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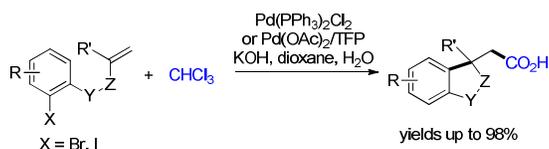


Palladium-Catalyzed Heck-type Domino Cyclization and Carboxylation to Synthesize Carboxylic Acids by Utilizing Chloroform as the Carbon Monoxide Source

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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

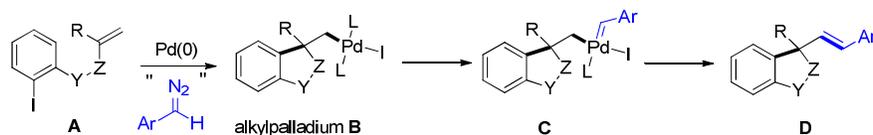
Since developed by Heck and co-workers in early 1970s,¹ the transition metal-catalyzed carbonylation with carbon monoxide became one of the most powerful methods for the synthesis of carbonyl compounds. In comparison with the traditional magnesium- or lithium-mediated reactions, transition metal-catalyzed carbonylation provides a mild and well-functional group tolerated method to prepare carbonyl substances.² Despite 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

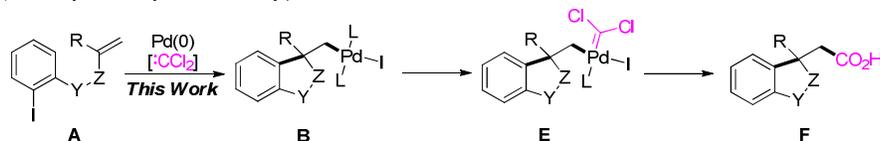
various dichlorocyclopropanes,⁹ which was further applied in the synthesis of 3-chloropyridine derivatives via Ciamician-Dennstedt rearrangement.¹⁰ The formylation of phenols named as Reimer-Tiemann reaction¹¹ and trichloromethylation of aldehyde¹² with chloroform are important one-carbon elongation methods. In the transition metal-involved reactions, chloroform was ever used for the synthesis of metalcarbonyl complexes,¹³ oxidative reagents¹⁴ and trichloromethylation reagents¹⁵ 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

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

(a) Alkenes Synthesis via Alkylpalladium and Aryl Carbenes



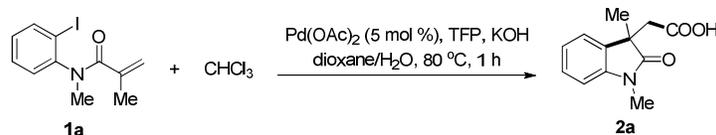
(b) Carboxylic Acid Synthesis via Alkylpalladium and Dichlorocarbene



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/H₂O, 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).

Table 1. Reaction Condition Optimization ^a



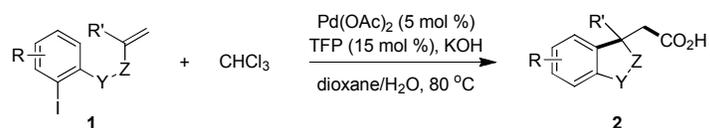
Entry	CHCl ₃ (equiv)	Dioxane/H ₂ O (2.0 mL)	TFP (mol %)	Yield of 2a /%
1	8.0	1:4	5	54
2	8.0	1:4	10	73
3	8.0	1:4	15	96
4	8.0	0:1	15	59-92
5	6.0	1:4	15	96
6	4.0	1:4	15	94
7	3.0	1:4	15	88
8	4.0 ^b	1:4	15	78

^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 CHBr₃ (4.0 equiv) was used instead of CHCl₃.

