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Carbonylation Access to Phthalimides Using Self-Sufficient Directing Group and Nucleophile

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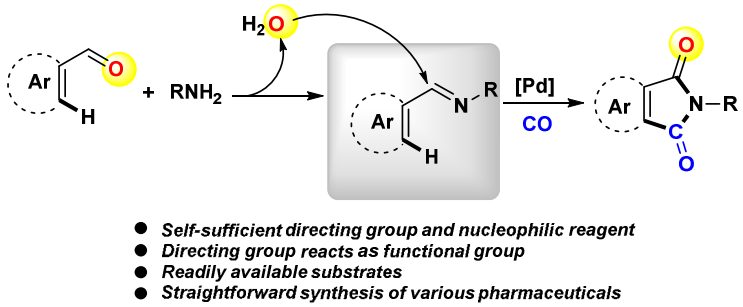
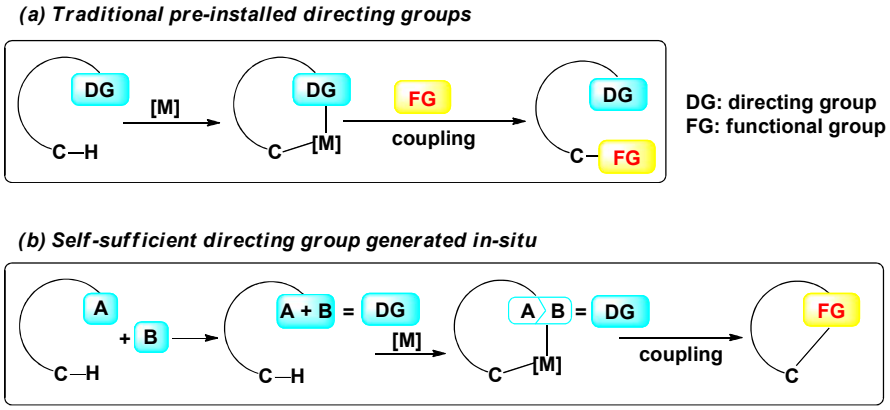


Abstract: Herein we report a novel palladium-catalyzed oxidative carbonylation reaction for the synthesis of phthalimides with high atom- and step- economy. In our strategy, the imine and H_2O, which are generated *in situ* from the condensation of aldehyde and amine, serve as self-sufficient directing group and nucleophile respectively. This method provides rapid access to phthalimides starting from readily available materials in a one-pot manner. Various phthalimide derivatives are constructed efficiently, including medicinally and biologically active phthalimide-containing compounds.

INTRODUCTION

Transition metal-catalyzed C-H functionalization has emerged as a powerful tool in organic synthesis.[1] Although this method eliminates the need for preactivation of the starting materials, high reactivity and regioselectivity is still a challenging issue. To overcome this limitation, directing group-assisted C-H bond cleavage is considered to be a promising and fundamental protocol (Scheme 1a).[2] Despite of the significant progress in this field, the introduction of an external directing group usually requires tedious preparations and results in limited substrate applicability.

Scheme 1. Two strategies for directed C-H functionalization

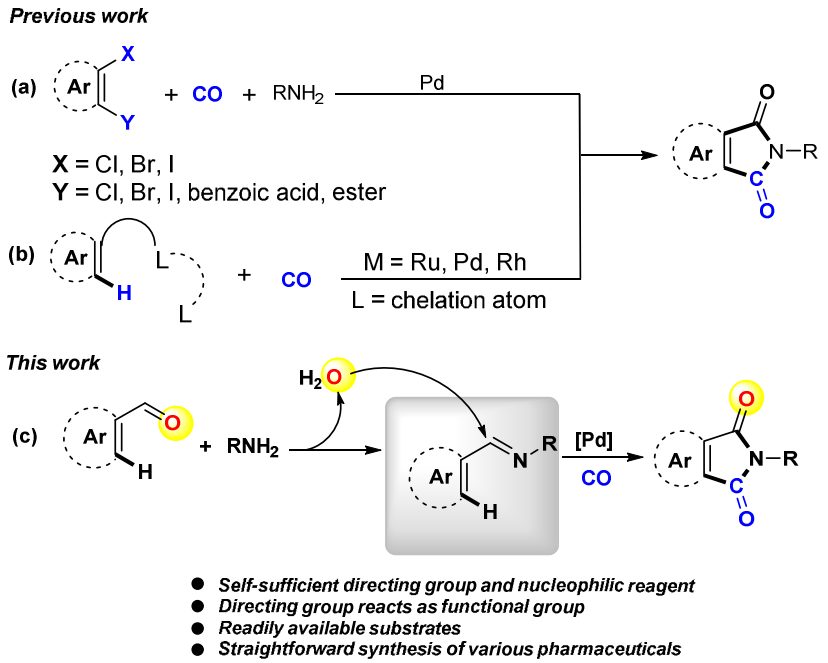


Advantages: ***directing groups are generated in-situ and react as functional groups***

In addition, sometimes the reaction conditions for installing and removing directing groups are incompatible with other functional groups in the same reaction system. Owing to the concept of "*green chemistry*" and the increasing pressure to reduce energy consumption,[3] the development of novel, efficient and self-sufficient directing strategy with maximized atom- and step-economy is highly desirable. Consequently, we envisioned that the directing group could be generated *in situ*[4] and incorporated into the target molecule playing the role of coupling partner without further synthetic manipulations (Scheme 1b).

Within this reaction class, Pd-catalyzed direct oxidative carbonylation has attracted considerable attention due to the prevalent presence of carbonyl-containing compounds in organic molecules.[5] In recent years, several approaches have been reported for the synthesis of phthalimides by palladium-catalyzed carbonylation.[6] Moreover, oxidative carbonylation of simple nucleophiles such as C-H and Y-H (Y= O, N, etc), has been considered as an ideal carbonylation protocol in recent years. Employing this strategy, Chatani and Rovis reported ruthenium- and rhodium-catalyzed oxidative carbonylation for the synthesis of phthalimides via directing group assisted C-H bond activation (Scheme 2a, 2b). Despite of their advantages, these methods have one drawback: complicated starting materials is required. On the basis of our previous work,[7] we report a straightforward oxidative carbonylation reaction for the construction of *N*-substituted phthalimides (Scheme 2c). In our protocol, we suppose that the *in-situ* generated imine could be used as self-sufficient directing group, which is derived from the condensation of aldehyde and amine, furnishing the carbonylation reaction with high efficiency. H_2O as benign byproduct is liberated in the first condensation step and consumed in the second nucleophilic step. The process employing *in-situ* generated imine and H_2O as directing group and nucleophile respectively is coherent with the principle of high atom- and step- economy. Furthermore, the use of simple aldehyde and amine as substrates makes this approach particularly attractive. The transformation provides a concise and convenient entry to the core structure of phthalimides, which are the key structural motif in many drug candidates.[8]

