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Asymmetric Synthesis of *trans*-2,3-Disubstituted Indoline Derivatives

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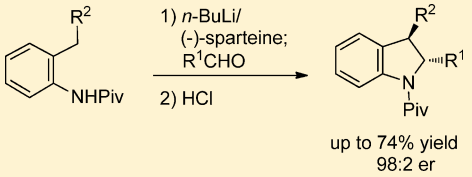
Supporting Information

ABSTRACT: A novel method for asymmetric synthesis of *trans*-2,3-disubstituted indolines has been developed. The strategy involves the (−)-sparteine-mediated electrophilic substitution of 2-benzyl *N*-pivaloylaniline with aromatic or α,β-unsaturated aldehydes and subsequent intramolecular nucleophilic substitution. The simple protocol for two-step process can produce highly enantioenriched indolines **3a**−**o** up to 98:2 er.



Indolines bearing substituents at both 2- and 3-positions are frequently found as a substructure in a number of alkaloids and natural products.[1] Since individual stereoisomers display different biological acitivities, it is desirable to develop a highly stereoselective route to 2,3-disubstituted indolines. Although some progress has recently been made toward the development of asymmetric synthetic methods for 2,3-disubstituted indolines, it still remains a great challenge in organic synthesis.[2] In the course of our studies on asymmetric substitution of 2-substituted aniline derivatives, we envisaged a simple synthetic method for indolines bearing two substituents at both 2- and 3-positions. Our strategy involves an asymmetric electrophilic substitution of 2-alkyl aniline with aldehydes (step A) and subsequent intramolecular nucleophilic substitution (step B) as illustrated retrosynthetically in Figure 1. Herein, we report a

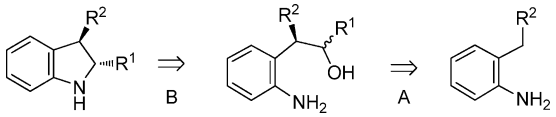
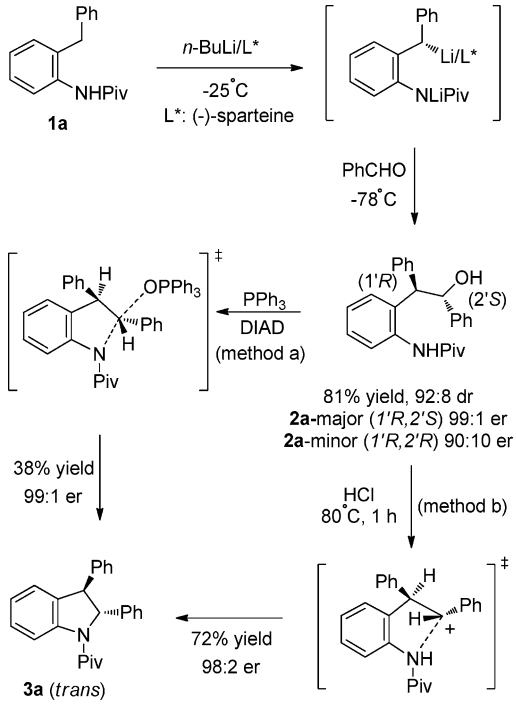


Figure 1. Restrosynthesis of *trans*-2,3-disubstituted indolines.

novel asymmetric synthetic method for *trans*-2,3-disubstituted indolines via (−)-sparteine-mediated electrophilic substitution of 2-(α-lithiobenzyl)-*N*-pivaloylaniline with various aldehydes and subsequent acid-catalyzed intramolecular substitution.

We have recently reported that (−)-sparteine-mediated asymmetric lateral substitutions of 2-benzyl-*N*-pivaloylaniline **1a** take place with almost complete control of the configuration at benzylic position.[3] For example, the substitution of **1a** with benzaldehyde can provide highly enantioenriched 2-(1′,2′-diphenyl-2′-hydroxyethyl)-*N*-pivaloylaniline **2a** by allowing the diastereomeric organolithium intermediates to reach thermodynamic equilibrium prior to electrophilic substitution (Scheme 1). When the lithiation was carried out in the presence of (−)-sparteine at −25 °C and followed by the addition of benzaldehyde at −78 °C, (1′*R*)-**2a** was obtained in 81% yield as a 92:8 mixture of two inseparable diastereomers with enantiomeric ratios (er) of 99:1 and 90:10.[3a] Since the hydroxyl group can be converted to a leaving group, we envisioned that the enantioenriched 2-aminophenethyl alcohol

Scheme 1. Asymmetric Electrophilic Substitution and Cyclization



2a could serve as a substrate for the synthesis of 2,3-disubstituted indolines by intramolecular nucleophilic substitution.