The generality of this domino cyclization and carboxylation reaction was demonstrated by subsection 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 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 consistent with the stereochemistry for the *cis*-insertion of C=C double bond to carbon-palladium bond. The reaction of allylic ether **1r** only

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3 resulted a complicated mixture (entry 18), and the malonate derivative **1s** decomposed under the
4 standard aqueous basic conditions (entry 19).
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8 **Table 2. Substrate Scope of Organic Iodides^a**
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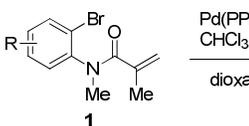
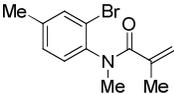
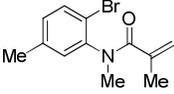
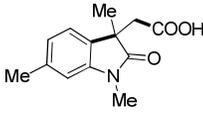
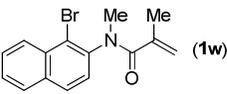
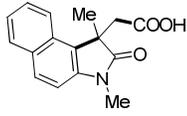


entry	halide 1	structure of 2	yield of 2 (%) ^p
1	R = Me (1b)		98 (2b)
2	R = Cl (1c)		94 (2c)
3	R = F (1d)		93 (2d)
4	R = CF ₃ (1e)		93 (2e)
5	R = NO ₂ (1f)		27 (2f)
6	(1g)		96 (2g)
7	(1h)		88 (2h)
8	R = Ac, n = 1 (1i)		93 (2i)
9	R = Ac, n = 2 (1j)		93 (2j)
10 ^c	R = Ts, n = 2 (1k)		82 (2k)
11	R = Bn (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
18	(1r)		complex
19	(1s)		decomposition

^a Reaction conditions: **1** (0.20 mmol), CHCl₃ (0.80 mmol), Pd(OAc)₂ (5 mol %), TFP (15 mol %), KOH (1.60 mmol) and dioxane/H₂O (1:4, 2.0 mL) at 80 °C for 1 h. ^b Isolated yields. ^c CHCl₃ (1.60 mmol) at 100 °C for 3 h.

For the aryl bromides, Pd(PPh₃)₂Cl₂ was found to be the optimum palladium catalyst (Table 3). For instance, the reaction of **1t-w** in dioxane/H₂O at 100 °C gave the desired products in good to excellent yields (entries 1-3). An incomplete conversion was observed with 2-bromo-1-aminonaphthalene derivative **1w** as the substrate, and the reaction afforded the **2w** in 62% yield along with 28% starting material being recovered (entry 4).

Table 3. Substrate Scope of Organic Bromides^a

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

^a Reaction conditions: **1** (0.20 mmol), CHCl₃ (0.80 mmol), Pd(PPh₃)₂Cl₂ (5 mol %), KOH (1.60 mmol) and dioxane/H₂O (1:4, 2.0 mL) at 100 °C for 1-3 h. ^b Isolated yields. ^c With 28% starting material being recovered.

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 N₂. Dioxane was distilled from sodium-benzophenone under an atmosphere of nitrogen. Dichloromethane were distilled from calcium hydride in a still under an atmosphere of nitrogen. Room temperature reactions were carried out between 20-25 °C. Flash column chromatography was performed using 40-63 μm silica gel as the stationary phase. ¹H, ¹³C and ¹⁹F NMR spectra were referenced by using solvent residue as an internal reference (¹H NMR: 7.26 ppm for CDCl₃; 2.50 ppm for DMSO-*d*₆; ¹³C NMR: 77.00 ppm for CDCl₃; 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

