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Metal-free $(Boc)_2O$-mediated C4-selective direct indolation of pyridines using TEMPO†

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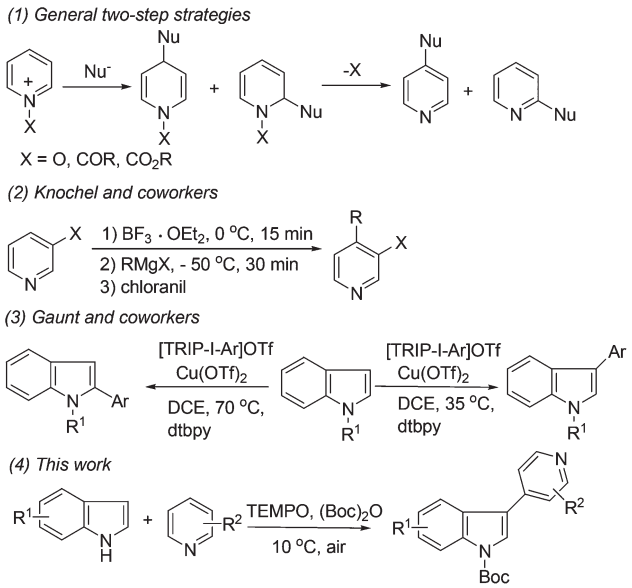
Direct metal-free C-4-selective indolation of pyridines is achieved for the first time using TEMPO and $(Boc)_2O$. A variety of substituents on both indoles and pyridines are tolerated to give 3-(pyridin-4-yl)-1*H*-indole derivatives in moderate to excellent yields. This finding provides a novel approach for developing metal-free C–H functionalization of pyridines.

Introduction

Substituted pyridines are important intermediates in the synthesis of pharmaceuticals and functional materials.[1] In addition, a pyridine core plays a key role in a number of natural products, pharmaceuticals, ligands, and functional materials. However, the presence of electron-withdrawing and Lewis-basic sp^2 nitrogen limits a repertoire of methods to decorate the heteroaromatic ring.[2] The chemistry to directly functionalize pyridine remains a significant challenge due to the poor chemoselectivity and the lower energy of the π-system relative to benzene.[3] As a result, most of the synthetic methods require prefunctionalization, for example by halogenation or metalation, before subsequent coupling reactions owing to the low reactivity of pyridine derivatives towards aromatic electrophilic substitution reactions such as the Friedel–Crafts reaction.[4]

These factors have led to the use of pyridines functionalized at nitrogen to generate cationic pyridinium salts or neutral, but similarly activated, pyridinium ylides. Generally, the direct alkylation and arylation of pyridines were carried out using derivatives (*e.g.*, *N*-oxides[5] and *N*-iminopyridinium ylides[6]) ((1) in Scheme 1). However, this approach necessitates two additional steps: activation of the pyridine starting material, and then unmasking of the arylated product. The use of pyridines directly would clearly represent the ideal situation in terms of both cost and simplicity. To tackle such a problem, methodologies for the direct alkylation and arylation of pyridines have been developed. Recently, transition-metal-catalyzed pyridyl C–H functionalizations have received extensive attention. Accordingly, significant progress in this field has been achieved.[7–12] More recently, Knochel and co-workers reported a novel transition-metal-free $BF_3{\cdot}OEt_2$ mediated regioselective synthesis of 4-substituted pyridine derivatives using LiCl activated Grignard or organozinc reagents. Despite such progress, the direct indolation of pyridines still remained elusive ((3) in Scheme 1).[13] As a solution, we report a novel metal-free regioselective direct indolation of pyridines using TEMPO and $(Boc)_2O$.



Scheme 1 Regioselective direct alkylation and arylation of pyridines.

We commenced our study with the reaction of **1a** with pyridine and TBHP as an oxidant (Table 1). To our delight, the reaction in $(Boc)_2O$ at rt for 24 h afforded the desired product **3a** in 17% yield (entry 1). To our knowledge, this is the first example of a metal-free regioselective direct synthesis of *tert*-butyl 3-(pyridin-4-yl)-1*H*-indole-1-carboxylate using $(Boc)_2O$

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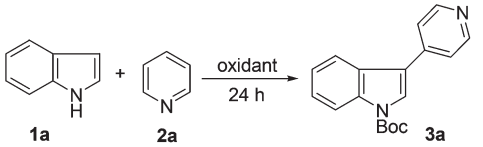
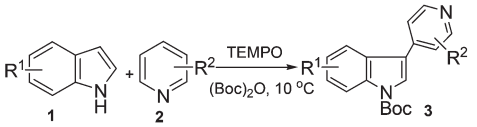
Table 1 Optimization of reaction conditions[a]



Entry	Oxidant (equiv.)	$(Boc)_2O$ (equiv.)	Temp (°C)	Yield[b] (%)
1	TBHP (2.0)	2.0	25	17
2	H_2O_2 (2.0)	2.0	25	0
3	DDQ (1.2)	2.0	25	23
4	TEMPO (0.3)	2.0	25	35
5	—	2.0	25	Trace
6	TEMPO (0.3)	2.0	0	36
7	TEMPO (0.3)	2.0	10	45
8	TEMPO (0.3)	2.0	35	23
9	TEMPO (0.3)	2.0	45	Trace
10	TEMPO (0.2)	—	10	0
11	TEMPO (0.6)	2.0	10	62
12	TEMPO (0.7)	2.0	10	80
13	TEMPO (0.8)	2.0	10	78
14	TEMPO (0.7)	1.0	10	36
15	TEMPO (0.7)	1.5	10	70
16	TEMPO (0.7)	2.5	10	79

[a] Reaction conditions: indole (0.5 mmol), pyridine (0.8 mmol). [b] Isolated yield.

