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Ru(II)-catalyzed C7-acyloxylation of indolines with carboxylic acids

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Ruthenium(II)-catalyzed site-selective C7-acyloxylation of indolines with carboxylic acids is presented. The substrate scope and functional group tolerance are the important practical features. The kinetic isotope studies suggests that C-H bond activation may be the rate-determining step.

Introduction

Transition-metal-catalyzed chelation-guided site-selective C-H functionalization[1] has appeared as a prospective synthetic tool for the regioselective formation of carbon-heteroatom bonds.[2] In this context, direct C-H oxygenations are focused on site-selective C-O bond construction, because of the prevalence of C-O bonds in pharmaceuticals, agrochemicals and material science. Due to the biological prominence of the indole moiety, functionalization of its core has attracted considerable attention (Figure 1).[3] Several efforts have thus been made for the functionalization of indoles.[4] The C7 functionalization on indole scaffolds has thus far proven elusive, while it can be assembled by incorporating directing group on the N-atom of indoline, followed by C-H functionalization and late-stage oxidation.[5-7] In 2004, Sanford and co-workers reported a Pd-catalyzed directd acetoxylation of C-H bonds using $PhI(OAc)_2$ as an acylating agent,[8a] while Yu group showed a directed Pd-catalyzed acetoxylation of methyl C-H bond utilizing acetic anhydride.[8b] Subsequently, much attention has been devoted for the acyloxylation of C-H bonds using transition metal catlaysis.[8c-n] Among them, the direct C-H acyloxylation using RCOOH is attractive as they are atom economical. In continuation of our study on C-H acyloxylation,[9] we here report a Ru(II)-catalyzed C7- acyloxylation of indolines with carboxylic acids, which can be subsequently oxidized using DDQ to furnish C7-oxygenated indoles. The reaction of aryl, alkyl and α,β-unsaturated carboxylic acids can be accomplished with diverse functional groups in good yields.

Results and discussion

Initially, our optimization studies commenced by employing N-pyrimidyl indoline **1a** with benzoic acid **2a** as the model substrates using Ru(II) with different additives, oxidants and solvents at varied temperature (Table 1). To our delight, the C7 oxygenated indoline **3a** was produced in 7% yield utilizing 5 mol % $[Ru(p\text{-cymene})Cl_2]_2$ and 20 mol % KPF_6 as an additive in $(CH_2Cl)_2$ at 100 °C. The yield increased to 64% upon addition of 2 equiv Ag_2CO_3 as an oxidant, whereas $Cu(OAc)_2•H_2O$, $K_2S_2O_8$ and $Na_2S_2O_8$ gave inferior results (entries 2-5). Subsequent screening of the additives led to an enhancement in the yield to 77% using $AgSbF_6$, while the reaction with NaOAc gave 34% yield (entries 6-7). $(CH_2Cl)_2$ was found to be the solvent of choice, whereas toluene, DMSO and 1,4-dioxane produced <48% yield (entries 8-10). Altering the reaction temperature (80 °C and 120 °C) led to the drop the yield to 51% (entry 11-12). A control experiment confirmed that no desired C-H oxygenation was observed in the absence of the Ru-catalyst (entry 13). In addition, the effect of directing groups such as acetyl (**1A'**), pivalyl (**1B'**), *N,N*-dimethyl carbamoyl (**1C'**) and Boc (**1D'**) was investigated (Scheme 1). The substrates **1A-C'** underwent reaction to produce the acyloxylation products **3A'-C'** in 46-62% yields, whereas **1D'** was an unsuccessful substrate and **3D'** was not formed.

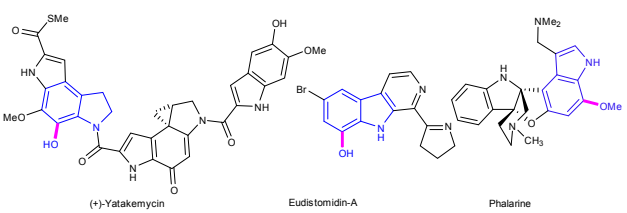

Figure 1 Some examples of bio-active C7-oxygenated indole derivatives.

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Electronic Supplementary Information (ESI) available: Supporting information for this article having experimental procedure, characterization data and NMR spectra (^1H and ^{13}C) of **3a-af**, **4**, and **5** is given via a link at the end of the document. See DOI: 10.1039/x0xx00000x

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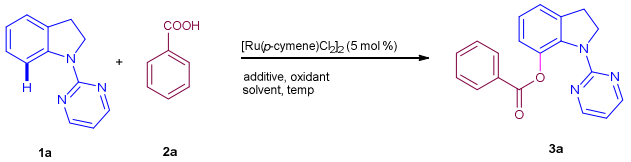
Having optimized the reaction condition, we explored the substrate scope utilizing diversely substituted carboxylic acids with indoline **1a** as a representative example (Scheme 2). The reaction of *ortho*-substituted benzoic acids such as 2-chloro **2b** and 2-iodo **2c** delivered **3b** and **3c** in 73 and 55% yields, respectively. Pleasingly, medicinally essential drug aspirin **2d** was effectively engaged to produce **3d** in 40% yield. Similarly, *meta*-substituted benzoic acids such as 3-chloro **2e**, 3-methyl **2f** and 3-methoxy **2g** underwent coupling to give **3e-g** in 68-73% yields. Similar results observed with substituted benzoic acids at the *para*-position, such as chloro **2h**, fluoro **2i**, methyl **2j** and nitro **2k** groups, affording **3h-k** in 74-81% yields. A strong electron withdrawing group, 4-CF_3 substituted benzoic acid **2l** was also operative and provided **3l** in 80% yield. Gratifyingly, the di-substituted benzoic acid bearing 3,4-dimethyl group **2m** and 1-naphthoic acid **2n** successfully reacted to afford **3m** and **3n** in 69 and 54% yields, respectively. In addition, heterocyclic carboxylic acid like 2-thienyl carboxylic acid **2o** was amenable, giving **3o** in 64% yield, while picolinic acid **2p** and isonicotinic acid **2q** showed no reaction, which may be due to chelation of nitrogen lone pair to the Ru-complex.

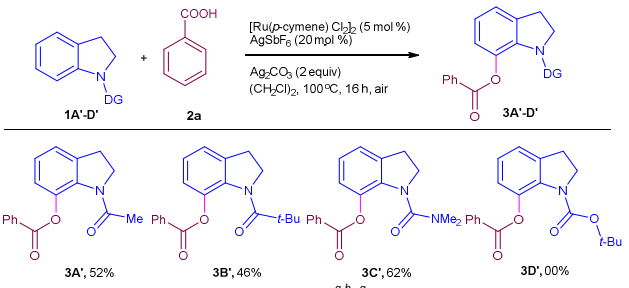
However, the coupling of *α,β*-unsaturated and aliphatic carboxylic acids can be readily accomplished (Scheme 3). For examples, crotonic **2r** and cinnamic **2s** acids reacted to deliver **3r** and **3s** in 65 and 67% yields, respectively, whereas ethanoic **2t**, pivalic **2u** and 1-adamentylcarboxylic **2v** acids underwent reaction to convey the C7-oxygenated indolines **3t-v** in 69-70% yields.

