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Rhodium-catalyzed coupling of α-lactams with indole derivatives

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ABSTRACT

We report herein a method that allows for the formation of a C–N bond between the *C*–3 carbon of α-lactams and the nitrogen atom of indoles. A general procedure for the coupling of indoles and α-lactams in only 25 min with high yield is reported. The scope of the reaction was extended by the development of a method for the in situ generation of less stable phenyl-substituted α-lactams. The developed method provides an atom-economical method for the formation of substituted α-amino amides that are found in a variety of biologically-active compounds.

1. Introduction

Recent reaction development has focused on methods devoted to either the synthesis or utilization of strained heterocycles, such as, epoxides and aziridines.[1] Aziridinones (α-lactams) are another class of strained heterocycles that were first reported as intermediates in the reaction of diazomethane with isocyanates in 1949 by Sheehan.[2] Since their initial discovery, limited research has been performed on this class of compounds. The presence of a carbonyl group adds additional strain to the molecule as compared to epoxides or aziridines, making them highly reactive.[3] The nucleophilic ring opening of α-lactams with strong nucleophiles results in the product formation from nucleophilic *C*–2 addition, while the addition of weak nucleophiles results in *C*–3 addition.[4,5] In 1984, Alper and co-workers reported the ring-expansion of α-lactams in the presence of Rh and Co catalysts yielding azetidine-2,4-diones.[6] More recently, Jeffrey and co-workers were able to provide the first example of [4+3] cycloaddition involving α-lactams.[7–9] To our knowledge, these are the only two examples in the literature of the ring-expansion of α-lactams.

The indole framework is found in a variety of biologically active compounds and natural products.[10–14] For this reason, the development of catalytic methods for selective functionalization of indole has drawn much attention.[15–17] The preparation of indoles bearing amino acid derivatives would provide a new class of compounds to screen for their biologically-active properties. While the majority of reactions are *C*–3 functionalization, several methods have been developed for the N-functionalization of the indole ring.[18–20] The formation of C–N bonds has played an increasing role in the development of new pharmaceutical compounds over the last 15 years.[21,22] Since initial reports of practical methods for C–N bond formation by Buchwald and Hartwig, this process has been one of the most utilized transformations in organic synthesis.[23–27] Herein we report a Rh-catalyzed *C*–3-*N*–1 ring opening reaction of α-lactams in the formation of a C–N bond with indoles.

2. Results/discussion

A variety of transition metal catalysts were screened and gave <5% of the product (Entries 1–4), however, the reaction proceeded smoothly in the presence of either $[Rh(COD)Cl]_2$ or $[Ir(COD)Cl]_2$ (Entries 5–6). Product formation occurs in both non-polar (Entries 5, 7, 9, 10) and polar aprotic (Entry 8) organic solvents. The desired product was obtained in 88% yield using $[Rh(COD)Cl]_2$, benzene as the solvent, and a microwave reactor as the heat source (Table 1, Entry 5). While a traditional heat source provides the desired product in high yield, the reaction time increases from 25 min to 48 h (Entry 11). The reaction did not proceed in the absence of $[Rh(COD)Cl]_2$ (Entry 12). To exclude the possibility of a nucleophilic substitution mechanism, α-lactam was reacted with an indole anion generated by potassium *tert*-butoxide. The reaction resulted in

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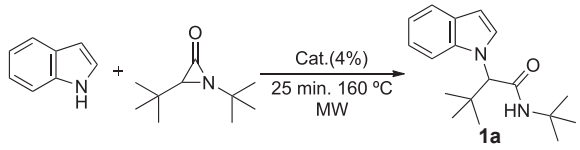
Table 1
Optimization of N-functionalization of indole[a]



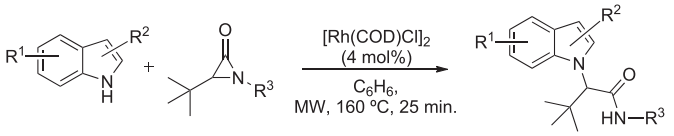
Entry	Cat.	Solvent	Yield (%)[b]
1	$Cu(OTf)_2$	Benzene	<5
2	$[RuCl_2(dmso)_4]$	Benzene	<5
3	[Ir(acac) (COD)]	Benzene	<5
4	$[Rh(nbd)_2]BF_4$	Benzene	<5
5	$[Rh(COD)Cl]_2$	Benzene	88
6	$[Ir(COD)Cl]_2$	Benzene	30
7	$[Rh(COD)Cl]_2$	THF	83
8	$[Rh(COD)Cl]_2$	1,4-Dioxane	81
9	$[Rh(COD)Cl]_2$	Chlorobenzene	80
10	$[Rh(COD)Cl]_2$	Toluene	70
11	$[Rh(COD)Cl]_2$	Benzene	81[c]
12	—	Benzene	0

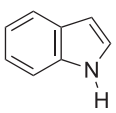
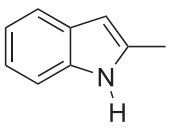
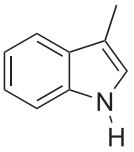
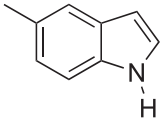
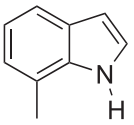
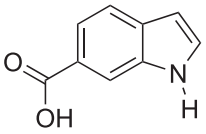
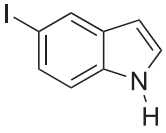
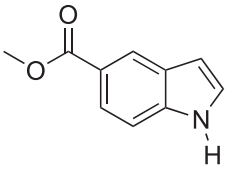
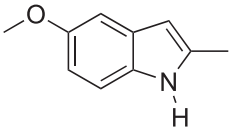
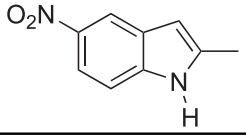
[a] Indole (0.250 mmol), α-lactam (0.280 mmol), cat. (0.0100 mmol), solvent (1.5 mL).
[b] Yields calculated by GC against an internal standard.
[c] Traditional heating source.

the addition of the indole nucleophile to the carbonyl group of the α-lactam and no desired product was observed.

The scope of the indole nucleophile was studied under the optimal conditions (Table 1, Entry 5). Additionally, α-lactams with both *tert*-butyl and trityl groups on the nitrogen atom were evaluated. The reaction proved to be general in terms of the structure and electronics of the indole derivative (Table 2). The use of both electron-deficient and electron-rich indole derivatives resulted in the formation of the desired product in good to excellent yields. The reaction of 5-iodoindole with α-lactams resulted in the formation of the desired product with the iodide bond intact in good yield (Entries 13–14). The resulting product provides a reactive handle that could be further functionalized by transition metal-mediated coupling methods. The use of an indole derivative with a nucleophilic carboxylic acid group also provided the desired product in good yield (Entries 11–12). The reaction proceeded with indoles substituted at the hindered *C*–2 and *C*–7 positions in moderate yield (Entries 3,4,9,10,17–20). In all case the use of a trityl-protecting group resulted in the formation of the desired product in a lower yield than the reactions employing *tert*-butyl protected α-lactams, which was attributed to the increased steric interactions.

Table 2
N-functionalization of substituted indoles with *tert*-butyl substituted α-lactams

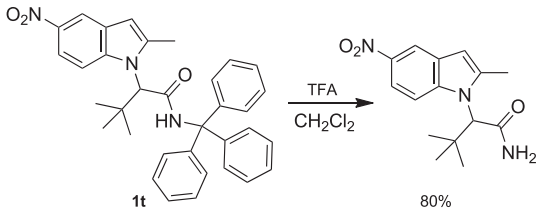


Entry	Indole derivative	R^3	Product	Yield (%)[a]
1		*t*-Bu	**1a**	88
2		Tr	**1b**	73
3		*t*-Bu	**1c**	88
4		Tr	**1d**	75
5		*t*-Bu	**1e**	70
6		Tr	**1f**	68
7		*t*-Bu	**1g**	66
8		Tr	**1h**	63
9		*t*-Bu	**1i**	50
10		Tr	**1j**	46
11		*t*-Bu	**1k**	64
12		Tr	**1l**	59
13		*t*-Bu	**1m**	64
14		Tr	**1n**	61
15		*t*-Bu	**1o**	67
16		Tr	**1p**	54
17		*t*-Bu	**1q**	82
18		Tr	**1r**	62
19		*t*-Bu	**1s**	83
20		Tr	**1t**	80

[a] Isolated yields.

