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Article

Rhodium(III)-Catalyzed Addition of Indoles with Boc-Imines via C–H Bond Activation

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A rhodium-catalyzed alkylation reaction of indoles with *N*-Boc-imines has been developed via C–H activation to afford a series of substituted 2-indolyl-methanamine derivatives with good functional group tolerance and regioselectivity. A wide range of indole-based alkylation products could be obtained in up to 95% yield.

Keywords: rhodium(III)-catalysis, C–H activation, indole

Introduction

Transition-metal-catalyzed aromatic C–H functionalization has been recognized to be a highly important synthetic tool for its atom-economical routes to functionalized aromatic molecules.[1] Recently, it has been demonstrated that Rh^{III} catalysts are highly efficient for the activation of sp^2 C–H bonds of aromatic compounds in the coupling with unsaturated molecules and with electrophilic reagents.[2] Particularly, Rh^{III} catalytic C–H bond activation is an attractive strategy for preparing amino-containing aromatic compounds which are commonly found in pharmaceuticals as well as natural products and functional materials.[3]

Indoles derivatives are of great interest in organic synthesis because of their presence in numerous natural products and pharmaceuticals.[4] Among them, 2-indolyl-methanamine derivatives are particularly important because of their ubiquitous presence in numerous biologically active compounds.[5-9] Therefore, methods for a general, rapid, and regioselective preparation of 2-indolyl-methanamines would be highly desirable. Zhou *et al.*[10] successfully reported a Rh^{III}-catalyzed regioselective addition of indole C–H bonds to aryl- and alkyl-*N*-sulfonylimines for the preparation of 2-indolyl-methanamine derivatives with good functional group tolerance, but in relatively low yields (between 42 to 71%, see Scheme 1). Due to the importance of 2-indolyl methanamine derivatives, herein we report a rhodium(III)-catalyzed direct and selective C-2 alkylation reaction of indoles with *N*-Boc-imines via C–H activation, affording a series of substituted 2-indolyl-methanamine derivatives with good functional group tolerance and in high yields under mild conditions. These compounds are potential building blocks for preparing biologically active compounds.

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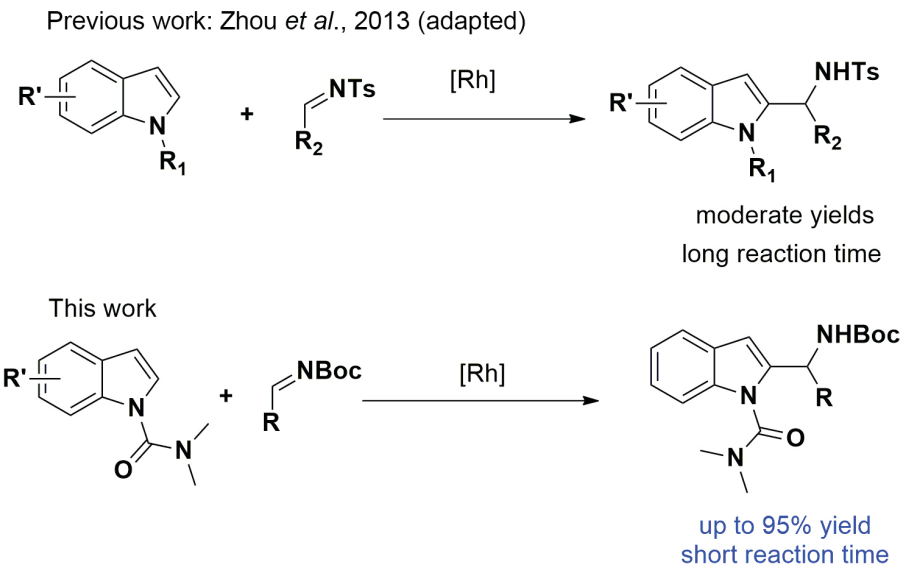
Results and Discussion

To explore the optimum reaction conditions, 1-(*N*,*N*-dimethylcarbamoyl) indole (**1a**) and benzaldehyde *N*-(*tert*-butoxycarbonyl)imine (**2a**) were chosen as model substrates for the synthesis of 2-indolylmethanamine derivative (**3a**) (Table 1). Initially, we applied $[RhCp^*Cl_2]_2$ (5 mol%) as a catalyst without any additive. However, no desired product was detected after 6 h, and **1a** was mostly recovered (Table 1, entry 1). Then we chose $AgCO_2CF_3$ as an additive and partial conversion of **1a** was observed after 6 h at 75 °C with a low yield of 30% (Table 1, entry 2). Replacement of $AgCO_2CF_3$ with $AgSO_3CF_3$ did not give a satisfactory result (Table 1, entry 3) too. To our delight, switching the additive to $AgSbF_6$ gave rise to an efficient coupling with up to 85% isolated yield (Table 1, entry 4). When the reaction was not performed under an inert nitrogen atmosphere, the yield decreased sharply from 85 to 34% (Table 1, entry 5). Strong solvent effects have also been observed, such as the reaction proceeded well in 1,2-dichloroethane (DCE) and dichloromethane (DCM), whereas toluene (PhMe) and *tert*-butyl alcohol (*t*-BuOH) were not suitable for this reaction, in which we could not observe the full conversion of starting materials despite prolonging the reaction time to 24 h (Table 1, entries 6-8). Reducing the amount of either catalyst or additive led to decreased yields (Table 1, entries 9-10).

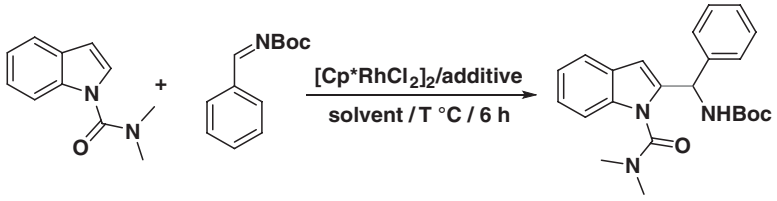


Scheme 1. Synthetic strategies to produce 2-indolyl-methanamines.

