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Synthetic Route to Chiral Indolines via Ring-Opening/C−N Cyclization of Activated 2-Haloarylaziridines

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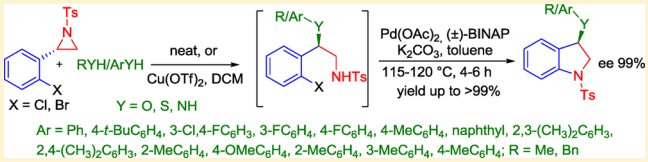
Supporting Information

ABSTRACT: A practical approach for the synthesis of 3-substituted indolines via regio- and stereoselective S_N2-type ring-opening of 2-(2-halophenyl)-*N*-tosylaziridines with heteroatomic nucleophiles (O, N, and S) followed by palladium-catalyzed intramolecular C−N cyclization is reported in excellent yields (up to >99%) and enantiomeric excess (ee 99%).



INTRODUCTION

Indolines and their derivatives are found as essential subunits in a number of naturally occurring and biologically active alkaloids and other natural products.[1] Some of the important natural products containing the indoline ring system are pentopril (**1**),[2] (−)-physostigmine (**2**),[3] *N*-[1-(4-methoxybenzenesulfonyl)-2,3-dihydro-1*H*-indol-7-yl]isonicotinamide (J30) (**3**),[4] etc. (Figure 1). Several of them exhibit a wide spectrum of

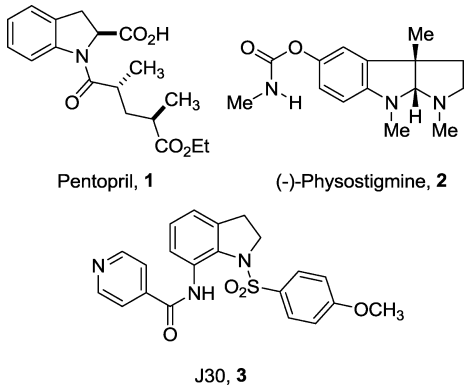


Figure 1. Some biologically active indolines.

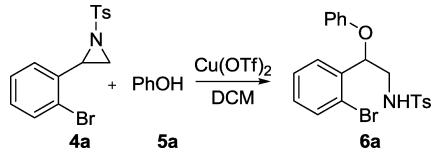
biological activities and also are of pharmacological utility as antihypertensive[2] and antitumor/anticancer agents,[4] etc. A number of attractive methodologies have been developed for the synthesis of substituted indolines,[5] although efficient routes for their enantioselective synthesis are limited.[6−10] Palladium-catalyzed amination reactions made a significant contribution in organic synthesis for the construction of C_{aryl}−N bonds from both activated and nonactivated aryl halogenides.[11]

We anticipated that indolines could easily be synthesized from the ring-opening of 2-(2-haloaryl)-*N*-activated aziridines with any nucleophile followed by palladium-catalyzed intramolecular C−N cyclization. For operational simplicity, we considered 2-(2-halophenyl)-*N*-tosylaziridine as the starting substrate and easily available phenols, anilines, and thiols as the heteroatomic nucleophiles. Several interesting strategies have been reported for the ring-opening of aziridines with different heteroatomic and C-nucleophiles,[12,13] and a number of reports for aziridine-mediated heterocycle syntheses are known in the literature.[14] In continuation of our research activities in S_N2-type ring-opening cyclization of aziridines and azetidines,[15] we have developed a simple strategy for the synthesis of 3-heteroatom-substituted racemic as well as chiral indolines with excellent yields (up to 99%) and ee (99%) via the regio- and stereoselective ring-opening of aziridines by phenols, anilines, and thiophenols followed by palladium-catalyzed intramolecular C−N cyclization. Herein, we report our results.

RESULTS AND DISCUSSION

To realize our idea, initially we studied the ring-opening of 2-(2-bromophenyl)-*N*-tosylaziridine **4a** with phenol **5a** in the presence of $Cu(OTf)_2$ as the Lewis acid in CH_2Cl_2 at 0 °C to produce the corresponding ring-opening product **6a** (Scheme 1) in almost quantitative yield.

Scheme 1. Regioselective Ring-Opening of 4a with Phenol



Next **6a** was subjected to Pd-catalyzed cyclization to obtain indoline **7a** (Scheme 2).

To find out the optimum reaction conditions, **6a** was subjected to different Pd-catalysts, solvents, ligands, and a number of bases. The results are summarized in Table 1, and the best result was obtained with $Pd(OAc)_2$, (±)-BINAP, and

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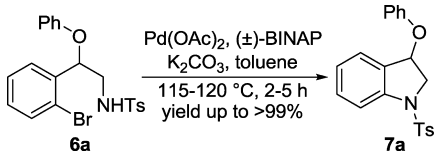
Scheme 2. Pd-Catalyzed C−N Cyclization of 6a



K_2CO_3 as the base in toluene at 115−120 °C (Table 1, entry 9).

Table 1. Pd-Catalyzed Intramolecular C−N Cyclization of 6a

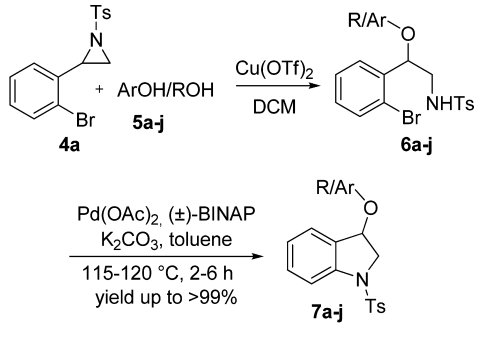
entry	reaction conditions[a]	yield (%) of 7a
1	$Pd_2(dba)_3$ (2 mol %), P(*o*-tolyl)$_3$ (8 mol %), K_2CO_3, toluene, 100 °C, 8 h	40
2	$Pd_2(dba)_3$ (5 mol %), P(2-furyl)$_3$ (20 mol %), Cs_2CO_3, toluene, 100 °C, 9 h	60
3	CuI (0.5 equiv), K_2CO_3, DMSO, 70 °C, 8 h	30
4	$Pd(OAc)_2$, (*o*-tolyl)$_3$P, K_2CO_3, DMF, 110 °C, 7 h	Nr
7	$Pd(OAc)_2$, dppb, toluene, K_2CO_3, reflux, 5 h	38
8	$Pd(OAc)_2$, dpp, toluene, K_2CO_3, reflux, 5 h	12
9[b]	$Pd(OAc)_2$, (±)-BINAP, K_2CO_3, toluene, 4 h	>99
10[b]	$Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, toluene, 4 h	85
11	$Pd(OAc)_2$, dppb, toluene, *t*-BuOK, reflux, 4 h	25
12	$Pd(OAc)_2$, DPE-Phos, Cs_2CO_3, toluene, 100 °C, 4 h	30

[a]All of the reactions were carried out with **6a** (1.0 mmol), Pd catalyst (20 mol %), ligand (40 mmol %), and base (2.5 equiv) in solvent (6.0 mL) under argon. [b]The reaction mixtures were refluxed at 115−120 °C for 3−6 h.

Compound **7a** was characterized by ^{1}H NMR, ^{13}C NMR, ^{1}H COSY spectra, and mass spectral data. The structure of **7b** was unequivocally confirmed by X-ray crystallographic analysis. To generalize this approach, several *N*-[2-(2-bromophenyl)-2-aryloxyethyl]-4-methylbenzenesulfonamides **6b−i** were prepared from aziridine **4a** and phenols **5b−i**. Similarly, *N*-[2-(2-bromophenyl)-2-methoxyethyl]-4-methylbenzenesulfonamide **6j** was prepared from **4a** using MeOH as the nucleophile. Compounds **6b−j** were cyclized under the optimized conditions to afford the corresponding indolines **7b−j** (Scheme 3) in excellent yields, and the results are shown in Table 2.

To extend the scope of the methodology, the reaction of aziridine **4a** with a *N*-nucleophile was studied. The aziridine **4a** was treated with aniline in the presence of $Cu(OTf)_2$ as the Lewis acid in CH_2Cl_2 at 0 °C to afford the corresponding

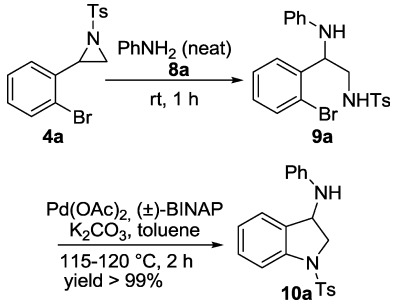
Scheme 3. Synthesis of Indolines 7a−j



Ar = Ph, 4-OMeC$_6$H$_4$, 2-MeC$_6$H$_4$, 4-*t*-BuC$_6$H$_4$, 3-MeC$_6$H$_4$, 2, 3-(CH$_3$)$_2$C$_6$H$_3$, naphthyl, 4-FC$_6$H$_4$, 4-MeC$_6$H$_4$; R = Me

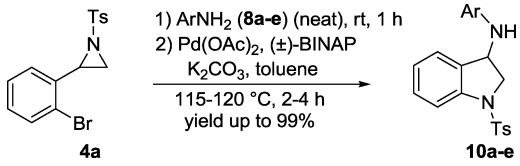
diamino compound **9a** in almost quantitative yield in 2 h. When the aziridine **4a** was treated with aniline (neat) at rt, the corresponding diamino compound **9a** was obtained in almost quantitative yield within 1 h. Next, the Pd-catalyzed cyclization of **9a** employing $Pd(OAc)_2$, (±)-BINAP, and K_2CO_3 afforded the corresponding indoline **10a** (Scheme 4) in almost quantitative yield.

Scheme 4. Synthesis of Indoline 10a



To make our strategy more attractive and straightforward as a synthetic methodology, a one-pot (stepwise) protocol for the synthesis of indolines **10a−e** via the ring-opening of monosubstituted aziridine **4a** was explored. Interestingly, the same reaction sequence as shown in Scheme 4, under one-pot conditions, produced the indoline **10a** in excellent yield. Generalization of this approach was made by studying the reaction of aziridine **4a** with a number of anilines **8b−e** (Scheme 5) and the results are shown in Table 3.

Scheme 5. Synthesis of Indolines 10a−e



The strategy was further extended to sulfur-nucleophiles (thiols). When the aziridine **4a** was treated with thiophenol **11a** in the presence of $Cu(OTf)_2$ as the Lewis acid in CH_2Cl_2 at rt, the corresponding ring-opening product **12a** was produced (Scheme 6) in almost quantitative yield. Next, the Pd-catalyzed cyclization of **12a** employing $Pd(OAc)_2$, (±)-BINAP, and K_2CO_3 afforded the corresponding indoline **13a** (Scheme 6) in almost quantitative yield. Unfortunately, $Cu(OTf)_2$-catalyzed ring-opening followed by Pd-catalyzed cyclization was not successful under the one-pot conditions. To make the one-pot

Scheme 6. Synthesis of Indoline 13a

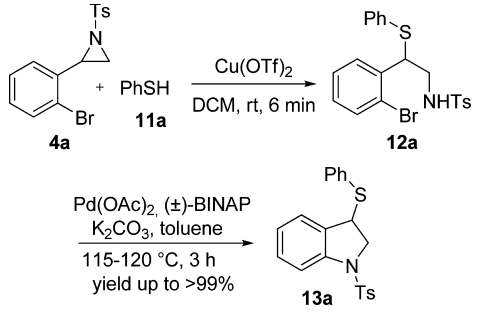


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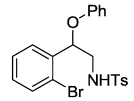
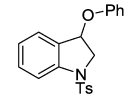
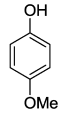
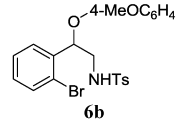
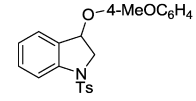
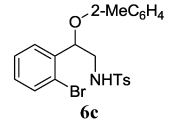
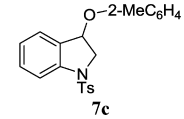
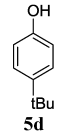
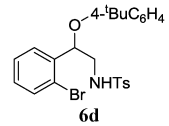
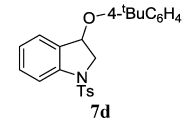
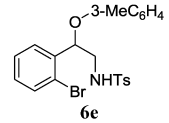
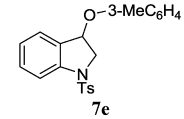
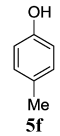
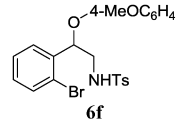
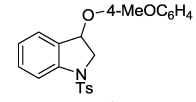
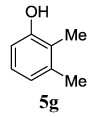
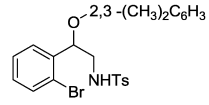
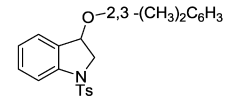
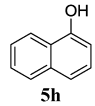
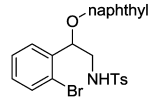
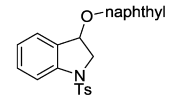
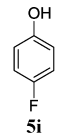
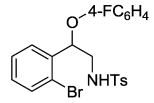
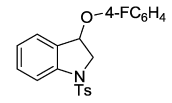
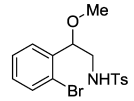
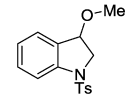
Table 2. Regioselective Ring-Opening of 4a and Pd-Catalyzed Intramolecular C−N Cyclization of 6a−j[a,b]

Entry	ArOH/ROH **5**	**6**[a]	Time (h)	Yield (%)	**7**[b]	Time (h)	Yield (%)
1	 **5a**	 **6a**	1	>99	 **7a**	3	>99
2	 **5b**	 **6b**	1	99	 **7b**	6	93
3	 **5c**	 **6c**	1	>99	 **7c**	5	97
4	 **5d**	 **6d**	1	99	 **7d**	5	96
5	 **5e**	 **6e**	1	99	 **7e**	2	95
6	 **5f**	 **6f**	1	98	 **7f**	3	97
7	 **5g**	 **6g**	1	98	 **7g**	4	93
8	 **5h**	 **6h**	1	>99	 **7h**	5	96
9	 **5i**	 **6i**	1	95	 **7i**	4	92
10	MeOH **5j**	 **6j**	5	75	 **7j**	4	93

[a]All of the reactions were carried out with **4a** (1.0 mmol) and **5a−j** (1.0 mmol) in dry DCM (2.0 mL) under N_2 atmosphere in the presence of $Cu(OTf)_2$ (30 mol %). [b]All of the reactions were carried out with **6a−j** (1.0 mmol), $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mmol %), and K_2CO_3 (2.5 equiv) in toluene (6.0 mL) under argon for 2−6 h under reflux at 110−115 °C.

protocol to work, the reaction was studied in the absence of a Lewis acid. The reaction of **4a** with thiophenol was found to be slower (2 h) without using a base, and it was completed within 25 min in the presence of K_2CO_3 as the base probably because of greater nucleophilicity of a thiophenolate ion.

