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Protecting Group-directed Diastereodivergent Synthesis of Chiral Tetrahydronaphthalene-fused Spirooxindoles *via* Bifunctional Tertiary Amine Catalysis

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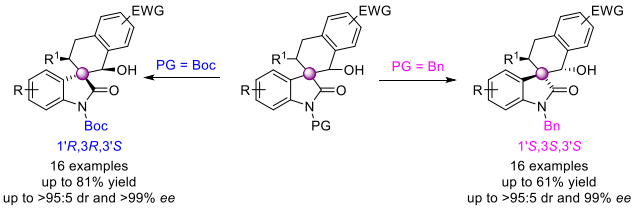


ABSTRACT: A collection of chiral spirocyclic THN-oxindole hybrids bearing a quaternary carbon center at the β-position of THN have been developed. The diastereodivergent direct catalytic Michael-aldol reaction between 3-ylideneoxindole and 2-methylbenzaldehyde was accomplished by using bifunctional tertiary amine. Simply by changing the protecting group on the substrate in the organocatalytic cascade reaction led to inverted diastereoselectivity in good yields with high *ee* value. To explain the diastereodivergence of the organocatalytic Michael-aldol cascade, we also proposed plausible transition-state models for the [4+2] annulation based on the observed stereochemistry of the products.

INTRODUCTION

Both tetrahydronaphthalene (THN) and spirooxindole are privileged frameworks that can be found frequently in a vast number of natural products and pharmaceuticals with antitumor activity (Figure 1a).[1, 2] As a combination of privileged frameworks is a useful way for systematically enhancing molecular diversity and thus discovering novel

chemical entities in drug discovery,[3] the easy construction of THN incorporated spirooxindoles with a simple starting material is significant for natural product-like molecule synthesis, drug discovery and biomedical research.

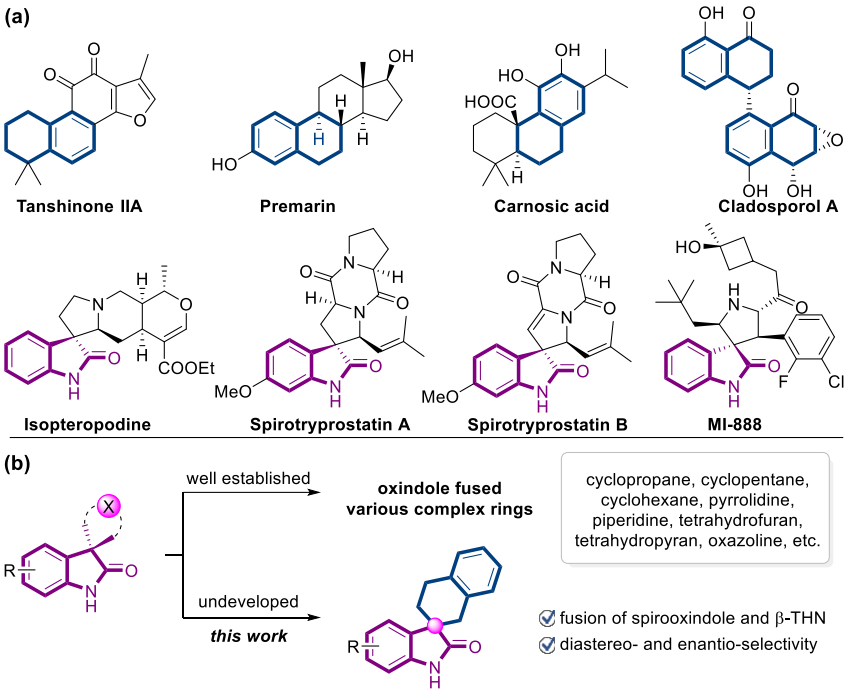
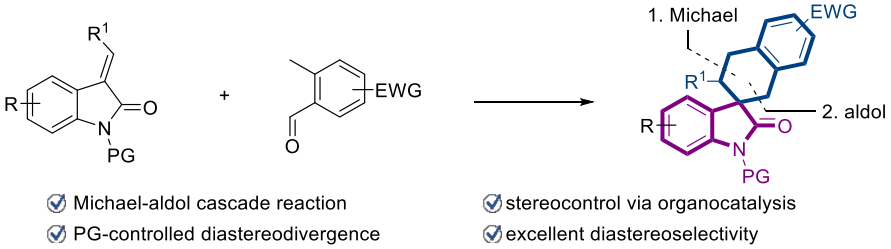


Figure 1. (a) Example bioactive compounds with the privileged skeleton. (b) Asymmetric construction of the C3-spirooxindole bearing various chemically complex rings.

It has been demonstrated that the stereochemistry in spirocyclic oxindoles has a significant effect on their binding affinities to drug targets,[4] so the asymmetric synthesis of the optically pure C3-spirooxindole molecules has become a hot topic in medicinal chemistry.[5] Many methods have been established for enantio-selective synthesis of C3-spirooxindoles fused with various chemically complex rings from three to seven members (Figure 1b).[6] For the synthetic methodologies of the designed architectures, few attempts for the incorporation of the pharmacologically important THN with spirooxindoles have been reported in the past few decades.[7]

Although the Smith's groups firstly reported the asymmetric synthesis of THN-fused spirooxindole bearing a quaternary carbon center at the α-position of THN,[7a] and the Connon's group documented the enantio- and diastereoselective synthesis of spirooxindole analogues bearing a quaternary carbon center at the β-position of THN,[7b] to the best of our knowledge, the protocols for the asymmetric construction of chiral

spirooxindole-THN hybrids are still underdeveloped.[8] From the retrosynthetic analysis, the desired structure can be from 3-ylideneoxindole and 2-methylbenzaldehyde by performing a tandem Michael-aldol reaction, and the chiral bifunctional H-Bonding catalyst may afford the asymmetric version of the final products (Scheme 1).



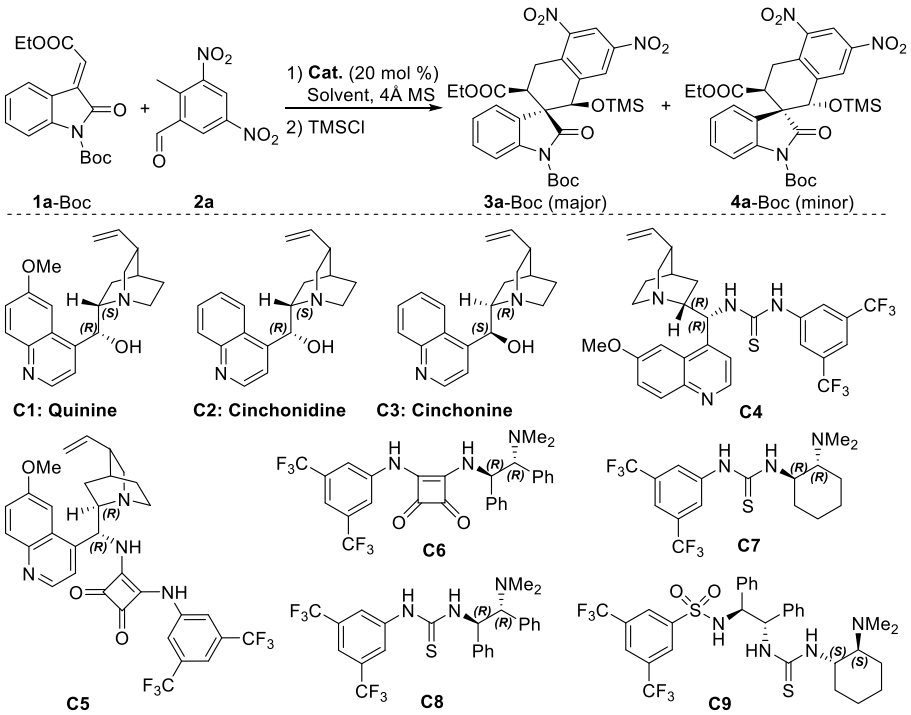
Scheme 1. Synthetic design of the THN-fused C3-spirooxindole scaffold bearing a hydrogen bond acceptor on the hydronaphthalene moiety.

Despite great progress made on asymmetric synthesis, it remains a great challenge for researchers to realize both enantio- and diastereocontrol for a complex molecule bearing multiple stereogenic centers. To date, different approaches have been developed to tune the diastereoselectivity efficiently in asymmetric catalysis,[9] such as using different chiral catalysts,[10] central metals,[11] ligands,[12] the additives,[13] or utilizing the dual catalytic systems.[14] However, it is rare for just changing the protecting group (PG) of the substrate to inverse the diastereoselectivity,[15] and it is still a promising field for both asymmetric catalysis and medicinal chemistry. We wondered whether the different PG could modulate the diastereoselectivity of the final products via distinct transition state. If successful, we can evaluate how the stereochemistry of the all-carbon-based chiral C3-spirooxindole scaffold influence the bioactivity.

RESULTS AND DICUSSION

We commenced our research by screening the reaction between Boc-protected 3-ylideneoxindole **1a**-Boc and nitro-substituted 2-methylbenzaldehyde **2a** (Table 1), promoted by a range of bifunctional hydrogen-bonding catalysts or chiral tertiary amine catalysts (**C1**-**C9**). We planned to convert the intermediate product to its analogue **3a**-Boc and isomer **4a**-Boc in order to protect the hydroxyl group and thereby ensure solubility in $CDCl_3$ for clear NMR spectra.

Table 1. Optimization of reaction conditions.[a]



entry	**Cat.**	solvent	product (major)	yield (%)[b]	dr[c]	*ee*[d]
1	**C1**	CH_2Cl_2	**3a**	47	65:35	24%
2	**C2**	CH_2Cl_2	**3a**	54	73:27	8%
3	**C3**	CH_2Cl_2	**3a**	52	75:25	7%
4	**C4**	CH_2Cl_2	**3a**	65	71:29	72%
5	**C5**	CH_2Cl_2	**3a**	59	78:22	78%
6	**C6**	CH_2Cl_2	**3a**	66	55:45	82%
7	**C7**	CH_2Cl_2	**3a**	73	80:20	96%
8	**C8**	CH_2Cl_2	**3a**	63	70:30	92%
9	**C9**	CH_2Cl_2	**3a**	45	81:19	95%
10	**C7**	Toluene	**3a**	47	60:40	92%
11	**C7**	THF	**3a**	49	55:45	65%
12	**C7**	MeCN	**3a**	84	50:50	71%
13[e]	**C7**	CH_2Cl_2	**3a**	80	88:12	99%
14[f]	**C7**	CH_2Cl_2	**3a**	65	90:10	99%

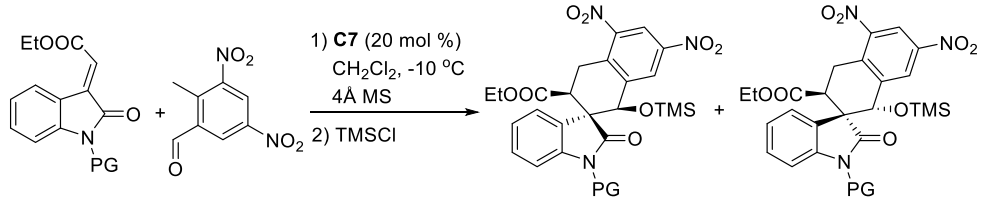
[a] Unless noted otherwise, reactions were performed with **1a**-Boc (47.6 mg, 0.15 mmol), **2a** (37.8 mg, 0.18 mmol) and **Cat.** (0.03 mmol) in anhydrous solvent (4 mL) at 0 °C for 24 h under N_2; [b] Yield of isolated major isomer. [c] Calculated based on ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by chiral HPLC analysis of major isomer. [e] Reaction was performed at -10 °C for 48h. [f] Reaction was performed at -20 °C for 48h.

To our satisfaction, using Takemoto's bifunctional chiral thiourea catalyst **C7** gave high diastereo- and enantioselectivities (Table 1, entry 7). Then we explored more reaction parameters in order to improve yield. The choice of solvent affected the

reaction, the yield and *dr* were sharply declined (entries 10-12). Reducing the reaction temperature to -10 °C and -20 °C, and extending the reaction time led to a high *dr* and *ee* (entries 13 and 14) but lower yield (entry 14). The optimal conditions were found to be reaction in anhydrous CH_2Cl_2 at -10 °C for 48 hours (entry 13).

Next, we investigated the *N*-protected group of the 3-ylideneoxindole, such as Cbz, COOEt, and Ac, affording the corresponding compounds in weak yield (Table 2, entries 2-4). The *dr* and *ee* value were obviously changed. Thus, the Boc-protected substrate was preferable for the cascade reaction.