Most reported cross-coupling procedures that result in the α-functionalization of amides require the use of an amide, that is, substituted with two carbon-protecting groups that are not as readily removed as a trityl group.[28] A trityl-protected indole provides a product that can easily be deprotected to yield the amide product in 80% yield as presented in Scheme 1. This results in the formation of a product, that is, more readily transformed into other highly functionalized organic molecules such as analogues of α-amino acids.

Using the previously established method for the coupling of *tert*-butyl substituted α-lactams to indole derivatives as a starting point, a method for the in situ generation of the less stable phenyl substituted α-lactams and subsequent reaction with indole was optimized (Table 3). Several bases were screened for the generation

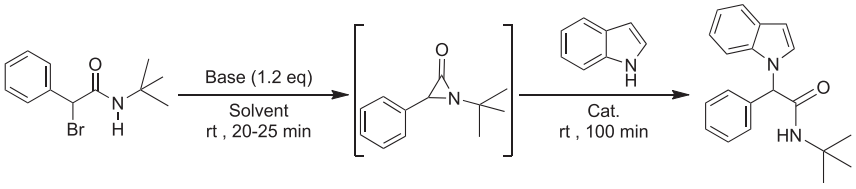


Scheme 1. Deprotection of trityl-protected product.

of the α-lactam (Entries 1–3), with the highest conversion resulting KO*t*Bu. The reaction provided the desired product in 100 min at room temperature. This is presumably due to a decrease in the C–N bond strength in the phenyl substituted a-lactams. This allows for a more rapid oxidative addition of the transition metal catalyst. Varying the transition metal used to catalyze the reaction from $[Rh(COD)Cl]_2$ to $[Ir(COD)Cl]_2$ or Pd_2dba_3 provided only trace amounts of the desired product (Entries 4–5) similar to the absence of a transition metal catalyst (Entry 10). Increasing the mol % of $[Rh(COD)Cl]_2$ gave only a slight increase in yield (Entry 3 vs 6). Lastly, the reaction was run in nonpolar (Entries 6–8) and polar aprotic (Entry 9) solvents with the reaction proceeding well in benzene and toluene (Entries 6–7).

While increasing the mol % of catalyst gave a slight increase in product formation, it was not significant enough to justify the additional catalyst. For this reason, 10 mol % was used over 20 mol % for the remaining reactions. The optimized conditions were applied to the coupling of a variety of substituted indoles (Table 4). Moderate to high yields were achieved in all reactions, even with substituents at the hindered 2- and 7-position of the indole ring

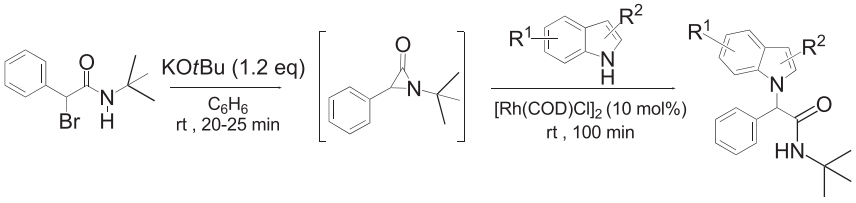
Table 3
Optimization for the in situ generation of phenyl substituted α-lactams[a]

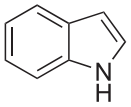
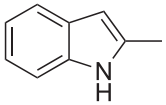
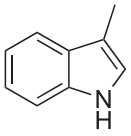


Entry	Cat. (mol %)	Solvent	Base	Yield (%)[b]
1	$[Rh(COD)Cl]_2$ (10)	Benzene	NaH	<5
2	$[Rh(COD)Cl]_2$ (10)	Benzene	NaO*t*Bu[c]	72
3	$[Rh(COD)Cl_2$ (10)	Benzene	KO*t*Bu[c]	90
4	$Pd(dba)_2$ (10)	Benzene	KO*t*Bu	<5
5	$[Ir(COD)Cl]_2$ (10)	Benzene	KO*t*Bu	<5
6	$[Rh(COD)Cl]_2$ (20)	Benzene	KO*t*Bu[c]	93
7	$[Rh(COD)Cl]_2$ (20)	Toluene	KO*t*Bu[c]	86
8	$[Rh(COD)Cl]_2$ (20)	1,4-Dioxane	KO*t*Bu	<5
9	$[Rh(COD)Cl]_2$ (20)	THF	KO*t*Bu	<5
10	—	Benzene	KO*t*Bu	<5

[a] α-bromoamide (0.190 mmol), indole (0.0950 mmol), and Solvent (1.5 mL).
[b] Isolated yields.
[c] Additional 0.4 equiv of base added after 90 min.

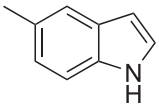
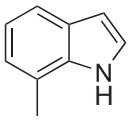
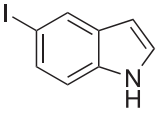
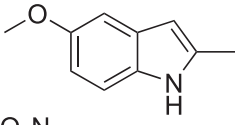
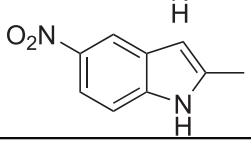
Table 4
N-functionalization of indole derivatives with phenyl substituted α-lactams



Entry	Indole derivative	Product	Yield (%)[a]
1		**2a**	90
2		**2b**	67
3		**2c**	80

(*continued on next page*)

Table 4 (*continued*)

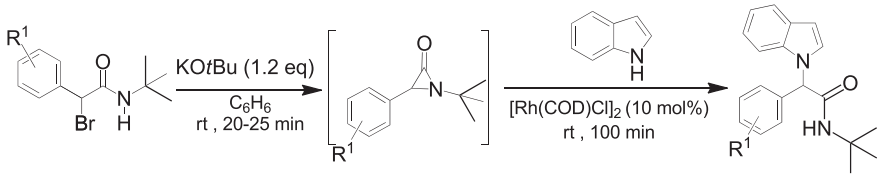
Entry	Indole derivative	Product	Yield (%)[a]
4		**2d**	77
5		**2e**	93
6		**2f**	98
7		**2g**	70
8		**2h**	63

[a] Isolated yields.

(Entries 2, 5). The reaction also provided the desired product in good yield for both electron-rich indole derivatives as well as electron deficient ones (Entries 7,8).

The next focus was to determine the reaction scope in terms of the α-lactam. A series of functionalized α-lactams were generated in situ, and then reacted with indole to assess the viability of this approach (Table 5). The in situ generation of the α-lactam was monitored and confirmed via ^{1}H NMR. The reaction proved to be general in terms of the structure and electronics of the substituent connected to the phenyl ring and proceeded in moderate to high yield with substitution at the *ortho*- (Entry 7), *meta*- (Entries 4 and 6), or *para*-position (Entries 1–3, 5).

Table 5
Scope of in situ generated functionalized α-lactams



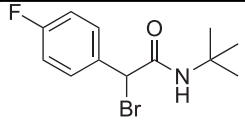
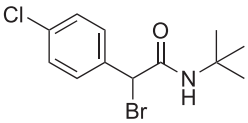
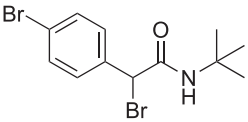
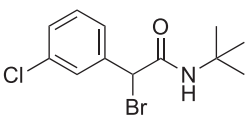
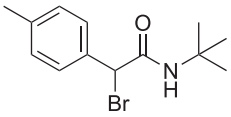
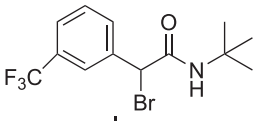
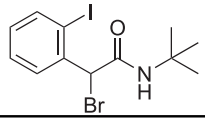
Entry	α-bromo amide	Product	Yield (%)[a]
1		**3a**	90
2		**3b**	81
3		**3c**	71
4		**3d**	70

Table 5 (*continued*)

Entry	α-bromo amide	Product	Yield (%)[a]
5		**3e**	60
6		**3f**	63
7		**3g**	75

[a] Isolated yields.

3. Conclusions

We report a novel Rh-mediated method for the coupling of indoles with α-lactams. The developed method results in the formation of the desired product in good to excellent yield. The reaction was found to be tolerant of functional groups around the indole ring. The use of trityl protecting groups results in a slight decrease in the yield of the desired product but can easily be deprotected to provide an α-amino amide analogue. The scope of this methodology was extended to include the less stable phenyl substituted α-lactams by in situ generation. Future work will focus on the development of a more general reaction in terms of both nucleophiles and α-lactams.

