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Palladium-Catalyzed Heck-type Domino Cyclization and Carboxylation to Synthesize Carboxylic Acids by Utilizing Chloroform as the Carbon Monoxide Source

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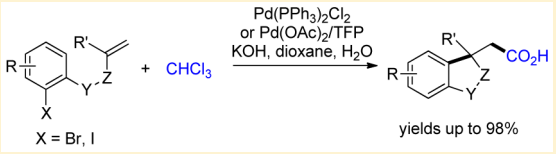
Supporting Information

ABSTRACT: A palladium-catalyzed domino cyclization and carboxylation reaction for synthesis of a variety of carboxylic acids was developed, where chloroform was used as "carbon monoxide" source. The in situ generated neopentylpalladium species by Heck cyclization was efficiently trapped by dichlorocarbene to form a series of carboxylic acids. It was found that in this type of domino reaction $CHCl_3$ is a convenient and safe alternation for CO gas.



INTRODUCTION

Since being developed by Heck and co-workers in early 1970s,[1] the transition metal-catalyzed carbonylation with carbon monoxide became one of the most powerful methods for the synthesis of carbonyl compounds. In comparison with the traditional magnesium- or lithium-mediated reactions, transition metal-catalyzed carbonylation provides a mild and well-functional group tolerated method to prepare carbonyl substances.[2] Despite that it is cheap and readily available on large scale, carbon monoxide still has some disadvantages for laboratory use, such as its high toxicity and explosiveness. Thus, it has advantages and is desirable to seek alternative, easy to handle and safe CO sources.[3] Aromatic aldehydes were found to be able to serve as efficient CO sources in the rhodium-catalyzed carbocyclization reactions.[4] Phenyl formate was an efficient alternation for CO gas in nickel and palladium-catalyzed carbonylations.[5] Lindhardt, Skrydstrup and co-workers found the release of CO could be realized by a palladium-catalyzed decarbonylation of tertiary acid chlorides. It was found that only near stoichiometric amount of carbon monoxide precursor was needed in the aminocarbonylation and carbonylative Heck reactions.[6,7] We also developed an efficient borrowing hydrogen strategy for the synthesis of a series of linear carboxylic acids by the use of chloroform as CO source, where $CHCl_3$ showed superior performance over CO gas and phenyl formate in the linear/branched selectivity.[8]

Besides being used as solvent, chloroform as well as bromoform have been proven as useful reagents in organic synthesis. Chloroform was used as a dichlorocarbene precursor to construct various dichlorocyclopropanes,[9] which were further applied in the synthesis of 3-chloropyridine derivatives via Ciamician−Dennstedt rearrangement.[10] The formylation of phenols named as Reimer−Tiemann reaction[11] and trichloromethylation of aldehyde[12] with chloroform are important one-carbon elongation methods. In the transition metal-involved reactions, chloroform was ever used for the synthesis of metalcarbonyl complexes,[13] oxidative reagents[14] and trichloromethylation reagents[15] and so on. Herein we report a palladium-catalyzed Heck-type domino cyclization and carboxylation reaction by utilizing chloroform as the carbonyl source.[16−18] One of our research interests is the reaction between alkylpalladium species with carbenes. It was demonstrated by us and other groups that the in situ generated alkylpalladium **B** readily reacted with aryl carbene to form *E*-alkene derivatives **D** via migration and *β*-hydride elimination processes (Scheme 1a).[19] We reasoned that alkylpalladium **B** was possibly able to coordinate with dichlorocarbene to form complex **E**.[20,21] Under aqueous basic conditions **E** would hydrolyze and deliver carboxylic acid **F** (Scheme 1b).[22]

RESULTS AND DISCUSSION

Our initial studies commenced with readily available acrylamide **1a**. In the presence of $Pd(OAc)_2$ (5 mol %) and trifurylphosphine (TFP, 5 mol %), the reaction of **1a** with chloroform in aqueous dioxane afforded the acid **2a** in 54% of isolated yield after acidic workup (Table 1, entry 1). The yields were significantly improved by increasing the loading of phosphine ligand (entries 2 and 3). Probably due to the solubility problem the reaction became inconstant when water was used as the single solvent in lieu of the mixed dioxane/H_2O, and the isolated yield was varied from moderate to excellent (entry 4). The amount of chloroform could be reduced to 4.0 equiv without great decreasing the yields of **2a** (entries 5−7). By the use of bromoform instead of chloroform, the reaction afforded **2a** in a relatively lower yield (entry 8).

The generality of this domino cyclization and carboxylation reaction was demonstrated by subjection of various organic iodides to the optimized reaction conditions. The reactions of 2-methylacrylamides with either electron-rich group (**1b**) or electron-withdrawing groups (**1c−1e**) at the phenyl ring

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Scheme 1. Domino Heck-type Cyclization and Carbene-Trapping Reactions

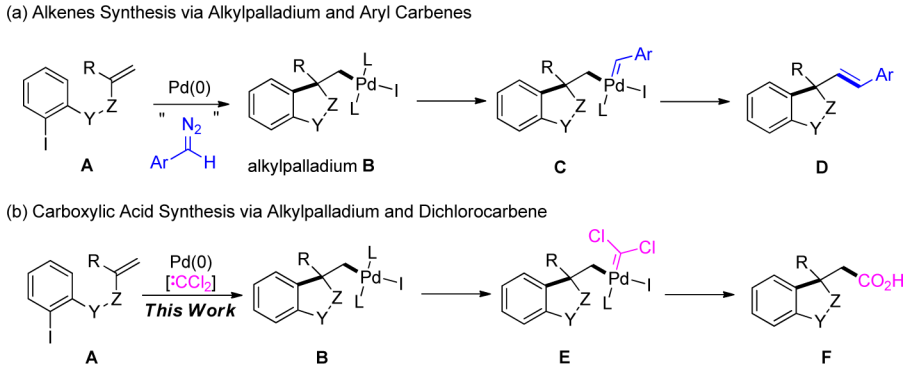
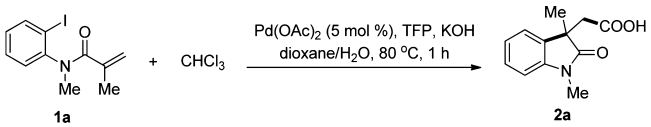


Table 1. Reaction Condition Optimization[a]



entry	$CHCl_3$ (equiv)	dioxane/H_2O (2.0 mL)	TFP (mol %)	yield of **2a** (%)
1	8.0	1:4	5	54
2	8.0	1:4	10	73
3	8.0	1:4	15	96
4	8.0	0:1	15	59−92
5	6.0	1:4	15	96
6	4.0	1:4	15	94
7	3.0	1:4	15	88
8	4.0[b]	1:4	15	78

[a]The reaction was conducted on 0.20 mmol scale of **1a**, palladium (5 mol %), TFP (5−15 mol %), KOH (8.0 equiv), in solvent (2.0 mL) at 80 °C for 1 h. [b]$CHBr_3$ (4.0 equiv) was used instead of $CHCl_3$.

