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Mitsunobu cyclodehydration of *N*-pivaloyl-2-aminophenethyl alcohol for asymmetric synthesis of *trans*-2,3-disubstituted indolines

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ABSTRACT

Highly enantioenriched *trans*-2,3-disubstituted indolines have been prepared by Mitsunobu cyclodehydration of the amino alcohols obtained from (−)- or (+)-sparteine-mediated lithiation–substitution of *ortho*-alkyl substituted *N*-pivaloylanilines. Optimized cyclodehydration conditions are described, from which the combination of DEAD and PBu_3 in CH_3CN provides the best results.

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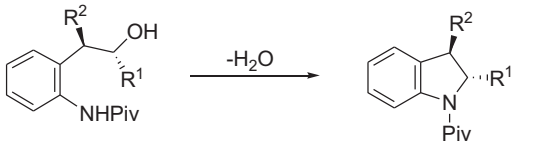
1. Introduction

Cyclodehydration of amino alcohol is an attractive method to make saturated nitrogen containing heterocycles.[1] We recently reported an acid-catalyzed cyclodehydration of *N*-pivaloyl-2-aminophenethyl alcohol for the asymmetric synthesis of 2,3-disubstituted indoline rings as shown in Fig. 1.[2] The amino alcohols with an aryl or styryl substituent (R^1) produced indoline derivatives in good yields via a carbocation. However, the scope of the reaction was narrow and aliphatic alkyl or electron-withdrawing aryl substituted amino alcohols gave none of product desired for a route to alkaloids.[3] In continuation of our work in the asymmetric synthesis of selected indoline derivatives, we report herein a novel asymmetric synthetic method for a wide range of *trans*-2,3-disubstituted indolines by Mitsunobu intramolecular cyclization.



HCl catalyzed : when R^1=Ph, Styryl, 62-78% yields
when R^1 = Alkyl, *p*-CF_3-Ph, **No Reactions**

Present Study: Broad substrate scope
Mild condition
Better enantioselectivity

Fig. 1. Cyclodehydrations for indoline synthesis.

2. Results and discussion

A few reports have shown that the Mitsunobu reaction, traditionally a proven stereospecific cyclodehydration methodology, can be applied to the intramolecular displacement of secondary alcohols by amide nucleophiles.[4] These earlier findings stimulated our interest in exploring Mitsunobu cyclodehydration of an aliphatic alkyl (R^1) substituted alcohol with *N*-pivaloylamino group as shown in Scheme 1. Highly enantioenriched amino alcohol **2** was prepared from the asymmetric lateral lithiation of *ortho*-benzyl substituted *N*-pivaloylaniline **1** and subsequent electrophilic substitution.[5] When the lithiation was carried out in the presence of (−)-sparteine at −20 °C and followed by the addition of hydrocinnamaldehyde at −78 °C, amino alcohol (*R*,*R*)-**2** was obtained in 81% yield as a 98:2 mixture of two inseparable diastereomers with enantiomeric ratios (ers) of 99:1 and 91:9, respectively.[6]

When the 98:2 diastereomeric mixture of **2** was treated with PPh_3 and diisopropyl azodicarboxylate (DIAD) in THF at room temperature, the nucleophilic attack by *N*-pivaloyl amide nucleophile provided *trans*-indoline **3a** with 99:1 er and no *cis*-indoline was detected.[6] Compound *trans*-**3a** might be produced from the major diastereomer of **2** (99:1 er) via S_N2 mechanism with inversion of configuration as depicted in Scheme 1. We reasoned that the repulsion between phenyl and phenethyl group in the transition state structure of minor diastereomer prevents formation of the cis-product. However, the Mitsunobu condition afforded a large amount of elimination product **4** (**3a**/**4**=62:38). Alkene **4** results from the elimination of triphenylphosphine oxide as shown in Scheme 1 and the driving force of the elimination is perhaps the extended conjugation in the product. The bulky amide nitrogen may be involved in a competing act as a nucleophile and as an acceptor of the benzylic proton in the elimination.[7]

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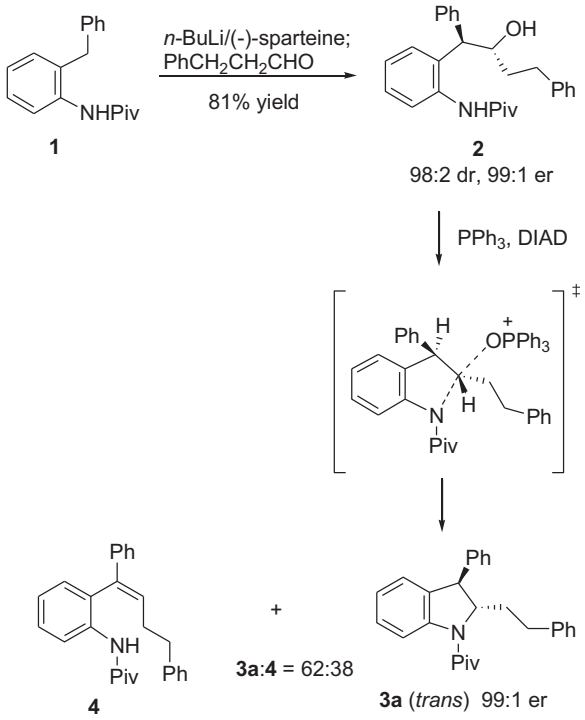


Scheme 1. Mitsunobu cyclodehydration of amino alcohol **2**.

The undesired formation of elimination product led us to seek a more efficient condition for the preparation of *trans*-2,3-disubstituted indolines. As shown in Table 1, various Mitsunobu conditions were examined with *N*-pivaloylamino alcohol **2** of 98:2 diastereomeric ratio (dr). When diethyl azodicarboxylate (DEAD) was used as azo reagent, a slightly improved ratio (69:31) was observed (entry 2). With the choice of DEAD as azo reagent and varying solvents, the best result was obtained in CH_3CN, in which **3a** and **4** were obtained in a ratio of 78:22 in 92% combined yield (entries 3–7).

Table 1
Optimization of Mitsunobu cyclodehydration of **2**

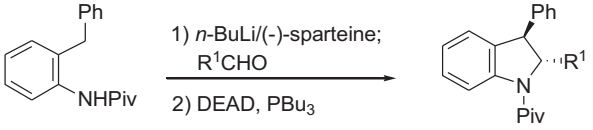
Entry[a]	Condition	Ratio[b] (**3a**/**4**)	Yield[c] (%)
1	DIAD, PPh_3, THF	62:38	80
2	DEAD, PPh_3, THF	69:31	82
3	DEAD, PPh_3, toluene	66:34	64
4	DEAD, PPh_3, *n*-hexane	31:69	21
5	DEAD, PPh_3, DMF	54:46	93
6	DEAD, PPh_3, $CHCl_3$	76:24	73
7	DEAD, PPh_3, CH_3CN	78:22	92
8	DEAD, PEt_2Ph, CH_3CN	85:15	91
9	DEAD, PBu_3, CH_3CN	98:2	92
10	DEAD, PCy_3, CH_3CN	—	—
11	DEAD, P(*o*-Tol)$_3$, CH_3CN	—	—

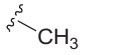
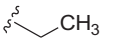
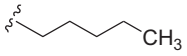
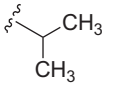
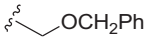
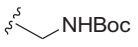
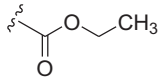
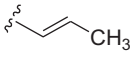
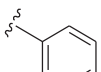
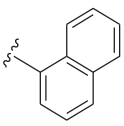
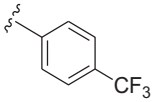
[a] All reactions were performed with a 98:2 diastereomeric mixture of **2** for 6 h at rt.
[b] The ratio was determined by ^1H NMR of the reaction mixture.
[c] Combined isolated yield of **3a** and **4**.

