JOC The Journal of Organic Chemistry

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pubs.acs.org/joc

Synthesis of Isoindolinones by Pd-Catalyzed Coupling between *N*-Methoxybenzamide and Styrene Derivatives

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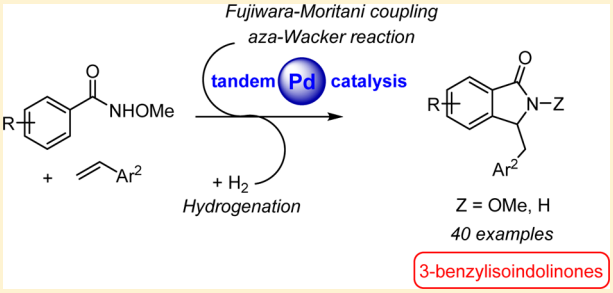
Supporting Information

ABSTRACT: An atom-economical protocol for a tandem process involving Fujiwara–Moritani–aza-Wacker reactions has been developed for the Pd-catalyzed coupling between *N*-methoxy benzamide and styrene derivatives. The generality of the methodology was demonstrated by the synthesis of a library of 25 3-benzylidene isoindolinones in moderate to good yields. A further 40 3-benzyl derivatives were obtained by telescoping the process with a catalytic hydrogenation reaction.



INTRODUCTION

3-Benzyl-substituted-isodolinones (**I**) constitute a family of privileged pharmacophores (Figure 1) with significant therapeutic potential, such as glycine transporter (GlyT1) inhibitors (Abbvie)[1] and aldosterone synthase (CYP11B2 or CYP11B1) inhibitors (Hoffmann-la Roche).[2] The substructure is also found in many natural products, including isoindolobenzazepine alkaloids (e.g., lennoxamine[3]) and aristolactam alkaloids (including piperolactams[4]), known to have potent antitumor activities.[5]

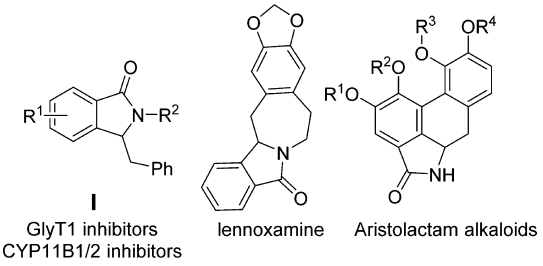
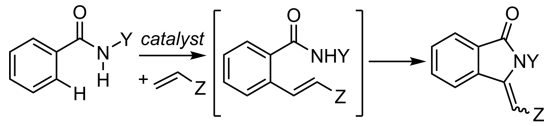


Figure 1. Biologically active 3-benzyl-substituted isoindolinones (**I**) and natural products containing the substructure.

Conceptually, structure **I** can be constructed in two steps: By a Fujiwara–Moritani (FM) reaction between benzamide and styrene derivatives, followed by an intramolecular aza-Wacker reaction (Scheme 1); the resultant product **2** can then be subjected to catalytic hydrogenation to yield the target structure. The FM reaction between a benzamide derivative and an alkene can be achieved using Rh,[6] Ru,[7] or Ir[8] catalysts. However, with these catalysts, the reaction terminates at the formation of the acyclic compound (**1**). In contrast, both reactions can be effected in tandem under Pd catalysis to give the *N*-heterocycle **2** as the final product. This was first reported independently by the research groups of Wrigglesworth et al.[9]

Scheme 1. Proposed Route for Assembling I



and Li et al. in 2011,[10] when $Pd(OAc)_2$ was used to catalyze the coupling between *N*-methoxybenzamides with activated alkenes containing electron-withdrawing substituents, that is, Z = CO_2R, $CONR_2$, SO_2Ph, or COR. One example using styrene as the alkene reactant was reported to afford the 2-benzylidene derivative (Z = Ph, **2aa**) in a moderate yield (≤50%); notably, no further examples of other conjugated alkenes were provided. In this work, we have modified the catalytic protocol to widen the scope of this methodology to a wide range of styrene derivatives (Z = Ar), with the aim of synthesizing a library of 3-benzyl substituted isoindolinones (analogues of compound **I**) for biological evaluation (Scheme 2).

RESULTS AND DISCUSSION

N-Methoxybenzamide and styrene were initially employed as model substrates in the evaluation of reaction parameters (Table 1). Following the reported procedure by Li et al.,[10] palladium(II) acetate was employed as a catalyst precursor with 2 equiv of the oxidant (benzoquinone, BQ), and the reaction was performed in acetic acid at 100 °C. This afforded the expected product **2aa** in 27% yield (entry 1). This was lower than the reported yields of 46%, which may be due to the prolonged reaction time (48 h vs 10 h). Subsequent studies at lower reaction temperatures did not lead to any improvement (entry 2), and the addition of TFA only has a marginally

Received: July 14, 2016
Published: August 5, 2016

DOI: 10.1021/acs.joc.6b01696
J. Org. Chem. 2016, 81, 7931–7938

Scheme 2. Modification of the Tandem FM–aza-Wacker Reactions for the Synthesis of I

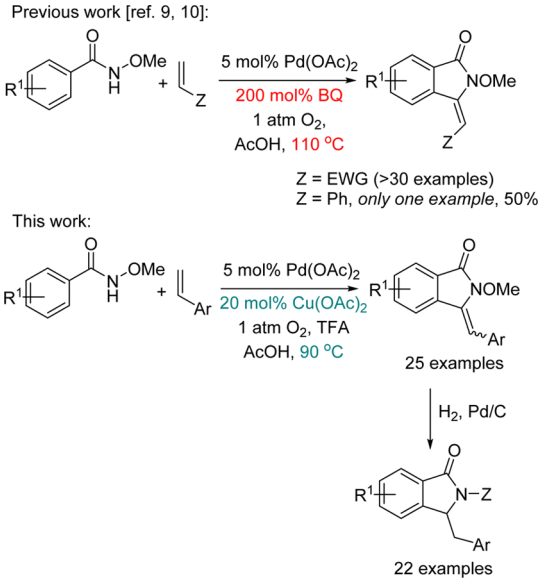
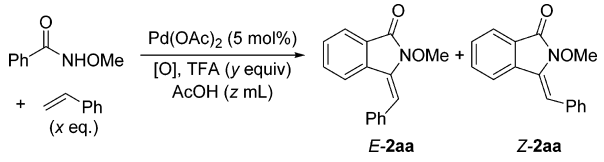


Table 1. Initial Evaluation of Reaction Parameters[a]



entry	[O][b]	x	y	z	T (°C)	t (h)	yield[c] (%)
1	BQ (2)	2		3	100	48	27
2	BQ (2)	2		3	80	48	30
3	BQ (2)	2	1	3	70	48	34
4	BQ (2.5)	3	1	3	70	48	69
5	BQ (2.5)	3	1	1.5	70	24	66
6	BQ (1), O_2	2	1	3	70	48	34
7	$Cu(OAc)_2$ (0.2), O_2	3	1	1.5	80	24	48
8	$Cu(OAc)_2$ (0.2), O_2	3	1	1.5	90	24	60
9	$Cu(OAc)_2$ (0.2), O_2	3		1.5	90	24	44
10	$Cu(OAc)_2$ (0.2), O_2	3	1	1.5	100	24	50

[a]General conditions: Reactions were performed using *N*-methoxybenzamide as the limiting reagent (0.3 mmol). More results are listed in Table S1 (Supporting Information). [b]Equivalents indicated in parentheses. [c]Isolated yield after column chromatography.

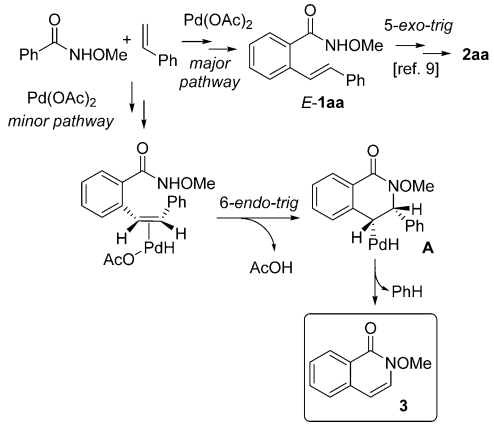
beneficial effect under these conditions (entry 3). By increasing the amount of oxidant and styrene, the product yield may be improved (entry 4), which also allowed the reaction time to be shortened (entry 5).

Notably, an attempt to lower the amount of oxidant from 2 equiv to 1 equiv adversely affected the reaction, even in the presence of O_2 (entry 6); that is, we were unable to replicate the 50% yield achieved by using 20 mol % of BQ, as reported by Wrigglesworth et al.[9] The need to use an excess of BQ is a significant issue; apart from poor atom-economy, benzoquinone is also genotoxic,[11] which may interfere with subsequent biological testing should any residue remain in the product. Therefore, although a reasonable yield (69%) can be achieved using this oxidant, it was decided that a safer alternative should be sought. With this in mind, a number of more benign oxidants were evaluated, including potassium and ammonium persulfates, as well as *tert*-butyl perbenzoate (Table S1, Supporting Information). The use of these strong oxidants was found to be incompatible with the benzamide substrates, causing them to decompose at temperatures >50 °C. After some further investigation, we were able to identify O_2/20 mol % $Cu(OAc)_2$ as a good replacement for benzoquinone, delivering **2aa** at a slightly elevated temperature of 90 °C (entries 7–8); in this case, the beneficial effect of TFA was more pronounced (entries 8 vs 9), because it suppressed the competitive hydrolysis of *N*-methoxybenzamide under these conditions.