worked as efficiently as the reaction of **1a**, which gave the desired carboxylic acids in excellent yields (Table 2, entries 1−4). However, the nitro-substituted iodide **1f** only afforded 27% of desired carboxylic acid (entry 5). The reaction of electron-rich compound *N*-(2-iodo-5-methoxyphenyl)-*N*-methylmethacrylamide gave 96% of acid **2g** (entry 6). The *N*-benzylated amide **1h** also smoothly reacted with chloroform to give the cyclized compound **2h** in excellent yield (entry 7). The reaction proceeded equally efficiently with acetamides **1i**, **1j** and sulfonamide **1k**, which furnished the five- or six-membered *N*-heterocycles in good to excellent yields (entries 8−10). Other substituted acrylamides, such as **1l** and **1m** were competent substrates and they were smoothly converted to the corresponding acids in 94 and 96%, respectively (entries 11−12). However, only a complex mixture was formed when 2-phenylacrylamide **1n** was used (entry 13). The reaction of **1o** gave the carboxylic acid **2o** in 68% yield, along with reductive product **3o** being isolated in 27% yield (entry 14). Allylic amide **1p** underwent the cyclization to furnish the acid in 58% yield (entry 15). It was found that the reaction of **1q** delivered the acid **2q** in 81% yield as a single isomer (entry 16). The relative stereochemistry of **2q** was unambiguously confirmed by single crystal X-ray analysis,[23] which is consisted with the stereochemistry for the *cis*-insertion of C═C double bond to carbon−palladium bond. The reaction of allylic ether **1r** only resulted a complicated mixture (entry 17), and the malonate derivative **1s** decomposed under the standard aqueous basic conditions (entry 18).

For the aryl bromides, $Pd(PPh_3)_2Cl_2$ was found to be the optimum palladium catalyst (Table 3). For instance, the reaction of **1t−w** in dioxane/H_2O at 100 °C gave the desired products in good to excellent yields (entries 1−3). An incomplete conversion was observed with 2-bromo-1-amino-naphthalene derivative **1w** as the substrate, and the reaction afforded the **2w** in 62% yield along with 28% starting material being recovered (entry 4).

CONCLUSION

In summary we disclosed a palladium-catalyzed domino cyclization and carboxylation reaction for the synthesis of a variety of carboxylic acids. In these reactions chloroform was used as CO source, which showed advantages in both safety and laboratory operation aspects.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under a nitrogen atmosphere in flame-dried glassware, unless the reaction procedure states otherwise. Tetrahydrofuran (THF) was distilled from sodium-benzophenone in a continuous still under an atmosphere of N_2. Dioxane was distilled from sodium-benzophenone under an atmosphere of nitrogen. Dichloromethane was distilled from calcium hydride in a still under an atmosphere of nitrogen. Room temperature reactions were carried out between 20 and 25 °C. Flash column chromatography was performed using 40−63 μm silica gel as the stationary phase. ^1H, ^{13}C and ^{19}F NMR spectra were referenced by using solvent residue as an internal reference (^1H NMR: 7.26 ppm for $CDCl_3$; 2.50 ppm for DMSO-d_6; ^{13}C NMR: 77.00 ppm for $CDCl_3$; 39.52 ppm for DMSO-d_6; 30.92 ppm for acetone-d_6). Electron spray ionization (ESI) mass spectrometry data were acquired by using LTQ analyzer type.

Compounds **1a**, **1b**, **1c**, **1h**, **1i**, **1k**, **1n**, **1t** were known compounds and prepared by following the literature.[24]

***N*-(2-Iodo-4-(fluorophenyl)-*N*-methylmethacrylamide (1d).** Methacryloyl chloride (0.35 mL, 3.60 mmol, 1.2 equiv) was added to a mixture of 4-fluoro-2-iodoaniline (0.71 g, 3.00 mmol, 1.0 equiv), DMAP (18.3 mg, 0.10 mmol, 5 mol %), Et_3N (0.84 mL, 6.00 mmol, 2.0 equiv) in CH_2Cl_2 (10 mL) at −20 °C dropwise. After stirring at −20 °C for 30 min and room temperature overnight, the mixture was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. After filtration and concentration, the obtained crude amide was used in the next step without purification.

Sodium hydride (240 mg, 60% in mineral oil, 4.00 mmol, 2.0 equiv) was added to a solution of the above amide in THF (15 mL) at 0 °C for portions. After stirring at 0 °C for 20 min MeI (0.56 mL, 9.00 mmol, 3.0 equiv) added dropwise and the reaction mixture was allowed to stir at room temperature for 3 h. The reaction was quenched with water and THF was removed by evaporation. The residue was extracted with ethyl acetate. The organic phase was

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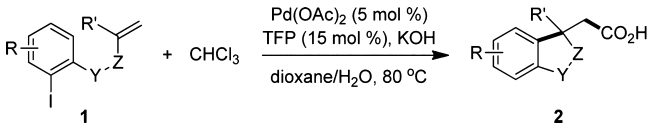
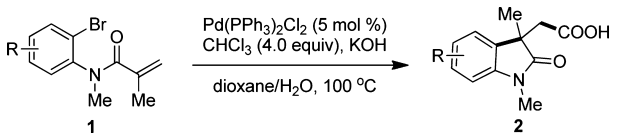
Table 2. Substrate Scope of Organic Iodides[a]



entry	halide **1**	structure of **2**	yield of **2** (%)[b]
1	R = Me (**1b**)		98 (**2b**)
2	R = Cl (**1c**)		94 (**2c**)
3	R = F (**1d**)		93 (**2d**)
4	R = CF_3 (**1e**)		93 (**2e**)
5	R = NO_2 (**1f**)		27 (**2f**)
6	(**1g**)		96 (**2g**)
7	(**1h**)		88 (**2h**)
8	R = Ac, *n* = 1 (**1i**)		93 (**2i**)
9	R = Ac, *n* = 2 (**1j**)		93 (**2j**)
10[c]	R = Ts, *n* = 2 (**1k**)		82 (**2k**)
11	R = Bn (**1l**)		94 (**2l**)
12	R = $Ph(CH_2)_2$ (**1m**)		96 (**2m**)
13	R = Ph (**1n**)		complex
14	(**1o**)		68 (**2o**) + 27 (**3o**)
15	(**1p**)		58 (**2p**)
16	(**1q**)		81 (**2q**) single isomer
17	(**1r**)		complex
18	(**1s**)		decomposition

[a]Reaction conditions: **1** (0.20 mmol), $CHCl_3$ (0.80 mmol), $Pd(OAc)_2$ (5 mol %), TFP (15 mol %), KOH (1.60 mmol) and dioxane/H_2O (1:4, 2.0 mL) at 80 °C for 1 h. [b]Isolated yields. [c]$CHCl_3$ (1.60 mmol) at 100 °C for 3 h.

Table 3. Substrate Scope of Organic Bromides[a]



entry	halide **1**	yield of **2** (%)[b]
1	(**1t**)	87 (**2a**)
2	(**1u**)	89 (**2b**)
3	(**1v**)	81 (**2v**)
4[c]	(**1w**)	62 (**2w**)

[a]Reaction conditions: **1** (0.20 mmol), $CHCl_3$ (0.80 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol %), KOH (1.60 mmol) and dioxane/H_2O (1:4, 2.0 mL) at 100 °C for 1−3 h. [b]Isolated yields. [c]With 28% starting material being recovered.

washed with brine, dried over Na_2SO_4, filtered, concentrated, and the residue was purified by column chromatography on silica gel (10% ethyl acetate/hexanes) to afford the desired amide **1d** (0.73 g, 77%) as solid: mp 61.2−62.6 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 7.6, 2.8 Hz, 1H), 7.19−7.12 (m, 1H), 7.12−7.04 (m, 1H), 5.05 (s, 1H), 5.01 (s, 1H), 3.22 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 160.8 (d, J = 252.1 Hz), 143.3, 140.0, 129.8 (d, J = 8.4 Hz), 126.9 (d, J = 24.4 Hz), 119.0, 116.4 (d, J = 22.7 Hz), 98.9, 36.9, 20.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.1. HRMS (ESI) calcd. for $C_{11}H_{11}NOFINa^+$ $(M + Na)^+$ 341.9796, found 341.9769.

