Synthesis Z. Sun et al. Paper

Oxidative Desymmetrization of Isoindolines Realized by *tert*-Butyl Nitrite (TBN) Initiated Radical sp^3 C–H Activation Relay (CHAR)

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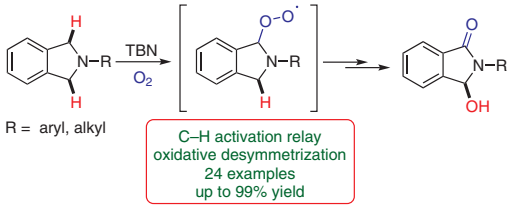

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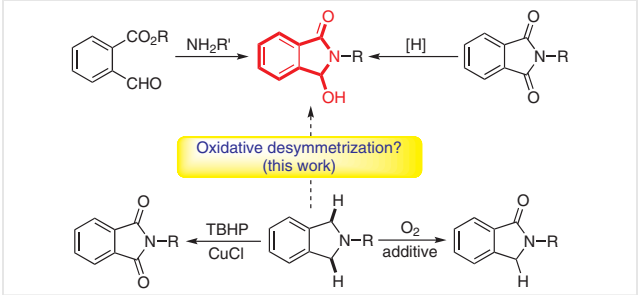
Abstract An oxidative desymmetrization of isoindolines was realized by TBN initiated radical sp^3 C–H activation relay (CHAR), providing a series of ω-hydroxylactams in high yields. This reaction exhibits broad substrate scope and functional group tolerance, and even *N*-alkyl isoindolines can be well tolerated. The mechanistic study shows that the C–H bond oxidation, dioxygen trapping and intramolecular 1,5-H shift might be the key steps to achieve the oxidative desymmetrization.

Key words radicals, C–H bond activation, oxidative desymmetrization, *tert*-butyl nitrite, isoindolines

Cyclic lactams and imides exist widely in pharmaceuticals, agrochemicals and other medicinally important compounds with diverse biological activities.[1,2] For example, indoprofen, which bears an isoindolinone skeleton, exhibits broad physiological activities and can be used for the treatment of rheumatoid arthritis, osteoarthritis, spondylosis and other conditions.[3] As lactam derivatives, ω-hydroxylactams are also important and versatile building blocks in natural products and pharmaceuticals.[4] In organic synthesis, they can be employed as precursors of *N*-acyliminium ions, which are involved in the construction of various nitrogen-containing heterocycles and alkaloids.[4,5]

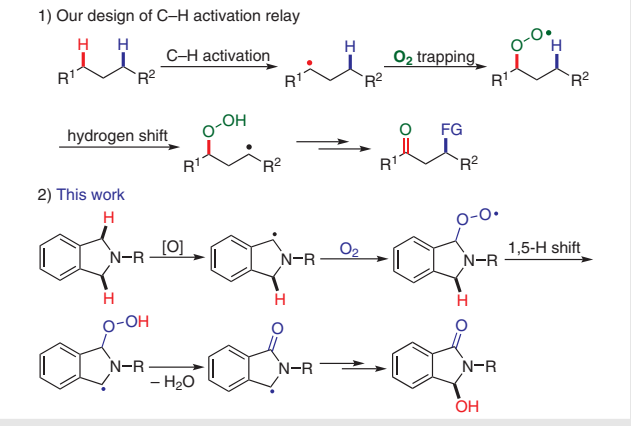
Due to the continuing interest in this class of heterocycles, various synthetic procedures for the construction of ω-hydroxylactams have been established (Scheme 1).[6] The ω-hydroxylactam skeleton can be directly constructed through the condensation of alkyl 2-formylbenzoates and amines; however, pre-functionalized starting materials are needed, which restricts their diverse synthesis.[6a] Although reductive desymmetrization of phthalimides, using over-stoichiometric amount of Zn or Sn under acidic conditions or organometallic hydrides, is an efficient strategy to construct the ω-hydroxylactam structure, some drawbacks still exist, such as unsatisfactory functional group tolerance, the generation of overreduction products, and large amount of waste.[6b–f] With the development of the direct functionalization of C–H bonds,[7,8] we wondered whether ω-hydroxylactams could be obtained by the strategy of oxidative desymmetrization, using those unfunctionalized substrates, isoindolines, and thus avoiding the tedious synthesis of the starting materials. However, some challenges still exist and need to be overcome. In the presence of weak oxidizer, only one side of the α-C–H bonds adjacent to the nitrogen atom can be oxidized, providing isoindolinone derivatives in high yields.[9a–d] When over-stoichiometric amount of TBHP were employed as the oxidizer, isoindolines were smoothly oxidized to phthalimides and no ω-hydroxylactams were provided.[9e] Therefore, appropriate oxidizer and the corresponding reaction conditions are crucial to achieve the synthesis of ω-hydroxylactams through the oxidative desymmetrization of isoindolines.



