Advanced Synthesis & Catalysis

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201700106

Link to VoR: http://dx.doi.org/10.1002/adsc.201700106

10.1002/adsc.201700106

UPDATE

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Enantioselective Synthesis of 2-Bromomethyl Indolines via BINAP(S)-Catalyzed Bromoaminocyclization of Allyl Aniline

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. An enantioselective bromoamination of allyl aniline with *N*-bromosuccinimide (NBS) catalyzed by BINAP(S), BINAP monosulfide is described. This protocol could provide a range of chiral 2-bromomethyl indolines in good to excellent yields with up to 87% ee. Furthermore, the resulting chiral 2-bromomethyl indolines could be easily converted into synthetically useful chiral building blocks.

Keywords: enantioselective synthesis; indolines; bromoaminocyclization; allyl aniline; *N*-bromosuccinimide (NBS); BINAP(S)

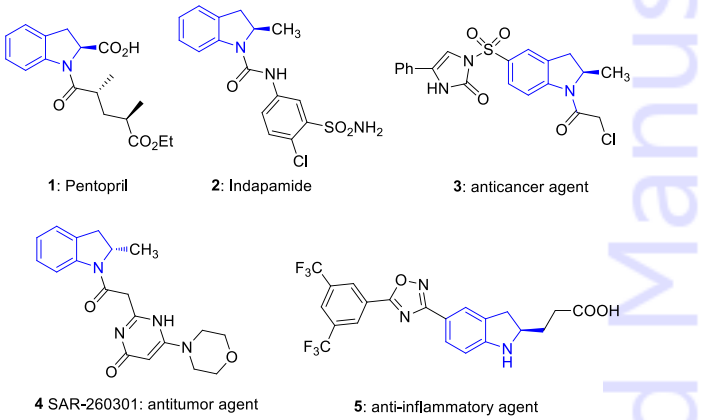
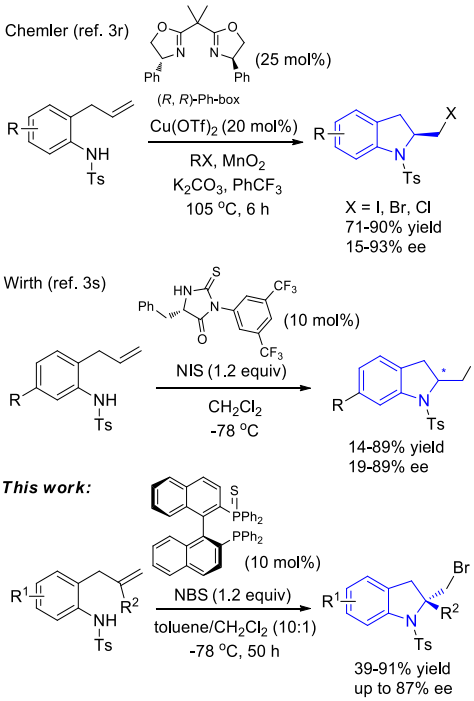


Figure 1. Examples of chiral bioactive indoline derivatives.

Chiral indolines have been found in a wide range of natural products and synthetic compounds as well as pharmaceuticals,[1] and the indoline derivatives possess diverse biological activities and have received considerable attention from the medicinal chemistry community.[2] For example, Pentopril, containing the indoline-2-carboxylate moiety could inhibit angiotensin converting enzyme.[2a-c] Indapamide, which contains both a polar sulfamoyl chlorobenzamide moiety and a lipid-soluble methylindoline moiety, is an oral antihypertensive/diuretic.[2d] Especially, some indoline derivatives have the antitumor and anticancer activities, such as the compound **3**, which could be an anticancer agent,[2e] SAR-260301 is an antitumor agent.[2f] In addition, the anti-inflammatory agent **5** also contains the chiral indoline skeleton (Figure 1).[2g]

Due to the unique biological activities and the wide application in pharmaceuticals, the development of new and efficient methods to synthesize chiral indolines has become a booming research topic over the past decade.[3] Although a diverse array of elegant work has been established, including asymmetric



Scheme 1. Haloaminocyclization approaches to chiral indolines.

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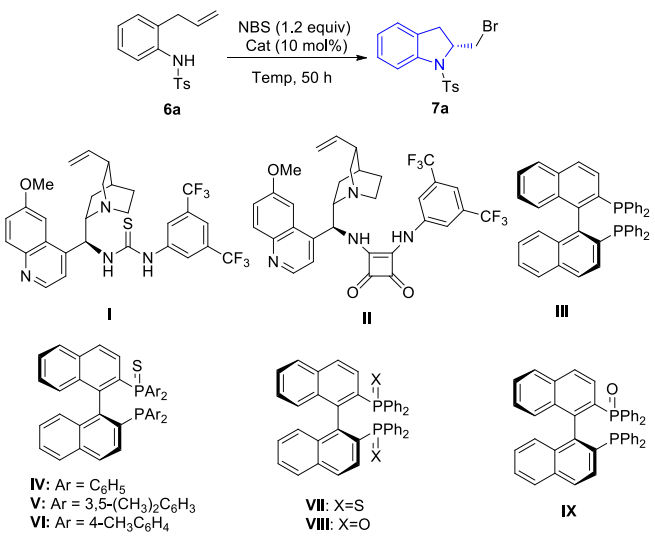
Table 1. Studies of the reaction conditions.[a]



Entry	Cat.	Solvent	Temp [°C]	Yield [%][b]	ee [%][c]
1	**I**	toluene	-40	--	--
2	**II**	toluene	-40	70	15
3	**III**	toluene	-40	81	49
4	**IV**	toluene	-40	82	64
5	**V**	toluene	-40	81	53
6	**VI**	toluene	-40	80	59
7	**IV**	toluene	-50	83	69
8	**IV**	toluene	-78	76	77
9	**IV**	THF	-78	38	14
10	**IV**	EtOAc	-78	43	20
11	**IV**	$CHCl_3$	-78	82	60
12	**IV**	toluene/$CHCl_3$	-78	84	79
13	**IV**	toluene/DCE	-78	75	51
14	**IV**	**toluene/CH_2Cl_2**	**-78**	**90**	**85**
15	**VII**	toluene/CH_2Cl_2	-78	65	66
16	**VIII**	toluene/CH_2Cl_2	-78	11	70
17[d]	**IX**	toluene/CH_2Cl_2	-78	93	82

[a] Reaction condition: **6a** (0.1 mmol), NBS (0.12 mmol), catalyst (0.01 mmol), solvent (2.2 mL).
[b] Isolated yields.
[c] Determined by chiral HPLC analysis.
[d] The reaction was run for 24 h.

hydrogenation,[3h-n] asymmetric hydrosilylation,[3o] asymmetric hydroamination/cyclization of aminoalkenes,[3p] enzymatic or non-enzymatic kinetic resolutions or aminohalogenation/cyclization.[3q-s]

The catalytic asymmetric alkene halogenation has witnessed an explosive growth in recent years,[4] the reactions involved halolactonizations,[5] haloetherifications,[6] haloaminocyclizations[3r,3s, 7] and so on.[8] It is worth noting that enantioselective haloaminocyclizations of alkenes could deliver the chiral vicinal amino halide products which are versatile synthetic intermediates, have been received considerable scientific attention. A series of catalysis systems have been developed, such as chiral Lewis bases,[7b-d] Lewis acids,[7e-j] chiral amines,[7k] as well as chiral phosphoric acids.[7l-m] Specifically, the chiral thiourea-based catalysts and Cu(II)-complex have achieved great progress in the haloaminocyclization approaches to chiral indolines. Chemler and co-workers have accomplished a Cu-catalyzed highly enantioselective aminohalogenation reaction for the synthesis of indolines.[3r] More recently, a newly developed thiourea-based catalyst has been applied in the synthesis of indolines via iodoamination of alkenes by Wirth group (Scheme 1).[3s] For its inherent importance of the chiral indolines, more types of chiral catalyst for convenient, practical production of these compounds still remains one of the top goals to pursuit. Although a few of chiral phosphines and related compounds have been applied in asymmetric halogenations of alkene, their diversity and complexity make them show great potential.[9] Therefore, we wish to communicate here our success in achieving the enantioselective synthesis of 2-bromomethyl indolines via BINAP(S), BINAP monosulfide catalyzed bromoaminocyclization of allyl aniline.

