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Thermal *Hetero*-Diels-Alder Reaction of Benzocyclobutenones with Isatins to Form 2-Oxindole Spirolactones

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Abstract

Benzocyclobutenones **1a–1g** undergo cycloreversion at 150 °C in *m*-xylene solvent to form transient α -oxo-*ortho*-quinodimethanes or “*ortho*-quinoid ketene methides,” which engage in intermolecular [4+2] cycloadditions with isatins **2a–2f** to form 2-oxindole spirolactones **3a–3l**. This process tolerates an array of different functional groups and substitution patterns, and is applicable to unprotected isatins **2b–2f** bearing free NH-functionalities. The superior performance of isatins compared to other carbonyl based dienophiles was demonstrated and rationalized with the aid of quantum chemical calculations.

Graphical Abstract

Due to ring-strain and their ability to undergo cycloreversion to form highly reactive *ortho*-quinodimethanes,¹ benzocyclobutenes have emerged as versatile building blocks in chemical synthesis.² In the course of developing catalytic processes that convert lower alcohols to higher alcohols *via* hydrogen auto-transfer,³ we recently discovered a suite of redox-independent ruthenium(0) catalyzed [4+2] cycloadditions between diols, α -ketols or diones and diverse unsaturated partners,⁴ including benzocyclobutenones.⁵ During investigation of the mechanism of the latter process, it was found that benzocyclobutenones engage in thermally promoted *hetero*-Diels-Alder cycloadditions with isatins. As the resulting oxindole spirolactones represent a medicinally relevant class of bioactive compounds⁵ and thermally promoted *hetero*-Diels-Alder reactions of isatins with *ortho*-quinodimethanes were unknown,^{1,2,7,8,9} the optimization and evaluation of scope for this process was

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Notes.

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Supporting Information. ¹H and ¹³C NMR spectra, single crystal X-ray diffraction data for compound **3h** and computational details. This material is available free of charge *via* the internet at <http://pubs.acs.org>

undertaken. Here, we disclose that upon heating at 150 °C in *m*-xylene, diverse benzocyclobutenones engage in highly efficient intermolecular [4+2] cycloaddition with unprotected isatins by way of transient α -oxo-*ortho*-quinodimethanes to form 2-oxindole spirolactones (Figure 1).

Initial experiments were aimed at identifying optimal conditions for the thermal [4+2] cycloaddition of benzocyclobutenone **1a** (100 mol %) and *N*-benzyl isatin **2a** (100 mol %) in *m*-xylene solvent (0.8 M). A lower temperature threshold of 150 °C was required to promote cycloreversion of the benzocyclobutenone such that reasonable reaction rates were observed. Under these conditions, the spirolactone **3a** was formed in 49% yield. Analysis of the crude reaction mixture revealed that while benzocyclobutenone **1a** was completely consumed, significant quantities of isatin **2a** were still present. This observation suggests that apart from the desired *hetero*-Diels-Alder reaction pathway, the α -oxo-*ortho*-quinodimethane reacts through alternate manifolds to form undefined side products. To compensate, an excess of benzocyclobutenone **1a** (150 mol%) was employed, which enabled formation of spirolactone **3a** in 81% yield.

Under these optimized conditions, the thermal [4+2] cycloaddition of benzocyclobutenone **1a** (150 mol %) with diverse isatins **2a–2f** (100 mol %) was explored (Table 1). The corresponding spirolactones **3a–3f**, which derive from isatins bearing substituents in the 5-, 6-, or 7-position, were formed in good to excellent yields. Notably, it was found that *N*-benzyl substitution is not required. The unprotected N-H derivatives **2b–2f** engage in highly efficient cycloadditions. Variation of the benzocyclobutenone also was explored (Table 2). The unsubstituted benzocyclobutenone **1b** and a diverse range of polysubstituted benzocyclobutenones **1c–1g** each underwent thermal [4+2] cycloaddition to form the respective spirolactones **3g–3l** in good to excellent yields. The structural assignment of spirolactones **3a–3l** is made in analogy to that for cycloadduct **3h**, which was determined by single crystal x-ray diffraction analysis (Figure 2).

