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Chiral Phosphoric Acid-Catalyzed Pictet–Spengler Reactions for Synthesis of 5′,11′-Dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-ones Containing Quaternary Stereocenters

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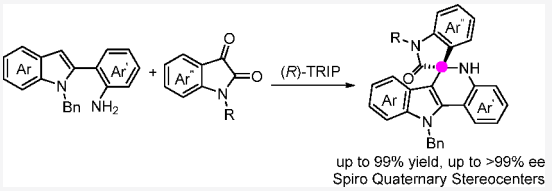
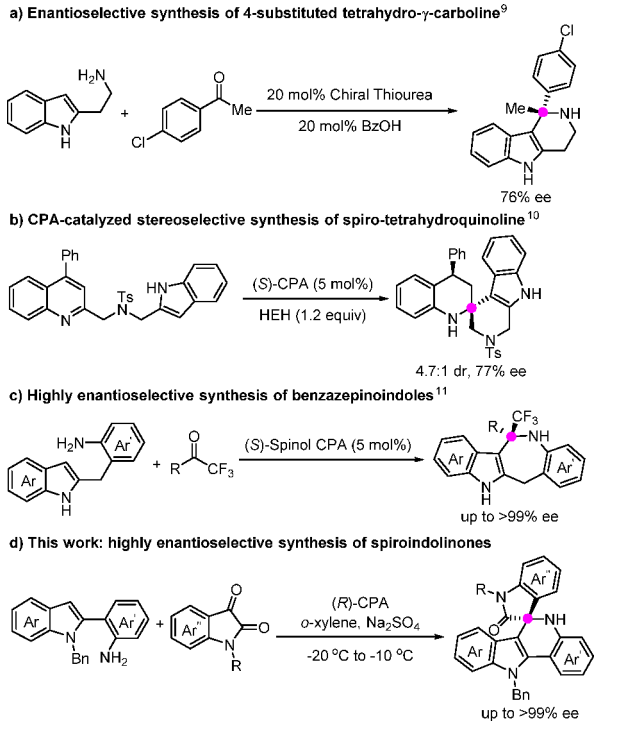
ABSTRACT: Chiral phosphoric acid-catalyzed Pictet–Spengler reactions of 2-(1*H*-indolyl)aniline derivatives and isatins by the condensation/cyclization process have been realized. A series of enantioenriched 5′,11′-dihydrospiro-[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-ones bearing quaternary stereogenic centers were obtained with excellent yields and up to >99% ee. This protocol was suitable for the Pictet–Spengler reactions of 2-(1-benzyl-5-methyl-1*H*-pyrrol-2-yl)aniline, and a variety of 1′,5′-dihydro-spiro[indoline-3,4′-pyrrolo-[3,2-*c*]quinolin]-2-ones could also be obtained in good yields and up to 88% ee.



Indole alkaloids have received considerable attention for their fascinating architecture and a wide spectrum of biological activity.[1] The Pictet–Spengler reactions provided an efficient and straightforward access to these enantioenriched compounds. In 2004, Jacobsen and co-workers reported the first enantioselective catalytic Pictet–Spengler reactions of *N*-acyliminium ions using chiral thiourea catalyst.[2] An elegant chiral phosphoric acid-catalyzed transformation of tryptamines and aldehydes was developed by List's group.[3] In the following decades, the highly enantioselective Pictet–Spengler reactions of tryptamine derivatives to form tetrahydro-γ-carboline cores have been realized by different groups.[4,5] In these research studies, C-2 functionalized adducts of indoles were obtained. Another two independent reports of highly enantioselective Pictet–Spengler reactions with C-2 selectivity of indoles were carried out using 2-(1*H*-indol-1-yl)ethanamine[6] or 2-(1*H*-indol-1-yl)anilines.[7]

Compared to the Pictet–Spengler reactions with C-2 selectivity of indoles, catalytic C-3 functionalization of indoles by cyclizations was relatively less studied. Tian and co-workers developed enantioselective Pictet–Spengler-type reactions by replacing the aldehydes with imines employing 4-(2-aminoaryl)indoles for the first construction of seven-membered ring systems.[8] Jacobsen and co-workers described an enantioselective synthesis of 4-substituted tetrahydro-γ-carbolines through the one-pot condensation/cyclization of 2-substituted indolylethylamines and aldehydes.[9] Ketones were also successfully applied to the protocol, and the tetrahydro-γ-carboline bearing a quaternary stereogenic center could be obtained (Scheme 1a). An efficient chiral phosphoric acid-catalyzed stereoselective synthesis of spiro-tetrahydroquinoline through cascade hydrogenative dearomatization of quinolines and Pictet–Spengler reaction in moderate yield, diastereoselectivity and enantioselectivity was realized by You and co-

Scheme 1. Catalytic C-3 Functionalization of Indoles by Pictet–Spengler Reactions for Construction of Quaternary Stereocenters



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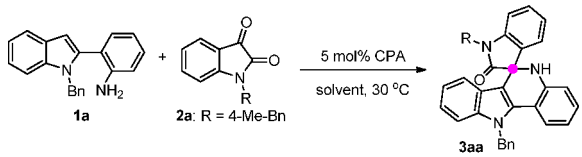
workers (Scheme 1b).[10] The first highly enantioselective iso-Pictet−Spengler reaction of *o*-aminobenzyl indoles and trifluoromethyl ketones for synthesis of benzazepinoindoles bearing trifluoromethylated quaternary stereocenters was developed by Lin and co-workers using chiral spirocyclic phosphoric acid as catalyst (Scheme 1c).[11]

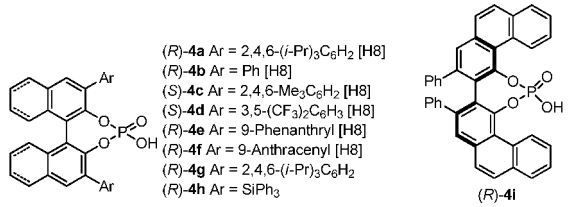
Very recently, we reported the chiral phosphoric acid-catalyzed regioselective synthesis of spiro aminals bearing quaternary stereocenters.[12a] In this research, the C3-alkylation product bearing a quaternary stereogenic center was isolated as a side-product with 28% ee. Considering that the C-3 functionalization of indoles via the catalytic highly enantioselective Pictet−Spengler reaction to form a quaternary stereocenter (especially for a spiro quaternary stereocenter) was less reported,[11] we have interest in investigating the transformation between 2-(1*H*-indolyl)aniline derivatives and isatins to achieve indole C-3 alkylation products bearing spiro quaternary stereocenters.[12b,c] In this Note, we report chiral phosphoric acid-catalyzed Pictet−Spengler reactions between 2-(1*H*-indolyl)aniline derivatives and isatins for synthesis of enantioenriched 5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-ones bearing quaternary stereogenic centers with excellent yields and up to >99% ee (Scheme 1d).

As the *N*-H of indole usually plays a crucial rule in controlling the activity and enantioselectivity,[4a,d,8,11] we first evaluated the influence of *N*-H. To our delight, when 2-(1-benzyl-1*H*-indol-2-yl)aniline **1a** was tested under our previous optimal conditions,[12] the enantioselectivity was significantly increased to 50%. Therefore, 2-(1-benzyl-1*H*-indol-2-yl)aniline **1a** and isatin **2a** were chosen as model substrates for further explorations. In the absence of 50 mg of 5 Å MS, the reaction proceeded smoothly, affording the desired product with 55% ee after slightly prolonged reaction time (Table 1, entry 2). Then various solvents were screened (Table1, entries 2−8). Among these tested solvents, toluene gave the best reactivity and enantioselectivity. The aromatic solvents including benzene, trifluorotoluene, chlorobenzene, xylene, and mesitylene were further investigated, and *o*-xylene gave a slightly better result (Table 1, entries 9−15). Subsequently, chiral phosphoric acids with diverse aromatic groups at 3,3′-positions were explored using *o*-xylene as reaction media (Table 1, entries 16−20). However, no catalyst was more superior to (*R*)-**4a**. Further screening of BINOL and VAPOL-derived phosphoric acids showed that (*R*)-**4g** was the optimal catalyst (Table 1, entries 21−23). Gratifying, the ee value of **3aa** could be improved to 80% by lowering the reaction temperature to 0 °C and prolonging the reaction time (Table 1, entry 24). When the temperature was further lowered to −20 °C, the desired product could be obtained with 83% yield and 86% ee (Table 1, entry 25). When the reaction was performed in the presence of 50 mg of sodium sulfate as dehydrating reagent, the yield was increased to 86% without the loss of enantioselectivity (Table 1, entry 26). Increasing the ratio of **2a** to 1.3 equiv, the yield and ee could not be further improved (Table 1, entry 27). When the ratio of **1a** was increased to 1.5 equiv, full conversion was achieved with 89% ee (Table 1, entry 28). Increasing the catalyst loading to 10 mol %, the enantioselectivity of the transformation could not be improved. Finally, the optimized reaction conditions were established: 5 mol % (*R*)-**4g** as catalyst, 1.5 equiv of **1a** to **2a** in the presence of 50 mg of sodium sulfate in *o*-xylene at −20 °C.