Initially, we chose *N*-tosyl-2-allylaniline **6a** as the model substrate to evaluate the catalysts and optimize the reaction conditions (Table 1). The quinine-based thiourea catalyst **I** only gave a trace amount of product **7a** (Table 1, entry 1). The desired product was obtained in 70% yield with low enantioselectivity by using the catalyst **II** (Table 1, entry 2). However, the moderate ee value was generally obtained with BINAP as the catalyst (Table 1, entry 3). Gratifyingly, when chiral P/P=S double-site Lewis base catalyst BINAP(S) **IV** which has been applied previously in asymmetric catalysis as chiral ligand was used,[10] the desired product could be isolated in 84% yield and 64% ee (Table 1, entry 4). Other chiral BINAP-derivatives such as **V** and **VI** have been proved ineffective to improve the ee value of **7a**. Therefore, BINAP(S) **IV** was the most effective catalyst for this reaction in terms of the conversion and enantioselectivity. The various other parameters of this reaction by using BINAP(S) as catalyst have been investigated systematically afterwards. Eventually, the reaction temperature has an obvious influence on the enantioselectivity (Table 1, entries 4, 7, 8). The highest ee and yield could be obtained at -78 °C. Our attention then turned to evaluate the solvent effect on this reaction, various solvents were examined including THF, $CHCl_3$, ethyl acetate, and combined solvents (Table 1, entries 9 to 14). Finally, to our delight, the combination of toluene/CH_2Cl_2 (10:1) could provide the best result, 90% yield and 85% ee (Table 1, entry 14). In addition, the lower enantioselectivities were obtained when catalyzed by BINAP disulfide (VII), BINAP dioxide (VIII), or BINAP monoxide (IX) under the standard

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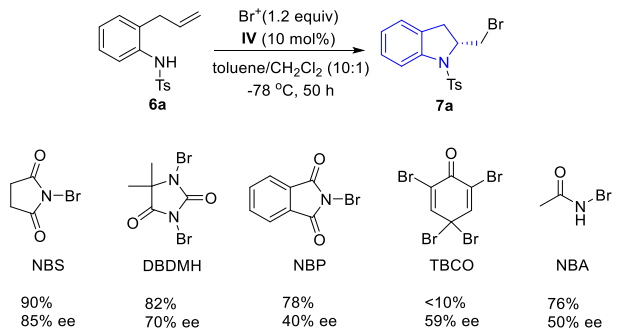


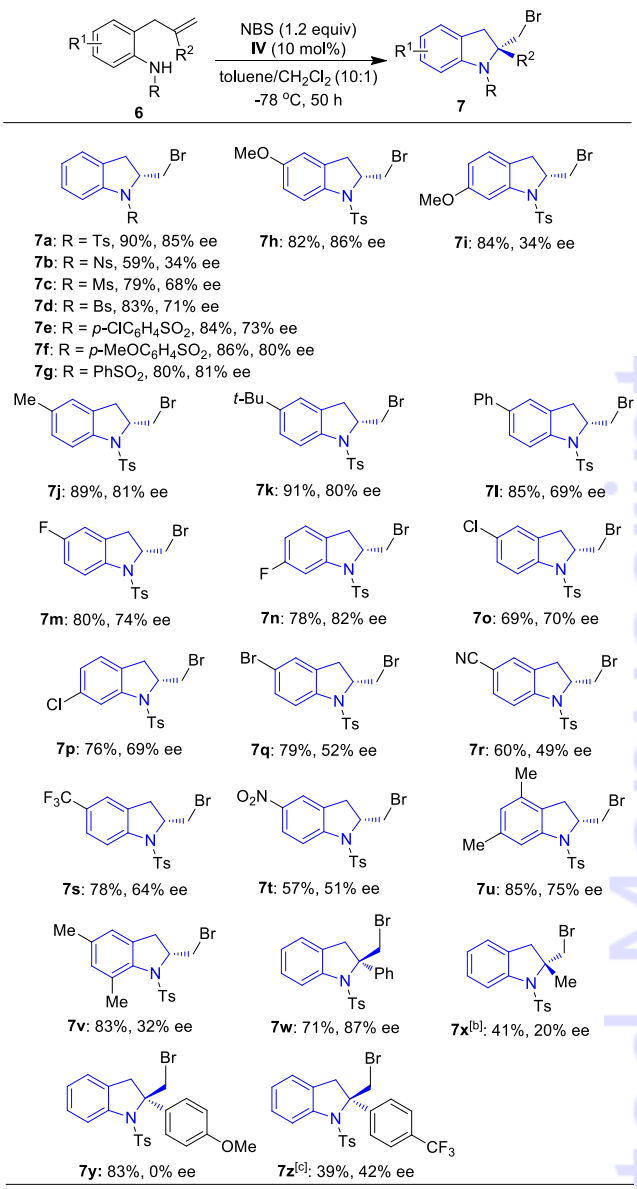
Scheme 2. Effect of the halogen sources.

conditions (Table 1, entries 15-17). On the basis of these results, we speculated that BINAP monosulfide (IV) is the best catalytic specie for this reaction. The absolute stereochemistry of **7a** was determined to be *R* by comparing the optical rotation with the reported value.[3r]

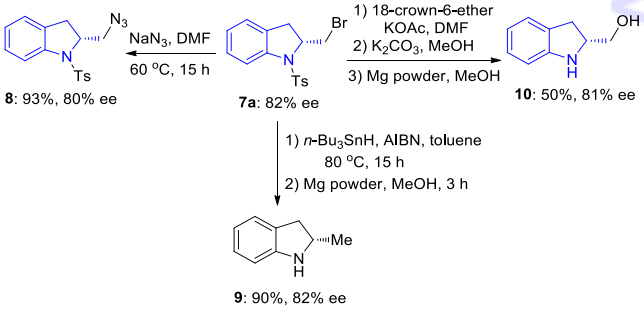
Next, the efficiency of other brominating reagents such as 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), *N*-bromophthalimide (NBP), *N*-bromoacetamide (NBA) and 2,4,4,6-tetrabromo-2,5-cyclo-hexadienone (TBCO) were explored (Scheme 2). Unfortunately, none of them gave as favorable result as NBS in terms of the ee value and yield (Scheme 2). Further attempts to increase the enantioselectivity including changes in the loadings of brominating reagent and catalyst proved to be ineffective. Finally, the optimal reaction conditions for this transformation have been established [**6a** (1.0 equiv) and NBS (1.2 equiv) in toluene/CH_2Cl_2 (10:1) at -78 °C catalyzed by BINAP(S) **IV** for 50 hours].

