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

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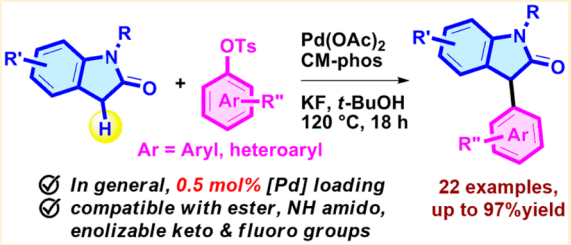
Supporting Information

ABSTRACT: A palladium-catalyzed monoselective 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 (≤97%). The reaction conditions are mild (using 0.5 mol % Pd in general and KF as a base), and functional groups such as methyl ester, NH amido, and enolizable keto moieties are found to be compatible.



Oxindoles constitute an important heterocyclic subunit in various natural products and biologically active molecules.[1] In particular, the C3 aryl-containing oxindoles are useful lead compounds in drug discovery, for instance, as an anticancer agent,[2] a neuroprotective agent,[3] and a potent growth hormone secretagogue (Figure 1).[4] Synthetic methods

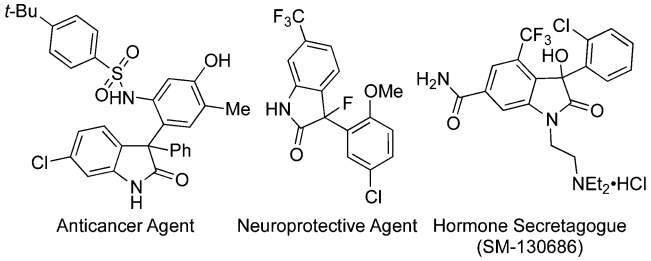
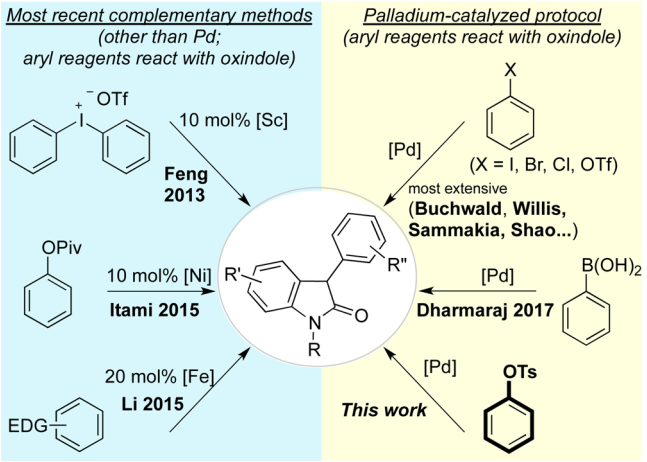


Figure 1. Examples of useful C3 aryl-containing oxindole bioactive molecules.

for accessing this class of scaffold include nucleophilic substitution with isatins,[5] palladium-mediated[6] and copper-mediated[7] cyclization reaction, and the recent transition metal-free pathways.[8] Indeed, having an approach that allows the integration of two individual components for preparing a cross array of structurally similar yet diversified compounds is highly significant.[9] Thus, a versatile coupling of the already assembled oxindole core with arene is often desirable.

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 a Ni complex was recently disclosed by Yamaguchi, Itami, and co-workers (Scheme 1).[11] In 2015, Li and co-workers 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 to be feasible.[13] Apart from these

Scheme 1. Recent Pd-Catalyzed and Complementary Methods for C3-Aryloxindole Synthesis from Already Assembled Oxindoles and Arenes



complementary developments, investigations of 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 that of arenes coming from traditional halogenation.[15] Nevertheless, the most reactive aryl triflates are easily decomposed when a strong base and an alcoholic solvent are used as the reaction medium. To overcome this drawback, aryl tosylate is therefore a better alternative in terms of superior stability toward alkaline hydrolysis as well as high economic attractiveness, yet this stable aryl tosylate leads to the requirement of using a more active palladium complex to permit $C_{(Ar)}$–O bond cleavage in

