Published in final edited form as:

ChemSusChem. 2019 July 05; 12(13): 3144–3151. doi:10.1002/cssc.201900438.

Oxidative Coupling of 3-Oxindoles with Indoles and Arenes

Houng Kang, Adriana L. Jemison, Erin Nigro, Marisa C. Kozlowski^a

Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104, United States

Abstract

A highly efficient method for the oxidative coupling of 2-substituted-3-oxindoles with aromatic compounds to form 2,2-disubstituted indolin-3-ones with broad scope is described. This work utilizes oxygen as the terminal oxidant and a base metal catalyst under mild conditions instead of toxic/precious metal reagents and higher molecular weight oxidants. Quaternary structures are produced in modest to excellent yields (up to 96%) without pre-functionalization.

Graphical Abstract

Keywords

catalysis; oxidative coupling; sustainable; coinage metal; oxygen

Introduction

Quaternary structures featuring the 2,2-disubstituted indolin-3-one moiety are common in nature, especially among the indole alkaloid natural products (Figure 1).^[1] Many efforts to synthesize these types of molecular frameworks have relied upon rearrangements and cyclization reactions that require designed substrates or strongly acidic/basic conditions, limiting functional group compatibility.^[2] Recent advances in oxidative dearomatization^[3] chemistry have allowed a more convergent approach to synthesis of 2,2,-disubstituted indolin-3-one scaffolds.

In 2011, the Baran group reported the oxidative coupling of oxindoles with indoles and pyrroles using an excess of ammonium nitrate (CAN) under basic conditions (Scheme 1A).^[4] However, this method was limited to electron-poor coupling partners and yields with pyrrole were also quite low. Another oxidative transformation was reported by Guchhait and coworkers, utilizing the dearomatization and oxidation of one indole partner to affect the coupling with the nucleophile (Scheme 1B).^[5] While functional group compatibility of this

^[a] marisa@sas.upenn.edu.

method is good, it requires an expensive palladium catalyst and multiple equivalents of oxidant. A similar reaction was reported by Zhou and coworkers using ruthenium for the oxidative coupling of indoles where one molecule of indole is oxidized to form the oxindole and a molecule of the indole acts as the nucleophile to form the C-C bond (Scheme 1C).^[6] A similar mechanism has been employed to construct spirocycles via an intramolecular cyclization of a substituted indole.^[7]

An earlier report by Liu and Qin described similar reactivity with TEMPO and silver nitrate to give 3,3'-biindolin-2-ones from the homocoupling of unsubstituted indoles.^[8] Indoles lacking substitution at the 2-position have also been shown to form trimers in good yield under oxidative conditions.^[9] Notably, these oxidation methods proceed well regardless of the electronic character of the indole substrate. Recently, dearomative coupling reactions have also been affected in an asymmetric manner utilizing a chiral phosphoric acid catalyst and DDQ in an oxidative aza-Friedel-Crafts alkylation of indoles with 3-oxindoles as the nucleophile (Scheme 1D).^[10]

Coupling strategies for indoles with other aromatic compounds have also been reported (Scheme 2). Vincent and coworkers described the coupling of a substituted indole with an electron rich phenol, giving a benzofuroindoline scaffold.^[11] The reported method, while diastereoselective, has limited scope and moderate yields. Other 3-aryl indolines are readily accessible through a variety of oxidation methods.^[12]

Results and Discussion

Recent work in our laboratory has shown that salen/salan transition metal catalysts are effective in oxidative coupling transformations using dioxygen as the terminal oxidant.^[13] Inspired by this and the literature cited above, we aimed to develop a general and mild method for the oxidative coupling of oxindoles with a broad range of aromatic molecules. A high-throughput experimentation (HTE) screen utilizing twenty-four unique catalysts spanning seven metals and five ligands was performed to find candidates for the oxidative coupling of oxindoles with indole substrates (Figure 2).

Cobalt, copper, and vanadium catalysts gave the best results, while chromium, iron, manganese, and ruthenium catalysts gave more moderate yields. In general, the imine type salen ligands outperformed the amine-type salan ligands though no strong preference for any one ligand was observed (Figure 3). The screen revealed **Cu-salan-Ph** (catalyst **D**, M = Cu) to be the most efficient among the working catalysts for the test reaction as judged by both amount of product formed and amount of byproducts formed. Thus, this catalyst was used to probe the scope of coupling partners.

Using the best of the screening conditions, we were able to couple the oxindole substrate with twelve electronically and sterically diverse indoles in good to excellent yield. Notably, the screening conditions could be used directly and the only modification necessary was increased temperature to 80 °C for a longer reaction period for those substrates that were less reactive (Scheme 3). Indoles react selectively at the more nucleophilic 3-position, unless this site is blocked, as with substrate **2j**, which reacts at the 2-position. The method tolerates

both electron withdrawing and donating groups for indole substrates, making it more general than the current state of the art. Compatibility with an array of functional groups, such as halogens, ethers, esters, and nitriles, provides opportunity for later modification of the resultant quaternary structures.

Several of the resulting molecules are known in the literature as products of similar transformations. However, these reactions are milder, give better yield, and allow access to more substrates than previously reported methods. For example, Baran and coworkers report a poor 17% yield for substrate **2g** and modest yields of 48% and 66% for substrates **2j** and **2f**, respectively.^[4] The method is readily scalable and no decrease in yield was observed when moving from 0.1 mmol to 1 mmol for **2a**.

The scope of the 3-oxindole coupling partner was also explored (Scheme 4). Substituents of both electron donating (**1m**) and withdrawing (**1o**) character had only a moderate effect on yield. *N*-Substitution had a much more dramatic effect, decreasing the yield from 96% to 25% in the case of **1n**. The outcome was somewhat improved by heating the reaction to 80 °C. The steric bulk of the ester also significantly affects the outcome of the reaction with the hindered adamantyl group giving only 57% yield, relative to 98% for the methyl ester **1** and 90% for the benzyl ester **1p**. Both of these observations might be attributed to less efficient binding of the oxidized species to the active catalyst.

After exploring the efficacy in the oxidative coupling of oxindoles with indoles, we turned our attention to other arene coupling partners. Pyrroles, substituted furans, anilines, and trimethoxy benzene were all shown to be competent coupling partners across nine examples (Scheme 5). For these aromatic compounds, the electron-withdrawing substituents have a much more pronounced effect on reactivity and the yield is significantly reduced as in the case of substrate **4b** relative to **4a** and **4c**. Modest to good yields are possible for electron-rich coupling partners. No reaction or low yield is observed for less electron-rich furans and dimethoxybenzene. This trend is further supported by the low product yield with phenol **4f**, which has a much higher oxidation potential than the coupling partners shown in Figure 4.

Pyrroles (**4a-d**, **4i**) and 2-methoxy furan (**4e**) couple selectively at the 2-position. Similarly, adducts arising from *N,N*-dialkyl anilines (**4g**, **4h**) undergo coupling at the less hindered *para*-position. The majority of these structures have not been reported to date, highlighting the broader scope of this method.