In earlier work,[9,10] **2aa** was reported to be formed exclusively as an *E*-isomer. In the present study, however, it was obtained as a mixture of isomers, irrespective of the oxidant or reaction conditions, typically in a ratio of approximately 2:1. This was established by integrating the methoxy proton resonance at 4.1 and 3.5 ppm, respectively. The configuration isomers were subsequently separated by column chromatography, and the *E*-configuration of the major isomer was confirmed by X-ray crystallography (Figure S1, Supporting Information). In the solid state structure, the pendant phenyl is twisted out-of-plane from the isoindolinone ring, in order to avoid unfavorable interactions between the *ortho* H's.

Under these reaction conditions, polymerization of styrene is a minor competitive process. However, the NMR spectrum of the reaction mixture contained additional resonance peaks, indicating the presence of a persistent side product (ca. 20%), identified by a distinct ^{1}H NMR singlet signal at 8.51 ppm. A small amount of this impurity was isolated. Its ^{1}H NMR spectrum, with the accompanying mass ion (MH^+) of 176, is consistent with the formation of the six-membered *N*-methoxy isoquinolinone **3** (Scheme 3).[12] The formation of this

Scheme 3. Competitive Formation of Side Product 3

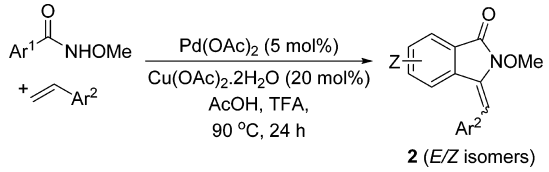


unexpected side product is attributed to the formation of the minor *Z*-isomer of **1aa**, which undergoes 6-*endo*-*trig* cyclization in the subsequent aza-Wacker reaction (*anti*-addition). In the absence of an accessible *β*-hydride, the putative intermediate (**A**) undergoes a *syn*-coplanar *β*-phenyl elimination to afford compound **3**. Such *β*-aryl elimination processes involving C–C cleavage are rare, known only to occur in reactions involving sterically bulky arylmethanols.[13]

Next, the generality of the catalytic methodology was tested. Using the new protocol, a small library of 25 new 3-benzylidene isoindolinone derivatives was constructed from readily available benzamide and styrene derivatives (Table 2). Reaction yields are moderate to good, ranging between 49% and 72%. In

DOI: 10.1021/acs.joc.6b01696
J. Org. Chem. 2016, 81, 7931–7938

Table 2. Tandem Reaction between *N*-Methoxybenzamide and Styrene Derivatives[a]



2 (*E*/*Z* isomers)

entry	Ar^1, Ar^2	product	yield[b] (%)	*E*/*Z*
1	Ph, Ph	**2aa**[c]	60	2/1
2	Ph, 4-Cl-Ph	**2ab**[c]	68	2.1/1
3	Ph, 4-F-Ph	**2ac**	53	2/1
4	Ph, 4-Me-Ph	**2ad**	53	5/1
5	Ph, 2-Nap	**2ae**	59	2.3/1
6	Ph, 4-CF_3-Ph	**2af**	72	2.4/1
7	4-Me-Ph, Ph	**2da**	63	1.9/1
8	4-Me-Ph, 4-Cl-Ph	**2db**[c]	61	1.9/1
9	4-Me-Ph, 4-F-Ph	**2dc**	71	1.5/1
10	4-Me-Ph, 4-Me-Ph	**2dd**	65	1.9/1
11	4-Me-Ph, 2-Nap	**2de**	66	3.5/1
12	4-Me-Ph, 4-CF_3-Ph	**2df**	70	1.8/1
13	2-Me-Ph, Ph	**2ga**	69	2.7/1
14	2-Me-Ph, 4-Cl-Ph	**2gb**[c]	62	3.1/1
15	2-Me-Ph, 4-Me-Ph	**2gd**	58	2.9/1
16	2-Me-Ph, 2-Nap	**2ge**	68	3.5/1
17	2-Me-Ph, 4-CF_3-Ph	**2gf**	59	2.5/1
18	2-MeO-Ph, Ph	**2ha**	58	4.3/1
19	2-MeO-Ph, 4-Cl-Ph	**2hb**[c]	63	3.1/1
20	2-MeO-Ph, 4-Me-Ph	**2hd**	52	4.2/1
21	2-MeO-Ph, 2-Nap	**2he**	48	3.7/1
22	4-MeO-Ph, 4-Cl-Ph	**2ib**[c]	49	1.9/1
23	4-MeO-Ph, 4-Me-Ph	**2id**	55	1.7/1
24	4-MeO-Ph, 4-CF_3-Ph	**2if**	46	1.8/1
25	4-CF_3-Ph, 4-Cl-Ph	**2jb**[c]	17	1/0

[a]Reaction conditions: *N*-methoxybenzamide (0.3 mmol, 1 equiv), styrene (0.9 mmol, 3 equiv), $Pd(OAc)_2$ (0.015 mmol, 5 mol %), $Cu(OAc)_2{\cdot}_2H_2O$ (0.06 mmol, 20 mol %), acetic acid (1.5 mL), trifluoroacetic acid (TFA, 0.3 mmol, 1 equiv), O_2 balloon, 90 °C. [b]Isolated yield obtained after column chromatography. [c]Characterized by NMR spectroscopy after column chromatography.

general, better yields were obtained with styrene derivatives bearing electron-withdrawing substituents. Again, in all cases, a mixture of *E*/*Z*-isomers was obtained, typically in a 2:1 ratio in favor of the *E*-isomer. The *E*-configuration is favored when 2-methyl- or 2-methoxy-substituted *N*-methoxy-benzamides (entries 13−21) were used as substrates; particularly in combination with 2-vinyl naphthalene (entries 5, 11, 16, and 21).

In some cases, the *E*/*Z* isomers may be separated by column chromatography for characterization purposes (these include **2aa**, **2ab**, **2db**, **2gb**, **2hb**, **2ib**, and **2jb**). In other cases, the isomeric mixture was directly subjected to hydrogenation reactions over Pd/C in a telescoped process, affording 22 novel 3-benzyl-substituted isoindolinones (Figure 2). The hydrogenation reaction is known to proceed well in high yields for similar benzylideneisoindolidinones, when the exocyclic alkene contains an electron-withdrawing ester group.[9,14] In the present case, the reduction of aryl-substituted **2** required slightly elevated temperatures of between 40 and 50 °C. This was attributed to the twisted alkene moiety observed in the X-ray crystal structure (See Supporting Information), sterically

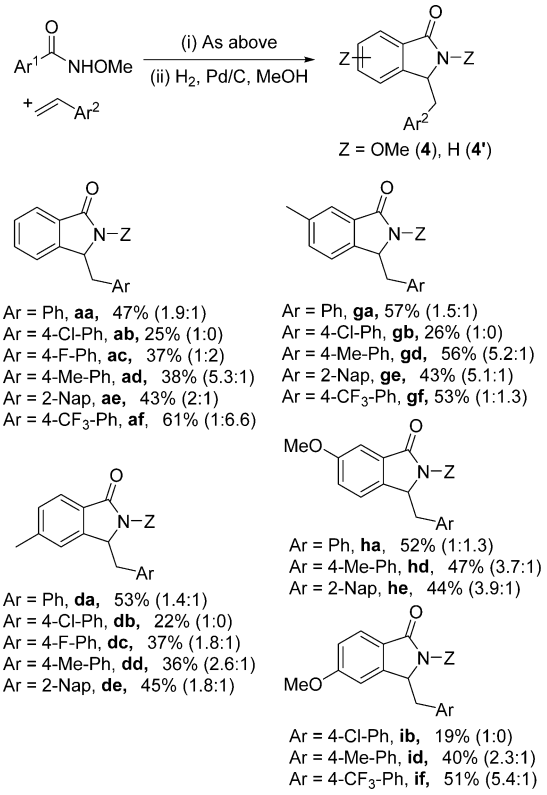


Figure 2. Reduced isoquinolines synthesized via telescoped steps (reported yields were calculated over two steps). Ratio of **4**/**4′** is indicated in parentheses.

hindering the accessibility to surface-adsorbed hydrides. Under these conditions, the substrate may be reduced further to the *N*-demethoxylated product **4′**. Interestingly, the outcome of the catalytic hydrogenation process is rather dependent upon the nature of the pendant aryl group. Notably, **4′** was obtained as the major product when the aryl group contains fluorinated substituents. The yields of chloro-substituted compounds (**4ab**, **4gb**, **4db**, and **4ib**) were also affected by the competitive dehalogenation of the chloride during the catalytic hydrogenation process. In this part of the work, X-ray crystallographic structures of reduced **4aa** and **4aa′** were obtained (Figures S2 and S3, Supporting Information), providing additional information on their structure features that may be useful for fragment-based discovery.

■ CONCLUSION

The scope of the Pd-catalyzed tandem Fujiwara−Moritani (FM)−intramolecular aza-Wacker cyclization has been substantially expanded to styrene derivatives, replacing the use of excess genotoxic benzoquinone by benign O_2, in the presence of $Cu(OAc)_2$ as cocatalyst. By telescoping the process with catalytic hydrogenation, we could prepare a series of 3-benzyl-substituted isoindolinones from readily available *N*-methoxybenzamide and styrene derivatives in two synthetic operations. The methodology has good generality, providing access to >60 novel isoindolinone structures containing either a benzylidene or a benzyl substituent at position-3.