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 %), Et₃N (0.84 mL, 6.00 mmol, 2.0 equiv) in CH₂Cl₂ (10 mL) at -20 °C dropwise. After stirring at -20 °C for 30 min and room temperature overnight, the mixture was quenched with saturated NaHCO₃, extracted with CH₂Cl₂, washed with brine, and dried over Na₂SO₄. 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 washed with brine, dried over Na₂SO₄, 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). ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): δ 171.8, 160.8 (d, *J* = 252.1Hz), 143.3, 140.0, 129.8 (d, *J* = 8.4Hz), 126.9 (d, *J* = 24.4Hz), 119.0, 116.4 (d, *J* = 22.7 Hz), 98.9, 36.9, 20.5. ¹⁹F NMR (376 MHz, CDCl₃): δ -112.1. HRMS (ESI) calcd. for C₁₁H₁₁NOFINa⁺ (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). ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): δ 171.5, 150.4 (bs), 139.8, 137.2, 131.1 (q, *J* = 31.5Hz), 129.4, 126.5, 122.5 (q, *J* = 271.1Hz), 119.8 (bs), 98.9, 36.8, 20.4. ¹⁹F NMR (376 MHz, CDCl₃): δ -62.6. HRMS (ESI) calcd. for C₁₂H₁₁NOF₃INa⁺ (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 %), Et₃N (0.84 mL, 6.00 mmol, 2.0 equiv) in CH₂Cl₂ (10 mL) at -20 °C dropwise. After stirring at

-20 °C for 30 min and room temperature overnight, the mixture was quenched with saturated NaHCO₃, extracted with CH₂Cl₂, washed with brine, and dried over Na₂SO₄. 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 Na₂SO₄, filtered and concentrated afforded the crude product. After purified by column chromatography on silica 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). ¹H NMR (400 MHz, CDCl₃): 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), ¹³C NMR (100 MHz, CDCl₃): 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 C₁₁H₁₁N₂O₃INa⁺ (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). ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₂H₁₄NO₂INa⁺ (M+Na)⁺ 353.9967, found 353.9964.

***N*-(2-Bromo-4-methylphenyl)-*N*-methylmethacrylamide (**1u**):**

1u (Rf = 0.3, PE: EA = 5: 1) (0.48 g, 85%) as oil was prepared following the procedure of **1d** in 2.00 mmol scale. ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₂H₁₅NO⁷⁹Br⁺ (M+H)⁺ 268.0332, found 268.0331.

***N*-(2-Bromo-5-methylphenyl)-*N*-methylmethacrylamide (**1v**):**

1v (Rf = 0.3, PE: EA = 5: 1) (0.50 g, 94%, as oil) was prepared following the procedure of **1d** in 2.00 mmol scale. ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₂H₁₅NO⁷⁹Br⁺ (M+H)⁺ 268.0332, found 268.0334.

***N*-(1-Bromonaphthalen-2-yl)-*N*-methylmethacrylamide (**1w**):**

1w (Rf = 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). ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz,

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3 CDCl₃): 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,
4 36.4, 20.2. HRMS (ESI) calcd. for C₁₅H₁₅NO⁷⁹Br⁺ (M+H)⁺ 304.0332, found 304.0334.

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6 ***N*-(2-Iodophenyl)-*N*-(3-methylbut-3-enyl)acetamide (**1j**):²⁵**

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8 Potassium hydroxide (0.21 g, 4.00 mmol, 2.0 equiv) and ⁿBu₄NHSO₄ (33.9 mg, 0.10 mmol,
9 0.05 equiv) was added successively to a solution of *N*-(2-iodophenyl)acetamide (0.52 g, 2.00
10 mmol, 1.0 equiv) in toluene (5 mL) at 20 °C and the mixture was stirred at this temperature for 1 h
11 before warmed to 80 °C. 3-Methylbut-3-enyl 4-methylbenzenesulfonate (0.58 g, 2.40 mmol, 1.2
12 equiv) was added to the mixture and stirred at 80 °C for 1 h. The resulted solution was cooled to
13 room temperature, quenched with 10 mL water, extracted with EtOAc, dried over Na₂SO₄, filtered
14 and concentrated. The residue was purified by column chromatography on silica gel (PE: EA = 10:
15 1 to PE: EA: DCM = 10: 1: 1) to afford **1j** (0.50 g, 1.50 mmol, 75%) as oil. ¹H NMR (400 MHz,
16 CDCl₃): 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,
17 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),
18 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); ¹³C NMR (100
19 MHz, CDCl₃): 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,
20 22.5. HRMS (ESI) calcd. for C₁₃H₁₇NOI⁺ (M+H)⁺ 330.0349, found 330.0349.