Scheme 2. New strategy of carbonylation for N-substituted phthalimides



RESULTS AND DISCUSSION

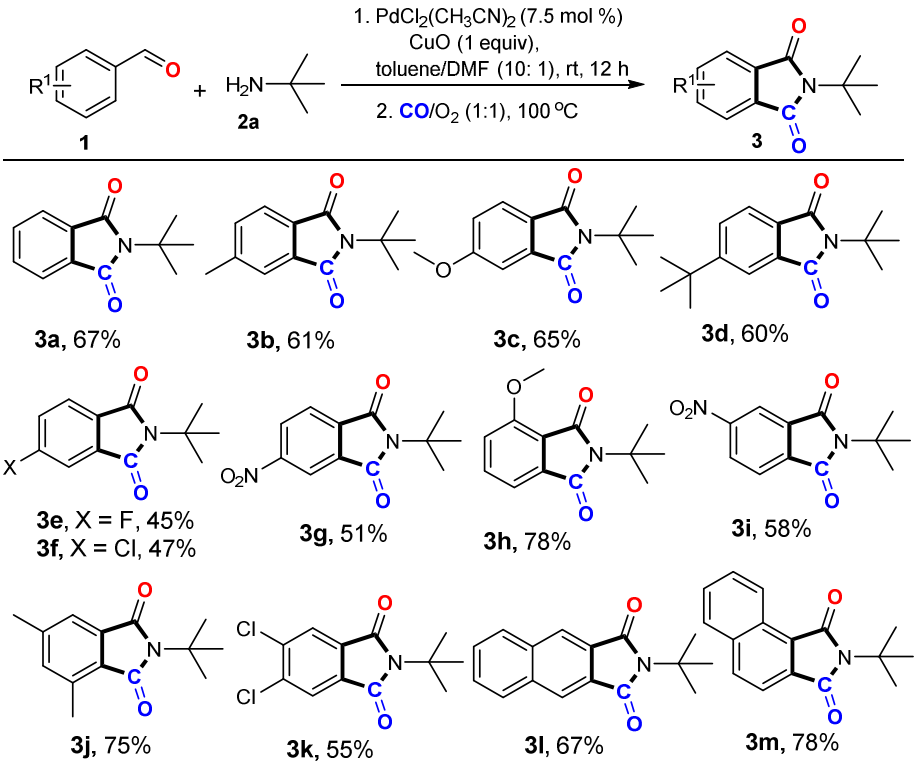
We began our investigation by utilizing benzaldehyde (**1a**) and *tert*-butylamine (**2a**) as model substrates under the treatment of $PdCl_2$ with CuO/O_2 as oxidant under CO atmosphere. After screening several parameters (e.g., catalyst, oxidant, solvent and temperature), we found that the corresponding product 2-(*tert*-butyl)isoindoline-1,3-dione (**3a**) was obtained in 67% yield in the presence of $PdCl_2(CH_3CN)_2$ (7.5 mol %), 1 atm of CO/O_2, and CuO (1 equiv) in a mixture of toluene and DMF (10: 1) (see the Supporting Information for details).

Subsequently, the scope of the aryl-substituted benzaldehydes was investigated. As summarized in Table 1, mono or di-substituted substrates bearing electron-donating groups (R^1 = Me, OMe, *t*-butyl) or electron-withdrawing groups (R^1 = Cl, NO_2) on benzaldehyde moiety were well-tolerated under the optimal reaction conditions, and transferred to the corresponding products **3a-3k** in moderate to good

yields. In addition, the reaction started from 1-naphthaldehyde or 2-naphthaldehyde also proceeded efficiently and provided **3l** and **3m** in good yields. It was found that the electronic and steric properties have significant effects on the reaction efficiency. Electron-rich substrates are more efficient than those with electron-deficient substituents, which suggested the C-H bond activation might be electrophilic in nature.[9] Meanwhile, this transformation favored less steric position (**3i**, **3k**, **3l**).

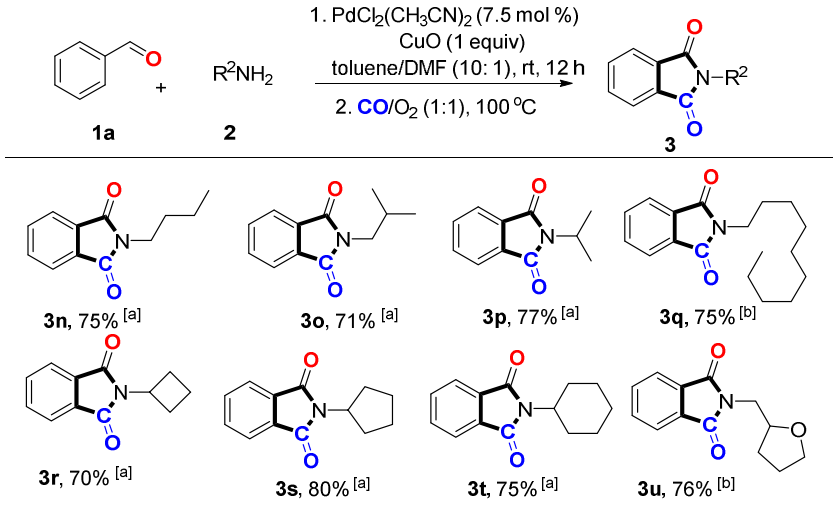
We next examined the scope of the amines (Table 2). A variety of aliphatic amines could be efficiently converted into the corresponding products (**3n-3u**). To our delight, the substrate decan-1-amine bearing ten-carbon chain could be converted to the corresponding product **3q** in 75% yield. Pleasingly, all the tested cyclic amines, such as cyclobutanamine, cyclopentanamine and cyclohexanamine, transferred to the desired phthalimides in moderate to good yields (**3r-3t**). Heterocyclic aliphatic amine was also reactive in this catalytic system, and converted to **3u** in 76% yield. It is important that the aromatic amines are also well-tolerated in this reaction. Different substituted aromatic amines with important functional groups were compatible to this catalytic system, such as methyl, phenoxyl and halogen (F, Cl, Br), which could be subjected to further synthetic transformations (**3v-3ab**). Naphthalen-1-amine and 1-naphthaldehyde could also transfer to the corresponding products with extended π-system (**3ac**, **3ad**). Moreover, this transformation was compatible with benzylamine to give the desired product **3ae** in 68% yield.

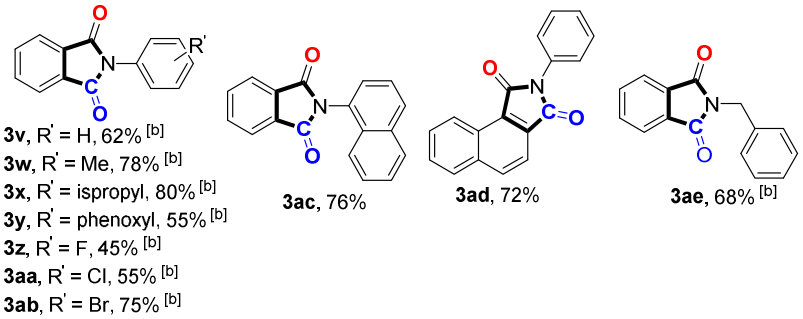
Table 1. Scope of aryl-substituted benzaldehydes



Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), $PdCl_2(CH_3CN)_2$ (7.5 mol %), CuO (0.2 mmol), and toluene/DMF (10: 1) (2.5 mL) at room temperature and then added a balloon with CO/O_2 at 100 °C. Yields referred to isolated yields.

Table 2. Scope of amines

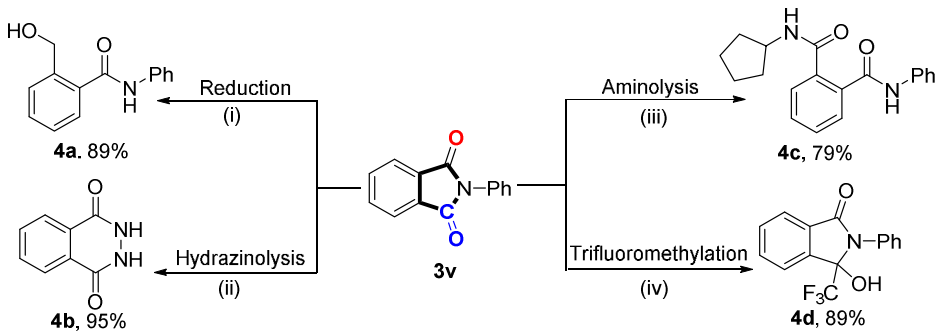




Reaction conditions: [a] **1a** (0.2 mmol), **2** (0.24 mmol), $PdCl_2(CH_3CN)_2$ (7.5 mol %), CuO (0.2 mmol), and toluene/DMF (10: 1) (2.5 mL) at room temperature. [b] **2** (0.2 mmol), **1a** (1.2 equiv), $PdCl_2(CH_3CN)_2$ (7.5 mol %), CuO (0.2 mmol), and toluene/DMF (10: 1) (2.5 mL) at room temperature and then added a balloon with CO/O_2 at 100 ^oC. Yields referred to isolated yields.

