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Pd-Catalyzed Aminocarbonylation of the Blaise Reaction Intermediate: One-Pot Synthesis of (*Z*)-3-Methyleneisoindolin-1-ones from Nitriles

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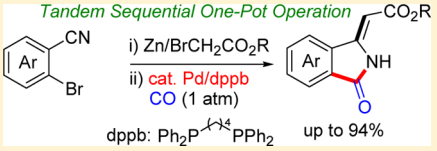
Supporting Information

ABSTRACT: A highly efficient method for the one-pot synthesis of stereocontrolled (*Z*)-3-methyleneisoindolin-1-ones was developed starting from 2-bromoarylnitriles via tandem sequential reaction with a Reformatsky reagent (Blaise reaction), followed by Pd-catalyzed intramolecular aminocarbonylation with carbon monoxide at 1 atm pressure. It has been found that the conformational flexibility of the bisphophine ligand is of great importance to the success of this tandem aminocarbonylation reaction.

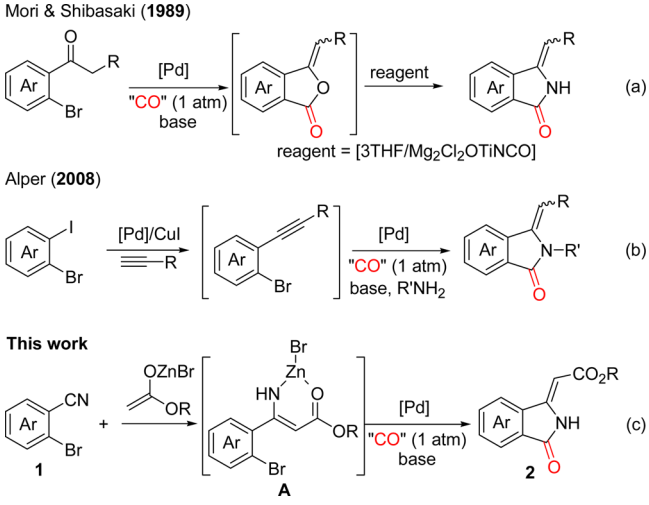


Sequential tandem one-pot reactions can efficiently increase the complexity of a substrate without the isolation of intermediates, minimizing waste generation. Therefore, tandem reactions have become an area of great interest to synthetic chemists.[1] Since the initial studies by Heck et al.,[2] the palladium-catalyzed carbonylation reactions with carbon monoxide (CO) have proven to be of utmost importance for the introduction of the carbonyl moiety in complex molecules.[3] In addition, the carbon monoxide used as C1 source is inexpensive and readily available furthering the goal of developing sustainable processes.[4] Therefore, the incorporation of Pd-catalyzed carbonylation in a tandem scheme would increase the sustainability of the processes.

With a diverse set of biological activities, 3-methyleneisoindolin-1-ones are present in a range of natural products.[5] Owing to their great importance, many reliable methods have been developed for the preparation of 3-methyleneisoindolin-1-ones.[6] However, very limited tandem Pd-catalyzed carbonylations have been investigated for the synthesis of 3-methyleneisoindolin-1-one derivatives. Uozomi et al. utilized a unique titanium-isocyanate complex as an amine source for a one-pot synthesis of 3-methyleneisoindolin-1-ones starting from *o*-halogenated alkyl ketones (Scheme 1a).[7a] More recently, Alper and co-workers developed tandem alkynylation, followed by carbonylative annulation of 1,2-dihaloarenes (Scheme 1b).[7b] However, these methods suffer from poor *E*/*Z*-stereoselectivity of the methylene moiety. In our ongoing studies regarding the Blaise reaction intermediate and its use in catalytic tandem processes,[8] we envisioned that aminocarbonylation of intermediate **A** with carbon monoxide could be utilized for the one-pot synthesis of stereocontrolled (*Z*)-3-methyleneisoindolin-1-ones **2** starting from nitriles **1** (Scheme 1c).

Our investigation commenced with intermediate **Aa**, prepared from 2-bromobenzonitrile (**1a**) and the *in situ* generated Reformatsky reagent. We first carried out the tandem reaction of **Aa** under a CO atmosphere (1 atm) in the presence of $Pd(PPh_3)_4$ and ^{t}BuOK in a 1/10 v/v solution of THF and

Scheme 1. Tandem Pd-Catalyzed Carbonylations for the Synthesis of 3-Methyleneisoindolin-1-one Derivatives