Table 1 Optimization of the reaction conditions[a]

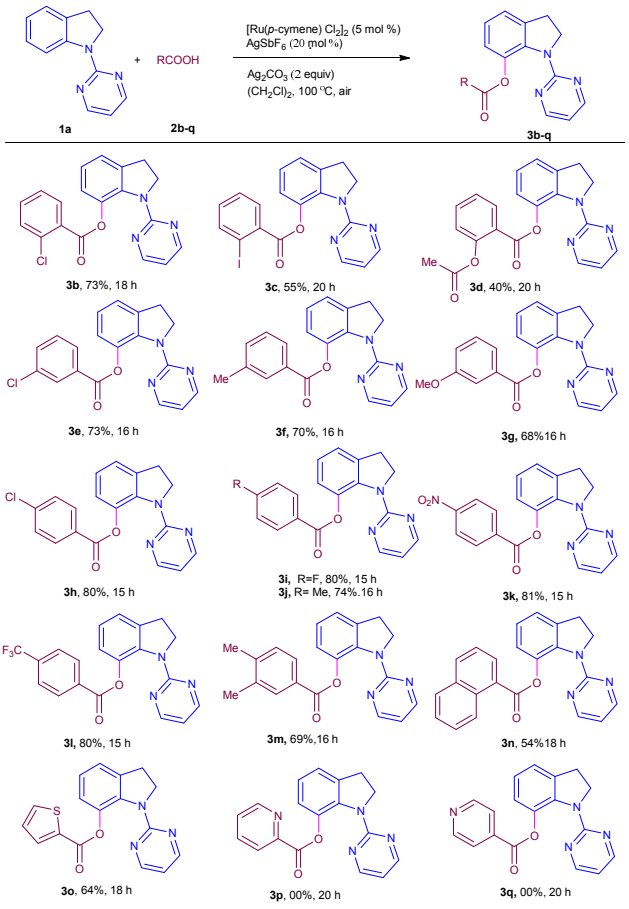


Entry	Additive	Oxidant	Solvent	Yield(%)[b]
1	KPF_6	-	$(CH_2Cl)_2$	7
2	KPF_6	Ag_2CO_3	$(CH_2Cl)_2$	64
3	KPF_6	$Cu(OAc)_2•H_2O$	$(CH_2Cl)_2$	trace
4	KPF_6	$K_2S_2O_8$	$(CH_2Cl)_2$	13
5	KPF_6	$Na_2S_2O_8$	$(CH_2Cl)_2$	n.d.
6	$AgSbF_6$	Ag_2CO_3	$(CH_2Cl)_2$	77
7	NaOAc	Ag_2CO_3	$(CH_2Cl)_2$	34
8	$AgSbF_6$	Ag_2CO_3	toluene	48
9	$AgSbF_6$	Ag_2CO_3	DMSO	9
10	$AgSbF_6$	Ag_2CO_3	1,4-dioxane	6
11	$AgSbF_6$	Ag_2CO_3	$(CH_2Cl)_2$	51[c]
12	$AgSbF_6$	Ag_2CO_3	$(CH_2Cl)_2$	74[d]
13[e]	$AgSbF_6$	Ag_2CO_3	$(CH_2Cl)_2$	n.d.

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), additive (20 mol %), oxidant (0.4 mmol), solvent (2 mL), 100 °C, 16 h. [b]Isolated yield. [c]Reaction at 80 °C. [d]Reaction at 120 °C. [e]Without [Ru] catalyst. n.d. = not detected.



Scheme 1 Screening of directing groups.[a,b] [a]Reaction conditions: **1A'-D'** (0.2 mmol), **2a** (0.4 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.4 mmol), $(CH_2Cl)_2$ (2 mL), 100 °C, 16 h. [b]Isolated yield.



Scheme 2 Substrate scope of carboxylic acids **2b-q** with indoline **1a.**[a,b] [a]Reaction conditions: **1a** (0.2 mmol), **2b-q** (0.4 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.4 mmol), $(CH_2Cl)_2$ (2 mL), 100 °C, 15-20 h. [b]Isolated yield.

The utility of the methodology was extended to the reaction of electronically varied indolines with benzoic acid **2a** as a standard substrate (Scheme 4). Diverse functionalities ranging from 2 to 6 positions on the indoline moiety reacted smoothly to deliver the target products. Indolines having 2-methyl **1b**, 3-methyl **1c** and 4-bromo **1d** substituents underwent reaction to furnish the target products **3w-y** in 69-75% yields. Moreover, 5-substituted indolines with bromo **1e**, fluoro **1f** and methoxy **1g** groups found to be well tolerated under identical

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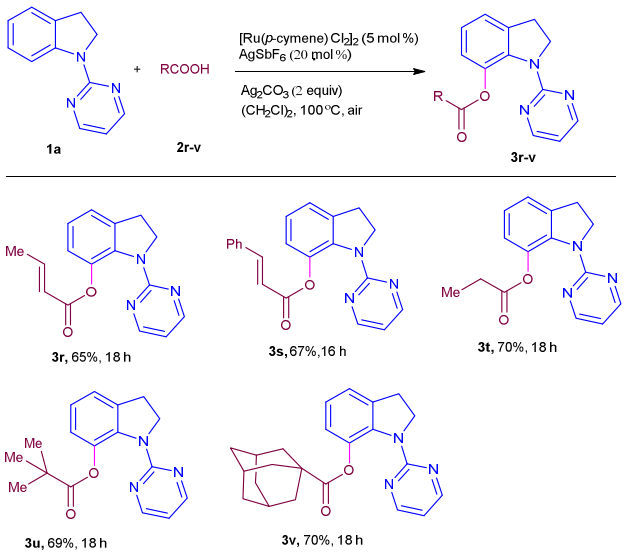
conditions, giving **3z-ab** in 69-77% yields. Similar results observed for the sterically demanding indoline substrate bearing 6-bromo **1h** and 6-chloro **1i** functionalities, affording **3ac** and **3ad** in 67 and 71% yields, respectively. Furthermore, carboxylation of a carbazole derivative **1j** was effective, furnishing a mixture of **3ae** (mono) and **3af** (di) in 22 and 51% yields, respectively.

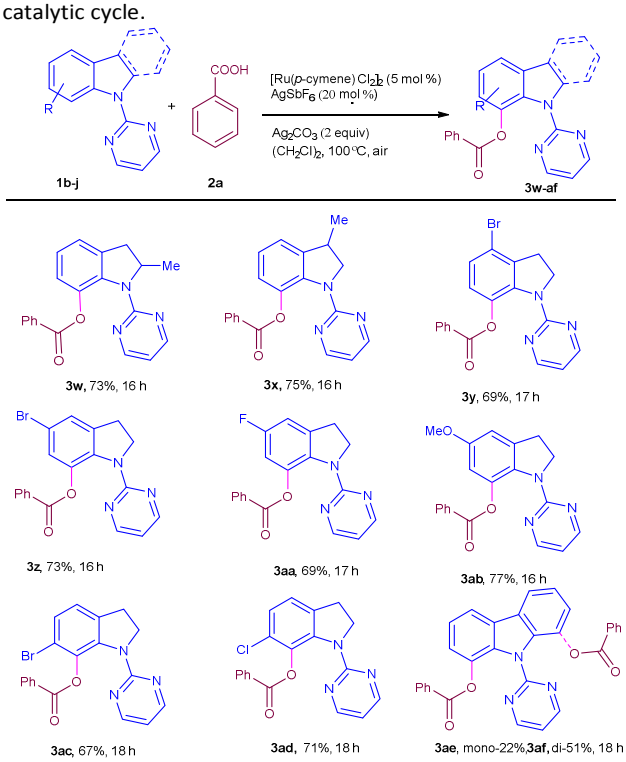
To reveal the scale-up, the reaction of indoline **1a** with carboxylic acid **2a** was investigated as the representative substrate (Scheme 5). The oxygenation readily occurred to give **3a** in 53% yield, which suggests that the reaction can be utilized for the gram scale synthesis.

