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Direct One-Pot Synthesis of Naphthoxindoles from 4-Bromooxindoles by Suzuki–Miyaura Coupling and Aldol Condensation Reactions

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An efficient one-pot synthesis of naphthoxindoles by using 4-bromoindolin-2-ones and 2-formylphenylboronic acids has been developed. The coupling reaction proceeds in good to excellent yields under microwave irradiation through a Suzuki–Miyaura coupling and an aldol condensation cascade reaction. In addition, this protocol permits the facile construction of naphthoxindoles through an expanded scope of substrates.

Introduction

Polycyclic compounds that contain an oxindole moiety are important to the search for new biologically active agents for the pharmaceutical and agrochemical industries.[1] Naturally occurring oxindoles include aristolactams **1**, anhydrohapaloxindole A (**2**), and prioline (**3**, see Figure 1). The aristolactams are a large family of compounds that exhibit various bioactivities, which include antitumor effects against human cancer cell lines.[2] Anhydrohapaloxindole A (**2**) was isolated from a cultured strain of a terrestrial blue-green alga.[3] Prioline (**3**) was isolated from the roots of a species of *Salvia*, a genus whose plants are used in Chinese folk medicine for the treatment of tonsillitis, pharyngitis, pulmonary tuberculosis, and bacillary dysentery.[4] Of particular interest is sunitinib (**4**), which is a highly active receptor tyrosine kinase inhibitor that is used in the treatment of advanced renal cell carcinoma and gastrointestinal stromal tumors.[5]

As part of a drug discovery program for the synthesis of unusual heterocycles,[6] we became interested in heteroaromatic scaffolds that contain oxindole, particularly naphthoxindoles (i.e., **5**). The synthesis of these compounds would provide access to a new ring system with highly diversified options for substitution. Reports of syntheses of naphthoxindoles are limited. For example, Felpin and coworkers reported a linear three-step sequence that employed a complete palladium-catalyzed Heck coupling, C–H arylation, and reductive cyclization reactions.[7] In addition, Li and co-workers employed a Diels–Alder reaction between arynes and methyleneindolinones to obtain naphthoxindoles.[8] However, a simple, rapid, and convergent method is needed to construct this tetracyclic ring system. Herein, we describe a generalized synthetic method for naphthoxindole that is tolerant of various substituents and functional groups.

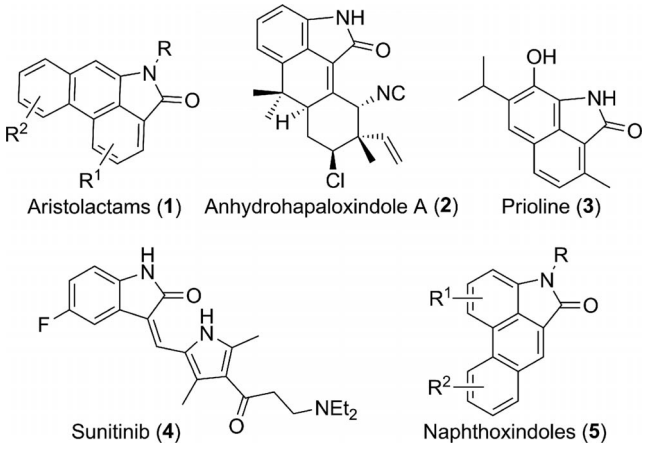

Figure 1. Natural and pharmaceutical compounds that contain the oxindole core.

Results and Discussion

Recently, we disclosed the total synthesis of aristolactam derivatives by employing Suzuki–Miyaura coupling and aldol condensation cascade reactions.[6a] This protocol is highly efficient for furnishing aristolactams **1** through the one-pot reaction of 4-bromoisoindolin-1-ones **6** with 2-formylphenylboronic acid (**7a**) under microwave irradiation (see Figure 2, A). The design of a new synthetic approach toward naphthoxindoles **5** began by the simple replacement of isoindolin-1-one **6** with oxindole **9** (see Figure 2, B). We anticipated that the aldol condensation would be ac-

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celerated by the presence of the more acidic C-3 methylene protons of oxindole **9**. Microwave irradiation was used to facilitate the rapid construction of a wide range of naphthoxindole libraries.[9]

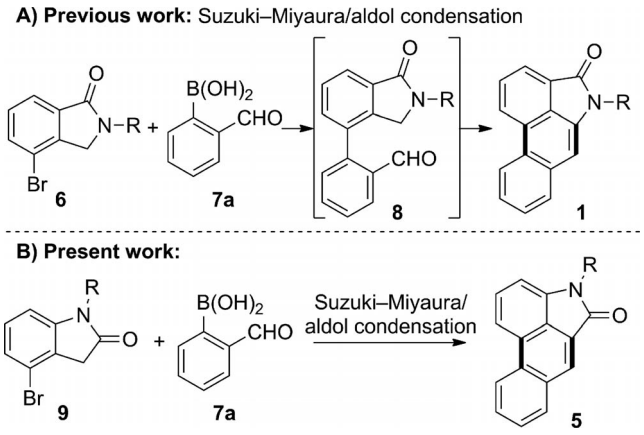


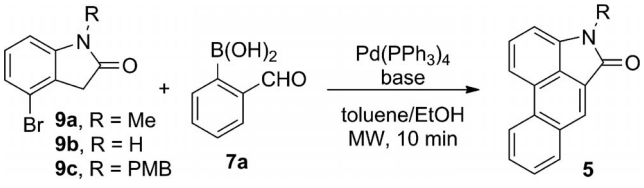
Figure 2. One-pot synthesis by Suzuki–Miyaura coupling and aldol condensation reactions.

On the basis of our previous work, this reaction was optimized by using 4-bromooxindole **9a**[10] and 2-formylphenylboronic acid (**7a**) as the coupling partners in a Pd system under microwave irradiation (see Table 1). Using our previously reported conditions, the desired naphthoxindole **5a** was obtained in 74% yield. Decreasing the irradiation temperature to 130 or 110 °C led to incomplete conversion with yields of 68 and 63%, respectively (see Table 1, Entries 2 and 3). Various inorganic bases, including K_3PO_4, K_2CO_3, and Na_2CO_3, were examined (see Table 1, Entries 4–6). The most effective one was K_2CO_3, which afforded a 93% yield (see Table 1, Entry 5). The optimized conditions to provide a reliable Pd catalytic system that employed microwave irradiation (MW) included $Pd(PPh_3)_4$ (5 mol-%), K_2CO_3 (3 equiv.), and toluene/EtOH (2:1) at 150 °C for 10 min.

