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Asymmetric Organocatalytic Cascade Synthesis of Tetrahydrofuranyl Spirooxindoles

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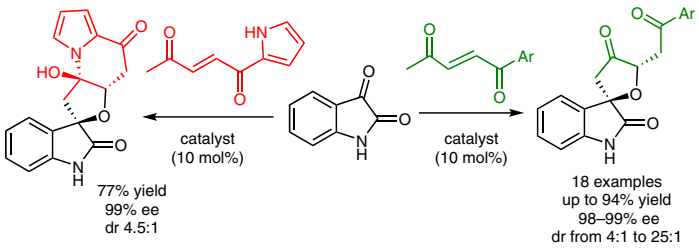
Dedicated to Professor Victor Snieckus on the occasion of his 80th birthday



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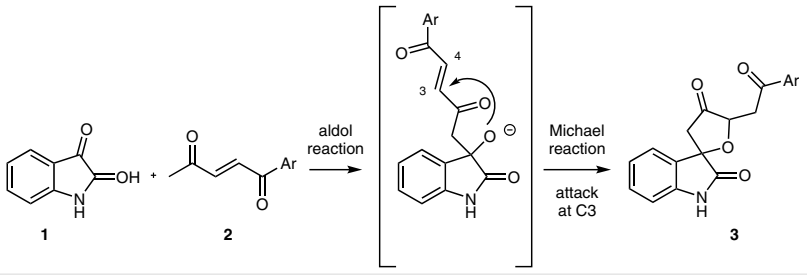
Abstract An enantio- and regioselective organocatalytic cascade starting from isatin has been disclosed to construct tetrahydrofuranyl spirooxindoles in high yields and stereoselectivities. Also, a triple cascade leading to the pentacyclic compound with two quaternary and a tertiary stereocenter is described. The reactions were catalyzed by cinchonine-based thiourea.

Key words organocatalysis, domino reaction, enantioselectivity, heterocycles, Michael addition

Spirooxindoles are important targets for pharmaceutical chemistry, and they are also of interest in asymmetric synthesis. Their broad spectrum of biological activities is well known.[2] This has led to the development of a plethora of methods applied to the synthesis of spirooxindoles.[3] The most efficient methods are catalytic cascade reactions allowing for the construction of the target skeleton in one step.[4] In the course of the reaction, the planar structure of the oxindole scaffold is converted into a nonplanar, rigid, and spatially orientated chiral spiro-ring fused bicyclic system containing quaternary stereocenter and usually a tertiary center in the formed ring. The control of enantio- and diastereoselectivity in one step remains a challenge.

Spirooxindoles with oxacycles have been found in many biologically important synthetic and natural compounds.[5] Different approaches have been used to reach the target. Enantiomerically enriched oxa-spirooxindoles (excluding spirolactones) have been obtained via an aminocatalytic vinylogous cascade reaction of 3-hydroxyoxindoles,[6] [3+2] annulation,[7] or by step-by-step reaction of isatin and 1,3-diketones.[8] Racemic derivatives have been synthesized by a cooperative Lewis acid-NHC catalyzed addition of alkynyl aldehydes to isatins,[9] by a Friedel–Crafts reaction,[10] a DBU-induced aldol reaction of a pyruvic aldehyde derivative with isatin,[11] and by formal NHC-catalyzed [3+2] annulations.[5c]

Isatin (**1**)[12] and multifunctional enolizable unsaturated 1,4-diketones **2** are perfect starting materials for the cascade synthesis of tetrahydrofuranyl spirooxindoles (Scheme 1). The aldol reaction between C1 enol nucleophile derived from compound **2** and isatin followed by the intramolecular Michael addition at C3 leads directly to the cyclization and



Scheme 1 Principal scheme of synthesis of tetrahydrofuranyl spirooxindoles

the formation of spiro compounds **3** containing quaternary and tertiary stereogenic centers. Alternatively, a six-membered tetrahydropyranyl derivative could be obtained via attack at C4.[13]

Our previous experience in the field of asymmetric organocatalytic reactions of 1,4-unsaturated dicarbonyl compounds[14] and oxindole derivatives[15] enabled us to substantially restrict the list of potential catalysts and solvents. Only thioureas derived from cinchonine (catalyst **I**) and dihydroquinine (catalyst **II**) were screened (Figure 1) and toluene was the solvent of choice.

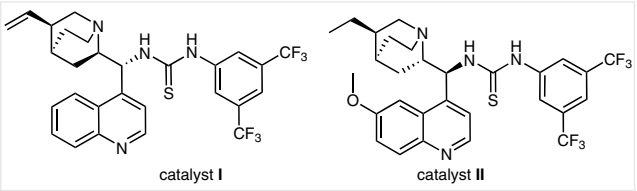
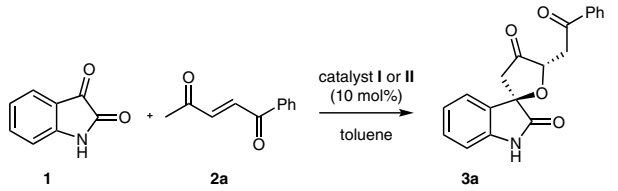


Figure 1 Catalysts screened

To our great delight, both catalysts revealed high efficiency and selectivity (Table 1). The model reaction between unprotected isatin (**1**) and phenyl diketone **2a** in toluene afforded the title compound in high yield and selectivity (Table 1, entries 1 and 2). No six-membered-ring product was detected, nor were N-alkylated derivatives obtained by us previously under the same reaction conditions with isatin *N*-phenylimine.[14c] Because of the higher diastereoselectivity of the reaction, catalyst **I** was chosen for further studies. The diastereoselectivity was increased to a very high level in the presence of that catalyst at –20 °C (entry 3). These good results enabled us to keep the optimization procedure short and start an investigation into the scope of the reaction.

Table 1 Screening of the Catalyst[a]

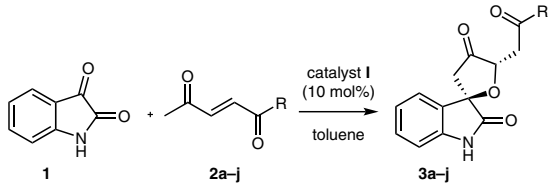


Entry	Catalyst	Time (h)	Yield (%)[b]	ee (%)[c]	dr[d]
1	**I**	0.5	88	99	9:1
2	**II**	0.5	90	–97	6:1
3[e]	**I**	24	92	99	20:1

[a] Reaction conditions: **1** (1 equiv), **2a** (2 equiv) in toluene at r.t.
[b] Isolated yield.
[c] ee of the major diastereoisomer determined by chiral HPLC.
[d] Determined by ^{1}H NMR analysis of the crude mixture.
[e] Reaction at –20 °C.

First, the influence of substituents of unsaturated 1,4-diketones **2** was explored (Table 2). Differently substituted aryl, heteroaryl, or aliphatic diketones were used. The reaction was carried out in toluene for 24 hours. Depending on the temperature this was enough to achieve high to full conversion of the starting materials and high yield of the products within 24 hours. The substitution pattern did not affect the enantioselectivity of the reaction and it was equally high for all substrates. Also, the diastereoselectivity was not substantially dependent on the electronic effects of substituents. More evidence was provided by the dependence on temperature. A decrease in temperature increased the diastereolectivity (Table 2, entries 1 and 2). The obtained diastereoisomers were in most cases chromatographically separable, allowing for further increase in the purity of products. Pyrrolyl-substituted diketone **2i** and aliphatic symmetric diketone **2j** were exceptional due to their lower reactivities and diastereoselectivities (entries 10 and 11) (the reaction with pyrrole derivative **2i** will be discussed later). It is worth mentioning that in the case of less reactive aliphatic diketone **2j**, the five-membered product was exclusively obtained meaning that the regioselectivity is not connected with the reactivity of the Michael acceptor. Other unsaturated 1,4-dicarbonyl compounds, such as keto esters, afforded only the products of the aldol reaction and no cyclization followed.

