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DOUBLE MICHAEL ADDITION OF OXINDOLES TO DIENONES CATALYZED BY TBAB: AN EFFICIENT ROUTE TO SPIROCYCLIC OXINDOLES

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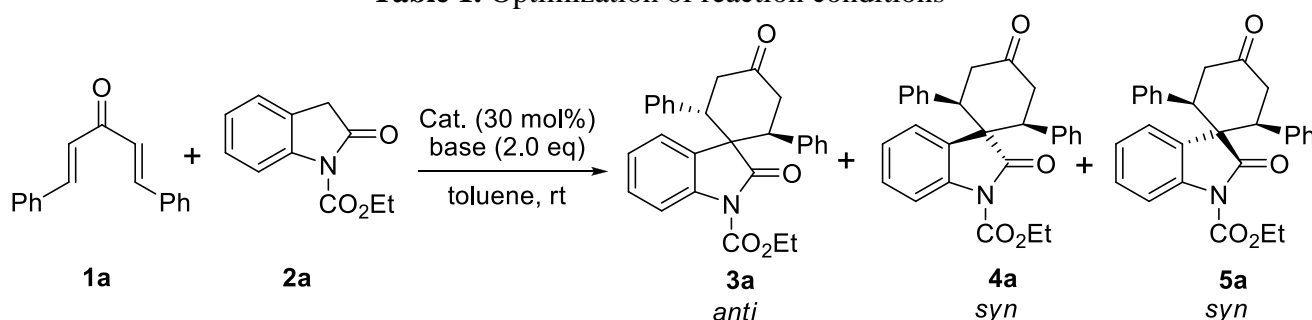
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Abstract – The efficient synthesis of biologically active spiro compounds is a challenge for organic chemists and pharmaceutical chemists. Herein we describe a synthesis strategy of spirocyclic oxindoles via double Michael reaction of *N*-protected-oxindoles to dienones using tetrabutylammonium bromide (TBAB) as catalyst. The desired spirocyclic oxindoles were obtained with both high yields up to 99% and diastereoselectivity up to >95:5 dr.

Spirocyclic oxindoles¹⁻¹² represent important intermediates for the preparation of a wide variety of bioactive compounds¹³ and may be found in various active drug molecules,¹⁴ including Sunitinib and Ropinilol. Presently, the preparation of spirocyclic oxindoles mainly focuses on the modification of the 3-position carbon in oxindoles. In doing so, 3-nonsubstituted oxindoles¹⁵ become versatile and useful building blocks for the construction of spirooxindoles, but there are only a few reports up to now. Wang and coworkers¹⁶ reported a double Michael reaction of oxindoles and dienones with a chiral primary amine as catalyst, leading to spirocyclic oxindoles in excellent yields and enantioselectivities. In 2012, Wang *et al.*¹⁷ employed the same concept starting from *N*-unprotected oxindoles and dienones, with similar results. Meanwhile, Companyó *et al.*¹⁸ showed the potential of organocatalysis for the synthesis complex structures via a cascade Michael–Michael-aldol reaction between oxindoles and α,β -unsaturated aldehydes, which led to the synthesis of spirooxindole derivatives with almost diastereo- and enantiopure forms. When catalyzing the Michael addition reaction of oxindoles, chiral primary amine,¹⁹ chiral

thiourea²⁰ and alkaloids²¹ are frequently used as catalysts.²²⁻²³ However, these catalysts are relatively expensive to produce and often require harsh experimental conditions. Phase-transfer catalysis (PTC)²⁴⁻²⁹ has been recognized as an efficient strategy in organic synthesis because it offers several advantages, such as less expensive, high efficiency, operational simplicity, mild reaction conditions and environmental benefits. Herein we disclose that double Michael additions between 3-nonsubstituted oxindoles and dienones can be efficiently catalyzed by tetrabutylammonium bromide (TBAB) to furnish the desired multisubstituted spirocyclic oxindoles in moderate to good yields and with high diastereoselectivities.

Table 1. Optimization of reaction conditions^a



Entry	Cat.	Base	<i>dr</i> ^b (<i>anti</i> / <i>syn</i>)	Yield ^c /%
1	TBAB	K ₂ CO ₃	68/32	94
2	TBAB	Na ₂ CO ₃	95/5	89
3	TBAB	KOH	70/30	90
4	TBAB	NaOH	71/28	77
5	TBAB	NaHCO ₃	nd	<5
6	TBAB	AcOK	>95/5	98
7	TBAB	AcONa	90/10	45
8	TBAF	AcOK	93/7	85
9	TBAI	AcOK	nd	15
10	none	AcOK	nd	<5

^aUnless otherwise noted, the reaction was carried out with 0.2 mmol **2a**, 0.24 mmol **1a**, 30 mol% catalyst and 2.0 eq base in 1 mL toluene at room temperature for 24 h. ^bDetermined by HPLC and ¹H NMR.

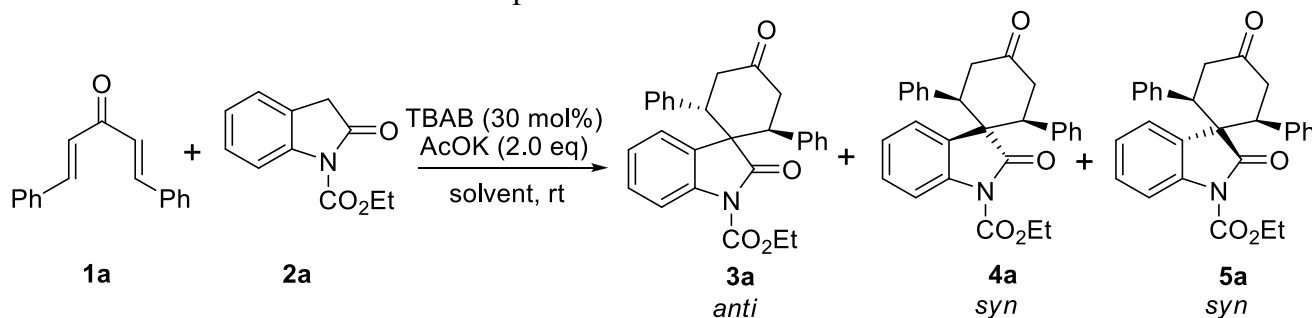
^cTotal yield of isomers.