In order to shed light on the mechanism, cyclic voltammetry measurements were undertaken for the 3-oxindole substrate (**1**) as well as for 2-phenyl indole (**2a**) and *N,N*-dimethyl aniline (**4g**) (Figure 4). Typically, the second coupling partner is more oxidizable than or comparable to **1**. Partners with higher oxidation potentials, such as **4b** and **4f** give much lower yield indicating that oxidation of this component is key. However, oxidation of the 3-oxindole leads quickly to formation of homo-dimers. This species is observed under the reaction conditions after only a few minutes. Notably, this homo-dimer of 3-oxindole has a high oxidation potential and may induce oxidation of the second coupling partner.

A mechanism consistent with these observations is outlined in Figure 5. Coordination of the hydroxyl group of substrate **1** with the Cu(II) salen gives rise to enolate that **6** can undergo rapid, reversible inner sphere oxidation and dimerization to form **7**, which can be observed during the reaction. Outer sphere oxidation of the other reaction partner by either Cu(II) or the dimer **7** generates a radical cation **8** which then reacts with the copper(II) enolate **6** to yield **9**. A second oxidation of **9** with the copper from the enolate leads to stabilized cation **10**, which undergoes proton elimination to regenerate the aromatic ring of **3d**. The rearomatization to **3d** is irreversible such that **3d** cannot reenter the reaction cycle in the same manner as **6**. The cross selectivity is controlled by the nucleophilic nature of copper enolate **6** and the electrophilic character of **8**.

Conclusions

In summary, HTE screening allowed rapid identification of a general method for the cross-coupling of 3-oxindoles with an electronically and structurally diverse set of aromatic compounds. Using dioxygen as the terminal oxidant significantly reduces the amount of chemical waste generated. Copper is also an abundant base metal, and the copper (II) catalyst is bench stable. This convergent method accesses novel structures as well as improving the yields for similar transformations. Overall, this method is broader in scope, more general, and more efficient than similar reports^[4–6, 10] in the literature, providing easy access to new quaternary structures.

Experimental Section

Unless otherwise noted, all non-aqueous reactions were carried out under an atmosphere of dry N₂ in dried glassware. When necessary, solvents and reagents were dried prior to use. THF was distilled from sodium benzophenone ketyl. CH₂Cl₂, ClCH₂CH₂Cl, and toluene were distilled from CaH₂. High throughput experiments were performed at the Penn/Merck High Throughput Experimentation Laboratory at the University of Pennsylvania. The screens were analyzed by HPLC by addition of an internal standard. Analytical thin layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica-gel 254-F plates. Visualization was accomplished with UV light. Chromatography was performed using a forced flow of the indicated solvent system on EM Reagents Silica Gel 60 (230–400 mesh). When necessary, the column was pre-washed with 1% Et₃N in the eluent system. Compounds chromatographed via autocolumn were separated using pre-packed silica columns on a Biotage CombiFlash system. ¹H NMR spectra were recorded on a 500 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane (0 ppm) or from the solvent resonance (CDCl₃ 7.26 ppm, DMSO-*d*₆ 3.58 ppm, acetone-*d*₆ 2.05 ppm, DMF-*d*₇ 2.50 ppm, CD₃CN 1.94 ppm, CD₂Cl₂ 5.32 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. Decoupled ¹³C NMR spectra were recorded at 125 MHz. IR spectra were taken on an FT-IR spectrometer. Accurate mass measurement analyses were conducted via time-of-flight mass analyzer GCMS with electron ionization (EI) or via time-of-flight mass analyzer LCMS with electrospray ionization (ESI). The signals were measured against an internal reference of perfluorotributylamine for EI-GCMS and leucine enkephalin for ESI-LCMS. The instrument was calibrated, and measurements

were made using neutral atomic masses; the mass of the electron removed or added to create the charged species is not taken into account. Low resolution LCMS data were obtained by use of a UPLC system with a SQD mass analyzer equipped with electrospray ionization. Cyclic voltammograms were recorded using a CH Instruments CHI600E Electrochemical Analyzer. Measurements were taken using 0.02 M tetrabutylammonium hexafluorophosphate as electrolyte in distilled acetonitrile. Substrate was dissolved at a concentration of approximately 0.001 M and voltammograms were internally referenced using an equimolar concentration of ferrocene. Measurements employed glassy carbon and platinum working electrodes, and an Ag/AgCl wire reference electrode. Voltammograms were recorded at a scan rate of 100 mV/s in the positive direction to observe irreversible oxidation.

General procedure: oxidative 3-oxindole coupling

To a microwave vial was added 3-oxindole (0.13 mmol), indole (0.13 mmol) and Cu-salan-Ph catalyst (9.3 mg, 0.01 mmol). The vial was sealed with a septum and the 1,2-dichloroethane (1.3 mL) was added. After purging and refilling with O₂ three times, the vial was sealed with a microwave vial cap and was stirred at 50 °C for 20 h. Upon completion, the reaction mixture was then directly chromatographed using silica gel.

Methyl-3-hydroxy-1*H*-indole-2-carboxylate (1)

Following the literature protocol, the product was obtained as a yellow solid (1.74 g). Spectral data were in agreement with those reported.^[4]

Methyl-3-hydroxy-5-methoxy-1*H*-indole-2-carboxylate (1m)

Commercially available methyl-5-methoxy-2-amino benzoate (0.45 g, 2.5 mmol) was dissolved in DMF (2.5 mL) with methyl- α -bromo-acetate (0.33 mL, 3.5 mmol) and sodium carbonate (0.27 g, 2.6 mmol) before heating to 80 °C under argon. The suspension was stirred for 10 h before cooling and pouring into water. The aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine before drying over Na₂SO₄ and evaporating. The residue was chromatographed via autocolumn using 0–25% EtOAc/hexanes to give an off-white solid (0.40 g) in 63% yield.

The diester synthesized above was dissolved in anhydrous THF (5 mL) and cooled to 0 °C under argon. Potassium *tert*-butoxide (0.19 g, 1.7 mmol) was added as a suspension in THF (1.7 mL) dropwise, which caused the mixture to turn brown. After 25 min the reaction was complete as judged by TLC. The THF was evaporated and the residue dissolved in 20% aq AcOH and CH₂Cl₂. The aqueous was extracted a second time with CH₂Cl₂. The combined organic layers were washed with brine before drying over Na₂SO₄ and concentrating. The residue was chromatographed via autocolumn using 20% CH₂Cl₂/hexanes to give an off-white solid (0.11 g) in 31% yield. **R_f** = 0.3 (EtOAc:hexanes 1:9) **¹H NMR** (500 MHz, CDCl₃) δ 7.64 (br s, 1H), 7.17 (d, *J* = 9.0 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 7.02 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.96 (s, 3H), 3.85 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 154.0, 131.1, 123.1, 119.5, 117.7, 114.9, 113.3, 108.8, 99.7, 55.8, 51.7; **IR** (neat) 3352, 3004, 2961, 2845, 1662, 1555, 1439, 1389, 1280, 1254, 1205, 1167, 1135, 1019, 995, 933, 851, 823, 810, 770,

595, 574, 512; **HRMS** (ES-TOF) calcd for $C_{11}H_{11}NO_4$ [M-H] m/z = 220.0610; found 220.0618.