Having established the optimum reaction conditions, a wide range of substrates to synthesize various chiral 2-bromomethyl indolines were next investigated (Table 2). Initially, a variety of substituents on the nitrogen atom have been examined. It was found that there is a sharp loss of yield and ee value when the nosyl group was used (Table 2, **7b**). Changing the tosyl to mesyl, brosyl or 4-chlorobenzensulfonyl group, the enantioselectivities were also diminished (Table 2, **7c-e**). Whereas, when tosyl substituent replaced by 4-methoxylbenzenesulfonyl group, the yield and enantioselectivity were only slightly decreased (Table 2, **7f**). The benzenesulfonyl substituted substrate still did not offer better ee by comparing with tosyl (Table 2, **7g**). After the identification of an appropriate N substituent, a series of substituted *N*-tosyl-2-allylanilines **6**, including different *para*-, *meta*- and even disubstituted on the aryl unit were examined (Table 2, **7h-v**). Substrates with electron-rich substituent at the para position of aromatic ring afforded the desired products with better enantioselectivities than electron-deficient group, for example, the best result was provided by *para*-methoxyl substitued substrate (Table 2, **7h**). However, switching the substituents from *para* position to *meta*

Table 2. Scope of substrate.[a]



[a] Reaction condition: **6** (0.1 mmol), NBS (0.12 mmol), catalyst (0.01 mmol), solvent (2.2 mL). Yield of isolated product. The ees were determined by chiral HPLC analysis.
[b] The reaction was run for 60 h in toluene (2.0 mL).
[c] The reaction was run for 60 h.



Scheme 3. Demonstration of synthetic utility.

position, the opposite results were obtained. Thus, the electron-withdrawing groups were more helpful to promote the enantioselectivity than electron-donating groups (Table 2, **7i, 7n, 7p**). Additionally, 3,5-dimethyl-substituted and 4,6-dimethyl-substituted substrates could provide the corresponding desired products in 75% and 32% ee, respectively (Table 2, **7u,v**). Substituents on alkene also have great impact on enantioselectivity. When R^2 is phenyl group, the desired product could be obtained in excellent yield and up to 87% ee (Table 2, **7w**). Although this highly enantioselective construction of a chiral tetrasustituted carbon center is another feature of this methodology and would be fascinating to synthetic organic chemist, unfortunately, there is a dramatic loss of ee value whether the electron-rich or electron-deficient substituent on the phenyl ring (Table 2, **7y** and **7z**). In addition, changing the aromatic ring to methyl group also led to lower enantioselectivity (Table 2, **7x**).

To demonstrate the potential synthetic utility of this reaction, we then investigated the transformation of this 2-bromomethyl indoline as the chiral intermediate (Scheme 3). Firstly, the chiral azide **8** has been successfully provided by substitution of the bromine atom with NaN_3 in 93% yield and 80% ee. In addition, the reduction of the bromide was accomplished by AIBN/Bu_3SnH followed by removal of the tosyl group to give 2-methyl indoline **9** in 90% yield with 82% ee, the product could be used in synthesis of some important bioactive compounds.[2] Furthermore, the 2-hydroxymethylindoline **10** was readily obtained in 50% total yield with good stereochemical integrity through substitution, hydrolysis and detosylation reactions.

In summary, an enantioselective organocatalytic bromoaminocyclization of *N*-tosyl-2-allylanilines with NBS using BINAP(S) as catalyst has been described, and a series of chiral 2-bromomethyl indolines with various functional groups have been synthesized in good to excellent yields with high enantioselectives. The utility of this methodology is also highlighted by the products can be easily transformed into other useful synthetic intermediates and bioactive compounds. This method could be used by the researchers in the areas of organic and medicinal chemistry. Further investigations on catalytic asymmetric alkene halogenation are ongoing in our group.

Experimental Section

General Information

All purchased chemicals were used as received without further purification. Solvents were distilled prior to use. Chromatographic separations were performed using silica gel 200-300 mesh. ^1H and ^{13}C NMR spectra were obtained on 400 or 600 MHz (100 or 150 MHz for ^{13}C NMR) spectrometers using $CDCl_3$ with TMS or residual solvent as standard unless otherwise noted. The chemical shifts are reported in ppm relative to solvent residual peak. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; dd, doublet of doublets, and br s, broad singlet. The coupling constants (*J*) are reported in Hertz (Hz). Melting points were determined using a micromelting point apparatus and were uncorrected/calibrated. TLC analysis was performed over glass-backed plates (60 Å, 250 μm) and visualized using UV. High-resolution mass spectra were obtained using a Q-TOF micro spectrometer. Enantiomeric excess was determined by high performance liquid chromatography (HPLC) using Daicel ® Chiralcel OJ-H, OD-H or Daicel® Chiralpak AD-H, AS-H chiral analytical columns (UV detection at 254 nm).

General Procedure for Synthesis of Chiral Indolines

To an oven-dried flask with a stir bar was added substrate **6** (0.1 mmol, 1.0 equiv), catalyst **VI** (6.6 mg, 0.01 mmol, 1.0 equiv) and toluene/CH_2Cl_2 (10:1, 2.2 mL) and the flask was placed in a -78 °C for 10 min, then NBS (21 mg, 0.12 mmol, 1.2 equiv) was added to the resulting mixture and continued to stirred at -78 °C for 50 h. Upon completion, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ (2.0 mL) at -78 °C and was gradually warmed to room temperature. The separated aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (petro ether/ethyl acetate = 10:1) to give the product **7**.

(*R*)-2-(bromomethyl)-1-tosylindoline (7a).[11] Yield: 32.8 mg, 90%, white solid, mp: 91-93 °C. $[\alpha]_D^{24}$= -63.6 (*c* =0.11, $CHCl_3$), 85% ee, determined by HPLC analysis [Daicel Chiralcel OD-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 6.6 min, $t_{(major)}$ = 7.4 min]. ^1H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.24-7.20 (m, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.07-7.03 (m, 2H), 4.46-4.39 (m, 1H), 3.81 (dd, *J* = 9.9, 3.7 Hz, 1H), 3.41 (t, *J* = 9.9 Hz, 1H), 2.95-2.87 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.3, 141.1, 134.5, 130.6, 129.8, 128.0, 127.1, 125.3, 125.0, 116.9, 62.2, 36.0, 33.2, 21.6. HRMS-ESI (*m/z*): calcd for $C_{16}H_{16}BrNNaO_2S$ $[M+Na]^+$ 387.9977, found 387.9968.

(*R*)-2-(bromomethyl)-1-((4-nitrophenyl)sulfonyl)indoline (7b). Yield: 23.3 mg, 59%, yellow solid, mp: 98-101 °C. $[\alpha]_D^{15}$= -20 (*c* = 0.10, $CHCl_3$), 34% ee, determined by HPLC analysis [Daicel Chiralpak AD-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 19.4 min, $t_{(major)}$ = 24.6 min]. ^1H NMR (600 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.7 Hz, 2H), 7.89 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.32-7.23 (m, 1H), 7.15-7.05 (m, 2H), 4.47-4.44 (m, 1H), 3.80 (dd, *J* = 10.0, 3.7 Hz, 1H), 3.44 (t, *J* = 9.8 Hz, 1H), 3.01-2.91 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.5, 143.0, 140.1, 130.5, 128.4, 128.3, 125.8, 125.7, 124.4, 116.6, 62.5, 35.4, 33.2. HRMS-ESI (*m/z*): calcd for $C_{15}H_{13}BrN_2NaO_4S$ $[M+Na]^+$ 418.9672, found 418.9648.