With the optimal conditions identified, a variety of substrates were tested to evaluate the generality of this methodology. When the reaction was enlarged to 0.20 mmol under the optimal conditions, the desired product **3aa** could be isolated in 98% yield with 90% ee (Scheme 2, **3aa**). The influence of substituents at the N atom of indole was first investigated. 2-(1*H*-indolyl)aniline derivative **1b** bearing a small methyl furnished the reaction in only 31% yield with moderate enantioselectivity (Scheme 2, **3ba**). We presumed the more bulky benzyl substituent compressed the conformational space and favored the cyclization. The *N*-tosyl protected indole could not afford cyclization product, probably due to the decreased nucleophilicity of indole. In order to achieve better results, we attempted to prepare sterically hindered

Table 1. Optimization of Reaction Conditions[a]





entry	CPA	solvent	*t* (h)	yield (%)[b]	ee (%)[c]
1[d]	(*R*)-**4a**	toluene	18	>95	50
2	(*R*)-**4a**	toluene	22	>95	55
3	(*R*)-**4a**	DCM	28	93	35
4	(*R*)-**4a**	Et_2O	48	>95	44
5	(*R*)-**4a**	EtOAc	48	94	30
6	(*R*)-**4a**	dioxane	48	75	23
7	(*R*)-**4a**	MeCN	48	93	26
8	(*R*)-**4a**	$CHCl_3$	28	88	18
9	(*R*)-**4a**	benzene	40	>95	56
10	(*R*)-**4a**	$PhCF_3$	16	93	53
11	(*R*)-**4a**	PhCl	40	95	54
12	(*R*)-**4a**	*p*-xylene	26	93	59
13	(*R*)-**4a**	mesitylene	26	92	57
14	(*R*)-**4a**	*o*-xylene	24	>95	60
15	(*R*)-**4a**	*m*-xylene	24	92	58
16	(*R*)-**4b**	*o*-xylene	27	>95	5
17	(*S*)-**4c**	*o*-xylene	27	95	53
18	(*S*)-**4d**	*o*-xylene	36	90	31
19	(*R*)-**4e**	*o*-xylene	8	>95	14
20	(*R*)-**4f**	*o*-xylene	16	>95	10
21	(*R*)-**4g**	*o*-xylene	8	>95	67
22	(*R*)-**4h**	*o*-xylene	48	53	28
23	(*R*)-**4i**	*o*-xylene	36	>95	4
24[e]	(*R*)-**4g**	*o*-xylene	48	95	80
25[f]	(*R*)-**4g**	*o*-xylene	120	83	86
26[f,g]	(*R*)-**4g**	*o*-xylene	120	87	86
27[f,g,h]	(*R*)-**4g**	*o*-xylene	120	86	86
28[f,g,i]	(*R*)-**4g**	*o*-xylene	120	>95	89
29[f,g,i,j]	(*R*)-**4g**	*o*-xylene	90	>95	88

[a]Reactions were performed with **1a** (0.10 mmol) and **2a** (0.11 mmol) in solvent (1.0 mL) using 5 mol % CPA as catalyst at 30 °C. [b]NMR yield. [c]Determined by HPLC. [d]50 mg 5 Å molecular sieves were used. [e]At 0 °C. [f]At −20 °C. [g]50 mg of Na_2SO_4 was used. [h]**1a** (0.10 mmol) and **2a** (0.13 mmol) were used. [i]**1a** (0.15 mmol) and **2a** (0.10 mmol) were used. [j]10 mol % (*R*)-**4g** was used.

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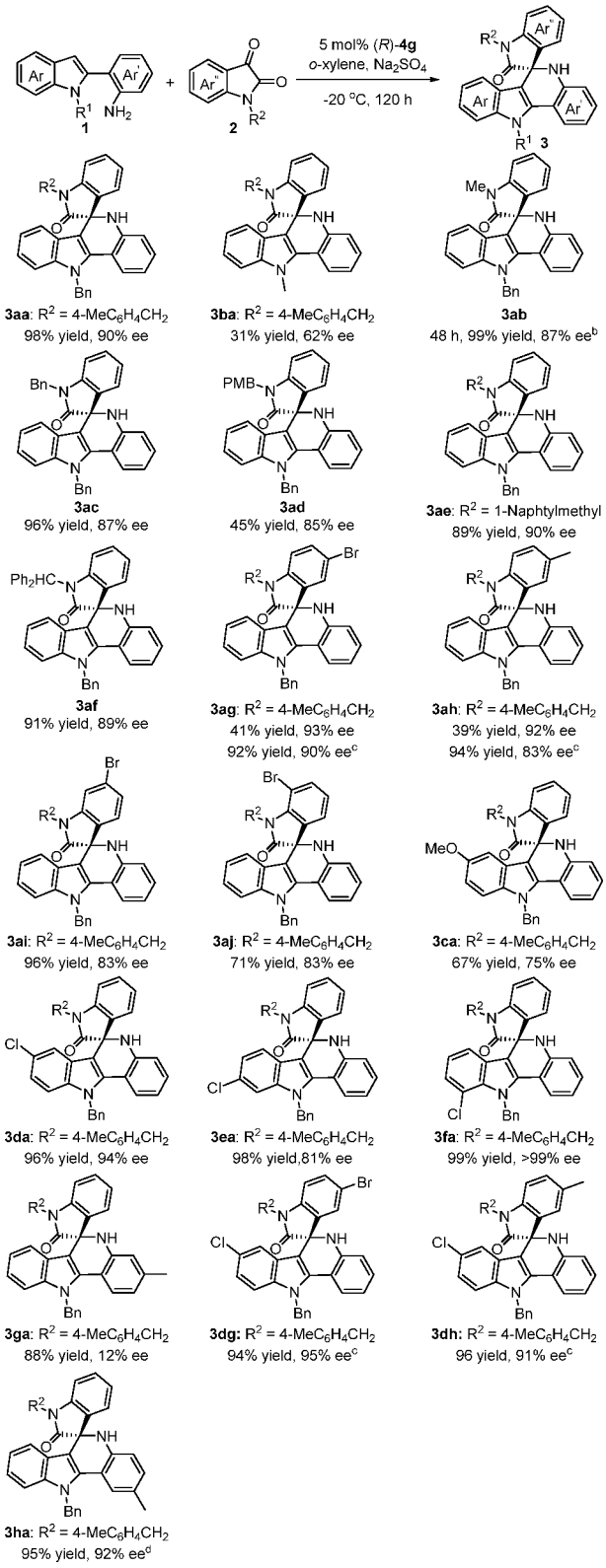
Scheme 2. Substrate Scope[a]



[a]Conditions: **1** (0.30 mmol) and **2** (0.20 mmol) in *o*-xylene (2.0 mL) using 5 mol % (*R*)-**4g** as catalyst in the presence of 100 mg of Na_2SO_4 at −20 °C for 120 h. [b]48 h. [c]10 mol % (*R*)-**4g** at −10 °C. [d]72 h.

substrates (R^1 = 1-naphtylmethyl and Ph_2CH). Unfortunately, the experiment failed. Subsequently, the scope of *N*-substituted isatins were investigated using 2-(1-benzyl-1*H*-indol-2-yl)-aniline **1a** (Scheme 2, **3ab**−**3af**). The steric hindrance of *N*-substituted groups had remarkable effects on reaction activities. *N*-methyl isatin **2b** led to the reaction with 99% yield and 87% ee in a significantly short reaction time (Scheme 2, **3ab**). Most of aromatic methyl substituted isatins delivered the corresponding products with comparable yields and enantioselectivities (Scheme 2, **3ac**, **3ae**, **3af**). To our surprise, *N*-PMB protecting isatin **2d** provided product **3ad** in low yield under the same conditions (Scheme 2, **3ad**). A range of *N*-4-methylbenzyl protected isatins with different groups at the various positions were explored and dramatic effects were observed. With either electron-withdrawing group 5-Br or electron-donating group 5-Me, the corresponding adducts were obtained in relatively low yields but light increased the ee values (Scheme 2, **3ag** and **3ah** vs **3aa**). Excellent yields and good enantioselectivities were achieved when reactions were carried out at −10 °C using 10 mol % (*R*)-**4g**. 6-Bromo and 7-bromo isatins were tolerated in the catalytic system and afforded the desired spiro chiral amines with good enantioselectivities (Scheme 2, **3ai** and **3aj**).

The influences of the substituted groups in the indole ring were also studied. Indole **1c** with an electron donating group at the 5-position gave 67% yield and 75% ee (Scheme 2, **3ca**). Indoles with electron withdrawing groups led to excellent yields and enantioselectivities (Scheme 2, **3da**−**3fa**). 5-Chloroindole **1d** gave **3da** with 96% yield and 94% ee (Scheme 2, **3da**). 7-Chloroindole **1f** performed outstandingly, affording **3fa** with quantitative yield and complete enantioselectivity (Scheme 2, **3fa**). The substituted group at the meta-position of the aniline moiety led to poor enantioselectivity due to the space effect which did not favor the transfer of chiral information (Scheme 2, **3ga**). Indole **1d** reacted with isatin **2g** or **2h** gave excellent yields and enantioselectivities under changed conditions (Scheme 2, **3dg**, **3dh**). The substituted group at the *para*-position of the aniline moiety furnished the transformation with excellent yield and enantioselectivity (Scheme 2, **3ha**).

The catalytic asymmetric Pictet−Spengler reactions of pyrrole derivatives have been pioneeringly studied by Jacobsen,[13] Antilla,[14] Tian[15] and other groups.[7,16] In most cases, the cyclizations took place selectively at the 2-position of pyrroles as the intrinsic nucleophilicity. Jacobsen reported an elegant thiourea-catalyzed regio- and enantioselective C-4 cyclization of pyrrolohydroxylactams via employing the bulky triisoproylsilyl (TIPS) group.[13] After establishing the C-3 cyclization of indole derivatives, we attempted the C-3 cyclization of 2-(1-benzyl-5-methyl-1*H*-pyrrol-2-yl)aniline **1i** and isatins, and the protocol was applied to the synthesis of 1′,5′-dihydrospiro[indoline-3,4′-pyrrolo[3,2-*c*]quinolin]-2-ones. Under previous optimal conditions, **1i** furnished the reaction providing the spiro product with 83% yield and 88% ee (Scheme 3, **3ia**). Isatins **2g** and **2h** were also suitable and corresponding adducts were obtained in good yields and enantioselectivities (Scheme 3, **3ig** and **3ih**).

