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A Catalyst-Free Approach to Construct C−C Bond Initiated by N−O Bond Cleavage under Thermal Conditions

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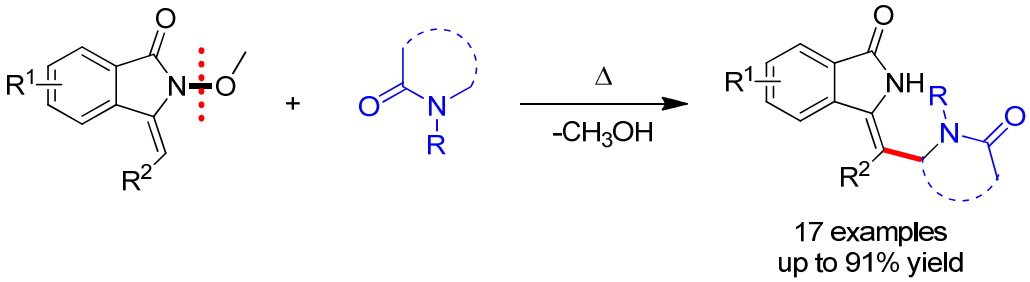
ABSTRACT



An unexpected and novel approach to construct sp^2 C−sp^3 C bond has been developed via N–O bond cleavage without any external catalysts or additives. It is a very simple, efficient, and environmentally friendly method and will be a very attractive radical process towards new C−C bond formation.

INTRODUCTION

The direct and regioselective formation of C–C bonds via the cleavage of

unactivated C−H bonds is a long-standing goal in organic chemistry. In particular, the C–C bond formations are among the most important processes in chemistry, because they provide key steps to build more complex molecules from simple precursors. In recent years, transition-metal-catalyzed C−H bond activations and subsequent C–C bond formations have attracted great interest.[1] However, achieving the sp^3 C–H bond cleavages to construct C–C bonds for preparing diverse compounds from simple starting materials remains a challenge due to the lack of a π-electron system. Over the past decades, cross-dehydrogenative-coupling (CDC) reaction to construct new C–C bonds has emerged as a powerful and efficient protocol in organic chemistry.[2] Substantial efforts have been devoted to the construction of numerous C–C bonds via metal-catalyzed oxidative functionalization of sp^3 C–H bonds. However, most of the works were still limited to aryl-substituted substrates, such as the sp^3 C−H bond adjacent to the nitrogen of *N*,*N*-dimethylaniline and 1,2,3,4-tetrahydroisoquinoline and the sp^3 C−H bond adjacent to the oxygen of isochroman.[3,4] Although considerable efforts have been made to realize the functionalization of the sp^3 C–H bonds of simple aliphatic amides,[5] the formation of C–C bonds using a similar strategy received less attention.[5a-c, 5i] Moreover, most of the reactions[5a-c, 5i] required metal catalysts and/or additional oxidants and rarely focused on functionalization of the sp^3 C–H bonds to construct C–C bonds without any external catalysts or additives.

On the other hand, the N−O bond is highly active and easily broken. Usually,

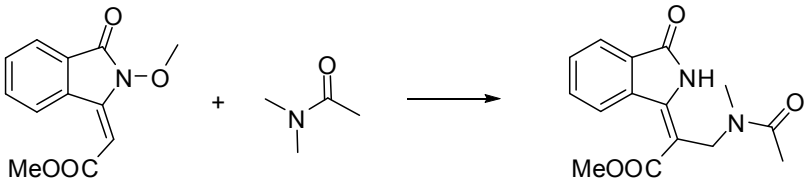
the N−O bond cleavage could be realized by heating,[6] light,[7] metal catalysis,[8] and reduction.[9] It is worthy to note that the thermal decomposition of *N*,*N*-dialkoxyamides brings out alkoxyl radicals and alkoxyamidyl radicals, of them the latter are prone to HERON rearrangements to give esters.[6] Unexpectedly, we found that isoindolinones bearing an *E*-configured exocyclic C=C bond could react with both acyclic *N*,*N*-dimethylacetamide (DMAc) and cyclic *N*-alkyl pyrrolidones without any external catalysts or oxidants under thermal conditions. Intriguingly, the reaction involves the construction of sp^2 C–sp^3 C bond initiated by the N–O bond cleavage.

RESULTS AND DISCUSSION

Initially, we chose the reaction of (*E*)-methyl 2-(2-methoxy-3-oxoisoindolin-1-ylidene) acetate (**1a**) with DMAc (**2a**) as the model reaction to explore the optimal conditions. At the outset, when **1a** (0.25 mmol) and 2.0 mL (86 equiv) of **2a** was heated at 100 ^{o}C for 12 h under an air atmosphere, product **3aa** could be obtained in 42% yield (Table 1, entry 1). When the reaction temperature was elevated to 110 ^{o}C, the yield of **3aa** was slightly increased to 58% (Table 1, entry 2). Much to our pleasure, when the temperature was further increased to 120 ^{o}C, product **3aa** could be isolated in 91% yield after 4 h (Table 1, entry 3). However, when the amount of DMAc was decreased to 1.5 mL (Table 1, entry 4) or 1.0 mL (Table 1, entry 5), the yield of **3aa** became lower even if the reaction time was prolonged to 12 h. Disappointingly, when

1,2-dichloroethane (DCE), toluene, ethanol, dimethyl sulfoxide (DMSO), and acetonitrile (CH_3CN) were employed as the solvent and 10.0 equiv of DMAc was added, the reaction failed to give product **3aa** (Table 1, entries 6−10).