Scheme 1 Synthetic strategies to access ω-hydroxylactams

Recently, our research interests focused on aerobic oxidation of sp^3 C–H bonds, and, in this research, the C–H bonds adjacent to nitrogen were found to be extremely active and could be easily oxidized to the corresponding radi-

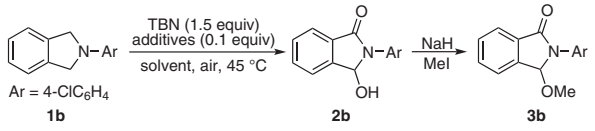
cal species. Therefore, we proposed that if the active C–H bond was initially oxidized to a free radical, under aerobic conditions, the generated radical might be captured by dioxygen, giving a peroxide radical. After a subsequent intramolecular hydrogen shift, another C–H bond would be activated and further functionalized. We believe that this strategy, named C–H activation relay (CHAR), might be a new way to realize C–H bond activation and 1,3-difunctionalization (Scheme 2, eq. 1). In 2016, we reported an interesting synthesis of isatins through the aerobic oxidation of glycine esters using this strategy.[10] So we questioned whether CHAR could also be used to achieve the oxidative desymmetrization of isoindolines (Scheme 2, eq. 2). According to our design, when the C–H bond adjacent to nitrogen atom is oxidized to a radical intermediate under aerobic atmosphere, dioxygen trapping will generate a peroxide radical. Fast intramolecular 1,5-H shift would then occur smoothly, giving a new radical intermediate. After elimination of water and further single-electron transfer, the desired ω-hydroxylactam structure might be constructed. Herein, we reported an oxidative desymmetrization of isoindolines initiated by TBN via the process of C–H activation relay (CHAR).



Scheme 2 Our design of C–H activation relay

With our design in mind, the substrate isoindoline derivative **1b** was chosen as a model compound to test the strategy of oxidative desymmetrization. Considering the reaction diversity and high activity in the activation of inert chemical bonds, TBN was employed as the initiator under air atmosphere (Table 1).[11,12] To our delight, in the presence of 1.5 equivalent of TBN at 45 °C, the desired ω-hydroxylactams **2b** was obtained in 47% yield (entry 1). When 5 equivalents of water was added into the reaction solution, the yield was increased to 54% (entry 2). Increasing the amount of water to 10 and 15 equivalents resulted in slightly higher yields of the ω-hydroxylactam **2b** (entries 3 and 4). Under O_2 atmosphere, the yield of the desired product was reduced to 38%, which might be due to overoxidation (entry 5). To improve the reaction efficiency, the model reaction was performed in the presence of a catalytic amount of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO); however, similar a result was obtained (entry 6). Since a small amount of the nitrated product on the phenyl ring was detected, one equivalent of *p*-nitrobenzoic acid (*p*-NBA) was added to inhibit the TBN initiated nitration (entry 7).[12c] To our disappointment, the reaction outcome remained unsatisfactory. Several solvents were then screened, and the results shown that 1,4-dioxane remained the best choice (entries 8 and 9). The results also showed that increasing of the amount of TBN or elevating the reaction temperature also do not improve the reaction efficiency (entries 10 and 11). Since the reaction is rather clean and the formation of byproducts is almost undetectable by TLC, the lower isolated yield was attributed to the absorption of acidic silica gel column, a conclusion that was supported by the ^{1}H NMR yield of the crude reaction mixture (entry 4). To avoid the silica gel column absorption, the acidic hydroxyl group was etherified with NaH and MeI, and the desired ω-methoxylactam **3b** was smoothly obtained in 73% isolated yield (entry 12). In the presence of MeOH instead of water, the ω-

Table 1 Optimization of the Reaction Conditions

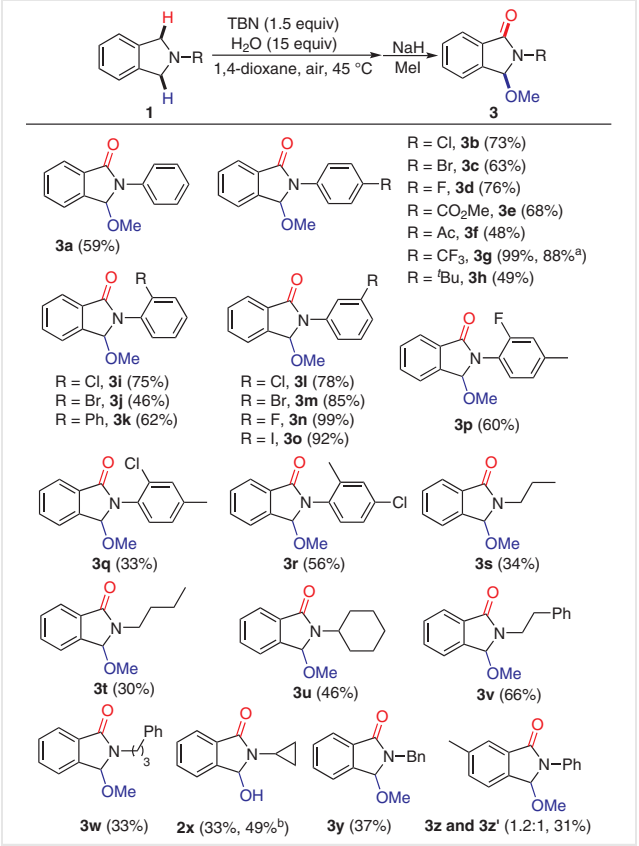


Entry	Additive (mol%)	Solvent	H_2O (mol%)	Yield (%)[a]
1	none	1,4-dioxane	–	47
2	none	1,4-dioxane	5	54
3	none	1,4-dioxane	10	52
4	none	1,4-dioxane	15	57 (84)[h]
5	none	1,4-dioxane	15	38[b]
6	TEMPO (10)[c]	1,4-dioxane	15	56
7	*p*-NBA (10)[d]	1,4-dioxane	15	55
8	none	THF	15	34
9	none	MeCN	15	17
10	none	1,4-dioxane	15	50[e]
11	none	1,4-dioxane	15	52[f]
12	none	1,4-dioxane	15	73[g]
13	none	1,4-dioxane	15	54[g,i]

[a] Isolated yield of **2b**.
[b] Under O_2 atmosphere.
[c] TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy.
[d] *p*-NBA = *p*-nitrobenzoic acid.
[e] Two equivalents of TBN were added.
[f] At 60 °C.
[g] Isolated yield of **3b** after methylation.
[h] The yield in parentheses is crude ^{1}H NMR yield, using 1,3,5-trimethoxylbenzene as the internal standard.
[i] In the presence of 15 mol% MeOH instead of H_2O.

methoxylactam **3b** was isolated in 54% yield, suggesting that the presence of water is beneficial to enhance the reaction efficiency (entry 13).

