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Pd^{II}/Ag^{I}-Catalyzed Room-Temperature Reaction of γ-Hydroxy Lactams: Mechanism, Scope, and Antistaphylococcal Activity

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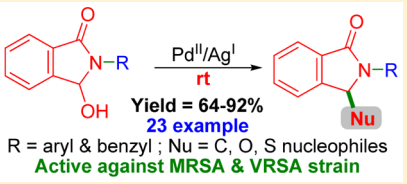
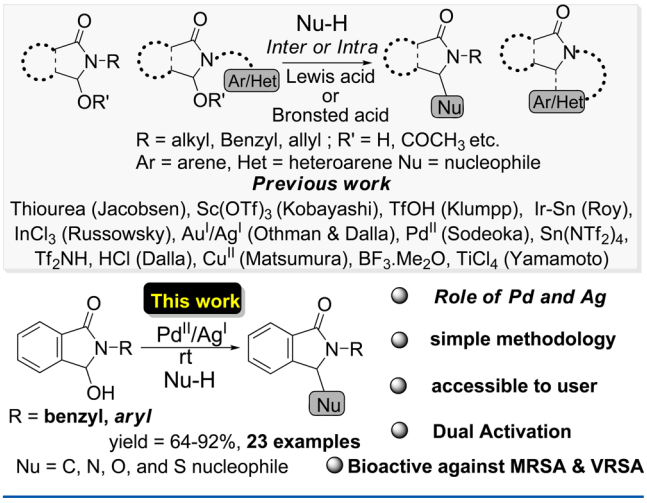
Supporting Information

ABSTRACT: The present work reports a Pd^{II}/Ag^{I}-promoted amidoalkylation reaction involving various γ-hydroxy lactams and C/O/S nucleophiles at room temperature. The dual mode of activation of both the electrophile and nucleophile by in situ generated catalytically active cationic Pd^{II} species facilitates the reaction at room temperature. Among the synthesized isoindoline derivatives, three compounds are found to be active against vancomycin and methicillin-resistant *S. aureus* strain with appreciable MIC values.



The development of a selective catalytic system for a particular type of bond-forming reaction between electrophiles (E) and nucleophiles (N) needs tunable accessibility of the catalyst active site, by which one can activate either N or E or both in tandem.[1] In this regard, various Lewis acids or Brønstead acids were successfully utilized for both E or N activation and successive bond formation between them.[2,3] In case of bi- or polyfunctional substrate, the choice of catalysts for the desired transformations relies on the relative ability of the metals to make a σ- or a π-complex with appropriate substrates.[4] In this context, heterobimetallic or multimetallic catalysis has received much attention since synergistic functions of more than one active center in the catalyst could lead to superior activity and selectivity via substrate activation using both σ or π complexes.[5] Toward this end, development of cooperative homo- and/or hetero-bimetallics,[6] LA-NHCs,[7] tandem catalysts,[8] or dual metal reagents[9] for various types of bond-forming methodologies are noteworthy. Similarly, development of a single metal catalyst for the activation of both E and N in a particular type of bond-forming reaction is an important theme of research in modern organic reactions.[10] Thus, various catalysts based on gold,[11] silver,[12] indium,[13] ruthenium,[14] rhodium,[15] and platinum[16] have been reported for the synthesis of various C–C and C–heteroatom bond-forming reactions. Simultaneously, utilization of $Pd(OAc)_2$ both as a Lewis acid and as a transition-metal catalyst for the synthesis of cyclic alkenyl ethers from acetylenic aldehyde[17] or other types of bond formation methodologies are noteworthy.[18,19] On the other hand, *N*-acyliminium ions represent important electron-deficient carbocations intermediates in organic synthesis because they provide various biologically important natural and unnatural products via C–C and C–heteoatom bond-forming methodologies using an inter- or intramolecular path.[20,21] The removal of a good leaving group at the α-position of amides or lactams usually generates *N*-acyliminium ions, which act as more electron-deficient carbocations toward nucleophiles. In this regard, chiral thiourea derivatives,[22,23] superacidic reagents,[24] and various Lewis[25] and Brønsted acidic[26] systems have been utilized for the generation of *N*-acyliminium ions and subsequent catalytic intra- or intermolecular amidoalkylation reactions (Scheme 1). Along with that, utilization of various interesting transition-metal complexes, including Au^{I}/Ag^{I},[27] $Sn(NTf)_4$,[28] and Ir–Sn[29] for nucleophilic substitution of γ-hydroxy lactams, Cu^{II} for enantioselective reaction between *N*-acyliminium ions and diaryl malonote,[30] and Pd^{II} for asymmetric addition of malonates to dihydroisoquinolines[31] are noteworthy. Herein, we report the utilization of in situ generated cationic Pd^{II} catalyst in room-temperature amidoalkylation reactions with a variety of C/N/O/S nucleophilea via a dual mode of activation.

Scheme 1. Catalytic α-Amidoalkylation Reaction



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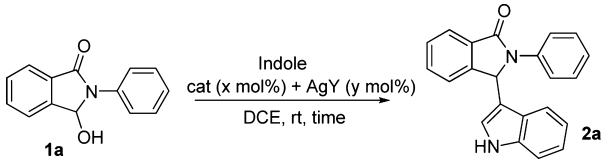
Initially, the reaction between **1a** and indole was chosen as a model reaction in the presence of different Brønsted acids, Lewis acids, palladium, and other transition-metal catalysts. After the optimization of reaction conditions from the screening of solvent, temperature, and catalyst loading, our study began with $PdCl_2(MeCN)_2$ as a catalyst.[32] Although $PdCl_2(MeCN)_2$ was found to be active in producing the desired **2a** in 62% yield at 90 °C, the model reaction failed at room temperature. Encouraged by the aforementioned result, other reaction conditions and catalyst were investigated, and the results are summarized in Table 1. To our delight, the model