Methyl-3-hydroxy-4-chloro-1*H*-indole-2-carboxylate (1o)

Commercially available methyl-4-chloro-2-amino benzoate (1.85 g, 10 mmol) was dissolved in DMF (10 mL) with methyl- α -bromo-acetate (1.34 mL, 14 mmol) and sodium carbonate (1.09 g, 10.3 mmol) before heating to 80 °C under argon. The suspension was stirred for 20 h before adding an additional aliquot of methyl- α -bromo-acetate (0.20 mL, 2 mmol). After a further 8 h, the mixture was cooled and poured into water. The aqueous portion was then extracted with Et₂O. The organic layer was washed with brine before drying over Na₂SO₄ and evaporating. The residue was loaded onto silica and chromatographed via autocolumn using 5% EtOAc/hexanes to give a white solid (0.70 g) in 27% yield.

The diester synthesized above was dissolved in anhydrous THF (4 mL) and added dropwise to a stirring suspension of potassium *tert*-butoxide (0.45 g, 4 mmol in 7 mL THF) at 0 °C under argon. The flask was warmed to room temperature. After the starting material was consumed as judged by TLC, the mixture was diluted with water and acidified with glacial HOAc. The mixture was extracted twice with CH₂Cl₂. The combined organic layer were dried over Na₂SO₄ and concentrated. The residue was chromatographed via autocolumn using 10%:9 EtOAc:hexanes to give a pale yellow solid. This material was triturated with hexanes to remove hydrocarbon impurities and gave the pure solid (0.06 g) in 14% yield. **R_f** = 0.3 (1:9 EtOAc:hexanes); **¹H NMR** (500 MHz, CDCl₃) δ 7.77 (br s, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.27 (d, J = 1.6 Hz, 1H), 7.07 (dd, J = 8.6, 1.7 Hz, 1H), 3.97 (s, 3H); **¹³C NMR** (125 MHz, *d*₆-acetone) δ 163.8, 146.0, 136.6, 132.8, 121.9, 120.7, 117.6, 112.9, 110.2, 51.8; **IR** (neat) 3447, 3289, 2956, 2450, 1695, 1619, 1578, 1547, 1505, 1497, 1320, 1266, 1223, 1204, 1135, 1104, 1055, 976, **921, 849, 797, 763, 587**; **HRMS** (ES-TOF) calcd for C₁₀H₈ClNO₃ [M-H] m/z = 224.0114; found 224.0138.

Methyl-3-hydroxy-1-methyl-indole-2-carboxylate (1n)

Commercially available *N*-methyl methyl anthranilate (1.5 mL, 10 mmol) was dissolved in DMF (10 mL) with methyl- α -bromo-acetate (1.3 mL, 14 mmol) and sodium carbonate (1.09 g, 10.3 mmol) before heating to 80 °C under argon. The suspension was stirred for 20 h before it was cooled and poured into water. The aqueous portion was extracted with Et₂O and the layers separated. The organic layer was washed with brine before drying over Na₂SO₄ and evaporating. The residue was loaded onto silica and chromatographed via autocolumn using 10% EtOAc/hexanes to give a yellow oil (0.92 g) in 39% yield.

The diester synthesized above was dissolved in anhydrous THF (7 mL) and cooled to 0 °C under argon. Potassium *tert*-butoxide (0.26 g, 2.3 mmol) was added dropwise as a suspension in THF (2.3 mL) causing the mixture to turn yellow. After the reaction was complete as judged by TLC, the THF was evaporated and the residue dissolved in 20% aq AcOH and CH₂Cl₂. The layers were separated and the aqueous layer was extracted again with CH₂Cl₂. The combined organic layers were washed with brine before drying over Na₂SO₄ and loading onto silica. The material was chromatographed via autocolumn using 1:4 CH₂Cl₂:hexanes to give a pale yellow solid (0.28 g) in 64% yield. **R_f** = 0.6 (1:9

EtOAc:hexanes); **¹H NMR** (500 MHz, CDCl₃) δ 8.59 (br s, 1H), 7.75 (dt *J* = 8.1, 0.9 Hz, 1H), 7.38 (ddd, *J* = 7.8, 1.4, 1.2 Hz, 1H), 7.26 (m, 1H), 7.07 (ddd, *J* = 7.5, 1.0, 0.8 Hz, 1H), 4.00 (s, 3H), 3.88 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 164.7, 148.8, 137.8, 127.4, 120.4, 119.1, 116.5, 110.0, 109.5, 51.7, 31.8; **IR** (neat) 3300, 2951, 1651, 1615, 1542, 1458, 1433, 1390, 1371, 1299, 1233, 1194, 1166, 1150, 1121, 1044, 982, 967, 734, 636, 604, 544 **HRMS** (ES-TOF) calcd for C₁₁H₁₁NO₃ [M-H] *m/z* = 204.0661; found 204.0649.

Benzyl-3-hydroxy-1*H*-indole-2-carboxylate (1p)

Commercially available methyl anthranilate (5.0 mL, 28 mmol) was dissolved in DMF (29 mL) with benzyl-bromoacetate (8.0 mL, 24 mmol) and sodium carbonate (4.50 g, 43 mmol) before heating to 80 °C under argon. The suspension was stirred for 31 h before the mixture was cooled and poured into water. The aqueous layer was extracted with Et₂O. The organic layer was washed with brine before drying over Na₂SO₄ and concentrating. The residue was chromatographed to give pure diester as needle-like crystals (7.20 g) in 62% yield.

The diester synthesized above was dissolved in anhydrous THF (10 mL) and was cooled to 0 °C under argon. Potassium *tert*-butoxide (0.37 g, 3.3 mmol) was added dropwise as a suspension in THF (3.3 mL). After the addition was complete, *i*-PrOH was added to quench the remaining base at 0 °C. The THF and alcohol mixture was evaporated and the crude residue dissolved in 20% aq AcOH and CH₂Cl₂. The layers were separated and the organic layer was washed with brine before drying over Na₂SO₄ and concentrating. The material was chromatographed via autocolumn using 0–50% CH₂Cl₂/hexanes to give a white solid after trituration with hexanes (0.06 g) in 24% yield. *R_f* = 0.6 (EtOAc:hexanes 1:9) **¹H NMR** (500 MHz, CDCl₃) δ 7.76 (br s, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.40 (m, 5H), 7.24 (m, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 5.4 (br s, 2H); **¹³C NMR** (125 MHz, *d*₆-acetone) δ 163.8, 137.5, 136.8, 129.47, 129.45, 129.2, 129.1, 127.6, 120.4, 120.0, 118.7, 113.4, 66.5; **IR** (neat) 3328, 3205, 2964, 2491, 1678, 1619, 1479, 1457, 1447, 1390, 1356, 1326, 1249, 1198, 1151, 1130, 1100, 948, 759, 736, 697, 597.37, 494; **HRMS** (ES-TOF) calcd for C₁₆H₁₃NO₃ [M-H] *m/z* = 266.0817; found 266.0819.