Initially, we investigated the model reaction of *N*-CO₂Et-3-nonsubstituted oxindole **2a** with dienone **1a** catalyzed by TBAB in the presence of K₂CO₃ as base. To our delight, the desired products were formed with a mixture of diastereomers **3a**, **4a** and **5a** in 94% total yield, *anti*-isomer **3a** as a major diastereomer (Table 1, Entry 1). Use of weakly basic Na₂CO₃ under the same conditions afforded products with 95/5 diastereoselectivity, however with inferior yield (Table 1, Entry 2). KOH and NaOH gave moderate to good yields and poor diastereoselectivities (Table 1, Entries 3, 4). When NaHCO₃ was used, only trace desired product was observed (Table 1, Entry 5). Encouraged by this outcome, the effect of AcOK was

investigated, and excellent yield and diastereoselectivity were obtained (Table 1, Entry 6). Importantly, when no phase-transfer catalyst was present in the reaction mixture, even after a reaction time of 72 hours, product formation was negligible (Table 1, Entry 10). Tetrabutylammonium fluoride (TBAF) and tetrabutylammonium iodide (TBAI) showed very low reactivities and gave disappointing results (Table 1, Entries 8, 9).

The effect of reaction solvents was also evaluated and the results were demonstrated in Table 2. CH_2Cl_2 gave high yield with only moderate diastereoselectivity (Table 2, Entry 1). Ether, THF and benzene provided similar diastereoselectivities with CH_2Cl_2 , however in inferior yields (Table 2, Entries 2–4). MeCN and 1,4-dioxane were also examined (94%–95% yield, 95/5 dr, Table 2, Entries 5–6), but toluene was still the suitable one for this transformation and gave 98% yield and >95/5 dr (Table 2, Entry 7). Finally, the optimized reaction conditions for the double Michael addition between *N*-CO₂Et-3-nonsubstituted oxindole **2a** and dienone **1a** were established: 1.2 equiv. of **1a** to **2a**, 30 mol% TBAB as catalyst and 2.0 equiv. of AcOK as base in toluene at room temperature for 24 hours.

Table 2. Optimization of reaction conditions^a



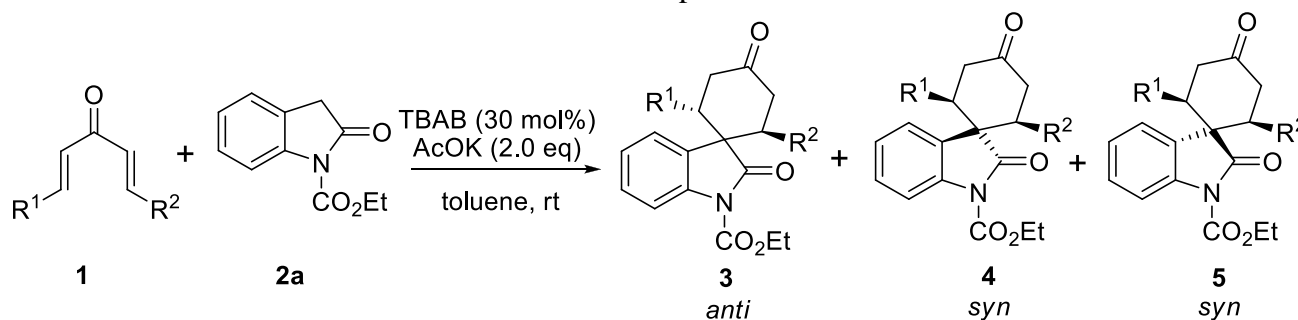
Entry	Cat.	Solvent	dr ^b (<i>anti</i> / <i>syn</i>)	Yield ^c /%
1	TBAB	CH_2Cl_2	89/11	95
2	TBAB	Et_2O	90/10	91
3	TBAB	THF	85/15	84
4	TBAB	benzene	90/10	95
5	TBAB	MeCN	95/5	95
6	TBAB	1,4-dioxane	95/5	94
7	TBAB	toluene	>95/5	98

^aUnless otherwise noted, the reaction was carried with 0.2 mmol **2a**, 0.24 mmol **1a**, 30 mol% TBAB and 2.0 eq AcOK in 1 mL solvent at room temperature for 24 h. ^bDetermined by HPLC and ¹H NMR. ^cTotal yield of isomers.

With the optimized conditions in hand, the scope of substrates was investigated, and the results are summarized in Table 3. A variety of symmetric dienones were found to be well tolerated in this transformation and afforded the desired products in good to excellent yields and high

diastereoselectivities (up to 98% yield, up to 95/5 dr). For dienones with electron-withdrawing (Table 3, Entries 4–6, 11, 12) and electron-donating (Table 3, Entries 2, 3, 13) substituents on the phenyl groups were also suitable substrates, while 4-nitro-substituted dienone only gave 61% yield even after a longer reaction time (Table 3, Entry 7). However, the presence of *ortho*-substituents on the dienones resulted in products with slightly lower yields (Table 3, Entries 9, 10). Additionally, 4-dimethylamino-substituted dienone turned out to be completely ineffective for this process (Table 3, Entry 8). The heteroaromatic derivative also gave the product in 86% yield and >95/5 dr (Table 3, Entry 14). The major diastereomer **3a** is a known compound and its configuration has been determined. Therefore, the relative configuration of compound **3a** was confirmed by ^1H NMR, and the chemical shifts were consistent with reported literature.¹⁶

Table 3. Substrate scope for this reaction^a



Entry	R ¹ , R ²	dr ^b (<i>anti</i> / <i>syn</i>)	Yield ^c /%
1	Ph, 1a	>95/5	3a /98
2	4-MeC ₆ H ₄ , 1b	>95/5	3b /99
3	4-MeOC ₆ H ₄ , 1c	>95/5	3c /82
4	4-FC ₆ H ₄ , 1d	>95/5	3d /98
5	4-ClC ₆ H ₄ , 1e	>95/5	3e /98
6	4-BrC ₆ H ₄ , 1f	>95/5	3f /99
7	4-NO ₂ C ₆ H ₄ , 1g	>95/5	3g /61
8	4-(Me) ₂ NC ₆ H ₄ , 1h	nd	3h /0
9	2-MeOC ₆ H ₄ , 1i	>95/5	3i /93
10	2-ClC ₆ H ₄ , 1j	>95/5	3j /97
11	3-MeOC ₆ H ₄ , 1k	>95/5	3k /83
12	2,4-Cl ₂ C ₆ H ₃ , 1l	>95/5	3l /96
13	3,4-(MeO) ₂ C ₆ H ₃ , 1m	>95/5	3m /98
14	2-furyl, 1n	>95/5	3n /86

^aUnless otherwise noted, the reaction was carried out with 0.2 mmol **2a**, 0.24 mmol **1**, 30 mol% TBAB and 2.0 eq AcOK in 1 mL toluene at room temperature for 24 h. ^bDetermined by HPLC and ^1H NMR.