Table 1. Screening of Catalysts



no.	cat.	AgY	X/Y	T (°C)	time (h)	yield (%)
1	$PdCl_2(MeCN)_2$		5	90	6	62[a]
2	$PdCl_2(MeCN)_2$		5	rt	6	0
3	$PdCl_2(MeCN)_2$	$AgPF_6$	2/2	rt	12	74
4		$AgPF_6$	10	rt	12	<10
5	**$PdCl_2(MeCN)_2$**	**$AgPF_6$**	**2/4**	**rt**	**4**	**90**
6	$[Pd(MeCN)_4]^{2+}$		2	rt	4	86[b]
7	$PdCl_2(MeCN)_2$	$AgSbF_6$	2/4	rt	4	84
8	$PdCl_2(MeCN)_2$	$AgBF_4$	2/4	rt	4	85
9	$Pd(COD)Cl_2$	$AgPF_6$	5/10	rt	6	15
10	$Pd(BPy)Cl_2$	$AgPF_6$	5/10	rt	6	8
11	$Pd(DPPE)Cl_2$	$AgPF_6$	5/10	rt	6	16
12	$Pd(PPh_3)_2Cl_2$	$AgPF_6$	5/10	rt	6	12
13	$FeCl_3$		5	rt	6	26
14	$SnCl_4$		5	rt	6	21
15	$BF_3{\cdot}Et_2O$		5	rt	6	15
16	pTSA		5	rt	6	20
17	TfOH		5	rt	6	52
18	HPF_6		100	rt	6	<10
19	HCl		100	rt	6	<10

[a]Reaction performed at 90 °C in 1,2-dichloroethane. [b]BF_4^- used as an anion.

reaction proceeds at room temperature with $PdCl_2(MeCN)_2$ after the introduction of 2 equiv of $AgPF_6$ as a halide-trapping agent. However, the use of only $AgPF_6$ failed to produce any desired product **2a** at room temperature. On the other hand, other Pd^{II} complexes (Table 1, entry 9−12) in combination with $AgPF_6$ were found to be inactive for the desired transformation. The inactivity of stronger ligand (BPy, DPPE, PPh_3, COD) containing Pd^{II} complexes suggests that a vacant coordination site at the Pd^{II} center was required for the reaction, which encouraged us to look for the active species of the catalytic combination.[33] For this, model reaction was performed with the synthesized $[Pd(MeCN)_4]^{2+}$ complex and found to be reactive for producing the desired **2a** in 86% yield, which also confirmed the role of $AgPF_6$ in the in situ generation of active cationic species from inactive neutral $PdCl_2(MeCN)_2$.[34] Further, to check the effect of anions, two different silver salts (Table 1, entries 7 and 8) were tested in the model reaction and showed no further improvement in the product yield as compared to $AgPF_6$.

At the same time, all of the tested Lewis acids inclusive of $BF_3{\cdot}Et_2O$, $FeCl_3$, $SnCl_4$, and Brønsted acids such as HCl, HPF_6, and pTSA were less effective for the reaction. However, a catalytic amount of TfOH gave a 52% yield of **2a**. The substrate scope of Pd^{II}/Ag^{I}-catalyzed alkylation reaction for γ-hydroxy lactam derivatives is illustrated in Figure 1. Under optimized

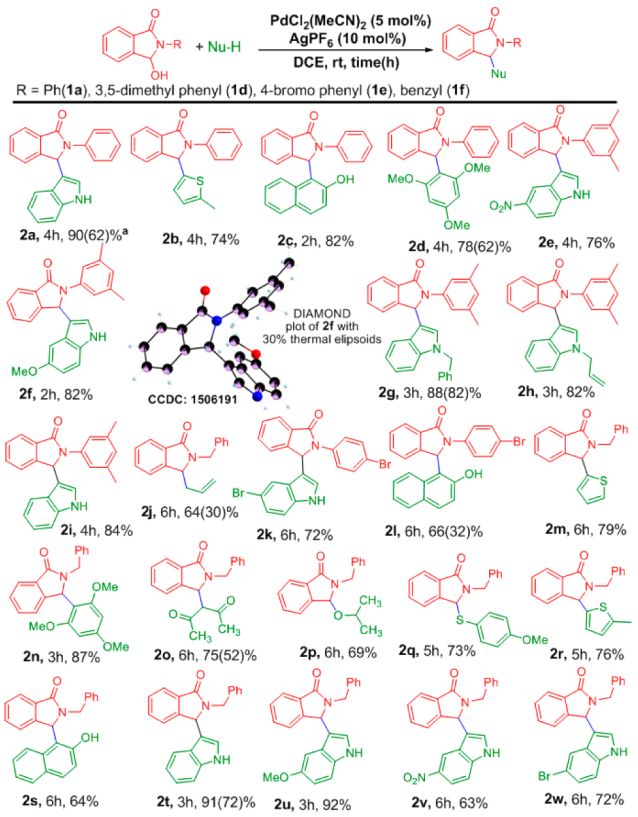


Figure 1. Substrate scope for Pd^{II}/Ag^{I}-catalyzed reaction of γ-hydroxy lactam. (a) Yield in parentheses represents the isolated yield of the corresponding reaction at 90 °C with 5 mol % of $PdCl_2(MeCN)_2$ in 1,2-dichloroethane.