4. Experimental

4.1. General methods

The following reagents were purchased and used as received: indole derivatives (Sigma Aldrich), benzene (Sigma Aldrich; anhydrous), and chloro(1,5-cyclooctadiene)rhodium(I) dimer (Strem). Unless otherwise noted, reactions were conducted with stirring in oven-dried glassware under an inert atmosphere. Reactions were performed in the Biotage Initiator^{+} microwave reactor and flash column chromatography was performed on a Biotage Isolera One system using silica gel. Mass spectrometry was performed on a Bruker UHPLC-Micro-Q/T ESI-MS in positive mode. All NMR spectra were taken on a Bruker ADVANCE III 600 MHz spectrometer.

4.2. Synthesis of α-lactams

4.2.1. 1,3-Di-tert-butylaziridin-2-one. 2-Bromo-*N*-(*tert*-butyl)-3,3-dimethylbutanamide (0.0600 mol) was dissolved in anhydrous Et_2O (60 mL), cooled to 0 °C, and KO*t*Bu (0.0900 mol) was added to the reaction. The reaction stirred for 10 min at 0 °C. The mixture was then filtered through a bed of Celite and concentrated under reduced pressure. With no further purification, an oil was recovered (8.00 g 78%). The spectroscopic data matches previously reported literature.[29–32]

4.2.2. 3-(tert-Butyl)-1-tritylaziridin-2-one. 2-Bromo-3,3-dimethyl-*N*-tritylbutanamide (0.0110 mol) was dissolved in Et_2O (80 mL), cooled to 0 °C, and NaO*t*Bu (0.0210 mol) was added to the reaction. The reaction warmed to room temperature and proceeded 2 h. The reaction was washed with water (1 x 80 mL) and brine (1×80 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The solid was washed with pentane and dried under high vacuum. With no further purification, a white solid was recovered (2.50 g, 68%). The spectroscopic data matches previously reported literature.[29,30,33]

4.3. General procedure for 1a–t

In a glove box, a microwave vial was charged with α-lactam (0.250 mmol), indole (0.280 mmol), and $[RhCODCl]_2$ (0.0100 mmol). The vial was closed with a cap fitted with a septum and benzene (1.5 mL) was added via syringe. The reaction was removed from the glove box and heated in the microwave reactor for 25 min at 160 °C. The reaction mixture cooled to room temperature and was removed from reactor. The mixture was exposed to air, filtered through a bed of silica, and washed with CH_2Cl_2. Compounds were purified using flash column chromatography (hexanes/CH_2Cl_2).

*4.3.1. N-(tert-Butyl)-2-(1H-indol-1-yl)-3,3-dimethylbutanamide (**1a**).* The compound was obtained as a white solid, 62.6 mg, 88% yield, mp 58–60 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.68–7.65 (m, 2H), 7.36 (d, 1H, J=8.2 Hz), 7.23 (t, 1H, J=15.1 Hz), 7.13 (t, 1H, J=14.8 Hz), 6.57 (d, 1H, J=3.3 Hz), 5.36 (s, 1H), 4.49 (s, 1H), 1.30 (s, 9H), 1.13 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.2, 131.9, 131.1, 130.6, 129.7, 124.0, 122.2, 112.0, 104.6, 69.8, 54.3, 39.7, 31.2, 30.3; HRMS (ESI) *m/z* calculated for $C_{18}H_{26}N_2NaO$ $[M+Na]^+$: 309.1943, found 309.1953.

*4.3.2. 2-(1H-Indol-1-yl)-3,3-dimethyl-N-tritylbutanamide (**1b**).* The compound was obtained as a white solid, 87.0 mg, 73% yield, mp 56–59 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.68 (d, 1H, J=7.8 Hz), 7.45 (s, 1H), 7.42 (d, 1H, J=8.2 Hz), 7.32 (t, 1H, J=14.9 Hz), 7.24–7.22 (m, 10H), 7.16 (t, 1H, J=14.7 Hz), 7.07–7.06 (m, 5H), 6.68 (s, 1H), 6.59 (d, 1H, J=3.1 Hz), 4.70 (s, 1H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.8, 146.7, 131.2, 131.1, 130.7, 130.6, 129.8, 129.7, 124.4, 123.7, 122.4, 105.1, 73.2, 39.7, 30.3, 29.8, 21.1; HRMS (ESI) *m/z* calculated for $C_{33}H_{32}N_2NaO$ $[M+Na]^+$: 495.2412, found 495.2368.

*4.3.3. N-(tert-Butyl)-3,3-dimethyl-2-(2-methyl-1H-indol-1-yl) butanamide (**1c**).* The compound was obtained as a white solid, 66.2 mg, 88% yield, mp 100–102 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.51 (d, 1H, J=7.3 Hz), 7.45 (d, 1H, J=7.8 Hz), 7.10–7.06 (m, 2H), 6.34 (s, 1H), 5.20 (s, 1H), 4.52 (s, 1H), 2.47 (s, 3H), 1.19 (s, 9H), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.3, 137.5, 135.7, 128.8, 120.4, 119.9, 119.6, 113.9, 102.2, 65.7, 51.2, 38.3, 29.2, 28.4, 14.2; HRMS (ESI) *m/z* calculated for $C_{19}H_{28}N_2NaO$ $[M+Na]^+$: 323.2099, found 323.2116.

*4.3.4. 3,3-Dimethyl-2-(2-methyl-1H-indol-1-yl)-N-trityl butanamide (**1d**).* The compound was obtained as a white solid, 91.4 mg, 75%

yield, mp 60–64 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.51 (d, 1H, J=7.9 Hz), 7.46 (d, 1H, J=8.4 Hz), 7.33–7.16 (m, 10H), 7.11–7.06 (m, 2H), 7.01–6.98 (m, 5H), 6.62 (s, 1H), 6.35 (s, 1H), 4.60 (s, 1H), 2.49 (s, 3H), 1.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 146.9, 139.7, 131.1, 131.0, 130.6, 130.5, 129.5, 123.5, 122.6, 122.2, 117.0, 105.2, 69.6, 40.7, 31.7, 29.8, 17.1; HRMS (ESI) *m/z* calculated for $C_{34}H_{34}N_2NaO$ $[M+Na]^+$: 509.2569, found 509.2525.

*4.3.5. N-(tert-Butyl)-3,3-dimethyl-2-(3-methyl-1H-indol-1-yl) butanamide (**1e**).* The compound was obtained as a white solid, 52.8 mg, 70% yield, mp 125–127 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.59 (d, 1H, J=7.8 Hz), 7.42 (s, 1H), 7.31 (d, 1H, J=8.2 Hz), 7.22 (t, 1H, J=15.0 Hz), 7.13 (t, 1H, J=14.7 Hz), 5.37 (s, 1H), 4.44 (s, 1H), 2.35 (s, 3H), 1.30 (s, 9H), 1.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.5, 137.7, 128.4, 125.1, 121.3, 119.0, 118.8, 111.0, 109.1, 67.1, 51.6, 37.0, 28.6, 27.7, 9.7; HRMS (ESI) *m/z* calculated for $C_{19}H_{28}N_2NaO$ $[M+Na]^+$: 323.2099, found 323.2096.

*4.3.6. 3,3-Dimethyl-2-(3-methyl-1H-indol-1-yl)-N-trity l butanamide (**1f**).* The compound was obtained as a white solid, 84.0 mg, 68% yield, mp 53–56 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.61 (d, 1H, J=7.8 Hz), 7.38 (d, 1H, J=8.2 Hz), 7.34–7.15 (m, 11H), 7.06–7.05 (m, 5H), 6.66 (s, 1H), 4.66 (s, 1H), 2.35 (s, 3H), 1.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9, 146.7, 131.3, 131.1, 130.7, 130.5, 129.8, 129.6, 124.4, 121.9, 121.8, 114.3, 105.2, 73.1, 39.4, 30.4, 29.8, 12.3; HRMS (ESI) *m/z* calculated for $C_{34}H_{34}N_2NaO$ $[M+Na]^+$: 509.2569, found 509.2503.