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3aa**

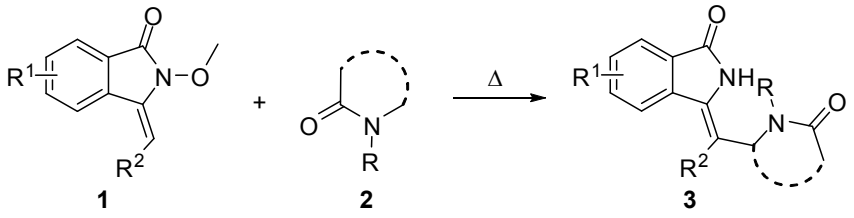
entry	temp (^oC)	t (h)	solvent	yield (%)[b]
1	100	12	DMAc (2.0 mL)	42
2	110	12	DMAc (2.0 mL)	58
3	**120**	**4**	DMAc (**2.0 mL**)	**91**
4	120	12	DMAc (1.5 mL)	53
5	120	12	DMAc (1.0 mL)	45
6[c]	120	4	DCE (2.0 mL)	NR
7[c]	120	4	PhMe (2.0 mL)	NR
8[c]	120	4	EtOH (2.0 mL)	NR
9[c]	120	4	DMSO (2.0 mL)	NR
10[c]	120	4	CH_3CN (2.0 mL)	NR

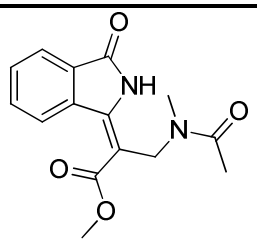
[a]Reaction conditions: unless otherwise noted, all reactions were carried out with 0.25 mmol of **1a** in 2.0 mL of **2a** under an air atmosphere. [b]Isolated yield. [c]10.0 equiv of DMAc was used.

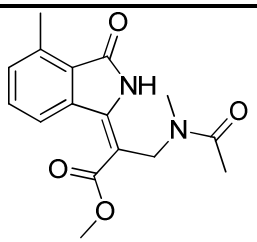
With the optimal conditions in hand, then we investigated various isoindolinones and aliphatic amides to examine the substrate scope and limitation of the current reaction. The results are summarized in Table 2. Substrates bearing either electron-donating or electron-withdrawing groups on the phenyl ring of isoindolinones could be applied to afford the corresponding products **3aa−3fc** in moderate to good yields. (*E*)-Methyl 2-(2-methoxy-3-oxoisoindolin-1-ylidene)acetate (**1a**) generally afforded higher yields (91% for **3aa**, 86% for **3ab**, and 82% for **3ac**) compared to other substituted substrates. Interestingly, the *o*-Me on the phenyl ring of **1b** proceeded better and provided higher yields relative to the *p*- and *m*-substituted counterparts (**3ba** vs **3ca** and **3da**, **3bb** vs **3cb**). Similarly, substrates with the electron-donating groups at the *meta*- or *para*-position of the phenyl ring (**1c−1e**) were smoothly converted to the corresponding products. It should be noted that substrates **1f** and **1g** containing a halogen atom such as chlorine and bromine could also give fairly good yields. However, isoindolinones bearing strong electron-withdrawing groups such as nitro and ester groups on the phenyl ring performed much worse than other substrates. In general, the substituents on the phenyl ring of isoindolinones had an obvious influence on the reaction. Moreover, (*E*)-3-benzylidene-2-methoxyisoindolin-1-one (**1h**), in which the ester moiety was replaced by a phenyl group, could also react with DMAc to bring out the desired product, albeit in a relatively low yield.

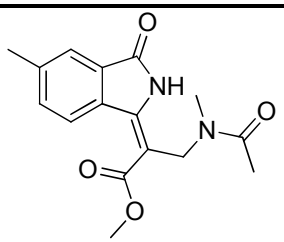
Encouraged by the above results, we next explored the scope of cyclic amides. Interestingly, when *N*-methyl pyrrolidone (NMP, **2b**) was subjected to this procedure, the methylene C–H bond reacted in high regioselectivity to provide products **3ab**, **3bb**, **3cb**, **3eb**, and **3fb** in 64-85% yields. Similarly, *N*-ethyl pyrrolidone **2c** could also react with isoindolinones **1a**, **1b**, **1e**, and **1f** smoothly to give the corresponding products **3ac**, **3bc**, **3ec**, and **3fc** in 68-82% yields. It should be pointed out that a small amount of byproducts resulting from the reactions at the *N*-alkyl group for **2b** and **2c** could also be observed, yet the reactions still demonstrated good selectivity of the current procedure and predominantly furnished the corresponding products in good to excellent yields.

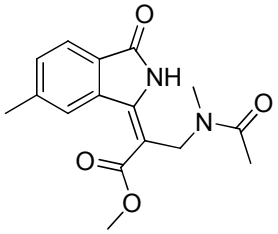
Table 2. Results for the Construction of sp^2 C–sp^3 C Bond Initiated by N–O Bond Cleavage[a,b]