Table 2 Oxidative coupling reaction of indoles with pyridines[a]



Entry	R^1	R^2	Product	t (h)	Yield[b] (%)
1	H	H	**3a**	24	80
2	5-F	H	**3b**	24	75
3	5-Br	H	**3c**	24	71
4	5-Me	H	**3d**	24	82
5	5-OMe	H	**3e**	24	80
6	5-OBn	H	**3f**	24	76
7	5-CN	H	**3g**	36	56
8	6-F	H	**3h**	24	77
9	6-Cl	H	**3i**	24	72
10	6-OBn	H	**3j**	24	79
11	6-CO_2Me	H	**3k**	24	60
12	7-Cl	H	**3l**	24	80
13	7-Me	H	**3m**	24	84
14	7-OBn	H	**3n**	24	88
15	7-NO_2	H	**3o**	36	46
16	2-Me	H	**3p**	30	75
17	2-Ph	H	**3q**	30	90
18	H	3-CN	**3r**	24	74
19	5-F	2-(*p*-Cl-Bn)	**3s**	48	57
20	5-Me	2-Bn	**3t**	48	68
21	5-Me	2-(*p*-Cl-Bn)	**3u**	48	56
22	6-F	2-(*p*-Cl-Bn)	**3v**	48	70
23	6-F	2-Bn	**3w**	48	65
24	H	2-CH_3	**3x**	48	Trace

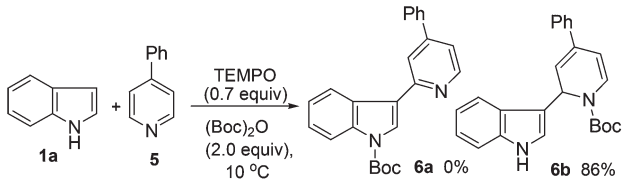
[a] Reaction conditions: indole (0.5 mmol), pyridine (0.8 mmol), TEMPO (0.35 mmol), $(BoC)_2O$ (1.0 mmol). [b] Isolated yield.

as an activating agent. Hannah and co-workers reported a chemoselective four-step Suzuki reaction towards 6-bromo-3-(pyridin-4-yl)-1*H*-indole, which was found to be an IMPDA inhibitor.[14]

Encouraged by this finding, we continued our investigations by optimizing the reaction conditions (Table 1). A screen of oxidants showed that TEMPO was more efficient than TBHP, H_2O_2, and DDQ (entries 1–4). In contrast to TEMPO, when H_2O_2 was used this transformation did not occur. Besides, only a trace amount of the desired product was detected when the reaction was performed in the absence of TEMPO (entry 5). The influence of the solvent was also studied. When other solvents, such as benzene, toluene, DCM, and THF, were applied, a trace or none of the desired product was observed. To our delight, the yield of **3a** was improved to 62% when the reaction was carried out in the absence of a solvent at 10 °C (entry 11). Control experiments indicated that $(Boc)_2O$ is essential for this transformation (entry 10). After extensive screening of other parameters (see the ESI, Table S1†), we found that the indolation of pyridine using TEMPO (70 mol%) in air as an oxidant and pyridine (160 mol%) in $(Boc)_2O$ (200 mol%) at 10 °C led to the highest efficiency (80% yield, entry 12).

With optimized conditions established we explored the scope of the reaction (Table 2). First, a series of substituted indoles were subjected to react with pyridine (entries 1–17). The reaction can tolerate a variety of functional groups at the 2, 5, 6, and 7 positions of indoles, such as F, Cl, Br, CH_3, CH_3O, Ph, BnO, CO_2CH_3, CN, and NO_2. The substituent effect on the indole ring was then investigated. Electron-rich and electron-neutral indoles gave reaction products in good to excellent yields. Electron-donating substituents showed better results than electron-withdrawing substituents in this transformation. For example, 7-benzyloxy-1*H*-indole was transformed into **3n** in 88% yield (entry 14). Interestingly, we observed that indoles with strong electron-withdrawing substituents at the 5 and 7 positions of indoles, such as CN and NO_2, could provide the corresponding products in lower yields (entries 7 and 15). Sterically encumbered 2-substituted indoles also proceeded in good to excellent yields, though extended reaction times were required (entries 16 and 17). Treatment of **3c** with a methanolic solution of hydrochloric acid at room temperature gave the *N*-Boc-deprotection product **4**, which was confirmed by X-ray crystallography (see ESI†).

Subsequently, the substrate scope of pyridines was then investigated (entries 18–23). Pyridines with a substituent at C-2 or C-3 on the pyridyl ring could undergo the expected C-4 coupling reaction to give moderate yields. When using the pyridine with an electron-withdrawing cyano group at the C-3 position as a coupling partner (entry 18), the yield was obviously higher than those using C-2 substituted pyridines (entries 19–23). Unexpectedly, only a trace amount of **3x** was detected when 2-methylpyridine was used as a coupling partner (entry 24).



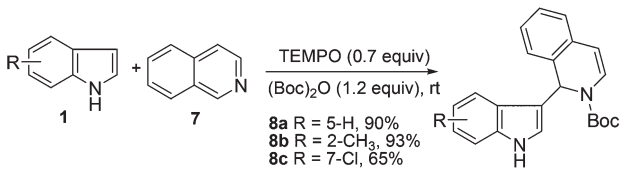
Scheme 2 Addition of indole to 4-phenyl pyridine.

The protocol of the present reaction was very simple: the substrate, reagent, and catalyst were stirred together in simple glassware. Thus, this reaction could be applied to a large-scale synthesis without any difficulties. When the reaction of indole (1.17 g, 10 mmol) was performed with pyridine (1.26 g, 15.9 mmol), $(Boc)_2O$ (4.36 g, 20 mmol), and TEMPO (1.09 g, 7 mmol) under the optimized reaction conditions for 24 h, the desired product was obtained in 81% yield.

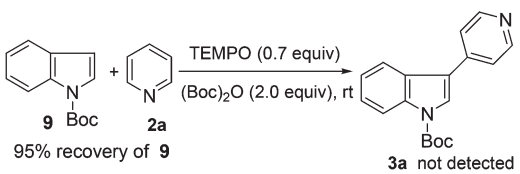
Some control experiments were also established. While employing pyridine with a phenyl group at the C-4 position as a coupling partner, it did not afford the expected 3-pyridylindole **6a**, only the dihydropyridine *N*-Boc **6b** was obtained in good yields (Scheme 2). Similarly, when isoquinoline was subjected to the standard reaction conditions, the additive products **8** were obtained in good yields (Scheme 3). In addition, when H_2O was added, a significant decrease in the yield of **3a** was observed (see ESI†).

We next initiated studies to gain more detailed insights into the role of $(Boc)_2O$ in the cross-coupling. Under optimized conditions, *N*-Boc indole **9** was chosen as a substrate instead of indole. To our surprise, no conversion was observed (Scheme 4), indicating that the substituents at the N1-position of the indole had a great influence on the reactivity.