Pursuant to this evaluation of reaction scope, the feasibility of utilizing less activated carbonyl partners was assessed. The electron deficient, electroneutral and electron rich aldehydes *p*-trifluoromethyl benzaldehyde, benzaldehyde and *p*-anisaldehyde were exposed to benzocyclobutenone **1a** under standard conditions, however, products of [4+2] cycloaddition were not observed. The aliphatic aldehyde octanal and even ethyl pyruvate, which incorporates a vicinal dicarbonyl motif, failed to undergo cycloaddition. These results were surprising, as the thermal [4+2] cycloaddition of the parent benzocyclobutenone **1b** with benzaldehyde and ethyl pyruvate is reported to occur at 160 °C, albeit in the absence of solvent.^{7a}

Our observations demonstrate that isatins are significantly more efficient partners for [4+2] cycloaddition compared to other carbonyl dienophiles in the context of benzocyclobutenone derived α -oxo-*ortho*-quinodimethanes. To better understand the origins of their superior reactivity, quantum chemical calculations were conducted (Table 3). It is well known that the rate of Diels-Alder reactions is strongly influenced by the energy gap between the frontier molecular orbitals of the diene and dienophile, as well as the shapes of these orbitals.¹⁰ Looking at the energies of the reaction partners, the smallest frontier orbital energy gaps are,

in all considered systems, observed between the LUMO of the carbonyl compound and the HOMO of the diene. The investigated reactions are therefore “normal electron demand” *hetero*-Diels-Alder reactions. Among the indicated carbonyl compounds, a consideration of LUMO energies reveals that isatin is by far the most electrophilic. Therefore, the smallest gap in energy between frontier molecular orbitals is found for α -oxo-*ortho*-quinodimethane and isatin. Apart from these energetic criteria, the shape of the frontier molecular orbitals of the reactants (Figure 3), that is, the diene moiety of the α -oxo-*ortho*-quinodimethane and carbonyl moiety of the isatin, are such that good orbital overlap for the hetero-Diels-Alder reaction is anticipated. Thus, the experimentally observed and theoretically predicted reactivities are in alignment.

In summary, we report the first *hetero*-Diels-Alder reactions of benzocyclobutenones with isatins to form oxindole spiro lactones. These [4+2] cycloadditions occur through cycloreversion of the benzocyclobutenones to form transient α -oxo-*ortho*-quinodimethanes. Isatins were shown to be superior dienophiles compared to other carbonyl compounds. These experimental observations are readily understood upon consideration of the calculated frontier molecular orbital energies for certain diene and carbonyl dienophile partners.

Experimental Section

General Information

Unless otherwise noted, all reactions were performed using oven-dried glassware under an atmosphere of dry Ar. Thermal *hetero*-Diels-Alder reactions were conducted in pressure tubes (13 x 100 mm) sealed with PTFE-lined caps. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates. Visualization was conducted with UV light and then treatment with a cerium ammonium molybdate or *p*-anisaldehyde solution followed by heating. Isolation of reaction products was conducted via flash column chromatography using 40–63 μ m silica gel. Unless otherwise noted, reagents were purchased from commercial sources and used as received. Benzocyclobutenones **1a** and **1b**,¹¹ **1c**,¹² **1d–f**¹³ and **1g**¹⁴ were prepared according to literature procedures. ¹H Nuclear magnetic resonance spectra were recorded using a 400 or 500 MHz spectrometer. Coupling constants are reported in Hertz (Hz) and protons chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the proton resonance of the residual protic solvent (CHCl₃, δ = 7.26 ppm; acetone, δ = 2.05 ppm; DMSO, δ = 2.50 ppm). ¹³C Nuclear magnetic resonance spectra were recorded using a 125 MHz spectrometer and chemical shifts are reported as parts per million (ppm) relative to the carbon resonances of residual protic solvent (CHCl₃, δ = 77.16 ppm; acetone: δ = 29.84 ppm; DMSO: δ = 39.52 ppm). High-resolution mass spectra (HRMS) are reported as *m/z* (relative intensity) using time-of-flight (TOF) analyzers. Accurate masses are reported for the molecular ion (M+H, M+Na) or a suitable fragment ion.

