethyl acetate (3 × 5.0 mL). The combined organic extract was washed with H_2O (3 × 5.0 mL) and brine (15.0 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel (230−400 mesh) using ethyl acetate in petroleum ether to afford the pure products as a thick liquid.

DOI: 10.1021/acs.joc.5b02251
J. Org. Chem. 2015, 80, 12659−12667

*N-(1-(2-Bromophenyl)-1-(phenylthio)propan-2-yl)-4-methylbenzenesulfonamide (**4b**).* The general method **B** described above was followed when **3b** (73.3 mg, 0.2 mmol) was reacted with thiophenol (20.4 μL,0.2 mmol) in the presence of $BF_3{\cdot}OEt_2$ (15 mol %) at rt for 2 h to afford **4b** (92.4 mg, 0.188 mmol) as a thick liquid in 94% yield (dr 4:1): R_f 0.52 (20% ethyl acetate in petroleum ether); IR ν_{max} (neat, cm^{-1}): 3270, 3059, 2925, 1597, 1480, 1461, 1438, 1380, 1331, 1161, 1092, 1023, 986, 907, 814, 738, 689, 670, 549; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, *J* = 6.9 Hz, 3H), 1.20 (t, *J* = 6.4 Hz, 3H), 2.35 (s, 3H), 2.39 (s, 3H), 3.70−3.75 (m, 1H), 3.82−3.90 (m, 1H), 4.74 (d, *J* = 4.9 Hz, 1H), 5.09 (d, *J* = 9.2 Hz, 1H), 6.98−7.08 (m, 5H), 7.13−7.15 (m, 6H), 7.18−7.21 (m, 3H), 7.43−7.45 (m, 3H), 7.61−765 (m, 4H), 7.68−7.69 (m, 2H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 18.3, 20.5, 21.6, 52.3, 58.4, 124.4, 126.9, 127.1, 127.3, 127.5, 127.6, 127.7, 129.1, 129.3, 129.6, 130.1, 131.0, 131.8, 133.0, 134.4, 138.0, 138.0, 143.3; HRMS (ESI) calcd for $C_{22}H_{26}BrN_2O_2S_2$ $(M + NH_4)^+$ 493.0619, found 493.0618.

General Procedure for a One-Pot Protocol for the Synthesis of 2-Alkyl Indole. *Method C.* To a stirred solution of aziridine (1.0 equiv) under a N_2 atmosphere in dry DCM (0.5 mL) was added thiophenol (1.0 equiv), followed by $BF_3{\cdot}OEt_2$ (15 mol %). The reaction mixture was stirred at rt for 0.15−2 h. Cu powder (2.0 equiv) and DMF were added, and the mixture was heated to 120−125 °C for 8−24 h. The reaction was monitored by TLC. It was cooled to room temperature and quenched with water and extracted with ethyl acetate (3 × 5.0 mL). The combined organic extract was washed with H_2O (3 × 5.0 mL) and brine (5.0 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel (230−400 mesh) using ethyl acetate in petroleum ether to afford the pure products as white solids.

*2-Methyl-1-tosyl-1H-indole (**5b**).* The general method **C** described above was followed when **3b** (73.2 mg, 0.2 mmol) was reacted with thiophenoxide [(20.4 μL, 0.20 mmol), $BF_3{\cdot}OEt_2$ (3.8 μL, 0.03 mmol)] at rt for 2 h, followed by treatment with Cu powder (2.0 equiv) and 2 mL of DMF at 120 °C for 22 h to afford **5b** (41.7 mg, 0.146 mmol) as a thick liquid in 73% yield; R_f 0.53 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2926, 1596, 1452, 1367, 1294, 1240, 1218, 1187, 1174, 1150, 1091, 1052, 1022, 1001, 913, 810, 747, 704, 690, 659, 632, 583, 543; ^1H NMR (500 MHz, $CDCl_3$): δ 2.33 (s, 3H), 2.59 (s, 3H), 6.33 (s, 1H), 7.18−7.20 (m, 3H), 7.23−7.26 (m, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 2H), 8.15 (d, *J* = 8.6 Hz 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.9, 21.6, 109.6, 114.6, 120.0, 123.5, 123.8, 126.4, 129.8, 129.9, 136.4, 137.1, 137.4, 144.8; HRMS (ESI) calcd for $C_{16}H_{16}NO_2S$ $(M + H)^+$ 286.0902, found 286.0901.

*2-Ethyl-1-tosyl-1H-indole (**5c**).* The general method **C** described above was followed when **3c** (76.0 mg, 0.2 mmol) was reacted with thiophenoxide [(20.4 μL, 0.20 mmol), $BF_3{\cdot}OEt_2$ (3.8 μL, 0.03 mmol)] at rt for 2 h, followed by treatment with Cu powder (2.0 equiv) and 2 mL of DMF at 120 °C for 22 h to afford **5c** (41.3 mg, 0.14 mmol) as a thick liquid in 70% yield; R_f 0.66 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 3065, 2973, 2927, 1913, 1739, 1596, 1567, 1493, 1451, 1432, 1369, 1305, 1292, 1276, 1225, 1205, 1187, 1174, 1146, 1119, 1091, 1051, 1022, 986, 937, 905, 812, 747, 705, 694, 659, 626, 542, 492, 431; ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.3 Hz, 3H), 2.31 (s, 3H), 2.96−3.03 (m, 2H), 6.37 (s, 1H), 7.15−7.18 (m, 3H), 7.20−7.26 (m, 1H), 7.40 (d, *J* = 6.8 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 2H), 8.16 (d, *J* = 8.2 Hz 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.0, 21.6, 22.4, 107.8, 114.8, 120.2, 123.5, 123.9, 126.3, 129.9, 136.4, 137.3, 143.9, 144.7; HRMS (ESI) calcd for $C_{17}H_{18}NO_2S$ $(M + H)^+$ 300.1058, found 300.1055.

*2-Propyl-1-tosyl-1H-indole (**5d**).* The general method **C** described above was followed when **3d** (78.9 mg, 0.2 mmol) was reacted with thiophenoxide [(20.4 μL, 0.20 mmol), $BF_3{\cdot}OEt_2$ (3.8 μL, 0.03 mmol)] at rt for 2 h, followed by treatment with Cu powder (2.0 equiv) and 2 mL of DMF at 120 °C for 20 h to afford **5d** (42.0 mg, 0.134 mmol) as a thick liquid in 67% yield; R_f 0.73 (10% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2927, 1594, 1451, 1366, 1219, 1173, 1144, 1118, 1090, 1050, 809, 745, 705, 688, 666, 577, 541; ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.3 Hz, 3H), 1.77 (h, *J* = 7.4 Hz, 2H), 2.31 (s, 3H), 2.95 (t, *J* = 8.2 Hz, 2H), 6.36 (s, 1H), 7.15−7.18 (m, 2H), 7.20−7.25 (m, 2H), 7.38−7.40 (m, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 8.15 (d, *J* = 8.3 Hz 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 21.6, 22.2, 108.8, 114.9, 120.1, 123.5, 123.8, 126.3, 129.8, 129.9, 136.3, 137.3, 142.4, 144.6; HRMS (ESI) calcd for $C_{18}H_{20}NO_2S$ $(M + H)^+$ 314.1215, found 314.1210.

