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An Economical, Sustainable Pathway to Indole-Containing Oxindoles: Iron-Catalyzed 1,6-Conjugate Addition in Glycerol

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Abstract: The search for economical, sustainable and practical pathways in synthetic science would contribute to improving resource efficiency, developing a recycling economy and driving new-type urbanization. Green synthesis has established firm ground providing the right green yardstick for development of a sustainable approach to bioactive high-added value molecules and drug discovery, and further development of sustainable manufacturing processes in the pharmaceutical industry toward a green resource efficient economy. In this study, the combination of FeCl₃ and glycerol exhibits a versatile and high catalytic activity in the atom economical 1,6-conjugated addition of *para*-quinone methides derived from isatins with indoles using the right green yardstick. The sustainable pathway provides the preparation of bioactive indole-containing oxindoles in excellent yields with superior advantages, such as the ready availability, low price and environmentally benign character of iron catalysis, easy product separation, cheap and safe bio-renewable glycerol as a green solvent, and catalytic system recycling under mild conditions.

Keywords: atom economy; sustainable pathway; recycling economy; resource efficient economy; glycerol; iron; catalysis; 1,6-conjugate addition

1. Introduction

Resource efficiency is the maximising of the supply of funds, materials, staff, and other assets in order to function effectively in a sustainable manner, with minimum wasted resource expenses to minimise environmental impact [1]. In today's environment, the demand for the production of high-quality products with minimum waste and energy demands is a very important challenge to the coordinated development of new urbanization and employment growth via the economic analysis of resource efficiency policies [2,3]. In the field of synthetic science, the concept of sustainability is clearly expressed by the use of low-waste organic transformations to achieve high incorporation of the starting materials into the final product, avoiding the formation of waste by-products, plus the use of catalysts to reduce energy needed [4–6]. Atom economy [7] has become one of 12 principles of green synthetic science [8]. Both green synthesis and resource efficiency are two key factors towards a green sustainable economy [9,10]. Thus, developing sustainable and practical pathways will be a long-term concerted and challenging task for scientists. In this regard, the 1,6-conjugated addition reaction catalyzed by Brønsted acids or Lewis acids for new chemical bond formation can provide a variety of bioactive compounds, and has complete atom economy [11]. Thus, the 1,6-conjugated addition reaction is attracting much research interest in academia [12–14].

The development of sustainability has led to the resurrection of iron catalysis in synthetic science. Currently, iron catalysis has been recognized as an environmentally friendly methodology in organic synthesis, due to its ready availability, low price and low toxicity, which is of great importance for many practical applications especially in the pharmaceutical industry, the food industry, and cosmetics. Thus, iron-catalyzed reactions have drawn much attention, which reflects an increasing demand for sustainable synthesis [15,16].

Developments in green reaction media with the ultimate goal of solving the environment problem are strongly needed [17]. In this regard, glycerol as a solvent derived from biomass is drawing increasing interest in the scientific community [18–22]. The bio-renewable glycerol is considered as “organic water”. Glycerol behaves like water, but it is better than water because of its high boiling point, lower vapor pressure and also dissolutions of most of the organic compound which are insoluble in water. Furthermore, it is abundant and inexpensive, non-toxic, highly polar, recyclable, biodegradable, immiscible with ether and hydrocarbons (this ability makes it possible remove the reaction products simply through liquid–liquid extraction), and compatible with most inorganic compounds (salts and transition metal complexes) [23].

3,3-Disubstituted oxindoles represent an important family of bioactive and pharmaceutical molecules, and their synthesis has drawn much attention [24–26]. In this paper, we report a highly efficient FeCl_3 dissolved in glycerol catalyzed 1,6-conjugated addition reaction of *para*-quinone methides derived from isatins with indoles to afford bioactive indole-containing oxindoles in excellent yields. The superior advantages of the sustainable approach mainly include: (i) the environmentally benign character of iron catalysis; (ii) the first example of 1,6-conjugated addition reaction in glycerol; (iii) oxindoles containing an indolyl unit; (iv) complete atom economy, and easy product separation; (v) a recyclable catalytic system. The current sustainable iron catalysis meets the increasing demand of sustainability, such as energy resources, cheap catalysts, non-toxic reagents and green solvents.

2. Materials and Methods

2.1. General Information

^1H NMR (nuclear magnetic resonance), and ^{13}C NMR spectra were measured at 400, 100 MHz spectrometer, respectively. The Supplementary Materials are NMR Spectra for all products. The shifts were reported relative to internal standard tetramethylsilane (TMS, 0 ppm) and referenced to solvent peaks in the NMR solvent (CDCl_3 = δ 7.26 ppm; δ 77.16 ppm; d_6 -DMSO = δ 2.50 ppm; δ 39.52 ppm). Data are reported as: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in hertz (Hz) and signal area integration in natural numbers. High-resolution mass spectrometry (HRMS) spectra was obtained using EI ionization. Infrared spectra were recorded on an ATR-FTIR spectrometer. HRMS were obtained using EI or ESI ionization. All the reagents used were of analytical grade without further purification. Oxindole-derived methide derivatives was obtained following the literature [12].

