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A Palladium-Catalyzed α-Arylation of Oxindoles with Aryl Tosylates

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Abstract:

A palladium-catalyzed mono-selective C3-arylation of 2-oxindoles with aryl tosylates is described. With the Pd/CM-phos catalyst system, the corresponding 3-arylated oxindoles can be obtained in good-to-excellent yields (up to 97%). The reaction conditions are mild (using 0.5 mol% Pd in general and KF as base) and functional groups, such as methyl ester, NH amido and enolizable keto moieties are found compatible.

Keywords: oxindoles, heteroarylation, palladium, arylation, cross-coupling

Oxindoles constitute an important heterocyclic subunit in various natural products and biologically active molecules.[1] Particularly the C3 aryl-containing oxindoles are useful lead compounds in drug discovery, for instances, the anti-cancer agent,[2] neuroprotective agent[3] and potent growth hormone secretagogue (Figure 1).[4] Synthetic methods for accessing this class of scaffold include nucleophilic substitution to isatins,[5] palladium[6] and copper-mediated[7] cyclization reaction, as well as the recently transition metal-free pathways.[8] Indeed, it is of high significance to have an approach which allows the integration of two individual components for preparing a cross array of structurally similar yet diversified compounds.[9] Thus, a versatile coupling of the already assembled oxindole core with arene is often desirable.

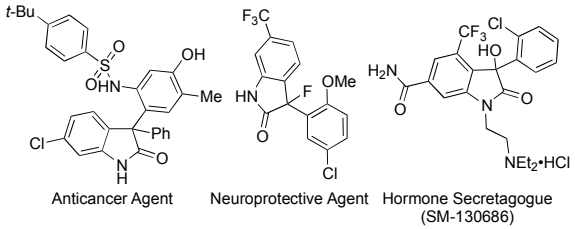
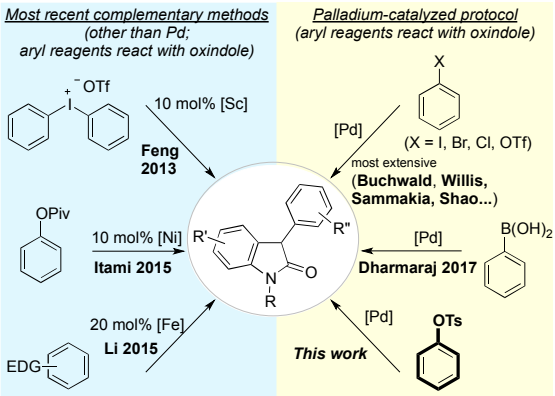


Figure 1. Examples of useful C3 aryl-containing oxindoles bioactive molecules

In 2013, Feng and co-workers reported scandium(III)-catalyzed α-arylation of oxindoles with diaryliodonium salts (Scheme 1).[10] The coupling of arylpivalates with oxindole catalyzed by Ni complex was disclosed by Yamaguchi and Itami recently (Scheme 1).[11] In 2015, Li described the Fe(III)-catalyzed cross-dehydrogenative arylation (CDA) between oxindoles and electron-rich arenes (Scheme 1).[12] The coupling of arylboronic acids with oxindoles was very recently found feasible.[13] Apart from these complementary developments, the investigations on the palladium-catalyzed coupling of oxindole enolates with aryl halides remain the most extensive (Scheme 1).[14] In fact, aryl sulfonates are worthy alternatives to aryl halides as their available phenolic substitution pattern would be different from arenes coming from traditional halogenation.[15] Nevertheless, the most reactive aryl triflates are easily decomposed when strong base and alcoholic solvent are used as the reaction medium. To overcome this drawback, aryl tosylate is therefore a better alternative in terms of superior stability towards alkaline hydrolysis as well as high economic attractiveness. Yet, this stable aryl tosylate leads to the requirement of using more active palladium complex to enable

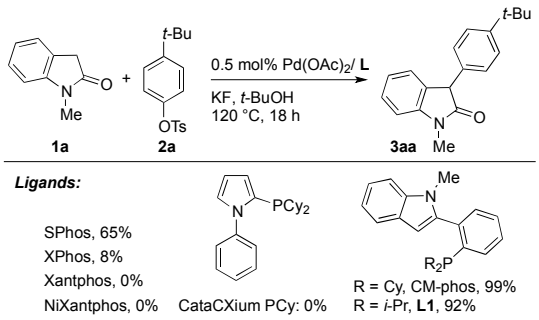
the $C_{(Ar)}$–O bond cleavage in the oxidative addition step. Thus, it is of demanding to develop an effective system for this direct arylation reaction. Herein, we report the first examples of α-arylation of oxindoles with aryl tosylates (Scheme 1). This process generally requires 0.5 mol% of palladium loading.