To get insight in the reaction pathway, intermolecular competitive experiments have been performed employing electronically dissimilar benzoic acids **2j** and **2k** with indoline **1a** as a representative example. The results revealed that electron-deficient aromatic carboxylic acid reacts at a faster rate than the other one. This may be reflected in terms of lower pK_a value of *p*-NO_2-benzoic acid **2k** (Scheme 6a). In addition, the competition experiment between aryl and alkyl carboxylic acids **2j** and **2u** indicated that, aryl substrate facilitates the reaction to a greater extent, owing to the resonance stabilization of the corresponding conjugate base of the acid (Scheme 6b). Further,

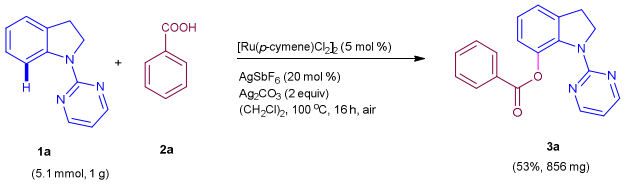


Scheme 3 Substrate scope of *α,β*-unsaturated and aliphatic carboxylic acids **2r-v** with indoline **1a.**[a,b] [a]Reaction conditions: **1a** (0.2 mmol), **2r-v** (0.4 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.4 mmol), $(CH_2Cl)_2$ (2 mL), 100 °C, 16-18 h. [b]Isolated yield.

a significant H/D exchange (40%) was witnessed at the C7 position of the parent indoline upon addition of D_2O as the co-solvent (Scheme 7a), which confides that a reversible C-H activation at C7 position of the indoline is involved by Ru-catalysis.[7b] Moreover, isotope experiment using **1a** and **1a-*d*** with **2a** gave k_H/k_D = 6.7 (Scheme 7b). In addition, parallel experiment of **1a** and *deuterio*-**1a** with **2a** under optimal conditions exhibited k_H/k_D = 2.65, which implies that the C–H bond cleavage might be the rate-determining step (see SI).[9,10c] Thus, the reaction of [Ru(*p*-cymene)Cl_2]$_2$ with silver salt may lead to the formation of the reactive Ru(II) carboxylate ***a*** (Scheme 8).[10] Co-ordination of the pyrimidyl-nitrogen with complex ***a***, may generate intermediate ***b*** along with elimination of RCOOH. The proximal C-H metalation may produce a six-membered ruthenacycle ***c***. Reductive elimination of **c** may provide the desired **3** and regenerate the catalytically active Ru species upon oxidation with Ag(I) to fulfil the catalytic cycle.



Scheme 4 Substrate scope of indolines **1b-j** with benzoic acid **2a.**[a,b] [a]Reaction conditions: **1b-j** (0.2 mmol), **2a** (0.4 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.4 mmol), $(CH_2Cl)_2$ (2 mL), 100 °C, 16-18 h. [b]Isolated yield.



Scheme 5 Scale-up synthesis.

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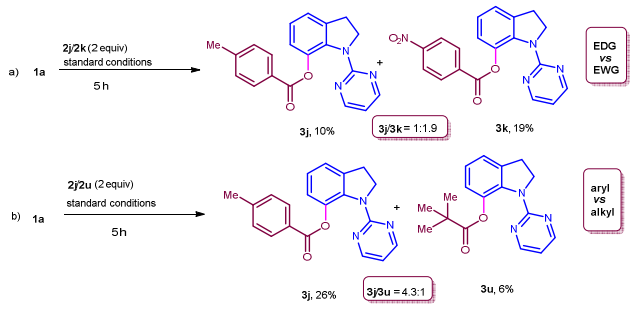
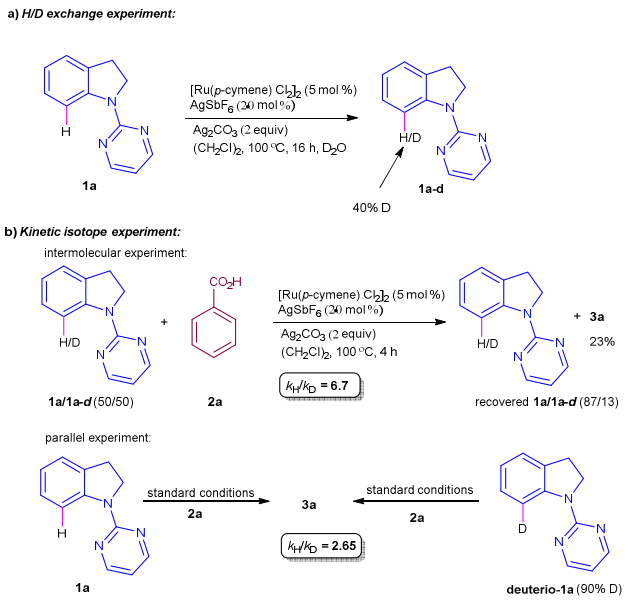
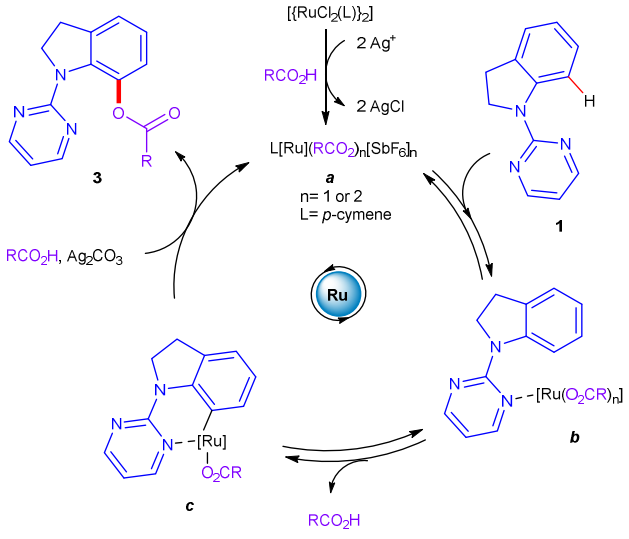


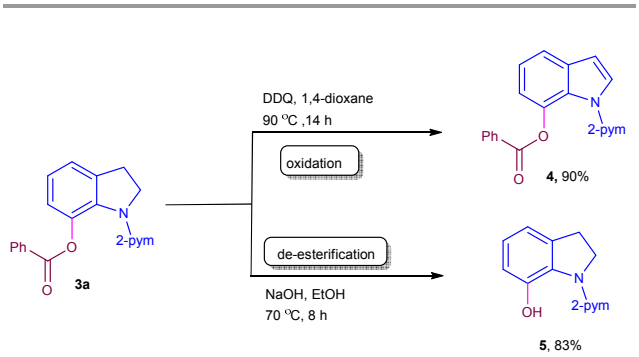
Scheme 6 Competitive experiments.



Scheme 7 Preliminary mechanistic investigations.



Scheme 8 Plausible catalytic cycle.



Scheme 9 Post-synthetic application of **3a**.

Finally, the oxidation of C7-oxygenated indoline was studied using **3a** as a representative example (Scheme 9).[9] The oxidation occurred to produce indole **4** in presence of DDQ in 90% yield.[9] In addition, the ester can be readily hydrolysed using base to afford 7-hydroxy indole scaffold **5** in high yield.

In summary, we have demonstrated a Ru(II)-catalyzed site-selective C7-oxygenation of indolines with carboxylic acids and subsequent oxidation to produce C7-oxygenated indoles. The reaction of aryl, alkyl and α,β-unsaturated carboxylic acids can be accomplished with functional group tolerance.

Experimental section

General information

2-Chloropyrimidine (95%), $[Ru(p\text{-cymene})Cl_2]_2$, $AgSbF_6$ (98%), KPF_6 (≥99%), Ag_2CO_3 (99%), $Cu(OAc)_2{\cdot}2H_2O$ and DDQ (98%) were purchased from Aldrich. $NaCNBH_3$ was procured from Spectrochem. $K_2S_2O_8$ and $Na_2S_2O_8$ were obtained from Molychem. N-Acetyl **1A'**, N-pivaloyl **1B'** and *N*-carbamoyl Indolines **1C'** were synthesized according to the literature.[5j] Merck silica gel G/GF 254 plates were utilized for analytical TLC. Rankem silica gel (100-200 mesh) was employed for column chromatography. DRX-400 Varian, and Bruker Avance III 600 and 400 spectrometers were used for recording NMR (^1H and ^{13}C) spectra utilizing $CDCl_3$ as solvent and TMS as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in ppm and in Hz, respectively, and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, and br s = broad singlet. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. FT-IR spectra were collected on PerkinElmer IR spectrometer. Q-Tof ESI-MS instrument (model HAB 273) was used mass spectra.