2.2. General Sustainable Procedure for Atom-Economical Synthesis of 3,3-Disubstituted Oxindoles

As shown in Figure 1, *para*-Quinone methides derived from isatins **1** (2 mmol) and indoles **2** or pyrrole (2 mmol) were added to a solution of FeCl_3 (0.2 mmol) in glycerol (4 mL), and the resulting mixture was stirred at 120 °C under an air atmosphere for 24 h (Table 1, entry 8). Complete consumption of starting materials was observed by thin-layer chromatography (TLC). After cooling, the reaction mixture was extracted with 2-methyltetrahydrofuran (an immiscible solvent, 2×4 mL), to separate the product, while the residue (glycerol layer), still containing the catalyst FeCl_3 dissolved in the glycerol, was used as such for the recycling experiments. The collected organic phases were concentrated by distillation to recover 2-methyltetrahydrofuran and give the solid crude products **3** after washing with water (10 mL) and drying under a vacuum. The analytically pure products **3** could be obtained by

flash silica gel column chromatography (petroleum ether/ethyl acetate = 4:1 as the eluent). The yield obtained in each experiment is reported in Table 2.

2.3. General Procedure for Catalytic System Recycling

The recyclability of our catalytic system was investigated using the 1,6-conjugated addition reaction of *para*-quinone methide derived from isatin **1a** and indole **2a** as a model reaction. To the residue (the retained glycerol layer) obtained as described above, still containing the catalyst FeCl_3 dissolved in glycerol, was added **1a** (2 mmol) and **2a** (2 mmol), and the resulting mixture was stirred at 120 °C under an air atmosphere for 24 h. Complete consumption of starting materials was observed by TLC. After cooling, the reaction mixture was extracted with 2-methyltetrahydrofuran (2×4 mL), and the collected organic phases were concentrated and gave the crude products **3a** after washing with water (10 mL) and drying under vacuum. The analytically pure product **3a** was obtained after flash silica gel column chromatography (petroleum ether/ethyl acetate = 4:1 as the eluent). To the retained glycerol layer, the substrates were again added, and the mixture was stirred under the same conditions described above to provide the desired product **3a** after the same work up. This procedure was repeated up to five consecutive times. The yield obtained in each recycling experiment is reported in Table 3.

Figure 1. Synthesis of 3,3-Disubstituted Oxindoles.

Table 1. Optimized reaction conditions ^a.

Entry	Catalyst	x	Temperature [°C]	Isolated Yield [%]
1	(PhO) ₂ PO ₂ H	15	25	no reaction
2	(PhO) ₂ PO ₂ H	15	60	trace
3	(PhO) ₂ PO ₂ H	15	80	60
4	(PhO) ₂ PO ₂ H	15	120	86
5	H ₃ PO ₄ (85%)	15	120	trace
6	PhCO ₂ H	15	120	85
7	FeCl ₃	15	120	93
8	FeCl ₃	10	120	93
9	FeCl ₃	5	120	80
10 ^b	FeCl ₃	10	110	45
11 ^c	FeCl ₃	10	120	50
12 ^d	FeCl ₃	10	80	76

^a Reactions were performed with **1** (2 mmol), **2** (2 mmol) and catalyst in glycerol (4 mL) for 24 h; ^b With toluene (4 mL) as the solvent; ^c With xylene (4 mL) as the solvent; ^d With $\text{ClCH}_2\text{CH}_2\text{Cl}$ (4 mL) as the solvent.

Table 2. Sustainable approach for synthesis of indole-containing oxindoles ^a.

Entry	1	R ¹	R ²	2	R ³	R ⁴	Product (3)	Isolated Yield [%]
1	1a	H	H	2a	H	H	3a	93
2	1a	H	H	2b	4-Me	H	3b	91
3	1a	H	H	2c	5-Me	H	3c	93
4	1a	H	H	2d	7-Me	H	3d	90
5	1a	H	H	2e	6-Br	H	3e	88
6	1a	H	H	2f	7-Cl	H	3f	89
7	1a	H	H	2g	5-OMe	H	3g	92
8	1a	H	H	2h	7-OMe	H	3h	90
9	1b	Me	H	2b	H	H	3i	89
10	1b	Me	H	2b	4-Me	H	3j	87
11	1b	Me	H	2d	7-Me	H	3k	91
12	1b	Me	H	2e	6-Br	H	3l	85
13	1b	Me	H	2f	7-Cl	H	3m	87
14	1b	Me	H	2i	4-Br	H	3n	88
15	1c	Cl	H	2b	4-Me	H	3o	90
16	1c	Cl	H	2e	6-Br	H	3p	93
17	1d	Br	H	2a	H	H	3q	87
18	1d	Br	H	2b	4-Me	H	3r	88
19	1e	H	Me	2a	H	H	3s	92
20	1f	H	H	2j	H	Me	3t	94

^a Reactions were performed with **1** (2 mmol), **2** (2 mmol) and FeCl₃ (0.2 mmol) in glycerol (4 mL) at 120 °C for 24 h.

Table 3. Study of catalytic system recycling ^a.

Run	Crude Yield (%)	Isolated Yield (%)
1	97	93
2	99	95
3	98	94
4	98	93
5	99	94

^a Reactions were performed using FeCl₃ (0.2 mmol) in glycerol (4 mL) at 120 °C for 24 h, and 2 mmol of **1a** and **2a** was always employed.