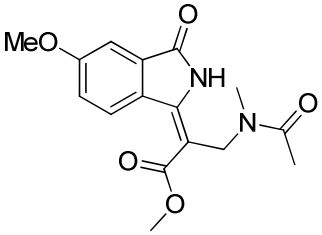


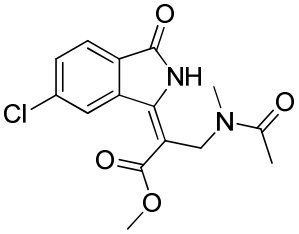

3aa; 4 h, 91%

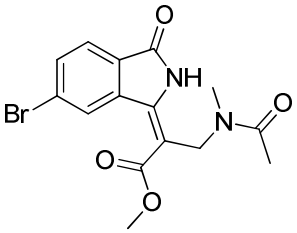

3ba; 4 h, 87%

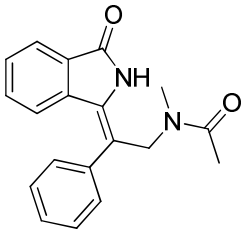

3ca; 3 h, 74%

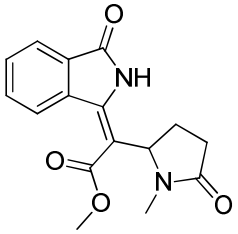

3da; 3 h, 73%

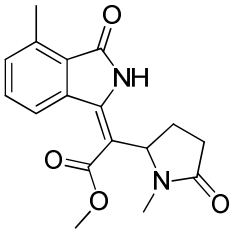

3ea; 6 h, 72%

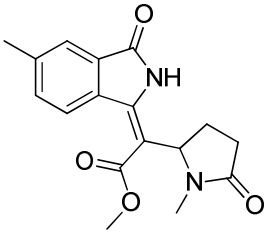

3fa, 6 h, 70%

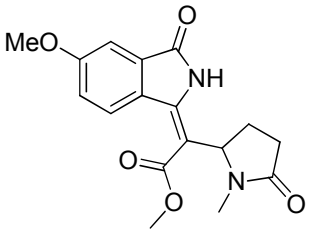

3ga; 6 h, 79%

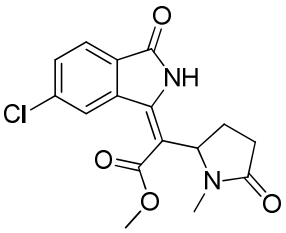

3ha; 6 h, 47%

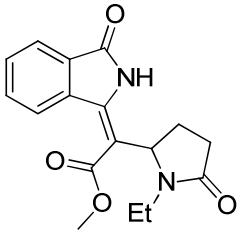

3ab; 3 h, 86%[c]

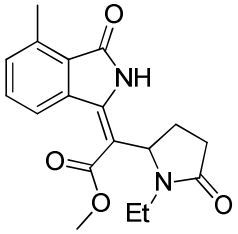

3bb; 3 h, 81%[c]

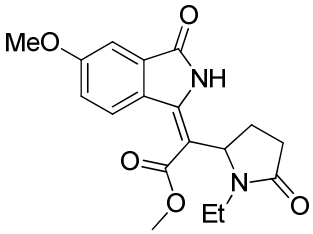

3cb; 6 h, 64%[c]

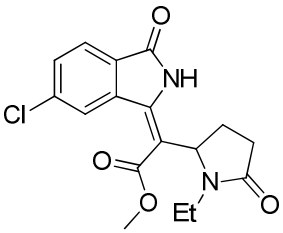

3eb; 6 h, 64%[c]


3fb; 6 h, 69%[c]


3ac; 3 h, 82%[c]


3bc; 12 h, 79%[c]

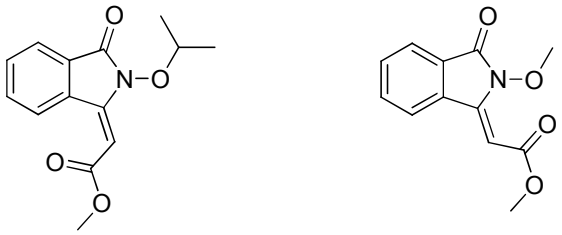

3ec; 12 h, 72%[c]


3fc; 12 h, 68%[c]

[a]Reaction conditions: all reactions were carried out with 0.25 mmol of **1a** in 2.0 mL of **2a** at

120 °C under an air atmosphere. [b]Isolated yield. [c]100 °C was employed.

In addition, we also examined other isoindolinones with different alkoxy substituent or different exocyclic C=C configuration (Figure 1). (*E*)-Methyl 2-(2-isopropoxy-3-oxoisoindolin-1-ylidene)acetate **1i**, in which the methoxy moiety was replaced by an isopropoxy group, could also react with DMAc to give product **3aa** in 62% yield. Meanwhile, when (*Z*)-methyl 2-(2-methoxy-3-oxoisoindolin-1-ylidene)acetate **1j**, a *Z* isomer of **1a**, was allowed to react with DMAc, the same product **3aa** could be obtained in 59% yield. Nevertheless, both **1i** and **1j** showed inferior efficiency and provided lower product yields than **1a**.



1i; 12 h, 62% **1j**; 4 h, 59%

Figure 1. Other isoindolinones affording product **3aa**.

Products **3aa**-**3fc** were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS. In addition, the molecular structure was unequivocally established by the X-ray crystallography of representative **3da**.

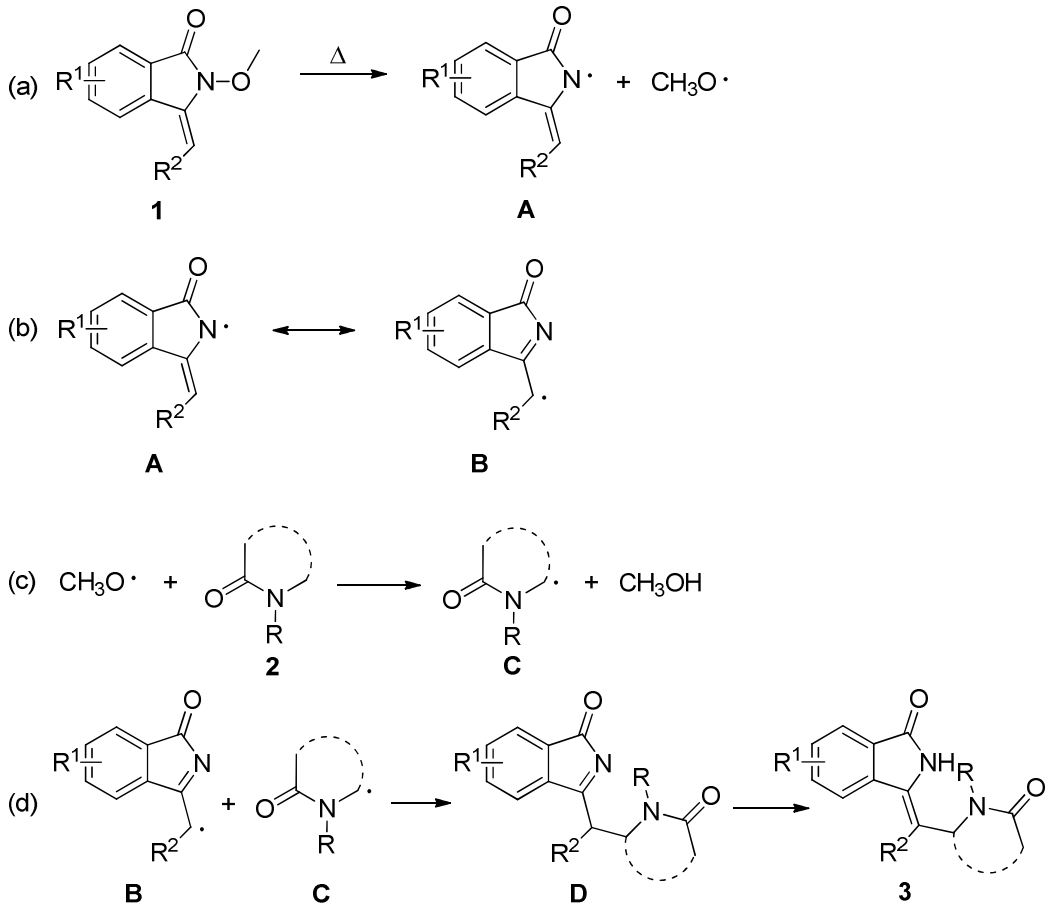
To gain more insights into the reaction mechanism, a free radical scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), was added to the reaction mixture,