The synthetic utility of the resultant phthalimides is then demonstrated by conducting further transformations of **3v** (Scheme 3).[10] For example, the reduction of **3v** with an excess of $NaBH_4$ resulted in the hydrogenation of imides, leading to amide **4a** in 89% yield. When **3v** was submitted to hydrazine hydrate, the phthalhydrazide product **4b**, an important intermediate for the synthesis of phthalazinones, was obtained in high yield. In addition, aminolysis reaction could also occur upon **3v,** and provided the diamide product **4c** in 79% yield. It should be noted that compound **4d** bearing a trifluolomethyl group, which might profoundly alter the biological and pharmaceutical properties of substrates,[11] could be also constructed from **3v** via a trifluolomethylation process.

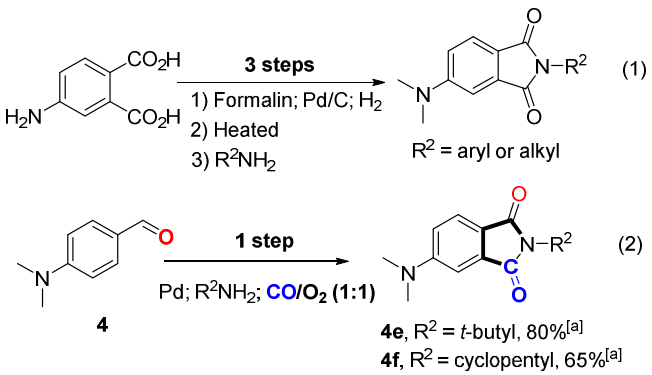
Scheme 3. Further transformations of 3v



Reaction conditions: (i) 2-Phenylisoindoline-1,3-dione (**3v**) (0.5 g, 2.2 mmol), $NaBH_4$ (3 equiv, 0.25 g, 6.6 mmol) , and methanol (25 mL) at 0 °C for 4 h. Yields referred to isolated yields; (ii) 2-Phenylisoindoline-1,3-dione (**3v**) (0.5 g, 2.2 mmol) , hydrazine hydrate (1.2 equiv, 2.6 mmol) in methanol (20 mL) refluxed at 70 °C for 16 h. Yields referred to isolated yields; (iii) 2-Phenylisoindoline-1,3-dione (**3v**) (0.50 g, 2.2 mmol), cyclopentamine (2 equiv, 0.37 g, 4.4 mmol) in dioxane (20 mL) refluxed at 80 °C for 3 h. Yields referred to isolated yields; (iv) 2-Phenylisoindoline-1,3-dione (**3v**) (0.5 g, 2.2 mmol), (Trifluoromethyl)trimethyl silane (CF_3TMS, 0.3 g, 2.6 mmol), 1.0 M solution of TBAF in dry THF (10 mL) under N_2 atmosphere. Yields referred to isolated yields.

Notably, phthalimides containing a 4-amino substituent have been recognized to be an important class of fluorescent bioactive compounds.[12] The synthesis of this kind of compounds is generally realized with three steps (methylation; dehydration; amination) using 4-aminophthalic acid as the starting material [Scheme 4, Eq. (1)].[12a] Under our catalytic system, 4-amino substituted phthalimides **4e** and **4f** could be achieved efficiently in a one-step manner starting from available and inexpensive 4-(dimethylamino)benzaldehyde (**4**) [Scheme 4, Eq. (2)], thus providing novel and straightforward access to different fluorescent bioactive compounds.

Scheme 4. The synthesis of 4-amino substituted phthalimides

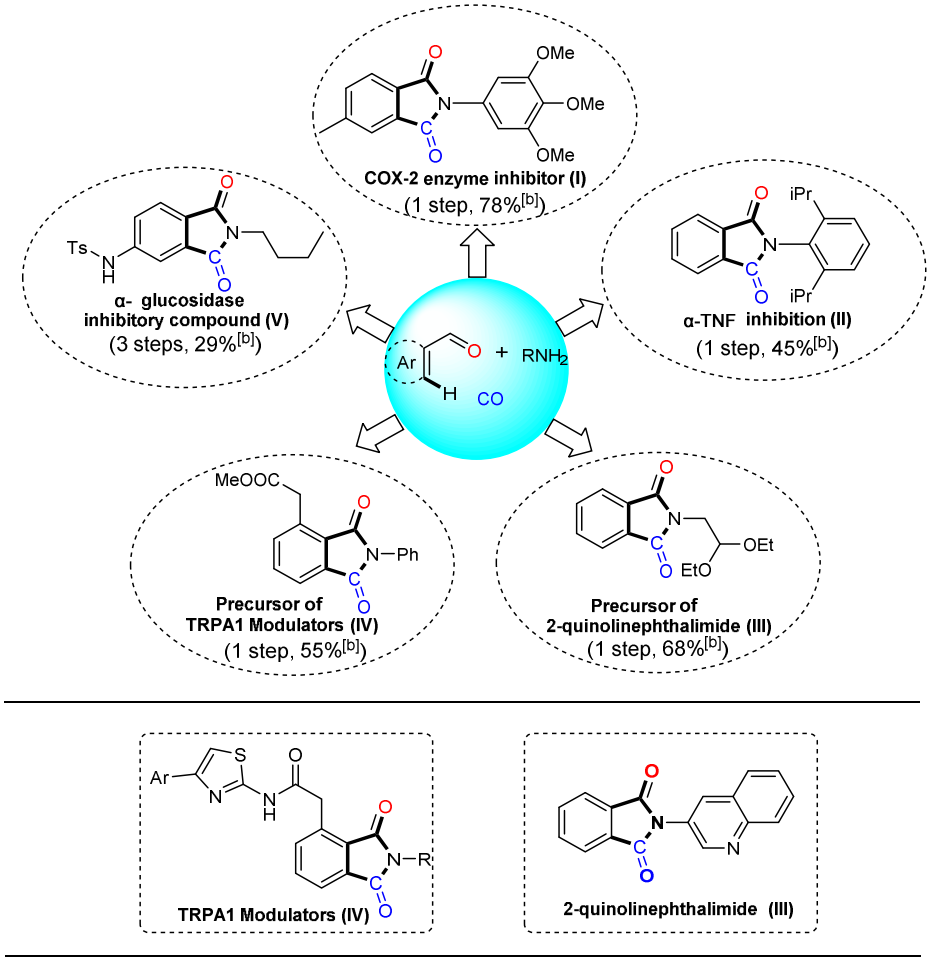


Reaction conditions: **4** (0.2 mmol), amine (0.24 mmol), $PdCl_2(CH_3CN)_2$ (7.5 mol %), CuO (0.2 mmol), and toluene/DMF (10: 1) (2.5 mL) at room temperature and then added a balloon with CO/O_2 at 100 ^oC. Yields referred to isolated yields.

