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# Enantio- and Diastereoselective Synthesis of Spiro-epoxyoxindoles

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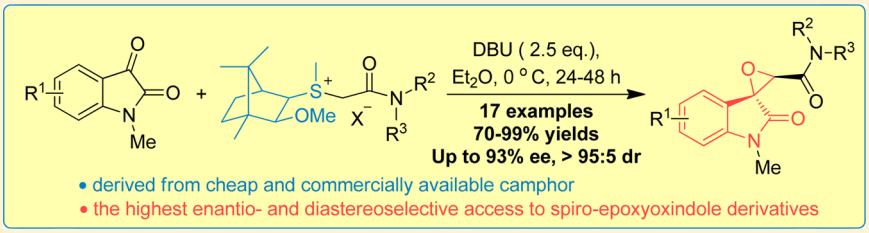
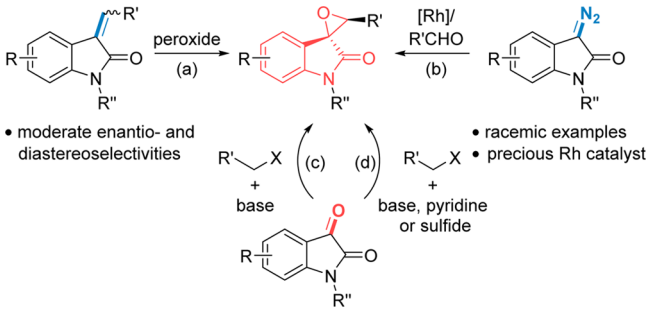
Supporting Information



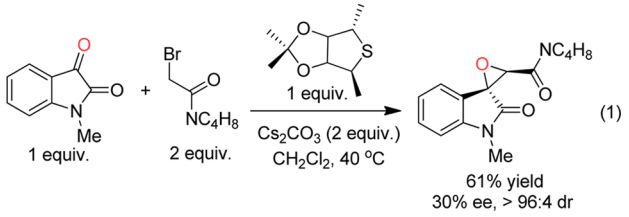

**ABSTRACT:** An asymmetric synthesis of epoxyoxindoles from isatins has been developed by employing chiral sulfur ylides generated in situ from camphor-derived sulfonium salts. This reaction allows an efficient access to enantioenriched spiro-epoxyoxindoles under mild reaction conditions, featuring high yields and excellent enantio- and diastereoselectivities.

Spirooxindole derivatives are widely found in natural products and synthetic therapeutic agents,[1] among which spiro-epoxyoxindoles and related 3-hydroxyoxindoles are particularly useful.[2] Not surprisingly, this "privileged" spiro skeleton has become an important target for synthetic efforts. Many elegant synthetic methods for their preparation (Scheme 1) have been developed, generally including: (a) selective

**Scheme 1. Synthetic Routes toward Spiro-epoxyoxindoles**




epoxidation of $\alpha$-ylideneoxindoles with peroxides (i.e., $H_2O_2$, *t*-$BuO_2H$ and *m*-CPBA);[3] (b) precious metal-catalyzed addition reaction of diazo oxindoles to aromatic aldehydes;[4] (c) Darzens-type reaction of isatins with halogenated carbonyls in the presence of bases;[5] and (d) epoxidation of isatins with reactive sulfur ylides.[6] Despite these advances, efficient approaches to construct chiral spiro-epoxyoxindole skeleton in a high enantio- and diastereoselective fashion are still rare. For instance, in 2007, a highly diastereoselective epoxide synthesis from isatins was disclosed by Metzner and Brière.[6b] In their elegant publication, only one enantioselective variant was included by using a stoichiometric C2 symmetric chiral sulfide, affording the corresponding epoxyoxindole in 30% ee (eq 1).




Another seminal contribution was made by the Gasperi group in 2011,[3e] in which (*S*)-$\alpha$,$\alpha$-diphenylprolinol was employed to promote the nucleophilic epoxidation of $\alpha$-ylideneoxindoles, giving epoxyoxindoles with moderate to good stereoselectivities. Therefore, it is still of great interest to develop more efficient and enantioselective methods for the construction of enantioenriched and structurally diverse spiro-epoxyoxindoles.

On the other hand, camphor has been established as a privileged chiral controlling element for its cheap commercial source and wide applications in a range of asymmetric transformations.[7−9] In particular, camphor-derived chiral sulfur ylides have proven to be powerful reagents in asymmetric cyclization reactions.[8,9] For example, Dai and co-workers have developed an asymmetric epoxide formation from aldehydes[9h] with camphor-derived chiral sulfonium salts (i.e., **2a**′) in the presence of bases, to afford the corresponding epoxides in good yields with moderate enantiomeric excesses. In their work, the hydroxyl group of the chiral auxiliary was proposed to be