Table 2. Scope for the protecting group of **1**.[a]



1a **2a** **3a** **4a**

entry	PG	**1a**	product (major)	yield (%)[b]	dr[c] (**3a**:**4a**)	*ee*[d]
1	Boc	**1a**-Boc	**3a**-Boc	80	88:12	99%
2	Cbz	**1a**-Cbz	**3a**-Cbz	70	90:10	99%
3	COOEt	**1a**-COOEt	**3a**-COOEt	75	75:25	99%
4	Ac	**1a**-Ac	**3a**-Ac	78	68:32	69%
5[e]	Bn	**1a**-Bn	**4a**-Bn	51	6:94	89%
6[e]	Me	**1a**-Me	**4a**-Me	45	7:93	67%
7[e]	Allyl	**1a**-Allyl	**4a**-Allyl	41	5:95	57%
8[e]	CPh_3	**1a**-CPh_3	**4a**-CPh_3	10	<5:95	51%

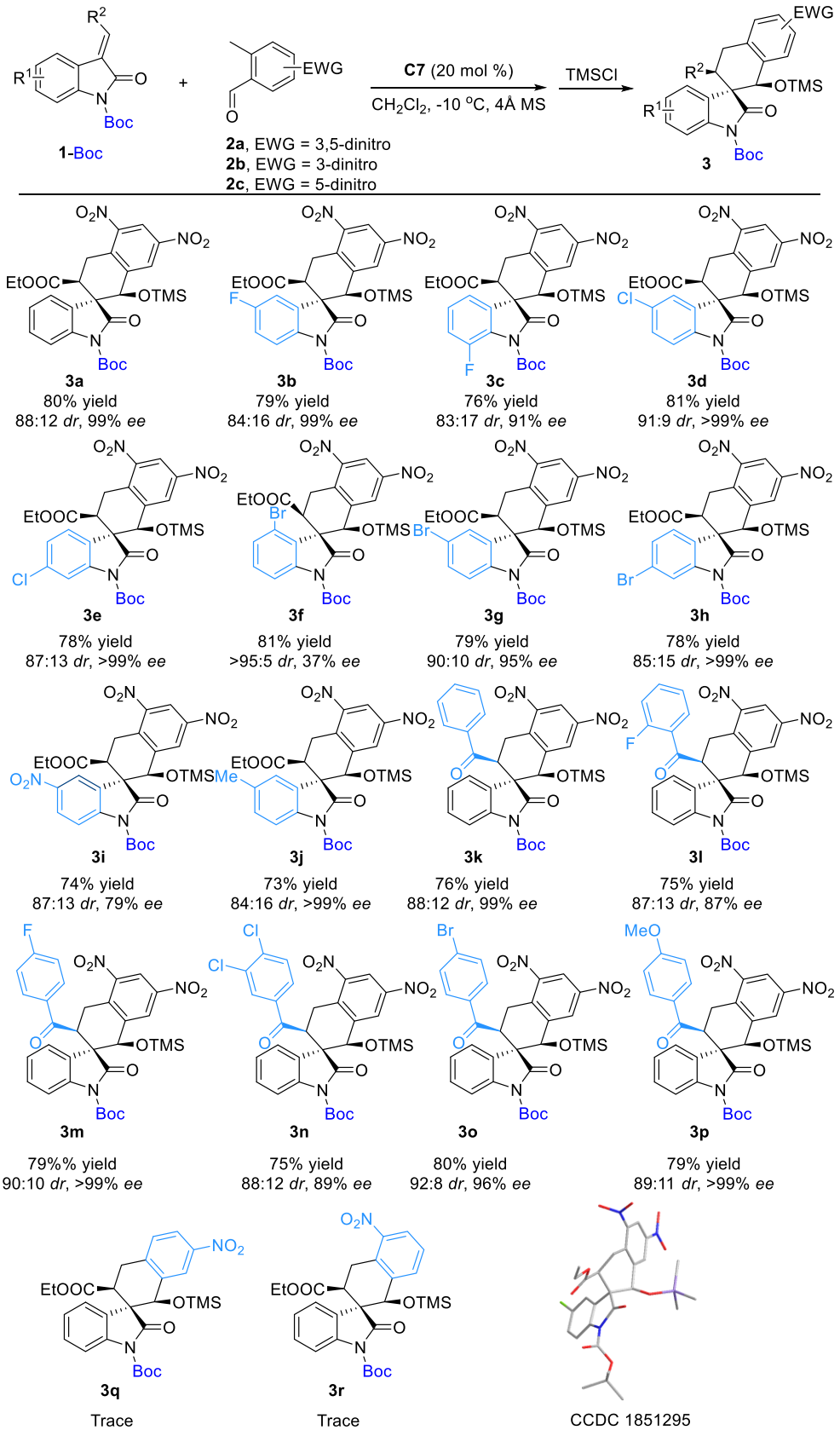
[a] Unless noted otherwise, reactions were performed with **1a** (0.15 mmol), **2a** (37.8 mg, 0.18 mmol) and **C7** (12.4 mg, 0.03 mmol) in anhydrous CH_2Cl_2 (4 mL) at -10 °C for 24 hours under N_2. [b] Yield of isolated major isomer. [c] Calculated based on ^1H NMR analysis of the crude reaction mixture. [d] Determined by chiral HPLC analysis of major isomer. [e] Reaction was performed at -10 °C for 7 days.

Furthermore, applying these optimized conditions to the other *N*-protected substrates **1a**, like the *N*-Bn, *N*-Me, *N*-Allyl, and *N*-CPh_3, led to inverted diastereoselectivity, generating the reversed products (entries 5-8). The results showed that the Bn-protected compound **4a**-Bn was the best in 51% yield with 91:9 *dr* and 89% *ee* (entry 5 *vs* 6-8). Hence, the optimal reaction conditions were established: (i) for the Boc-protected substrates, 20 mol % of **C7** and 4Å MS (25 mg) in anhydrous CH_2Cl_2 at -10 °C for 48

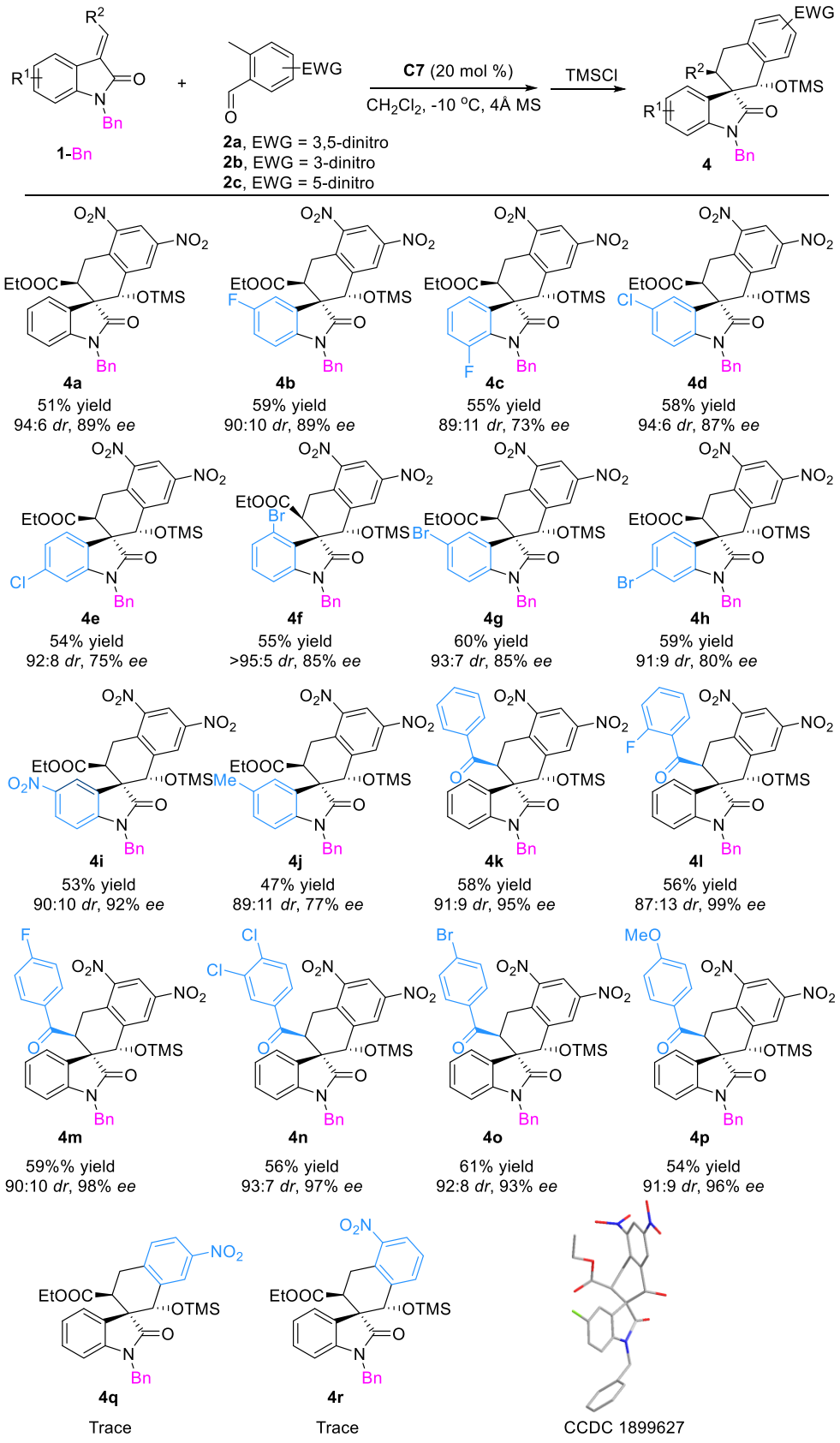
h under N_2; (ii) for the Bn-protected substrates, 20 mol % of **C7** and 4Å MS (25 mg) in anhydrous CH_2Cl_2 at -10 ºC for 7 days under N_2.

With these optimal conditions in hand, we investigated the scope of the reaction using Boc-protected substrate **1**-Boc for the preparation of **3** and Bn-protected substrate **1**-Bn for the synthesis of **4** (Scheme 2 and 3). These two sets of compounds are diastereoisomers with different protecting groups. The electronic properties and position of R^1 substituents on the oxoindole moiety slightly affected the reaction, except in the case of 4-Br 3-ylideneoxindole. In the case of Boc-protected substrates, target products were obtained in high yield with good stereoselectivities; in the case of Bn-protected substrates, moderate yield and good stereoselectivities were observed. Apart from ester group, we also examined different benzoyl group for R^2 variation. The reaction worked well for substrates carrying benzoyl groups at the R^2 position, except the product **4l** in which the major isomer and minor isomer could not be isolated by column chromatography and reverse-phase chromatography. However, monosubstituted **2b** and **2c** showed poor nucleophilicity: the target chiral compounds **3q**-**3r** and **4q**-**4r** were not obtained under optimal reaction conditions, and only racemic products were obtained when the strong base DBU was used and the temperature was below 40 ºC. In order to verify the practical utility of the methodology, we demonstrated the large-scale reaction of 3-ylideneoxidole (**1a**-Boc, 2.0 mmol) and 2-methylbenzaldehyde **2a** (2.4 mmol) under optimal reaction conditions. The desired product **3a** was obtained in 76% yield with 98% *ee* (Scheme 4a). We also performed the large-scale reaction of 3-ylideneoxidole (**1a**-Bn, 2.0 mmol) and 2-methylbenzaldehyde **2a** (2.4 mmol) under optimal reaction conditions, smoothly affording the desired product **4a** in 47% yield with 85% *ee* (Scheme 4b).

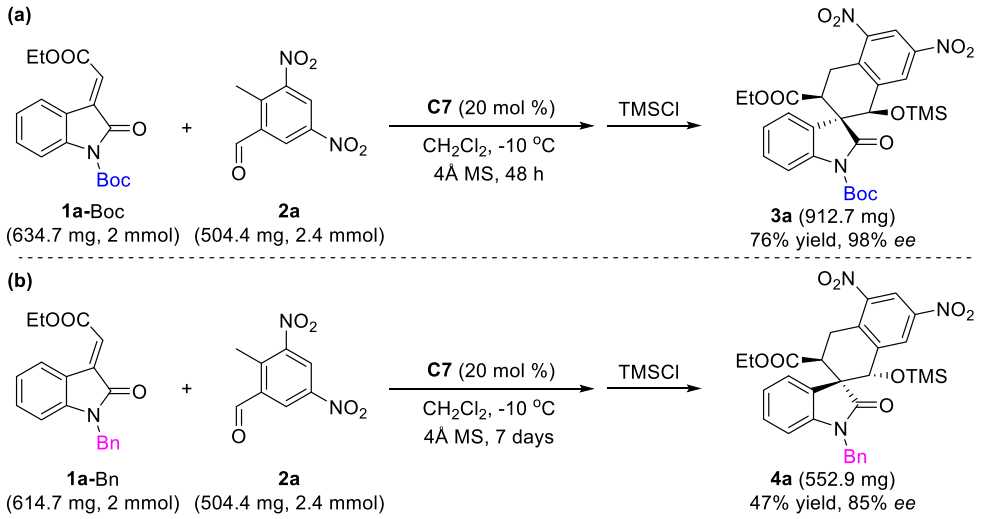
The absolute configurations of compound **3d** and **4d** (the TMS-protected group of **4d** was removed) were determined by X-ray crystallographic analysis.[16] These results were used to tentatively infer the absolute configuration of the other chiral products **3** and **4**.



Scheme 2. Substrate scope of the annulation reaction. Yield was calculated from the isolated major isomer **3**. The *dr* was determined by ^{1}H NMR of the crude reaction mixture. The *ee* was determined by chiral HPLC.



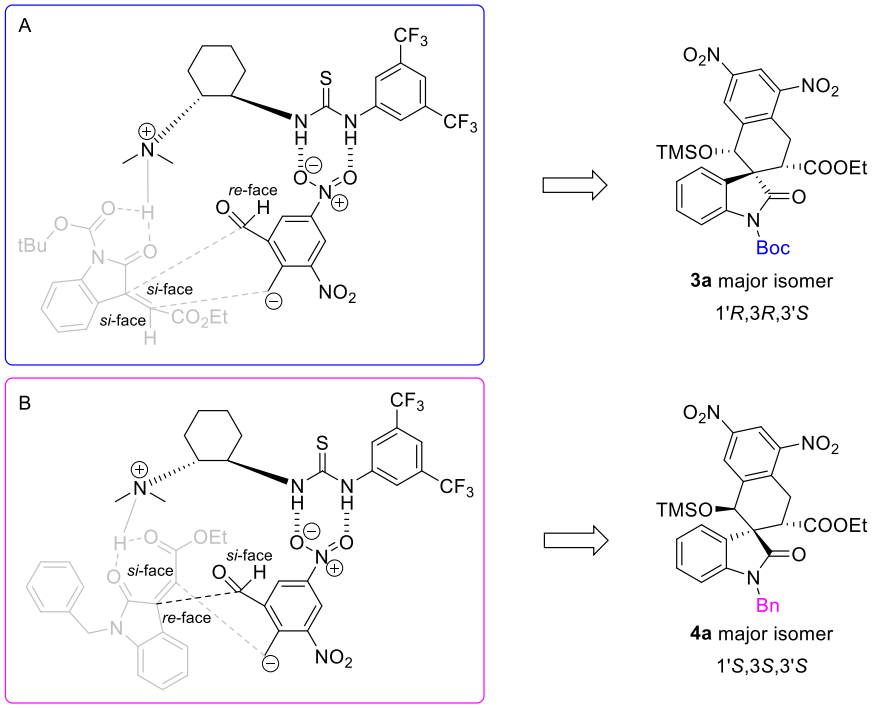
Scheme 3. Substrate scope of the annulation reaction. Yield was calculated from the isolated major isomer **4**. The *dr* was determined by ^{1}H NMR of the crude reaction mixture. The *ee* was determined by chiral HPLC.



