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Co(III)-Catalyzed C−H Activation: A Site-Selective Conjugate Addition of Maleimide to Indole at the C-2 Position

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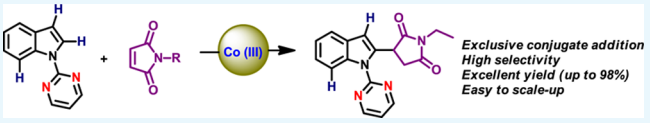
Supporting Information

ABSTRACT: The cobalt(III)-catalyzed site-selective C-2 functionalization of indole has been developed using the pyrimidinyl group as a directing group. This reaction furnishes 3-arylated succinimide derivatives in excellent yields in a shorter duration using an inexpensive Co catalyst. Highly selective C-2 functionalization of indoles was achieved in the presence of the highly reactive C-3 position. This protocol is compatible with a variety of *N*-pyrimidinyl indole and maleimide derivatives, and it can be easily scaled-up. This method is also applicable for maleic ester and heteroarenes.



INTRODUCTION

C−H activation followed by conjugate addition to maleimides has recently emerged as a powerful method for synthesizing 3-substituted succinimides.[1,2] The succinimide skeleton is found in several natural products and biologically active molecules. Succinimides are also found in some commercially available and commonly used anticonvulsants such as phensuximide, ethosuximide, and mesuximide.[3] Also, the succinimide rings are easily reduced to pyrrolidine rings or lactams.[4] Similarly, the indole ring is found in a variety of natural products and pharmaceutically active molecules.[5] These reasons account for the ever-continuing interest in the manipulation and derivatization of indole scaffolds. Of late, the directing group strategy has provided a great opportunity for the selective functionalization of indole at the C-2, C-4, and C-7 positions. This has been achieved by using a variety of transition metal catalysts such as Rh,[6] Ru,[7] Ir,[8] Pd,[9] and more recently, Co.[10]

In continuation of our own work on conjugate addition of maleimides with oxygen-based directing groups (amide, ketone, and carboxylic acid),[1] we decided to explore the prospect of using nitrogen-based directing groups for the same purpose. Typically, oxygen-based directing groups are weaker coordinating groups and behave as hard electron donors. Therefore, most reports with oxygen-based directing groups utilize oxophilic metals such as Ru, Rh, Pd,[6−9] and Co.[11,18d] Nitrogen-based directing groups have been used with several metal catalysts such as Rh, Ru, Ir, Pd, Ni, Pt, Co, and Cu. Initially, the Co(III)-catalyzed C−H activation reaction was reported by Kanai and Matsunaga,[12] and it was then further developed by Ellman,[13] Glorius,[14] Chang,[15] Ackermann,[16] Daugulis,[17] and others.[18] The conjugate addition of indole (at the C-2 position) to maleimides using a Ru(II) catalyst and the benzoyl group as a directing group was first reported by our group.[1] Recently, the Co(III)-catalyzed conjugate addition of enamides to maleimides was reported by Zhang.[2h] The pyrimidinyl group has also been used as a directing group to functionalize proximal C−H bonds with the help of various transition metals.[6−10,19] In this direction, and to achieve the current work, we used cobalt catalysts as they are easy to synthesize, bench stable, easy to handle, and inexpensive (Scheme 1).

RESULTS AND DISCUSSION

The initial screening studies were performed using *N*-pyrimidinyl indole (**1a**) and *N*-ethylmaleimide (**2a**) as the starting materials (Table 1). The reaction of **1a** with **2a** with $Cp^*Co(CO)I_2$ (5 mol %), $AgSbF_6$ (20 mol %) as an activator, and NaOAc as an additive (20 mol %) in DCE (2 mL) at 100 °C for 2 h furnished the product **3aa** in 10% yield (entry 1). The same reaction, when performed using trifluoroethanol (TFE) as solvent, increased the yield of **3aa** to 44% (entry 2). Changing the activator from $AgSbF_6$ to $AgBF_4$ or $AgPF_6$ afforded **3aa** in 20 and 19% yields, respectively (entries 3 and 4). An excellent increase in the yield was observed (98%, entry 5) when the activator was changed to AgOAc. The yield of the reaction was unchanged in the absence of NaOAc (entry 6). Carrying out the reactions at 80, 50 °C, and at ambient temperature resulted in a lower yield of **3aa** (entries 7−9). Decreasing the catalyst loading to 2.5 mol % led to the formation of **3aa** in low yield (30%, entry 10). However, decreasing the amount of activator (AgOAc) to 10 mol % still resulted in the formation of **3aa** in 98% yield (entry 11). Also, reducing the amount of **2a** to 1.2 equiv furnished **3aa** in low yield (80%, entry 12). Finally, the optimal reaction conditions were achieved by performing the reaction of **1a** (1 equiv) with **2a** (1.5 equiv) using Co(III) catalyst (5 mol %) and AgOAc (10 mol %) in TFE at 100 °C, which furnished the product **3aa** in 98% isolated yield (entry 13). The reaction of **1a** with **2a** did not proceed either in the absence of AgOAc or the Co catalyst (entries 14 and 15).

Having found the optimal reaction conditions, we started exploring the scope of the reaction (Scheme 2). Initially, the C5-

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Scheme 1. Comparison with Previous Work

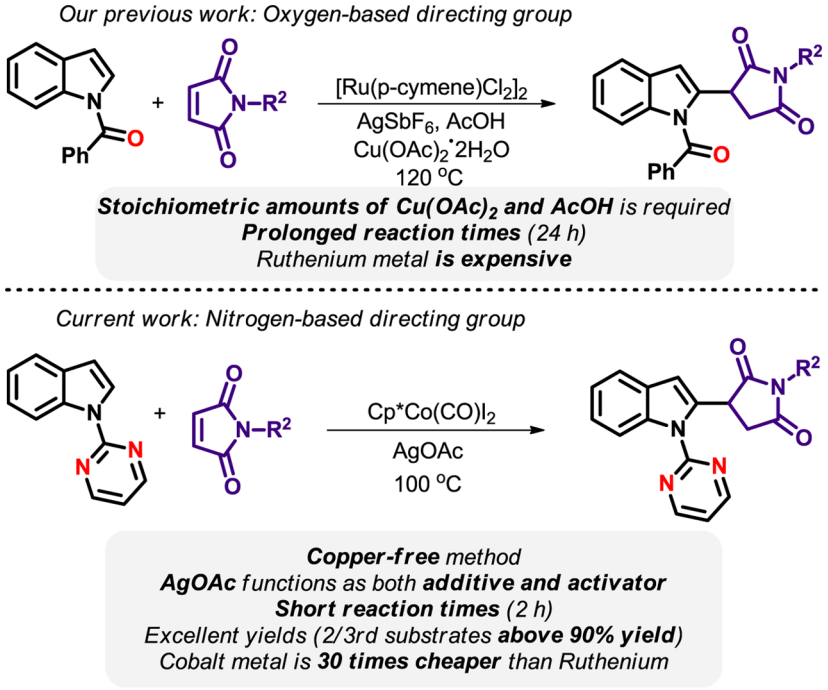
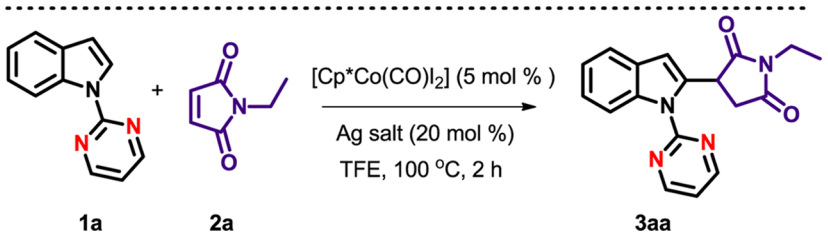