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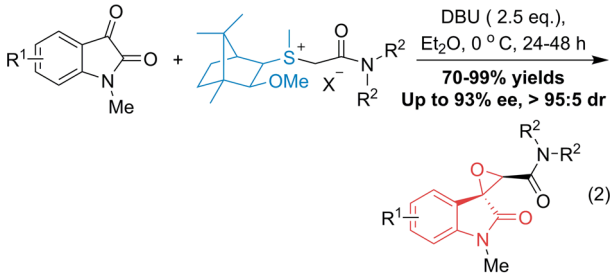
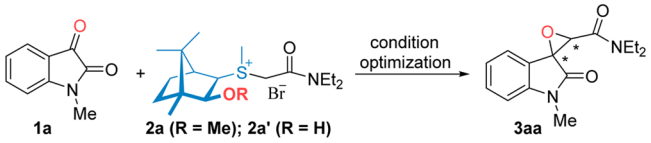
important for directing the attack of amide-stabilized sulfur ylides to aldehydes by H-bonding interaction.[9c] However, Aggarwal et al. have found that the protection of the hydroxyl group in the camphor-derived auxiliary as a methyl ether (i.e., **2a**) gave rise to significantly improved enantioselectivities.[9d,g] Recently, the Tang group[9j] and our group[10f] also demonstrated that camphor-derived, chiral sulfonium salts **2a** can be successfully applied as auxiliaries to the annulation reaction between unsaturated ketones and salicylaldehyde-derived imines, providing the corresponding furans and 2,3-dihydrobenzofurans with high stereoselectivity. As part of our continuing efforts toward the synthesis of molecules with complex carbo- and heterocyclic structures,[10] we recently extended the utility of such a stereocontrolling unit to asymmetric spiroepoxide synthesis from isatins (eq 2). While




derived from simple oxindoles, the resultant amide-substituted epoxyoxindoles are of great potential for the preparation of benzoyl-substituted epoxyoxindoles, which have showed promising antifungal and antitubercular activities.[11]

Initially, stereochemically pure sulfonium salt **2a** was prepared conveniently from readily available camphor and 2-bromo-*N*,*N*-diethylacetamide.[9d,f] To our delight, the reaction of this chiral sulfonium salt with *N*-methyl isatin **1a** did indeed provide the desired spiro-epoxyoxindole **3aa** in good yield and high stereoselectivity (92% yield, 74% ee, and >95:5 dr) in the presence of 1,1,3,3-tetramethylguanidine (TMG) as the base (Table1, entry 1). Encouraged by this result, condition optimization was performed to further improve the reaction efficiency and enantioselectivity. As highlighted in Table 1, the reaction medium played an important role in the reaction efficiency (Table 1, entries 1−6), and spiro-epoxyoxindole products were obtained in excellent yields and high enantioselectivities in less polar solvents such as $Et_2O$ or toluene (Table 1, entries 5 and 6). Variation of the concentration of the substrate or the amount of TMG base (Table 1, entries 7 and 8) did not significantly affect the reaction. In addition, the evaluation of other bases (Table 1, entries 5, 8−11) disclosed that, except for KOH, the base employed in this transformation has no dramatic effect on the stereoselectivities of the reaction. It was found that the chiral spiro-epoxyoxindole product **3aa** was afforded in excellent results (Table 1, entry 12: 99% yield, 93% ee, and >95:5 dr), when the reaction was performed at 0 °C in the presence of 2.5 equiv of DBU.[12] Note that the enantioselectivity of the reaction was only slightly decreased (Table 1, entry 14: 88% yield, 88% ee, and >95:5 dr), when free hydroxyl-containing chiral sulfide was utilized as the chiral control element. This result implied that hydrogen bonding interaction did not have any crucial

**Table 1. Optimization of Reaction Conditions for Asymmetric Epoxidation of Camphor-Derived Sulfonium Salt 2a with Isatin 1a**[a]



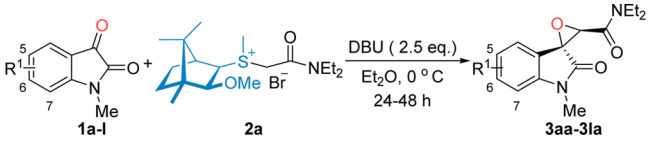

| entry | solvent | base | yield [%][b] | dr[c] | ee [%][d] |
|---|---|---|---|---|---|
| 1 | $CH_3CN$ | TMG | 92 | >95:5 | 74 |
| 2 | MeOH | TMG | 43 | >95:5 | 78 |
| 3 | $CH_2Cl_2$ | TMG | 92 | >95:5 | 85 |
| 4 | THF | TMG | 95 | >95:5 | 90 |
| 5 | $Et_2O$ | TMG | 99 | >95:5 | 91 |
| 6 | toluene | TMG | 99 | >95:5 | 89 |
| 7[e] | $Et_2O$ | TMG | 99 | >95:5 | 90 |
| 8[f] | $Et_2O$ | TMG | 89 | >95:5 | 90 |
| 9 | $Et_2O$ | KOH | 78 | >95:5 | 90 |
| 10 | $Et_2O$ | $Cs_2CO_3$ | 98 | >95:5 | 90 |
| 11 | $Et_2O$ | DBU | 99 | >95:5 | 90 |
| 12[g] | $Et_2O$ | DBU | 99 | >95:5 | 93 |
| 13[g] | $Et_2O$ | TMG | 99 | >95:5 | 90 |
| 14[g,h] | $Et_2O$ | DBU | 88 | >95:5 | 88 |