The steric bulk of tertiary phosphine has been known as a major factor governing the stereochemistry of various organic reactions.[8] We envisioned that the proportion of substitution would increase with the decreased crowding at the electrophilic carbon, and thus examined small cone angle phosphines for the activation of the amino alcohol.[9] Pleasingly, the proportion of substitution relative to the elimination was slightly improved to a ratio of 85:15 when PPh_3 (θ=145°) was replaced by sterically less demanding PEt_2Ph (θ=136°) with DEAD in CH_3CN (entry 8). Furthermore, as steric hindrance around the electrophilic center was decreased using PBu_3 (θ=132°), the proportion of substitution was significantly increased to a ratio of 98:2 (entry 9). On the other hand, the reactions with more bulky phosphines such as PCy_3 (θ=170°) and P(*o*-Tol)$_3$ (θ=194°) gave neither substitution product nor elimination product and *N*-pivaloylamino alcohol **2** was recovered (entries 10 and 11). These results indicate that the substitution seems dependent on the steric bulk of phosphine, with the greater extent of steric congestion resulting in competing elimination.[10]

Thus, the optimized combination of DEAD/PBu_3 in CH_3CN was selected for the subsequent studies to expand the scope of this methodology to a series of 2-alkyl substituted 3-phenylindolines as shown in Table 2. Lithiation of **1** in the presence of (−)-sparteine at −20 °C in methyl *tert*-butyl ether (MTBE) and following addition of acetaldehyde at −78 °C provided corresponding amino alcohol as a 98:2 mixture of two inseparable diastereomers. Since the minor diastereomer did not provide the cyclized product, separation of the major diastereomer was not required. Therefore, the crude mixture of diastereomers was directly subjected to our optimized Mitsunobu

Table 2
Asymmetric synthesis of 3-phenylindolines with various R^1 substituents



Entry	R^1	Yield[a] (%)	er[b]
1		63 (**3b**)	99:1
2		70 (**3c**)	99:1
3		72 (**3d**)	99:1
4		67 (**3e**)	99:1
5		68 (**3f**)	99:1
6		66 (**3g**)	99:1
7		68 (**3h**)	97:3
8		70 (**3i**)	99:1
9		75 (**3j**)	99:1
10		70 (**3k**)	99:1
11		72 (**3l**)	98:2

[a] Overall yields after two steps.
[b] Determined by CSP-HPLC using Chiralpak AD-H column.

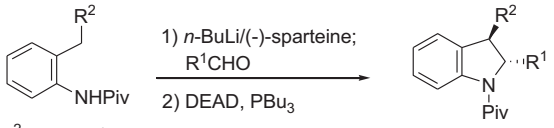
cyclodehydration condition, which afforded *trans*-2-methyl-3-phenylindoline **3b** of 99:1 er in 63% overall yield (entry 1). As shown in entries 2–4, the same procedure with propionaldehyde, hexanal, and isobutyraldehyde provided 2,3-disubstituted indolines **3c**–**e** with an excellent level of asymmetric induction in 72–67% overall yields. To demonstrate the compatibility with other functional groups, we carried out the cyclodehydration of amino alcohols obtained from the reactions with selected aldehydes including benzyloxyacetaldehyde, *N*-Boc aminoacetaldehyde, ethyl oxoacetate, and 2-butenal. It is noteworthy that the mild cyclodehydration condition with DEAD and PBu_3 gave highly enantioenriched 2-hydroxymethyl, 2-aminomethyl, 2-carboxylate, and 2-alkenyl substituted 3-phenylindolines **3f**–**i** with good yields (entries 5–8).

We have previously reported that the HCl-catalyzed cyclodehydration of amino alcohols from benzaldehyde and 1-naphthaldehyde produced indolines **3j** and **3k** with 98:2 er and 96:4 er, respectively.[2] A better enantioselectivity was observed under the Mitsunobu cyclodehydration condition to afford both indolines **3j** and **3k** with 99:1 er (entries 9 and 10). Also, it was reported that an electron-withdrawing *p*-trifluoromethylphenyl-substituted amino alcohol did not undergo cyclodehydration to give indoline product under the acid-catalyzed condition.[2] In the case of the amino alcohol, which is not capable of ionization to form a reasonable carbocation, cyclodehydration with DEAD and PBu_3 is an efficient way to make indoline ring. For example, *p*-trifluoromethylphenyl-substituted indoline **3l** was obtained under the Mitsunobu condition with 98:2 er in 68% overall yield (entry 11). The reactions with the aldehydes shown in Table 2 show that the substitution–cyclodehydration sequence provides highly enantioenriched indolines **3b**–**l** regardless of steric and electronic character of aldehydes.

These results encouraged us to apply this synthetic methodology to other *ortho*-alkyl substituted *N*-pivaloylanilines in order to synthesize selected R^2 substituted indolines as shown in Table 3. Previous report showed that (−)-sparteine-mediated lithiation–substitution of *ortho*-ethyl substituted *N*-pivaloylaniline **5** with various electrophiles gave substituted products with enantioselectivities ranging from 95:5 er to 83:17 er.[11a] The analogous reaction of **5** in the presence of (−)-sparteine at −20 °C and following addition of hydrocinnamaldehyde at −78 °C in MTBE provided the corresponding amino alcohol as an 86:14 mixture of two diastereomers. Subsequent Mitsunobu cyclodehydration of the amino alcohol afforded *trans*-indoline **3m** with 92:8 er in 50% overall yield[6] (entry 1). Similarly, as shown in entries 2–4, 3-methyl substituted indolines **3n**–**p** were obtained by the substitution–cyclodehydration sequence with somewhat lower enantioselectivities and yields when compared to the reactions of *ortho*-benzyl *N*-pivaloylaniline **1** in Table 2.