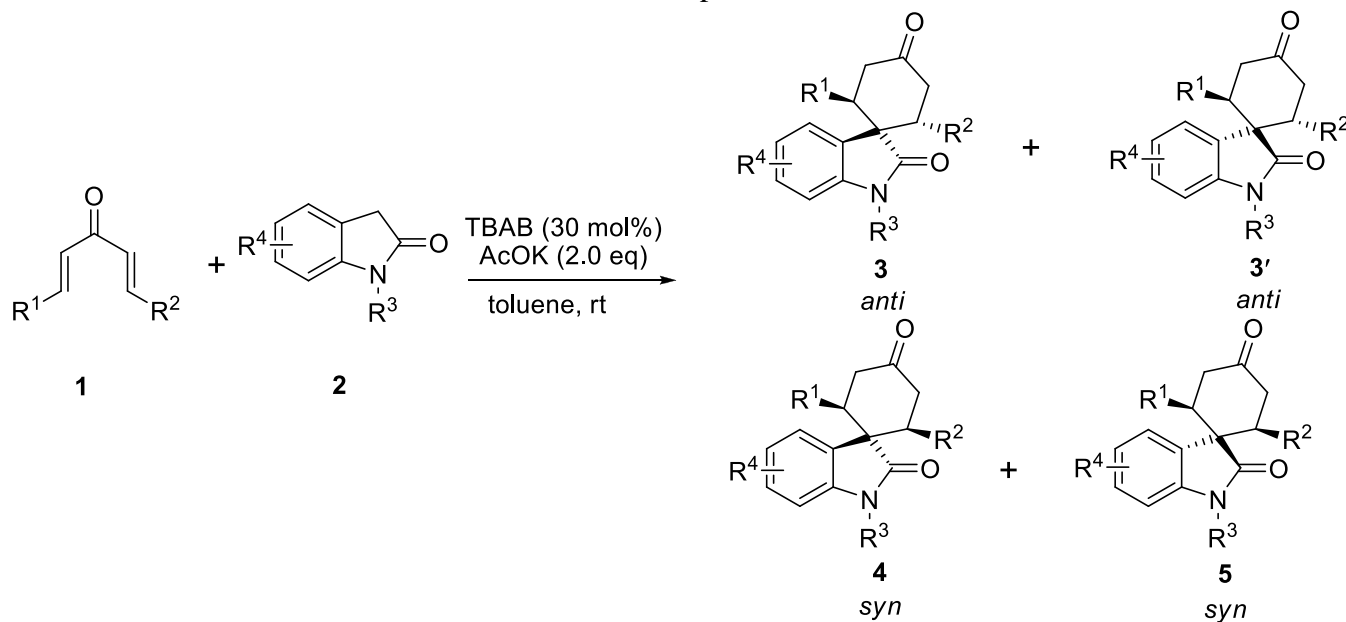
^cTotal yield of isomers.

Unsymmetric dienones with electron-donating and electron-withdrawing groups were also examined. The corresponding products were obtained in good yield, but the diastereoselectivity significantly decreased in

contrast with symmetric dienones (Table 4, Entries 1–3). In addition, the double Michael addition between 5-bromooxindole and dienone **1a** performed very well and was seen to give the product in high yield (93%) and good diastereoselectivity (>95/5 dr, Table 4, Entry 4). Notably, other electron-withdrawing substituents such as Ac and Boc on the nitrogen atom of oxindoles ring were also proved to be effective in this transformation, achieving the products in 97–98% yields and > 95/5 dr (Table 4, Entries 5, 6).

In summary, we have successfully developed a cheaper strategy for the construction of highly diastereoselective spirocyclic oxindoles via double Michael additions between dienones and *N*-protected-3-nonsubstituted oxindoles by using easily available tetrabutylammonium bromide (TBAB) as the catalyst. A number of spirocyclic oxindoles have been isolated in high yields, with excellent diastereoselectivities. Further application of the current methodology and study of the chiral phase-transfer catalysis are ongoing in our laboratory.

Table 4. Substrate scope for this reaction^a



Entry	R ¹	R ²	R ³	R ⁴	dr ^b	Yield ^c /%
1	Ph	4-MeC ₆ H ₄ , 1o	CO ₂ Et	H, 2a	53:47 (3o/3'o)	92/(3o+3'o)
2	Ph	4-ClC ₆ H ₄ , 1p	CO ₂ Et	H, 2a	50:50 (3p/3'p)	93/(3p+3'p)
3	Ph	4-BrC ₆ H ₄ , 1q	CO ₂ Et	H, 2a	52:48 (3q/3'q)	95/(3q+3'q)
4	Ph	Ph, 1a	CO ₂ Et	5-Br, 2b	>95/5 (<i>anti/syn</i>)	93/ 3r
5	Ph	Ph, 1a	Ac	H, 2c	>95/5 (<i>anti/syn</i>)	97/ 3s
6	Ph	Ph, 1a	Boc	H, 2d	>95/5 (<i>anti/syn</i>)	98/ 3t

^aUnless otherwise noted, the reaction was conducted with 0.2 mmol **2**, 0.24 mmol **1**, 30 mol% TBAB and 2.0 eq AcOK in 1 mL toluene at room temperature for 24 h. ^bMeasured by HPLC and ¹H NMR. ^cThe total yield of isomers.

EXPERIMENTAL

All reactions were carried out under inert atmosphere in schlenk tube equipped with magnetic stir bar and monitored by TLC using Merck 60 F254 pre coated silica gel plates. Flash chromatography was carried out with silica gel (200-300 mesh). FT-IR spectra were recorded on a Bruker ALPHA II spectrometer. ^1H and ^{13}C NMR spectra were recorded using a Bruker Avance III HD 600 MHz NMR spectrometer (100 MHz and 125 MHz for carbon). Chemical shifts were reported in ppm down field from internal Me₄Si. High resolutions mass spectral analyses (HRMS) were measured on a AB SCIEX TripleTOF5600+. HPLC analyses were carried out on a Hewlett Packard Model HP 1200 instrument. All of the organic solvents used in this study were dried over appropriate agents under argon atmosphere and distilled prior to use.