DMF for 12 h at 120 °C, which is the reaction conditions for the previously reported Ullmann-type homocoupling of **Aa**.[8f] Disappointingly, neither desired carbonylated product **2a** nor the homocoupled product were formed, and the intermediate **Aa** remained unreacted (entry 1, Table 1). To find the optimal conditions for the aminocarbonylation, different reaction conditions were screened, and some selected conditions are shown in Table 1. It was found that the base, Pd(0) source, and the choice of ligand affected the efficiency of the aminocarbonylation utilizing Blaise reaction intermediate **Aa**. For example, when the base was changed from ^{t}BuOK to the weak base K_2CO_3, the desired isoindolinone **2a** was formed in 51% yield (entry 2, Table 1). However, when utilizing this base and

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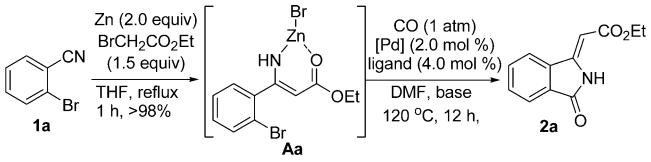
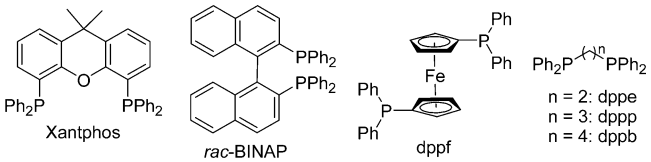
Table 1. Selected Conditions for Optimization[a]



Entry	[Pd]	ligand	base	2a (%)[b]
1	$Pd(PPh_3)_4$		^tBuOK	0
2	$Pd(PPh_3)_4$		K_2CO_3	51
3	$Pd(P^tBu_3)_2$		K_2CO_3	N.R.
4	$Pd_2(dba)_3$	Xantphos	K_2CO_3	39
5	$Pd(OAc)_2$	PPh_3	K_2CO_3	N.R.
6	$Pd(OAc)_2$	BINAP	K_2CO_3	36
7	$Pd(OAc)_2$	dppf	K_2CO_3	57
8	$Pd(OAc)_2$	dppe	K_2CO_3	N.R.
9	$Pd(OAc)_2$	dppp	K_2CO_3	44
10	$Pd(OAc)_2$	dppb	K_2CO_3	63
11	$Pd(OAc)_2$	dppb	^tBuOK	N.R.
12	$Pd(OAc)_2$	dppb	Na_2CO_3	60
13	$Pd(OAc)_2$	dppb	DBU	>5
14	$Pd(OAc)_2$	dppb	$(^iPr)_2NEt$	55
15	$Pd(OAc)_2$	dppb	Et_3N	64
16[c]	$Pd(OAc)_2$	dppb	Et_3N	76
17[d]	$Pd(OAc)_2$	dppb	Et_3N	75
18[e]	$Pd(OAc)_2$	dppb	Et_3N	86
19[ef]	$Pd(OAc)_2$	dppb	Et_3N	76
20[eg]	$Pd(OAc)_2$	dppb	Et_3N	74

[a]Reaction conditions: intermediate **Aa** was generated by the reaction of **1a** (2.0 mmmol) with ethyl bromoacetate (3.0 mmol, 1.5 equiv) and zinc (4.0 mmol, 2.0 equiv) in THF under reflux. After complete conversion of **1a** to **Aa** (by GC and TLC), add [Pd] source (2.0 mol%), ligand (4 mol%), base (4.0 mmol, 2.0 equiv), and DMF (6.0 mL) at room temperature. The reaction was charged with a balloon of carbon monoxide and the reaction was conducted at 120 °C for 12 h. [b]Isolated yield. [c]Reaction with 5.0 mol% $Pd(OAc)_2$ and 10 mol% dppb for 8 h. [d]Reaction with 5.0 mol% $Pd(OAc)_2$ and 5.0 mol% dppb for 5 h. [e]Reaction with 7.0 mol% $Pd(OAc)_2$ and 7.0 mol% dppb for 5 h. [f]Reaction in 1,4-dioxane for 12 h. [g]Reaction in *N*,*N*-dimethylacetamide (DMA). N.R. denotes no reaction.

changing the catalyst to the bulky and electron-rich $Pd(P^tBu_3)_2$, no reaction occurred (entry 3, Table 1). Although using $Pd_2(dba)_3$/bidentate phosphine ligand catalyst systems ($Pd_2(dba)_3$/xantphos) afforded **2a**, the yields were not sufficiently high (entry 4, Table 1). Reactions did not proceed at all by using *in situ* generated Pd(0) and monodentate phosphine ligands, such as PPh_3 (entry 5, Table 1), while bidentate bisphosphine ligands with rigid binaphthyl or ferrocene backbones did afford **2a** albeit in low yields (entries 6–7, Table 1).