(*R*)-2-(bromomethyl)-1-(methylsulfonyl)indoline (7c). Yield: 22.8 mg, 79%, white solid, mp: 151-153 °C. $[\alpha]_D^{24}$= +25 (*c* =0.08, $CHCl_3$), 68% ee, determined by HPLC analysis [Daicel Chiralcel OD-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 17.6 min, $t_{(major)}$ = 25.7 min]. ^1H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.3 Hz, 1H), 7.23 (d, *J* = 5.1 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 4.58-4.54 (m, 1H), 3.78 (dd, *J* = 10.0, 3.3 Hz, 1H), 3.50-3.46 (m, 2H), 3.16 (dd, *J* = 16.8, 3.3 Hz, 1H), 2.88 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.1, 129.7, 128.3, 125.6, 124.8, 115.2, 62.3, 36.3, 36.2, 33.8. HRMS-ESI (*m/z*): calcd for $C_{10}H_{12}BrNNaO_2S$ $[M+Na]^+$ 311.9664, found 311.9666.

(*R*)-2-(bromomethyl)-1-((4-bromophenyl)sulfonyl)indoline (7d). Yield: 35.6 mg, 83%, white solid, mp: 90-93 °C; $[\alpha]_D^{15}$= -41.7 (*c* = 0.12, $CHCl_3$), 71% ee, determined by HPLC analysis [Daicel Chiralcel OD-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 7.5 min, $t_{(major)}$ = 8.5 min]. ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.63 (d, *J* = 8.4 Hz, 1H), 7.54 (s, 4H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.10-7.06 (m, 2H), 4.46-4.36 (m, 1H), 3.80 (dd, *J* = 10.2, 3.7 Hz, 1H), 3.42 (t, *J* = 9.9 Hz, 1H), 2.96-2.95 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 140.7, 136.4, 132.5, 130.6, 128.6, 128.5, 128.2, 125.5, 125.3, 116.8, 62.3, 35.7, 33.2. HRMS-ESI (*m/z*): calcd for $C_{15}H_{13}Br_2NNaO_2S$ $[M+Na]^+$ 451.8926, found 451.8905.

(*R*)-2-(bromomethyl)-1-((4-chlorophenyl)sulfonyl)indoline (7e). Yield: 32.3 mg, 84%, white solid, mp: 95-97 °C. $[\alpha]_D^{24}$= -67 (*c* =0.06, $CHCl_3$), 73% ee, determined by HPLC analysis [Daicel Chiralcel OD-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 7.4 min, $t_{(major)}$ = 8.1 min]; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.65-7.61 (m, 3H), 7.40-7.36 (m, 2H), 7.26-7.22 (m, 1H), 7.10-7.06 (m, 2H), 4.44-4.39 (m, 1H), 3.80 (dd, *J* = 10.0, 3.8 Hz, 1H), 3.42 (t, *J* = 9.9 Hz, 1H), 3.00-2.89 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 140.7, 140.1, 135.9, 130.6, 129.5, 128.4, 128.1, 125.5, 125.3, 116.8, 62.3, 35.7, 33.2. HRMS-ESI (*m/z*): calcd for $C_{15}H_{13}BrClNNaO_2S$ $[M+Na]^+$ 407.9431, found 407.9423.

(*R*)-2-(bromomethyl)-1-((4-methoxyphenyl)sulfonyl)indoline (7f). Yield: 32.8 mg, 86%, white solid, mp: 105-107 °C. $[\alpha]_D^{24}$= -83 (*c* =0.12, $CHCl_3$), 80% ee, determined by HPLC analysis [Daicel Chiralcel OD-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 10.4 min, $t_{(major)}$ = 12.2 min]. ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.65 (d, *J* = 8.1 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.08-7.04 (m, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.44-4.39 (m, 1H), 3.83 (d, *J* = 3.7 Hz, 1H), 3.81 (s, 3H), 3.41 (t, *J* = 9.9 Hz, 1H), 2.96-2.88 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 163.4, 141.2, 130.7, 129.2, 129.0, 128.0, 125.3, 125.0, 117.0, 114.3, 62.2, 55.6, 36.0, 33.2. HRMS-ESI (*m/z*): calcd for $C_{16}H_{16}BrNNaO_3S$ $[M+Na]^+$ 403.9926, found 403.9923.

(*R*)-2-(bromomethyl)-1-(phenylsulfonyl)indoline (7g). Yield; 28.1 mg, 80%, white solid, mp: 117-119 °C. $[\alpha]_D^{24}$= -78 (*c* =0.09, $CHCl_3$), 81% ee, determined by HPLC analysis [Daicel Chiralcel OJ-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 13.5 min, $t_{(major)}$ = 16.0 min]. ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.68 (dd, *J* = 12.7, 8.0 Hz, 3H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.18-7.04 (m, 2H), 4.47-4.42 (m, 1H), 3.82 (dd, *J* = 9.9, 3.7 Hz, 1H), 3.42 (t, *J* = 9.9 Hz, 1H), 2.96-2.87 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 139.9, 136.3, 132.2, 129.5, 128.0, 126.9, 125.9, 124.2, 124.0, 115.7, 61.1, 34.7, 32.0. HRMS-ESI (*m/z*): calcd for $C_{15}H_{14}BrNNaO_2S$ $[M+Na]^+$, 373.9821, found 373.9814.

(*R*)-2-(bromomethyl)-5-methoxy-1-tosylindoline (7h).[11] Yield: 32.4 mg, 82%, white solid, mp: 130-132 °C. $[\alpha]_D^{24}$= -137.5 (*c* = 0.08, $CHCl_3$), 86% ee, determined by HPLC analysis [Daicel Chiralcel OD-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 17.2 min, $t_{(major)}$ = 18.5 min]. ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.56 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.76 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.60 (d, *J* = 2.3 Hz, 1H), 4.41-4.37 (m, 1H), 3.81-3.74 (m, 4H), 3.37 (t, *J* = 10.0 Hz, 1H), 2.87-2.75 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 157.6, 144.2, 134.4, 134.2, 132.6, 129.7, 127.2, 118.2, 113.1, 110.9, 62.5, 55.6, 35.8, 33.3, 21.6. HRMS-ESI (*m/z*): calcd for $C_{17}H_{18}BrNNaO_3S$ $[M+Na]^+$ 418.0083, found 418.0079.

(*R*)-2-(bromomethyl)-6-methoxy-1-tosylindoline (7i). Yield: 33.1 mg, 84%, white solid, mp: 125-127 °C. $[\alpha]_D^{15}$= -50 (*c* = 0.10, $CHCl_3$), 34% ee, determined by HPLC analysis [Daicel Chiralpak AD-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(major)}$ =14.5 min, $t_{(minor)}$ =15.9 min). ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.58 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 2.2 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.60 (dd, *J* = 8.3, 2.3 Hz, 1H), 4.45-4.40 (m, 1H), 3.83 (s, 3H),3.81 (dd, *J* = 10.2, 3.6 Hz, 1H), 3.41 (t, *J* = 9.9 Hz, 1H), 2.85-2.83 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 159.9, 144.3, 142.3, 134.5, 129.8, 127.1, 125.5, 122.3, 111.2, 102.7, 63.0, 55.7, 36.0, 32.5, 21.6. HRMS-ESI (*m/z*): calcd for $C_{17}H_{18}BrNNaO_3S$ $[M+Na]^+$ 418.0083, found 418.0085.

