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Copper(II)-Catalyzed Direct C−H (Hetero)arylation at the C3 Position of Indoles Assisted by a Removable *N,N*-Bidentate Auxiliary Moiety

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ABSTRACT: The regioselective arylation of inert C3−H bonds in indoles reacting with arylboronates *via* effective copper-mediated catalysis with the aid of a facile and removable 2-pyridinylisopropyl (PIP) group without ligand participation is reported. This newly established method features high compatibility with diverse functional groups between coupling partners, including both indole substrates and arylboron reagents, consequentially leading to operational simplicity and providing access to generate the desired arylated products in good to excellent yields of up to 97%. Synthetically, the PIP-derived amide moiety could subsequently be readily removed under mild reaction conditions to produce useful indole carboxylic acids for further transformation.

INTRODUCTION

Indole has been deemed a critical and privileged structural scaffold in drug discovery and is frequently encountered in bioactive natural products and drug candidates, such as the compounds listed in Figure 1. This moiety therefore occupies a principal position in the production of functional group-substituted indoles in organic synthesis and medicinal chemistry.[1] In this context, a growing number of important studies have explored indole C3 functionalization.[2] In particular, C3-arylated indoles[3] are often produced from synthesis reactions using typical compounds, considering the biological significance of 3-arylindole derivatives (Figure 1).[4] Among the available synthetic protocols, transition-metal-catalyzed aromatic C−H activation strategies have been used to synthesize 3-arylated indoles in a site-selective manner.[1a,5] Pioneering studies were conducted with several classes of coupling partners, most of which were aryl halides, to develop diverse methods for oxidative arylation involving C−H activation/C−C formation sequences at the C-3 position of indoles.[6] In addition to halides, other functional groups or heterocycles have been shown to be suitable for this transformation.[7] In 2008, Gaunt et al. reported a seminal study using [TRIP-I-Ar]OTf salts in a Cu-catalyzed process, which successfully enabled high C3 site selectivity for indole arylation under mild conditions, though minor C2-arylated products were also provided.[7a] Similarly, Larrosa[7b] and Su[7c] found that ortho-substituted benzoic acids were useful arylating reagents for Pd-mediated decarboxylative cross-coupling reactions for the regioselective C3 arylation of indoles. However, these protocols produced C3-arylated indoles under uneconomical or harsh conditions (such as using costly reagents or high temperatures) or in relatively low yields.

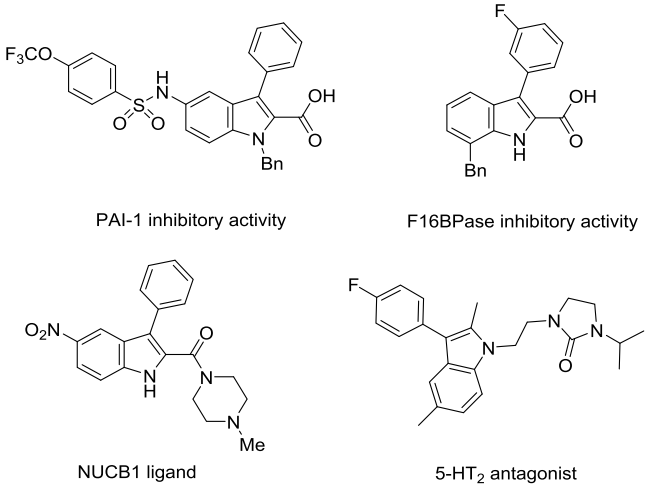

Figure 1. Selected biologically active indole-containing compounds.

Recently, chelation assistance has become an engaging and reliable strategy for the ortho-selective C−H arylation of benzamides with organometallic reagents to generate biaryl derivatives, in which an *N,N*-bidentate directing group plays a pivotal role.[8] A typical case is the $Cu(OAc)_2$-catalyzed coupling of aromatic C−H bonds with inexpensive arylboro-

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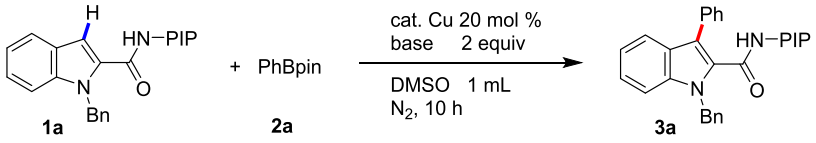
Table 1. Copper-Catalyzed Phenylation of Compound 1a[a]



entry	solvent	catalyst	oxidant	base	yield[b] (%)
1	DMSO	$Cu(OAc)_2$	Ag_2O	Na_2CO_3	52
2	PhMe	$Cu(OAc)_2$	Ag_2O	Na_2CO_3	trace
3	DMF	$Cu(OAc)_2$	Ag_2O	Na_2CO_3	38
4	DMSO	$CuBr_2$	Ag_2O	Na_2CO_3	43
5	DMSO	CuI	Ag_2O	Na_2CO_3	29
6	DMSO	CuBr	Ag_2O	Na_2CO_3	13
7	DMSO	CuCl	Ag_2O	Na_2CO_3	12
8	DMSO	CuTc	Ag_2O	Na_2CO_3	trace
9	DMSO	$Cu(OAc)_2$	Ag_3PO_4	Na_2CO_3	16
10	DMSO	$Cu(OAc)_2$	Ag_2CO_3	Na_2CO_3	trace
11	DMSO	$Cu(OAc)_2$	Ag_2SO_4	Na_2CO_3	trace
12	DMSO	$Cu(OAc)_2$	Ag_2O	K_2CO_3	44
13	DMSO	$Cu(OAc)_2$	Ag_2O	NaOAc	82
14	DMSO	$Cu(OAc)_2$	Ag_2O	Cs_2CO_3	trace
15	DMSO	$Cu(OAc)_2$	Ag_2O	Et_3N	38
16	DMSO	$Cu(OAc)_2$	Ag_2O	KOAc	73
17	DMSO	$Cu(OAc)_2$	Ag_2O	*t*-BuOK	trace
18[c]	DMSO	$Cu(OAc)_2$	Ag_2O	NaOAc	76
19[d]	DMSO	$Cu(OAc)_2$	Ag_2O	NaOAc	89
20	DMSO	$Cu(OAc)_2$		NaOAc	NR
21	DMSO		Ag_2O	NaOAc	NR

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.25 mmol), oxidant (0.15 mmol), base (0.2 mmol), DMSO (1.0 mL), 100 °C, N_2, 10 h. [b]Isolated yield. [c]Reaction temperature, 130 °C. [d]Reaction temperature, 70 °C.

nates using an amide-oxazoline directing group to achieve *ortho*-arylation of benzamides *via* transmetallation at a relatively low temperature.[8a] In addition, organoboron compounds or other aryl metal reagents have also been applied to various metal-catalyzed *ortho*-C−H arylation reactions of benzamides, including Fe(III)-,[8b] Ni(II)-,[8c,d] Ru(II)-,[8e] or Co(II)-mediated[8f] catalysis by taking advantage of an *N*,*N*-bidentate auxiliary moiety. Despite these encouraging precedents, the catalytic arylation of indoles through directed aryl C−H activation *via* transmetallation has rarely been investigated with chelation-assisted methods. Enlightened by the pioneering studies[8d,h] on the direct nickel-catalyzed *ortho*-C−H arylation of benzamides utilizing the *N*,*N*-bidentate directing group amide-2-pyridinylisopropyl (PIP),[9] we contemplated that ortho-selectivity might be extended by introducing a bidentate directing group at the C2 position of the indole nucleus to ensure direct C3 selectivity. In this manuscript, we report a novel and efficient method using copper salts to catalyze the direct C3 arylation of indoles with an amide-PIP directing group, in reactions with aromatic boronate esters under nonligand conditions. The developed method provides several advantages for the C3 arylation of indoles, such as a simple experimental procedure, a shorter reaction time, milder conditions, environmental friendliness, higher yields, and a broader substrate scope than previously reported protocols.

RESULTS AND DISCUSSION

We began the studies by investigating the reaction conditions for the envisaged reaction of indole-carboxamide **1a** and phenylboronic acid pinacol ester (PhBpin) **2a** in dimethyl sulfoxide (DMSO) using $Cu(OAc)_2$ as the initial catalyst (Table 1). Encouragingly, in the presence of 2.5 equiv of PhBpin, 1.5 equiv of Ag_2O, 20 mol % $Cu(OAc)_2$, and 2.0 equiv of Na_2CO_3 at 100 °C, the reaction produced the C3 arylation product **3a** in a yield of 52%, although 16% of unreacted substrate **1a** remained. Normally, organic boronic acids can replace boronate esters participating in Suzuki−Miyaura cross-coupling,[10] and thus we tested the reaction of phenylboronic acid with **1a** under the same conditions. However, no product was detected, indicating that boronic acid was unsuitable for the reaction. Moreover, the solvents dimethylformamide (DMF) and toluene had no further contributions to the improvement of the reaction (entries 2 and 3 in Table 1).

Other copper catalysts and silver oxidants were separately screened to increase the yield of this reaction (entries 4−11 in Table 1). Initially, when $CuBr_2$ was tested, the reaction produced compound **3a** in a slightly lower yield of 43% (entry 4 in Table 1) compared with the $Cu(OAc)_2$-catalyzed reaction described above. In addition, selected Cu(I) salts (entries 5−8 in Table 1) did not promote the reaction. Based on these results, Cu(I) was not able to serve as an appropriate catalyst. Furthermore, three other Ag salts, Ag_3PO_4, Ag_2CO_3, and Ag_2SO_4, were used to replace Ag_2O in the reaction and exhibited only up to 16% reaction yield (entries 9−11 in Table 1). Apparently, no alternative silver oxidant or copper catalyst proved to be more effective; therefore, Ag_2O and $Cu(OAc)_2$ remained the best choices.

We shifted our focus to the base to further advance the investigation. According to published studies, the nature of the base is presumed to substantially affect the reaction process in which a bidentate auxiliary moiety is applied.[11] Thus, a variety

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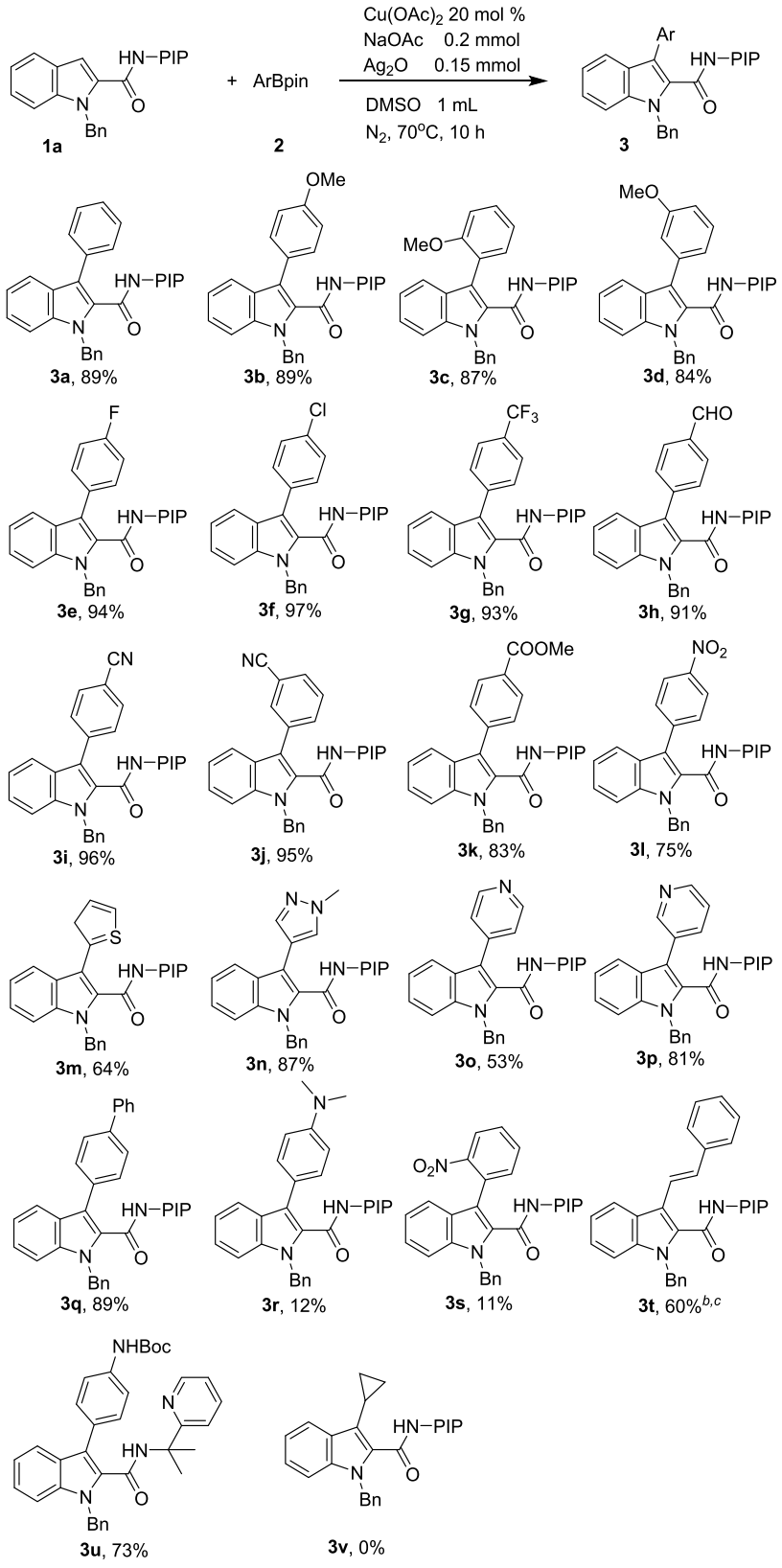
Scheme 1. Scope of (Hetero)arylboronates Used for the C3 Arylation of Indoles[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.25 mmol), $Cu(OAc)_2$ (20 mol %), Ag_2O (0.15 mmol), and NaOAc (0.2 mmol) in DMSO (1.0 mL) at 70 °C for 10 h under N_2. Isolated yield. [b]Reaction time, 18 h. [c]An inseparable diastereomer was obtained at a ratio of 6:1 (*E*/*Z*).

