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Palladium(II)/Copper Halide/Solvent Combination for Selective Intramolecular Domino Reactions of Indolecarboxylic Acid Allylamides: An Unprecedented Arylation/Esterification Sequence

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Abstract: Intramolecular oxidative palladium-catalyzed reactions of indolylallylamides in the presence of the couple bis(acetonitrile) palladium dichloride and copper(II) halide are described. Starting from 2- and 3-indolylallylamides and involving in both cases the C-3 position of the indole nucleus, variously substituted β-carbolinones were obtained by arylation/halogenation, arylation/esterification or arylation/carboalkoxylation processes. On the other hand, an unusual aminohalogenation/halogenation sequence performed on 2-indolylallylamides gave rise to pyrazino[1,2-*a*]indole products. The carboesterification process is the result of an unknown path that involves the DMF or DMA used as solvent. The outcome of the reactions of the 3-indolylallylamides arises from a totally selective 1,2-migration of the acyl group on the supposed spiro intermediates formed from the nucleophilic attack of the C-3 indole position.

Keywords: copper; domino reactions; homogeneous catalysis; palladium

Introduction

The transformation of unsaturated hydrocarbons through the action of transition metal catalysts continues to represent a very important topic in organometallic chemistry. In this field, oxidative Pd(II)-catalyzed alkene functionalization has emerged as one of the main focuses to build carbon-carbon and carbon-heteroatom bonds.[1] The classic pathway for this procedure typically requires the activation of the ethylenic bond induced by its coordination to the metal, which makes the bond susceptible to addition reactions, and the presence of a reoxidant agent in order to generate the suitable catalytic species. In the context of oxidative Pd(II) catalysis, domino processes such as carboaminations,[2] diaminations,[3] aminooxygenations[4] and aminohalogenations,[5] enabling easy access to (poly)functionalized acyclic and cyclic compounds as well as bicyclic ring systems, are particularly fascinating and useful in organic synthesis. As a consequence, the set-up of selective and tailored procedures based on new combinations of various kinds of bonds constitutes a challenge that justifies ongoing efforts in this field.

The indole nucleus represents a basic motif with broad occurrence in biologically or synthetically relevant molecules endowed with pharmacological and agrochemical activities.[6] For this reason, great efforts have been devoted to improve the preparation of indolyl compounds employing innovative synthetic methodologies.[7] Within these synthetic protocols, several oxidative reactions based on Pd(II) catalysis have been used for indole functionalization, some of which represent a convenient tool for the direct elaboration of the indole core motif.[8]

Following our interest towards transition metal-catalyzed reactions[9] as well as towards the synthesis of complex heteropolycyclic structures containing the indole nucleus,[10] herein we present the results of a project aimed at developing domino procedures for the regioselective cyclization of indole derivatives bearing an ethylenic moiety. More specifically, our work focused on the behavior of allylamides of 2- and 3-indolecarboxylic acids. This search relies on the re-

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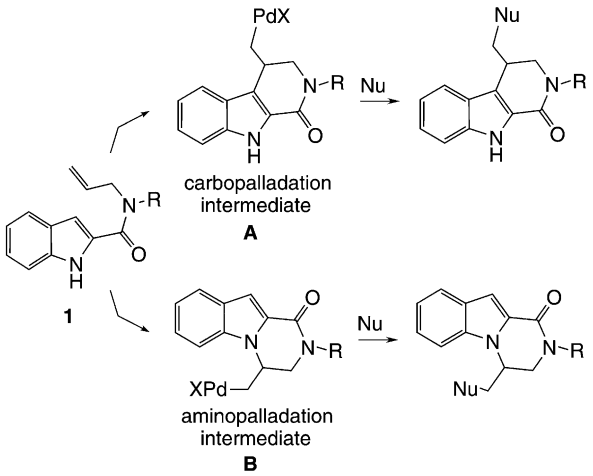


Figure 1. Concept of the present work.

activity of the 2-indolylallylamides (**1**), that undergo carbopalladation or aminopalladation of the carbon-carbon double bonds (previously converted in π-olefin complexes) exploiting the nucleophilicity of the C-3 and N-1 indole positions (Figure 1).

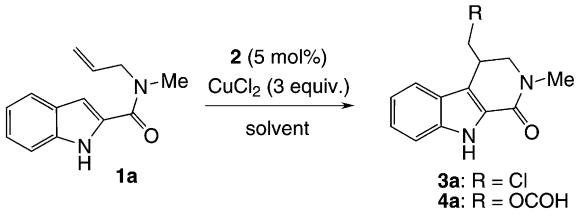
The so-formed **A** and **B** intermediates could then evolve affording variously substituted 3,4-dihydro-β-carbolinones and pyrazino[1,2-*a*]indoles by means of an appropriate nucleophile combined with a catalytic system that prevents the usual β-hydride elimination.

Results and Discussion

At the outset of the investigation, we considered the *N*-allylmethylindole-2-carboxamide (**1a**) and we envisioned as suitable catalytic system $PdCl_2(MeCN)_2$ (**2**) (5 mol%) and $CuCl_2$ (3 equiv.), typically effective in domino reactions that rely upon a first carbon-carbon or carbon-heteroatom bond forming reaction.[2h,3-f,4i,5a,b,11] In agreement with this assumption, the use of this bimetallic couple in THF at room temperature allowed the conversion of the *N*-allylmethylindole-2-carboxamide **1a** to the chloro derivative **3a** arising from an arylation/chlorination process (Table 1, entry 1). On increasing the temperature, the reaction was cleaner giving compound **3a** in a shorter time and higher yield (entry 2). The same outcome was observed when the reaction was performed in MeOH or dioxane as solvent (entries 3 and 4). Conversely, we found that the use of DMF as solvent triggers a competitive reaction pathway giving the formic ester **4a**, beside the chloro derivative **3a**. This unusual domino pathway, which is based on an oxidative Pd(II)-catalyzed arylation/esterification sequence involving the solvent, prompted us to further undertake investigations. The ratio of the carbochlorination and carboesterification products is markedly depending on the reaction temperature, as shown by entries 5–7, and a decisive improvement to yield formate **4a** was achieved by heating the reaction mixture at 150 °C (entry 8). We also tried to individualize less harsh selective conditions for the carboesterification process by using oxidant agents unable to promote the competitive chlorination process. However, the attempts to obtain **4a** from **1a** with $Cu(OAc)_2$, $CuCl_2$ (5 mol%)/O_2, and O_2 as oxidant agents failed, thus confirming the pivotal role of $CuCl_2$ in our procedures.

According to the optimal conditions previously reported, the divergent carbochlorination and carboesterification processes were probed on 2-indolylallylamides differently substituted at the amide group. In all cases, the outcome of the reaction was consistent with our prior results on the model substrate **1a**. As

Table 1. Optimization of selective reaction conditions.



Entry	Solvent	Temperature [°C]	Time [h]	Conversion [%]	Yield[a] of **3a** [%]	Yield[a] of **4a** [%]
1	THF	r.t.	3	100	65	
2	**THF**	**reflux**	**2**	**100**	**92**	
3	dioxane	reflux	2	100	81	
4	MeOH	reflux	3	100	70	
5	DMF	r.t.	72	30	20	7
6	DMF	60	3	100	61	29
7	DMF	100	3	100	68	33
8	**DMF**	**150**	**3**	**100**	**2**	**87**

[a] Isolated yield.

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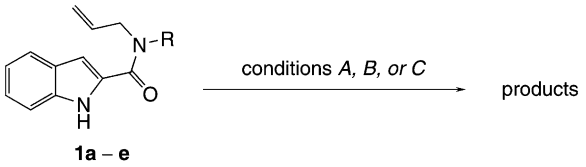
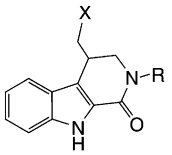
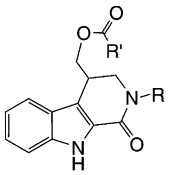
Table 2. Scope of carbohalogenation and carboesterification reactions.



