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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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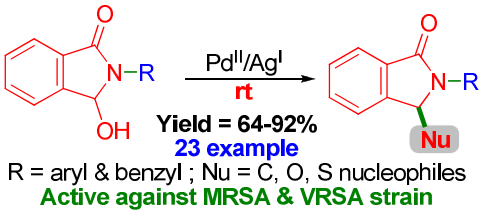
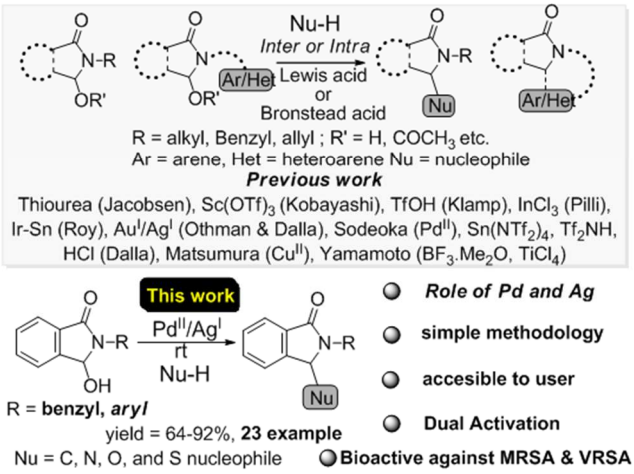


ABSTRACT: The present work reports a Pd^{II}/Ag^{I} promoted amidoalkylation reaction involving various γ-hydroxy lactam and C/O/S nucleophile at room temperature. The dual mode of activation of both the electrophile and nucleophile by *in-situ* generated catalytically active cationic Pd^{II} species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

The development of a selective catalytic system for a particular type of bond forming reaction between electrophiles (E) and nucleophile (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-complex.[5] Towards this, development of cooperative homo or/and hetero bimetallic,[6] LA-NHC,[7] tandem catalyst,[8] 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] 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 an important electron-deficient carbocations intermediates in organic synthesis because it provides various biologically important natural and unnatural products *via* C-C and C-heteoatom bond forming methodologies using inter or intra molecular path. [20, 21] The removal of good leaving group at the α-position of amides or lactams usually generates N-Acyliminium ions, which acts as more electron-deficient carbocations toward nucleophiles. In this regard, chiral thiourea derivatives,[22, 23] superacidic reagents,[24] various Lewis[25] and Brønsted acidic[26] systems have been utilized for the generation of N-acyliminium ions and subsequent catalytic intra or inter molecular 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 nucleophlic substitution of γ-hydroxy lactams, Cu^{II} for enantioselective reaction between N-Acyliminium ions and diaryl malonate,[30] 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 reaction with variety of *C/N/O/S* nucleophile *via* dual mode of activation.

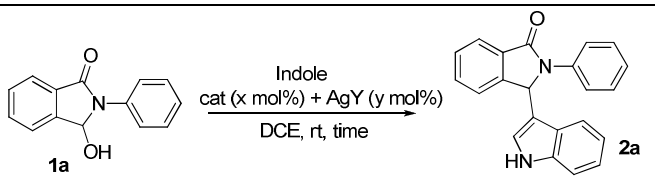
Scheme 1. Catalytic α-amidoalkylation reaction



Initially, the reaction between **1a** and indole was chosen as a model reaction in presence of different Brønsted acids, Lewis acids, palladium and other transition metal catalysts. After the optimization of reaction condition 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 to produce desired **2a** in 62% yield at 90 °C, but 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 reaction proceeds at room temperature with $PdCl_2(MeCN)_2$ after the introduction of 2 eqv. of $AgPF_6$ as a halide trapping agent. However, 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 desired transformation. The inactivity of stronger ligand (BPy, DPPE, PPh_3, COD) containing Pd^{II} complexes suggest that vacant coordination site at Pd^{II} centre 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 synthesized $[Pd(MeCN)_4]^{2+}$ complex and found to be reactive to produce 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, entry 7-8) were tested in the model reaction and showed no further improvement in the product yield as compared to $AgPF_6$.