For the intramolecular nucleophilic substitution of **2a**, the key is how to effect the cyclization in an efficient and stereocontrolled manner. Several reports have shown that a Mitsunobu type displacement of secondary alcohols by amide nucleophile is a useful and practical method for stereospecific intramolecular C−N bond formation.[4] Thus, we examined whether the *N*-pivaloyl amine of **2a** could be used as the

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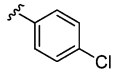
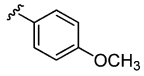
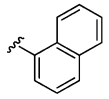
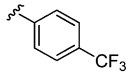
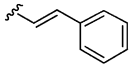
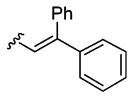
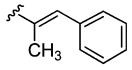
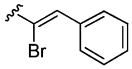
nucleophilic component for the intramolecular cyclization in Mitsunobu conditions without affecting the integrity of the stereogenic centers of **2a**. When a 92:8 diastereomeric mixture of **2a** was treated with PPh_3 and DIAD in THF at rt, the reaction provided the desired 2,3-disubstituted indoline **3a** in 34% yield. Only *trans*-indoline was produced with 99:1 er, and no *cis*-indoline was detected.[5] The *trans*-**3a** might be produced from the major diastereomer of **2a** (99:1 er) via S_N2 mechanism with inversion of configuration as depicted in Scheme 1 (method a). We reasoned that the repulsion between two phenyl substituents in the transition state structure of **2a**-minor prevents formation of the *cis*-product. However, the standard Mitsunobu conditions afforded a large amount (45%) of the elimination products. The mixture of isomeric alkenes results from dehydration of secondary alcohol **2a** by conversion of a hydroxyl group to an oxyphosphonium ion intermediate and elimination of triphenylphosphine oxide in succession.[6] The undesired formation of elimination products led us to seek a more efficient cyclization method of **2a** for the preparation of 2,3-disubstituted indolines.

Recent reports on the preparation of indoline derivatives by the acid-catalyzed intramolecular nucleophilic substitution of 2-aminophenethyl alcohol derivatives led us to explore acid-catalyzed substitution of **2a** via carbocationic intermediate.[7] In our preliminary investigation of the acid-catalyzed reaction, we found that treatment of **2a** with a refluxing 6 M HCl solution for 0.5 h produced 2,3-disubstituted indoline **3a** with 98:2 er in 53% yield. Hydrolysis of the pivalamide moiety was not observed in the reaction, and isomeric alkenes resulting from dehydration were produced as side products (14% yield). Analogous to the Mitsunobu reaction of **2a**, only *trans*-indoline was detected, and no *cis*-indoline was tracked in the reaction of a 92:8 diastereomeric mixture of **2a**.[7c] This result can be taken to suggest a cationic transition state as shown in Scheme 1 (method b), which avoids repulsion between two phenyl substituents. Following nucleophilic attack of amino group on the carbocation can give *trans*-indoline **3a** with 98:2 er from the reaction of a 92:8 diastereomeric mixture of **2a**-major (99:1 er) and **2a**-minor (90:10 er). After trying different acids (HBr, HI, CF_3CO_2H) and various reaction conditions such as temperature, concentration, solvent, and reaction time, we found that the best conditions for the cyclization involved the use of 4.5 M HCl solution in water and *p*-dioxane (3:1) for 1 h at 80 °C to give *trans*-**3a** in 72% isolated yield with 98:2 er and the elimination products with less than 10% yield.

Next, we initiated investigations into the reaction's scope with various aldehydes for the preparation of 2-substituted 3-phenylindolines as shown in Table 1.[8,9] Lithiation of **1a** in the presence of (−)-sparteine at −25 °C in MTBE and following addition of 4-chlorobenzaldehyde at −78 °C provided 2-aminophenethyl alcohol **2b** in 82% yield as an 94:6 mixture of two inseperable diastereomers with ers of 99:1 and 92:8. Subjecting this material to our optimized cyclization condition afforded *trans*-2-(*p*-chlorophenyl)-3-phenylindoline **3b** of 98:2 er in 65% yield. As shown in entries 2 and 3 (Table 1), the same procedure with 4-methoxybenzaldehyde and 1-naphthaldehyde provided 2,3-disubstituted indolines **3c** and **3d** with excellent levels of asymmetric induction. However, intramolecular cyclization of 2-aminonophenethyl alcohol **2e** from the reaction with 4-trifluoromethylbenzaldehyde did not occur under the same reaction condition, and **2e** was quantitatively recovered. (Table 1, entry 4) Also, the reactions of 2-aminophenethyl alcohols from aliphatic aldehydes (R^1 = CH_3 or CH_2CH_2Ph) gave no cyclized products. These results imply that the formation of stable carbocation intermediate is required prior to cyclization. In addition, 2-styryl-substituted 3-phenylindolines **3f–i** were successfully prepared by the electrophilic substitution with corresponding cinnamaldehydes and following cyclization (Table 1, entries 5–8).