Although the exact reason is not clear at present, we observed efficiency of this process depended greatly upon the conformational flexibility of the ligands. Accordingly, when the reaction was conducted using dppe forming a five-membered metal complex, no reaction proceeded at all (entry 8, Table 1), but the same reaction with the one carbon longer dppp ligand, forming a 6-membered Pd-complex, provided **2a** in 44% yield (entry 9, Table 1). A meaningful 63% yield of **2a** could be obtained by employing the more flexible dppb ligand (entry 10, Table 1). However, when the same reaction was conducted using ^tBuOK as a base, the reaction did not occur, and the Blaise reaction intermediate was isolated (entry 11, Table 1). After screening different bases (entries 12–15, Table 1), it was found that the organic base Et_3N showed the most efficient production resulting in a 64% yield of **2a**. Increasing the catalytic loading of Pd (5.0 mol%) and ligand (10 mol%), increased the yield to 76% (entry 16, Table 1). Decreasing the ligand loading to obtain a 1:1 ratio with the Pd catalyst did not diminish the yield, and the reaction was completed within 5 h (entry 17, Table 1). Finally, optimal reaction conditions for the tandem aminocarbonylation of the Blaise reaction intermediate **Aa** were established. Thus, reaction in the presence of 7.0 mol% $Pd(OAc)_2$, 7.0 mol% dppb, and 2.0 equiv of Et_3N in DMF for 5 h at 120 °C afforded the desired product **2a** in an optimal 86% yield (entry 18, Table 1). The yields were not improved further in other solvents such as 1,4-dioxane or DMA (entries 19 and 20, Table 1). X-ray structural analysis determined that the reaction provided (*Z*)-stereochemistry, which is ascribed to the ZnBr chelation of intermediate **Aa** (Figure 1).[9]

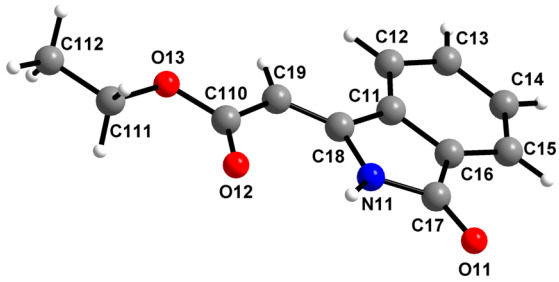


Figure 1. Crystal structure of **2a** with the atomic labeling scheme.

Employing the optimized conditions, various 2-bromoaryl nitriles were used to synthesize methyleneisoindolin-1-ones in excellent yields (Table 2). Methyl, methoxy, and dioxolane substituted 2-bromophenyl nitriles (**1b**-**1f**) provided good to excellent yields (73% to 94%) of the corresponding methyleneisoindolin-1-ones **2b**–**2f** presumably due to the electron-donating nature of the substituents. The benzonitriles containing *ortho*-, *meta*-, and *para*-fluorine-, *m*-chlorine-, and *m*-trifluoromethyl-functionalities also produced methyleneisoindolin-1-ones **2g**–**2k** in good yields (71–87%). Furthermore, we tested 2-bromo-4-fluorophenylacetonitrile as the nitrile source to undergo aminocarbonlyation. However, due to the isomerization of the double bond, **2l** was formed in low yield (36%) as a result of a competing direct *N*-arylation reaction.[8a] The present tandem Blaise/carbonylation protocol was also applied to the one-pot synthesis of a precursor to the aristolactams, which exhibit immunostimulant and anticancer activities.[10] Thus, when the tandem aminocarbonylation was carried out utilizing ethyl 2-chlorophenyl acetate to produce the Reformatsky-derived Blaise reaction intermediate, 67% yield of product **2m** was formed. The free N–H group was protected with PMBCl providing **3m** in 89% yield, which may be easily transformed to the Aristolactam derivatives through the reported procedures (eq 1).[11]

Under the same reaction conditions, the isolated Blaise adduct **4** also afforded **2a** in 87% yield (eq 2). Moreover, a competition experiment with an excess amount (ca. 5.0 equiv) of an external amine, such as aniline, gave only intramolecular