Scheme 4. The large-scale experiment for the synthesis of **3a** and **4a**.

We hypothesized about plausible transition states that could explain the high diastereo- and enantioselectivities observed. These transition states and the associated catalytic modes are consistent with the mechanistic models proposed by Takemoto and others.[17] In our proposal, two hydrogen bonds form between the nitro group of substrate **2a** and the two *N*-H groups of the thiourea catalyst (Scheme 5A).[17b, c] The protonated tertiary amine group may form another two hydrogen-bonding interactions with the two carbonyls of the Boc-protected 3-ylideneoxindole **1a**-Boc.[17a] The first Michael addition of carbanion to substrate **2a** occurs *via* attack from the *Si* face of the electron-deficient olefin. A subsequent intramolecular aldol reaction takes place between the *Si* face of the C3-position on the oxindole and the *Re* face of the aldehyde group. This affords the major isomer **3a** with a (*1'R,3R,3'S*)-configuration.

We further predict that substrate **2a** can be activated and fixed through two hydrogen bonds with the thiourea catalyst (Scheme 5B). In the presence of the Bn group on the 3-ylideneoxindole, reaction stereochemistry inverts as follows. The protonated tertiary amine group form the hydrogen-bonds with the C2 carbonyl and ethyl ester groups on substrate **1a**-Bn. While the first Michael addition of carbanion to substrate **2a** occurs *via* attack from the *Si* face of the electron-deficient olefin as in the preceding case, subsequent carbon-carbon bond formation takes place from the *Re* face of the C3-position on the oxindole and the *Si* face of the aldehyde group. This affords the major isomer **4a** with a (*1'S,3S,3'S*)-configuration.



Scheme 5. Proposed transition states to explain the observed stereochemistry.

CONCLUSION

We have used organocatalytic [4+2] annulation to prepare, in good yield, a collection of chiral spirocyclic THN-oxindole hybrids bearing multiple stereocenters and various functional groups. Simply by changing the protecting group of the substrate in the Michael-aldol cascade reaction, we accomplished controlled-diastereodivergence, generating the reversed products with high stereoselectivities. The proposed transition state indicated that the protecting group was a significant role in the diastereoselectivity switching.

EXPERIMENTAL SECTION

General information

Nuclear Magnetic Resonance (NMR) data were obtained for ^{1}H at 400 MHz or 600 MHz, and for ^{13}C at 100 MHz or 150 MHz. Chemical shifts were reported in parts per million (ppm) with tetramethylsilane resonance as the internal standard in $CDCl_3$ solution. Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet), coupling constant(s) (Hz), integration]. ESI high resolution mass spectra (HRMS) were recorded using

electrospray ionization on a Waters SYNAPT G2 (Q-TOF) instrument. The enantiomeric ratio was determined by High Performance Liquid Chromatography (HPLC) analysis on chiral column in comparison with authentic racemates, using the Daicel Chiralpak AD/OD/IE (250 x 4.6 mm). UV detection was monitored at 254 nm. Optical rotation data were examined in CH_2Cl_2 solution at 25 °C and λ = 589 nm. Column chromatography was performed on a silica gel (200-300 mesh) using an eluent of ethyl acetate and petroleum ether. TLC was performed on glass backed silica plates; products were visualized using UV light. Melting points were determined on a Mel-Temp apparatus.

General procedure for the synthesis of the *N*-Boc-3-ylideneoxindoles (1-Boc).

The Wittig olefination was carried out by mixing the corresponding isatin (3.4 mmol) with the appropriate Wittig reagent (1.05 equiv.) in toluene (20 mL). The reaction was stirred at 90 ºC for 0.5 h. Then the reaction was cooling and filtrated during a silica pad. The crude mixture was dissolved in MeCN (25 mL), and Boc_2O (1.2 equiv.) and DMAP (0.2 equiv.) were added. The mixture was stirred at ambient temperature until the reaction was completed based on TLC. The solvent was removed under reduced pressure and the mixture was purified by flash chromatography to yield the respective products, which was was further analyzed by ^{1}H NMR, ^{13}C{^{1}H} NMR, and HRMS.

Reported compounds *N*-Boc-3-ylideneoxindoles **1a**, **1b**, **1d**, **1k**,[18e] **1c**, **1i**,[18b] **1g**,[18d] **1h**, **1j**,[18c] and **1m**, **1o**, **1p**,[18a] were prepared according to the literature.[18] The new substrates **1e**-Boc, **1f**-Boc, **1l**-Boc, and **1n**-Boc were obtained according to the literature procedure with functional group modifications,[18e] and the detailed data was listed below.

*tert-butyl (E)-6-chloro-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (**1e**-Boc)*. Light green solid, 813.5 mg, 68% yield, m.p. 63-65 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.67 (d, J = 9.0 Hz, 1H), 7.99 (d, J = 2.4 Hz, 1H), 7.18 (dd, J = 9.0, 1.8 Hz, 1H), 6.91 (s, 1H), 4.33 (q, J = 7.2 Hz, 2H), 1.65 (s, 9H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 165.4, 165.3, 148.6, 142.6, 138.7, 135.5, 129.4, 124.8, 123.5, 118.5, 115.7, 85.3, 61.5, 28.0, 14.1; HRMS (ESI-TOF) *m/z*:

[M + Na] calcd for $C_{17}H_{18}ClNO_5Na$ 374.0771; found 374.0772.

*tert-butyl (E)-4-bromo-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (**1f**-Boc)*. White solid, 892.3 mg, 66% yield, m.p. 78-80 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.89 (d, J = 7.8 Hz, 1H), 7.83 (s, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.22 (t, J = 8.4 Hz, 1H), 4.42 (q, J = 7.2 Hz, 2H), 1.63 (s, 9H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm)166.1, 162.5, 148.6, 141.9, 131.4, 129.7, 129.2, 128.3, 119.1, 118.5, 114.3, 85.1, 61.9, 28.0, 14.0; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{17}H_{18}BrNO_5Na$ 418.0266; found 418.0263.

*tert-butyl (E)-3-(2-(2-fluorophenyl)-2-oxoethylidene)-2-oxoindoline-1-carboxylate (**1l**-Boc)*. Orange solid, 398.2 mg, 32% yield m.p. 49-50 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.54 (d, J = 7.8 Hz, 1H), 7.95−7.92 (m, 2H), 7.77 (d, J = 4.2 Hz, 1H), 7.61−7.57 (m, 1H), 7.47−7.44 (m, 1H), 7.31−7.27 (m, 1H), 7.21−7.16 (m, 2H), 1.67 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 188.6, 166.3, 161.8 (d, J_{CF} = 256.4 Hz), 148.9, 142.0, 135.4 (d, J_{CF} = 9.3 Hz), 134.8 (d, J_{CF} = 2.0 Hz), 133.2, 131.0 (d, J_{CF} = 2.0 Hz), 129.1 (d, J_{CF} = 6.3 Hz), 127.2, 126.6 (d, J_{CF} = 11.7 Hz), 124.7 (d, J_{CF} = 3.6 Hz), 124.6, 120.4, 116.5 (d, J_{CF} = 22.8 Hz), 115.0, 84.7, 28.1; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{21}H_{18}FNO_4Na$ 390.1118; found 390.1116.

*tert-butyl (E)-3-(2-(3,4-dichlorophenyl)-2-oxoethylidene)-2-oxoindoline-1-carboxylate (**1n**-Boc)*. Yellow solid. 472.3 mg, 32% yield, m.p. 120-122 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.43 (d, J = 7.8 Hz, 1H), 8.16 (d, J = 1.8 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.90 (dd, J = 8.4, 1.8 Hz, 1H), 7.77 (s, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 7.8 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 1.67 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 188.4, 166.0, 148.7, 142.2, 138.6, 137.1, 136.2, 133.8, 133.5, 131.1, 130.6, 127.7, 127.4, 125.2, 124.7, 120.1, 115.2, 84.9, 28.08; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{21}H_{17}Cl_2NO_4Na$ 440.0432; found 440.0431.

General procedure for the asymmetric synthesis of 3.

The reaction was carried out with 3-ylideneoxidole **1**-Boc (0.3 mmol), 2-methylbenzaldehyde **2** (0.36 mmol) and **C7** (49.6 mg, 0.06 mmol) with 4Å in anhydrous CH_2Cl_2 (4.0 mL) at -10 ºC for 48 hours under N_2. The reaction mixture was direct purified by flash chromatography on a silica gel to afford the intermediate.

The protection hydroxyl group of the intermediate gave the corresponding easily separable THN-fused spirooxindole derivative **3.** To a solution of intermediate in CH_2Cl_2 (4 mL) was added TMSCl (25.9 μL, 0.3 mmol) and imidazole (45.8 mg, 0.6 mmol). The mixture was stirred at 0 ºC until the reaction was completed based on TLC. The reaction was quenched with aqueous $NaHCO_3$ (aq) and CH_2Cl_2. The organic layer was dried by Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel to give the major isomer product **3** which were dried under vacuum and further analyzed by ^{1}H NMR, $^{13}C\{^1H\}$ NMR, HRMS and HPLC.

*1-(tert-butyl) 3'-ethyl (1'R,3R,3'S)-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1,3'-dicarboxylate (**3a**)*. White solid, 144.5 mg, 80% yield, 88:12 *dr*, 99% *ee* by HPLC on Chiralpak OD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 7.75 min, t_{major} = 10.31 min, $[\alpha]_D^{25}$ = +62.64 (*c* 1.00, CH_2Cl_2), m.p. 158-160 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.75 (s, 1H), 8.51 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 5.01 (s, 1H), 3.93 (dd, *J* = 12.8 Hz, 1H), 3.76−3.63 (m, 2H), 3.24 (q, *J* = 12.4 Hz, 2H), 1.64 (s, 9H), 0.73 (t, *J* = 7.2 Hz, 3H), -0.16 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 174.8, 170.3, 149.1, 148.4, 146.8, 143.6, 141.6, 137.6, 129.9, 128.8, 124.8, 124.0, 123.1, 119.0, 115.5, 85.0, 75.8, 61.4, 55.9, 47.2, 28.3, 25.7, 13.5, -0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{28}H_{33}N_3O_{10}SiNa$ 622.1833; found 622.1832.

*1-(tert-butyl) 3'-ethyl (1'R,3R,3'S)-5-fluoro-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1,3'-dicarboxylate (**3b**)*. White solid, 145.8 mg, 79% yield, 84:16 *dr*, 99% *ee* by HPLC on Chiralpak IE column (30%

2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{major} = 7.11 min, t_{minor} = 8.08 min, $[\alpha]_D^{25}$ = -14.55 (*c* 1.00, CH_2Cl_2), m.p. 140-142 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.82 (s, 1H), 8.28 (s, 1H), 7.88 (dd, *J* = 9.2, 4.8 Hz, 1H), 7.07 (td, *J* = 8.8, 2.8 Hz, 1H), 6.78 (dd, *J* = 8.0, 2.8 Hz, 1H), 4.83 (s, 1H), 4.03−3.97 (m, 2H), 3.79 (dd, *J* = 17.2, 5.6 Hz, 1H), 3.72−3.60 (m, 2H), 1.60 (s, 9H), 1.06 (t, *J* = 7.2 Hz, 3H), 0.03 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.8, 170.1, 158.9 (d, J_{CF} = 242.1 Hz), 148.3, 148.0, 145.3, 140.5, 137.6, 135.5 (d, J_{CF} = 2.5 Hz), 129.1 (d, J_{CF} = 8.2 Hz), 126.8, 119.2, 115.6 (d, J_{CF} = 7.9 Hz), 115.1 (d, J_{CF} = 22.5 Hz), 112.0 (d, J_{CF} = 25.0 Hz), 84.4, 72.2, 61.1, 52.1, 42.8, 27.5, 26.0, 13.1, -0.3; ^{19}F NMR (565 MHz, $CDCl_3$): δ (ppm) -117.12; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{28}H_{32}FN_3O_{10}SiNa$ 640.1739; found 640.1738.

1-(tert-butyl) 3'-ethyl (1'R,3R,3'S)-7-fluoro-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1,3'-dicarboxylate ***(3c)***. White solid, 140.1 mg, 76% yield, 83:17 *dr*, 91% *ee* by HPLC on Chiralpak OD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 5.92 min, t_{major} = 10.80 min, $[\alpha]_D^{25}$ = +15.40 (*c* 1.00, CH_2Cl_2), m.p. 83-85 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.81 (s, 1H), 8.29 (s, 1H), 7.16−7.06 (m, 2H), 6.77 (dd, *J* = 7.2, 0.8 Hz, 1H), 4.89 (s, 1H), 4.08−3.95 (m, 2H), 3.80 (dd, *J* = 16.0, 4.0 Hz, 1H), 3.70−3.59 (m, 2H), 1.59 (s, 9H), 1.05 (t, *J* = 7.2 Hz, 3H), 0.03 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.4, 170.5, 148.5, 148.4 (d, J_{CF} = 249.4 Hz), 147.2, 145.9, 141.3, 138.7 (d, J_{CF} = 1.8 Hz), 138.1, 131.3 (d, J_{CF} = 1.9 Hz), 127.0, 125.0 (d, J_{CF} = 6.8 Hz), 120.6 (d, J_{CF} = 3.6 Hz), 119.7, 117.6 (d, J_{CF} = 20.4 Hz), 85.4, 72.7, 61.8, 53.5, 43.8, 27.7, 26.4, 13.6, 0.3; ^{19}F NMR (565 MHz, $CDCl_3$): δ (ppm) -118.59; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{28}H_{32}FN_3O_{10}SiNa$ 640.1739; found 640.1738.