General Procedure for the synthesis of 2-Oxindole Spirolactones

A resealable pressure tube (13 x 100 mm) was charged with reactant isatin (0.20 mmol, 100 mol%), and reactant benzocyclobutenone (0.30 mmol, 150 mol%). The tube was sealed with a rubber septum and purged with argon for 10 min. *m*-Xylene (0.25 mL, 0.80 M with respect

to the isatin reactant) was injected and the rubber septum was replaced with a PTFE-lined screw cap. The tube was placed in a 150 °C oil bath for 48 h. After cooling to room temperature, the crude reaction mixture was subjected to flash column chromatography (SiO₂) to furnish the product of cycloaddition.

1-Benzyl-8'-methoxyspiro[indoline-3,3'-isochroman]-1',2-dione (3a)—The reaction was conducted in accordance with the general procedure. Flash column chromatography (SiO₂, hexanes:acetone = 1:1 to 0:1) provided the title compound (62 mg, 0.16 mmol) in 81 % yield as a white solid. TLC (SiO₂): R_f = 0.32 (hexanes : EtOAc = 1:1, UV). ¹H NMR (500 MHz, DMSO-d₆): δ 7.62 (dd, *J* = 7.5, 8.5 Hz, 1H), 7.38–7.26 (m, 6H), 7.18 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 4.2 Hz, 2H), 6.95 (d, *J* = 7.5 Hz, 1H), 4.92 (d, *J* = 15.8 Hz, 1H), 4.88 (d, *J* = 15.8 Hz, 1H), 3.90 (s, 3H), 3.55 (d, *J* = 16.5 Hz, 1H), 3.45 (d, *J* = 16.5 Hz, 1H). ¹³C NMR (100 MHz, DMSO-d₆): δ 172.3, 160.4, 159.4, 142.1, 138.8, 135.7, 135.4, 130.8, 128.8 (2C), 127.6, 127.2 (2C), 127.1, 124.0, 123.1, 120.1, 112.5, 111.9, 110.1, 79.4, 56.0, 42.8, 33.9. HRMS (ESI-TOF) *m/z*: [M + K]⁺ Calcd for C₂₄H₁₉KNO₄ 424.0946; Found 424.0953. FTIR (neat): 1720, 1598 cm⁻¹. Melting Point: 232 °C.

8'-Methoxyspiro[indoline-3,3'-isochroman]-1',2-dione (3b)—The reaction was conducted in accordance with the general procedure. Flash column chromatography (SiO₂, hexanes : acetone = 1:1 to 0:1) provided the title compound (42 mg, 0.16 mmol) in 81% yield as an off-white solid. TLC (SiO₂): R_f = 0.17 (hexanes: EtOAc = 1:1, UV). ¹H NMR (500 MHz, DMSO-d₆): δ 10.75 (bs, 1H), 7.6 (dd, *J* = 7.5, 8.6 Hz, 1H), 7.31 (dt, *J* = 1.56, 7.7 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 1H), 6.96–6.86 (m, 4H), 3.89 (s, 3H), 3.43 (d, *J* = 16.6 Hz, 1H), 3.36 (d, *J* = 16.6 Hz, 1H). ¹³C NMR (125 MHz, DMSO-d₆): δ 173.7, 160.3, 159.5, 141.7, 138.9, 135.3, 130.8, 127.6, 124.0, 122.3, 120.0, 112.6, 111.8, 110.5, 79.8, 56.0, 33.9. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ Calcd for C₁₇H₁₃NNaO₄ 318.0737; Found 318.0739. FTIR (neat): 3271, 1740, 1706, 1615 cm⁻¹. Melting Point: 313 °C (decomposition).

