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ULTRAFAST AND DIASTEREOSELECTIVE SYNTHESIS OF 3-SPIROCYCLOPROPYL-2-OXINDOLES BEARING THREE CONTINUOUS ALL-CARBON QUATERNARY CENTERS

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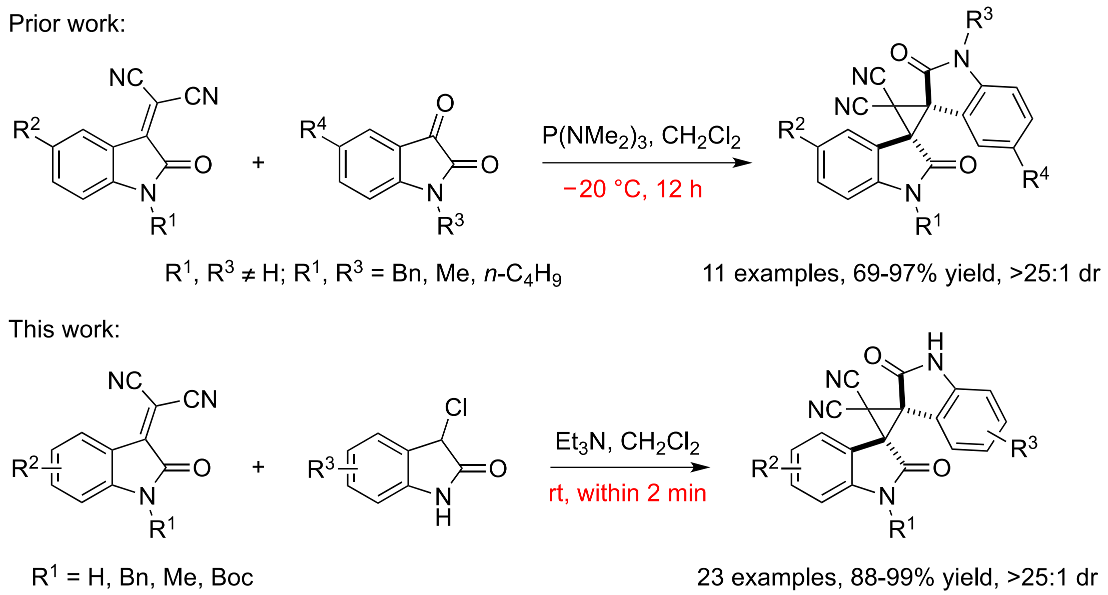
Abstract – Synthesis of 3-spirocyclopropyl-2-oxindoles bearing three continuous all-carbon quaternary centers by the domino Michael-alkylation reaction between 3-chlorooxindole and isatylidenemalononitrile is described. Remarkably, the reaction proceeded in exceptionally high efficiency (up to 99% yield within 2 min) and excellent diastereoselectivity (>25:1 dr for all the examples).

3,3'-Disubstituted oxindole is a key structural motif widely present in natural products and biologically active compounds.[1-3] In the meantime, the cyclopropyl group is another fragment frequently found in pharmaceutical drugs.[4,5] Not surprisingly, combination of these two moieties can lead to molecules (i.e. 3-spirocyclopropyl-2-oxindoles) possessing promising biological activities.[6-9] Accordingly, development of new methods for the synthesis of diverse spirocyclopropyloxindoles is highly desirable, and much efforts have been devoted toward this end in recent years.[10-13]

Great successes have been achieved for the preparation of various 3-spirocyclopropyl-2-oxindoles,[14-18] however, synthesis of 3-spirocyclopropyl-2-oxindoles bearing multiple all-carbon quaternary centers is much less explored.[19-24] In particular, 3-spirocyclopropyl-2-oxindoles bearing three continuous all-carbon quaternary centers[25] represents one of the most challenging spirooxindoles to access. One successful example was reported by the group of Yan and Han: diastereoselective synthesis of fully substituted 3-spirocyclopropyl-2-oxindoles was achieved via cyclopropanation reaction of isatins with isatylidene-malononitriles promoted by hexamethylphosphorous triamide.[26] The products obtained in this reaction contain not only the 3-spirocyclopropyl-2-oxindoles bearing three continuous all-carbon quaternary centers, but also the biologically important bisoxindole structure,[27,28] thus is of great interest for further studies. Herein, we would like to report an alternative approach to the synthesis of this type of highly congested cyclopropyl-bisoxindoles. Compared with the prior route, the new method reported here features mild condition, high efficiency, and a broad substrate scope (Scheme 1).

