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Pd-catalyzed direct C2-acylation and C2,C7-diacylation of indoles: Pyrimidine as easily removable C-H directing group

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

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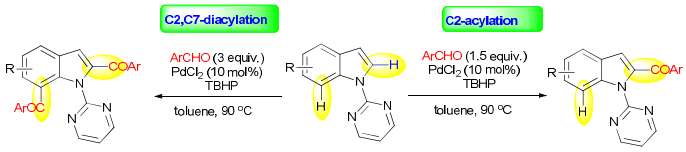
Govindharaj Kumar,[a] and Govindasamy Sekar*[a]

Pyrimidine is successfully used as an easily removable $C_{(sp2)}$-H directing group for the synthesis of 2-acyl indoles and 2,7-diacyl indoles through direct C-H functionalization using Pd-catalyst from 1-(pyrimidin-2-yl)-1H-indoles and aldehydes. Easily removal of pyrimidine directing group using EtONa in DMSO provides C2-acyl indoles.

Introduction

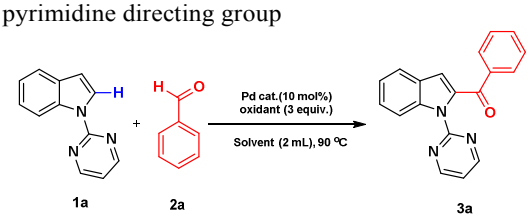
Transformation of unactivated C(sp^2)-H bonds to C(sp^2)-C and C(sp^2)-hetero atom bond is one the most important chemical transformations in synthetic chemistry.[1] Transition metal catalysts such as Rh, Ru, Pd, Cu, Fe, etc. play vital role in C-H bond functionalization reactions. Particularly, Pd compounds occupy central role as catalyst for C-H bond functionalization reactions.[2] The nature of the directing groups have play crucial role in the activation of unactivated C-H bonds.[3] Easily removable directing groups add more advantages to C-H bond functionalization reactions.[4] Herein, we report, direct C2-acylation and C2,C7-diacylation of *N*-pyrimidine substituted indoles to synthesize C2-acyl and C2,C7-diacyl indoles using Pd-catalyst and aldehyde as acyl source (Scheme 1).



Scheme 1 Pd-catalyzed direct C2-acylation and C2,C7-diacylation of indoles using removable pyrimidine directing group

The direct C-H bond functionalization of indole was started with 1-(pyrimidin-2-yl)-1H-indole **1a**. The initial reaction was carried out with 10 mol% of $Pd(OAc)_2$ in chlorobenzene at 90 °C using benzaldehyde **2a** as acyl source in the presence of *tert*-butyl hydrogen peroxide (TBHP) oxidant.[5] The pyrimidine group directed the acyl group to the less reactive C2 position of indole ring yielding 43% of expected selective C2-acylated product **3a** (Table 1, entry 1). In this reaction, neither C3-acylation nor C7-acylation product was observed. To increase the efficiency of this pyrimidine directed C2-acylation reaction, several Pd-salts were screened and among them $PdCl_2$ provided a maximum of 70% isolated yield of **3a** (entry 2).

Table 1 Optimization for Pd-catalyzed C2-acylation of indole using pyrimidine directing group