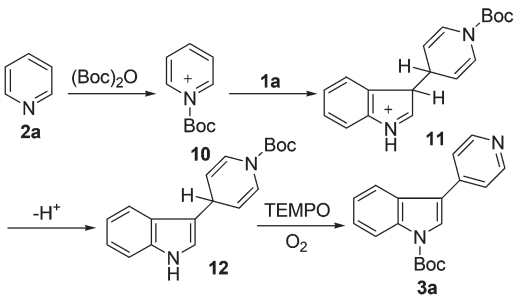
Although the exact mechanism of this cross-coupling reaction is still not clear, based on these preliminary results and previous reports in the literature,[13] a tentative reaction path is proposed in Scheme 5. In the initial step, treatment of **2a** with $(Boc)_2O$ affords the intermediate **10**. Subsequent addition of



Scheme 3 Addition of indole to isoquinoline.



Scheme 4 Reaction of *N*-Boc indole **9** with pyridine.



Scheme 5 A plausible pathway for the formation of **3a**.

10 to indole leads to the intermediate **11**, which is converted into the intermediate **12** by C-3 proton elimination from the indole ring. Finally, **12** undergoes aromatization to afford the corresponding product **3a**.

Conclusions

In conclusion, the metal-free direct indolation of pyridines by TEMPO and $(Boc)_2O$ has been realized. This reaction has revealed an efficient and new strategic way to access 3-(pyridin-4-yl)-1*H*-indole derivatives from readily available starting materials in one step. The protocol was very simple, and tolerated an array of functional groups at the 2, 5, 6, and 7 positions of indoles, including F, Cl, Br, CH_3, CH_3O, Ph, BnO, CO_2CH_3, CN, and NO_2 groups. In addition, all the reagents could be used without purification, and the reaction could be readily applied to a large-scale synthesis without any difficulties. Importantly, our findings further encouraged us to design and explore such a dehydrogenation based on cross-coupling because it has great potential in enabling the rapid construction of functionalized compounds from simple starting materials in an atom- and step-economical fashion.

Experimental section

General

Melting points were determined on a digital melting point apparatus and temperatures were uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ^1H and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 400 and 100 MHz, respectively. Chemical shifts were reported in ppm relative to TMS for ^1H and ^{13}C NMR spectra. $CDCl_3$ or DMSO-d_6 was used as the NMR solvent. Mass spectra were recorded with Bruker Dalton Esquire 3000 plus LC-MS apparatus. Elemental analyses were carried out on a Perkin-Elmer 240B instrument. HRFABMS spectra were recorded on a FTMS apparatus. Silica gel (300–400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with an ethyl acetate–petroleum ether (PE) (60–90 °C) mixture.

General procedure for the indolation of pyridines

To a solution of indole (0.5 mmol) and TEMPO (0.35 mmol) in pyridine (0.8 mmol) was added $(Boc)_2O$ (1.0 mmol) under an air atmosphere and the mixture was stirred at 10 °C for 24–48 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc–PE = 1 : 4) to yield the corresponding product.

***tert*-Butyl 3-(pyridin-4-yl)-1*H*-indole-1-carboxylate (3a).** R_f 0.25 (EtOAc–PE = 1/4). White solid, m.p. 90.3–91.8 °C. IR (KBr) ν_{max}: 1727, 1378, 1243, 1160, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 5.8 Hz, 2H, Ar-H), 8.26 (d, J = 8.0 Hz, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.87 (d, J = 8.0 Hz, 1H, Ar-H), 7.59 (d, J = 5.8 Hz, 2H, Ar-H), 7.43 (t, J = 7.5 Hz, 1H, Ar-H), 7.35 (t, J = 7.5 Hz, 1H, Ar-H), 1.73 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 149.4, 141.8, 136.0, 127.9, 125.1, 124.4, 123.4, 122.2, 119.6, 119.4, 115.7, 84.5, 28.2. HRESIMS calcd for $[C_{18}H_{18}N_2O_2 + H]^+$ 295.14465 (100%), found 295.14389 (100%).

***tert*-Butyl 5-fluoro-3-(pyridin-4-yl)-1*H*-indole-1-carboxylate (3b).** R_f 0.20 (EtOAc–PE = 1/4). White solid, m.p. 139–140 °C. IR (KBr) ν_{max}: 1737, 1598, 1464, 1377, 1258, 1152, 1098, 1051, 804 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.71 (s, 2H, Ar-H), 8.22–8.17 (m, 1H, Ar-H), 7.90 (s, 1H, Ar-H), 7.54 (d, J = 5.6 Hz, 2H, Ar-H), 7.50 (dd, J = 9.1, 2.6 Hz, 1H, Ar-H), 7.14 (dt, J = 2.6, 9.1 Hz, 1H, Ar-H), 1.72 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7 (d, J = 240.2 Hz), 150.4, 149.1, 141.3, 132.4, 128.8 (d, J = 9.6 Hz), 125.7, 122.0, 119.1 (d, J = 4.2 Hz), 116.7 (d, J = 9.1 Hz), 112.9 (d, J = 25.0 Hz), 105.3 (d, J = 24.7 Hz), 84.8, 28.1. HRESIMS calcd for $[C_{18}H_{17}FN_2O_2 + H]^+$ 313.13523 (100%), found 313.13361 (100%).

***tert*-Butyl 5-bromo-3-(pyridin-4-yl)-1*H*-indole-1-carboxylate (3c).** R_f 0.20 (EtOAc–PE = 1 : 4). Pale yellow, m.p. 130.7–132.6 °C. IR (KBr) ν_{max}: 1744, 1379, 1245, 1160, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 6.0 Hz, 2H, Ar-H), 8.13 (d, J = 8.8 Hz, 1H, Ar-H), 7.96 (d, J = 1.8 Hz, 1H, Ar-H), 7.86 (s, 1H, Ar-H), 7.54 (d, J = 6.0 Hz, 1H, Ar-H), 7.52 (d, J = 6.0 Hz, 1H, Ar-H), 7.50 (dd, J = 8.8, 1.8 Hz, 1H, Ar-H), 1.72 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 149.0, 141.1, 134.7, 129.6, 128.0, 125.3, 122.3, 122.2, 118.7, 117.1, 116.9, 85.0, 28.2. HRESIMS calcd for $[C_{18}H_{17}BrN_2O_2 + H]^+$ 373.05517 (100%), 375.05312 (100%), found 373.05420 (100%), 375.05197 (100%).