***N*-(2-Iodo-4-(trifluoromethyl)phenyl)-*N*-methylmethacrylamide (1e).** **1e** (10% ethyl acetate/hexanes) (0.53 g, 48%) was prepared following the procedure of **1d** in 3.00 mmol scale. Solid: mp 72.1−74.9 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.33−7.26 (m, 1H), 5.04 (s, 2H), 3.25 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 150.4 (bs), 139.8, 137.2, 131.1 (q, J = 31.5 Hz), 129.4, 126.5, 122.5 (q, J = 271.1 Hz), 119.8 (bs), 98.9, 36.8, 20.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6. HRMS (ESI) calcd. for $C_{12}H_{11}NOF_3INa^+$ $(M + Na)^+$ 391.9735, found 391.9733.

***N*-(2-Iodo-4-nitrophenyl)-*N*-methylmethacrylamide (1f).** Methacryloyl chloride (0.35 mL, 3.60 mmol, 1.2 equiv) was added to a mixture of 2-iodo-4-nitroaniline (0.79 g, 3.00 mmol, 1.0 equiv), DMAP (18.3 mg, 0.10 mmol, 5 mol %), Et_3N (0.84 mL, 6.00 mmol, 2.0 equiv) in CH_2Cl_2 (10 mL) at −20 °C dropwise. After stirring at −20 °C for 30 min and room temperature overnight, the mixture was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. After filtration and concentration, the obtained crude amide was used in the next step without purification.

Sodium hydride (240 mg, 60% in mineral oil, 4.00 mmol, 2.0 equiv) was added to a solution of the above amide in THF/DMF (15/5 mL) at 0 °C for portions. After stirring at 0 °C for 20 min MeI (0.56 mL, 9.00 mmol, 3.0 equiv) added dropwise and the reaction mixture was allowed to stir at room temperature for 3 h. The reaction was quenched with water and THF was removed by evaporation and diluted with 100 mL ethyl acetate. The organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated afforded the crude pruduct. After purified by column chromatography on silica

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gel (PE:EA = 10:1 to PE:EA = 5:1) the desired amide **1f** (0.73 g, 77%) was obtained as solid: mp 97.1−101.4 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) 8.73 (s, 1H), 8.23 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 6.8 Hz, 1H), 5.10 (s, 2H), 3.28 (s, 3H), 1.90 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 152.9 (bs), 146.6, 139.7, 135.3, 129.4, 124.5, 120.1 (bs), 98.6, 36.7 (bs), 20.3 HRMS (ESI) calcd. for $C_{11}H_{11}N_2O_3INa^+$ $(M + Na)^+$ 368.9712, found 368.9709.

***N*-(2-Iodo-5-methoxyphenyl)-*N*-methylmethacrylamide (1g).** **1g** (10% ethyl acetate/hexanes) (0.80 g, 80%) was prepared following the procedure of **1d** in 3.00 mmol scale. Solid: mp 128.9−132.8 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.8 Hz, 1H), 6.73 (d, J = 2.0 Hz, 1H), 6.62 (dd, J = 8.8, 2.8 Hz, 1H), 5.10 (s, 1H), 5.01 (s, 1H), 3.78 (s, 3H), 3.22 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 160.6, 147.6, 140.2, 140.0, 119.0, 115.4, 115.3, 87.2, 55.5, 36.7, 20.6. HRMS (ESI) calcd. for $C_{12}H_{14}NO_2INa^+$ $(M + Na)^+$ 353.9967, found 353.9964.

***N*-(2-Bromo-4-methylphenyl)-*N*-methylmethacrylamide (1u).** **1u** (R_f = 0.3, PE:EA = 5:1) (0.48 g, 85%) as oil was prepared following the procedure of **1d** in 2.00 mmol scale. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 5.01 (s, 1H), 4.96 (s, 1H), 3.22 (s, 3H), 2.33 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 140.8, 140.2, 139.6, 134.1, 129.4, 129.2, 122.5, 118.4, 36.4, 20.7, 20.3. HRMS (ESI) calcd. for $C_{12}H_{15}NO^{79}Br^+$ $(M + H)^+$ 268.0332, found 268.0331.

***N*-(2-Bromo-5-methylphenyl)-*N*-methylmethacrylamide (1v).** **1v** (R_f = 0.3, PE:EA = 5:1) (0.50 g, 94%, as oil) was prepared following the procedure of **1d** in 2.00 mmol scale. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.0 Hz, 1H), 7.03−6.95 (m, 2H), 5.03 (s, 1H), 4.98 (s, 1H), 3.23 (s, 3H), 2.30 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 143.2, 140.2, 138.8, 133.3, 130.4, 130.0, 119.3, 118.5, 36.4, 20.8, 20.3. HRMS (ESI) calcd. for $C_{12}H_{15}NO^{79}Br^+$ $(M + H)^+$ 268.0332, found 268.03334.

***N*-(1-Bromonaphthalen-2-yl)-*N*-methylmethacrylamide (1w).** **1w** (R_f = 0.3, PE:EA = 5:1) (0.49 g, 89%) was prepared following the procedure of **1d** in 1.80 mmol scale. Solid: mp 78.4−80.8 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 8.8 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.68−7.61 (m, 1H),7.69−7.54 (m, 1H), 7.30 (d, J = 8.6 Hz, 1H), 5.03 (s, 1H), 4.93 (s, 1H), 3.34 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 141.4, 140.0, 133.2, 132.7, 128.9, 128.2, 128.1, 127.7, 127.2, 126.8, 123.1, 118.9, 36.4, 20.2. HRMS (ESI) calcd. for $C_{15}H_{15}NO^{79}Br^+$ $(M + H)^+$ 304.0332, found 304.0334.

***N*-(2-Iodophenyl)-*N*-(3-methylbut-3-enyl)acetamide (1j).**[25] Potassium hydroxide (0.21 g, 4.00 mmol, 2.0 equiv) and ^{n}Bu$_4$NHSO$_4$ (33.9 mg, 0.10 mmol, 0.05 equiv) was added successively to a solution of *N*-(2-iodophenyl)acetamide (0.52 g, 2.00 mmol, 1.0 equiv) in toluene (5 mL) at 20 °C and the mixture was stirred at this temperature for 1 h before warmed to 80 °C. 3-Methylbut-3-enyl 4-methylbenzenesulfonate (0.58 g, 2.40 mmol, 1.2 equiv) was added to the mixture and stirred at 80 °C for 1 h. The resulted solution was cooled to room temperature, quenched with 10 mL of water, extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (PE:EA = 10:1 to PE:EA:DCM = 10:1:1) to afford **1j** (0.50 g, 1.50 mmol, 75%) as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, J = 8.0, 1.6 Hz, 1H), 7.41 (td, J = 7.6, 1.6 Hz, 1H), 7.24 (dd, J = 8.0, 1.6 Hz, 1H), 7.08 (td, J = 8.0, 1.6 Hz, 1H), 4.76 (s, 1H), 4.71 (s, 1H), 4.34 (ddd, J = 13.2, 9.6, 6.4 Hz, 1H), 3.13 (ddd, J = 13.2, 9.6, 5.6 Hz, 1H), 2.38−2.17 (m, 2H), 1.76 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 145.0, 142.9, 140.3, 130.4, 129.8, 129.5, 111.7, 100.4, 46.6, 35.5, 23.0, 22.5. HRMS (ESI) calcd. for $C_{13}H_{17}NOI^+$ $(M + H)^+$ 330.0349, found 330.0349.