Table 1. Electrophilic Substitution of 1a with Various Aldehydes and Cyclization

1a **3b-i**

Entry	R^1	2b-i			3b-i	
		Yield[a]	Dr[b]	Er[c,d]	Yield	Er[c]
1		82 (**2b**)	94:6	99:1 92:8	65 (**3b**)	98:2
2		87 (**2c**)	88:12	99:1 90:10	67 (**3c**)	96:4
3		68 (**2d**)	75:25	98:2 91:9	63 (**3d**)	96:4
4		64 (**2e**)	89:11	98:2 91:9	- (**3e**)	-
5		87 (**2f**)	74:26	99:1 94:6	78 (**3f**)	97:3
6		78 (**2g**)	76:24	94:6 96:4	62 (**3g**)	95:5
7		77 (**2h**)	73:27	95:5 96:4	70 (**3h**)	95:5
8		87 (**2i**)	77:23	99:1 95:5	73 (**3i**)	97:3

[a]Combined isolated yield of two diastereomers. [b]The ratio was determined by ^{1}H NMR of the reaction mixture. [c]Determined by CSP-HPLC using racemic material as a standard. [d]Er-values of major and minor products.

We next investigated the feasibility of a procedure that avoids purification of 2-aminophenethyl alcohol and uses the crude material in the subsequent cyclization step as shown in Table 2. After extractive workup of the reaction mixture of the first step, subjecting the crude reaction mixture to the optimized cyclization condition afforded 2,3-disubstituted indolines in comparable yields and enantioselectivities over the two steps. For the synthesis of 3-phenyl-2-styrylindoline **3f**, the procedure leads to the product with 97:3 er in 74% yield over the two steps (Table 2, entry 1), which compares well with the result using purified alcohol shown in Table 1, entry 5. With a

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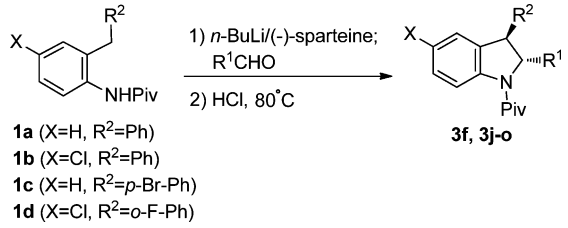
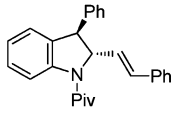
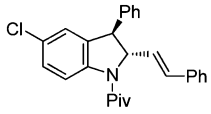
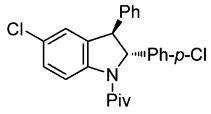
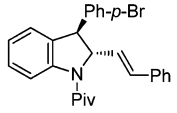
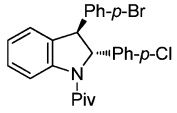
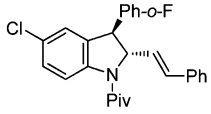
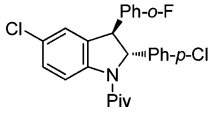
Table 2. Asymmetric Synthesis of Indolines by Practical Two-Step Process



1a (X=H, R^2=Ph)
1b (X=Cl, R^2=Ph)
1c (X=H, R^2=*p*-Br-Ph)
1d (X=Cl, R^2=*o*-F-Ph)

3f, 3j-o

Entry	Product	Yield[a] (%)	Er[b]
1		74 (**3f**)	97:3
2		69 (**3j**)	96:4
3		71 (**3k**)	95:5
4		74 (**3l**)	97:3
5		69 (**3m**)	96:4
6		70 (**3n**)	95:5
7		65 (**3o**)	96:4

[a]Overall yields after two steps. [b]Determined by CSP-HPLC using racemic material as a standard.

