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 improvedCu-catalyzed inter- and intramolecular versions were achieved by Brasche and Buchwald,13c Li et al.,13d Su et al.,13e and John and
Nicholas. 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. Wang and Schreiber, Chang et al., and others. More recently, Daugulis et al. and Chen et al. 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, is inevitable. All of these pioneering studies inspired us to pursue a simple Cu/O₂ catalytic system for the sp² C–H amination process. The use of Cu(OAc)₂, Cu(OTrf)₂, and Cu(OPiv), also provided the desired amination product 3a with a slightly decreased yield compared to CuOAc (Table 1, entries 2–4). In contrast, CuCl, CuBr₂, and CuCl₃ 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, CH₃CN, 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 desired 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 O₂ 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 conditions: substrate 1a (0.3 mmol), phthalimide (0.36 mmol), cat. (20 mol %), solvent (2 mL), O₂ (1 atm), 150 °C. Isolated yields.

### RESULTS AND DISCUSSION

Encouraged by Yu et al.’s report, 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.

### Table 1. Cu-Catalyzed sp² C–H Amination of N-Pyrimidyl Indole

| entry | cat [20 mol %] | solvent | T (h) | yield (%) |
|-------|----------------|---------|-------|-----------|
| 1     | CuOAc          | toluene | 48    | 60        |
| 2     | Cu(OAc)₂       | toluene | 48    | 37        |
| 3     | Cu(OTrf)₂      | toluene | 52    | 49        |
| 4     | Cu(OPiv)₂      | toluene | 72    | 40        |
| 5     | CuCl           | toluene | 48    | trace     |
| 6     | CuBr₂          | toluene | 48    | trace     |
| 7     | CuCl₂          | toluene | 48    | trace     |
| 8     | Cu(OH)₂        | toluene | 48    | trace     |
| 9     | CuOAc          | DMF     | 70    | trace     |
| 10    | CuOAc          | DMSO    | 70    | trace     |
| 11    | CuOAc          | CH₃CN   | 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    | CuOAc          | toluene/o-dichlorobenzene (1:1) | 60 | 71        |
| 20    | none           | toluene | 60    | 0         |

*Conditions: substrate 1a (0.3 mmol), phthalimide (0.36 mmol), cat. (20 mol %), solvent (2 mL), O₂ (1 atm), 150 °C. Isolated yield.

### Table 2. Amidation of N-Heteroarylindoles

| R¹ | R² | R³ | R⁴ |
|----|----|----|----|
| X | N | H | Phth |
| CH₃ | CH₂ | OMe | NPhth |
| Me | Me | NPhth | NPhth |
| O | O | NPhth | NPhth |
| | | | |

*Conditions: substrate (0.3 mmol), phthNH (0.36 mmol), CuOAc (20 mol %), O₂ (1 atm), toluene/o-dichlorobenzene (1:1, 2 mL), 150 °C, 2–3 days. Isolated yield.
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 polymerization, 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 sp2 C–H amination reaction, efficiently giving the amination products. The strongly electron-deficient NO2-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), CF3 (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-pyridyl 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 amidines with strong electron-withdrawing groups.

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, 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 O2. 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. 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
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.

#### Scheme 1. Radical Inhibitor Experiments

![Scheme 1](image)

Table 4. Scope and Limitation of Amines$^{a,b,c}$

| Entry | substrate | amine | product | yield (%) |
|-------|-----------|-------|---------|-----------|
| 1     | ![Substrate 1](image) | ![Amine 1](image) | ![Product 1](image) | 43        |
| 2     | ![Substrate 2](image) | ![Amine 2](image) | ![Product 2](image) | 32        |
| 3     | ![Substrate 3](image) | ![Amine 3](image) | ![Product 3](image) | 48        |
| 4     | ![Substrate 4](image) | ![Amine 4](image) | ![Product 4](image) | 22        |
| 5     | ![Substrate 5](image) | ![Amine 5](image) | ![Product 5](image) | N.D.$^c$  |
| 6     | ![Substrate 6](image) | ![Amine 6](image) | ![Product 6](image) | 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 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-arylpidine derivatives) (0.3 mmol), and phthalimide (0.33 mmol, 48.5 mg) were dissolved in the mixed solvent of toluene and then 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 Na2SO4, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give the corresponding products.