Table 1. Optimization Studies[a]



entry	Ag salt (mol %)	additive (20 mol %)	solvent (2 mL)	temperature (°C)	NMR yield (%)[b]
1	$AgSbF_6$ (20)	NaOAc	$ClCH_2CH_2Cl$ (DCE)	100	10
2	$AgSbF_6$ (20)	NaOAc	CF_3CH_2OH (TFE)	100	44
3	$AgBF_4$ (20)	NaOAc	TFE	100	20
4	$AgPF_6$ (20)	NaOAc	TFE	100	10
5	AgOAc (20)	NaOAc	TFE	100	98
6	AgOAc (20)	none	TFE	100	98[c]
7	AgOAc (20)	none	TFE	80	73
8	AgOAc (20)	none	TFE	50	65
9	AgOAc (20)	none	TFE	ambient	33
10	AgOAc (20)	none	TFE	100	30[d]
11	AgOAc (10)	none	TFE	100	98[e]
12	AgOAc (10)	none	TFE	100	80[f]
13	**AgOAc (10)**	**none**	**TFE**	**100**	**98[c,g]**
14	none	none	TFE	100	nd
15	AgOAc (10)	none	TFE	100	nd[h]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [Cp*Co(CO)I_2] (5 mol %), solvent (2 mL), for 2 h. [b]^{1}H NMR yield (using terephthalaldehyde as an internal standard). [c]Isolated yield. [d]2.5 mol % of Co(III) catalyst. [e]10 mol % of AgOAc. [f]1.2 equiv of **2a**. [g]1.5 equiv of **2a**. [h]In the absence of Co catalyst. nd = not detected.

substituted derivatives of indole were used as the precursors. Accordingly, the 2-pyrimidinyl derivatives of 5-methoxyindole and 5-bromoindole furnished the corresponding adducts **3ba** and **3ca** in excellent yields (93 and 95%, respectively). 5-Cyanoindole furnished **3da** in 65% yield, whereas 5-nitroindole and 5-phenylindole afforded **3ea** and **3fa** in 91 and 95% yields, respectively. The reactions of the 6-substituted-*N*-pyrimidinyl indoles with *N*-ethylmaleimide were also facile. Thus, the 6-bromoindole and 6-methylester derivatives reacted smoothly with *N*-ethylmaleimide (**2a**) and furnished the corresponding conjugate addition products **3ga** and **3ha** in 97 and 97% yields, respectively. Even the sterically hindered 3-methyl substituted indole derivative underwent a facile reaction with **2a**, furnishing the product **3ia** in 70% yield.

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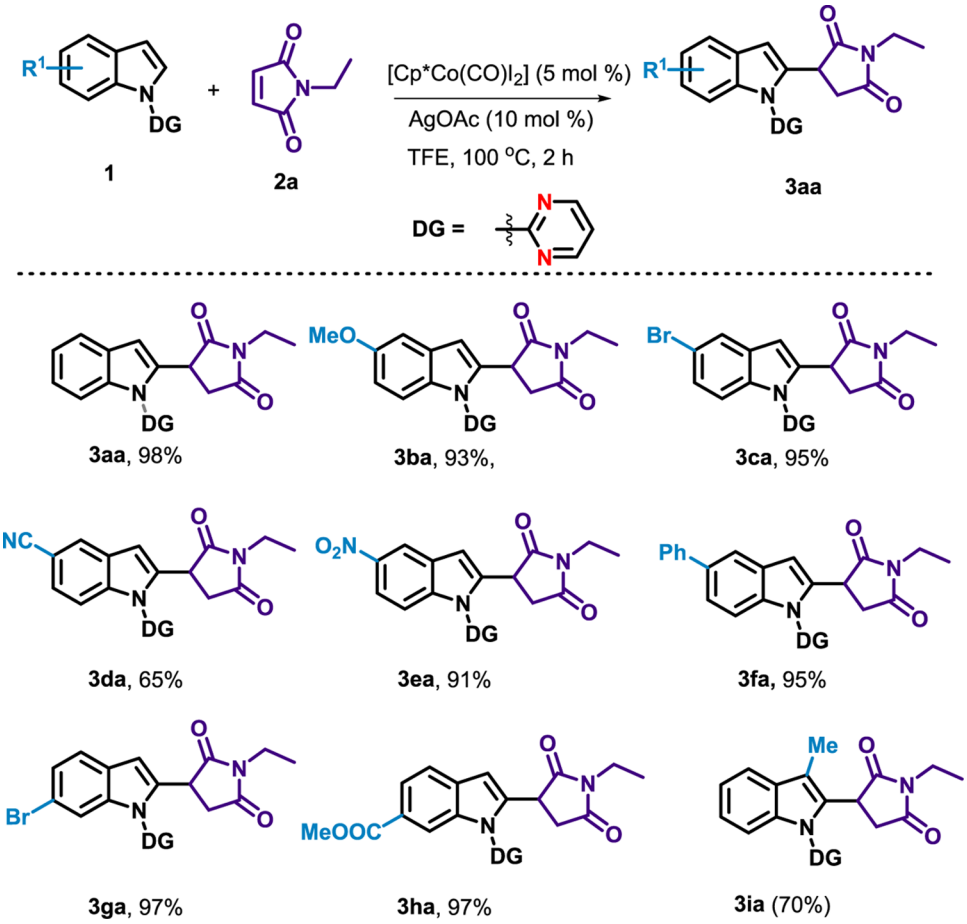
Scheme 2. Substrate Scope for Indole Derivatives[a,b]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [Cp*Co(CO)I_2] (5 mol %), AgOAc (10 mol %), TFE (2 mL), at 100 °C for 2 h. [b]Isolated yield.

After successful reactions of the 2-pyrimidinyl indole derivatives with *N*-ethylmaleimide, we continued the exploration with a variety of maleimide derivatives (Scheme 3). Thus, the reaction of 2-pyrimidinyl indole with *N*-benzylmaleimide, *N*-phenylmaleimide, maleimide, *N*-cyclohexylmaleimide, and *N*-(4-acetyl)phenylmaleimide furnished the corresponding conjugate products **4ab**, **4ac**, **4ad**, **4ae**, and **4af** in excellent yields (98, 98, 80, 83, and 79%, respectively). Similarly, 5-methoxy-*N*-pyrimidinyl indole underwent a smooth reaction with *N*-benzylmaleimide, *N*-phenylmaleimide, and maleimide, affording the conjugate products **4bb**, **4bc**, and **4bd** in excellent yields (97, 98, and 93% respectively). 5-Bromo-*N*-pyrimidinyl indole reacted well with *N*-benzylmaleimide, *N*-phenylmaleimide, and maleimide, furnishing the products **4cb**, **4cc**, and **4cd** in yields of 96, 95, and 82%, respectively. Although the reaction of dimethyl maleate with **1a** proceeded well, the reaction furnished the product **5** in low yield (30%).

The scope of the reaction was further extended to arenes and heteroarenes (Scheme 4). Thus, 2-phenylpyridine and 2-phenylpyrimidine reacted with *N*-ethylmaleimide (**2a**), affording the corresponding conjugated products **7aa** and **7ba** in moderate yields (35 and 40%, respectively). Similarly, *N*-pyrmidinylpyrrole reacted with **2a**, furnishing a mixture of the mono- and di-activated products **7ca** and **7ca′** in 55 and 20% yields, respectively.

After successfully synthesizing 3-arylated succinimide derivatives, a scaling up experiment was performed to demonstrate the efficiency of these reactions (Scheme 5). Hence, the reaction of **1a** (2.56 mmol, 500 mg) with **2a** under optimal reaction conditions afforded the corresponding product **3aa** in 96% yield. Further, the conjugated product **3aa**, which contained a pyrimidyl group, was subjected to another C−H activation reaction using ethyl acrylate and Rh(III) catalyst.[20a] Interestingly, this reaction led to the formation of the corresponding C-7 alkenylated product **8** in 74% yield (Scheme 5).