1a – e

Entry	Substrate	Conditions[a]	Products	Yield [%]
1	**1b**	*A*	 **3b** X = Cl; R = cyclohexyl	82
2	**1c**	*A*	**3c** X = Cl; R = phenyl	76
3	**1d**	*A*	**3d** X = Cl; R = allyl	77
4	**1e**	*A*	**3e** X = Cl; R = cyclopentyl	88
5	**1a**	*A*	**5a** X = Br; R = methyl	78
6	**1b**	*A*	**5b** X = Br; R = cyclohexyl	71
7	**1b**	*B*	 **4b** R = cyclohexyl; R′ = H	84
8	**1c**	*B*	**4c** R = phenyl; R′ = H	73
9	**1d**	*B*	**4d** R = allyl; R′ = H	75
10	**1e**	*B*	**4e** R = cyclopentyl; R′ = H	86
11	**1a**	*C*	**6a** R = methyl; R′ = methyl	65
12	**1b**	*C*	**6b** R = cyclohexyl; R′ = methyl	68
13	**1c**	*C*	**6c** R = phenyl; R′ = methyl	62

[a] *Conditions A:* **2** (5 mol%), CuX_2 (3 equiv.), THF, reflux. *Conditions B:* **2** (5 mol%), $CuCl_2$ (3 equiv.), DMF, 150 °C. *Conditions C:* **2** (5 mol%), $CuCl_2$ (3 equiv.), DMA, 150 °C.

shown in Table 2, the indole derivatives **1b–e** underwent carbochlorination giving compounds **3b–e** (entries 1–4) when conducting the reactions in THF as solvent (i.e., the conditions of entry 2, Table 1). On replacing $CuCl_2$ with $CuBr_2$, bromo derivatives **5a** and **b** were isolated as final products (entries 5 and 6). Conversely, using the conditions referred to in entry 8 of Table 1, allylamides **1b–e** underwent an arylation/esterification sequence with formation of compounds **4b–e**. Gratifyingly, the reaction was demonstrated to be more general. When carried out in DMA as solvent, acetate derivatives **6a–c** were achieved in satisfactory yields (entries 11–13). Under these conditions, chloro derivatives **3a–e** were never detected.

Concerning the mechanistic aspects of the above reactions, the following picture may be suggested. While the formation of the chloroarylation product, arising from a domino process with participation of $CuCl_2$ in the chlorine transfer step, could be foreseeable having precedents in literature,[5,8i,j,12] the formation of compound **4a** is somehow unexpected. This new domino arylation/esterification reaction, whose detailed mechanism should be elucidated, clearly involves the amidic solvent in determining the final structure. The reasonably first-formed σ-alkylpalladium complex is possibly stabilized by the intervention of $CuCl_2$ that inhibits the more common palladium β-hydride elimination through a transient palladium oxidation[3f,13] or a heterobimetallic σ-Pd/Cu complex (Figure 2, L = DMF or DMA).[14] Reductive metal elimination may result in the iminium intermediate **C**, susceptible to hydrolysis to the final product **4a**. However, we cannot exclude that the iminium species **C** arises from a direct nucleophilic attack by the solvent oxygen on the exocyclic carbon of the σ-palladium complex. An alternative mechanism involving a

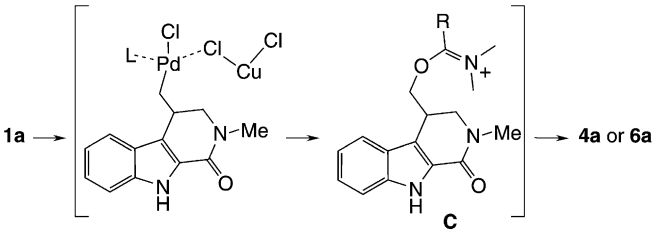


Figure 2. Iminium intermediate for the carboesterification reaction.

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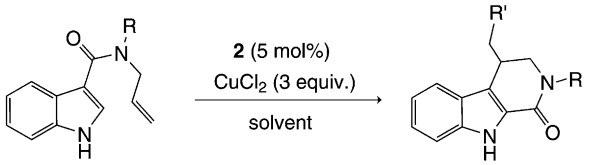
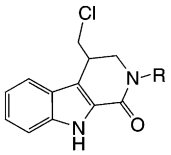
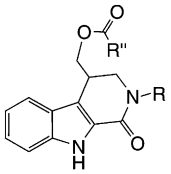
Table 3. Carbohalogenation and carboesterification reactions on allylamides of 3-indolecarboxylic acid.



7a – e

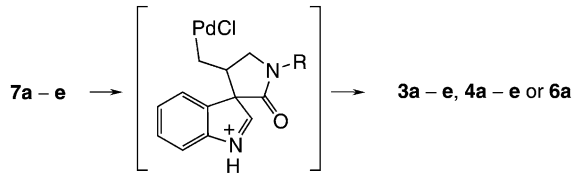
Entry	Substrate	Conditions[a]	Products	Yield [%]
1	**7a**	*A*	 **3a** R = methyl	79
2	**7b**	*A*	**3b** R = cyclohexyl	75
3	**7c**	*A*	**3c** R = phenyl	74
4	**7d**	*A*	**3d** R = allyl	83
5	**7e**	*A*	**3e** R = cyclopentyl	81
6	**7a**	*B*	 **4a** R = methyl; R″ = H	81
7	**7b**	*B*	**4b** R = cyclohexyl; R″ = H	72
8	**7c**	*B*	**4c** R = phenyl; R″ = H	69
9	**7d**	*B*	**4d** R = allyl; R″ = H	81
10	**7e**	*B*	**4e** R = cyclopentyl; R″ = H	70
11	**7a**	*C*	**6a** R = methyl; R″ = methyl	73

[a] *Conditions A:* **2** (5 mol%), $CuCl_2$ (3 equiv.), THF, reflux. *Conditions B:* **2** (5 mol%), $CuCl_2$ (3 equiv.), DMF, 150 °C. *Conditions C:* **2** (5 mol%), $CuCl_2$ (3 equiv.), DMA, 150 °C.

Pd(IV) intermediate can be ruled out because the reaction did not occur when changing $CuCl_2$ with $PhI(OAc)_2$, which is an established oxidant for Pd(II)/Pd(IV) reactivity.[15] On the other hand, the hypothesis that chloro derivative **3a** may act as the precursor of **4a** by a non-metal- or metal-promoted displacement of the chloride anion was excluded on the basis of its inactivity when heated in DMF either in the absence or in the presence of the catalytic system.

The chloroarylation and carboesterification reactions were then proven also on the allylamides of the 3-indolecarboxylic acid **7a–e**. The cyclizations, performed in the conditions of entries 2 and 8 of Table 1, proceeded satisfactorily giving, however, the compounds **3a–e** and **4a–e**, already obtained starting from the allylamides of the 2-indolecarboxylic acid (entries 1–10, Table 3). The treatment of the amide **7a** with **2** as catalyst and $CuCl_2$ (3 equiv.) in DMA at 150 °C confirmed the behaviour previously observed, affording the product **6a** (entry 11, Table 3).

The isolation of the rearranged products **3a–e**, **4a–e** and **6a** suggests that cyclizations of C-3 substituted indoles, catalyzed by the **2**/$CuCl_2$ system, take place by an initial formation of C–C bond at C-3 followed by



D

Figure 3. Spiro intermediate from allylamides of 3-indolecarboxylic acid.

1,2-migration of the acyl moiety to give the final products.[16] Thus, the 6-*exo-trig* cyclizations on the allylamides **7a–e** presumably proceed *via* spiro intermediates of type **D**, which undergo selectively acyl migration before or after the elimination of the metal (Figure 3).

