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Enantioselective Assembly of Spirocyclic Oxindole-dihydropyranones through NHC-Catalyzed Cascade Reaction of Isatins with *N*-Hydroxybenzotriazole Esters of α,β-Unsaturated Carboxylic Acid

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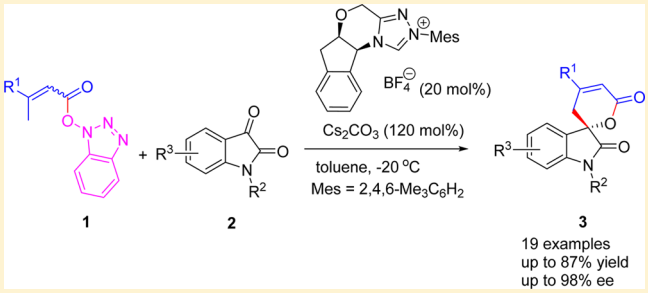
Supporting Information

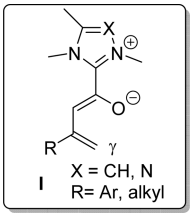
ABSTRACT: An NHC-catalyzed formal [4 + 2] reaction of isatins with *N*-hydroxybenzotriazole ester of α,β-unsaturated carboxylic acids bearing γ-H to construct spirocyclic oxindole-dihydropyranones featuring a chiral tetrasubstituted carbon stereogenic center was developed. The high enantioselectivity, the ready availability of the raw materials, the facile assembly, and the potential biological significance of the final products make this protocol an attractive alternative for the synthesis of spirocyclic heterocycles.



The occurrence of the indole and dihydropyranone units in the skeletons of numerous biologically active compounds has greatly motivated the design and development of new synthetic procedures to assemble these important structural motifs.[1] To date, several strategies including oxidative spirocyclization,[2] metal-mediated multistep transformations,[3] Prins-type cyclization,[4] and amino enyne catalysis[5] have been employed to assemble these pharmacologically attractive pyran and oxindole units successfully. In addition, some recent reports disclosed that the N-heterocyclic carbenes (NHCs) could promote a host of reactions such as ring−opening polymerization, homoenolate formation, and transesterification besides the widely known benzoin condensation and Stetter reaction.[6] Thus, much effort has been devoted to the study on the generation and reactivity of NHC-bonded intermediates, e.g., **I**. Ye et al. put forward an elegant formation of NHC-bonded vinyl enolate **I** from α,β-unsaturated acyl chlorides.[7] Later, the Chi group presented an efficient oxidative conversion of enal into **I**.[8] Our research revealed that the Breslow intermediate generated from NHC and 2-bromo-2-enal bearing γ-H could be transformed into **I** readily through debromination and deprotonation.[9] More recently, the work of Chi and co-workers showed that the reaction of NHC and the α,β-unsaturated carboxylic esters of 4-nitrophenol could deliver the same intermediate successfully (Scheme 1; the detailed pathways for the generation of **I** are given in Supporting Information).[10]

The annulation of these NHC-bonded vinyl enolates with substrates containing polar double bonds paved new avenues to a variety of highly functionalized molecules.[7,9−11] The preparation and isolation of 1-hydroxybenzotriazole (HOBt) esters of carboxylic acids were more convenient than that of α,β-unsaturated carboxylic esters of 4-nitrophenol and our previously used α-bromoenal, and they were employed widely as key intermediates in the creation of the amide bond.[12] Thus, we envisioned that the HOBt ester of α,β-unsaturated carboxylic acid possessing γ-H would react with NHC to give the similar intermediate effectively under basic conditions and that its subsequent reaction with activated C−O double bond could provide a new alternative to assemble the scaffold of dihydropyranone (Scheme 2).

Scheme 1. Structure of NHC-Bonded Vinyl Enolates



To continue our work on NHC-catalyzed cascade synthesis of heterocycles,[9b] herein we shall report our recent results of enantioseletive synthesis of spirocyclic oxindole-dihydropyranones via the reaction of isatin and the HOBt ester of α,β-unsaturated carboxylic acid bearing γ-H promoted by NHC under basic conditions.

To test our hypothesis, a parallel experiment was initially conducted to examine the differential of reactivity of esters

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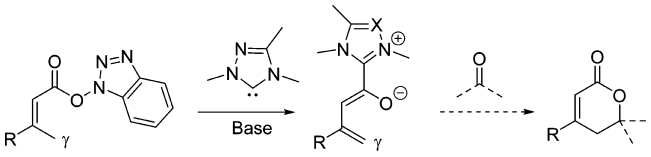
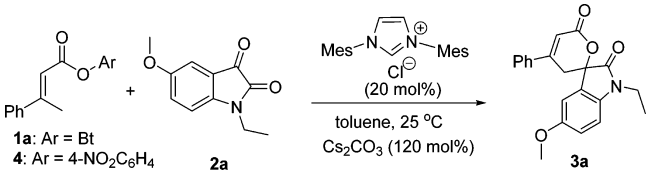
Scheme 2. Our Proposal for the Formation of NHC-Bonded Vinyl Enolates



derived from 3-phenylbut-2-enoic acid, HOBt, and 4-nitrophenol (Scheme 3). To our delight, the reaction involving the

Scheme 3. Parallel Experiment for Comparison of the Reactivity of Esters



HOBt ester proceeded more efficiently and was faster (4 h versus 16 h), and gave the expected product in higher yield (69% versus 51%) as compared with the corresponding reaction using 4-nitrophenol ester as substrate.

