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Selective Access to 3-Cyano-1*H*-indoles, 9*H*-Pyrimido[4,5-*b*]indoles, or 9*H*-Pyrido[2,3-*b*]indoles through Copper-Catalyzed One-Pot Multicomponent Cascade Reactions

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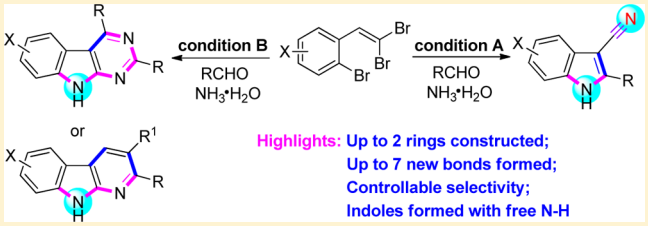
Supporting Information

ABSTRACT: Novel and selective synthetic approaches toward indole derivatives via copper-catalyzed one-pot multicomponent cascade reactions of 1-bromo-2-(2,2-dibromovinyl)benzenes with aldehydes and aqueous ammonia are presented. Intriguingly, the concentration of ammonia, the molar ratio of reagents, and the structural features of the aldehyde substrate serve as key factors in controlling the selective formation of 3-cyano-1*H*-indoles, 9*H*-pyrimido[4,5-*b*]indoles, or 9*H*-pyrido[2,3-*b*]indoles. Compared with literature procedures, the synthetic approaches reported herein have advantages such as readily available starting materials, mild reaction conditions, and divergent reaction patterns toward different products with easily tunable selectivity.



INTRODUCTION

Indole and its derivatives are attracting tremendous attention because of their wide range of medicinal activities, frequent occurrence in natural products, and multiple uses in organic synthesis.[1−4] Among them, 3-cyanoindoles[5] and pyrimido[4,5-*b*]indoles[6] show remarkable biological significance and have therefore been used as key building blocks in the construction of medicinal and functional materials.[7] In addition, 9*H*-pyrimido[4,5-*b*]indoles can act as extended purine bases to form unnatural nucleosides, which were successfully utilized as probes in studying single-nucleotide polymorphism typing and hole transport through DNA and to build DNA logic gates in nucleic acid chemistry.[8] To date, a number of synthetic strategies toward 3-cyanoindoles[9] or pyrimido[4,5-*b*]indoles[10] have been developed. While those pioneering methods are generally efficient and reliable, they usually start from substrates that already have an indole scaffold. Moreover, some of those syntheses require harsh reaction conditions and necessitate toxic reagents and multistep processes. Therefore, the development of simple synthetic methods in which both the indole framework and the cyano/pyrimidine unit are constructed simultaneously via a one-pot procedure featuring facile operation and easily accessible starting materials remains an attractive but still challenging task.

Transition-metal-catalyzed cascade cyclization of *ortho*-functionalized (2-bromovinyl)benzenes has recently evolved as a direct and efficient approach toward substituted indoles. For example, Lautens has reported an elegant strategy leading to 2-substituted indoles via Pd-catalyzed tandem C−N/C−C coupling of 2-(2,2-dibromovinyl)anilines.[11] Willis revealed a Cu−diamine complex-catalyzed tandem C−N bond formation of 2-(2-haloalkenyl)aryl halides with anilines, amides, or carbamates to afford a series of N-functionalized indoles.[12] Meanwhile, multicomponent reactions (MCRs) in which three or more different starting materials undergo sequential transformations in the same vessel to form multiple C−C and/or C−heteroatom bonds are rapidly prevailing.[13] Compared with step-by-step operations, this protocol is advantageous because it obviates the need to isolate and purify the intermediates. In particular, copper-catalyzed MCRs with C−N bond formation as a key step have turned out to be a powerful tool for the construction of N-fused heterocycles.[14] In this regard, we have developed some efficient syntheses of N-heterocycles through Cu-catalyzed MCRs by using aqueous ammonia as a cheap nitrogen source.[15] As a continuation of our study in this field, we have discovered a new synthetic approach toward indole-related heterocycles through Cu-catalyzed one-pot MCRs of 1-bromo-2-(2,2-dibromovinyl)benzenes[16] with aldehydes and aqueous ammonia. In this approach, different reaction modes of the same starting materials can be realized in a controllable manner through tuning of the concentration of ammonia and the dosage of reagents to give 3-cyano-1*H*-indoles or 9*H*-pyrimido[4,5-*b*]indoles/9*H*-pyrido[2,3-*b*]-indoles.

RESULTS AND DISCUSSION

Initially, treatment of 1-bromo-2-(2,2-dibromovinyl)benzene (**1a**) (0.5 mmol), benzaldehyde (**2a**) (1 mmol), and aqueous

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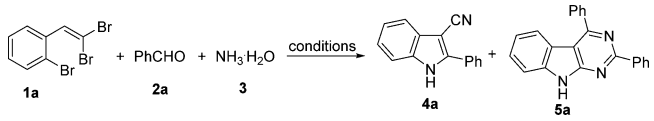
Table 1. Optimization Study on the Formation of 3-Cyano-1*H*-indole (4a) and 9*H*-Pyrimido[4,5-*b*]indole (5a)[a]



					Yield (%)[b]	
entry	mL of **3**	catalyst	additive (equiv)	solvent (mL)	**4a**	**5a**
1	1.5	CuI	–	DMF (3)	15	21
2	1.5	CuI	1,10-phen (0.2)	DMF (3)	19	24
3	1.5	CuI	L-Proline (0.2)	DMF (3)	15	24
4	1.5	CuI	DABCO (A) (0.2)	DMF (3)	22	30
5	1.5	CuI	PivOH (B) (1)	DMF (3)	26	24
6	1.5	CuI	A (0.2) + B (1)	DMF (3)	32	30
7	1.5	CuI	A (0.2) + B (1)	DMF (2)	56	13
8	**1.5**	**CuI**	**A (0.2) + B (1)**	**DMF (1.5)**	**62**	**trace**
9	0.75	CuI	A (0.2) + B (1)	DMF (0.75)	25	13
10	3	CuI	A (0.2) + B (1)	DMF (3)	52	trace
11	1.5	CuI	A (0.2) + B (1)	DMSO (1.5)	60	trace
12	1.5	CuI	A (0.2) + B (1)	NMP (1.5)	53	trace
13	1.5	CuBr	A (0.2) + B (1)	DMF (1.5)	58	trace
14	1.5	$Cu(OAc)_2$	A (0.2) + B (1)	DMF (1.5)	32	trace
15	1	CuI	A (0.2) + B (1)	DMF (3)	22	35
16[c]	1	CuI	A (0.2) + B (1)	DMF (3)	16	42
17[c]	**0.5**	**CuI**	**A (0.2) + B (1)**	**DMF (3)**	**trace**	**55**
18[c]	0.25	CuI	A (0.2) + B (1)	DMF (1.5)	trace	35
19[c]	1	CuI	A (0.2) + B (1)	DMF (6)	5	47

[a]Reaction conditions: 0.5 mmol of **1a**, 1 mmol of **2a**, and 0.05 mmol of catalyst at 80 °C under air in a sealed tube for 24 h. [b]Isolated yields. [c]With 1.5 mmol of **2a** for 30 h.

ammonia (**3**) (26%, 1.5 mL) with CuI (0.05 mmol) in DMF (3 mL) at 80 °C for 24 h gave 2-phenyl-1*H*-indole-3-carbonitrile (**4a**) in 15% yield and 2,4-diphenyl-9*H*-pyrimido[4,5-*b*]indole (**5a**) in 21% yield (Table 1, entry 1). To improve the efficiency, several ligands including 1,10-phenanthroline (1,10-phen), L-proline, and 1,4-diazabicyclo[2.2.2]octane (DABCO) were tried (entries 2−4). Among them, DABCO showed a positive effect in raising the yields of both **4a** and **5a** (entry 4). Next, inspired by the fact that pivalic acid (PivOH) has frequently been used as an additive to facilitate Cu-catalyzed coupling reactions,[17] we tried PivOH in the reaction of **1a**, **2a**, and **3**. As expected, addition of PivOH did indeed improve the reaction, but the yields were still not satisfactory (entry 5). Gratifyingly, using a combination of DABCO (0.2 equiv) with PivOH (1 equiv) gave better yields of both **4a** and **5a** than using DABCO or PivOH alone, although the selectivity was only marginal (entry 6). In following studies, we were pleased to find that in the presence of CuI (0.1 equiv), DABCO (0.2 equiv), and PivOH (1 equiv), reducing the amount of solvent (DMF) amplified the selectivity for **4a** significantly (entry 7), and 1.5 mL of DMF was found to be the most optimal (entry 8; concentration of ammonia ≈ 7 M, **1a**:**2a**:**3** molar ratio = 1:2:42; condition A). Notably, when the other conditions were kept unchanged, halving the amounts of both aqueous ammonia **3** and DMF (concentration of ammonia ≈ 7 M, **1a**:**2a**:**3** molar ratio = 1:2:21) resulted in reduced yield and selectivity (entry 9). On the other hand, doubling the amounts of both **3** and DMF (concentration of ammonia ≈ 7 M, **1a**:**2a**:**3** molar ratio = 1:2:84) did not improve the reaction further (entry 10). Next, other solvents such as DMSO and 1-methyl-2-pyrrolidinone (NMP) were screened, and they were less effective than DMF in mediating this reaction (entries 11 and 12). Studies with CuBr or $Cu(OAc)_2$ as the catalyst resulted in decreased yields (entries 13 and 14). In further optimization, it was revealed that the selectivity of this MCR could be changed in the opposite direction to favor the formation of **5a** when the amount of ammonia was reduced from 1.5 to 1 mL in the presence of 3 mL of DMF (entry 15). The selectivity could be amplified by increasing the amount of **2a** from 1 to 1.5 mmol (entry 16) and by reducing the amount of **3** from 1 to 0.5 mL (entry 17; concentration of ammonia ≈ 2 M, **1a**:**2a**:**3** molar ratio = 1:3:14; condition B). It was also found that decreasing the amounts of **3** and DMF to 0.25 and 1.5 mL (entry 18; concentration of ammonia ≈ 2 M, **1a**:**2a**:**3** molar ratio = 1:3:7) or increasing them to 1 and 6 mL (entry 19, concentration of ammonia ≈ 2 M, **1a**:**2a**:**3** molar ratio = 1:3:28) resulted in reduced yields of **5a**.

With the optimized conditions in hand, we then examined the scope of **1** and **2** for the synthesis of 3-cyanoindoles under condition A (Table 1, entry 8). First, diversely substituted benzene substrates **1** were evaluated with **2a** and **3**. The results listed in Table 2 show that various R^1, including hydrogen, chloro, fluoro, trifluoromethyl, methyl, and methoxy, were well-tolerated (entries 1−8). It was also found that the electronic nature of these substituents did not affect the efficiency in an obvious way. Next, the effect of varying the aldehyde substrate **2** was tested by treating different aldehydes **2** with **1a** and **3** (entries 9−24). Aryl-substituted aldehydes bearing various functional groups (from alkyl or alkoxyl to halides) on the aryl ring underwent this tandem reaction smoothly to afford the desired 3-cyanoindoles **4i−q** in reasonably good yields. The position of the substituent on the aryl ring had little effect on the efficiency, as representatively demonstrated by a methyl group (entries 13−15). With 1-naphthoaldehyde and thiophene-2-carboxaldehyde, **4r** and **4s** were obtained in 68% and 45% yield, respectively. It is noteworthy that aliphatic aldehydes

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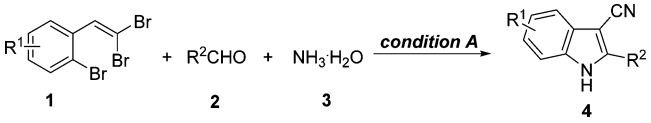
Table 2. Substrate Scope for the Synthesis of 3-Cyanoindoles 4[a,18]



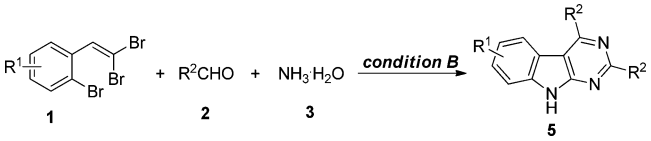
entry	R^1	R^2	product	yield (%)[b]
1	H	Ph	**4a**	62
2	4-F	Ph	**4b**	64
3	5-F	Ph	**4c**	63
4	4-Cl	Ph	**4d**	61
5	4-CF_3	Ph	**4e**	59
6	5-CH_3	Ph	**4f**	56
7	4-CH_3O	Ph	**4g**	58
8	4,5-OCH_2O-	Ph	**4h**	53
9	H	3-FC_6H_4	**4i**	66
10	H	4-ClC_6H_4	**4j**	71
11	H	4-BrC_6H_4	**4k**	65
12	H	4-$CF_3C_6H_4$	**4l**	63
13	H	2-$CH_3C_6H_4$	**4m**	57
14	H	3-$CH_3C_6H_4$	**4n**	64
15	H	4-$CH_3C_6H_4$	**4o**	61
16	H	4-$CH_3OC_6H_4$	**4p**	62
17	H	3,4-$(CH_3O)_2C_6H_3$	**4q**	68
18	H	1-naphthyl	**4r**	68
19	H	2-thienyl	**4s**	45
20	H	CH_3	**4t**	42
21	H	CH_3CH_2	**4u**	51
22	H	$CH_3CH_2CH_2$	**4v**	54
23	H	$(CH_3)_2CHCH_2$	**4w**	49
24	H	$C_6H_5CH_2CH_2$	**4x**	61
25	4-F	4-$CH_3OC_6H_4$	**4y**	60
26	5-F	4-$CH_3OC_6H_4$	**4z**	63
27	5-F	$CH_3CH_2CH_2$	**4aa**	57
28	4-Cl	4-ClC_6H_4	**4bb**	63
29	4-Cl	4-$CH_3OC_6H_4$	**4cc**	62
30	4-Cl	$CH_3CH_2CH_2$	**4dd**	55
31	4-CF_3	4-$CH_3OC_6H_4$	**4ee**	62
32	4-CF_3	$CH_3CH_2CH_2$	**4ff**	52
33	5-CH_3	4-$CH_3OC_6H_4$	**4gg**	65
34	4-CH_3O	$CH_3CH_2CH_2$	**4hh**	52
35	4,5-OCH_2O-	$CH_3CH_2CH_2$	**4ii**	53

[a]Reactions were run with **1** (0.5 mmol), **2** (1 mmol), CuI (0.05 mmol), DABCO (0.1 mmol), PivOH (0.5 mmol), and **3** (26%, 1.5 mL) in DMF (1.5 mL) at 80 °C under air in a sealed tube for 24 h. [b]Isolated yields.

were also found to be suitable for this reaction, giving 2-alkyl-3-cyanoindoles (entries 20−24). In further studies, different **1** were allowed to react with various **2** and **3**. Promisingly, all of these substrates were compatible with this reaction and give 3-cyanoindoles bearing diverse functional groups (entries 25−35).