■ EXPERIMENTAL SECTION

General Experimental Methods. Unless otherwise stated, all precursors were obtained from commercial suppliers and used as

DOI: 10.1021/acs.joc.6b01696
J. Org. Chem. 2016, 81, 7931−7938

received without purification. Solvents were dried by passing through the columns of molecular sieves in a solvent purification system. All reactions were carried out in oven-dried glassware. Reaction temperatures are reported as the temperature of the bath/heating block surrounding the vessel unless otherwise stated. Analytical thin layer chromatography was performed on silica plates. Visualization was accomplished with UV light (254 nm) or $KMnO_4$ staining solutions followed by heating. Column chromatography was performed on flash silica gel (40−63 mesh). ^1H and ^{13}C NMR spectra were recorded at ambient temperature (25 °C) on spectrometers. Residual protic solvents were used as an internal standard and ^{13}C resonances were referenced to the deuterated carbon. Chemical shifts (δ) are reported in ppm. Monoisotopic values for chlorinated compounds were reported and calculated using the major isotope (^{35}Cl).

Single crystals of *E*-**2aa**, **4aa**, and **4′aa** suitable for X-ray crystallography were obtained as needles by recrystallization from EtOAc and hexane at room temperature. Selected crystals were centered on the mounting, and X-ray crystal structural data were collected using a diffractometer equipped with a CCD detector and a graphite monochromated Mo Kα radiation (λ = 0.71073 Å). The data collection routine, unit cell refinement, and data processing were carried out with the program CrysAlis.[15] Structures were solved by the direct method and refined by full-matrix least-squares methods with SHELXL-97 programs.[16] X-ray crystal data and structure refinement parameters are listed in Table S2 (Supporting Information). The data were deposited at the CCDC database, with the reference numbers 1472315−1472317 for *E*-**2aa**, **4aa**, and **4′aa**, respectively.

N-Methoxy benzamide derivatives (precursors for the catalytic reaction) were prepared from commercially available benzoyl chloride and *O*-methylhydroxylamine, by a published procedure.[17] The characterization data of these compounds are entirely consistent with the literature values.[17]

General Procedure for the Tandem Fujiwara−Moritani−aza-Wacker Reaction. A reduced volume Radley's reaction tube was charged with a stir bar, the appropriate styrene (0.9 mmol, 3 equiv) and *N*-methoxybenzamide (0.3 mmol, 1 equiv) derivative, $Pd(OAc)_2$ (0.05 equiv), $Cu(OAc)_2{\cdot}2H_2O$ (0.2 equiv), and acetic acid (1.5 mL) at room temperature. The tube was evacuated briskly under vacuum and recharged with oxygen three times. The O_2 atmosphere in the tube was maintained by connecting a balloon of O_2 to the reaction tube through a needle pierced through the septum. The reaction vessel was then placed in an aluminum heating block heated to 90 °C and stirred. The reaction was monitored by TLC until the starting material was consumed. The reaction mixture was concentrated under vacuum, and the residue was subjected directly to column chromatography using petroleum ether/EtOAc (6/1) as the eluent. A selection of the *Z*- and *E*-isomer may be collected as separate fractions for characterization purposes or as a combined fraction for the telescoped process.

The reaction can be successfully replicated on a larger scale using *N*-methoxybenzamide (136 mg, 0.9 mmol, 1 equiv), styrene (281 mg, 2.7 mmol, 3 equiv), $Pd(OAc)_2$ (0.05 equiv), $Cu(OAc)_2{\cdot}2H_2O$ (0.2 equiv), TFA (1 equiv), and acetic acid (4.5 mL). Following column chromatography, 43 mg (19%) of the *Z*-isomer and 91 mg (40%) of the *E*-isomer were isolated separately.

Catalytic Hydrogenation of 2 to 4. A mixture of *Z*/*E*-**2** was dissolved in anhydrous methanol (10 mL) in a Radley's reaction tube. Pd/C (10 wt %) was added to this mixture before the system was then sealed with a cap and a balloon of hydrogen attached via a needle pierced through the septum. The reaction vessel was placed in the aluminum block, and the mixture was stirred and heated between 40 and 50 °C for 2 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated to give a yellow solid, which was then purified by flash column chromatography (petroleum ether/EtOAc, 4/1).

(*Z*)-3-Benzylidene-2-methoxyisoindolin-1-one, *Z*-2aa. Light yellow solid (15 mg, 0.059 mmol, 20%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.87−7.84 (m, 1H), 7.75−7.72 (m, 1H), 7.62 (td, 1H, *J* = 7.6 Hz, 1.2 Hz), 7.59−7.54 (m, 2H), 7.50 (td, 1H, *J* = 7.5, 1.0 Hz), 7.39−7.34 (m, 2H), 7.34−7.27 (m, 1H), 6.70 (s, 1H), 3.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 162.8, 134.6, 133.2, 132.5, 130.3, 129.5, 129.3, 127.9, 127.8, 126.0, 123.5, 119.5, 107.0, 63.4. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}H_{14}NO_2$ 252.1024; Found 252.1046; $[M + H + CH_3CN]^+$ Calcd for $C_{18}H_{17}N_2O_2$ 293.1290; Found 293.1334.

(*E*)-3-Benzylidene-2-methoxyisoindolin-1-one, *E*-2aa. Previously reported either as a slightly yellow oil[9] or a pale yellow solid.[10] In this work, it is isolated as a colorless solid (30 mg, 0.12 mmol, 40%), mp 133−134 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.86−7.81 (m, 1H), 7.50−7.34 (m, 8H), 6.76 (s, 1H), 4.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 161.0, 134.5, 132.0, 131.8, 131.4, 129.6, 129.5, 128.8, 128.1, 127.9, 123.4, 123.0, 110.1, 64.3. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}H_{14}NO_2$ 252.1024; Found 252.1029; $[M + H + CH_3CN]^+$ Calcd for $C_{18}H_{17}N_2O_2$ 293.1290; Found 293.1292.

(*Z*)-3-(4-Chlorobenzylidene)-2-methoxyisoindolin-1-one, *Z*-2ab. Light yellow solid (19 mg, 0.067 mmol, 22%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.90−7.84 (m, 1H), 7.74−7.71 (m, 1H), 7.64 (td, 1H, *J* = 7.6, 1.2 Hz), 7.54−7.48 (m, 2H), 7.38−7.30 (m, 4H), 6.62 (s, 1H), 3.51 (s, 3H). Insufficient quantity obtained for ^{13}C NMR spectroscopy. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}H_{13}NO_2Cl$ 286.0634; Found 286.0635.

(*E*)-3-(4-Chlorobenzylidene)-2-methoxyisoindolin-1-one, *E*-2ab. Light yellow solid (40 mg, 0.139 mmol, 46%), mp 110−111 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.86−7.83 (m, 1H), 7.51−7.37 (m, 7H), 6.67 (s, 1H), 4.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 161.1, 134.0, 133.0, 132.4, 132.2, 131.2, 130.9, 129.9, 129.1, 128.0, 123.6, 122.9, 108.5, 64.4. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}NO_2H_{13}Cl$ 286.0634; Found 286.0630; $[M + H + CH_3CN]^+$ Calcd for $C_{18}H_{16}N_2O_2Cl$ 327.0900; Found 327.0910.

(*Z*)-3-(4-Chlorobenzylidene)-2-methoxy-5-methyl-isoindolin-1-one, *Z*-2db. Light yellow solid (28 mg, 0.093 mmol, 31%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, 1H, *J* = 7.9 Hz), 7.53−7.46 (m, 3H), 7.35−7.30 (m, 3H), 6.58 (s, 1H), 3.48 (s, 3H), 2.50 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 163.1, 143.5, 134.8, 133.6, 131.9, 131.6, 130.9, 130.63, 130.2, 129.0, 128.1, 123.6, 119.9, 105.0, 63.3, 22.3. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{17}H_{15}NO_2Cl$300.0791; Found 300.0800; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{18}N_2O_2Cl$ 341.1056; Found 341.1052.

(*E*)-3-(4-Chlorobenzylidene)-2-methoxy-5-methyl-isoindolin-1-one, *E*-2db. Light yellow solid (36 mg, 0.120 mmol, 40%), mp 137−139 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.73 (dd, 1H, *J* = 7.5, 0.9 Hz), 7.45−7.38 (m, 4H), 7.29−7.26 (m, 2H), 6.62 (s, 1H), 4.08 (s, 3H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 161.3, 143.0, 133.9, 133.1, 132.5, 131.5, 130.9, 129.9, 128.1, 125.4, 123.5, 123.4, 123.3, 108.2, 22.3. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{17}H_{15}NO_2Cl$ 300.0791; Found 300.0779; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{18}N_2O_2Cl$ 341.1056; Found 341.1057.

(*Z*)-3-(4-Chlorobenzylidene)-2-methoxy-6-methyl-isoindolin-1-one, *Z*-2gb. Light yellow solid (13 mg, 0.043 mmol, 15%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.67−7.68 (m, 1H), 7.62−7.59 (m, 1H), 7.51−7.47 (m, 2H), 7.45−7.42 (m, 1H), 7.35−7.30 (m, 2H), 6.55 (s, 1H), 3.49 (s, 3H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 163.1, 140.1, 133.7, 133.6, 131.9, 131.6, 130.2, 128.1, 126.1, 123.8, 119.4, 104.8, 63.3, 21.7. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{17}H_{15}NO_2Cl$ 300.0791; Found 300.0800; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{18}N_2O_2Cl$ 341.1056; Found 341.1055.

(*E*)-3-(4-Chlorobenzylidene)-2-methoxy-6-methyl-isoindolin-1-one, *E*-2gb. Light yellow solid (42 mg, 0.14 mmol, 47%), mp 141−142 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, 1H, *J* = 2.7 Hz), 7.45−7.32 (m, 5H), 7.20 (dd, 1H, *J* = 8.1, 1.8 Hz), 6.61 (s, 1H), 4.09 (s, 3H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 161.3, 140.5, 133.8, 133.2,133.1, 132.5, 130.9, 129.0, 128.6, 128.1, 123.8, 122.8, 107.6, 64.3, 21.7. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{17}NO_2H_{15}Cl$ 300.0791; Found 300.0807; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{18}N_2O_2Cl$ 341.1056; Found 341.1083.