Further investigations revealed that the reaction could occur at a milder temperature (Table 1, entry 11). When the temperature was raised to 50 °C, the yield dropped down to 68% (Table 1, entry 12) and many side products were detected. Altogether, the optimal result was obtained by treating **1a** and 1.5 equivalent of **2a** in DCE using catalyst $[RhCp^*Cl_2]_2$ (5 mol%) and additive $AgSbF_6$ (20 mol%) at 75 °C for 6 h under an inert nitrogen atmosphere.

Under the aforementioned optimized reaction condition, we examined the substrate scope of this reaction with various substituted 1-(*N*,*N*-dimethylcarbamoyl) indoles and imines (Table 2). In general, a range of substituted

Table 1. Optimization of the Rh-catalyzed direct addition reaction[a]

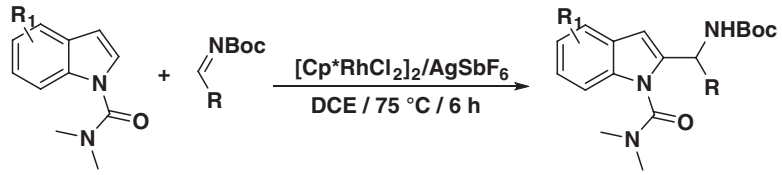


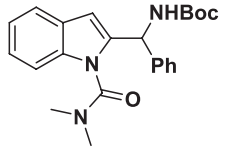
1a **2a** **3a**

entry	Catalyst	Solvent	Additive	Temperature / °C	time / h	Yield[b] / %
1	$[Cp^*RhCl_2]_2$	DCE	–	75	6	0
2	$[Cp^*RhCl_2]_2$	DCE	$AgCO_2CF_3$	75	6	30
3	$[Cp^*RhCl_2]_2$	DCE	$AgSO_3CF_3$	75	6	37
4	$[Cp^*RhCl_2]_2$	DCE	$AgSbF_6$	75	6	85
5[c]	$[Cp^*RhCl_2]_2$	DCE	$AgSbF_6$	75	6	34
6	$[Cp^*RhCl_2]_2$	PhMe	$AgSbF_6$	75	24	61
7	$[Cp^*RhCl_2]_2$	*t*-BuOH	$AgSbF_6$	75	24	23
8	$[Cp^*RhCl_2]_2$	DCM	$AgSbF_6$	75	6	71
9[d]	$[Cp^*RhCl_2]_2$	DCE	$AgSbF_6$	75	6	47
10[e]	$[Cp^*RhCl_2]_2$	DCE	$AgSbF_6$	75	6	62
11	$[Cp^*RhCl_2]_2$	DCE	$AgSbF_6$	25	6	72
12	$[Cp^*RhCl_2]_2$	DCE	$AgSbF_6$	50	6	68

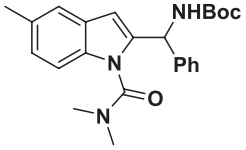
[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), catalyst (5 mol%), additive (20 mol%), and solvent (1.0 mL) at 75 °C for 6 h under nitrogen; [b]yield of isolated product; [c]the reaction was carried out under air; [d]the amount of catalyst was decreased to 2.5 mol%; [e]the amount of additive was decreased to 10 mol%; DCE: 1,2-dichloroethane; PhMe: toluene; *t*-BuOH: *tert*-butyl alcohol; DCM: dichloromethane.

Table 2. Substrate scope for the Rh^{III}-catalyzed addition reaction[a,b]