***tert*-Butyl 5-methyl-3-(pyridin-4-yl)-1*H*-indole-1-carboxylate (3d).** R_f 0.20 (EtOAc–PE = 1/4). White solid, m.p. 124–125 °C. IR (KBr) ν_{max}: 1725, 1601, 1371, 1243, 1150 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 5.7 Hz, 2H, Ar-H), 8.12 (d, J = 8.3 Hz, 1H, Ar-H), 7.84 (s, 1H, Ar-H), 7.65 (s, 1H, Ar-H), 7.59 (d, J = 5.7 Hz, 2H, Ar-H), 7.24 (d, J = 8.3 Hz, 1H, Ar-H), 2.51 (s, 3H, CH_3), 1.72 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 149.5, 141.9, 134.2, 133.0, 128.1, 126.4, 124.4, 122.3, 119.5, 119.1, 115.3, 84.3, 28.2, 21.5. HRESIMS calcd for $[C_{19}H_{20}N_2O_2 + H]^+$ 309.16030 (100%), found 309.15875 (100%).

***tert*-Butyl 5-methoxy-3-(pyridin-4-yl)-1*H*-indole-1-carboxylate (3e).** R_f 0.40 (EtOAc–PE = 1/2). White solid, m.p. 106–107 °C. IR (KBr) ν_{max}: 1723, 1608, 1385, 1249, 1164, 1115 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.85–8.60 (br s, 2H, Ar-H), 8.14 (d, J = 9.0 Hz, 1H, Ar-H), 7.85 (s, 1H, Ar-H), 7.63–7.54 (br s, 2H, Ar-H), 7.30 (d, J = 2.5 Hz, 1H, Ar-H), 7.04 (dd, J = 9.0, 2.5 Hz, 1H, Ar-H), 3.90 (s, 3H, OCH_3), 1.72 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 150.3, 149.4, 141.9, 130.7, 128.8, 125.0, 122.3, 119.2, 116.4, 113.6, 102.5, 84.3, 55.8, 28.2. HRESIMS calcd for $[C_{19}H_{20}N_2O_3 + H]^+$ 325.15522 (100%), found 325.15341 (100%).

***tert*-Butyl 5-(benzyloxy)-3-(pyridin-4-yl)-1*H*-indole-1-carboxylate (3f).** R_f 0.40 (EtOAc–PE = 1/2). White solid, m.p. 136–137 °C. IR (KBr) ν_{max}: 1730, 1605, 1371, 1225, 1156, 816 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 2H, Ar-H), 8.14 (d, J = 8.7 Hz, 1H, Ar-H), 7.85 (s, 1H, Ar-H), 7.56–7.48 (m, 4H, Ar-H), 7.43 (dt, J = 6.1, 1.6 Hz, 2H, Ar-H), 7.39–7.35 (m, 2H, Ar-H), 7.12 (dd, J = 9.1, 2.4 Hz, 1H, Ar-H), 5.16 (s, 2H, OCH_2), 1.72 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 150.2, 149.4, 141.9, 137.1, 130.9, 128.7, 128.6, 128.0, 127.5, 125.0, 122.1, 119.2, 116.4, 114.3, 104.2, 84.4, 70.8, 28.2. HRESIMS calcd for $[C_{25}H_{24}N_2O_3 + H]^+$ 401.18652 (100%), found 401.18503 (100%).

***tert*-Butyl 5-cyano-3-(pyridin-4-yl)-1*H*-indole-1-carboxylate (3g).** R_f 0.20 (EtOAc–PE = 1/4). Pale yellow solid, m.p. 144–145 °C. IR (KBr) ν_{max}: 2225, 1743, 1603, 1465, 1372, 1289, 1254, 1157, 815 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.77 (s, 2H, Ar-H), 8.38 (d, J = 8.7 Hz, 1H, Ar-H), 8.18 (d, J = 1.3 Hz, 1H, Ar-H), 7.97 (s, 1H, Ar-H), 7.68 (dd, J = 8.7, 1.3 Hz, 1H, Ar-H), 7.56 (s, 1H, Ar-H), 7.55 (s, 1H, Ar-H), 1.74 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 148.7, 140.4, 137.8, 128.1, 128.0, 126.2, 124.6, 122.3, 119.4, 119.3, 116.6, 107.0, 85.8, 28.1. MS (ESI): 320 ($M + H^+$, 100). Anal calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found C, 71.27; H, 5.63; N, 12.85.

***tert*-Butyl 6-fluoro-3-(pyridin-4-yl)-1*H*-indole-1-carboxylate (3h).** R_f 0.20 (EtOAc–PE = 1/4). White solid, m.p. 113–114 °C. IR (KBr) ν_{max}: 1731, 1601, 1483, 1444, 1388, 1252, 1167, 807 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, J = 4.8 Hz, 2H, Ar-H), 7.98 (dd, J = 8.8, 1.4 Hz, 1H, Ar-H), 7.85 (s, 1H, Ar-H), 7.76 (dd, J = 8.8, 5.3 Hz, 1H, Ar-H), 7.56 (dd, J = 4.8, 1.4 Hz, 2H, Ar-H), 7.10 (dt, J = 2.4, 8.8 Hz, 1H, Ar-H), 1.72 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2 (d, J = 240.7 Hz), 150.4, 149.1, 141.4, 136.3 (d, J = 12.8 Hz), 124.4 (d, J = 3.6 Hz), 124.3, 122.1, 120.4 (d, J = 10.0 Hz), 119.3, 117.0 (d, J = 24.3 Hz), 103.0 (d, J = 28.6 Hz), 84.9, 28.1. HRESIMS calcd for $[C_{18}H_{17}FN_2O_2 + H]^+$ 313.13523 (100%), found 313.13358 (100%).

***tert*-Butyl 6-chloro-3-(pyridin-4-yl)-1*H*-indole-1-carboxylate (3i).** R_f 0.30 (EtOAc–PE = 1/4). White solid, m.p. 164–165 °C. IR (KBr) ν_{max}: 1729, 1600, 1463, 1437, 1382, 1252, 1171, 805 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 5.9 Hz, 2H, Ar-H), 8.30 (s, 1H, Ar-H), 7.85 (s, 1H, Ar-H), 7.76 (d, J = 8.5 Hz, 1H, Ar-H), 7.55 (d, J = 5.9 Hz, 2H, Ar-H), 7.32 (dd, J = 8.5, 1.9 Hz, 1H, Ar-H), 1.73 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 149.0, 141.2, 136.4, 131.1, 126.4, 124.7, 124.0, 122.2, 120.4, 119.3, 116.0, 85.1, 28.1. HRESIMS calcd for $[C_{18}H_{17}ClN_2O_2 + H]^+$ 329.10568 (100%), 331.10273 (33%), found 329.10403 (100%), 331.10080 (33%).