The tendency of the spiro intermediates **D** to give a totally selective migration of the acyl group from the quaternary centre was confirmed submitting the allylamides of the 3-indolecarboxylic acid to a palladium-catalyzed carbonylative process (Scheme 1). In fact, treatment of allylamides **7a–e** with a catalytic amount of **2** (5 mol%) and a stoichiometric amount of $CuCl_2$

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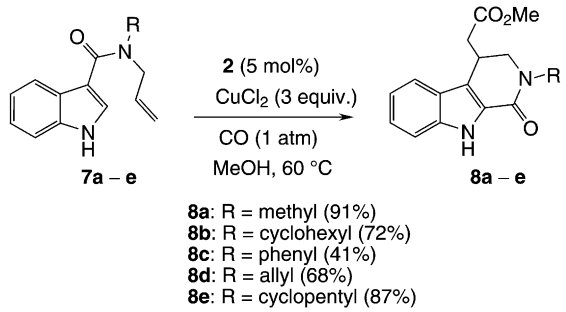


Scheme 1. Arylation/carboalkoxylation reaction of the indole nucleus.

(3 equiv.) in methanol under CO (1 atm) for 3 h at 60 °C gives the methyl β-carbolin-4-ylacetates **8a–e**, arising from an arylation/carboalkoxylation reaction.[17]

The β-carboline structure was unambiguously determined by an X-ray diffraction analysis carried out on the compound **8b** (Figure 4).

After the success in the synthesis of variously functionalized β-carbolinones involving the C-3 position of the indole nucleus, having in mind an opposite regioselective path at the indolyl nitrogen, we tried to develop a new protocol in a basic medium. For this purpose, allylamides **1a–d** were subjected to the treatment with **2** (5 mol%) and a Cu(II) salt (5 equiv.) as catalytic system in the presence of K_2CO_3 (1 equiv.). The reactions proceeded cleanly giving dihalogenated pyrazino[1,2-*a*]indoles **9a–d** and **10a–c** in good yields by an aminohalogenation/halogenation sequence (Table 4). Acetonitrile was proved to be the best solvent, while DMF and dioxane allow the formation of the dihalogenated products in traces.

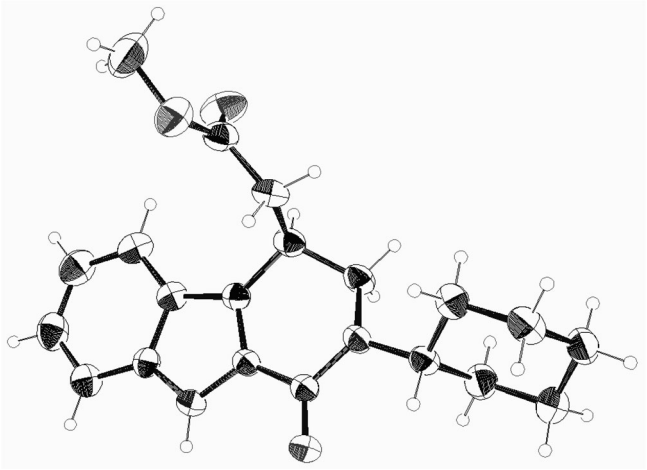
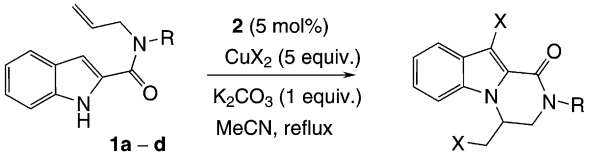


Figure 4. ORTEP representation, at 30% probability level, of the molecular structure of compound **8b**. One of the two molecules of the asymmetric unit was arbitrarily chosen for the picture.

Table 4. Base-promoted cyclization reactions.



Entry	Substrate	Products	Yield[a] [%]
1	**1a**	**9a** X = Cl; R = methyl	91
2	**1b**	**9b** X = Cl; R = cyclohexyl	85
3	**1c**	**9c** X = Cl; R = phenyl	81
4	**1d**	**9d** X = Cl; R = allyl	83
5	**1a**	**10a** X = Br; R = methyl	73
6	**1b**	**10b** X = Br; R = cyclohexyl	75
7	**1c**	**10c** X = Br; R = phenyl	71

[a] Isolated yield.

To explain the formation of the products **9** and **10**, we propose a mechanism which implies two independent reactions, as depicted in Figure 5. In the light of previous literature data,[8e,18] the halogenation of the indolyl 3-position leading to the 3-halo derivative **E** can be due solely to the Cu(II) salt without involvement of the palladium catalyst. On the other hand, an aminopalladation of the π-olefin complexes **F** allows the formation of the σ-alkylpalladium complexes **G**, the evolution of which implies, rather than the usual β-hydride elimination, a chlorine transfer on the tran-

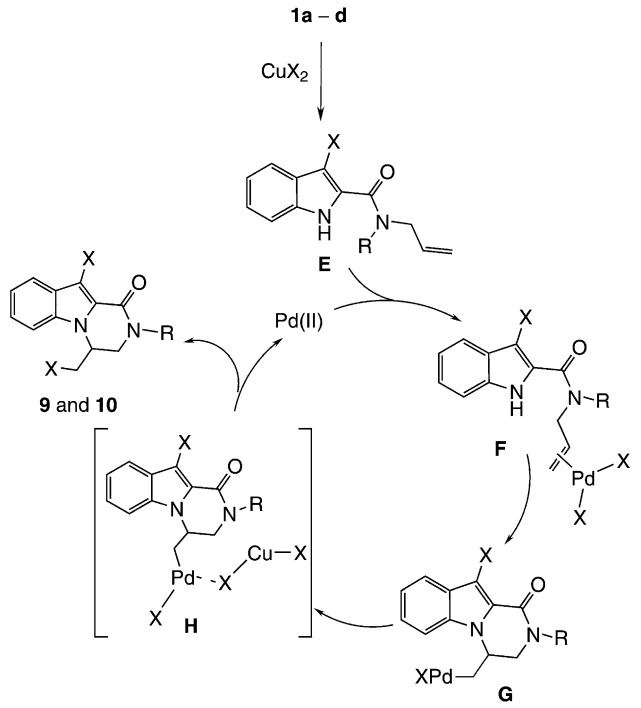


Figure 5. Proposed mechanism for the aminohalogenation/halogenation reaction.

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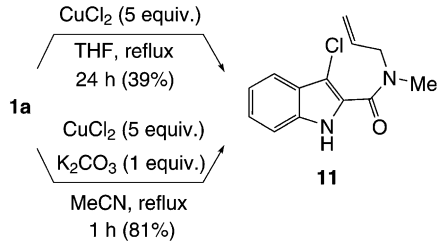

Scheme 2. Simple halogenation reaction of the indole nucleus.

sient species **H** to produce the halomethyl-substituted pyrazino[1,2-*a*]indoles **9** and **10**.

A sequence involving two independent processes is supported by the observed behaviour of allylamide **1a** in the presence of $CuCl_2$ and absence of catalyst **2** (Scheme 2). In these conditions, the chlorination of the indole nucleus was really effective leading to the *N*-allyl-*N*-methyl amide of 3-chloro-2-indolecarboxylic acid (**11**), while the aminochlorination process was not operative. In the presence of K_2CO_3, the formation of **11** was faster and took place in a shorter time in comparison to that required for the complete aminohalogenation/halogenation sequence occurring in the presence of palladium (entry 1, Table 4). On the other hand, in the absence of K_2CO_3, the reaction was much slower than the arylation/chlorination process reported in entry 2 of Table 1, so indicating that the direct carbopalladation is really operative in the formation of **3a**. Such a hypothesis was also supported by the following findings: (i) the interruption of the arylation/chlorination of compound **1a** (entry 2, Table 1) after 30 min provided a mixture containing only the unreacted compound **1a** and the cyclized product **3a**; (ii) conversely, the analogous interruption of the aminochlorination/chlorination sequence (entry 1, Table 4) gave, beside **1a** and the cyclized product **9a**, also 3-chloroindole derivative **11**.