Scheme 1. Recent Pd-catalyzed and complementary methods for C3-aryloxindole synthesis from already assembled oxindoles and arenes



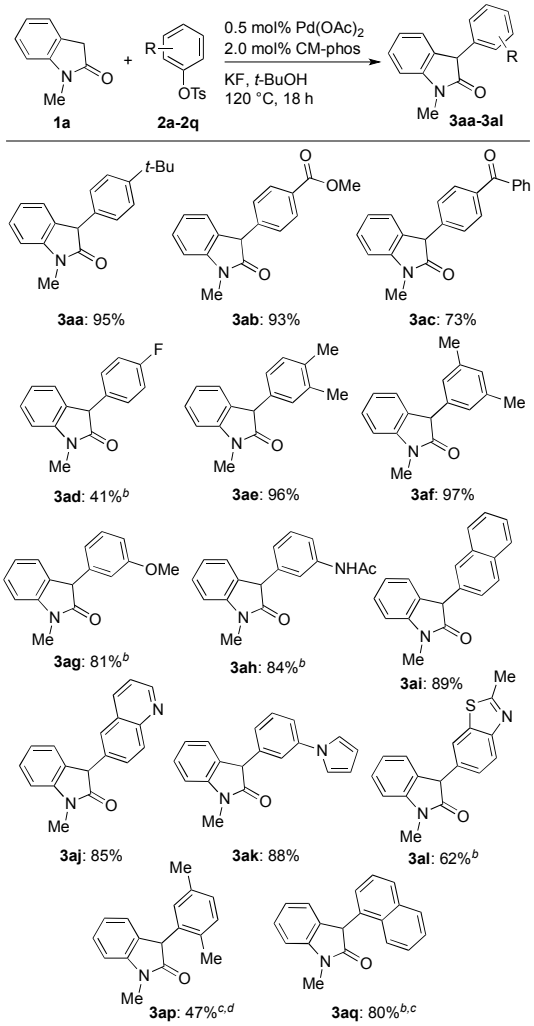
We initially selected the oxindole **1a** and non-activated aryl tosylate **2a** for feasibility test. Poor conversion was observed with XPhos,[16] whereas CataCXium PCy,[17] and Xantphos series did not promote this α-arylation. SPhos[16] gave the moderate product yield. In this ligand evaluation, CM-phos gave the best result and **L1** gave a slightly lower yield than CM-phos (Scheme 2).

Scheme 2. Evaluation of ligand efficacy for palladium-catalyzed direct arylation of *N*-methyloxindole[a]



[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), $Pd(OAc)_2$ (0.5 mol%), **L** (1.0-2.0 mol%), KF (0.9 mmol) and *t*-BuOH (1 mL) were stirred at 120 °C under nitrogen for 18 h. Yields were determined by GC-FID with dodecane as the internal standard.

Scheme 3. Palladium-catalyzed direct arylation of *N*-methyloxindole with ArOTs[a]

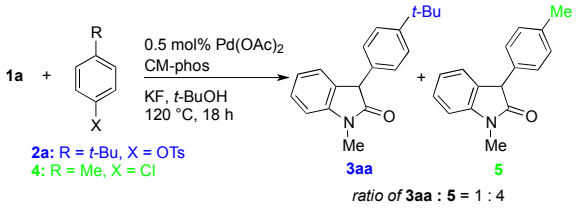


[a]Reaction conditions: **1a** (0.3 mmol), ArOTs **2** (0.45 mmol), $Pd(OAc)_2$ (0.5 mol%), CM-phos (2.0 mol%, Pd/L = 1:4), KF (0.9 mmol) and *t*-BuOH (1 mL) were stirred at 120 °C under nitrogen for 18 h. Isolated yields were reported. Reaction times were not optimized for each substrate. [b]1.0 mol% of $Pd(OAc)_2$ was used. [c]CsF was used instead of KF. [d]2.0 mol% of $Pd(OAc)_2$ was used.