(*Z*)-3-(4-Chlorobenzylidene)-2,6-dimethoxy-isoindolin-1-one, *Z*-2hb. Light yellow solid (14 mg, 0.044 mmol, 15%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.63−7.59 (m, 1H), 7.50−7.46 (m, 2H), 7.35−7.30 (m, 3H), 7.17 (dd, 1H, *J* = 8.5, 2.5 Hz), 6.50 (s, 1H), 3.89 (s, 3H), 3.49 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 163.0, 161.2, 133.5, 131.9, 131.6, 130.0, 128.1, 127.5, 127.0, 121.1, 121.0, 106.3,

DOI: 10.1021/acs.joc.6b01696
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104.5, 63.4, 56.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}NO_3Cl$ 316.0740; Found 316.0727; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{18}N_2O_3Cl$ 357.1006; Found 357.0928.

(*E*)-3-(4-Chlorobenzylidene)-2,6-dimethoxy-isoindolin-1-one, *E*-2hb. Light yellow solid (45 mg, 0.145 mmol, 49%), mp 109−110 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39−7.34 (m, 5H), 7.30 (d, 1H, J = 2.6 Hz), 6.91 (dd, 1H, J = 8.6, 2.5 Hz), 6.55 (s, 1H), 4.08 (s, 3H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 161.2, 161.1, 133.7, 133.2, 132.3, 130.8, 129.7, 129.9, 124.3, 123.7, 119.9, 107.0, 106.6, 64.4, 55.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}NO_3Cl$ 316.0740; Found 316.0735; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{18}N_2O_3Cl$ 357.1006; Found 357.1006.

(Z)-3-(4-Chlorobenzylidene)-2,5-dimethoxy-isoindolin-1-one, Z-2ib. Light yellow solid (16 mg, 0.051 mmol, 17%), mp 140−141 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.80−7.75 (m, 1H), 7.53−7.47 (m, 2H), 7.36−7.31 (m, 2H), 7.18−7.16 (m, 1H), 7.04 (dd, 1H, J = 8.4, 2.2 Hz), 6.56 (s, 1H), 3.93 (s, 3H), 3.48 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 163.8, 163.1, 136.8, 133.7, 131.8, 131.6, 130.3, 128.2, 125.4, 118.7, 116.5, 108.9, 105.1, 104.2, 63.2, 56.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}NO_3Cl$ 316.0740; Found 316.0725; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{18}N_2O_3Cl$ 357.1006; Found 357.0992.

(*E*)-3-(4-Chlorobenzylidene)-2,5-dimethoxy-isoindolin-1-one, *E*-2ib. Light yellow solid (30 mg, 0.095 mmol, 32%), mp 151−153 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.79−7.73 (m, 1H), 7.45−7.38 (m, 4H), 7.01−6.92 (m, 2H), 6.63 (s, 1H), 4.08 (s, 3H), 3.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 163.1, 161.4, 134.0, 133.3, 133.1,132.7, 131.6, 130.9, 129.0, 128.1, 125.2, 120.5, 116.1, 108.3, 108.2, 64.3, 55.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}NO_3Cl$ 316.0740; Found 316.0727; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{18}N_2O_3Cl$ 357.1006; Found 357.0990.

(*E*)-3-(4-Chlorobenzylidene)-5-trifluoromethyl-2-methoxy-isoindolin-1-one, *E*-2jb. Colorless solid (18 mg, 0.051 mmol, 17%), mp 147−149 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.99−7.97 (m, 1H), 7.79−7.71 (m, 2H), 7.48−7.40 (m, 4H), 6.80 (s, 1H), 4.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 159.6, 134.8, 134.3, 133.9, 132.2, 131.5, 131.3, 130.9, 130.7, 129.3, 126.8, 126.8, 126.8, 126.7, 124.2, 120.1, 120.1, 120.0, 120.0, 110.5, 64.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{12}NO_2ClF_3$ 354.0508; Found 354.0501; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{15}N_2O_2ClF_3$ 395.0774; Found 395.0730.

3-Benzyl-3-hydro-2-methoxy-isoindolin-1-one, 4aa. Colorless solid (24 mg, 0.094 mmol, 31%), mp 94−95 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.75−7.72 (m, 1H), 7.47−7.36 (m, 2H), 7.26−7.18 (m, 3H), 7.13−7.08 (m, 2H), 6.99−6.96 (m, 1H), 4.98 (dd, 1H, J = 7.6, 4.4 Hz), 3.99 (s, 3H), 3.45 (dd, 1H, J = 13.8, 4.4 Hz), 3.02 (dd, 1H, J = 13.8, 7.6 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.6, 141.6, 135.5, 131.7, 130.1, 129.8, 128.5, 128.5, 127.1, 123.8, 123.1, 63.9, 60.4, 37.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{16}NO_2$ 254.1181; Found 254.1181.

3-Benzyl-2,3-dihydro-isoindolin-1-one, 4′aa. Colorless solid (11 mg, 0.049 mmol, 16%), mp 134−135 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.83 (dt, 1H, J = 7.3, 1.0 Hz), 7.53 (td, 1H, J = 7.5, 1.3 Hz), 7.46 (td, 1H, J = 7.4, 1.0 Hz), 7.34−7.28 (m, 3H, Ar−H), 7.27 (d, 2H, J = 6.6 Hz), 7.20 (d, 1H, J = 1.4 Hz), 7.08 (br s, 1H, NH), 4.81 (dd, 1H, J = 8.5, 5.5 Hz), 3.18 (dd, 1H, J = 13.6, 5.5 Hz), 2.87 (dd, 1H, J = 13.6, 8.5 Hz).^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.6, 146.9, 137.0, 132.1, 131.8, 129.4, 128.9, 128.4, 127.2, 123.9, 122.8, 58.1, 41.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{14}NO$ 224.1075; Found 224.1079; $[M + H + CH_3CN]^+$ Calcd for $C_{17}H_{17}N_2O$ 265.1341; Found 265.1236.

3-(4-Chlorobenzyl)-3-hydro-2-methoxy-isoindolin-1-one, 4ab. Colorless solid (22 mg, 0.076 mmol, 25%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.72−7.69 (m, 1H), 7.47 (td, 1H, J = 7.5, 1.3 Hz), 7.39 (ddd, 1H, J = 8.2, 7.5, 1.0 Hz), 7.18−7.06 (m, 3H), 7.02−6.95 (m, 2H), 4.97 (dd, 1H, J = 6.8, 4.2 Hz), 3.98 (s, 3H), 3.33 (dd, 1H, J = 13.9, 4.2 Hz), 3.11 (dd, 1H, J = 13.9, 6.8 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.4, 141.1, 133.5, 132.9, 131.8, 131.2, 130.1, 128.7, 128.5, 123.9, 122.9,63.8, 59.8, 36.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{15}NO_2Cl$ 288.0791; Found 288.0782; $[M + H + CH_3CN]^+$ Calcd for $C_{18}H_{18}N_2O_2Cl$ 329.1057; Found 329.1043.

3-(4-Fluorobenzyl)-3-hydro-2-methoxy-isoindolin-1-one, 4ac. Colorless solid (10 mg, 0.036 mmol, 12%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.72 (dt, 1H, J = 7.5, 1.0 Hz), 7.47 (td, 1H, J = 7.5, 1.3 Hz), 7.40−7.37 (m, 1H), 7.09−7.06 (m, 1H), 7.02−6.99 (m, 2H,), 6.90−6.84 (m, 2H), 4.97 (dd, 1H, J = 6.8, 4.2 Hz), 3.99 (s, 3H), 3.35 (dd, 1H, J = 14.0, 4.2 Hz), 3.12 (dd, 1H, J = 14.0, 6.8 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.5, 162.0 (d, J = 254 Hz), 141.3, 131.6 (d, J = 8.0 Hz), 131.3, 130.7, 130.2, 128.7, 123.9, 122.9, 115.3 (d, J = 22 Hz), 63.8, 60.0, 36.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{15}NO_2F$ 272.1086; Found 272.1086; $[M + H + CH_3CN]^+$ Calcd for $C_{18}H_{18}N_2O_2F$ 313.1352; Found 313.1275.

3-(4-Fluorobenzyl)-2,3-dihydro-isoindolin-1-one, 4′ac. Colorless solid (18 mg, 0.075 mmol, 25%), mp 147−149 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.81 (dt, 1H, J = 7.5, 1.0 Hz, Ar−H), 7.54 (td, 1H, J = 7.5, 1.3 Hz, Ar−H), 7.50−7.43 (m, 1H, F Ar−H), 7.38 (d, 1H, J = 6.0 Hz, Ar−H), 7.29−7.26 (m, 1H), 7.17−7.10 (m, 2H), 7.01−6.92 (m, 2H), 4.97−4.67 (m, 1H), 3.15 (dd, 1H, J = 13.7, 5.6 Hz), 2.90 (dd, 1H, J = 13.7, 7.9 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.9, 162.0 (d, J = 245 Hz), 146.7, 132.4 (d, J = 3.2 Hz), 132.1, 131.8, 131.0 (d, J = 8.1 Hz), 128.5, 124.0, 122.8, 115.6 (d, J = 21.6 Hz), 58.0, 40.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{13}NOF$ 242.0981; Found 242.0983; $[M + H + CH_3CN]^+$ Calcd for $C_{17}H_{16}N_2OF$ 283.1247; Found 283.1242.

