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Diastereo- and Enantioselective [3 + 2] Cycloaddition Reaction of Morita–Baylis–Hillman Carbonates of Isatins with *N*-Phenylmaleimide Catalyzed by Me-DuPhos

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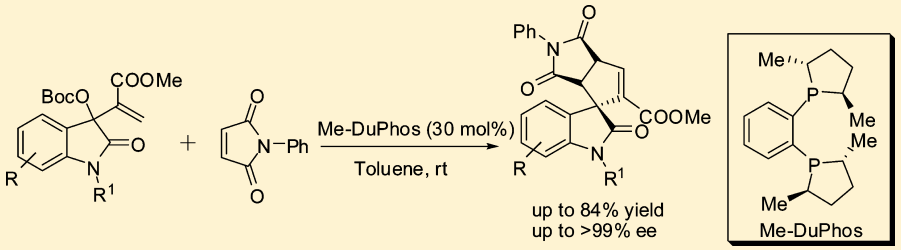
Supporting Information



ABSTRACT: A Me-DuPhos-catalyzed efficient asymmetric [3 + 2] cycloaddition reaction between Morita–Baylis–Hillman carbonates of isatins and *N*-phenylmaleimide has been developed. This reaction constructs three chiral centers in one step to afford spirocyclopentaneoxindoles in good yields (up to 84%) with excellent diastereo- and enantioselectivies (up to 99% ee).

Spirocyclic oxindoles are attractive synthetic targets because their significant biological activity and resulting applications in medicine chemistry.[1] Among many spirooxindole cores, the spirocyclopentaneoxindole scaffold is frequently found in a large number of natural products and drug candidates, for example, sclerotiamide, (−)-paraherquamide A, and citrinalin A.[2] The potential pharmaceutical significance of these enantiomerically pure backbones has led to a demand for the synthetic studies toward this spirocyclic system. It has been addressed in part in developed works,[3] such as cycloaddition reactions[4] and the intramolecular Heck reactions.[5] However, there are only few catalytic asymmetric syntheses for constructing this structural skeleton.[6] The synthesis of the spirocyclopentaneoxindole backbone in regioselective and stereoselective fashion, which contains multichiral centers including the stereogenic quaternary carbon center, is still a challenge.

On the other hand, Mortia–Baylis–Hillman (MBH) adducts have been proven to be suitable precursors for the synthesis of many heterocycles and biologically active molecules owing to their dense functionality.[7] Recently, Lu and co-workers developed cycloaddition of MBH carbonates by a modified allylic phosphonium ylide strategy.[8] Since this pioneering work, several phosphine-catalyzed [3 + 2] annulation of MBH carbonates have been reported.[4d,6b,d,e,9] However, there are only three examples of the asymmetric variants on [3 + 2] annulation.[6b,d,e] Zhou and co-workers[6b] reported the intramolecular asymmetric cylization of MBH carbonates derived from aldehyde and olefins using chiral spirocylic phosphine catalysts. Barbas' and Lu's groups independently reported the intermolecular [3 + 2] annulation of the phosphine–ylide, which was generated from MBH carbonates (A) (Figure 1) derived from aromatic aldehyde and olefins containing oxindole scaffold (B).[6d,e] On the basis of the results of the retro-analysis, we proposed another synthetic way to synthesize optically active spirocyclopentaneoxindoles using MBH carbonates derived from isatins (D) to generate modified allylic phosphonium ylide and electron-deficient olefin (E) for enhancing the structural diversity of optically active spirocyclopentaneoxindole molecule. With the Barbas method, substituent R^1 was from olefin (B) and R^2 (aromatic group) was from MBH carbonate (A), and the ester group was locateds at the C3 position of the cyclopentene ring of the product molecule (C). In our proposed route, the substituents, both R^3 and R^4, were from the electron-deficient olefin (E), while the ester group went to the C2 position of the cyclopentene ring (F). Meanwhile, the three newly formed stereocenters could be constructed by the phosphine-catalyzed [3 + 2] asymmetric cycloaddition reaction. Herein, we report the asymmetric [3 + 2] cycloaddition reaction of MBH carbonates of isatin with *N*-phenylmaleimide catalyzed by chiral diphosphine reagent (Me-DuPhos) for the asymmetric synthesis of spirocyclopentaneoxindole derivatives.

Initially, the model reaction between the MBH carbonate of Bn-protected isatin **2a** and *N*-phenylmaleimide **3** in the presence of catalyst, triarylphosphine (*R*)-BINAP (**1a**), in toluene was carried out at room temperature (Table 1, entry 1).