This tandem oxidative carbonylation reaction was also applied to the construction of a series important drug candidates bearing phthalimide skeleton, such as cycloxygenase-2 (COX-2) enzyme inhibitor (**I**),[13] inhibitor of tumor necrosis factor-α (TNF-α) (**II**),[14] 2-quinolinephthalimide (**III**), TRPA1 (Transient Receptor Potential subfamily A1) modulators (**IV**)[15] and anti-glucosidase[16](**V**). As shown in Figure 1, 5-methyl-2-(3,4,5-trimethoxyphenyl)isoindoline-1,3-dione (**I**), which is responsible for the formation of different biological mediators, was obtained efficiently in 78% yield. Moreover, **II** as an important inhibitor of α-TNF was also synthesized from benzaldehyde with this newly developed method. Gratifyingly, the precursor of 2-quinolinephthalimide (**III**), an important bioactive compound, could be achieved conveniently and the yield was up to 68%. Moreover, the precursor of TRPA1 (**IV**), which is a peripheral damage receptor involved in prolonged pain response, was also prepared directly in 55% yield under the standard conditions. Besides, α-glucosidase inhibitory compound (**V**) could be also synthesized from the

corresponding materials 4-nitrobenzaldehyde using our present method after three step transformation (Figure 1).

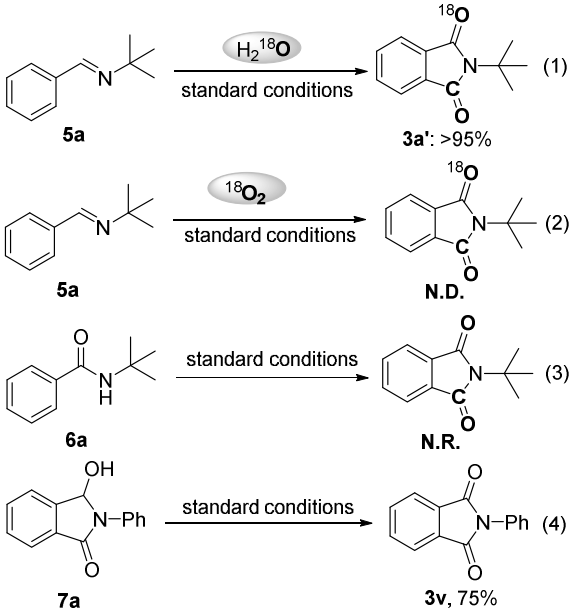
Figure 1. The synthesis of bioactive phthalimides



Having demonstrated the synthetic utility of this process, a series of mechanistic experiments were performed to gain further insight into the mechanistic pathway. The results of ^{18}O-labeling experiments proved that the oxygen atom in the carbonyl group should be originated from molecular water [Scheme 5, Eq. (1) and Eq. (2)]. Additionally, amide **6a** is one of the most common substrates for the construction of phthalimides,[17] however, no reaction occurred starting from amide **6a**, indicating that amide was not the intermediate in this catalytic system [Scheme 5, Eq. (3)]. To our

delight, 3-hydroxy-2-phenylisoindolin-1-one (**7a**), a possible precursor of phthalimide,[18] was detected in this reaction system. When we submitted **7a** to the standard conditions, the corresponding product **3v** was obtained in 75% yield [Scheme 5, Eq. (4)]. Furthermore, it was observed that no reaction occurred in the absence of Pd catalyst using benzaldehyde as initial material, which suggested that **7a** was the unique possible intermediate in this process.

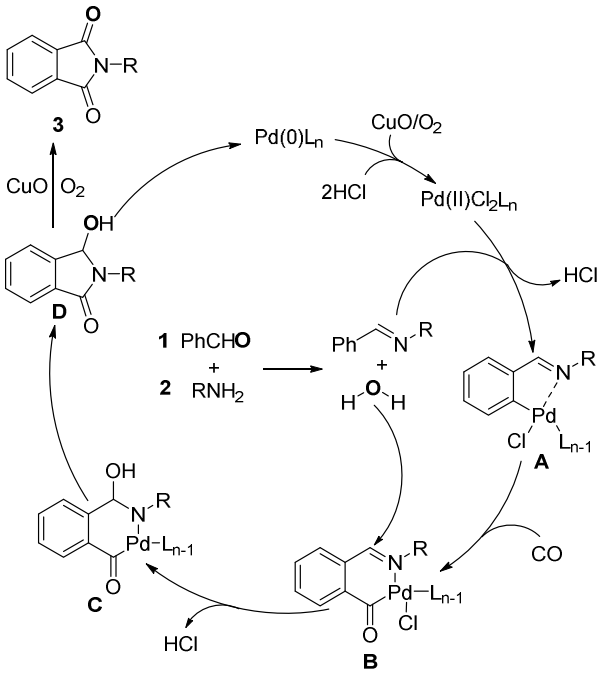
Scheme 5 Mechanistic studies



On the basis of the above results and literature precedence,[19] a plausible reaction mechanism is proposed in Figure 2. Initially, the imine is generated *in situ* as a directing group from the condensation of aldehyde and amine. Subsequent C-H activation directed by imine group leads to the generation of intermediate **A**, followed by CO insertion to afford the intermediate **B**. H_2O, which is also generated in situ from the condensation process, undergoes nucleophilic reaction to C=N bond to generate intermediate **C**.[20] The reductive elimination of intermediate **C** would afford the annulation product **D**. Finally, further oxidation of **D** gives the desired product.

Finally, Pd(0) species formed from the reductive elimination step is recycled by CuO/O_2 oxidant.

Figure 2. Proposed mechanism



CONCLUSION

In summary, we have developed a novel and efficient protocol for the synthesis of phthalimides in a one-pot manner. The directing group and nucleophile are all generated *in situ*, making the reaction feature high atom and step economy. From the point of "*green chemistry*", energy-saving and environment-friendly strategy, this method provides an ideal pathway for the synthesis of various medicinally and biologically active compounds. Further efforts toward the synthetic applications for the drug delivery as well as mechanistic studies are underway in our laboratory.

EXPERIMENTAL SECTION

General Information. Melting points were measured with a BÜCHI B-545 melting point instrument and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using

a Bruker Avance 400 MHz NMR spectrometer. The chemical shifts are referenced to signals at 7.24 and 77.0 ppm, respectively, and chloroform is solvent with TMS as the internal standard. IR spectra were obtained either as potassium bromide pellets or as liquid films between two potassium bromide pellets with a Bruker Vector 22 spectrometer. GC–MS was obtained using electron ionization. HRMS (LCMS-IT-TOF) was carried out on a MAT 95XP (Thermo). TLC was performed by using commercially prepared 100–400 mesh silica gel plates (GF_{254}) and visualization was effected at 254 nm.

Typical Experimental Procedure for Synthesis of *N*-substituted phthalimides. When RNH_2 is aliphatic amine with low boiling point, condition A: A mixture of aryl-substituted aldehyde (0.2 mmol), aliphatic amine (0.24 mmol), $PdCl_2(CH_3CN)_2$ (4.8 mg, 7.5 mol %), CuO (0.2 mmol), toluene/DMF (10: 1, 2.5 mL) in a test tube (25 mL) equipped with a magnetic stirring bar;When RNH_2 is aromatic amine or aliphatic amine with high boiling point, condition B: A mixture of aryl-substituted aldehyde (0.24 mmol), aromatic amine (0.2 mmol), $PdCl_2(CH_3CN)_2$ (4.8 mg, 7.5 mol %), CuO (0.2 mmol), toluene/DMF (10:1, 2.5 mL) in a test tube (25 mL) equipped with a magnetic stirring bar; The mixture was stirred under the atmosphere of air at room temperature for 12 h. After the condensation was completed, a balloon with CO and O_2 was added into the tube and the mixture was stirred at 100 ^oC for 48 h. When the reaction was completed (detected by TLC), the mixture was cooled to room temperature, and then the solvent was removed under reduced pressure. The residue

was purified by column chromatography on silica gel to afford the corresponding products with petroleum ether/ethyl acetate (4:1).