3-Hydro-2-methoxy-3-(4-methylbenzyl)-isoindolin-1-one, 4ad. Colorless solid (26 mg, 0.097 mmol, 32%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.73 (ddd, 1H, J = 7.3, 1.5, 0.8 Hz), 7.47−7.34 (m, 2H), 7.05−6.95 (m, 5H), 4.95 (dd, 1H, J = 7.7, 4.3 Hz), 3.98 (s, 3H), 3.41 (dd, 1H, J = 13.8, 4.3 Hz), 2.96 (dd, 1H, J = 13.8, 7.7 Hz), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.5, 141.7, 136.6, 132.2, 131.7, 130.0, 129.6, 129.1, 128.4, 123.7, 123.1, 63.9, 60.4, 37.3, 21.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}NO_2$ 268.1337; Found 268.1328.

2,3-Dihydro-3-(4-methylbenzyl)-isoindolin-1-one, 4′ad. Colorless solid (4 mg, 0.017 mmol, 6%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.85−7.82 (m, 1H), 7.56 (td, 1H, J = 7.5, 1.2 Hz), 7.49−7.46 (m, 1H), 7.37−7.34 (m, 1H), 7.18−7.10 (m, 4H), 6.33 (br s, 1H), 4.76 (dd, 1H, J = 9.4, 4.9 Hz), 3.22 (dd, 1H, J = 13.6, 4.9 Hz), 2.72 (dd, 1H, J = 13.6, 9.4 Hz), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.4, 147.0, 137.0, 134.0, 131.9, 129.7, 129.2, 128.5, 124.1, 122.8, 58.3, 41.2, 21.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{16}NO$ 238.1231; Found 238.1237; $[M + H + CH_3CN]^+$ Calcd for $C_{18}H_{19}N_2O$ 279.1497; Found 279.1386.

3-Hydro-2-methoxy-3-(2-naphthylmethyl)-isoindolin-1-one, 4ae. Colorless solid (27 mg, 0.088 mmol, 29%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.83−7.77 (m, 1H), 7.76−7.71 (m, 3H), 7.60−7.56 (m, 1H), 7.48−7.40 (m, 2H), 7.40−7.34 (m, 2H), 7.31−7.23 (m, 1H), 6.98−6.94 (m, 1H), 5.07 (dd,1H, J = 7.8, 4.4 Hz), 4.01 (s, 3H), 3.63 (dd, 1H, J = 13.9, 7.8 Hz), 3.14 (dd, 1H, J = 13.8, 7.8 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.6, 141.6, 133.4, 133.1, 132.5, 131.8, 130.0, 128.6, 128.6, 128.2, 127.8, 126.2, 125.8, 123.8, 123.2, 63.9, 60.3, 38.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{18}NO_2$ 304.1337; Found 304.1330.

2,3-Dihydro-3-(2-naphthylmethyl)-isoindolin-1-one, 4′ae. Colorless solid (12 mg, 0.043 mmol, 14%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.84 (ddd, 3H, J = 8.2, 3.2, 2.1 Hz), 7.80−7.74 (m, 1H), 7.70−7.66 (m, 1H), 7.59−7.45 (m, 4H), 7.37 (ddd, 2H, J = 7.5, 4.5, 1.4 Hz), 6.73 (br s, 1H), 4.89 (dd, 1H, J = 9.1, 5.1 Hz), 3.38 (dd, 1H, J = 13.6, 5.1 Hz), 2.95 (dd, 1H, J = 13.6, 9.1 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.5, 147.0, 134.6, 133.6, 132.6, 132.0, 131.9, 128.8, 128.5, 128.1, 127.8, 127.7, 127.2, 126.5, 126.0, 124.1, 122.8, 58.1, 41.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{16}NO$ 274.1231; Found 274.1242; $[M + H + CH_3CN]^+$ Calcd for $C_{21}H_{19}N_2O$315.1497; Found 315.1387.

3-(4-Trifluoromethyl-benzyl)-3-hydro-2-methoxy-isoindolin-1-one, 4af. Colorless solid (8 mg, 0.024 mmol, 8%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.74−7.71 (m, 1H), 7.52−7.38 (m, 4H), 7.21−7.17 (m, 2H), 7.12−7.09 (m, 1H), 5.03 (dd, 1H, J = 6.7, 4.2 Hz), 3.99 (s, 3H), 3.42 (dd, 1H, J = 13.9, 4.2 Hz), 3.22 (dd, 1H, J = 13.9, 6.7 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.6, 141.0, 139.3, 132.0, 130.2, 130.1, 128.9, 125.3 (q, J = 3.7 Hz), 124.0, 122.8, 63.9, 59.7, 37.3.

DOI: 10.1021/acs.joc.6b01696
J. Org. Chem. 2016, 81, 7931−7938

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}NO_2F_3$ 322.1054; Found 322.1056; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{18}N_2O_2F_3$ 363.1320; Found 363.1281.

3-(4-Trifluoromethylbenzyl)-2,3-dihydro-isoindolin-1-one, 4′af. Colorless solid (46 mg, 0.159 mmol, 53%), mp 167−168 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85−7.71 (m, 2H), 7.59−7.45 (m, 4H), 7.30 (dd, 3H, J = 7.8, 6.2 Hz), 4.88−4.84 (m, 1H), 3.25 (dd, 1H, J = 13.7, 5.7 Hz), 3.02 (dd, 1H, J = 13.7, 7.6 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.0, 146.5, 140.8, 132.1, 132.0, 129.9, 129.6, 129.3, 128.7, 125.6 (q, J = 3.6 Hz), 124.0, 122.8, 57.7, 40.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{13}NOF_3$ 292.0949; Found 292.0950; $[M + H + CH_3CN]^+$ Calcd for $C_{18}H_{16}N_2OF_3$ 333.1214; Found 333.1068.

3-Benzyl-3-hydro-2-methoxy-5-methyl-isoindolin-1-one, 4da. Colorless solid (25 mg, 0.093 mmol, 31%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, 1H, J = 7.7 Hz), 7.25−7.15 (m, 4H), 7.12−7.07 (m, 2H), 6.79−6.76 (m, 1H), 4.92 (dd, 1H, J = 7.4, 4.5 Hz), 3.94 (s, 3H), 3.40 (dd, 1H, J = 13.8, 4.5 Hz), 3.01 (dd, 1H, J = 13.8, 7.4 Hz), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.9, 142.4, 142.0, 135.6, 129.8, 129.4, 128.4, 127.3, 127.0, 123.6, 63.8, 60.3, 37.8, 22.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}NO_2$ 268.1337; Found 268.1324.

3-Benzyl-2,3-dihydro-5-methyl-isoindolin-1-one, 4′da. Colorless solid (15 mg, 0.065 mmol, 22%), mp 147−148 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, 1H, J = 7.7 Hz), 7.37−7.26 (m, 4H), 7.24−7.20 (m, 2H), 7.13 (br s, 1H), 6.63−6.60 (m, 1H), 4.73 (dd, 1H, J = 9.1, 5.0 Hz), 3.22 (dd, 1H, J = 13.6, 5.0 Hz), 2.76 (dd, 1H, J = 13.6, 9.1 Hz), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.0, 147.0, 142. 6, 137.2, 129.5, 129.4, 129.3, 128.9, 127.2, 123.8, 123.3, 58.0, 41.6, 22.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{16}NO$ 238.1231; Found 238.1229; $[M + H + CH_3CN]^+$ Calcd for $C_{18}H_{19}N_2O$ 279.1497; Found 279.1414.

3-(4-Chlorobenzyl)-3-hydro-2-methoxy-5-methyl-isoindolin-1-one, 4db. Colorless solid (20 mg, 0.066 mmol, 22%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60 (d, 1H, J = 7.7 Hz), 7.23−7.14 (m, 3H), 7.02−6.97 (m, 2H, Ar−H), 6.92−6.89 (m, 1H), 4.92 (dd, 1H, J = 6.5, 4.3 Hz), 3.95 (s, 3H), 3.29 (dd, 1H, J = 13.9, 4.3 Hz), 3.12 (dd, 1H, J = 14.0, 6.5 Hz), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.9, 142.7, 141.5, 133.8, 132.9, 131.2, 129.7, 128.5, 127.4, 123.8, 123.3, 63.8, 59.8, 36.9, 22.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{17}NO_2Cl$ 302.0947; Found 302.0933; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{20}N_2O_2Cl$ 343.1213; Found 343.1199.

3-(4-Fluorobenzyl)-3-hydro-2-methoxy-5-methyl-isoindolin-1-one, 4dc. Colorless solid (21 mg, 0.073 mmol, 24%), mp 95−96 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (d, 1H, J = 7.8 Hz), 7.18 (ddt, 1H, J = 7.8, 1.5, 0.7 Hz), 7.04−6.96 (m, 2H), 6.91−6.82 (m, 3H), 4.91 (dd, 1H, J = 6.6, 4.3 Hz), 3.94 (s, 3H), 3.29 (dd, 1H, J = 14.0, 4.3 Hz), 3.10 (dd, 1H, J = 14.0, 6.6 Hz), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.7, 162.0 (d, J = 245 Hz), 142.4, 141.5, 131.3 (d, J = 8.0 Hz), 130.8, 129.4, 127.3, 123.6, 123.3, 115.1 (d, J = 21 Hz), 63.6, 59.8, 36.6, 22.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{17}NO_2F$ 286.1243; Found 286.1237; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{20}N_2O_2F$ 327.1509; Found 327.1559.

3-(4-Fluorobenzyl)-2,3-dihydro-5-methyl-isoindolin-1-one, 4′dc. Colorless solid (10 mg, 0.039 mmol, 13%), mp 191−193 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (d, 1H, J = 7.8 Hz), 7.31−7.24 (m, 1H), 7.19−7.10 (m, 3H), 7.01−6.93 (m, 3H), 4.73 (dd, 1H, J = 8.5, 5.2 Hz), 3.18 (dd, 1H, J = 13.7, 5.2 Hz), 2.81 (dd, 1H, J = 13.7, 8.5 Hz), 2.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.8, 162.1 (d, J = 245 Hz), 147.2, 142.6, 132.7 (d, J = 3.2 Hz), 130.9 (d, J = 7.9 Hz), 129.6, 129.5, 123.8, 123.3, 115.7 (d, J = 22 Hz), 57.9, 40.6, 22.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{15}NOF$ 256.1137; Found 256.1151; $[M + H + CH_3CN]^+$ Calcd for $C_{18}H_{18}N_2OF$ 297.1403; Found 297.1427.