(*R*)-2-(bromomethyl)-5-methyl-1-tosylindoline (7j).[11] Yield: 33.7 mg, 89%, white solid, mp: 121-123 °C. $[\alpha]_D^{24}$= -137.5 (*c* = 0.09, $CHCl_3$), 81% ee, determined by HPLC analysis [Daicel Chiralcel OD-H, 2% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 8.7 min, $t_{(major)}$ = 9.3 min]. ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.54 (dd, *J* = 15.7, 8.2 Hz, 3H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.87 (s, 1H), 4.42-4.38 (m, 1H), 3.80 (dd, *J* = 9.9, 3.8 Hz, 1H), 3.39 (t, *J* = 9.9 Hz, 1H), 2.89-2.82 (m, 2H), 2.36 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 144.2, 138.7, 134.8, 134.4, 130.8, 129.7, 128.6, 127.1, 125.9, 116.7, 62.3, 36.0, 33.1, 21.6, 21.0. HRMS-ESI (*m/z*): calcd for $C_{17}H_{18}BrNaNO_2S$ $[M+Na]^+$ 402.0134, found 402.0131.

(*R*)-2-(bromomethyl)-5-(tert-butyl)-1-tosylindoline (7k). Yield: 38.3 mg, 91%, white solid, mp: 136-138 °C. $[\alpha]_D^{24}$= -100 (*c* = 0.14, $CHCl_3$), 80% ee, determined by HPLC analysis [Daicel Chiralcel OD-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 5.3 min; $t_{(major)}$ = 5.7 min]. ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.57 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.08 (s, 1H), 4.42-4.38 (m, 1H), 3.83 (dd, *J* = 9.8, 3.8 Hz, 1H), 3.39 (t, *J* = 10.0 Hz, 1H), 2.94-2.87 (m, 2H), 2.37 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 147.2, 143.1, 137.5, 133.5, 129.1, 128. 7, 126.1, 123.9, 121.2, 115.1, 61.3, 34.8, 33.4, 32.3, 30.4, 20.5. HRMS-ESI (*m/z*): calcd for $C_{20}H_{24}BrNNaO_2S$ $[M+Na]^+$ 444.0603, found 444.0600.

(*R*)-2-(bromomethyl)-5-phenyl-1-tosylindoline (7l). Yiled: 37.5 mg, 85%, colorless oil. $[\alpha]_D^{24}$= -130 (*c* = 0.1, $CHCl_3$), 69% ee, determined by HPLC analysis [Daicel Chiralcel OD-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 11.8 min, $t_{(major)}$ = 16.8 min]. ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.70 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 7.8 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.32 (dd, *J* = 15.3, 8.0 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 4.49-4.44 (m, 1H), 3.85 (dd, *J* = 9.9, 3.6 Hz, 1H), 3.46 (t, *J* = 9.9 Hz, 1H), 3.04-2.92 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 144.4, 140.5, 140.3, 138.2, 134.5, 131.2, 129.8, 128.8, 127.3, 127.1, 127.0, 126.8, 123.9, 116.9, 62.4, 36.0, 33.3, 21.6. HRMS-ESI (*m/z*): calcd for $C_{22}H_{20}BrNNaO_2S$ $[M+Na]^+$ 464.0290, found 464.0291.

(*R*)-2-(bromomethyl)-5-fluoro-1-tosylindoline (7m).[11] Yield: 30.6 mg, 80%, light yellow solid, mp: 108-109 °C. $[\alpha]_D^{24}$= -87.5 (*c* = 0.12, $CHCl_3$), 74% ee, determined by HPLC analysis [Daical Chiralpak AD-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(major)}$ =12.6 min, $t_{(minor)}$ = 13.3 min]. ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.60 (dd, *J* = 8.8, 4.6 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 6.94-6.91 (m, 1H), 6.77 (dd, *J* = 8.0, 2.4 Hz, 1H), 4.46-4.41 (m, 1H), 3.78 (dd, *J* = 10.0, 3.8 Hz, 1H), 3.41 (t, *J* = 9.9 Hz, 1H), 2.91-2.82 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 159.7 (d, *J* = 241.8 Hz), 144.5, 137.2, 134.1, 132.9, 129.8, 127.1, 118.1 (d, *J* = 8.7 Hz), 114.6 (d, *J* = 8.7 Hz), 112.4 (d, *J* = 24 Hz), 62.6, 35.7, 33.2, 21.6. HRMS-ESI (*m/z*): calcd for $C_{16}H_{15}BrFNNaO_2S$ $[M+Na]^+$ 405.9883, found 405.9864.

(*R*)-2-(bromomethyl)-6-fluoro-1-tosylindoline (7n). Yiled: 29.8 mg, 78%, light yellow solid, mp: 120-121 °C. $[\alpha]_D^{15}$= -15.4 (*c* = 0.13, $CHCl_3$), 82% ee, determined by HPLC analysis [Daicel Chiralpak AD-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(major)}$ = 9.7 min, $t_{(minor)}$ = 10.3 min)]. ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.60 (d, *J* = 8.4

Hz, 2H), 7.40-7.38 (m, 1H), 7.22 (d, *J* = 7.8 Hz, 2H), 6.98 (dd, *J* = 7.5, 6.1 Hz, 1H), 6.74-6.71 (m, 1H), 4.47-4.44 (m, 1H), 3.80 (dd, *J* = 9.9, 3.5 Hz, 1H), 3.44 (t, *J* = 9.8 Hz, 1H), 2.90 (d, *J* = 6.6 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.5(d, *J* = 197.4Hz), 143.6, 141.5 (d, *J* = 12 Hz), 133.3, 128.9, 126.0, 124.8, 124.7, 110.6 (d, *J* = 22.6 Hz), 103.7(d, *J* = 27.8 Hz), 61.9, 34.9, 31.6, 20.6. HRMS-ESI (*m/z*): calcd for $C_{16}H_{15}BrFNNaO_2S$ $[M+Na]^+$ 405.9883, found 405.9868.

(*R*)-2-(bromomethyl)-5-chloro-1-tosylindoline (7o).[11] Yield: 27.4 mg, 69%, white solid, mp: 109-111 °C. $[\alpha]_D^{24}$= -42.9 (*c* = 0.07, $CHCl_3$), 70% ee, determined by HPLC analysis [Daicel Chiralpak AD-H, 1% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(major)}$ = 38.1 min, $t_{(minor)}$ = 42.7 min]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 12.3, 8.4 Hz, 3H), 7.22-7.18 (m, 3H), 7.04 (s, 1H), 4.45-4.41 (m, 1H), 3.79 (dd, *J* = 10.0, 3.7 Hz, 1H), 3.42 (t, *J* = 9.8 Hz, 1H), 2.93-2.86 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.6, 138.9, 133.2, 131.5, 129.2, 128.9, 127.1, 126.0, 124.4, 116.7, 61.3, 34.8, 32.0, 20.6. HRMS-ESI (*m/z*): calcd for $C_{16}H_{15}BrClNNaO_2S$ $[M+Na]^+$ 421.9588, found 421.9589.