8'-Methoxy-5-methylspiro[indoline-3,3'-isochroman]-1',2-dione (3c)—The reaction was conducted in accordance with the general procedure. Flash column chromatography (SiO₂, hexanes : acetone = 1:1 to 0:1) provided the title compound (48 mg, 0.18 mmol) in 89 % yield as a beige solid. TLC (SiO₂): R_f = 0.18 (hexanes: ethyl acetate 1:1, UV). ¹H NMR (500 MHz, DMSO-d₆): δ 10.64 (bs, 1H), 7.59 (dd, *J* = 7.4, 8.58 Hz, 1H), 7.15 (d, *J* = 8.58 Hz, 1H), 7.12 (d, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.81–6.77 (m, 2H), 3.89 (s, 3H), 3.45 (d, *J* = 16.6 Hz, 1H), 3.31 (d, *J* = 16.6 Hz, 1H), 2.16 (s, 3H). ¹³C NMR (100 MHz, DMSO-d₆): δ 173.9, 160.3, 159.6, 139.1, 138.9, 135.2, 131.2, 131.0, 127.7, 124.7, 120.0, 112.6, 111.8, 110.2, 79.8, 56.0, 33.9, 20.6. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ Calcd for C₁₈H₁₅NNaO₄ 332.0893; Found 332.0895. FTIR (neat): 3295, 1740, 1706 cm⁻¹. Melting Point: 297 °C (decomposition).

6-bromo-8'-methoxyspiro[indoline-3,3'-isochroman]-1',2-dione (3d)—The reaction was conducted in accordance with the general procedure. Flash column chromatography (SiO₂, hexanes : acetone = 1:1 to 0:1) provided the title compound (59 mg, 0.18 mmol) in 88% yield as a beige solid. TLC (SiO₂): R_f = 0.24 (hexanes : EtOAc = 1:1,

UV). ^1H NMR (500 MHz, DMSO- d_6): δ 10.09 (bs, 1H), 7.6 (dd, J = 7.46, 8.56 Hz, 1H), 7.18–7.12 (m, 2H), 7.05 (d, J = 1.88 Hz, 1H), 6.9 (d, J = 7.65 Hz, 1H), 6.87 (d, J = 8.03 Hz, 1H), 3.88 (s, 3H), 3.48 (d, J = 16.6 Hz, 1H), 3.35 (d, J = 16.6 Hz, 1H). ^{13}C NMR (125 MHz, DMSO- d_6): δ 174.1, 160.8, 159.8, 143.8, 139.2, 135.9, 127.4, 126.5, 125.5, 124.0, 120.5, 113.9, 112.4, 79.9, 56.5, 34.1. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{12}\text{BrNNaO}_4$ 395.9842; Found 395.9848. FTIR (neat): 3257, 1744, 1706 cm^{-1} . Melting Point: 317 $^\circ\text{C}$ (decomposition).