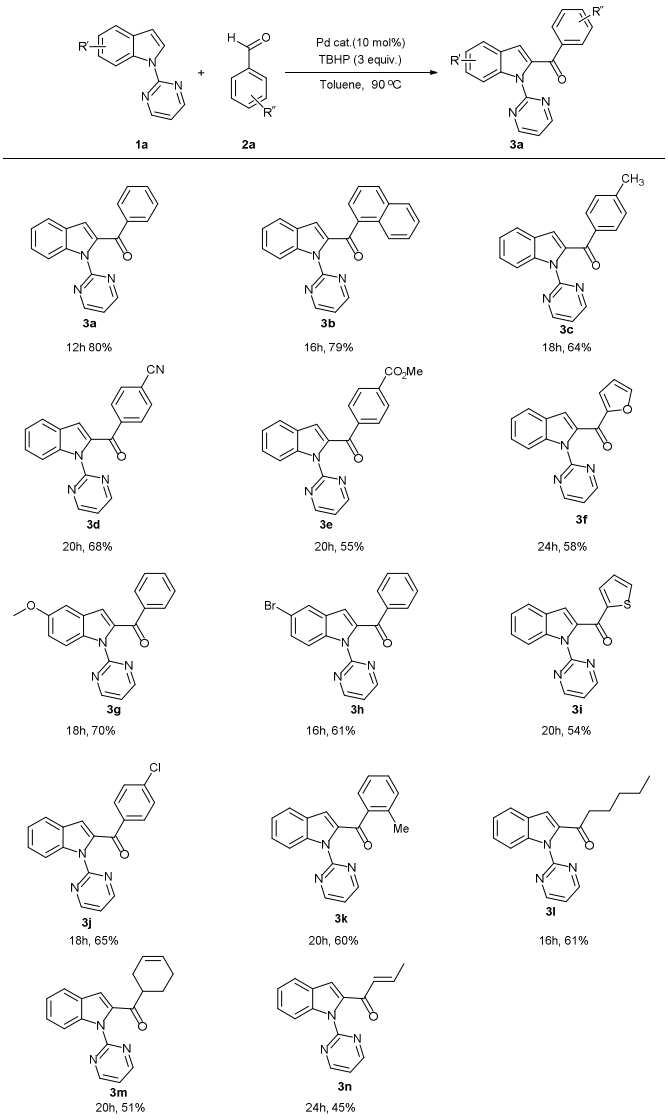


1a 2a 3a

Entry	Pd salt	Oxidant	Solvent	Time (h)	Yield (%)[b]
1	$Pd(OAc)_2$	TBHP	PhCl	24	43
2	$PdCl_2$	TBHP	PhCl	12	70
3	$Pd(CH_3CN)_2Cl_2$	TBHP	PhCl	24	47
4	$Pd(PPh_3)_2Cl_2$	TBHP	PhCl	24	20
5	$Pd(TFA)_2$	TBHP	PhCl	24	55
6	$Pd_2(dba)_3$	TBHP	PhCl	24	51
7	$PdCl_2$	DTBP	PhCl	36	40
8	$PdCl_2$	TBPB	PhCl	36	22
9	$PdCl_2$	H_2O_2	PhCl	36	20
10	$PdCl_2$	O_2	PhCl	36	14
11	$PdCl_2$	$K_2S_2O_8$	PhCl	36	17
12	$PdCl_2$	TBHP	THF	26	21
13	$PdCl_2$	TBHP	DMF	36	<5
14	$PdCl_2$	TBHP	Benzene	15	62
15	$PdCl_2$	TBHP	Toluene	12	80
16	$PdCl_2$	TBHP	dioxane	24	44
17	$PdCl_2$	TBHP	DCE	24	60
18	$PdCl_2$	TBHP	Hexanes	24	26
19	$PdCl_2$	TBHP	Toluene	12	67[c]
20	-	TBHP	Toluene	25	00
21	$PdCl_2$	-	Toluene	26	00

[a] Reaction condition: **1a** (0.5 mmol), **2a** (0.75 mmol), and 70% of *aq.*TBHP. [b] Isolated yield. [c] TBHP (5.0 equiv).

Table 2 Pd-catalyzed direct C2-acylation of indoles using removable pyrimidine directing group[a]

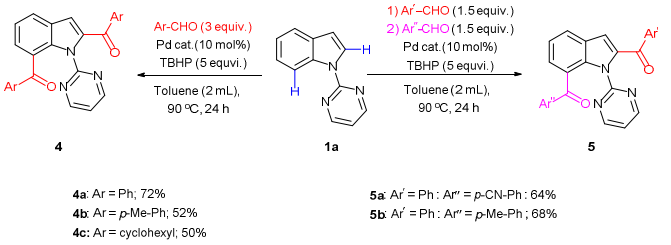


[a] Reaction condition: **1a** (0.5 mmol), **2a** (0.75 mmol), 70% *aq.* TBHP in toluene (2 mL), [b] Isolated yield.

Then the reaction was screened with several oxidants such as di-*tert*-butyl peroxide, *tert*-butyl peroxybenzoate (TBPB), H_2O_2 etc. and all of them gave inferior result compared with TBHP (entries 6-11). Solvent screening (entries 12-18) was fruitful and toluene provided a maximum of 80% isolated yield of **3a** (entry 15). Increasing the quantity of TBHP reduced the efficiency of the C-H activation reaction. And the reaction without Pd-catalyst or oxidant TBHP failed to yield any 2-acylation product (entries 20 and 21).

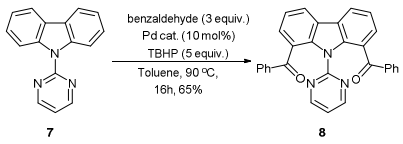
After successful optimizing the reaction conditions for the synthesis of C2-acylated indole, the substrate scope of this synthetic methodology was examined and the results are summarized in Table 2. Both electron-releasing (**3c**) and electron-withdrawing group (**3d** and **3e**) containing aromatic aldehydes yielded the corresponding 2-acylated products in moderate to good yields. Sterically hindered 1-naphthyl aldehyde also gave C2-acylated product in 79% yield (**3b**). Heteroaromatic aldehydes such as furan-2-carbaldehyde and thiophene-2-carbaldehyde also provided the corresponding C-H activation product in good yields (**3f** and **3i**). Electron-releasing and electron-withdrawing groups at 5th position of indole also yielded the C2-acylated product in moderate yield range (**3g** and **3h**). Sterically hindered *ortho*-substituted aldehyde, aliphatic aldehyde, cyclic and α-β unsaturated aldehydes were yielded the expected acylated product in good yield (**3k, 3l**, **3m** and **3n**). When a mixture of benzaldehyde and acetaldehyde were used for acylation, only C2-benzoylated indole was selectively obtained. In this reaction condition, acylation took place neither at C2 position nor at C7 position of indole ring.