To understand the selectivity for metallacycle formation, the reaction of **1a** was performed using MeOD as a co-solvent under optimal reaction conditions (Scheme 6). In this reaction, 16% deuteration occurred at the C-2 position of indole, which indicated that the cobalt(III) catalyst preferentially formed a five-membered cobaltacycle at the C-2 position of indole. On the basis of this observation, our previous results,[1e] and the literature,[1a,10,11d] a reversible C−H activation step is proposed in Scheme 7.

Thus, the reaction of [Cp*Co(CO)I_2] with AgOAc generates a cationic species of Co(III) (**A**) with dissociation of CO. After the formation of the catalytically active species **A**, C−H metalation takes place at the proximal C-2 position of indole with the nitrogen of the pyrimidinyl group to generate **B**. Following the insertion of maleimides into the cobaltacycle **B**, a seven-membered intermediate **C** is formed. This intermediate **C**

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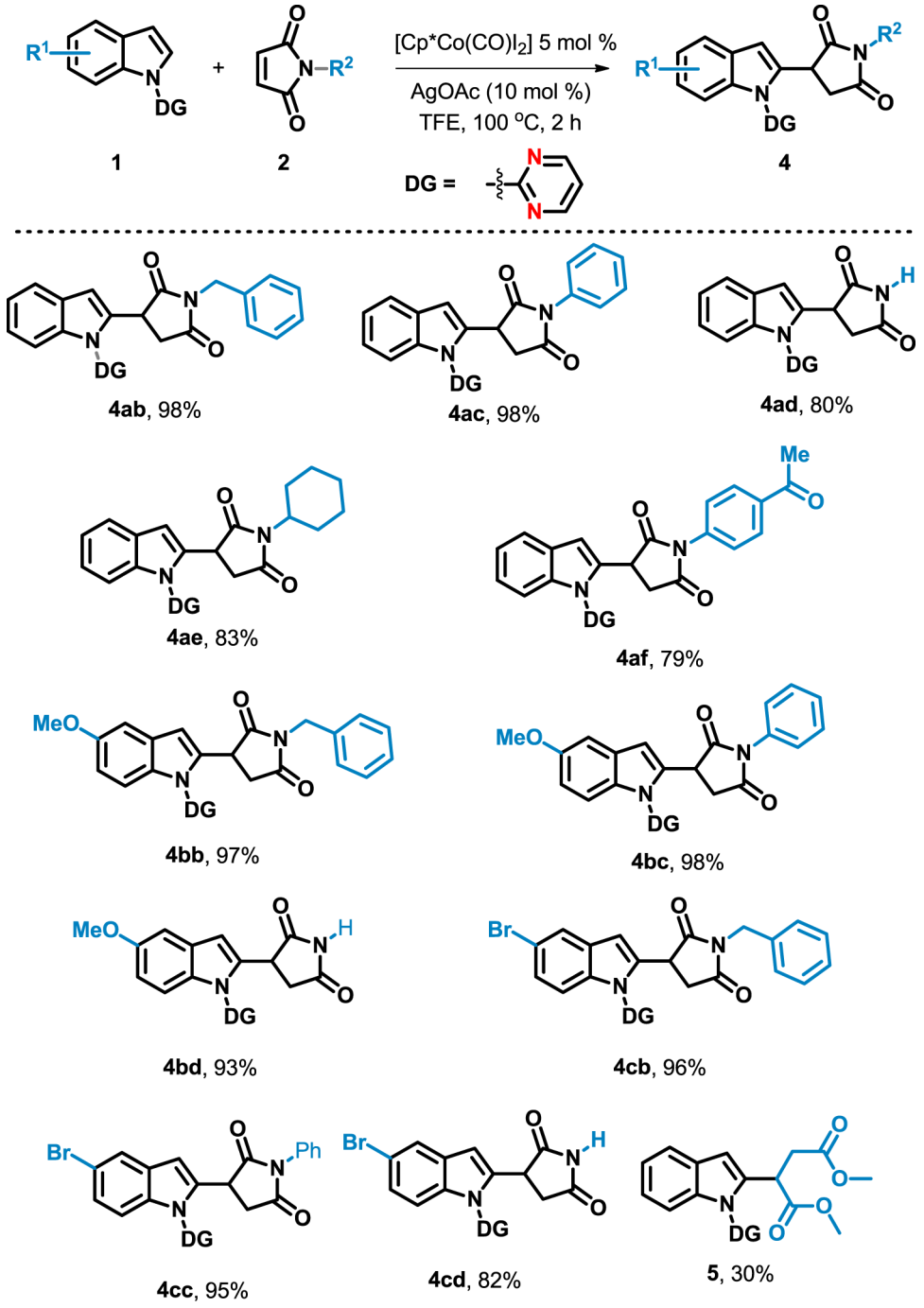
Scheme 3. Substrate Scope for Indole and Maleimide Derivatives[a,b]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [Cp*Co(CO)I_2] (5 mol %), AgOAc (10 mol %), TFE (2 mL), at 100 °C for 2 h. [b]Isolated yield.

cannot undergo β-hydride elimination due to the unavailability of the syn-periplanar β-hydrogen atom. As a result, acetic acid, which is formed in the reaction, promotes protodemetallation, thereby regenerating the active species **A** along with the desired product **3aa**.

CONCLUSIONS

In conclusion, we have developed a novel and efficient Co(III)-catalyzed functionalization at the C-2 position of indole with maleimides using the pyrimidinyl group as a directing group to obtain 3-arylated succinimide derivatives in excellent yields. This reaction proceeds quickly and employs an inexpensive Co catalyst, compared to precious Rh and Ru catalysts. Importantly, unlike other known catalytic systems such as those based on Rh and Ru, this method requires a catalytic amount of additive.

EXPERIMENTAL SECTION

General Information. All reactions were carried out using distilled solvents. Reactions were monitored by using precoated silica thin-layer chromatography (TLC) plates. Mass spectra were recorded in electron ionization and electrospray ionization (ESI) (time of flight) modes. NMR spectra were recorded at 400

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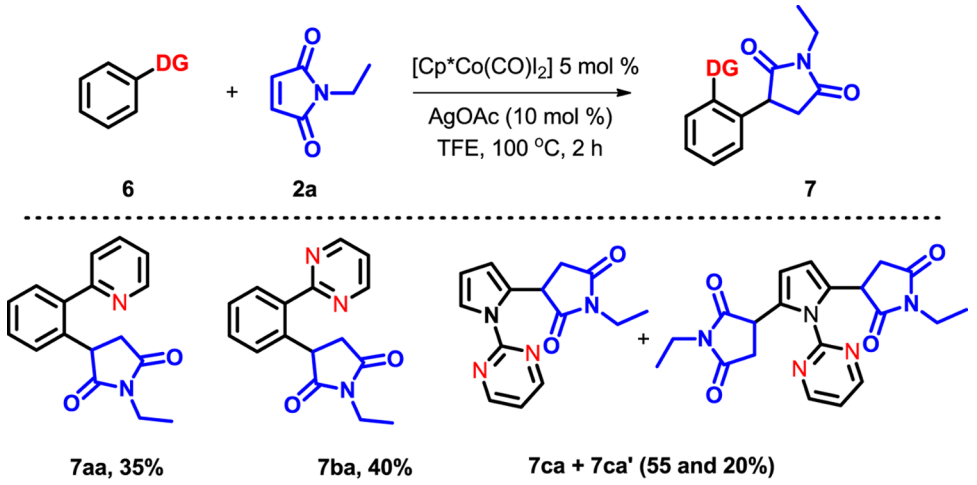
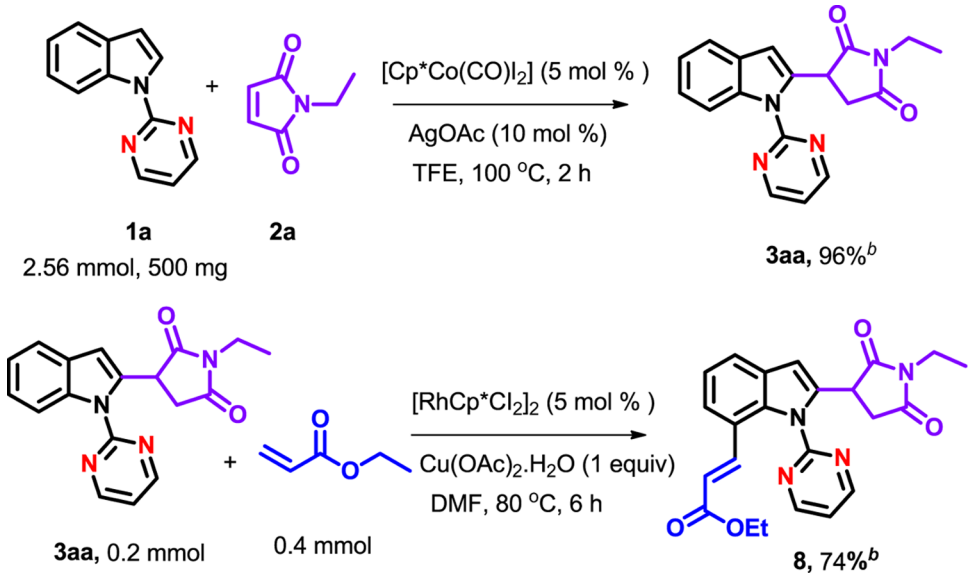
Scheme 4. Substrate Scope for Arenes and Heteroarenes[a,b]