Next, we explored the compatibility of the *N*-substituent of 4-bromooxindole under the optimized conditions. The proton at N-1 of **9b** tolerated the conditions of this coupling reaction, and the corresponding product **5b** was produced, but the yield was lower (see Table 1, Entry 7). We hypothesized that the facile N–H proton abstraction ($pK_a \approx 18.2$) from 4-bromooxindole **9b** caused the transformation to be less effective under basic conditions.[11] The *para*-methoxybenzyl (PMB) group of **9c** tolerated the coupling reaction, and an excellent product yield was obtained (see Table 1, Entry 8).

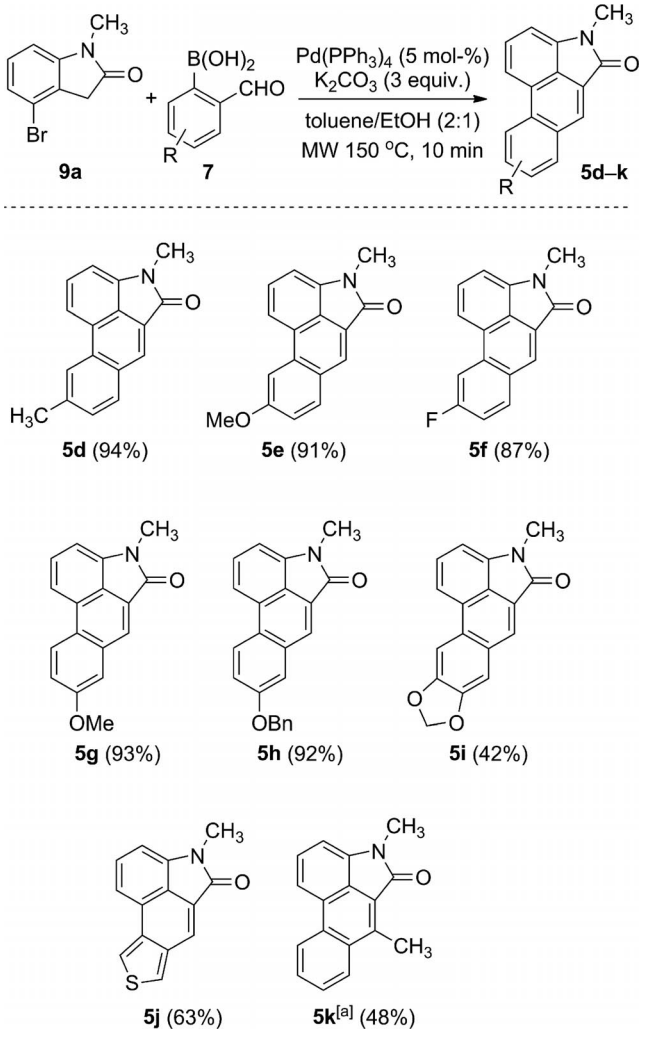
With the suitable reaction conditions in hand, a variety of substituted 2-formylphenylboronic acids and heteroarylboronic acids were coupled with 4-bromooxindole **9a** under microwave irradiation (see Scheme 1). The reaction proceeded smoothly and afforded excellent yields with both

Table 1. Optimization of the one-pot naphthoxindole procedure.[a]



Entry	R	Base	Temp. [°C]	Product	% Yield[b]
1	CH_3	Cs_2CO_3	150	**5a**	74
2	CH_3	Cs_2CO_3	130	**5a**	68
3	CH_3	Cs_2CO_3	110	**5a**	63
4	CH_3	K_3PO_4	150	**5a**	85
5	CH_3	K_2CO_3	150	**5a**	93
6	CH_3	Na_2CO_3	150	**5a**	25
7	H	K_2CO_3	150	**5b**	76
8	PMB	K_2CO_3	150	**5c**	88

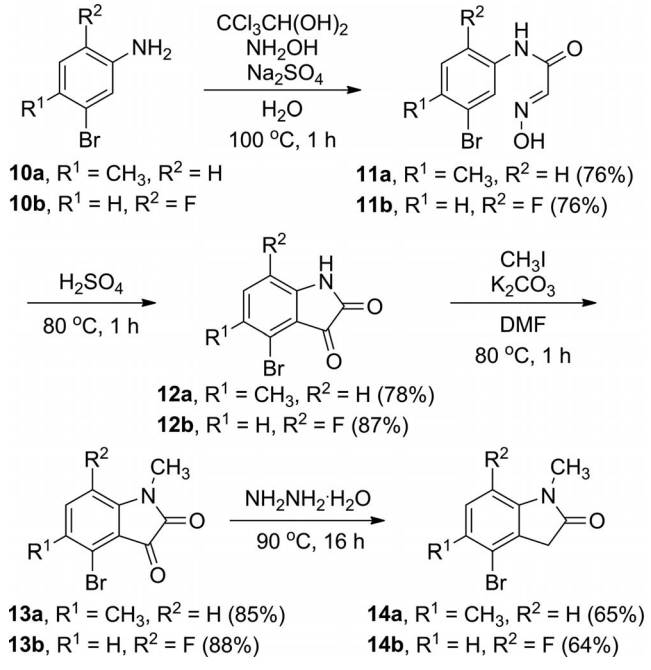
[a] Reagents and conditions: oxindole **9** (0.5 mmol), boronic acid **7a** (0.6 mmol), $Pd(PPh_3)_4$ (5 mol-%), base (1.5 mmol), toluene/EtOH (2:1, 3 mL), microwave irradiation, 10 min. [b] Isolated yield.



Scheme 1. The scope of substituted 2-formylphenylboronic acids and heteroarylboronic acid. Reagents and conditions: oxindole **9a** (0.5 mmol), the boronic acid (0.6 mmol), $Pd(PPh_3)_4$ (5 mol-%), K_2CO_3 (1.5 mmol), toluene/EtOH (2:1, 3 mL), MW, 150 °C, 10 min. [a] 2-Acetylphenylboronic acid (**7k**) was used as a coupling partner.