and no desired product **3aa** was obtained, indicating that the reaction probably proceeded through a free radical process.

Based on the above results and the previously reported radical reactions, a plausible reaction mechanism is proposed and shown in Scheme 1. Firstly, thermal decomposition of the isoindolinone derivative proceeds by homolysis of the N–O bond, which generates the amidyl radical **A** and methoxyl radical under the thermal conditions.[6] The electron on the nitrogen atom of the amidyl radical **A** can delocalize to the C=C bond to generate the resonance structure **B**. Meanwhile, the generated methoxyl radical selectively abstracts a hydrogen atom from the α-carbon of aliphatic amides to form a nitrogen-stabilized *C*-centred radical **C**,[5f,6] which subsequently couples with the radical **B** to produce the intermediate **D**. Finally, the intermediate **D** undergoes isomerization to give product **3** with an exocyclic C=C *E*-configuration. The exact reason for the favorable formation of the product with *E*-configuration is unclear now. The key to success in the radical coupling between **B** and **C** should be ascribed to the absence of an oxidant, which would oxidize **C** to an iminium intermediate[5d-f,h-j] and thus inhibit the radical coupling process. The above proposed reaction pathway can also elucidate why the same product **3aa** is generated from **1i** bearing a different alkoxyl group attached to the nitrogen atom (*N*–O^{i}Pr for **1i** vs *N*–OMe for **1a**) as well as from **1j** containing different exocyclic C=C configuration (*Z* isomer for **1j** vs *E* isomer for **1a**). It should be noted that a chain mechanism is also possible: the reaction of the methoxyl radical created in the initiation step with the amide would generate the radical **C**, which undergoes addition to substrate **1** to give

the final product **3**, accompanied with generation of a new methoxyl radical to propagate the chain.

Scheme 1. Plausible Reaction Mechanism



CONCLUSION

In summary, we have developed a novel method for the formation of sp^2 C–sp^3 C bond without any catalysts or external additives. To the best of our knowledge, there is still no precedent for a catalyst-free radical-based approach to construct sp^2 C–sp^3 C bond just under thermal conditions. Compared with those metal-catalyzed reactions,

this is a novel, highly effective, and environmentally friendly process. We believe that this radical process will become a new strategy for the formation of C–C bonds and will be a very attractive method towards new bond formation.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all commercial materials and solvents were used without further purification. Isoindolinones **1a−1h** were prepared by the reactions of *N*-methoxybenzamides with methyl acrylate or styrene, using $Pd(OAc)_2$ as the catalyst and benzoquinone (BQ) as the oxidant according to our previous procedure.[10] ^1H NMR and ^{13}C NMR spectra were referenced to TMS and residue $CHCl_3$ at 0.00 ppm and 77.16 ppm, respectively. High-resolution mass spectra (HRMS) were measured with ESI-Orbitrap, APCI-Orbitrap or EI-TOF in positive mode.

Synthesis of 1i. A mixture of *N*-isopropoxybenzamide (89.6 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), BQ (108.0 mg, 1.0 mmol), and methyl acrylate (90.6 μL, 1.0 mmol) was dissolved in HOAc (5.0 mL). Then the solution was stirred at 100 ^oC. The reaction was monitored by TLC and stopped after 12 h. Then the solvent was evaporated to dryness in vacuo. The residual was separated on a silica gel column with petroleum ether/ethyl acetate (6/1) as the eluent to get product **1i** (49.6 mg, 38%): white solid, m.p. 74–75 ^oC; IR ν/cm^{-1} (KBr) 2983, 2940, 1737, 1639, 1456, 1385, 1311, 1146, 982, 838, 763, 682; ^1H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 7.3 Hz, 1H), 7.69 (t, J = 7.7 Hz, 1H), 7.61 (t, J = 7.4 Hz, 1H), 6.00

(s, 1H), 4.70–4.63 (m, 1H), 3.83 (s, 3H), 1.39 (d, J = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 163.0, 146.3, 133.6, 131.6, 130.4, 128.1, 127.5, 123.4, 97.8, 80.1, 51.8, 21.0 (2C); HRMS (EI-TOF) *m/z* [M^+] calcd for $C_{14}H_{15}NO_4$ 261.1001, found 261.1000.