Experimental Procedure for 4a. 2-Phenylisoindoline-1,3-dione (**3v**) (0.5 g, 2.2 mmol) was dissolved in methanol in a 25 mL flask and cooled to 0 °C. $NaBH_4$ (3 equiv, 0.25 g, 6.6 mmol) was added and the reaction mixture was stirred at 0 °C for 4 h. When the reaction was completed (detected by TLC), the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding products **4a** (0.44 g, 89%) with petroleum ether/ethyl acetate (2:1).

Experimental Procedure for 4b. 2-Phenylisoindoline-1,3-dione (**3v**) (0.5 g, 2.2 mmol) was dissolved in 20 mL methanol in a 50mL flask and hydrazine hydrate (1.2 equiv, 2.6 mmol) was added. The solution was refluxed at 70 °C for 16 h. When the reaction was completed (detected by TLC), the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding products **4b** (0.34 g, 95%) with petroleum ether/ethyl acetate (1:1).

Experimental Procedure for 4c. 2-Phenylisoindoline-1,3-dione (**3v**) (0.50 g, 2.2 mmol) was dissolved in 20 mL dioxane in a 50 mL flask and cyclopentamine (2 equiv, 0.37 g, 4.4 mmol) was added. The solution was refluxed at 80 °C for 3 h. When the reaction was completed (detected by TLC), the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding products **4c** (0.54 g, 79%) with petroleum ether/ethyl acetate (4:1).

Experimental Procedure for 4d. 2-Phenylisoindoline-1,3-dione (**3v**) (0.5 g, 2.2 mmol) was dissolved in dry THF (10 mL) in a reaction tube under N_2 atmosphere and cooled to 0 °C. (Trifluoromethyl)trimethyl silane (CF_3TMS, 0.3 g, 2.6 mmol) was added, followed by 1.0 M solution of TBAF in THF (1−2 mol %, 20−34 μL), and the reaction mixture was warmed to room temperature and stirred for 1 h. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding products **4d** (0.58 g, 89%) with petroleum ether/ethyl acetate (4:1).

Experimental Procedure for V. (1) A mixture of benzaldehyde (0.2 mmol), *n*-butylamine (0.24 mmol), $PdCl_2(CH_3CN)_2$ (4.8 mg, 7.5 mol %), CuO (0.2 mmol), toluene/DMF (10: 1, 2.5 mL) in a test tube (25 mL) equipped with a magnetic stirring bar; The mixture was stirred under the atmosphere of air at room temperature for 12 h. After the condensation was completed, a balloon with CO and O_2 was added into the tube and the mixture was stirred at 100 ^oC for 48 h. When the reaction was completed (detected by TLC), the mixture was cooled to room temperature, and then the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding crude product.

(2) The crude product from step 1 was dissolved in EtOH (5 mL) in a test tube (25 mL). Iron powder (0.6 mmol) was added, followed by 1.0 M solution of HCl (1.2 mmol), and the reacton mixture was stirred at 100 °C. When the reaction was completed (detected by TLC), the mixture was cooled to room temperature and reacted with NaOH until the solution is neutral. Then the mixture was filtrated and

extracted. The residue was purified by column chromatography on silica gel to afford the corresponding crude product.

(3) The crude product from step 2 was dissolved in CH_2Cl_2 (5 mL) in a test tube (25 mL) and Et_3N (0.4 mmol) was added. Tosyl chloride (0.3 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h. When the reaction was completed (detected by TLC), the mixture was cooled to room temperature, and then the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding product **V** (22 mg, 29%) with petroleum ether/ethyl acetate (10:1).

2-(*tert*-Butyl)isoindoline-1,3-dione (3a)[21]

Colorless solid (27 mg, 67 %), mp: 58.9-60.3 ^oC;^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.71 (m, 2H), 7.68-7.66 (m, 2H), 1.70 (s, 9H); ^{13}C NMR (100MHz, $CDCl_3$) δ 169.5, 133.6, 132.1, 122.5, 57.7, 29.1 ppm; IR (KBr) ν_{max} 1708, 1362, 1312, 1094, 715 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{12}H_{13}NNaO_2$ $[M+Na]^+$, 226.0838; found, 226.0837.

2-(*tert*-Butyl)-5-methylisoindoline-1,3-dione (3b)

White solid (26 mg, 61 %), mp: 66.9-68.1 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.6 Hz, 1H), 7.55 (s, 1H), 7.45 (d, J = 7.2 Hz, 1H), 2.48 (s, 3H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 169.7, 144.8, 134.2, 132.6, 129.6, 123.0, 122.5, 57.7, 29.1, 21.9 ppm; IR (KBr) ν_{max} 1708, 1354, 1093, 741 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{13}H_{15}NNaO_2$ $[M+Na]^+$, 240.0995; found, 240.0994.

2-(*tert*-Butyl)-5-methoxyisoindoline-1,3-dione (3c)

White solid (30 mg, 65 %), mp: 131.6-132.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.4 Hz, 1H), 7.22 (s, 1H), 7.12 (d, J = 8.0 Hz, 1H), 3.91 (s, 3H), 1.68 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 164.5, 134.7, 124.2, 119.8, 106.9, 57.7, 56.0, 29.1 ppm; IR (KBr) ν_{max} 1703, 1328, 1013, 744 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{13}H_{15}NNaO_3$ $[M+Na]^+$, 256.0944; found, 256.0949.

2,5-di-*tert*-Butylisoindoline-1,3-dione (3d)

Colorless solid (31 mg, 60 %), mp: 97.1-98.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.68 (s, 2H), 1.68 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 169.8, 158.2, 132.4, 130.7, 129.6, 122.4, 119.7, 57.7, 35.7, 31.2, 29.1 ppm; IR (KBr) ν_{max} 1708, 1351, 1262, 748 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{21}NNaO_2$ $[M+Na]^+$, 282.1464; found, 282.1469.

2-(*tert*-Butyl)-5-fluoroisoindoline-1,3-dione (3e)

Colorless solid (20 mg, 45 %), mp: 59.9-61.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.75 (m, 1H), 7.43 (d, J = 6.8 Hz, 1H), 7.33 (t, J = 8.6 Hz, 1H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 168.2, 167.6, 165.0, 134.9, 134.9, 127.9, 125.0, 124.9, 120.9, 120.6, 110.4, 110.1, 58.2, 29.0 ppm; IR (KBr) ν_{max} 1710, 1357, 1012, 748 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{12}H_{12}FNNaO_2$ $[M+Na]^+$, 244.0744; found, 244.0742.

2-(*tert*-Butyl)-5-chloroisoindoline-1,3-dione (3f)

White solid (22 mg, 47 %), mp: 89.0-89.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.67 (m, 2H), 7.66-7.59 (m, 1H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 168.3, 140.3, 133.8, 130.2, 123.9, 123.0, 58.2, 29.0 ppm; IR (KBr) ν_{max} 1710,

1346, 1093, 748 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{12}H_{12}ClNNaO_2$ $[M+Na]^+$, 260.0449; found, 260.0443.

2-(*tert*-Butyl)-5-nitroisoindoline-1,3-dione (3g)

Yellow solid (25 mg, 51 %), mp: 119.5-120.5 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.55 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 1.71 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 167.1, 151.7, 136.5, 133.4, 129.0, 123.9, 118.2, 59.0, 28.9 ppm; IR (KBr) ν_{max} 1711, 1536, 1324, 754, 716 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{12}H_{13}N_2O_4$ $[M+H]^+$, 249.0870; found, 249.0869.