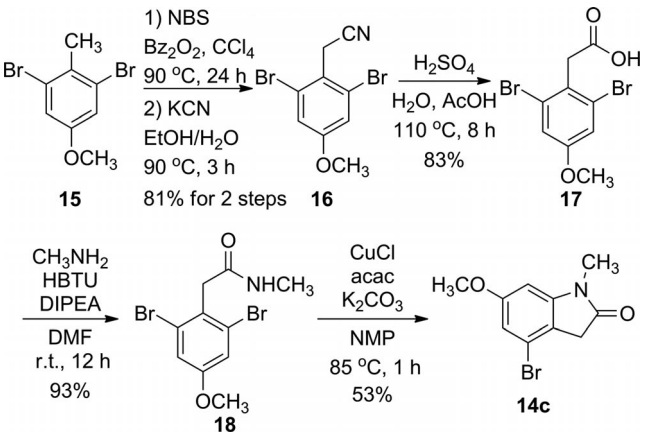
electron-rich and electron-deficient substituents on the phenylboronic acids **7d**–**7h** to give compounds **5d**–**5h**. However, the 1,3-dioxolyl-substituted phenylboronic acid **7i** was less effective and gave a 42% yield for naphthoxindole **5i**. Naphthoxindole **5j** was also obtained by coupling **9a** with a thiophenylboronic acid **7j**, but the product was produced in a slightly lower yield, potentially from the poisoning of the Pd catalyst. This protocol was compatible with 2-acetylphenylboronic acid **7k**, which contains a less reactive ketone moiety, and afforded 6-methylnaphthoxindole **5k** in moderate yield.[6b]

Encouraged by these results, we further investigated the scope of the reaction by employing other substituted 4-bromooxindoles, which included those with fluoro, methyl, and methoxy groups. Substituted 4-bromooxindoles **14a**, **14b**, and **14c** were readily prepared by following modified literature methods. The 5-methyl- and 7-fluoro-substituted 4-bromooxindoles **14a** and **14b**, respectively, were obtained in good yield in four steps through an acid-catalyzed Friedel–Crafts cyclization of a hydroxyimine and a Wolff–Kishner reduction (see Scheme 2). The key intermediate isatins **12a** and **12b** were obtained in two steps from the corresponding anilines **10a** and **10b** through a coupling reaction with $CCl_3CH(OH)_2$ and Friedel–Crafts cyclization of the resulting hydroxyimines **11a** and **11b**, respectively.[12] Methylation of isatins **12a** and **12b** by treatment with CH_3I afforded the *N*-methylated isatins **13a** and **13b** in good yields.[13] Finally, a Wolff–Kishner reduction in the presence of hydrazine provided the desired 4-bromooxindoles **14a** and **14b**.[10b]

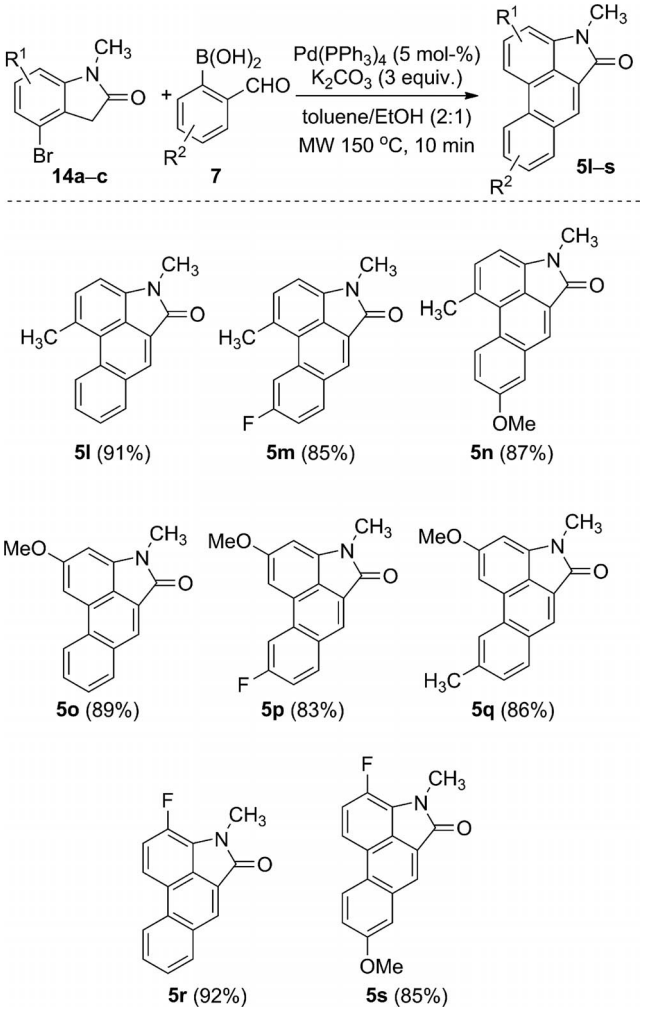


Scheme 2. Preparation of substituted 4-bromoindolin-2-ones **14a** and **14b** (DMF = *N*,*N*-dimethylformamide).

We envisioned the alternative approach to the targeted 6-methoxy-substituted 4-bromooxindole **14c** to occur through a Cu-catalyzed Ullmann-type cyclization of a 2-bromophenylacetamide (see Scheme 3). The conversion of toluene **15** into phenylacetonitrile **16** was accomplished through a two-step sequence that consisted of benzylic bromination



Scheme 3. Preparation of 4-bromo-6-methoxy-1-methylindolin-2-one (**14c**, NBS = *N*-bromosuccinimide, HBTU = *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, DIPEA = *N*,*N*-diisopropylethylamine, acac = acetylacetonate, NMP = *N*-methylpyrrolidone).



Scheme 4. The scope of substituted oxindoles.

followed by nitrile substitution of the resulting benzyl bromide. The acid-catalyzed hydrolysis of **16** and condensation of the resulting carboxylic acid by treatment with methylamine gave amide **18** in good yield. Finally, the intramolecular formation of a five-membered lactam ring through the Cu-catalyzed amidation reaction reported by van den Hoogenband and co-workers produced 4-bromooxindole **14c** in 53% yield.[14]

The scope of the reaction of the substituted 4-bromooxindoles (i.e., **14a**, **14b**, and **14c**) was evaluated with respect to 2-formylphenylboronic acids **7a**, **7d**, **7f**, and **7g** (see Scheme 4). The one-pot reaction was compatible with various electron-withdrawing and electron-donating substituents on the substrates. Notably, the Suzuki–Miyaura coupling reaction tolerated the steric hindrance from the methyl group in 4-bromooxindole **14a** to provide **5l**–**5n** in excellent yields.

Conclusions

In summary, we have developed a one-pot method that proceeds through Suzuki–Miyaura coupling and aldol condensation reactions to synthesize naphthoxindoles in good to excellent yields. This reaction employs 4-bromooxindoles and 2-formylphenylboronic acids as coupling partners under microwave irradiation. In addition, the substituted oxindoles were prepared either by a Friedel–Crafts cyclization and Wolff–Kishner reduction of an isatin or by a Cu-catalyzed amidation of a 2-bromophenylacetamide. Further studies that are aimed at evaluating the bioactivities of these new naphthoxindoles, particularly against human cancer cell lines, are being pursued.

