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Rapid access to diverse α-carbolines through sequential transition metal catalyzed amination and direct C–H arylation

Masahiro Mineno *, Misayo Sera, Tsuyoshi Ueda, Masahiro Mizuno, Mitsuhisa Yamano, Hideya Mizufune *, Atsuhiko Zanka

Chemical Development Laboratories, CMC Center, Takeda Pharmaceutical Company Limited, 17-85 Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532-8686, Japan

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ABSTRACT

An efficient sequence of Pd catalyzed amination and direct C–H arylation for a synthesis of pharmacologically important α-carbolines is described. The outstanding feature in the synthetic sequence is that a combination of DBU and 2-(dicyclohexylphosphino)biphenyl (DCHPB) plays a critical role to not only enhance the reactivity but also suppress hydrodehalogenation in the direct C–H arylation step. The reaction protocol provides α-carbolines with various substituents including base-sensitive ester and ketone moieties in moderate to excellent yields. Moreover, combination with Cu catalyzed amination further enhanced the versatility of the α-carboline synthesis.

1. Introduction

α-Carbolines (pyrido[2,3-*b*]indoles) (**1**) have recently received much interest since the discovery of various biologically active natural products, such as mescengricin (**2**),[1] neocryptolepine (**3**),[2] grossularine-1 (**4a**) and grossularine-2 (**4b**)[3] (Fig. 1). Additionally, synthetic α-carbolines have been found to exhibit a wide variety of biological properties, such as anxiolytic,[1,4] anti-inflammatory[5] and CNS-stimulating activities.[6] Furthermore, the tricyclic ring system has recently attracted increasing attention as a pharmacophore for kinase inhibitors, such as cyclin-dependent kinase (CDK) inhibitors,[7] glycogen synthetase kinase (GSK) inhibitors,[8] and anaplastic lymphoma kinase (ALK) inhibitors,[9] which are being explored as various anticancer and antidiabetic agents. These attractive biological properties have intrigued the synthetic chemists and encouraged them to develop new synthetic pathways to these ring systems.

For the preparation of this ring system, various synthetic methods have been developed and they can be classified into the following four strategies; (i) intramolecular biaryl coupling reaction of *N*-arylaminopyridine derivatives,[10,11] (ii) intramolecular amination reaction to form the pyrrole C–N bond,[12–14] (iii) benzannulation,[15–17] and (iv) pyridine ring formation (Scheme 1).[16c,18–21]

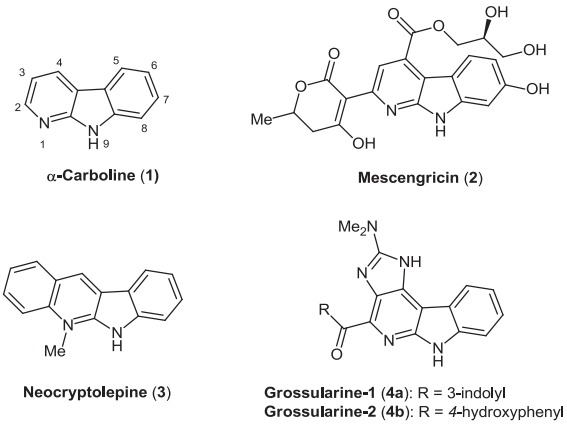

Fig. 1. Chemical structures of α-carboline (**1**) and α-carboline structure based biologically active natural products.

Among these synthetic methods, the Graebe–Ullmann reaction, classified as an intramolecular biaryl coupling strategy (i), has been most often employed, due to the easy access to the penultimate precursors.[9–11] However, the reaction requires a benzotriazole intermediate, which is considered a significant drawback because of the high temperature conditions needed for cyclization with

* Corresponding authors. Tel.: +81 6 6300 6784; fax: +81 6 6300 6251; e-mail addresses: masahiro.mineno@takeda.com (M. Mineno), hideya.mizufune@takeda.com (H. Mizufune).

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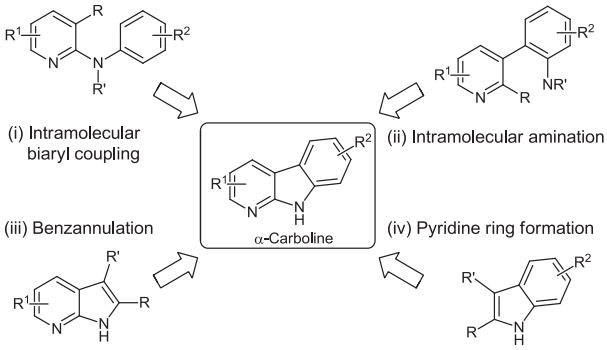


Scheme 1. Common α-carboline syntheses.

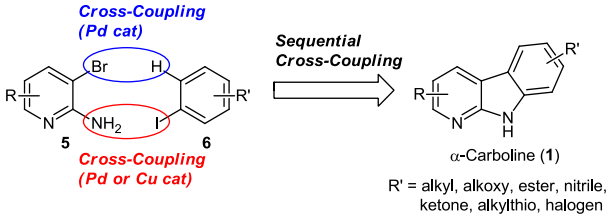
a potential risk of explosion. Even in the case of the modified reaction employing UV light, or microwave irradiation, the protocol is still not practical.[11d,e] Likewise, other protocols have drawbacks from a practical perspective, particularly for the preparation of complex substrates. For example, the intramolecular amination strategy (ii) requires the preparation of 3-(2-aminophenyl)-2-fluoropyridine,[12] 3-(2-nitrophenyl)pyridine,[13] or 3-(2-azidophenyl)pyridine,[14] which are prepared by a combination of biaryl coupling and functionalization at the *ortho* position of the phenyl ring. Regarding the benzannulation strategy (iii), the complicated 7-aza-indole derivatives are prepared for aromatization reaction after a Fisher's indole synthesis[15] or a Diels–Alder reaction,[8b,16] and an intramolecular Friedel–Crafts type acylation.[17] As for the pyridine ring formation strategy (iv), multi-step syntheses are also required for the substrate, such as *N*-phenyl-aminopyrazine derivatives for the Diels–Alder reaction,[16c] 2-aminoindole derivatives[7a,18] and 3-substituted indoles[19] for cyclization. Thus, while those strategies provide regiospecific syntheses of substituted α-carbolines, they require complex substrates as the precursors, which cause multi-step syntheses for their preparation and limits both the availability of the starting materials and the scope for further functionalization on the α-carboline. Additionally, substituent diversity on the benzene ring has not been systematically studied to date, in comparison with that on the pyridine ring.

Sakamoto and co-workers have reported an intramolecular biaryl coupling strategy, utilizing a sequential Pd catalyzed cross coupling method employing amination and direct C–H arylation.[20] The method offered an effective and convenient access to α-carbolines, particularly from the viewpoint of substrate preparations, but it needs harsh conditions (reflux in DMF for 67 h) and gave the product in low yield (31%) for the direct C–H arylation, and was only applied to one example of a non-substituted α-carboline. Therefore, a mild and efficient protocol for direct C–H arylation is still desired, which would contribute to the easy and rapid accesses to various α-carbolines.