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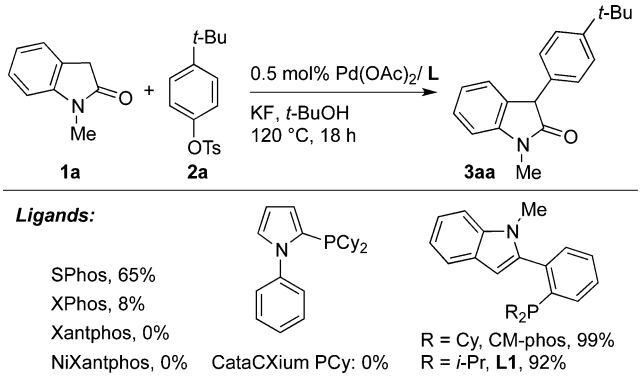
the oxidative addition step. Thus, developing an effective system for this direct arylation reaction is demanding. Herein, we report the first examples of α-arylation of oxindoles with aryl tosylates (Scheme 1). This process generally requires 0.5 mol % palladium loading.

We initially selected oxindole **1a** and nonactivated aryl tosylate **2a** for a 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 a moderate product yield. In this ligand evaluation, CM-phos gave the best result and **L1** gave a yield slightly lower than that of CM-phos (Scheme 2).

Scheme 2. Evaluation of Ligand Efficacy for Palladium-Catalyzed Direct Arylation of *N*-Methyloxindole[a]

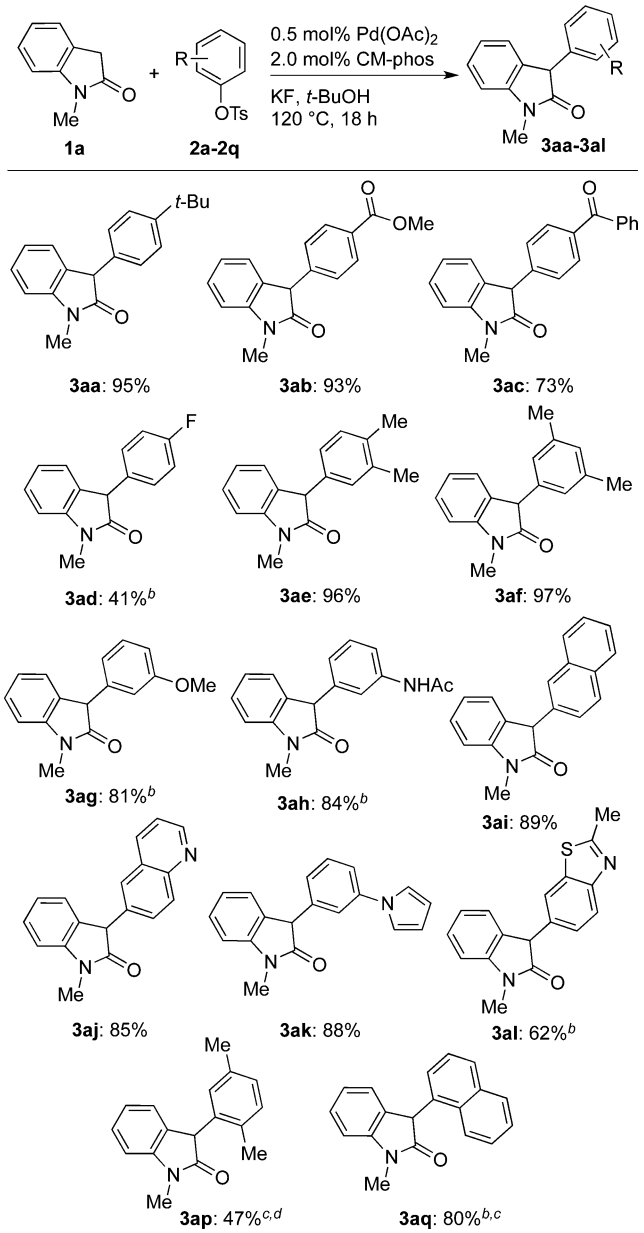


[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), $Pd(OAc)_2$ (0.5 mol %), **L** (1.0–2.0 mol %), KF (0.9 mmol), and *t*-BuOH (1 mL) were stirred at 120 °C under nitrogen for 18 h. Yields were determined by GC-FID with dodecane as the internal standard.