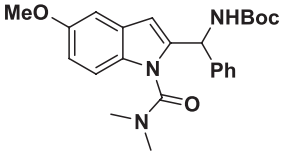




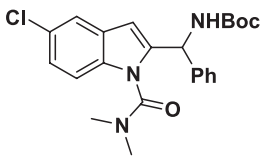
3a, 88%



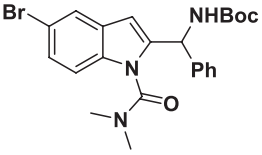
3b, 95%



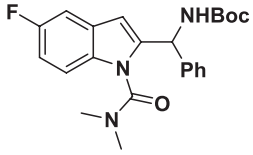
3c, 88%



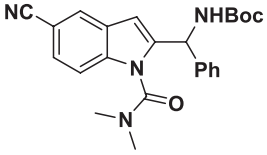
3d, 72%



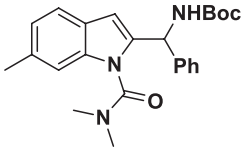
3e, 84%



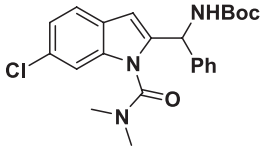
3f, 71%



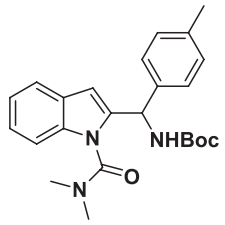
3g, 70%



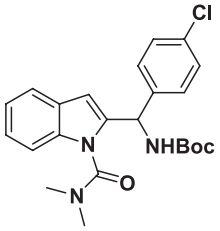
3h, 87%



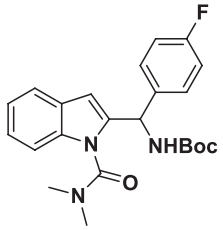
3i, 74%



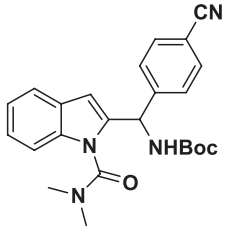
3j, 84%



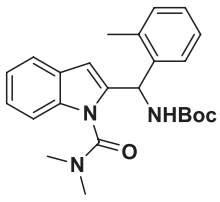
3k, 85%



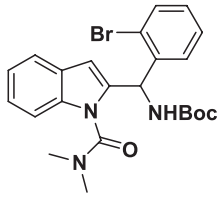
3l, 87%



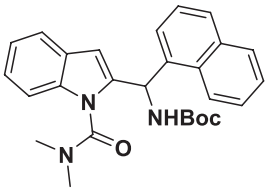
3m, 90%



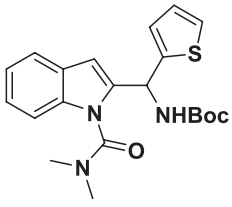
3n, 80%



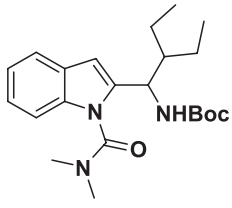
3o, 81%



3p, 77%



3q, 72%



3r, 68%

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.30 mmol), catalyst (5 mol%), additive (20 mol%), and solvent (2.0 mL) at 75 ºC for 6 h under nitrogen; [b]yield of isolated product.

1-(*N*,*N*-dimethylcarbamoyl) indole derivatives and imines with electron-withdrawing or electron-donating groups were all successfully transformed into the corresponding adducts in good to excellent yields (68-95%, **3a**-**3o**). Introduction of electron-donating groups (-Me, and -OMe) to the indole ring gave high yields (**3b** and **3c**). The chloro (**3d**) and bromo (**3e**) atoms were highly compatible with this addition reaction. Tolerance to the chloro and bromo is especially noteworthy since they are useful for subsequent cross-coupling reactions. However, the substrates substituted by a fluoro and cyano moiety at the 5-position of the indole resulted in slightly decreased yields, respectively (**3f** and **3g**). Substitution with methyl or chloro at 6-position of indole also gave good yields (**3h** and **3i**). The results also indicated that the electronic property of the substitutes and the positions of substitution on the benzene ring of imines have no significant influence on the yields of these adducts (**3j**-**3o**). Nathphyl, thiofuran and 3-amyl groups were also introduced to the imines and good yields were obtained (**3p**-**3r**).

Furthermore, a gram-scale reaction was conducted to evaluate the reaction efficacy on a preparative scale. The reaction of 1-(*N*,*N*-dimethylcarbamoyl)indole (**1a**) with benzaldehyde *N*-(*tert*-butoxycarbonyl)imine (**2a**) under the standard conditions provided the target product in 87% yield (Scheme 2). Therefore, the present method is very effective for the synthesis of **3a**.

Based on the previous work,[3,11,12] we proposed the following mechanism (Scheme 3). First, an active catalyst is generated through anion exchange with $AgSbF_6$, then a *N*,*N*-dimethylcarbamoyl-directed C–H bond activation occur through deprotonation-metalation to give **A**, coordination of the *N*-Boc-imine (**B**) would then activate the imine for migratory insertion to form the *N*-Rh species **C**. In the last step, **C** is protonated to provide the desired indole derivative **3** accompanied by the regeneration of the active catalyst.

Conclusions

In summary, we have developed an efficient methodology for the addition of 1-(*N*,*N*-dimethylcarbamoyl) indoles with *tert*-butyloxy carbonyl protected imines via Rh^{III}-catalyzed C–H activation reaction to afford biologically relevant 2-indolylmethanamines with good functional group tolerance and selectivity in good to excellent yields. In view of the potential use of these 2-indolylmethanamines, we expect this method to be widely used in the pharmaceutical field.