Having established a general method for the synthesis of 3-cyanoindoles **4**, we moved on to study the substrate scope for the synthesis of 9*H*-pyrimido[4,5-*b*]indoles **5** from the reaction of **1** with **2** and **3** under condition B (Table 1, entry 17). It was found that diversely substituted 1-bromo-2-(2,2-dibromovinyl)-benzenes **1** reacted smoothly with various aryl aldehydes **2** and aqueous ammonia **3** to give a series of 9*H*-pyrimido[4,5-*b*]indoles **5** irrespective of the electronic and steric nature of the substituents (Table 3, entries 1−21).

Table 3. Substrate Scope for the Synthesis of 9*H*-Pyrimido[4,5-*b*]indoles 5[a]



entry	R^1	R^2	product	yield (%)[b]
1	H	Ph	**5a**	55
2	4-F	Ph	**5b**	56
3	5-F	Ph	**5c**	54
4	4-Cl	Ph	**5d**	58
5	4-CF_3	Ph	**5e**	57
6	5-CH_3	Ph	**5f**	54
7	4-CH_3O	Ph	**5g**	50
8	4,5-OCH_2O-	Ph	**5h**	47
9	H	3-FC_6H_4	**5i**	58
10	H	4-ClC_6H_4	**5j**	61
11	H	4-BrC_6H_4	**5k**	63
12	H	4-$CF_3C_6H_4$	**5l**	47
13	H	2-$CH_3C_6H_4$	**5m**	48
14	H	3-$CH_3C_6H_4$	**5n**	53
15	H	4-$CH_3C_6H_4$	**5o**	51
16	H	4-$CH_3OC_6H_4$	**5p**	52
17	H	1-naphthyl	**5q**	46
18	H	2-thienyl	**5r**	40
19	4-Cl	4-ClC_6H_4	**5s**	52
20	4-CF_3	4-$CH_3OC_6H_4$	**5t**	48
21	5-CH_3	4-$CH_3OC_6H_4$	**5u**	46

[a]Reactions were run with **1** (0.5 mmol), **2** (1.5 mmol), CuI (0.05 mmol), DABCO (0.1 mmol), PivOH (0.5 mmol), and **3** (26%, 0.5 mL) in DMF (3 mL) at 80 °C under air in a sealed tube for 30 h. [b]Isolated yields.

In further studies, the scope of the aldehyde substrates was extended to acetaldehyde. To our surprise, the reaction of acetaldehyde with **1a** and **3** under condition B afforded 2-methyl-9*H*-pyrido[2,3-*b*]indole (**6a**) rather than the expected 2,4-dimethyl-9*H*-pyrimido[4,5-*b*]indole. Literature searching revealed that the pyrido[2,3-*b*]indole scaffold, also known as *α*-carboline,[19−21] has been found in numerous natural products and synthetic compounds with an array of biological activities. Thus, the development of practical methods for the synthesis of pyrido[2,3-*b*]indoles would enable the facile preparation of families of biologically significant compounds. Hence, our study continued with an exploration of the scope and generality of this new entry into pyrido[2,3-*b*]indole derivatives. The results listed in Table 4 show that not only acetaldehyde but also propionaldehyde, butyraldehyde, 3-methylbutanal, and 3-phenylpropanal were also compatible substrates to react with **1a** and **3**, giving *α*-carbolines **6a−e** in moderate yields. Notably, with acetaldehyde a monosubstituted 9*H*-pyrido[2,3-*b*]indole was obtained (entry 1), while the other aldehydes gave 2,3-disubstituted *α*-carboline analogues (entries 2−5). Next, propionaldehyde was used as a model substrate to react with different **1** and **3**. Compounds **1** substituted with either electron-withdrawing or electron-donating groups took part in this reaction readily (entries 6−10), allowing for a highly convenient preparation of *α*-carboline derivatives.

Interestingly, the reaction was also found to be suitable for an *α*,*β*-unsaturated aldehyde. Thus, treatment of 1-bromo-2-(2,2-dibromovinyl)benzenes **1** with cinnamaldehyde and aqueous

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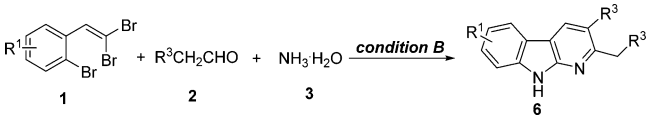
Table 4. Substrate Scope for the Synthesis of 9*H*-Pyrido[2,3-*b*]indoles 6[a,18]

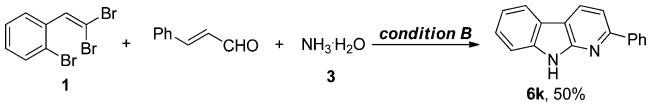


entry	R^1	R^3	product	yield (%)[b]
1	H	H	**6a**	38
2	H	CH_3	**6b**	43
3	H	CH_3CH_2	**6c**	46
4	H	$(CH_3)_2CH$	**6d**	42
5	H	$C_6H_5CH_2$	**6e**	52
6	5-F	CH_3CH_2	**6f**	46
7	4-Cl	CH_3CH_2	**6g**	47
8	4-CF_3	CH_3CH_2	**6h**	49
9	4-CH_3O	CH_3CH_2	**6i**	41
10	4,5-OCH_2O-	CH_3CH_2	**6j**	44

[a]Reactions were run with **1** (0.5 mmol), **2** (1.5 mmol), CuI (0.05 mmol), DABCO (0.1 mmol), PivOH (0.5 mmol), and **3** (26%, 0.5 mL) in DMF (3 mL) at 80 °C in a sealed tube under air for 30 h. [b]Isolated yields.

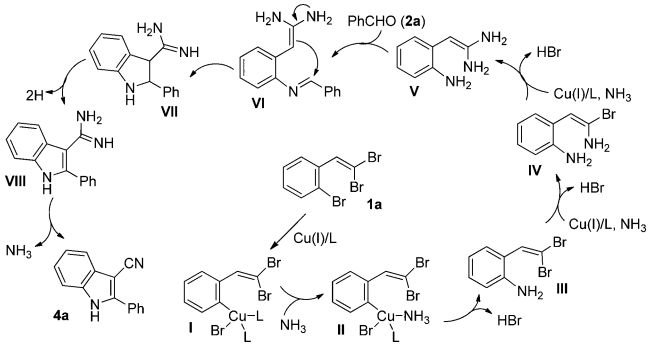
ammonia under **condition B** afforded 2-phenyl-9*H*-pyrido[2,3-*b*]indole (**6k**) in 50% yield (Scheme 1)

Scheme 1. Formation of 6k from the Reaction of Cinnamaldehyde



On the basis of the above results and our previous studies,[15] a plausible pathway for the formation of **4a** is proposed in Scheme 2. First, Cu(I)-catalyzed aryl amination of **1a** with **3**

Scheme 2. Plausible Mechanism for the Formation of 4a



with the assistance of DABCO and PivOH affords 2-(2,2-dibromovinyl)aniline (**III**). At a high concentration of **3** (condition A), **III** undergoes two sequential intermolecular vinyl aminations to afford intermediates **IV** and **V**, respectively. In the next stage, condensation of **V** with **2a** gives imine **VI**. Subsequent intramolecular nucleophilic addition in **VI** affords intermediate **VII**, and oxidative dehydrogenation of **VII** affords **VIII**. Finally, elimination of NH_3 from **VIII** affords **4a**.

On the other hand, it is suggested that the initial step in the formation of **5a** also involves a Cu(I)-catalyzed aryl amination of **1a** to give intermediate **III**. At a lower concentration of **3** (condition B), **III** first undergoes an intramolecular C–N coupling to give 2-bromoindole (**IX**), which then undergoes an aryl amination to give 2-aminoindole (**X**). Nucleophilic addition of **X** onto imine **XI**, formed in situ from the condensation of **2a** with **3**, affords **XII**. Subsequent condensation of **XII** with **2a** gives imine **XIII**, and then nucleophilic cyclization of **XIII** occurs to afford tetrahydro-1*H*-pyrimido[4,5-*b*]indole (**XIV**). Finally, oxidative aromatization of **XIV** gives **5a** as the final product (Scheme 3).

As for the formation of **6a**, it should start with the reaction of **1a** with **3** under condition B to give intermediates **III**, **IX**, and **X** sequentially. Meanwhile, self-aldol condensation of acetaldehyde gives but-2-enal (**XV**) as another key intermediate. Michael addition of **X** toward **XV** affords the adduct **XVI**, which then undergoes an intramolecular aldol-type reaction to sequentially give **XVII** and **XVIII**. Finally, oxidative dehydrogenation of **XVIII** affords **6a** (Scheme 4).

The proposed mechanisms for the formation of **4a**, **5a**, and **6a** as shown in Schemes 2–4 were partially confirmed by the following experiments. First, **III**,[11a] **IX**,[11b] and 2-benzyl-5-phenylpent-2-enal were prepared. Then **III** was treated with **2a** and **3** under condition A. From this reaction, **4a** was obtained in a yield of 76% (Scheme 5). This result is consistent with that obtained by using **1a** as a starting material and might be considered as positive evidence for the proposed reaction mechanism, in which **III** is considered to be a key intermediate for the formation of **4a**.

Second, **III** was treated with **2a** and **3** under condition B to give **5a** in 68% yield (Scheme 6). This result showed that **III** might be a key intermediate for the formation of **5a**.

Third, **IX** was treated with **2a** and **3** under condition B to give **5a** in a yield of 80% (Scheme 7). This result is positive in supporting the proposed mechanism, in which **IX** is considered to be a key intermediate in the formation of **5a**.

Fourth, 2-benzyl-5-phenylpent-2-enal was treated **1a** and **3** under condition B to give **6e** in a yield of 57% (Scheme 8). This result is consistent with that obtained using 3-phenylpropanal as the starting material and should be considered as positive evidence for the mechanism, in which an *α*,*β*-unsaturated aldehyde is considered to be a key intermediate for the formation of **6**.

Finally, 2-benzyl-5-phenylpent-2-enal was treated with **IX** and **3** under condition B. From this reaction, **6e** was obtained in a yield of 73% (Scheme 9). This result is consistent with that obtained by using **1a** and 3-phenylpropanal as the starting materials and should be considered as positive evidence for the proposed reaction mechanism, in which both **IX** and an *α*,*β*-unsaturated aldehyde are considered to be key intermediates for the formation of **6**.

In order to showcase the applicability of the method for the synthesis of 4-cyanoindoles developed herein, a larger-scale preparation of 2-(4-methoxyphenyl)-1*H*-indole-3-carbonitrile (**4p**) was carried out. Thus, **1a** (5 mmol) was treated with 4-methoxybenzaldehyde (10 mmol) and aqueous ammonia (26%, 15 mL) in the presence of CuI (0.5 mmol), DABCO (1 mmol), and PivOH (5 mmol) in DMF (15 mL) at 80 °C in a sealed vessel under air for 24 h. This reaction afforded **4p** in 48% yield.

