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Copper-Catalyzed Direct C2-Benzylation of Indoles with Alkylarenes

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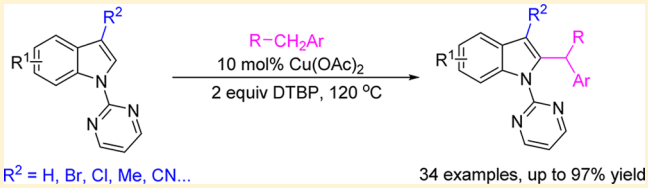
Supporting Information

ABSTRACT: The copper-catalyzed regioselective cross-dehydrogenative coupling of *N*-pyrimidylindoles with benzylic C(sp^3)−H bonds has been developed. Di-*tert*-butyl peroxide was employed as a mild oxidant, and benzaldehyde proved to be an effective additive. This reaction provides a direct and pratical route to a variety of 2-benzylindoles.

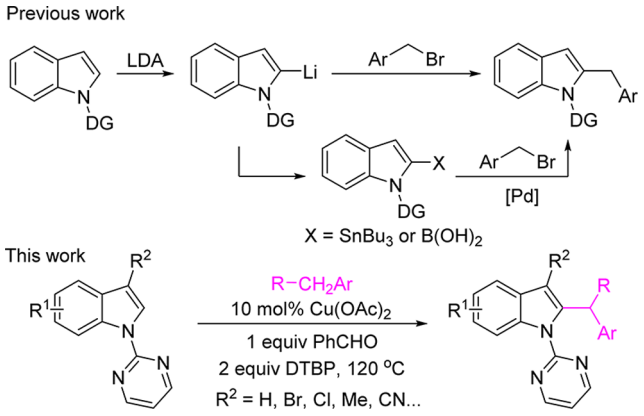


INTRODUCTION

Indoles are important structural motifs found ubiquitously in biologically active compounds and pharmaceuticals.[1] Therefore, the construction and functionalization of indole skeletons has attracted considerable attention.[2] Furthermore, the synthesis of 2-benzylindole frameworks is of particular interest, as this structural motif has been incorporated into a number of bioactive compounds including luzindole.[3−5] Recently, a few strategies for the construction of 2-benzylindole derivatives based on the cyclization of suitable substrates were disclosed.[4a−d] For example, in 2014, Ghorai et al. reported an efficient method for the synthesis of 3-substituted 2-benzylindoles via Pd-catalyzed intramolecular oxidative annulation of *o*-allylanilines.[4b] Utilizing more classical methods, syntheses of 2-benzylindoles based on the regioselective lithiation of the C2-position of indoles have been extensively investigated (Scheme 1).[5] Unfortunately, however, these multistep approaches suffer from relatively low yields and require the use of air- and moisture-sensitive organolithium reagents.

In recent years, cross-dehydrogenative coupling (CDC) has emerged as an atom-economic and sustainable process.[6] In this context, the transition-metal-catalyzed direct alkenylation, (hetero)arylation, and the acylation of indoles has been investigated.[7] Moreover, the unique activity of relatively cheap and abundant copper salts in C−H functionalization has recently attracted plenty of interest.[8,9] Several examples concerning the copper-promoted C2−H functionalization of indoles have been already reported.[10,11] In 2008, Gaunt et al. developed a direct and site-selective C3- and C2-arylation of indoles with diaryliodine(III) reagents under mild conditions.[10] In 2012, Miura and co-workers reported the first copper-catalyzed oxidative coupling reaction between *N*-(2-pyrimidyl)-indoles and 1,3-azoles.[11a,b] Subsequently, Zhu et al. developed a copper-mediated C2-cyanation of indoles with acetonitrile.[11d] Continuing with our interest in the regioselective C−H functionalization of indoles,[12] we envisioned that the synthesis of 2-benzylindoles could be readily accomplished employing a copper-catalyzed regioselective CDC reaction between indoles and benzylic Csp^3−H bonds. To this end, we herein report the $Cu(OAc)_2$-catalyzed direct C2-benzylation of *N*-(2-pyrimidyl)-indoles with alkylarenes (Scheme 1).

Scheme 1. 2-Benzylation of Indoles



RESULTS AND DISCUSSION

Our initial study began with the reactions of *N*-(2-pyrimidyl)-indole **1a** with toluene (**2a**) in the presence of different transition-metal catalysts and oxidants. After a careful screening of reaction conditions (see the Supporting Information), we found that the direct cross coupling between **1a** and **2a** took place in the presence of 10 mol % of $Cu(OAc)_2$, 2 equiv of DTBP, and 1 equiv of benzaldehyde at 120 °C to afford the desired product **3aa** in 45% yield after 12 h (Table 1). The homocoupling of **1a** that provided the corresponding 2,2′-bisindole derivative was observed to account for the relatively low yield of **3aa**.[11c] With the optimized reaction conditions in hand, the scope of the reaction in regard to both the arylmethane and indole substrates was surveyed (Table 1). It was observed that the presence of electron-withdrawing groups (−Cl, −Br, −CN) on the phenyl ring of arylmethanes slightly increased the yields of the reaction process to afford the

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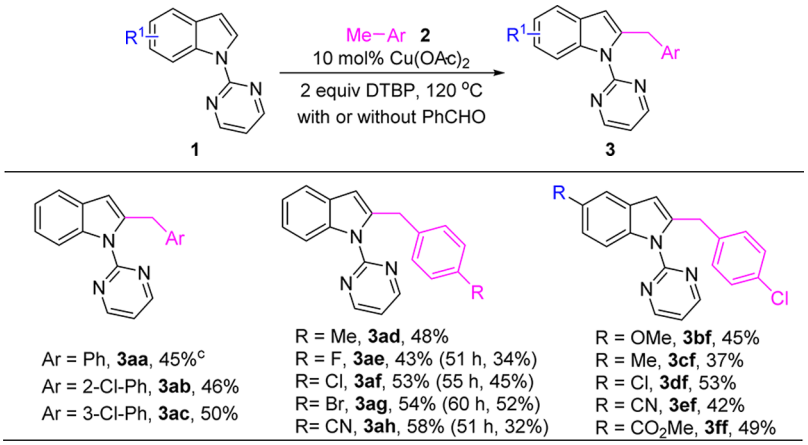
Table 1. Scope of Indoles.[a,b]

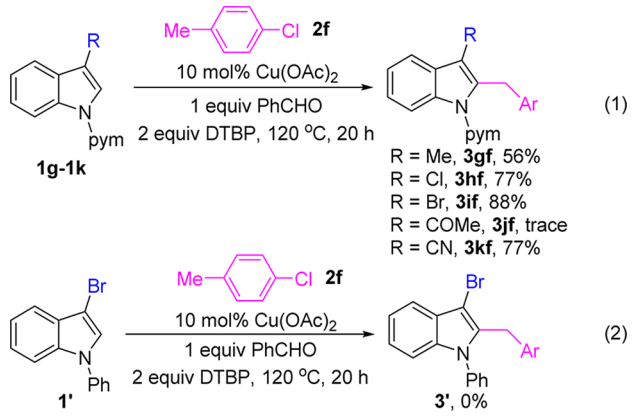


[a]Reaction conditions: **1a** (0.2 mmol), ArMe (2 mL), $Cu(OAc)_2$ (10 mol %), DTBP (2 equiv), and PhCHO (1 equiv) under Ar atmosphere at 120 °C, sealed tube, 20 h. [b]Isolated yields for the reactions in the absence of PhCHO are shown in parentheses. [c]12 h.

corresponding products (**3ab**,**ac**,**af**−**ah**). In addition, substituents on the phenyl ring of the indole had little effect on the oxidative cross couplings between **1** and 4-chlorotoluene **2f** (Table 1, **3bf**−**ff**). Notably, the reaction also worked in the absence of benzaldehyde, whereas the desired products **3** were isolated in lower yields even after a prolonged reaction times (Table 1, **3ae**−**ah**).