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26 ***2*-Benzyl-*N*-(2-iodophenyl)-*N*-methylacrylamide (**1l**):**

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28 Sodium hydride (0.40 g, 60% in mineral oil, 10.0 mmol, 1.0 equiv) was added to a solution of
29 dimethyl malonate (1.14 mL, 10.0 mmol, 1.0 equiv) in THF (20 mL) at 0 °C for portions under
30 nitrogen, after stirring for 20 min BnBr (1.20 mL, 10.0 mmol, 1.0 equiv) was added to the mixture
31 dropwise and the reaction mixture was allowed to warm to room temperature, and heated to reflux
32 for 24 h. After cooling to room temperature, NaOH aq. (2 M, 10 mL) and MeOH (10 mL) was
33 added to the reaction mixture and stirred at 90 °C for 1 h. After cooling down, MeOH and THF
34 was removed by evaporation. The residue was acidized with 2 M HCl, extracted with ethyl acetate,
35 dried over Na₂SO₄, concentrated, and the resulted mixture was added to a solution of diethylamine
36 (1.2 mL, 11.5 mmol, 1.15 equiv) in EtOAc (20 mL) at 0 °C. Then paraformaldehyde (0.42 g, 14.0
37 mmol, 1.4 equiv) was added in portions. The mixture was warmed to reflux and maintained for 2 h.
38 After cooled to room temperature, the reaction was acidized with 2 M HCl, extracted with EtOAc,
39 washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by
40 column chromatography on silica gel (PE: EA = 20: 1 to PE: EA = 7: 1) to afford 2-benzylacrylic
41 acid (1.08 g, 6.70 mmol, 67%).²⁶

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

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48 The above acid chloride in DCM (10 mL) was added to a mixture of 2-iodoaniline (0.44 g, 2.00
49 mmol, 1.0 equiv), DMAP (12.2 mg, 0.10 mmol, 0.05 equiv), Et₃N (0.56 mL, 4.00 mmol, 2.0 equiv)
50 in CH₂Cl₂ (10 mL) at -20 °C dropwise. After stirring at -20 °C for 30 min and room temperature
51 overnight, the mixture was quenched with saturated NaHCO₃, extracted with CH₂Cl₂, washed with
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3 brine, and dried over Na₂SO₄. After filtration and concentration, the crude amide was used in next
4 step without further purification.
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6 Sodium hydride (0.24 g, 60% in mineral oil, 6.00 mmol, 3.0 equiv) was added to a solution of
7 the above amide in THF (10 mL) at 0 °C for portions. After stirring for 20 min at 0 °C MeI (0.37
8 mL, 6.00 mmol, 3.0 equiv) added dropwise and the reaction mixture was stirred at room
9 temperature for 2 h and 50 °C overnight. The reaction was quenched by the addition of water,
10 extracted with ethyl acetate, washed with brine, dried over Na₂SO₄, filtered and concentrated. The
11 crude product was purified by column chromatography on silica (PE: EA = 10: 1) to afford **11**
12 (0.31 g, 0.84 mmol, 42%) as oil. Rotamers (10: 1) were observed. The major isomer ¹H NMR
13 (400 MHz, CDCl₃): 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,
14 *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
15 (d, *J* = 15.2 Hz, 1H), 3.42 (d, *J* = 15.2 Hz, 1H), 3.20 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ
16 170.9, 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.
17 HRMS (ESI) calcd. for C₁₇H₁₇NOI⁺ (M+H)⁺ 378.0349, found 378.0346.
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19 ***N*-(2-Iodophenyl)-*N*-methyl-2-methylene-4-phenylbutanamide (1m):**