Table 1. Screening of Catalyst



#	Cat.	AgY	X/Y	T, °C	t, h	Yield,%
1	$PdCl2(MeCN)_2$	-	5	90	6	62[a]
2	$PdCl2(MeCN)_2$	-	5	rt	6	0
3	$PdCl2(MeCN)_2$	$AgPF_6$	2/2	rt	12	74
4	-	$AgPF_6$	10	rt	12	<10
5	$PdCl2(MeCN)_2$	$AgPF_6$	2/4	rt	4	90
6	$[Pd(MeCN)_4]^{2+}$	-	2	rt	4	86[b]
7	$PdCl2(MeCN)_2$	$AgSbF_6$	2/4	rt	4	84
8	$PdCl2(MeCN)_2$	$AgBF_4$	2/4	rt	4	85
9	Pd(COD)Cl2	$AgPF_6$	5/10	rt	6	15
10	Pd(BPy)Cl2	$AgPF_6$	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	FeCl3	-	5	rt	6	26
14	$SnCl_4$	-	5	rt	6	21
15	$BF_3.Et_2O$	-	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 done at 90°C in 1,2 dichloro ethane, [b]BF_4^- used as an anion.

At the same time, all of the tested Lewis acids inclusive of $BF_3{\cdot}Et_2O$, $FeCl_3$, $SnCl_4$ and Brønsted acids like; HCl, HPF_6, pTSA were less effective on the reaction. However, catalytic amount of TfOH gave 52% yield of **2a**. The substrate scope of Pd^{II}/Ag^{I} catalyzed alkylation reaction for γ-Hydroxy Lactam derivatives was illustrated in Figure 1. Under optimized reaction condition, 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-napthol) 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, relatively lower yield of product was achieved in case of of 2-(4-bromophenyl)-3-hydroxyisoindolin-1-one (**1e**), which suggest both the generation and stability of the N-acyliminium ion is important for the reaction. However, less electron rich arenes like; toluene, p-xylene, mesitylene remained inactive in all the 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-nuclephiles, oxygen (isopropanol) and sulphur (4-methoxy thiophenol) nucleophiles were also found to provide the corresponding **2p** and **2q** in 69% and 73% yield respectively. However, N-nucleophiles (aniline, p-toluenesulfonamide, benzamide) failed to produce any desired product.[35]

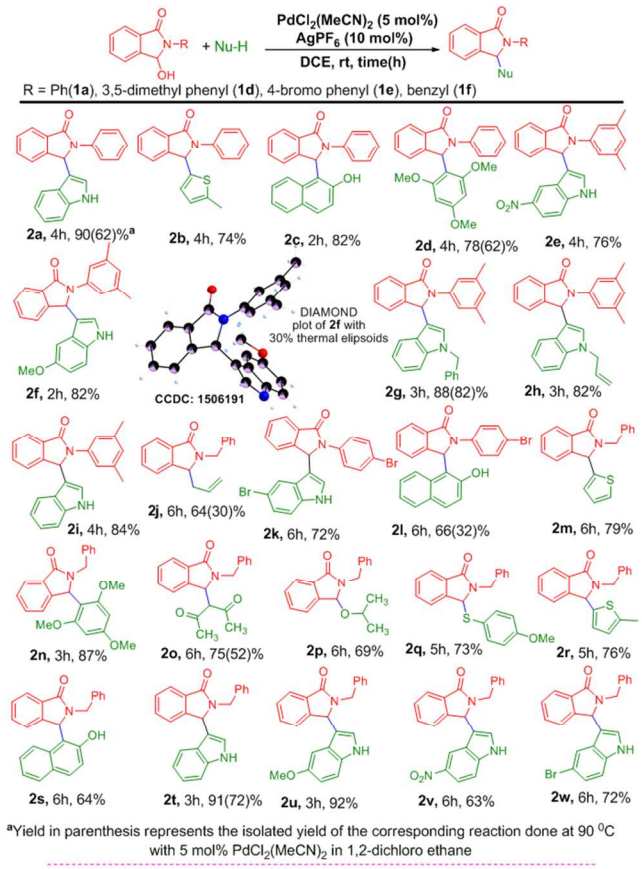


Figure 1. Substrate scope for Pd^{II}/Ag^{I} catalyzed reaction of γ-hydroxy lactam.