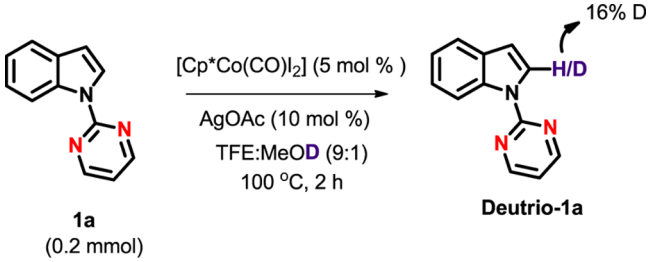
[a]Reaction conditions: **6** (0.2 mmol), **2a** (0.3 mmol), [Cp*Co(CO)I_2] (5 mol %), AgOAc (10 mol %), TFE (2 mL), at 100 °C for 2 h. [b]Isolated yield.

Scheme 5. Scale-Up Experiment[a] **and Synthetic Transformation**



[b]Isolated yield. [a]Reaction conditions: **1a** (2.56 mmol), **2a** (3.84 mmol), [Cp*Co(CO)I_2] (5 mol %), AgOAc (10 mol %), TFE (25 mL), at 100 °C for 2 h.

Scheme 6. Deuterium Labeling Studies



MHz in $CDCl_3$ and dimethyl sulfoxide (DMSO)-d_6, and tetramethylsilane (δ = 0.00 ppm) served as an internal standard for ^{1}H NMR. The corresponding residual nondeuterated solvent signal ($CDCl_3$, δ = 77.00 ppm and DMSO-d_6, δ = 39.52 ppm) was used as the internal standard for ^{13}C NMR. Column chromatography was carried out with 230−400 or 100−200 mesh silica gel (Merck) and thin-layer chromatography was carried out using SILICA GEL GF-254. Chemicals obtained from commercial suppliers were used without further purification. All *N*-pyrimidinyl indole derivatives[20b] and the cobalt catalyst[19c] were synthesized according to reported literature procedures.

Experimental Section. *General Experimental Procedure.* In an 8 mL screw cap reaction vial, *N*-pyrimidinyl indole (0.2 mmol), maleimide derivative (0.3 mmol), cobalt catalyst (4.76 mg, 5 mol %), and AgOAc (3.32 mg, 10 mol %) were added, followed by the addition of TFE (2 mL). This vial was sealed with a screw cap and placed in a preheated metal block at 100 °C, the reaction mixture was then stirred at the same temperature for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and concentrated under vacuum. The crude products were purified

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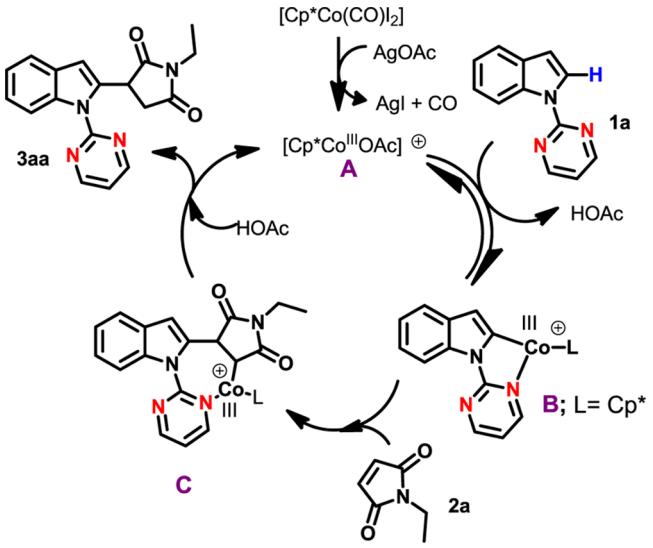
Scheme 7. Proposed Mechanism



on a silica gel column using an ethyl acetate (EtOAc)/PET mixture.

Experimental Procedure for Scale-Up Reaction. In a 50 mL pressure tube, *N*-pyrimidinyl indole (2.56 mmol, 500 mg), *N*-ethylmaleimide (3.84 mmol, 480 mg), cobalt catalyst (61 mg, 5 mol %), and AgOAc (42.5 mg, 10 mol %) were added, followed by the addition of TFE (25 mL). This tube was sealed with a screw cap and placed in a preheated oil bath at 100 °C, the reaction mixture was then stirred at the same temperature for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and concentrated under vacuum. The crude products were purified on a silica gel column using an EtOAc/poly(ethylene terephthalate) (PET) mixture.

Experimental Procedure for Synthesis of Compound ***8.*** In an 8 mL screw cap reaction vial, **3aa** (0.2 mmol, 64 mg), methyl acrylate (0.4 mmol, 40 mg), $[Cp^*RhCl_2]_2$ (5 mol %, 6.18 mg), and $Cu(OAc)_2{\cdot}H_2O$ (0.2 mmol, 40 mg) were added, followed by the addition of dimethylformamide (2 mL). This vial was sealed with a screw cap and placed in a preheated metal block at 60 °C, the reaction mixture was then stirred at the same temperature for 6 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and concentrated under vacuum. The crude products were purified on a silica gel column using an EtOAc/PET mixture.

*1-Ethyl-3-(1-(pyrimidin-2-yl)-1H-indol-2-yl)pyrrolidine-2,5-dione (**3aa**).* Pale brown solid; yield: (63 mg, 98%); mp: 188−190 °C; R_f (30% EtOAc/PET) 0.2; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1698, 1577, 1445; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.24 (t, J = 7.2 Hz, 3H), 2.91 (dd, J = 18.0, 6.0 Hz, 1H), 3.12 (dd, J = 18.0, 9.2 Hz, 1H), 3.59−3.73 (m, 2H), 4.80 (dd, J = 8.4, 6.0 Hz, 1H), 6.68 (s, 1H), 7.09 (t, J = 4.8 Hz, 1H), 7.22−7.26 (m, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 8.60−8.64 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.2, 33.8, 36.5, 42.3, 110.7, 115.7, 116.7, 120.3, 122.4, 124.1, 128.6, 133.8, 137.2, 157.6, 157.7, 176.1, 176.6; HRESI-MS (m/z): calcd for $C_{18}H_{16}N_4O_2$ (M + Na): 343.1171, found (M + Na): 343.1174.