of bases were examined and NaOAc emerged as the best candidate (entries 12−17 in Table 1). Additionally, a high temperature might be detrimental to this directed arylation process, as shown in Table 1. When the temperature decreased

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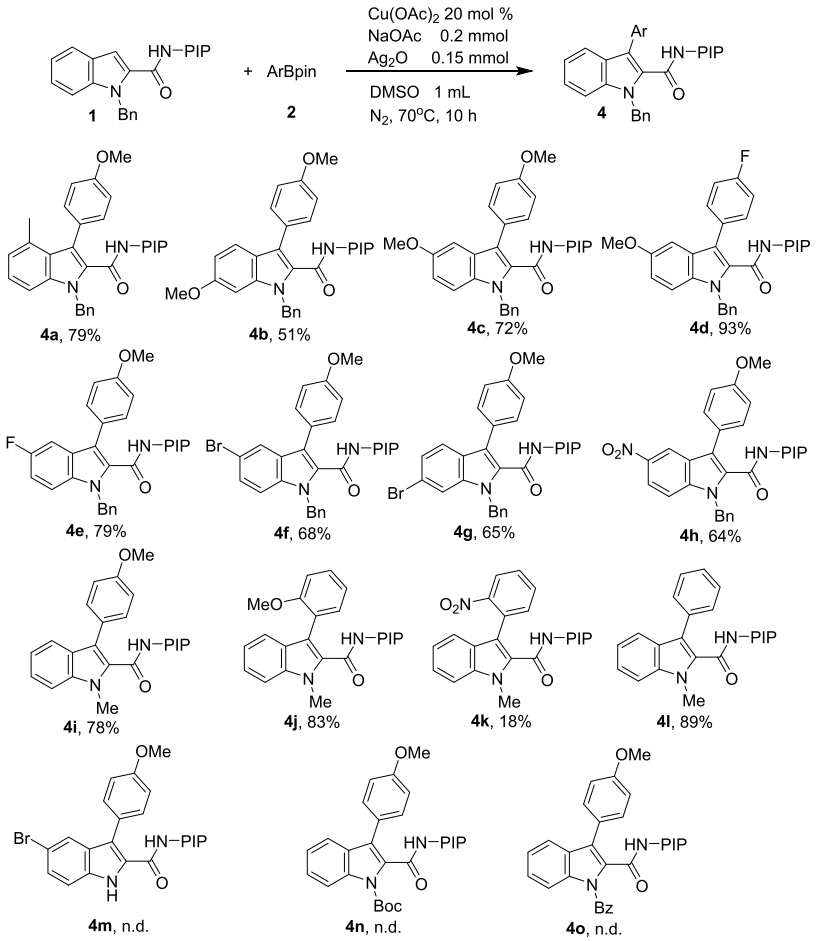
Scheme 2. Scopes of Indoles with Different Substituents Used in the Reaction[a]



[a]Reaction conditions: **1** (0.1 mmol), **2** (0.25 mmol), $Cu(OAc)_2$ (20 mol %), Ag_2O (0.15 mmol), and NaOAc (0.2 mmol) in DMSO (1.0 mL) at 70 °C for 10 h under N_2. Isolated yield.

to 70 °C (entry 19 in Table 1), the isolated yield increased to the highest value of 89% without signals attributed to impurities detected using NMR. Moreover, as expected, control experiments revealed that no reaction occurred in the absence of $Cu(OAc)_2$ or Ag_2O. In summary, the C3 arylation of indoles coupled with PhBpin was efficiently catalyzed by $Cu(OAc)_2$ in DMSO at 70 °C using the oxidant Ag_2O and the base NaOAc under a N_2 atmosphere.

After determining optimized reaction conditions, the scope of the reaction with respect to different arylboronic acid pinacol esters (ArBpins) to produce various C3-(hetero)-arylated indoles was evaluated, as listed in Scheme 1. Overall, a broad range of ArBpins with various functional groups on the phenyl ring and hetero-ArBpins were well tolerated under the optimized conditions in the reaction with compound **1a**, affording (hetero)arylated products in good to excellent yields of up to 97% (Scheme 1, compounds **3b**−**3q**). First, the results demonstrated that electron-rich ArBpins containing a methoxy group on the aromatic ring at the ortho-, meta-, or para-position reacted smoothly with compound **1a** to provide desired products **3b**−**3d** in yields of 84−89%. In addition, C3 arylation of compound **1a** reacting with the PhBpin coupling partners possessing various electron-withdrawing groups on the phenyl ring, such as nitrile, nitro, or halogen groups, afforded the corresponding products **3e**−**3l** (Scheme 1) in yields of 75−97%. Generally, PhBpins with an electron-withdrawing group, such as a halogen, $-CF_3$, −CN, or −CHO group, at the para-position of the phenyl ring reacted completely with compound **1a** in high yields of more than 90%. Electron-withdrawing groups might be propitious to the leaving of boric acid, thereby facilitating PhBpins to coordinate with Cu in the reaction pathway. On the other hand, *p*-nitro PhBpin reacted with compound **1a** to generate product **3l** in a relatively low yield of 75% compared with the products **3e**−**3h** described above, while *o*-nitro product **3s** was isolated in an extremely low yield of 11%, probably due to the adverse effects of increasing the steric hindrance from the *o*-NO_2 group conjugated with the phenyl ring. In stark contrast to **3s**, the above-mentioned compound **3c** with an *o*-methoxy group on the phenyl ring was synthesized at an 87% yield, similar to the yields of products **3b** and **3d** with a *para*-/*meta*-MeO group, respectively. Because of the rotatable characteristics of the methoxy group on the phenyl ring, the methoxy group might not induce a marked steric hindrance effect on the reaction. Therefore, the reaction might be sensitive to the steric effects of the phenyl ortho-group of PhBpin.

We performed biphenyl or heteroaryl ArBpin reactions with compound **1a** to further broaden the scope of the indole substrates, affording the corresponding products **3m**−**3q** in good yields of 53−89%. As shown in Scheme 1, product **3o** (53%) with a 4-pyridyl group was obtained at a lower yield than compound **3p** (81%) with a 3-pyridine functionality. We

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also obtained product **3m** with indole C3 arylation of the thiophene ring in a good yield of 64% using the developed protocol. Moreover, the coupling of phenyl vinyl boronate with compound **1a** produced compound **3t** at a 60% yield with a prolonged reaction time of 18 h. On the other hand, it was worth noting that only a small amount of product **3r**, containing a 4-NMe_2 group, was formed at a quite low yield of 12%, whereas product **3u** with a Boc-protected 4-amino group was generated at a dramatically increased yield of 73%. The lone pair of electrons on the amino-*N*, unlike the amide-*N* or methoxy-*O*, might tend to coordinate with Cu(II), leading to the unfavorable formation of a reaction intermediate or transition state (TS) during the reaction. Moreover, the use of alkylboronic acid pinacol esters as a coupling reagent to generate a C3-alkylated indole derivative was tested and regrettably failed to yield the desired cyclopropanation product **3v**.

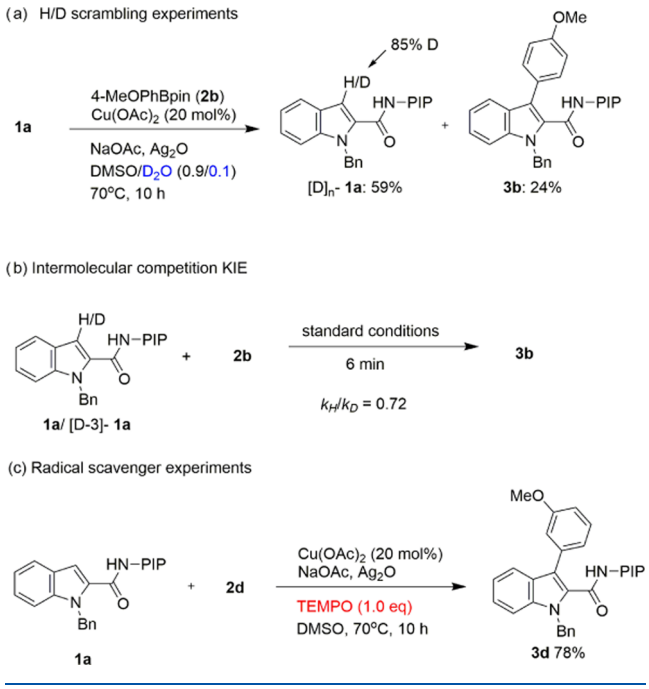
In view of the gratifying results obtained with arylboronates, the scope of the reaction of indoles with ArBpins with different substituents was successively examined, and the corresponding products **4a**−**4l** were produced, as listed in Scheme 2. Generally, various indole products **4a**−**4h**, which contained either electron-donating groups (Me and OMe) or electron-withdrawing groups (F, Br, and NO_2) on the indole moieties, were acquired in the relatively lower yields of 51−79% than the unsubstituted compound **3b**. Specifically, 5- and 6-bromo-substituted indole derivatives reacted with ArBpins to generate the corresponding products **4f** and **4g** in yields of 68% and 65%, respectively, whereas the 6-methoxy indole derivative **4b** was obtained at a lower yield of 51% than the 5-methoxy-substituted product **4c** with a yield of 72%. Furthermore, we analyzed the reaction of 5-methoxy indole and *p*-F phenyl PhBpin to produce compound **4d** in the near-quantitative yield of 93%, showing that this electron-withdrawing group was favorable for the reaction. Moreover, two additional 5-substituted indoles containing fluoro and nitro groups were successfully arylated in good yields (**4e** and **4h**).

Furthermore, 4-methyl substitution also generated product **4a** in a yield of 79%. Notably, when a methyl group was used as a replacement for the Bn group for protection of the N−H group of the indole, the reaction with four different PhBpins produced the corresponding products **4i**−**4l** (Scheme 2) in similar yields to the Bn-protected products **3a**, **3b**, **3c**, and **3s**, respectively. On the other hand, the *N*-*tert*-butyloxycarbonyl (Boc) indole and the *N*-benzoyl (Bz) indole provided no product. Thus, it seems that the developed protocol is not applicable for the C3 arylation of indoles bearing electron-withdrawing protecting groups. Furthermore, N-unprotected indoles did not react with PhBpins to produce the corresponding products, such as compound **4m**. We presumed that the presence of the free NH moiety may thoroughly inhibit the reaction. As discussed above, amino-*N* protection is necessary for the reaction, and the exposed sp^2−N−H group of the indole also must be protected.

A 1 mmol scale experiment was performed employing compound **1a** as the substrate to further illustrate the practical utility of this newly established protocol, and the reaction proceeded under the standard catalytic conditions to obtain product **3a** in good yield (82% yield, 365.5 mg of compound **3a**). Moreover, the PIP directing group could be readily removed after adopting a previously reported method.[7h,8h,9b]

A set of preliminary mechanistic experiments were conducted to obtain additional insights into the mechanism of this C−H arylation reaction of indoles (Scheme 3). An H/D scrambling experiment revealed that the C−H cupperation is

Scheme 3. Mechanistic Studies



supposed to be fast and reversible with a significant H/D exchange at the C3 position of compound **1a**. In the competitive investigation, a small intermolecular kinetic isotope effect (KIE) value of 0.72 was measured, indicating that C−H bond cleavage may not be involved in the turnover-limiting step. Moreover, the reaction of compound **1a** proceeded in the presence of a radical quencher 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 1.0 equiv). A significant decrease in the yield of **3d** was not observed, implying that an SET pathway is unlikely to be required for this copper-catalyzed arylation process.

Based on our findings and other related studies,[8a,d,h,12] a plausible catalytic cycle was proposed to account for the amide-PIP directed C3 arylation of indoles in the reaction with an ArBpin (Scheme 4). First, amide **1a** may coordinate to the copper center followed by C−H bond activation at the C3 position of the indole nucleus to produce Cu(II)−aryl complex **A**. Then, oxidation occurs with the formed five-membered metallacycle **B** to generate the Cu(III) intermediate **C**. Finally, complex **C** undergoes reductive elimination to afford target product **3a** with the regeneration of copper acetate.

