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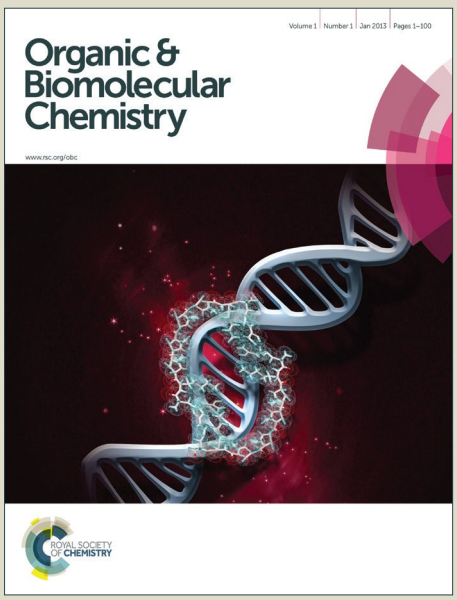

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Stereoselective Synthesis of Spirooxindole Derivatives using an Organocatalyzed Tandem Michael-Michael Reaction

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A highly efficient stereoselective method for the synthesis of functionalized spirooxindole derivatives with three stereogenic centers was realized through an organocatalytic tandem Michael-Michael reaction. By employing (*S*)-α,α-diphenylprolinol trimethylsilyl ether as the catalyst and *N*,*N*'-bis[3,5-bis(trifluoromethyl)phenyl]thiourea as the cocatalyst, the reaction between *N*-tritylisatylidenemalononitriles and (*E*)-7-alkyl-7-oxohept-5-enals yields the desired spirooxindole products in good yields (76-95%) and with excellent diastereoselectivities (up to 97:3 dr) and enantioselectivities (up to 98% ee), which can be stereoselectively converted to the spiro[indoline-3,8'-isoquinoline] derivative through an intramolecular reductive amination reaction.

Introduction

Spirocyclic oxindole is a very important structural motif in medicinal chemistry,[1] since it can be found in a variety of biological active natural or synthetic products that exhibit many interesting biological activities, such as anti-HIV, anticancer, antitubercular, and antimalarial activities.[1,2] Among the spirocyclic oxindole derivatives, spirocyclohexane oxindoles are of particular significance. A few examples of natural and synthetic spirocyclohexane oxindole derivatives are collected in Figure 1. (+)-Gelsemine and Gelsevirine are representative examples of many indole alkaloids isolated from the genus Gelsemium that contain the spirocyclohexane oxindole backbone.[3] Recent studies revealed that (+)-Gelsemine has nephroprotective effect against cisplatin-induced toxicity[4a] and anti-hyperlipidemic and anti-oxidative effects.[4b] In addition, some of these derivatives show potent cytotoxicity.[3b] (-)-Spindomycin A and (+)-Spindomycin B are two new spirocyclohexane oxindole derivatives isolated from *Streptomyces* sp xzqh-9 recently.[5] Satavaptan is a synthetic vasopressin-2 receptor antagonist undergoing research for the treatment of hyponatremia and ascites.[6] Because of their biological relevance and the unique structural feature (containing a spiro quaternary stereogenic center) that poses a challenge to their asymmetric synthesis, developing highly stereoselective methods for the synthesis of spirocyclic oxindoles have received a lot of attentions in recent years,[7-10] and many asymmetric synthetic methods, including organocatalytic methods, have been reported.[7-10] For the organocatalytic asymmetric synthesis of spirocyclohexane oxindole derivatives there are also several reports.[10]

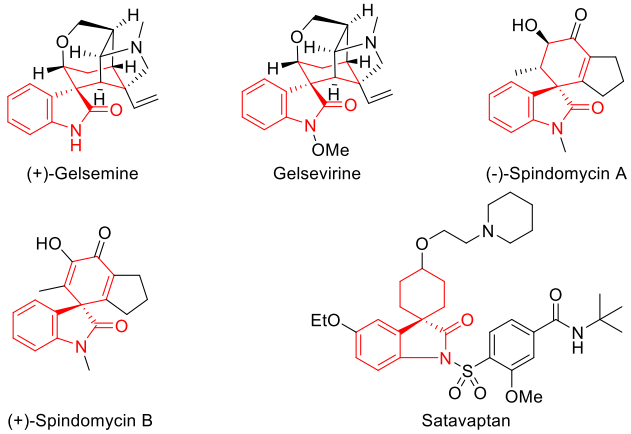

Figure 1 Selected examples of natural and synthetic spiro[cyclohexane-1,3'-indoline]-2'-one derivatives

The tandem reaction is a powerful tool in organic synthesis as they allow the synthesis of sophisticated structures from relatively simple starting materials.[11] This strategy has been widely used in organocatalysis in recent years,[12] and it is one of the most important methods for the asymmetric synthesis of spirocyclohexane oxindole deriatives.[10] Previously we and others have demonstrated that 7-oxohept-5-enals are excellent substrates for tandem reactions.[13] During our recent study of isatin derivatives,[14] we envisioned that these substrates should be also useful for the synthesis of spirocyclohexane oxindole derivatives. Herein we wish to report a highly stereoselective synthesis of spirocyclohexane oxindole derivatives using 7-oxohept-5-enals and isatylidenemalononitriles via an organocatalyzed tandem Michael-Michael reaction.[15]

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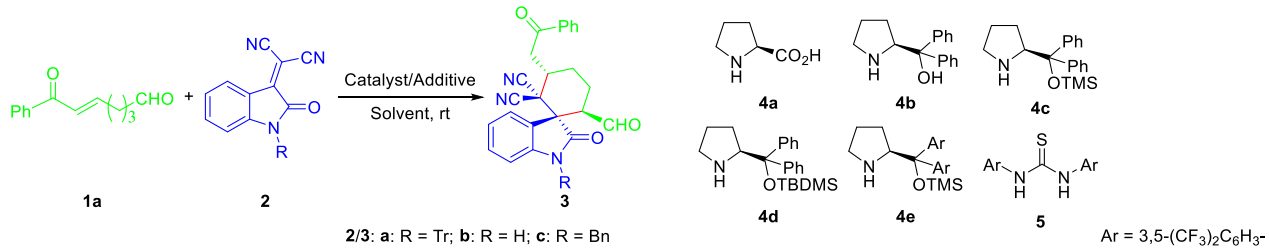
Results and discussion