2.4. Characterization Data of Product 3 Is Listed Below

3-(3,5-Di-tert-butyl-4-hydroxyphenyl)-3',3'-biindolin-2-one (**3a**) [27], 93% yield; ¹H NMR (400 MHz, CDCl₃) δ 8.88 (s, 1H), 8.12 (s, 1H), 7.28 (s, 2H), 7.25–7.22 (m, 2H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.87 (t, *J* = 7.5 Hz, 2H), 6.78 (s, 1H), 5.17 (s, 1H), 1.32 (s, 18H); ¹³C NMR (101 MHz, CDCl₃) δ 180.9, 153.0, 140.2, 136.9, 135.4, 134.9, 130.0, 127.89, 125.9, 125.8,

124.9, 124.6, 122.5, 122.0, 120.9, 119.5, 117.0, 111.3, 110.1, 57.7, 34.5, 30.3; infrared (IR) (film): γ = 3648, 3353, 2956, 2925, 1710, 1618, 1580, 1491, 1436, 1261, 826, 782 cm^{-1} ; HRMS (electron impact time of flight (EI-TOF)): calculated (calcd.) for $\text{C}_{30}\text{H}_{32}\text{N}_2\text{O}_2$ 452.2464, found 452.2462.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-4'-methyl-3,3'-biindolin-2-one (**3b**), 91% yield; ^1H NMR (400 MHz, CDCl_3) δ 8.73 (s, 1H), 8.08 (s, 1H), 7.20 (t, J = 7.7 Hz, 1H), 7.11 (t, J = 7.0 Hz, 2H), 7.04 (s, 1H), 6.97 (t, J = 7.6 Hz, 2H), 6.87 (d, J = 7.7 Hz, 1H), 6.71 (d, J = 7.1 Hz, 1H), 6.49 (s, 1H), 5.19 (s, 1H), 1.94 (s, 3H), 1.32 (s, 18H); ^{13}C NMR (101 MHz, CDCl_3) δ 153.0, 140.1, 138.0, 136.0, 127.9, 126.1, 124.8, 122.2, 122.1, 110.3, 109.1, 58.3, 34.5, 30.3, 20.4; IR (film): γ = 3637, 3342, 2956, 2925, 1706, 1618, 1322, 1021, 910, 747, 664 cm^{-1} ; HRMS (EI-TOF): calcd. for $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_2$ 466.2620, found 466.2621.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-5'-methyl-3,3'-biindolin-2-one (**3c**), 93% yield, ^1H NMR (400 MHz, CDCl_3) δ 8.86 (s, 1H), 7.95 (d, J = 1.7 Hz, 1H), 7.21 (s, 2H), 7.15–7.07 (m, 2H), 7.05 (d, J = 8.3 Hz, 1H), 6.88 (dd, J = 11.0, 4.1 Hz, 1H), 6.84–6.80 (m, 2H), 6.68 (s, 1H), 6.66 (d, J = 2.5 Hz, 1H), 5.09 (s, 1H), 2.14 (s, 3H), 1.24 (s, 18H); ^{13}C NMR (101 MHz, CDCl_3) δ 181.1, 153.0, 140.2, 135.3, 135.2, 135.1, 130.0, 128.5, 127.8, 126.1, 125.8, 125.0, 124.7, 123.6, 122.4, 120.4, 116.4, 110.9, 110.0, 57.7, 34.4, 30.3, 21.5; IR (film): γ = 3637, 2956, 2925, 1706, 1618, 1471, 1157, 910, 747, 695 cm^{-1} ; HRMS (EI-TOF): calcd. for $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_2$ 466.2623, found 466.2621.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-7'-methyl-3,3'-biindolin-2-one (**3d**), 90% yield, ^1H NMR (400 MHz, CDCl_3) δ 8.90 (s, 1H), 8.03 (d, J = 1.3 Hz, 1H), 7.28 (s, 2H), 7.16 (ddd, J = 14.8, 13.7, 8.0 Hz, 3H), 6.96 (t, J = 7.3 Hz, 1H), 6.92–6.87 (m, 2H), 6.76 (s, 1H), 6.73 (d, J = 2.5 Hz, 1H), 5.16 (s, 1H), 2.22 (s, 3H), 1.32 (s, 18H); ^{13}C NMR (101 MHz, CDCl_3) δ 181.1, 153.0, 140.1, 135.3, 135.2, 135.1, 130.0, 128.5, 127.8, 126.1, 125.8, 125.0, 124.7, 123.6, 122.4, 120.5, 116.4, 110.8, 110.0, 57.7, 34.4, 30.3, 21.5; IR (film): γ = 3537, 3241, 2956, 2925, 1706, 1618, 1471, 1236, 1157, 910, 747 cm^{-1} ; HRMS (EI-TOF): calcd. for $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_2$ 466.2620, found 466.2621.

6'-Bromo-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3,3'-biindolin-2-one (**3e**), 88% yield, ^1H NMR (400 MHz, CDCl_3) δ 8.69 (s, 1H), 8.24 (s, 1H), 7.38 (s, 1H), 7.21 (s, 2H), 7.19 (dd, J = 7.4, 3.2 Hz, 2H), 7.02–6.96 (m, 2H), 6.89 (dd, J = 8.1, 5.1 Hz, 2H), 6.74 (d, J = 2.3 Hz, 1H), 5.18 (s, 1H), 1.31 (s, 18H); ^{13}C NMR (101 MHz, CDCl_3) δ 153.1, 139.9, 137.7, 135.5, 134.6, 129.7, 128.0, 125.6, 125.0, 124.8, 124.7, 122.7, 122.6, 122.3, 117.2, 115.7, 114.1, 110.1, 57.5, 34.4, 30.2; IR (film): γ = 3537, 3441, 2956, 2925, 1706, 1618, 1471, 1322, 1157, 910, 750 cm^{-1} ; HRMS (EI-TOF): calcd. for $\text{C}_{30}\text{H}_{31}\text{BrN}_2\text{O}_2$ 530.1569, found 530.1570.