Usage of excess (3 equiv.) aldehyde under same reaction conditions yielded symmetric C2,C7-diacylated product **4** through functionalization of C2 and C7 C-H bonds with good yields. Acylation of two different aldehydes (1.5 equiv. each) one after another aldehyde yielded unsymmetric diacylated products **5**. These results clearly shows that in indole molecule, pyrimidine group functionalize both C2 and C7 C-H bonds whereas C2 C-H bond functionalization is more facile than C7 C-H bond of indole moiety (Scheme 2).



Scheme 2 Double C-H functionalization using pyrimidine directing group

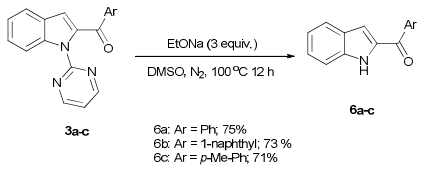
When pyrrole and carbazole were used instead of indole molecule, both of them gave mixture of mono and diacylated products as both the C2 and C5 C-H bonds of pyrrole and C2 and C8 C-H bonds of carbazole are identical for C-H functionalization. Using excess of benzaldehyde with *N*-pyrimidine protected carbazole, the reaction gave C2 and C8-dibenzoylated carbazole (**8**) with 65% isolated yield (Scheme 3).



Scheme 3 C-H functionalization of carbazole using pyrimidine directing group

The pyrimidine group in acylated indole molecule could be easily removed as shown in Scheme 3.[6] Reaction of **3a-c** with EtONa in DMSO yielded 2-acylated indole **6a-c**. In this C-H acylation, the palladium catalyst will coordinate with pyrimidine nitrogen before activating nearby C-H bond. In the presence of Pd catalyst and TBHP, acyl radical will be generated from aldehyde[7] which will be attached to Pd catalyst. Reductive elimination of palladium complex should yield C2-acylated indole. In the presence of excess aldehyde, the mono acylated indole will be acylated at C7 position. This result shows that functionalization at C2 position is easier that

functionalization of indole at C7 which is slightly far from indole nitrogen atom



Scheme 3 Synthesis of 2-acyl indole by removal of pyrimidine directing group

Conclusions

In conclusion, we have demonstrated an efficient methodology using Pd-catalyst for the synthesis of C2-acylated indole using pyrimidine as directing group. Usage of excess aldehyde provides C2, C7-diacylated indole through double C-H functionalization reaction. Easily removal of pyrimidine directing group using EtONa in DMSO yields C2-acyl indoles.

Typical Experimental procedure

General Considerations

All the reactions were carried out in reaction tubes. All the solvents were obtained from Merck or RANKEM chemicals. Reactions were monitored by Thin-layer Chromatography (TLC) using Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching using appropriate mixture of ethyl acetate and hexanes. $PdCl_2$, TBHP were purchased from Sigma Aldrich chemicals. Benzaldehyde was distilled before use. Other aldehydes were used as received. All the 2-pyrimidine indoles were prepared according to the literature procedure.[8] Silica gel (particle size 100-200 mesh) was purchased from SRL India and used for column chromatography using hexanes and ethyl acetate mixtures as eluent. ^1H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument. ^1H NMR spectra were reported relative to residual $CHCl_3$ (δ 7.26 ppm) or DMSO-d_6 (δ 2.50 ppm). ^{13}C NMR were reported relative to $CDCl_3$ (δ 77.16 ppm) or DMSO-d_6 (δ 39.52 ppm). FT-IR spectra were recorded on a JASCO spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were recorded on Q-Tof Micro mass spectrometer.

Typical Experimental procedure for C2-acylation

Indole (0.5 mmol, 97.6 mg), $PdCl_2$ (0.05 mmol, 8.9 mg), benzaldehyde (0.75 mmol, 76 μL), TBHP (1.5 mmol, 193 μL, 70% *aq*.) and toluene (2 mL) were taken in a reaction tube. The reaction mixture was heated at 90 °C. The progress of the reaction was monitored by TLC. Upon disappearance of indole, the reaction mixture was brought to room temperature. The reaction mixture was dissolved in ethyl acetate (30 mL), and washed with saturated solution of sodium bicarbonate (2×10 mL). The combined organic layers were dried with Na_2SO_4. The organic solvent was evaporated under reduced pressure and the resulting crude product was purified by silica gel column chromatography (hexanes/ethyl acetate) to give the desired acylation product. The product was confirmed by ^1H and ^{13}C NMR, FT-IR and HRMS spectroscopic analysis.

Typical Experimental procedure for C2, C7-acylation

Indole (0.5 mmol, 97.6 mg), $PdCl_2$ (0.05 mmol, 8.9 mg), benzaldehyde (3 equiv.), TBHP (2.5 mmol, 321 µL, 70% aquiv.) and toluene (2 mL) were taken in a reaction tube. The reaction mixture was heated at 90 °C. The progress of the reaction was monitored by TLC. Upon disappearance of indole, the reaction mixture was brought to room temperature. The reaction mixture was dissolved in ethyl acetate (30 mL), and washed with saturated solution of sodium bicarbonate (2×10 mL). The combined organic layers were dried with Na_2SO_4. The organic solvent was evaporated under reduced pressure and the resulting crude product was purified by silica gel column chromatography (hexanes/ethyl acetate) to give the desired acylation product. The product was confirmed by ^1H and ^{13}C NMR, FT-IR and HRMS spectroscopic analysis