reaction conditions, good to excellent yields were achieved for the reaction between 3-hydroxy-2-phenylisoindolin-1-one (**1a**) and various electron-rich arenes (1,3,5-trimethoxybenzene and 2-naphthol) and heteroarenes (2-methylthiophene, 2-methylfuran and various indole derivatives). Similarly, the reaction of 2-(3,5-dimethylphenyl)-3-hydroxyisoindolin-1-one (**1d**) was found to proceed smoothly with various arenes and heteroarenes (Figure 1). On the other hand, a relatively lower yield of product was achieved in the case of of 2-(4-bromophenyl)-3-hydroxyisoindolin-1-one (**1e**), which suggests both the generation and stability of the *N*-acyliminium ion are important for the reaction. However, less electron-rich arenes such as toluene, *p*-xylene, and mesitylene remained inactive in all three cases. Next, the methodology was also found to be successful for the reaction between 2-benzyl-3-hydroxyisoindolin-1-one (**1f**) with various aromatics and indoles to produce the corresponding product almost quantitatively. Organotin nucleophiles (allyltributyltin) and β-dicarbonyl nucleophiles (acetyl acetone) also afforded the corresponding products **2j** and **2o** in 64 and 75% yield, respectively. Apart from C-nucleophiles, oxygen (2-propanol) and sulfur (4-methoxythiophenol) nucleophiles were also found to provide the corresponding **2p** and **2q** in 69% and 73% yield, respectively.

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However, N-nucleophiles (aniline, *p*-toluenesulfonamide, benzamide) failed to produce the desired product.[35]

Next, to check the role of the catalytic species and involvement of Lewis or Brønsted acid, indole was chosen as a representative model, and its reaction with **1a**–**c** was studied under a variety of reaction conditions (Figure 2). The reaction

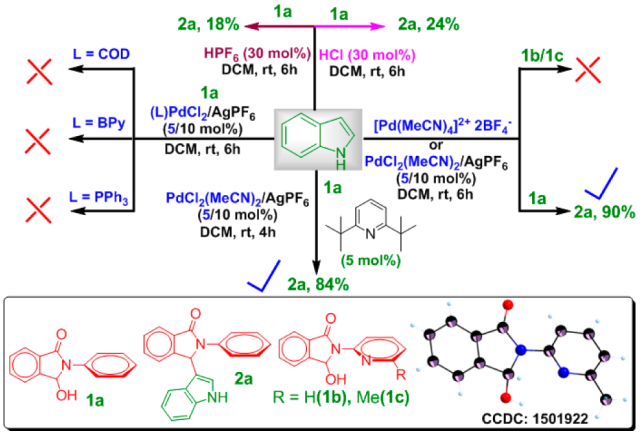

Figure 2. *α*-Amidoalkylation reaction of indole under various reaction conditions.

between **1a** and indole failed to produce any desired product in the presence of Pd^{II} complexes containing stronger ligand like BPy, PPh_3, and COD. On the other hand, Pd^{II}/Ag^{I}-catalyzed reaction of indole for both **1b** and **1c** was found to be unsuccessful. All of the above-mentioned observations suggested the need for an available vacant site at the Pd^{II} center for binding of both the indole and *γ*-hydroxy lactam, which brings them in close proximity to each other for facile interaction and successive product formation.

However, the same reaction in the presence of 30 mol % of HPF_6 or even 30 mol % of HCl afforded the desired product in 18% and 24% yield, respectively (Figure 2). To check the involvement of any in situ generated Brønsted acid, 2,6-di-*tert*-butylpyridine (2,6-DTBP) was used as a proton scavenger. The addition of 5 mol % of 2,6-DTBP Pd^{II}/Ag^{I}-catalyzed reaction still resulted in the formation of the product **2a** in 84% after 4 h, which directly ruled out the possible in situ generated Brønsted acid catalysis.

The *γ*-lactam derivatives are known to contain a good bioactive core[36] because they are similar to *β*-lactam group containing antibiotics with an additional carbon in the core ring. However, bacteria often develop resistance to *β*-lactam antibiotics through the synthesis of *β*-lactamase enzymes, which could hydrolyze the *β*-lactam ring.[37] To date, several approaches have been attempted to prevent this bacterial resistance. Among various approaches, *γ*-lactams and their analogues may be an alternative, and thus, various derivatives have been synthesized and tested previously against broad-spectrum antibacterial agents.[38] Currently, methicillin-resistant *Staphylococcus aureus* (MRSA) strains are also resistant to other group of antibiotics like vancomycin, which is the second choice of antibiotics next to methicillin for the treatment of complicated skin and skin structure infection including surgical site infections.[39] Toward the search for new classes of antimicrobials to address the emergence of multidrug-resistant MRSA and VRSA, synthesized analogues were tested against both Gram-positive and Gram-negative bacteria. Activity against Gram-negative bacteria was very weak compared to that of Gram-positive bacteria. We have selected the *S. aureus* strain, a deadly infectious strain when it develops resistance to both vancomycin and methicillin. Activities of all the synthesized compounds were checked against the control-type strain of *S. aureus* as well as the pathogenic vancomycin- and methicillin-resistant *S. aureus* strain. Among all synthesized isoindoline derivatives, compounds **2d**, **2e**, and **2l** were found to be active against all types of strains with an appreciable MIC value.[40] Antibiotic-resistant ability was also confirmed with standard antibiotics such as methicillin, vancomycin, tetracycline, levofloxacin, and gentamicin. To our delight, comound **2w** was found to be most active and showed comparable activity with levofloxacin with an MIC value of 0.48 against control as well as resistant strain (Table 2).

Table 2. Effect of Isoindolinone Derivatives against MRSA and VRSA Positive Strains[a]

no.	*S. aureus* U07 (VRSA + MRSA +)	*S. aureus* ATCC25923 (control strain)	*S. aureus* ATCC43300 (MRSA + control)
vancomycin	31.2	1.95	3.9
methicillin	125	1.95	31.2
tetracycline	500	3.9	500
gentamicin	16	0.975	0.975
levofloxacin	0.48	0.24	0.24
2c	15.6	7.8	15.6
2d	3.9	1.95	3.9
2e	1.95	0.975	0.975
2k	15.6	7.8	15.6
2l	1.95	0.975	0.975
2w	0.487	0.487	0.487

[a]MIC values ($\mu g\ mL^{-1}$) were determined in vitro against both clinical and control strains.