[a]Unless noted, reactions were performed with **1a** (0.15 mmol), **2a** (0.18 mmol), and 2.5 equiv of base in 3 mL of solvent at room temperature for 24 h. [b]Isolated yield. [c]Estimated by the $^1H$ NMR of crude product. [d]Determined by chiral HPLC analysis. [e]Conducted in 6 mL of solvent. [f]Using 1.5 equiv of base. [g]Conducted at 0 °C for 48 h. [h]Replace **2a** with **2a'**. TMG = 1,1,3,3-tetramethylguanidine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

effect on this reaction, which was in accordance with Aggarwal's observation.[9c]

With the optimized conditions in hand, we examined the scope of the *N*-methyl isatin component coupling partner in this asymmetric epoxidation reaction (Table 2). To our delight,

**Table 2. Synthesis of Spiro-epoxyoxindole from Various Substituted *N*-Methyl Isatins**[a]




| entry | substrate: $R^1$ | product | yield[b] [%] | dr[c] | ee[d] [%] |
|---|---|---|---|---|---|
| 1 | **1a** H | **3aa** | 99 | >95:5 | 93 |
| 2 | **1b** 5-OMe | **3ba** | 70 | >95:5 | 90 |
| 3 | **1c** 5-Me | **3ca** | 94 | >95:5 | 93 |
| 4 | **1d** 5-F | **3da** | 87 | >95:5 | 92 |
| 5 | **1e** 5-Cl | **3ea** | 98 | >95:5 | 92 |
| 6 | **1f** 5-$NO_2$ | **3fa** | 85 | >95:5 | 88 |
| 7 | **1g** 6-Cl | **3ga** | 91 | >95:5 | 92 |
| 8 | **1h** 6-Br | **3ha** | 75 | >95:5 | 88 |
| 9 | **1i** 7-F | **3ia** | 96 | >95:5 | 92 |
| 10 | **1j** 7-Cl | **3ja** | 96 | >95:5 | 92 |
| 11 | **1k** 7-Br | **3ka** | 92 | >95:5 | 92 |
| 12 | **1l** 7-$CF_3$ | **3la** | 70 | >95:5 | 93 |

[a]Unless noted, reactions were performed with **1a−l** (0.15 mmol), **2a** (0.18 mmol) in $Et_2O$ in the presence of 2.5 equiv of DBU at 0 °C for 48 h. [b]Isolated yield. [c]Determined by $^1H$ NMR methods. [d]Determined by HPLC analysis.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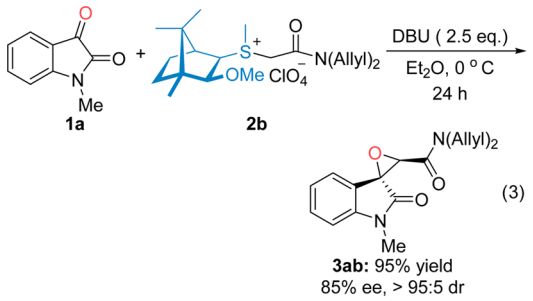
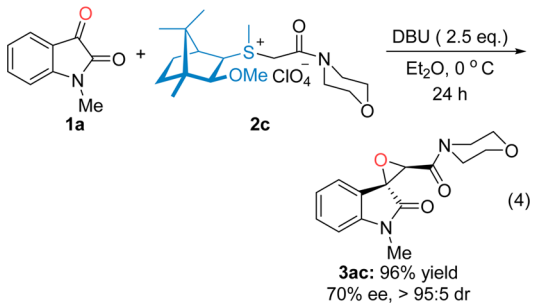
a broad range of substituents on the 5-position of isatins, including electron-donating groups (such as methoxyl and methyl) and electron-withdrawing groups (such as chloro, fluoro, and nitro), were found to be accommodated, providing the corresponding spiro-epoxyoxindoles in good to high yields and excellent stereoselectivities (Table 2, entries 2−6: 70−98% yields, 88−93% ee, and >95:5 dr). Moreover, variation of steric properties was also readily exploited on the benzene ring (Table 2, entries 4 and 9; entries 5, 7, and 10; entries 8 and 11). Notably, halogen-substituted substrates, such as chloro-substituted **1e**, **1g**, and **1j**, and bromo-substituted **1h** and **1k**, are well tolerated in this asymmetric transformation, allowing further modification of the structures. Since incorporation of fluorine sometimes dramatically alters their pharmaceutical properties, we also used fluorine-containing isatins **1d**, **1i**, and **1l** as substrates, affording the products with high diastereo- and enantioselectivity in high yields (Table 2).

To introduce diverse amide functionalities, some other tertiary amide derived chiral sulfonium salts were also examined under the optimal reaction conditions. In particular, acyclic amide derived substrate **2b** and cyclic amide derived substrate **2c** were successfully applied to this process, and the desired spiro-epoxyoxindoles were obtained with excellent yields and diastereoselectivities (eq 3, **3ab**: 95% yield, 85% ee, >95:5 dr; eq 4, **3ac**: 96% yield, 70% ee, >95:5 dr). However, the enantiomeric excess was found to decrease to 85% and 70%, when **2b** and **2c** were employed as the substrate, respectively. This was probably due to the variation of steric hindrance in the course of the reaction. In addition, a manipulation of **3ab** can be carried out through ring-closing metathesis according to our previous procedure,[13] providing the corresponding pyrrolidine derivative in high yield.