In the course of our drug research and development, an efficient synthetic strategy for α-carbolines with various substituents on the benzene ring was required, and we developed several Pd catalyzed syntheses, which we disclosed in a patent.[21] Herein, we describe in more detail our studies on a versatile and practical synthetic protocol for α-carbolines through a sequence of transition metal catalyzed amination and direct C–H arylation (Scheme 2).

2. Results and discussions

Our initial studies were commenced by establishing an efficient catalyst system for Pd catalyzed amination of 2-amino-3-bromopyridine (**5**) with aryl iodide (**6**). To identify the optimal reaction condition for this reaction, an extensive screening of catalyst systems, including ligands and bases, was performed, which

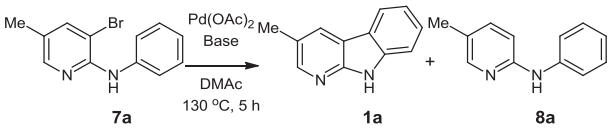


Scheme 2. Synthetic strategy toward α-carboline.

identified the ligand XANTPHOS (4,5-bis(diphenylphosphino)-9,9-dimethyl xanthene) in the presence of $Pd(OAc)_2$ and Cs_2CO_3 as the most active catalyst system for the amination.

Next, our efforts were turned toward the Pd catalyzed direct C–H arylation. Direct C–H arylation of 3-bromo-5-methyl-*N*-phenylpyridine-2-amine (**7a**) was examined under the original conditions reported by Sakamoto group[20] (Table 1, run 1), and it was found that only a small amount of the desired α-carboline (**1a**) was obtained with undesired **8a** arising from hydrodebromination of **7a**, as expected.[22]

Table 1
Base effect on direct C–H arylation of **7a**[a]



Run	Base	Conversion (%)[b]	
		1a	**8a**
1	K_2CO_3	2	1
2	Cs_2CO_3	7	3
3	NaOAc	10	1
4	K_3PO_4	13	3
5	*i*-Pr_2NEt	11	16
6	NEt_3	11	22
7	Cy_2NMe	6	16
8	DABCO	20	<1
9	DBU	32	<1
10	DBN	50	<1

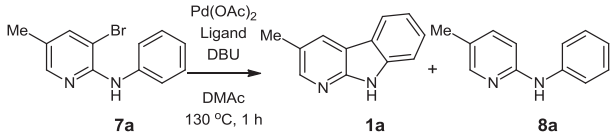
[a] Reaction condition: **7a** (1.0 mmol), $Pd(OAc)_2$ (5 mol %), Base (2 equiv), DMAc (1 mL), 130 °C, 5 h.
[b] Determined by HPLC analysis.

The result led us to further investigate how to enhance the reactivity and suppress the side reaction. First, a series of bases were examined in the presence of $Pd(OAc)_2$ in DMAc (Table 1).

Although some prior literature suggested that inorganic bases are effective to enhance the reaction rate and suppress the hydrodebromination,[23] several inorganic bases (Cs_2CO_3, NaOAc and K_3PO_4) were found to be ineffective in this reaction, giving low conversions and a considerable amount of **8a** (runs 2–4). Next, organic amines were examined, and it was found that although alkyl acyclic amines (*i*-Pr_2NEt, Et_3N,[24] and Cy_2NMe)[25] gave a large amount of **8a** (runs 5–7), satisfactory results could be obtained with cyclic tertiary amines DABCO (1,4-diazabicyclo[2.2.2]octane),[26] DBU (1,8-diazabicyclo [5.4.0]undec-7-ene) and DBN (1,5-diazabicyclo [4.3.0]non-5-ene), which exclusively provided **1a** in moderate yield (runs 8–10). While DBN displays the highest conversion among cyclic tertiary amines, DBU was finally selected as the optimal base for the reaction, on consideration of its wide applicability even for base-sensitive substituents.[27]

With DBU as the base, the influence of ligand on the reactivity was examined. A screening of different ligands was performed at 130 °C for 1 h in the presence of 5 mol % of $Pd(OAc)_2$ and 2.0 equiv of DBU (Table 2). A large number of ligands including monodentate triarylphosphines (PPh_3, P(*o*-Tolyl)$_3$), trialkylphosphines (P(*t*-Bu)$_3$,

Table 2
Ligand effect on direct C–H arylation of **7a**[a]



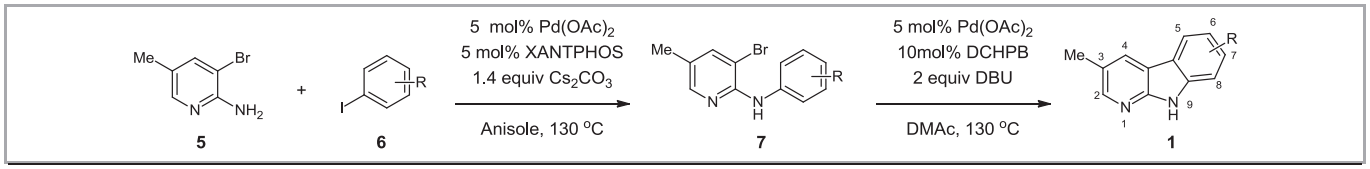
Run	Ligand	Conversion (%)[b]	
		1a	8a
1	PPh_3	19	—
2	P(*o*-Tolyl)$_3$	6	—
3	P(*t*-Bu)$_3$	17	—
4	P(*t*-Bu)$_2$Me	73	—
5	PCy_3	42	—
6	X-Phos[c]	56	—
7	DavePhos[d]	4	—
8	DTBPB[e]	12	—
9	DCHPB[f]	99	—
10	DPPE	26	—
11	DPPF	27	—
12	*rac*-BINAP	6	3
13	XANTPHOS	13	—
14	[^{i}Pr]HCl	4	2

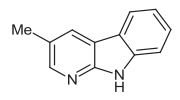
[a] Reaction conditions: **7a** (1.0 mmol), Pd(OAc)$_2$ (5 mol %), Ligand (10 mol %), DBU (2 equiv), DMAc (1 mL), 130 °C, 1 h.
[b] Determined by HPLC analysis.
[c] 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.
[d] 2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethyl amino)biphenyl.
[e] 2-(Di-*tert*-butylphosphino)biphenyl.
[f] 2-(Dicyclo hexylphosphino)biphenyl.