CONCLUSION

We have developed a synthetically attractive approach employing in situ generated cationic Pd^{II} catalyst using a catalytic combination of Pd^{II}/Ag^{I} for amidoalkylation reactions between various *γ*-hydroxy lactam and C/O/S nucleophiles at room temperature. The origin of reactivity in cationic Pd^{II} mainly lies on its coordination ability to both the nucleophile and electrophile, which brings them in close proximity to each other for facile interaction and successive product formation. The synthesized isoindolinone darivatives were screened for bioactivity against MRSA and VRSA strains, and some of them were found found to be effective with appreciable MIC value.

EXPERIMENTAL SECTION

All of the reactions were performed under a dry, oxygen-free argon atmosphere using standard vacuum lines and Schlenk techniques. All of the solvents used for the study have been dried and distilled by standard methods and previously deoxygenated in the vacuum line. ^{1}H (200, 400 MHz) and ^{13}C NMR (54.6, 100 MHz) spectra (chemical shifts referenced to signals for residual solvent) were recorded on 200 and 400 MHz spectrometers at 298 K. High-resolution mass spectra (HRMS) were recorded on an ESI-Q-TOF mass spectrophotometer.

Synthesis of Isoindoline-1,3-dione Derivatives. In a 250 mL round-bottom flask, phthalic anhydride (7.4 g, 50 mmol) and the corresponding amine (50 mmol) were taken in 150 mL of dry toluene. To this, 50 g of molecular sieves (4 Å) and 300 mg of Amberlite IR-120 resin were added, and the mixture was stirred for 10 min at room temperature. After that, the reaction mixture was refluxed at 150 °C for

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24 h using a Dean−Stark apparatus. During the course of the reaction, an appropriate amount of water generated from the reaction was collected. After completion of the reaction, the remaining amount of toluene was evaporated under reduced pressure, and the as-obtained yellow condensed product was dried under reduced pressure and collected for further use.

Synthesis of γ-Hydroxy Lactam Derivatives. In a 100 mL round-bottom flask, isoindoline-1,3-dione derivative (5 mmol) was taken in 30 mL of methanol and stirred for 5−10 min to obtain a solution. After that, the reaction mixture was cooled to 0−5 °C, solid NaBH4 (50 mmol) was gradually added, and the reaction continued for the desired time. After the completion of the reaction (via TLC), around 50 mL of ice−water was added. Next, a dilute H_2SO_4 acid solution was dropwise added to decompose the excess $NaBH_4$. During the decomposition process, a solid crystalline product was found to appear in the round-bottom flask, which was collected by filtration and dried under reduced pressure for further use.

General Procedure for Pd^{II}/Ag^{I}-Promoted Reaction γ-Hydroxy Lactam Derivatives. A 10 mL Schlenk flask equipped with a magnetic bar was charged with $PdCl_2(MeCN)_2$ (0.025 mmol) and $AgPF_6$ (0.025 mmol) in dichloroethane (3 mL) and stirred for 30 min under argon atmosphere. After that, an appropriate arene or heteroarene (0.5 mmol) and hydroxy lactam (0.5 mmol) were added to the flask, and the reaction was allowed to continue at room temperature under vigorous stirring. After completion of the reaction (via TLC monitoring), water was added to the reaction mixture to quench the reaction, and product was extracted with ethyl acetate (30 mL × 3), washed with water (20 mL × 3) and brine (10 mL), and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to silica gel column chromatography (60−120 mesh, ethyl acetate−petroleum ether, and gradient elution) to afford the pure isoindolinone derivative.

Spectral and Analytical Data. *3-(1H-Indol-2-yl)-2-phenylisoindolin-1-one (**2a**).*[41] Colorless solid (145 mg, 90%). Mp: 253−255 °C. δ_H (400 MHz, DMSO-d_6): 11.06 (1H, s), 7.90 (1H, d, J = 8.0 Hz), 7.69 (2H, d, J = 8.0 Hz), 7.63 (1H, s), 7.60−7.54 (2H, m), 7.34−7.25 (4H, m), 7.05 (1H, t, J = 8.0 Hz), 6.95 (1H, d, J = 8 Hz), 6.76 (3H, m). δ_C (100 MHz, DMSO-d_6): 166.9, 146.7, 138.1, 137.1, 133.0, 131.5, 129.0, 128.9, 126.7, 125.1, 125.0, 123.8, 123.6, 123.3, 121.7, 119.4, 118.5, 112.3, 110.2, 59.4. Anal. ($C_{22}H_{16}N_2O$) Calcd: C, 81.46; H, 4.97; N, 8.64; O, 4.93. Found: C, 81.41; H, 4.76; N, 8.56.

*3-(5-Methylthiophene-2-yl)-2-phenylisoindolin-1-one (**2b**).* White solid (112 mg, 74%). Mp: 206−207 °C. δ_H (400 MHz, DMSO-d_6): 7.79 (1H, d, J = 8 Hz), 7.65−7.61 (3H, t, J = 8 Hz), 7.56−7.53 (1H, m) 7.39−7.31 (3H, m), 7.13−7.07 (2H, m), 6.84 (1H, s), 6.55 (1H, d, J = 4 Hz), 2.21 (3H, s). δ_C (100 MHz, DMSO-d_6): 166.4, 146.1, 140.5, 139.1, 133.4, 130.5, 129.4, 129.2, 128.3, 125.6, 125.5, 123.9, 123.9, 123.5, 60.7, 15.5. Anal. ($C_{19}H_{15}NOS$) Calcd: C, 74.72; H, 4.95; N, 4.59; O, 5.24; S, 10.50. Found: C, 74.61; H, 4.89; N, 4.51.