2-Benzyl-*N*-(2-iodophenyl)-*N*-methylacrylamide (1l). Sodium hydride (0.40 g, 60% in mineral oil, 10.0 mmol, 1.0 equiv) was added to a solution of dimethyl malonate (1.14 mL, 10.0 mmol, 1.0 equiv) in THF (20 mL) at 0 °C for portions under nitrogen, after stirring for 20 min BnBr (1.20 mL, 10.0 mmol, 1.0 equiv) was added to the mixture dropwise and the reaction mixture was allowed to warm to room temperature, and heated to reflux for 24 h. After cooling to room temperature, NaOH aq. (2 M, 10 mL) and MeOH (10 mL) was added to the reaction mixture and stirred at 90 °C for 1 h. After cooling down, MeOH and THF was removed by evaporation. The residue was acidized with 2 M HCl, extracted with ethyl acetate, dried over Na_2SO_4, concentrated, and the resulted mixture was added to a solution of diethylamine (1.2 mL, 11.5 mmol, 1.15 equiv) in EtOAc (20 mL) at 0 °C. Then paraformaldehyde (0.42 g, 14.0 mmol, 1.4 equiv) was added in portions. The mixture was warmed to reflux and maintained for 2 h. After cooled to room temperature, the reaction was acidized with 2 M HCl, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (PE:EA = 20:1 to PE:EA = 7:1) to afford 2-benzylacrylic acid (1.08 g, 6.70 mmol, 67%).[26]

Oxalyl dichloride (0.34 mL, 4.00 mmol, 2.0 equiv) was added to a solution of 2-benzylacrylic acid (0.32 g, 2.00 mmol, 1.0 equiv) with a drop of DMF in DCM (10 mL) at room temperature dropwise. The reaction was maintain at room temperature for 30 min and the excess oxalyl dichloride and DCM was removed by evaporation.

The above acid chloride in DCM (10 mL) was added to a mixture of 2-iodoaniline (0.44 g, 2.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.10 mmol, 0.05 equiv), Et_3N (0.56 mL, 4.00 mmol, 2.0 equiv) in CH_2Cl_2 (10 mL) at −20 °C dropwise. After stirring at −20 °C for 30 min and room temperature overnight, the mixture was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. After filtration and concentration, the crude amide was used in next step without further purification.

Sodium hydride (0.24 g, 60% in mineral oil, 6.00 mmol, 3.0 equiv) was added to a solution of the above amide in THF (10 mL) at 0 °C for portions. After stirring for 20 min at 0 °C MeI (0.37 mL, 6.00 mmol, 3.0 equiv) added dropwise and the reaction mixture was stirred at room temperature for 2 h and 50 °C overnight. The reaction was quenched by the addition of water, extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica (PE:EA = 10:1) to afford **1l** (0.31 g, 0.84 mmol, 42%) as oil. Rotamers (10:1) were observed. The major isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.0 Hz, 1H), 7.35−7.19 (m, 3H), 7.14 (t, J = 7.2 Hz, 1H), 7.07 (d, J = 6.8 Hz, 2H), 6.95 (t, J = 7.6 Hz, 1H), 6.43 (d, J = 7.2 Hz, 1H), 5.08 (s, 1H), 4.84 (s, 1H), 3.71 (d, J = 15.2 Hz, 1H), 3.42 (d, J = 15.2 Hz, 1H), 3.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 146.7, 143.7, 140.0, 137.8, 129.6, 129.5, 129.3, 129.1, 128.4, 126.4, 118.7, 98.9, 40.3, 36.9. HRMS (ESI) calcd. for $C_{17}H_{17}NOI^+$ $(M + H)^+$ 378.0349, found 378.0346.

***N*-(2-Iodophenyl)-*N*-methyl-2-methylene-4-phenylbutanamide (1m).** Sodium hydride (0.37 g, 60% in mineral oil, 9.20 mmol, 1.2 equiv) was added to MeOH (10 mL) at 0 °C for portions under nitrogen. Then dimethyl malonate (0.89 mL, 7.70 mmol, 1.0 equiv) was added to the solution and the mixture was warmed to 65 °C. Followed by this $BnCH_2I$ (1.80 g, 7.70 mmol, 1.0 equiv) in MeOH (10 mL) was added to the above mixture in dropwise. After stirring at 65 °C for 4 h, NaOH (1 M, 40 mL) was added to the reaction mixture and stirred for 1 h. After cooling down, MeOH was removed by evaporation. The residue was acidized with 2 M HCl, extracted with ethyl acetate, dried over Na_2SO_4, concentrated, and the resulted mixture was added to a solution of diethylamine (0.90 mL, 8.90 mmol, 1.15 equiv) in EtOAc (20 mL) at 0 °C. After stirring at 0 °C for 5 min, paraformaldehyde (0.32 g, 10.0 mmol, 1.4 equiv) was added in portions. The mixture was heated to reflux for 2 h. After cooled to room temperature, the reaction was acidized by 2 M HCl, extracted with EtOAc, washed with brine, dried over Na_2SO_4, concentrated. The residue was purified by column chromatography on silica (PE:EA = 5:1) to afford 2-methylene-4-phenylbutanoic acid (0.24 g, 1.35 mmol, 18%).

Oxalyl dichloride (0.23 mL, 2.70 mmol, 2.0 equiv) was added to a solution of 2-methylene-4-phenylbutanoic acid (0.24 g, 1.35 mmol, 1.0 equiv) with a drop of DMF in DCM (6 mL) at room temperature dropwise. The reaction maintained at room temperature for 30 min and the excess oxalyl dichloride and DCM was removed by evaporation.

The above acid chloride in DCM (6 mL) was added to a mixture of 2-iodoaniline (0.30 g, 1.35 mmol, 1.0 equiv), DMAP (8.2 mg, 0.067

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J. Org. Chem. 2015, 80, 7547−7554

mmol, 0.05 equiv), Et_3N (0.38 mL, 2.70 mmol, 2.0 equiv) in CH_2Cl_2 (6 mL) at −20 °C dropwise. After stirring at −20 °C for 30 min and room temperature overnight, the mixture was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. After filtration and concentration, the crude amide was used in next step without further purification.