7'-Chloro-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3,3'-biindolin-2-one (**3f**), 89% yield, ^1H NMR (400 MHz, CDCl_3) δ 9.04 (s, 1H), 8.32 (s, 1H), 7.26 (s, 2H), 7.19 (t, J = 8.1 Hz, 2H), 7.10 (d, J = 7.5 Hz, 1H), 6.97 (dd, J = 14.3, 6.9 Hz, 1H), 6.91 (dd, J = 6.8, 4.2 Hz, 3H), 6.83 (t, J = 7.8 Hz, 1H), 5.19 (s, 1H), 1.32 (s, 18H); ^{13}C NMR (101 MHz, CDCl_3) δ 180.6, 153.1, 140.2, 135.5, 134.5, 134.1, 129.7, 128.0, 127.3, 125.7, 125.1, 124.8, 122.5, 121.5, 120.3, 119.7, 118.4, 116.5, 110.2, 57.6, 34.4, 30.2; IR (film): γ = 3437, 3241, 3056, 2925, 1706, 1618, 1471, 1256, 1157, 910 cm^{-1} ; HRMS (EI-TOF): calcd. for $\text{C}_{30}\text{H}_{31}\text{ClN}_2\text{O}_2$ 486.2074, found 486.2075.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-5'-methoxy-3,3'-biindolin-2-one (**3g**), 92% yield, ^1H NMR (400 MHz, CDCl_3) δ 8.38 (s, 1H), 8.02 (s, 1H), 7.29 (d, J = 6.4 Hz, 2H), 7.26 (s, 1H), 7.21 (t, J = 7.7 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.94 (d, J = 7.7 Hz, 1H), 6.82 (d, J = 2.5 Hz, 1H), 6.75 (dd, J = 8.8, 2.4 Hz, 1H), 6.36 (d, J = 2.3 Hz, 1H), 5.17 (s, 1H), 3.53 (s, 3H), 1.33 (s, 18H); ^{13}C NMR (101 MHz, CDCl_3) δ 180.3, 153.5, 152.9, 140.0, 135.4, 134.8, 131.9, 130.0, 127.9, 126.4, 125.9, 124.9, 122.5, 116.9, 112.3, 111.8, 109.8, 102.5, 57.5, 55.4, 34.4, 30.2; IR (film): γ = 3337, 3141, 2956, 2870, 1706, 1618, 1471, 1206, 1157, 910, 750, 624 cm^{-1} ; HRMS (EI-TOF): calcd. for $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_3$ 482.2569, found 482.2570.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-7'-methoxy-3,3'-biindolin-2-one (**3h**), 90% yield, ^1H NMR (400 MHz, CDCl_3) δ 9.18 (s, 1H), 8.59–8.20 (m, 1H), 7.29 (s, 1H), 7.22 (d, J = 6.0 Hz, 1H), 7.15 (t, J = 8.2 Hz, 1H), 6.94 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H), 6.83 (d, J = 2.5 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 6.54 (d, J = 7.7 Hz, 1H), 5.16 (s, 1H), 3.88 (s, 1H), 1.32 (s, 1H); ^{13}C NMR

(101 MHz, CDCl₃) δ 181.1, 153.0, 145.9, 140.3, 135.3, 135.1, 135.0, 130.1, 127.8, 127.4, 127.2, 125.8, 125.0, 124.1, 122.4, 119.8, 117.6, 113.7, 110.1, 101.9, 57.7, 55.2, 34.5, 30.3; IR (film): γ = 3537, 3241, 3056, 2925, 2870, 1706, 1618, 1236, 1157, 910, 747, 650 cm⁻¹; HRMS (EI-TOF): calcd. for C₃₁H₃₄N₂O₃ 482.2569, found 482.2568.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-5-methyl-3,3'-biindolin-2-one (**3i**), 89% yield; ¹H NMR (400 MHz, DMSO) δ 10.94 (d, *J* = 2.0 Hz, 1H), 10.48 (s, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.17 (s, 2H), 7.04–6.97 (m, 2H), 6.92 (dd, *J* = 11.4, 6.3 Hz, 3H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.3 Hz, 1H), 6.76 (d, *J* = 2.5 Hz, 1H), 2.19 (s, 3H), 1.28 (s, 18H); ¹³C NMR (101 MHz, DMSO) δ 179.1, 152.6, 138.8, 138.3, 136.7, 134.7, 131.0, 130.1, 128.0, 125.8, 125.6, 124.7, 124.1, 120.9, 120.2, 118.2, 115.9, 111.5, 109.3, 56.9, 34.5, 30.2, 20.7; IR (film): γ = 3423, 2968, 2254, 1657, 1487, 1435, 1386, 825, 763, 630 cm⁻¹; HRMS (EI-TOF): calcd. for C₃₁H₃₄N₂O₂ 466.2620, found 466.2619.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-4',5-dimethyl-3,3'-biindolin-2-one (**3j**), 87% yield; ¹H NMR (400 MHz, CDCl₃) δ 8.65 (s, 1H), 8.07 (d, *J* = 1.8 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 7.05 (s, 1H), 6.97 (t, *J* = 7.5 Hz, 2H), 6.92 (s, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 7.1 Hz, 1H), 6.46 (s, 1H), 2.24 (s, 3H), 1.97 (d, *J* = 5.4 Hz, 3H), 1.34 (d, *J* = 4.6 Hz, 18H); ¹³C NMR (101 MHz, CDCl₃) δ 153.0, 138.0, 137.5, 136.0, 131.5, 128.2, 126.9, 124.9, 122.2, 122.1, 109.8, 109.1, 34.6, 30.2, 21.1; IR (film): γ = 3403, 2956, 2925, 1699, 1622, 1464, 1238, 1076, 1016 cm⁻¹; HRMS (EI-TOF): calcd. for C₃₂H₃₆N₂O₂ 480.2777, found 480.2776.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-5,5'-dimethyl-3,3'-biindolin-2-one (**3k**), 91% yield; ¹H NMR (400 MHz, CDCl₃) δ 8.81 (s, 1H), 8.00 (d, *J* = 1.6 Hz, 1H), 7.31 (s, 2H), 7.02 (d, *J* = 3.8 Hz, 2H), 6.96 (d, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.77 (d, *J* = 7.9 Hz, 1H), 6.72 (dd, *J* = 5.9, 1.8 Hz, 2H), 5.15 (s, 1H), 2.35 (s, 3H), 2.21 (s, 3H), 1.33 (s, 18H); ¹³C NMR (101 MHz, CDCl₃) δ 181.0, 152.9, 137.7, 137.3, 135.2, 135.0, 131.7, 131.6, 130.2, 128.1, 126.5, 125.0, 124.0, 123.8, 121.2, 120.5, 117.0, 111.1, 109.7, 57.8, 34.5, 30.3, 21.6, 21.2; IR (film): γ = 3627, 3403, 2956, 1701, 1624, 1492, 1390, 1322, 1160, 1096, 1051, 881 cm⁻¹; HRMS (EI-TOF): calcd. for C₃₂H₃₆N₂O₂ 480.2777, found 480.2775.