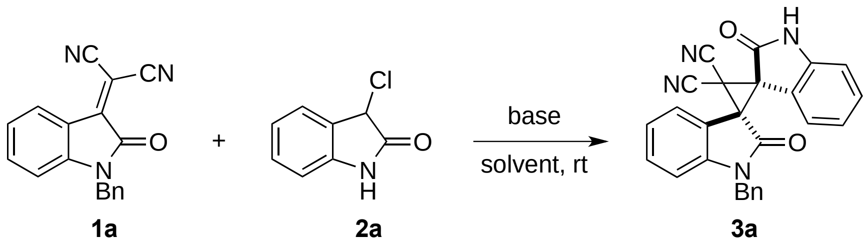


Scheme 1. Divergent approaches to the synthesis of targeted 3-spirocyclopropyl-2-oxindoles

3-Chlorooxindoles are easily prepared from readily available nitroolefins,[29,30] and they proved to be versatile synthons in the synthesis of diverse oxindole products. In particular, synthesis of spirocyclopropyloxindoles from 3-chlorooxindoles, via either the stepwise or domino Michael addition-alkylation reaction, proved to be feasible.[23,31-34] We then envisaged that a base-promoted domino Michael-alkylation reaction of 3-chlorooxindole with isatylidenemalononitriles may furnish the desired 3-spirocyclopropyl-2-oxindoles. However, there are several challenges to overcome in the projected reaction. First, the reaction may stop at the Michael addition step without forming the cyclopropyl ring.[35,36] Moreover, control of the diastereoselectivity can be difficult as two quaternary stereogenic centers are formed simultaneously.

With all these challenges in mind, we commenced our investigation with the model reaction between isatylidenemalononitriles **1a** and 3-chlorooxindole **2a**, and the results are summarized in Table 1. In the first set of the experiments, different bases were evaluated for the domino Michael addition-alkylation reaction, and we were pleased to find that both inorganic and organic bases efficiently promoted the reaction to furnish the desired products in high yields with excellent diastereoselectivities (entries 1–4). A further study on the effect of different solvents showed that diverse solvents could be used in the reaction system without compromising the reaction efficiency (entries 5–7). At last we found that the reaction could complete within two minutes using Et_3N as the base and dichloromethane as the solvent at room temperature, and the product **3a** was obtained in 96% yield as a single diastereomer (entry 8).

Table 1. Domino Michael-alkylation reaction of isatylidenemalononitrile **1a** with 3-chlorooxindole **2a**[a]

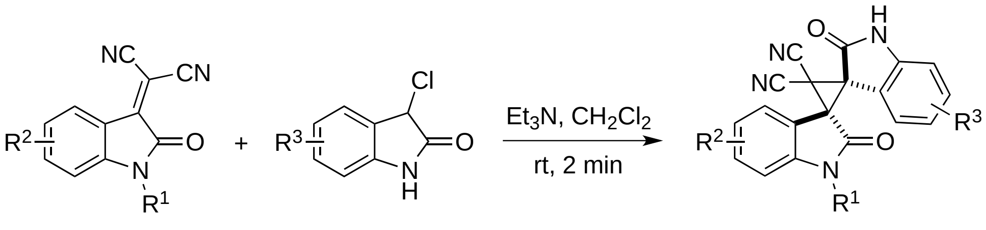


Entry	Conditions	Yield of **3a** %[b]	dr[c]
1	K_2CO_3 (2.0 equiv), CH_2Cl_2, 30 min	91	>25:1
2	DBU (2.0 equiv), CH_2Cl_2, 30 min	92	>25:1
3	DIPEA (2.0 equiv), CH_2Cl_2, 30 min	95	>25:1
4	Et_3N (2.0 equiv), CH_2Cl_2, 30 min	97	>25:1
5	Et_3N (2.0 equiv), acetone, 30 min	97	>25:1
6	Et_3N (2.0 equiv), DMF, 30 min	95	>25:1
7	Et_3N (2.0 equiv), EtOAc, 30 min	95	>25:1
8	Et_3N (3.0 equiv), CH_2Cl_2, 2 min	96	>25:1

[a]Reagents and conditions: **1a** (0.24 mmol), **2a** (0.20 mmol), and base in solvent (1.0 mL) at room temperature for 30 min. [b]Isolated yield of **3a**. [c]Determined by ^1H NMR.