To demonstrate the potential synthetic utility of the method, product transformations were conducted. The spiro chiral amine (+)-**3aa** could be transformed into formamide (−)-**5** via in the presence of mixed formic acid and acetic anhydride in 77% yield without loss of optical purity (Scheme 4). The absolute configuration of formamide (−)-**5** was unambiguously determined as *R* based on the X-ray diffraction analysis after recrystallization from mixed solvents of dicloromethane/hexanes to upgrade the ee to >99%. Therefore, the absolute

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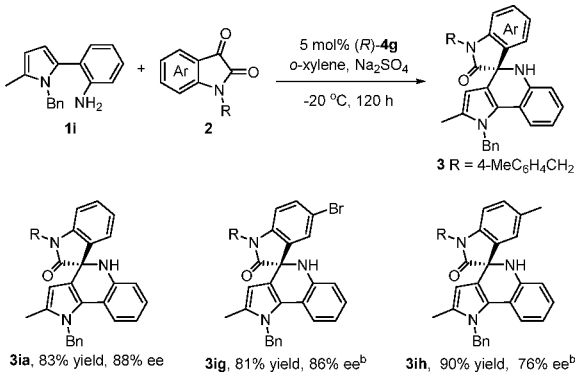
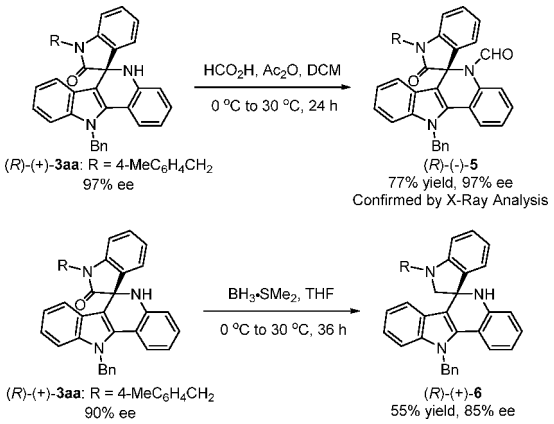
Scheme 3. Substrate Scope: 2-(1-benzyl-5-methyl-1*H*-pyrrol-2-yl)Aniline[a]



[a]Conditions: **1i** (0.30 mmol) and **2** (0.20 mmol) in *o*-xylene (2.0 mL) using 5 mol % (*R*)-**4g** as the catalyst in the presence of 100 mg of Na_2SO_4 at −20 °C for 120 h. [b]10 mol % (*R*)-**4g** at −10 °C.

Scheme 4. Product Transformation



configuration of product (+)-**3aa** was assigned as (*R*)-(+)-**3aa**. Furthermore, the spiroindolin-2-one (*R*)-(+)-**3aa** could be converted to indoline (*R*)-(+)-**6** upon exposure to the borane−methyl sulfide complex in THF with 55% yield and slightly decreased enantioselectivity (85% ee) (Scheme 4).

Finally, we proposed a plausible transition-state model based on the above experimental results to illustrate the absolute stereochemistry of the cyclization products (Figure 1). In the

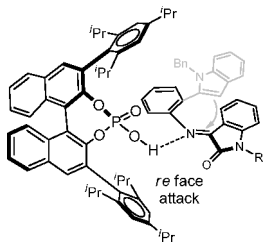


Figure 1. Plausible transition state.

presence of chiral phosphoric acid (*R*)-**4g**, the 2-(1-benzyl-1H-indol-2-yl)aniline **1a** reacts with isatin to form ketimine via dehydration. The chiral phosphoric acid activates the C═N bond via hydrogen-bonding, and the cyclization process occurs. The triisopropyl phenyl groups at the 3,3′-positions of the catalyst shield the *Si*-face of ketimine, and nucleophilic attack preferentially occurs at the *Re*-face to give the *R*-configured adduct.

In summary, we demonstrated chiral phosphoric acid-catalyzed Pictet−Spengler reactions of 2-(1*H*-indolyl)aniline derivatives and isatins for synthesis of chiral 5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-ones by the condensation/cyclization process. This protocol was also suitable for the Pictet−Spengler reactions of 2-(1*H*-pyrrol-2-yl)aniline derivatives. A series of 5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-ones and 1′,5′-dihydrospiro-[indoline-3,4′-pyrrolo[3,2-*c*]quinolin]-2-ones were achieved with excellent yields and enantioselectivities.

EXPERIMENTAL SECTION

Commercially, all reactions were carried out under an atmosphere of nitrogen using the standard Schlenk techniques, unless otherwise noted. Commercially available reagents were used without further purification. Solvents were treated prior to use according to the standard methods. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz with a Bruker spectrometer. Chemical shifts are reported in ppm using tetramethylsilane as an internal standard when using $CDCl_3$ as solvent for ^{1}H NMR spectra. The following abbreviations were used to symbolize the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Flash column chromatography was performed on silica gel (200−300 mesh). All reactions were monitored by TLC analysis. Optical rotations were measured by the polarimeter. Enantiomeric excess was determined by HPLC analysis using the chiral column described below in detail. High-resolution mass spectrometry (HRMS) was measured on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry. All the chiral phosphoric acids were known compounds and commercially available.

2-(1*H*-Indolyl)aniline derivatives **1a** and **1b** were prepared according to known methods.[17−19] 2-(1*H*-Indolyl)aniline derivatives **1c**−**1g** could be prepared according to the reported methods with minor modification.[18−21] 2-(3,5-Dimethyl-1*H*-pyrrol-2-yl)aniline **1h** could be synthesized from 2,4-dimethyl-1*H*-pyrrole and 2-nitrobromobenzene in two steps according to a similar report.[12,22] Among them, compounds **1a** and **1b** are the known compounds.[19,23]

Procedures for Synthesis of 2-(1-Benzyl-1*H*-indol-2-yl)-anilines 1d−1h. To a 120 mL sealed bottle charged with indoles (7.5 mmol, 1.0 equiv), 1-iodo-2-nitrobenzenes (9.0 mmol, 1.2 equiv), potassium acetate (2.208 g, 22.5 mmol, 3.0 equiv), bis-(diphenylphosphino)methane (dppm) (0.173 g, 0.45 mmol, 0.06 equiv), and palladium acetate (0.101 g, 0.45 mmol, 0.06 equiv) was added water (22.5 mL) and stirred at 110 °C (oil bath temperature) for 26−48 h. After cooled to room temperature, water was added and the mixture was extracted with dichloromethane (3 × 30 mL). The combined organic phase was concentrated under reduced pressure. The residue was purified by flash column chromatography using hexanes/ethyl acetate as eluent to give products **S-1**.

To a solution of the above products **S-1**(0.771 g, 2.88 mmol, 1.0 equiv) in *N*,*N*-dimethylformamide (29 mL) at 0 °C, sodium hydride (0.173 g, 4.32 mmol, 1.5 equiv., 60% in oil) was added. The mixture was stirred at the same temperature for 20 min before tetrabutylammonium iodide (0.107 g, 0.29 mmol, 0.1 equiv) and benzyl bromide (0.41 mL, 3.46 mmol, 1.2 equiv) were added. The mixture was warmed to room temperature and stirred for 1 h. Water was added, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine and evaporated under vacuum. The resulting residue was purified by flash column chromatography to give the crude products **S-2**.

1c, **1g**, and **1h** were prepared by reduction of **S-2c**, **S-2g**, and **S-2h** using Pd/C as catalyst under hydrogen. **1d**, **1e**, and **1f** were synthesized from **S-2d**, **S-2e**, and **S-2f** using iron and concentrated hydrochloric acid.

Procedures for Synthesis of 2-(1-Benzyl-1*H*-indol-2-yl)-anilines 1c, 1g, and 1h. To a 50 mL Schlenk bottle charged with

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S-2 (1.042 g, 2.88 mmol) and Pd/C (0.115 g, 10 wt %) was added ethanol/dicloromethane (55 mL/1 mL) and stirred under hydrogen gas (balloon pressure) for 24 h. The mixture was filtered through Celite, and the solvent was evaporated under reduced pressure. The crude mixture could be purified by recrystallization from hexanes/ether to give the products **1**.

Procedures for Synthesis of 2-(1-Benzyl-1*H*-indol-2-yl)-anilines 1d, 1e, and 1f. To a 50 mL Schlenk tube charged with **S-2** (0.841 g, 2.50 mmol, 1.0 equiv), iron powder (0.700 g, 12.5 mmol, 5.0 equiv), and ethanol (10.0 mL) was added concentrated hydrogen chloride (2.5 mL, 30.0 mmol, 12.0 equiv) under nitrogen. The mixture was heated to reflux for 4 h. After cooled to room temperature, the solution was neutralized by sodium hydroxide solution. The mixture was extracted with ethyl acetate (3 × 30 mL). The organic solvents were concentrated under vacuum and the residue was purified by flash column chromatography to afford products **1**.

2-(1-Benzyl-5-methoxy-1*H*-indol-2-yl)aniline (1c). 0.471 g, 29% yield in 3 steps, light yellow solid, mp = 118−119 °C, new compound, R_f = 0.25 (hexanes/ethyl acetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.08 (m, 7H), 6.91 (d, J = 6.3 Hz, 2H), 6.79−6.70 (m, 1H), 6.74 (dd, J = 12.9, 7.6 Hz, 2H), 6.54 (s, 1H), 5.19 (s, 2H), 3.86 (s, 3H), 3.82 (brs, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.4, 145.6, 138.5, 138.2, 132.5, 131.5, 129.9, 128.8, 128.5, 127.1, 126.4, 118.1, 117.7, 115.3, 112.0, 111.4, 102.3, 102.2, 55.9, 47.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{21}N_2O$ 329.1648, found 329.1646.