6'-Bromo-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-methyl-3,3'-biindolin-2-one (**3l**), 85% yield, ¹H NMR (400 MHz, CDCl₃) δ 8.49 (s, 1H), 8.21 (s, 1H), 7.39 (d, *J* = 1.6 Hz, 1H), 7.23 (s, 2H), 7.03–6.96 (m, 3H), 6.89 (d, *J* = 8.6 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.75 (d, *J* = 2.5 Hz, 1H), 5.17 (s, 1H), 2.24 (s, 3H), 1.32 (s, 18H); ¹³C NMR (101 MHz, CDCl₃) δ 180.5, 153.0, 137.7, 137.5, 135.4, 134.6, 132.0, 129.9, 128.4, 126.3, 125.1, 124.8, 124.7, 122.7, 122.4, 117.3, 115.6, 114.1, 109.7, 57.6, 34.4, 30.2, 21.2; IR (film): γ = 3437, 3141, 2956, 2925, 1706, 1618, 1471, 1322, 1157, 1021, 910, 747, 644 cm⁻¹; HRMS (EI-TOF): calcd. for C₃₁H₃₄BrN₂O₂ 545.1804, found 545.1805.

7'-Chloro-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-methyl-3,3'-biindolin-2-one (**3m**), 87% yield, ¹H NMR (400 MHz, CDCl₃) δ 8.61 (s, 1H), 8.28 (s, 1H), 7.27 (s, 2H), 7.11 (d, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 6.9 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 2.5 Hz, 1H), 6.88–6.79 (m, 1H), 5.18 (s, 1H), 2.25 (s, 3H), 1.33 (s, 18H); ¹³C NMR (101 MHz, CDCl₃) δ 180.3, 153.0, 137.6, 135.4, 134.5, 134.1, 131.9, 129.8, 128.4, 127.4, 126.4, 125.1, 124.9, 121.4, 120.3, 119.8, 118.6, 116.4, 109.7, 57.6, 34.4, 30.2, 21.2. IR (film): γ = 3137, 3041, 2956, 2870, 1706, 1618, 1378, 1322, 1157, 910, 744, 603 cm⁻¹; HRMS (EI-TOF): calcd. for C₃₁H₃₄ClN₂O₂ 501.2309, found 501.2308.

4'-Bromo-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-methyl-3,3'-biindolin-2-one (**3n**), 88% yield, ¹H NMR (400 MHz, CDCl₃) δ 8.57 (s, 1H), 8.40 (s, 1H), 7.92 (s, 1H), 7.17–7.05 (m, 2H), 7.02 (s, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.81 (t, *J* = 7.4 Hz, 2H), 6.70 (d, *J* = 7.6 Hz, 1H), 6.35 (s, 1H), 5.21 (s, 1H), 2.23 (s, 3H), 1.34 (d, *J* = 33.0 Hz, 18H); ¹³C NMR (101 MHz, CDCl₃) δ 183.7, 153.1, 138.9, 138.5, 135.9, 135.3, 134.9, 131.0, 130.0, 128.1, 126.4, 125.9, 124.9, 124.7, 122.8, 113.8, 110.7, 110.0, 57.7, 34.6, 30.4, 30.1, 21.2; IR (film): γ = 3537, 3241, 3024, 2956, 2870, 1706, 1471, 1322, 1157, 1021, 910, 747, 644 cm⁻¹; HRMS (EI-TOF): calcd. for C₃₁H₃₄BrN₂O₂ 545.1804, found 545.1805.

5-Chloro-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4'-methyl-3,3'-biindolin-2-one (**3o**), 90% yield; ^1H NMR (400 MHz, CDCl_3) δ 8.62 (s, 1H), 8.28 (s, 1H), 7.27 (s, 2H), 7.11 (d, $J = 7.4$ Hz, 1H), 7.01 (d, $J = 6.9$ Hz, 2H), 6.96 (d, $J = 8.0$ Hz, 1H), 6.92 (d, $J = 2.5$ Hz, 1H), 6.89–6.79 (m, 1H), 5.18 (s, 1H), 2.25 (s, 3H), 1.33 (s, 18H); ^{13}C NMR (101 MHz, CDCl_3) δ 180.3, 153.0, 137.6, 135.4, 134.5, 134.1, 131.9, 129.8, 128.43, 127.4, 126.4, 125.1, 124.8, 121.4, 120.3, 119.8, 118.6, 116.4, 109.7, 57.6, 34.4, 30.2, 21.2; IR (film): $\gamma = 3403, 2955, 2924, 2254, 1714, 1613, 1472, 1435, 1160, 1007, 763, 630\text{ cm}^{-1}$; HRMS (EI-TOF): calcd. for $\text{C}_{31}\text{H}_{34}\text{ClN}_2\text{O}_2$ 501.2309, found 501.2308.