With the optimal reaction conditions in hand, we continued to examine the generality of the reaction (Table 2). Different isatylidenemalononitriles could be employed, including those substrates bearing substitutions with different electronic properties, different halogen substitutions, as well as substitutions at different positions, and universally high yields and perfect diastereoselectivities were attainable (entries 1–11). Besides, the reaction was also applicable to 3-chlorooxindoles containing different substitutions (entries 12–14). The reactions between substituted isatylidenemalononitriles and substituted 3-chlorooxindoles worked equally well under optimal conditions (entries 15–20). Moreover, isatylidene-malononitriles bearing other N-protecting groups than benzyl group were also well-tolerated (entries 21–22). Finally, isatylidenemalononitrile without any protecting group was also found to be good substrate, and the reaction proceeded smoothly to furnish the desired product **3w** in high efficiency with perfect diastereoselectivity (entry 23). The structure and the relative configuration of the products were confirmed by single-crystal X-ray diffraction analysis of **3w** (Figure 1).[37]

Table 2. Scope of the domino Michael-alkylation reaction of isatylidenemalononitrile **1** with 3-chlorooxindole **2**[a]



Entry	**3** R^1/R^2/R^3	Yield of **3** %[b]	dr[c]
1	**3a** Bn/H/H	96	>25:1
2	**3b** Bn/5-Br/H	95	>25:1
3	**3c** Bn/5-Cl/H	98	>25:1
4	**3d** Bn/5-Me/H	96	>25:1
5	**3e** Bn/5-OMe/H	96	>25:1
6	**3f** Bn/6-Br/H	99	>25:1
7	**3g** Bn/6-Cl/H	97	>25:1
8	**3h** Bn/6-OMe/H	90	>25:1
9	**3i** Bn/7-Br/H	91	>25:1
10	**3j** Bn/7-Cl/H	91	>25:1
11	**3k** Bn/7-Me/H	91	>25:1
12	**3l** Bn/H/5-Me	94	>25:1
13	**3m** Bn/H/6-Br	95	>25:1
14	**3n** Bn/H/6-Cl	98	>25:1
15	**3o** Bn/5-Br/6-Cl	94	>25:1
16	**3p** Bn/5-Me/6-Cl	97	>25:1
17	**3q** Bn/6-Cl/6-Cl	99	>25:1
18	**3r** Bn/6-OMe/6-Cl	98	>25:1
19	**3s** Bn/7-Cl/6-Cl	99	>25:1
20	**3t** Bn/7-Me/6-Cl	98	>25:1
21	**3u** Me/H/H	98	>25:1
22	**3v** Boc/H/H	88	>25:1
23	**3w** H/H/H	98	>25:1

[a]Reagents and conditions: **1** (0.24 mmol), **2** (0.20 mmol), and Et_3N (0.60 mmol) in CH_2Cl_2 (1.0 mL) at room temperature for 2 min. [b]Isolated yield of **3**. [c]Determined by ^{1}H NMR.

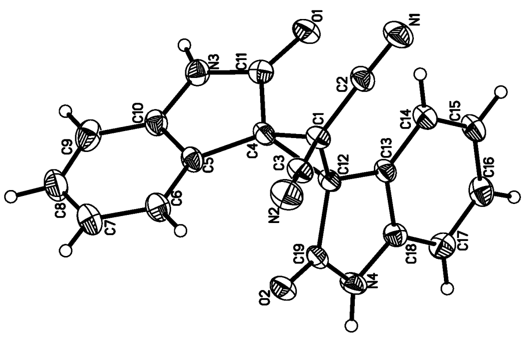


Figure 1. ORTEP-drawing of the crystal structure of product **3w**

In summary, we have developed a highly efficient synthesis of 3-spirocyclopropyl-2-oxindoles bearing three continuous all-carbon quaternary centers. Compared with the prior route, the new method reported here features mild condition, high efficiency, and broad substrate scope. Further studies on the synthesis of other types of spirooxindoles based on current system are ongoing in our laboratory.

EXPERIMENTAL

General Information

^{1}H and ^{13}C NMR spectra were recorded at 300 MHz (^{1}H NMR) and 75 or 126 MHz (^{13}C NMR). Chemical shifts were reported in ppm from the solvent resonance as the internal standard (DMSO-*d*$_6$: 2.50 ppm, 39.5 ppm). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br (broad). Coupling constants were reported in Hertz (Hz). HRMS were recorded on an APEXIII 7.0 TESLA FTMS (ESI resource).

All commercially available reagents were used without further purification. Analytical thin layer chromatography was performed on 0.20 mm silica gel plates. Silica gel (200-300 mesh) was used for flash chromatography.