In summary, we have developed some novel strategies for the preparation of indole-related heterocycles, including 1*H*-indole-3-carbonitriles, 9*H*-pyrimido[4,5-*b*]indoles, and 9*H*-pyrido[2,3-*b*]indoles. These protocols show some notable features. First, both the indole framework and the cyano/pyrimidine/pyridine

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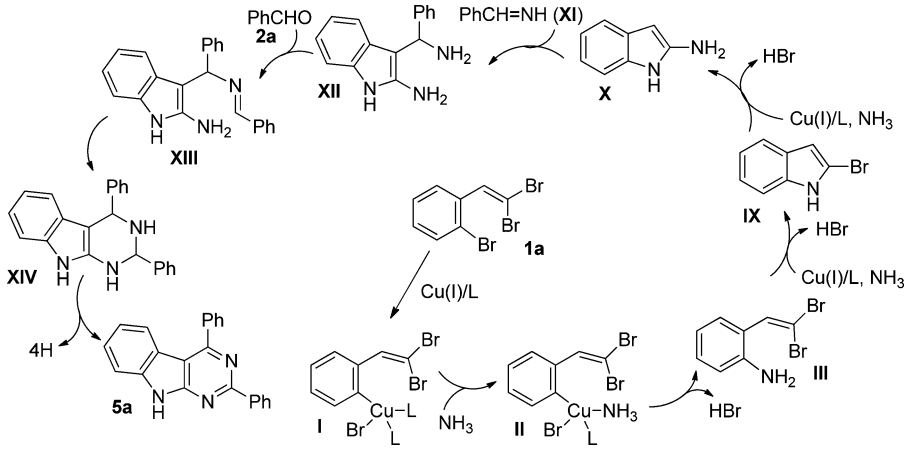
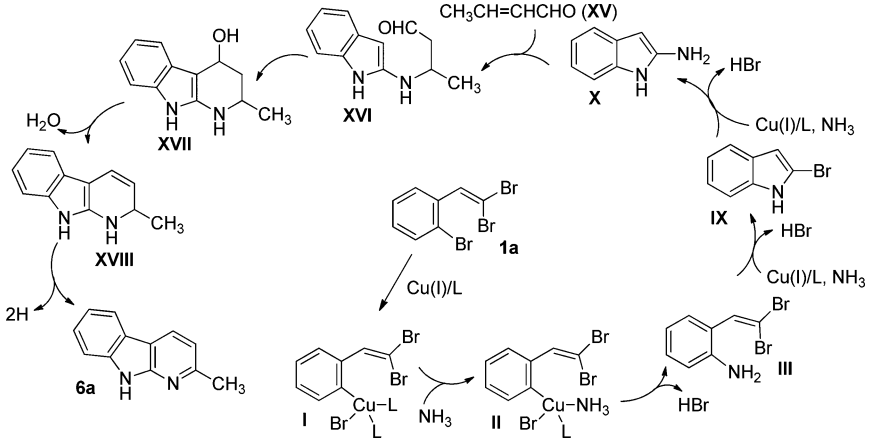
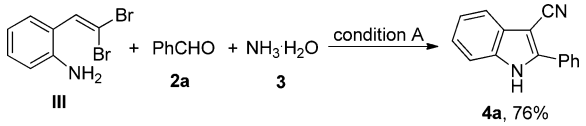
Scheme 3. Plausible Mechanism for the Formation of 5a



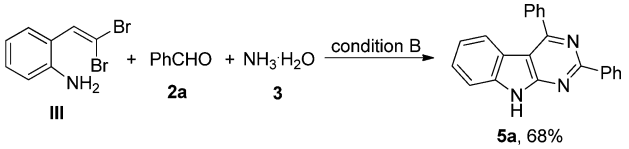
Scheme 4. Plausible Mechanism for the Formation of 6a



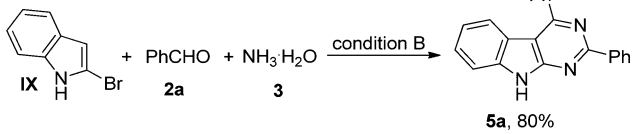
Scheme 5. Formation of 4a from the Reaction of III, 2a, and 3 under Condition A



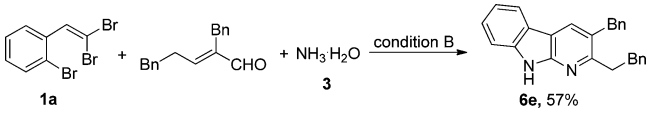
Scheme 6. Formation of 5a from the Reaction of III, 2a, and 3 under Condition B



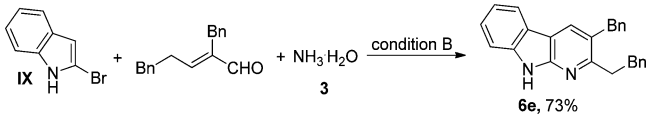
Scheme 7. Formation of 5a from the Reaction of IX, 2a, and 3 under Condition B



Scheme 8. Formation of 6e from 1a, α,β-Unsaturated Aldehyde, and 3 under Condition B



Scheme 9. Formation of 6e from IX, α,β-Unsaturated Aldehyde, and 3 under Condition B



unit are constructed simultaneously through the formation of multiple C−N and C−C bonds. Second, either 1*H*-indole-3-carbonitriles or 9*H*-pyrimido[4,5-*b*]indoles/9*H*-pyrido[2,3-*b*]-indoles could be obtained as dominant products from the same starting materials simply by tuning the concentration of ammonia and the molar ratio of the reagents. Moreover, the reactions are realized under mild conditions, and the substrates are readily available and generally broad in scope. With all of these advantages, the methods developed herein should find wide application in the synthesis of relevant heterocyclic compounds. Further study to gain deeper insight into the reaction mechanisms is currently underway.

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EXPERIMENTAL SECTION

1. General Methods. 1-Bromo-2-(2,2-dibromovinyl)benzenes **1** were prepared through the reaction of 2-bromobenzaldehydes with carbon tetrabromide according to a literature procedure.[22] Other reagents and solvents were purchased from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts (in ppm) were referenced to tetramethylsilane in $CDCl_3$ or DMSO-d_6. ^{13}C NMR spectra were calibrated with $CDCl_3$ (δ = 77.00 ppm) or DMSO-d_6 (δ = 39.50 ppm). Multiplicities are indicated as follows: s (singlet); d (doublet); t (triplet); m (multiplet); dd (doublet of doublets); td (triplet of doublets); br s (broad singlet), etc. Coupling constants are given in hertz. High-resolution mass spectrometry (HRMS) was performed in ESI mode using a MicrOTOF mass spectrometer. The conversion of starting materials was monitored by thin-layer chromatography (TLC) using silica gel plates (silica gel 60 F254, 0.25 mm), and components were visualized by observation under UV light (254 and 365 nm).

2. General Procedure for the Preparation of 3-Cyanoindoles 4. To a tube containing a solution of 1-bromo-2-(2,2-dibromovinyl)-benzene (**1a**) (170 mg, 0.5 mmol) in DMF (1.5 mL) were added CuI (9.5 mg, 0.05 mmol), DABCO (11.2 mg, 0.1 mmol), PivOH (51 mg, 0.5 mmol), benzaldehyde (**2a**) (106 mg, 1 mmol), and aqueous ammonia (**3**) (26%, 1.5 mL). The tube was sealed, and the mixture was stirred at 80 °C under an atmosphere of air for 24 h. After the reaction mixture was cooled to room temperature, the reaction was quenched with H_2O, and the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (5:1) as the eluent to give 2-phenyl-1*H*-indole-3-carbonitrile (**4a**) (68 mg, 62%). Other 3-cyanoindoles (**4b**−**ii**) were obtained in a similar manner.

*2-Phenyl-1H-indole-3-carbonitrile (**4a**).*[9d] Eluent: petroleum ether/ethyl acetate (5:1). White solid (67 mg, 62%), mp 233−234 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26−7.33 (m, 2H), 7.44−7.53 (m, 4H), 7.74−7.76 (m, 1H), 7.90 (q, *J* = 8.0 Hz, 2H), 9.14 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 83.9, 111.8, 117.0, 119.6, 122.5, 124.4, 126.9, 128.9, 129.4, 130.1, 135.1, 144.8. MS: *m*/*z* 219 [M + H]$^+$.

*5-Fluoro-2-phenyl-1H-indole-3-carbonitrile (**4b**).*[9d] Eluent: petroleum ether/ethyl acetate (5:1). White solid (76 mg, 64%), mp 248−249 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.14 (t, *J* = 9.2 Hz, 1H), 7.38 (d, *J* = 9.2 Hz, 1H), 7.53 (d, *J* = 6.4 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 2H), 7.95 (d, *J* = 7.2 Hz, 2H), 12.66 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 82.2, 103.9, 104.1, 112.6, 112.9, 114.5, 114.6, 117.0, 127.5, 129.3, 129.4, 129.6, 129.8, 130.6, 132.6, 146.7, 157.7, 160.1. MS: *m*/*z* 237 [M + H]$^+$.

*6-Fluoro-2-phenyl-1H-indole-3-carbonitrile (**4c**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (77 mg, 63%), mp 274−276 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.11 (t, *J* = 9.2 Hz, 1H), 7.31 (d, *J* = 9.2 Hz, 1H), 7.51−7.54 (m, 1H), 7.59−7.65 (m, 3H), 7.94 (d, *J* = 7.6 Hz, 2H), 12.68 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 82.0, 99.2, 99.5, 111.0, 111.3, 117.1, 120.2, 120.3, 125.3, 127.4, 129.6, 129.8, 130.5, 136.0, 136.1, 146.11, 146.14, 159.1, 161.5. HRMS: calcd for $C_{15}H_{10}FN_2$ 237.0828 [M + H], found 237.0822.

*5-Chloro-2-phenyl-1H-indole-3-carbonitrile (**4d**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (77 mg, 61%), mp 284−286 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.29 (d, *J* = 8.0 Hz, 1H), 7.53−7.55 (m, 2H), 7.59−7.62 (m, 3H), 7.95 (d, *J* = 8.0 Hz, 2H), 12.76 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 81.7, 114.8, 116.8, 118.0, 124.5, 127.2, 127.6, 129.4, 129.8, 130.8, 134.5, 146.6. HRMS: calcd for $C_{15}H_{10}ClN_2$ 253.0532 [M + H], found 253.0538.

*2-Phenyl-5-(trifluoromethyl)-1H-indole-3-carbonitrile (**4e**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (84 mg, 59%), mp 321−323 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.54−7.65 (m, 4H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.93 (s, 1H), 7.98 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 82.8, 114.2, 116.1, 116.17, 116.21, 116.6, 120.70, 120.73, 123.0, 123.3, 123.9, 126.7, 127.6, 128.2, 129.3, 129.8, 130.9, 137.8, 147.6. HRMS: calcd for $C_{16}H_{10}F_3N_2$ 287.0796 [M + H], found 287.0812.

*6-Methyl-2-phenyl-1H-indole-3-carbonitrile (**4f**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (64 mg, 56%), mp 248−250 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.42 (s, 3H), 7.07 (d, *J* = 8.4 Hz, 1H), 7.32 (s, 1H), 7.49−7.53 (m, 2H), 7.60 (t, *J* = 7.6 Hz, 2H), 7.95 (d, *J* = 7.6 Hz, 2H), 12.41 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.8, 81.7, 112.8, 117.6, 118.5, 124.2, 126.6, 127.3, 129.8, 130.0, 130.2, 133.9, 136.4, 144.7. HRMS: calcd for $C_{16}H_{13}N_2$ 233.1078 [M + H], found 233.1075.

*5-Methoxy-2-phenyl-1H-indole-3-carbonitrile (**4g**).*[9a] Eluent: petroleum ether/ethyl acetate (5:1). White solid (72 mg, 58%), mp 246−248 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.82 (s, 3H), 6.91−6.93 (m, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 2H), 7.95 (d, *J* = 7.2 Hz, 2H), 12.49 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.9, 81.6, 100.1, 114.1, 114.8, 117.7, 127.2, 129.6, 129.8, 130.0, 130.2, 130.9, 145.0, 156.0. MS: *m*/*z* 249 [M + H]$^+$.

*6-Phenyl-5H-[1,3]dioxolo[4,5-f]indole-7-carbonitrile (**4h**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (69 mg, 53%), mp 264−266 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.04 (s, 2H), 7.02 (s, 1H), 7.06 (s, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 2H), 7.89 (d, *J* = 7.6 Hz, 2H), 12.40 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 82.2, 93.6, 97.4, 101.6, 123.0, 126.8, 128.5, 129.7, 129.8, 130.1, 131.0, 143.2, 145.0, 146.4. HRMS: calcd for $C_{16}H_{11}N_2O_2$ 263.0820 [M + H], found 263.0829.

*2-(3-Fluorophenyl)-1H-indole-3-carbonitrile (**4i**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (78 mg, 66%), mp 271−272 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.24−7.41 (m, 3H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.63−7.69 (m, 2H), 7.75−7.78 (m, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 12.67 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 82.5, 113.2, 114.0, 114.2, 117.08, 117.13, 117.3, 119.0, 122.7, 123.5, 123.6, 124.7, 128.6, 131.8, 131.9, 132.0, 136.0, 143.42, 143.44, 161.6, 164.0. HRMS: calcd for $C_{15}H_9FN_2Na$ 259.0648 [M + Na], found 259.0657.

*2-(4-Chlorophenyl)-1H-indole-3-carbonitrile (**4j**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (89 mg, 71%), mp 287−289 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.23−7.33 (m, 2H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.97 (d, *J* = 9.2 Hz, 2H), 12.64 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 82.2, 113.1, 117.2, 118.9, 122.6, 124.6, 128.63, 128.65, 129.1, 129.9, 135.1, 136.0, 143.8. HRMS: calcd for $C_{15}H_{10}ClN_2$ 253.0532 [M + H], found 253.0526.