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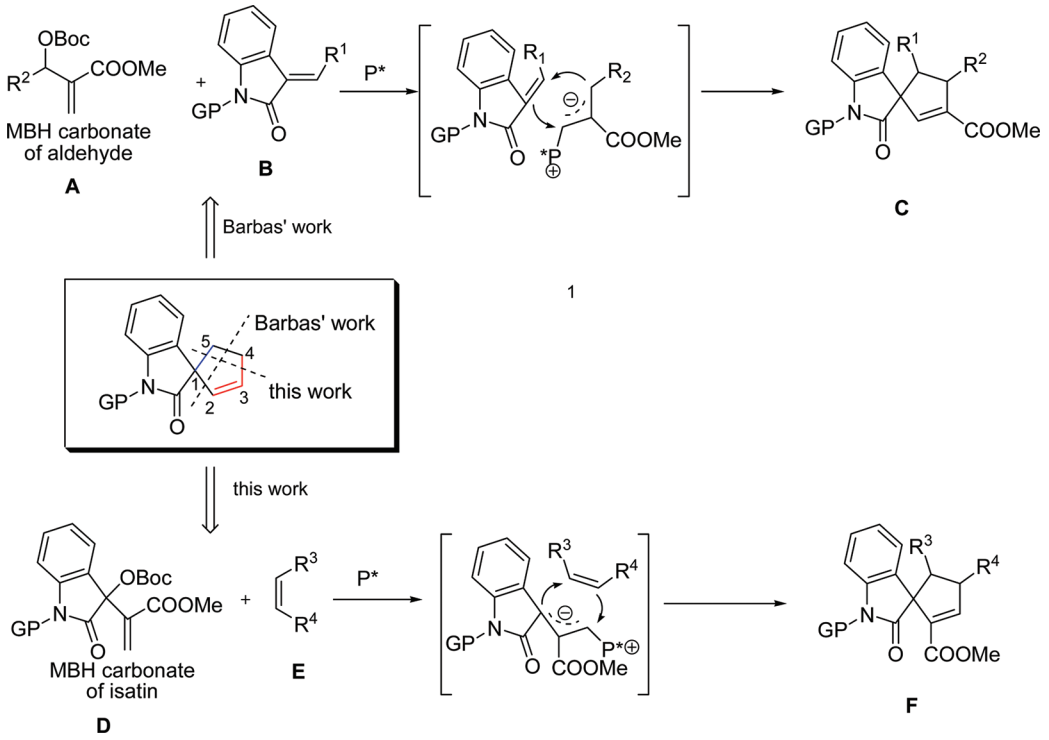

Figure 1. Strategy for spirocyclopentaneoxindole scaffold synthesis.

Unfortunately, no corresponding product was obtained after 60 h. The lack of reaction was probably owing to the weak nucleophilicity of the triarylphosphine. Hence, various more nucleophilic phosphine-containing catalysts were examined in the model reaction under the same conditions. At first, more active diphenylphosphine catalyst **1b** was used instead of **1a** to give the annulation product **4a** in 57% yield, which was a mixture of two diastereoisomers in 1:1 ratio with 23% ee and 19% ee, respectively (entry 2). As indicated by Barbas,[6d] the catalyst **1c** was very efficient in the asymmetric [3 + 2] cycloaddition between methyleneindolinones and allylic compounds. However, when **1c** was employed as a catalyst in the reaction of **2a** with **3** under the same conditions, the enantioselectivity of the product **4a** was moderate (60% ee) (entry 3). To our delight, the reaction of **2a** with **3** in the presence of diphosphine catalyst, (2*R*,5*R*)-Me-DuPhos (**1d**, 20 mol %), proceeded smoothly to afford the annulation product **4a** with excellent diastereoselectivity and high enatioselectivity (91% ee) in spite of the low yield (entry 4). The diastereoselectivity (*syn*, *syn*) in 20:1 dr opposite to the case of catalyst **1c** (*syn*, *anti*) was observed (entry 4 vs 3). Although Me-DuPhos could be considered as a "privileged ligand",[10] which has been widely applied in organometallics-catalyzed asymmetric reactions, to our knowledge no examples of Me-DuPhos directly catalyzed asymmetric reaction have been reported until now.[6d,11] The increase in steric hindrance of the substituent in the phosphine−cyclopentane ring of the catalyst, from methyl (**1d**) to isopropyl (**1e**), resulted in a loss of catalytic ability (entry 5). Changing the linker between two phosphine−cyclopentane rings (**1f** and **1g**) showed poor catalytic abilities as well (entry 6 and 7). In contrast, monophosphine catalyst (**1h**) was used in the reaction of **2a** with **3** under the same conditions, giving the annulation product **4a** in very poor yield (7.5%) with moderate enantioselectivity (entry 8). It was found that the polymerization of **3** occurred under the reaction conditions leading to the low yields of annulation product. The amount of **3** could be increased to 4: 1 (maleimide/MBH carbonate) and the catalyst loading of **1d** could also be increased to 30 mol % totally, which was added in two portions during the reaction course. Thus, the yield of **4a** was increased to 62% and high enantioselectivity (93% ee) still remained (entry 10).