Table 2 Scope of Unsaturated Diketones[a]



entry	R	Temp (°C)	Yield (%)[b]	ee (%)[c]	dr[d]
1	**a**: Ph	20	88	99	9:1
2	**a**: Ph	–20	92	99	20:1
3	**b**: 4-MeOC$_6$H$_4$	2	91	99	11:1
4	**c**: 4-NO$_2$C$_6$H$_4$	2	70	99	10:1
5	**d**: 4-BrC$_6$H$_4$	–20	92	99	>25:1
6	**e**: 4-ClC$_6$H$_4$	–20	91	98	>25:1
7	**f**: 2-naphthyl	2	90	99	12:1
8	**g**: 2-thienyl	2	89	99	11:1
9	**h**: 2-furyl	2	90	99	10:1
10	**i**: 2-pyrrolyl[e]	20	93	99	7:1
11	**j**: Me	2	88	99	4:1

[a] Reaction conditions: **1** (1 equiv), **2a** (2 equiv) in toluene.
[b] Isolated yield.
[c] ee of the major diastereoisomer determined by chiral HPLC.
[d] Determined by ^{1}H NMR analysis of the crude mixture.
[e] Reaction time: 4 days.

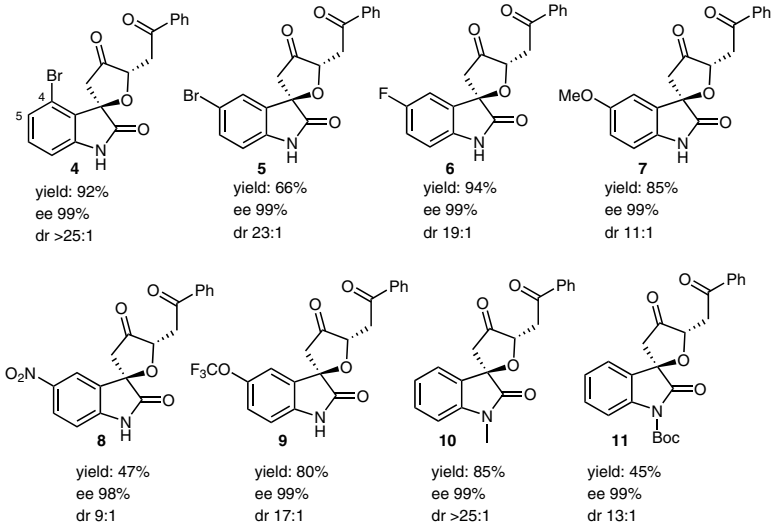


Figure 2 Scope of isatin derivatives. Yields given are for isolated products; ee of the major diastereoisomer determined by chiral HPLC analysis; dr determined by ^{1}H NMR analysis of the crude mixture.

To further expand the substrate scope, a series of substituted isatins were used in the cascade reaction (Figure 2).

The introduction of electron-donating or electron-withdrawing groups in the fourth or fifth position of isatin was tolerated and showed little effect on the outcomes, with stereoselectivity (both enantio- and diastereolecectivity) remaining high (Figure 2, compounds **4**–**10**). It is worth mentioning that the reaction with *N*-methylisatin afforded the product with as high enantiomeric purity as in the case of unprotected isatin indicating that the NH proton is not involved in the formation of the stereodetermining transition state. Yields of the products were more variable (from 45 to 94%). The low yield of nitro compound **8** was most probably caused by solubility problems.

Boc-protected isatin was less reactive affording product **11** only in 45% yield after 24-hour reaction. However, when isatin *S*- or *O*-equivalents benzo[*b*]thiophene-2,3-dione and 2,3-benzofurandione were used, no corresponding products were formed at all. The absolute configuration of product **10** was determined by single-crystal X-ray crystallography and other products were assigned by analogy (Figure 3, left).

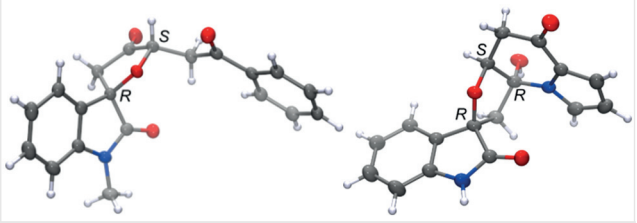
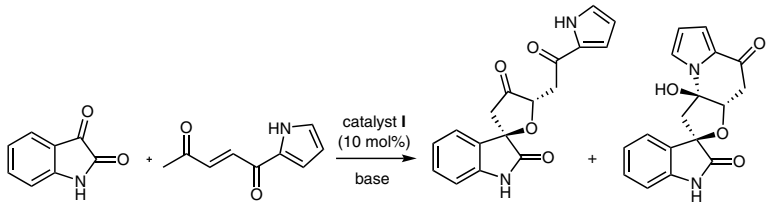


Figure 3 X-ray crystal structures of compound **10** (left) and **12** (right); see Supporting Information for details

Pyrrole-substituted diketone **2i** has lower reactivity than other diketones and higher temperature and longer reaction time were needed to achieve high yield (Table 2, entry 10). It was found that the obtained spirooxindole **3i** can further be converted to pentacyclic spirocompound **12**. The reaction was explored in detail (Table 3). Under standard conditions, the reaction afforded only traces of the pentacyclic compound **12** (Table 3, entry 1). Because of the long reaction time and low solubility of the starting compounds and intermediates in toluene, other solvents were tested (DCE, DMSO, and MeCN). The change of the nonpolar solvent to the more polar acetonitrile led to the increase in the yield of the pentacycle (entry 2). It was assumed that the use of an additional base as a cocatalyst would accelerate the reaction. Of the various bases used (DBU, NaOMe, and DIPEA) only DIPEA afforded reasonable results (entry 3). However, the reaction without the base was found to be most reasonable. As products **3i** and **12** are chromatographically separable, the pentacycle **12** was isolated in 77% yield with 99% of enantiomeric purity. The diastereomeric purity of the pentacycle was increased considerably during column chromatography and a single diastereoisomer was isolated. A triple cascade consists of the aldol reaction, oxa-Michael addition affording enolate, which is in equilibrium with the deprotonated pyrrole followed by the nucleophilic addition to the carbonyl group of the tetrahydrofuranyl cycle (Scheme 2). The direct conversion of the tricyclic compound **3i** into pentacyclic in the presence of a base was very slow indicating the essential role of the thiourea catalyst in the course of the reaction. The absolute configuration of the product **12** was determined by X-ray crystallography (Figure 3, right). It is noteworthy that the quaternary stereo-