Starting Materials. All of the dienones used in this study were synthesized according to the reported literatures.³⁰ *N*-Substituted oxindole (**2a–2d**) were prepared by *N*-acylation reaction of oxindoles with ethyl chloroformate, acetic anhydride and (Boc)₂O according to the reported procedure.³¹

Typical Procedure for the Preparation of Products 3. To a stirred solution of (*1E*, *4E*)-1,5-diphenylpenta-1,4-dien-3-one **1a** (56.2 mg, 0.24 mmol) and ethyl 2-oxindoline-1-carboxylate **2a** (41.0 mg, 0.2 mmol) in toluene (1.0 mL) under nitrogen atmosphere was added tetrabutylammonium bromide (TBAB, 19.3 mg, 0.06 mmol) and anhydrous AcOK (39.3 mg, 0.4 mmol) at room temperature. The mixture was stirred for 24 h at the same temperature, then monitored by TLC. After completion, the mixture was diluted with AcOEt (20 mL) and washed with brine (15 mL). The organic layer was dried with anhydrous MgSO₄, concentrated and purified by flash chromatography on silica gel (PE/EA) to afford the desired product **3a** (86.1 mg, 98%) as white solid.

Ethyl 2',4-dioxo-2,6-diphenylspiro[cyclohexane-1,3'-indoline]-1'-carboxylate (3a): White solid; ^1H NMR (600 MHz, CDCl₃) δ 7.49 (d, $J = 7.8$ Hz, 1H), 7.23-7.19 (m, 3H), 7.09-7.01 (m, 4H), 6.93 (dd, $J = 7.8, 1.8$ Hz, 2H), 6.87 (dt, $J = 7.8, 1.2$ Hz, 1H), 6.83-6.81 (m, 2H), 6.29 (d, $J = 7.2$ Hz, 1H), 4.43-4.38 (m, 2H), 3.92 (t, $J = 15.0$ Hz, 1H), 3.81-3.75 (m, 2H), 3.56 (dd, $J = 16.8, 6.0$ Hz, 1H), 3.04 (dd, $J = 16.2, 7.2$ Hz, 1H), 2.74 (dd, $J = 15.6, 3.6$ Hz, 1H), 1.42 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (151 MHz, CDCl₃) δ 210.4, 177.1, 150.2, 139.2, 138.7, 137.1, 129.1, 128.4, 128.3, 128.2, 128.0, 128.0, 127.6, 127.4, 125.3, 123.5, 114.3, 63.3, 56.0, 46.7, 46.6, 42.4, 41.8, 14.2. HRMS (ESI) m/z calcd for C₂₈H₂₆NO₄ [M+H]⁺: 440.1862, Found 440.1833.

Ethyl 2',4-dioxo-2,6-di(*p*-tolyl)spiro[cyclohexane-1,3'-indoline]-1'-carboxylate (3b): White solid; ^1H NMR (600 MHz, CDCl₃) δ 7.53 (d, $J = 7.8$ Hz, 1H), 7.10 (dt, $J = 7.2, 1.2$ Hz, 1H), 7.02 (d, $J = 7.8$ Hz, 2H), 6.88 (dt, $J = 7.8, 1.2$ Hz, 1H), 6.83-6.80 (m, 4H), 6.71 (d, $J = 7.8$ Hz, 2H), 6.28 (d, $J = 7.8$ Hz, 1H), 4.45-4.39 (m, 2H), 3.88 (t, $J = 15.0$ Hz, 1H), 3.74-3.70 (m, 2H), 3.55 (dd, $J = 16.2, 6.0$ Hz, 1H), 2.98 (dd, $J = 16.2, 6.0$ Hz, 1H), 2.71 (dd, $J = 16.2, 3.0$ Hz, 1H), 2.31 (s, 3H), 2.16 (s, 3H), 1.43 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 210.7, 177.2, 150.3, 138.7, 137.2, 136.9, 136.3, 134.2, 129.0, 128.8, 128.7, 128.6, 128.2, 127.8, 125.4, 123.4, 114.3, 63.3, 55.9, 46.5, 46.2, 42.7, 42.0, 21.0, 20.9, 14.2. HRMS (ESI) m/z calcd for $\text{C}_{30}\text{H}_{30}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 468.2175, Found 468.2130.

Ethyl 2,6-bis(4-methoxyphenyl)-2',4-dioxospiro[cyclohexane-1,3'-indoline]-1'-carboxylate (3c):

White solid; mp 53–55 °C; IR (KBr) 3450, 2959, 2836, 1787, 1726, 1601, 1484, 1465, 1284, 1235, 1164, 1104 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.52 (d, $J = 7.8$ Hz, 1H), 7.14–7.08 (m, 2H), 6.94 (t, $J = 7.8$ Hz, 1H), 6.89 (t, $J = 7.8$ Hz, 1H), 6.75 (d, $J = 7.8$ Hz, 1H), 6.59 (d, $J = 7.8$ Hz, 1H), 6.55 (d, $J = 7.2$ Hz, 1H), 6.44–6.37 (m, 3H), 6.30 (s, 1H), 4.41–4.38 (m, 2H), 3.86 (t, $J = 15.0$ Hz, 1H), 3.76–3.73 (m, 2H), 3.65 (s, 3H), 3.55–3.50 (m, 4H), 3.01 (dd, $J = 16.2, 6.6$ Hz, 1H), 2.72 (d, $J = 16.2$ Hz, 1H), 1.41 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ 210.3, 177.1, 159.2, 159.1, 150.3, 140.8, 138.9, 138.6, 129.3, 129.0, 128.5, 128.4, 125.4, 123.5, 121.3, 120.4, 115.1, 114.4, 113.6, 113.2, 113.1, 63.4, 55.9, 55.2, 54.9, 46.8, 46.8, 42.4, 41.8, 14.2. HRMS (ESI) m/z calcd for $\text{C}_{30}\text{H}_{30}\text{NO}_6$ $[\text{M}+\text{H}]^+$: 500.2073, Found 500.2063.