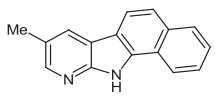
P(*t*-Bu)$_2$Me, PCy_3), dialkylbiphenylphosphines (2-dicyclo hexylphosphino-2′,4′,6′-triisopropyl biphenyl (XPhos), 2-dicyclohexyl phosphino-2′-(*N*,*N*-dimethylamino)biphenyl (DavePhos), 2-(di-*tert*-butylphosphino)biphenyl (DTBPB), 2-(dicyclohexylphosphino) biphenyl (DCHPB)), bidentate phosphines, (dppp, dppf, *rac*-BINAP, XANTPHOS) and *N*-heterocyclic carbene (1,3-bis(2,6-diisopropylphenyl) imidazolium chloride ([IPr]HCl)) were screened. As shown in Table 2, the DCHPB-based catalyst system gave fast reaction that reached full conversion within 1 h (run 9), though P(*t*-Bu)$_2$Me (run 4) gave moderate conversion among monodentate triarylphosphines and bulky trialkylphosphines, standard ligands for intramolecular direct C–H arylations.[28] To our knowledge, it is uncommon that dialkylbiphenylphosphines, such as DCHPB is effective in this kind of intramolecular C–H arylation.[29] Furthermore, since DCHPB was quite effective for the reaction, compared with other dialkylbiphenylphosphines (X-Phos, DavePhos and DTBPB) (runs 6–8), we consider a balance of bulkiness between dialkyl and biphenyl group on the phosphine might be a key to accelerate the reaction.[30]

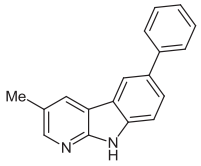
Having established the optimal catalyst systems for both the Pd catalyzed amination and direct C–H arylation, a versatile synthesis of α-carbolines was addressed (Table 3).[31] Gratifyingly, it was found that various electronically and structurally diverse substrates could be applied in this sequence. As can be seen in the synthesis of **1g**, **1h**, **1j** and **1k**, a variety of base-sensitive functional groups including ester, ketone, nitrile and amide were tolerant. Additionally, the catalyst system also worked even in the presence of bromide and chloride substituents on the α-carbolines, allowing the opportunity

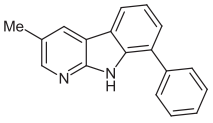
Table 3
Synthesis of α-carboline **1** by a sequence of Pd catalyzed amination and direct C–H arylation[a]

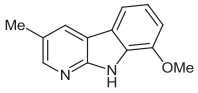


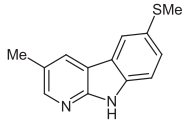

1a
87%[b]/ 97%

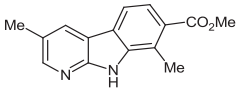

1b
63% / 87%

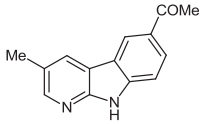

1c
24% / 99%

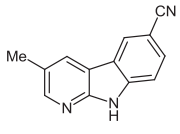

1d
81%[c]/ 97%

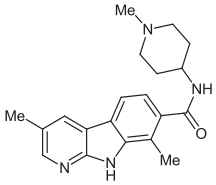

1e
91%[c]/ 95%

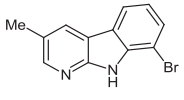

1f
20% / 86%

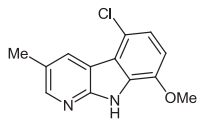

1g
43% / 59% (81%)[d]


1h
45% / 84%


1j
68% / 99%


1k
38%/ 65% (93%)[d]

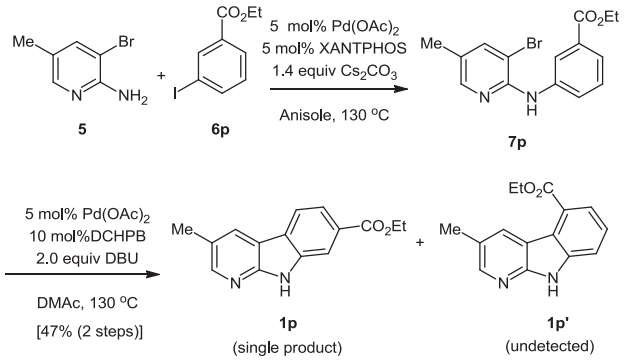

1m
67% /15%


1n
79%[c]/ 55% (87%)[d]

[a] Percentage on the left refers to isolated yield of **7** obtained by the first cross coupling reaction. Percentage on the right refers to isolated yield of **1** obtained by the second cross coupling reaction. Standard reaction condition for the first coupling: **5** (10.7 mmol), **6** (10.7 mmol), Pd(OAc)$_2$ (5 mol%), XANTPHOS (5 mol%), Cs_2CO_3 (1.4 equiv), anisole (30 ml), 130 °C, Standard reaction condition for the second coupling: **7** (3.1 mmol), Pd(OAc)$_2$ (5 mol%), DCHPB (10 mol%), DBU (2 equiv), DMAc (3 ml), 130 °C. [b] Solvent: *t*-BuOH (reflux), [c] Catalyst: $Pd_2(dba)_3$, ligand: dppf, solvent: toluene (100 °C). [d] HPLC assay yield.

for further other transition metal catalyzed functionalizations (**1m** and **1n**). It is noteworthy from practical perspectives that this reaction system was successfully performed on multigram scales and allowed isolation of the desired α-carboline products as nearly pure materials by just adding water to the resulting reaction mixture.

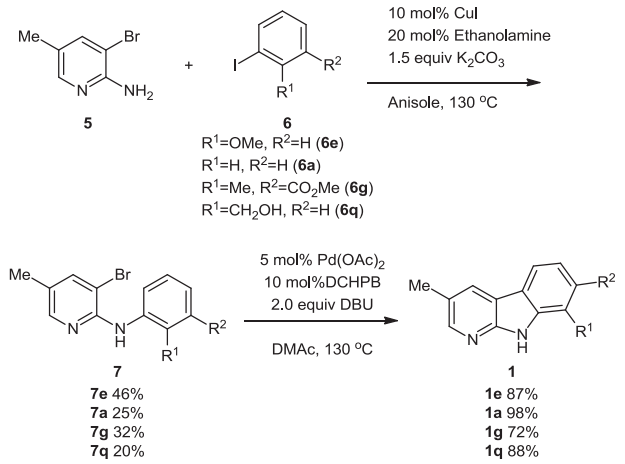
Moreover, to confirm the regioselectivity of the Pd catalyzed cyclization, the reaction starting from 3-substituted aryl iodide (**6p**) was attempted, and it was found that the 7-substituted α-carboline (**1p**) was exclusively obtained, with no 5-substituted compound (**1p′**) detected (Scheme 3). Thus, we achieved selective functionalization at the 6-, 7- and 8-positions of the α-carbolines. As for the preparation of 5-substituted α-carbolines, the 8-substituent appears to be essential, as shown in the synthesis for **1n**.



Scheme 3. Regioselective direct C–H arylation.