*3-(2-Hydroxynaphthalen-1-yl)-2-phenylisoindolin-1-one (**2c**).* Brown solid (143 mg, 82%). Mp: 273−275 °C. δ_H (400 MHz, DMSO-d_6): 10.64 (1H, s), 7.92 (1H, d, J = 8 Hz), 7.67 (1H, d, J = 12 Hz), 7.63−7.51 (5H, m), 7.33 (1H, s), 7.25 (1H, d, J = 8 Hz), 7.21−7.14 (3H, m), 7.08−7.02 (2H, m), 6.98−6.92 (2H, m). δ_C (100 MHz, DMSO-d_6): 167.2, 155.5, 146.6, 138.0, 133.3, 132.5, 132.0, 131.3, 129.3, 129.1, 129.0, 128.9, 127.1, 124.9, 124.1, 123.2, 122.9, 122.3, 121.7, 118.4, 112.1, 57.1 Anal. ($C_{24}H_{17}NO_2$) Calcd: C, 82.03; H, 4.88; N, 3.99. Found: C, 81.95; H, 4.58; N, 3.73.

*2-Phenyl-3-(2,4,6-trimethoxyphenyl)isoindolin-1-one (**2d**).* White solid (146 mg, 78%). δ_H (400 MHz, DMSO-d_6): 7.74 (1H, d, J = 8.0 Hz), 7.54 (2H, d, J = 8.0 Hz), 7.50−7.42 (2H, m), 7.25 (2H, t, J = 8.0 Hz), 7.16 (1H, d, J = 8.0 Hz), 7.00 (1H, t, J = 7.8 Hz), 6.71 (1H, s), 6.26 (1H, d, J = 4.0 Hz), 5.91 (1H, d, J = 4.0 Hz), 3.93 (3H, s), 3.65 (3H, s), 3.18 (3H, s). δ_C (100 MHz, DMSO-d_6): 167.4, 161.5, 159.9, 159.8, 146.1, 138.4, 132.9, 132.4, 128.9, 128.3, 124.5, 123.2, 122.6, 122.1, 104.8, 100.0, 92.5, 91.5, 57.1, 56.2, 55.6. Anal. ($C_{23}H_{21}NO_4$) Calcd: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.41; H, 5.76; N, 3.56.

*2-(3,5-Dimethylphenyl)-3-(5-nitro-1H-indol-2-yl)isoindolin-1-one (**2e**).* Green solid (150 mg, 76%). Mp: 245−248 °C. δ_H (400 MHz, DMSO-d_6): 10.90 (NH, s), 8.02 (1H, s), 7.65 (2H, t), 7.90 (1H, s), 7.60 (2H, t), 7.52 (1H, d), 7.42 (1H, t), 7.39 (2H, s), 6.85 (1H, s), 6.69 (1H, s), 2.16 (6H, s). δ_C (100 MHz, DMSO-d_6): 166.7, 146.2, 141.0, 140.1, 138.0, 137.6, 133.2, 131.4, 130.4, 129.3, 126.9, 124.7, 123.8, 121.3, 117.2, 115.5, 113.6, 113.0, 58.4, 21.4. HRMS (ESI) calcd for $C_{24}H_{19}N_3O_3$ $[M + H]^+$ = 398.1499, found 398.1503.

*2-(3,5-Dimethylphenyl)-3-(5-methoxy-1H-indol-3-yl)isoindolin-1-one (**2f**).* White solid (156 mg, 82%). Mp: 204−207 °C. δ_H (400 MHz, DMSO- d_6): 10.60 (1H, d), 7.61 (1H, d, J = 4.0 Hz), 7.27 (2H, m), 7.03 (3H, d, J = 8.0 Hz), 6.89 (1H, dd, J = 8.0 Hz), 6.43 (2H, d, J = 8.0 Hz), 6.35 (1H, d, J = 8.0 Hz), 5.95 (1H, s), 3.23 (3H, s, OMe, merge with DMSO water), 1.90 (6H, s). δ_C (100 MHz, DMSO-d_6): 166.6, 153.1, 146.3, 137.6, 132.8, 131.9, 131.3, 128.6, 126.8, 126.4, 125.4, 123.6, 123.1, 120.9, 112.6, 110.8, 109.7, 100.7, 59.09, 55.3, 21.2. Anal. ($C_{25}H_{22}N_2O_2$) Calcd: C, 78.51; H, 5.80; N, 7.32. Found: C, 78.31; H, 5.71; N, 7.21.

*3-(1-Benzyl-1H-indol-2-yl)-2-(3,5-dimethylphenyl)isoindolin-1-one (**2g**).* White solid (182 mg, 82%). Mp: 188−192 °C. δ_H (400 MHz, DMSO-d_6): 7.86−7.84 (1H, m), 7.78 (1H, s), 7.57−7.51 (2H, m), 7.33−7.26 (4H, m), 7.19−7.18 (3H, t, J = 4 Hz), 6.98−6.89 (3H, m), 6.82−6.68 (4H, m), 5.33 (2H, s), 2.13 (6H, s). δ_C (100 MHz, DMSO-d_6): 166.8, 146.4, 144.9, 138.5, 138.1, 137.9, 137.7, 136.9, 133.0, 131.7, 129.0, 128.9, 127.8, 127.2, 126.5, 125.8, 124.1, 123.8, 123.6, 121.9, 123.3, 120.9, 120.7, 119.8, 118.9, 111.1, 110.1, 59.2, 49.3, 21.5. HRMS (ESI): calcd for $C_{31}H_{26}N_2O$ $[M + H]^+$ = 443.2079, found 443.2043.