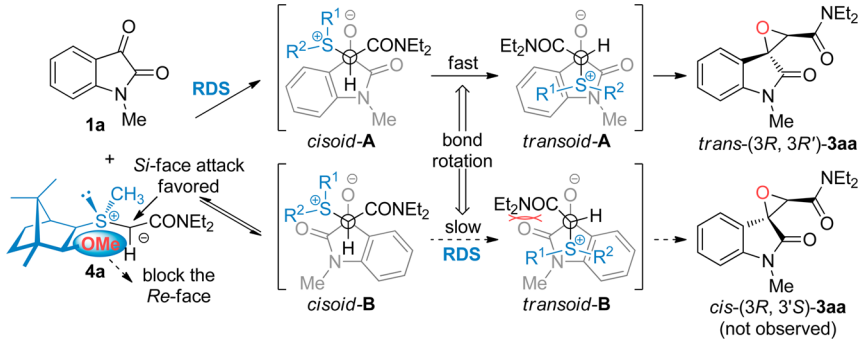

A possible mechanism was also proposed to explain the stereochemistry of the products according to Aggarwal,[9d,f] Metzner, and Brière's works.[6b] With the model reaction of **1a** and **2a** as the example (Scheme 2), oxindole **1a** would approach the amide-stabilized sulfonium ylide **4a** (in situ generated from **2a** in the presence of DBU) from its *Si*-face to form betaine intermediate *cisoid*-**A** or *cisoid*-**B**. A bond rotation of *cisoid*-**A** and *cisoid*-**B** could generate the corresponding transient species *transoid*-**A** or *transoid*-**B**, which underwent an intramolecular $S_N2$ substitution to afford *trans*-(3*R*,3′*R*)-**3aa** or *cis*-(3*R*,3′*S*)-**3aa** products, respectively. Based on Aggarwal's[9d,f] as well as Metzner and Brière's[6b] works on the epoxidation reaction of aldehydes with amide-stabilized sulfonium ylides, the formation of *cisoid*-**B** was reversible and the subsequent rotation process to *transoid*-**B** was slow due to the steric repulsion between two amide groups. In addition, the rotation process from *cisoid*-**A** to *transoid*-**A** might be faster, which favorably resulted in the formation of *trans*-(3*R*,3′*R*)-**3aa**). Importantly, the absolute configuration of **3ka** established by single crystal X-ray diffraction analysis is in accordance with the proposed transition-state model (see Supporting Information).

In summary, we have developed an efficient process to prepare enantioenriched and synthetically important spiro-epoxyoxindoles. The reaction of isatins and camphor-derived sulfur ylides exhibits remarkably high stereoselectivities (70−99% yields, up to 93% ee, >95:5 dr). Moreover, the reaction itself features a cheap and readily available chiral source as well as mild reaction conditions. Further biological activity evaluation of the products is currently underway in our laboratory.

## EXPERIMENTAL SECTION

**General Methods.** Reactions were monitored by thin layer chromatography (TLC), and column chromatography purifications were performed using 200−300 mesh silica gel. $^1$H NMR spectra were recorded on 400 or 600 MHz spectrometers. The solvent for NMR was $CDCl_3$. Chemical shifts were reported on the delta ($\delta$) scale in parts per million (ppm) relative to the singlet (0 ppm) for tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s = single, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets), coupling constants (Hz), and integration; $^{13}$C

**Scheme 2. Proposed Stereocontrol Model for the Asymmetric Epoxidation of Isatins**





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NMR spectra were recorded at 100/150 MHz with complete proton decoupling. Chemical shifts are reported in ppm relative to the central line of the triplet at 77.0 ppm for $CDCl_3$. Mass spectra ($m/z$) data were measured on an MS spectrometer (EI). Melting points (mp) were determined on an electrothermal melting point apparatus. HRMS analyses were performed using a TOF mass analyzer. Enantiomeric ratios were determined by chiral HPLC with different chiral columns (chiralpak OD-H column, chiralpak AD-H column) with hexane and *i*-PrOH as solvents. Optical rotations were measured with a polarimeter.

**Materials.** Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. All the solvents were treated according to general methods. *N*-Methyl isatins **1a−l** were prepared according to literature procedures from commercially available isatins using a methyl protection reaction.[14] Sulfonium salts **2a−c**, **2a′** were prepared as described in the literature from optically active Camphor,[9d,g] which was commercially available and used as received.

**Typical Procedure for the Synthesis of Compound 3.** To a 10 mL Schlenk tube equipped with a magnetic stir bar was added *N*-methyl isatin **1** (0.15 mmol), and camphor-derived sulfonium salts 2 (0.18 mmol, 1.2 equiv) in dry $Et_2O$ (3.0 mL). This resulting solution was stirred at 0 °C for 0.5 h, then DBU (0.375 mmol, 2.5 equiv) was introduced directly and stirring continued at the same temperature. Upon completion of the reaction monitored by TLC, the crude product was separated by flash chromatography on silica gel, eluting with petroleum ether/ethyl acetate (1:1) to provide pure product **3**. The absolute configuration of spiro-epoxyoxindoles **3** were assigned by the X-ray crystallographic analysis of **3ka** according to an analogous enantioinduction. The diastereomer ratio was determined by $^1$H NMR of the reaction mixture. The enantiomeric excess was determined by chiral HPLC analysis.