Thus, we set about our study on the NHC-catalyzed formal [4 + 2] synthesis of spirocyclic oxindole-dihydropyranones using α,β-unsaturated ester **1a** and isatin derivative **2a** as model substrates. Under the basic reaction conditions, no formation of the desired product **3a** was observed in the absence of an NHC (Table 1, entry 1). With imidazolium **A** as the NHC precatalyst, **3a** was formed in 69% yield (Table 1, entry 2). Then we moved to chiral triazolium NHC catalysts and found that catalyst **C** displayed promising catalytic activity with 35% ee during the preliminary screening (entries 3–6). Subsequently, the influences of solvents, bases, and temperatures on the reaction were surveyed (Table 1 in Supporting Information, entries 7–22). Finally, we found that toluene was the best solvent among THF, toluene, and CH_2Cl_2 and that Cs_2CO_3 was superior to other bases. After the optimization of the temperature, the ee values were improved to 80% with 84% yield when the reaction was carried out with Cs_2CO_3 as the base and toluene as the solvent under −20 °C (Table 1 in Supporting Information, entry 16).

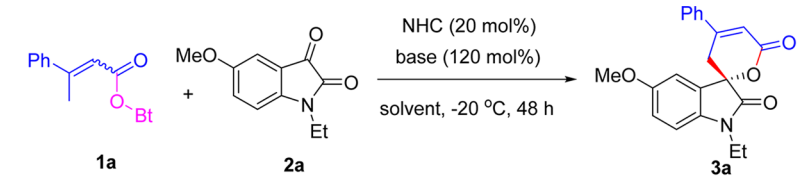
With the optimized reaction conditions, the scope of the substrates was briefly explored (Table 2). It was found that HOBt esters with both electron-withdrawing groups (4-F, 4-Br, and 4-Cl,) and electron-donating groups (4-MeO) were compatible with the reaction conditions. HOBt esters having an ortho-substitute (2-Br, 2,4-Cl_2) were tolerated and gave good yields with high enantioselectivities. Besides, HOBt esters possessing a *t*-butyl group, a hetercycle (thiophene), or a fused aryl group could also take part in this reaction and deliver the expected product successfully (Table2, entry 17–19). Then the scope of istains was examined. The substitutes such as methyl, ethyl, and allyl on the N atom of the istains also showed good tolerance. Notably, the aromatic ring of the istains with the other substitutes (4-Br) gave 75% yield with 95% ee (Table2, entry 16). These results highlighted the broad generality of this protocol.

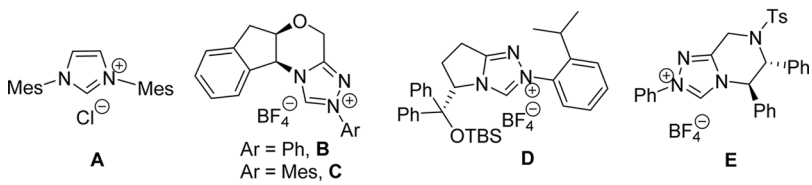
The structure of spirocyclic oxindole-dihydropyranone **3o** was established by the X-ray analysis of its crystal. Other product configurations were deduced based on analogy (see the Supporting Information for further details).

The possible catalytic cycle of this NHC-catalyzed reaction is initiated by the addition of the NHC to the α,β-unsaturated ester **1a** to give intermediate **I**, which then underwent γ-deprotonation to afford vinyl enolate intermediate **II** (Scheme 4).[8] Nucleophilic γ-carbon addition of intermediate **II** to isatin **2a** eventually afforded product **3a** and regenerated the NHC catalyst.[7a,8]

In summary, we have developed a chiral NHC-catalyzed formal [4 + 2] annulation of α,β-unsaturated esters of HOBt bearing γ-H with isatin derivatives to prepare spirocyclic oxindole-dihydropyranones in good yield and with high

Table 1. Optimization of the Reaction Conditions





entry	catalyst	T (°C)	solvent	base	yield (%)[a]	ee (%)[b]
1		r.t.	toluene	Cs_2CO_3		
2	**A**	r.t.	toluene	Cs_2CO_3	69	
3	**B**	r.t.	toluene	Cs_2CO_3	21	5
4	**C**	r.t.	toluene	Cs_2CO_3	80	35
5	**D**	r.t.	toluene	Cs_2CO_3	83	0
6	**E**	r.t.	toluene	Cs_2CO_3	65	0

[a]Yield of the isolated product. [b]Determined by HPLC.