(*E*)-7-Phenyl-7-oxohept-5-enal (**1a**) and *N*-tritylisatylidene-malononitrile (R = Tr, **2a**) were adopted as the model substrates. Several proline derivatives were first screened for their capability in catalyzing the desired tandem Michael-Michael reaction. The results are summarized in Table 1. As shown in Table 1, when L-proline (**4a**) was used as the catalyst in CH_2Cl_2 at rt, the desired product **3a** was obtained in a high yield of 92% in 48 h; however, the dr and ee value of **3a** were low (entry 1). Under similar conditions, no formation of **3a** was achieved when (*S*)-α,α-diphenylprolinol (**4b**) was used as the catalyst (entry 2). When Jørgensen-Hayashi's catalyst (**4c**) was applied, product **3a** were obtained in 51% yield, 90:10 dr, and 92% ee (entry 3). Slightly better ee values were obtained with similar prolinol silyl ether catalysts **4d** and **4e**; however, their catalytic activities were much lower (entries 4 and 5). Using the most reactive catalyst **4c** as the model catalyst, we next evaluate the additive effects on the reactivities and/or the stereoselectivities of the catalyst. As is evident from the data in Table 1, weak acids, such as benzoic acid (entry 6) and acetic acid (entry 7), slightly improved the catalytic activity; nonetheless, both the dr and ee value of the product dropped. On the other hand, strong acids, such as TFA (entry 8) and

Table 1 Optimization of the reaction conditions[a]



entry	R	catalyst	additive	solvent	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	Tr	**4a**	---	CH_2Cl_2	48	92	66:34	45
2	Tr	**4b**	---	CH_2Cl_2	48	0[e]	---	---
3	Tr	**4c**	---	CH_2Cl_2	48	51	90:10	92
4	Tr	**4d**	---	CH_2Cl_2	48	25	90:10	94
5	Tr	**4e**	---	CH_2Cl_2	48	15	91:9	94
6	Tr	**4c**	$PhCO_2H$	CH_2Cl_2	48	65	66:34	84
7	Tr	**4c**	AcOH	CH_2Cl_2	48	65	79:21	84
8	Tr	**4c**	$PhSO_3H$	CH_2Cl_2	48	43	71:29	83
9	Tr	**4c**	TFA	CH_2Cl_2	48	35	70:30	90
10	Tr	**4c**	Et_3N	CH_2Cl_2	48	68	63:37	69
11	Tr	**4c**	DIPEA	CH_2Cl_2	48	30	62:38	77
12	Tr	**4c**	**5**	CH_2Cl_2	72	84	93:7	95
13	Tr	**4d**	**5**	CH_2Cl_2	72	75	91:9	93
14	Tr	**4c**	**5**	$CHCl_3$	72	92	94:6	97
15	Tr	**4c**	**5**	$ClCH_2CH_2Cl$	72	87	93:7	95
16	Tr	**4c**	**5**	toluene	72	28	76:24	81
17	Tr	**4c**	**5**	THF	72	18	70:30	82
18	Tr	**4c**	**5**	CH_3CN	72	78	81:19	80
19	Tr	**4c**	**5**	DMSO	72	92	83:17	78
20	Tr	**4c**	**5**	MeOH	72	<5	---	---
21[f]	Tr	**4c**	**5**	$CHCl_3$	72	42	95:5	97
22[g]	Tr	**4c**	**5**	$CHCl_3$	48	85	89:11	70
23	H	**4c**	**5**	$CHCl_3$	72	0[e]	---	---
24	Bn	**4c**	**5**	$CHCl_3$	72	72	73:27	54

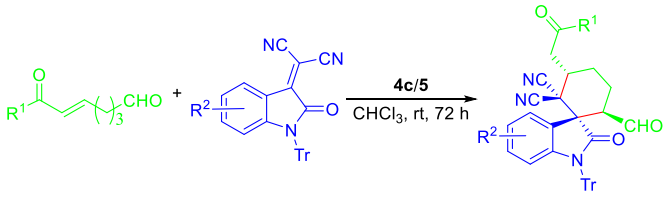
[a]Unless otherwise noted, all reactions were carried out with **1a** (0.10 mmol), **2** (0.12 mmol), the catalyst (10 mol %), and the additive (10 mol %) in the specified solvent (0.5 mL) at rt. [b]Yield of the isolated product after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude reaction product. [d]Determined by HPLC analysis using a ChiralPak IC column. [e]No reaction. [f]The reaction temperature was 0 °C. [g]The reaction temperature was 50 °C.

benzenesulfonic acid (entry 9), diminished both the catalytic activity and the stereoselectivity. Similarly, basic additives, such as Et_3N and DIEPA, did not work, either (entries 10 and 11). Next the achiral thiourea **5**[16] was added, and to our pleasure, much improved product yield (84%) and slightly improved dr and ee value were obtained, although the reaction needed longer time to complete (72 h). Slightly lower yield, dr, and ee value of **3a** was achieved when catalyst **4d** was used together with 5 (entry 13). Thus, the combination of **4c** and **5** was identified as the best catalytic system for this reaction. The solvent was then screened with this combination. Chlorinated solvents, such as CH_2Cl_2 (entry 12), $CHCl_3$ (entry 14), and $ClCH_2CH_2Cl$ (entry 15), yielded very good results, and among them $CHCl_3$ gave the best yield, dr, and ee value of **3a** (entry 14). In contrast, lower product yields and/or stereoselectivities were achieved in nonchlorinated solvents, such as toluene, THF, CH_3CN, DMSO, and MeOH (entries 16-20). Among these solvent, MeOH is an especially poor solvent, as almost no product could be obtained (entry 20). When the reaction temperature was lowered to 0 °C, the product yield diminished without any improvement in the stereoselectivities (entry 21). On the other hand, when the reaction temperature was raised to 50 °C, the reaction time could be shortened to 48 h, but the stereoselectivity became much worse (entry 22). Finally, the effects of the *N*-substituent on **2** were evaluated under the optimized conditions, and it was found that the *N*-trityl group is essential[17] for both the reactivity and the stereoselectivity of this reaction, since much worse results were obtained with the *N*-unsubstituted **2b** (R = H, entry 23) and the *N*-benzyl substituted **2c** (R = Bn, entry 24).