***tert*-Butyl 6-(benzyloxy)-3-(pyridin-4-yl)-1*H*-indole-1-carboxylate (3j).** R_f 0.38 (EtOAc–PE = 1/2). White solid, m.p. 135–136 °C. IR (KBr) ν_{max}: 1733, 1601, 1374, 1227, 1152,

815 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.68 (s, 2H, Ar-H), 7.94 (s, 1H, Ar-H), 7.78 (s, 1H, Ar-H), 7.74 (d, J = 8.7 Hz, 1H, Ar-H), 7.58 (d, J = 4.3 Hz, 2H, Ar-H), 7.51 (dd, J = 8.4, 1.3 Hz, 2H, Ar-H), 7.44 (dt, J = 1.3, 8.4 Hz, 2H, Ar-H), 7.37 (dt, J = 2.4, 8.4 Hz, 1H, Ar-H), 7.07 (dd, J = 8.7, 2.4 Hz, 1H, Ar-H), 5.19 (s, 1H, OCH_2), 1.71 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 150.2, 149.5, 141.9, 137.1, 136.9, 128.6, 128.0, 127.6, 123.1, 122.2, 121.9, 120.2, 119.4, 113.4, 100.9, 84.3, 70.5, 28.2. HRESIMS calcd for $[C_{25}H_{24}N_2O_3 + H]^+$ 401.18652 (100%), found 401.18460 (100%).

1-*tert*-Butyl 6-methyl 3-(pyridin-4-yl)-1*H*-indole-1,6-dicarboxylate (3k). R_f 0.30 (EtOAc–PE = 1/2). Pale yellow solid, m.p. 135–137 °C. IR (KBr) ν_{max}: 1740, 1717, 1604, 1438, 1377, 1298, 1241, 1189, 1155, 1100 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.97 (s, 1H, Ar-H), 8.73 (dd, J = 5.9, 1.4 Hz, 2H, Ar-H), 8.05 (dd, J = 8.4, 1.4 Hz, 1H, Ar-H), 8.02 (s, 1H, Ar-H), 7.89 (d, J = 8.4 Hz, 1H, Ar-H), 7.58 (d, J = 5.9 Hz, 2H, Ar-H), 3.99 (s, 3H, OCH_3), 1.75 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 150.4, 149.0, 141.1, 135.5, 131.5, 127.0, 126.8, 124.5, 112.2, 119.4, 119.3, 117.6, 85.2, 52.2, 28.1. MS (ESI): 353 (M + H^+, 100). Anal calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found C, 67.83; H, 6.01; N, 7.72.

***tert*-Butyl 7-chloro-3-(pyridin-4-yl)-1*H*-indole-1-carboxylate (3l).** R_f 0.30 (EtOAc–PE = 1/2). Amorphous solid. IR (KBr) ν_{max}: 1753, 1605, 1353, 1266, 1152 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.71 (s, 2H, Ar-H), 7.80 (s, 1H, Ar-H), 7.75 (dd, J = 7.9, 0.9 Hz, 1H, Ar-H), 7.54 (d, J = 7.9 Hz, 2H, Ar-H), 7.43 (dd, J = 7.9, 0.9 Hz, 1H, Ar-H), 7.27 (t, J = 7.9 Hz, 1H, Ar-H), 1.70 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 148.5, 141.2, 132.9, 131.4, 127.8, 127.2, 124.3, 122.4, 121.0, 119.2, 118.2, 85.2, 27.9. MS (ESI): 329 (M + H^+, 100), 331 (M + H^+, 30). Anal calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; N, 8.52. Found C, 65.61; H, 5.36; N, 8.20.

***tert*-Butyl 7-methyl-3-(pyridin-4-yl)-1*H*-indole-1-carboxylate (3m).** R_f 0.35 (EtOAc–PE = 1/2). Amorphous solid. IR (KBr) ν_{max}: 1750, 1604, 1355, 1260, 1225, 1152 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.70 (s, 2H, Ar-H), 7.77 (s, 1H, Ar-H), 7.68 (d, J = 7.5 Hz, 1H, Ar-H), 7.57 (d, J = 5.6 Hz, 2H, Ar-H), 7.27 (t, J = 7.5 Hz, 1H, Ar-H), 7.22 (d, J = 5.6 Hz, 1H, Ar-H), 2.68 (s, 3H, CH_3), 1.69 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 149.2, 141.9, 135.6, 129.3, 128.4, 126.6, 126.0, 123.8, 122.5, 119.5, 117.1, 84.1, 28.0, 22.1. MS (ESI): 309 (M + H^+, 100). Anal calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found C, 73.63; H, 6.91; N, 8.71.

***tert*-Butyl 7-(benzyloxy)-3-(pyridin-4-yl)-1*H*-indole-1-carboxylate (3n).** R_f 0.38 (EtOAc–PE = 1/2). White solid, m.p. 112–113 °C. IR (KBr) ν_{max}: 1744, 1604, 1366, 1239, 1152, 1047 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.68 (s, 2H, Ar-H), 7.77 (s, 1H, Ar-H), 7.58 (d, J = 7.1 Hz, 2H, Ar-H), 7.56 (d, J = 8.5 Hz, 2H, Ar-H), 7.48 (dd, J = 7.1, 1.0 Hz, 1H, Ar-H), 7.40 (dt, J = 1.0, 8.5 Hz, 2H, Ar-H), 7.36 (dt, J = 1.0, 7.1 Hz, 1H, Ar-H), 7.28 (t, J = 8.0 Hz, 1H, Ar-H), 6.99 (d, J = 8.0 Hz, 1H, Ar-H), 5.27 (s, 2H, OCH_2), 1.58 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 148.9, 147.9, 141.9, 137.0, 130.9, 128.4, 127.8, 127.5, 127.0, 125.9, 124.5, 122.3, 119.1, 112.5, 109.0, 84.1, 71.1, 27.8. MS (ESI): 401 (M + H^+, 100). Anal calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 7.00. Found C, 74.67; H, 6.32; N, 6.86.