Next, to check the role of the catalytic species, involvement of Lewis or Brønsted acid, indole was chosen as a representative model and its reaction with **1a-1c** was studied under a variety of reaction conditions (Figure 2). The reaction between **1a** and indole failed to produce any desired product in 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 also found to be unsuccessful. All the above mentioned observation suggested the need of available vacant site at the Pd^{II} centre for binding of both the indole and γ-hydroxy lactam, which bring them close proximity to each other for facile interaction and successive product formation.

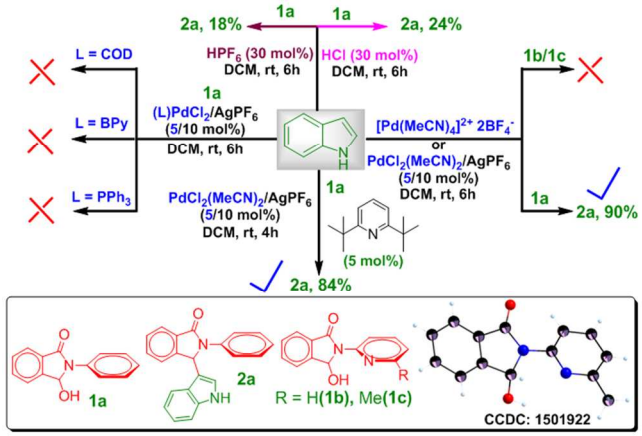


Figure 2. α-amidoalkylation reaction of indole under various reaction conditions.

However, the same reaction in presence of 30 mol% HPF_6 or even 30 mol% HCl afforded the desired product in 18% and 24% yield respective-

ly (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 4h, which directly ruled out the possible *in-situ* generated Brønsted acid catalysis.

The γ-lactam derivatives were known to be good bioactive core[36] because it is similar to ß-lactam group containing antibiotics with one more number of carbon in the core ring. However, bacteria often develop resistance to ß-lactam antibiotics through the synthesis of ß-lactamases enzyme, which could hydrolyze the ß-lactam ring.[37] Till date, several approaches have been tried to prevent this bacterial resistance. Amongst 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, methiciliin 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] Towards the search for new classes of antimicrobials to address the emergence of multidrug-resistant MRSA and VRSA, synthesized analogues were tested against both Gram(+)ve and Gram(-)ve bacteria. Activity against Gram-negative bacteria was very weak compare to Gram-positive bacteria. We have selected *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 control type strain of *S. aureus* as well as pathogenic vancomycin and methicillin resistant *S. aureus* strain. Amongst all synthesized isoindoline derivatives, compound **2d**, **2e** and **2l** were found to be active against all type of strain with an appreciable MIC value.[40] Antibiotics resistant ability was also confirmed with standard antibiotics like; methicillin, vancomycin, tetracycline, levofloxacin and gentamicin. To our delight, comound **2w** was found to be most active and showed comparable activity with levofloxacin with 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

#	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

MIC values (μg. 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 catalytic combination of Pd^{II}/Ag^{I} for amidoalkylation reaction between various γ-hydroxy lactam and C/O/S nucleophile at room temperature. The origin of reactivity in cationic Pd^{II} mainly lies on its coordination ability to both the nucleophile and electrophile, which bring them in close proximity to each other for facile interaction and successive product formation. The synthesized isoindolinone darivatives were screened for the bioactivity against MRSA and VRSA strain and some of them found to be effective with appreciable MIC value.