2-(*tert*-Butyl)-4-methoxyisoindoline-1,3-dione (3h)

White solid (36 mg, 78 %), mp: 110.1-111.5 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 7.2 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H), 1.64 (s, 9H); ^{13}C NMR (100MHz, $CDCl_3$) δ 169.1, 168.5, 156.3, 135.7, 134.5, 117.4, 116.8, 114.7, 57.7, 56.2, 29.1 ppm; IR (KBr) ν_{max} 1705, 1315, 1277, 753 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{13}H_{15}NNaO_3$ $[M+Na]^+$, 256.0944; found, 256.0949.

2-(*tert*-Butyl)-5-nitroisoindoline-1,3-dione (3i)

Yellow solid (28 mg, 58 %), mp: 62.0-63.2 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.62-8.53 (m, 2H), 7.97 (d, J = 8.0 Hz, 1H), 1.72 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 167.1, 151.7, 136.5, 133.4, 129.0, 123.9, 118.2, 59.0, 28.9 ppm; IR (KBr) ν_{max} 1711, 1536, 1336, 1098, 756 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{12}H_{13}N_2O_4$ $[M+H]^+$, 249.0870; found, 249.0862.

2-(*tert*-Butyl)-4,6-dimethylisoindoline-1,3-dione (3j)

White solid (34 mg, 75 %), mp: 62.3-63.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.19 (s, 1H), 2.60 (s, 3H), 2.41 (s, 3H), 1.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 169.9, 144.1, 137.0, 136.6, 133.1, 126.2, 120.8, 57.5, 29.2, 21.7, 17.5 ppm; IR (KBr) ν_{max} 1703, 1355, 1310, 1011, 750 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{14}H_{17}NNaO_2$ $[M+Na]^+$, 254.1151; found, 254.1155.

2-(*tert*-Butyl)-5,6-dichloroisoindoline-1,3-dione (3k)

Colorless solid (30 mg, 55 %), mp: 105.7-106.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 2H), 1.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 138.6, 131.3, 124.8, 58.5, 28.9 ppm; IR (KBr) ν_{max} 1710, 1589, 1349, 1099, 752 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{12}H_{12}Cl_2NO_2$ $[M+H]^+$, 272.0240; found, 272.0233.

2-(*tert*-Butyl)-1*H*-benzo[f]isoindole-1,3(2H)-dione (3l)

White solid (34 mg, 67 %), mp: 128.5-129.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 2H), 8.08-7.97 (m, 2H), 7.72-7.58 (m, 2H), 1.75 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 135.6, 130.1, 128.8, 128.2, 123.7, 58.2, 29.1 ppm; IR (KBr) ν_{max} 1708, 1327, 1101, 755 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{15}NNaO_2$ $[M+Na]^+$, 276.0995; found, 276.1001.

2-(*tert*-Butyl)-1*H*-benzo[e]isoindole-1,3(2H)-dione (3m)

Colorless solid (39 mg, 78 %), mp: 98.6-99.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.63 (t, J = 7.4 Hz, 1H), 1.74 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.2, 136.6, 134.6, 131.5, 129.3, 128.7, 128.4, 127.8,

127.0, 124.9, 118.1, 57.7, 29.2 ppm; IR (KBr) ν_{max} 1713, 1586, 1346, 1055, 755 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{15}NNaO_2$ $[M+H]^+$, 276.0995; found, 276.0997.

2-Butylisoindoline-1,3-dione (3n)

Yellow oil (30 mg, 75 %): ^1H NMR (400 MHz, $CDCl_3$) δ 7.84-7.83 (m, 2H), 7.71-7.70 (m, 2H), 3.69 (t, J = 7.2, 2H), 1.66-1.64 (m, 2H), 1.39-1.34 (m, 2H), 0.95 (t, J = 7.4, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 133.8, 132.2, 123.1, 37.8, 30.7, 20.1, 13.6 ppm; IR (KBr) ν_{max} 1712, 1390, 1047, 733 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{12}H_{14}NO_2$ $[M+H]^+$, 204.1019; found, 204.1018

2-Isobutylisoindoline-1,3-dione (3o)

Colorless solid (29 mg, 71 %), mp: 92.8-93.8 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 2.4 Hz, 2H), 7.72 (d, J = 2.4 Hz, 2H), 3.51 (d, J = 7.2 Hz, 2H), 2.16-2.09 (m, 1H), 0.95 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 133.9, 132.0, 123.2, 45.3, 27.8, 20.1 ppm; IR (KBr) ν_{max} 1706, 1392, 1050, 716 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{12}H_{13}NNaO_2$ $[M+Na]^+$, 226.0838; found, 226.0835.

2-Isopropylisoindoline-1,3-dione (3p)

Colorless solid (29 mg, 77 %), mp: 84.1-85.0 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 1.6 Hz, 2H), 7.70 (d, J = 2.4 Hz, 2H), 4.57-4.50 (m, 1H), 1.50 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 133.7, 132.1, 123.0, 43.0, 20.1 ppm; IR (KBr) ν_{max} 1692, 1369, 1034, 869, 753, 710 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{11}H_{11}NNaO_2$ $[M+Na]^+$, 212.0682; found, 212.0684.

2-Decylisoindoline-1,3-dione (3q)

Colorless solid (43 mg, 75 %), mp: 58.3-59.6 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 2.4 Hz, 2H), 7.71 (d, J = 2.4 Hz, 2H), 3.67 (t, J = 6.8 Hz, 1H), 1.67-1.65 (m, 2H), 1.25-1.23 (m, 14H), 0.87-0.86 (m, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 133.8, 132.2, 123.1, 38.1, 31.9, 29.5, 29.5, 29.3, 29.2, 28.6, 26.9, 22.7, 14.1 ppm; IR (KBr) ν_{max} 1713, 1588, 1390, 717 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{18}H_{25}NNaO_2$ $[M+Na]^+$, 310.1777; found, 310.1778.

2-Cyclobutylisoindoline-1,3-dione (3r)

Colorless solid (28 mg, 70 %), mp: 108.3-110.0 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 2.6 Hz, 2H), 7.67 (d, J = 2.6 Hz, 2H), 4.75 (p, J = 8.8 Hz, 1H), 2.93 (p, J = 9.2 Hz, 2H), 2.26-2.24 (m, 2H), 1.93 (dd, J = 19.6, 10.0 Hz, 1H), 1.78 (dd, J = 19.6, 10.0 Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 133.9, 132.0, 123.1, 44.7, 27.7, 15.3 ppm; IR (KBr) ν_{max} 1713, 1591, 1377, 755 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{12}H_{11}NNaO_2$ $[M+Na]^+$, 224.0682; found, 224.0679.

2-Cyclopentylisoindoline-1,3-dione (3s)

Colorless solid (34 mg, 80 %), mp: 101.5-102.7 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 2H), 7.70 (s, 2H), 4.64-4.61(m, 1H), 2.11-2.04(m, 2H), 1.96-1.94 (m, 4H), 1.69-1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 133.7, 132.2, 123, 51.0, 29.6, 25.1 ppm; IR (KBr) ν_{max} 1709, 1593, 1376, 1080, 715 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{13}H_{13}NNaO_2$ $[M+Na]^+$, 238.0838; found, 238.0841.

2-Cyclohexylisoindoline-1,3-dione (3t)

Yellow solid (34 mg, 75 %), mp: 166.7-168.2 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.75 (m, 2H), 7.74-7.62 (m, 2H), 4.11 (t, J = 8.2 Hz, 1H), 2.21 (q, J = 12.4 Hz,

1H), 1.87 (d, J = 12.0 Hz, 1H), 1.73 (d, J = 12.8 Hz, 1H), 1.50-1.13 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 133.7, 132.1, 123.0, 50.9, 29.9, 26.0, 25.1 ppm; IR (KBr) ν_{max} 1708, 1383, 1083, 711 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{14}H_{15}NNaO_2$ $[M+Na]^+$, 252.0995; found, 252.0993.