*4.3.7. N-(tert-Butyl)-3,3-dimethyl-2-(5-methyl-1H-indol-1-yl) butanamide (**1g**).* The compound was obtained as a white solid, 49.8 mg, 66% yield, mp 143–147 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.61 (d, 1H, J=3.0 Hz), 7.45 (s, 1H), 7.25 (d, 1H, J=8.4 Hz), 7.06 (d, 1H, J=8.4 Hz), 6.49 (d, 1H, J=2.7 Hz), 6.49 (d, 1H, J=2.7 Hz), 6.06 (s, 1H), 4.46 (s, 1H), 2.48 (s, 3H), 1.30 (s, 9H), 1.13 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 138.5, 131.4, 131.0, 130.2, 125.6, 123.3, 111.7, 104.2, 69.9, 54.3, 39.7, 31.2, 30.3, 23.9; HRMS (ESI) *m/z* calculated for $C_{19}H_{28}N_2NaO$ $[M+Na]^+$: 323.2099, found 323.2124.

*4.3.8. 3,3-Dimethyl-2-(5-methyl-1H-indol-1-yl)-N-trityl butanamide (**1h**).* The compound was obtained as a white solid, 77.4 mg, 63% yield, mp 52–55 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.47 (s, 1H), 7.40 (m, 1H), 7.34–7.23 (m, 11H), 7.09–7.07 (m, 6H), 6.70 (s, 1H), 6.51 (d, 1 Hz, J=3.0 Hz), 4.66 (s, 1H), 2.49 (s, 3H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 146.7, 131.6, 131.3, 131.1, 130.7, 130.6, 129.8, 129.6, 125.9, 123.4, 104.6, 73.2, 39.7, 30.3, 29.8, 23.9, 16.7; HRMS (ESI) *m/z* calculated for $C_{34}H_{34}N_2NaO$ $[M+Na]^+$: 509.2569, found 509.2516.

*4.3.9. N-(tert-Butyl)-3,3-dimethyl-2-(7-methyl-1H-indol-1-yl) butanamide (**1i**).* The compound was obtained as a white solid, 37.6 mg, 50% yield, mp 53–54 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.53 (d, 1H, J=7.7 Hz), 7.49 (d, 1H, J=3.3 Hz), 7.04 (t, 1H, J=14.9 Hz), 6.97 (d, 1H, J=7.0 Hz), 6.60 (d, 1H, J=3.3 Hz), 5.41 (s, 1H), 5.21 (s, 1H), 2.75 (s, 3H), 1.30 (s, 9H), 1.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8, 138.9, 131.4, 130.1, 128.6, 123.0, 122.5, 122.2, 106.0, 70.4, 54.2, 39.7, 31.3, 30.7, 24.5; HRMS (ESI) *m/z* calculated for $C_{19}H_{28}N_2NaO$ $[M+Na]^+$: 323.2099, found 323.2113.

*4.3.10. 3,3-Dimethyl-2-(7-methyl-1H-indol-1-yl)-N-trityl butanamide (**1j**).* The compound was obtained as a white solid, 56.2 mg, 46% yield, mp 112–115 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.54–7.50 (m, 1H), 7.44 (m, 1H), 7.32–7.22 (m, 10H), 7.07–6.99 (m, 7H), 6.77 (s, 1H), 6.63 (m, 1H), 4.11 (s, 1H), 2.75 (s, 3H), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.4, 146.9, 131.2, 131.0, 130.6, 129.8, 129.6, 128.9, 122.8, 122.4, 106.7, 70.9, 39.6, 38.5, 30.8, 29.5, 24.5; HRMS (ESI) *m/z* calculated for $C_{34}H_{34}N_2NaO$ $[M+Na]^+$: 509.2569, found 509.2504.

*4.3.11. 1-(1-(tert-Butylamino)-3,3-dimethyl-1-oxobutan-2-yl)-1H-indole-6-carboxylic acid (**1k**).* The compound was obtained as a white solid, 53.1 mg, 64% yield, mp 226–227 °C; ^{1}H NMR (CD_3OD, 600 MHz) δ 8.22 (s, 1H), 7.77–7.76 (m, 1H), 7.64 (d, 1H, J=8.1 Hz), 7.48–7.47 (m, 2H), 6.56–6.55 (m, 1H), 4.80 (s, 1H), 1.38 (s, 9H), 1.17 (s, 9H); ^{13}C NMR (CD_3OD, 125 MHz) δ 169.1, 167.3, 135.4, 132.1, 128.3, 122.0, 119.6, 119.5, 113.4, 101.5, 80.9, 51.0, 33.6, 27.48, 25.5; HRMS (ESI) *m/z* calculated for $C_{19}H_{26}N_2NaO_3$ $[M+Na]^+$: 353.1841, found 353.1892.

*4.3.12. 1-(3,3-Dimethyl-1-oxo-1-(tritylamino)butan-2-yl)-1H-indole-6-carboxylic acid (**1l**).* The compound was obtained as a white solid, 76.5 mg, 59% yield, mp 119–121 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.65 (s, 1H), 8.23 (s, 1H), 7.86–7.85 (m, 1H), 7.68 (d, 1H, J=8.2 Hz), 7.38–7.37 (m, 1H), 7.33 (s, 1H), 7.22–7.19 (m, 15H), 6.63 (s, 1H), 5.19 (s, 1H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6, 166.5, 144.4, 135.1, 132.1, 128.5, 128.1, 127.9, 126.9, 122.5, 120.6, 120.5, 113.9, 103.0, 81.3, 70.1, 34.8, 26.5; HRMS (ESI) *m/z* calculated for $C_{34}H_{32}N_2NaO_3$ $[M+Na]^+$: 539.2311, found 539.2243.

*4.3.13. N-(tert-Butyl)-2-(5-iodo-1H-indol-1-yl)-3,3-dimethyl butanamide (**1m**).* The compound was obtained as a white solid, 65.9 mg, 64% yield, mp 142–144 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.98 (s, 1H), 7.68 (s, 1H), 7.46 (d, 1H, J=8.4 Hz), 7.14 (d, 1H, J=8.4 Hz), 6.48 (s, 1H), 5.35 (s, 1H), 4.39 (s, 1H), 1.31 (s, 9H), 1.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 139.1, 133.3, 132.4, 132.3, 131.3, 114.0, 103.8, 85.4, 70.0, 54.5, 39.7, 31.2, 30.2; HRMS (ESI) *m/z* calculated for $C_{18}H_{25}IN_2NaO$ $[M+Na]^+$: 435.0909, found 435.0870.

*4.3.14. 2-(5-Iodo-1H-indol-1-yl)-3,3-dimethyl-N-tritylbutanamide (**1n**).* The compound was obtained as a white solid, 90.9 mg, 61% yield, mp 69–73 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.01 (m, 1H), 7.49 (d, 1H, J=9.3 Hz), 7.42 (s, 1H), 7.34–7.23 (m, 11H), 7.07–7.06 (m, 5H), 6.66 (s, 1H), 6.50 (d, 1H, J=3.2 Hz), 4.60 (s, 1H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2146.9, 146.6, 132.6, 132.5, 131.2, 131.1, 130.7, 130.6, 129.8, 123.2, 104.1, 85.7, 73.4, 39.7, 30.1, 29.8; HRMS (ESI) *m/z* calculated for $C_{33}H_{31}IN_2NaO$ $[M+Na]^+$: 621.1379, found 621.1311.

*4.3.15. Methyl 1-(1-(tert-butylamino)-3,3-dimethyl-1-oxobutan-2-yl)-1H-indole-5-carboxylate (**1o**).* The compound was obtained as a white solid, 57.4 mg, 67% yield, mp 188–189 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.41 (s, 1H), 7.92 (d, 1H, J=8.7 Hz), 7.83 (d, 1H, J=3.1 Hz), 7.36 (d, 1H, J=8.7 Hz), 6.65 (d, 1H, J=3.1 Hz), 5.47 (s, 1H), 4.49 (s, 1H), 3.95 (s, 3H), 1.32 (s, 9H), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.1, 167.7, 139.8, 129.5, 127.6, 123.91, 123.90, 122.7, 121.5, 109.1, 103.1, 67.3, 51.8, 37.1, 28.5, 27.5; HRMS (ESI) *m/z* calculated for $C_{20}H_{28}N_2NaO_3$ $[M+Na]^+$: 367.1998, found 367.1985.