Experimental Section

General Procedure for the Direct One-Pot Synthesis of Naphthoxindoles: To a thick-walled borosilicate glass vial (3 mL) were sequentially added oxindole **9** (0.5 mmol), the boronic acid (0.6 mmol), $Pd(PPh_3)_4$ (5 mol-%), and K_2CO_3 (1.5 mmol). The mixture was suspended in toluene/EtOH (2:1, 3 mL). The reaction vial was sealed and then placed into a microwave reactor and irradiated at 150 °C for 10 min. (Usually, the average microwave power ranged from 60 to 80 W, and the internal pressure was 6–8 bars.) After cooling to room temperature, the mixture was treated with EtOAc, and the resulting mixture was filtered through a short pad of Celite. The solvents were removed with a rotary evaporator, and the residue was purified by silica gel flash column chromatography (EtOAc/hexanes) to afford the naphthoxindole product.

4-Methylnaphtho[3,2,1-*cd*]indol-5(4*H*)-one (5a): Yellow solid (93% yield); m.p. 148 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.79 (d, J = 8.3 Hz, 1 H), 8.54 (s, 1 H), 8.31 (d, J = 8.1 Hz, 1 H), 8.26 (d, J = 8.3 Hz, 1 H), 7.86 (t, J = 7.9, 7.4 Hz, 1 H), 7.75 (t, J = 7.6 Hz, 1 H), 7.67 (t, J = 7.9, 7.8 Hz, 1 H), 7.23 (d, J = 7.3 Hz, 1 H), 3.38 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.7, 140.0, 133.0, 131.9, 131.4, 129.4, 129.3, 127.3, 126.8, 126.0, 124.6, 123.8, 120.7, 116.1, 105.9, 26.3 ppm. HRMS (EI): calcd. for $C_{16}H_{11}NO$ [M]$^+$ 233.0841; found 233.0845.

Naphtho[3,2,1-*cd*]indol-5(4*H*)-one (5b): Pale yellow solid (76% yield); m.p. 233 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.86 (s, 1 H), 8.79 (d, J = 8.0 Hz, 1 H), 8.51 (s, 1 H), 8.33 (d, J = 7.9 Hz, 1 H), 8.23 (d, J = 8.4 Hz, 1 H), 7.86 (t, J = 7.0, 8.2 Hz, 1 H), 7.75 (t, J = 7.6 Hz, 1 H), 7.62 (t, J = 7.8 Hz, 1 H), 7.08 (d, J = 7.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 168.9, 139.0, 133.6, 132.4, 131.9, 129.8, 129.7, 127.7, 126.9, 126.8, 125.9, 124.2, 122.5, 115.9, 107.1 ppm. HRMS (EI): calcd. for $C_{15}H_9NO$ [M]$^+$ 219.0684; found 219.0684.

4-(4-Methoxybenzyl)naphtho[3,2,1-*cd*]indol-5(4*H*)-one (5c): Yellow solid (88% yield); m.p. 173 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.78 (d, J = 8.0 Hz, 1 H), 8.59 (s, 1 H), 8.33 (d, J = 8.0 Hz, 1 H), 8.25 (d, J = 8.5 Hz, 1 H), 7.86 (t, J = 7.5 Hz, 1 H), 7.75 (t, J = 7.4 Hz, 1 H), 7.61 (t, J = 7.8 Hz, 1 H), 7.34 (d, J = 9.0 Hz, 2 H), 7.17 (d, J = 7.4 Hz, 1 H), 6.86 (d, J = 8.5 Hz, 2 H), 5.05 (s, 2 H), 3.67 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 167.1, 159.0, 139.4, 133.5, 132.4, 131.9, 130.0, 129.7, 129.6, 129.4 (2), 127.8, 127.6, 126.7, 124.7, 124.2, 121.2, 116.7, 114.5 (2), 107.1, 55.5, 43.1 ppm. HRMS (EI): calcd. for $C_{23}H_{17}NO_2$ [M]$^+$ 339.1259; found 339.1251.

4,9-Dimethylnaphtho[3,2,1-*cd*]indol-5(4*H*)-one (5d): Yellow solid (94% yield); m.p. 218 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.61 (s, 1 H), 8.50 (s, 1 H), 8.25 (d, J = 8.0 Hz, 1 H), 8.20 (d, J = 8.3 Hz, 1 H), 7.66 (t, J = 7.7, 8.0 Hz, 1 H), 7.59 (d, J = 8.2 Hz, 1 H), 7.22 (d, J = 7.3 Hz, 1 H), 3.38 (s, 3 H), 2.61 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.7, 139.9, 139.6, 131.7, 131.5, 131.0, 129.0, 128.9, 126.7, 125.7, 123.6, 123.4, 120.9, 116.0, 105.8, 26.3, 21.6 ppm. HRMS (EI): calcd. for $C_{17}H_{13}NO$ [M]$^+$ 247.0997; found 247.0994.

9-Methoxy-4-methylnaphtho[3,2,1-*cd*]indol-5(4*H*)-one (5e): Yellow solid (91% yield); m.p. 197 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.46 (s, 1 H), 8.31 (d, J = 8.0 Hz, 1 H), 8.22 (d, J = 9.0 Hz, 1 H), 8.18 (d, J = 2.5 Hz, 1 H), 7.63 (t, J = 8.3, 7.4 Hz, 1 H), 7.37 (dd, J = 2.6, 8.8 Hz, 1 H), 7.20 (d, J = 7.2 Hz, 1 H), 4.01 (s, 3 H), 3.37 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.8, 160.4, 139.8, 133.5, 133.4, 128.5, 127.5, 126.7, 125.5, 122.0, 121.2, 117.7, 116.4, 105.8, 104.9, 55.8, 26.2 ppm. HRMS (EI): calcd. for $C_{17}H_{13}NO_2$ [M]$^+$ 263.0946; found 263.0942.

