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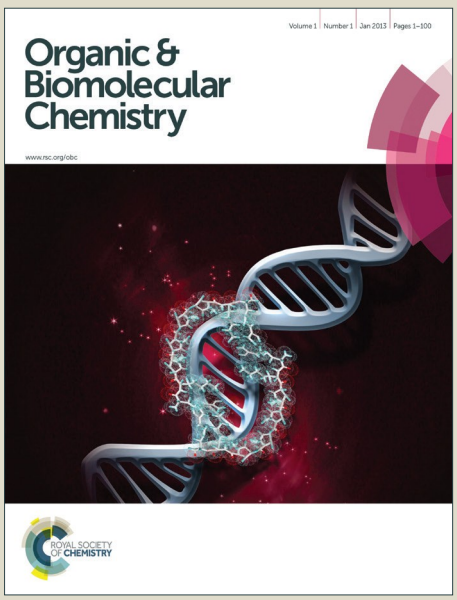

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ARTICLE

N-Heterocyclic carbene-catalyzed [4+2] cyclization of a,β-unsaturated carboxylic acids bearing γ-H with isatins: An enantioselective synthesis of spirocyclic oxindole–dihydropyranones

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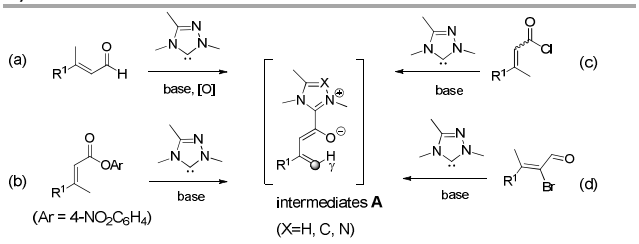
An NHC-catalyzed asymmetric [4+2] annulation of isatins and a,β-unsaturated carboxylic acids bearing γ-H gave spirocyclic oxindole–dihydropyranones successfully via in situ activation strategy. This protocol featured easy availability of raw materials, good yields and excellent enantioselevities (up to 99% ee).

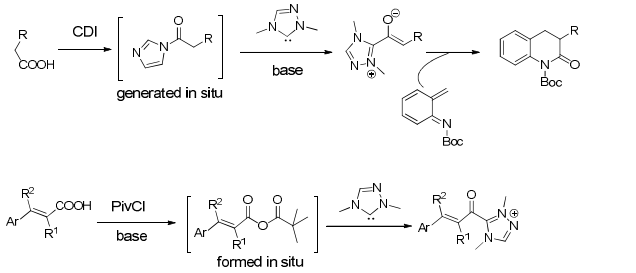
Introduction

The wide distribution of spirooxindole cores in numerous bioactive natural products and synthetic pharmaceutically relevant compounds stimulated a great deal of interest in the efficient construction and modification of this skeleton.[1] In past decades, successful assemblies of spirooxindoles were realized through the elegant strategies including oxidative spirocyclization,[2] metal-mediated multi-step transformations,[3] Prins-type cyclization[4] and amino enyne catalysis.[5] However, the association of harsh conditions, tediousness of multi-step procedures and the involvement of metal catalyst with these protocols necessitate the development of new and facile approaches to this spirocyclic framework with biological significance.

N-heterocyclic carbene (NHC) has been proven to be a powerful kind of catalysis for a variety of domino transformations to obtain heterocycles.[6] NHC-catalyzed reactions have been widely applied for organic chemistry, such as the benzoin condensation,[7] Stetter reaction,[8] a^3-d^3 umpolung.[9] In recent years, as a crucial intermediate, NHC-bounded vinyl enolate **A** has been converted from β,β-disubstituted enals, α,β-unsaturated esters, a,β-unsaturated acyl chlorides, α-bromo-α,β-unsaturated aldehydes successfully (**Scheme 1**).[10] Compared to these feedstocks, a,β-unsaturated carboxylic acids are more stable and accessible, which makes them ideal starting materials for NHC-catalyzed reactions. In 2014, Scheidt and co-workers reported the formation of azolium enolates from carboxylic acids and N,N-carbonyldiimidazole (CDI) in the presence of NHCs.[11] Recently, Ye's group discovered an NHC-catalyzed generation of a,β-unsaturated acyl azoliums from α,β-unsaturated carboxylic acids via in situ generated mixed anhydrides for the synthesis of pyrrolidinone and dihydropyridinone derivatives (**Scheme 2**).[12]



Scheme 1. Formation of NHC-bounded vinyl enolate.



Scheme 2. NHC-bounded intermediates generated through in situ activation of carboxylic acids.