*1-Ethyl-3-(5-methoxy-1-(pyrimidin-2-yl)-1H-indol-2-yl)-pyrrolidine-2,5-dione (**3ba**).* Pale brown solid; yield: (65 mg, 93%); mp: 183−185 °C; R_f (30% EtOAc/PET) 0.2; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1699, 1572, 1436; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.25 (t, J = 7.20 Hz, 3H), 2.90 (dd, J = 18.0, 6.0 Hz, 1H), 3.11 (dd, J = 18.0, 9.6 Hz, 1H), 3.59−3.73 (m, 2H), 3.86 (s, 3H), 4.74 (t, J = 6.4 Hz, 1H), 6.61 (s, 1H), 6.94 (dd, J = 9.2, 2.8 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 7.05 (t, J = 4.8 Hz, 1H), 8.56 (d, J = 9.2 Hz, 1H), 8.59 (d, J = 4.80 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.2, 33.8, 36.5, 42.5, 55.6, 102.4, 11.4, 113.1, 116.5, 117.0, 129.5, 132.1, 134.2, 155.6, 157.5, 157.6, 176.1, 176.6; HRESI-MS (m/z): calcd for $C_{19}H_{18}N_4O_3$ (M + Na): 373.1277, found (M + Na): 373.1274.

*3-(5-Bromo-1-(pyrimidin-2-yl)-1H-indol-2-yl)-1-ethylpyrro-lidine-2,5-dione (**3ca**).* Pale brown solid; yield: (79.6 mg, 95%); mp: 199−201 °C; R_f (30% EtOAc/PET) 0.2; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1679, 1564, 1418; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.24 (t, J = 7.2 Hz, 3H), 2.91 (dd, J = 18.0, 6.1 Hz, 1H), 3.13 (dd, J = 18.1, 9.31 Hz, 1H), 3.56−3.73 (m, 2H), 4.72−4.87 (m, 1H), 6.62 (s, 1H), 7.13 (t, J = 4.7 Hz, 1H), 7.39 (dd, J = 9.0, 1.98 Hz, 1H), 7.68 (d, J = 2.1 Hz, 1H), 8.50 (d, J = 9.1 Hz, 1H), 8.65 (d, J = 4.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.2, 33.9, 36.5, 42.2, 110.0, 115.7, 117.1, 117.4, 122.8, 126.8, 130.3, 135.2, 135.9, 157.4, 157.8, 175.8, 176.3; HRESI-MS (m/z): calcd for $C18H_{15}BrN_4O_2$ (M + Na): 421.0276, found (M + Na): 421.0272.

*2-(1-Ethyl-2,5-dioxopyrrolidin-3-yl)-1-(pyrimidin-2-yl)-1H-indole-5-carbonitrile (**3da**).* Pale brown solid; yield: (45 mg, 65%); mp: 194−196 °C; R_f (50% EtOAc/PET) 0.3; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1685, 1567, 1421, 1216; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.23 (t, J = 7.2 Hz, 4H), 2.92 (dd, J = 18.0, 5.8 Hz, 1H), 3.17 (dd, J = 18.1, 9.3 Hz, 1H), 3.59−3.69 (m, 2H), 4.89 (t, J = 8.4 Hz, 1H), 6.73 (s, 1H), 7.22 (t, J = 4.58 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.88 (s, 1H), 8.63 (d, J = 8.5 Hz, 1H), 8.71 (d, J = 4.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.2, 34.0, 36.4, 41.9, 105.6, 109.9, 116.5, 118.0, 119.9, 125.2, 126.9, 128.5, 136.7, 138.9, 157.2, 158.1, 175.6, 176.0; HRESI-MS (m/z): calcd for $C_{19}H_{15}N_5O_2$ (M + Na): 368.1123, found (M + Na): 368.1124.

*1-Ethyl-3-(5-nitro-1-(pyrimidin-2-yl)-1H-indol-2-yl)-pyrrolidine-2,5-dione (**3ea**).* Pale yellow solid; yield: (66 mg, 91%); mp: 239−241 °C; R_f (50% EtOAc/PET) 0.3; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1694, 1568, 1420, 1331; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.24 (t, J = 7.2 Hz, 3H), 2.95 (dd, J = 18.01, 6.1 Hz, 1H), 3.19 (dd, J = 18.1, 9.3 Hz, 1H), 3.58−3.72 (m, 2H), 4.91 (dd, J = 9.0, 5.9 Hz, 1H), 6.82 (s, 1H), 7.24−7.27 (m, 1H), 8.17 (dd, J = 9.3, 2.3 Hz, 1H), 8.47 (d, J = 2.1 Hz, 1H), 8.63 (d, J = 9.1 Hz, 1H), 8.73 (d, J = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.2, 34.0, 36.3, 41.9, 110.8, 115.8, 116.7, 118.2, 119.1, 128.2, 137.5, 140.2, 143.4, 157.1, 158.2, 175.5, 175.9; HRESI-MS (m/z): calcd for $C_{18}H_{15}N_5O_4$ (M + Na): 388.1022, found (M + Na): 388.1021.

*1-Ethyl-3-(5-phenyl-1-(pyrimidin-2-yl)-1H-indol-2-yl)-pyrrolidine-2,5-dione (**3fa**).* Brown solid; yield: (75.6 mg, 95%); mp: 206−208 °C; R_f (30% EtOAc/PET) 0.2; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1700, 1579, 1430; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.10 (t, J = 7.3 Hz, 3H), 2.90 (dd, J = 17.4, 6.10 Hz, 1H), 3.12 (dd, J = 17.8, 9.00 Hz, 1H), 3.41−3.54 (m, 2H), 4.95−4.98 (m, 1H), 6.86 (s, 1H), 7.32−7.39 (m, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.60 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 7.6 Hz, 2H), 7.88 (s, 1H), 8.54 (d, J = 8.8 Hz, 1H), 8.79 (d, J = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.9, 33.1, 35.9, 41.4, 110.7, 115.7, 117.9, 118.1, 122.6, 126.7, 126.8, 128.8, 128.9, 134.4, 135.4, 136.0, 140.6,

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156.7, 158.5, 175.8, 176.6; HRESI-MS (m/z): calcd for $C_{24}H_{20}N_4O_2$ (M + Na): 419.1484, found (M + Na): 419.1483.

*3-(6-Bromo-1-(pyrimidin-2-yl)-1H-indol-2-yl)-1-ethylpyrrolidine-2,5-dione (**3ga**).* Pale brown solid; yield: (77.1 mg, 97%); mp: 184−186 °C; R_f (30% EtOAc/PET) 0.2; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1688, 1561, 1415, 1213; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.24 (t, J = 7.2, 3H), 2.89 (dd, J = 18.0, 5.9 Hz, 1H), 3.13 (dd, J = 18.0, 9.3 Hz, 1H), 3.57−3.71 (m, 2H), 4.78−4.81 (m, 1H), 6.64 (s, 1H), 7.12 (t, J = 4.8 Hz, 1H), 7.34 (dd, J = 8.2, 1.7 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 8.65 (d, J = 4.8 Hz, 2H), 8.83 (d, J = 0.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.2, 33.9, 36.5, 42.5, 110.8, 117.2, 117.8, 118.9, 121.4, 125.8, 127.5, 134.6, 137.9, 157.4, 157.9, 175.9, 176.4; HRESI-MS (m/z): calcd for $C18H_{15}BrN_4O_2$ (M + Na): 421.0276, found (M + Na): 421.0275.