9-Fluoro-4-methylnaphtho[3,2,1-*cd*]indol-5(4*H*)-one (5f): Yellow solid (87% yield); m.p. 232 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.60 (dd, J = 2.6, 10.6 Hz, 1 H), 8.5 (s, 1 H), 8.39 (dd, J = 6.0, 8.9 Hz, 1 H), 8.27 (d, J = 8.0 Hz, 1 H), 7.68–7.61 (m, 2 H), 7.24 (d, J = 7.3 Hz, 1 H), 3.37 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 166.5, 162.4 (J = 246.8 Hz), 139.9, 134.5 (J = 9.0 Hz), 133.3 (J = 9.7 Hz), 129.9, 129.2, 126.3, 125.6 (J = 4.5 Hz), 124.0 (J = 3.0 Hz), 121.0, 116.4, 116.3 (J = 24.0 Hz), 109.0 (J = 21.7 Hz), 106.3, 26.3 ppm. HRMS (EI): calcd. for $C_{16}H_{10}FNO$ [M]$^+$ 251.0746; found 251.0755.

8-Methoxy-4-methylnaphtho[3,2,1-*cd*]indol-5(4*H*)-one (5g): Yellow solid (93% yield), m.p. 163 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.68 (d, J = 9.0 Hz, 1 H), 8.44 (s, 1 H), 8.18 (d, J = 8.4 Hz, 1 H), 7.81 (d, J = 2.6 Hz, 1 H), 7.62 (t, J = 7.6, 8.0 Hz, 1 H), 7.47 (dd, J = 2.6, 8.9 Hz, 1 H), 7.15 (d, J = 7.2 Hz, 1 H), 3.92 (s, 3 H), 3.36 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.7, 158.2, 140.0, 134.7, 129.3, 126.1, 126.0, 125.7, 125.2, 125.1, 125.0, 119.8, 115.8, 112.0, 105.0, 55.5, 26.3 ppm. HRMS (EI): calcd. for $C_{17}H_{13}NO_2$ [M]$^+$ 263.0946; found 263.0941.

8-(Benzyloxy)-4-methylnaphtho[3,2,1-*cd*]indol-5(4*H*)-one (5h): Yellow solid (92% yield); m.p. 170 °C. ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 8.70 (d, J = 8.7 Hz, 1 H), 8.40 (s, 1 H), 8.19 (d, J = 8.4 Hz, 1 H), 7.94 (d, J = 2.7 Hz, 1 H), 7.63 (t, J = 7.8, 7.8 Hz, 1 H), 7.57–7.51 (m, 3 H), 7.44–7.31 (m, 3 H), 7.16 (d, J = 7.3 Hz, 1 H), 5.27 (s, 2 H), 3.37 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]-

DMSO): δ = 166.7, 157.3, 140.0, 136.6, 134.7, 129.4, 128.5 (2), 128.0 (2), 126.1, 126.0, 125.8, 125.3, 125.1, 120.1, 119.8, 115.8, 113.3, 107.5, 105.1, 69.6, 26.3 ppm. HRMS (EI): calcd. for $C_{23}H_{17}NO_2$ $[M]^+$ 339.1259; found 339.1254.

4-Methyl-[1,3]dioxolo[4′,5′:6,7]naphtho[3,2,1-*cd*]indol-5(4*H*)-one (5i): Yellow solid (42% yield); m.p. 238 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.37 (s, 1 H), 8.26 (s, 1 H), 8.17 (d, *J* = 8.0 Hz, 1 H), 7.73 (s, 1 H), 7.58 (t, *J* = 7.8, 7.9 Hz, 1 H), 7.14 (d, *J* = 7.2 Hz, 1 H), 6.25 (s, 2 H), 3.35 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 166.8, 150.1, 147.8, 139.8, 129.6, 128.8, 128.6, 125.9, 125.8, 122.6, 120.5, 116.3, 108.2, 105.0, 102.2, 101.7, 26.2 ppm. HRMS (EI): calcd. for $C_{17}H_{11}NO_3$ $[M]^+$ 277.0739; found 277.0742.

4-Methylthieno[3′,4′:4,5]benzo[1,2,3-*cd*]indol-5(4*H*)-one (5j): Yellow solid (63% yield); m.p. 138 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.66 (d, *J* = 3.0 Hz, 1 H), 8.51 (d, *J* = 3.1 Hz, 1 H), 8.26 (s, 1 H), 7.91 (d, *J* = 8.1 Hz, 1 H), 7.56 (t, *J* = 7.7, 7.8 Hz, 1 H), 7.11 (d, *J* = 7.4 Hz, 1 H), 3.32 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 171.8, 145.2, 143.3, 140.1, 134.6, 131.9, 129.3, 129.0, 127.5, 123.8, 121.6, 111.0, 107.2, 31.5 ppm. HRMS (EI): calcd. for $C_{14}H_9NOS$ $[M]^+$ 239.0405; found 239.0401.

4,6-Dimethylnaphtho[3,2,1-*cd*]indol-5(4*H*)-one (5k): Yellow solid (48% yield); m.p. 216 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.80 (d, *J* = 8.0 Hz, 1 H), 8.38 (d, *J* = 8.0 Hz, 1 H), 8.23 (d, *J* = 8.4 Hz, 1 H), 7.87 (t, *J* = 6.9, 8.0 Hz, 1 H), 7.79 (t, *J* = 7.6, 7.3 Hz, 1 H), 7.60 (t, *J* = 7.7, 7.9 Hz, 1 H), 7.19 (d, *J* = 7.3 Hz, 1 H), 3.37 (s, 3 H), 3.06 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 167.5, 138.7, 138.6, 133.1, 131.2, 129.0, 128.2, 127.3, 127.1, 124.9, 124.0, 120.8, 120.3, 115.7, 105.5, 26.2, 12.9 ppm. HRMS (EI): calcd. for $C_{17}H_{13}NO$ $[M]^+$ 247.0997; found 247.0999.

1,4-Dimethylnaphtho[3,2,1-*cd*]indol-5(4*H*)-one (5l): Yellow solid (91% yield); m.p. 172 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.91 (d, *J* = 8.0 Hz, 1 H), 8.53 (s, 1 H), 8.35 (d, *J* = 8.0 Hz, 1 H), 7.88 (t, *J* = 7.4, 7.6 Hz, 1 H), 7.76 (t, *J* = 7.6, 7.4 Hz, 1 H), 7.48 (d, *J* = 7.3 Hz, 1 H), 7.14 (d, *J* = 7.3 Hz, 1 H), 3.37 (s, 3 H), 3.00 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 171.7, 143.7, 139.1, 138.1, 137.7, 137.0, 134.5, 133.9, 132.5, 131.9, 131.8, 130.3, 126.8, 111.2, 100.0, 31.4, 29.7 ppm. HRMS (EI): calcd. for $C_{17}H_{13}NO$ $[M]^+$ 247.0997; found 247.1005.