Subsequently, to prevent the undesired homocoupling of *N*-(2-pyrimidyl)indoles **1**, the reactions of several C3-substituted *N*-(2-pyrimidyl)indoles (**1g**−**k**) with 4-chlorotoluene **2f** were performed (Scheme 2, eq 1). To our delight, a series of

Scheme 2. Benzylation of 3-Substituted Indoles



substituents at the C3-position of indoles had a significant effect on the yield of the reaction. Among the five substituents (−Me, −Cl, −Br, −COMe, −CN) that we tested, the *N*-pyrimidylindole with the bromo substituent at the C3-position gave the best result, and the corresponding product **3if** was obtained in 88% yield. To further explore this reaction process, 3-bromo-1-phenyl-1*H*-indole **1′** and 4-chlorotoluene **2f** were subjected to the same reaction conditions (eq 2). The corresponding benzylation product **3′** was not observed, indicating that the 2-pyrimidinyl directing group is essential for C2−H bond activation during the reaction process.

Next, the scope of the reaction of 3-bromo-substituted indoles **1** with various alkylarenes **2** was investigated (Table 2). Initially, 3-bromo-*N*-(2-pyrimidyl)indole **1i** was reacted with toluene, *p*-xylene, *o*-xylene, and mesitylene, respectively, to afford the corresponding products **3ia**, **3id**, **3ii**, and **3ij** in high yields (82−89%). Moreover, the reactions of several arylmethanes bearing electron-withdrawing groups (−Cl, −F, −Br, −CN, $-CO_2Me$, −COMe) with **1i** also led to the formation of the desired 2-benzylation products **3ib**−**ic**,**ie**,**ig**,**ih**,**ik**,**il** in good yields (54−97%). Notably, several C2-benzylation reactions were performed in the absence of benzaldehyde and still gave the desired products **3ia**,**ic**,**ig**,**ih** in high yields, which may be ascribed to the inhibition of homocoupling of indoles by the introduction of bromo group at the C-3 position. Besides toluene derivatives, 2-methylthiophene (**2m**) also reacted with **1i**, providing the desired product **3im** in 63% yield. When ethylbenzene (**2n**) was reacted with **1i**, the corresponding benzylation product **3in** was obtained in only 37% yield.[13] Furthermore, both the electron-rich and electron-deficient substituents (−OMe, −Me, and $-CO_2Me$) on the phenyl ring of 3-bromo-*N*-pyrimidylindoles **1** were compatible, and the corresponding products **3lf**−**nf** were obtained in good yields (Table 2, 66−88%).

Having established the reaction scope, several experiments were conducted to study the reaction mechanism (Scheme 3). First, 3-bromo-*N*-pyrimidylindole **1i** alone underwent homocoupling in DCE to give 2,2′-bisindole **1i′** in 59% yield, which suggested the involvement of chelation-assisted C−H cupration of *N*-pyrimidylindole in the reaction process (eq 3, also see the Supporting Information).[11c] Furthermore, treatment of **1a** with $Cu(OAc)_2$ in the presence of AcOH-d_4 at 120 °C led to the incorporation of deuterium at the C2-position selectively (12 h, 18% D; 24 h, 28% D; eq 4). Exposure of **1i** to the same reaction system led to increased deuterium incorporation (12 h, 35% D; 24 h, 46% D; eq 5), consistent with the improved performance of 3-bromo-*N*-pyrimidylindole **1i** over **1a** in the coupling. Subsequently, the kinetic isotope effect experiment on **1i** and **1i-d** (98% D) with toluene was carried out under the standard conditions resulting in a KIE value of 1.4 (see the Supporting Information), which indicated that the C2-H cleavage is not likely to be the rate-limiting step (eq 6). Furthermore, the intermolecular competing reactions of **1i** with toluene and deuterated toluene exhibited a kinetic isotopic effect of 7.3, which suggested that the benzylic C−H bond cleavage is more likely to be involved in the rate-determining step (eq 7). It was also observed that, upon addition of 1.5 equiv of TEMPO to

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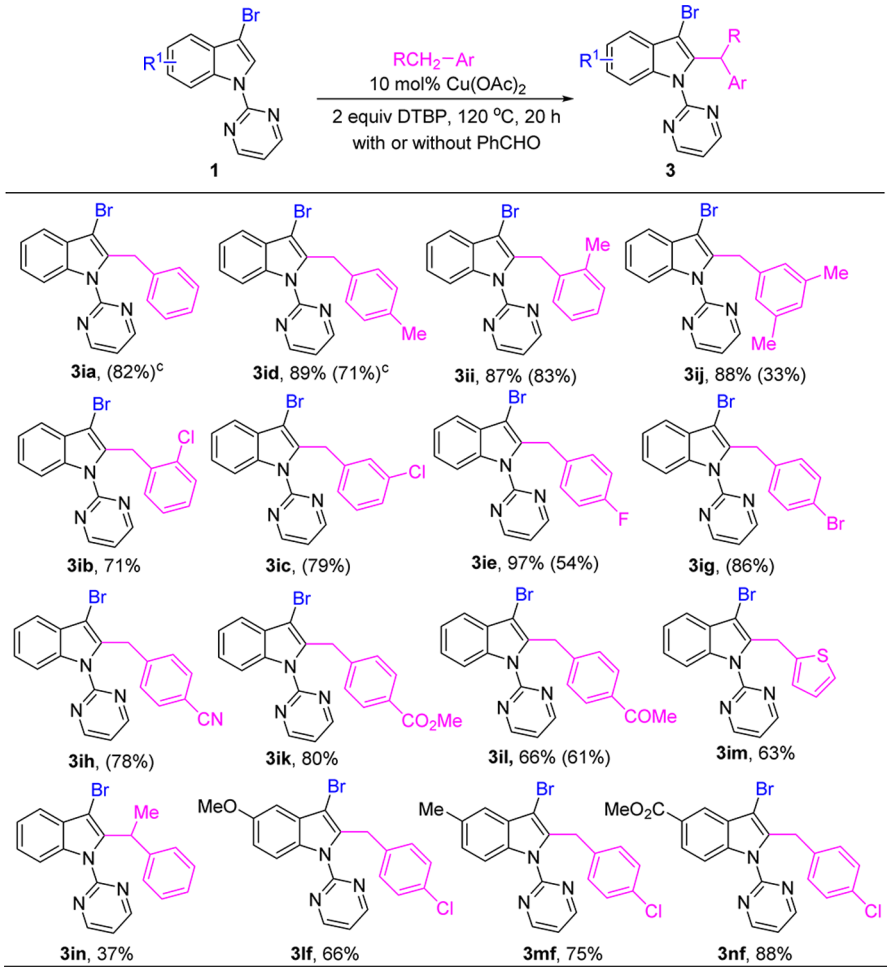
Table 2. Benzylation of 3-Bromo-Substituted Indoles[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (2 mL), $Cu(OAc)_2$ (10 mol %), DTBP (2 equiv), and PhCHO (1 equiv) under Ar atmosphere at 120 °C, sealed tube, 20 h. [b]Isolated yields for the reactions in the absence of PhCHO are shown in parentheses. [c]24 h.

the reaction of **1i** with toluene, the desired product was only isolated in 11% yield (see the Supporting Information), which confirmed the involvement of a radical process.[14] The addition of benzaldehyde in the catalytic system significantly enhanced the transformation, which might be attributed to the involvement of benzoyl radical. Subsequently, the cross-coupling reaction between **1i** and **2f** using *t*-BuOOCOPh instead of DTBP as oxidant was performed, which provided the corresponding product **3if** in only 56% yield (eq 8). Therefore, the real effect of benzaldehyde in the reaction remains unclear; however, it is worth mentioning that, in contrast to the previous results,[12a] the direct C2-acylation of **1** with benzaldehyde was not observed under our standard conditions.