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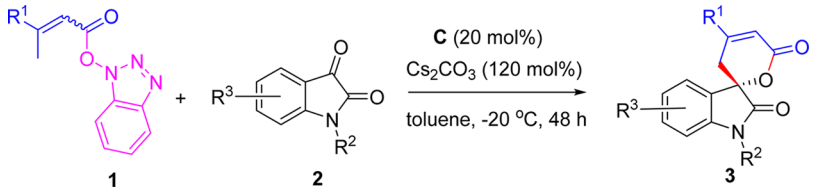
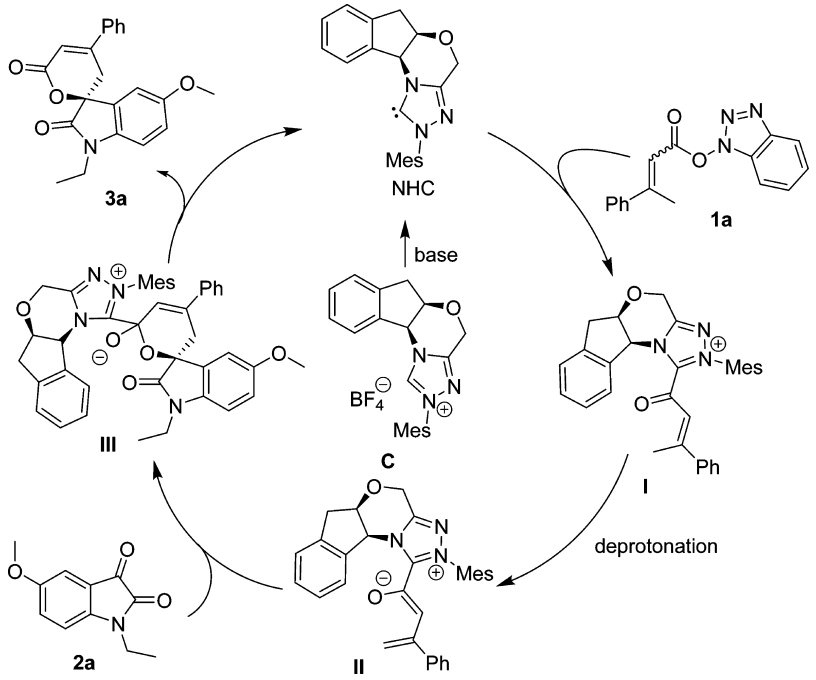
Table 2. Enantioselective Synthesis of Spirocyclic Oxindole-dihydropyranones



entry	R^1	R^2	R^3	product	yield (%)[a]	ee (%)[b]
1	Ph	Et	5-MeO	**3a**	84	80
2	4-BrC_6H_4	Et	5-MeO	**3b**	87	89
3	4-$MeOC_6H_4$	Et	5-MeO	**3c**	82	85
4	2-BrC_6H_4	Et	5-MeO	**3d**	79	88
5	2,4-$Cl_2C_6H_3$	Et	5-MeO	**3e**	83	89
6	4-ClC_6H_4	Me	5-MeO	**3f**	77	81
7	4-FC_6H_4	Me	5-MeO	**3g**	86	98
8	2,4-$Cl_2C_6H_3$	Me	5-MeO	**3h**	80	83
9	4-BrC_6H_4	Me	5-MeO	**3i**	83	90
10	4-BrC_6H_4	Allyl	5-MeO	**3j**	75	80
11	4-$MeOC_6H_4$	Allyl	5-MeO	**3k**	71	83
12	2-BrC_6H_4	Allyl	5-MeO	**3l**	77	85
13	4-ClC_6H_4	Allyl	5-MeO	**3m**	82	81
14	2,4-$Cl_2C_6H_3$	Allyl	5-MeO	**3n**	76	89
15	4-FC_6H_4	Allyl	5-MeO	**3o**	81	80
16	4-BrC_6H_4	Bn	4-Br	**3p**	75	95
17	2-naphthyl	Et	5-MeO	**3q**	85	88
18	thien-2-yl	Et	5-MeO	**3r**	73	75
19	*t*-Bu	Et	5-MeO	**3s**	71	98

[a]Yield of the isolated product. [b]Determined by HPLC.

Scheme 4. Possible Catalytic Cycle



enantioselectivity. This protocol is attractive due to the potential utilization value of final products in the pharmaceuticals and biology. In addition, this manuscript may also promote the development of NHC catalysis. Other studies concerning the reactivity of NHC-bonded intermediates generated from HOBt esters of carboxylic acids are underway in our laboratory.

EXPERIMENTAL SECTION

General Procedure for Asymmetric Synthesis of Spirocyclic Oxindole-dihydropyranone 3. A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with **1** (0.3 mmol), **2** (0.2 mmol), Cs_2CO_3 (78 mg, 0.24 mmol), and chiral catalyst **C** (17 mg, 0.04 mmol). The tube was closed with a septum. Freshly distilled toluene (4 mL) was added, and the mixture was stirred for 48 h at −20 °C.

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After the completion of the reaction, the solvent was removed under reduced pressure to afford the residue. The residue was purified by column chromatography (silicagel, mixtures of ethyl acetate/petrolem ether, 1:5, v/v) to afford **3**.

*(S)-1-Ethyl-5-methoxy-4′-phenylspiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3a**).* Yield 84% (59 mg), white solid. M.P.: 145−146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.55−7.57 (m, 2H), 7.43−7.48 (m, 3H), 7.10 (d, J = 2.4 Hz, 1H), 6.90 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.60 (s, 1H), 3.69−3.81 (m, 5H), 3.38 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H), 3.09 (dd, J_1 = 17.6 Hz, J_2 = 0.8 Hz, 1H), 1.30 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.8, 163.3, 156.2, 152.0, 135.9, 135.5, 131.0, 129.1, 129.1, 126.1, 115.0, 114.7, 111.8, 109.6, 80.0, 55.9, 35.2, 32.6, 12.5. IR (potassium bromide) (v, cm^{-1}): 3415, 1719, 1638, 1618, 1494, 1385, 1259, 1172, 1036, 1009, 735, 626. HRMS (TOF, ESI, m/z): Calcd for $[M + Na]^+$ $C_{21}H_{19}NNaO_4$, 372.1212; found, 372.1235. $[\alpha]_D^{25}$ = +61.7 (c = 0.2, $CHCl_3$). HPLC analysis: 80% ee, [Daicel Chiralpak AD-H, n-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 16.3 min, t (minor) = 17.6 min].