Adamantyl-3-hydroxy-1*H*-indole-2-carboxylate (1p)

Commercially available methyl anthranilate (10 mL, 56 mmol) was dissolved in dry THF (175 mL) and cooled to 0 °C. Sodium bicarbonate (7.14 g, 85 mmol) was added, followed by benzyl chloroformate (12 mL, 59 mmol). The mixture was stirred for 15 min before warming to room temperature. After stirring a further 20 h, the reaction was then quenched with water and extracted with EtOAc. The organic layer was dried over Mg₂SO₄ before concentrating. The residue was eluted from a pad of silica gel using 5% EtOAc/ hexanes to give the protected aniline as a colorless solid (18.0 g) in 82% yield.

The protected aniline (1.4 g, 5 mmol) was dissolved in DMF (10 mL) with 1-adamantyl 2-bromoacetate (2.0 g, 7.5 mmol) prepared according to a literature procedure^[14] and cesium carbonate (3.3 g, 10 mmol) under argon. The suspension was stirred for 18 h before it was cooled and acidified with saturated aqueous NH₄Cl. The aqueous layer was extracted with Et₂O (3X). The combined organic layers were washed with water and brine before drying

over Na₂SO₄ and concentrating. The residue chromatographed via autocolumn using 0–25% EtOAc/hexanes to give a clear viscous oil (1.8 g) in 76% yield.

The diester synthesized above was dissolved in anhydrous THF (38 mL) and cooled to –78 °C under argon. Potassium *tert*-butoxide (0.63 g, 5.6 mmol) was added in one portion. The mixture was allowed to warm slowly to room temperature. After 3 h, saturated aqueous NH₄Cl was added to quench the remaining base. The aqueous layer was extracted with CH₂Cl₂ (2X). The combined organic layers were washed with brine before drying over Na₂SO₄ and loading onto silica. The resultant material was used without further purification.

The protected 3-oxindole was dissolved in EtOAc (38 mL) under argon. Pd/C (0.40 g, 10 wt % Pd) was added to the flask before purging and backfilling with H₂ 3X. The suspension was stirred for 3 h at room temperature. The H₂ was removed before filtering the mixture through Celite®. The Celite® pad was washed with MeOH and the filtrate was concentrated to give analytically pure oxindole as a pale yellow solid (0.93 g, 79% over two steps) **R_f** = 0.8 (1:9 EtOAc:hexanes); **¹H NMR** (500 MHz, CDCl₃) δ 8.35 (br s, 1H), 7.72 (m, 2H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 2.29 (br s, 6H), 2.25 (br s, 3H), 1.73 (m, 6H); **¹³C NMR** (125 MHz, *d*₆-acetone) 163.8, 146.9, 136.2, 127.3, 120.2, 119.9, 118.5, 113.3, 110.3, 82.5, 42.5, 36.8, 31.9; **IR** (neat) 3483, 3320, 2907, 1682, 1622, 1581, 1548, 1509, 1492, 1337, 1231, 1203, 1184, 1127, 1097 1048, 963, 923, 736, 621, 532; **HRMS** (ES-TOF) calcd for C₁₉H₂₁NO₃ [M-H] *m/z* = 310.1443; found 310.1458.

Methyl-3-oxo-2-(2-phenyl-1*H*-indol-3-yl)indoline-2-carboxylate (3a)

Following the **General Procedure** for 19 h, the product was obtained as a yellow solid (47 mg) in 94% yield. **R_f** = 0.27 (EtOAc:Hexanes = 1:2); **¹H NMR** (500 MHz, CDCl₃) δ 8.31 (br s, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.37–7.34 (m, 3H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.19–7.14 (m, 2H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 5.61 (br s, 1H), 3.18 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 195.2, 168.8, 160.9, 138.1, 138.0, 135.5, 132.5, 129.6, 128.8, 128.4, 126.8, 125.3, 122.7, 120.6, 120.4, 120.2, 119.7, 113.4, 111.2, 108.2, 73.3, 53.2; **IR** (neat) 3345, 3052, 2950, 2920, 1697, 1613, 1485, 1457, 1431, 1323, 1292, 1233, 1196, 1150, 1099, 1072, 1013, 972, 896 cm^{–1}; **HRMS** (ESI-TOF) calcd for C₂₄H₁₉N₂O₃ [M+H]⁺ *m/z* = 383.1396; found 383.1414.

Methyl-2-(2-(4-chlorophenyl)-1*H*-indol-3-yl)-3-oxoindoline-2-carboxylate (3b)

Following the **General Procedure** for 22 h, the product was obtained as a yellow solid (40 mg) in 73% yield. **R_f** = 0.40 (EtOAc:Hexanes = 1:2); **¹H NMR** (500 MHz, CDCl₃) δ 8.27 (br s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.55 (td, *J* = 8.5, 1.5 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 1H), 7.18 (td, *J* = 8.0, 1.0 Hz, 1H), 7.03 (td, *J* = 8.0, 1.0 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 5.59 (br s, 1H), 3.32 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 195.0, 168.9, 160.6, 138.1, 136.6, 135.6, 135.0, 131.1, 130.9, 128.6, 126.9, 125.3, 123.0, 120.8, 120.6, 120.3, 119.6, 113.4, 111.3, 108.8, 73.1, 53.4; **IR** (neat) 3341, 3052, 2950, 1698, 1610, 1483, 1467, 1456, 1432, 1324, 1293, 1234, 1196, 1150, 1089, 1014, 973, 893, cm^{–1}; **HRMS** (ESI-TOF) calcd for C₂₄H₁₈ClN₂O₃ [M+H]⁺ 417.1006, Found 417.1012.

Methyl-2-(2-(4-fluorophenyl)-1*H*-indol-3-yl)-3-oxoindoline-2-carboxylate (3c)

Following the **General Procedure** for 21 h, the product was obtained as a yellow solid (50 mg) in 96% yield. $R_f = 0.4$ (EtOAc:Hexanes = 1:2): $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.35 (br s, 1H), 7.57 (d, $J = 8.0$ Hz, 1H), 7.54 (td, $J = 8.0, 1.0$ Hz, 1H), 7.38–7.35 (m, 2H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.21 (d, $J = 8.0$ Hz, 1H), 7.16 (td, $J = 8.0, 1.0$ Hz, 1H), 7.03 (td, $J = 8.0, 1.0$ Hz, 1H), 6.99–6.95 (m, 3H), 6.93 (t, $J = 7.5$ Hz, 1H), 5.62 (br s, 1H), 3.30 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 195.2, 168.9, 163.0 (d, $J = 249$ Hz), 160.7, 138.1, 136.8, 135.5, 131.6 (d, $J = 8.3$ Hz), 128.7, 126.9, 125.3, 122.8, 120.7, 120.5, 120.3, 119.5, 115.4 (d, $J = 21.5$ Hz), 113.4, 111.4, 108.5, 73.1, 53.4; **IR** (neat) 3354, 2951, 1704, 1613, 1498, 1457, 1434, 1325, 1294, 1225, 1197, 1157, 1094, 1015, 974, 894 cm^{-1} ; **HRMS** (ESI-TOF) calcd for $\text{C}_{24}\text{H}_{18}\text{FN}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 401.1301, found 401.1306.