Sodium hydride (0.11 g, 60% in mineral oil, 2.7 mmol, 2.0 equiv) was added to a solution of the above amide in THF (10 mL) at 0 °C for portions. After stirring at 0 °C for 20 min MeI (0.25 mL, 4.05 mmol, 3.0 equiv) added dropwise and the reaction mixture was allowed to stir at room temperature for 3 h. The reaction was quenched by the addition of water, extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, concentrated. The crude product was purified by column chromatography on silica (PE:EA = 10:1 to PE:EA = 5:1) to afford **1m** (0.32 g, 0.82 mmol, 61%) as oil. Rotamers (8:1) were observed. The major isomer's ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.0 Hz, 1H), 7.37−7.09 (m, 7H), 7.01 (t, J = 7.6 Hz, 1H), 5.16 (s, 1H), 5.02 (s, 1H), 3.26 (s, 3H), 2.87−2.65 (m, 2H), 2.57−2.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 146.7, 143.8, 141.3, 140.2, 129.6, 129.3, 129.2, 128.3, 128.2, 125.9, 118.2, 99.1, 36.9, 35.2, 34.1. HRMS (ESI) calcd. for $C_{18}H_{19}NOI^+$ $(M + H)^+$ 392.0506, found 392.0502.

***N*-(2-Iodophenyl)-2-(methoxymethyl)-*N*-methylacrylamide (1o).** Thionyl chloride (0.87 mL, 12.0 mmol, 1.2 equiv) was added to acrylic acid (0.90 mL, 13.0 mmol, 1.3 equiv) at 80 °C dropwise. The reaction was stirred at 80 °C for 30 min. After cooling down, the excess thionyl chloride was carefully removed by evaporation at about 40 mmHg.

The above acid chloride in DCM (20 mL) was added to a mixture of 2-iodoaniline (2.2 g, 10.0 mmol, 1.0 equiv), DMAP (60.0 mg, 0.50 mmol, 0.05 equiv), Et_3N (2.8 mL, 20.0 mmol, 2.0 equiv) in CH_2Cl_2 (20 mL) at −20 °C dropwise. After stirring at −20 °C for 30 min and room temperature overnight, the mixture was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. After filtration and concentration, the crude amide was used in next step without further purification.

Sodium hydride (0.80 g, 60% in mineral oil, 20.0 mmol, 2.0 equiv) was added to a solution of the above amide in THF (10 mL) at 0 °C for portions. After stirring at 0 °C for 20 min MeI (1.90 mL, 30.0 mmol, 3.0 equiv) added dropwise and the reaction mixture was allowed to stir at room temperature for 3 h. The reaction was quenched by the addition of water, extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, concentrated. The crude product was purified by column chromatography on silica gel (PE:EA = 10:1) to afford *N*-(2-iodophenyl)-*N*-methylacrylamide (1.47 g, 5.00 mmol, 50%).[27] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, J = 8.0, 1.2 Hz, 1H), 7.42 (td, J = 7.6, 1.6 Hz, 1H), 7.29−7.22 (m, 1H), 7.08 (td, J = 7.6, 1.6 Hz, 1H), 6.38 (dd, J = 16.4, 1.6 Hz, 1H), 5.83 (dd, J = 16.8, 10.4 Hz, 1H), 5.51 (dd, J = 10.4, 2.0 Hz, 1H), 3.24 (s, 3H).

N-(2-Iodophenyl)-*N*-methylacrylamide (1.44 g, 5.00 mmol, 1.0 equiv) was added to a mixture of paraformaldehyde (0.75 g, 25.0 mmol, 5.0 equiv), DABCO (0.56 g, 5.00 mmol, 1.0 equiv), BnOH (130 μL, 1.25 mmol, 0.25 equiv) in *t*-BuOH/H_2O (1:4, 2.0 mL) at 55 °C dropwise. The reaction mixture was stirred at 55 °C for 5 h. After cooling down, ^{t}BuOH was removed by evaporation. The residue was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated. the crude product was purified by column chromatography on silica gel (PE:EA = 1:1) to afford 2-(hydroxymethyl)-*N*-(2-iodophenyl)-*N*-methylacrylamide **4** (1.23 g, 3.90 mmol, 77%).[28] Rotamers (13:1) were observed. The major isomer's ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.6 Hz, 1H), 7.36 (t, J = 7.2 Hz, 1H), 7.24 (d, J = 6.8 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 5.27 (s, 1H), 5.06 (s, 1H), 4.36 (d, J = 13.6 Hz, 1H), 4.10 (d, J = 13.6 Hz, 1H), 3.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 146.6, 142.5, 140.2, 129.6, 129.4, 119.9, 98.8, 64.6, 37.0. HRMS (ESI) calcd. for $C_{11}H_{13}NO_2I^+$ $(M + H)^+$ 317.9986, found 317.9984.

Sodium hydride (0.12 g, 60% in mineral oil, 3.0 mmol, 1.5 equiv) was added to a solution of the 2-(hydroxymethyl)-*N*-(2-iodophenyl)-*N*-methylacrylamide **4** (0.63 g, 2.00 mmol, 1.0 equiv) in THF (5 mL) at 0 °C for portions. After stirring at 0 °C for 20 min MeI (0.25 mL, 4.00 mmol, 2.0 equiv) added dropwise and the reaction mixture was allowed to stir at room temperature for 2 h. The reaction was quenched by the addition of water, extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (PE:EA = 7:1 to PE:EA = 5:1) to afford **1o** (0.39 g, 1.17 mmol, 60%) as viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 7.6 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.25−7.19 (m, 1H), 7.05−6.95 (m, 1H), 5.22 (s, 1H), 5.17 (s, 1H), 4.16 (d, J = 13.2 Hz, 1H), 3.87 (d, J = 13.2 Hz, 1H), 3.27 (s, 3H), 3.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 146.6, 140.7, 140.0, 129.8, 129.4, 129.2, 119.0, 98.9, 72.8, 58.4, 36.9. HRMS (ESI) calcd. for $C_{12}H_{15}NO_2I^+$ $(M + H)^+$ 332.0142, found 332.0139.

***N*-Butyl-2-iodo-*N*-(2-methylallyl)benzamide (1p).** Sodium hydride (0.26 g, 60% in mineral oil, 6.70 mmol, 1.3 equiv) was added to a solution of *N*-butyl-2-iodobenzamide (1.56 g, 5.15 mmol, 1.0 equiv) in DMF (10 mL) at 0 °C for portions. The reaction mixture was warmed to 50 °C and stirred for 20 min. Then the mixture was cooled to 35 °C and 3-chloro-2-methylprop-1-ene (0.71 mL, 7.73 mmol, 1.5 equiv) added dropwise. After stirring at 35 °C for 1 h the reaction was quenched by the addition of water and extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel to afford **1p** (R_f = 0.7, PE:EA = 3:1) (1.42 g, 3.98 mmol, 77%) as oil. Rotamers (~1.6:1) were observed. The ^{1}H NMR as follows: **major** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 8.0, 0.8 Hz, 1H), 7.33 (td, J = 7.6, 1.2 Hz, 1H), 7.21 (d, J = 1.6 Hz, 1H), 7.09−6.98 (m, 1H), 4.92−4.87 (m, 1H), 4.85 (t, J = 1.6 Hz, 1H), 3.66 (d, J = 16.0 Hz, 1H), 3.60 (d, J = 16.0 Hz, 1H), 3.10−2.88 (m, 2H), 1.80−1.59 (m, 2H), 1.56 (s, 3H), 1.47−1.31 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H); **minor** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 8.0, 1.2 Hz, 1H), 7.37 (td, J = 7.6, 1.2 Hz, 1H), 7.19 (d, J = 1.6 Hz, 1H), 7.09−6.98 (m, 1H), 5.00 (d, J = 1.6 Hz, 1H), 4.96 (t, J = 1.6 Hz, 1H), 4.39 (d, J = 15.2 Hz, 1H), 4.04−3.82 (m, 3H), 1.85 (s, 3H), 1.80−1.59 (m, 1H), 1.47−1.31 (m, 1H), 1.14−1.02 (m, 2H), 0.74 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), (selected peaks) δ 170.7, 170.6, 142.8, 142.3, 140.6, 140.2, 139.3, 139.0, 129.93, 129.90, 128.03, 128.00, 127.3, 127.2, 113.6, 112.9, 92.7, 92.5, 54.3, 44.3, 49.2, 47.2, 28.7, 29.9, 20.8, 20.5, 20.1, 19.8, 13.9, 13.5. HRMS (ESI) calcd. for $C_{15}H_{21}NOI^+$ $(M + H)^+$ 358.0662, found 358.0663.