Several MBH carbonates derived from isatins (**2b−d**) were used as substrates in **1d**-catalyzed asymmetric [3 + 2] cycloaddition with **3**, and *N*-Me-substituted MBH carbonates (**2b**) showed results similar to those for the *N*-Bn substituted one (**2a**) (entry 9). For the MBH carbonate **2d** (R^2 = Ac), no reaction was detected (entry 12). Interestingly, if a base such as K_2CO_3 was added in the reaction mixture, high diastereoselectivity (dr 20: 1) and enantioselectivity (91% ee) of the product **4a** were obtained (entry 13). It was attributed to the fact that the addition of a base was helpful in forming the key allylic phosphonium ylide intermediate.[8]

To examine the solvent effects, various solvents, including THF, DCM, ethyl acetate, methanol, toluene, xylene, and so on, were employed in the **1d**-catalyzed asymmetric [3 + 2] cycloaddition reaction (detailed results are listed in the Supporting Information). Toluene was found to be the best solvent for the reaction. The optimized temperature was room temperature.

Under the optimal conditions, a wide range of MBH carbonates (**2b,e−o**) derived from substituted isatins were treated with *N*-phenylmaleimide **3** in toluene at room temperature in the presence of catalyst **1d** to give the corresponding products (**4b,e−o**). The results are summarized in Table 2. In general, excellent diastereoselectivities, even a single diastereoisomer in some case, and high enantionselectivities (up to >99% ee) were obtained (Table 2, entries 2 and 11). It should be noted that the MBH carbonates bearing a nitro group (**2i**) at the C5-position of the indole ring provided

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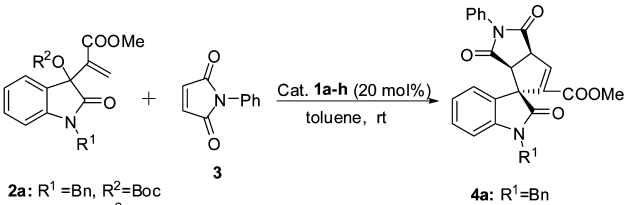
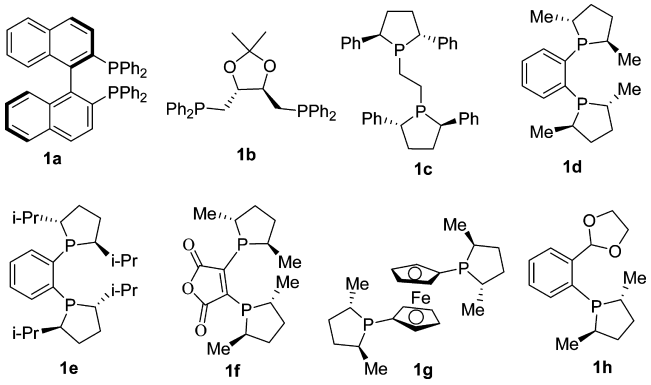
Table 1. Catalytic Reaction of 2 with 3[a]



2a: R^1 =Bn, R^2=Boc
2b: R1=Me, R^2=Boc
2c: R^1=Boc, R^2=Boc
2d: R^1=Me, R^2=Ac

4a: R^1=Bn
4b: R^1=Me
4c: R^1=Boc



entry	catalyst	2	time (h)	product	yield[b] (%)	*syn,syn*/*syn,anti*[c]	ee[d] (%)
1	**1a**	**2a**	60	**4a**	NR[e]		
2	**1b**	**2a**	60	**4a**	57	1:1	23, 19
3	**1c**	**2a**	17	**4a**	70	0:1	60
4	**1d**	**2a**	40	**4a**	24	20:1	91
5	**1e**	**2a**	48	**4a**	NR		
6	**1f**	**2a**	84	**4a**	<20	ND[f]	ND
7	**1g**	**2a**	20	**4a**	85	0:1	−24
8	**1h**	**2a**	72	**4a**	7.5	ND	66
9	**1d**	**2b**	72	**4b**	27	20:1	93
10[g]	**1d**	**2b**	72	**4b**	62	20:1	93
11	**1d**	**2c**	20	**4c**	10	1:0	ND
12	**1d**	**2d**	72	**4b**	NR		
13[h]	**1d**	**2d**	72	**4b**	34	20:1	91

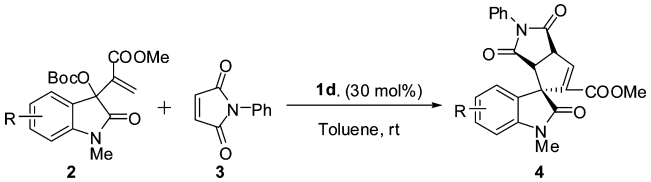
[a]Unless otherwise specified, all reactions were carried out using MBH carbonates (0.1 mmol) and *N*-phenylmaleimide **3** (0.15 mmol) in toluene at room temperature. Catalyst loading: 20 mol %. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Major diastereoisomer's ee determined by chiral HPLC. [e]No reaction was detected. [f]Not determined. [g]Catalyst loading: 30 mol % added in two parts. **3**/**2b** = 4:1. [h]Additional K_2CO_3 (1 equiv) was added.

poor yields (entry 6). Moreover, the electron-withdrawing substitution at the C7-position of the indole ring led to the low yields of the reactions (40−42%) although with very high enantioselectivities (entries 10 and 11).