Once the reaction conditions were optimized, the substrate scope of this reaction then studied. The results are collected in Table 2. Firstly, using 7-oxohept-5-enal **1a**, we evaluated several substituted *N*-tritylisatylidenemalononitriles **2**. As the results in Table 2 show, the electronic nature and the position of the substituent on the isatin ring have almost no influence on the product dr and ee values, as well as the product yields (entries 1-8), except that a slightly lower yield was obtained for the 5-methoxy derivative (entry 7). Similarly, with 7-aryl-7-oxohept-5-enals **1**, the electronic nature and the position of the substituent on the phenyl ring have almost no influence on the product yields, dr, and ee values (entries 1, 9-14). Finally, a 7-*tert*-butyl-substittued 7-oxohept-5-enal also gave the expected product **3q** in high yield, dr, and ee value (entry 15).

The spirooxindole derivatives obtained in this study is very useful for the synthesis other spirooxindole derivatives. For example, when product **3e** was reduced by $NaBH_4$ at -78 °C, an unexpected spiro[indoline-3,8'-isoquinoline] derivative **6** was obtained as an essentially pure enantiomer of a single diastereomer (>99% ee, Eq. 1). This product contains a novel spirooxindole skeleton with five stereogenic centers. Compound **6** was most likely formed through an unusual reductive amination of the γ-cyanoketone moiety via the amide intermediate **7** and the imine intermediate **8** formed in situ from **3e** (Scheme 1). While this reaction is unprecedented in the literature, formation of imine intermediates similar to **8** from γ-cyanoketones under oxidative conditions is known.[18] The absolute structure of **6** was determined by X-ray crystallography.[19] On the basis of the absolute stereochemistry of **6**, the absolute stereochemistry of the reaction products was assigned as 1*R*,3*S*,6*R*.

Table 2 The scope of the tandem Michael-Michael reaction[a]



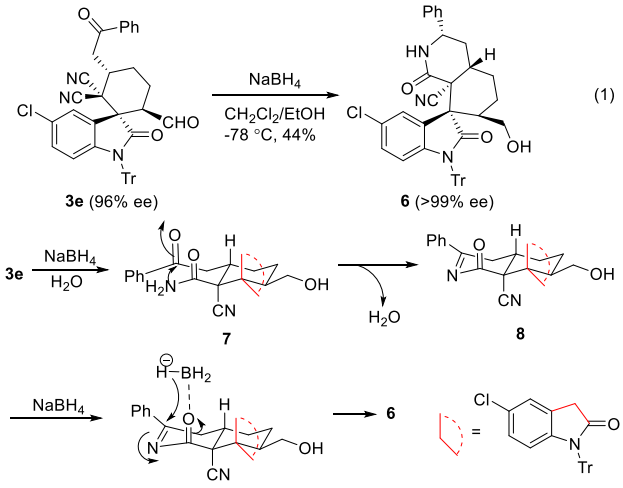
1 2 3

entry	R^1	R^2	yield	dr[c]	ee
1	Ph	H	92/**3a**	94:6	97
2	Ph	5-F	93/**3d**	93:7	96
3	Ph	5-Cl	91/**3e**	94:6	96
4	Ph	5-Br	89/**3f**	93:7	96
5	Ph	5-NO_2	85/**3g**	95:5	97
6	Ph	5-Me	82/**3h**	95:5	97
7	Ph	5-MeO	76/**3i**	95:5	98
8	Ph	6-Cl	87/**3j**	95:5	96
9	4-FC_6H_4	H	86/**3k**	95:5	97
10	4-ClC_6H_4	H	95/**3l**	94:6	92
11	4-BrC_6H_4	H	91/**3m**	95:5	96
12	4-CNC_6H_4	H	93/**3n**	95:5	96
13	2-ClC_6H_4	H	85/**3o**	94:6	98
14	3-BrC_6H_4	H	87/**3p**	95:5	94
15	*t*-Bu	5-Cl	83/**3q**	97:3	93

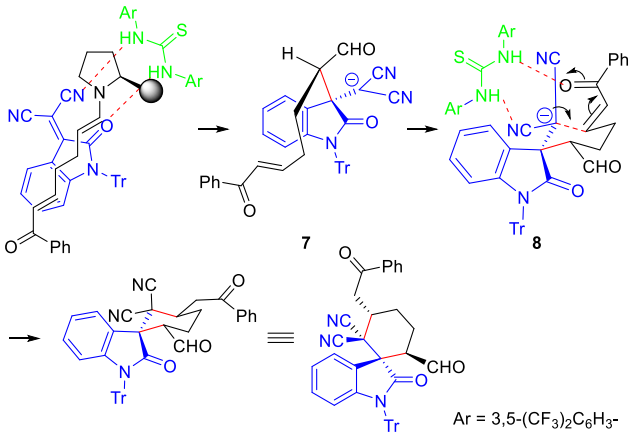
[a]All reactions were carried out with **1** (0.20 mmol), **2** (0.24 mmol) in $CHCl_3$ (1.0 mL) at rt using catalyst **4c** and additive **5** (10 mol % each). [b]Yield of the isolated product after column chromatography. [c]Determined by ^1H NMR analysis of the crude reaction product. [d]Determined by HPLC analysis using a ChiralPak IC column.

On the basis of the absolute stereochemistry of **3a**, a plausible transition state model is proposed. As shown in Scheme 2, hydrogen-bonded with **5**, substrate **2a** approaches from the backside of the enamine to minimize the steric interactions. The attack of the enamine onto the *Si* face of isatylidenemalononitrile to yield intermediate **7**, which then cyclizes through a six-membered ring transition state **8** to give the expected product **3a**. The fact that MeOH, which can disrupt the hydrogen bonding, can totally inhibit this reaction (vide supra) supports the proposed hydrogen bonding between **2a** and **5**. Additionally, **5** may also facilitate the

second Michael reaction through hydrogen bonding, as shown in **8**, although there is no direct evidence for this.



Scheme 1 Proposed Formation of **6**



Scheme 2. Proposed Transition State Model

Conclusions

In summary, we have developed a highly stereoselective method for the synthesis of functionalized spirooxindole derivatives containing three stereogenic centers. Using a prolinol silyl ether catalyst together with an achiral thiourea cocatalyst, the corresponding spirooxindole derivatives may be obtained in good yields, high dr (up to 97:3), and high ee values (up to 98% ee). The product can be stereoselectively converted to the spiro[indoline-3,8'-isoquinoline] derivative through a novel intramolecular reductive amination reaction of the γ-cyanoketone moiety.