*5-Fluoro-2-methyl-1-tosyl-1H-indole (**5e**).* The general method **C** described above was followed when **3e** (76.8 mg, 0.2 mmol) was reacted with thiophenoxide [(20.4 μL, 0.20 mmol), $BF_3{\cdot}OEt_2$ (3.8 μL, 0.03 mmol)] at rt for 2 h, followed by treatment with Cu powder (2.0 equiv) and 2 mL of DMF at 120 °C for 16 h to afford **5e** (39.4 mg, 0.13 mmol) as a thick liquid in 65% yield; R_f 0.61 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2929, 2855, 1732, 1599, 1494, 1469, 1447, 1390, 1369, 1313, 1292, 1216, 1180, 1168, 1129, 1115, 1091, 1054, 1017, 1004, 958, 897, 859, 810, 778, 704, 684, 668, 635, 592, 566, 545, 494, 433; ^1H NMR (500 MHz, $CDCl_3$): δ 2.34 (s, 3H), 2.57 (s, 3H), 6.29 (s, 1H), 6.96 (td, *J* = 2.5, 9.2 Hz, 1H), 7.03 (dd, *J* = 2.5, 8.6 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 8.08 (dd, *J* = 4.3, 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.0, 15.8, 21.6, 105.5, 105.7, 109.4, 109.4, 111.5, 115.4, 115.5, 126.3, 129.9, 130.6, 130.7, 133.3, 136.1, 139.2, 144.9, 158.8, 160.7; HRMS (ESI) calcd for $C_{16}H_{15}FNO_2S$ $(M + H)^+$ 304.0808, found 304.0807.

*2-Ethyl-5-fluoro-1-tosyl-1H-indole (**5f**).* The general method **C** described above was followed when **3f** (79.7 mg, 0.2 mmol) was reacted with thiophenoxide [(20.4 μL, 0.20 mmol), $BF_3{\cdot}OEt_2$ (3.8 μL, 0.03 mmol)] at rt for 2 h, followed by treatment with Cu powder (2.0 equiv) and 2 mL of DMF at 120 °C for 17 h to afford **5f** (41.2 mg, 0.13 mmol) as a thick liquid in 65% yield; R_f 0.62 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2974, 2928, 1597, 1493, 1468, 1448, 1370, 1306, 1267, 1230, 1210, 1189, 1179, 1156, 1131, 1117, 1091, 1055, 1017, 986, 958, 877, 860, 808, 778, 734, 703, 683, 663, 581, 557, 542; ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.3 Hz, 3H), 2.33 (s, 3H), 2.96−3.01 (m, 2H), 6.33 (s, 1H), 6.95 (td, *J* = 2.3, 8.7 Hz, 1H), 7.05 (dd, *J* = 2.3, 8.7 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 8.10 (dd, *J* = 4.6, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.9, 21.6, 22.5, 105.7, 105.8, 107.6, 107.7, 111.4, 111.6, 115.7, 115.8, 126.3, 130.0, 130.9, 130.9, 133.6, 136.1, 144.9, 145.7, 158.8, 160.7; HRMS (ESI) calcd for $C_{17}H_{17}FNO_2S$ $(M + H)^+$ 318.0964, found 318.0969.

*5-Fluoro-2-propyl-1-tosyl-1H-indole (**5g**).* The general method **C** described above was followed when **3g** (82.5 mg, 0.2 mmol) was reacted with thiophenoxide [(20.4 μL, 0.20 mmol), $BF_3{\cdot}OEt_2$ (3.8 μL, 0.03 mmol)] at rt for 2 h, followed by treatment with Cu powder (2.0 equiv) and 2 mL of DMF at 120 °C for 16 h to afford **5g** (43.1 mg, 0.13 mmol) as a thick liquid in 65% yield; R_f 0.66 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2963, 2873, 1693, 1597, 1466, 1449, 1369, 1266, 1209, 1189, 1179, 1157, 1116, 1091, 1053, 959, 859, 810, 780, 736, 711, 670, 616, 584, 573, 543; ^1H NMR (400 MHz, $CDCl_3$): δ 1.00 (t, *J* = 7.3 Hz, 3H), 1.76 (h, *J* = 7.3 Hz, 2H), 2.32 (s, 3H), 2.91−2.95 (m, 2H), 6.32 (d, *J* = 0.9 Hz, 1H), 6.95 (td, *J* = 2.8, 9.2 Hz, 1H), 7.04 (dd, *J* = 2.8, 8.7 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.56−7.59 (m, 2H), 8.08 (dd, *J* = 4.6, 9.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 21.7, 22.2, 31.2, 105.6, 105.8, 108.6, 108.7, 111.4, 111.6, 115.9, 116.0, 126.3, 129.9, 130.9, 131.0, 133.5, 136.0, 144.2, 144.9, 158.8, 160.8; HRMS (ESI) calcd for $C_{18}H_{18}FNNaO_2S$ $(M + Na)^+$ 354.0940, found 354.0949.

*5-Chloro-2-methyl-1-tosyl-1H-indole (**5h**).* The general method **C** described above was followed when **3h** (71.3 mg, 0.2 mmol) was reacted with thiophenoxide [(20.4 μL, 0.20 mmol), $BF_3{\cdot}OEt_2$ (3.8 μL, 0.03 mmol)] at rt for 2 h, followed by treatment with Cu powder (2.0 equiv) and 2 mL of DMF at 125 °C for 21 h to afford **5h** (44.8 mg, 0.14 mmol) as a thick liquid in 70% yield; R_f 0.56 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2925, 2853, 1596, 1441, 1370, 1305, 1239, 1217, 1174, 1151, 1132, 1090, 1072, 1003, 885, 808, 722, 672, 664, 600, 543; ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H), 2.56 (s, 3H), 6.26 (s, 1H), 7.17−7.21 (m, 3H), 7.34 (d, *J* = 1.8 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 2H), 8.06 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.8, 21.7, 108.9, 115.6, 119.6, 123.9, 126.4, 129.2, 130.0, 131.0, 135.4, 136.1, 139.0, 145.1; HRMS (ESI) calcd for $C_{16}H_{15}ClNO_2S$ $(M + H)^+$ 320.0512, found 320.0513.

DOI: 10.1021/acs.joc.5b02251
J. Org. Chem. 2015, 80, 12659−12667

*5-Chloro-2-propyl-1-tosyl-1H-indole (**5i**).* The general method **C** described above was followed when **3i** (76.8 mg, 0.2 mmol) was reacted with thiophenoxide [(20.4 μL, 0.20 mmol), $BF_3{\cdot}OEt_2$ (3.8 μL, 0.03 mmol)] at rt for 2 h, followed by treatment with Cu powder (2.0 equiv) and 2 mL of DMF at 125 °C for 24 h to afford **5i** (45.2 mg, 0.13 mmol) as a thick liquid in 65% yield; R_f 0.73 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2961, 2928, 2871, 1596, 1444, 1371, 1271, 1221, 1199, 1173, 1148, 1132, 1091, 1072, 1052, 871, 808, 738, 723, 689, 668, 601, 581, 543, 564; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (t, *J* = 7.3 Hz, 3H), 1.75 (h, *J* = 7.3 Hz, 2H), 2.33 (s, 3H), 2.90−2.94 (m, 2H), 6.3 (d, *J* = 0.9 Hz, 1H), 7.17−7.19 (m, 3H), 7.35(d, *J* = 2.3 Hz, 1H), 7.56−7.59 (m, 2H), 8.07 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 21.7, 22.1, 31.1, 108.1, 115.91, 119.7, 123.9, 126.3, 129.1, 129.2, 130.0, 131.2, 135.6, 136.0, 143.9, 145.0; HRMS (ESI) calcd for $C_{18}H_{19}ClNO_2S$ $(M + H)^+$ 348.0825, found 348.0817.