***(E)*-*N*-(2-Iodophenyl)-N,2-dimethyl-3-phenylacrylamide (1q).** Oxalyl dichloride (0.51 mL, 6.0 mmol, 2.0 equiv) was added to a solution of 2-phenylacrylic acid (0.49 g, 3.0 mmol, 1.0 equiv) with a drop of DMF in DCM (10 mL) at room temperature dropwise. The reaction maintained at room temperature for 30 min and the excess oxalyl dichloride and DCM was removed by evaporation.

The above acid chloride in DCM (10 mL) was added to a mixture of 2-iodoaniline (0.66 g, 3.0 mmol, 1.0 equiv), DMAP (18.3 mg, 0.15 mmol, 0.05 equiv), Et3N (0.84 mL, 6.0 mmol, 2.0 equiv) in CH_2Cl_2 (10 mL) at −20 °C dropwise. After stirring at −20 °C for 30 min and room temperature overnight, the mixture was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. After filtration and concentration, the crude amide was used in next step without further purification.

Sodium hydride (0.36 g, 60% in mineral oil, 9.0 mmol, 3.0 equiv) was added to a solution of the above amide in THF (10 mL) at 0 °C for portions. After stirring at 0 °C for 20 min MeI (0.56 mL, 9.00 mmol, 3.0 equiv) added dropwise and the reaction mixture was allowed to stir at room temperature for 2 h. After quenched with water and evaporated THF, the residue was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, concentrated, and the crude product was purified by column chromatography on silica gel (PE:EA = 10:1) to afford **1q** (0.59 g, 1.56 mmol, 52%) as solid: mp 114.0−118.0 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 7.6, 1.2 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.29−7.15 (m, 4H), 7.08−6.95 (m, 3H), 6.69 (s, 1H), 3.31 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 147.1, 140.3, 136.0, 133.1, 132.9, 129.40, 129.39, 129.1, 128.9, 128.1, 127.3, 99.0, 37.1, 16.2. These data are identical with the reproted results.[29]

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2-(1,3-Dimethyl-2-oxoindolin-3-yl)acetic acid (2a). *Typical Procedure A.* (Table 1, entry 6): Chloroform (65 μL, 0.80 mmol, 4.0 equiv) was added to a mixture of **1a** (60.2 mg, 0.20 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 5 mol %), KOH (89.8 mg, 1.60 mmol, 8.0 equiv) and TFP (7.0 mg, 0.03 mmol, 15 mol %) under nitrogen, followed by H_2O (1.6 mL) was added. After stirring at room temperature for 0.5 min, dioxane (0.4 mL) was added and the reaction mixture was stirred at room temperature for additional 0.5 min before heated to 80 °C for 1 h. The reaction was quenched with 1 M HCl (6 mL) and extracted with EtOAc (3 × 20 mL) and dichloromethane (2 × 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1) to afford **2a** (41.2 mg, 94%). Solid: mp 172.0−176.0 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (td, *J* = 7.6, 1.2 Hz,1H), 7.19 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.07 (td, *J* = 7.6, 1.2 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 3.22 (s, 3H), 2.98 (d, *J* = 16.4 Hz, 1H), 2.80 (d, *J* = 16.4 Hz, 1H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 173.4, 143.0, 132.7, 128.3, 122.9, 122.3, 108.5, 45.3, 41.3, 26.5, 23.8. HRMS (ESI) calcd. for $C_{12}H_{12}NO_3^-$ $(M - H)^-$ 218.0812, found 218.0819. These data are identical with the reproted results.[30]

2-(1,3,5-Trimethyl-2-oxoindolin-3-yl)acetic acid (2b). Table 1, entry 1: **2b** (45.8 mg, 98%) (dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1b** (63.0 mg, 0.20 mmol, 1.0 equiv) at 80 °C for 1 h. Solid: mp 162.6 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 7.6 Hz, 1H), 7.00 (s, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 3.20 (s, 3H), 2.97 (d, *J* = 16.8 Hz, 1H), 2.77 (d, *J* = 16.8 Hz, 1H), 2.33 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 173.4, 140.6, 132.8, 132.5, 128.6, 123.2, 108.2, 45.3, 41.4, 26.5, 23.9, 21.1. HRMS (ESI) calcd. for $C_{13}H_{14}NO_3^-$ $(M - H)^-$ 232.0968, found 232.0976.

2-(5-Chloro-1,3-dimethyl-2-oxoindolin-3-yl)acetic acid (2c). **2c** (47.7 mg, 94%) (dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1c** (67.1 mg, 0.20 mmol, 1.0 equiv) at 80 °C for 1 h. Solid: mp 167.3−171.3 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 1H), 7.17 (s, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 3.19 (s, 3H), 3.00 (d, *J* = 16.8 Hz, 1H), 2.80 (d, *J* = 17.2 Hz, 1H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 173.8, 141.9, 134.4, 128.2, 128.0, 122.9, 109.3, 45.5, 41.0, 26.6, 24.0. HRMS (ESI) calcd. for $C_{12}H_{13}NO_3{}^{35}Cl^+$ $(M + H)^+$ 254.0579, found 254.0578.

2-(5-Fluoro-1,3-dimethyl-2-oxoindolin-3-yl)acetic acid (2d). **2d** (46.1 mg, 97%) (dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1d** (63.8 mg, 0.20 mmol, 1.0 equiv) at 80 °C for 1 h. Solid: mp 202.4−205.6 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03−6.95 (m, 2H), 6.78 (dd, *J* = 8.4, 4.0 Hz, 1H), 3.22 (s, 3H), 3.00 (d, *J* = 16.7 Hz, 1H), 2.81 (d, *J* = 16.7 Hz, 1H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 181.2, 172.5, 160.9 (d, *J* = 235.8 Hz), 142.2 (d, *J* = 1.5 Hz), 137.5 (d, *J* = 8.2 Hz), 115.6 (d, *J* = 23.4 Hz), 112.4 (d, *J* = 25.0 Hz), 110.5 (d, *J* = 8.1 Hz), 47.5, 42.5, 27.7, 25.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −120.0. HRMS (ESI) calcd. for $C_{12}H_{12}NO_3FNa^+$ $(M + Na)^+$ 260.0699, found 260.0699.