Conclusions

In conclusion, we have developed some efficient and practical $PdCl_2(MeCN)_2/CuX_2$ mediated domino reactions that provide rapid and selective access to variously functionalized β-carbolinones and pyrazino[1,2-*a*]indoles. Among these oxidative Pd(II)-catalyzed processes, the pathway leading directly to formic or acetic esters represents, to the best of our knowledge, the first example of evolution of a σ-alkyl-palladium complex by means of DMF or DMA used as solvent. While pyrazino[1,2-*a*]indoles arise from 2-indolylallylamides, β-carbolinone derivatives can be achieved starting either from 2- or 3-indolylallylamides. These latter, in fact, follow an outcome that involves the 1,2-migration of the amide group in a totally selective manner. Further studies are currently addressed to gain more insights on the mechanism of the carboesterification reaction.

Experimental Section

General Remarks

Reagents and solvents were used as received from commercial sources. Flash column chromatography was performed employing 230–400 mesh silica gel. Analytical thin layer chromatography was performed on silica gel 60 F254. Melting points were measured with a Büchi B-540 apparatus and are uncorrected. IR spectra were recorded on a FT-IR spectrophotometer. Nuclear magnetic resonance spectra were acquired on an AVANCE 400 Bruker spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. ^{13}C spectra were ^{1}H decoupled and multiplicities were determined by the APT pulse sequence. Mass spectra were determined on an HPLC-MS LCQ-Advantage Thermo Finnigan instrument. Elemental analyses were executed on a Perkin–Elmer CHN Analyzer Series II 2400.

Detailed procedures for the preparation of allylamides and details on the X-ray diffraction measurement and analysis are available as Supporting Information.

General Procedure for the Arylation/Halogenation Reactions (Conditions *A*)

A solution of 2-indolylallylamide (1 mmol), $PdCl_2(MeCN)_2$ (0.05 mmol) and CuX_2 (3 mmol) in THF (5 mL) was refluxed for 2 h. After cooling, the solvent was evaporated under reduced pressure, brine was added (10 mL) and the solution was extracted with CH_2Cl_2 (3×20 mL). The organic phase was dried over Na_2SO_4, then the solvent was evaporated under reduced pressure. The products were purified by flash chromatography.

4-(Chloromethyl)-2-methyl-2,3,4,9-tetrahydropyrido[3,4-*b*]indol-1-one (3a): Yield: 92%; eluent: hexane/AcOEt 1:1; pale orange solid; mp 166 °C (*i*-Pr_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.24 (s, 3H), 3.49–3.53 (m, 1H), 3.62 (t, *J* = 11.0 Hz, 1H), 3.80 (dd, *J* = 3.8, 11.0 Hz, 1H), 3.87 (dd, *J* = 2.3, 12.9 Hz, 1H), 3.97 (dd, *J* = 5.3, 12.9 Hz, 1H), 7.20 (dd, *J* = 7.5, 7.8 Hz, 1H), 7.35 (dd, *J* = 7.5, 8.2 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 9.99 (s br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.8 (q), 35.5 (d), 44.7 (t), 52.0 (t), 113.4 (d), 117.7 (s), 120.1 (d), 121.1 (d), 125.0 (s), 125.4 (d), 127.5 (s), 138.1 (s), 161.5 (s); IR: ν = 3432, 1667 cm^{-1}; MS: *m/z* = 248 (M^+); anal. calcd. for $C_{13}H_{13}ClN_2O$: C 62.78, H 5.27, N 11.26; found: C 62.83, H 5.43, N 11.40.

4-(Chloromethyl)-2-cyclohexyl-2,3,4,9-tetrahydropyrido-[3,4-*b*]indol-1-one (3b): Yield: 82%; eluent: hexane/AcOEt 8:2; pale yellow solid; mp 224 °C (*i*-Pr_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91–2.00 (m, 10H), 3.37–3.43 (m, 2H), 3.61–3.71 (m, 2H), 3.96 (d, *J* = 12.9 Hz, 1H), 4.66–4.72 (m, 1H), 7.18 (dd, *J* = 7.4, 7.9 Hz. 1H), 7.32 (dd, *J* = 7.4, 8.3 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 10.39 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9 (t), 26.1 (t), 30.1 (t), 30.4 (t), 31.1 (t), 35.2 (d), 43.8 (t), 43.9 (t), 52.1 (d), 113.3 (d), 117.3 (s), 120.0 (d), 121.0 (d), 124.7

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(s), 125.3 (d), 128.1 (s), 138.1 (s), 160.5 (s); IR: ν = 3427, 1661 cm^{-1}; MS: *m/z* = 316 (M^+); anal. calcd. for $C_{18}H_{21}ClN_2O$: C 68.24, H 6.68, N 8.84; found: C 68.21, H 6.51, N 8.73.

4-(Chloromethyl)-2-phenyl-2,3,4,9-tetrahydropyrido[3,4-*b*]indol-1-one (3c): Yield: 76%; eluent: hexane/AcOEt 65:35; yellow solid; mp 206 °C (*i*-Pr_2O). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.59–3.62 (m. 1H), 3.80 (t, *J* = 10.7 Hz, 1H), 3.89 (dd, *J* = 4.0, 10.7 Hz, 1H), 4.32 (dd, *J* = 1.8, 12.8 Hz, 1H), 4.41 (dd, *J* = 4.5, 12.8 Hz, 1H), 7.21 (dd, *J* = 7.5, 8.0 Hz, 1H), 7.37–7.39 (m, 3H), 7.49–7.54 (m, 4H), 7.68 (d, *J* = 8.0 Hz, 1H), 10.63 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.9 (d), 44.4 (t), 53.6 (t), 113.5 (d), 118.7 (s), 120.3 (d), 121.2 (d), 124.8 (s), 125.8 (d), 126.4 (d), 127.2 (d), 127.7 (s), 129.5 (d), 138.3 (s), 142.4 (s), 160.6 (s); IR: ν = 3442, 1675 cm^{-1}; MS: *m/z* = 310 (M^+); anal. calcd. for $C_{18}H_{15}ClN_2O$: C 69.57, H 4.86, N 9.01; found: C 69.41, H 5.09, N 9.23.

2-Allyl-4-(chloromethyl)-2,3,4,9-tetrahydropyrido[3,4-*b*]indol-1-one (3d): Yield: 77%; eluent: hexane/AcOEt 7:3; pale yellow solid; mp171 °C (*i*-Pr_2O). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.49–3.54 (m, 1H), 3.60 (t, *J* = 10.8 Hz, 1H), 3.79 (dd, *J* = 3.7, 10.8 Hz, 1H), 4.18 (dd, *J* = 6.4, 15.0 Hz, 1H), 4.48 (dd, *J* = 6.0, 15.0 Hz, 1H), 5.35 (d, *J* = 10.8 Hz, 1H), 5.40 (dd, *J* = 1.1, 17.1 Hz, 1H), 5.92–6.00 (m, 1H), 7.20 (dd, *J* = 7.3, 8.0 Hz, 1H), 7.35 (dd, *J* = 7.3, 8.3 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 11.05 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.5 (d), 44.5 (t), 49.3 (t), 113.6 (d), 117.9 (s), 119.1 (t), 120.1 (d), 121.0 (d), 124.9 (s), 125.4 (d), 127.5 (s), 133.2 (d), 138.3 (s), 161.1 (s); IR: ν = 3455, 1668 cm^{-1}; MS: *m/z* = 274 (M^+); anal. calcd. for $C_{15}H_{15}ClN_2O$: C 65.57, H 5.50, N 10.20; found: C 65.55, H 5.31, N 10.36.

4-(Chloromethyl)-2-cyclopentyl-2,3,4,9-tetrahydropyrido-[3,4-*b*]indol-1-one (3e): Yield: 88%; eluent: hexane/AcOEt 8:2; white solid; mp 209 °C (*i*-Pr_2O). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.70–2.07 (m, 8H), 3.45–3.55 (m, 2H), 3.74–3.90 (m, 2H), 3.91 (d, *J* = 13.3 Hz, 1H), 5.31–5.35 (m, 1H), 7.19 (dd, *J* = 7.5, 8.0 Hz, 1H), 7.35 (dd, *J* = 7.5, 8.3 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 11.08 (s br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9 (t), 25.2 (t), 28.6 (t), 30.2 (t), 35.3 (d), 43.9 (t), 44.0 (t), 53.8 (d), 113.5 (d), 117.3 (s), 120.0 (d), 121.0 (d), 124.8 (s), 125.3 (d), 128.1 (s), 138.3 (s), 161.2 (s); IR: ν = 3439, 1671 cm^{-1}; MS: *m/z* = 302 (M^+); anal. calcd. for $C_{17}H_{19}ClN_2O$: C 67.43, H 6.32, N 9.25; found: C 67.55, H 6.05, N 9.12.