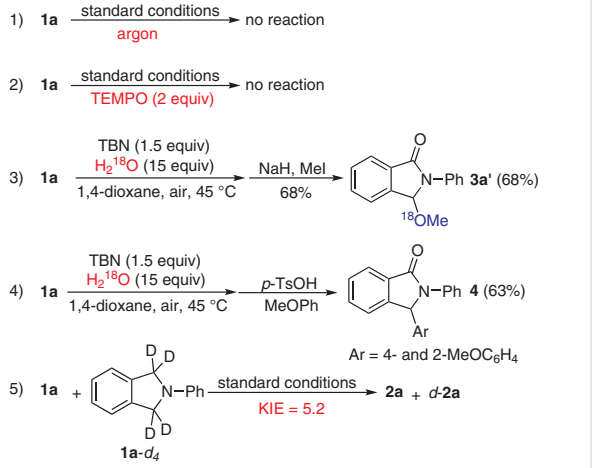
With the best reaction conditions established, the reaction scope and limitations were then evaluated. Overall, N-substituted isoindolines **1a–x** gave the corresponding ω-methoxylactams in good to excellent yields (Scheme 3). Initially, various *para*-groups on the *N*-phenyl ring were tested. Halogen groups including Cl, Br, and F, gave the corresponding products **3b–d** in higher yields than the *N*-phenyl product (**3a**). The presence of ester and acyl functional groups, which could be used in further transformations, did not affect the reaction efficiency, providing the desired product **3e** and **3f** in 68% and 48% yields, respectively. The strong electron-withdrawing group CF_3 enhanced this C–H bond oxidation, and the corresponding ω-methoxylactam **3g** was isolated in nearly quantitative yield. When this reaction was scaled up to 10 mmol, the desired product was isolated in 88% yield. In contrast, electron-donating substituent *tert*-butyl reduced the yield to 49% (**3h**). This is probably because when the *N*-aryl group is electron-rich, the desired C–H bond oxidation will be disturbed by TBN initiated direct nitration on the *N*-phenyl ring. When *ortho*-substituted substrates were tested, moderate to good yields were obtained (**3i–j**), and even biphenyl-2-amine derived isoindoline was smoothly tolerated, giving the expected product **3k** in 62% yield. When the halogen atoms were connected on the *meta*-position, the reaction occurred smoothly, giving the desired products **3l–o** in 78–99% yields. It is worth noting that the iodo-substituted substrates are not well tolerated in transition-metal initiated C–H bond activation, but reacted under the developed conditions to give the product **3o**, which could be further functionalized to construct more complex molecules. The reaction of various 2,4-disubstituted isoindolines were also performed under the standard reaction conditions, and slightly diminished reaction yields were observed (**3p–r**; 33–60%), which might be due to the steric hindrance of the *ortho*-groups. Since the *N*-aryl groups could dramatically stabilize the generated radical intermediate, in most cases, the presence of these groups is crucial to accomplish an efficient C–H bond activation. Therefore, *N*-alkyl isoindolines were investigated under the optimized reaction conditions, and, to our delight, not only linear but also bulky alkyl groups were well tolerated in this oxidative desymmetrization, giving the desired ω-methoxylactams **3s–w** in moderate yields (33–66%).[13] For *N*-cyclopropylisoindoline **1x**, the O-methylation step led to fragmentation of the cyclopropyl ring, therefore, the expected product **2x** was isolated in only 33% yield (49% crude ^{1}H NMR yield), probably due to the silica gel column absorption. When *N*-benzylisoindoline **1y** was employed, a competitive 1,5-H shift on the benzyl position disturbed the desired reaction process, and only 37% yield of **3y** was obtained.[14] This result also supported the conclusion that the C–H oxidation was mediated by a 1,5-H shift process. When methyl group was connected on the phenyl ring of isoindoline, a mixture of two regioisomers **3z** and **3z′** was obtained in 31% yield, and oxidation on the methyl group was observed, reducing the reaction outcome.



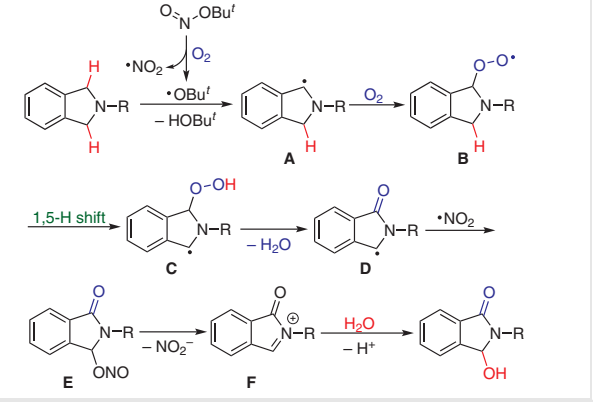
Scheme 3 Substrate scope. [a] 10 mmol scale. [b] Crude yield based on ^{1}H NMR analysis.