2-((Tetrahydrofuran-2-yl)methyl)isoindoline-1,3-dione (3u)

White solid (35 mg, 76 %), mp: 88.4-89.7 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 2.4 Hz, 2H), 7.71 (d, J = 2.4 Hz, 2H), 4.28-4.25 (m, 1H), 3.92 (dd, J = 10.0,7.2 Hz, 1H), 3.85-3.72 (m, 2H), 3.71-3.60 (m, 1H), 2.01-1.89(m, 2H), 1.85-1.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 133.9, 132.1, 123.3, 76.2, 67.9, 41.8, 29.2, 25.3 ppm; IR (KBr) ν_{max} 1711, 1584, 1387, 714 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{13}H_{13}NNaO_3$ $[M+Na]^+$, 254.0788; found, 254.0792.

2-Phenylisoindoline-1,3-dione (3v)

White solid (28 mg, 62 %), mp: 205.5-207.3 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02-7.90 (m, 2H), 7.79-7.77 (m, 2H), 7.51 (t, J = 7.6 Hz, 2H), 7.45-7.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 134.4, 131.8, 129.1, 128.1, 126.6, 123.8 ppm; IR (KBr) ν_{max} 1764, 1243, 755 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{14}H_9NNaO_2$ $[M+Na]^+$, 246.0525; found, 246.0520.

2-(*p*-Tolyl)isoindoline-1,3-dione (3w)

White solid (37 mg, 78 %), mp: 203.9-205.3 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.90 (m, 2H), 7.80-7.74 (m, 2H), 7.30 (s, 4H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 138.2, 134.3, 131.9, 129.8, 129.0, 126.5, 123.7, 21.2 ppm. IR (KBr)

ν_{max} 1716, 1383, 1108, 718 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{15}H_{12}NO_2$ $[M+Na]^+$, 238.0863; found, 238.0863.

2-(4-Isopropylphenyl)isoindoline-1,3-dione (3x)

White solid (42 mg, 80 %), mp: 216.8-218.1 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01-7.90 (m, 2H), 7.83-7.75 (m, 2H), 7.42-7.31 (m, 4H), 2.97 (dt, J = 13.8, 6.9 Hz, 1H), 1.28 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 148.9, 134.3, 131.9, 129.2, 127.2, 126.4, 123.7, 33.9, 23.9 ppm. IR (KBr) ν_{max} 1706, 1110, 882, 746 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{17}H_{15}NNaO_2$ $[M+Na]^+$, 288.0992; found, 288.0995.

2-(4-Phenoxyphenyl)isoindoline-1,3-dione (3y)

White solid (35 mg, 55 %), mp: 153.1-154.8 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02-7.92 (m, 2H), 7.86-7.76 (m, 2H), 7.40 (t, J = 8.0 Hz, 4H), 7.20-7.09 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 157.2, 156.5, 134.4, 131.8, 129.9, 128.1, 126.4, 123.9, 123.8, 119.5, 118.8 ppm. IR (KBr) ν_{max} 1711, 1590, 1291, 748 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{20}H_{13}NNaO_3$ $[M+Na]^+$, 338.0789; found, 338.0788.

2-(4-Fluorophenyl)isoindoline-1,3-dione (3z)

White solid (22 mg, 45 %), mp: 178.0-179.4 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97-7.94 (m, 2H), 7.85-7.76 (m, 2H), 7.46-7.37 (m, 2H), 7.20 (t, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 134.5, 131.7, 128.4, 128.3, 123.8, 116.2, 116.0 ppm. IR (KBr) ν_{max} 1715, 1113, 885, 755 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{14}H_8FNNaO_2$ $[M+Na]^+$, 264.0431; found, 264.0431.

2-(4-Chlorophenyl)isoindoline-1,3-dione (3aa)

White solid (28 mg, 55 %), mp: 179.4-181.5 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.95 (m, 2H), 7.83-7.78 (m, 2H), 7.48 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 134.6, 133.8, 131.7, 130.2, 129.3, 127.7, 123.9 ppm. IR (KBr) ν_{max} 1714, 1495, 1120, 822, 754 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{14}H_9ClNO_2$ $[M+H]^+$, 258.0319; found, 258.0316.

2-(4-Bromophenyl)isoindoline-1,3-dione (3ab)

White solid (45 mg, 75 %), mp: 196.3-198.4 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.92 (m, 2H), 7.83-7.77 (m, 2H), 7.63 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 134.6, 132.3, 131.6, 130.8, 127.9, 123.9, 121.8 ppm. IR (KBr) ν_{max} 1712, 1392, 1119, 884, 712 cm^{-1}; MS (EI) m/z 104, 151, 178, 257, 301.

2-(Naphthalen-1-yl)isoindoline-1,3-dione (3ac)

Brown solid (41 mg, 76 %), mp: 180.4-181.7 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.4, 1H), 8.09 (d, J = 8.4, 1H), 8.02 (d, J = 7.2, 1H), 7.92 (d, J = 8.0, 1H), 7.87 (d, J = 8.4, 1H), 7.78-7.74 (m, 2H), 7.70 (t, J = 7.2, 2H), 7.65 (t, J = 7.6 1H), 6.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 162.8, 139.8, 137.4, 137.2, 133.9, 131.6, 131.4, 129.9, 128.4, 127.6, 127.2, 126.9, 125.9, 125.1, 124.4, 124.3, 114.3, 86.4 ppm; IR (KBr) ν_{max} 1727, 1409, 1373, 1009, 757 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{18}H_{11}NNaO_2$ $[M+Na]^+$, 296.0682; found, 296.0679.

2-Phenyl-1*H*-benzo[e]isoindole-1,3(2*H*)-dione (3ad)

Yellow solid (39 mg, 72%), mp: 166.3-167.0 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 7.96 (dd, J = 16.4, 8.0 Hz, 2H), 7.74 (d,

J = 7.2 Hz, 1H), 7.69 (d, *J* = 7.2 Hz, 1H), 7.51-7.48 (m, 4H), 7.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 167.8, 136.8, 135.4, 131.8, 131.1, 129.7, 129.1, 128.9, 128.8, 128.2, 127.9, 127.0, 126.7, 125.1, 118.7 ppm; IR (KBr) ν_{max} 1714, 1376, 1099, 756 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{18}H_{11}NNaO_2$ $[M+Na]^+$, 296.0682; found, 296.0681.

2-Benzylisoindoline-1,3-dione (3ae)

Yellow solid (32 mg, 68%), mp: 105.6-107.4 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.78 (m, 2H), 7.69 (d, *J* = 2.5 Hz, 2H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.33-7.25 (m, 3H), 4.84 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 136.4, 134.0, 132.1, 128.7, 128.6, 127.8, 123.4, 41.6 ppm; IR (KBr) ν_{max} 1712, 1390, 1343, 943, 754 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{15}H_{11}NNaO_2$ $[M+Na]^+$, 260.0682; found, 260.0684.

2-(Hydroxymethyl)-*N*-phenylbenzamide (4a)

White solid (0.44 g, 89 %), mp: 134.1-135.7 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.54-7.49 (m, 1H), 7.44-7.37 (m, 4H), 7.18 (t, *J* = 7.4 Hz, 1H), 5.35 (s, 1H), 4.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 139.2, 137.9, 136.1, 131.5, 131.0, 129.1, 128.5, 128.4, 124.8, 120.4, 64.6 ppm; IR (KBr) ν_{max} 3063, 2925, 1594, 1542, 1323, 1009, 753 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{14}H_{13}NNaO_2$ $[M+Na]^+$, 250.0838; found, 250.0842.