Ethyl 2,6-bis(4-fluorophenyl)-2',4-dioxospiro[cyclohexane-1,3'-indoline]-1'-carboxylate (3d):

White solid; ^1H NMR (600 MHz, CDCl_3) δ 7.51 (d, $J = 8.4$ Hz, 1H), 7.13 (t, $J = 7.8$ Hz, 1H), 6.94 (t, $J = 7.8$ Hz, 1H), 6.89 (d, $J = 7.2$ Hz, 4H), 6.78–6.76 (m, 2H), 6.74–6.71 (m, 2H), 6.43 (d, $J = 7.8$ Hz, 1H), 4.43–4.38 (m, 2H), 3.88–3.81 (m, 2H), 3.70 (dd, $J = 14.4, 3.6$ Hz, 1H), 3.45 (dd, $J = 16.8, 6.0$ Hz, 1H), 3.04 (dd, $J = 16.2, 7.8$ Hz, 1H), 2.70 (dd, $J = 16.2, 3.6$ Hz, 1H), 1.41 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ 209.7, 176.9, 161.9 (d, $J = 245.7$ Hz), 161.8 (d, $J = 245.1$ Hz), 150.0, 138.7, 134.8, 134.7, 132.6, 132.6, 130.5 (d, $J = 7.9$ Hz), 129.6 (d, $J = 7.5$ Hz), 128.6, 128.2, 124.9, 123.8, 115.2, 115.1, 115.0, 114.9, 114.6, 63.5, 56.2, 45.9, 45.8, 42.3, 41.7, 14.2. HRMS (ESI) m/z calcd for $\text{C}_{28}\text{H}_{24}\text{F}_2\text{NO}_4$ $[\text{M}+\text{H}]^+$: 476.1673, Found 476.1643.

Ethyl 2,6-bis(4-chlorophenyl)-2',4-dioxospiro[cyclohexane-1,3'-indoline]-1'-carboxylate (3e):

White solid; ^1H NMR (600 MHz, CDCl_3) δ 7.53 (d, $J = 7.8$ Hz, 1H), 7.27 (t, $J = 7.2$ Hz, 1H), 7.19–7.14 (m, 4H), 7.03–7.00 (m, 2H), 6.96 (dt, $J = 7.8, 1.2$ Hz, 1H), 6.86–6.84 (m, 2H), 6.75–6.73 (m, 2H), 6.47 (dd, $J = 7.8, 1.2$ Hz, 1H), 4.45–4.39 (m, 2H), 3.88–3.81 (m, 2H), 3.68 (dd, $J = 14.4, 3.6$ Hz, 1H), 3.44 (dd, $J = 16.8, 5.4$ Hz, 1H), 3.04 (dd, $J = 16.2, 7.2$ Hz, 1H), 2.70 (dd, $J = 16.2, 3.0$ Hz, 1H), 1.42 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ 209.4, 176.7, 149.9, 138.7, 137.3, 135.3, 133.5, 133.4, 130.2, 129.3, 128.8, 128.4, 128.3, 127.9, 124.8, 123.9, 114.7, 63.6, 55.9, 46.1, 45.9, 42.1, 41.5, 14.2. HRMS (ESI) m/z calcd for $\text{C}_{28}\text{H}_{24}\text{Cl}_2\text{NO}_4$ $[\text{M}+\text{H}]^+$: 508.1082, Found 508.1055.

Ethyl 2,6-bis(4-bromophenyl)-2',4-dioxospiro[cyclohexane-1,3'-indoline]-1'-carboxylate (3f):

White solid; ^1H NMR (600 MHz, CDCl_3) δ 7.53 (d, $J = 8.4$ Hz, 1H), 7.33–7.31 (m, 2H), 7.18–7.15 (m, 3H), 6.96 (dt, $J = 7.8, 1.2$ Hz, 1H), 6.79–6.77 (m, 2H), 6.68–6.66 (m, 2H), 6.47 (dd, $J = 7.8, 1.2$ Hz, 1H), 4.44–4.38 (m, 2H), 3.87–3.78 (m, 2H), 3.66 (dd, $J = 14.4, 3.6$ Hz, 1H), 3.43 (dd, $J = 16.8, 6.0$ Hz, 1H), 3.03 (dd, $J = 16.8, 7.8$ Hz, 1H), 2.69 (dd, $J = 16.2, 3.0$ Hz, 1H), 1.42 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (151 MHz, CDCl_3)

δ 209.3, 176.7, 149.9, 138.7, 137.8, 135.8, 131.4, 131.2, 131.2, 130.6, 129.7, 129.7, 128.8, 127.9, 124.8, 123.9, 121.7, 121.6, 114.7, 63.6, 55.8, 46.1, 46.0, 42.0, 41.4, 14.2. HRMS (ESI) m/z calcd for $C_{28}H_{24}Br_2NO_4$ $[M+H]^+$: 598.0052, Found 598.0057.

Ethyl 2,6-bis(4-nitrophenyl)-2',4-dioxospiro[cyclohexane-1,3'-indoline]-1'-carboxylate (3g): White solid; 1H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, $J = 8.4$ Hz, 2H), 7.93 (d, $J = 9.0$ Hz, 2H), 7.50 (d, $J = 8.4$ Hz, 1H), 7.20-6.96 (m, 6H), 6.70 (d, $J = 7.2$ Hz, 1H), 4.41-4.36 (m, 2H), 4.08 (dd, $J = 9.6, 5.4$ Hz, 1H), 3.96-3.91 (m, 1H), 3.86-3.83 (m, 1H), 3.38 (dd, $J = 16.8, 4.8$ Hz, 1H), 3.20 (dd, $J = 16.8, 3.0$ Hz, 1H), 2.77 (dd, $J = 16.2, 2.4$ Hz, 1H), 1.39 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.7, 176.1, 149.5, 147.2, 147.2, 145.5, 143.7, 138.6, 129.6, 129.4, 129.0, 127.1, 124.4, 124.2, 123.4, 123.3, 123.1, 115.1, 63.9, 55.9, 46.6, 46.0, 41.3, 40.9, 14.1. HRMS (ESI) m/z calcd for $C_{28}H_{24}N_3O_8$ $[M+H]^+$: 530.1563, Found 530.1563.

Ethyl 2,6-bis(2-methoxyphenyl)-2',4-dioxospiro[cyclohexane-1,3'-indoline]-1'-carboxylate (3i): White solid; mp 130–131 °C; IR (KBr) 3451, 2959, 2837, 1786, 1727, 1601, 1484, 1465, 1284, 1235, 1164, 1104 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, $J = 7.8$ Hz, 1H), 7.25-7.15 (m, 3H), 6.98-6.94 (m, 3H), 6.73 (t, $J = 7.8$ Hz, 1H), 6.63-6.59 (m, 2H), 6.44 (d, $J = 8.4$ Hz, 1H), 6.02 (d, $J = 7.8$ Hz, 1H), 4.61 (d, $J = 12.0$ Hz, 1H), 4.52-4.47 (m, 2H), 4.11-4.09 (m, 1H), 3.80 (t, $J = 15.6$ Hz, 1H), 3.56 (dd, $J = 16.2, 7.2$ Hz, 1H), 3.40 (s, 3H), 3.25 (s, 3H), 2.93 (dd, $J = 16.2, 4.8$ Hz, 1H), 2.56 (dd, $J = 16.8, 3.6$ Hz, 1H), 1.51-1.47 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 211.1, 178.0, 157.1, 155.9, 150.8, 138.5, 129.0, 128.8, 128.7, 128.6, 128.2, 128.1, 127.4, 126.9, 125.3, 122.1, 120.3, 120.3, 113.2, 110.1, 109.9, 63.2, 54.6, 54.6, 54.3, 42.4, 41.6, 14.4. HRMS (ESI) m/z calcd for $C_{30}H_{30}NO_6$ $[M+H]^+$: 500.2073, Found 500.2060.