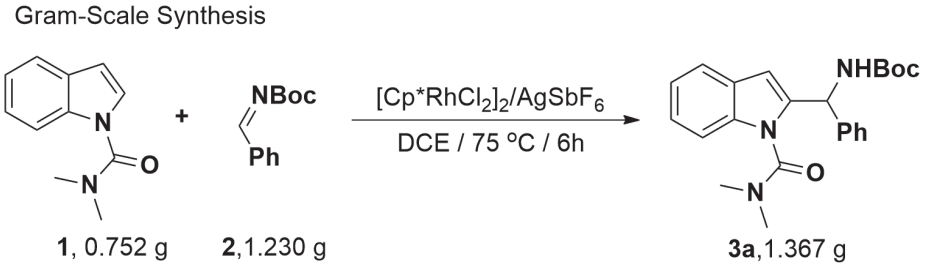
Experimental

General information

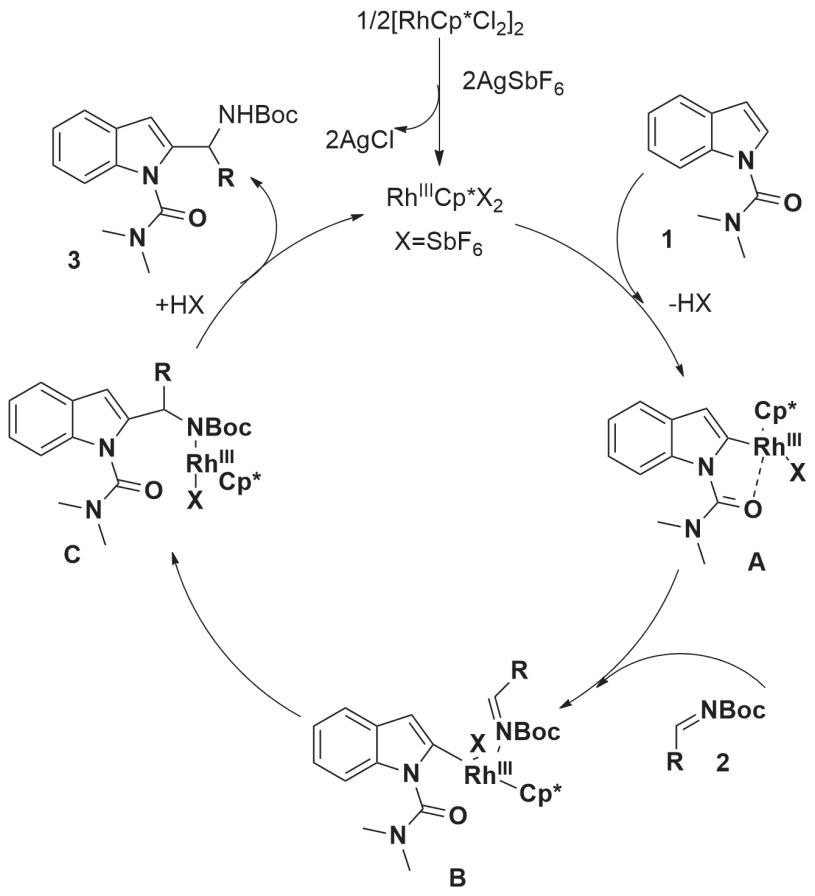
The analytical thin layer chromatography (TLC) used was HSGF 254 (0.15-0.2 mm thickness). All products were characterized by their nuclear magnetic resonance (NMR) and mass spectrometry (MS) spectra. ^1H and ^{13}C NMR spectra were recorded on a 400 or 500 MHz instrument using tetramethylsilane as internal reference. Data are presented as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, t = triplet, m = multiplet), *J* = coupling constant in hertz (Hz). Silica gel 60H (200-300 mesh) manufactured by Qingdao Haiyang Chemical Group Co. (China) was used for general chromatography. Dichloromethane, 1,2-dichloroethane and toluene were distilled over CaH_2. $AgSbF_6$, AgOTf, $AgSO_3CF_3$ and $[Cp^*RhCl_2]_2$ were purchased from Energy Chemical Co. and used without further purification. Substrate 1-(*N*,*N*-dimethylcarbamoyl) indoles[10] and *N*-boc imines[13-18] were synthesized according to published procedures.

General synthesis procedures of **3a** to **3r**

In a reaction tube, $[Cp^*RhCl_2]_2$ (0.01 mmol, 6.2 mg), $AgSbF_6$ (0.04 mmol, 13.7 mg), substrate **1a** (0.20 mmol, 1.0 equiv), and **2a** (0.30 mmol, 1.5 equiv) were added followed by addition of DCE (2.0 mL). The vessel was sealed and heated at 75 °C (oil bath temperature) for 6 h under an inert nitrogen atmosphere. The resulting mixture was cooled to room temperature, filtered through a short silica gel pad and transferred to silica gel column directly to give the product. Following general procedure,



Scheme 2. Gram-scale synthesis.



Scheme 3. Proposed catalytic cycle.

compound **3a** was purified by column chromatography on silica gel using petroleum ether:ethyl acetate (5:1) in 85% isolated yield as an off-white solid.

Analytical characterization data of products

tert-Butyl((1-(dimethylcarbamoyl)-1*H*-indol-2-yl)(phenyl) methyl)carbamate (**3a**)

Following a general procedure: 69 mg, 88% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.62 (d, 1H, *J* 8.0 Hz, Ar-H), 7.47-7.45 (d, 1H, *J* 8.0 Hz, Ar-H), 7.39-7.26 (m, 6H, Ar-H, N-H), 7.15 (m,1H, Ar-H), 6.95 (s, 1H, Ar-H), 6.20 (s, Ar-1H), 5.22 (s, 1H, C-H), 3.06 (s, 6H, $N(CH_3)_2$), 1.48 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.10, 154.85, 136.25, 128.58, 127.60, 127.51, 126.95, 124.93, 124.00, 121.82, 120.84, 119.88, 113.60, 79.82, 51.42, 38.44, 28.40; HRMS (ESI) *m/z* calcd. for $C_{23}H_{28}N_3O_3^+$ [M + H]$^+$: 394.2125; found: 394.2121.

tert-Butyl((1-(dimethylcarbamoyl)-5-methyl-1*H*-indol-2-yl) (phenyl)methyl)carbamate (**3b**)

Following a general procedure: 77.3 mg, 95% yield; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.50 (d, 1H, *J* 8.4 Hz, Ar-H), 7.41-7.36 (m, 4H, Ar-H, N-H), 7.33-7.30 (m, 2H, Ar-H), 7.15-7.13 (dd, 1H, *J* 8.4, 1.1 Hz, Ar-H), 6.87 (s, 1H, Ar-H), 6.18 (d, *J* 6.8 Hz, 1H, Ar-H), 5.21 (s, 1H, C-H), 3.04 (s, 6H, $N(CH_3)_2$), 2.42 (s, 3H, CH_3), 1.49 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.17, 154.98, 141.07, 134.48, 131.36, 128.56, 127.89, 127.45, 126.91, 125.50, 125.09, 119.61, 113.31, 79.92, 51.22, 38.45, 28.41, 21.39; HRMS (ESI) *m/z* calcd. for $C_{24}H_{30}N_3O_3^+$ [M + H]$^+$: 408.2282; found: 408.2280.

tert-Butyl((1-(dimethylcarbamoyl)-5-methoxy-1*H*-indol-2-yl) (phenyl)methyl)carbamate (**3c**)