practical procedure in hand, we examined the scope of the methodology with three different 2-benzyl-*N*-pivaloylanilines **1b–d**. Under the same reaction conditions, this methodology is also efficient for the asymmetric preparation of 5-chloro-substituted indolines **3j** and **3k** with 96:4 and 95:5 er. (Table 2, entries 2 and 3) The simple two-step reactions of 2-(*p*-bromobenzyl)-*N*-pivaloylaniline **1c** and 5-chloro-2-(*o*-fluorobenzyl)-*N*-pivaloylaniline **1d** afforded 3-styryl-substituted indolines **3l**, **3n** and 3-*p*-chlorophenyl substituted indolines **3m**, **3o** with er-values ranging from 97:3 to 95:5 in 74–65% overall yields. (Table 2, entries 4–7)

In summary, we have developed a novel method for the asymmetric synthesis of *trans*-2,3-disubstituted indolines. The highly enantioselective process includes the stereoselective acid-catalyzed intramolecular substitution of secondary alcohol by *N*-pivaloyl amine as the key reaction. The simple protocol can provide highly functionalized indoline rings and would allow further functionalization and growing to access more complex target molecules.

EXPERIMENTAL SECTION

General Procedure for the Preparation of Indolines 3a–o. To a solution of *N*-pivaloylaniline **1a–d** (0.5 mmol) and (−)-sparteine (258 mg, 2.2 equiv) in MTBE (3 mL) at −25 °C was added *n*-BuLi (0.7 mL, 1.6 M in hexane, 2.2 equiv). After the mixture was stirred at −25 °C for 1 h, an aldehyde (2.5 equiv) was added at −78 °C. The mixture was stirred for 10 min at −78 °C and then quenched with excess methanol. The resulting mixture was dissolved in EtOAc, washed with saturated NH_4Cl, dried with $MgSO_4$, and concentrated in vacuo. Chromatographic separation on silica gel (EtOAc/hexanes solvents) afforded **2a–i** as an inseparable mixture of two diastereomers (87–64% yields shown in Table 1). To a solution of 2-aminophenethyl ethanol **2a–i** (or crude product from **1b–d**) in 1,4-dioxane (2 mL) were added water (3 mL) and concentrated HCl (3 mL). The solution was heated at 80 °C for 1 h. Upon cooling of the solution to room temperature, the solvent was removed in vacuo. Chromatographic separation on silica gel (EtOAc/hexanes solvents) afforded indolines **3a–i** in 78–62% yields shown in Table 1 and indolines **3j–o** in 74–65% overall yields shown in Table 2.

***N*-Pivaloyl-(*R*)-2-phenyl-(*R*)-3-phenylindoline (3a).** A colorless oil (103 mg, 58% overall yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.36 (d, J = 8.0 Hz, 1H), 7.35–7.04 (m, 13H), 5.61 (s, 1H), 4.26 (s, 1H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.8 (quat.), 145.4 (quat.), 143.4 (quat.), 142.9 (quat.), 131.9 (quat.), 129.0 (CH), 128.3 (CH), 127.33 (CH), 127.31 (CH), 127.2 (CH), 125.8 (CH), 125.1 (CH), 124.8 (CH), 119.1 (CH), 72.2 (CH), 58.2 (CH), 40.6 (quat.), 28.5 (CH_3); HRMS calcd for $C_{25}H_{26}NO$ (M^+ + 1) 356.2014, found 356.2015; CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min) 95:5 er, 10.3 min (major enantiomer), 13.6 min (minor enantiomer).

***N*-Pivaloyl-(*R*)-2-(*p*-chlorophenyl)-(*R*)-3-phenylindoline (3b).** A colorless oil (103 mg, 53% overall yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (d, J = 8.0 Hz, 1H), 7.68–7.01 (m, 12H), 5.60 (s, 1H), 4.30 (s, 1H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.3 (quat.), 145.1 (quat.), 142.5 (quat.), 141.9 (quat.), 133.2 (quat.), 131.6 (quat.), 129.1 (CH), 129.0 (CH), 128.5 (CH), 127.5 (CH), 127.1 (CH), 126.6 (CH), 125.8 (CH), 125.0 (CH), 119.2 (CH), 71.5 (CH), 58.1 (CH), 40.6 (quat.), 28.4 (CH_3); HRMS calcd for $C_{25}H_{25}ClNO$ (M^+ + 1) 390.1625, found 390.1624; CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min) 98:2 er, 9.3 min (major enantiomer), 12.9 min (minor enantiomer).