*6-Chloro-2-ethyl-1-tosyl-1H-indole (**5j**).* The general method **C** described above was followed when **3j** (74.1 mg, 0.2 mmol) was reacted with thiophenoxide [(20.4 μL, 0.20 mmol), $BF_3{\cdot}OEt_2$ (3.8 μL, 0.03 mmol)] at rt for 2 h, followed by treatment with Cu powder (2.0 equiv) and 2 mL of DMF at 125 °C for 20 h to afford **5j** (44.7 mg, 0.13 mmol) as a thick liquid in 67% yield; R_f 0.62 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 3114, 2973, 2924, 1589, 1561, 1494, 1453, 1420, 1369, 1307, 1289, 1219, 1203, 1187, 1173, 1151, 1123, 1092, 1061, 1049, 1017, 988, 929, 866, 829, 811, 731, 703, 680, 661, 543, 490, 430; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, *J* = 7.3 Hz, 3H), 2.34 (s, 3H), 2.94−3.00 (m, 2H), 6.33 (s, 1H), 7.15−7.21 (m, 3H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.60−7.63(m, 2H), 8.20 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.8, 21.7, 22.3, 107.2, 114.9, 120.8, 124.1, 126.4, 128.3, 129.8, 130.1, 136.1, 137.6, 144.6, 145.1; HRMS (ESI) calcd for $C_{17}H_{17}ClNO_2S$ $(M + H)^+$ 334.0669, found 334.0668.

*6-Chloro-2-propyl-1-tosyl-1H-indole (**5k**).* The general method **C** described above was followed when **3k** (76.8 mg, 0.2 mmol) was reacted with thiophenoxide [(20.4 μL, 0.20 mmol), $BF_3{\cdot}OEt_2$ (3.8 μL, 0.03 mmol)] at rt for 2 h, followed by treatment with Cu powder (2.0 equiv) and 2 mL of DMF at 125 °C for 24 h to afford **5k** (44.5 mg, 0.127 mmol) as a thick liquid in 64% yield; R_f 0.73 (10% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 3113, 2958, 2926, 2868, 1694, 1586, 1557, 1493, 1460, 1419, 1372, 1306, 1283, 1249, 1219, 1199, 1171, 1152, 1123, 1073, 1049, 1034, 1015, 948, 904, 859, 844, 823, 812, 741, 703, 663, 543 543; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.5 Hz, 3H), 1.74 (h, *J* = 7.5 Hz, 2H), 2.34 (s, 3H), 2.91 (t, *J* = 6.9 Hz, 2H), 6.33 (s, 1H), 7.16−7.18 (m, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 1H), 7.61 (m, *J* = 8.6 Hz 2H), 8.19 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 21.7, 22.1, 31.0, 108.2, 115.1, 120.8, 124.1, 126.2, 126.4, 128.4, 129.7, 130.1, 134.2, 136.1, 137.6, 137.6, 143.1, 145.0; HRMS (ESI) calcd for $C_{18}H_{18}ClNNaO_2S$ $(M + H)^+$ 370.0644, found 370.0642.

*1-Tosyl-1H-indole (**5a**).* The general method **C** described above was followed when **3a** (71 mg, 0.2 mmol) was reacted with thiophenoxide [(20.4 μL, 0.20 mmol), $BF_3{\cdot}OEt_2$ (3.8 μL, 0.03 mmol)] at rt for 15 min, followed by treatment with Cu powder (2.0 equiv) and 2 mL of DMF at 120 °C for 5 h to afford **5a** (46.1 mg, 0.172 mmol) as a white solid in 86% yield: mp 80−82 °C; R_f 0.46 (5% ethyl acetate in petroleum ether);

*4-Fluoro-1-tosyl-1H-indole (**5l**).* The general method **C** described above was followed when **3l** (65.1 mg, 0.2 mmol) was reacted with thiophenoxide [(20.4 μL, 0.20 mmol), $BF_3{\cdot}OEt_2$ (3.8 μL, 0.03 mmol)] at rt for 15 min, followed by treatment with Cu powder (2.0 equiv) and 2 mL of DMF at 125 °C for 16 h to afford **5l** (46.3 mg, 0.16 mmol) as a white solid in 80% yield: mp 72−74 °C; R_f 0.53 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2924, 2854, 1626, 1583, 1527, 1486, 1430, 1375, 1307, 1289, 1248, 1208, 1182, 1165, 1145, 1127, 1089, 1052, 1029, 946, 812, 786, 751, 703, 688, 670, 580, 560, 546, 520; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 6.73 (dd *J* = 0.9, 3.9, Hz, 1H), 6.86−6.91 (m, 1H),7.19−7.25 (m, 3H), 7.52 (d, *J* = 3.6 Hz, 1H), 7.74−7.46 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 104.6, 108.5, 108.7, 109.6, 109.6, 119.9, 125.4, 125.5, 126.3, 126.9, 130.1, 135.0, 136.9, 137.0 145.3, 154.6, 157.2; HRMS (ESI) calcd for $C_{15}H_{13}$ FNO_2S $(M + H)^+$ 290.0651, found 290.0657.

*5-Chloro-1-tosyl-1H-indole (**5m**).* The general method **C** described above was followed when **3m** (68.4 mg, 0.2 mmol) was reacted with thiophenoxide [(20.4 μL, 0.20 mmol), $BF_3{\cdot}OEt_2$ (3.8 μL, 0.03 mmol)] at rt for 15 min, followed by treatment with Cu powder (2.0 equiv) and 2 mL of DMF at 125 °C for 16 h to afford **5m** (52.0 mg, 0.17 mmol) as a white solid in 85% yield: mp 65−67 °C; R_f 0.46 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2922, 2850, 1596, 1440, 1374, 1336, 1285, 1249, 1197, 1170, 1145, 1129, 1092, 991, 810, 762, 720, 669, 586, 538; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 6.57 (d, *J* = 3.7 Hz, 1H), 7.20−7.25 (m, 3H), 7.5 (d, *J* = 1.8 Hz, 1H), 7.56 (d, *J* = 3.6 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.89 (d, *J* = 8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 108.5, 114.6, 121.0, 124.9, 126.9, 127.8, 129.2, 130.1, 132.0, 133.2, 135.1, 145.3; HRMS (ESI) calcd for $C_{15}H_{13}ClNO_2S$ $(M + H)^+$ 306.0356, found 306.0350.

*6-Chloro-1-tosyl-1H-indole (**5n**).* The general method **C** described above was followed when **3n** (68.4 mg, 0.2 mmol) was reacted with thiophenoxide [(20.4 μL, 0.20 mmol), $BF_3{\cdot}OEt_2$ (3.8 μL, 0.03 mmol)] at rt for 15 min, followed by treatment with Cu powder (2.0 equiv) and 2 mL of DMF at 125 °C for 16 h to afford **5n** (49.7 mg, 0.163 mmol) as a white solid in 82% yield: mp 102−104 °C; R_f 0.46 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 3141, 2919, 1723, 1596, 1523, 1493, 1454, 1423, 1374, 1306, 1267, 1203, 1188, 1172, 1138, 1092, 1018, 996, 899, 867, 812, 761, 714, 668, 609, 596, 578, 541, 525; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.34 (s, 3H), 6.60 (d, *J* = 3.68 Hz, 1H), 7.17−7.24 (m, 3H),7.41 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 3.6 Hz, 1H), 7.75 (d, *J* = 10.6 Hz, 2H), 7.99 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 108.8, 113.8, 122.2, 124.1, 126.9, 127.0, 129.3, 130.1, 130.7, 135.1, 135.2, 145.4; HRMS (ESI) calcd for $C_{15}H_{13}ClNO_2S$ $(M + H)^+$ 306.0356, found 306.0350.