2,3-Dihydrophthalazine-1,4-dione (4b)

White solid (0.34 g, 95%), mp: >300 °C; ^{1}H NMR (400 MHz, DMSO-d^6) δ 8.18-7.97 (m, 2H), 7.85-7.72 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d^6) δ 156.5, 131.6, 128.6, 125.4 ppm; IR (KBr) ν_{max} 3080, 1713, 1584, 1368, 9401, 755 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_8H_6N_2NaO_2$ $[M+Na]^+$, 185.0321; found, 185.0319.

N^1-Cyclopentyl-N^2-phenylphthalamide (4c)

White solid (0.54 g, 79 %), mp: 204.1-206.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 7.78 (d, J = 6.8 Hz, 1H), 7.67 (d, J = 8.0 Hz, 2H), 7.49 (s, 3H), 7.35 (t, J = 7.4 Hz, 2H), 7.14 (t, J = 7.4 Hz, 1H), 6.42 (s, 1H), 4.31 (dd, J = 13.2, 6.8 Hz, 1H), 1.96-1.94 (m, 2H), 1.58-1.56 (m, 4H), 1.41-1.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 166.6, 138.1, 134.6, 130.6, 130.3, 129.4, 129.0, 127.9, 124.6, 120.1, 52.1, 33.0, 23.7 ppm; IR (KBr) ν_{max} 3067, 1743, 1589, 1546, 941, 755 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{19}H_{21}N_2O_2$ $[M+H]^+$, 309.1598; found, 309.1594.

3-Hydroxy-2-phenyl-3-(trifluoromethyl)isoindolin-1-one (4d)

White solid (0.58 g, 89 %), mp: 189.8-191.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.6 Hz, 1H), 7.63 (t, J = 7.4Hz, 1H), 7.46 (t, J = 7.4 Hz, 1H), 7.40-7.35 (m, 1H), 7.32 (t, J = 7.4 Hz, 2H), 7.20 (d, J = 7.2 Hz, 1H), 7.16 (d, J = 7.6 Hz, 2H), 5.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 140.4, 133.9, 133.2, 131.1, 131.0, 129.1, 128.6, 128.4, 124.0, 123.8, 121.2, 89.9, 89.4, 89.1, 88.6 ppm; IR (KBr) ν_{max} 3072, 1702, 1593, 1368, 1182, 953, 696 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{15}H_{11}F_3NO_2$ $[M+H]^+$, 294.0736; found, 294.0735.

2-(*tert*-Butyl)-5-(dimethylamino)isoindoline-1,3-dione (4e)

Fluorescence yellow solid (39 mg, 80 %), mp: 109.4-110.6 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 18.9 Hz, 1H), 6.79 (t, J = 9.3 Hz, 1H), 3.09 (s, 6H), 1.67 (s, 9H); ^{13}C NMR (100MHz, $CDCl_3$) δ 170.4, 170.2, 154.2, 134.7, 124.1, 118.5, 115.0, 104.9, 57.3, 40.6, 29.2 ppm; IR (KBr) ν_{max} 1700, 1320, 753 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{14}H_{18}N_2NaO_2$ $[M+Na]^+$, 269.1260; found, 269.1267.

2-Cyclopentyl-5-(dimethylamino)isoindoline-1,3-dione (4f)

Fluorescence yellow solid (33 mg, 65 %), mp: 87.1-88.1 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.4 Hz, 1H), 7.04 (s, 1H), 6.77 (d, J = 8.4 Hz, 1H), 4.62-4.52 (m, 1H), 3.10 (s, 6H), 2.08-2.05 (m, 2H), 1.97-1.86 (m, 4H), 1.62-1.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 169.0, 154.3, 134.8, 124.5, 118.0, 114.5, 105.5, 50.7, 40.5, 29.6, 25.0. IR (KBr) ν_{max} 1699, 1368, 1078, 750 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{15}H_{19}N_2O_2$ $[M+H]^+$, 259.1444; found, 259.1441.

5-Methyl-2-(3,4,5-trimethoxyphenyl)isoindoline-1,3-dione (I)

White solid (51 mg, 78 %), mp: 214.4-216.0 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.6 Hz, 1H), 7.74 (s, 1H), 7.58 (d, J = 7.6 Hz, 1H), 6.65 (s, 2H), 3.88 (d, J = 3.8 Hz, 9H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 167.5, 153.4, 145.9, 137.9, 135.0, 132.1, 129.1, 127.3, 124.2, 123.7, 104.5, 60.9, 56.2, 22.1 ppm. IR (KBr) ν_{max} 1704, 1598, 1131, 742 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{18}H_{17}NNaO_5$ $[M+Na]^+$, 350.0991; found, 350.0999.

2-(2,6-Diisopropylphenyl)isoindoline-1,3-dione (II)

White solid (28 mg, 45 %), mp: 169.8-172.4 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 4.6, 3.2 Hz, 2H), 7.81 (dd, J = 4.6, 3.2 Hz, 2H), 7.46 (t, J = 7.8 Hz, 1H), 7.29 (d, J = 7.8 Hz, 2H), 2.72-2.66 (m, 2H), 1.17 (d, J = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 147.3, 134.3, 132.0, 130.2, 126.9, 124.0, 123.9, 29.4, 24.0 ppm; IR (KBr) ν_{max} 1712, 1587, 1369, 756 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{20}H_{21}NNaO_2$ $[M+Na]^+$, 330.1464; found, 330.1469.

2-(2,2-Diethoxyethyl)isoindoline-1,3-dione (precursor of III)

Yellow oil (36 mg, 68 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 2.4 Hz, 2H), 7.72 (d, J = 2.5 Hz, 2H), 4.89 (t, J = 4.8 Hz, 1H), 3.83 (d, J = 5.2 Hz, 2H), 3.78-3.69 (m, 2H), 3.59-3.50 (m, 2H), 1.16 (t, J = 6.8 Hz, 6H);^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 134.0, 132.1, 123.3, 98.5, 61.8, 39.8, 15.2 ppm; IR (KBr) ν_{max} 1714, 1388, 1019, 716 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{14}H_{17}NNaO_4$ $[M+Na]^+$, 286.1050; found, 286.1051.

Methyl 2-(1,3-Dioxo-2-phenylisoindolin-4-yl)acetate (precursor of IV)

White solid (32 mg, 55 %), mp: 98.3-99.7 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 7.2 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.47-7.33 (m, 3H), 4.22 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.6, 167.0, 136.7, 134.3, 133.6, 132.4, 131.6, 129.1, 128.1, 126.6, 122.9, 52.3, 36.2 ppm; IR (KBr) ν_{max} 1714, 1585, 1377, 754 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{17}H_{13}NNaO_4$ $[M+Na]^+$, 318.0737; found, 318.0741.

***N*-(2-Butyl-1,3-dioxoisoindolin-5-yl)-4-methylbenzenesulfonamide (V)**

White solid (22 mg, 29 %), mp: 147.5-149.1 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.78(m, 4H), 7.37-7.33 (m, 4H), 3.68 (t, J = 7.2 Hz, 2H), 2.47 (s, 3H), 1.70-1.61 (m, 2H), 1.38 (dt, J = 15.0, 7.4 Hz, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 166.9, 145.7, 139.6, 137.3, 136.0, 133.2, 133.1, 129.9, 128.6, 126.3, 123.8, 38.1, 30.5, 21.7, 20.1, 13.6; IR (KBr) ν_{max} 1715, 1382, 1170, 932, 665, 551 cm^{-1}; MS (EI) m/z 91, 155, 174, 217, 329, 372.

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Supporting Information

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

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