***N*-Pivaloyl-(*R*)-2-(*p*-methoxyphenyl)-(*R*)-3-phenylindoline (3c).** A pale yellow oil (114 mg, 58% overall yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.36 (d, J = 8.2 Hz, 1H), 7.36–6.81 (m, 12H), 5.56 (s, 1H), 4.22 (s, 1H), 3.75 (s, 3H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.5 (quat.), 158.8 (quat.), 145.4 (quat.), 142.9 (quat.), 135.5 (quat.), 132.1 (quat.), 128.9 (CH), 128.3 (CH), 127.3 (CH), 127.2 (CH), 126.3 (CH), 125.8 (CH), 124.8 (CH), 119.1 (CH), 114.3 (CH), 71.6 (CH), 58.2 (CH), 55.2 (CH_3), 40.6 (quat.), 28.4 (CH_3); HRMS calcd for $C_{26}H_{28}NO_2$ (M^+ + 1) 386.2120, found 386.2121; CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min) 95:5 er, 12.3 min (major enantiomer), 31.7 min (minor enantiomer).

***N*-Pivaloyl-(*R*)-2-(1-naphtyl)-(*R*)-3-phenylindoline (3d).** A pale yellow oil (87 mg, 43% overall yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.5 (quat.), 145.4 (quat.), 142.9 (quat.), 138.3 (quat.), 134.3 (quat.), 133.6 (quat.), 129.6 (CH), 129.3 (quat.), 129.1 (CH), 128.3 (CH), 128.0 (CH), 127.5 (CH), 127.4 (CH), 126.7 (CH), 125.9 (CH), 125.6 (CH), 125.5 (CH), 124.8 (CH), 122.7 (CH), 119.2 (CH), 68.8 (CH), 56.8 (CH), 40.8 (quat.), 28.4 (CH_3); HRMS calcd for $C_{29}H_{28}NO$ (M^+ + 1) 406.2171, found 406.2170; CSP-HPLC

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(Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min) 95:5 er, 12.8 min (major enantiomer), 14.7 min (minor enantiomer).

***N*-Pivaloyl-(*R*)-3-phenyl-(*S*)-2-styrylindoline (3f).** A colorless oil (130 mg, 68% overall yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28 (d, J = 8.0 Hz, 1H), 7.28−7.01 (m, 14H), 6.47 (d, J = 16.0 Hz, 1H), 6.34 (dd, J = 5.2 and 16.0 Hz, 1H), 5.19 (d, J = 5.2 Hz, 1H), 4.21 (s, 1H), 1.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.2 (quat.), 144.6 (quat.), 142.3 (quat.), 136.2 (quat.), 132.6 (quat.), 130.3 (CH), 129.8 (CH), 128.8 (CH), 128.6 (CH), 128.2 (CH), 127.9 (CH), 127.3 (CH), 127.2 (CH), 126.5 (CH), 125.6 (CH), 124.6 (CH), 119.7 (CH), 70.1 (CH), 55.1 (CH), 40.6 (quat.), 28.6 (CH_3); HRMS calcd for $C_{27}H_{28}NO$ (M^+ + 1) 382.2171, found 382.2171; CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min) 97:3 er, 11.1 min (major enantiomer), 12.9 min (minor enantiomer).

***N*-Pivaloyl-(*R*)-3-phenyl-(*S*)-2-(*β*-phenylstyryl)indoline (3g).** A pale yellow oil (110 mg, 48% overall yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28 (d, J = 8.0 Hz, 1H), 7.34−7.13 (m, 16H), 6.68 (m, 2H), 6.16 (d, J = 8.0 Hz, 1H), 5.11 (d, J = 8.0 Hz, 1H), 4.25 (s, 1H), 0.99 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.2 (quat.), 143.9 (quat.), 142.7 (quat.), 141.3 (quat.), 138.9 (quat.), 134.2 (quat.), 131.0 (CH), 129.7 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.5 (CH), 127.2 (CH), 127.0 (CH), 125.2 (CH), 124.6 (CH), 120.6 (CH), 70.1 (CH), 55.1 (CH), 40.6 (quat.), 28.5 (CH_3); HRMS calcd for $C_{33}H_{32}NO$ (M^+ + 1) 458.2484, found 458.2484; CSP-HPLC (Chiralpak AD-H column; 1% 2-propanol in hexane; 0.5 mL/min) 95:5 er, 48.9 min (major enantiomer), 42.9 min (minor enantiomer).