Typical Experimental procedure for unsymmetrical acylation

Monosubstituted indole **3a** (0.33 mmol, 100 mg), $PdCl_2$ (0.033 mmol, 5.9 mg), aldehyde (Ar"-CHO) (1.5 equiv.), TBHP (0.99 mmol, 127 µL, 70% *aq*.) and toluene (2 mL) were taken in a reaction tube. The reaction mixture was heated at 90 °C. The progress of the reaction was monitored by TLC. Upon disappearance of indole **3a**, the reaction mixture was brought to room temperature. The reaction mixture was dissolved in ethyl acetate (30 mL), and washed with saturated solution of sodium bicarbonate (2×10 mL). The combined organic layers were dried with Na_2SO_4. The organic solvent was evaporated under reduced pressure and the resulting crude product was purified by silica gel column chromatography (hexanes/ethyl acetate) to give the desired acylation product. The product was confirmed by ^1H and ^{13}C NMR, FT-IR and HRMS spectroscopic analysis

Typical Experimental procedure for removal of pyrimidine directing group

Under N_2 atmosphere, monoacylated indole (0.41 mmol 124 mg) and sodium ethoxide (3.0 equiv.) were dissolved in DMSO (5 mL) at room temperature. Then the reaction mixture was heated upto 100 °C for 12 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were dried with Na_2SO_4. The organic solvent was evaporated under reduced pressure and the resulting crude product was purified by silica gel column

chromatography (hexanes/ethyl acetate) to give the desired acylation product. The product was confirmed by ^{1}H and ^{13}C NMR, FT-IR and HRMS spectroscopic analysis.

Phenyl(1-(pyrimidin-2-yl)-1H-indol-2-yl)methanone 3a:
Yield 80%; colorless solid; mp = 121-123 °C [122-124 °C][9a] ; R_f = 0.23 (hexanes:ethyl acetate (8:2); IR (KBr) 3408, 2327, 1655, 1570, 1523, 1426, 1277, 748, 717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (m, 1H), 7.15 (s, 1H), 7.28-7.36 (m, 1H) 7. 46 (m, 3H), 7.53-7.63 (m, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 7.6 Hz, 2H), 8.43 (d, *J* = 8.4, 1H), 8.65 (d, *J* = 4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.4, 115.5, 117.4, 122.6, 122.9, 126.6, 128.1, 128.4, 129.6, 132.8, 137.3, 138.1, 138.4, 157.4, 158.0, 187.7; HRMS (ESI) calcd for $C_{19}H_{13}N_3O$ $[M+H]^+$ 300.1137; found 300.1136.

Naphthalen-1-yl(1-(pyrimidin-2-yl)-1H-indol-2-yl)methanone 3b:
Yield 79%; colorless solid; mp = 136-138 °C [136-138 °C][9a]; R_f = 0.25 (hexanes:ethyl acetate (8:2); IR (KBr) 3048, 1653, 1573, 1449, 813, 777, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (t, *J* = 4.8 Hz, 1H), 7.16 (s, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 8.4 Hz, 1H), 7.51-7.56 (m, 1H), 7.57-7.64 (m, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 8.38 (d, *J* = 8.4 Hz), 8.53 (d, *J* = 4.8 Hz, 2H), 8.72 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.4, 116.3, 117.4, 122.8, 123.0, 124.3, 126.2, 126.5, 126.8, 127.7, 128.1, 128.3, 129.1, 131.2, 132.4, 133.8, 136.2, 138.6, 139.1, 157.5, 158.0, 189.0; HRMS (ESI) calcd for $C_{23}H_{15}N_3O$ $[M+H]^+$ 350.1288; found 350.1281.

(1-(Pyrimidin-2-yl)-1H-indol-2-yl)(p-tolyl)methanone 3c:
Yield 64%; colorless solid; mp = 128-130 °C [121-123 °C][9a]; R_f = 0.3 (hexanes:ethyl acetate (8:2); IR (KBr) 2924, 2856, 1643, 1570, 1434, 1282, 958, 826, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 7.04 (t, *J* = 5.2 Hz, 1H),7.09 (s, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.40-7.46 (m, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 8.40 (d, *J* = 8.4 Hz, 1H), 8.62 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 114.4, 115.0, 117.4, 122.5, 122.9, 126.4, 128.2, 129.2, 129.9, 135.6, 137.6, 138.4, 143.6, 157.5, 158.1, 187.5; HRMS (ESI) calcd for $C_{20}H_{15}N_3O$ $[M+H]^+$ 314.1281; found 314.1288.

4-(1-(Pyrimidin-2-yl)-1H-indole-2-carbonyl)benzonitrile 3d:
Yield 68%; white solid; mp = 150-153 °C; R_f = 0.26 (hexanes:ethyl acetate 7:3); IR (KBr) 3122, 2226, 1646, 1564, 1434, 1208, 7601 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, *J* = 4.4 Hz, 1H), 7.20 (s, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.44-7.52 (m, 1H), 7.68-7.76 (m, 3H), 8.01 (d, *J* = 8.4 Hz, 2H), 8.45 (d, *J* = 8.4 Hz, 1H), 8.61 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.7, 115.8, 116.1, 117.6, 118.2, 122.8, 123.3, 127.2, 128.1, 129.7, 132.3, 136.4, 138.5, 141.7, 157.2, 158.1, 186.0; HRMS (ESI) calcd for $C_{20}H_{12}N_4O$ $[M+H]^+$ 325.1089; found 325.1100.