9-Fluoro-1,4-dimethylnaphtho[3,2,1-*cd*]indol-5(4*H*)-one (5m): Yellow solid (85% yield); m.p. 210 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.50 (s, 1 H), 8.45–8.37 (m, 2 H), 7.67 (t, *J* = 8.6, 8.7 Hz, 1 H), 7.44 (d, *J* = 7.0 Hz, 1 H), 7.13 (d, *J* = 7.4 Hz, 1 H), 3.35 (s, 3 H), 2.93 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.1, 161.7 (*J* = 244.5 Hz), 138.3, 134.7 (*J* = 9.8 Hz), 134.0 (*J* = 9.7 Hz), 131.5, 130.7, 128.6, 126.6, 124.5 (*J* = 4.5 Hz), 124.4 (*J* = 3.0 Hz), 121.7, 115.4 (*J* = 23.2 Hz), 111.7 (*J* = 24.0 Hz), 106.3, 26.0, 23.8 ppm. HRMS (EI): calcd. for $C_{17}H_{12}FNO$ $[M]^+$ 265.0903; found 265.0903.

8-Methoxy-1,4-dimethylnaphtho[3,2,1-*cd*]indol-5(4*H*)-one (5n): Yellow solid (87% yield); m.p. 180 °C. ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 8.80 (d, *J* = 10.0 Hz, 1 H), 8.44 (s, 1 H), 7.84 (s, 1 H), 7.49 (d, *J* = 9.2 Hz, 1 H), 7.44 (d, *J* = 6.7 Hz, 1 H), 7.07 (d, *J* = 6.3 Hz, 1 H), 3.94 (s, 3 H), 3.35 (s, 3 H), 2.95 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 171.7, 162.5, 143.7, 141.0, 136.9, 133.3, 133.2, 132.3, 131.7, 130.7, 125.9, 125.8, 124.4, 118.0, 110.3, 60.6, 33.3, 29.6 ppm. HRMS (EI): calcd. for $C_{18}H_{15}NO_2$ $[M]^+$ 277.110; found 247.1099.

2-Methoxy-4-methylnaphtho[3,2,1-*cd*]indol-5(4*H*)-one (5o): Yellow solid (89% yield); m.p. 152 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.54 (d, *J* = 8.0 Hz, 1 H), 8.26 (s, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 7.77 (t, *J* = 7.5 Hz, 1 H), 7.67 (t, *J* = 7.5 Hz, 1 H), 7.40 (s, 1 H), 7.67 (s, 1 H), 4.04 (s, 3 H), 3.44 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 168.5, 161.8, 141.6, 134.0, 131.9, 131.6, 128.5, 127.3, 127.0, 124.8, 124.3, 123.4, 117.3, 97.8, 95.6, 60.0, 26.5 ppm. HRMS (EI): calcd. for $C_{17}H_{13}NO_2$ $[M]^+$ 263.0946; found 263.0950.

9-Fluoro-2-methoxy-4-methylnaphtho[3,2,1-*cd*]indol-5(4*H*)-one (5p): Yellow solid (83% yield); m.p. 208 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.23 (s, 1 H), 8.14–8.07 (m, 2 H), 7.42 (dt, *J* = 8.3, 2.5 Hz, 1 H), 7.27 (s, 1 H), 6.68 (s, 1 H), 4.03 (s, 3 H), 3.44 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 168.2, 162.5 (*J* = 249.0 Hz), 161.7, 141.6, 133.9 (*J* = 9.0 Hz), 133.2 (*J* = 9.0 Hz), 130.6, 126.7 (*J* = 4.5 Hz), 124.2 (*J* = 3.0 Hz), 123.6, 117.5, 116.3 (*J* = 24.0 Hz), 108.5 (*J* = 21.7 Hz), 98.4, 95.4, 55.9, 26.5 ppm. HRMS (EI): calcd. for $C_{17}H_{12}FNO_2$ $[M]^+$ 281.0852; found 281.0858.

2-Methoxy-4,9-dimethylnaphtho[3,2,1-*cd*]indol-5(4*H*)-one (5q): Yellow solid (86% yield); m.p. 194 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.30 (s, 1 H), 8.22 (s, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 7.49 (d, *J* = 8.3 Hz, 1 H), 7.37 (s, 1 H), 6.65 (s, 1 H), 4.04 (s, 3 H), 3.43 (s, 3 H), 2.66 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 168.6, 161.6, 141.5, 138.8, 131.9, 131.7, 131.6, 128.9, 126.9, 124.2, 123.9, 123.1, 117.5, 97.7, 95.5, 56.0, 26.5, 22.1 ppm. HRMS (EI): calcd. for $C_{18}H_{15}NO_2$ $[M]^+$ 277.1103; found 277.1098.

3-Fluoro-4-methylnaphtho[3,2,1-*cd*]indol-5(4*H*)-one (5r): Yellow solid (92% yield); m.p. 190 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.57 (d, *J* = 8.0 Hz, 1 H), 8.45 (s, 1 H), 8.13 (d, *J* = 8.1 Hz, 1 H), 8.06 (dd, *J* = 3.3, 9.1 Hz, 1 H), 7.81 (t, *J* = 7.6, 7.8 Hz, 1 H), 7.68 (t, *J* = 7.6, 7.7 Hz, 1 H), 7.38 (t, *J* = 10.1, 10.0 Hz, 1 H), 3.65 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 167.2, 144.5 (*J* = 246.0 Hz), 132.8, 131.9, 131.8, 129.4, 128.4, 127.0, 124.7 (*J* = 3.7 Hz), 124.1 *J* = (9.0 Hz), 123.8 (*J* = 6.7 Hz), 123.4 (*J* = 1.5 Hz), 123.2, 119.0 (*J* = 22.5 Hz), 117.8 (*J* = 6.7 Hz), 28.6 (*J* = 3.0 Hz) ppm. HRMS (EI): calcd. for $C_{16}H_{10}FNO$ $[M]^+$ 251.0746; found 251.0760.