1-(tert-butyl) 3'-ethyl (1'R,3R,3'S)-5-chloro-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1,3'-dicarboxylate ***(3d)***. White solid, 154.7 mg, 81% yield, 91:9 *dr*, >99% *ee* by HPLC on Chiralpak IE column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{major} = 7.33 min, $[\alpha]_D^{25}$ = -25.85 (*c* 1.00, CH_2Cl_2), m.p. 141-143 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.75 (s, 1H), 8.54 (s,

1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.38 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.21 (d, *J* = 2.0 Hz, 1H), 5.08 (s, 1H), 4.01−3.92 (m, 3H), 3.60 (dd, *J* = 18.8, 6.0 Hz, 1H), 3.44 (dd, *J* = 12.0, 6.4 Hz, 1H), 1.59 (s, 9H), 1.01 (t, *J* = 7.2 Hz, 3H), -0.08 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 171.7, 169.6, 148.7, 148.0, 146.4, 142.1, 140.3, 136.6, 130.1, 129.8, 129.4, 125.9, 122.2, 119.1, 116.8, 84.7, 76.2, 61.7, 52.5, 46.1, 28.0, 26.8, 13.5, -0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{28}H_{32}ClN_3O_{10}SiNa$ 656.1443; found 656.1440.

1-(tert-butyl) 3'-ethyl (1'R,3R,3'S)-6-chloro-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1,3'-dicarboxylate ***(3e)***. White solid, 148.6 mg, 78% yield, 87:13 *dr*, >99% *ee* by HPLC on Chiralpak OD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{major} = 7.13 min, $[\alpha]_D^{25}$ = -58.19 (*c* 1.00, CH_2Cl_2), m.p. 130-132 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.80 (s, 1H), 8.42 (s, 1H), 7.99 (s, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 5.88 (d, *J* = 8.0 Hz, 1H), 5.23 (s, 1H), 3.93−3.82 (m, 3H), 3.78 (t, *J* = 8.4 Hz, 1H), 3.61 (dd, *J* = 19.2, 8.0 Hz, 1H), 1.67 (s, 9H), 0.97 (t, *J* = 7.2 Hz, 3H), 0.20 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 175.8, 169.2, 148.4, 148.3, 146.3, 143.0, 142.0, 135.8, 134.9, 124.4, 123.9, 123.8, 122.9, 118.9, 115.3, 84.9, 74.8, 61.5, 54.6, 44.1, 27.8, 25.0, 13.2, -0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{28}H_{32}ClN_3O_{10}SiNa$ 656.1443; found 656.1445.

1-(tert-butyl) 3'-ethyl (1'R,3R,3'S)-4-bromo-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1,3'-dicarboxylate ***(3f)***. White solid, 166.2 mg, 81% yield, >95:5 *dr*, 37% *ee* by HPLC on Chiralpak OD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{major} = 5.70 min, t_{minor} = 7.39 min, $[\alpha]_D^{25}$ = +28.80 (*c* 1.00, CH_2Cl_2), m.p. 161-163 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.74 (s, 1H), 8.52 (s, 1H), 7.93 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.38 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 5.70 (s, 1H), 4.26 (dd, *J* = 8.8, 6.4 Hz, 1H), 4.05 (dd, *J* = 18.0, 8.8 Hz, 1H), 3.95 (q, *J* = 7.2 Hz, 2H), 3.49 (dd, *J* = 17.6, 6.4 Hz, 1H), 1.58 (s, 9H), 1.01 (t, *J* = 7.2 Hz, 3H), -0.07 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 171.7, 170.1, 148.4, 148.2, 146.2, 143.7, 142.7, 137.2, 130.8, 128.9, 126.4, 125.3, 118.6, 117.8, 114.4,

84.8, 71.7, 61.5, 55.8, 43.1, 27.9, 25.9, 13.5, -0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{28}H_{32}BrN_3O_{10}SiNa$ 700.0938; found 700.0941.

*1-(tert-butyl) 3'-ethyl (1'R,3R,3'S)-5-bromo-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1,3'-dicarboxylate (**3g**)*. White solid, 161.4 mg, 79% yield, 90:10 *dr*, 95% *ee* by HPLC on Chiralpak IE column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{major} = 7.65 min, t_{minor} = 8.58 min, $[\alpha]_D^{25}$ = -38.84 (*c* 1.00, CH_2Cl_2), m.p. 123-125 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.76 (s, 1H), 8.54 (s, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.53 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.34 (d, *J* = 2.0 Hz, 1H), 5.07 (s, 1H), 4.01−3.93 (m, 3H), 3.60 (dd, *J* = 18.8, 6.0 Hz, 1H), 3.44 (dd, *J* = 12.0, 6.4 Hz, 1H), 1.59 (s, 9H), 1.01 (t, *J* = 7.2 Hz, 3H), -0.08 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.6, 169.6, 148.7, 148.1, 146.3, 142.1, 140.8, 136.8, 132.3, 130.5, 125.8, 125.0, 119.1, 117.2, 117.1, 84.8, 76.3, 61.7, 52.5, 46.1, 28.0, 26.8, 13.5, -0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{28}H_{32}BrN_3O_{10}SiNa$ 700.0938; found 700.0939.

*1-(tert-butyl) 3'-ethyl (1'R,3R,3'S)-6-bromo-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1,3'-dicarboxylate (**3h**)*. White solid, 158.3 mg, 78% yield, 85:15 *dr*, >99% *ee* by HPLC on Chiralpak OD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{major} = 7.23 min, $[\alpha]_D^{25}$ = -30.75 (*c* 1.00, CH_2Cl_2), m.p. 128-130 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.80 (s, 1H), 8.42 (s, 1H), 8.14 (s, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 5.82 (d, *J* = 8.0 Hz, 1H), 5.22 (s, 1H), 3.93−3.83 (m, 3H), 3.78 (t, *J* = 8.4 Hz, 1H), 3.61 (dd, *J* = 19.2, 8.0 Hz, 1H), 1.67 (s, 9H), 0.97 (t, *J* = 7.2 Hz, 3H), 0.20 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 175.7, 169.1, 148.4, 148.3, 146.3, 143.0, 142.1, 135.8, 126.8, 124.4, 124.1, 123.4, 122.8, 118.9, 118.1, 84.9, 74.8, 61.5, 54.6, 44.0, 27.8, 25.0, 13.2, -0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{28}H_{32}BrN_3O_{10}SiNa$ 700.0938; found 700.0938.

*1-(tert-butyl) 3'-ethyl 6-bromo-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1,3'-dicarboxylate (minor isomer of **3h**)*.

White solid, 14.2 mg, 7% yield, 96% *ee* by HPLC on Chiralpak OD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 6.13 min t_{major} = 9.50 min, $[\alpha]_D^{25}$ = +23.20 (*c* 1.00, CH_2Cl_2), m.p. 101-103 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.81 (s, 1H), 8.28 (s, 1H), 8.13 (d, *J* = 1.6 Hz, 1H), 7.28 (d, *J* = 1.6 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 4.84 (s, 1H), 4.04−3.96 (m, 2H), 3.79 (dd, *J* = 16.8, 4.8 Hz, 1H), 3.68 – 3.57 (m, 2H), 1.61 (s, 9H), 1.07 (t, *J* = 7.2 Hz, 3H), 0.02 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* (ppm) 173.3, 170.6, 148.7, 148.5, 145.9, 141.3, 141.1, 138.0, 127.1, 126.9, 125.9, 123.1, 119.7, 118.4, 85.3, 72.8, 61.7, 52.6, 43.6, 28.0, 26.4, 13.7, 0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{28}H_{32}BrN_3O_{10}SiNa$ 700.0938; found 700.0937.

*1-(tert-butyl) 3'-ethyl (1'R,3R,3'S)-5,5',7'-trinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1,3'-dicarboxylate (**3i**)*. White solid, 143.3 mg, 74% yield, 87:13 *dr*, 79% *ee* by HPLC on Chiralpak OD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 8.63 min, t_{major} = 10.87 min, $[\alpha]_D^{25}$ = -13.05 (*c* 1.00, CH_2Cl_2), m.p. 109-111 °C. ^1H NMR (400 MHz, $CDCl_3$): *δ* (ppm) 8.79 (s, 1H), 8.54 (s, 1H), 8.35 (dd, *J* = 9.2, 2.4 Hz, 1H), 8.15 (d, *J* = 2.0 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 5.18 (s, 1H), 4.02−3.93 (m, 3H), 3.68 (dd, *J* = 18.8, 6.0 Hz, 1H), 3.58 (dd, *J* = 11.6, 6.4 Hz, 1H), 1.61 (s, 9H), 1.04 (t, *J* = 7.2 Hz, 3H), -0.11 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* (ppm) 175.5, 169.0, 148.3, 146.4, 142.7, 140.2, 135.6, 131.9, 126.7, 126.1, 124.7, 119.1, 116.8, 116.1, 84.7, 74.9, 61.6, 54.6, 44.1, 27.8, 25.1, 13.2, -0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{28}H_{32}N_4O_{12}SiNa$ 667.1684; found 667.1685.

*1-(tert-butyl) 3'-ethyl (1'R,3R,3'S)-5-methyl-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1,3'-dicarboxylate (**3j**)*. White solid, 135.1 mg, 73% yield, 84:16 *dr*, >99% *ee* by HPLC on Chiralpak OD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{major} = 8.33 min, $[\alpha]_D^{25}$ = -74.09 (*c* 1.00, CH_2Cl_2), m.p. 146-148 °C. ^1H NMR (400 MHz, $CDCl_3$): *δ* (ppm) 8.80 (s, 1H), 8.44 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 5.74 (d, *J* = 1.2 Hz, 1H), 5.24 (s, 1H), 3.94 (dd, *J* = 19.2, 8.4 Hz, 1H), 3.85−3.74 (m, 3H), 3.59 (dd, *J* = 19.2, 8.0 Hz,

1H), 2.07 (s, 3H), 1.66 (s, 9H), 0.91 (t, J = 7.2 Hz, 3H), 0.19 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 176.3, 169.3, 148.6, 148.3, 146.2, 143.4, 138.7, 136.1, 133.3, 129.4, 124.4, 124.3, 123.7, 118.7, 114.2, 84.1, 74.9, 61.3, 54.8, 44.1, 27.8, 25.0, 20.9, 13.1, -0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{29}H_{35}N_3O_{10}SiNa$ 636.1989; found 636.1987.

*1-(tert-butyl) 3'-ethyl 5-methyl-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1,3'-dicarboxylate (minor isomer of **3j**)*. White solid, 11.3 mg, 6% yield, 99% *ee* by HPLC on Chiralpak OD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 5.53 t_{major} = 7.32 min, $[\alpha]_D^{25}$ = +67.99 (*c* 1.00, CH_2Cl_2), m.p. 125-126 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.75 (s, 1H), 8.51 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.08 (s, 1H), 5.00 (s, 1H), 3.93 (dd, J = 14.8, 2.0 Hz, 1H), 3.75−3.67 (m, 2H), 3.27−3.16 (m, 2H), 2.36 (s, 3H), 1.63 (s, 9H), 0.73 (t, J = 7.2 Hz, 3H), -0.17 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 175.0, 170.4, 149.2, 148.4, 146.9, 143.8, 139.2, 137.6, 134.6, 130.2, 128.8, 124.0, 123.7, 118.9, 115.4, 84.8, 75.8, 61.4, 56.0, 47.3, 28.4, 25.8, 21.3, 13.6, -0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{29}H_{35}N_3O_{10}SiNa$ 636.1989; found 636.1990.

*tert-butyl (1'R,3R,3'S)-3'-benzoyl-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1-carboxylate (**3k**)*. White solid, 143.6 mg, 76% yield, 88:12 *dr*, >99% *ee* by HPLC on Chiralpak AD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 4.99 min, t_{major} = 10.46 min, $[\alpha]_D^{25}$ = +121.73 (*c* 1.00, CH_2Cl_2), m.p. 178-180 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.84 (s, 1H), 8.37 (s, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.43−7.35 (m, 3H), 7.23 (t, J = 7.6 Hz, 2H), 7.10 (t, J = 8.4 Hz, 1H), 6.75 (t, J = 7.6 Hz, 1H), 5.57 (d, J = 7.2 Hz, 1H), 5.36 (s, 1H), 4.74 (dd, J = 7.6, 5.6 Hz, 1H), 4.10 (dd, J = 17.6, 5.6 Hz, 1H), 3.36 (dd, J = 17.6, 7.6 Hz, 1H), 1.61 (s, 9H), 0.15 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 197.8, 176.9, 148.4, 148.0, 146.1, 143.7, 140.5, 137.7, 135.9, 133.0, 128.6, 128.2, 127.6, 124.4, 123.9, 123.8, 118.8, 114.0, 84.3, 74.6, 55.8, 48.1, 27.8, 25.1, -0.3; HRMS (ESI-

TOF) *m/z*: [M + Na] calcd for $C_{32}H_{33}N_3O_9SiNa$ 654.1884; found 654.1886.