Methyl 4-(1-(pyrimidin-2-yl)-1H-indole-2-carbonyl)benzoate 3e:
Yield 55%; colorless solid; mp = 134-136 °C; R_f = 0.22 (hexanes:ethyl acetate (8:2); IR (KBr) 2938, 1723, 1653, 1569, 1438, 1287, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 7.04 (t, *J* = 4.8 Hz, 1H), 7.16 (s, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 2H), 8.08 (d, *J* = 8.4 Hz, 2H), 8.43 (d, *J* = 8.4 Hz, 1H), 8.60 (d, *J* = 4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.6, 114.6, 115.8, 117.5, 122.7, 123.1, 126.9, 128.1, 129.3, 129.7, 133.5, 136.9, 138.4, 141.7, 157.2, 158.1, 166.5, 187.0; HRMS (ESI) calcd for $C_{21}H_{16}N_3O_3$ $[M+H]^+$ 358.1192; found 358.1184.

Furan-2-yl(1-(pyrimidin-2-yl)-1H-indol-2-yl)methanone 3f:
Yield 58%; Light yellow solid; mp = 120-122 °C [122-124 °C][9a]; R_f = 0.26 (hexanes:ethyl acetate 7:3); IR (KBr) 2926, 1640, a1568, 1468, 1292, 827, 793, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (d, *J* = 1.6 Hz, 1H), δ 7.03 (t, *J* = 4.8 Hz, 1H), δ 7.16-7.25 (m, 2H), δ 7.29 (s, 1H), δ 7.36 (t, *J* = 7.6 Hz, 1H), δ 7.55 (s, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), δ 8.27 (d, *J* = 8.4 Hz, 1H), δ 8.61 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.4, 114.2, 115.4, 117.6, 119.5, 122.7, 122.9, 126.8, 128.0, 136.2, 138.7, 147.0, 152.7, 157.5, 158.2, 174.4; HRMS (ESI) calcd for $C_{17}H_{12}N_3O_2$ $[M+H]^+$ 290.0930; found 290.0933.

(5-Methoxy-1-(pyrimidin-2-yl)-1H-indol-2-yl)(phenyl)methanone 3g:
Yield 70%; colorless solid; mp = 129-131 °C [134-135 °C][9a]; R_f = 0.20 (hexanes-ethyl acetate 8:2); IR (KBr) 2987, 2361, 1657, 1607, 1440, 1234, 804, 706 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 7.02 (t, *J* = 4.8 Hz, 1H), 7.05 (d, *J* = 0.4 Hz, 1H), 7.08 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 7.39-7.46 (m, 1H), 7.50-7.56 (m, 1H), 7.92-7.98 (m, 2H), 8.34 (d, *J* = 9.2 Hz, 1H), 8.59 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 103.6, 115.1, 115.5, 116.6, 117.3, 128.4, 128.8, 129.6, 132.8, 133.3, 137.7, 138.2, 156.1, 157.3, 158.0, 187.8; HRMS (ESI) calcd for $C_{20}H_{16}N_3O_2$ $[M+H]^+$ 330.1243; found 330.1230.

(5-Bromo-1-(pyrimidin-2-yl)-1H-indol-2-yl)(phenyl)methanone 3h:
Yield 61%; light yellow solid; mp = 116-118 °C [120-122 °C][9a]; R_f = 0.25 (hexanes:ethyl acetate); IR (KBr) 2922, 1667, 1572, 1443, 800, 713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 1H), 7.04 (t, *J* = 8.4 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.50 (dd, *J* = 9.2 , 2.0 Hz, 1H), 7.52-757 (m, 1H), 7.81 (d, *J* = 1.6 Hz, 1H), 7.91- 7.98 (m, 2H), 8.32 (d, *J* = 9.2 Hz, 1H), 8.59 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.7, 116.0, 116.1, 117.7, 124.8, 128.5, 129.2, 129.5, 129.8, 133.0, 136.7, 137.7, 138.1, 156.9, 158.1, 187.5; HRMS (ESI) calcd for $C_{19}H_{13}N_3OBr$ $[M+H]^+$ 378.0242; found 378.0229.

(1-(Pyrimidin-2-yl)-1H-indol-2-yl)(thiophen-2-yl)methanone 3i:
Yield 54%; colorless solid; mp = 144-146 °C [136-138 °C][9a]; R_f = 0.20 (hexanes:ethyl acetate (8:2); IR (KBr) 3071, 1624, 1570, 1521, 1425, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00-7.04 (m, 1H), 7.05-7.09 (m, 1H), 7.17-7.25 (m, 2H), 7.33-7.39 (m, 1H), 7.60-7.66 (m, 2H), 7.75 (dd, *J* = 4, 1.2 Hz, 1H), 8.29 (dd, *J* = 8.4, 0.4 Hz, 1H), 8.61 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 113.7, 116.2, 116.3, 117.8, 124.9, 128.9, 129.4, 129.8, 130.9, 136.2, 136.7, 137.7, 139.5, 157.0, 158.2, 186.4; HRMS (ESI) calcd for $C_{17}H_{12}N_3O$ $[M+H]^+$ 306.0701; found 306.0711.