6'-Bromo-5-chloro-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3,3'-biindolin-2-one (**3p**), 93% yield; ^1H NMR (400 MHz, DMSO) δ 11.17 (d, $J = 2.1$ Hz, 1H), 10.79 (s, 1H), 7.58 (d, $J = 1.7$ Hz, 1H), 7.30 (dd, $J = 8.3, 2.1$ Hz, 1H), 7.11 (d, $J = 2.1$ Hz, 1H), 7.09 (s, 2H), 7.03–6.99 (m, 3H), 6.94–6.86 (m, 2H), 1.28 (s, 18H); ^{13}C NMR (101 MHz, DMSO) δ 178.6, 152.9, 140.1, 138.7, 137.7, 136.4, 130.1, 127.9, 125.9, 125.5, 124.9, 124.4, 123.8, 121.9, 121.3, 115.1, 114.3, 113.9, 111.3, 57.1, 34.5, 30.2; IR (film): $\gamma = 3628, 3345, 2957, 2925, 1711, 1615, 1436, 1375, 1079, 1021, 1007, 808\text{ cm}^{-1}$; HRMS (EI-TOF): calcd. for $\text{C}_{30}\text{H}_{30}\text{BrClN}_2\text{O}_2$ 564.1179, found 564.1179.

5-Bromo-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3,3'-biindolin-2-one (**3q**), 87% yield; ^1H NMR (400 MHz, DMSO) δ 11.02 (d, $J = 2.0$ Hz, 1H), 10.77 (s, 1H), 7.43 (dd, $J = 8.3, 2.0$ Hz, 1H), 7.36 (d, $J = 8.2$ Hz, 1H), 7.20 (d, $J = 1.9$ Hz, 1H), 7.14 (s, 2H), 7.08–7.02 (m, 2H), 6.96 (d, $J = 8.3$ Hz, 1H), 6.89 (d, $J = 7.9$ Hz, 1H), 6.86–6.79 (m, 2H), 1.28 (s, 18H); ^{13}C NMR (101 MHz, DMSO) δ 178.7, 152.9, 140.6, 138.6, 137.0, 136.8, 130.6, 130.1, 127.7, 125.3, 24.8, 123.9, 121.1, 119.8, 118.4, 115.0, 113.1, 111.7, 57.1, 34.6, 30.2; IR (film): $\gamma = 3404, 2983, 2356, 1677, 1472, 1359, 1251, 905, 826, 764\text{ cm}^{-1}$; HRMS (EI-TOF): calcd. for $\text{C}_{30}\text{H}_{31}\text{BrN}_2\text{O}_3$ 530.1569, found 530.1572.