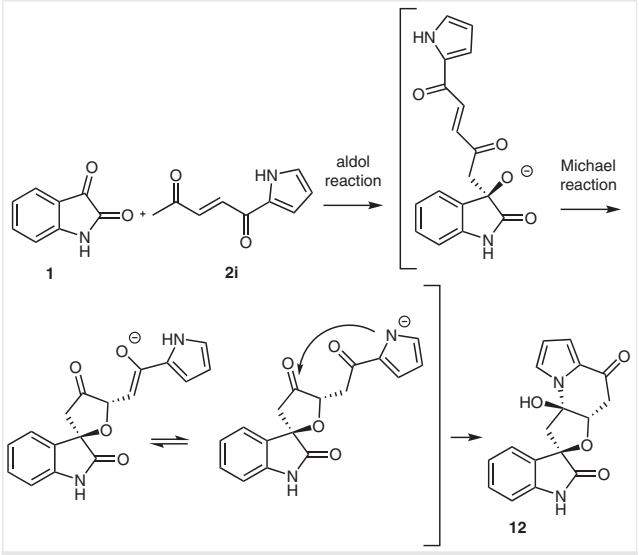
Table 3 Synthesis of Pentacycle **12** via Triple Cascade[a]



Entry	Solvent	Base	Time (d)	Yield (%) of **3i**[b]	Yield (%) of **12**[b]	ee (%) of **12**[c]	dr of **12**[d]	Ratio **3i**/**12**
1	toluene	–	4	93	~3	nd	nd	31:1
2	MeCN	–	3	19	77	>99	4.5:1	1:4
3	toluene	DIPEA (30 mol%)	6	14	75	98	4.5:1	1:5.4

[a] Reaction conditions: **1** (1 equiv), **2i** (1.5 equiv) at r.t.
[b] Isolated yield.
[c] ee of the major diastereoisomer determined by chiral HPLC; nd = not determined.
[d] Determined by ^{1}H NMR analysis of the crude mixture.

center at C3 of isatin has the same configuration in compounds **10** and **12**, again revealing a similar activation mode for NMe protected and unprotected NH isatin.



Scheme 2 Formation of the pentacycle **12** via triple cascade

Based on the experimental and crystallographic data, we propose a model of the transition state. The first aldol step is the stereodetermining step of the cascade. Achieving enantiofacial discrimination of the planar isatin molecule attack to one face of it is clearly preferable. The catalyst should act as a base allowing enolization of the diketone. The formation of the second stereogenic center in the oxa-Michael reaction is also stereoselective. Thus, it is expected that bifunctional catalyst **I** is bonded via hydrogen bonds with both starting materials keeping them in close proximity for the stereoselective reactions (Figure 4). The quinuclidine unit of the catalyst is pointed backwards, placing enolized diketone (fixed by hydrogen bonds at O2 and O5) in the position of allowing nucleophilic attack on the carbonyl group of isatin from the *si*-face, affording the product with *R*-configuration. The hydrogen bond between the thiourea moiety and O5 of diketone prevents the free rotation of the chain attached to isatin and activates the C3 position for the oxa-Michael attack. Isatin is fixed to this catalytic complex via the hydrogen bond of another thiourea NH-proton and possible π–π interaction of aromatic rings.

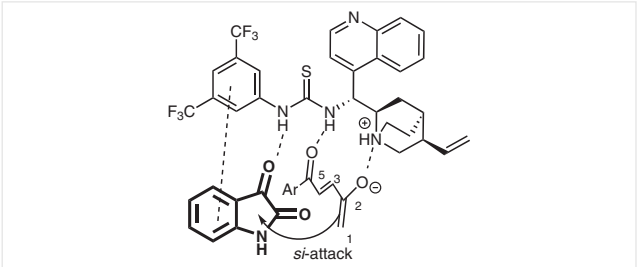


Figure 4 Plausible reaction course

In conclusion, we have revealed a new efficient organocatalytic cascade to tetrahydrofuranyl spirooxindoles. It is the first example where enolizable unsaturated 1,4-diketones were used as multifunctional synthons in a cascade reaction. High levels of diastereoselectivity and enantioselectivity (ee up to 99%) were observed, with yields ranging from 45 to 94%. Both electron-donating and -withdrawing groups were well tolerated at the aromatic ring of diketones as were the heteroaromatic substituents. A new triple cas-

cade afforded a pentacyclic compound with two quaternary, and one tertiary, stereogenic centers in high enantiomeric purity.

Full assignments of ^{1}H and ^{13}C chemical shifts are based on the 1D and 2D FT NMR spectra measured on a Bruker Avance III 400 MHz instrument. Residual solvent signals were used [$CDCl_3$ δ = 7.26 (^{1}H NMR), 77.16 (^{13}C NMR)] as internal standards. High-resolution mass spectra were recorded by using an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. Single crystal X-ray diffraction data was collected at 123K on Rigaku Compact HomeLab diffractometer, equipped with a Saturn 944 HG CCD detector and Oxford Cryostream cooling system using monochromatic Cu-Kα radiation (1.54178Å) from a MicroMax™-003 sealed tube microfocus X-ray source. Optical rotations were obtained using an Anton Paar GWB Polarimeter MCP 500. Chiral HPLC was performed using Chiralpak AD-H (250 × 4.6 mm), Chiralcel OD-H (250 × 4.6 mm) columns. Precoated silica gel 60 F_{254} plates from Merck were used for TLC, whereas for column chromatography silica gel 40–63 µm was used. The measured melting points are uncorrected. Purchased chemicals and solvents were used as received. CH_2Cl_2 was distilled over P_2O_5. Petroleum ether (PE) has a boiling point 40–60 °C. The reactions were performed without additional moisture elimination unless stated otherwise. Racemic standards were obtained by reactions of the corresponding starting compounds in the presence of racemic Takemoto catalyst in toluene.

Bifunctional thiourea catalysts **I**,[16] **II**,[16] Takemoto catalyst,[17] and unsaturated 1,4-diketones[14b] were prepared by corresponding literature procedures and the analytical data matched with that of the literature.

Asymmetric Synthesis of Tetrahydrofuranyl Spirooxindoles; (2*R*,5*S*)-5-(2-Oxo-2-phenylethyl)-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (3a); Typical Procedure

Isatin **1** (147.1 mg, 1 mmol), (*E*)-1-phenylpent-2-ene-1,4-dione (**2a**, 348.4 mg, 2 mmol), and thiourea **I** (57 mg, 0.1 mmol) were cooled to –20 °C, dissolved in toluene (3 mL), and the mixture was stirred at –20 °C for 24 h. The progress of the reaction was monitored by TLC and NMR spectroscopy. The product was isolated by direct column chromatography on silica gel (CH_2Cl_2/EtOAc 95:5 to 85:15) in 92% yield (296 mg, 0.92 mmol) as a white solid; mp 74–76 °C; $[\alpha]_D^{22}$ +134.8 (*c* 0.097, $CHCl_3$); dr 20:1, ee 99% (Chiralcel OD-H, hexane/*i*-PrOH 90:10, 1.2 mL/min, 25 °C, λ= 210 nm; major t_R = 28.7 min, minor t_R = 20.4 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1 H), 7.99–7.92 (m, 2 H), 7.58–7.51 (m, 1 H), 7.46–7.35 (m, 3 H), 7.29–7.21 (m, 1 H), 7.12–7.04 (m, 1 H), 6.84 (d, *J* = 7.7 Hz, 1 H), 5.13 (dd, *J* = 8.6, 2.9 Hz, 1 H), 3.81 (dd, *J* = 17.9, 8.6 Hz, 1 H), 3.51 (dd, *J* = 17.9, 2.9 Hz, 1 H), 3.06 (d, *J* = 18.0 Hz, 1 H), 2.94 (dd, *J* = 18.0, 0.9 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.5, 196.5, 177.8, 141.0, 136.6, 133.6, 130.9, 128.8 (2 C), 128.6, 128.5 (2 C), 124.6, 123.7, 110.8, 80.7, 77.3, 43.9, 42.2.