Experimental

General information

Unless otherwise noted, all reactions were carried out in closed vial. ^{1}H NMR spectra was recorded on a 500 MHz spectrometer (125 MHz for ^{13}C). The following abbreviations were used to designate chemical shift mutiplicities: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m). TLC was performed with silica gel GF254 precoated on aluminum plates and spots were visualized with UV. Flash column chromatography was performed on silica gel. HPLC analysis was performed on an HPLC instrument equipped with a UV-Vis detector. Solvents were freshly distilled under nitrogen atmosphere before use using the normal protocols. (*E*)-7-Oxo-7-phenylhept-5-enal[13a,20] and isatylidene malononitriles derivatives[21] were prepared according to reported methods. All the other reagents were purchased from commercial sources and used as received.

General procedure for the tandem Michael-Michael addition: Aldehyde **1** (0.20 mmol), catalyst **4c** (6.5 mg, 0.02 mmol), achiral thiourea **5** (10 mg, 0.02 mmol) and isatylidene malononitriles **2** (0.24 mmol) were dissolved in $CHCl_3$ (1.0 ml). The reaction mixture was stirred at rt for 72 h, and then subjected to column chromatography (eluted with EtOAc/hexane) to afford product aldehyde **3**. The enantiomeric ratio was determined by HPLC analysis on chiral column.

(1*R*,3*S*,6*R*)-6-Formyl-2'-oxo-3-(2-oxo-2-phenylethyl)-1'-tritylspiro[cyclohexane-1,3'-indoline]-2,2-dicarbonitrile (3a). White solid, 117.5 mg, 92% yield; mp: > 240 °C; $[\alpha]_D^{24}$ = -35.1 (c 1.0, $CHCl_3$, 94:6 dr, 97% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 2H), 7.70 – 7.65 (m, 7H), 7.58 – 7.55 (m, 3H), 7.34 – 7.30 (m, 6H), 7.28 – 7.25 (m, 3H), 7.18 – 7.14 (m, 1H), 7.10 – 7.02 (m, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 3.52 – 3.42 (m, 3H), 3.28 (dd, *J* = 4.5, 13.5 Hz, 1H), 2.43 (d, *J* = 14 Hz, 1H), 2.27 – 2.24 (m, 1H), 2.13 – 2.04 (m, 1H), 1.78 – 1.73 (m, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 196.8, 195.8, 173.5, 144.0, 141.4, 136.1, 134.1, 129.5, 128.9, 128.8, 127.9, 127.1, 125.9, 124.3, 123.1, 116.9, 113.6, 110.8, 75.9, 52.2, 51.1, 46.1, 41.2, 36.1, 26.3, 20.3; ν_{max} (neat, cm^{-1}): 1723, 1682, 1598, 1477, 1460, 1448, 1276, 1215; HRMS (ESI): m/z calcd for $C_{43}H_{33}N_3O_3$ ([M]$^+$) 639.2527, found 639.2542; Enantiomeric excess of **3a** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 8.2 min, minor enantiomer: t_R = 26.7 min.

(1*R*,3*S*,6*R*)-1'-Benzyl-6-formyl-2'-oxo-3-(2-oxo-2-phenylethyl)spiro[cyclohexane-1,3'-indoline]-2,2-dicarbonitrile (3c). White solid, 35.0 mg, 72% yield; mp: > 240 °C; $[\alpha]_D^{24}$ = -10.8 (c 1.0, $CHCl_3$, 73:27 dr, 54% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (s, 1H), 7.93 (d, *J* = 7.8 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.38 (d, *J* = 7.6 Hz, 2H), 7.33 – 7.27 (m, 3H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.20 (s, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 5.03 (q, *J* = 15.8 Hz, 2H), 3.46 – 3.25 (m, 4H), 2.44 (d, *J* = 14.5 Hz, 1H), 2.34 (dd, *J* = 14.4, 2.7 Hz, 1H), 2.13 (qd, *J* = 13.9, 4.3 Hz, 1H), 1.81 – 1.70 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.0, 195.6, 172.8, 144.1, 135.9, 134.6, 133.9, 130.8, 128.8, 128.0, 127.9, 127.4, 126.3, 123.4, 123.2, 112.1, 110.9, 110.7, 52.1, 50.9, 46.0, 44.8, 41.0, 35.9, 26.5, 20.4; ν_{max} (neat, cm^{-1}): 1726, 1681, 1612, 1490, 1473, 1372, 1286, 1217, 1182; HRMS (ESI): m/z calcd

for $C_{31}H_{25}N_3O_3$ ([M+Na]$^+$) 510.1788, found 510.1777; Enantiomeric excess of **3c** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (85: 15 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 12.3 min, minor enantiomer: t_R = 14.8 min.

(1*R*,3*S*,6*R*)-5'-Fluoro-6-formyl-2'-oxo-3-(2-oxo-2-phenylethyl)-1'-tritylspiro[cyclohexane-1,3'-indoline]-2,2-dicarbonitrile (3d). White solid, 122.1 mg, 93% yield; mp: > 240 °C; $[\alpha]_D^{24}$ = -25.8 (c 1.0, $CHCl_3$, 93:7 dr, 96% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 2H), 7.69 – 7.66 (m, 1H), 7.63 – 7.61 (m, 6H), 7.57 – 7.54 (m, 2H), 7.33 – 7.24 (m, 10H), 6.88 – 6.84 (m, 1H), 6.62 (dd, *J* = 4.5, 9.0 Hz, 1H), 3.51 – 3.41 (m, 2H), 3.36 – 3.27 (m, 2H), 2.43 (d, *J* = 14.5 Hz, 1H), 2.29 – 2.26 (m, 1H), 2.04 – 1.95 (m, 1H), 1.79 – 1.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 195.5, 173.2, 159.2, 157.2, 141.2, 140.2 (d, J_{CF} = 2.5 Hz), 136.0, 134.1, 129.0, 128.9, 128.8, 128.2, 128.0, 127.2, 125.7 (d, J_{CF} = 7.5 Hz), 117.6 (d, J_{CF} = 7.4 Hz), 115.9 (d, J_{CF} = 12.5 Hz), 113.8 (d, J_{CF} = 25.1 Hz), 110.5, 110.0, 76.0, 52.3, 51.1, 45.9, 41.2, 36.2, 26.4, 20.3; ν_{max} (neat, cm^{-1}): 1725, 1683, 1597, 1477, 1447, 1366, 1280, 1349, 1215, 1183; HRMS (ESI): *m/z* calcd for $C_{43}H_{32}FN_3O_3$ ([M]$^-$) 657.2433, found 657.2452; Enantiomeric excess of **3d** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 7.1 min, minor enantiomer: t_R = 25.3 min.