3-Hydro-2-methoxy-5-methyl-3-(4-methylbenzyl)-isoindolin-1-one, 4dd. Colorless solid (22 mg, 0.078 mmol, 26%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, 1H, J = 7.8 Hz), 7.20−7.17 (m, 1H), 7.05−6.96 (m, 4H), 6.82−6.79 (m, 1H), 4.89 (dd, 1H, J = 7.4, 4.4 Hz), 3.95 (s, 3H), 3.36 (dd, 1H, J = 13.8, 4.4 Hz), 2.98 (dd, 1H, J = 13.8, 7.4 Hz), 2.36 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.0, 142.4, 142.1, 136.5, 132.4, 129.7, 129.4, 129.1, 127.4, 123.6, 63.8, 60.4, 37.4, 22.1, 21.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}NO_2$ 282.1494; Found 282.1485; $[M + Na + CH_3CN]^+$ Calcd for $C_{20}H_{22}N_2O_2Na$ 345.1579; Found 345.1548.

2,3-Dihydro-5-methyl-3-(4-methylbenzyl)isoindolin-1-one, 4′dd. Colorless solid (8 mg, 0.031 mmol, 10%), mp 165−166 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (d, 1H, J = 7.8 Hz), 7.28 (ddd, 1H, J = 8.4, 1.4, 0.6 Hz), 7.21−7.18 (m, 1H), 7.18−7.10 (m, 4H), 6.15 (br s, 1H), 4.70 (dd, 1H, J = 9.8, 4.5 Hz), 3.30−3.15 (m, 1H), 2.64 (dd, 1H, J = 13.6, 9.8 Hz), 2.46 (s, 3H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.4, 147.5, 142.6, 136.9, 134.3, 129.7, 129.5, 129.4, 129.1, 123.8, 123.2, 58.1, 41.3, 22.1, 21.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}NO$ 252.1388; Found 252.1400; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{21}N_2O$ 293.1654; Found 293.1678.

3-Hydro-2-methoxy-5-methyl-3-(2-naphthylmethyl)-isoindolin-1-one, 4de. Colorless solid (28 mg, 0.088 mmol, 29%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82−7.71 (m, 3H), 7.64−7.57 (m, 2H), 7.48−7.41 (m, 2H), 7.28−7.25 (m, 1H), 7.18 (ddt, 1H, J = 7.8, 1.5, 0.7 Hz), 6.81−6.78 (m, 1H), 5.01 (dd, 1H, J = 7.5, 4.6 Hz), 3.97 (s, 3H), 3.57 (dd, 1H, J = 13.8, 4.6 Hz), 3.16 (dd, 1H, J = 13.8, 7.5 Hz), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.0, 142.5, 142.1, 133.4, 133.3, 132.5, 129.5, 128.6, 128.1, 127.8, 127.7, 127.3, 126.2, 125.8, 123.7, 123.6, 63.9, 60.3, 38.1, 22.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{20}NO_2$ 318.1494; Found 318.1482.

2,3-Dihydro-5-methyl-3-(2-naphthylmethyl)-isoindolin-1-one, 4′de. Colorless solid (14 mg, 0.048 mmol, 16%), mp 179−180 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (dd, 2H, J = 9.0, 2.8 Hz), 7.80−7.75 (m, 1H), 7.72 (d, 1H, J = 7.8 Hz), 7.69−7.66 (m, 1H), 7.53−7.44 (m, 2H), 7.37 (dd, 1H, J = 8.4,1.8 Hz), 7.29 (dd, 1H, J = 7.8, 1.3 Hz), 7.21 (dd, 1H, J = 1.5, 0.8 Hz), 6.51 (br s, 1H), 4.82 (dd, 1H, J = 9.5, 4.7 Hz), 3.41 (dd, 1H, J = 13.6, 4.7 Hz), 2.87 (dd, 1H, J = 13.6, 9.5 Hz), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.5, 147.5, 142.7, 134.8, 133.7, 132.6, 129.6, 129.4, 128.7, 128.0, 127.8, 127.7, 127.2, 126.5, 126.0, 123.9, 123.2, 58.0, 41.9, 22.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{18}NO$ 288.1388; Found 288.1378; $[M + H + CH_3CN]^+$ Calcd for $C_{22}H_{21}N_2O$ 329.1654; Found 329.1651; $[M + Na + CH_3CN]^+$ Calcd for$C_{22}H_{20}N_2ONa$ 351.1473; Found 351.1459.

3-Benzyl-3-hydro-2-methoxy-6-methyl-isoindolin-1-one, 4ga. Colorless solid (27 mg, 0.102 mmol, 34%), mp 105−106 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54−7.52(m, 1H), 7.25−7.17 (m, 4H), 7.12−7.08 (m, 2H), 6.83 (d, 1H, J = 7.7 Hz), 4.92 (dd, 1H, J = 7.6, 4.4 Hz), 3.96 (s, 3H), 3.42 (dd, 1H, J = 13.7, 4.4 Hz), 2.96 (dd, 1H, J = 13.7, 7.6 Hz), 2.35 (s, 3H).^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.7, 138.8, 138.5, 135.6, 132.6, 132.6, 129.8, 128.4, 126.9, 123.9, 122.8, 63.8, 60.2, 37.8, 21.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}NO_2$ 268.1337; Found 268.1342; $[M + Na + CH_3CN]^+$ Calcd for$C_{19}H_{20}N_2O_2$ Na333.1422; Found 331.1426.

3-Benzyl-2,3-dihydro-6-methyl-isoindolin-1-one, 4′ga. Colorless solid (17 mg, 0.069 mmol, 23%), mp 131−133 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65−7.62(m, 1H), 7.40−7.26 (m, 4H), 7.25−7.17 (m, 3H), 6.58 (br s, 1H), 4.75 (dd, 1H, J = 9.1, 5.2 Hz), 3.19 (dd, 1H, J = 13.6, 5.2 Hz), 2.78 (dd, 1H, J = 13.6, 9.1 Hz), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.6, 144.3, 138.5, 137.2, 133.7, 132.9, 132.1, 129.3, 129.0, 127.2, 124.2, 122.5, 57.9, 41.7, 21.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{16}NO$ 238.1231; Found 238.1229; $[M + H + CH_3CN]^+$ Calcd for $C_{18}H_{19}N_2O$279.1497; Found 279.1508; $[M + Na + CH_3CN]^+$ Calcd for$C_{18}H_{18}N_2ONa$ 301.1317; Found 301.1316.

3-(4-Chlorobenzyl)-3-hydro-2-methoxy-6-methyl-isoindolin-1-one, 4gb. Colorless solid (24 mg, 0.079 mmol, 26%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55−7.52 (m, 1H), 7.29−7.26 (m, 1H), 7.19−7.14 (m, 2H), 7.04−6.92 (m, 3H), 4.93 (dd, 1H, J = 6.9, 4.2 Hz), 3.97 (s, 3H), 3.33 (dd, 1H, J = 13.9, 4.2 Hz), 3.06 (dd, 1H, J = 13.9, 6.9 Hz), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.58, 138.7, 138.2, 133.6, 132.8, 132.7, 131.1, 130.0, 128.4, 124.1, 122.5, 63.7, 59.6, 36.8, 21.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{17}NO_2Cl$ 302.0947; Found 302.0939; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{20}N_2O_2Cl$ 343.1213; Found 343.1205; $[M + Na + CH_3CN]^+$ Calcd for$C_{19}H_{19}N_2O_2ClNa$ 365.1033; Found 365.1009.

DOI: 10.1021/acs.joc.6b01696
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3-Hydro-2-methoxy-5-methyl-3-(4-methylbenzyl)-isoindolin-1-one, 4gd. Colorless solid (40 mg, 0.142 mmol, 47%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55−7.52 (m, 1H), 7.23−7.21 (m, 1H), 7.05−6.96 (m, 4H), 6.84 (d, 1H, J = 7.8 Hz), 4.89 (dd, 1H, J = 7.8, 4.3 Hz), 3.97 (s, 3H), 3.40 (dd, 1H, J = 13.7, 4.3 Hz), 2.90 (dd, 1H, J = 13.7, 7.8 Hz), 2.36 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.8, 138.9, 138.5, 136.5, 132.6, 132.4, 130.0, 129.6, 129.1, 124.0, 122.9, 63.8, 60.3, 37.4, 21.4, 21.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}NO_2$ 282.1494; Found 282.1497.

2,3-Dihydro-6-methyl-3-(4-methylbenzyl)-isoindolin-1-one, 4′gd. Colorless solid (7 mg, 0.027 mmol, 9%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65−7.63 (m, 1H), 7.38−7.33 (m, 1H), 7.22 (d, 1H, J = 7.8 Hz), 7.17−7.10 (m, 4H), 6.36 (br s, 1H), 4.72 (dd, 1H, J = 9.3, 5.0 Hz), 3.20−3.14 (m, 1H), 2.70 (dd, 1H, J = 13.6, 9.3 Hz), 2.44 (s, 3H), 2.35 (s, 3H).^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.5, 144.4, 138.5, 136.9, 134.2, 132.9, 132.1, 129.7, 129.2, 124.2, 122.5, 58.1, 41.3, 21.5, 21.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}NO$ 252.1388; Found 252.1393; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{21}N_2O$ 293.1654; Found 293.1649; $[M + Na + CH_3CN]^+$Calcd for$C_{19}H_{20}N_2ONa$ 315.1473; Found 315.1470.