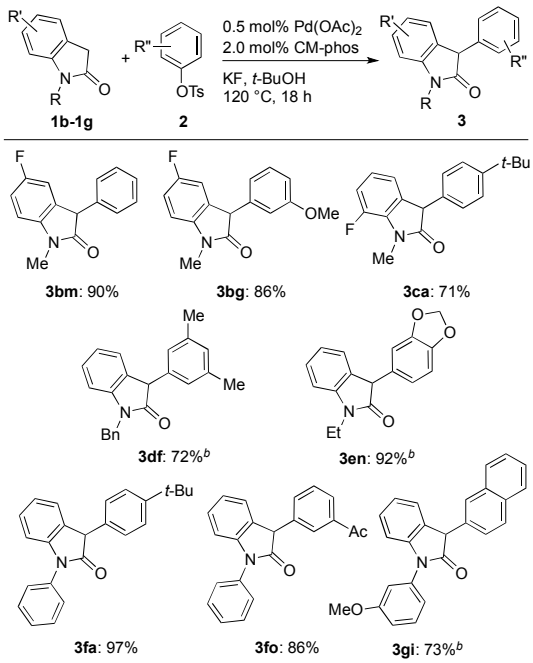
With the optimized reaction conditions in hand, the generality of the coupling reactions between oxindole **1a** and aryl tosylates were investigated (Scheme 3). To the best of our knowledge, there has been no successful example of aryl tosylates reported to-date in the direct arylation of oxindole derivatives. Aryl tosylates with different substitution patterns, in terms of electronic properties and substitution positions on the aromatic ring were tested. The corresponding products were afforded in good-to-

excellent yields. Particular functional groups including methyl ester, NH amido and keto moieties (Scheme 3, products **3ab**, **3ac** and **3ah**) remained intact under these reaction conditions. However, this reaction system did not tolerate unprotected oxindole. When 4-fluorophenyl tosylate was applied as the coupling partner, only 41% yield was obtained (Scheme 3, product **3ad**). Heterocycles such as quinoline, pyrrole and thiazole were all compatible under this catalytic system (Scheme 3, products **3aj**, **3ak**, and **3al**). The coupling of oxindole with sterically congested substrates proceeded smoothly upon using a slightly higher catalyst loading (1-2 mol% of Pd; Scheme 3, products **3ap** and **3aq**). Chloro group was found to react competitively (about 4 folds faster) than tosyloxy group as determined by GC analysis (Scheme 4, products **3aa** and **5**).

Scheme 4. A competitive experiment between the reactivity of –Cl and –OTs groups in oxindole arylation



Scheme 5. Palladium-catalyzed direct arylation of substituted oxindoles with ArOTs[a]



[a]Reaction conditions: oxindole **1** (0.3 mmol), aryl tosylate **2** (0.45 mmol), $Pd(OAc)_2$ (0.5 mol%), CM-phos (2.0 mol%, Pd/L = 1:4), KF (0.9 mmol) and *t*-BuOH (1 mL) were stirred at 120 °C under nitrogen for 18 h. Isolated yields were reported. Reaction times were not optimized for each substrate. [b]1.0 mol% of $Pd(OAc)_2$ was used.

We next turned our attention to survey the scope of substituted oxindoles (Scheme 5). When a fluoro-group was substituted at the C-5 position of the oxindole, good product yields were obtained (Scheme 5, products **3bm** and **3bg**). When the fluoro-group was at C-7 position, a moderate product yield was afforded (Scheme 5, product **3ca**). Other *N*-substituted oxindoles proceeded smoothly to give the corresponding products in good yields (Scheme 5, products **3df** and **3en**). *N*-Aryloxindoles were also applicable substrates for this direct arylation (Scheme 5, products **3fa** and **3fo**). 1-(3-Methoxyphenyl)indolin-2-one afforded the coupling product in 73% yield (Scheme 5, product **3gi**).

In conclusion, we have succeeded in showing the first examples of C3-direct arylation of oxindoles using aryl tosylates.[18] This method is complementary to aryl halides, as the arene sulfonates (coming from phenols) are generally having different substitution pattern to them. In the reported procedures, 0.5 mol% palladium catalyst

was found to promote the reaction in general, and the corresponding C3-arylated oxindoles were obtained in good-to-excellent yields (up to 97%) with good functional group compatibility (e.g. methyl ester, NH amido, enolizable keto and etc.). We believe this method is useful for a late-stage functionalization as the tosyloxy group is comparatively inert to other aryl sulfonates and would serve as a good protecting group at the beginning of the synthetic sequence.