2-(5-Methyl-1-(pyrimidin-2-yl)-1H-indol-2-yl)isoindoline-1,3-dione (3a). Yellow solid (72 mg, 71% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); Rf = 0.28 (petroleum ether:EtOAc = 3:1, v:v); mp 216–217 °C; 1H NMR (400 MHz, CDCl3) δ 8.52 (d, J = 8.4 Hz, 1H), 8.43 (d, J = 4.8 Hz, 2H), 8.00–7.96 (m, 2H), 7.85–7.81 (m, 2H), 7.46 (s, 1H), 7.21 (d, J = 8.8, 2.0 Hz, 1H), 6.94 (t, J = 4.4 Hz, 1H), 6.81 (s, 1H), 2.48 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 167.9, 158.2, 157.6, 154.6, 136.5, 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, 2923, 1727, 1452, 1433, 1344, 1562, 1601, 1232, 1082, 714 cm⁻¹; HRMS (ESI+, QTOF) exact mass calc'd for C21H18N4O3 [M + H]+ 355.1195, found: 355.1180.

2-(5-Methyl-1-(pyrimidin-2-yl)-1H-indol-2-yl)isoindoline-1,3-dione (3b). Yellow solid (76 mg, 71% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); Rf = 0.28 (petroleum ether:EtOAc = 3:1, v:v); mp 216–217 °C; 1H NMR (400 MHz, CDCl3) δ 8.52 (d, J = 8.4 Hz, 1H), 8.43 (d, J = 4.8 Hz, 2H), 8.00–7.96 (m, 2H), 7.85–7.81 (m, 2H), 7.46 (s, 1H), 7.21 (d, J = 8.8, 2.0 Hz, 1H), 6.94 (t, J = 4.4 Hz, 1H), 6.81 (s, 1H), 2.48 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 167.9, 158.2, 157.6, 154.6, 136.5, 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, 2923, 1727, 1452, 1433, 1344, 1562, 1601, 1232, 1082, 714 cm⁻¹; HRMS (ESI+, QTOF) exact mass calc'd for C21H18N4O3 [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 (76 mg, 71% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); Rf = 0.28 (petroleum ether:EtOAc = 3:1, v:v); mp 216–217 °C; 1H NMR (400 MHz, CDCl3) δ 8.52 (d, J = 8.4 Hz, 1H), 8.43 (d, J = 4.8 Hz, 2H), 8.00–7.96 (m, 2H), 7.85–7.81 (m, 2H), 7.46 (s, 1H), 7.21 (d, J = 8.8, 2.0 Hz, 1H), 6.94 (t, J = 4.4 Hz, 1H), 6.81 (s, 1H), 2.48 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 167.9, 158.2, 157.6, 154.6, 136.5, 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, 2923, 1727, 1452, 1433, 1344, 1562, 1601, 1232, 1082, 714 cm⁻¹; HRMS (ESI+, QTOF) exact mass calc'd for C21H18N4O3 [M + H]+ 355.1195, found: 355.1180.
1H, 3.89 (s, 3H); 1H, 3.89 (s, 3H); 1C NMR (100 MHz, CDCl3) 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, 2726, 1582, 1482, 1437, 1213, 1098, 797, 721, 709 cm⁻¹; HRMS (EI+, QTOF) exact mass calc'd for C₂₆H₂₃N₅O₈ [M + H⁺] 730.1192, found: 730.1182.

1-(3-Diazoindolin-2-yl)-4-(pyrindin-2-yl)-1H-indole-5-carboxylic acid (3b). Yellow solid (57 mg, 52% yield), purified by column chromatography (petroleum ether:EtOAc = 3:1, v/v); mp 229–230 °C; HR NMR (400 MHz, CDCl3) 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, 2.4 Hz, 2H), 7.64 (d, J = 8.4, 1.6 Hz, 1H), 7.54 (d, 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); 1C NMR (100 MHz, CDCl3) δ 166.8, 150.0, 149.3, 139.2, 137.1, 135.1, 131.7, 127.9, 127.1, 126.8, 124.3, 123.1, 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 (EI+, QTOF) exact mass calc'd for C₂₆H₂₃N₅O₈ [M + H⁺] 595.1039, found: 595.1066.

1-(3-Diazoindolin-2-yl)-4-(pyrindin-2-yl)-1H-indole-5-carboxylic acid (3c). Yellow solid (67 mg, 72% yield), purified by column chromatography (petroleum ether:EtOAc = 3:1, v/v); ν 2924, 2351, 2218, 1734, 1471, 1583, 1398, 1366, 1082, 883, 802, 717 cm⁻¹; HRMS (EI+, QTOF) exact mass calc'd for C₂₆H₂₃N₅O₈ [M + H⁺] 595.1039, found: 595.1066.

1-(2-Benzyl-1H-indol-3-yl)-1H-indole-3,1-dione (3p). Yellow oil (20 mg, 27% yield); purified by column chromatography (petroleum ether:EtOAc = 3:1, v/v); ν 2924, 2351, 2218, 1734, 1471, 1583, 1398, 1366, 1082, 883, 802, 717 cm⁻¹; HRMS (EI+, QTOF) exact mass calc'd for C₂₆H₂₃N₅O₈ [M + H⁺] 679.1083, found: 679.1079.