To our delight, **4a** on treatment with thiophenol **11a** in the presence of K_2CO_3 as the base followed by Pd-catalyzed cyclization under one-pot condition produced the corresponding indoline **13a** in excellent yield. To generalize this approach, a number of thiols **11b−h** (Scheme 7) were studied, and the results are shown in Table 4.

Finally, the synthetic potential of the strategy is demonstrated by the synthesis of chiral indolines. To our great pleasure, ring-opening of chiral aziridine (*S*)-**4b**[16] with aniline **8a** afforded the ring-opening product **14a** with excellent yield and ee (99%) (Scheme 8).

The compound **14a** upon Pd-catalyzed intramolecular cyclization produced the corresponding indoline (*R*)-**10a**

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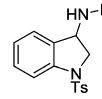
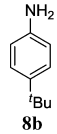
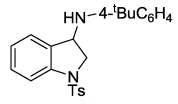
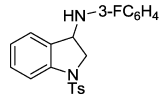
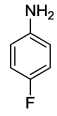
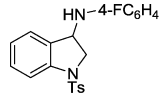
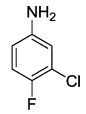
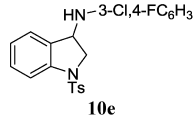
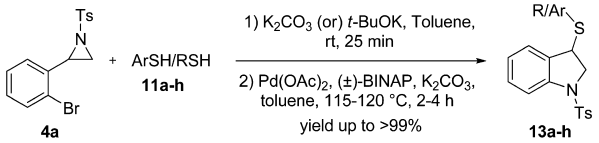
Table 3. Synthesis of Indolines 10a−e[a]

Entry	$ArNH_2$ **8**	Time (h)	**10**	Yield (%)
1	 **8a**	2	 **10a**	99
2	 **8b**	3	 **10b**	95
3	 **8c**	4	 **10c**	90
4	 **8d**	3	 **10d**	89
5	 **8e**	4	 **10e**	95

[a]All of the reactions were carried out with **4a** (1.0 mmol), **8** (2.2 mmol), and toluene (6.0 mL), rt, 1 h; $Pd(OAc)_2$ (20 mol), (±)-BINAP (40 mol %), K_2CO_3 (2.5 equiv), under reflux at 115−120 °C, 2−4 h.

Scheme 7. Synthesis of Indolines 13a−h from 4a under One-Pot Conditions



Ar = Ph, 4-MeC_6H_4, naphthyl, 4-*t*-BuC_6H_4, 2,4-$(CH_3)_2C_6H_3$, 2-MeC_6H_4, 4-FC_6H_4; R = Bn

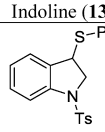
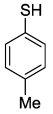
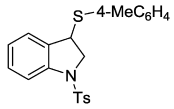
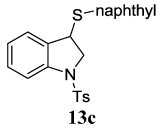
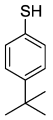
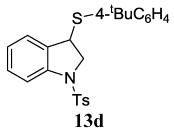
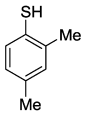
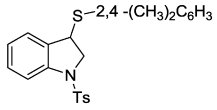
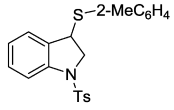
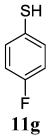
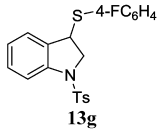
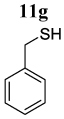
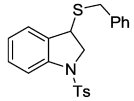
(Scheme 8) in good overall yield and excellent ee (99%). Similar ring-opening cyclization of (*S*)-**4b** with the other anilines **8b−d** gave similar results (Scheme 8, Table 5).

Mechanism. We do believe that the reaction follows a similar mechanistic pathway as reported by us earlier.[15f,g] A probable mechanism for the formation of indolines **10a−d** is described in Figure 2. S_N2-type ring-opening of *N*-tosylaziridine **4** by the heteroatomic nucleophiles (O, N, and S) generates the corresponding ring-opening products **15a−d** which undergo Pd-catalyzed intramolecular C−N coupling to obtain the corresponding indolines **10a−d**.

CONCLUSION

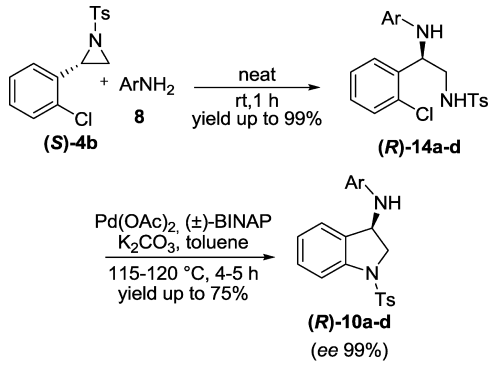
In conclusion, we have developed a simple and practical strategy for the synthesis of racemic and nonracemic 3-heteroatom-substituted indolines via S_N2-type ring-opening of 2-(2-halophenyl)-*N*-tosylaziridines with heteroatomic nucleophiles (O, N, and S) followed by Pd-catalyzed C−N cyclization in excellent yields and ee's under a two-step (for O-nucleophiles) or one-pot (stepwise for N- and S-nucleophiles) protocol.

Table 4. One-Pot Ring-Opening/C−N Cyclization of Activated Aziridines with Sulfur Nucleophiles[a]

Entry	ArSH/RSH (**11**)	Time (h)	Indoline (**13**)	Yield (%)
1	 **11a**	3	 **13a**	98
2	 **11b**	4	 **13b**	>99
3	 **11c**	4	 **13c**	94
4	 **11d**	3	 **13d**	96
5	 **11e**	4	 **13e**	98
6	 **11f**	3	 **13f**	99
7	 **11g**	4	 **13g**	98
8	 **11h**	4	 **13h**	94

[a]All of the reactions were carried out with **4a** (1.0 mmol), **11** (1.1 mmol), K_2CO_3 (1.1 equiv), and toluene (6.0 mL), rt, 25 min; $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (2.5 equiv), under reflux at 110−115 °C, 2−4 h.

Scheme 8. Synthesis of Chiral 3-Substituted Indolines



8a: Ar = Ph; **8b**: 4-*t*-BuC_6H_4; **8c**: 3-FC_6H_4; **8d**: 4-FC_6H_4.

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Table 5. Synthesis of Chiral 3-Substituted Indolines from Chiral Aziridine (*S*)-4b

Entry	$ArNH_2$ **8**	(*R*)-**14**	Yield (%)	ee (%)[a]	Time (h)	(*R*)-**10**	Yield (%)	ee (%)[a]
1	**8a**	(*R*)-**14a**	>99	99	5	(*R*)-**10a**	64	99
2	**8b**	(*R*)-**14b**	>99	99	4	(*R*)-**10b**	71	99
3	**8c**	(*R*)-**14c**	99	99	5	(*R*)-**10c**	75	99
4	**8d**	(*R*)-**14d**	99	99	4	(*R*)-**10d**	60	99

[a]ee was determined by HPLC using a Chiralpak AS-H or OD-H column.

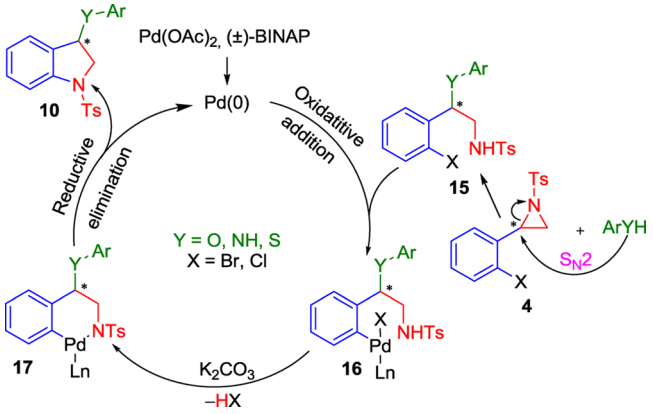

Figure 2. Proposed reaction mechanism.

EXPERIMENTAL SECTION

General Procedures. Analytical thin-layer chromatography (TLC) was carried out using silica gel 60 F_{254} precoated plates. Visualization was accomplished with UV lamp or I_2 stain. Silica gel 230−400 mesh size was used for flash column chromatography using the combination of ethyl acetate and petroleum ether as eluent. Unless noted, all of the reactions were carried out in oven-dried glassware under an atmosphere of nitrogen/argon using anhydrous solvents. Where appropriate, all of the reagents were purified prior to use following the guidelines of Perrin and Armerego.[17] All commercial reagents were used as received. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 MHz/500 MHz. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), multiplet (m). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 MHz/125 MHz. HRMS were obtained using (ESI) mass spectrometer (TOF). IR spectra were recorded as neat for liquid and in KBr for solids. Melting points were determined using a hot-stage apparatus and are uncorrected. Optical rotations were measured using a 2.0 mL cell with a 1.0 dm path length and are reported as $[\alpha]^{25}_{D}$ (c in g per 100 mL of solvent) at 25 °C. Enantiomeric ratios (er) were determined by HPLC using Chiralpak AH-H and OD-H analytical column (detection at 254 nm). 2-(2-Bromophenyl)-1-tosylaziridine and (2-(2-chlorophenyl)-1-tosylaziridine were prepared from 2-bromo- and 2-chlorostyrene, respectively, following a reported procedure.[16a] (*S*)-2-(2-Chlorophenyl)-1-tosylaziridine was prepared from the corresponding amino alcohol employing known procedures.[16b,c]

*2-(2-Bromophenyl)-1-tosylaziridine (**4a**).* Obtained as a solid compound in 90% yield: mp 85−87 °C; R_f 0.57 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3359, 3261, 3051, 1595, 1566, 1496, 1472, 1453, 1432, 1378, 1323, 1228, 1185, 1137, 1042, 1023, 981, 908, 843, 817, 769, 728, 698, 673, 650, ; ^{1}H NMR (500 MHz, $CDCl_3$) 2.26 (d, J = 4.30 Hz, 1H), 2.44 (s, 3H), 3.02 (d, J = 7.45 Hz, 1H), 3.97−3.99 (m, 1H), 7.11−7.22 (m, 3 H), 7.35 (d, J = 8.00 Hz, 1H), 7.50 (d, J = 8.05 Hz, 2H), 7.90 (d, J = 8.05 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 36.0, 41.3, 123.4, 126.5, 127.7, 127.9, 128.2, 129.7, 129.8, 130.0, 132.5, 134.7, 134.8, 145.0; HRMS (ESI) calcd for $C_{15}H_{15}BrNO_2S$ (M + H)$^+$ 352.0007, found 352.0007.

*(S)-2-(2-Chlorophenyl)-1-tosylaziridine (**4b**).* Obtained as a thick liquid in 85% yield: R_f 0.57 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3646, 3066, 2925, 1595, 1453, 1379, 1325, 1227, 1162, 1093, 908, 843, 818, 766, 731, 712, 690, 656, 569, 557; ^{1}H NMR (500 MHz, $CDCl_3$) 2.28 (d, J = 4.28 Hz, 1H), 2.44 (s, 3H), 3.03 (d, J = 7.33 Hz, 1H), 4.02−4.04 (m, 1H), 7.15−7.22 (m, 3 H), 7.32 (d, J = 7.94 Hz, 1H), 7.35 (d, J = 7.94 Hz, 2H), 7.89 (d, J = 8.25 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 35.7, 39.1, 127.1, 127.6, 128.2, 129.3, 129.4, 129.9, 133.2, 133.9, 134.7, 144.9; HRMS (ESI) calcd for $C_{15}H_{15}ClNO_2S$ (M + H)$^+$ 308.0512, found 308.0519. The enantiomeric excess was 99%; the enantiomeric excess was determined

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by chiral HPLC analysis (Chiralpak AS-H column), *n*-hexane/2-propanol = 99:1, flow rate = 1.0 mL/min, $t_R(1)$ = 55.22 min (minor, *R*), $t_R(2)$ = 65.26, min (major, *S*).