*2-(4-Bromophenyl)-1H-indole-3-carbonitrile (**4k**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (96 mg, 65%), mp 301−302 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H), 7.53−7.56 (m, 2H), 7.60−7.63 (m, 3H), 7.95 (d, *J* = 7.6 Hz, 2H), 12.78 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 81.7, 114.8, 116.7, 118.0, 124.5, 127.2, 127.5, 129.4, 129.8, 130.7, 134.5, 146.6. HRMS: calcd for $C_{15}H_9BrN_2Na$ 318.9847 [M + Na], found 318.9838.

*2-(4-(Trifluoromethyl)phenyl)-1H-indole-3-carbonitrile (**4l**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (90 mg, 63%), mp 260−262 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.25−7.36 (m, 2H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.65−7.67 (m, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 8.17 (d, *J* = 8.4 Hz, 2H), 12.78 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 83.2, 113.3, 117.0, 119.1, 122.8, 123.0, 124.9, 125.8, 126.65, 126.68, 126.72, 126.76, 128.1, 128.6, 133.6, 136.2, 143.1. HRMS: calcd for $C_{16}H_9F_3N_2Na$ 309.0616 [M + Na], found 309.0619.

*2-(o-Tolyl)-1H-indole-3-carbonitrile (**4m**).*[9d] Eluent: petroleum ether/ethyl acetate (5:1). White solid (66 mg, 57%), mp 181−183 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.59−7.67 (m, 3H), 7.94−7.63 (m, 1H), 8.01−8.02 (m, 1H), 12.70 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 82.6, 113.3, 117.1, 119.0, 122.7, 124.8, 126.1, 126.3, 127.0, 128.6, 130.2, 131.8, 134.5, 136.1, 143.3. MS: *m*/*z* 233 [M + H]$^+$.

*2-(m-Tolyl)-1H-indole-3-carbonitrile (**4n**).*[9d] Eluent: petroleum ether/ethyl acetate (5:1). White solid (74 mg, 64%), mp 248−250 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 7.26−7.30 (m, 3H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.45−7.47 (m, 1H), 7.69−7.70 (m, 1H),

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7.75−7.77 (m, 1H), 9.06 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 83.9, 111.6, 116.8, 119.6, 122.4, 124.0, 124.3, 127.4, 128.9, 129.30, 129.35, 130.9, 134.9, 139.3, 144.9. MS: *m/z* 233 [M + H]$^+$.

*2-(p-Tolyl)-1H-indole-3-carbonitrile (**4o**).*[9d] Eluent: petroleum ether/ethyl acetate (5:1). White solid (71 mg, 61%), mp 288−290 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 7.26−7.32 (m, 4H), 7.44−7.46 (m, 1H), 7.73−7.80 (m, 3H), 9.06 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 83.3, 111.7, 119.4, 122.4, 124.2, 126.6, 126.7, 128.9, 130.1, 135.0, 140.4, 145.1. MS: *m/z* 233 [M + H]$^+$.

*2-(4-Methoxyphenyl)-1H-indole-3-carbonitrile (**4p**).*[9d] Eluent: petroleum ether/ethyl acetate (5:1). White solid (77 mg, 62%), mp 280−282 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.84 (s, 3H), 7.16−7.29 (m, 4H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.93−7.95 (m, 2H), 12.43 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.9, 80.7, 112.9, 115.2, 117.8, 118.6, 122.2, 122.3, 124.0, 128.88, 128.93, 135.9, 145.4, 161.0. MS: *m/z* 249 [M + H]$^+$.

*2-(3,4-Dimethoxyphenyl)-1H-indole-3-carbonitrile (**4q**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (94 mg, 68%), mp 220−222 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.84 (s, 3H), 3.87 (s, 3H), 7.18−7.26 (m, 2H), 7.28−7.30 (m, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.56−7.60 (m, 3H), 12.44 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.11, 56.15, 80.8, 110.7, 112.6, 112.8, 117.9, 118.6, 120.3, 122.2, 122.4, 124.1, 128.8, 135.8, 145.6, 149.4, 150.7. HRMS: calcd for $C_{17}H_{14}N_2O_2Na$ 301.0953 [M + Na], found 301.0971.

*2-(Naphthalen-1-yl)-1H-indole-3-carbonitrile (**4r**).*[9d] Eluent: petroleum ether/ethyl acetate (5:1). White solid (91 mg, 68%), mp 266−268 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.29−7.38 (m, 2H), 7.58−7.64 (m, 3H), 7.69−7.30 (m, 2H), 7.79−7.81 (m, 1H), 7.86−7.89 (m, 1H), 8.08−8.10 (m, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 12.71 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 85.6, 113.2, 116.8, 118.9, 122.5, 124.2, 125.5, 125.9, 127.1, 127.8, 127.9, 128.1, 129.1, 129.4, 130.8, 131.2, 133.8, 136.0, 145.4. MS: *m/z* 269 [M + H]$^+$.

*2-(Thiophen-2-yl)-1H-indole-3-carbonitrile (**4s**).*[9d] Eluent: petroleum ether/ethyl acetate (5:1). White solid (50 mg, 45%), mp 206−208 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13−7.16 (m, 1H), 7.25−7.26 (m, 2H), 7.42−7.44 (m, 2H), 7.68−7.71 (m, 1H), 7.78 (d, *J* = 3.6 Hz, 1H), 9.56 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 83.3, 111.7, 119.3, 122.5, 124.4, 127.41, 127.43, 128.4, 128.6, 129.6, 131.4, 135.1, 139.3. MS: *m/z* 225 [M + H]$^+$.

*2-Methyl-1H-indole-3-carbonitrile (**4t**).*[9d] Eluent: petroleum ether/ethyl acetate (5:1). White solid (33 mg, 42%), mp 166−168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H), 7.22−7.26 (m, 2H), 7.35−7.37 (m, 1H), 7.64−7.66 (m, 1H), 8.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.0, 85.7, 111.2, 116.3, 118.9, 122.0, 123.4, 127.6, 134.6, 144.5. MS: *m/z* 157 [M + H]$^+$.

*2-Ethyl-1H-indole-3-carbonitrile (**4u**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (43 mg, 51%), mp 117−118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (t, *J* = 7.6 Hz, 3H), 3.00 (q, *J* = 7.6 Hz, 2H), 7.22−7.28 (m, 2H), 7.40−7.42 (m, 1H), 7.65−7.67 (m, 1H), 8.94 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.3, 21.0, 84.0, 111.5, 116.5, 118.9, 122.0, 123.4, 127.7, 134.6, 150.5. HRMS: calcd for $C_{11}H_{11}N_2$ 171.0922 [M + H], found 171.0921.

*2-Propyl-1H-indole-3-carbonitrile (**4v**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (50 mg, 54%), mp 115−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (t, *J* = 7.2 Hz, 3H), 1.79−1.88 (m, 2H), 2.94 (t, *J* = 7.2 Hz, 2H), 7.24−7.26 (m, 2H), 7.38 (d, *J* = 5.2 Hz, 1H), 7.66−7.68 (m, 1H), 8.83 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 22.5, 29.5, 85.0, 111.4, 116.5, 119.0, 122.0, 123.4, 127.7, 134.6, 149.1. HRMS: calcd for $C_{12}H_{13}N_2$ 185.1078 [M + H], found 185.1086.

*2-Isobutyl-1H-indole-3-carbonitrile (**4w**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (48 mg, 49%), mp 116−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (d, *J* = 6.4 Hz, 6H), 2.09−2.16 (m, 1H), 2.82 (d, *J* = 7.2 Hz, 2H), 7.22−7.28 (m, 2H), 7.37−7.39 (m, 1H), 7.66−7.68 (m, 1H), 8.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 29.2, 36.6, 85.8, 111.3, 116.4, 119.0, 122.0, 123.4, 127.6, 134.5, 148.2. HRMS: calcd for $C_{13}H_{14}N_2Na$ 221.1055 [M + Na], found 221.1043.

*2-Phenethyl-1H-indole-3-carbonitrile (**4x**).*[9d] Eluent: petroleum ether/ethyl acetate (5:1). White solid (75 mg, 61%), mp 125−126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.10 (t, *J* = 7.2 Hz, 2H), 3.27 (t, *J* = 7.2 Hz, 2H), 7.18 (d, *J* = 6.8 Hz, 2H), 7.21−7.32 (m, 6H), 7.65−7.69 (m, 1H), 8.33 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.4, 35.2, 85.3, 111.4, 116.1, 119.1, 122.1, 123.5, 126.8, 127.5, 128.4, 128.8, 134.5, 139.8, 147.9. MS: *m/z* 247 [M + H]$^+$.

*5-Fluoro-2-(4-methoxyphenyl)-1H-indole-3-carbonitrile (**4y**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (80 mg, 60%), mp 257−259 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.83 (s, 3H), 7.07−7.17 (m, 3H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.48−7.50 (m, 1H), 7.91 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.9, 81.0, 103.6, 103.9, 112.0, 112.3, 114.2, 114.3, 115.2, 117.3, 122.1, 129.0, 129.5, 129.6, 132.6, 147.0, 157.7, 160.0, 161.2. HRMS: calcd for $C_{16}H_{11}FN_2ONa$ 289.0753 [M + Na], found 289.0749.

*6-Fluoro-2-(4-methoxyphenyl)-1H-indole-3-carbonitrile (**4z**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (84 mg, 63%), mp 283−285 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.84 (s, 3H), 7.06−7.11 (m, 3H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.26−7.29 (m, 1H), 7.57−7.61 (m, 1H), 7.90 (d, *J* = 8.8 Hz, 2H), 12.53 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.9, 80.8, 99.0, 99.3, 110.7, 110.9, 115.2, 117.3, 119.8, 119.9, 122.0, 125.3, 128.8, 135.8, 136.0, 146.29, 146.32, 158.9, 161.1, 161.3. HRMS: calcd for $C_{16}H_{11}FN_2ONa$ 289.0753 [M + Na], found 289.0746.

*6-Fluoro-2-propyl-1H-indole-3-carbonitrile (**4aa**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (57 mg, 57%), mp 113−115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (t, *J* = 7.2 Hz, 3H), 1.78−1.87 (m, 2H), 2.92 (t, *J* = 7.2 Hz, 2H), 6.98−7.03 (m, 1H), 7.07−7.09 (m, 1H), 7.55−7.58 (m, 1H), 8.68 (s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 22.0, 29.4, 85.2, 98.0, 98.3, 110.6, 110.8, 116.0, 119.8, 119.9, 123.9, 134.5, 134.6, 149.5, 159.1, 161.5. HRMS: calcd for $C_{12}H_{11}FN_2Na$ 225.0804 [M + Na], found 225.0815.

*5-Chloro-2-(4-chlorophenyl)-1H-indole-3-carbonitrile (**4bb**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (90 mg, 63%), mp 332−333 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30−7.33 (m, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.64 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 9.2 Hz, 2H), 12.82 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 82.0, 114.8, 116.5, 118.1, 124.7, 127.3, 128.2, 129.2, 129.7, 129.9, 134.5, 135.4, 145.2. HRMS: calcd for $C_{15}H_9Cl_2N_2$ 287.0143 [M + H], found 287.0152.

*5-Chloro-2-(4-methoxyphenyl)-1H-indole-3-carbonitrile (**4cc**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (87 mg, 62%), mp 288−290 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.87 (s, 3H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 9.2 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.61 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 12.65 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.8, 80.6, 114.5, 115.4, 117.0, 117.8, 121.8, 124.1, 127.0, 129.1, 130.0, 134.4, 146.8, 161.3. HRMS: calcd for $C_{16}H_{11}ClN_2ONa$ 305.0458 [M + Na], found 305.0462.

*5-Chloro-2-propyl-1H-indole-3-carbonitrile (**4dd**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (60 mg, 55%), mp 159−161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.2 Hz, 3H), 1.78−1.87 (m, 2H), 2.92 (t, *J* = 7.2 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.62 (s, 1H), 9.41 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 22.4, 29.5, 84.8, 112.4, 115.8, 118.5, 123.7, 127.8, 129.1, 133.0, 150.3. HRMS: calcd for $C_{12}H_{11}ClN_2Na$ 241.0509 [M + Na], found 241.0519.

*2-(4-Methoxyphenyl)-5-(trifluoromethyl)-1H-indole-3-carbonitrile (**4ee**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (98 mg, 62%), mp 306−308 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.83 (s, 3H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.85 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 2H), 12.78 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.9, 81.6, 113.8, 115.3, 115.8, 115.9, 116.8, 120.41, 120.44, 121.5, 122.9, 123.2, 124.0, 126.7, 128.3, 129.2, 137.6, 147.6, 161.4. HRMS: calcd for $C_{17}H_{11}F_3N_2ONa$ 339.0721 [M + Na], found 339.0726.

*2-Propyl-5-(trifluoromethyl)-1H-indole-3-carbonitrile (**4ff**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (65 mg, 52%), mp 171−173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (t, *J* = 7.2 Hz, 3H), 1.82−1.92 (m, 2H), 2.98 (t, *J* = 7.6 Hz, 2H), 7.48−7.52 (m, 2H), 7.94 (s, 1H), 9.29 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 22.3, 29.6, 85.6, 112.0, 115.7, 116.47, 116.51, 116.55, 120.2, 120.3, 123.3,

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124.4, 124.7, 126.0, 127.1, 136.1, 151.2. HRMS: calcd for $C_{13}H_{11}F_3N_2Na$ 275.0772 [M + Na], found 275.0783.