4-(Bromomethyl)-2-methyl-2,3,4,9-tetrahydropyrido[3,4-*b*]indol-1-one (5a): Yield: 78%; eluent: hexane/AcOEt 1:1; white solid; mp 202 °C (*i*-Pr_2O). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.29 (s, 3H), 3.49–3.51 (m, 1H), 3.52–3.55 (m, 1H), 3.61–3.65 (m, 1H), 3.80–3.85 (m, 1H), 3.91–3.99 (m, 1H), 7.27 (dd, *J* = 7.8, 7.0 Hz, 1H), 7.39 (dd, *J* = 7.0, 8.2 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 10.5 (s br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.7 (t), 34.6 (q), 35.1 (d), 52.9 (t), 113.3 (d), 119.2 (s), 119.7 (d), 121.1 (d), 124.1 (s), 125.1 (s), 125.8 (d), 126.7 (s), 161.0 (s); IR: ν = 3437, 1660 cm^{-1}; MS: *m/z* = 293 (M^+); anal. calcd. for $C_{13}H_{13}BrN_2O$: C 53.26, H 4.47, N 9.56; found: C 53.44, H 4.65, N 9.77.

4-(Bromomethyl)-2-cyclohexyl-2,3,4,9-tetrahydropyrido-[3,4-*b*]indol-1-one (5b): Yield: 71%; eluent: hexane/AcOEt 8:2; pale yellow solid; mp 209 °C (*i*-Pr_2O). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.10–2.97 (m, 10H), 3.31–3.41 (m, 1H), 3.47–3.51 (m, 1H), 3.58–3.63 (m, 1H), 3.71–3.79 (m, 1H), 3.91–4.08 (m, 1H), 4.61–4.75 (m, 1H), 7.20 (dd, *J* = 7.1, 8.0 Hz, 1H), 7.35 (dd, *J* = 1.1 ,7.1 Hz, 1H), 7.50 (d, *J* = 1.1 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 10.00 (s br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1 (t), 31.2 (t), 32.1 (t), 33.2 (t), 35.1 (d), 45.3 (t), 51.9 (d), 113.1 (d), 117.2 (s), 120.1 (d), 121.1 (d), 124.9 (s), 125.2 (d), 127.7 (s), 137.5 (s), 158.0 (s); IR: ν = 3441, 1668 cm^{-1}; MS: *m/z* = 361 (M^+); anal. calcd. for $C_{18}H_{21}BrN_2O$: C 59.84, H 5.86, N 7.75; found: C 59.68, H 5.99, N 7.64.

General Procedure for the Arylation/Esterification Reactions (Conditions *B*)

A solution of 2-indolylallylamide (1 mmol), $PdCl_2(MeCN)_2$ (0.05 mmol) and $CuCl_2$ (3 mmol) in DMF (5 mL) was refluxed for 3 h. After cooling, brine was added (10 mL) and the solution was extracted with Et_2O (3 × 20 mL). The organic phase was dried over Na_2SO_4, then the solvent was evaporated under reduced pressure. The products were purified by flash chromatography.

(2-Methyl-1-oxo-2,3,4,9-tetrahydropyrido[3,4-*b*]indol-4-yl)methyl formate (4a): Yield: 87%; eluent: hexane/AcOEt 1:1; pale orange solid; mp 129 °C (*i*-Pr_2O). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.23 (s, 3H), 3.56–3.65 (m, 2H), 3.97 (dd, *J* = 5.2, 10.1 Hz, 1H), 4.26 (t, *J* = 10.1 Hz, 1H), 4.53 (dd, *J* = 4.7, 11.2 Hz, 1H), 7.18 (dd, *J* = 7.3, 7.9 Hz, 1H), 7.34 (t, *J* = 7.3, 8.2 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 8.15 (s, 1H), 9.97 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.4 (d), 34.8 (q), 52.0 (t), 63.7 (t), 113.5 (d), 117.2 (s), 120.3 (d), 120.9 (d), 125.3 (d), 125.4 (s), 127.7 (s), 137.9 (s), 161.2 (s), 161.8 (s); IR: ν = 3421, 1658, 1730 cm^{-1}; MS: *m/z* = 258 (M^+); anal. calcd. for $C_{14}H_{14}N_2O_3$: C 65.11, H 5.46. N 10.85; found: C 65.24, H 5.21, N 11.04.

(2-Cyclohexyl-1-oxo-2,3,4,9-tetrahydropyrido[3,4-*b*]indol-4-yl)methyl formate (4b): Yield: 84%; eluent: hexane/AcOEt 8:2; pale yellow solid; mp 179 °C (*i*-Pr_2O); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.17–1.92 (m, 10H), 3.52–3.56 (m, 1H), 3.69–3.79 (m, 2H), 4.11 (t, *J* = 10.2 Hz, 1H), 4.51 (dd, *J* = 4.7, 11.1 Hz, 1H), 4.69–4.71 (m, 1H), 7.18 (dd, *J* = 7.5, 7.8 Hz, 1H), 7.33 (dd, *J* = 7.5, 8.2 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 8.16 (s, 1H), 10.30 (br s, ν); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0 (t), 26.2 (t), 30.1 (t), 30.5 (t), 31.0 (t), 32.0 (d), 43.8 (t), 51.9 (d), 63.1 (t), 113.1 (d), 116.3 (s), 120.4 (d), 121.0 (d), 125.1 (s), 125.2 (d), 128.4 (s), 138.0 (s), 160.6 (s), 161.1 (s); IR: ν = 3425, 1650, 1718 cm^{-1}; MS: *m/z* = 326 (M^+); anal. calcd. for $C_{19}H_{22}N_2O_3$: C 69.92, H 6.79, N 8.58; found: C 69.65, H 7.04, N 8.72.

(2-Phenyl-1-oxo-2,3,4,9-tetrahydropyrido[3,4-*b*]indol-4-yl)methyl formate (4c): Yield: 73%; eluent: hexane/AcOEt 65:35; pale yellow solid; mp 143 °C (*i*-Pr_2O). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.66–3.71 (m, 1H), 4.07 (dd, *J* = 2.6, 12.7 Hz, 1H), 4.34–4.44 (m, 2H), 4.65 (dd, *J* = 4.8, 11.2 Hz, 1H), 7.20 (dd, *J* = 7.5, 7.8 Hz, 1H), 7.28–7.40 (m, 5H), 7.46–7.54 (m, 2H), 7.71 (d, *J* = 8.0 Hz, 1H), 8.12 (s, 1H), 10.93 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.8 (d), 53.4 (t), 63.5 (t), 113.5 (d), 117.8 (s), 120.5, (d), 121.1 (d), 125.1 (s), 125.7 (d), 126.2 (d), 127.1 (d), 127.8 (s), 129.5 (d), 138.5 (s), 142.6 (s), 161.0 (s), 161.1 (s); IR: ν = 3441, 1682, 1710 cm^{-1}; MS: *m/z* = 320 (M^+); anal. calcd. for $C_{19}H_{16}N_2O_3$: C 71.24, H 5.03, N 8.74; found: C 71.27, H 4.85, N 8.59.