***tert*-Butyl 7-nitro-3-(pyridin-4-yl)-1*H*-indole-1-carboxylate (3o).** R_f 0.20 (EtOAc–PE = 1/2). Yellow solid, m.p. 116–118 °C. IR (KBr) ν_{max}: 1745, 1606, 1531, 1371, 1259, 1149, 818 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.75 (s, 2H, Ar-H), 8.08 (dd, J = 8.0, 0.8 Hz, 1H, Ar-H), 7.91 (s, 1H, Ar-H), 7.88 (dd, J = 8.0, 0.8 Hz, 1H, Ar-H), 7.56 (d, J = 8.0 Hz, 2H, Ar-H), 7.45 (t, J = 8.0 Hz, 1H, Ar-H), 1.65 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 148.3, 140.5, 139.5, 131.6, 127.8, 126.2, 124.6, 123.1, 122.5, 120.9, 119.5, 86.8, 27.9. MS (ESI): 340 (M + H^+, 100), 362 (M + Na^+, 15). Anal calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found C, 63.98; H, 4.89; N, 12.02.

***tert*-Butyl 2-methyl-3-(pyridin-4-yl)-1*H*-indole-1-carboxylate (3p).** R_f 0.20 (EtOAc–PE = 1/6). Pale yellow solid, m.p. 80–81 °C. IR (KBr) ν_{max}: 1736, 1603, 1358, 1319, 1152, 1119, 834 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 2H, Ar-H), 8.19 (d, J = 8.4 Hz, 1H, Ar-H), 7.49 (d, J = 7.6 Hz, 1H, Ar-H), 7.40 (d, J = 7.6 Hz, 2H, Ar-H), 7.33 (dt, J = 1.0, 7.6 Hz, 1H, Ar-H), 7.25 (dt, J = 8.4, 1.0 Hz, 1H, Ar-H), 2.65 (s, 3H, CH_3), 1.74 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 150.0, 142.4, 135.8, 134.8, 128.3, 125.0, 124.1, 123.1, 118.5, 118.2, 115.6, 84.3, 28.3, 14.8. MS (ESI): 309 (M + H^+, 100). Anal calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found C, 73.88; H, 6.73; N, 8.89.

***tert*-Butyl 2-phenyl-3-(pyridin-4-yl)-1*H*-indole-1-carboxylate (3q).** R_f 0.31 (EtOAc–PE = 1/4). Pale yellow solid, m.p. 136–138 °C. IR (KBr) ν_{max}: 1727, 1604, 1357, 1321, 1154 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, J = 3.4 Hz, 2H, Ar-H), 8.35 (d, J = 8.4 Hz, 1H, Ar-H), 7.63 (d, J = 7.8 Hz, 1H, Ar-H), 7.44 (dt, J = 1.2, 7.3 Hz, 1H, Ar-H), 7.39–7.31 (m, 4H, Ar-H), 7.30–7.26 (m, 2H, Ar-H), 7.15 (d, J = 5.9 Hz, 2H, Ar-H)), 1.28 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.9, 149.6, 142.0, 136.9, 136.6, 133.2, 130.2, 130.1, 128.1, 128.0, 125.1, 124.8, 124.7, 123.4, 119.0, 115.5, 83.8, 27.5. MS (ESI): 371 (M + H^+, 100). Anal calcd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56. Found C, 77.65; H, 6.18; N, 7.39.

***tert*-Butyl 3-(3-cyanopyridin-4-yl)-1*H*-indole-1-carboxylate (3r).** R_f 0.33 (EtOAc–PE = 1/4). Pale yellow solid, m.p. 116–118 °C. IR (KBr) ν_{max}: 2231, 1725, 1608, 1374, 1259, 1160, 1094, 1055, 798 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 2H, Ar-H), 8.30 (d, J = 8.3 Hz, 1H, Ar-H), 8.22 (s, 1H, Ar-H), 7.95–7.80 (br s, 1H, Ar-H), 7.72 (d, J = 7.9 Hz, 1H, Ar-H), 7.47 (dt, J = 0.9, 8.3 Hz, 1H, Ar-H), 7.38 (dt, J = 0.9, 7.9 Hz, 1H, Ar-H), 1.73 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 152.0, 149.0, 145.1, 135.7, 127.4, 126.9, 125.6, 123.7, 119.2, 116.9, 115.9, 115.4, 85.1, 28.1. MS (ESI): 320 (M + H^+, 100). Anal calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found C, 71.20; H, 5.61; N, 12.83.

***tert*-Butyl 3-(2-(4-chlorobenzyl)pyridin-4-yl)-5-fluoro-1*H*-indole-1-carboxylate (3s).** R_f 0.25 (EtOAc–PE = 1/6). Pale yellow solid, m.p. 131–133 °C. IR (KBr) ν_{max}: 1725, 1609, 1374, 1260, 1161, 798 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 5.2 Hz, 1H, Ar-H), 8.18 (dd, J = 8.5, 4.1 Hz, 1H, Ar-H), 7.86 (s, 1H, Ar-H), 7.41 (dd, J = 8.9, 2.4 Hz, 1H, Ar-H), 7.38 (dd, J = 4.1, 1.6 Hz, 1H, Ar-H), 7.35 (s, 1H, Ar-H), 7.31 (d, J = 8.5 Hz, 1H, Ar-H), 7.30

(s, 1H, Ar-H), 7.29–7.26 (m, 2H, Ar-H), 7.13 (dd, J = 8.9, 2.4 Hz, 1H, Ar-H), 4.21 (s, 2H, CH_2), 1.71 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 159.6 (d, J = 240.1 Hz), 150.1, 149.3 (d, J = 30.5 Hz), 142.0, 137.9, 136.7, 132.4, 130.4, 128.8, 128.7, 125.7, 121.4, 119.9, 119.2 (d, J = 4.1 Hz), 116.7 (d, J = 9.2 Hz), 112.9 (d, J = 25.0 Hz), 105.3 (d, J = 24.7 Hz), 84.8, 44.0, 28.1. MS (ESI): 437 (M + H^+, 100), 439 (M + H^+, 30). Anal calcd for $C_{25}H_{22}ClFN_2O_2$: C, 68.73; H, 5.08; N, 6.41. Found C, 68.39; H, 5.37; N, 6.14.