*4-Chloro-1-tosyl-1H-indole (**5o**).* The general method **C** described above was followed when **3o** (68.4 mg, 0.2 mmol) was reacted with thiophenoxide [(20.4 μL, 0.20 mmol), $BF_3{\cdot}OEt_2$ (3.8 μL, 0.03 mmol)] at rt for 15 min, followed by treatment with Cu powder (2.0 equiv) and 2 mL of DMF at 125 °C for 16 h to afford **5o** (49.1 mg, 0.16 mmol) as a white solid in 80% yield: mp 78−80 °C; R_f 0.6 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2924, 2850, 1596, 1572, 1523, 1471, 1419, 1374, 1285, 1225, 1194, 1169, 1132, 1101, 1003, 896, 811, 753, 703, 678, 643, 626, 576, 542; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.33 (s, 3H), 6.74−6.82 (m, 1H), 7.18−7.29 (m, 4H), 7.58−7.64 (m, 1H), 7.74 (d, *J* = 7.4 Hz, 2H), 7.88−7.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 107.2, 112.1, 123.2, 125.3, 126.6, 126.9, 129.6, 130.1, 135.1, 135.5, 145.4; HRMS (ESI) calcd for $C_{15}H_{13}ClNO_2S$ $(M + H)^+$ 306.0356, found 306.0350.

*5-Fluoro-1-tosyl-1H-indole (**5p**).* The general method **C** described above was followed when **3p** (74.0 mg, 0.2 mmol) was reacted with thiophenoxide [(20.4 μL, 0.20 mmol), $BF_3{\cdot}OEt_2$ (3.8 μL, 0.03 mmol)] at rt for 15 min, followed by treatment with Cu powder (2.0 equiv) and 2 mL of DMF at 120 °C for 8 h to afford **5p** (49.7 mg, 0.163 mmol) as a white solid in 81% yield: mp 102−104 °C; R_f 0.54 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 3145, 2924, 1615, 1594, 1530, 1493, 1460, 1444, 1399, 1372, 1348, 1307, 1291, 1259, 1216, 1188, 1172, 1139, 1114, 1091, 1040, 1018, 996, 950, 857, 810, 799, 761, 721, 703, 674, 626, 613, 590, 541, 524, 491, 473, 429; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.33 (s, 3H), 6.60 (d, *J* = 3.4 Hz, 1H), 7.02 (td, *J* = 2.9, 9.2 Hz, 1H), 7.16 (dd, *J* = 2.9, 9.2 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 3.4 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.91 (dd, *J* = 4.6, 9.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.7, 106.8, 107.0, 109.0, 109.1, 112.6, 112.8, 114.6, 114.7, 126.9, 128.1, 130.0, 131.3, 131.8, 135.1, 145.2, 158.7, 160.6; HRMS (ESI) calcd for $C_{15}H_{13}FNO_2S$ $(M + H)^+$ 290.0651, found 290.0651.

*Ethyl 1-Tosyl-1H-indole-2-carboxylate (**10**).* The general method **C** described above was followed when **9** (76.0 mg, 0.2 mmol) was reacted with thiophenoxide [(20.4 μL, 0.20 mmol), $BF_3{\cdot}OEt_2$ (3.8 μL, 0.03 mmol)] at rt for 2 h, followed by treatment with Cu powder (2.0 equiv) and 2 mL of DMF at 125 °C for 20 h to afford **10** (41.2 mg, 0.12 mmol) as a thick liquid in 60% yield; R_f 0.53 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2924, 2854, 1742, 1626, 1583, 1527, 1486, 1430, 1375, 1307, 1289, 1248, 1208, 1182, 1165, 1145,

DOI: 10.1021/acs.joc.5b02251
J. Org. Chem. 2015, 80, 12659−12667

1127, 1089, 1052, 1029, 946, 812, 786, 751, 703, 688, 670, 580, 560, 546, 520; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (t, J = 7.3 Hz, 3H), 2.35 (s, 3H), 4.39 (q, J = 7.3 Hz, 2H), 7.13 (d, J = 1.1 Hz, 1H), 7.23−7.27 (m, 3H), 7.38−7.43 (m, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.90 (d, J = 8.7 Hz, 2H), 8.309 (d, J = 9.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 21.7, 62.1, 115.5, 116.6, 122.5, 124.1, 127.0, 127.5, 128.3, 129.6, 131.9, 135.7, 138.2, 145.0, 161.5; HRMS (ESI) calcd for $C_{18}H_{18}NO_4S$ $(M + H)^+$ 344.0957, found 344.0955.

General Procedure for Preparation of Aziridines.[16] To a mixture of styrene derivatives (230 mg, 1.329 mmol) and anhydrous Chloramine-T (375 mg, 1.329 mmol) in CH_3CN (10 mL) was added PTAB (101 mg, 0.265 mmol) at 25 °C. After vigorous stirring for 12 h, the reaction mixture was diluted with ethyl acetate (40 mL) and water (20 mL). The organic layer was separated and washed with brine (20 mL), followed by drying over $MgSO_4$. The solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel (60−120 mesh) using ethyl acetate in petroleum ether to afford the pure products as white solids in good to moderate yield.

*2-(2-Bromophenyl)-3-methyl-1-tosylaziridine (**3b**).* Obtained as a thick liquid in 68% yield with *cis*/*trans* ratio 1:1: R_f 0.45 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2928, 1596, 1566, 1473, 1439, 1405, 1325, 1305, 1291, 1235, 1184, 1162, 1117, 1090, 1047, 1026, 985, 888, 815, 756, 710, 685, 589, 577, 552; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, J = 5.5 Hz, 3H), 1.19 (d, J = 5.9 Hz, 3H), 2.42 (s, 3H), 2.43 (s, 3H), 2.71−2.75 (m, 1H), 3.96 (dd, J = 7.2 Hz, 1H), 3.97 (dd, J = 4.5 Hz, 1H), 6.82−6.84 (m, 1H), 7.05−7.18 (m, 5H), 7.20−7.35 (m, 4H), 7.46−7.50 (m, 2H), 7.86−7.89 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 14.1, 21.7, 21.8, 41.9, 47.1, 49.0, 49.5, 123.0, 123.2, 127.3, 127.6, 128.0, 129.4, 129.7, 129.9, 130.0, 132.3, 132.9, 135.2, 135.6, 137.7, 144.3, 144.7; HRMS (ESI) calcd for $C_{16}H_{17}$ $BrNO_2S$ $(M + H)^+$ 366.0163, found 366.0164.

*2-(2-Bromophenyl)-3-ethyl-1-tosylaziridine (**3c**).* Obtained as a thick liquid in 71% yield with *cis*/*trans* ratio 1:1: R_f 0.48 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2968, 1596, 1439, 1327, 1231, 1184, 1162, 1091, 1019, 939, 908, 814, 754, 677, 591, 576, 557; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (t, J = 14.7 Hz, 3H), 0.97−1.06 (m, 1H), 1.22 (t, J = 7.8 Hz, 3H), 1.27−1.34 (m, 1H), 2.15−2.22 (m, 1H), 2.24−2.34 (m, 1H), 2.40 (s, 3H), 2.43 (s, 3H), 2.61−2.66 (m, 1H), 3.07−3.12 (m, 1H), 3.99−4.02 (m, 2H), 6.85−6.88 (m, 1H), 7.05−7.14 (m, 3H), 7.16−7.22 (m, 2H), 7.28 (d, J = 7.8 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H), 7.47−7.50 (m, 2H), 7.85 (d, J = 8.2 Hz, 2H), 7.89 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3, 12.6, 21.7, 22.2, 47.1, 48.0, 48.8, 55.3, 123.1, 123.3, 127.2, 127.3, 127.5, 127.6, 128.2, 129.3, 129.4, 129.7, 129.8, 129.9, 132.3, 132.4, 133.1, 135.1, 135.4, 137.7, 144.2, 144.7; HRMS (ESI) calcd for $C_{17}H_{19}$ $BrNO_2S$ $(M + H)^+$ 380.0320, found 380.0320.