HRMS (ESI): *m*/*z* calcd for $(C_{19}H_{15}NO_4Na)^+$ [M + Na]$^+$: 344.0893; found: 344.0890.

(2*R*,5*S*)-5-[2-(4-Methoxyphenyl)-2-oxoethyl]-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (3b)

The title compound was obtained according to the typical procedure from isatin (**1**; 14.7 mg, 0.1 mmol) and (*E*)-1-(4-methoxyphenyl)pent-2-ene-1,4-dione (**2b**; 40.8 mg, 0.2 mmol). The reaction was carried out at +2 °C for 24 h. The product was isolated by direct column chromatography on silica gel (PE/EtOAc 77:33 to 60:40) in 91% yield (31.9 mg, 0.091 mmol) as a white solid; mp 148–152 °C; $[\alpha]_D^{22}$ +142.3 (*c* 0.123, $CHCl_3$); dr 11:1, ee 99% (Chiralcel OD-H, hexane/*i*-PrOH 90:10, 1.2 mL/min, 35 °C, λ = 254 nm; major t_R = 41.0 min, minor t_R = 24.4 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (s, 1 H), 7.98–7.89 (m, 2 H), 7.38 (d, *J* = 7.5 Hz, 1 H), 7.25 (td, *J* = 7.8, 1.2 Hz, 1 H), 7.07 (td, *J* = 7.6, 0.8 Hz, 1 H), 6.91–6.86 (m, 2 H), 6.84 (d, *J* = 7.8 Hz, 1 H), 5.12 (dd, *J* = 8.6, 2.7 Hz, 1 H), 3.83 (s, 3 H), 3.77 (dd, *J* = 17.6, 8.7 Hz, 1 H), 3.43 (dd, *J* = 17.6, 2.8 Hz, 1 H), 3.05 (d, *J* = 18.0 Hz, 1 H), 2.98–2.88 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.7, 195.0, 177.8, 163.9, 141.0, 130.8 (3 C), 129.7, 128.7, 124.6, 123.7, 113.9 (2 C), 110.8, 80.7, 77.5, 55.6, 43.9, 41.8.

HRMS (ESI): *m*/*z* calcd for $(C_{20}H_{17}NO_5Na)^+$ [M + Na]$^+$: 374.0999; found: 374.1001.

(2*R*,5*S*)-5-[2-(4-Nitrophenyl)-2-oxoethyl]-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (3c)

The title compound was obtained according to the typical procedure from isatin (**1**; 14.7 mg, 0.1 mmol) and (*E*)-1-(4-nitrophenyl)pent-2-ene-1,4-dione (**2c**; 43.8 mg, 0.2 mmol). The reaction was carried out at +2 °C for 24 h. The product was isolated by direct column chromatography on silica gel (CH_2Cl_2/EtOAc 95:5 to 85:15) in 70% yield (25.6 mg, 0.070 mmol) as a white solid; mp 85–87 °C; $[\alpha]_D^{22}$ +157.2 (*c* 0.086, $CHCl_3$); dr 10:1, ee 99% (Chiralpak AD-H, hexane/*i*-PrOH 70:30, 1 mL/min, 30 °C, λ = 254 nm; major t_R = 56.5 min, minor t_R = 33.0 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33–8.23 (m, 3 H), 8.16–8.05 (m, 3 H), 7.98 (s, 1 H), 7.40 (d, *J* = 7.4 Hz, 1 H), 7.33–7.24 (m, 2 H), 7.11 (t, *J* = 7.6 Hz, 1 H), 6.86 (d, *J* = 7.8 Hz, 1 H), 5.11 (dd, *J* = 8.7, 2.8 Hz, 1 H), 3.87 (dd, *J* = 17.8, 8.7 Hz, 1 H), 3.53 (dd, *J* = 17.8, 2.9 Hz, 1 H), 3.04 (d, *J* = 18.1 Hz, 1 H), 2.97 (d, *J* = 18.1 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 211.8, 195.4, 177.7, 150.6, 141.0, 140.9, 131.1, 129.5 (2 C), 128.2, 124.7, 124.0 (2 C), 123.9, 110.8, 80.9, 77.2, 43.8, 42.7.

HRMS (ESI): *m*/*z* calcd for $(C_{19}H_{14}N_2O_6Na)^+$ [M + Na]$^+$: 389.0744; found: 389.0745.

(2*R*,5*S*)-5-[2-(4-Bromophenyl)-2-oxoethyl]-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (3d)

The title compound was obtained according to the typical procedure from isatin (**1**; 14.7 mg, 0.1 mmol) and (*E*)-1-(4-bromophenyl)pent-2-ene-1,4-dione (**2d**; 50.6 mg, 0.2 mmol). The reaction was carried out at –20 °C for 24 h. The product was isolated by direct column chromatography on silica gel (CH_2Cl_2/EtOAc 95:5 to 85:15) in 92% yield (36.8 mg, 0.092 mmol) as a white solid; mp 78–81 °C; $[\alpha]_D^{22}$ +150.3 (*c* 0.138, $CHCl_3$); dr >25:1, ee 99% (Chiralpak AD-H, hexane/*i*-PrOH 80:20, 1 mL/min, 30 °C, λ = 254 nm; major t_R = 40.6 min, minor t_R = 44.9 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (s, 1 H), 7.81 (d, *J* = 8.6 Hz, 2 H), 7.57 (d, *J* = 8.6 Hz, 2 H), 7.39 (d, *J* = 7.5 Hz, 1 H), 7.27 (td, *J* = 7.7, 1.1 Hz, 1 H), 7.09 (t, *J* = 7.3 Hz, 1 H), 6.84 (d, *J* = 7.8 Hz, 1 H), 5.10 (dd, *J* = 8.6, 2.7 Hz, 1 H), 3.78 (dd, *J* = 17.8, 8.6 Hz, 1 H), 3.46 (dd, *J* = 17.8, 2.9 Hz, 1 H), 3.04 (d, *J* = 18.0 Hz, 1 H), 2.95 (d, *J* = 17.9 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.3, 195.6, 177.9, 141.0, 135.3, 132.1 (2 C), 130.9, 130.0 (2 C), 128.9, 128.5, 124.6, 123.7, 110.8, 80.8, 77.2, 43.9, 42.1.

HRMS (ESI): *m*/*z* calcd for $(C_{19}H_{14}BrNO_4Na)^+$ [M + Na]$^+$: 421.9998; found: 422.0001.