2-(1-Benzyl-5-chloro-1*H*-indol-2-yl)aniline (1d). 0.671 g, 20% yield in 3 steps, yellow solid, mp = 102−104 °C, new compound, R_f = 0.25 (hexanes/ethyl acetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 1.8 Hz, 1H), 7.27−7.12 (m, 7H), 6.97−6.89 (m, 2H), 6.83−6.76 (m, 2H), 6.59 (s, 1H), 5.24 (s, 2H), 3.73 (brs, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.5, 139.4, 137.6, 135.7, 131.5, 130.2, 129.5, 128.6, 127.3, 126.4, 125.7, 122.1, 119.9, 118.2, 117.1, 115.5, 111.6, 102.3, 47.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{18}ClN_2$ 333.1153 (^{35}Cl) and 335.1131 (^{37}Cl), found 333.1155 (^{35}Cl) and 335.1127 (^{37}Cl).

2-(1-Benzyl-6-chloro-1*H*-indol-2-yl)aniline (1e). **1e** was prepared from **S-2e** (0.728 g, 2.01 mmol) using same method, but iron powder (1.126 g, 20.10 mmol, 10.0 equiv) and concentrated hydrogen chloride (4.0 mL) were used. 0.600 g, 25% yield in 3 steps, colorless oil, new compound, R_f = 0.70 (hexanes/ethyl acetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 1.8 Hz, 1H), 7.27−7.12 (m, 7H), 6.97−6.89 (m, 2H), 6.83−6.76 (m, 2H), 6.59 (s, 1H), 5.24 (s, 2H), 3.73 (brs, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.5, 139.4, 137.6, 135.7, 131.5, 130.2, 129.5, 128.6, 127.3, 126.4, 125.7, 122.1, 119.9, 118.2, 117.1, 115.5, 111.6, 102.3, 47.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{18}ClN_2$ 333.1153 (^{35}Cl) and 335.1136 (^{37}Cl), found 333.1158 (^{35}Cl) and 335.1128 (^{37}Cl).

2-(1-Benzyl-7-chloro-1*H*-indol-2-yl)aniline (1f). 0.244 g, 10% yield in 3 steps, white solid, mp = 90−91 °C, new compound, R_f = 0.55 (hexanes/ethyl acetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.4 Hz, 1H), 7.33−7.19 (m, 5H), 7.18−7.08 (dd, J = 10.4, 3.8 Hz, 2H), 6.99−6.87 (m, 2H), 6.84−6.72 (m, 2H), 6.62 (s, 1H), 5.21 (s, 2H), 3.81 (brs, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.6, 138.7, 137.7, 137.5, 131.5, 130.1, 128.7, 127.7, 127.3, 127.0, 126.3, 121.4, 120.7, 118.1, 117.1, 115.4, 110.5, 102.8, 47.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{18}ClN_2$ 333.1153 (^{35}Cl) and 335.1136 (^{37}Cl), found 333.1156 (^{35}Cl) and 335.1127 (^{37}Cl).

2-(1-Benzyl-1*H*-indol-2-yl)-5-methylaniline (1g). 0.580 g, 26% yield in 3 steps, light yellow solid, mp = 98−99 °C, new compound, R_f = 0.75 (hexanes/ethyl acetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.63 (m, 1H), 7.28−7.13 (m, 6H), 7.05 (d, J = 7.6 Hz, 1H), 7.01−6.94 (m, 2H), 6.71−6.53 (m, 3H), 5.26 (s, 2H), 4.19−3.02 (brs, 2H), 2.34 (s, 3H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.4, 140.0, 138.2, 138.0, 137.2, 131.4, 128.5, 127.1, 126.4, 121.7, 120.5, 119.9, 119.1, 116.0, 114.9, 110.6, 102.6, 47.5, 21.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{21}N_2$ 313.1699, found 313.1699.

2-(1-Benzyl-1H-indol-2-yl)-4-methylaniline (1h). 0.333 g, 31% yield in 3 steps, colorless oil, new compound, R_f = 0.50 (hexanes/ethyl acetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.57 (m, 1H), 7.29−7.09 (m, 6H), 7.00 (dd, J = 8.1, 1.3 Hz, 1H), 6.96−6.86 (m, 3H), 6.67 (d, J = 8.1 Hz, 1H), 6.58 (s, 1H), 5.21 (s, 2H), 3.65 (s, 2H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 138.2, 138.2, 137.3, 132.0, 130.5, 128.5, 127.2, 127.1, 126.5, 121.7, 120.5, 119.9, 117.7, 115.5, 110.6, 102.6, 47.6, 20.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{21}N_2$ 313.1699, found 313.1699.

Procedures for Synthesis of 2-(1-Benzyl-5-methyl-1*H*-pyrrol-2-yl)aniline (1i). In a dried 250 mL Schlenk bottle was added 2-methyl-1*H*-pyrrole (5.0 mL, 60.0 mmol, 4.0 equiv), 1-bromo-2-nitrobenzene (3.030 g, 15.0 mmol, 1.0 equiv), cesium carbonate (Cs_2CO_3, 9.775 g, 30.0 mmol, 2.0 equiv), and anhydrous acetonitrile (MeCN, 150 mL). The resulting suspension was heated to reflux using an oil bath for 48 h. After cooled to room temperature, the solvent was evaporated under vacuum and water was added. The mixture was extracted with ethyl acetate (3 × 50 mL). The solvent was evaporated under reduced pressure and the mixture was purified by flash column chromatography using hexanes/ethyl acetate as the eluent to give the product **S-1i** (2.576 g, 85% yield).

1-Benzyl-2-methyl-5-(2-nitrophenyl)-1H-pyrrole **S-2i** was prepared from **S-1i** by similar method as 1-benzyl-2-(2-nitrophenyl)-1*H*-indole. Reduction of **S-2i** using Pd/C under hydrogen provided **1i**.

2-(1-Benzyl-5-methyl-1*H*-pyrrol-2-yl)aniline (1i). 0.513 g, 33% yield in 3 steps, white solid, mp = 93−94 °C, new compound, R_f = 0.40 (hexanes/ethyl acetate 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.17 (m, 3H), 7.12 (dd, J = 11.2, 4.1 Hz, 1H), 7.05 (d, J = 7.5 Hz, 1H), 6.85 (d, J = 7.3 Hz, 2H), 6.80−6.62 (m, 2H), 6.19 (d, J = 3.3 Hz, 1H), 6.08 (d, J = 3.0 Hz, 1H), 4.99 (s, 2H), 4.05−3.09 (brs, 2H), 2.18 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.7, 139.0, 131.9, 129.9, 129.8, 129.0, 128.5, 126.9, 126.0, 119.2, 118.0, 115.2, 108.1, 107.0, 47.6, 12.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{19}N_2$ 263.1543, found 263.1540.

Procedure for Synthesis of *N*-Substituted Isatins. The *N*-substituted isatins **2** could be synthesized from commercially available isatins according to the known methods.[24] Among them, compounds **2a−2h** are the known compounds.[24]

To a solution of indoline-2,3-diones (4.0 mmol, 1.0 equiv) in *N*,*N*-dimethylformamide (8 mL) was added sodium hydride (0.208 g, 5.2 mmol, 1.3 equiv) at 0 °C under nitrogen. The mixture was stirred at the same temperature for 20 min before 1-(bromomethyl)-4-methylbenzene (0.888 g, 4.8 mmol, 1.2 equiv) was added. The mixture was warmed to room temperature and stirred for 1 h. After complete consumption of indoline-2,3-diones monitored by TLC, water (20 mL) was added and the mixture was stirred for 30 min during which the precipitate formed. The solid was collected by filtration, washed with water and petroleum ether, and dried under vacuum. The product was further purified by recrystallization from ethanol to provide the desired product **2**.

6-Bromo-1-(4-methylbenzyl)indoline-2,3-dione (2i). 0.965 g, 73% yield, orange solid, mp = 165−166 °C, new compound, R_f = 0.60 (hexanes/ethyl acetate 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 7.9 Hz, 1H), 7.29−7.16 (m, 5H), 6.99 (d, J = 1.2 Hz, 1H), 4.89 (s, 2H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 182.1, 158.1, 151.6, 138.3, 133.5, 130.9, 129.9, 127.5, 127.1, 126.3, 116.4, 114.6, 44.0, 21.2. HRMS (ESI) m/z: $[M + NH_4]^+$ calcd for $C_{16}H_{13}BrNO_2$ 347.0390 (^{79}Br) and 349.0376 (^{81}Br), found 347.0388 (^{79}Br) and 349.0370 (^{81}Br).

7-Bromo-1-(4-methylbenzyl)indoline-2,3-dione (2j). 0.761 g, 58% yield, red solid, mp = 189−190 °C, new compound, R_f = 0.80 (hexanes/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 15.2, 7.7 Hz, 2H), 7.23−7.11 (m, 4H), 7.02 (t, J = 7.7 Hz, 1H), 5.42 (s, 2H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 182.5, 159.1, 147.9, 144.2, 137.4, 133.0, 129.5, 126.5, 125.2, 124.8, 120.9, 104.5, 44.4, 21.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{13}BrNO_2$ 330.0124 (^{79}Br) and 332.0111 (^{81}Br), found 330.0123 (^{79}Br) and 332.0106 (^{81}Br).

Procedure for Enantioselective Pictet−Spengler Reactions. To a dry 25 mL Schlenk tube charged with chiral phosphoric acid (*R*)-**4g** (7.5 mg, 0.01 mmol, 0.05 equiv), *N*-substituted isatins **2** (0.20 mmol, 1.0 equiv), and anhydrous sodium sulfate (100 mg) was added

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dry *o*-xylene (2.0 mL) under nitrogen and the mixture was stirred at −20 °C for 10 min. Anilines **1** (0.30 mmol, 1.5 equiv) were added, and the mixture was stirred for 120 h at the same temperature. Then the reaction was quenched with saturated aqueous sodium bicarbonate and warmed to room temperature. The mixture was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, and concentrated. The residue was purified by flash column chromatography on silica gel to give the desirable products **3**.