*3-(1-Allyl-1H-indol-2-yl)-2-(3,5-dimethylphenyl)isoindolin-1-one (**2h**).* White crystalline solid (160 mg, 82%). δ_H (400 MHz, $CDCl_3$): 8.02 (1H, dd, J = 8.0 Hz), 7.51−7.45 (2H, m), 7.30 (1H, d, J = 8.0 Hz), 7.25 (1H, s), 7.20 (1H, d, J = 8.0 Hz), 7.13−7.04 (5H, m), 6.92 (1H, t, J = 8.0 Hz), 6.71 (1H, s), 6.32 (1H, s), 5.93−5.86 (1H, m), 5.11 (1H, d, J = 12 Hz), 4.82 (1H, d, J = 12 Hz), 4.62 (2H, d, J = 4 Hz), 2.20 (6H, s). δ_C (100 MHz, $CDCl_3$): 167.7, 145.9, 138.2, 137.4, 136.9, 133.2, 132.3, 131.8, 128.5, 127.9, 127.3, 126.0, 124.0, 123.2, 122.1, 121.8, 119.8, 119.5, 117.2, 110.7, 109.8, 60.1, 48.6, 21.4. Anal. ($C_{27}H_{24}N_2O$) Calcd: C, 82.62; H, 6.16; N, 7.14. Found: C, 82.75; H, 6.48; N, 7.34.

*2-(3,5-Dimethylphenyl)-3-(1H-indol-2-yl)isoindolin-1-one (**2i**).* White crystalline solid (147 mg, 84%). Mp: 236−238 °C. δ_H (400 MHz, $CDCl_3$): 8.01 (1H,m), 7.52−7.44 (2H, m), 7.32−7.25 (3H, m), 7.16−7.08 (5H, m), 6.96−6.92 (1H, t, J = 4.0 Hz), 6.71 (1H, s), 5.84 (1H, s), 6.36 (1H, s), 2.19 (6H, s). δ_C (100 MHz, $CDCl_3$): 138.2, 137.3, 136.6, 132.3, 131.7, 128.5, 127.3, 124.0, 123.1, 121.7, 120.1, 120.1, 119.2, 111.4, 77.4, 77.1, 76.6, 76.6, 59.9, 43.5, 21.4.Anal. ($C_{24}H_{20}N_2O$) Calcd: C, 81.79; H, 5.72; N, 7.95. Found: C, 81.62; H, 5.53; N, 7.68.

*3-Allyl-2-benzylisoindolin-1-one (**2j**).*[25b] White crystalline solid (75 mg, 64%). δ_H (200 MHz, $CDCl_3$): 7.87−7.91 (1H, m), 7.22−7.55 (8H, m), 5.42 (1H, d, J = 15.2 Hz), 5.24−5.41 (1H, m), 4.96−5.07 (2H, m), 4.42 (1H, t, J = 5.2 Hz), 4.17 (1H, d, J = 15.2 Hz), 2.56−2.80 (2H, m). δ_C (54.6 MHz, $CDCl_3$): 168.5, 144.9, 137.1, 132.3, 131.4, 131.2, 128.8, 128.1, 127.6, 123.8, 122.4, 119.3, 58.0, 43.9, 35.2.

*3-(5-Bromo-1H-indol-2-yl)-2-(4-bromophenyl)isoindolin-1-one (**2k**).* White crystalline solid (173 mg, 72%). Mp: 294−297 °C. δ_H (400 MHz, DMSO-d_6): 11.27 (1H, NH, s), 7.89 (1H, d, J = 8 Hz), 7.63−7.56 (5H, m), 7.44 (2H, d, J = 12 Hz), 7.26 (2H, dd, J = 8 Hz), 7.06 (1H, d, J = 8 Hz), 6.90 (1H, s), 6.77 (1H, s). δ_C (100 MHz, DMSO-d_6): 166.9, 146.3, 137.3, 135.8, 133.4, 131.8, 131.1, 129.2, 128.3, 126.9, 125.0, 124.4, 123.9, 120.5, 117.4, 114.5, 112.1, 109.9, 58.9. Anal. ($C_{22}H_{14}Br_2N_2O$) Calcd: C, 54.80; H, 2.93; Br, 33.14; N, 5.81; O, 3.32. HRMS (ESI): calcd for $C_{22}H_{14}Br_2N_2O$ $[M + H]^+$ = 482.9530, found 482.9541.

*2-(4-Bromophenyl)-3-(2-hydroxynaphthalen-1-yl)isoindolin-1-one (**2l**).* Brown solid (141 mg, 66%). Mp: 261−263 °C. δ_H (400 MHz, DMSO-d_6): 10.74 (1H, s), 7.92 (1H, t, J = 8.0 Hz), 7.78 (1H, m), 7.71 (1H, d, J = 8.0 Hz), 7.58−7.64 (2H, m), 7.52−7.56 (6H, m), 7.25−7.39 (6H, m), 7.15 (1H, t, J = 8.0 Hz), 7.04 (2H, m), 6.92 (1H, m). δ_C (100 MHz, DMSO-d_6): 187.3, 155.6, 154.4, 146.5, 145.7, 137.2, 134.3, 133.2, 131.8, 131.7, 129.1, 128, 127.2, 124.2, 124.2, 123.2, 123.0, 121.5, 118.4, 117.2, 111.7, 87.5, 57.8. Anal. ($C_{24}H_{16}BrNO_2$) Calcd: C, 66.99; H, 3.75; N, 3.26. Found: C, 66.72; H, 3.53; N, 3.11.