General procedure for the preparation of *N*-pyrimidyl indolines 1.[7] Indole (5.0 mmol) and $NaCNBH_3$ (25.0 mmol) were stirred in AcOH (25 mL) at room temperature. The progress of the reaction was monitored using TLC with ethyl acetate and hexane as an eluent. The resultant mixture was treated with water (15 mL) and neutralized using aq. NaOH. The solution was extracted with ethyl acetate (3 x 30 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate to give indoline. Indoline (1.0 mmol) was then stirred with 2-chloropyrimidine (1.2 mmol) at 100 °C

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in DMSO (3 mL). The reaction was monitored using TLC with a mixture of ethyl acetate and hexane. After completion, the reaction mixture was diluted with ethyl acetate (30 mL) and washed with brine (2 x 5 mL) and water (1 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and ethyl acetate as an eluent to afford 1-(pyrimidin-2-yl)indoline.

General procedure for Ru(II)-catalyzed C7-oxygenation of indolines. To a stirred solution of 1-(pyrimidin-2-yl)indoline (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %, 0.01 mmol, 6.1 mg), $AgSbF_6$ (20 mol%, 0.04 mmol, 13.7 mg) and Ag_2CO_3 (2 equiv, 0.4 mmol, 110.2 mg) in $(CH_2Cl)_2$ (2 mL) under air, carboxylic acid (0.4 mmol) was added. The resultant mixture was stirred at 100 °C and the progress of the reaction was monitored by TLC using a mixture of ethyl acetate and hexane. The reaction mixture was then diluted with dichloromethane (30 mL) and passed through a short pad of celite. Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford analytically pure substituted C7 oxygenated indolines.

Characterization Data

1-Acetylindolin-7-yl benzoate 3A'. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.18; colorless solid; yield 52% (29.2 mg); mp 120-121°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.2 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.13-7.11 (m, 2H), 7.07– 7.06 (m, 1H), 4.15 (t, *J* = 7.8 Hz, 2H), 3.13 (t, *J* = 7.8 Hz, 2H), 2.15 (s, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 139.6, 136.7, 134.3, 133.5, 130.4, 129.8, 128.7, 125.6, 122.7, 122.4, 50.8, 29.5, 23.5; FT-IR (KBr) 2963, 2924, 2892, 1736, 1674, 1607, 1474, 1454, 1395, 1265, 1231, 1065 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{16}NO_3$:282.1125, found: 282.1138.

1-Pivaloylindolin-7-yl benzoate 3B'. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.45; colorless solid; yield 46% (29.7 mg); mp 142-143°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 – 8.18 (m, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.13 – 7.08 (m, 3H), 4.18 (t, *J* = 7.8 Hz, 2H), 3.13 (t, *J* = 7.8 Hz, 2H), 1.18 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.0, 163.6, 140.5, 136.0, 135.9, 133.2, 130.4, 130.0, 128.4, 125.2, 122.3, 121.8, 51.1, 39.9, 31.1, 28.3; FT-IR (KBr) 2958, 2924, 2853, 1742, 1647, 1474, 1263, 1095 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{22}NO_3$:324.1594, found: 324.1603.

1-(Dimethylcarbamoyl)indolin-7-yl benzoate 3C'. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.14; yellow liquid; yield 62% (38.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 – 8.15 (m, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.08-7.05 (m, 2H), 7.05 – 6.97 (m, 1H), 3.91 (t, *J* = 7.8 Hz, 2H), 3.15 (t, *J* = 7.8 Hz, 2H), 2.74 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.1, 160.3, 138.8, 137.1, 135.2, 133.4, 130.3, 129.9, 128.5, 123.3 , 122.2, 121.9, 52.4, 37.6, 30.2; FT-IR (neat) 2959, 2924, 2853, 1738, 1643, 1478, 1385, 1262, 1090, 1065 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{18}H_{19}N_2O_3$:311.1390, found: 311.1396.

1-(Pyrimidin-2-yl)indolin-7-yl benzoate 3a. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.49; colorless solid; mp 124-125 °C; yield 77% (48.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 4.8 Hz, 2H), 8.01-8.00 (m, 2H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.14 (t, *J* = 8.4 Hz, 2H), 7.08-7.06 (m, 1H), 6.39 (t, *J* = 4.8 Hz, 1H), 4.41 (t, *J* = 7.8 Hz, 2H), 3.18 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 159.9, 157.5, 139.2, 136.9, 135.2, 133.2, 130.5, 130.0, 128.5, 123.8, 123.3, 122.2, 112.1, 52.4, 29.4; FT-IR (KBr) 2958, 2923, 2852, 1740, 1636, 1577, 1552, 1473, 1431, 1382, 1265,1240, 1191, 1174, 1085, 1067, 1024 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}N_3O_2$: 318.1237, found: 318.1257.

1-(Pyrimidin-2-yl)indolin-7-yl 2-chlorobenzoate 3b. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.47; colorless solid; yield 73% (51.2 mg); mp 115-116 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, *J* = 4.8 Hz, 2H), 7.85 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.42–7.39 (m, 1H), 7.24–7.23 (m, 1H), 7.16 – 7.14 (m, 2H), 7.09–7.06 (m, 1H), 6.50 (t, *J* = 4.8 Hz, 1H), 4.43 (t, *J* = 7.8 Hz, 2H), 3.17 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.9, 160.1, 157.6, 139.1, 137.0, 135.2, 135.0, 133.2, 132.5, 131.6, 129.0, 126.6, 123.9, 123.1, 122.4, 112.3, 52.4, 29.4; FT-IR (KBr) 2958, 2923, 2852, 1750, 1578,1553, 1471, 1433, 1383, 1281, 1237, 1215, 1190, 1110, 1037 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{15}ClN_3O_2$: 352.0847, found: 352.0852.

1-(Pyrimidin-2-yl)indolin-7-yl 2-iodobenzoate 3c. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.39; colorless solid; mp 148-149 °C; yield 55% (48.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, *J* = 4.8 Hz, 2H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.88 (dd, *J* = 7.8 , 1.8 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.16-7.12 (m, 3H), 7.09-7.06 (m, 1H), 6.50 (t, *J* = 4.8 Hz, 1H), 4.43 (t, *J* = 7.8 Hz, 2H), 3.17 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.5, 160.0, 157.7, 142.2, 139.1, 137.0, 135.1, 133.3, 133.2, 132.2, 128.0, 123.9, 123.1, 122.4, 112.3, 95.4, 52.4, 29.4; FT-IR (KBr) 2926, 2654, 1658, 1440, 1390, 1256, 1101 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{15}IN_3O_2$: 444.0203, found: 444.0203.

1-(Pyrimidin-2-yl)indolin-7-yl 2-acetoxybenzoate 3d. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.37; colorless liquid; yield 40% (30 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (d, *J* = 4.8 Hz, 2H), 7.95 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.56-7.53 (m, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 6.6 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.07-7.05 (m, 1H), 6.45 (t, *J* = 4.8 Hz, 1H), 4.40 (t, *J* = 7.8 Hz, 2H), 3.16 (t, *J* = 7.8 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 162.5, 160.0, 157.7, 151.6, 138.9, 137.0, 135.2, 134.4, 132.4, 126.1, 124.3, 123.8, 123.5, 122.9, 122.3, 112.4, 52.4, 29.4, 21.2; FT-IR (neat) 2924, 2853, 1745, 1639, 1578, 1554, 1471, 1433, 1240, 1191cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{18}N_3O_4$: 376.1292, found: 376.1307.