The X-ray analysis of the crystal structure of the product **4f** (see the Supporting Information) was performed, which deduced the absolute configuration for **4f** as 3a*S*,6a*S*,6*R*. Recently, Chen and co-workers[6c] reported the chiral tertiary amine-catalyzed cycloaddition reaction of **2c** with **3** to give the annulation product **4c**, but with a different configuration 3a*S*,6a*S*,6*S*.

On the basis of the results described above, a plausible transition state was proposed. As shown in Figure 2, Me-DuPhos as diphosphine organocatalyst could activate both MBH carbonate and *N*-phenylmaleimide. One of the phosphine moieties attacked the MBH carbonate to form the

Table 2. Asymmetric [3 + 2] Cycloaddition Reaction of MBH Carbonate 2 with 3[a]



entry	MBH carbonate (R)	time (h)	product (R)	dr (*syn,syn*/*syn,anti*)[b]	yield[c] (%)	ee[d] (%)
1	**2b**, H	48	**4b**, H	20:1	62	93
2	**2e**, 5-F	60	**4e**, 5-F	1:0	84	90
3	**2f**, 5-Cl	60	**4f**, 5-Cl	13:1	61	95
4	**2g**, 5-Br	48	**4g**, 5-Br	15:1	63	91
5	**2h**, 5-I	72	**4h**, 5-I	20:1	62	95
6	**2i**, 5-NO_2	72	**4i**, 5-NO_2	12:1	32	92
7	**2j**, 5-OMe	48	**4j**, 5-OMe	13:1	77	94
8	**2k**, 5-Me	72	**4k**, 5-Me	20:1	50	95
9	**2l**, 5-OCF_3	72	**4l**, 5-OCF_3	13:1	65	88
10	**2m**, 7-F	72	**4m**, 7-F	14:1	40	>99
11	**2n**, 7-Br	72	**4n**, 7-Br	14:1	42	98
12	**2o**, 5,7-di-Me	72	**4o**, 5,7-di-Me	13:1	58	93

[a]Reaction conditions: MBH carbonate **2** (0.1 mmol) and *N*-phenylmaleimide **3** (0.4 mmol) with 30 mol % of catalyst added in two parts in toluene (1 mL). [b]Determined by ^{1}H NMR of the crude product. [c]Isolated yield. [d]Determined by chiral HPLC analysis.

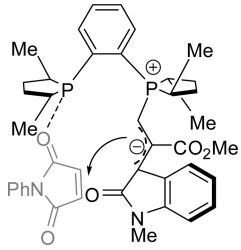


Figure 2. Proposed transition state.

allylic phosphonium ylide, whereas the other one may interact with the carbonyl of the *N*-phenylmaleimide to make two reactants locked in the open U-shaped cleft of the catalyst (see the Supporting Information). The catalyst **1f** gives a poor yield (Table 1, entry 6) probably because the different U-shaped cleft provided by the change of the linker could not match the two reaction substrates. The three new formed chiral centers in the cycloaddition product **4** have the configuration as 3a*S*,6a*S*,6*R*, which is a different diastereoselectivity compared with the one developed by Chen using the tertiary amine catalyst (the configurations as 3a*S*,6a*S*,6*S*). Nevertheless, further studies should be required to elucidate the mechanism and the reason why only the *N*-phenylmaleimide is appropriate for this reaction.

In summary, we have developed a method for the construction of the spirocyclopentaneoxindole scaffold by the chemoselective and asymmetric [3 + 2] cycloaddition reaction between Morita−Baylis−Hillman carbonates of isatins and *N*-phenylmaleimide catalyzed by Me-DuPhos. The reaction provided the corresponding spirooxindoles in excellent diastereoselectivities and high enantioselectivities starting from the easily prepared MBH carbonates of isatins.

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EXPERIMENTAL SECTION

General procedure for [3 + 2] Cycloaddition Reaction between MBH Carboantes 2 and *N*-Phenylmaleimide 3. The phosphine catalyst Me-DuPhos **1d** (0.015 mmol, 0.15 equiv) was added to a solution of MBH carbonates **2** (0.10 mmol, 1.0 equiv) and *N*-phenylmaleimide **3** (0.10 mmol, 1.0 equiv) in toluene (1.0 mL) at room temperature (25 °C). The reaction was monitored by TLC. After the *N*-phenylmaleimide disappeared, additional *N*-phenylmaleimide **3** (0.20 mmol, 2.0 equiv) was added two times. No *N*-phenylmaleimide, Me-DuPhos **1d** (0.015 mmol, 0.15 equiv), or *N*-phenylmaleimide **3** (0.10 mmol, 1.0 equiv) was added again. After 24–48 h, the product was purified by silica gel flash column chromatography (EtOAc/petroleum ether: 2/3).