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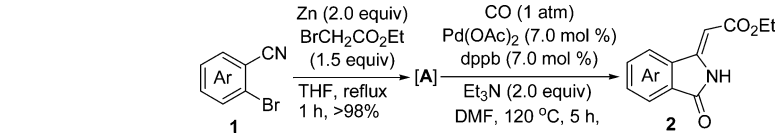
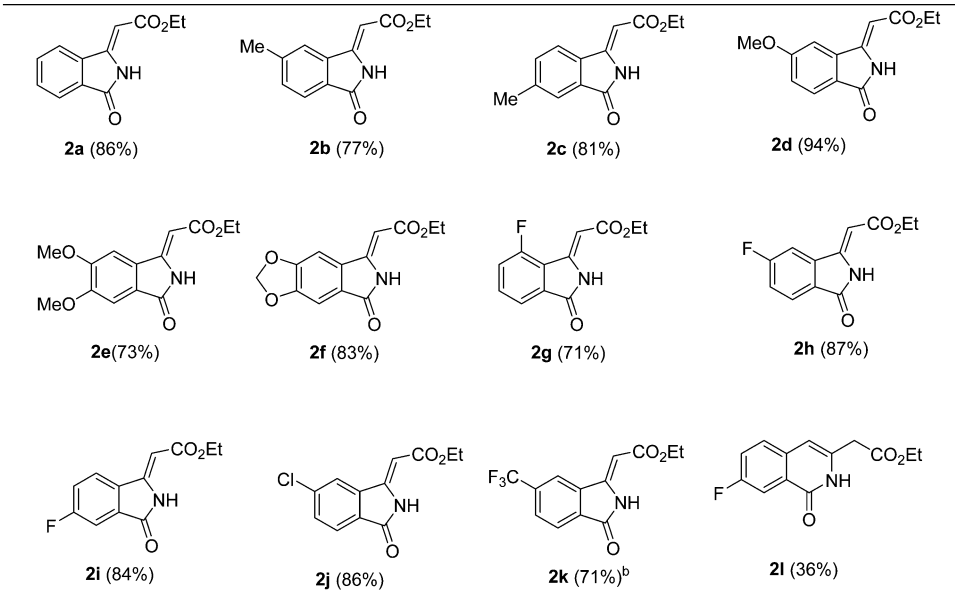
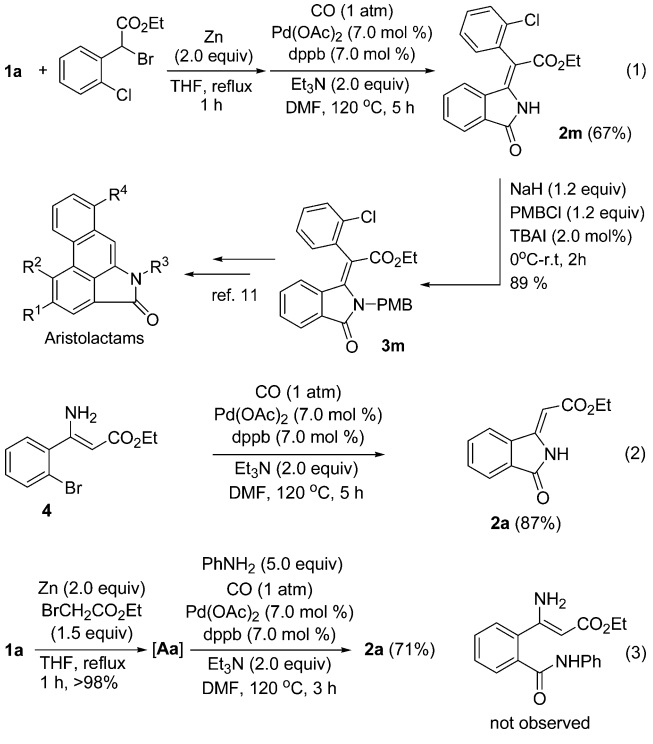
Table 2. Synthesis of (Z)-3-Methyleneisoindolin-1-ones 2 through Tandem Blaise/Pd-Catalyzed Aminocarbonylation[a]





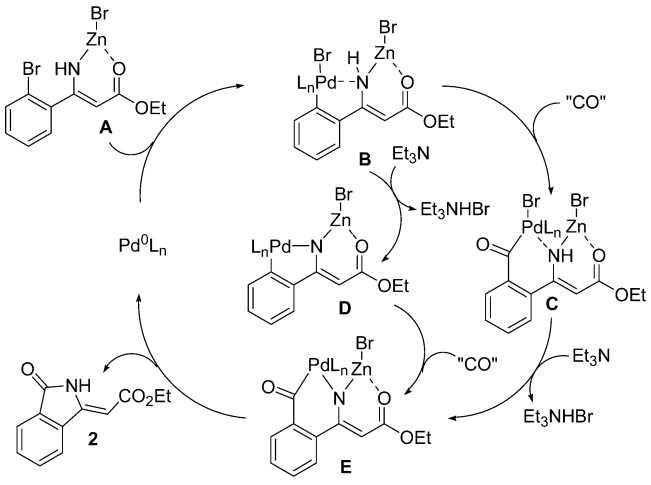
[a]Reaction conditions: intermediate **A** was generated by the reaction of nitriles (2.0 mmmol) with ethyl bromoacetate (3.0 mmol, 1.5 equiv) and zinc (4.0 mmol, 2.0 equiv) in THF under reflux. After complete conversion to **A** (by GC and TLC), add $Pd(OAc)_2$ (7.0 mol%), dppb (7.0 mol%), base (4.0 mmol, 2.0 equiv), and DMF (6.0 mL) at room temperature. The reaction was charged with carbon monoxide (balloon) and the reaction was conducted at 120 °C for 5 h. [b]Reaction for 10 h.