On the basis of these observations and the previous reports,[11,15] a tentative mechanism is proposed (Scheme 4). First, the $Cu(OAc)_2$ precatalyst is transformed to the Cu^I catalyst **A** via disproportionation or reduction by the aldehyde. The Cu^I catalyst **A** could then be reoxidized by DTBP to afford the active Cu^{II} species **B** and *tert*-butoxy radical.[16] The coordination-directed C−H cupration of *N*-(2-pyrimidyl)-indoles **1** with Cu^{II} species affords the metalacycle intermediate **C**.[17] The benzyl radical that arises from the reaction between toluene and *tert*-butoxy radical could interact with intermediate **C** to form the desired benzylation product **3** and Cu^I species.[18−20]

Subsequently, we investigated the synthetic applications of the benzylation product **3ia** (Scheme 5). For example, 3-arylindole **4** was generated in 49% yield from phenylboronic acid via Suzuki coupling. Application of a Heck reaction enabled generation of 3-styrylindole **5** in 87% yield. Furthermore, treatment of **3ia** with 3 equiv of benzaldehyde in the presence of 5 mol % $Pd(OAc)_2$ and 4 equiv of TBHP in toluene at 120 °C gave rise to 7-benzoylindole derivative **6** in 44% yield. Similar reaction of **3ia** with 4 equiv of 4-chlorobenzaldehyde produced the corresponding 7-acylation product **7** in 66% yield. In addition, as illustrated in eq 9, removal of a pyrimidyl group from 2-benzylindole **3aa** could be achieved easily by treating **3aa** with NaOEt in DMSO at 110 °C, and the desired product **8** was isolated in 83% yield.

■ CONCLUSIONS

In summary, we have developed an efficient regioselective copper-catalyzed direct coupling of *N*-pyrimidylindoles with alkylarenes. A substituent at the C3-position of indoles has a significant effect on the reaction selectivity. 3-Bromo-*N*-pyrimidylindoles were reacted with various alkylarenes to afford a series of C2-benzylated indoles in moderate to good yields. Furthermore, due to the involvement of bromo and pyrimidyl substituents, the benzylation product **3ia** was readily further functionalized through Pd-catalyzed cross-coupling

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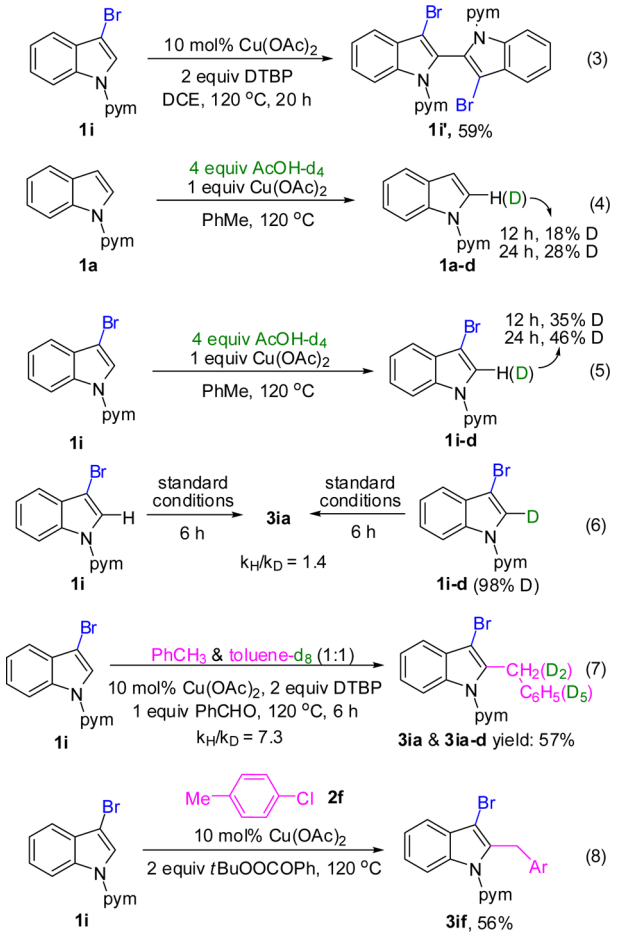
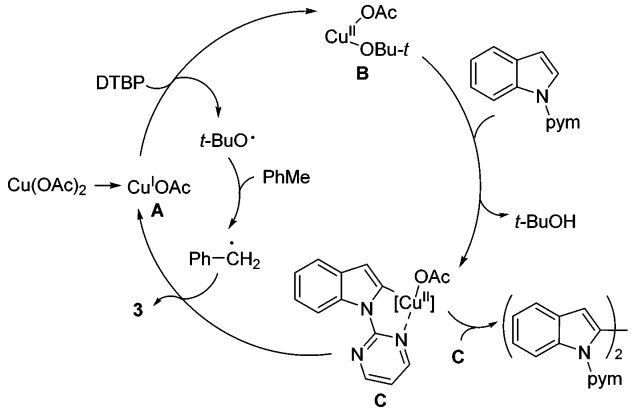
Scheme 3. Preliminary Mechanism Study



Scheme 4. Proposed Mechanism



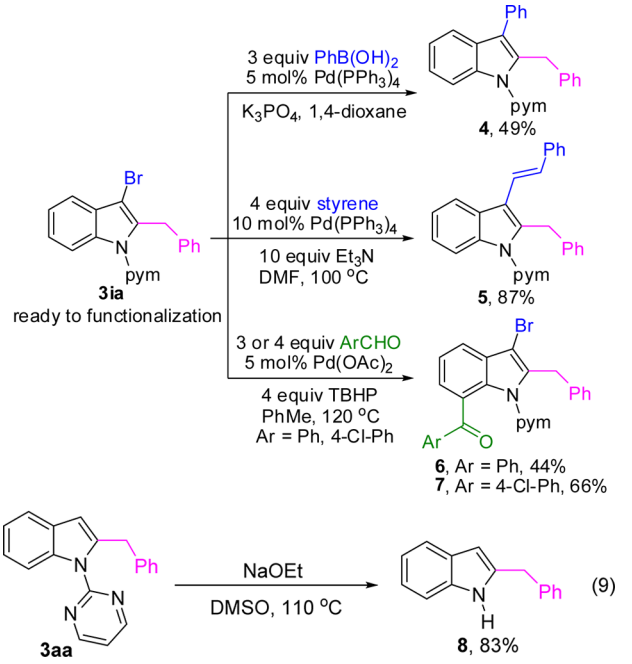
reactions. The present protocol would provide a useful synthetic strategy to access to various biologically active 2-benzylindoles.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under Ar atmosphere. Toluene was distilled from sodium. All other commercial reagents were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz in $CDCl_3$ as solvent. High-resolution mass spectra were recorded on an FT-MS instrument using the ESI technique.