1-(Pyrimidin-2-yl)indolin-7-yl 3-chlorobenzoate 3e. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.40; colorless solid; yield 73% (51.2 mg); mp 117-118°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 4.8 Hz, 2H), 7.99 (t, *J* = 1.8 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 9.0 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.09 – 7.06 (m, 1H), 6.44 (t, *J* = 4.8 Hz, 1H), 4.42 (t, *J* = 7.8 Hz, 2H), 3.18 (t, *J* = 7.8 Hz, 2H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.7,

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159.9, 157.6, 138.9, 137.0, 135.1, 134.6, 133.3, 132.2, 130.1, 129.8, 128.1, 123.9, 123.1, 122.5, 112.2, 52.4, 29.4 ; FT-IR (KBr) 2961, 2924, 2853, 1732, 1636, 1577, 1554, 1466, 1417, 1254, 1109 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{15}ClN_3O_2$: 352.0847, found: 352.0856.

1-(Pyrimidin-2-yl)indolin-7-yl 3-methylbenzoate 3f. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 91-92°C; yield 70% (46.3 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J* = 4.8 Hz, 2H), 7.84 (s, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 8.4 Hz, 2H), 7.10–7.08 (m, 1H), 6.43 (t, *J* = 4.8 Hz, 1H), 4.44 (t, *J* = 7.8 Hz, 2H), 3.20 (t, *J* = 7.8 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.0, 159.9, 157.6, 139.2, 138.2, 136.8, 135.2, 134.0, 130.5, 130.3, 128.3, 127.2, 123.8, 123.3, 122.2, 112.1, 52.4, 29.4, 21.4; FT-IR (KBr) 2956, 2924, 2853, 1739, 1578, 1553, 1472, 1443, 1383, 1275, 1186, 1092, 1073 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}N_3O_2$: 332.1394, found: 332.1400.

1-(Pyrimidin-2-yl)indolin-7-yl 3-methoxybenzoate 3g. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.34; colorless solid; yield 68% (47.1 mg); mp 119-120 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, *J*=4.8 Hz, 2H), 7.60(d, *J* =7.2 Hz, 1H), 7.51 (s,1H), 7.29 (t, *J* =7.8 Hz, 1H), 7.16 – 7.12(m, 2H), 7.09 -7.06(m, 2H), 6.41 (t, *J* =4.8 Hz, 1H), 4.41 (t, *J* = 8.4 Hz, 2H), 3.79(s, 3H), 3.18 (t, *J* = 7.8Hz, 2H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.7, 159.6, 157.6, 139.1, 136.9, 135.2, 131.7, 129.5, 123.8, 123.3, 122.6, 122.3, 120.0, 114.1, 112.1, 55.6, 52.4, 29.4 ; FT-IR (KBr) 2924, 2853, 1737, 1639, 1576, 1551, 1466, 1424, 1277, 1107 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{18}N_3O_3$: 348.1343, found: 348.1357.

1-(Pyrimidin-2-yl)indolin-7-yl 4-chlorobenzoate 3h. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; colorless solid; mp 137-138 °C; yield 80% (56.1 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 4.8 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.16-7.15 (m, 1H), 7.13 (d, *J* = 7.2Hz, 1H), 7.08-7.06 (m, 1H), 6.43 (t, *J* = 4.8 Hz, 1H), 4.41 (t, *J* = 8.4 Hz, 2H), 3.17 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.1, 159.9, 157.6, 139.6, 139.0, 137.0, 135.1, 131.4, 128.93, 128.91, 123.9, 123.1, 122.4, 112.2, 52.4, 29.4; FT-IR (KBr) 2958, 2924, 2853, 1741, 1591, 1578, 1553, 1471, 1433, 1400, 1263, 1171, 1089, 1014 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}ClN_3O_2$: 352.0847, found: 352.0856.

1-(Pyrimidin-2-yl)indolin-7-yl 4-fluorobenzoate 3i. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.44; colorless solid, mp 151-152 °C; yield 80% (53.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 4.8 Hz, 2H), 8.04-8.01 (m, 2H), 7.16-7.12 (m, 2H), 7.08-7.05 (m, 3H), 6.42 (t, *J* = 4.8 Hz, 1H), 4.41 (t, *J* = 7.8 Hz, 2H), 3.17 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.7 (J_{C-F} = 252.76 Hz), 163.9, 159.9, 157.5, 139.0, 136.9, 135.1, 132.6 (J_{C-F} = 9.3 Hz), 126.7 (J_{C-F} = 3.15 Hz), 123.9, 123.2, 122.4, 115.7 (J_{C-F} = 21.75 Hz), 112.2, 52.4, 29.4; FT-IR (KBr) 2956, 2924, 2854, 1735, 1637, 1603, 1552, 1488, 1446, 1271, 1234, 1160, 1108, 991 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}FN_3O_2$: 336.1143, found: 336.1152.

1-(Pyrimidin-2-yl)indolin-7-yl 4-methylbenzoate 3j. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.46; colorless solid, mp 172-173 °C; yield 74% (48.9 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, *J* = 4.8 Hz, 2H), 7.92 (d, *J* = 7.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 2H), 7.10-7.07 (m, 1H), 6.43 (t, *J* = 4.8 Hz, 1H), 4.43 (t, *J* = 8.4 Hz, 2H), 3.20 (t, *J* = 8.4 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (150 MHz,) δ 165.0, 159.9, 157.5, 143.9, 139.2, 136.8, 135.2, 130.1, 129.2, 127.7, 123.8, 123.4, 122.2, 112.1, 52.4, 29.4, 21.9; FT-IR (KBr) 2923, 2853, 1730, 1610, 1576, 1549, 1485, 1471, 1445, 1433, 1270, 1140, 1173, 1085, 1018 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}N_3O_2$: 332.1394, found: 332.1398.

1-(Pyrimidin-2-yl)indolin-7-yl 4-nitrobenzoate 3k. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; yellow solid; mp 159-160 °C; yield 81% (58.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz, 2H), 8.20 (d, *J* = 8.4 Hz, 2H), 8.04 (d, *J* = 4.0 Hz, 2H), 7.20 – 7.10 (m, 3H), 6.42 (t, *J* = 4.0 Hz, 1H), 4.43 (t, *J* = 8.0 Hz, 2H), 3.19 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.0, 159.9, 157.6, 150.7, 138.8, 137.2, 135.9, 135.0, 131.1, 124.0, 123.7, 122.9, 122.8, 112.3, 52.4, 29.3; FT-IR (KBr) 2958, 2923, 2852, 1744, 1638, 1578, 1527, 1472, 1432, 1347, 1265, 1240, 1191, 1088, 1014 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}N_4O_4$: 363.1088, found: 363.1091.

1-(Pyrimidin-2-yl)indolin-7-yl 4-(trifluoromethyl)benzoate 3l. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.40; colorless solid, mp 126-127 °C; yield 80% (61.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.8 Hz, 2H), 8.05 (d, *J* = 4.8 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.10-7.07 (m, 1H), 6.42 (t, *J* = 4.8 Hz, 1H), 4.42 (t, *J* = 8.4 Hz, 2H), 3.18 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.7, 159.9, 157.6, 138.9, 137.1, 135.0, 134.7 (q, *J* = 32.7 Hz), 133.7, 130.4, 125.6 (q, *J* = 3.9 Hz), 124.0, 123.8 (q, *J* = 271.05 Hz), 123.0, 122.6, 112.2, 52.4, 29.4; FT-IR (KBr) 2956, 2921, 2850, 1743, 1638, 1579, 1471, 1434, 1263, 1130, 1109, 966 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{15}F_3N_3O_2$: 386.1111, found: 386.1118.