Thus, having established a versatile and practical α-carboline synthesis employing sequential Pd catalyzed amination and direct C–H arylation, our interests were then directed toward extending the application to include Cu catalyzed amination. Copper is considered a more attractive catalyst than palladium due to its relative inexpensiveness, ready availability, lower toxicity and robustness even under atmospheric condition.[32] Also, Cu catalyzed amination could be expected to broaden the range of the applicable substrates for the system.[33]

For optimization of the reaction, the coupling reaction of **5** with **6e** was investigated. Initially, several different ligands (*N*,*N*′-dimethylaminocyclohexane, 1,10-phenathroline, 2-acetylcyclohexanone,[34] ethylene glycol, L-proline, ethanolamine) were screened in the presence of CuI, and K_2CO_3. Consequently, ethanolamine was found as the best ligand for the reaction (Scheme 4). The reaction system was then successfully applied to other aryl iodides (**6a**, **6g** and **6q**), providing desired products in moderate yield. The obtained *N*-arylpyridin-2-amines (**7**) successfully underwent the Pd catalyzed direct C–H arylation to provide the corresponding series of α-carbolines (**1**). It is noteworthy that the aryl iodide with a hydroxy methyl group (**6q**), which was considered difficult to be applied to the Pd catalyzed amination, could be successfully converted to **7q** without involving intermolecular *O*-arylation, and the subsequent Pd catalyzed C–H arylation was carried out with no intramolecular *O*-arylation.



Scheme 4. α-Carboline synthesis through Cu catalyzed amination and Pd catalyzed direct C–H arylation.

3. Summary

We have developed a versatile and practical synthetic protocol for pharmacologically important α-carbolines, through a sequence of Pd catalyzed amination and direct C–H arylation. The outstanding feature in the direct C–H arylation is that a combination of DBU and DCHPB plays a critical role to not only enhance the reactivity but also suppress hydrodehalogenation. The reaction system enables the versatile synthesis of α-carbolines in moderate to excellent yields. Moreover, the combination with Cu catalyzed amination afforded a wide diversity of α-carbolines. The protocol readily affords various α-carbolines that could be useful for new drug development.

4. Experimental section

4.1. General

All materials were purchased from commercial suppliers and used without further purification. Melting points were recorded on a Büchi B-540 micromelting apparatus and were uncorrected. NMR spectra were run at either 300 MHz (1H)/75 MHz (13C) (Bruker DPX-300) or 500 MHz (1H)/125 MHz (13C) (Bruker UltraShield-500 PLUS). Chemical shifts are reported as δ values using tetramethylsilane as an internal standard and coupling constants (*J*) are given in hertz (Hertz).

4.2. General procedure for 7 (Pd catalyzed procedure)

Under N_2 atmosphere, to a solution of palladium acetate (120 mg, 0.53 mmol, 5 mol %) and XANTPHOS (309 mg, 0.53 mmol, 5 mol %) in anisole (30 mL) was added 3-bromo-5-methyl-pyridin-2-ylamine (**5**) (2.0 g, 10.7 mmol, 1.0 equiv), aryl iodides (**6**) (10.7 mmol) and cesium carbonate (4.9 g, 15.0 mmol, 1.4 equiv), and the mixture was stirred at 130 °C for 1–13 h. After cooling to room temperature, water (40 mL) was added to the mixture. The mixture was concentrated in vacuo and ethyl acetate (100 mL) was added to the residue. The organic layer was washed with water (20 mL) and concentrated in vacuo to give the crude product, which was purified by flash chromatography to give **7**.

*4.2.1. 3-Bromo-5-methyl-N-phenylpyridine-2-amine (**7a**).* The title compound was prepared from **5** (9.4 g) and iodobenzene (**6a**) (10.2 g), according to the general procedure using *t*-BuOH as a solvent under reflux conditions. Yield: 87% (11.5 g). White solid. Mp 62.5–64.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.24 (s, 3H), 6.89 (br s, 1H), 7.01–7.06 (m, 1H), 7.31–7.36 (m, 2H), 7.58–7.61 (m, 3H), 7.80 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=17.1, 106.1, 119.4, 122.3, 125.1, 128.9, 140.2, 140.9, 146.1, 149.8. HRMS (FAB): *m*/*z* $[M-H]^+$ (calcd for $C_{12}H_{11}BrN_2$: 261.0027; found: 261.0027.).

*4.2.2. 3-Bromo-5-methyl-N-1-naphtylpyridine-2-amine (**7b**).* The title compound was prepared according to the general procedure. Yield: 63% (2.1 g), Brown solid. Mp 127.7–132.6 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ=2.15 (s, 3H), 7.41–7.53 (m, 3H), 7.55–7.61 (m, 1H), 7.71–7.78 (m, 2H), 7.80–7.87 (m, 2H), 7.90–7.96 (m, 1H), 8.16 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=16.4, 105.5, 121.5, 122.9, 124.4, 124.8, 125.6, 125.7, 125.8, 128.1, 129.1, 134.0, 136.7,

141.2, 146.1, 152.0. HRMS (FAB): *m/z* $[M-H]^+$ (calcd for $C_{16}H_{13}BrN_2$: 311.0184; found: 311.0179).

*4.2.3. N-([1,1′-Biphenyl]-4-yl)-3-bromo-5-methylpyridin-2-amine (**7c**).* The title compound was prepared according to the general procedure. Yield: 24% (860 mg), Yellow solid. Mp 90.0–91.3 °C. ^1H NMR (500 MHz, DMSO-d_6): δ=2.21 (s, 3H), 7.28–7.34 (m, 1H), 7.44 (t, *J*=7.7 Hz, 2H), 7.59 (m, 2H), 7.62–7.68 (m, 2H), 7.73 (m, 2H), 7.80–7.89 (m, 1H), 8.00–8.07 (m, 1H), 8.10 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=16.5, 106.1, 120.0, 125.7, 126.0, 126.5, 126.6, 128.8, 133.1, 140.0, 140.5, 141.6, 145.9, 149.9. HRMS (EI): *m/z* $[M]^+$ (calcd for $C_{18}H_{15}BrN_2$: 337.0340; found: 337.0341).

*4.2.4. N-([1,1′-Biphenyl]-2-yl)-3-bromo-5-methylpyridin-2-amine (**7d**).* The title compound was prepared under the following conditions; catalyst: $Pd_2(dba)_3$, ligand: dppf, solvent: toluene, base: NaO*t*-Bu, temperature: 100 °C. Yield: 2.9 g (81%). Off-white solid. Mp 229.2–231.2 °C. ^1H NMR (500 MHz, DMSO-d_6): δ=2.14 (s, 3H), 7.14 (td, *J*=7.5, 1.4 Hz, 1H), 7.26 (dd, *J*=7.6, 1.9 Hz, 1H), 7.31–7.49 (m, 8H), 7.72 (d, *J*=2.2 Hz, 1H), 7.92 (dd, *J*=1.7, 0.8 Hz, 1H), 8.15 (dd, *J*=8.2, 1.3 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=16.4, 105.6, 121.6, 122.8, 125.1, 127.6, 127.9, 128.8, 128.9, 129.9, 133.1, 137.3, 138.5, 141.0, 145.8, 149.8. HRMS (EI): *m/z* $[M-H]^+$ (calcd for $C_{18}H_{15}BrN_2$: 337.0340; found: 337.0337).