General procedure for the synthesis of the 3-spirocyclopropyl-2-oxindoles

To a solution of isatylidenemalononitrile **1** (0.2 mmol, 1 eq) and TEA (0.6 mmol, 3 eq) in 1.0 mL DCM was added 3-chlorooxindole **2** (0.24 mmol, 1.2 eq) at room temperature. Then the mixture was stirred vigorously at room temperature for 2 min. After completion of the reaction, the mixture was diluted with DCM, washed with water and saturated brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 5:1 to 1:1) to afford target product **3**.

Characterization of the products

1-Benzyl-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3a):

95% yield, white solid, **mp** 237-239 ºC; **^{1}H NMR** (300 MHz, DMSO-*d*$_6$) δ 11.20 (s, 1H), 8.25-8.20 (m, 2H), 7.40-7.24 (m, 7H), 7.16-7.06 (m, 2H), 6.99-6.93 (m, 2H), 4.97 (d, *J* = 16.2 Hz, 1H), 4.90 (d, *J* = 15.9 Hz, 1H); **^{13}C NMR** (300 MHz, DMSO-*d*$_6$) δ 168.2, 167.1, 144.1, 143.8, 136.1, 130.7, 130.4, 129.0, 128.4, 128.1, 128.0, 127.8, 122.2, 121.6, 119.9, 119.5, 110.5, 110.1, 110.0, 45.7, 45.1, 44.0, 25.6; **HRMS** (ESI) found: *m/z* 439.1169 [M+Na]$^+$; calcd. for $C_{26}H_{16}N_4NaO_2^+$ 439.1165.

1-Benzyl-5-bromo-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3b):

95% yield, white solid, **mp** 244-246 ºC; **^{1}H NMR** (300 MHz, DMSO-*d*$_6$) δ 11.21 (s, 1H), 8.40 (s, 1H), 8.20 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.40-7.25 (m, 6H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.97-6.90 (m, 2H), 4.97 (d, *J* = 15.9 Hz, 1H), 4.88 (d, *J* = 16.2 Hz, 1H); **^{13}C NMR** (75 MHz, DMSO-*d*$_6$) δ 168.3, 166.8, 143.8, 143.6, 135.7, 132.8, 130.8, 129.0, 128.4, 128.0, 127.8, 122.0, 121.7, 119.9, 114.0, 111.7, 110.5, 109.9, 100.0, 46.0, 44.6, 44.1, 26.0; **HRMS** (ESI) found: *m/z* 517.0278 $[M+Na]^+$; calcd. for $C_{26}H_{15}{}^{79}BrN_4NaO_2^+$ 517.0271; *m/z* 519.0254 $[M+Na]^+$; calcd. for $C_{26}H_{15}{}^{81}BrN_4NaO_2^+$ 519.0250.

1-Benzyl-5-chloro-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3c):

98% yield, white solid, **mp** 250-252 ºC; **^{1}H NMR** (300 MHz, DMSO-*d$_6$*) δ 11.21 (s, 1H), 8.27 (d, *J* = 2.1 Hz, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 7.45 (dd, *J* = 8.4 Hz and 2.1 Hz), 7.43-7.25 (m, 6H), 7.08 (td, *J* = 7.8 Hz and 0.9 Hz, 1H), 6.98-6.94 (m, 2H), 4.96 (d, *J* = 15.9 Hz, 1H), 4.88 (d, *J* = 16.2 Hz, 1H); **^{13}C NMR** (75 MHz, DMSO-*d$_6$*) δ 168.3, 166.9, 143.8, 143.2, 135.7, 130.8, 130.0, 129.0, 128.4, 128.0, 127.8, 126.2, 121.7, 121.6, 119.9, 111.2, 110.5, 109.9, 46.0, 44.7, 44.2, 26.0; **HRMS** (ESI) found: *m/z* 473.0777 $[M+Na]^+$; calcd. for $C_{26}H_{15}ClN_4NaO_2^+$ 473.0776.

1-Benzyl-5-methyl-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3d):

96% yield, white solid, **mp** 244-246 ºC; **^{1}H NMR** (300 MHz, DMSO-*d$_6$*) δ 11.15 (s, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 8.06 (s, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.30-7.23 (m, 5H), 7.18 (d, *J* = 8.1 Hz, 1H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 4.94 (d, *J* = 15.9 Hz, 1H), 4.86 (d, *J* = 16.2 Hz, 1H), 2.30 (s, 3H); **^{13}C NMR** (75 MHz, DMSO-*d$_6$*) δ 168.1, 166.9, 143.7, 141.7, 136.1, 131.1, 130.7, 130.6, 129.0, 128.8, 128.3, 128.0, 127.8, 121.6, 119.9, 119.4, 110.5, 110.1, 110.0, 109.7, 45.6, 45.1, 44.0, 25.4, 21.5; **HRMS** (ESI) found: *m/z* 453.1332 $[M+Na]^+$; calcd. for $C_{27}H_{18}N_4NaO_2^+$ 453.1322.