More recently, our group have developed an NHC-catalyzed in situ activation strategy to β-functionalize the saturated carboxylic acids.[13c] Thus we speculated that the combination of a,β-unsaturated carboxylic acids bearing γ-H with a condensing agent under the catalysis of NHCs could release the corresponding intermediates **A** and the subsequent annulation with isatins may provide a new access to spirocyclic oxindole–dihydropyranone

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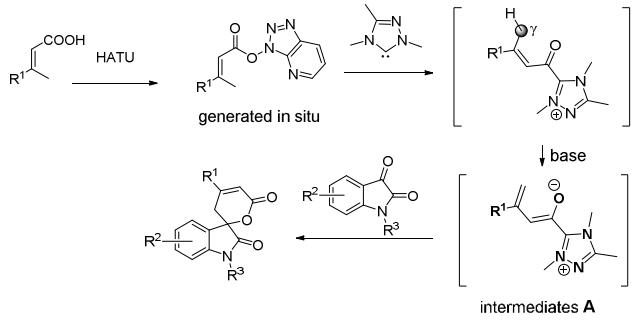
(**Scheme 3**).[14] In conjunction upon our previous work on NHC-catalyzed synthesis of heterocycles,[13] herein, we shall report our preliminary results of NHC-catalyzed [4+2] cyclization of a,β-unsaturated carboxylic acids bearing γ-H with isatins for the efficient asymmetric construction of spirocyclic oxindole–dihydropyranone.

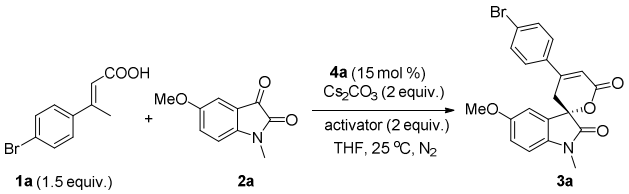


Scheme 3. Vinyl enolates generated from a,β-unsaturated carboxylic acids possessing γ-H via in situ activation.

Results and discussion

Initially, the NHC-catalyzed [4+2] annulation of 3-(4-bromophenyl)but-2-enoic acid **1a** and 5-methoxy-1-methylindoline-2,3-dione **2a** was investigated as a model reaction. Our attempts started from screening a series of activators including CDI, HATU, BOP-Cl and DCC/HOBt. To our delight, the desired product **3a** was only obtained successfully in the presence of HATU (Table 1).

Table 1. screening of the activators

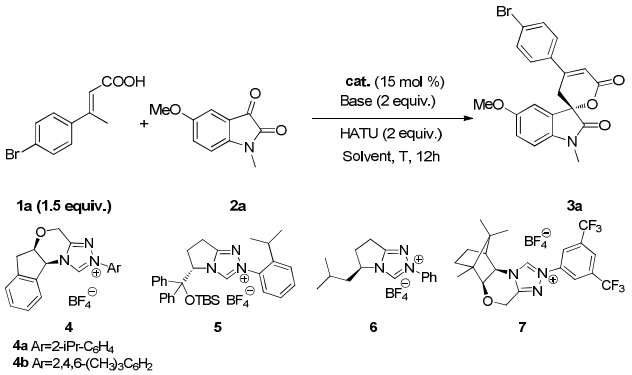


Entry	activator	Yield(%)[a]	ee(%)[b]
1	HATU	40	55
2	CDI	--	--
3	BOP-Cl	--	--
4	DCC/HOBT	--	--

[a]. Isolated yield. [b]. Enantioselctivity determined by HPLC.

The influences of chiral triazolium salts **4-7** were investigated to optimize the reaction conditions. As shown in table 2, **4b** was the best precatalyst to give the desired cycloadduct **3a** in 70% yield with 60% ee (Table 2, entry 2). However, other triazolium salts such as **5, 6, 7** were absolutely ineffective. Then, DABCO (1,4- Diazabicyclo[2.2.2]octane), NaOAc, t-BuOK, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), Cs_2CO_3 and K_2CO_3 were tested to evaluate the scope of the base and only Cs_2CO_3 was the most valid among the bases employed (Table 2, entries 6-10). Compared to THF, ether, 1,4-dioxane and DCM, toluene was found to be optimal in 85% yield with 91% ee (Table 2, entry 11 to 14). The screening of the temperature revealed that 0 °C afforded the best yield and enantioselctivity (92% ee). At the same time, lowering (-10 °C) or increasing (room temperature) the temperature had no positive effect on the reaction (Table 2, entries 15 and 16).

Table 2. Optimization of the reaction conditions.