General Procedure for the Cu(OTf)$_2$-Catalyzed Ring-Opening of Aziridines. *Method A.* To a stirred suspension of anhydrous copper triflate (30 mol %) in dry DCM (2.0 mL) under N_2 atmosphere was added a solution of aziridine **4a** (1.0 equiv) in dry DCM (2.0 mL) dropwise at rt. The reaction mixture was stirred at rt for 5 min, and a solution of phenols (1.0 equiv) in dry DCM (2.0 mL) was added dropwise over a period of 1 min at rt. The reaction mixture was further stirred for 1 h at rt. The reaction was monitored by TLC and quenched with saturated aqueous sodium bicarbonate solution (1.0 mL). The aqueous layer was extracted with DCM (3 × 15.0 mL). The combined organic extract was washed with H_2O (3 × 15.0 mL) and brine (20.0 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude products 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.

General Procedure for the C−N Cyclization. *Method B.* *N*-(2-(2-Bromophenyl)-2-aryloxyethyl)-4-methylbenzenesulfonamide **6** (1.0 equiv) in dry toluene (2.0 mL) was added to a suspension of $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (2.5 equiv) in 6.0 mL of dry toluene under argon at room temperature. The reaction mixture was heated at 110−115 °C for 2−6 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 × 10 mL). The combined organic extract was washed with H_2O (3 × 10 mL) and brine (30 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 products as white solids.

General Procedure for a One-Pot (Stepwise) Protocol for the Synthesis of Indolines (Ring-Opening with Nitrogen Nucleophiles). *Method C.* A solution of aziridine **4a** (1.0 equiv) in anilines (2.2 equiv) was taken under N_2 atmosphere in a three-necked round-bottom flask. The reaction mixture was further stirred for 1 h at rt. Subsequently, $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), K_2CO_3 (2.5 equiv), and toluene (6.0 mL) were introduced to the reaction mixture. Then the reaction mixture was heated at 115−120 °C for 2−4 h, and the progress of the reaction was monitored by TLC. It was cooled to room temperature, quenched with water, and extracted with ethyl acetate (3 × 10 mL). The combined organic extract was washed with H_2O (3 × 10.0 mL) and brine (30.0 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give 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 solid.

General Procedure for a One-Pot (Stepwise) Protocol for the Synthesis of Indolines (Ring-Opening with Sulfur Nucleophiles). *Method D.* To a stirred suspension of K_2CO_3 (1.1 equiv) in dry toluene (2.0 mL) under N_2 atmosphere was added a solution of thiophenols **11** (1.1 equiv) in dry toluene (2.0 mL) dropwise at rt. The reaction mixture was stirred at rt for 25 min, and a solution of aziridine **4a** (1.0 equiv) in dry toluene (2.0 mL) was added dropwise over a period of 1 min at rt. The reaction mixture was further stirred for 25 min at the same temperature. $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (2.5 equiv) were added subsequently to the reaction mixture, and then the reaction mixture was heated at 115−120 °C for 2−5 h. The reaction was monitored by TLC. It was cooled to room temperature, quenched with water, and extracted with ethyl acetate (3 × 10.0 mL). The combined organic extract was washed with H_2O (3 × 10.0 mL) and brine (30.0 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.

General Procedure for the Ring-Opening of Chiral Aziridines. *Method E.* A solution of aziridine **4b** (1.0 equiv) in aniline (2.2 equiv) was taken under N_2 atmosphere in a two-necked round-bottom flask. The reaction mixture was stirred for 1 h at rt, and the reaction was monitored by TLC. The solvent was removed under reduced pressure to give the crude reaction mixture which was purified by flash column chromatography on silica gel (230−400 mesh) using ethyl acetate in petroleum ether to afford the pure product as a white solid.

*N-(2-(2-Bromophenyl)-2-phenoxyethyl)-4-methylbenzenesulfonamide (**6a**).* The general method A described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with phenol **5a** (19 μL, 0.22 mmol) in the presence of $Cu(OTf)_2$ (30 mol %) at rt for 1 h to afford **6a** (89.0 mg, 0.199 mmol) as a white solid in >99% yield: mp 59−61 °C; R_f 0.47 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3286, 2922, 2851, 1595, 1492, 1409, 1330, 1233, 1160, 1093, 1065, 1021, 753, 689, 661, 548; ^1H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H) 3.16−3.21 (m, 1H), 3.58−3.63 (m, 1H), 5.10−5.13 (m, 1H), 5.36−5.39 (m, 1H), 6.61 (d, *J* = 8.25 Hz, 2H), 6.87−6.90 (m, 1H), 7.10−7.21 (m, 6H), 7.29−7.31 (m, 1H), 7.51 (d, *J* = 7.95 Hz, 1H), 7.73 (d, *J* = 8.25 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 47.5, 76.9, 115.4, 121.6, 121.9, 127.2, 127.9, 128.1, 129.5, 129.8, 129.9, 133.1, 136.9, 137.4, 143.5, 156.8; HRMS (ESI) calcd for $C_{21}H_{20}BrNNaO_3S$ $(M + Na)^+$ 468.0245, found 468.0245.

*3-Phenoxy-1-tosylindoline (**7a**).* The general method B described above was followed when **6a** (67.0 mg, 0.15 mmol) was reacted with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (51.8 mg, 0.375 mmol) at 110−115 °C for 3 h to afford **7a** (55.0 mg, 0.150 mmol) as a white solid in >99% yield: mp 136−138 °C; R_f 0.25 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3423, 3055, 2921, 1597, 1487, 1468, 1348, 1246, 1222, 1162, 1107, 1088, 1071, 1055, 755, 671, 578; ^1H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H), 4.03−4.06 (m, 1H), 4.13−4.17 (m, 1H), 5.55−5.56 (m, 1H), 6.71 (d, *J* = 8.56 Hz, 2H), 6.98−7.01 (m, 1H), 7.05−7.08 (m, 1H), 7.19 (d, *J* = 8.25 Hz, 2H), 7.25−7.29 (m, 3H), 7.37−7.40 (m, 1H), 7.62 (d, *J* = 8.25 Hz, 2H), 7.76 (d, *J* = 7.95 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 55.8, 74.6, 115.7, 115.8, 121.8, 124.2, 126.5, 127.4, 129.7, 129.8, 129.9, 130.8, 133.9, 142.8, 144.3, 156.7; HRMS (ESI) calcd for $C_{21}H_{19}NNaO_3S$ $(M + Na)^+$ 388.0983, found 388.0984.

*N-(2-(2-Bromophenyl)-2-(4-methoxyphenoxy)ethyl)-4-methylbenzenesulfonamide (**6b**).* The general method A described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with phenol **5b** (27.3 mg, 0.22 mmol) in the presence of $Cu(OTf)_2$ (30 mol %)] at rt for 1 h to afford **6b** (94.0 mg, 0.197 mmol) as a white solid in 99% yield: mp 85−87 °C; R_f 0.35 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3289, 2921, 2837, 1506, 1439, 1325, 1228, 1159, 1093, 1059, 1033, 938, 830, 815, 760, 735, 665; ^1H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H) 3.16−3.22 (m, 1H), 3.59−3.65 (m, 1H), 3.74 (s, 3H), 5.16−5.19 (m, 1H), 5.34−5.37 (m, 1H), 6.58−6.61 (m, 2H), 6.71−6.74 (m, 2H), 7.14−7.18 (m, 1H), 7.23−7.27 (m, 3H), 7.35−7.37 (m, 1H), 7.53−7.55 (m, 1H), 7.77 (d, *J* = 6.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 47.5, 55.7, 77.5, 114.6, 116.3, 122.0, 127.2, 128.0, 128.1, 129.8, 129.9, 133.1, 137.0, 137.3, 143.5, 150.8, 154.3; HRMS (ESI) calcd for $C_{22}H_{22}BrNNaO_4S$ $(M + Na)^+$ 498.0351, found 498.0357.

*3-(4-Methoxyphenoxy)-1-tosylindoline (**7b**).* The general method B described above was followed when **6b** (72.0 mg, 0.15 mmol) was reacted with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (51.8 mg, 0.375 mmol) at 110−115 °C for 6 h to afford **7b** (55.0 mg, 0.139 mmol) as a white solid in 93% yield: mp 50−52 °C; R_f 0.38 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3388, 3047, 2924, 2835, 1600, 1505, 1465, 1355, 1221, 1166, 1108, 1090, 1035, 825, 673, 578; ^1H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.77 (s, 3H), 4.06−4.09 (m, 2H), 5.44−5.46 (m, 1H), 6.63 (d, *J* = 9.17 Hz, 2H), 6.80 (d, *J* = 9.17 Hz, 2H), 7.03−7.06 (m, 1H), 7.19 (d, *J* = 8.56 Hz, 2H), 7.22 (d, *J* = 7.34 Hz, 1H), 7.35−7.38 (m, 1H), 7.63 (d, *J* = 8.25 Hz, 2H), 7.75 (d, *J* = 7.95 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 55.7, 55.8, 75.7, 114.8, 115.6, 117.5, 124.1, 126.4, 127.5, 129.8, 130.0, 130.8, 134.0, 142.7, 144.2, 150.6 154.7; HRMS (ESI) calcd for $C_{22}H_{21}NNaO_4S$ $(M + Na)^+$ 418.1089, found 418.1089.

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*N-(2-(2-Bromophenyl)-2-(o-tolyloxy)ethyl)-4-methylbenzenesulfonamide (**6c**).* The general method A described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with phenol **5c** (23 μL, 0.22 mmol) in the presence of $Cu(OTf)_2$ (30 mol %) at rt for 1 h to afford **6c** (92.0 mg, 0.199 mmol) as a white solid in >99% yield: mp 75−77 °C; R_f 0.40 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3296, 2921, 2851, 1596, 1492, 1464, 1437, 1330, 1236, 1160, 1124, 1093, 1020, 813, 750, 660, 550; ^1H NMR (500 MHz, $CDCl_3$) δ 2.29 (s, 3H) 2.36 (s, 3H), 3.21−3.26 (m, 1H), 3.58−3.63 (m, 1H), 5.03−5.06 (m, 1H), 5.29−5.41 (m, 1H), 6.20 (d, *J* = 8.02 Hz, 1H), 6.78−6.81 (m, 1H), 6.88−6.91 (m, 1H), 7.10−7.13 (m, 2H), 7.17−7.21 (m, 3H), 7.25−7.26 (m, 1H), 7.51 (d, *J* = 8.02 Hz, 1H), 7.71 (d, *J* = 8.31 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.6, 21.6, 47.6, 76.5, 112.2, 121.2, 121.9, 126.5, 126.8, 127.1, 127.7, 128.2, 129.8, 130.0, 130.9, 133.1, 136.9, 137.3, 143.6, 154.6; HRMS (ESI) calcd for $C_{22}H_{22}BrNNaO_3S$ $(M + Na)^+$ 482.0401, found 482.0407.

*3-(o-Tolyloxy)-1-tosylindoline (**7c**).* The general method B described above was followed when **6c** (69.0 mg, 0.15 mmol) was reacted with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (51.8 mg, 0.375 mmol) at 110−115 °C for 5 h to afford **7c** (55.0 mg, 0.144 mmol) as a white solid in 97% yield: mp 106−108 °C; R_f 0.44 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3417, 2918, 1599, 1492, 1462, 1353, 1237, 1186, 1160, 1110, 1010, 978, 937, 814, 748, 675, 653, 581, 541; ^1H NMR (500 MHz, $CDCl_3$) δ 1.85 (s, 3H), 2.35 (s, 3H), 4.06 (dd, *J* = 3.06, 12.53 Hz, 1H), 4.20 (dd, *J* = 7.03, 12.53 Hz, 1H), 5.54 (dd, *J* = 2.45, 6.72 Hz, 1H), 6.77 (d, *J* = 8.25 Hz, 1H), 6.89−6.92 (m, 1H), 7.03−7.06 (m, 1H), 7.11 (d, *J* = 7.34 Hz, 1H), 7.14−7.25 (m, 4H), 7.36−7.39 (m, 1H), 7.66 (d, *J* = 8.25 Hz, 2H), 7.76 (d, *J* = 8.25 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.1, 21.6, 56.1, 75.1, 112.9, 115.3, 121.6, 124.0, 126.4, 126.8, 127.4, 128.2, 129.8, 130.1, 130.7, 131.3, 134.0, 142.6, 144.3, 155.1; HRMS (ESI) calcd for $C_{22}H_{21}NNaO_3S$ $(M + Na)^+$ 402.1140, found 402.1140.