*(S)-4′-(4-Bromophenyl)-1-ethyl-5-methoxyspiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3b**).* Yield 87% (74 mg), white solid. M.P.: 182−183 °C.^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.58−7.61 (m, 2H), 7.42−7.44 (m, 2H), 7.08 (d, J = 2.4 Hz, 1H), 6.91 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.69 (s, 1H), 3.69−3.81 (m, 5H), 3.30 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H), 3.08 (dd, J_1 = 17.6 Hz, J_2 = 0.8 Hz, 1H), 1.30 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.8, 163.0, 156.3, 150.5, 135.5, 134.8, 132.3, 128.9, 127.5, 125.4, 115.2, 115.1, 111.8, 109.7, 79.9, 55.9, 35.2, 32.5, 12.5. IR (potassium bromide) (v, cm^{-1}): 3073, 2941, 1718, 1649, 1603, 1586, 1491, 1458, 1434, 1384, 1266, 1219, 1141, 1074, 1006, 957, 822, 810. HRMS (TOF, ESI, m/z): Calcd for $[M + Na]^+$ $C_{21}H_{18}BrNNaO_4$, 450.0317; found, 450.0340. $[\alpha]_D^{25}$ = +85.3 (c = 0.2, $CHCl_3$). HPLC analysis: 89% ee, [Daicel Chiralpak AD-H, n-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 25.1 min, t (minor) = 27.0 min].

*(S)-1-Ethyl-5-methoxy-4′-(4-methoxyphenyl)spiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3c**).* Yield 82% (62 mg), white solid. M.P.: 119−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.53 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 2.4 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 6.90 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.53 (s, 1H), 3.86 (s, 3H), 3.69−3.81 (m, 5H), 3.36 (dd, J_1 = 17.6 Hz, J_2 = 1.2 Hz, 1H), 3.04 (d, J = 17.6 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.9, 163.5, 162.0, 156.2, 151.4, 135.5, 129.4, 128.0, 127.7, 115.0, 114.5, 112.3, 111.9, 109.5, 79.9, 55.9, 55.5, 35.1, 32.3, 12.5. IR (potassium bromide) (v, cm^{-1}): 2987, 2937, 1723, 1626, 1604, 1494, 1435, 1356, 1245, 1215, 1180, 1032, 993, 959, 827, 805. HRMS (TOF, ESI, m/z): Calcd for $[M + Na]^+$ $C_{22}H_{21}NNaO_5$, 402.1317; found, 402.1317. $[\alpha]_D^{25}$ = +62.8 (c = 0.2, $CHCl_3$). HPLC analysis: 85% ee, [Daicel Chiralpak AD-H, n-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 27.1 min, t (minor) = 30.6 min].

*(S)-4′-(2-Bromophenyl)-1-ethyl-5-methoxyspiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3d**).* Yield 79% (68 mg), white solid. M.P.: 159−160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.63 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.40 (td, J_1 = 7.4 Hz, J_2 = 1.2 Hz, 1H), 7.25−7.33 (m, 3H), 6.92 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.34 (t, J = 1.6 Hz, 1H), 3.82 (s, 3H), 3.69−3.80 (m, 2H), 3.28 (dd, J_1 = 18.4 Hz, J_2 = 1.6 Hz, 1H), 3.16 (dd, J_1 = 18.4 Hz, J_2 = 1.6 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.8, 162.5, 156.2, 153.8, 138.8, 135.5, 133.6, 130.7, 129.7, 128.7, 127.9, 120.6, 119.9, 115.6, 111.8, 109.6, 80.3, 56.0, 35.1, 34.6, 12.5. IR (potassium bromide) (v, cm^{-1}): 2980, 2933, 1727, 1712, 1607, 1494, 1438, 1250, 1217, 1141, 1035, 958, 868, 818, 775, 699. HRMS (TOF, ESI, m/z): Calcd for $[M + Na]^+$ $C_{21}H_{18}BrNNaO_4$, 450.0317; found, 450.0351. $[\alpha]_D^{25}$ = +44.8 (c = 0.2, $CHCl_3$). HPLC analysis: 88% ee, [Daicel Chiralpak AD-H, n-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 13.2 min, t (minor) = 21.9 min].

*(S)-4′-(2,4-Dichlorophenyl)-1-ethyl-5-methoxyspiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3e**).* Yield 83% (69 mg), white solid. M.P.: 151−152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.46 (d, J = 2.0 Hz, 1H), 7.34 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.29 (d, J = 6.4 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 6.92 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.35 (t, J = 1.6 Hz, 1H), 3.68−3.82 (m, 5H), 3.22 (dd, J_1 = 18.0 Hz, J_2 = 1.6 Hz, 1H), 3.14 (dd, J_1 = 18.0 Hz, J_2 = 1.2 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.7, 162.3, 156.2, 151.3, 136.2, 135.4, 135.3, 132.5, 130.4, 130.3, 128.5, 127.8, 120.4, 115.6, 111.7, 109.6, 80.2, 55.9, 35.1, 34.4, 12.5. IR (potassium bromide) (v, cm^{-1}): 3084, 1726, 1677, 1586, 1498, 1384, 1252, 1218, 1145, 1075, 986, 822. HRMS (TOF, ESI, m/z): Calcd for $[M + Na]^+$ $C_{21}H_{17}Cl_2NNaO_4$, 440.0426; found, 440.0420. $[\alpha]_D^{25}$ = +37.3 (c = 0.2, $CHCl_3$). HPLC analysis: 89% ee, [Daicel Chiralpak AD-H, n-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 13.9 min, t (minor) = 25.1 min].