(1*R*,3*S*,6*R*)-5'-Chloro-6-formyl-2'-oxo-3-(2-oxo-2-phenylethyl)-1'-tritylspiro[cyclohexane-1,3'-indoline]-2,2-dicarbonitrile (3e). White solid, 122.3 mg, 91% yield; mp: > 240 °C; $[\alpha]_D^{24}$ = -72.9 (c 1.0, $CHCl_3$, 94:6 dr, 96% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 2H), 7.69 – 7.66 (m, 1H), 7.63 – 7.61 (m, 6H), 7.57 – 7.54 (m, 2H), 7.47 – 7.46 (m, 1H), 7.34 – 7.31 (m, 6H), 7.29 – 7.25 (m, 3H), 7.13 – 7.11 (m, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 3.53 – 3.42 (m, 2H), 3.36 – 3.27 (m, 2H), 2.47 – 2.44 (m, 1H), 2.31 – 2.28 (m, 1H), 2.07 – 1.97 (m, 1H), 1.79 – 1.70 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 195.5, 173.0, 142.8, 141.1, 136.0, 134.1, 129.4, 128.9, 128.8, 128.5, 128.2, 128.0, 127.2, 126.1, 125.8, 117.6, 113.4, 110.5, 76.0, 52.2, 51.2, 46.0, 41.2, 36.3, 26.4, 20.4; ν_{max} (neat, cm^{-1}): 1726, 1683, 1597, 1470, 1448, 1367, 1260, 1215, 1188; HRMS (ESI): *m/z* calcd for $C_{43}H_{32}ClN_3O_3$ ([M]$^-$) 673.2138, found 673.2143; Enantiomeric excess of **3e** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 6.7 min, minor enantiomer: t_R = 24.3 min.

(1*R*,3*S*,6*R*)-5'-Bromo-6-formyl-2'-oxo-3-(2-oxo-2-phenylethyl)-1'-tritylspiro[cyclohexane-1,3'-indoline]-2,2-dicarbonitrile (3f). White solid, 127.3 mg, 89% yield; mp: > 240 °C; $[\alpha]_D^{24}$ = -22.7 (c 1.0, $CHCl_3$, 93:7 dr, 96% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 2.0 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 2H), 7.68 – 7.65 (m, 1H), 7.62 – 7.59 (m, 7H), 7.57 – 7.53 (m, 2H), 7.33 – 7.28 (m, 6H), 7.25 – 7.24 (m, 4H), 6.55 (d, *J* = 8.0 Hz, 1H), 3.52 – 3.40 (m, 2H), 3.34 – 3.26 (m, 2H), 2.46 – 2.43 (m, 1H), 2.31 – 2.28 (m, 1H), 2.05 – 1.96 (m, 1H), 1.78 – 1.69 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 195.5, 173.0, 143.3, 141.1, 136.0, 134.1, 132.3, 128.9, 128.8, 128.4, 128.2, 128.0, 127.2, 126.5, 118.0, 115.9, 113.4, 110.5, 76.0, 52.1, 51.2, 46.0, 41.2, 36.3, 26.4, 20.4; ν_{max} (neat, cm^{-1}): 1725, 1683, 1596, 1468, 1447, 1417, 1369, 1260, 1215, 1188; HRMS (ESI): *m/z* calcd for $C_{43}H_{32}BrN_3O_3$ ([M]$^-$) 717.1633, found 717.1655; Enantiomeric excess of **3f** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 6.9 min, minor enantiomer: t_R = 25.0 min.

(1*R*,3*S*,6*R*)-6-Formyl-5'-nitro-2'-oxo-3-(2-oxo-2-phenylethyl)-1'-tritylspiro[cyclohexane-1,3'-indoline]-2,2-dicarbonitrile (3g). White solid, 116.1 mg, 85% yield; mp: > 240 °C; $[\alpha]_D^{25}$ = -71.3 (c 1.0, $CHCl_3$, 95:5 dr, 97% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.34 – 8.33 (m, 1H), 8.08 (d, *J* = 9.0 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 2H), 7.68 – 7.65 (m, 1H), 7.61 – 7.60 (m, 6H), 7.56 – 7.53 (m, 2H), 7.35 – 7.32 (m, 6H), 7.29 – 7.26 (m, 3H), 6.83 (d, *J* = 9.0 Hz, 1H), 3.51 – 3.37 (m, 4H), 2.55 – 2.53 (m, 1H), 2.45 – 2.42 (m, 1H), 2.19 – 2.09 (m, 1H), 1.87 – 1.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 195.3, 173.7, 150.6, 142.9, 140.9, 136.2, 134.4, 129.2, 129.1, 129.0, 128.4, 128.3, 127.7, 127.6, 125.9, 125.7, 120.8, 116.4, 113.5, 110.4, 76.9, 52.0, 51.8, 46.1, 41.4, 36.8, 26.9, 20.8; ν_{max} (neat, cm^{-1}): 1734, 1679, 1597, 1517, 1448, 1337, 1276, 1216, 1185; HRMS (ESI): *m/z* calcd for $C_{43}H_{32}N_4O_5$ ([M]$^-$) 684.2378, found 684.2351; Enantiomeric excess of **3g** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 14.2 min, minor enantiomer: t_R = 78.6 min.

(1*R*,3*S*,6*R*)-6-Formyl-5'-methyl-2'-oxo-3-(2-oxo-2-phenylethyl)-1'-tritylspiro[cyclohexane-1,3'-indoline]-2,2-dicarbonitrile (3h). White solid, 106.9 mg, 82% yield; mp: > 240 °C; $[\alpha]_D^{25}$ = -64.7 (c 1.0, $CHCl_3$, 95:5 dr, 97% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 2H), 7.67 – 7.64 (m, 7H), 7.57 – 7.54 (m, 2H), 7.33 – 7.29 (m, 7H), 7.26 – 7.23 (m, 3H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.53 (d, *J* = 8.5 Hz, 1H), 3.51 – 3.40 (m, 3H), 3.24 (d, *J* = 4.5, 13.5 Hz, 1H), 2.41 (d, *J* = 13.5 Hz, 1H), 2.32 (s, 3H), 2.24 – 2.20 (m, 1H), 2.10 – 2.01(m, 1H), 1.76 – 1.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.9, 195.8, 173.5, 141.5, 141.4, 136.1, 134.1, 132.7, 130.1, 128.9, 128.8, 128.2, 127.9, 127.1, 126.5, 124.3, 116.6, 113.7, 110.8, 75.8, 52.3, 51.0, 46.1, 41.3, 36.0, 26.3, 21.2, 20.3; ν_{max} (neat, cm^{-1}): 1722, 1682, 1594, 1482, 1448, 1368, 1274, 1213; HRMS (ESI): *m/z* calcd for $C_{44}H_{35}N_3O_3$ ([M]$^-$) 653.2684, found 653.2663; Enantiomeric excess of **3h** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 7.6 min, minor enantiomer: t_R = 25.3 min.