*N-(2-(2-Bromophenyl)-2-(4-tert-butylphenoxy)ethyl)-4-methylbenzenesulfonamide (**6d**).* The general method A described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with phenol **5d** (33.0 mg, 0.22 mmol) in the presence of $Cu(OTf)_2$ (30 mol %) at rt for 1 h to afford **6d** (99.0 mg, 0.197 mmol) as a white solid in 99% yield: mp 62−64 °C; R_f 0.28 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3287, 2961, 2867, 1605, 1511, 1331, 1237, 1184, 1161, 1094, 1070, 830, 813, 756, 661; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 9H) 2.37 (s, 3H), 3.13−3.19 (m, 1H), 3.55−3.60 (m, 1H), 5.08−5.10 (m, 1H), 5.31−5.33 (m, 1H), 6.54 (d, *J* = 8.86 Hz, 2H), 7.10−7.25 (m, 6H), 7.31−7.33 (m, 1H), 7.50−7.51 (m, 1H), 7.72 (d, *J* = 8.25 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 31.5, 34.1, 47.6, 77.0, 114.8, 121.8, 126.3, 127.2, 128.0, 128.1, 129.8, 129.9, 133.0, 137.1, 137.3, 143.5, 144.3, 154.6; HRMS (ESI) calcd for $C_{25}H_{28}BrNNaO_3S$ $(M + Na)^+$ 524.0871, found 524.0876.

*3-(4-tert-Butylphenoxy)-1-tosylindoline (**7d**).* The general method B described above was followed when **6d** (75.4 mg, 0.15 mmol) was reacted with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (51.8 mg, 0.375 mmol) at 110−115 °C for 5 h to afford **7d** (61.0 mg, 0.144 mmol) as a white solid in 96% yield: mp 97−99 °C; R_f 0.44 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3426, 3029, 2968, 2870, 1602, 1510, 1366, 1356, 1225, 1180, 1166, 1055, 1010, 832, 805, 756, 647; ^1H NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 9H), 2.37 (s, 3H), 4.01−4.05 (m, 1H), 4.13−4.17 (m, 1H), 5.53−5.55 (m, 1H), 6.67 (d, *J* = 8.88 Hz, 2H), 7.05−7.08 (m, 1H), 7.19 (d, *J* = 8.02 Hz, 2H), 7.25−7.38 (m, 4H), 7.63 (d, *J* = 8.31 Hz, 2H), 7.74 (d, *J* = 8.02 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 31.6, 34.2, 55.9, 74.7, 115.2, 115.5, 124.2, 126.4, 126.5, 127.5, 129.8, 130.0, 130.8, 134.0, 142.7, 144.3, 144.6, 154.5; HRMS (ESI) calcd for $C_{25}H_{27}NNaO_3S$ $(M + Na)^+$ 444.1609, found 444.1609.

*N-(2-(2-Bromophenyl)-2-(m-tolyloxy)ethyl)-4-methylbenzenesulfonamide (**6e**).* The general method A described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with phenol **5e** (23 μL, 0.22 mmol) in the presence of $Cu(OTf)_2$ (30 mol %) at rt for 1 h to afford **6e** (91.0 mg, 0.197 mmol) as a white solid in 99% yield: mp 106−108 °C; R_f 0.40 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3279, 2922, 1591, 1491, 1468, 1422, 1332, 1258, 1157, 1091, 1060, 1021, 957, 904, 861, 807, 766, 683, 545; ^1H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 3H) 2.38 (s, 3H), 3.14−3.19 (m, 1H), 3.56−3.61 (m, 1H), 5.07−5.10 (m, 1H), 5.35−5.37 (m, 1H), 6.35−6.37 (m, 1H), 6.48 (s, 1H), 6.70 (d, *J* = 7.45 Hz, 1H), 7.01 (t, *J* = 7.73 Hz, 1H), 7.10−7.13 (m, 1H), 7.19−7.21 (m, 3H), 7.29−7.31 (m, 1H), 7.51 (d, *J* = 8.02 Hz, 1H), 7.72 (d, *J* = 8.02 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 21.6, 47.6, 76.8, 112.1, 116.4, 121.8, 122.5, 127.2, 127.9, 128.1, 129.2, 129.8, 129.9, 133.0, 137.0, 137.5, 139.6, 143.5, 156.8; HRMS (ESI) calcd for $C_{22}H_{22}BrNNaO_3S$ $(M + Na)^+$ 482.0401, found 482.0401.

*3-(m-Tolyloxy)-1-tosylindoline (**7e**).* The general method B described above was followed when **6e** (69.0 mg, 0.15 mmol) was reacted with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (51.8 mg, 0.375 mmol) at 110−115 °C for 2 h to afford **7e** (54.0 mg, 0.142 mmol) as a white solid in 95% yield: mp 52−54 °C; R_f 0.55 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3404, 3046, 2920, 1601, 1488, 1465, 1356, 1254, 1166, 1090, 1065, 765, 735, 675, 653; ^1H NMR (500 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.37 (s, 3H), 4.02 (dd, *J* = 2.45, 12.53 Hz, 1H), 4.15 (dd, *J* = 6.72, 12.84 Hz, 1H), 5.54 (dd, *J* = 2.45, 6.72 Hz, 1H), 6.49−6.54 (m, 2H), 6.81 (d, *J* = 7.34 Hz, 1H), 7.06−7.09 (m, 1H), 7.16 (t, *J* = 7.64 Hz, 1H), 7.19 (d, *J* = 7.95 Hz, 2H), 7.29 (d, *J* = 7.34 Hz, 1H), 7.36−7.39 (m, 1H), 7.62 (d, *J* = 8.25 Hz, 2H), 7.76 (d, *J* = 8.25 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 21.7, 55.8, 74.5, 112.5, 115.7, 116.7, 122.6, 124.2, 126.4, 127.5, 129.4, 129.8, 130.0, 130.8, 133.9, 139.9, 142.7, 144.2, 156.7; HRMS (ESI) calcd for $C_{22}H_{21}NNaO_3S$ $(M + Na)^+$ 402.1140, found 402.1145.

*N-(2-(2-Bromophenyl)-2-(p-tolyloxy)ethyl)-4-methylbenzenesulfonamide (**6f**).* The general method A described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with phenol **5f** (23.8 mg, 0.22 mmol) in the presence of $Cu(OTf)_2$ (30 mol %) at rt for 1 h to afford **6f** (90.0 mg, 0.195 mmol) as a white solid in 98% yield: mp 144−146 °C; R_f 0.41 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3295, 2919, 1615, 1509, 1439, 1329, 1229, 1160, 1092, 1021, 813, 757, 660; ^1H NMR (500 MHz, $CDCl_3$) δ 2.21 (s, 3H) 2.37 (s, 3H), 3.13−3.19 (m, 1H), 3.56−3.61 (m, 1H), 5.12−5.14 (m, 1H), 5.33−5.35 (m, 1H), 6.51 (d, *J* = 8.59 Hz, 2H), 6.94 (d, *J* = 8.88 Hz, 2H), 7.09−7.12 (m, 1H), 7.18−7.20 (m, 3H), 7.29−7.31 (m, 1H), 7.50 (d, *J* = 7.73 Hz, 1H), 7.73 (d, *J* = 8.31 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 21.6, 47.5, 77.0, 115.2, 121.9, 127.2, 127.9, 128.1, 129.8, 129.9, 130.0, 130.9, 133.0, 137.0, 137.4, 143.5, 154.7; HRMS (ESI) calcd for $C_{22}H_{22}BrNNaO_3S$ $(M + Na)^+$ 482.0401, found 482.0409.

*3-(p-Tolyloxy)-1-tosylindoline (**7f**).* The general method B described above was followed when **6f** (69.0 mg, 0.15 mmol) was reacted with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (51.8 mg, 0.375 mmol) at 110−115 °C for 3 h to afford **7f** (55.0 mg, 0.145 mmol) as a white solid in 97% yield: mp 104−106 °C; R_f 0.50 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3415, 2921, 1603, 1508, 1355, 1289, 1226, 1166, 1109, 1090, 812, 755, 723, 704, 673, 651, 578; ^1H NMR (500 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.36 (s, 3H), 4.03 (dd, *J* = 2.45, 12.55 Hz, 1H), 4.13 (dd, *J* = 6.70, 12.55 Hz, 1H), 5.51−5.52 (m, 1H), 6.60 (d, *J* = 8.55 Hz, 2H), 7.04−7.07 (m, 3H), 7.18 (d, *J* = 8.55 Hz, 2H), 7.25−7.28 (m, 1H), 7.36−7.39 (m, 1H), 7.62 (d, *J* = 8.25 Hz, 2H), 7.74 (d, *J* = 8.25 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 21.6, 55.8, 74.9, 115.6, 115.8, 124.2, 126.5, 127.5, 129.8, 130.0, 130.2, 130.8, 131.2, 133.9, 142.7, 144.2, 154.6; HRMS (ESI) calcd for $C_{22}H_{21}NNaO_3S$ $(M + Na)^+$ 402.1140, found 402.1146.

*N-(2-(2-Bromophenyl)-2-(2,3-dimethylphenoxy)ethyl)-4-methylbenzenesulfonamide (**6g**).* The general method A described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with phenol **5g** (26.9 mg, 0.22 mmol) in the presence of $Cu(OTf)_2$ (30 mol %) at rt for 1 h to afford **6g** (93.0 mg, 0.196 mmol) as a white solid in 98% yield: mp 119−121 °C; R_f 0.45 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3284, 3060, 2922, 1584, 1469, 1432, 1326, 1251, 1156, 1093, 1067, 952, 875, 861, 811, 756, 708, 662; ^1H NMR (500 MHz, $CDCl_3$) δ 2.21 (s, 3H) 2.26 (s, 3H), 2.37 (s, 3H), 3.21−3.26 (m, 1H), 3.57−3.62 (m, 1H), 5.01−5.03 (m, 1H), 5.37−5.40 (m, 1H), 6.10 (d, *J* = 8.31 Hz, 1H), 6.71 (d, *J* = 7.45 Hz, 1H), 6.80 (t, *J* =

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8.02 Hz, 1H), 7.09−7.12 (m, 1H), 7.18−7.27 (m, 4H), 7.50 (d, J = 8.02 Hz, 1H), 7.71 (d, J = 8.31 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 20.2, 21.6, 47.6, 76.8, 110.0, 121.9, 123.0, 124.9, 125.8, 127.1, 127.7, 128.2, 129.8, 129.9, 133.0, 137.1, 137.3, 138.2, 143.5, 154.4; HRMS (ESI) calcd for $C_{23}H_{24}BrNNaO_3S$ (M + Na)$^+$ 496.0558, found 496.0558.

*3-(2,3-Dimethylphenoxy)-1-tosylindoline (**7g**).* The general method B described above was followed when **6g** (71.0 mg, 0.15 mmol) was reacted with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (51.8 mg, 0.375 mmol) at 110−115 °C for 4 h to afford **7g** (55.0 mg, 0.139 mmol) as a white solid in 93% yield: mp 147−149 °C; R_f 0.6 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3437, 3068, 2922, 1600, 1581, 1466, 1356, 1253, 1167, 1090, 1019, 840, 813, 756, 669, 579; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.78 (s, 3H), 2.23 (s, 3H), 2.35 (s, 3H), 4.05 (dd, J = 3.06, 12.53 Hz, 1H), 4.17 (dd, J = 7.03, 12.53 Hz, 1H), 5.51(dd, J = 2.25, 7.03 Hz, 1H), 6.66 (d, J = 7.95 Hz, 1H), 6.82 (d, J = 7.64 Hz, 1H),7.02−7.07 (m, 2H), 7.19 (d, J = 8.25 Hz, 2H), 7.22 (d, J = 7.64 Hz, 1H), 7.35−7.38 (m, 1H), 7.67 (d, J = 8.56 Hz, 2H), 7.75 (d, J = 8.25 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 20.2, 21.6, 56.1, 75.5, 111.0, 115.2, 123.5, 124.0, 125.9, 126.4, 126.7, 127.4, 129.8, 130.1, 130.6, 134.0, 138.6, 142.6, 144.3, 155.0; HRMS (ESI) calcd for $C_{23}H_{23}NNaO_3S$ (M + Na)$^+$ 416.1296, found 416.1297.

*N-(2-(2-Bromophenyl)-2-(naphthalen-1-yloxy)ethyl)-4-methylbenzenesulfonamide (**6h**).* The general method A described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with phenol **5h** (31.0 mg, 0.22 mmol) in the presence of $Cu(OTf)_2$ (30 mol %) at rt for 1 h to afford **6h** (99.0 mg, 0.199 mmol) as a white solid in >99% yield: mp 47−49 °C; R_f 0.3 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3370, 2919, 1628, 1599, 1466, 1439, 1329, 1254, 1214, 1159, 1121, 1092, 1019, 969, 811, 750, 661; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.22 (s, 3H) 3.23−3.28 (m, 1H), 3.65−3.70 (m, 1H), 5.14−5.17 (m, 1H), 5.48−5.50 (m, 1H), 6.64 (d, J = 8.31, 2.58 Hz, 1H), 7.03 (dd, J = 2.58, 8.88 Hz, 1H), 7.10−7.13 (m, 3H), 7.17−7.19 (m, 1H), 7.29−7.38 (m, 4H), 7.52−7.55 (m, 2H), 7.67−7.73 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 47.6, 76.9, 109.0, 118.4, 122.1, 124.2, 126.5, 127.0, 127.1, 127.6, 127.8, 128.2, 129.3, 129.6, 129.7, 130.0, 133.1, 134.2, 136.7, 137.5, 143.6, 154.5; HRMS (ESI) calcd for $C_{25}H_{22}BrNNaO_3S$ (M + Na)$^+$ 518.0401, found 518.0406.