*4.2.5. 3-Bromo-N-(2-methoxyphenyl)-5-methylpyridine-2-amine (**7e**).* The title compound was prepared from **5** (10.0 g) and 2-iodoanisole (**6e**) (12.5 g), according to the general procedure under the following conditions; catalyst: $Pd_2(dba)_3$, ligand: dppf, solvent: toluene, base: NaO*t*-Bu, temperature: 100 °C. Yield: 91% (14.8 g), White solid. Mp 111.8–114.4 °C. ^1H NMR (500 MHz, DMSO-d_6): δ=2.20 (s, 3H), 3.91 (s, 3H), 6.87–7.00 (m, 2H), 7.01–7.12 (m, 1H), 7.71 (s, 1H), 7.80–7.90 (m, 1H), 7.99–8.11 (m, 1H), 8.39–8.50 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=16.5, 56.0, 106.1, 110.5, 117.5, 120.5, 121.4, 125.2, 129.5, 141.1, 145.9, 147.7, 149.2. HRMS (EI): *m/z* $[M]^+$ (calcd for $C_{13}H_{13}BrN_2O$: 292.0211; found: 292.0205).

*4.2.6. 3-Bromo-5-methyl-N-[4-(methylthio)phenylpyridine-2-amine (**7f**).* The title compound was prepared according to the general procedure. Yield: 20% (500 mg); White solid. Mp 54.5–57.3 °C. ^1H NMR (500 MHz, DMSO-d_6): δ=2.19 (s, 3H), 2.44 (s, 3H), 7.16–7.25 (m, 2H), 7.54–7.63 (m, 2H), 7.81 (d, *J*=2.5 Hz, 1H), 7.92–8.03 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=16.2, 16.4, 105.8, 120.6, 125.4, 127.5, 129.5, 138.7, 141.5, 145.8, 149.9. HRMS (FAB): *m/z* $[M-H]^+$ (calcd for $C_{13}H_{13}BrN_2S$: 306.9905; found: 306.9904).

*4.2.7. Methyl 3-[(3-bromo-5-methylpyridin-2-yl)amino]-2-methylbenzoate (**7g**).* The title compound was prepared from **5** (6.2 g) and methyl 3-iodo-2-methylbenzoate (**6g**) (9.2 g), according to the general procedure using toluene as a solvent at 100 °C. Yield: 43% (4.8 g). White solid. Mp 63.9–64.7 °C. ^1H NMR (500 MHz, DMSO-d_6): δ=2.15 (s, 3H), 2.26 (s, 3H), 3.83 (s, 3H), 7.27 (t, *J*=7.9 Hz, 1H), 7.51–7.56 (m, 1H), 7.56–7.61 (m, 1H), 7.75–7.79 (m, 2H), 7.81–7.87 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=15.1, 16.4, 52.0, 105.2, 124.6, 125.6, 129.0, 131.4, 133.5, 140.3, 141.2, 146.0, 148.0, 151.3, 168.0. HRMS (EI): *m/z* $[M]^+$ (calcd for $C_{15}H_{15}BrN_2O_2$: 334.0317; found: 334.0313).

*4.2.8. 1-{4-[(3-Bromo-5-methylpyridin-2-yl)amino] phenyl}ethanone (**7h**).* The title compound was prepared according to the general procedure. Yield: 1.5 g (45%); White solid. Mp 91.9–93.0 °C. ^1H NMR (500 MHz, DMSO-d_6): δ=2.23 (s, 3H), 2.50 (s, 3H), 7.67–7.74 (m, 2H), 7.83–7.89 (m, 2H), 7.91 (d, *J*=2.2 Hz, 1H), 8.06–8.11 (m, 1H), 8.50 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=16.5, 26.2, 107.3, 117.6, 127.4, 129.2, 129.3, 141.9, 145.9, 146.0, 149.1, 196.0. HRMS (FAB): *m/z* $[M-H]^+$ (calcd for $C_{14}H_{13}BrN_2O$: 303.0133; found: 303.0132).

*4.2.9. 4-[(3-Bromo-5-methylpyridin-2-yl)amino]benzonitrile (**7j**).* The title compound was prepared from **5** (2.0 g) and 4-iodobenzonitrile (**6j**) (2.5 g), according to the general procedure. Yield: 68% (2.1 g). Off-white solid. Mp 163.4–165.3 °C. ^1H NMR (500 MHz, DMSO-d_6): δ=2.24 (s, 3H), 7.67 (dd, *J*=7.0, 1.9 Hz, 2H), 7.77 (dd, *J*=7.0, 1.9 Hz, 2H), 7.92 (s, 1H), 8.10 (s, 1H), 8.64 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=16.6, 101.8, 107.6, 118.3, 119.6, 127.9, 132.7, 142.1, 145.7, 146.0, 148.8. HRMS (FAB): *m/z* $[M-H]^+$ (calcd for $C_{13}H_{10}BrN_3$: 285.9980; found: 285.9972).

*4.2.10. 3-[3-Bromo-5-methylpyridin-2-yl)amino]-2-methyl-N-(1-methylpiperidin-4-yl)benzamide (**7k**).* The title compound was prepared from **5** (350 mg) and 3-iodo-2-methyl-*N*-(1-methylpiperidin-4-yl)benzamide (**6k**) (670 mg), according to the general procedure. Yield: 38% (295 mg). Reddish white solid. Mp 262.1–266.5 °C. ^1H NMR (500 MHz, DMSO-d_6): δ=1.46–1.59 (m, 2H), 1.72–1.81 (m, 2H), 1.90–1.99 (m, 2H), 2.12 (s, 3H), 2.15 (s, 3H), 2.16 (s, 3H), 2.66–2.80 (m, 2H), 3.59–3.79 (m, 1H), 6.98–7.11 (m, 1H), 7.19 (t, *J*=7.7 Hz, 1H), 7.52 (d, *J*=7.3 Hz, 1H), 7.60 (s, 1H), 7.74–7.82 (m, 1H), 7.82–7.90 (m, 1H), 8.21 (d, *J*=7.9 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=14.4, 16.4, 31.4, 45.96, 46.04, 54.3, 105.3, 122.7, 124.6, 125.4, 129.3, 133.5, 138.9, 139.5, 141.2, 126.0, 151.1, 168.6. HRMS (EI): *m/z* $[M]^+$ (calcd for $C_{20}H_{25}BrN_4O$: 416.1212; found: 416.1202).