*2-(4-Methoxyphenyl)-6-methyl-1H-indole-3-carbonitrile (**4gg**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (85 mg, 65%), mp 251−253 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.41 (s, 3H), 3.83 (s, 3H), 7.04 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 9.2 Hz, 2H), 7.29 (s, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 8.8 Hz, 2H), 12.26 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.8, 55.9, 80.5, 112.6, 115.2, 117.9, 118.3, 122.4, 124.0, 126.7, 128.8, 133.5, 136.3, 144.9, 160.9. HRMS: calcd for $C_{17}H_{14}N_2ONa$ 285.1004 [M + Na], found 285.1001.

*5-Methoxy-2-propyl-1H-indole-3-carbonitrile (**4hh**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (55 mg, 52%), mp 125−127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (t, J = 7.2 Hz, 3H), 1.77−1.86 (m, 2H), 2.90 (t, J = 7.2 Hz, 2H), 3.86 (s, 3H), 6.86−6.89 (m, 1H), 7.10 (s, 1H), 7.24 (d, J = 8.8 Hz, 1H), 8.37 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 22.3, 29.3, 55.7, 85.1, 100.6, 112.0, 113.8, 116.5, 128.4, 129.2, 148.8, 155.9. HRMS: calcd for $C_{13}H_{15}N_2O$ 215.1184 [M + H], found 215.1202.

*6-Propyl-5H-[1,3]dioxolo[4,5-f]indole-7-carbonitrile (**4ii**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid (60 mg, 53%), mp 172−173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, J = 7.6 Hz, 3H), 1.74−1.83 (m, 2H), 2.86 (t, J = 7.6 Hz, 2H), 5.96 (s, 2H), 6.81 (s, 1H), 7.02 (s, 1H), 8.36 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 22.5, 29.4, 85.1, 92.4, 97.9, 101.0, 116.5, 121.8, 129.2, 144.4, 145.6, 147.2. HRMS: calcd for $C_{13}H_{13}N_2O_2$ 229.0977 [M + H], found 229.0986.

3. General Procedure for the Preparation of 9*H*-Pyrimido[4,5-*b*]indoles 5. To a tube containing a solution of 1-bromo-2-(2,2-dibromovinyl)benzene (**1a**) (170 mg, 0.5 mmol) in DMF (3 mL) were added CuI (9.5 mg, 0.05 mmol), DABCO (11.2 mg, 0.1 mmol), PivOH (51 mg, 0.5 mmol), benzaldehyde (**2a**) (159 mg, 1.5 mmol), and aqueous ammonia (**3**) (26%, 0.5 mL). The tube was sealed, and the mixture was stirred at 80 °C under an atmosphere of air for 30 h. After the reaction mixture was cooled to room temperature, the reaction was quenched with H_2O, and the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (10:1) as the eluent to give 2,4-diphenyl-9*H*-pyrimido[4,5-*b*]indole (**5a**) (88 mg, 55%). Other 9*H*-pyrimido[4,5-*b*]indoles (**5b**−**u**) were obtained in a similar manner.

*2,4-Diphenyl-9H-pyrimido[4,5-b]indole (**5a**).*[10g] Eluent: petroleum ether/ethyl acetate (10:1). White solid (88 mg, 55%), mp 299−301 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.18 (t, J = 7.2 Hz, 1H), 7.47−7.58 (m, 5H), 7.66 (d, J = 7.2 Hz, 3H), 7.81 (d, J = 7.6 Hz, 1H), 8.01 (d, J = 6.4 Hz, 2H), 8.55 (d, J = 6.0 Hz, 2H), 12.56 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 109.4, 112.4, 119.3, 121.2, 122.3, 128.0, 128.3, 129.0, 129.3, 129.4, 130.5, 130.7, 138.6, 139.1, 139.6, 157.7, 159.6, 159.9. MS: m/z 322 $[M + H]^+$.

*6-Fluoro-2,4-diphenyl-9H-pyrimido[4,5-b]indole (**5b**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (94 mg, 56%), mp 295−297 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.35−7.45 (m, 2H), 7.52−7.60 (m, 4H), 7.66−7.71 (m, 3H), 7.99 (d, J = 5.6 Hz, 2H), 8.53−8.55 (m, 2H), 12.61 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 107.7, 108.0, 109.3, 113.6, 113.7, 115.6, 115.9, 119.8, 119.9, 128.4, 129.1, 129.27, 129.34, 130.8, 130.9, 136.1, 138.4, 138.7, 156.3, 158.3, 160.3, 160.4. HRMS: calcd for $C_{22}H_{15}FN_3$ 340.1250 [M + H], found 340.1242.

*7-Fluoro-2,4-diphenyl-9H-pyrimido[4,5-b]indole (**5c**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (91 mg, 54%), mp 301−302 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.04−7.08 (m, 1H), 7.33−7.35 (m, 1H), 7.52−7.56 (m, 3H), 7.65−7.68 (m, 3H), 7.77−7.80 (m, 1H), 8.00 (d, J = 5.6 Hz, 2H), 8.54 (d, J = 6.0 Hz, 2H), 12.67 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 99.0, 99.2, 109.16, 109.22, 109.4, 116.1, 123.9, 124.0, 128.4, 129.1, 129.26, 129.30, 130.6, 130.8, 138.4, 138.8, 140.5, 140.6, 158.4, 159.3, 159.8, 161.0, 163.5. HRMS: calcd for $C_{22}H_{15}FN_3$ 340.1250 [M + H], found 340.1248.

*6-Chloro-2,4-diphenyl-9H-pyrimido[4,5-b]indole (**5d**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (103 mg, 58%), mp 289−291 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.48−7.67 (m, 9H), 7.98 (d, J = 5.6 Hz, 2H), 8.53 (d, J = 5.6 Hz, 2H), 12.69 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 108.8, 114.0, 120.7, 121.4, 125.3, 127.8, 128.4, 129.1, 129.27, 129.30, 130.8, 130.9, 138.1, 138.3, 138.7, 158.0, 160.3, 160.5. HRMS: calcd for $C_{22}H_{15}ClN_3$ 356.0954 [M + H], found 356.0958.

*2,4-Diphenyl-6-(trifluoromethyl)-9H-pyrimido[4,5-b]indole (**5e**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (110 mg, 57%), mp 317−319 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.53−7.54 (m, 3H), 7.56−7.71 (m, 3H), 7.76 (d, J = 8.8 Hz, 1H), 7.81−7.83 (m, 1H), 8.02−8.05 (m, 3H), 8.54−8.57 (m, 2H), 12.98 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 109.2, 113.3, 119.10, 119.14, 119.2, 121.5, 121.8, 123.9, 124.5, 126.6, 128.4, 128.5, 129.1, 129.30, 129.33, 131.0, 131.1, 132.0, 138.2, 138.6, 141.7, 158.6, 160.6, 160.9. HRMS: calcd for $C_{23}H_{15}F_3N_3$ 390.1218 [M + H], found 390.1200.

*7-Methyl-2,4-diphenyl-9H-pyrimido[4,5-b]indole (**5f**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (90 mg, 54%), mp 269−271 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.46 (s, 3H), 7.01 (d, J = 8.0 Hz, 1H), 7.37 (s, 1H), 7.53 (d, J = 7.6 Hz, 3H), 7.65−7.70 (m, 4H), 8.01 (d, J = 6.4 Hz, 2H), 8.54 (d, J = 6.4 Hz, 2H), 12.42 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.0, 109.5 112.4, 116.9, 122.1, 122.7, 128.2, 129.0, 129.2, 129.3, 130.5, 130.6, 138.0, 138.6, 139.1, 140.1, 157.8, 158.9, 159.5. HRMS: calcd for $C_{23}H_{18}N_3$ 336.1500 [M + H], found 336.1471.

*6-Methoxy-2,4-diphenyl-9H-pyrimido[4,5-b]indole (**5g**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (88 mg, 50%), mp 299−301 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.68 (s, 3H), 7.14−7.17 (m, 1H), 7.27 (s, 1H), 7.49−7.55 (m, 4H), 7.65−7.71 (m, 3H), 8.02 (d, J = 7.2 Hz, 2H), 8.54 (d, J = 6.0 Hz, 2H), 12.38 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.8, 105.8, 109.4, 113.2, 116.5, 119.8, 128.3, 129.0, 129.1, 129.4, 130.6, 130.7, 134.2, 138.6, 138.8, 154.4, 157.8, 159.6, 159.7. HRMS: calcd for $C_{23}H_{18}N_3O$ 352.1450 [M + H], found 352.1458.

*7,9-Diphenyl-5H-[1,3]dioxolo[4,5-f]pyrimido[4,5-b]indole (**5h**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (86 mg, 47%), mp 324−326 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.05 (s, 2H), 7.09 (d, J = 6.0 Hz, 2H), 7.48−7.54 (m, 3H), 7.63−7.69 (m, 3H), 7.95 (d, J = 7.6 Hz, 2H), 8.51 (d, J = 6.8 Hz, 2H), 12.41 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 93.6, 101.1, 101.8, 109.8, 111.9, 128.1, 129.0, 129.16, 129.20, 130.35, 130.40, 135.4, 138.7, 139.0, 143.2, 148.5, 157.1, 158.2, 158.3. HRMS: calcd for $C_{23}H_{16}N_3O_2$ 366.1241 [M + H], found 366.1228.

*2,4-Bis(3-fluorophenyl)-9H-pyrimido[4,5-b]indole (**5i**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (103 mg, 58%), mp 239−241 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.19−7.23 (m, 1H), 7.32−7.37 (m, 1H), 7.47−7.56 (m, 2H), 7.58−7.61 (m, 2H), 7.70−7.82 (m, 3H), 7.86 (d, J = 7.6 Hz, 1H), 8.21−8.24 (m, 1H), 8.38 (d, J = 7.6 Hz, 1H), 12.65 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 109.8, 112.6, 114.5, 114.7, 116.0, 116.2, 117.3, 117.46, 117.54, 117.7, 118.9, 121.5, 122.4, 124.3, 125.5, 128.4, 131.1, 131.2, 131.3, 131.4, 139.8, 140.9, 141.0, 141.1, 141.2, 157.6, 158.0, 158.5, 161.6, 161.8, 164.0, 164.2. HRMS: calcd for $C_{22}H_{14}F_2N_3$ 358.1156 [M + H], found 358.1142.

*2,4-Bis(4-chlorophenyl)-9H-pyrimido[4,5-b]indole (**5j**).*[10g] Eluent: petroleum ether/ethyl acetate (10:1). White solid (118 mg, 61%), mp 319−320 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.21 (t, J = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.58−7.61 (m, 3H), 7.74 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.0 Hz, 2H), 8.53 (d, J = 8.4 Hz, 2H), 12.59 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 109.6, 112.5, 119.1, 121.5, 122.5, 128.2, 129.1, 129.4, 130.0, 131.2, 135.4, 135.6, 137.3, 137.7, 139.7, 157.7, 158.3, 158.8. MS: m/z 390 $[M + H]^+$.

*2,4-Bis(4-bromophenyl)-9H-pyrimido[4,5-b]indole (**5k**).*[10g] Eluent: petroleum ether/ethyl acetate (10:1). White solid (150 mg, 63%), mp 301−302 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.22 (t, J = 7.6 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.97 (d, J = 8.0 Hz, 2H), 8.46 (d, J = 8.8 Hz, 2H), 12.60 (s, 1H). ^{13}C

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NMR (100 MHz, DMSO-d_6): δ 109.6, 112.6, 119.1, 121.5, 122.5, 124.1, 124.6, 128.3, 130.3, 131.5, 132.1, 132.3, 137.7, 138.0, 139.8, 157.7, 158.4, 158.9. MS: m/z 478 $[M + H]^+$.

*2,4-Bis(4-(trifluoromethyl)phenyl)-9H-pyrimido[4,5-b]indole (**5l**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (107 mg, 47%), mp 315−317 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.22 (t, J = 7.6 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.0 Hz, 2H), 8.05 (d, J = 8.0 Hz, 2H), 8.23 (d, J = 8.0 Hz, 2H), 8.71 (d, J = 7.6 Hz, 2H), 12.72 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 110.3, 112.6, 118.8, 121.6, 122.6, 125.9, 126.0, 126.20, 126.23, 127.8, 128.0, 128.6, 128.8, 128.9, 130.2, 134.1, 140.0, 142.1, 142.7, 148.6, 157.6, 157.9, 158.4, 162.3. HRMS: calcd for $C_{24}H_{14}F_6N_3$ 458.1092 $[M + H]$, found 458.1077.

*2,4-Di-o-tolyl-9H-pyrimido[4,5-b]indole (**5m**).*[10g] Eluent: petroleum ether/ethyl acetate (10:1). White solid (84 mg, 48%), mp 212−214 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 2.62 (s, 3H), 6.14 (d, J = 7.6 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.25−7.26 (m, 1H), 7.37−7.51 (m, 6H), 7.55 (d, J = 7.2 Hz, 1H), 7.92 (d, J = 7.2 Hz, 1H), 12.86 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6, 20.6, 111.1, 111.8, 119.3, 121.1, 122.1, 126.1, 126.3, 127.4, 128.9, 129.0, 129.2, 130.5, 130.7, 131.2, 135.9, 137.0, 137.9, 138.8, 139.6, 156.8, 160.7, 162.9. MS: m/z 350 $[M + H]^+$.