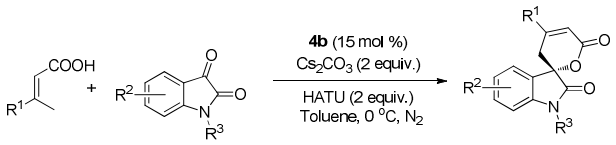
Entry	NHC cat.	Base	*T* [°C]	Solvent	Yield [%][a]	ee [%][b]
1	**4a**	Cs_2CO_3	25	THF	40	55
2	**4b**	Cs_2CO_3	25	THF	70	60
3	**5**	Cs_2CO_3	25	THF	Trace	--
4	**6**	Cs_2CO_3	25	THF	Trace	-
5	**7**	Cs_2CO_3	25	THF	Trace	--
6	**4b**	K_2CO_3	25	THF	--	--
7	**4b**	NaOAc	25	THF	-	-
8	**4b**	DABCO	25	THF	--	--
9	**4b**	DBU	25	THF	-	-
10	**4b**	*t*BuOK	25	THF	-	-
11	**4b**	Cs_2CO_3	25	Toluene	88	91
12	**4b**	Cs_2CO_3	25	ether	-	-
13	**4b**	Cs_2CO_3	25	dioxane	83	70
14	**4b**	Cs_2CO_3	25	DCM	-	-
15	**4b**	Cs_2CO_3	0	Toluene	91	92
16	**4b**	Cs_2CO_3	-10	Toluene	35	70

[a].Isolated yield. [b]. Enantioselctivity determined by HPLC.

With the optimized reaction conditions in hand, the exploration of substrate scope was then briefly achieved. We observed that both electron-deficient (4-Br, 4-Cl, 4-F) and electron-rich (4-CH_3, 4-MeO) moieties were tolerated well on the aryl group of the a,β-unsaturated acids **1**. Furthermore, 2-

naphthyl substituted a,β-unsaturated carboxylic acid could also take part in this asymmetric protocol and delivered the corresponding product **3m** in excellent yield. However, when the aryl group at 3-position of **1** was replaced with a Me group, the reaction gave the expected product in poor yield with moderate enantioselectivity. This should be attributed to the conjugation effect of aryl group. The different substituted groups (such as methyl, ethyl, allyl and benzyl) on the N-atom of isatin were also explored. We discovered that these desired cycloadducts were isolated in high yield with good enantioselectivity (Table 3, entrys 1-3 and 12). Moreover, isatins with both electron-withdrawing groups (4-Br) and electron-donating group (5-MeO) were well compatible with the reaction conditions.

Table 3. Synthesis of spirocyclic oxindole



1 (1.5 equiv.) **2** **3**

Entry	R^1	R^2	R^3	Product	Yield(%)[a]	ee(%)[b]
1	4-BrC_6H_4	5-MeO	Me	**3a**	91	92
2	4-BrC_6H_4	5-MeO	Et	**3b**	90	92
3	4-BrC_6H_4	5-MeO	allyl	**3c**	87	84
4	4-ClC_6H_4	5-MeO	Me	**3d**	81	80
5	4-FC_6H_4	5-MeO	Me	**3e**	88	99
6	4-FC_6H_4	5-MeO	Et	**3f**	82	81
7	4-FC_6H_4	5-MeO	allyl	**3g**	83	86
8	4-MeC_6H_4	5-MeO	Et	**3h**	84	86
9	4-MeC_6H_4	5-MeO	allyl	**3i**	82	82
10	4-MeOC_6H_4	5-MeO	Et	**3j**	73	86
11	4-MeOC_6H_4	5-MeO	allyl	**3k**	78	90
12	4-BrC_6H_4	4-Br	Bn	**3l**	82	84
13	2-naphthyl	5-MeO	Et	**3m**	85	80
14	4-BrC_6H_4	5-Me	Et	**3n**	85	73
15	Me	5-Me	Et	**3o**	35	80

[a].Isolated yield. [b]. Enantioselctivity determined by HPLC.

The absolute stereochemistry of (+)-**3a** was unambiguously established by the X-ray analysis of its crystal (Figure 1).[15] Other product configurations were deduced based on analogy (see the supporting information for details).

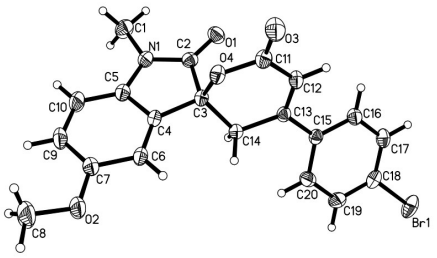
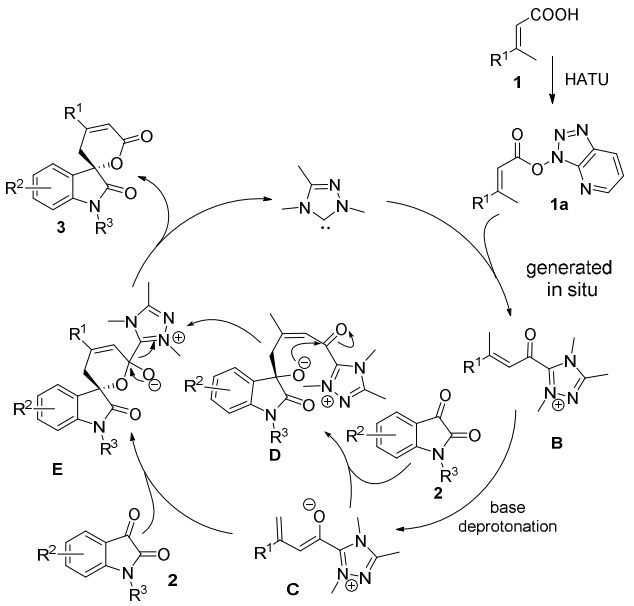


Figure 1. X-ray structure of **3a**.