1-Benzyl-5-methoxy-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3e):

96% yield, white solid, **mp** 232-234 ºC; **^{1}H NMR** (300 MHz, DMSO-*d$_6$*) δ 11.19 (s, 1H), 8.23 (d, *J* = 8.1 Hz, 1H), 7.94 (s, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.31-7.24 (m, 5H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.98-6.86 (m, 3H), 4.94 (d, *J* = 15.9 Hz, 1H), 4.86 (d, *J* = 15.9 Hz, 1H), 3.73 (s, 3H); **^{13}C NMR** (75 MHz, DMSO-*d$_6$*) δ 168.3, 166.9, 143.8, 143.2, 135.7, 130.8, 120.0, 129.0, 128.4, 128.0, 127.8, 126.2, 121.7, 121.6, 119.9, 111.2, 110.5, 109.9, 46.0, 44.7, 44.2, 26.0; **HRMS** (ESI) found: *m/z* 447.1435 $[M+H]^+$; calcd. for $C_{27}H_{19}N_4O_3^+$ 447.1452.

1-Benzyl-6-bromo-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3f):

99% yield, white solid, **mp** 209-211 ºC; **^{1}H NMR** (300 MHz, DMSO-*d$_6$*) δ 11.20 (s, 1H), 8.20-8.12 (m, 2H), 7.40-7.27 (m, 7H), 7.21 (s, 1H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 4.97 (d, *J* = 16.2 Hz, 1H), 4.80 (d, *J* = 15.9 Hz, 1H); **^{13}C NMR** (126 MHz, DMSO-*d$_6$*) δ 167.5, 166.4, 145.1, 143.1, 135.1, 130.1, 128.4, 127.36, 127.1, 124.2, 123.0, 121.0, 119.1, 118.3, 112.3, 109.9, 109.2, 45.2, 44.3, 43.5, 24.9; **HRMS** (ESI) found: *m/z* 517.0278 $[M+Na]^+$; calcd. for $C_{26}H_{15}{}^{79}BrN_4NaO_2^+$ 517.0271.

1-Benzyl-6-chloro-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3g):

97% yield, yellow solid, **mp** 234-236 ºC; **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.20 (s, 1H), 8.22-8.17 (m, 2H), 7.40-7.20 (m, 7H), 7.10-7.05 (m, 2H), 6.94 (d, J = 7.5 Hz, 1H), 4.97 (d, J = 15.9 Hz, 1H), 4.90 (d, J = 16.2 Hz, 1H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 167.5, 166.5, 145.1, 143.2, 135.1, 134.6, 130.1, 128.8, 128.4, 127.6, 127.4, 127.1, 121.2, 121.0, 119.1, 117.9, 109.9, 109.5, 109.2, 45.2, 44.2, 43.5, 24.9; **HRMS** (ESI) found: *m/z* 473.0779 [M+Na]$^+$; calcd. for $C_{26}H_{15}ClN_4NaO_2^+$ 473.0776.

1-Benzyl-6-methoxy-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3h):

90% yield, yellow solid, **mp** 183-185 ºC; **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.17 (s, 1H), 8.21-8.12 (m, 2H), 7.39-7.24 (m, 6H), 7.08 (t, J = 7.8 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.69 (dd, J = 8.7 Hz and 2.4 Hz, 1H), 6.61 (d, J = 2.1 Hz, 1H), 4.96 (d, J = 16.2 Hz, 1H), 4.89 (d, J = 15.9 Hz, 1H), 3.73 (s, 3H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 168.3, 167.5, 161.5, 145.5, 143.7, 136.1, 130.6, 129.3, 129.2, 129.1, 128.3, 128.0, 127.9, 121.6, 119.9, 110.9, 110.5, 110.1, 106.4, 97.9, 56.0, 45.4, 45.2, 44.0, 25.3; **HRMS** (ESI) found: *m/z* 447.1438 [M+H]$^+$; calcd. for $C_{27}H_{19}N_4O_3^+$ 447.1452.