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*2-Benzyl-3-(thiophene-2-yl)isoindolin-1-one (**2m**).*[29] Sticky liquid (120 mg, 79%). δ_H (400 MHz, $CDCl_3$): 7.92−7.96 (m, 1H), 7.46−7.51 (m, 2H), 7.23−7.33 (m, 7H), 7.00−7.04 (m, 2H), 5.57 (s, 1H), 5.40 (d, 1H, *J* = 14.8 Hz), 3.89 (d, 1H, *J* = 14.8 Hz). δ_C (100 MHz, $CDCl_3$): 167.9, 145.5, 139.9, 137.1, 131.7, 131.0, 128.6, 128.5, 128.3, 127.6, 127.5, 126.8, 126.6, 123.8, 123.1, 58.7, 43.5.

*2-Benzyl-3-(2,4,6-trimethoxyphenyl)isoindolin-1-one (**2n**).*[29] White solid (169 mg, 87%). δ_H (400 MHz, DMSO-d_6): 7.68 (1H, d, *J* = 8.0 Hz), 7.44−7.37 (2H, m), 7.25−7.16 (3H, m), 7.08−7.02 (3H, m), 6.28 (1H, d, *J* = 4.0 Hz), 6.03 (1H, d, *J* = 4.0 Hz), 5.84 (1H, s), 4.89 (1H, d, *J* = 16.0 Hz), 3.73 (3H, s), 3.67 (3H, s), 3.17 (3H, s). δ_C (100 MHz, DMSO-d_6): 168.0, 161.8, 160.3, 147.0, 138.2, 132.8, 131.7, 128.8, 128.2, 127.9, 127.5, 122.9, 122.4, 103.4, 92.2, 91.4, 56.6, 56.0, 55.7, 54.6, 43.8. Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.02, H, 5.95; N, 3.60. Found: C, 73.92, H, 5.75; N, 3.42.

*3-(2-Benzyl-3-oxoisoindolin-1-yl)pentane-2,4-dione (**2o**).*[25b] Sticky liquid (120 mg, 75%). δ_H (400 MHz, $CDCl_3$): 7.95 (d, *J* = 7.0 Hz, 1H), 7.53 (quint, *J* = 7.8 Hz, 2 H), 7.22−7.35 (m, 6 H), 5.43 (d, *J* = 14.8 Hz, 1 H), 5.24 (s, 1 H), 3.94 (d, *J* = 14.6 Hz, 1 H), 1.81 (s, 3H), 1.42 (s, 3 H). δ_C (100 MHz, DMSO-d_6): 197.4, 190.2, 168.6, 145.0, 136.9, 132.5, 132.0, 129.2, 128.9, 128.2, 127.9, 124.2, 122.1, 104.9, 57.6, 43.6, 24.2, 22.1.

*2-Benzyl-3-isopropoxyisoindolin-1-one (**2p**).*[29] Liquid (96 mg, 69%). δ_H (400 MHz, $CDCl_3$): 7.85 (1H, d, *J* = 7.4 Hz), 7.48−7.57 (3H, m), 7.26−7.31 (5H, m), 5.64 (1H, s), 5.27 (1H, d, *J* = 15.0 Hz), 4.25 (1H, d, *J* = 15.0 Hz), 3.64 (1H, septet, *J* = 6.0 Hz), 1.21 (3H, d, *J* = 6.0 Hz), 1.07 (3H, d, *J* = 6.2 Hz). δ_C (54.6 MHz, $CDCl_3$): 167.3. 142.2, 137.0, 132.3, 131.9, 129.7, 128.7, 128.4, 128.2, 127.5, 123.5, 85.2, 68.7, 43.1, 23.7, 23.4.

*2-Benzyl-3-((4-methoxyphenyl)thio)isoindolin-1-one (**2q**).*[29] Liquid (131 mg, 73%). δ_H (400 MHz, $CDCl_3$): 7.58−7.59 (2H, m), 7.52 (1H, t, *J* = 7.6 Hz), 7.26−7.36 (6H, m), 6.94 (2H, d, *J* = 8.4 Hz), 6.57 (2H, d, *J* = 8.4 Hz), 5.44 (1H, d, *J* = 14.8 Hz), 5.40 (1H, s), 4.55 (1H, d, *J* = 14.4 Hz), 3.68 (3H, s). δ_C (100 MHz, $CDCl_3$): 167.3, 160.4, 143.0, 137.2, 136.7, 131.5, 128.7, 128.5, 128.4, 127.6, 123.7, 123.3, 117.7, 114.1, 65.7, 55.1, 43.0.

*2-Benzyl-3-(5-methylthiophene-2-yl)isoindolin-1-one (**2r**).*[29] White solid (121 mg, 76%). Mp: 103−108 °C. δ_H (400 MHz, DMSO-d_6): 7.74 (1H, d, *J* = 8.0 Hz), 7.55−7.48 (2H, m), 7.30−7.22 (4H, m), 7.13 (2H, d, *J* = 8.0 Hz), 7.01 (1H, s), 6.68 (1H, s,), 5.72 (1H, s), 5.03 (1H, d, *J* = 16 Hz), 3.92 (1H, d, *J* = 16 Hz), 2.32 (3H, s). δ_C (100 MHz, DMSO-d_6): 168.0, 146.5, 141.2, 138.1, 137.6, 132.7, 130.9, 129.1, 128.2, 125.8, 124.2, 123.5, 59.3, 43.7, 15.9.