General Procedures for Direct C2-Benzylation of Indoles with Alkylarenes. To a 25 mL tube were added *N*-(2-pyrimidyl)-

Scheme 5. Applications of 3-Bromo-Substituted Indole 3ia



indole **1** (0.2 mmol, 1 equiv), $Cu(OAc)_2$ (0.02 mmol, 10 mol %), benzaldehyde (0.2 mmol, 1 equiv), and 2 mL of alkylarene **2** under the argon atmosphere. After the reaction mixture was stirred at room temperature for 2 min, DTBP (0.4 mmol, 2 equiv) was added dropwise. Then the tube was sealed with a Teflon lined cap, and the reaction mixture was stirred at 120 °C for 20 h. Subsequently, the resulting mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 30:1−5:1) to afford the product **3**.

*2-Benzyl-1-(pyrimidin-2-yl)-1H-indole (**3aa**):* white solid; mp 104−106 °C; yield 45% (25.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, J = 4.8 Hz, 2H), 8.29 (d, J = 8.2 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.26−7.22 (m, 3H), 7.22−7.15 (m, 4H), 7.09 (t, J = 4.8 Hz, 1H), 6.35 (s, 1H), 4.60 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 157.9, 140.5, 139.4, 137.1, 129.1, 129.0, 128.2, 126.0, 122.7, 121.8, 119.9, 116.9, 113.9, 107.9, 36.0; HRMS m/z (ESI) calcd for $C_{19}H_{15}N_3Na$ $(M + Na)^+$ 308.1164, found 308.1156.

*2-(2-Chlorobenzyl)-1-(pyrimidin-2-yl)-1H-indole (**3ab**):* brown solid; mp 97−98 °C; yield 46% (29.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, J = 4.8 Hz, 2H), 8.39 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.29 (dd, J = 9.8, 5.5 Hz, 1H), 7.23 (t, J = 7.4 Hz, 1H), 7.17−7.08 (m, 3H), 7.06 (t, J = 4.8 Hz, 1H), 6.33 (s, 1H), 4.72 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 157.9, 138.8, 137.5, 137.1, 134.0, 130.4, 129.2, 129.2, 127.5, 126.7, 122.9, 121.9, 119.9, 116.8, 114.3, 108.2, 33.8; HRMS m/z (ESI) calcd for $C_{19}H_{14}ClN_3Na$ $(M + Na)^+$ 342.0774, found 342.0770.

*2-(3-Chlorobenzyl)-1-(pyrimidin-2-yl)-1H-indole (**3ac**):* brown liquid; yield 50% (32 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, J = 4.8 Hz, 2H), 8.33 (dd, J = 8.2, 0.7 Hz, 1H), 7.56 (d, J = 7.1 Hz, 1H), 7.28 (ddd, J = 8.5, 7.3, 1.4 Hz, 1H), 7.24−7.20 (m, 2H), 7.15 (dd, J = 5.0, 1.8 Hz, 2H), 7.10 (t, J = 4.8 Hz, 1H), 7.08−7.05 (m, 1H), 6.40 (s, 1H), 4.58 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 158.0, 141.6, 139.4, 137.2, 133.9, 129.4, 129.1, 129.0, 127.1, 126.3, 123.0, 122.0, 120.0, 117.0, 114.2, 108.3, 35.7; HRMS m/z (ESI) calcd for $C_{19}H_{14}ClN_3Na$ $(M + Na)^+$ 342.0774, found 342.0769.

*2-(4-Methylbenzyl)-1-(pyrimidin-2-yl)-1H-indole (**3ad**):* brown liquid; yield 48% (28.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (d, J = 4.8 Hz, 2H), 8.29 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.27−7.23 (m, 1H), 7.20 (t, J = 7.3 Hz, 1H), 7.11−7.04 (m, 5H), 6.33 (s, 1H), 4.55 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 158.0, 140.9, 137.2, 136.2, 135.5, 129.2, 128.9, 122.7, 121.8,

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119.8, 116.9, 113.9, 107.7, 35.5, 21.0; HRMS *m/z* (ESI) calcd for $C_{20}H_{17}N_3Na$ $(M + Na)^+$ 322.1320, found 322.1314.

2-(4-Fluorobenzyl)-1-(pyrimidin-2-yl)-1H-indole (**3ae**): brown liquid; yield 46% (28.1 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.73 (dd, J = 4.7, 1.2 Hz, 2H), 8.30 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 7.21 (t, J = 7.4 Hz, 1H), 7.16−7.12 (m, 2H), 7.09 (t, J = 4.7 Hz, 1H), 6.92 (t, J = 8.0 Hz, 2H), 6.36 (s, 1H), 4.57 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.3 (d, J = 243.8 Hz), 158.1, 158.0, 140.2, 137.2, 135.0 (d, J = 3.2 Hz), 130.3 (d, J = 7.9 Hz), 129.0, 122.9, 121.9, 119.9, 117.0, 114.9 (d, J = 21.2 Hz), 114.0, 107.9, 35.2; HRMS *m/z* (ESI) calcd for $C_{19}H_{14}FN_3Na$ $(M + Na)^+$ 326.1069, found 326.1064.

2-(4-Chlorobenzyl)-1-(pyrimidin-2-yl)-1H-indole (**3af**): yellow solid; mp 109−110 °C; yield 53% (33.6 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, J = 4.7 Hz, 2H), 8.31 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.29−7.25 (m, 1H), 7.23−7.18 (m, 3H), 7.13−7.08 (m, 3H), 6.37 (s, 1H), 4.57 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 157.9, 139.7, 138.0, 137.1, 131.8, 130.2, 129.0, 128.3, 122.9, 121.9, 119.9, 117.0, 114.1, 108.1, 35.4; HRMS *m/z* (ESI) calcd for $C_{19}H_{14}ClN_3Na$ $(M + Na)^+$ 342.0774, found 342.0770.

2-(4-Bromobenzyl)-1-(pyrimidin-2-yl)-1H-indole (**3ag**): brown solid; mp 112−113 °C; yield 54% (39.2 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, J = 4.8 Hz, 2H), 8.32 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 7.1 Hz, 1H), 7.39−7.32 (m, 2H), 7.29−7.25 (m, 1H), 7.21 (td, J = 7.4, 0.9 Hz, 1H), 7.10 (t, J = 4.8 Hz, 1H), 7.06 (d, J = 8.3 Hz, 2H), 6.37 (s, 1H), 4.55 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 158.0, 139.6, 138.5, 137.2, 131.3, 130.6, 129.0, 123.0, 122.0, 119.93, 119.85, 117.0, 114.1, 108.2, 35.5; HRMS *m/z* (ESI) calcd for $C_{19}H_{14}BrN_3Na$ $(M + Na)^+$ 386.0269, found 386.0265.

4-((1-(Pyrimidin-2-yl)-1H-indol-2-yl)methyl)benzonitrile (**3ah**): yellow liquid; yield 58% (36 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 4.6 Hz, 2H), 8.36 (d, J = 8.3 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 7.9 Hz, 2H), 7.31−7.23 (m, 4H), 7.08 (t, J = 4.7 Hz, 1H), 6.43 (s, 1H), 4.67 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 157.9, 145.5, 138.2, 137.1, 132.0, 129.5, 128.9, 123.3, 122.1, 120.0, 119.0, 117.0, 114.4, 109.9, 108.8, 36.2; HRMS *m/z* (ESI) calcd for $C_{20}H_{14}N_4Na$ $(M + Na)^+$ 333.1116, found 333.1111.