***tert*-Butyl 3-(3-benzylpyridin-4-yl)-5-methyl-1*H*-indole-1-carboxylate (3t).** R_f 0.19 (EtOAc–PE = 1/8). Amorphous solid. IR (KBr) ν_{max}: 1735, 1372, 1248, 1156 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 5.2 Hz, 1H, Ar-H), 8.09 (d, J = 8.3 Hz, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 7.49 (s, 1H, Ar-H), 7.42 (dd, J = 5.2, 1.6 Hz, 1H, Ar-H), 7.40 (s, 1H, Ar-H), 7.39–7.35 (m, 4H, Ar-H), 7.30–7.26 (m, 1H, Ar-H), 7.23 (dd, J = 8.3, 1.0 Hz, 1H, Ar-H), 4.27 (s, 2H, CH_2), 2.48 (s, 3H, CH_3), 1.73 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 149.8, 149.5, 142.4, 139.6, 132.9, 129.2, 128.7, 126.5, 126.3, 124.3, 121.7, 119.9, 119.5, 119.3, 115.2, 84.3, 44.7, 28.2, 21.5. MS (ESI): 399 (M + H^+, 100). Anal calcd for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; N, 7.03. Found C, 78.04; H, 6.91; N, 6.70.

***tert*-Butyl 3-(2-(4-chlorobenzyl)pyridin-4-yl)-5-methyl-1*H*-indole-1-carboxylate (3u).** R_f 0.32 (EtOAc–PE = 1/6). Amorphous solid. IR (KBr) ν_{max}: 1736, 1604, 1371, 1248, 1155 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, J = 5.2 Hz, 1H, Ar-H), 8.09 (d, J = 8.4 Hz, 1H, Ar-H), 7.79 (s, 1H, Ar-H), 7.49 (s, 1H, Ar-H), 7.43 (dd, J = 5.2, 1.6 Hz, 1H, Ar-H), 7.37 (s, 1H, Ar-H), 7.31 (t, J = 1.6 Hz, 2H, Ar-H), 7.30 (s, 1H, Ar-H), 7.27 (dd, J = 5.2, 1.2 Hz, 1H, Ar-H), 7.22 (dd, J = 8.4, 1.2 Hz, 1H, Ar-H), 4.22 (s, 2H, CH_2), 2.48 (s, 3H, CH_3), 1.72 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 149.9, 149.5, 142.6, 138.0, 132.9, 132.3, 130.5, 130.4, 128.7, 128.2, 126.4, 124.3, 121.6, 120.1, 119.4, 119.2, 115.3, 84.3, 44.0, 28.2, 21.4. MS (ESI): 433 (M + H^+, 100), 435 (M + H^+, 30). Anal calcd for $C_{26}H_{25}ClN_2O_2$: C, 72.13; H, 5.82; N, 6.47. Found C, 72.51; H, 5.59; N, 6.13.

***tert*-Butyl 3-(2-(4-chlorobenzyl)pyridin-4-yl)-6-fluoro-1*H*-indole-1-carboxylate (3v).** R_f 0.29 (EtOAc–PE = 1/6). Pale yellow solid, m.p. 141–143 °C. IR (KBr) ν_{max}: 1734, 1605, 1484, 1380, 1274, 1155 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, J = 6.1 Hz, 1H, Ar-H), 7.95 (d, J = 8.8 Hz, 1H, Ar-H), 7.81 (s, 1H, Ar-H), 7.66 (dd, J = 8.8, 5.3 Hz, 1H, Ar-H), 7.40 (dd, J = 5.3, 1.6 Hz, 1H, Ar-H), 7.36 (s, 1H, Ar-H), 7.32 (d, J = 6.1 Hz, 1H, Ar-H), 7.30 (t, J = 1.6 Hz, 2H, Ar-H), 7.27 (dd, J = 6.1, 2.3 Hz, 1H, Ar-H), 7.08 (dd, J = 8.8, 2.3 Hz, 1H, Ar-H), 4.21 (s, 2H, CH_2), 1.72 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1 (d, J = 241.6 Hz), 161.0, 150.0, 149.1, 142.1, 137.9, 132.4, 130.4, 128.9, 128.7, 124.4 (d, J = 3.6 Hz), 124.3, 121.5, 120.3 (d, J = 9.8 Hz), 120.0, 119.3, 111.6 (d, J = 24.2 Hz), 103.1 (d, J = 28.6 Hz), 84.9, 44.0, 28.1. MS (ESI): 437 (M + H^+, 100), 439 (M + H^+, 30). Anal calcd for $C_{25}H_{22}ClFN_2O_2$: C, 68.73; H, 5.08; N, 6.41. Found C, 68.50; H, 5.47; N, 6.62.

***tert*-Butyl 3-(3-benzylpyridin-4-yl)-6-fluoro-1*H*-indole-1-carboxylate (3w).** R_f 0.19 (EtOAc–PE = 1/6). Amorphous solid. IR (KBr) ν_{max}: 1739, 1602, 1374, 1222, 1153 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 5.1 Hz, 1H, Ar-H), 7.95 (d, J = 9.3 Hz, 1H, Ar-H), 7.79 (s, 1H, Ar-H), 7.65 (dd, J = 8.8, 5.3 Hz, 1H, Ar-H), 7.41–7.33 (m, 6H, Ar-H), 7.30–7.23 (m, 1H, Ar-H), 7.07 (dd, J = 8.8, 2.4 Hz, 1H, Ar-H), 4.26 (s, 2H, CH_2), 1.73 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 161.1 (d, J = 241.6 Hz), 149.9, 149.2, 141.9, 139.4, 129.2, 129.1, 128.8, 128.6, 126.5, 124.3 (d, J = 3.9 Hz), 121.6, 120.4 (d, J = 9.8 Hz), 119.9, 119.5, 111.6 (d, J = 24.2 Hz), 103.0 (d, J = 28.6 Hz), 84.9, 44.8, 28.1. MS (ESI): 403 (M + H^+, 100). Anal calcd for $C_{25}H_{23}FN_2O_2$: C, 74.61; H, 5.76; N, 6.96. Found C, 74.27; H, 6.13; N, 6.61.

General procedure for the synthesis of 4

To a solution of **3c** (75 mg, 0.2 mmol) in THF (1 mL) was added a methanolic solution of hydrochloric acid (0.2 mL) at 0 °C under an air atmosphere. It was stirred for 2 h at room temperature and quenched with saturated aq. $NaHCO_3$ (1 mL) and water (5 mL). It was extracted with ethyl acetate (8 mL × 3). The combined organic layer was washed with brine and dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE = 1 : 2) to give the corresponding product **4** (49 mg, 90%).