Experimental Section

General Information. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All the reactions were performed in Rotaflo®(England) re-sealable screw-cap Schlenk tube (approx. 20 mL volume) in the presence of Teflon coated magnetic stirrer bar (4 mm × 10 mm). Dioxane and toluene were freshly distilled over sodium under nitrogen.[19] *t*-BuOH was first distilled over sodium and stored with calcium hydride under nitrogen. Thin layer chromatography was performed on precoated silica gel 60 F_{254} plates. Silica gel (230-400 mesh) was used for column chromatography. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer. Spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm), or with TMS (δ 0.00 ppm) as the internal standard. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. ^{13}C NMR spectra were recorded on a 100 MHz spectrometer and the spectra were referenced to $CDCl_3$ (δ 77.0 ppm, the middle peak). Coupling constants (*J*) were reported in Hertz (Hz). Mass spectra (EI-MS and ES-MS) were recorded on a Mass Spectrometer. High-resolution mass spectra (HRMS) were obtained on a Q-Exactive Hybrid Quadrupole-Orbitrap Mass Spectrometer. Products described in GC yield were accorded to the authentic samples/dodecane calibration standard from GC-FID system.

General Procedures for Ligand and Reaction Condition Screenings

Palladium source (3.0 mol%), ligand (12.0 mol%), *N*-methyloxindole (**1a**) (44.1 mg, 0.3 mmol), 4-*tert*-butylphenyl tosylate (**2a**) (136.8 mg, 0.45 mmol), and KF (0.9 mmol) were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar. The tube was evacuated and flushed with nitrogen for three cycles. Solvent (1.0 mL) was then added with stirring at room temperature for about 5 minutes. The tube was then placed into a preheated oil bath (120 °C) and stirred for 18 hours. After completion of reaction, the reaction tube was allowed to reach room temperature. Ethyl acetate (~10 mL), dodecane (68 μL, internal standard) and water (~3 ml) were added. The organic layer was subjected to GC analysis. The GC yield obtained was previously calibrated by authentic sample/dodecane calibration curve.

General Procedures for Direct α-Arylation of Oxindoles with Aryl Tosylates

A stock solution of $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) in freshly distilled dichloromethane (0.2 mL) was initially prepared with continuously stirring at room temperature with 5 minutes in Schlenk tube. 10 μL (0.5 mol% of Pd loading indicated in Scheme 3, 4, or 5) or 20 μL (1.0 mol% of Pd loading indicated in Scheme 3 or 5) of the stock solution was transferred to another Schlenk tube equipped with a Teflon-coated magnetic stir bar *via* syringe. The solvent was then evaporated under high vacuum. CM-phos (2.0 mol% or 4.0 mol%, Pd/L = 1:4), oxindoles **1** (0.3 mmol), aryl tosylates **2** (0.45 mmol) and KF (52 mg, 0.9 mmol) were loaded into the tube. The tube was evacuated and backfilled with nitrogen (3 cycles). The solvent *t*-BuOH (1.0 mL) was then added with continuous stirring at room temperature for about 5 minutes. The tube was then placed into a preheated oil bath (120 °C) and stirred for 18 hours. After completion of reaction, the reaction tube was allowed to reach room temperature and quenched with water and diluted with ethyl acetate. The organic layer was separated and the aqueous layer was washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (230-400 mesh) to afford the desired product.

3-(4-(*tert*-Butyl)phenyl)-1-methylindolin-2-one (Table 1 and Scheme 3, compound 3aa)[13]

Yield: 95% (79 mg); viscous pale yellow oil; R_f = 0.4 (EA: Hexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.34 (m, 3H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 4.62 (s, 1H), 3.27 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 150.3, 144.5, 133.5, 128.9, 128.3, 128.0, 125.8, 125.1, 122.6, 108.1, 51.5, 34.5, 31.3, 26.4; HRMS (ESI): m/z calcd for $C_{19}H_{22}NO$ $[M+H]^+$ 280.1696, Found 280.1688.

Methyl 4-(1-methyl-2-oxoindolin-3-yl)benzoate (Scheme 3, compound 3ab)[11]

Yield: 93% (78 mg); white solid, m.p. = 108-109 °C; R_f = 0.3 (EA: Hexane = 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.4 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 4.67 (s, 1H), 3.90 (s, 3H), 3.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 166.7, 144.4, 141.8, 130.1, 129.4, 128.7, 128.5, 128.0, 125.0, 122.8, 108.3, 52.1, 51.9, 26.5; HRMS (ESI): m/z calcd for $C_{17}H_{16}NO_3$ $[M+H]^+$ 282.1125, Found 282.1119.