(4-chlorophenyl)(1-(pyrimidin-2-yl)-1H-indol-2-yl)methanone 3j:

Yield 54%; colorless solid; mp = 144-146 °C [136-138 °C][9a]; R_f = 0.20 (hexanes:ethyl acetate (8:2); IR (KBr) 3072, 1623, 1569, 1520, 1426, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.00-7.04 (m, 1H), 7.05-7.08 (m, 1H), 7.17-7.24 (m, 2H), 7.34-7.39 (m, 1H), 7.60-7.65 (m, 2H), 7.75 (dd, *J* = 4, 1.2 Hz, 1H), 8.29 (dd, *J* = 8.4, 0.4 Hz, 1H), 8.61 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.7, 116.2, 116.3, 117.8, 124.9, 128.9, 129.4, 129.8, 130.9, 136.2, 136.7, 137.7, 139.5, 157.0, 158.2, 186.4; HRMS (ESI) calcd for $C_{17}H_{12}N_3O$ $[M+H]^+$ 306.0701; found 306.0711.

(1-(Pyrimidin-2-yl)-1H-indol-2-yl)(o-tolyl)methanone 3k:

Yield 60%; colorless solid; mp = 124-126 °C; R_f = 0.20 (hexanes:ethyl acetate (8:2); IR (KBr) 3050, 1653, 1540, 1520, 1450, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.59 (s, 3H), 7.11 (s, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.24-7.33 (m, 2H), 7.37 (td, *J* = 6, 1.2 Hz, 1H), 7.43-7.49 (m, 1H), 7.56-7.61 (m, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 8.32 (d, *J* = 8.4 Hz, 1H), 8.69 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 114.1, 116.3, 117.7, 122.8, 122.9, 125.2, 126.9, 128.0, 130.1, 131.2, 131.3, 138.3, 138.8, 138.9, 157.6, 158.1, 189.4; HRMS (ESI) calcd for $C_{20}H_{15}N_3O$ $[M+H]^+$ 314.1284; found 314.1288.

1-(1-(Pyrimidin-2-yl)-1H-indol-2-yl)hexan-1-one 3l:

Yield 61%; liquid; R_f = 0.34 (hexanes:ethyl acetate (8:2); IR (KBr) 3069, 1640, 1558, 1510, 1458, 860, 790, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, *J* = 7.2 Hz, 3H), 1.23-1.36 (m, 4H), 1.63-1.74 (m, 2H), 2.84 (t, *J* = 7.2 Hz, 2H), 7.12 (t, *J* = 4.8 Hz, 1H), 7.14-7.19 (m, 1H), 7.21 (s, 1H), 7.27-7.33 (m, 1H), 7.59-7.62 (m, 1H), 7.89-7.92 (m, 1H), 8.68 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 24.5, 31.6, 40.6, 113.3, 113.5, 118.3, 122.7, 122.8, 126.8, 127.6, 138.1, 139.3, 158.0, 158.1, 158.4, 194.1; HRMS (ESI) calcd for $C_{18}H_{19}N_3O$ $[M+H]^+$ 294.1597; found 294.1601.

Cyclohex-3-en-1-yl(1-(pyrimidin-2-yl)-1H-indol-2-yl)methanone 3m:

Yield 51%; colourless solid; mp = 122-124 °C R_f = 0.23 (hexanes:ethyl acetate (8:2); IR (KBr) 3040, 1655, 1556, 1515, 1470, 1100, 840, 800, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.73-1.87 (m, 1H), 2.08-2.23 (m, 3H), 2.27-2.37 (m, 1H), 2.40-2.52 (m, 1H), 3.26-3.35 (m, 1H), 5.80 (s, 2H), 7.21 (t, *J* = 4.8 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.42 (td, *J* = 7.2, 1.2 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.80 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 25.9, 28.0, 44.8, 113.0, 113.8, 118.1, 122.7, 122.8, 125.9, 126.7, 126.7, 127.9, 137.7, 139.1, 158.0, 158.3, 197.3; HRMS (ESI) calcd for $C_{19}H_{17}N_3O$ $[M+H]^+$ 304.1450; found 304.1446

(*E*)-1-(1-(pyrimidin-2-yl)-1H-indol-2-yl)but-2-en-1-one 3n:

Yield 45%; light yellow solid; mp = 123-125 °C; R_f = 0.30 (hexanes:ethyl acetate (6:4); IR (KBr) 3100, 3020, 1665, 1585, 1520, 1426, 1010, 860, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.00 (d, *J* = 6.8 Hz, 3H), 6.71 (d, *J* = 15.6 Hz, 1H), 6.97-7.09 (m, 1H), 7.21 (t, *J* = 4.8 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.79 (d, *J* = 4.8 Hz, 2H) ; ^{13}C NMR 18.6, 113.6, 114.3, 118.1, 122.7, 126.7, 127.8, 130.3, 138.0, 139.2, 144.4, 157.9, 158.3, 184.1 ; HRMS (ESI) calcd for $C_{16}H_{13}N_3O$ $[M+H]^+$ 264.1137; found 264.1129