***N*-Pivaloyl-(*R*)-2-(*α*-methylstyryl)-(*R*)-3-phenylindoline (3h).** A yellow oil (107 mg, 54% overall yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30 (d, J = 8.0 Hz, 1H), 7.30−7.04 (m, 13H), 6.31 (s, 1H), 4.93 (s, 1H), 4.25 (s, 1H), 2.05 (s, 3H), 1.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.4 (quat.), 145.4 (quat.), 143.3 (quat.), 137.1 (quat.), 136.5 (quat.), 132.6 (quat.), 128.9 (CH), 128.2 (CH), 128.1 (CH), 127.2 (CH), 127.1 (CH), 126.6 (CH), 125.6 (CH), 125.1 (CH), 124.5 (CH), 119.0 (CH), 74.5 (CH), 53.8 (CH), 40.8 (quat.), 28.3 (CH_3), 15.8 (CH_3); HRMS calcd for $C_{28}H_{30}NO$ (M^+ + 1) 396.2327, found 396.2326; CSP-HPLC (Chiralpak AD-H column; 1% 2-propanol in hexane; 0.5 mL/min) 95:5 er, 29.1 min (major enantiomer), 32.1 min (minor enantiomer).

***N*-Pivaloyl-(*R*)-2-(*α*-bromostyryl)-(*R*)-3-phenylindoline (3i).** A pale yellow oil (147 mg, 64% overall yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30 (d, J = 8.0 Hz, 1H), 7.43−7.10 (m, 13H), 6.78 (s, 1H), 5.20 (s, 1H), 4.63 (s, 1H), 1.15 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.2 (quat.), 144.9 (quat.), 142.1 (quat.), 134.7 (quat.), 131.5 (quat.), 129.0 (CH), 128.8 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 126.1 (quat.), 126.0 (CH), 125.0 (CH), 118.9 (CH), 75.8 (CH), 53.5 (CH), 40.8 (quat.), 28.1 (CH_3); HRMS calcd for $C_{27}H_{27}BrNO$ (M^+ + 1) 460.1276, found 460.1277; CSP-HPLC (Chiralpak AD-H column; 1% 2-propanol in hexane; 0.5 mL/min) 97:3 er, 19.1 min (major enantiomer), 21.3 min (minor enantiomer).

***N*-Pivaloyl-5-chloro-(*R*)-3-phenyl-(*S*)-2-styrylindoline (3j).** A pale yellow oil (143 mg, 69% overall yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, J = 8.8 Hz, 1H), 7.29−7.00 (m, 13H), 6.44 (d, J = 16.0 Hz, 1H), 6.33 (dd, J = 5.2 and 16.0 Hz, 1H), 5.19 (d, J = 5.2 Hz, 1H), 4.17 (s, 1H), 1.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.2 (quat.), 143.3 (quat.), 141.5 (quat.), 135.9 (quat.), 134.6 (quat.), 130.5 (CH), 129.4 (quat.), 129.3 (CH), 128.9 (CH), 128.6 (CH), 128.2 (CH), 128.0 (CH), 127.6 (CH), 127.1 (CH), 126.5 (CH), 125.7 (CH), 120.6 (CH), 70.2 (CH), 54.9 (CH), 40.6 (quat.), 28.4 (CH_3); HRMS calcd for $C_{27}H_{27}ClNO$ (M^+ + 1) 416.1781, found 416.1779; CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min) 96:4 er, 13.6 min (major enantiomer), 20.5 min (minor enantiomer).

***N*-Pivaloyl-5-chloro-(*R*)-2-(*p*-chlorophenyl)-(*R*)-3-phenylindoline (3k).** A pale yellow oil (150 mg, 71% overall yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (d, J = 8.0 Hz, 1H), 7.34−7.01 (m, 11H), 5.58 (s, 1H), 4.16 (s, 1H), 1.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.4 (quat.), 143.8 (quat.), 141.8 (quat.), 141.5 (quat.), 133.6 (quat.), 133.5 (quat.), 129.8 (quat.), 129.3 (CH), 129.1 (CH), 128.6 (CH), 127.8 (CH), 127.0 (CH), 126.5 (CH), 125.9 (CH), 120.1 (CH), 71.6 (CH), 57.9 (CH), 40.6 (quat.), 28.3 (CH_3); HRMS calcd for $C_{25}H_{24}Cl_2NO$ (M^+ + 1) 424.1235, found 424.1236; CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min) 95:5 er, 10.7 min (major enantiomer), 12.3 min (minor enantiomer).

***N*-Pivaloyl-(*R*)-3-(*p*-bromophenyl)-(*S*)-2-styrylindoline (3l).** A pale yellow oil (170 mg, 74% overall yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28 (d, J = 8.0 Hz, 1H), 7.32−6.88 (m, 13H), 6.46 (d, J = 16.0 Hz, 1H), 6.31 (dd, J = 5.2 and 16.0 Hz, 1H), 5.15 (d, J = 5.2 Hz, 1H), 4.16 (s, 1H), 1.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.3 (quat.), 144.6 (quat.), 141.3 (quat.), 136.1 (quat.), 132.2 (quat.), 131.9 (CH), 130.6 (CH), 129.5 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 126.5 (CH), 125.5 (CH), 124.8 (CH), 121.2 (quat.), 119.8 (CH), 69.8 (CH), 54.6 (CH), 40.6 (quat.), 28.5 (CH_3); CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min) 97:3 er, 10.7 min (major enantiomer), 9.5 min (minor enantiomer). Anal. Calcd for $C_{27}H_{26}BrNO$: C, 70.44; H, 5.69; N, 3.04. Found: C, 70.34; H, 5.71; N, 3.13.