Methyl-2-(1*H*-indol-3-yl)-3-oxoindoline-2-carboxylate (3d)

Following the **General Procedure** for 22 h, the product was obtained as a yellow solid in 90% NMR yield (50 mg, 82% isolated yield). Spectral data were in agreement with those reported.^[4]

Methyl-2-(7-iodo-1*H*-indol-3-yl)-3-oxoindoline-2-carboxylate (3e)

Following the **General Procedure** for 16 h, the product was obtained as a yellow solid (58 mg) in 95% yield. $R_f = 0.27$ (EtOAc:Hexanes = 1:2): $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.35 (br s, 1H), 7.68 (d, $J = 8.0$ Hz, 1H), 7.62 (d, $J = 8.0$ Hz, 1H), 7.55–7.50 (m, 2H), 7.48 (d, $J = 2.0$ Hz, 1H), 7.00 (d, $J = 8.5$ Hz, 1H), 6.93 (t, $J = 7.5$ Hz, 1H), 6.86 (t, $J = 8.0$ Hz, 1H), 5.76 (br s, 1H), 3.80 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 194.4, 168.8, 161.1, 138.3, 138.0, 131.4, 125.6, 124.0, 122.0, 120.6, 120.0, 119.8, 113.6, 113.2, 77.0, 72.6, 53.9, 29.8; **IR** (neat) 3348, 2920, 2850, 1731, 1693, 1611, 1485, 1466, 1428, 1323, 1291, 1230, 1150, 1101, 1083, 1050, 971 cm^{-1} ; **HRMS** (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{14}\text{IN}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 433.0049, found 433.0045.

Methyl-2-(7-bromo-1*H*-indol-3-yl)-3-oxoindoline-2-carboxylate (3f)

Following the **General Procedure** for 22 h, the product was obtained as a brown solid (47 mg) in 94% yield. Spectral data were in agreement with those reported.^[4]

Methyl-2-(6-methoxy-1*H*-indol-3-yl)-3-oxoindoline-2-carboxylate (3g)

Following the **General Procedure** for 21 h, the product was obtained as a yellow solid (37 mg) in 84% yield. Spectral data were in agreement with those reported.^[4]

Methyl-3-(2-(methoxycarbonyl)-3-oxoindolin-2-yl)-1*H*-indole-4-carboxylate (3h)

Following the **General Procedure** for 22 h at 80 °C, the product was obtained as a yellow solid (37 mg) in 77% yield. Spectral data were in agreement with those reported.^[4]

Methyl-2-(5-cyano-1*H*-indol-3-yl)-3-oxoindoline-2-carboxylate (3i)

Following the **General Procedure** for 16 h, the product was obtained as a yellow solid (39 mg) in 88% yield. Spectral data were in agreement with those reported.^[4]

Methyl-2-(3-methyl-1*H*-indol-2-yl)-3-oxoindoline-2-carboxylate (3j)

Following the **General Procedure** for 19 h, the product was obtained as a yellow solid (26 mg) in 62% yield. Spectral data were in agreement with those reported.^[4]

Methyl-2-(1-methyl-1*H*-indol-3-yl)-3-oxoindoline-2-carboxylate (3k)

Following the **General Procedure** for 19 h, the product was obtained as a yellow solid (45 mg) in 88% yield. Spectral data were in agreement with those reported.^[4]

Methyl-2-(2-methyl-1*H*-indol-3-yl)-3-oxoindoline-2-carboxylate (3l)

Following the **General Procedure** for 19 h, the product was obtained as a yellow solid (58 mg) in 77% yield. Spectral data were in agreement with those reported.^[4]

Methyl-2-(2-(4-fluorophenyl)-1*H*-indol-3-yl)-3-oxo-5-methoxy-indoline-2-carboxylate (3m)

Following the **General Procedure** for 18 h, the product was obtained as a yellow solid (48 mg) in 85% yield. $R_f = 0.2$ (1:9 EtOAc:hexanes) **¹H NMR** (500 MHz, CDCl₃) δ 8.18 (br s, 1H), 7.41 (dd, $J = 6.7, 6.5$ Hz, 2H), 7.34 (d, $J = 8.1$ Hz, 1H), 7.24 (dd, $J = 8.8, 2.7$ Hz, 1H), 7.18 (d, $J = 6.6$ Hz, 1H), 7.17 (d, $J = 5.2$ Hz, 1H), 7.04 (m, 4H), 6.98 (d, $J = 8.9, 1.0$ Hz, 1H), 3.79 (s, 3H), 3.32 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 195.4, 169.1, 163.1 (d, $J = 249.2$ Hz), 162.1, 156.6, 154.7, 136.8, 135.6, 131.6 (d, $J = 8.3$ Hz), 128.7, 126.9, 123.0, 120.9, 120.8, 119.6, 115.5 (d, $J = 11.7$ Hz), 115.3, 111.4, 108.9, 104.9, 74.3, 56.0, 53.5; **IR** (neat); 3341, 3061, 2951, 1731, 1693, 1491, 1456, 1435, 1265, 1220, 1193, 1156, 1094, 1070, 1026, 840, 805, 793, 745, 696, 568, 538; **HRMS** (ES-TOF) calcd for C₂₅H₁₉FN₂O₄ [M-H] $m/z = 429.1251$; found 429.1246.

Methyl-2-(2-(4-fluorophenyl)-1-methyl-indol-3-yl)-3-oxo-indoline-2-carboxylate (3n)

Following the **General Procedure** for 20 h, the product was obtained as a yellow solid (14 mg) in 25% yield. $R_f = 0.3$ (1:9 EtOAc:hexanes); **¹H NMR** (500 MHz, CDCl₃) δ 8.35 (br s, 1H), 7.55 (ddd, $J = 8.4, 8.4, 1.3$ Hz, 1H), 7.49 (m, 3H), 7.36 (d, $J = 8.1$ Hz, 1H), 7.18 (m, 2H), 7.04 (t, $J = 7.4$ Hz, 1H), 6.98 (m, 2H), 6.81 (d, $J = 8.3$ Hz, 1H), 6.77 (t, $J = 7.4$ Hz, 1H), 3.40 (br s, 3H), 3.00 (s, 3H); **¹³C NMR** (125 MHz, *d*₆-acetone) δ 167.9, 164.7, 160.9, 139.1, 139.0, 136.9, 132.4 (d, $J = 8.3$ Hz), 130.8, 128.2, 125.5, 122.9, 120.9, 120.1, 119.9, 118.6, 115.7 (d, $J = 21.5$ Hz), 112.4, 109.6, 105.9, 77.1, 52.7; **IR** (neat); 3324, 3063, 2925, 1736, 1696, 1613, 1497, 1457, 1432, 1366, 1321, 1221, 1198, 1159, 1114, 1094, 1016, 993, 840, 803, 745, 706, 565; **HRMS** (ES-TOF) calcd for C₂₅H₁₉FN₂O₃ [M-H] $m/z = 413.1301$; found 413.1298.