Synthesis of (*Z*)-Methyl 2-(2-methoxy-3-oxoisoindolin-1-ylidene)acetate (1j). To 50 mL of methanol was added **1a** (58.3 mg, 0.25 mmol), the solution was placed in a Pyrex photoreactor (λ > 290 nm), and irradiated with a 300 W high-pressure Hg lamp while bubbling with high pure N_2 for 6 h. Upon completion, the solvent was evaporated to dryness in vacuo. The residual was separated on a silica gel column with petroleum ether/ethyl acetate (6/1) as the eluent to get **1j** (28.0 mg, 48%): white solid, m.p. 73–74 ^{o}C; IR ν/cm^{-1} (KBr) 2940, 1748, 1659, 1471, 1434, 1296, 1191, 1168, 1148, 1130, 997, 907, 814, 767, 682; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.2 Hz, 1H), 7.67–7.57 (m, 3H), 5.87 (s, 1H), 4.14 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 164.3, 139.4, 133.7, 133.3, 131.3, 126.4, 124.0, 120.4, 94.3, 65.3, 52.1; HRMS (EI-TOF) *m/z* [M^+] calcd for $C_{12}H_{11}NO_4$ 233.0688, found 233.0686.

General Procedure for the Synthesis of 3aa−3ha. A solution of isoindolinone **1a** (**1b−1j**, 0.25 mmol) in *N*,*N*-dimethylacetamide (**2a**, 2.0 mL) was stirred under an air atmosphere at 120 ^{o}C for a desired time (monitored by TLC). After the reaction was finished, the mixture was filtered by a silica gel plug with ethyl acetate (30 mL) as the eluent. The filtrate was washed with saturated brine (3×10 mL) and the organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The

residue was separated on a silica gel column with petroleum ether/ethyl acetate (1/3) as the eluent to get product **3aa** (**3ba**−**3ha**).

*(E)-Methyl 3-(N-methylacetamido)-2-(3-oxoisoindolin-1-ylidene)propanoate (**3aa**)*. By following the general procedure, the reaction of **1a** (58.3 mg, 0.25 mmol) with **2a** (2.0 mL) for 4 h afforded **3aa** (65.7 mg, 91% yield): white solid, m.p. 131–132 ^{o}C; IR ν/cm^{-1} (KBr) 3103, 3004, 2953, 2813, 1728, 1706, 1620, 1438, 1414, 1360, 1293, 1246, 1134, 1082, 771, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.62 (bs, 1H), 8.36 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 6.8 Hz, 1H), 7.62-7.53 (m, 2H), 4.54 (s, 2H), 3.94 (s, 3H), 3.09 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 168.1, 168.0, 147.3, 135.0, 132.7, 131.7, 131.0, 126.8, 123.5, 106.1, 52.3, 46.1, 36.4, 21.7; HRMS (APCI-Orbitrap) m/z $[M+H]^+$ calcd for $C_{15}H_{17}N_2O_4^+$ 289.1183, found 289.1178.

*(E)-Methyl 2-(4-methyl-3-oxoisoindolin-1-ylidene)-3-(N-methylacetamido)propanoate (**3ba**)*. By following the general procedure, the reaction of **1b** (61.8 mg, 0.25 mmol) with **2a** (2.0 mL) for 4 h afforded **3ba** (65.5 mg, 87% yield): white solid, m.p. 140–141 ^{o}C; IR ν/cm^{-1} (KBr) 3093, 2944, 2814, 1708, 1615, 1437, 1365, 1289, 1243, 1180, 1132, 1087, 786, 707; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (bs, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 4.52 (s, 2H), 3.91 (s, 3H), 3.07 (s, 3H), 2.70 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 168.8, 168.5, 147.0, 138.0, 135.7, 133.4, 132.2, 128.5, 124.2, 105.0, 52.2, 46.2, 36.4, 21.7, 17.6; HRMS (APCI-Orbitrap) m/z $[M+H]^+$ calcd for $C_{16}H_{19}N_2O_4^+$ 303.1339, found

303.1335.

(E)-Methyl 2-(5-methyl-3-oxoisoindolin-1-ylidene)-3-(N-methylacetamido)propanoate ***(3ca)***. By following the general procedure, the reaction of **1c** (61.8 mg, 0.25 mmol) with **2a** (2.0 mL) for 3 h afforded **3ca** (55.8 mg, 74% yield): white solid, m.p. 115–116 ^{o}C; IR ν/cm^{-1} (KBr) 3095, 2948, 2814, 1731, 1702, 1615, 1484, 1437, 1360, 1291, 1246, 1181, 1146, 1126, 1078, 788, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.53 (bs, 1H), 8.25 (d, J = 8.4 Hz, 1H), 7.66 (t, J = 0.8 Hz, 1H), 7.40–7.37 (m, 1H), 4.53 (s, 2H),3.92 (s, 3H), 3.07 (s, 3H), 2.46 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 168.22, 168.19, 147.8, 141.9, 133.6, 132.5, 132.1, 126.8, 124.0, 105.3, 52.2, 46.1, 36.4, 21.7, 21.6; HRMS (APCI-Orbitrap) *m/z* $[M+H]^+$ calcd for $C_{16}H_{19}N_2O_4^+$ 303.1339, found 303.1334.

(E)-Methyl 2-(6-methyl-3-oxoisoindolin-1-ylidene)-3-(N-methylacetamido)propanoate ***(3da)***. By following the general procedure, the reaction of **1d** (61.7 mg, 0.25 mmol) with **2a** (2.0 mL) for 3 h afforded **3da** (55.1 mg, 73% yield): white solid, m.p. 159–161 ^{o}C; IR ν/cm^{-1} (KBr) 3114, 2952, 1736, 1704, 1621, 1432, 1358, 1245, 1139, 1077, 783, 710; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.46 (bs, 1H), 8.17 (s, 1H), 7.74 (d, J = 7.2 Hz, 1H), 7.36 (1H, d, J = 7.2 Hz, 1H), 4.53 (s, 2H), 3.93 (s, 3H), 3.07 (s, 3H), 2.48 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 168.2, 168.1, 147.6, 143.4, 135.5, 132.0, 129.3, 127.4, 123.4, 105.7, 52.2, 46.1, 36.4, 22.4, 21.7; HRMS (APCI-Orbitrap) *m/z* $[M+H]^+$ calcd for $C_{16}H_{19}N_2O_4^+$ 303.1339, found 303.1333.