A plausible catalytic cycle was illustrated in Scheme **4**. The addition of NHC to α,β-unsaturated ester substrate, which was generated in situ from the α,β-unsaturated acid, formed the corresponding NHC-bounded intermediate **B**. **B** was deprotonated at *γ*-position to give the vinyl enolate **C** in the presence of base. The key intermediate **C** attacked the isatin **2** through a Diels–Alder reaction to give zwitterionic intermediate **E**. Moreover, the C=C bonds in intermediates **B** and **C** should adopt a E-configuration due to the steric effect, which made these intermediates more thermodynamically stable. Thus, a non-concerted nucleophilic addition with subsequent intramolecular cascade reaction of **C** and **2** could also generate intermediate **E**. The collapse of zwitterion **E** furnished the final [4+2] cycloadduct **3** and regenerated the catalyst[10c, 10f].



Scheme 4. Plausible catalytic cycle.

Conclusions

In summary, we have developed an NHC-catalyzed in situ activation strategy to promote α,β-unsaturated carboxylic acid to involve a formal [4+2] annulation for the assembly of spirocyclic oxindole–dihydropyranone in good yields with up to

99% ee. Studies aimed at the expansion the reaction scope and the further development of analogous cyclization reactions of α,β-unsaturated carboxylic acid are underway in our lab.

Experimental

Typical procedure for the NHC-catalyzed reaction of α,β-unsaturated carboxylic acid with isatins. An oven-dried 10-mL Schlenk tube equipped with a magnetic stir bar was charged with triazolium salt **4b** (12.6 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), α,β-unsaturated carboxylic acid **1** (0.3 mmol), isatin **2** (0.2 mmol) and HATU (228 mg, 0.6 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen. The freshly distilled toluene (2 mL) was added into the mixture with a syringe. Then the mixture was stirred at 0 °C until completion (monitored by TLC). After removal of the solvent under reduced pressure, the resulting crude residue was purified by column chromatography (silicagel, mixtures of petroleum ether/ethyl acetate, 3:1, v/v) to afford the desired product **3**.

(S)-4'-(4-bromophenyl)-5-methoxy-1-methylspiro[indoline-3,2'-pyran]-2,6'(3'H)-dione (3a). 75 mg, 91% yield; white solid, M.P.: 181-183 °C (reported 187-188 °C[13d]), (204-205 °C, recrystal from the solution in petroleum ether/ethyl acetate=3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.60 (m, 2H, ArH), 7.40-7.44 (m, 2H, ArH), 7.08 (d, J = 2.4 Hz, 1H, ArH), 6.92 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, ArH), 6.81 (d, J = 8.8 Hz, 1H, ArH), 6.58 (t, J = 1.6 Hz, 1H, CH=), 3.78 (s, 3H, OCH_3), 3.29 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H, HCH), 3.21 (s, 3H, CH_3), 3.10 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H, HCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 162.9, 156.5, 150.4, 136.5, 134.8, 132.4, 128.7, 127.5, 125.5, 115.2, 111.7, 109.5, 79.9, 55.9, 32.5, 26.6; IR (potassium bromide) (v, cm^{-1}): 3071, 2952, 2926, 1733, 1649, 1580, 1480, 1405, 1366, 1247, 1070, 1005, 807; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{20}H_{16}BrNNaO_4$: 436.0160 found: 436.0177. $[\alpha]_D^{25}$= +83.3 (c = 0.2, $CHCl_3$). HPLC analysis: 92% ee, [Daicel Chiralpak AD-H, n-hexane/2-propanol = 65/35, v = 0.8 mL.min^{-1}, λ = 254 nm, t (major) = 29.5 min, t (minor) = 40. 6 min].

(S)-4'-(4-bromophenyl)-1-ethyl-5-methoxyspiro[indoline-3,2'-pyran]-2,6'(3'H)-dione (3b), 77 mg, 90% yield; white solid; M.P.: 176-178 °C (reported 182-183 °C[13d]); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.56 (m, 2H, ArH), 7.42-7.40 (m, 2H, ArH), 7.06 (d, J = 2.4 Hz, 1H, ArH), 6.89 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, ArH), 6.80 (d, J = 8.4 Hz, 1H, ArH), 6.57 (s, 1H, CH=), 3.77-3.70 (m, 5H, CH_2, OCH_3), 3.28 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H, HCH), 3.06 (dd, J_1 = 17.6 Hz, J_2 = 0.8 Hz, 1H, HCH), 1.28 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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}): 3071, 2940, 1728, 1655, 1604, 1579, 1491, 1458, 1435, 1388, 1266, 1220, 1133, 1077, 1008, 950, 832, 807; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{21}H_{18}BrNNaO_4$: 450.0317 found: 450.0329. $[\alpha]_D^{25}$= +88.1 (c = 0.2, $CHCl_3$). HPLC analysis: 92 % ee, [Daicel Chiralpak AD-H, n-hexane/2-propanol = 65/35, v = 0.8 mL.min^{-1}, λ = 254 nm, t (major) =31.1 min, t (minor) = 34.2 min].