(2*R*,5*S*)-5-[2-(4-Chlorophenyl)-2-oxoethyl]-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (3e)

The title compound was obtained according to the typical procedure from isatin (**1**; 14.7 mg, 0.1 mmol) and (*E*)-1-(4-chlorophenyl)pent-2-ene-1,4-dione (**2e**; 41.6 mg, 0.2 mmol). The reaction was carried out at –20 °C for 24 h. The product was isolated by direct column chromatography on silica gel (CH_2Cl_2/EtOAc 95:5 to 85:15) in 91% yield (32.4 mg, 0.091 mmol) as a white solid; mp 75–78 °C; $[\alpha]_D^{22}$ +136.5 (*c* 0.092; $CHCl_3$); dr >25:1, ee 98% (Chiralpak AD-H, hexane/*i*-PrOH 90:10, 1 mL/min, 35 °C, 254 nm; major t_R = 23.8 min, minor t_R = 19.4 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (s, 1 H), 7.94–7.85 (m, 2 H), 7.45–7.36 (m, 3 H), 7.28 (td, *J* = 7.8, 1.2 Hz, 1 H), 7.14–7.05 (m, 1 H), 6.84 (d, *J* = 7.8 Hz, 1 H), 5.11 (dd, *J* = 8.6, 2.8 Hz, 1 H), 3.79 (dd, *J* = 17.8, 8.7 Hz, 1 H), 3.47 (dd, *J* = 17.8, 2.9 Hz, 1 H), 3.04 (d, *J* = 18.1 Hz, 1 H), 2.95 (dd, *J* = 18.0, 0.9 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.3, 195.4, 177.93, 141.0, 140.1, 134.9, 130.9, 129.9 (2 C), 129.1 (2 C), 128.5, 124.6, 123.8, 110.8, 80.8, 77.3, 43.9, 42.1.

HRMS (ESI): *m*/*z* calcd for $(C_{19}H_{14}ClNO_4Na)^+$ [M + Na]$^+$: 378.0504; found: 378.0506.

(2*R*,5*S*)-5-[2-(Naphthalen-2-yl)-2-oxoethyl]-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (3f)

The title compound was obtained according to the typical procedure from isatin (**1**; 14.7 mg, 0.1 mmol) and (*E*)-1-(naphthalen-2-yl)pent-2-ene-1,4-dione (**2f**; 44.8 mg, 0.2 mmol). The reaction was carried out at +2 °C for 24 h. The product was isolated by direct column chromatography on silica gel (PE/EtOAc 77:33 to 60:40) in 90% yield (33.4 mg, 0.090 mmol) as a white solid; mp 98–101 °C; $[\alpha]_D^{22}$ +189.8 (*c* 0.105, $CHCl_3$); dr 12:1, ee 99% (Chiralpak AD-H, hexane/*i*-PrOH 80:20, 1 mL/min, 30 °C, λ = 254 nm; major t_R = 53.0 min, minor t_R = 37.4 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (s, 1 H), 8.04 (dd, *J* = 8.7, 1.7 Hz, 1 H), 7.98 (d, *J* = 8.0 Hz, 1 H), 7.91–7.83 (m, 2 H), 7.65–7.50 (m, 2 H), 7.43 (d, *J* = 7.5 Hz, 1 H), 7.35–7.24 (m, 1 H), 7.11 (td, *J* = 7.6, 0.9 Hz, 1 H), 6.83 (d, *J* = 7.8 Hz, 1 H), 5.21 (dd, *J* = 8.8, 2.7 Hz, 1 H), 3.99 (dd, *J* = 17.7, 8.8 Hz, 1 H), 3.63 (dd, *J* = 17.7, 2.8 Hz, 1 H), 3.08 (d, *J* = 18.0 Hz, 1 H), 2.98 (dd, *J* = 18.0, 0.9 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.6, 196.5, 177.9, 141.0, 135.8, 133.9, 132.5, 130.8, 130.5, 129.8, 128.7, 128.60, 128.57, 127.8, 126.9, 124.6, 123.9, 123.6, 110.8, 80.8, 77.4, 43.9, 42.2.

HRMS (ESI): *m*/*z* calcd for $(C_{23}H_{18}NO_4)^+$ [M + H]$^+$: 372.1230; found: 372.1231.

(2*R*,5*S*)-5-[2-Oxo-2-(thiophen-2-yl)ethyl]-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (3g)

The title compound was obtained according to the typical procedure from isatin (**1**; 14.7 mg, 0.1 mmol) and (*E*)-1-(thiophen-2-yl)pent-2-ene-1,4-dione (**2g**; 36 mg, 0.2 mmol). The reaction was carried out at +2 °C for 24 h. The product was isolated by direct column chromatography on silica gel (CH_2Cl_2/EtOAc 95:5 to 85:15) in 89% yield (29.1 mg, 0.091 mmol) as a white solid; mp 65–67 °C; $[\alpha]_D^{22}$ +85.9 (*c* 0.108; $CHCl_3$); dr 11:1, ee 99% (Chiralpak AD-H, hexane/*i*-PrOH 70:30, 1 mL/min, 30 °C, λ = 254 nm; major t_R = 20.5 min, minor t_R = 15.4 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (s, 1 H), 7.75 (d, *J* = 3.5 Hz, 1 H), 7.63 (d, *J* = 4.8 Hz, 1 H), 7.38 (d, *J* = 7.4 Hz, 1 H), 7.32–7.23 (m, 1 H), 7.13–7.05 (m, 2 H), 6.86 (d, *J* = 7.8 Hz, 1 H), 5.10 (dd, *J* = 8.9, 2.4 Hz, 1 H), 3.78 (dd, *J* = 17.0, 9.0 Hz, 1 H), 3.39 (dd, *J* = 17.1, 2.8 Hz, 1 H), 3.03 (d, *J* = 18.0 Hz, 1 H), 2.94 (d, *J* = 18.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.0, 189.4, 177.8, 143.9, 141.0, 134.5, 133.1, 130.9, 128.5, 128.4, 124.6, 123.7, 110.8, 80.8, 77.5, 43.9, 42.76.

HRMS (ESI): *m*/*z* calcd for $(C_{17}H_{13}N_2O_4SNa)^+$ [M + Na]$^+$: 350.0457; found: 350.0458.

(2*R*,5*S*)-5-[2-(Furan-2-yl)-2-oxoethyl]-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (3h)

The title compound was obtained according to the typical procedure from isatin (**1**; 14.7 mg, 0.1 mmol) and (*E*)-1-(furan-2-yl)pent-2-ene-1,4-dione (**2h**; 32.8 mg, 0.2 mmol). The reaction was carried out at +2 °C for 24 h. The product was isolated by direct column chromatography on silica gel (CH_2Cl_2/EtOAc 95:5 to 85:15) in 90% yield (28 mg, 0.085 mmol) as a white solid; mp 58–62 °C; $[\alpha]_D^{22}$ +85.4 (*c* 0.099, $CHCl_3$); dr 10:1, ee 99% (Chiralpak AD-H, hexane/*i*-PrOH 80:20, 1 mL/min, 30 °C, λ = 254 nm; major t_R = 30.5 min, minor t_R = 21.4 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (s, 1 H), 7.59–7.53 (m, 1 H), 7.37 (d, *J* = 7.4 Hz, 1 H), 7.30–7.24 (m, 1 H), 7.23 (d, *J* = 3.6 Hz, 1 H), 7.13–7.02 (m, 1 H), 6.87 (d, *J* = 7.8 Hz, 1 H), 6.50 (dd, *J* = 3.6, 1.7 Hz, 1 H), 5.07 (dd, *J* = 8.8, 3.0 Hz, 1 H), 3.67 (dd, *J* = 17.2, 8.8 Hz, 1 H), 3.35 (dd, *J* = 17.3, 3.0 Hz, 1 H), 3.04 (d, *J* = 18.0 Hz, 1 H), 2.93 (d, *J* = 18.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.0, 185.4, 177.8, 152.4, 147.1, 141.1, 130.9, 128.5, 124.6, 123.7, 118.6, 112.5, 110.8, 80.8, 77.1, 43.8, 41.9.

HRMS (ESI): *m*/*z* calcd for $(C_{17}H_{13}NO_5Na)^+$ [M + Na]$^+$: 334.0686; found: 334.0681.