*3-(Naphthalen-1-ylosy)-1-tosylindoline (**7h**).* The general method B described above was followed when **6h** (74.0 mg, 0.15 mmol) was reacted with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (51.8 mg, 0.375 mmol) at 110−115 °C for 5 h to afford **7h** (60.0 mg, 0.144 mmol) as a white solid in 96% yield: mp 62−64 °C; R_f 0.4 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3399, 3056, 2921, 2850, 1628, 1599, 1509, 1465, 1357, 1253, 1214, 1167, 1118, 1064, 1007, 965, 812, 751, 672, 579; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3H), 4.10−4.13 (m, 1H), 4.25 (dd, J = 6.59, 12.60 Hz, 1H), 5.68−5.70 (m, 1H), 6.83 (d, J = 2.58, 8.88 Hz, 1H), 7.02 (d, J = 2.29 Hz, 1H), 7.10 (t, J = 7.45 Hz 1H), 7.18 (d, J = 8.31 Hz, 2H), 7.39−7.42 (m, 3H), 7.48 (t, J = 7.16 Hz, 1H), 7.61 (d, J = 8.31 Hz, 2H), 7.72 (d, J = 8.59 Hz, 2H), 7.78 (t, J = 8.02 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 55.6, 74.6, 108.3, 115.8, 119.3, 124.3, 124.4, 126.6, 126.8, 126.9, 127.5, 127.8, 129.4, 129.8, 129.9, 131.0, 133.8, 134.2, 142.9, 144.3, 154.5; HRMS (ESI) calcd for $C_{25}H_{21}NNaO_3S$ (M + Na)$^+$ 438.1140, found 438.1140.

*N-(2-(2-Bromophenyl)-2-(4-fluorophenoxyoxy)ethyl)-4-methylbenzenesulfonamide (**6i**).* The general method A described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with phenol **5i** (24.7 mg, 0.22 mmol) in the presence of $Cu(OTf)_2$ (30 mol %) at rt for 1 h to afford **6i** (88.0 mg, 0.189 mmol) as a white solid in 95% yield: mp 46−48 °C; R_f 0.3 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3434, 2923, 2853, 1637, 1502, 1439, 1241, 1329, 1203, 1159, 1093, 1021, 813, 741, 661; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (s, 3H) 3.14−3.19 (m, 1H), 3.56−3.61 (m, 1H), 5.09−5.12 (m, 1H), 5.31−5.34 (m, 1H), 6.53−6.57 (m, 2H), 6.83 (t, J = 8.56 Hz, 2H), 7.11−7.15 (m, 1H), 7.20−7.29 (m, 4H), 7.52 (d, J = 7.95 Hz, 1H), 7.73 (d, J = 7.95 Hz, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 47.5, 77.6, 115.9, 116.0, 116.4, 116.5, 122.0, 127.2, 127.8, 128.2, 129.8, 130.1, 133.2, 136.6, 137.3, 143.6, 152.9, 156.6, 158.5; HRMS (ESI) calcd for $C_{21}H_{19}BrFNNaO_3S$ (M + Na)$^+$ 486.0151, found 486.0151.

*3-(4-Fluorophenoxy)-1-tosylindoline (**7i**).* The general method B described above was followed when **6i** (70.0 mg, 0.15 mmol) was reacted with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (51.8 mg, 0.375 mmol) at 110−115 °C for 4 h to afford **7i** (53.0 mg, 0.138 mmol) as a white solid in 92% yield: mp 64−66 °C; R_f 0.45 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3436, 2924, 2854, 1601, 1503, 1466, 1355, 1292, 1201, 1166, 1091, 1065, 1006, 979, 911, 828, 765, 725, 704, 673, 651; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3H), 4.03−4.12 (m, 2H), 5.46−5.48 (m, 1H), 6.62−6.65 (m, 2H), 6.94−6.97 (m, 2H), 7.04−7.07 (m, 1H), 7.19 (d, J = 7.95 Hz 1H), 7.23 (d, J = 7.34 Hz, 2H), 7.37−7.40 (m, 1H), 7.62−7.64 (m, 2H), 7.76 (d, J = 8.25 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 55.6, 75.6, 115.7, 116.1, 116.3, 117.3, 117.4, 124.2, 126.4, 127.5, 129.6, 129.8, 131.0, 133.8, 142.8, 144.3, 152.7, 157.0, 158.5; HRMS (ESI) calcd for $C_{21}H_{18}ClFNO_3S$ (M + Cl)$^-$ 418.0680, found 418.0689.

*N-(2-(2-Bromophenyl)-2-methoxyethyl)-4-methylbenzenesulfonamide (**6j**).* The general method A described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with methanol **5j** (1.0 mL) in the presence of $Cu(OTf)_2$ (100 mol %) at rt for 5 h to afford **6j** (58.0 mg, 0.15 mmol) as a white solid in 75% yield: mp 99−101 °C; R_f 0.3 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3265, 3988, 2922, 2821, 1597, 1567, 1493, 1459, 1417, 1354, 1325, 1259, 1160, 1113, 1093, 1077, 967, 911, 870, 813, 768, 681; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.81−2.86 (m, 1H), δ 3.15 (s, 3H) 3.35−3.40 (m, 1H), 4.56 (dd, J = 3.05, 9.61 Hz, 1H), 5.11−5.13 (m, 1H), 7.11−7.15 (m, 1H), 7.25−2.31 (m, 4H), 7.48 (d, J = 7.94 Hz, 1H), 7.74 (d, J = 8.25 Hz, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 47.6, 57.2, 80.7, 123.1, 127.3, 127.6, 127.9, 129.7, 129.8, 133.1, 137.2, 137.3, 143.5; HRMS (ESI) calcd for $C_{16}H_{19}BrNO_3S$ (M + H)$^+$ 384.0264, found 384.0260.

*3-Methoxy-1-tosylindoline (**7j**).* The general method B described above was followed when **6j** (58.0 mg, 0.15 mmol) was reacted with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (51.8 mg, 0.375 mmol) at 110−115 °C for 4 h to afford **7j** (43.0 mg, 0.14 mmol) as a white solid in 93% yield: mp 56−58 °C; R_f 0.32 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1})2925, 1599, 1475, 1465, 1354, 1165, 1237, 1210, 1165, 1091, 1026, 974, 814, 756, 731, 676; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.18 (s, 3H), 3.83−3.88 (m, 1H), 3.95−3.97 (m, 1H), 4.71 (bd, J = 6.59 Hz, 1H), 7.04 (t, J = 7.45 Hz, 1H), 7.20 (d, J = 7.73 Hz, 2H), 7.29 (d, J = 7.45 Hz 1H), 7.33 (t, J = 7.45 Hz, 1H), 7.67 (d, J = 8.31 Hz, 2H), 7.71 (d, J = 8.31 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 55.2, 55.3, 77.8, 115.2, 123.8, 126.3, 127.4, 129.7, 130.3, 130.5, 133.8, 142.5, 144.3; HRMS (ESI) calcd for $C_{16}H_{18}NO_3S$ (M + H)$^+$ 304.1002, found 304.1004.

*N-Phenyl-1-tosylindolin-3-amine (**10a**).* The general method C described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with aniline **8a** (40 μL, 0.44 mmol) at rt for 1 h followed by treatment with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (69.1 mg, 0.5 mmol) at 110−115 °C for 2 h to afford **10a** (72.0 mg, 0.197 mmol) as a white solid in 99% yield: mp 153−155 °C; R_f 0.43 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3388, 2992, 1600, 1502, 1476, 1461, 1353, 1307, 1165, 1090, 1017, 813, 751, 693, 673; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.24 (bd, J = 7.95 Hz, 1H), 3.84 (dd, J = 3.67, 11.62 Hz, 1H), 4.12 (dd, J = 7.34, 11.62 Hz, 1H), 4.84−4.87 (m, 1H), 6.42 (d, J = 7.64 Hz, 2H), 6.75−6.78 (m, 1H), 7.05−7.08 (m, 1H), 7.16−7.21 (m, 4H), 7.25−7.27 (m, 1H), 7.33−7.36 (m, 1H), 7.60 (d, J = 8.25 Hz, 2H) 7.74 (d, J = 8.25 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 53.3, 56.8, 113.3, 116.0, 118.5, 124.5, 125.6, 127.4, 129.5, 129.8, 130.1, 132.4, 133.8, 142.2, 144.3, 145.7; HRMS (ESI) calcd for $C_{21}H_{21}N_2O_2S$ (M + H)$^+$ 365.1324, found 365.1325.

*(R)-N-(2-(2-Chlorophenyl)-2-(phenylamino)ethyl)-4-methylbenzenesulfonamide (**14a**).* The general method E described above was followed when (*S*)-**4b** (62.0 mg, 0.2 mmol) was reacted with aniline **8a** (40 μL, 0.44 mmol) at rt for 1 h to to afford (*R*)-**14a** (80.0 mg, 0.199 mmol) as a white solid in >99% yield: mp 150−152 °C; R_f 0.40 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}); 3396,

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3288, 3055, 2924, 1602, 1499, 1468, 1438, 1321, 1267, 1158, 1092, 1047, 1034, 873, 813, 752, 706, 692, 663; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (S, 3H), 3.14−3.20 (m, 1H), 3.40−3.45 (m, 1H), 4.73−4.84 (m, 3H), 6.41 (d, J = 7.64 Hz, 2H), 6.66 (t, J = 7.33 Hz, 1H), 7.07 (t, J = 7.33 Hz, 2H), 7.17−7.20 (m, 2H), 7.28 (d, J = 8.55 Hz, 2H), 7.32−7.34 (m, 1H), 7.43−7.44 (m, 1H), 7.23 (d, J = 8.25 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 46.9, 54.3, 113.6, 118.1, 127.2, 127.6, 128.3, 129.1, 129.2, 130.0, 132.8, 136.8, 137.0, 143.9, 146.3; HRMS (ESI) calcd for $C_{21}H_{22}ClN_2O_2S$ (M + H)$^+$ 401.1085, found 401.1090; $[\alpha]^{25}_D$ = +43.6 (c 0.92, CH_2Cl_2) for a 99% ee sample, the enantiomeric excess was determined by chiral HPLC analysis (chiralpak AS-H column), n-hexane/2-propanol = 70:30, flow rate = 1.0 mL/min, $t_R(1)$ = 19.39 min (minor, S), $t_R(2)$ = 59.59, min (major, R).

*(R)-N-Phenyl-1-tosylindolin-3-amine (**10a**).* The general method B described above was followed when (R)-**14a** (60.0 mg, 0.15 mmol) obtained from (S)-**4b** was reacted with Pd(OAc)$_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (51.8 mg, 0.375 mmol) at 110−115 °C for 5 h to afford (R)-**10a** (35.0 mg, 0.096 mmol) as a white solid in 64% yield; $[\alpha]^{25}_D$ = +4.8 (c 0.58, CH_2Cl_2) for a 99% ee sample, the enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AS-H column), n-hexane/2-propanol = 95:5, flow rate =1.0 mL/min, $t_R(1)$ = 68.2 min (minor, S), $t_R(2)$ = 82.8, min (major, R).

*N-(4-tert-Butylphenyl)-1-tosylindolin-3-amine (**10b**).* The general method C described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with aniline **8b** (70 μL, 0.44 mmol), at rt for 1 h followed by treatment with Pd(OAc)$_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (69.1 mg, 0.5 mmol) at 110−115 °C for 3 h to afford **10b** (80.0 mg, 0.190 mmol) as a white solid in 95% yield: mp 114−116 °C; R_f 0.45 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3387, 2953, 2864, 1613, 1518, 1476, 1461, 1351, 1317, 1257, 1165, 1100, 1089, 947, 808, 766, 670, 586; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (s, 9H), 2.39 (s, 3H), 3.22 (bd, J = 8.3 Hz, 1H), 3.83 (dd, J = 3.72, 11.74 Hz, 1H), 4.13 (dd, J = 7.45, 11.46 Hz, 1H), 4.83−4.87 (m, 1H), 6.40 (d, J = 8.59 Hz, 2H), 7.04−7.07 (m, 1H), 7.20−7.25 (m, 5H), 7.32−7.35 (m, 1H), 7.62 (d, J = 8.31 Hz, 2H), 7.73 (d, J = 8.31 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 31.6, 34.0, 53.5, 57.0, 113.0, 115.9, 124.4, 125.6, 126.3, 127.4, 129.8, 129.9, 132.6, 133.9, 141.4, 142.1, 143.4, 144.3; HRMS (ESI) calcd for $C_{25}H_{29}N_2O_2S$ (M + H)$^+$ 421.1950, found 421.1956.