*4.2.11. 3-Bromo-N-(2-bromophenyl)-5-methylpyridine-2-amine (**7m**).* The title compound was prepared according to the general procedure. Yield: 67% (2.5 g); Off-white solid. Mp 54.7–56.5 °C. ^1H NMR (500 MHz, DMSO-d_6): δ=2.21 (s, 3H), 6.90–7.06 (m, 1H), 7.35–7.42 (m, 1H), 7.65 (dd, *J*=8.0, 1.7 Hz, 1H), 7.73 (s, 1H), 7.81–7.96 (m, 1H), 7.97–8.09 (m, 1H), 8.27 (dd, *J*=8.4, 1.7 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=16.5, 106.2, 114.6, 121.6, 123.8, 126.2, 128.2, 132.4, 138.1, 141.4, 145.9, 149.3. HRMS (EI): *m/z* $[M]^+$ (calcd for $C_{12}H_{10}Br_2N_2$: 339.9211; found: 339.9211).

*4.2.12. 3-Bromo-N-(5-chloro-2-methoxyphenyl)-5-methyl pyridine-2-amine (**7n**).* The title compound was prepared from **5** (9.8 g) and 4-chloro-2-iodo-1-methoxybenzene (**6n**) (13.4 g), according to the general procedure under the following conditions; catalyst: $Pd_2(dba)_3$, ligand: dppf, solvent: toluene, base: NaO*t*-Bu, temperature: 100 °C. Yield: 79% (12.9 g). White solid. Mp 139.2–141.2 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=2.23 (s, 3H), 3.92 (s, 3H), 6.77 (d, *J*=8.6 Hz, 1H), 6.87 (dd, *J*=8.6, 2.5 Hz, 1H), 7.59 (d, *J*=1.5 Hz, 1H), 7.75 (br s, 1H), 8.05 (d, *J*=1.0 Hz, 1H), 8.69 (d, *J*=2.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ=17.1, 56.2, 106.8, 110.4, 117.1, 120.1, 125.4, 126.0, 131.2, 140.9, 146.0, 146.3, 149.3. MS: *m/z*=327 $[M+H]^+$. Anal. Calcd for $C_{13}H_{12}N_2OBrCl$: C, 47.66; H, 3.69; N, 8.55; Br 24.39; Cl 10.82. found: C, 47.94; H, 3.62; N, 8.68; Br, 24.36; Cl, 10.86.

*4.2.13. Ethyl 3-((3-bromo-5-methylpyridin-2-yl)amino)-benzoate (**7p**).* The title compound was prepared from **5** (10.0 g) and ethyl 2-iodobenzoate (**6p**) (14.8 g), according to the general procedure. **7p** was telescoped to the subsequent step. White solid. Mp 50.8–52.8 °C. ^1H NMR (500 MHz, DMSO-d_6): δ=1.33 (t, *J*=7.1 Hz, 3H), 2.21 (s, 3H), 4.32 (q, *J*=7.3 Hz, 2H), 7.40 (t, *J*=7.9 Hz, 1H), 7.54 (dt, *J*=7.7, 1.3 Hz, 1H), 7.85 (d, *J*=2.2 Hz, 1H), 7.89 (ddd, *J*=8.2, 2.2, 1.0 Hz, 1H), 8.01 (dd, *J*=1.9, 0.6 Hz, 1H), 8.23 (t, *J*=2.1 Hz, 1H), 8.31 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=14.2, 16.5, 60.6, 106.2, 120.2, 121.9, 124.1, 126.2, 128.5, 130.1, 141.4, 141.7, 145.8, 149.8, 165.9. MS (ESI): *m/z*=335 $[M+H]^+$. Anal. Calcd for $C_{15}H_{15}BrN_2O_2$; C,53.75; H, 4.41; N, 8.36; Br, 23.84. found: C, 53.88; H, 4.43; N, 8.18; Br, 23.49.

4.3. General procedure for 7 (Cu catalyzed procedure)

Under N_2 atmosphere, to a solution of copper iodide (204 mg, 0.11 mmol, 10 mol %) and ethanolamine (131 mg, 0.22 mmol,

20 mol %) in anisole (30 mL) was added aryl iodides (**6**) (10.7 mmol), 3-bromo-5-methyl-pyridin-2-ylamine (**5**) (10.7 mmol) and potassium carbonate (2.2 g, 16.0 mmol, 1.5 equiv), and the mixture was stirred at 130 °C for 4–18 h. After cooling to room temperature, water (30 mL) was added to the mixture. The mixture was concentrated in vacuo and ethyl acetate (50 mL) was added to the residue. The organic layer was washed with water (20 mL) and concentrated in vacuo to give the crude product. The crude product was purified by flash chromatography to give the title compound.

*4.3.1. 3-Bromo-N-(2-methoxyphenyl)-5-methylpyridine-2-amine (**7e**).* The title compound was prepared from **5** (1.0 g) and **6e** (1.3 g), according to the general procedure. Yield: 46% (720 mg).

*4.3.2. 3-Bromo-5-methyl-N-phenylpyridine-2-amine (**7a**).* The title compound was prepared according to the general procedure. Yield: 25% (700 mg).

*4.3.3. Methyl 3-[(3-bromo-5-methylpyridin-2-yl)amino]-2-methylbenzoate (**7g**).* The title compound was prepared according to the general procedure. Yield: 32% (1.1 g).

*4.3.4. {2-[(3-Bromo-5-methylpyridin-2-yl)amine]phenyl} methanol (**7q**).* The title compound was prepared from **5** (1.5 g) and (2-iodophenyl)methanol (**6q**) (1.9 g), according to the general procedure. Yield: 20% (470 mg); Off-white solid. Mp 129.3–131.8 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ=2.20 (s, 3H), 4.56 (d, J=5.0 Hz, 2H), 5.67 (t, J=5.0 Hz, 1H), 6.96 (td, J=7.4, 1.3 Hz, 1H), 7.25 (d, J=7.3 Hz, 2H), 7.84 (d, J=2.2 Hz, 1H), 7.93–8.00 (m, 1H), 8.09 (dd, J=8.7, 1.1 Hz, 1H), 8.66 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=16.5, 62.5, 105.7, 120.2, 121.5, 125.1, 127.5, 128.3, 130.5, 139.7, 141.3, 145.8, 150.0. HRMS (EI): m/z [M]$^+$ (calcd for $C_{13}H_{13}BrN_2O$: 292.0211; found: 292.0208).

4.4. General procedure for 1

Under N_2 atmosphere, to a solution of palladium acetate (21 mg, 0.09 mmol, 5 mol %) and 2-(di-cyclohexylphosphino)biphenyl (DCHPB) (65 mg, 0.19 mmol, 10 mol %) in *N*,*N*-dimethylacetamide (3 mL) was added *N*-arylpyridin-2-amines (**7**) (3.09 mmol) and DBU (942 mg, 6.19 mmol, 2.0 equiv), and the mixture was stirred at 130 °C for 1–8 h. After cooling to room temperature, water (6 mL) was added to the mixture. The mixture was then stirred at ambient temperature for 0.5 h before the precipitate was filtered and washed with methanol (4 mL) and water (2 mL) to give the title compound.