1-Benzyl-7-bromo-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3i):

91% yield, yellow solid, **mp** 234-236 ºC; **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.19 (s, 1H), 8.31 (d, J = 7.8 Hz, 1H), 8.12 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.29-7.17 (m, 5H), 7.12-7.02 (m, 2H), 6.94 (d, J = 7.8 Hz, 1H), 5.33 (d, J = 20.1 Hz, 1H), 5.23 (d, J = 17.1 Hz, 1H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 167.5, 167.2, 143.2, 140.8, 136.8, 135.4, 130.2, 128.1, 127.5, 126.7, 126.5, 125.9, 122.9, 122.3, 121.0, 119.1, 109.9, 109.2, 101.3, 45.5, 45.0, 43.9, 25.1; **HRMS** (ESI) found: *m/z* 517.0274 [M+Na]$^+$; calcd. for $C_{26}H_{15}{}^{79}BrN_4NaO_2^+$ 517.0271; *m/z* 519.0258 [M+Na]$^+$; calcd. for $C_{26}H_{15}{}^{81}BrN_4NaO_2^+$ 519.0250.

1-Benzyl-7-chloro-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3j):

91% yield, yellow solid, **mp** 241-243 ºC; **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.22-8.17 (m, 2H), 7.40-7.20 (m, 7H), 7.10-7.05 (m, 2H), 6.94 (d, J = 7.5 Hz, 1H), 4.97 (d, J = 16.2 Hz, 1H), 4.90 (d, J = 15.9 Hz, 1H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 168.0, 143.8, 140.1, 137.6, 132.6, 130.8, 128.8, 128.2, 127.4, 126.8, 126.5, 123.2, 122.8, 121.6, 119.8, 114.7, 110.5, 110.0, 46.1, 45.9, 44.6, 26.0; **HRMS** (ESI) found: *m/z* 473.0779 [M+Na]$^+$; calcd. for $C_{26}H_{15}ClN_4NaO_2^+$ 473.0776.

1-Benzyl-7-methyl-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3k):

91% yield, yellow solid, **mp** 220-222 ºC; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 11.16 (s, 1H), 8.14 (d, J = 7.2

Hz, 2H), 7.39-7.24 (m, 4H), 7.17-7.11 (m, 3H), 7.08-7.02 (m, 2H), 6.94 (d, J = 7.8 Hz, 1H), 5.17 (d, J = 17.1 Hz, 1H), 5.11 (d, J = 18.6 Hz, 1H), 2.19 (s, 3H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 168.0, 143.7, 142.1, 137.8, 134.3, 130.7, 129.2, 128.2, 127.6, 126.1, 125.8, 122.1, 121.6, 120.2, 120.0, 119.9, 110.4, 110.1, 60.2, 45.7, 44.8, 25.6, 18.8; **HRMS** (ESI) found: *m/z* 453.1332 [M+Na]$^+$; calcd. for $C_{27}H_{18}N_4NaO_2^+$ 453.1322.

1-Benzyl-5''-methyl-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3l):

94% yield, white solid, **mp** 235-237 ºC; **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.09 (s, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.06 (s, 1H), 7.38-7.25 (m, 6H), 7.19 (d, J = 7.8 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 4.98 (d, J = 16.2 Hz, 1H), 4.89 (d, J = 16.2 Hz, 1H), 2.31 (s, 3H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 168.2, 167.1, 144.1, 141.3, 136.0, 131.0, 130.4, 130.3, 129.0, 128.2, 128.0, 127.8, 122.2, 119.9, 119.5, 110.2, 110.1, 110.1, 110.0, 45.7, 45.1, 44.1, 25.5, 21.6; **HRMS** (ESI) found: *m/z* 453.1328 [M+Na]$^+$; calcd. for $C_{27}H_{18}N_4NaO_2^+$ 453.1322.

1-Benzyl-6''-bromo-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3m):

95% yield, white solid, **mp** 234-236 ºC; **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.29 (s, 1H), 8.21 (d, J = 7.8 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.39-7.23 (m, 7H), 7.15-7.07 (m, 2H), 6.97 (d, J = 7.8 Hz, 1H), 4.92 (s, 2H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 168.2, 167.1, 145.4, 144.2, 136.0, 130.5, 130.0, 129.0, 128.1, 128.0, 127.8, 124.2, 123.7, 122.2, 119.6, 119.5, 113.1, 110.0, 45.5, 45.2, 44.1, 25.7; **HRMS** (ESI) found: *m/z* 517.0276 [M+Na]$^+$; calcd. for $C_{26}H_{15}{}^{79}BrN_4NaO_2^+$ 517.0271.