*4.3.16. Methyl-1-(3,3-dimethyl-1-oxo-1-(tritylamino)butan-2-yl)-1H-indole-5-carboxylate (**1p**).* The compound was obtained as a white solid, 71.5 mg, 54% yield, mp 231–233 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.44 (s, 1H), 7.95 (d, 1H, J=8.2 Hz), 7.54 (s, 1H), 7.43 (d, 1H, J=8.5 Hz), 7.23–7.14 (m, 10H), 7.07–7.06 (m, 5H), 6.72 (s, 1H), 6.66 (s, 1H), 4.70 (s, 1H), 3.95 (s, 3H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.0, 167.5, 144.0, 143.9, 128.6, 128.4, 128.0, 127.8, 127.2, 127.1, 124.0, 123.1, 121.9, 109.1, 103.6, 70.7, 51.9, 51.8, 37.0, 27.4; HRMS (ESI) *m/z* calculated for $C_{35}H_{34}N_2NaO_3$ $[M+Na]^+$: 553.2467, found 553.2388.

*4.3.17. N-(tert-Butyl)-2-(5-methoxy-2-methyl-1H-indol-1-yl)-3,3-dimethylbutanamide (**1q**).* The compound was obtained as a white solid, 67.5 mg, 82% yield, mp 101–104 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.33 (d, 1H, J=9.0 Hz), 6.98 (d, 1H, J=2.4 Hz), 6.75 (dd, 1H,

J_1=9.0 Hz, J_2=2.5 Hz), 5.23 (s, 1H), 4.47 (s, 1H), 3.86 (s, 3H), 2.44 (s, 3H), 1.19 (s, 9H), 1.15 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.4, 154.0, 138.2, 130.7, 129.4, 114.6, 110.1, 102.0, 101.5, 65.8, 55.6, 51.2, 38.3, 29.1, 28.4, 14.2; HRMS (ESI) *m/z* calculated for $C_{20}H_{30}N_2NaO_2$ $[M+Na]^+$: 353.2205, found 353.2188.

*4.3.18. 2-(5-Methoxy-2-methyl-1H-indol-1-yl)-3,3-dimethyl-N-tritylbutanamide (**1r**).* The compound was obtained as a white solid, 81.1 mg, 62% yield, mp 63–66 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.31 (d, 1H, *J*=9.0 Hz), 7.27–7.17 (m, 10H), 7.10 (d, 1H, *J*=6.9 Hz), 7.01–6.99 (m, 5H), 6.98 (d, 1H, *J*=2.0 Hz), 6.65–6.63 (m, 1H), 6.27 (s, 1H), 4.56 (s, 1H), 3.86 (s, 3H), 2.47 (s, 3H), 1.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.6, 159.9, 146.9, 138.6, 135.8, 132.1, 131.0, 130.5, 129.5, 125.3, 117.7, 113.0, 105.0, 73.0, 69.5, 58.4, 40.6, 31.6, 17.1; HRMS (ESI) *m/z* calculated for $C_{35}H_{36}N_2NaO_2$ $[M+Na]^+$: 539.2674, found 539.2619.

*4.3.19. N-(tert-Butyl)-3,3-dimethyl-2-(2-methyl-5-nitro-1H-indol-1-yl)butanamide (**1s**).* The compound was obtained as a yellow solid, 71.5 mg, 83% yield, mp 176–178 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.44 (s, 1H), 8.00 (d, 1H, *J*=9.1 Hz), 7.61 (d, 1H, *J*=9.1 Hz), 6.53 (s, 1H), 4.98 (s, 1H), 4.48 (s, 1H), 2.52 (s, 3H), 1.20 (s, 9H), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.1, 141.8, 141.0, 139.1, 127.9, 116.4, 116.1, 113.7, 104.4, 66.2, 51.6, 38.3, 28.8, 28.4, 14.4; HRMS (ESI) *m/z* calculated for $C_{19}H_{27}N_3NaO_3$ $[M+Na]^+$: 368.1950, found 368.1926.

*4.3.20. 3,3-Dimethyl-2-(2-methyl-5-nitro-1H-indol-1-yl)-N-trityl butanamide (**1t**).* The compound was obtained as a yellow solid, 106 mg, 80% yield, mp 249–250 °C (decomposed); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.42 (m, 1H), 7.80–7.78 (m, 1H), 7.44 (d, 1H, *J*=9.2 Hz), 7.21–7.15 (m, 10H), 7.01–6.99 (m, 5H), 6.54 (s, 1H), 6.41 (s, 1H), 4.60 (s, 1H), 2.56 (s, 3H), 1.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.0, 146.5, 144.3, 143.0, 142.4, 130.8, 130.6, 130.5, 129.8, 118.9, 118.7, 117.1, 107.3, 73.3, 69.9, 40.7, 31.1, 17.3; HRMS (ESI) *m/z* calculated for $C_{34}H_{33}N_3NaO_3$ $[M+Na]^+$: 554.2420, found 554.2370.

4.4. Deprotection

4.4.1. 3,3-Dimethyl-2-(2-methyl-5-nitro-1H-indol-1-yl) butanamide. 3,3-Dimethyl-2-(2-methyl-5-nitro-1*H*-indol-1-yl)-*N*-trityl butanamide (0.0280 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and cooled to 10 °C followed by the slow addition of TFA (1.30 mmol). The reaction stirred for 3 h. The solution was concentrated and the crude residue was dissolved in methyl-*t*-butyl ether followed by concentration. The crude product was again dissolved in methyl-*tert*-butyl ether followed by the addition of hexanes. The compound was obtained as a white solid, 11.0 mg, 80% yield, mp 153.2–155.6 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.45 (s, 1H), 8.01 (d, 1H, *J*=9.0 Hz), 7.55 (d, 1H, *J*=9.1 Hz), 6.54 (s, 1H), 5.25 (s, 2H), 4.63 (s, 1H), 2.54 (s, 3H), 1.19 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 143.6, 141.7, 130.7, 130.5, 119.2, 119.0, 116.0, 107.1, 67.9, 40.8, 31.4, 17.0; HRMS (ESI) *m/z* calculated for $C_{19}H_{26}N_2NaO_3$ $[M+Na]^+$: 312.1324, found 312.1342.

4.5. General procedure for the synthesis of α-bromoamides

In air, a two neck oven dried round bottom flask equipped with a reflux condenser capped with a calcium chloride drying tube was charged with the substituted phenyl acetic acid (1.0 equiv) and phosphorous trichloride (1.0 equiv). Bromine (2.0 equiv) was added via syringe and the reaction mixture was heated for 1.5 h at 70–90 °C. After 1.5 h, excess bromine (0.4–0.6 equiv) was added and reaction was stirred for another 18 h at 70–90 °C. The mixture was cooled to room temperature and poured into 150 mL of ice water. The mixture was extracted using toluene (2×150 mL), dried over anhydrous Na_2SO_4, and the residual bromine and toluene were removed under reduced pressure. The crude bromo(phenyl)acetyl chloride was used directly for the next step.

N,N′-Diisopropylethylamine or triethylamine (1.0–2.0 equiv) was charged to a solution of *tert*-butylamine (1.0–1.1 eq) in CH_2Cl_2. The reaction mixture was cooled to 0 °C and the crude bromo(-phenyl)acetyl chloride was added slowly via syringe over 45–60 min. The reaction warmed to room temperature and stirred for 3–5 h. Products were purified by flash column chromatography (hexanes/CH_2Cl_2).

4.5.1. 2-Bromo-N-(tert-butyl)-2-phenylacetamide. Phenyl acetic acid (15.0 mmol), phosphorous trichloride (15.0 mmol), bromine (30.0 mmol, excess 9.00 mmol), *tert*-butylamine (15.0 mmol), *N,N′*-diisopropylethylamine (30.0 mmol), CH_2Cl_2 (75 mL). The compound was obtained as a white solid, 3.30 g, 81% yield, mp 134–136 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.43 (d, 2H, *J*=7.2 Hz), 7.34–7.29 (m, 3H), 6.56 (s, 1H), 5.33 (s, 1H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.1, 137.8, 128.9, 128.8, 128.2, 52.1, 51.9, 28.4; HRMS (ESI) *m/z* calculated for $C_{12}H_{17}BrNO$ $[M+H]^+$: 270.0494; found: 270.0495.