(*R*)-11′-Benzyl-1-(4-methylbenzyl)-5′,11′-dihydrospiro-[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one (3aa). 104 mg, 98% yield, light yellow solid, mp = 133−134 °C, new compound, R_f = 0.40 (hexanes/ethyl acetate 5:1), 90% ee, $[\alpha]_D^{20}$ = +45.67 (*c* 1.04, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.4 Hz, 1H), 7.46−7.30 (m, 9H), 7.25−7.15 (m, 3H), 7.15−7.04 (m, 3H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.88−6.79 (m,1H), 6.78−6.65 (m, 2H), 6.37 (d, *J* = 7.9 Hz, 1H), 5.79 (d, *J* = 17.9 Hz, 1H), 5.66 (d, *J* = 17.9 Hz, 1H), 5.12 (d, *J* = 15.4 Hz, 1H), 4.78 (d, *J* = 15.4 Hz, 1H), 4.47 (brs, 1H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.5, 143.3, 142.5, 139.7, 137.5, 137.5, 133.9, 132.7, 132.3, 130.0, 129.6, 129.1, 128.5, 127.8, 127.5, 126.1, 126.1, 123.9, 123.5, 122.7, 122.4, 120.4, 119.0, 118.5, 114.7, 114.5, 109.8, 109.5, 108.6, 63.7, 49.2, 43.9, 21.2. Enantiomeric excess was determined by HPLC (IC column; eluent, *n*-hexane/*i*-PrOH = 70/30; detector, 254 nm; flow rate, 0.7 mL/min; 30 °C), retention times 9.9 and 10.9 min (major). HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{37}H_{30}N_3O$ 532.2383, found 532.2386.

(+)-11′-Methyl-1-(4-methylbenzyl)-5′,11′-dihydrospiro-[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one (3ba). 28 mg, 31% yield, red oil, new compound, R_f = 0.50 (hexanes/ethyl acetate 5:1), 62% ee, $[\alpha]_D^{20}$ = +29.64 (*c* 0.56, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 7.0 Hz, 1H), 7.36−7.30 (m, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 7.20−7.03 (m, 5H), 6.96−6.83 (t, *J* = 8.3 Hz, 2H), 6.82−6.64 (m, 2H), 6.23 (d, *J* = 8.0 Hz, 1H), 5.09 (d, *J* = 15.3 Hz, 1H), 4.69 (d, *J* = 15.3 Hz, 1H), 4.43 (brs, 1H), 4.13 (s, 3H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.6, 143.4, 142.6, 139.4, 137.5, 133.6, 132.7, 132.3, 129.9, 129.5, 128.4, 127.7, 126.1, 123.5, 123.4, 122.8, 122.0, 119.8, 118.8, 118.3, 115.3, 114.6, 109.4, 109.3, 107.8, 63.6, 43.8, 33.1, 21.2. Enantiomeric excess was determined by HPLC (AD-H column; eluent, *n*-hexane/*i*-PrOH = 70/30; detector, 254 nm; flow rate, 0.7 mL/min; 30 °C), retention times 17.5 and 24.9 min (major). HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{31}H_{26}N_3O$ 456.2070, found 456.2071.

(+)-11′-Benzyl-1-methyl-5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one (3ab). 88 mg, 99% yield, yellow oil, new compound, R_f = 0.35 (hexanes/ethyl acetate 3:1), 87% ee, $[\alpha]_D^{20}$ = +75.11 (*c* 0.88, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.30 (m, 8H), 7.22 (d, *J* = 8.3 Hz, 1H), 7.16−7.02 (m, 4H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.79−6.62 (m, 2H), 6.46 (d, *J* = 8.0 Hz, 1H), 5.82−5.60 (m, 2H), 4.48 (brs, 1H), 3.32 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.5, 143.5, 143.1, 139.6, 137.5, 133.8, 132.3, 130.1, 129.1, 128.5, 127.5, 126.1, 125.9, 123.8, 123.6, 122.7, 122.4, 120.5, 119.0, 118.2, 114.8, 114.7, 109.9, 108.5, 108.4, 63.7, 49.0, 26.4. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 70/30; detector, 254 nm; flow rate, 0.7 mL/min; 30 °C), retention times 9.4 min (major) and 12.0 min. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{30}H_{24}N_3O$ 442.1914, found 442.1919.

(+)-1,11′-Dibenzyl-5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one (3ac). 100 mg, 96% yield, light yellow oil, new compound, R_f = 0.40 (hexanes/ethyl acetate 5:1), 87% ee, $[\alpha]_D^{20}$ = +33.80 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.3 Hz, 1H), 7.41−7.36 (m, 5H), 7.35−7.27 (m, 7H), 7.18 (d, *J* = 8.3 Hz, 1H), 7.09−7.02 (m, 3H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.79 (t, *J* = 7.5 Hz, 1H), 6.71−6.64 (m, 2H), 6.31 (d, *J* = 8.0 Hz, 1H), 5.75 (d, *J* = 17.7 Hz, 1H), 5.62 (d, *J* = 17.9 Hz, 1H), 5.12 (d, *J* = 15.4 Hz, 1H), 4.78 (d, *J* = 15.4 Hz, 1H), 4.44 (brs, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.7, 138.6, 137.7, 135.0, 132.7, 131.0, 129.1, 127.5, 125.2, 124.4, 124.1, 123.8, 123.1, 122.7, 121.4, 121.3, 119.1, 118.8, 117.9, 117.7, 115.6, 114.2, 113.7, 110.0, 109.8, 105.1, 104.7, 103.8, 59.0, 44.4, 39.4. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 70/30; detector, 254 nm; flow rate, 0.7 mL/min; 30 °C), retention times 12.7 min (major) and 17.0 min. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{36}H_{28}N_3O$ 518.2227, found 518.2223.

(+)-11′-Benzyl-1-(4-methoxybenzyl)-5′,11′-dihydrospiro-[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one (3ad). 50 mg, 45% yield, yellow oil, new compound, R_f = 0.35 (hexanes/ethyl acetate 5:1), 85% ee, $[\alpha]_D^{20}$ = +31.10 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.3 Hz, 1H), 7.44−7.30 (m, 9H), 7.20 (d, *J* = 8.2 Hz, 1H), 7.12−7.01 (m, 3H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.75−6.62 (m, 2H), 6.31 (d, *J* = 8.0 Hz, 1H), 5.77 (d, *J* = 17.9 Hz, 1H), 5.65 (d, *J* = 17.9 Hz, 1H), 5.08 (d, *J* = 15.2 Hz, 1H), 4.74 (d, *J* = 15.2 Hz, 1H), 4.44 (brs, 1H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.4, 159.2, 143.3, 142.4, 139.7, 137.4, 133.8, 132.3, 129.9, 129.2, 129.1, 128.5, 127.8, 127.5, 126.1, 123.8, 123.5, 122.6, 122.4, 120.3, 118.9, 118.4, 114.7, 114.5, 114.2, 109.8, 109.5, 108.5, 63.7, 55.3, 49.1, 43.6. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 70/30; detector, 254 nm; flow rate, 0.7 mL/min; 30 °C), retention times 17.5 min (major) and 18.8 min. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{37}H_{30}N_3O_2$ 548.2333, found 548.2329.

(−)-11′-Benzyl-1-(naphthalen-1-ylmethyl)-5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one (3ae). 101 mg, 89% yield, yellow solid, new compound, mp = 166−168 °C, R_f = 0.25 (hexanes/ethyl acetate 5:1), 90% ee, $[\alpha]_D^{20}$ = −9.60 (*c* 1.01, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.1 Hz, 1H), 7.99−7.89 (m, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.59−7.47 (m, 4H), 7.42 (t, *J* = 7.1 Hz, 4H), 7.37−7.31 (m, 3H), 7.30−7.20 (m, 2H), 7.15−7.00 (m, 3H), 6.93−6.68 (m, 4H), 6.34 (d, *J* = 7.9 Hz, 1H), 5.80 (d, *J* = 17.9 Hz, 1H), 5.67 (d, *J* = 17.9 Hz, 1H), 5.51 (d, *J* = 16.0 Hz, 1H), 5.40 (d, *J* = 16.0 Hz, 1H), 4.48 (brs, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.5, 143.3, 142.9, 139.7, 137.4, 134.0, 133.9, 132.1, 131.2, 130.6, 130.0, 129.1, 129.0, 128.5, 128.5, 127.5, 126.7, 126.1, 126.1, 125.6, 125.3, 123.8, 123.5, 123.1, 122.7, 122.4, 120.4, 119.1, 118.5, 114.9, 114.6, 110.0, 109.8, 108.4, 63.6, 49.1, 42.3. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 70/30; detector, 254 nm; flow rate, 0.7 mL/min; 30 °C), retention times 12.0 min (major) and 17.9 min. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{40}H_{30}N_3O$ 568.2383, found 568.2383.