2-(4-Chlorobenzyl)-5-methoxy-1-(pyrimidin-2-yl)-1H-indole (**3bf**): brown liquid; yield 45% (31.8 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, J = 4.8 Hz, 2H), 8.30 (d, J = 9.1 Hz, 1H), 7.22−7.19 (m, 2H), 7.12 (d, J = 8.5 Hz, 2H), 7.05 (t, J = 4.8 Hz, 1H), 7.02 (d, J = 2.5 Hz, 1H), 6.91 (dd, J = 9.1, 2.6 Hz, 1H), 6.29 (s, 1H), 4.57 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 157.9, 155.5, 140.5, 138.1, 132.0, 131.7, 130.2, 129.8, 128.3, 116.7, 115.4, 111.9, 108.2, 102.3, 55.7, 35.7; HRMS *m/z* (ESI) calcd for $C_{20}H_{16}ClN_3ONa$ $(M + Na)^+$ 372.0880, found 372.0875.

2-(4-Chlorobenzyl)-5-methyl-1-(pyrimidin-2-yl)-1H-indole (**3cf**): brown liquid; yield 37% (24.6 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 4.8 Hz, 2H), 8.24 (d, J = 8.5 Hz, 1H), 7.33 (s, 1H), 7.23−7.17 (m, 2H), 7.13−7.08 (m, 3H), 7.05 (t, J = 4.8 Hz, 1H), 6.31 (s, 1H), 4.57 (s, 2H), 2.47 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 157.9, 139.8, 138.1, 135.4, 131.7, 131.3, 130.2, 129.3, 128.3, 124.3, 119.8, 116.7, 114.0, 108.0, 35.5, 21.3; HRMS *m/z* (ESI) calcd for $C_{20}H_{16}ClN_3Na$ $(M + Na)^+$ 356.0930, found 356.0926.

5-Chloro-2-(4-chlorobenzyl)-1-(pyrimidin-2-yl)-1H-indole (**3df**): yellow solid; mp 75−78 °C; yield 45% (31.5 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, J = 4.8 Hz, 2H), 8.26 (d, J = 8.9 Hz, 1H), 7.49 (d, J = 2.1 Hz, 1H), 7.21 (d, J = 8.4 Hz, 3H), 7.11 (dd, J = 11.4, 6.6 Hz, 3H), 6.29 (s, 1H), 4.56 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 157.8, 141.3, 137.6, 135.5, 131.9, 130.2, 130.1, 128.4, 127.4, 123.0, 119.3, 117.3, 115.4, 107.4, 35.5; HRMS *m/z* (ESI) calcd for $C_{19}H_{13}Cl_2N_3Na$ $(M + Na)^+$ 376.0384, found 376.0380.

2-(4-Chlorobenzyl)-1-(pyrimidin-2-yl)-1H-indole-5-carbonitrile (**3ef**): pale yellow solid; mp 110−111 °C; yield 42% (28.8 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, J = 4.8 Hz, 2H), 8.32 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 1.1 Hz, 1H), 7.49 (dd, J = 8.7, 1.6 Hz, 1H), 7.24−7.18 (m, 3H), 7.09 (d, J = 8.4 Hz, 2H), 6.39 (s, 1H), 4.56 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.3, 157.4, 142.5, 138.8, 137.0, 132.2, 130.2, 128.8, 128.5, 126.0, 124.9, 120.3, 118.1, 114.8, 107.5, 105.0, 35.2; HRMS *m/z* (ESI) calcd for $C_{20}H_{13}ClN_4Na$ $(M + Na)^+$ 367.0726, found 367.0722.

Methyl 2-(4-chlorobenzyl)-1-(pyrimidin-2-yl)-1H-indole-5-carboxylate (**3ff**): brown solid; mp 100−102 °C; yield 49% (37 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, J = 4.8 Hz, 2H), 8.28 (dd, J = 5.0, 3.5 Hz, 2H), 7.96 (dd, J = 8.9, 1.2 Hz, 1H), 7.20 (d, J = 8.3 Hz, 2H), 7.14 (t, J = 4.8 Hz, 1H), 7.08 (d, J = 8.3 Hz, 2H), 6.43 (s, 1H), 4.55 (s, 2H), 3.95 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 158.1, 157.6, 141.3, 139.7, 137.4, 131.9, 130.2, 128.6, 128.4, 124.3, 123.8, 122.4, 117.6, 113.6, 108.4, 51.8, 35.2; HRMS *m/z* (ESI) calcd for $C_{21}H_{16}ClN_3O_2Na$ $(M + Na)^+$ 400.0829, found 400.0826.

2-(4-Chlorobenzyl)-3-methyl-1-(pyrimidin-2-yl)-1H-indole (**3gf**): yellow solid; yield 56% (37.2 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, J = 4.8 Hz, 2H), 8.34−8.28 (m, 1H), 7.62−7.60 (m, 1H), 7.33−7.26 (m, 2H), 7.13−7.10 (m, 2H), 7.01 (t, J = 4.8 Hz, 1H), 6.97 (d, J = 8.6 Hz, 2H), 4.64 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 157.9, 138.6, 136.4, 134.1, 131.3, 130.2, 129.4, 128.1, 123.3, 121.6, 118.2, 116.6, 114.8, 113.9, 31.5, 9.0; HRMS *m/z* (ESI) calcd for $C_{20}H_{16}ClN_3Na$ $(M + Na)^+$ 356.0930, found 356.0923.

3-Chloro-2-(4-chlorobenzyl)-1-(pyrimidin-2-yl)-1H-indole (**3hf**): white solid; mp 99−100 °C ; yield 77% (54.7 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, J = 4.8 Hz, 2H), 8.38−8.32 (m, 1H), 7.72−7.67 (m, 1H), 7.39−7.31 (m, 2H), 7.14−7.09 (m, 2H), 7.07 (t, J = 4.8 Hz, 1H), 7.01 (d, J = 8.6 Hz, 2H), 4.74 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 157.5, 137.4, 135.3, 134.2, 131.6, 129.5, 128.2, 126.7, 124.4, 122.5, 117.9, 117.3, 114.4, 111.6, 31.4; HRMS *m/z* (ESI) calcd for $C_{19}H_{13}Cl_2N_3Na$ $(M + Na)^+$ 376.0384, found 376.0380.

3-Bromo-2-(4-chlorobenzyl)-1-(pyrimidin-2-yl)-1H-indole (**3if**): yellow solid; mp 115−117 °C; yield 88% (70.2 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, J = 4.8 Hz, 2H), 8.35−8.30 (m, 1H), 7.68−7.65 (m, 1H), 7.39−7.33 (m, 2H), 7.15−7.11 (m, 2H), 7.07 (t, J = 4.8 Hz, 1H), 7.01 (d, J = 8.6 Hz, 2H), 4.76 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 157.4, 137.3, 135.90, 135.88, 131.6, 129.5, 128.2, 128.1, 124.4, 122.6, 119.0, 117.4, 114.3, 99.7, 32.5; HRMS *m/z* (ESI) calcd for $C_{19}H_{13}BrClN_3Na$ $(M + Na)^+$ 419.9879, found 419.9877.

2-(4-Chlorobenzyl)-1-(pyrimidin-2-yl)-1H-indole-3-carbonitrile (**3kf**): white solid; yield 77% (53.2 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, J = 4.8 Hz, 2H), 8.19−8.10 (m, 1H), 7.81−7.74 (m, 1H), 7.41−7.35 (m, 2H), 7.24 (t, J = 4.8 Hz, 1H), 7.14−7.07 (m, 2H), 6.96 (d, J = 8.5 Hz, 2H), 4.80 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 156.7, 147.4, 136.0, 135.7, 132.3, 129.6, 128.5, 127.0, 125.0, 123.7, 119.1, 118.9, 115.4, 114.4, 92.4, 33.2; HRMS *m/z* (ESI) calcd for $C_{20}H_{13}ClN_4Na$ $(M + Na)^+$ 367.0726, found 367.0721.