Following general procedure: 74.5 mg, 88% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, 1H, *J* 8.7 Hz, Ar-H), 7.38-7.29 (m, 5H, Ar-H, N-H), 6.93-6.85 (m, 3H, Ar-H), 6.15 (s, 1H, Ar-1H), 5.17 (s, 1H, C-H), 3.77 (s, 3H, CH_3), 3.01 (s, 6H, $N(CH_3)_2$), 1.45 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.54, 155.33, 155.15, 131.31, 128.79, 128.58, 127.72, 127.13, 125.69, 114.68, 113.74, 102.13, 79.75, 55.89, 51.22, 38.68, 28.61; HRMS (ESI) *m/z* calcd. for $C_{24}H_{30}N_3O_4^+$ [M + H]$^+$: 424.2231; found: 424.2232.

tert-Butyl((5-chloro-1-(dimethylcarbamoyl)-1*H*-indol-2-yl)(phenyl)methyl)carbamate (**3d**)

Following general procedure: 61.5 mg, 72% yield; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.38-7.37 (m, 4H, Ar-H, N-H), 7.34-7.32 (m, 2H, Ar-H), 7.14 (dd, 1H, *J* 8.4 Hz, 1.5 Hz, Ar-H), 6.96 (s, 1H, Ar-H), 6.17 (s, 1H), 5.17 (s, 1H), 3.06 (s, 6H, $N(CH_3)_2$), 1.48 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.07, 154.40, 136.71, 130.10, 128.70, 127.72, 126.97, 126.06, 125.29, 122.56, 120.71, 113.80, 77.23, 51.29, 38.45, 28.38; HRMS (ESI) *m/z* calcd. for $C_{23}H_{27}ClN_3O_3^+$ $[M + H]^+$: 428.1735; found: 428.1727.

tert-Butyl((5-bromo-1-(dimethylcarbamoyl)-1*H*-indol-2-yl)(phenyl)methyl)carbamate (**3e**)

Following general procedure: 79.1 mg, 84% yield; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.53-7.51 (d, 1H, *J* 8.8 Hz, Ar-H), 7.41-7.38 (m, 5H, Ar-H), 7.35-7.33 (m, 1H, Ar-H), 6.92 (s, 1H, Ar-H), 6.16 (s, 1H, Ar-H), 5.19 (s, 1H), 3.04 (s, 6H, $N(CH_3)_2$), 1.49 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.05, 154.37, 135.02, 129.26, 128.72, 127.74, 126.96, 126.91, 125.88, 122.57, 120.45, 115.19, 115.12, 99.99, 80.10, 51.30, 38.44, 28.40; HRMS (ESI) *m/z* calcd. for $C_{23}H_{27}BrN_3O_3^+$ $[M + H]^+$: 472.1231; found: 472.1233.

tert-Butyl((1-(dimethylcarbamoyl)-5-fluoro-1*H*-indol-2-yl)(phenyl)methyl)carbamate (**3f**)

Following general procedure: 58.3 mg, 71% yield; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60-7.59 (s, 1H, Ar-H), 7.38-7.28 (m, 5H, Ar-H, N-H), 7.06-6.99 (m, 3H, Ar-H), 6.14 (s, 1H, Ar-H), 5.20 (s, 1H), 3.06 (s, 6H, $N(CH_3)_2$), 1.48 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.58, 157.69, 155.08, 154.65, 140.54, 132.79, 128.72, 127.72, 126.96, 126.22, 114.62, 112.09, 105.36, 79.94, 51.19, 38.47, 28.38; HRMS (ESI) *m/z* calcd. for $C_{23}H_{27}FN_3O_3^+$ $[M + H]^+$: 412.2031; found: 412.2033.

tert-Butyl((5-cyano-1-(dimethylcarbamoyl)-1*H*-indol-2-yl)(phenyl)methyl)carbamate (**3g**)

Following general procedure: 58.5 mg, 70% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.69 (m, 2H, Ar-H), 7.53-7.51 (d, 1H, *J* 8.0 Hz, Ar-H), 7.37-7.33 (m, 5H, Ar-H, N-H), 7.08 (s, 1H, Ar-H), 6.15 (s, 1H), 5.13 (s, 1H), 3.05 (s, 6H, $N(CH_3)_2$), 1.46 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.18, 153.98, 140.35, 138.38, 129.13, 128.27, 127.64, 127.18, 126.82, 125.43, 121.43, 119.95, 114.75, 105.49, 80.53, 51.67, 38.63, 28.58; HRMS (ESI) *m/z* calcd. for $C_{24}H_{27}N_4O_3^+$ $[M + H]^+$: 419.2078; found: 419.2077.

tert-Butyl((1-(dimethylcarbamoyl)-6-methyl-1*H*-indol-2-yl)(phenyl)methyl)carbamate (**3h**)

Following general procedure: 70.8 mg, 87% yield; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H, Ar-H), 7.41-7.35 (m, 4H, Ar-H, N-H), 7.32-7.30 (m, 2H, Ar-H), 7.00 (d, 1H, *J* 10.0 Hz, Ar-H), 6.87 (s, 1H, Ar-H), 6.17 (s, 1H), 5.21 (s, 1H), 3.05 (s, 6H, $N(CH_3)_2$), 2.48 (s, 3H), 1.48 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.13, 155.01, 141.04, 136.74, 134.12, 128.55, 127.46, 126.95, 125.38, 124.25, 123.44, 119.46, 113.74, 79.78, 51.21, 38.42, 28.40, 21.84; HRMS (ESI) *m/z* calcd. for $C_{24}H_{30}N_3O_3^+$ $[M + H]^+$: 408.2282; found: 408.2279.

tert-Butyl((6-chloro-1-(dimethylcarbamoyl)-1*H*-indol-2-yl)(phenyl)methyl)carbamate (**3i**)