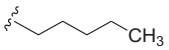
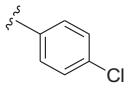
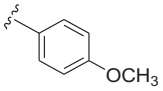
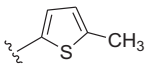
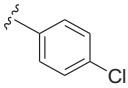
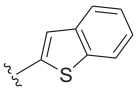
To further probe the scope of the reaction, we have prepared two different *ortho*-thienylmethyl substituted *N*-pivaloylanilines **6** and **7**. There are no examples reported in the literature of the lateral lithiation–substitution of the *ortho*-thienylmethyl substituted anilines, so we first applied the original lithiation–substitution condition in MTBE. We were pleased to find that the reaction of *ortho*-(5-methyl-2-thienylmethyl) *N*-pivaloylaniline **6** with hydrocinnamaldehyde gave corresponding amino alcohols with 89:11 dr and 95:5 er. To improve the stereoselectivity of the substitution, we tested several solvents and found that the use of diethyl ether resulted in the best stereoselectivities of 95:5 dr and 97:3 er. Subsequent Mitsunobu cyclodehydration afforded highly enantioenriched 3-thiophenyl substituted indoline **3q** with 97:3 er in 75% overall yields[6] (entry 5). Moreover, the analogous reactions of **6** with cinnamaldehyde and 4-chlorobenzaldehyde successfully afforded indolines **3r** and **3s** with 96:4 and 99:1 ers, respectively (entries 6 and 7). The results demonstrate that the thiophene group of *N*-pivaloylaniline is tolerant to the reaction conditions employed and gives high stereoselectivity. In addition, the substitution of *ortho*-(2-benzothienylmethyl) *N*-pivaloylaniline **7** with selected aldehydes and subsequent cyclodehydration proceeded generally in good yields to provide highly enantioenriched indolines **3t**–**v** as shown in entries 8–10. Many mild and chemoselective desulfurization procedures of thiophene are well established, hence the thiophenyl substituted indolines can be readily transformed into highly functionalized indolines that are otherwise difficult to access.[12]

Table 3
Asymmetric synthesis of indolines with various R^1 and R^2 substituents



5 (R^2 = methyl)
6 (R^2 = 5-methyl-2-thienyl)
7 (R^2 = 2-benzothienyl)

3m-v

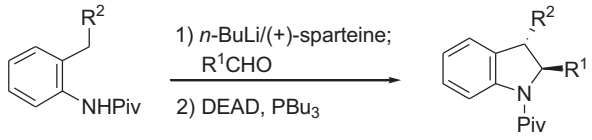
Entry[a]	R^2	R^1	Yield[b] (%)	er[c]
1	CH_3		50 (**3m**)	92:8
2			55 (**3n**)	90:10
3			64 (**3o**)	92:8
4			58 (**3p**)	91:9
5			75 (**3q**)	97:3
6			70 (**3r**)	96:4
7			73 (**3s**)	99:1
8			74 (**3t**)	97:3
9			69 (**3u**)	97:3
10			70 (**3v**)	97:3

[a] The lithiation–substitution was performed in *t*-BuOMe for entries 1–4 and in diethyl ether for entries 5–10.
[b] Overall yields after two steps.
[c] Determined by CSP-HPLC using Chiralpak AD-H and Chiralcel OD columns.

The opposite enantiomers of *trans*-2,3-disubstituted indolines **3** can be readily obtained by the use of commercially available (+)-sparteine. As shown in Scheme 2, (+)-sparteine-mediated substitution with selected aldehydes and subsequent cyclodehydration provided highly enantioenriched *trans*-2,3-disubstituted indolines *ent*-**3j**, *ent*-**3o**, *ent*-**3s**, and *ent*-**3v** from *ortho*-alkyl substituted *N*-pivaloylanilines **1**, **5**, **6**, and **7**, respectively.[13]

3. Conclusion

We have described the successful use of the Mitsunobu reaction for the synthesis of highly enantioenriched *trans*-2,3-disubstituted indolines from *ortho*-alkyl substituted *N*-pivaloylanilines. The facile



1, **5**, **6** and **7**

ent-**3j** 99:1 er, 69% yield
ent-**3o** 93:7 er, 62% yield
ent-**3s** 98:2 er, 73% yield
ent-**3v** 97:3 er, 65% yield

Scheme 2. Asymmetric synthesis of *ent*-**3j**, *ent*-**3o**, *ent*-**3s**, and *ent*-**3v** using (+)-sparteine.

access to both enantiomers of a broad range of *trans*-2,3-disubstituted indolines makes this an attractive route to this important class of molecules. Further application of this methodology to the asymmetric synthesis of various indoline alkaloids is in progress.

4. Experimental

4.1. General

All reactions were performed in oven-dried glassware under nitrogen atmosphere with freshly distilled solvents. *tert*-Butyl methyl ether (MTBE) and tetrahydrofuran (THF) were distilled from sodium/benzophenone under nitrogen. Toluene was distilled from CaH_2 under nitrogen. All other commercial reagents were used without further purification, unless otherwise indicated. Analytical thin layer chromatography (TLC) was performed on silica gel plates with QF-254 indicator and TLC visualization was carried out with UV-light. Flash column chromatography was performed with 230–400 mesh silica gel. Analytical chiral stationary phase HPLC was performed on pump system coupled to absorbance detector (217 nm). Chiralpak AD-H column (25 cm×4.6 mm i.d.) and Chiralcel OD column (25 cm×4.6 mm i.d.) with isopropanol/hexane mobile phase were used to determine enantiomeric ratios. ^{1}H and ^{13}C NMR spectra were acquired on Bruker (400 MHz ^{1}H, 100.6 MHz ^{13}C) spectrometer using chloroform-*d* ($CDCl_3$) as the internal standard. Chemical shifts (δ) are reported in parts per million (ppm) relative to chloroform-*d* (7.26 ppm ^{1}H, 77.07 ppm ^{13}C). Multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet), and br (broad). Coupling constants (*J*) are reported in hertz (Hz). Purity of the compounds was established to be >95% based on ^{1}H and ^{13}C NMR spectra. Infrared (IR) spectra were recorded on a Nicolet 6700 FT-IR spectrometer. Optical rotations were measured at 20 °C on a JASCO P-2000 polarimeter using a quartz cell with a Na high-pressure lamp. Elemental analyses were performed by the Organic Chemistry Research Center (OCRC) operated by Sogang University. Mass spectrometric data were acquired at Korea Basic Science Institute (KBSI), mass spectrometry laboratory.

4.2. General procedure for the asymmetric preparation of indolines 3

To a solution of *N*-pivaloylanilines **1**, **5**, **6**, and **7** (0.5 mmol) and (−)-sparteine (258 mg, 2.2 equiv) in 3 mL of MTBE (or diethyl ether) at −20 °C was added *n*-BuLi (0.7 mL, 1.6 M in hexane, 2.2 equiv). After the mixture was stirred at −20 °C for 1 h, an aldehyde (2.5 equiv) was added at −78 °C. The mixture was stirred for 20 min at −78 °C and then quenched with excess methanol. The resulting mixture was dissolved in EtOAc, washed with satd NH_4Cl, dried with $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by passing through a short silica gel column (EtOAc/hexanes solvents) to afford the amino alcohol as an inseparable mixture of two diastereomers. To a solution of the products in CH_3CN (2 mL) was added PBu_3 (2.5 equiv) and DEAD (2.5 equiv) and the mixture was stirred at room temperature for 6 h. After the solvent was removed in vacuo, chromatographic separation of the crude mixture on silica gel (EtOAc/hexanes solvents) afforded indolines **3a**–**v** in 75–50% overall yields shown in Tables 2 and 3.

*4.2.1. N-Pivaloyl-(S)-2-phenethyl-(R)-3-phenylindoline (**3a**).* A colorless oil (142 mg, 74% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.14 (d, *J*=8.4 Hz, 1H), 7.31–6.94 (m, 14H), 4.44 (dd, *J*=8.8 and 4.0 Hz, 1H), 4.21 (s, 1H), 2.97–2.76 (m, 2H), 2.07–1.94 (m, 2H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.5 (quat.), 144.4 (quat.), 142.3 (quat.), 140.6 (quat.), 133.3 (quat.), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.3 (CH), 127.1 (CH), 126.3 (CH), 125.7 (CH), 124.5 (CH), 119.8 (CH), 68.9 (CH), 51.9 (CH), 40.5 (quat.), 37.2 (CH_2), 32.1 (CH_2), 28.1 (CH_3); IR (neat, cm^{-1}) 3206, 2923, 2853, 1644, 1494, 1370, 1357, 1190, 699; HRMS (FAB) calcd for $C_{27}H_{30}NO$ (M^++1): 384.2327. Found 384.2328; $[\alpha]_D^{20}$ −37.5 (*c* 0.013, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 2% 2-propanol in hexane; 0.5 mL/min) 99:1 er, 31.2 min (major enantiomer), 49.0 min (minor enantiomer).