*tert-butyl (1'R,3R,3'S)-3'-(2-fluorobenzoyl)-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1-carboxylate (**3l**)*. White solid, 145.4 mg, 75% yield, 87:11 *dr*, 87% *ee* by HPLC on Chiralpak OD column (20% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{major} = 8.54 min, t_{minor} = 12.27 min, $[\alpha]_D^{25}$ = +16.80 (*c* 1.00, CH_2Cl_2), m.p. 191-193 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.74 (s, 1H), 8.58 (s, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.56−7.53 (m, 2H), 7.32 (t, *J* = 8.4 Hz, 1H), 7.18−7.12 (m, 3H), 7.09 (t, *J* = 7.2 Hz, 1H), 5.23 (s, 1H), 4.54 (dd, *J* = 12.6, 6.0 Hz, 1H), 3.88 (dd, *J* = 19.2, 12.6 Hz, 1H), 3.62 (dd, *J* = 19.2, 6.0 Hz, 1H), 1.64 (s, 9H), -0.12 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 195.4, 173.2, 160.5, 149.1, 147.2 (d, J_{CF} = 253.7 Hz), 142.8, 142.1, 137.3, 135.7 (d, J_{CF} = 10.2 Hz), 131.5, 129.3, 128.6, 126.2, 125.1, 124.2, 121.2, 119.0, 116.7 (d, J_{CF} = 24.5 Hz), 115.8, 84.3, 52.3, 52.1, 28.1, 26.8, -0.2; ^{19}F NMR (565 MHz, $CDCl_3$): δ (ppm) -111.69; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{32}H_{32}N_3O_9FSiNa$ 672.1790; found 672.1793.

*tert-butyl (1'R,3R,3'S)-3'-(4-fluorobenzoyl)-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1-carboxylate (**3m**)*. White solid, 153.9 mg, 79% yield, 90:10 *dr*, >99% *ee* by HPLC on Chiralpak IE column (20% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{major} = 17.04 min, $[\alpha]_D^{25}$ = -57.69 (*c* 2.00, CH_2Cl_2), m.p. 173-175 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.74 (s, 1H), 8.59 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.83 (dd, *J* = 9.0, 5.4 Hz, 2H), 7.32 (t, *J* = 8.4 Hz, 1H), 7.13 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.12−7.09 (m, 3H), 5.25 (s, 1H), 4.52 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.93 (dd, *J* = 18.6, 12.0 Hz, 1H), 3.57 (dd, *J* = 19.2, 6.0 Hz, 1H), 1.63 (s, 9H), -0.11 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 195.3, 173.2, 166.3 (d, J_{CF} = 255.9 Hz), 149.0, 148.0, 146.4, 142.8, 142.1, 137.2, 131.4, 131.2 (d, J_{CF} = 9.3 Hz), 129.5, 128.5, 126.1, 124.3, 120.8, 119.0, 116.3 (d, J_{CF} = 22.2 Hz), 115.9, 84.3, 76.7, 52.2, 47.7, 28.1, 27.8, -0.3; ^{19}F NMR (565 MHz, $CDCl_3$): δ (ppm) -102.55; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{32}H_{32}N_3O_9FSiNa$ 672.1790; found 672.1792.

*tert-butyl (1'R,3R,3'S)-3'-(3,4-dichlorobenzoyl)-5',7'-dinitro-2-oxo-1'-((trimethylsilyl) oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1-carboxylate (**3n**)*. White solid, 157.9 mg, 75% yield, 88:12 *dr*, 89% *ee* by HPLC on Chiralpak OD column (20% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{major} = 11.90 min, t_{minor} = 16.56 min, $[\alpha]_D^{25}$ = -50.69 (*c* 1.00, CH_2Cl_2), m.p. 183-185 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.76 (s, 1H), 8.58 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 2.0 Hz, 1H), 7.59 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.36–7.32 (m, 1H), 7.16–7.11 (m, 2H), 5.24 (s, 1H), 4.45 (dd, *J* = 11.6, 5.8 Hz, 1H), 3.93 (dd, *J* = 18.6, 11.6 Hz, 1H), 3.54 (dd, *J* = 18.6, 5.8 Hz, 1H), 1.61 (s, 9H), -0.12 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 195.0, 173.1, 149.1, 148.2, 146.6, 142.9, 142.2, 139.2, 137.1, 134.6, 134.1, 131.4, 130.4, 129.8, 128.6, 127.5, 126.2, 124.6, 121.0, 119.2, 116.1, 84.61, 76.7, 52.5, 48.1, 28.3, 27.7, -0.1; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{32}H_{31}N_3O_9Cl_2SiNa$ 722.1104; found 722.1102.

*tert-butyl (1'R,3R,3'S)-3'-(4-bromobenzoyl)-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1-carboxylate (**3o**)*. White solid, 169.8 mg, 80% yield, 92:8 *dr*, 96% *ee* by HPLC on Chiralpak IE column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{major} = 14.23 min, t_{minor} = 16.58 min, $[\alpha]_D^{25}$ = -78.14 (*c* 2.00, CH_2Cl_2), m.p. 204-206 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.74 (s, 1H), 8.58 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.33 (t, *J* = 8.4 Hz, 1H), 7.13−7.09 (m, 2H), 5.24 (s, 1H), 4.50 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.93 (dd, *J* = 18.6, 12.0 Hz, 1H), 3.56 (dd, *J* = 19.2, 6.0 Hz, 1H), 1.62 (s, 9H), -0.12 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 195.9, 173.1, 149.0, 148.0, 146.4, 142.8, 142.0, 137.1, 133.6, 132.4, 129.8, 129.6, 129.5, 128.5, 126.1, 124.3, 120.8, 119.0, 115.9, 84.3, 76.6, 52.2, 47.8, 28.1, 27.7, -0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{32}H_{32}N_3O_9BrSiNa$ 732.0989; found 732.0991.

*tert-butyl (1'R,3R,3'S)-3'-(4-methoxybenzoyl)-5',7'-dinitro-2-oxo-1'-((trimethylsilyl) oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-1-carboxylate (**3p**)*. White solid, 158.2 mg, 79% yield, 89:11 *dr*, >99% *ee* by HPLC on Chiralpak OD column (20%

2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{major} = 8.33 min, $[\alpha]_D^{25}$ = -171.87 (*c* 2.00, CH_2Cl_2), m.p. 178-180 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.73 (s, 1H), 8.59 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 9.0 Hz, 2H), 7.30 (t, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 6.6 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.25 (s, 1H), 4.52 (dd, *J* = 12.6, 6.0 Hz, 1H), 3.92 (dd, *J* = 19.2, 12.2 Hz, 1H), 3.86 (s, 3H), 3.58 (dd, *J* = 19.2, 6.0 Hz, 1H), 1.63 (s, 9H), -0.12 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 195.1, 173.4, 164.3, 149.1, 148.0, 146.3, 142.9, 142.1, 137.5, 130.8, 129.3, 128.8, 127.8, 126.1, 124.2, 120.8, 118.9, 115.9, 114.3, 84.1, 55.6, 52.1, 47.4, 28.1, 28.1, -0.2; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{33}H_{35}N_3O_{10}SiNa$ 684.1989; found 684.1987.

General procedure for the asymmetric synthesis of 4.

The reaction was carried out with 3-ylideneoxidole **1**-Bn (0.3 mmol), 2-methylbenzaldehyde **2** (0.36 mmol) and **C7** (24.8 mg, 0.06 mmol) with 4Å in anhydrous CH_2Cl_2 (4.0 mL) at -10 ºC for 7days under N_2. The reaction mixture was direct purified by flash chromatography on a silica gel to afford the intermediate.

The protection hydroxyl group of the intermediate gave the corresponding easily separable THN-fused spirooxindole derivative **4**. To a solution of intermediate in CH_2Cl_2 (4 mL) was added TMSCl (25.9 μL, 0.3 mmol) and imidazole (45.8 mg, 0.6 mmol). The mixture was stirred at 0 ºC until the reaction was completed based on TLC. The reaction was quenched with aqueous $NaHCO_3$ (aq) and CH_2Cl_2. The organic layer was dried by Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel to give the major isomer product **4** which were dried under vacuum and further analyzed by ^{1}H NMR, ^{13}C{^{1}H} NMR, HPLC and HRMS.

*ethyl (1'S,3S,3'S)-1-benzyl-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro [indoline-3,2'-naphthalene]-3'-carboxylate (**4a**)*. White solid, 90.8 mg, 51% yield, 91:9 *dr*, 89% *ee* by HPLC on Chiralpak OD column (25% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 10.40 min, t_{major} = 16.35 min, $[\alpha]_D^{25}$ = +55.09 (*c* 1.00, CH_2Cl_2), m.p. 133-135 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.76 (s, 1H), 8.56 (s,

1H), 7.38−7.22 (m, 7H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 5.17 (s, 1H), 4.88 (s, 2H), 3.96 (dd, *J* = 16.0, 4.0 Hz, 1H), 3.68 (q, *J* = 7.2 Hz, 2H), 3.33−3.20 (m, 2H), 0.60 (t, *J* = 7.2 Hz, 3H), -0.21 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 176.5, 170.9, 148.4, 146.8, 144.7, 144.3, 137.5, 135.8, 129.6, 129.6, 128.9, 128.1, 127.9, 123.8, 123.6, 122.9, 118.8, 109.5, 74.6, 61.3, 54.8, 46.8, 44.4, 25.7, 13.5, -0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{30}H_{31}N_3O_8SiNa$ 612.1778; found 612.1779.

*ethyl (1'S,3S,3'S)-1-benzyl-5-fluoro-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-3'-carboxylate (**4b**)*. White solid, 107.6 mg, 59% yield, 90:10 *dr*, 89% *ee* by HPLC on Chiralpak OD column (25% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 10.23 min, t_{major} = 16.64 min, $[\alpha]_D^{25}$ = +84.39 (*c* 1.00, CH_2Cl_2), m.p. 105-107 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.77 (s, 1H), 8.55 (s, 1H), 7.34−7.28 (m, 5H), 7.04 (dd, *J* = 8.0, 2.8 Hz, 1H), 6.96 (td, *J* = 8.8, 2.4 Hz, 1H), 6.69 (q, *J* = 4.4 Hz, 1H), 5.17 (s, 1H), 4.87 (s, 2H), 3.98 (dd, *J* = 15.6, 3.2 Hz, 1H), 3.84−3.72 (m, 2H), 3.32−3.21 (m, 2H), 0.70 (t, *J* = 7.2 Hz, 3H), -0.16 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 176.1, 170.7, 159.2 (d, J_{CF} = 241.1 Hz), 148.4, 146.8, 143.8, 140.7, 137.2, 135.4, 131.1 (d, J_{CF} = 7.4 Hz), 129.0, 128.1, 127.8, 123.9, 118.9, 115.7 (d, J_{CF} = 23.2 Hz), 112.0 (d, J_{CF} = 24.3 Hz), 110.0 (d, J_{CF} = 7.6 Hz), 74.4, 61.4, 55.1, 46.5, 44.5, 25.8, 13.6, -0.3; ^{19}F NMR (565 MHz, $CDCl_3$): δ (ppm) -119.48; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{30}H_{30}N_3O_8FSiNa$ 630.1684; found 630.1683.

*ethyl (1'S,3S,3'S)-1-benzyl-7-fluoro-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-3'-carboxylate (**4c**)*. White solid, 100.7 mg, 55% yield, 89:11 *dr*, 73% *ee* by HPLC on Chiralpak AD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 7.00 min, t_{major} = 14.37 min, $[\alpha]_D^{25}$ = +49.74 (*c* 1.00, CH_2Cl_2), m.p. 84-86 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.76 (s, 1H), 8.54 (s, 1H), 7.39 (d, *J* = 7.4 Hz, 2H), 7.32–7.25 (m, 3H), 7.08–6.99 (m, 3H), 5.12 (s, 1H), 5.02 (q, *J* = 15.2 Hz, 2H), 3.95 (dd, *J* = 15.2, 3.2 Hz, 1H), 3.75–3.59 (m, 2H), 3.30–3.18 (m, 2H), 0.61 (t, *J* = 7.2 Hz, 3H), -0.19 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100

MHz, $CDCl_3$): δ (ppm) 176.2, 170.5, 148.3, 147.5 (d, J_{CF} = 245.1 Hz), 146.7, 143.9, 137.3, 136.9, 132.7 (d, J_{CF} = 3.6 Hz), 131.3 (d, J_{CF} = 8.6 Hz), 128.6, 128.1 (d, J_{CF} = 1.5 Hz), 127.9, 123.7, 123.5 (d, J_{CF} = 6.4 Hz), 119.4 (d, J_{CF} = 3.2 Hz), 118.7, 117.7 (d, J_{CF} = 19.6 Hz), 74.7, 61.2, 55.2, 46.8, 45.8, 25.7, 13.5, -0.4; ^{19}F NMR (565 MHz, $CDCl_3$): δ (ppm) -133.04; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{30}H_{30}N_3O_8FSiNa$ 630.1684; found 630.1685.

*ethyl (1'S,3S,3'S)-1-benzyl-5-chloro-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-3'-carboxylate (**4d**)*. White solid, 107.2 mg, 58% yield, 94:6 *dr*, 86% *ee* by HPLC on Chiralpak OD column (10% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 15.31 min, t_{major} = 18.68 min, $[\alpha]_D^{25}$ = +153.03 (*c* 1.00, CH_2Cl_2), m.p. 104-106 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.77 (s, 1H), 8.55 (s, 1H), 7.34−7.21 (m, 7H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.18 (s, 1H), 4.86 (s, 2H), 3.98 (dd, *J* = 16.0, 4.0 Hz, 1H), 3.85−3.74 (m, 2H), 3.32−3.20 (m, 2H), 0.72 (t, *J* = 7.2 Hz, 3H), -0.16 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 175.9, 170.6, 148.3, 146.7, 143.7, 143.1, 137.2, 135.2, 131.3, 129.3, 129.0, 128.2, 128.2, 127.8, 124.1, 123.6, 119.0, 110.4, 74.3, 61.5, 54.8, 46.5, 44.5, 25.8, 13.6, -0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{30}H_{30}N_3O_8ClSiNa$ 646.1388; found 646.1390.