1-(Pyrimidin-2-yl)indolin-7-yl 3,4-dimethylbenzoate 3m. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.43; colorless solid, mp 135-136 °C; yield 69% (47.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 4.8 Hz, 2H), 7.76 (s, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 3H), 7.07-7.05 (m, 1H), 6.41 (t, *J* = 4.8 Hz, 1H), 4.41 (t, *J* = 7.8 Hz, 2H), 3.17 (t, *J* = 7.8 Hz, 2H), 2.29 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 160.0, 157.6, 142.5, 139.3, 136.8, 135.3, 131.1, 129.7, 128.0, 127.7, 123.8, 123.4, 122.1, 112.1, 52.4, 29.4, 20.2, 19.8; FT-IR (KBr) 2957, 2923, 2853, 1734, 1611, 1578, 1553, 1479, 1469, 1432, 1405, 1286, 1260, 1169, 1088 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{20}N_3O_2$: 346.1550, found: 346.1553.

1-(Pyrimidin-2-yl)indolin-7-yl 1-naphthoate 3n. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; colorless liquid; yield 54% (39.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.09 (d, *J* = 9.0 Hz, 1H), 8.20 (dd, *J* = 7.2, 1.2 Hz, 1H), 8.03 – 8.01 (m, 3H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.61 – 7.59 (m, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J*=7.8 Hz, 1H), 7.21- 7.17 (m, 2H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.29 (t, *J* = 4.8 Hz, 1H), 4.45 (t, *J* = 8.4 Hz, 2H), 3.20 (t, *J* = 7.8 Hz, 2H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.0, 160.0, 157.6, 139.2, 137.0, 135.3, 134.1, 133.9, 131.8, 131.4, 128.7, 128.2, 126.4, 126.2, 126.0, 124.5, 123.9, 123.4, 122.3, 112.2, 52.4, 29.4; FT-IR (neat) 2963, 2924, 2853, 1732, 1639, 1577, 1552,

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1471, 1432, 1236, 1186, 1120 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{18}N_3O_2$: 368.1394, found: 368.1408.

1-(Pyrimidin-2-yl)indolin-7-yl thiophene-2-carboxylate 3o. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.40; colorless solid, mp 102-103 °C; yield 64% (41.3 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 4.8 Hz, 2H), 7.80 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.53 (dd, *J* = 5.4, 1.8 Hz, 1H), 7.14 (t, J = 6.0 Hz, 2H), 7.07-7.04 (m, 2H), 6.45 (t, *J* = 4.8 Hz, 1H), 4.40 (t, *J* = 7.8 Hz, 2H), 3.17 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.3, 159.9, 157.5, 138.8, 136.9, 135.2, 134.1, 134.0, 132.9, 127.8, 123.8, 123.3, 122.4, 112.2, 52.3, 29.4; FT-IR (KBr) 2922, 2851, 1730, 1639, 1577, 1553, 1472, 1442, 1432, 1416, 1383, 1239, 1190, 1070, 1030 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{14}N_3O_2S$: 324.0801, found: 324.0801.

1-(Pyrimidin-2-yl)indolin-7-yl (*E*)-but-2-enoate 3r. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.28; colorless solid; yield 65% (37 mg); mp 112-113°C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.32 (d, *J* = 4.2 Hz, 2H), 7.11 – 7.09 (m, 1H), 7.04 – 6.97 (m, 3H), 6.64 (t, *J* = 4.8 Hz, 1H), 5.88 (dd, *J* = 15.6, 1.8 Hz, 1H), 4.38 (t, *J* = 7.8 Hz, 2H), 3.14 (t, *J* = 8.4 Hz, 2H), 1.86 (dd, *J* =7.2, 1.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 160.0, 157.7, 145.8, 139.1, 136.8, 135.1, 123.8, 123.1, 122.8, 122.0, 112.2, 52.3, 29.4, 18.2; FT-IR (KBr) 2961, 2924, 2854, 1733, 1653, 1577, 1554, 1467, 1102 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{16}N_3O_2$:282.1237, found: 282.1249.

1-(Pyrimidin-2-yl)indolin-7-yl cinnamate 3s. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.38; colorless solid; mp 101-102 °C; yield 67% (46 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.31 (d, *J* = 4.8 Hz, 2H), 7.73 (d, *J* = 15.6 Hz, 1H), 7.50-7.48 (m, 2H), 7.39-7.38 (m, 3H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.09-7.04 (m, 2H), 6.57 (t, *J* = 4.8 Hz, 1H), 6.48 (d, *J* = 16.2 Hz, 1H), 4.41 (t, *J* = 8.4 Hz, 2H), 3.16 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 160.0, 157.7, 145.6, 139.1, 136.9, 135.1, 134.4, 130.6, 129.1, 128.3, 123.8, 123.2, 122.2, 118.2, 112.3, 52.3, 29.4; FT-IR (KBr) 2956, 2923, 2852, 1731, 1637, 1577, 1552, 1472, 1442, 1383, 1328, 1309, 1237, 1191, 1138, 1065, 990 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{18}N_3O_2$: 344.1394, found: 344.1400.

1-(Pyrimidin-2-yl)indolin-7-yl propionate 3t. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.35; yellow liquid; yield 70% (37.6 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.39 (d, *J* = 4.8 Hz, 2H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.70 (t, *J* = 4.8 Hz, 1H), 4.39 (t, *J* = 7.8 Hz, 2H), 3.13 (t, *J* = 7.8 Hz, 2H), 2.37 (q, *J* = 7.2 Hz, 2H), 1.10 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.3, 160.2, 157.6, 139.3, 136.9, 135.1, 124.0, 122.9, 122.1, 112.4, 52.5, 29.5, 28.0, 9.0; FT-IR (neat) 2956, 2924, 2853, 1761, 1638, 1578, 1551, 1470, 1432, 1382, 1243, 1139, 1080 cm-1; HRMS (ESI) m/z [M+H]+ calcd for: $C_{15}H_{16}N_3O_2$: 270.1237, found: 270.1239.

1-(Pyrimidin-2-yl)indolin-7-yl pivalate 3u. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.35; colorless liquid; yield 69% (41 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.8 Hz, 2H), 7.10 (d, J = 7.2 Hz, 1H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.70 (t, *J* = 4.8 Hz, 1H), 4.38 (t, *J* = 7.8 Hz, 2H), 3.12 (t, *J* = 7.8 Hz, 2H), 1.12 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.2, 160.8, 157.9, 140.2, 136.8, 135.6, 124.3, 122.2, 122.0, 112.5, 52.9, 39.2, 29.8, 27.2; FT-IR (neat) 2959, 2924, 2853, 1750, 1592, 1577, 1552, 1472, 1400, 1382, 1243, 1120, 1030 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{20}N_3O_2$: 298.1550, found: 298.1559.

1-(Pyrimidin-2-yl)indolin-7-yl (3r,5r,7r)-adamantane-1-carboxylate 3v. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.34; yellow liquid; yield 70% (52.5 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.43 (d, *J* = 4.8 Hz, 2H), 7.09-7.08 (m, 1H), 7.02 (t, *J* = 8.4 Hz, 1H), 6.93 – 6.91 (m, 1H), 6.71 (t, *J* = 4.8 Hz, 1H), 4.38 (t, *J* = 8.4 Hz, 2H), 3.11 (t, *J* = 8.4 Hz, 2H), 1.94 – 1.91 (m, 4H), 1.795-1.791 (m, 5H), 1.72-1.62 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.2, 160.8, 157.9, 140.2, 136.7, 135.6, 124.2, 122.2, 121.8, 112.4, 52.9, 41.1, 38.8, 36.6, 29.8, 28.0; FT-IR (neat) 2920, 2852, 1747, 1578, 1552, 1479, 1433, 1382, 1211, 1179, 1103, 1065 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{26}N_3O_2$: 376.2020, found: 376.2029.