*4.2.2. N-Pivaloyl-2-(1′,4′-diphenyl-1′-butenyl)aniline (**4**).* ^{1}H NMR ($CDCl_3$, 400 MHz) 8.38 (d, *J*=8.0 Hz, 1H), 7.38–6.96 (m, 13H), 6.45 (t, *J*=7.2 Hz, 1H), 2.73 (t, *J*=7.6 Hz, 2H), 2.34 (q, *J*=7.2 Hz, 2H), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.3 (quat.), 141.1 (quat.), 139.5 (quat.), 138.1 (quat.), 135.8 (quat.), 131.5 (CH), 130.3 (CH), 128.7 (quat.), 128.6 (CH), 128.5 (CH), 128.43 (CH), 128.42 (CH), 127.8 (CH), 126.1 (CH), 126.0 (CH), 123.7 (CH), 120.6 (CH), 39.7 (quat.), 35.7 (CH_2), 31.5 (CH_2), 27.2 (CH_3); IR (neat, cm^{-1}) 3427, 3024, 2958, 2863, 1686, 1581, 1518, 1443, 1303, 1159, 762, 697. Anal. Calcd for $C_{27}H_{29}NO$: C, 84.55; H, 7.62; N, 3.65. Found: C, 84.43; H, 7.55; N, 3.75.

*4.2.3. N-Pivaloyl-(S)-2-methyl-(R)-3-phenylindoline (**3b**).* A colorless oil (92 mg, 63% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.17 (d, *J*=8.4 Hz, 1H), 7.33–6.91 (m, 8H), 4.60 (q, *J*=6.0 Hz, 1H), 3.95 (s, 1H), 1.43 (d, *J*=6.0 Hz, 3H), 1.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.5 (quat.), 143.7 (quat.), 142.4 (quat.), 133.3 (quat.), 128.7 (CH), 128.0 (CH), 127.2 (CH), 127.1 (CH), 125.7 (CH), 124.4 (CH), 120.1 (CH), 64.8 (CH), 54.9 (CH), 40.6 (quat.), 28.3 (CH_3), 22.6 (CH_3); IR (neat, cm^{-1}) 3446, 2975, 2925, 2854, 1633, 1472, 1400, 1359, 1242, 1196, 755, 668. Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.75; H, 7.92; N, 4.71; $[\alpha]_D^{20}$ −27.7 (*c* 0.016, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 5% 2-propanol in hexane; 0.5 mL/min) 99:1 er, 11.8 min (major enantiomer), 28.9 min (minor enantiomer). Removal of *N*-pivaloyl group of **3b**: To a solution of **3b** (50 mg, 0.17 mmol) in 1,4-dioxane (1 mL) was added water (1 mL) and concd HCl (1 mL). The solution was heated at reflux for 36 h. Upon cooling of the solution to room temperature, the solvent was removed in vacuo. Chromatographic separation on silica gel afforded *trans*-2-methyl-3-phenylindoline (21 mg, 0.10 mmol) in 61% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.33–6.68 (m, 9H), 3.93 (d, *J*=9.6 Hz, 1H), 3.85 (q, *J*=5.9 Hz, 1H), 1.33 (d, *J*=6.0 Hz, 3H). The spectral data were identical to those of the authentic material reported previously.[6]

*4.2.4. N-Pivaloyl-(S)-2-ethyl-(R)-3-phenylindoline (**3c**).* A colorless oil (108 mg, 70% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.17 (d, *J*=8.0 Hz, 1H), 7.32–6.92 (m, 8H), 4.27 (dd, *J*=10.4 and 2.0 Hz, 1H), 4.12 (s, 1H), 1.83–1.65 (m, 2H), 1.12 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.5 (quat.), 144.5 (quat.), 142.6 (quat.), 133.2 (quat.), 128.7 (CH), 128.0 (CH), 127.3 (CH), 126.9 (CH), 125.7 (CH), 124.3 (CH), 119.6 (CH), 70.8 (CH), 51.3 (CH), 40.6 (quat.), 28.5 (CH_2), 28.2 (CH_3), 10.1 (CH_3); IR (neat, cm^{-1}) 2961, 2929, 1645, 1475, 1399, 1357, 1190, 1077, 699. Anal. Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.12; H, 8.30; N, 4.43; $[\alpha]_D^{20}$ −40.8 (*c* 0.011, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min) 99:1 er, 12.3 min (major enantiomer), 17.9 min (minor enantiomer).

*4.2.5. N-Pivaloyl-(S)-2-pentyl-(R)-3-phenylindoline (**3d**).* A colorless oil (126 mg, 72% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.16 (d, *J*=8.4 Hz, 1H), 7.32–6.91 (m, 8H), 4.23 (dd, *J*=10.4 and 2.4 Hz, 1H), 4.11 (s, 1H), 1.74–1.33 (m, 8H), 1.12 (s, 9H), 0.91 (t, *J*=8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.4 (quat.), 144.4 (quat.), 142.6 (quat.), 133.2 (quat.), 128.7 (CH), 128.0 (CH), 127.3 (CH), 126.9 (CH), 125.7 (CH), 124.3 (CH), 119.7 (CH), 69.7 (CH), 51.8 (CH), 40.6 (quat.), 35.6 (CH_2), 31.7 (CH_2), 28.2 (CH_3), 25.6 (CH_2), 22.6 (CH_2), 14.0 (CH_3); IR (neat, cm^{-1}) 2923, 2853, 1649, 1596, 1473, 1357, 1245, 1185, 1096; HRMS (FAB) calcd for $C_{24}H_{32}NO$ (M^++1): 350.2484. Found 350.2486; $[\alpha]_D^{20}$ −29.7 (*c* 0.012, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 1% 2-propanol in hexane; 0.5 mL/min) 99:1 er, 42.5 min (major enantiomer), 50.1 min (minor enantiomer).

*4.2.6. N-Pivaloyl-(S)-2-isopropyl-(R)-3-phenylindoline (**3e**).* A yellow oil (108 mg, 67% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.11 (d, *J*=8.0 Hz, 1H), 7.30–6.93 (m, 8H), 4.38 (d, *J*=3.2 Hz, 1H), 4.16 (s, 1H), 2.24–2.20 (m, 1H), 1.15 (m, 12H), 0.64 (d, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 177.3 (quat.), 145.5 (quat.), 143.5 (quat.), 134.3 (quat.), 128.7 (CH), 127.9 (CH), 127.4 (CH), 126.8 (CH), 124.6 (CH), 124.3 (CH), 118.7 (CH), 73.3 (CH), 47.1 (CH), 41.2 (quat.), 33.9 (CH), 28.7 (CH_3), 18.8 (CH_3), 16.2 (CH_3); IR (neat, cm^{-1}) 2951, 2923, 2847, 1645, 1477, 1357, 1189, 699; HRMS (FAB) calcd for $C_{22}H_{28}NO$ (M^++1): 322.2171. Found 322.2173; $[\alpha]_D^{20}$ −22.7 (*c* 0.016, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 1% 2-propanol in hexane; 0.5 mL/min) 99:1 er, 16.3 min (major enantiomer), 25.8 min (minor enantiomer).