Following general procedure: 63.2 mg, 74% yield; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, 1H, *J* 10.0 Hz, Ar-H), 7.43 (s, 1H, Ar-H), 7.39-7.38 (m, 4H, Ar-H, N-H), 7.36-7.32 (m, 1H, Ar-H), 7.27 (dd, 1H, *J* 8.8, 1.9 Hz, Ar-H), 6.96 (s, 1H, Ar-H), 6.16 (s, 1H), 5.18 (s, 1H), 3.05 (s, 6H, $N(CH_3)_2$), 1.48 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.08, 154.44, 134.72, 128.73, 127.75, 127.59, 126.93, 126.01, 124.34, 120.47, 119.50, 114.74, 80.07, 51.21, 38.45, 28.39; HRMS (ESI) *m/z* calcd. for $C_{23}H_{27}ClN_3O_3^+$ $[M + H]^+$: 428.1736; found: 428.1733.

tert-Butyl((1-(dimethylcarbamoyl)-1*H*-indol-2-yl)(*p*-tolyl)methyl)carbamate (**3j**)

Following general procedure: 68.4 mg, 84% yield; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, 1H, *J* 10.0 Hz, Ar-H), 7.43 (d, 1H, *J* 10.0 Hz, Ar-H), 7.30-7.25 (m, 3H, Ar-H, N-H), 7.16-7.13 (m, 3H, Ar-H), 6.95 (s, 1H, Ar-H), 6.14 (s, 1H), 5.16 (s, 1H), 3.04 (s, 6H, $N(CH_3)_2$), 2.35 (s, 3H, CH_3), 1.46 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.11, 154.92, 137.13, 136.28, 129.28, 127.66, 126.88, 124.83, 123.95, 121.78, 121.04, 120.99, 119.94, 113.59, 100.23, 79.91, 50.99, 38.45, 28.41, 21.13; HRMS (ESI) *m/z* calcd. for $C_{24}H_{30}N_3O_3^+$ $[M + H]^+$: 408.2282; found: 408.2282.

tert-Butyl((4-chlorophenyl)(1-(dimethylcarbamoyl)-1*H*-indol-2-yl)methyl)carbamate (**3k**)

Following general procedure: 72.6 mg, 85% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 1H, *J* 8.0 Hz, Ar-H), 7.42 (d, 1H, *J* 8.0 Hz, Ar-H), 7.32-7.28 (m, 5H, Ar-H, N-H), 7.17 (t, 1H, *J* 8.0 Hz, Ar-H), 6.91 (s, 1H, Ar-H), 6.15 (s, 1H), 5.14 (s, 1H), 3.04 (s, 6H, $N(CH_3)_2$), 1.45 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.26, 154.94, 139.98, 136.46, 133.44, 128.94, 128.52, 127.58, 125.17, 124.37, 122.14, 120.46, 119.94, 113.86, 80.27, 51.17, 38.64, 28.59; HRMS (ESI) *m/z* calcd. for $C_{23}H_{27}N_3O_3Cl^+$ $[M + H]^+$: 428.1736; found: 428.1736.

tert-Butyl((1-(dimethylcarbamoyl)-1*H*-indol-2-yl)(4-fluorophenyl)methyl)carbamate (**3l**)

Following general procedure: 71.5 mg, 87% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, 1H, *J* 6.6 Hz, Ar-H), 7.43 (d, 1H, *J* 6.1 Hz, Ar-H), 7.39-7.36 (m, 2H, Ar-H), 7.34-7.30 (m, 1H, Ar-H), 7.17-7.20 (m, 1H, Ar-H), 7.06 (t, 2H, *J* 6.2 Hz, Ar-H), 6.95 (s, 1H, Ar-H), 6.17 (s, 1H), 5.20 (s, 1H), 3.06 (s, 6H, $N(CH_3)_2$), 1.48 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.10, 161.15, 155.06, 154.78, 136.25, 130.92, 128.52, 127.41, 124.91, 124.12, 121.89, 120.58, 119.79, 115.52, 113.64, 80.00, 50.86, 38.45, 28.38; HRMS (ESI) *m/z* calcd. for $C_{23}H_{27}FN_3O_3^+$ $[M + H]^+$: 412.2031; found: 412.2023.

tert-Butyl((4-cyanophenyl)(1-(dimethylcarbamoyl)-1*H*-indol-2-yl)methyl)carbamate (**3m**)

Following general procedure: 75.2 mg, 90% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61(d, 2H, *J* 8.0 Hz, Ar-H), 7.57 (d, 1H, *J* 8.0 Hz, Ar-H), 7.50 (d, 2H, *J* 8.0 Hz, Ar-H), 7.41 (d, 1H, *J* 8.0 Hz, Ar-H), 7.32-7.28 (m, 1H, Ar-H), 7.17 (t, 1H, *J* 8.0 Hz, Ar-H), 6.89 (s, 1H, Ar-H), 6.19 (s, 1H), 5.37 (s, 1H), 3.01 (s, 6H, $N(CH_3)_2$), 1.44 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.08, 157.50, 149.73, 139.07, 135.39, 130.59, 130.09, 128.09, 127.33, 125.07, 122.47, 122.25, 121.72, 116.67, 114.25, 83.29, 54.22, 41.39, 31.33; HRMS (ESI) *m/z* calcd. for $C_{24}H_{27}N_4O_3^+$ $[M + H]^+$: 419.2078; found: 419.2075.

tert-Butyl((1-(dimethylcarbamoyl)-1*H*-indol-2-yl)(*o*-tolyl)methyl)carbamate (**3n**)