*4.4.1. 3-Methyl-9H-pyrido[2,3-b]indole (**1a**).* The title compound was prepared from **7a** (10.5 g), according to the general procedure. Yield: 97% (7.5 g). Off-white solid. Mp 269.4–271.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ=2.45 (s, 3H), 7.16–7.21 (m, 1H), 7.39–7.48 (m, 2H), 8.11 (d, J=7.8 Hz, 1H), 8.26 (d, J=1.5 Hz, 1H), 8.30 (s, 1H), 11.59 (br s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ=18.2, 111.3, 115.1, 119.3, 120.3, 121.2, 123.6, 126.5, 128.6, 139.3, 146.7, 150.7. HRMS (EI): m/z [M]$^+$ (calcd for $C_{12}H_{10}N_2$: 182.0841; found: 182.0844.).

*4.4.2. 8-Methyl-11H-benzo[g]pyrido[2,3-b]indole (**1b**).* The title compound was prepared from **7b** (500 mg), according to the general procedure. Yield: 87% (322 mg). Yellow solid. Mp 301.1–303.5 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ=2.50 (s, 3H), 7.58 (ddd, J=8.2, 6.8, 1.4 Hz, 1H), 7.64 (td, J=7.5, 1.4 Hz, 1h), 7.67 (d, J=8.5 Hz, 1H), 8.04 (d, J=7.9 Hz, 1H), 8.19 (d, J=8.5 Hz, 1H), 8.33 (d, J=2.2 Hz, 1H), 8.38 (dd, J=1.9, 0.6 Hz, 1H), 8.60 (d, J=7.6 Hz, 1H), 12.64 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=18.1, 114.9, 115.6, 119.66, 119.69, 121.2, 122.2, 124.1, 125.6, 127.9, 128.5, 132.2, 135.0, 141.2, 145.9, 149.7. HRMS (EI): m/z [M]$^+$ (calcd for $C_{16}H_{12}N_2$: 232.1000; found: 232.0996).

*4.4.3. 3-Methyl-6-phenyl-9H-pyrido[2,3-b]indole (**1c**).* The title compound was prepared from **7c** (500 mg), according to the general procedure. Yield: 99% (375 mg). Pale yellow solid. Mp 300.1–302.8 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ=2.47 (s, 3H), 7.31–7.38 (m, 1H), 7.49 (t, J=7.9 Hz, 2H), 7.57 (d, J=8.5 Hz, 1H), 7.69–7.92 (m, 3H), 8.17–8.36 (m, 1H), 8.46 (dt, J=8.1, 1.1 Hz, 2H), 11.78 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=18.0, 111.6, 115.6, 119.2, 120.8, 123.7, 125.6, 126.5, 126.6, 128.9, 129.3, 131.8, 138.7, 141.0, 146.0, 150.4. HRMS (EI): m/z [M]$^+$ (calcd for $C_{18}H_{14}N_2$: 258.1157; found: 258.1157).

*4.4.4. 3-Methyl-8-phenyl-9H-pyrido[2,3-b]indole (**1d**).* The title compound was prepared from **7d** (500 mg), according to the general procedure. Yield: 97% (370 mg). White solid. Mp 229.2–231.2 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.47 (s, 3H), 7.31 (t, J=7.6 Hz, 1H), 7.41–7.48 (m, 2H), 7.55 (t, J=7.7 Hz, 2H), 7.71 (dd, J=8.2, 1.3 Hz, 2H), 8.14 (dd, J=7.6, 1.3 Hz, 1H), 8.28 (d, J=2.5 Hz, 2H), 8.34–8.39 (m, 1H), 11.51 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d $_6$): δ 18.0, 115.1, 119.8, 120.1, 121.2, 123.8, 125.2, 126.7, 127.3, 128.4, 128.5, 128.9, 136.4, 138.2, 146.8, 151.1. HRMS (EI): m/z [M]$^+$ (calcd for $C_{18}H_{14}N_2$: 258.1157; found: 258.1154).

*4.4.5. 8-Methoxy-3-methyl-9H-pyrido[2,3-b]indole (**1e**).* The title compound was prepared from **7e** (32.0 g), according to the general procedure. Yield: 95% (22.1 g). Brown solid. Mp 215.9–220.2 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ=2.44 (s, 3H), 3.97 (s, 3H), 7.03 (d, J=7.9 Hz, 1H), 7.13 (t, J=7.7 Hz, 1H), 7.69 (d, J=7.9 Hz, 1H), 8.27 (q, J=2.6 Hz, 2H), 11.72 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=18.0, 55.5, 107.3, 113.3, 115.1, 119.7, 121.2, 123.5, 128.4, 129.1, 145.7, 146.5, 150.3. HRMS (EI): m/z [M]$^+$ (calcd for $C_{13}H_{12}N_2O$: 212.0950; found: 212.0946).

*4.4.6. 3-Methyl-6-(methylthio)-9H-pyrido[2,3-b]indole (**1f**).* The title compound was prepared from **7f** (400 mg), according to the general procedure. Yield: 86% (253 mg). Orange solid. Mp 155 °C dec. ^{1}H NMR (500 MHz, DMSO-d_6): δ=2.46 (s, 3H), 2.55 (s, 3H), 7.42–7.49 (m, 2H), 8.13–8.18 (m, 1H), 8.27–8.34 (m, 1H), 8.41–8.49 (m, 1H), 11.88 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=17.2, 17.9, 112.0, 115.3, 120.7, 120.9, 123.8, 127.4, 127.6, 129.9, 137.5, 145.1, 149.5. HRMS (EI): m/z [M]$^+$ (calcd for $C_{13}H_{12}N_2S$: 288.0721; found: 288.0711).

*4.4.7. Methyl 3,8-dimethyl-9H-pyrido[2,3-b]indole-7-carboxylate (**1g**).* The title compound was prepared from **7g** (4.8 g), according to the general procedure. Yield: 59% (2.1 g). Off-white solid. Mp 296.6–298.7 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ=2.46 (s, 3H), 2.77 (s, 3H), 3.87 (s, 3H), 7.67 (d, J=8.2 Hz, 1H), 8.04 (d, J=8.5 Hz, 1H), 8.37 (dd, J=9.9, 2.4 Hz, 2H), 11.90 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=14.9, 18.0, 51.8, 114.6, 118.1, 120.9, 122.4, 123.0, 124.2, 126.6, 129.3, 138.9, 148.0, 151.4, 168.0. HRMS (EI): m/z [M]$^+$ (calcd for $C_{15}H_{14}N_2O_2$: 254.1055; found: 254.1056).