3-Fluoro-8-methoxy-4-methylnaphtho[3,2,1-*cd*]indol-5(4*H*)-one (5s): Yellow solid (85% yield); m.p. 206 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.44 (d, *J* = 10.0 Hz, 1 H), 8.34 (s, 1 H), 7.95 (dd, *J* = 3.2, 9.0 Hz, 1 H), 7.44 (s, 1 H), 7.41–7.31 (m, 2 H), 4.00 (s, 3 H), 3.64 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 167.3, 158.3, 143.9 (*J* = 245.3 Hz), 134.3, 127.5, 126.2 125.2 (*J* = 4.5 Hz), 124.4, 123.9 (*J* = 8.2 Hz), 123.4 (*J* = 1.5 Hz), 122.8 (*J* = 6.0 Hz), 120.3, 119.1 (*J* = 22.5 Hz), 117.3 (*J* = 6.0 Hz), 111.3, 55.5, 28.5 (*J* = 3.0 Hz) ppm. HRMS (EI): calcd. for $C_{17}H_{12}FNO_2$ $[M]^+$ 281.0852; found 281.0858.

Preparation of isonitrosoacetanilides 11a and 11b: To a solution chloral hydrate (3.2 g, 19.34 mmol) in H_2O (20 mL) were added Na_2SO_4 (6.46 g, 35.46 mmol), 3-bromoaniline **10a** or **10b** (16.12 mmol) in a mixture of 37% HCl (1.3 mL) and water (60 mL), and a solution of hydroxylamine sulfate (9.53 g, 58.03 mmol) in water (20 mL). The resulting mixture was stirred at 100 °C for 1 h and then cooled to room temperature. The resulting precipitate was collected by filtration, washed with water (3 × 100 mL), and then dried in vacuo to provide isonitrosoacetanilide **11a** or **11b**.

(*E*)-*N*-(3-Bromo-4-methylphenyl)-2-(hydroxyimino)acetamide (11a): (3.16 g, 76% yield). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.18 (s, 1 H), 10.23 (s, 1 H), 8.01 (d, *J* = 2.0 Hz, 1 H), 2.27 (s, 1 H), 7.59 (s, 1 H), 7.27 (d, *J* = 8.3 Hz, 1 H), 2.27 (s, 3 H) ppm. MS (EI): *m*/*z* (%) = 258 (51) $[M + 2]^+$, 256 (48) $[M]^+$, 227 (19), 225 (22), 187 (31), 185 (32), 160 (92), 77 (100).

(*E*)-*N*-(5-Bromo-2-fluorophenyl)-2-(hydroxyimino)acetamide (11b): (3.19 g, 76% yield), ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.37 (s, 1 H), 9.95 (s, 1 H), 8.13–8.10 (m, 1 H), 7.75 (s, 1 H), 7.40–7.25

(m, 2 H) ppm. MS (EI): *m*/*z* (%) = 261 (41) $[M + 2]^+$, 259 (42) $[M]^+$, 216 (31), 214 (32), 190 (92), 188 (100), 162 (36), 160 (37).

Preparation of 4-Bromoisatin 12a and 12b: Isonitrosoacetanilide **11a** or **11b** (11.67 mmol) was added to concentrated sulfuric acid (13 mL) that was rapidly stirred at 0 °C. The resulting solution was stirred at 80 °C for 1 h and then cooled to room temperature. The mixture was poured carefully onto crushed ice. The orange precipitate was collected by filtration, washed with H_2O and benzene, and then purified by column chromatography on silica gel (MeOH/CH_2Cl_2) to give **12a** or **12b**.

4-Bromo-5-methylisatin (12a): (2.20 g, 78% yield). ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 11.06 (s, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 6.78 (d, *J* = 7.9 Hz, 1 H), 2.26 (s, 3 H) ppm. MS (EI): *m*/*z* (%) = 240 (41) $[M + 2]^+$, 238 (41) $[M]^+$, 212 (97), 210 (100), 185 (30), 183 (37).

4-Bromo-7-fluoroisatin (12b): (2.47 g, 87% yield). ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 11.67 (s, 1 H), 7.48–7.41 (m, 1 H), 7.22–7.18 (m, 1 H) ppm. MS (EI): *m*/*z* (%) = 245 (36) $[M + 2]^+$, 243 (32) $[M]^+$, 217 (67), 215 (77), 190 (15), 188 (21), 108 (100).

Preparation of 4-Bromo-1-methylisatin 13a and 13b: To a solution of 4-bromoisatin **12a** or **12b** (8.75 mmol) in DMF (30 mL) were added potassium carbonate (1.81 g, 13.12 mmol) and methyl iodide (3.73 g, 26.24 mmol). The mixture was heated at 80 °C for 1 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 and H_2O. The biphasic layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried with Na_2SO_4 and concentrated to yield 4-bromo-1-methylisatin **13a** or **13b** as an orange solid.

4-Bromo-1,5-dimethylisatin (13a): (1.89 g, 85% yield). ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 7.59 (d, *J* = 8.0 Hz, 1 H), 7.04 (d, *J* = 8.0 Hz, 1 H), 3.09 (s, 3 H), 2.29 (s, 3 H) ppm. MS (EI): *m*/*z* (%) = 254 (57) $[M + 2]^+$, 252 (60) $[M]^+$, 226 (48), 224 (49), 198 (53), 196 (55), 118 (100).

4-Bromo-7-fluoro-1-methylisatin (13b): (1.98 g, 88% yield). ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 7.54–7.47 (m, 1 H), 7.29–7.25 (m, 1 H), 3.27 (d, *J* = 3.1 Hz, 3 H) ppm. MS (EI): *m*/*z* (%) = 258 (41) $[M + 2]^+$, 256 (52) $[M]^+$, 230 (31), 228 (32), 202 (44), 200 (45), 122 (100).

Preparation of 4-Bromo-1-methyloxindole 14a and 14b: To a solution of 4-bromo-1-methylisatin **13a** or **13b** (7.28 mmol) in ethanol (48 mL) was added hydrazine hydrate (85%, 12 mL) under nitrogen. The mixture was stirred at 90 °C for 24 h. After cooling to room temperature, the solution was concentrated. The residue was diluted with H_2O, and the resulting solution was extracted with EtOAc. The combined organic phases were washed with H_2O and brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexanes) to provide 4-bromo-1-methyloxindole **14a** or **14b** as a light yellow solid.

4-Bromo-1,5-dimethyloxindole (14a): (1.14 g, 65% yield), ^1H NMR (300 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 7.0 Hz, 1 H), 6.67 (d, *J* = 7.9 Hz, 1 H), 3.48 (s, 2 H), 3.19 (s, 3 H), 2.38 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 143.6, 131.4, 129.5, 125.9, 121.6, 106.7, 37.8, 26.4, 22.0 ppm. MS (EI): *m*/*z* (%) = 240 (64) $[M + 2]^+$, 238 (65) $[M]^+$, 211 (16), 209 (17), 160 (32), 132 (26), 131 (100).