(+)-1-Benzhydryl-11′-benzyl-5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one (3af). 108 mg, 91% yield, yellow oil, new compound, R_f = 0.40 (hexanes/ethyl acetate 10:1), 89% ee, $[\alpha]_D^{20}$ = +0.93 (*c* 1.08, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 6.9 Hz, 1H), 7.50−7.30 (m, 16H), 7.24−7.15 (m, 2H), 7.14−7.01 (m, 4H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.76−6.63 (m, 3H), 6.30 (d, *J* = 8.0 Hz, 1H), 5.78 (d, *J* = 17.8 Hz, 1H), 5.65 (d, *J* = 17.9 Hz, 1H), 4.46 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.5, 143.3, 142.2, 139.7, 137.8, 137.7, 137.4, 134.0, 132.3, 129.5, 129.1, 128.8, 128.7, 128.7, 128.6, 128.5, 127.9, 127.9, 127.5, 126.1, 126.1, 123.9, 123.2, 122.7, 122.4, 120.3, 119.0, 118.6, 114.8, 114.7, 112.3, 109.8, 108.8, 63.3, 58.6, 49.1. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 70/30; detector, 254 nm; flow rate, 0.7 mL/min; 30 °C), retention times 12.9 and 22.4 min (major). HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{42}H_{32}N_3O$ 594.2540, found 594.2542.

(+)-11′-Benzyl-5-bromo-1-(4-methylbenzyl)-5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one (3ag). 50 mg, 41% yield, yellow oil, new compound, R_f = 0.45 (hexanes/ethyl acetate 5:1), 93% ee, $[\alpha]_D^{20}$ = +34.70 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 1.8 Hz, 1H), 7.48−7.38 (m, 4H), 7.38−7.31 (m, 3H), 7.30−7.20 (m, 3H), 7.20−7.04 (m, 4H), 6.86 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.76−6.66 (m, 2H), 6.41 (d, *J* = 8.0 Hz, 1H), 5.78 (d, *J* = 17.9 Hz, 1H), 5.67 (d, *J* = 17.9 Hz, 1H), 5.10 (d, *J* = 15.3 Hz, 1H), 4.74 (d, *J* = 15.4 Hz, 1H), 4.44 (brs, 1H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.0, 142.9, 141.4, 139.7, 137.8, 137.3, 134.4, 133.8, 132.8, 132.2, 129.6, 129.2, 128.6, 127.8, 127.5, 126.1, 123.6, 122.7, 122.6, 120.6, 119.2, 118.3, 116.3, 114.5, 114.3, 111.0, 109.9, 107.7, 63.9, 49.2, 44.0, 21.2. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 70/30; detector, 254 nm; flow rate, 0.7 mL/min; 30 °C), retention times 14.4 min (major) and 20.2 min. HRMS (ESI)

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m/*z*: [M + H]$^+$ calcd for $C_{37}H_{29}BrN_3O$ 610.1489 (^{79}Br) and 612.1475 (^{81}Br), found 610.1484 (^{79}Br) and 612.1465 (^{81}Br).

(+)-11′-Benzyl-5-methyl-1-(4-methylbenzyl)-5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one (3ah). 43 mg, 39% yield, yellow oil, new compound, R_f = 0.35 (hexanes/ethyl acetate 5:1), 92% ee, $[\alpha]_D^{20}$ = +35.46 (*c* 0.86, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.39 (m,3H), 7.38−7.29 (m, 6H), 7.25−7.05 (m, 6H), 6.88−6.80 (m, 2H), 6.77−6.66 (m, 2H), 6.41 (d, *J* = 8.0 Hz, 1H), 5.79 (d, *J* = 17.9 Hz, 1H), 5.67 (d, *J* = 17.9 Hz, 1H), 5.10 (d, *J* = 15.3 Hz, 1H), 4.75 (d, *J* = 15.3 Hz, 1H), 4.45 (brs, 1H), 2.39 (s, 3H), 2.28 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.5, 143.4, 140.0, 139.7, 137.5, 133.8, 133.1, 132.8, 132.4, 130.2, 129.5, 129.1, 128.5, 127.9, 127.5, 126.7, 126.1, 123.9, 122.6, 122.4, 120.4, 118.9, 118.6, 114.6, 114.5, 109.8, 109.3, 108.6, 63.9, 49.2, 43.9, 21.2, 21.1. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 60/40; detector, 254 nm; flow rate, 0.6 mL/min; 30 °C), retention times 13.3 min (major) and 20.6 min. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{38}H_{32}N_3O$ 546.2540, found 546.2543.

(+)-11′-Benzyl-6-bromo-1-(4-methylbenzyl)-5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one (3ai). 117 mg, 96% yield, yellow solid, new compound, mp = 150−151 °C, R_f = 0.25 (hexanes/ethyl acetate 5:1), 83% ee, $[\alpha]_D^{20}$ = +18.12 (*c* 1.17, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.40 (m, 3H), 7.39−7.27 (m, 6H), 7.27−7.18 (m, 4H), 7.17−7.03 (m, 3H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.79−6.61 (m, 2H), 6.43 (d, *J* = 7.9 Hz, 1H), 5.78 (d, *J* = 17.9 Hz, 1H), 5.66 (d, *J* = 17.9 Hz, 1H), 5.09 (d, *J* = 15.4 Hz, 1H), 4.70 (d, *J* = 15.4 Hz, 1H), 4.49 (brs, 1H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.3, 143.8, 143.1, 139.7, 137.8, 137.4, 133.9, 132.1, 131.3, 129.8, 129.2, 128.7, 127.8, 127.6, 127.4, 126.5, 126.1, 123.7, 123.6, 122.7, 122.6, 120.6, 119.2, 118.3, 114.6, 114.6, 112.9, 110.0, 107.8, 63.5, 49.2, 44.0, 21.3. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 60/40; detector, 254 nm; flow rate, 0.6 mL/min; 30 °C), retention times 13.3 min (major) and 16.8 min. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{37}H_{29}BrN_3O$ 610.1489 (^{79}Br) and 612.1475 (^{81}Br), found 610.1491 (^{79}Br) and 612.1478 (^{81}Br).

(+)-11′-Benzyl-7-bromo-1-(4-methylbenzyl)-5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one (3aj). 87 mg, 71% yield, yellow oil, new compound, R_f = 0.20 (hexanes/ethyl acetate 10:1), 83% ee, $[\alpha]_D^{20}$ = +1.06 (*c* 0.85, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.1 Hz, 1H), 7.49 (d, *J* = 6.9 Hz, 1H), 7.46−7.20 (m, 9H), 7.18−7.04 (m, 4H), 6.99−6.89 (m, 2H), 6.77−6.66 (m, 2H), 6.50 (d, *J* = 8.0 Hz, 1H), 5.77 (d, *J* = 17.9 Hz, 1H), 5.66 (d, *J* = 17.9 Hz, 1H), 5.53−5.38 (m, 2H), 4.46 (brs, 1H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.2, 143.0, 140.1, 139.7, 137.4, 136.9, 135.9, 135.7, 134.3, 134.0, 129.3, 129.2, 128.6, 127.6, 127.1, 126.1, 125.5, 124.9, 123.6, 122.7, 122.6, 120.6, 119.3, 118.4, 114.7, 110.0, 108.2, 102.7, 63.1, 49.1, 44.4, 21.2. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 70/30; detector, 254 nm; flow rate, 0.7 mL/min; 30 °C), retention times 18.3 min (major) and 20.4 min. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{37}H_{29}BrN_3O$ 610.1489 (^{79}Br) and 612.1475 (^{81}Br), found 610.1488 (^{79}Br) and 612.1475 (^{81}Br).

(+)-11′-Benzyl-8′-methoxy-1-(4-methylbenzyl)-5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one (3ca). 75 mg, 67% yield, light yellow solid, new compound, R_f = 0.30 (hexanes/ethyl acetate 5:1), 75% ee, $[\alpha]_D^{20}$ = +41.86 (*c* 0.75, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.2 Hz, 1H), 7.48−7.25 (m, 9H), 7.20−7.03 (m, 5H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.82−6.64 (m, 3H), 5.75 (d, *J* = 17.8 Hz, 1H), 5.65 (d, *J* = 2.0 Hz, 1H), 5.59 (d, *J* = 17.8 Hz, 1H), 5.17 (d, *J* = 15.4 Hz, 1H), 4.66 (d, *J* = 15.4 Hz, 1H), 4.52 (brs, 1H), 3.29 (s, 3H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.5, 154.3, 143.5, 142.9, 137.6, 137.5, 134.9, 134.3, 132.7, 132.2, 129.9, 129.6, 129.1, 128.5, 127.7, 127.5, 126.4, 126.1, 124.1, 123.5, 122.6, 119.0, 114.9, 114.6, 112.5, 110.6, 109.4, 108.2, 99.7, 63.7, 54.9, 49.2, 43.8, 21.2. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 60/40; detector, 254 nm; flow rate, 0.6 mL/min; 30 °C), retention times 14.5 min (major) and 22.5 min. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{38}H_{32}N_3O_2$ 562.2489, found 562.2486.

(+)-11′-Benzyl-8′-chloro-1-(4-methylbenzyl)-5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one (3da). 108 mg, 96% yield, light yellow solid, new compound, R_f = 0.50 (hexanes/ethyl acetate 5:1), 94% ee, $[\alpha]_D^{20}$ = +48.52 (*c* 1.08, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.1 Hz, 1H), 7.46−7.26 (m, 9H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.15−7.00 (m, 4H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.78−6.62 (m, 2H), 6.30 (d, *J* = 1.7 Hz, 1H), 5.74 (d, *J* = 17.9 Hz, 1H), 5.62 (d, *J* = 17.9 Hz, 1H), 5.15 (d, *J* = 15.4 Hz, 1H), 4.73 (d, *J* = 15.4 Hz, 1H), 4.48 (brs, 1H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.3, 143.5, 142.4, 138.0, 137.6, 137.0, 135.1, 132.5, 131.8, 130.3, 129.8, 129.2, 129.0, 127.7, 127.6, 126.1, 126.0, 125.9, 124.8, 123.7, 122.8, 122.6, 119.0, 117.8, 114.7, 114.2, 110.9, 109.8, 108.0, 63.5, 49.2, 43.9, 21.3. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 60/40; detector, 254 nm; flow rate, 0.6 mL/min; 30 °C), retention times 14.3 min (major) and 17.1 min. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{37}H_{29}ClN_3O$ 566.1994 (^{35}Cl) and 568.1984 (^{37}Cl), found 566.1997 (^{35}Cl) and 568.1976 (^{37}Cl).