*(3R,3′R)-N,N-Diethyl-1-methyl-2-oxospiro[indoline-3,2′-oxirane]-3′-carboxamide (**3aa**).* 48 h, white solid (40.7 mg, 99% yield); mp 101−103 °C; $[\alpha]_D^{19} = -69.7$ ($c$ = 2.0, $CHCl_3$); Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate = 1.0 mL/min; 254 nm, $t_R$ = 7.48 min (major), $t_R$ = 10.15 min (minor), dr > 95:5, 93% ee; **$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ = 7.39 (t, $J$ = 7.8 Hz, 1H), 7.28 (d, $J$ = 7.4 Hz, 1H), 7.04 (t, $J$ = 7.6 Hz, 1H), 6.92 (d, $J$ = 7.9 Hz, 1H), 4.32 (s, 1H), 3.52−3.58 (m, 1H), 3.18−3.34 (m, 3H), 3.30 (s, 3H), 1.11 (t, $J$ = 7.1 Hz, 3H), 1.05 (t, $J$ = 7.1 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 169.9, 162.8, 144.8, 130.6, 123.9, 122.7, 119.4, 108.7, 60.2, 59.4, 40.9, 39.9, 26.5, 13.7, 12.7; MS (EI) $m/z$ 274.16 ($M^+$); HRMS (ESI-TOF) for $C_{15}H_{18}N_2O_3Na$ [M + $Na^+$]: calcd, 297.1215; found, 297.1213.

*(3R,3′R)-N,N-Diethyl-5-methoxy-1-methyl-2-oxospiro[indoline-3,2′-oxirane]-3′-carboxamide (**3ba**).* 48 h, brown solid (32.0 mg, 70% yield); mp 99−101 °C; $[\alpha]_D^{25} = -24.2$ ($c$ = 2.0, $CHCl_3$); Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate = 1.0 mL/min; 254 nm, $t_R$ = 8.14 min (minor), $t_R$ = 9.26 min (major); dr > 95:5, 90% ee; **$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ = 6.92 (d, $J$ = 8.4 Hz, 2H), 6.83 (d, $J$ = 8.1 Hz, 1H), 4.32 (s, 1H), 3.74 (s, 3H), 3.53−3.59 (m, 1H), 3.19−3.35 (m, 3H), 3.27 (s, 3H), 1.12 (t, $J$ = 7.1 Hz, 3H), 1.04 (t, $J$ = 7.1 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 169.8, 162.9, 156.0, 138.3, 120.6, 116.2, 110.3, 109.3, 60.3, 59.8, 55.6, 41.1, 40.2, 26.6, 13.9, 12.9; MS (EI) $m/z$ 304.31 ($M^+$); HRMS (ESI-TOF) for $C_{16}H_{21}N_2O_4$ [M + $H^+$]: calcd, 305.1501; found, 305.1506.

*(3R,3′R)-N,N-Diethyl-1,5-dimethyl-2-oxospiro[indoline-3,2′-oxirane]-3′-carboxamide (**3ca**).* 48 h, white solid (40.7 mg, 94% yield); mp 115−117 °C; $[\alpha]_D^{30} = -45.1$ ($c$ = 2.0, $CHCl_3$); Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate = 1.0 mL/min; 254 nm, $t_R$ = 9.42 min (minor), $t_R$ = 9.97 min (major); dr > 95:5, 93% ee; **$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ = 7.17 (d, $J$ = 8.1 Hz, 1H), 7.08 (s, 1H), 6.79 (d, $J$ = 8.0 Hz, 1H), 4.30 (s, 1H), 3.55−3.61 (m, 1H), 3.18−3.31 (m, 3H), 3.27 (s, 3H), 2.28 (s, 3H), 1.11 (t, $J$ = 7.1 Hz, 3H), 1.05 (t, $J$ = 7.1 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 170.0, 163.1, 142.8, 132.7, 131.0, 124.8, 119.6, 108.5, 60.3, 59.7, 41.1, 40.2, 26.7, 20.8, 13.9, 12.9; MS (EI) $m/z$ 288.18 ($M^+$); HRMS (ESI-TOF) for $C_{16}H_{21}N_2O_3$ [M + $H^+$]: calcd, 289.1552; found, 289.1554.

*(3R,3′R)-N,N-Diethyl-5-fluoro-1-methyl-2-oxospiro[indoline-3,2′-oxirane]-3′-carboxamide (**3da**).* 48 h, yellow solid (38.2 mg, 87% yield); mp 106−108 °C; $[\alpha]_D^{25} = -56$ ($c$ = 2.0, $CHCl_3$); Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate = 1.0 mL/min; 254 nm, $t_R$ = 8.10 min (major), $t_R$ = 8.74 min (minor); dr > 95:5, 92% ee; **$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ = 7.09 (t, $J$ = 9.1 Hz, 2H), 6.86 (dd, $J_1$ = 8.2 Hz, $J_2$ = 3.8 Hz, 1H), 4.34 (s, 1H), 3.52−3.58 (m, 1H), 3.21−3.36 (m, 3H), 3.29 (s, 3H), 1.13 (t, $J$ = 7.1 Hz, 3H), 1.08 (t, $J$ = 7.1 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 169.8, 162.6, 159.0 (d, $J$ = 242 Hz), 141.0, 121.2, 117.12 (d, $J$ = 24 Hz), 112.4 (d, $J$ = 27 Hz), 109.5 (d, $J$ = 8 Hz), 60.3, 59.4, 41.1, 40.3, 26.7, 14.0, 12.8; MS (EI) $m/z$ 292.27 ($M^+$); HRMS (ESI-TOF) for $C_{15}H_{18}FN_2O_3$ [M + $H^+$]: calcd, 293.1301; found, 293.1310.