5-Bromo-3-(pyridin-4-yl)-1*H*-indole (4). R_f 0.15 (EtOAc–PE = 1 : 1). Waxy solid. IR (KBr) ν_{max}: 3410, 1685, 1602, 1208, 802 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.11 (s, 1H, NH), 8.55 (d, J = 6.0 Hz, 2H, Ar-H), 8.12 (d, J = 1.2 Hz, 2H, Ar-H), 7.74 (d, J = 6.0 Hz, 2H, Ar-H), 7.49 (d, J = 8.6 Hz, 1H, Ar-H), 7.32 (dd, J = 8.6, 1.2 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.9, 143.5, 136.4, 128.2, 126.8, 125.0, 121.8, 121.0, 114.8, 113.7, 112.8. HRESIMS calcd for $[C_{13}H_9BrN_2 + H]^+$ 273.00274 (100%), 275.00069 (100%), found 273.00177 (100%), 274.99942 (100%).

General procedure for the synthesis of 6b

To a solution of indole (85 mg, 0.5 mmol) and TEMPO (55 mg, 0.35 mmol) in 4-phenylpyridine (124 mg, 0.8 mmol) was added $(Boc)_2O$ (202 mg, 1.0 mmol) under an air atmosphere and the mixture was stirred at 10 °C for 24 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc–PE = 1 : 4) to yield the corresponding product **6b** (159 mg, 86%).

***tert*-Butyl 2-(1*H*-indol-3-yl)-4-phenylpyridine-1(2*H*)-carboxylate (6b).** R_f 0.3 (EtOAc–PE = 1/8). Amorphous solid. IR (KBr) ν_{max}: 1680, 1615, 1371, 1232, 1151 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H, NH), 8.03 (s, 1H, Ar-H), 7.55–7.45 (m, 2H, Ar-H), 7.43–7.30 (m, 4H, Ar-H), 7.25–7.19 (m, 2H, Ar-H), 8.64 (dt, J = 0.8, 7.9 Hz, 1H, Ar-H), 6.84 (s, 1H), 6.42 (s, 1H), 6.00 (s, 1H), 5.80 (s, 1H), 1.53 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 139.1, 136.6, 133.1, 128.5, 127.5, 126.4, 125.9, 125.7, 124.5, 122.1, 120.8, 119.8, 117.8, 116.0, 111.1, 105.9, 81.4, 48.3, 28.3. MS (ESI): 373 (M + H^+, 100). Anal calcd for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52. Found C, 77.05; H, 6.80; N, 7.31.

General procedure for the indolation of isoquinoline

To a solution of indole (0.5 mmol), TEMPO (0.35 mmol) and isoquinoline (0.6 mmol) in THF (1 mL) was added $(Boc)_2O$ (0.6 mmol) under an air atmosphere and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc–PE = 1 : 8) to yield the corresponding product.

***tert*-Butyl 1-(1*H*-indol-3-yl)isoquinoline-2(1*H*)-carboxylate (8a).** R_f 0.20 (EtOAc–PE = 1/10). White amorphous solid. IR (KBr) ν_{max}: 1686, 1634, 1362, 1240, 1164, 772 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 2H, Ar-H), 7.32 (d, J = 7.9 Hz, 1H, Ar-H), 7.29–7.24 (br s, 1H, Ar-H), 7.21–7.11 (m, 5H, Ar-H), 6.89 (s, 1H, Ar-H), 6.77 (s, 1H, Ar-H), 6.62 (s, 1H, Ar-H), 6.00 (s, 1H, Ar-H), 1.57 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 136.3, 132.5, 130.8, 127.5, 126.9, 126.8, 125.7, 125.6, 124.5, 124.4, 122.1, 120.5, 119.8, 117.8, 111.0, 108.6, 81.5, 50.8, 28.3. MS (ESI): 347 ($M + H^+$, 100). Anal calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found C, 75.91; H, 6.73; N, 7.86.

***tert*-Butyl 1-(2-methyl-1*H*-indol-3-yl)isoquinoline-2(1*H*)-carboxylate (8b).** R_f 0.23 (EtOAc–PE = 1/8). White amorphous solid. IR (KBr) ν_{max}: 1682, 1635, 1456, 1341, 1290, 1236, 1164, 769 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 1H, Ar-H), 7.68 (d, J = 6.8 Hz, 1H, Ar-H), 7.22 (d, J = 8.0 Hz, 1H, Ar-H), 7.14–7.04 (m, 4H, Ar-H), 7.02 (dd, J = 8.0, 1.7 Hz, 2H, Ar-H), 7.00 (d, J = 6.8 Hz, 1H, Ar-H), 6.75 (s, 1H, Ar-H), 5.98 (d, J = 8.0 Hz, 1H, Ar-H), 2.58 (s, 3H, CH_3), 1.43 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 135.1, 132.9, 131.8, 129.9, 127.1, 127.0, 126.8, 126.7, 126.5, 124.4, 120.9, 120.2, 119.6, 119.4, 116.7, 110.0, 106.4, 81.3, 51.7, 28.3, 12.6. MS (ESI): 361 ($M + H^+$, 100). Anal calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found C, 76.93; H, 6.57; N, 7.61.

***tert*-Butyl 1-(7-chloro-1*H*-indol-3-yl)isoquinoline-2(1*H*)-carboxylate (8c).** R_f 0.22 (EtOAc–PE = 1/16). White amorphous solid. IR (KBr) ν_{max}: 1694, 1634, 1446, 1342, 1241, 1122, 771 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 1H, Ar-H), 7.85 (s, 1H, Ar-H), 7.32–7.12 (m, 5H, Ar-H), 7.06 (d, J = 7.9 Hz, 1H, Ar-H), 6.86 (s, 1H, Ar-H), 6.76 (s, 1H, Ar-H), 6.70 (s, 1H, Ar-H), 5.99 (s, 1H, Ar-H), 1.54 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 133.5, 132.1, 130.8, 127.7, 127.0, 126.9, 126.8, 125.5, 125.0, 124.6, 121.4, 120.6, 119.2, 118.9, 116.5, 108.5, 81.6, 50.7, 28.3. MS (ESI): 381 ($M + H^+$, 100), 383 ($M + H^+$, 30). Anal calcd for $C_{22}H_{21}ClN_2O_2$: C, 69.38; H, 5.56; N, 7.36. Found C, 69.25; H, 5.87; N, 7.13.

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