7-Fluoro-8'-methoxyspiro[indoline-3,3'-isochroman]-1',2-dione (3e)—The reaction was conducted in accordance with the general procedure. Flash column chromatography (SiO_2 , hexanes : acetone = 1:1 to 0:1) provided the title compound (49 mg, 0.18 mmol) in 88% yield as an off white solid. TLC (SiO_2): R_f = 0.25 (hexanes : EtOAc = 1:1, UV). ^1H NMR (500 MHz, DMSO- d_6): δ 11.29 (bs, 1H), 7.61 (dd, J = 7.6, 8.6 Hz, 1H), 7.26 (dd, J = 8.5, 10.4 Hz, 1H), 7.17 (d, J = 8.6 Hz, 1H), 6.99–6.94 (m, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 3.89 (s, 3H), 3.49 (d, J = 16.6 Hz, 1H), 3.39 (d, J = 16.6 Hz, 1H). ^{13}C NMR (125 MHz, DMSO- d_6): δ 173.5, 160.3, 159.2, 146.5 (d, J_{FC} = 247 Hz), 138.7, 135.4, 130.4, 128.9 (d, J_{FC} = 13 Hz), 123.4 (d, J_{FC} = 5.3 Hz), 120.1 (d, J_{FC} = 19.3 Hz), 117.9 (d, J_{FC} = 16.9 Hz), 112.4, 111.9, 79.7, 56.0, 33.7. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{12}\text{NNaO}_4$ 336.0643; Found 336.0639. FTIR (neat): 3230, 1746, 1717 cm^{-1} . Melting Point: 315 $^\circ\text{C}$ (decomposition).

8'-Methoxy-5-(trifluoromethoxy)spiro[indoline-3,3'-isochroman]-1',2-dione (3f)—The reaction was conducted in accordance with the general procedure. Flash column chromatography (SiO_2 , hexanes : acetone = 1:1 to 0:1) provided the title compound (53 mg, 0.14 mmol) in 72% yield as a beige solid. TLC (SiO_2): R_f = 0.21 (hexanes: ethyl acetate = 1:1, UV). ^1H NMR (500 MHz, DMSO- d_6): δ 10.91 (bs, 1H), 7.6 (dd, J = 7.5, 8.6 Hz, 1H), 7.35 (dd, J = 2.5, 8.3 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.10 (d, J = 2.5 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 6.91 (d, J = 7.7 Hz, 1H), 3.88 (s, 3H), 3.63 (d, J = 16.6 Hz, 1H), 3.34 (d, J = 16.6 Hz, 1H). ^{13}C NMR (125 MHz, DMSO- d_6): δ 174.0, 160.3, 159.3, 143.3, 140.9, 138.6, 135.3, 129.1, 124.1, 120.1 (q, J_{FC} = 256 Hz), 119.9, 118.1, 112.5, 111.8, 111.6, 79.6, 56.0, 33.5. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{18}\text{H}_{12}\text{F}_3\text{NNaO}_5$ 402.0560; Found 402.0566. FTIR (neat): 3290, 1743, 1713 cm^{-1} . Melting Point: 266 $^\circ\text{C}$.

Spiro[indoline-3,3'-isochroman]-1',2-dione (3g)—The reaction was conducted in accordance with the general procedure. Flash column chromatography (SiO_2 , hexanes : acetone = 9:1 to 0:1) provided the title compound (52 mg, 0.19 mmol) in 98% yield as a white solid. TLC (SiO_2): R_f = 0.50 (DCM : acetone = 9:1). ^1H NMR (400 MHz, DMSO- d_6): δ 10.79 (br. s, 1H), 8.02–7.99 (m, 1H), 7.70–7.65 (m, 1H), 7.53–7.48 (m, 1H), 7.40–7.38 (m, 1H), 7.36–7.32 (m, 1H), 7.13–7.11 (m, 1H), 7.00–6.96 (m, 1H), 6.94–6.91 (m, 1H), 3.64 (d, J = 17.0 Hz, 1H), 3.40 (d, J = 17.1 Hz, 1H). ^{13}C NMR (125 MHz, DMSO- d_6): δ 173.9, 163.6, 141.6, 136.7, 134.2, 131.0, 128.9, 128.2, 127.8, 127.6, 124.4, 124.3, 122.4, 110.5, 80.6, 32.8. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{16}\text{H}_{11}\text{NO}_3\text{Na}$ 288.0631; Found 288.0641. FTIR (neat): 3271, 1727, 1705 cm^{-1} . Melting Point: 246–248 $^\circ\text{C}$.