CONCLUSIONS

We developed a Cu(II)-catalyzed protocol for the regioselective C−H arylation of indoles at the C3 position through a reaction with ArBpins and with assistance of a facile and removable directing group. Most indole substrates and pinacol arylboronic esters, which serve as arylating reagents, exhibited good compatibility with various functional groups under standard reaction conditions. In addition to the generality and efficiency of this method, the arylation product could smoothly give rise to a valuable 3-arylindole-carboxylic acid and its derivatives or analogues following the removal of directing group. Ultimately, with the development and

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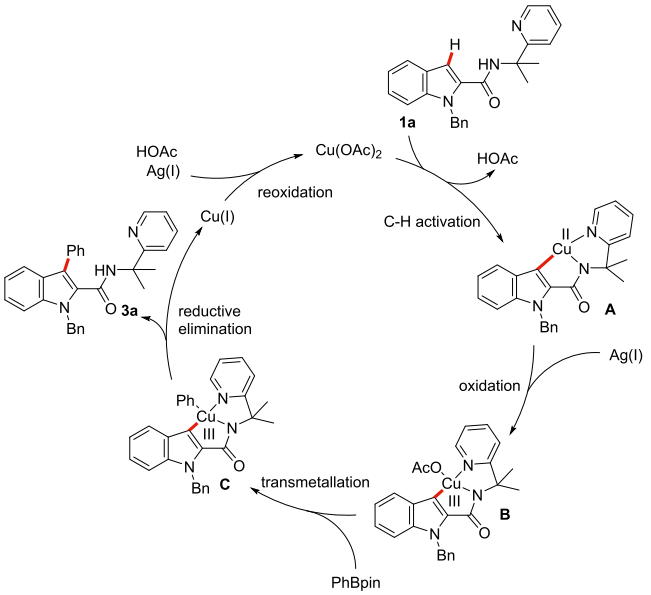
Scheme 4. Proposed Reaction Pathway



application of promising copper-mediated crossing-coupling arylation reactions, additional novel aryl-substituted indole carboxylic acids will undoubtedly be generated through cost-effective and environmentally benign synthetic methodologies for the direct C−H arylation of indoles.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were commercially available and used directly without further purification. NMR spectra were recorded at room temperature on a Bruker Avance-500 spectrometer operating for ^{1}H NMR at 500 MHz and ^{13}C NMR at 126 MHz, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ relative to TMS, and the coupling constants J are given in hertz. The peaks were internally referenced to $CDCl_3$ (7.26 ppm) or residual undeuterated solvent signal (77.20 ppm for ^{13}C NMR). The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, brs = broad. High-resolution mass spectra (HRMS) were recorded on an Agilent 6200 LC/MS TOF using APCI or ESI in positive mode.

Materials. 2-(Pyridin-2-yl)isopropyl (PIP) amine was synthesized by the reaction according to the literature procedures.[13]

General Procedures for the Preparation of Substrates. General Procedure A. According to the literature procedure,[13] a mixture of amine (1.4 mmol), an acid (1.4 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI, 1.54 mmol), HOBt·H_2O (1.54 mmol), and *N*,*N*-diisopropylethylamine (DIPEA, 2.8 mmol) in anhydrous dichloromethane (DCM, 6 mL) was stirred at room temperature overnight. Water was added, and the mixture was extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography to give the amide.

General Procedure B. According to the literature procedure,[14] a mixture of amide (0.70 mmol) and NaH (30.8 mg, 60% dispersion, 0.77 mmol) in tetrahydrofuran (THF, 5 mL) was stirred at 0 °C for 1 h and benzyl bromide (156 mg, 0.91 mmol) was added. The reaction mixture was stirred at room temperature (rt) overnight, and a solution of 10% NH_4Cl (5 mL) and H_2O (10 mL) was carefully added. The resulting mixture was extracted with EtOAc (15 × 3 mL), and the combined organic layer was washed with brine and evaporated under vacuum. The residue was purified by flash column chromatography to give the amide.

*General Procedure C for the Synthesis of **5g** or **6**.* **5g**: Commercially available 5-nitro-1*H*-indole-2-carboxylic acid (350 mg, 1.70 mmol) and concentrated H_2SO_4 (0.5 mL) were refluxed in MeOH (20 mL) in an oil bath for 12 h. The solution was then cooled to room temperature and concentrated under reduced pressure, followed by partitioning between $NaHCO_3$/ethyl acetate and reextraction of the combined aqueous layers three times. The combined organic phases were washed with water and brine and then dried over Na_2SO_4 before concentrating in vacuo and, without further purification, used in the next step. A mixture of the crude product and NaH (74.8 mg, 60% dispersion, 1.87 mmol) in DMSO (3 mL) was stirred at 50 °C in an oil bath for 30 min, and then benzyl bromide (188 mg, 1.87 mmol) was added. The reaction mixture was stirred at 80 °C in an oil bath for another 30 min, and then a solution of 10% NH_4Cl (5 mL) and H_2O (10 mL) was carefully added. The resulting mixture was extracted with EtOAc (15 × 3 mL), and the combined organic layer was washed with water (×2) and brine (×2) and evaporated under vacuum. The residue was purified by flash column chromatography to give **5g** (246 mg, 46.7%).[15]

6: Commercially available indole-2-carboxylic acid (9.80 g, 60.8 mmol) and concentrated H_2SO_4 (1.5 mL) were refluxed in MeOH (50 mL) in an oil bath for 7 h. The solution was then cooled to room temperature and concentrated under reduced pressure, followed by partitioning between $NaHCO_3$/ethyl acetate and reextraction of the combined aqueous layers three times. The combined organic phases were washed with water and brine and then dried over Na_2SO_4 before concentrating in vacuo and, without further purification, used in the next step.[16]

A mixture of the crude product and NaH (2.67 g, 60% dispersion, 66.8 mmol) in DMF (60 mL) was stirred at 0 °C for 1 h, and benzyl bromide (13.5 g, 79.0 mmol) was added. The reaction mixture was stirred at rt overnight, and a solution of 10% NH_4Cl (25 mL) and H_2O (50 mL) was carefully added. The resulting mixture was extracted with EtOAc (75 × 3 mL) and the combined organic layer was washed with brine and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate = 3/1 to give **6** (8.34 g, 51.7%). Characterizations were consistent with the literature.[17]

*General Procedure D for the Synthesis of **1a** or **1h**.* **1a**: Methyl 1-benzyl-1*H*-indole-2-carboxylate **6** (7.13 g, 26.9 mmol) was added to a solution of NaOH (6.46 g, 161 mmol) in EtOH·H_2O (2:1) and stirred for 2 h at 70 °C in an oil bath. The solution was then cooled to 0 °C and acidified by 6 N HCl to a pH of 2−3. The solution was extracted with ethyl acetate and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated by rotary evaporation to give the crude carboxylic acid (6.54 g). A mixture of amine (3.54 g, 26.0 mmol), an acid (6.54 g, 26.0 mmol), EDCI (5.48 g, 28.6 mmol), HOBt·H_2O (4.38 g, 28.6 mmol), and DIPEA (6.72 g, 52.0 mmol) in anhydrous DCM (50 mL) was stirred at room temperature overnight. Water was added, and the mixture was extracted with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate = 3/1 to give **1a** (5.41 g, 59.4%).

1h: Methyl 1-benzyl-5-nitro-1*H*-indole-2-carboxylate **5g** (246 mg, 0.79 mmol) was added to a solution of NaOH (300 mg, 7.5 mmol) in EtOH·H_2O (2:1) and stirred for 2 h at 70 °C in an oil bath. The solution was then cooled to 0 °C and acidified by 6 N HCl to a pH of 2−3. The solution was extracted with ethyl acetate and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated by rotary evaporation to give the crude carboxylic acid (215 mg). A mixture of amine (99 mg, 0.73 mmol), an acid (215 mg, 0.73 mmol), EDCI (153 mg, 0.80 mmol), HOBt·H_2O (123 mg, 0.80 mmol), and DIPEA (189 mg, 1.46 mmol) in anhydrous DCM (4 mL) was stirred at room temperature overnight. Water was added, and the mixture was extracted with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash

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column chromatography on silica gel using petroleum ether/ethyl acetate = 3/1 to give **1h** (105.2 mg, 32.0%).

*4-Methyl-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**5a**).* Compound **5a** was prepared according to general procedure A on a 1.4 mmol scale. Purification by flash chromatography in petroleum ether/ethyl acetate = 2/1 gave **5a** as a white solid (290 mg, 69.3% yield), m.p.: 194−195 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (brs, 1H), 8.80 (brs, 1H), 8.64 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 7.78−7.72 (m, 1H), 7.51−7.46 (m, 1H), 7.29−7.25 (m, 1H), 7.24 (dd, J = 4.9, 1.0 Hz, 1H), 7.20−7.12 (m, 1H), 7.05−6.98 (m, 1H), 6.95−6.89 (m, 1H), 2.60 (s, 3H), 1.94 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.3, 161.0, 147.8, 137.2, 136.1, 131.6, 131.4, 128.0, 124.1, 122.0, 120.3, 119.5, 109.6, 100.4, 56.8, 27.8, 18.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{20}N_3O$ 294.1606; found 294.1651.

*6-Methoxy-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**5b**).* Compound **5b** was prepared according to general procedure A on a 1.3 mmol scale. Purification by flash chromatography in petroleum ether/ethyl acetate = 2/1 gave **5b** as a white solid (262 mg, 65.2% yield), m.p.: 199−201 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (brs, 1H), 8.82 (brs, 1H), 8.61 (ddd, J = 4.9, 1.6, 0.9 Hz, 1H), 7.75 (td, J = 7.8, 1.8 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.25−7.22 (m, 1H), 6.97 (dd, J = 11.4, 1.8 Hz, 2H), 6.81 (dd, J = 8.7, 2.3 Hz, 1H), 3.86 (s, 3H), 1.94 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.3, 160.1, 156.8, 146.7, 136.4, 136.2, 130.2, 121.5, 121.0, 118.4, 110.7, 101.2, 93.1, 55.7, 54.5, 26.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{20}N_3O_2$ 310.1556; found 310.1611.

*5-Methoxy-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**5c**).* Compound **5c** was prepared according to general procedure A on a 2.0 mmol scale. Purification by flash chromatography in petroleum ether/ethyl acetate = 2/1 gave **5c** as a white solid (339.1 mg, 54.9% yield), m.p.: 127−129 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (brs, 1H), 8.84 (brs, 1H), 8.61 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 7.76 (ddd, J = 8.0, 7.5, 1.8 Hz, 1H), 7.48 (dt, J = 8.1, 0.9 Hz, 1H), 7.32 (d, J = 8.9 Hz, 1H), 7.26−7.23 (m, 1H), 7.10 (d, J = 2.4 Hz, 1H), 6.97−6.92 (m, 2H), 3.86 (s, 3H), 1.92 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.3, 160.9, 154.5, 147.7, 137.3, 132.7, 131.7, 128.2, 122.0, 119.5, 115.2, 112.9, 102.3, 101.5, 56.8, 55.7, 27.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{20}N_3O_2$ 310.1556; found 310.1588.

*5-Fluoro-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**5d**).* Compound **5d** was prepared according to general procedure A on a 1.4 mmol scale. Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **5d** as a white solid (260 mg, 66.7% yield), m.p.: 175−176 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.51 (brs, 1H), 8.95 (brs, 1H), 8.62 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 7.81−7.72 (m, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.36 (dd, J = 8.9, 4.5 Hz, 1H), 7.31 (dd, J = 9.4, 2.4 Hz, 1H), 7.27−7.24 (m, 1H), 7.04−6.97 (m, 2H), 1.95 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.1, 160.8, 158.1 (d, $^1J_{C\text{-}F}$ = 235.6 Hz), 147.7, 137.4, 133.8, 133.2, 127.9 (d, $^3J_{C\text{-}F}$ = 11.3 Hz), 122.2, 119.5, 113.0 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 112.9 (d, $^2J_{C\text{-}F}$ = 40.3 Hz), 106.0 (d, $^2J_{C\text{-}F}$ = 23.9 Hz), 101.9 (d, $^3J_{C\text{-}F}$ = 5.0 Hz), 56.9, 27.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{17}FN_3O$ 298.1356; found 298.1386.

*5-Bromo-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**5e**).* Compound **5e** was prepared according to general procedure A on a 2.0 mmol scale. Purification by flash chromatography in petroleum ether/ethyl acetate = 2/1 gave **5e** as a white solid (615 mg, 85.9% yield), m.p.: 179−180 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.45 (brs, 1H), 8.97 (brs, 1H), 8.63 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 7.80 (d, J = 0.7 Hz, 1H), 7.77 (td, J = 7.8 Hz, 1.8, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.35−7.30 (m, 2H), 7.28−7.26 (m, 1H), 6.95 (d, J = 2.0 Hz, 1H), 1.94 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.1, 160.7, 147.7, 137.4, 135.1, 133.4, 129.4, 126.9, 124.1, 122.2, 119.5, 113.7, 113.4, 101.3, 56.9, 27.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{17}BrN_3O$ 358.0555; found 358.0563.

*6-Bromo-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**5f**).* Compound **5f** was prepared according to general procedure A on a 2.0 mmol scale. Purification by flash chromatography in petroleum ether/ethyl acetate = 2/1 gave **5f** as a white solid (455 mg, 63.5% yield), m.p.: 202−203 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.51 (brs, 1H), 9.00 (brs, 1H), 8.62 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 7.81−7.74 (m, 1H), 7.72−7.67 (m, 1H), 7.53 (dd, J = 15.3, 8.3 Hz, 2H), 7.28−7.26 (m, 1H), 7.23 (dd, J = 8.5, 1.7 Hz, 1H), 7.01 (dd, J = 2.1, 0.7 Hz, 1H), 1.96 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.01, 160.7, 147.7, 137.4, 137.2, 132.9, 126.6, 123.7, 123.0, 122.2, 119.5, 117.5, 115.1, 102.0, 56.9, 27.7. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{17}BrN_3O$ 358.0555; found 358.0536.

*Methyl 1-Benzyl-5-nitro-1H-indole-2-carboxylate (**5g**).* Compound **5g** was prepared according to general procedure C. Purification by flash chromatography in petroleum ether/ethyl acetate = 8/1 gave **5g** as a white solid (246 mg, 46.7% yield), m.p.: 131−132 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 2.1 Hz, 1H), 8.19 (dd, J = 9.2, 2.2 Hz, 1H), 7.54 (d, J = 0.7 Hz, 1H), 7.42 (d, J = 9.3 Hz, 1H), 7.30−7.26 (m, 2H), 7.26−7.22 (m, 1H), 7.06−7.01 (m, 2H), 5.90 (s, 2H), 3.91 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.6, 142.6, 141.7, 137.0, 130.6, 128.9, 127.7, 126.2, 125.2, 120.3, 120.1, 113.0, 111.2, 52.2, 48.5. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{15}N_2O_4$ 311.1032; found 311.1035.

*1-Benzyl-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**1a**).* White solid, m.p.: 138−139 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (brs, 1H), 8.55 (d, J = 4.8 Hz, 1H), 7.75−7.64 (m, 2H), 7.38 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.24−7.18 (m, 4H), 7.18−7.10 (m, 4H), 7.06 (s, 1H), 5.84 (s, 2H), 1.82 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.4, 161.9, 147.7, 138.6, 138.6, 137.2, 133.5, 128.5, 127.0, 126.8, 126.5, 123.9, 121.9, 121.8, 120.5, 119.4, 110.8, 104.5, 57.0, 47.7, 27.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{24}H_{24}N_3O$ 370.1919; found 370.1882.

*1-Benzyl-4-methyl-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**1b**).* White solid, m.p.: 180−181 °C. Compound **1b** was prepared according to general procedure B on a 0.8 mmol scale. Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **1b** as a white solid (128 mg, 40.1% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (dd, J = 4.8, 0.7 Hz, 1H), 8.48 (brs, 1H), 7.69 (td, J = 7.9, 1.8 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.24−7.13 (m, 6H), 7.11 (d, J = 7.2 Hz, 2H), 7.05 (s, 1H), 6.94 (d, J = 6.7 Hz, 1H), 5.82 (s, 2H), 2.60 (s, 3H), 1.82 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.44, 162.0, 147.8, 138.7, 138.4, 137.1, 132.9, 131.4, 128.5, 127.0, 126.8, 126.5, 124.1, 121.9, 120.6, 119.4, 108.4, 103.0, 57.0, 47.8, 27.7, 18.7. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{25}H_{26}N_3O$ 384.2076; found 384.2038.

*1-Benzyl-6-methoxy-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**1c**).* White solid, m.p.: 130−131 °C. Compound **1c** was prepared according to general procedure B on a 0.64 mmol scale. Purification by flash chromatography in petroleum ether/ethyl acetate = 2/1 gave 1c as a white solid (84 mg, 32.5% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 8.47 (brs, 1H), 7.72−7.65 (m, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.37 (dt, J = 8.1, 0.9 Hz, 1H), 7.25−7.15 (m, 4H), 7.15−7.08 (m, 2H), 7.00 (s, 1H), 6.81 (dd, J = 8.7, 2.2 Hz, 1H), 6.74 (d, J = 2.1 Hz, 1H), 5.80 (s, 2H), 3.79 (s, 3H), 1.81 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.5, 161.9, 157.8, 147.8, 139.6, 138.6, 137.1, 132.5, 128.5, 127.0, 126.8, 122.5, 121.9, 120.7, 119.4, 111.3, 104.8, 93.4, 56.9, 55.5, 47.7, 27.7. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{25}H_{26}N_3O_2$ 400.2025; found 400.2029.

*1-Benzyl-5-methoxy-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**1d**).* White solid, m.p.: 121−122 °C. Compound **1d** was prepared according to general procedure B on a 1.0 mmol scale. Purification by flash chromatography in petroleum ether/ethyl acetate = 5/1 gave **1d** as a white solid (110 mg, 28.4% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (brs, 1H), 8.54 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 7.70 (td, J = 7.8, 1.8 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.24−7.19 (m, 4H), 7.19−7.14 (m, 1H), 7.13−7.06 (m, 3H), 6.98 (s, 1H), 6.91 (dd, J = 9.0, 2.5 Hz, 1H), 5.81 (s, 2H), 3.85 (s, 3H), 1.82 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.4, 161.8, 154.6, 147.7, 138.7, 137.2, 134.0, 133.8, 128.5, 127.0, 126.8, 126.7, 121.9, 119.4, 114.8, 111.7,

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104.0, 102.5, 56.9, 55.8, 47.8, 27.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{26}N_3O_2$ 400.2025; found 400.1989.

*1-Benzyl-5-fluoro-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**1e**).* Compound **1e** was prepared according to general procedure B on a 0.36 mmol scale. Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **1e** as a white solid (50 mg, 36.0% yield), m.p.: 123−124 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (brs, 1H), 8.58−8.52 (m, 1H), 7.74−7.69 (m, 1H), 7.41−7.37 (m, 1H), 7.34−7.29 (m, 1H), 7.25−7.15 (m, 5H), 7.13−7.07 (m, 2H), 7.03−6.94 (m, 2H), 5.82 (s, 2H), 1.82 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.2, 161.5, 158.2 (d, $^1J_{C-F}$ = 235.6 Hz), 147.7, 138.3, 137.2, 135.1, 134.9, 128.5, 127.1, 127.0, 126.6 (d, $^3J_{C-F}$ = 10.1 Hz), 122.0, 119.4, 112.6 (d, $^2J_{C-F}$ = 26.5 Hz), 111.6 (d, $^3J_{C-F}$ = 8.8 Hz), 106.1 (d, $^2J_{C-F}$ = 23.9 Hz), 104.1 (d, $^4J_{C-F}$ = 5.0 Hz), 56.9, 47.9, 27.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{23}FN_3O$ 388.1825; found 388.1786.

*1-Benzyl-5-bromo-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**1f**).* Compound **1f** was prepared according to general procedure B on a 1.2 mmol scale. Purification by flash chromatography in petroleum ether/ethyl acetate = 5/1 gave **1f** as a white solid (89 mg, 23.9% yield), m.p.: 133−135 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (brs, 1H), 8.67 (d, J = 4.4 Hz, 1H), 8.62 (d, J = 1.6 Hz, 1H), 7.81 (s, 1H), 7.80−7.73 (m, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.34−7.27 (m, 4H), 7.26−7.23 (m, 1H), 7.16 (d, J = 8.7 Hz, 1H), 7.12 (d, J = 6.7 Hz, 2H), 5.32 (s, 2H), 1.92 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.8, 163.5, 147.5, 137.3, 135.9, 135.5, 132.9, 129.0, 128.1, 127.3, 126.9, 125.3, 123.8, 122.0, 119.6, 115.1, 112.9, 111.9, 56.8, 50.8, 27.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{23}BrN_3O$ 448.1024; found 448.1073.

*1-Benzyl-6-bromo-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**1g**).* Compound **1g** was prepared according to general procedure B on a 0.8 mmol scale. Purification by flash chromatography in petroleum ether/ethyl acetate = 5/1 gave **1g** as a white solid (161 mg, 29.9% yield), m.p.: 91−92 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (brs, 1H), 8.55 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 7.81 (d, J = 1.7 Hz, 1H), 7.76−7.68 (m, 1H), 7.43−7.37 (m, 1H), 7.31 (dd, J = 8.8 Hz, 1.9, 1H), 7.25−7.15 (m, 5H), 7.11−7.07 (m, 2H), 6.98 (d, J = 0.6 Hz, 1H), 5.81 (s, 2H), 1.82 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.2, 161.4, 147.7, 138.1, 137.2, 137.1, 134.5, 128.5, 128.1, 127.2, 126.7, 126.7, 124.2, 122.0, 119.4, 113.7, 112.3, 103.6, 57.0, 47.8, 27.5. HRMS (ESI-TOF) m/z:: $[M + H]^+$ calcd for $C_{24}H_{23}BrN_3O$ 448.1024; found 448.1021.

*1-Benzyl-5-nitro-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**1h**).* White solid, m.p.: 180−181 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (brs, 1H), 8.66 (d, J = 2.1 Hz, 1H), 8.55 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 8.14 (dd, J = 9.2, 2.2 Hz, 1H), 7.80−7.71 (m, 1H), 7.44−7.37 (m, 2H), 7.26−7.18 (m, 5H), 7.15−7.09 (m, 2H), 5.87 (s, 2H), 1.83 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.9, 160.8, 147.6, 142.4, 141.0, 137.4, 137.4, 136.8, 128.7, 127.6, 126.8, 125.7, 122.2, 119.4, 119.2, 119.1, 110.4, 106.3, 57.1, 48.3, 27.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{23}N_4O_3$ 415.1770; found 415.1737.

*1-Methyl-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**1i**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (brs, 1H), 8.58 (ddd, J = 4.9, 1.6, 0.9 Hz, 1H), 7.75 (td, J = 7.8, 1.8 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.34−7.27 (m, 1H), 7.23 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 7.17−7.12 (m, 1H), 7.01 (s, 1H), 4.07 (s, 3H), 1.89 (s, 6H). The analytical data above was matched with literature.[13]

*tert-Butyl 2-((2-(pyridin-2-yl)propan-2-yl)carbamoyl)-1H-indole-1-carboxylate (**1j**).* A mixture of amine (340 mg, 2.5 mmol), 1*H*-indole-2-carboxylic acid (400 mg, 2.5 mmol), EDCI (527 mg, 2.75 mmol), HOBt·H_2O (421 mg, 2.75 mmol), and *N*,*N*-diisopropylethylamine (0.83 mL, 5.0 mmol) in anhydrous DCM (8 mL) was stirred at room temperature overnight. Water was added, and the mixture was extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 3/1) to give *N*-(2-(pyridin-2-yl)propan-2-yl)-1*H*-indole-2-carboxamide (405 mg, 58%). To a stirred solution of *N*-(2-(pyridin-2-yl)propan-2-yl)-1*H*-indole-2-carboxamide (70 mg, 0.25 mmol) and 4-dimethylaminopyridine (3.0 mg, 0.025 mmol) in dry DCM (3 mL) was carefully added di-*tert*-butyl dicarbonate (86 μL, 0.38 mmol) at 0 °C under an nitrogen atmosphere. The solution was stirred at the same temperature for 30 min. Water was then added, and the mixture was extracted with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 4/1) to give **1j** as a white solid (82 mg, 85.8%), m.p.: 167−168 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (brs, 1H), 8.52 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 8.12 (dd, J = 8.4, 0.7 Hz, 1H), 7.75 (ddd, J = 8.0, 7.6, 1.8 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.48 (dt, J = 8.1, 0.9 Hz, 1H), 7.37 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.26−7.20 (m, 2H), 6.94 (d, J = 0.4 Hz, 1H), 1.90 (s, 6H), 1.63 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.2, 161.2, 149.6, 147.6, 137.4, 137.2, 136.2, 127.8, 125.8, 123.0, 122.0, 121.5, 119.5, 115.1, 111.1, 84.3, 57.0, 28.0, 27.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{26}N_3O_3$ 380.1974; found 380.1985.

*1-Benzoyl-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**1k**).* To a stirred solution of 1*H*-indole-2-carboxylic acid (500 mg, 3.1 mmol) in dry DCM (8 mL) was added *N*,*N*-dimethylpyridin-4-amine (37 mg, 0.3 mmol) and Et_3N (0.86 mL, 6.2 mmol). After the mixture was cooled to 0 °C, benzoyl chloride (0.4 mL, 3.4 mmol) was added dropwise. The reaction mixture was maintained at 0 °C for 15 min, and then the solution was stirred at room temperature for 4 h. Upon complete reaction, the resulting mixture was diluted with DCM (20 mL) and successively washed with 5% aqueous $NaHSO_4$ solution (2 × 20 mL) and brine (25 mL), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to give the 1-benzoyl-1*H*-indole-2-carboxylic acid (327 mg). A mixture of amine (168 mg, 1.2 mmol), an acid (327 mg, 1.2 mmol), EDCI (259 mg, 1.35 mmol), HOBt·H_2O (207 mg, 1.35 mmol), and DIPEA (0.4 mL, 2.5 mmol) in anhydrous DCM (8 mL) was stirred at room temperature overnight. Water was added, and the mixture was extracted with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 3/1) to give **1k** as an off-white solid (210 mg, 44.4%), m.p.: 148−149 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (brs, 1H), 8.55 (d, J = 4.4 Hz, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.76−7.65 (m, 4H), 7.49 (t, J = 7.4 Hz, 1H), 7.41−7.34 (m, 3H), 7.32 (d, J = 8.1 Hz, 1H), 7.31−7.27 (m, 1H), 7.23 (dd, J = 7.4, 5.0 Hz, 1H), 7.13 (s, 1H), 1.50 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.5, 164.0, 160.1, 147.5, 138.2, 137.3, 136.6, 136.1, 132.5, 129.3, 128.5, 127.6, 126.1, 123.3, 122.0, 121.9, 119.4, 114.2, 110.2, 56.70, 26.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{22}N_3O_2$ 384.1712; found 384.1729.

*Representative General Procedure for the Preparation of Product **3a**.* To a 10 mL Schlenk tube was added amide **1a** (0.1 mmol), **2a** (0.25 mmol), NaOAc (16.4 mg, 2 equiv), $Cu(OAc)_2$ (3.6 mg, 20 mol %), Ag_2O (34.8 mg, 1.5 equiv), and DMSO (1 mL) under N_2 atmosphere. The mixture was stirred at 70 °C in a preheated oil bath for 10 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate, and quenched with saturated sodium chloride. The aqueous phase was extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. After concentration, the resulting residue was purified by flash chromatography on silica gel with a gradient eluent of petroleum ether/ethyl acetate (3:1) to afford the product (39.8 mg, 89%). A 1 mmol scale reaction afforded 365.5 mg of **3a** (82%).

*1-Benzyl-3-phenyl-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**3a**).* White solid, m.p.: 127−128 °C, yield: 39.5 mg (89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.60 (dd, J = 8.1, 1.2 Hz, 2H), 7.48 (ddd, J = 8.0, 7.5, 1.8 Hz, 1H), 7.45 (s, 1H), 7.43−7.38 (m, 3H), 7.31−7.21 (m, 4H), 7.21−7.13 (m, 4H), 7.05−6.99 (m, 2H), 5.77 (s, 2H), 1.56 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.8, 161.7, 147.6, 138.5, 137.4, 136.7, 133.9, 130.6, 128.6, 127.2, 127.2, 127.0, 126.6, 124.2, 121.4, 120.8, 120.7, 119.0, 118.9, 110.5, 57.2, 47.6, 27.0.

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HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{30}H_{28}N_3O$ 446.2232; found 446.2216.

*1-Benzyl-3-(4-methoxyphenyl)-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**3b**):* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **3b** as a white solid (42.3 mg, 89%), m.p.: 131−133 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (dd, J = 4.8, 0.7 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.52−7.47 (m, 3H), 7.46 (s, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.30−7.26 (m, 1H), 7.24 (dd, J = 8.2, 6.2 Hz, 2H), 7.20−7.12 (m, 4H), 7.05 (d, J = 8.1 Hz, 1H), 7.02 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 6.98−6.94 (m, 2H), 5.78 (s, 2H), 3.78 (s, 3H), 1.58 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.9, 161.7, 159.0, 147.6, 138.6, 137.4, 136.7, 131.7, 130.3, 128.5, 127.1, 127.0, 126.8, 126.1, 124.1, 121.4, 120.8, 120.6, 119.0, 118.7, 114.1, 110.5, 57.2, 55.4, 47.6, 27.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{31}H_{30}N_3O_2$ 476.2338; found 476.2352.

*1-Benzyl-3-(2-methoxyphenyl)-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**3c**):* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **3c** as a white solid (41.3 mg, 87%), m.p.: 118-119 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (ddd, J = 4.8, 1.7, 0.8 Hz, 1H), 7.52 (brs, 1H), 7.47 (dd, J = 7.4, 1.7 Hz, 1H), 7.46−7.41 (m, 2H), 7.39 (d, J = 8.4 Hz, 1H), 7.36−7.31 (m, 1H), 7.29−7.25 (m, 2H), 7.25−7.23 (m, 1H), 7.22−7.15 (m, 3H), 7.13−7.07 (m, 2H), 7.01 (ddd, J = 7.4, 4.9, 1.0 Hz, 1H), 6.97 (d, J = 7.7 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 5.78 (brs, 2H), 3.76 (s, 3H), 1.51 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.2, 161.8, 157.4, 147.8, 138.7, 137.5, 136.6, 132.9, 131.3, 129.2, 128.5, 127.2, 127.1, 127.0, 123.9, 123.0, 121.3, 121.0, 120.9, 120.4, 119.0, 114.3, 111.2, 110.4, 57.2, 55.6, 47.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{31}H_{30}N_3O_2$ 476.2338; found 476.2332.

*1-Benzyl-3-(3-methoxyphenyl)-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**3d**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **3d** as a colorless oil (39.8 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.54−7.46 (m, 2H), 7.40 (d, J = 8.4 Hz, 1H), 7.34−7.30 (m, 1H), 7.30−7.25 (m, 1H), 7.25−7.21 (m, 2H), 7.20−7.13 (m, 6H), 7.07−7.04 (m, 1H), 7.02 (ddd, J = 7.4, 4.9, 1.0 Hz, 1H), 6.83 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 5.77 (s, 2H), 3.80 (s, 3H), 1.58 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.8, 161.6, 159.8, 147.6, 138.4, 137.3, 136.7, 135.3, 130.7, 129.5, 128.6, 127.2, 127.0, 126.6, 124.2, 123.1, 121.5, 120.8, 120.7, 119.0, 118.8, 115.8, 113.2, 110.5, 57.2, 55.3, 47.7, 27.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{31}H_{30}N_3O_2$ 476.2338, found 476.2339.

*1-Benzyl-3-(4-fluorophenyl)-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**3e**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **3e** as a white solid (43.5 mg, 94%), m.p.: 110−112 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16−8.13 (m, 1H), 7.76 (brs, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.58−7.51 (m, 3H), 7.41 (d, J = 8.4 Hz, 1H), 7.30−7.26 (m, 1H), 7.25−7.21 (m, 2H), 7.20−7.13 (m, 4H), 7.13−7.07 (m, 3H), 7.04 (ddd, J = 7.4, 4.9, 1.0 Hz, 1H), 5.76 (s, 2H), 1.61 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.7, 162.2 (d, $^1J_{C\text{-}F}$ = 247.0 Hz), 161.5, 161.2, 147.3, 138.4, 137.3, 136.9, 132.2 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 132.1, 131.0, 129.9 (d, $^4J_{C\text{-}F}$ = 2.5 Hz), 129.9, 128.7, 127.2, 127.0, 126.5, 124.2, 121.6, 120.8, 120.5, 119.0, 117.6, 115.4 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 115.3, 110.6, 57.1, 47.7, 27.0. HRMS (ESI-TOF) m/z:: calcd for $C_{30}H_{27}FN_3O$ $[M + H]^+$ 464.2138; found 464.2155.

*1-Benzyl-3-(4-chlorophenyl)-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**3f**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **3f** as a white solid (46.7 mg, 97%), m.p.: 159−161 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 7.85 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.58−7.50 (m, 3H), 7.41 (d, J = 8.4 Hz, 1H), 7.38−7.33 (m, 2H), 7.31−7.26 (m, 1H), 7.26−7.21 (m, 2H), 7.21−7.14 (m, 4H), 7.13 (dd, J = 8.1, 0.8 Hz, 1H), 7.05 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 5.77 (s, 2H), 1.63 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.6, 161.4, 147.3, 138.3, 137.3, 136.9, 133.0, 132.5, 131.9, 131.1, 128.7, 128.6, 127.2, 127.0, 126.3, 124.3, 121.7, 120.9, 120.4, 119.0, 117.3, 110.7, 57.1, 47.7, 26.9. HRMS (ESI-TOF) m/z: calcd for $C_{30}H_{27}ClN_3O$ $[M + H]^+$ 480.1843, found 480.1857.

*1-Benzyl-N-(2-(pyridin-2-yl)propan-2-yl)-3-(4-(trifluoro-methyl)-phenyl)-1H-indole-2-carboxamide (**3g**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **3g** as a white solid (47.8 mg, 93%), m.p.: 138−139 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03−7.97 (m, 2H), 7.72 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.57−7.52 (m, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.33−7.28 (m, 1H), 7.26−7.16 (m, 6H), 7.14 (d, J = 8.1 Hz, 1H), 7.01 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 5.77 (s, 2H), 1.64 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.3, 161.2, 147.1, 138.1, 138.0, 137.3, 137.0, 131.6, 130.8, 128.9 (q, $^2J_{C\text{-}F}$ = 32.4 Hz), 128.6, 127.3, 127.1, 126.1, 125.3 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 124.4, 124.3 (q, $^1J_{C\text{-}F}$ = 272.2 Hz), 121.6, 121.2, 120.3, 119.0, 117.0, 110.8, 57.0, 47.8, 26.8. HRMS (ESI-TOF) m/z:: $[M + H]^+$ calcd for $C_{31}H_{27}F_3N_3O$ 514.2106; found 514.2125.

*1-Benzyl-3-(4-formylphenyl)-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**3h**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **3h** as a white solid (43.1 mg, 91%), m.p.: 165−167 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 1H), 8.04 (s, 1H), 8.00 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 7.90−7.87 (m, 2H), 7.79 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 8.0 Hz, 1H), 7.54 (td, J = 7.8, 1.8 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.31 (ddd, J = 8.3, 7.0 Hz, 1.1 Hz, 1H), 7.26−7.17 (m, 6H), 7.14 (d, J = 8.1 Hz, 1H), 7.00 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 5.75 (s, 2H), 1.64 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 191.9, 163.3, 161.2, 147.0, 140.9, 138.0, 137.3, 137.0, 134.8, 132.1, 130.9, 129.8, 1286, 127.4, 127.0, 125.9, 124.4, 121.7, 121.3, 120.3, 119.0, 116.9, 110.8, 57.0, 47.8, 26.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{31}H_{28}N_3O_2$ 474.2182; found 474.2175.

*1-Benzyl-3-(4-cyanophenyl)-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**3i**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **3i** as a white solid (45.4 mg, 96%), m.p.: 177−179 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (brs, 1H), 8.03 (ddd, J = 4.9, 1.6, 0.9 Hz, 1H), 7.75−7.69 (m, 2H), 7.68−7.63 (m, 3H), 7.63−7.58 (m, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.32 (ddd, J = 8.3, 7.0, 1.1 Hz, 1H), 7.25−7.16 (m, 7H), 7.08 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 5.74 (s, 2H), 1.65 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.2, 161.0, 146.9, 139.3, 137.9, 137.2, 137.2, 132.2, 132.1, 131.0, 128.6, 127.4, 127.0, 125.7, 124.4, 121.9, 121.4, 120.1, 119.1, 116.3, 110.9, 110.1, 57.0, 47.8, 26.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{31}H_{27}N_4O$ 471.2185; found 471.2191.

*1-Benzyl-3-(3-cyanophenyl)-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**3j**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **3j** as a pale yellow oil (44.8 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14−8.03 (m, 2H), 7.94 (s, 1H), 7.83 (dt, J = 7.3, 1.7 Hz, 1H), 7.66−7.57 (m, 2H), 7.52−7.41 (m, 3H), 7.32 (ddd, J = 8.3, 7.0, 1.1 Hz, 1H), 7.25−7.13 (m, 7H), 7.07 (ddd, J = 7.4, 4.9, 0.8 Hz, 1H), 5.75 (s, 2H), 1.65 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.3, 161.0, 147.0, 137.9, 137.2, 137.1, 135.6, 135.0, 133.8, 132.0, 130.3, 129.2, 128.6, 127.4, 127.1, 125.9, 124.4, 121.8, 121.3, 120.0, 119.1, 118.9, 115.9, 112.5, 110.8, 56.9, 47.8, 26.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{31}H_{27}N_4O$ 471.2185; found 471.2188.

*Methyl-4-(1-benzyl-2-((2-(pyridin-2-yl)propan-2-yl)-carbamoyl)-1H-indol-3-yl)benzoate (**3k**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **3k** as an off-white solid (41.9 mg, 83%), m.p.: 161−163 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09−8.02 (m, 3H), 7.86 (brs, 1H), 7.71−7.66 (m, 3H), 7.52 (td, J = 7.8, 1.8 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.33−7.27 (m, 1H), 7.26−7.21 (m, 2H), 7.21−7.15 (m, 4H), 7.11 (d, J = 8.1 Hz, 1H), 7.00 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 5.75 (s, 2H), 3.90 (s, 3H), 1.62 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.1, 163.4, 161.4, 147.2, 139.1, 138.1, 137.3, 136.9, 131.7, 130.4, 129.7, 128.6, 128.4, 127.3, 127.0, 126.1, 124.3, 121.6, 121.1, 120.4, 119.0, 117.3, 110.7, 57.1, 52.1, 47.8, 26.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{32}H_{30}N_3O_3$ 504.2287; found 504.2263.

*1-Benzyl-3-(4-nitrophenyl)-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**3l**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **3l** as a yellow solid (36.9 mg, 75%), m.p.: 173−175 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24−8.20 (m, 2H), 8.19 (s, 1H), 8.01−7.97 (m, 1H), 7.81−7.75 (m, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.61−7.56 (m, 1H), 7.45 (d, J = 8.4 Hz,

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1H), 7.33 (ddd, J = 8.3, 7.0, 1.1 Hz, 1H), 7.27−7.16 (m, 7H), 7.03 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 5.75 (s, 2H), 1.66 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 163.1, 161.0, 146.8, 146.4, 141.5, 137.7, 137.3, 137.2, 132.5, 130.9, 128.7, 127.4, 127.0, 125.7, 124.5, 123.7, 121.9, 121.6, 120.0, 119.1, 115.8, 111.0, 57.0, 47.9, 26.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{30}H_{27}N_4O_3$ 491.2083; found 491.2094.

*1-Benzyl-N-(2-(pyridin-2-yl)propan-2-yl)-3-(thiophen-2-yl)-1H-indole-2-carboxamide (**3m**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 1/1 gave **3m** as a dark purple oil (29.0 mg, 64%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.28 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 7.76 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.56−7.49 (m, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.35 (dd, J = 5.2, 1.1 Hz, 1H), 7.28 (ddd, J = 8.3, 7.0, 1.1 Hz, 1H), 7.26−7.22 (m, 3H), 7.18 (ddd, J = 11.9, 5.6, 4.2 Hz, 4H), 7.12 (d, J = 8.1 Hz, 1H), 7.09 (dd, J = 5.2, 3.5 Hz, 1H), 7.05 (ddd, J = 7.4, 4.9, 1.0 Hz, 1H), 5.76 (s, 2H), 1.62 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 163.9, 161.2, 147.6, 138.2, 137.1, 136.8, 134.6, 131.7, 128.6, 128.0, 127.3, 127.2, 127.2, 126.9, 126.1, 124.4, 121.5, 121.0, 120.9, 119.1, 110.8, 110.5, 57.3, 47.8, 27.1. HRMS (ESI-TOF) m/z: calcd for $C_{28}H_{26}N_3OS$ $[M + H]^+$ 452.1797; found 452.1799.

*1-Benzyl-3-(1-methyl-1H-pyrazol-4-yl)-N-(2-(pyridin-2-yl)-propan-2-yl)-1H-indole-2-carboxamide (**3n**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 1/1 gave **3n** as a gray brown solid (39.7 mg, 87%), m.p.: 151−152 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.32 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 7.99 (brs, 1H), 7.76 (d, J = 0.6 Hz, 1H), 7.68−7.62 (m, 2H), 7.59 (td, J = 7.9, 1.8 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.27 (ddd, J = 8.3, 7.0, 1.1 Hz, 1H), 7.25−7.20 (m, 3H), 7.19−7.12 (m, 4H), 7.10 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 5.75 (s, 2H), 3.87 (s, 3H), 1.67 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 163.8, 161.6, 147.4, 139.8, 138.4, 137.3, 137.0, 130.5, 129.8, 128.5, 127.1, 126.9, 126.8, 124.1, 121.7, 120.6, 120.5, 119.2, 113.6, 110.4, 109.0, 57.0, 47.7, 38.9, 27.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{28}N_5O$ 450.2294; found 450.2309.

*1-Benzyl-N-(2-(pyridin-2-yl)propan-2-yl)-3-(pyridin-4-yl)-1H-indole-2-carboxamide (**3o**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 2/1 gave **3o** as a yellow solid (23.5 mg, 53%), m.p.: 132−133 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.59 (brs, 2H), 8.17 (s, 1H), 8.17 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.63−7.50 (m, 3H), 7.43 (d, J = 8.4 Hz, 1H), 7.34−7.29 (m, 1H), 7.25−7.12 (m, 7H), 7.05 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 5.74 (s, 2H), 1.67 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 163.2, 161.1, 149.7, 147.1, 142.4, 137.8, 137.3, 137.1, 132.4, 128.6, 127.4, 127.0, 125.6, 125.2, 124.4, 121.8, 121.4, 120.1, 119.0, 115.1, 110.9, 57.0, 47.8, 26.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{29}H_{27}N_4O$ 447.2185; found 447.2177.

*1-Benzyl-N-(2-(pyridin-2-yl)propan-2-yl)-3-(pyridin-3-yl)-1H-indole-2-carboxamide (**3p**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 2/1 gave **3p** as a sandy beige solid (36.2 mg, 81%), m.p.: 148−149 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.88 (d, J = 1.7 Hz, 1H), 8.46 (dd, J = 4.8, 1.5 Hz, 1H), 8.13 (s, 1H), 8.08 (dd, J = 4.8, 0.6 Hz, 1H), 7.90 (dt, J = 7.8, 1.9 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.56 (td, J = 7.8, 7.6, 1.8 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.34−7.27 (m, 2H), 7.25−7.14 (m, 7H), 7.06−7.01 (m, 1H), 5.78 (s, 2H), 1.65 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 163.4, 161.3, 151.0, 148.0, 147.2, 138.1, 137.8, 137.3, 137.0, 131.9, 130.2, 128.6, 127.3, 127.1, 126.2, 124.4, 123.3, 121.6, 121.2, 120.2, 119.0, 114.6, 110.8, 57.0, 47.8, 26.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{29}H_{27}N_4O$ 447.2185; found 447.2180.

*3-([1,1′-Biphenyl]-4-yl)-1-benzyl-N-(2-(pyridin-2-yl)-propan-2-yl)-1H-indole-2-carboxamide (**3q**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **3q** as a white solid (46.4 mg, 89%), m.p.: 146−148 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 4.6 Hz, 1H), 7.74−7.65 (m, 4H), 7.63 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 7.3 Hz, 2H), 7.48−7.40 (m, 4H), 7.34 (t, J = 7.4 Hz, 1H), 7.32−7.27 (m, 1H), 7.27−7.23 (m, 2H), 7.18 (dd, J = 14.7, 7.3 Hz, 4H), 7.06 (d, J = 8.1 Hz, 1H), 6.93 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 5.80 (s, 2H), 1.61 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 163.7, 161.6, 147.4, 141.0, 140.0, 138.5, 137.4, 136.7, 133.0, 131.0, 130.8, 128.8, 128.9, 127.3, 127.2, 127.2, 127.1, 127.0, 126.5, 124.2, 121.5, 120.8, 120.8, 119.0, 118.4, 110.6, 57.2, 47.7, 27.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{36}H_{32}N_3O$ 522.2545; found 522.2550.

*1-Benzyl-3-(4-(dimethylamino)phenyl)-N-(2-(pyridin-2-yl)-propan-2-yl)-1H-indole-2-carboxamide (**3r**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 4/1 gave **3r** as a pale yellow oil (5.9 mg, 12%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.48−7.43 (m, 3H), 7.39 (d, J = 8.4 Hz, 1H), 7.29−7.26 (m, 1H), 7.23 (dd, J = 6.1, 1.4 Hz, 2H), 7.21−7.17 (m, 2H), 7.15−7.11 (m, 3H), 7.04−6.99 (m, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.79 (s, 2H), 2.95 (s, 6H), 1.55 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 164.1, 161.9, 147.8, 138.7, 137.4, 136.6, 136.1, 131.3, 129.5, 128.5, 127.0, 127.0, 126.8, 124.1, 121.2, 121.0, 120.3, 119.6, 119.0, 112.8, 110.3, 57.3, 47.5, 40.7, 27.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{32}H_{33}N_4O$ 489.2654; found 489.2666.

*1-Benzyl-3-(2-nitrophenyl)-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**3s**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **3s** as a dark brown oil (5.6 mg, 11%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (ddd, J = 4.8, 1.7, 0.9, 1H), 8.04 (dd, J = 8.2, 1.0, 1H), 7.99 (brs, 1H), 7.64−7.59 (m, 1H), 7.59−7.55 (m, 1H), 7.52−7.45 (m, 2H), 7.37 (d, J = 8.4, 1H), 7.30−7.27 (m, 2H), 7.26−7.18 (m, 3H), 7.15−7.08 (m, 3H), 7.06−6.99 (m, 2H), 5.88 (d, J = 16.3, 1H), 5.69 (d, J = 16.2, 1H), 1.56 (s, 3H), 1.43 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 163.7, 160.9, 150.4, 147.3, 138.1, 137.2, 136.8, 134.3, 132.6, 132.0, 129.4, 128.6, 127.2, 126.6, 126.3, 124.4, 124.1, 121.5, 121.1, 119.8, 119.0, 113.9, 110.7, 57.2, 47.8, 27.5, 26.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{30}H_{27}N_4O_3$ 491.2083; found 491.2083.

*(E)-1-Benzyl-N-(2-(pyridin-2-yl)propan-2-yl)-3-styryl-1H-indole-2-carboxamide (**3t**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **3t** as a colorless oil (28.3 mg, 60%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.17−8.12 (m, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 16.5 Hz, 1H), 7.64 (td, J = 7.8, 1.8 Hz, 1H), 7.52 (d, J = 7.4 Hz, 2H), 7.39−7.34 (m, 2H), 7.29 (ddd, J = 10.4, 6.1, 4.7 Hz, 4H), 7.24−7.21 (m, 4H), 7.19−7.17 (m, 1H), 7.16−7.13 (m, 2H), 7.06 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 5.70 (s, 2H), 1.82 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 163.9, 161.5, 147.9, 138.4, 138.2, 137.9, 137.0, 132.8, 129.8, 128.6, 128.6, 127.2, 127.0, 126.9, 126.1, 125.2, 124.3, 121.8, 121.6, 121.2, 121.0, 119.2, 115.2, 110.8, 57.6, 47.7, 27.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{32}H_{30}N_3O$ 472.2389; found 472.2399.

*tert-Butyl (4-(1-Benzyl-2-((2-(pyridin-2-yl)propan-2-yl)-carbamoyl)-1H-indol-3-yl)phenyl)carbamate (**3u**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **3u** as a white solid (41.0 mg, 73%), m.p.: 87−88 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.25−8.16 (m, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.56−7.48 (m, 4H), 7.46−7.36 (m, 3H), 7.30−7.26 (m, 1H), 7.25−7.21 (m, 2H), 7.21−7.12 (m, 4H), 7.07 (d, J = 8.1 Hz, 1H), 7.04−6.99 (m, 1H), 6.51 (brs, 1H), 5.77 (s, 2H), 1.59 (s, 6H), 1.53 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 163.8, 161.7, 152.6, 147.6, 138.5, 137.5, 137.3, 136.7, 131.2, 130.4, 128.5, 128.5, 127.1, 126.9, 126.6, 124.2, 121.4, 120.7, 120.6, 119.0, 118.5, 118.4, 110.5, 80.6, 57.2, 47.6, 28.4, 27.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{35}H_{37}N_4O_3$ 561.2866; found 561.2867.

*1-Benzyl-3-(4-methoxyphenyl)-4-methyl-N-(2-(pyridin-2-yl)-propan-2-yl)-1H-indole-2-carboxamide (**4a**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **4a** as an off-white solid (38.5 mg, 79%), m.p.: 136−137 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.34 (dd, J = 4.8, 0.7 Hz, 1H), 7.48 (td, J = 7.8, 1.8 Hz, 1H), 7.45−7.40 (m, 2H), 7.26 (d, J = 2.0 Hz, 1H), 7.24 (d, J = 7.7 Hz, 2H), 7.22−7.11 (m, 4H), 7.05 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.96−6.89 (m, 3H), 6.84 (d, J = 7.1 Hz, 1H), 5.77 (s, 2H), 3.80 (s, 3H), 2.11 (s, 3H), 1.44 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 164.1, 161.7, 159.3, 147.8, 138.7, 137.4, 136.5, 132.7, 132.5, 130.7, 128.5, 128.2, 127.0, 126.9, 125.4, 124.0, 122.0, 121.4, 119.4, 119.0, 113.6, 108.4, 57.3, 55.3, 47.6, 27.3, 20.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{32}H_{32}N_3O_2$ 490.2495; found 490.2495.

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*1-Benzyl-6-methoxy-3-(4-methoxyphenyl)-N-(2-(pyridin-2-yl)-propan-2-yl)-1H-indole-2-carboxamide (**4b**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **4b** as an off-white solid (26.0 mg, 51%), m.p.: 115−117 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 4.2 Hz, 1H), 7.52−7.44 (m, 4H), 7.29 (brs, 1H), 7.27−7.23 (m, 2H), 7.21−7.18 (m, 1H), 7.18−7.14 (m, 2H), 7.05−6.99 (m, 2H), 6.98−6.93 (m, 2H), 6.80 (dq, J = 4.1, 2.1 Hz, 2H), 5.74 (s, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 1.56 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.1, 161.7, 159.0, 158.1, 147.6, 138.6, 138.4, 136.6, 131.7, 129.0, 128.5, 127.1, 126.9, 126.2, 121.6, 121.3, 121.2, 119.2, 119.0, 114.1, 111.1, 93.1, 57.1, 55.6, 55.4, 47.6, 27.2. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{32}H_{32}N_3O_3$ 506.2444; found 506.2447.

*1-Benzyl-5-methoxy-3-(4-methoxyphenyl)-N-(2-(pyridin-2-yl)-propan-2-yl)-1H-indole-2-carboxamide (**4c**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **4c** as a yellow solid (36.2 mg, 72%), m.p.: 132−134 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 4.2 Hz, 1H), 7.54−7.46 (m, 3H), 7.40 (brs, 1H), 7.28 (d, J = 9.0 Hz, 1H), 7.23 (d, J = 7.6 Hz, 2H), 7.20−7.16 (m, 1H), 7.14 (d, J = 7.2 Hz, 2H), 7.08−7.00 (m, 3H), 6.99−6.95 (m, 2H), 6.94 (dd, J = 9.0, 2.4 Hz, 1H), 5.74 (s, 2H), 3.79 (s, 3H), 3.79 (s, 3H), 1.57 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.0, 161.7, 158.9, 154.9, 147.6, 138.6, 136.7, 132.7, 131.7, 130.7, 128.5, 127.1, 127.0, 126.9, 126.3, 121.4, 119.0, 118.2, 115.1, 114.2, 111.4, 101.4, 57.2, 55.8, 55.3, 47.8, 27.2. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{32}H_{32}N_3O_3$ 506.2444; found 506.2455.

*1-Benzyl-3-(4-fluorophenyl)-5-methoxy-N-(2-(pyridin-2-yl)-propan-2-yl)-1H-indole-2-carboxamide (**4d**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **4d** as an off-white solid (46.1 mg, 93%), m.p.: 150−151 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (ddd, J = 4.8, 1.6, 0.8 Hz, 1H), 7.72 (brs, 1H), 7.59−7.49 (m, 3H), 7.29 (d, J = 9.0 Hz, 1H), 7.26−7.21 (m, 2H), 7.20−7.15 (m, 3H), 7.13−7.08 (m, 3H), 7.04 (ddd, J = 7.4, 4.9, 1.0 Hz, 1H), 7.00 (d, J = 2.4 Hz, 1H), 6.95 (dd, J = 8.9, 2.5 Hz, 1H), 5.73 (s, 2H), 3.79 (s, 3H), 1.61 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.7, 162.2 (d, $^1J_{C\text{-}F}$ = 245.7 Hz), 161.4, 155.1, 147.3, 138.4, 136.9, 132.6, 132.1 (d, $^3J_{C\text{-}F}$ = 7.6 Hz), 131.4, 130.1 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 128.6, 127.2, 126.9, 126.8, 121.6, 119.1, 117.2, 115.5 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 115.0, 111.6, 101.2, 57.0, 55.8, 47.8, 27.0. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{31}H_{29}FN_3O_2$ 494.2244; found 494.2253.

*1-Benzyl-5-fluoro-3-(4-methoxyphenyl)-N-(2-(pyridin-2-yl)-propan-2-yl)-1H-indole-2-carboxamide (**4e**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **4e** as a white solid (38.8 mg, 79%), m.p.: 118−119 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 7.59 (brs, 1H), 7.55−7.50 (m, 1H), 7.49−7.46 (m, 2H), 7.30 (dd, J = 9.0, 4.2 Hz, 1H), 7.27−7.26 (m, 1H), 7.25−7.23 (m, 2H), 7.22−7.17 (m, 1H), 7.17−7.13 (m, 2H), 7.11−7.07 (m, 1H), 7.06−6.98 (m, 2H), 6.98−6.93 (m, 2H), 5.75 (s, 2H), 3.79 (s, 3H), 1.59 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.7, 161.4, 158.5 (d, $^1J_{C\text{-}F}$ = 236.9 Hz), 157.5, 147.4, 138.2, 136.7, 133.8, 131.8, 131.5, 128.6, 127.2, 127.0 (d, $^3J_{C\text{-}F}$ = 10.1 Hz), 126.9, 125.6, 121.4, 119.0, 118.4 (d, $^4J_{C\text{-}F}$ = 5.0 Hz), 114.1, 112.8 (d, $^2J_{C\text{-}F}$ = 26.5 Hz), 111.4 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 105.2 (d, $^2J_{C\text{-}F}$ = 22.7 Hz), 57.1, 55.3, 47.9, 27.0. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{31}H_{29}FN_3O_2$ 494.2244; found 494.2254.

*1-Benzyl-5-bromo-3-(4-methoxyphenyl)-N-(2-(pyridin-2-yl)-propan-2-yl)-1H-indole-2-carboxamide (**4f**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **4f** as an off-white solid (37.7 mg, 68%), m.p.: 157−158 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (dd, J = 4.8, 0.7 Hz, 1H), 7.73 (d, J = 1.0 Hz, 1H), 7.61 (brs, 1H), 7.52 (ddd, J = 8.0, 7.5, 1.8 Hz, 1H), 7.49−7.44 (m, 2H), 7.33 (dd, J = 8.8, 1.9 Hz, 1H), 7.27−7.25 (m, 1H), 7.25−7.22 (m, 2H), 7.22−7.16 (m, 1H), 7.14 (d, J = 7.2 Hz, 2H), 7.08 (d, J = 8.1 Hz, 1H), 7.03 (ddd, J = 7.4, 4.9, 1.0 Hz, 1H), 6.98−6.93 (m, 2H), 5.74 (s, 2H), 3.78 (s, 3H), 1.59 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.7, 161.2, 159.2, 147.5, 138.1, 136.8, 135.9, 131.7, 131.3, 128.6, 128.4, 127.3, 127.0, 126.9, 125.3, 123.2, 121.5, 119.0, 118.0, 114.2, 113.8, 112.1, 57.2, 55.4, 47.8, 27.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{31}H_{29}BrN_3O_2$ 554.1443; found 554.1429.

*1-Benzyl-6-bromo-3-(4-methoxyphenyl)-N-(2-(pyridin-2-yl)-propan-2-yl)-1H-indole-2-carboxamide (**4g**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **4g** as a colorless oil (36.3 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21−8.15 (m, 1H), 7.59−7.54 (m, 2H), 7.52 (td, J = 7.8, 1.8 Hz, 1H), 7.49−7.45 (m, 3H), 7.30−7.26 (m, 1H), 7.26−7.18 (m, 3H), 7.17−7.12 (m, 2H), 7.07 (d, J = 8.1 Hz, 1H), 7.05−7.01 (m, 1H), 6.97−6.93 (m, 2H), 5.72 (s, 2H), 3.79 (s, 3H), 1.58 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.7, 161.2, 159.1, 147.4, 138.0, 138.0, 136.7, 131.6, 130.7, 128.6, 127.3, 126.8, 125.6, 125.4, 124.0, 122.1, 121.4, 119.0, 118.7, 117.8, 114.1, 113.3, 57.1, 55.3, 47.7, 27.0. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{31}H_{29}BrN_3O_2$ 554.1443; found 554.1437.

*1-Benzyl-3-(4-methoxyphenyl)-5-nitro-N-(2-(pyridin-2-yl)-propan-2-yl)-1H-indole-2-carboxamide (**4h**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **4h** as a yellow solid (33.1 mg, 64%), m.p.: 166−167 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, J = 2.1 Hz, 1H), 8.21−8.12 (m, 2H), 7.90 (brs, 1H), 7.57 (td, J = 7.9, 1.8 Hz, 1H), 7.53−7.46 (m, 2H), 7.44 (d, J = 9.2 Hz, 1H), 7.29−7.26 (m, 1H), 7.26-7.24 (m, 1H), 7.24−7.16 (m, 3H), 7.14 (d, J = 8.1, 1H), 7.06 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 7.02−6.94 (m, 2H), 5.81 (s, 2H), 3.80 (s, 3H), 1.62 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.5, 160.6, 159.6, 147.3, 142.5, 139.8, 137.3, 136.9, 133.4, 131.6, 128.8, 127.6, 127.0, 126.3, 124.3, 121.6, 120.6, 119.4, 119.0, 118.4, 114.4, 110.6, 57.2, 55.4, 48.3, 26.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{31}H_{29}N_4O_4$ 521.2189; found 521.2172.

*3-(4-Methoxyphenyl)-1-methyl-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**4i**):* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **4i** as a white solid (31.2 mg, 78%), m.p.: 164−165 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27−8.20 (m, 1H), 7.65−7.54 (m, 3H), 7.49−7.42 (m, 2H), 7.39 (d, J = 8.3 Hz, 1H), 7.35−7.30 (m, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.17−7.11 (m, 1H), 7.07 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 6.98−6.92 (m, 2H), 4.01 (s, 3H), 3.78 (s, 3H), 1.67 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.0, 161.8, 158.9, 147.6, 137.6, 136.8, 131.7, 130.6, 126.6, 126.3, 123.9, 121.5, 120.7, 120.3, 119.1, 118.0, 114.1, 109.9, 57.1, 55.3, 31.5, 27.3. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{25}H_{26}N_3O_2$ 400.2025; found 400.2028.

*3-(2-Methoxyphenyl)-1-methyl-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**4j**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **4j** as a white solid (33.0 mg, 83%), m.p.: 112−114 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32−8.26 (m, 1H), 7.67 (brs, 1H), 7.54 (td, J = 7.8, 1.8 Hz, 1H), 7.43−7.36 (m, 3H), 7.35−7.27 (m, 2H), 7.13 (d, J = 8.1 Hz, 1H), 7.12−7.02 (m, 3H), 6.96 (d, J = 8.2 Hz, 1H), 4.01 (s, 3H), 3.75 (s, 3H), 1.60 (brs, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.2, 161.8, 157.4, 147.8, 137.7, 136.6, 132.9, 131.5, 129.1, 126.9, 123.7, 123.0, 121.3, 120.9, 120.8, 120.1, 119.0, 113.7, 111.1, 109.8, 57.1, 55.5, 31.6, 27.5. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{25}H_{26}N_3O_2$ 400.2025; found 400.2041.

*1-Methyl-3-(2-nitrophenyl)-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**4k**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **4k** as a yellow solid (7.3 mg, 18%), m.p.: 171−173 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (brs, 1H), 8.17 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 8.02 (dd, J = 8.2, 1.1 Hz, 1H), 7.64−7.59 (m, 1H), 7.56 (td, J = 7.5, 1.3 Hz, 1H), 7.50 (dd, J = 7.7, 1.4 Hz, 1H), 7.46−7.38 (m, 2H), 7.32 (ddd, J = 8.3, 6.9, 1.1 Hz, 1H), 7.25−7.18 (m, 2H), 7.13−7.05 (m, 2H), 4.04 (s, 3H), 1.73 (s, 3H), 1.56 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.8, 161.0, 150.3, 147.3, 137.4, 136.9, 134.5, 132.5, 132.1, 129.5, 128.5, 126.1, 124.1, 124.1, 121.6, 120.8, 119.7, 119.1, 113.2, 110.2, 57.1, 31.5, 27.2, 27.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{24}H_{23}N_4O_3$ 415.1770; found 415.1767.

*1-Methyl-3-phenyl-N-(2-(pyridin-2-yl)propan-2-yl)-1H-indole-2-carboxamide (**4l**).* Purification by flash chromatography in petroleum ether/ethyl acetate = 3/1 gave **4l** as a pale orange solid (32.7 mg, 89%), m.p.: 174−175 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 7.67−7.57 (m, 3H), 7.57−7.51 (m, 2H), 7.44−7.36 (m, 3H), 7.36−7.31 (m, 1H), 7.28−7.24 (m, 2H), 7.18−

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7.11 (m, 1H), 7.05 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 4.00 (s, 3H), 1.66 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 163.9, 161.7, 147.6, 137.6, 136.8, 134.1, 131.0, 130.6, 128.5, 127.1, 126.4, 124.0, 121.5, 120.6, 120.5, 119.1, 118.2, 109.9, 57.1, 31.5, 27.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{24}N_3O$ 370.1919; found 370.1922.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02631.

Mechanistic studies and copies of NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Cacchi, S.; Fabrizi, G. Synthesis and Functionalization of Indoles Through Palladium-catalyzed Reactions. *Chem. Rev.* **2005**, *105*, 2873−2920. (b) Zhang, M.-Z.; Chen, Q.; Yang, G.-F. A review on recent developments of indole-containing antiviral agents. *Eur. J. Med. Chem.* **2015**, *89*, 421−441. (c) Singh, T. P.; Singh, O. M. Recent progress in biological activities of indole and indole alkaloids. *Mini Rev. Med. Chem.* **2018**, *18*, 9−25. (d) Humphrey, G. R.; Kuethe, J. T. Practical methodologies for the synthesis of indoles. *Chem. Rev.* **2006**, *106*, 2875−2911. (e) Zoidis, G.; Giannakopoulou, E.; Stevaert, A.; Frakolaki, E.; Myrianthopoulos, V.; Fytas, G.; Mavromara, P.; Mikros, E.; Bartenschlager, R.; Vassilaki, N.; Naesens, L. Novel indole−flutimide heterocycles with activity against influenza PA endonuclease and hepatitis C virus. *Med. Chem. Commun.* **2016**, *7*, 447−456. (f) Kumari, A.; Singh, R. K. Medicinal chemistry of indole derivatives: Current to future therapeutic prospectives. *Bioorg. Chem.* **2019**, *89*, No. 103021. (g) Chadha, N.; Silakari, O. Indoles as therapeutics of interest in medicinal chemistry: Bird's eye view. *Eur. J. Med. Chem.* **2017**, *134*, 159−184. (h) Huang, Z.; Kwon, O.; Huang, H.; Fadli, A.; Marat, X.; Moreau, M.; Lumb, J. P. A bioinspired synthesis of polyfunctional indoles. *Angew. Chem.* **2018**, *130*, 12139−12143.

(2) (a) Zhang, W.; Tang, J.; Yu, W.; Huang, Q.; Fu, Y.; Kuang, G.; Pan, C.; Yu, G. Visible light-driven C-3 functionalization of indoles over conjugated microporous polymers. *ACS Catal.* **2018**, *8*, 8084−8091. (b) Lang, R.; Wu, J.; Shi, L.; Xia, C.; Li, F. Regioselective Rh-catalyzed direct carbonylation of indoles to synthesize indole-3-carboxylates. *Chem. Commun.* **2011**, *47*, 12553−12555. (c) Beck, E. M.; Gaunt, M. J. Pd-Catalyzed C−H Bond Functionalization on the Indole and Pyrrole Nucleus. In *CH Activation*; Springer, 2009; pp 85−121. (d) Zhu, Y.; Rawal, V. H. Palladium-catalyzed C3-benzylation of indoles. *J. Am. Chem. Soc.* **2012**, *134*, 111−114. (e) Das, D.; Roy, S. Palladium (II)-Catalyzed Efficient C-3 Functionalization of Indoles with Benzylic and Allylic Alcohols under Co-Catalyst, Acid, Base, Additive and External Ligand-Free Conditions. *Adv. Synth. Catal.* **2013**, *355*, 1308−1314. (f) Peng, J.; Liu, L.; Hu, Z.; Huang, J.; Zhu, Q. Direct carboxamidation of indoles by palladium-catalyzed C−H activation and isocyanide insertion. *Chem. Commun.* **2012**, *48*, 3772−3774. (g) Wang, C.; Wang, S.; Li, H.; Yan, J.; Chi, H.; Chen, X.; Zhang, Z. Copper-catalyzed decarboxylative C3-acylation of free (N−H) indoles with α-oxocarboxylic acids. *Org. Biomol. Chem.* **2014**, *12*, 1721−1724. (h) Liu, S.; Zhao, F.; Chen, X.; Deng, G.-J.; Huang, H. Aerobic Oxidative Functionalization of Indoles. *Adv. Synth. Catal.* **2020**, *362*, 3795−3823.

(3) (a) Sandtorv, A. H. Transition Metal-Catalyzed C−H Activation of Indoles. *Adv. Synth. Catal.* **2015**, *357*, 2403−2435. (b) Joucla, L.; Djakovitch, L. Transition Metal-Catalysed, Direct and Site-Selective N1-, C2-or C3-Arylation of the Indole Nucleus: 20 Years of Improvements. *Adv. Synth. Catal.* **2009**, *351*, 673−714. (c) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. Ruthenium (II)-catalyzed C−H bond activation and functionalization. *Chem. Rev.* **2012**, *112*, 5879−5918. (d) Yamaguchi, M.; Suzuki, K.; Sato, Y.; Manabe, K. Palladium-Catalyzed Direct C3-Selective Arylation of N-Unsubstituted Indoles with Aryl Chlorides and Triflates. *Org. Lett.* **2017**, *19*, 5388−5391. (e) Zhang, T.-Y.; Liu, C.; Chen, C.; Liu, J.-X.; Xiang, H.-Y.; Jiang, W.; Ding, T.-M.; Zhang, S.-Y. Copper-Mediated Cascade C−H/N−H Annulation of Indolocarboxamides with Arynes: Construction of Tetracyclic Indoloquinoline Alkaloids. *Org. Lett.* **2018**, *20*, 220−223. (f) Modha, S. G.; Greaney, M. F. Atom-economical transformation of diaryliodonium salts: tandem C−H and N−H arylation of indoles. *J. Am. Chem. Soc.* **2015**, *137*, 1416−1419. (g) Medina-Mercado, I.; Asomoza-Solís, E. O.; Martínez-González, E.; Ugalde-Saldívar, V. M.; Ledesma-Olvera, L. G.; Barquera-Lozada, J. E.; Gómez-Vidales, V.; Barroso-Flores, J.; Frontana-Uribe, B. A.; Porcel, S. Ascorbic Acid as an Aryl Radical Inducer in the Gold-Mediated Arylation of Indoles with Aryldiazonium Chlorides. *Chem. − Eur. J.* **2020**, *26*, 634−642.

(4) (a) Hu, B.; Jetter, J. W.; Wrobel, J. E.; Antrilli, T. M.; Bauer, J. S.; Di, L.; Polakowski, S.; Jain, U.; Crandall, D. L. Synthesis and SAR of 2-carboxylic acid indoles as inhibitors of plasminogen activator inhibitor-1. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3514−3518. (b) Andersen, K.; Perregaard, J.; Arn, J.; Nielsen, J. B.; Begtrup, M. Selective, centrally acting serotonin 5-HT2 antagonists. 2. Substituted 3-(4-fluorophenyl)-1H-indoles. *J. Med. Chem.* **1992**, *35*, 4823−4831. (c) Niphakis, M. J.; Lum, K. M.; Cognetta, A. B., III; Correia, B. E.; Ichu, T.-A.; Olucha, J.; Brown, S. J.; Kundu, S.; Piscitelli, F.; Rosen, H.; Cravatt, B. F. A global map of lipid-binding proteins and their ligandability in cells. *Cell* **2015**, *161*, 1668−1680. (d) Bie, J.; Liu, S.; Zhou, J.; Xu, B.; Shen, Z. Design, synthesis and biological evaluation of 7-nitro-1H-indole-2-carboxylic acid derivatives as allosteric inhibitors of fructose-1, 6-bisphosphatase. *Bioorg. Med. Chem.* **2014**, *22*, 1850−1862.

(5) (a) McGlacken, G. P.; Bateman, L. M. Recent advances in aryl−aryl bond formation by direct arylation. *Chem. Soc. Rev.* **2009**, *38*,

2447−2464. (b) Seregin, I. V.; Gevorgyan, V. Direct transition metal-catalyzed functionalization of heteroaromatic compounds. *Chem. Soc. Rev.* **2007**, *36*, 1173−1193. (c) Alberico, D.; Scott, M. E.; Lautens, M. Aryl− aryl bond formation by transition-metal-catalyzed direct arylation. *Chem. Rev.* **2007**, *107*, 174−238. (d) El Kazzouli, S.; Koubachi, J.; El Brahmi, N.; Guillaumet, G. Advances in direct C−H arylation of 5, 5-6, 5-and 6, 6-fused-heterocycles containing heteroatoms (N, O, S). *RSC Adv.* **2015**, *5*, 15292−15327. (e) Utepova, I. A.; Trestsova, M. A.; Chupakhin, O. N.; Charushin, V. N.; Rempel, A. A. Aerobic oxidative C−H/C−H coupling of azaaromatics with indoles and pyrroles in the presence of TiO2 as a photocatalyst. *Green Chem.* **2015**, *17*, 4401−4410. (f) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition Metals for C−H Activation. *Chem. Rev.* **2019**, *119*, 2192−2452.

(6) (a) Cusati, G.; Djakovitch, L. First heterogeneously palladium-catalysed fully selective C3-arylation of free NH-indoles. *Tetrahedron Lett.* **2008**, *49*, 2499−2502. (b) Zhang, Z.; Hu, Z.; Yu, Z.; Lei, P.; Chi, H.; Wang, Y.; He, R. Direct palladium-catalyzed C-3 arylation of indoles. *Tetrahedron Lett.* **2007**, *48*, 2415−2419. (c) Bellina, F.; Benelli, F.; Rossi, R. Direct palladium-catalyzed C-3 arylation of free (NH)-indoles with aryl bromides under ligandless conditions. *J. Org. Chem.* **2008**, *73*, 5529−5535. (d) Lane, B. S.; Brown, M. A.; Sames, D. Direct palladium-catalyzed C-2 and C-3 arylation of indoles: a mechanistic rationale for regioselectivity. *J. Am. Chem. Soc.* **2005**, *127*, 8050−8057. (e) Stuart, D. R.; Fagnou, K. The catalytic cross-coupling of unactivated arenes. *Science* **2007**, *316*, 1172−1175.

(7) (a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. Cu (II)-catalyzed direct and site-selective arylation of indoles under mild conditions. *J. Am. Chem. Soc.* **2008**, *130*, 8172−8174. (b) Cornella, J.; Lu, P.; Larrosa, I. Intermolecular decarboxylative direct C-3 arylation of indoles with benzoic acids. *Org. Lett.* **2009**, *11*, 5506−5509. (c) Zhou, J.; Hu, P.; Zhang, M.; Huang, S.; Wang, M.; Su, W. A versatile catalyst for intermolecular direct arylation of Indoles with benzoic acids as arylating reagents. *Chem. − Eur. J.* **2010**, *16*, 5876−5881. (d) Caramenti, P.; Nicolai, S.; Waser, J. Indole-and Pyrrole-BX: Bench-Stable Hypervalent Iodine Reagents for Heterocycle Umpolung. *Chem. − Eur. J.* **2017**, *23*, 14702−14706. (e) Caramenti, P.; Nandi, R. K.; Waser, J. Metal-Free Oxidative Cross Coupling of Indoles with Electron-Rich (Hetero) arenes. *Chem. − Eur. J.* **2018**, *24*, 10049−10053. (f) Gong, X.; Song, G.; Zhang, H.; Li, X. Palladium-catalyzed oxidative cross-coupling between pyridine N-oxides and indoles. *Org. Lett.* **2011**, *13*, 1766−1769. (g) Chen, Y.; Guo, S.; Li, K.; Qu, J.; Yuan, H.; Hua, Q.; Chen, B. Palladium-Catalyzed Direct Denitrogenative C-3-Arylation of 1H-Indoles with Arylhydrazines using Air as the Oxidant. *Adv. Synth. Catal.* **2013**, *355*, 711−715. (h) Zhao, S.; Liu, Y.-J.; Yan, S.-Y.; Chen, F.-J.; Zhang, Z.-Z.; Shi, B.-F. Copper-/Silver-Mediated Arylation of C (sp2)−H Bonds with 2-Thiophenecarboxylic Acids. *Org. Lett.* **2015**, *17*, 3338−3341.

(8) (a) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. Cu $(OAc)_2$-catalyzed coupling of aromatic C−H bonds with arylboron reagents. *Org. Lett.* **2014**, *16*, 5666−5669. (b) Shang, R.; Ilies, L.; Asako, S.; Nakamura, E. Iron-catalyzed C (sp2)−H bond functionalization with organoboron compounds. *J. Am. Chem. Soc.* **2014**, *136*, 14349−14352. (c) Yokota, A.; Aihara, Y.; Chatani, N. Nickel (II)-Catalyzed Direct Arylation of C−H Bonds in Aromatic Amides Containing an 8-Aminoquinoline Moiety as a Directing Group. *J. Org. Chem.* **2014**, *79*, 11922−11932. (d) Zhao, S.; Liu, B.; Zhan, B. B.; Zhang, W. D.; Shi, B. F. Nickel-Catalyzed Ortho-Arylation of Unactivated (Hetero)aryl C−H Bonds with Arylsilanes Using a Removable Auxiliary. *Org. Lett.* **2016**, *18*, 4586. (e) Aihara, Y.; Chatani, N. Ruthenium-catalyzed direct arylation of C−H bonds in aromatic amides containing a bidentate directing group: significant electronic effects on arylation. *Chem. Sci.* **2013**, *4*, 664−670. (f) Bu, Q.; Gońka, E.; Kuciński, K.; Ackermann, L. Cobalt-Catalyzed Hiyama-Type C− H Activation with Arylsiloxanes: Versatile Access to Highly ortho-Decorated Biaryls. *Chem. − Eur. J.* **2019**, *25*, 2213−2216. (g) Rej, S.; Ano, Y.; Chatani, N. Bidentate Directing Groups: An Efficient Tool in C−H Bond Functionalization Chemistry for the Expedient Construction of C−C Bonds. *Chem. Rev.* **2020**, *120*, 1788−1887. (h) Liu, B.; Zhang, Z.-Z.; Li, X.; Shi, B.-F. Nickel (II)-catalyzed direct arylation of aryl C−H bonds with aryl-boron reagents directed by a removable bidentate auxiliary. *Org. Chem. Front.* **2016**, *3*, 897−900.

(9) (a) Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F. J.; Shi, B. F. Stereoselective Synthesis of Chiral α-Amino-β-Lactams through Palladium (II)-Catalyzed Sequential Monoarylation/Amidation of C (sp3)- H Bonds. *Angew. Chem., Int. Ed.* **2013**, *52*, 13588−13592. (b) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. Pd (II)-catalyzed alkoxylation of unactivated C (sp3)−H and C (sp2)−H bonds using a removable directing group: efficient synthesis of alkyl ethers. *Chem. Sci.* **2013**, *4*, 4187−4192.

(10) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457−2483.

(11) (a) Rouquet, G.; Chatani, N. Ruthenium-catalyzed ortho-C−H bond alkylation of aromatic amides with α, β-unsaturated ketones via bidentate-chelation assistance. *Chem. Sci.* **2013**, *4*, 2201−2208. (b) Aihara, Y.; Chatani, N. Nickel-catalyzed direct arylation of C (sp3)−H bonds in aliphatic amides via bidentate-chelation assistance. *J. Am. Chem. Soc.* **2014**, *136*, 898−901. (c) Aihara, Y.; Chatani, N. Nickel-catalyzed direct alkylation of C−H bonds in benzamides and acrylamides with functionalized alkyl halides via bidentate-chelation assistance. *J. Am. Chem. Soc.* **2013**, *135*, 5308−5311.

(12) (a) Tang, H.; Zhou, B.; Huang, X.-R.; Wang, C.; Yao, J.; Chen, H. Origins of Selective C(sp2)−H Activation Using Transition Metal Complexes with N,N-Bidentate Directing Groups: A Combined Theoretical−Experimental Study. *ACS Catal.* **2014**, *4*, 649−656. (b) Zhao, S.; Yuan, J.; Li, Y.-C.; Shi, B.-F. Copper-catalyzed oxidative C−H/C−H cross-coupling of benzamides and thiophenes. *Chem. Commun.* **2015**, *51*, 12823−12826.

(13) Li, Y.; Liu, Y. J.; Shi, B. F. Copper-Mediated Thiolation of Unactivated Heteroaryl C−H Bonds with Disulfides under Ligand- and Metal-Oxidant-Free Conditions. *Adv. Synth. Catal.* **2017**, *359*, 4117−4121.

(14) Ai, T.; Xu, Y.; Qiu, L.; Geraghty, R. J.; Chen, L. Hydroxamic acids block replication of hepatitis C virus. *J. Med. Chem.* **2015**, *58*, 785−800.

(15) Murakami, Y.; Watanabe, T.; Kobayashi, A.; Yokoyama, Y. A Novel Method for the Debenzylation of Protected Indole Nitrogen. *Synthesis* **1984**, *1984*, 738−740.

(16) Ganton, M. D.; Kerr, M. A. A Domino Amidation Route to Indolines and Indoles: Rapid Syntheses of Anhydrolycorinone, Hippadine, Oxoassoanine, and Pratosine. *Org. Lett.* **2005**, *7*, 4777−4779.

(17) Vieira, T. O.; Meaney, L. A.; Shi, Y.-L.; Alper, H. Tandem Palladium-Catalyzed N,C−Coupling/Carbonylation Sequence for the Synthesis of 2-Carboxyindoles. *Org. Lett.* **2008**, *10*, 4899−4901.

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