*4.2.7. N-Pivaloyl-(R)-2-benzyloxymethyl-(R)-3-phenylindoline (**3f**).* A yellow oil (136 mg, 68% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.11 (d, *J*=8.0 Hz, 1H), 7.38–6.96 (m, 13H), 4.64–4.59 (m, 2H), 4.50 (d, *J*=12.0 Hz, 1H), 4.45 (s, 1H), 3.68 (dd, *J*=9.2 and 3.6 Hz, 1H), 3.36 (dd, *J*=9.6 and 9.6 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.7 (quat.), 144.7 (quat.), 142.1 (quat.), 137.7 (quat.), 132.8 (quat.), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 126.9 (CH), 125.9 (CH), 124.6 (CH), 119.5 (CH), 73.4 (CH_2), 71.3 (CH_2), 68.0 (CH), 50.5(CH), 40.6 (quat.), 28.0 (CH_3); IR (neat, cm^{-1}) 3028, 2972, 2863, 1649, 1474, 1400, 1353, 1245, 1188, 1088, 699; HRMS (FAB) calcd for $C_{27}H_{30}NO_2$ (M^++1): 400.2277. Found 400.2278; $[\alpha]_D^{20}$ −34.2 (*c* 0.022, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min) 99:1 er, 11.8 min (major enantiomer), 21.4 min (minor enantiomer).

*4.2.8. N-Pivaloyl-(R)-2-(N-Boc-aminomethyl)-(R)-3-phenylindoline (**3g**).* A colorless oil (135 mg, 66% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.08 (d, *J*=8.4 Hz, 1H), 7.33–6.89 (m, 8H), 4.90 (br, 1H), 4.72 (br, 1H), 4.29 (s, 1H), 3.51 (m, 1H), 3.05 (m, 1H), 1.49 (s, 9H), 1.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 177.3 (quat.), 155.9 (quat.), 144.2 (quat.), 141.9 (quat.), 132.5 (quat.), 128.7 (CH), 128.1 (CH), 127.5 (CH), 127.0 (CH), 125.9 (CH), 124.7 (CH), 120.0 (CH), 79.8 (quat.), 68.0 (CH), 49.8 (CH), 44.0 (CH_2), 40.6 (quat.), 28.4 (CH_3), 28.2 (CH_3); IR (neat, cm^{-1}) 3343, 2976, 2929, 1708, 1633, 1475, 1401, 1363, 1276, 1168, 700; HRMS (FAB) calcd for $C_{25}H_{33}N_2O_3$ (M^++1): 409.2491. Found 409.2491; $[\alpha]_D^{20}$ −16.4 (*c* 0.016, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min) 99:1 er, 14.0 min (major enantiomer), 15.5 min (minor enantiomer).

*4.2.9. N-Pivaloyl-(R)-2-ethoxycarbonyl-(R)-3-phenylindoline (**3h**).* A colorless oil (119 mg, 68% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.26 (d, *J*=8.4 Hz, 1H), 7.32–7.04 (m, 8H), 5.06 (s, 1H), 4.50 (s, 1H), 4.23 (q, *J*=7.2 Hz, 2H), 1.27 (t, *J*=7.2 Hz, 3H), 1.15 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.4 (quat.), 171.4 (quat.), 144.8 (quat.), 141.9 (quat.), 131.5 (quat.), 128.9 (CH), 128.5 (CH), 127.6 (CH), 127.1 (CH), 124.9 (CH), 124.5 (CH), 119.1 (CH), 70.2 (CH), 61.9 (CH_2), 52.4 (CH), 40.3 (quat.), 27.8 (CH_3), 14.1 (CH_3); IR (neat, cm^{-1}) 3422, 2973, 2924, 2360, 2341, 1745, 1650, 1480, 1399, 1358, 1245, 1187, 1115, 1019, 775, 701. Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.11; H, 7.20; N, 3.95; $[\alpha]_D^{20}$ −33.2 (*c* 0.016, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 2% 2-propanol in hexane; 0.5 mL/min) 97:3 er, 55.4 min (major enantiomer), 83.1 min (minor enantiomer).

*4.2.10. N-Pivaloyl-(R)-3-phenyl-(S)-2-(1-propenyl)indoline (**3i**).* A colorless oil (112 mg, 70% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.22 (d, *J*=8.0 Hz, 1H), 7.33–6.96 (m, 8H), 5.59 (m, 2H), 4.95 (m, 1H), 4.09 (s, 1H), 1.64 (m, 3H), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 177.2 (quat.), 144.7 (quat.), 142.5 (quat.), 132.8 (quat.), 131.4 (CH), 128.7 (CH), 128.0 (CH), 127.2 (CH), 127.1 (CH), 126.2 (CH), 125.5 (CH), 124.4 (CH), 119.5 (CH), 69.8 (CH), 55.0 (CH), 40.5 (quat.), 28.4 (CH_3), 17.7 (CH_3); IR (neat, cm^{-1}) 2923, 2850, 1646, 1479, 1397, 963, 701; HRMS (FAB) calcd for $C_{22}H_{26}NO$ (M^++1): 320.2014. Found 320.2014; $[\alpha]_D^{20}$ −34.4 (*c* 0.020, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min) 99:1 er, 8.8 min (major enantiomer), 17.7 min (minor enantiomer).

*4.2.11. N-Pivaloyl-(R)-2-phenyl-(R)-3-phenylindoline (**3j**).* A colorless oil (133 mg, 75% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.35 (d, *J*=8.0 Hz, 1H), 7.38–7.03 (m, 13H), 5.61 (s, 1H), 4.26 (s, 1H), 1.02 (s, 9H). The spectral data of **3j** were identical to those of the authentic material reported previously.[2] $[\alpha]_D^{20}$ −27.9 (*c* 0.034, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min) 99:1 er, 10.0 min (major enantiomer), 13.0 min (minor enantiomer).

*4.2.12. N-Pivaloyl-(R)-2-(1-naphthyl)-(R)-3-phenylindoline (**3k**).* A pale yellow oil (142 mg, 70% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.48 (d, *J*=8.4 Hz, 1H), 8.03–6.91 (m, 15H), 6.31 (s, 1H), 4.21 (s, 1H), 1.06 (s, 9H). The spectral data of **3k** were identical to those of the authentic material reported previously.[2] $[\alpha]_D^{20}$ −44.0 (*c* 0.018, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min) 99:1 er, 13.1 min (major enantiomer), 15.4 min (minor enantiomer).