*Methyl-2-(1-ethyl-2,5-dioxopyrrolidin-3-yl)-1-(pyrimidin-2-yl)-1H-indole-6-carboxylate (**3ha**).* Pale yellow solid; yield: (73.4 mg, 97%); mp: 181−183 °C; R_f (50% EtOAc/PET) 0.3; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1694, 1566, 1422, 1217; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.23 (t, J = 7.2 Hz, 3H), 2.92 (dd, J = 18.0, 6.1 Hz, 1H), 3.15 (dd, J = 18.0, 9.4 Hz, 1H), 3.58−3.71 (m, 2H), 3.95 (s, 3H), 4.87 (dd, J = 8.7, 6.2 Hz, 1H), 6.71 (s, 1H), 7.15 (t, J = 4.7 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.92 (d, J = 7.9 Hz, 1H), 8.69 (d, J = 4.6 Hz, 2H), 9.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.2, 34.0, 36.5, 42.1, 52.0, 76.7, 77.0, 77.4, 110.2, 117.4, 117.7, 120.0, 123.6, 125.7, 132.3, 136.7, 137.3, 157.4, 158.1, 167.9, 175.8, 176.2; HRESI-MS (m/z): calcd for $C_{20}H_{18}N_4O_4$ (M + Na): 401.1226, found (M + Na): 401.1225.

*1-Ethyl-3-(3-methyl-1-(pyrimidin-2-yl)-1H-indol-2-yl)-pyrrolidine-2,5-dione (**3ia**).* Pale brown solid; yield: (47 mg, 70%); mp: 127−129 °C; R_f (30% EtOAc/PET) 0.2; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1700, 1571, 1440; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.25 (t, J = 7.2 Hz, 3H), 2.95 (dd, J = 17.81, 6.44 Hz, 1H), 3.09 (dd, J = 17.6, 9.35 Hz, 1H), 3.57−3.74 (m, 2H), 4.62 (dd, J = 9.3, 6.5 Hz, 1H), 7.02 (t, J = 4.8 Hz, 1H), 7.25−7.27 (m, 1H), 7.31−7.35 (m, 1H), 7.54−7.56 (m, 1H), 8.56 (d, J = 4.8 Hz, 2H), 8.66 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 9.4, 13.3, 33.8, 36.2, 39.8, 113.6, 115.8, 116.2, 118.8, 122.3, 124.5, 128.6, 130.1, 136.4, 157.6, 176.5, 177.0; HRESI-MS (m/z): calcd for $C_{19}H_{18}N_4O_2$ (M + Na): 357.1327, found (M + Na): 357.1324.

*1-Benzyl-3-(1-(pyrimidin-2-yl)-1H-indol-2-yl)pyrrolidine-2,5-dione (**4ab**).* Brown solid; yield: (74.5 mg, 98%); mp: 206−208 °C; R_f (30% EtOAc/PET) 0.2; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1694, 1564, 1434, 1155; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.89 (dd, J = 17.8, 6.2 Hz, 1H), 3.08 (dd, J = 18.0, 9.1 Hz, 1H), 4.66 (t, J = 7.6 Hz, 1H), 4.68−4.78 (m, 2H), 6.68 (s, 1H), 6.79 (t, J = 4.7 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.29−7.34 (m, 4H), 7.51−7.55 (m, 3H), 8.04 (d, J = 4.6 Hz, 2H), 8.64 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 36.5, 42.7, 42.8, 112.0, 116.1, 116.5, 120.3, 122.6, 124.2, 128.1, 128.7, 128.8, 129.9, 133.2, 136.0, 137.3, 157.5, 157.6, 175.8, 176.5; HRESI-MS (m/z): calcd for $C_{23}H_{18}N_4O_2$ (M + Na): 405.1327, found (M + Na): 405.1324.

*1-Phenyl-3-(1-(pyrimidin-2-yl)-1H-indol-2-yl)pyrrolidine-2,5-dione (**4ac**).* Brown solid; yield: (72 mg, 98%); mp: 245−247 °C; R_f (30% EtOAc/PET) 0.2; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1701, 1570, 1423, 1178; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.08 (dd, J = 17.7, 6.4 Hz, 1H), 3.27 (dd, J = 17.7, 9.4 Hz, 1H), 5.13 (t, J = 8.8 Hz, 1H), 6.92 (s, 1H), 7.21−7.44 (m, 6H), 7.52 (t, J = 8.0 Hz, 2H), 7.63 (d, J = 7.6 Hz, 1H), 8.53 (d, J = 8.2 Hz, 1H), 8.82 (d, J = 4.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 36.1, 41.8, 111.1, 115.4, 118.0, 120.3, 122.3, 123.7, 126.7, 128.2, 128.4, 129.0, 132.6, 134.3, 136.6, 156.9, 158.6, 175.2, 176.0; HRESI-MS (m/z): calcd for $C_{22}H_{16}N_4O_2$ (M + Na): 391.1171, found (M + Na): 391.1175.

*3-(1-(Pyrimidin-2-yl)-1H-indol-2-yl)pyrrolidine-2,5-dione (**4ad**).* White solid; yield: (46.5 mg, 80%); mp: 201−203 °C; R_f (30% EtOAc/PET) 0.2; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1775, 1699, 1569, 1425, 1174; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.83 (dd, J = 17.8, 6.26 Hz, 1H), 3.05 (dd, J = 17.7, 9.4 Hz, 1H), 4.95 (dd, J = 8.8, 6.4 Hz, 1H), 6.79 (s, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.28 (t, J = 7.3 Hz, 1H), 7.41 (t, J = 4.7 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 8.47 (d, J = 8.2 Hz, 1H), 8.80 (d, J = 4.8 Hz, 2H), 11.24 (br. s., 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 37.2, 42.6, 110.1, 115.1, 117.9, 120.2, 122.1, 123.5, 128.3, 135.1, 136.5, 156.8, 158.4, 177.6, 178.3; HRESI-MS (m/z): calcd for $C_{16}H_{12}N_4O_2$ (M + Na): 315.0858, found (M + Na): 315.0856.

*1-Cyclohexyl-3-(1-(pyrimidin-2-yl)-1H-indol-2-yl)-pyrrolidine-2,5-dione (**4ae**).* White solid; yield: (62 mg, 83%); mp: 256−258 °C; R_f (30% EtOAc/PET) 0.3; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1685, 1568, 1422, 1188; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.21−1.38 (m, 3H), 1.64−1.67 (m, 3H), 1.84 (d, J = 11.9 Hz, 2H), 2.16−2.25 (m, 2H), 2.89 (dd, J = 17.8, 5.6 Hz, 1H), 3.06 (dd, J = 17.8, 9.3 Hz, 1H), 4.04 (t, J = 11.9 Hz, 1H), 4.80 (br. s., 1H), 6.64 (s, 1H), 7.09 (t, J = 4.1 Hz, 1H), 7.20−7.25 (m, 1H), 7.28−7.32 (m, 1H), 7.55 (d, J = 7.6 Hz, 1H), 8.58 (d, J = 8.2 Hz, 1H), 8.67 (d, J = 4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 25.0, 25.9, 28.9, 29.0, 36.6, 42.0, 51.8, 110.6, 115.6, 116.8, 120.3, 122.5, 124.0, 128.7, 134.8, 137.3, 157.8, 157.9, 176.2, 176.7; HRESI-MS (m/z): calcd for $C_{22}H_{22}N_4O_2$ (M + Na): 397.1640, found (M + Na): 397.1640.