3-(4-Benzoylphenyl)-1-methylindolin-2-one (Scheme 3, compound 3ac)

Yield: 73% (72 mg); white solid, m.p. = 125-127 °C; R_f = 0.3 (EA: Hexane = 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.78 (m, 4H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.50-7.46 (m, 2H), 7.38-7.34 (m, 3H), 7.21-7.19 (m, 1H), 7.13-7.09 (m, 1H), 6.96 (d, *J* = 8.0Hz, 1H), 4.72 (s, 1H), 3.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 175.2, 144.4, 1412, 137.5, 136.8, 132.4, 130.6, 130.3, 130.0, 128.8, 128.4, 128.2, 128.0, 125.0, 122.9, 108.4, 51.9, 26.5; HRMS (ESI): m/z calcd for $C_{22}H_{18}NO_2$ $[M+H]^+$ 328.1332, Found 328.1327.

3-(4-Fluorophenyl)-1-methylindolin-2-one (Scheme 3, compound 3ad)[20]

Yield: 41% (29 mg); viscous pale yellow oil; R_f = 0.3 (EA: Hexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (t, *J* = 7.6 Hz, 1H), 7.22-7.17 (m, 3H), 7.12-7.01 (m, 3H), 6.93 (d, *J* = 7.6 Hz, 1H), 4.61 (s, 1H), 3.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 163.5

(J_{C-F} = 244.5 Hz), 161.0, 144.4, 132.3 (J_{C-F} = 2.3 Hz), 130.0 (J_{C-F} = 8.7 Hz), 128.6, 128.5, 125.0, 122.8, 115.8 (J_{C-F} = 21.3 Hz), 108.2, 51.2, 26.4; HRMS (ESI): m/z calcd for $C_{15}H_{13}FNO$ $[M+H]^+$ 242.0976, Found 242.0972.

3-(3,4-Dimethylphenyl)-1-methylindolin-2-one (Scheme 3, compound 3ae)

Yield: 96% (72 mg); white solid, m.p. = 93-95 °C; R_f = 0.6 (EA: Hexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (t, J = 7.6 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 7.14-7.07 (m, 2H), 7.01 (s, 1H), 6.97-6.92 (m, 2H), 4.58 (s, 1H), 3.29 (s, 3H), 2.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 144.5, 137.1, 135.9, 134.0, 130.1, 129.6, 129.2, 128.3, 125.8, 125.0, 122.7, 108.1, 51.8, 26.4, 19.8, 19.4; HRMS (ESI): m/z calcd for $C_{17}H_{18}NO$ $[M+H]^+$ 252.1383, Found 252.1378.

3-(3,5-Dimethylphenyl)-1-methylindolin-2-one (Scheme 3, compound 3af)[11]

Yield: 97% (73 mg); white solid, m.p. = 87-89 °C; R_f = 0.6 (EA: Hexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (t, J = 7.6 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 6.96-6.93 (m, 2H), 6.84 (s, 2H), 4.56 (s, 1H), 3.30 (s, 3H), 2.32 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 144.4, 138.4, 136.5, 129.3, 129.2, 128.3, 126.2, 125.0, 122.7, 108.1, 52.1, 26.4, 21.3; HRMS (ESI): m/z calcd for $C_{17}H_{18}NO$ $[M+H]^+$ 252.1383, Found 252.1378.

3-(3-Methoxyphenyl)-1-methylindolin-2-one (Scheme 3, compound 3ag)[21]

Yield: 81% (61 mg); pale yellow sticky oil; R_f = 0.3 (EA: Hexane = 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (t, J = 7.6 Hz, 1H), 7.29-7.25 (m, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 6.86-6.81 (m, 2H), 6.77 (s, 1H), 4.60 (s, 1H), 3.79 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 159.9, 144.4, 138.0, 129.8, 128.7, 128.4, 125.0, 122.7, 120.7, 114.4, 112.8, 108.1, 55.2, 52.0, 26.4; HRMS (ESI): m/z calcd for $C_{16}H_{16}NO_2$ $[M+H]^+$ 254.1176, Found 254.1171.