To gain mechanistic insight into this transformation a series of control experiments were performed (Scheme 4). In the absence of dioxygen, the C–H bond oxidation was totally inhibited, and the starting material **1a** was fully recovered (eq. 1). This result suggested that the presence of dioxygen is crucial to initiate the sp^3 C–H activation. Then, 2 equivalents of TEMPO was added as a radical inhibitor, and no reaction occurred, which supported the conclusion that this reaction is mediated by a radical intermediate (eq. 2). To reveal the origin of the oxygen atom, the standard reaction was conducted in the presence of $H_2{}^{18}O$, and, after methylation, **3a′** was isolated in 68% yield, in which only one ^{18}O atom was incorporated into the desired product (eq. 3). Since two oxygen atoms were incorporated in the target ω-methoxylactam, Brönsted acid catalyzed Friedel–Crafts reaction was performed after the C–H bond oxidation, using anisole as a nucleophile (eq. 4). The Friedel–Crafts product **4** was isolated in 63% yield as a mixture of regioisomers, in which no ^{18}O atom was incorporated. These results con-

firmed that the oxygen atom in the methoxyl group comes from water via hydrolysis of the acyliminium ion. On the other hand, the oxygen atom in the carbonyl group originates from dioxygen, implying the existence of a peroxide intermediate (**B**, Scheme 4). Next, the reaction of the 1:1 mixture of the **1a** and **1a**-d_4 was performed under the optimized conditions (eq. 5); the KIE value of 5.2 supported the conclusion that cleavage of the C–H bond adjacent to nitrogen atom might be involved in the rate-determining step.



Scheme 4 Control experiments



Scheme 5 Proposed mechanism

Based on the control experiments and on previous precedent of TBN initiated reactions,[12] a possible mechanism was proposed to rationalize the product formation (Scheme 5). In the presence of dioxygen, a *tert*-butoxyl radical is generated by β-fragmentation of TBN, followed by intermolecular H-abstraction, generating radical intermediate **A**. This radical is then captured by dioxygen, affording a peroxide radical **B**. Next, the other C–H bond adjacent to nitrogen atom is further activated by the intramolecular 1,5-H shift, giving radical **C**. After water elimination, radical **D** might be trapped by the persistent nitro radical, giving intermediate **E**. Finally, the nitrite anion is excluded, forming an iminium ion **F**, which is subsequently trapped by water to provide the desired product.

In summary, we have developed an efficient oxidative desymmetrization of isoindolines to ω-hydroxylactams. This transformation features a TBN initiated sp^3 C–H bond functionalization under aerobic conditions, in which the C–H activation relay (CHAR) is the key step to accomplish the desymmetric oxidation. It is worth noting that this method provides a direct way to construct the pharmaceutically and synthetically important ω-hydroxylactam skeleton from unfunctionalized starting materials. The transition-metal free and mild reaction conditions as well as good functional group tolerance also highlight its potential applications in the synthesis of heterocyclic compounds. Further applications of this reaction and mechanistic studies are under way in our laboratory.

TBN were purchased from commercial sources and used without further purification. Flash chromatography was carried out with silica gel (200–300 mesh). Analytical TLC was performed with silica gel GF254 plates, and the products were visualized by UV detection. ^{1}H and ^{13}C NMR (400 MHz, 600MHz and 100 MHz, 150MHz respectively) spectra were recorded in $CDCl_3$. Chemical shifts (δ) are reported in ppm using TMS as internal standard, and spin-spin coupling constants (*J*) are given in Hz. High-resolution mass spectra (HRMS) were measured with an electrospray ionization (ESI) apparatus using time of flight (TOF) mass spectrometry.

Substrate Preparation

A solution of 1,2-bis(bromomethyl)benzene (10 mmol) and anilines (12 mmol) in toluene (10 mL) was mixed fully, then *N*,*N*-diisopropylethanamine (24 mmol) was added dropwise under argon atmosphere. The reaction solution was stirred under 110 °C. After completion (reaction monitored by TLC with UV visualization), the solvent was removed under reduced pressure. The products were separated by silica gel column chromatography eluted with petroleum ether/acetone (v/v 20:1) to afford the products.

TBN Initiated Oxidative Desymmetrization of Isoindolines; General Procedure 1

A solution of **1** (0.5 mmol) and H_2O (7.5 mmol) in 1,4-dioxane (5 mL) was mixed fully, then TBN (0.75 mmol) was added dropwise under air atmosphere. The reaction solution was stirred at 45 °C. After completion (reaction monitored by TLC with UV visualization), the solvent was removed under reduced pressure. The reaction mixture was used in the methylation step without further purification.

Methylation of the Product 2; General Procedure 2

The reaction mixture was dissolved in anhydrous THF (5 mL), then MeI (1.5 mmol) and NaH (1.5 mmol) were added dropwise, sequentially. The reaction solution was stirred at 45 °C. After completion (reaction monitored by TLC with UV visualization), the solvent was removed under reduced pressure. The products were separated by silica gel column chromatography eluted with petroleum ether/acetone (v/v 10:1) to afford the products.

Oxidative Desymmetrization of Isoindolines in the Presence of $H_2{}^{18}O$

Following General Procedures 1 and 2 in the presence of $H_2{}^{18}O$ (15 equiv), the corresponding product **3a′** was isolated in 68% yield.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{13}NO^{18}O + Na^+$: 264.0881; found: 264.0880.

Performed by following General Procedure 1 in the presence of $H_2{}^{18}O$ (15 equiv). The solvent was removed under reduced pressure, then anisole (15 equiv) and *p*-TsOH (0.2 mmol) were added and the reaction mixture was stirred at 80 °C for 12 hours. After completion (reaction monitored by TLC with UV visualization), the solvent was removed under reduced pressure. The product **4** was separated by silica gel column chromatography eluted with petroleum ether/acetone (v/v 10:1).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{17}NO_2 + H^+$: 316.1332; found: 316.1345.