(3a*S*,3′*R*,6a*S*)-Methyl 1′-methyl-1,2′,3-trioxo-2-phenyl-2,3,3a,6a-tetrahydro-1*H*-spiro[cyclopenta[*c*]pyrrole-4,3′-indoline]-5-carboxylate (4b): white powder, 25 mg, 62% yield; mp 235–237 °C; IR (KBr, cm^{-1}) 3471, 3426, 3059, 2951, 2850, 1716; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.27 (s, 3H), 3.57 (s, 3H), 3.75–3.78 (d, 1H, J = 8.4 Hz), 4.38–4.41 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.4 Hz), 6.89–6.91 (d, 1H, J = 7.8 Hz), 7.06–7.09 (m, 2H), 7.20–7.21 (d, 1H, J = 3.0 Hz), 7.32–7.49 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.9, 52.1, 52.8, 53.6, 63.1, 108.8, 122.3, 123.0, 127.0, 129.0, 129.2, 129.5, 131.5, 131.7, 139.5, 140.7, 144.3, 161.9, 173.3, 174.4, 174.9; ESI-HRMS calcd for $C_{23}H_{18}N_2O_5$ $[M + Na]^+$ 425.1108, found 425.1105. $[\alpha]^{25}_D$ = +158.5 (c 0.2, CH_2Cl_2), 93% ee. The enantiomeric ratio was determined by HPLC on Chiralpak OD column (66.7% 2-propanol/hexane, 0.6 mL/min), t_{major} = 15.6 min, t_{minor} = 31.9 min.

(3a*S*,3′*R*,6a*S*)-Methyl 5′-fluoro-1′-methyl-1,2′,3-trioxo-2-phenyl-2,3,3a,6a-tetrahydro-1*H*-spiro[cyclopenta[*c*]pyrrole-4,3′-indoline]-5-carboxylate (4e): white powder, 35 mg, 84% yield; mp 135–137 °C; IR (KBr, cm^{-1}) 3477, 3415, 3070, 2955, 2929, 1713; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.25 (s, 3H), 3.60 (s, 3H), 3.71–3.74 (d, 1H, J = 8.4 Hz), 4.36–4.48 (dd, 1H, J_1 = 3.0 Hz, J_2 = 8.7 Hz), 6.80–6.87 (m, 2H), 7.02–7.08 (m, 1H), 7.20–7.21 (d, 1H, J = 3.0 Hz), 7.34–7.49 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.0, 52.2, 52.8, 53.5, 63.3, 109.4 (d, $J_{C,F}$ = 8.1 Hz), 110.7 (d, $J_{C,F}$ = 24.8 Hz), 115.7 (d, $J_{C,F}$ = 23.3 Hz), 126.9, 129.0, 129.3, 131.6, 132.7 (d, $J_{C,F}$ = 7.8 Hz), 139.0, 140.3, 141.2, 159.4 (d, $J_{C,F}$ = 240.0 Hz), 161.8, 173.1, 174.2, 174.7; ESI-HRMS calcd for $C_{23}H_{17}FN_2O_5$ $[M + Na]^+$ 443.1014, found 443.1012. $[\alpha]^{25}_D$ = +125.8 (c 1.32, CH_2Cl_2), 90% ee. The enantiomeric ratio was determined by HPLC on Chiralpak OD column (66.7% 2-propanol/hexane, 0.6 mL/min), t_{major} = 14.6 min, t_{minor} = 33.3 min.

(3a*S*,3′*R*,6a*S*)-Methyl 5′-chloro-1′-methyl-1,2′,3-trioxo-2-phenyl-2,3,3a,6a-tetrahydro-1*H*-spiro[cyclopenta[*c*]pyrrole-4,3′-indoline]-5-carboxylate (4f): white powder, 27 mg, 61% yield; mp 140–142 °C; IR (KBr, cm^{-1}) 3475, 3427, 3070, 2953, 2851, 1714; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.25 (s, 3H), 3.60 (s, 3H), 3.72–3.74 (d, 1H, J = 8.4 Hz), 4.37–4.40 (dd, 1H, J_1 = 3.0 Hz, J_2 = 8.4 Hz), 6.81–6.84 (d, 1H, J = 8.4 Hz), 7.08–7.09 (d, 1H, J = 1.8 Hz), 7.20–7.21 (d, 1H, J = 2.7 Hz), 7.31–7.49 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.0, 52.3, 52.8, 53.5, 63.0, 109.7, 123.0, 127.0, 128.2, 129.0, 129.3, 129.5, 131.6, 133.0, 139.0, 141.2, 142.9, 161.8, 173.0, 174.1, 174.6; ESI-HRMS calcd for $C_{23}H_{17}ClN_2O_5$ $[M + Na]^+$ 459.0718, found 459.0718. $[\alpha]^{25}_D$ = +125.3 (c 1.0, CH_2Cl_2), 93% ee. The enantiomeric ratio was determined by HPLC on Chiralpak OD column (66.7% 2-propanol/hexane, 0.6 mL/min), t_{major} = 13.3 min, t_{minor} = 35.9 min.