2-Benzyl-3-bromo-1-(pyrimidin-2-yl)-1H-indole (**3ia**): pale yellow solid; mp 115−117 °C; yield 82% (59.8 mg, for the reaction without PhCHO); ^1H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, J = 4.8 Hz, 2H), 8.26−8.20 (m, 1H), 7.65−7.60 (m, 1H), 7.35−7.30 (m, 2H), 7.12 (t, J = 7.3 Hz, 2H), 7.10−7.06 (m, 2H), 7.05−7.01 (m, 2H), 4.79 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 157.5, 138.7, 136.5, 136.0, 128.23, 128.15, 128.1, 125.9, 124.2, 122.5, 119.0, 117.4, 114.0, 99.5, 33.0; HRMS *m/z* (ESI) calcd for $C_{19}H_{14}BrN_3Na$ $(M + Na)^+$ 386.0269, found 386.0266.

3-Bromo-2-(4-methylbenzyl)-1-(pyrimidin-2-yl)-1H-indole (**3id**): pale brown solid; mp 86−88 °C; yield 89% (67.3 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 4.8 Hz, 2H), 8.27−8.23 (m, 1H), 7.66−7.62 (m, 1H), 7.35−7.32 (m, 2H), 7.08 (t, J = 4.8 Hz, 1H), 6.93 (s, 4H), 4.76 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 157.5, 136.8, 136.0, 135.6, 135.3, 128.8, 128.2, 128.0, 124.1, 122.4, 119.0, 117.4, 114.0, 99.3, 32.5, 20.9; HRMS *m/z* (ESI) calcd for $C_{20}H_{16}BrN_3Na$ $(M + Na)^+$ 400.0425, found 400.0423.

3-Bromo-2-(2-methylbenzyl)-1-(pyrimidin-2-yl)-1H-indole (**3ii**): white solid; mp 182−186 °C; yield 87% (66.0 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, J = 4.8 Hz, 2H), 8.34−8.25 (m, 1H), 7.70−7.62 (m, 1H), 7.40−7.32 (m, 2H), 7.09 (d, J = 7.4 Hz, 1H), 6.99 (dd, J = 10.1, 5.5 Hz, 2H), 6.89 (t, J = 7.4 Hz, 1H), 6.68 (d, J = 7.6 Hz, 1H), 4.72 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 157.9, 157.5, 136.9, 136.0, 135.9, 135.6, 129.6, 128.3, 127.2, 125.78, 125.76, 124.2, 122.5, 118.9, 117.3, 114.1, 100.0, 30.6, 19.7; HRMS *m/z* (ESI) calcd for $C_{20}H_{16}BrN_3Na$ $(M + Na)^+$ 400.0425, found 400.0424.

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*3-Bromo-2-(3,5-dimethylbenzyl)-1-(pyrimidin-2-yl)-1H-indole (**3ij**):* brown liquid; yield 88% (69.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, J = 4.8 Hz, 2H), 8.26−8.20 (m, 1H), 7.67−7.63 (m, 1H), 7.36−7.31 (m, 2H), 7.09 (t, J = 4.8 Hz, 1H), 6.71 (s, 1H), 6.65 (s, 2H), 4.72 (s, 2H), 2.17 (s, 6H); ^{13}C NMR (126 MHz, CDCl3) δ 158.0, 157.6, 138.5, 137.5, 136.8, 136.0, 128.2, 127.6, 126.0, 124.1, 122.4, 119.0, 117.4, 113.9, 99.1, 32.7, 21.2; HRMS m/z (ESI) calcd for $C_{21}H_{18}BrN_3Na$ (M + Na)$^+$ 414.0582, found 414.0573.

*3-Bromo-2-(2-chlorobenzyl)-1-(pyrimidin-2-yl)-1H-indole (**3ib**):* pale yellow solid; mp 163−164 °C; yield 71% (56.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, J = 4.8 Hz, 2H), 8.42−8.34 (m, 1H), 7.70−7.62 (m, 1H), 7.40−7.34 (m, 2H), 7.32 (dd, J = 7.9, 1.3 Hz, 1H), 7.07−6.94 (m, 3H), 6.82 (dd, J = 7.7, 1.4 Hz, 1H), 4.85 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 157.4, 136.6, 135.8, 135.1, 133.4, 129.0, 128.8, 128.2, 127.1, 126.6, 124.4, 122.6, 119.0, 117.2, 114.6, 100.6, 31.1; HRMS m/z (ESI) calcd for $C_{19}H_{13}BrClN_3Na$ (M + Na)$^+$ 419.9879, found 419.9876.

*3-Bromo-2-(3-chlorobenzyl)-1-(pyrimidin-2-yl)-1H-indole (**3ic**):* yellow solid; mp 96−98 °C; yield 79% (62.7 mg, for the reaction without PhCHO); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 4.8 Hz, 2H), 8.35−8.25 (m, 1H), 7.69−7.60 (m, 1H), 7.40−7.30 (m, 2H), 7.15−7.01 (m, 4H), 6.96−6.91 (m, 1H), 4.75 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 157.5, 140.9, 135.9, 135.6, 133.9, 129.4, 128.39, 128.2, 126.3, 126.1, 124.4, 122.6, 119.1, 117.5, 114.3, 99.9, 32.9; HRMS m/z (ESI) calcd for $C_{19}H_{13}BrClN_3Na$ (M + Na)$^+$ 419.9879, found 419.9874.

*3-Bromo-2-(4-fluorobenzyl)-1-(pyrimidin-2-yl)-1H-indole (**3ie**):* white solid; mp 106−107 °C; yield 97% (73.9 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, J = 4.8 Hz, 2H), 8.26 (ddd, J = 5.0, 2.3, 0.6 Hz, 1H), 7.67−7.59 (m, 1H), 7.34 (ddd, J = 4.8, 2.1, 1.1 Hz, 2H), 7.09 (t, J = 4.8 Hz, 1H), 7.03−6.98 (m, 2H), 6.85−6.78 (m, 2H), 4.75 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.2 (d, J = 243.8 Hz), 158.1, 157.5, 136.3, 135.9, 134.3 (d, J = 3.2 Hz), 129.5 (d, J = 7.9 Hz), 128.2, 124.3, 122.6, 119.1, 117.5, 114.9 (d, J = 21.3 Hz), 114.1, 99.5, 32.3; HRMS m/z (ESI) calcd for $C_{19}H_{13}BrFN_3Na$ (M + Na)$^+$ 404.0175, found 404.0169.

*3-Bromo-2-(4-bromobenzyl)-1-(pyrimidin-2-yl)-1H-indole (**3ig**):* pale yellow solid; mp 133−134 °C; yield 86% (76.0 mg, for the reaction without PhCHO); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, J = 4.8 Hz, 2H), 8.32 (dd, J = 6.0, 3.2 Hz, 1H), 7.66 (dd, J = 5.9, 3.2 Hz, 1H), 7.41−7.32 (m, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.07 (t, J = 4.8 Hz, 1H), 6.95 (d, J = 8.2 Hz, 2H), 4.74 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 157.4, 137.8, 135.9, 135.8, 131.2, 129.9, 128.1, 124.4, 122.6, 119.7, 119.1, 117.5, 114.3, 99.8, 32.7; HRMS m/z (ESI) calcd for $C_{19}H_{13}Br_2N_3Na$ (M + Na)$^+$ 463.9374, found 463.9367.