***N*-Pivaloyl-(*R*)-3-(*p*-bromophenyl)-(*S*)-2-(*p*-chlorophenyl)-indoline (3m).** A pale yellow oil (162 mg, 69% overall yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (d, J = 8.0 Hz, 1H), 7.44−6.93 (m, 11H), 5.53 (s, 1H), 4.15 (s, 1H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.4 (quat.), 145.0 (quat.), 141.6 (quat.), 141.5 (quat.), 133.4 (quat.), 132.1 (CH), 131.1 (quat.), 129.2 (CH), 128.9 (CH), 128.8 (CH), 126.5 (CH), 125.7 (CH), 125.1 (CH), 121.4 (quat.), 119.3 (CH), 71.2 (CH), 57.5 (CH), 40.6 (quat.), 28.4 (CH_3); HRMS calcd for $C_{25}H_{24}BrClNO$ (M^+ + 1) 470.0709, found 470.0707; CSP-HPLC (Chiralcel OD column; 1% 2-propanol in hexane; 0.5 mL/min) 96:4 er, 22.9 min (major enantiomer), 20.7 min (minor enantiomer).

***N*-Pivaloyl-5-chloro-(*R*)-3-(*o*-fluorophenyl)-(*S*)-2-styrylindoline (3n).** A pale yellow oil (152 mg, 70% overall yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (d, J = 8.8 Hz, 1H), 7.34−7.11 (m, 9H), 6.97 (t, J = 7.6 Hz, 1H), 6.53−6.46 (m, 2H), 6.34 (dd, J = 4.8 and 16.0 Hz, 1H), 5.21 (d, J = 4.4 Hz, 1H), 4.52 (s, 1H), 1.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.2 (quat.), 160.0 (d, quat.), 143.7 (quat.), 135.9 (quat.), 132.7 (quat.), 130.9 (CH), 129.5 (quat.), 129.2 (d, CH), 128.8 (quat.), 128.74 (CH), 128.72 (d, CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 126.6 (CH), 125.9 (CH), 124.5 (d, CH), 120.7 (CH), 115.3 (d, CH), 69.4 (CH), 47.2 (CH), 40.4 (quat.), 28.3 (CH_3); HRMS calcd for $C_{27}H_{26}ClFNO$ (M^+ + 1) 434.1687, found 434.1688; CSP-HPLC (Chiralcel AD-H column; 10% 2-propanol in hexane; 0.5 mL/min) 95:5 er, 13.7 min (major enantiomer), 25.7 min (minor enantiomer).

***N*-Pivaloyl-5-chloro-(*R*)-2-(*p*-chlorophenyl)-(*R*)-3-(*o*-fluorophenyl)indoline (3o).** A pale yellow oil (144 mg, 65% overall yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, J = 8.8 Hz, 1H), 7.38−7.16 (m, 7H), 7.06 (s, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.52 (t, J = 7.6 Hz, 1H), 5.60 (s, 1H), 4.53 (s, 1H), 0.96 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.3 (quat.), 160.1 (d, quat.), 144.1 (quat.), 140.7 (quat.), 133.5 (quat.), 131.7 (quat.), 129.9 (quat.), 129.4 (d, CH), 129.2 (CH), 128.9 (CH), 128.8 (d, CH), 127.7 (quat.), 126.8 (CH), 126.1 (CH), 124.6 (d, CH), 120.3 (CH), 115.5 (d, CH), 70.8 (CH), 50.0 (CH), 40.4 (quat.), 28.0 (CH_3); HRMS calcd for $C_{25}H_{23}Cl_2FNO$ (M^+ + 1) 442.1141, found 442.1140; CSP-HPLC (Chiralcel AD-H column; 10% 2-propanol in hexane; 0.5 mL/min) 96:4 er, 10.2 min (major enantiomer), 28.3 min (minor enantiomer).