20 Sodium hydride (0.37 g, 60% in mineral oil, 9.20 mmol, 1.2 equiv) was added to MeOH (10
21 mL) at 0 °C for portions under nitrogen. Then dimethyl malonate (0.89 mL, 7.70 mmol, 1.0 equiv)
22 was added to the solution and the mixture was warmed to 65 °C. Followed by this BnCH₂I (1.80 g,
23 7.70 mmol, 1.0 equiv) in MeOH (10 mL) was added to the above mixture in dropwise. After
24 stirring at 65 °C for 4 h, NaOH (1 M, 40 mL) was added to the reaction mixture and stirred for 1 h.
25 After cooling down, MeOH and was removed by evaporation. The residue was acidized with 2 M
26 HCl, extracted with ethyl acetate, dried over Na₂SO₄, concentrated, and the resulted mixture was
27 added to a solution of diethylamine (0.90 mL, 8.90 mmol, 1.15 equiv) in EtOAc (20 mL) at 0 °C.
28 After stirring at 0 °C for 5 min, paraformaldehyde (0.32 g, 10.0 mmol, 1.4 equiv) was added in
29 portions. The mixture was heated to reflux for 2 h. After cooled to room temperature, the reaction
30 was acidized by 2 M HCl, extracted with EtOAc, washed with brine, dried over Na₂SO₄,
31 concentrated. The residue was purified by column chromatography on silica (PE: EA = 5: 1) to
32 afford 2-methylene-4-phenylbutanoic acid (0.24 g, 1.35 mmol, 18%).
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34 Oxalyl dichloride (0.23 mL, 2.70 mmol, 2.0 equiv) was added to a solution of
35 2-methylene-4-phenylbutanoic acid (0.24 g, 1.35 mmol, 1.0 equiv) with a drop of DMF in DCM
36 (6 mL) at room temperature dropwise. The reaction was maintain at room temperature for 30 min
37 and the excess oxalyl dichloride and DCM was removed by evaporation.
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39 The above acid chloride in DCM (6 mL) was added to a mixture of 2-iodoaniline (0.30 g, 1.35
40 mmol, 1.0 equiv), DMAP (8.2 mg, 0.067 mmol, 0.05 equiv), Et₃N (0.38 mL, 2.70 mmol, 2.0 equiv)
41 in CH₂Cl₂ (6 mL) at -20 °C dropwise. After stirring at -20 °C for 30 min and room temperature
42 overnight, the mixture was quenched with saturated NaHCO₃, extracted with CH₂Cl₂, washed with
43 brine, and dried over Na₂SO₄. After filtration and concentration, the crude amide was used in next
44 step without further purification.
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3 Sodium hydride (0.11 g, 60% in mineral oil, 2.7 mmol, 2.0 equiv) was added to a solution of the
4 above amide in THF (10 mL) at 0 °C for portions. After stirring at 0 °C for 20 min MeI (0.25 mL,
5 4.05 mmol, 3.0 equiv) added dropwise and the reaction mixture was allowed to stir at room
6 temperature for 3 h. The reaction was quenched by the addition of water, extracted with ethyl
7 acetate, washed with brine, dried over Na₂SO₄, concentrated. The crude product was purified by
8 column chromatography on silica (PE: EA = 10: 1 to PE: EA = 5: 1) to afford **1m** (0.32 g, 0.82
9 mmol, 61%) as oil. Rotamers (8: 1) were observed. The major isomer's ¹H NMR (400 MHz,
10 CDCl₃): 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
11 (s, 1H), 3.26 (s, 3H), 2.87-2.65 (m, 2H), 2.57-2.36 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 171.4,
12 146.7, 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.
13 HRMS (ESI) calcd. for C₁₈H₁₉NOI⁺ (M+H)⁺ 392.0506, found 392.0502.

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15 ***N*-(2-Iodophenyl)-2-(methoxymethyl)-*N*-methylacrylamide (1o):**

16 Thionyl chloride (0.87 mL, 12.0 mmol, 1.2 equiv) was added to acrylic acid (0.90 mL, 13.0
17 mmol, 1.3 equiv) at 80 °C dropwise. The reaction was stirred at 80 °C for 30 min. After cooling
18 down, the excess thionyl chloride was carefully removed by evaporation at about 40 mmHg.