Ethyl 2,6-bis(2-chlorophenyl)-2',4-dioxospiro[cyclohexane-1,3'-indoline]-1'-carboxylate (3j): White solid; 1H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, $J = 7.8$ Hz, 1H), 7.45-7.43 (m, 2H), 7.35 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.32-7.29 (m, 1H), 7.21 (d, $J = 7.8$ Hz, 1H), 7.09-7.04 (m, 3H), 6.96 (dt, $J = 8.4, 1.8$ Hz, 1H), 6.66 (dt, $J = 7.8, 1.2$ Hz, 1H), 5.81 (dd, $J = 7.8, 1.2$ Hz, 1H), 4.71 (dd, $J = 14.4, 4.8$ Hz, 1H), 4.58-4.54 (m, 2H), 4.25 (dd, $J = 8.4, 1.2$ Hz, 1H), 3.88 (dd, $J = 16.2, 7.8$ Hz, 1H), 3.77 (t, $J = 15.0$ Hz, 1H), 2.73-2.69 (m, 2H), 1.54 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 209.4, 177.4, 150.5, 138.5, 137.6, 136.5, 136.4, 133.4, 129.6, 129.6, 129.4, 129.1, 128.5, 128.5, 127.3, 127.2, 127.1, 126.7, 124.5, 123.5, 113.8, 63.7, 53.4, 43.4, 42.8, 41.8, 39.6, 14.3. HRMS (ESI) m/z calcd for $C_{28}H_{24}Cl_2NO_4$ $[M+H]^+$: 508.1082, Found 508.1089.

Ethyl 2,6-bis(3-methoxyphenyl)-2',4-dioxospiro[cyclohexane-1,3'-indoline]-1'-carboxylate (3k): White solid; mp 57–58 °C; IR (KBr) 3445, 2959, 2836, 1724, 1601, 1464, 1284, 1234, 1163, 1044 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, $J = 8.4$ Hz, 1H), 7.14-7.08 (m, 2H), 6.94 (t, $J = 7.8$ Hz, 1H), 6.89 (t, $J = 7.8$ Hz, 1H), 6.76 (d, $J = 7.8$ Hz, 1H), 6.59 (dd, $J = 7.8, 2.4$ Hz, 1H), 6.55 (d, $J = 7.8$ Hz, 1H), 6.43 (d, $J = 7.8$ Hz, 1H), 6.39 (t, $J = 1.8$ Hz, 1H), 6.37 (d, $J = 7.2$ Hz, 1H), 6.30 (t, $J = 1.8$ Hz, 1H), 4.43-4.37

(m, 2H), 3.86 (t, $J = 15.6$ Hz, 1H), 3.76-3.73 (m, 2H), 3.65 (s, 3H), 3.55 (s, 3H), 3.52-3.49 (m, 1H), 3.01 (dd, $J = 16.2, 6.6$ Hz, 1H), 2.72 (dd, $J = 15.6, 3.6$ Hz, 1H), 1.41 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 210.2, 177.1, 159.2, 159.0, 150.2, 140.7, 138.8, 138.6, 129.3, 129.0, 128.5, 128.4, 125.3, 123.5, 121.2, 120.3, 115.1, 114.3, 113.6, 113.1, 113.1, 63.3, 55.9, 55.1, 54.9, 46.8, 46.7, 42.3, 41.7, 14.2. HRMS (ESI) m/z calcd for $\text{C}_{30}\text{H}_{30}\text{NO}_6$ $[\text{M}+\text{H}]^+$: 500.2073, Found 500.2087.

Ethyl 2,6-bis(2,4-dichlorophenyl)-2',4-dioxospiro[cyclohexane-1,3'-indoline]-1'-carboxylate (3l):

White solid; mp 186–187 °C; IR (KBr) 3448, 2958, 2838, 1785, 1740, 1713, 1587, 1473, 1370, 1286, 1235, 1104 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.63 (d, $J = 7.8$ Hz, 1H), 7.41 (dd, $J = 8.4, 1.8$ Hz, 1H), 7.35-7.32 (m, 1H), 7.29-7.24 (m, 2H), 7.16 – 7.09 (m, 2H), 7.05 (dd, $J = 8.4, 1.8$ Hz, 1H), 6.75 (t, $J = 7.8$ Hz, 1H), 5.90 (d, $J = 6.6$ Hz, 1H), 4.59-4.54 (m, 3H), 4.18 (d, $J = 6.6$ Hz, 1H), 3.85 (dd, $J = 16.2, 7.8$ Hz, 1H), 3.74 (t, $J = 14.4$ Hz, 1H), 2.68-2.64 (m, 2H), 1.54 (t, $J = 7.2$ Hz, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 208.7, 177.1, 150.4, 138.5, 137.3, 136.1, 135.0, 134.4, 134.1, 133.7, 130.0, 129.6, 129.5, 129.5, 129.0, 128.7, 128.1, 127.8, 127.5, 126.9, 126.2, 124.2, 123.8, 114.2, 63.9, 53.3, 49.3, 44.1, 43.3, 42.5, 41.6, 39.2, 14.3. HRMS (ESI) m/z calcd for $\text{C}_{28}\text{H}_{22}\text{Cl}_4\text{NO}_4$ $[\text{M}+\text{H}]^+$: 578.0273, Found 578.0266.