(+)-11′-Benzyl-9′-chloro-1-(4-methylbenzyl)-5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one (3ea). 111 mg, 98% yield, yellow oil, new compound, R_f = 0.40 (hexanes/ethyl acetate 5:1), 81% ee, $[\alpha]_D^{20}$ = +41.80 (*c* 1.11, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.45−7.16 (m, 10H), 7.08 (d, *J* = 7.2 Hz, 2H), 7.04−6.92 (m, 3H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.69−6.52 (m, 3H), 6.25−6.02 (m, 2H), 5.88 (d, *J* = 17.9 Hz, 1H), 5.03 (d, *J* = 15.3 Hz, 1H), 4.65 (d, *J* = 15.3 Hz, 1H), 4.39 (brs, 1H), 2.30 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.2, 143.6, 142.4, 139.4, 137.7, 136.4, 135.0, 132.6, 131.9, 130.2, 129.6, 129.0, 128.9, 127.9, 127.2, 127.1, 126.2, 126.0, 124.5, 123.6, 123.4, 121.1, 119.2, 117.2, 117.1, 114.8, 114.1, 109.7, 109.4, 63.4, 50.4, 43.9, 21.3. Enantiomeric excess was determined by HPLC (IC column; eluent, *n*-hexane/*i*-PrOH = 70/30; detector, 254 nm; flow rate, 0.7 mL/min; 30 °C), retention times 8.0 and 9.1 min (major). HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{37}H_{29}ClN_3O$ 566.1994 (^{35}Cl) and 568.1989 (^{37}Cl), found 566.1991 (^{35}Cl) and 568.1977 (^{37}Cl).

(+)-11′-Benzyl-10′-chloro-1-(4-methylbenzyl)-5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin] -2-one (3fa). 112 mg, 99% yield, yellow oil, new compound, R_f = 0.40 (hexanes/ethyl acetate 5:1), >99% ee, $[\alpha]_D^{20}$ = +50.98 (*c* 1.12, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.16 (m, 10H), 7.13 (s, 1H), 7.09 (d, *J* = 7.7 Hz, 2H), 6.99 (dd, *J* = 12.7, 7.2 Hz, 2H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.74−6.54 (m, 3H), 6.12 (d, *J* = 8.5 Hz, 1H), 5.64 (d, *J* = 17.9 Hz, 1H), 5.51 (d, *J* = 17.9 Hz, 1H), 5.04 (d, *J* = 15.3 Hz, 1H), 4.61 (d, *J* = 15.3 Hz, 1H), 4.41 (brs, 1H), 2.30 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.3, 143.4, 142.4, 140.1, 137.7, 136.9, 134.7, 132.6, 132.0, 130.2, 129.6, 129.3, 128.9, 128.3, 127.8, 127.7, 126.0, 123.6, 122.7, 122.4, 121.1, 119.2, 119.1, 114.7, 114.3, 109.9, 109.7, 108.5, 63.6, 49.2, 43.9, 21.3. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 70/30; detector, 254 nm; flow rate, 0.7 mL/min; 30 °C), retention times 13.9 min (major). HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{37}H_{29}ClN_3O$ 566.1994 (^{35}Cl) and 568.1989 (^{37}Cl), found 566.1994 (^{35}Cl) and 568.1979 (^{37}Cl).

(+)-11′-Benzyl-3′-methyl-1-(4-methylbenzyl)-5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin] −2-one (3ga). 96 mg, 88% yield, light yellow solid, new compound, mp = 200−201 °C, R_f = 0.25 (hexanes/ethyl acetate 5:1), 12% ee, $[\alpha]_D^{20}$ = +4.37 (*c* 0.96, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.2 Hz, 1H), 7.49−7.30 (m, 9H), 7.27−7.17 (m, 3H), 7.11 (t, *J* = 7.5 Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.86 (t, *J* = 7.5 Hz, 1H), 6.67−7.51 (m, 2H), 6.37 (d, *J* = 8.0 Hz, 1H), 5.79 (d, *J* = 17.9 Hz, 1H), 5.67 (d, *J* = 17.9 Hz, 1H), 5.15 (d, *J* = 15.4 Hz, 1H), 4.79 (d, *J* = 15.4 Hz, 1H), 4.45 (brs, 1H), 2.42 (s, 3H), 2.29 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.7, 143.4, 142.6, 139.6, 138.7, 137.6, 137.5, 134.2, 132.7, 132.4, 130.0, 129.6, 129.1, 127.8, 127.5, 126.2, 124.0, 123.5, 122.6, 122.2, 120.3, 120.0, 118.3, 115.3, 112.2, 109.8, 109.6, 107.8, 63.8, 49.1, 43.9, 21.5, 21.3. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 60/40; detector, 254 nm;

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flow rate, 0.6 mL/min; 30 °C), retention times 12.0 min (major) and 20.6 min. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{38}H_{32}N_3O$ 546.2540, found 546.2540.

(+)-11′-Benzyl-5-bromo-8′-chloro-3′-methyl-1-(4-methylbenzyl)-5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one (3dg). 121 mg, 94% yield, light yellow solid, new compound, mp = 150−152 °C, R_f = 0.35 (hexanes/ethyl acetate 5:1), 95% ee, $[\alpha]_D^{20}$ = +62.31 (*c* 1.21, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 1.9 Hz, 1H), 7.51−7.26 (m, 9H), 7.22 (d, J = 7.9 Hz, 2H), 7.18−7.03 (m, 3H), 6.82 (d, J = 8.4 Hz, 1H), 6.76−6.64 (m, 2H), 6.41 (d, J = 1.7 Hz, 1H), 5.75 (d, J = 17.9 Hz, 1H), 5.64 (d, J = 17.9 Hz, 1H), 5.16 (d, J = 15.4 Hz, 1H), 4.69 (d, J = 15.4 Hz, 1H), 4.50 (brs, 1H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.9, 143.0, 141.2, 138.1, 137.9, 136.8, 135.0, 134.0, 133.1, 132.0, 129.9, 129.3, 129.1, 129.0, 127.7, 127.7, 126.4, 126.0, 124.5, 122.9, 122.8, 119.2, 117.5, 116.4, 114.7, 113.8, 111.3, 111.0, 107.1, 63.7, 49.3, 44.1, 21.3. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 60/40; detector, 254 nm; flow rate, 0.6 mL/min; 30 °C), retention times 13.4 min (major) and 19.1 min. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{37}H_{28}BrClN_3O_2$ 644.1099 (^{35}Cl + ^{79}Br) and 646.1081 (^{35}Cl + ^{81}Br), found 644.1097 (^{35}Cl + ^{79}Br) and 646.1084 (^{35}Cl + ^{81}Br).

(+)-11′-Benzyl-8′-chloro-3′,5-dimethyl-1-(4-methylbenzyl)-5′,11′-dihydrospiro[indoline-3,6′-indolo [3,2-*c*]quinolin]-2-one (3dh). 111 mg, 96% yield, yellow oil, new compound, R_f = 0.30 (hexanes/ethyl acetate 5:1), 91% ee, $[\alpha]_D^{20}$ = +50.18 (*c* 1.11, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.48−7.39 (m, 3H), 7.39−7.26 (m, 6H), 7.26−7.00 (m, 6H), 6.85 (d, J = 7.9 Hz, 1H), 6.78−6.64 (m, 2H), 6.39 (s, 1H), 5.75 (d, J = 17.9 Hz, 1H), 5.64 (d, J = 17.9 Hz, 1H), 5.16 (d, J = 15.3 Hz, 1H), 4.71 (d, J = 15.4 Hz, 1H), 4.51 (brs, 1H), 2.40 (s, 3H), 2.30 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.4, 143.5, 139.9, 138.1, 137.6, 137.0, 135.1, 133.4, 132.7, 132.0, 130.6, 129.8, 129.2, 129.0, 127.7, 126.6, 126.2, 126.0, 124.8, 122.8, 122.6, 118.9, 117.9, 114.7, 114.0, 110.9, 109.6, 108.1, 63.7, 49.2, 44.0, 21.3, 21.1. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 60/40; detector, 254 nm; flow rate, 0.6 mL/min; 30 °C), retention times 13.0 min (major) and 20.8 min. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{38}H_{31}ClN_3O$ 580.2150 (^{35}Cl) and 582.2141 (^{37}Cl), found 580.2146 (^{35}Cl) and 582.2136 (^{37}Cl).

(+)-11′-benzyl-2′-methyl-1-(4-methylbenzyl)-5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one (3ha). 104 mg, 95% yield, light yellow solid, new compound, mp = 127−128 °C, R_f = 0.25 (hexanes/ethyl acetate 5:1), 92% ee, $[\alpha]_D^{20}$ = +46.63 (*c* 0.98, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 7.3 Hz, 1H), 7.37−6.92 (m, 14H), 6.90−6.68 (m, 3H), 6.52 (d, J = 8.0 Hz, 1H), 6.28 (d, J = 8.0 Hz, 1H), 5.60 (m, 2H), 5.00 (d, J = 15.4 Hz, 1H), 4.66 (d, J = 15.4 Hz, 1H), 4.28 (brs, 1H), 2.28 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 142.5, 141.1, 139.8, 137.8, 137.5, 134.1, 132.8, 132.4, 129.9, 129.6, 129.1, 127.9, 127.9, 127.5, 126.2, 126.1, 123.9, 123.5, 122.4, 120.4, 118.5, 114.8, 114.6, 109.8, 109.5, 108.9, 63.7, 49.2, 43.9, 21.3, 21.0. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 60/40; detector, 254 nm; flow rate, 0.6 mL/min; 30 °C), retention times 10.7 min and 16.1 (major) min. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{38}H_{32}N_3O$ 546.2540, found 546.2543.