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(2-Allyl-1-oxo-2,3,4,9-tetrahydropyrido[3,4-*b*]indol-4-yl)-methyl formate (4d): Yield: 75%; eluent: hexane/AcOEt 7:3; pale yellow solid; mp 113 °C (*i*-Pr_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.57–3.61 (m, 1H), 3.66 (dd, *J* = 2.5, 12.8 Hz, 1H), 3.91 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.16 (dd, *J* = 6.5, 15.0 Hz, 1H), 4.23 (t, *J* = 10.1 Hz, 1H), 4.44 (dd, *J* = 5.9, 15.0 Hz, 1H), 4.51 (dd, *J* = 4.8, 11.1 Hz, 1H), 5.30–5.37 (m, 2H), 5.88–5.97 (m, 1H), 7.19 (dd, *J* = 7.5, 7.9 Hz, 1H), 7.34 (dd, *J* = 7.5, 8.2 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 8.14 (s, 1H), 10.91 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.2 (d), 49.1 (t), 49.2 (t), 63.6 (t), 113.4 (d), 117.0 (s), 118.9 (t), 120.4 (d), 121.0 (d), 125.2 (s), 125.4 (d), 127.7 (s), 133.4 (d), 138.3 (s), 161.1 (s), 161.3 (d); IR: ν = 3432, 1678, 1728 cm^{-1}; MS: *m/z* = 284 (M^+); anal. calcd. for $C_{16}H_{16}N_2O_3$: C 67.59, H 5.67, N 9.85; found: C 67.48, H 5.91, N 9.76.

(2-Cyclopentyl-1-oxo-2,3,4,9-tetrahydropyrido[3,4-*b*]indol-4-yl)methyl formate (4e): Yield: 86%; eluent: hexane/AcOEt 8:2; pale yellow solid; mp 131 °C (*i*-Pr_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62–2.01 (m, 8H), 3.55–3.58 (m, 1H), 3.67 (dd, *J* = 2.5, 12.9 Hz, 1H), 3.78 (dd, *J* = 4.8, 12.9 Hz, 1H), 4.10 (t, *J* = 10.3 Hz, 1H), 4.54 (dd, *J* = 4.8, 10.3 Hz, 1H), 5.26–5.31 (m, 1H), 7.17 (dd, *J* = 7.4, 7.8 Hz, 1H), 7.33 (t, *J* = 7.4, 8.2 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 8.16 (s, 1H), 10.81 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8 (t), 25.0 (t), 28.5 (t), 29.9 (t), 32.1 (d), 44.0 (t), 53.8 (d), 63.1 (t), 113.3 (d), 116.4 (s), 120.4 (d), 120.9 (d), 125.1 (s), 125.2 (d), 128.3 (s), 138.2 (s), 161.1 (s), 161.3 (s); IR: ν = 3440, 1664, 1738 cm^{-1}; MS: *m/z* = 312 (M^+); anal. calcd. for $C_{18}H_{20}N_2O_3$: C 69.21, H 6.45, N 8.97; found: C 69.33, H 6.28, N 8.78.

General Procedure for the Arylation/Esterification Reactions (Conditions *C*)

A solution of 2-indolylallylamide (1 mmol), $PdCl_2(MeCN)_2$ (0.05 mmol) and $CuCl_2$ (3 mmol) in DMA (5 mL) was refluxed for 3 h. After cooling, brine was added (10 mL) and the solution was extracted with Et_2O (3 × 20 mL). The organic phase was dried over Na_2SO_4 then the solvent was evaporated under reduced pressure. The products were purified by flash chromatography.

(2-Methyl-1-oxo-2,3,4,9-tetrahydropyrido[3,4-*b*]indol-4-yl)methyl acetate (6a): Yield: 65%; eluent: hexane/AcOEt 1:1; white solid; mp 196 °C (*i*-Pr_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 (s, 3H), 3.21 (s, 3H), 3.52–3.58 (m, 1H), 3.60 (dd, *J* = 2.6, 12.7 Hz, 1H), 3.96 (dd, *J* = 5.3, 12.7 Hz, 1H), 4.18 (dd, *J* = 9.1, 11.1 Hz, 1H), 4.44 (dd, *J* = 5.3, 11.1 Hz, 1H), 7.18 (dd, *J* = 7.5, 7.8 Hz, 1H), 7.33 (dd, *J* = 7.5, 8.2 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 10.62 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (d), 32.5 (q), 34.7 (q), 52.2 (t), 64.5 (t), 113.1 (d), 117.3 (s), 120.6 (d), 121.0 (d), 125.3 (s), 125.4 (d), 127.7 (s), 137.9 (s), 161.6 (s), 171.3 (s). IR: ν = 3444, 1675, 1733 cm^{-1}; MS: *m/z* = 272 (M^+); anal. calcd. for $C_{15}H_{16}N_2O_3$: C 66.16, H 5.92, N 10.29; found: C 66.31, H 5.84, N 10.26.

(2-Cyclohexyl-1-oxo-2,3,4,9-tetrahydropyrido[3,4-*b*]indol-4-yl)methyl acetate (6b): Yield: 68%; eluent: hexane/AcOEt 8:2; white solid; mp 151 °C (*i*-Pr_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81–2.21 (m, 10H), 2.11 (s, 3H), 3.45–3.53 (m, 1H), 3.68–3.75 (m, 2H), 4.02–4.07 (m, 1H), 4.36–4.40 (m, 1H), 4.58–4.79 (m, 1H), 7.15 (dd, *J* = 7.4, 8.3 Hz, 1H), 7.30 (dd, *J* = 7.4, 8.0 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 10.45 (s br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0 (q), 25.8 (t), 30.1 (t), 30.5 (t), 31.7 (d), 43.6 (t), 51.6 (d), 63.6 (t), 112.7 (d), 116.6 (s), 120.1 (d), 120.4 (d), 124.7 (d), 124.9 (s), 127.8 (s), 137.6 (s), 159.2 (s), 170.8 (s); IR: ν = 3441, 1668, 1720 cm^{-1}; MS: *m/z* = 340 (M^+); anal. calcd. for $C_{20}H_{24}N_2O_3$: C 70.57, H 7.11, N 8.23; found: C 70.62, H 7.32, N 8.07.

(2-Phenyl-1-oxo-2,3,4,9-tetrahydropyrido[3,4-*b*]indol-4-yl)methyl acetate (6c): Yield: 62%; eluent: hexane/AcOEt 65:35; pale yellow solid; mp 156 °C (*i*-Pr_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 3.58–3.69 (m, 1H), 4.02–4.04 (m, 1H), 4.27 (dd, *J* = 9.1, 2.0 Hz, 1H), 4.38–4.40 (m, 1H), 4.53–4.56 (m, 1H), 7.18–7.72 (m, 9H), 9.98 (s br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0 (q), 32.4 (d), 53.2 (t), 63.9 (t), 112.8 (d), 118.0 (s), 120.4 (d), 120.7 (d), 124.9 (s), 125.3 (d), 125.7 (d), 126.6 (d), 127.3 (s), 129.1 (d), 137.7 (s), 142.2 (s), 160.3 (s), 170.8 (s); IR: ν = 3427, 1667, 1730 cm^{-1}; MS: *m/z* = 334 (M^+); anal. calcd. for $C_{20}H_{18}N_2O_3$: C 71.84, H 5.43, N 8.38; found: C 71.52, H 5.56, N 8.57.

General Procedure for the Carbonylation Reactions

A solution of 3-indolylallylamide (1 mmol), $PdCl_2(MeCN)_2$ (0.05 mmol) and $CuCl_2$ (3 mmol) in MeOH (5 mL) was stirred at 60 °C for 3 h under CO atmosphere. After cooling, brine was added (10 mL) and the solution was extracted with Et_2O (3 × 20 mL). The organic phase was dried over Na_2SO_4 then the solvent was evaporated under reduced pressure. The products were purified by flash chromatography.