3-Methoxy-2-phenylisoindolin-1-one (3a)

Compound **3a** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 59% (71 mg); red oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 7.4 Hz, 1 H), 7.81 (d, *J* = 8.1 Hz, 2 H), 7.71–7.63 (m, 1 H), 7.61–7.55 (m, 2 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 7.22 (t, *J* = 7.5 Hz, 1 H), 6.46 (s, 1 H), 2.90 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.7, 139.7, 137.3, 132.9, 132.8, 130.3, 129.1, 125.3, 123.9, 123.4, 121.7, 87.2, 49.1.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{13}NO_2 + Na^+$: 262.0844; found: 262.0832.

2-(4-Chlorophenyl)-3-methoxyisoindolin-1-one (3b)

Compound **3b** purified by TLC (petroleum ether/acetone, 10:1).

Yield: 73% (100 mg); yellow solid; mp 160–162 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.2 Hz, 1 H), 7.80 (d, *J* = 8.5 Hz, 2 H), 7.64 (d, *J* = 7.2 Hz, 1 H), 7.58 (d, *J* = 7.7 Hz, 2 H), 7.41–7.33 (m, 2 H), 6.41 (s, 1 H), 2.87 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.6, 139.5, 136.0, 133.0, 132.6, 130.4, 130.3, 129.1, 123.9, 123.4, 122.4, 87.1, 49.0.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}ClNO_2 + Na^+$: 296.0454; found: 296.0449.

2-(4-Bromophenyl)-3-methoxyisoindolin-1-one (3c)

Compound **3c** purified by TLC (petroleum ether/acetone, 10:1).

Yield: 63% (100 mg); red solid; mp 158–160 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.4 Hz, 1 H), 7.76 (d, *J* = 8.9 Hz, 2 H), 7.69–7.62 (m, 1 H), 7.60–7.55 (m, 2 H), 7.52 (d, *J* = 9.0 Hz, 2 H), 6.42 (s, 1 H), 2.87 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.6, 139.4, 136.5, 133.0, 132.6, 132.1, 130.4, 124.0, 123.4, 122.7, 120.7, 118.1, 87.1, 49.0.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}BrNO_2 + Na^+$: 339.9949; found: 339.9938.

2-(4-Fluorophenyl)-3-methoxyisoindolin-1-one (3d)

Compound **3d** purified by TLC (petroleum ether/acetone, 15:1).

Yield: 76% (98 mg); red solid; mp 123–125 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.4 Hz, 1 H), 7.79–7.74 (m, 2 H), 7.68–7.63 (m, 1 H), 7.62–7.54 (m, 2 H), 7.11 (t, *J* = 8.7 Hz, 2 H), 6.39 (s, 1 H), 2.90 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.7, 160.1 (d, J_{CF} = 245.3 Hz), 139.6, 133.3 (d, *J* = 2.0 Hz), 132.9, 132.7, 130.4, 124.0, 123.6 (d, J_{CF} = 8.0 Hz), 123.4, 115.9 (d, J_{CF} = 22.4 Hz), 87.5, 49.2.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}FNO_2 + Na^+$: 280.0750; found: 280.0740.

Methyl 4-(1-Methoxy-3-oxoisoindolin-2-yl)benzoate (3e)

Compound **3e** purified by TLC (petroleum ether/acetone, 15:1).

Yield: 68% (101 mg); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.8 Hz, 2 H), 7.99 (d, *J* = 8.9 Hz, 2 H), 7.89 (d, *J* = 7.5 Hz, 1 H), 7.66 (t, *J* = 7.4 Hz, 1 H), 7.61–7.52 (m, 2 H), 6.50 (s, 1 H), 3.89 (s, 3 H), 2.85 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.8, 166.6, 141.6, 139.4, 133.2, 132.5, 130.6, 130.5, 126.0, 124.1, 123.5, 119.8, 86.8, 52.0, 48.9.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{15}NO_4 + Na^+$: 320.0899; found: 320.0898.

2-(4-Acetylphenyl)-3-methoxyisoindolin-1-one (3f)

Compound **3f** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 48% (68 mg); yellow solid; mp 99–100 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06–7.95 (m, 4 H), 7.89 (d, *J* = 7.5 Hz, 1 H), 7.67 (t, *J* = 7.4 Hz, 1 H), 7.63–7.53 (m, 2 H), 6.51 (s, 1 H), 2.85 (s, 3 H), 2.58 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.0, 166.8, 141.7, 139.4, 133.3, 133.1, 132.4, 130.6, 129.5, 124.1, 123.6, 119.8, 86.7, 48.8, 26.4.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{15}NO_3 + Na^+$: 304.0950; found: 304.0945.

3-Methoxy-2-(4-(trifluoromethyl)phenyl)isoindolin-1-one (3g)

Compound **3g** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 99% (152 mg); yellow solid; mp 56–59 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.5 Hz, 2 H), 7.89 (d, *J* = 7.5 Hz, 1 H), 7.71–7.64 (m, 3 H), 7.62–7.57 (m, 2 H), 6.50 (s, 1 H), 2.87 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.8, 140.6, 139.4, 133.3, 132.4, 130.5, 126.5 (d, J_{CF} = 32.5 Hz), 126.2 (q, J_{CF} = 3.8 Hz), 124.1 (d, J_{CF} = 271.8 Hz), 124.1, 123.5, 120.3, 86.9, 48.9.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{12}F_3NO_2 + Na^+$: 330.0718; found: 330.0706.