***N*-(3-(1-Methyl-2-oxoindolin-3-yl)phenyl)acetamide (Scheme 3, compound 3ah)**

Yield: 84% (71 mg); white solid, m.p. = 112-114 °C;R_f = 0.2 (EA: Hexane = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.38 (s, 2H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.19-7.14 (m, 2H), 7.08-7.04 (t, *J* = 7.2 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 7.2 Hz, 1H), 4.56 (s, 1H), 3.24 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 168.8, 144.2, 138.9, 136.9, 129.3, 128.7, 128.5, 125.0, 123.5, 123.0, 120.0, 119.1, 108.3, 52.2, 26.4, 24.2; HRMS (ESI): m/z calcd for $C_{17}H_{17}N_2O_2$ $[M+H]^+$ 281.1290, Found 281.1285.

1-Methyl-3-(naphthalen-2-yl)indolin-2-one (Scheme 3, compound 3ai)[13]

Yield: 89% (73 mg); colorless oil; R_f = 0.4 (EA: Hexane = 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85-7.81 (m, 3H), 7.75 (s, 1H), 7.51-7.47 (m, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.31-7.28 (m, 1H), 7.23 (d, *J* = 7.2Hz, 1H), 7.11 (t, *J* = 7.2Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 4.81 (s, 1H), 3.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 144.5, 134.1, 133.5, 132.8, 128.9, 128.7, 128.5, 127.8, 127.6, 127.5, 126.2, 126.1, 126.0, 125.1, 122.8, 108.2, 52.2, 26.5; HRMS (ESI): m/z calcd for $C_{19}H_{16}NO$ $[M+H]^+$ 274.1226, Found 274.1221.

1-Methyl-3-(quinolin-6-yl)indolin-2-one (Scheme 3, compound 3aj)

Yield: 85% (70 mg); pale yellow sticky oil; R_f = 0.2 (EA: Hexane = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89-8.88 (m, 1H), 8.09 (t, *J* = 9.2 Hz, 2H), 7.72-7.71 (m, 1H), 7.52-7.50 (m, 1H), 7.39-7.35 (m, 2H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 4.81 (s, 1H), 3.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 150.4, 147.7, 144.5, 135.9, 134.9, 130.2, 129.7, 128.7, 128.4, 128.3, 127.4, 125.1, 122.9, 121.3, 108.4, 51.9, 26.6; HRMS (ESI): m/z calcd for $C_{18}H_{15}N_2O$ $[M+H]^+$ 275.1179, Found 275.1172.

3-(3-(1*H*-Pyrrol-1-yl)phenyl)-1-methylindolin-2-one (Scheme 3, compound 3ak)

Yield: 88% (76 mg); white solid, m.p. = 105-106 °C; R_f = 0.4 (EA: Hexane = 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.34 (m, 3H), 7.28-7.22 (m, 2H), 7.16-7.11 (m, 2H), 7.09-7.08 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.37-6.35 (m, 2H), 4.69 (s, 1H), 3.30 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 144.5, 141.2, 138.2, 130.0, 128.7, 128.2, 125.8, 125.0, 122.9, 120.7, 119.8, 119.4, 110.4, 108.4, 51.8, 26.5; HRMS (ESI): m/z calcd for $C_{19}H_{17}N_2O$ $[M+H]^+$ 289.1335, Found 289.1329.

1-Methyl-3-(2-methylbenzo[d]thiazol-6-yl)indolin-2-one (Scheme 3, compound 3al)

Yield: 62% (55 mg); white solid, m.p. = 84-86 °C; R_f = 0.4 (EA: Hexane = 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80-7.75 (m, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.28-7.25 (m, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 4.74 (s, 1H), 3.26 (s, 3H), 2.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 167.6, 153.7, 144.5, 134.9, 134.8, 128.7, 128.6, 125.3, 125.1, 122.8, 122.0, 121.7, 108.2, 51.8, 26.4, 20.1; HRMS (ESI): m/z calcd for $C_{17}H_{15}N_2OS$ $[M+H]^+$ 295.0899, Found 295.0892.