*2-Benzyl-3-(2-hydroxynaphthalen-1-yl)isoindolin-1-one (**2s**).* White crystalline solid (116 mg, 64%). δ_H (400 MHz, DMSO-d_6): 10.31 (1H, s), 7.88 (1H, d, *J* = 8 *Hz*), 7.78 (1H, d, *J* = 8 Hz), 7.72 (1H, d, *J* = 8 Hz), 7.52−7.44(2H, m), 7.28 (1H, d, *J* = 8 Hz), 7.21−7.15 (3H, m), 7.12−7.04 (6H, m), 6.74 (1H, d, *J* = 8 Hz), 6.56 (1H, s), 4.94 (1H, d, *J* = 16 Hz), 3.63 (1H, d, *J* = 16 Hz). δ_C (100 MHz, DMSO-d_6): 168.1, 156.1, 147.2, 137.8, 132.8, 132.7, 132.2, 129.4, 128.8, 128.2, 127.6, 127.0, 123.8, 123.3, 123.0, 121.7, 118.5, 111.0, 87.2, 56.3. HRMS (ESI): calcd for $C_{25}H_{19}NO_2$ $[M + H]^+$ = 366.1449, found 366.1437.

*2-Benzyl-3-(1H-indol-2-yl)isoindolin-1-one (**2t**).*[25b] White solid (153 mg, 91%). Mp: 199−203 °C. δ_H (400 MHz, DMSO-d_6): 11.22 (1H, s), 7.81 (1H, d, *J* = 8 Hz), 7.53 (1H, s), 7.48 (2H, d, *J* = 8 Hz), 7.34−7.20 (5H, m), 7.12 (2H, d, *J* = 8 Hz), 7.02 (1H, t), 6.98 (1H, t, *J* = 8.2 Hz), 6.72 (1H, t, *J* = 8.2 Hz), 6.52 (1H, s), 5.72 (1H, d), 4.99 (1H, d, *J* = 16 Hz), 3.76 (1H, d, *J* = 16 Hz). δ_C (100 MHz, DMSO-d_6): 167.6, 146.9, 138.1, 137.5, 132.4, 131.8, 129.1, 128.8, 128.0, 127.6, 124.1, 123.3, 121.9, 119.5, 118.4, 112.5, 109.1, 57.9, 44. Anal. ($C_{23}H_{18}N_2O$) Calcd: C, 81.63; H, 5.36; N, 8.28. Found: C, 81.32; H, 5.62; N, 8.35.

*2-Benzyl-3-(5-methoxy-1H-indol-2-yl)isoindolin-1-one (**2u**).* White solid (169 mg, 92%). Mp: 118−120 °C. δ_H (400 MHz, DMSO-d_6): 11.05 (1H, s), 7.82 (1H, q, *J* = 8 Hz), 7.50 (3H, q, *J* = 8 Hz), 7.35−7.23 (6H, m), 7.13 (2H, d, *J* = 8 Hz), 6.66 (1H, dd, *J* = 8 Hz), 5.71 (1H, s), 5.0 (1H, d, *J* = 16 Hz), 3.79 (1H, d, *J* = 16 Hz), 3.35 (3H, s). δ_C (100 MHz, DMSO-d_6): 167.6, 153.5, 142.2, 138.3, 132.5, 132.4, 131.9, 129.0, 128.8, 128.0, 127.6, 124.2, 123.2, 113.1, 111.4, 100.8, 57.2, 55.4, 43.4. Anal. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 78.15; H, 5.35; N, 7.29.

*2-Benzyl-3-(5-nitro-1H-indol-2-yl)isoindolin-1-one (**2v**).* White solid (120 mg, 63%). Mp: 225−227 °C. δ_H (400 MHz, acetone-d_6): 11.08 (NH, s), 7.97−7.91 (2H, m), 7.80 (1H, s), 7.65 (1H, s), 7.58−7.49 (4H, m), 7.30−7.28 (1H, d, *J* = 8 Hz), 7.21−7.14 (4H, m), 5.85 (1H, s), 5.09 (1H, d, *J* = 16 Hz), 4.03 (1H, d, *J* = 16 Hz); δ_C (100 MHz, acetone-d_6): 167.3, 146.1, 140.5, 137.9, 132.0, 131.9, 128.6, 128.4, 128.1, 127.1, 123.5, 123.2, 117.2, 115.5, 113.1, 112.2, 87.2, 57.01, 43.6. Anal. Calcd for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 4.47; N, 10.96. Found: C, 71.92; H, 4.35; N, 10.82.

*2-Benzyl-3-(5-bromo-1H-indol-2-yl)isoindolin-1-one (**2w**).* White solid (150 mg, 72%). Mp: 205−207 °C. δ_H (400 MHz,acetone-d_6): 10.62 (NH, s), 7.89 (1H, dd, *J* = 8 Hz), 7.59 (1H, s), 7.55−7.48 (2H, m), 7.39−7.37 (1H, d, *J* = 8 Hz), 7.27−7.14 (7H, m), 6.81 (1H, s), 5.72 (1H, s), 5.15 (1H, d, *J* = 16 Hz), 3.88 (1H, d, *J* = 16 Hz); δ_C (100 MHz, acetone-d_6): 167.8, 146.4, 138.0, 136.2, 132.1, 131.9, 128.5, 128.0, 127.2, 124.6, 123.6, 123.1, 120.9, 113.8, 112.2, 109.9, 57.2, 48.9, 43.3. Anal. Calcd for $C_{23}H_{17}BrN_2O$: C, 66.20; H, 4.11; N, 6.71. Found: C, 66.05; H, 4.22; N, 6.52.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02378.

Procedural, spectral, biological data, optimized coordinates, geometries including frequency data (PDF)

X-ray data for **1c** (CIF)

X-ray data for **2f** (CIF)

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Notes

The authors declare no competing financial interest.

Crystallographic cif files for **1c** and **2f** (CCDC Nos. 1501922 and 1506191) are available at www.ccdc.cam.ac.uk/data_request/cif.

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