(1*R*,3*S*,6*R*)-6-Formyl-5'-methoxy-2'-oxo-3-(2-oxo-2-phenylethyl)-1'-tritylspiro[cyclohexane-1,3'-indoline]-2,2-dicarbonitrile (3i). White solid, 101.5 mg, 76% yield; mp: > 240 °C; $[\alpha]_D^{25}$ = -136.5 (c 1.0, $CHCl_3$, 95:5 dr, 98% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.03 (d, *J* = 7.5 Hz, 2H), 7.67 – 7.63 (m, 7H), 7.56 – 7.53 (m, 2H), 7.33 – 7.29 (m, 6H), 7.26 – 7.23 (m, 3H), 7.11 (d, *J* = 2.5 Hz, 1H), 6.65 (dd, *J* = 2.5, 9.5 Hz, 1H), 6.55 (d, *J* = 9.0 Hz, 1H), 3.76 (s, 3H), 3.50 – 3.42 (m, 3H), 3.25 (dd, *J* = 4.5, 13.5 Hz, 1H), 2.39 (d, *J* = 13.5 Hz, 1H), 2.24 – 2.20 (m, 1H), 2.06 – 1.98 (m, 1H), 1.76 – 1.67 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 195.6, 173.2, 155.3, 141.5, 136.9, 136.1, 134.0, 128.9, 128.8, 128.2, 127.9, 127.1, 125.5, 117.3, 113.9, 113.6, 112.9, 110.8, 75.8, 55.6, 52.3, 51.0, 46.1, 41.2, 35.9, 26.3, 20.3; ν_{max}

(neat, cm^{-1}): 1721, 1683, 1593, 1480, 1448, 1367, 1281, 1206; HRMS (ESI): *m/z* calcd for $C_{44}H_{35}N_3O_4$ ($[M]^-$) 669.2633, found 669.2657; Enantiomeric excess of **3i** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 9.2 min, minor enantiomer: t_R = 37.1 min.

(1*R*,3*S*,6*R*)-6'-Chloro-6-formyl-2'-oxo-3-(2-oxo-2-phenylethyl)-1'-tritylspiro[cyclohexane-1,3'-indoline]-2,2-dicarbonitrile (3j). White solid, 117.4 mg, 87% yield; mp: > 240 °C; $[\alpha]_D^{23}$ = -27.1 (c 1.0, $CHCl_3$, 95:5 dr, 96% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.03 (dd, *J* = 1.0, 8.0 Hz, 2H), 7.68 – 7.65 (m, 1H), 7.63 – 7.61 (m, 6H), 7.57 – 7.54 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.35 – 7.32 (m, 6H), 7.28 – 7.25 (m, 3H), 7.05 (dd, *J* = 2.0, 8.5 Hz, 1H), 6.59 (d, *J* = 2.0 Hz, 1H), 3.50 – 3.41 (m, 2H), 3.38 – 3.32 (m, 1H), 3.26 (dd, *J* = 4.5, 14.0 Hz, 1H), 2.42 – 2.39 (m, 1H), 2.28 – 2.24 (m, 1H), 2.05 – 1.96 (m, 1H), 1.78 – 1.69 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 195.6, 173.4, 145.4, 141.0, 136.0, 135.6, 134.1, 129.0, 128.8, 128.0, 127.3, 126.4, 122.9, 122.8, 117.3, 113.4, 110.6, 76.2, 51.9, 51.1, 46.0, 41.2, 36.2, 26.4, 20.3; ν_{max} (neat, cm^{-1}): 1728, 1683, 1597, 1475, 1448, 1418, 1260, 1215; HRMS (ESI): *m/z* calcd for $C_{43}H_{32}ClN_3O_3$ ($[M]^-$) 673.2138, found 673.2123; Enantiomeric excess of **3j** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 6.9 min, minor enantiomer: t_R = 16.5 min.

(1*R*,3*S*,6*R*)-3-(2-(4-Fluorophenyl)-2-oxoethyl)-6-formyl-2'-oxo-1'-tritylspiro[cyclohexane-1,3'-indoline]-2,2-dicarbonitrile (3k). White solid, 113.2 mg, 86% yield; mp: > 240 °C; $[\alpha]_D^{24}$ = -44.9 (c 1.0, $CHCl_3$, 95:5 dr, 97% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.06 (dd, *J* =5.0, 8.5 Hz, 2H), 7.65 – 7.63 (m, 6H), 7.54 – 7.53 (m, 1H), 7.32 – 7.28 (m, 6H), 7.26 – 7.20 (m, 5H), 7.16 – 7.12 (m, 1H), 7.08 – 7.05 (m, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 3.47 – 3.38 (m, 3H), 3.26 (dd, *J* = 4.0, 13.5 Hz, 1H), 2.41 – 2.38 (m, 1H), 2.25 – 2.22 (m, 1H), 2.11 – 2.01 (m, 1H), 1.76 – 1.71 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 194.1, 173.5, 167.3, 165.3, 144.0, 141.4, 132.5 (d, J_{CF} = 3.0 Hz), 130.9 (d, J_{CF} = 10.0 Hz), 129.5, 128.8, 128.7, 127.9, 127.1, 125.8, 124.2, 123.1, 116.9, 116.2, 116.1, 113.6, 110.8, 75.9, 52.1, 51.0, 46.1, 41.1, 36.1, 26.4, 20.3; ν_{max} (neat, cm^{-1}): 1723, 1683, 1596, 1460, 1448, 1410, 1277, 1212, 1156; HRMS (ESI): *m/z* calcd for $C_{43}H_{32}FN_3O_3$ ($[M]^-$) 657.2433, found 657.2448; Enantiomeric excess of **3k** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 8.7 min, minor enantiomer: t_R = 29.4 min.