2-Methyl-1-(pyrimidin-2-yl)indolin-7-yl benzoate 3w. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.51; brown liquid; yield 73% (48.3 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 4.8 Hz, 2H), 8.02-8.01 (m, 2H), 7.54-7.52 (m, 1H), 7.40-7.38 (m, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.09-7.07 (m, 1H), 6.37 (t, *J* = 4.8 Hz, 1H), 4.96-4.93 (m, 1H), 3.51 (dd, *J* = 15.0, 8.4 Hz, 1H), 2.64 (d, *J* = 15.6 Hz, 1H), 1.47 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.7, 159.7, 157.6, 139.8, 135.8, 133.9, 133.1, 130.5, 130.1, 128.4, 123.9, 123.2, 122.7, 112.1, 60.0, 36.9, 21.2; FT-IR (neat) 2957, 2923, 2851, 1740, 1578, 1552, 1479, 1433, 1385, 1265, 1242, 1199, 1086, 1068, 1025 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}N_3O_2$: 332.1394, found: 332.1399.

3-Methyl-1-(pyrimidin-2-yl)indolin-7-yl benzoate 3x. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.51; yellow liquid; yield 75% (49.6 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.05-8.00 (m, 4H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.14-7.08 (m, 3H), 6.38 (t, *J* = 4.8 Hz, 1H), 4.60 (t, *J*= 9.6 Hz, 1H), 3.94-3.90 (m, 1H), 3.53-3.48 (m, 1H), 1.37 (d, *J* = 6.4 Hz, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.8, 159.9, 157.6, 142.0, 139.1, 134.8, 133.2, 130.5, 130.0, 128.4, 124.0, 123.4, 121.0, 112.0, 60.1, 36.0, 19.0.; FT-IR (neat) 2959, 2925, 2854, 1742, 1578, 1553, 1470, 1434, 1383, 1265, 1242, 1190, 1087, 1023 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}N_3O_2$: 332.1394, found: 332.1397.

4-Bromo-1-(pyrimidin-2-yl)indolin-7-yl benzoate 3y. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.49; colorless solid; mp 86-87 °C; yield 69% (54.5 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 4.8 Hz, 2H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.43 (t, *J* = 4.8 Hz, 1H), 4.42 (t, *J* = 8.4 Hz, 2H), 3.17 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 159.8, 157.6, 138.1, 136.9, 136.4, 133.4, 130.16, 130.10, 128.5, 126.4, 125.1, 116.0, 112.6, 51.7, 31.0; FT-IR (KBr) 2961, 2924, 2853, 1741, 1640, 1563, 1551, 1460, 1407, 1261, 1238, 1100, 1023 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}BrN_3O_2$: 396.0342, found: 396.0343.

5-Bromo-1-(pyrimidin-2-yl)indolin-7-yl benzoate 3z. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.44; yellow solid, mp 98-99 °C; yield 73% (57.6 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 4.8 Hz, 2H), 7.99-7.97 (m, 2H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.39 (t, J = 8.4 Hz, 2H), 7.30 (s, 1H), 7.27 (s,

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1H), 6.41 (t, *J* = 4.8 Hz, 1H), 4.41 (t, *J* = 7.8 Hz, 2H), 3.17 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 159.7, 157.6, 139.2, 138.5, 134.8, 133.4, 130.1, 129.9, 128.5, 126.3, 125.4, 115.1, 112.5, 52.4, 29.2; FT-IR (KBr) 2951, 2923, 2852, 1746, 1578, 1552, 1477, 1451, 1411, 1380, 1262, 1250, 1239, 1191, 1078, 996 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}BrN_3O_2$: 396.0342, found: 396.0344.

5-Fluoro-1-(pyrimidin-2-yl)indolin-7-yl benzoate 3aa. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.58; yellowish solid; mp 175-176 °C; yield 69% (46.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 4.8 Hz, 2H), 7.99-7.98 (m, 2H), 7.56-7.53 (m, 1H), 7.40-7.37 (m, 2H), 6.92-6.90 (m, 2H), 6.39 (t, *J* = 4.8 Hz, 1H), 4.43 (t, *J* = 8.4 Hz, 2H), 3.15 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 159.9, 159.8 ($J_{C\text{-}F}$ = 241.5 Hz), 157.6, 139.1($J_{C\text{-}F}$ =11.55 Hz), 138.0 ($J_{C\text{-}F}$ =9.45 Hz), 133.4, 131.7 ($J_{C\text{-}F}$ =2.7 Hz), 130.1, 130.0, 128.5, 112.2, 110.5 ($J_{C\text{-}F}$ =25.8 Hz), 110.0 ($J_{C\text{-}F}$ =23.7 Hz), 52.5, 29.7 ($J_{C\text{-}F}$ =2.1 Hz); FT-IR (KBr) 2956, 2924, 2853, 1736, 1596, 1580, 1552, 1490, 1467, 1424, 1386, 1255, 1124, 1083, 1026 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}FN_3O_2$: 336.1143, found: 336.1151.

5-Methoxy-1-(pyrimidin-2-yl)indolin-7-yl benzoate 3ab. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.44; yellow liquid; yield 77% (53.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 8.01 (m, 4H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 2H), 6.77 (s, 1H), 6.70-6.69 (m, 1H), 6.35 (t, *J* = 4.8 Hz, 1H), 4.40 (t, *J* = 8.0 Hz, 2H), 3.81 (s, 3H), 3.13 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 160.1, 157.6, 156.8, 139.4, 137.8, 133.2, 130.4, 130.1, 128.8, 128.5, 111.7, 109.7, 107.8, 56.1, 52.3, 29.8; FT-IR (neat) 2958, 2924, 2852, 1739, 1622, 1579, 1550, 1488, 1424, 1381, 1261, 1190, 1140, 1088, 1069, 1026 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}N_3O_3$: 348.1343, found: 348.1347.

6-Bromo-1-(pyrimidin-2-yl)indolin-7-yl benzoate 3ac. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.40; yellow liquid; yield 67% (53 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 – 8.06 (m, 4H), 7.57 – 7.54 (m, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.44 (t, *J* = 4.2 Hz, 1H), 4.40 (s, 2H), 3.12 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.3, 159.5, 157.5, 137.3, 136.7, 136.4, 133.4, 130.2, 129.9, 128.5, 127.6, 123.2, 117.1, 112.5, 52.9, 29.1; FT-IR (neat) 2923, 2852, 1744, 1576, 1553, 1438, 1381, 1260, 1221, 1108 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}BrN_3O_2$: 396.0342, found: 396.0361.

6-Chloro-1-(pyrimidin-2-yl)indolin-7-yl benzoate 3ad. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 129-130 °C; yield 71% (49.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.05 (m, 4H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 6.44 (t, *J* = 4.8 Hz, 1H), 4.41 (s, 2H), 3.13 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.6, 159.6, 157.5, 137.3, 135.8, 135.6, 133.4, 130.2, 129.9, 128.5, 127.9, 124.4, 122.6, 112.5, 53.0, 29.0; FT-IR (KBr) 2958, 2922, 2852, 1748, 1635, 1577, 1554, 1468, 1383, 1261, 1223, 1175, 1080, 1024 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}ClN_3O_2$: 352.0847, found: 352.0852.

9-(Pyrimidin-2-yl)-9H-carbazol-1-yl benzoate 3ae. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.44; colorless solid; yield 22% (16 mg); mp 150-151°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.44 (d, *J* = 4.8 Hz, 2H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 7.2 Hz, 1H), 8.03 (d, *J* = 7.2 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 2H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.46 -7.35 (m, 6H), 6.77 (t, *J* = 4.8 Hz, 1H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.3, 158.2, 140.9, 137.7, 133.6, 131.0, 130.0, 129.8, 128.9, 128.6, 127.2, 125.1, 122.5, 122.4, 121.6, 120.2, 117.8, 117.2, 112.9 ; FT-IR (KBr) 2963, 2924, 2852, 1729, 1637, 1566, 1452, 1413, 1211, 1090 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{16}N_3O_2$:366.1237, found: 366.1251.