1-Benzyl-6''-chloro-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3n):

98% yield, white solid, **mp** 244-246 ºC; **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.31 (s, 1H), 8.23-8.16 (m, 2H), 7.39-7.25 (m, 6H), 7.19-7.09 (m, 2H), 6.98-6.94 (m, 2H), 4.92 (s, 2H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 168.3, 167.1, 145.3, 144.2, 136.0, 135.2, 130.5, 129.7, 129.0, 128.1, 128.0, 127.8, 122.2, 121.3, 119.5, 119.1, 110.4, 110.0, 45.4, 45.2, 44.1, 25.8; **HRMS** (ESI) found: *m/z* 473.0775 [M+Na]$^+$; calcd. for $C_{26}H_{15}ClN_4NaO_2^+$ 473.0776.

1-Benzyl-5-bromo-6''-chloro-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3o):

94% yield, white solid, **mp** 214-216 ºC; **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.33 (s, 1H), 8.38 (s, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.33-7.23 (m, 5H), 7.16 (d, J = 8.7 Hz, 1H), 6.96 (s, 1H), 6.90 (d, J = 8.4 Hz, 1H), 4.95 (d, J = 15.9 Hz, 1H), 4.88 (d, J = 16.5 Hz, 1H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 168.4, 166.9, 145.4, 143.7, 135.7, 135.2, 132.9, 130.7, 129.7, 129.0, 128.0, 127.8, 122.0, 121.3, 119.2, 114.0, 111.7, 110.4, 109.9, 45.7, 44.8, 44.2, 26.2; **HRMS** (ESI) found: *m/z* 550.9903

[M+Na]$^+$; calcd. for $C_{26}H_{14}{}^{79}BrClN_4NaO_2{}^+$ 550.9881.

1-Benzyl-6''-chloro-5-methyl-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3p):

97% yield, white solid, **mp** 235-237 ºC; **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.27 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.05 (s, 1H), 7.31-7.24 (m, 5H), 7.18-7.15 (m, 2H), 6.95 (s, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 4.93 (d, *J* = 17.1 Hz, 1H), 4.87 (d, *J* = 17.4 Hz, 1H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 168.2, 167.0, 145.3, 141.8, 136.1, 135.2, 131.1, 130.6, 129.7 129.0, 128.8, 128.0, 127.8, 121.3, 119.4, 119.1, 110.4, 110.0, 109.9, 109.8, 45.4, 45.2, 44.1, 25.6, 21.5; **HRMS** (ESI) found: *m/z* 487.0922 [M+Na]$^+$; calcd. for $C_{27}H_{17}ClN_4NaO_2$ 487.0932.

1-Benzyl-6,6''-dichloro-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3q):

99% yield, white solid, **mp** 240-242 ºC; **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.32 (s, 1H), 8.25 (d, *J* = 7.8 Hz, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.28-7.12 (m, 7H), 6.95 (s, 1H), 5.26 (d, *J* = 17.7 Hz, 1H), 5.20 (d, *J* = 18.0 Hz, 1H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 167.3, 144.7, 139.6, 136.9, 134.7, 132.0, 128.9, 128.1, 126.8, 125.9, 122.6, 122.1, 120.6, 118.3, 114.2, 109.8, 109.1, 45.3, 45.2, 44.1, 25.3; **HRMS** (ESI) found: *m/z* 507.0396 [M+Na]$^+$; calcd. for $C_{26}H_{14}Cl_2N_4NaO_2{}^+$ 507.0386.

1-Benzyl-6''-chloro-6-methoxy-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3r):

98% yield, white solid, **mp** 239-241 ºC; **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.30 (s, 1H), 8.18-8.10 (m, 2H), 7.32-7.28 (m, 5H), 7.16 (d, *J* = 8.7 Hz, 1H), 6.94 (s, 1H), 6.69 (d, *J* = 8.7 Hz, 1H), 6.70 (s, 1H), 4.95 (d, *J* = 16.8 Hz, 1H), 4.89 (d, *J* = 16.5 Hz, 1H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 168.4, 167.6, 161.6, 145.6, 145.3, 136.1, 135.1, 129.6, 129.3, 129.1, 127.9, 121.3, 119.1, 110.9, 110.4, 110.0, 106.4, 97.9, 56.0, 45.4, 45.1, 44.0, 25.5; **HRMS** (ESI) found: *m/z* 503.0893 [M+Na]$^+$; calcd. for $C_{27}H_{17}ClN_4NaO_3{}^+$ 503.0881.