*2-(2-Bromophenyl)-3-propyl-1-tosylaziridine (**3d**).* Obtained as a thick liquid in 65% yield with *cis*/*trans* ratio 1:1: R_f 0.51 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2959, 1596, 1439, 1327, 1184, 1162, 1092, 1025, 917, 814, 758, 678, 592, 576, 546; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (t, J = 7.36 Hz, 3H), 0.90−0.97 (m, 1H), 0.99 (t, J = 14.68 Hz, 3H), 1.18−1.33 (m, 4H), 1.62−1.71 (m, 2H), 2.08−2.17 (m, 1H), 2.24−2.35 (m, 1H), 2.40 (s, 3H), 2.43 (s, 3H), 2.66−2.70 (m, 1H), 3.15−3.19 (m, 1H), 3.99−4.02 (m, 2H), 6.85−6.88 (m, 1H), 7.05−7.10 (m, 2H), 7.11−7.14(m, 1H), 7.19 (d, J = 4.6 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.46−7.50 (m, 2H), 7.84 (d, J = 8.7 Hz, 2H), 7.88 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 14.1, 20.3, 21.5, 21.7, 21.8, 28.7, 30.7, 46.5, 47.0, 48.9, 53.9, 123.1, 123.3, 127.2, 127.5, 127.6, 128.1, 129.4, 129.7, 129.8, 129.8, 132.3, 132.5, 133.2, 135.1, 135.4, 137.7, 144.2, 144.7; HRMS (ESI) calcd for $C_{18}H_{21}$ $BrNO_2S$ $(M + H)^+$ 394.0476, found 394.0474.

*2-(2-Bromo-5-fluorophenyl)-3-methyl-1-tosylaziridine (**3e**).* Obtained as a thick liquid in 58% yield with *cis*/*trans* ratio 1:4: R_f 0.43 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 3052, 2924, 2855, 1730, 1624, 1596, 1480, 1460, 1408, 1379, 1360, 1304, 1293, 1237, 1185, 1122, 1090, 1054, 1026, 1001, 943, 870, 847, 800, 813, 740, 705, 690, 658, 628, 583, 530; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (d, J = 5.7 Hz, 3H), 1.89 (d, J = 5.7 Hz, 3H), 2.44 (s, 3H), 2.45 (s, 3H), 2.70−2.74 (m, 1H), 3.26−3.31 (m, 1H), 3.92 (d, J = 1.7 Hz, 1H), 3.92−3.94 (m, 2H), 6.56 (dd, J = 9.1, 2.8 Hz, 1H), 6.81 (td, J = 8.0, 2.8 Hz, 1H), 6.86 (td, J = 8.0, 2.8 Hz, 1H), 6.91 (dd, J = 9.1, 2.8 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.44 (dd, J = 8.2, 4.5 Hz, 1H), 7.45−7.47 (m, 1H), 7.87−7.89 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) 12.0, 14.0, 21.7, 42.1, 46.6, 48.8, 49.3, 114.7, 114.9, 116.5, 116.7, 117.1, 117.3, 127.5, 128.0, 130.0, 133.6, 133.7, 137.5, 137.9, 138.0, 144.6, 161.1, 163.0; HRMS (ESI) calcd for $C_{16}H_{16}BrFNO_2S$ $(M + H)^+$ 384.0069, found 384.0068.

*2-(2-Bromo-5-fluorophenyl)-3-ethyl-1-tosylaziridine (**3f**).* Obtained as a thick liquid in 65% yield with *cis*/*trans* ratio 1:1: R_f 0.46 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 3068, 2969, 2934, 2878, 1598, 1579, 1469, 1418, 1328, 1305, 1290, 1270, 1220, 1184, 1162, 1091, 1038, 1018, 957, 940, 904, 876, 850, 813, 736, 714, 695, 673, 607, 575, 564; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.77 (t, J = 7.4 Hz, 3H), 1.00−1.06 (m, 1H), 1.23 (t, J = 7.4, Hz, 3H), 1.28−1.33 (m, 1H), 2.16−2.22 (m, 1H), 2.30−233 (m, 1H), 2.42 (s, 3H), 2.45 (s, 3H), 2.59−2.62 (m, 1H), 3.09−3.13 (m, 1H), 3.95 (d, J = 4.0 Hz, 1H), 3.99 (d, J = 7.4 Hz, 1H), 6.59 (dd, J = 9.1, 2.8 Hz, 1H), 6.80 (td, J = 8.0, 2.8 Hz, 1H), 6.85 (td, J = 8.6, 3.4 Hz, 1H), 6.96 (dd, J = 9.1, 2.8 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.44 (m, 2H), 7.86 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.0 Hz, 2H); ^{13}C NMR (1 MHz, $CDCl_3$): 11.2, 12.6, 20.1, 21.7, 21.8, 22.1, 114.4, 114.6, 116.5, 116.6, 116.7, 116.8, 117.1, 117.3, 127.4, 128.1, 129.4, 129.8, 129.9, 133.6, 133.7, 133.8, 134.9, 135.5, 135.6, 137.5, 137.8, 144.5, 144.9, 160.8, 161.1, 162.8, 163.1; HRMS (ESI) calcd for $C_{17}H_{18}BrFNO_2S$ $(M + H)^+$ 398.0226, found 398.0229.

*2-(2-Bromo-5-fluorophenyl)-3-propyl-1-tosylaziridine (**3g**).* Obtained as a thick liquid in 67% yield with *cis*/*trans* ratio 1:1.4: R_f 0.48 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2961, 2932, 2873, 1598, 1580, 1470, 1418, 1328, 1305, 1269, 1218, 1184, 1162, 1093, 1031, 1018, 957, 922, 866, 814, 716, 693, 675, 590, 575, 538; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (t, J = 7.3 Hz, 3H), 0.91−0.96 (m, 1H), 1.00 (t, J = 7.3 Hz, 3H), 1.16−1.29 (m, 2H), 1.58−1.70 (m, 3H), 2.07−2.17 (m, 1H), 2.23−2.33 (m, 1H), 2.41 (s, 3H), 2.44 (s, 3H), 2.62−2.66 (m, 1H), 3.14−3.19 (m, 1H), 3.95−3.97 (m, 2H), 6.58 (dd, J = 9.1, 3.2 Hz, 1H), 6.79 (td, J = 8.2, 3.2 Hz, 1H), 6.85 (td, J = 8.2, 3.2 Hz, 1H), 6.94 (dd, J = 9.1, 2.7 Hz, 1H), 7.30 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.42−7.46 (m, 2H), 7.85 (d, J = 8.2 Hz, 2H), 7.88 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 13.7, 14.0, 20.3, 21.5, 21.7, 21.8, 28.6, 30.5, 46.4, 46.7, 48.2, 54.3, 114.4, 114.5, 116.5, 116.6, 116.7, 116.8, 117.0, 117.1, 117.3, 127.5, 128.1, 129.8, 129.9, 133.7, 133.7, 133.8, 134.9, 135.5, 135.6, 137.4, 137.7, 137.8, 144.5, 145.0, 160.8, 161.1, 162.7, 163.1; HRMS (ESI) calcd for $C_{18}H_{20}BrFNO_2S$ $(M + H)^+$ 412.0382, found 412.0382.