(1-(Pyrimidin-2-yl)-1H-indole-2,7-diyl)bis(phenylmethanone) 4a:

Yield 72%; light yellow solid; mp = 160-161 °C; R_f = 0.25 (hexanes:ethyl acetate 7:3); IR (KBr) 3042, 1645, 1562, 1443, 863, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (t, *J* = 4.8 Hz, 1H), 7.19 (s, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.37-7.40 (m, 2H), 7.41-7.44 (m, 2H), 7.45-7.48 (m, 2H), 7.49-7.53 (m, 1H), 7.54-7.59 (m, 1H), 7.78-7.82 (m, 2H), 7.86 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.98 (dd, *J* = 8.0, 1.2 Hz, 2H), 8.34 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.8, 118.9, 121.4, 125.6, 125.9, 127.8, 128.3, 128.5, 128.8, 129.9, 130.1, 132.8, 133.0, 135.2, 137.3, 137.7, 137.7, 157.6, 157.9, 187.1, 195.4; HRMS (ESI) calcd for $C_{26}H_{18}N_3O_2$ $[M+H]^+$ 404.1399; found 404.1392.

(1-(Pyrimidin-2-yl)-1H-indole-2,7-diyl)bis(p-tolylmethanone) 4b:

Yield 52%; white solid mp = 179-180 °C R_f = 0.26 (hexanes:ethyl acetate 7:3); IR (KBr) 3036, 1650, 1602, 1427, 1276, 1214, 749, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.36 (s, 3H), 2.36 (s, 3H), 6.91 (t, *J* = 4.8 Hz, 1H), 7.09 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.17-7.22 (m, 3H), 7.31 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.77 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 8.29 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 114.5, 118.9, 121.3, 125.4, 126.1, 127.6, 128.8, 129.1, 129.2, 130.2, 130.4, 135.1, 135.2, 137.4, 143.7, 143.9, 157.7, 157.9, 186.9, 195.3; HRMS (ESI) calcd for $C_{28}H_{22}N_3O_2$ $[M+H]^+$ 432.1712; found 432.1709.

(1-(pyrimidin-2-yl)-1H-indole-2,7-diyl)bis(cyclohexylmethanone) 4c:

Yield 50%; white solid; mp = 163-165 °C R_f = 0.26 (hexanes-ethyl acetate 7:3); IR (KBr) 3058, 1656, 1573, 1428, 1350, 1214, 1150, 835, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.3-1.24 (m, 3H), 1.25-1.45 (m, 4H), 1.47-1.60 (m, 4H), 1.69-1.90 (m, 5H), 1.96-2.12 (m, 5H), 2.68 (tt, *J* = 11.6, 3.6 Hz, 1H), 3.08 (tt, *J* = 11.2, 3.6 Hz, 1H), 7.19 (t, *J* = 4.8 Hz, 1H), 7.36-7.47 (m, 2H), 7.85-7.92 (m, 1H), 8.69 (d, *J* = 8.4, Hz) 8.74 (d, *J* = 4.8, Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 26.1, 26.2, 29.0, 29.1, 50.3, 51.6, 116.0, 118.0, 121.0, 121.3, 124.2, 125.5, 126.7, 135.9, 140.6, 156.9, 158.1, 201.9, 202.2; HRMS (ESI) calcd for $C_{18}H_{19}N_3O$ $[M+H]^+$ 294.1597; found 294.160.

4-(2-Benzoyl-1-(pyrimidin-2-yl)-1H-indole-7-carbonyl)benzonitrile 5a:

Yield 64%; white solid; mp = 190-191 °C R_f = 0.26 (hexanes-ethyl acetate 7:3); IR (KBr) 2924, 2231, 1656, 1573, 1428, 1255, 1214, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (t, *J* = 4.8 Hz, 1H), 7.21 (s, 1H), 7.29-7.37 (m, 2H), 7.45-7.51 (m, 2H), 7.60 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.70-7.76 (m, 2H), 7.89-7.95 (m, 3H), 7.96-8.01 (m, 2H), 8.35 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114. 8, 116.1, 118.2, 119.0, 121.7, 125.0, 126.3, 127.5, 128.6, 129.2, 129.9, 130.3, 132.3, 134.8, 137.6,

137.8, 141.1, 157.3, 157.8, 187.2, 193.6; HRMS (ESI) calcd for $C_{27}H_{17}N_4O_2$ $[M+H]^+$ 429.1352; found 429.1355.