With the optimized reaction conditions in hand, the generality of the coupling reactions between oxindole **1a** and aryl tosylates was 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**, respectively), 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, an 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**, respectively). The coupling of oxindole with sterically congested substrates proceeded smoothly upon using a slightly higher catalyst loading [1–2 mol % Pd (Scheme 3, products **3ap** and **3aq**)]. The chloro group was found to react competitively (~4-fold faster) than the tosyloxy group as determined by GC analysis (Scheme 4, products **3aa** and **5**).

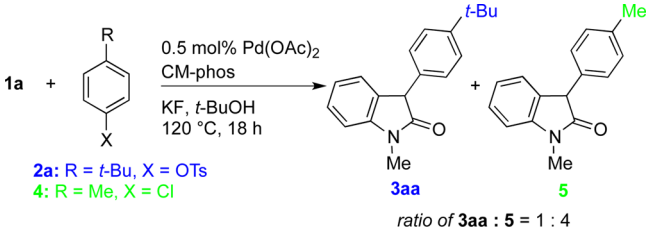
We next turned our attention to survey the scope of substituted oxindoles (Scheme 5). When a fluoro group was substituted at the C5 position of the oxindole, good product yields were obtained (Scheme 5, products **3bm** and **3bg**). When the fluoro group was at the C7 position, a moderate product yield was afforded (Scheme 5, product **3ca**). Other N-

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

Scheme 4. Competitive Experiment between the Reactivity of -Cl and -OTs Groups during Oxindole Arylation



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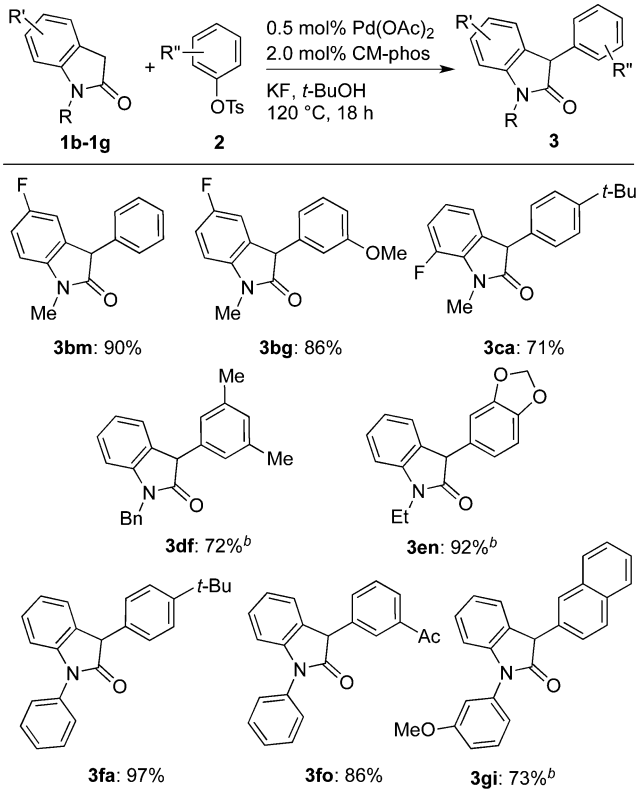
Scheme 5. Palladium-Catalyzed Direct Arylation of Substituted Oxindoles with ArOTs[a]



[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 %, 1:4 Pd:L), KF (0.9 mmol), and *t*-BuOH (1 mL) were stirred at 120 °C under nitrogen for 18 h. Isolated yields are reported. Reaction times were not optimized for each substrate. [b]1.0 mol % $Pd(OAc)_2$ was used.