(3a*S*,3′*R*,6a*S*)-Methyl 5′-bromo-1′-methyl-1,2′,3-trioxo-2-phenyl-2,3,3a,6a-tetrahydro-1*H*-spiro[cyclopenta[*c*]pyrrole-4,3′-indoline]-5-carboxylate (4g): white powder, 30 mg, 63% yield; mp 148–150 °C; IR (KBr, cm^{-1}) 3475, 3426, 3069, 2953, 2925, 1714; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.25 (s, 3H), 3.61 (s, 3H), 3.71–3.74 (d, 1H, J = 8.4 Hz), 4.36–4.40 (dd, 1H, J_1 = 3.0 Hz, J_2 = 8.4 Hz), 6.77–6.80 (d, 1H, J = 8.1 Hz), 7.19–7.22 (m, 2H), 7.34–7.49 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.0, 52.3, 52.8, 53.5, 63.0, 110.3, 115.4, 125.7, 127.0, 129.0, 129.3, 131.6, 132.4, 133.3, 139.0, 141.3, 143.4, 161.8, 173.1, 174.2, 174.5; ESI-HRMS calcd for $C_{23}H_{17}BrN_2O_5$ $[M + Na]^+$ 503.0213, found 503.0214. $[\alpha]^{25}_D$ = +132.7 (c 1.2, CH_2Cl_2), 90% ee. The enantiomeric ratio was determined by HPLC on Chiralpak OD column (66.7% 2-propanol/hexane, 0.6 mL/min), t_{major}= 12.9 min, t_{minor} = 34.4 min.

(3a*S*,3′*R*,6a*S*)-Methyl 5′-iodo-1′-methyl-1,2′,3-trioxo-2-phenyl-2,3,3a,6a-tetrahydro-1*H*-spiro[cyclopenta[*c*]pyrrole-4,3′-indoline]-5-carboxylate (4h): white powder, 33 mg, 62% yield; mp 152–154 °C; IR (KBr, cm^{-1}) 3475, 3425, 3067, 2952, 2851, 1716; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.24 (s, 3H), 3.61 (s, 3H), 3.71–3.74 (d, 1H, J = 8.4 Hz), 4.36–4.40 (dd, 1H, J_1 = 3.0 Hz, J_2 = 8.4 Hz), 6.68–6.70 (d, 1H, J = 8.1 Hz), 7.19–7.20 (d, 1H, J = 3.0 Hz), 7.39–7.49 (m, 6H), 7.64–7.68 (dd, 1H, J_1 = 1.8 Hz, J_2 = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.9, 52.3, 52.8, 53.5, 62.8, 110.8, 126.9, 129.0, 129.3, 131.2, 131.6, 133.7, 138.3, 139.0, 141.2, 144.0, 161.8, 173.1, 174.2, 174.3; ESI-HRMS calcd for $C_{23}H_{17}IN_2O_5$ $[M + Na]^+$ 551.0075, found 551.0074. $[\alpha]^{25}_D$ = +154.2 (c 1.3, CH_2Cl_2), 95% ee. The enantiomeric ratio was determined by HPLC on Chiralpak OD column (66.7% 2-propanol/hexane, 0.6 mL/min), t_{major} = 14.6 min, t_{minor} = 43.4 min.

(3a*S*,3′*R*,6a*S*)-Methyl 1′-methyl-5′-nitro-1,2′,3-trioxo-2-phenyl-2,3,3a,6a-tetrahydro-1*H*-spiro[cyclopenta[*c*]pyrrole-4,3′-indoline]-5-carboxylate (4i): white powder, 15 mg, 32% yield; mp 152–154 °C; IR (KBr, cm^{-1}) 3475, 3422, 3073, 2924, 2854, 1717; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.35 (s, 3H), 3.63 (s, 3H), 3.80–3.83 (d, 1H, J = 8.4 Hz), 4.49–4.53 (dd, 1H, J_1 = 3.0 Hz, J_2 = 8.4 Hz), 7.00–7.01 (d, 1H, J = 8.7 Hz), 7.27–7.28 (d, 1H, J = 3.0 Hz), 7.34–7.37 (m, 2H), 7.42–7.51 (m, 3H), 8.03–8.04 (d, 1H, J = 2.1 Hz), 8.33–8.37 (dd, 1H, J_1 = 2.1 Hz, J_2 = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.3, 29.7, 52.4, 53.0, 53.4, 62.6, 108.39, 118.5, 126.8, 126.9, 129.1, 129.3, 131.4, 132.1, 138.5, 141.9, 143.6, 150.0, 161.8, 172.7, 173.8, 175.3; ESI-HRMS calcd. for $C_{23}H_{17}N_3O_7$ $[M + H]^+$ 448.1139, found 448.1141. $[\alpha]^{25}_D$ = +124.7 (c 0.54, CH_2Cl_2), 93% ee. The enantiomeric ratio was determined by HPLC on Chiralpak OD column (66.7% 2-propanol/hexane, 0.6 mL/min), t_{major} = 28.1 min, t_{minor} = 65.0 min.