aminocarbonylation reaction product **2a** in 71% within 3 h, and thus the amide-functionalized β-enamino ester was not formed at all (eq 3). This result strongly suggests that the nitrogen atom of the Blaise reaction intermediate may coordinate with the Pd(II) species facilitating the intramolecular aminocarbonylation reaction.

Although a more detail mechanistic study is necessary, a plausible reaction mechanism is depicted in Scheme 2. The

Scheme 2. Plausible Reaction Mechanism



nitrogen-coordinated intermediate **B** may be formed by oxidative addition of Pd^0 to the aryl bromide. Intermediate **B** may undergo CO insertion generating the acylated Pd^{II}-complex intermediate **C** followed by nucleophilic substitution affording intermediate **E**. However, the possible formation of intermediate **E** via the 5-membered palladacycle intermediate

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D generated by nucleophilic substitution first in intermediate **B** could not be excluded at present time. Intermediate **E** then undergoes reductive elimination to afford the 3-methyleneisoindolin-1-ones **2** with regeneration of Pd(0) catalyst.

In summary, we have developed a novel tandem palladium-catalyzed aminocarbonylation of the Blaise reaction intermediate that facilitates the stereocontrolled one-pot synthesis of (*Z*)-3-methyleneisoindolin-1-one derivatives in excellent yields starting from common nitriles, Reformatsky reagents, and carbon monoxide.

EXPERIMENTAL SECTION

All reactions and manipulations were performed under an argon atmosphere using standard Schlenk techniques. Reaction flasks were flamed-dried under a stream of argon. The reaction solvents were distilled prior to used (THF was distilled over sodium and benzophenone). Anhydrous solvents were transferred by oven-dried syringe. All purchased reagents were used as received. Ethyl 2-bromo-2-(2-chlorophenyl) acetate was synthesized according to the reported procedure.[12] The NMR spectra were recorded at 300 MHz for ^{1}H, 75.5 MHz for ^{13}C. HRMS data were obtained by electron ionization with a magnetic sector-electronic sector double focusing mass analyzer.

General Procedure for the Tandem Synthesis of Compounds 2a−2l. To a stirred suspension of commercial zinc dust (10 μm, 254 mg, 4.0 mmol) in THF (1.0 mL) was added a solution of methanesulfonic acid in THF (1.0 M, 0.2 mL) at 80 °C (bath temperature). After stirring for 10 min, 2-bromo-aryl nitriles **1a−1l** (2.0 mmol) were added all at once. While maintaining at the same temperature, ethyl bromoacetate (3.0 mmol) was added over 1 h using syringe pump, and then the reaction mixture was further stirred for 1 h. After confirming conversion of nitrile **1** (>95%) to the Blaise reaction intermediate **A** by using gas chromatography and TLC, the reaction mixture was cooled down to room temperature. The solvent of THF was evaporated under vacuum, then $Pd(OAc)_2$ (31.4 mg, 7.0 mol%) and dppb (60.9 mg, 7.0 mol%) were added under Ar atmostphere in glovebox followed by the addition of dried trimethylamine (0.56 mL, 4.0 mmol) and anhydrous DMF solvent (6 mL) under the nitrogen atmosphere. The reaction was charged with a balloon of carbon monoxide and was conducted at 120 °C for 5 h. After reaction completion (confirmed by TLC), the reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl solution, neutralized with saturated aqueous Na_2CO_3 solution. The organic compounds were extracted with ethyl acetate (50 mL × 3). The combined organic layer was dried with anhydrous Na_2SO_4, filtered through a pad of Celite 545, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to afford pure **2**.

*Ethyl (Z)-2-(3-Oxoisoindolin-1-ylidene) Acetate (**2a** CAS No: 69452-25-1).*[13] Yield: 86% (374 mg); Eluent: *n*-hexane/ethyl acetate = 6/1; White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, J = 7.1 Hz, 3H), 4.28 (q, J = 7.1 Hz, 2H), 5.77(s, 1H), 7.56−7.69 (m, 3H), 7.83−7.86 (m, 1H), 9.70 (brs, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 60.7, 91.7, 121.0, 124.1, 129.6, 131.6, 132.8, 136.5, 147.4, 167.6, 168.1 ppm.