*4.2.13. N-Pivaloyl-(R)-3-phenyl-(R)-2-(4-trifluoromethylphenyl) indoline (**3l**).* A colorless oil (152 mg, 72% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.35 (d, *J*=8.0 Hz, 1H), 7.58–7.03 (m, 12H), 5.65 (s, 1H), 4.22 (s, 1H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 177.3 (quat.), 147.4 (quat.), 145.0 (quat.), 142.4 (quat.), 131.4 (quat.), 129.1 (CH), 128.6 (CH), 127.6 (CH), 127.1 (CH), 126.0 (CH), 125.9 (quat.), 125.7 (CH), 125.6 (CH), 125.1 (CH), 119.2 (CH), 71.7 (CH), 57.9 (CH), 40.5 (quat.), 28.3 (CH_3); IR (neat, cm^{-1}) 3423, 2978, 2926, 1650, 1476, 1359, 1324, 1184, 1126, 1066, 1017, 830, 759, 702. Anal. Calcd for $C_{26}H_{24}F_3NO$: C, 73.74; H, 5.71; N, 3.31. Found: C, 73.77; H, 5.68; N, 3.21; $[\alpha]_D^{20}$ −16.9 (*c* 0.013, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 5% 2-propanol in hexane; 0.5 mL/min) 98:2 er, 8.68 min (major enantiomer), 10.55 min (minor enantiomer).

*4.2.14. N-Pivaloyl-(S)-3-methyl-(S)-2-phenethylindoline (**3m**).* A colorless oil (80 mg, 50% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.05 (d, *J*=8.4 Hz, 1H), 7.29–7.02 (m, 8H), 4.25 (dd, *J*=10.4 and 2.4 Hz, 1H), 3.08 (q, *J*=7.2 Hz, 1H), 2.75–2.61 (m, 2H), 1.94–1.81 (m, 2H), 1.27 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.6 (quat.), 143.0 (quat.), 140.7 (quat.), 136.3 (quat.), 128.5 (CH), 128.4 (CH), 127.4 (CH), 126.2 (CH), 124.2 (CH), 124.0 (CH), 119.5 (CH), 66.8 (CH), 41.0 (CH), 40.6 (quat.), 36.5 (CH_2), 32.0 (CH_2), 28.3 (CH_3), 20.9 (CH_3); IR (neat, cm^{-1}) 2922, 2853, 1642, 1474, 1460, 1357, 1287; HRMS (FAB) calcd for $C_{22}H_{28}NO$ (M^++1): 322.2171. Found 322.2172; $[\alpha]_D^{20}$ −21.3 (*c* 0.028, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 5% 2-propanol in hexane; 0.5 mL/min) 92:8 er, 27.7 min (major enantiomer), 17.1 min (minor enantiomer).

*4.2.15. N-Pivaloyl-(S)-3-methyl-(S)-2-pentylindoline (**3n**).* A colorless oil (79 mg, 55% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.08 (d, *J*=8.4 Hz, 1H), 7.27–7.01 (m, 3H), 4.16 (dd, *J*=10.8 and 2.4 Hz, 1H),

2.96 (q, J=7.2 Hz, 1H), 1.61–1.25 (m, 8H), 1.38 (s, 9H), 1.22 (d, J=7.2 Hz, 3H), 0.87 (t, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.5 (quat.), 143.0 (quat.), 136.4 (quat.), 127.4 (CH), 124.2 (CH), 123.9 (CH), 119.3 (CH), 67.9 (CH), 41.0 (CH), 40.8 (quat.), 36.2 (CH_2), 31.7 (CH_2), 28.4 (CH_3), 25.4 (CH_2), 22.5 (CH_2), 21.1 (CH_3), 13.9 (CH_3); IR (neat, cm^{-1}) 2958, 2923, 2853, 1652, 1562, 1473, 1391, 668, 647; HRMS (FAB) calcd for $C_{19}H_{30}NO$ (M^++1): 288.2327. Found 288.2328; $[\alpha]_D^{20}$ −20.8 (c 0.018, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 2% 2-propanol in hexane; 0.5 mL/min) 90:10 er, 61.6 min (major enantiomer), 13.0 min (minor enantiomer).

*4.2.16. N-Pivaloyl-(R)-2-(4-chlorophenyl)-(S)-3-methylindoline (**3o**).* A colorless oil (105 mg, 64% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.25 (d, J=8.4 Hz, 1H), 7.29–7.04 (m, 7H), 5.39 (s, 1H), 3.08 (q, J=7.2 Hz, 1H), 1.42 (d, J=7.2 Hz, 3H), 1.22 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 177.4 (quat.), 143.7 (quat.), 142.0 (quat.), 134.4 (quat.), 132.9 (quat.), 128.9 (CH), 127.9 (CH), 126.4 (CH), 124.5 (CH), 124.3 (CH), 118.8 (CH), 69.9 (CH), 47.3 (CH), 40.7 (quat.), 28.5 (CH_3), 22.1 (CH_3); IR (neat, cm^{-1}) 3423, 2964, 2924, 2854, 1643, 1475, 1400, 1355, 1322, 1190, 1088, 1013, 811, 758, 669. Anal. Calcd for $C_{20}H_{22}ClNO$: C, 73.27; H, 6.76; N, 4.27. Found: C, 73.28; H, 6.74; N, 4.25; $[\alpha]_D^{20}$ +49.4 (c 0.038, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 2% 2-propanol in hexane; 0.5 mL/min) 92:8 er, 15.0 min (major enantiomer), 13.3 min (minor enantiomer).

*4.2.17. N-Pivaloyl-(R)-2-(4-methoxyphenyl)-(S)-3-methylindoline (**3p**).* A colorless oil (94 mg, 58% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.27 (d, J=8.4 Hz, 1H), 7.28–6.75 (m, 7H), 5.38 (s, 1H), 3.73 (s, 3H), 3.09 (q, J=7.2 Hz, 1H), 1.40 (d, J=7.2 Hz, 3H), 1.23 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 177.6 (quat.), 158.6 (quat.), 144.0 (quat.), 135.6 (quat.), 134.9 (quat.), 127.7 (CH), 126.1 (CH), 124.3 (CH), 118.8 (CH), 114.0 (CH), 70.0 (CH), 55.2 (CH_3), 47.4 (CH), 40.7 (quat.), 28.5 (CH_3), 22.1 (CH_3); IR (neat, cm^{-1}) 3447, 2963, 2924, 2863, 1639, 1511, 1475, 1357, 1247, 1177, 1030, 820, 765, 669. Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.89; H, 7.65; N, 4.17; $[\alpha]_D^{20}$ +52.0 (c 0.015, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 2% 2-propanol in hexane; 0.5 mL/min) 91:9 er, 27.4 min (major enantiomer), 32.2 min (minor enantiomer).

*4.2.18. N-Pivaloyl-(R)-3-(5-methyl-2-thienyl)-(S)-2-phenethylindoline (**3q**).* A colorless oil (151 mg, 75% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.09 (d, J=8.0 Hz, 1H), 7.30–7.06 (m, 8H), 6.47 (dd, J=2.8 and 0.8 Hz, 1H), 6.28 (d, J=3.2 Hz, 1H), 4.53 (dd, J=10.4 and 2.8 Hz, 1H), 4.32 (s, 1H), 2.88–2.72 (m, 2H), 2.38 (s, 3H), 2.03–1.94 (m, 2H), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.6 (quat.), 143.8 (quat.), 143.3 (quat.), 140.5 (quat.), 138.8 (quat.), 132.9 (quat.), 128.6 (CH), 128.5 (CH), 128.3 (CH), 126.3 (CH), 125.5 (CH), 124.8 (CH), 124.4 (CH), 124.2 (CH), 119.5 (CH), 68.9 (CH), 47.0 (CH), 40.5 (quat.), 36.6 (CH_2), 32.1 (CH_2), 28.1 (CH_3), 15.3 (CH_3); IR (neat, cm^{-1}) 3059, 2920, 2853, 1645, 1475, 1403, 1357, 1189, 1083, 795, 700; HRMS (FAB) calcd for $C_{26}H_{30}NOS$ (M^++1): 404.2048. Found 404.2047; $[\alpha]_D^{20}$ +18.0 (c 0.012, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 5% 2-propanol in hexane; 0.5 mL/min) 97:3 er, 18.4 min (major enantiomer), 36.9 min (minor enantiomer).