2-(4-(*tert*-Butyl)phenyl)-3-methoxyisoindolin-1-one (3h)

Compound **3h** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 49% (72 mg); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 7.4 Hz, 1 H), 7.70 (d, *J* = 8.6 Hz, 2 H), 7.65–7.54 (m, 3 H), 7.45 (d, *J* = 8.7 Hz, 2 H), 6.43 (s, 1 H), 2.91 (s, 3 H), 1.33 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.7, 148.3, 139.7, 134.5, 133.0, 132.6, 130.3, 125.9, 123.8, 123.4, 121.5, 87.3, 49.1, 34.4, 31.3.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{21}NO_2 + Na^+$: 318.1470; found: 318.1470.

2-(2-Chlorophenyl)-3-methoxyisoindolin-1-one (3i)

Compound **3i** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 75% (102 mg); yellow solid; mp 89–90 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.4 Hz, 1 H), 7.66 (dd, *J* = 7.2, 1.0 Hz, 1 H), 7.62–7.56 (m, 2 H), 7.52–7.54 (m, 1 H), 7.43–7.32 (m, 3 H), 6.35 (s, 1 H), 3.11 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.9, 140.8, 133.9, 132.9, 132.7, 132.1, 130.6, 130.2, 129.5, 127.7, 124.3, 123.8, 88.6, 51.3.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}ClNO_2$ + Na^+: 296.0454; found: 296.0445.

2-(2-Bromophenyl)-3-methoxyisoindolin-1-one (3j)

Compound **3j** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 46% (73 mg); red solid; mp 105–107 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.95 (s, 1 H), 7.76–7.64 (m, 2 H), 7.60 (d, *J* = 6.1 Hz, 2 H), 7.49–7.36 (m, 2 H), 7.29 (s, 1 H), 6.35 (s, 1 H), 3.14 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.0, 140.8, 135.6, 133.8, 132.8, 132.1, 130.2, 129.9, 128.4, 124.4, 123.8, 123.1, 88.8, 51.7.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}BrNO_2$ + Na^+: 339.9949; found: 339.9954.

2-(Biphenyl-2-yl)-3-methoxyisoindolin-1-one (3k)

Compound **3k** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 62% (98 mg); yellow solid; mp 101–103 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.89 (m, 1 H), 7.56–7.49 (m, 2 H), 7.46 (m, 4 H), 7.37–7.33 (m, 3 H), 7.33–7.21 (m, 3 H), 5.35 (s, 1 H), 2.85 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.1, 140.7, 139.2, 132.3, 132.2, 131.1, 129.9, 129.8, 128.6, 128.5, 128.4 (two ^{13}C), 127.5, 124.0, 123.5, 51.3.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{17}NO_2$ + Na^+: 338.1157; found: 338.1164.

2-(3-Chlorophenyl)-3-methoxyisoindolin-1-one (3l)

Compound **3l** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 78% (106 mg); yellow solid; mp 137–139 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (s, 1 H), 7.89 (d, *J* = 7.3 Hz, 1 H), 7.76 (d, *J* = 8.2 Hz, 1 H), 7.71–7.64 (m, 1 H), 7.62–7.55 (m, 2 H), 7.34 (t, *J* = 8.1 Hz, 1 H), 7.17 (d, *J* = 8.0 Hz, 1 H), 6.43 (s, 1 H), 2.88 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.6, 139.4, 138.6, 134.7, 133.1, 132.5, 130.5, 130.0, 125.1, 124.0, 123.5, 121.2, 119.0, 87.1, 49.0.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}ClNO_2$ + Na^+: 296.0454; found: 296.0449.

2-(3-Bromophenyl)-3-methoxyisoindolin-1-one (3m)

Compound **3m** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 85% (135 mg); brown solid; mp 67–70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 7.89 (d, *J* = 7.4 Hz, 1 H), 7.80 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.64 (d, *J* = 7.2 Hz, 1 H), 7.61–7.53 (m, 2 H), 7.33–7.25 (m, 2 H), 6.42 (s, 1 H), 2.87 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.6, 139.5, 138.7, 133.1, 132.5, 130.4, 130.3, 128.0, 124.0 (two ^{13}C), 123.5, 122.7, 119.5, 87.1, 49.0.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}BrNO_2$ + Na^+: 339.9949; found: 339.9940.

2-(3-Fluorophenyl)-3-methoxyisoindolin-1-one (3n)

Compound **3n** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 99% (127 mg); red solid; mp 70–73 °C.

^{1}H NMR (400 MHz,$CDCl_3$): δ = 7.90 (d, *J* = 7.5 Hz, 1 H), 7.74 (dt, *J* = 11.3, 2.3 Hz, 1 H), 7.68–7.63 (m, 2 H), 7.58 (ddd, *J* = 8.4, 7.1, 1.9 Hz, 2 H), 7.36 (td, *J* = 8.3, 6.7 Hz, 1 H), 6.90 (tdd, *J* = 8.3, 2.5, 0.8 Hz, 1 H), 6.43 (s, 1 H), 2.88 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.7, 162.9 (d, J_{CF} = 244.6 Hz), 139.4, 139.0 (d, J_{CF} = 10.5 Hz), 133.1, 132.5, 130.4, 130.1 (d, J_{CF} = 9.3 Hz), 124.0, 123.4, 116.2 (d, J_{CF} = 3.0 Hz), 111.7 (d, J_{CF} = 21.2 Hz), 108.4 (d, J_{CF} = 26.2 Hz), 87.1 (d, J_{CF} = 3.0 Hz), 48.9.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}FNO_2$ + Na^+: 280.0750; found: 280.0738.