Ethyl 2,6-bis(3,4-dimethoxyphenyl)-2',4-dioxospiro[cyclohexane-1,3'-indoline]-1'-carboxylate (3m):

White solid; mp 138–139 °C; IR (KBr) 3448, 2958, 2838, 1725, 1600, 1460, 1285, 1164, 1095 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.49 (d, $J = 7.8$ Hz, 1H), 7.10 (t, $J = 7.2$ Hz, 1H), 6.90 (t, $J = 7.2$ Hz, 1H), 6.72 (dd, $J = 8.4, 1.8$ Hz, 1H), 6.56-6.51 (m, 2H), 6.41 (d, $J = 8.4$ Hz, 1H), 6.35 (d, $J = 6.6$ Hz, 1H), 6.25 (d, $J = 17.4$ Hz, 2H), 4.39-4.38 (m, 2H), 3.84-3.83 (m, 4H), 3.72 (d, $J = 1.8$ Hz, 3H), 3.68-3.63 (m, 5H), 3.56 (d, $J = 1.8$ Hz, 3H), 3.53-3.49 (m, 1H), 2.97 (dd, $J = 16.2, 6.6$ Hz, 1H), 2.70 (d, $J = 15.6$ Hz, 1H), 1.41-1.38 (m, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 210.5, 177.2, 150.1, 148.2, 148.1, 148.0, 147.9, 138.9, 131.8, 129.6, 128.8, 128.3, 125.5, 123.3, 120.9, 120.3, 114.5, 113.0, 110.9, 110.7, 110.4, 63.4, 56.3, 55.8, 55.7, 55.6, 55.4, 46.6, 46.1, 42.6, 42.0, 14.2. HRMS (ESI) m/z calcd for $\text{C}_{32}\text{H}_{34}\text{NO}_8$ $[\text{M}+\text{H}]^+$: 560.2284, Found 560.2286.

Ethyl 2,6-di(furan-2-yl)-2',4-dioxospiro[cyclohexane-1,3'-indoline]-1'-carboxylate (3n):

White solid; mp 145–146 °C; IR (KBr) 3448, 3052, 2982, 2926, 1789, 1729, 1606, 1480, 1467, 1287, 1167, 1095 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.71 (d, $J = 7.8$ Hz, 1H), 7.42 (d, $J = 1.2$ Hz, 1H), 7.21 (dt, $J = 7.8, 1.2$ Hz, 1H), 7.03 (d, $J = 1.8$ Hz, 1H), 6.94 (dt, $J = 7.8, 1.2$ Hz, 1H), 6.34 (q, $J = 1.8$ Hz, 1H), 6.02 (q, $J = 1.8$ Hz, 1H), 6.00 (dd, $J = 7.8, 0.6$ Hz, 1H), 5.94 (d, $J = 3.6$ Hz, 1H), 5.72 (d, $J = 3.0$ Hz, 1H), 4.50 (q, $J = 7.2$ Hz, 2H), 4.14 (dd, $J = 13.2, 4.2$ Hz, 1H), 3.82 (dd, $J = 15.6, 7.2$ Hz, 1H), 3.76 (dd, $J = 15.6, 1.8$ Hz, 1H), 3.57 (dd, $J = 7.2, 2.4$ Hz, 1H), 2.77 (ddd, $J = 15.6, 4.8, 1.8$ Hz, 1H), 2.62 (dt, $J = 15.6, 2.4$ Hz, 1H), 1.48 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 207.7, 175.7, 153.2, 152.1, 150.5, 142.2, 141.6, 138.7, 128.6, 128.2, 124.5, 123.9, 114.4, 110.5, 110.0, 109.2, 106.9, 63.5, 53.4, 41.8, 41.3, 41.2, 40.9, 14.3. HRMS (ESI) m/z calcd for $\text{C}_{24}\text{H}_{22}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 420.1447, Found 420.1451.

Ethyl 2',4-dioxo-2-phenyl-6-*p*-tolylspiro[cyclohexane-1,3'-indoline]-1'-carboxylate (3o): White solid; 92% total yield, 53:47 dr, mp 113–114 °C; IR (KBr) 3448, 3052, 2982, 2926, 1789, 1729, 1606, 1480, 1346, 1287, 1238, 1167, 1095 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ (mixture of two diastereomers) 7.51 (t, *J* = 7.8 Hz, 1H), 7.22–7.19 (m, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 7.06–7.01 (m, 3H), 6.92 (dd, *J* = 7.8 Hz and 1.2 Hz, 1H), 6.87 (dq, *J* = 7.8 Hz and 1.2 Hz, 1H), 6.84–6.81 (m, 3H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.29 (t, *J* = 7.2 Hz, 1H), 4.44–4.39 (m, 2H), 3.93–3.87 (m, 1H), 3.79–3.72 (m, 2H), 3.59–3.53 (m, 1H), 3.03–2.98 (m, 1H), 2.75–2.71 (m, 1H), 2.31 (s, 1H), 2.17 (s, 2H), 1.43 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ (mixture of two diastereomers) 210.5, 210.5, 177.2, 177.1, 150.3, 150.3, 139.3, 138.8, 138.8, 137.3, 137.3, 137.0, 136.3, 134.1, 129.1, 129.0, 128.9, 128.7, 128.3, 128.2, 128.0, 128.0, 127.9, 127.5, 127.4, 125.5, 125.3, 123.5, 114.3, 114.3, 63.3, 63.3, 56.0, 55.9, 46.8, 46.7, 46.5, 46.2, 42.6, 42.5, 42.0, 41.8, 21.0, 20.9, 14.2. HRMS (ESI) *m/z* calcd for C₂₉H₂₈NO₄ [M+H]⁺: 454.2018, Found 454.2017.

Ethyl 2-(4-chlorophenyl)-2',4-dioxo-6-phenylspiro[cyclohexane-1, 3'-indoline]-1'-carboxylate (3p): White solid; 93% total yield, 50:50 dr, mp 73–75 °C; IR (KBr) 3449, 2959, 2836, 1785, 1724, 1635, 1286, 1236 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ (mixture of two diastereomers) 7.51 (t, *J* = 8.4 Hz, 1H), 7.23–7.16 (m, 2H), 7.14–7.00 (m, 4H), 6.96–6.86 (m, 3H), 6.82–6.75 (m, 2H), 6.48–6.27 (m, 1H), 4.45–4.36 (m, 2H), 3.92–3.69 (m, 3H), 3.55–3.44 (m, 1H), 3.06–3.01 (m, 1H), 2.75–2.69 (m, 1H), 1.44 (t, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃) δ (mixture of two diastereomers) 209.9, 209.8, 176.9, 176.9, 150.1, 150.0, 139.0, 138.8, 138.7, 137.6, 136.7, 135.7, 133.4, 133.3, 130.3, 129.4, 129.0, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.6, 127.5, 125.1, 125.0, 123.7, 123.6, 114.5, 114.5, 63.5, 63.4, 56.0, 55.8, 46.8, 46.8, 45.9, 45.9, 42.3, 42.2, 41.7, 41.6, 14.2, 14.2. HRMS (ESI) *m/z* calcd for C₂₈H₂₅ClNO₄ [M+H]⁺: 474.1472, Found 474.1470.