3-(2,5-Dimethylphenyl)-1-methylindolin-2-one (Scheme 3, compound 3ap)

Yield: 47% (35 mg); orange solid, m.p. = 133-135 °C; R_f = 0.45 (EA: Hexane = 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (t, *J* = 7.6 Hz, 1H), 7.12-7.00 (m, 4H), 7.91 (d, *J* = 8.0 Hz, 1H), 6.71 (bs, 1H), 4.80 (bs, 1H), 3.29 (s, 3H), 2.24 (bs, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 144.0, 135.5, 135.0, 133.6, 130.6, 129.1, 128.1, 127.9, 124.2, 122.4, 107.8, 50.1, 26.1, 20.6, 19.0; HRMS (ESI): m/z calcd for $C_{17}H_{18}NO$ $[M+H]^+$ 252.1388, Found 252.1390.

1-Methyl-3-(naphthalen-1-yl)indolin-2-one (Scheme 3, compound 3aq)[22]

Yield: 80% (66 mg); pale yellow solid; R_f = 0.4 (EA: Hexane = 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (bs, 1H), 7.91 (d, *J* = 6.8 Hz, 2H), 7.84-7.33 (m, 4H), 7.12-6.95 (m, 4H), 5.51 (bs, 1H), 3.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 144.1, 134.1, 129.3, 128.7, 128.2, 126.3, 125.7, 125.3, 124.5, 123.9, 122.6, 108.1, 47.6, 26.3; HRMS (ESI): m/z calcd for $C_{19}H_{16}NO$ $[M+H]^+$ 274.1232, Found 274.1233.

5-Fluoro-1-methyl-3-phenylindolin-2-one (Scheme 5, compound 3bm)[23]

Yield: 90% (65 mg); yellow oil; R_f = 0.4 (EA: Hexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.31 (m, 3H), 7.22-7.20 (m, 2H), 7.08-7.03 (m, 1H), 6.95-6.93 (m, 1H), 6.85-6.82 (m, 1H), 4.62 (s, 1H), 3.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 160.5 (J_{C-F} = 238.9 Hz), 158.1, 140.4, 136.0, 130.4 (J_{C-F} = 7.8 Hz), 129.0, 128.3, 127.7, 114.7 (J_{C-F} = 23.3 Hz), 113.2 (J_{C-F} = 24.9 Hz), 108.6 (J_{C-F} = 8.0 Hz), 52.3 (J_{C-F} = 1.6 Hz), 26.6; HRMS (ESI): m/z calcd for $C_{15}H_{13}FNO$ $[M+H]^+$ 242.0976, Found 242.0971.

5-Fluoro-3-(3-methoxyphenyl)-1-methylindolin-2-one (Scheme 5, compound 3bg)

Yield: 86% (70 mg); yellow oil; R_f = 0.3 (EA: Hexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.25 (m, 1H), 7.06-7.02 (m, 1H), 6.95-6.93 (m, 1H), 6.86-6.78 (m, 3H), 6.74 (s, 1H), 4.58 (s, 1H), 3.79 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 160.5 (J_{C-F} = 239.1 Hz), 159.9, 158.1, 140.4 (J_{C-F} = 2.5 Hz), 137.4, 130.3 (J_{C-F} = 8.4 Hz), 129.9, 120.6, 114.8 (J_{C-F} = 23.4 Hz), 114.5, 113.2, 113.0, 108.6 (J_{C-F} = 7.8 Hz), 55.2, 52.2 (J_{C-F} = 1.5 Hz), 26.6; HRMS (ESI): m/z calcd for $C_{16}H_{15}FNO_2$ $[M+H]^+$ 272.1081, Found 272.1076.

3-(4-(*tert*-Butyl)phenyl)-7-fluoro-1-methylindolin-2-one (Scheme 5, compound 3ca)

Yield: 71% (63 mg); pale yellow sticky oil; R_f = 0.4 (EA: Hexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 7.10-6.98 (m, 3H), 4.62 (s, 1H), 3.49 (d, J = 2.8 Hz, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 150.5, 148.8 (J_{C-F} = 241.4 Hz), 146.4, 133.0, 131.7 (J_{C-F} = 3.0 Hz), 131.1 (J_{C-F} = 7.5 Hz), 127.9, 125.9, 123.1 (J_{C-F} = 6.6 Hz), 121.0 (J_{C-F} = 3.7 Hz), 116.3 (J_{C-F} = 18.7Hz), 51.7 (J_{C-F} = 1.7 Hz), 34.5, 31.3, 28.9 (J_{C-F} = 5.9 Hz); HRMS (ESI): m/z calcd for $C_{19}H_{21}FNO$ $[M+H]^+$ 298.1602, Found 298.1596.