Experimental

All the reactions were performed under a dry oxygen free argon atmosphere using standard vacuum lines and Schlenk techniques. All 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 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 corresponding amine (50 mmol) was taken in 150 ml dry toluene. To this, 50 g molecular sieves (4 Å) and 300 mg Ambertlite IR-120 resin was added and stirred for 10 minutes at room temperature. After that, the reaction mixture was refluxed at 150 °C for 24 h using a Dean Stark apparatus. During the course of the reaction appropriate amount of water, generated from the reaction was collected. After the completion of the reaction, remaining amount of toluene was evaporated in reduced pressure and 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 derivatives (5 mmol) was taken in 30 ml methanol and stirred for 5-10 minute to get a solution. After that, reaction mixture was cooled down to 0-5 ˚C and gradually solid NaBH4 (50 mmol) added to it and continued for desired time. After the completion of reaction (vide TLC), around 50 ml ice-water was added to it. Next, a dilute H_2SO_4 acid solution was drop wise added to decompose the excess $NaBH_4$. During the decomposition process, a solid crystalline product was found to appeared 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 $PdCl_2(MeCN)_2$ (0.01 mmol) and $AgPF_6$ (0.02 mmol) in dichloroethane (3 mL) and stirred for 30 min. under argon atmosphere. After that, an appropriate arene or heteroarene (0.5 mmol) and hydroxylactam (0.5 mmol) was added to the flask and allowed to continue at room temperature under vigorous stirring. After completion of the reaction (vide TLC monitoring), water was added to the reaction mixture to quench the reaction and product was extracted with ethylacetate (30 ml ×3) and washed with water (20 ml ×3), brine (10 mL) and dried over anhydrous Na_2SO_4. After removing 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 (400MHz, DMSO-d6): 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 (100MHz, DMSO-d6): 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: ($C_{22}H_{16}N2O$). 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-methylthiophen-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 (100MHz, 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 (400MHz, 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 (146mg, 78%). δ_H (400MHz, 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 (100MHz, 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 (150mg, 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 (156mg, 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 (182mg, 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 (100MHz, 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 (160mg, 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 (100MHz, $CDCl_3$): 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 (147mg, 84%). mp 236-238 °C; δ_H (400MHz, $CDCl_3$): 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 (100MHz, $CDCl_3$): 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 (200MHz, $CDCl_3$): 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; δH (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); δC (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 (C22H14Br2N2O) Calcd C: 54.80, H: 2.93, Br: 33.14, N: 5.81, O: 3.32. HRMS (ESI) calcd for C22H14Br2N2O $[M+H]^+$ = 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; δH (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.

2-benzyl-3-(thiophen-2-yl)isoindolin-1-one (2m):[29] sticky liquid (120 mg, 79%). δ_H (400MHz, $CDCl_3$): 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 (100MHz, $CDCl_3$): 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 (400MHz, 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 (100MHz, 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 (400MHz, $CDCl_3$): 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 (100MHz, 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 (400MHz, $CDCl_3$): 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 (54.6MHz, $CDCl_3$): 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%). Yield: δ_H (400MHz, $CDCl_3$): 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(100MHz, $CDCl_3$): 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-methylthiophen-2-yl)isoindolin-1-one (2r):[29] White solid (121 mg, 76%). mp 103-108 °C; δ_H (400MHz, 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=16Hz*), 2.32 (3H, s). δ_C (100MHz, 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%). δH (400MHz, DMSO-d6): 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 (100MHz, DMSO-d6): 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 C25H19NO2 $[M+H]+$ = 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 (400MHz, 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 = 16Hz). δ_C (100MHz, 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 (400MHz, 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 (100MHz, 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 (400MHz, 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 (100MHz, 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 (400MHz, 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 (100MHz, 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

Procedural, spectral, biological data, optimized coordinates, geometries including frequency data in Supporting Information (SI). Crystallographic cif files (CCDC Nos. 1501922 and 1506191) are available at www.ccdc.cam.ac.uk/data_request/cif or as part of the Supporting Information (SI). "This material is available free of charge *via* the Internet at http://pubs.acs.org."

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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[32] Please see Table S1 for details in SI.

[33] In presence of added PPh_3 or COD or BPy in 1:2 combination with $PdCl_2(MeCN)_2$ and $AgPF_6$, model reaction failed to produce any desired product, which also suggest the need of vacant coordination site at Pd^{II} centre for activation of the substrates.

[34] Although silver salts are widely used as additives in palladium-catalyzed C−H functionalization reactions, the role of these silver additives is often not fully understood. For some recent demonstration regarding the role of silver salt please see; (a) Lotz, M. D.; Camasso, N. M.; Canty, A. J.; Sanford, M. S. Organometallics, **2016** (DOI: 10.1021/acs.organomet. 6b00437). (b) Lee, S. Y.; Hartwig, J. F. *J. Am. Chem. Soc*, **2016**, *138*, 15278-84. (c) Anand, M.; Sunoj, R. B.; Schaefer, H. F. *ACS Catal*. **2016**, 6, 696−708. We are thankful to the esteemed reviewer for raising this point.

[35] Under optimized reaction condition, the reaction between 2-benzyl-3-hydroxyisoindolin-1-one (**1f**) and N-nucleophiles offered unidentified complex mixture along with recovery of the starting materials.

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