*(3R,3′R)-5-Chloro-N,N-diethyl-1-methyl-2-oxospiro[indoline-3,2′-oxirane]-3′-carboxamide (**3ea**).* 48 h, yellow solid (45.4 mg, 98% yield); mp 106−108 °C; $[\alpha]_D^{25} = -22.6$ ($c$ = 2.0, $CHCl_3$); Daicel Chirapak OD-H, hexane/isopropanol = 70/30, flow rate = 1.0 mL/min; 254 nm, $t_R$ = 13.45 min (minor), $t_R$ = 15.34 min (major); dr > 95:5, 92% ee; **$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ = 7.36 (dd, $J_1$ = 8.3 Hz, $J_2$ = 2.1 Hz, 1H), 7.25−7.29 (m, 1H), 6.84 (d, $J$ = 8.3 Hz, 1H), 4.32 (s, 1H), 3.54−3.60 (m, 1H), 3.34−3.20 (m, 3H), 3.27 (s, 3H), 1.13 (t, $J$ = 7.1 Hz, 3H), 1.08 (t, $J$ = 7.2 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 169.7, 162.6, 143.6, 130.6, 128.6, 124.6, 121.4, 109.7, 60.4, 59.3, 41.2, 40.4, 26.8, 14.1, 12.9; MS (EI) $m/z$ 308.17 ($M^+$); HRMS (ESI-TOF) for $C_{15}H_{18}ClN_2O_3$ [M + $H^+$]: calcd, 309.1006; found, 309.1011.

*(3R,3′R)-N,N-Diethyl-1-methyl-5-nitro-2-oxospiro[indoline-3,2′-oxirane]-3′-carboxamide (**3fa**).* 48 h, yellow solid (40.7 mg, 85% yield); mp 163−165 °C; $[\alpha]_D^{19}$ =14.3 ($c$ = 2.0, $CHCl_3$); Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate = 1.0 mL/min; 254 nm, $t_R$ = 12.98 min (major), $t_R$ = 23.59 min (minor); dr > 95:5, 88% ee; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 8.36 (dd, $J_1$ = 8.7 Hz, $J_2$ = 2.3 Hz, 1H), 8.10 (d, $J$ = 2.3 Hz, 1H), 7.02 (d, $J$ = 8.7 Hz, 1H), 4.38 (s, 1H), 3.49−3.57 (m, 1H), 3.33−3.44 (m, 3H), 3.37 (s, 3H), 1.17 (q, $J$ = 7.1 Hz, 6H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 170.3, 162.2, 150.4, 143.5, 127.6, 120.8, 120.1, 108.7, 60.6, 59.0, 41.5, 40.6, 27.1, 14.2, 12.8; MS (EI) $m/z$ 319.26 ($M^+$); HRMS (ESI-TOF) for $C_{15}H_{18}N_3O_5$ [M + $H^+$]: calcd, 320.1246; found, 320.1232.

*(3R,3′R)-6-Chloro-N,N-diethyl-1-methyl-2-oxospiro[indoline-3,2′-oxirane]-3′-carboxamide (**3ga**).* 48h, yellow solid (42.2 mg, 91% yield); mp 157−159 °C; $[\alpha]_D^{30} = -74$ ($c$ = 2.0, $CHCl_3$); Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate = 1.0 mL/min; 254 nm, $t_R$ = 7.56 min (major), $t_R$ = 22.90 min (minor); dr > 95:5, 92% ee; **$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ = 7.22 (d, $J$ = 8.0 Hz, 1H), 7.02 (dd, $J_1$ = 8.0 Hz, $J_2$ = 1.7 Hz, 1H), 6.93 (d, $J$ = 1.6 Hz, 1H), 4.32 (s, 1H), 3.51−3.57 (m, 1H), 3.20−3.34 (m, 3H), 3.28 (s, 3H), 1.11 (t, $J$ = 7.1 Hz, 3H), 1.07 (t, $J$ = 7.1 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 170.1, 162.7, 146.2, 136.8, 125.3, 122.9, 118.0, 109.6, 60.3, 59.3, 41.1, 40.3, 26.8, 14.0, 12.9; MS (EI) $m/z$ 308.22 ($M^+$); HRMS (ESI-TOF) for $C_{15}H_{18}ClN_2O_3$ [M + $H^+$]: calcd, 309.1006; found, 309.1008.