(S)-1-allyl-4'-(4-bromophenyl)-5-methoxyspiro[indoline-3,2'-pyran]-2,6'(3'H)-dione (3c), 76 mg, 87% yield; white solid; M.P.: 140-142 °C (reported 141-142 °C[13d]); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.56 (m, 2H, ArH), 7.41-7.39 (m, 2H, ArH), 7.05 (d, J = 2.4 Hz, 1H, ArH), 6.86 (dd, J_1 = 8.6 Hz, J_2 = 2.6 Hz, 1H, ArH), 6.78 (d, J = 8.8 Hz, 1H, ArH), 6.56 (s, 1H, CH=), 5.86-5.77 (m, 1H, CH=), 5.28-5.24 (m, 2H, $=CH_2$), 4.30-4.29 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.28 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H, HCH), 3.08 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H, HCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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}): 3071, 2959, 2898, 1717, 1620, 1588, 1498, 1441, 1362, 1250, 1179, 1020, 980, 867, 828, 812; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{22}H_{18}BrNNaO_4$: 462.0317 found: 462.0322. $[\alpha]_D^{25}$= +73.8 (c = 0.2, $CHCl_3$). HPLC analysis: 84% 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) = 30.2 min].

(S)-4'-(4-chlorophenyl)-5-methoxy-1-methylspiro[indoline-3,2'-pyran]-2,6'(3'H)-dione (3d), 60 mg, 81% yield; white solid; M.P.: 143-144 °C (reported 148-149 °C[13d]); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 8.8 Hz, 2H, ArH), 7.41 (d, J = 8.4 Hz, 2H, ArH), 7.06 (d, J = 2.4 Hz, 1H, ArH), 6.90 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, ArH), 6.79 (d, J = 8.4 Hz, 1H, ArH), 6.56 (s, 1H, CH=), 3.76 (s, 3H, OCH_3), 3.28 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H, HCH), 3.19 (s, 3H, CH_3), 3.07 (dd, J_1 = 17.6 Hz, J_2 = 1.2 Hz, 1H, HCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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}): 2926, 2850, 1717, 1671, 1590, 1470, 1394, 1281, 1232, 1139, 998, 816; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{20}H_{16}ClNNaO_4$: 392.0666 found: 392.0681. $[\alpha]_D^{25}$= +87.0 (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) = 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 (3e), 62 mg, 80% yield; white solid; M.P.: 210-211 °C (reported 208-209 °C[13d]); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.52 (m, 2H, ArH), 7.13 (t, J = 8.4 Hz, 2H, ArH), 7.07 (d, J = 2.4 Hz, 1H, ArH), 6.90 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, ArH), 6.79 (d, J = 8.8 Hz, 1H, ArH), 6.53 (s, 1H, CH=), 3.76 (s, 3H, OCH_3), 3.29 (d, J = 18 Hz, 1H, HCH), 3.20 (s, 3H, CH_3), 3.08 (dd, J_1 = 17.6 Hz, J_2 = 0.8 Hz, 1H, HCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 164.3 (J_{CF}= 251.2 Hz), 156.5, 150.5, 136.5, 132.1 (J_{CF}= 3.4 Hz), 128.8, 128.1 (J_{CF}= 8.6 Hz), 116.3 (J_{CF}= 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}): 3081, 2946, 2926, 1722, 1698, 1589, 1499, 1410, 1361, 1230, 1159, 1062, 1008, 956, 830, 807, 682, 557; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{20}H_{16}FNNaO_4$: 376.0961 found: 376.0974. $[\alpha]_D^{25}$= +36.1(c = 0.2, $CHCl_3$). HPLC analysis: 99% 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)-1-ethyl-4'-(4-fluorophenyl)-5-methoxyspiro[indoline-3,2'-pyran]-2,6'(3'H)-dione (3f), 62 mg, 82% yield; white solid; M.P: 183-184 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.52 (m, 2H, ArH), 7.16-7.10 (m, 2H, ArH), 7.07 (d, J = 2.4 Hz, 1H, ArH), 6.90 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, ArH), 6.81 (d, J = 8.8 Hz, 1H, ArH), 6.53 (s, 1H, CH=), 3.79-3.67 (m, 5H, CH_2, OCH_3), 3.30 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H, HCH), 3.06 (dd, J_1 = 18 Hz, J_2 = 1.2 Hz, 1H, HCH), 1.28 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 164.3 (J_{CF}= 251.0 Hz), 163.1, 156.2, 150. 6, 135.5, 132.0 (J_{CF}= 3.3 Hz), 129.0, 128.2 (J_{CF}= 8. 6 Hz), 116.3 (J_{CF}= 21.8 Hz), 115.1, 114.5, 111.8, 109.6, 79.9, 55.9, 35.2, 32.6, 12.5; IR (potassium bromide) (v, cm^{-1}): 2360, 2341, 1707, 1603, 1496, 1218, 1035, 852, 807, 668; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{21}H_{18}FNNaO_4$: 390.1118 found: 390.1125. $[\alpha]_D^{25}$= +78.4 (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) = 19.7 min, t (minor) = 23.3 min].