*ethyl (1'S,3S,3'S)-1-benzyl-6-chloro-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-3'-carboxylate (**4e**)*. White solid, 101.4 mg, 54% yield, 92:8 *dr*, 75% *ee* by HPLC on Chiralpak AD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 9.18 min, t_{major} = 11.66 min, $[\alpha]_D^{25}$ = +59.34 (*c* 1.00, CH_2Cl_2), m.p. 106-108 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.77 (s, 1H), 8.54 (s, 1H), 7.3−7.29 (m, 5H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.04 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.77 (d, *J* = 1.6 Hz, 1H), 5.13 (s, 1H), 4.85 (s, 2H), 3.96 (dd, *J* = 16.0, 3.6 Hz, 1H), 3.74 (q, *J* = 7.2 Hz, 2H), 3.31−3.19 (m, 2H), 0.70 (t, *J* = 7.2 Hz, 3H), -0.16 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 176.3, 170.6, 148.3, 146.7, 145.9, 143.8, 137.2, 135.4, 135.1, 129.0, 128.2, 127.9, 127.7, 124.4, 123.8, 122.4, 118.9, 109.9, 74.3, 61.4, 54.4, 46.5, 44.4, 25.7, 13.6, -0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for

$C_{30}H_{30}N_3O_8ClSiNa$ 646.1388; found 646.1385.

*ethyl (1'S,3S,3'S)-1-benzyl-4-bromo-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-3'-carboxylate (**4f**)*. White solid, 110.3 mg, 55% yield, >95:5 *dr*, 85% *ee* by HPLC on Chiralpak AD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{major} = 5.15 min, t_{minor} = 23.35 min, $[\alpha]_D^{25}$ = -45.14 (*c* 1.00, CH_2Cl_2), m.p. 152-154 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.75 (s, 1H), 8.56 (s, 1H), 7.35−7.08 (m, 7H), 6.68 (d, *J* = 6.8 Hz, 1H), 5.80 (s, 1H), 5.12 (d, *J* = 15.6 Hz, 1H), 4.56 (d, *J* = 16.0 Hz, 1H), 4.32 (dd, *J* = 10.0, 6.4 Hz, 1H), 4.13−4.10 (m, 1H), 3.99−3.90 (m, 2H), 3.54 (dd, *J* = 18.0, 6.4 Hz, 1H), 0.97 (t, *J* = 7.2 Hz, 3H), -0.11 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 173.8, 170.4, 148.1, 146.8, 146.3, 143.0, 137.4, 135.1, 130.8, 128.7, 127.7, 127.4, 126.9, 126.8, 125.3, 118.7, 118.2, 108.5, 71.7, 61.3, 54.9, 43.9, 42.4, 26.2, 13.7, -0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{30}H_{30}N_3O_8BrSiNa$ 690.0883; found 690.0881.

*ethyl (1'S,3S,3'S)-1-benzyl-5-bromo-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-3'-carboxylate (**4g**)*. White solid, 120.1 mg, 60% yield, 93:7 *dr*, 85% *ee* by HPLC on Chiralpak OD column (10% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 14.65 min, t_{major} = 19.58 min, $[\alpha]_D^{25}$ = +26.15 (*c* 1.00, CH_2Cl_2), m.p. 161-163 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.78 (s, 1H), 8.55 (s, 1H), 7.38–7.32 (m, 4H), 7.30–7.29 (m, 3H), 6.63 (d, *J* = 8.5 Hz, 1H), 5.17 (s, 1H), 4.85 (s, 2H), 3.97 (dd, *J* = 16.4, 4.0 Hz, 1H), 3.85–3.75 (m, 2H), 3.28 (dd, *J* = 16.4, 11.2 Hz, 1H), 3.20 (dd, *J* = 11.2, 4.0 Hz, 1H), 0.73 (t, *J* = 7.2 Hz, 3H), -0.16 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 175.8, 170.6, 148.3, 146.7, 143.7, 143.6, 137.2, 135.2, 132.2, 131.7, 129.0, 128.2, 127.7, 126.8, 123.8, 118.9, 115.2, 110.8, 74.3, 61.5, 54.7, 46.5, 44.4, 25.7, 13.6, -0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{30}H_{30}N_3O_8BrSiNa$ 690.0883; found 690.0880.

*ethyl (1'S,3S,3'S)-1-benzyl-6-bromo-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-3'-carboxylate (**4h**)*. White solid, 118.5

mg, 59% yield, 91:9 *dr*, 80% *ee* by HPLC on Chiralpak AD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 10.69 min, t_{major} = 13.53 min, $[\alpha]_D^{25}$ = +45.44 (*c* 1.00, CH_2Cl_2), m.p. 89-91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.77 (s, 1H), 8.53 (s, 1H), 7.35−7.28 (m, 5H), 7.20 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.92 (s, 1H), 5.13 (s, 1H), 4.85 (s, 2H), 3.95 (dd, *J* = 16.0, 3.6 Hz, 1H), 3.74 (q, *J* = 7.2 Hz, 2H), 3.31−3.19 (m, 2H), 0.71 (t, *J* = 7.2 Hz, 3H), -0.16 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 176.2, 170.6, 146.7, 146.0, 143.7, 137.2, 135.1, 129.0, 128.5, 128.2, 127.7, 125.5, 124.7, 123.8, 123.1, 118.9, 112.6, 74.3, 61.4, 54.5, 46.4, 44.4, 25.7, 13.6, -0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{30}H_{30}N_3O_8BrSiNa$ 690.0883; found 690.0884.

*ethyl (1'S,3S,3'S)-1-benzyl-5,5',7'-trinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-3'-carboxylate (**4i**)*. White solid, 100.6 mg, 53% yield, 90:10 *dr*, 92% *ee* by HPLC on Chiralpak AD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{major} = 7.75 min, t_{minor} = 12.00 min, $[\alpha]_D^{25}$ = -20.85 (*c* 1.00, CH_2Cl_2), m.p. 111-113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.89 (s, 1H), 8.44 (s, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.41−7.30 (m, 5H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.69 (s, 1H), 5.42 (d, *J* = 15.6 Hz, 1H), 5.31 (s, 1H), 4.68 (d, *J* = 16.0 Hz, 1H), 3.99 (dd, *J* = 18.4, 7.6 Hz, 1H), 3.89 (t, *J* = 7.6 Hz, 1H), 3.82−3.72 (m, 2H), 3.61 (dd, *J* = 18.4, 7.6 Hz, 1H), 0.80 (t, *J* = 7.2 Hz, 3H), 0.17 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 177.4, 169.1, 149.7, 148.3, 146.2, 142.7, 142.5, 136.0, 133.7, 128.6, 127.8, 127.1, 126.8, 125.6, 124.2, 119.2, 118.9, 108.3, 73.9, 61.3, 54.5, 44.4, 44.3, 25.2, 13.2, -0.2; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{30}H_{30}N_4O_{10}SiNa$ 657.1629; found 657.1628.

*ethyl (1'S,3S,3'S)-1-benzyl-5-methyl-5',7'-dinitro-2-oxo-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalene]-3'-carboxylate (**4j**)*. White solid, 86.5 mg, 47% yield, 89:11 *dr*, 77% *ee* by HPLC on Chiralpak OD column (10% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 12.81 min, t_{major} = 16.61 min, $[\alpha]_D^{25}$ = +50.99 (*c* 1.00, CH_2Cl_2), m.p. 90-92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.76 (s, 1H), 8.56 (s, 1H), 7.36−7.25 (m, 5H), 7.08 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 6.65 (d,

J = 7.9 Hz, 1H), 5.16 (s, 1H), 4.86 (dd, *J* = 23.6, 15.6 Hz, 2H), 3.96 (dd, *J* = 16.0, 4.0 Hz, 1H), 3.75−3.66 (m, 2H), 3.32−3.18 (m, 2H), 2.31 (s, 3H), 0.62 (t, *J* = 7.2 Hz, 3H), -0.20 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 176.4, 170.9, 148.4, 146.7, 144.4, 142.2, 137.5, 135.9, 132.5, 129.7, 129.7, 129.0, 128.0, 128.0, 124.4, 123.8, 118.8, 109.3, 74.6, 61.2, 54.8, 46.7, 44.4, 25.9, 21.3, 13.5, -0.3; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{31}H_{33}N_3O_8SiNa$ 626.1935; found 626.1931.

*(1'S,3S,3'S)-3'-benzoyl-1-benzyl-5',7'-dinitro-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalen]-2-one (**4k**)*. White solid, 108.1 mg, 58% yield, 91:9 *dr*, 95% *ee* by HPLC on Chiralpak OD column (25% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 11.24 min, t_{major} = 18.78 min, $[\alpha]_D^{25}$ = +36.34 (*c* 1.00, CH_2Cl_2), m.p. 146-148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.81 (s, 1H), 8.59 (s, 1H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.32−7.12 (m, 10H), 7.04−6.96 (m, 2H), 6.32 (d, *J* = 7.2 Hz, 1H), 5.17 (s, 1H), 5.03 (d, *J* = 15.2 Hz, 1H), 4.10−3.95 (m, 3H), 3.47 (dd, *J* = 16.8, 11.6 Hz, 1H), -0.27 (s, 9H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ (ppm) 199.3, 177.1, 148.7, 146.9, 144.6, 144.4, 138.4, 137.0, 135.7, 133.4, 129.5, 129.2, 128.7, 128.6, 128.3, 128.2, 128.1, 125.1, 123.9, 123.3, 119.1, 109.3, 75.2, 55.3, 49.2, 44.7, 26.0, -0.2; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{34}H_{31}N_3O_7SiNa$ 644.1829; found 644.1832.

*(1'S,3S,3'S)-1-benzyl-3'-(2-fluorobenzoyl)-5',7'-dinitro-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalen]-2-one (**4l**)*. White solid, 107.8 mg, 56% yield, 86:14 *dr*, 99% *ee* by HPLC on Chiralpak OD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 7.98 min, t_{major} = 19.94 min, $[\alpha]_D^{25}$ = +261.51 (*c* 2.00, CH_2Cl_2), m.p. 102-104 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.80 (s, 1H), 8.57 (s, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 2H), 7.24 (d, *J* = 7.2 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 6.92 (t, *J* = 7.8 Hz, 1H), 6.82 (dd, *J* = 10.9, 8.3 Hz, 1H), 6.42 (d, *J* = 7.8 Hz, 1H), 5.24 (s, 1H), 4.97 (d, *J* = 15.6 Hz, 1H), 4.14−4.10 (m, 3H), 4.04 (dd, *J* = 16.8, 4.8 Hz, 1H), 3.43 (dd, *J* = 16.6, 10.6 Hz, 1H), -0.26 (s, 9H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ (ppm) 197.1, 176.3, 147.5 (d, J_{CF} = 277.9 Hz), 144.3, 137.7, 135.5, 134.5 (d, J_{CF} = 9.3 Hz), 130.5, 129.3,

128.8 (d, J_{CF} = 9.7 Hz), 128.5, 127.8, 124.6, 124.2, 123.9, 123.0, 122.3, 118.9, 116.3 (d, J_{CF} = 22.8 Hz), 109.1, 74.6, 60.6, 54.4, 51.5, 44.3, -0.4; ^{19}F NMR (565 MHz, $CDCl_3$): δ (ppm) -111.27; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{34}H_{30}N_3O_7FSiNa$ 662.1735; found 662.1732.

*(1'S,3S,3'S)-1-benzyl-3'-(4-fluorobenzoyl)-5',7'-dinitro-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalen]-2-one (**4m**)*. White solid, 113.9 mg, 59% yield, 90:10 *dr*, 98% *ee* by HPLC on Chiralpak OD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 6.49 min, t_{major} = 18.86 min, $[\alpha]_D^{25}$ = 209.32 (*c* 2.00, CH_2Cl_2), m.p. 99-101 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.86 (s, 1H), 8.39 (s, 1H), 7.40 (dd, *J* = 9.0, 5.4 Hz, 2H), 7.27 (dd, *J* = 6.6, 3.0 Hz, 3H), 7.15 (dd, *J* = 6.6, 2.4 Hz, 2H), 6.99 (t, *J* = 7.8 Hz, 1H), 6.77 (t, *J* = 9.0 Hz, 2H), 6.66 (t, *J* = 7.8 Hz, 1H), 6.45 (d, *J* = 7.8 Hz, 1H), 5.54 (d, *J* = 7.2 Hz, 1H), 5.39 (s, 1H), 4.78−4.74 (m, 2H), 4.70 (d, *J* = 15.6 Hz, 1H), 4.10 (dd, *J* = 17.4, 4.8 Hz, 1H), 3.32 (dd, *J* = 17.4, 7.8 Hz, 1H), 0.12 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 196.6, 177.6, 165.7 (d, J_{CF} = 254.3 Hz), 148.8, 146.3, 144.2, 143.9, 138.6, 135.0, 132.7, 130.8 (d, J_{CF} = 9.0 Hz), 128.9, 128.8, 127.9, 127.6, 125.5, 125.1, 124.1, 122.6, 119.1, 115.6 (d, J_{CF} = 21.8 Hz), 109.0, 73.9, 55.9, 47.1, 44.5, 25.8, 0.2; ^{19}F NMR (565 MHz, $CDCl_3$): δ (ppm) -104.12; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{34}H_{30}N_3O_7FSiNa$ 662.1735; found 662.1730.