*(E)-Methyl 2-(5-methoxy-3-oxoisoindolin-1-ylidene)-3-(N-methylacetamido)propanoate (**3ea**).* By following the general procedure, the reaction of **1e** (65.9 mg, 0.25 mmol) with **2a** (2.0 mL) for 6 h afforded **3ea** (57.5 mg, 72% yield): pale yellow solid, m.p. 106–107 ^{o}C; IR ν/cm^{-1} (KBr) 3106, 2925, 2854, 1728, 1626, 1485, 1438, 1409, 1362, 1290, 1238, 1176, 1124, 1075, 1019, 838, 780, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.61 (bs, 1H), 8.34 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 2.6 Hz, 1H), 7.10 (dd, J = 8.8, 2.6 Hz, 1H), 4.53 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.07 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 168.2, 167.9, 162.2, 148.0, 134.2, 128.7, 127.5, 120.0, 106.9, 104.7, 55.9, 52.1, 46.0, 36.4, 21.7; HRMS (APCI-Orbitrap) *m/z* $[M+H]^+$ calcd for $C_{16}H_{19}N_2O_5^+$ 319.1289, found 319.1282.

*(E)-Methyl 2-(6-chloro-3-oxoisoindolin-1-ylidene)-3-(N-methylacetamido)propanoate (**3fa**).* By following the general procedure, the reaction of **1f** (67.0 mg, 0.25 mmol) with **2a** (2.0 mL) for 6 h afforded **3fa** (56.2 mg, 70% yield): white solid, m.p. 177–178 ^{o}C; IR ν/cm^{-1} (KBr) 3130, 2955, 2814, 1734, 1709, 1616, 1424, 1358, 1249, 1144, 1087, 784, 707; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.72 (bs, 1H), 8.44 (d, J = 1.8 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.54 (dd, J = 8.0, 1.8 Hz, 1H), 4.54 (s, 2H), 3.95 (s, 3H), 3.08 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 166.7, 166.0, 145.6, 138.2, 135.6, 130.4, 129.1, 126.5, 123.6, 106.1, 51.4, 45.2, 35.6, 20.7; HRMS (APCI-Orbitrap) *m/z* $[M+H]^+$ calcd for $C_{15}H_{16}N_2O_4{}^{35}Cl^+$ 323.0793, found 323.0789.

(E)-Methyl

*2-(6-bromo-3-oxoisoindolin-1-ylidene)-3-(N-methylacetamido)propanoate (**3ga**)*. By following the general procedure, the reaction of **1g** (78.0 mg, 0.25 mmol) with **2a** (2.0 mL) for 6 h afforded **3ga** (72.7 mg, 79% yield): white solid, m.p. 154–155 ^{o}C; IR *v*/cm^{-1} (KBr) 3085, 2952, 2808, 1732, 1710, 1616, 1418, 1356, 1251, 1139, 1082, 995, 781, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.71 (bs, 1H), 8.60 (s, 1H), 7.73–7.68 (m, 2H), 4.54 (s, 2H), 3.95 (s, 3H), 3.08 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 167.7, 167.1, 146.5, 136.7, 134.3, 130.6, 130.4, 127.6, 124.9, 107.1, 52.4, 46.2, 36.6, 21.7; HRMS (ESI-Orbitrap) *m/z* $[M+H]^+$ calcd for $C_{15}H_{16}N_2O_4{}^{79}Br^+$ 367.0288, found 367.0290.

*(Z)-N-Methyl-N-(2-(3-oxoisoindolin-1-ylidene)-2-phenylethyl)acetamide (**3ha**)*. By following the general procedure, the reaction of **1h** (62.8 mg, 0.25 mmol) with **2a** (2.0 mL) for 6 h afforded **3ha** (36.3 mg, 47% yield): white solid, m.p. 230–231 ^{o}C; IR *v*/cm^{-1} (KBr) 3133, 3027, 2788, 1702, 1612, 1418, 1351, 1304, 1279, 1200, 1142, 1033, 1018, 766, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (bs, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.51–7.44 (m, 3H), 7.42–7.33 (m, 3H), 7.19 (t, J = 7.6 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 4.48 (s, 2H), 2.82 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 168.2, 140.1, 136.6, 135.3, 131.7, 131.5, 129.6 (2C), 129.4 (2C), 129.0, 128.4, 123.49, 123.47, 118.1, 51.8, 37.7, 21.8; HRMS (ESI-Orbitrap) *m/z* $[M+H]^+$ calcd for $C_{19}H_{19}N_2O_2{}^+$ 307.1441, found 307.1443.

General Procedure for the Synthesis of 3ab−3fb. A solution of isoindolinone **1a** (**1b**, **1c**, **1e**, and **1f**, 0.25 mmol) in *N*-methyl pyrrolidone (**2b**, 2.0 mL) was stirred under an air atmosphere at 100 ^{o}C for a desired time (monitored by TLC). After the

reaction was finished, the mixture was filtered by a silica gel plug with ethyl acetate (30 mL) as the eluent. The filtrate was washed with saturated brine (3×10 mL) and the organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was separated on a silica gel column with acetone/ethyl acetate (1/1) as the eluent to get product **3ab** (**3bb**, **3cb**, **3eb**, and **3fb**).