*4.4.8. 1-(3-Methyl-9H-pyrido[2,3-b]indol-6-yl)ethanone (**1h**).* The title compound was prepared from **7h** (1.0 g), according to the general procedure. Yield: 84% (0.6 g). Off-white solid. Mp 287.6–290.6 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ=2.48 (s, 3H), 2.67 (s, 3H), 7.55 (d, J=8.5 Hz, 1H), 8.07 (dd, J=8.5, 1.9 Hz, 1H), 8.22–8.42 (m, 1H), 8.51 (dd, J=1.9, 0.6 Hz, 1H), 8.86 (d, J=1.9 Hz, 1H), 12.14 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=18.0, 26.5, 111.0, 115.7, 120.0, 122.9, 124.6, 126.7, 129.0, 129.6, 142.1, 146.5, 150.6, 196.9. HRMS (EI): m/z [M]$^+$ (calcd for $C_{14}H_{12}N_2O$: 224.0950; found: 224.0948).

*4.4.9. 3-Methyl-9H-pyrido[2,3-b]indole-6-carbonitrile (**1j**).* The title compound was prepared from **7j** (1.0 g), according to the general

procedure. Yield: 99% (0.7 g). Pale yellow solid. Mp 285.6–288.6 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ=2.47 (s, 3H), 7.62 (d, J=8.5 Hz, 1H), 7.80 (dd, J=8.4, 1.7 Hz, 1H), 8.37–8.40 (m, 1H), 8.41–8.48 (m, 1H), 8.69 (d, J=1.9 Hz, 1H), 12.27 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=18.0, 101.0, 112.2, 114.2, 120.2, 120.4, 125.0, 126.3, 129.4, 129.5, 141.2, 148.0, 150.8. HRMS (EI): m/z [M]$^+$ (calcd for $C_{13}H_9N_3$: 207.0796; found: 207.0789).

*4.4.10. 3,8-Dimethyl-N-(1-methylpiperidin-4-yl)-9H-pyrido[2,3-b] indole-7-carboxamide (**1k**).* The title compound was prepared from **7k** (250 mg), according to the general procedure. Yield: 65% (130 mg). White solid. Mp 335.8–336.8 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.58 (d, J=8.8 Hz, 2H), 1.84 (d, J=11.3 Hz, 2H), 2.00 (t, J=10.9 Hz, 2H), 2.20 (s, 3H), 2.49 (s, 3H), 2.58 (s, 3H), 2.79 (d, J=11.0 Hz, 2H), 3.77 (br s, 1H), 7.17 (d, J=7.6 Hz, 1H), 8.00 (d, J=7.9 Hz, 1H), 8.20 (d, J=7.8 Hz, 1H), 8.35 (d, J=9.7 Hz, 1H), 11.7 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=14.0, 17.8, 28.8, 31.3, 45.8, 54.2, 113.7, 117.7, 118.0, 118.3, 121.0, 123.6, 124.1, 125.1, 128.6, 140.2, 151.0, 167.8. HRMS (EI): m/z [M]$^+$ (calcd for $C_{20}H_{24}N_4O$: 336.1950; found: 336.1954).

*4.4.11. 8-Bromo-3-methyl-9H-pyrido[2,3-b]indole (**1m**).* The title compound was prepared from **7m** (500 mg), according to the general procedure. Yield: 15% (90 mg). Yellow solid. Mp 389.0 °C dec. ^{1}H NMR (500 MHz, DMSO-d_6): δ=2.47 (s, 3H), 7.16 (t, J=7.7 Hz, 1H), 7.65 (d, J=6.9 Hz, 1H), 8.15 (d, J=7.3 Hz, 1H), 8.32–8.40 (m, 2H), 11.93 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=18.0, 103.7, 115.1, 120.3, 120.6, 122.0, 124.5, 128.9, 129.1, 137.7, 147.5, 150.6. HRMS (EI): m/z [M]$^+$ (calcd for $C_{12}H_9BrN_2$: 259.9949; found: 259.9940).

*4.4.12. 5-Chloro-8-methoxy-3-methyl-9H-pyrido[2,3-b] indole (**1n**).* The title compound was prepared from **7n** (3.0 g), according to the general procedure. Yield: 55% (1.25 g). White solid. Mp 299.5–301.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ=2.48 (s, 3H), 3.98 (s, 3H), 7.05 (d, J=8.5 Hz, 1H), 7.17 (d, J=8.5 Hz, 1H), 8.35 (d, J=1.7 Hz, 1H), 8.50 (d, J=1.7 Hz, 1H), 12.11 (br s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ=18.2, 56.1, 108.1, 114.1, 117.9, 119.2, 119.6, 124.3, 129.9, 130.2, 144.9, 147.5, 150.1. MS: m/z=247 [M+H]$^+$. Anal. Calcd for $C_{13}H_{11}N_2OCl$: C, 63.29; H, 4.49; N, 11.36; Cl, 14.37. found: C, 63.21; H, 4.26; N, 11.44; Cl, 14.37.

*4.4.13. Ethyl 3-methyl-9H-pyrido[2,3-b]indole-7-carboxylate (**1p**).* The title compound was prepared from telescoped **7p**, according to the general procedure (6.4 g, two steps total: 47%). Yellow solid. Mp 304.2–306.0 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.37 (t, J=7.1 Hz, 3H), 2.47 (s, 3H), 4.37 (q, J=6.9 Hz, 2H), 7.81 (dd, J=8.2, 1.6 Hz, 1H), 8.10 (d, J=1.0 Hz, 1H), 8.23 (d, J=8.2 Hz, 1H), 8.37 (s, 1H), 8.41 (s, 1H), 11.92 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=14.2, 18.0, 60.7, 112.3, 114.2, 119.7, 121.0, 123.9, 124.3, 127.3, 129.5, 138.4, 148.3, 151.4, 166.1. HRMS (EI): m/z [M]$^+$ (calcd for $C_{15}H_{14}N_2O_2$: 254.1055; found: 254.1054).

*4.4.14. (3-Methyl-9H-pyrido[2,3-b]indol-8-yl)methanol (**1q**).* The title compound was prepared from **7q** (300 mg), according to the general procedure. Yield: 88% (192 mg). Yellow solid. Mp 226.1–229.8 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ=2.46 (s, 3H), 4.86 (d, J=5.7 Hz, 2H), 5.23 (t, J=5.8 Hz, 1H), 7.19 (d, J=7.6 Hz, 1H), 7.33–7.54 (m, 1H), 8.01 (d, J=7.6 Hz, 1H), 8.28 (d, J=2.5 Hz, 1H), 8.31 (d, J=2.5 Hz, 1H), 11.48 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=18.0, 59.6, 115.0, 119.0, 119.4, 120.0, 123.5, 124.3, 125.5, 128.3, 136.6, 146.4, 150.7. HRMS (EI): m/z [M]$^+$ (calcd for $C_{13}H_{12}N_2O$: 212.0950; found: 212.0947).

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