*4-((3-Bromo-1-(pyrimidin-2-yl)-1H-indol-2-yl)methyl)benzonitrile (**3ih**):* white solid; mp 123−125 °C; yield 78% (60.4 mg, for the reaction without PhCHO); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, J = 4.8 Hz, 2H), 8.38−8.33 (m, 1H), 7.66−7.62 (m, 1H), 7.47−7.43 (m, 2H), 7.39−7.33 (m, 2H), 7.19 (d, J = 8.5 Hz, 2H), 7.10 (t, J = 4.8 Hz, 1H), 4.82 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 157.4, 144.7, 135.9, 134.7, 132.0, 128.9, 128.1, 124.7, 122.8, 119.2, 118.9, 117.5, 114.6, 109.8, 100.5, 33.6; HRMS m/z (ESI) calcd for $C_{20}H_{13}BrN_4Na$ (M + Na)$^+$ 411.0221, found 411.0216.

*Methyl 4-((3-bromo-1-(pyrimidin-2-yl)-1H-indol-2-yl)methyl)-benzoate (**3ik**):* white solid; mp 167−168 °C; yield 80% (67.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, J = 4.8 Hz, 2H), 8.32−8.30 (m, 1H), 7.82 (d, J = 8.2 Hz, 2H), 7.67−7.62 (m, 1H), 7.38−7.31 (m, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.07 (t, J = 4.5 Hz, 1H), 4.83 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 158.0, 157.3, 144.4, 135.9, 135.4, 129.4, 128.4, 128.1, 127.8, 124.4, 122.6, 119.0, 117.4, 114.3, 99.9, 51.9, 33.4; HRMS m/z (ESI) calcd for $C_{21}H_{16}BrN_3O_2Na$ (M + Na)$^+$ 444.0324, found 444.0320.

*1-(4-((3-Bromo-1-(pyrimidin-2-yl)-1H-indol-2-yl)methyl)phenyl)-ethanone (**3il**):* brown solid; mp 104−106 °C; yield 66% (53.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, J = 4.7 Hz, 2H), 8.34−8.29 (m, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.66−7.62 (m, 1H), 7.38−7.32 (m, 2H), 7.16 (d, J = 8.2 Hz, 2H), 7.08 (t, J = 4.7 Hz, 1H), 4.83 (s, 2H), 2.51 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 158.1, 157.4, 144.7, 135.9, 135.4, 135.1, 128.30, 128.28, 128.2, 124.5, 122.7, 119.1, 117.5, 114.4, 100.1, 33.4, 26.5; HRMS m/z (ESI) calcd for $C_{21}H_{16}BrN_3ONa$ (M + Na)$^+$ 428.0374, found 428.0373.

*3-Bromo-1-(pyrimidin-2-yl)-2-(thiophen-2-ylmethyl)-1H-indole (**3im**):* yellow solid; mp 92−93 °C; yield 63% (46.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, J = 4.8 Hz, 2H), 8.35−8.30 (m, 1H), 7.64−7.59 (m, 1H), 7.37−7.29 (m, 2H), 7.15 (t, J = 4.8 Hz, 1H), 7.01 (dd, J = 5.1, 1.2 Hz, 1H), 6.78 (dd, J = 5.1, 3.5 Hz, 1H), 6.73−6.69 (m, 1H), 4.98 (d, J = 0.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 157.6, 141.2, 136.0, 135.8, 128.2, 126.4, 125.1, 124.4, 123.6, 122.6, 119.1, 117.5, 114.4, 99.1, 27.9; HRMS m/z (ESI) calcd for $C_{17}H_{12}BrN_3SNa$ (M + Na)$^+$ 391.9833, found 391.9829.

*3-Bromo-2-(1-phenylethyl)-1-(pyrimidin-2-yl)-1H-indole (**3in**):* pale brown liquid; yield 37% (29.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, J = 4.8 Hz, 2H), 7.92 (dd, J = 5.8, 3.3 Hz, 1H), 7.60 (dd, J = 5.7, 3.2 Hz, 1H), 7.29 (dt, J = 4.1, 2.3 Hz, 2H), 7.23 (d, J = 7.8 Hz, 2H), 7.19 (t, J = 7.6 Hz, 2H), 7.14 (t, J = 4.8 Hz, 1H), 7.10 (t, J = 7.1 Hz, 1H), 5.17 (q, J = 7.2 Hz, 1H), 1.98 (d, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.3, 157.5, 142.9, 140.5, 135.7, 128.5, 127.8, 127.3, 125.7, 124.0, 122.3, 118.8, 118.0, 112.8, 97.1, 36.5, 18.0; HRMS m/z (ESI) calcd for $C_{20}H_{16}BrN_3Na$ (M + Na)$^+$ 400.0425, found 400.0421.

*3-Bromo-2-(4-chlorobenzyl)-5-methoxy-1-(pyrimidin-2-yl)-1H-indole (**3if**):* white solid; mp 123−124 °C, yield 66% (56.9 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, J = 4.8 Hz, 2H), 8.26 (d, J = 9.1 Hz, 1H), 7.14−7.10 (m, 2H), 7.07 (d, J = 2.5 Hz, 1H), 7.05 (t, J = 4.8 Hz, 1H), 7.01 (d, J = 8.5 Hz, 2H), 6.97 (dd, J = 9.1, 2.6 Hz, 1H), 4.74 (s, 2H), 3.94 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 157.4, 156.1, 137.4, 136.4, 131.6, 130.6, 129.5, 128.9, 128.2, 117.2, 115.8, 113.9, 100.9, 99.7, 55.8, 32.8; HRMS m/z (ESI) calcd for $C_{20}H_{15}BrClN_3ONa$ (M + Na)$^+$ 449.9985, found 449.9985.

*3-Bromo-2-(4-chlorobenzyl)-5-methyl-1-(pyrimidin-2-yl)-1H-indole (**3mf**).* white solid; mp 109−110 °C; yield 75% (62.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, J = 4.8 Hz, 2H), 8.21 (d, J = 8.5 Hz, 1H), 7.43 (s, 1H), 7.17 (d, J = 8.5 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.05 (t, J = 4.8 Hz, 1H), 7.00 (d, J = 8.4 Hz, 2H), 4.75 (s, 2H), 2.53 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 157.5, 137.5, 135.9, 134.2, 132.3, 131.5, 129.5, 128.3, 128.2, 125.9, 118.8, 117.2, 114.3, 99.6, 32.7, 21.3; HRMS m/z (ESI) calcd for $C_{20}H_{15}BrClN_3Na$ (M + Na)$^+$ 434.0036, found 434.0033.

*Methyl 3-bromo-2-(4-chlorobenzyl)-1-(pyrimidin-2-yl)-1H-indole-5-carboxylate (**3nf**):* white solid; mp 141−143 °C; yield 88% (80.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 4.8 Hz, 2H), 8.35 (dd, J = 1.7, 0.5 Hz, 1H), 8.25 (dd, J = 8.8, 0.5 Hz, 1H), 8.02 (dd, J = 8.8, 1.8 Hz, 1H), 7.14 (t, J = 4.8 Hz, 1H), 7.10 (d, J = 8.5 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H), 4.72 (s, 2H), 3.99 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4, 158.2, 157.1, 138.5, 137.5, 136.8, 131.8, 129.4, 128.3, 127.9, 125.6, 124.6, 121.5, 118.1, 114.0, 99.9, 52.0, 32.5; HRMS m/z (ESI) calcd for $C_{21}H_{15}BrClN_3O_2Na$ (M + Na)$^+$ 477.9934, found 477.9939.