*(1'S,3S,3'S)-1-benzyl-3'-(3,4-dichlorobenzoyl)-5',7'-dinitro-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalen]-2-one (**4n**)*. White solid, 114.3 mg, 56% yield, 93:7 *dr*, 97% *ee* by HPLC on Chiralpak OD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 6.52 min, t_{major} = 21.28 min, $[\alpha]_D^{25}$ = +129.38 (*c* 2.00, CH_2Cl_2), m.p. 109-111 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.82 (s, 1H), 8.58 (s, 1H), 7.34−7.29 (m, 4H), 7.28−7.26 (m, 2H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.10 (dd, *J* = 18.0, 8.4 Hz, 2H), 7.05−7.01 (m, 2H), 6.43 (d, *J* = 7.8 Hz, 1H), 5.11 (s, 1H), 5.08 (d, *J* = 15.0 Hz, 1H), 4.13 (d, *J* = 15.6 Hz, 1H), 3.98−3.94 (m, 2H), 3.45 (dd, *J* = 16.8, 13.2 Hz, 1H), -0.27 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 197.1, 176.9, 148.6, 147.0, 144.4, 144.3, 138.0, 137.9, 136.4, 135.5, 133.4, 130.6, 130.1, 129.8, 129.2,

128.4, 128.3, 128.2, 127.0, 125.0, 123.8, 123.5, 119.2, 109.4, 75.2, 55.2, 49.5, 44.8, 25.7, -0.2; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{34}H_{29}N_3O_7Cl_2SiNa$ 712.1050; found 712.1049.

*(1'S,3S,3'S)-1-benzyl-3'-(4-bromobenzoyl)-5',7'-dinitro-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalen]-2-one (**4o**)*. White solid, 125.7 mg, 61% yield, 92:8 *dr*, 93% *ee* by HPLC on Chiralpak OD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 6.86 min, t_{major} = 23.91 min, $[\alpha]_D^{25}$ = +207.72 (*c* 2.00, CH_2Cl_2), m.p. 108-110 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.81 (s, 1H), 8.58 (s, 1H), 7.32 (d, *J* = 6.6 Hz, 3H), 7.26−7.21 (m, 5H), 7.16 (d, *J* = 6.6 Hz, 1H), 7.08 (dd, *J* = 15.6, 7.8 Hz, 3H), 7.00 (t, *J* = 7.2 Hz, 1H), 6.42 (d, *J* = 7.8 Hz, 1H), 5.12 (s, 1H), 4.96 (d, *J* = 15.0 Hz, 1H), 4.19 (d, *J* = 15.6 Hz, 1H), 4.01 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.95 (d, *J* = 16.8 Hz, 1H), 3.46 (dd, *J* = 15.6, 12.0 Hz, 1H), -0.27 (s, 9H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ (ppm) 198.2, 177.0, 148.6, 146.9, 144.4, 144.3, 138.2, 135.6, 135.5, 131.9, 129.6, 129.6, 129.2, 128.7, 128.4, 128.3, 128.2, 125.1, 123.8, 123.3, 119.1, 109.4, 75.2, 55.3, 49.1, 44.7, 25.8, -0.2; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{34}H_{30}N_3O_7BrSiNa$ 722.0934; found 722.0932.

*(1'S,3S,3'S)-1-benzyl-3'-(4-methoxybenzoyl)-5',7'-dinitro-1'-((trimethylsilyl)oxy)-3',4'-dihydro-1'H-spiro[indoline-3,2'-naphthalen]-2-one (**4p**)*. White solid, 106.2 mg, 54% yield, 91:9 *dr*, 96% *ee* by HPLC on Chiralpak OD column (30% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 7.77 min, t_{major} = 16.34 min, $[\alpha]_D^{25}$ = +138.38 (*c* 1.00, CH_2Cl_2), m.p. 103-105 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.86 (s, 1H), 8.41 (s, 1H), 7.48 (d, *J* = 9.0 Hz, 2H), 7.25 (dd, *J* = 6.6, 4.2 Hz, 3H), 7.10 (dd, *J* = 6.6, 2.4 Hz, 2H), 6.99 (dd, *J* = 8.4, 7.2 Hz, 1H), 6.68−6.66 (m, 3H), 6.44 (d, *J* = 7.8 Hz, 1H), 5.66 (d, *J* = 7.8 Hz, 1H), 5.41 (s, 1H), 4.86 (d, *J* = 15.6 Hz, 1H), 4.75 (dd, *J* = 7.2, 6.0 Hz, 1H), 4.66 (d, *J* = 15.6 Hz, 1H), 4.05 (dd, *J* = 18.0, 6.0 Hz, 1H), 3.78 (s, 3H), 3.35 (dd, *J* = 17.4, 7.2 Hz, 1H), 0.13 (s, 9H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ (ppm) 196.1, 177.6, 163.7, 148.7, 146.2, 144.2, 143.8, 138.8, 135.1, 130.6, 129.1, 128.8, 128.5, 127.7, 127.4, 125.7, 125.0, 124.2, 122.5, 119.0, 113.7, 109.0, 74.1, 55.9, 55.6, 46.4, 44.4, 26.3,

0.2; HRMS (ESI-TOF) *m/z*: [M + Na] calcd for $C_{35}H_{33}N_3O_8SiNa$ 674.1935; found 674.1934.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

Crystal data for **3d** and **4d** (the TMS-protected group of **4d** was removed).

^1H and ^{13}C NMR spectra and HPLC chromatograms for products **3** and **4**.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Han, N.-n.; Zhou, Q.; Huang, Q.; Liu, K.-j. Carnosic acid cooperates with tamoxifen to induce apoptosis associated with Caspase-3 activation in breast cancer cells in vitro and in vivo. *Biomed. Pharmacother.* **2017**, *89*, 827-837. (b) Zurlo, D.;

Ziccardi, P.; Votino, C.; Colangelo, T.; Cerchia, C.; Dal Piaz, F.; Dallavalle, S.; Moricca, S.; Novellino, E.; Lavecchia, A.; Colantuoni, V.; Lupo, A. The antiproliferative and proapoptotic effects of cladosporols A and B are related to their different binding mode as PPAR gamma ligands. *Biomed. Pharmacother.* **2016**, *108*, 22-35. (c) Zhou, Y.; Yang, B.; Jiang, Y.; Liu, Z.; Liu, Y.; Wang, X.; Kuang, H. Studies on Cytotoxic Activity against HepG-2 Cells of Naphthoquinones from Green Walnut Husks of Juglans mandshurica Maxim. *Molecules* **2015**, *20*, 15572-15588. (d) Gonzalez, M. A. Aromatic abietane diterpenoids: their biological activity and synthesis. *Nat. Prod. Rep.* **2015**, *32*, 684-704. (e) Zurlo, D.; Leone, C.; Assante, G.; Salzano, S.; Renzone, G.; Scaloni, A.; Foresta, C.; Colantuoni, V.; Lupo, A. Cladosporol a stimulates G1-phase arrest of the cell cycle by up-regulation of p21waf1/cip1 expression in human colon carcinoma HT-29 cells. *Mol. Carcinog.* **2013**, *52*, 1-17. (f) Hatfield, M. J.; Tsurkan, L. G.; Hyatt, J. L.; Edwards, C. C.; Lemoff, A.; Jeffries, C.; Yan, B.; Potter, P. M. Modulation of Esterified Drug Metabolism by Tanshinones from Salvia miltiorrhiza ("Danshen"). *J. Nat. Prod.* **2013**, *76*, 36-44. (g) Yang, N.-Y.; Liu, L.; Tao, W.-W.; Duan, J.-A.; Tian, L.-J. Diterpenoids from Pinus massoniana resin and their cytotoxicity against A431 and A549 cells. *Phytochemistry* **2010**, *71*, 1528-1533. (h) Yang, B. H.; Zhang, W. D.; Liu, R. H.; Li, T. Z.; Zhang, C.; Zhou, Y.; Su, J. Lignans from Bark of Larix olgensis var. koreana. *J. Nat. Prod.* **2005**, *68*, 1175-1179.

(2) (a) Panda, S. S.; Jones, R. A.; Bachawala, P.; Mohapatra, P. P. Spirooxindoles as Potential Pharmacophores. *Mini-Rev. Med. Chem.* **2017**, *17*, 1515-1536. (b) Yu, B.; Zheng, Y.-C.; Shi, X.-J.; Qi, P.-P.; Liu, H.-M. Natural Product-Derived Spirooxindole Fragments Serve as Privileged Substructures for Discovery of New Anticancer Agents. *Anticancer Agents Med. Chem.* **2016**, *16*, 1315-1324. (c) Saraswat, P.; Jeyabalan, G.; Hassan, M. Z.; Rahman, M. U.; Nyola, N. K. Review of synthesis and various biological activities of spiro heterocyclic compounds comprising oxindole and pyrrolidine moities. *Synth. Commun.* **2016**, *46*, 1643-1664. (d) Lemos, A.; Leao, M.; Soares, J.; Palmeira, A.; Pinto, M.; Saraiva, L.; Sousa, M. E. Medicinal Chemistry Strategies to Disrupt the p53-MDM2/MDMX Interaction. *Med. Res. Rev.* **2016**, *36*, 789-844. (e) Gupta, A. K.; Bharadwaj, M.; Kumar, A.; Mehrotra, R. Spiro-oxindoles as a Promising Class of Small

Molecule Inhibitors of p53-MDM2 Interaction Useful in Targeted Cancer Therapy. *Top. Curr. Chem.* **2016**, *375*, 3. (f) Yu, B.; Yu, D.-Q.; Liu, H.-M. Spirooxindoles: Promising scaffolds for anticancer agents. *Eur. J. Med. Chem.* **2015**, *97*, 673-698. (g) Santos, M. M. M. Recent advances in the synthesis of biologically active spirooxindoles. *Tetrahedron* **2014**, *70*, 9735-9757. (h) Galliford, C. V.; Scheidt, K. A. Pyrrolidinyl-spirooxindole natural products as inspirations for the development of potential therapeutic agents. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748-8758.

(3) (a) Silva, C. F. M.; Batista, V. F.; Pinto, D. C. G. A.; Silva, A. M. S. Challenges with chromone as a privileged scaffold in drug discovery. *Expert Opinion on Drug Discovery* **2018**, *13*, 795-798. (b) Zhuang, C.; Zhang, W.; Sheng, C.; Zhang, W.; Xing, C.; Miao, Z. Chalcone: A Privileged Structure in Medicinal Chemistry. *Chem. Rev.* **2017**, *117*, 7762-7810. (c) Garcia-Castro, M.; Zimmermann, S.; Sankar, M. G.; Kumar, K. Scaffold Diversity Synthesis and Its Application in Probe and Drug Discovery. *Angew. Chem., Int. Ed.* **2016**, *55*, 7586-7605. (d) O'Connor, C. J.; Beckmann, H. S. G.; Spring, D. R. Diversity-oriented synthesis: producing chemical tools for dissecting biology. *Chem. Soc. Rev.* **2012**, *41*, 4444-4456. (e) Oh, S.; Park, S. B. A design strategy for drug-like polyheterocycles with privileged substructures for discovery of specific small-molecule modulators. *Chem. Commun.* **2011**, *47*, 12754-12761.

(4) Zhao, Y.; Liu, L.; Sun, W.; Lu, J.; McEachern, D.; Li, X.; Yu, S.; Bernard, D.; Ochsenbein, P.; Ferey, V.; Carry, J.-C.; Deschamps, J. R.; Sun, D.; Wang, S. Diastereomeric Spirooxindoles as Highly Potent and Efficacious MDM2 Inhibitors. *J. Am. Chem. Soc.* **2013**, *135*, 7223-7234.

(5) (a) Mei, G.-J.; Shi, F. Catalytic asymmetric synthesis of spirooxindoles: recent developments. *Chem. Commun.* **2018**, *54*, 6607-6621. (b) Kandimalla, S. R.; Sabitha, G. Diversity-Oriented Synthesis of Oxacyclic Spirooxindole Derivatives through Ring-Closing Enyne Metathesis and Intramolecular Pauson-Khand (2+2+1) Cyclization of Oxindole Enynes. *Adv. Synth. Catal.* **2017**, *359*, 3444-3453. (c) Franz, A. K.; Hanhan, N. V.; Ball-Jones, N. R. Asymmetric Catalysis for the Synthesis of Spirocyclic Compounds. *ACS Catal.* **2013**, *3*, 540-553. (d) MacDonald, J. P.; Badillo, J. J.; Arevalo, G. E.; Silva-Garcia, A.; Franz, A. K. Catalytic Stereoselective Synthesis of Diverse

Oxindoles and Spirooxindoles from Isatins. *ACS Comb. Sci.* **2012**, *14*, 285-293. (e) Badillo, J. J.; Hanhan, N. V.; Franz, A. K. Enantioselective synthesis of substituted oxindoles and spirooxindoles with applications in drug discovery. *Curr. Opin. Drug Disc.* **2010**, *13*, 758-776.

(6) (a) Zhao, Q.; Peng, C.; Huang, H.; Liu, S.-J.; Zhong, Y.-J.; Huang, W.; He, G.; Han, B. Asymmetric synthesis of tetrahydroisoquinoline-fused spirooxindoles as Ras-GTP inhibitors that inhibit colon adenocarcinoma cell proliferation and invasion. *Chem. Commun.* **2018**, *54*, 8359-8362. (b) Zhu, L.; Chen, Q.; Shen, D.; Zhang, W.; Shen, C.; Zeng, X.; Zhong, G. Enantioselective Construction of Spirocyclic Oxindole Derivatives with Multiple Stereocenters via an Organocatalytic Michael/Aldol/Hemiacetalization Cascade Reaction. *Org. Lett.* **2016**, *18*, 2387-2390. (c) Cheng, D.; Ishihara, Y.; Tan, B.; Barbas, C. F., III Organocatalytic Asymmetric Assembly Reactions: Synthesis of Spirooxindoles via Organocascade Strategies. *ACS Catal.* **2014**, *4*, 743-762. (d) Hong, L.; Wang, R. Recent Advances in Asymmetric Organocatalytic Construction of 3,3′-Spirocyclic Oxindoles. *Adv. Synth. Catal.* **2013**, *355*, 1023-1052. (e) Singh, G. S.; Desta, Z. Y. Isatins As Privileged Molecules in Design and Synthesis of Spiro-Fused Cyclic Frameworks. *Chem. Rev.* **2012**, *112*, 6104-6155. (f) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. Strategies for the enantioselective synthesis of spirooxindoles. *Org. Biomol. Chem.* **2012**, *10*, 5165-5181. (g) Zhou, F.; Liu, Y.-L.; Zhou, J. Catalytic Asymmetric Synthesis of Oxindoles Bearing a Tetrasubstituted Stereocenter at the C-3 Position. *Adv. Synth. Catal.* **2010**, *352*, 1381-1407. (h) Trost, B. M.; Brennan, M. K. Asymmetric Syntheses of Oxindole and Indole Spirocyclic Alkaloid Natural Products. *Synthesis* **2009**, 3003-3025.