*2-(2,5-Dichlorophenyl)-3-methyl-1-tosylaziridine (**3h**).* Obtained as a thick liquid in 62% yield with *cis*/*trans* ratio 1:2.8: R_f 0.42 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2929, 1597, 1469, 1398, 1327, 1234, 1185, 1162, 1091, 1054, 987, 912, 858, 814, 748, 714, 685, 598, 568, 528; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (d, J = 5.9 Hz, 3H), 1.86 (d, J = 5.9 Hz, 3H), 2.43 (s, 3H), 2.44 (s, 3H), 2.72−2.78 (m, 1H), 3.23−3.27 (m, 1H), 3.95−3.96 (m, 2H), 6.78 (d, J = 2.2 Hz, 1H), 7.11 (dd, J = 8.2, 2.2 Hz, 1H), 7.16−7.19 (m, 2H), 7.23−7.26 (m, 2H), 7.32 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 7.8 Hz, 2H), 7.83−7.89 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): 12.1, 139, 21.7, 21.8, 42.1, 44.3, 46.4, 49.0, 127.5, 127.6, 128.0, 129.2, 129.3, 129.8, 129.9, 130.3, 131.8, 132.8, 133.0, 133.1, 134.7, 135.6, 137.4, 144.6, 145.0; HRMS (ESI) calcd for $C_{16}H_{16}Cl_2NO_2S$ $(M + H)^+$ 356.0279, found 356.0279.

*2-(2,5-Dichlorophenyl)-3-propyl-1-tosylaziridine (**3i**).* Obtained as a thick liquid in 54% yield with *cis*/*trans* ratio 1:2: R_f 0.52 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2960, 2932, 2873, 1597, 1494, 1467, 1398, 1329, 1305, 1291, 1256, 1230, 1185, 1162, 1120, 1092, 1054, 1019, 999, 925, 814, 760, 730, 694, 673, 637, 593, 570, 561, 529; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.75 (t, J = 7.3 Hz, 3H), 0.91−0.96 (m, 1H), 1.00 (t, J = 7.3 Hz, 3H), 1.14−1.28 (m, 3H), 1.57−1.66 (m, 2H), 2.04−2.13 (m, 1H), 2.21−2.30 (m, 1H), 2.42 (s, 3H), 2.44 (s, 3H), 2.65−2.69 (m, 1H), 3.11−3.16 (m, 1H), 3.97 (d, J = 4.1 Hz, 1H), 4.00 (d, J = 7.3 Hz, 1H), 6.80 (d, J = 2.3 Hz, 1H), 7.10 (dd, J = 8.6, 2.7 Hz, 1H), 7.15−7.21 (m, 2 H), 7.23−7.25 (m, 2H),

DOI: 10.1021/acs.joc.5b02251
J. Org. Chem. 2015, 80, 12659−12667

7.31 (d, J = 7.8 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 7.85 (d, J = 8.2 Hz, 2H), 7.88 (d, J = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 13.6, 14.0, 20.2, 21.4, 21.7, 21.8, 28.6, 30.5, 44.1, 45.8, 46.7, 53.8, 127.2, 127.6, 128.2, 129.2, 129.3, 129.6, 129.8, 129.9, 130.3, 130.4, 131.8, 132.8, 133.1, 133.4, 134.8, 135.6, 137.3, 144.6, 150.0; HRMS (ESI) calcd for $C_{18}H_{20}Cl_2NO_2S$ $(M + H)^+$ 384.0592, found 384.0594.

*2-(2,4-Dichlorophenyl)-3-ethyl-1-tosylaziridine (**3j**).* Obtained as a thick liquid in 70% yield with *cis*/*trans* ratio 1:1: R_f 0.48 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2970, 2934, 2878, 1593, 1560, 1476, 1412, 1380, 1329, 1305, 1291, 1232, 1185, 1163, 1119, 1092, 1054, 1019, 940, 897, 866, 814, 782, 738, 715, 695, 673, 573, 563, 543; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.75 (t, J = 7.4 Hz, 3H), 1.01−1.07 (m, 1H), 1.19 (t, J = 7.4 Hz, 3H), 1.23−1.28 (m, 1H), 2.13−2.18 (m, 1H), 2.26−2.28 (m, 1H), 2.41 (s, 3H), 2.44 (s, 3H), 2.62−2.65 (m, 1H), 3.06−3.11 (m, 1H), 3.96 (d, J = 4.6 Hz, 1H), 4.00 (d, J = 7.4 Hz, 1H), 6.82 (d, J = 8.5 Hz, 1H), 7.05 (dd, J = 8.0, 1.7 Hz, 1H), 7.12−7.17 (m, 2H), 7.28−7.35 (m, 6H), 7.84 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H); ^{13}C NMR (1 MHz, $CDCl_3$): 11.1, 12.4, 20.1, 21.8, 22.2, 44.4, 46.0, 47.9, 55.0, 127.1, 127.4, 127.5, 128.0, 128.2, 129.0, 129.7, 129.9, 130.2, 130.5, 132.5, 134.2, 134.3, 134.4, 134.9, 137.5, 144.4, 144.9; HRMS (ESI) calcd for $C_{17}H_{18}Cl_2NO_2S$ $(M + H)^+$ 370.0435, found 370.0438.

*2-(2,4-Dichlorophenyl)-3-propyl-1-tosylaziridine (**3k**).* Obtained as a thick liquid in 54% yield with *cis*/*trans* ratio 1:1: R_f 0.51 (5% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2960, 2932, 2873, 1593, 1560, 1476, 1410, 1381, 1329, 1305, 1291, 1229, 1163, 1119, 1093, 1054, 1018, 997, 918, 897, 815, 762, 746, 717, 693, 594; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.75 (t, J = 7.3 Hz, 3H), 1.00 (t, J = 7.3 Hz, 3H), 1.16−1.23 (m, 4H), 1.60−1.66 (m, 2H), 2.03−2.13 (m, 1H), 2.21−2.30 (m, 1H), 2.41 (s, 3H), 2.43 (s, 3H), 2.65−2.30 (m, 1H), 3.12−3.17 (m, 1H), 3.97−3.99 (m, 2H), 6.81 (d, J = 8.7 Hz, 1H), 7.04 (dd, J = 1.8, 8.2 Hz, 1H), 7.13 (m, 2H), 7.27 (s, 1H), 7.29 (s, 1H), 7.31−7.36 (m, 4H), 7.82 (d, J = 8.2 Hz, 2H), 7.87 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 14.0, 20.2, 21.4, 21.7, 28.6, 30.6, 44.3, 46.0, 46.4, 53.6, 127.1, 127.4, 127.5, 128.0, 128.1, 129.0, 129.1, 129.7, 129.9, 130.5, 132.4, 134.2, 134.3, 134.4, 134.8, 137.5, 144.4, 144.9; HRMS (ESI) calcd for $C_{18}H_{20}Cl_2NO_2S$ $(M + H)^+$ 384.0592, found 384.0598.

*2-(2-Chloro-6-fluorophenyl)-1-tosylaziridine (**3l**).* Obtained as a thick liquid in 62% yield: IR ν_{max} (neat, cm^{-1}): 3509, 3092, 2924, 2854, 1606, 1576, 1494, 1453, 1370, 1329, 1306, 1291,1244, 1185, 1117, 1162, 1093, 1039, 1019, 985, 918, 896, 815, 788, 772, 730, 712, 694, 666, 640, 576, 555, 475; ^{1}H NMR (400 MHz, CDCl3): δ 2.43 (s, 3H), 2.73 (d, J = 4.56 Hz, 1H), 3.02 (dd, J = 1.36, 7.32 Hz, 1H), 3.86 (dd, J = 4.60, 7.32 Hz, 1H), 6.86−6.91 (m, 1H), 7.10−7.20 (m, 2H), 7.33 (d, J = 7.8 Hz, 2H), 7.86−7.89 (m, 2H); ^{13}C NMR (100 MHz,$CDCl_3$): δ 21.8, 33.5, 36.5, 114.7, 114.9, 120.8, 120.9, 125.6, 125.6, 128.5, 129.7, 130.2, 130.3, 134.7, 136.1, 136.1, 144.8, 160.7, 163.2; HRMS (ESI) calcd for $C_{15}H_{14}ClFNO_2S$ $(M + H)^+$ 326.0418, found 326.0413.