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) generally have a different substitution pattern. 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 (≤97%) with good functional group compatibility (e.g., methyl ester, NH amido, enolizable keto, 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 being purified. All the reactions were performed in a Rotaflo resealable screw-cap Schlenk tube (approximately 20 mL volume) in the presence of a 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) or TMS (δ 0.00) as the internal standard. Chemical shifts (δ) are reported as parts per million 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, middle peak). Coupling constants (J) are reported in hertz. Mass spectra (EI-MS and ES-MS) were recorded on a mass spectrometer. High-resolution mass spectra were recorded on a Q-Exactive Hybrid Quadrupole-Orbitrap Mass Spectrometer. Products described in GC yield were in accord with the authentic samples/dodecane calibration standard from the GC-FID system.

General Procedures for Ligand and Reaction Condition Screenings. A palladium source (3.0 mol %), a 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. The solvent (1.0 mL) was then added while the mixture was being stirred at room temperature for ∼5 min. The tube was then placed in a preheated oil bath (120 °C), and its contents were stirred for 18 h. After the reaction had reached completion, 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 with an 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 while being continuously stirred at room temperature over 5 min in a Schlenk tube. Ten microliters (0.5 mol % Pd loading indicated in Scheme 3, 4, or 5) or 20 μL (1.0 mol % 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 or 4.0 mol %, 1:4 Pd:L), 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 (three cycles). The solvent *t*-BuOH (1.0 mL) was then added while the mixture was being continuously stirred at room temperature for ∼5 min. The tube was then placed into a preheated oil bath (120 °C), and its contents were stirred for 18 h. After the reaction had reached completion, the tube was allowed to reach room temperature, the reaction quenched with water, and the mixture 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*-Butylphenyl)-1-methylindolin-2-one (Scheme 3, compound 3aa).[13] Yield: 95% (79 mg). Viscous pale yellow oil. R_f = 0.4 (1:5 EA:hexane). ^{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. Mp: 108−109 °C. R_f = 0.3 (1:4 EA:hexane). ^{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.

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3-(4-Benzoylphenyl)-1-methylindolin-2-one (Scheme 3, compound 3ac). Yield: 73% (72 mg). White solid. Mp: 125−127 °C. R_f = 0.3 (1:4 EA:hexane). ^{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 = 8.0 Hz, 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 (1:5 EA:hexane). ^{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. Mp: 93−95 °C. R_f = 0.6 (1:5 EA:hexane). ^{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. Mp: 87−89 °C. R_f = 0.6 (1:5 EA:hexane). ^{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 (1:4 EA:hexane). ^{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. Mp: 112−114 °C. R_f = 0.2 (1:1 EA:hexane). ^{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 (1:4 EA:hexane). ^{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 = 7.2 Hz, 1H), 7.11 (t, J = 7.2 Hz, 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 (2:1 EA:hexane). ^{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. Mp: 105−106 °C. R_f = 0.4 (1:3 EA:hexane). ^{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. Mp: 84−86 °C. R_f = 0.4 (1:3 EA:hexane). ^{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. Mp: 133−135 °C. R_f = 0.45 (1:3 EA:hexane). ^{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 (1:3 EA:hexane). ^{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 (1:5 EA:hexane). ^{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 (1:5 EA:hexane). ^{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*-Butylphenyl)-7-fluoro-1-methylindolin-2-one (Scheme 5, compound 3ca). Yield: 71% (63 mg). Pale yellow sticky oil. R_f = 0.4 (1:5 EA:hexane). ^{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} = 18.7 Hz), 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 (1:5 EA:hexane). ^{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).

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^{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 (1:3 EA:hexane). ^{1}H 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*-Butylphenyl)-1-phenylindolin-2-one (Scheme 5, compound 3fa). Yield: 97% (99 mg). White solid. Mp: 117−119 °C. R_f = 0.5 (1:5 EA:hexane). ^{1}H 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. Mp: 103−104 °C. R_f = 0.4 (1:3 EA:hexane). ^{1}H 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. Mp: 115−117 °C. R_f = 0.4 (1:5 EA:hexane). ^{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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00855.

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

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Notes

The authors declare no competing financial interest.

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