*Ethyl (Z)-2-(6-Methyl-3-oxoisoindolin-1-ylidene) Acetate (**2b**).* Yield: 77% (356 mg); Eluent: *n*-hexane/ethyl acetate = 10/1; White solid; mp: 108−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.1 Hz, 3H), 2.49 (s, 3H), 4.27 (q, *J* = 7.1 Hz, 2H), 5.73(s, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.47 (s, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 9.55 (brs, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.4, 22.1, 60.7, 91.4, 121.5, 123.9, 127.2, 132.6, 137.0, 143.9, 147.7, 167.7, 168.2 ppm; HRMS (EI) *m*/*z* Cal. for $[M]^+$: $C_{13}H_{13}NO_3$: 231.0895. Found: 231.0897.

*Ethyl (Z)-2-(5-Methyl-3-oxoisoindolin-1-ylidene) Acetate (**2c**).* Yield: 81% (375 mg); Eluent: *n*-hexane/ethyl acetate = 10/1; White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.1 Hz, 3H), 2.48 (s, 3H), 4.27 (q, *J* = 7.1 Hz, 2H), 5.71(s, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.64 (s, 1H), 9.59 (brs, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.4, 21.8, 60.6, 91.2, 120.9, 124.4, 129.9, 133.7, 134.0, 142.5, 147.6, 167.7, 168.3 ppm; ; HRMS (EI) *m*/*z* Cal. for $[M]^+$: $C_{13}H_{13}NO_3$: 231.0895. Found: 231.0896.

*Ethyl (Z)-2-(6-Methoxy-3-oxoisoindolin-1-ylidene) Acetate (**2d**).* Yield: 94% (465 mg); Eluent: *n*-hexane/ethyl acetate = 15/1 ; White solid; mp: 120−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.1 Hz, 3H), 3.90 (s, 3H), 4.27 (q, *J* = 7.1 Hz, 2H), 5.71(s, 1H), 7.05−7.12 (m, 2H), 7.74 (d, *J* = 8.3 Hz, 1H), 9.48 (brs, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.4, 55.9, 60.6, 91.3, 105.8, 117.8, 122.0, 125.5, 138.8, 147.4, 163.8, 167.6, 167.9 ppm; HRMS (EI) *m*/*z* Cal. for $[M]^+$: $C_{13}H_{13}NO_4$: 247.0845. Found: 247.0847.

*Ethyl (Z)-2-(5,6-Dimethoxy-3-oxoisoindolin-1-ylidene) Acetate (**2e** CAS No:1627538-59-3).*[14] Yield: 73% (405 mg); Eluent: *n*-hexane/ethyl acetate = 6/1 ; White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.1 Hz, 3H), 3.97 (s, 3H), 3.99 (s, 3H), 4.27 (q, *J* = 7.1 Hz, 2H), 5.68 (s, 1H), 7.09 (s, 1H), 7.30 (s, 1H), 9.43 (brs, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.5, 56.5 (56.51), 56.5 (56.54), 60.7, 91.0, 102.9, 105.5, 122.9, 130.1, 147.7, 152.6, 153.5, 167.7, 168.4 ppm.

*Ethyl (Z)-2-(7-oxo-6,7-Dihydro-5H-[1,3]dioxolo-[4,5-f]isoindol-5-ylidene) Acetate (**2f**).* Yield: 83% (434 mg); Eluent: *n*-hexane/ethyl acetate = 6/1 ; White solid; mp: 172−174 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.1 Hz, 3H), 4.26 (q, *J* = 7.1 Hz, 2H), 5.61 (s, 1H), 6.13 (s, 2H), 7.04 (s, 1H), 7.22(s, 1H),9.45 (brs, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.5, 60.8, 91.4, 101.3, 102.8, 104.0, 124.9, 132.2, 147.4, 151.2, 152.4, 167.7 (167.67), 167.7 (167.69) ppm; HRMS (EI) *m*/*z* Cal. for $[M]^+$: $C_{13}H_{11}NO_5$: 261.0637. Found: 261.0639.