8'-Bromospiro[indoline-3,3'-isochroman]-1',2-dione (3h)—The reaction was conducted in accordance with the general procedure. Flash column chromatography (SiO₂, DCM : EtOAc = 1:0 to 9:1) provided the title compound (68 mg, 0.20 mmol) in 98% yield as a white solid. TLC (SiO₂): R_f = 0.57 (DCM : EtOAc = 4:1, UV). ¹H NMR (400 MHz, acetone-d₆): δ 9.68 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.55–7.49 (m, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.39–7.33 (m, 1H), 7.12–7.08 (m, 1H), 7.04–6.99 (m, 2H), 3.69 (d, J = 16.7 Hz, 1H), 3.53 (d, J = 16.7 Hz, 1H). ¹³C NMR (125 MHz, acetone-d₆): δ 174.3, 161.0, 142.7, 140.7, 135.5, 135.0, 131.9, 128.9, 128.5, 125.4, 125.2, 124.3, 123.5, 111.5, 80.7, 35.7. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ Calcd for C₁₆H₁₀BrNO₃Na 365.9736; Found 356.9737. FTIR (neat): 3333, 1742, 1714 cm⁻¹. Melting Point: 254–256 °C.

Spiro[[1,3]dioxolo[4,5-*h*]isochromene-7,3'-indoline]-2',9(6*H*)-dione (3i)—The reaction was conducted in accordance with the general procedure. Flash column chromatography (SiO₂, hexanes : acetone = 9:1 to 0:1) provided the title compound (46 mg, 0.15 mmol) in 74% yield as a white solid. TLC (SiO₂): R_f = 0.40 (DCM : acetone = 9:1). ¹H NMR (400 MHz, DMSO-d₆): δ 10.77 (br. s, 1H), 7.36–7.32 (m, 1H), 7.16 (d, J = 7.8 Hz, 1H), 7.12 (d, J = 7.4 Hz, 1H), 6.99–6.96 (m, 1H), 6.91 (d, J = 7.8 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 6.24 (app. d, J = 4.1 Hz, 2H), 3.45 (d, J = 16.5 Hz, 1H), 3.29 (d, J = 16.7 Hz, 1H). ¹³C NMR (125 MHz, DMSO-d₆): δ 173.7, 160.2, 148.8, 147.9, 141.6, 130.9, 128.7, 127.5, 124.3, 122.4, 120.3, 112.9, 110.5, 107.4, 102.8, 80.9, 32.7. HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₇H₁₂NO₅ 310.0710; Found 310.0716. FTIR (neat): 3322, 1726, 1705 cm⁻¹. Melting Point: 296–298 °C.

6',8'-Dimethoxyspiro[indoline-3,3'-isochroman]-1',2-dione (3j)—The reaction was conducted in accordance with the general procedure. Flash column chromatography (SiO₂, acetone : hexanes = 1:9 to 1:0) provided the title compound (60 mg, 0.18 mmol) in 92% yield as a beige solid. TLC (SiO₂): R_f = 0.30 (DCM : acetone = 9:1, UV). ¹H NMR (400 MHz, DMSO-d₆): δ 10.76 (br. s, 1H), 7.32–7.28 (m, 1H), 6.94–6.87 (m, 3H), 6.64 (d, J = 2.3 Hz, 1H), 6.54 (d, J = 2.3 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.32 (s, 2H). ¹³C NMR (125 MHz, DMSO-d₆): δ 173.7, 164.5, 162.5, 159.2, 141.6, 140.9, 130.8, 127.8, 124.1, 122.3, 110.5, 105.6, 105.5, 98.0, 79.4, 56.0, 55.7, 34.2. HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₈H₁₆NO₅ 326.1023; Found 326.1028. FTIR (neat): 3253, 1734, 1704 cm⁻¹. Melting Point: 265–267 °C.