19 The above acid chloride in DCM (20 mL) was added to a mixture of 2-iodoaniline (2.2 g, 10.0
20 mmol, 1.0 equiv), DMAP (60.0 mg, 0.50 mmol, 0.05 equiv), Et₃N (2.8 mL, 20.0 mmol, 2.0 equiv)
21 in CH₂Cl₂ (20 mL) at -20 °C dropwise. After stirring at -20 °C for 30 min and room temperature
22 overnight, the mixture was quenched with saturated NaHCO₃, extracted with CH₂Cl₂, washed with
23 brine, and dried over Na₂SO₄. After filtration and concentration, the crude amide was used in next
24 step without further purification.

25 Sodium hydride (0.80 g, 60% in mineral oil, 20.0 mmol, 2.0 equiv) was added to a solution of
26 the above amide in THF (10 mL) at 0 °C for portions. After stirring at 0 °C for 20 min MeI (1.90
27 mL, 30.0 mmol, 3.0 equiv) added dropwise and the reaction mixture was allowed to stir at room
28 temperature for 3 h. The reaction was quenched by the addition of water, extracted with ethyl
29 acetate, washed with brine, dried over Na₂SO₄, concentrated. The crude product was purified by
30 column chromatography on silica gel (PE: EA = 10: 1) to afford
31 *N*-(2-iodophenyl)-*N*-methylacrylamide (1.47 g, 5.00 mmol, 50%).²⁷ ¹H NMR (400 MHz, CDCl₃):
32 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,
33 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,
34 2.0 Hz, 1H), 3.24 (s, 3H).

35 *N*-(2-Iodophenyl)-*N*-methylacrylamide (1.44 g, 5.00 mmol, 1.0 equiv) was added to a mixture
36 of paraformaldehyde (0.75 g, 25.0 mmol, 5.0 equiv), DABCO (0.56 g, 5.00 mmol, 1.0 equiv),
37 BnOH (130 μL, 1.25 mmol, 0.25 equiv) in *t*-BuOH/H₂O (1:4, 2.0 mL) at 55 °C dropwise. The
38 reaction mixture was stirred at 55 °C for 5 h. After cooling down, ^tBuOH was removed by
39 evaporation. The residue was extracted with CH₂Cl₂, dried over Na₂SO₄, filtered and concentrated.
40 the crude product was purified by column chromatography on silica gel (PE: EA = 1: 1) to afford
41 2-(hydroxymethyl)-*N*-(2-iodophenyl)-*N*-methylacrylamide **4** (1.23 g, 3.90 mmol, 77%).²⁸
42 Rotamers (13: 1) were observed. The major isomer's ¹H NMR (400 MHz, CDCl₃): 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 $\text{C}_{11}\text{H}_{13}\text{NO}_2\text{I}^+$ ($\text{M}+\text{H}$) $^+$ 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. ^1H 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 $\text{C}_{12}\text{H}_{15}\text{NO}_2\text{I}^+$ ($\text{M}+\text{H}$) $^+$ 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 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 ^1H NMR as follows : **major** ^1H 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** ^1H 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 $\text{C}_{15}\text{H}_{21}\text{NOI}^+$ ($\text{M}+\text{H}$) $^+$ 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 was 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 CH₂Cl₂ (10 mL) at -20 °C dropwise. After stirring at -20 °C for 30 min and room temperature overnight, the mixture was quenched with saturated NaHCO₃, extracted with CH₂Cl₂, washed with brine, and dried over Na₂SO₄. 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 Na₂SO₄, 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). ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 reported results.²⁹

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 H₂O (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 Na₂SO₄, 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). ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₂H₁₂NO₃⁻ (M-H)⁻ 218.0812, found 218.0819. These data are identical with the reported 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). ¹H NMR (400