*(S)-4′-(4-Chlorophenyl)-5-methoxy-1-methylspiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3f**).* Yield 77% (57 mg), white solid. M.P.: 148−149 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.50 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 2.4 Hz, 1H), 6.93 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.85 (s, 1H), 3.79 (s, 3H), 3.30 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H), 3.22 (s, 3H), 3.10 (dd, J_1 = 17.6 Hz, J_2 = 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.2, 162.9, 156.5, 150.4, 137.1, 136.5, 134.3, 129.4, 128.7, 127.3, 115.2, 115.1, 111.7, 109.5, 79.9, 55.9, 32.5, 26.6. IR (potassium bromide) (v, cm^{-1}): 2924, 2852, 1714, 1678, 1592, 1471, 1384, 1278, 1237, 1138, 997, 826. HRMS (TOF, ESI, m/z): Calcd for $[M + Na]^+$ $C_{20}H_{16}ClNNaO_4$: 392.0666; found, 392.0656. $[\alpha]_D^{25}$ = +84.0 (c = 0.2, $CHCl_3$). HPLC analysis: 81% ee, [Daicel Chiralpak AD-H, n-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 23.8 min, t (minor) = 31.8 min].

*(S)-4′-(4-Fluorophenyl)-5-methoxy-1-methylspiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3g**).* Yield 86% (61 mg), white solid. M.P.: 208−209 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.56 (dd, J_1 = 8.8 Hz, J_2 = 5.2 Hz, 2H), 7.15 (t, J = 8.4 Hz, 2H), 7.09 (d, J = 2.4 Hz, 1H), 6.92 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.55 (s, 1H,), 3.78 (s, 3H), 3.31 (d, J = 18 Hz, 1H), 3.22 (s, 3H), 3.10 (dd, J_1 = 17.6 Hz, J_2 = 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.3, 164.3 (J_{C-F} = 251.2 Hz), 156.5, 150.5, 136.5, 132.1 (J_{C-F} = 3.4 Hz), 128.8, 128.1 (J_{C-F} = 8.6 Hz), 116.3 (J_{C-F} = 21.8 Hz), 115.1, 114.6, 114.6, 111.7, 109.5, 79.9, 55.9, 32.7, 26.6. IR (potassium bromide) (v, cm^{-1}): 3091, 2956, 2924, 1723, 1699, 1599, 1494, 1417, 1367, 1236, 1169, 1069, 1003, 956, 830, 810, 685, 552. HRMS (TOF, ESI, m/z): Calcd for $[M + Na]^+$ $C_{20}H_{16}FNNaO_4$, 376.0961; found, 376.0960. $[\alpha]_D^{25}$ = +36.0 (c = 0.2, $CHCl_3$). HPLC analysis: 98% ee, [Daicel Chiralpak AD-H, n-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 21.9 min, t (minor) = 29.4 min].

*(S)-4′-(2,4-Dichlorophenyl)-5-methoxy-1-methylspiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3h**).* Yield 80% (65 mg), white solid. M.P.: 148−149 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.47 (d, J = 2.0 Hz, 1H), 7.35 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.28−7.31 (m, 1H), 7.19 (d, J = 2.4 Hz, 1H), 6.93 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.36 (t, J = 1.6 Hz, 1H,), 3.81 (s, 3H), 3.20 (s, 3H), 3.19 (t, J = 1.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.1, 162.2, 156.4, 151.2, 136.4, 136.2, 135.3, 132.5, 130.4, 130.3, 128.2, 127.8, 120.4, 115.6, 111.6, 109.5, 80.2, 55.9, 34.3, 26.6. IR (potassium bromide) (v, cm^{-1}): 3091, 2937, 2903, 1721, 1632, 1584, 1501, 1384, 1258, 1141, 1000, 883, 819, 803, 681. HRMS (TOF, ESI, m/z): Calcd for $[M + Na]^+$ $C_{20}H_{15}Cl_2NNaO_4$, 426.0270; found, 426.0274. $[\alpha]_D^{25}$ = +83.0 (c = 0.2, $CHCl_3$). HPLC analysis: 83% ee, [Daicel Chiralpak AD-H, n-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 15.7 min, t (minor) = 28.0 min].