5',8'-Dimethoxyspiro[indoline-3,3'-isochroman]-1',2-dione (3k)—The reaction was conducted in accordance with the general procedure. Flash column chromatography (SiO₂, DCM : EtOAc = 1:0 to 4:1) provided the title compound (62 mg, 0.19 mmol) in 95% yield as a white solid. TLC (SiO₂): R_f = 0.25 (DCM : EtOAc = 4:1, UV). ¹H NMR (500 MHz, acetone-d₆): δ 9.60 (s, 1H), 7.35–7.28 (m, 2H), 7.12 (d, J = 9.2 Hz, 1H), 7.02–6.97 (m, 2H), 6.95 (t, J = 7.6 Hz, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.36 (d, J = 17.1 Hz, 1H), 3.32 (d, J = 17.1 Hz, 1H). ¹³C NMR (125 MHz, acetone-d₆): δ 173.7, 159.2, 154.8, 149.8, 141.7, 130.7, 128.4, 126.5, 124.2, 122.4, 117.1, 114.6, 112.3, 110.5, 79.6, 55.9, 55.7, 29.3. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ Calcd for C₁₈H₁₅NO₅Na 348.0842; Found 348.0847. FTIR (neat): 3300, 1748, 1708 cm⁻¹. Melting Point: 283–285 °C.

7'-Bromo-5',8'-dimethoxyspiro[indoline-3,3'-isochroman]-1',2-dione (3I)—The reaction was conducted in accordance with the general procedure. Flash column chromatography (SiO₂, DCM : EtOAc = 1:0 to 9:1) provided the title compound (51 mg, 0.13 mmol) in 63% yield as a white solid. TLC (SiO₂): R_f = 0.58 (DCM : EtOAc = 4:1, UV). ¹H NMR (500 MHz, acetone-d₆): δ 9.63 (s, 1H), 7.55 (s, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.23 (d, J = 7.4 Hz, 1H), 7.07–6.97 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.42 (d, J = 17.4 Hz, 1H), 3.31 (d, J = 17.4 Hz, 1H). ¹³C NMR (125 MHz, acetone-d₆): δ 174.7, 160.0, 153.5, 152.3, 142.6, 131.8, 128.7, 127.0, 125.2, 123.6, 121.4, 121.1, 118.6, 111.5, 80.7, 61.9, 57.0, 30.2. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ Calcd for C₁₈H₁₄BrNO₅Na 425.9948; Found 425.9958. FTIR (neat): 3291, 1740, 1711 cm⁻¹. Melting Point: 248–250 °C.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Prior Work: Electron rich dienes (ref. 8)

This Work: α -Oxo-*ortho*-quinodimethanes

Figure 1.
hetero-Diels-Alder cycloadditions of isatins.

Figure 2. Molecular solid state structure of compound **3h** as determined by single crystal x-ray diffraction.^a

^aSee Supporting Information for tabulated crystallographic data.

Figure 3.

Shape of the HOMO of the parent α -oxo-*ortho*-quinodimethane (left) and the LUMO of isatin (right).^a

^aCalculated at the B3LYP-d3(BJ)/cc-pVTZ level of theory at fully optimized geometries.

Table 1

Cycloaddition of benzocyclobutenone **1a** with isatins **2a–2f** to form spirolactones **3a–3f**.^a ^aYields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.

Table 2

Cycloaddition of benzocyclobutenones **1b–1f** with isatin **2b** to form spirolactones **3g–3l**.^a ^aYields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.

Table 3Calculated frontier molecular orbital energies of representative diene and carbonyl compounds.^a

Diene or Dienophile	E_{HOMO} [eV]	E_{LUMO} [eV]
(<i>s-cis</i>)-1,3-butadiene	−6.53	−1.27
α-oxo-ortho-quinodimethane	−5.19	−1.81
acetaldehyde	−7.22	−0.90
benzaldehyde	−7.23	−2.03
(<i>s-trans</i>)-ethyl pyruvate	−7.13	−2.18
isatin	−6.84	−2.95

^a Calculated at the B3LYP-d3(BJ)/cc-pVTZ level of theory at fully optimized geometries.