*(R)-N-(2-(4-tert-Butylphenylamino)-2-(2-chlorophenyl)ethyl)-4-methylbenzenesulfonamide (**14b**).* The general method E described above was followed when (S)-**4b** (62.0 mg, 0.2 mmol) was reacted with aniline **8b** (70 μL, 0.44 mmol) at rt for 1 h to afford (R)-**14b** (91.0 mg, 0.199 mmol) as a white solid in >99% yield: mp 160−162 °C; R_f 0.35 (10% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3393, 3239, 2956, 1615, 1522, 1468, 1362, 1288, 1194, 1100, 1034, 961, 819, 755, 707, 663, 546, 499; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (s, 9H), 2.42 (s, 3H), 3.17−3.13 (m, 1H), 3.41−3.36 (m, 1H), 4.65 (m, 1H), 4.86−4.80 (m, 1H), 6.37 (d, J = 8.25 Hz, 2H), 7.10 (d, J = 8.25 Hz, 2H), 7.19−7.18 (m, 2H), 7.28−7.25 (m, 2H), 7.34−7.32 (m, 1H), 7.47−7.45 (m, 1H), 7.73 (d, J = 7.94 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 31.6, 33.9, 47.02, 54.7, 113.3, 126.0, 127.2, 127.6, 128.4, 129.1, 129.9, 130.0, 132.8, 136.8, 137.3, 140.8, 143.9, 144.1; HRMS (ESI) calcd for $C_{25}H_{30}ClN_2O_2S$ (M + H)$^+$ 457.1711, found 457.1710; $[\alpha]^{25}_D$ = +24.8 (c 0.68, CH_2Cl_2) for a 99% ee sample, the enantiomeric excess was determined by chiral HPLC analysis (chiralpak AS-H column), n-hexane/2-propanol = 80:20, flow rate = 1.0 mL/min, $t_R(1)$ = 25.10 min (minor, S), $t_R(2)$ = 40.4, min (major, R).

*(R)-N-(4-tert-Butylphenyl)-1-tosylindolin-3-amine (**10b**).* The general method B described above was followed when (R)-**14b** (68.0 mg, 0.15 mmol) obtained from (S)-**4b** was reacted with Pd(OAc)$_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (51.8 mg, 0.375 mmol) at 110−115 °C for 4 h to afford (R)-**10b** (45.0 mg, 0.107 mmol) as a white solid in 71% yield; $[\alpha]^{25}_D$ = +1.6 (c 0.83, CH_2Cl_2) for a 99% ee sample, the enantiomeric excess was determined by chiral HPLC analysis (Chiralpak OD-H column), n-hexane/i-propanol = 95:5, flow rate = 1.0 mL/min, $t_R(1)$ = 19.90 min (major, S), $t_R(2)$ = 29.56, min (minor, R).

*N-(3-Fluorophenyl)-1-tosylindolin-3-amine (**10c**).* The general method C described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with aniline **8c** (42 μL, 0.22 mmol) at rt for 1 h followed by treatment with Pd(OAc)$_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (69.1 mg, 0.5 mmol) at 110−115 °C for 4 h to afford **10c** (69.0 mg, 0.180 mmol) as a white solid in 90% yield: mp 106−108 °C; R_f 0.45 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}); 3393, 2919, 2849, 1619, 1477, 1462, 1354, 1165, 1090, 1018, 813, 757, 704, 674, 578, 543; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.31 (bd, J = 8.31 Hz, 1H), 3.84 (dd, J = 3.15, 11.74 Hz, 1H), 4.08 (dd, J = 7.16, 11.7 Hz, 1H), 4.77−4.81 (m, 1H), 6.06−6.08 (m, 1H), 6.16−6.18 (m, 1H), 6.42−6.46 (m, 1H), 7.06−7.12 (m, 2H), 7.20 (d, J = 8.31 Hz, 2H), 7.25−7.26 (m, 1H), 7.34−7.37 (m, 1H), 7.59 (d, J = 8.31 Hz, 2H), 7.75 (d, J = 8.31 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 53.1, 56.4, 100.0, 100.2, 104.8, 105.0, 108.8, 116.1, 124.5, 125.5, 127.3, 129.8, 130.2, 130.5, 130.6, 131.8, 133.7, 142.1, 144.3, 147.2, 147.3, 162.9, 164.9; HRMS (ESI) calcd for $C_{21}H_{20}FN_2O_2S$ (M + H)$^+$ 383.1230, found 383.1230.

*(R)-N-(2-(2-Chlorophenyl)-2-(2-fluorophenylamino)ethyl)-4-methylbenzenesulfonamide (**14c**).* The general method E described above was followed when (S)-**4b** (62.0 mg, 0.2 mmol) was reacted with aniline **8c** (42 μL, 0.44 mmol) at rt for 1 h to afford (R)-**14c** (83.0 mg, 0.198 mmol) as a white solid in 99% yield: mp 90−92 °C; R_f 0.40 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3394, 3283, 3065, 2924, 1621, 1595, 1517, 1495, 1442, 1325, 1092, 1042, 813, 756, 681, 662, 550; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.16−3.21 (m, 1H), 3.40−3.45 (m, 1H), 4.69−4.72 (m, 2H), 4.78−4.81 (m, 1H), 5.01−5.02 (m, 1H), 6.02−6.04 (m, 1H), 6.21−6.22 (m, 1H), 6.32−6.36 (m, 1H), 6.98−7.03 (m, 1H), 7.20−7.23 (m, 2H), 7.29 (d, J = 8.25 Hz, 2H), 7.34−7.36 (m, 1H), 7.41−7.42 (m, 1H), 7.73 (d, J = 8.25 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 46.7, 54.4, 100.2, 100.4, 104.4, 104.6, 109.4, 127.1, 127.7, 128.2, 129.3, 130.0, 130.1, 130.3, 130.3, 132.8, 136.4, 136.8, 144.1, 148.1, 148.2; HRMS (ESI) calcd for $C_{21}H_{21}ClFN_2O_2S$ (M + H)$^+$ 419.0991, found 419.0997; $[\alpha]^{25}_D$ = +4.1 (c 0.77, CH_2Cl_2) for a 99% ee sample, the enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AS-H column), n-hexane/2-propanol = 70:30, flow rate = 1.0 m.L/min, $t_R(1)$ = 17.17 min (minor, S), $t_R(2)$ = 66.42, min (major, R).

*(R)-N-(3-Fluorophenyl)-1-tosylindolin-3-amine (**10c**).* The general method B described above was followed when (R)-**14c** (62.0 mg, 0.15 mmol) obtained from (S)-**4b** was reacted with Pd(OAc)$_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (51.8 mg, 0.375 mmol) at 110−115 °C for 5 h to afford (R)-**10c** (43.0 mg, 0.112 mmol) as a white solid in 75% yield; $[\alpha]^{25}_D$ = +8.1 (c 0.44, CH_2Cl_2) for a 99% ee sample, the enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AS-H column), n-hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, $t_R(1)$ = 33.85 min (major, S), $t_R(2)$ = 45.50, min (minor, R).

*N-(4-Fluorophenyl)-1-tosylindolin-3-amine (**10d**).* The general method C described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with aniline **8d** (42 μL, 0.44 mmol) at rt for 1 h followed by treatment with Pd(OAc)$_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (69.1 mg, 0.5 mmol) at 110−115 °C for 3h to afford **10d** (68.0 mg, 0.177 mmol) as a white solid in 89% yield: mp 55−57 °C; R_f 0.45 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}); 3398, 2923, 1600, 1511, 1511, 1477, 1353, 1223, 1166, 1091, 1052, 819, 757, 731, 704; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.13 (bs, 1H), 3.82 (dd, J = 3.36, 11.62 Hz, 1H), 4.07 (dd, J = 7.34, 11.62 Hz, 1H), 4.79 (bs, 1H), 6.33−6.36 (m, 2H), 6.86−6.90 (m, 2H), 7.04−7.08 (m, 1H), 7.20 (d, J = 7.95 Hz, 2H), 7.24−7.25 (m, 1H), 7.33−7.36 (m, 1H), 7.60 (d, J = 8.25 Hz, 2H), 7.74 (d, J = 8.25 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 53.9, 56.4, 114.2, 114.3, 115.9, 116.0, 124.5, 125.6, 127.4, 129.9, 130.1, 132.2, 133.8, 142.0, 142.1, 144.3, 155.4, 157.3; HRMS (ESI) calcd for $C_{21}H_{20}FN_2O_2S$ (M + H)$^+$ 383.1230, found 383.1237.

*(R)-N-(2-(2-Chlorophenyl)-2-(4-fluorophenylamino)ethyl)-4-methylbenzenesulfonamide (**14d**).* The general method E described

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above was followed when (*S*)-**4b** (62 mg, 0.2 mmol) was reacted with aniline **8d** (42 μL, 0.44 mmol) at rt for 1 h to afford (*R*)-**14d** (83.0 mg, 0.198 mmol) as a white solid in 99% yield: mp 76−78 °C; R_f 0.40 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3394, 3284, 2925, 1598, 1511, 1444, 1322, 1222, 1093, 1047,1035, 819, 757, 662, 551; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41(s, 3H), 3.12−3.17 (m, 1H), 3.38−3.43 (m, 1H), 4.75 (bs, 1H), 4.94 (t, *J* = 6.59 Hz 1H), 6.31−6.34 (m, 2H), 6.76 (t, *J* = 8.59 Hz, 2H), 7.17−7.20 (m, 2H), 7.25−7.28 (m, 2H), 7.32−7.34 (m, 1H), 7.40−7.42 (m, 1H), 7.72 (d, *J* = 8.31 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 46.9, 54.9, 114.3, 114.4, 115.6, 115.8, 127.2, 127.6, 128.2, 129.2, 129.98, 130.0, 132.9, 136.8, 136.8, 142.7, 144.0, 155.2, 157.1; HRMS (ESI) calcd for $C_{21}H_{21}ClFN_2O_2S$ $(M + H)^+$ 419.0991, found 419.0999; $[\alpha]^{25}_D$ = −12.8 (*c* 0.5, CH_2Cl_2) for a 99% ee sample, the enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AS-H column), *n*-hexane/2-propanol = 70:30, flow rate = 1.0 mL/min, $t_R(1)$ = 19.05 min (minor, *S*), $t_R(2)$ = 74.02, min (major, *R*).

*(R)-N-(4-Fluorophenyl)-1-tosylindolin-3-amine (**10d**).* The general method B described above was followed when (*R*)-**14d** (62.0 mg, 0.15 mmol) obtained from (*S*)-**4b** was reacted with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (51.8 mg, 0.375 mmol) at 110−115 °C for 4 h to afford (*R*)-**10d** (35.0 mg, 0.09 mmol) as a white solid in 60% yield; $\alpha]^{25}_D$ = +1.0 (*c* 0.2, CH_2Cl_2) for a 99% ee sample, the enantiomeric excess was determined by chiral HPLC analysis (Chiralpak OD-H column), *n*-hexane/2-propanol = 98:2, flow rate = 0.5 mL/min, $t_R(1)$ = 88.47 min (minor, *S*), $t_R(2)$ = 98.03 min (major, *R*).

*N-(3-Chloro-4-fluorophenyl)-1-tosylindolin-3-amine (**10e**).* The general method **C** described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with aniline **8e** (64.0 mg, 0.44 mmol) at rt for 1 h followed by treatment with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (69.1 mg, 0.5 mmol) at 110−115 °C for 4 h to afford **10e** (79.0 mg, 0.189 mmol) as a white solid in 95% yield: mp 104−106 °C; R_f 0.40 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3393, 2924, 2853, 1603, 1504, 1463, 1353, 1223, 1166, 1090, 1051, 976, 945, 909, 811, 785, 757, 734, 704, 672; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.07 (bd, *J* = 8.59 Hz, 1H), 3.81 (dd, *J* = 2.86, 11.74 Hz, 1H), 4.05 (dd, *J* = 7.16, 11.74 Hz, 1H), 4.71−4.75 (m, 1H), 6.22−6.25 (m, 1H), 6.33−6.34 (m, 1H), 6.93−6.96 (m, 1H), 7.07−7.10 (m, 1H), 7.20−7.25 (m, 3H), 7.35−7.38 (m, 1H), 7.59 (d, *J* = 8.59 Hz, 2H), 7.75 (d, *J* = 8.02 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 53.7, 56.2, 112.2, 112.3, 114.6, 116.3, 117.0, 117.2, 121.0, 121.2, 124.7, 125.6, 127.4, 129.9, 130.4, 131.8, 133.8, 142.2, 142.5, 144.4, 150.56, 152.47; HRMS (ESI) calcd for $C_{21}H_{19}ClFN_2O_2S$ $(M + H)^+$ 417.0840, found 417.0846.

*N-(2-(2-Bromophenyl)-2-(phenylthio)ethyl)-4-methylbenzenesulfonamide (**12a**).* The general method A described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with thiophenol **11i** (23 μL, 0.22 mmol) in the presence of $Cu(OTf)_2$ (30 mol %) at rt for 6 min to afford **12a** (91.6 mg, 0.198 mmol) as a thick liquid in 99% 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, $CDCl_3$) δ 2.42 (s, 3H) 3.30−3.36 (m, 1H), 3.42−3.47 (m, 1H), 4.65 (t, *J* = 7.35 Hz, 1H), 4.82 (t, *J* = 6.40 Hz, 1H), 7.08−7.15 (m, 2H), 7.18−7.25 (m, 5H), 7.52 (dd, *J* = 7.95, 1.25 Hz, 1H), 7.64 (d, *J* = 8.55 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.