Methyl 2-(2-methyl-1-oxo-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indol-4-yl)acetate (8a): Yield: 91%; eluent: hexane/AcOEt 1:1; white solid; mp 168 °C (*i*-Pr_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69 (dd, *J* = 9.4, 15.8 Hz, 1H), 2.78 (dd, *J* = 5.0, 15.8 Hz, 1H), 3.22 (s, 3H), 3.54 (dd, *J* = 2.7, 12.7 Hz, 1H), 3.71 (s, 3H), 3.74–3.77 (m, 1H), 4.01 (dd, *J* = 5.0, 12.7 Hz, 1H), 7.16 (t, *J* = 7.6, 8.0 Hz, 1H), 7.32 (t, *J* = 7.6, 8.2 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 10.36 (s br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.4 (d), 34.8 (q), 37.6 (t), 52.3 (q), 54.9 (t), 113.2 (d), 120.4 (d), 120.5 (d), 120.7 (s), 124.8 (s), 125.2 (d), 127.1 (s), 138.1 (s), 161.9 (d), 172.9 (s); IR: ν = 3425, 1733, 1678 cm^{-1}; MS: *m/z* = 272 (M^+); anal. calcd. for $C_{15}H_{16}N_2O_3$: C 66.16, H 5.92, N 10.29; found: C 66.27, H 5.74, N 10.15.

Methyl 2-(2-cyclohexyl-1-oxo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-4-yl)acetate (8b): Yield: 72%; eluent: hexane/AcOEt 2:3; white solid; mp 151 °C (*i*-Pr_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18–1.92 (m, 10H), 2.63 (dd, *J* = 9.3, 16.1 Hz, 1H), 2.70 (dd, *J* = 5.0, 16.1 Hz, 1H), 3.66–3.80 (m, 6H), 4.72–4.77 (m, 1H), 7.15 (t, *J* = 7.4, 7.8 Hz, 1H), 7.31 (t, *J* = 7.4, 8.2 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 11.03 (s br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0 (t), 26.3 (t), 29.1 (d), 30.5 (t), 30.7 (d), 30.9 (t), 36.7 (t), 46.7 (t), 51.9 (q), 52.2 (d), 113.2 (d), 120.2 (s), 120.4 (d), 120.5 (d), 124.6 (s), 125.0 (d), 127.8 (s), 138.3 (s), 161.1 (s), 173.1 (s); IR: ν = 3225, 1742, 1665 cm^{-1}; MS: *m/z* = 340 (M^+); anal. calcd. for $C_{20}H_{24}N_2O_3$: C 70.56, H 7.11, N 8.23; found: C 70.27, H 7.25, N 8.14.

Methyl 2-(2-phenyl-1-oxo-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indol-4-yl)acetate (8c): Yield: 41%; eluent: hexane/AcOEt 7:3; white solid; mp 171 °C (*i*-Pr_2O). ^{1}H NMR

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(400 MHz, $CDCl_3$): δ = 2.80–2.91 (m, 2H), 3.68 (s, 3H), 3.83–3.88 (m, 1H), 3.98 (dd, *J* = 2.5, 12.6 Hz, 1H), 4.47 (dd, *J* = 4.7, 12.6 Hz, 1H), 7.18 (dd, *J* = 7.5, 8.0 Hz, 1H), 7.30–7.38 (m, 3H), 7.46–7.52 (m, 4H), 7.67 (d, *J* = 8.0 Hz, 1H), 10.44 (s br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9 (d), 37.5 (t), 52.3 (q), 56.3 (t), 113.3 (d), 120.7 (d), 120.9 (d), 121.6 (s), 124.6 (s), 125.6 (d), 126.1 (d), 126.9 (d), 127.2 (s), 129.4 (d), 138.4 (s), 142.7 (s), 161.0 (s), 172.8 (s); IR: ν = 3278, 1732, 1651 cm^{-1}; MS: *m/z* = 334 (M^+); anal. calcd. for $C_{20}H_{18}N_2O_3$: C 71.84, H 5.43, N 8.38; found: C 71.66, H 5.52, N 8.55.

Methyl 2-(2-allyl-1-oxo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-4-yl)acetate (8d): Yield: 68%; eluent: hexane/AcOEt 3:2; white solid; mp 93 °C (*i*-Pr_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.66 (dd, *J* = 9.4, 16.0 Hz, 1H), 2.75 (dd, *J* = 5.2, 16.0 Hz, 1H), 3.55 (dd, *J* = 2.5, 12.8 Hz, 1H), 3.70 (s, 3H), 3.74–3.76 (m, 1H), 3.95 (dd, *J* = 5.4, 12.8 Hz, 1H), 4.09 (dd, *J* = 6.7, 15.0 Hz, 1H), 4.48 (dd, *J* = 5.4, 15.0 Hz, 1H), 5.29 (d, *J* = 11.2 Hz, 1H), 5.34 (dd, *J* = 1.2, 17.2 Hz, 1H), 5.87–5.97 (m, 1H), 7.16 (dd, *J* = 7.4, 7.8 Hz, 1H), 7.32 (dd, *J* = 7.8, 8.2 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 10.68 (s br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.3 (d), 37.5 (t), 49.2 (t), 52.0 (t), 52.2 (q), 113.3 (d), 118.8 (t), 120.5 (d), 120.7 (d), 120.8 (s), 124.7 (s), 125.2 (d), 127.1 (s), 133.5 (d), 138.3 (s), 161.4 (s), 172.9 (s); IR: ν = 3218, 1738, 1661 cm^{-1}; MS: *m/z* = 298 (M^+); anal. calcd. for $C_{17}H_{18}N_2O_3$: C 68.44, H 6.08, N 9.39; found: C 68.28, H 6.32, N 9.17.

Methyl 2-(2-cyclopentyl-1-oxo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-4-yl)acetate (8e): Yield: 87%; eluent: hexane/AcOEt 1:1; white solid; mp 154 °C (*i*-Pr_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62–2.03 (m, 8H), 2.63 (dd, *J* = 0.9, 16.0.1 Hz, 1H), 2.72 (dd, *J* = 5.0, 16.0 Hz, 1H), 3.60 (dd, *J* = 2.2, 12.8 Hz, 1H), 3.69–3.72 (m, 1H), 3.72 (m, 3H), 3.82 (dd, *J* = 4.7, 12.8 Hz, 1H), 5.31 (m, 1H), 7.15 (dd, *J* = 7.5, 8.0 Hz, 1H), 7.31 (t, *J* = 7.5, 8.3 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 11.04 (s br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8 (t), 25.0 (t), 28.6 (t), 29.2 (d), 29.8 (t), 36.7 (t), 46.8 (t), 52.2 (q), 53.7 (d), 113.3 (d), 120.2 (s), 120.4 (d), 120.6 (d), 124.6 (s), 125.0 (d), 127.7 (s), 138.4 (s), 161.6 (s), 173.1 (s); IR: ν = 3330, 1748, 1677 cm^{-1}; MS: *m/z* = 326 (M^+); anal. calcd. for $C_{19}H_{22}N_2O_3$: C 69.92, H 6.79, N 8.58; found: C 70.18, H 6.65, N 8.81.

General Procedure for the Aminohalogenation/Halogenation Reactions

A solution of 2-indolylallylamide (1 mmol), $PdCl_2(MeCN)_2$ (0.05 mmol), CuX_2 (5 mmol) and K_2CO_3 (1 mmol) in MeCN (5 mL) was refluxed for 3 h. After cooling, solvent was evaporated under reduced pressure, brine was added (10 mL) and the solution was extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was dried over Na_2SO_4 then the solvent was evaporated under reduced pressure. The products were purified by flash chromatography.

10-Chloro-4-(chloromethyl)-2-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (9a): Yield: 91%; eluent: hexane/AcOEt 2:1; white solid; mp 151 °C (*i*-Pr_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.20 (s, 3H), 3.62–3.74 (m, 2H), 3.90 (dd, *J* = 1.2, 13.2 Hz, 1H), 4.04 (dd, *J* = 4.0, 13.2 Hz, 1H), 4.68–4.72 (m, 1H), 7.25 (dd, *J* = 8.1, 8.2 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.42 (dd, *J* = 8.2, 8.3 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.4 (q), 41.1 (t), 48.5 (t), 52.1 (d), 109.4 (d), 111.7 (s), 112.9 (s), 120.6 (d), 121.8 (d), 126.1 (s), 126.4 (d), 133.5 (s), 158.7 (s); IR: ν = 1672 cm^{-1}; MS: *m/z* = 282 (M^+); anal. calcd. for $C_{13}H_{12}Cl_2N_2O$: C 55.14, H 4.27, N 9.89; found: C 55.36, H 4.06, N 9.78.