(1*R*,3*S*,6*R*)-3-(2-(4-Chlorophenyl)-2-oxoethyl)-6-formyl-2'-oxo-1'-tritylspiro[cyclohexane-1,3'-indoline]-2,2-dicarbonitrile (3l). White solid, 127.7 mg, 95% yield; mp: > 240 °C; $[\alpha]_D^{24}$ = -92.8 (c 1.0, $CHCl_3$, 94:6 dr, 92% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.97 – 7.95 (m, 2H), 7.64 – 7.62 (m, 6H), 7.53 – 7.50 (m, 3H), 7.32 – 7.28 (m, 6H), 7.25 – 7.22 (m, 3H), 7.15 – 7.12 (m, 1H), 7.07– 7.04 (m, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 3.46 – 3.37 (m, 3H), 3.25 (dd, *J* = 4.5, 13.5 Hz, 1H), 2.40 – 2.37 (m, 1H), 2.24 – 2.21 (m, 1H), 2.10 – 2.00 (m, 1H), 1.76 – 1.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 194.6, 173.5, 144.0, 140.7, 134.4, 129.6, 129.3, 128.8, 127.9, 127.1, 125.8, 124.2, 123.1, 116.9, 113.5, 110.7, 75.9, 52.1, 51.0, 46.1, 41.2, 36.1, 26.3, 20.2; ν_{max} (neat, cm^{-1}): 1723, 1683, 1589, 1477, 1460, 1448, 1399, 1276, 1213; HRMS (ESI): *m/z* calcd for $C_{43}H_{32}ClN_3O_3$ ($[M]^-$) 673.2138, found 673.2157; Enantiomeric excess of **3l** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 9.0 min, minor enantiomer: t_R = 28.9 min.

(1*R*,3*S*,6*R*)-3-(2-(4-Bromophenyl)-2-oxoethyl)-6-formyl-2'-oxo-1'-tritylspiro[cyclohexane-1,3'-indoline]-2,2-dicarbonitrile (3m). White solid, 130.7 mg, 91% yield; mp: > 240 °C; $[\alpha]_D^{24}$ = -94.7 (c 1.0, $CHCl_3$, 95:5 dr, 96% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 7.5 Hz, 2H), 7.64 – 7.62 (m, 6H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.32 – 7.28 (m, 6H), 7.25 – 7.22 (m, 3H), 7.15 – 7.12 (m, 1H), 7.08 – 7.05 (m, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 3.45 – 3.36 (m, 3H), 3.25 (dd, *J* = 4.5, 13.5 Hz, 1H), 2.38 (d, *J* = 13.5 Hz, 1H), 2.25 – 2.22 (m, 1H), 2.10 – 2.01 (m, 1H), 1.76 – 1.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 194.8, 173.5, 144.0, 141.4, 134.7, 132.3, 129.6, 129.5, 129.4, 128.8, 127.9, 127.1, 125.8, 124.2, 123.1, 116.9, 113.5, 110.7, 75.9, 52.1, 51.0, 46.1, 41.2, 36.1, 26.3, 20.2; ν_{max} (neat, cm^{-1}): 1724, 1683, 1584, 1477, 1460, 1448, 1366, 1275, 1215; HRMS (ESI): *m/z* calcd for $C_{43}H_{32}BrN_3O_3$ ($[M]^-$) 717.1633, found 717.1653; Enantiomeric excess of **3m** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 9.7 min, minor enantiomer: t_R = 29.9 min.

(1*R*,3*S*,6*R*)-3-(2-(4-Cyanophenyl)-2-oxoethyl)-6-formyl-2'-oxo-1'-tritylspiro[cyclohexane-1,3'-indoline]-2,2-dicarbonitrile (3n). White solid, 123.3 mg, 93% yield; mp: > 220 °C; $[\alpha]_D^{24}$ = -74.5 (c 1.0, $CHCl_3$, 95:5 dr, 96% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.12 (d, *J* = 8.5 Hz, 2H), 7.84 (d, *J* = 8.5 Hz, 2H),7.64 – 7.63 (m, 6H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.32 – 7.29 (m, 6H), 7.25 – 7.22 (m, 3H), 7.16 – 7.13 (m, 1H), 7.09 – 7.06 (m, 1H), 6.67 (d, *J* = 8.5 Hz, 1H), 3.53 – 3.39 (m, 3H), 3.26 (dd, *J* = 4.5, 13.5 Hz, 1H), 2.39 (d, *J* = 13.5 Hz, 1H), 2.27 – 2.23 (m, 1H), 2.12 – 2.03 (m, 1H), 1.79 – 1.70 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.6, 194.6, 173.4, 144.0, 141.4, 138.8, 132.8, 129.6, 128.8, 128.6, 127.9, 127.2, 125.7, 124.1, 123.1, 117.7, 117.3,117.0, 113.5, 110.7, 75.9, 52.1, 51.0, 46.0, 41.6, 36.0, 26.3, 20.2; ν_{max} (neat, cm^{-1}): 1723, 1691, 1600, 1477, 1460, 1448, 1403, 1261, 1213; HRMS (ESI): *m/z* calcd for $C_{44}H_{32}N_4O_3$ ($[M]^-$) 664.2480, found 664.2461; Enantiomeric excess of **3n** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (60:40 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 18.6 min, minor enantiomer: t_R = 70.1 min.

(1*R*,3*S*,6*R*)-3-(2-(2-Chlorophenyl)-2-oxoethyl)-6-formyl-2'-oxo-1'-tritylspiro[cyclohexane-1,3'-indoline]-2,2-dicarbonitrile (3o). White solid, 114.1 mg, 85% yield; mp: > 240 °C; $[\alpha]_D^{25}$ = -193.2 (c 1.0, $CHCl_3$, 94:6 dr, 98% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.65 – 7.63 (m, 6H), 7.56 – 7.48 (m, 4H), 7.42 – 7.39 (m, 1H), 7.33 – 7.29 (m, 6H), 7.26 – 7.23 (m, 3H), 7.16 – 7.13 (m, 1H), 7.09 – 7.106 (m, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 3.50 – 3.39 (m, 3H), 3.26 (dd, *J* = 4.5, 13.5 Hz, 1H), 2.45 – 2.42 (m, 1H), 2.27 – 2.23 (m, 1H), 2.10 – 2.01 (m, 1H), 1.83 – 1.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 196.7, 173.5, 144.0, 141.4, 138.0, 132.6, 131.2, 131.0, 129.5, 129.1, 128.9, 128.8, 127.9, 127.3, 127.1, 125.8, 124.2, 123.1, 116.9,

113.5, 110.6, 75.9, 52.1, 51.0, 45.9, 45.5, 36.2, 26.1, 20.3; ν_{max} (neat, cm^{-1}): 1720, 1599, 1478, 1450, 1432, 1406, 1375, 1297, 1209, 1120; HRMS (ESI): *m/z* calcd for $C_{43}H_{32}ClN_3O_3$ ($[M]^-$) 673.2138, found 673.2162; Enantiomeric excess of **3o** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 8.3 min, minor enantiomer: t_R = 24.2 min.