4-Bromo-7-fluoro-1-methyloxindole (14b): (1.13 g, 64% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.08 (dd, *J* = 8.9, 3.8 Hz, 1 H), 6.97–6.90 (m, 1 H), 3.49 (s, 2 H), 3.41 (d, *J* = 3.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 146.7 (*J* = 242.2 Hz), 132.7 (*J* = 9.0 Hz), 127.6 (*J* = 4.5 Hz), 125.3 (*J* = 6.8 Hz), 117.7 (*J* = 20.3 Hz), 113.4 (*J* = 3.0 Hz), 37.5 (*J* = 2.3 Hz), 28.7 (*J* = 5.3 Hz) ppm. MS (EI): *m*/*z* (%) = 244 (38) $[M + 2]^+$, 242 (39) $[M]^+$, 215 (11), 213 (11), 136 (16), 135 (100).

2-(2,6-Dibromo-4-methoxyphenyl)acetonitrile (16)

1,3-dibromo-2-(bromomethyl)-5-methoxybenzene: To a solution of 2,6-dibromotoluene **15** (1.8 g, 6.43 mmol) in CCl_4 (20 mL) were added *N*-bromosuccinimide (2.29 g, 12.86 mmol) and benzoyl peroxide (0.16 g, 0.64 mmol). The reaction mixture was stirred at 90 °C for 12 h and then cooled to room temperature. The mixture was diluted with H_2O, and the resulting solution was extracted with EtOAc (3× 50 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, and concentrated to provide 1,3-dibromo-2-(bromomethyl)-5-methoxybenzene (2.1 g) as a pale brown solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.11 (s, 2 H), 4.82 (s, 2 H), 3.80 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 128.2, 125.8 (2), 118.6 (2), 55.9, 34.3 ppm. MS (EI): *m*/*z* (%) = 357 (5) $[M + 2]^+$, 355 (2) $[M]^+$, 281 (49), 278 (100), 276 (53), 119 (19), 91 (20), 76 (29).

2-(2,6-Dibromo-4-methoxyphenyl)acetonitrile (16): To a suspension of 1,3-dibromo-2-(bromomethyl)-5-methoxybenzene (2.0 g, 5.57 mmol) in EtOH/H_2O (4:1 v/v, 40 mL) was added KCN (0.98 g, 15.05 mmol). The reaction mixture was stirred at 90 °C for 3 h. The reaction was cooled to room temperature and then extracted with EtOAc (3× 50 mL). The aqueous layer was additionally extracted with EtOAc (2×). The combined organic phases were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10% EtOAc/hexanes) to provide phenylacetonitrile **16** (1.6 g, 81% for 2 steps) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.15 (s, 2 H), 4.04 (s, 2 H), 3.81 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 125.2, 122.0, 118.5 (2), 117.8, 115.9, 55.9, 25.0 ppm. MS (EI): *m*/*z* (%) = 304 (97) $[M + 2]^+$, 302 (48) $[M]^+$, 225 (98), 223 (100), 182 (12), 180 (11), 145 (14), 144 (35).

2-(2,6-Dibromo-4-methoxyphenyl)acetic Acid (17): To a solution of phenylacetonitrile **16** (1.5 g, 4.92 mmol) in acetic acid (5 mL) and H_2O (5 mL) was added dropwise concentrated sulfuric acid (5 mL). The mixture was heated at 110 °C for 8 h, cooled to room temperature, and then poured onto crushed ice. The resulting white precipitate was removed by filtration and then dissolved in CH_2Cl_2. The resulting solution was extracted with NaOH (1 N solution). The aqueous layer was acidified to pH ≈ 2 with HCl (1 N solution), and the solution was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried with Na_2SO_4, and concentrated in vacuo to provide phenylacetic acid **17** (1.32 g, 83%) as a white solid. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 12.60 (s, 1 H), 7.26 (s, 2 H), 3.85 (s, 2 H), 3.78 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 170.4, 158.9, 126.4, 125.5 (2), 117.8 (2), 56.0, 41. ppm. MS (EI): *m*/*z* (%) = 323 (47) $[M + 2]^+$, 321 (22) $[M]^+$, 279 (100), 277 (55), 245 (41), 243 (39), 164 (12), 119 (13).

2-(2,6-Dibromo-4-methoxyphenyl)-*N*-methylacetamide (18): To a solution of phenylacetic acid **17** (1.30 g, 3.92 mmol) in DMF (10 mL) were added HBTU (3.71 g, 9.79 mmol), diisopropylethylamine (2.09 mL, 12.04 mmol), and methylamine (0.38 g, 12.04 mmol). The reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with NH_4Cl (1 N solution), and the resulting solution was extracted with EtOAc (3× 50 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30% EtOAc/hexanes) to provide acetamide **18** (1.26 g, 93%) as a white solid. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 7.79 (s, 1 H), 7.23 (s, 2 H), 3.77

(s, 3 H), 3.74 (s, 2 H), 2.57 (d, J = 4.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 168.0, 158.7, 127.2, 125.8 (2), 117.7 (2), 55.9, 42.0, 25.7 ppm. MS (EI): m/z (%) = 335 (1) $[M]^+$, 279 (51), 277 (22), 258 (100), 256 (96), 199 (16), 177 (16), 119 (14).

4-Bromo-6-methoxy-1-methyloxindole (14c): A screw-capped test tube was charged with acetamide **18** (1.25 g, 3.71 mmol), K_2CO_3 (2.56 g, 18.5 mmol), copper(I) chloride (37 mg, 0.37 mmol), and acetylacetone (96 μL, 0.93 mmol). Anhydrous *N*-methyl-2-pyrrolidone (30 mL) was added by syringe. The reaction tube was evacuated and then backfilled with nitrogen (3×). The mixture was heated at 90 °C for 1 h and then cooled to room temperature. The reaction mixture was diluted with NH_4Cl (1 N solution), and the resulting solution was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20% EtOAc/hexanes) to provide oxindole **14c** (0.51 g, 53%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.68 (s, 1 H), 6.35 (s, 1 H), 3.82 (s, 3 H), 3.41 (s, 2 H), 3.17 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5, 160.7, 146.7, 118.9, 117.3, 109.1, 95.7, 55.8, 36.4, 26.5 ppm. MS (EI): m/z (%) = 256 (57) $[M + 2]^+$, 254 (57) $[M]^+$, 176 (25), 148 (21), 147 (100), 133 (19), 132 (14).

Supporting Information (see footnote on the first page of this article): Characterization of all new compounds, which includes m.p. data and MS spectra as well as ^{1}H and ^{13}C NMR spectra.

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