4.5.2. 2-Bromo-N-(tert-butyl)-2-(4-fluorophenyl)acetamide. 2-Bro mo-*N*-(tert-butyl)-2-(4-fluorophenyl)acetamide (4-Fluorophe nyl) acetic acid (18.0 mmol), phosphorous trichloride (18.0 mmol), bromine (36.0 mmol, excess 11 mmol), *tert*-butylamine (18.0 mmol), *N,N′*-diisopropylethylamine (36.0 mmol), CH_2Cl_2 (75 mL). The compound was obtained as a white solid, 2.90 g, 56% yield, mp 133–135 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.41 (dd, 2H, *J*=5.4, 8.4 Hz), 7.02 (t, 2H, *J*=8.4 Hz), 5.32 (s, 1H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.9, 163.6 (d, *J*=990 Hz), 133.8 (d, *J*=12 Hz), 130.2 (d, *J*=36 Hz), 115.9 (d, *J*=84 Hz), 52.2, 50.8, 28.4; HRMS (ESI) *m/z* calculated for $C_{12}H_{16}BrFNO$ $[M+H]^+$: 288.0399; found: 288.0407.

4.5.3. 2-Bromo-N-(tert-butyl)-2-(4-chlorophenyl)acetamide. 2-Bro mo-*N*-(tert-butyl)-2-(4-chlorophenyl)acetamide (4-chlorophenyl) acetic acid (30.0 mmol), phosphorous trichloride (30.0 mmol), bromine (60.0 mmol, excess 11 mmol), *tert*-butylamine (68.0 mmol), *N,N′*-diisopropylethylamine (77.0 mmol), CH_2Cl_2 (50 mL). The compound was obtained as a white solid, 6.60 g, 72% yield, mp 156–158 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.37 (d, 2H, *J*=8.4 Hz), 7.32 (d, 2H, *J*=8.4 Hz), 6.48 (s, 1H), 5.28 (s, 1H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.6, 136.5, 134.9, 129.7, 129.1, 52.3, 50.9, 28.4; HRMS (ESI) *m/z* calculated for $C_{12}H_{15}BrClNNaO$ $[M+Na]^+$: 327.9897; found: 327.9901.

4.5.4. 2-Bromo-2-(4-bromophenyl)-N-(tert-butyl)acetamide. 2-Bro mo-2-(4-bromophenyl)-*N*-(tert-butyl)acetamide (4-bromophenyl) acetic acid (4.90 mmol), phosphorous trichloride (4.90 mmol), bromine (9.80 mmol, excess 2.50 mmol), *tert*-butylamine (5.10 mmol), triethylamine (7.00 mmol), CH_2Cl_2 (50 mL). The compound was obtained as a white solid, 0.500 g, 30% yield, mp 177–179 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.49 (d, 2H, *J*=8.4 Hz), 7.31 (d, 2H, *J*=8.4 Hz), 6.48 (s, 1H), 5.27 (s, 1H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.5, 137.0, 132.1, 129.9, 123.1, 52.3, 50.9, 28.39; HRMS (ESI) *m/z* calculated for $C_{12}H_{15}Br_2NNaO$ $[M+Na]^+$: 371.9393; found: 371.9394.

4.5.5. 2-bromo-N-(tert-butyl)-2-(3-chlorophenyl)acetamide. 2-bro mo-*N*-(tert-butyl)-2-(3-chlorophenyl)acetamide (3-chlorophenyl) acetic acid (18.0 mmol), phosphorous trichloride (18.0 mmol), bromine (36.0 mmol, excess 11.0 mmol), *tert*-butylamine (18.0 mmol), *N,N′*-diisopropylethylamine (36.0 mmol), CH_2Cl_2 (75 mL). The compound was obtained as a white solid, 3.10 g, 56% yield, mp 124–127 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.41 (s, 1H), 7.30 (m, 3H), 6.56 (s, 1H), 5.26 (s, 1H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$,

125 MHz) δ 165.4, 139.7, 134.6, 130.2, 129.1, 128.5, 126.5, 52.3, 50.6, 28.4; HRMS (ESI) *m/z* calculated for $C_{12}H_{15}BrClNNaO$ $[M+Na]^+$: 327.9897; found: 327.9910.

4.5.6. 2-Bromo-N-(tert-butyl)-2-(4-methylphenyl) acetamide. - Under the general procedure, (4-methylphenyl) acetic acid (12.0 mmol), dimethylformamide (2 drops), chloroform (15 mL), phosphorous trichloride (12.0 mmol) were reacted. The mixture was cooled to 0 °C and thionyl chloride (18.0 mmol) was added via syringe. The mixture warmed to room temperature and stirred for 2 h, bromine (14.4 mmol, excess 11.0 mmol) was added, and stirred for 16 h at 80 °C. *N,N′*-diisopropylethylamine/triethylamine (24.0 mmol) was charged to a solution of *tert*-butylamine (18.0 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was cooled to 0 °C and the crude bromo(phenyl)acetyl chloride was added slowly via syringe over 45–60 min. The reaction warmed to room temperature and stirred for 3–5 h. Product purified by flash column chromatography (hexanes/EtOAc). The compound was obtained as a white solid 0.800 g, 24% yield, mp 135–138 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.32 (d, 2H, *J*=7.8 Hz), 7.17 (d, 2H, *J*=7.8 Hz), 6.53 (s, 1H), 5.33 (s, 1H), 2.33 (s, 3H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.1, 139.0, 134.9, 129.6, 128.1, 52.2, 52.1, 28.4, 21.2; HRMS (ESI) *m/z* calculated for $C_{13}H_{18}BrNNaO$ $[M+Na]^+$: 306.0464; found: 306.0457.

4.5.7. 2-Bromo-N-(tert-butyl)-2-(3-(trifluoromethyl)phenyl) acetamide. 2-Bromo-*N*-(tert-butyl)-2-(3-(trifluoromethyl)phenyl) acetamide [3-(trifluoromethyl) phenyl] acetic acid (44.1 mmol), phosphorous trichloride (44.1 mmol), bromine (88.2 mmol, excess 44.1 mmol), *tert*-butylamine (48.5 mmol), triethylamine (66.2 mmol), CH_2Cl_2 (250 mL). The compound was obtained as a white solid, 12.7 g, 85% yield, mp 97–100 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.67 (s, 1H), 7.64 (d, 1H, *J*=7.8 Hz), 7.59 (d, 1H, *J*=7.8 Hz), 7.50 (t, 1H, *J*=7.8 Hz), 6.55 (s, 1H), 5.33 (s, 1H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.3, 139.0, 131.8, 131.3 (q, *J*=132 Hz), 129.5, 125.7 (q, *J*=12.0 Hz), 125.1 (q, *J*=18.0 Hz), 124.6 (q, *J*=1086.0 Hz), 52.4, 50.3, 28.4; HRMS (ESI) *m/z* calculated for $C_{13}H_{15}BrF_3NNaO$ $[M+Na]^+$: 360.0181; found: 360.018.

4.5.8. 2-Bromo-N-(tert-butyl)-2-(2-iodophenyl)acetamide. 2-Bro mo-*N*-(tert-butyl)-2-(2-iodophenyl)acetamide (2-iodophenyl) acetic acid (10.0 mmol), phosphorous trichloride (10.0 mmol), bromine (20.0 mmol, excess 8.00 mmol), *tert*-butylamine (10.0 mmol), *N,N′*-diisopropylethylamine (20.0 mmol), CH_2Cl_2 (50 mL). The compound was obtained as a white solid, 2.60 g, 64% yield, mp 118–120 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.83 (d, 1H, *J*=8.4 Hz), 7.55 (d, 1H, *J*=7.8 Hz), 7.35 (t, 1H, *J*=7.8 Hz), 6.97 (t, 1H, *J*=7.8 Hz), 6.58 (s, 1H), 5.65 (s, 1H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.2, 140.6, 139.8, 130.3, 129.1, 129.1, 100.7, 56.0, 52.3, 28.3; HRMS (ESI) *m/z* calculated for $C_{12}H_{15}BrINNaO$ $[M+Na]^+$: 417.9297; found: 417.9279.