*Ethyl (Z)-2-(7-Fluoro-3-oxoisoindolin-1-ylidene) Acetate (**2g**).* Yield: 71% (334 mg); Eluent: *n*-hexane/ethyl acetate = 15/1 ; White solid; mp: 132−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.1 Hz, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 6.00 (s, 1H), 7.29−7.36 (m, 1H), 7.55−7.62 (m, 1H), 7.70 (d, *J* = 7.4 Hz, 1H), 9.79 (brs, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.4, 60.9, 96.8 (d, *J* = 7.6 Hz), 120.3 (t, *J* = 3.8 Hz), 120.5, 122.9 (d, *J* = 12.8 Hz), 132.4 (d, *J* = 2.3 Hz), 133.3 (d, *J* = 7.6 Hz), 144.1 (d, *J* = 3.8 Hz), 158.2(d, *J* = 259 Hz), 166.9 (d, *J* = 2.3 Hz), 167.7 ppm; HRMS (EI) *m*/*z* Cal. for $[M]^+$: $C_{12}H_{10}FNO_3$: 235.0645. Found: 235.0646.

*Ethyl (Z)-2-(6-Fluoro-3-oxoisoindolin-1-ylidene) Acetate (**2h**).* Yield: 87% (409 mg); Eluent: *n*-hexane/ethyl acetate = 10/1; White solid; mp: 128−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.1 Hz, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 5.75 (s, 1H), 7.26−7.33 (m, 1H), 7.34−7.37 (m, 1H), 7.84−7.89 (m, 1H), 9.67 (brs, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 60.9, 92.6, 108.4 (d, *J* = 24.9 Hz), 119.1 (d, *J* = 23.4 Hz), 125.6 (d, *J* = 2.3 Hz), 126.2 (d, *J* = 9.8 Hz), 139.0 (d, *J* = 10.6 Hz), 146.2 (d, *J* = 3.8 Hz), 165.8 (d, *J* = 253.7 Hz), 167.0, 167.3 ppm; HRMS (EI) *m*/*z* Cal. for $[M]^+$: $C_{12}H_{10}FNO_3$: 235.0645. Found: 235.0641.

*Ethyl (Z)-2-(5-Fluoro-3-oxoisoindolin-1-ylidene) Acetate (**2i**).* Yield: 84% (395 mg); Eluent: *n*-hexane/ethyl acetate = 15/1 ; White solid; mp: 130−132 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.1 Hz, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 5.75 (s, 1H), 7.34 (td, *J* = 8.6 Hz, 2.4 Hz, 1H), 7.53 (dd, *J* = 7.2 Hz, 2.2 Hz, 1H), 7.69 (dd, *J* = 8.4 Hz, 4.3 Hz), 9.77 (brs, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 60.8, 92.2 (d, *J* = 1.5 Hz), 111.2 (d, *J* = 24.2 Hz), 120.4 (d, *J* = 24.2 Hz), 123.1 (d, *J* = 9.1 Hz), 132.0 (d, *J* = 9.1 Hz), 132.3 (d, *J* = 3.0 Hz), 146.4, 164.8 (d, *J* = 253.7 Hz), 166.8 (d, *J* = 3.8 Hz), 167.5 ppm; HRMS (EI) *m*/*z* Cal. for $[M]^+$: $C_{12}H_{10}FNO_3$: 235.0645. Found: 235.0647.

*Ethyl (Z)-2-(6-Chloro-3-oxoisoindolin-1-ylidene) Acetate (**2j**).* Yield: 86% (433 mg); Eluent: *n*-hexane/ethyl acetate = 6/1 ; White solid; mp: 148−150 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.1 Hz, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 5.76 (s, 1H), 7.57 (dd, *J* = 8.1 Hz, 1.7 Hz, 1H), 7.66 (dd, *J* = 1.7 Hz, 0.5 Hz, 1H), 7.81 (dd, *J* = 8.1 Hz, 0.5 Hz, 1H), 9.67 (brs, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.4, 61.0, 92.8, 121.5, 125.4, 128.0, 132.0, 138.2, 139.5, 146.2, 167.1, 167.4 ppm; HRMS (EI) *m*/*z* Cal. for $[M]^+$: $C_{12}H_{10}ClNO_3$: 251.0349. Found: 251.0350.

*Ethyl (Z)-2-(3-oxo-6-(Trifluoromethyl)isoindolin-1-ylidene) Acetate (**2k**).* Yield: 71% (405 mg); Eluent: *n*-hexane/ethyl acetate = 10/1 ; White solid; mp: 168−170 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.1 Hz, 3H), 4.30 (q, *J* = 7.1 Hz, 2H), 5.89 (s, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.96 (s, 1H), 8.02 (d, *J* = 7.9 Hz, 1H), 9.84 (brs, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.4, 61.1, 93.4, 118.4 (q,

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J = 3.8 Hz), 123.5 (q, J = 273.3 Hz), 124.8, 128.6 (q, J = 4.2 Hz), 132.6, 134.5 (q, J = 65.7, 33.2 Hz), 137.0, 145.9, 166.7, 167.3 ppm; HRMS (EI) m/z Cal. for $[M]^+$: $C_{13}H_{10}F_3NO_3$: 285.0613 Found: 285.0609.