*(S)-4′-(4-Bromophenyl)-5-methoxy-1-methylspiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3i**).* Yield 83% (69 mg), white solid. M.P.: 187−188 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.58−7.60 (m, 2H), 7.40−7.44 (m, 2H), 7.08 (d, J = 2.4 Hz, 1H), 6.92 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H). 6.81 (d, J = 8.8 Hz, 1H), 6.58 (t, J = 1.6 Hz, 1H), 3.78 (s, 3H), 3.29 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H), 3.21 (s, 3H), 3.10 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.2, 162.9, 156.5, 150.5, 136.4, 134.8, 132.3, 128.7, 127.5, 125.4, 115.2, 111.6, 109.5, 79.9, 55.9, 32.5, 26.6. IR (potassium bromide) (v, cm^{-1}): 3081, 2954, 2926, 1723, 1649, 1586, 1495, 1405, 1364, 1235, 1073, 1005, 817. HRMS (TOF, ESI, m/z): Calcd for $[M + Na]^+$

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$C_{20}H_{16}BrNNaO_4$, 436.0160; found, 436.0173. $[\alpha]_D^{25}$ = +80.3 (c = 0.2, $CHCl_3$). HPLC analysis: 90% ee, [Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 28.8 min, t (minor) = 38.5 min].

(S)-1-Allyl-4′-(4-bromophenyl)-5-methoxyspiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3j**). Yield 75% (66 mg), white solid. M.P.: 141−142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.59−7.61 (m, 2H), 7.42−7.44 (m, 2H), 7.08 (d, J = 2.4 Hz, 1H), 6.89 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.59 (s, 1H), 5.80−5.89 (m, 1H), 5.27−5.31 (m, 2H), 4.32−4.33 (m, 2H), 3.78 (s, 3H), 3.31 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H), 3.11 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.0, 162.9, 156.4, 150.4, 135.6, 134.8, 132.4, 130.7, 128.7, 127.5, 125.5, 118.3,115.2, 111.6, 110.5, 79.8, 55.9, 42.7, 32.6. IR (potassium bromide) (v, cm^{-1}): 3081, 2954, 2899, 1716, 1625, 1586, 1498, 1439, 1360, 1256, 1188, 1010, 987, 869, 827, 812. HRMS (TOF, ESI, m/z): Calcd for [M + Na]$^+$ $C_{22}H_{18}BrNNaO_4$, 462.0317; found, 462.0329. $[\alpha]_D^{25}$ = +72.5 (c = 0.2, $CHCl_3$). HPLC analysis: 80% ee, [Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 26.1 min, t (minor) = 28.9 min].

(S)-1-Allyl-5-methoxy-4′-(4-methoxyphenyl)spiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3k**). Yield 71% (55 mg), white solid. M.P.: 124−125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.52−7.55 (m, 2H), 7.10 (d, J = 2.4 Hz, 1H), 6.95−6.98 (m, 2H), 6.87 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.54 (s, 1H), 5.80−5.90 (m, 1H). 5.27−5.32 (m, 2H), 4.32−4.34 (m, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 3.37 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H), 3.07 (dd, J_1 = 17.6 Hz, J_2 = 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.1, 163.5, 162.0, 156.3, 151.3, 135.6, 130.8, 129.1, 128.0, 127.7, 118.2, 115.0, 114.5, 112.4, 111.7, 110.4, 79.8, 55.9, 55.5, 42.7, 32.5. IR (potassium bromide) (v, cm^{-1}): 3078, 2950, 2833, 1705, 1655, 1573, 1492, 1434, 1361, 1259, 1245, 1035, 987, 835. HRMS (TOF, ESI, m/z): Calcd for [M + Na]$^+$ $C_{23}H_{21}NNaO_5$, 414.1317; found, 414.1318. $[\alpha]_D^{25}$ = +62.0 (c = 0.2, $CHCl_3$). HPLC analysis: 83% ee, [Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 27.9 min, t (minor) = 35.3 min].

(S)-1-Allyl-4′-(2-bromophenyl)-5-methoxyspiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3l**). Yield 77% (68 mg), white solid. M.P.: 141−142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.63 (d, J = 8.0 Hz, 1H), 7.38−7.41 (m, 1H), 7.24−7.32 (m, 3H), 6.89 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 6.34 (s, 1H), 5.79−5.88 (m, 1H), 5.25−5.29 (m, 2H), 4.30−4.33 (m, 2H), 3.80 (s, 3H), 3.29 (dd, J_1 = 18.0 Hz, J_2 = 1.6 Hz, 1H), 3.19 (dd, J_1 = 18.0 Hz, J_2 = 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.0, 162.5, 156.3, 153.7, 138.8, 135.6, 133.6, 130.8, 130.8, 129.7, 128.4, 127.9, 120.6,120.0,118.2, 115.6, 111.6, 110.4, 80.2, 56.0, 42.7, 34.7. IR (potassium bromide) (v, cm^{-1}): 3083, 2983, 2926, 1725, 1601, 1434, 1354, 1249, 1198, 1023, 1005, 957, 875, 765, 699, 660. HRMS (TOF, ESI, m/z): Calcd for [M + Na]$^+$ $C_{22}H_{18}BrNNaO_4$, 462.0317; found, 462.0329. $[\alpha]_D^{25}$ = +57.0 (c = 0.2, $CHCl_3$). HPLC analysis: 85% ee, [Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 13.4 min, t (minor) = 24.1 min].