5-Bromo-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4'-methyl-3,3'-biindolin-2-one (**3r**), 88% yield; ^1H NMR (400 MHz, DMSO) δ 10.99 (d, $J = 1.9$ Hz, 1H), 10.68 (s, 1H), 7.44 (dd, $J = 8.2, 1.8$ Hz, 1H), 7.23 (d, $J = 8.0$ Hz, 1H), 7.08 (d, $J = 15.5$ Hz, 2H), 6.95 (t, $J = 7.9$ Hz, 3H), 6.63 (d, $J = 7.1$ Hz, 1H), 6.45 (s, 1H), 1.86 (s, 3H), 1.31 (s, 18H); ^{13}C NMR (101 MHz, DMSO) δ 152.9, 140.4, 138.5, 137.9, 130.6, 127.9, 124.4, 121.3, 121.1, 112.9, 111.9, 109.6, 57.9, 34.6, 30.2; IR (film): $\gamma = 3421, 2924, 2256, 1655, 1472, 1379, 1051, 1005, 826, 764\text{ cm}^{-1}$; HRMS (EI-TOF): calcd. for $\text{C}_{31}\text{H}_{33}\text{BrN}_2\text{O}_2$ 544.1725, found 544.1721.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1-methyl-3,3'-biindolin-2-one (**3s**), 92% yield; ^1H NMR (400 MHz, CDCl_3) δ 8.07 (s, 1H), 7.29 (q, $J = 7.9$ Hz, 3H), 7.25 (d, $J = 1.3$ Hz, 1H), 7.22–7.16 (m, 1H), 7.15–7.05 (m, 1H), 7.02 (t, $J = 7.2$ Hz, 1H), 6.94 (dd, $J = 7.6, 4.2$ Hz, 2H), 6.91–6.84 (m, 1H), 6.80 (d, $J = 2.5$ Hz, 1H), 5.14 (s, 1H), 3.32 (s, 3H), 1.32 (s, 18H); ^{13}C NMR (101 MHz, CDCl_3) δ 178.2, 152.9, 143.0, 136.9, 135.2, 134.2, 130.1, 127.9, 125.9, 125.6, 124.9, 124.3, 124.1, 122.5, 121.9, 120.8, 120.7, 119.8, 119.4, 117.5, 111.1, 108.1, 102.5, 57.1, 34.5, 30.2, 26.6; IR (film): $\gamma = 3637, 3301, 2956, 2925, 1706, 1471, 1436, 1237, 1143, 909, 803, 750, 668\text{ cm}^{-1}$; HRMS (EI-TOF): calcd. for $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_2$ 466.2620, found 466.2617.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1'-methyl-3,3'-biindolin-2-one (**3t**), 94% yield; ^1H NMR (400 MHz, CDCl_3) δ 8.07 (s, 1H), 7.29 (q, $J = 7.9$ Hz, 3H), 7.25 (d, $J = 1.3$ Hz, 1H), 7.22–7.16 (m, 1H), 7.15–7.05 (m, 1H), 7.02 (t, $J = 7.2$ Hz, 1H), 6.94 (dd, $J = 7.6, 4.2$ Hz, 2H), 6.91–6.84 (m, 1H), 6.80 (d, $J = 2.5$ Hz, 1H), 5.14 (s, 1H), 3.32 (s, 3H), 1.32 (s, 18H); ^{13}C NMR (101 MHz, CDCl_3) δ 178.2, 152.9, 143.0, 136.9, 135.2, 134.2, 130.1, 127.9, 125.9, 125.6, 124.9, 124.3, 124.1, 122.5, 121.9, 120.8, 120.7, 119.7, 119.4, 117.5, 111.1, 108.1, 102.5, 57.1, 34.4, 30.2, 26.6; IR (film): $\gamma = 3637, 3301, 2956, 1706, 1619, 1471, 1321, 1237, 1143, 909, 803, 750\text{ cm}^{-1}$; HRMS (EI-TOF): calcd. for $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_2$ 466.2620, found 466.2617.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(1H-pyrrol-2-yl)indolin-2-one (**3u**), 94% yield; ^1H NMR (400 MHz, DMSO) δ 10.57 (s, 2H), 7.39 (d, $J = 7.4$ Hz, 1H), 7.22 (td, $J = 7.7, 1.1$ Hz, 1H), 7.01 (td, $J = 7.6, 0.8$ Hz, 1H), 6.95–6.89 (m, 2H), 6.83 (s, 2H), 6.68 (dd, $J = 4.3, 2.6$ Hz, 1H), 5.91 (dd, $J = 5.6, 2.6$ Hz, 1H), 5.82 (dd, $J = 4.5, 3.0$ Hz, 1H), 1.26 (s, 18H); ^{13}C NMR (101 MHz, DMSO) δ 177.9, 152.8, 141.2, 138.5, 133.7, 132.1, 129.3, 127.8, 125.3, 123.6, 121.6, 118.9, 109.5, 107.3, 106.2, 57.3, 34.4, 30.1; IR (film): $\gamma = 3637, 3201, 2956, 1706, 1645, 1540, 1436, 955, 803, 750, 608\text{ cm}^{-1}$; HRMS (EI-TOF): calcd. for $\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_2$ 402.2707, found 402.2701.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-5-methyl-3-(1H-pyrrol-2-yl)indolin-2-one (**3v**), 95% yield, ^1H NMR (400 MHz, CDCl_3) δ 9.00 (s, 1H), 8.71 (dd, J = 28.4, 6.2 Hz, 1H), 7.10 (s, 1H), 7.01 (d, J = 7.9 Hz, 1H), 6.88 (s, 2H), 6.81 (d, J = 8.0 Hz, 2H), 6.13 (dd, J = 5.2, 2.5 Hz, 1H), 6.05 (t, J = 2.8 Hz, 1H), 5.15 (s, 1H), 2.31 (s, 3H), 1.33 (s, 18H); ^{13}C NMR (101 MHz, CDCl_3) δ 180.4, 180.4, 153.0, 135.7, 134.0, 132.3, 132.1, 128.4, 126.3, 123.9, 118.6, 109.9, 108.6, 107.7, 57.8, 34.3, 30.2, 21.3. IR (film): γ = 3337, 3141, 3025, 2956, 2870, 1706, 1618, 1471, 1378, 1322, 910, 750, 644 cm^{-1} ; HRMS (EI-TOF): calcd. for $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_2$ 416.2464, found 416.2464.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-5-methoxy-3-(1H-pyrrol-2-yl)indolin-2-one (**3w**), 97% yield, ^1H NMR (400 MHz, CDCl_3) δ 9.02 (s, 1H), 8.62 (s, 1H), 6.89 (d, J = 2.4 Hz, 1H), 6.87 (s, 2H), 6.84 (d, J = 8.5 Hz, 1H), 6.81 (dd, J = 3.9, 2.4 Hz, 1H), 6.75 (dd, J = 8.5, 2.5 Hz, 1H), 6.14 (dd, J = 5.9, 2.8 Hz, 1H), 6.08 (t, J = 3.5 Hz, 1H), 5.14 (s, 1H), 3.77 (s, 3H), 1.32 (s, 18H); ^{13}C NMR (101 MHz, CDCl_3) δ 180.2, 155.9, 153.1, 135.7, 135.3, 133.3, 131.9, 128.2, 123.8, 118.7, 112.9, 112.5, 110.5, 108.6, 107.8, 58.1, 55.8, 34.3, 30.2; IR (film): γ = 3037, 3141, 2956, 2925, 2770, 1706, 1618, 1471, 1436, 1378, 1322, 1236, 1157, 1021, 850, 747, 624 cm^{-1} ; HRMS (EI-TOF): calcd. for $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_3$ 432.2413, found 432.2414.