3-Hydro-2-methoxy-6-methyl-3-(2-naphthylmethyl)-isoindolin-1-one, 4ge. Colorless solid (34 mg, 0.107 mmol, 36%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82−7.72 (m, 3H), 7.60−7.53 (m, 2H), 7.47−7.41 (m, 2H), 7.31−7.24 (m, 2H), 7.18 (ddd, 1H, J = 7.9, 1.7, 0.8 Hz), 6.81 (d, 1H, J = 7.7 Hz), 5.02 (dd, 1H, J = 7.9, 4.5 Hz), 3.99 (s, 3H), 3.62 (dd, 1H, J = 13.8, 4.5 Hz), 3.09 (dd, 1H, J = 13.8, 7.9 Hz), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.8, 138.9, 138.6, 133.4, 133.3, 132.7, 132.5, 129.9, 128.6, 128.1, 127.8, 127.7, 126.2, 125.8, 124.1, 122.9, 63.9, 60.2, 38.1, 21.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{20}NO_2$ 318.1494; Found 318.1495.

2,3-Dihydro-6-methyl-3-(2-naphthylmethyl)-isoindolin-1-one, 4′ge. Colorless solid (6 mg, 0.020 mmol, 7%), mp 159−160 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88−7.76 (m, 3H), 7.71−7.63 (m, 2H), 7.53−7.45 (m, 2H), 7.42−7.33 (m, 2H), 7.25 (d, 1H, J = 7.7 Hz), 6.42 (br s, 1H), 4.84 (dd, 1H, J = 9.4, 5.0 Hz), 3.37 (dd, 1H, J = 13.6, 5.0 Hz), 2.90 (dd, 1H, J = 13.6, 9.4 Hz), 2.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.5, 144.3, 138.6, 134.8, 133.7, 133.0, 132.6, 132.1, 128.8, 128.1, 127.9, 127.7, 127.3, 126.5, 126.0, 124.3, 122.5, 58.0, 42.0, 21.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{18}NO$ 288.1388; Found 288.1400; $[M + H + CH_3CN]^+$ Calcd for $C_{22}H_{21}N_2O$ 329.1653; Found 329.1673; $[M + Na + CH_3CN]^+$ Calcd for$C_{22}H_{20}N_2ONa$ 351.1473 Found 351.1480.

3-(4-Trifluoromethyl-benzyl)-3-hydro-2-methoxy-6-methyl-isoindolin-1-one, 4gf. Colorless solid (23 mg, 0.069 mmol, 23%).^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54−7.51 (m, 1H), 7.47−7.43 (m, 2H), 7.28 (ddd, 1H, J = 7.7, 1.7, 0.8 Hz), 7.21−7.16 (m, 2H), 6.96 (d, 1H, J = 7.8 Hz), 4.98 (dd, 1H, J = 6.8, 4.3 Hz), 3.97 (s, 3H), 3.44−3.36 (m, 1H), 3.17 (dd, 1H, J = 13.8, 6.8 Hz), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.7, 139.5, 139.0, 138.2, 132.9, 131.0, 130.2, 130.1, 125.3 (q, J = 3.6 Hz), 124.3, 124.2, 122.6, 63.8, 59.6, 37.4, 21.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}NO_2F_3$ 336.1211; Found 336.1205; $[M + H + CH_3CN]^+$ Calcd for $C_{20}H_{20}N_2O_2F_3$ 377.1477; Found 377.1468.

3-(4-Trifluoromethyl-benzyl)-2,3-dihydro-6-methyl-isoindolin-1-one, 4′gf. Colorless solid (27 mg, 0.087 mmol, 30%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63−7.60 (m, 1H), 7.56 (d, 2H, J = 7.9 Hz), 7.37 (ddd, 1H, J = 7.8, 1.7, 0.8 Hz), 7.32 (d, 2H, J = 8.0 Hz), 7.20 (d, 1H, J = 7.7 Hz), 6.89 (s, 1H), 4.79 (dd, 1H, J = 8.3, 5.3 Hz), 3.25 (dd, 1H, J = 13.6, 5.3 Hz), 2.91 (dd, 1H, J = 13.6, 8.3 Hz), 2.44 (s, 3H).^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.8, 143.8, 141.1, 138.9, 133.1, 132.1, 129.8, 125.8 (q, J = 3.7 Hz), 125.6, 124.4, 122.4, 57.5, 41.3, 21.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}NOF_3$306.1105; Found 306.1115; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{18}N_2OF_3$ 347.1371; Found 347.1367.

3-Benzyl-3-hydro-2,6-dimethoxy-isoindolin-1-one, 4ha. Colorless solid (21 mg, 0.072 mmol, 23%), mp 100−101 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25−7.19 (m, 3H), 7.12−7.08 (m, 2H), 6.97 (dd, 1H, J = 8.4, 2.5 Hz), 6.83 (dt, 1H, J = 8.4, 0.6 Hz), 4.91 (ddd, 1H, J = 7.7, 4.3, 0.7 Hz), 3.98 (s, 3H), 3.79 (s, 3H), 3.43 (dd, 1H, J = 13.7, 4.3 Hz), 2.95 (dd, 1H, J = 13.7, 7.7 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.5, 160.0, 135.4, 133.7, 131.2, 129.7, 128.4, 126.9, 124.1, 119.8, 106.6, 63.8, 60.0, 55.6, 37.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}NO_3$ 284.1286; Found 284.1276.

3-Benzyl-2,3-dihydro-6-methoxy-isoindolin-1-one, 4′ha. Colorless solid (23 mg, 0.091 mmol, 29%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39−7.28 (m, 4H), 7.26−7.21 (m, 3H), 7.11 (dd, 1H, J = 8.3, 2.5 Hz), 6.15 (br s, 1H), 4.71−4.75 (m, 1H), 3.86 (s, 3H), 3.22 (dd, 1H, J = 13.4, 5.0 Hz), 2.72 (dd, 1H, J = 13.5, 9.4 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.1, 160.2, 139.1, 137.1, 133.2, 129.1, 128.9, 127.2, 123.5, 120.3, 106.5, 57.6, 55.7, 41.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{16}NO_2$ 254.1181; Found 254.1179; $[M + H + CH_3CN]^+$ Calcd for $C_{18}H_{19}N_2O_2$ 295.1446; Found 295.1449; $[M + Na + CH_3CN]^+$ Calcd for $C_{18}H_{18}N_2O_2Na$ 317.1266; Found 317.1256.

3-Hydro-2,5-dimethoxy-3-(4-methylbenzyl)-isoindolin-1-one, 4hd. Colorless solid (33 mg, 0.111 mmol, 37%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 (d, 1H, J = 2.4 Hz), 7.05−6.95 (m, 5H), 6.85−6.82 (m, 1H), 4.88 (ddd, 1H, J = 7.8, 4.2, 0.7 Hz), 3.98 (s, 3H), 3.79 (s, 3H), 3.39 (dd, 1H, J = 13.7, 4.2 Hz), 2.90 (dd, 1H, J = 13.7, 7.8 Hz), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.6, 160.1, 136.5, 133.9, 132.3, 131.3, 129.7, 129.2, 124.2, 119.8, 106.6, 63.9, 60.1, 55.7, 37.5, 21.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}NO_3$ 298.1443; Found 298.1452.

2,3-Dihydro-6-methoxy-3-(4-Methylbenzyl)-isoindolin-1-one, 4′hd. Colorless solid (8 mg, 0.029 mmol, 10%), mp 147−148 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31 (d, 1H, J = 2.4 Hz), 7.21 (d, 1H, J = 8.3 Hz), 7.17−7.08 (m, 5H), 6.37 (br s, 1H), 4.74−4.65 (m, 1H), 3.86 (s, 3H), 3.20−3.11 (m, 1H), 2.71 (dd, 1H, J = 13.6, 9.2 Hz), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.3, 160.3, 139.4, 136.9, 134.1, 133.3, 129.7, 129.2, 123.7, 120.3, 106.6, 77.5, 77.2, 76.8, 57.9, 55.8, 41.3, 21.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}NO_2$ 268.1337; Found 268.1344; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{21}N_2O_2$ 309.1603; Found 309.1613; $[M + Na + CH_3CN]^+$ Calcd for $C_{19}H_{20}N_2O_2Na$ 331.1422 Found 331.1424.

3-Hydro-2,6-dimethoxy-3-(2-naphthylmethyl)-isoindolin-1-one, 4he. Colorless solid (35 mg, 0.105 mmol, 35%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83−7.71 (m, 3H), 7.58 (d, 1H, J = 1.8 Hz), 7.48−7.40 (m, 2H), 7.30−7.20 (m, 3H), 6.93 (dd, 1H, J = 8.4, 2.5 Hz), 6.81 (dt, 1H, J = 8.3, 0.6 Hz), 5.01 (ddd, 1H, J = 7.9, 4.4, 0.7 Hz), 4.01 (s, 3H), 3.77 (s, 3H), 3.61 (dd, 1H, J = 13.7, 4.4 Hz), 3.09 (dd, 1H, J = 13.7, 7.9 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.7, 160.1, 133.8, 133.4, 133.2, 132.5, 131.3, 128.6, 128.1, 127.8, 127.7, 126.2, 125.8, 124.2, 119.9, 106.7, 63.9, 60.1, 55.7, 38.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{20}NO_3$ 334.1443; Found 334.1428; $[M + H + CH_3CN]^+$ Calcd for $C_{23}H_{23}N_2O_3$ 375.1708; Found 375.1662.