(2*R*,5*S*)-5-[2-Oxo-2-(1*H*-pyrrol-2-yl)ethyl]-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (3i)

Isatin (**1**; 14.7 mg, 0.1 mmol), (*E*)-1-(1*H*-pyrrol-2-yl)pent-2-ene-1,4-dione (**2i**; 24.5 mg, 0.15 mmol), and thiourea **I** (5.7 mg, 0.01 mmol) were dissolved in toluene (1 mL) and the reaction mixture was stirred at +20 °C for 4 days. The product was isolated by direct column chromatography on silica gel (CH_2Cl_2/MeOH 99:1 to 96:4) in 93% yield (28.8 mg, 0.093 mmol) as a white solid; mp 180–182 °C; $[\alpha]_D^{25}$ +71.2 (*c* 0.078, $CHCl_3$); dr 7:1, ee 99% (Chiralcel OD-H, hexane/*i*-PrOH 92:8, 1.2 mL/min, 25 °C, λ = 254 nm; major t_R = 31.0 min, minor (t_R = 34.6 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.42 (s, 1 H), 7.64 (s, 1 H), 7.37 (d, *J* = 7.4 Hz, 1 H), 7.27 (td, *J* = 7.8, 1.2 Hz, 2 H), 7.08 (td, *J* = 7.6, 0.8 Hz, 1 H), 7.01 (td, *J* = 2.7, 1.3 Hz, 1 H), 6.98 (ddd, *J* = 3.8, 2.4, 1.3 Hz, 1 H), 6.84 (d, *J* = 7.7 Hz, 1 H), 6.25 (dt, *J* = 3.9, 2.5 Hz, 2 H), 5.06 (dd, *J* = 9.0, 3.0 Hz, 1 H), 3.65 (dd, *J* = 16.6, 9.0 Hz, 1 H), 3.26 (dd, *J* = 16.6, 3.1 Hz, 1 H), 3.06 (d, *J* = 18.0 Hz, 1 H), 2.91 (dd, *J* = 18.0, 1.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.2, 186.2, 177.4, 140.8, 131.7, 130.7, 128.7, 125.3, 124.4, 123.5, 117.6, 111.0, 110.6, 80.5, 77.6, 43.7, 41.1.

HRMS (ESI): *m*/*z* calcd for $(C_{14}H_{14}N_2O_4Na)^+$ [M + Na]$^+$: 333.0846; found: 333.0857.

(2*R*,5*S*)-5-(2-Oxopropyl)-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (3j)

The title compound was obtained according to the typical procedure from isatin (**1**; 14.7 mg, 0.1 mmol) and (*E*)-hex-3-ene-2,5-dione (**2j**; 22.4 mg, 0.2 mmol). The reaction was carried out at +2 °C for 24 h. The product was isolated by direct column chromatography on silica gel (CH_2Cl_2/EtOAc 95:5 to 85:15) in 88% yield (22.8 mg, 0.088 mmol) as a yellow oil; dr 4:1, ee 99% (Chiralcel OD-H, hexane/*i*-PrOH 90:10, 1.2 mL/min, λ = 25 °C, λ = 254 nm; major t_R = 25.2 min, minor t_R = 18.5 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (s, 1 H), 7.35 (d, *J* = 7.4 Hz, 1 H), 7.32–7.26 (m, 2 H), 7.14–7.04 (m, 1 H), 6.86 (d, *J* = 7.8 Hz, 1 H), 4.88 (dd, *J* = 8.4, 3.0 Hz, 1 H), 3.21 (dd, *J* = 17.9, 8.4 Hz, 1 H), 3.02 (dd, *J* = 17.9, 3.1 Hz, 1 H), 3.00 (d, *J* = 18.0 Hz, 1 H), 2.88 (d, *J* = 18.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.2, 205.1, 177.4, 140.9, 130.9, 128.6, 124.6, 123.7, 110.7, 80.6, 77.0, 46.6, 43.8, 30.6.

HRMS (ESI): *m*/*z* calcd for $(C_{14}H_{14}NO_4)^+$ [M + H]$^+$: 260.0917; found: 260.0915.

(2*R*,5*S*)-4′-Bromo-5-(2-oxo-2-phenylethyl)-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (4)

The title compound was obtained according to the typical procedure from 4-bromoindoline-2,3-dione (22.6 mg, 0.1 mmol) and (*E*)-1-phenylpent-2-ene-1,4-dione (**2a**; 34.8 mg, 0.2 mmol). The reaction was carried out at +2 °C for 24 h. The product was isolated by direct column chromatography on silica gel (CH_2Cl_2/EtOAc 95:5 to 85:15) in 92% yield (36.8 mg, 0.092 mmol) as a yellow solid; mp 57–59 °C; $[\alpha]_D^{22}$ +107.5 (*c* 0.099, $CHCl_3$); dr >25:1, ee 99% (Chiralpak AD-H, hexane/*i*-PrOH 80:20, 1 mL/min, 30 °C, λ = 254 nm; major t_R = 20.4 min, minor t_R = 15.0 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (s, 1 H), 8.03–7.89 (m, 2 H), 7.61–7.51 (m, 1 H), 7.50–7.38 (m, 2 H), 7.16 (d, *J* = 8.1 Hz, 1 H), 7.08 (t, *J* = 7.9 Hz, 1 H), 6.76 (d, *J* = 7.6 Hz, 1 H), 5.21 (dd, *J* = 9.0, 2.1 Hz, 1 H), 3.74 (dd, *J* = 17.5, 9.1 Hz, 1 H), 3.47 (dd, *J* = 17.5, 2.7 Hz, 1 H), 3.39 (d, *J* = 18.5 Hz, 1 H), 2.92 (d, *J* = 18.6 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.4, 196.7, 177.5, 143.1, 136.6, 133.7, 132.1, 128.9 (2 C), 128.6 (2 C), 127.4, 127.2, 120.2, 109.9, 81.8, 78.2, 42.7, 40.9.

HRMS (ESI): *m*/*z* calcd for $(C_{19}H_{14}BrNO_4Na)^+$ [M + Na]$^+$: 421.9998; found: 421.9999.

(2*R*,5*S*)-5′-Bromo-5-(2-oxo-2-phenylethyl)-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (5)

The title compound was obtained according to the typical procedure from 5-bromoindoline-2,3-dione (22.6 mg, 0.1 mmol) and **2a** (34.8 mg, 0.2 mmol). The reaction was carried out at +2 °C for 24 h. The product was isolated by direct column chromatography on silica gel (CH_2Cl_2/EtOAc 95:5 to 85:15) in 66% yield (26.4 mg, 0.066 mmol) as a white solid; mp 190–192 °C; $[\alpha]_D^{22}$ +173.2 (*c* 0.083, $CHCl_3$); dr 23:1, ee 98% (Chiralpak AD-H, hexane/*i*-PrOH 80:20, 1 mL/min, 30 °C, λ = 254 nm; major t_R = 25.7 min, minor t_R = 21.0 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (s, 1 H), 7.97–7.90 (m, 2 H), 7.58–7.52 (m, 1 H), 7.49 (d, *J* = 1.9 Hz, 1 H), 7.46–7.41 (m, 2 H), 7.35 (dd, *J* = 8.3, 1.9 Hz, 1 H), 6.72 (d, *J* = 8.3 Hz, 1 H), 5.08 (dd, *J* = 8.6, 2.6 Hz, 1 H), 3.77 (dd, *J* = 18.0, 8.6 Hz, 1 H), 3.53 (dd, *J* = 18.0, 2.7 Hz, 1 H), 3.06 (d, *J* = 18.0 Hz, 1 H), 2.91 (d, *J* = 18.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 211.8, 196.5, 177.3, 140.0, 136.4, 133.7, 133.6, 130.6, 128.8 (2 C), 128.4 (2 C), 127.8, 116.1, 112.4, 80.6, 77.3, 43.8, 42.1.