2-(3-Iodophenyl)-3-methoxyisoindolin-1-one (3o)

Compound **3o** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 92% (168 mg); red solid; mp 166–168 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (s, 1 H), 7.94–7.86 (m, 1 H), 7.87–7.78 (m, 1 H), 7.66 (ddd, *J* = 7.6, 2.8, 1.4 Hz, 1 H), 7.62–7.50 (m, 3 H), 7.13 (td, *J* = 8.1, 2.4 Hz, 1 H), 6.42 (s, 1 H), 2.89 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.5, 139.5, 138.6, 134.0, 133.1, 132.5, 130.5, 130.4, 129.8, 124.0, 123.5, 120.3, 94.3, 87.0, 49.1.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}INO_2$ + Na^+: 387.9810; found: 387.9804.

2-(2-Fluoro-4-methylphenyl)-3-methoxyisoindolin-1-one (3p)

Compound **3p** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 60% (81 mg); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 7.4 Hz, 1 H), 7.70–7.62 (m, 1 H), 7.61–7.54 (m, 2 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.09–6.99 (m, 2 H), 6.37 (s, 1 H), 3.00 (s, 3 H), 2.38 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.7, 157.5 (d, J_{CF} = 249.9 Hz), 140.7, 139.7, 139.8, 132.6, 132.3, 130.1, 128.5 (d, J_{CF} = 2.1 Hz), 125.3 (d, J_{CF} = 3.1 Hz), 124.1, 123.6, 117.2 (d, J_{CF} = 19.9 Hz), 88.3, 50.3, 21.1.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{14}FNO_2$ + Na^+: 294.0906; found: 294.0909.

2-(2-Chloro-4-methylphenyl)-3-methoxyisoindolin-1-one (3q)

Compound **3q** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 33% (47 mg); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 7.4 Hz, 1 H), 7.69–7.62 (m, 1 H), 7.55–7.60 (m, 2 H), 7.35 (d, *J* = 1.0 Hz, 1 H), 7.27 (d, *J* = 8.0 Hz, 1 H), 7.17 (dd, *J* = 8.0, 1.3 Hz, 1 H), 6.31 (s, 1 H), 3.11 (s, 3 H), 2.38 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.1, 140.8, 140.0, 132.6, 132.4, 132.2, 131.0, 130.8, 130.1, 128.5, 124.3, 124.0, 123.7, 88.6, 51.3, 21.0.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{14}ClNO_2$ + Na^+: 310.0611; found: 310.0614.

2-(4-Chloro-2-methylphenyl)-3-methoxyisoindolin-1-one (3r)

Compound **3r** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 56% (80 mg); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.92 (m, 1 H), 7.69–7.63 (m, 1 H), 7.61–7.56 (m, 2 H), 7.33 (d, *J* = 2.4 Hz, 1 H), 7.28–7.24 (m, 1 H), 7.18 (d, *J* = 8.4 Hz, 1 H), 6.10 (s, 1 H), 3.13 (s, 3 H), 2.25 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.7, 141.0, 138.6, 133.8, 132.6, 132.0, 131.2, 130.2, 129.1, 127.0, 126.9, 124.2, 123.6, 89.6, 18.3.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{14}ClNO_2$ + Na^+: 310.0611; found: 310.0608.

2-Methoxy-2-propylisoindolin-1-one (3s)

Compound **3s** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 34% (35 mg); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.1 Hz, 1 H), 7.58–7.52 (m, 1 H), 7.52–7.46 (m, 2 H), 5.86 (s, 1 H), 3.76–3.68 (m, 1 H), 3.21–3.14 (m, 1 H), 2.85 (s, 3 H), 1.78–1.53 (m, 2 H), 0.94 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.7, 140.3, 133.2, 131.8, 129.9, 123.4, 123.3, 86.2, 49.0, 41.1, 21.4, 11.4.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{15}NO_2$ + Na^+: 228.1001; found: 228.0996.

2-Butyl-3-methoxyisoindolin-1-one (3t)

Compound **3t** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 30% (33 mg); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.1 Hz, 1 H), 7.58–7.53 (m, 1 H), 7.52–7.46 (m, 2 H), 5.86 (s, 1 H), 3.84–3.71 (m, 1 H), 3.23–3.16 (m, 1 H), 2.85 (s, 3 H), 1.67–1.59 (m, 2 H), 1.41–1.30 (m, 2 H), 0.93 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.6, 140.3, 133.2, 131.8, 129.9, 123.4, 123.3, 86.2, 49.0, 39.2, 30.2, 20.2, 13.7.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{17}NO_2$ + Na^+: 242.1157; found: 242.1151.

2-Cyclohexyl-3-methoxyisoindolin-1-one (3u)

Compound **3u** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 46% (46 mg); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.3 Hz, 1 H), 7.58–7.52 (m, 1 H), 7.48 (t, *J* = 7.4 Hz, 2 H), 6.00 (s, 1 H), 4.06–3.95 (m, 1 H), 2.87 (s, 3 H), 2.03–1.64 (m, 8 H), 1.47–1.33 (m, 2 H), 1.31–1.13 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.6, 140.4, 133.2, 131.8, 129.7, 123.3, 123.1, 85.7, 51.9, 48.8, 31.2, 30.4, 26.0, 25.9, 25.4.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{19}NO_2$ + Na^+: 268.1314; found: 268.1311.

3-Methoxy-2-phenethylisoindolin-1-one (3v)

Compound **3v** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 66% (88 mg); yellow solid; mp 89–92 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.3 Hz, 1 H), 7.59–7.43 (m, 3 H), 7.31–7.15 (m, 5 H), 5.62 (s, 1 H), 4.10–3.97 (m, 1 H), 3.57–3.40 (m, 1 H), 3.04–2.95 (m, 2 H), 2.83 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.7, 140.3, 138.7, 133.0, 132.0, 129.9, 128.7, 128.6, 126.5, 123.4 (two ^{13}C), 86.6, 49.2, 41.0, 34.4.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{17}NO_2$ + Na^+: 290.1157; found: 290.1164.