Methyl-2-(2-(4-fluorophenyl)-1*H*-indol-3-yl)-3-oxo-4-chloro-indoline-2-carboxylate (3o)

Following the **General Procedure** for 16 h, the product was obtained as a yellow solid (48 mg) in 77% yield. $R_f = 0.3$ (1:9 EtOAc:hexanes) **¹H NMR** (500 MHz, CDCl₃) δ 8.36 (br s, 1H), 7.47 (d, $J = 8.3$ Hz, 1H), 7.33 (m, 2H), 7.28 (d, $J = 8.1$ Hz, 1H), 7.19 (d, $J = 8.5$ Hz, 1H), 7.16 (d, $J = 7.4$ Hz, 1H), 7.05 (t, $J = 7.6$ Hz, 1H), 6.94 (m, 3H), 6.88 (dd, $J = 8.2, 1.4$ Hz, 1H), 5.70 (br s, 1H), 3.30 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 193.8, 168.6, 163.1 (d, $J = 247.8$ Hz), 160.8, 144.6, 137.0, 135.5, 131.6 (d, $J = 8.14$ Hz), 128.6, 126.8, 126.3, 123.0, 121.3, 120.9, 119.4, 118.6, 115.5 (d, $J = 21.7$ Hz), 113.2, 111.5, 108.1, 73.6, 53.5; **IR**

(neat); 3351, 3059, 2952, 1705, 1606, 1578, 1498, 1456, 1433, 1319, 1287, 1222, 1193, 1158, 1105, 1094, 1062, 1015, 919, 840, 812, 744, 538; **HRMS** (ES-TOF) calcd for $C_{24}H_{16}ClFN_2O_3$ [M-H] m/z = 433.0753; found 433.0769.

Benzyl-2-(2-(4-fluorophenyl)-1*H*-indol-3-yl)-3-oxo-indoline-2-carboxylate (3p)

Following the **General Procedure** for 16 h, the product was obtained as a yellow solid (48 mg) in 90% yield (31 mg remained after precipitation from chloroform with hexanes to remove hydrocarbon impurities). R_f = 0.3 (1:9 EtOAc:hexanes) **¹H NMR** (500 MHz, $CDCl_3$) δ 8.22 (br s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.53 (td J = 7.7, 1.2 Hz, 1H), 7.33 (dd, J = 8.6, 5.3 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 7.23 (m, 4H), 7.14 (t, J = 5.1 Hz, 1H), 7.10 (m, 2H), 6.98 (t, J = 7.6 Hz, 1H), 6.91 (m, 4H), 5.54 (br s, 1H), 4.81 (d, J = 12.6 Hz, 1H), 4.58 (d, J = 12.6 Hz, 1H); **¹³C NMR** (125 MHz, $CDCl_3$) δ 195.0, 168.4, 163.1 (d, J = 249.0 Hz), 138.0, 136.7, 135.5, 134.9, 131.6 (d, J = 8.3 Hz), 128.74, 128.71, 128.5, 128.3, 127.9, 126.9, 125.3, 122.8, 120.7, 120.5, 120.3, 119.8, 115.5 (d, J = 21.6 Hz), 113.3, 111.3, 108.4, 73.2, 68.06; **IR** (neat); 3356, 3064, 1704, 1609, 1498, 1486, 1467, 1457, 1435, 1324, 1220, 1197, 1152, 1093, 1071, 1015, 891, 840, 743, 696, 666; **HRMS** (ES-TOF) calcd for $C_{30}H_{21}FN_2O_3$ [M-H] m/z = 475.1458; found 475.1443.

Adamantyl-2-(2-(4-fluorophenyl)-1*H*-indol-3-yl)-3-oxo-indoline-2-carboxylate (3q)

Following the **General Procedure** for 16 h, the product was obtained as a yellow solid (48 mg) in 57% yield (15 mg remained after precipitation from chloroform with hexanes to remove hydrocarbon impurities). R_f = 0.4 (1:9 EtOAc:hexanes) **¹H NMR** (500 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.40 (dd, J = 8.3, 5.5 Hz, 2H), 7.23 (d, J = 8.1 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 7.00 (dd, J = 9.5, 8.5 Hz, 2H), 6.90 (m, 2H), 5.41 (br s, 1H), 2.02 (br s, 3H), 1.77 (m, 6H), 1.51 (m, 6H); **¹³C NMR** (125 MHz, $CDCl_3$) δ 195.5, 166.9, 163.2 (d, J = 248.8 Hz), 160.4, 137.6, 136.4, 135.7, 131.4 (d, J = 8.2 Hz), 129.5, 127.2, 125.2, 122.7, 120.6, 120.5, 120.4, 120.2, 115.6 (d, J = 21.6 Hz), 113.1, 111.1, 108.5, 83.8, 74.0, 40.6, 36.0, 30.9; **IR** (neat) 3340, 3058, 2912, 2853, 1704, 1614, 1498, 1485, 1468, 1458, 1439, 1321, 1224, 1197, 1155, 1102, 1093, 1046, 963, 839, 740, 700, 667; **HRMS** (ES-TOF) calcd for $C_{33}H_{29}FN_2O_3$ [M+H]⁺ m/z = 521.2240; found 521.2253.

Methyl-3-oxo-2-(1*H*-pyrrol-2-yl)indoline-2-carboxylate (5a)

Following the **General Procedure** for 15 h, the product was obtained as a brown oil (16 mg) in 49% yield. The C2-substitution on this and related pyrroles was assigned on the basis of a vicinal coupling >3 Hz, which is absent in the C3-substituted version. R_f = 0.50 (EtOAc:Hexanes = 1:2); **¹H NMR** (500 MHz, $CDCl_3$) δ 9.38 (br s, 1H), 7.59 (ddd, J = 7.7, 1.3, 0.7 Hz, 1H), 7.52 (ddd, J = 8.4, 7.1, 1.3 Hz, 1H), 7.05 (dt, J = 8.2, 0.8 Hz, 1H), 6.91 (ddd, J = 7.9, 7.1, 0.8 Hz, 1H), 6.83 (td, J = 2.6, 1.6 Hz, 1H), 6.29 (ddd, J = 3.5, 2.5, 1.6 Hz, 1H), 6.14 (dt, J = 3.5, 2.7 Hz, 1H), 5.61 (br s, 1H), 3.81 (s, 3H); **¹³C NMR** (125 MHz, $CDCl_3$) δ 193.2, 167.7, 161.7, 138.1, 125.8, 124.9, 120.8, 119.3, 118.9, 113.6, 108.3, 106.3, 71.9, 54.0; **IR** (neat) 3364, 2951, 1733, 1693, 1613, 1486, 1467, 1433, 1324, 1233, 1197, 1153, 1139, 1101, 1028, 1008, 950 cm^{-1} ; **HRMS** (ESI-TOF) calcd for $C_{14}H_{12}N_2O_3Na$ [M+Na]⁺ m/z = 279.0746; found 279.0756.