(S)-1-Allyl-4′-(4-chlorophenyl)-5-methoxyspiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3m**). Yield 82% (65 mg), white solid. M.P.: 152−153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.49−7.52 (m, 2H), 7.42−7.45 (m, 2H), 7.09 (d, J = 2.4 Hz, 1H), 6.89 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.59 (t, J = 1.6 Hz, 1H), 5.80−5.90 (m, 1H), 5.27−5.31 (m, 2H), 4.32−4.34 (m, 2H), 3.78 (s, 3H), 3.32 (dd, J_1 = 18.0 Hz, J_2 = 1.6 Hz, 1H), 3.11 (dd, J_1 = 18.0 Hz, J_2 = 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.0, 162.9, 156.4, 150.4, 137.1, 135.6, 134.3, 130.7, 129.4, 128.7, 127.3, 118.3, 115.2, 115.1, 111.6, 110.5, 79.8, 55.9, 42.7, 32.7. IR (potassium bromide) (v, cm^{-1}): 3081, 2954, 2902, 1715, 1649, 1601, 1498, 1408, 1361, 1257, 1188, 1096, 1188, 1001, 925, 870, 831, 783, 662. HRMS (TOF, ESI, m/z): Calcd for [M + Na]$^+$ $C_{22}H_{18}ClNNaO_4$, 418.0822; found, 418.0821. $[\alpha]_D^{25}$ = +33.2 (c = 0.2, $CHCl_3$). HPLC analysis: 81% ee, [Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 23.2 min, t (minor) = 26.9 min].

(S)-1-Allyl-4′-(2,4-dichlorophenyl)-5-methoxyspiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3n**). Yield 76% (65 mg), white solid. M.P.: 154−155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.47 (d, J = 2.0 Hz, 1H), 7.35 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.28−7.30 (m, 1H), 7.19 (d, J = 2.8 Hz, 1H), 6.89 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.36 (t, J = 1.6 Hz, 1H,), 5.79−5.88 (m, 1H), 5.25−5.29 (m, 2H), 4.30−4.32 (m, 2H), 3.80 (s, 3H), 3.24 (dd, J_1 = 18.0 Hz, J_2 = 1.6 Hz, 1H), 3.18 (dd, J_1 = 18.0 Hz, J_2 = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.9, 162.2, 156.3, 151.2, 136.2, 135.5, 135.3, 132.5, 130.7, 130.4, 130.3, 128.2, 127.8, 120.4, 118.2, 115.6, 111.5, 110.5, 80.2, 55.9, 42.7, 34.5. IR (potassium bromide) (v, cm^{-1}): 3079, 1726, 1632, 1603, 1584, 1488, 1436, 1263, 1204, 1079, 1009, 967, 932, 817, 762, 686. HRMS (TOF, ESI, m/z): Calcd for [M + Na]$^+$ $C_{22}H_{17}Cl_2NNaO_4$, 452.0432; found, 452.0450. $[\alpha]_D^{25}$ = +91.0 (c = 0.2, $CHCl_3$). HPLC analysis: 89% ee, [Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 14.8 min, t (minor) = 29.2 min].

(S)-1-Allyl-4′-(4-fluorophenyl)-5-methoxyspiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3o**). Yield 81% (61 mg), white solid. M.P.: 155−157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.55−7.58 (m, 2H), 7.13−7.18 (m, 2H), 7.09 (d, J = 2.5 Hz, 1H), 6.89 (dd, J_1 = 8.6 Hz, J_2 = 2.5 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 6.56 (s, 1H), 5.80−5.90 (m, 1H), 5.27−5.32 (m, 2H), 4.33 (dt, J_1 = 5.3 Hz, J_2 = 1.5 Hz, 2H), 3.78 (s, 3H), 3.33 (dd, J_1 = 18.0 Hz, J_2 = 1.6 Hz, 1H), 3.11 (dd, J_1 = 18.0 Hz, J_2 = 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.0, 164.3 (J_{C-F} = 255.7 Hz), 156.4, 150.5, 135.6, 132.0 (J_{C-F} = 3.4 Hz), 130.7, 128.8, 128.1 (J_{C-F} = 8.6 Hz), 118.3, 116.3 (J_{C-F} = 22.0 Hz), 115.1, 114.6, 111.6, 110.5, 79.8, 55.9, 42.7, 32.8. IR (potassium bromide) (v, cm^{-1}): 3081, 2960, 1714, 1602, 1494, 1440, 1365, 1235, 1182, 1021, 946, 872, 841, 812, 684. HRMS (TOF, ESI, m/z): Calcd for [M + Na]$^+$ $C_{22}H_{18}FNNaO_4$, 402.1118; found, 402.1102. $[\alpha]_D^{25}$ = +12.0 (c = 0.2, $CHCl_3$). HPLC analysis: 80% ee, [Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 20.0 min, t (minor) = 25.4 min].

(S)-1-Benzyl-4-bromo-4′-(4-bromophenyl)spiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3p**). Yield 75% (80 mg), white solid. M.P.: 162−164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.63−7.59 (m, 2H), 7.47−7.44 (m, 2H), 7.38−7.26 (m, 6H), 7.17 (t, J = 8.0 Hz, 1H) 6.72 (d, J = 7.5 Hz, 1H), 6.59 (d, J = 2.5 Hz, 1H), 4.85 (s, 2H), 4.04 (dd, J = 18.3, 2.7 Hz, 1H), 2.88 (d, J = 18.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.0, 163.0, 149.1, 144.3, 134.9, 134.4, 132.3, 132.3, 129.1, 128.1, 127.8, 127.5, 127.3, 125.3, 124.9, 120.3, 114.8, 109.0, 80.2, 44.0, 29.4. IR (potassium bromide) (v, cm^{-1}):1733, 1684, 1602, 1584, 1540, 1496, 1452, 1361, 1255, 1076, 1007, 835, 668. HRMS (TOF, ESI, m/z): Calcd for [M + Na]$^+$ $C_{25}H_{17}Br_2NNaO_3$, 561.9452; found, 561.9463. $[\alpha]_D^{25}$ = +40.5 (c = 0.2, $CHCl_3$). HPLC analysis: 95% ee, [Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 59.5 min, t (minor) = 30.8 min].