(E)-Methyl 2-(1-methyl-5-oxopyrrolidin-2-yl)-2-(3-oxoisoindolin-1-ylidene)acetate ***(3ab)***. By following the general procedure, the reaction of **1a** (58.3 mg, 0.25 mmol) with **2b** (2.0 mL) for 3 h afforded **3ab** (64.5 mg, 86% yield): white solid, m.p. 200–201 ^{o}C; IR ν/cm^{-1} (KBr) 3183, 3059, 2951, 2827, 1712, 1694, 1650, 1467, 1399, 1359, 1309, 1236, 1165, 1082, 960, 773, 715, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.62 (bs, 1H), 7.91 (d, J = 6.8 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.64 (t, J = 6.8 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 5.01–4.97 (m, 1H), 3.92 (s, 3H), 2.86 (s, 3H), 2.69–2.45 (m, 3H), 2.30–2.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 169.9, 167.5, 137.8, 135.0, 133.2, 130.7, 130.5, 124.1, 123.9, 113.5, 59.7, 52.9, 30.2, 28.6, 24.2; HRMS (APCI-Orbitrap) m/z [M+H$^+$] calcd for $C_{16}H_{17}N_2O_4^+$ 301.1183, found 301.1178.

(E)-Methyl 2-(4-methyl-3-oxoisoindolin-1-ylidene)-2-(1-methyl-5-oxopyrrolidin-2-yl)acetate ***(3bb)***. By following the general procedure, the reaction of **1b** (61.8 mg, 0.25 mmol) with **2b** (2.0 mL) for 3 h afforded **3bb** (63.6 mg, 81% yield): white solid, m.p. 159–160 ^{o}C; IR ν/cm^{-1} (KBr) 3176, 3048, 2955, 1714, 1699, 1652, 1434, 1366, 1310, 1249, 1101, 805, 765, 700, 647; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (bs, 1H), 7.58 (d,

J = 8.0 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 4.97–4.93 (m, 1H), 3.90 (s, 3H), 2.85 (s, 3H), 2.70 (s, 3H), 2.64–2.40 (m, 3H), 2.29–2.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 170.8, 167.7, 138.3, 137.5, 135.5, 132.9, 132.8, 127.4, 121.6, 112.3, 59.8, 52.9, 30.2, 28.6, 24.4, 17.6; HRMS (ESI-Orbitrap) *m/z* $[M+H]^+$ calcd for $C_{17}H_{19}N_2O_4^+$ 315.1339, found 315.1342.

(E)-Methyl 2-(5-methyl-3-oxoisoindolin-1-ylidene)-2-(1-methyl-5-oxopyrrolidin-2-yl)acetate ***(3cb)***. By following the general procedure, the reaction of **1c** (61.8 mg, 0.25 mmol) with **2b** (2.0 mL) for 6 h afforded **3cb** (50.4 mg, 64% yield): brown yellow solid, m.p. 230–231 ^{o}C; IR *v*/cm^{-1} (KBr) 3191, 2972, 2905, 1705, 1652, 1486, 1394, 1350, 1311, 1251, 1142, 1072, 895, 827, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (bs, 1H), 7.70 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 4.93–4.90 (m, 1H), 3.90 (s, 3H), 2.84 (s, 3H), 2.64–2.43 (m, 3H), 2.50 (s, 3H), 2.27–2.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 170.0, 167.6, 141.5, 138.3, 134.1, 132.5, 130.8, 124.1, 124.0, 112.5, 59.6, 52.8, 30.3, 28.5, 24.2, 21.6; HRMS (ESI-Orbitrap) *m/z* $[M+H]^+$ calcd for $C_{17}H_{19}N_2O_4^+$ 315.1339, found 315.1341.

(E)-Methyl 2-(5-methoxy-3-oxoisoindolin-1-ylidene)-2-(1-methyl-5-oxopyrrolidin-2-yl)acetate ***(3eb)***. By following the general procedure, the reaction of **1e** (65.8 mg, 0.25 mmol) with **2b** (2.0 mL) for 6 h afforded **3eb** (53.2 mg, 64% yield): brown yellow solid, m.p. 172–173 ^{o}C; IR *v*/cm^{-1} (KBr) 2960, 2929, 1725, 1670, 1644, 1493, 1453, 1289, 1138, 1071, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (bs, 1H), 7.76 (d, *J* = 8.8 Hz, 1H),

7.34 (d, J = 2.4 Hz, 1H), 7.15 (dd, J = 8.8, 2.4 Hz, 1H), 4.95–4.91 (m, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 2.84 (s, 3H), 2.65–2.44 (m, 3H), 2.27–2.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 169.6, 167.6, 162.0, 138.6, 132.6, 127.4, 125.9, 120.9, 111.6, 106.7, 59.7, 56.1, 52.8, 30.3, 28.5, 24.3; HRMS (ESI-Orbitrap) *m/z* $[M+H]^+$ calcd for $C_{17}H_{19}N_2O_5^+$ 331.1289, found 331.1295.

*(E)-Methyl 2-(6-chloro-3-oxoisoindolin-1-ylidene)-2-(1-methyl-5-oxopyrrolidin-2-yl)acetate (**3fb**).* By following the general procedure, the reaction of **1f** (66.9 mg, 0.25 mmol) with **2b** (2.0 mL) for 6 h afforded **3fb** (57.7 mg, 69% yield): pale yellow solid, m.p. 231–232 ^{o}C; IR v/cm^{-1} (KBr) 3191, 3062, 2952, 1714, 1645, 1429, 1351, 1253, 1165, 1087, 968, 837, 785; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (bs, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.83 (s, 1H), 7.57 (dd, J = 8.0, 1.6 Hz, 1H), 4.89–4.85 (m, 1H), 3.94 (s, 3H), 2.83 (s, 3H), 2.67–2.43 (m, 3H), 2.27–2.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 168.8, 167.1, 139.8, 137.1, 136.4, 131.1, 128.8, 124.9, 124.8, 114.6, 59.7, 53.0, 30.2, 28.6, 24.2; HRMS (ESI-Orbitrap) *m/z* $[M+H]^+$ calcd for $C_{16}H_{16}N_2O_4{}^{35}Cl^+$ 335.0793, found 335.0796.