Methyl-2-(3,5-dimethyl-1*H*-pyrrol-2-yl)-3-oxoindoline-2-carboxylate (5c)

Following the **General Procedure** for 16 h, the product was obtained as a yellow solid (25 mg) in 65% yield. Spectral data were in agreement with those reported.^[4]

Methyl-2-(1-methyl-1*H*-pyrrol-2-yl)-3-oxoindoline-2-carboxylate (5d)

Following the **General Procedure** for 18 h, the product was obtained as a yellow solid (13 mg) in 37% yield. $R_f = 0.5$ (EtOAc:Hexanes = 1:2): $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.67 (d, $J = 7.5$ Hz, 1H), 7.53 (td, $J = 7.5, 1.2$ Hz, 1H), 7.00 (d, $J = 8.0$ Hz, 1H), 6.95 (t, $J = 7.5$ Hz, 1H), 6.61 (dd, $J = 2.7, 1.9$ Hz, 1H), 6.13 (dd, $J = 3.7, 1.8$ Hz, 1H), 6.06 (dd, $J = 3.8, 2.7$ Hz, 1H), 5.50 (br s, 1H), 3.87 (s, 3H), 3.42 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 193.8, 168.4, 160.6, 138.1, 126.2, 125.5, 125.4, 120.9, 119.9, 113.8, 110.8, 107.2, 73.1, 54.2, 35.0; **IR** (neat) 3352, 2950, 1737, 1703, 1613, 1484, 1467, 1434, 1322, 1306, 1291, 1246, 1230, 1196, 1150, 1092, 1027 cm^{-1} ; **HRMS** (ESI-TOF) calcd for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 271.1083, found 271.1095.

Methyl-2-(5-methoxyfuran-2-yl)-3-oxoindoline-2-carboxylate (5e)

Following the **General Procedure** for 21 h, the product was obtained as a brown oil (26 mg) in 68% yield. $R_f = 0.33$ (EtOAc:Hexanes = 1:2): $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.64 (d, $J = 8.0$ Hz, 1H), 7.51 (td, $J = 8.0, 1.0$ Hz, 1H), 6.97 (d, $J = 8.0$ Hz, 1H), 6.91 (t, $J = 8.0$ Hz, 1H), 6.37 (d, $J = 3.5$ Hz, 1H), 5.56 (br s, 1H), 5.12 (d, $J = 3.5$ Hz, 1H), 3.81 (s, 6H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 191.8, 167.1, 162.0, 161.2, 138.4, 138.2, 125.7, 120.7, 119.4, 113.7, 110.7, 80.5, 71.6, 58.0, 54.2; **IR** (neat) 3358, 2920, 1744, 1705, 1613, 1576, 1486, 1467, 1435, 1367, 1324, 1295, 1258, 1199, 1152, 1099, 1027, 962 cm^{-1} ; **HRMS** (ESI-TOF) calcd for $\text{C}_{15}\text{H}_{14}\text{NO}_5$ $[\text{M}+\text{H}]^+$ 288.0872, found 288.0860.

Methyl-2-(4-(dimethylamino)phenyl)-3-oxoindoline-2-carboxylate (5g)

Following the **General Procedure** for 19 h at 80 °C, the product was obtained as a yellow solid (21 mg) in 52% yield. $R_f = 0.4$ (EtOAc:Hexanes = 1:2): $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.60 (d, $J = 8.0$ Hz, 1H), 7.57 (d, $J = 9.0$ Hz, 2H), 7.49 (td, $J = 7.0, 1.0$ Hz, 1H), 7.01 (d, $J = 8.0$ Hz, 1H), 6.88 (t, $J = 7.5$ Hz, 1H), 6.70 (d, $J = 9.0$ Hz, 2H), 5.61 (br s, 1H), 3.80 (s, 3H), 2.93 (s, 6H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 194.5, 169.0, 160.8, 150.8, 137.6, 127.2, 125.6, 123.4, 120.3, 120.0, 113.3, 112.5, 74.8, 53.8, 40.6; **IR** (neat) 3352, 2950, 2922, 1740, 1698, 1608, 1519, 1485, 1468, 1434, 1355, 1322, 1291, 1233, 1195, 1166, 1152, 1096, 1061, 984 cm^{-1} ; **HRMS** (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 311.1396, Found 311.1408.

Methyl-2-(4-(diethylamino)phenyl)-3-oxoindoline-2-carboxylate (5h)

Following the **General Procedure** for 18 h at 80 °C, the product was obtained as a yellow solid (29 mg) in 66% yield. $R_f = 0.50$ (EtOAc:Hexanes = 1:2): $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.60 (d, $J = 7.5$ Hz, 1H), 7.51 (d, $J = 9.0$ Hz, 2H), 7.48 (td, $J = 7.5, 1.0$ Hz, 1H), 7.00 (d, $J = 8.0$ Hz, 1H), 6.87 (t, $J = 7.5$ Hz, 1H), 6.63 (d, $J = 9.0$ Hz, 2H), 5.60 (br s, 1H), 3.80 (s, 3H), 3.33 (q, $J = 7.0$ Hz, 4H), 1.13 (t, $J = 7.0$ Hz, 6H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 194.7, 169.1, 160.8, 148.0, 137.6, 127.4, 125.6, 124.3, 120.2, 120.0, 113.3, 111.6, 74.9, 53.7, 44.5, 12.7; **IR** (neat) 3355, 2970, 1738, 1697, 1607, 1589, 1517, 1486, 1468, 1452,

1434, 1355, 1321, 1291, 1264, 1231, 1194, 1153, 1089 cm^{-1} ; **HRMS** (ESI-TOF) calcd for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 339.1709, Found 339.1719.

Methyl-2-(1-(2-cyanoethyl)-1H-pyrrol-2-yl)-3-oxoindoline-2-carboxylate (5i)

Following the **General Procedure** for 24 h at 80 °C, the product was obtained as a brown oil (24 mg) in 60% yield. R_f = 0.25 (EtOAc:Hexanes = 1:2); ^1H NMR (500 MHz, CDCl_3) δ 7.67 (dd, J = 8.0, 1.0 Hz, 1H), 7.57 (td, J = 8.0, 1.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.80 (t, J = 2.4 Hz, 1H), 6.16 (d, J = 2.3 Hz, 2H), 5.55 (s, 1H), 3.98–3.89 (m, 2H), 3.88 (s, 3H), 2.73 (t, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 193.8, 168.1, 160.4, 138.4, 125.7, 125.6, 124.0, 121.5, 119.6, 117.4, 113.8, 111.7, 109.0, 73.1, 54.3, 43.3, 20.0; **IR** (neat) 3347, 2952, 2250, 1737, 1704, 1613, 1483, 1468, 1434, 1323, 1292, 1234, 1198, 1151, 1085, 1045, 979, 894 cm^{-1} ; **HRMS** (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{16}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$ m/z = 310.1192; found 310.1180.