*3,3′-Dibromo-1,1′-di(pyrimidin-2-yl)-1H,1′H-2,2′-biindole (**1i′**).* yellow solid; mp 222−223 °C; yield 59% (32.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, J = 8.4 Hz, 2H), 8.38 (d, J = 4.8 Hz, 4H), 7.70 (d, J = 7.9 Hz, 2H), 7.47−7.44 (m, 2H), 7.41−7.35 (m, 2H), 6.87 (t, J = 4.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.7, 157.3, 135.6, 129.0, 128.6, 125.1, 122.6, 119.6, 116.7, 115.4, 102.4; HRMS m/z (ESI) calcd for $C_{24}H_{14}Br_2N_6Na$ (M + Na)$^+$ 566.9544, found 566.9547.

Experimental Procedure for the Synthesis of 2-Benzyl-3-phenyl-1-(pyrimidin-2-yl)-1*H*-indole (4). To a 25 mL tube were added **3ia** (0.2 mmol, 1 equiv), $PhB(OH)_2$ (0.8 mmol, 4 equiv), $Pd(PPh_3)_4$ (0.01 mmol, 5 mol %), K_3PO_4 (0.6 mmol, 3 equiv), and 1 mL of 1,4-dioxane under Ar atmosphere. The tube was sealed with a Teflon-lined cap, and the reaction mixture was stirred at 70 °C for 18 h. The resulting mixture was concentrated under vacuum, and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1−10:1) to afford the desired product **4**: 35.3 mg, yield 49%; white solid; mp 140−141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, J = 4.8 Hz, 2H), 8.22 (d, J = 8.3 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.59 (dd, J = 8.1, 1.2 Hz, 2H), 7.49 (t, J = 7.7 Hz, 2H), 7.38 (t, J = 7.4 Hz, 1H), 7.34−7.29 (m, 1H), 7.27−7.23

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(m, 1H), 7.06 (t, J = 7.3 Hz, 2H), 7.03−6.97 (m, 2H), 6.92 (d, J = 7.0 Hz, 2H), 4.74 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 157.9, 140.0, 136.5, 135.1, 134.4, 130.2, 129.1, 128.6, 127.98, 127.96, 126.9, 125.5, 123.5, 122.9, 121.7, 119.2, 117.1, 113.5, 32.4; HRMS m/z (ESI) calcd for $C_{25}H_{19}N_3Na$ $(M + Na)^+$ 384.1477, found 384.1476.

Experimental Procedure for the Synthesis of 2-Benzyl-1-(pyrimidin-2-yl)-3-styryl-1*H*-indole (5). To a 25 mL tube were added **3ia** (0.2 mmol, 1 equiv), styrene (0.8 mmol, 4 equiv), $Pd(PPh_3)_4$ (0.02 mmol, 10 mol %), Et_3N (2 mmol, 10 equiv), and 1.5 mL of DMF under Ar atmosphere. Then the tube was sealed with a Teflon lined cap, and the reaction mixture was stirred at 100 °C for 36 h. The resulting mixture was concentrated under vacuum, and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the desired product **5**: 67.6 mg, yield 87%; pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 4.8 Hz, 2H), 8.23−8.20 (m, 1H), 8.12−8.10 (m, 1H), 7.57 (d, J = 7.3 Hz, 2H), 7.46 (d, J = 16.4 Hz, 1H), 7.40 (t, J = 7.7 Hz, 2H), 7.38−7.27 (m, 4H), 7.15 (t, J = 7.3 Hz, 2H), 7.11−7.02 (m, 4H), 4.83 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 157.7, 139.4, 138.4, 137.5, 137.0, 129.1, 128.6, 128.2, 128.1, 127.5, 127.0, 126.0, 125.8, 123.5, 122.3, 120.9, 119.9, 117.4, 116.9, 113.6, 32.0; HRMS m/z (ESI) calcd for $C_{27}H_{21}N_3Na$ $(M + Na)^+$ 410.1633, found 410.1631.

*Experimental Procedures for the C7-Acylation of **3ia** with Aldehydes.* To a 25 mL tube were added **3ia** (0.2 mmol, 1 equiv), aldehyde (PhCHO: 0.6 mmol; *p*-Cl-PhCHO: 0.8 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol %), TBHP in decane (0.8 mmol, 4 equiv), and 0.4 mL of toluene under Ar atmosphere. Then the tube was sealed with a Teflon lined cap, and the reaction mixture was stirred at 120 °C for 18 h. Finally, the resulting mixture was concentrated under vacuum, and the residue was purified by column chromatography on silica gel or by PTLC (petroleum ether/ethyl acetate = 5:1) to afford the desired product.

*(2-benzyl-3-bromo-1-(pyrimidin-2-yl)-1H-indol-7-yl) (phenyl)-methanone (**6**):* pale yellow liquid; yield 44% (30.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (dd, J = 4.8, 0.5 Hz, 2H), 7.82 (dd, J = 7.2, 1.3 Hz, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.36 (dq, J = 15.2, 7.7 Hz, 4H), 7.04 (t, J = 7.4 Hz, 2H), 6.99 (t, J = 7.1 Hz, 1H), 6.91 (d, J = 7.4 Hz, 2H), 6.84 (td, J = 4.8, 0.5 Hz, 1H), 4.63 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.2, 157.9, 157.6, 137.9, 137.6, 137.3, 133.3, 132.5, 129.9, 129.3, 128.1, 128.05, 128.03, 125.9, 125.0, 122.4, 121.2, 118.5, 97.3, 31.9; HRMS m/z (ESI) calcd for $C_{26}H_{18}BrN_3ONa$ $(M + Na)^+$ 490.0531, found 490.0532.

*(2-Benzyl-3-bromo-1-(pyrimidin-2-yl)-1H-indol-7-yl)(4-chlorophenyl)methanone (**7**):* yellow solid; mp 160−162 °C; yield 66% (66.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, J = 4.8 Hz, 2H), 7.82 (dd, J = 7.4, 1.7 Hz, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.37−7.30 (m, 4H), 7.06−6.97 (m, 3H), 6.91 (d, J = 7.0 Hz, 2H), 6.87 (t, J = 4.8 Hz, 1H), 4.63 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.1, 157.9, 157.6, 139.0, 138.1, 137.6, 135.7, 133.2, 131.3, 129.4, 128.5, 128.1, 128.0, 126.0, 125.7, 124.6, 122.6, 121.3, 118.6, 97.4, 31.9; HRMS m/z (ESI) calcd for $C_{26}H_{17}BrClN_3ONa$ $(M + Na)^+$ 524.0141, found 524.0135.

Experimental Procedure for the Synthesis of 2-Benzyl-1*H*-indole (8). To a 25 mL tube were added **3aa** (0.2 mmol, 1 equiv), EtONa (0.8 mmol, 4 equiv), and 2 mL of DMSO under Ar atmosphere. Then the tube was sealed with a Teflon lined cap, and the reaction mixture was stirred at 110 °C for 24 h. After the reaction was complete, 6 mL of water was added, and the reaction mixture was stirred in an ice−water bath for 30 min. Then the reaction mixture was diluted with EtOAc, washed with water, and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to afford the desired product **8**: 34.2 mg; yield 83%; white solid; mp 82−84 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.41−7.33 (m, 2H), 7.33−7.26 (m, 4H), 7.18−7.14 (m, 1H), 7.14−7.10 (m, 1H), 6.37 (s, 1H), 4.16 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 137.8, 136.3, 128.8, 128.7, 126.7, 121.3, 120.0, 119.7, 110.4, 101.1, 34.7; HRMS m/z (ESI) calcd for $C_{15}H_{13}NNa$ $(M + Na)^+$ 230.0946, found 230.0946.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01935.

Text, figures, and tables giving optimization and mechanism study details; NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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