*4.2.19. N-Pivaloyl-(R)-3-(5-methyl-2-thienyl)-(S)-2-styrylindoline (**3r**).* A colorless oil (140 mg, 70% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.25 (d, J=8.0 Hz, 1H), 7.34–7.06 (m, 8H), 6.51–6.26 (m, 4H), 5.29 (d, J=5.2 Hz, 1H), 4.35 (s, 1H),2.39 (s, 3H), 1.21 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 177.3 (quat.), 144.0 (quat.), 143.0 (quat.), 139.1 (quat.), 136.1(quat.), 132.4 (quat.), 130.7 (CH), 129.2 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 126.5 (CH), 125.4 (CH), 124.8 (CH), 124.5 (CH), 119.7 (CH), 70.3 (CH), 50.2 (CH), 40.6 (quat.), 28.5 (CH_3), 15.4 (CH_3); IR (neat, cm^{-1}) 2961, 2922, 1646, 1474, 1401, 1356, 1186, 967, 799, 737, 693; HRMS (FAB) calcd for $C_{26}H_{28}NOS$ (M^++1): 402.1892. Found 402.1891; $[\alpha]_D^{20}$ −49.7 (c 0.018, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 5% 2-propanol in hexane; 0.5 mL/min) 96:4 er, 15.0 min (major enantiomer), 20.3 min (minor enantiomer).

*4.2.20. N-Pivaloyl-(R)-2-(4-chlorophenyl)-(R)-3-(5-methyl-2-thienyl) indoline (**3s**).* A yellow oil (149 mg, 73% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.31 (d, J=8.4 Hz, 1H), 7.37–7.05 (m, 7H), 6.53 (m, 1H), 6.49 (d, J=3.2 Hz, 1H), 5.68 (s, 1H), 4.34 (s, 1H), 2.41 (s, 3H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 177.4 (quat.), 144.6 (quat.), 143.3 (quat.), 141.3 (quat.), 139.3 (quat.), 133.3 (quat.), 131.2 (quat.), 129.2 (CH), 128.8 (CH), 126.7 (CH), 125.6 (CH), 124.9 (CH), 124.8 (CH), 124.4 (CH), 119.3 (CH), 71.9 (CH), 53.0 (CH), 40.6 (quat.), 28.4 (CH_3), 15.4 (CH_3); IR (neat, cm^{-1}) 2970, 2928, 1652, 1475, 1355, 1188, 1092, 1013, 754, 737. Anal. Calcd for $C_{24}H_{24}ClNOS$: C, 70.31; H, 5.90; N, 3.42; S, 7.82. Found: C, 70.38; H, 5.81; N, 3.32; S, 7.67; $[\alpha]_D^{20}$ −38.4 (c 0.055, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 5% 2-propanol in hexane; 0.5 mL/min) 99:1 er, 11.0 min (major enantiomer), 19.2 min (minor enantiomer).

*4.2.21. N-Pivaloyl-(R)-3-(2-benzothienyl)-(S)-2-ethylindoline (**3t**).* A colorless oil (134 mg, 74% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.18 (d, J=8.4 Hz, 1H), 7.73–7.10 (m, 7H), 6.68 (s, 1H), 4.52 (dd, J=10.8 and 2.4 Hz, 1H), 4.37 (s, 1H), 1.84–1.63 (m, 2H), 1.17 (s, 9H), 1.13 (t, J=7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.6 (quat.), 146.7 (quat.), 144.0 (quat.), 140.0 (quat.), 139.4 (quat.), 132.1 (quat.), 128.6 (CH), 125.7 (CH), 124.4 (CH), 124.3 (CH), 124.0 (CH), 123.4 (CH), 122.3 (CH), 121.3 (CH), 119.8 (CH), 70.4 (CH), 47.1 (CH), 40.7 (quat.), 28.3 (CH_3), 28.2 (CH_2), 10.0 (CH_3); IR (neat, cm^{-1}) 2961, 2923, 2869, 1644, 1473, 1457, 1356, 1185, 1077, 723. Anal. Calcd for $C_{23}H_{25}NOS$: C, 75.99; H, 6.93; N, 3.85; S, 8.82. Found: C, 75.81; H, 6.99; N, 3.91; S, 8.82; $[\alpha]_D^{20}$ +10.1 (c 0.011, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 1% 2-propanol in hexane; 0.5 mL/min) 97:3 er, 38.4 min (major enantiomer), 49.4 min (minor enantiomer).

*4.2.22. N-Pivaloyl-(R)-3-(2-benzothienyl)-(S)-2-styrylindoline (**3u**).* A colorless oil (151 mg, 69% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.30 (d, J=8.0 Hz, 1H), 7.75–7.10 (m, 13H), 6.78 (s, 1H), 6.51 (d, J=16.0 Hz, 1H), 6.34 (dd, J=16.0 and 5.2 Hz, 1H), 5.43 (d, J=5.2 Hz, 1H), 4.48 (s, 1H), 1.19 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 177.3 (quat.), 145.8 (quat.), 144.2 (quat.), 139.5 (quat.), 139.4 (quat.), 136.0 (quat.), 131.6 (quat.), 131.0 (CH), 129.0 (CH), 128.8 (CH), 128.6 (CH), 128.0 (CH), 126.5 (CH), 125.6 (CH), 124.6 (CH), 124.5 (CH), 124.2 (CH), 123.5 (CH), 122.3 (CH), 121.6 (CH), 119.9 (CH), 69.7 (CH), 50.8 (CH), 40.7 (quat.), 28.5 (CH_3); IR (neat, cm^{-1}) 3442, 3026, 2973, 2930, 2360, 2341, 1641, 1476, 1401, 1356, 1186, 739, 691. Anal. Calcd for $C_{29}H_{27}NOS$: C, 79.60; H, 6.22; N, 3.20; S, 7.33. Found: C, 79.72; H, 6.28; N, 3.31; S, 7.42; $[\alpha]_D^{20}$ −39.2 (c 0.013, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 2% 2-propanol in hexane; 0.5 mL/min) 97:3 er, 41.0 min (major enantiomer), 34.2 min (minor enantiomer).