Methyl 3-oxo-2-(2,4,6-trimethoxyphenyl)indoline-2-carboxylate (5j)

Following the **General Procedure** for 24 h at 80 °C, the product was obtained as a yellow solid (29 mg) in 62% yield. R_f = 0.13 (EtOAc:Hexanes = 1:2); ^1H NMR (500 MHz, CDCl_3) δ 7.66 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H), 6.13 (s, 2H), 5.47 (br s, 1H), 3.77 (s, 6H), 3.65 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 195.1, 169.8, 161.7, 160.2, 159.4, 136.7, 124.7, 120.9, 120.0, 113.5, 108.5, 92.5, 72.3, 56.0, 55.6, 53.6; **IR** (neat) 3353, 2948, 1716, 1605, 1587, 1484, 1468, 1435, 1417, 1322, 1226, 1204, 1152, 1126, 1093, 1057, 1029, 993 cm^{-1} ; **HRMS** (ESI-TOF) calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_6$ $[\text{M}+\text{H}]^+$ 358.1291 Found: 358.1281.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We are grateful to the NIH (GM-112684) and the NSF (CHE1764298) for financial support of this research. Partial instrumentation support was provided by the NIH and NSF (1S10RR023444, 1S10RR022442, CHE-0840438, CHE-0848460, 1S10OD011980). Drs. Rakesh Kohli and Charles W. Ross III (UPenn) are acknowledged for obtaining HRMS data.

References

- [1]. a. Wu P-L, Hsu Y-L, Jao C-W, J. Nat. Prod 2006, 69, 1467–1470; [PubMed: 17067163] b. Liu J-F, Jiang Z-Y, Wang R-R, Zheng Y-T, Chen J-J, Zhang X-M, Ma Y-B, Org. Lett 2007, 9, 4127–4129; [PubMed: 17850153] c. Tsukamoto S, Umaoka H, Yoshikawa K, Ikeda T, Hirota H, J. Nat. Prod 2010, 73, 1438–1440; [PubMed: 20795742] d. Liu R-R, Ye S-C, Lu C-J, Zhuang G-L, Gao J-R, Jia Y-X, Angew. Chem. Int. Ed 2015, 54, 11205–11208.
- [2]. a. Wetzel A, Gagosz F, Angew. Chem. Int. Ed 2011, 50, 7354–7358; b. Ardakani MA, Smalley RK, Tetrahedron Lett. 1979, 20, 4769–4772; c. Goriya Y, Ramana CV, Chem. Commun 2013, 49, 6376–6378; d. Liu Y, McWhorter WW, J. Org. Chem 2003, 68, 2618–2622; [PubMed: 12662030] e. Witkop B, Patrick JB, J. Am. Chem. Soc 1951, 73, 2188–2195; f. Witkop B, J. Am. Chem. Soc 1950, 72, 614–620; g. Xia Z, Hu J, Gao Y-Q, Yao Q, Xie W, Chem. Commun 2017, 53, 7485–7488.

- [3]. For reviews of oxidative C-H coupling chemistry, see: Liu C, Yuan J, Gao M, Tang S, Li W, Shi R, Lei A, Chem. Rev 2015, 115, 12138–12204; [PubMed: 26558751] Kozlowski MC, Acc. Chem. Res 2017, 50, 638–643; [PubMed: 28945389] For reviews of dearomatization, see: Sun W, Li G, Hong L, Wang R, Org. Biomol. Chem 2016, 14, 2164–2176; [PubMed: 26740241] Wu W-T, Zhang L, You S-L, Chem. Soc. Rev 2016, 45, 1570–1580; [PubMed: 26796922] Zheng C, You S-L, Chem 2016, 1, 830–857.
- [4]. Jessing MB, Baran PS, Heterocycles 2011, 82, 1739–1745.
- [5]. Guchhait SK, Chaudhary V, Rana VA, Priyadarshani G, Kandekar S, Kashyap M, Org. Lett 2016, 18, 1534–1537. [PubMed: 26986450]
- [6]. Zhou X-Y, Chen X, Wang L-G, Yang D, Li J-H, Synlett 2018, 29, 835–839.
- [7]. Kong L, Wang M, Zhang F, Xu M, Li Y, Org. Lett 2016, 18, 6124–6127. [PubMed: 27934344]
- [8]. Lin F, Chen Y, Wang B, Qin W, Liu L, RSC Advances 2015, 5, 37018–37022.
- [9]. a. Kong Y-B, Zhu J-Y, Chen Z-W, Liu L-X, Can. J. Chem 2014, 92, 269; b. Kothandapani J, Reddy SMK, Thamotharan S, Kumar SM, Byrappa K, Ganesan SS, Eur. J. Org. Chem 2018, 2018, 2762–2767.
- [10]. Yarlagadda S, Sridhar B, Subba BV Reddy, Chemistry – An Asian Journal 2018, 13, 1327–1334.
- [11]. Denizot N, Guillot R, Kouklovsky C, Vincent G, Synthesis 2018, 50, 4823–4828.
- [12]. Denizot N, Tomakinian T, Beaud R, Kouklovsky C, Vincent G, Tetrahedron Lett. 2015, 56, 4413–4429.
- [13]. Lee YE, Cao T, Torruellas C, Kozlowski MC, J. Am. Chem. Soc 2014, 136, 6782–6785. [PubMed: 24797179]
- [14]. Avery TD, Fallon G, Greatrex BW, Pyke SM, Taylor DK, Tiekink ERT, J. Org. Chem 2001, 66, 7955–7966. [PubMed: 11722191]

Figure 1.
Examples of 2,2-Disubstituted 3-Oxindole Natural Products.

Figure 2.
Catalysts Screened for Activity in the Cross-Coupling of 3-Oxindoles and Indoles.

Figure 3. Catalyst Screening Results, Size of the Sphere Indicates Yield of **3** Relative to An Internal Standard (see Supporting Information for Product/Internal Standard Ratios).

Figure 4.
Measured Oxidation Potentials for Select Substrates.

Figure 5.
Possible Mechanism for the Oxidative Cross-Coupling of Oxindoles and Simple Aromatics.

Scheme 1.

Reported Methods for the Formation of 2,2-Disubstituted 3-Oxindoles by Oxidative Methods

Scheme 2.
Oxidative coupling of indole and phenol moieties

Scheme 3.
Scope of the Coupling of 3-Oxindoles with Indoles

^areaction at 80 °C^brecovered after precipitation with hexanes from chloroform to remove grease from solvent

Scheme 4.
Scope of 3-oxindoles with indole **2c**.

Scheme 5.

Scope of the Cross-Coupling of 3-Oxindoles with Simple Arenes