*1-(4-Acetylphenyl)-3-(1-(pyrimidin-2-yl)-1H-indol-2-yl)-pyrrolidine-2,5-dione (**4af**).* Pale yellow solid; yield: (65 mg, 79%); mp: 247−249 °C; R_f (50% EtOAc/PET) 0.3; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1709, 1570, 1438; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.62 (s, 3H), 3.09 (dd, J = 17.8, 6.5 Hz, 1H), 3.29 (dd, J = 17.7, 9.4 Hz, 1H), 5.14 (t, J = 8.8 Hz, 1H), 6.94 (s, 1H), 7.24 (t, J = 7.3 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.38 (t, J = 4.7 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 7.6 Hz, 1H), 8.09 (d, J = 8.2 Hz, 2H), 8.55 (d, J = 8.2 Hz, 1H), 8.80 (d, J = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 26.8, 36.0, 41.8, 111.4, 115.5, 117.8, 120.3, 122.3, 126.5, 127.0, 128.8, 134.1, 136.0, 136.5, 136.6, 156.8, 158.5, 174.8, 175.7, 197.2; HRESI-MS (m/z): calcd for $C_{24}H_{18}N_4O_3$ (M + Na): 433.1277, found (M + Na): 433.1279.

*1-Benzyl-3-(5-methoxy-1-(pyrimidin-2-yl)-1H-indol-2-yl)-pyrrolidine-2,5-dione (**4bb**).* Brown solid; yield: (80.2 mg, 97%); mp: 201−203 °C; R_f (30% EtOAc/PET) 0.2; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1685, 1568, 1427, 1335, 1146; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.87 (dd, J = 17.7, 5.8 Hz, 1H), 3.14 (dd, J = 17.7, 9.4 Hz, 1H), 3.79 (s, 3H), 4.59 (d, J = 14.3 Hz, 1H), 4.71 (d, J = 14.3 Hz, 1H), 4.97 (dd, J = 8.7, 6.2 Hz, 1H), 6.74 (s, 1H), 6.90 (dd, J = 9.1, 2.4 Hz, 1H), 7.11 (d, J = 2.1 Hz, 1H), 7.15 (t, J = 4.7 Hz, 1H), 7.34 (s, 5H), 8.39 (d, J = 4.5 Hz, 2H), 8.44 (d, J = 9.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 35.9, 41.7, 55.3, 102.4, 111.2, 112.6, 116.5, 117.2, 127.6, 128.3, 128.6, 129.2, 131.3, 134.8, 136.3, 155.2, 156.6, 158.1, 176.0, 176.8; HRESI-MS (m/z): calcd for $C_{24}H_{20}N_4O_3$ (M + Na): 435.1433, found (M + Na): 435.1435.

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*3-(5-Methoxy-1-(pyrimidin-2-yl)-1H-indol-2-yl)-1-phenylpyrrolidine-2,5-dione (**4bc**).* Brown solid; yield: (78 mg, 98%); mp: 198−200 °C; R_f (30% EtOAc/PET) 0.2; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1715, 1438, 1214; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.05 (dd, J = 18.01, 6.41 Hz, 1H), 3.26 (dd, J = 18.0, 9.4 Hz, 1H), 3.87 (s, 2H), 4.80 (t, J = 6.8 Hz, 1H), 6.70 (s, 1H), 6.96 (dd, J = 9.1, 2.4 Hz, 1H), 7.01−7.03 (m, 2H), 7.36−7.40 (m, 3H), 7.46−7.50 (m, 2H), 8.60 (d, J = 4.6 Hz, 2H), 8.64 (d, J = 9.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 36.4, 42.9, 55.7, 102.5, 112.6, 113.3, 116.5, 117.4, 125.9, 128.3, 129.1, 129.6, 132.2, 132.3, 133.7, 155.8, 157.5, 157.8, 175.3, 175.6; HRESI-MS (m/z): calcd for $C_{23}H_{18}N_4O_3$ (M + Na): 421.1277, found (M + Na): 421.1277.

*3-(5-Methoxy-1-(pyrimidin-2-yl)-1H-indol-2-yl)pyrrolidine-2,5-dione (**4bd**).* Pale yellow solid; yield: (60 mg, 93%); mp: 218−220 °C; R_f (50% EtOAc/PET) 0.2; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1691, 1569, 1419, 1167; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.81 (dd, J = 17.5, 6.2 Hz, 1H), 3.03 (dd, J = 17.7, 9.4 Hz, 1H), 3.79 (s, 3H), 4.89 (dd, J = 9.0, 6.2 Hz, 1H), 6.71 (s, 1H), 6.89 (dd, J = 9.1, 2.7 Hz, 1H), 7.11 (d, J = 2.1 Hz, 1H), 7.36 (t, J = 4.8 Hz, 1H), 8.42 (d, J = 9.1 Hz, 1H), 8.75 (d, J = 4.9 Hz, 2H), 11.23 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 37.2, 42.9, 55.3, 102.3, 110.4, 112.5, 116.3, 117.5, 129.2, 131.2, 135.5, 155.1, 156.7, 158.2, 177.6, 178.3; HRESI-MS (m/z): calcd for $C_{17}H_{14}N_4O_3$ (M + Na): 345.0964, found (M + Na): 345.0963.

*1-Benzyl-3-(5-bromo-1-(pyrimidin-2-yl)-1H-indol-2-yl)-pyrrolidine-2,5-dione (**4cb**).* Brown solid; yield: (88 mg, 96%); mp: 154−156 °C; R_f (30% EtOAc/PET) 0.2; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1689, 1567, 1424, 1154; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.87 (dd, J = 17.8, 6.2 Hz, 1H), 3.06 (dd, J = 18.0, 9.4 Hz, 1H), 4.62 (t, J = 6.8 Hz 1H), 4.68−4.76 (m, 2H), 6.58 (s, 1H), 6.78 (t, J = 4.9 Hz, 1H), 7.31−7.37 (m, 4H), 7.49−7.51 (m, 2H), 7.63−7.64 (m, 1H), 8.01 (d, J = 4.2 Hz, 2H), 8.52 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 36.4, 42.8, 42.8, 111.2, 115.8, 116.9, 117.8, 122.8, 126.9, 128.1, 128.8, 129.9, 130.4, 134.5, 135.9, 136.0, 157.2, 157.6, 175.6, 176.2; HRESI-MS (m/z): calcd for $C_{23}H_{17}BrN_4O_2$ (M + Na): 483.0433, found (M + Na): 483.0430.

*3-(5-Bromo-1-(pyrimidin-2-yl)-1H-indol-2-yl)-1-phenylpyrrolidine-2,5-dione (**4cc**).* Brown solid; yield: (85 mg, 95%); mp: 239−241 °C; R_f (30% EtOAc/PET) 0.2; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1701, 1571, 1420, 1169; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.09 (dd, J = 17.7, 6.1 Hz, 1H), 3.27 (dd, J = 17.7, 9.4 Hz, 1H), 5.13−5.17 (m, 1H), 6.91 (s, 1H), 7.34 (d, J = 7.9 Hz, 2H), 7.40−7.44 (m, 3H), 7.51 (t, J = 7.6 Hz, 2H), 7.85 (s, 1H), 8.47 (d, J = 8.8 Hz, 1H), 8.83 (d, J = 4.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 35.9, 41.7, 110.2, 114.7, 117.3, 118.3, 122.6, 126.1, 126.6, 128.1, 128.9, 130.2, 132.5, 135.3, 135.8, 156.6, 158.7, 175.0, 175.8; HRESI-MS (m/z): calcd for $C_{22}H_{15}BrN_4O_2$ (M + Na): 469.0276, found (M + Na): 469.0276.

*3-(5-Bromo-1-(pyrimidin-2-yl)-1H-indol-2-yl)pyrrolidine-2,5-dione (**4cd**).* Brown solid; yield: (60 mg, 82%); mp: 272−274 °C; R_f (50% EtOAc/PET) 0.2; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1693, 1571, 1416, 1117; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.84 (dd, J = 17.7, 6.10 Hz, 1H), 3.05 (dd, J = 17.7, 9.4 Hz, 1H), 4.97 (dd, J = 9.1, 6.4 Hz, 1H), 6.78 (s, 1H), 7.39−7.45 (m, 2H), 7.81 (d, J = 1.2 Hz, 1H), 8.41 (d, J = 8.8 Hz, 1H), 8.81 (d, J = 4.9 Hz, 2H), 11.27 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 37.1, 42.5, 109.1, 114.5, 117.0, 118.2, 122.5, 125.9, 130.2, 135.2, 136.6, 156.5, 158.5, 177.5, 178.1; HRESI-MS (m/z): calcd for $C_{16}H_{11}BrN_4O_2$ (M + Na): 392.9963, found (M + Na): 392.9963.