4.6. General procedure for 2a–h and 3a–g

In a glove box, α-bromoamide (0.190 mmol) and KO*t*-Bu (0.230 mmol) were weighed to an oven dried vial while indole derivatives (0.0950 mmol) and $[Rh(COD)Cl]_2$ (0.00950 mmol) were measured into a separate vial. Benzene (0.7 mL) was then added via syringe to the mixture of α-bromoamide and KO*t*-Bu and stirred for 20–25 min at room temperature. Benzene (0.50 mL) was added via syringe to mixture of indole derivative and $[Rh(COD)Cl]_2$ and then transferred via syringe to the vial containing the *in situ* generated aziridinone. Another portion of benzene (0.30 mL) was used to rinse the vial and added to the reaction vial. The reaction mixture was stirred for 70 min at room temperature and excess KO*t*Bu (0.4–0.5 equiv) was added. The reaction mixture stirred for another 30 min at room temperature. The reaction mixture was diluted with dichloromethane and filtered through plug of silica. The crude reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (hexanes/CH_2Cl_2).

*4.6.1. N-(tert-butyl)-2-(1H-indol-1-yl)-2-phenylacetamide (**2a**).* The compound was obtained as a white solid, 26.2 mg, 90% yield, mp 174–177 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.64 (d, 1H, *J*=7.8 Hz), 7.39–7.33 (m, 6H), 7.23 (t, 1H, *J*=7.8 Hz), 7.15 (t, 1H, *J*=7.8 Hz), 6.86 (d, 1H, *J*=3.0 Hz), 6.52 (d, 1H, *J*=3.0 Hz), 6.01 (s, 1H), 5.35 (s, 1H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.2, 136.6, 135.6, 129.0, 128.9, 128.8, 128.7, 126.0, 122.3, 121.3, 120.5, 109.6, 103.1, 64.7, 51.8, 28.5; HRMS (ESI) *m/z* calculated for $C_{20}H_{22}N_2NaO$ $[M+Na]^+$: 329.1624; found: 329.1623.

*4.6.2. N-(tert-butyl)-2-(2-methyl-1H-indol-1-yl)-2-phenyl acetamide (**2b**).* The compound was obtained as a white solid, 20.5 mg, 67% yield, mp 161–164 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.53 (d, 1H, *J*=7.2 Hz), 7.31–7.25 (m, 3H), 7.22 (d, 2H, *J*=7.2 Hz), 7.06 (dd, 1H, *J*=7.8, 6.6 Hz), 6.99 (dd, 1H, *J*=8.4, 6.6 Hz), 6.96 (d, 1H, *J*=7.8 Hz), 6.37 (s, 1H), 6.10 (s, 1H), 5.48 (s, 1H), 2.35 (s, 3H), 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.4, 137.1, 136.3, 135.5, 128.8, 128.6, 128.0, 127.9, 121.2, 120.2, 120.0, 111.0, 102.7, 62.5, 51.8, 28.5, 13.7; HRMS (ESI) *m/z* calculated for $C_{21}H_{25}N_2O$ $[M+H]^+$: 321.1967; found: 321.1966.

*4.6.3. N-(tert-butyl)-2-(3-methyl-1H-indol-1-yl)-2-phenyl acetamide (**2c**).* The compound was obtained as a white solid, 24.3 mg, 80% yield, mp 186–189 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.57 (d, 1H, *J*=7.8 Hz), 7.40–7.36 (m, 3H), 7.34–7.30 (m, 3H), 7.23 (t, 1H, *J*=7.8 Hz), 7.16 (t, 1H, *J*=7.8 Hz), 6.61 (s, 1H), 5.96 (s, 1H), 5.39 (s, 1H), 2.26 (s, 3H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.5, 137.0, 135.9, 129.3, 129.0, 128.7, 128.6, 123.3, 122.3, 119.8, 119.3, 112.3, 109.5, 64.5, 51.7, 28.5, 9.7; HRMS (ESI) *m/z* calculated for $C_{21}H_{25}N_2O$ $[M+H]^+$: 321.1961; found: 321.1964.

*4.6.4. N-(tert-butyl)-2-(5-methyl-1H-indol-1-yl)-2-phenyl acetamide (**2d**).* The compound was obtained as a white solid, 23.4 mg, 77% yield, mp 187–189 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.42 (s, 1H), 7.39–7.32 (m, 5H), 7.24 (dd, 1H, *J*=9.6, 1.2 Hz), 7.06 (dd, 1H, *J*=8.4, 1.2 Hz), 6.81 (d, 1H, *J*=3.6 Hz), 6.43 (d, 1H, *J*=3.0 Hz), 5.98 (s, 1H), 5.37 (s, 1H), 2.44 (s, 3H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.3, 135.7, 135.0, 129.7, 129.2, 129.0, 128.7, 128.7, 126.0, 123.9, 120.9, 109.3, 102.6, 64.8, 51.7, 28.5, 21.4; HRMS (ESI) *m/z* calculated for $C_{21}H_{24}N_2NaO$ $[M+Na]^+$: 343.1781; found: 343.1763.

*4.6.5. N-(tert-butyl)-2-(7-methyl-1H-indol-1-yl)-2-phenyl acetamide (**2e**).* The compound was obtained as a white solid, 28.2 mg, 93% yield, mp 170–173 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.47 (d, 1H, *J*=7.8 Hz), 7.40–7.36 (m, 3H), 7.32 (d, 2H, *J*=7.2 Hz), 7.03 (t, 1H, *J*=7.2 Hz), 6.97 (d, 1H, *J*=7.2 Hz), 6.73 (s, 1H), 6.56 (s, 1H), 6.49 (s, 1H), 5.19 (s, 1H), 2.75 (s, 3H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.2, 136.6, 135.8, 129.9, 129.0, 128.9, 128.6, 126.6, 125.7, 121.2, 120.6, 119.5, 103.6, 66.3, 51.7, 28.4, 20.3; HRMS (ESI) *m/z* calculated for $C_{21}H_{25}N_2O$ $[M+H]^+$: 321.1967; found: 321.1973.

*4.6.6. N-(tert-butyl)-2-(5-iodo-1H-indol-1-yl)-2-phenylacetamide (**2f**).* The compound was obtained as a white solid, 40.2 mg, 98% yield, mp 206–208 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) 7.96 (s, 1H), 7.46 (d, 1H, *J*=8.4 Hz), 7.39 (d, 3H, *J*=5.4 Hz), 7.29 (d, 2H, *J*=6.0 Hz), 7.11 (d, 1H, *J*=8.4 Hz), 6.86 (d, 1H, *J*=3.0 Hz), 6.44 (d, 1H, *J*=3.0 Hz), 5.94 (s, 1H), 5.36 (s, 1H), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6, 135.6, 135.2, 131.4, 130.5, 130.1, 129.1, 128.9, 128.5, 127.0, 111.5, 102.2, 84.0, 64.7, 51.9, 28.5; HRMS (ESI) *m/z* calculated for $C_{20}H_{21}IN_2NaO$ $[M+Na]^+$: 455.0596 found: 455.0558.

*4.6.7. N-(tert-butyl)-2-(2-methyl-5-methoxy-1H-indol-1-yl)-2-phenylacetamide (**2g**).* The compound was obtained as a white solid, 23.2 mg, 70% yield, mp 131–133 °C; ^{1}H NMR ($CDCl_3$,

600 MHz) δ 7.31–7.29 (m, 3H), 7.22 (d, 2H, *J*=7.2 Hz), 6.99 (s, 1H), 6.79 (d, 1H, *J*=9.0 Hz), 6.64 (dd, 1H, *J*=7.2, 1.8 Hz), 6.29 (s, 1H), 6.04 (s, 1H), 5.47 (s, 1H), 3.81 (s, 3H), 2.34 (s, 3H), 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.4, 154.3, 137.8, 135.6, 131.3, 129.4, 128.6, 128.0, 127.9, 111.8, 110.8, 102.4, 102.2, 62.6, 55.7, 51.7, 28.6, 13.7; HRMS (ESI) *m/z* calculated for $C_{22}H_{26}N_2NaO_2$ $[M+Na]^+$: 373.1886; found: 373.1877.