(7) (a) Richmond, E.; Duguet, N.; Slawin, A. M. Z.; Lébl, T.; Smith, A. D. Asymmetric Pericyclic Cascade Approach to Spirocyclic Oxindoles. *Org. Lett.* **2012**, *14*, 2762-2765. (b) Manoni, F.; Connon, S. J. Catalytic Asymmetric Tamura Cycloadditions. *Angew. Chem., Int. Ed.* **2014**, *53*, 2628-2632. (c) England, D. B.; Merey, G.; Padwa, A. Substitution and Cyclization Reactions Involving the Quasi-Antiaromatic 2H-Indol-2-one Ring System. *Org. Lett.* **2007**, *9*, 3805-3807.

(8) For the racemic synthesis of the target scaffold, see: Wang, B.; Leng, H.-J.; Yang,

X.-Y.; Han, B.; Rao, C.-L.; Liu, L.; Peng, C.; Huang, W. Efficient synthesis of tetrahydronaphthalene- or isochroman-fused spirooxindoles using tandem reactions. *RSC Adv.* **2015**, *5*, 88272-88276.

(9) (a) Bihani, M.; Zhao, J. C.-G. Advances in Asymmetric Diastereodivergent Catalysis. *Adv. Synth. Catal.* **2017**, *359*, 534-575. (b) Oliveira, M. T.; Luparia, M.; Audisio, D.; Maulide, N. Dual Catalysis Becomes Diastereodivergent. *Angew. Chem., Int. Ed.* **2013**, *52*, 13149-13152.

(10) For selected examples, see: (a) Li, X.; Huang, W.; Liu, Y.-Q.; Kang, J.-W.; Xia, D.; He, G.; Peng, C.; Han, B. Control of Activation Mode to Achieve Diastereodivergence in Asymmetric Syntheses of Chiral Spiropiperidinone Derivatives. *J. Org. Chem.* **2017**, *82*, 397-406. (b) Zhan, G.; Shi, M.-L.; He, Q.; Lin, W.-J.; Ouyang, Q.; Du, W.; Chen, Y.-C. Catalyst-Controlled Switch in Chemo- and Diastereoselectivities: Annulations of Morita-Baylis-Hillman Carbonates from Isatins. *Angew. Chem., Int. Ed.* **2016**, *55*, 2147-2151. (c) Verrier, C.; Melchiorre, P. Diastereodivergent organocatalysis for the asymmetric synthesis of chiral annulated furans. *Chem. Sci.* **2015**, *6*, 4242-4246. (d) Guo, C.; Sahoo, B.; Daniliuc, C. G.; Glorius, F. *N*-Heterocyclic Carbene Catalyzed Switchable Reactions of Enals with Azoalkenes: Formal [4+3] and [4+1] Annulations for the Synthesis of 1,2-Diazepines and Pyrazoles. *J. Am. Chem. Soc.* **2014**, *136*, 17402-17405. (e) Feng, X.; Zhou, Z.; Zhou, R.; Zhou, Q.-Q.; Dong, L.; Chen, Y.-C. Stereodivergence in Amine-Catalyzed Regioselective [4+2] Cycloadditions of β-Substituted Cyclic Enones and Polyconjugated Malononitriles. *J. Am. Chem. Soc.* **2012**, *134*, 19942-19947.

(11) (a) Kuang, Y.; Shen, B.; Dai, L.; Yao, Q.; Liu, X.; Lin, L.; Feng, X. Diastereodivergent asymmetric Michael-alkylation reactions using chiral N,N′-dioxide/metal complexes. *Chem. Sci.* **2018**, *9*, 688-692. (b) Lu, G.; Yoshino, T.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. Stereodivergent Direct Catalytic Asymmetric Mannich-Type Reactions of α-Isothiocyanato Ester with Ketimines. *Angew. Chem., Int. Ed.* **2011**, *50*, 4382-4385. (c) Nojiri, A.; Kumagai, N.; Shibasaki, M. Linking Structural Dynamics and Functional Diversity in Asymmetric Catalysis. *J. Am. Chem. Soc.* **2009**, *131*, 3779-3784.

(12) (a) Weidner, K.; Sun, Z.; Kumagai, N.; Shibasaki, M. Direct Catalytic Asymmetric Aldol Reaction of an α-Azido Amide. *Angew. Chem., Int. Ed.* **2015**, *54*, 6236-6240. (b) Mechler, M.; Peters, R. Diastereodivergent Asymmetric 1,4-Addition of Oxindoles to Nitroolefins by Using Polyfunctional Nickel-Hydrogen-Bond-Azolium Catalysts. *Angew. Chem., Int. Ed.* **2015**, *54*, 10303-10307. (c) Li, C.-Y.; Yang, W.-L.; Luo, X.; Deng, W.-P. Diastereodivergent Asymmetric Michael Addition of Cyclic Azomethine Ylides to Nitroalkenes: Direct Approach for the Synthesis of 1,7-Diazaspiro[4.4]nonane Diastereoisomers. *Chem. -Eur. J.* **2015**, *21*, 19048-19057. (d) Hao, X.; Lin, L.; Tan, F.; Yin, C.; Liu, X.; Feng, X. Ligand Control of Diastereodivergency in Asymmetric Inverse Electron Demand Diels–Alder Reaction. *ACS Catal.* **2015**, *5*, 6052-6056. (e) Maroto, E. E.; Filippone, S.; Suárez, M.; Martínez-Álvarez, R.; de Cózar, A.; Cossío, F. P.; Martín, N. Stereodivergent Synthesis of Chiral Fullerenes by [3+2] Cycloadditions to C_{60}. *J. Am. Chem. Soc.* **2014**, *136*, 705-712. (f) Audisio, D.; Luparia, M.; Oliveira, M. T.; Klütt, D.; Maulide, N. Diastereodivergent De-epimerization in Catalytic Asymmetric Allylic Alkylation. *Angew. Chem., Int. Ed.* **2012**, *51*, 7314-7317. (g) Luparia, M.; Oliveira, M. T.; Audisio, D.; Frébault, F.; Goddard, R.; Maulide, N. Catalytic Asymmetric Diastereodivergent Deracemization. *Angew. Chem., Int. Ed.* **2011**, *50*, 12631-12635. (h) Yan, X.-X.; Peng, Q.; Li, Q.; Zhang, K.; Yao, J.; Hou, X.-L.; Wu, Y.-D. Highly Diastereoselective Switchable Enantioselective Mannich Reaction of Glycine Derivatives with Imines. *J. Am. Chem. Soc.* **2008**, *130*, 14362-14363. (i) Trost, B. M.; Cramer, N.; Silverman, S. M. Enantioselective Construction of Spirocyclic Oxindolic Cyclopentanes by Palladium-Catalyzed Trimethylenemethane-[3+2]-Cycloaddition. *J. Am. Chem. Soc.* **2007**, *129*, 12396-12397.

(13) (a) Ramachandran, P. V.; Chanda, P. B. Solvent- or Temperature-Controlled Diastereoselective Aldol Reaction of Methyl Phenylacetate. *Org. Lett.* **2012**, *14*, 4346-4349. (b) Martínez-Castañeda, Á.; Rodríguez-Solla, H.; Concellón, C.; del Amo, V. Switching Diastereoselectivity in Proline-Catalyzed Aldol Reactions. *J. Org. Chem.* **2012**, *77*, 10375-10381. (c) Tian, X.; Cassani, C.; Liu, Y.; Moran, A.; Urakawa, A.; Galzerano, P.; Arceo, E.; Melchiorre, P. Diastereodivergent Asymmetric Sulfa-Michael

Additions of α-Branched Enones using a Single Chiral Organic Catalyst. *J. Am. Chem. Soc.* **2011**, *133*, 17934-17941. (d) Gao, J.; Bai, S.; Gao, Q.; Liu, Y.; Yang, Q. Acid controlled diastereoselectivity in asymmetric aldol reaction of cycloketones with aldehydes using enamine-based organocatalysts. *Chem. Commun.* **2011**, *47*, 6716-6718.

(14) (a) Sandmeier, T.; Krautwald, S.; Zipfel, H. F.; Carreira, E. M. Stereodivergent Dual Catalytic α-Allylation of Protected α-Amino- and α-Hydroxyacetaldehydes. *Angew. Chem., Int. Ed.* **2015**, *54*, 14363-14367. (b) Rana, N. K.; Huang, H.; Zhao, J. C.-G. Highly Diastereodivergent Synthesis of Tetrasubstituted Cyclohexanes Catalyzed by Modularly Designed Organocatalysts. *Angew. Chem., Int. Ed.* **2014**, *53*, 7619-7623. (c) Krautwald, S.; Schafroth, M. A.; Sarlah, D.; Carreira, E. M. Stereodivergent α-Allylation of Linear Aldehydes with Dual Iridium and Amine Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 3020-3023. (d) Han, B.; Xie, X.; Huang, W.; Li, X.; Yang, L.; Peng, C. Organocatalytic Morita-Baylis-Hillman/Michael/Acetalization Cascade: Procedure-Controlled Diastereodivergence in the Asymmetric Synthesis of Fully Substituted Tetrahydropyrans. *Adv. Synth. Catal.* **2014**, *356*, 3676-3682. (e) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. Enantio- and Diastereodivergent Dual Catalysis: α-Allylation of Branched Aldehydes. *Science* **2013**, *340*, 1065-1068. (f) Wang, Y.; Han, R.-G.; Zhao, Y.-L.; Yang, S.; Xu, P.-F.; Dixon, D. J. Asymmetric Organocatalytic Relay Cascades: Catalyst-Controlled Stereoisomer Selection in the Synthesis of Functionalized Cyclohexanes. *Angew. Chem., Int. Ed.* **2009**, *48*, 9834-9838. (g) Simmons, B.; Walji, A. M.; MacMillan, D. W. C. Cycle-Specific Organocascade Catalysis: Application to Olefin Hydroamination, Hydro-oxidation, and Amino-oxidation, and to Natural Product Synthesis. *Angew. Chem., Int. Ed.* **2009**, *48*, 4349-4353. (h) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. Enantioselective Organo-Cascade Catalysis. *J. Am. Chem. Soc.* **2005**, *127*, 15051-15053.

(15) (a) Haghshenas, P.; Quail, J. W.; Gravel, M. Substrate-Controlled Diastereoselectivity Reversal in NHC-Catalyzed Cross-Benzoin Reactions Using *N*-Boc-*N*-Bn-Protected α-Amino Aldehydes. *J. Org. Chem.* **2016**, *81*, 12075-12083. (b) Hernández-Toribio, J.; Gómez Arrayás, R.; Carretero, J. C. Substrate-Controlled Diastereoselectivity Switch in Catalytic Asymmetric Direct Mannich Reaction of

Glycine Derivatives with Imines: From *anti*- to *syn*-α,β-Diamino Acids. *Chem. -Eur. J.* **2010**, *16*, 1153-1157. (c) Huber, J. D.; Leighton, J. L. Highly Enantioselective Imine Cinnamylation with a Remarkable Diastereochemical Switch. *J. Am. Chem. Soc.* **2007**, *129*, 14552-14553.

(16) CCDC 1851295 (**3d**) and 1899627 (the TMS-protected group of **4d** was removed) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

(17) (a) Tian, X.; Jiang, K.; Peng, J.; Du, W.; Chen, Y.-C. Organocatalytic Stereoselective Mannich Reaction of 3-Substituted Oxindoles. *Org. Lett.* **2008**, *10*, 3583-3586. (b) Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. Bifunctional-Thiourea-Catalyzed Diastereo- and Enantioselective Aza-Henry Reaction. *Chem. -Eur. J.* **2006**, *12*, 466-476. (c) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. Enantioselective Aza-Henry Reaction Catalyzed by a Bifunctional Organocatalyst. *Org. Lett.* **2004**, *6*, 625-627.

(18) (a) Zhao, B.-L.; Du, D.-M. Organocatalytic Enantioselective Cascade Aza-Michael/Michael Addition Sequence for Asymmetric Synthesis of Chiral Spiro[pyrrolidine-3,3′-oxindole]s. *Asian J. Org. Chem.* **2015**, *4*, 1120-1126. (b) Noole, A.; Ošeka, M.; Pehk, T.; Öeren, M.; Järving, I.; Elsegood, M. R. J.; Malkov, A. V.; Lopp, M.; Kanger, T. 3-Chlorooxindoles: Versatile Starting Materials for Asymmetric Organocatalytic Synthesis of Spirooxindoles. *Adv. Synth. Catal.* **2013**, *355*, 829-835. (c) Li, G.; Liang, T.; Wojtas, L.; Antilla, J. C. An Asymmetric Diels–Alder Reaction Catalyzed by Chiral Phosphate Magnesium Complexes: Highly Enantioselective Synthesis of Chiral Spirooxindoles. *Angew. Chem., Int. Ed.* **2013**, *52*, 4628-4632. (d) Noole, A.; Sucman, N. S.; Kabeshov, M. A.; Kanger, T.; Macaev, F. Z.; Malkov, A. V. Highly Enantio- and Diastereoselective Generation of Two Quaternary Centers in Spirocyclopropanation of Oxindole Derivatives. *Chemistry – A European Journal* **2012**, *18*, 14929-14933. (e) Halskov, K. S.; Johansen, T. K.; Davis, R. L.; Steurer, M.; Jensen, F.; Jørgensen, K. A. Cross-trienamines in Asymmetric Organocatalysis. *J. Am. Chem. Soc.* **2012**, *134*, 12943-12946.