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3 MHz, CDCl₃): 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
4 (d, *J* = 16.8 Hz, 1H), 2.77 (d, *J* = 16.8 Hz, 1H), 2.33 (s, 3H), 1.38 (s, 3H); ¹³C NMR (100 MHz,
5 CDCl₃): 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.
6 HRMS (ESI) calcd. for C₁₃H₁₄NO₃⁻ (M-H)⁻ 232.0968, found 232.0976.
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9 **2-(5-Chloro-1,3-dimethyl-2-oxindolin-3-yl)acetic acid (2c):**

10 **2c** (47.7 mg, 94%) (dichloromethane: ethyl acetate = 20: 3 to ethyl acetate: hexanes: AcOH = 50:
11 50: 1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1c** (67.1 mg, 0.20
12 mmol, 1.0 equiv) at 80 °C for 1 h. Solid: mp 167.3-171.3 °C (PE/EA). ¹H NMR (400 MHz,
13 CDCl₃): 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* =
14 16.8 Hz, 1H), 2.80 (d, *J* = 17.2 Hz, 1H), 1.35 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 179.6, 173.8,
15 141.9, 134.4, 128.2, 128.0, 122.9, 109.3, 45.5, 41.0, 26.6, 24.0. HRMS (ESI) calcd. for
16 C₁₂H₁₃NO₃³⁵Cl⁺ (M+H)⁺ 254.0579, found 254.0578.
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19 **2-(5-Fluoro-1,3-dimethyl-2-oxindolin-3-yl)acetic acid (2d):**

20 **2d** (46.1 mg, 97%) (dichloromethane: ethyl acetate = 20: 3 to ethyl acetate: hexanes: AcOH = 50:
21 50: 1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1d** (63.8 mg, 0.20
22 mmol, 1.0 equiv) at 80 °C for 1 h. Solid: mp 202.4-205.6 °C (PE/EA). ¹H NMR (400 MHz,
23 CDCl₃): 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,
24 1H), 2.81 (d, *J* = 16.7 Hz, 1H), 1.40 (s, 3H); ¹³C NMR (100 MHz, Acetone-d₆): δ 181.2, 172.5,
25 160.9 (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* =
26 25.0 Hz), 110.5 (d, *J* = 8.1 Hz), 47.5, 42.5, 27.7, 25.6. ¹⁹F NMR (376 MHz, CDCl₃): δ -120.0.
27 HRMS (ESI) calcd. for C₁₂H₁₂NO₃FNa⁺ (M+Na)⁺ 260.0699, found 260.0699.
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30 **2-(1,3-Dimethyl-2-oxo-5-(trifluoromethyl)indolin-3-yl)acetic acid (2e):**

31 **2e** (53.1 mg, 93%) (dichloromethane: ethyl acetate = 20: 3 to ethyl acetate: hexanes: AcOH = 50:
32 50: 1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1e** (73.8 mg, 0.20
33 mmol, 1.0 equiv) at 80 °C for 1 h. Solid: mp 167.8-170.0 °C (PE/EA). ¹H NMR (400 MHz,
34 CDCl₃): δ ¹H NMR (400 MHz, CDCl₃) δ 7.56 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.41 (s, 1H), 6.91 (d, *J* =
35 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); ¹³C
36 NMR (100 MHz, CDCl₃): δ 180.0, 173.7, 146.4, 133.3, 126.1 (q, *J* = 3.9 Hz), 124.8 (q, *J* = 32.5
37 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. ¹⁹F NMR (376
38 MHz, CDCl₃): δ -61.4. HRMS (ESI) calcd. for C₁₃H₁₂NO₃F₃Na⁺ (M+Na)⁺ 310.0667, found
39 310.0661.
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42 **2-(1,3-Dimethyl-5-nitro-2-oxindolin-3-yl)acetic acid (2f):**