(S)-1-allyl-4'-(4-fluorophenyl)-5-methoxyspiro[indoline-3,2'-pyran]-2,6'(3'H)-dione (3g), 63 mg, 83% yield; white solid; M.P.: 150-152 °C (reported 155-156 °C[13d]); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.53 (m, 2H, ArH), 7.13 (t, J= 8.4 Hz, 2H, ArH), 7.07 (d, J = 2.4 Hz, 1H, ArH), 6.87 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H, ArH), 6.79 (d, J = 8.8 Hz, 1H, ArH), 6.54 (s, 1H, CH=), 5.88-5.78 (m, 1H, CH=), 5.30-5.25 (m, 2H, =CH_2), 4.31 (d, J = 5.2 Hz, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.31 (dd, J_1 = 18.0 Hz, J_2 = 1.6 Hz, 1H, HCH), 3.09 (dd, J_1 = 17.8 Hz, J_2 = 1.4 Hz, 1H, HCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 164.3 (J_{CF}= 251.0 Hz), 163.0, 156.4, 150.5, 135.6, 132.0 (J_{CF}= 3.4 Hz), 130.7, 128.8, 128.1 (J_{CF}= 8.5 Hz), 118.3, 116.3 (J_{CF}= 21.8 Hz), 115.1, 114.6, 111.6, 110.5, 79.8, 55.9, 42.7, 32.8; IR (potassium bromide) (v, cm^{-1}): 3071, 2962, 1717, 1609, 1496, 1439, 1361, 1238, 1181, 1020, 956, 870, 831, 807, 621; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{22}H_{18}FNNaO_4$: 402.1118 found: 402.1122. $[\alpha]_D^{25}$= +45.2 (c = 0.2, $CHCl_3$). HPLC analysis: 86% ee, [Daicel Chiralpak AD-H, n-hexane/2-propanol = 65/35, v = 0.8 mL.min^{-1}, λ = 254 nm, t (major) = 21.0min, t (minor) = 27.0 min].

(S)-1-ethyl-5-methoxy-4'-(p-tolyl)spiro[indoline-3,2'-pyran]-2,6'(3'H)-dione (3h), 61 mg, 84% yield; white solid; M.P: 145-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.44 (m, 2H, ArH), 7.24 (d, J = 8 Hz, 2H, ArH), 7.08 (d, J = 2.8 Hz, 1H, ArH), 6.88 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, ArH), 6.80 (d, J = 8.8 Hz, 1H, ArH), 6.57 (t, J = 1.2 Hz, 1H, CH=), 3.79-3.67 (m, 5H, CH_2, OCH_3), 3.35 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H, HCH), 3.03 (dd, J_1 = 18 Hz, J_2 = 1.2 Hz, 1H, HCH), 2.38 (s, 3H, CH_3), 1.27 (t, J = 7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 163.4, 156.2, 151.9, 141.6, 135.5, 133.0, 129.8, 129.3, 126.0, 115.3, 113.6, 111.8, 109.6, 80.0, 55.9, 35.1, 32.5, 21.4, 12.5; IR (potassium bromide) (v, cm^{-1}): 2360, 2341, 1707, 1635, 1500, 1213, 1033, 867, 816, 682; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{22}H_{21}NNaO_4$: 386.1368 found: 386.1390. $[\alpha]_D^{25}$= +83.9 (c = 0.2, $CHCl_3$). HPLC analysis: 86% ee, [Daicel Chiralcel OD-H, n-hexane/2-propanol = 65/35, v = 0.8 mL.min^{-1}, λ = 254 nm, t (major) = 28.3 min, t (minor) = 13.8 min].