(3a*S*,3′*R*,6a*S*)-Methyl 5′-methoxy-1′-methyl-1,2′,3-trioxo-2-phenyl-2,3,3a,6a-tetrahydro-1*H*-spiro[cyclopenta[*c*]pyrrole-4,3′-indoline]-5-carboxylate (4j): white powder, 33 mg, 77% yield; mp 152–154 °C; IR (KBr, cm^{-1}) 3475, 3425, 3068, 2996, 2954, 1712; ^{1}HNMR ($CDCl_3$, 300 MHz) δ 3.25 (s, 3H), 3.59 (s, 3H), 3.74–3.77 (d, 1H, J = 8.4 Hz), 3.79 (s, 3H), 4.38–4.42 (dd, 1H, J_1 = 3.0 Hz, J_2 = 8.4 Hz), 6.70–6.71 (d, 1H, J = 2.4 Hz), 6.79–6.88 (m, 2H), 7.20–7.21 (d, 1H, J = 3.0 Hz), 7.39–7.47 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.0, 52.1, 52.8, 53.7, 55.8, 63.4, 109.1, 110.3, 113.1, 127.0, 128.9, 129.2, 131.7, 132.7, 137.8, 139.4, 140.8, 156.3, 161.9, 173.3, 174.4, 174.6; ESI-HRMS calcd for $C_{24}H_{20}N_2O_6Na$ 455.1214, found 455.1212. $[\alpha]^{25}_D$ = +125.0 (c 1.32, CH_2Cl_2), 94% ee. The enantiomeric ratio was determined by HPLC on Chiralpak OD column (66.7% 2-propanol/hexane, 0.6 mL/min), t_{major} = 17.5 min, t_{minor} = 51.5 min.

(3a*S*,3′*R*,6a*S*)-Methyl 1′,5′-dimethyl-1,2′,3-trioxo-2-phenyl-2,3,3a,6a-tetrahydro-1*H*-spiro[cyclopenta[*c*]pyrrole-4,3′-indoline]-5-carboxylate (4k): white powder, 21 mg, 50% yield; mp 233–235 °C; IR (KBr, cm^{-1}) 3475, 3417, 3067, 2952, 2924, 1781; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 3H), 3.25 (s, 3H), 3.59 (s, 3H), 3.74–3.77 (d, 1H, J = 8.4 Hz), 4.37–4.41 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.1 Hz), 6.78–6.80 (d, 1H, J = 7.8 Hz), 6.91 (s, 1H), 7.12–7.15 (d, 1H, J = 7.8 Hz), 7.19–7.20 (d, 1H, J = 3.0), 7.36–7.49 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.1, 26.9, 52.1, 52.8, 53.7, 63.2, 108.5, 123.2, 127.0, 128.9, 129.2, 129.8, 131.4, 131.7, 132.6, 139.6, 140.6, 141.9, 162.0, 173.4, 174.5, 174.9; ESI-HRMS calcd for $C_{24}H_{20}N_2O_5$ $[M + Na]^+$ 439.1264, found 439.1261. $[\alpha]^{25}_D$ = +117.8 (c 0.8, CH_2Cl_2), 92% ee. The enantiomeric ratio was determined by HPLC on Chiralpak OD column (66.7% 2-propanol/hexane, 0.5 mL/min), t_{major} = 15.2 min, t_{minor} = 37.3 min.

(3a*S*,3′*R*,6a*S*)-Methyl 7′-fluoro-1′-methyl-1,2′,3-trioxo-2-phenyl-2,3,3a,6a-tetrahydro-1*H*-spiro[cyclopenta[*c*]pyrrole-4,3′-indoline]-5-carboxylate (4m): white powder, 17 mg, 40% yield; mp 135–137 °C; IR (KBr, cm^{-1}) 3477, 3419, 3070, 2956, 2926, 1715; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.48 (s, 3H), 3.60 (s, 3H), 3.73–3.76 (d, 1H, J = 8.1 Hz), 4.38–4.41 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.1 Hz), 6.86–6.89 (d, 1H, J = 7.8 Hz), 7.00–7.16 (m, 2H), 7.21(s, 1H), 7.35–7.47 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.3, 29.4, 52.3, 52.8, 53.8, 63.2, 117.6 (d, $J_{C,F}$ = 19.3 Hz), 118.2, 123.6 (d, $J_{C,F}$ = 6.2

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Hz),, 126.4, 126.9, 129.0, 129.3, 131.1, 131.6, 134.2, 139.2, 141.0, 161.9, 173.1, 174.2, 174.7; ESI-HRMS calcd. for $C_{23}H_{17}FN_2O_5$ $[M + Na]^+$ 443.1014, found 443.1015. $[\alpha]^{25}_D$ = +125.8 (*c* 0.3, CH_2Cl_2), >99% ee. The enantiomeric ratio was determined by HPLC on Chiralpak OD column (66.7% 2-propanol/hexane, 0.5 mL/min), t_{major} = 16.6 min, t_{minor} = 50.7 min.