(−)-1′-Benzyl-2′-methyl-1-(4-methylbenzyl)-1′,5′-dihydrospiro[indoline-3,4′-pyrrolo[3,2-*c*]quinolin]-2-one (3ia). 82 mg, 83% yield, light yellow oil, new compound, R_f = 0.10 (hexanes/ethyl acetate 10:1), 88% ee, $[\alpha]_D^{20}$ = −17.32 (*c* 0.82, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.37 (m, 3H), 7.35−7.14 (m, 9H), 7.05 (t, J = 7.4 Hz, 1H), 6.93 (t, J = 7.4 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.69−6.58 (m, 2H), 5.52−5.37 (m, 3H), 5.05 (d, J = 15.5 Hz, 1H), 4.77 (d, J = 15.5 Hz, 1H), 4.28 (brs, 1H), 2.38 (s, 3H), 2.14 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.4, 141.7, 141.4, 137.7, 137.4, 133.7, 133.0, 132.3, 129.5, 129.4, 129.1, 127.6, 127.3, 126.1, 126.0, 125.9, 125.1, 123.3, 120.0, 118.9, 117.4, 116.3, 114.4, 109.3, 103.0, 63.8, 48.9, 43.7, 21.2, 12.4. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 70/30; detector, 254 nm; flow rate, 0.7 mL/min; 30 °C), retention times 13.4 min (major) and 18.2 min. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{30}N_3O$ 496.2383, found 496.2382.

(−)-1′-Benzyl-5-bromo-2′-methyl-1-(4-methylbenzyl)-1′,5′-dihydrospiro[indoline-3,4′-pyrrolo[3,2-*c*]quinolin]-2-one (3ig). 93 mg, 81% yield, yellow oil, new compound, R_f = 0.40 (hexanes/ethyl acetate 5:1), 86% ee, $[\alpha]_D^{20}$ = −46.52 (*c* 0.46, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.44−7.11 (m, 11H), 6.93 (t, J = 7.4 Hz, 1H), 6.73−6.56 (m, 3H), 5.54−5.34 (m, 3H), 5.01 (d, J = 15.6 Hz, 1H), 4.73 (d, J = 15.6 Hz, 1H), 4.24 (brs, 1H), 2.37 (s, 3H), 2.14 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.9, 140.9, 140.7, 137.6, 137.5, 135.7, 132.5, 132.5, 132.2, 129.6, 129.1, 128.4, 127.5, 127.4, 126.1, 126.1, 125.8, 120.0, 119.1, 116.5, 116.0, 115.9, 114.4, 110.9, 103.0, 63.9, 48.9, 43.7, 21.2, 12.4. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 60/40; detector, 254 nm; flow rate, 0.6 mL/min; 30 °C), retention times 14.4 min (major) and 16.4 min. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{29}BrN_3O$ 574.1489 (^{79}Br) and 576.1474 (^{81}Br), found 574.1486 (^{79}Br) and 576.1477 (^{81}Br).

(−)-1′-Benzyl-2′,5-dimethyl-1-(4-methylbenzyl)-1′,5′-dihydrospiro[indoline-3,4′-pyrrolo[3,2-*c*]quinolin]-2-one (3ih). 92 mg, 90% yield, yellow oil, new compound, R_f = 0.45 (hexanes/ethyl acetate 5:1), 76% ee, $[\alpha]_D^{20}$ = −19.42 (*c* 0.87, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, J = 7.5 Hz, 2H), 7.37−7.26 (m, 4H), 7.25−7.15 (m, 5H), 7.05 (d, J = 8.6 Hz, 1H), 6.93 (t, J = 7.3 Hz, 1H), 6.76−6.57 (m, 3H), 5.57−5.35 (m, 3H), 5.03 (d, J = 16.0 Hz, 1H), 4.76 (d, J = 15.9 Hz, 1H), 4.27 (brs, 1H), 2.38 (s, 3H), 2.30 (s, 3H), 2.15 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.4, 141.5, 139.3, 137.7, 137.3, 133.8, 133.1, 132.9, 132.3, 129.7, 129.5, 129.1, 127.6, 127.3, 126.0, 126.0, 125.9, 125.8, 119.9, 118.8, 117.4, 116.2, 114.3, 109.1, 103.1, 63.9, 48.9, 43.7, 21.2, 21.1, 12.5. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 60/40; detector, 254 nm; flow rate, 0.6 mL/min; 30 °C), retention times 12.7 min (major) and 17.6 min. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{35}H_{32}N_3O$ 510.2540, found 510.2539.

Synthesis of Formamide (*R*)-5. To a solution of (*R*)-**3aa** (170 mg, 0.32 mmol, 1.0 equiv, 97% ee) and formic acid (0.24 mL, 6.40 mmol, 20.0 equiv) in dicloromethane (3 mL) was added acetic anhydride (0.24 mL, 2.56 mmol, 8.0 equiv) at 0 °C under nitrogen. After stirring at 30 °C for 24 h, the mixture was quenched with saturated aqueous sodium bicarbonate and extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, and concentrated under vacuum. The crude mixture was purified by flash column chromatography on a silica gel using hexanes/dichloromethane/ethyl acetate as the eluent to give (*R*)-**5**.

(*R*)-11′-Benzyl-1-(4-methylbenzyl)-2-oxospiro[indoline-3,6′-indolo[3,2-*c*]quinoline]-5′(11′*H*)-carbal-dehyde (5). 138 mg, 77% yield, light yellow solid, new compound, mp = 142−144 °C, R_f = 0.25 (hexanes/ethyl acetate/dicloromethane 5:1:1), 97% ee, $[\alpha]_D^{20}$ = −446.43 (*c* 0.48, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.69 (d, J = 6.3 Hz, 2H), 7.56 (d, J = 7.6 Hz, 1H), 7.49−7.09 (m, 13H), 7.08−6.79 (m, 5H), 5.76 (d, J = 18.0 Hz, 1H), 5.43 (d, J = 15.1 Hz, 1H), 5.29 (d, J = 17.8 Hz, 1H), 5.16 (d, J = 15.3 Hz, 1H), 2.46 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.4, 159.9, 141.7, 140.0, 137.5, 137.2, 134.9, 132.7, 131.0, 129.7, 129.7, 129.2, 128.6, 128.6, 128.2, 127.6, 126.0, 125.9, 123.8, 123.6, 123.4, 123.2, 123.2, 121.1, 119.9, 119.2, 119.1, 111.6, 110.4, 109.6, 65.0, 49.0, 45.1, 21.4. Enantiomeric excess was determined by HPLC (IA column; eluent, *n*-hexane/*i*-PrOH = 60/40; detector, 230 nm; flow rate, 0.6 mL/min; 30 °C), retention times 34.2 min (major) and 38.7 min. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{38}H_{30}N_3O_2$ 560.2333, found 560.2331.

Synthesis of Formamide Indoline (*R*)-6. To a solution of (*R*)-**3aa** (91 mg, 0.17 mmol, 1.0 equiv, 90% ee) in tetrahydrofuran (4 mL) was added borane−methyl sulfide complex (85 μL, 0.85 mmol, 5.0 equiv) at 0 °C under nitrogen. After stirring at 30 °C for 24 h, borane−methyl sulfide complex (51 μL, 0.51 mmol, 3.0 equiv) was added, and the mixture was stirred for 12 h. The reaction was quenched with methanol at 0 °C and concentrated under vacuum.

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The crude mixture was purified by preparative TLC on silica gel (hexanes/ethyl acetate 10:1) to give (*R*)-**6**.

(*R*)-11′-Benzyl-1-(4-methylbenzyl)-5′,11′-dihydrospiro-[indoline-3,6′-indolo[3,2-*c*]quinoline] (6). 49 mg, 55% yield, colorless oil, new compound, R_f = 0.70 (hexanes/ethyl acetate 10:1), 85% ee, $[\alpha]_D^{20}$ = +37.24 (*c* 0.98, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.27 (m, 10H), 7.26−7.14 (m, 4H), 7.08−6.98 (m, 3H), 6.91−6.81 (m, 2H), 6.71−6.62 (dd, *J* = 9.5, 8.2 Hz, 2H), 5.76 (d, *J* = 17.9 Hz, 1H), 5.63 (d, *J* = 17.9 Hz, 1H), 4.61 (brs, 1H), 4.52 (d, *J* = 14.6 Hz, 1H), 4.31 (d, *J* = 14.6 Hz, 1H), 3.72 (d, *J* = 10.1 Hz, 1H), 3.64 (d, *J* = 10.1 Hz, 1H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.4, 143.2, 139.8, 137.8, 137.0, 134.7, 133.3, 132.5, 129.7, 129.3, 129.1, 128.2, 128.2, 127.5, 126.2, 126.0, 124.3, 122.4, 122.2, 120.2, 120.0, 118.8, 118.3, 114.9, 114.9, 112.7, 109.7, 108.2, 66.4, 63.6, 52.7, 48.9, 21.2. Enantiomeric excess was determined by HPLC (AD-H column; eluent, *n*-hexane/*i*-PrOH = 90/10; detector, 254 nm; flow rate, 0.8 mL/min; 30 °C), retention times 8.6 min (major) and 11.6 min. HRMS (ESI) *m*/*z*: $[M + K]^+$ calcd for $C_{37}H_{31}KN_3$ 556.2150, found 556.2151.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00289.

NMR spectra of products and HPLC for racemic and chiral products of all compounds (PDF)

Accession Codes

CCDC 2041080 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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