(2-Benzoyl-1-(pyrimidin-2-yl)-1H-indol-7-yl)(p-tolyl)methanone 5b:

Yield 68%; light yellow solid; mp = 179-180 ^oC R_f = 0.26 (hexanes:ethyl acetate 7:3); IR (KBr) 2925, 1649, 1570, 1422, 1262, 747, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 6.92 (t, *J* = 4.8 Hz, 1H), 7.12 (s, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.17-7.23 (m, 1H), 7.32 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 6.8 Hz, 2H), 8.30 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 114.9, 119.0, 121.4, 125.5, 126.1, 127.8, 128.4, 128.5, 128.8, 129.1, 130.0, 130.2, 130.4, 133.1, 135.1, 135.3, 137.2, 137.8, 143.7, 157.7, 158.0, 187.1, 195.2; HRMS (ESI) calcd for $C_{27}H_{20}N_3O_2$ $[M+H]^+$ 418.1556; found 418.1572.

(9-(Pyrimidin-2-yl)-9H-carbazole-1,8-diyl)bis(phenylmethanone) 8:

Yield 62%; light yellow solid; mp = 160-162 ^oC; R_f = 0.28 (hexanes:ethyl acetate 7:3); IR (KBr) 3090, 1670, 1530, 1510 1434, 1208, 854, 800, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.72 (t, *J* = 5.2 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 4H), 7.42-7.49 (m, 4H), 7.50-7.52 (m, 2H), 7.83 (d, *J* = 7.2 Hz, 4H), 7.96 (d, *J* = 4.8 Hz, 2H), 8.27 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.0, 122.1, 122.2, 126.7, 127.6, 128.0, 128.3, 129.9, 134.5, 136.9, 137.9, 156.6, 156.8, 194.7; HRMS (ESI) calcd for $C_{30}H_{19}N_3O_2$ $[M+H]^+$ 454.1556; found 454.1551.

(1H-Indol-2-yl)(phenyl)methanone 6a:

Yield 75%; white solid; mp = 145-146 ^oC [149-150 ^oC][9b]; R_f = 0.26 (hexanes:ethyl acetate 9:1); IR (KBr) 3354, 1620, 1517, 1260, 1125, 736, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14-7.21 (m, 2H), 7.35-7.42 (m, 1H), 7.47-7.59 (m, 3H), 7.60-7.67 (m, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.98-8.1 (m, 2H), 9.56 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.4, 113.0, 121.2, 123.4, 126.7, 127.9, 128.6, 129.4, 132.5, 134.5, 137.7, 138.2,187.4; HRMS (ESI) calcd for $C_{15}H_{12}NO$ $[M+H]^+$ 222.0919; found 222.0917.

(1H-Indol-2-yl)(naphthalen-1-yl)methanone 6b:

Yield 73%; light yellow solid; mp = 144-145 ^oC [150-151 ^oC][9c]; R_f = 0.26 (hexanes:ethyl acetate 9:1); IR (KBr) 3327, 1614, 1520, 783, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.98 (dd, *J* = 2.0, 0.8 Hz, 1H), 7.13-7.19 (m, 1H), 7.35-7.42 (m, 1H), 7.52 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.54-7.60 (m, 3H), 7.66 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.90 (dd, *J* = 7.2, 1.2 Hz, 1H) 7.92-7.98 (m, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 8.28-8.34 (m, 1H), 9.75 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.5, 113.9, 121.2, 123.5, 124.5, 125.7, 126.7, 126.9, 127.5, 127.7, 127.9, 128.5, 131.0, 131.7, 134.0, 135.8, 136.2, 138.2, 189.0; HRMS (ESI) calcd for $C_{19}H_{14}NO$ $[M+H]^+$ 272.1075; found 272.1077.

(1H-Indol-2-yl)(p-tolyl)methanone 6c:

Yield 71%; light yellow solid; mp = 174-176 ^oC [187-188 ^oC][9d]; R_f = 0.26 (hexanes-ethyl acetate 9:1); IR (KBr) 3350, 1616, 1515, 1261, 825, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 7.14-7.20 (m, 2H), 7.32-7.41 (m, 3H), 7.50 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.94 (dd, *J* = 8.4, 1.6 Hz, 2H), 9.54 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 112.3, 112.5, 121.1, 123.3, 126.5, 127.9, 129.3, 134.7, 135.5, 137.6, 143.3, 187.1; HRMS (ESI) calcd for $C_{16}H_{14}NO$ $[M+H]^+$ 236.1075; found 236.1071.

Acknowledgement

We thank DST (Project No. SB/S1/OC-72/2013) and DST nano mission (SR/NM/NS-1034/2012(G) for financial support. G. K thanks for UGC, New Delhi for Senior Research fellowship.

Notes and references

[a] Department of Chemistry, Indian Institute of Technology Madras, Chennai, Tamil Nadu-600 036, India. E-mail: gsekar@iitm.ac.in, http://chem.iitm.ac.in/faculty/sekar/.

Electronic Supplementary Information (ESI) available: Copy of all the compounds ^1H and ^{13}C spectra See. DOI: 10.1039/c000000x/data

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Pd-Catalyzed direct C2-acylation and C2,C7-diacylation of indoles: Pyrimidine as easily removable C-H directing group

Govindharaj Kumar, and Govindasamy Sekar.*

Pyrimidine is successfully used as an easily removable $C_{(sp2)}$-H directing group for the synthesis of 2-acyl indoles using Pd-catalyst.