3-Methoxy-2-(3-phenylpropyl)isoindolin-1-one (3w)

Compound **3w** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 33% (46 mg); yellow solid; mp 95–98 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.81 (m, 1 H), 7.59–7.49 (m, 3 H), 7.27–7.13 (m, 5 H), 5.85 (s, 1 H), 3.79–3.86 (m, 1 H), 3.35–3.26 (m, 1 H), 2.86 (s, 3 H), 2.74–2.65 (m, 2 H), 2.05–1.96 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.7, 141.3, 140.3, 133.1, 131.9, 129.9, 128.4, 128.3, 125.9, 123.4, 123.4, 86.3, 49.2, 39.4, 33.4, 29.7.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}NO_2$ + Na^+: 304.1314; found: 304.1326.

2-Cyclopropyl-3-hydroxyisoindolin-1-one (2x)

Compound **2x** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 33% (31 mg); yellow solid; mp 158–161 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.48 (m, 3 H), 7.36 (t, *J* = 6.8 Hz, 1 H), 5.65 (s, 1 H), 2.81–2.63 (m, 1 H), 1.05–1.04 (m, 1 H), 0.96–0.68 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.6, 143.6, 132.2, 131.6, 129.7, 123.1, 123.1, 83.1, 23.1, 5.6, 4.9.

HRMS (ESI): *m*/*z* calcd for $C_{11}H_{11}NO_2$ + Na^+: 212.0688; found: 212.0683.

2-Benzyl-3-methoxyisoindolin-1-one (3y)

Compound **3y** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 37% (47 mg); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 6.8 Hz, 1 H), 7.60–7.50 (m, 2 H), 7.50–7.44 (m, 1 H), 7.39–7.33 (m, 2 H), 7.33–7.28 (m, 2 H), 7.28–7.22 (m, 1 H), 5.70 (s, 1 H), 5.17 (d, *J* = 14.7 Hz, 1 H), 4.20 (d, *J* = 14.7 Hz, 1 H), 2.87 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.7, 143.9, 136.5, 132.5, 131.0, 129.8, 128.7, 128.4, 127.7, 123.5, 123.4, 81.1, 42.7.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{15}NO_2$ + Na^+: 276.0995; found: 276.0998.

3-Methoxy-5-methyl-2-phenylisoindolin-1-one and 3-Methoxy-6-methyl-2-phenylisoindolin-1-one and (3z and 3z′)

The mixture of compounds **3z** and **3z′** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 31% (39 mg); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.59 (m, 4.3 H), 7.50 (d, *J* = 7.6 Hz, 1.2 H), 7.45 (d, *J* = 7.7 Hz, 1 H), 7.42 (s, 1 H), 7.38–7.26 (m, 7.2 H), 7.17–7.12 (m, 3.4 H), 6.27 (s, 1 H), 6.24 (s, 1.2 H), 2.44 (s, 3 H), 2.28 (s, 3.9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.89, 166.76, 143.75, 143.17, 140.39, 140.16, 137.24, 133.69, 131.32, 130.91, 128.86, 128.83, 128.62, 124.95, 123.96, 123.64, 123.55, 122.92, 121.44, 121.32, 82.88, 82.77, 21.96, 21.37.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{15}NO_2$ + Na^+: 276.0995; found: 276.1002.

3-(2-Methoxyphenyl)-2-phenylisoindolin-1-one (4a)

Compound **4a** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 23% (36 mg); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 6.9 Hz, 1 H), 7.65 (d, *J* = 7.9 Hz, 2 H), 7.50–7.41 (m, 3 H), 7.33 (d, *J* = 6.4 Hz, 1 H), 7.26–7.13 (m, 3 H), 6.96 (s, 1 H), 6.73 (s, 3 H), 4.00 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.5, 146.0, 134.2, 132.4, 131.1, 129.3, 128.8, 128.8, 128.5, 128.2, 125.0, 124.0, 123.5, 123.0, 122.8, 114.4, 65.2, 55.2.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{17}NO_2$ + Na^+: 338.1157; found: 338.1161.

2-(4-methoxyphenyl)-2-phenylisoindolin-1-one (4b)

Compound **4b** was purified by TLC (petroleum ether/acetone, 10:1).

Yield: 40% (63 mg); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.1 Hz, 1 H), 7.57–7.52 (m, 2 H), 7.49 (t, *J* = 7.5 Hz, 2 H), 7.20–7.25 (m, 3 H), 7.15–7.04 (m, 2 H), 6.78 (d, *J* = 7.6 Hz, 2 H), 5.98 (s, 1 H), 3.72 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.3, 134.4, 131.7, 130.0, 129.7, 129.1, 128.8, 128.8, 128.1, 126.6, 123.7, 113.8, 113.7, 113.4, 55.2, 51.6.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{17}NO_2$ + Na^+: 338.1157; found: 338.1159.

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Supporting Information

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(13) Analysis of the reaction solution of **1u** by GC-MS showed that, besides the desired product, *N*-alkylisoindolin-1-one and *N*-alkyphthalimide as well as the C–N bond cleaved side-products were detected. We think that when intermediate **B** (Scheme 5) was generated, a series of competitive reactions, such as direct elimination to *N*-alkylisoindolin-1-one, over-oxidation of intermediate **D** to *N*-alkylphthalimide and hydrolysis of iminium intermediate **F** might occur, leading to decline of the yields of the desired product.

(14) Benzoic acid together with a small amount of benzaldehyde were detected by GC-MS analysis.