(S)-1-allyl-5-methoxy-4'-(p-tolyl)spiro[indoline-3,2'-pyran]-2,6'(3'H)-dione (3i), 62 mg, 82% yield; white solid; M.P: 158-159 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.40 (m, 2H, ArH), 7.24 (d, J =8.0 Hz, 2H, ArH), 7.08 (d, J = 2.8 Hz, 1H, ArH), 6.85 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, ArH), 6.78(d, J =8.8 Hz, 1H, ArH), 6.56 (t, J = 1.4 Hz, 1H, CH=), 5.88-5.78 (m, 1H, CH=), 5.30-5.25 (m, 2H, =CH_2), 4.32-4.30 (m, 2H, CH_2), 3.74 (s, 3H, OCH_3), 3.37 (dd, J_1 = 17. 6 Hz, J_2 = 1.6 Hz, 1H, HCH), 3.07 (dd, J_1 = 17. 6 Hz, J_2 = 1.2 Hz, 1H, HCH), 2.39 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 163.3, 156.3, 151.9, 141.6, 135.6, 133.0, 130.8, 129.8, 129.0, 126.0, 118.3, 115.0, 113.7, 111. 6, 110.4, 79.9, 55.9, 42.7, 32.6, 21.4; IR (potassium bromide) (v, cm^{-1}): 2360, 2341, 1708, 1609, 1499, 1362, 1252, 1021, 869, 814, 684; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{23}H_{21}NNaO_4$: 398.1368 found: 398.1388. $[\alpha]_D^{25}$= +88.5 (c = 0.2, $CHCl_3$). HPLC analysis: 82% ee, [Daicel Chiralcel OD-H, n-hexane/2-propanol = 65/35, v = 0.8 mL.min^{-1}, λ = 254 nm, t (major) = 30.8 min, t (minor) = 15.1 min].

(S)-1-ethyl-5-methoxy-4'-(4-methoxyphenyl)spiro[indoline-3,2'-pyran]-2,6'(3'H)-dione (3j), 55 mg, 73% yield; white solid; M.P.: 118-120 °C (reported 119-121 °C[13d]); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 8.8 Hz, 2H , ArH), 7.08 (d, J = 2.4 Hz, 1H , ArH), 6.94 (d, J = 8.8 Hz, 2H , ArH), 6.88 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H, ArH), 6.79 (d, J = 8.4 Hz, 1H, ArH), 6.51 (s, 1H, CH=), 3.85 (s, 3H, CH_3), 3.78-3.69 (m, 5H, CH_2, OCH_3), 3.34 (dd, J_1 = 17.6 Hz, J_2 = 1.2 Hz, 1H, HCH), 3.02 (d, J = 18 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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}): 2986, 2934, 1721, 1620, 1606, 1499, 1432, 1358, 1240, 1212, 1180, 1039, 998, 963, 817, 807; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{22}H_{21}NNaO_5$: 402.1317 found: 402.1325. $[\alpha]_D^{25}$= +74. 6 (c = 0.2, $CHCl_3$). HPLC analysis: 86% 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) = 30.7 min].

(S)-1-allyl-5-methoxy-4'-(4-methoxyphenyl)spiro[indoline-3,2'-pyran]-2,6'(3'H)-dione (3k), 61 mg, 78% yield; white solid; M.P.: 120-121 °C (reported 124-125 °C[13d]); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.50 (m, 2H, ArH), 7.08 (d, J = 2.4 Hz, 1H, ArH), 6.96-6.92 (m, 2H, ArH), 6.85 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, ArH), 6.79 (d, J = 8.4 Hz, 1H, ArH), 6.52 (s, 1H, CH=), 5.88-5.78 (m, 1H, CH=), 5.30-5.25 (m, 2H, =CH_2), 4.32-4.30 (m, 2H, CH_2), 3.85 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.35 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H, HCH), 3.05 (dd, J_1 = 17.6 Hz, J_2 = 0.8 Hz, 1H, HCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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}): 3069, 2961, 2830, 1709, 1650, 1577, 1482, 1439, 1360, 1262, 1247, 1039, 977, 832; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{23}H_{21}NNaO_5$: 414.1317 found: 414.1309. $[\alpha]_D^{25}$= +68.1 (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) = 28.3 min, t (minor) = 36.6 min].

(S)-1-benzyl-4-bromo-4'-(4-bromophenyl)spiro[indoline-3,2'-pyran]-2,6'(3'H)-dione (3l), 88 mg, 82% yield; white solid; M.P.: 158-159 °C (reported 162-164 [13d]); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.57 (m, 2H, ArH), 7.45-7.42 (m, 2H, ArH), 7.35-7.23 (m, 6H, ArH), 7.15 (t, J = 8.0 Hz, 1H, ArH), 6.70 (d, J = 7.2 Hz, 1H, ArH), 6.57

(d, J = 2.4 Hz, 1H, CH=), 4.83 (s, 2H, CH_2), 4.02 (dd, J_1 = 18.4 Hz, J_2 = 2.8 Hz, 1H, HCH), 2.86 (d, J = 18.4 Hz, 1H, HCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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 (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{25}H_{17}Br_2NNaO_3$: 561.9452 found: 561.9463. $[\alpha]_D^{25}$= +72.6 (c = 0.2, $CHCl_3$). HPLC analysis: 84% ee, [Daicel Chiralpak AD-H, n-hexane/2-propanol = 65/35, v = 0.8 mL.min^{-1}, λ = 254 nm, t (major) = 54.5 min, t (minor) = 28.1 min].