10-Chloro-4-(chloromethyl)-2-cyclohexyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (9b): Yield: 85%; eluent: hexane/AcOEt 7:3; white solid; mp 163 °C (*i*-Pr_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13–1.98 (m, 10H), 3.61–3.69 (m, 2H), 3.75–3.78 (m, 1H), 3.99–4.02 (m, 1H), 4.61–4.77 (m, 2H), 7.24–7.42 (m, 3H), 7.75 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4 (t), 25.6 (t), 25.7 (t), 30.1 (t), 30.3 (t), 40.5 (t), 40.9 (t), 51.1 (d), 52.2 (d), 109.3 (d), 111.7 (s), 120.5 (d), 121.7 (d), 122.0 (s), 126.2 (s), 126.3 (d), 133.3 (s), 158.0 (s); IR: ν = 1678 cm^{-1}; MS: *m/z* = 350 (M^+); anal. calcd. for $C_{18}H_{20}Cl_2N_2O$: C 61.55, H 5.93, N 7.97; found: C 61.45, H 5.83, N 8.12.

10-Chloro-4-(chloromethyl)-2-phenyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (9c): Yield: 81%; eluent: hexane/AcOEt 65:35; white solid; mp 197 °C (*i*-Pr_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.77 (d, *J* = 10.3 Hz, 1H), 3.90 (dd, *J* = 10.3, 10.5 Hz, 1H), 4.31 (d, *J* = 12.6 Hz, 1H), 4.44 (d, *J* = 12.6 Hz, 1H), 4.76–4.82 (m, 1H), 7.27–7.46 (m, 8H), 7.78 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.1 (t), 50.1 (t), 52.5 (d), 109.5 (d), 113.0 (s), 120.7 (d), 121.7 (s), 121.9 (d), 125.7 (d), 126.2 (s), 126.8 (d), 127.1 (d), 129.3 (d), 133.7 (s), 141.1 (s), 157.8 (s); IR: ν = 1673 cm^{-1}; MS: *m/z* = 344 (M^+); anal. calcd. for $C_{18}H_{14}Cl_2N_2O$: C 62.62, H 4.09, N 8.11; found: C 62.43, H 4.18, N 8.23.

2-Allyl-10-chloro-4-(chloromethyl)-3,4-dihydro-pyrazino-[1,2-*a*]indol-1(2*H*)-one (9d): Yield: 83%; eluent: hexane/AcOEt 7:3; pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.60–3.68 (m, 2H), 3.90–3.93 (m, 2H), 4.00–4.06 (m, 1H), 4.41–4.48 (m, 1H), 4.62–4.73 (m, 1H), 5.31–5.38 (m, 2H), 5.81–5.93 (m, 1H), 7.26 (dd, *J* = 7.1, 7.9 Hz, 1H), 7.36 (dd, *J* = 7.1, 8.1 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.0 (t), 45.6 (t), 48.6 (t), 52.2 (d), 109.4 (d), 112.0 (s), 119.8 (t), 120.6 (d), 121.6 (s), 121.8 (d), 126.1 (s), 126.5 (d), 132.2 (d), 133.6 (s), 158.1 (s); IR: ν = 1668 cm^{-1}; MS: *m/z* = 308 (M^+); anal. calcd. for $C_{15}H_{14}Cl_2N_2O$: C 58.27, H 4.56, N 9.06; found: C 58.44, H 4.25, N 8.82.

10-Bromo-4-(bromomethyl)-2-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (10a): Yield: 73%; eluent: hexane/AcOEt 1:1; pale yellow solid; mp 141 °C (*i*-Pr_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.21 (s, 3H), 3.41–3.49 (m, 1H), 3.51–3.61 (m, 1H), 3.91–3.99 (m, 1H), 4.05–4.11 (m, 1H), 4.73–4.83 (m, 1H), 7.25 (dd, *J* = 8.1, 8.8 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.41 (dd, *J* = 8.1, 7.9 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.7 (t), 34.6 (q), 49.0 (t), 52.1 (d), 97.4 (s), 109.6 (d), 120.6 (s), 121.7 (d), 121.9 (d), 123.0 (s), 126.4 (d), 134.2 (s), 158.8 (s); IR: ν = 1665 cm^{-1}; MS: *m/z* = 372 (M^+); anal. calcd. for $C_{13}H_{12}Br_2N_2O$: C 41.97, H 3.25, N 7.53; found: C 41.88, H 3.44 N, 7.41.

10-Bromo-4-(bromomethyl)-2-cyclohexyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (10b): Yield: 75%; eluent: hexane/AcOEt 8:2; light orange solid; mp 159 °C (*i*-Pr_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.72–2.12 (m, 10H), 3.43–3.55 (m 2H), 3.72–3.81 (m, 1H), 4.05–4.09 (m, 1H), 4.65–4.79 (m, 2H), 7.26–7.43 (m, 3H), 7.71 (d, *J* = 8.1 Hz, 1H);

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^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6 (t), 28.2 (t), 30.1 (t), 30.5 (t), 41.4 (t), 51.2 (d), 52.1 (d), 97.4 (s), 109.3 (d), 121.7 (d), 121.9 (d), 123.3 (d), 126.3 (s), 128.0 (s), 134.0 (s), 158.0 (s); IR: ν = 1669 cm^{-1}; MS: *m/z* = 440 (M^+); anal. calcd. for $C_{18}H_{20}Br_2N_2O$: C 49.12, H 4.58, N 6.36; found: C 49.25, H 4.31, N 6.40.

10-Bromo-4-(bromomethyl)-2-phenyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (10c): Yield: 71%; eluent: hexane/AcOEt 65:35; pale orange solid; mp 164 °C (*i*-Pr_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.55–3.62 (m, 1H), 3.69–3.79 (m, 1H), 4.44–4.49 (m, 2H), 4.83–4.95 (m, 1H), 7.20–7.47 (m, 8H), 7.72–7.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.5 (t), 50.5 (t), 52.5 (d), 98.1 (s), 109.5 (d), 121.8 (d), 122.1 (d), 125.8 (d), 126.8 (d), 127.3 (d), 128.0 (s), 129.3 (d), 132.7 (s), 134.3 (s), 141.1 (s), 157.9 (s); IR: ν = 1658 cm^{-1}; MS: *m/z* = 434 (M^+); anal. calcd. for $C_{18}H_{14}Br_2N_2O$: C 49.80, H 3.25, N 6.45; found: C 50.01, H 3.02, N 6.62.

Synthesis of *N*-Allyl-3-chloro-*N*-methyl-1*H*-indole-2-carboxamide (11)

A solution of *N*-allyl-*N*-methyl-1*H*-indole-2-carboxamide **1a** (1 mmol), $CuCl_2$ (5 mmol) and K_2CO_3 (1 mmol) in MeCN (5 mL) was refluxed for 3 h. After cooling, the solvent was evaporated under reduced pressure, brine was added (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was dried over Na_2SO_4 then the solvent was evaporated under reduced pressure. The product was purified by flash chromatography (eluent: hexane/AcOEt 1:1) to afford a yellow oil; yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.17 (s, 3H), 4.20–4.21 (m, 2H), 5.25–5.32 (m, 2H), 5.84–5.89 (m, 1H), 7.19 (dd, *J* = 7.2, 8.0 Hz, 1H), 7.28 (dd, *J* = 7.2, 8.3 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 9.71 (s br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.4 (q), 53.1 (t), 112.1 (d), 118.3 (t), 119.0 (d), 120.9 (d), 122.1 (d), 124.8 (d), 125.3 (s), 126.5 (s), 130.8 (s), 134.9 (s), 163.6 (s); IR: ν = 1658 cm^{-1}; MS: *m/z* = 248 (M^+); anal. calcd. for $C_{13}H_{13}ClN_2O$: C 62.78, H 5.27, N 11.26; found: C 62.91, H 5.01, N 11.07.

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