*4.2.23. N-Pivaloyl-(R)-3-(2-benzothienyl)-(R)-2-phenylindoline (**3v**).* A colorless oil (144 mg, 70% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.39 (d, J=8.0 Hz, 1H), 7.78–7.09 (m, 13H), 6.83(s, 1H), 5.86(s, 1H), 4.53 (s, 1H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 177.6 (quat.), 146.6 (quat.), 145.0 (quat.), 142.7 (quat.), 139.6 (quat.), 139.5 (quat.), 130.7 (quat.), 129.0 (CH), 128.9 (CH), 127.6 (CH), 125.8 (CH), 125.2 (CH), 124.7 (CH), 124.5 (CH), 124.2 (CH), 123.5 (CH), 122.4 (CH), 121.4 (CH), 119.3 (CH), 71.6 (CH), 53.6 (CH), 40.7 (quat.), 28.4 (CH_3); IR (neat, cm^{-1}) 3056, 2971, 2920, 1641, 1473, 1356, 1185, 748, 694. Anal. Calcd for $C_{27}H_{25}NOS$: C, 78.80; H, 6.12; N, 3.40; S, 7.79. Found: C, 78.97; H, 6.20; N, 3.41; S, 7.81; $[\alpha]_D^{20}$ −20.4 (c 0.010, $CHCl_3$); CSP-HPLC (Chiralcel OD column; 1% 2-propanol in hexane; 0.5 mL/min) 97:3 er, 15.9 min (major enantiomer), 23.8 min (minor enantiomer).

4.3. Asymmetric preparation of indolines *ent*-3j, *ent*-3o, *ent*-3s, and *ent*-3v

The same procedure with (−)-sparteine described above was used for the preparation of indolines *ent*-**3j**, *ent*-**3o**, *ent*-**3s**, and *ent*-**3v** using commercially available (+)-sparteine (CAS No: 492-08-0). From the reactions of **1**, **5**, **6**, and **7** (0.5 mmol), enantioenriched indolines *ent*-**3j**, *ent*-**3o**, *ent*-**3s**, and *ent*-**3v** were obtained in 73–62% yields as shown in Scheme 2.

4.4. Asymmetric preparation of amino alcohol 2

To a solution of *N*-pivaloylaniline **1** (0.5 mmol) and (−)-sparteine (258 mg, 2.2 equiv) in 3 mL of MTBE (or diethyl ether) at −20 °C was added *n*-BuLi (0.7 mL, 1.6 M in hexane, 2.2 equiv). After the mixture was stirred at −20 °C for 1 h, hydrocinnamaldehyde (2.5 equiv) was added at −78 °C. The mixture was stirred for 20 min at −78 °C and then quenched with excess methanol. The resulting mixture was dissolved in EtOAc, washed with satd NH_4Cl, dried with $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by a silica gel column chromatography (EtOAc/hexanes solvents) to afford amino alcohol **2** as an inseparable mixture of two diastereomers (98:2 dr) in 81% yield (163 mg) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.70 (d, *J*=8.0 Hz, 1H), 7.35–7.11 (m, 14H), 4.34 (m, 1H), 4.03 (d, *J*=6.0 Hz, 1H), 2.86–2.72 (m, 2H), 1.99 (m, 1H), 1.70 (m, 1H), 1.55 (d, *J*=5.6 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 176.8 (quat.), 141.6 (quat.), 139.5 (quat.), 135.7 (quat.), 134.2 (quat.), 129.5 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.5 (CH), 127.2 (CH), 126.0 (CH), 125.3 (CH), 125.2 (CH), 72.7 (CH), 51.8 (CH), 39.5 (quat.), 37.3 (CH_2), 32.3 (CH_2), 27.6 (CH_3); IR (neat, cm^{-1}) 3398, 3297, 2957, 2923, 2843, 1654, 1516, 1449, 1302, 1170, 699. Anal. Calcd for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.78; N, 3.49. Found: C, 80.61; H, 7.59; N, 3.60; $[\alpha]_D^{20}$ −17.6 (*c* 0.019, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min) major diastereomer, 99:1 er, 17.7 min (major enantiomer), 19.4 min (minor enantiomer); minor diastereomer, 91:9 er, 37.9 min (major enantiomer), 35.2 min (minor enantiomer).

4.5. General procedure for the preparation of 6 and 7

To a solution of 2-methylthiophene (or thionaphthene) (4.5 mmol) in 25 mL of anhydrous THF at −78 °C was added *n*-BuLi (1.6 M in hexane, 1.0 equiv). After the solution was allowed to warm to room temperature and stirred for 12 h, the solution of 2-cyanoaniline (1.0 equiv) in 5 mL of anhydrous THF was slowly added at −78 °C. The mixture was stirred for additional 10 h at room temperature and then quenched with 4 N HCl solution (100 mL) at 0 °C. The resulting mixture was dissolved in diethyl ether, washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by passing through a short silica gel column (EtOAc/hexanes solvents) to afford corresponding ketone. The solution of the product in ether (20 mL) was added dropwise to a suspension of lithium aluminum hydride (1.0 equiv) in ether (10 mL) and the mixture was refluxed for 6 h. The solution was cooled, the excess of lithium aluminum hydride was destroyed with water, and the solids were removed. The filtrate was concentrated and the residue was treated with pivaloyl chloride (1.0 equiv) and Et_3N (2.0 equiv) for 3 h in methylene chloride. The resulting mixture was dissolved in EtOAc, washed with satd NH_4Cl, dried with $MgSO_4$, and concentrated in vacuo. Chromatographic separation on silica gel (EtOAc/hexanes solvents) afforded the product.

*4.5.1. N-Pivaloyl-2-(5′-methyl-2′-thienylmethyl)aniline (**6**).* A colorless oil (54% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.93 (d, *J*=8.0 Hz, 1H), 7.32–7.10 (m, 3H), 6.57–6.49 (m, 2H), 4.05 (s, 2H), 2.41 (s, 3H), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.7 (quat.), 139.6 (quat.), 139.3 (quat.), 136.2 (quat.), 130.5 (quat.), 130.3 (CH), 128.0 (CH), 125.0 (CH), 124.9 (CH), 123.7 (CH), 39.6 (quat.), 33.4 (CH_2), 27.4 (CH_3), 15.3 (CH_3); IR (neat, cm^{-1}) 3421, 3269, 2956, 2870, 1644, 1485, 1186, 804, 757, 669. Anal. Calcd for $C_{17}H_{21}NOS$: C, 71.04; H, 7.36; N, 4.87; S, 11.16. Found: C, 71.06; H, 7.44; N, 4.74; S, 11.28.

*4.5.2. N-Pivaloyl-2-(2′-benzothienylmethyl)aniline (**7**).* A colorless oil (60% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.89 (d, *J*=8.0 Hz, 1H), 7.76–7.16 (m, 7H), 6.93 (s, 1H), 4.21 (s, 2H), 1.13 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.8 (quat.), 143.2 (quat.), 139.8 (quat.), 139.6 (quat.), 136.1 (quat.), 130.5 (CH), 130.4 (quat.), 128.2 (CH), 125.4 (CH), 124.5 (CH), 124.4 (CH), 124.1 (CH), 123.1 (CH), 122.2 (CH), 121.8 (CH), 39.5 (quat.), 33.9 (CH_2), 27.5 (CH_3); IR (neat, cm^{-1}) 3421, 2956, 2927, 1661, 1516, 1448, 1434, 1301, 1168, 761, 561. Anal. Calcd for $C_{20}H_{21}NOS$: C, 74.27; H, 6.54; N, 4.33; S, 9.91. Found: C, 74.34; H, 6.63; N, 4.41; S, 9.86.

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Supplementary data

The NMR and/or HPLC data of compounds **3a**–**v**, **2**, **4**, **6**, and **7**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.01.063.

References and notes

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13. We have prepared indolines *ent*-**3a**–**v** for the convenience of chiral stationary phase HPLC analysis (see Supplementary data for details).