2,3-Dihydro-6-methoxy-3-(2-naphthylmethyl)-isoindolin-1-one, 4′he. Colorless solid (8 mg, 0.026 mmol, 9%), mp 212−215 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89−7.76 (m, 3H), 7.68 (d, 1H, J = 1.7 Hz), 7.55−7.45 (m, 2H), 7.38 (dd, 1H, J = 8.4, 1.8 Hz), 7.33 (d, 1H, J = 2.4 Hz), 7.25−7.20 (m, 1H), 7.11 (dd, 1H, J = 8.3, 2.5 Hz), 6.43 (br s, 1H), 4.83 (ddd, 1H, J = 9.2, 5.1, 0.9 Hz), 3.86 (s, 3H), 3.36 (dd, 1H, J = 13.6, 5.1 Hz), 2.91 (dd, 1H, J = 13.6, 9.2 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.3, 160.4, 139.3, 134.7, 133.7, 133.3, 132.6, 128.8, 128.1, 127.9, 127.7, 127.2, 126.6, 126.1, 123.7, 120.4, 106.7, 57.8, 55.8, 42.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{18}NO_2$ 304.1337; Found 304.1333; $[M + Na + CH_3CN]^+$ Calcd for $C_{20}H_{17}NO_2Na$ 326.1157; Found 326.1151.

3-(4-Chlorobenzyl)-3-hydro-2,5-dimethoxy-isoindolin-1-one, 4ib. Colorless solid (18 mg, 0.057 mmol, 19%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, 1H, J = 8.4 Hz), 7.22−7.16 (m, 2H), 7.07−7.01 (m, 2H), 6.91 (dd, 1H, J = 8.4, 2.3 Hz), 6.59−6.46 (m, 1H), 4.90 (dd, 1H, J = 7.0, 4.4 Hz), 3.96 (s, 3H), 3.78 (s, 3H), 3.33 (dd, 1H, J = 13.9, 4.4 Hz), 3.07 (dd, 1H, J = 13.9, 7.0 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.1, 162.9, 143.5, 133.8, 133.0, 131.2, 128.6, 125.6, 122.4, 114.8, 108.3, 63.9, 60.0, 55.7, 37.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{17}NO_3Cl$ 318.0896; Found 318.0905.

3-Hydro-2,5-dimethoxy-3-(4-methylbenzyl)-isoindolin-1-one, 4id. Colorless solid (25 mg, 0.084 mmol, 28%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66 (d, 1H, J = 8.4 Hz), 7.08−6.99 (m, 4H), 6.90 (dd, 1H, J = 8.4, 2.3 Hz), 6.41−6.38 (m, 1H), 4.86 (dd, 1H, J = 8.0, 4.4 Hz), 3.96 (s, 3H), 3.72 (s, 3H), 3.42 (dd, 1H, J = 13.7, 4.4

DOI: 10.1021/acs.joc.6b01696
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Hz), 2.91 (dd, 1H, J = 13.7, 8.0 Hz), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.2, 162.8, 144.1, 136.6, 132.5, 129.7, 129.2, 125.3, 122.3, 115.0, 108.3, 64.0, 60.6, 55.6, 37.5, 21.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}NO_3$ 298.1443; Found 298.1437; $[M + Na + CH_3CN]^+$ Calcd for $C_{20}H_{22}N_2O_3Na$ 361.1528; Found 361.1526.

2,3-Dihydro-5-methoxy-3-(4-methylbenzyl)-isoindolin-1-one, 4′id. Colorless solid (10 mg, 0.037 mmol, 12%), mp 181−182 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, 1H, J = 8.4 Hz), 7.19−7.09 (m, 4H), 6.98 (dd, 1H, J = 8.4, 2.2 Hz), 6.81−6.76 (m, 1H), 6.31 (br s, 1H), 4.69 (dd, 1H, J = 9.2, 5.1 Hz), 3.84 (s, 3H), 3.15 (dd, 1H, J = 13.5, 5.1 Hz), 2.74 (dd, 1H, J = 13.5, 9.2 Hz), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.3, 163.0, 149.4, 136.9, 134.0, 129.7, 129.2, 125.4, 124.5, 115.1, 107.6, 58.0, 55.7, 41.3, 21.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}NO_2$ 268.1337; Found 268.1344; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{21}N_2O_2$ 309.1603; Found 309.1610; $[M + Na + CH_3CN]^+$ Calcd for $C_{19}H_{20}N_2O_2Na$ 331.1422; Found 331.1451.

3-(4-Trifluoromethyl-benzyl)-3-hydro-2,5-dimethoxy-isoindolin-1-one 4if. Colorless solid (45 mg, 0.128 mmol, 43%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (d, 1H, J = 8.4 Hz), 7.45 (d, 2H, J = 8.0 Hz), 7.21 (d, 2H, J = 8.0 Hz), 6.89 (dd, 1H, J = 8.5, 2.3 Hz), 6.51 (d, 1H, J = 2.3 Hz), 4.94 (dd, 1H, J = 6.8, 4.4 Hz), 3.94 (s, 3H), 3.75 (s, 3H), 3.39 (dd, 1H, J = 14.0, 4.4 Hz), 3.17 (dd, 1H, J = 14.0, 6.8 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.1, 163.0, 143.3, 139.5, 130.2, 125.6, 125.3 (q, J = 3.6 Hz), 125.0, 122.2, 115.0, 108.2, 63.9, 59.8, 55.6, 37.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}NO_3F_3$ 352.1160; Found 352.1154; $[M + H + CH_3CN]^+$ Calcd for $C_{20}H_{20}N_2O_3F_3$ 393.1426; Found 393.1397.

3-(4-Trifluoromethyl-benzyl)-2,3-dihydro-5-methoxy-isoindolin-1-one, (4′if). Colorless solid (8 mg, 0.024 mmol, 8%), mp 142−143 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, 1H, J = 8.4 Hz), 7.63−7.57 (m, 2H), 7.38−7.33 (m, 2H), 7.00 (dd, 1H, J = 8.5, 2.2 Hz), 6.80−6.75 (m, 1H), 6.32 (br s, 1H), 4.94 (dd, 1H, J = 10.9, 2.4 Hz), 3.85 (s, 3H), 3.27 (dd, 1H, J = 13.6, 5.1 Hz), 2.89 (dd, 1H, J = 13.6, 8.8 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.3, 163.2, 148.8, 141.1, 129.8, 125.9 (q, J = 3.6 Hz), 125.6, 124.4, 115.2, 107.7, 57.3, 55.8, 41.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}NO_2F_3$ 322.1055; Found 322.1062; $[M + H + CH_3CN]^+$ Calcd for $C_{19}H_{18}N_2O_2F_3$ 363.1320; Found 363.1333.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01696.

Additional experimental results, copies of NMR spectra, and ORTEP diagrams (PDF)

X-ray crystallographic data for *E*-**2aa**, **4aa**, and **4′aa** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The work was performed during C.K.X.'s sabbatical sojourn at Imperial College London as a Visiting Researcher. The authors are grateful to National Natural Science Foundation of China (Grant No. 21171075) for financial support during this period. We also acknowledge Johnson Matthey PLC for supplying Pd salts.

■ REFERENCES

(1) International Patent, WO2013/120835A1, 2013.

(2) International Patent PCT/CN2011/083229, WO2013/079452, 2013.

(3) Valencia, E.; Freyer, A. J.; Shamma, M.; Fajardo, V. *Tetrahedron Lett.* **1984**, *25*, 599−602.

(4) Desai, S. J.; Chaturvedi, R.; Mulchandani, N. B. *J. Nat. Prod.* **1990**, *53*, 496−497.

(5) Choi, Y. L.; Kim, J. K.; Choi, S. U.; Min, Y. K.; Bae, M. A.; Kim, B. T.; Heo, J. N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3036−3040.

(6) (a) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350−2353. (b) Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1064−1067. (c) Fabry, D. C.; Zoller, J.; Raja, S.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10228−10231.

(7) (a) Yang, F.; Ackermann, L. *J. Org. Chem.* **2014**, *79*, 12070−12082. (b) Manoharan, R.; Jeganmohan, M. *Chem. Commun.* **2015**, *51*, 2929−2932.

(8) Kim, J.; Park, S. W.; Baik, M. H.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 13448−13451.

(9) Wrigglesworth, J. W.; Cox, B.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. I. *Org. Lett.* **2011**, *13*, 5326−5329.

(10) Li, D. D.; Yuan, T. T.; Wang, G. W. *Chem. Commun.* **2011**, *47*, 12789−12791.

(11) Das, A.; Chakrabarty, S.; Choudhury, D.; Chakrabarti, G. *Chem. Res. Toxicol.* **2010**, *23*, 1054−1066.

(12) Fisher, L. E.; Caroon, J. M.; Jahangir, S.; Stabler, R.; Lundberg, S.; Muchowski, J. M. *J. Org. Chem.* **1993**, *58*, 3643−3647.

(13) (a) Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407−10408. (b) Bour, J. R.; Green, J. C.; Winton, V. J.; Johnson, J. B. *J. Org. Chem.* **2013**, *78*, 1665−1669.

(14) Li, X. G.; Sun, M.; Liu, K.; Liu, P. N. *Adv. Synth. Catal.* **2015**, *357*, 395−399.

(15) *CrysAlis*, V1.171.34.44; Oxford Diffraction Ltd., Wroclaw, Poland, 2010.

(16) Sheldrick, G. M., *SHELXL-97, Program for Crystal Structure Refinement*; Göttingen University: Göttingen, Germany, 1997.

(17) Fukui, Y.; Liu, P.; Liu, Q.; He, Z. T.; Wu, N. Y.; Tian, P.; Lin, G. Q. *J. Am. Chem. Soc.* **2014**, *136*, 15607−15614.

DOI: 10.1021/acs.joc.6b01696
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