General Procedure for the Preparation of 1b−d. A solution of the corresponding 2-aminobenzophenone (1.0 mmol) in ether (5 mL) was added dropwise to a suspension of lithium aluminum hydride (152 mg, 4.0 equiv) in ether (5 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.[10] The filtrate was concentrated, and the residue was treated with pivaloyl chloride (1.2 equiv) and Et_3N (2.5 equiv) for 3 h in methylene chloride. The resulting mixture was dissolved in EtOAc, washed with saturated NH_4Cl, dried with $MgSO_4$, and concentrated in vacuo. Chromatographic separation on silica gel (EtOAc/hexanes solvents) afforded **1b−d** in 67−81% yields.

***N*-Pivaloyl-2-benzyl-4-chloroaniline (1b).** The general procedure was followed with 2-amino-5-chlorobenzophenone to afford **1b**

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(245 mg) in 81% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (d, J = 8.4 Hz, 1H), 7.35−7.12 (m, 7H), 6.98 (br, 1H), 3.97 (s, 2H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.6 (quat.), 137.8 (quat.), 134.9 (quat.), 132.0 (quat.), 130.8 (CH), 129.7 (quat.), 129.2 (CH), 128.2 (CH), 127.6 (CH), 127.2 (CH), 124.6 (CH), 39.5 (quat.), 38.4 (CH_2), 27.3 (CH_3). Anal. Calcd for $C_{18}H_{20}ClNO$: C, 71.63; H, 6.68; N, 4.64. Found: C, 71.65; H, 6.77; N, 4.77.

***N*-Pivaloyl-2-(*p*-bromobenzyl)aniline (1c).** The general procedure was followed with 2-amino-4′-bromobenzophenone to afford **1c** (266 mg) in 77% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, J = 8.4 Hz, 1H), 7.32−6.99 (m, 8H), 3.94 (s, 2H), 1.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.5 (quat.), 137.9 (quat.), 136.0 (quat.), 132.0 (CH), 131.0 (CH), 130.4 (quat.), 130.0 (CH), 127.9 (CH), 125.2 (CH), 124.0 (CH), 120.6 (quat.), 39.5 (quat.), 37.8 (CH_2), 27.4 (CH_3). Anal. Calcd for $C_{18}H_{20}BrNO$: C, 62.44; H, 5.82; N, 4.05. Found: C, 62.50; H, 5.97; N, 4.20.

***N*-Pivaloyl-4-chloro-2-(*o*-fluorobenzyl)aniline (1d).** The general procedure was followed with 2-amino-5-chloro-2′-fluorobenzophenone to afford **1d** (214 mg) in 67% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (d, J = 8.4 Hz, 1H), 7.27−6.97 (m, 7H), 3.94 (s, 2H), 1.15 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.7 (quat.), 160.6 (d, quat.), 134.4 (quat.), 131.9 (quat.), 130.5 (CH), 130.2 (quat.), 130.0 (d, CH), 128.9 (d, CH), 127.7 (CH), 125.3 (CH), 125.0 (d, quat.), 124.8 (d, CH), 115.5 (d, CH), 39.6 (quat.), 30.4 (CH_2), 27.3 (CH_3). Anal. Calcd for $C_{18}H_{19}ClFNO$: C, 67.60; H, 5.99; N, 4.38. Found: C, 67.60; H, 5.94; N, 4.53.

■ ASSOCIATED CONTENT

Supporting Information

The NMR and/or HPLC data of compounds **1b−d** and **3a−o** and the X-ray crystal structure and CIF file of **3l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) The absolute and relative configurations of 3-(4-bromophenyl)-substituted **3l** were confirmed by X-ray crystallographic analysis. Since indoline **3l** exhibits *S*-configuration at the 2-position and *R*-configuration at the 3-position, we assume the same stereochemical outcome for all indolines **3a−o** that were obtained as exclusive products. Also, the trans-relationship of two substituents of **3a−o** is assigned by NMR spectroscopy, which shows no coupling between C2−C3 hydrogens.[7c,8]

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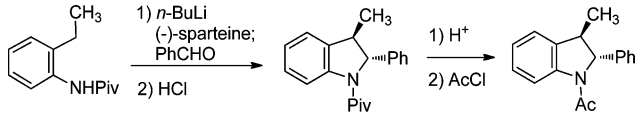

81:19 er

(9) In our investigation with ketone electrophiles, the reaction of **1a** with benzophenone produced 2-(1′,2′,2′-triphenyl-2′-hydroxyethyl)-*N*-pivaloylaniline with 96:4 er. The subsequent acid-catalyzed cyclization, however, gave only elimination product. Also, the electrophilic substitution of **1a** with chalcone under the same reaction condition gave mainly 1,4-addition products with 70:30 dr and 98:2 er for both isomers.

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