*Ethyl 2-(7-Fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)acetate(**2l**).* Yield: 36% (180 mg); Eluent: *n*-hexane/ethyl acetate = 4/1; Yellow solid; mp: 150−152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H), 3.71 (s, 2H), 4.20 (q, J = 7.1 Hz, 2H), 6.44 (s, 1H), 7.32−7.38 (m, 1H), 7.45−7.50 (m, 1H), 7.97−8.00 (m, 1H), 12.11 (brs, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 38.5, 61.6, 105.9, 112.2 (d, J = 22.7 Hz), 121.5 (d, J = 24.2 Hz), 126.3 (d, J = 7.6 Hz), 128.4 (d, J = 7.6 Hz), 133.4, 134.8, 161.2 (d, J = 246.9 Hz), 163.9 (d, J = 3.0 Hz), 169.3 ppm; HRMS (EI) m/z Cal. for $[M]^+$: $C_{13}H_{12}FNO_3$: 249.0801; Found: 249.0798.

Typical Procedures for Synthesis of Compound 2m and 3m. To a stirred suspension of commercial zinc dust (10 μm, 254 mg, 4.0 mmol) in THF (1.0 mL) was added a solution of methanesulfonic acid in THF (1.0 M, 0.2 mL) at 80 °C (bath temperature). After stirring for 10 min, 2-bromobenzonitrile (2.0 mmol) was added all at once. While maintaining at the same temperature, 2-bromo-2-(2-chlorophenyl) acetate (3.0 mmol) was added over 1 h using syringe pump, and then the reaction mixture was further stirred for 1 h. For the Palladium catalyzed carbonylation reaction, all the manipulation and reaction condition was the same as the general procedure. Yield: 67% (439 mg); Eluent: *n*-hexane/ethyl acetate = 10/1 ; White solid; mp: 146−148 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, J = 7.1 Hz, 3H), 4.11−4.22 (m,1H), 4.26−4.36 (m, 1H), 6.17 (d, J = 7.9 Hz, 1H), 7.23−7.29 (m, 1H), 7.35−7.48 (m, 4H), 7.54−7.57 (m, 1H), 7.84 (d, J = 7.4 Hz, 1H), 10.44 (brs, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 61.2, 106.8, 123.7, 124.5, 127.2, 129.8, 130.0,130.3, 130.9, 132.4, 132.5, 133.3, 135.3, 135.9, 145.2, 167.1, 167.7 ppm; HRMS (EI) m/z Cal. for $[M]^+$: $C_{18}H_{14}{}^{35}ClNO_3$: 327.0662. Found: 327.0663; Cal. For $[M+2]^+$: $C_{18}H_{14}{}^{37}ClNO_3$: 329.0639; Found: 329.0645.

To a solution of compound **2m** (164 mg, 0.5 mmol) in anhydrous DMF (1.6 mL) was added NaH (12.6 mg, 0.6 mmol) at 0 °C. After stirring for 10 min, *p*-methoxybenzyl chloride (83 μL, 0.6 mmol) was added via micro syringe, and the reaction mixture was stirred at room temperature for an additional 2 h. The reaction was quenched by H_2O and extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 10/1) to afford **3m** as a pale yellow solid. Yield: 89% (199 mg); Eluent: *n*-hexane/ethyl acetate = 10/1 ; Pale yellow solid; mp: 130−132 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, J = 7.1 Hz, 3H), 3.76 (s, 3H), 3.93−4.04 (m, 1H), 4.06−4.17 (m, 1H), 5.12 (d, J = 15.9 Hz, 1H), 5.56 (d, J = 15.9 Hz, 1H), 6.00 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 8.2 Hz, 3H), 7.17−7.26 (m, 2H), 7.35−7.49 (m, 3H), 7.88 (d, J = 7.5 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 44.8, 55.4, 61.5, 113.9 (113.85), 113.9 (113.91), 123.9, 124.5, 127.6, 128.4, 128.5, 129.2, 130.0, 130.3, 132.7, 133.4, 135.0, 135.9, 137.6, 141.1, 158.9, 165.8, 169.1 ppm; HRMS (EI) m/z Cal. for $[M]^+$: $C_{26}H_{22}{}^{35}ClNO_4$: 447.1237. Found: 447.1237; Cal. For $[M+2]^+$: $C_{26}H_{22}{}^{37}ClNO_4$: 449.1208; Found: 449.1236.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02095.

Copies of ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

X-ray crystallographic data of **2a** (CIF)

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Notes

The authors declare no competing financial interest.

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