*2,4-Di-m-tolyl-9H-pyrimido[4,5-b]indole (**5n**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (92 mg, 53%), mp 230−231 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.42 (s, 3H), 2.47 (s, 3H), 7.16−7.20 (m, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.40−7.51 (m, 3H), 7.56 (t, J = 7.6 Hz, 2H), 7.77−7.79 (m, 3H), 8.33−8.35 (m, 2H), 12.50 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.53, 21.66, 109.4, 112.4, 119.4, 121.2, 122.3, 125.6, 126.4, 127.9, 128.87, 128.93, 129.1, 129.8, 131.0, 131.4, 138.1, 138.5, 138.6, 139.1, 139.6, 157.7, 159.9, 160.0. HRMS: calcd for $C_{24}H_{20}N_3$ 350.1657 $[M + H]$, found 350.1669.

*2,4-Di-p-tolyl-9H-pyrimido[4,5-b]indole (**5o**).*[10g] Eluent: petroleum ether/ethyl acetate (10:1). White solid (89 mg, 51%), mp 312−314 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3H), 2.47 (s, 3H), 7.17 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.47−7.50 (m, 3H), 7.56 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 7.6 Hz, 2H), 8.43 (d, J = 8.0 Hz, 2H), 12.44 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.5, 21.6, 109.1, 112.3, 119.5, 121.1, 122.3, 127.8, 128.3, 129.3, 129.6, 129.7, 136.0, 136.3, 139.5, 140.2, 140.4, 157.8, 159.7, 160.0. MS: m/z 350 $[M + H]^+$.

*2,4-Bis(4-methoxyphenyl)-9H-pyrimido[4,5-b]indole (**5p**).*[10g] Eluent: petroleum ether/ethyl acetate (10:1). White solid (99 mg, 52%), mp 311−313 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.83 (s, 3H), 3.89 (s, 3H), 7.08 (d, J = 8.8 Hz, 2H), 7.17 (t, J = 7.2 Hz, 1H), 7.22 (d, J = 8.8 Hz, 2H), 7.44−7.48 (m, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.8 Hz, 2H), 8.48 (d, J = 8.4 Hz, 2H), 12.40 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.7, 55.8, 108.4, 112.2, 114.3, 114.5, 119.6, 121.0, 122.2, 127.5, 129.9, 130.9, 131.1, 131.4, 139.3, 157.8, 159.3, 159.7, 161.2, 161.6. MS: m/z 382 $[M + H]^+$.

*2,4-Bis(naphthalen-1-yl)-9H-pyrimido[4,5-b]indole (**5q**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (97 mg, 46%), mp 305−306 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.81 (d, J = 8.0 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 8.0 Hz, 2H), 7.52−7.55 (m, 2H), 7.58 (t, J = 7.6 Hz, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.75−7.78 (m, 2H), 7.88 (d, J = 7.2 Hz, 1H), 7.99−8.02 (m, 1H), 8.05 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.17−8.21 (m, 2H), 8.88−8.90 (m, 1H), 12.68 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.5, 112.1, 119.1, 121.0, 122.6, 123.6, 125.4, 125.57, 125.62, 125.9, 126.1, 126.2, 126.8, 127.0, 127.3, 128.4, 128.50, 128.52, 129.2, 129.9, 130.7, 131.5, 133.8, 134.2, 135.9, 137.2, 138.7, 157.0, 159.8, 162.4. HRMS: calcd for $C_{30}H_{20}N_3$ 422.1657 $[M + H]$, found 422.1642.

*2,4-Bis(thiophen-2-yl)-9H-pyrimido[4,5-b]indole (**5r**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (67 mg, 40%), mp 317−319 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.21−7.24 (m, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.38−7.40 (m, 1H), 7.50−7.57 (m, 2H), 7.74 (d, J = 5.6 Hz, 1H), 7.95 (d, J = 4.8 Hz, 1H), 7.99−8.00 (m, 1H), 8.13 (d, J = 4.0 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H), 12.59 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 107.6, 112.4, 119.3, 121.5, 122.4, 128.0, 128.7, 128.8, 128.9, 129.8, 130.6, 131.2, 139.5, 142.3, 144.1, 152.9, 156.5, 157.8. HRMS: calcd for $C_{18}H_{12}N_3S_2$ 334.0472 $[M + H]$, found 334.0460.

*6-Chloro-2,4-bis(4-chlorophenyl)-9H-pyrimido[4,5-b]indole (**5s**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (110 mg, 52%), mp 324−326 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.53−7.59 (m, 4H), 7.67 (s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.8 Hz, 2H), 8.49 (d, J = 8.0 Hz, 2H), 12.73 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 108.8, 114.1, 120.3, 121.5, 125.5, 128.0, 129.1, 129.4, 130.0, 131.2, 135.7, 135.8, 137.0, 137.3, 138.2, 157.9, 158.8, 159.3. HRMS: calcd for $C_{22}H_{13}Cl_3N_3$ 424.0175 $[M + H]$, found 424.0167.

*2,4-Bis(4-methoxyphenyl)-6-(trifluoromethyl)-9H-pyrimido[4,5-b]indole (**5t**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (108 mg, 48%), mp 316−318 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.83 (s, 3H), 3.89 (s, 3H), 7.07 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 7.6 Hz, 2H), 7.70 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 2H), 8.12 (s, 1H), 8.48 (d, J = 8.4 Hz, 2H), 12.62 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.8, 55.9, 108.1, 113.0, 114.4, 114.6, 115.0, 118.9, 119.5, 121.6, 124.0, 126.8, 130.1, 130.8, 130.9, 132.2, 141.4, 158.7, 160.2, 160.7, 161.6, 161.8. HRMS: calcd for $C_{25}H_{19}F_3N_3O_2$ 450.1429 $[M + H]$, found 450.1423.

*2,4-Bis(4-methoxyphenyl)-7-methyl-9H-pyrimido[4,5-b]indole (**5u**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (91 mg, 46%), mp 296−298 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.45 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 7.00 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.33 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.8 Hz, 2H), 8.47 (d, J = 8.8 Hz, 2H), 12.27 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.0, 55.7, 55.8, 108.5, 112.3, 114.3, 114.6, 117.3, 122.0, 122.5, 129.8, 130.4, 130.9, 131.5, 137.4, 139.8, 158.0, 158.6, 159.4, 161.2, 161.5. HRMS: calcd for $C_{25}H_{22}N_3O_2$ 396.1712 $[M + H]$, found 396.1699.

4. General Procedure for the Preparation of 9*H*-Pyrido[2,3-*b*]indoles 6. To a tube containing a solution of 1-bromo-2-(2,2-dibromovinyl)benzene (**1a**) (170 mg, 0.5 mmol) in DMF (3 mL) were added CuI (9.5 mg, 0.05 mmol), DABCO (11.2 mg, 0.1 mmol), PivOH (51 mg, 0.5 mmol), acetaldehyde (66 mg, 1.5 mmol), and aqueous ammonia (**3**) (26%, 0.5 mL). The tube was sealed, and the mixture was stirred at 80 °C under an atmosphere of air for 30 h. After the mixture was cooled to room temperature, the reaction was quenched with H_2O, and the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (10:1) as the eluent to give 2-methyl-9*H*-pyrido[2,3-*b*]indole (**6a**) (35 mg, 38%). Other 9*H*-pyrido[2,3-*b*]indoles (**6b**−**j**) were obtained in a similar manner.

*2-Methyl-9H-pyrido[2,3-b]indole (**6a**).*[23] Eluent: petroleum ether/ethyl acetate (10:1). White solid (34 mg, 38%), mp 205−206 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.88 (s, 3H), 7.02 (d, J = 5.2 Hz, 1H), 7.30 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.38 (d, J = 8.8 Hz, 1H), 10.46 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 111.8, 115.1, 120.8, 121.0, 127.4, 129.4, 129.6, 131.0, 138.4, 149.3, 151.7. MS: m/z 183 $[M + H]^+$.

*2-Ethyl-3-methyl-9H-pyrido[2,3-b]indole (**6b**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (45 mg, 43%), mp 214−216 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (t, J = 7.6 Hz, 3H), 2.50 (s, 3H), 3.02 (q, J = 7.2 Hz, 2H), 7.22−7.24 (m, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.09 (s, 1H), 9.88 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 19.0, 29.0, 111.0, 114.2, 119.7, 120.6, 121.2, 122.1, 126.0, 130.0, 138.6, 150.8, 158.8. HRMS: calcd for $C_{14}H_{15}N_2$ 211.1235 $[M + H]$, found 211.1240.

*3-Ethyl-2-propyl-9H-pyrido[2,3-b]indole (**6c**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (55 mg, 46%), mp 173−175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (t, J = 7.2 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.80−1.90 (m, 2H), 2.85 (q, J = 8.0 Hz, 2H), 2.98 (t, J = 8.0 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 8.02 (d, J = 7.2 Hz, 1H), 8.13 (s, 1H), 9.75 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 15.8, 23.5, 25.5, 37.2,

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111.0, 114.6, 119.8, 120.6, 121.3, 126.2, 128.7, 138.6, 150.4, 156.9. HRMS: calcd for $C_{16}H_{19}N_2$ 239.1548 [M + H], found 239.1540.

*2-Isobutyl-3-isopropyl-9H-pyrido[2,3-b]indole (**6d**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (56 mg, 42%), mp 206−207 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (d, J = 6.8 Hz, 6H), 1.40 (d, J = 6.8 Hz, 6H), 2.20−2.28 (m, 1H), 3.19 (d, J = 7.2 Hz, 2H), 3.41−3.48 (m, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 8.46 (s, 1H), 11.00 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 24.6, 27.1, 29.0, 37.4, 111.2, 114.8, 119.5, 121.4, 123.0, 125.8, 134.1, 139.1, 143.4, 143.8, 150.7. HRMS: calcd for $C_{18}H_{23}N_2$ 267.1861 [M + H], found 267.1846.

*3-Benzyl-2-phenethyl-9H-pyrido[2,3-b]indole (**6e**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (94 mg, 52%), mp 200−202 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.86−2.90 (m, 2H), 3.02−3.06 (m, 2H), 4.11 (s, 2H), 7.11−7.28 (m, 10H), 7.37−7.39 (m, 1H), 7.44 (d, J = 7.2 Hz, 1H), 8.04 (d, J = 7.6 Hz, 1H), 8.27 (s, 1H), 11.63 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.3, 37.4, 38.4, 111.6, 113.7, 119.6, 120.9, 121.2, 125.3, 126.2, 126.4, 126.5, 128.73, 128.74, 128.87, 128.89, 130.7, 139.4, 141.5, 142.4, 151.2, 156.7. HRMS: calcd for $C_{26}H_{23}N_2$ 363.1861 [M + H], found 363.1851.

*3-Ethyl-7-fluoro-2-propyl-9H-pyrido[2,3-b]indole (**6f**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (59 mg, 46%), mp 192−194 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (t, J = 7.2 Hz, 3H), 1.34 (t, J = 7.6 Hz, 3H), 1.64−1.71 (m, 2H), 2.84 (q, J = 7.2 Hz, 2H), 2.96 (t, J = 7.6 Hz, 2H), 6.97 (t, J = 8.8 Hz, 1H), 7.17 (d, J = 9.2 Hz, 1H), 7.90−7.94 (m, 1H), 8.06 (s, 1H), 10.01 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 15.8, 23.6, 25.5, 37.3, 97.8, 98.1, 107.7, 108.0, 114.1, 117.7, 121.5, 121.6, 128.1, 129.1, 139.2, 139.4, 148.2, 151.0, 156.6, 160.8, 163.2. HRMS: calcd for $C_{16}H_{18}FN_2$ 257.1454 [M + H], found 257.1475.

*6-Chloro-3-ethyl-2-propyl-9H-pyrido[2,3-b]indole (**6g**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (64 mg, 47%), mp 214−216 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.76−1.85 (m, 2H), 2.84 (q, J = 7.2 Hz, 2H), 3.15 (t, J = 8.0 Hz, 2H), 7.41−7.46 (m, 2H), 7.97 (s, 1H), 8.30 (s, 1H), 10.02 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 16.6, 22.4, 23.0, 31.3, 112.1, 114.0, 122.28, 122.30, 125.2, 126.0, 129.5, 137.2, 145.5, 146.9, 151.5. HRMS: calcd for $C_{16}H_{18}ClN_2$ 273.1158 [M + H], found 273.1166.

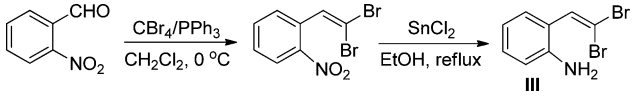
*3-Ethyl-2-propyl-6-(trifluoromethyl)-9H-pyrido[2,3-b]indole (**6h**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (75 mg, 49%), mp 227−229 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (t, J = 7.2 Hz, 3H), 1.36 (t, J = 7.6 Hz, 3H), 1.80−1.90 (m, 2H), 2.86 (q, J = 7.6 Hz, 2H), 3.02 (t, J = 8.0 Hz, 2H), 7.57 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 8.18 (s, 1H), 8.30 (s, 1H), 10.80 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 15.6, 23.5, 25.4, 37.3, 111.0, 114.1, 118.09, 118.13, 118.17, 118.21, 120.9, 121.8, 122.1, 122.8, 112.9, 128.9, 129.6, 140.3, 151.0, 158.2. HRMS: calcd for $C_{17}H_{18}F_3N_2$ 307.1422 [M + H], found 307.1426.