HRMS (ESI): *m*/*z* calcd for $(C_{19}H_{14}BrNO_4Na)^+$ [M + Na]$^+$: 421.9998; found: 422.0003.

(2*R*,5*S*)-5′-Fluoro-5-(2-oxo-2-phenylethyl)-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (6)

The title compound was obtained according to the typical procedure from 5-fluoroindoline-2,3-dione (16.5 mg, 0.1 mmol) and **2a** (34.8 mg, 0.2 mmol). The reaction was carried out at –20 °C for 24 h. The product was isolated by direct column chromatography on silica gel (CH_2Cl_2/EtOAc 95:5 to 85:15) in 94% yield (31.9 mg, 0.94 mmol) as a yellow solid; mp 63–65 °C; $[\alpha]_D^{22}$ +123.2 (*c* 0.090, $CHCl_3$); dr 19:1, ee 99% (Chiralcel OD-H, hexane/*i*-PrOH 90:10, 1.2 mL/min, 25 °C, λ = 254 nm; major t_R = 28.5 min, minor t_R = 22.4 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (s, 1 H), 7.99–7.91 (m, 1 H), 7.60–7.51 (m, 1 H), 7.48–7.39 (m, 2 H), 7.17–7.10 (m, 1 H), 7.01–6.91 (m, 1 H), 6.82–6.74 (m, 1 H), 5.10 (dd, *J* = 8.6, 2.6 Hz, 1 H), 3.80 (dd, *J* = 18.0, 8.7 Hz, 1 H), 3.52 (dd, *J* = 18.0, 2.7 Hz, 1 H), 3.06 (d, *J* = 18.0 Hz, 1 H), 2.92 (d, *J* = 18.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 211.8, 196.4, 177.8, 159.6 (d, *J* = 243.1 Hz), 136.9 (d, *J* = 2.3 Hz), 136.5, 133.7, 130.1 (d, *J* = 7.6 Hz), 128.8 (2 C), 128.4 (2 C), 117.3 (d, *J* = 23.6 Hz), 112.6 (d, *J* = 24.9 Hz), 111.6 (d, *J* = 7.9 Hz), 80.9, 77.3, 43.9, 42.2.

HRMS (ESI): *m*/*z* calcd for $(C_{19}H_{14}FNO_4Na)^+$ [M + Na]$^+$: 362.0799; found: 362.0792.

(2*R*,5*S*)-5′-Methoxy-5-(2-oxo-2-phenylethyl)-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (7)

The title compound was obtained according to the typical procedure from 5-methoxyindoline-2,3-dione (17.7 mg, 0.1 mmol) and **2a** (34.8 mg, 0.2 mmol). The reaction was carried out at +2 °C for 24 h. The product was isolated by direct column chromatography on silica gel (CH_2Cl_2/EtOAc 95:5 to 83:17) in 85% yield (29.8 mg, 0.085 mmol) as a rose solid; mp 148–150 °C; $[\alpha]_D^{22}$ +156.2 (*c* 0.117, $CHCl_3$); dr 11:1, ee 99% (Chiralcel OD-H, hexane/*i*-PrOH 90:10, 1.2 mL/min, 25 °C, λ = 254 nm; major t_R = 31.1 min, minor t_R = 26.5 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 1 H), 7.96 (d, *J* = 7.3 Hz, 2 H), 7.54 (t, *J* = 7.4 Hz, 1 H), 7.47–7.39 (m, 2 H), 7.01–6.96 (m, 1 H), 6.83–6.71 (m, 2 H), 5.14 (dd, *J* = 8.7, 2.5 Hz, 1 H), 3.84 (dd, *J* = 17.9, 8.7 Hz, 1 H), 3.79 (s, 3 H), 3.50 (dd, *J* = 17.9, 2.7 Hz, 1 H), 3.04 (d, *J* = 18.0 Hz, 1 H), 2.93 (d, *J* = 18.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.4, 196.6, 177.9, 156.65, 136.6, 134.1, 133.6, 129.6, 128.8 (2 C), 128.5 (2 C), 115.8, 111.3, 111.3, 81.2, 77.4, 56.0, 44.1, 42.2.

HRMS (ESI): *m*/*z* calcd for $(C_{20}H_{17}NO_5Na)^+$ [M + Na]$^+$: 374.0999; found: 374.0995.

(2*R*,5*S*)-5′-Nitro-5-(2-oxo-2-phenylethyl)-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (8)

The title compound was obtained according to the typical procedure from 5-nitroindoline-2,3-dione (19.2 mg, 0.1 mmol) and **2a** (34.8 mg, 0.2 mmol). The reaction was carried out at +2 °C for 24 h. The product was isolated by direct column chromatography on silica gel (CH_2Cl_2/EtOAc 95:5 to 85:15) in 47% yield (17.2 mg, 0.047 mmol) as a white solid; mp 182–185 °C; $[\alpha]_D^{22}$ +217.3 (*c* 0.075, $CHCl_3$); dr 9:1, ee 98% (Chiralpak AD-H, hexane/*i*-PrOH 70:30, 1 mL/min, 30 °C, λ = 254 nm; major t_R = 26.9 min, minor t_R = 15.1 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1 H), 8.27 (d, *J* = 2.2 Hz, 1 H), 8.18 (dd, *J* = 8.6, 2.3 Hz, 1 H), 7.98–7.91 (m, 2 H), 7.62–7.53 (m, 1 H), 7.50–7.41 (m, 2 H), 6.96 (d, *J* = 8.6 Hz, 1 H), 5.12 (dd, *J* = 8.6, 2.5 Hz, 1

H), 3.76 (dd, *J* = 18.0, 8.7 Hz, 1 H), 3.59 (dd, *J* = 18.0, 2.7 Hz, 1 H), 3.12 (d, *J* = 18.1 Hz, 1 H), 3.01 (d, *J* = 18.1 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 210.8, 196.5, 177.3, 146.7, 144.1, 136.3, 133.9, 129.6, 128.9 (2 C), 128.5 (2 C), 127.6, 120.8, 110.7, 80.1, 77.4, 43.6, 42.1.

HRMS (ESI): *m*/*z* calcd for $(C_{19}H_{15}N_2O_6)^+$ [M + H]$^+$: 367.0925; found: 367.0925.