*(3R,3′R)-6-Bromo-N,N-diethyl-1-methyl-2-oxospiro[indoline-3,2′-oxirane]-3′-carboxamide (**3ha**).* 48 h, yellow solid (39.8 mg, 75% yield); mp 177−179 °C; $[\alpha]_D^{25} = -46.2$ ($c$ = 2.0, $CHCl_3$); Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate = 1.0 mL/min; 254 nm, $t_R$ = 7.98 min (major), $t_R$ = 20.94 min (minor); dr > 95:5, 88% ee; **$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ = 7.18 (s, 1H), 7.16 (s, 1H), 7.07 (s, 1H), 4.32 (s, 1H), 3.50−3.56 (m, 1H), 3.21−3.34 (m, 3H), 3.27 (s, 3H), 1.11 (t, $J$ = 7.1 Hz, 3H), 1.08 (t, $J$ = 7.1 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 170.0, 162.7, 146.3, 125.9, 125.6, 124.8, 118.6, 112.4, 60.3, 59.4, 41.2, 40.3, 26.8, 14.1, 12.9; MS (EI) $m/z$ 352.11 ($M^+$); HRMS (ESI-TOF) for $C_{15}H_{18}BrN_2O_3$ [M + $H^+$]: calcd, 353.0501; found, 353.0506.

*(3R,3′R)-N,N-Diethyl-7-fluoro-1-methyl-2-oxospiro[indoline-3,2′-oxirane]-3′-carboxamide (**3ia**).* 48 h, white solid (42.1 mg, 96% yield); mp 108−110 °C; $[\alpha]_D^{17} = -93.4$ ($c$ = 2.0, $CHCl_3$); Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate = 1.0 mL/min; 254 nm, $t_R$ = 7.14 min (major), $t_R$ = 11.87 min (minor); dr > 95:5, 92% ee; **$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ = 7.12 (dd, $J_1$ = 11.5 Hz, $J_2$ = 8.5 Hz, 1H), 7.07 (d, $J$ = 7.5 Hz, 1H), 6.96−6.99 (m, 1H), 4.32 (s, 1H), 3.48−3.59 (m, 1H), 3.51 (d, $J$ = 2.8 Hz, 3H), 3.37−3.17 (m, 3H), 1.11 (t, $J$ = 7.1 Hz, 3H), 1.07 (t, $J$ = 7.1 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 169.9, 162.7, 147.8 (d, $J$ = 360 Hz), 131.6 (d, 15


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Hz), 123.8 (d, $J$ = 10 Hz), 122.6, 120,2 (d, $J$ = 5 Hz), 118.9 (d, $J$ = 29 Hz), 60.8, 59.5, 41.2, 40.2, 29.3, 14.0, 12.9; MS (EI) $m/z$ 292.14 ($M^+$); HRMS (ESI-TOF) for $C_{15}H_{18}FN_2O_3$ [M + $H^+$]: calcd, 293.1301; found, 293.1291.

*(3R,3′R)-7-Chloro-N,N-diethyl-1-methyl-2-oxospiro[indoline-3,2′-oxirane]-3′-carboxamide (**3ja**).* 48 h, yellow solid (44.5 mg, 96% yield); mp 98−100 °C; $[\alpha]_D^{30}$ = −86.4 ($c$ = 2.0, $CHCl_3$); Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate = 1.0 mL/min; 210 nm, $t_R$ = 8.10 min (major), $t_R$ = 15.15 min (minor); dr > 95:5, 92% ee; **$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ = 7.30 (dd, $J_1$ = 8.2 Hz, $J_2$ = 1.1 Hz, 1H), 7.17 (dd, $J_1$ = 7.5 Hz, $J_2$ = 1.1 Hz, 1H), 6.95 (t, $J$ = 7.9 Hz, 1H), 4.32 (s, 1H), 3.66 (s, 3H), 3.52−3.58 (m, 1H), 3.19−3.32 (m, 3H), 1.11 (d, $J$ = 7.1 Hz, 3H), 1.08 (t, $J$ = 6.9 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 170.5, 162.6, 140.7, 133.0, 123.7, 122.7, 122.6, 116.2, 61.0, 59.1, 41.1, 40.1, 30.1, 14.0, 12.8; MS (EI) $m/z$ 308.17 ($M^+$); HRMS (ESI-TOF) for $C_{15}H_{18}ClN_2O_3$ [M + $H^+$]: calcd, 309.1006; found, 309.1011.

*(3R,3′R)-7-Bromo-N,N-diethyl-1-methyl-2-oxospiro[indoline-3,2′-oxirane]-3′-carboxamide (**3ka**).* 48 h, yellow solid (48.8 mg, 92% yield); mp 104−106 °C; $[\alpha]_D^{30}$ = −111.9 ($c$ = 2.0, $CHCl_3$); Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate = 1.0 mL/min; 254 nm, $t_R$ = 8.92 min (major), $t_R$ = 17.55 min (minor); dr > 95:5, 92% ee; **$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ = 7.48 (d, $J$ = 8.2 Hz, 1H), 7.21 (d, $J$ = 7.4 Hz, 1H), 6.88 (t, $J$ = 7.8 Hz, 1H), 4.32 (s, 1H), 3.68 (s, 3H), 3.51−3.57 (m, 1H), 3.19−3.33 (m, 3H), 1.10 (t, $J$ = 6.3 Hz, 3H), 1.08 (t, $J$ = 6.3 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 170.7, 162.5, 142.2, 136.3, 124.1, 123.2, 123.1, 102.9, 61.1, 59.0, 41.1, 40.1, 30.3, 14.0, 12.8; MS (EI) $m/z$ 352.09 ($M^+$); HRMS (ESI-TOF) for $C_{15}H_{18}BrN_2O_3$ [M + $H^+$]: calcd, 353.0501; found, 353.0502.