(1*R*,3*S*,6*R*)-3-(2-(3-Bromophenyl)-2-oxoethyl)-6-formyl-2'-oxo-1'-tritylspiro[cyclohexane-1,3'-indoline]-2,2-dicarbonitrile (3p). White solid, 124.5 mg, 87% yield; mp: > 240 °C; $[\alpha]_D^{25}$ = -53.0 (c 1.0, $CHCl_3$, 95:5 dr, 94% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.17 – 8.16 (m, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.67 – 7.65 (m, 6H), 7.56 – 7.54 (m, 1H), 7.45 – 7.42 (m, 1H), 7.34 – 7.30 (m, 6H), 7.27 – 7.24 (m, 3H), 7.17 – 7.14 (m, 1H), 7.10 – 7.07 (m, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 3.49 – 3.40 (m, 3H), 3.28 (dd, *J* = 4.5, 13.5 Hz, 1H), 2.41 – 2.38 (m, 1H), 2.27 – 2.23 (m, 1H), 2.12 – 2.03 (m, 1H), 1.79 – 1.71 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 194.5, 173.5, 144.0, 141.4, 137.7, 136.9, 131.2, 130.6, 129.5, 128.9, 128.0, 127.9, 127.2, 126.7, 125.8, 124.2, 123.1, 116.9, 113.6, 110.8, 75.9, 52.2, 51.0, 46.1, 41.4, 36.1, 26.4, 20.3; ν_{max} (neat, cm^{-1}): 1721, 1686, 1589, 1497, 1446, 1366, 1279, 1205; HRMS (ESI): *m/z* calcd for $C_{43}H_{32}BrN_3O_3$ ($[M]^-$) 717.1633, found 717.1649; Enantiomeric excess of **3p** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 8.8 min, minor enantiomer: t_R = 28.9 min.

(1*R*,3*S*,6*R*)-5'-Chloro-3-(3,3-dimethyl-2-oxobutyl)-6-formyl-2'-oxo-1'-tritylspiro[cyclohexane-1,3'-indoline]-2,2-dicarbonitrile (3q). White solid, 102.9 mg, 83% yield; mp: 160-161 °C; $[\alpha]_D^{24}$ = -76.6 (c 1.0, $CHCl_3$, 93:7 dr, 93% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.58 – 7.56 (m, 6H), 7.39 – 7.38 (m, 1H), 7.29 – 7.26 (m, 6H), 7.23 – 7.21 (m, 3H), 7.08 – 7.06 (m, 1H), 6.55 (d, *J* = 8.5 Hz, 1H), 3.21 (dd, *J* = 4.0, 14.0 Hz, 1H), 3.14 – 3.09 (m, 1H), 2.97 – 2.87 (m, 2H), 2.23 – 2.19 (m, 2H), 1.95 – 1.91 (m, 1H), 1.64 – 1.59 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 196.2, 172.9, 142..7, 141.1, 129.4, 128.8, 128.4, 127.9, 127.2, 126.0, 125.8, 117.6, 113.3, 110.4, 76.0, 52.1, 51.1, 45.8, 44.4, 39.4, 35.8, 26.2, 26.1, 20.2; ν_{max} (neat, cm^{-1}): 1728, 1585, 1470, 1449, 1425, 1367, 1290, 1189; HRMS (ESI): *m/z* calcd for $C_{41}H_{36}ClN_3O_3$ ($[M]^-$) 653.2451, found 653.2463; Enantiomeric excess of **3q** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 4.8 min, minor enantiomer: t_R = 14.5 min.

Synthesis of compound 6

The cyclohexanecarbaldehyde **3e** (134.6 mg, 0.20 mmol) was dissolved in a mixture of dry CH_2Cl_2 (2.0 mL) and dry ethanol (0.5 mL). The reaction mixture was then cooled to -78 °C and $NaBH_4$ (22.8 mg, 0.60 mmol) was added. The mixture was stirred for 2 h at the same temperature. Excessive $NaBH_4$ was quenched with acetaldehyde (0.20 mL). Then the reaction temperature was allowed to warm to room temperature. The mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine (2 × 10 mL). After drying the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography get compound **6** as a white solid (59.2 mg, 44% yield).

(3*R*,3'*S*,4a'*S*,7'*R*,8a'*S*)-5-Chloro-7'-(hydroxymethyl)-1',2-dioxo-3'-phenyl-1-trityl-1',2',3',4',4a',5',6',7'-octahydro-8a'*H*-spiro[indoline-3,8'-isoquinoline]-8a'-carbonitrile (6). White solid, 59.2 mg, 44% yield; mp: 228-229 °C; $[\alpha]_D^{23}$ = -96.2 (c 0.5, $CHCl_3$, >99% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.65 – 7.63 (m, 6H), 7.41 – 7.40 (m, 4H), 7.35 – 7.34 (m, 1H), 7.24 – 7.21 (m, 6H), 7.17 – 7.14 (m, 3H), 6.95 (dd, *J* = 2.5, 9.0 Hz, 1H), 6.31 (d, *J* = 9.0 Hz, 1H), 5.03 (dd, *J* = 3.0, 12.0 Hz, 1H), 2.85 – 2.79 (m, 1H), 2.46 – 2.38 (m, 2H), 2.11 – 2.07 (m, 3H), 1.94 – 1.88 (m, 2H), 1.62 – 1.53 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 159.2, 142.8, 138.9, 129.7, 128.9, 128.8, 127.6, 126.8, 126.7, 124.8, 116.4, 115.5, 82.1, 75.6, 61.6, 51.9, 51.3, 46.6, 37.3, 36.3, 27.9, 22.9; ν_{max} (neat, cm^{-1}): 3061, 2933, 1723, 1671, 1598, 1492, 1468, 1450, 1421, 1328, 1290, 1214; HRMS (ESI): *m/z* calcd for $C_{43}H_{36}ClN_3O_3$ ($[M]^-$) 677.2445, found 677.2457. Enantiomeric excess of **6** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (95:5 hexanes/*i*-PrOH at 0.8 mL/min, λ = 220 nm), major enantiomer: t_R = 30.9 min, minor enantiomer: t_R = 38.7 min.

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