9-(Pyrimidin-2-yl)-9H-carbazole-1,8-diyl dibenzoate 3af. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.24; colorless solid; yield 51% (49.4 mg); mp 240-241°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.99 (d, *J* = 4.8 Hz, 2H), 7.77 – 7.76 (m, 4H), 7.53 (t, *J* = 7.21 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 4H), 7.28 (d, *J* = 7.8, 2H), 6.32 (t, *J* = 4.8 Hz, 1H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.4, 159.2, 158.1, 136.5, 133.6, 132.9, 130.1, 129.2, 128.4, 127.3, 121.7, 121.3, 118.9, 118.3 ; FT-IR (KBr) 2924, 2853, 1748, 1632, 1583, 1566, 1450, 1432, 1408, 1260, 1213, 1174, 1062, 1051 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{30}H_{20}N_3O_4$:486.1448, found: 486.1458.

1-(Pyrimidin-2-yl)-1H-indol-7-yl benzoate 4. To a stirred solution of 1-(pyrimidin-2-yl)indolin-7-yl benzoate **3a** (0.1 mmol, 31.7 mg) in 1,4-dioxane, DDQ (0.2 mmol, 45.4 mg) was added at room temperature. The resultant solution was further stirred at 90 °C for 14 h. After completion, as indicated by TLC, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (15 mL). The mixture was successively washed with brine (2 x 5 mL) and water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford 1-(pyrimidin-2-yl)-1H-indol-7-yl benzoate **4** as a colorless liquid. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.50; colorless liquid; yield 84% (56.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, *J* = 4.8 Hz, 2H), 8.10 – 8.08 (m, 2H), 8.03 (d, *J* = 3.6 Hz, 1H), 7.62 – 7.59 (m, 1H), 7.57-7.55 (m, 1H), 7.47 – 7.45 (m, 2H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.16-7.15 (m, 1H), 6.76 – 6.73 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.2, 158.2, 157.4, 137.8, 134.9, 133.3, 130.5, 130.2, 129.5, 128.6, 127.0, 122.7, 119.2, 118.9, 116.7, 107.2; FT-IR (neat) 2923, 2852, 1738, 1637, 1572, 1482, 1421, 1357, 1264, 1217, 1093 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{14}N_3O_2$: 316.1081, found: 316.1097.

1-(Pyrimidin-2-yl)indolin-7-ol 5. 1-(Pyrimidin-2-yl)indolin-7-yl benzoate **3a** (0.1 mmol, 31.7 mg) and NaOH (40% solution, 2 mL) (2 mL) were stirred at 70 °C for 2 h in ethanol (4 mL). The resultant mixture was treated with water (2 mL) and the stirring was continued at 70 °C for 6 h. After completion, as indicated by TLC, the reaction mixture was neutralized using 1N HCL. Ethanol was removed on a rotary evaporator and aqueous solution was extracted with ethyl acetate (3 x 15 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford 1-(pyrimidin-2-yl)indolin-7-ol **5** as a yellow solid. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.55; yield 83% (42.6 mg); mp 98-

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99 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.0 (br s, 1H), 8.49-8.26 (m, 2H), 6.94 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.63 (t, *J* = 4.8 Hz, 1H), 4.26 (t, *J* = 8.4 Hz, 2H), 3.14 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.3, 157.4, 145.5, 135.2, 129.6, 125.4, 117.9, 116.1, 110.3, 49.7, 28.2; FT-IR (KBr) 3436, 2925, 2854, 1633, 1596, 1554, 1482, 1465, 1424 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{12}N_3O$: 214.0975, found: 214.0982 .

Competition experiment using acids 2j and 2k (Scheme 6a). 1-(Pyrimidin-2-yl)indoline **1a** (19.7 mg, 0.1 mmol), **2j** (13.6 mg, 0.1 mmol), **2k** (16.7 mg, 0.1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3.0 mg, 5.0 mol %), $AgSbF_6$ (7.0 mg, 20 mol %) and Ag_2CO_3 (55.2 mg, 0.2 mmol) in $(CH_2Cl)_2$ (1.0 mL) were subjected to the reaction conditions described in the general procedure (100 °C) for 5 h and **3j** and **3k** were formed in 10 and 19% yields, respectively.

Competition experiment using acids 2j and 2u (Scheme 6b). The reaction of 1-(pyrimidin-2-yl)indoline **1a** (19.7 mg, 0.1 mmol) was performed with **2j** (13.6 mg, 0.1 mmol) and **2u** (10.2 mg, 0.1 mmol) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (3.0 mg, 5.0 mol %), $AgSbF_6$ (7.0 mg, 20 mol %) and Ag_2CO_3 (55.2 mg, 0.2 mmol) for 5 h in $(CH_2Cl)_2$ (1.0 mL) as described above to produce **3j** and **3u** in 26 and 6% yields, respectively.

H/D Exchange with D_2O. 1-(Pyrimidin-2-yl)indoline **1a** (19.7 mg, 0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$] (6.0 mg, 5.0 mol %), $AgSbF_6$ (13.7 mg, 20 mol %) and Ag_2CO_3 (110 mg, 0.4 mmol) were stirred at 100 °C for 16 h in $(CH_2Cl)_2$:D_2O (1.8:0.2) under air. The reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL), and passed through a short pad of celite using dichloromethane (25 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified using column chromatography on silica gel to give **1a-*d*** in 87% (34.4 mg) yield with 40% deuterium incorporation as estimated by 400 MHz ^{1}H NMR.

Preparation of 1-(pyrimidin-2-yl)indoline-7-d (1a-d).[7a] The titled compound was prepared according to the reported procedure as a pale yellow liquid. The deuterium incorporation was determined using 600 MHz ^{1}H NMR as 90%.

Intermolecular kinetic isotope study.[5j] Benzoic acid **2a** (0.2 mmol, 24.4 mg) was reacted with 1-(pyrimidin-2-yl)indoline **1a** (0.1 mmol, 19.7 mg) and 1-(pyrimidin-2-yl)indoline-7-*d* **1a-*d*** (0.1 mmol, 19.8 mg) for 4 h under standard reaction condition. The reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL), and passed through a short pad of celite using dichloromethane (25 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford **3a** and a mixture of unreacted **1a** and **1a-*d*** as a yellowish liquid. The intermolecular k_H/k_D was found to be 6.67 after 4 h at 23% conversion, based on 400 MHz ^{1}H NMR of the recovered substrates **1a** and **1a-*d***.

Independent kinetic isotope effect study.[5j] In a set of two experiments: in first set, benzoic acid **2a** (0.2 mmol, 24.4 mg) was reacted with 1-(pyrimidin-2-yl)indoline **1a** (0.1 mmol, 19.7 mg) under standard reaction conditions. Whereas in another set, 1-(pyrimidin-2-yl)indoline-7-d **1a-*d*** (0.1 mmol, 19.8 mg, 90% D) was used instead of **1a** in the reaction with benzoic acid **2a** under the standard reaction conditions. The two reactions were allowed to stir at 100 °C for 4 h. For the both cases, was cooled to room temperature, diluted with dichloromethane (10 mL), and passed through a short pad of celite using dichloromethane (25 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and ethyl acetate as an eluent to afford **3a**. The yield of **3a** was obtained as 18% and 43% yields respectively. The KIE value of 2.65 was determined by the ratio of obtained yield of **3a** (KIE = 43%/18%/90% = 2.65).

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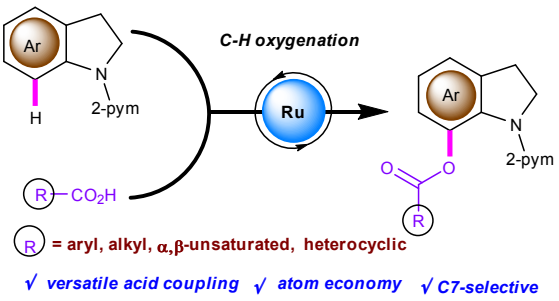

Ruthenium-catalyzed site-selective C7-acyloxyation of indolines with carboxylic acids is presented that can be oxidized to indoles with diverse functional groups.