(S)-1-ethyl-5-methoxy-4'-(naphthalen-2-yl)spiro[indoline-3,2'-pyran]-2,6'(3'H)-dione (3m), 68 mg, 85% yield; white solid; M.P.: 144-145 °C (reported 148-150 °C[13d]); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H, ArH), 7.91-7.83 (m, 3H, ArH), 7.70 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H, ArH), 7.56-7.51 (m, 2H, ArH), 7.12 (d, J = 2.4 Hz, 1H, ArH), 6.89 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, ArH), 6.81 (d, J = 8.4 Hz, 1H, ArH), 6.73 (s, 1H, CH=), 3.81-3.69 (m, 5H, CH_2CH_3, CH_3), 3.48 (dd, J_1 = 17.6 Hz, J_2 = 1.6 Hz, 1H, HCH), 3.23 (dd, J_1 = 17.6 Hz, J_2 = 1.0 Hz, 1H, HCH), 1.30 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 163.3, 156.2, 151.5, 135.5, 134.3, 133.0, 132.9, 129.2, 129.0, 128.7, 127.8, 127.7, 127.0, 126.6, 122.7, 115.1, 114.8, 111.8, 109.6, 80.0, 55.9, 35.2, 32.5, 12.5; IR (potassium bromide) (v, cm^{-1}): 1710, 1660, 1575, 1496, 1434, 1247, 1035, 990, 869, 837. HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{25}H_{21}NNaO_4$: 422.1368 found: 422.1359. $[\alpha]_D^{25}$= +115.4 (c = 0.2, $CHCl_3$). HPLC analysis: 80% ee, [Daicel Chiralcel OD-H, n-hexane/2-propanol = 65/35, v = 0.8 mL.min^{-1}, λ = 254 nm, t (major) = 39.5 min, t (minor) = 22.7 min].

(S)-4'-(4-bromophenyl)-1-ethyl-5-methylspiro[indoline-3,2'-pyran]-2,6'(3'H)-dione(3n), 70 mg, 85% yield; white solid; M.P.:180-182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.57 (m, 2H, ArH), 7.43-7.40 (m, 2H, ArH), 7.26 (s, 1H, ArH), 7.18 (d, J = 8 Hz, 1H, ArH), 6.89 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, ArH), 6.80 (d, J = 8.4 Hz, 1H, ArH), 6.57 (s, 1H, CH=), 3.81-3.67 (m, 2H, CH_2), 3.28 (d, J = 17.6 Hz, 1H, HCH), 3.06 (d, J = 17.6 Hz, 1H, HCH), 2.29 (s, 3H, CH_3), 1.28 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 163.1, 156.6, 139.8, 134.8, 133.1, 132.3, 131.3, 127.9, 125.4, 125.0, 115.2, 109.0, 79.8, 35.1, 32.4, 21.1, 12.5; IR (potassium bromide) (v, cm^{-1}): 3416, 2975, 2360, 1712, 1625, 1604, 1586, 1497, 1447, 1363, 1279, 1234, 1115, 1092, 1020, 1007, 822, 805; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{21}H_{18}BrNNaO_3$: 434.0368 found: 434.0379. $[\alpha]_D^{25}$= +167.0 (c = 0.1, $CHCl_3$). HPLC analysis: 73% ee, [Daicel Chiralpak AD-H, n-hexane/2-propanol = 65/35, v = 0.8 mL.min^{-1}, λ = 254 nm, t (major) = 28.7 min, t (minor) = 30. 7 min].

(S)-1-ethyl-4',5-dimethylspiro[indoline-3,2'-pyran]-2,6'(3'H)-dione (3o), 19 mg, 35 % yield; white solid; M.P.: 117-118 °C (reported 103-105 °C[13b]); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (s, 1H, ArH), 7.15 (d, J = 8 Hz, 1H, ArH), 6.75 (d, J = 7.6 Hz, 1H, ArH), 6.052-6.048 (m, 1H, ArH), 3.76-3.65 (m, 2H, CH_2), 2.87 (d, J = 18.4 Hz, HCH), (d, J = 18.4 Hz, HCH), 2.30 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 1.25 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 163.0, 154.3, 140.0, 135.5, 132.9, 131.1, 129.2, 124.8, 116.5, 116.5, 108.9, 35.2, 35.0, 23.3, 21.5, 12.5; IR (potassium bromide) (v, cm^{-1}): 2960, 2946, 1717, 1640, 1560, 1491, 1372, 1260, 1201, 1130, 950, 832, 807; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{16}H_{17}NNaO_3$: 294.1106 found: 294.1122. $[\alpha]_D^{25}$= +94.2 (c = 0.2, $CHCl_3$). HPLC analysis: 80% ee, [Daicel Chiralpak AD-H, n-hexane/2-propanol = 95/5, v = 0.8 mL.min^{-1}, λ = 254 nm, t (major) = 49.6 min, t (minor) = 53.3 min].

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15 Crystallographic data (excluding structure factors) for the structures (**3a**) in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1046964. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, CambridgeCB21EZ, UK (fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk).