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Cu-Catalyzed Direct Amidation of Aromatic C−H Bonds: An Access to Arylamines

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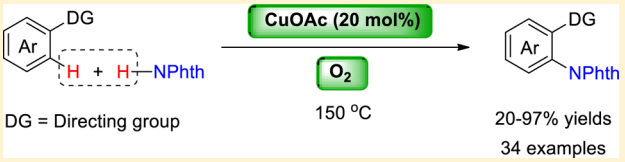
Supporting Information

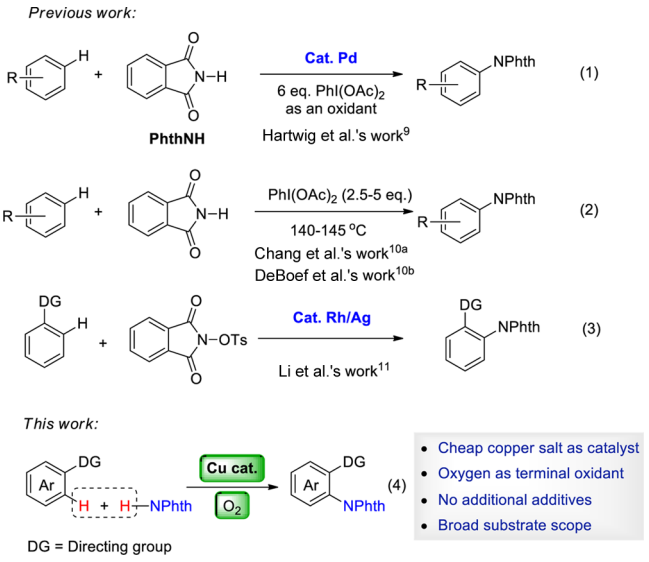
ABSTRACT: A Cu-catalyzed aromatic C−H amidation with phthalimide under oxygen as a terminal oxidant without using additional additives has been achieved. This reaction has the broad substrate scope and shows moderate to good yields in most cases. This method is complementary to the previously reported metal-catalyzed C−H amination systems.



INTRODUCTION

The ubiquity of (hetero)arylamines in natural products, pharmaceuticals, agrochemicals, and organic materials inspires chemists to develop efficient synthetic methodologies for constructing C−N bonds.[1] Traditional approaches for the synthesis of arylamines involve nitration of arenes, followed by reduction.[2] Using strongly acidic nitric acid and harsh conditions in these systems have hampered their broad applicability. Metal-catalyzed C−N cross-coupling reactions, such as the Buchwald−Hartwig coupling, Cu-catalyzed Ullman coupling, and Chan−Evans−Lam coupling, have been developed as alternative protocols for C−N bond formation and are a powerful tool for organic chemists.[3] Despite these advances, the requirement for prefunctionalization of arenes to aryl (pseudo)halides or boronic acids as coupling partner is inherently required.

Recently, the dehydrogenative cross-coupling of amines and aromatic C−H moieties as coupling partners has emerged as a straightforward pathway for the synthesis of (hetero)-arylamines, which has been a complementary and potentially more effective process for the formation of C−N bonds.[4] However, most cases of metal-catalyzed C−H/N−H cross-coupling reactions are limited to the use of expensive transition metals, such as Pd,[5] Rh,[6] and Ru.[7] The amine reagents used in those amination reactions can be classified as amines, amides, sulfonamides, N−O reagents, or N−X (X = halogen) reagents.[4] Interestingly, phthalimide, which is a valuable ammonia equivalent and used to synthesize primary amines, called the Gabriel reaction,[8] has recently captured much attention from chemists. For example, Hartwig and co-workers documented a Pd-catalyzed intermolecular C−H amination reaction of arenes with phthalimide to form *N*-aryl phthalimides using 6 equiv of $PhI(OAc)_2$ as an oxidant (eq 1).[9] Similar works reported by Chang et al.[10a] and DeBoef et al.[10b] were performed in the presence of $PhI(OAc)_2$ (2.5−5 equiv) without adding any metal species (eq 2). At the same time, Li et al. demonstrated a Rh(III) and Ag cocatalyzed C−H amination of arenes bearing directing groups using *N*-OTs phthalimide as amidating reagent (eq 3).[11] We wondered whether an inexpensive copper catalyst and green and abundant molecular oxygen as a terminal oxidant are feasible for the intermolecular amination of indoles and 2-arylpyridines using phthalimide as the amine source (eq 4).



Recently, much effort has been directed toward exploring economical and environmentally friendly catalysts, which led to various pioneering advances in Cu-mediated and Cu-catalyzed direct C−H amination reactions.[12] In this context, Yu and co-workers first reported the stoichiometric Cu-mediated Ar−H amination of 2-arylpyridines.[13a] Later, a similar work was reported by the Chatani group.[13b] Several improved Cu-catalyzed inter- and intramolecular versions were achieved by Brasche and Buchwald,[13c] Li et al.,[13d] Su et al.,[13e] and John and

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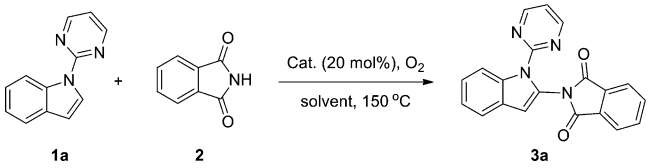
Nicholas.[13f] In addition, aminations of acidic C−H bonds of heterocycles using catalytic Cu/ligand or stoichiometric Ag/base systems were independently reported by Mori et al.,[14a] Wang and Schreiber,[14b] Chang et al.,[14c] and others.[14d−g] More recently, Daugulis et al.[15a] and Chen et al.,[15b] respectively, documented Cu-catalyzed direct aminations of aromatic C−H bonds using removable directing groups. However, in some cases, the use of a stoichiometric amount of oxidant, such as silver species, N−O oxides, and hypervalent iodine, is inevitable. All of these pioneering studies inspired us to pursue a simple Cu/O_2 catalytic system for the sp^2 C−H bond amination. Herein, we document a Cu-catalyzed C−H amidation of *N*-pyrimidyl(pyridyl) indoles and 2-arylpyridines under oxygen using phthalimide as an aminating source (eq 4), which is complementary to the previously reported metal-catalyzed C−H amination systems.[9−11,13−15]

RESULTS AND DISCUSSION

Encouraged by Yu et al.'s report,[13a] we began our study by examining the reaction of *N*-pyrimidyl-substituted indole **1a** with phthalimide **2** in the presence of CuOAc (20 mol %) under an oxygen atmosphere at 150 °C (Table 1, entry 1). To our delight, the desired C−H aminated product **3a** was obtained in 60% yield with specific regioselectivity. The coupling occurred exclusively at the 2-position of the indole. A series of Cu salts examined during the optimization of reaction conditions showed a significant role in promoting the sp^2 C−H amination process. The use of $Cu(OAc)_2$, $Cu(OTf)_2$, and $Cu(OPiv)_2$ also provided the desired amination product **3a** with a slightly decreased yield compared to CuOAc (Table 1, entries 2−4). In contrast, CuCl, $CuBr_2$, and $CuCl_2$ showed no reactivity for this transformation (Table 1, entries 5−8). Notably, running reactions in the absence of a copper catalyst or under a nitrogen atmosphere resulted in no aminated products, indicating that both oxygen and the copper catalyst are critical for amination (Table 1, entry 20). The screening of solvents indicated that nonpolar solvents, including DCE, anisole, *o*-dichlorobenzene, and chlorobenzene, efficiently promoted this transformation, giving 62−81% yields. On the contrary, performing reactions in polar solvents, such as DMF, DMSO, CH_3CN, 1,4-dioxane, and THF, resulted in nearly no desired product (Table 1, entries 9−13). Finally, the mixed solvent of toluene and *o*-dichlorobenzene (1:1) produced the corresponding aminated product **3a** in 86% yield (Table 1, entry 18). By reducing the amount of catalyst from 20 to 10 mol %, a decreased yield (71%) was observed (Table 1, entry 19). Hence, the optimal conditions are CuOAc (20 mol %) and phthalimide (1.2 equiv) under an O_2 atmosphere at 150 °C in toluene/*o*-dichlorobenzene (1:1).

This protocol for CuOAc-catalyzed aromatic C−N coupling via C−H activation is practical and efficient because green molecular oxygen is used as oxidant, no additional additives are needed, and the only byproduct is water. With these optimal conditions in hand, we explored the scope and limitations of this method, as shown in Table 2. A wide range of electron-rich and electron-poor substituted indoles bearing a pyrimidine directing group were first examined under the standard

Table 1. Cu-Catalyzed sp^2 C−H Amination of *N*-Pyrimidyl Indole[a]

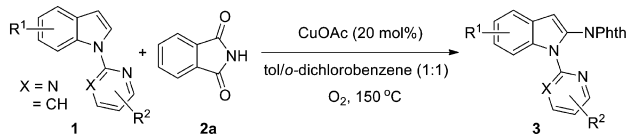


1a 2 3a

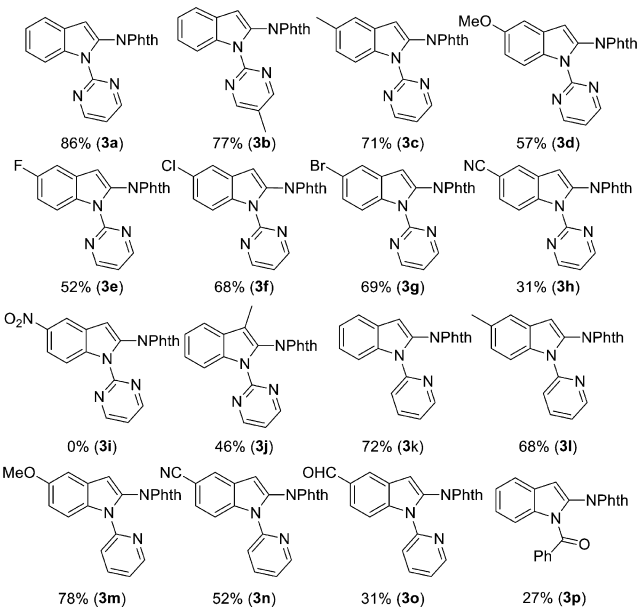
entry	[cat] (20 mol %)	solvent	*T* (h)	yield (%)[b]
1	CuOAc	toluene	48	60
2	$Cu(OAc)_2$	toluene	48	37
3	$Cu(OTf)_2$	toluene	52	49
4	$Cu(OPiv)_2$	toluene	72	40
5	CuCl	toluene	48	trace
6	$CuBr_2$	toluene	48	trace
7	$CuCl_2$	toluene	48	trace
8	$Cu(OH)_2$	toluene	48	trace
9	CuOAc	DMF	70	trace
10	CuOAc	DMSO	70	trace
11	CuOAc	CH_3CN	70	trace
12	CuOAc	1,4-dioxane	70	trace
13	CuOAc	THF	70	trace
14	CuOAc	DCE	60	81
15	CuOAc	anisole	60	61
16	CuOAc	*o*-dichlorobenzene	60	56
17	CuOAc	chlorobenzene	60	62
18	CuOAc	toluene/*o*-dichlorobenzene (1:1)	60	86
19[c]	CuOAc	toluene/*o*-dichlorobenzene (1:1)	60	71
20	none	toluene	60	0

[a]Conditions: substrate **1a** (0.3 mmol), phthalimide (0.36 mmol), cat. (20 mol %), solvent (2 mL), O_2 (1 atm), 150 °C. [b]Isolated yield. [c]10 mol % CuOAc.

Table 2. Amidation of *N*-Heteroarylindoles[a,b]



1 2a 3



[a]Conditions: substrate (0.3 mmol), phthNH (0.36 mmol), CuOAc (20 mol %), O_2 (1 atm), toluene/*o*-dichlorobenzene (1:1, 2 mL), 150 °C, 2−3 days. [b]Isolated yield.

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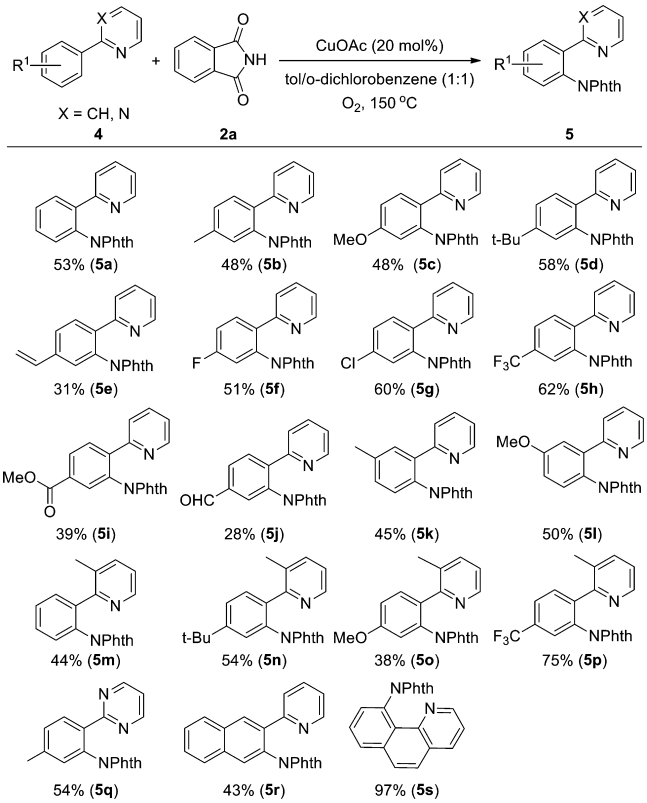
conditions. To our delight, electron-donating groups such as Me or MeO, on either the indole ring or the pyrimidine directing group, all provided the corresponding amination products in moderate to good yields (57−77%). We reasoned that electron-rich indole substrates are prone to proceeding intermolecular polymization,[16] and resulted in moderate yield in MeO-substituted substrate **3d**. Substrates with electron-withdrawing groups, including 5-F (**1e**), 5-Cl (**1f**), 5-Br (**1g**), and 5-CN (**1h**), which could be used as functional handles for further transformations, were subjected to the Cu-catalyzed sp^2 C−H amination reaction, efficiently giving the amination products. The strongly electron-deficient NO_2-substituted indole **1i** did not undergo amination under the standard conditions. Besides the pyrimidine group as a directing group, substrates with pyridine as a directing group also worked well under the standard conditions (31−78% yields). Notably, the aldehyde group (**1o**) was compatible in this system with 31% yield. Some byproducts were observed possibly due to decarbonylation, oxidation, or polymerization from **1o**, but because of the complexity of byproducts from **1o**, structures could not be determined yet. Unexpectedly, by switching the directing group from pyridyl to carbonyl group, *N*-benzoyl indole **1p** gave the corresponding product **3p**, albeit with a low 27% yield. Most of unreacted starting material **1p** was recovered. Other heterocycles, such as benzo[*d*]oxazole and benzo[*d*]thiazole, were attempted, but no desired C−N coupling product was obtained.

Encouraged by the success of a direct C−H amination reaction of indole derivatives, various substituted 2-arylpyridines were investigated to further extend the generality of this approach. As shown in Table 3, either electron-rich or electron-poor groups on the aryl ring gave the corresponding products with moderate yields. We found that the efficiency of 2-arylpyridines or 2-arylpyrimidines in this system was inferior to that of *N*-substituted indoles. Starting materials did not disappear completely after 3−4 days. For example, substrate **4a** was subjected to the standard conditions to afford the monoaminated **5a** as a major product in 53% yield along with 19% of recovered **4a**. By further prolonging the reaction time, a trace amount of bisamination product could be observed. Gratifyingly, electron-withdrawing F (**4f**), Cl (**4g**), CF_3 (**4h**), COOMe (**4i**), and CHO (**4j**) groups were all well-tolerated under the standard conditions. It is worth noting that substrate **4e**, containing an alkene group on the aryl ring, performed in this case to provide the desired product **5e** in 31% yield. In addition, our efforts to apply the conditions optimized for 2-pyrimidyl indole substrates to other types of substrates, such as 2-(naphthalen-2-yl)pyridine and benzo[*h*]quinoline, were fruitful. Notably, benzo[*h*]quinoline **4s** underwent amination in almost quantitative yield (97%).

To test the scope and limitations of amines, the treatment of *N*-pyridyl indole **1k** with saccharin **2b** under the standard conditions was first carried out. As expected, saccharin **2b** worked well, giving the corresponding product **6a** in 43% yield (Table 4, entry 1). *N*-pyrimidyl indole **1a** and 2-phenylpyridine **5a** could also react with saccharin **2b** (Table 4, entries 2−4). To our surprise, benzamide **2c** as an amine coupling partner provided the desired C−N coupling product **6d**, although with a low 22% yield (Table 4, entry 5). We continued attempting other amine reagents, such as 4-nitroaniline **2d** and 2-amine pyridine **2e**, while no obvious corresponding products were observed (Table 4, entries 5 and 6). Therefore, there is still a limitation in amine reagents, which are restricted to amides with strong electron-withdrawing groups.

Table 3. Amidation of 2-Arylpyridine Derivatives[a,b]



[a]Conditions: substrate (0.3 mmol), PhthNH (0.36 mmol), CuOAc (20 mol %), toluene/*o*-dichlorobenzene (1:1, 2 mL), 3−4 days, O_2 (1 atm), 150 °C. [b]Isolated yield.

In order to gain an understanding of the mechanism of this aromatic C−H amination, we performed some mechanistic studies. First, radical inhibitors, such as TEMPO, BHT (2,6-di-*tert*-butyl-4-methylphenol), and 1,4-dinitrobenzene, were added to the reaction under standard conditions, and no significant decrease in yield was observed (Scheme 1). This result suggests that a radical pathway for the C−H amination reaction is possibly unlikely. Next, we investigated the kinetic isotope effect via intermolecular and intramolecular competition experiments. The competition between substrate **4a** and deuterated substrate [**D2**]-**4a** under the standard conditions revealed a primary isotope effect (KIE = 3.7, Scheme 2, eq 5). An intramolecular competition experiment using substrate [**D**]-**4a** was further measured, giving a KIE of 2.1 (Scheme 2, eq 6). These experiments indicated that the C−H bond activation is a rate-determining step in the Cu-catalyzed C−H amination reaction.

On the basis of the above mechanistic studies and previous findings,[17] a tentative mechanism was proposed as shown in Scheme 3. First, the *in situ* generation of the active Cu(II) species occurs by oxidation with O_2. The coordination of pyrimidyl group in the substrate **1a** to the copper(II) center is followed by the disproportionative C−H activation reaction with another Cu(II) species that produces the aryl-Cu(III) intermediate **8** and a Cu(I) species.[17] Subsequently, phthalimide coordinates to the aryl-Cu(III) center and the reductive elimination of Cu(III) intermediate **9** takes place to provide the corresponding aminated product **3a** and a Cu(I) species, which

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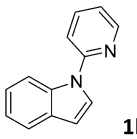
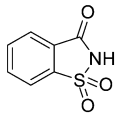
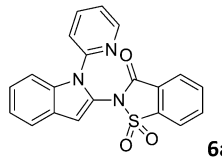
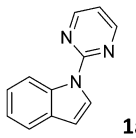
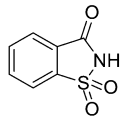
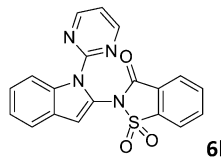
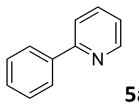
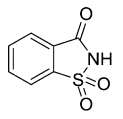
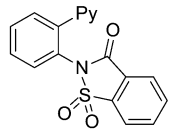
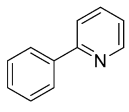
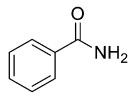
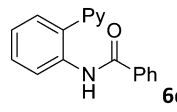
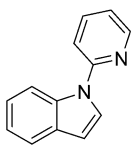
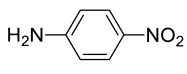
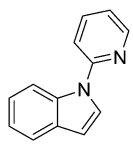
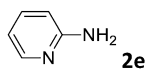
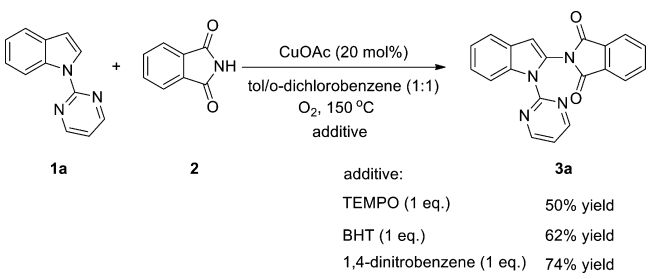
Table 4. Scope and Limitation of Amines[a,b,c]

Entry	substrate	amine	product	yield (%)
1	 1k	 2b	 6a	43
2	 1a	 2b	 6b	32
3	 5a	 2b	 6c	48
4	 5a	 2c	 6d	22
5	 1k	 2d	N.D.[c]	–
6	 1k	 2e	N.D.[c]	–

[a]Conditions: substrate (0.2 mmol), CuOAc (20 mol %), amine (0.2 mmol), toluene/o-dichlorobenzene (1:1, 2 mL), 2–3.5 days, O_2 (1 atm), 150 °C. [b]Isolated yield. [c]Not determined.

Scheme 1. Radical Inhibitor Experiments



would be oxidized by O_2 under acidic conditions to regenerate the Cu(II) species and water as a byproduct. Nevertheless, at present, we cannot completely exclude a single electron transfer (SET) pathway as proposed by Yu et al.[13a]

■ CONCLUSIONS

In conclusion, we have developed a simple and practical Cu-catalyzed C–H amination of *N*-pyrimidyl(pyridyl) indoles and 2-arylpyridines using phthalimide as an aminating source. The employment of inexpensive CuOAc as the catalyst and molecular oxygen as the terminal oxidant is a significant advantage for this intermolecular transformation. This reaction has the broad substrate scope and shows moderate to good yields in most cases. Further exploration of the generality and application of this approach is ongoing in our lab.

■ EXPERIMENTAL SECTION

General. All experiments were carried out under an oxygen atmosphere unless otherwise noted. Reactions were monitored using thin-layer chromatography (TLC). Toluene was dried and distilled before use according to the standard method.[18] ^{1}H, ^{13}C, and ^{19}F NMR spectra were obtained at 400, 100, and 400 MHz, respectively. NMR spectra were run in a solution of deuterated chloroform ($CDCl_3$) and were reported in parts per million (ppm). Abbreviations for signal multiplicity are as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublet, etc. Coupling constants (*J* values) were calculated directly from NMR spectra. High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) techniques. Infrared spectra were obtained using an FT-IR spectrometer.

Preparation of Starting Materials 1 and 4. *N*-Substituted indole derivatives (**1a–1o**) were prepared according to the literature procedure.[19] Pyridine derivatives (**4a–4s**) were prepared via Suzuki coupling with the corresponding boronic acids and 2-bromopyridines according to the reported procedure.[20]

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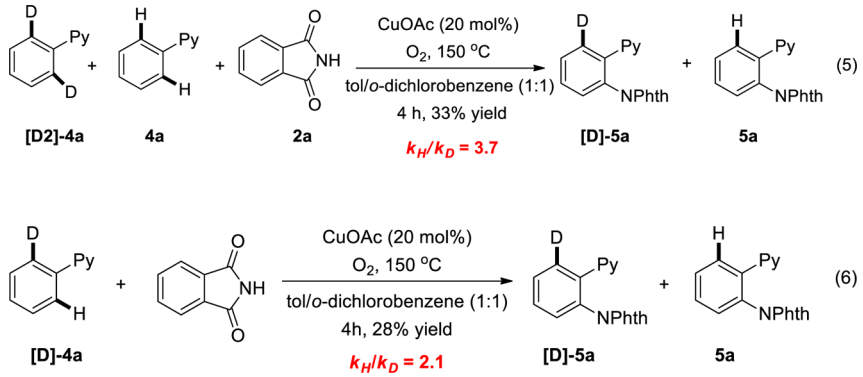
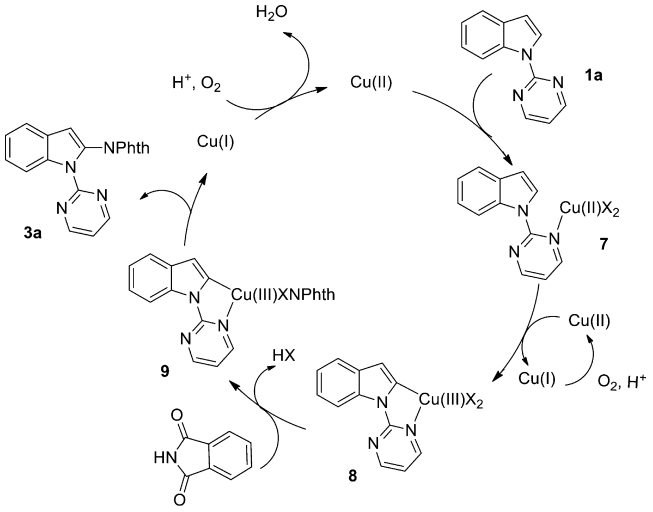
Scheme 2. KIE Experiments



Scheme 3. Proposed Mechanism for the Aromatic C−H Bond Amination



General Procedure for Cu-Catalyzed Direct Amidation of Aromatic C−H Bonds. An oven-dried Schlenk tube equipped with a magnetic stir bar was evacuated and backfilled with oxygen three times. Under oxygen, CuOAc (0.06 mmol, 7.4 mg), indole derivatives (or 2-arylpyridine derivatives) (0.3 mmol), and phthalimide (0.33 mmol, 48.5 mg) were dissolved in the mixed solvent of toluene and *o*-dichlorobenzene (1:1, 2 mL) in the tube. The reaction mixture was stirred at 150 °C for 2.5 days. Then, it was quenched with NaOH solution (10%, 10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give the corresponding products.

2-(1-(Pyrimidin-2-yl)-1H-indol-2-yl)isoindoline-1,3-dione (***3a***). Yellow solid (88 mg, 86% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.43 (petroleum ether:-EtOAc = 3:1, v:v); mp 232−233 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 8.8 Hz, 1H), 8.45 (d, J = 4.8 Hz, 2H), 7.97 (dd, J = 5.4, 3.1 Hz, 2H), 7.82 (dd, J = 5.4, 3.1 Hz, 2H), 7.68 (d, J = 7.6, 1H), 7.41−7.37 (m, 1H), 7.31−7.27 (m, 2H), 6.96 (t, J = 4.8 Hz, 1H), 6.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 158.3, 157.6, 135.9, 134.7, 132.5, 127.6, 125.4, 125.0, 124.2, 122.8, 121.4, 117.3, 116.0, 109.6; IR (KBr) ν 2926, 2855, 1727, 1564, 1452, 1421, 1241, 1083, 753, 718, 709 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{20}H_{13}N_4O_2$ [M + H] 341.1039, found: 341.1044.

2-(1-(5-Methylpyrimidin-2-yl)-1H-indol-2-yl)isoindoline-1,3-dione (***3b***). Yellow solid (82 mg, 77% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.29 (petroleum ether:EtOAc = 3:1, v:v); mp 245−247 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 8.4 Hz, 1H), 8.28 (s, 2H), 7.97−7.95 (m, 2H), 7.83−7.81 (m, 2H), 7.87 (d, J = 7.6 Hz, 1H), 7.38 (t, J = 8.4 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 6.87 (s, 1H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 158.3, 155.7, 135.8, 134.6, 132.5, 127.5, 126.6, 125.3, 124.8, 124.2, 123.7, 122.5, 121.3, 115.6, 108.8, 14.8; IR (KBr) ν 3047, 2925 1727, 1452, 1433, 1344, 1562, 1601, 1232, 1082, 714 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{21}H_{15}N_4O_2$ [M + H]$^+$ 355.1195, found: 355.1180.

2-(5-Methyl-1-(pyrimidin-2-yl)-1H-indol-2-yl)isoindoline-1,3-dione (***3c***). Yellow solid (72 mg, 71% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.28 (petroleum ether:EtOAc = 3:1, v:v); mp 216−217 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 8.4 Hz, 1H), 8.43 (d, J = 4.8 Hz, 2H), 8.00−7.96 (m, 2H), 7.83−7.81 (m, 2H), 7.46 (s, 1H), 7.21 (dd, J = 8.8, 2.0 Hz, 1H), 6.94 (t, J = 4.4 Hz, 1H), 6.81 (s, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 158.2, 157.6, 134.6, 134.2, 132.6, 132.2, 127.8, 126.5, 125.3, 124.2, 121.1, 117.0, 115.8, 109.5, 21.6; IR (KBr) ν 2920, 1725,1425 1246 1100 718 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{21}H_{15}N_4O_2$ [M + H]$^+$ 355.1195, found: 355.1205.

2-(5-Methoxy-1-(pyrimidin-2-yl)-1H-indol-2-yl)isoindoline-1,3-dione (***3d***). Yellow solid (63 mg, 57% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.39 (petroleum ether:EtOAc = 3:1, v:v); mp 230−231 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 9.2 Hz, 1H), 8.41 (d, J = 4.8 Hz, 2H), 7.97 (dd, J = 5.4, 3.0 Hz, 2H), 7.82 (dd, J = 5.4, 3.0 Hz, 2H), 7.13 (d, J = 2.4 Hz, 1H), 7.02 (dd, J = 9.2, 2.4 Hz, 1H), 6.93 (t, J = 4.8 Hz, 1H), 6.82 (s, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 157.9, 157.3, 155.7, 134.3, 132.3, 130.6, 128.1, 125.5, 123.9, 117.1, 116.7, 114.2, 109.4, 103.0, 55.7; IR (KBr) ν 2959, 2927, 2855, 1727, 1450, 1421, 1385, 1211, 1152, 1081, 810, 717 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{21}H_{15}N_4O_3$ [M + H]$^+$ 371.1144, found: 371.1127.

2-(5-Fluoro-1-(pyrimidin-2-yl)-1H-indol-2-yl)isoindoline-1,3-dione (***3e***). Yellow solid (56 mg, 52% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.27 (petroleum ether:EtOAc = 3:1, v:v); mp 244 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (dd, J = 9.2, 4.7 Hz, 1H), 8.45 (d, J = 4.8 Hz, 2H), 7.98 (dd, J = 5.6, 3.2 Hz, 2H), 7.83 (dd, J = 5.6, 3.2 Hz, 2H), 7.33 (dd, J = 8.8, 2.6 Hz, 1H), 7.13 (dt, J = 9.2, 2.6 Hz, 1H), 6.98 (t, J = 4.8 Hz, 1H), 6.86 (s, 1H); ^{19}F NMR (400 MHz, $CDCl_3$) δ −120.8; ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.2 (d, J_{C-F} = 31 Hz), 109.1 (d, J_{C-F} = 5.0 Hz), 112.8 (d, J_{C-F} = 33 Hz), 117.1, 117.3, 124.0, 126.5, 128.0 (d, J_{C-F} = 14 Hz), 132.1, 132.2, 134.5, 157.1, 158.0, 159.1 (d, J_{C-F} = 288 Hz), 167.5; IR (KBr) ν 2924, 2853, 1787, 1731, 1447, 1421, 1202, 1084, 807, 717 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{20}H_{12}N_4O_2F$ [M + H]$^+$ 359.0944, found: 359.0928.

2-(5-Chloro-1-(pyrimidin-2-yl)-1H-indol-2-yl)isoindoline-1,3-dione (***3f***). Yellow solid (76 mg, 68% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.40 (petroleum ether:EtOAc = 3:1, v:v); mp 237−239 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 9.2 Hz, 1H), 8.46 (d, J = 4.8, 2H), 7.97 (dd, J = 5.6, 3.2 Hz, 2H), 7.83 (dd, J = 5.6, 3.2 Hz, 2H), 7.65 (d, J = 2.4 Hz, 1H), 7.35 (dd, J = 8.8, 2.0 Hz, 1H), 7.00 (t, J = 9.6, 4.8 Hz, 1H), 6.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 158.5,

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157.1, 134.5, 133.9, 132.2, 128.4, 128.1, 126.3, 124.9, 124.0, 120.4, 117.3, 117.1, 108.6; IR (KBr) ν 3121, 2926, 1725, 1442, 1423, 1386, 1100, 811, 721 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{20}H_{12}N_4O_2Cl$ $[M + H]^+$ 375.0649, found: 375.0653.

*2-(5-Bromo-1-(pyrimidin-2-yl)-1H-indol-2-yl)isoindoline-1,3-dione (**3g**).* Yellow solid (56 mg, 69% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.31 (petroleum ether:EtOAc = 3:1, v:v); mp 222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 9.0 Hz, 1H), 8.46 (d, J = 4.8 Hz, 2H), 8.01−7.93 (m, 2H), 7.87−7.79 (m, 3H), 7.47 (dd, J = 9.0, 2.0 Hz, 1H), 7.00 (t, J = 4.8 Hz, 1H), 6.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 158.1, 157.1, 134.5, 134.3, 132.2, 129.0, 127.5, 126.3, 124.0, 123.5, 117.5, 117.3, 115.7, 108.5; IR (KBr) ν 3120, 2924, 1725, 1566, 1441, 1421, 1387, 1099, 811, 720 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{20}H_{12}N_4O_2Br$ $[M + H]^+$ 419.0144, found: 419.0147.

*2-(1,3-Dioxoisoindolin-2-yl)-1-(pyrimidin-2-yl)-1H-indole-5-carbonitrile (**3h**).* Yellow solid (34 mg, 31% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.33 (petroleum ether:EtOAc = 3:1, v:v); mp 271−272 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 8.8 Hz, 1H), 8.51 (d, J = 4.8 Hz, 2H), 8.04 (s, 1H), 7.98 (dd, J = 5.6, 2.8 Hz, 2H), 7.85 (dd, J = 5.6, 3.2 Hz, 2H), 7.62 (dd, J = 8.8, 1.6 Hz, 1H), 7.08 (t, J = 4.8 Hz, 1H), 6.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 158.3, 156.8, 137.3, 134.6, 132.1, 129.9, 127.5, 127.2, 126.1, 124.1, 119.8, 118.0, 116.7, 108.8, 105.9; IR (KBr) ν 2923, 2852, 2223, 1725, 1576, 1469, 1422, 1388, 1101, 1084, 822, 707 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{21}H_{12}N_5O_2$ $[M + H]^+$ 366.0991, found: 366.0981.

*2-(3-Methyl-1-(pyrimidin-2-yl)-1H-indol-2-yl)isoindoline-1,3-dione (**3j**).* Yellow solid (49 mg, 46% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.29 (petroleum ether:EtOAc = 3:1, v:v); mp 182−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 8.4 Hz, 1H), 8.40 (d, J = 4.8 Hz, 2H), 7.98 (dd, J = 5.6, 3.2 Hz, 2H), 7.84 (dd, J = 5.6, 3.2 Hz, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.42 (dt, J = 7.2, 1.2 Hz, 1H), 7.32−7.28 (m, 1H), 6.90 (t, J = 4.8 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 157.8, 157.4, 135.3, 134.3, 132.5, 128.5, 128.3, 124.9, 123.9, 122.2, 119.2, 117.6, 116.4, 115.9, 8.2; IR (KBr) ν 2923, 1726, 1562, 1459, 1426, 1369, 712 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{21}H_{15}N_4O_2$ $[M + H]^+$ 355.1195, found: 355.1217.

*2-(1-(Pyridin-2-yl)-1H-indol-2-yl)isoindoline-1,3-dione (**3k**).* Yellow solid (73 mg, 72% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.41 (petroleum ether:-EtOAc = 3:1, v:v); mp 174−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30−8.28 (m, 1H), 7.91−7.88 (dd, J = 5.6, 3.2 Hz, 2H), 7.82−7.80 (m, 1H), 7.77 (dd, J = 5.6, 3.2 Hz, 2H), 7.74−7.72 (m, 1H), 7.60 (dd, J = 8.4, 1.2 Hz, 1H), 7.53−7.51 (m, 1H), 7.32−7.24 (m, 2H), 7.15 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 6.84 (d, J = 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 150.3, 149.7, 138.8, 135.5, 134.8, 131.9, 127.2, 125.6, 124.2, 124.1, 122.1, 121.8, 121.8, 119.5, 111.2, 105.2; IR (KBr) ν 3084, 2925, 1722, 1583, 1454, 1371, 736, 712, 883, 608 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{21}H_{14}N_3O_2$ $[M + H]^+$ 340.1086, found: 340.1068.

*2-(5-Methyl-1-(pyridin-2-yl)-1H-indol-2-yl)isoindoline-1,3-dione (**3l**).* Yellow solid (72 mg, 68% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.41 (petroleum ether:EtOAc = 3:1, v:v); mp 213-215 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26−8.24 (m, 1H), 7.89 (dd, J = 5.6, 3.2 Hz, 2H), 7.79−7.74 (m, 3H), 7.50−7.46 (m, 3H), 7.12−7.10 (m, 2H), 6.74 (s, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4,150.5, 149.6, 138.7, 135.0, 134.7, 133.8, 132.0, 131.1, 125.6, 125.4, 124.4, 124.2, 121.9, 121.4, 119.2, 110.9, 21.7; IR (KBr) ν 2924, 1726, 1471, 1590, 1432, 1394, 1337, 1079, 721, 708 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{22}H_{16}N_3O_2$ $[M + H]^+$ 354.1243, found: 354.1226.

*2-(5-Methoxy-1-(pyridin-2-yl)-1H-indol-2-yl)isoindoline-1,3-dione (**3m**).* Yellow solid (86 mg, 78% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.27 (petroleum ether:EtOAc = 3:1, v:v); mp 199−200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30−8.25 (m, 1H), 7.90 (dd, J = 5.6, 2.8 Hz, 2H), 7.82−7.74 (m, 3H), 7.51−7.47 (m, 2H), 7.16 (d, J = 2.4 Hz, 1H), 7.13 (ddd, J = 7.2, 4.8, 0.8 Hz, 1H), 6.95 (dd, J = 9.2, 2.8 Hz, 1H), 6.7 (s, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 155.2, 150.2, 149.4, 138.5, 134.4, 131.8, 130.4, 127.5, 125.5, 124.0, 121.6, 118.8, 114.0, 111.9, 104.8, 103.0, 55.8; IR (KBr) ν 2927, 1726, 1582, 1482, 1437, 1213, 1098, 1079, 789, 721, 709 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{22}H_{16}N_3O_3$ $[M + H]^+$ 370.1192, found: 370.1152.

*2-(1,3-Dioxoisoindolin-2-yl)-1-(pyridin-2-yl)-1H-indole-5-carbonitrile (**3n**).* Yellow solid (57 mg, 52% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.22 (petroleum ether:EtOAc = 3:1, v:v); mp 223−225 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39−8.37 (m, 1H), 8.09 (d, J = 1.6 Hz, 1H), 7.91 (dd, J = 5.6, 3.2 Hz, 2H), 7.85 (dt, J = 7.6, 1.6 Hz, 1H), 7.81 (dd, J = 5.6, 3.2 Hz, 2H), 7.64 (d, J = 8.8 Hz, 1H), 7.54 (dd, J = 8.4, 1.6 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.25−7.23 (m, 1H), 6.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 150.0, 149.3, 139.2, 137.1, 135.1, 131.7, 127.9, 127.1, 126.8, 124.4, 123.1, 120.3, 119.7, 112.3, 105.2, 104.9, 104.6; IR (KBr) ν 2924, 2351, 2218, 1734, 1471, 1583, 1398, 1366, 1082, 883, 802, 717 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{22}H_{13}N_4O_2$ $[M + H]^+$ 365.1039, found: 365.1066.

*2-(1,3-Dioxoisoindolin-2-yl)-1-(pyridin-2-yl)-1H-indole-5-carbaldehyde (**3o**).* White solid (34 mg, 31% yield), purified by column chromatography (petroleum ether:EtOAc = 3:1, v:v); R_f = 0.16 (petroleum ether:EtOAc = 3:1, v:v); mp 185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.38−8.34 (m, 1H), 8.27 (d, J = 1.2 Hz, 1H), 7.92−7.79 (m, 6H), 7.66 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.21−7.26 (m, 1H), 6.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 166.9, 149.9, 149.5, 139.1, 138.8, 134.9, 131.8, 131.2, 127.5, 126.9, 126.6, 124.4, 124.1, 122.9, 119.8, 111.9, 106.3; IR (KBr) ν 2927, 2814, 1732, 1683, 1588, 1477, 1392, 1348, 1303, 1104, 715 cm^{-1}; HRMS (ESI+, QTOF) m/z calc'd for $C_{22}H_{14}N_3O_3$ $[M + H]^+$ 368.1035, found: 368.1028.

*2-(1-Benzoyl-1H-indol-2-yl)isoindoline-1,3-dione (**3p**).* Yellow oil (20 mg, 27% yield); purified by column chromatography (petroleum ether:EtOAc = 8:1, v:v); R_f = 0.46 (petroleum ether:EtOAc = 3:1, v:v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 3.2, 5.6 Hz, 2H), 7.71 (dd, J = 3.2, 5.6 Hz, 2H), 7.67−7.62 (m, 3H), 7.49−7.47 (m, 1H), 7.29−7.26 (m, 5H), 6.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 166.5, 135.8, 134.6, 134.5, 132.3, 131.4, 129.3, 128.4, 127.4, 125.6, 125.1, 123.8, 123.3, 121.3, 114.8, 109.0; IR (KBr) ν 2923, 1727, 1683, 1451, 1379, 1324, 1079, 701; HRMS (ESI+, QTOF) exact mass calc'd for $C_{23}H_{15}N_2O_3$ $[M + H]^+$ 367.1083, found: 367.1079.

*2-(2-(Pyridin-2-yl)phenyl)isoindoline-1,3-dione (**5a**).*[11] Yellow solid (48 mg, 53% yield), purified by column chromatography (petroleum ether:EtOAc = 3:1, v:v); R_f = 0.22 (petroleum ether:-EtOAc = 3:1, v:v); mp 168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29−8.27 (m, 1H), 7.85 (dd, J = 5.6, 3.2 Hz, 2H), 7.73−7.70 (m, 3H), 7.65 (dt, J = 8.0, 2.0 Hz, 1H), 7.60−7.54 (m, 2H), 7.48 (d, J = 8.0 Hz, 1H), 7.44−7.38 (m, 1H), 7.08−7.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 157.2, 149.5, 138.7, 136.9, 134.3, 132.3, 130.7, 130.3, 129.8, 129.7, 123.8, 123.0, 122.3; IR (KBr) ν 2925, 2854, 1713, 1469, 1426, 1382, 1116, 1099, 1084, 756, 720 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{19}H_{13}N_2O_2$ $[M + H]^+$ 301.0977, found: 301.0979.

*2-(5-Methyl-2-(pyridin-2-yl)phenyl)isoindoline-1,3-dione (**5b**).*[11] Yellow solid (45 mg, 48% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.41 (petroleum ether:-EtOAc = 3:1, v:v); mp 178−180 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27−8.25 (m, 1H), 7.85 (dd, J = 5.6, 3.2 Hz, 2H), 7.73 (dd, J = 5.6, 3.2 Hz, 2H), 7.65−7.60 (m, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.40−7.37 (m, 1H), 7.22 (s, 1H), 7.04 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 157.1, 149.4, 140.0, 136.9, 135.8, 134.2, 132.4, 130.9, 130.7, 130.5, 129.6, 123.8, 122.9, 122.1, 22.2; IR (KBr) ν 3057, 2923, 1719, 1711, 1467, 1428, 1379, 1120, 880, 786, 715 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{20}H_{15}N_2O_2$ $[M + H]^+$ 315.1134, found: 315.1112.

*2-(5-Methoxy-2-(pyridin-2-yl)phenyl)isoindoline-1,3-dione (**5c**).*[11] Yellow solid (48 mg, 48% yield), purified by column chromatography (petroleum ether:EtOAc = 3:1, v:v); R_f = 0.22 (petroleum ether:-EtOAc = 3:1, v:v); mp 157−158 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24−8.22 (m, 1H), 7.85 (dd, J = 5.6, 3.2 Hz, 2H), 7.73 (dd, J = 5.6,

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3.2 Hz, 2H), 7.67 (d, J = 8.8 Hz, 1H), 7.61 (dt, J = 7.6, 2 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.11 (dd, J = 8.8, 2.8 Hz, 1H), 7.04−7.00 (m, 1H), 6.93 (d, J = 2.8 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 160.2, 156.6, 149.1, 136.5, 133.9, 132.0, 131.3, 130.8, 130.6, 123.5, 122.3, 121.5, 115.4, 55.5; IR (KBr) ν 3002, 1712, 1375, 1281, 1466, 1427, 1113, 875, 788, 716 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{20}H_{15}N_2O_3$ $[M + H]^+$ 331.1083, found: 331.1070.

*2-(5-(tert-Butyl)-2-(pyridin-2-yl)phenyl)isoindoline-1,3-dione (**5d**).* Yellow solid (62 mg, 58% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.45 (petroleum ether:-EtOAc = 3:1, v:v); mp 180−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28−8.27 (m, 1H), 7.85 (dd, J = 5.6, 3.2 Hz, 2H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.68−7.58 (m, 3H), 7.46 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 2.0 Hz, 1H), 7.09−7.02 (m, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 157.2, 153.1, 149.5, 136.8, 135.7, 134.2, 132.4, 130.3, 129.4, 127.4, 126.9, 123.8, 122.8, 122.1, 34.8, 31.2; IR (KBr) ν 3047, 2925, 1727, 1452, 1433, 1344, 1601, 1232, 1082, 887, 816, 741, 714 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{23}H_{21}N_2O_2$ $[M + H]^+$ 357.1603, found: 357.1604.

*2-(2-(Pyridin-2-yl)-5-vinylphenyl)isoindoline-1,3-dione (**5e**).* Yellow solid (30 mg, 31% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.41 (petroleum ether:-EtOAc = 2:1, v:v); mp 135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27−8.26 (m, 1H), 7.86 (dd, J = 5.6, 3.2 Hz, 2H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.66−7.59 (m, 2H), 7.47 (d, 8.0 Hz, 1H), 7.43 (d, J = 1.6 Hz, 1H), 7.06 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 6.78 (dd, J = 17.6, 11.2 Hz, 1H), 5.85 (d, J = 17.6 Hz, 1H), 5.37 (d, J = 10.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 156.8, 149.5, 139.3, 137.7, 136.9, 135.6, 134.3, 132.3, 130.8, 130.1, 128.2, 127.5, 123.8, 122.9, 122.3, 116.1; IR (KBr) ν 2927, 2308, 1717, 1466, 1424, 1377, 1116, 719, 715 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{21}H_{15}N_2O_2$ $[M + H]^+$ 327.1134, found: 327.1123.

*2-(5-Fluoro-2-(pyridin-2-yl)phenyl)isoindoline-1,3-dione (**5f**).*[11] Yellow solid (49 mg, 51% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.27 (petroleum ether:-EtOAc = 3:1, v:v); mp 196−197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28−8.27 (m, 1H), 7.86 (dd, J = 5.6, 3.2 Hz, 2H), 7.76−7.70 (m, 3H), 7.65 (dt, J = 8.0, 2.0 Hz, 1H), 7.44 (dt, J = 7.6, 0.8 Hz, 1H), 7.31−7.26 (m, 1H), 7.17 (dd, J = 8.8, 2.4 Hz, 1H), 7.10−7.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 164.0, 161.6, 156.4, 149.5, 137.1, 134.5, 132.2, 123.9, 122.9, 122.4, 117.9, 117.6, 116.9, 116.8; ^{19}F NMR (400 MHz, $CDCl_3$) δ −62.6; IR (KBr) ν 3069, 2925, 1720, 1468, 1424, 1374, 1269, 1115, 789, 718 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{19}H_{12}N_2O_2F$ $[M + H]^+$ 319.0883, found: 319.0903.

*2-(5-Chloro-2-(pyridin-2-yl)phenyl)isoindoline-1,3-dione (**5g**).* Yellow solid (60 mg, 60% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.28 (petroleum ether:-EtOAc = 3:1, v:v); mp 210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28−8.27 (m, 1H), 7.85 (dd, J = 5.2, 2.8 Hz, 2H), 7.75 (dd, J = 5.2, 2.8 Hz, 2H), 7.68−7.62 (m, 2H), 7.55 (dd, J = 8.4, 2.0 Hz, 1H), 7.49−7.43 (m, 2H), 7.10 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 155.9, 149.3, 136.9, 136.8, 134.8, 134.1, 131.8, 131.4, 130.6, 130.2, 129.6, 123.6, 122.6, 122.3; IR (KBr) ν 3085, 1726, 1712, 1465, 1420, 1374, 1118, 1103, 1082, 717, 709 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{19}H_{12}N_2O_2Cl$ $[M + H]^+$ 335.0587, found: 335.0602.

*2-(2-(Pyridin-2-yl)-5-(trifluoromethyl)phenyl)isoindoline-1,3-dione (**5h**).* Yellow solid (68 mg, 62% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.35 (petroleum ether:EtOAc = 3:1, v:v); mp 164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32−8.31 (m, 1H), 7.88−7.83 (m, 4H), 7.76 (dd, J = 5.2, 3.2 Hz, 2H), 7.72−7.68 (m, 2H), 7.50 (d, J = 8.0 Hz, 1H), 7.14 (ddd, J = 7.6, 4.8, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 155.9, 149.7, 142.1, 137.2, 134.5, 132.1, 131.6, 131.3, 130.5, 127.7, 126.6, 124.0, 123.7, 123.1, 123.1; ^{19}F NMR (400 MHz, $CDCl_3$) δ −111.4; IR (KBr) ν 2922, 1722, 1371, 1321, 1115, 1079, 719, 874, 788 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{20}H_{12}N_2O_2F_3$ $[M + H]^+$ 369.0851, found: 369.0820.

*Methyl 3-(1,3-Dioxoisoindolin-2-yl)-4-(pyridin-2-yl)benzoate (**5i**).* Yellow solid (42 mg, 39% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.35 (petroleum ether:-EtOAc = 2:1, v:v); mp 184 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32−8.31 (m, 1H), 8.24 (dd, J = 8.0, 1.6 Hz, 1H), 8.10 (d, J = 1.6 Hz, 1H), 7.87−7.85 (m, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.77−7.73 (m, 2H), 7.68 (dt, J = 7.6, 1.6 Hz, 1H), 7.54−7.49 (m, 1H), 7.12 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 166.0, 156.2, 149.7, 142.8, 137.1, 134.4, 132.2, 131.8, 131.4, 130.9, 130.8, 130.2, 123.9, 123.2, 122.9, 52.7; IR (KBr) ν 3070, 2998, 2949, 1784, 1717, 1586, 1422, 1440, 1288, 1216, 1114, 765, 718 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{21}H_{15}N_2O_4$ $[M + H]^+$ 359.1032, found: 359.1002.

*3-(1,3-Dioxoisoindolin-2-yl)-4-(pyridin-2-yl)benzaldehyde (**5j**).* Yellow solid (27 mg, 28% yield), purified by column chromatography (petroleum ether:EtOAc = 3:1, v:v); R_f = 0.29 (petroleum ether:-EtOAc = 2:1, v:v); mp 217 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.32 (dd, J = 4.4, 0.8 Hz, 1H), 8.11−8.01 (m, 1H), 7.94−7.90 (m, 2H), 7.88−7.7.86 (m, 2H), 7.78−7.68 (m, 3H), 7.54 (d, J = 8.0 Hz, 1H), 7.16−7.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 167.5, 156.0, 149.7, 144.1, 143.0, 137.2, 134.5, 132.1, 131.9, 131.6, 130.9, 130.3, 124.0, 123.3, 123.2; IR (KBr) ν 3070, 2818, 2724, 1715, 1695, 1465, 1385, 1111, 1084, 795, 716 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{20}H_{13}N_2O_3$ $[M + H]^+$ 329.0926, found: 329.0924.

*2-(4-Methyl-2-(pyridin-2-yl)phenyl)isoindoline-1,3-dione (**5k**).*[11] Yellow solid (42 mg, 45% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.35 (petroleum ether:-EtOAc = 3:1, v:v); mp 164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32−8.31 (m, 1H), 7.84 (dd, J = 5.2, 2.0 Hz, 2H), 7.72 (dd, J = 5.2, 2.0 Hz, 2H), 7.62 (dt, J = 7.6, 2.8 Hz, 1H), 7.55 (s, 1H), 7.47−7.42 (m, 1H), 7.38−7.35 (m, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.07 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 157.0, 149.3, 139.6, 138.3, 136.5, 133.9, 132.1, 131.2, 130.1, 129.7, 126.9, 123.5, 122.6, 122.0, 21.3; IR (KBr) ν 3077, 2925, 1726, 1588, 1471, 1429, 1380, 1105, 1084, 892, 826, 721 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{20}H_{15}N_2O_2$ $[M + H]^+$ 315.1134, found: 315.1133.

*2-(4-Methoxy-2-(pyridin-2-yl)phenyl)isoindoline-1,3-dione (**5l**).* Yellow solid (49 mg, 50% yield), purified by column chromatography (petroleum ether:EtOAc = 3:1, v:v); R_f = 0.24 (petroleum ether:-EtOAc = 3:1, v:v); mp 170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33−8.31 (m, 1H), 7.84 (dd, J = 5.6, 3.2 Hz, 2H), 7.72 (dd, J = 5.6, 3.2 Hz, 2H), 7.63 (dt, J = 8.0, 2.0 Hz, 1H), 7.44 (dt, J = 8.0, 1.2 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.25 (d, J = 3.2 Hz, 1H), 7.10−7.07 (m, 2H), 3.91(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 160.4, 156.9, 149.5, 139.9, 136.9, 134.2, 132.3, 131.4, 123.8, 122.9, 122.5, 122.3, 116.0, 115.1, 55.9; IR (KBr) ν 3014, 2973, 2934, 1720, 1561, 1498, 1459, 1380, 1295, 1222, 1031, 796, 719 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{20}H_{15}N_2O_3$ $[M + H]^+$ 331.1083, found: 331.1054.

*2-(2-(3-Methylpyridin-2-yl)phenyl)isoindoline-1,3-dione (**5m**).* Yellow solid (41 mg, 44% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.35 (petroleum ether:-EtOAc = 3:1, v:v); mp 182 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 4.0 Hz, 1H), 7.78 (dd, J = 5.6, 3.2 Hz, 2H), 7.68 (dd, J = 5.6, 3.2 Hz, 2H), 7.57−7.49 (m, 4H), 7.47−7.41 (m, 1H), 6.99 (dd, J = 7.6, 4.8 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 156.3, 146.6, 139.1, 138.5, 134.2, 132.2, 131.9, 130.7, 130.5, 129.9, 129.2, 128.9, 123.7, 122.5, 19.7; IR (KBr) ν 2923, 1710, 1461, 1446, 1381, 1121, 1083, 759, 721 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{20}H_{15}N_2O_2$ $[M + H]^+$ 315.1134, found: 315.1117.

*2-(5-(tert-Butyl)-2-(3-methylpyridin-2-yl)phenyl)isoindoline-1,3-dione (**5n**).* Yellow solid (60 mg, 54% yield), purified by column chromatography (petroleum ether:EtOAc = 8:1, v:v); R_f = 0.48 (petroleum ether:EtOAc = 3:1, v:v); mp 203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16−8.15 (m, 1H), 7.78 (d, J = 5.2, 3.2 Hz, 2H), 7.67 (d, J = 5.2, 3.2 Hz, 2H), 7.54 (dd, J = 8.4, 2.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1H), 6.97 (dd, J = 7.6, 4.8 Hz, 1H), 2.35 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz,

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$CDCl_3$) δ 167.6, 156.4, 152.4, 146.6, 138.4, 136.1, 134.1, 132.2, 132.1, 130.3, 130.0, 126.8, 126.1, 123.6, 122.3, 35.0, 31.5; IR (KBr) ν 2965, 2868, 1715, 1423, 1373, 1360, 1122, 1086, 722 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{24}H_{23}N_2O_2$ $[M + H]^+$ 371.1760, found: 371.1730.

*2-(5-Methoxy-2-(3-methylpyridin-2-yl)phenyl)isoindoline-1,3-dione (**5o**).* Yellow solid (39 mg, 38% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); R_f = 0.19 (petroleum ether:EtOAc = 3:1, v:v); mp 188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, J = 4.8, 0.8 Hz, 1H), 7.78 (dd, J = 5.2, 3.2 Hz, 2H), 7.68 (dd, J = 5.2, 3.2 Hz, 2H), 7.50−7.47 (m, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.07 (dd, J = 8.8, 2.8 Hz, 1H), 6.97−6.93 (m, 2H), 3.88 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 159.9, 156.2, 146.6, 138.4, 134.2, 132.3, 132.0, 131.5, 123.7, 122.2, 115.1, 114.9, 55.8, 19.8; IR (KBr) ν 3010, 2937, 1720, 1617, 1433, 1377, 1295, 1272, 1238, 1085, 716 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{21}H_{17}N_2O_3$ $[M + H]^+$ 345.1239, found: 345.1236.

*2-(2-(3-Methylpyridin-2-yl)-5-(trifluoromethyl)phenyl)isoindoline-1,3-dione (**5p**).* Yellow solid (85 mg, 75% yield), purified by column chromatography (petroleum ether:EtOAc = 10:1, v:v); R_f = 0.51 (petroleum ether:EtOAc = 3:1, v:v); mp 159−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, J = 4.4, 1.2 Hz, 1H), 7.80−7.78 (m, 3H), 7.74 (s, 1H), 7.71 (dd, J = 5.6, 3.2 Hz, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.56−7.52 (m, 1H), 7.03 (dd, J = 7.6, 4.8 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 155.1, 146.9, 142.7, 138.8, 134.5, 132.3, 131.8, 131.6, 131.4, 131.3, 127.3, 125.8, 123.9, 123.1, 122.4, 19.5; ^{19}F NMR (400 MHz, $CDCl_3$) δ −62.6; IR (KBr) ν 3068, 2962, 1716, 1433, 1376, 1323, 1211, 1167, 1143; HRMS (ESI+, QTOF) exact mass calc'd for $C_{21}H_{14}N_2O_2F_3$ $[M + H]^+$ 383.1007, found: 383.0979.

*2-(5-Methyl-2-(pyrimidin-2-yl)phenyl)isoindoline-1,3-dione (**5q**).*[17] Yellow solid (51 mg, 54% yield), purified by column chromatography (petroleum ether:EtOAc = 8:1, v:v); R_f = 0.41 (petroleum ether:EtOAc = 3:1, v:v); mp 234 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 4.8 Hz, 2H), 8.34 (d, J = 8.0 Hz, 1H), 7.90 (dd, J = 5.6, 3.2 Hz, 2H), 7.76 (dd, J = 5.6, 3.2 Hz, 2H) 7.42 (d, J = 8.0 Hz, 1H), 7.23 (s, 1H), 7.00 (t, J = 9.6, 4.8 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 164.0, 156.9, 141.6, 133.9, 132.5, 132.4, 131.5, 131.2, 130.40, 130.37, 123.5, 118.8, 21.2; IR (KBr) ν 2917, 1719, 1709, 1566, 1551, 1410, 1378, 1112, 1085, 805, 716 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{19}H_{14}N_3O_2$ $[M + H]^+$ 316.1086, found: 316.1066.

*2-(3-(Pyridin-2-yl)naphthalen-2-yl)isoindoline-1,3-dione (**5r**).* Yellow solid (45 mg, 43% yield), purified by column chromatography (petroleum ether:EtOAc = 8:1, v:v); R_f = 0.41 (petroleum ether:EtOAc = 3:1, v:v); mp 248−250 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27−8.26 (m, 1H), 8.19 (s, 1H), 7.98−7.95 (m, 3H), 7.87 (dd, J = 5.6, 3.2 Hz, 2H), 7.76 (dd, J = 5.6, 3.2 Hz, 2H), 7.69 (td, J = 7.6, 1.6 Hz, 1H), 7.63−7.57 (m, 3H), 7.10−7.07 (m,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 157.4, 149.4, 137.0, 136.0, 134.3, 133.6, 133.4, 132.4, 130.5, 130.0, 128.4, 128.2, 127.6, 127.4, 123.8, 123.3, 122.3; IR (KBr) ν 3057, 2924, 1716, 1587, 1466, 1425, 1384, 1110, 869, 749, 711 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{23}H_{15}N_2O_2$ $[M + H]^+$ 351.1134, found: 351.1142.

*2-(Benzo[h]quinolin-10-yl)isoindoline-1,3-dione (**5s**).* Yellow solid (94 mg, 97% yield), purified by column chromatography (petroleum ether:EtOAc = 8:1, v:v); R_f = 0.46 (petroleum ether:EtOAc = 3:1, v:v); mp 299−300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, J = 4.4, 1.6 Hz, 1H), 8.09 (d, J = 8.0 Hz, 2H), 8.02 (dd, J = 5.6, 3.2 Hz, 2H), 7.89 (d, J = 8.8 Hz, 1H), 7.85−7.80 (m, 3H), 7.72−7.68 (m, 2H), 7.31 (dd, J = 8.4, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 148.1, 145.5, 135.8, 133.7, 133.4, 131.1, 130.4, 129.2, 128.0, 127.8, 127.3, 127.1, 126.5, 123.5, 121.6; IR (KBr) ν 2925, 2854, 1727, 1399, 1382, 1117, 1086, 844, 726, 717 cm^{-1}; HRMS (ESI+, QTOF) exact mass calc'd for $C_{21}H_{13}N_2O_2$ $[M + H]^+$ 325.0977, found: 325.0951.

*2-(1-(Pyridin-2-yl)-1H-indol-2-yl)benzo[d]isothiazol-3(2H)-one 1,1-Dioxide (**6a**).* Yellow solid (32 mg, 43% yield), purified by column chromatography (petroleum ether:EtOAc = 3:1, v:v); R_f = 0.27 (petroleum ether:EtOAc = 3:1, v:v); mp 195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47−8.46 (m, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.94−7.82 (m, 3H), 7.78−7.72 (m, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.27−7.19 (m, 2 H), 7.06 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 149.8. 149.4, 138.4, 137.7, 136.2, 135.3, 134.4, 126.5, 126.4, 125.8, 124.6, 122.2, 121.7, 121.5, 120.6, 119.7, 111.6, 107.2; IR (KBr) ν 2926, 1745, 1590, 1470, 1453, 1331, 1348, 1187, 748, 584; HRMS (ESI+, QTOF) exact mass calc'd for $C_{20}H_{14}N_3O_3S$ $[M + H]^+$ 376.0756, found: 376.0748.

*2-(1-(Pyrimidin-2-yl)-1H-indol-2-yl)benzo[d]isothiazol-3(2H)-one 1,1-Dioxide (**6b**).* Yellow solid (36 mg, 32% yield), purified by column chromatography (petroleum ether:EtOAc = 3:1, v:v); R_f = 0.27 (petroleum ether:EtOAc = 3:1, v:v); mp 235−236 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 8.4 Hz, 1H), 8.46 (d, J = 4.4 Hz, 2H), 8.19 (d, J = 6.8 Hz, 1H), 7.96−7.88 (m, 3H), 7.71 (d, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.30 (t, J = 7.2 Hz, 1H), 7.14 (s, 1 H), 6.99 (t, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 157.9, 157.0, 138.0, 136.3, 135.1, 134.4, 127.1, 126.9, 125.7, 125.5, 122.7, 121.5, 121.4, 120.5, 117.3, 115.7, 111.9; IR (KBr): ν 2976, 1751, 1443, 1424, 1347, 1186, 755; HRMS (ESI+, QTOF) exact mass calc'd for $C_{19}H_{13}N_4O_3S$ $[M + H]^+$ 377.0708, found: 376.0708.

*2-(2-(Pyridin-2-yl)phenyl)benzo[d]isothiazol-3(2H)-one 1,1-Dioxide (**6c**).* Yellow solid (32 mg, 48% yelid), purified by column chromatography (petroleum ether:EtOAc = 3:1, v:v); R_f = 0.22 (petroleum ether:EtOAc = 3:1, v:v); mp 188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 4.4 Hz, 1H), 8.05 (d, J = 7.6 Hz, 1 H), 7.89 (t, J = 7.2 Hz, 1H), 7.85−7.79 (m, 3H), 7.67−7.58 (m, 5 H), 7.14−7.11 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 156.2, 149.4, 140.9, 137.7, 136.3, 134.8, 134.2, 131.5, 131.0, 130.9, 129.8, 127.0, 125.9, 125.4, 122.9, 122.3, 121.1; IR (KBr) ν 3095, 1748, 1587, 1471, 1332, 1311, 1184, 759, 747, 732, 586; HRMS (ESI+, QTOF) exact mass calc'd for $C_{18}H_{13}N_2O_3S$ $[M + H]^+$ 337.0647, found: 337.0638.

*N-(2-(Pyridin-2-yl)phenyl)benzamide (**6d**).* Yellow solid (12 mg, 22% yield); purified by column chromatography (petroleum ether:-EtOAc = 1:1, v:v); R_f = 0.70 (petroleum ether:EtOAc = 3:1, v:v); mp 89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.30 (br, 1H), 8.79 (d, J = 8.4 Hz, 1H), 8.68 (d, J = 4.4 Hz, 1H), 8.04 (d, J = 7.6 Hz, 2H), 7.86−7.79 (m, 2 H), 7.73 (d, J = 7.6 Hz, 1H), 7.52−7.46 (m, 4H), 7.29 (t, J = 6.4 Hz, 1H), 7.29 (t, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 158.3, 147.3, 138.1, 137.9, 135.7, 131.5, 130.3, 128.8, 128.6, 127.4, 125.6, 123.6, 123.0, 122.0, 121.9; IR (KBr) ν 2960, 2927, 1666, 1589, 1475, 1439, 1323, 1262, 748, 669; HRMS (ESI+, QTOF) exact mass calc'd for $C_{18}H_{15}N_2O$ $[M + H]^+$ 275.1184, found: 275.1183.

KIE Experiment with [D]-4a as Substrate. Compounds [**D**]-**4a** and [**D2**]-**4a** were synthesized according to the literature procedure.[19] Under oxygen, CuOAc (0.04 mmol, 4.9 mg), [**D**]-**4a** (0.2 mmol, 31.2 mg), and phthalimide (0.24 mmol, 35.3 mg) were dissolved in toluene and *o*-dichlorobenzene (1:1, 2 mL) in an oven-dried 25 mL Schlenk tube. The mixture was stirred at 150 °C for 4 h. The reaction was then stopped stirring, cooled down to room temperature, and poured into NaOH solution (10%, 10 mL). It was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give the corresponding products [**D**]-**5a** and **5a** (28% yield). The ^{1}H NMR analysis showed that the ratio of **5a**/[**D**]-**5a** is 2.1.

KIE Experiment with [D2]-4a and 4a as Substrates. Under oxygen, CuOAc (0.04 mmol, 4.9 mg), [**D2**]-**4a** (0.1 mmol, 15.7 mg), **4a** (0.1 mmol, 15.5 mg), and phthalimide (0.24 mmol, 35.3 mg) were dissolved in toluene and *o*-dichlorobenzene (1:1, 2 mL) in an oven-dried 25 mL Schlenk tube. The mixture was stirred at 150 °C for 4 h. The reaction was then stopped stirring, cooled down to room temperature, and poured into NaOH solution (10%, 10 mL). It was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give the corresponding products [**D**]-**5a** and **5a** (33% yield). The ^{1}H NMR analysis showed that the ratio of **5a**/[**D**]-**5a** is 3.7.

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■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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