2-(1,3-Dimethyl-2-oxo-5-(trifluoromethyl)indolin-3-yl)acetic acid (2e). **2e** (53.1 mg, 93%) (dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1e** (73.8 mg, 0.20 mmol, 1.0 equiv) at 80 °C for 1 h. Solid: mp 167.8−170.0 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.41 (s, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 3.24 (s, 3H), 3.04 (d, *J* = 17.0 Hz, 1H), 2.87 (d, *J* = 17.0 Hz, 1H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 173.7, 146.4, 133.3, 126.1 (q, *J* = 3.9 Hz), 124.8 (q, *J* = 32.5 Hz), 124.3(q, *J* = 270.0 Hz), 119.3 (q, *J* = 3.6 Hz), 108.0, 45.2, 40.9, 26.6, 24.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.4. HRMS (ESI) calcd. for $C_{13}H_{12}NO_3F_3Na^+$ $(M + Na)^+$ 310.0667, found 310.0661.

2-(1,3-Dimethyl-5-nitro-2-oxoindolin-3-yl)acetic acid (2f). **2f** (14.5 mg, 27%) (dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1f** (69.2 mg, 0.20 mmol, 1.0 equiv) at 80 °C for 1 h. Solid: mp 168.8−172.5 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 8.6, 1.8 Hz, 1H), 8.07 (d, *J* = 1.7 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 3.27 (s, 3H), 3.10 (d, *J* = 17.4 Hz, 1H), 2.93 (d, *J* = 17.3 Hz, 1H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 173.5, 149.3, 133.7, 125.7, 118.1, 107.8, 45.2, 40.8, 26.8, 24.1. HRMS (ESI) calcd. for $C_{12}H_{11}N_2O_5^-$ $(M - H)^-$ 263.0668, found 263.0673.

2-(6-Methoxy-1,3-dimethyl-2-oxoindolin-3-yl)acetic acid (2g). **2g** (48.0 mg, 96%) (dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1g** (66.2 mg, 0.20 mmol, 1.0 equiv) at 80 °C for 1 h. Solid: mp 165.0−167.2 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 7.6 Hz, 1H), 6.55 (d, *J* = 7.3 Hz, 1H), 6.44 (s, 1H), 3.82 (s, 3H), 3.20 (s, 3H), 2.94 (d, *J* = 15.7 Hz, 1H), 2.77 (d, *J* = 15.9 Hz, 1H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.0, 173.4, 160.3, 144.3, 124.7, 123.0, 106.5, 96.6, 55.5, 44.8, 41.5, 26.5, 24.0. HRMS (ESI) calcd. for $C_{13}H_{15}NO_4Na^+$ $(M + Na)^+$ 272.0899, found 272.0897.

2-(1-Benzyl-3-methyl-2-oxoindolin-3-yl)acetic acid (2h). **2h** (52.0 mg, 88%) (dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1h** (75.4 mg, 0.20 mmol, 1.0 equiv) at 80 °C for 1 h. Solid: mp 159.6−164.5 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.23 (m, 5H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.15 (td, *J* = 8.0, 1.2 Hz, 1H), 7.02 (td, *J* = 7.6, 0.8 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 4.98 (d, *J* = 16.0 Hz, 1H), 4.88 (d, *J* = 15.6 Hz, 1H), 3.09 (d, *J* = 16.8 Hz, 1H), 2.89 (d, *J* = 16.8 Hz, 1H), 1.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 173.5, 142.2, 135.6, 132.7, 128.8, 128.2, 127.6, 127.2, 122.9, 122.2, 109.6, 45.3, 44.0, 41.1, 24.6. The compound was identical with the reported data.[31]

2-(*N*-Acetyl-3-methylindolin-3-yl)acetic acid (2i). **2i** (43.5 mg, 93%) (dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1i** (63.0 mg, 0.20 mmol, 1.0 equiv) at 80 °C for 1 h. Solid: mp 168.5−170.4 °C (PE/EA). Rotamers (10:1) were abserved. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 4.28 (d, *J* = 10.8 Hz, 1H), 3.86 (d, *J* = 10.8 Hz, 1H), 2.73 (d, *J* = 15.6 Hz, 1H), 2.67 (d, *J* = 15.6 Hz, 1H), 2.25 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 169.2, 141.5, 138.0, 128.4, 124.1, 122.1, 117.3, 60.9, 44.5, 42.0, 26.3, 24.1. HRMS (ESI) calcd. for $C_{13}H_{14}NO_3^-$ $(M - H)^-$ 232.0968, found 232.0976.

2-(*N*-Acetyl-4-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetic acid (2j). **2j** (46.1 mg, 93%) (dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1j** (65.8 mg, 0.20 mmol, 1.0 equiv) at 80 °C for 1 h. Solid: mp 132.2 °C (PE/EA). Rotamers were observed, and as a result broad peaks were observed in both ^{1}H and ^{13}C NMR spectroscopies. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (bs, 1H), 7.34−7.24 (m, 1H), 7.22−6.81 (m, 3H), 4.44−4.05 (brs, 1H), 3.44 (brs, 1H), 2.63 (d, *J* = 14.8 Hz, 1H), 2.58 (d, *J* = 14.8 Hz, 1H), 2.31−2.10 (m, 4H), 1.80−1.62 (m, 1H), 1.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 170.8, 138.1(brs), 126.4, 125.9, 125.6, 124.8, 44.3(brs), 40.9(brs), 35.8, 35.5, 28.2, 22.8. HRMS (ESI) calcd. for $C_{14}H_{18}NO_3^+$ $(M + H)^+$ 248.1281, found 248.1281.

2-(4-Methyl-*N*-tosyl-1,2,3,4-tetrahydroquinolin-4-yl)acetic acid (2k). **2k** (58.9 mg, 82%, as oil) (dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1k** (88.3 mg, 0.20 mmol, 1.0 equiv) with $CHCl_3$ (8.0 equiv) at 100 °C for 3 h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.79 (m, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.24−7.16 (m, 4H), 7.16−7.09 (m, 1H), 3.89 (ddd, *J* = 14.0, 8.4, 3.6 Hz, 1H), 3.78 (ddd, *J* = 14.0, 7.6, 3.6 Hz, 1H), 2.42 (d, *J* = 14.4 Hz, 1H), 2.36 (s, 3H), 2.16 (d, *J* = 14.4 Hz, 1H), 1.87 (ddd, *J* = 14.0, 7.6, 3.6 Hz, 1H), 1.49 (ddd, *J* = 14.0, 8.4, 3.6 Hz, 1H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 143.8, 136.7, 136.3, 135.7, 129.6, 127.2, 126.9, 126.7, 125.2, 124.8, 45.9, 43.3, 34.6, 32.7, 28.5, 21.5. HRMS (ESI) calcd. for $C_{19}H_{20}NO_4S^-$ $(M - H)^-$ 358.1108, found 358.1114.

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J. Org. Chem. 2015, 80, 7547−7554

2-(3-Benzyl-*N*-methyl-2-oxoindolin-3-yl)acetic acid (2l). **2l** (56.2 mg, 94%) (dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1l** (75.4 mg, 0.20 mmol, 1.0 equiv) at 80 °C for 1 h. Solid: mp 136.6−142.6 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (td, J = 7.6, 1.2 Hz, 1H), 713−7.00 (m, 5H), 6.75 (d, J = 7.2 Hz, 2H), 6.58 (d, J = 7.6 Hz, 1H), 3.14 (d, J = 16.4 Hz, 1H), 3.07 (d, J = 12.8 Hz, 1H), 3.03 (d, J = 13.2 Hz, 1H), 2.94 (s, 3H), 2.91 (d, J = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 173.5, 143.6, 134.4, 129.9, 128.4, 127.5, 126.8, 123.2, 122.4, 108.1, 51.0, 43.6, 40.1, 26.1. HRMS (ESI) calcd. for $C_{18}H_{18}NO_3^+$ $(M + H)^+$ 296.1281, found 296.1278.