*3-Ethyl-6-methoxy-2-propyl-9H-pyrido[2,3-b]indole (**6i**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (55 mg, 41%), mp 246−248 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (t, J = 7.2 Hz, 3H), 1.34 (t, J = 7.6 Hz, 3H), 1.81−1.91 (m, 2H), 2.83 (q, J = 8.0 Hz, 2H), 2.98 (t, J = 8.0 Hz, 2H), 3.91 (s, 3H), 7.09−7.12 (m, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.49 (s, 1H), 8.20 (s, 1H), 10.06 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 15.6, 23.3, 25.1, 35.9, 56.0, 103.7, 112.4, 116.1, 116.3, 121.0, 128.2, 130.7, 133.4, 148.4, 153.8, 154.6. HRMS: calcd for $C_{17}H_{21}N_2O$ 269.1654 [M + H], found 269.1676.

*8-Ethyl-7-propyl-5H-[1,3]dioxolo[4,5-b]carbazole (**6j**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (62 mg, 44%), mp 265−267 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (t, J = 7.2 Hz, 3H), 1.36 (t, J = 7.6 Hz, 3H), 1.91−2.01 (m, 2H), 2.85 (q, J = 7.6 Hz, 2H), 3.08 (t, J = 7.6 Hz, 2H), 6.09 (s, 2H), 7.08 (s, 1H), 7.38 (s, 1H), 8.33 (s, 1H), 11.6 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.5, 16.1, 22.8, 25.3, 36.8, 92.8, 100.4, 101.1, 113.7, 121.1, 127.3, 127.8, 134.6, 142.1, 147.1, 150.5, 154.8. HRMS: calcd for $C_{18}H_{20}NO_2$ 282.1494 [M + H], found 282.1481.

*2-Phenyl-9H-pyrido[2,3-b]indole (**6k**).*[21j] Eluent: petroleum ether/ethyl acetate (5:1). White solid (61 mg, 50%), mp 244−246 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.02 (t, J = 7.6 Hz, 1H), 7.09 (d, J = 5.2 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.51−7.63 (m, 5H), 7.66−7.68 (m, 2H), 8.45 (d, J = 5.2 Hz, 1H), 12.00 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 111.8, 112.6, 116.4, 119.6, 120.2, 122.3, 127.0, 128.9, 129.2, 129.3, 139.0, 139.5, 144.7, 146.5, 152.8. MS: m/z 245 [M + H]$^+$.

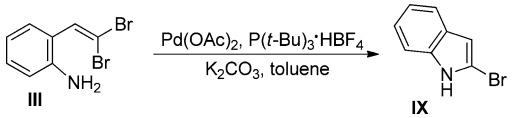
5. Preparation of 2-(2,2-Dibromovinyl)aniline (III).[11a]



III

To a flask containing a solution of 2-nitrobenzaldehyde (1.51g, 10 mmol) and CBr_4 (4.97 g, 15 mmol) in DCM (50 mL) at 0 °C was added dropwise a solution of PPh_3 (7.86 g, 30 mmol) in DCM (15 mL). Then the mixture was stirred for another 0.5 h, warmed to room temperature, and stirred for an additional 0.5 h. Next, diethyl ether (50 mL) was added to the reaction mixture, which was then filtered through a short plug of Celite and washed with diethyl ether (10 mL). The filtrates were concentrated under vacuum, and EtOH (50 mL) and $SnCl_2$ (13.3 g, 70 mmol) were added to the crude product. The suspension was then placed into a preheated oil bath with stirring at 100 °C for 1 h. Upon completion of the reaction as monitored by TLC, the reaction flask was allowed to cool to room temperature. After most of the ethanol was removed under vacuum, H_2O (30 mL) and EtOAc (30 mL) were added to the residue. Solid K_2CO_3 was carefully added to the resulting mixture until pH was above 10. The EtOAc layer was separated from the heterogeneous mixture, and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (5:1) as the eluent to give 2-(2,2-dibromovinyl)-aniline (**III**) (2.3 g, 83% over two steps) as a white solid (mp 41−42 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (br, s, 2H), 6.71 (d, J = 8.0 Hz, 1H), 6.79 (t, J = 7.6 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.34 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 92.8, 115.8, 118.4, 121.8, 129.2, 129.7, 134.1, 143.7. MS: m/z 278 [M + H]$^+$.

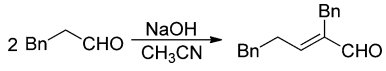
6. Preparation of 2-Bromoindole (IX).[11b]



III IX

To a tube equipped with a magnetic stir bar were added 2-(2,2-dibromovinyl)aniline (**III**) (277 mg, 1 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), $P(t\text{-}Bu)_3{\cdot}HBF_4$ (17.4 mg, 0.06 mmol), and K_2CO_3 (276 mg, 2 mmol). The tube was flushed with nitrogen three times, after which toluene (3 mL) was added and the tube was sealed. The mixture in the tube was stirred at room temperature for 5 min, and then the tube was placed into a preheated oil bath at 100 °C. After 14 h of stirring, the reaction tube was allowed to cool to room temperature. Then the reaction was quenched with H_2O, and the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (5:1) as the eluent to give 2-bromoindole (**IX**) (166 mg, 85%) as a white solid (mp 81−83 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.69 (s, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.30−7.37 (m, 2H), 7.71 (d, J = 7.6 Hz, 1H), 7.80 (dr, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 105.0, 109.1, 110.8, 119.9, 120.8, 122.5, 128.9, 136.6. MS: m/z 196 [M + H]$^+$.

7. Preparation of 2-Benzyl-5-phenylpent-2-enal.



To a flask containing a solution of 3-phenylpropanal (670 mg, 5 mmol) in CH_3CN (20 mL) was added NaOH (80 mg, 2 mmol), then the mixture was stirred at room temperature for 1.5 h. Upon

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completion of the reaction, the mixture was concentrated, treated with saturated aqueous NH_4Cl, and extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (50:1) as the eluent to give 2-benzyl-5-phenylpent-2-enal (550 mg, 88%) as a faint-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.80−2.85 (m, 4H), 3.68 (s, 2H), 6.69 (t, J = 6.8 Hz, 1H), 7.21−7.41 (m, 10H), 9.52 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 31.1, 34.5, 126.2, 126.5, 128.4, 128.5, 128.6, 128.7, 139.2, 140.6, 142.8, 154.9, 194.7. MS: m/z 251 $[M + H]^+$.

8. Preparation of 4a from the Reaction of III, 2a, and 3 under Condition A. To a tube containing a solution of 2-(2,2-dibromovinyl)aniline (**III**) (138 mg, 0.5 mmol) in DMF (1.5 mL) were added CuI (9.5 mg, 0.05 mmol), DABCO (11.2 mg, 0.1 mmol), PivOH (51 mg, 0.5 mmol), benzaldehyde (**2a**) (106 mg, 1 mmol), and aqueous ammonia (**3**) (26%, 1.5 mL). The tube was sealed, and the mixture was stirred at 80 °C under an atmosphere of air for 20 h. After the mixture was cooled to room temperature, the reaction was quenched with H_2O, and the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (5:1) as the eluent to give 2-phenyl-1*H*-indole-3-carbonitrile (**4a**) (82.8 mg, 76%).

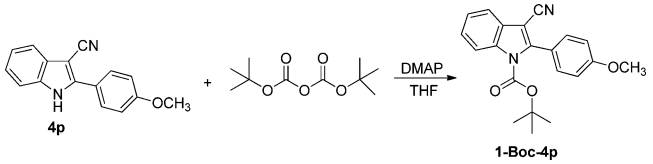
9. Preparation of 5a from the Reaction of III, 2a, and 3 under Condition B. To a tube containing a solution of 2-(2,2-dibromovinyl)aniline (**III**) (138 mg, 0.5 mmol) in DMF (3 mL) were added CuI (9.5 mg, 0.05 mmol), DABCO (11.2 mg, 0.1 mmol), PivOH (51 mg, 0.5 mmol), benzaldehyde (**2a**) (159 mg, 1.5 mmol), and aqueous ammonia (**3**) (26%, 0.5 mL). The tube was sealed, and the mixture was stirred at 80 °C under an atmosphere of air for 25 h. After the mixture was cooled to room temperature, the reaction was quenched with H_2O, and the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (10:1) as the eluent to give 2,4-diphenyl-9*H*-pyrimido[4,5-*b*]indole (**5a**) (109 mg, 68%).

10. Preparation of 5a from the Reaction of IX, 2a, and 3 under Condition B. To a tube containing a solution of benzaldehyde (**2a**) (159 mg, 1.5 mmol) in DMF (3 mL) were added CuI (9.5 mg, 0.05 mmol), DABCO (11.2 mg, 0.1 mmol), PivOH (51 mg, 0.5 mmol), 2-bromoindole (**IX**) (98 mg, 0.5 mmol), and aqueous ammonia (**3**) (26%, 0.5 mL). The tube was sealed, and the mixture was stirred at 80 °C under an atmosphere of air for 18 h. After the mixture was cooled to room temperature, the reaction was quenched with H_2O, and the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (10:1) as the eluent to give 2,4-diphenyl-9*H*-pyrimido[4,5-*b*]indole (**5a**) (128 mg, 80%).

11. Preparation of 6e from the Reaction of 1a, 2-Benzyl-5-phenylpent-2-enal, and 3 under Condition B. To a tube containing a solution of 1-bromo-2-(2,2-dibromovinyl)benzene (**1a**) (170 mg, 0.5 mmol) in DMF (3 mL) were added CuI (9.5 mg, 0.05 mmol), DABCO (11.2 mg, 0.1 mmol), PivOH (51 mg, 0.5 mmol), 2-benzyl-5-phenylpent-2-enal (188 mg, 0.75 mmol), and aqueous ammonia (**3**) (26%, 0.5 mL). The tube was sealed, and the mixture was stirred at 80 °C under air for 25 h. After the mixture was cooled to room temperature, the reaction was quenched with H_2O, and the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (10:1) as the eluent to give 3-benzyl-2-phenethyl-9*H*-pyrido[2,3-*b*]indole (**6e**) (103 mg, 57%).

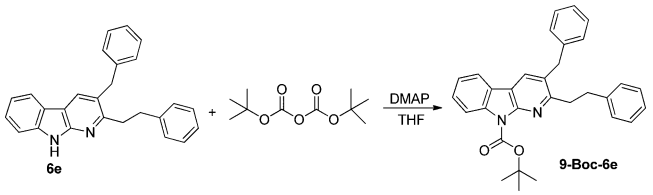
12. Preparation of 6e from the Reaction of IX, 2-Benzyl-5-phenylpent-2-enal, and 3 under Condition B. To a tube containing a solution of 2-benzyl-5-phenylpent-2-enal (188 mg, 0.75 mmol) in DMF (3 mL) were added CuI (9.5 mg, 0.05 mmol), DABCO (11.2 mg, 0.1 mmol), PivOH (51 mg, 0.5 mmol), 2-bromoindole (**IX**) (98 mg, 0.5 mmol), and aqueous ammonia (**3**) (26%, 0.5 mL). The tube was sealed, and the mixture was stirred at 80 °C under air for 18 h. After the mixture was cooled to room temperature, the reaction was quenched with H_2O, and the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (10:1) as the eluent to give 3-benzyl-2-phenethyl-9*H*-pyrido[2,3-*b*]indole (**6e**) (132 mg, 73%).

13. Preparation of 1-Boc-4p.



To facilitate crystallization, 2-(4-methoxyphenyl)-1*H*-indole-3-carbonitrile (**4p**) was transformed into its Boc derivative **1-Boc-4p**. To a flask containing a solution of **4p** (248 mg, 1 mmol) in THF (4 mL) were added di-*tert*-butyl dicarbonate (240 mg, 1.1 mmol) and DMAP (12 mg, 0.1 mmol). The mixture was stirred at room temperature for 2 h. Upon completion of the reaction, the mixture was concentrated. To the residue were added H_2O and ethyl acetate. The organic layer was separated, washed with brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (20:1) as the eluent to give *tert*-butyl 3-cyano-2-(4-methoxyphenyl)-1*H*-indole-1-carboxylate (**1-Boc-4p**) (327 mg, 94%) as a white solid (mp 125−127 °C). Single crystals of **1-Boc-4p** were grown from chloroform/petroleum ether (4:1) by slow evaporation. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 9H), 3.88 (s, 3H), 7.03 (dd, J_1 = 6.8 Hz, J_2 = 2.4 Hz, 2H), 7.37−7.45 (m, 4H), 7.70−7.72 (m, 1H), 8.17−8.19 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.4, 55.4, 85.3, 93.3, 113.8, 115.1, 115.4, 119.2, 123.2, 124.3, 125.9, 127.2, 130.4, 135.8, 147.7, 148.9, 160.6. MS: m/z 349 $[M + H]^+$.