(*R*)-2-(bromomethyl)-6-chloro-1-tosylindoline (7p). Yield: 30.3 mg, 76%, white solid, mp: 94-97°C. $[\alpha]_D^{15}$= -26.7 (*c* = 0.15, $CHCl_3$), 69% ee, determined by HPLC analysis [Daicel Chiralcel OD-H, 2% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 9.2 min, $t_{(major)}$ = 9.7 min]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.18 (t, *J* = 8.1 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 4.49-4.40 (m, 1H), 3.83 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.47 (t, *J* = 9.8 Hz, 1H), 3.02-2.89 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.7, 142.5, 134.2, 130.9, 130.0, 129.5, 129.1, 127.1, 124.8, 114.6, 61.9, 36.0, 33.0, 21.6. HRMS-ESI (*m/z*): calcd for $C_{16}H_{15}BrClNNaO_2S$ $[M+Na]^+$ 421.9588, found 421.9584.

(*R*)-2-(bromomethyl)-5-bromo-1-tosylindoline (7q).[11] Yield: 36.3 mg, 79%, white solid, mp: 123-125 °C. $[\alpha]_D^{24}$= -62.5 (*c* = 0.08, $CHCl_3$), 52% ee, determined by HPLC analysis [Daicel Chiralpak AD-H, 2% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(major)}$ = 22.9 min, $t_{(minor)}$ = 25.4 min]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.19 (s, 1H), 4.46-4.36 (m, 1H), 3.79 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.42 (t, *J* = 9.8 Hz, 1H), 2.96-2.85 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.6, 140.5, 134.2, 132.9, 131.0, 129.9, 128.4, 127.0, 118.1, 117.7, 62.3, 35.8, 33.0, 21.6. HRMS-ESI (*m/z*): calcd for $C_{16}H_{15}Br_2NNaO_2S$ $[M+Na]^+$ 465.9082, found 465.9086.

(*R*)-2-(bromomethyl)-5-cyano-1-tosylindoline (7r). Yield: 23.3 mg, 60%, white solid, mp: 132-135 °C. $[\alpha]_D^{24}$= -64 (*c* = 0.11, $CHCl_3$), 49% ee, determined by HPLC analysis ([Daicel Chiralcel OD-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 29.5 min, $t_{(major)}$ = 33.2 min]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.35 (s, 1H), 7.26 (d, *J* = 9.2 Hz, 2H), 4.53-4.49 (m, 1H), 3.82 (dd, *J* = 10.1, 3.3 Hz, 1H), 3.52-3.48 (m, 1H), 3.10-3.01 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.3, 144.1, 133.3, 131.9, 130.4, 129.1, 127.9, 125.9, 117.7, 115.2, 106.9, 61.2, 34.9, 32.0, 20.6. HRMS-ESI (*m/z*): calcd for $C_{17}H_{15}BrN_2NaO_2S$ $[M+Na]^+$ 412.9930, found 412.9918.

(*R*)-2-(bromomethyl)-1-tosyl-5-(trifluoromethyl)indoline (7s). Yield: 33.7 mg, 78%, white solid, mp: 78-80 °C. $[\alpha]_D^{24}$= -16.7 (*c* = 0.11, $CHCl_3$), 64% ee, determined by HPLC analysis [Daicel Chiralpak AD-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 10.2 min, $t_{(major)}$ = 11.4 min]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, J = 8.5 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.32 (s, 1H), 7.24 (d, *J* = 8.2 Hz, 2H), 4.52-4.48 (m, 1H), 3.83 (dd, *J* = 10.1, 3.5 Hz, 1H), 3.48 (t, *J* = 9.7 Hz, 1H), 3.03 (d, *J* = 5.4 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.9, 144.3, 134.3, 131.0, 130.0, 127.0, 125.7, 125.0, 123.2, 122.5, 116.0, 62.4, 35.9, 33.1, 21.6. HRMS-ESI (*m/z*): calcd for $C_{17}H_{15}BrF_3NNaO_2S$ $[M+Na]^+$ 455.9851, found 455.9850.

(*R*)-2-(bromomethyl)-5-nitro-1-tosylindoline (7t). Yield: 23.5 mg, 57%, yellow solid, mp: 158-161°C. $[\alpha]_D^{24}$= -16.7 (*c* = 0.06, $CHCl_3$), 51% ee, determined by HPLC analysis [Daicel Chiralpak AD-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(major)}$ = 35.7 min, $t_{(minor)}$ = 43.7 min]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.96 (s, 1H), 7.73 (d, *J* = 8.9 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 9.1Hz 2H), 4.58 (m, 1H), 3.84 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.56 (dd, *J* = 10.1, 8.9 Hz, 1H), 3.15-3.06 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.0, 145.3, 144.7, 134.2, 131.5, 130.2, 127.0, 124.8, 121.1, 115.2, 62.8, 36.0, 33.0, 21.6. HRMS-ESI (*m/z*): calcd for $C_{16}H_{15}BrN_2NaO_4S$ $[M+Na]^+$ 432.9828, found 432.9800.

(*R*)-2-(bromomethyl)-4,6-dimethyl-1-tosylindoline (7u). Yield: 33.4 mg, 85%, colorless oil. $[\alpha]_D^{24}$= -84.6 (*c* = 0.13, $CHCl_3$), 75% ee, determined by HPLC analysis [Daicel Chiralcel OJ-H, 2% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(major)}$ = 11.3 min, $t_{(minor)}$ = 14.1 min]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.32 (s, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 6.68 (s, 1H), 4.44-4.40 (m, 1H), 3.83 (dd, *J* = 9.8, 3.6 Hz, 1H), 3.40 (t, *J* = 9.9 Hz, 1H), 2.81-2.76 (m, 2H), 2.37 (s, 3H), 2.33 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.2, 140.9, 138.1, 134.6, 134.4, 129.8, 127.1, 126.8, 126.3, 114.6, 62.4, 36.4, 32.0, 21.6, 21.5, 18.7. HRMS-ESI (*m/z*): calcd for $C_{18}H_{20}BrNNaO_2S$ $[M+Na]^+$ 416.0290, found 416.0277.

(*R*)-2-(bromomethyl)-5,7-dimethyl-1-tosylindoline (7v). Yield: 32.6 mg, 83%, white solid, mp: 152-154 °C. $[\alpha]_D^{24}$= -30 (*c* =0.10, $CHCl_3$), 32% ee, determined by HPLC analysis [Daicel Chiralcel OD-H, 2% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 11.8 min , $t_{(major)}$ = 13.4 min]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.92 (s, 1H), 6.68 (s, 1H), 4.46-4.42 (m, 1H), 3.55 (dd, *J* = 10.0, 4.9 Hz, 1H), 3.11 (t, *J* = 10.1 Hz, 1H), 2.51 (s, 3H), 2.46 (d, *J* = 16.3 Hz, 1H), 2.39 (s, 3H), 2.28 (s, 3H), 2.11 (dd, *J* = 16.3, 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.2, 137.7, 136.7, 135.3, 134.1, 132.4, 131.3, 129.5, 127.7, 123.2, 64.2, 34.0, 32.3, 21.6, 21.0, 19.8. HRMS-ESI (*m/z*): calcd for $C_{18}H_{20}BrNNaO_2S$ $[M+Na]^+$ 416.0290, found 416.0287.