2-(*N*-Methyl-2-oxo-3-phenethylindolin-3-yl)acetic acid (2m). **2m** (59.7 mg, 96%) (dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1m** (78.2 mg, 0.20 mmol, 1.0 equiv) at 80 °C for 1 h. Solid: mp 95.4−99.6 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (td, J = 7.6, 1.2 Hz, 1H), 7.24−7.17 (m, 3H), 7.16−7.08 (m, 2H), 7.02−6.96 (m, 2H), 6.86 (d, J = 7.8 Hz, 1H), 3.20 (s, 3H), 3.01 (d, J = 16.4 Hz, 1H), 2.82 (d, J = 16.0 Hz, 1H), 2.35−2.16 (m, 2H), 2.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 173.6, 144.0, 140.6, 130.5, 128.6, 128.3, 128.2, 126.0, 123.0, 122.6, 108.4, 49.5, 41.1, 39.3, 30.0, 26.4. HRMS (ESI) calcd. for $C_{19}H_{18}NO_3^-$ $(M - H)^-$ 308.1281, found 308.1288.

2-(3-(Methoxymethyl)-*N*-methyl-2-oxoindolin-3-yl)-aceticacid (2o), and 3-(Methoxymethyl)-1,3-dimethylindolin-2-one (3o). The reaction of chloroform (65 μL, 0.80 mmol, 4.0 equiv) and **1o** (66.2 mg, 0.20 mmol, 1.0 equiv) following **Typical Procedure A** at 80 °C for 1 h afforded **2o** (31.1 mg, 68% as oil) and **3o** (11.2 mg, 27%, as viscous oil), (ethyl acetate:hexanes = 1:5 to dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.24 (m, 2H), 7.05 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 3.64 (d, J = 8.8 Hz, 1H), 3.45 (d, J = 8.8 Hz, 1H), 3.23 (s, 3H), 3.21 (s, 3H), 2.96 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.7, 173.6, 144.0, 129.8, 128.6, 123.4, 122.6, 108.2, 76.1, 59.6, 50.5, 37.5, 26.5. HRMS (ESI) calcd. for $C_{13}H_{16}NO_4^+$ $(M + H)^+$ 250.1074, found 250.1069. **3o**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.22 (m, 2H), 7.07 (td, J = 7.6, 0.8 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 3.63 (d, J = 9.0 Hz, 1H), 3.62 (d, J = 9.0 Hz, 1H), 3.23 (s, 3H), 3.22 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 143.5, 132.8, 128.0, 122.8, 122.4, 108.0, 77.1, 59.5, 49.3, 26.2, 19.7. HRMS (ESI) calcd. for $C_{12}H_{16}NO_2^+$ $(M + H)^+$ 206.1176, found 206.1173.

2-(*N*-Butyl-4-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetic acid (2p). **2p** (32.0 mg, 58%, as viscous oil) (dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1p** (71.4 mg, 0.20 mmol, 1.0 equiv) at 80 °C for 1 h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 3.78−3.61 (m, 2H), 3.55−3.37 (m, 2H), 2.71 (d, J = 14.4 Hz, 1H), 2.51 (d, J = 14.4 Hz, 1H), 1.70−1.54 (m, 2H), 1.50 (s, 3H), 1.43−1.30 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 164.2, 144.4, 132.2, 128.7, 128.2, 127.4, 123.6, 55.0, 47.4, 42.6, 36.2, 29.5, 22.5, 20.2, 13.8. HRMS (ESI) calcd. for $C_{16}H_{20}NO_3^-$ $(M - H)^-$ 274.1438, found 274.1444.

2-(1,3-Dimethyl-2-oxoindolin-3-yl)-2-phenylacetic acid (2q). **2q** (47.7 mg, 81%) (dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1q** (75.4 mg, 0.20 mmol, 1.0 equiv) at 80 °C for 1 h. Solid: mp 163.8−168.6 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.21 (m, 2H), 7.19−7.05 (m, 4H), 7.01−6.95 (m, 2H), 6.71−6.66 (m, 1H), 4.27 (s, 1H), 3.06 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 172.1, 142.2, 133.2, 131.7, 128.7, 128.5, 128.1, 128.0, 123.6, 123.2, 108.8, 59.9, 50.7, 26.4, 22.8. HRMS (ESI) calcd. for $C_{18}H_{18}NO_3^+$ $(M + H)^+$ 296.1279, found 296.1281.

Typical Procedure B. The reaction of chloroform (65 μL, 0.80 mmol, 4.0 equiv), **1t** (50.8 mg, 0.20 mmol, 1.0 equiv), $Pd(PPh_3)_2Cl_2$ (7.0 mg, 0.01 mmol, 5 mol %), KOH (89.8 mg, 1.60 mmol, 8.0 equiv) in H_2O (1.6 mL)/dioxane (0.4 mL) at 100 °C for 1 h afforded **2a** (38.3 mg, 87%) (dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1).

2-(1,3,6-Trimethyl-2-oxoindolin-3-yl)acetic acid (2v). **2v** (37.8 mg, 81%) (dichloromethane:ethyl acetate = 20:3 to ethyl acetate:hexanes:AcOH = 50:50:1) was obtained following **Typical Procedure B** at 0.20 mmol scale of **1v** (53.6 mg, 0.20 mmol, 1.0 equiv) at 100 °C for 1 h. Solid: mp 168.6−170.5 °C (PE/EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.69 (s, 1H), 3.21 (s, 3H), 2.96 (d, J = 16.4 Hz, 1H), 2.77 (d, J = 16.4 Hz, 1H), 2.38 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.8, 173.5, 143.1, 138.5, 129.8, 123.4, 122.1, 109.5, 45.0, 41.4, 26.4, 23.9, 21.8. HRMS (ESI) calcd. for $C_{13}H_{14}NO_3^-$ $(M - H)^-$ 232.0968, found 232.0977.

2-(1,3-Dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*g*]indol-3-yl)-acetic acid (2w). The reaction of chloroform (65 μL, 0.80 mmol, 4.0 equiv) and **1w** (60.8 mg 0.20 mmol, 1.0 equiv) following **Typical Procedure B** at 100 °C for 3 h afforded **1w** (16.9 mg, 28%) (dichloromethane:ethyl acetate = 200:5 to dichloromethane:ethyl acetate = 20:3 to ethyl acetate:AcOH = 100:1) and **2w** (33.2 mg, 62%). Solid: mp 259.3−261.9 °C (PE/EA). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (bs, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.93 (dd, J = 8.4, 3.2 Hz, 2H), 7.50 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.34 (t, J = 7.2 Hz, 1H), 3.24 (s, 3H), 3.03 (d, J = 16.6 Hz, 1H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 180.5, 170.9, 141.4, 129.9, 129.5, 129.0, 128.6, 127.0, 124.0, 123.1, 121.8, 110.3, 46.5, 41.4, 26.4, 23.9. HRMS (ESI) calcd. for $C_{16}H_{16}NO_3^+$ $(M + H)^+$ 270.1125, found 270.1122.

■ ASSOCIATED CONTENT

Supporting Information

CIF file for compound **2q**, copies of ^{1}H, ^{13}C and ^{19}F NMR spectra for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01126.

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Notes

The authors declare no competing financial interest.

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