43 **2f** (14.5 mg, 27%) (dichloromethane: ethyl acetate = 20: 3 to ethyl acetate: hexanes: AcOH = 50:
44 50: 1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1f** (69.2 mg, 0.20
45 mmol, 1.0 equiv) at 80 °C for 1 h. Solid: mp 168.8-172.5 °C (PE/EA). ¹H NMR (400 MHz,
46 CDCl₃): 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,
47 3H), 3.10 (d, *J* = 17.4 Hz, 1H), 2.93 (d, *J* = 17.3 Hz, 1H), 1.39 (s, 3H); ¹³C NMR (100 MHz,
48 CDCl₃): 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)
49 calcd. for C₁₂H₁₁N₂O₅⁻ (M-H)⁻ 263.0668, found 263.0673.
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52 **2-(6-Methoxy-1,3-dimethyl-2-oxindolin-3-yl)acetic acid (2g):**

53 **2g** (48.0 mg, 96%) (dichloromethane: ethyl acetate = 20: 3 to ethyl acetate: hexanes: AcOH = 50:
54 50: 1) was obtained following **Typical Procedure A** at 0.20 mmol scale of **1g** (66.2 mg, 0.20
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mmol, 1.0 equiv) at 80 °C for 1 h. Solid: mp 165.0-167.2 °C (PE/EA). ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₃H₁₅NO₄Na⁺ (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). ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 observed. ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₃H₁₄NO₃⁻ (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 ¹H and ¹³C NMR spectroscopies. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₁₄H₁₈NO₃⁺ (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 CHCl₃ (8.0 equiv) at 100 °C for 3 h. ¹H NMR (400 MHz, CDCl₃): 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 $\text{C}_{19}\text{H}_{20}\text{NO}_4\text{S}^-$ (M-H) $^-$ 358.1108, found 358.1114.

2-(3-Benzyl- N-methyl-2-oxindolin-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). ^1H NMR (400 MHz, CDCl_3): δ 7.19 (td, $J = 7.6, 1.2$ Hz, 1H), 7.13-7.00 (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 $\text{C}_{18}\text{H}_{18}\text{NO}_3^+$ (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). ^1H 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 $\text{C}_{19}\text{H}_{18}\text{NO}_3^-$ (M-H) $^-$ 308.1281, found 308.1288.

2-(3-(Methoxymethyl)-N-methyl-2-oxindolin-3-yl)acetic acid (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). ^1H 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 $\text{C}_{13}\text{H}_{16}\text{NO}_4^+$ (M+H) $^+$ 250.1074, found 250.1069. **3o**: ^1H 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 $\text{C}_{12}\text{H}_{16}\text{NO}_2^+$ (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

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3 mg, 0.20 mmol, 1.0 equiv) at 80 °C for 1 h. ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₆H₂₀NO₃⁻ (M-H)⁻ 274.1438, found 274.1444.

11 **2-(1,3-Dimethyl-2-oxoindolin-3-yl)-2-phenylacetic acid (2q):**

12 **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). ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₈H₁₈NO₃⁺ (M+H)⁺ 296.1279, found 296.1281.

23 **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(PPh₃)₂Cl₂ (7.0 mg, 0.01 mmol, 5 mol %), KOH (89.8 mg, 1.60 mmol, 8.0 equiv) in H₂O (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).

29 **2-(1,3,6-Trimethyl-2-oxoindolin-3-yl)acetic acid (2v):**

30 **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). ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₃H₁₄NO₃⁻ (M-H)⁻ 232.0968, found 232.0977.

41 **2-(1,3-Dimethyl-2-oxo-2,3-dihydro-1H-benzo[g]indol-3-yl)acetic acid (2w):**

42 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). ¹H 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); ¹³C 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 C₁₆H₁₆NO₃⁺ (M+H)⁺ 270.1125, found 270.1122.

56 **ASSOCIATED CONTENT**

57 **Supporting Information**

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3 CIF file for compound **2q**, copies of ^1H , ^{13}C and ^{19}F NMR spectra for all new compounds. This
4 material is available free of charge via the Internet at <http://pubs.acs.org>
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9 Notes

10 The authors declare no competing financial interest.

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