(*R*)-2-(bromomethyl)-2-phenyl-1-tosylindoline (7w). Yield: 30.9 mg, 71%, white solid, mp: 167-169 °C. $[\alpha]_D^{24}$= +55.6 (*c* = 0.11, $CHCl_3$), 87% ee, determined by HPLC analysis [Daicel Chiralpak AD-H, 5% *i*-PrOH/hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 17.2 min, $t_{(major)}$ = 18.1 min]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 4H), 7.18 (d, *J* = 7.4 Hz, 1H), 7.14 (t, *J* = 7.7 Hz, 2H), 7.03 (dd, *J* = 13.1, 7.8 Hz, 3H), 6.94 (d, *J* = 8.2 Hz, 2H), 4.66 (d, *J* = 10.5 Hz, 1H), 4.49 (d, *J* = 10.5 Hz, 1H), 3.89 (d, *J* = 17.1 Hz, 1H), 3.57 (d, *J* = 17.1 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.2, 142.2, 140.0, 137.1, 129.0, 128.1, 128.0, 127.6, 127.3, 126.9, 124.6, 123.1, 113.4, 73.4, 46.8, 39.9, 21.4. HRMS-ESI (*m/z*): calcd for $C_{22}H_{20}BrNNaO_2S$ $[M+Na]^+$ 464.0290, found 464.0285.

(*R*)-2-(bromomethyl)-2-methyl-1-tosylindoline (7x). Yield: 15.5 mg, 41%, white solid, mp: 74-76 °C. $[\alpha]_D^{18}$= +20 (*c* = 0.10, $CHCl_3$), 20% ee, determined by HPLC analysis [Daicel Chiralpak AD-H, 5% *i*-PrOH/hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 12.5 min, $t_{(major)}$ = 15.9 min]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.16-7.11 (m, 2H), 6.97 (t, *J* = 7.4 Hz, 1H), 3.98 (d, *J* = 10.2 Hz, 1H), 3.92 (d, *J* = 10.2 Hz, 1H), 3.50 (d, *J* = 16.3 Hz, 1H), 2.92 (d, *J* = 16.3 Hz, 1H), 2.39 (s, 3H), 1.82-1.75 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.0, 141.8, 138.4, 129.8, 127.8, 127.5, 126.9, 125.1, 123.2, 113.9, 71.5, 42.6, 40.9, 24.4, 21.6. HRMS-ESI (*m/z*): calcd for $C_{17}H_{18}BrNNaO_2S$ $[M+Na]^+$ 402.0134, found 402.0135.

(*R*)-2-(bromomethyl)-2-(4-methoxyphenyl)-1-tosylindoline (7y). Yield: 38.9 mg, 83%, white solid, mp: 121-124 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, J = 8.2 Hz, 1H), 7.27–7.20 (m, 1H), 7.16 (dd, J = 16.6, 8.1 Hz, 3H), 7.08 (d, J = 8.2 Hz, 2H), 7.02 (t, J = 7.4 Hz, 1H), 6.94 (d, J = 8.1 Hz, 2H), 6.62 (d, J = 8.8 Hz, 2H), 4.65 (d, J = 10.5 Hz, 1H), 4.41 (d, J = 10.5 Hz, 1H), 3.85 (d, J = 17.1 Hz, 1H), 3.78 (s, 3H), 3.54 (d, J = 17.1 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 143.1, 142.2, 137.4, 131.8, 128.9, 128.7, 128.1, 127.6, 126.8, 124.6, 123.1, 113.5, 113.2, 73.2, 55.3, 46.6, 40.0, 21.4. HRMS-ESI (*m/z*): calcd for $C_{23}H_{22}BrNNaO_3S$ $[M+Na]^+$ 494.0401, found 494.0408.

(*R*)-2-(bromomethyl)-1-tosyl-2-(4-(trifluoromethyl)-phenyl)indoline (7z). Yield: 19.9 mg, 39%, white solid, mp: 127-130 °C. $[\alpha]_D^{18}$= +11.8 (c = 0. 17, $CHCl_3$) 42% ee, determined by HPLC analysis [Daicel Chiralpak OD-H, 5% *i*-PrOH/hexane, 1.0 mL/min, λ= 254 nm, $t_{(major)}$ = 7.8 min, $t_{(minor)}$ = 10.2 min]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, J = 8.2 Hz, 1H), 7.33-7.27 (m, 5H), 7.20 (d, J = 7.4 Hz, 1H), 7.07 (t, J = 7.4 Hz, 3H), 6.92 (d, J = 8.0 Hz, 2H), 4.72 (d, J = 10.7 Hz, 1H), 4.37 (d, J = 10.7 Hz, 1H), 3.91 (d, J = 17.2 Hz, 1H), 3.52 (d, J = 17.2 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.64, 143.29, 142.32, 137.27, 129.14, 128.46, 127.75, 127.17, 126.21, 124.89, 124.87, 124.84, 124.81, 123.52, 113.73, 72.60, 46.82, 39.01, 21.31. HRMS-ESI (*m/z*): calcd for $C_{23}H_{19}BrF_3NNaO_2S$ $[M+Na]^+$ 532.0170, found 532.0163.

Preparation of (*R*)-2-(azidomethyl)-1-tosylindoline (8).[3r] To an oven dried flask with a stir bar was added (*R*)-2-(bromomethyl)-1-tosylindoline (**7a**) (36.6 mg, 0.10 mmol, 1.0 equiv, 82% ee) under argon, sodium azide (20 mg, 0.30 mmol, 3.0 equiv) and DMF (2.0 mL). The mixture was then allowed to stir at room temperature for 24 h, then quenched by water (25.0 mL) and extracted with EtOAc (5 mL×3). The combined organic layers were washed with brine, dried by Na_2SO_4 then dried by Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, gradient eluent: 10% to 20% EtOAc in hexanes) to provide the azide **8.**[12] 30.5 mg, 93% yield, white crystals, mp: 108-110 °C. $[\alpha]_D^{15}$= -125 (c = 0.20, $CHCl_3$), 80% ee, determined by HPLC analysis [Daicel Chiralcel OD-H, 2% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 14.3 min, $t_{(major)}$ = 15.3 min]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 8.3 Hz, 2H), 7.25-7.21 (m, 1H), 7.18 (d, J = 8.1 Hz, 2H), 7.08-7.03 (m, 2H), 4.36-4.28 (m, 1H), 3.62 (dd, J = 12.3, 4.4 Hz, 1H), 3.52 (dd, J = 12.3, 7.3 Hz, 1H), 2.85-2.78 (m, 1H), 2.72 (dd, J = 16.4, 2.9 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.2, 141.2, 134.6, 131.1, 129.7, 128.0, 127.1, 125.1, 125.0, 117.3, 61.0, 55.3, 32.1, 21.5. HRMS-ESI (*m/z*): calcd for $C_{16}H_{16}N_4NaO_2S$ $[M+Na]^+$ 351.0892, found 351.0893.