*3-(Phenylthio)-1-tosylindolinone (**13a**).* The general method D described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with thiophenoxide from **11a** [(23 μL, 0.22 mmol), K_2CO_3 (30.4 mg, 0.22 mmol)] at rt for 25 min followed by treatment with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (69.1 mg, 0.5 mmol) at 110−115 °C for 3 h to afford **13a** (75.0 mg, 0.196 mmol) as a white solid in 98% yield: mp 110−112 °C; R_f 0.33 (10% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}); 3419, 3070, 2919, 2885, 1596, 1580, 1477, 1350, 1254, 1165, 1102, 1087, 1061, 1027, 976, 868, 807, 756, 738, 666, 578; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.99 (dd, *J* = 3.97, 11.62 Hz, 1H), 4.17 (dd, *J* = 8.25, 11.62 Hz, 1H), 4.64 (dd, *J* = 3.97, 8.25 Hz, 1H), 6.99−7.02 (m, 1H), 7.18−7.22 (m, 3H), 7.24−7.27 (m, 6H), 7.62−7.65 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 46.9, 57.0, 115.0, 124.0, 125.8, 127.5, 127.9, 129.3, 129.6, 129.8, 130.7, 132.2, 133.6, 134.0, 141.9, 144.4; HRMS (ESI) calcd for $C_{21}H_{19}NNaO_2S_2$ $(M + Na)^+$ 404.0755, found 404.0750.

*3-(p-Tolylthio)-1-tosylindoline (**13b**).* The general method D described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with thiophenoxide from **11b** [(27.3 mg, 0.22 mmol), K_2CO_3 (30.4 mg, 0.22 mmol)] at rt for 25 min followed by treatment with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (69.1 mg, 0.5 mmol) at 110−115 °C for 4 h to afford **13b** (79.0 mg, 0.199 mmol) as a white solid in >99% yield: mp 79−81 °C; R_f 0.34 (10% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}); 3394, 3030, 2920, 1598, 1492, 1475, 1462, 1356, 1253, 1168, 1105, 1055, 811, 754, 731, 670, 578; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.37 (s, 3H), 3.98 (dd, *J* = 4.30, 11.74 Hz, 1H), 4.13 (dd, *J* = 8.31, 11.74 Hz, 1H), 4.57 (dd, *J* = 4.30, 8.59 Hz, 1H), 6.98−7.01 (m, 1H), 7.08 (d, *J* = 8.02 Hz, 2H), 7.15−7.26 (m, 6H), 7.62 (d, *J* = 8.02 Hz, 1H), 7.65 (d, *J* = 8.31 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 21.7, 47.4, 56.9, 115.0, 123.9, 125.8, 127.5, 129.5, 129.7, 130.0, 131.0, 133.0, 134.1, 138.2, 141.9, 144.3; HRMS (ESI) calcd for $C_{22}H_{21}NNaO_2S_2$ $(M + Na)^+$ 418.0911, found 418.0916.

*3-(Naphthalen-1-ylthio)-1-tosylindoline (**13c**).* The general method D described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with thiophenoxide from **11c** [(35.2 mg, 0.22 mmol), K_2CO_3 (30.4 mg, 0.22 mmol)] at rt for 25 min followed by treatment with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (69.1 mg, 0.5 mmol) at 110−115 °C for 4 h to afford **13c** (81.0 mg, 0.187 mmol) as a white solid in 94% yield: mp 40−42 °C; R_f 0.33 (10% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}); 3448, 3051, 2923, 2853, 1729, 1623, 1596, 1475, 1461, 1355, 1253, 1185, 1104, 1089, 1054, 850, 811, 747, 704, 670, 578; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H), 4.03 (dd, *J* = 4.30, 11.74 Hz, 1H), 4.22 (dd, *J* = 8.31, 11.74 Hz, 1H), 4.75 (dd, *J* = 4.30, 8.02 Hz, 1H), 7.00−7.03 (m, 1H), 7.16 (d, *J* = 8.31 Hz, 2H), 7.23−7.31 (m, 3H), 7.48−7.52 (m, 2H), 7.61−7.64 (m, 3H), 7.71−7.74 (m, 3H), 7.80−7.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 46.8, 56.9, 115.1, 124.0, 125.8, 126.6, 126.9, 127.4, 127.6, 127.8, 128.9, 129.2, 129.6, 129.7, 130.7, 131.0, 131.1, 132.6, 133.6, 134.0, 142.0, 144.3; HRMS (ESI) calcd for $C_{25}H_{21}NNaO_2S_2$ $(M + Na)^+$ 454.0911, found 454.0919.

*3-(4-tert-Butylphenylthio)-1-tosylindoline (**13d**).* The general method D described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with thiophenoxide from **11d** [(36.6 mg, 0.22 mmol), K_2CO_3 (30.4 mg, 0.22 mmol)] at rt for 25 min followed by treatment with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (69.1 mg, 0.5 mmol) at 110−115 °C for 3 h to afford **13d** (84.0 mg, 0.191 mmol) as a white solid in 96% yield: mp 59−61 °C; R_f 0.47 (10% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}); 3400, 3067, 2961, 2868, 1598, 1475, 1462, 1398, 1357, 1305, 1291, 1168, 1090, 1055, 1028, 979, 813, 752, 733, 705 ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 9H), 2.37 (s, 3H), 4.02 (dd, *J* = 4.01, 11.46 Hz, 1H), 4.14 (dd, *J* = 8.02, 11.74 Hz, 1H), 4.60 (dd, *J* = 4.01, 8.02 Hz, 1H), 6.99−7.02 (m, 1H), 7.19−7.27 (m, 6H), 7.30−7.32 (m, 2H), 7.63 (d, *J* = 8.31 Hz, 1H), 7.67 (d, *J* = 8.31 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 31.3, 34.7, 47.3, 57.3, 115.1, 124.0, 125.8, 126.4, 127.5, 129.5, 129.8, 130.2, 130.9, 132.3, 134.1, 141.9, 144.3, 151.3; HRMS (ESI) calcd for $C_{25}H_{27}NNaO_2S_2$ $(M + Na)^+$ 460.1381, found 460.1385.

*3-(2,4-Dimethylphenylthio)-1-tosylindoline (**13e**).* The general method D described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with thiophenoxide from **11e** [(29 μL, 0.22 mmol), K_2CO_3 (30.4 mg, 0.22 mmol)] at rt for 25 min followed by treatment with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %) and K_2CO_3 (69.1 mg, 0.5 mmol) at 110−115 °C for 4 h to afford **13e** (80.0 mg, 0.195 mmol) as a white solid in 98% yield: mp 63−65 °C; R_f 0.35 (10% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 2920, 1599, 1475, 1463, 1357, 1253, 1169, 1105, 1090, 979, 812, 754, 671, 579; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.30 (s, 3H), 2.96 (s, 3H), 3.97 (dd, *J* = 3.72, 11.46 Hz, 1H), 4.12 (dd, *J* = 8.02, 11.74 Hz, 1H), 4.53 (dd, *J* = 3.72, 7.75 Hz, 1H), 6.93−6.98 (m, 2H),

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7.02 (s, 1H), 7.05 (dd, J = 7.45 Hz, 1H), 7.14 (d, J = 8.02 Hz, 1H), 7.22 (d, J = 8.59 Hz, 2H), 7.25 (t, 1H), 7.65 (d, J = 8.02 Hz, 1 H), 7.67 (d, J = 8.31 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 21.1, 21.6, 46.5, 57.0, 115.0, 123.9, 125.6, 127.5, 129.5, 129.6, 129.7, 131.1, 131.6, 132.8, 134.2, 138.1, 140.2, 141.8, 144.3; HRMS (ESI) calcd for $C_{23}H_{27}N_2O_2S_2$ $(M + NH_4)^+$ 427.1514, found 427.1513.

*3-(o-Tolylthio)-1-tosylindoline (**13f**).* The general method D described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with thiophenoxide from **11f** [(26 μL, 0.22 mmol), K_2CO_3 (30.4 mg, 0.22 mmol)] at rt for 10 min followed by treatment with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %) and K_2CO_3 (69.1 mg, 0.5 mmol) at 110−115 °C for 3 h to afford **13f** (78.0 mg, 0.197 mmol) as a white solid in 99% yield: mp 102−104 °C; R_f 0.35 (10% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3061, 2924, 2855, 1598, 1475, 1357, 1169, 1105, 1090, 750, 670, 579, 545; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.36 (s, 3H), 3.99 (dd, J = 4.01, 11.74 Hz, 1H), 4.19 (dd, J = 8.02, 11.74 Hz, 1H), 4.61 (dd, J = 3.72, 8.02 Hz, 1H), 6.98 (t, 1H), 7.07 (d, J = 7.45 Hz, 1H), 7.12−7.16 (m, 1H), 7.18−7.28 (m, 6 H), 7.65−7.68 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 21.6, 45.9, 57.1, 115.1, 123.9, 125.7, 126.8, 127.5, 127.6, 129.6, 129.8, 130.7, 130.9, 131.3, 133.5, 134.1, 139.5, 141.9, 144.3; HRMS (ESI) calcd for $C_{22}H_{21}NNaO_2S_2$ $(M + Na)^+$ 418.0911, found 418.0911.

*3-(4-Fluorophenylthio)-1-tosylindoline (**13g**).* The general method D described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with thiophenoxide from **11g** [(23 μL, 0.22 mmol), K_2CO_3 (30.4 mg, 0.22 mmol)] at rt for 25 min followed by treatment with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (69.1 mg, 0.5 mmol) at 110−115 °C for 4 h to afford **13g** (78.0 mg, 0.195 mmol) as a white solid in 98% yield: mp 73−75 °C; R_f 0.35 (10% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3067, 2924, 2855, 1589, 1489, 1475, 1463, 1356, 1226, 1169, 1105, 1090, 1056, 832, 754, 671, 579; ^{1}H NMR (400 MHz, $CDCl_3$) 2.37 (s, 3 H), 3.92 (dd, J = 4.58, 10.6 Hz, 1H), 4.12 (dd, J = 8.59, 11.46 Hz, 1H), 4.53 (dd, J = 4.30, 8.31 Hz, 1H), 6.89−6.92 (m, 2 H), 6.99−7.02 (m, 1H), 7.17−7.26 (m, 6 H), 7.59 (d, J = 8.02 Hz, 1H), 7.62 (d, J = 8.31 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 47.5, 56.4, 114.8, 116.2, 116.4, 123.8, 125.8, 127.4, 127.6, 129.6, 129.7, 130.6, 134.0, 135.8, 135.9, 142.0, 144.4, 162.0, 164.0; HRMS (ESI) calcd for $C_{21}H_{18}NFNaO_2S_2$ $(M + Na)^+$ 422.0661, found 422.0670.

*3-(Benzylthio)-1-tosylindoline (**13h**).* The general method D described above was followed when **4a** (71 mg, 0.2 mmol) was reacted with thiophenoxide from **11h** [(26 μL, 0.22 mmol), K_2CO_3 (30.4 mg, 0.22 mmol)] at rt for 25 min followed by treatment with $Pd(OAc)_2$ (20 mol %), (±)-BINAP (40 mol %), and K_2CO_3 (69.1 mg, 0.5 mmol) at 110−115 °C for 4 h to afford **13h** (74.0 mg, 0.187 mmol) as a white solid in 94% yield: mp 50−52 °C; R_f 0.43 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}); 3397, 2923, 2853, 1597, 1459, 1354, 1238, 1167, 1089, 1027, 812, 752, 703, 658, 578; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.48 (s, 2H), 3.82−3.89 (m, 1H), 4.10−4.16 (m, 2H), 6.99−7.03 (m, 1H), 7.16−7.32 (m, 9H), 7.64−7.67 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 35.1, 43.3, 57.4, 115.0, 124.2, 125.7, 127.4, 127.5, 128.7, 128.9, 129.3, 129.8, 131.3, 133.8, 137.4, 141.8, 144.4; HRMS (ESI) calcd for $C_{22}H_{25}N_2O_2S_2$ $(M + NH_4)^+$ 413.1357, found 413.1359.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra for all new compounds and X-ray crystallographic data of **7b**, **10e**, and **12b** (CIF). 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) (a) Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. *Tetrahedron* **2010**, *66*, 4687. (b) Liu, D.; Zhao, G.; Xiang, L. *Eur. J. Org. Chem.* **2010**, 3975. (c) Va, P.; Campbell, E. L.; Robertson, W. M.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 8489. (d) Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 7119. (e) Nicolaou, K. C.; Bheema Rao, P.; Hao, J.; Venkat Reddy, M.; Rassias, G.; Huang, X.; Chen, D. Y.-K.; Snyder, S, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1753. (f) Gan, Z.; Thirupathi Reddy, P.; Quevillon, S.; Couve-Bonnaire, S.; Arya, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1366.

(2) (a) Rakhit, A.; Hurley, M. E.; Tipnis, V.; Coleman, J.; Rommel, A.; Brunner, H. R. *J. Clin. Pharmacol.* **1986**, *26*, 156. (b) Gruenfeld, N.; Stanton, J. L.; Yuan, A. M.; Ebetino, F. H.; Browne, L. J.; Gude, C.; Huebner, C. F. *J. Med. Chem.* **1983**, *26*, 1277.