*Dimethyl 2-(1-(pyrimidin-2-yl)-1H-indol-2-yl)succinate (**5**).* Yellow liquid; yield: (20.5 mg, 30%); R_f (30% EtOAc/PET) 0.5; prepared as shown in general experimental procedure (a). IR (neat, cm^{-1}): 1720, 1579, 1420, 1137; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.97 (dd, J = 16.8, 6.0 Hz, 1H), 3.28 (dd, J = 16.4, 98.0 Hz, 1H), 3.57 (s, 3H), 3.68 (s, 3H), 5.01−5.06 (m, 1H), 6.63 (s, 1H), 7.13 (t, J = 4.8 Hz, 1H), 7.19−7.23 (m, 1H), 7.26−7.31 (m, 1H), 7.56 (d, J = 7.6 Hz, 1H), 8.47 (d, J = 8.0 Hz, 1H), 8.73 (d, J = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 36.8, 42.2, 51.9, 52.2, 108.3, 114.9, 116.9, 120.4, 122.2, 123.6, 128.8, 136.6, 136.9, 157.8, 157.9, 172.1, 172.5; HRESI-MS (m/z): calcd for $C_{16}H_{17}N_3O_4$ (M + Na): 362.1117, found (M + Na): 362.1119.

*1-Ethyl-3-(2-(pyridin-2-yl)phenyl)pyrrolidine-2,5-dione (**7aa**).* Brownish semisolid; yield: (20 mg, 35%); R_f (50% EtOAc/PET) 0.3; prepared as shown in general experimental procedure (a). IR (neat, cm^{-1}): 1670, 1432, 1265, 1115; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.16 (t, J = 7.2 Hz, 3H), 2.87 (dd, J = 18.3, 5.5 Hz, 1H), 3.15 (dd, J = 18.4, 9.6 Hz, 1H), 3.46−3.61 (m, 2H), 4.37 (dd, J = 9.6, 5.6 Hz, 1H), 7.18−7.20 (m, 1H), 7.23−7.26 (m, 1H), 7.36−7.43 (m, 2H), 7.44−7.47 (m, 1H), 7.55−7.57 (m, 1H), 7.78 (td, J = 7.6, 1.8 Hz, 1H), 8.56−8.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.0, 33.8, 38.7, 44.3, 122.1, 124.3, 127.9, 128.7, 129.2, 130.5, 135.7, 136.8, 140.3, 148.7, 159.0, 176.5, 178.3; HRESI-MS (m/z): calcd for $C_{17}H_{16}N_2O_2$ (M + Na): 303.1109, found (M + Na): 303.1111.

*1-Ethyl-3-(2-(pyrimidin-2-yl)phenyl)pyrrolidine-2,5-dione (**7ba**).* Brownish semisolid; yield: (22.5 mg, 40%); R_f (50% EtOAc/PET) 0.3; prepared as shown in general experimental procedure (a). IR (neat, cm^{-1}): 1675, 1548, 1420, 1281, 1120; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.21 (t, J = 7.2 Hz, 3H), 2.83 (dd, J = 18.1, 5.9 Hz, 1H), 3.22 (dd, J = 18.3, 9.4 Hz, 1H), 3.52−3.67 (m, 2H), 4.71 (dd, J = 9.4, 6.1 Hz, 1H), 7.17−7.26 (m, 2H), 7.42−7.47 (m, 2H), 8.16−8.18 (m, 1H), 8.75 (d, J = 4.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.1, 33.8, 38.3, 45.7, 118.9, 128.1, 130.4, 130.6, 131.8, 136.2, 137.0, 156.8, 165.7, 176.5, 178.3; HRESI-MS (m/z): calcd for $C_{16}H_{15}N_3O_2$ (M + Na): 304.1062, found (M + Na): 304.1060.

*1-Ethyl-3-(1-(pyrimidin-2-yl)-1H-pyrrol-2-yl)pyrrolidine-2,5-dione (**7ca**).* Pale yellow solid; yield: (30 mg, 55%); mp: 140−142 °C; R_f (50% EtOAc/PET) 0.5; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1683, 1573, 1434, 1405, 1124; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.23 (t, J = 7.2 Hz, 3H), 2.86 (dd, J = 17.7, 6.1 Hz, 1H), 3.06 (dd, J = 17.8, 9.3 Hz, 1H), 3.59−3.72 (m, 2H), 4.56 (s, 1H), 6.24−6.29 (m, 2H), 7.03 (t, J = 4.9 Hz, 1H), 7.91 (dd, J = 3.3, 1.8 Hz, 1H), 8.49 (d, J = 4.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.2, 33.7, 36.6, 41.8, 110.3, 117.2, 122.5, 126.9, 156.3, 157.9, 176.5, 177.3; HRESI-MS (m/z): calcd for $C_{14}H_{14}N_4O_2$ (M + Na): 293.1014, found (M + Na): 293.1016.

*3,3′-(1-(Pyrimidin-2-yl)-1H-pyrrole-2,5-diyl)bis(1-ethylpyrrolidine-2,5-dione) (**7ca′**).* Pale greenish solid; yield: (16 mg, 20%); mp: 215−217 °C; R_f (50% EtOAc/PET) 0.1; prepared as shown in general experimental procedure (a). IR (KBr, cm^{-1}): 1691, 1580, 1425, 1216, 1125; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.13−1.18 (m, 6H), 2.84−2.94 (m, 2H), 3.00−3.11 (m, 2H), 3.46−3.61 (m, 4H), 4.65−4.73 (m, 2H), 6.20 (d, J = 1.5 Hz, 2H), 7.15 (td, J = 4.9, 1.83 Hz, 1H), 8.56 (d, J = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.0, 13.1, 33.7, 36.0, 36.5, 41.0, 41.1, 112.5, 118.1, 129.6, 129.9, 156.8, 157.0, 157.9, 158.0,

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176.0, 176.0, 176.7, 176.8; HRESI-MS (m/z): calcd for $C_{20}H_{21}N_5O_4$ (M + Na): 418.1491, found (M + Na): 418.1490.

*(E)-Ethyl 3-(2-(1-ethyl-2,5-dioxopyrrolidin-3-yl)-1-(pyrimidin-2-yl)-1H-indol-7-yl)acrylate (**8**).* Pale yellow semisolid; yield−(62 mg, 74%); R_f (50% EtOAc/PET) 0.3; prepared as shown in the experimental procedure (c). IR (neat, cm^{-1}): 1688, 1579, 1452; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.16 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 2.91 (dd, J = 18.31, 5.49 Hz, 1H), 3.05 (dd, J = 18.3, 9.46 Hz, 1H), 3.46−3.60 (m, 2H), 4.13 (q, J = 7.0 Hz, 2H), 4.72 (dd, J = 9.4, 5.5 Hz, 1H), 6.18 (d, J = 15.5 Hz, 1H), 6.62 (s, 1H), 7.17−7.22 (m, 2H), 7.30 (t, J = 4.9 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.59−7.61 (m, 1H), 8.76 (d, J = 4.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.0, 14.3, 34.0, 36.4, 39.8, 60.1, 106.3, 117.2, 119.3, 120.9, 122.2, 122.6, 123.5, 129.6, 135.6, 136.4, 142.6, 158.1, 158.7, 166.7, 175.4, 175.7; HRESI-MS (m/z): calcd for $C_{23}H_{22}N_4O_4$ (M + Na): 441.1539, found (M + Na): 441.1541.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b00870.

^1H and ^{13}C NMR spectral data of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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