*(3R,3′R)-N,N-Diethyl-1-methyl-2-oxo-7-(trifluoromethyl)spiro-[indoline-3,2′-oxirane]-3′-carboxamide (**3la**).* 48 h, white solid (36.0 mg, 70% yield); mp 85−87 °C; $[\alpha]_D^{25}$ = −63.3 ($c$ = 2.0, $CHCl_3$); Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate = 1.0 mL/min; 254 nm, $t_R$ = 6.44 min (major), $t_R$ = 7.12 min (minor); dr > 95:5, 93% ee; **$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ = 7.68 (d, $J$ = 8.1 Hz, 1H), 7.47 (d, $J$ = 7.4 Hz, 1H), 7.13 (t, $J$ = 7.8 Hz, 1H), 4.36 (s, 1H), 3.52−3.58 (m, 1H), 3.50 (s, 3H), 3.21−3.34 (m, 3H), 1.11 (t, $J$ = 7.3 Hz, 3H), 1.08 (t, $J$ = 7.2 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 171.2, 162.5, 142.9, 128.6 (q, $J$ = 6.1 Hz), 127.6, 123.1 (q, $J$ = 270 Hz), 113.4 (q, $J$ = 33 Hz), 61.3, 58.3, 41.2, 40.2, 29.5 (q, $J$ = 6.3 Hz), 14.0, 12.9; MS (EI) $m/z$ 342.18 ($M^+$); HRMS (ESI-TOF) for $C_{16}H_{18}F_3N_2O_3$ [M + $H^+$]: calcd, 343.1270; found, 343.1277.

*(3R,3′R)-N,N-Diallyl-1-methyl-2-oxospiro[indoline-3,2′-oxirane]-3′-carboxamide (**3ab**).* 24 h, white solid (42.5 mg, 95% yield); mp 105−107 °C; $[\alpha]_D^{19}$ = −45.6 ($c$ = 2.0, $CHCl_3$); Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate = 1.0 mL/min; 254 nm, $t_R$ = 7.62 min (major), $t_R$ = 9.01 min (minor); dr > 95:5, 85% ee; **$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ = 7.40 (t, $J$ = 7.5 Hz, 1H), 7.29 (d, $J$ = 7.4 Hz, 1H), 7.05 (t, $J$ = 7.3 Hz, 1H), 6.91 (d, $J$ = 7.7 Hz, 1H), 5.63−5.71 (m, 1H), 5.51−5.57 (m, 1H), 5.14 (d, $J$ = 10.2 Hz, 1H), 5.02−5.05 (m, 3H), 4.34 (s, 1H), 4.21 (dd, $J_1$ = 15.9 Hz, $J_2$ = 4.8 Hz, 1H), 3.87 (dd, $J_1$ = 15.4 Hz, $J_2$ = 6.5 Hz, 1H), 3.79 (s, 2H), 3.28 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 169.9, 163.9, 145.1, 132.0, 131.7, 130.8, 124.2, 122.9, 119.4, 118.1, 117.4, 108.7, 60.3, 59.7, 48.5, 48.1, 26.6; MS (EI) $m/z$ 298.31 ($M^+$); HRMS (ESI-TOF) for $C_{17}H_{19}N_2O_3$ [M + $H^+$]: calcd, 299.1396; found, 299.1379.

*(3R,3′R)-1-Methyl-3′-(morpholine-4-carbonyl)spiro[indoline-3,2′-oxiran]-2-one (**3ac**).* Twenty-four h, white solid (41.5 mg, 96% yield); mp 164−165 °C; $[\alpha]_D^{20}$ = −55.4 ($c$ = 2.0, $CHCl_3$); Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate = 1.0 mL/min; 254 nm, $t_R$ = 10.63 min (major), $t_R$ = 21.84 min (minor); d.r. > 95:5, 70% ee; **$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ = 7.42 (t, $J$ = 7.8 Hz, 1H), 7.17 (d, $J$ = 7.3 Hz, 1H), 7.08 (t, $J$ = 7.6 Hz, 1H), 6.94 (d, $J$ = 7.9 Hz, 1H), 4.34 (s, 1H), 3.78−3.83 (m, 1H), 3.68−3.74 (m, 1H), 3.60−3.63 (m, 1H), 3.49−3.55 (m, 3H), 3.29 (s, 3H), 3.25−3.28 (m, 1H), 3.13−3.17 (m, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 169.6, 162.4, 144.9, 130.9, 123.5, 122.9, 119.1, 108.9, 66.3, 66.0, 60.0, 59.5, 44.9, 41.8, 26.5; MS (EI) $m/z$ 288.31 ($M^+$); HRMS (ESI-TOF) for $C_{15}H_{17}N_2O_4$ [M + $H^+$]: calcd, 289.1188; found, 289.1183.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Details for condition optimization, HPLC data for chiral products, X-ray crystal structure of compound (3*R*,3′*R*)-**3ka**, and $^1$H and $^{13}$C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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