*2-(2,5-Dichlorophenyl)-1-tosylaziridine (**3m**).* Obtained as a thick liquid in 52% yield: R_f 0.52 (30% ethyl acetate in petroleum ether); IR ν_{max} (neat, cm^{-1}): 3067, 2924, 1596, 1563, 1493, 1469, 1398, 1373, 1330, 1306, 1292, 1257, 1228, 1186, 1163, 1138, 1109, 990, 919, 886, 849, 814, 732, 706, 691, 664, 604, 586, 562, 513, 456; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.24 (d, J = 4.00 Hz, 1H), 2.45 (s, 3H), 3.01 (d, J = 6.9 Hz, 1H), 3.99 (dd, J = 2.65, 6.9 Hz, 1H), 7.16−7.18 (m, 2H), 7.24−7.26 (m, 1H), 7.36 (d, J = 8.05 Hz, 2H), 7.89 (d, J = 8.00 Hz, 2H); ^{13}C NMR (100 MHz,$CDCl_3$): δ 21.8, 36.0, 38.3, 127.6, 128.2, 129.4, 130.0, 130.4, 132.0, 133.2, 134.5, 135.0, 145.2; HRMS (ESI) calcd for $C_{15}H_{14}Cl_2NO_2S$ $(M + H)^+$ 342.0122, found 342.0121.

*2-(2,4-Dichlorophenyl)-1-tosylaziridine (**3n**).* Obtained as a thick liquid in 74% yield: IR ν_{max} (neat, cm^{-1}): 2923, 1594, 1560, 1478, 1376, 1228, 1185, 1163, 1093, 1051, 982, 910, 865, 815, 731, 690, 664, 576, 557; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (d, J = 4.56 Hz, 1H), 2.43 (s, 3H), 3.01 (d, J = 7.32 Hz, 1H), 3.96 (dd, J = 4.12, 7.32 Hz, 1H), 7.09−7.15 (m, 2H), 7.32−7.35 (m, 3H), 7.85−7.88 (m, 2H); ^{13}C NMR (100 MHz,$CDCl_3$): δ 21.8, 35.8, 38.5, 127.5, 128.2, 128.5, 129.2, 129.9, 131.9, 134.5, 134.5, 134.6, 145.1; HRMS (ESI) calcd for $C_{15}H_{14}Cl_2NO_2S$ $(M + H)^+$ 342.0122, found 342.0128.

*2-(2,6-Dichlorophenyl)-1-tosylaziridine (**3o**).* Obtained as a thick liquid in 45% yield: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.48 (s, 3H), 2.52 (d, J = 4.60 Hz, 1H), 3.11 (d, J = 7.32 Hz, 1H), 3.86 (dd, J = 4.56, 6.88 Hz, 1H), 7.11−7.15 (m, 1H), 7.21−7.23 (m, 2H), 7.33 (d, J = 8.28 Hz, 2H), 7.88−7.90 (m, 2H); ^{13}C NMR (100 MHz,$CDCl_3$): δ 21.8, 35.1, 39.8, 128.7, 128.8, 129.7, 129.9, 130.6, 134.9, 136.2, 144.9.

*2-(2-Bromo-5-fluorophenyl)-1-tosylaziridine (**3p**).* Obtained as a thick liquid in 67% yield: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.22 (d, J = 4.16 Hz, 1H), 2.44 (s, 3H), 3.02 (d, J = 6.88 Hz, 1H), 3.94 (dd, J = 4.12, 7.32 Hz, 1H), 6.82−6.92 (m, 2H), 7.35 (d, J = 7.8 Hz, 2H), 7.44 (dd, J = 5.04, 8.68 Hz, 1H), 7.88 (d, J = 8.24 Hz, 2H); ^{13}C NMR (100 MHz,$CDCl_3$): δ 21.8, 36.2, 40.8, 115.1, 115.3, 116.8, 117.0, 117.3, 128.2, 130.0, 133.8, 133.9, 134.5, 137.1, 137.2, 145.2, 161.1, 163.1

*Ethyl 3-(2-Chlorophenyl)-1-tosylaziridine-2-carboxylate (**9**).* Obtained as a thick liquid in 62% yield with *cis*/*trans* ratio 1:1: R_f 0.27 (10% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 2982, 1749, 1596, 1477, 1444, 1370, 1337, 1292, 1197, 1163, 1090, 1035, 917, 814, 759, 707, 684, 597, 561; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, J = 6.8 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H), 2.43 (s, 3H), 2.45 (s, 3H), 3.40 (d, J = 3.6 Hz, 1H), 3.75 (d, J = 7.2 Hz, 1H), 3.91−4.00 (m, 2H), 4.21 (d, J = 7.1 Hz, 1H), 4.28−4.37 (m, 2H), 4.65 (d, J = 3.6 Hz, 1H), 7.05 (dd, J = 7.7, 1.8 Hz, 1H), 7.13−7.17 (m, 2H), 7.18−7.22 (m, 1H), 7.23−7.26 (m, 1H), 7.27−7.33 (m, 5H), 7.36 (d, J = 8.6 Hz, 2H), 7.82 (d, J = 8.1 Hz, 2H), 7.92 (d, J = 8.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 13.8, 14.1, 21.7, 21.8, 42.7, 44.0, 45.9, 46.7, 61.7, 62.6, 126.6, 126.9, 127.8, 128.1, 128.3, 128.9, 129.5, 129.7, 129.9, 130.1, 131.2, 133.5, 133.9, 134.7, 140.0, 144.6, 145.5, 164.4, 165.5; HRMS (ESI) calcd for $C_{18}H_{18}ClNNaO_4S$ $(M + Na)^+$ 402.0543, found 402.0549.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02251.

NMR spectra for all the new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mkghorai@iitk.ac.in. Fax: (+91)-512-2597436. Phone: (+91)-512-2597518.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

M.S. and Y.N. thank CSIR, India, for a research fellowship, and M.K.G. is grateful to IIT-Kanpur and DST, India, for financial support for conducting this research.

■ REFERENCES

(1) Feniuk, W.; Humphrey, P. P. A. *Drug Dev. Res.* **1992**, *26*, 235. (b) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620. (c) Gul, W.; Hamann, M. T. *Life Sci.* **2005**, *78*, 442.

(2) For recent reviews on indole synthesis, see: (a) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (b) Higuchi, K.; Kawasaki, T. *Nat. Prod. Rep.* **2007**, *24*, 843. (c) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (d) Cacchi, S.; Fabrizi, G. C. *Chem. Rev.* **2005**, *105*, 2873. (e) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (f) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (g) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215. (h) Patureau, F. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1977. (i) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508.

(3) Robinson, B. *The Fisher Indole Synthesis*; Wiley-Interscience: New York, 1982.

(4) (a) Vieira, T. O.; Meaney, L. A.; Shi, Y.-L.; Alper, H. *Org. Lett.* **2008**, *10*, 4899. (b) Wang, C.; Huang, Y. *Org. Lett.* **2013**, *15*, 5294.

DOI: 10.1021/acs.joc.5b02251
J. Org. Chem. 2015, 80, 12659−12667

(c) Xiao, X.; Chen, T.-Q.; Ren, J.; Chen, W.-D.; Zeng, B.-B. *Tetrahedron Lett.* **2014**, *55*, 2056. (d) Yamagishi, M.; Nishigai, K.; Ishii, A.; Hata, T.; Urabe, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 6471. (e) Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2010**, *132*, 11416. (f) Pan, Y.-Y.; Wu, Y.-N.; Chen, Z.-Z.; Hao, W.-J.; Li, G.; Tu, S.-J.; Jiang, B. *J. Org. Chem.* **2015**, *80*, 5764. (g) Liang, Y.; Yu, K.; Li, B.; Xu, S.; Song, H.; Wang, B. *Chem. Commun.* **2014**, *50*, 6130. (h) Zhu, C.; Ma, S. *Org. Lett.* **2013**, *15*, 2782.