1-Benzyl-3-(3,5-dimethylphenyl)indolin-2-one (Scheme 5, compound 3df)

Yield: 72% (71 mg); yellow oil; R_f = 0.4 (EA: Hexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 7.26-7.18 (m, 2H), 7.07-7.03 (m, 1H), 6.97 (s, 1H), 6.86-6.83 (m, 3H), 5.06-4.94 (dd, J = 33.2, 15.2 Hz, 2H), 4.66 (s, 1H), 2.33 (s, 6H); ^{13}C NMR (100

MHz, $CDCl_3$): δ 176.4, 143.5, 138.4, 136.6, 136.0, 135.9, 129.4, 129.3, 128.7, 128.5, 128.4, 128.2, 127.6, 127.4, 127.1, 126.2, 125.1, 122.7, 109.1, 52.1, 44.1, 43.9, 21.5, 21.3; HRMS (ESI): m/z calcd for $C_{23}H_{22}NO$ $[M+H]^+$ 328.1696, Found 328.1688.

3-(Benzo[*d*][1,3]dioxol-5-yl)-1-ethylindolin-2-one (Scheme 5, compound 3en)

Yield: 92% (77 mg); pale yellow sticky oil; R_f = 0.4 (EA: Hexane = 1:3); ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.06 (t, *J* = 7.2 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.73-6.71 (m, 1H), 6.63 (d, *J* = 1.6 Hz, 1H), 5.93 (s, 2H), 4.51 (s, 1H), 3.82 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 148.0, 147.1, 143.4, 130.4, 129.2, 128.4, 125.1, 122.5, 121.9, 108.6, 108.5, 108.3, 101.1, 51.7, 34.8, 12.7; HRMS (ESI): m/z calcd for $C_{17}H_{16}NO_3$ $[M+H]^+$ 282.1125, Found 282.1119.

3-(4-(*tert*-Butyl)phenyl)-1-phenylindolin-2-one (Scheme 5, compound 3fa)

Yield: 97% (99 mg); white solid, m.p. = 117-119 °C; R_f = 0.5 (EA: Hexane = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ 7.59-7.55 (m, 2H), 7.52 (d, *J* =7.2 Hz, 2H), 7.47-7.43 (m, 3H), 7.32 (d, *J* = 8.0 Hz, 4H), 7.15 (t, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 4.84 (s, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 150.5, 144.4, 134.7, 133.7, 129.6, 128.8, 128.2, 128.1, 128.0, 126.6, 125.9, 125.5, 123.1, 109.5, 51.7, 34.5, 31.4; HRMS (ESI): m/z calcd for $C_{24}H_{24}NO$ $[M+H]^+$ 342.1852, Found 342.1847.

3-(3-Acetylphenyl)-1-phenylindolin-2-one (Scheme 5, compound 3fo)

Yield: 86% (84 mg); white solid, m.p. = 103-104 °C; R_f = 0.4 (EA: Hexane = 1:3); ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.56-7.41 (m, 7H), 7.31-7.27 (m, 1H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 4.89 (s, 1H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 174.8, 144.4, 137.7, 137.4, 134.4, 133.1, 129.6, 129.2, 128.6, 128.4, 128.2, 127.9, 127.8, 126.6, 125.3, 123.4, 109.7, 51.9, 26.7; HRMS (ESI): m/z calcd for $C_{22}H_{18}NO_2$ $[M+H]^+$ 328.1332, Found 328.1324.

1-(3-Methoxyphenyl)-3-(naphthalen-2-yl)indolin-2-one (Scheme 5, compound 3gi)

Yield: 73% (80 mg); white solid, m.p. = 115-117 °C; R_f = 0.4 (EA: Hexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.84 (m, 4H), 7.54-7.45 (m, 3H), 7.43-7.40 (m, 1H), 7.34-7.28 (m, 2H), 7.16-7.06 (m, 3H), 7.02 (d, *J* = 8.0 Hz, 2H), 5.00 (s, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 160.6, 144.4, 135.6, 134.1, 133.5, 132.9, 130.3, 128.8, 128.7, 128.4, 127.8, 127.7, 127.7, 126.3, 126.2, 126.0, 125.5, 123.2, 118.7, 114.1, 112.3, 109.7, 55.5, 52.4; HRMS (ESI): m/z calcd for $C_{25}H_{20}NO_2$ $[M+H]^+$ 366.1489, Found 366.1483.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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