(S)-1-Ethyl-5-methoxy-4′-(naphthalen-2-yl)spiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3q**). Yield 85% (68 mg), white solid. M.P.: 158−159 °C. ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 7.96 (d, J = 1.6 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.83−7.87 (m, 2H), 7.70 (dd, J_1 = 8.8 Hz, J_2 =2.0 Hz, 1H), 7.51−7.58 (m, 2H), 7.12 (d, J = 2.4 Hz, 1H), 6.89 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.73 (s, 1H), 3.69−3.81 (m, 5H), 3.48 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H), 3.23 (dd, J_1 = 18.0 Hz, J_2 = 1.2 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.9, 163.3, 156.2, 151.5, 135.5, 134.3, 133.0, 132.9, 129.2, 129.0, 128.8, 127.8, 127.8, 127.1, 126.6, 122.7, 115.1, 114.8, 111.9, 109.6, 80.0, 55.9, 35.2, 32.5, 12.5. IR (potassium bromide) (v, cm^{-1}):1714, 1614, 1493, 1456, 1368, 1345, 1303, 1282, 1216, 1164, 1144, 1116, 1037, 1010, 959, 859, 820, 746, 683. HRMS (TOF, ESI, m/z): Calcd for [M + Na]$^+$ $C_{25}H_{21}NNaO_4$: 422.1363; found, 422.1351. $[\alpha]_D^{25}$ = +126.3 (c = 0.6, $CHCl_3$). HPLC analysis: 88% ee, [Daicel Chiralpak OD-H, *n*-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 39.1 min, t (minor) = 22.5 min].

(S)-1-Ethyl-5-methoxy-4′-(thiophen-2-yl)spiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3r**). Yield 73% (52 mg), white solid. M.P.: 179−181 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.51 (dd, J_1 = 5.2 Hz, J_2 = 1.2 Hz, 1H), 7.33 (dd, J_1 = 4.0 Hz, J_2 = 1.2 Hz, 1H), 7.11 (dd, J_1 = 4.0 Hz, J_2 = 3.6 Hz, 1H), 7.08 (d, J = 2.4 Hz, 1H), 6.89 (dd, J_1 = 8.4

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Hz, J_2 = 2.4 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.50 (s, 1H), 3.68−3.80 (m, 5H), 3.35 (dd, J_1 = 17.6 Hz, J_2 = 2.0 Hz, 1H), 3.06 (dd, J_1 = 17.6 Hz, J_2 = 0.8 Hz, 1H), 1.29 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.7, 163.2, 156.2, 145.1, 139.9, 135.5, 129.9, 129.0, 128.5, 128.3, 115.0, 111.9, 111.7, 109.6, 79.7, 55.9, 35.2, 32.7, 12.5. IR (potassium bromide) (v, cm^{-1}): 2981, 1717, 1693, 1653, 1612, 1491, 1457, 1281, 1255, 1216, 1142, 1040, 1010, 886, 838, 805, 732, 687. HRMS (TOF, ESI, m/z): Calcd for $[M + Na]^+$ $C_{19}H_{17}NNaO_4S$, 378.0770; found, 378.0778. $[\alpha]_D^{25}$ = +63.3 (c = 0.6, $CHCl_3$). HPLC analysis: 75% ee, [Daicel Chiralpak OD-H, n-hexane/2-propanol = 65/35, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 25.7 min, t (minor) = 16.4 min].

*(S)-4′-(tert-Butyl)-1-ethyl-5-methoxyspiro[indoline-3,2′-pyran]-2,6′(3′H)-dione (**3s**).* Yield 71% (47 mg), white solid. M.P.: 160−161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.00 (d, J = 2.4 Hz, 1H), 6.88 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 6.08 (d, J = 0.8 Hz, 1H), 3.66−3.79 (m, 5H), 2.97 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H), 2.59 (d, J = 18.0 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.15 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.8, 165.1, 163.5, 156.0, 135.4, 129.2, 115.0, 113.1, 111.6, 109.5, 80.0, 55.9, 36.3, 35.1, 30.8, 27.5, 12.5. IR (potassium bromide) (v, cm^{-1}): 2955, 1710, 1653, 1633, 1600, 1494, 1438, 1346, 1285, 1217, 1078, 1041, 943, 866, 814, 755, 675. HRMS (TOF, ESI, m/z): Calcd for $[M + Na]^+$ $C_{19}H_{23}NNaO_4$, 352.1519; found, 352.1529. $[\alpha]_D^{25}$ = −11.9 (c = 0.94, $CHCl_3$). HPLC analysis: 98% ee, [Daicel Chiralpak OD-H, n-hexane/2-propanol =80/20, v = 0.8 mL·min^{-1}, λ = 254 nm, t (major) = 11.9 min, t (minor) = 10.6 min].

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR, ^{13}C NMR, and HPLC spectra for all products; summary of the optimization of reaction conditions, and crystal structure data of spirocyclic oxindole-dihydropyranone **3o** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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