1-(2-(Pyrindin-2-yl)phenyl)isoindolin-1,3-dione (5a). Yellow solid (48 mg, 53% yield), purified by column chromatography (petroleum ether:EtOAc = 3:1, v/v); mp 175–176 °C; H NMR (400 MHz, CDCl3) δ 3.80–3.82 (m, 1H), 3.79–3.80 (m, 1H), 3.77–3.78 (m, 1H), 3.69 (dd, J = 4.8, 1.2 Hz, 1H), 2.37–2.38 (m, 2H), 2.15 (dd, J = 7.6, 4.8, 1.2 Hz, 1H), 2.64 (d, J = 8.0 Hz, 1H); 1C NMR (100 MHz, CDCl₃) δ 167.4, 150.3, 149.7, 138.4, 135.6, 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, 2722, 1583, 1454, 1371, 736, 712, 833, 608 cm⁻¹; HRMS (EI+, QTOF) exact mass calc'd for C₂₆H₂₃N₅O₈ [M + H⁺] 597.1083, found: 597.1079.

1-(2-(2-pyridin-2-yl)phenyl)isoindolin-1,3-dione (5b). Yellow oil (45 mg, 48% yield), purified by column chromatography (petroleum ether:EtOAc = 3:1, v/v); ν 2924, 2351, 2218, 1734, 1471, 1583, 1398, 1366, 1082, 883, 802, 717 cm⁻¹; HRMS (EI+, QTOF) exact mass calc'd for C₂₆H₂₃N₅O₈ [M + H⁺] 570.1077, found: 570.1076.
2H), 7.67 (d, J = 8.8 Hz, 1H), 7.61 (dt, J = 7.6, 2.7 Hz), 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); 13C NMR (100 MHz, CDCl3) δ 167.6, 160.2, 156.6, 149.1, 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 C21H15N2O2 [M + H]+ 331.1083, found: 331.1075.

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); Rf = 0.45 (petroleum ether:EtOAc = 1:1, v:v); mp 181–181.5 °C; H NMR (400 MHz, CDCl3) δ 6.28–6.27 (m, 1H), 7.85 (dd, J = 5.6, 3.2 Hz, 2H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.68–7.68 (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); 13C NMR (100 MHz, CDCl3) 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, 121.4, 31.2; IR (KBr) ν 3074, 2925, 1742, 1452, 1344, 1601, 1232, 1082, 887, 816, 741, 714 cm−1; HRMS (ESI+, QTOF) exact mass calc’d for C21H15N2O2 [M + H]+ 331.1083, found: 331.1075.

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); Rf = 0.45 (petroleum ether:EtOAc = 1:1, v:v); mp 181–181.5 °C; H NMR (400 MHz, CDCl3) δ 6.28–6.27 (m, 1H), 7.85 (dd, J = 5.6, 3.2 Hz, 2H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.68–7.68 (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); 13C NMR (100 MHz, CDCl3) 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, 121.4, 31.2; IR (KBr) ν 3074, 2925, 1742, 1452, 1344, 1601, 1232, 1082, 887, 816, 741, 714 cm−1; HRMS (ESI+, QTOF) exact mass calc’d for C21H15N2O2 [M + H]+ 331.1083, found: 331.1075.

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); Rf = 0.45 (petroleum ether:EtOAc = 1:1, v:v); mp 181–181.5 °C; H NMR (400 MHz, CDCl3) δ 6.28–6.27 (m, 1H), 7.85 (dd, J = 5.6, 3.2 Hz, 2H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.68–7.68 (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); 13C NMR (100 MHz, CDCl3) 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, 121.4, 31.2; IR (KBr) ν 3074, 2925, 1742, 1452, 1344, 1601, 1232, 1082, 887, 816, 741, 714 cm−1; HRMS (ESI+, QTOF) exact mass calc’d for C21H15N2O2 [M + H]+ 331.1083, found: 331.1075.

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); Rf = 0.45 (petroleum ether:EtOAc = 1:1, v:v); mp 181–181.5 °C; H NMR (400 MHz, CDCl3) δ 6.28–6.27 (m, 1H), 7.85 (dd, J = 5.6, 3.2 Hz, 2H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.68–7.68 (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); 13C NMR (100 MHz, CDCl3) 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, 121.4, 31.2; IR (KBr) ν 3074, 2925, 1742, 1452, 1344, 1601, 1232, 1082, 887, 816, 741, 714 cm−1; HRMS (ESI+, QTOF) exact mass calc’d for C21H15N2O2 [M + H]+ 331.1083, found: 331.1075.
CDCl₃ 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, 126.3, 122.3, 30.5, 31.5; IR (KBr) ν 2965, 2868, 1715, 1423, 1373, 1360, 1122, 1086, 722 cm⁻¹; HRMS (ESI+, QTOF) exact mass calc’d for C₅₀H₄₃NO₂ [M + H]+ 371.1760, found: 371.1763.