14. Preparation of 9-Boc-6e.



To facilitate crystallization, 3-benzyl-2-phenethyl-9*H*-pyrido[2,3-*b*]-indole (**6e**) was transformed into its Boc derivative **9-Boc-6e**. To a flask containing a solution of **6e** (180 mg, 0.5 mmol) in THF (2 mL) were added di-*tert*-butyl dicarbonate (120 mg, 0.55 mmol) and DMAP (6 mg, 0.05 mmol). The mixture was stirred at room temperature for 2 h. Upon completion of the reaction, the mixture was concentrated. To the residue were added H_2O and ethyl acetate. The organic layer was separated, washed with brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (20:1) as the eluent to give *tert*-butyl 3-benzyl-2-phenethyl-9*H*-pyrido[2,3-*b*]indole-9-carboxylate (**9-Boc-6e**) (210 mg, 91%) as a white solid (mp 109−111 °C). Single crystals of **9-Boc-6e** were grown from chloroform/petroleum ether (3:1) by slow evaporation. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79 (s, 9H), 3.09−3.13 (m, 2H), 3.16−3.20 (m, 2H), 4.07 (s, 2H), 7.09 (d, J = 7.2 Hz, 2H), 7.14 (d, J = 6.8 Hz, 2H), 7.18−7.30 (m, 6H), 7.34 (d, J = 7.2 Hz, 1H), 7.47−7.51 (m, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.92 (s, 1H), 8.39 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.5, 35.2, 37.6,

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38.5, 83.7, 116.2, 116.7, 119.9, 122.7, 123.0, 125.8, 126.3, 127.4, 128.3, 128.56, 128.59, 128.7, 128.8, 129.5, 138.2, 140.0, 142.3, 149.8, 150.5, 157.6. MS: m/z 463 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra and X-ray crystallographic data (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00239.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Sundberg, R. J. *Indoles*; Academic Press: San Diego, CA, 1996. (b) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*; Wiley-VCH: Weinheim, Germany, 2003. (c) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761.

(2) (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (b) Campo, J.; Garcia-Valverde, M.; Marcaccini, S.; Rojo, M. J.; Torroba, T. *Org. Biomol. Chem.* **2006**, *4*, 757. (c) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (d) Barluenga, J.; Rodríguez, F.; Fañanás, F. J. *Chem.—Asian J.* **2009**, *4*, 1036. (e) Bartoli, G.; Benciveni, G.; Dalpozzo, R. *Chem. Soc. Rev.* **2010**, *39*, 4449. (f) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489. (g) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508. (h) Lancianesi, S.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2014**, *114*, 7108.

(3) For recent examples of the synthesis of indole derivatives, see: (a) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2304. (b) Pei, T.; Chen, C. Y.; Dormer, P. G.; Davies, I. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4231. (c) Cui, S. L.; Wang, J.; Wang, Y. G. *J. Am. Chem. Soc.* **2008**, *130*, 13526. (d) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572. (e) Barluenga, J.; Jiménez-Aquino, A.; Aznar, F.; Valdés, C. *J. Am. Chem. Soc.* **2009**, *131*, 4031. (f) Wei, Y.; Deb, I.; Yoshikai, N. *J. Am. Chem. Soc.* **2012**, *134*, 9098. (g) Sharma, U.; Kancherla, R.; Naveen, T.; Agasti, S.; Maiti, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 11895 and references cited therein.

(4) For copper-catalyzed indole synthesis through cascade processes, see: (a) Chen, Y.; Xie, X.; Ma, D. *J. Org. Chem.* **2007**, *72*, 9329. (b) Liu, F.; Ma, D. *J. Org. Chem.* **2007**, *72*, 4844. (c) Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 3535. (d) Yang, X.; Fu, H.; Qiao, R.; Jiang, Y.; Zhao, Y. *Adv. Synth. Catal.* **2010**, *352*, 1033. (e) Wang, Z. J.; Yang, J. G.; Yang, F.; Bao, W. L. *Org. Lett.* **2010**, *12*, 3034. (f) Wang, Z. J.; Yang, F.; Lv, X.; Bao, W. L. *J. Org. Chem.* **2011**, *76*, 967. (g) Gogoi, A.; Guin, S.; Rout, S. K.; Patel, B. K. *Org. Lett.* **2013**, *15*, 1802−1805. (h) Besandre, R.; Jaimes, M.; May, J. A. *Org. Lett.* **2013**, *15*, 1666.

(5) (a) Chonan, T.; Tanaka, H.; Yamamoto, D.; Yashiro, M.; Oi, T.; Wakasugi, D.; Ohoka-Sugita, A.; Io, F.; Koretsune, H.; Hiratate, A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3965. (b) Patil, S. A.; Patil, R.; Miller, D. D. *Curr. Med. Chem.* **2011**, *18*, 615. (c) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. Biomol. Chem.* **2011**, *9*, 641.

(6) (a) Traxler, P. M.; Furet, P.; Mett, H.; Buchdunger, E.; Meyer, T.; Lydon, N. *J. Med. Chem.* **1996**, *39*, 2285. (b) Showalter, H. D. H.; Bridges, A. J.; Zhou, H.; Sercel, A. D.; McMichael, A.; Fry, D. W. *J. Med. Chem.* **1999**, *42*, 5464. (c) Tichy, M.; Pohl, R.; Xu, H. Y.; Chen, Y. L.; Yokokawa, F.; Shi, P. Y.; Hocek, M. *Bioorg. Med. Chem.* **2012**, *20*, 6123.

(7) (a) Swain, C. J.; Baker, R.; Kneen, C.; Moseley, J.; Saunders, J.; Seward, E. M.; Stevenson, G.; Beer, M.; Stanton, J.; Watling, K. *J. Med. Chem.* **1991**, *34*, 140. (b) Kumar, D.; Kumar, N. M.; Chang, K. H.; Gupta, R.; Shah, K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5897. (c) Wu, S.; Wang, L.; Guo, W.; Liu, X.; Liu, J.; Wei, X.; Fang, B. *J. Med. Chem.* **2011**, *54*, 2668.

(8) (a) Okamoto, A.; Tanaka, K.; Fukuta, T.; Saito, I. *J. Am. Chem. Soc.* **2003**, *125*, 9296. (b) Okamoto, A.; Tanaka, K.; Nishiza, K.; Saito, I. *Bioorg. Med. Chem.* **2004**, *12*, 5875. (c) Okamoto, A.; Kamei, T.; Saito, I. *J. Am. Chem. Soc.* **2006**, *128*, 658.

(9) For recent examples of the preparation of 3-cyanoindoles, see: (a) Swamy, N. K.; Yazici, A.; Pyne, S. G. *J. Org. Chem.* **2010**, *75*, 3412. (b) Yan, G.; Kuang, C.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 1052. (c) Ding, S.; Jiao, N. *J. Am. Chem. Soc.* **2011**, *133*, 12374. (d) Peng, J.; Zhao, J.; Hu, Z.; Liang, D.; Huang, J.; Zhu, Q. *Org. Lett.* **2012**, *14*, 4966. (e) Bobko, M. A.; Evans, K. A.; Kaura, A. C.; Shuster, L. E.; Su, D. S. *Tetrahedron Lett.* **2012**, *53*, 200. (f) Zhang, L.; Wen, Q.; Jin, J.; Wang, C.; Lu, P.; Wang, Y. *Tetrahedron* **2013**, *69*, 4236. (g) Yuen, O. Y.; Choy, P. Y.; Chow, W. K.; Wong, W. T.; Kwong, F. Y. *J. Org. Chem.* **2013**, *78*, 3374 and references cited therein. (h) Li, X.; Du, Y.; Liang, Z.; Li, X.; Pan, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2643.

(10) For the preparation of pyrimido[4,5-*b*]indoles, see: (a) Hyatt, J. A.; Swenton, J. S. *J. Org. Chem.* **1972**, *37*, 3216. (b) Venugopalan, B.; Desai, P. D.; de Souza, N. J. *J. Heterocycl. Chem.* **1988**, *25*, 1633. (c) Hubschwerlen, C.; Pflieger, P.; Specklin, J.-L.; Gubernator, K.; Gmünder, H.; Angehrn, P.; Kompis, I. *J. Med. Chem.* **1992**, *35*, 1385. (d) Ple, N.; Turck, A.; Heynderickx, A.; Queguiner, G. *J. Heterocycl. Chem.* **1994**, *31*, 1311. (e) Bundy, G. L.; Banitt, L. S.; Dobrowolski, P. J.; Palmer, J. R.; Schwartz, T. M.; Zimmermann, D. C.; Lipton, M. F.; Mauragis, M. A.; Veley, M. F.; Appell, R. B.; Clouse, R. C.; Daugs, E. D. *Org. Process Res. Dev.* **2001**, *5*, 144. (f) Zhang, Y. M.; Razler, T.; Jackson, P. F. *Tetrahedron Lett.* **2002**, *43*, 8235. (g) Adib, M.; Mohammadi, B.; Bijanzadeh, H. R. *Synlett* **2008**, 177.

(11) (a) Fang, Y. Q.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 538. (b) Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2010**, *132*, 11416.

(12) (a) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403. (b) Hodgkinson, R. C.; Schulz, J.; Willis, M. C. *Org. Biomol. Chem.* **2009**, *7*, 432.

(13) (a) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (b) Shaabani, A.; Maleki, A.; Rezayan, A. H.; Sarvary, A. *Mol. Diversity* **2011**, *15*, 41. (c) Volla, C. M.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390.

(14) (a) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. (b) Beletskaya, I. P.; Cheprakov, A. V. *Organometallics* **2012**, *31*, 7753. (c) Liu, Y.; Wan, J. P. *Chem.—Asian J.* **2012**, *7*, 1488. (d) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829. (e) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450. (f) Rao, H.; Fu, H. *Synlett* **2011**, 745. (g) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (h) Liu, Y.; Wan, J.-P. *Org. Biomol. Chem.* **2011**, *9*, 6873.

(15) (a) Guo, S.; Wang, J.; Fan, X.; Zhang, X. *J. Org. Chem.* **2013**, *78*, 3262. (b) Fan, X.; Li, B.; Guo, S.; Wang, Y.; Zhang, X. *Chem.—Asian J.* **2014**, *9*, 739. (c) Zhang, X.; Guo, X.; Fan, X. *Chem.—Asian J.* **2015**, *10*, 106. (d) Li, B.; Guo, C.; Fan, X.; Zhang, J.; Zhang, X. *Tetrahedron Lett.* **2014**, *55*, 5944. (e) Guo, S.; Li, Y.; Tao, L.; Zhang, W.; Fan, X. *RSC Adv.* **2014**, *4*, 59289.

(16) For a review of the preparation and applications of 1-bromo-2-(2,2-dibromovinyl)benzenes, see: Chelucci, G. *Chem. Rev.* **2012**, *112*, 1344 and references cited therein.

(17) (a) Kitahara, M.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2011**, *133*, 2160. (b) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 6993. (c) Sudheendran,

DOI: 10.1021/acs.joc.5b00239
J. Org. Chem. 2015, 80, 5444−5456

K.; Malakar, C. C.; Conrad, J.; Beifuss, U. *J. Org. Chem.* **2012**, *77*, 10194.
(18) The structures of **4p** and **6e** were confirmed by X-ray diffraction analysis. CCDC 1026548 (**1-Boc-4p**) and CCDC 1026549 (**9-Boc-6e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(19) For natural products containing α-carboline, see: (a) Moquin-Pattey, C.; Guyot, M. *Tetrahedron* **1989**, *45*, 3445. (b) Sharaf, M. H. M.; Schiff, P. L., Jr.; Tackie, A. N.; Phoebe, C. H., Jr.; Martin, G. E. *J. Heterocycl. Chem.* **1996**, *33*, 239. (c) Kim, J.-S.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1997**, *38*, 3431. (d) Molina, P.; Fresneda, P. M.; Sanz, M. A.; Foces Foces, C.; de Arellano, M. C. R. *Tetrahedron* **1998**, *54*, 9623.
(20) For the biological activities of α-carboline, see: (a) Peczynska Czoch, W.; Pognan, F.; Kaczmarek, L.; Boratynski, J. *J. Med. Chem.* **1994**, *37*, 3503. (b) Verbitski, S. M.; Mayne, C. L.; Davis, R. A.; Concepcion, G. P.; Ireland, C. M. *J. Org. Chem.* **2002**, *67*, 7124. (c) Davidson, H. M. *Curr. Atheroscler. Rep.* **2009**, *11*, 67.
(21) For recent examples of the preparation of α-carbolines, see: (a) Laha, J. K.; Petrou, P.; Cuny, G. D. *J. Org. Chem.* **2009**, *74*, 3152 and references cited therein. (b) Chavan, N. L.; Nayak, S. K.; Kusurkar, R. S. *Tetrahedron* **2010**, *66*, 1827. (c) Schneider, C.; Goyard, D.; Gueyrard, D.; Joseph, B.; Goekjian, P. G. *Eur. J. Org. Chem.* **2010**, 6665. (d) Laha, J. K.; Barolo, S. M.; Rossi, R. A.; Cuny, G. D. *J. Org. Chem.* **2011**, *76*, 6421. (e) Kumar, A. S.; Nagarajan, R. *Org. Lett.* **2011**, *13*, 1398. (f) Gupta, S.; Kumar, B.; Kundu, B. *J. Org. Chem.* **2011**, *76*, 10154. (g) Basavaiah, D.; Reddy, D. M. *Org. Biomol. Chem.* **2012**, *10*, 8774. (h) Pumphrey, A. L.; Dong, H.; Driver, T. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 5920. (i) Zhang, X.; He, Q.; Xiang, H.; Song, S.; Miao, Z.; Yang, C. *Org. Biomol. Chem.* **2014**, *12*, 355 and references cited therein. (j) Portela-Cubillo, F.; Surgenor, B. A.; Aitken, R. A.; Walton, J. C. *J. Org. Chem.* **2008**, *73*, 8124.
(22) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.
(23) Ono, A.; Narasaka, K. *Chem. Lett.* **2001**, 146.

DOI: 10.1021/acs.joc.5b00239
J. Org. Chem. 2015, 80, 5444−5456