(2*R*,5*S*)-5-(2-Oxo-2-phenylethyl)-5′-(trifluoromethoxy)-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (9)

The title compound was obtained according to the typical procedure from 5-(trifluoromethoxy)indoline-2,3-dione (23.1 mg, 0.1 mmol) and **2a** (34.8 mg, 0.2 mmol). The reaction was carried out at –20 °C for 24 h. The product was isolated by direct column chromatography on silica gel (CH_2Cl_2/EtOAc 95:5 to 85:15) in 80% yield (32.4 mg, 0.080 mmol) as a white solid; mp 64–66 °C; $[\alpha]_D^{22}$ +128.2 (*c* 0.106, $CHCl_3$); dr 17:1, ee 99% (Chiralpak AD-H, hexane/*i*-PrOH 90:10, 1 mL/min, 25 °C, λ = 254 nm; major t_R = 34.8 min, minor t_R = 32.8 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (s, 1 H), 8.03–7.86 (m, 2 H), 7.60–7.50 (m, 1 H), 7.50–7.37 (m, 2 H), 7.28 (s, 1 H), 7.16–7.09 (m, 1 H), 6.84 (d, *J* = 8.5 Hz, 1 H), 5.11 (dd, *J* = 8.7, 2.4 Hz, 1 H), 3.81 (dd, *J* = 18.0, 8.7 Hz, 1 H), 3.54 (dd, *J* = 18.0, 2.7 Hz, 1 H), 3.07 (d, *J* = 18.0 Hz, 1 H), 2.94 (d, *J* = 18.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 211.5, 196.5, 177.7, 145.3 (q, *J* = 1.8 Hz), 139.7, 136.4, 133.7, 130.0, 128.8, 128.5, 124.0, 120.6 (q, *J* = 257.4 Hz), 118.6, 111.5, 80.7, 77.4, 43.8, 42.2.

HRMS (ESI): *m*/*z* calcd for $(C_{20}H_{14}F_3NO_5Na)^+$ [M + Na]$^+$: 428.0716; found: 428,0714.

(2*R*,5*S*)-1′-Methyl-5-(2-oxo-2-phenylethyl)-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (10)

The title compound was obtained according to the typical procedure from 1-methylindoline-2,3-dione (16.1 mg, 0.1 mmol) and **2a** (34.8 mg, 0.2 mmol). The reaction was carried out at –20 °C for 2 h. The product was isolated by direct column chromatography on silica gel (CH_2Cl_2/EtOAc 95:5 to 85:15) in 85% yield (28.5 mg, 0.085 mmol) as a white solid; mp 158–160 °C; $[\alpha]_D^{22}$ +132.2 (*c* 0.145, $CHCl_3$); dr >25:1, ee 99% (Chiralpak AD-H, hexane/*i*-PrOH 70:30, 1 mL/min, 30 °C, λ = 254 nm; major t_R = 17.5 min, minor t_R = 13.2 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.94 (m, 2 H), 7.60–7.51 (m, 1 H), 7.48–7.40 (m, 3 H), 7.35 (td, *J* = 7.8, 1.1 Hz, 1 H), 7.17–7.08 (m, 1 H), 6.81 (d, *J* = 7.8 Hz, 1 H), 5.15 (dd, *J* = 8.8, 2.6 Hz, 1 H), 3.85 (dd, *J* = 18.0, 8.8 Hz, 1 H), 3.52 (dd, *J* = 18.0, 2.7 Hz, 1 H), 3.15 (s, 3 H), 3.01 (d, *J* = 18.0 Hz, 1 H), 2.94 (d, *J* = 18.1 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.6, 196.5, 175.9, 144.0, 136.6, 133.5, 130.9, 128.7 (2 C), 128.5, 128.1 (2 C), 124.3, 123.7, 108.9, 80.5, 77.4, 43.9, 42.4, 26.4.

HRMS (ESI): *m*/*z* calcd for $(C_{20}H_{17}NO_4Na)^+$ [M + Na]$^+$: 358.1050; found: 358.1050.

tert-Butyl (2*R*,5*S*)-2′,4-Dioxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-3*H*-spiro[furan-2,3′-indoline]-1′-carboxylate (11)

tert-Butyl 2,3-dioxoindoline-1-carboxylate (49.5 mg, 0.2 mmol), **2a** (26.1 mg, 0.15 mmol), and thiourea **I** (8.5 mg, 0.015 mmol) were dissolved in toluene (450 µL) and the reaction mixture was stirred at 20 °C. The reaction was quenched after 24 h by direct column chromatography on silica gel (PE/EtOAc 91:9 to PE/CH_2Cl_2/EtOAc 37.5:12.5:50) providing the product **11** in 45% yield (23.9 mg, 0.077 mmol) as a yellow oil; dr 13:1, ee 99% (was determined after deprotection of Boc-group).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.96 (m, 2 H), 7.84 (d, *J* = 8.2 Hz, 1 H), 7.60–7.54 (m, 1 H), 7.49–7.43 (m, 3 H), 7.43–7.37 (m, 1 H), 7.27–7.22 (m, 1 H), 5.17 (dd, *J* = 8.7, 2.7 Hz, 1 H), 3.78 (dd, *J* = 18.0, 8.7 Hz, 1 H), 3.53 (dd, *J* = 18.0, 2.8 Hz, 1 H), 3.07 (d, *J* = 18.1 Hz, 1 H), 2.95 (dd, *J* = 18.1, 1.0 Hz, 1 H), 1.62 (s, 8 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 211.7, 196.4, 175.0, 148.7, 140.2, 136.5, 133.6, 131.2, 128.8 (2 C), 128.5 (2 C), 127.0, 125.5, 124.3, 115.8, 85.2, 80.2, 44.6, 42.2, 28.2 (3 C).

(2*R*,3a*S*,9a*S*)-9a-Hydroxy-1,3a,4,9a-tetrahydro-5*H*-spiro[furo[3,2-*e*]indolizine-2,3′-indoline]-2′,5-dione (12)

Isatin (**1**; 14.7 mg, 0.1 mmol), (*E*)-1-(1*H*-pyrrol-2-yl)pent-2-ene-1,4-dione (**2i**; 24.5 mg, 0.15 mmol), and thiourea **I** (5.7 mg, 0.01 mmol) were dissolved in MeCN (1 mL) and the mixture was stirred at 20 °C for 3 days. The product was isolated by direct column chromatography on silica gel (CH_2Cl_2/MeOH 99:1 to 96:4) in 77% yield (23.9 mg, 0.077 mmol) as a white solid; mp 175–177 °C; $[\alpha]_D^{25}$ –91.9 (*c* 0.109, $CHCl_3$); dr 4.5:1 (after chromatographic purification), ee 99% (Chiralpak AD-H, hexane/*i*-PrOH 85:15, 1 mL/min, 30 °C, λ = 254 nm; major t_R = 18.7 min, minor t_R = 21.0 min).

^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6): δ = 10.06 (s, 1 H), 7.75 (d, *J* = 7.2 Hz, 1 H), 7.34 (dd, *J* = 2.5, 1.7 Hz, 1 H), 7.28 (d, *J* = 1.0 Hz, 1 H), 7.21 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.01 (td, *J* = 7.6, 0.9 Hz, 1 H), 6.94 (dd, *J* = 3.9, 1.6 Hz, 1 H), 6.82 (d, *J* = 7.7 Hz, 1 H), 6.39 (dd, *J* = 3.9, 2.6 Hz, 1 H), 2.92 (dd, *J* = 13.3, 1.4 Hz, 1 H), 2.82 (d, *J* = 13.3 Hz, 1 H), 3.02–2.97 (m, 4 H), 4.87 (dd, *J* = 8.7, 5.8 Hz, 1 H), 3.44 (dd, *J* = 17.1, 8.7 Hz, 1 H), 3.07–2.96 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 183.6, 176.9, 141.2, 130.3, 129.2, 128.6, 125.0, 123.7, 121.8, 112.8, 111.3, 109.5, 89.4, 82.9, 82.3, 46.9, 41.7.

HRMS (ESI): *m*/*z* calcd for $(C_{14}H_{14}NO_4Na)^+$ [M + Na]$^+$: 333.0846; found: 333.0854.

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Supporting Information

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