1-Benzyl-6'',7-dichloro-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3s):

99% yield, white solid, **mp** 254-256 ºC; **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.33 (s, 1H), 8.17 (m, 2H), 7.34-7.14 (m, 7H), 7.09 (s, 1H), 6.94 (s, 1H), 4.96 (d, *J* = 16.8 Hz, 1H), 4.91 (d, *J* = 16.8 Hz, 1H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 167.6, 166.6, 145.2, 144.7, 135.0, 134.7, 129.0, 128.7, 128.4, 127.4, 127.1, 121.2, 120.7, 118.3, 117.9, 109.8, 109.5, 109.2, 44.9, 44.3, 43.6, 25.1; **HRMS** (ESI) found: *m/z* 507.0393 [M+Na]$^+$; calcd. for $C_{26}H_{14}Cl_2N_4NaO_2{}^+$ 507.0386.

1-Benzyl-6''-chloro-7-methyl-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3t):

98% yield, yellow solid, **mp** 241-243 ºC; **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.29 (s, 1H), 8.13 (d, *J* =

8.4 Hz, 2H), 7.31-7.27 (m, 3H), 7.20-7.12 (m, 4H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.95 (s, 1H), 5.17 (d, *J* = 19.2 Hz, 1H), 5.11 (d, *J* = 18.0 Hz, 1H), 2.19 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-*d$_6$*) δ 167.5, 167.3, 144.6, 141.5, 137.1, 134.6, 133.8, 128.9, 128.5, 126.9, 125.4, 125.1, 121.5, 120.6, 119.5, 119.2, 118.3, 109.7, 109.3, 109.3, 45.2, 44.8, 44.3, 25.0, 18.1; **HRMS** (ESI) found: *m/z* 487.0938 $[M+Na]^+$; calcd. for $C_{27}H_{17}ClN_4NaO_2^+$ 487.0933.

1-Methyl-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3u):
98% yield, white solid, **mp** 229-230 ºC; **^{1}H NMR** (300 MHz, DMSO-*d$_6$*) δ 11.15 (s, 1H), 8.22-8.19 (m, 2H), 7.47 (td, *J* = 7.8 Hz and 1.5 Hz, 1H), 7.36 (td, *J* = 7.8 Hz and 1.2 Hz, 1H), 7.17-7.04 (m, 3H), 6.93 (d, *J* = 7.8 Hz, 1H), 3.16 (s, 3H); **^{13}C NMR** (75 MHz, DMSO-*d$_6$*) δ 168.2, 166.7, 145.2, 143.7, 130.7, 128.4, 127.9, 122.2, 121.6, 119.9, 119.3, 110.4, 110.0, 109.5, 45.5, 44.9, 27.3, 25.2; **HRMS** (ESI) found: *m/z* 363.0858 $[M+Na]^+$; calcd. for $C_{20}H_{12}N_4NaO_2^+$ 363.0852.

***tert*-Butyl 3',3'-dicyano-2,2''-dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-1-carboxylate (3v):**
88% yield, white solid, **mp** 230-233 ºC; **^{1}H NMR** (300 MHz, DMSO-*d$_6$*) δ 11.15 (s, 1H), 8.30 (d, *J* = 7.8 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 8.1 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 1.55 (s, 9H); **^{13}C NMR** (75 MHz, DMSO-*d$_6$*) δ 168.2, 168.0, 165.1, 148. 3, 144.0, 143.7, 141.2, 130.7, 130.6, 130.5, 128.3, 128.0, 127.8, 123.8, 121.6, 119.9, 119.8, 119.1, 114.5, 110.5, 110.0, 109.9, 85.1, 46.3, 45.6, 45.3, 28.0, 25.9; **HRMS** (ESI) found: *m/z* 427.1408 $[M+H]^+$; calcd. for $C_{24}H_{19}N_4O_4^+$ 427.1401.

2,2''-Dioxodispiro[indoline-3,1'-cyclopropane-2',3''-indoline]-3',3'-dicarbonitrile (3w):
98% yield, white solid, **mp** 222-224 ºC; **^{1}H NMR** (300 MHz, DMSO-*d$_6$*) δ 11.16 (s, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.36 (td, *J* = 7.8 Hz and 1.2 Hz, 1H), 7.07 (td, *J* = 7.8 Hz and 1.2 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H); **^{13}C NMR** (75 MHz, DMSO-*d$_6$*) δ 168.2, 143.7, 130.6, 128.3, 121.6, 119.8, 110.5, 110.0, 45.3, 24.9; **HRMS** (ESI) found: *m/z* 349.0702 $[M+Na]^+$; calcd. for $C_{19}H_{10}N_4NaO_2^+$ 349.0696.

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SUPPORTING INFORMATION

The supporting information (crystallographic data of **3w**, copies of ^{1}H NMR and ^{13}C NMR spectra) associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26320/98/5.

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37. CCDC 1587297 (3w) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.