(3a*S*,3′*R*,6a*S*)-Methyl 1′,5′,7′-trimethyl-1,2′,3-trioxo-2-phenyl-2,3,3a,6a-tetrahydro-1*H*-spiro[cyclopenta[*c*]pyrrole-4,3′-indoline]-5-carboxylate (4o): white powder, 25 mg, 58% yield; mp 150−152 °C; IR (KBr, cm^{-1}) 3475, 3424, 3068, 2953, 2922, 1714; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H), 2.55 (s, 3H), 3.51 (s, 3H), 3.60 (s, 3H), 3.69−3.72 (d, 1H, *J* = 8.4 Hz), 4.35−4.39 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.4 Hz), 6.71 (s, 1H), 6.86 (s, 1H), 7.17−7.18 (d, 1H, *J* = 3.0 Hz), 7.36−7.49 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.8, 20.8, 30.2, 52.1, 52.8, 54.1, 62.9, 120.1, 121.0, 127.0, 128.9, 129.2, 131.8, 132.2, 132.4, 133.7, 139.6, 139.8, 140.3, 162.0, 173.4, 174.5, 175.6; ESI-HRMS calcd for $C_{25}H_{22}N_2O_5$ $[M + Na]^+$ 453.1421, found 453.1420. $[\alpha]^{25}_D$ = +128.0 (*c* 0.8, CH_2Cl_2), 92% ee. The enantiomeric ratio was determined by HPLC on Chiralpak OD column (66.7% 2-propanol/hexane, 0.6 mL/min), t_{major} = 11.6 min, t_{minor} = 33.5 min.

(3a*S*,3′*R*,6a*S*)-Methyl 1′-methyl-1,2′,3-trioxo-2-phenyl-5′-(trifluoromethoxy)-2,3,3a,6a-tetrahydro-1*H*-spiro[cyclopenta-[*c*]pyrrole-4,3′-indoline]-5-carboxylate (4l): white powder, 32 mg, 65% yield; mp 118−120 °C; IR (KBr, cm^{-1}) 3481, 3426, 3070, 2955, 2882, 1717; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.28 (s, 3H), 3.61 (s, 3H), 3.74−3.77 (d, 1H, *J* = 8.4 Hz), 4.40−4.44 (dd, 1H, J_1 = 3.0 Hz, J_2 = 8.4 Hz), 6.87−6.90 (d, 1H, *J* = 8.7 Hz), 6.99−6.99 (d, 1H, *J* = 1.2 Hz), 7.22−7.26 (m, 2 Hz), 7.34−7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.0, 51.3, 51.8, 52.5, 62.1, 108.2, 115.4, 119.5 (t, $J_{C,F}$ = 255.0 Hz), 121.6, 125.9, 128.0, 128.3, 130.6, 131.7, 137.9, 140.3, 142.0, 144.0, 160.8, 172.0, 173.1, 173.8; ESI-HRMS calcd for $C_{24}H_{17}F_3N_2O_6$ $[M + Na]^+$ 509.0931, found 509.0928. $[\alpha]^{25}_D$ = +72.1 (*c* 1.1, CH_2Cl_2), 88% ee. The enantiomeric ratio was determined by HPLC on Chiralpak OD column (66.7% 2-propanol/hexane, 0.6 mL/min), t_{major} = 9.6 min, t_{minor} = 21.7 min.

(3a*S*,3′*R*,6a*S*)-Methyl 7′-bromo-1′-methyl-1,2′,3-trioxo-2-phenyl-2,3,3a,6a-tetrahydro-1*H*-spiro[cyclopenta[*c*]pyrrole-4,3′-indoline]-5-carboxylate (4n): white powder, 20 mg, 42% yield; mp 118−120 °C; IR (KBr, cm^{-1}) 3477, 3424, 3071, 2955, 2925, 1715; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.61 (s, 3H), 3.65 (s, 3H), 3.70−3.73 (d, 1H, *J* = 8.4 Hz), 4.38−4.41 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.4 Hz), 6.87−6.90 (d, 1H, *J* = 8.7 Hz), 6.91−6.94 (d, 1H, *J* = 7.8 Hz), 7.00−7.01 (m, 1 Hz), 7.20−7.21 (d, 1H, J = 2.7 Hz), 7.35−7.50 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.5, 52.3, 52.8, 54.0, 62.8, 103.1, 121.5, 124.1, 126.9, 129.0, 129.3, 131.6, 134.4, 135.2, 139.3, 141.0, 141.7, 161.8, 173.0, 174.1, 175.5; ESI-HRMS calcd. for $C_{23}H_{17}BrN_2O_5$ $[M + Na]^+$ 503.0213, found 503.0214. $[\alpha]^{25}_D$ = +67.5 (*c* 0.5, CH_2Cl_2), 98% ee. The enantiomeric ratio was determined by HPLC on Chiralpak OD column (66.7% 2-propanol/hexane, 0.5 mL/min), t_{major} = 18.3 min, t_{minor} = 39.8 min.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C spectra for compounds **4b,e−o**, X-ray crystallographic data (CIF file), and additional reaction data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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