2.5-(Methoxy-2-(3-methylpyridin-2-yl)phenyl)isoindoline-1,3-dione (5a). Yellow solid (39 mg, 38% yield), purified by column chromatography (petroleum ether:EtOAc = 5:1, v:v); νRf 0.27 (petroleum ether:EtOAc = 3:1, v:v); mp 188 °C; ¹H NMR (400 MHz, CDCl₃) 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 (J = 8.8 Hz, 1H), 7.07 (dd, J = 7.8, 8.8 Hz, 1H), 6.97–6.93 (m, 2H), 3.88 (3H), 2.33 (3H); ¹C NMR (100 MHz, CDCl₃) δ 167.3, 159.9, 156.2, 146.6, 138.4, 134.2, 132.3, 132.0, 131.5, 132.7, 122.2, 111.5, 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 C₂₉H₂₉N₂O₂ [M + H]+ 435.1239, found: 435.1236.

2-(3-Methylpyridin-2-yl)-5-(trifluoromethyl)phenylisoindoline-1,3-dione (5p). Yellow solid (85 mg, 75% yield), purified by column chromatography (petroleum ether:EtOAc = 10:1, v:v); νRf 0.21 (petroleum ether:EtOAc = 3:1, v:v); mp 159–160 °C; ¹H NMR (400 MHz, CDCl₃) 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 (J = 8.0 Hz, 1H), 7.56–7.52 (m, 1H), 7.03 (J = 7.6, 8.8 Hz, 1H), 2.53 (s, 3H); ¹C NMR (100 MHz, CDCl₃) δ 166.9, 155.1, 146.9, 142.7, 138.8, 134.5, 132.3, 131.8, 131.6, 131.4, 131.3, 125.8, 125.9, 123.9, 123.1, 18.5; ¹H NMR (400 MHz, CDCl₃) δ 6–6.2; IR (KBr) ν 3068, 2962, 1716, 1433, 1376, 1233, 1211, 1167, 1143; HRMS (ESI+, QTOF) exact mass calc’d for C₁₈H₁₆F₃N₂O₂ [M + H]+ 383.0077, found: 383.0079.

2-(5-Methyl-2-(pyrimidin-2-yl)phenyl)isoindoline-1,3-dione (5s).¹ ¹H NMR (400 MHz, CDCl₃) δ 8.17 (d, J = 7.2 Hz, 1H), 7.94 (m, 1H); ¹C NMR (100 MHz, CDCl₃) δ 168.2, 164.0, 156.9, 141.6, 133.9, 132.5, 132.4, 131.5, 131.2, 130.4, 130.3, 118.5, 21.2; ¹H NMR (400 MHz, CDCl₃) δ 7.47 (m, 1H), 7.42 (J = 7.2 Hz, 1H), 7.33 (s, 1H), 7.24 (J = 8.0 Hz, 1H), 7.12 (d, J = 8.4 Hz, 2H), 4.80 (s, 3H); ¹H NMR (100 MHz, CDCl₃) δ 162.8, 162.0, 154.7, 146.1, 143.9, 133.9, 132.5, 132.4, 131.5, 131.2, 130.4, 130.3, 118.5, 118.8, 21.2; IR (KBr) ν 2971, 1719, 1709, 1596, 1551, 1410, 1378, 1112, 1085, 805, 716 cm⁻¹; HRMS (ESI+, QTOF) exact mass calc’d for C₂₃H₂₁N₂O₂ [M + H]+ 337.1506, found: 337.1506.

KIE Experiment with [D-4a] as Substrate. Compounds [D-4a] and [D-2a] were synthesized according to the literature procedure.¹ Under oxygen, CuOAc (0.04 mmol, 4.9 mg), [D-4a] (0.2 mmol, 31.2 mg), and phthalimide (0.24 mmol, 33.5 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 Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give the corresponding products [D]-5a and 5a (28% yield). The ¹H NMR analysis showed that the ratio of 5a/[D]-5a is 2.1.

KIE Experiment with [D-2a] as Substrate. Under oxygen, CuOAc (0.04 mmol, 4.9 mg), [D-2a] (0.1 mmol, 15.7 mg), 4a (0.1 mmol, 15.5 mg), and phthalimide (0.24 mmol, 33.5 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 Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give the corresponding products [D]-5a and 5a (33% yield). The ¹H NMR analysis showed that the ratio of 5a/[D]-5a is 3.7.
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