Ethyl 2-(4-bromophenyl)-2',4-dioxo-6-phenylspiro[cyclohexane-1, 3'-indoline]-1'-carboxylate (3q): White solid; 95% total yield, 52:48 dr, mp 104–105 °C; IR (KBr) 3448, 2959, 2836, 1786, 1724, 1602, 1482, 1370, 1285, 1235, 1165, 1012 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ (mixture of two diastereomers) 7.53–7.49 (m, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.23–7.02 (m, 5H), 6.96–6.86 (m, 2H), 6.82–6.78 (m, 2H), 6.73–6.69 (m, 1H), 6.48–6.27 (m, 1H), 4.45–4.37 (m, 2H), 3.92–3.68 (m, 3H), 3.55–3.44 (m, 1H), 3.06–3.01 (m, 1H), 2.75–2.69 (m, 1H), 1.44 (t, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃) δ (mixture of two diastereomers) 209.9, 209.8, 176.9, 176.9, 150.1, 150.1, 139.0, 138.8, 138.7, 138.1, 136.7, 136.3, 131.3, 131.2, 130.6, 129.8, 129.1, 128.6, 128.6, 128.3, 128.3, 128.1, 128.0, 128.0, 127.7, 127.5, 125.1, 125.0, 123.8, 123.6, 121.6, 121.5, 114.6, 114.5, 63.5, 63.4, 56.0, 55.8, 46.8, 46.8, 45.9, 42.3, 42.2, 41.7, 41.6, 14.2, 14.2. HRMS (ESI) *m/z* calcd for C₂₈H₂₅BrNO₄ [M+H]⁺: 518.0967, Found 518.0964.

Ethyl 5'-bromo-2',4-dioxo-2,6-diphenylspiro[cyclohexane-1,3'-indoline]-1'-carboxylate (3r): White solid; ¹H NMR (600 MHz, CDCl₃) δ 7.40 (d, *J* = 9.0 Hz, 1H), 7.31–7.27 (m, 3H), 7.21 (dd, *J* = 8.4, 1.8 Hz,

1H), 7.10-7.05 (m, 3H), 6.92 (dd, $J = 7.2, 1.8$ Hz, 2H), 6.84 (dd, $J = 7.2, 1.8$ Hz, 2H), 6.21 (d, $J = 1.8$ Hz, 1H), 4.44-4.39 (m, 2H), 3.89 (t, $J = 15.0$ Hz, 1H), 3.74 (t, $J = 6.0$ Hz, 1H), 3.71 (dd, $J = 14.4, 3.6$ Hz, 1H), 3.59 (dd, $J = 16.2, 6.0$ Hz, 1H), 3.01 (dd, $J = 16.2, 6.0$ Hz, 1H), 2.75 (dd, $J = 16.2, 3.6$ Hz, 1H), 1.43 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ 209.8, 176.2, 150.0, 138.8, 137.7, 136.7, 131.1, 130.5, 129.1, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.6, 116.5, 115.9, 63.6, 56.0, 46.8, 46.5, 42.3, 41.6, 14.2. HRMS (ESI) m/z calcd for $\text{C}_{28}\text{H}_{25}\text{BrNO}_4$ $[\text{M}+\text{H}]^+$: 518.0967, Found 518.0971.

1'-Acetyl-2,6-diphenylspiro[cyclohexane-1,3'-indoline]-2',4-dione (3s): White solid; mp 140–141 °C; IR (KBr) 3449, 2958, 2838, 1728, 1604, 1482, 1466, 1285, 1164, 1104 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.81 (d, $J = 7.8$ Hz, 1H), 7.18-7.16 (m, 3H), 7.13-7.11 (m, 2H), 7.05 (dt, $J = 7.8, 1.2$ Hz, 2H), 7.00 (dt, $J = 7.8, 0.6$ Hz, 1H), 6.93-6.91 (m, 2H), 6.76 (d, $J = 7.2$ Hz, 2H), 6.69 (dd, $J = 7.8, 0.6$ Hz, 1H), 3.94 (q, $J = 4.8$ Hz, 1H), 3.88 (dd, $J = 16.2, 1.8$ Hz, 1H), 3.78 (dd, $J = 14.4, 3.6$ Hz, 1H), 3.34 (dd, $J = 16.8, 5.4$ Hz, 1H), 3.20 (dd, $J = 16.8, 9.0$ Hz, 1H), 2.76 (dd, $J = 15.6, 3.0$ Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 210.2, 179.6, 170.2, 139.5, 138.6, 136.7, 128.6, 128.3, 128.0, 127.8, 127.5, 115.7, 56.7, 47.0, 46.1, 41.9, 41.5, 26.5. HRMS (ESI) m/z calcd for $\text{C}_{27}\text{H}_{24}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 410.1756, Found 410.1753.

tert-Butyl 2',4-dioxo-2,6-diphenylspiro[cyclohexane-1,3'-indoline]-1'-carboxylate (3t): White solid; ^1H NMR (600 MHz, CDCl_3) δ 7.41 (d, $J = 7.8$ Hz, 1H), 7.24-7.21 (m, 3H), 7.07-7.03 (m, 4H), 6.96-6.94 (m, 2H), 6.85 (dt, $J = 7.8, 1.2$ Hz, 1H), 6.81 (d, $J = 6.6$ Hz, 2H), 6.28 (d, $J = 7.2$ Hz, 1H), 3.92 (t, $J = 15.6$ Hz, 1H), 3.81 (t, $J = 6.6$ Hz, 1H), 3.74 (dd, $J = 13.8, 3.6$ Hz, 1H), 3.58 (dd, $J = 16.2, 6.0$ Hz, 1H), 3.04 (dd, $J = 16.8, 6.6$ Hz, 1H), 2.74 (dd, $J = 16.2, 3.0$ Hz, 1H), 1.58 (s, 9H). ^{13}C NMR (151 MHz, CDCl_3) δ 210.5, 177.2, 148.5, 139.4, 139.1, 137.1, 129.1, 128.4, 128.2, 128.2, 128.0, 127.9, 127.5, 127.3, 125.2, 123.3, 114.1, 84.3, 55.8, 46.9, 46.5, 42.4, 41.8, 28.0. HRMS (ESI) m/z calcd for $\text{C}_{30}\text{H}_{29}\text{NNaO}_4$ $[\text{M}+\text{Na}]^+$: 490.1994, Found 490.2002.

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