General Procedure for the Synthesis of 3ac−3fc. A solution of isoindolinone **1a** (**1b**, **1e**, and **1f**, 0.25 mmol) in *N*-ethyl pyrrolidone (**2c**, 2.0 mL) was stirred under an air atmosphere at 100 ^{o}C for a desired time (monitored by TLC). After the reaction was finished, the mixture was filtered by a silica gel plug with ethyl acetate (30 mL) as the eluent. The filtrate was washed with saturated brine (3×10 mL) and the organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The

residue was separated on a silica gel column with acetone/ethyl acetate (1/1) as the eluent to get product **3ac** (**3bc**, **3ec**, and **3fc**).

*(E)-Methyl 2-(1-ethyl-5-oxopyrrolidin-2-yl)-2-(3-oxoisoindolin-1-ylidene)acetate (**3ac**).* By following the general procedure, the reaction of **1a** (58.3 mg, 0.25 mmol) with **2c** (2.0 mL) for 3 h afforded **3ac** (64.7 mg, 82% yield): white solid, m.p. 204–205 ^{o}C; IR ν/cm^{-1} (KBr) 3266, 3122, 2951, 1724, 1668, 1644, 1457, 1421, 1355, 1304, 1244, 1152, 1079, 969, 770, 710; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.57 (bs, 1H), 7.90 (d, J = 6.8 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.64 (t, J = 7.2 Hz, 1H), 7.59 (t, J = 7.2 Hz, 1H), 5.18–5.14 (m, 1H), 3.92 (s, 3H), 3.83–3.73 (m, 1H), 2.98–2.88 (m, 1H), 2.69–2.44 (m, 3H), 2.33–2.23 (m, 1H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 169.8, 167.6, 137.8, 135.0, 133.2, 130.7, 130.5, 124.2, 123.8, 114.0, 57.0, 52.9, 36.1, 30.6, 24.5, 12.4; HRMS (ESI-Orbitrap) *m/z* $[M+H]^+$ calcd for $C_{17}H_{19}N_2O_4^+$ 315.1339, found 315.1341.

*(E)-Methyl 2-(1-ethyl-5-oxopyrrolidin-2-yl)-2-(4-methyl-3-oxoisoindolin-1-ylidene)acetate (**3bc**).* By following the general procedure, the reaction of **1b** (61.8 mg, 0.25 mmol) with **2c** (2.0 mL) for 12 h afforded **3bc** (64.5 mg, 79% yield): pale yellow solid, m.p. 150–151 ^{o}C; IR ν/cm^{-1} (KBr) 3178, 3052, 2955, 1715, 1672, 1641, 1459, 1425, 1381, 1360, 1311, 1245, 1098, 930, 719, 645; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.75 (bs, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 7.2 Hz, 1H), 5.23–5.18 (m, 1H), 3.90 (s, 3H), 3.84–3.74 (m, 1H), 2.97–2.88 (m, 1H), 2.69 (s, 3H), 2.67–2.40 (m,

3H), 2.32–2.24 (m, 1H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 171.1, 167.7, 138.2, 137.3, 135.6, 132.8, 132.7, 127.5, 121.6, 113.2, 56.8, 52.8, 36.0, 30.6, 24.6, 17.6, 12.4; HRMS (ESI-Orbitrap) *m/z* $[M+H]^+$ calcd for $C_{18}H_{21}N_2O_4^+$ 329.1496, found 329.1502.

*(E)-Methyl 2-(1-ethyl-5-oxopyrrolidin-2-yl)-2-(5-methoxy-3-oxoisoindolin-1-ylidene)acetate **(3ec)***. By following the general procedure, the reaction of **1e** (65.8 mg, 0.25 mmol) with **2c** (2.0 mL) for 12 h afforded **3ec** (62.4 mg, 72% yield): pale yellow solid, m.p. 192–193 ^{o}C; IR ν/cm^{-1} (KBr) 3172, 3112, 2986, 2937, 2809, 1723, 1661, 1623, 1488, 1434, 1349, 1287, 1235, 1172, 1135, 1072, 1021, 814, 735, 674; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (bs, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.15 (dd, J = 8.8, 2.4 Hz, 1H), 5.13–5.08 (m, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.80–3.70 (m, 1H), 2.98–2.88 (m, 1H), 2.68–2.44 (m, 3H), 2.30–2.20 (m, 1H), 1.13 t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 169.5, 167.6, 161.9, 138.6, 132.6, 127.5, 126.0, 120.8, 112.1, 106.7, 57.0, 56.0, 52.7, 36.1, 30.7, 24.5, 12.4; HRMS (ESI-Orbitrap) *m/z* $[M+H]^+$ calcd for $C_{18}H_{21}N_2O_5^+$ 345.1445, found 345.1452.

*(E)-Methyl 2-(6-chloro-3-oxoisoindolin-1-ylidene)-2-(1-ethyl-5-oxopyrrolidin-2-yl)acetate **(3fc)***. By following the general procedure, the reaction of **1f** (67.0 mg, 0.25 mmol) with **2c** (2.0 mL) for 12 h afforded **3fc** (59.3 mg, 68% yield): pale yellow solid, m.p. 238–239 ^{o}C; IR ν/cm^{-1} (KBr) 3070, 2981, 1705, 1645, 1612, 1454, 1425, 1354, 1253, 1163, 1135, 1084, 970, 840, 787, 725, 677; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (bs, 1H),

7.83 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.57 (dd, J = 8.0, 1.6 Hz, 1H), 5.08–5.04 (m, 1H), 3.93 (s, 3H), 3.81–3.72 (m, 1H), 2.95-2.85 (m, 1H), 2.69–2.43 (m, 3H), 2.29–2.20 (m, 1H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 168.8, 167.1, 139.8, 137.0, 136.4, 131.1, 128.8, 124.94, 124.89, 115.1, 57.0, 53.0, 36.2, 30.6, 24.5, 12.4; HRMS (ESI-Orbitrap) *m/z* $[M+H]^+$ calcd for $C_{17}H_{18}N_2O_4{}^{35}Cl^+$ 349.0950, 349.0959.

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of products **3aa–fc** and X-ray data of **3da**. This material is available free of charge via the Internet at http://pubs.acs.org.

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