Following general procedure: 70.8 mg, 87% yield; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* 8.2 Hz, 1H), 7.54-7.53 (m, 1H, Ar-H), 7.34-7.31 (m, 2H, Ar-H), 7.24-7.20 (m, 4H, Ar-H), 6.78 (s, 1H, Ar-H), 6.38 (s, 1H, Ar-H), 5.19 (s, 1H), 3.02 (s, 6H, $N(CH_3)_2$), 2.36 (s, 3H, CH_3), 1.49 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.01, 154.83, 139.17, 136.27, 135.77, 130.67, 127.81, 127.43, 126.17, 125.83, 125.04, 124.04, 121.85, 120.46, 119.80, 113.57, 79.74, 48.22, 38.40, 28.41, 19.17; HRMS (ESI) *m/z* calcd. for $C_{24}H_{30}N_3O_3^+$ $[M + H]^+$: 408.2282; found: 408.2279.

tert-Butyl((2-bromophenyl)(1-(dimethylcarbamoyl)-1*H*-indol-2-yl)methyl)carbamate (**3o**)

Following general procedure: 76.3 mg, 81% yield; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64-7.60 (m, 3H, Ar-H), 7.50 (d, 1H, *J* 5.0 Hz, Ar-H), 7.39-7.32 (m, 2H, Ar-H), 7.25-7.19 (m, 2H, Ar-H), 6.78 (s, 1H, Ar-H), 6.48 (s, 1H, Ar-H), 5.27 (s, 1H), 3.03 (s, 6H, $N(CH_3)_2$), 1.49 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.89, 154.75, 136.18, 133.33, 129.05, 127.97, 127.65, 125.24, 124.11, 121.93, 119.72, 113.59, 79.99, 51.37, 38.44, 28.38; HRMS (ESI) *m/z* calcd. for $C_{23}H_{27}N_3O_3^+$ $[M + H]^+$: 472.1231; found 472.1231.

tert-Butyl((1-(dimethylcarbamoyl)-1*H*-indol-2-yl)(naphthalen-1-yl)methyl)carbamate (**3p**)

Following general procedure: 68.2 mg, 77% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, 1H, *J* 8.0 Hz, Ar-H), 7.89-7.81 (m, 2H, Ar-H), 7.64 (d, 1H, *J* 8.2 Hz, Ar-H), 7.51-7.44 (m, 5H, Ar-H), 7.32 (t, 1H, *J* 8.0 Hz, Ar-H), 7.18 (t, 1H, *J* 7.5 Hz, Ar-H), 6.96 (d, 1H, *J* 7.6 Hz, Ar-H), 6.80 (s, 1H, Ar-H), 5.27 (s, 1H), 2.93 (s, 6H, $N(CH_3)_2$), 1.48 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.02, 157.77, 139.26, 136.92, 133.97, 131.70, 131.39, 130.72, 129.28, 128.70, 128.36, 128.29, 127.04, 126.76, 124.87, 123.67, 122.87, 116.61, 82.87, 51.20, 41.34, 31.39; HRMS (ESI) *m/z* calcd. for $C_{27}H_{30}N_3O_3^+$ $[M + H]^+$: 444.2282; found: 444.2284.

tert-Butyl((1-(dimethylcarbamoyl)-1*H*-indol-2-yl)(thiophen-2-yl)methyl)carbamate (**3q**)

Following general procedure: 57.4 mg, 72% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, 1H, *J* 8.0 Hz, Ar-H), 7.47 (d, 1H, *J* 8.0 Hz, Ar-H), 7.32-7.23 (m, 2H, Ar-H, N-H), 7.20-7.15 (m, 2H, Ar-H), 6.98-6.96 (m, 2H, Ar-H), 6.41 (s, 1H, Ar-H), 5.24 (s, 1H), 3.07 (s, 6H, $N(CH_3)_2$), 1.46 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.08, 155.02, 145.65, 136.46, 127.50, 127.06, 125.34, 124.86, 124.77, 124.28, 122.09, 120.49, 120.01, 113.91, 80.32, 47.75, 38.68, 28.59; HRMS (ESI) *m/z* calcd. for $C_{21}H_{26}N_3O_3S^+$ $[M + H]^+$: 400.1690; found: 400.1689.

tert-Butyl(1-(1-(dimethylcarbamoyl)-1*H*-indol-2-yl)-2-ethylbutyl)carbamate (**3r**)

Following general procedure: 52.6 mg, 68% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.59 (m, 2H), 7.31-7.29 (m, 1H, Ar-H), 7.21-7.17 (m, 2H, Ar-H), 5.04 (s, 1H), 4.78 (s, 1H), 3.08 (s, 6H, $N(CH_3)_2$), 1.81 (s, 1H), 1.57 (m, 2H, CH_2), 1.42-1.38 (m, 11H, $C(CH_3)_3$, CH_2), 0.97 (t, *J* 8.0 Hz, 3H, CH_3), 0.89 (t, *J* 8.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.77, 155.32, 136.36, 128.17, 123.97, 123.54, 121.81, 120.65, 119.87, 113.92, 79.65, 49.73, 45.21, 38.70, 29.91, 28.62, 22.87, 21.85, 11.81; HRMS (ESI) *m/z* calcd for. $C_{22}H_{34}N_3O_3^+$ $[M + H]^+$: 388.2595; found: 388.2596.

Supplementary Information

Supplementary information (NMR spectra of new compounds) is available free of charge at http://jbcs.sbq.org.br as PDF file.