3. Results and Discussion

3.1. Sustainable Methodology

To start this work, firstly we investigated the model 1,6-conjugate addition reaction between *para*-quinone methide derived from isatin (**1a**) and indole (**2a**) in glycerol, and screened the reaction conditions. The procedure of the reaction was monitored by TLC and the results are summarized in Table 1. It is noted that 2-methyltetrahydrofuran as a biomass-derived solvent, is an immiscible solvent with glycerol. The desired product **3a** can be extracted with 2-methyltetrahydrofuran from the reaction mixture in glycerol at room temperature, because **3a** is insoluble in high viscous glycerol at room temperature although it is soluble in low viscous glycerol at high temperature ($>100^\circ\text{C}$). To optimize the reaction conditions, firstly, we investigated the catalytic effect of diphenyl phosphoric acid on reaction at different temperatures for 24 h, and noted that there was no reaction at 25°C because of the insolubility of substrate (**1a**) in high viscous glycerol (Table 1, entry 1). When we increased the reaction temperature from 25°C to 60°C to make the solvent low viscous and improved the solubility of substrate (**1a**), a rare amount of desired product (**3a**) was observed on TLC (Table 1, entry 2). A continuous increase of temperature to 80°C and 120°C increased the yield of the required product to rare, 60% and 86% respectively (Table 1, entries 3 and 4). When we set the temperature of reaction according to the yield, then we screened the different type of catalyst to identify the best reaction protocol. After further screening the different catalysts like H_3PO_4 , PhCO_2H , FeCl_3 , we found that FeCl_3 could be easily dissolved in glycerol and became the best choice of catalysts according to the yield (Table 1, entries 5–7). After the loading of FeCl_3 catalyst was investigated, we found that 10 mol% is the best loading of catalyst to give the desired indole-containing oxindole **3a** in 93% yield (Table 1, entries 7–9). For comparison, we have studied the catalytic activity of FeCl_3 in different conventional volatile organic solvents, such as toluene, xylene and 1,2-dichloroethane under reflux, finding that the efficiency of the 1,6-conjugate addition reaction was remarkably lowered (Table 1, entries 10–12). Thus, the optimized reaction conditions were identified (Table 1, entry 8).

With the optimized reaction conditions in hand, our next step was to investigate the scope of substrate with a different type and at different position of substitutions. To our delight, FeCl_3 dissolved in glycerol showed near-perfect performance for such an organic transformation and the results are summarized in Table 2. Firstly, we observed that a wide range of indoles with electron-withdrawing or electron-donating groups are suitable nucleophiles to afford the corresponding products with high yields (88–93%, Table 2, entries 1–8). Meanwhile, we also examined the effect of substitution on *para*-quinone methides derived from isatins, and no obvious electron effect was observed. Various electron-withdrawing or electron-donating groups, such as Me, Cl and Br, could also be successfully employed in the 1,6-conjugate addition reaction to reveal excellent results (85–93%,

Table 2, entries 9–18). It is noteworthy that the effect of protecting the group on the reaction protocol was also examined to show that there was no significant effect on the yield of required products when indole or *para*-quinone methide derived from isatin was protected with *N*-methylation consecutively (Table 2, entries 19–20).

Furthermore, we then expanded the generality of the FeCl_3 dissolved in glycerol catalyzed 1,6-conjugate addition reaction by using new nucleophile pyrrole, and the results obtained are shown in Scheme 1. The different *para*-quinone methides derived from isatins could react with pyrrole to afford the corresponding product pyrrole-containing oxindoles in excellent yields (94–97%) under the above standard conditions.

Scheme 1. 1,6-Conjugate addition reaction with pyrrole.

3.2. Catalytic System Recycling

The good results prompted us to study the recyclability of the catalytic system in a batch. We developed FeCl_3 dissolved in glycerol as the catalytic system recycling for 1,6-conjugate addition reaction of oxindole-derived methides and indoles for the construction of 3,3-disubstituted oxindoles. The separation of the products was realized by a simple extraction with 2-methyltetrahydrofuran, which is an immiscible solvent with glycerol, while the retained glycerol layer still contained the catalyst FeCl_3 . The catalytic system with FeCl_3 dissolved in glycerol has some obvious advantages, such as, long life time and high level of reusability. When the reaction between **1a** and **2a** was completed under the standard reaction conditions, the final product **3a** was extracted using 2-methyltetrahydrofuran, and the retained glycerol phase with FeCl_3 was reused by just adding the substrates again under the same reaction protocol. As shown in Table 3, we observed that this procedure could be repeated up to 5 times with no loss of catalytic activity, and the desired product **3a** was obtained in excellent yield every time, which bears witness to the catalyst's robustness.

4. Conclusions

A highly efficient and atom-economical synthesis of bioactive indole-containing oxindoles was developed by using a FeCl_3 dissolved in glycerol catalyzed 1,6-conjugated addition reaction of *para*-quinone methides derived from isatins and indoles. Pyrrole was also applicable to afford the corresponding pyrrole-containing oxindoles in excellent yields with this protocol. The desired 3,3-disubstituted oxindoles could be extracted using the biomass-derived solvent 2-methyltetrahydrofuran and the retained glycerol layer with FeCl_3 could be reused up to 5 times with very high efficiency. The superior advantages of the sustainable methodology include the ready availability, low price and environmentally benign character of iron catalysis, easy product separation, and a recyclable catalyst system. The current iron catalysis meets the increasing demand of sustainability, such as energy resources, cheap catalysts, non-toxic reagents and green solvents.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2071-1050/10/8/2922/s1>, NMR spectra for all products.

Author Contributions: L.T. conceived and directed the project, and analyzed the data; A.R. performed the experiments and the characterizations. Both authors co-wrote the manuscript.

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