Procedure for synthesis of (*S*)-2-methylindoline(9).[7e, 9c] To a solution of **7a** (36.6 mg, 0.1 mmol, 1.0 equiv, 82% ee) in toluene (10 mL) was added *n*-Bu_3SnH (72.5 mg, 0.25 mmol, 2.5 equiv), then the solution was heated at 80 °C for 15 h. Solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, petro ether/EtOAc=4:1) to give (*S*)-2-methyl-1-tosylindoline.[3p] 27.2 mg, 95% yield, pale pink oil. $[\alpha]_D^{15}$= -151.9 (c = 0.20, $CHCl_3$), 82% ee, determined by HPLC analysis [Daicel Chiralpak AD-H, 5% *i*-PrOH /hexane, 1 mL/min, λ = 254 nm, $t_{(major)}$ = 9.7 min, $t_{(minor)}$ = 13.3 min]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.20 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 7.8 Hz, 2H), 7.05-7.00 (m, 2H), 4.37-4.32 (m, 1H), 2.88 (dd, J = 15.9, 9.4 Hz, 1H), 2.43 (dd, J = 15.9, 2.6 Hz, 1H), 2.34 (s, 3H), 1.42 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.7, 141.1, 135.3, 131.6, 129.5, 127.7, 127.0, 125.2, 124.5, 117.2, 58.5, 36.2, 23.4, 21.5. HRMS-ESI (*m/z*): calcd for $C_{16}H_{17}NNaO_2S$ $[M+Na]^+$ 310.0872, found 310.0878.

A mixture of (*S*)-2-methyl-1-tosylindoline (27.2 mg, 0.09mmol, 1.0 equiv) and Mg powder (10.7 mg, 0.45 mmol, 5.0 equiv) in dry MeOH (1.0 mL) was sonicated under N_2 atmosphere, then the mixture was stirred at room temperature for 3 h, quenched with saturated NH_4Cl (2.0 mL), and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (silica gel, eluent: *n*-hexane/ethyl acetate = 4/1 to 1/1) to give (*S*)-2-methylindoline **9.**[3p] 11.0 mg, 90% yield, colorless oil. $[\alpha]_D^{18}$= -12.5 (c = 0.08, PhH), 82% ee, determined by HPLC analysis [Daicel Chiralcel OD-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 7.6 min, $t_{(major)}$ = 8.6 min]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (d, J = 7.2 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.71 (dd, J = 10.8, 4.0 Hz, 1H), 6.63 (d, J = 7.7 Hz, 1H), 4.04-3.97 (m, 1H), 3.15 (dd, J = 15.4, 8.5 Hz, 1H), 2.64 (dd, J = 15.4, 7.8 Hz, 1H), 1.30 (d, J = 6.2 Hz, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.6, 128.0, 126.2, 123.7, 117.7, 108.4, 54.2, 36.7, 21.2. HRMS-ESI (*m/z*): calcd for $C_9H_{12}N$ $[M+H]^+$ 134.0970, found 134.0976.

Synthesis of (*R*)-indolin-2-ylmethanol 10.[7e, 9c] A flame-dried 10 mL flask was charged with **7a** (62.2 mg, 0.17 mmol, 1.0 equiv, 82% ee), anhydrous KOAc (68.7 mg, 0.70 mmol, 4.1 equiv), 18-crown-6 (92.4 mg, 0.35 mmol, 2.1 equiv), then dry DMF (4.0 mL) was added to the mixture and the resulting solution was stirred at 100 ºC for 6 h under N_2. After the mixture was cooled down to room temperature, the reaction was diluted with water and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure, then K_2CO_3 (27.6 mg, 0.20 mmol. 1.2 equiv) and MeOH (5.0 mL) were added to the resulting residue. The resulting mixture at reflux for 1 h, then 1 N HCl aq. was slowly added to the solution at 0 ºC and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (silica gel, eluent: *n*-hexanes/ethyl acetate = 4/1 to 1/1) to give (*R*)-(1-tosylindolin-2-yl)methanol.[13] 28.3 mg, 55% yield, white solid, mp: 92-93°C, $[\alpha]_D^{15}$= -150 (c = 0.12, $CHCl_3$), 81% ee, determined by HPLC analysis [Daicel Chiralcel OD-H, 2% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(major)}$ = 27.4 min, $t_{(minor)}$ = 33.2 min]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 1H), 7.53 (d, J = 8.3 Hz, 2H), 7.24-7.20 (m, 1H), 7.18 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 4.7 Hz, 2H), 4.32-4.28 (m, 1H), 3.72 (d, J = 5.7 Hz, 2H), 2.80 (dd, J = 16.2, 9.8 Hz, 1H), 2.64 (dd, J = 16.3, 3.1 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.3, 141.3, 134.4, 132.0, 129.7, 127.8, 127.2, 125.1, 125.0, 117.7, 65.6, 63.6, 31.3, 21.6. HRMS-ESI (*m/z*): calcd for $C_{16}H_{16}NNaO_3S$ $[M+Na]^+$ 326.0827, found 326.0827.

A mixture of (*R*)-(1-tosylindolin-2-yl)methanol (28.3 mg, 0.09 mmol, 1.0 equiv) and Mg powder (11.7 mg, 0.48 mmol, 5.0 equiv) in dry MeOH (1.0 mL) was sonicated under N_2 atmosphere, then the mixture was stirred at room temperature for 3 h, quenched with saturated NH_4Cl (2.0 mL), and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (silica gel, eluent: *n*-hexanes/ethyl acetate = 4/1 to 1/1) to give the (*R*)-indolin-2-ylmethanol (**10**).[14] 12.1 mg, 90% yield, pale yellow oil, $[\alpha]_D^{15}$= -200 (c = 0.13, EtOH), 81% ee, determined by HPLC analysis [Daicael Chiralpak AD-H, 5% *i*-PrOH /hexane, 1.0 mL/min, λ= 254 nm, $t_{(minor)}$ = 21.0 min, $t_{(major)}$ = 24.7 min]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.10 (d, J = 7.2 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.75 (t, J = 7.4 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 4.08 (s, 1H), 3.75 (dd, J = 10.9, 3.7 Hz, 1H), 3.60 (dd, J = 10.9, 6.3 Hz, 1H), 3.13 (dd, J = 15.7, 9.3 Hz, 1H), 2.86 (dd, J = 15.7, 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.2, 128.9, 127.4, 124.9, 119.4, 110.2, 65.1, 60.4, 32.0. HRMS-ESI (*m/z*): calcd for $C_9H_{12}NO$ $[M+H]^+$ 150.0919, found 150.0920.

Acknowledgements

This work is founded by the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry, and the National Natural Science Foundation of China (grant no. 21572154).

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10.1002/adsc.201700106

UPDATE

Enantioselective Synthesis of 2-Bromomethyl Indolines via BINAP(S)-Catalyzed Bromoaminocyclization of Allyl Aniline

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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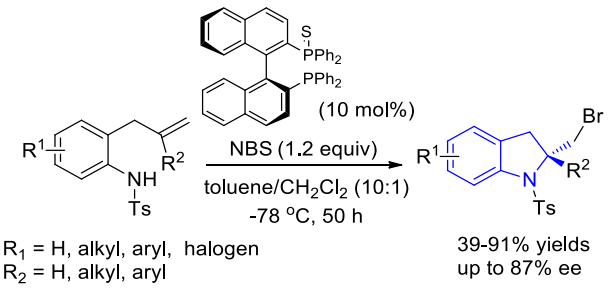

R_1 = H, alkyl, aryl, halogen
R_2 = H, alkyl, aryl

39-91% yields
up to 87% ee