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References

1. Colby, D. A.; Bergman, R. G.; Ellman, J. A.; *Chem. Rev.* **2010**, *110*, 624; Song, G.; Wang, F.; Li, X.; *Chem. Soc. Rev.* **2012**, *41*, 3651; Zhang, B.; Li, B.; Zhang, X.; Fan, X.; *Org. Lett.* **2017**, *19*, 2294; Chen, X.; Yang, S.; Li, H.; Wang, B.; Song, G.; *ACS Catal.* **2017**, *7*, 2392; Cai, S.; Lin, S.; Yi, X.; Xi, C.; *J. Org. Chem.* **2017**, *82*, 512; Li, Y.; Wang, Q.; Yang, X.; Xie, F.; Li, X.; *Org. Lett*. **2017**, *19*, 3410; Satoh, T.; Miura, M.; *Chem.-Eur. J.* **2010**, *16*, 11212; Patureau, F. W.; Wencel-Delord, J.; Glorius, F.; *Aldrichimica Acta* **2012**, *45*, 31.
2. Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A.; *Acc. Chem. Res*. **2012**, *45*, 814; Kuhl, N.; Schröder, N.; Glorius, F.; *Adv. Synth. Catal.* **2014**, *356*, 1443; Hyster, T. K.; Dalton, D. M.; Rovis, T.; *Chem. Sci.* **2015**, *6*, 254; Michailidis, F. R.; Sedillo, K. F.; Neely, J. M.; Rovis, T.; *J. Am. Chem. Soc.* **2015**, *137*, 8892; Jia, J. L.; Shi, J. J.; Zhou, J.; Liu, X. L.; Song, Y. L.; Xu, E.; Yi, W.; *Chem. Commun.* **2015**, *51*, 2925; Lu, M. Z.; Lu, P.; Xu, Y. H.; Loh, T.-P.; *Org. Lett.* **2014**, *16*, 2614.
3. Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A.; *J. Am. Chem. Soc.* **2011**, *133*, 1248; Li, X.; Yu, S.; Wang, F.; Wan, B.; Yu, X.; *Angew. Chem., Int. Ed.* **2013**, *52*, 2577; Zhu, C.; Falck, J. R.; *Chem. Commun.* **2012**, *48*, 1674; Wu, X.; Wang, B.; Zhou, Y.; Liu, H.; *Org. Lett.* **2017**, *19*, 12944.
4. Arunotayanun, W.; Gibbons, S.; *Nat. Prod. Rep.* **2012**, *29*, 1304; Ishikura, M.; Yamada, K.; Abe, T.; *Nat. Prod. Rep.* **2010**, *27*, 1630; Lavrado, J.; Moreira, R.; Paulo, A.; *Curr. Med. Chem.* **2010**, *17*, 2348.
5. Bosch, J.; Bennasar, M. L.; *Synlett* **1995**, 587.
6. Faulkner, D. J.; *Nat. Prod. Rep.* **2002**, *19*, 1.
7. Agarwal, S.; Caemmerer, S.; Filali, S.; Froehner, W.; *Curr. Org. Chem.* **2005**, *9*, 1601.
8. O'Connor, S. E.; Maresh, J. J.; *Nat. Prod. Rep.* **2006**, *23*, 532.
9. Zhou, H.; Wang, J.; Yao, B.; Wong, S.; Djakovic, S.; Kumar, B.; Rice, J.; Valle, E.; Soriano, F.; Menon, M. K.; Madriaga, A.; Soly, S. K.; Kumar, A.; Parlati, F.; Yakes, F. M.; Shawver, L.; Moigne, R. L.; Anderson, D. J.; Rolfe, M.; Wustrow, D.; *J. Med. Chem.* **2015**, *58*, 9480.
10. Zhou, B.; Yang, Y.; Lin, S.; Li, Y.; *Adv. Synth. Catal.* **2013**, *355*, 360.
11. Li, Y.; Li, B.; Wang, W.; Huang, W.; Zhang, X.; Chen, K.; Shi, Z.; *Angew. Chem., Int. Ed.* **2011**, *123*, 2163; Liu, X.; Li, X.; Liu, H.; Guo, Q.; Lan, J.; Wang, R.; You, J.; *Org. Lett.* **2015**, *17*, 2936; Wang, H.; Yu, S.; Qi, Z.; Li, X.; *Org. Lett.* **2015**, *17*, 2812; Feng, C.; Loh, T.-P.; *Angew. Chem., Int. Ed.* **2014**, *53*, 2722; Zhou, B.; Du, J.; Yang, Y.; Li, Y.; *Chem.-Eur. J.* **2014**, *20*, 12768; Liu, B.; Hu, P.; Zhou, X.; Bai, D.; Chang, J.; Li, X.; *Org. Lett.* **2017**, *19*, 2086.
12. Chen, J.; Song, G.; Pan, C.-L.; Li, X.; *Org. Lett.* **2010**, *12*, 5426; Huestis, M. P.; Chan, L. N.; Stuart, D. R.; Fagnou, K.; *Angew. Chem., Int. Ed.* **2011**, *50*, 1338; Hoshino, Y.; Shibata, Y.; Tanaka, K.; *Adv. Synth. Catal.* **2014**, *356*, 1577; Shibata, Y.; Tanaka, K.; *Angew. Chem., Int. Ed.* **2011**, *50*, 10917; Ackermann, L.; Lygin, A. V.; *Org. Lett.* **2012**, *14*, 764.
13. Schipper, D. J.; Hutchinson, M.; Fagnou, K.; *J. Am. Chem. Soc*. **2010**, *132*, 6910.
14. Kanazawa, A. M.; Denis, J.; Greene, A. E.; *J. Org. Chem*. **1994**, *59*, 1238.
15. Wenzel, A. G.; Jacobsen, E. N.; *J. Am. Chem. Soc*. **2002**, *124*, 12964.
16. Song, J.; Wang, Y.; Deng, L.; *J. Am. Chem. Soc*. **2006**, *128*, 6048.
17. Gizecki, P.; Ait Youcef, R.; Poulard, C.; Dhal, R.; Dujardin, G.; *Tetrahedron Lett*. **2004**, *45*, 9589.
18. Rampalakos, C.; Wulff, W. D.; *Adv. Synth. Catal*. **2008**, *350*, 1785.

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