(3) (a) Bui, T.; Syed, S.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2009**, *131*, 8758. (b) Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.* **1991**, *56*, 872. (c) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590. (d) Mukai, C.; Yoshida, T.; Sorimachi, M.; Odani, A. *Org. Lett.* **2006**, *8*, 83.

(4) Liou, J.-P.; Hsu, K.-S.; Kuo, C.-C.; Chang, C.-Y.; Chang, J.-Y. *J. Pharm. Exp. Ther.* **2007**, *323*, 398.

(5) (a) Liu, K. G.; Lo, J. R.; Robichaud, A. J. *Tetrahedron* **2010**, *66*, 573. (b) Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Org. Chem.* **2006**, *71*, 4255. (c) Ruano, J. L. G.; Parra, A.; Marcos, V.; del Pozo, C.; Catalán, S.; Monteagudo, S.; Fustero, S.; Poveda, A. *J. Am. Chem. Soc.* **2009**, *131*, 9432. (d) Wang, Z.; Wan, W.; Jiang, H.; Hao, J. *J. Org. Chem.* **2007**, *72*, 9364. (e) Kang, K. H.; Do, J.; Park, Y. S. *J. Org. Chem.* **2012**, *77*, 808. (f) Clive, D. L. J.; Peng, J.; Fletcher, S. P.; Ziffle, V. E.; Wingert, D. *J. Org. Chem.* **2008**, *73*, 2330. (g) Wipf, P.; Maciejewski, J. P. *Org. Lett.* **2008**, *10*, 4383. (h) Sun, K.; Sachwani, R.; Richert, K. J.; Driver, T. G. *Org. Lett.* **2009**, *11*, 3598. (i) Tan, M.; Zhang, Y. *Tetrahedron Lett.* **2009**, *50*, 4912. (j) Correa, A.; Tellitu, I.; Domínguez, E.; Sanmartin, R. *J. Org. Chem.* **2006**, *71*, 8316. (k) Beemelmanns, C.; Lentz, D.; Reissig, H.-U. *Chem.—Eur. J.* **2011**, *17*, 9720.

(6) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264. (b) Hou, X. L.; Zheng, B. H. *Org. Lett.* **2009**, *11*, 1789. (c) Mealy, M. J.; Luderer, M. R.; Bailey, W. F.; Sommer, M. B. *J. Org. Chem.* **2004**, *69*, 6042. (d) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451. (e) Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638. (f) Anas, S.; Cordi, A.; Kagan, H. B. *Chem. Commun.* **2011**, *47*, 11483. (g) Pineschi, M.; Bertolini, F.; Crotti, P.; Macchia, F. *Org. Lett.* **2006**, *8*, 2627. (h) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3.

(7) (a) Kuwano, R.; Kashiwabara, M.; Sato, K.; Ito, T.; Kaneda, K.; Ito, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 521. (b) Maj, A. M.; Suisse, I.; Méliet, C.; Agbossou-Niedercorn, F. *Tetrahedron: Asymmetry* **2010**, *21*, 2010. (c) Wang, D.-S.; Tang, J.; Zhou, Y.-G.; Chen, M.-W.; Yu, C.-B.; Duan, Y.; Jiang, G.-F. *Chem. Sci.* **2011**, *2*, 803. (d) Duan, Y.; Chen, M.-W.; Chen, Q.-A.; Yu, C.-B.; Zhou, Y.-G. *Org. Biomol. Chem.* **2012**, *10*, 1235. (e) Kuwano, R.; Kashiwabara, M. *Org. Lett.* **2006**, *8*, 2653. (f) Rueping, M.; Brinkmann, C.; Antonchick, A. P.; Atodiresei, I. *Org. Lett.* **2010**, *12*, 4604. (g) Wang, D.-S.; Chen, Q.-A.; Li, W.; Yu, C.-B.; Zhou, Y.-G.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 8909. (h) Kuwano, R.; Kaneda, K.; Ito, T.; Sato, K.; Kurokawa, T.; Ito, Y. *Org. Lett.* **2004**, *6*, 2213. (i) Vickers, C. J.; Mei, T.-S; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 2511. (j) Wang, L.; Shao, Y.; Liu, Y. *Org. Lett.* **2012**, *14*, 3978. (k) Anderson, J. C.; Noble, A.; Tocher, D. A. *J. Org. Chem.* **2012**, *77*, 6703.

(8) (a) Guthrie, D. B.; Curran, D. P. *Org. Lett.* **2009**, *11*, 249. (b) Viswanathan, R.; Mutnick, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 7266. (c) Johnston, J. N.; Plotkin, M. A.; Viswanathan, R.; Prabhakaran, E. N. *Org. Lett.* **2001**, *3*, 1009. (d) Fuwa, H.; Sasaki, M. *Org. Lett.* **2007**, *9*, 3347. (e) Leroi, C.; Bertin, D.; Dufils, P.-E.; Gigmes,

D.; Marque, S.; Tordo, P.; Couturier, J.-L.; Guerret, O.; Ciufolini, M. A. *Org. Lett.* **2003**, *5*, 4943. (f) Cossy, J.; Poitevin, C.; Pardo, D. G. *Synlett* **1998**, 251.

(9) (a) Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638. (b) Minatti, A.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2721. (c) Kubo, T.; Katoh, C.; Yamada, K.; Okano, K.; Tokuyama, H.; Fukuyama, T. *Tetrahedron* **2008**, *64*, 11230.

(10) (a) Neumann, J. J.; Rakshit, S.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892. (b) Rogers, M. M.; Wendlandt, J. E.; Guzei, I. A.; Stahl, S. S. *Org. Lett.* **2006**, *8*, 2257. (c) Newman, S. S.; Howell, J. K.; Nicolaus, N.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 14916. (d) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906. (e) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (f) Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett.* **2007**, *9*, 5255. (g) Wantanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759. (h) López-Iglesia, M.; Busto, E.; Gotor, V.; Gotor-Fernández, V. *J. Org. Chem.* **2012**, *77*, 8049. (i) Ganton, M. D.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777. (j) He, G.; Lu, C.; Zhao, Y.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2944.

(11) (a) Wolfe, J. P.; Wangw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (b) Shen, Q.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 4109. (c) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423. (d) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965. (e) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552. (f) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35. (g) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron.* **1996**, *52*, 7525. (h) Bower, J. F.; Rujirawanich, J.; Gallagher, T. *Org. Biomol. Chem.* **2010**, *8*, 1505.

(12) (a) Minakata, S.; Okada, Y.; Oleraotoshi, Y.; Komastu, M. *Org. Lett.* **2005**, *7*, 3509. (b) D'hooghe, M.; Rottiers, M.; Kerkaert, I.; De Kimpe, N. *Tetrahedron.* **2005**, *61*, 8746. (c) D'hooghe, M.; Waterinckx, A.; Vanlangendonck, T.; De Kimpe, N. *Tetrahedron* **2006**, *62*, 2295. (d) Karikomi, M.; D'hooghe, M.; Verniest, G.; De Kimpe, N. *Org. Biomol. Chem.* **2008**, *6*, 1902. (e) D'hooghe, M.; Kenis, S.; Vervisch, K.; Lategan, C.; Smith, P. J.; Chibale, K.; De Kimpe, N. *Eur. J. Med. Chem.* **2011**, *46*, 579. (f) De Rycke, N.; David, O.; Couty, F. *Org. Lett.* **2011**, *13*, 1836. (g) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080. (h) Concellón, J. M.; Rodriguez-Solla, H.; Amo, V.; Diaz, P. *J. Org. Chem.* **2010**, *75*, 2407. (i) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701 and references cited therein. (j) Forbeck, E. M.; Evans, C. D.; Gilleran, J. A.; Li, P.; Joullié, M. M. *J. Am. Chem. Soc.* **2007**, *129*, 14463. (k) Concellón, J. M.; Bernad, P. L.; Suárez, J. R. *J. Org. Chem.* **2005**, *70*, 9411. (l) Kelley, B. T.; Joullié, M. M. *Org. Lett.* **2010**, *12*, 4244. (m) Couty, F.; Evano, G.; Prim, D. *Tetrahedron Lett.* **2005**, *46*, 2253. (n) Minakata, S.; Hotta, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* **2006**, *71*, 7471. (o) Zeng, F.; Alper, H. *Org. Lett.* **2010**, *12*, 5567. (p) Yadav, J. S.; Satheesh, G.; Murthy, C. V. S. R. *Org. Lett.* **2010**, *12*, 2544. (q) Bera, M.; Pratihar, S.; Roy, S. *J. Org. Chem.* **2011**, *76*, 1475. (r) Ghorai, M. K.; Kumar, A.; Das, K. *Org. Lett.* **2007**, *9*, 5441. (s) Ghorai, M. K.; Kumar, A.; Tiwari, D. P. *J. Org. Chem.* **2010**, *75*, 137. (t) Ghorai, M. K.; Das, K.; Shukla, D. *J. Org. Chem.* **2007**, *72*, 5859. (u) Wu, B.; Gallucci, J. C.; Parquette, J. R.; RajanBabu, T. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 1126. (v) Wu, B.; Parquette, J. R.; RajanBabu, T. V. *Science* **2009**, *326*, 1662. (w) Stanković, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; Speybroeck, V. V.; De Kimpe, N.; Ha, H.-J. *Chem. Soc. Rev.* **2012**, *41*, 643.

(13) (a) Minakata, S.; Murakami, Y.; Satake, M.; Hidaka, I.; Okada, Y.; Komatsu, M. *Org. Biomol. Chem.* **2009**, *7*, 641. (b) Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Tetrahedron.* **2005**, *61*, 9. (c) Blyumin, E. V.; Gallon, H. J.; Yudin, A. K. *Org. Lett.* **2007**, *9*, 4677. (d) Moss, T. A.; Fenwick, D. R.; Dixon, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 10076. (e) Paixão, M. W.; Nielsen, M.; Jacobsen, C. B.; Jørgensen, K. A. *Org. Biomol. Chem.* **2008**, *6*, 3467. (f) Enders, D.; Janeck, C. F.; Raabe, G. *Eur. J. Org. Chem.* **2000**, 3337. (g) Xu, Y.; Lin, L.; Kanai, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2011**, *133*, 5791.

(14) For some recent examples of aziridine-mediated heterocycle synthesis, see: (a) Kiss, L.; Mangelinckx, S.; Fülöp, F.; De Kimpe, N. *Org. Lett.* **2007**, *9*, 4399. (b) Du, X.; Yang, S.; Yang, J.; Liu, Y. *Chem.—Eur. J.* **2011**, *17*, 4981. (c) Wu, Y.-C.; Zhu, J. *Org. Lett.* **2009**, *11*, 5558. (d) Baktharaman, S.; Afagh, N.; Vandersteen, A.; Yudin, A. K. *Org. Lett.* **2010**, *12*, 240. (e) Samanta, K.; Panda, G. *Chem.—Asian J.* **2011**, *6*, 189. (f) Wang, J.-Y.; Guo, X.-F.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2008**, *73*, 1979. (g) Wang, L.; Liu, Q.-B.; Wang, D.-S.; Li, X.; Han, X.-W.; Xiao, W.-J.; Zhou, Y.-G. *Org. Lett.* **2009**, *11*, 1119. (h) Hong, D.; Lin, X.; Zhu, Y.; Lei, M.; Wang, Y. *Org. Lett.* **2009**, *11*, 5678. (i) Rao, R. K.; Naidu, A. B.; Sekar, G. *Org. Lett.* **2009**, *11*, 1923. (j) D'hooghe, M.; Aelterman, W.; De Kimpe, N. *Org. Biomol. Chem.* **2009**, *7*, 135. (k) Brabandt, W. V.; Dejaegher, Y.; Landeghem, R. V.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 1101. (l) Žukauskaité, A.; Mangelinckx, S.; Buinauskaité, V.; Šačkus, A.; De Kimpe, N. *Amino Acids* **2011**, *41*, 541.

(15) (a) Ghorai, M. K.; Tiwari, D. P. *J. Org. Chem.* **2010**, *75*, 6173. (b) Ghorai, M. K.; Shukla, D.; Das, K. *J. Org. Chem.* **2009**, *74*, 7013. (c) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2007**, *48*, 4373. (d) Ghorai, M. K.; Ghosh, K. *Tetrahedron Lett.* **2007**, *48*, 3191. (e) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2009**, *50*, 1105. (f) Ghorai, M. K.; Nanaji, Y.; Yadav, A. K. *Org. Lett.* **2011**, *13*, 4256. (g) Ghorai, M. K.; Sahoo, S. K.; Kumar, S. *Org. Lett.* **2011**, *13*, 5972. (h) Ghorai, M. K.; Shukla, D.; Bhattacharyya, A. *J. Org. Chem.* **2012**, *77*, 3740. (i) Ghorai, M. K.; Tiwari, D. P. *J. Org. Chem.* **2013**, *78*, 2617.

(16) (a) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844. (b) Ghorai, M. K.; Das, K.; Kumar, A.; Das, A. *Tetrahedron Lett.* **2006**, *47*, 5393. (c) Jeffs, L.; Arquier, D.; Kariuki, B.; Bethell, D.; Bulman page, P. C.; Hutchings, G. J. *Org. Biomol. Chem.* **2011**, *9*, 1079.

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