*4.6.8. N-(tert-Butyl)-2-(2-methyl-5-nitro-1H-indol-1-yl)-2-pheny l acetamide (**2h**).* The compound was obtained as a yellow solid, 22.0 mg, 63% yield, mp 73–75 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.45 (d, 1H, *J*=1.8 Hz), 7.91 (dd, 1H, *J*=9.0, 1.8 Hz), 7.35 (d, 3H, *J*=4.8 Hz), 7.18 (d, 2H, *J*=4.8 Hz), 7.04 (d, 1H, *J*=9.0 Hz), 6.54 (s, 1H), 6.10 (s, 1H), 5.50 (s, 1H), 2.41 (s, 3H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.3, 141.9, 140.8, 139.5, 134.7, 129.1, 128.7, 128.0, 127.7, 116.9, 116.8, 110.9, 104.4, 63.2, 52.3, 28.5, 13.8; HRMS (ESI) *m/z* calculated for $C_{21}H_{23}N_3NaO_3$ $[M+Na]^+$: 388.1632; found: 388.1623.

*4.6.9. N-(tert-Butyl)-2-(4-fluorophenyl)-2-(1H-indol-1-yl) acetamide (**3a**).* The compound was obtained as a white solid, 27.6 mg, 90% yield, mp 174–177 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.65 (d, 1H, *J*=7.8 Hz), 7.34–7.30 (m, 3H), 7.24 (t, 1H, *J*=7.8 Hz), 7.17 (t, 1H, *J*=7.8 Hz), 7.07 (t, 2H, *J*=8.4 Hz), 6.86 (d, 1H, *J*=3.0 Hz), 6.54 (d, 1H, *J*=3.0 Hz), 5.99 (s, 1H), 5.35 (s, 1H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.0, 163.6 (d, *J*=990 Hz), 136.5, 131.5 (d, *J*=12 Hz), 130.5 (d, *J*=36 Hz), 129.0, 125.8, 122.5, 121.4, 120.6, 116.1 (d, *J*=84 Hz), 109.6, 103.4, 63.9, 51.9, 28.5; HRMS (ESI) *m/z* calculated for $C_{20}H_{21}FN_2NaO$ $[M+Na]^+$: 347.1530; found 347.1514.

*4.6.10. N-(tert-Butyl)-2-(4-chlorophenyl)-2-(1H-indol-1-yl) acetamide (**3b**).* The compound was obtained as a white solid, 26.1 mg, 81% yield, mp 143–146 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.65 (d, 1H, *J*=7.8 Hz), 7.35 (d, 2H, *J*=8.4 Hz), 7.32 (d, 1H, *J*=7.8 Hz), 7.24–7.20 (m, 3H), 7.16 (t, 1H, *J*=7.2 Hz), 6.87 (d, 1H, *J*=3.0 Hz), 6.55 (d, 1H, *J*=3.0 Hz), 5.98 (s, 1H), 5.35 (s, 1H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 136.5, 134.7, 134.2, 130.0, 129.2, 129.0, 125.8, 122.5, 121.4, 120.7, 109.6, 103.6, 63.9, 51.9, 28.5; HRMS (ESI) *m/z* calculated for $C_{20}H_{21}ClN_2NaO$ $[M+Na]^+$: 363.1235; found: 363.1228.

*4.6.11. 2-(4-Bromophenyl)-N-(tert-butyl)-2-(1H-indol-1-yl) acetamide (**3c**).* The compound was obtained as a white solid, 26.1 mg, 71% yield, mp 159–161 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.65 (d, 1H, *J*=7.8 Hz), 7.51 (d, 2H, *J*=7.8 Hz), 7.32 (d, 1H, *J*=8.4 Hz), 7.24 (d, 1H, *J*=7.8 Hz), 7.20–7.15 (m, 3H), 6.87 (s, 1H), 6.55 (s, 1H), 5.96 (s, 1H), 5.34 (s, 1H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6, 136.4, 134.7, 132.2, 130.3, 128.9, 125.8, 122.9, 122.5, 121.4, 120.7, 109.6, 103.6, 64.0, 51.9, 28.5; HRMS (ESI) *m/z* calculated for $C_{20}H_{21}BrKN_2O$ $[M+K]^+$: 423.0469; found: 423.0453.

*4.6.12. N-(tert-Butyl)-2-(3-chlorophenyl)-2-(1H-indol-1-yl) acetamide (**3d**).* The compound was obtained as a white solid, 22.8 mg, 70% yield, mp 195–198 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.65 (d, 1H, *J*=8.4 Hz), 7.35–7.30 (m, 4H), 7.25 (t, 1H, *J*=7.2 Hz), 7.21 (d, 1H, *J*=7.2 Hz), 7.17 (t, 1H, *J*=7.2 Hz), 6.89 (d, 1H, *J*=3.0 Hz), 6.57 (d, 1H, *J*=3.0 Hz), 5.98 (s, 1H), 5.35 (s, 1H), 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.4, 137.6, 136.5, 134.9, 130.2, 129.0, 128.9, 128.8, 126.8, 125.8, 122.6, 121.4, 120.7, 109.5, 103.6, 64.0, 51.9, 28.5; HRMS (ESI) *m/z* calculated for $C_{20}H_{21}ClN_2NaO$ $[M+Na]^+$: 363.1235; found: 363.1236.

*4.6.13. N-(tert-Butyl)-2-(1H-indol-1-yl)-2-(4-methylphenyl) acetamide (**3e**).* The compound was obtained as a white solid, 18.2 mg, 60% yield, mp 162–165 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.65 (d, 1H, *J*=7.8 Hz), 7.37 (d, 1H, *J*=7.8 Hz), 7.26 (d, 3H, *J*=8.4 Hz), 7.21 (d, 2H, 7.8 Hz), 7.16 (t, 1H, *J*=7.8 Hz), 6.86 (d, 1H, *J*=3.0 Hz), 6.52 (d, 1H, *J*=3.0 Hz), 5.98 (s, 1H), 5.33 (s, 1H), 2.36 (s, 3H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.4, 138.7, 136.4, 132.4, 129.7, 128.8, 128.6, 125.9, 122.2, 121.2, 120.4, 109.6, 102.9, 64.4, 51.7, 28.4, 21.2; HRMS (ESI) *m/z* calculated for $C_{21}H_{24}N_2NaO$ $[M+Na]^+$: 343.1781; found: 343.1794.

*4.6.14. N-(tert-Butyl)-2-(1H-indol-1-yl)-2-[4-(trifluoromethyl) phenyl]acetamide (**3f**).* The compound was obtained as a white solid, 22.4 mg, 63% yield, mp 188–191 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.66 (d, 1H, *J*=7.8 Hz), 7.63 (d, 2H, *J*=5.4 Hz), 7.52–7.49 (m, 2H), 7.34 (d, 1H, *J*=7.8 Hz), 7.27 (d, 1H, *J*=7.2 Hz), 7.18 (t, 1H, *J*=7.8 Hz), 6.86 (d, 1H, *J*=3.0 Hz), 6.58 (d, 1H, *J*=3.0 Hz), 6.06 (s, 1H), 5.37 (s, 1H), 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.3, 136.7, 136.5, 132.0, 131.3 (q, *J*=132.0 Hz), 129.5, 128.9, 125.6, 125.5, 124.7, 122.9, 122.7, 121.5, 120.8, 109.5, 103.9, 64.0, 52.0, 28.5; HRMS (ESI) *m/z* calculated for $C_{21}H_{21}F_3N_2NaO$ $[M+Na]^+$: 397.1498; found: 397.1474.

*4.6.15. N-(tert-Butyl)-2-(1H-indol-1-yl)-2-(2-iodophenyl) acetamide (**3g**).* The compound was obtained as a white solid, 30.7 mg, 75% yield, mp 189–191 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.90 (d, 1H, *J*=7.8 Hz), 7.66 (d, 1H, *J*=7.8 Hz), 7.39–7.37 (m, 2H), 7.23 (t, 2H, *J*=7.8 Hz), 7.22 (d, 1H, *J*=7.8 Hz), 7.17 (t, 1H, *J*=7.8 Hz), 7.06 (t, 1H, *J*=7.8 Hz), 6.84 (d, 1H, *J* 3.0 Hz), 6.57 (d, 1H, *J*=3.0 Hz), 6.17 (s, 1H), 5.39 (s, 1H), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.4, 140.1, 138.6, 136.5, 130.3, 129.0, 128.8, 128.6, 125.4, 122.4, 121.2, 120.5, 109.7, 103.3, 101.4, 68.5, 51.9, 28.4; HRMS (ESI) *m/z* calculated for $C_{20}H_{21}IN_2NaO$ $[M+Na]^+$: 455.0596; found: 455.0588.

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