(5) 2-Alkyl indoles synthesis, see: (a) Cajaraville, A.; Lopez, S.; Varela, J. A.; Saa, C. *Org. Lett.* **2013**, *15*, 4576. (b) Gong, T.-J.; Cheng, W.-M; Su, W.; Xiao, B.; Fu, Y. *Tetrahedron Lett.* **2014**, *55*, 1859. (c) Nallagonda, R.; Rehan, M.; Ghorai, P. *Org. Lett.* **2014**, *16*, 4786. (d) Ambrogio, I.; Cacchi, S.; Fabrizi, G. *Tetrahedron Lett.* **2007**, *48*, 7721. (e) Gschwend, H. W.; Rodriguez, H. R. *Heteroatom-Facilitated Lithiations in Organic Reactions* **1979**, *26*, 1−360 and references therein. (f) Jiao, L.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 12990.

(6) Azirines to indoles references; see: (a) Li, X.; Du, Y.; Liang, Z.; Li, X.; Pan, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2643. (b) Taber, D. F.; Tian, W. *J. Am. Chem. Soc.* **2006**, *128*, 1058. (c) Novikov, M. S.; Khlebnikov, A. F.; Rostovskii, N. V.; Tcyrulnikov, S.; Suhanova, A. A.; Zavyalov, K. V.; Yufit, D. S. *J. Org. Chem.* **2015**, *80*, 18. (d) Candito, D. A.; Lautens, M. *Org. Lett.* **2010**, *12*, 3312. (e) Jana, S.; Clements, M. D.; Sharp, B. K.; Zheng, N. *Org. Lett.* **2010**, *12*, 3736. (f) Wendling, L. A.; Bergman, R. G. *J. Org. Chem.* **1976**, *41*, 831. (g) Nair, V.; Kim, K. H. *J. Org. Chem.* **1975**, *40*, 3784.

(7) Ghorai, M. K.; Nanaji, Y. *J. Org. Chem.* **2013**, *78*, 3867.

(8) Ring-opening of aziridines with sulfur nucleophiles; see references: (a) Zeng, F.; Alper, H. *Org. Lett.* **2010**, *12*, 5567. (b) Karikomi, M.; D'hooghe, M.; Verniest, G.; De Kimpe, N. *Org. Biomol. Chem.* **2008**, *6*, 1902. (c) D'hooghe, M.; Rottiers, M.; Kerkaert, I.; De Kimpe, N. *Tetrahedron* **2005**, *61*, 8746. (d) Cernerud, M.; Adolfsson, H.; Moberg, C. *Tetrahedron: Asymmetry* **1997**, *8*, 2655. (e) Concellón, J. M.; Bernad, P. L.; Suárez, J. R.; García-Granda, S.; Díaz, M. R. *J. Org. Chem.* **2005**, *70*, 9411. (f) Prasad, D. J. C.; Sekar, G. *Org. Biomol. Chem.* **2009**, *7*, 5091. (g) Alcaide, A.; Llebaria, A. *J. Org. Chem.* **2014**, *79*, 2993. (h) Ghorai, M. K.; Sayyad, M.; Nanaji, Y.; Jana, S. *Chem. - Asian J.* **2015**, *10*, 1480. (i) Ghorai, M. K.; Sahoo, A. K.; Bhattacharyya, A. *J. Org. Chem.* **2014**, *79*, 6468.

(9) (a) Minakata, S.; Okada, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* **2005**, *7*, 3509. (b) Ghorai, M. K.; Kumar, A.; Tiwari, D. P. *J. Org. Chem.* **2010**, *75*, 137. (c) Ghorai, M. K.; Das, K.; Shukla, D. *J. Org. Chem.* **2007**, *72*, 5859. (d) Ghorai, M. K.; Tiwari, D. P. *J. Org. Chem.* **2013**, *78*, 2617. (e) Stanković, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N.; Ha, H.-J. *Chem. Soc. Rev.* **2012**, *41*, 643. (f) Xing, S.; Ren, J.; Wang, K.; Cui, H.; Li, W.; Yan, H. *Tetrahedron* **2015**, *71*, 6290. (g) Wu, B.; Gallucci, J. C.; Parquette, J. R.; Rajanbabu, T. V. *Chem. Sci.* **2014**, *5*, 1102.

(10) Copper powder-catalyzed C−N cyclization references; see: (a) Wolf, C.; Liu, S.; Mei, X.; August, A. T.; Casimir, M. D. *J. Org. Chem.* **2006**, *71*, 3270. (b) Chen, Z.-G.; Wei, J.-F.; Li, R.-T.; Shi, X.-Y.; Zhao, P.-F. *J. Org. Chem.* **2009**, *74*, 1371. (c) Lee, H. K.; Cho, C. S. *Synth. Commun.* **2013**, *43*, 915. (d) Jiao, J.; Zhang, X.-R.; Chang, N.-H.; Wei, J.; Wang, J.-F.; Shi, X.-Y.; Chen, Z.-G. *J. Org. Chem.* **2011**, *76*, 1180. (e) Ghorai, M. K.; Shahi, C. K.; Bhattacharyya, A.; Sayyad, M.; Mal, A.; Wani, I. A.; Chauhan, N. *Asian J. Org. Chem.* **2015**, *4*, 1103.

(11) Cu(I)-catalyzed C−N cyclization references; see: (a) Jiang, L. *Molecules* **2014**, *19*, 13448. (b) Xu, H.; Wolf, C. *Chem. Commun.* **2009**, 3035. (c) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742. (d) Mirallai, S. I.; Koutentis, P. A. *J. Org. Chem.* **2015**, *80*, 8329. (e) Ma, D. W.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453. (f) He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; Li, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6414. (g) Kong, L.; Zhou, Y.; Huang, H.; Yang, Y.; Liu, Y.; Li, Y. *J. Org. Chem.* **2015**, *80*, 1275. (h) Liu, H.; Duan, T.; Zhang, Z.; Xie, C.; Ma, C. *Org. Lett.* **2015**, *17*, 2932.

(12) Earlier, we reported that the *cis*-aziridines are less reactive toward S_N2-type nucleophilic ring-opening compared to *trans*-aziridines, and under the present reaction conditions, *cis*-aziridines remained unreactive to thiophenol. (a) Ghorai, M. K.; Tiwari, D. P. *J. Org. Chem.* **2010**, *75*, 6173. (b) Ghorai, M. K.; Shukla, D.; Bhattacharyya, A. *J. Org. Chem.* **2012**, *77*, 3740.

(13) (a) Cohen, T.; Herman, G.; Falck, J. R.; Mura, A. J., Jr. *J. Org. Chem.* **1975**, *40*, 812. (b) Cohen, T.; Kuhn, D.; Falck, J. R. *J. Am. Chem. Soc.* **1975**, *97*, 4749. (c) Cohen, T.; Mura, A. J.; Shull, D. W.; Fogel, E. R.; Ruffner, R. J.; Falck, J. R. *J. Org. Chem.* **1976**, *41*, 3218. (d) Cotton, F. A.; Wilkinson, Q. *Advanced lnorganic Chemistry: A Comprehensive Text*, 2nd ed.; John Wiley & Sons: New York, 1966; p 105.

(14) Perrin, D. D.; Armarego, W. L. F. In *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, U.K., 1988.

(15) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. In *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman Group: London, 1989.

(16) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844.

(17) Zhang, L., Jr.; Dolbier, W. R.; Sheeller, B.; Ingold, K. U. *J. Am. Chem. Soc.* **2002**, *124*, 6362.

DOI: 10.1021/acs.joc.5b02251
J. Org. Chem. 2015, 80, 12659−12667